Structure–Activity Studies of Antitumor Taxanes: Synthesis of Novel C-13 Side Chain Homologated Taxol and Taxotere Analogs

Lalith R. Jayasinghe*
Oread Laboratories, Inc., 1501 Wakarusa Drive, Lawrence, Kansas 66047

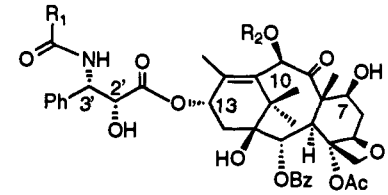
Apurba Datta, Syed M. Ali, Jan Zygmunt, David G. Vander Velde, and Gunda I. Georg
Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

Received May 2, 1994[⊗]

Taxol and taxotere analogs with one carbon homologated side chains were synthesized from 10-deacetylbaccatin III and a key oxazolidineacetic acid intermediate, which was synthesized in four steps from (*S*)-(+)-2-phenylglycine. 10-Deacetyl-1a′-homotaxol and 1a′-homotaxotere were at least 27 times less active than taxol in the microtubule assembly assay. The inability of these homologs to induce microtubule formation may be due to unfavorable solution conformations, preventing productive interactions with the taxol binding site on microtubules.

The anticancer drug taxol (**1a**, Figure 1), a diterpenoid isolated from several *Taxus* species,[1–3] is probably the most promising antitumor agent currently under investigation for cancer chemotherapy.[4] Besides being remarkably active against drug refractory, advanced ovarian cancer,[4] recent clinical studies have also indicated taxol to be a promising chemotherapeutic agent for the treatment of metastatic breast cancer,[5] non-small cell lung cancer,[6,7] and head and neck cancer.[8] These promising clinical results have stimulated a multitude of investigations aimed at a better understanding of the chemistry and mode of action of this exciting compound.[9–11]

It has been shown that the presence of both the C-13 phenylisoserine side chain and the diterpene moiety of taxol are essential for its biological properties, whereas individually they are devoid of any significant activity.[12] Thus, the C-13 side chain has been the focus of extensive modifications.[9–11,13–15] This is due to its biological importance and also a result of efficient methodologies, developed for the synthesis of this structural unit.[16] Studies directed at elucidating the minimal structural requirement for the C-13 side chain have shown that the hydroxyl group at C-2′ is essential for maximum activity[14,17] and that the C-3′ phenyl group or a related substituent is necessary for strong microtubule binding and cytotoxicity.[17,18] A free amino group at C-3′ decreased the activity, but replacement of the acyl substituent at 3′-N with a tigloyl (cephalomannine) or *tert*-butoxycarbonyl (taxotere **1b**, Figure 1) group provided analogs with equal or better activity than taxol.[17] The natural stereochemistry at C-2′ and C-3′ (i.e. 2′*R*,3′*S*) of the C-13 side chain was found to be necessary for superior bioactivity.[17] Transposition of the 2′-hydroxy and 3′-*N*-acyl groups produced analogs with decreased activity.[17] However, to date no information is available regarding the effect of an increase in length of the C-13 phenylisoserine side chain on overall activity. Hence, as part of an ongoing program directed toward evaluating structure–activity relationships of antitumor taxanes, we decided to synthesize analogs of taxol (**1a**) and its potent analog taxotere (**1b**)[17] possessing a one carbon homologated C-13 side chain and to study their biological activities. The results of our investigations are described herein.



1a R_1 = Ph, R_2 = Ac (Taxol)
b R_1 = *t*-BuO, R_2 = H (Taxotere)

Figure 1. Structures of taxol and taxotere.

Results and Discussion

A number of methods have been developed for the synthesis of the C-13 phenylisoserinate side chain,[16] of which the use of *N*-acyl β-lactams[19] and 2,2-dimethyloxazolidinecarboxylic acids[20] continue to be the methods of choice because of their relative ease of reaction with baccatin III analogs. Since only the latter strategy is suitable for the synthesis of taxol analogs with homologated side chains, the key intermediate, oxazolidine acetic acid **6**, was synthesized by an efficient four step sequence starting with (*S*)-(+)-2-phenylglycine (**2**)[20,21] (Scheme 1).

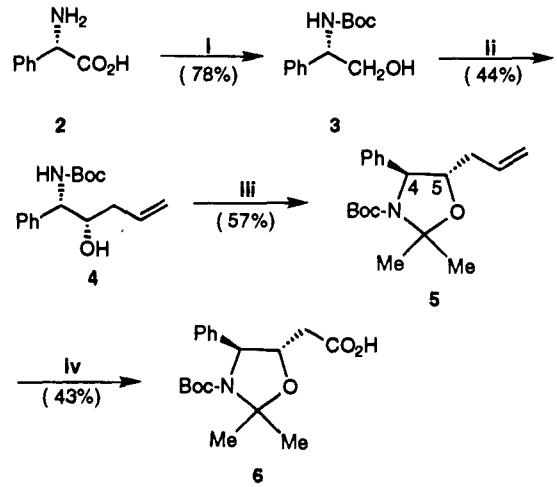
N-Boc-2-phenylglycinol **3** was obtained by reduction and *in situ* derivatization of (*S*)-(+)-2-phenylglycine (**2**) (Scheme 1).[21] Swern oxidation of **3** followed by Grignard reaction with allylmagnesium bromide yielded the allylic alcohol **4** with good syn diastereoselection (syn/anti = 4.5/1),[22] which is in accordance with earlier reported observations.[21] The syn product **4** was isolated by flash column chromatography and treated with 2,2-dimethoxypropane to afford oxazolidine derivative **5**. Oxidation of the terminal olefin under modified Sharpless conditions with sodium periodate and catalytic ruthenium chloride furnished the key intermediate oxazolidineacetic acid **6**.[21] Reaction between intermediate **6** and 10-deacetylbaccatin III derivative **7**,[17] utilizing the method reported by Commerçon *et al.*,[20] provided the coupled product **8** (Scheme 2) in good yield. Treatment of **8** with formic acid yielded the common intermediate amino alcohol **9**, which on *N*-acylation, followed by 7,10-*O*-deprotection of **10a** and **10b**, completed the syntheses of the desired side chain homologated analogs 10-deacetyl-1a′-homotaxol (**11a**) and 1a′-homotaxotere (**11b**).

Surprisingly, the one carbon elongation of the C-13 side chain resulted in very poor ability of **11a** and **11b** to induce the formation of microtubules (Table 1).[23]

[⊗] Abstract published in *Advance ACS Abstracts*, August 1, 1994.

0022-2623/94/1837-2981$04.50/0

Scheme 1



[a] (i) $LiAlH_4$, THF, then $(Boc)_2O$, CH_2Cl_2; (ii) Swern oxidation, then $H_2C{=}CHCH_2MgBr$; (iii) $Me_2C(OMe)_2$, PPTS; (iv) $NaIO_4$, $RuCl_3$, $NaHCO_3$.

Recent conformational studies on taxol (**1a**) and taxotere (**1b**) in hydrophobic ($CDCl_3$) and hydrophilic (DMSO/water) solvent systems demonstrated that the DMSO/water conformation is substantially different from the conformation observed in $CDCl_3$.[24] Due to loss of hydrogen bonding in the C-13 side chain[25] and hydrophobic collapse, the 3′-phenyl, the 2-benzoate, and the 4-acetoxy groups are in close proximity in the DMSO/water solvent system.[24] This water induced conformation may be necessary for recognition at the taxol binding site on microtubules. Comparison of the NOE data of 10-deacetyl-1a′-homotaxol (**11a**) and 1a′-homotaxotere (**11b**) with those of taxol and taxotere in DMSO/water mixtures indicated the absence of the characteristic aromatic–aromatic NOE interactions between the 2-benzoyl and 3′-phenyl groups, observed in the parent compounds.[24] These results point toward a solution conformation of these homologs in which the 2-benzoyl and 3′-phenyl rings cannot assume the specific conformation exhibited by taxol and taxotere, thus probably inhibiting their interaction with the microtubule binding site, and diminishing their activity.

Experimental Section[23]

(1*S*,2*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-hydroxy-1-phenyl-4-pentene (4). To a stirred solution of oxalyl chloride (2 M solution in CH_2Cl_2, 19 mL, 37.7 mmol) and CH_2Cl_2 (50 mL) at −75 °C under argon was added dimethyl sulfoxide (2.9 mL, 40.3 mmol) dropwise. After being stirred for 10 min at −75 °C the mixture was allowed to warm to −60 °C in 30 min and a solution of *N*-Boc-2-phenylglycinol (**3**)[21] (6.3 g, 26.5 mmol) in CH_2Cl_2 (100 mL) was added over 30 min. The mixture was then warmed to −35 °C in 30 min, stirred for another 5 min at this temperature, and then treated with diisopropylethylamine (26.8 mL, 153.4 mmol) over 5 min. The mixture was then brought to 0 °C in 15 min and transferred with a cannula to a room temperature solution of allylmagnesium bromide (1 M solution in Et_2O, 200 mL, 200 mmol) in CH_2Cl_2 (150 mL) over 30 min. The reaction mixture was stirred at room temperature for 1.5 h and quenched by sequential addition of ethanol (50 mL) and saturated aqueous NH_4Cl (100 mL). The mixture was then acidified to pH 4 by adding 10% aqueous HCl solution. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (1 × 150 mL); the combined organic layers were washed with water and brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and crude product purified by flash column chromatography (hexanes/ethyl acetate, 5:1 to 4:1) to yield 0.7 g (10%) of the anti product and 3.2 g (44%) of the syn product as a white solid. mp 96–97 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (br s, 9H), 1.97 (br s, 1H, exchangeable with D_2O), 2.24–2.36 (m, 2H), 3.88–3.99 (m, 1H), 4.69 (br s, 1H), 5.15 (m, 2H), 5.46 (m, 1H), 5.73–5.95 (m, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.30, 38.64, 74.22, 79.67, 118.45, 126.56, 127.41, 127.85, 128.61, 134.03, 155.35; MS (FAB^+) *m/e* 284 (M + Li), 278 (M + 1); $[\alpha]_D$ + 6.42° (*c* = 1.2, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO_3$: C, H, N.

(4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-phenyl-5-(2′-propenyl)-1,3-oxazolidine (5). To a solution of **4** (2.8 g, 10 mmol) and 2,2-dimethoxypropane (12.5 g, 120 mmol) in anhydrous toluene (50 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate, and the mixture was stirred at 80 °C for 3h. The solvent was then removed under reduced pressure and the product purified by flash column chromatography (hexanes/ethyl acetate, 19:1) to afford the pure product as a light yellow oil (1.8 g, 57%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (br s, 9H), 1.69 (s, 3H), 1.73 (s, 3H), 2.26–2.48 (m, 2H), 3.89–3.95 (m, 1H), 4.32 (br d, *J* = 7 Hz, 1H), 5.09–5.15 (m, 2H), 5.75–5.89 (m, 1H), 7.22–7.35 (m, 5H); MS (FAB^+) *m/e* 318 (M + 1); $[\alpha]_D$ + 22.96° (*c* = 2.6, $CHCl_3$).

(4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-5-acetic Acid (6). To a stirred solution of oxazolidine **5** (1.4 g, 4.4 mmol) in acetonitrile (10 mL) and carbon tetrachloride (10 mL) was added a suspension of sodium bicarbonate (2.4 g, 28.6 mmol) in water (20 mL) at room temperature. Then sodium periodate (5.17 g, 24.2 mmol) was added in small portions to the mixture, and the mixture was stirred for 10 min. The reaction mixture was treated with ruthenium(III) chloride hydrate (165 mg, 0.8 mmol), and stirring was continued at room temperature for 48 h. The heterogeneous mixture was then diluted with water (100 mL) and filtered through a sintered funnel, and the residue was washed with water (2 × 25 mL). The combined filtrate was then extracted with CH_2Cl_2 (50 mL), and the aqueous layer was cooled to 0 °C and acidified to pH 4 with aqueous 10% HCl solution. The solution was then extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to a volume of 50 mL. The product was then extracted from the $CHCl_3$ layer with a saturated sodium bicarbonate solution (4 × 50 mL). The bicarbonate extract was cooled to 0 °C and acidified to pH 4 by the addition of an aqueous 10% HCl solution followed by extraction with $CHCl_3$ (4 × 100 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After the solvent was removed *in vacuo*, the crude product was dissolved in hot pentane and left at 0 °C overnight to yield the product as a white solid (0.6 g, 43%): mp 121–123 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (br s, 9H), 1.73 and 1.78 (2s, 6H), 2.68 (m, 2H), 4.25–4.39 (m, 2H), 7.27–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.50, 25.57, 26.26, 27.85, 28.04, 36.42, 36.47, 66.44, 78.50, 126.43, 127.68, 128.60, 152.05, 175.68; IR (KBr, cm^{-1}) 1720, 1640, 1410; MS (FAB) *m/e* 336 (M + 1); $[\alpha]_D$ + 26.2° (*c* = 0.95, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_5$: C, H, N.

Baccatin III, 13-[[(4*S*,5*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-phenyl-1,3-oxazolidin-5-yl]acetyl]-10-deacetyl-7,10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]- (8). To a solution of oxazolidine acid **6** (0.5 g, 1.5 mmol) and 10-deacetylbaccatin III derivative **7**[17] (1.34 g, 1.5 mmol) in dry toluene (30 mL) was added dicyclohexylcarbodiimide (0.4 g, 1.8 mmol) and a catalytic amount of 4-(dimethylamino)-pyridine. The mixture was stirred at 80 °C for 2 h and then cooled to room temperature. The filtered solution was concentrated to yield the crude product which was purified by flash column chromatography (hexanes/ethyl acetate, 7.5:2.5), affording 1 g (56%) of **8** as a colorless solid: mp 171–176 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (br s, 9H), 1.19 (s, 3H), 1.25 (s, 3H), 1.50 (s, 3H), 1.72 (s, 3H), 1.80 (2s, 6H), 1.84 (m,1H), 1.86 (s, 3H), 2.05 (s, 3H), 2.12–2.32 (m, 2H), 2.60–2.73 (m, 1H), 3.89 (d, *J* = 7 Hz, 1H), 4.17 and 4.30 (2d, *J* = 8 Hz, 2H), 4.39 (m, 2H), 4.63 and 4.94 (2d, *J* = 11 Hz, 2H), 4.79 (s, 2H), 4.94 (br s, 1H), 5.56 (dd, *J* = 8 and 3 Hz, 1H), 5.67 (d, *J* = 6 Hz, 1H), 6.22 (t, *J* = 8 Hz, 1H), 6.26 (s, 1H), 7.32–7.66 (m, 8H), 8.05 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.66, 15.06, 20.64, 24.92, 26.23, 27.91, 33.26, 33.95, 35.53, 42.95, 46.95, 56.22, 66.91, 69.85, 74.12, 76.31, 76.43, 77.09, 78.75, 79.19, 80.54, 83.55, 94.12, 95.03, 126.50, 127.85, 127.90,

Scheme 2

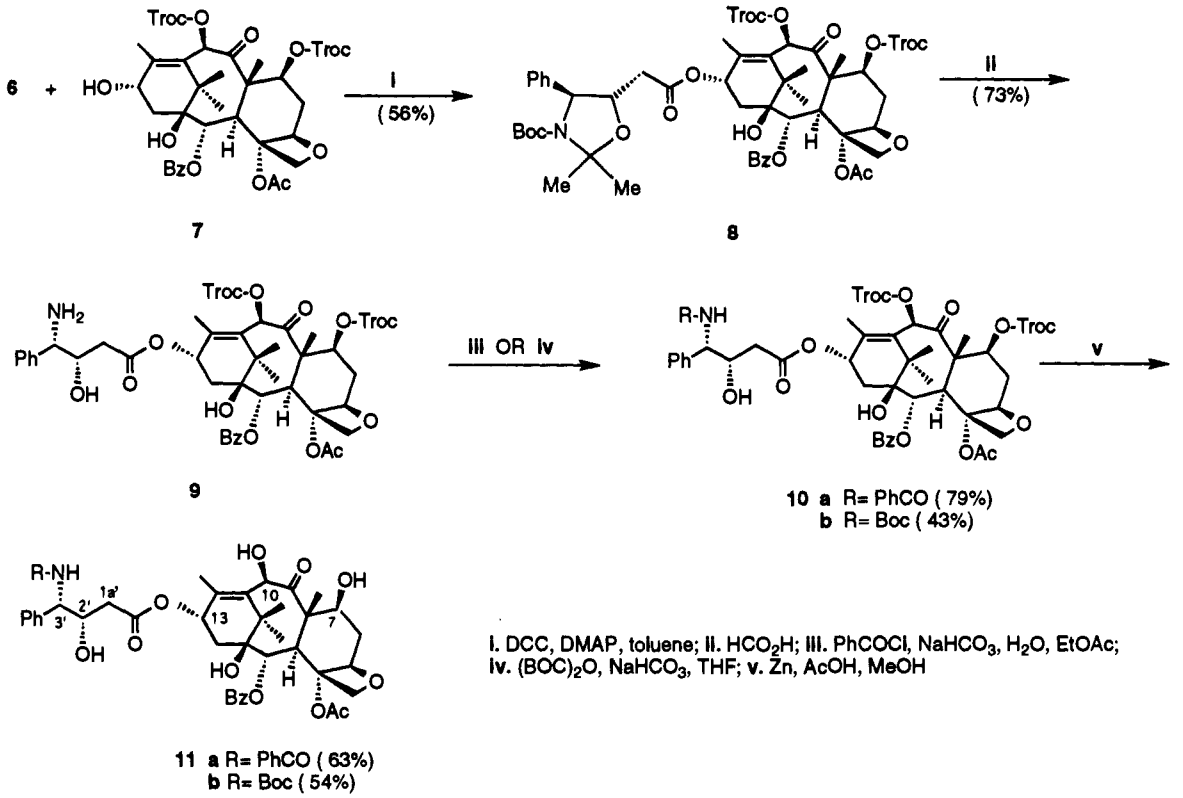


Table 1. Activity of **11a** and **11b** in Tubulin Assembly Assay[23]

analog	tubulin assembly[a] (ED_{50},[b] μM)	tubulin assembly ($ED_{50}/ED_{50\ taxol}$)
1a (taxol)	0.93	1
11a	>25[c]	>27
11b	>25[c]	>27

[a] Tubulin at 1 mg/mL was incubated with various concentrations of the analogs at 37 °C for 15 min in 0.5 mL of PEM buffer (0.1 M Pipes, 1 mM EDTA, 1 mM $MgSO_4$, pH 6.9). Samples were centrifuged, and the protein concentration in the supernatant was determined. [b] ED_{50} = Concentration (μM) which reduces the supernatant protein concentration by 50%. [c] The highest concentration used without achieving 50% effect.

128.65, 128.82, 129.03, 129.95, 130.01, 131.62, 133.81, 140.08, 143.15, 151.69, 153.15, 153.25, 166.75, 169.36, 169.68, 200.79; HRMS (FAB) *m/e* calcd 1216.1181 (M + Li), found 1216.2192; $[\alpha]_D$ −41° (*c* = 1.2, $CHCl_3$). Anal. Calcd for $C_{53}H_{61}Cl_6NO_{18}$: C, H, N.

10-Deacetyl-3′-*N*-debenzoyl-7,10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]-1a′-homotaxol (9). A solution of **7** (0.8 g) in 90% formic acid (15 mL) was stirred at room temperature for 4 h. After the excess acid was removed under reduced pressure at room temperature, the residue was dissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (CH_2Cl_2/MeOH, 24:1) to yield **9** as a colorless solid (510 mg, 73%): mp 143–149 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.23 (s, 3H), 1.80 (s, 3H), 1.98 (s, 3H), 2.10 (s, 3H), 2.21 (m, 2H), 2.43 (d, *J* = 6.3 Hz, 2H), 2.61 (m, 1H), 3.79 (d, *J* = 6 Hz, 1H), 3.89 (d, *J* = 7 Hz, 1H), 4.12 (m, 2H), 4.30 (d, *J* = 8 Hz, 1H), 4.60 and 4.91 (2d, *J* = 11 Hz, 2H), 4.77 (s, 2H), 4.96 (br s, 1H), 5.55 (m, 2H), 5.66 (d, *J* = 7 Hz, 1H), 6.18 (t, *J* = 8 Hz, 1H), 6.23 (s, 1H), 7.33–7.66 (m, 8H), 8.06 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.65, 14.90, 20.65, 22.35, 26.21, 33.23, 35.55, 38.86, 42.93, 47.00, 56.15, 60.82, 69.68, 72.32, 74.11, 76.25, 76.45, 77.36, 78.72, 79.18, 80.54, 83.63, 94.16, 94.19, 126.97, 128.07, 128.68, 128.97, 130.02, 131.63, 133.82, 142.26, 143.12, 153.18, 153.21, 166.75, 169.95, 171.53, 200.80; MS (FAB) *m/e* 1113 (M + 2Na); $[\alpha]_D$ −51.6° (*c* = 0.82, $CHCl_3$). Anal. Calcd for $C_{45}H_{49}Cl_6NO_{16}$: C, H, N.

10-Deacetyl-7,10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]-1a′-homotaxol (10a). To a stirred heterogeneous mixture of amino alcohol **9** (120 mg, 0.1 mmol) in ethyl acetate (3 mL), saturated $NaHCO_3$ solution (7 mL), and water (7 mL) was added benzoyl chloride (0.013 mL, 0.11 mmol) dropwise at room temperature and stirring continued for 20 min. The reaction mixture was diluted with ethyl acetate (50 mL), and the layers were separated. The organic layer was washed with brine and dried (Na_2SO_4). The crude product was purified by flash chromatography (hexanes/ethyl acetate, 3:2) to yield **10a** as a colorless solid (104 mg, 79%): mp 168–176 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.25 (s, 3H), 1.72 (m, 1H), 1.87 (s, 3H), 2.01 (m, 1H), 2.05 (s, 3H), 2.23 (m, 1H), 2.25 (s, 3H), 2.63 (m, 1H), 2.77 (m, 2H), 3.49 (d, *J* = 4 Hz, 1H), 3.94 (d, *J* = 7 Hz, 1H), 4.18 (d, *J* = 8 Hz, 1H), 4.35 (d, *J* = 8 Hz, 1H), 4.62 (m, 1H), 4.64 and 4.95 (2d, *J* = 11 Hz, 2H), 4.81 (s, 2H), 5.00 (br s, 1H), 5.35 (dd, *J* = 3 and 6 Hz, 1H), 5.59 (dd, *J* = 3 and 7 Hz, 1H), 5.70 (d, *J* = 7 Hz, 1H), 6.25 (t, *J* = 8 Hz, 1H), 6.27 (s, 1H), 7.05 (br d, *J* = 9 Hz, 1H), 7.38–7.68 (m, 11H), 7.89 (d, *J* = 8 Hz, 2H), 8.09 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.66, 14.95, 22.46, 26.25, 33.23, 33.25, 35.40, 39.32, 42.98, 47.02, 56.21, 57.17, 69.98, 71.15, 74.09, 76.26, 76.42, 78.68, 79.16, 80.61, 83.65, 94.16, 126.88, 127.05, 128.16, 128.71, 128.76, 128.95, 129.04, 130.04, 131.91, 132.01, 133.86, 142.72, 153.18, 166.83, 169.92, 171.83, 200.76; MS (FAB) *m/e* 1176 (M^+); $[\alpha]_D$ −58.15° (*c* = 0.65, $CHCl_3$).

7,10-Bis[[(2,2,2-trichloroethyl)oxy]carbonyl]-1a′-homotaxotere (10b). To a solution of amino alcohol **9** (200 mg, 0.18 mmol) and di-*tert*-butyl dicarbonate (61 mg, 0.28 mmol) in anhydrous THF (5 mL) was added powdered $NaHCO_3$ (25 mg, 0.29 mmol) under argon. After stirring at room temperature for 4 h, the reaction mixture was diluted with ethyl acetate (50 mL), washed with water and brine, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the product was purified by flash column chromatography (hexanes/ethyl acetate, 7:3) to yield 86 mg (43%) of **10b** as a colorless solid: mp 152–159 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.27 (s, 3H), 1.49 (br s, 9H), 1.88 (s, 3H), 2.05 (s, 3H), 2.06 (m, 1H), 2.28 (m, 2H), 2.32 (s, 3H), 2.69 (m, 3H), 3.95 (d, *J* = 7 Hz, 1H), 4.20 and 4.37 (2d, *J* = 9 Hz, 2H), 4.45 (m, 1H), 4.64 and 4.94 (2d, *J* = 12 Hz, 2H), 4.81 (s, 2H), 5.01 (d, *J* = 9 Hz, 1H), 5.41 (br d, *J* = 8 Hz, 1H), 5.60 (dd, *J* = 3 and 8 Hz, 1H), 5.71 (d, *J* = 7 Hz, 1H), 6.26 (t, *J* = 8 Hz, 1H), 6.28 (s, 1H), 7.36–7.70 (m, 8H), 8.10 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.66, 14.95, 20.61, 22.55, 26.24, 28.32, 33.23, 35.44, 39.12,

42.96, 47.02, 56.19, 69.86, 74.09, 76.25, 76.28, 76.41, 78.74, 79.16, 80.61, 83.65, 94.14, 126.66, 127.98, 128.71, 128.91, 128.96, 130.04, 133.87, 142.86, 153.17, 153.21, 153.25, 169.89, 171.61, 204.30; HRMS (FAB) m/e calcd for $C_{50}H_{57}Cl_6NO_{18}$ 1178.1868 (M +Li), found 1178.1853; $[\alpha]_D$ −45.6° (c = 1.6, $CHCl_3$).

10-Deacetyl-1a′-homotaxol (11a). To a solution of the taxol derivative **10a** (90 mg, 0.07 mmol) in methanol (2 mL) and acetic acid (1.5 mL) was added zinc powder (−325 mesh, 50 mg, 0.7 mmol). The mixture was stirred at 60 °C for 1.5 h, cooled to room temperature, diluted with ethyl acetate (50 mL), and filtered. The filtrate was washed with dilute $NaHCO_3$ solution and brine and was then dried (Na_2SO_4). The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 24:1) to afford 40 mg (63%) of the product as a colorless solid: mp 209−217 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.16 (s, 3H), 1.71 (s, 3H), 1.81 (m, 1H), 1.88 (s, 3H), 2.12 (m, 2H), 2.15 (s, 3H) 2.53 (m, 1H), 2.71 (m, 2H), 3.60 (d, J = 4 Hz, 1H), 3.88 (d, J = 7 Hz, 1H), 4.14 (d, J = 9 Hz, 1H), 4.22 (br s, 1H), 4.27 (d, J = 9 Hz, 1H), 4.56 (dd, J = 3 and 9 Hz, 1H), 4.90 (d, J = 6 Hz, 1H), 5.19 (br s, 1H), 5.29 (dd, J = 3 and 8 Hz, 1H), 5.63 (d, J = 8 Hz, 1H), 6.17 (t, J = 8 Hz, 1H), 7.12 (br d, J = 9 Hz, 1H), 7.32−7.64 (m, 11H), 7.84 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.81, 14.63, 20.25, 22.44, 26.36, 35.81, 36.85, 39.31, 42.89, 46.55, 56.99, 57.59, 70.28, 70.91, 71.91, 74.51, 74.74, 76.50, 77.37, 77.57, 78.77, 80.89, 84.15, 126.87, 127.05, 128.02, 128.66, 128.71, 128.93, 129.15, 129.99, 131.98, 133.72, 133.80, 135.85, 138.59, 139.28, 166.88, 167.43, 169.78, 171.92, 211.24; IR (KBr, cm^{-1}) 3420, 1730, 1720, 1705, 1640; HRMS (FAB) m/e calcd for $C_{46}H_{51}NO_{13}$ 832.3521 (M + Li), found 832.3558; $[\alpha]_D$ −81.2° (c = 1.0, $CHCl_3$).

1a′-Homotaxotere (11b). To a solution of the taxotere derivative **10b** (75 mg, 0.06 mmol) in methanol (2 mL) and acetic acid (1.5 mL) was added zinc powder (−325 mesh, 40 mg, 0.6 mmol), and the mixture was stirred at 60 °C for 1.5 h and cooled to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrate was washed with dilute $NaHCO_3$ solution and brine, and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (CH_2Cl_2/MeOH, 24:1) to provide 28 mg (54%) of **11b** as a colorless solid: mp 198−208 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H) 1.22 (s, 3H), 1.48 (br s, 9H), 1.73 (m, 1H), 1.77 (s, 3H), 1.89 (m, 1H), 1.94 (s, 3H), 2.25 (br d, J = 9 Hz, 1H), 2.29 (s, 3H), 2.64 (m, 1H), 2.70 (m, 2H), 3.96 (d, J = 7 Hz, 1H), 4.19−4.35 (m, 3H), 4.43 (m, 1H), 4.98 (d, J = 9 Hz, 1H), 5.24 (br s, 1H), 5.45 (d, J = 9 Hz, 1H), 5.69 (d, J = 7 Hz, 1H), 6.22 (t, J = 8 Hz, 1H), 7.35−7.69 (m, 8H), 8.10 (d, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.83, 14.69, 20.28, 22.61, 26.36, 28.34, 35.89, 36.95, 39.10, 42.91, 46.57, 57.60, 70.20, 71.99, 74.57, 74.76, 76.04, 76.43, 76.45, 78.88, 80.91, 84.12, 126.68, 127.88, 128.69, 128.85, 128.90, 129.18, 130.04, 133.77, 135.80, 138.75, 166.95, 169.80, 171.77, 211.39; IR (KBr, cm^{-1}) 3445, 1735, 1715, 1700, 1490; HRMS (FAB) m/e calcd for $C_{44}H_{55}NO_{14}$ 822.3704 (M + 1), found 822.3715; $[\alpha]_D$ −60.3° (c = 0.62, $CHCl_3$).

Acknowledgment. These studies were supported by a grant from Oread Laboratories (Grant No. 5339). Partial support to G.I.G. from the National Institutes of Health is acknowledged. The authors would like to thank Professor Richard H. Himes for performing the microtubule assembly assays.

References

(1) Suffness, M.; Cordell, G. A. The Alkaloids. Chemistry and Pharmacology. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 25; pp 3−355.
(2) Blechert, S.; Guénard, D. Taxus Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1990; Vol. 39; pp 195−238.
(3) Georg, G. I.; Gollapudi, S. R.; Grunewald, G. L.; Gunn, C. W.; Himes, R. H.; Kessava Rao, B.; Liang, X.-Z.; Mirhom, Y. W.; Mitscher, L. A.; Vander Velde, D. G.; Ye, Q.-M. A Reinvestigation of Himalayan *Taxus Wallichiana* Zucc. and a Revision of the Structure of Brevifoliol. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1345−1348.
(4) Rowinsky, E. K.; Donehower, R. C. The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics. *Pharmacol. Ther.* **1991**, *52*, 35−84.
(5) Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. Phase II Trial of Taxol, an Active Drug in the Treatment of Metastatic Breast Cancer. *J. Natl. Cancer Inst.* **1991**, *83*, 1797−1805.
(6) Chang, A. Y.; Kim, K.; Glick, J.; Anderson, T.; Karp, D.; Johnson, D. Phase II Study of Taxol, Merbarone, and Piroxantrone in Stage IV Non-Small Cell Lung cancer: The Eastern Cooperative Oncology Group Results. *J. Natl. Cancer Inst.* **1993**, *85*, 388−394.
(7) Murphy, W. K.; Fossella, F. V.; Winn, R. J.; Shin, D. M.; Hynes, H. E.; Gross, H. M.; Davilla, E.; Leimert, J.; Dhingra, H.; Raber, M. N.; Krakoff, I. H.; Hong, W. K. Phase II Study of Taxol in Patients with Untreated Advanced Non-Small Cell Lung Cancer. *J. Natl. Cancer Inst.* **1993**, *85*, 384−388.
(8) Forastiere, A. A. Use of Paclitaxel (Taxol) in Squamous Cell Carcinoma of the Head and Neck. *Semin. Oncol. Suppl. 3* **1993**, *20*, 56−60.
(9) Suffness, M. Taxol: From Discovery to Therapeutic Use. *Annu. Rep. Med. Chem.* **1993**, *28*, 305−314.
(10) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. The Taxane Diterpenoids. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich W., Tamm, C., Eds.; Springer: New York, 1993; Vol. 61; pp 1−206.
(11) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Clowers, J. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. The Medicinal Chemistry of Taxol. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC: Boca Raton, 1994 (in press).
(12) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. Plant Antitumor Agents. VI. The Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor Agent from *Taxus Brevifolia*. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.
(13) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H.; Himes, R. H. Schotten-Baumann Acylation of Baccatin III 13-[(2′*R*,3′*S*)-3-phenylisoserinate]: An Efficient Route to *N*-Acyl Taxol Analogues and their Microtubule Assembly Activity. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335−338.
(14) Kant, J.; Huang, S.; Wong, H.; Fairchild, C.; Vyas, D.; Farina, V. Studies Toward Structure-Activity Relationships of Taxol®: Synthesis and Cytotoxicity of Taxol® Analogues with C-2′ Modified Phenylisoserine Side Chains. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2471−2474.
(15) Ojima, I.; Zucco, M.; Duclos, O.; Kuduk, S. D.; Sun, C. M.; Park, Y. H. *N*-Acyl-3-Hydroxy-β-Lactams as Key Intermediaes for Taxotere and its Analogs. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2479−2482.
(16) Georg, G. I.; Ali, S. M.; Zygmunt, J.; Jayasinghe, L. R. Taxol: A Novel Antitumor Agent. *Exp. Opin. Ther. Pat.* **1994**, *4*, 109−120.
(17) Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M.-T.; Mangatal, L.; Potier, P. Relationships Between the Stucture of Taxol Analogues and their Antimitotic Activity. *J. Med. Chem.* **1991**, *34*, 992−998.
(18) Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. Biologically Active Taxol Analogues with Deleted A-Ring Side Chain Substituents and Variable C-2′ Configurations. *J. Med. Chem.* **1991**, *34*, 1176−1184.
(19) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. An Efficient Semisynthesis of Taxol from (3*R*,4*S*)-*N*-Benzoyl-3-[(*t*-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone and 7-(Triethylsilyl)baccatin III. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467−2470.
(20) Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. Improved Protection and Esterification of a Precursor of the Taxotere® and Taxol Side Chains. *Tetrahedron Lett.* **1992**, *33*, 5185−5188.
(21) Denis, J.-N.; Correa, A.; Greene, A. E. Direct, Highly Efficient Synthesis from (*S*)-(+)-Phenylglycine of the Taxol and Taxotére Side Chains. *J. Org. Chem.* **1991**, *56*, 6939−6942.
(22) The syn stereochemistry of the major reaction product **4** was verified through NOE experiments ($CDCl_3$ at −20 °C, 500 MHz) of oxazolidine **5**. An observed NOE of 2% and a coupling constant of J = 8.8 Hz between the two protons at the oxazolidine ring system (positions 4 and 5) are indicative of a trans relationship.
(23) For general experimental information, including the microtubule assembly assay, see: Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. Synthesis of Biologically Active Taxol Analogues with Modified Phenylisoserine Side Chains. *J. Med. Chem.* **1992**, *35*, 4230−4237.
(24) Vander Velde, D. G.; Georg, G. I.; Grunewald, G. L.; Gunn, K.; Mitscher, L. A. "Hydrophobic Collapse" of Taxol and Taxotere Solution Conformations in Mixtures of Water and Organic Solvents. *J. Am. Chem. Soc.* **1993**, *115*, 11650−11651.
(25) Williams, H. J.; Scott, A. I.; Dieden, R. A.; Swindell, C. S.; Chirlian, L. E.; Francl, M. M.; Heerding, J. M.; Krauss, N. E. NMR and Molecular Modeling Study of the Conformations of Taxol and of its Side Chain Methylester in Aqueous and Non-Aqueous Solution. *Tetrahedron* **1993**, *49*, 6545−6560.