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STUDIES ON THE PHOTOCHEMISTRY OF TAXOL®

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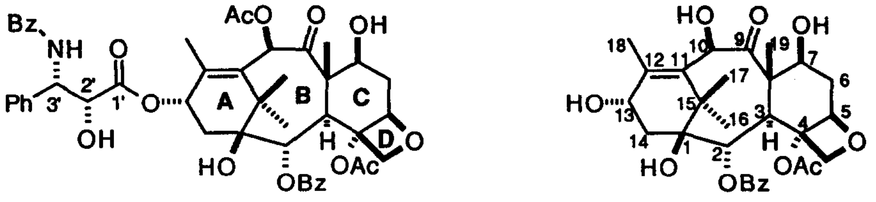
Abstracts: *Irradiation of taxol at 280 nm in a Rayonet reactor yielded a novel pentacyclic derivative containing a new bond between C-3 and C-11. The proposed mechanism involves a triplet intermediate and the first event of the oxa-di-π-methane rearrangement. Taxane derivatives that lack both the benzoate at C-2 and the benzamide function at C-3' do not undergo the rearrangement, suggesting the intervention of an intramolecular energy transfer. Irradiation at 300 nm also effects extrusion of the C-9 carbonyl, yielding a ring-contracted product.*

INTRODUCTION

The unique antimitotic agent taxol,[1] the first compound in the taxane family shown to possess antineoplastic activity, has become a very important anticancer agent.[2]

Structurally, taxol is a highly oxygenated tetracyclic diterpenoid.[3] The ABCD ring system of taxol, along with the numbering of the carbon skeleton of 10-deacetylbaccatin III,[4] another important member of the taxane family, are shown in Figure 1.

Figure 1

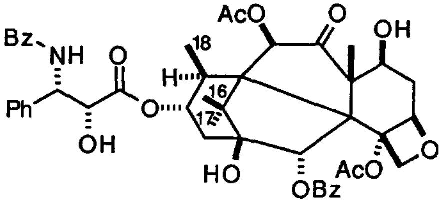


1 *Taxol* *10-Desacetylbaccatin*

Despite the promising antitumor activity, the development of taxol was hindered due to the difficulty in its isolation and formulation. However, the interest in taxol was later rekindled by the discovery of its unique cytotoxic mechanism *via* inhibition of microtubules disassembly.[5] During the past decade, taxol has shown good activity against several human tumors,[6] and has received FDA approval for the treatment of refractory ovarian cancer in 1992.

During the course of our development of taxol as a commercial antitumor drug, **1** was subjected to a series of stability tests, including exposure to sunlight. In this test traces of a taxol isomer were isolated by semipreparative HPLC. After extensive NMR studies, the structure was identified as the pentacyclic taxol isomer **2** (Figure 2), containing a bond between C-3 and C-11.[7] Since very limited amounts of **2** were produced by sunlight exposure, an efficient method for its production was highly desirable for biological evaluation. At the same time, we were also interested in the mechanistic aspects of this remarkable photochemical transformation. In this report we disclose further details on the photochemistry of the taxanes, and we demonstrate the direct role of the C-13 side chain and the C-2 benzoate substituent on the course of this photoisomerization.

Figure 2



2

RESULTS AND DISCUSSION

A Rayonet Photoreactor was used for the photochemical studies. The cooling fan was always turned on in order to keep the temperature inside the photoreactor at 48-50°C. The photochemical reactions were initially performed with the 254 nm UV lamp. The taxol concentraction was kept at 0.05 M. Under the above conditions, the effect of changing the solvent and filter type were examined. The results are shown in Table 1.

It is important to note that none of the taxol isomer **2** was produced either by performing the reaction in quartz glassware or in acetone solvent. Exposure of taxol to the more energetic UV light obtained with quartz presumably resulted in extensive excitation of the many functional groups of taxol, resulting in a complex mixture of products. A very clean result (55% of **2**) was obtained by the use of Pyrex filter and carbon tetrachloride as the solvent. It should be noted that taxol was not very soluble in carbon tetrachloride, and the incompleteness of this reaction may be in part due to the poor solubility. Photolysis of taxol in benzene and toluene was also successful.

Surprisingly, no UV spectrum of taxol was reported. We then decided to examine the UV absorption of taxol in CCl_4 and benzene. It was then found that the UV spectrum of taxol in benzene exhibited only one broad absorption peak centered around 280 nm. Similar broad UV absorption signal centered around 262 nm was seen in carbon tetrachloride.

Table 1: Solvent and filter effects on the conversion of 1 into 2

Solvent	Filter	2 (%)	Recovered 1 (%)
Toluene	Quartz	0	decomposition
Toluene	Pyrex	29	66
Benzene	Pyrex	31	59
CCl_4	Pyrex	55	44
Acetone	Pyrex	0	decomposition

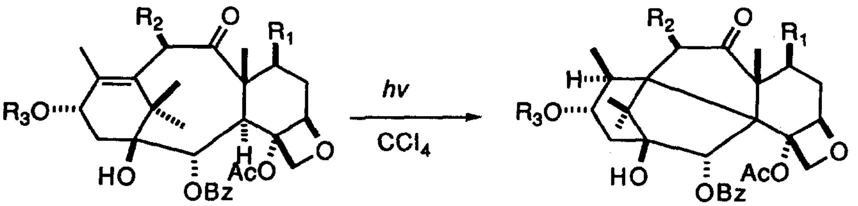
The structure of isomer 2, which contains a pentacyclic taxane, was identified after extensive NMR analysis. Specifically, the ^{1}H-NMR spectrum featured the disappearance of a C-18 methyl singlet at 1.79 d, with the appearance of a new methyl doublet at 0.90 d, indicating saturation of the C11-12 double bond. The signal due to H-2, a doublet in taxol, now became a singlet at 5.56 d, while the H-3 proton (3.77 d in taxol) was missing. The stereochemistry of the C-18 methyl group was determined to be β on the basis of NOE analysis. Specifically, positive NOE was observed between the H-18 methyl and H-13 as well as H-17 methyl group.

The structural complexity of 2 makes it an interesting target for X-ray analysis.[8] Many efforts were made to crystallize 2, without success. Our next attempt was to crystallize its core, the pentacyclic ring system, since we have noticed that baccatin derivatives give crystals that are much more amenable to X-ray crystallography than the parent taxol.[9] Several literature methods, such as tetrabutylammonium borohydride[10] or lithium iodide[11], failed to cleave the phenyl-isoserine side chain from 2. We then turned to the photochemistry of baccatin III derivatives (their preparation is described later in the paper), and found them to yield similar products (Scheme 1). In particular, very little effect on the reaction pathway is exercized by the C-10 acetoxy substituent. Derivative **4a** was acetylated to yield 5, which gave crystals that were found suitable for X-ray analysis. The result of this X-ray analysis confirms the presence of the C-3 to C-11 bond as well as our stereochemical assignment at C-12.

The C-3/C-11 and C-3/C-8 bond lengths were found to be 1.644A and 1.622A, respectively. These bonds are significantly longer than standard C-C bonds.[12] The X-ray structure of 5 is shown below (Figure 3).

In order to examine the structural novelty of 2 and the baccatin-like derivative 5, we have scrutinized the literature, and found a few taxane derivatives containing a C-3/C-11 bond: the earliest was reported in the1960s by Nakanishi,[13,14] and more recently Appendino[15] and Ettouati[16] reported additional examples. None of these taxinine derivatives contain the oxetane, and all contain a keto group at C-13. The stereochemistry at C-12 was assigned by Nakanishi as β on the basis of mechanistic considerations.[13] Therefore, our X-ray crystallography determination has indirectly confirmed this early assignment.

Scheme 1



3a: R_1 = OTES, R_2 = OAc, R_3 = H

3b: R_1 = OTES, R_2 = H, R_3 = H

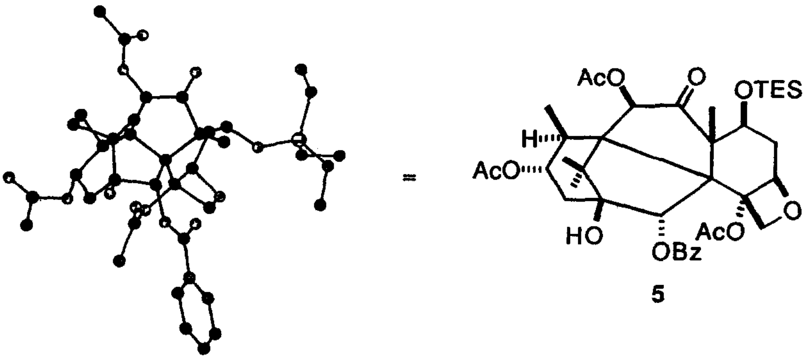
3c: R_1 = H, R_2 = H, R_3 = TES

4a: R_1 = OTES, R_2 = OAc, R_3 = H (Y=23%)

4b: R_1 = OTES, R_2 = H, R_3 = H (Y=20%)

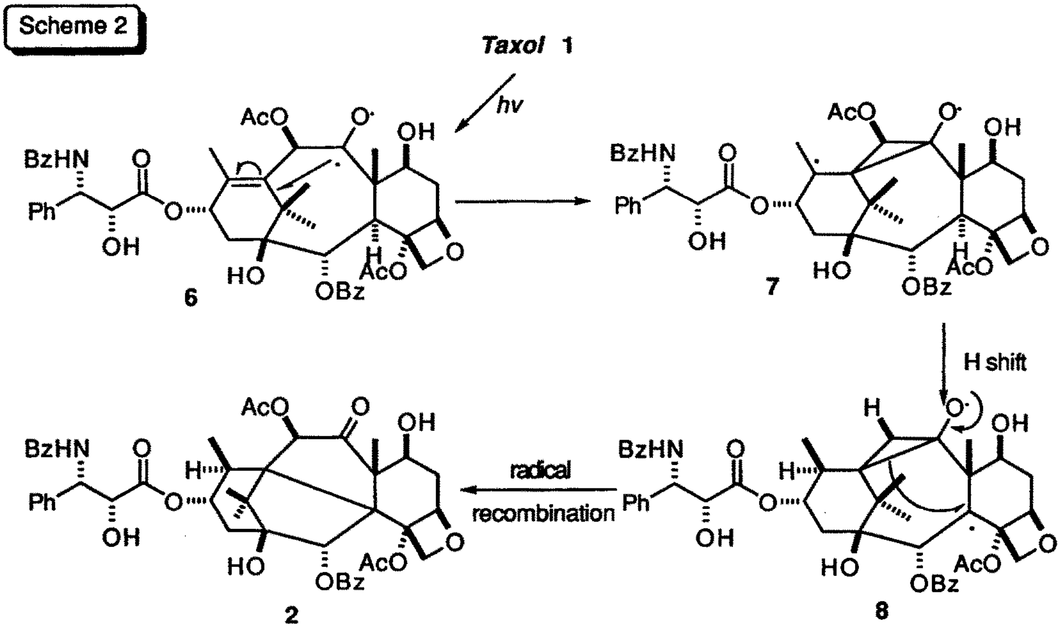
4c: R_1 = H, R_2 = H, R_3 = TES (Y=21%)

Figure 3



5

Mechanistically, this remarkable photochemical skeletal rearrangement can be considered to follow in part the well-known oxa-di-π-methane rearrangement.[17] Nakanishi[13] was the first to describe a similar bond formation between C-3 and C-11, but taxinine differs from taxol in that an enone system is present at C-11/C-12/C-13, and it is undoubtedly excitation of this function initiates the rearrangement. In our case, the photoexcited moiety must be the β,γ-unsaturated ketone,[18] and we propose the mechanism shown in Scheme 2.



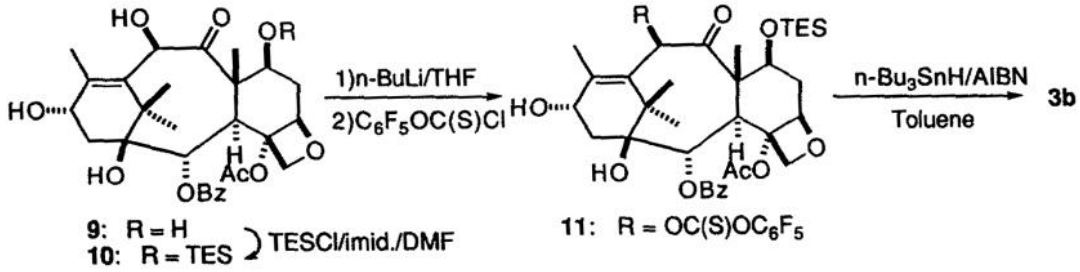
The excited state responsible for the rearrangement must be the $T_1(\pi,\pi^*)$ of the C-9 carbonyl group, which is represented as the diradicaloid species **6**, as postulated in the first step of the oxa-di-π-methane rearrangement.[17] The diradicaloid **6** rearranges to **7** by a 3-exo cyclization, and at this point an intramolecular hydrogen transfer from C-3 to C-12 occurs. Finally, transannular bond formation in **8** leads to **2**. The fact that similar transannular bond formation is formed in our recently described radical cascade[9] also indirectly suggests the intervention of radicaloid intermediates.

Although the above proposed mechanism is reasonable on the basis of the literature, one can wonder whether the C-9 keto group is directly excited, or whether some of the aromatic groups in the molecule are involved in the absorption and in some kind of intramolecular energy transfer. In general, keto group absorbs 270-300 nm UV light weakly (ε=10-40, n-π^*).[19] However, aromatic esters or amides absorb UV light in this region much more efficiently (ε=970, π–π^*).[20] So-called antenna effects are well-precedented in organic photochemistry,[21] and we were led to suspect the occurrence of such an effect here on the basis of the experimental results described below.

We first examined the photochemistry of baccatin derivatives, *i.e.* compounds lacking the C-13 side chain.

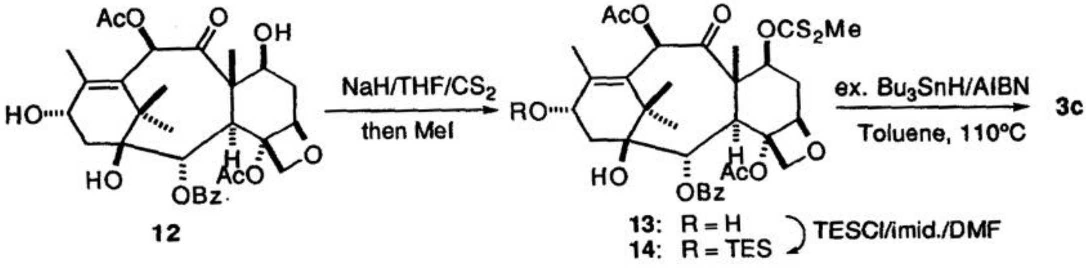
The preparation of 10-deoxy-7-TES baccatin III **3b** is outlined in Scheme 3. Silylation of 10-desacetyl baccatin III **9**, a natural occuring taxane,[4] afforded derivative **10**. This compound was further transformed into its C-10 thiocarbonate **11**, and into **3b** by Barton deoxygenation.

Scheme 3



Likewise, the 7,10-dideoxybaccatin III derivative **3c** was prepared via a radical deoxygenation reaction. In this case, the C-7 xanthate and the C-10 acetate in **14** were removed in one pot by Bu_3SnH/AIBN in toluene at elevated temperature (110°C; Scheme 4).[22]

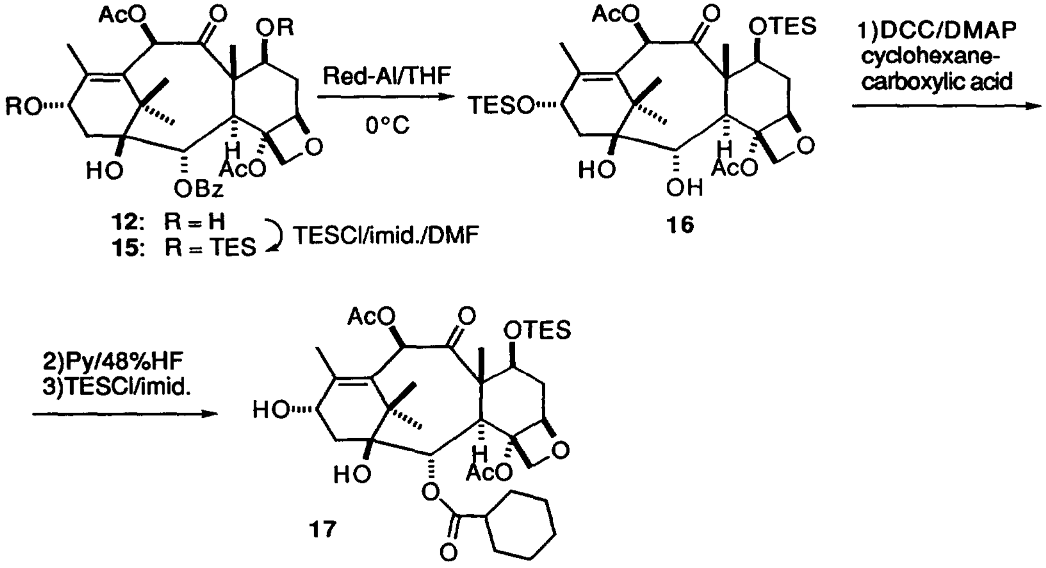
Scheme 4



As illustrated in Scheme 5, the synthesis of the C-2 cyclohexyl ester **17** began with 7,13-bisTES baccatin III **15**, which was prepared in turn by the silylation of baccatin III **12**.

The benzoate moiety in **15** was selectively removed by Red-Al,[23] affording diol **16**. Treatment of **16** with a large excess of DCC/DMAP/cyclohexanoic acid [23] led to **17**.

Scheme 5



As shown in Scheme 1, the three baccatin III derivatives **3a**, **3b** and **3c**, bearing a benzoate group at C-2, when subjected to photolysis under standard reaction conditions (254 nm/ Pyrex filter/ 0.05 M CCl_4 / 20 hr) gave the expected rearranged products **4a-c** in around 20% yield. It should be pointed out that triethylsilyl group was introduced at C-7 and C-13 only to solubilize the compunds.

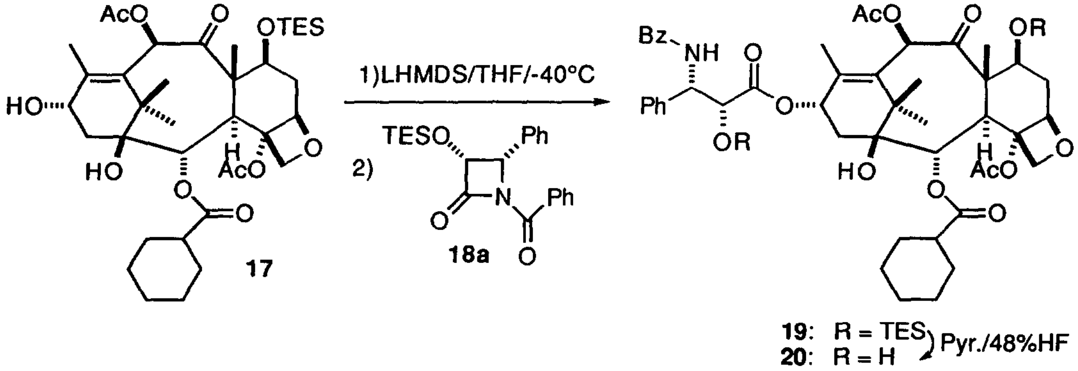
In striking contrast to the above observations, attempted photolysis of **17** failed to produce any rearranged pentacyclic derivative. Thus, by comparing the above results, one is led to postulate that a benzoate group at C-2 is indeed necessary for the photoisomerization. The C-9 ketone alone cannot bring about the photoinduced skeletal rearrangement.

After addressing the role of C-2 benzoate in the photoisomerization of baccatin III derivatives, we next turned to examine the contribution of the side chain N-benzoyl amide moiety towards the photochemistry of taxol involving excitation at the C-9 keto group. The key substrate needed is the C-2 taxol analog, **20**, in which the C-2 benzoyl moiety was replaced by the cyclohexanoyl ester. As shown on Scheme 6, the synthesis of **20** was achieved by the side chain attachment onto baccatin core **17** *via* Holton's protocol,[24] employing the known β-lactam **18a** as the side chain source.[25]

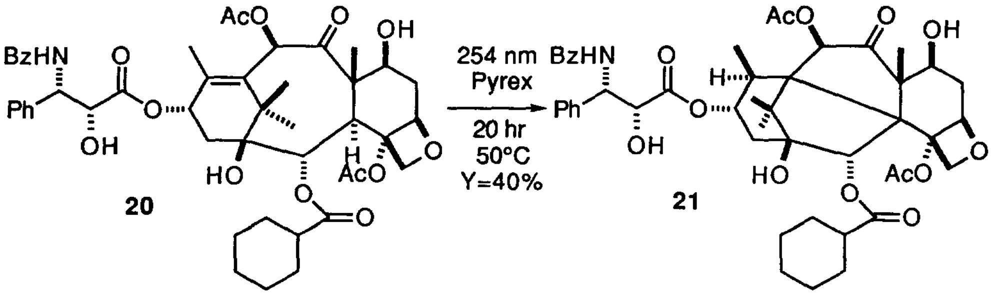
The photolysis of **20** was performed in CCl_4 solution for 20 hours as usual, affording 40% of **21** together with 20% of remaining starting material (Scheme 7). The NMR spectrum of **21** was very similar to that of the pentacyclic taxol isomer **2**, featuring a doublet for the C-18 methyl group, a singlet for H-2 signal and the absence of an H-3 doublet.

By comparing the outcomes of the photochemical reactions described above, one may be led to conclude that the 3'-N-benzoyl amide of the side chain is also involved in an initial intramolecular energy transfer process, since its presence restores the normal reaction mode absent in **17**.

Scheme 6

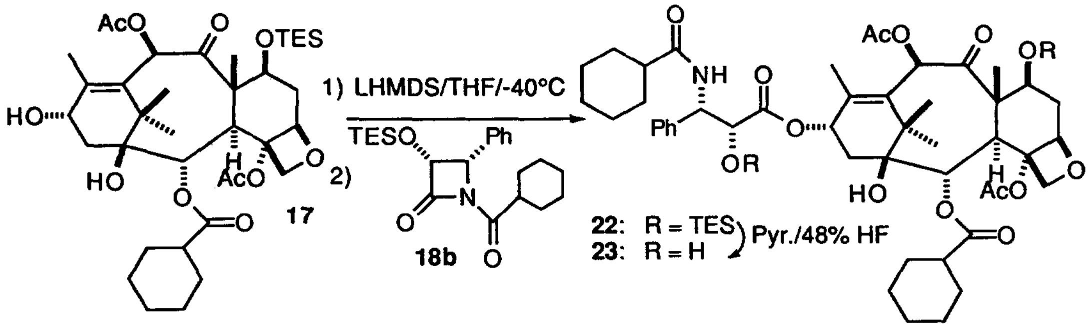


Scheme 7



Finally, we felt that photoinduced isomerization should not be observed for analog **23** because there are no aromatic ester nor amide moieties at C-2 and C-3'. As shown in Scheme 8, the synthesis of **23** was accomplished via the coupling of the baccatin core **17** and the side chain β-lactam**18b**,[25] followed by the standard desilylation reaction. Under standard photolysis conditions, compound **23** was found, as expected, structurally unchanged. Thus, this experiment has further confirmed our hypothesis: the C-9 ketone alone is not sufficient for the photoisomerization.

Scheme 8



As we were investigating the photochemistry of taxol using 254 nm wavelength, we also wondered about any possible relation between the product distribution and the wavelength used. We carried out several experiments by exciting at 300 nm, instead of 254 nm, and the results are summarized in Table II. In addition to **2**, the new compound **24** was isolated in variable yield (Scheme 9).

The structure of **24** was established on the basis of extensive NMR and mass spectral analysis. In particular, the ^{13}C NMR and mass spectra indicated the absence of a keto group absorption (200 ppm) and the loss of 28 mass units, respectively. The diagnostic ^1H NMR data are listed in Table III; these include a doublet for the C-18 methyl protons, a singlet for H-2 and the usual disappearance of the H-3 doublet. In the NOESY experiment, NOE were observed between H-10 and H-19; H-13 and H-17; H-2 and H-7; H-7 and H-16; as well as between H-17 and H-16, H-18. These NOE data led us to assign H-7 as β. Likewise, the C-19 methyl is assigned to be α (NOE between H-19 and H-10); the β configuration was assigned for the C-18 methyl group (NOE between H-18 and H-17). The energy-minimized three dimensional drawing of the core portion of compound **24** is provided in Figure 4.

Interestingly, a variety of experiments in acetone, a known triplet sensitizer, always led to complex mixtures. Also, the presence of another triplet sensitizer, benzophenone, on the photolysis of taxol **1** did not influence product distribution and did not improve the yield.

Table II: Solvent effect on the conversion of taxol to 2 and 24 (Pyrex filter, 300nm)

Solvent	**2 (%)**	**24 (%)**	**Recovered 1 (%)**
Toluene	31	30	-
CCl_4	41	21	20
Acetone	-	-	-

Scheme 9

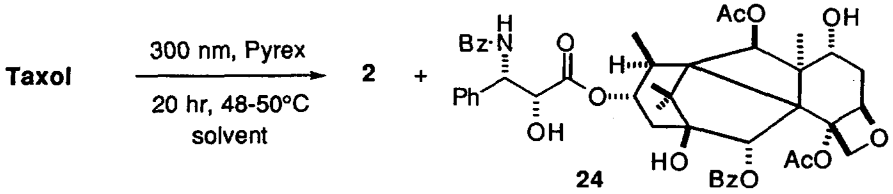
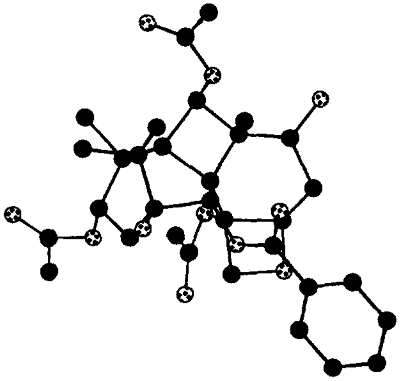


Table III: Diagnostic ^{1}H-NMR signal changes between taxol 1 and 24 (CDCl$_3$, d)

Proton(s)	Taxol	Compound 24	Proton(s)	Taxol	Compound 24
H-2	5.67(d)	5.07(s)	H-13	6.23(m)	5.62(m)
H-3	3.77(d)	none	H-14	2.35;2.28(m)	3.15;2.20(m)
H-5	4.94(d)	5.81(s)	H-16	1.14(s)	1.67(s)
H-6	2.54;1.88(m)	2.36;2.01(m)	H-17	1.24(s)	1.22(s)
H-7	4.40(m)	3.91(m)	H-18	1.79(s)	0.94(d,J=7.3)
H-10	6.26(s)	6.20(s)	H-19	1.68(s)	1.67(s)
H-12	none	1.90(m)	H-20	4.25(AB)	4.53(AB)

Figure 4



The formation of compound 24 can be rationalized by invoking the occurrence, after the photoisomerization, of a Norrish type I process.[26] The epimerization at C-7 may not be a photochemical event. Interestingly, only one configuration out of two possible ones at C-8 and C-10 was formed in the reaction. The observed stereoselectivity at C-8 as well as C-10 may be due to preference for the formation of less strained pentacyclic ring system.

In conclusion, our data so far suggest a role for the C-2 benzoate and/or the C-3' benzoyl amide functions in the photoisomerization of taxanes. A triplet-triplet intramolecular energy transfer may be responsible for the photochemical activation of the C-9 carbonyl, which we have postulated as the key function leading to bond formation bewteen C-3 and C-11. This interesting observation would be further corroborated if photophysical studies on the various excited states could be carried out.

EXPERIMENTAL

Dichloromethane was distilled from calcium hydride. Anhydrous pyridine and methanol were obtained from Aldrich, and used directly. Nuclear magnetic resonance (NMR) data were obtained on a Bruker AC-300 (at 300 MHz for ^1H and 75.5 MHz for ^{13}C). Long-range carbon-proton couplings were determined by the HMBC technique.[27] ^{13}C-NMR spectra were partially assigned with the aid of INEPT and HETCOR experiments. Accurate mass measurements were obtained with a Kratos MS50RF mass spectrometer in the positive ion FAB mode, with m-nitrobenzyl alcohol as the matrix. Sodium iodide and/or potassium iodide were added when Na(K) adducts were determined. Preparative silica chromatography was carried out according to Still.[28] X-ray diffraction data were collected on an Enraf-Nonius CAD4 diffractometer at room temperature.

Photo-isomerization of taxol (1) to (2) under 254 nm and Pyrex filter:

Taxol **1** (256 mg, 0.30 mmol) was placed in Pyrex glassware. Carbon tetrachloride (6.0 mL) was added. This suspension was degassed with a stream of dry nitrogen for 5 mins. The reaction mixture was subjected to photolysis (254 nm/50°C) for 20 hr. The solvent was then partially removed by a stream of N_2. The residue was chromatographed (60-70-100% ethyl acetate in hexane) to give 141 mg (55%) of **2**, together with 112.6 mg (44%) of the remaining taxol **1**.

^1H NMR of **2** ($CDCl_3$): δ 8.03-7.14 (m, 16H), 5.98 (m, 2H), 5.68 (dd, J=2.9 Hz, J'=8.7 Hz, 1H), 5.58 (m, 2H), 4.68 (d, J=3.0 Hz, 1H), 4.47 (AB q, J=9.2 Hz, 2H), 4.40 (m, 1H), 3.08 (dd, J=8.2 Hz, J'=14.8 Hz, 1H), 2.56-1.83 (m, 10H, incl. singlets at 2.56, 2.19, 3H each), 1.69 (s, 3H), 1.27 (s, 3H), 0.94 (s, 3H), 0.88 (d, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 207.2, 172.7, 170.5, 169.3, 167.2, 166.8, 137.8, 134.0, 133.7, 132.0, 130.6, 129.7, 129.5, 129.1, 128.8, 128.7, 128.5, 127.0, 126.8, 87.2, 83.1, 81.6, 80.5, 79.2, 77.0, 76.8, 76.6, 76.4, 75.3, 69.7, 60.2, 57.2, 56.6, 55.6, 46.6, 40.7, 35.7, 26.5, 23.5, 23.1, 20.7, 20.6, 17.5. HRMS calcd. for $C_{47}H_{52}NO_{14}$ (MH^+): 854.3388, found: 854.3407.

Photo-induced transformation of taxol (1) to (2) and (24) under 300 nm and Pyrex filter:
The photolysis of taxol at 300 nm was done very similarly to the procedure described above (at 254 nm). The reaction mixture was subjected to silica gel chromatography (60-70-100% ethyl acetate in hexane) to afford taxol isomer **2** and **24**. The detailed yields are listed in Table 2.

^{1}H NMR ($CDCl_3$) of **24**: δ 7.94-7.23 (m, 15H), 7.04 (d, J=8.5 Hz, 1H), 6.20 (s, 1H), 5.81 (s, 1H), 5.62 (m, 2H), 5.07 (s, 1H), 4.84 (d, J=8.7 Hz, 1H), 4.65 (dd, J=3.2 Hz, J'=6.8 Hz, 1H), 4.22 (d, J=8.6 Hz, 1H), 3.91 (m, 1H), 3.15 (dd, J=7.9 Hz, J'=15.2 Hz, 1H), 2.51-1.87 (m, 10H, incl. singlets at 2.51, 2.11, 3H each), 1.67 (s, 6H), 1.22 (s, 3H), 0.94 (d, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.1, 169.8, 169.7, 167.2, 137.7, 133.9, 132.0, 129.5, 129.1, 128.7, 128.4, 127.1, 127.0, 87.1, 83.1, 82.0, 78.8, 73.6, 73.4, 72.3, 60.0, 55.8, 53.3, 53.2, 44.9, 42.7, 36.7, 30.5, 26.0, 25.0, 24.4, 20.8, 15.2, 13.4. HRMS calcd. for $C_{46}H_{51}NO_{13}$ Na (MNa^+): 848.3258, found: 848.3248.

General procedure for the photo-isomerization of baccatin III drivatives 3(a,b,c) to 4(a,b,c) under 254 nm and Pyrex filter:
A carbon tetrachloride solution (0.05M) of **3** (a,b,c) (0.5 mmol) was degassed with dry N_2 for 5 mins. This solution was then subjected to photolysis for 15 hr at 50°C. The resulting mixture was conc. *in vacuo*. The residue was chromatographed to afford the expected product **4** (a,b,c), along with some recovered starting material. The detailed yields were shown in Scheme 2.

^{1}H NMR ($CDCl_3$) of **4a**: δ 8.12-8.09 (m, 2H), 7.64-7.44 (m, 3H), 6.25 (s, 1H), 5.96 (s, 1H), 5.67 (s, 1H), 5.12 (d, J=7.7 Hz, 1H), 4.25 (m, 2H), 3.83 (s, 1H), 3.00 (dd, J=7.6 Hz, J'=14.8 Hz, 1H), 2.49-1.88 (m, 10H, incl. singlets at 2.49, 2.20, 3H each), 1.53 (s, 3H), 1.18 (s, 3H), 1.11 (d, J=7.7 Hz, 3H), 0.98 (s, 3H), 0.90 (m, 9H), 0.58 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 213.2, 171.0, 169.5, 166.9, 133.8, 129.8, 129.3, 128.6, 88.6, 82.7, 82.0, 81.0, 79.5, 79.4, 73.2, 71.9, 58.8, 58.3, 56.5, 46.4, 42.9, 38.2, 34.7, 26.9, 23.4, 22.1, 20.8, 19.6, 18.3, 6.8, 4.7. HRMS calcd. for $C_{37}H_{53}O_{11}Si$ (MH^+): 701.3357, found: 701.3338.

^{1}H NMR ($CDCl_3$) of **4b**: δ 8.10-8.07 (m, 2H), 7.65-7.30 (m, 3H), 6.22 (s, 1H), 5.89 (s, 1H), 5.13 (d, J=~8.0 Hz, 1H), 4.20 (m, 2H), 3.84 (s, 1H), 3.00 (m, 1H), 2.53-0.51 (m, 36H, incl. singlets at 2.47, 1.46, 0.98, 0.78, 3H each, doublet (J=7.2 Hz, 3H), at 1.04). ^{13}C NMR ($CDCl_3$): δ 220.2, 171.2, 167.1, 133.7, 129.8, 129.5, 128.6, 88.8, 82.4, 82.0, 81.4, 80.1, 73.8, 72.4, 62.4, 61.0, 55.7, 47.4, 44.6, 42.5, 38.4, 35.1, 27.0, 22.5, 22.3, 19.9, 19.0, 6.8, 4.8. Mass expected: 642, found: 642.

^{1}H NMR ($CDCl_3$) of **4c**: δ 8.04-8.01 (m, 2H), 7.64-7.24 (m, 3H), 6.03 (s, 1H), 5.88 (s, 1H), 4.58 (AB q, J=8.9 Hz, 2H), 4.22 (m, 1H), 3.02 (dd, J=8.1 Hz, J'=14.6 Hz, 1H), 2.55-0.58 (m, 38H, incl. singlets at 2.51, 1.51, 1.05, 3H each, doublet (J=7.3 Hz, 3H) at 1.04). ^{13}C NMR ($CDCl_3$): δ 219.2, 170.2, 167.3, 133.8, 129.7, 129.3, 128.7, 86.9, 84.2, 81.9, 80.7, 80.4, 72.8, 59.6, 56.4, 55.6, 47.6, 45.5, 42.8, 39.3, 33.2, 28.0, 26.2, 23.5, 22.4, 18.7, 17.5, 13.6, 7.0, 5.1. Mass expected: 626, found: 626.

Preparation of baccatin III derivative 3b (*via* 10, 11):

10-desacetyl baccatin **9** was converted to 7-TES-10-desacetyl baccatin **10** according to the procedure of Greene et al *J. Am. Chem. Soc.* **1988**, *110*, 5919.

Compound **10** (319 mg, 0.485 mmol) was dissolved in dry THF (5 mL), cooled to -40°C, and treated with n-butyllithium (1.58M in hexanes, 0.384 mL, 0.606 mmol). After 40 min at this temperature, pentafluorophenyl chlorothionoformate (0.086 mL, 0.536 mmol) was added neat by syringe. The reaction was stirred at -20°C for 90 min, then quenched with saturated ammonium chloride solution, and extracted with ethyl acetate. The ethyl acetate layer was dried, evaporated and the residue chromatographed (silica, 40% ethyl acetate in hexane) to afford **11** as a foam (320 mg, 74%).

^{1}H NMR of **11** ($CDCl_3$): δ 8.09 (d, 2H) 7.56 (t, 1H) 7.44 (m, 2H) 6.78 (s, 1H) 5.64 (d, J=6.9 Hz, 1H) 4.96-4.89 (m, 2H) 4.49 (dd, J=10.2 Hz, J'=6.6 Hz, 1H) 4.12 (AB q, 2H) 3.80 (d, J=6.9 Hz, 1H) 2.55-0.44 (m, 43H). ^{13}C NMR ($CDCl_3$): δ 199.6, 190.7, 170.7, 167.1, 146.7, 133.7, 130.9, 130.1, 129.3, 128.6, 87.3, 84.1, 80.8, 78.7, 74.5, 72.2, 67.9, 60.4, 59.0, 47.4, 42.9, 38.1, 37.2, 26.4, 22.7, 21.0, 20.1, 16.1, 14.2, 10.1, 6.7, 5.8, 5.3.

HRMS Calcd for $C_{42}H_{50}F_5O_{11}SSi$ (MH^+): 885.2763, found: 885.2742.

Thionocarbonate **11** (119 mg, 0.135 mmol) was dissolved in dry toluene (3 mL) and treated with AIBN (2 mg). The solution was degassed with dry nitrogen, then tributyltin hydride (0.055 mL, 0.202 mmol) was added and the solution was heated for 1 h (90°C). Solvent evaporation and chromatography (silica, 40% ethyl acetate in hexane) gave a colorless foam **3b** (87 mg, 99%).

^{1}H NMR ($CDCl_3$) of **3b**: δ 8.08-8.05 (d, 2H), 7.59-7.41 (m, 3H), 5.57 (d, J=6.7 Hz, 1H), 4.93 (d, J=9.3 Hz, 1H), 4.78 (m, 1H), 4.26 (d, J=8.2 Hz, 1H), 4.08 (m, 2H), 3.74 (d, J=14.8 Hz, 1H), 3.35 (d, J=14.5 Hz, 1H), 2.48 (m, 1H), 2.25-0.45 (m, 33H, incl. singlets at 2.25, 1.93, 1.58, 1.10, 1.01, 3H each). ^{13}C NMR ($CDCl_3$): δ 207.5, 170.9, 167.0, 136.6, 133.5, 132.8, 130.1, 129.5, 128.5, 84.4, 81.0, 78.9, 76.7, 75.1, 72.1, 67.9, 60.4, 60.1, 46.7, 45.6, 43.6, 38.8, 37.3, 26.0, 22.7, 22.2, 15.0, 10.2, 6.8, 5.3. HRMS calcd. for $C_{35}H_{51}O_9Si$ (MH^+): 643.3302, found: 643.3316.

Preparation of baccatin III derivative 3c (*via* 13, 14):

Baccatin III **12** (866 mg, 1.480 mmol) was dissolved in dry THF (20 mL) and CS_2 (4.5 mL). To this solution at R.T. was added NaH (88.7 mg, 60% in mineral oil, 2.22 mmol). The reaction was stirred at R.T. for 1.5 hr, then MeI (0.276 mL, 4.43 mmol) was added. After 14 hr at R.T., the reaction mixture was diluted with EtOAc (150 mL), and washed with H_2O and brine. The organic layer was dried and conc. *in vacuo*. The residue was chromatographed (70-70% ethyl acetate in hexane) to afford C-7 xanthate **13** (539 mg, 54%). This material was subjected to C-13 silylation (4 eq. TESCl/imidazole /DMF / 0.25M/R.T.) to give the corresponding C-13 triethylsilyl protected baccatin derivative **14** in 87% yield.

To a toluene solution (0.05M) of **14** (743 mg, 0.977 mmol) was added a catalytic amount of AIBN, followed by tributyltin hydride (1.60 mL, 5.94 mmol). The reaction was heated at 110°C for 12 hr. The crude reaction mixture was then chromatographed (20% ethyl acetate in hexane) to afford **3c** (330 mg, 56%), together with 20% of the remaining starting material **14**. Compound **3c** was characterized as its C-13 desilylated derivative.

^{1}H NMR ($CDCl_3$) of C-13 desilylated **3c**: δ 8.10 (d, J=7.3 Hz, 2H) 7.56 (m, 1H) 7.45 (m, 2H) 5.62 (d, J=7.2 Hz, 1H) 4.94 (br d, 1H) 4.79 (br s, 1H) 4.29 (d, J=8.0 Hz, 1H) 4.18 (d, J=8.0 Hz, 1H) 4.09 (d, J=7.2 Hz, 1H) 3.83 (d, J=16.2 Hz, 1H) 3.34 (br d, J=16.2 Hz, 1H) 2.35- 1.40 (m, 17H, incl. singlets at 2.27, 1.90, 1.67, 3H each) 1.06 (s, 3H) 1.02 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 207.3, 170.6, 167.2, 136.3, 133.5, 132.3, 130.1, 129.6, 128.6, 125.0, 84.5, 82.1, 79.1, 76.8, 76.0, 67.8, 55.0, 45.1, 44.8, 43.2, 39.1, 34.9, 32.2, 27.1, 26.4, 25.3, 22.7, 15.1, 14.5.

HRMS Calcd for $C_{29}H_{37}O_8$ (MH^+): 513.2488, found 513.2502.

Preparation of baccatin III derivative 17 (*via* 15, 16):

Baccatin III **12** (1 mmol) was dissolved in dry DMF (5 mL). To this solution at 0°C was added imidazole (5 mmol), followed by TESCl (5 mmol). The reaction was stirred at R.T. overnight. After standard aqueous work-up and silica gel chromatography (20% ethyl acetate in hexane), 7,13-bisTES baccatin **15** was obtained in 80-85% yield.

Compound **15** (0.45 mmol) was then dissolved in dry THF (4.5 mL). To this solution at 0°C was added Red-Al (0.352 mL, 60% solution in toluene, 1.80 mmol). After 30 mins at 0°C, the reaction was quenched with a saturated solution of potassium tartrate (2 mL). After extraction with EtOAc (100 mL), aqueous wash, and silica gel chromatography (40% ethyl acetate in hexane), 2-debenzoyl baccatin III **16** was obtained in 83% yield.

The above 2-debenzoyl baccatin III derivative **16** (0.25 mmol) was subjected to (i) C-2 esterification (20 eq. of DCC/DMAP/c-$C_6H_{11}CO_2H$/R.T. ; 100%); (ii) C-7,13 desilylation (Pyridine/48%HF/CH3CN/5°C; 68%); and (iii) C-7 resilylation (4 eq. of TESCl/ imidazole /DMF/0.2 M; 92%) to give desired mono-silylated baccatin derivative **17**.

^{1}H NMR of **17** ($CDCl_3$): δ 6.35 (s, 1H), 5.30 (d, J=7.0 Hz, 1H), 4.88 (d, J=8.4 Hz, 1H), 4.71 (m, 1H), 4.37 (m, 2H), 4.05 (d, J=7.9 Hz, 1H), 3.66 (d, J=6.9 Hz, 1H), 2.56-0.94 (m, 33H, incl. singlets at 2.12, 2.10, 2.09, 1.54, 1.04, 0.94, 3H each), 0.84 (m, 9H), 0.48 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 202.3, 176.9, 170.6, 169.2, 144.2, 132.1, 84.2, 80.3, 78.6, 76.4, 75.6, 74.0, 72.1, 67.6, 58.4, 46.9, 43.4, 42.6, 37.8, 37.0, 29.2, 28.2, 26.6, 25.6, 25.4, 25.0, 22.4, 20.8, 19.9, 14.7, 9.7, 6.6, 5.1. HRMS calcd. for $C_{37}H_{59}O_{11}Si$ (MH^+): 707.3807, found: 707.3851.

Preparation of β-lactam 18a & 18b:

Similar to the preparation of **18a**, β-lactam **18b** was prepared from (3R,4S)-3-hydroxyl-4-phenylazetidin-2-one *via* (i) O-silylation (1.1 eq. TESCl/1.1 eq. imidazole/DMF/0°C), (ii) N-acylation (1.0 eq. c-$C_6H_{11}COCl/Et_3N$/DMAP/ CH_2Cl_2/0°C), in 96% yield. For detailed reaction conditions, see: Ojima et al *Tetrahedron* **1992**, *48*, 6985.

^{1}H NMR of **18b** ($CDCl_3$): δ 7.31-7.18 (m, 5H), 5.09 (AB q, J=5.9 Hz, 2H), 3.20 (m, 1H), 2.06-1.26 (m, 11H), 0.76 (m, 9H), 0.44 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 174.2, 166.2, 133.5, 128.0, 127.9, 127.5, 76.5, 60.5, 44.6, 29.0, 27.5, 25.6, 25.5, 25.1, 6.1, 4.3.

Preparation of taxol analog 20 (from 17, 18a and 19):

To a THF (4.8 mL) solution of **17** (172 mg, 0.244 mmol) at -40°C was added LHMDS (0.365 mL, 1M, 0.365 mmol), followed by a THF (2.4 mL) solution of β-lactam **18a** (139 mg, 0.365 mmol). The reaction was then stirred at 0°C for 1 hr, and quenched with a saturated solution of NH_4Cl. The reaction mixture was extracted with EtOAc (75 mL). The organic layer was washed and dried and conc. *in vacuo*. The residue was chromatographed (25% ethyl acetate in hexane) to afford **19** (225 mg, 85%).

Compound **19** (222.5 mg, 0.205 mmol) was then dissolved in CH_3CN (10 mL). To this solution at 0°C was added pyridine (0.57 mL), followed by 48%HF (1.7 mL). The reaction was kept at 5°C for 12 hr. The reaction mixture was diluted with EtOAc (150 mL), washed with 1N HCl, saturated $NaHCO_3$ (3 X 15 mL), and brine. The resulting organic layer was dried and conc. *in vacuo*. The residue was chromatographed (60-75% ethyl acetate in hexane) to afford **20** (174 mg, 99%).

^{1}H NMR ($CDCl_3$) of **20**: δ 7.73-7.19 (m, 11H), 6.19 (s, 1H), 6.10 (m, 1H), 5.65 (dd, J=2.5 Hz, J'=8.7 Hz, 1H), 5.37 (d, J=6.9 Hz, 1H), 4.88 (d, J=8.9 Hz, 1H), 4.68 (dd, J=2.9 Hz, J'=5.7 Hz, 1H), 4.41 (d, J=8.1 Hz, 1H), 4.29 (m, 1H), 4.11 (m, 2H), 3.59 (d, J=6.8 Hz, 1H), 2.62-1.00 (m, 33H, incl. singlets at 2.19, 2.15, 1.69, 1.57, 1.14, 1.01, 3H each). ^{13}C NMR ($CDCl_3$): δ 203.5, 176.8, 172.5, 171.0, 170.3, 167.2, 141.8, 138.0, 133.6, 132.8, 131.8, 128.8, 128.5, 128.1, 127.0, 126.9, 84.4, 80.7, 78.8, 76.5, 75.4, 74.2, 73.1, 71.9, 58.4, 55.1, 45.4, 43.4, 43.0, 35.5, 35.1, 29.2, 28.3, 26.7, 25.6, 25.5, 25.1, 22.4, 21.5, 20.8, 14.6, 9.4. HRMS calcd. for $C_{47}H_{58}NO_{14}$ (MH^+): 860.3857, found: 860.3888.

Photo-isomerization of 20 to 21 under 254 nm and Pyrex filter:

Compound **20** (50 mg, 0.0582 mmol) was dissolved in CCl_4 (1.1 mL). This solution was subjected to photolysis at 50°C for 20 hr. The reaction mixture was chromatographed (70-100% ethyl acetate in hexane) to afford **21** (20 mg, 40%), together with recovered starting material **20** (10.5 mg, 20%).

^{1}H NMR ($CDCl_3$) of **21**: δ 7.78-7.24 (m, 11H), 5.88 (s, 1H), 5.62 (m, 2H), 5.50 (m, 2H), 4.64 (m, 1H), 4.52 (AB q, J=9.3 Hz, 2H), 4.39 (m, 1H), 2.79 (dd, J=7.9 Hz, J'=15.0 Hz, 1H), 2.45-0.81 (m, 33H, incl. singlets at 2.42, 2.16, 1.55, 1.23, 0.90, 3H each, doublet (J=7.2 Hz, 3H) at 0.82). ^{13}C NMR ($CDCl_3$): δ 206.9, 176.6, 172.4, 170.7, 169.2, 167.1, 137.7, 133.6, 131.9, 128.9, 128.6, 128.2, 127.0, 126.9, 86.4, 83.7, 81.4, 80.4, 78.6, 76.5, 75.2, 73.9, 69.5, 60.3, 59.6, 56.7, 56.3, 55.7, 46.6, 43.7, 41.0, 35.6, 35.3, 29.8, 29.7, 28.4, 26.1, 25.3, 25.2, 24.8, 23.2, 22.7, 20.6, 20.0, 17.4, 14.1. HRMS calcd. for $C_{47}H_{58}NO_{14}$ (MH^+): 860.3857, found: 860.3828.

Preparation of taxol analog 23 (from 17, 18b and 22):

7-TES baccatin drivative **17** (42 mg, 0.059 mmol) was dissolved in dry THF (1.5 mL). To this solution at -40°C was added LHMDS (0.077 mL, 1M, 0.077 mmol), followed by β-lactam **18b** (34.2 mg, 0.0885 mmol, in 0.5 mL THF). The reaction mixture was stirred at 0°C for 1 hr, and it was quenched with a saturated solution of NH_4Cl (1 mL). After extraction (EtOAc) and brine washed, the organic layer was dried and conc. *in vacuo*. The residue was chromatographed (20% ethyl acetate in hexane) to afford **22** as a foam (56.7 mg, 87%).

Compound **22** thus obtained (44.4 mg, 0.0406 mmol) was dissolved in acetonitrile (1 mL). This solution was treated at 0°C with pyridine (0.12 mL) and 48%HF (0.36 mL). The reaction mixture was kept at 5°C for 12 hr, and then diluted with EtOAc (50 mL). The organic layer was washed with saturated solution of $NaHCO_3$ (3 X 6 mL) and brine. The organic phase was dried and conc. *in vacuo*, the residue was chromatographed (60-70% ethyl acetate in hexane) to afford **23** as a foam (33 mg, 94%).

^{1}H NMR ($CDCl_3$) of **23**: δ 7.40-7.26 (m, 5H), 6.28 (d, J=8.9 Hz, 1H), 6.23 (s, 1H), 6.12(m, 1H), 5.49 (dd, J=2.6 Hz, J'=8.9 Hz, 1H), 5.42 (d, J=6.9 Hz, 1H), 4.93 (d, J=8.1 Hz, 1H), 4.63 (d, J=2.8 Hz, 1H), 4.34 (m, 1H), 4.28 (AB q, J=8.1 Hz, 2H), 3.63 (d, J=6.9 Hz, 1H), 2.57-1.06 (m, 44H, incl. singlets at 2.22, 2.18, 1.75, 1.62, 1.22, 1.06, 3H each). ^{13}C NMR ($CDCl_3$): δ 203.6, 177.0, 175.7, 172.7, 171.1, 170.2, 142.0, 138.0, 132.9, 128.8, 128.0, 126.7, 84.4, 80.7, 78.9, 75.4, 74.2, 73.0, 72.2, 72.0, 58.5, 54.1, 45.3, 45.2, 43.4, 43.0, 35.3, 35.0, 29.6, 29.4, 29.3, 28.3, 26.7, 25.6, 25.5, 25.0, 22.4, 21.6, 20.7, 14.7, 9.4. HRMS calcd. for $C_{47}H_{64}NO_{14}$ (MH^+): 866.4327, found: 866.4296.

Photolysis of 23 under 254 nm and Pyrex filter:

The photolysis of **23** was performed under the same conditions as for taxol (0.05M solution in CCl_4/50°C/20 hour). After 20hr photolysis, the solvent was removed, and the residue was chromatographed (70% ethyl acetate in hexane) to yield only the recovered starting material. No C3-C11 bonded taxol derivative was produced.

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REFERENCES AND NOTES:

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