Design and Synthesis of a Combinatorial Chemistry Library of 7-Acyl, 10-Acyl, and 7,10-Diacyl Analogues of Paclitaxel (Taxol) Using Solid Phase Synthesis

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Received November 2, 2001

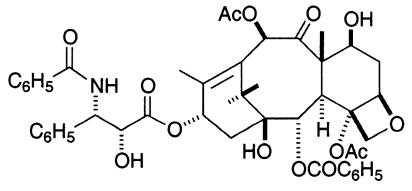
A series of 10-acyl and 7,10-diacyl paclitaxel analogues (**7a**−**7e** and **9a**−**9u**) have been synthesized using a solid phase combinatorial chemistry approach, and a second series of 7-acyl-10-deacetylpaclitaxel analogues have been prepared by conventional chemistry. In the first series, 10-deacetylpaclitaxel (**4**) was linked through its 2′-hydroxyl group using 1% polystyrene−divinyl benzene resin functionalized with butyldiethylsilane linker (PS-DES) and then acylated at the C-10 hydroxyl group with various anhydrides and dialkyl dicarbonates in the presence of $CeCl_3$. The resin-bound C-10 acylated paclitaxel derivatives (**6a**−**6e**) were then treated with various carboxylic acids in the presence of 1,3-diisopropylcarbodiimide in toluene to provide polymer-supported 7,10-diacylpaclitaxels (**8a**−**8u**). These 7-acyl- and 7,10-diacylpaclitaxels (**6a**−**6e** and **8a**−**8u**) were cleaved from the resin to give the 24 paclitaxel analogues **7a**−**7e** and **9a**−**9u**. Nine 7-acyl-10-deacetylpaclitaxel analogues were also prepared by conventional chemistry. Methodology to determine the tubulin-assembly activity of compounds prepared in small quantities by a combinatorial approach has been developed, and four analogues with improved tubulin-assembly activity as compared with paclitaxel were found, together with two analogues with improved cytotoxicity.

The natural diterpenoid paclitaxel (Taxol) (**1**) has become a major anticancer drug, with U.S. sales in 2000 estimated at over $1.5 billion.[1] Its interesting mechanism of action as a promoter of tubulin polymerization[2] and its commercial success have combined to maintain a high level of interest in the preparation of paclitaxel analogues with improved bioactivity, and large numbers of analogues have been prepared.[3,4] Among the compounds that have been prepared are many with modified acyl groups at the C-10[5−7] and C-7[8,9] positions, and one of the compounds in a clinical trial conducted by Bristol-Myers Squibb as a second-generation paclitaxel analogue is a C-7 derivative.[10]

Most of the studies to date have focused on paclitaxel analogues modified at one site only, although recently work has begun to appear where modifications are carried out at two or more sites simultaneously.[11−14] The preparation of analogues modified at more than one site can most efficiently be carried out by the methods of combinatorial chemistry, and thus the development of some general methods that could be applied to the synthesis of paclitaxel analogues was sought. To date, only one publication on the combinatorial synthesis of paclitaxel analogues has appeared. Xiao et al.[15] described the use of radio frequency encoded tags to do combinatorial chemistry on a resin, but, as discussed below, they were restricted to the preparation of analogues of the general structure **2**. In some related work Georg and co-workers have prepared a number of C-7[16] and C-10[17] analogues by a parallel synthesis approach, but this work has not yet been extended to the combinatorial synthesis of C-7, C-10 analogues.

Results and Discussion

Since combinatorial chemistry can be carried out efficiently by the "split and pool" technique in a resin-based methodology,[18] this approach was used in our synthetic design. The key question in the design of such an approach then becomes the selection of the attachment of the paclitaxel substrate to the resin. On the basis of the known SAR of paclitaxel[3,4,19] an attachment through the 2′-hydroxyl group appeared to be the most desirable, since modifications at this position are usually deleterious to activity. The previous resin-based approach[15] had attempted to link at this position, but had found that the THP ether linker or related alkoxy linkers were unsatisfactory due to steric hindrance. These workers thus developed an approach through a glutamic acid "handle" (**2**), but this



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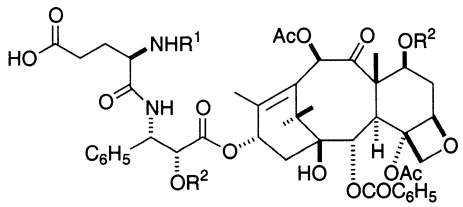

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limited them to preparing *N*-glutamyl analogues and precluded the synthesis of analogues with a normal *N*-benzoyl function. Since it was desired to develop a combinatorial approach to paclitaxel analogues that would allow the preparation of *N*-benzoyl analogues, the use of alter-

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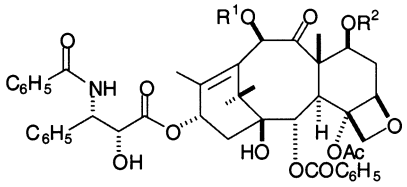
10.1021/np010552a CCC: $22.00
Published on Web 07/11/2002

Table 1. Tubulin Polymerization Data of 10-Acyl and 7,10-Diacyl Paclitaxels (**7a**−**7e** and **9a**−**9u**)



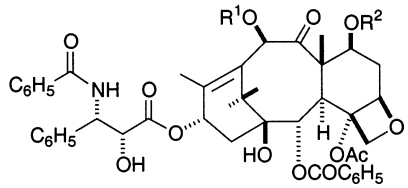
cmpd	R^1 C-10	R^2 C-7	% yield	% tubulin polymerization at the indicated dose (μM) 0.1	1.0	10	activity (rel. to PTX)[a]
1	$COCH_3$	H	NA	2.3	66	100	NA
7a	COC_6H_5	H	60	46	78	113	+++
7b	$COCH{=}CHCH_3$	H	56	26	80	117	+++
7c	$COOCH_2C_6H_5$	H	60	34	83	115	+++
7d	$COCH_2CH_3$	H	54	13	54	114	++
7e	$COCH_2CH_2CH_3$	H	69	NT	NT	NT	NA
9a	COC_6H_5	$COC_6H_4OCH_3$ (*m*)	62	22	52	78	+
9b	COC_6H_5	$COCH{=}C(CH_3)_2$	59	24	53	67	+
9c	COC_6H_5	$COCH_2Cl$	61	29	56	92	+
9d	COC_6H_5	COC_3H_5	58	30	61	91	+
9e	$COCH{=}CHCH_3$	COC_6H_5	57	33	66	81	+
9f	$COCH{=}CHCH_3$	$COCH_2Cl$	55	29	66	116	++
9g	$COCH{=}CHCH_3$	COC_3H_5	59	27	41	109	++
9h	$COOCH_2C_6H_5$	COC_6H_5	64	10	32	33	+
9i	$COOCH_2C_6H_5$	$COCH{=}C(CH_3)_2$	56	10	39	43	+
9j	$COOCH_2C_6H_5$	$COCH_2Cl$	66	0	20	48	−
9k	$COOCH_2C_6H_5$	$COCH_2CH_3$	59	0	3	24	−
9l	$COOCH_2C_6H_5$	COC_3H_5	56	10	26	53	+
9m	$COCH_2CH_3$	COC_6H_5	66	0	33	97	−
9n	$COCH_2CH_3$	$COCH_2Cl$	69	20	72	114	+++
9o	$COCH_2CH_3$	COC_3H_5	58	6	62	113	++
9p	$COCH_2CH_3$	$COCH_3$	52	5	44	111	++
9q	$COCH_2CH_3$	$COCH_2CH_2CH_2CH_3$	62	10	51	102	++
9r	$COCH_2CH_3$	$COCH{=}C(CH_3)_2$	54	20	51	120	++
9s	$COCH_2CH_3$	$COCH_2CH_3$	59	5	37	111	++
9t	$COCH_2CH_3$	$COCH_2CH_2CH_3$	58	4	52	123	++
9u	$COCH_2CH_2CH_3$	$COCH_2CH_3$	71	NT	NT	NT	NA

[a] Activity relative to paclitaxel (PTX). +++ More active than PTX at all three doses. ++ More active than PTX at two doses. + More active than PTX at one dose. − Less active than PTX. NT = Not tested. NA = Not applicable.

nate linkers was investigated. After some experimentation, the PS-DES resin was selected as being the most suitable for this purpose. The PS-DES resin is a 1% cross-linked polystyrene-divinyl benzene resin functionalized with a butyldiethylsilane linker, and it has the advantage of being stable under normal conditions. Although hydrosilanes can be reacted directly with alcohols,[20,21] it was found to be expedient to convert the resin to its chloro derivative **3** by treatment with 1,3-dichloro-5,5-dimethylhydantoin.[22,23] Treatment of the PS silyl chloride resin **3** with excess 10-deacetylpaclitaxel (**4**)[24] in CH_2Cl_2 in the presence of imidazole provided resin-bound 10-deacetylpaclitaxel (**5**), with a loading of 265 mg of **5** per gram of initial resin. Unreacted 10-deacetylpaclitaxel was recovered and was recycled after purification.

The conversion of the resin-bound paclitaxel derivatives to 7-acyl and 7,10-diacyl analogues of paclitaxel was investigated next as a test of the chemistry involved. A variety of acyl groups were thus selected, with the selection based in part on those groups that have given improved activity as single modifiers and in part on a desire to test a wide range of acyl groups. The actual conversions were accomplished by standard paclitaxel chemistry. The formation of 10-acyl derivatives was achieved using Holton's method.[25] Thus, the derivatized resin **5** was treated with excess of a carboxylic acid anhydride or an alkyl carbonate in THF, using a catalytic amount of $CeCl_3$, to give the 10-acyl derivatives **6a**−**6e**. Acylation at C-10 proceeded as selectively on the resin as in solution, and after washing to remove excess reagent and catalyst the product was cleaved from the resin using HF/pyridine in THF to give the 10-acyl derivatives **7a**−**7e**.

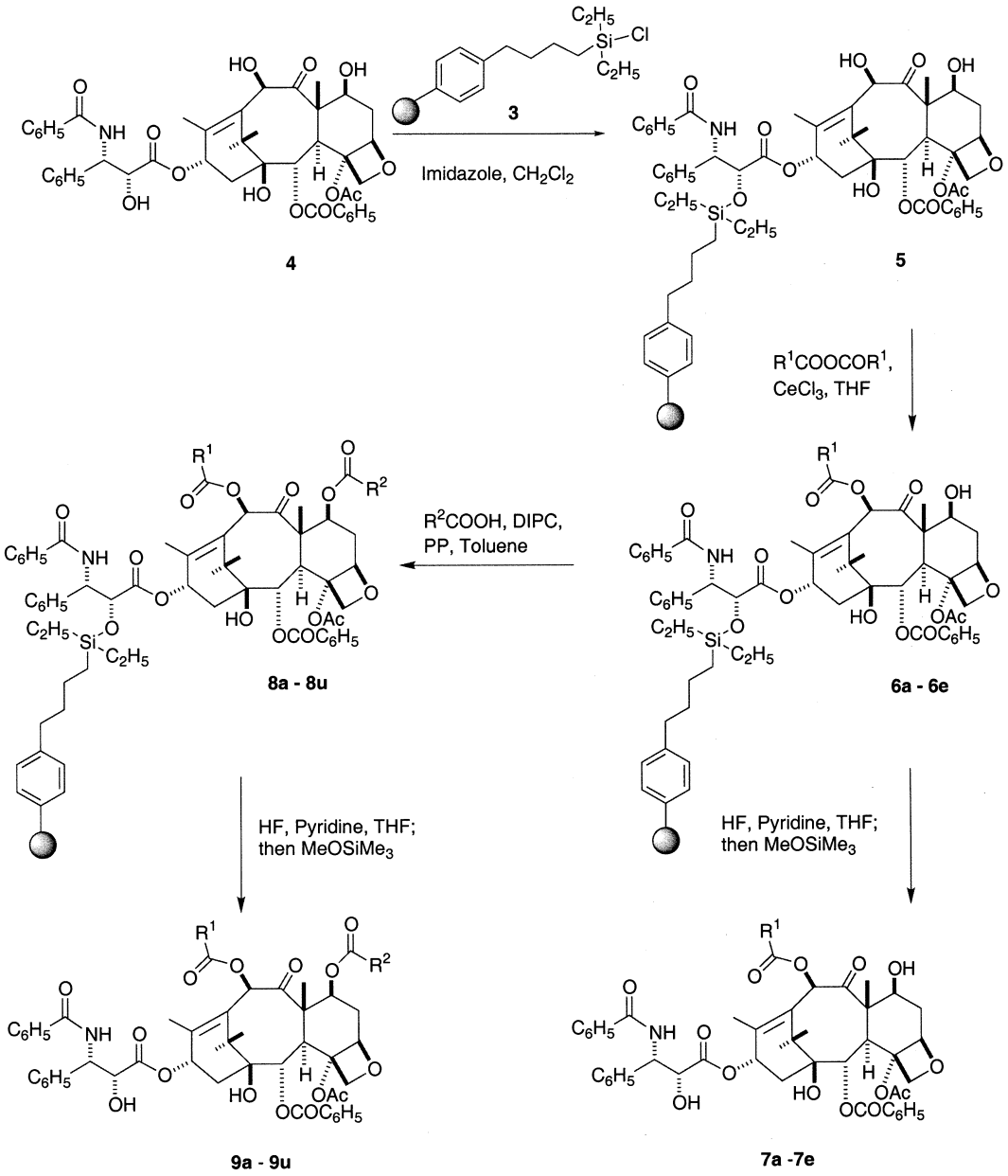
Acylation of the resin-bound intermediates **6a**−**6e** at the C-7 position was achieved by the well-established carbodiimide route[26] using 1,3-diisopropylcarbodiimide (DIPC) and acid. This gave derivatives **8a**−**8u**, which were again treated to remove excess reagents by washing the resin with MeOH, EtOAc, DMF, and CH_2Cl_2. The 7,10-diacylpaclitaxel analogues **9a**−**9u** were isolated from the resin after the final cleavage with HF/pyridine in THF followed by quenching the reaction mixture with methoxytrimethylsilane. The percentage yields of compounds **7a**−**7e** and **9a**−**9u** are shown in Table 1.



Diacylpaclitaxel analogs **7a - 9u**

The purities of all final compounds were determined on the basis of their ^1H NMR spectra and TLC analysis. After the final cleavage with HF/pyridine compounds **7a**−**7b** and **9a**−**9g**, **9i**, **9j**, **9n**, and **9r** were observed to be contaminated with urea that had not been completely washed away; ^1H NMR analysis showed purities of less than 80%. These

Scheme 1



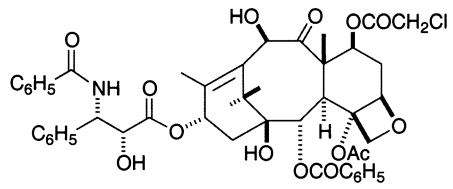
compounds were thus purified by preparative TLC on silica gel and had purities of 95% or higher (as judged by ^{1}H NMR and TLC) after purification. The analogues **7c**, **7d**, **9h**, **9k**, **9l**, **9m**, **9o**, **9p**, **9q**, **9s**, and **9t** were less contaminated; their analyses by ^{1}H NMR spectroscopy showed purities in the range of 80−90%.

The initial method development was done on a medium scale, using 450 mg of resin-bound paclitaxel for the initial derivatization and 50−60 mg for subsequent reactions. When the appropriate conditions had been developed, small MikroKan reactors were used, which allowed the reactions to be carried out using 30 mg of resin, corresponding to about 6 mg of paclitaxel. A test run with these reactors indicated that the syntheses could be carried out successfully on this scale.

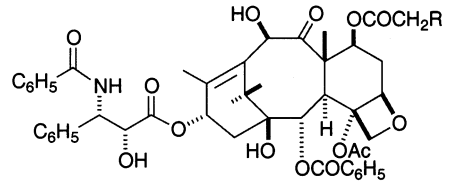
A final set of analogues was prepared from 7-chloroacetyl-10-deacetylpaclitaxel. Preliminary studies with 7-chloroacetyl-10-deacetylbaccatin III[27] indicated that the chlorine could readily be replaced with amines by a nucleophilic displacement reaction, and the substrate 7-chloroacetyl-10-deacetylpaclitaxel was then selected in part on the basis of the good activity of the 7-chloroacetylpaclitaxel analogue **9n**. A variety of mono-, di-, and tribasic amines were selected for reaction with this substrate, with the concept that these could be converted into salts with increased water solubility as compared with paclitaxel.

7-Chloroacetyl-10-deacetylpaclitaxel (**10a**) was prepared by reaction of 2′-(*tert*-butyldimethylsilyl)-10-deacetylpaclitaxel[28] with chloroacetic anhydride, followed by desilylation. Reaction of **10a** with the appropriate amines gave the analogues **10b**−**10j** in good to excellent yields.

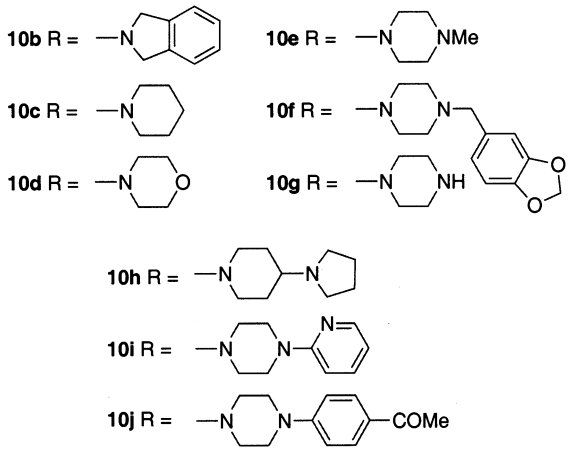
The tubulin-assembly activities of the 10-acyl analogues **7a**−**7d** and the 7,10-diacyl paclitaxel analogues **9a**−**9t** were determined by a new method that has been adapted to the measurement of activity on microtiter plates. In brief, tubulin assembly was assessed by monitoring the emission intensity of solutions containing tubulin (5 μM), 4′,6-diamidino-2-phenylindole (DAPI, 10 μM), and the drug to be tested as a function of time. The extent of microtubule assembly is directly proportional to the change in the intensity of DAPI fluorescence under these assay conditions.[29] Concentrations over 2 orders of magnitude of



10a



10b -10j



paclitaxel (control) and each drug candidate were tested. The results of these assays are shown in Table 1. The activities of the analogues were scored in comparison with paclitaxel, with analogues showing a higher percent polymerization than paclitaxel at a single dose being scored as +, those with higher activity at two doses being scored ++, and the four analogues that were more active at all three doses being scored +++. The most active analogues were the three 10-acyl derivatives **7a**, **7b**, and **7c** and the 7,10-diacyl derivative **9n**. The derivatives **7a** and **7b** have previously been prepared by conventional chemistry,[30−32] and both derivatives were reported to have cytotoxicities comparable to that of paclitaxel. Surprisingly, compound **7a** was reported to have significantly poorer tubulin-assembly activity than paclitaxel, but this different result may be explained by the different way the assay was run. The enhanced activity of the 7,10-diacyl compound **9n** is of interest because this is one of the few 7-acylpaclitaxels to show enhanced bioactivity. Although the chloroacetyl group is more labile than the acetyl group, the enhanced activity is unlikely to be due to hydrolysis of **9n** to **7c**, because acyl groups at the 7-position are relatively resistant to hydrolysis.[33]

In addition to the four analogues mentioned above, nine additional analogues (**7d**, **9f**, **9g**, **9o**−**9t**) were more potent than paclitaxel at two concentrations. These compounds have varying groups at the 7-position, but all had either an ethanoyl or a 2-butenoyl group at the 10-position. It thus appears that these groups are favorable to the activity of 7-acyl analogues, and further study of additional analogues of this type is warranted.

The analogues **10b**−**10h** were prepared in larger amounts than those described earlier, and they were thus assayed in both a cytotoxicity assay and a tubulin-assembly assay. The results of these assays are given in Table 2. All the analogues were comparable to or less active than paclitaxel in the tubulin polymerization assay, but compound **10i** was almost 10-fold more cytotoxic than paclitaxel, while compound **10f** was approximately 5-fold more cytotoxic. These results indicate that 7-acylpaclitaxel analogues with basic substituents have the potential to be more potent drugs than paclitaxel and would have the benefit of combining improved water solubility with improved activity.

Table 2. Biological Evaluation of 7-Acyl-10-deacetylpaclitaxel Analogues

structure	cytotoxicity to A2780 ovarian cancer cells (IC_{50}, μg/mL)	microtubule assembly I_{50} (μM)
10b	± 0.07 (5)	2.04 ± 0.94
10c	0.18, 0.25	1.02 ± 0.15
10d	0.25, 0.2	1.30 ± 0.32
10e	0.67 ± 0.35 (3)	0.59 ± 0.22
10f	0.03, 0.02	7.80 ± 2.33
10g	0.86 ± 0.1 (3)	N/A
10h	0.96	0.85 ± 0.37
10i	0.014, 0.11	1.65 ± 0.75
10j	0.9 ± 0.04 (3)	4.34 ± 0.62
1	0.136 ± 0.08 (7)	0.55 ± 0.1

Due to its promising cytotoxic activity, a comparison of the water solubility of analogue **10i** (as its hydrochloride salt) and paclitaxel was made, using a water−butanol partition method. The results indicated that the hydrochloride salt of **10i** is approximately 9 times more soluble in 0.1 N aqueous HCl than paclitaxel, again suggesting that it is a promising lead compound.

In summary, the methodology has been developed for an efficient resin-based combinatorial synthesis of 7-acyl- and 7,10-diacylpaclitaxel analogues and was applied to the synthesis of 24 analogues. In addition, nine 7-acyl-10-deacetylpaclitaxel analogues were prepared by conventional chemistry. Methodology was also developed to determine the tubulin-assembly activity of compounds prepared in small quantities by a combinatorial approach, and four analogues with improved tubulin-assembly activity as compared with paclitaxel and two analogues with improved cytotoxicity have been discovered; one of these also has improved water solubility as compared with paclitaxel.

Experimental Section

General Experimental Procedures. PS-DES resin was purchased from Argonaut Technologies, Inc, CA. Other chemicals were obtained from Aldrich Chemical Co. and were used without further purification; the HF/pyridine used was approximately 70% HF, 30% pyridine. All anhydrous reactions were performed under argon. THF was dried over sodium/benzophenone. ^{1}H NMR spectra were obtained in $CDCl_3$ at 400 MHz and were assigned by comparison of chemical shifts and coupling constants with those of related compounds. Some of the ^{1}H NMR spectra showed the presence of traces of EtOAc; paclitaxel and its derivative retain EtOAc very tightly, and it cannot be removed completely even on prolonged treatment in vacuo at 38 °C. MicroKan reactors were purchased from IRORI, Inc., CA. The Cytofluor 4000 was obtained from PerSeptive Biosystems, Framingham, MA.

10-Deacetyl-2′-(PS-DES)-paclitaxel (5). To PS-DES resin (750 mg, 0.83 mmol/g, 0.62 mmol) under argon was added a solution of 1,3-dichloro-5,5-dimethylhydantoin (365 mg, 1.86 mmol) in CH_2Cl_2 (6 mL), and the mixture was stirred at room temperature for 2 h. The chlorinated resin (**3**) was washed with CH_2Cl_2 (4 × 5 mL) using a cannula under an argon atmosphere. A solution of 10-deacetylpaclitaxel[24] (**4**, 485 mg, 0.59

mmol) and imidazole (385 mg, 6.0 mmol) in CH_2Cl_2 (6 mL) was immediately added to the washed resin, and the reaction mixture was further stirred at room temperature. After 24 h CH_3OH (1 mL) was added, and the resin was washed with CH_2Cl_2 (2 × 5 mL), water (5 mL), EtOAc (2 × 5 mL), and finally CH_2Cl_2 (2 × 5 mL) and dried under vacuum for 12 h to give resin **5** loaded with 10-deacetylpaclitaxel (950 mg). The filtrate was transferred to a separatory funnel and washed with H_2O (10 mL) and brine (10 mL) and dried over Na_2SO_4. The organic layer was filtered and concentrated, and the residue obtained was purified by column chromatography on silica gel using 60% EtOAc/hexane to give unreacted 10-deacetylpaclitaxel (270 mg).

10-Acyl-10-deacetyl-2′-(PS-DES)-paclitaxels 6a−6e and 7,10-Diacyl-10-deacetyl-2′-(PS-DES)-paclitaxels 8a−8u. To resin **5** (450 mg) under argon was added a solution of the corresponding carboxylic acid anhydride or carbonate (10 equiv) in THF (6 mL), followed by addition of $CeCl_3$ (2 mg). The reaction mixture was stirred under argon at room temperature for 24 h. The resin was washed and dried under vacuum overnight to give resins **6a−6e**. These resins (50−60 mg each) were subjected to coupling with the appropriate acid (10 equiv), diisopropylcarbodiimide (DIPC,10 equiv), and pyrrolidinopyridine (PP, 2.0 mg) in toluene (2.0 mL) at room temperature. After 24 h, MeOH (0.5 mL) was added, and the resin was washed thoroughly and dried under vacuum to yield the resin-bound 7,10-diacylpaclitaxel derivatives **8a−8u**.

10-Acyl-10-deacetylpaclitaxels 7a−7e and 7,10-Diacyl-10-deacetylpaclitaxels 9a−9u. The resins **6a−6e** and **8a−8u** were taken individually and suspended in dry THF (1.5 mL). HF/pyridine (0.5 mL) was added to each and the resulting mixture stirred at room temperature. After 2 h, the mixture was treated with $MeOSiMe_3$ and stirred at room temperature for a further 30 min. The reaction mixture was diluted with EtOAc (5 mL), and the resin was washed with EtOAc (2 × 5 mL). The combined organic layers were washed thoroughly with dilute $NaHCO_3$, HCl (1.0 N), water, and finally brine, dried over Na_2SO_4, filtered, and evaporated to afford the desired 10-acyl-10-deacetylpaclitaxel derivatives **7a−9e** and the 7,10-diacyl-10-deacetylpaclitaxel derivatives **9a−9u** (Table 1). Samples that were contaminated with impurities, as judged by TLC and ^{1}H NMR spectroscopy, were purified by PTLC on Si gel (500 μM, 40% EtOAc/hexane).

Synthesis of 7e and 9u Using Microreactor Vials. Resin **5** was distributed into two MicroKan vials (30 mg each) and then immersed in dry THF (6 mL). A solution of butyric anhydride (10 equiv) and $CeCl_3$ (2 mg) was added, and the reaction mixture was stirred under argon at room temperature for 24 h. The vials were washed and dried under vacuum overnight to give the resin-bound 10-butanoyl-10-deacetylpaclitaxel derivative **7e**. One vial was placed in dry toluene (2 mL) and reacted with propionic acid (10 equiv), DIPC (10 equiv), and PP (2.0 mg). After 24 h, MeOH (0.5 mL) was added, and the vial was washed thoroughly and dried under vacuum to yield the resin-bound 10-butanoyl-10-deacetyl-7-propanoylpaclitaxel derivative **9u**. The two microreactor vials containing resins **7e** and **9u** were placed in separate 5 mL Teflon vials and then immersed in dry THF (1.5 mL) and treated with HF-pyridine (0.5 mL). The reaction mixtures were stirred at room temperature for 2 h. After 2 h, they were treated with $MeOSiMe_3$ and stirred at room temperature for 30 min. The reaction mixtures were diluted with EtOAc (5 mL), and the resin was washed with EtOAc (2 × 5 mL). The combined organic layers were washed thoroughly with dilute $NaHCO_3$, HCl (1.0 N), H_2O, and finally brine, dried over Na_2SO_4, and evaporated to afford the paclitaxel derivatives 10-butanoyl-10-deacetylpaclitaxel (**7e**, 69%) and 10-butanoyl-10-deacetyl-7-propanoylpaclitaxel derivative (**9u**, 71%), each in a purity of 90% or better as judged by TLC.

7-Chloroacetyl-10-deacetylpaclitaxel (10a). To a stirred solution of 2′-*O*-(*tert*-butyldimethylsilyl)-10-deacetylpaclitaxel[28] (0.725 mg, 0.78 mmol) in THF at room temperature was added chloroacetic anhydride (1.34 g, 7.8 mmol), the mixture was stirred for 2 h, and the product was worked up by standard methods to give 2′-*O*-(*tert*-butyldimethylsilyl)-7-chloroacetyl-10-deacetylpaclitaxel, which was used directly in the next step. To a stirred solution of a portion of 2′-*O*-(*tert*-butyldimethylsilyl)-7-chloroacetyl-10-deacetylpaclitaxel (0.204 g, 0.203 mmol) in THF (12 mL) was added pyridine (3.2 mL) at 0 °C, the mixture was stirred for 5 min, and HF-pyridine (3.2 mL) was introduced. The reaction mixture was allowed to come to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution, and worked up in the usual way. The crude product was purified by preparative TLC (Si gel, 60% EtOAc/hexane) to give 7-chloroacetyl-10-deacetylpaclitaxel (95%). ^{1}H NMR ($CDCl_3$, 399.951 MHz): δ 8.1 (d, 2H), 7.30 (d, 2H), 7.61 (tt, 1H), 7.52−7.32 (m, 10H), 7.16 (d, J = 8.8, 1H, NH), 6.17 (t, 1H, C-13), 5.76 (d, J = 9.2, 1H, C-3′), 5.67 (d, J = 6.8, 1H, C-2), 5.49 (m, 1H, C-7), 5.26 (s, 1H, C-10), 4.92 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.8, 1H, C-20), 4.22 (d, J = 8.8, 1H, C-20), 3.97 (m, 4H, CH_2−Cl, C-3 and C-2′-OH), 2.56 (m, 1H, C-6), 2.39 (s, 3H, C-4 Ac), 2.29 (m, 2H, C-6, C-14), 1.96 (m, 1H, C-14), 1.92 (s, 1H, C-1-OH), 1.85 (s, 3H, C-18 Me), 1.8 (s, 3H, C-19 Me), 1.17 (s, 3H, C-17 Me), 1.06 (s, 3H, C-16 Me). ^{13}C NMR ($CDCl_3$, 100.578 MHz): δ 210.6 (C-9), 172.5 (C-1′), 170.5 (C-7 C=O), 167.1 (C-4 Ac C=O), 166.8 (NH C=O), 166.4 (C-2 Bz C=O), 138.6, 137.9, 135.6, 133.7, 133.6, 131.9, 130.1, 129.0, 128.9, 128.7, 128.6, 128.3, 127.0, 126.9, 83.4 (C-5), 80.5 (C-4), 78.6 (C-1), 76.5 (C-20), 74.5 (C-10), 74.5 (C-2), 73.7 (C-2′), 73.2 (C-13), 72.2 (C-7), 60.4 (C-6), 56.3 (C-8), 55.0 (C-3′), 45.9 (C-3), 42.8 (C-17 Me), 40.5 (CH_2Cl), 35.9 (C-14), 33.1 (C-6), 26.2 (C-15), 22.4 (C-4 Me), 20.5, 14.13 (C-18), 14.1, 10.9 (C-19 Me).

General Procedure for the Substitution of Chlorine with Nucleophilic Amines. Synthesis of the Paclitaxel Derivatives 10b−10j. To a stirred solution of 7-chloroacetyl-10-deacetylpaclitaxel (**10a**, 0.033 mmol) in DMF (0.3 mL) at room temperature was added the selected amine (0.099 mmol), and the mixture was stirred for 3−4 h. The reaction mixture was then diluted with EtOAc and worked up in the usual way. The crude product was purified by preparative TLC (Si gel, 60−70% EtOAc/hexane), and the desired product was isolated in 85−95% yield.

Paclitaxel derivative 10b: ^{1}H NMR δ 8.11 (d, 2H), 7.75 (d, 2H), 7.61 (tt, 1H), 7.52−7.33 (m, 10H), 7.20 (s, 4H), 7.13 (d, J = 8.8, 1H, NH), 6.18 (t, 1H, C-13), 5.78 (d, J = 8.8, 1H, C-3′), 5.67 (d, J = 6.8, 1H, C-2), 5.49 (m, 1H, C-7), 5.35 (s, 1H, C-10), 4.92 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.34 (d, J = 8.8, 1H, C-20), 4.22 (d, J = 8.8, 1H, C-20), 4.15 (s, 4H), 4.05 (s, 1H), 3.97 (d, J = 6.8, 1H, C-3), 3.67 (bs, 1H, C-2′-OH), 3.59 (s, 2H), 2.54 (m, 1H, C-6), 2.39 (s, 3H, C-4 Ac), 2.29 (m, 2H, C-6, C-14), 1.95 (m, 1H, C-1-OH), 1.83 (s, 3H, C-18 Me), 1.81 (s, 3H, C-19 Me), 1.69 (s, 1H), 1.2 (s, 3H, C-17 Me), 1.07 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.2 (C-9), 172.5 (C-1′), 170.4 (C-7 C=O), 166.9 (C-4 Ac C=O), 138.6, 137.9, 15.7, 133.8, 133.6, 131.9, 130.2, 129.1, 128.3, 127.2, 127.05, 127.00, 122.4, 85.5 (C-5), 80.6 (C-4), 78.7 (C-1), 74.5 (C-10), 73.2 (C-2), 72.3 (C-7), 58.6, 56.5, 55.3 (C-8), 55.0 (C-3′), 46.0 (C-3), 42.9 (C-17 Me), 36.0 (C-14), 33.4 (C-6), 26.3 (C-15), 22.5 (C-4 Me), 20.5, 14.2 (C-18 Me), 11.0 (C-19 Me); HRFABMS m/z 971.4000 (calc for $C_{55}H_{59}N_2O_{14}$, MH^+, 971.3966).

Paclitaxel derivative 10c: ^{1}H NMR δ 8.11 (d, 2H), 7.75 (d, 2H), 7.60 (tt, 1H), 7.52−7.33 (m, 10H), 7.07 (d, J = 8.8, 1H, NH), 6.18 (t, 1H, C-13), 5.79 (d, J = 8.8, 1H, C-3′), 5.66 (d, J = 6.8, 1H, C-2), 5.53 (m, 1H, C-7), 5.30 (s, 1H, C-10), 4.90 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.4, 1H, C-20), 4.21 (d, J = 8.4, 1H, C-20), 3.96 (d, J = 6.8, 1H, C-3), 3.69 (bs, 1H, C-2′-OH), 3.1 (s, 2H), 2.52 (m, 2H), 2.45 (m, 2H), 2.39 (s, 3H), 2.29 (m, 2H), 1.94 (m, 2H), 1.84 (s, 3H, C-18 Me), 1.80 (s, 3H, C-19 Me), 1.62−1.54 (m, 8), 1.25 (s, 3H, C-17 Me), 1.19 (s, 3H, C-16 Me).

Paclitaxel derivative 10d: ^{1}H NMR δ 8.11 (d, 2H), 7.75 (d, 2H), 7.60 (tt, 1H), 7.52−7.33 (m, 10H), 7.09 (d, J = 9.2, 1H, NH), 6.18 (t, 1H, C-13), 5.79 (d, J = 8.8, 1H, C-3′), 5.66 (d, J = 6.8, 1H, C-2), 5.53 (m, 1H, C-7), 5.30 (s, 1H, C-10), 4.90 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.4, 1H, C-20), 4.21 (d, J = 8.4, 1H, C-20), 3.98 (s, 1H), 3.96 (s, 1H), 3.73 (t, 4H), 3.58 (bs, 1H), 3.13 (s, 2H), 2.53 (m, 5H), 2.39 (s, 3H, C-4-Ac), 2.29 (m, 2H, C-6, C-14), 1.94 (m, 1H, C-1-OH),

1.84 (s, 3H, C-18 Me), 1.81 (s, 3H, C-19 Me), 1.73 (s, 1H), 1.18 (s, 3H, C-17 Me), 1.07 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.0 (C-9), 172.5 (C-1′), 170.4 (C-7 C═O), 169.0, 167.0 (C-4-Ac C═O), 166.9 (NH C═O), 138.6, 137.9, 135.7, 133.8, 133.6, 131.9, 130.2, 129.1, 129.0, 128.3, 127.0, 83.6 (C-5), 80.6 (C-4), 78.7 (C-1), 76.6, 74.6 (C-10), 74.5, 73.2 (C-2), 72.3 (C-7), 72.0, 66.7, 59.2, 56.5, 54.9 (C-3′), 53.0, 46.0 (C-3), 42.9 (C-17 Me), 35.9 (C-14), 33.5 (C-6), 26.3 (C-15), 22.5 (C-4 Me), 20.4, 14.2 (C-18 Me), 10.9 (C-19 Me); HRFABMS *m/z* 939.3914 (calc for $C_{51}H_{59}N_2O_{15}$, MH^+, 939.3915).

Paclitaxel derivative 10e: ^{1}H NMR δ 8.12 (d, 2H), 7.77 (d, 2H), 7.61 (tt, 1H), 7.53−7.26 (m, 10H), 7.15 (bs, 1H), 6.18 (t, 1H, C-13), 5.79 (d, J = 8.8, 1H, C-3′), 5.66 (d, J = 6.8, 1H, C-2), 5.53 (m, 1H, C-7), 5.30 (s, 1H, C-10), 4.90 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.4, 1H, C-20), 4.21 (d, J = 8.4, 1H, C-20), 3.96 (d, J = 6.8, 1H, C-3), 3.69 (bs, 1H, C-2′-OH), 3.42 (d, 2H), 3.25 (bs, 1H), 3.00 (bs, 5H), 2.76 (s, 2H), 2.58 (m, 2H), 2.4 (s, 3H, C-4-Ac), 2.28 (m, 2H, C-6, C-14), 2.03 (m, 2H), 1.83 (s, 3H, C-18 Me), 1.81 (s, 3H, C-19 Me), 1.62 (s, 1H), 1.21 (s, 3H, C-17 Me), 1.16 (s, 3H), 1.06 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.9 (C-9), 172.5 (C-1′), 170.3 (C-7 C═O), 169.1, 167.1 (C-4 Ac), 166.8 (NH C═O), 138.5, 138.0, 135.7, 133.7, 131.9, 130.1, 129.1, 128.9, 128.7, 128.6, 128.2, 127.0, 126.9, 83.6 (C-5), 80.6 (C-4), 78.5 (C-1), 76.5, 74.6 (C-10), 74.4, 73.1 (C-2), 72.2 (C-7), 72.0, 58.7, 56.4, 55.0, 54.5, 55.3, 46.0, 45.7, 42.9 (C-17 Me), 35.2 (C-14), 33.4 (C-6), 26.3 (C-15), 22.4 (C-4 Me), 20.5, 14.1 (C-18 Me), 10.9 (C-19 Me); HRFABMS *m/z* 952.4241 (calc for $C_{52}H_{62}N_3O_{14}$, MH^+, 952.4232).

Paclitaxel derivative 10f: ^{1}H NMR δ 8.11 (d, 2H), 7.74 (d, 2H), 7.60 (tt, 1H), 7.52−7.34 (m, 12H), 7.08 (d, J = 8.8, 1H, NH), 6.85 (s, 1H), 6.73 (s, 2H), 6.17 (t, 1H, C-13), 5.9 (s, 2H), 5.78 (d, J = 6.8, 1H, C-3′), 5.66 (s, 1H, C-2), 5.5 (m, 1H, C-7), 5.27 (s, 1H, C-10), 4.91 (d, J = 8.4, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.8, 1H, C-20), 4.21 (d, J = 8.8, 1H, C-20), 4.02 (s, 1H), 3.96 (d, J = 7.2, 1H, C-3), 3.52 (d, J = 4.4, 1H), 3.41 (s, 2H), 3.13 (s, 2H), 2.61−2.49 (m, 11H), 2.39 (s, 3H, C-4 Ac), 2.29 (m, 2H), 1.94 (m, 1H), 1.84 (s, 3H, C-18 Me), 1.79 (s, 3H, C-19 Me), 1.66 (s, 3H), 1.18 (s, 3H, C-17 Me), 1.07 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.9 (C-9), 172.4 (C-13), 170.4 (C-7 C═O), 169.2, 166.9 (C-4 Ac), 147.6, 146.6, 138.5, 137.9, 135.7, 133.7, 131.9, 130.2, 129.0, 128.7, 128.7, 128.3, 127.0, 122.2, 109.5, 107.8, 100.8, 83.6 (C-5), 80.7 (C-4), 79.5, 78.7 (C-1), 74.6 (C-10), 74.5, 73.2 (C-2), 72.3 (C-7), 72.1, 69.8, 62.6, 59.0, 56.4, 54.9, 52.7, 52.6, 46.1, 42.9, 38.5, 35.9 (C-14), 34.4, 33.5 (C-6), 26.3 (C-15), 22.5 (C-4 Me), 21.7, 20.4, 19.2, 17.8, 14.2 (C-18 Me), 10.9 (C-19 Me); HRFABMS *m/z* 1072.4497 (calc for $C_{59}H_{66}N_3O_{16}$, MH^+, 1072.4443).

Paclitaxel derivative 10g: ^{1}H NMR δ 8.11 (d, 2H), 7.75 (d, 2H), 7.60 (tt, 1H), 7.52−7.33 (m, 10H), 7.11 (d, J = 8.8, 1H, NH), 6.18 (t, 1H, C-13), 5.79 (d, J = 8.8, 1H, C-3′), 5.66 (d, J = 6.8, 1H, C-2), 5.53 (m, 1H, C-7), 5.30 (s, 1H, C-10), 4.90 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.4, 1H, C-20), 4.21 (d, J = 8.4, 1H, C-20), 3.96 (d, J = 6.8, 1H, C-3), 3.1 (d, 2H), 2.6 (m, 5H), 2.4 (s, 3H, C-4 Ac), 2.29 (m, 2H, C-6, C-14), 1.93 (m, 1H, C-14), 1.84 (s, 3H, C-18 Me), 1.82 (s, 3H, C-19 Me), 1.67 (s, 1H), 1.2 (s, 3H, C-17 Me), 1.07 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 205.9 (C-9), 172.5 (C-1′), 170.4 (C-7 C═O), 169.1, 167.1 (C-4 Ac), 138.5, 135.7, 133.7, 131.9, 130.2, 129.0, 128.8, 128.7, 128.3, 127.0, 83.6 (C-5), 80.7 (C-4), 78.8 (C-1), 74.6 (C-10), 73.2 (C-2′), 72.3 (C-7), 72.0, 58.9 (C-8), 56.4 (C-8), 54.9 (C-9), 52.3, 46.1 (C-3), 42.9 (C-17 Me), 33.4, 26.3 (C-15), 22.5 (C-4 Me), 20.5, 14.2 (C-18 Me), 10.9 (C-19 Me).

Paclitaxel derivative 10h: ^{1}H NMR δ 8.11 (d, 2H), 7.75 (d, 2H), 7.61 (tt, 1H), 7.52−7.34 (m, 10H), 7.08 (d, J = 8.8, 1H, NH), 6.18 (t, 1H, C-13), 5.78 (d, J = 6.8, 1H, C-3′), 5.66 (s, 1H, C-2), 5.5 (m, 1H, C-7), 5.29 (s, 1H, C-10), 4.91 (d, J = 8.4, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.8, 1H, C-20), 4.21 (d, J = 8.8, 1H, C-20), 4.01 (bs, 1H, C-2′-OH), 3.96 (d, J = 7.2, 1H, C-3), 3.15 (s, 2H), 2.84 (t, 2H), 2.55 (m, 5H), 2.39 (s, 3H, C-4 Ac), 2.31−2.19 (m, 5H), 1.96 (m, 2H), 1.84 (s, 3H, C-18 Me), 1.81 (s, 3H, C-19 Me), 1.77 (m, 5H), 1.19 (s, 3H, C-17 Me), 1.08 (s, 3H, C-16 Me); HRFABMS *m/z* 1006.4735 (calc for $C_{56}H_{68}N_3O_{14}$ MH^+, 1006.4701).

Paclitaxel derivative 10i: ^{1}H NMR δ 8.18 (d, 1H), 8.11 (d, 2H), 7.74 (d, 2H), 7.61 (tt, 1H), 7.52−7.34 (m, 13H), 7.1 (d, J = 8.8, 1H, NH), 6.6 (m, 2H), 6.18 (t, 1H, C-13), 5.78 (d, J = 6.8, 1H, C-3′), 5.66 (s, 1H, C-2), 5.5 (m, 1H, C-7), 5.29 (s, 1H, C-10), 4.91 (d, J = 8.4, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.8, 1H, C-20), 4.21 (d, J = 8.8, 1H, C-20), 3.99 (bs, 1H), 3.97 (bs, 1H), 3.59 (m, 5H), 3.19 (s, 2H), 2.64 (t, 5H), 2.53 (m, 1H), 2.39 (s, 3H, C-4 Ac), 2.32 (m, 2H, C-6, C-14), 1.94 (m, 1H, C-14), 1.84 (s, 3H, C-18 Me), 1.81 (s, 3H, C-19 Me), 1.69 (s, 2H), 1.19 (s, 3H, C-17 Me), 1.07 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.0 (C-9), 172.5 (C-1′), 170.4 (C-7 C═O), 169.1, 166.9 (C-4 Ac), 159.4, 147.9, 138.6, 137.9, 137.5, 135.7, 133.8, 131.9, 130.2, 129.0, 128.7, 127.0, 127.0, 113.4, 107.1, 83.6 (C-5), 80.6 (C-4), 78.7 (C-1), 74.6 (C-10), 74.5 (C-2), 73.2, 72.3 (C-7), 72.0, 59.0, 56.4 (C-8), 54.9 (C-3′), 52.5, 46.1 (C-3), 45.0, 42.9 (C-17 Me), 35.9 (C-14 Me), 33.5 (C-6), 26.3 (C-15), 22.5 (C-4 Me), 20.4, 14.2 (C-18 Me), 10.9 (C-19 Me); HRFABMS *m/z* 1015.4310 (calc for $C_{56}H_{63}N_4O_{14}$, MH^+, 1015.4341).

Paclitaxel derivative 10j: ^{1}H NMR δ 8.11 (d, 2H), 7.85 (d, 2H), 7.74 (d, 2H), 7.62 (t, 1H), 7.53−7.34 (m, 12H), 7.05 (d, J = 8.8, 1H, NH), 6.86 (d, J = 8.8, 2H), 6.19 (t, 1H, C-13), 5.79 (d, J = 8.8, 1H, C-3′), 5.66 (d, J = 6.8, 1H, C-2), 5.53 (m, 1H, C-7), 5.31 (s, 1H, C-10), 4.92 (d, J = 8.8, 1H, C-5), 4.77 (s, 1H, C-2′), 4.32 (d, J = 8.4, 1H, C-20), 4.21 (d, J = 8.4, 1H, C-20), 3.96 (d, 1H, C-3), 3.95 (s, 1H, C-2′-OH), 3.5 (d, 1H), 3.39 (t, 4H), 3.21 (s, 2H), 2.69 (t, 4H), 2.55 (m, 2H), 2.52 (s, 3H), 2.4 (s, 3H, C-4 Ac), 2.3 (s, 2H, C-6, C-14), 1.95 (m, 1H, C-14), 1.85 (s, 3H, C-18 Me), 1.82 (s, 3H, C-19 Me), 1.2 (s, 3H, C-17 Me), 1.09 (s, 3H, C-16 Me); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.1 (C-9), 195.7, 175.3, 172.5 (C-13), 170.4 (C-7 C═O), 166.9 (NH C═O), 154.1, 138.7, 135.7, 133.8, 131.9, 130.4, 129.2, 128.8, 128.7, 127.0, 131.9, 130.4, 130.2, 129.2, 128.7, 127.0, 113.5, 83.6 (C-5), 80.6 (C-4), 78.7 (C-1), 74.6 (C-10), 73.2 (C-13), 72.3, 72.1 (C-7), 58.8, 56.5 (C-8), 54.9 (C-3′), 52.2, 47.23, 42.9 (C-17 Me), 33.5 (C-14), 26.3 (C-15), 26.1, 22.5 (C-4 Me), 20.4, 14.2 (C-18 Me), 10.9 (C-19 Me); HRFABMS *m/z* 1056.4519 (calc for $C_{59}H_{66}N_3O_{15}$, MH^+, 1056.4494).

Microtiter-Based Tubulin Polymerization Bioassay. Microtubule assembly assays were carried out in 96-well plates and read by a fluorescence plate reader. Samples were prepared as follows: PMEG buffer, consisting of 100 mM PIPES, 1 mM $MgSO_4$, 2 mM EGTA, 0.1 mM GTP, at pH 6.9, and also containing the ligand to be tested, was pipetted into each well in the plate. DAPI (4′,6-diamidino-2-phenylindole) was added to yield a final concentration of 10 μM. Tubulin in PMEG buffer was added using a multichannel pipettor to a final concentration of 5 μM. The solutions in the wells were mixed using the pipettor, and care was taken to avoid introduction of bubbles into the well. Each sample was prepared in duplicate, triplicate, or quadruplicate, depending on sample size. Polymerization was monitored using a CytoFluor 4000; the excitation filter was set at 360/40 nm and the emission filter at 460/40 nm. The temperature of the instrument was set at 37 °C. The change in fluorescence of each solution was determined and was normalized with respect to the polymerization curve for the standard, 10 μM paclitaxel. All polymerizations were run in triplicate or quadruplicate.

Standard Tubulin Polymerization Bioassay. The standard tubulin polymerization bioassay was performed as previously described.[34]

Determination of the Octanol−Water Partition of Paclitaxel and 10i. Paclitaxel and analogue **10i** were each partitioned between 1-octanol and 0.1 N aqueous HCl solution with vigorous shaking for 1 h. After the layers were separated the UV absorbance of each layer of paclitaxel and **10i** was determined at 229 nm. For paclitaxel, the absorbance ratio of the aqueous layer to the 1-octanol layer was 0.017, and for compound **10i** it was 0.155.

Acknowledgment. This work was supported by a research grant from the National Institutes of Health (CA-69571), and this support is gratefully acknowledged.

Supporting Information Available: ^{1}H NMR spectral data for compounds **7a**−**e**, **9a**−**g**,**i**−**u**, **10b**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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NP010552A