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Studies on the chemistry of Taxol®

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Abstract: The diterpenoid taxol has become an important first-line treatment for ovarian and breast cancer in women, and has potential applications in the treatment of other cancers. Studies over the last decade in several laboratories have led to a greatly increased understanding of its chemistry, culminating in three impressive syntheses of the natural product. The results of studies carried out in the author's laboratory are discussed, leading to conclusions about taxol's structure-activity relationships.

INTRODUCTION

The novel diterpenoid taxol (*1*) (Note a) was first isolated from the bark of the Western Yew, *Taxus brevifolia,* in the late 1960's by Wall and Wani and their collaborators (ref. 1). Following a hiatus due to a lack of interest because of perceived problems with solubility and supply, it was approved for clinical development by the National Cancer Institute in the late 1970's. The decision to do this was made on the basis of encouraging results in some new *in vivo* bioassays, but it was largely due to the foresight of the late Dr. Matthew Suffness of the National Cancer Institute that these results were acted on. Interest in taxol was increased significantly by the discovery by Dr. Susan Horwitz of its unusual activity in promoting the assembly of tubulin into stable microtubules and thus disrupting mitosis (ref. 2). Clinical trials of taxol began in the early 1980's, and after some initial problems with administration were overcome it was found to be an excellent drug for the treatment of ovarian cancer and breast cancer (ref. 3). It has now become widely accepted for these indications, but it is also used for treatment of other cancers, and it can truthfully be called the most important new anti-cancer drug to enter clinical use in the last ten years.

Although Taxol® has many great advantages, it is by no means perfect. Its lack of water-solubility is a problem, although not an insuperable one, but more significantly it is not effective with all tumors nor even, regrettably, with all cases of ovarian and breast cancer. Because of its molecular complexity, it is an ideal candidate for systematic modification to develop an understanding of its structure-activity relationships and thus eventually to develop an analog or analogs with improved activity. In this paper I will describe some recent results from my group; extensive work has also been done by several other groups, and is described in various recent reviews (refs. 4-9).

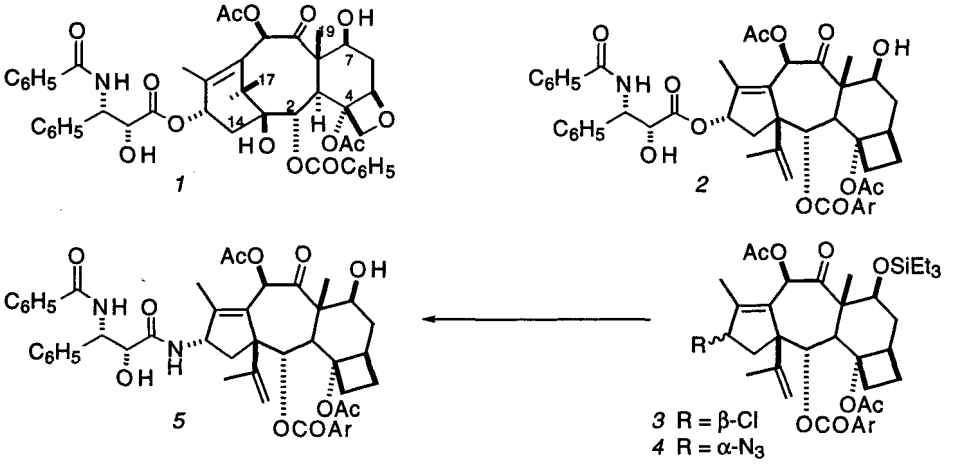
RING A MODIFICATIONS

Ring A of taxol is functionalized with a double bond, a hydroxyl group at C-1, and the all-important N-benzoyl-β-phenylisoserine ester at C-13. The double bond is not highly reactive, surviving treatment with osmium tetroxide (ref. 10) bromination (ref. 11), and hydrogenation (ref. 12), but the C-1 hydroxyl group is vulnerable to reaction. Thus treatment of a suitably protected taxol with thionyl chloride followed by deprotection yields the A-nortaxol analog *2* (Ar = phenyl), which is less cytotoxic than taxol, but which retains much of the tubulin-assembly activity of taxol. Following up on this discovery we prepared a series of analogs of *2* with various substituted benzoyl groups at C-2 (*2*, R = substituted phenyl), and some of these analogs have cytotoxicities comparable to that of taxol (ref. 13).

A related series of compounds was prepared with an amide group in place of the ester group at C-13. Treatment of 7-(triethylsilyl)baccatin III with thionyl chloride gave the β-chloro A-nor derivative *3* (Ar = phenyl), and reaction of *3* with sodium azide gave the α-azido analog *4*. Reaction of *4* with a protected ester side chain followed by deprotection gave the amido-A-nor analog *5* (Ar = phenyl) (ref. 13). The use of 2-

Note a: The name Taxol® has been registered by Bristol-Myers Squibb as the name for their formulated drug. The use of the uncapitalized name taxol in this paper refers to the chemical entity originally reported in the literature (ref. 1), and no infringement of the trademark rights of Bristol-Myers Squibb is intended.

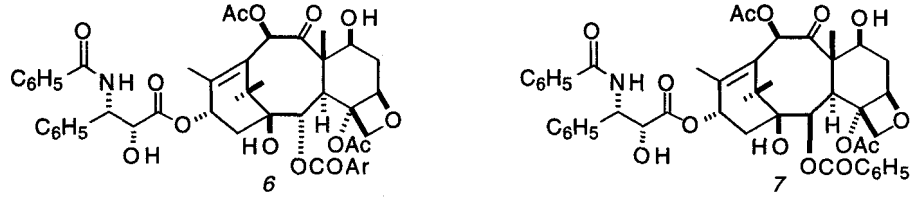
aroyl analogs of baccatin as starting materials gave the corresponding analogs *5* (Ar = substituted phenyl). None of the analogs prepared, however, showed any significant activity, indicating that an amido group at C-13 is a deleterious modification. A similar conclusion was reached by Chen et al. from studies of a C-13 amide-linked taxol analog (ref. 14).



RING B MODIFICATIONS

The most exciting modification of ring B has been the finding that taxol analogs with improved cytotoxicity and tubulin-assembly activity can be prepared by replacing the 2-benzoyl group with appropriately substituted 2-aroyl groups (refs. 15-16). Thus treatment of 2',7-di(triethylsilyl)taxol with base under phase transfer conditions, or with Triton B, gave selectively a 2-debenzoyl derivative which could be reacylated with substituted benzoic acids to give the substituted analogs *6*. The effect of the substituent turns out to be very dependent on its size and location. All *para*-substituted derivatives are less active than taxol, as are *ortho*- or *meta*-substituted derivatives with bulky substituents. Several *ortho*- or *meta*- substituted derivatives with smaller substituents (methoxy, chloro, azido) have, however, turned out to be more active than taxol, and the *meta*-azido analog in particular has proven to be significantly more active than taxol. Regrettably these enhanced activities have not yet translated into improved *in vivo* activity, since the substituted analogs tested to date all appear to be more toxic than taxol, but it may be possible to overcome this problem by modifying other positions or using other substituents.

Another possible modification at the 2-position is inversion of stereochemistry. This was achieved by oxidizing a protected 2-debenzoyltaxol to the 2-oxo derivative, and then reducing with $NaBH_4$ to give the 2-*epi* -alcohol. Benzoylation of this alcohol and deprotection gave 2-*epi*-taxol (*7*), which was inactive in a cytoxicity assay (ref. 17).

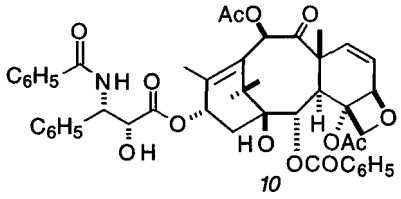


A final modification of ring B was discovered on attempted conversion of 13-*epi*- chlorobaccatin III (*8*) to its 13-azido analog. Treatment of *8* with sodium azide gave no displacement product, but instead gave the β-seco derivative *9* by a process involving neighboring group attack by the 10-acetate (ref. 18). Interestingly, a

similar reaction on a 1-dimethylsilyl protected analog gave an azide displacement product without any accompanying rearrangement (ref. 14).

RING C MODIFICATIONS

The chemistry of the C-ring of taxol has been relatively unexplored until the last few years, when we (ref. 19) and others (refs. 20,21) found that a protected 7-0-triflate derivative of taxol could be converted to its 6,7-dehydro derivative *10*. The availability of *10* then opened up the chemistry of ring C; hydroxylation with osmium tetroxide, for example, gave the diol *11* in which the stereochemistry is probably controlled by complexation of the reagent with the 4-acetoxyl group, while epoxidation with dimethyl dioxirane gave the epoxide *12* in which the stereochemistry is controlled by attack from the less hindered β-face. Cleavage of *11* with lead tetraacetate gave the C-nortaxol analog *13* by a mechanism presumably involving a retro-Claisen reaction on the putative dialdehyde intermediate, followed by aldol cyclization (ref. 22).



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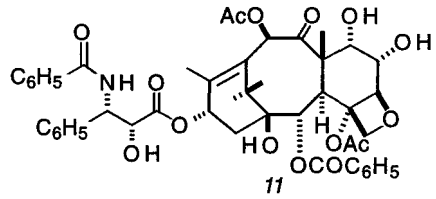

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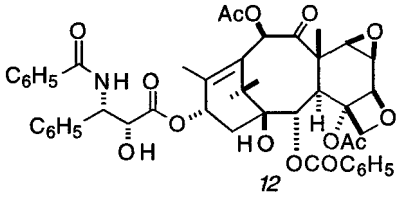

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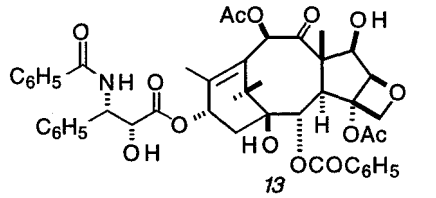

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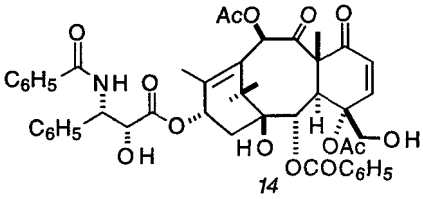
Regrettably, the new analogs *11-13* were all less active than taxol, but it is likely that further studies in this area will provide analogues with improved bioactivity.

THE OXETANE RING

The oxetane ring has been known to be essential for the bioactivity of taxol for several years, since our studies with ring-opened products such as the D-secotaxols *14* (ref. 23) and *15* (ref. 24), showed them to be inactive.



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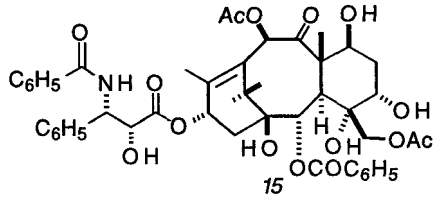

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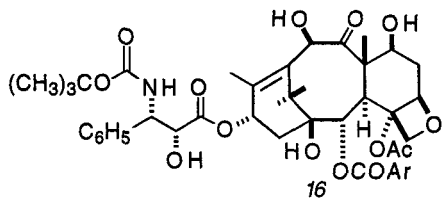
The reason for the importance of the oxetane ring is not well understood, since it is not chemically reactive under physiological conditions, and presumably subtle steric or conformational effects are involved. In support of this, it has been shown that the "hydrophopic collapse" observed for taxol in aqueous solutions does not occur with the seco-taxol *15* (ref. 8).

CONCLUSIONS

The work that we and others have carried out on the structural modification of taxol has shown that its bioactivity is very sensitive to its precise functionalization. Most modifications that have been reported to date have deleterious effects on its activity, but some, including notably substitution at the 2-benzoyl group, provide significantly enhanced activities, at least in *in vitro* assays. It should be noted that analogs with improved activities have also been reported by others, including Georg (ref. 25), Ojima (ref. 26), Vyas (ref. 27), Nicolaou (ref. 28), Klein (ref. 29), Commerçon (ref.30), and Holton (ref. 31) among others. Perhaps most importantly, the taxol analog docetaxel (Taxotere®) (*16*) has been found to be clinically active, and it is

in clinical use in Europe (refs. 32-33). Its spectrum of activity differs significantly from that of taxol (ref. 34), and this finding, coupled with the work described above, indicates that the outlook for producing a taxol analog with significantly improved activity as compared with taxol is very good. Although it is rash to speculate, it has been suggested that the type of structure which will give good activity, based on the available evidence, might be similar to that shown below as *17* (ref. 35).



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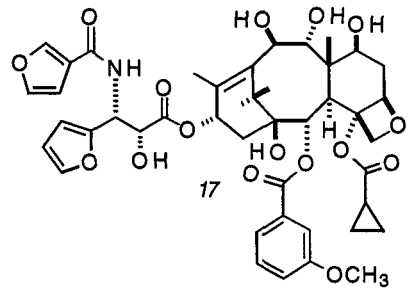

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