Design, Synthesis, and Bioactivities of Steroid-Linked Taxol Analogues as Potential Targeted Drugs for Prostate and Breast Cancer[⊥]

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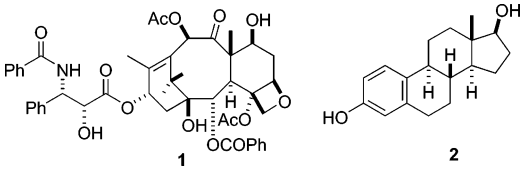
The female steroid hormone 3,17β-estradiol (**2**) was selected as an agent to target taxol (**1**) to estrogen receptor (ER) positive breast cancer cells. Estradiol−taxol conjugates (ETC) were synthesized through linkages from the 11- or 16-position of estradiol to the 2′-, 7-, or 10-position of taxol. All conjugates were cytotoxic to the A2870 ovarian cancer cell line, although less so than taxol. The MCF-7 breast cancer cell line (ER-α positive) and MDA-MB-231 breast cancer cell line (ER-α negative) were also used to evaluate the selectivity and cytotoxicity of these conjugates. One conjugate showed some selectivity for ER positive cells, but it was less potent than taxol. Two ETC hemisuccinates were also prepared to improve the solubility of the conjugates. The corresponding Na and triethanolammonium salts were slightly more cytotoxic than the acid form but were much less cytotoxic than the corresponding ETC.

Taxol[1] (**1**) was first isolated from the bark of the Pacific yew about 35 years ago by Drs. Wall and Wani.[2] Although its development as an anticancer agent was delayed by numerous reasons, including its scarcity and insolubility,[3] the discovery of its tubulin-assembly activity[4] and other factors motivated oncologists to overcome these problems. It has since become one of the most important current drugs for the treatment of several cancers, including breast and ovarian cancers;[5] its importance in the treatment of breast cancer has been reviewed,[6] as has its chemistry.[7]

Like almost all anticancer drugs taxol does have some toxic side effects, such as bone marrow suppression and neutropenia,[8] and many tumors also show significant resistance to therapy with taxol.[9] One approach to improving its selectivity and efficacy is by targeting it to selected tumors through the use of various conjugates, and several taxol conjugates have been synthesized recently with improved selectivity and solubility.[10] Thus Safavy reported a water-soluble and tumor-recognizing conjugate of taxol and BBN[7-13], which retained binding ability to the BBN/GRP receptor compared to the free BBN[7-13] molecule.[10a] Huang used the binding ability of somatostatin (SST) to its receptors (SSTRs) to specifically target taxol to tumor cells.[10b] A report from Luo revealed that a conjugate of hyaluronic acid and taxol was selectively toxic toward the human cancer cell lines that are known to overexpress HA receptors.[10c] Fuchs and co-workers have reported the preparation and evaluation of taxol−folic acid conjugates.[10d] Finally, Ojima has reported a C-10 methyldisulfanylpropanoyl taxoid conjugated to monoclonal antibodies; these conjugates were shown to possess selective in vivo antitumor activity against EGFR-expressing A431 tumor xenografts.[10e]

One approach that has not yet been explored is that of targeting taxol to breast cancer by means of selected steroid hormone conjugates. The female hormone estradiol (**2**) plays an important role in breast cancer, and the hormone dependence of breast cancer was first reported by Beatson in the late 1800s.[11] Further studies revealed the interaction between steroid hormones and their receptors[12] and, thus, led to a better understanding of the hormone in controlling the growth of breast cancer.[13] The hormone dependence of breast cancer can also be used as a drug delivery target through the recognition and binding of estrogen to its receptor, and several studies have investigated the targeting of drug molecules into breast cancer cells by linking them to estradiol or other estrogens.[14] The potential benefits of this approach include the improvement of a drug's therapeutic effectiveness and bioavailability, coupled with a reduction in multidrug resistance (MDR) and toxic side-effects.



The goal of the present research was to target taxol to estrogen receptor (ER) positive breast cancer cells through the interaction between estradiol and its corresponding receptor, with the goal of developing new drug candidates against breast cancer, responsible for the second largest number of cancer deaths in women.[15] From previous studies of the structure−activity relationships (SAR) of estradiol, it is known that estradiol can be modified at the 16- and 11-positions without losing its ability to bind to the ER.[14] As for taxol, SAR studies have shown that the 10- and 7-positions can be acylated with only relatively minor effects on the drug's activity.[7a,16] Another position that can be used for targeting is the 2′-position, because ester linkages at this position can be hydrolyzed in vivo,[17] and hence an estradiol−taxol conjugate at the 2′-position could serve as a "targeted pro-drug" if the targeting occurred before hydrolysis. In this paper, we describe the synthesis and biological evaluation of estradiol−taxol

[⊥] Dedicated to the late Dr. Monroe E. Wall and to Dr. Mansukh C. Wani of Research Triangle Institute for their pioneering work on bioactive natural products.

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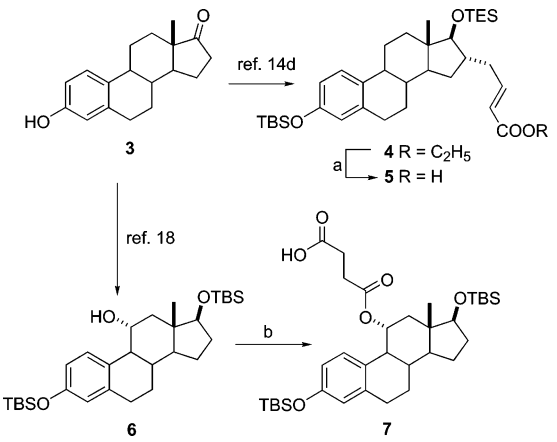
Scheme 1[a]



[a] Reagents and conditions: (a) LiOH, THF/H_2O, RT, 36 h, 72%; (b) LHMDS, THF, then succinic anhydride, RT, overnight, 70%.

conjugates through ester linkers from the 11- and 16-positions of estradiol to the 2′-, 7-, and 10-positions of taxol.

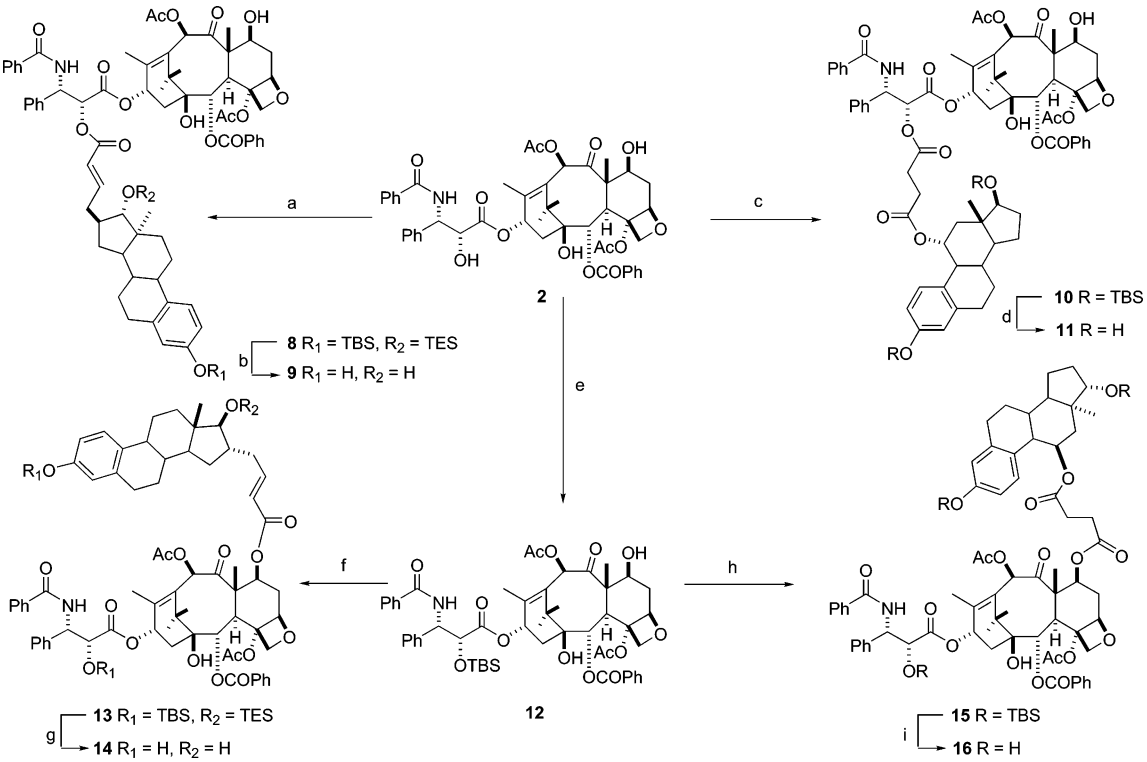
Results and Discussion

Synthesis. The synthesis of estradiol linkers **5** and **7** is outlined in Scheme 1. The commercially available estrone (**3**) was converted to compounds **4**[14d] and **6**[18] through reported procedures. Compound **4** was hydrolyzed to generate compound **5** with a free carboxyl group for coupling. The linker **7** was obtained by reacting **6** with succinic anhydride. The use of pyridine as solvent only gave a 30% yield, but deprotonation of **6** with LHMDS in THF followed by addition of succinic anhydride gave **7** in 70% yield based on unrecovered starting materials.

With the two estradiol linkers **5** and **7** in hand, the estradiol−taxol conjugates could be assembled. According to SAR studies, the most reactive hydroxyl group in taxol is the 2′-OH, followed by the 7- and 10-OH groups; the 1-OH group is inert to ester formation under normal conditions.[19] Direct acylation of taxol with compounds **5** and **7** thus yielded the 2′-acyl derivatives **8** and **10** (Scheme 2), respectively. Protection of the 2′-hydroxyl group as its *tert*-butyldimethylsilyl ether **12**, followed by acylation with compounds **5** and **7**, gave the 7-acyl analogues **13** and **15**. In general, conjugate formation occurred in low yield, with conversion percentages of 25−35%, and with significant amounts of unreacted taxol; the yields based on unrecovered taxol were in the range 60−70%. Deprotection of the silyl groups with HF−pyridine proceeded in good yields to give the estradiol−taxol complexes **9**, **11**, **14**, and **15**.

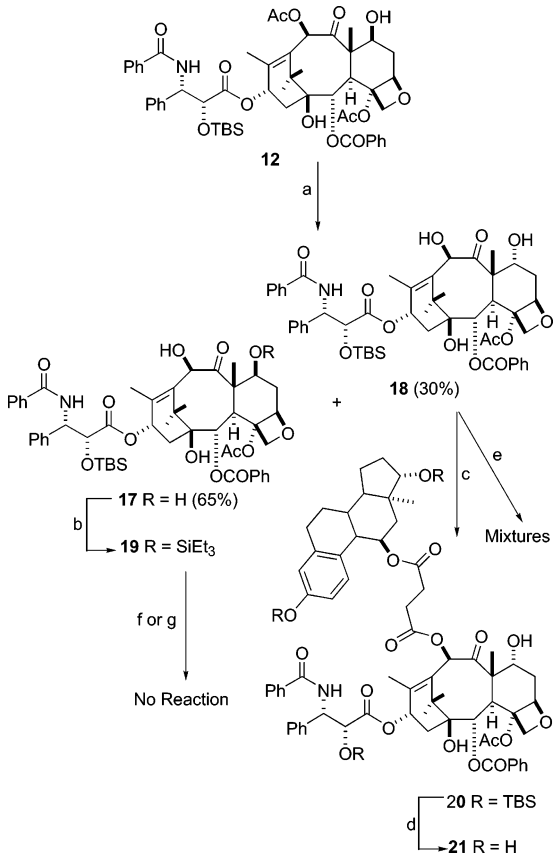
The synthesis of estradiol−taxol conjugates at the 10-position was achieved by converting 2′-(*tert*-butyldimethylsilyl)taxol (**12**) to 2′-(*tert*-butyldimethylsilyl)-10-deacetyltaxol (**17**) and hence to 2′-(*tert*-butyldimethylsilyl)-10-deacetyl-7-(triethylsilyl)taxol (**19**) through a known procedure.[20] During the deacetylation of **12** using hydrazine monohydrate in ethanol, a byproduct of 30% of 2′-(*tert*-butyldimethylsilyl)-7-*epi*-taxol (**18**) was observed (Scheme 3). Unfortunately, compound **19** did not undergo ester formation using standard EDC/DMAP conditions. One possibility is that the 10-position was too sterically hindered to accept the relatively short linkage to estradiol because the bulky 7-TES group might somehow block this position. To test this hypothesis, 2′-(*tert*-butyldimethylsilyl)-7-*epi*-taxol was used as a substrate, since this not only lacked the bulky 7-TES group but also had an unreactive 7-*epi*-hydroxyl group.[21] Compound **18** reacted with estradiol **7** smoothly under EDC/DMAP conditions in CH_2Cl_2 to give product **20** in 79% yield. Deprotection of **20** by HF−pyridine gave **21** in good yield. Coupling of linker **5** with **18** was also attempted under the same conditions, but two

Scheme 2[a]



[a] Reagents and conditions: (a) **5**, EDC/DMAP, toluene, 60 °C, 24 h, 73%; (b) HF−pyridine, THF, RT, overnight, 97%; (c) **7**, EDC/DMAP, toluene, 60 °C, 24 h, 78%; (d) HF−pyridine, THF, RT, overnight, 92%; (e) TBSCl, imidazole, DMF, 65 °C, 3 h, 95%; (f) **5**, EDC/DMAP, toluene, 60 °C, 48 h, 65%; (g) HF−pyridine, THF, RT, overnight, 82%; (h) **7**, EDC/DMAP, toluene, 60 °C, 48 h, 65%; (i) HF−pyridine, THF, RT, overnight, 91%.

Scheme 3[a]



[a] Reagents and conditions: (a) hydrazine monohydrate, EtOH, RT, 1.5 h; (b) TESCl, imidazole, DMF, RT, 10 min, 89%; (c) **7**, EDC/DMAP, CH_2Cl_2, RT, 24 h, 79%; (d) HF−pyridine, THF, RT, overnight, 90%; (e) **5**, EDC/DMAP, toluene or CH_2Cl_2, RT, 24 h; (f) **5**, EDC/DMAP, toluene, or CH_2Cl_2, RT, 72 h; (g) **7**, EDC/DMAP, toluene, or CH_2Cl_2, RT, 72 h.

inseparable products were obtained as determined by NMR spectroscopy.

It is well known that taxol has very low solubility in water, and the estradiol−taxol conjugates would be expected to be even less soluble, since estradiol is hydrophobic. We thus synthesized two estradiol−taxol conjugates with improved water solubility. It is been reported that a hemisuccinate at the 2′-position of taxol can improve the drug's solubility when the free carboxyl group was neutralized as its sodium or (triethanol)ammonium salts.[19a] Scheme 4 shows the synthesis of two estradiol−taxol conjugates with either a 2′-hemisuccinate or a 7-hemisuccinate ester group. Compound **22** was prepared by reaction of taxol with monobenzyl succinate using EDC/DMAP conditions to protect the 2′-position. This was followed by introduction of the estradiol linker **7** at the 7-position using the conditions described previously. The desired compound **25** was obtained after desilylation and hydrogenolysis; its sodium and triethanolamine salts (**26** and **27**) were also prepared. The 7-hemisuccinate **30** was obtained using the reverse order of steps, with initial acylation of taxol with estradiol **7** followed by acylation with monobenzyl succinate at C-7 and deprotection; its sodium and triethanolamine salts (**31** and **32**) were also prepared by a previously reported procedure.[19a]

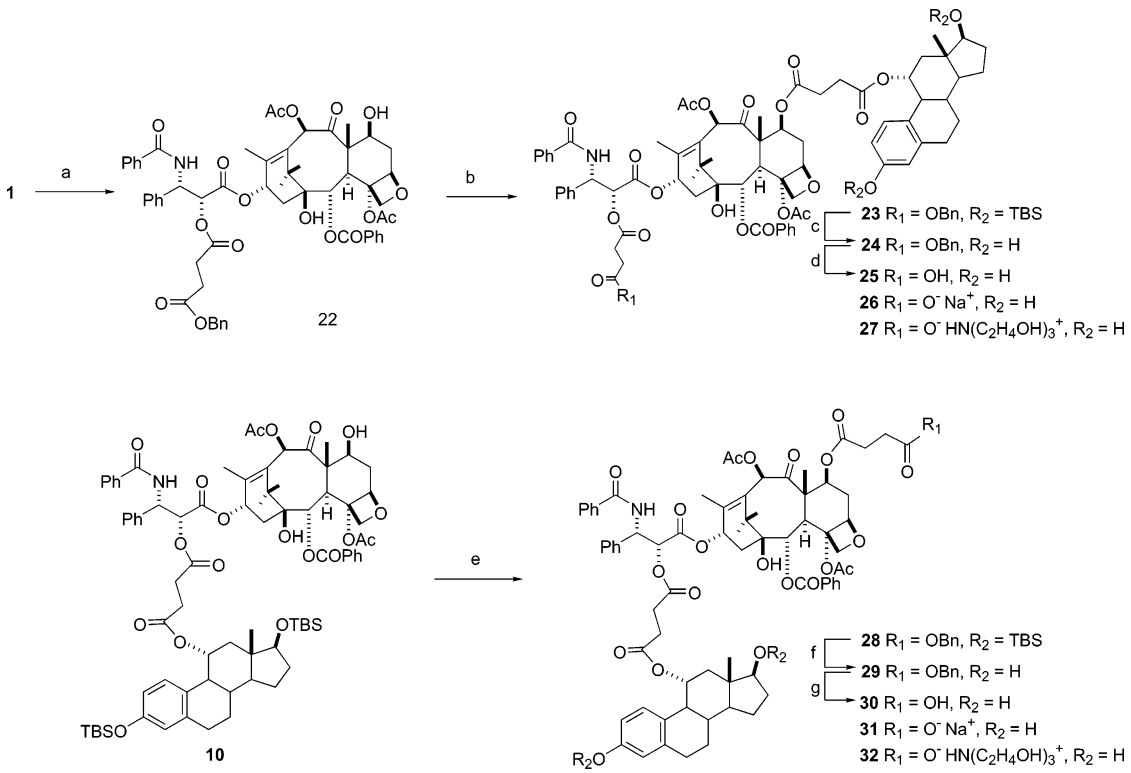
Biological Results. The biological activities of taxol and of the estrogen conjugates **9**, **11**, **14**, **16**, and **21** were compared in a tubulin-assembly assay, for cytotoxicity to estrogen receptor (ER) negative A2780 ovarian cancer cells, ER (beta) positive PC-3 prostate cancer cells, and two lines of human breast tumor cells (Table 1). The taxol IC_{50} value estimated by nonlinear regression analysis was similar in the ER-α positive MCF-7 and ER-α negative MDA-231 lines, 4.9 and 4.5 nM, respectively, and both these values were lower by over an order of magnitude than the IC_{50} value in the PC-3 prostate cancer cell line. The 2′-substituted taxol conjugates **9** and **11** were both about as active as taxol in the PC-3 cell line, but were less active than taxol in the breast cancer lines. They were also less active than taxol in the tubulin-assembly assay. These results are explicable by postulating that the 2′-derivatives undergo slow conversion to taxol under the conditions of the cell culture, with the conversion being more rapid in the PC-3 assay than in the two breast cancer cell lines; the lower activity of both compounds in the tubulin-assembly assay is consistent with this hypothesis. Similar results were obtained for the activity of 2′-acetyltaxol.[22] Neither compound **9** nor **11** showed any significant selectivity for the ER-α positive cell line MCF-7 as compared with the ER-α negative line MDA-MB-231; this result is also consistent with hydrolysis under cell culture conditions. Interestingly, the MDA-MB-231 breast tumor cell line which expresses ER-β receptors was more sensitive to compounds **9** and **11** than the ER-α positive MCF-7 breast tumor line. In addition, the steroid conjugate **11** may show improved activity compared with taxol against the PC-3 line. Recently, clinical samples of prostate cancer as well as certain prostate cell lines (PC-3) have been found to express ER-β receptors, and expression is correlated with tumor aggressiveness on the Gleason scale.[23] These data raise the possibility that these derivatives target the beta form of the estrogen receptor.

Table 1. Cytotoxicity and Tubulin-Assembly Activity of Steroid-Linked Taxol Derivatives

compound	% assembly, 0.2 μM[a]	% assembly, 1.0 μM[a]	A2780 IC_{50} (nM)	PC-3 IC_{50} (nM)	MDA-MB-231 IC_{50} (nM)	MCF-7 IC_{50} (nM)
taxol (**1**)	100	100	25	77 ± 3	4.5 ± 1.2	4.9 ± 1.8
9	45	55	180	73 ± 12	22 ± 4.5	39 ± 0.6
11	60	60	680	40 ± 10	51 ± 4.6	62 ± 12
14	100	100	8300	120 ± 20	2200 ± 800	1600 ± 90
16	100	100	2900	320 ± 80	780 ± 100	557 ± 117
21	100	100	1900	68 ± 7	304 ± 12[b]	103 ± 3.4[b]
25	NT	NT	15 000	NT	NT	NT
26	NT	NT	10 000	NT	NT	NT
27	NT	NT	13 000	NT	NT	NT
30	NT	NT	15 000	NT	NT	NT
31	NT	NT	12 000	NT	NT	NT
32	NT	NT	10 000	NT	NT	NT

[a] The extent of tubulin assembly induced by 0.2 and 1.0 μM taxol and by each compound with 10 μM tubulin was determined. The extent of tubulin assembly in the presence of taxol is defined as 100%, and the extent of tubulin assembly with each ligand was compared with this value. [b] $n = 3$ experiments in quadruplicate, $p < 0.001$.

Scheme 4[a]



[a] Reagents and conditions: (a) $BnOCOCH_2CH_2COOH$, EDC/DMAP, CH_2Cl_2, RT, 24 h, 40%; (b) **7**, EDC/DMAP, CH_2Cl_2, RT, 48 h, 70%; (c) HF−pyridine, THF, RT, overnight, 98%; (d) H_2, Pd−C, EtOAc, 30 psi, 24 h, 80%; (e) $BnOCOCH_2CH_2COOH$, EDC/DMAP, CH_2Cl_2, RT, 48 h, 90%; (f) HF−pyridine, THF, RT, overnight, 99%; (g) H_2, Pd−C, EtOAc, 50 psi, 24 h, 50%.

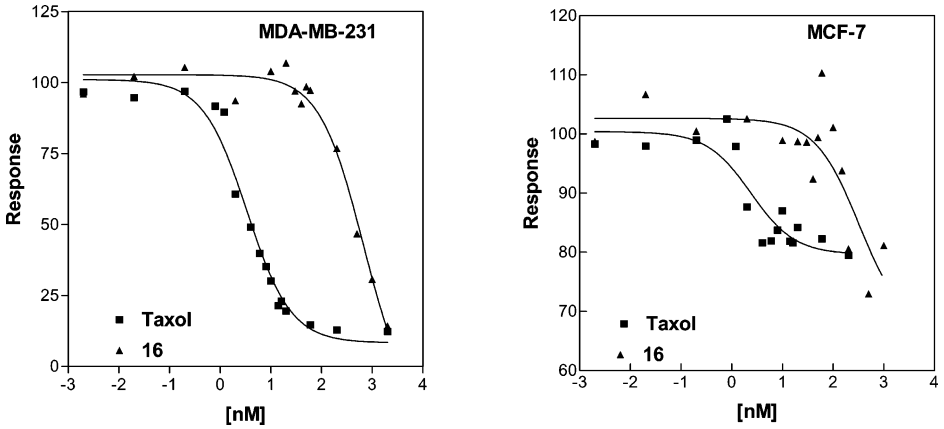


Figure 1. Inhibition of breast tumor cell survival in vitro by taxol and compound **16**. Human breast tumor cell lines were incubated for 48 h with the indicated drug concentrations. The cell survival response in estrogen-receptor negative MDA-MB-231 cells and estrogen-receptor positive MCF-7 cells was determined using the MTS assay. Response (A_{490} nm) is plotted as a fraction of control cells, which was set to 100%. A nonlinear regression fit to a sigmoidal dose−response equation is shown. Data are representative of $n = 2$ independent experiments performed in quintuplicate.

The two C-7-substituted derivatives **14** and **16** were both significantly less potent cytotoxic agents than taxol in the two breast cancer cell lines, although both compounds were comparable to taxol in their tubulin-assembly activity and were only less active in the PC-3 cell line by factors of 1.6 and 4.2, respectively. Although both compounds showed modest selectivities toward the ER-α positive cell line MCF-7, the observed differences were not statistically significant.

The dose−response curves for taxol and compound **16** are shown in Figure 1. The maximal antiproliferative response to either taxol or **16** was 85−90% inhibition of cell survival by 48 h; thus the efficacy of both compounds was equivalent. In MCF-7 cells, the maximal reduction in cell survival elicited by either taxol or **16** in a 48 h incubation was 20−30%. When MCF-7 cells were incubated with taxol or **16** for 7 days, the maximal decrease in cell survival was approximately 70%. The difference in the efficacy of taxol and the steroid-conjugated derivative between MDA-MB-231 cells and MCF-7 cells is most likely the differences in the cell doubling time. For MDA-MB-231 cells with a cell doubling time of approximately 22 h, nearly all cells are exposed to taxol or **16** during a sensitive stage of the cell cycle during the 48 h incubation period. However, MCF-7 cells, with a doubling time of nearly 60 h, require a much longer period of drug exposure before a similar fraction of the cells enter or transit the taxol-sensitive phase of the cell cycle.

The 10-substituted derivative **21** gave the most interesting results. It had comparable activity to taxol in both the tubulin-assembly and PC-3 assays, and it also showed a 3-fold greater activity ($p < 0.001$) toward the ER-α positive MCF-7 cell line than the ER-α negative MDA-MB-231 cell

line. It was however significantly less potent than taxol to both these cell lines. Our results do, however, suggest that future efforts at targeting taxol to ER-α positive breast cancer cells would be most fruitful if centered around modifications at the C-10 position.

The hemisuccinates **25**−**27** and **30**−**32** were tested only in the A2780 ovarian cancer cell line; they were all found to be significantly less active that taxol, and so were not subjected to further testing.

Experimental Section

General Experimental Procedures. Chemicals were obtained from Aldrich Chemical Co. and were used without further purification. All solvents were of reagent grade or HPLC grade. THF was distilled over sodium/benzophenone, and CH_2Cl_2 was distilled over calcium hydride. All ^{1}H NMR spectral data were obtained in $CDCl_3$ or CD_3OD on a Varian Unity 400 spectrometer (operating at 399.951 MHz for ^{1}H and 100.578 MHz for ^{13}C). Mass spectra were obtained at Analytical Service in the Department of Chemistry (HRFABMS) or the Department of Biochemistry (MALDI-TOFMS) at Virginia Tech.

7-{4-[3-*tert*-Butyldimethylsilyloxy-17*β*-triethylsilyloxyestra-1,3,5(10)-triene-16α-yl]-2*E*-but-2-enoic Acid (5). To a solution of **4** (836 mg, 1.36 mmol) in THF (8 mL) was added LiOH (131 mg, 5.44 mmol) in water (8 mL). After stirring at room temperature for 36 h, the reaction mixture was quenched with saturated ammonium chloride and extracted three times with ethyl acetate (50 mL). The combined organic phase was washed through water and brine, dried over sodium sulfate, and concentrated in a vacuum. The residue was purified by column chromatography (10% EtOAc/hexane) to give **5** (560 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 0.21 (6H, s), 0.64 (6H, q, J = 7.9 Hz), 0.82 (3H, s), 1.00 (9H, s), 1.01 (9H, t, J = 7.9 Hz), 1.20−2.90 (16H, steroid skeleton), 3.33 (1H, d, J = 7.3 Hz), 5.88 (1H, d, J = 15.6 Hz), 6.56 (1H, d, J = 2.7 Hz, Ar), 6.63 (1H, dd, J = 8.5, 2.7 Hz, Ar), 7.07−7.16 (2H, overlapped); ^{13}C NMR ($CDCl_3$) δ −4.1, 5.7, 7.3, 12.4, 18.4, 26.0, 26.5, 27.5, 29.4, 29.8, 37.5, 37.8, 38.8, 43.1,44.2, 44.6, 48.6, 87.8, 117.4, 120.2, 121.7, 126.3, 133.2, 138.1, 151.7, 153.5, 172.3; HRFABMS m/z 584.3707 [$M^{+\bullet}$] (calcd for $C_{34}H_{56}O_4Si_2$, 584.3717).

Succinic Acid, Mono-3,17*β*-di-*tert*-butyldimethylsilyloxyestra-1,3,5(10)-triene-11*β*-yl Ester (7). To a solution of **6** (275 mg, 0.532 mmol) in 20 mL of dry THF was added LHMDS (1 M, 0.80 mL, 0.798 mmol) at 0 °C. After stirring for 1 h, succinic anhydride (1.06 g, 10.64 mmol) was added in one portion. The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then poured into 200 mL of water, and EtOAc (150 mL) was used to extract the product. The extract was washed through water and brine, dried over sodium sulfate, and concentrated in a vacuum. The residue was purified by column chromatography (25% EtOAc/hexane) to give **7** (164 mg, 50%) and recovered **6** (55 mg, 20%). **7**: ^{1}H NMR ($CDCl_3$): δ 0.02 (3H, s), 0.03 (3H, s), 0.19 (6H, s), 0.79 (3H, s), 0.89 (9H, s), 0.98 (9H, s), 1.10−2.85 (17H, steroid skeleton), 3.67 (1H, t, J = 8.5 Hz), 5.45 (1H, td, J = 10.6, 5.2 Hz), 6.58−6.63 (2H, m, Ar), 6.93 (1H, d, 8.1 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ −4.5, −4.3, −4.17, −4.15, 12.2, 18.3, 18.4, 23.4, 26.0, 26.1, 27.1, 28.4, 29.2, 29.6, 31.3, 37.7, 42.6, 44.5, 46.6, 49.7, 74.8, 81.2, 117.3, 120.0, 125.5, 132.4, 139.3, 153.9, 171.9, 179.0; HRFABMS m/z 616.3619 [$M^{+\bullet}$] (calcd for $C_{34}H_{56}O_6Si_2$, 616.3615).

General Procedure for Preparation of Estradiol−Taxol Conjugates. To a solution of estradiol derivative **5** (13.7 mg, 0.0234 mmol) in 2 mL of toluene was added EDC (4.5 mg, 0.0234 mmol). After 15 min stirring, DMAP (2 mg, cat.) was added and stirring continued for 5 min before taxol (20 mg, 0.0234 mmol) was added. The reaction mixture was allowed to stir at 60 °C for 24−48 h. Then, 50 mL of EtOAc was added to the reaction mixture, and the organic phase was washed with sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated in a vacuum. The residue was applied to preparative TLC (50% EtOAc/hexane) to give silyl-protected estradiol−taxol conjugate **8** (15.1 mg, 73%). A similar procedure was applied to estradiol derivative **7** to give **10** and to the reaction of 2′-*tert*-butyldimethylsilyltaxol (**12**) with estradiols **5** and **7** to give the 7-acyl analogues **13** and **14**, respectively.

2′-{4-[3-*tert*-Butyldimethylsilyloxy-17*β*-triethylsilyloxyestra-1,3,5(10)-triene-16α-yl]-2*E*-but-2-enoyl}taxol (8): ^{1}H NMR ($CDCl_3$) δ 0.19 (6H, s), 0.61 (6H, q, J = 7.9 Hz), 0.79 (3H, s), 0.97 (9H, t, J = 7.9 Hz), 0.98 (9H, s), 1.13 (3H, s), 1.24 (3H, s), 1.68 (3H, s), 1.95 (3H, brs), 2.23 (3H, s), 2.44 (3H, s), 1.20−2.90 (20H, taxol and steroid skeletons), 3.29 (1H, d, J = 7.4 Hz), 3.82 (1H, d, J = 7.4 Hz), 4.20 (1H, d, J = 8.4 Hz), 4.32 (1H, d, J = 8.4 Hz), 4.46 (1H, m), 4.98 (1H, dd, J = 9.6, 2.0 Hz), 5.56 (1H, d, J = 3.6 Hz), 5.58 (1H, d, J = 7.2 Hz), 5.93 (1H, d, J = 15.6 Hz), 5.96 (1H, dd, J = 9.3, 3.6 Hz), 6.26 (1H, t, J = 9.1 Hz), 6.30 (1H, s), 6.55 (1H, d, J = 2.6 Hz, Ar), 6.61 (1H, dd, J = 8.5, 2.6 Hz, Ar), 6.93 (1H, d, J = 9.3 Hz), 7.10 (1H, d, J = 8.5 Hz, Ar), 7.30−7.70 (11H, m, Ar), 7.75 (2H, m, Ar), 8.13 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ −4.2, 5.6, 7.3, 9.8, 12.3, 15.1, 18.4, 21.1, 22.9, 25.9, 26.4, 26.5, 27.1, 29.3, 29.8, 35.7, 35.8, 37.4, 37.9, 38.8, 43.1, 43.4, 44.2, 44.5, 45.8, 48.4, 53.2, 58.7, 72.0, 72.4, 74.0, 75.3, 75.8, 76.6, 79.5, 81.2, 84.7, 87.8, 117.4, 120.1, 126.3, 126.9, 127.3, 128.7, 128.9, 129.0, 129.3, 129.4, 130.4, 132.2, 132.9, 133.1, 133.92, 133.95, 137.3, 138.0, 143.2, 152.3, 153.5, 165.6, 167.25, 167.29, 168.5, 170.0, 171.5, 204.1; HRFABMS m/z 1442.6644 [M + Na^+] (calcd for $C_{81}H_{105}NO_{17}Si_2Na$, 1442.6819).

Succinic acid, 3,17*β*-di-*tert*-butyldimethylsilyloxyestra-1,3,5(10)-triene-11*β*-yl ester 2′-taxol ester (10): ^{1}H NMR ($CDCl_3$) δ 0.02 (6H, brs), 0.17 (6H, s), 0.77 (3H, s), 0.88 (9H, s), 0.96 (9H, s), 1.13 (3H, s), 1.23 (3H, s), 1.68 (3H, s), 1.94 (3H, brs), 2.22 (3H, s), 2.45 (3H, s), 1.15−2.90 (21H, taxol and steroid skeletons), 3.66 (1H, t, J = 8.4 Hz), 3.82 (1H, d, J = 7.2 Hz), 4.20 (1H, d, J = 8.6 Hz), 4.32 (1H, d, J = 8.6 Hz), 4.45 (1H, dd, J = 9.7, 7.2 Hz), 4.97 (1H, dd, J = 9.6, 1.7 Hz), 5.41 (1H, td, J = 10.5, 5.2 Hz), 5.54 (1H, d, J = 3.0 Hz), 5.68 (1H, d, J = 7.0 Hz), 6.00 (1H, dd, J = 9.2, 3.0 Hz), 6.24−6.31 (2H, overlapped), 6.54−6.61 (2H, overlapped, Ar), 6.85 (1H, d, J = 8.3 Hz, Ar), 6.99 (1H, d, J = 9.2 Hz), 7.30−7.65 (11H, Ar), 7.76 (2H, m, Ar), 8.15 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.3, −4.1, 9.8, 12.2, 15.1, 18.3, 18.4, 21.1, 22.4, 22.9, 23.4, 25.9, 26.1, 27.0, 27.1, 28.4, 29.1, 29.7, 31.2, 35.7, 35.8, 37.7, 42.6, 43.4, 44.6, 45.7, 46.6, 49.7, 53.0, 59.7, 72.0, 72.4, 74.3, 75.0, 75.3, 75.8, 76.6, 79.4, 81.2, 81.3, 84.7, 117.4, 120.2, 125.2, 126.8, 127.4, 128.7, 128.9, 129.0, 129.3, 129.4, 130.5, 132.2, 132.4, 132.9, 133.8, 133.9, 137.2, 139.4, 143.1, 153.9, 167.28, 167.30, 168.1, 170.0, 171.47, 171.54, 204.1; HRFABMS m/z 1452.6803 [M + H^+] (calcd for $C_{81}H_{106}NO_{19}Si_2$, 1452.6898).

7-{4-[3-*tert*-Butyldimethylsilyloxy-17*β*-triethylsilyloxyestra-1,3,5(10)-triene-16α-yl]-2*E*-but-2-enoyl}-2′-*tert*-butyldimethylsilyl taxol (13): ^{1}H NMR ($CDCl_3$) δ −0.30 (3H, s), −0.02 (3H, s), 0.18 (6H, s), 0.61 (6H, q, J = 7.9 Hz), 0.79 (3H, s), 0.80 (9H, s), 0.98 (9H, t, J = 7.9 Hz), 1.18 (3H, s), 1.21 (3H, s), 1.86 (3H, s), 2.01 (3H, brs), 2.11 (3H, s), 2.59 (3H, s), 1.10−2.85 (20H, taxol and steroid skeletons), 3.29 (1H, d, J = 7.1 Hz), 4.00 (1H, d, J = 7.1 Hz), 4.23 (1H, d, J = 8.1 Hz), 4.36 (1H, d, J = 8.1 Hz), 4.68 (1H, d, J = 2.0 Hz), 5.00 (1H, d, J = 9.4 Hz), 5.64 (1H, dd, J = 10.5, 7.2 Hz), 5.68−5.82 (3H, overlapped), 6.26 (1H, t, J = 9.2 Hz), 6.35 (1H, s), 6.54 (1H, d, J = 2.5 Hz, Ar), 6.61 (1H, dd, J = 8.5, 2.5 Hz, Ar), 6.89 (1H, m), 7.09 (1H, d, J = 8.8 Hz), 7.11 (1H, d, J = 8.5 Hz, Ar), 7.28−7.66 (11H, Ar), 7,76 (2H, m, Ar), 8.14 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ −5.6, −4.9, −4.2, 5.7, 7.3, 11.2, 12.4, 14.9, 18.35, 18.40, 20.8, 21.6, 23.3, 25.8, 25.9, 26.6, 27.5, 29.3, 29.8, 33.6, 35.8, 37.5, 37.6, 38.8, 43.0, 43.6, 44.2, 44.5, 47.0, 48.4, 55.9, 56.4, 71.52, 71.55, 74.8, 75.2, 75.3, 76.7, 78.9, 81.2, 84.3, 87.8, 117.3, 120.2, 122.0, 126.3, 126.6, 127.2, 128.2, 128.97, 129.02, 129.3, 130.4, 132.0, 133.0, 133.4, 134.0, 134.3, 138.1, 138.5, 141.1, 149.1, 153.5, 165.6, 167.20, 167.21, 168.6, 170.0, 171.7, 202.3; HRFABMS m/z 1534.7910 [M + H^+] (calcd for $C_{87}H_{120}NO_{17}Si_3$, 1534.7864).

Succinic acid, 3,17*β*-di-*tert*-butyldimethylsilyloxyestra-1,3,5(10)-triene-11α-yl ester 2′-*tert*-butyldimethylsilyl-7-taxol ester (15): ^{1}H NMR ($CDCl_3$) δ −0.31 (3H, s), −0.03 (3H, s), 0.01 (3H, s), 0.02 (3H, s), 0.19 (6H, s), 0.77 (3H, s), 0.80

(9H, s), 0.88 (9H, s), 0.97 (9H, s), 1.15 (3H, s), 1.21 (3H, s), 1.81 (3H, s), 1.97 (3H, brs), 2.11 (3H, s), 2.58 (3H, s), 1.10−2.80 (21H, taxol and steroid skeletons), 3.65 (1H, t, J = 8.4 Hz), 3.97 (1H, d, J = 6.8 Hz), 4.21 (1H, d, J = 8.5 Hz), 4.34 (1H, d, J = 8.5 Hz), 4.67 (1H, d, J = 2.1 Hz), 4.97 (1H, d, J = 9.3 Hz), 5.40 (1H, td, J = 10.4, 5.2 Hz), 5.61 (1H, dd, J = 10.6, 7.1 Hz), 5.70 (1H, d, J = 7.0 Hz), 5.73 (1H, dd, J = 8.9, 1.7 Hz), 6.25 (1H, s), 6.27 (1H, t, J = 9.4 Hz), 6.57 (1H, d, J = 2.5 Hz, Ar), 6.61 (1H, dd, J = 8.5, 2.5 Hz, Ar), 6.91 (1H, d, J = 8.5 Hz, Ar), 7.08 (1H, d, J = 8.9 Hz), 7.30−7.65 (11H, m, Ar), 7.75 (2H, m, Ar), 8.13 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ −5.6, −4.9, −4.5, −4.2, −4.15, −4.13, 11.1, 12.2, 14.8, 18.28, 18.34, 18.39, 20.9, 21.7, 23.2, 23.4, 25.7, 25.9, 26.1, 26.6, 27.0, 28.5, 29.5, 29.9, 31.1, 33.5, 35.8, 37.7, 42.7, 43.6, 44.6, 46.7, 47.0, 49.7, 55.9, 56.2, 71.5, 71.8, 74.5, 74.7, 75.3, 75.4, 76.6, 77.6, 78.9, 81.2, 84.2, 117.4, 119.9, 125.6, 126.6, 127.2, 128.2, 128.96, 129.01, 129.3, 130.4, 132.0, 132.5, 132.8, 134.0, 134.3, 138.5, 139.2, 141.2, 153.9, 167.15, 167.17, 169.2, 170.0, 171.6, 171.7, 172.2, 202.2; HRFABMS m/z 1566.7789 [M + H$^+$] (calcd for $C_{87}H_{120}NO_{19}Si_3$, 1566.7762).

Succinic acid, 3,17*β*-di-*tert*-butyldimethylsilyloxyestra-1,3,5(10)-triene-11α-yl ester 2′-*tert*-butyldimethylsilyl-10-deacetyl-7-*epi*-taxol ester (20): ^{1}H NMR ($CDCl_3$) δ −0.30 (3H, s), −0.04 (3H, s), 0.02 (3H, s), 0.03 (3H, s), 0.19 (6H, s), 0.77 (3H, s), 0.78 (9H, s), 0.88 (9H, s), 0.98 (9H, s), 1.13 (3H, s), 1.19 (3H, s), 1.67 (3H, s), 1.88 (3H, brs), 2.67 (3H, s), 1.10−2.96 (21H, taxol and steroid skeletons), 3.67 (1H, t, J = 8.3 Hz), 3.71 (1H, m), 3.92 (1H, d, J = 7.5 Hz), 4.40 (2H, brs), 4.66 (1H, d, J = 2.2 Hz), 4.71 (1H, d, J = 11.7 Hz), 4.94 (1H, dd, J = 8.9, 3.5 Hz), 5.44 (1H, td, J = 10.3, 5.2 Hz), 5.75 (1H, d, J = 7.5 Hz), 5.78 (1H, dd, J = 9.0, 1.8 Hz), 6.30 (1H, t, J = 8.9 Hz), 6.58 (1H, d, J = 2.6 Hz, Ar), 6.61 (1H, dd, J = 8.4, 2.6 Hz, Ar), 6.86 (1H, s), 6.91 (1H, d, J = 8.4 Hz, Ar), 7.07 (1H, d, J = 9.0 Hz), 7.30−7.63 (11H, Ar), 7.72 (2H, m, Ar), 8.17 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.0, −4.5, −4.3, −4.1, 12.2, 15.2, 16.5, 18.3, 18.38, 18.39, 21.9, 23.1, 23.4, 25.7, 25.9, 26.12, 26.14, 27.1, 28.4, 29.3, 30.1, 31.3, 35.6, 36.5, 37.7, 40.5, 42.6, 42.9, 44.5, 46.6, 49.6, 55.8, 57.7, 71.1, 74.7, 75.52, 75.56, 76.0, 77.9, 78.5, 79.5, 81.2, 82.3, 83.0, 117.4, 119.9, 125.4,126.6, 127.2, 128.2, 128.9, 129.0, 129.1, 129.5, 130.5, 132.0, 132.6, 133.1, 133.9, 134.3, 138.5, 139.3, 140.6, 153.9, 167.1, 167.4, 170.9, 171.2, 171.9, 172.5, 207.3; HRFABMS m/z 1524.7583 [M + H$^+$] (calcd for $C_{85}H_{118}NO_{18}Si_3$, 1524.7657).

2′-(3-Benzyloxycarbonylpropanoyl)taxol (22): ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, s), 1.23 (3H, s), 1.68 (3H, s), 1.88 (1H, m), 1.93 (3H, brs), 2.16 (1H, m), 2.22 (3H, s), 2.38 (1H, m), 2.45 (3H, s), 2.55 (1H, m), 2.66 (2H, m), 2.77 (2H, m), 3.81 (1H, d, J = 7.0 Hz), 4.20 (1H, d, J = 8.4 Hz), 4.31 (1H, d, J = 8.4 Hz), 4.44 (1H, dd, J = 10.9, 6.6 Hz), 4.97 (1H, dd, J = 9.6, 2.0 Hz), 5.51 (1H, d, J = 3.1 Hz), 5.69 (1H, d, J = 7.0 Hz), 5.99 (1H, dd, J = 9.2, 3.1 Hz), 6.25 (1H, t, J = 9.0 Hz), 6.30 (1H, s), 7.11 (1H, d, J = 9.2 Hz), 7.25−7.65 (16H, Ar), 7.80 (2H, m, Ar), 8.14 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 9.8, 15.0, 21.1, 22.4, 22.9, 27.0, 29.4, 29.5, 35.76, 35.80, 43.3, 45.8, 53.0, 58.7, 67.0, 72.1, 72.4, 74.5, 75.3, 75.8, 76.7, 79.3, 81.2, 84.7, 126.8, 127.5, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 129.3, 129.4, 130.5, 132.2, 133.0, 133.8, 133.9, 135.7, 137.2, 143.0, 167.2, 167.5, 168.1, 170.0, 171.3, 171.5, 172.2, 204.1; HRFABMS m/z 1044.4032 [M + H$^+$] (calcd for $C_{58}H_{62}NO_{17}$, 1044.4018).

Succinic acid, 3,17*β*-di-*tert*-butyldimethylsilyloxyestra-1,3,5(10)-triene-11α-yl ester 2′-(3-benzyloxycarbonylpropanoyl)-7-taxol ester (23): ^{1}H NMR ($CDCl_3$) δ 0.00 (3H, s), 0.01 (3H, s), 0.17 (6H, s), 0.76 (3H, s), 0.86 (9H, s), 0.95 (9H, s), 1.14 (3H, s), 1.19 (3H, s), 1.79 (3H, s), 1.97 (3H, brs), 2.10 (3H, s), 2.44 (3H, s), 1.10−2.80 (25H, taxol and steroid skeletons), 3.64 (1H, t, J = 8.5 Hz), 3.94 (1H, d, J = 6.9 Hz), 4.18 (1H, d, J = 8.5 Hz), 4.31 (1H, d, J = 8.5 Hz), 4.94 (1H, d, J = 9.3 Hz), 4.99 (2H, s), 5.39 (1H, td, J = 10.4, 5.2 Hz), 5.52 (1H, d, J = 3.0 Hz), 5.58 (1H, dd, J = 10.5, 7.2 Hz), 5.68 (1H, d, J = 7.0 Hz), 5.99 (1H, dd, J = 9.2, 3.0 Hz), 6.22 (1H, t, J = 9.4 Hz), 6.23 (1H, s), 6.56 (1H, d, J = 2.6 Hz, Ar), 6.60 (1H, dd, J = 8.5, 2.6 Hz, Ar), 6.91 (1H, d, J = 8.5 Hz, Ar), 7.11 (1H, d, J = 9.2 Hz), 7.25−7.65 (16H, Ar), 7.80 (2H, m, Ar), 8.13 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.3, −4.2, 11.0, 12.1, 14.6, 18.2, 18.3, 20.8, 21.5, 22.8, 23.3, 25.9, 26.0, 26.6, 27.0, 28.4, 29.2, 29.4, 29.5, 29.8, 31.2, 33.4, 35.6, 37.6, 42.6, 43.4, 44.5, 46.6, 46.9, 49.6, 52.9, 56.1, 66.9, 71.7, 74.3, 74.4, 74.7, 75.3, 76.4, 78.8, 81.0, 81.1, 84.1, 117.3, 119.8, 125.5, 126.7, 127.4, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 129.3, 130.4, 132.1, 132.4, 132.6, 133.7, 133.8, 135.6, 137.1, 139.1, 141.4, 153.8, 167.1, 167.4, 168.1, 169.1, 169.7, 171.0, 171.3, 172.2, 202.2; MALDI-TOFMS m/z 1665 [M + Na$^+$] (calcd for $C_{92}H_{115}NO_{22}Si_2Na$, 1664.8).

Succinic acid, 3,17*β*-di-*tert*-butyldimethylsilyloxyestra-1,3,5(10)-triene-11α-yl ester 7-(3-benzyloxycarbonylpropanoyl)-2′-taxol ester (28): ^{1}H NMR ($CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.17 (6H, s), 0.77(3H, s), 0.88 (9H, s), 0.96 (9H, s), 1.15 (3H, s), 1.20 (3H, s), 1.79 (3H, s), 1.98 (3H, brs), 2.13 (3H, s), 2.45 (3H, s), 1.10−2.83 (25H, taxol and steroid skeletons), 3.67 (1H, t, J = 8.5 Hz), 3.95 (1H, d, J = 6.9 Hz), 4.19 (1H, d, J = 8.5 Hz), 4.32 (1H, d, J = 8.5 Hz), 4.93 (1H, d, J = 9.4 Hz), 5.12 (2H, AB, J = 12.4 Hz), 5.41 (1H, td, J = 10.4, 5.3 Hz), 5.58 (1H, d, J = 3.1 Hz), 5.60 (1H, dd, J = 10.5, 7.1 Hz), 5.68 (1H, d, J = 7.0 Hz), 6.01 (1H, dd, J = 9.3, 3.1 Hz), 6.22 (1H, s), 6.24 (1H, t, J = 9.1 Hz), 6.55−6.59 (2H, overlapped, Ar), 6.85 (1H, d, J = 8.0 Hz, Ar), 7.03 (1H, d, J = 9.3 Hz), 7.27−7.65 (16H, Ar), 7.77 (2H, m, Ar), 8.14 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ −4.5, −4.3, −4.2, 11.0, 12.1, 14.6, 18.2, 18.3, 20.9, 21.5, 22.8, 23.3, 25.9, 26.0, 26.6, 26.9, 28.1, 28.3, 29.2, 29.3, 29.7, 31.2, 33.3, 37.2, 37.6, 42.5, 43.3, 44.5, 46.5, 47.0, 49.6, 52.9, 56.1, 66.5, 71.7, 71.9, 74.1, 74.7, 74.9, 75.4, 76.5, 78.8, 81.00, 81.04, 84.2, 117.3, 119.9, 125.1, 126.7, 127.3, 128.31, 128.35, 128.37, 128.67, 128.71, 128.8, 129.25, 129.30, 130.4, 132.1, 132.4, 132.5, 133.7, 133.8, 136.1, 137.1, 139.3, 141.3, 153.9, 167.1, 167.4, 168.2, 169.0, 169.7, 171.2, 171.3, 171.6, 172.6, 202.2; HRFABMS m/z 1642.8468 [M + H$^+$] (calcd for $C_{92}H_{116}NO_{22}Si_2$).

General Procedure for Deprotection of Silyl Group. To a solution of silyl-protected estradiol−taxol conjugate **8** (15.1 mg, 0.0106 mmol), in 0.6 mL of dried THF, was added 0.1 mL of anhydrous pyridine, then the solution was cooled to 0 °C, and 0.1 mL of HF−pyridine was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc, and the organic phase was washed with sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated in a vacuum. The residue was purified by preparative TLC (50% EtOAc/hexane) to give **9** (12.3 mg, 97%). Compounds **11**, **14**, **16**, **21**, **24**, and **27** were prepared similarly.

2′-{4-[3,17*β*-Dihydroxyestra-1,3,5(10)-triene-16α-yl]-2*E*-but-2-enoyl}taxol (9): ^{1}H NMR (CD_3OD) δ 0.78 (3H, s), 1.11 (3H, s), 1.13 (3H, s), 1.65 (3H, s), 1.93 (3H, brs), 2.16 (3H, s), 2.40 (3H, s), 2.15−2.80 (20H, taxol and steroid skeletons), 3.23 (1H, d, J = 8.0 Hz), 3.81 (1H, d, J = 7.2 Hz), 4.18 (2H, brs), 4.34 (1H, dd, J = 11.0, 6.7 Hz), 4.99 (1H, dd, J = 9.6, 1.9 Hz), 5.50 (1H, d, J = 6.8 Hz), 5.63 (1H, d, J = 7.1 Hz), 5.85 (1H, d, J = 6.8 Hz), 5.99 (1H, d, J = 15.6 Hz), 6.06 (1H, t, J = 9.1 Hz), 6.45 (1H, s), 6.47 (1H, d, J = 2.6 Hz, Ar), 6.53 (1H, dd, J = 8.5, 2.6 Hz, Ar), 7.05 (1H, d, J = 8.5 Hz, Ar), 7.16 (1H, td, J = 15.6, 7.1 Hz), 7.23−7.70 (11H, Ar), 7.81 (2H, m, Ar), 8.11 (2H, m, Ar); ^{13}C NMR (CD_3OD) δ 9.3, 11.3, 13.8, 19.6, 21.2, 22.1, 25.7, 26.2, 27.3, 29.1, 29.5, 35.2, 36.3, 36.8, 37.6, 39.0, 42.0, 43.4, 43.9, 44.1, 46.7, 48.3, 54.2, 58.0, 71.1, 71.7, 74.7, 75.1, 75.6, 76.3, 77.8, 81.0, 84.7, 86.7, 112.5, 114.9, 120.3, 126.0, 127.4, 127.5, 128.4, 128.5, 128.9, 130.0, 130.2, 131.3, 131.7, 133.4, 133.7, 134.4, 137.2, 137.6, 141.3, 151.6, 154.7, 165.8, 166.4, 169.3, 169.4, 170.1, 170.4, 204.0; HRFABMS m/z 1192.5267 [M + H$^+$] (calcd for $C_{69}H_{78}NO_{17}$, 1192.5270).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11*β*-yl ester 2′-taxol ester (11): ^{1}H NMR (CD_3OD) δ 0.74 (3H, s), 1.15 (3H, s), 1.16 (3H, s), 1.65 (3H, s), 1.97 (3H, brs), 2.17 (3H, s), 2.42 (3H, s), 1.24−2.86 (21H, taxol and steroid skeletons), 3.59 (1H, t, J = 8.7 Hz), 3.84 (1H, d, J = 7.2 Hz), 4.20 (2H, brs), 4.36 (1H, dd, J = 11.1, 6.7 Hz), 5.02 (1H, dd, J = 9.6, 2.0 Hz), 5.29 (1H, td, J = 10.4, 5.3 Hz), 5.48 (1H, d, J = 5.2 Hz), 5.65 (1H, d, J = 7.1 Hz), 5.89 (1H, d, J = 5.2 Hz), 6.17 (1H, t, J = 9.1 Hz), 6.43 (1H, s), 6.52 (1H, d, J = 2.7 Hz, Ar), 6.54 (1H, dd, J = 8.4, 2.7 Hz, Ar), 6.83 (1H, d, J = 8.4 Hz, Ar), 7.25−7.69 (11H, Ar), 7.77 (2H, m, Ar), 8.13 (2H, m, Ar); ^{13}C NMR (CD_3OD) δ 9.3, 11.0, 14.1, 19.8, 21.2, 22.7, 25.9, 26.8,

28.1, 28.2, 29.2, 29.5, 35.3, 36.3, 37.9, 41.6, 43.5, 43.9, 45.7, 46.6, 49.5, 53.7, 58.0, 71.2, 71.6, 74.6, 75.09, 75.11, 75.7, 76.3, 77.8, 80.4, 81.1, 84.7, 112.5, 114.8, 125.0, 127.3, 127.4, 128.3, 128.54, 128.56, 128.9, 130.0, 130.2, 130.9, 131.6, 133.4, 133.8, 134.4, 137.1, 139.0, 141.3, 155.2, 166.5, 168.9, 169.6, 170.2, 170.4, 171.9, 172.3, 204.0; HRFABMS *m/z* 1224.5200 [M + H$^+$] (calcd for $C_{69}H_{78}NO_{19}$, 1224.5168).

7-{4-[3,17*β*-Dihydroxyestra-1,3,5(10)-triene-16α-yl]-2*E*-but-2-enoyl}taxol (14): ^{1}H NMR (CD_3OD) δ 0.82 (3H, s), 1.11 (3H, s), 1.15 (3H, s), 1.81 (3H, s), 1.90 (3H, brs), 2.13 (3H, s), 2.37 (3H, s), 1.20−2.80 (20H, taxol and steroid skeletons), 3.27 (1H, d, J = 7.7 Hz), 3.92 (1H, d, J = 7.1 Hz), 4.20 (2H, brs), 4.75 (1H, d, J = 5.2 Hz), 5.00 (1H, d, J = 9.3), 5.60 (1H, dd, J = 10.6, 7.4 Hz), 5.63−5.68 (2H, overlapped), 5.75 (1H, d, J = 15.6 Hz), 6.15 (1H, t, J = 9.1 Hz), 6.31 (1H, s), 6.37 (1H, d, J = 2.5 Hz, Ar), 6.53 (1H, dd, J = 8.5, 2.5 Hz, Ar), 6.92 (1H, td, J = 15.6, 7.3 Hz), 7.26−7.69 (11H, Ar), 7.85 (2H, m, Ar), 8.11 (2H, m, Ar); ^{13}C NMR (CD_3OD) δ 10.3, 11.3, 13.5, 19.5, 20.9, 22.0, 25.55, 25.58, 26.3, 27.3, 29.50, 29.55, 35.3, 36.9, 39.1, 42.2, 43.4, 44.0, 44.1, 46.8, 48.3, 56.2, 56.5, 71.0, 71.7, 73.6, 74.7, 75.4, 76.1, 77.7, 80.8, 84.0, 86.5, 112.5, 114.9, 121.6, 126.0, 127.3, 127.8, 128.4, 128.55, 128.57, 130.0, 130.1, 131.4, 131.7, 133.3, 133.5, 134.4, 137.6, 138.8, 140.9, 149.1, 154.7, 165.6, 166.4, 169.1, 169.7, 170.8, 173.3, 202.5; HRFABMS *m/z* 1192.5237 [M + H$^+$] (calcd for $C_{69}H_{78}NO_{17}$ 1192.5270).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11α-yl ester 7-taxol ester (16): ^{1}H NMR (CD_3OD) δ 0.76 (3H, s), 1.11 (3H, s), 1.15 (3H, s), 1.78 (3H, s), 1.89 (3H, brs), 2.11 (3H, s), 2.38 (3H, s), 1.17−2.81 (21H, taxol and steroid skeletons), 3.67 (1H, t, J = 8.7 Hz), 3.91 (1H, d, J = 7.1 Hz), 4.18 (1H, d, J = 8.5 Hz), 4.22 (1H, d, J = 8.5 Hz), 4.77 (1H, d, J = 5.3 Hz), 5.00 (1H, d, J = 9.5 Hz), 5.32 (1H, td, J = 10.6, 5.2 Hz), 5.68−5.78 (3H, overlapped), 6.16 (1H, t, J = 9.1 Hz), 6.21 (1H, s), 6.53 (1H, d, J = 2.7 Hz, Ar), 6.58 (1H, dd, J = 8.6, 2.7 Hz, Ar), 6.91 (1H, d, J = 8.6 Hz), 7.26−7.69 (11H, Ar), 7.85 (2H, m, Ar), 8.11 (2H, m, Ar); ^{13}C NMR (CD_3OD) δ 10.3, 11.0, 13.7, 19.5, 20.9, 22.0, 22.7, 25.6, 26.8, 28.1, 29.0, 29.3, 29.4, 33.0, 35.3, 37.9, 42.3, 43.4, 43.9, 46.3, 46.9, 49.7, 56.0, 56.5, 71.0, 72.0, 73.6, 74.59, 74.63, 75.5, 76.1, 77.7, 80.4, 80.8, 84.1, 112.6, 114.8, 125.4, 127.3, 127.8, 128.4, 128.56, 128.59, 130.0, 130.1, 130.6, 131.7, 133.1, 133.5, 134.4, 138.8, 139.0, 141.0, 155.2, 166.4, 169.1, 169.7, 170.9, 171.8, 172.8, 173.3, 202.4; HRFABMS *m/z* 1224.5176 [M + H$^+$] (calcd for $C_{69}H_{78}NO_{19}$, 1224.5168).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11α-yl ester 10-deacetyl-7-*epi*-taxol ester (21): ^{1}H NMR ($CDCl_3$) δ 0.74 (3H, s), 1.12 (3H, s), 1.14 (3H, s), 1.63 (3H, s), 1.77 (3H, brs), 2.47 (3H, s), 1.20−2.94 (21H, taxol and steroid skeletons), 3.6−3.74 (2H, overlapped), 3.87 (1H, d, J = 7.2 Hz), 4.22 (1H, brs), 4.37 (2H, brs), 4.78 (1H, d, J = 1.8 Hz), 4.84−4.92 (2H, overlapped), 5.38 (1H, td, J = 10.3, 5.5 Hz), 5.73 (1H, d, J = 7.2 Hz), 5.77 (1H, dd, J = 9.0, 2.0 Hz), 6.19 (1H, t, J = 8.7 Hz), 6.46−6.55 (2H, Ar), 6.76 (1H, s), 6.88 (1H, d, J = 8.1 Hz, Ar), 7.28 (1H, d, J = 8.9 Hz, Ar), 7.29−7.63 (12H, Ar and −NH), 7.72 (2H, d, J = 7.9 Hz, Ar), 8.14 (2H, d, J = 7.9 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 11.8, 15.0, 16.7, 21.6, 22.8, 23.2, 26.1, 27.0, 28.4, 29.4, 30.0, 30.3, 35.4, 36.3, 37.7, 40.5, 42.2, 42.8, 44.2, 46.3, 49.8, 55.4, 57.7, 72.3, 73.4, 74.6, 75.5, 76.1, 77.9, 78.7, 79.1, 81.1, 82.3, 82.9, 112.9, 115.3, 125.9, 127.1, 127.4, 128.4, 128.9, 129.0, 129.2, 129.5, 130.4, 131.3, 132.2, 133.4, 133.8, 133.9, 138.3, 139.4, 140.3, 154.4, 167.2, 167.9, 171.2, 172.1, 172.6, 173.1, 207.2; MALDI-TOFMS *m/z* 1204.5 [M + Na$^+$] (calcd for $C_{67}H_{75}NO_{18}Na$, 1204.5).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11α-yl ester 2′-(3-benzyloxycarbonylpropanoyl)-7-taxol ester (24): ^{1}H NMR ($CDCl_3$) δ 0.76 (3H, s), 1.16 (3H, s), 1.20 (3H, s), 1.83 (3H, s), 1.99 (3H, brs), 2.12 (3H, s), 2.47 (3H, s), 3.66 (1H, t, J = 8.6 Hz), 3.95 (1H, d, J = 6.8 Hz), 4.19 (1H, d, J = 8.4 Hz), 4.35 (1H, d, J = 8.4 Hz), 4.96 (2H, s), 5.00 (1H, d, J = 9.4 Hz), 5.37 (1H, td, J = 10.6, 5.3 Hz), 5.59 (1H, d, J = 3.1 Hz), 5.67−5.75 (2H, overlapped), 6.01 (1H, dd, J = 9.1, 3.1 Hz), 6.17−6.25 (2H, overlapped), 6.54 (1H, d, J = 2.5 Hz, Ar), 6.68 (1H, dd, J = 8.5, 2.5 Hz, Ar), 7.05 (1H, d, J = 8.5 Hz, Ar), 7.19 (1H, d, J = 9.1 Hz), 7.23−7.65 (16H, Ar), 7.83 (2H, m, Ar), 8.12 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 11.2, 11.9, 14.8, 20.9, 21.3, 23.0, 23.1, 26.6, 27.1, 28.5, 29.3, 29.5, 29.6, 29.7, 30.2, 33.5, 35.5, 37.8, 42.7, 43.5, 44.1, 46.5, 47.4, 49.8, 53.0, 56.2, 67.0, 71.6, 72.0, 74.46, 74.55, 74.57, 75.7, 76.7, 78.6, 81.1, 84.5, 113.1, 115.2, 126.6, 126.8, 127.5, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 129.28, 129.34, 130.4, 131.1, 132.3, 132.6, 133.8, 134.0, 135.7, 137.0, 139.2, 141.4, 154.6, 167.1, 167.8, 168.2, 169.1, 170.6, 171.6, 171.8, 172.4, 173.0, 202.2; HRFABMS *m/z* 1436.5613 [M + Na$^+$] (calcd for $C_{80}H_{87}NO_{22}Na$, 1436.5617).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11α-yl ester 7-(3-benzyloxycarbonylpropanoyl)-2′-taxol ester (29): ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, s), 1.15 (3H, s), 1.19 (3H, s), 1.78 (3H, s), 2.01 (3H, brs), 2.12 (3H, s), 2.42 (3H, s), 1.10−2.95 (25H, taxol and steroid skeletons), 3.71 (1H, t, J = 8.5 Hz), 3.93 (1H, d, J = 6.8 Hz), 4.17 (1H, d, J = 8.5 Hz), 4.32 (1H, d, J = 8.5 Hz), 4.95 (1H, d, J = 9.3 Hz), 5.11 (2H, AB, J = 12.3 Hz), 5.39 (1H, td, J = 10.4, 5.2 Hz), 5.44 (1H, d, J = 3.1 Hz), 5.63 (1H, dd, J = 10.6, 7.0 Hz), 5.69 (1H, d, J = 6.8 Hz), 5.92 (1H, dd, J = 9.0, 2.9 Hz), 6.22 (1H, t, J = 9.0 Hz), 6.24 (1H, s), 6.55−6.60 (2H, overlapped, Ar), 6.86 (1H, d, J = 8.2 Hz, Ar), 7.10 (1H, d, J = 9.0 Hz), 7.26−7.64 (16H, Ar), 7.77 (2H, m, Ar), 8.11 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 11.0, 11.9, 14.7, 21.0, 21.4, 22.9, 23.2, 26.6, 26.9, 28.3, 28.6, 29.2, 29.51, 29.54, 30.6, 33.3, 35.6, 37.7, 42.1, 43.5, 44.1, 46.2, 47.2, 49.9, 53.0, 56.2, 66.7, 71.8, 72.0, 74.2, 74.6, 74.7, 75.6, 76.5, 78.8, 81.0, 81.2, 84.1, 112.8, 115.5, 125.6, 126.9, 127.4, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.2, 129.3, 130.4, 131.2, 132.2, 132.6, 133.8, 134.0, 136.1, 137.1, 139.4, 141.7, 154.7, 167.1, 167.6, 168.3, 169.4, 170.2, 171.6, 171.7, 172.3, 172.6, 202.2; HRFABMS *m/z* 1436.5562 [M + Na$^+$] (calcd for $C_{80}H_{87}NO_{22}Na$, 1436.5617).

General Procedure for Deprotection of the Benzyl Group. To a solution of benzyl-protected estradiol−taxol conjugate **24** (38.3 mg, 0.0266 mmol), in 10 mL of EtOAc, was added 10 mg of Pd−C (10%), and the mixture was hydrogenated at 30 psi at room temperature for 24 h. The reaction mixture was filtered, and the organic phase was concentrated in a vacuum. The residue was purified by preparative TLC (70% EtOAc/hexane) to give **25** (27.0 mg, 74%).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11α-yl ester 2′-(3-carboxypropanoyl)-7-taxol ester (25): ^{1}H NMR ($CDCl_3$) δ 0.75 (3H, s), 1.14 (3H, s), 1.17 (3H, s), 1.81 (3H, s), 1.96 (3H, brs), 2.11 (3H, s), 2.43 (3H, s), 1.20−2.80 (25H, taxol and steroid skeletons), 3.67 (1H, t, J = 8.7 Hz), 3.91 (1H, d, J = 6.8 Hz), 4.17 (1H, d, J = 8.7 Hz), 4.32 (1H, d, J = 8.7 Hz), 4.97 (1H, d, J = 9.5 Hz), 5.36 (1H, td, J = 10.4, 7.8 Hz), 5.68 (1H, d, J = 6.7 Hz), 5.96 (1H, dd, J = 9.1, 3.9 Hz), 6.17 (1H, t, J = 8.7 Hz), 6.20 (1H, s), 6.55 (1H, d, J = 2.7, Ar), 6.67 (1H, dd, J = 8.5, 2.7 Hz, Ar), 7.02 (1H, d, J = 8.5 Hz, Ar), 7.24 (1H, d, J = 9.2 Hz), 7.28−7.65 (11H, Ar), 7.77 (2H, m, Ar), 8.10 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 11.2, 11.8, 14.8, 21.0, 21.3, 22.9, 23.1, 26.6, 27.1, 28.5, 28.77, 28.80, 29.13, 29.15, 29.2, 33.5, 35.4, 37.8, 42.6, 43.5, 44.1, 46.5, 47.4, 49.8, 53.3, 56.2, 71.7, 72.0, 74.4, 74.54, 74.56, 75.7, 76.6, 78.7, 81.2, 81.3, 84.4, 113.1, 115.1, 126.9, 127.4, 128.8, 129.0, 129.25, 129.34, 130.4, 131.3, 132.3, 132.6, 133.7, 134.0, 136.9, 139.3, 141.4, 154.3, 167.0, 167.7, 168.3, 169.2, 170.7, 171.8, 172.0, 172.9, 175.0, 202.2; HRFABMS *m/z* 1346.5162 [M + Na$^+$] (calcd for $C_{73}H_{81}NO_{22}Na$, 1346.5148).

Succinic acid, 3,17*β*-dihydroxyestra-1,3,5(10)-triene-11α-yl ester 7-(3-carboxypropanoyl)-2′-taxol ester (30): (Hydrogenation was carried out at 50 psi.) ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, s), 1.15 (3H, s), 1.19 (3H, s), 1.80 (3H, s), 2.01 (3H, brs), 2.13 (3H, s), 2.41 (3H, s), 1.23−2.93 (25H, taxol and steroid skeletons), 3.73 (1H, t, J = 8.6 Hz), 3.92 (1H, d, J = 6.9 Hz), 4.17 (1H, d, J = 8.4 Hz), 4.32 (1H, d, J = 8.4 Hz), 4.97 (1H, d, J = 9.3 Hz), 5.40 (1H, dt, J = 10.7, 5.2 Hz), 5.44 (1H, d, J = 3.2 Hz), 5.63 (1H, dd, J = 10.4, 7.2 Hz), 5.69 (1H, d, J = 6.9 Hz), 5.91 (1H, dd, J = 9.1, 3.0 Hz), 6.21 (1H, t, J = 9.3 Hz), 6.23 (1H, s), 6.55−6.62 (2H, overlapped, Ar), 6.86 (1H, d, J = 8.2 Hz, Ar), 7.15 (1H, d, J = 9.1 Hz), 7.31−7.65 (11H, Ar), 7.77 (2H, m, Ar), 8.11 (2H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 11.0, 11.9, 14.7, 21.0, 21.3, 22.9, 23.2, 26.6, 26.9, 28.3, 28.5, 28.7, 29.4, 29.5, 30.5, 33.3, 35.6, 37.7, 42.1, 43.4, 44.1, 46.2, 47.2, 49.9, 53.0, 56.3, 71.8, 72.1, 74.3, 74.6, 74.7, 75.7, 76.5, 78.8, 81.1, 81.2, 84.1, 112.8, 115.5, 125.5, 126.9, 127.4, 128.7,

128.95, 128.98, 129.24, 129.27, 130.4, 131.3, 132.3, 132.6, 133.8, 134.0, 137.1, 139.5, 141.7, 154.6, 167.1, 167.7, 168.4, 169.7, 170.2, 171.67, 171.71, 172.3, 176.1, 202.1; HRFABMS *m/z* 1346.5078 [M + Na^+] (calcd for $C_{73}H_{81}NO_{22}Na$, 1346.5148).

Cell Lines. MDA-MB-231 and MCF-7 human mammary carcinoma cells were propagated in Dulbecco's Modified Eagle's Medium (BioWhittaker, Walkersville, MD) supplemented with 10% fetal bovine serum (Summit Biotechnology, Fort Collins, CO) and 0.04 mg/mL gentamicin in a 7.5% CO_2 atmosphere at 37 °C.

MTS (3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) Cell Proliferation Assay. Experiments were performed using replicate plated cells growing in 96-well sterile culture plates and the Cell Titer96 AQ_{ueous} One Solution Cell Proliferation Assay (Promega, Madison, WI) as the source of MTS. Concentrated stocks of the test compounds dissolved in DMSO were added to the cells by diluting into culture medium supplemented with 5% serum. The DMSO concentration in each well was 0.1%. After 48 h incubation, MTS was added to the culture medium. Cell survival was assayed using the metabolic reduction MTS to a colored product by intact viable cells as the end point. Product formation at 37 °C, monitored by the increase in absorbance at 490 nM, was linear for 3 h. Cell survival curves were transformed to log-linear concentration response curves using Prism3.0 (GraphPad Software, Inc., San Diego, CA) and fit by nonlinear regression to the equation describing a sigmoidal dose−response relationship. Statistically significant differences in IC_{50} values between MCF-7 and MDA-MB-231 cells were determined by the Student's *t*-test.

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References and Notes

(1) The name taxol was assigned to the chemical compound **1** by Drs. Wall and Wani in 1971, and this name remained in general use until 1991. The name Taxol was then trademarked by Bristol-Myers Squibb for their formulation of the chemical compound taxol on the basis of an existing French trademark for a laxative compound with this name. Since this paper has been submitted in honor of Drs. Wall and Wani, the original name that they assigned for compound **1** is used, rather than the alternative name of paclitaxel. No infringement of the Bristol-Myers Squibb trademark is implied by this usage.

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