Synthesis and Antitumor Activity of Novel C-7 Paclitaxel Ethers: Discovery of BMS-184476

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The preparation of C-7 paclitaxel ethers is described. Various substituted ethers were prepared via activation of the corresponding methylthiomethyl ether followed by alcohol addition. Variation of the C-7 ether group as well the 3′ side chain position led to the discovery of a novel taxane, BMS-184476 (**4**), with preclinical antitumor activity superior to paclitaxel.

Paclitaxel **1**, the diterpenoid natural product isolated from *Taxus brevifolia* in 1971 by Wani and Wall[1] and the active constituent of the antitumor drug TAXOL, continues to have a major impact on the treatment of ovarian and breast cancer. TAXOL has been approved for first line treatment of refractory ovarian and breast cancer as well as Kaposi's sarcoma. Ongoing clinical research is demonstrating the usefulness of TAXOL for the treatment of cancers of the head, neck, and lung (SCLC and NSCLC). Encouraging phase III results have elevated TAXOL/platinum combinations to standard therapy for advanced disease. As the clinical potential of TAXOL continues to unfold, significant advances in cancer treatment could be realized by the discovery and development of novel taxanes with improved efficacy, reduced toxicity, and an expanded spectrum of activity. The search for novel taxane analogues has focused on regions directly interacting with tubulin, principally the side chain, the C-2 benzoate, and the C-4 acetate, as well as on the nontubulin binding C-7 and C-10 region.[2−4] Despite these efforts, identifying agents that have superior preclinical efficacy to TAXOL has proved extremely challenging. Herein, we describe the synthesis and biological activity of C-7 paclitaxel ethers that ultimately led to the identification of a novel taxane clinical candidate with superior preclinical antitumor activity to TAXOL.

Our focus on C-7 paclitaxel ethers was driven by following observations. First, the C-7 to C-10 region of paclitaxel does not interact directly with tubulin, but it has been postulated that changes in this region of the molecule may affect the specific binding of paclitaxel to P-glycoprotein. Disruption of binding to P-glycoprotein resulting in reduced P-glycoprotein mediated efflux, believed to be responsible for the MDR phenotype, could provide activity in tumors that are resistant or unresponsive to TAXOL treatment or become resistant as a result of treatment. It has been proposed that the ability of C-10 taxane derivatives to overcome MDR in vitro is the result of reduced binding affinity for P-gp.[5] Evidence for the proximity of C-7 to the P-glycoprotein binding site of paclitaxel was suggested by the fact that attachment of a photoaffinity label to the C-7 hydroxyl group of paclitaxel successfully labeled P-glycoprotein.[6] Second, C-7 derivatives may provide metabolical stability due to increased steric bulk around C-6, a major site of metabolism[7] as well as removing the possibility for retro-aldol at C-7.[8] The altered pharmacokinetics of C-7 paclitaxel ethers relative to paclitaxel itself may also provide an efficacy advantage over paclitaxel.

Chemistry

Entry into C-7 paclitaxel ethers started from paclitaxel **1** itself. Protection of the 2′ hydroxyl group as the TES ether **2** followed by methythiomethyl ether[9] formation provided intermediate **3**. The TES ether could be cleaved to provide MTM ether (**4**). Modification of the side chain was accomplished by reductive cleavage of the paclitaxel side chain using the Kingston[10] procedure to afford 7-methylthiomethyl baccatin III, **5**. Side chain analogues were then prepared by coupling **5** with a series of azetidinones[11−14] to provide derivatives **6a**−**f**.

Ethers **7a**−**d**, **f**−**i**, **k**−**m** were prepared from the corresponding methythiomethyl ether using NIS activation under TESOTf [15] catalysis followed by addition of the corresponding alcohols. The methyl ethers **7e** and **7j** were prepared from the corresponding methylthiomethyl ethers following desulfurization with Raney Nickel[16] (see Scheme 1).

Results and Discussion

The initial goal was to identify compounds that could overcome MDR-mediated resistance in vitro and test these compounds in paclitaxel-resistant tumor models. Compounds were evaluated in vitro in a tubulin polymerization assay[17] and for cytotoxicity against both a paclitaxel-sensitive cell line (HCT-116 human colon tumor) and paclitaxel-resistant cell line (HCT-116/ MDR resistant) (see Table 1). The potency differential in the MDR resistant cell line vs the sensitive cell line is expressed as a ratio (R/S ratio).[18]

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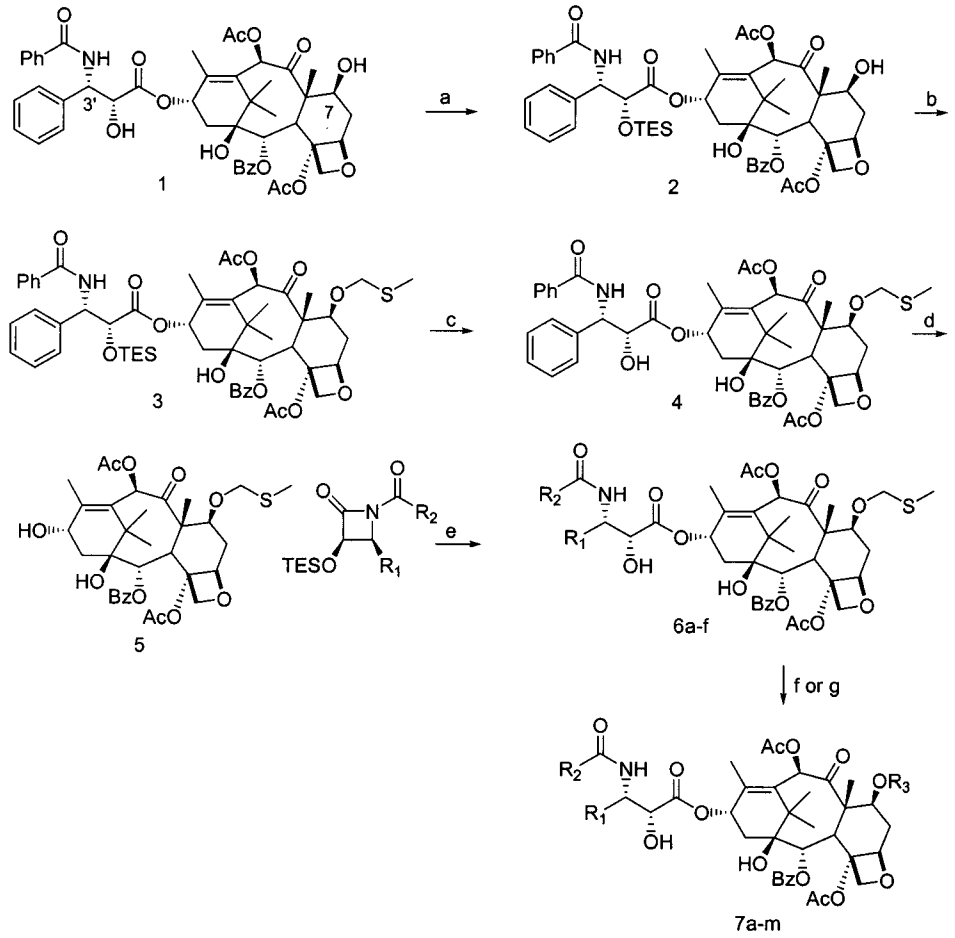
Scheme 1[a]



[a] Reagents and conditions: (a) TESCl, imidazole, CH_2Cl_2; (b) CH_3SCH_3, Bz_2O_2, CH_3CN, 0 °C; (c) 1 N HCl, CH_3CN, 0 °C; (d) Bu_4NBH_4, CH_2Cl_2, MeOH (cat); (e) LiHMDS, −78 °C, lactam, −78 to 0 °C; Bu_4NF, THF; (f) NIS, TESOTf, ROH, CH_2Cl_2 (**7a**−**d**, **f**−**i**, **k**−**m**); (g) Raney Nickel, EtOAc, H_2 (**7e**, **j**).

Table 1. In Vitro and In Vivo Profile for C-7 Paclitaxel Ethers that Overcome MDR

	R_1	R_2	R_3	tubulin[a]	HCT-116[b] (nM)	R/S ratio[c]	M109[d]
paclitaxel (**1**)	phenyl	phenyl	H	1.0	1.5−3.5	100−200	159−259 (40−60)
4	phenyl	phenyl	MTM	1.1	2.1	10.5	NT[e]
7a	phenyl	phenyl	MOM	0.5	1.4	10	192 (50)/217
6a	phenyl	*t*-butoxy	MTM	3.3	0.6	1.7	143 (12)/200
7f	phenyl	*t*-butoxy	MOM	0.2	1.1	2	118 (5)/168
7g	phenyl	*t*-butoxy	$CH_2O(CH_2)_2OH$	0.7	1.1	0.7	136 (25)/164
6d	2-furyl	*t*-butoxy	MTM	1.6	1.7	1	104 (3)/200
7i	2-furyl	*t*-butoxy	MOM	0.4	1.3	5.6	118 (0.32)/159
7j	2-furyl	*t*-butoxy	Me	0.4	1.3	1.7	121 (2)/200
7k	2-furyl	*t*-butoxy	$CH_2O(CH_2)_2OH$	0.3	1.7	4.1	158 (2)/200
6f	*i*-butenyl	*t*-butoxy	MTM	1.1	0.7	3.3	109 (4)/259

[a] Concentration of test compound to give a change of 0.01 OD/h expressed as a ratio to the concentration of paclitaxel. [b] IC_{50} human colon tumor cell line sensitive to paclitaxel. [c] Ratio of IC_{50} for HCT-116 MDR resistant cell line /IC_{50} for HCT-116 sensitive cell line. [d] Madison Murine Lung Carcinoma. M109 tumors implanted ip and the drug given ip on days 5 and 8 post implantation. Values are %T/C analogue (maximum tolerated dose)/% T/C for paclitaxel at a historically determined efficacious dose but does not represent the MTD. %T/C values of greater than 125% are considered active. [e] Not tested in the ip model but taken directly into the SC M109 model, see Table 2.

The initial observation that C-7 paclitaxel ethers **4** and **7a** had in vitro potency against both the sensitive and the MDR-resistant cell lines (R/S ratio of 10, see Table 1) served to focus our synthetic efforts on identifying other C-7 ethers that would possess antitumor efficacy against paclitaxel-resistant tumors. Toward this end, other C-7 ether modifications in combination with side chain changes were explored with the goal of identifying agents active against MDR-resistant tumors.

We chose to focus on compounds with R/S ratios of less than 5. Small ethers (R_3) such as MTM (**6a**, **6d**, and **6f**), MOM (**7f** and **7i**), methoxy-2-hydroxyethyl (**7g** and **7k**), and Me (**7j**) C-7 ethers gave good in vitro potency against the MDR resistant cell lines. In general, the replacement of the 3′-*N*-benzamide with an N-Boc group provided compounds with the greatest potency against the resistant cell line (lower R/S ratios). Replacement of the C-3′ phenyl with a 2-furyl (**6d**, **7i**−**k**)

Table 2. In Vitro and In Vivo Activity of C-7 Paclitaxel Ethers

	R_1	R_2	R_3	tubulin[a]	HCT-116[b] (nM)	M109[d]	Sc M109[e]
paclitaxel (**1**)	phenyl	phenyl	H	1.0	1.5−3.5	159−259 (40−60)	0.9−2.3
4	phenyl	phenyl	MTM	1.1	2.1	NT	1.0 (13,24)/0.9
7a	phenyl	phenyl	MOM	0.5	1.4	192 (50)/217	1.8 (16)/2.3
7b	phenyl	phenyl	MEM	1.1	0.9	132 (200)/232	
7c	phenyl	phenyl	$CH_2OCH_2CH_3$	0.6	2.2	132 (100)/232	
7d	phenyl	phenyl	$CH_2O(CH_2)_2OH$	1	1.1	238 (200)/217	0.9 (25)/0.9
7e	phenyl	phenyl	Me	1	2.3	121 (100)/194	
6b	phenyl	*n*-butoxy	MTM	0.6	1.2	177 (8)/259	0.2 (10)/1.2
6c	phenyl	*i*-propoxy	MTM	1.6	1.7	191 (8,16)/259	0.5 (4)/0.9
7h	phenyl	benzyloxy	MOM	0.6	1.4	139 (200)/243	
6d	2-furyl	*t*-butoxy	MTM	1.6	1.7	104 (3)/200	
7i	2-furyl	*t*-butoxy	MOM	0.4	1.3	118 (0.32)/159	
7k	2-furyl	*t*-butoxy	$CH_2O(CH_2)_2OH$	0.3	1.7	158 (2)/200	0.6 (1.0)/0.9
7l	2-furyl	*i*-propoxy	$CH_2O(CH_2)_2OH$	0.3	0.9	145 (25)/164	
6e	2-furyl	phenyl	MTM	1	0.6	191 (6)/259	1.1 (4.5)/1.4
7m	2-furyl	phenyl	MOM	2.3	2.1	115 (50)/223	

[a] Concentration of test compound to give a change of 0.01 OD/h expressed as a ratio to the concentration of paclitaxel. [b] IC_{50} human colon tumor cell line sensitive to paclitaxel. [c] Ratio of IC_{50} for HCT-116 MDR resistant cell line /IC_{50} for HCT-116 sensitive cell line. [d] Madison Murine Lung Carcinoma. M109 tumors implanted ip and the drug given ip on days 5 and 8 post implantation. Values are %T/C analogue (maximum tolerated dose)/% T/C for paclitaxel at a historically determined efficacious dose but does not represent the MTD. %T/C values of greater than 125% are considered active. [e] M109 tumors implanted subcutaneously and the drug administered iv every day ×5 beginning 4 days post implant. Activity is expressed as LCK of analogue (maximum tolerated dose)/LCK for paclitaxel at a historically determined efficacious dose but does not represent the MTD. An LCK of 1 is considered an active result.

or *iso*-butenyl moiety (**6f**) was also effective in combination with a 3′-*N*-Boc group at providing improved potency against the sensitive and MDR-resistant HCT-116 cell line. Potency in the tubulin assay was equivalent or better than paclitaxel for these taxanes.

Compounds with R/S ratios less than 5 were then evaluated for in vivo activity in the paclitaxel-sensitive Ip M109 Madison murine lung carcinoma model.[19] Only compounds **6a**, **7g**, and **7k** achieved an active result (T/C of greater than 125%). The two most active C-7 paclitaxel ethers **6a** and **7k** were then evaluated in the HCT/VM46 MDR resistant distal tumor model.[20] The 3′-*N*-Boc-7-MTM ether **6a** did achieve an active result of 1 LCK[21] in this experiment, but paclitaxel also achieved an equivalent result in this experiment. The C-3′-furyl-3′-*N*-Boc-7-methoxy-2-hydroxyethyl ether **7k** failed to show efficacy in the HCT/VM46 tumor model. The general lack of antitumor efficacy (T/C > 125%) in the Ip M109 tumor model for most of the compounds in Table 1 appears to stem from their low therapeutic index. All the compounds, with the exception of **6a** and **7g**, which were active in the Ip model, had MTDs[22] ranging from the extremely potent 0.32 mg/kg for **7i** to 5 mg/kg for **7f**. These MTDs were significantly lower than the 40−60 mg/kg MTDs necessary to achieve antitumor efficacy for paclitaxel (**1**) and **7a**. These results show that while the side chain modifications provided improved in vitro potency, this potency corresponded to a reduction in antitumor efficacy. Therefore, our goal shifted to identifying C-7 paclitaxel ethers with an efficacy advantage relative to paclitaxel.

To optimize for in vivo efficacy, the Ip M109 model[19] was used to develop the SAR. Active compounds were then evaluated in a distal Sc M109 model[23] (see Table 2). C-7 MTM, MOM, and methoxy-2-hydroxyethyl ethers showed activity in the Ip M109. Three of the eight compounds active in the Ip model were MTM derivatives (**6b**, **6c**, **6e**) along with three methoxy-2-hydroxyethyl derivatives (**7d**, **7k**, **7l**), and two MOM derivatives (**7a**, **7h**).

The SAR at the C-3′ position revealed that five (**7a**, **7d**, **6b**, **6c**, **7h**) out of the eight compounds active in the Ip model possessed the 3′-phenyl group of the natural product, while three 2-furyl derivatives (**7k**, **7l**, **6e**) gave active results. These compounds were subsequently tested in the distal model, and the C-3′ phenyl derivatives **4**, **7a**, **7d** gave activity, while the only 2-furyl derivative to show activity was **6e**. Compound **6e** was 5-fold more potent in vitro and had a significantly lower MTD in the distal site model as compared with the related C-3′ phenyl derivative **4**. Our experience with potent in vivo actives (see Table 1) coupled with the lack of activity for other analogues with this side chain in the A2780 human ovarian tumor xenograft model[24] indicated that better efficacy could best be achieved with compounds that had in vitro and in vivo potency similar to paclitaxel. For this reason, we chose to focus on C-3′ phenyl derivatives.

Modification of the 3′-N substituent revealed that three compounds (**7a**, **7d**, **6e**) out of the eight compounds active in the Ip model were benzamide derivatives. The remaining five compounds active in the Ip model were carbamate derivatives (two *iso*-propoxylcarbamates **6c**, **7l**; one Boc derivative **7j**; one *n*-butyoxycarbamate **6b**; and one benzylcarbamate **7h**). The benzylcarbamate **7h** was not tested in the distal model due to its high MTD and marginal activity in the Ip model. In the Sc M109 model, only the benzamides **4**, **7a**, **7d**, and **6e** gave active results.

Analysis of the SAR indicated a combination of a C-7 ether with the paclitaxel side chain was optimal for achieving distal site antitumor activity (**4**, **7a**, **7d**).

Compound **7d** was clearly inferior to the MTM ether **4** and MOM ether **7a** in the A2780 xenograft model[24] and was dropped from further consideration. Both **4** and **7a** were dosed intravenously to rats and plasma samples analyzed to determine the stability of the parent compounds in vivo. Plasma samples indicated that 32% of the dose of the MOM ether **7a** was converted to paclitaxel, while no paclitaxel was detected after dosing BMS-184476 (**4**). Because the MOM ether **7a** was functioning in vivo as a partial prodrug for paclitaxel, it was not considered for further development.[25] BMS-184476 (**4**) was then directly compared with paclitaxel

Table 3. Activity of BMS-184476 (**4**) in Human Tumor Xenografts

	BMS-184476 (**4**)			paclitaxel (**1**)	
tumor	schedule	OD[a]	LCK[b] (c/t)	OD[a]	LCK (c/t)
A2780 (*Ovarian* ca.)	q2d×5; 8[d]	30[c]	(8/8)	2[c]	6.1 (0/8)
L2987 (*Lung* ca.)	q2d×5; 26	22[c]	2.6 (0/7)	30[c]	1.3 (0/8)
HCT/pk (*Colon* ca.)	q2d×5; 10	24[c]	(6/8)	40[c]	2.8 (1/8)
HOC79, ip (*Ovarian* ca.)	q2d×5; 12	20[c]	321%[e] (1/7)	30[c]	273[e] (0/8)

[a] OD, optimal dose (i.e., the next highest dose was excessively toxic). All injections iv except where otherwise indicated. [b] LCK, gross log cell kill, with cures/total (c/t) shown in parentheses. [c] MTD (maximum tolerated dose) probably reached. [d] q2d×5 = test compound administered every other day ×5. The number after the semicolon refers to the day treatment was initiated relative to tumor implantation. [e] Data shown are median survival times % T/C values. Numbers in parentheses following median survival times refer to the number of animals surviving.

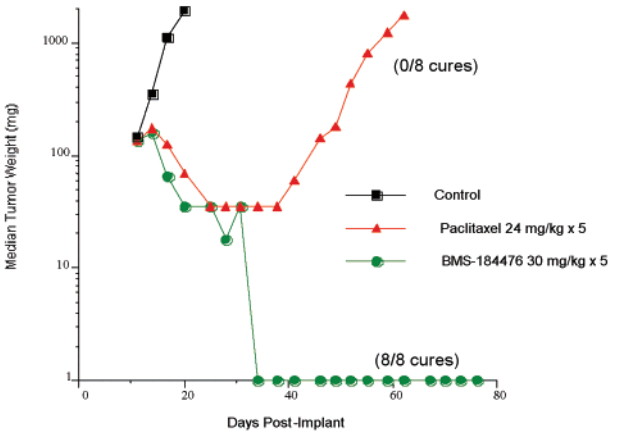


Figure 1. Optimal antitumor effects of BMS-184476 and paclitaxel (**1**) vs staged A2780. The optimal dose is reported (i.e., the next highest tested dose was excessively toxic). Compound was administered at the indicated doses by the intravenous route, every other day for a total of 5 doses starting 8 days after tumor implantation (q2dx5;d.8, iv). The incidence of cured mice/total is reported next to the graph corresponding to each compound.

in several human tumor xenograft models of varying responsiveness or resistance to paclitaxel to gauge the clinically potential of this novel taxane (see Table 3).

In A2780, a human ovarian tumor xenograft model that demonstrated excellent sensitivity to paclitaxel, BMS-184476 (**4**) was curative as compared with paclitaxel which achieved a very active 6.1 LCK but with no cures (see Figure 1). In the L2987 human lung carcinoma model, BMS-184476 (**4**) was also more efficacious (greater than 1 LCK) than paclitaxel.

Against HCT/pk,[26] BMS-184476 (**4**) was active with 6 of 8 cures as compared to a 2.8 LCK with 1 cure for paclitaxel. HCT/pk is an experimentally derived tumor model developed by exposing HCT-116 human colon tumor cells to concentrations of paclitaxel equivalent to plasma concentrations that can be achieved clinically for paclitaxel. HCT/pk expresses resistance to paclitaxel as compared to the parental line and is characterized by the MDR phenotype.

BMS-184476 (**4**) was also tested in HOC79,[27] a clinically derived ovarian carcinoma model. This model was our most paclitaxel-resistant ovarian carcinoma model derived from TAXOL-treated and unresponsive patients. In this model, BMS-184476 (**4**) showed superior activity to paclitaxel. On the basis of the impressive antitumor activity observed for BMS-184476 relative to paclitaxel,[28] this analogue was selected for clinical development.

Conclusion

The synthesis and biological activity of C-7 ethers of paclitaxel has been described. Variation of the C-7 ether group as well the 3′ position led to the discovery of BMS-184476, which demonstrated preclinical antitumor activity superior to paclitaxel and is presently being evaluated in clinical trials.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer and chemical shifts reported in ppm downfield from a TMS standard. ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz. High-resolution mass spectral analysis was performed on a Kratos MS50RF spectrometer in the FAB mode using *m*-nitrobenzyl alcohol as the matrix. Column chromatography was performed using silica gel 60 (200−400 mesh). Unless otherwise noted, materials were obtained from commercial sources and used without further purification. The *β*-lactams used in this paper were prepared according to the procedures outlined in the patent literature.[13,14]

2′-Triethylsilyl Paclitaxel (2). To a solution of paclitaxel (8.1 g, 9.49 mmol) in 40 mL of pyridine and 40 mL of methylene chloride at 0 °C was added TESCl (6.3 mL, 37.8 mmol). The solution was stirred at 0 °C for 1 h and then diluted with EtOAc and washed with water and brine. The organic fraction was dried over $MgSO_4$ and concentrated, and the residue was chromatographed over silica gel (3:1 hexane/EtOAc, then 2:1, and finally with 1:1 hexane/EtOAc) to give 9.34 g of 2′-triethylsilyl paclitaxel (95%).

2′-Triethylsilyl-7-methylthiomethylpaclitaxel (3). To a solution of 2′-triethylsilyl paclitaxel (20.1 g, 20.8 mmol) in 200 mL of acetonitrile was added dimethyl sulfide (16 mL, 216 mmol), and the solution was cooled to 0 °C. At 0 °C, benzoyl peroxide (20.2 g, 83.5 mmol) was added, and the solution was stirred for 90 min. The reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ and then brine. The solution was dried over $MgSO_4$ and concentrated, and the residue was chromatographed over silica gel (2:1 hexane/EtOAc) to give 20.4 g of product (95%). FABMS (NOBA) M+Na calcd for $C_{55}H_{69}NSiSO_{14}$: 1050. Found: 1050. IR (KBr) 3442, 1724, 1242, 1066 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J = 6.9 Hz, 2H), 7.73 (d, J = 6.9 Hz, 2H), 7.60−7.23 (m, 11H), 7.11 (d, J = 8.7 Hz, 1H), 6.54 (s, 1H), 6.22 (t, J = 9.3 Hz, 1H), 5.69 (d, J = 7.5 Hz, 2H), 4.95 (d, J = 8.1 Hz, 1H), 4.68 (d, J = 2.0 Hz, 1H), 4.65 (s, 1H), 4.27 (m, 3H), 3.88 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 2.52 (s, 3H), 2.39 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.85 (m, 2H), 1.75 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 0.80 (t, J = 7.8 Hz, 9H), 0.43 (m, 6H).

7-Methylthiomethylpaclitaxel (4). To a solution of the 2′-triethylsilyl-7-methylthiomethyl paclitaxel (3.9 g, 3.79 mmol) in 100 mL of acetonitrile at 0 °C was added 1 N HCl (7.6 mL, 7.6 mmol) and stirred 1 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. The solution was concentrated and chromatographed over silica gel (1:1 hexane/EtOAc) to give 3.3 g of product (95%). ESIMS M+H calcd for $C_{49}H_{55}NO_{14}S$: 914. Found: 914. IR (KBr) 3441, 1739, 1724, 1242, 1066, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 7.4 Hz, 2H), 7.63−7.31 (m, 11H), 7.04 (d, J = 9 Hz, 1H), 6.50 (s, 3H), 6.19 (t, J = 7.8 Hz, 1H), 5.79 (dd, J = 9, 2.4 Hz, 1H), 5.67 (d, J = 6.9 Hz, 1H), 4.93 (d, J = 7.8 Hz, 1H), 4.79 (d, J = 2.4 Hz, 1H), 4.66 (s, 2H), 4.28 (m, 2H), 4.18 (d, J = 8.4 Hz, 1H), 3.85 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 2.38 (s, 3H), 2.31 (d, J = 9 Hz, 2H), 2.17 (s, 3H), 2.11 (s, 3H), 1.93 (s,

3H), 1.93−1.56 (m, 1H), 1.76 (s, 3H), 1.21 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H). Anal. Calcd. For $C_{49}H_{55}NO_{14}S$; C, 64.39; H, 6.06; N, 1.53. Found: C, 64.35; H, 6.24; N, 1.37.

7-Methylthiomethyl Baccatin III (5). To a solution of 7-methylthiomethyl paclitaxel (1.9 g, 2.08 mmol) in 20 mL of dichloromethane was added tetrabutylammonium borohydride (936 mg, 3.63 mmol), and the sample was stirred for 16 h. The solution was diluted with dichloromethane and washed with water, saturated bicarbonate, and brine. The organic fraction was then dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/EtOAc) to give 980 mg of 7-MTM baccatin III (72%). HRFABMS (NOBA) M+H calcd for $C_{33}H_{43}SO_{11}$: 647.2526. Found: 647.2551. IR (KBr) 3474, 1746, 1724, 1712, 1270, 1240, 1070 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.1 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 6.55 (s, 1H), 4.94 (d, J = 8.1 Hz, 1H), 4.83 (br q, J = 5.1 Hz, 1H), 4.66 (ABq, J = 14.7, 12.3 Hz, 2H), 4.30 (m, 2H), 4.13 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 6.6 Hz, 1H), 2.79 (m, 1H), 2.27 (s, 3H), 2.25 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.10 (s, 4H), 1.81 (m, 1H), 1.72 (s, 3H), 1.61 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.3, 170.8, 169.3, 167.0, 144.2, 132.6, 132.1, 130.1, 129.4, 128.6, 83.9, 80.9, 78.7, 75.7, 74.5, 73.9, 67.9, 57.6, 47.6, 42.7, 38.3, 26.7, 22.6, 21.0, 20.1, 15.2, 15.0, 10.8.

Representine Coupling Procedure. To a solution of hexamethyldisilazane (HMDS) (0.275 mL, 1.30 mmol) in 8 mL of THF was added a solution of *n*-BuLi (0.48 mL, 2.5 M in hexanes, 1.20 mmol) and stirred 5 min at −55 °C. To this solution was added 7-MTM baccatin III (639 mg, 0.99 mmol) in 8 mL of THF and stirred for 10 min before addition of an 8 mL solution of azetidinone (575 mg, 1.52 mmol) in THF. The cold bath was removed and replaced with a 0 °C bath, and the reaction was stirred for 30 min. The solution was diluted with EtOAc and washed with saturated NH_4Cl solution, dried over $MgSO_4$, and concentrated. The residue was chromatographed over silica gel. To a solution of the silyl ether obtained above (269 mg, 0.26 mmol) in 6 mL of THF was added tetrabutylammonium fluoride (0.3 mL, 1.0 M in THF, 0.3 mmol) and stirred 10 min. The solution was diluted with EtOAc and washed with brine, dried over $MgSO_4$, and concentrated, and the residue was chromatographed over silica gel (1:1 hexane/EtOAc) to give the title compound.

3′-N-Boc-7-methylthiomethyl Paclitaxel (6a) (95%). FABMS (NOBA) M+Na calcd for $C_{47}H_{59}NO_{15}SNa$: 932. Found: 932. IR (film) 3440, 1720, 1370, 1242, 1170, 1108, 1066, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.35 (m, 5H), 6.52 (s, 1H), 6.16 (t, J = 8.7 Hz,1H), 5.64 (d, J = 6.9 Hz, 1H), 5.43 (br d, J = 9.3 Hz, 1H), 5.24 (br d, J = 8.1 Hz, 1H), 4.91 (d, J = 8.1 Hz, 1H), 4.63 (m, 3H), 4.26 (m, 2H), 4.14 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 6.9 Hz, 1H), 3.46 (d, J = 5.4 Hz, 1H), 2.77 (m, 1H), 2.34 (s, 3H), 2.27 (m, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.79 (m, 2H), 1.72 (s, 3H), 1.32 (s, 9H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.7, 170.3, 169.2, 167.0, 155.3, 140.3, 138.4, 133.7, 133.2, 130.2, 129.1, 128.8, 128.7, 128.0, 126.7, 83.9, 81.3, 80.2, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 73.6, 72.3, 57.4, 56.1, 47.1, 43.2, 35.3, 32.8, 28.2, 26.5, 22.6, 21.0, 15.1, 14.6, 10.9.

3′-*N*-Butoxycarbamoyl-7-methylthiomethyl Paclitaxel (6b) (77%). FABMS (NOBA) M+H calcd for $C_{47}H_{60}NO_{15}S$: 910. Found: 910. IR (KBr) 3444, 1722, 1372, 1242, 1108, 1066, 1026, 988 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.39−7.11 (m, 5H), 6.51 (s, 1H), 6.20 (t, J = 8.7 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.56 (d, J = 9.3 Hz, 1H), 5.29 (d, J = 8.4 Hz, 1H), 4.91 (d, J = 8.1 Hz, 1H), 4.65 (br s, 3H), 4.27 (m, 2H), 4.15 (d, J = 8.4 Hz, 1H), 3.97 (m, 2H), 3.84 (d, J = 6.9 Hz, 1H), 3.45 (d, J = 4.8 Hz, 1H), 2.78 (m, 1H), 2.33 (s, 6H), 2.25 (d, J = 8.7 Hz, 2H), 2.17 (s, 3H), 2.10 (s, 3H), 1.96 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.62 (s, 1H), 1.48 (m, 2H), 1.19 (m, 5H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.9, 172.3, 170.5, 169.2, 167.0, 156.3, 140.1, 138.4, 133.8, 133.4, 130.2, 129.2, 129.0, 128.9, 128.7, 128.2, 126.8, 125.3, 83.9, 81.4, 78.8, 77.3, 76.0, 75.6, 74.6, 74.1, 73.7, 72.2, 65.4, 57.5, 56.5, 47.2, 43.2, 35.4, 26.6, 22.6, 21.5, 21.0, 18.9, 15.1, 14.7, 13.7, 10.9. Anal. Calcd. for $C_{46}H_{59}NSO_{15}$; C, 62.03; H, 6.53; N, 1.54. Found: C, 62.16; H, 6.45; N, 1.57.

3′-*N*-Isopropoxycarbamoyl-7-methylthiomethyl Paclitaxel (6c) (84%). FABMS (NOBA) M+Na calcd for $C_{46}H_{57}NO_{15}SNa$: 918. Found: 918. IR (KBr) 3460, 1720, 1266, 1244, 1230 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.32 (m, 5H), 6.51 (s, 1H), 6.18 (t, J = 8.7 Hz, 1H), 5.65 (d, J = 6.6 Hz, 1H), 5.50 (d, J = 9.3 Hz, 1H), 5.28 (d, J = 8.4 Hz, 1H), 4.91 (d, J = 8.1 Hz, 1H), 4.77 (m, 1H), 4.64 (br s, 3H), 4.26 (m, 2H), 4.15 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 6.9 Hz, 1H), 3.44 (d, J = 5.1 Hz, 1H), 2.78 (m, 1H), 2.34 (s, 3H), 2.25 (d, J = 9 Hz, 2H), 2.17 (s, 3H), 2.14 (s, 1H), 2.10 (s, 3H), 1.96 (s, 3H), 1.83 (m, 1H), 1.73 (s, 3H), 1.15 (m, 12H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.8, 170.4, 169.2, 167.0, 156.3, 140.1, 138.3, 133.7, 133.3, 130.2, 129.1, 128.8, 128.6, 128.1, 126.8, 83.8, 81.4, 78.7, 76.0, 75.5, 74.5, 74.0, 73.6, 72.2, 68.9, 57.5, 56.4, 47.1, 43.2, 35.3, 32.9, 26.6, 22.6, 22.0, 21.9, 20.9, 15.1, 14.6, 10.9. Anal. Calcd. For $C_{46}H_{57}NSO_{15}$; C, 61.66; H, 6.41; N, 1.56. Found: C, 61.63; H, 6.36; N, 1.68.

3′-Furyl-3′-*N*-Boc-7-methylthiomethyl Paclitaxel (6d) (88%). FABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{16}S$: 900. Found: 900. IR (film) 3442, 1720, 1242, 1066, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.38 (s, 1H), 6.53 (s, 1H), 6.34 (d, J = 3.2 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 6.17 (t, J = 8.1 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.29 (m, 2H), 4.92 (d, J = 8.0 Hz, 1H), 4.70 (m, 1H), 4.64 (d, J = 4.6 Hz, 2H), 4.29 (m, 2H), 4.14 (d, J = 8.3 Hz, 1H), 3.86 (d, J = 6.8 Hz, 1H), 3.37 (d, J = 5.8 Hz, 1H), 2.77 (m, 1H), 2.38 (s, 3H), 2.32 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.75 (m, 6H), 1.33 (s, 9H), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.6, 170.3, 169.2, 167.0, 155.2, 151.3, 142.4, 140.4, 133.7, 133.2, 130.2, 129.1, 128.7, 110.7, 107.4, 83.9, 81.2, 80.5, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 72.5, 71.8, 57.4, 51.7, 47.2, 43.2, 35.2, 32.8, 28.1, 26.4, 22.6, 20.9, 15.2, 14.6, 10.9, 8.3.

3′-Furyl-7-methylthiomethyl Paclitaxel (6e) (95%). FABMS (NOBA) M+ calcd for $C_{47}H_{53}NO_{15}S$: 903. Found: 903. IR (film) 3432, 1722, 1240, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 7.2 Hz, 2H), 7.61−7.36 (m, 7H), 6.91 (d, J = 9 Hz, 1H), 6.51 (s, 1H), 6.38 (s, 2H), 6.19 (t, J = 7.8 Hz, 1H), 5.87 (dd, J = 9, 2.4 Hz, 1H), 5.67 (d, J = 6.9 Hz, 1H), 4.93 (d, J = 8.1 Hz, 1H), 4.80 (m, 1H), 4.65 (ABq, J = 14.7, 2.4 Hz, 2H), 4.28 (m, 2H), 4.17 (d, J = 8.4 Hz, 1H), 3.86 (d, J = 6.9 Hz, 1H), 3.56 (d, J = 5.4 Hz, 1H), 2.78 (m, 1H), 2.41 (s, 3H), 2.33 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.83 (m, 1H), 1.77 (s, 1H), 1.74 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H). Anal. Calcd. For $C_{47}H_{53}NSO_{15}$; C, 62.45; H, 5.91; N, 1.55. Found: C, 62.18; H, 6.02; N, 1.59.

3′-Isobutenyl-3′-*N*-Boc-7-methylthiomethyl Paclitaxel (6f) (78%). FABMS (NOBA) M+ calcd for $C_{45}H_{61}NO_{15}S$: 888. Found: 888. IR (KBr) 3452, 1724, 1242, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 6.54 (s, 1H), 6.11 (t, J = 9 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.29 (br d, J = 8.4 Hz, 1H), 4.94 (d, J = 7.8 Hz, 1H), 4.81−4.69 (m, 3H), 4.65 (Abq, J = 15, 2.7 Hz, 2H), 4.30−4.14 (m, 4H), 3.86 (d, J = 6 Hz, 1H), 3.37 (br s, 1H), 2.79 (m, 1H), 2.34 (s, 4H), 2.17 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.82 (m, 1H), 1.74 (s, 9H), 1.39 (s, 9H), 1.23 (d, J = 3 Hz, 1H), 1.20 (s, 3H), 1.18 (s, 3H). Anal. Calcd. For $C_{45}H_{61}NSO_{15}$; C, 60.86; H, 6.92; N, 1.58. Found: C, 60.25; H, 6.36; N, 1.51.

Representative Procedure for Conversion of Methylthiomethyl Ether to Methoxyalkoxy Ethers. To a solution of the 7-methylthiomethyl paclitaxel (48 mg, 0.047 mmol) in 1 mL of dichloromethane was added alcohol (20 mg, 0.6 mmol) and the solution cooled to 0 °C. Then NIS (13 mg, 0.058 mmol) and triethylsilyltriflate (1 μL, 0.004 mmol) were added and the dark red solution stirred 30 min and then warmed to 25 °C for 30 min. The solution was diluted with EtOAc and washed with 10% NaS_2O_8 and bicarbonate, dried ($MgSO_4$), and

concentrated. The residue was chromatographed over silica gel (1:1 hexane/EtOAc) to give the desired ether.

7-Methoxymethyl Paclitaxel (7a) (72%). ESIMS M+H calcd for $C_{49}H_{56}NO_{15}$: 898. Found: 898. IR(KBr) 3436, 1724, 1242, 1106, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 7.2 Hz, 2H), 7.62−7.30 (m, 11H), 7.06 (d, J = 8.5 Hz, 1H), 6.30 (s, 1H), 6.16 (t, J = 8.7 Hz, 1H), 5.78 (d, J = 9.0 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 4.90 (d, J = 8.1 Hz, 1H), 4.77 (m, 1H), 4.65 (ABq, J = 15.6, 7.8 Hz, 2H), 4.28 (d, J = 8.2 Hz, 1H), 4.16 (d, J = 8.2 Hz, 1H), 4.08 (m 1H), 3.81 (d, J = 6.9 Hz, 1H), 3.63 (d, J = 4.8 Hz, 1H), 3.28 (s, 3H), 2.77 (m, 1H), 2.34 (s, 3H), 2.29 (d, J = 8.4 Hz, 2H), 2.21 (s, 3H), 1.94 (m, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1.17 (s, 6H). Anal. Calcd. for $C_{49}H_{55}NO_{15}$; C, 65.54; H, 6.17; N, 1.56. Found: C, 65.62; H, 6.24; N, 1.37.

7-Methoxy-(2-methoxyethyl) Paclitaxel (7b) (69%). ESIMS M−H calcd for $C_{51}H_{58}NO_{16}$: 940. Found: 940. IR (KBr) 3434, 1724, 1242, 1109, 1025, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.2 Hz, 2H), 7.63−7.31 (m, 11H), 7.08 (d, J = 9 Hz, 1H), 6.28 (s, 1H), 6.16 (t, J = 8.7 Hz, 1H), 5.79 (dd, J = 9,2.4 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 4.91 (d, J = 8.7 Hz, 1H), 4.77 (m, 3H), 4.23 (Abq, J = 37, 8.3 Hz, 2H), 4.10 (m, 1H), 3.82 (d, J = 6.8 Hz, 1H), 3.74 (m, 1H), 3.67 (d, J = 4.7 Hz, 1H), 3.49 (m, 3H), 3.35 (s, 3H), 2.86 (m, 1H), 2.35 (s, 3H), 2.29 (d, J = 9 Hz, 2H), 2.18 (s, 3H), 1.95 (m, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.61 (s, 1H), 1.18 (s, 6H). Anal. Calcd. for $C_{51}H_{59}NO_{16}$; C, 65.03; H, 6.31; N, 1.49. Found: C, 64.64; H, 6.08; N, 1.51.

7-Methoxyethyl Paclitaxel (7c) (72%). ESIMS M+H calcd for $C_{50}H_{58}NO_{15}$: 912. Found: 912. IR (KBr) 3434, 1725, 1242, 1109, 1025, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.2 Hz, 2H), 7.63−7.30 (m, 11H), 7.08 (d, J = 9 Hz, 1H), 6.30 (s, 1H), 6.17 (t, J = 7.8 Hz, 1H), 5.79 (dd, J = 9,2.4 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 4.92 (d, J = 8.0 Hz, 1H), 4.78 (m, 1H), 4.71 (Abq, J = 12.3, 8.1 Hz, 2H), 4.23 (Abq, J = 37, 8.4 Hz, 2H) 4.08 (m, 1H), 3.82 (d, J = 6.9 Hz, 1H), 3.66 (m, 2H), 3.41 (m, 1H), 2.83 (m, 1H), 2.35 (s, 3H), 2.32 (d, J = 9 Hz, 2H), 2.19 (s, 3H), 1.99 (m, 1H), 1.79 (s, 3H), 1.75 (s, 4H), 1.89 (s, 6H), 1.41 (t, J = 7.2 Hz, 3H). Anal. Calcd. for $C_{50}H_{57}NO_{15}$; C, 65.85; H, 6.30; N, 1.54. Found: C, 65.81; H, 6.29; N, 1.55.

7-Methoxy-(2-hydroxyethyl) Paclitaxel (7d) (60%). IR (KBr) 3434, 1724, 1242, 1026, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 7.2 Hz, 2H), 7.74 (d, J = 7.2 Hz, 2H), 7.62−7.32 (m, 11H), 7.05 (d, J = 9 Hz, 1H), 6.33 (s, 1H), 6.15 (t, J = 9.3 Hz, 1H), 5.77 (dd, J = 9, 2.4 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 4.90 (d, J = 8 Hz, 1H), 4.77 (m, 1H), 4.74 (s, 2H), 4.22 (Abq, J = 39, 8.4 Hz, 2H), 3.81 (d, J = 6.9 Hz, 1H), 3.65 (m, 3H), 3.50 (m, 1H), 2.77 (m, 1H), 2.35 (s, 3H), 2.29 (d, J = 9 Hz, 2H), 2.18 (s, 4H), 1.92 (m, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.29 (s, 3H), 1.18 (s, 6H). Anal. Calcd. for $C_{50}H_{57}NO_{16}$; C, 64.71; H, 6.19; N, 1.51. Found: C, 64.64; H, 6.21; N, 1.50.

3′-*N*-Boc-7-methoxymethyl Paclitaxel (7f) (76%). HR-FABMS (NOBA) M+H calcd for $C_{47}H_{60}NO_{16}$: 894.3912. Found: 894.3943. IR (film) 3440, 1722, 1370, 1242, 1106, 1068, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.3 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.36 (m, 5H), 6.33 (s, 1H), 6.16 (t, J = 8.8 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 5.40 (d, J = 9.5 Hz, 1H), 5.24 (br d, J = 8.1 Hz, 1H), 4.90 (d, J = 7.9 Hz, 1H), 4.68 (d, J = 7.6 Hz, 1H), 4.62 (d, J = 7.6 Hz, 1H), 4.28 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 8.2 Hz, 1H), 4.08 (m, 1H), 3.82 (d, J = 6.8 Hz, 1H), 3.40 (d, J = 5.2 Hz, 1H), 3.27 (s, 3H), 2.77(m, 1H), 2.33 (s, 3H), 2.27 (d, J = 8.9 Hz, 2H), 2.19 (s, 3H), 1.94 (m, 1H), 1.86 (s, 3H), 1.73 (s, 3H), 1.72 (m, 1H), 1.63 (br s, 1H), 1.32 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 172.7, 170.2, 169.4, 167.0, 155.3, 140.2, 138.3, 133.7, 133.3, 130.2, 129.1, 128.8, 128.7, 128.1, 126.8, 98.2, 84.3, 81.2, 80.2, 79.9, 78.6, 75.3, 74.5, 73.6, 72.3, 57.3, 56.1, 55.8, 46.9, 43.2, 35.4, 35.3, 28.2, 26.5, 22.6, 20.9, 14.7, 10.7.

3′-*N*-Boc-7-(methoxy-2-hydroxyethyl) Paclitaxel (7g) (46%). HRFABMS (NOBA) M+H calcd for $C_{48}H_{62}NO_{17}$: 924.4018. Found: 924.4009. IR (film) 3440, 1720, 1242, 1070, 1026, 756 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.31 (m, 5H), 6.35 (s, 1H), 6.15 (t, J = 8.7 Hz, 1H) 5.63 (d, J = 6.9 Hz, 1H), 5.44 (br d, J = 9.2, 1H), 5.24 (br s, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.74 (s, 2H), 4.59 (br s, 1H), 4.27 (d, J = 8.4 Hz, 1H), 4.11 (m, 2H), 3.81 (d, J = 6.8 Hz, 1H), 3.66 (m, 3H), 3.48 (m, 2H), 2.75 (m, 1H), 2.33 (s, 3H), 2.26 (m, 2H), 2.18 (s, 3H), 1.90 (m, 2H), 1.87 (s, 3H), 1.78 (m, 1H), 1.72 (s, 3H), 1.32 (s, 9H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.8, 170.3, 169.6, 167.0, 155.3, 140.2, 138.3, 133.7, 133.3, 130.2, 129.1, 128.8, 128.7, 128.0. 126.8, 96.8. 84.1, 81.2, 80.2, 79.4, 78.6, 76.5, 75.2, 74.5, 73.6, 72.3, 70.0, 61.8, 57.3, 56.2, 46.9, 43.2, 35.3, 35.0, 28.2, 26.5, 22.6, 21.0, 20.9, 14.6, 10.6.

3′-*N*-Benzyloxycarbamoyl-7-methoxymethyl Paclitaxel (7h) (78%). ESIMS M+H calcd for $C_{50}H_{58}NO_{16}$: 928. Found: 928. IR (KBr) 3440, 1723, 1242, 1040, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J = 7.2 Hz, 2H), 7.63−7.22 (m, 13H), 6.33 (s, 1H), 6.17 (t, J = 9 Hz, 1H), 5.71 (d, J = 9.0 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 5.36 (br d, J = 9 Hz, 1H), 5.02 (ABq, J = 31.2, 12.1 Hz, 2H), 4.90 (d, J = 8.1 Hz, 1H), 4.66 (m, 2H), 4.23 (ABq, J = 15.6, 7.5 Hz, 2H), 4.09 (dd, J = 16.8, 6.6 Hz, 1H), 3.81 (d, J = 6.9 Hz, 1H), 3.45 (br s, 1H), 3.29 (s, 3H), 2.78 (m, 1H), 2.34 (s, 3H), 2.27−1.91 (m, 4H), 2.20 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H), 1.26 (s, 3H), 1.19 (s, 6H). Anal. Calcd. for $C_{50}H_{57}NO_{16}$; C, 64.71; H, 6.19; N, 1.51. Found: C, 64.74; H, 6.04; N, 1.56.

3′-Furyl-3′-N-Boc-7-methoxymethyl Paclitaxel (7i) (46%). HRFABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{17}$: 884.3705. Found: 884.3732. IR (film) 3442, 1720, 1268, 1242, 1040, 1026, 756 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39 (s, 1H), 6.35 (m, 2H), 6.30 (d, J = 3.2 Hz, 1H), 6.17 (t, J = 8.2 Hz, 1H) 5.65 (d, J = 6.9 Hz, 1H), 5.32 (d, J = 9.6, 1H), 5.24 (d, J = 9.8 Hz, 1H), 4.91 (d, J = 8.0 Hz, 1H), 4.69 (m, 2H), 4.62 (d, J = 7.5 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.10 (m, 2H), 3.84 (d, J = 6.9 Hz, 1H), 3.33 (d, J = 5.7 Hz, 1H), 3.27 (s, 3H), 2.77 (m, 1H), 2.37 (s, 3H), 2.31 (d, J = 9.0 Hz, 2H), 2.18 (s, 3H), 1.93 (m, 4H), 1.73 (m, 5H), 1.34 (s, 9H), 1.19 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 172.6, 170.2, 169.4, 167.0, 155.2, 151.3, 142.5, 140.2, 133.7, 133.3, 130.2, 129.1, 128.7, 110.7, 107.5, 98.2, 84.3, 81.1, 80.5, 79.8, 78.6, 75.3, 74.6, 72.5, 71.7, 57.4, 55.8, 51.7, 46.9, 43.2, 35.4, 35.2, 28.1, 26.4, 22.6, 21.0, 20.9, 14.6, 10.7.

3′-Furyl-3′-*N*-Boc-7-(methoxy-2-hydroxyethyl) Paclitaxel (7k) (66%). FABMS (NOBA) M+H calcd for $C_{46}H_{60}NO_{18}$ 914.3810. Found: 914.3781. IR (film) 3440, 1722, 1370, 1244, 1166, 1108, 1070, 1050, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.3 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39 (d, J = 1.7 Hz, 1H), 6.37 (s, 1H), 6.35 (m, 1H), 6.30 (d, J = 3.2 Hz, 1H), 6.16 (t, J = 8.3 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 5.27 (m, 2H), 4.91 (d, J = 8.0 Hz, 1H), 4.73 (m, 3H), 4.28 (d, J = 8.3 Hz, 1H), 4.16 (m, 2H), 3.84 (d, J = 6.9 Hz, 1H), 3.65 (m, 3H), 3.46 (m, 2H), 2.77 (m, 1H), 2.37 (s, 3H), 2.32 (m, 3H), 2.18 (s, 3H), 1.93 (m, 4H), 1.72 (m, 4H), 1.33 (s, 9H), 1.19 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.6, 170.4, 169.6, 167.0, 155.2, 151.3, 142.4, 140.2, 133.7, 133.4, 130.2, 129.1, 128.7, 110.7, 107.5, 96.7, 84.2, 81.1, 80.5, 79.4, 78.6, 76.5, 75.3, 74.5, 72.4, 71.7, 70.0, 61.8, 57.3, 51.7, 47.0, 43.3, 35.2, 35.0, 28.1, 26.4, 22.6, 21.1, 20.9, 14.6, 10.7.

3′-Furyl-3′-*N*-isopropoxycarbamoyl-7-(methoxy-2-hydroxyethyl) Paclitaxel (7l) (74%). HRFABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{18}$: 900.3654. Found: 900.3640. IR (film) 3440, 1722, 1242 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39 (s, 1H), 6.37 (s, 1H), 6.35 (m, 1H), 6.31 (m, 1H), 6.18 (t, J = 7.8 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.38 (m, 2H), 4.90 (d, J = 7.8 Hz, 1H), 4.75 (m, 4H), 4.28 (d, J = 8.4 Hz, 1H), 4.16 (m, 2H), 3.83 (d, J = 6.8 Hz, 1H), 3.66 (m, 3H), 3.50 (m, 2H), 2.77 (m, 1H), 2.37 (s, 3H), 2.29 (m, 2H), 2.18 (s, 3H), 1.91 (s, 4H), 1.75 (m, 2H), 1.72 (s, 4H), 1.20 (s, 3H), 1.18 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.3, 170.5, 169.6, 166.9, 155.8, 151.2, 142.5, 140.0, 133.7, 133.5, 130.2, 129.1, 128.7, 110.7, 107.6, 96.7, 84.1, 81.2, 79.2. 78.6, 75.3, 74.6, 72.3,

71.8, 70.0, 69.2, 61.8, 57.3, 52.0, 47.0, 43.3, 35.3, 35.0, 26.5, 22.5, 22.0, 21.9, 21.1, 20.9, 14.6, 10.7.

3′-Furyl-7-methoxymethyl Paclitaxel (7m) (47%). HRFABMS (NOBA) M+H calcd for $C_{47}H_{54}NO_{16}$: 888.3443. Found: 888.3432. IR (KBr) 3450, 1750, 1722, 1712, 1268, 1244, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 7.2 Hz, 2H), 7.57 (m, 1H), 7.45 (m, 6H), 6.92 (d, J = 9.2 Hz, 1H), 6.38 (s, 2H), 6.33 (s, 1H), 6.18 (t, J = 8.1 Hz, 1H), 5.86 (dd, J = 9.3, 2.4 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 4.91 (d, J = 8.4 Hz, 1H), 4.80 (m, 1H), 4.68 (d, J = 7.5 Hz, 1H), 4.62 (d, J = 7.5 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.16 (d, J = 8.4 Hz, 1H), 4.10 (dd, J = 10.5, 3.6 Hz, 1H), 3.84 (d, J = 6.9 Hz, 1H), 3.60 (d, J = 5.4 Hz, 1H), 3.27 (s, 3H), 2.78 (m, 1H), 2.40 (s, 3H), 2.34 (d, J = 8.7 Hz, 2H), 2.18 (s, 3H), 2.00 (m, 1H), 1.89 (s, 3H), 1.80 (s, 1H), 1.75 (s, 3H), 1.18 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.2, 170.4, 169.4, 167.0, 166.9, 150.8, 142.7, 139.9, 133.7, 133.6, 133.4, 132.1, 130.2, 129.2, 128.7, 127.1, 110.8, 108.0, 98.2, 84.3, 81.2, 79.8, 78.5, 75.3, 74.5, 72.3, 71.7, 57.4, 55.8, 50.2, 46.9, 43.2, 35.4, 29.5, 26.6, 22.6, 21.0, 20.9, 14.7, 10.7.

General Procedure for the Conversion of Methylthiomethyl Ethers to the Methyl Ether. Raney nickel (∼0.5 g) was added to a solution of 7-methylthiomethyl paclitaxel (73 mg, 0.0799 mmol) in 20 mL of EtOAc. This solution was hydrogenated on a Parr apparatus at 50 psi and ambient temperature for 6 h. Filtration through Celite, concentration in vacuo, and purification by flash chromatography over silica gel using 1:2 EtOAc:hexane as eluent provided 45 mg (65%) of the methyl ether.

7-Methoxy Paclitaxel (7e) (65%). HRFABMS (NOBA) M+H calcd for $C_{48}H_{53}NO_{14}$: 868.3544. Found 868.3511. IR (KBr) 3424, 3064, 2928, 1724, 1652, 1602, 1580, 1486, 1316, 1270, 1244, 1178 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.203 (s, 6H), 1.203−2.353 (obscured multiplets, 4H), 1749 (s, 3H), 1794 (s, 3H), 2.190 (s, 3H), 2.353 (s, 3H), 2.667 (m, 3H), 3.336 (s, 3H), 3.796 (d, 1H), 4.134 (d, 1H, 4.276 (d, 1H), 4.765 d, 1H), 4.875 (d, 1H), 5.630 (d, 1H), 5.768 (d, 1H), 6.155 (t, 1H), 6.333 (s, 1H), 7.096 (d, 1H), 7.348−8.150 (m, 15H).

3′-Furyl-3′-*N*-Boc-7-methoxy Paclitaxel (7j). Using a procedure similar as described above (16%). HRFABMS (NOBA) M+H calcd for $C_{44}H_{56}NO_{16}$: 854.3599. Found: 854.3608. IR (film) 3440, 1722, 1268, 1244, 1170, 1106, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.3, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.39 (m, 1H), 6.42 (s, 1H), 6.35 (m, 1H), 6.30 (m, 1H), 6.18 (t, J = 7.6 Hz, 1H), 5.64 (d, J = 7.0 Hz, 1H), 5.28 (m, 2H), 4.95 (d, J = 7.8 Hz, 1H), 4.69 (dd, J = 5.8, 2.1 Hz, 1H), 4.28 (d, J = 8.3 Hz, 1H), 4.13 (d, J = 8.3 Hz, 1H), 3.86 (m, 2H), 3.36 (d, J = 5.6 Hz, 1H), 3.32 (s, 3H), 2.70 (m, 1H), 2.38 (s, 3H), 2.32 (d, J = 8.9 Hz, 2H), 2.20 (s, 3H), 1.94 (s, 3H), 1.76 (m, 1H), 1.76 (m, 2H), 1.69 (m, 3H), 1.34 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (CDC_{l3}, 75.5 Hz) δ 202.2, 172.6, 170.4, 169.4, 167.1, 155.2, 151.3, 142.4, 140.0, 133.7, 130.2, 129.1, 128.7, 110.7, 107.5, 84.1, 81.5, 80.4, 78.6, 76.5, 74.7, 74.5, 72.5, 71.8, 57.6. 57.2, 51.7, 47.2, 43.3, 35.2, 32.3, 28.1, 26.5, 22.6, 21.1, 20.9, 14.6, 10.3.

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(17) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665−667. An $EC_{0.01}$ was determined for each analogue and expressed as a ratio relative to paclitaxel.

(18) HCT-116 is a human colon tumor cell line. The resistant HCT-116 cell line was established by exposing cells to VM-26 and establishing a cell line resistant to these drugs. The resistance is characterized by an MDR (multi-drug-resistance) phenotype. R/S ratio is defined as the IC_{50} in the HCT-116 MDR resistant cell line divided by the IC_{50} in the HCT-116 sensitive cell line. The R/S ratio for paclitaxel is approximately 300.

(19) Rose, W. *Cancer Treat. Rep.* **1981**, *65*, 299−312. In the Ip model, both the drug and tumor are delivered intraperitoneally (ip). %T/C refers to the median lifespan of the drug treated group/ lifespan of the control group × 100. %T/C values of greater than 125% are considered active.

(20) A distal tumor model refers to a model in which the tumor is implanted at a site distal to the site of administration of the drug. In the HCT/VM46 MDR tumor model, the tumor is implanted subcutaneously and the drug is administered intravenously every other day ×5. HCT/VM46 is a cell line in which resistance has been induced with VM-46 (topo II active agent). Resistance is characterized by an MDR phenotype.

(21) log cell kill (LCK) is defined as LCK = (T − C/TVDT) ÷ 3.32. T − C refers to the difference in days for the for the tumor to reach target size for the treated vs the control group. TVDT is the tumor volume doubling time which varies between in vivo models.

(22) MTD refers to the maximum tolerated dose that a given agent can be administered before undue toxicity is observed.

(23) Sc M109 refers to a distal tumor model in which the M109 murine tumor is implanted subcutaneously and the drug is administered intravenously.

(24) A2780 is a paclitaxel sensitive model that was used to further evaluate analogues of interest, unpublished results.

(25) Both **4** and **7a** were dosed IV to rats (three per group; 10 mg/kg; in 10:10:80 cremophor/ethanol/water by volume). Plasma samples were taken at 0, 15, 30 min, 1, 2, 4, 6, and 24 h and plasma samples analyzed by HPLC (UV or MS/MS detection).

(26) HCT/pk was established by exposing parental HCT-116 cells to concentrations of paclitaxel that mimic clinically achievable plasma levels. This resulted in a multidrug resistant tumor model that expressed elevated levels of P-glycoprotein, was cross resistant to a number of natural product anticancer agents, and was resistant to paclitaxel in vivo.

(27) The HOC79 tumor model was developed from a clinical sample of ovarian carcinoma cells derived from a woman whose tumor had relapsed following therapy with cisplatin, doxorubicin, and cytoxan and finally this tumor progressed in the face of paclitaxel therapy. As compared to other similar clinical specimens of ovarian carcinoma adapted to grow in nude mice, we consider HOC79 as the most resistant to paclitaxel treatment.

(28) For a more detailed discussion of the antitumor activity of BMS-184476, see: Rose, W. C.; Fairchild, C.; Lee, F. Y. F. *Cancer Chemother. Pharmacol.* **2001**, *47*, 97−105.

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