Pergamon

Tetrahedron, Vol. 53, No. 10, pp. 3441-3456, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00074-4

Paclitaxel Analogs Modified in Ring C: Synthesis and Biological Evaluation

Xian Liang and David G. I. Kingston*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212

Byron H. Long, Craig A. Fairchild, and Kathy A. Johnston

Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 05843,

Abstract: Lead tetracetate oxidation of 6α-hydroxy-7-*epi*-paclitaxel leads to C-*nor*-paclitaxel and C-*seco*-paclitaxel derivatives. Tetrapropylammonium perruthenate (TPAP) oxidation of a 6α-hydroxy-7-*epi*-paclitaxel derivative leads to a 6-formyl-C-*nor*-paclitaxel derivative. Reaction of a 6α-O-trifluoromethanesulfonyl-7-*epi*-paclitaxel derivative with DMAP yields a 20-O-acetyl-4-deacetyl-5,6-dehydro-6-formyl-C-*nor*-paclitaxel derivative. C-*nor*-paclitaxel analogs are less active than paclitaxel.

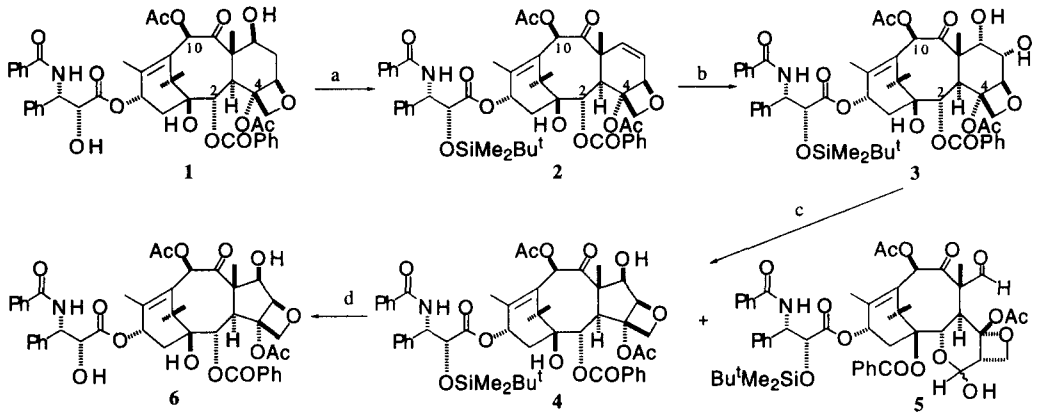
The importance of the novel diterpenoid paclitaxel (Taxol®) (**1**) in the clinical treatment of ovarian and breast cancers is now well established.[1] This importance has led to increased interest in understanding its structure-activity relationships, and significant advances have been made in this area.[2] Few reports, however, have focused on the polycyclic carbon skeleton of paclitaxel, although examples now exist of the preparation of *A-nor*,[3] *B-nor*,[4] and *C-homo*paclitaxels;[5] as expected, changes in the diterpenoid skeleton of paclitaxel cause significant changes in its biological activity. We have recently reported the synthesis of *C-nor*-paclitaxel and *C-seco*-paclitaxel in a preliminary communication,[6] and the synthesis of a *C-nor*-paclitaxel analogue with an opened oxetane ring was reported by Chen and his collaborators.[7] This paper reports the full details of the synthesis of *C-nor*-paclitaxel, a study of the oxidation of 6α-hydroxy-7-*epi*paclitaxel with TPAP, and an independent preparation of the *C-nor*-paclitaxel analogue prepared by Chen.

RESULTS AND DISCUSSION

Synthesis of C-nor-Paclitaxel and C-seco-Paclitaxel

The key starting material for our synthetic approach to *C-nor*-paclitaxel was 6α-hydroxy-7-*epi*paclitaxel (**3**), which was prepared as previously described from protected 7-deoxy-$\Delta^{6,7}$-paclitaxel (**2**).[8] Treatment of 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (**3**) with lead tetraacetate and sodium bicarbonate in anhydrous dichloromethane at 0 °C for 2 hours furnished two compounds, one in 67% yield which was slightly

more polar than the starting material and was identified as 2'-*O*-(*t*-butyldimethylsilyl)-*C-nor*-paclitaxel (**4**), and another in 11% yield which was slightly less polar than the starting material and was identified as the rearranged compound **5**. Deprotection of **4** with HF and pyridine afforded *C-nor*-paclitaxel (**6**) in 86% yield (Scheme 1).



Reagents: (a) Bu^tSiMe_2Cl/pyridine, then CF_3SO_2Cl, DMAP, 25 °C, 2 h, then DBU, dry CH_2Cl_2, 40 °C, 4 h; (b) OsO_4, NMO, 25 °C, 9h; (c) LTA, $NaHCO_3$, 2 hrs, 0 °C; (d) HF/pyridine, 1.5 h, r.t.

Scheme 1

The high resolution mass spectra (HRFABMS) of **6** showed a molecular ion $[MNa]^+$ at *m/z* 862.3064, indicating the loss of CH_2 as compared with paclitaxel (**1**). The protons and the carbons of **4** were assigned by a combination of ^1H, ^{13}C, DQCOSY, HETCOR and HMBC spectra. The ^1H, ^1H correlations from its DQCOSY spectrum and the three-bond ^1H, ^{13}C correlations from its HMBC spectrum revealed the formation of a 5-membered ring C as illustrated in Figure 1.

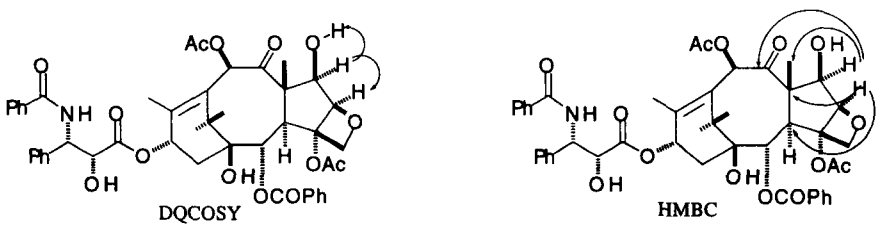
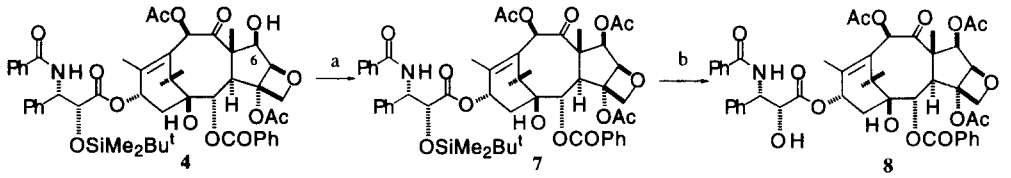


Figure 1: Key DQCOSY and HMBC correlations of C-*nor*-paclitaxel (6)

Acylation of **4** with acetyl chloride and DMAP yielded 2'-*O*-(*t*-butyldimethylsilyl)-6-*O*-acetyl-*C-nor*-paclitaxel (**7**) (Scheme 2). The C-6 proton was shifted downfield from 4.35 ppm to 5.44 ppm in its ^1H spectrum, providing further support for the structure of **4**. Deprotection of **7** with HF/pyridine yielded 6-*O*-acetyl-*C-nor*-paclitaxel (**8**) in 90% yield (Scheme 2).

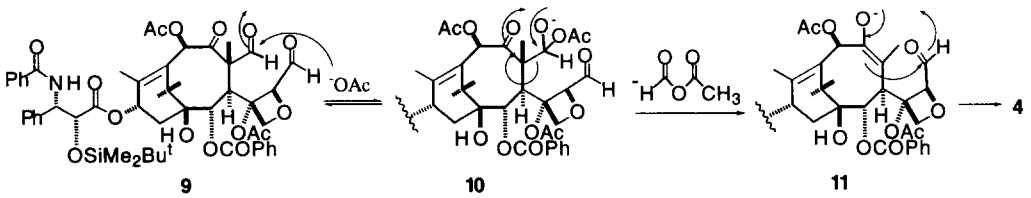


Reagents: (a) CH_3COCl, DMAP, 25 °C, 2 h; (b) HF/pyridine, 1.5 h, r.t.

Scheme 2

The proton signals of C-3, C-6, and C-20 were overlapped in the ^1H spectra of both **4** and **6**, but these signals were resolved in the acetyl derivative **7**, and this compound was thus selected for NOE studies. The NOE difference spectra of **7** showed that the C-6 and C-5 proton signals were enhanced when the C-3α proton was irradiated, and the C-6 and C-3 signals were enhanced when the C-5α proton was irradiated. No enhancement of the C-6 signal was observed when the C-19 methyl group was irradiated. The results of these experiments revealed that the proton at the C-6 position was on the same face of ring C as the protons at C-3 and C-5, which is the α face. The stereochemistry of the hydroxyl group at the C-6 position in **6** is thus β.

The formation of *C-nor*-paclitaxel can be explained by normal lead tetraacetate oxidation of **3** to the dialdehyde **9**, followed by the attack of an acetate ion on the electrophilic 7-carbonyl carbon to form the diol monoacetate **10** which then undergoes cleavage with loss of formic acetic anhydride and formation of the enolate **11**. Enolate **11** then attacks the 6-carbonyl carbon from the less hindered face (opposed to the oxetane ring which is on the β face of ring C) to form the *C-nor*-paclitaxel derivative with a 6β-hydroxyl group (Scheme 3). This is another example of a retro-aldol reaction on paclitaxel; such reactions were first observed and explained by Miller.[9]



Scheme 3

The structure of the *C-seco* compound **5** was established only after a careful analysis of its spectroscopic data. Its composition, as deduced from its HRFABMS, $(MLi)^+$ at *m/z* 988.4100, indicated the loss of two protons from the protected starting material 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (**3**), consistent with the formation of the dialdehyde **9**. However, the ^1H NMR spectrum of **5** showed only one aldehyde CH signal, and the aldehyde giving rise to this signal was assigned to the C-7 position from the three-bond proton and carbon correlations in its HMBC spectrum (Figure 2) which showed that the aldehyde CH proton had a three-bond correlation with the C-8 carbon, and that the protons at C-19 had a three-bond correlation with the aldehyde carbon. The C-2 proton correlated with a carbon resonating at 96.1 ppm and thus bearing two oxygen substituents, and the proton on this carbon (assigned from its HETCOR spectrum) correlated with the C-2 carbon in its HMBC spectrum. This evidence was consistent with the formation of a

lactol between the C-6 aldehyde and the C-2 hydroxyl group (Figure 2). The downfield shift of the C-1 carbon from 79.0 ppm to 91.1 ppm and the upfield shift of the C-2 carbon from 77.8 ppm to 66.1 ppm were consistent with a benzoyl group migration from the C-2 position to the C-1 position. The stereochemistry of the lactol hydroxyl group at C-6 was not established.

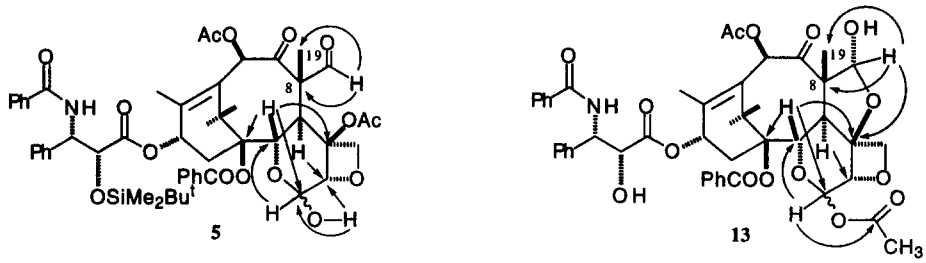
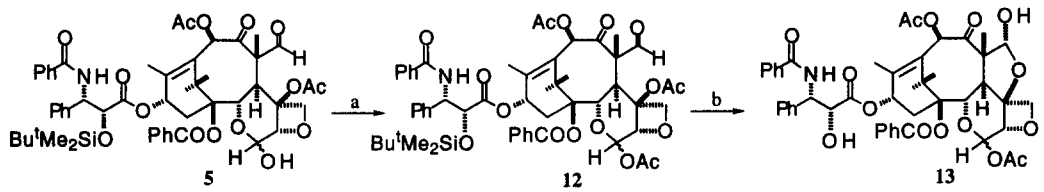


Figure 2: Key HMBC correlations of compound 5 and 13

In order to confirm the formation of a lactol between the C-6 aldehyde and the C-2 hydroxyl group, acylation on the lactol (C-6) hydroxyl group was attempted. This proved surprisingly difficult, and only starting material was recovered after treatment of **5** with acetyl chloride and DMAP at ambient temperature for 38 hours. Acylation of **5** with acetic anhydride, 1,3-dicyclohexylcarbodiimide (DCC), and 4-pyrrolidinopyridine (PP) did however yield the desired acetate **12** (Scheme 4). The product showed one additional methyl proton signal at 2.12 ppm, and the C-6 proton signal was shifted downfield from 5.38 ppm to 6.31 ppm, further confirming the structure of **5**. Removal of the 2'-*O*-*t*-butyldimethylsilyl protecting group from **12** with HF/pyridine yielded the unexpected compound **13** (Scheme 4), in which the aldehyde group and one acetyl group were lacking, in addition to the expected loss of the *t*-butyldimethylsilyl group.



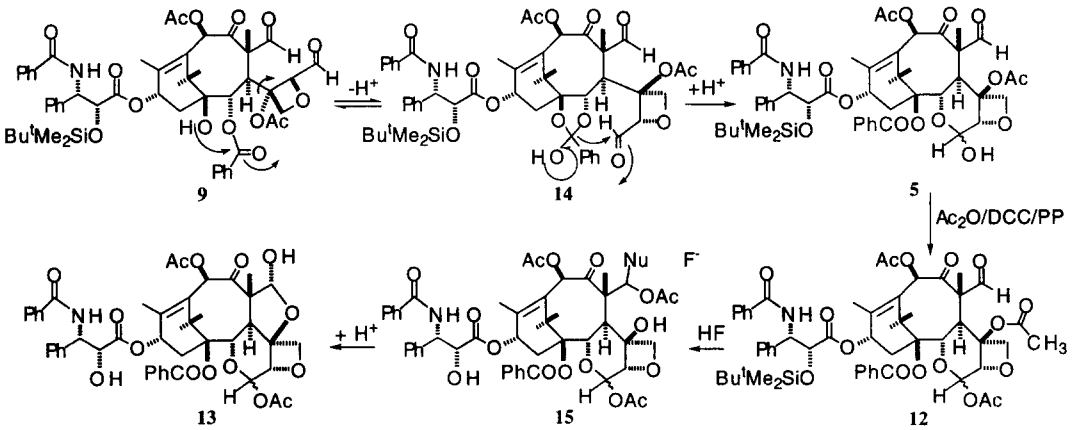
Reagents: (a) $(CH_3CO)_2O$, DCC, PP, 8 h, r.t., 92%; (b) HF/pyridine, 1.5 h, r.t., 90%

Scheme 4

The HRFABMS analysis of **13** yielded a molecular ion $[MNa]^+$ at *m/z* 890.3004, consistent with the molecular mass of the structure proposed. The three-bond proton and carbon correlations of the C-6 and C-10 protons with the carbonyl carbons of two acetyl groups in its HMBC spectrum indicated that the 4-acetyl group of **13** had been lost. The three-bond correlation of the C-7 proton with the C-4 carbon in its HMBC spectrum indicated the formation of a lactol between the C-7 aldehyde and the C-4 hydroxyl group (Figure 2). The stereochemistry of the C-7 position in **13** was confirmed by its NOESY spectrum; correlations between the C-7 proton signal and the C-19 methyl signal verified that the C-7 proton and the C-19 methyl group were on the same face of ring C, namely the β face. No correlations between the C-7 proton signal and the C-3 proton signal

were observed, which also supported the assignment of stereochemistry at the C-7 position in **13**. However, the stereochemistry of C-6 could not be established because the observed correlations between the C-6 and C-5 proton signals could arise either from NOE or from COSY correlations, and no other correlations were observed.

The formation of **5** and **13** can be explained by the mechanism proposed in Scheme 5, which differs in some respects from that proposed earlier.[6] Oxidation of **3** with lead tetraacetate to the dialdehyde **9** is followed by attack of the C-1 hydroxyl group on the electrophilic 2-carbonyl carbon to form the intermediate **14** which then undergoes another intramolecular nucleophilic attack to form the lactol **5**. Hydrolysis of the tertiary C-4 acetate on treatment with HF/pyridine may then occur *via* neighboring group participation involving attack by a nucleophile (either pyridine or perhaps hydroxide ion from traces of moisture in the reaction mixture) on the aldehyde carbonyl group followed by intramolecular acyl transfer to give the intermediate **15**. A similar mechanism has been shown by Bender to occur for *ortho*-formyl benzoate esters in the presence of morpholine,[10] although in this case the transition state is 5-membered. Hydrolysis of **15** on work-up would then yield **13**, formed by hydrolysis and cyclization from the β-face of the C-7 aldehyde to yield product with an α-hydroxyl group at C-7 from attack of the β-oriented C-4 hydroxyl group.



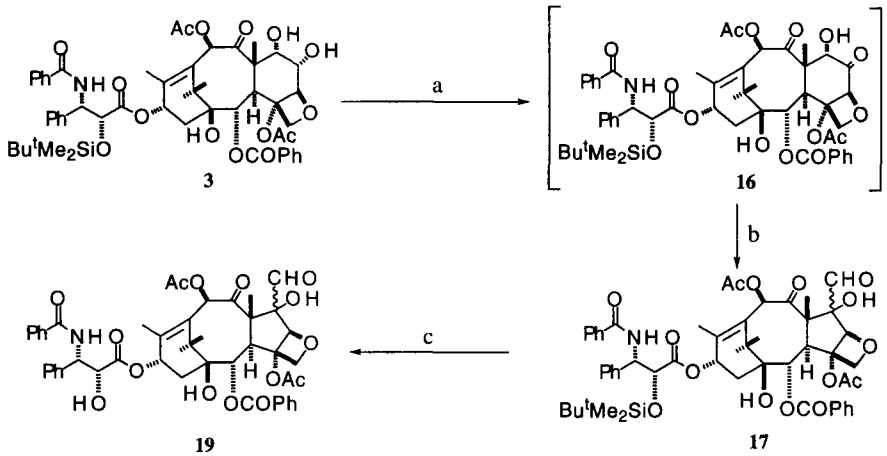
Scheme 5

Synthesis of 6-Formyl-C-nor-paclitaxel

The formation of *C-nor*-paclitaxel *via* a retro-aldol reaction, as described in Scheme 3, suggests that ring C contraction might take place in other situations where the C-6 carbon is electrophilic and could thus undergo attack by the C-8 carbanion. If this reasoning is correct, then 2'-*O*-(*t*-butyldimethylsilyl)-6-oxo-7-*epi*-paclitaxel (**16**) should undergo ring contraction on base treatment to the *C-nor*-hydroxyaldehyde **17** (Scheme 6).

It has been reported that tetrapropylammonium perruthenate (TPAP) is a mild and powerful oxidizing agent to oxidize secondary alcohols to ketones.[11] Treatment of 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (**3**) with TPAP and NMO in anhydrous dichloromethane at 0 °C for 30 minutes or at -20 °C for 20 hours gave a minor product (**17**) that was less polar than the starting material and a major product (**16**) that was much less polar than the starting material on TLC. Pure compound **17** was obtained from the upper band on preparative TLC, and a mixture of **16** and **17** was obtained from the lower band. Repurification of this mixture

again gave pure **17** and a mixture of **16** and **17**, as determined from its ^{1}H NMR spectrum. These observations indicated that compound **16** was slowly converted to compound **17** on silica gel (Scheme 6).



Reagents: (a)(i-Pr)$_4$NRuO$_4$/NMO, - 20 °C, 20 h; (b) Silica gel; (c) HF/pyridine, 25 °C, 2.5 h, 80%

Scheme 6

The ^{1}H NMR spectrum of the mixture of **16** and **17** was interpreted by subtracting the spectrum of **17**, and indicated that the major component had a spectrum consistent with the structure **16**. In particular, the downfield shifts of the C-7 and C-5 protons (C-7 from 3.70 to 5.00 ppm, C-5 from 4.68 to 5.06 ppm) resulting from an adjacent carbonyl group indicated the formation of the C-6 keto group, and the change of H-7 from a quartet to a doublet also indicated the formation of a C-6 keto group.

The less polar compound was fully characterized as 2'-*O*-(*t*-butyldimethylsilyl)-6-formyl-*C*-*nor*-paclitaxel (**17**). The proton assigments were based upon TOCSY and HMBC spectra and the carbon assignments were based upon HMQC and HMBC spectra. The aldehyde CH signal at 9.94 ppm was assigned to the C-7 position from its HMBC spectrum (Figure 3) which showed that the aldehyde CH proton had a three-bond correlation with the C-8 carbon. The key three-bond C-H correlations in its HMBC verified the formation of a five-membered ring as illustrated in Figure 3.

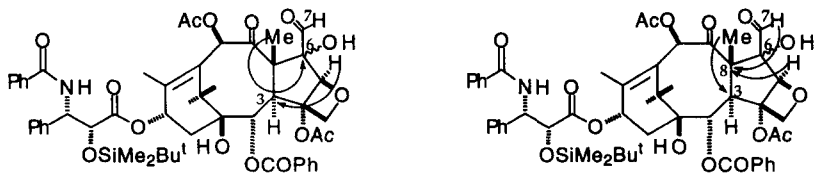
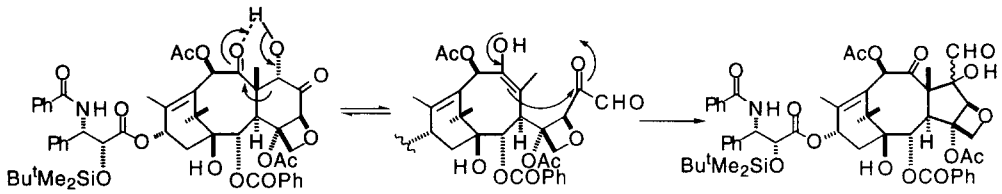


Figure 3: Key HMBC correlations of **17**

The formation of **17** can be explained by the mechanism of Scheme 7. Selective oxidation of the C-6 hydroxyl group to ketone **16** presumably occurs because this hydroxyl group is more accessible than the C-7 hydroxyl group. An equilibrium between the ketone **16** and the enol **18** on the silica gel surface would then set

up attack of the C-8 enol on the electrophilic C-6 carbonyl carbon, leading to the formation of the 5-membered ring compound **17**. This facile formation of **17** further confirmed the propensity of paclitaxel analogs to form 5-membered C-rings under appropriate conditions *via* a retro-aldol reaction followed by an aldol reaction.



16 **18** **17**

Scheme 7

Deprotection of **17** with HF and pyridine at ambient temperature for 2.5 hours afforded the desired 6-formyl-*C-nor*-paclitaxel (**19**) in 80% yield (Scheme 6). Unfortunately compound **19** was unstable, and decomposed on standing in solution in $CDCl_3$ for 3 days at ambient temperature to a mixture in which the aldehyde CH peak was no longer present. The mixture was very difficult to separate into pure compounds, and no pure compounds were isolated from it.

Synthesis of 20-O-Acetyl-4-deacetyl-5,6-dehydro-6-formyl-C-nor-paclitaxel

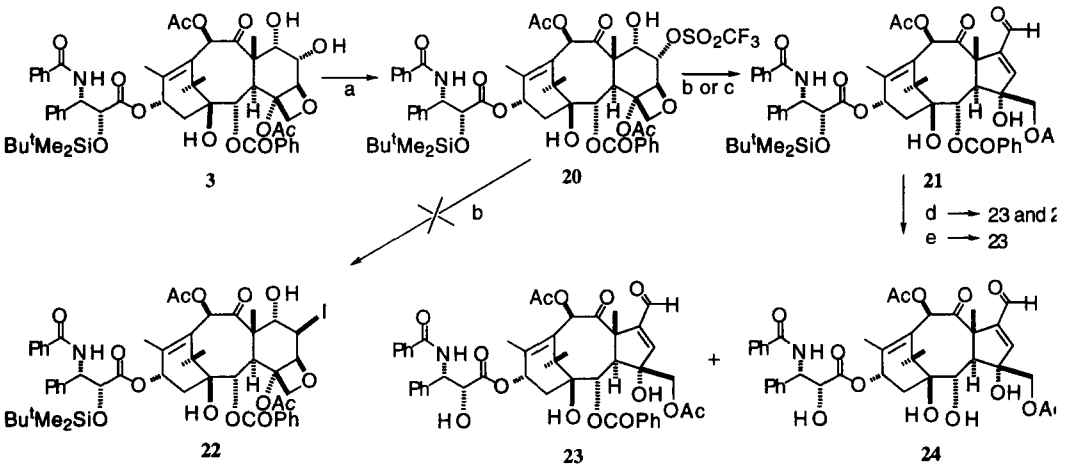
The sucessful synthesis of 6α-hydroxy-7-*epi*-paclitaxel (**2**) marked the first introduction of a hydroxyl group into the C-6 position of paclitaxel. It was of interest to attempt to introduce other heteroatoms into this position in order to obtain a variety of analogs for SAR studies. Since nucleophilic substitution is one of the best methods to achieve such introductions, a route was devised using this reaction.

In order to perform a nucleophilic substitution at the C-6 position, it is necessary to transform the C-6 hydroxyl group into a good leaving group, and the trifluoromethanesulfonate group was chosen for this purpose. Reaction of 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (**3**) with trifluoromethanesulfonyl chloride and DMAP at ambient temperature for 1 hour furnished 2'-*O*-(*t*-butyldimethylsilyl)-6α-*O*-trifluoromethanesulfonyl-7-*epi*-paclitaxel (**20**) in 95% yield (Scheme 8), in contrast to a recent paper[7] where reaction of **3** with triflic anhydride and DMAP failed to yield the desired C-6 triflate analog, giving instead a complex mixture of products. The selectivity was expected as demonstrated in our synthesis of 6-acylated paclitaxel analogs.[8a]

No reaction occurred on treatment of 2'-*O*-(*t*-butyldimethylsilyl)-6α-*O*-trifluoromethanesulfonyl-7-*epi*-paclitaxel (**20**) with tetrabutylammonium iodide in anhydrous dichloromethane at ambient temperature for 1 day, but raising the temperature of the reaction to 40 °C for 5 days led to a more polar compound in 15% yield along with recovered starting material in 65% yield. The new compound was fully characterized as the unexpected 20-*O*-acetyl-2'-*O*-(*t*-butyldimethylsilyl)-4-deacetyl-5,6-dehydro-6-formyl-*C-nor*-paclitaxel (**21**), a ring C rearranged compound, and not the desired 2'-*O*-(*t*-butyldimethylsilyl)-6-deoxy-6β-iodo-7-*epi*-paclitaxel (**22**) (Scheme 8).

The structure of **21** was established only after a careful analysis of its spectroscopic data. Its composition, as deduced from its LRFABMS, $[MNa]^+$ at *m/z* 988, indicated the loss of one molecule of trifluoromethanesulfonic acid from the starting material (**20**), consistent with the molecular mass of 20-*O*-acetyl-2'-*O*-(*t*-butyldimethylsilyl)-4-deacetyl-5,6-dehydro-6-formyl-*C-nor*-paclitaxel. The ^1H NMR spectrum of **21**

showed one aldehyde CH signal, and the aldehyde giving rise to this signal was assigned to the C-7 position from the three-bond proton and carbon correlations in its HMBC spectrum (Figure 4). These showed that the aldehyde CH proton at 9.60 ppm had a three-bond correlation with the C-8 carbon at 60.2 ppm and the C-5 carbon at 151.6 ppm, and the aldehyde carbon at 187.6 ppm had a correlation with the C-5 proton at 6.27 ppm. Protons at C-19 had a three-bond correlation with the quarternary olefinic carbon at 145.7 ppm (C-6 carbon). The C-3 proton showed three-bond correlations with both olefinic carbons at 145.7 and 151.6 ppm (assigned from HETCOR and HMBC spectra). The C-20 proton had a three-bond correlation with the olefinic carbon at 151.6 ppm. These correlations defined a five-membered ring C with a double bond at the C-5 and C-6 positions and a formyl group at the C-6 position. The geminal proton coupling constants at the C-20 protons (12.4 Hz) together with the carbon shift change in the C-20 carbon (70.6 ppm), indicated that the oxetane ring had opened and that migration of the C-4 acetyl group to the C-20 oxygen had occurred.



Reagents: (a) CF_3SO_2Cl/DMAP, 25 °C, 1 h, 95%; (b) Bu_4NI/CH_2Cl_2, 40 °C, 5 days, 15%; (c) DMAP/CH_2Cl_2, 40 °C, 1 day, 80%; (d) Bu_4NF/THF, 0 °C, 15 min; (e) HF/Pyridine, 25 °C, 1.5 h, 85%.

Scheme 8

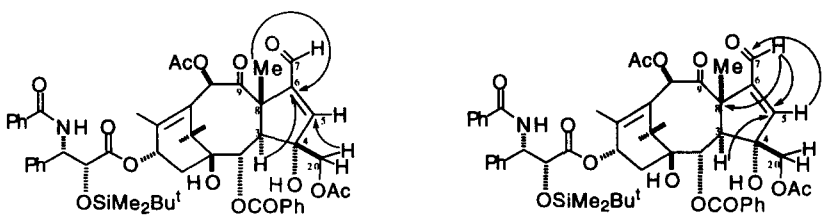
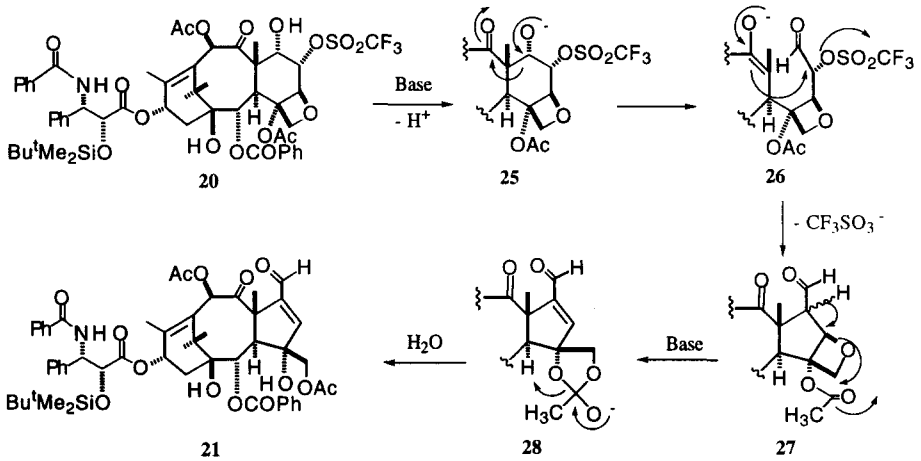


Figure 4. Key HMBC correlations of **21**

The formation of 20-*O*-acetyl-2'-*O*-(*t*-butyldimethylsilyl)-4-deacetyl-5,6-dehydro-6-formyl-*C-nor*-paclitaxel (**21**) can be explained as illustrated in Scheme 9. Deprotonation of the C-7 hydroxyl group would set

up a retro aldol reaction to give the enolate **26**. This enolate would then attack the C-6 carbon with loss of the good trifluoromethanesulfonate leaving group, generating the 5-membered ring C compound 2'-*O*-(*t*-butyldimethylsilyl)-6-dehydroxy-6-formyl-*C-nor*-paclitaxel (**27**). Removal of the acidic C-6 proton by base would then be followed by oxetane ring opening to release the oxetane strain and by migration of the acetyl group from the tertiary C-4 hydroxyl group to the primary C-20 hydroxyl group to form the more stable α,β-unsaturated aldehyde (Scheme 9). Support for this mechanistic hypothesis was provided by repeating the reaction under more basic conditions; treatment of **20** with the stronger base DMAP at 40 °C for 1.5 days yielded **21** in 80% yield together with recovered starting material in 10% yield (Scheme 8). This experiment thus supported the proposed base-catalyzed mechanism.



Scheme 9

Deprotection of **21** with tetrabutylammonium fluoride at 0 °C for 15 minutes gave a major product, 20-*O*-acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C-nor*-paclitaxel (**23**), and a minor product, 20-*O*-acetyl-4-deacetyl-2-debenzoyl-5,6-dehydro-6-formyl-*C-nor*-paclitaxel (**24**) (Scheme 8). Deprotection of **21** with HF and pyridine furnished exclusively **23** (Scheme 7). The HRFABMS analysis of the deprotected product **23** yielded a molecular ion $[MNa]^+$ at *m/z* 874.3035, consistent with the molecular mass of 20-*O*-acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C-nor*-paclitaxel; this evidence, together with the NMR data recorded in the experimental section, confirmed the structure of compound **23**.

Compound **23** has also recently been reported by Chen et al. by deprotection of the tosylate corresponding to **20** with TBAF.[7]

Biological Evaluation of C-nor-Paclitaxel Analogs

The *C-nor*-paclitaxel analogs **6** and **8**, the hemiacetal **13**, and the *C-nor-D-seco* analog **23** were tested in the human colon carcinoma HCT116 cell line, as well as in a tubulin assembly assay. From the data in Table 1, it can be seen that C-*nor*-paclitaxel (**6**) is somewhat less cytotoxic and significantly less effective at promoting the assembly of microtubules than paclitaxel, and the acetate **8**, the hemiacetal **13**, and the *C-nor-D-seco* analog **23** are even less active. Analog **23** was also evaluated in a microtubule assembly assay at the National Cancer

Institute, and preliminary results indicated that it was also devoid of any activity in this somewhat different assay.[12] Similar results were obtained by Chen[7] on this compound, presumably due in part to the loss of oxetane ring.

These results indicate that changes in the size and conformation of ring C and the attached oxetane ring make a significant difference to the activity of paclitaxel.

Table 1. Cytotoxicities and Effects of Analogs on Tubulin Polymerization

Compound	Tubulin Polymerization Ratio[a]	Cytotoxicity EC_{50} (nM) with HCT116 cells
Paclitaxel	1.0	6.9
6	8.3	15
8	47	44
13	>230	930
23	>230	960

[a] Concentration of analog required to effect tubulin polymerization under defined conditions relative to that of paclitaxel under the same conditions.

EXPERIMENTAL

General experimental procedures. All non-aqueous reactions were performed in oven-dried glassware. THF was distilled from Na/benzophenone. Dichloromethane was distilled from CaH_2. The HRFABMS data were obtained from the Nebraska Center for Mass Spectrometry, University of Nebraska. The LRFABMS data were obtained from either the Nebraska Center for Mass Spectrometry, University of Nebraska, or Department of Chemistry and Department of Biochemistry, Virginia Polytechnic Institute and State University. ^1H NMR spectra and NOE spectra were obtained on a Varian Unity 400 spectrometer operating at 399.95 MHz. ^{13}C NMR spectra were obtained on a Varian Unity 400 spectrometer operating at 100.57 MHz. All 2-D NMR spectra including COSY, DQCOSY, TOCSY, HETCOR, HMQC, HMBC and NOESY were obtained on a Varian Unity 400 spectrometer operating at 399.95 MHz or 100.57 MHz. All NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard unless otherwise noted. The phrase "worked up by standard methods" refers to diluting the reaction mixture with an excess of organic solvent (i.e. CH_2Cl_2, EtOAc, ethyl ether), successive washing with H_2O and brine, drying over Na_2SO_4, and evaporating the solvent *in vacuo* unless otherwise noted.

2'-*O*-(*t*-Butyldimethylsilyl)-7β-*O*-trifluoromethanesulfonylpaclitaxel. 2'-*O*-(*t*-Butyldimethylsilyl)-paclitaxel (180.0 mg, 0.19 mmol) was dissolved in dry CH_2Cl_2 (2 mL). To this solution 4-dimethyl-aminopyridine (61.0 mg, 0.5 mmol) and trifluoromethanesulfonyl chloride (50 μL, 0.5 mmol) were added successively at 0 °C and the mixture stirred at room temperature for 1 hour. Then to this solution additional 4-dimethylamino pyridine (61.0 mg, 0.5 mmol) and trifluoromethanesulfonyl chloride (50 μL, 0.5 mmol) were added successively and the mixture stirred for an additional 1.5 hours. The reaction mixture then was diluted with EtOAc (4.0 mL) and the precipitate filtered off on Celite. The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, 6:4 hexane:EtOAc) to furnish 2'-*O*-(*t*-butyldimethylsilyl)-7-*O*-trifluoromethanesulfonylpaclitaxel (187.0 mg, 92% yield). ^1H NMR δ 8.12 (d, 2H), 7.73 (d, 2H), 7.60 (t, 1H), 7.53-7.30 (m, 10H), 7.09 (d, 1H, *J* = 8.9, NH), 6.62 (s, 1H, H-10), 6.25 (t, 1H, *J* = 9.2, H-13), 5.76 (q, 1H, *J* = 8.9, 2.6, H-3'), 5.74 (d, 1H, *J* = 7.0, H-2), 5.49 (dd, 1H, *J* = 7.5, 10.1, H-7), 4.94 (d 1H, *J* = 8.6, H-5), 4.67 (d, 1H, *J* = 2.0, H-2'), 4.37 (d, 1H, *J* = 8.5, H-20), 4.22 (d, 1H, *J* = 8.5, H-20), 3.97 (d, 1H, *J* = 7.0, H-3),2.85 (m, 1H, H-6) 2.60 (s, 3H, $-CH_3$), 2.39 (m, 1H, H-14), 2.19 (s, 3H, $-CH_3$), 2.18 (m,

2 H, H-6, H-14), 2.08 (s, 3H, -CH_3), 1.89 (s, 3H, -CH_3), 1.22 (s, 3H, -CH_3), 1.18 (s, 3H, -CH_3), 0.8 (s, 9H), -0.02 (s, 3H), -0.29 (s, 3H). ^{13}C NMR δ 201.0, 171.9, 171.2, 169.3, 167.7, 167.4, 141.7, 138.8, 134.7, 134.4, 133.5, 132.5, 130.8, 129.5, 129.5, 129.4, 129.4, 128.6, 127.6, 127.0, 86.4, 83.7, 80.6, 79.2, 76.9, 75.8, 75.7, 74.9, 71.7, 58.0, 56.2, 47.5, 43.7, 36.3, 34.7, 26.8, 26.2, 26.1, 23.5, 22.0, 21.3, 18.7, 14.9, 14.8, 11.5, -4.5, -5.2. LRFABMS *m/z* calcd for $C_{54}H_{65}NO_{16}F_3SiS$ [MH]$^+$ 1100, found 1100.

2'-*O*-(*t*-Butyldimethylsilyl)-6,7-dehydropaclitaxel [2]. To a stirred solution of 2'-*O*-(*t*-butyldimethylsilyl)-7β-*O*-trifluoromethanesulfonylpaclitaxel (202.0 mg, 0.18 mmol) in dry CH_2Cl_2 (1.0 mL) was added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 300.0 μL, 2.0 mmol). The mixture was kept stirring at 40 °C for 4 hours. The reaction mixture then was diluted with EtOAc (2.0 mL) and washed with dilute HCl, followed by dilute $NaHCO_3$ solution, water, and brine. The aqueous layer was extracted with additional EtOAc (2 x 2 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give crude product. Purification of the crude product by preparative silica gel TLC (7:3 hexane : EtOAc) furnished two compounds: 2'-O-(*t*-butyldimethylsilyl)-6,7-dehydropaclitaxel (**2**, 150.0 mg, 86%) and 6,7-dehydropaclitaxel (21.3 mg, 13%). ^{1}H-NMR δ 8.12 (d, 2H), 7.73 (d, 2H), 7.60 (t, 1H), 7.53-7.30 (m, 10H), 7.07 (d, 1H, *J* = 8.9, NH), 6.24 (s, 1H, H-10), 6.25 (t, 1H, *J* = 9.2, H-13), 6.08 (dd,1H, *J* =9.9, 5.6, H-6), 5.87 (d, 1H, *J* = 9.9, H-7), 5.86 (d, 1H, *J* = 6.5, H-2), 5.72 (d, 1H, *J* = 8.6, H-3'), 5.12 (d 1H, *J* = 5.5, H-5), 4.65 (d, 1H, *J* = 2.0, H-2'), 4.45 (d, 1H, *J* = 8.1, H-20), 4.34 (d, 1H, *J* = 8.1, H-20), 4.03 (d, 1H, *J* = 6.5, H-3), 2.58 (s, 3H, -CH_3), 2.44 (m, 1H, H-14), 2.22 (s, 3H, -CH_3), 2.18 (m, 2 H, H-6, H-14), 1.88 (s, 3H, -CH_3), 1.83 (s, 3H, -CH_3), 1.24 (s, 3H, -CH_3), 1.14 (s, 3H, -CH_3), 0.79 (s, 9H), -0.05 (s, 3H), -0.32 (s, 3H). ^{13}C NMR δ 205.4, 171.3, 169.6, 169.4, 166.9, 166.9, 141.6, 140.0, 138.3, 134.1,133.7, 133.6, 131.8, 130.2, 129.2, 128.8, 128.7, 128.7, 128.7, 127.9, 127.0, 126.4, 126.1, 81.2, 81.1, 76.3, 75.8, 75.6, 75.1, 71.2, 60.4, 55.6, 55.4, 36.0, 26.3, 25.5, 23.1, 22.1, 22.0, 20.7, 20.5, 18.1, 14.6, 14.1, -5.3, -5.9. LRFABMS *m/z* calcd for $C_{53}H_{64}NO_{13}Si$ [MH]$^+$ 950, found 950.

2'-*O*-(*t*-Butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel [3]. To a solution of 2'-*O*-(*t*-butyldimethylsilyl)-6,7-dehydropaclitaxel (60.0 mg, 0.063 mmol) in THF (500 μL, 10 drops H_2O) were added osmium tetraoxide (2.5 wt. 2.5% solution in 2-methyl-2-propanol, 150 μL, 0.015 mmol) and 4-methyl morpholine-N-oxide (NMO, 50 mg, 0.42 mmol). The mixture was stirred at room temperature for 4 hours. Additional osmium tetraoxide solution (150 μL, 0.015 mmol) was then added to the reaction mixture to accelerate the reaction. The reaction mixture was kept stirring at room temperature for an additional 5 hours, and sodium bisulfite (25 mg) was then added. After stirring for a further 10 minutes, the mixture was diluted with EtOAc (1 mL), filtered through Celite, and washed with H_2O and brine. The aqueous layer was extracted with additional EtOAc (2 x 2 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Isolation of the residue by preparative TLC (silica gel, 1:1 hexane:EtOAc) furnished the starting material (7.2 mg, 12%) and a more polar compound 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (48.0 mg, 78%). ^{1}H NMR δ 8.15 (d, 2H), 7.70 (d, 2H), 7.64-7.26 (m, 6H), 7.07 (d, 1H, *J* = 8.8, NH), 6.83 (s, 1H, H-10), 6.29 (t, 1H, *J* = 8.8, H-13), 5.79 (q, 1H, *J* = 8.8, 2.4, H-3'), 5.74 (d, 1H, *J* = 7.6, H-2), 4.71 (d, 1H, *J* = 12.0, HO-7), 4.68 (d, 1H, *J* = 2.0, H-5), 4.66 (bs, 2H, H-20), 4.36 (s, 1H, H-2'), 4.18 (m, 1H, H-6), 3.87 (d, 1H, *J* = 7.6, H-3), 3.70 (q, 1H, *J* = 5.2, 12.0, H-7), 2.90 (d, 1H, *J* = 8.2, HO-6), 2.62 (s, 3H, -CH_3), 2.42-2.10 (m, 2H, H-14), 2.18 (s, 3H, -CH_3), 1.90 (s, 3H, -CH_3), 1.62 (s, 3H, -CH_3), 1.18 (s, 3H, -CH_3), 1.12 (s, 3H, -CH_3), 0.78 (s, 9H), -0.03 (s, 3H), -0.3 (s, 3H). LRFABMS *m/z* calcd for $C_{53}H_{65}NO_{15}Si$ [MH]$^+$ 984, found 984.

2'-*O*-(*t*-Butyldimethylsilyl)-*C*-*nor*-paclitaxel [4] and **2'-*O*-(*t*-butyldimethylsilyl)-*C*-*seco*-paclitaxel [5].** 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (10 mg) was dissolved in anhydrous CH_2Cl_2 (250 mL) with stirring. Sodium bicarbonate (2.4 mg, 4 eq.) and lead tetraacetate (9 mg, 2 eq.) was added and the reaction was allowed to proceed at 0 °C for 2 hours and then was worked up by standard methods to yield a crude mixture which was subjected to silica gel preparative TLC (7:3 hexane : EtOAc), affording 2'-*O*-(*t*-butyldimethylsilyl)-*C*-*nor*-paclitaxel (**4**, 5.9 mg, 67%) and 2'-*O*-(*t*-butyldimethylsilyl)-*C*-*seco*-paclitaxel (**5**, 1.3 mg, 11%).

2'-*O*-(*t*-Butyldimethylsilyl)-*C-nor*-paclitaxel (**4**): ^{1}H-NMR δ 8.17 (d, 2H), 7.66 (d, 2H), 7.60 (t, 1H), 7.58-7.30 (m, 10H), 7.06 (d, 1H, *J* = 8.7, NH), 6.48 (s, 1H, H-10), 6.30 (t, 1H, *J* = 8.4, H-13), 5.81 (d, 1H, *J* = 7.9, H-2), 5.76 (bd, 1H, *J* = 8.9, H-3'), 5.16 (d, 1H, *J* = 4.3, H-5), 4.63 (d, 1H, *J* = 2.1, H-2'), 4.46 (d, 1H, *J* = 8.1, H-20), 4.36 (d, 1H, *J* = 7.9, H-3), 4.34 (q, 1H, *J* = 4.3, 7.9, H-6), 4.29 (d, 1H, *J* = 8.1, H-20), 2.55 (s, 3H, -CH_3), 2.45 (d, 1H, J = 7.9, HO-6), 2.34-2.26 (m, 2H, H-14), 2.21 (s, 3H, -CH_3), 1.92 (s, 3H, -CH_3), 1.86 (s, 3H, -CH_3), 1.24 (s, 3H, -CH_3), 1.13 (s, 3H, -CH_3), 0.80 (s, 9H), -0.06 (s, 3H), -0.32 (s, 3H). ^{13}C NMR δ 204.4 (C-9), 170.8 (C-1'), 169.7 (C-4 carbonyl), 169.6 (C-10 carbonyl), 167.0 (amide carbonyl), 166.7 (C-2 carbonyl), 140.9 (C-12), 138.3, 135.6, 134.0, 133.7 (C-11), 131.7, 130.3, 128.7, 128.6, 128.6, 127.9, 126.9, 126.3, 87.0 (C-5), 81.7 (C-4), 78.6 (C-1), 77.0 (C-20), 75.6 (C-2), 75.3 (C-2'), 74.3 (C-6), 73.5 (C-10), 70.9 (C-13), 59.8 (C-8), 55.9 (C-3'), 44.5 (C-3), 42.7 (C-15), 37.0 (C-14), 26.4 (C-17), 25.4 (Si-C-CH_3), 22.2 (C-4 OAc), 21.2 (C-16), 20.7 (C-10 OAc), 18.1 (Si-C), 14.7 (C-18), 12.9 (C-19), -5.3 (Si-CH_3), -6.0 (Si-CH_3). HRFABMS *m/z* calcd for $C_{52}H_{63}O_{14}NSiNa$ $[MNa]^+$ 976.3915, found 976.3912.

2'-*O*-(*t*-Butyldimethylsilyl)-*C-seco*-paclitaxel (**5**): ^{1}H NMR δ 9.45 (s, 1H, H7), 7.95 (d, 2H), 7.80 (d, 2H), 7.30-7.60 (m, 6H), 7.14 (d, 1H, *J* = 8.1, NH), 6.40 (s, 1H, H-10), 6.22 (dd, 1H, *J* = 9.8, H-13), 5.66 (d, 1H, *J* = 9.2, H-3'), 5.52 (d, 1H, *J* = 8.0, H-20), 5.51 (d, 1H, *J* = 7.0, H-2), 5.38 (s, 1H, H-6), 4.85 (d, 1H, *J* = 8.0, H-20), 4.73 (d, 1H, *J* = 1.5, H-2'), 4.29 (s, 1H, H-5), 4.14 (d, 1H, *J* = 7.1, H-3), 3.37 (s, 1H, H-6-OH), 2.80-3.00 (m, 2H, H-14), 2.15 (s, 3H, -CH_3), 2.11 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3), 1.74 (s, 3H, -CH_3), 1.25 (s, 3H, -CH_3), 1.20 (s, 3H, -CH_3), 0.82 (s, 9H, -CH_3), -0.02 (s, 3H, -CH_3), -0.33 (s, 3H, -CH_3). ^{13}C NMR δ 197.8 (C-7), 197.7 (C-9), 171.0 (C-1'), 169.9 (C-4 carbonyl), 169.2 (C-10 carbonyl), 166.7 (amide carbonyl), 166.6 (C-2 carbonyl), 142.8 (C-12), 131.9 (C-11), 96.1 (C-6), 91.1 (C-1), 83.4 (C-5), 83.4 (C-4), 81.0 (C-20), 77.2 (C-10), 75.2 (C-2'), 70.8 (C-8), 70.5 (C-13), 66.0 (C-2), 55.6 (C-3'), 46.7 (C-3), 44.2 (C-15), 35.5 (C-14), 22.5 (C-10 OAc), 21.5 (C-17), 20.7 (C-4 OAc), 20.7 (C-16), 17.0 (C-18), 15.1 (C-19), 25.5 (Si-C-CH_3), 18.1 (Si-C), -5.4 (Si-CH_3), -6.0 (Si-CH_3). HRFABMS *m/z* calcd for $C_{53}H_{63}O_5NSiLi$ $[MLi]^+$ 988.4127, found 988.4100.

***C-nor*-Paclitaxel [6].** To the solution of 2'-*O*-(*t*-butyldimethylsilyl)-*C-nor*-paclitaxel (18 mg) in anhydrous THF (400 mL), 50 mL of HF·pyridine solution was added. The reaction proceeded then at room temperature for 1.5 hours and then was worked up by standard methods to yield the crude mixture which was subjected to silica gel preparative TLC (3:2 hexane : EtOAc), affording *C-nor*-paclitaxel (13.1 mg, 86% yield). ^{1}H-NMR δ 8.20 (d, 2H), 7.66 (d, 2H), 7.60 (t, 1H), 7.58-7.30 (m, 5H), 6.94 (d, 1H, *J* = 9.3, NH), 6.46 (s, 1H, H-10), 6.27 (t, 1H, *J* = 8.9, H-13), 5.81 (d, 1H, *J* = 8.0, H-3'), 5.81 (d, 1H, *J* = 7.9, H-2), 5.14 (d, 1H, *J* = 4.4, H-5), 5.14 (d, 1H, *J* = 4.6, H-2'), 4.45 (d, 1H, *J* = 8.2, H-20), 4.35 (d, 1H, *J* = 7.9, H-3), 4.33 (dd, 1H, *J* = 4.3, 7.8, H-6), 4.28 (d, 1H, *J* = 8.2, H-20), 3.46 (d, 1H, *J* = 4.5, H-2'-OH), 2.53 (d, 1H, *J* = 7.8, H-6-OH), 2.43 (s, 3H, -CH_3), 2.21 (s, 3H, -CH_3), 2.12-2.20 (m, 2H, H-14), 1.85 (s, 3H, -CH_3), 1.84 (s, 3H, -CH_3), 1.23 (s, 3H, -CH_3), 1.14 (s, 3H, -CH_3). ^{13}C NMR δ 204.3 (C-9), 172.6 (C-1'), 169.7 (C-4 carbonyl), 169.6 (C-10 carbonyl), 167.0 (amide carbonyl), 166.9 (C-2 carbonyl), 140.4 (C-12), 138.1, 136.0 (C-11), 133.8, 133.6, 131.9, 130.3, 129.0, 128.9, 128.7, 128.6, 128.3, 127.0, 126.8, 87.1 (C-5), 81.7 (C-4), 78.6 (C-1), 77.3 (C-20), 75.7 (C-2), 74.2 (C-6), 73.5 (C-10), 73.2 (C-2'), 72.3 (C-13), 59.8 (C-8), 54.7 (C-3'), 44.5 (C-3), 42.7 (C-15), 36.9 (C-14), 26.6 (C-17), 22.0 (C-4 OAc), 21.0 (C-16), 20.7 (C-10 OAc), 14.6 (C-18), 12.9 (C-19). HRFABMS *m/z* calcd for $C_{46}H_{49}O_{14}NNa$ $[MNa]^+$ 862.3051, found 862.3064.

6-*O*-Acetyl-2'-*O*-(*t*-butyldimethylsilyl)-*C-nor*-paclitaxel [7]. To the solution of 2'-*O*-(*t*-butyldimethylsilyl)-*C-nor*-paclitaxel (8 mg) in anhydrous CH_2Cl_2, DMAP (25 mg) and acetyl chloride (10 mL, 10 mg, 12 eq.) were added. The reaction was allowed to proceed at room temperature for 30 minutes, and then was worked up by standard methods to yield the crude mixture which was subjected to silica gel preparative TLC (7:3 hexane : EtOAc), affording 2'-*O*-(*t*-butyldimethylsilyl)-6-*O*-acetyl-*C-nor*-paclitaxel (7 mg, 87% yield). ^{1}H NMR δ 8.17 (d, 2H, *J* = 7.0), 7.75 (d, 2H, *J* = 7.2), 7.59 (t, 1H, *J* = 7.2), 7.58-7.30 (m, 5H), 7.06 (d, 1H, *J* = 9.2, NH), 6.56 (s, 1H, H-10), 6.29 (t, 1H, *J* = 8.6, H-13), 5.75 (q, 1H, *J* = 10.4, 1,9, H-3'), 5.82 (d, 1H, *J* = 7.9, H-2), 5.44 (d, 1H, *J* = 4.3, H-6), 5.25 (d, 1H, *J* = 4.4, H-5), 4.63 (d, 1H, *J* = 1.9, H-2'), 4.46 (d, 1H, *J* = 7.9, H-20), 4.45 (d, 1H, *J* = 7.9, H-3), 4.33 (d, 1H, *J* = 7.9, H-20), 2.55 (s, 3H, -CH_3), 2.30 (q, 1H, *J* = 15.9, 10.2, H-14), 2.18 (s, 3H, -CH_3), 2.09 (s, 3H, -CH_3), 2.09-2.04 (m, 1H, H-14), 1.98 (s, 3H, -

CH_3), 1.93 (s, 3H, -CH_3), 1.22 (s, 3H, -CH_3), 1.11 (s, 3H, -CH_3), 0.78 (s, 9H), -0.05 (s, 3H), -0.32 (s, 3H).

6-*O*-Acetyl-*C*-*nor*-paclitaxel [8]. A solution of 6-*O*-acetyl-2'-*O*-(t-butyldimethylsilyl)-*C*-*nor*-paclitaxel (8.9 mg) in anhydrous THF was treated with 100 μL HF·pyridine solution. The reaction was allowed to proceed at room temperature for 1.5 hours and then was worked up by standard methods to yield the crude mixture which was subjected to silica gel preparative TLC (3:2 hexane : EtOAc), affording 6-*O*-acetyl-*C*-*nor*-paclitaxel (7.0 mg, 90% yield). ^{1}H NMR δ 8.19 (d, 2H, *J* = 7.0), 7.75 (d, 2H, *J* = 7.2), 7.59 (t, 1H, *J* = 7.2), 7.58-7.30 (m, 10H), 7.02 (d, 1H, *J* = 9.2, NH), 6.58 (s, 1H, H-10), 6.29 (t, 1H, *J* = 8.6, H-13), 5.84 (d, 1H, *J* = 7.9, H-2), 5.73 (q, 1H, *J* = 10.4, 2.0 H-3'), 5.44 (d, 1H, *J* = 4.3, H-6), 5.25 (d, 1H, *J* = 4.4, H-5), 4.63 (q, 1H, *J* = 6.0, 2.0, H-2'), 4.46 (d, 1H, *J* = 7.9, H-20), 4.45 (d, 1H, *J* = 7.9, H-3), 4.33 (d, 1H, *J* = 7.9, H-20), 3.75 (d, 1H, *J* = 6.0, HO-2'), 2.58 (s, 3H, -CH_3), 2.30 (q, 1H, *J* = 15.9, 10.2, H-14), 2.20 (s, 3H, -CH_3), 2.11 (s, 3H, -CH_3), 2.14-2.00 (m, 1H, H-14), 1.98 (s, 3H, -CH_3), 1.90 (s, 3H, -CH_3), 1.22 (s, 3H, -CH_3), 1.14 (s, 3H, -CH_3). LRFABMS *m/z* calcd for $C_{48}H_{52}O_{15}N$ $[MH]^+$ 882, found 882.

Acetylation of 2'-*O*-(*t*-butyldimethylsilyl)-*C*-*seco*-paclitaxel [12]. To the solution of 2'-*O*-(*t*-butyldimethylsilyl)-*C*-*seco*-paclitaxel (7 mg) in anhydrous CH_2Cl_2, 1,3-dicyclohexylcarbodimide (DCC) (3 mg, 2 eq.), 4-pyrrolidinopyridine (PP) (catalytic amount) and acetic anhydride (6.7 mL, 7.3 mg, 8 eq.) were added. The reaction was allowed to proceed at room temperature for 2 hours and then was worked up by standard methods to yield the crude mixture which was subjected to silica gel preparative TLC (7:3 hexane:EtOAc), affording impure 6-*O*-acetyl-2'-*O*-(*t*-butyldimethylsilyl)-*C*-*seco*-paclitaxel (5.5 mg, 80% yield). ^{1}H NMR δ 9.48 (s, 1H, H-7), 7.85 (d, 2H), 7.80 (d, 2H), 7.30-7.60 (m, 6H), 7.12 (d, 1H, *J* = 8.9, NH), 6.41 (s, 1H, H-10), 6.31 (s, 1H, H-6), 6.23 (bd, 1H, *J* = 9.8, H-13), 5.67 (bd, 1H, *J* = 8.4, H-3'), 5.53 (d, 1H, *J* = 8.4, H-20), 5.43 (d, 1H, *J* = 7.9, H-2), 4.89 (d, 1H, *J* = 8.4, H-20), 4.70 (d, 1H, *J* = 1.5, H-2'), 4.25 (s, 1H, H-5), 4.24 (d, 1H, *J* = 7.8, H-3), 2.78-3.00 (m, 2H, H-14), 2.21 (s, 3H, -CH_3), 2.16 (s, 3H, -CH_3), 2.12 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.23 (s, 3H, -CH_3), 1.21 (s, 3H, -CH_3), 0.82 (s, 9H, -CH_3), -0.02 (s, 3H, -CH_3), -0.33 (s, 3H, -CH_3).

***C*-*seco*-Paclitaxel [13].** To the solution of 6-*O*-acetyl-2'-*O*-(*t*-butyldimethylsilyl)-*C*-*seco*-paclitaxel (5.5 mg) in anhydrous THF (250 mL), 100 mL HF·pyridine solution was added. The reaction then proceeded at room temperature for 1.5 hours and then was worked up by standard methods to yield the crude mixture which was subjected to silica gel preparative TLC twice (3:2 hexane:EtOAc), affording *C*-*seco*-paclitaxel (4 mg, 90% yield). ^{1}H NMR δ 7.89(d, 2H), 7.82 (d, 2H), 7.56 (t, 1H), 7.50-7.30 (m, 5H), 6.95 (d, 1H, *J* = 8.1, NH), 6.49 (s, 1H, H-10), 6.20 (t, 1H, *J* = 8.1, H-13), 6.14 (s, 1H, H-6), 5.78 (d, 1H, *J* = 9.1, H-2), 5.70 (dd, 1H, *J* = 8.2, 3.4, H-3'), 5.13 (d, 1H, *J* = 3.1, H-7), 4.85 (d, 1H, *J* = 7.5, H-20), 4.72 (d, 1H, *J* = 7.4, H-20), 4.72 (d, 1H, *J* = 5.2, H-2'), 4.43 (s, 1H, H-5), 3.86 (d, 1H, *J* = 9.0, H-3), 3.68 (d, 1H, *J* = 4.5, HO-2'), 3.28 (s, 1H, HO-7), 2.65-3.00 (m, 2H, H-14), 2.19 (s, 3H, -CH_3), 2.13 (s, 3H, -CH_3), 1.80 (s, 3H, -CH_3), 1.43 (s, 3H, -CH_3), 1.26 (s, 3H, -CH_3), 1.25 (s, 3H, -CH_3). ^{13}C NMR δ 202.5 (C9), 172.2 (C-1'), 169.6 (C-10 carbonyl), 168.3 (C-6 carbonyl), 167.3 (amide carbonyl), 165.8 (C-1 carbonyl), 140.5 (C-12), 136.2 (C-11), 103.0 (C-7), 90.8 (C-6), 90.8 (C-1), 84.3 (C-5), 80.3 (C-4), 84.0 (C-20), 76.7 (C-10), 74.0 (C-2'), 61.0 (C-8), 72.0 (C-13), 67.0 (C-2), 55.9 (C-3'), 40.8 (C-3), 43.8 (C-15), 35.8 (C-14), 20.8 (C-10 OAc), 22.6 (C-17), 20.9 (C-4 OAc), 27.8 (C-16), 15.1 (C-18), 19.0 (C
-19). LRFABMS *m/z* calcd for $C_{47}H_{50}O_{15}N$ $[MH]^+$ 868, found 868.

2'-*O*-(*t*-Butyldimethylsilyl)-6-keto-7-*epi*-paclitaxel [16] and 2'-*O*-(*t*-butyldimethylsilyl)-6-formyl-*C*-*nor*-paclitaxel [17]. To a solution of 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (15.0 mg) in anhydrous CH_2Cl_2 (500 mL) were added tetrapropylammonium perruthenate (TPAP, 1.0 mg, 0.2 eq.) and 4-methylmorpholine N-oxide (NMO, 10.0 mg, 6 eq.) at -20°C. The reaction mixture was allowed to proceed at -20 °C for 20 hours and then was worked up by standard methods to yield the crude mixture which was subjected to silica gel preparative TLC (7:3 hexane : EtOAc), affording a mixture (10 mg) of 2'-*O*-(*t*-butyldimethylsilyl)-6-keto-7-*epi*-paclitaxel (**16**, major) and a less polar product, 2'-*O*-(t-butyldimethylsilyl)-6-formyl-*C*-*nor*-paclitaxel (**17**, minor). Repurification of the mixture by silica gel preparative TLC (7:3 hexane :

EtOAc), afforded the same mixture and additional pure 2'-*O*-(*t*-butyldimethylsilyl)-6-formyl-*C*-*nor*-paclitaxel (**17**).

2'-*O*-(*t*-butyldimethylsilyl)-6-keto-7-*epi*-paclitaxel (impure) (**16**): ^{1}H NMR δ 8.16 (d, 2H), 7.70 (d, 2H), 7.64-7.26 (m, 11H), 7.08 (d, 1H, *J* = 8.8, NH), 6.54 (s, 1H, H-10), 6.29 (t, 1H, *J* = 8.8, H-13), 5.80 (bd, 1H, *J* = 8.8, H-3'), 5.76 (d, 1H, *J* = 7.6, H-2), 5.06 (s, 1H, H-5), 5.00 (d, 1H, *J* = 5.2, H-7), 4.66 (s, 1H, H-2'), 4.44 (d, 1H, *J* = 8.0 H-20), 4.40 (d, 1H, *J* = 8.0 H-20), 4.34 (d, 1H, *J* = 7.6, H-3), 3.60 (d, 1H, *J* = 5.2, HO-7), 2.64 (s, 3H, -CH_3), 2.40-2.10 (m, 2H, H-14), 2.18 (s, 3H, -CH_3), 1.90 (s, 3H, -CH_3), 1.60 (s, 3H, -CH_3), 1.18 (s, 3H, -CH_3), 1.12 (s, 3H, -CH_3), 0.78 (s, 9H), -0.05 (s, 3H), -0.3 (s, 3H).

2'-*O*-(*t*-butyldimethylsilyl)-6-formyl-*C*-*nor*-paclitaxel (**17**): ^{1}H NMR δ 9.94 (s, 1H, H7), 8.17 (d, 2H), 7.70 (d, 2H), 7.56-7.20 (m, 11H), 7.10 (d, 1H, *J* = 8.5, NH), 6.53 (s, 1H, H-10), 6.31 (t, 1H, *J* = 8.7, H-13), 5.92 (d, 1H, *J* = 7.8, H-2), 5.81 (bd, 1H, *J* = 9.0, H-3'), 5.18 (s, 1H, H-5), 4.69 (d, 1H, *J* = 7.9, H-20), 4.65 (d, 1H, *J* = 2.0, H-2'), 4.51 (s, 1H, HO-6), 4.47 (d, 1H, *J* = 7.7, H-3), 4.43 (d, 1H, *J* = 7.9, H-20), 2.40 (m,1H, H-14) 2.53 (s, 3H, -CH_3), 2.21 (s, 3H, -CH_3), 2.16 (s, 3H, -CH_3), 2.10 (m, 1H, H-14), 1.98 (s, 3H, -CH_3), 1.21 (s, 3H, -CH_3), 1.14 (s, 3H, -CH_3), 0.8 (s, 9H), -0.07 (s, 3H), -0.33 (s, 3H). ^{13}C NMR δ 203.5 (C-9), 198.8 (C-7), 170.7 (C-1'), 170.4 (C-4 carbonyl), 169.4 (C-10 carbonyl), 166.8 (amide carbonyl), 166.8 (C-2 carbonyl), 140.3 (C-12), 138.4, 134.4 (C-11), 133.8, 131.6, 130.2, 128.9, 128.8, 128.7, 127.9, 126.9, 126.2, 92.3 (C-5), 85.8 (C4), 85.1 (C-6), 78.4 (C1), 77.2 (C-10), 77.0 (C-20), 75.4 (C-2'), 74.0 (C-2), 70.6 (C-13), 64.3 (C-8), 55.6 (C-3'), 47.9 (C-3), 42.3 (C-15), 36.7 (C-14), 25.8 (C-17), 25.4 (Si-C-CH_3), 22.3 (C-4 OAc), 20.7 (C-16), 20.7 (C-10 OAc), 18.1(Si-C), 15.3 (C-19), 14.6 (C-18), -5.4 (Si-CH_3), -6.0 (Si-CH_3). LRFABMS *m/z* calcd for $C_{58}H_{63}O_{15}NSiNa$ $[MNa]^+$ 1004, found 1004.

6-Formyl-*C*-*nor*-paclitaxel [19]. To the solution of 2'-*O*-(*t*-butyldimethylsilyl)-6-formyl-*C*-*nor*-paclitaxel (3 mg) in anhydrous THF (250 mL), HF·pyridine solution (75 mL) was added. The reaction proceeded then at room temperature for 2.5 hours and then was worked up by standard methods to yield a crude mixture which was subjected to two-fold preparative TLC (silica gel, 3:2 hexane:EtOAc), affording 6-formyl-C-*nor*-paclitaxel (**19**, 2 mg, 80%). ^{1}H NMR δ 9.92 (s, 1H, H-7), 8.20 (d, 2H), 7.70 (d, 2H), 7.56-7.30 (m, 11H), 6.96 (d, 1H, *J* = 9.6, NH), 6.52 (s, 1H, H-10), 6.30 (t, 1H, *J* = 8.7, H-13), 5.93 (d, 1H, *J* = 8.0, H-2), 5.89 (bd, 1H, *J* = 9.5, H-3'), 5.15 (s, 1H, H-5), 4.82 (d, 1H, *J* = 2.0, H-2'), 4.69 (d, 1H, *J* = 8.1, H-20), 4.49 (d, 1H, *J* = 8.1, H-20), 4.42 (d, 1H, *J* = 7.9, H-3), 3.75 (s, 1H, HO-2'), 2.70 (q, 1H, *J* = 15.7, 9.0, H-14), 2.45 (s, 3H, -CH_3), 2.26 (m, 1H, H-14), 2.19 (s, 3H, -CH_3), 2.18 (s, 3H, -CH_3), 1.90 (s, 3H, -CH_3), 1.21 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3).

2'-*O*-(*t*-Butyldimethylsilyl)-6α-*O*-trifluoromethanesulfonyl-7-*epi*-paclitaxel [20]. 2'-*O*-(*t*-butyldimethylsilyl)-6α-hydroxy-7-*epi*-paclitaxel (**3**, 170.0 mg) was dissolved in dry CH_2Cl_2 (2 mL). To this solution dimethylaminopyridine (102 mg, 5 eq.) and trifluoromethanesulfonyl chloride (47 mL, 2 eq.) were added successively at 0 °C and the mixture was stirred at room temperature for 1 hour. The reaction mixture then was diluted with EtOAc (4.0 mL) and the precipitate was filtered through Celite. The solution wasevaporated, and the residue was purified by preparative TLC (silica gel, 1:1 hexane:EtOAc) to furnish 2'-*O*-(*t*-butyldimethylsilyl)-6α-*O*-trifluoromethanesulfonyl-7-*epi*-paclitaxel (175.6 mg, 96% yield). ^{1}H NMR δ 8.15 (d, 2H), 7.70 (d, 2H), 7.62 (t, 1H), 7.64-7.26 (m, 10H), 7.07 (d, 1H, *J* = 9.2, NH), 6.77 (s, 1H, H-10), 6.29 (t, 1H, *J* = 8.6, H-13), 5.80 (q, 1H, *J* = 8.8, 2.4, H-3'), 5.73 (d, 1H, *J* = 7.3, H-2), 5.28 (q, 1H, *J* = 4.6, 2.7, H-6), 4.93 (d, 1H, *J* = 2.8, H-5), 4.90 (d, 1H, *J* = 12.0, HO-7), 4.67 (d, 1H, *J* = 2.3, H-2'), 4.47 (d, 1H, *J* = 8,9, H-20), 4.38 (d, 1H, *J* = 8,9, H-20), 3.97 (d, 1H, *J* = 7.3, H-3), 3.92 (q, 1H, *J* = 4.6, 12.0, H-7), 2.71 (s, 3H, -CH_3), 2.40 (q, 1H, *J* = 9.6, 15.2, H-14), 2.20 (s, 3H, -CH_3), 2.11 (q, 1H, *J* = 9.6, 15.2, H-14), 1.91 (s, 3H, -CH_3), 1.68 (s, 3H, -CH_3), 1.20 (s, 3H, -CH_3), 1.13 (s, 3H, -CH_3), 0.78 (s, 9H), -0.05 (s, 3H), -0.3 (s, 3H). HRFABMS *m/z* calcd for $C_{53}H_{63}O_{14}NSiNa(MNa\text{-}CF_3SO_3)$ 988.3915. 988.3915, found 988.3913..

20-*O*-Acetyl-2'-*O*-(*t*-butyldimethylsilyl)-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel [21]. 2'-*O*-(*t*-Butyldimethylsilyl)-6α-*O*-trifluoromethane sulfonyl-7-*epi*-paclitaxel (10.0 mg) was dissolved in dry CH_2Cl_2 (2 mL). To this solution was added 4-dimethylaminopyridine (10.0 mg, 9 eq.). The mixture was stirred at 40 °C for 36 hours and then was worked up by standard methods to yield a residue which was purified

by preparative TLC (silica gel, 7:3 hexane:EtOAc) to furnish 20-*O*-acetyl-2'-*O*-(*t*-butyldimethylsilyl)-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel (**21**, 7.0 mg, 80% yield) and starting material (1 mg, 10%). ^{1}H NMR δ 9.60 (s, 1H, H-7), 8.03 (d, 2H, *J* = 8.4), 7.76 (d, 2H, *J* = 8.1), 7.57 (t, 1H, *J* = 7.5), 7.48-7.32 (m, 3H), 7.30 (d, 1H, *J* = 8.2, NH), 7.02 (m, 2H), 6.77 (s, 1H, H-5), 6.27 (s, 1H, H-10), 5.92 (t, 1H, *J* = 7.0, H-13), 5.87 (d, 1H, *J* = 9.0, H-3'), 5.79 (d, 1H, *J* = 6.2, H-2), 5.02 (bs, 1H, HO), 4.61 (d, 1H, *J* = 6.4, H-3), 4.53 (d, 1H, *J* = 1.4, H-2'), 4.47 (d, 1H, *J* = 12.2, H-20), 4.14 (d, 1H, *J* = 12.2, H-20), 2.87 (q, 1H, *J* = 15.7, 6.6, H-14), 2.56 (q, 1H, *J* = 15.7, 6.6, H-14), 2.23 (s, 3H, -CH_3), 1.97 (s, 3H, -CH_3), 1.91 (s, 3H, -CH_3), 1.67 (s, 3H, -CH_3), 1.17 (s, 3H, -CH_3), 1.13 (s, 3H, -CH_3), 0.86 (s, 9H), -0.03 (s, 3H), -0.29 (s, 3H). ^{13}C NMR δ 187.6 (C-7), 170.6 (C-4 carbonyl), 170.0 (C-1'), 169.3 (C-10 carbonyl), 167.6 (C-2 carbonyl), 167.2 (amide carbonyl), 151.6 (C-5), 145.7 (C-6), 139.7 (C-12), 137.5 (C-11), 84.2 (C-20), 78.5 (C-1), 76.0 (C-10), 75.7 (C-2'), 75.0 (C-2), 71.9 (C-13), 69.0 (C-4), 60.2 (C-8), 56.5 (C-3), 55.6 (C-3'), 42.9 (C-15), 36.8 (C- 14), 27.2 (C- 17), 20.8 (C-10 OAc), 20.5 (C-4 OAc), 20.5 (C-19), 20.1 (C-16),15.8 (C- 18), 25.5 (Si-C-CH_3), 18.3 (Si-C), -5.3 (Si-CH_3), -5.9 (Si-CH_3). LRFABMS *m/z* calcd for $C_{53}H_{63}O_{14}NSiNa$ $[MNa]^+$ 988, found 988.

20-*O*-Acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel [23]. HF·pyridine solution (100 mL) was added to a solution of 2'-*O*-(*t*-butyldimethylsilyl)-20-*O*-acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel (**21**, 11.0 mg) in anhydrous THF (500 mL). The reaction was allowed to proceed at room temperature for 1.5 hours and was then worked up by standard methods to yield a crude mixture which was twice subjected to preparative TLC (silica gel, 3:2 hexane:EtOAc) to afford 20-*O*-acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel (**23**, 8 mg, 85% yield). ^{1}H NMR δ 9.60 (s, 1H, H-7), 8.12 (d, 2H, *J* = 8.6), 7.71 (d, 2H, *J* = 8.1), 7.54-7.32 (m, 4H), 7.03 (m, 2H), 7.02 (d, 1H, *J* = 8.0, NH), 6.79 (s, 1H, H-5), 6.26 (s, 1H, H-10), 5.96 (t, 1H, *J* = 7.1, H-13), 5.90 (d, 1H, *J* = 10.1, H-3'), 5.83 (d, 1H, *J* = 6.4, H-2), 5.19 (s, 1H, HO), 4.68 (d, 1H, *J* = 6.4, H-3), 4.69 (bs, 1H, H-2'), 4.52 (d, 1H, *J* = 12.2, H-20), 4.14 (d, 1H, *J* = 12.0, H-20), 3.37 (d, 1H, *J* = 3.0, HO-2'), 2.95 (q, 1H, *J* = 14.8, 6.9, H-14), 2.58 (q, 1H, *J* = 15.1, 9.2, H-14), 2.23 (s, 3H, -CH_3), 1.93 (s, 3H, -CH_3), 1.92 (s, 3H, -CH_3), 1.68 (s, 3H, -CH_3), 1.17 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3). ^{13}C NMR δ 187.6 (C-7), 170.6 (C-4 carbonyl), 170.0 (C-1'), 169.3 (C-10 carbonyl), 167.6 (C-2 carbonyl), 167.2 (amide carbonyl), 151.6 (C-5), 145.8 (C-6), 139.7 (C-12), 137.5 (C-11), 84.3 (C-20), 78.4 (C-1), 75.9 (C-10), 74.8 (C-2), 73.4 (C-2'), 73.0 (C-13), 68.9 (C-4), 60.4 (C-8), 56.8 (C-3), 54.2 (C- 3'), 42.9 (C-15), 36.3 (C-14), 27.5 (C-17), 20.8 (C-10 OAc), 20.5 (C-4 OAc), 20.5 (C-19), 19.9 (C-16), 15.9 (C-18). HRFABMS *m/z* calcd for $C_{47}H_{49}O_{14}NNa$ $[MNa]^+$ 874.3050, found 874.3035.

20-*O*-Acetyl-4-deacetyl-2-debenzoyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel [24]. Tetrabutylammonium fluoride solution (100 mL) was added to a solution of 2'-*O*-(t-butyldimethylsilyl)-20-acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel (21, 5.0 mg) in anhydrous THF, and the reaction then allowed to proceed at room temperature for 15 minutes. At this time the reaction mixture was diluted with EtOAc, followed by H_2O. The aqueous layer was washed with additional EtOAc (2 x 2 mL). The combined organic layers were then washed with H_2O and brine, and after drying over sodium sulfate, the solution was filtered and evaporated to yield the crude mixture which was subjected to preparative TLC twice (silica gel, 3:2 hexane : EtOAc), affording 20-*O*-acetyl-4-deacetyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel (**23**, 0.8 mg, 20% yield) and 20-*O*-acetyl-4-deacetyl-2-debenzoyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel (**24**, 1.6 mg, 45% yield) ^{1}H NMR for 20-*O*-acetyl-4-deacetyl-2-debenzoyl-5,6-dehydro-6-formyl-*C*-*nor*-paclitaxel: δ 9.58 (s, 1H, H-7), 7.78 (d, 2H, *J* = 7.0), 7.71 (q, 1H, *J* = 5.7, 3.4), 7.57-7.34 (m, 7H), 7.20 (d, 1H, *J* = 10.1, NH), 6.84 (s, 1H, H-5), 6.19 (s, 1H, H-10), 5.92 (t, 1H, *J* = 7.1, H-13), 5.80 (d, 1H, *J* =9.2, H-3'), 5.19 (s, 1H, HO), 4.98 (d, 1H, *J* = 12.6, H-20), 4.76 (bs, 1H, H-2'), 4.51 (d, 1H, *J* = 12.6, H-20), 4.13 (d, 1H, *J* = 7.6, H-3), 3.90 (d, 1H, *J* = 7.9, H-2), 3.37 (bs, 1H, HO-2'), 3.33 (d, 1H, J = 7.9, HO-2), 2.30 (m, 1H, H-14), 2.18 (m, 1H, H-14), 2.20(s, 3H, -CH_3), 2.07 (s, 3H, -CH_3), 1.89 (s, 3H, -CH_3), 1.60 (s, 3H, -CH_3), 1.13 (s, 3H, -CH_3), 0.97 (s, 3H, -CH_3). LRFABMS *m/z* calcd for $C_{40}H_{46}O_{13}N$ $[MH]^+$ 748, found 748.

ACKNOWLEDGMENTS

Financial support for this work was provided by the National Cancer Institute (grant Number CA-55131) and is gratefully acknowledged. We also gratefully acknowledge assistance with bioassays from Chii M. Lin and

Ernest Hamel of the Laboratory of Molecular Pharmacology, Developmental Therapeutics Program, DCT, National Cancer Institute, NIH, Bethesda, Maryland. X. Liang thanks Drs. M. D. Chordia, A. A. L. Gunatilaka and B.-N. Zhou for helpful suggestions and discussions.

REFERENCES

1. (a) Holmes, F. A.; Kudelka, A. P.; Kavanagh, 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.; American Chemical Society: Washington, DC, 1994; Vol. ACS Symposium Series 583; 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, Inc.: New York, Basel, Hong Kong, 1995; Vol. 8; pp 1-349.
2. (a) Chen, S.-H.; Farina, V. Paclitaxel Structure-Activity Relationships and Core Skeletal Rearrangements. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I. and Vyas, D. M., Eds.; ACS Symposium Series 583, American Chemical Society: Washington, DC, 1994; pp 247-261. (b) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Clowers, J. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. The Medicinal Chemistry of Taxol. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press, Inc.: Boca Raton, FL, 1995; pp 317-375. (c) Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1-34. (d) Kingston, D. G. I. *Trends Biotechnol.* **1994**, *12*, 222-227. (e) Kingston, D. G. I. Recent Advances in the Chemistry and Structure-Activity Relationships of Paclitaxel. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I. and Vyas, D. M., Ed.; American Chemical Society: Washington, DC, 1994; Vol. ACS Symposium Series 583; pp 203-216. (f) Kingston, D. G. I. History and Chemistry. In *Paclitaxel in Cancer Treatment*; McGuire, W. P. and Rowinsky, E. K., Ed.; Marcel Dekker, Inc.: New York, Basel, Hong Kong, 1995; Vol. 8; pp 1-33. (g) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44.
3. (a) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114-5119. (b) Chen, S.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805-2828.
4. Klein, L. L.; Maring, C. J.; Li, L.; Yeung, C. M.; Thomas, S. A.; Grampovnik, D. J.; Plattner, J. J.; Henry, R. F. *J. Org. Chem.* **1994**, *59*, 2370-2373.
5. Bouchard, H.; Pulicani, J.-P.; Vuilhorgne, M.; Bourzat, J.-D.; Commerçon, A. *Tetrahedron Lett.* **1994**, *35*, 9713-9716.
6. Liang, X.; Kingston, D. G. I. *Tetrahedron Lett.* **1995**, *36*, 7795-7798.
7. Chen, S.-H.; Huang, S.; Roth, G. P. *Tetrahedron Lett.*, **1995**, 36, 8933-8936.
8. (a) Liang, X.; Kingston, D. G. I.; Lin, C. M.; Hamel, E. *Tetrahedron Lett.*, **1995**, 36, 2901-1904. (b) Johnson, R. A.; Nidy, E. G.; Dobrowolski, P. J.; Gebhard, I.; Qualls, S. J.; Wicnienski, N. A.; Kelly, R. C.*Tetrahedron Lett.* **1994**, *35*, 7893-7896.
9. Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469-1474.
10. Bender, M. L.; Reinstein, J. A.; Silver, M. S.; Mikulak, R. *J. Amer. Chem. Soc.*,**1965**, *87*, 4545-4553.
11. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta*, **1990**, 23, 13.
12. Assay carried out by Drs. E. Hamel and C. M. Lin.

(*Received in USA* 13 *November* 1996; *accepted* 14 *January* 1997)