Tetrahedron Letters, Vol. 33, No. 50, pp. 7679-7680, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

The Photochemistry of Taxol: Synthesis of a Novel Pentacyclic Taxol Isomer

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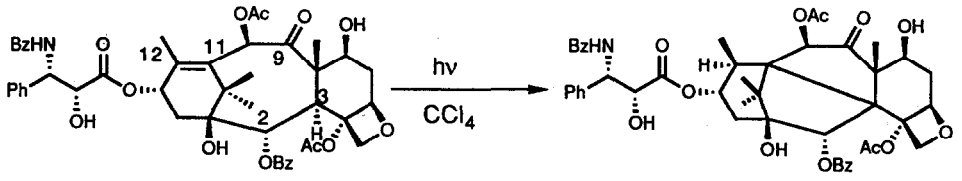
Abstract: Photolysis of taxol with 254 nm UV light is found to be a very effective method to prepare a novel taxol analog featuring a Carbon-Carbon bond between C_3 and C_{11}.

The remarkable anticancer activity of taxol, **1** , has stimulated an intense research effort in recent years.[1] Prompted by a study reporting that taxol can function as a direct photoaffinity labeling agent towards tubulin,[2] we have begun an examination of the photochemistry of taxol. Surprisingly, in view of the extensive chemical background on this important agent,[1] no report has been published on its photochemistry .

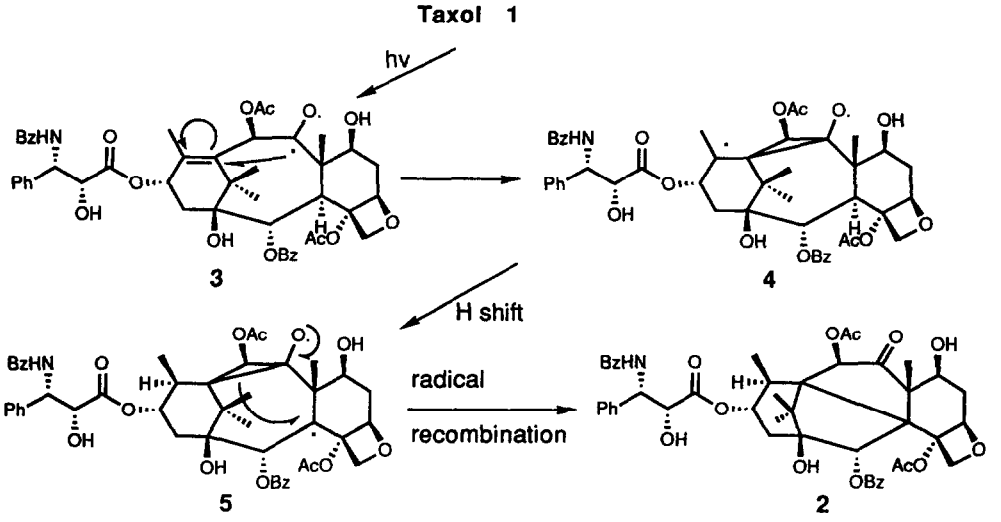
When **1** was irradiated in a Pyrex vessel (Hg lamp, 0.05M in CCl_4) a major product, isomeric with taxol, was isolated in ca. 55% yield. After extensive NMR analysis, the product was identified as **2**, which contains a new bond between C_3 and C_{11}. (Scheme 1).



1 Taxol **2**

Scheme 1

Specifically, the ^{1}H-NMR spectrum featured the disappearance of a methyl singlet at 1.79 δ, with the appearance of a new methyl doublet at 0.90 δ, indicating saturation of the C_{11}-C_{12} double bond. The signal due to H-2 , a doublet in taxol, was now a singlet at δ 5.56, while the absorption for H-3 (3.77 δ in taxol) was missing. Further data are shown in the Table. The reaction most likely proceeds through the $T_1(\pi,\pi^*)$ of the C_9 carbonyl group, which leads to diradicaloid species **4** (Scheme 2), as in the first step of the oxadi-π-methane rearrangement.[3] Intramolecular hydrogen transfer from C_3 to C_{12}, as observed in the related rearrangement of taxinine,[4] occurs due to the favorable geometry.[5] Finally, transannular bond formation in **5** leads to **2**.



Scheme 2

Not surprisingly in view of the dramatic change in topology brought about by the transannular reaction, isomer **2** displays very poor (>100 weaker than taxol) antimitotic activity *in vitro*. Further studies are in progress.

Acknowledgements: We thank Dr. S. Mamber for performing the tubulin polymerization assay.

Table: Diagnostic ^{1}H-NMR comparison between taxol and compound 2 ($CDCl_3$, 300 MHz, ppm).

Proton(s)	Taxol	Compound 2	Proton(s)	Taxol	Compound 2
H-2	5.67 (d)	5.56 (s)	H-13	6.23 (m)	5.60 (m)
H-3	3.77 (d)	none	H-14	2.35;2.28 (m)	3.08;2.14 (m)
H-5	4.94 (d)	5.98 (br d)	H-16	1.14 (s)	0.98 (s)
H-6	2.54;1.88 (m)	2.26;1.88 (m)	H-17	1.24 (s)	1.27 (s)
H-7	4.40 (m)	4.41 (m)	H-18	1.79 (s)	0.90 (d,J=7.2)
H-10	6.26 (s)	5.97 (s)	H-19	1.68 (s)	1.69 (s)
H-12	none	2.38 (m)	H-20	4.25 (AB)	4.48 (AB)

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(Received in USA 10 August 1992; accepted 11 September 1992)