Synthesis and Biological Evaluation of Novel Paclitaxel (Taxol) D-Ring Modified Analogues

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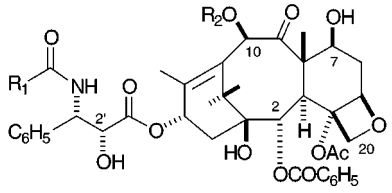
The semisynthesis and biological activity of paclitaxel (Taxol) analogues in which the oxygen atom in ring D is substituted by a sulfur or a selenium atom is presented. These derivatives were synthesized and tested in order to make more transparent the role of the oxetane ring in the biological activity of paclitaxel. The sulfur derivatives were found to be less active than paclitaxel in biological assays, while the selenium derivative could not be converted to its 4-acyl analogue. The results with the sulfur analogues suggest that the oxygen atom in the oxetane ring plays an important role in the mechanism by which paclitaxel exhibits its anticancer activity.

Introduction

The anticancer drug paclitaxel (Taxol, **1a**), a diterpenoid isolated from the bark of *Taxus brevifolia*, is clinically used in the treatment of ovarian and breast cancer.[1] Since its discovery in the late 1960s,[2] intensive studies of its chemistry and structure−activity relationships have been reported.[3] These studies have established that the C-13 side chain, the ester groups at C-2 and C-4, and the oxetane ring are all essential for biological activity,[3] but the precise role of these groups in paclitaxel's activity remains obscure.

It is known that paclitaxel binds to microtubules, thereby stabilizing them and disrupting the equilibrium between tubulin and microtubules, and thus halting cell division,[4] but the conformation in which paclitaxel binds to microtubules and the actual binding site are not known in detail. As far as the conformation of paclitaxel is concerned, NMR studies in aqueous solution indicate that a "hydrophobic collapse" conformation, resulting from hydrophobic clustering of the C-2 benzoyl, C-3′ phenyl, and C-4 acetate groups, is probably important for providing the critical side chain conformation relevant to the binding of paclitaxel to microtubules.[5] These findings provide at least a partial explanation for the importance of the groups indicated but do not provide any clue to the importance of the oxetane ring.



1a $R_1 = C_6H_5$, R_2 = Ac
1b $R_1 = OCMe_3$, R_2 = H

It is possible to devise various hypotheses for the importance of the oxetane ring to paclitaxel's activity. Thus it might cause the acetoxy group to adopt an orientation in space favorable for interaction with microtubules by increasing the rigidity of ring C (conformational role) or it might be directly involved in receptor binding by its oxygen atom through hydrogen bonding (electronic role). Thus the effect of replacement of the oxygen atom in the oxetane ring by another heteroatom on the activity of paclitaxel might clarify whether the role

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(1) (a) Holmes, F. A.; Kudelka, A. P.; Karanagh, J. J.; Huber, M. H.; Ajani, J. A.; Valero, V. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I.; Vyas, D. M., Eds.; ACS Symposium Series 583, American Chemical Society: Washington, DC, 1994; pp 31−57. (b) Arbuck, S. G.; Blaylock, B. A. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press Inc.: Boca Raton, FL, 1995; pp 379−415. (c) McGuire, W. P., Rowinsky, E. K., Eds. *Paclitaxel in Cancer Treatment;* Marcel Dekker: New York, Basel, Hong Kong, 1995; Vol. 8, pp 1−349.

(2) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.

(3) For recent reviews: (a) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1−188. (b) Suffness, M. *Annu. Rep. Med. Chem.* **1993**, *28*, 305−314. (c) Georg, G. I.; Ali, S. M.; Zymunt, J.; Jayasinghe, J. R. *Expert Opin. Ther. Pat.* **1994**, *12*, 222−227. (d) Chen, S. H.; Farina, V. Paclitaxel (Taxol) Chemistry and Structure Activity Relationships. In *The Chemistry and Pharmacology of Taxol and its Derivatives*; Farina, V., Ed.; Elsevier: New York, 1995; pp 165−223. (e) Kingston, D. G. I. *Trends Biotechnol.* **1994**, *12*, 222−227.

(4) Horwitz, S. B. *Trends Pharmacol. Sci.* **1992**, *13*, 134−136.

(5) (a) Vander Velde, D. G.; George, G. I.; Grunewald, G. L.; Gunn, C. W.; Mitscher, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 11650−11651. (b) Dubois, J.; Guenard, D.; Gueritte-Voegelein, F.; Guerida, N.; Potier, P.; Gillet, B.; Beloeil, J. C. *Tetrahedron* **1993**, *49*, 6533−6544. (c) Williams, H. J.; Scott, A. I.; Dieden, R. A.; Swindell, C. S.; Chirlian, L. E.; France, M. M.; Heerding, J. M.; Kraus, N. E. *Tetrahedron* **1993**, *49*, 6545−6560. (d) Paloma, L. G.; Guy, R. K.; Wrasidio, W.; Nicolaou, K. C. *Chem. Biol.* **1994**, *1*, 107−112.

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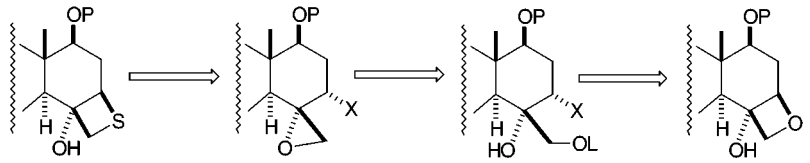
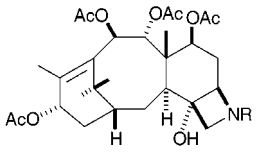
Scheme 1



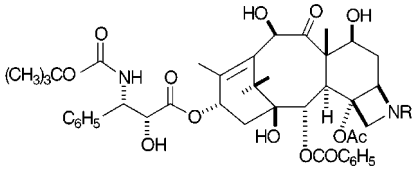
P = Protecting Group OL = Leaving Group

of the oxetane ring is primarily conformational or primarily electronic.

Recently, the syntheses of the azetidine derivatives **2a** and **2b**[6] and **3**a and **3b**[7] were reported. The derivatives



2a R = H
2b R = Ac



3a R = H
3b R = Bn

2a and **2b** lacked the benzoyloxy function at both the C-2 and the C-13 side chain, both of which are known to be important for biological activity,[3] and thus did not provide an appropriate model to test the importance of the oxetane ring. The azetidine analogues **3a** and **3b** were both inactive in an in vitro cytotoxicity assay; analogue **3a** did show some tubulin polymerization activity, but this was 16 times less than that of docetaxel (**1b**).[7] These results were explained in terms of a specific interaction of the heteroatom with the protein. The presence of a nitrogen atom in the azetidine ring also posed the problem of basicity, in that it would be protonated at neutral pH and thus would presumably interact with tubulin in a very different way than a neutral oxygen atom. For these reasons, the role of the oxetane ring on the activity of paclitaxel was still unclear, and the synthesis of other D-ring modified analogues of paclitaxel was necessary.

Replacement of the oxygen atom with a sulfur or a selenium atom would maintain the neutrality of the ring while at the same time change both steric and electronic effects in a predictable way. We thus decided to embark on the synthesis of the 5,20-thiapaclitaxel analogue **16** and the 5,20-selenapaclitaxel analogue **24**.

Results and Discussion

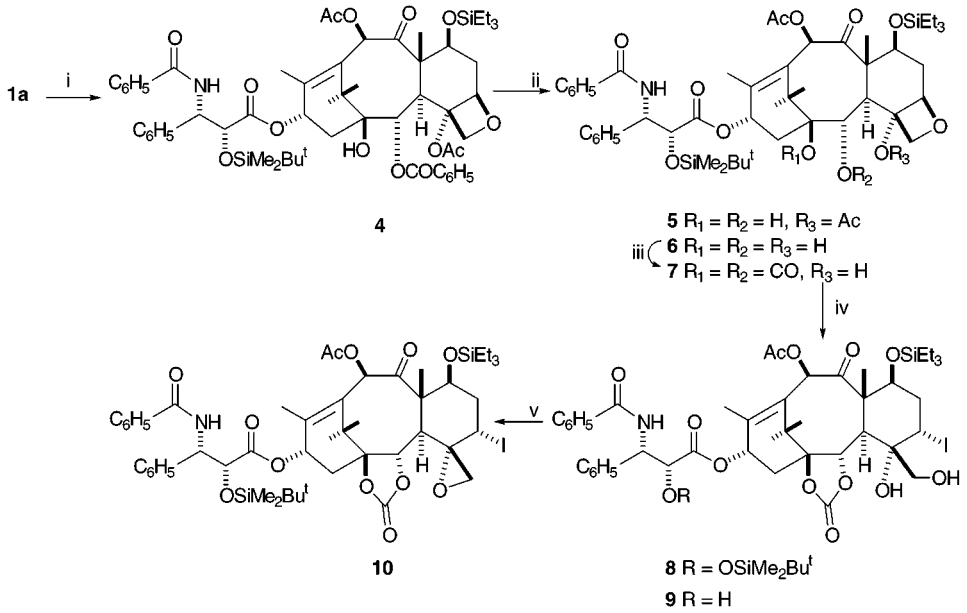
Chemistry. Our strategy for the synthesis of 5,20-thiapaclitaxel analogues was envisaged to involve reconstruction of the D-ring from a C-5α-halo-4,20-oxirane intermediate with simultaneous introduction of the heteroatom (Scheme 1). The C-5α leaving group could be introduced from the oxetane ring opening, and the 4,20-epoxy group would be formed from cyclization of the C-4-hydroxy group onto the appropriately functionalized C-20 hydroxyl group. Protection of C-1 and C-2 hydroxy groups was required to avoid the formation of undesired products in the oxetane ring opening step;[8] the protection of these groups as a cyclic carbonate was expected to facilitate acylation of C-4 and also to create conditions for the introduction of the benzoate functionality at C-2.[9]

The synthetic approach we have developed to the 4,20-oxirane intermediate **10** is shown in Scheme 2. The starting material, paclitaxel (**1a**), was protected at the C-2′ and C-7 positions by *tert*-butyldimethylsilyl and triethysilyl groups, respectively, to give the protected derivative **4** in 91% yield.[10] Selective hydrolysis of the C-2 benzoate and C-4 acetate groups of **4** with Triton B afforded the triol **6** in 66% yield.[10] Protection of the C-1 and C-2 hydroxy groups in **6** with carbonyldiimidazole and imidazole[11] gave the 1,2-carbonate derivative **7** in 85% yield.

Opening of the oxetane ring in the protected derivative **7** was first attempted with trimethylsilyl chloride and lithium iodide, but these conditions produced a mixture of compounds. After some experimentation, it was found that treatment of **7** at −78 °C in dichloromethane with iodotrimethylsilane followed by a careful workup afforded the 5α-iodo-20-hydroxy-D-seco-paclitaxel derivative **8** in 93% yield. When workup was effected at room temperature, the formation of the C-2′ desilylated compound **9** was also observed. Finally, the formation of the 5α-iodo-20-epoxy derivative **10** was achieved in 96% yield by the reaction of **8** with trifluoromethanesulfonyl chloride and DMAP.

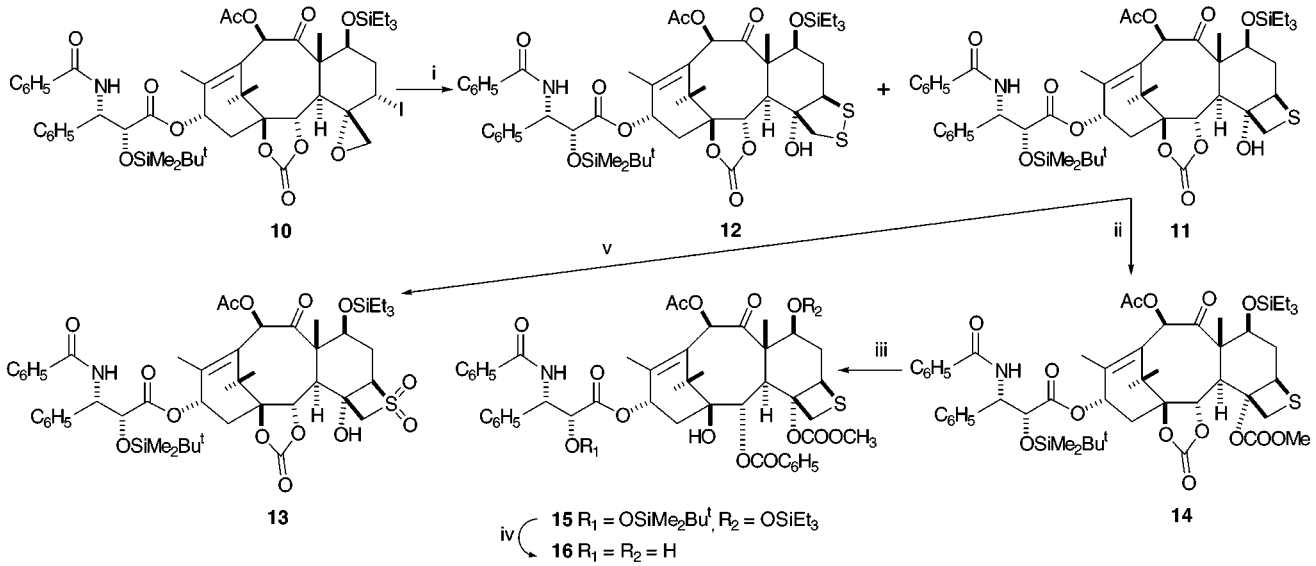
(6) Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendino, G. *Tetrahedron Lett*. **1996**, *37*, 3202−3206.
(7) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guénard, D.; Guéritte-Voegelein, F. *J. Org. Chem*. **1997**, *62*, 6631−6637.
(8) Chen, S. H.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805−2828.
(9) (a) Holton, R. A.; Somoza, C.; Kim, H. B. Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc*. **1994**, *116*, 1597−1599. (b) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E.; J. *Nature* **1994**, *367*, 630−634. (c) Masters, J. J.; Linj, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1723−1726.
(10) Chordia, M. D.; Kingston, D. G. I. *J. Org. Chem*. **1996**, *61*, 799−801.
(11) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc*. **1995**, *117*, 2409−2420.

Scheme 2[a]



[a] Key: (i) TBDMS/imidazole, DMF, 60 °C, 2 h, then Et_3SiCl/imiazole, 1 h, 91%; (ii) Triton B, CH_2Cl_2, −78 to −10 °C, TLC control, 66%; (iii) carbonyldiimidazole, CH_2Cl_2, 35−40 °C, 24 h, 85%; (iv) Me_3SiI, CH_2Cl_2, −78 °C, 45 min, 93%; (v) TfCl/DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 96%.

Scheme 3[a]

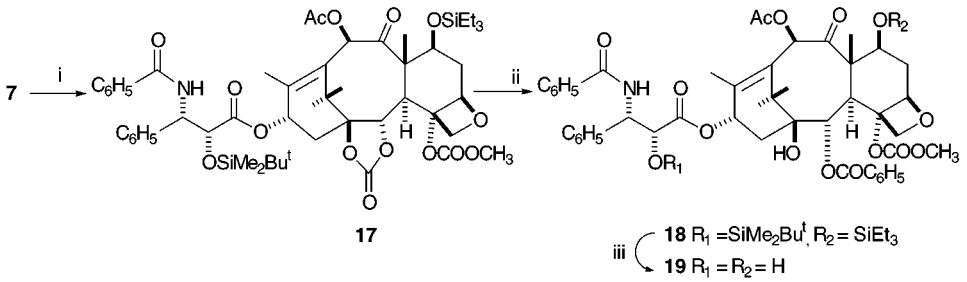


[a] Key: (i) Li_2S, THF, rt, 28 h, then carbonyldiimidazole/imidazole, rt, 12 h, **11** (56%), **12** (13%); (ii) LHMDS, THF, −78 °C (7 min), rt (1 min), −78 °C (2 min), then methyl chloroformate, −78 °C (10 min), **14** (39%), **11** (41%); (iii) PhLi, THF, −78 °C, 3 min, 61%; (iv) HF−pyridine, rt, 9 h, 76%; (v) m-CPBA, CH_2Cl_2, 0 °C to rt, 80 min, 61%.

Having made the key intermediate **10**, we next turned our attention to the preparation of 5,20-thiapaclitaxel analogues; the synthetic route is summarized in Scheme 3. Treatment of the intermediate **10** with lithium sulfide in THF at room temperature, with monitoring of the reaction by TLC, showed that there was a complete disappearance of starting material after 28 h. The ^1H NMR spectrum of the product obtained indicated it to be a 1,2,4-triol different from **6**. Treatment of the crude triol reaction product with carbonyldiimidazole and imidazole afforded two products after purification, namely the sulfide **11** (56%) as the major product and the disulfide **12** (13%) as the minor product. When a very large excess of Li_2S was used the major product from the reaction of **10** with Li_2S was the disulfide **12** (42%), and sulfide **11** (20%) became the minor product, so either **11** or **12** could be formed as the major product by controlling the concentration of Li_2S. The mechanism for the formation of **11** presumably involves nucleophilic attack on the primary C-20 of the 4,20-epoxy group by the sulfide ion, followed by a ring closure step involving attack on C-5 and displacement of iodide;[12] the alternative pathway of initial attack at C-5 is less likely on steric grounds. Thus,

(12) A similar cyclization was used in Wender's synthesis of taxol: Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757−2758.

Scheme 4[a]



[a] Key: (i) LHMDS, THF, −78 °C (7 min), rt (1 min), −78 °C (2 min), then methyl chloroformate, −78 °C (10 min), 69%; (ii) PhLi, THF, −78 °C, 3 min, 70%; (iii) HF−pyridine, rt, 9 h, 87%.

contrary to previous reports,[13] nucleophilic opening of the 4,20-epoxide is possible under the conditions employed. The sulfide **11** could be oxidized with 3-chloroperbenzoic acid to the sulfone (**13**) in 61% yield.

We next turned our attention to the subsequent steps of the synthesis, i.e acetylation of C-4, benzoylation of C-2 and deprotection of C-2′ and C-7 positions. Surprisingly, the C-4 hydroxy group in **11** was found to be resistant to several acylation conditions. For example, treatment of **11** with Ac_2O/DMAP in CH_2Cl_2 or LHMDS/AcCl, or the use of other acylating agents such as cyclopropyl carbonyl chloride or *N*-acetylimidazole, led only to the recovery of starting material. Attempted acetylation under forcing conditions with acetic anhydride and DMAP in toluene at 80 °C also failed to provide the acetylated product. After many attempts, it was found that treatment of **11** with LHMDS and methyl chloroformate afforded the derivative **14** in 39% yield, along with unreacted starting material (41%). Attempts to increase the yield by increasing the reaction time, temperature, or concentration of reagents gave a mixture of polar products. Benzoylation of the hydroxy group at C-2 in **14** was effected by reaction with phenyllithium, at −78 °C in THF,[14] affording **15** in 61% yield. Hydrolysis of the methoxycarbonyl group and formation of a complex mixture of products was observed when workup was carried out by standard methods. Thus a modified workup, involving quenching of the reaction with dilute aqueous HCl solution, was employed to avoid the hydrolysis of the methoxycarbonyl group. Conversion of **15** to the 5,20-thiapaclitaxel analogue **16** was achieved in 76% yield by treatment with HF−pyridine at room temperature. The spectroscopic data for **16** were consistent with its assigned structure.

Attempts to acetylate the C-4 hydroxy group of the disulfide **12** using the methods just described were also unsuccessful and led to the recovery of unreacted **12**. Also, attempts to react **12** with methyl chloroformate under the conditions that were used successfully with the sulfide, **11**, were also unsuccessful and led to the recovery of unreacted **12**. Thus, it appears that the C-4 hydroxy group of **12** is very sterically hindered and hence very difficult to acylate.

The sulfide analogue **16** of paclitaxel contains two structural changes compared to paclitaxel, in that the oxygen atom in the oxetane ring of paclitaxel has been replaced by a sulfur atom and the C-4 acetate group has been replaced by a methoxycarbonyl group. Hence, to get a better approximation of the independent effect of each of these structural changes on biological activity, we synthesized the paclitaxel derivative **19** (Scheme 4), in which only the C-4 acetate in paclitaxel has been replaced by a methoxycarbonyl group. By doing this we were able to compare the biological activity of paclitaxel with **19** and then the biological activity of **19** with the sulfide **16**. Thus, as shown in Scheme 4, treatment of the protected 1,2-carbonate derivative **7** with LHMDS and methyl chloroformate gave **17** (69% yield) substituted at the C-4 position by a methoxycarbonyl group. Benzoylation of **17** with phenyllithium gave the 4-methoxycarbonyl-2-benzoyl derivative **18** in 70% yield. Finally, removal of the C-2′ and C-7 silyl protecting groups in **18** with HF−pyridine gave the required product **19** in 87% yield.

The successful preparation of the 5,20-thiapaclitaxel analogue by reconstruction of the four-membered ring with the simultaneous introduction of a heteroatom from intermediate **10** led us to extend this strategy to the synthesis of the 5,20-selenapaclitaxel analogue **23** (Scheme 5).

A similar replacement of an oxygen atom for a selenium atom could be achieved by reaction of key intermediate **10** with lithium selenide. As reported,[15] organoselenium compounds can be prepared by reacting alkyl halides with lithium selenide, the latter being available from the reaction of $Li(C_2H_5)_3BH$ with gray selenium. Indeed, treatment of a THF solution of **10** with Li_2Se prepared as above resulted in the formation of the 5,20-selena derivative **20** in 67% yield.

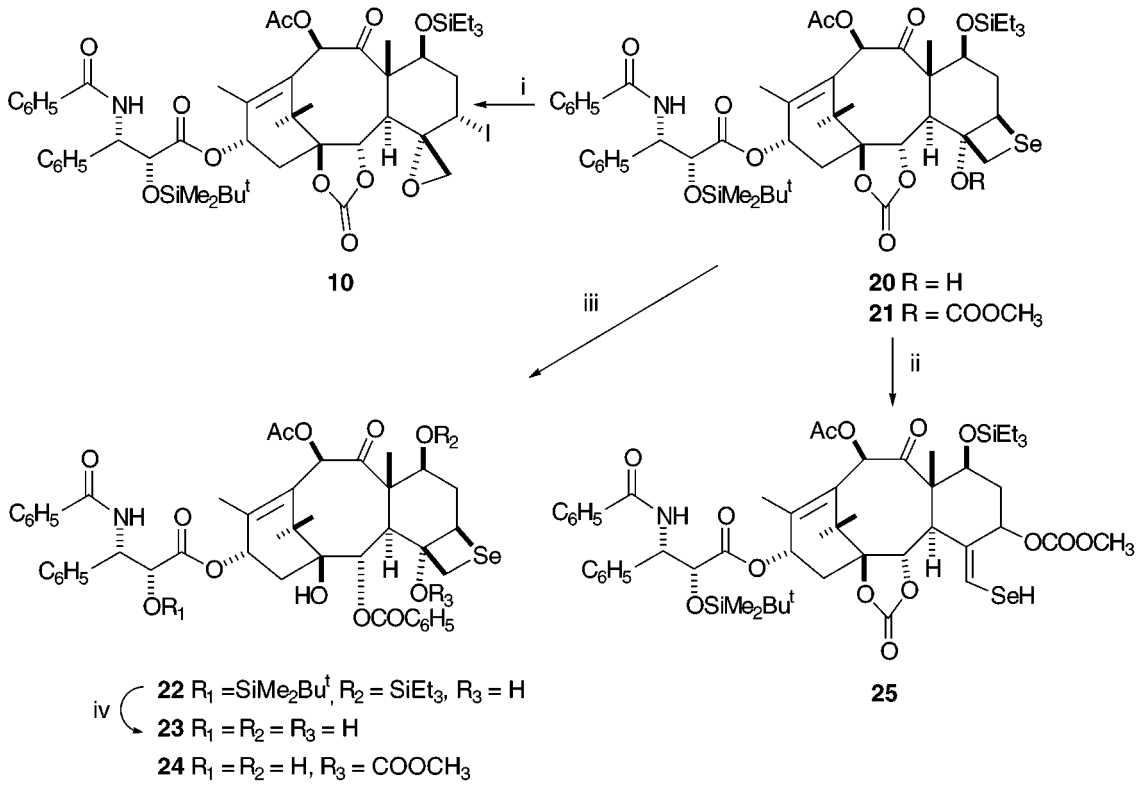
Regrettably we were unable to isolate the desired 4-acyl analogue **21** by acylation of **20**. The C-4 hydroxy group of **20** was unreactive toward several acylating conditions, such as Ac_2O/DMAP in CH_2Cl_2, LHMDS/AcCl in THF, acylimidazole/DMAP, or LHMDS and LHMDS/cyclopropyl carbonyl chloride. Attempted acylation with LHMDS/methyl chloroformate, which had proven to be successful in the case of the thiapaclitaxel analogue **11**, was unsuccessful in this case and afforded a reaction product that was tentatively identified as a mixture of the desired analogue **21** and the ring-opened derivative **25** (Scheme 5). The presumed compound **21** was however unstable and was converted to **25** either on attempted

(13) (a) Holton, R. Total Synthesis of Paclitaxel from Camphor. In *Taxane Anticancer Agents: Basic Science and Current Status*; George, I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583, American Chemical Society: Washington, DC, 1995; pp 288−301. (b) Margraff, R. M.; Bezard, D.; Bouzart, J. D.; Commerçon, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 233−236.

(14) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biendiger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Yu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N. Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599−1600.

(15) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1204−1208.

Scheme 5[a]



[a] Key: (i) Li_2Se, THF, −20 to 25 °C, 2 h, 67%; (ii) LHMDS, THF, −78 °C (5 min), rt (1 min), then methyl chloroformate, −78 °C (5 min), **25** (48%), **20** (14%); (iii) PhLi, THF, −78 °C, 3 min, 43%; (iv) HF−pyridine, rt, 8 h, 70.

Table 1. Comparison of Biological Activities of Compounds 16 and 19 with Those of Paclitaxel and Docetaxel

	enhancement of tubulin polymerization (EC_{50}, μM, ± SD)		effects on human cancer cell growth IC_{50} (nM)						
compound	condition 1[a]	condition 2[b]	Burkitt lymphoma[c]	prostate carcinoma[d]	melanoma[d]	breast carcinoma[d]	ovarian carcinoma[d]		
			CA46	PC3	LOX-IMV1	MCF-7	1A9	1A9PTX10	1A9PTX22
Paclitaxel	8.4 ± 0.8	1.5 ± 0.2	5	4	6	2	4	60	60
Docetaxel	5.2 ± 0.7	1.5 ± 0.2	3	0.9	0.9	0.5	2	10	20
16	>50	13 ± 0.7	>1000	>2500	NT[e]	NT	NT	NT	NT
19	4.2 ± 0.1	1.1 ± 0.1	2	1	0.6	0.2	2	20	20

[a] Reaction mixtures (100 μL) contained 1.0 mg/mL purified bovine brain tubulin, 0.4 M monosodium glutamate (pH 6.6 in 2.5 M stock solution with HCl), 5% (v/v) dimethyl sulfoxide as drug solvent, and varying drug concentrations. Incubation was for 20 min at room temperature. Samples were centrifuged at 14000 rpm for 10 min in an Eppendorf model 5417C centrifuge at room temperature, and the protein content of 20 μL of the supernatant was determined. Without drug the supernatant contained at least 95% as much protein as the total reaction mixture. The EC_{50} is the drug concentration that reduced supernatant protein by 50%. The experiment was performed 3 times. [b] Besides tubulin and drugs, reaction mixtures contained 0.65 M monosodium glutamate and 0.1 mM GTP. Conditions were otherwise unchanged. [c] Cells were grown for 4 days in suspension culture. The IC_{50} is the drug concentration that reduced cell number by 50%. [d] Cells were grown for 4 days as monolayer cultures in microtiter plates. The IC_{50} is the drug concentration that reduced cell protein by 50%. [e] Not tested.

purification or on standing in $CDCl_3$ solution. The formation of **25** presumably occurs by intramolecular attack of the carbomethoxy carbonyl group of **21** on C-5 with concomitant ring-opening, followed by a prototopic shift. A similar migration of an acetate group to C-5 with D-ring opening was observed by treating **20** with Ac_2O/DMAP in toluene at 80 °C.

Since **20** could not be converted to **21**, it was subjected directly to reaction with phenyllithium to afford the C-2 benzoylated analogue **22** in 43% yield. Deprotection of **22** with HF−pyridine led to compound **23** in 70% yield, and this was subjected to testing for cytotoxicity in the HCT 116 cell line.

Biological Activities. Compounds **16** and **19** were examined for effects on the polymerization of purified bovine brain tubulin and on the growth of several human cancer cell lines (Table 1). We found that **16** had negligible activity in all assays. Compound **19**, however, was clearly superior in activity to paclitaxel and even docetaxel with purified tubulin, and **19** was also more inhibitory than both paclitaxel and docetaxel against the growth of most of the human cancer cell lines examined.

Initial qualitative studies with tubulin were performed by turbidimetry, which demonstrated that **19** was more potent than paclitaxel, while **16** was much less active. Further work suggested that **19** would have biochemical properties similar to those of docetaxel, and no reaction condition was found where the slight activity of **16** could be demonstrated in the absence of GTP in the reaction mixture (GTP is an essential component for "normal" microtubule assembly, i.e., without drug). We had previously developed an assay for the ready quantitative

comparison of paclitaxel analogues with activity superior to that of the parent drug.[16] This was drug-induced assembly at room temperature in 0.4 M monosodium glutamate (pH 6.6) without GTP, with the EC_{50} defined as the drug concentration that reduced supernatant tubulin concentration by 50%. Although the tubulin used in current studies yields substantially lower EC_{50} values for paclitaxel and docetaxel (Table 1; condition 1, 8.4 and 5.2 μM), compounds such as **19**, which are more active than paclitaxel, can still be readily distinguished. In this assay, weakly active compounds such as **16** are indistinguishable from those devoid of activity. Although we had previously shown that increasing the glutamate concentration allowed one to identify many such weakly active compounds,[16] this was insufficient to obtain a quantitative evaluation of the partial activity of **16**.

We, therefore, evaluated GTP-containing reaction conditions that would permit quantitative evaluation of **16** and other poorly active paclitaxel analogues. As in the previous work, our goal was to obtain a reaction condition in which polymer formation at room temperature (measured by residual protein in supernatants following centrifugation at room temperature) would be negligible. The best results were obtained when reaction mixtures contained 0.65 M glutamate, 0.1 mM GTP, and 10 μM tubulin. As in higher glutamate alone, in this reaction condition compounds more active than paclitaxel yield EC_{50} values that differ little from that obtained with paclitaxel. But the partial activity of **16** could now be quantitated, and it appears to be at least 9-fold less active than paclitaxel.

Despite its weak activity with tubulin, compound **16** had no effect on the growth of the first two human cancer cell lines examined (a Burkitt lymphoma and a prostate carcinoma line), and so it was not studied further. Compound **19**, however, was highly active in these two lines, and we extended the analysis to a melanoma line, a breast carcinoma line, and a parental ovarian carcinoma line (1A9) and two paclitaxel-resistant lines derived from it. Paclitaxel resistance in these lines (PTX10 and PTX22) was shown to be caused by two different mutations in the dominant β-tubulin gene expressed in 1A9 cells.[17] All cell lines were modestly more sensitive to docetaxel than to paclitaxel, and all cells except the prostate carcinoma line and the paclitaxel-resistant mutants were more sensitive to **19** than to docetaxel. In the current experiments the 22-fold relative resistance to paclitaxel of 1A9PTX10 and 1A9PTX22 cells as compared with the parental cells was reduced to about 4−5-fold to docetaxel and about 10−12-fold to compound **19**.

The selenapaclitaxel analogue **23** was evaluated for cytotoxicity in the HCT 116 cell line. It showed no detectable activity, consistent with the fact that 4-acyl substitution is necessary for activity.[18]

Conclusion. Substitution of a sulfur for the oxygen of the oxetane ring in paclitaxel causes a significant diminution of its tubulin-assembly activity and cytotoxicity. This finding is consistent with the previous finding that substitution of the oxygen by a nitrogen also causes a marked reduction in activity,[7] but it extends it by demonstrating that the activity loss is not due to any basicity of the heteroatom. It can thus be concluded either that this region of the pharmacophore of paclitaxel is very sensitive to steric effects or that the oxetane oxygen is acting as a hydrogen bond acceptor.

Experimental Section

General Methods. All chemicals were purchased from Aldrich Chemical Co. with the exception of iodotrimethylsilane, which was obtained from Fluka. Chemicals were used without further purification, unless indicated otherwise. All anhydrous reactions were performed in oven-dried glassware under a positive pressure of argon. Anhydrous tetrahydrofuran (THF) and dimethylformamide (DMF) were purchased from Aldrich and used directly. Anhydrous CH_2Cl_2 was distilled from calcium hydride. All reactions were monitored by TLC (silica gel GF plates), visualized under short-wave UV light, and developed with vanillin/H_2SO_4 reagent spray. Analytical TLC was performed on kieselgel 60 F_{254} (E merck), 0.2 mm thickness. Preparative TLC was performed on silica gel GF plates (20 × 20 cm), 0.5 or 1.0 mm thickness, and purchased from Analtech. Flash chromatography was carried out on silica gel purchased from Baxter Scientific Products (S/P brand silica gel 60 Å, 230−400 mesh). Melting points were determined on a Kofler hot-stage apparatus and were uncorrected. All NMR spectra were recorded in $CDCl_3$ using solvent (δ_C 77.0 ppm) or residual $CHCl_3$ (δ_H 7.24 ppm) as internal standards. Coupling constants were reported in hertz. ^1H and ^{13}C NMR spectra were assigned primarily by comparison of the chemical shifts and coupling constants with those of related compounds or with the aid of 2D-NMR experiments (COSY, DEPT, HETCOR, HMQC, and HMBC). Microanalyses were obtained from Atlantic Microlabs, Inc., GA, and exact mass measurements were performed at the Nebraska Center for Mass Spectrometry. All solvent evaporation was done under reduced pressure.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (4). To a stirred solution of **1a** (1.525 g, 1.786 mmol) in anhydrous DMF (14.12 mL) were added imidazole (605 mg, 8.887 mmol) and *tert*-butyldimethylsilyl chloride (1.344 g, 8.917 mmol). The reaction mixture was stirred at 60 °C for 2 h and cooled to room temperature, and additional imidazole (605 mg, 8.887 mmol) and triethylsilyl chloride (0.85 mL, 5.064 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and then diluted with EtOAc (200 mL). The organic phase was washed successively with water (4 × 60 mL) and brine (60 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography (hexanes: EtOAc, 2:1) to give **4** (1.756 g, 91%) as a white amorphous solid: mp 129−130 °C. The NMR spectra for **4** were identical with those previously reported.[10]

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)paclitaxel (6). To a stirred solution of **4** (510 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (22.4 mL) at −78 °C was added benzyltrimethylammonium hydroxide (Triton B, 626 μL of 40% w/v solution in methanol). The reaction mixture was stirred at −78 °C for 10 min. The dry ice−acetone cooling bath was then replaced with a dry ice−diethylene glycol bath and the reaction mixture stirred at −10 to − 15 °C for a further 2 h. The progress of the reaction was monitored by TLC (silica gel, 50% hexanes in EtOAc), which indicated the initial formation of the compound 2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)paclitaxel[10] (**5**) with a lower R_f than that of the starting material (**4**). As the reaction progressed, **5** was converted to the required product, 2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)paclitaxel (**6**), which had an R_f intermediate between those of **4** and **5**. After 2 h there was no starting material remaining. The major product was **6**, as well as a very polar product at the origin of the TLC plate. The reaction mixture was then diluted with

(16) Lin, C. M.; Jiang, Y. Q.; Chaudhary, A. G.; Rimoldi, J. M.; Kingston, D. G. I.; Hamel, E. *Cancer Chemother. Pharmacol.* **1996**, *38*, 136−140.

(17) Giannakakou, P.; Sackett, D. L.; Kang, Y.-K.; Zhan, Z.; Buters, J. T. M.; Fojo, T.; Poruchynsky, M. S. *J. Biol. Chem*. **1997**, *272*, 17118−17125.

(18) Neidigh, K. A.; Gharpure, M. M.; Rimoldi, J. M.; Kingston, D. G. I.; Jiang, Y. Q.; Hamel, E. *Tetrahedron Lett.* **1994**, *35*, 6839−6842.

cold CH_2Cl_2 (−78 °C, 60 mL) and quenched with cold 0.1 N HCl (0 °C, 5 mL). The CH_2Cl_2 layer was washed successively with with water (2 × 10 mL), 5% $NaHCO_3$ (10 mL), H_2O (5 mL), and brine (5 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography (hexanes: EtOAc, 1:1) to give **6** (291 mg, 66%). The NMR data (^1H and ^{13}C) were identical with those reported previously.[10]

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)paclitaxel 1,2-Carbonate (7). To a solution of **6** (935 mg, 1 mmol) in anhydrous CH_2Cl_2 (19 mL) were added carbonyldiimidazole (3.523 g, 21.73 mmol) and imidazole (218 mg, 3.20 mmol). The reaction mixture was stirred under argon at 35−40 °C for 24 h. After this period, the reaction mixture was diluted with 200 mL of CH_2Cl_2 and washed successively with 5% HCl (5 × 60 mL), 5% $NaHCO_3$ (2 × 60 mL), H_2O (60 mL), and brine (60 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography (40% EtOAc in hexanes) to give **7** (818 mg, 85%) as a white crystalline solid: mp 222−224 °C; ^1H NMR δ −0.28 (s, 3H), −0.11 (s, 3H), 0.59 (q, 6H, J = 7.83 Hz), 0.82 (s, 9H), 0.92 (t, 9H, J = 7.86 Hz), 1.16 (s, 3H), 1.18 (s, 3H), 1.65 (s, 3H), 1.98 (m, 1H), 2.16 (s, 6H), 2.47 (dd, 1H, J = 9.77, 15.26 Hz), 2.57 (m, 1H), 2.75 (dd, 1H, J = 4.58, 15.71 Hz), 2.99 (d, 1H, J = 6.11 Hz), 4.21 (dd, 1H, J = 6.87, 10.53 Hz), 4.39 (d, 1H, J = 5.34 Hz), 4.53 (d, 1H, J = 8.70 Hz), 4.53 (d, 1H, J = 1.68 Hz), 4.59 (d, 1H, J = 8.69 Hz), 4.94 (dd, 1H, J = 2.29, 9.31 Hz), 5.15 (s, 1H), 5.85 (dd, 1H, J = 1.6, 9.0 Hz), 5.89 (brt, 1H, J = 7.0 Hz), 6.43 (s, 1H), 7.26−7.54 (m, 8H), 7.75 (d, 2H, J = 8.32 Hz); ^{13}C NMR δ −5.88, −5.58, 5.21, 6.75, 9.92, 16.54, 18.23, 19.22, 20.81, 25.50, 26.40, 32.46, 37.92, 41.05, 48.61, 55.24, 60.07, 71.04, 72.17, 73.19, 75.14, 76.00, 80.23, 81.17, 87.51, 89.80, 126.68, 127.05, 127.97, 128.55, 128.86, 132.14, 133.41, 133.98, 139.13, 141.29, 152.69, 167.38, 169.18, 170.42, 202.32. FABMS m/z 962 $[M + H]^+$. Anal. Calcd for $C_{51}H_{71}NO_{13}Si_2$: C, 63.65; H, 7.44; N, 1.46. Found: C, 63.77; H, 7.61; N, 1.46.

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5-α-iodo-20-hydroxy-D-seco-paclitaxel 1,2-Carbonate (8). To a stirred solution of **7** (389 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (23 mL) at −78 °C was added iodotrimethylsilane (220 μL, 1.62 mmol). The reaction mixture was stirred at −78 °C for 45 min and quenched with CH_2Cl_2 (180 mL) precooled to −78 °C, followed by water (100 mL, 0 °C). The organic layer was separated and washed successively with 0.05 M $Na_2S_2O_4$ (2 ×100 mL), water (25 mL), and brine (25 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by flash silica gel chromatography (EtOAc:hexanes, 2:3) to give 413 mg (93%) of **8** as a white crystalline solid: mp 153−155 °C; ^1H NMR δ −0.36 (s, 3H), −0.15 (s, 3H), 0.56 (q, 6H, J = 7.93 Hz), 0.75 (s, 9H), 0.92 (t, 9H, J = 7.94 Hz), 1.08 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H), 2.03 (m, 1H), 2.15 (s, 3H), 2.23 (td, 1H, J = 3.21, 15.72 Hz), 2.36 (dd, 1H, J = 9.77, 15.56 Hz), 2.45 (d, 3H, J = 1.07 Hz), 3.16 (dd, 1H, J = 5.72, 15.49 Hz), 3.54 (d, 1H, J = 10.98 Hz), 3.59 (d, 1H, J = 4.88 Hz), 3.99 (d, 1H, J = 11.14 Hz), 4.26 (d, 1H, J = 4.88 Hz), 4.50 (dd, 1H, J = 3.74, 10.61 Hz), 4.59 (d, 1H, J = 1.83 Hz), 5.07 (t, 1H, J = 2.98 Hz), 5.83 (dd, 1H, J = 1.30, 8.17 Hz), 6.11 (dd, 1H, J = 8.17 Hz), 6.54 (s, 1H), 7.17 (d, 1H, J = 8.24 Hz), 7.26−7.54 (m, 8H), 7.74 (d, 2H, J = 7.02 Hz); ^{13}C NMR δ −6.00, −5.61, 5.14, 6.75, 13.38, 17.67, 18.16, 19.70, 20.79, 25.45, 26.34, 32.49, 38.90, 41.01, 45.34, 46.52, 55.75, 60.73, 62.01, 70.61, 71.02, 73.58, 75.04, 75.43, 82.13, 89.74, 126.92, 127.06, 127.61, 128.35, 128.90, 132.01, 133.01, 133.79, 138.54, 143.22, 152.71, 167.32, 169.08, 171.18, 201.42; HRFABMS calcd for $C_{51}H_{72}NO_{13}Si_2INa$ $[M+Na]^+$ m/z 1112.3485, found 1112.3488. Anal. Calcd for $C_{51}H_{72}NO_{13}Si_2I$: C, 56.19; H, 6.66; N, 1.28. Found: C, 55.90; H, 6.62; N, 1.52.

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5-α-iodo-4,20-epoxy-D-seco-paclitaxel 1,2-Carbonate (10). To a stirred solution of **8** (288 mg, 0.26 mmol) and DMAP (425 mg, 3.48 mmol) in anhydrous CH_2Cl_2 at 0 °C was added trifluoromethanesulfonyl chloride (300 μL, 2.82 mmol). The reaction mixture was stirred at 0 °C for 2 min, at which time the solution became very viscous. It was kept in the 0 °C cooling bath for a total of 8 min and then left at room temperature for 50 min. After this period, 100 mL of EtOAc and 15 mL water were added to the reaction flask. The organic layer was separated from the aqueous layer, washed successively with water (2 × 15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. The organic phase was evaporated to dryness and the crude product purified by flash chromatography (EtOAc:hexanes, 3:7) to give **10** (266 mg, 96%) as a colorless crystalline solid: mp 241−243 °C; ^1H NMR δ −0.32 (s, 3H), −0.13 (s, 3H), 0.56 (q, 6H, J = 7.88 Hz), 0.80 (s, 9H), 0.89 (t, 9H, J = 7.94 Hz), 1.16 (s, 3H), 1.25 (s, 3H), 1.31 (s, 3H), 2.16 (s, 3H), 2.28 (m, 1H), 2.41 (s, 3H), 2.39 (m, 1H), 2.57 (dd, 1H, J = 9.77, 15.87 Hz), 2.68 (dd, 1H, J = 6.87, 15.87 Hz), 2.94 (d, 1H, J = 4.88 Hz), 3.86 (d, 1H, J = 4.73 Hz), 3.87 (d, 1H, J = 4.43 Hz), 4.18 (d, 1H, J = 5.03 Hz), 4.21 (m, 1H), 4.50 (d, 1H, J = 1.99 Hz), 4.53 (m, 1H), 5.71 (dd, 1H, J = 1.53, 8.85 Hz), 6.24 (t, 1H, J = 7.79 Hz), 6.54 (s, 1H), 7.07 (d, 1H, J = 8.69 Hz), 7.26−7.53 (m, 8H), 7.80 (d, 2H, J = 7.02 Hz); ^{13}C NMR δ −5.65, −5.32, 5.12, 6.63, 12.23, 17.34, 18.17, 19.86, 20.75, 25.56, 26.30, 33.18, 39.36, 40.10, 41.29, 41.89, 55.85, 58.79, 60.24, 62.82, 69.95, 70.56, 75.67, 75.83, 80.72, 89.08, 126.85, 127.05, 127.73, 128.52, 128.66, 131.58, 131.87, 134.33, 138.57, 143.96, 152.28, 166.55, 169.08, 171.16, 201.54; HR-FABMS calcd for $C_{51}H_{70}INO_{12}Si_2Na$ $[M + Na]^+$ m/z 1094.3379, found 1094.3347. Anal. Calcd for $C_{51}H_{70}INO_{12}Si_2$: C, 57.13; H, 6.68; N, 1.31. Found: C, C, 57.04; H, 6.50; N, 1.27.

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-sulfinylpaclitaxel 1,2-Carbonate (11) and 2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-dithiapaclitaxel 1,2-Carbonate (12). To a mixture of **10** (94.3 mg, 0.088 mmol) and Li_2S (25 mg, 0.544 mmol) was added anhydrous THF (7.8 mL). The resulting suspension was stirred under argon at room temperature for 28 h (TLC control for the disappearance of **10**). The reaction mixture was diluted with EtOAc (115 mL) and 0.05 M $Na_2S_2O_4$ (25 mL). The organic layer was separated from the aqueous phase and washed successively with 0.05 M $Na_2S_2O_4$ solution (25 mL), water (15 mL), and brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The major product had a lower R_f than **10**, and ^{13}C NMR indicated that the 1, 2-carbonate protecting group was absent in this product. Hence, the crude product was treated with carbonyldiimidazole in order to synthesize the 1,2-carbonate-protected compound; i.e to the previously dried crude product in anhydrous CH_2Cl_2 (1.9 mL) were added carbonyldiimidazole (201 mg, 1.24 mmol) and imidazole (56 mg, 0.82 mmol). The reaction mixture was stirred under argon at room temperature for 12 h and worked up as described in the preparation of **7**. The crude product was purified by preparative TLC (15% EtOAc in hexanes) to give two products. The major product was 2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-sulfinylpaclitaxel 1,2-carbonate (**11**) (48.1 mg, 56%) and the minor product was 2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-dithiapaclitaxel 1,2-carbonate (**12**) (11.2 mg, 13%). Compounds **11** and **12** had very similar R_f values and required multiple developments by preparative TLC to separate them. With a large excess of Li_2S (103.5 mg, 2.25 mmol) and **10** (64.4 mg, 0.06 mmol) in 5.4 mL of THF over 28 h at room temperature, the major product was **12** (25.4 mg, 42%) and the minor product was **11** (11.6 mg, 20%). Compound **11**: ^1H NMR δ −0.29 (s, 3H), −0.11 (s, 3H), 0.58 (q, 6H, J = 7.78 Hz), 0.83 (s, 9H), 0.91 (t, 9H, J = 7.94 Hz), 1.157 (s, 3H), 1.164 (s, 3H), 1.63 (s, 3H), 2.155 (s, 3H), 2.165 (s, 3H), 2.34 (m, 1H), 2.51 (m, 2H), 2.75 (d, 1H, J = 5.34 Hz), 2.90 (dd, 1H, J = 4.66, 15.34 Hz), 3.10 (d, 1H, J = 11.75 Hz), 3.47 (t, 1H, J = 9.00 Hz), 3.78 (d, 1H, J = 11.90 Hz), 4.08 (m, 1H), 4.29 (d, 1H, J = 5.34 Hz), 4.52 (d, 1H, J = 1.53 Hz), 5.35 (bs, 1H), 5.87 (m, 1H), 5.93 (d, 1H, J = 8.85 Hz), 6.41 (s, 1H), 7.27−7.52 (m, 8H), 7.78 (d, 2H, J = 7.02 Hz); ^{13}C NMR δ −5.89, −5.56, 5.25, 6.76, 11.32, 16.59, 18.23, 19.20, 20.80, 25.52, 26.46, 32.48, 39.73, 40.84, 41.08, 47.79, 51.44, 55.29, 60.28, 71.14, 72.44, 75.30, 75.95, 78.93, 81.44, 89.84, 126.63, 127.07, 127.92, 128.59, 128.83, 132.07, 133.58, 133.69, 139.33,

141.35, 152.78, 167.31, 169.21, 170.40, 202.27; HRFABMS calcd for $C_{51}H_{72}NO_{12}Si_2S$ [M + H]$^+$ *m/z* 978.4314, found 978.4290 (2.4 ppm dev). Compound **12**: ^{1}H NMR δ −0.28 (s, 3H), −0.12 (s, 3H), 0.59 (q, 6H, J = 7.78 Hz), 0.83 (s 9H), 0.91 (t, 9H, J = 7.94 Hz), 1.18 (s, 6H), 1.28 (s, 3H), 2.16 (s, 3H), 2.18 (d, 3H, J = 1.22 Hz), 2.22 (m, 1H), 2.47 (m, 2H), 3.04 (dd, 1H, J = 4.43, 15.72 Hz), 3.32 (bs, 2H), 3.37 (d, 1H, J = 5.34 Hz), 3.38 (m, 1H), 4.20 (dd, 1H, J = 4.50, 11.37 Hz), 4.29 (d, 1H, J = 5.04 Hz), 4.49 (d, 1H, J = 1.53 Hz), 4.66 (bs, 1H), 5.78 (dd, 1H, J = 1.30, 8.47 Hz), 5.92 (dd, 1H, J = 3.28, 10.00 Hz), 6.53 (s, 1H), 7.22 (d, 1H, J = 8.54 Hz), 7.27−7.53 (m, 8H), 7.76 (d, 2H, J = 6.87 Hz); ^{13}C NMR δ −5.86, −5.58, 5.19, 6.76, 10.88, 16.73, 18.23, 19.11, 20.80, 25.52, 26.68, 32.35, 35.48, 41.31, 49.32, 49.43, 55.31, 61.69, 64.95, 71.17, 72.57, 75.16, 75.64, 81.32, 86.13, 89.71, 126.72, 127.02, 127.94, 128.55, 128.78, 131.93, 133.70, 133.76, 139.11, 141.30, 152.37, 167.10, 169.19, 170.40, 201.86; HRFABMS calcd for $C_{51}H_{72}NO_{12}Si_2S_2$ [M + H]$^+$ *m/z* 1010.4035, found 1010.4051 (1.6 ppm dev).

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-sulfonylpaclitaxel 1,2-Carbonate (13). To a stirred solution of **11** (12.7 mg, 0.013 mmol) in anhydrous CH_2Cl_2 (250 μL) at 0 °C was added dropwise over 5 min a solution of 3-chloroperbenzoic acid (12.7 mg, 0.074 mmol) in 250 μL of anhydrous CH_2Cl_2. The reaction mixture was stirred at 0 °C for 30 min. The cooling bath was removed and the reaction mixture stirred at room temperature for 50 min. The reaction mixture was diluted with CH_2Cl_2 (45 mL) and saturated sodium sulfite (15 mL). The organic layer was separated from the aqueous phase and washed successively with 5% $NaHCO_3$ (2 × 17 mL), water (15 mL), and brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by preparative TLC (EtOAc:hexanes, 3:7) to give **13** (8 mg, 61%): ^{1}H NMR δ −0.21 (s, 3H), −0.08 (s, 3H), 0.62 (q, 6H, J = 7.71 Hz), 0.87 (s, 9H), 0.94 (t, 9H, J = 7.86 Hz), 1.19 (s, 3H), 1.20 (s, 3H), 1.38 (s, 3H), 2.18 (s, 3H), 2.20 (d, 3H, J = 1.07 Hz), 2.43 (m, 2H), 2.50 (dd, 1H, J = 9.77, 15.72 Hz), 2.70 (dd, 1H, J = 4.58, 15.72 Hz), 3.34 (d, 1H, J = 5.49 Hz), 4.22 (t, 1H, J = 8.39 Hz), 4.28 (dd, 1H, J = 4.28, 15.26 Hz), 4.33 (d, 1H, J = 5.49 Hz), 4.48 (m, 1H), 4.58 (d, 1H, J = 1.53 Hz), 5.89 (d, 1H, J = 9.62 Hz), 5.94 (dd, 1H, J = 3.37, 9.77 Hz), 6.24 (br s, 1H), 6.46 (s,1H), 7.28−7.56 (m, 8H), 7.77 (d, 2H, J = 7.02 Hz); ^{13}C NMR δ −5.73, −5.54, 5.18, 6.73, 10.78, 16.50, 18.26, 19.16, 20.76, 25.55, 26.37, 28.35, 32.52, 41.14, 50.43, 54.71, 59.74, 63.00, 70.70, 71.18, 75.23, 75.68, 77.65, 80.84, 82.82, 89.98, 127.02, 127.17, 128.17, 128.64, 128.85, 132.26, 133.11, 133.45, 138.66, 141.58, 152.03, 167.15, 169.13, 170.47, 200.95; HRFABMS calcd for $C_{51}H_{72}NO_{14}Si_2S$ [M + H]$^+$ *m/z* 1010.4212, found 1010.4206 (0.6 ppm dev).

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-4-methoxycarbonyl-7-(triethylsilyl)-5,20-deoxy-5,20-sulfinylpaclitaxel 1,2-Carbonate (14). To a stirred solution of **11** (23.3 mg, 0.024 mmol) in anhydrous THF (730 μL), at −78 °C under argon, was added 90 μL (0.09 mmol) of a 1.0 M of solution of lithium bis(trimethysilyl)amide (LHMDS) in THF. The reaction mixture was stirred at −78 °C for 7 min. The reaction flask was removed from the −78 °C bath and stirred at room temperature for 1 min. It was then placed in the −78 °C bath and stirred for 2 min, and freshly distilled methyl chloroformate (20 μL, 0.26 mmol) was added. The reaction mixture was stirred at −78 °C for 10 min and quenched with EtOAc (60 mL). The EtOAc layer was washed successively with 5% HCl (2 × 20 mL), 5% $NaHCO_3$ (2 × 20 mL), water (15 mL), and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by preparative TLC (hexanes:EtOAc, 4:1) to give unreacted **11** (9.5 mg, 41%) and **14** (9.7 mg, 39%): ^{1}H NMR δ −0.39 (s, 3H), −0.07 (s, 3H), 0.56 (q, 6H, J = 7.73 Hz), 0.77 (s, 9H), 0.88 (t, 9H, J = 7.94 Hz), 1.20 (s, 3H), 1.27 (s, 3H), 1.87 (s, 3H), 2.07 (d, 3H, J = 1.22 Hz), 2.14 (s, 3H), 2.17 (m, 2H), 2.47 (dd, 1H, J = 9.69, 15.64 Hz), 2.64 (m, 1H), 3.47 (d, 1H, J = 6.11 Hz), 3.54 (d, 1H, J = 12.82 Hz), 3.60 (d, 1H, J = 12.97 Hz), 3.99 (s, 3H), 4.17 (dd, 1H, J = 5.19, 10.99 Hz), 4.31 (dd, 1H, J = 6.18, 10.45 Hz), 4.44 (d, 1H, J = 6.10 Hz), 4.71 (d, 1H, J = 1.83 Hz), 5.86 (d, 1H, J = 8.55 Hz), 6.22 (t, 1H, J = 8.02 Hz), 6.41 (s, 1H), 7.05 (d, 1H, J = 9.31 Hz), 7.27−7.53 (m, 8H), 7.78 (d, 2H, J = 7.02 Hz); ^{13}C NMR δ −5.96, −5.28, 5.24, 6.73, 11.99, 15.34, 18.06, 20.39, 20.77, 25.48, 25.59, 32.24, 35.37, 40.35, 41.24, 41.67, 46.41, 54.88, 56.98, 59.90, 68.90, 72.10, 75.16, 75.78, 81.31, 89.31, 89.93, 126.35, 127.02, 127.62, 128.51, 128.79, 130.87, 131.78, 134.18, 138.62, 143.75, 150.86, 152.37, 166.73, 169.08, 171.47, 201.89; HRFABMS calcd for $C_{53}H_{73}NO_{14}Si_2SLi$ [M + Li]$^+$ *m/z* 1042.4450, found 1042.4465 (−1.4 ppm dev).

2′-(*tert*-Butyldimethylsilyl)-4-deacetyl-4-methoxycarbonyl-7-(triethylsilyl)-5,20-deoxy-5,20-sulfinylpaclitaxel (15). A solution of **14** (9.0 mg, 0.009 mmol) in anhydrous THF (160 μL) was stirred at −78 °C under argon. To the solution of **14** was added phenyllithium (0.045 mmol, 25 μL of a 1.8 M solution in cyclohexanes−ether). The reaction mixture was stirred at −78 °C for 3 min and quenched with EtOAc (25 mL). The EtOAc layer was washed successively with 5% HCl (2 × 8 mL), 5% $NaHCO_3$ (2 × 6 mL), water (6 mL), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification of the crude product by preparative TLC (hexanes:EtOAc, 4:1) gave 5.9 mg (61%) of **15**: ^{1}H NMR δ −0.37 (s, 3H), −0.07 (s, 3H), 0.56 (q, 6H, J = 7.68 Hz), 0.75 (s, 9H), 0.90 (t, 9H, J = 7.94 Hz), 1.11 (s, 3H), 1.19 (s, 3H), 1.79 (s, 3H), 2.02−2.21 (m, 2H), 2.11 (s, 3H), 2.15 (s, 3H), 2.38 (dd, 1H, J = 8.63, 15.65 Hz), 2.54 (m, 1H), 3.13 (d, 1H, J = 12.06 Hz), 3.48 (d, 1H, J = 12.20 Hz), 3.96 (d, 1H, J = 7.17 Hz), 4.05 (dd, 1H, J = 6.94, 10.61 Hz), 4.09 (s, 3H), 4.33 (dd, 1H, J = 5.65, 11.30 Hz), 4.73 (d, 1H, J = 1.83 Hz), 5.66 (d, 1H, J = 7.33 Hz), 5.93 (d, 1H, J = 8.32 Hz), 6.26 (t, 1H, J = 8.07 Hz), 6.44 (s, 1H), 7.09 (d, 1H, J = 9.30 Hz), 7.26−7.57 (m, 11H), 7.76 (d, 2H, J = 7.18 Hz), 8.12 (d, 2H, J = 7.02 Hz); ^{13}C NMR δ −6.06, −5.29, 5.31, 6.77, 11.85, 14.62, 18.11, 20.90, 21.06, 25.47, 26.61, 35.95, 40.03, 42.80, 42.91, 48.90, 55.13, 56.91, 58.67, 70.15, 72.36, 75.19, 75.29, 75.32, 78.88, 90.74, 126.37, 126.97, 127.58, 128.50, 128.77, 128.83, 129.59, 130.20, 131.69, 132.70, 133.64, 134.35, 138.79, 140.83, 151.42, 166.74, 167.30, 169.32, 171.36, 201.63; HRFABMS calcd for $C_{59}H_{79}NO_{14}Si_2SLi$ [M + Li]$^+$ *m/z* 1120.4920, found 1120.4948 (−2.5 ppm dev).

4-Deacetyl-4-methoxycarbonyl-5,20-deoxy-5,20-sulfinylpaclitaxel (16). Compound **15** (7.3 mg, 0.007 mmol) was dissolved in THF (830 μL) in a 5 mL Teflon flask. The solution of **15** was stirred at 0 °C and a cold solution (0 °C) of hydrogen fluoride−pyridine (60 μL) added. The reaction mixture was stirred at room temperature for 9 h and diluted with EtOAc (25 mL). The organic layer was washed successively with 5% $NaHCO_3$ (2 × 6 mL), 5% HCl (2 × 6 mL), water (6 mL), and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by preparative TLC (hexanes:EtOAc, 1:1) to give 4.4 mg (76%) of **16**: ^{1}H NMR δ 1.11 (s, 3H), 1.19 (s, 3H), 1.75 (s, 3H), 1.86 (d, 3H, J = 1.07 Hz), 2.19 (m, 1H), 2.22 (s, 3H), 2.33 (m, 2H), 2.56 (m, 2H), 3.12 (d, 1H, J = 11.90 Hz), 3.49 (d, 1H, J = 12.20 Hz), 3.58 (d, 1H, J = 3.66 Hz), 3.90 (d, 1H, J = 7.17 Hz), 3.93 (s, 3H), 4.01 (dd, 1H, J = 7.17, 10.38 Hz), 4.22 (m, 1H), 4.83 (dd, 1H, J = 2.29, 3.66 Hz), 5.66 (d, 1H, J = 7.17 Hz), 5.94 (d, 1H, J = 9.00 Hz), 6.16 (t, 1H, J = 8.47 Hz), 6.24 (s, 1H), 7.03 (d, 1H, J = 9.15 Hz), 7.31−7.59 (m, 11H), 7.76 (d, 2H, J = 7.02 Hz), 8.12 (d, 2H, J = 7.17 Hz); ^{13}C NMR δ 11.25, 15.18, 20.87, 21.56, 27.02, 36.01, 36.17, 38.43, 42.77, 43.00, 47.60, 54.33, 56.37, 58.87, 71.87, 72.14, 73.37, 75.25, 75.67, 79.06, 90.87, 126.88, 127.01, 128.07, 128.71, 128.82, 128.86, 129.44, 130.18, 131.88, 132.39, 133.74, 133.83, 138.49, 142.53, 151.99, 166.64, 167.14, 171.38, 172.70, 203.46; HRFABMS calcd for $C_{47}H_{51}NO_{14}SNa$ [M + Na]$^+$ *m/z* 908.2928, found 908.2933 (−0.8 ppm dev).

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-4-methoxycarbonyl-7-(triethylsilyl)paclitaxel 1,2-Carbonate (17). Acetylation of **7** to give **17** was done using the same methodology as for the preparation of **14** from **11**. Reaction of **7** (28.4 mg, 0.03 mmol) in anhydrous THF (906 μL) with LHMDS (96 μL) and methyl chloroformate (24 μL) gave 20.8 mg (69%) of **17** after workup and preparative TLC (hexanes: EtOAc), 4:1): ^{1}H NMR δ −0.38 (s, 3H), −0.08 (s, 3H), 0.56 (q, 6H, J = 7.58 Hz), 0.77 (s, 9H), 0.89 (t, 9H, J = 7.94 Hz), 1.21

(s, 3H), 1.28 (s, 3H), 1.75 (s, 3H), 1.94 (dd, 1H, J = 10.76, 14.73 Hz), 2.04 (d, 3H, J = 0.61 Hz), 2.14 (s, 3H), 2.24 (dd, 1H, J = 7.71, 15.80 Hz), 2.52 (dd, 1H, J = 9.61, 15.72 Hz), 2.62 (m, 1H), 3.53 (d, 1H, J = 5.65 Hz), 3.96 (s, 3H), 4.39 (dd, 1H, J = 7.1, 9.54 Hz), 4.51 (m, 2H), 4.69 (d, 1H, J = 1.53 Hz), 4.72 (d, 1H, J = 9.31 Hz), 5.09 (d, 1H, J = 8.69 Hz), 5.77 (d, 1H, J = 9.46 Hz), 6.22 (t, 1H, J = 8.17 Hz), 6.43 (s, 1H), 7.01 (d, 1H, J = 9.31 Hz), 7.26−7.54 (m, 8H), 7.77 (d, 2H, J = 6.86 Hz); ^{13}C NMR δ -5.91, −5.26, 5.16, 6.71, 10.06, 15.19, 18.06, 20.47, 20.73, 25.46, 32.09, 37.86, 41.40, 43.54, 54.96, 57.05, 59.92, 69.24, 71.49, 75.01, 75.74, 75.79, 80.98, 81.86, 83.53, 89.65, 126.36, 127.00, 127.72, 128.57, 128.78, 131.53, 131.79, 134.13, 138.41, 143.68, 151.57, 152.38, 166.82, 169.03, 171.55, 201.72; HRFABMS calcd for $C_{53}H_{74}NO_{15}Si_2$ $[M + H]^+$ m/z 1020.4597, found 1020.4568 (2.8 ppm dev).

2′-(*tert*-Butyldimethylsilyl)-4-deacetyl-4-methoxycarbonyl-7-(triethylsilyl)paclitaxel (18). The benzoylation of **17** to give **18** was done using the same methodology as for the preparation of **15** from **14**. Benzoylation of **17** (13.5 mg, 0.013 mmol) in anhydrous THF (250 μL) with phenyllithium (38 μL) afforded after workup and preparative TLC (hexanes:EtOAc, 3:1) 10.2 mg (70%) of **18**: ^{1}H NMR δ −0.35 (s, 3H), −0.05 (s, 3H), 0.56 (q, 6H, J = 7.58 Hz), 0.77 (s, 9H), 0.91 (t, 9H, J = 7.93 Hz), 1.13 (s, 3H), 1.20 (s, 3H), 1.69 (s, 3H), 1.91 (m, 1H), 2.06 (s, 3H), 2.07−2.15 (m, 1H), 2.16 (s, 3H), 2.41 (dd, 1H, J = 8.70, 15.72 Hz), 2.53 (m, 1H), 3.95 (d, 1H, J = 7.48 Hz), 4.05 (s, 3H), 4.24 (d, 1H, J = 8.70 Hz), 4.34 (d, 1H, J = 8.39 Hz), 4.45 (dd, 1H, J = 6.56, 10.68 Hz), 4.69 (d, 1H, J = 1.68 Hz), 4.98 (d, 1H, J = 7.94 Hz), 5.70 (d, 1H, J = 6.87 Hz), 5.79 (d, 1H, J = 8.39 Hz), 6.25 (t, 1H, J = 8.78 Hz), 6.45 (s, 1H), 7.08 (d, 1H, J = 9.01 Hz), 7.27−7.58 (m, 11H), 7.74 (d, 2H, J = 7.18 Hz), 8.11 (d, 2H, J = 7.17 Hz); ^{13}C NMR δ −5.94, −5.23, 5.24, 6.74, 10.12, 14.47, 18.11, 20.87, 21.04, 25.47, 26.51, 35.60, 37.16, 43.20, 46.72, 55.36, 56.66, 58.30, 70.64, 72.04, 74.86, 75.07, 75.15, 76.10, 78.50, 83.29, 84.01, 126.41, 126.96, 127.73, 128.58, 128.73, 128.76, 129.22, 130.13, 131.73, 133.67, 133.69, 134.22, 138.68, 140.41, 152.33, 166.85, 167.07, 169.30, 171.42, 201.57; HRFABMS calcd for $C_{59}H_{80}NO_{15}Si_2$ $[M + H]^+$ m/z 1098.5067, found 1098.5101 (−3.2 ppm dev).

4-Deacetyl-4-methoxycarbonylpaclitaxel (19). Deprotection of the C-2′ and C-7 position in **18** to give **19** was done using the same methodology as that used to convert **15** to **16**. Deprotection of the C-7 and C-2′ positions in **18** (13.1 mg, 0.012 mmol) with HF−pyridine (100 μL) in anhydrous THF (1.5 mL) afforded after preparative TLC (hexanes:EtOAc, 1:1) compound **19** (9 mg, 87%) as an amorphous solid: ^{1}H NMR δ 1.12 (s, 3H), 1.21 (s, 3H), 1.66 (s, 3H), 1.82 (s, 3H), 1.87 (m, 1H), 2.22 (s, 3H), 2.30 (dd, 1H, J = 9.09, 15.49 Hz), 2.43 (dd, 1H, J = 8.55, 15.72 Hz), 2.52 (m, 1H), 3.62 (bs, 1H), 3.80 (s, 3H), 3.84 (d, 1H, J = 7.02 Hz), 4.20 (d, 1H, J = 8.70 Hz), 4.33 (d, 1H, J = 8.54 Hz), 4.36 (dd, 1H, J = 6.72, 10.84 Hz), 4.79 (d, 1H, J = 1.83 Hz), 4.96 (dd, 1H, J = 1.83, 9.46 Hz), 5.69 (d, 1H, J = 7.02 Hz), 5.82 (dd, 1H, J = 1.99, 9.01 Hz), 6.18 (t, 1H, J = 8.32 Hz), 6.25 (s, 1H), 6.94 (d, 1H, J = 9.15 Hz), 7.31−7.60 (m, 11H), 7.72 (d, 2H, J = 7.01 Hz), 8.14 (d, 2H, J = 7.18 Hz); ^{13}C NMR δ 9.63, 14.96, 20.87, 21.72, 26.87, 35.38, 35.82, 43.08, 45.87, 54.74, 56.00, 58.33, 71.99, 72.30, 73.01, 74.87, 75.59, 75.99, 78.84, 83.14, 84.09, 127.01, 127.10, 128.28, 128.69, 128.74, 128.96, 129.11, 130.23, 131.91, 133.37, 133.73, 138.42, 142.08, 153.12, 166.89, 167.04, 171.32, 172.97, 203.48; HRFABMS calcd for $C_{47}H_{51}NO_{15}Li$ $[M + Li]^+$ m/z 876.3419, found 876.3402 (1.9 ppm dev).

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-selenapaclitaxel 1,2-Carbonate (20). To a stirred solution of Superhydride (0.6 mL, 1 M solution in THF, 0.6 mmol) was added selenium powder (25.3 mg, 0.32 mmol) under argon at room temperature. A further 3.7 mg (0.05 mmol) of selenium powder was added and the white suspension turned pale red. Sufficient Superhydride was syringed into the solution until the latter changed to a light pink color. The resulting suspension was stirred at room temperature for 20 min and cooled to −20 °C, and after 5 min a solution of epoxide **10** (7.0 mg, 0.0065 mmol) in anhydrous THF (0.25 mL) was added. The cooling bath was removed and stirring continued at room temperature for 2 h. The reaction mixture was worked up by adding excess EtOAc and a few crystals of BHT (2,6-di-*tert*-butyl-4-methylphenol). The resulting solution was filtered twice through a short column of silica gel and the filtrate evaporated to dryness. The crude product was purified by preparative TLC (30% hexanes in EtOAc) to give the selenapaclitaxel analogue **20** as a white foam (4.5 mg, 67%): ^{1}H NMR δ −0.28 (s, 3H), −0.10 (s, 3H), 0.60 (q, 6H, J = 7.9 Hz), 0.80 (s, 9H), 0.82 (t, 9H, J = 7.9 Hz), 1.18 (br s, 6H), 1.60 (br s, 3H), 2.16 (br s, 6H), 2.50 (m, 1H), 2.55 (m, 1H), 2.65 (d, 1H, J = 5.0 Hz), 3.00 (d, 1H, J = 11.0 Hz), 3.03 (m, 1H), 3.35 (t, 1H, J = 9.2 Hz), 3.94 (d, 1H, J = 11.0 Hz), 4.01 (m, 1H), 4.27 (d, 1H, J = 5.0 Hz), 4.51 (d, 1H, J = 1.7 Hz), 5.38 (s, 1H), 5.86 (m, 1H), 5.92 (dd, 1H, J = 1.7, 8.9 Hz), 6.41 (s, 1H), 7.20−7.60 (m, 8H), 7.80 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ −5.8, −5.5, 5.3, 6.7, 11.6, 16.6, 18.3, 19.8, 20.8, 25.5, 26.5, 28.4, 32.4, 37.5, 41.2, 41.6, 52.5, 55.4, 60.6, 71.2, 72.7, 75.3, 75.9, 80.9, 81.5, 89.8, 126.7, 127.1, 127.9, 128.6, 128.8, 132.0, 133.7, 139.4, 141.4, 152.9, 167.3, 169.2, 170.4, 202.2; HRFABMS calcd for $C_{51}H_{71}NO_{12}Si_2SeNa$ $[M + Na]^+$ m/z 1048.3578, found 1048.3587.

Acylation of Selenapaclitaxel 20. To a stirred solution of **20** (7.0 mg, 0.007 mmol) in anhydrous THF at −78 °C under argon was added 20 μL (0.02 mmol, 3 equiv) of a 1.0 M of solution of LHMDS in THF. The reaction mixture was stirred at −78 °C for 5 min. The reaction flask was removed from the −78 °C bath and stirred at room temperature for 1 min. At the end of this period, the reaction flask was returned to the −78 °C bath and stirred for 2 min, and freshly distilled methyl chloroformate (5 μL, 0.06 mmol, 9 equiv) was added. The reaction mixture was stirred at −78 °C for 5 min and quenched with EtOAc (60 mL). The EtOAc layer was washed successively with 5% HCl (2 × 20 mL), 5% $NaHCO_3$ (2 × 20 mL), water (15 mL), and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness, and the residue was purified by preparative TLC (hexanes:EtOAc, 4:1) to yield a mixture of unreacted starting material (**20**, 1.0 mg, 14%) and **25** (3.5 mg, 48%): ^{1}H NMR δ −0.24 (s, 3H), −0.01 (s, 3H), 0.51 (q, 6H, J = 7.9 Hz), 0.86 (s, 9H), 0.87 (t, 9H, J = 7.9 Hz), 1.19 (s, 3H), 1.22 (s, 3H), 1.26 (s, 3H), 1.80 (m, 1H), 2.17 (s, 3H), 2.22 (s, 3H), 2.32 (m, 2H), 2.51 (m, 1H), 3.62 (s, 3H), 3.78 (d, 1H, J = 5.2 Hz), 4.35 (m, 1H), 4.68 (d, 1H, J = 1.8 Hz), 5.24 (br t, 1H), 5.48 (br s, 1H), 5.57 (dd, 1H, J = 1.7, 8.6 Hz), 5.92 (br s, 1H), 6.23 (m, 1H), 6.57 (s, 1H), 7.08 (d, 1H, J = 8.7 Hz), 7.22−7.54 (m, 8H), 7.76 (d, 2H, J = 7.0 Hz); ^{13}C NMR δ −5.7, −5.2, 6.6, 10.4, 15.6, 18.2, 19.8, 20.8, 25.5, 26.2, 33.1, 35.8, 41.2, 43.6, 55.1, 55.7, 62.3, 69.5, 69.6, 74.7, 75.5, 81.8, 82.4, 89.4, 121.7, 126.8, 126.9, 127.8, 128.4, 128.7, 131.7, 136.6, 139.1, 143.0, 154.3, 166.3, 169.3, 171.3, 202.7; FABMS calcd for $C_{53}H_{75}NO_{14}Si_2Se$ $[M + H]^+$ m/z 1083, found m/z (rel int) 1083 $[M + H]^+$ (7%), 1026 $[M - Se + Na]^+$ (100%).

2′-(*tert*-Butyldimethylsilyl)-4-deacetyl-7-(triethylsilyl)-5,20-deoxy-5,20-selenapaclitaxel (22). The reaction of selenium compound **20** (10.0 mg, 0.01 mmol) in THF (0.2 mL) with phenyllithium (30 μL, 0.05 mmoL, 5 equiv) at −78 °C for 3 min afforded compound **22** (5.2 mg, 43%): ^{1}H NMR δ −0.30 (s, 3H), −0.10 (s, 3H), 0.60 (q, 6H, J = 8.0 Hz), 0.80 (s, 9H), 0.83 (t, 9H, J = 8.0 Hz), 1.18 (s, 3H), 1.20 (s, 3H), 1.60 (s, 3H), 2.18 (s, 3H), 2.20 (s, 3H), 2.38 (m, 1H), 2.60 (m, 2H), 2.70 (d, 1H, J = 11.0 Hz), 3.05 (m, 1H), 3.10 (d, 1H, J = 5.0 Hz), 3.30 (m, 1H), 3.82 (d, 1H, J = 11.0 Hz), 3.95 (m, 1H), 4.52 (d, 1H, J = 1.8 Hz), 5.05 (s, 1H), 5.60 (d, 1H, J = 5.0 Hz), 5.90 (m, 1H), 6.15 (dd, 1H, J = 1.7, 8.9 Hz), 6.49 (s, 1H), 7.20−7.60 (m, 11H), 7.80 (d, 2H, J = 8.0 Hz), 8.18 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ −5.8, −5.5, 5.3, 6.8, 10.9, 16.2, 18.3, 18.9, 20.9, 25.6, 27.3, 29.2, 35.5, 39.2, 41.3, 42.9, 54.7, 55.1, 60.4, 71.8, 72.8, 75.3, 75.4, 75.5, 77.3, 81.8, 126.9, 127.1, 128.3, 128.6, 128.8, 129.1, 130.4, 131.7, 133.3, 134.9, 135.9, 138.8, 139.6, 166.7, 167.6, 169.5, 170.3, 202.2; HRFABMS calcd for $C_{57}H_{77}NO_{12}Si_2SeNa$ $[M + Na]^+$ m/z 1126.4047, found 1126.4021.

4-Deacetyl-5,20-deoxy-5,20-selenapaclitaxel (23). Deprotection of the selena compound **22** (7.5 mg, 0.007 mmol) with hydrogen fluoride−pyridine (75 μL) yielded **23** (4.1 mg, 70%) as a colorless amorphous solid: ^{1}H NMR δ 1.20 (s, 6H), 1.60 (s, 3H), 2.00 (s, 3H), 2.12 (s, 3H), 2.40 (m, 1H), 2.50 (m, 2H), 2.67 (d, 1H, J = 10.0 Hz), 3.14 (d, 1H, J = 5.0 Hz), 3.19 (m,

1H), 3.28 (m, 1H), 3.38 (br s, 1H), 3.84 (m, 2H), 4.54 (br s, 1H), 5.30 (br s, 1H), 5.52 (d, 1H, $J = 5.0$ Hz), 5.59 (m, 1H), 6.20 (dd, 1H, $J = 1.7, 8.9$ Hz), 6.35 (s, 1H), 7.10−7.60 (m, 11H), 7.80 (d, 2H, $J = 8.0$ Hz), 8.20 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR δ 10.5, 16.6, 19.4, 20.9, 27.6, 29.7, 31.6, 35.2, 39.1, 42.8, 53.9, 60.0, 72.8, 73.5, 75.4, 75.7, 77.5, 81.9, 127.1, 127.2, 128.2, 128.7, 128.8, 129.0, 130.3, 131.8, 133.4, 134.5, 135.6, 139.8, 140.1, 166.8, 167.4, 170.9, 172.1, 204.2; HRFABMS calcd for $C_{45}H_{49}NO_{12}SeNa$ $[M + Na]^+$ m/z 898.2318, found 898.2333.

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Supporting Information Available: ^{1}H NMR spectra of compounds **8**, **10**, **11**−**20**, **22**, **23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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