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Review

The shape of things to come: Structural and synthetic studies of taxol and related compounds

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Abstract

The history of the development of Taxol® (paclitaxel) as an anticancer drug is reviewed, and some aspects of the phytochemistry of *Taxus* species and of the medicinal chemistry of taxol are discussed. The nature of the taxol–tubulin interaction is then described, with an emphasis on studies that led to the discovery and experimental proof of the T-taxol conformation as the tubulin-binding conformation of taxol. The implications of this conformation for future drug development are also briefly covered.

Keywords: *Taxus brevifolia*; Taxol; Taxaceae; Paclitaxel; Docetaxel; Tubulin; Medicinal chemistry; SAR; REDOR NMR; Molecular modeling

Contents

1. Introduction

Plants have long been a major source of new pharmaceuticals (Cragg and Newman, 2003; Kingston and Newman, 2002; Newman et al., 2002; Newman et al., 2003; Phillipson, 2001; Srivastava et al., 2005) but no plant compounds discovered in the last 30 years have generated as much public interest and excitement as has taxol (paclitaxel or Taxol™). This review will summarize the history of taxol's discovery and development, and will then describe some recent studies on the chemistry and biology of this fascinating compound.

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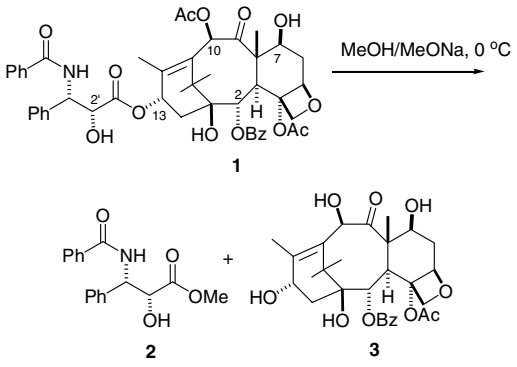
2. History of taxol's development as an anticancer drug

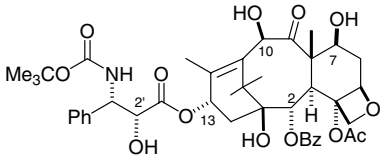
The first collection of *Taxus brevifolia* Nutt. for screening purposes was made by United States Department of Agriculture botanists in 1962, and screening for anticancer activity using the KB cytotoxicity assay led to the detection of activity in the bark. The cytotoxic activity against KB cells was confirmed in 1963, and a recollection of the bark was made in 1965 and assigned to Dr. Monroe Wall at Research Triangle Institute (RTI) in North Carolina. In vivo activity of the bark extract against mouse leukemia was confirmed in 1966, but this activity was not considered to be any better than that of several other extracts under investigation at that time. Nevertheless, work at RTI continued, and pure taxol was isolated in 1969 in 0.01% yield from the bark; the wood and needles of the tree contained much less taxol. The structure of taxol was finally published in 1971. Structure elucidation was assisted by a key degradation to cleave the side chain to give 10-deacetylbaccatin III (**3**) and the β-phenylisoserine ester (**2**), and X-ray studies by Andrew McPhail at Duke University on derivatives of **2** and **3** and ^{1}H NMR spectroscopic analysis of the intact molecule led to the structural assignment as **1** (Wani et al., 1971).



The initial reaction to taxol (**1**) as a potential anticancer drug could be described as one of underwhelming enthusiasm. It had only modest activity in vivo against various leukemias and the Walker 256 carcinosarcoma, it was highly insoluble in water, and it was isolated in only very modest yield from the bark of the slow-growing yew tree. In spite of these concerns, additional testing was carried out in some new in vivo bioassays that were introduced by the National Cancer Institute (NCI) in the early 1970s, and these results proved to be crucial in garnering support within the NCI for the development of taxol (**1**); activity in a B16 mouse melanoma model was particularly important in this respect. Taxol (**1**) was selected as a development candidate in 1977 following its good activity against the then new MX-1 and CX-1 mammary and colon xenografts in nude mice. Its drug development was challenging because of the problems with solubility and supply noted earlier, and also because of its relatively low potency, but these problems were eventually overcome with a formulation in ethanol and Cremophor EL (Suffness and Wall, 1995).

The discovery by Susan Horwitz in 1979 of taxol's mechanism of action as a promoter of tubulin assembly (Schiff et al., 1979) increased interest in the compound significantly. The normal function of a cell requires that microtubules be in dynamic equilibrium with monomeric tubulins, and any compound that disrupts this equilibrium is likely to be a cytotoxic agent. Although several compounds, including the clinically used drugs vinblastine (Velban™) and vincristine (Oncovin™) (Gueritte and Fahy, 2005) prevent the assembly of tubulin into microtubules, taxol (**1**) was the first compound which was able to promote microtubule assembly.

Taxol (**1**) completed preclinical formulation and toxicology studies in 1982 and entered Phase I clinical trials in 1984, and Phase II trials in 1985. The most serious side effect observed was that of hypersensitivity reactions, which were believed to be due to the Cremophor EL surfactant. These reactions were unpredictable, and led to two deaths, and they almost halted any further clinical trials. Fortunately Wiernik et al. (1987) were able to develop a 24 h infusion protocol which avoided these hypersensitivity reactions, and the trials continued. These trials gave the first clear evidence of activity with responses in melanoma reported in 1987 (Wiernik et al., 1987), in ovarian cancer in 1989 (McGuire et al., 1989) and in breast cancer in 1991 (Holmes et al., 1991). Taxol and its semisynthetic analog docetaxel (Taxotere™, **4**) (Gueritte-Voegelein et al., 1986) are now used (either as single agents or in combination with other drugs such as cisplatin) for the treatment of ovarian cancer (Piccart and Cardoso, 2003), breast cancer (Ozols, 2003), and non-small-cell lung cancer (Davies et al., 2003).



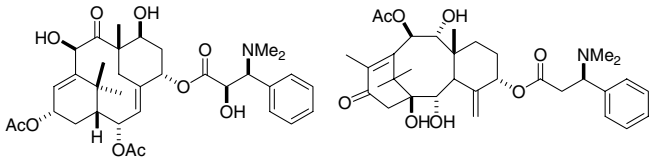
3. Other yew diterpenoids

Taxus brevifolia is only one of several yew species that occur around the world, primarily in temperate climates. Other yew species include *Taxus baccata*, *T. wallichiana*, *T. canadensis*, *T. cuspidata*, *T. media*, and *T. chinensis*. The common yew in Europe is *T. baccata*, known as English yew in the UK and as European yew in the rest of Europe. This is the yew that provided the wood for the famed English longbow that played a large part in English victories at Crecy and Agincourt, among others. It is also celebrated in literature: Wordsworth's poem "Yew Trees" extols a magnificent specimen in the village of Lorton which can still be seen today, although in

diminished form (http://www.visitcumbria.com/cm/lorton2.htm)

> There is a Yew-tree, pride of Lorton Vale,
> Which to this day stands single, in the midst
> Of its own darkness, as it stood of yore:
> Not loathe to furnish weapons for the Bands
> Of Umfraville or Percy ere they marched
> To Scotland's heaths; or those that crossed the sea
> And drew their sounding bows at Azincour,
> Perhaps at earlier Crecy, or Poictiers.
> Of vast circumference and gloom profound
> This solitary Tree! – a living thing
> Produced too slowly ever to decay;
> Of form and aspect too magnificent
> To be destroyed.
>
> (William Wordsworth)

The common yew *T. baccata* is quite toxic, and has been responsible for many stock poisonings and human poisonings, with records going back at least to the time of Julius Caesar. This toxicity is due to the significant amounts of the toxic alkaloids taxine A (**5**) and B (**6**) contained in this yew.



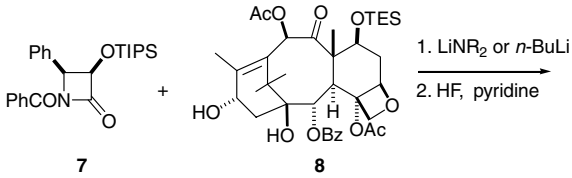
5 **6**

An interesting point made by Itokawa (2003) is that had Wall and Wani used *T. baccata* in their investigations, it is likely that they would either have found the extract to be toxic and not pursued fractionation, or would have isolated the taxines rather than taxol (**1**), given the bioassays that they were using at that time. In either case they would not have isolated taxol (**1**). Fortunately *T. brevifolia* (the only species collected by the USDA for the screening program) contains only very minor amounts of the taxines, and so the work described above was successful and taxol (**1**) was obtained.

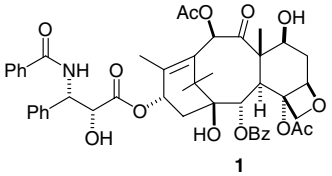
4. The taxol supply crisis

One of the initial concerns about taxol (**1**) as an anticancer drug was the obvious difficulty in ensuring an adequate supply of the drug, and these concerns reached a fever pitch in 1991 with the recognition of taxol's activity against breast cancer. The supply crisis created a conflict between environmentalists, who wished to preserve the old-growth forests of the Pacific Northwest of the USA, and cancer patients who were clamoring for the drug (Chase, 1991). The pharmaceutical company Bristol-Myers Squibb (BMS) had recently signed a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute for the development and commercialization of taxol (**1**), and so responsibility for solving this crisis fell to them.

The initial solution to the supply crisis came from an accelerated program of bark collection, carried out by Hauser Chemical Research in the Pacific Northwest under contract to BMS. This arrangement ended in 1994, however, with the announcement that BMS had licensed a semisynthetic process to make taxol (**1**) from 10-deacetylbaccatin III (10-DAB) (**3**), a more available taxane diterpenoid available from *T. baccata* and other yews (Denis et al., 1988). This process essentially involved the reversal of the reaction Wall and Wani had used to determine the structure of taxol; β-lactam **7** is coupled with the lithium alkoxide of the protected 10-DAB **8**, and the resulting product is deprotected to give taxol (**1**) (Holton et al., 1995).



7 **8**



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Efforts to provide a completely renewable source of taxol (**1**) continued after this breakthrough. Hopes were raised by the discovery of an endophytic fungus that produced taxol (Stierle et al., 1993), but the yields of taxol (**1**) obtained were very low and efforts to increase them to commercially relevant levels have not yet been successful. Likewise, although significant progress has been made in understanding the biosynthesis of taxol (Walker and Croteau, 1999; Sankawa and Itokawa, 1993; Croteau et al., 2006), it has not yet proved possible to clone all the necessary genes and express them in a suitable host. The one renewable approach that has proved productive is that of plant tissue culture, and BMS is currently producing taxol by this route in Germany (Leistner, 2005).

5. The taxol name game

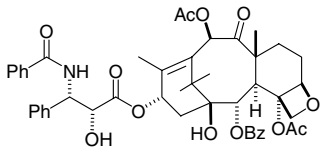
Because of the publicity surrounding the taxol (**1**) supply crisis and its initial perception as a "miracle drug", the name taxol (**1**) became well recognized by the general public; it has been remarked that it and aspirin are two of the most recognized drug names in the USA. The name thus became a valuable commercial property. Although it was generally assumed that Wall and Wani were the first to use this name, it turned out that the name "Taxol" had

been trademarked in the early years of the 20th century by Continental Laboratories for a laxative product. BMS acquired the rights to this trademark, and then succeeded in applying it to their formulation of taxol (**1**). The result of these maneuverings is that the official chemical name for the compound previously known as taxol (**1**) is now paclitaxel (**1**), and the name Taxol® applies to the BMS formulation of this chemical compound.[1] This appropriation of a common name as a trademark has been deplored (Anonymous, 1995) but has not been reversed. A more detailed account of this controversy is provided by Walsh and Goodman (2002).

6. The quest to understand taxol's (1) structure–activity relationships

The chemistry of taxol (**1**) has been thoroughly investigated by a large number of researchers, and this review will thus not attempt to provide a complete coverage. Readers interested in a more comprehensive review can consult two chapters in a recent book (Wang et al., 2003a,b) and several reviews (Zhang et al., 2005; Geney et al., 2005a; Fang and Liang, 2005; Kingston et al., 2002; Kingston, 2001). This section will thus describe some representative work from the author's laboratory, and will then summarize the major findings for each structural feature of taxol (**1**).

The example of the effects of modifying or removing the hydroxyl groups that decorate the taxane ring system is illustrative of the general approach that was used to uncover taxol's structure–activity relationships (SAR). Taxol (**1**) has eight oxygenated positions around its ring system, at positions 1, 2, 4, 5, 7, 9, 10, and 13. Barton deoxygenation chemistry allowed the removal of the C7 hydroxyl group, leading to 7-deoxytaxol (**9**), which was comparably cytotoxic to taxol (Chaudhary et al., 1993; Chen et al., 1993). Similar work at the 10-position led to 10-deacetoxytaxol **10**, which also showed cytotoxicity comparable to that of taxol (Chaudhary and Kingston, 1993).



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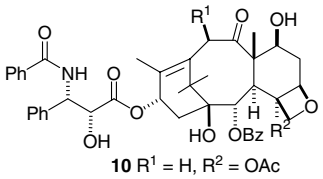
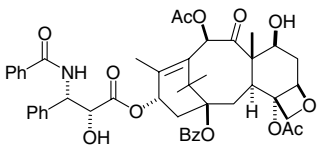


10 R^1 = H, R^2 = OAc
11 R^1 = OAc, R^2 = OH
12 R^1 = OAc, R^2 = H

[1] In view of the historical nature of this review, the word taxol is retained for the chemical substance of structure **1**. No infringement of the BMS trademark is implied.

Studies on the "southern hemisphere" of taxol (**1**) led to quite different conclusions. Both 4-deacetyltaxol (**11**) (Neidigh et al., 1994) and 4-deacetoxytaxol (**12**) (Chordia et al., 1994) were much less active than taxol (**1**). The C1 hydroxyl group could not be removed by the normal Barton method, since this method gave an interesting rearrangement leading to the inactive 1-benzoyl-2-debenzoyloxytaxol (**13**) (Chordia et al., 1994). A successful synthesis of a 1-deoxytaxol analog was eventually achieved by attaching the taxol side chain to baccatin VI to give **14**; this compound was about one-tenth as potent as the corresponding taxol analog **15** in promoting the assembly of tubulin (Kingston et al., 1999).



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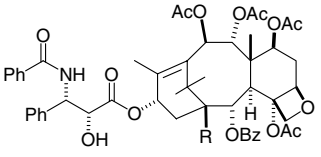
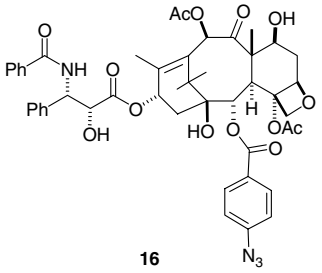


14 R = H
15 R = OH

Replacement of the 2-benzoyl group with substituted benzoyl groups gave the interesting result that taxol analogs with *para*-substituted 2-benzoyl substituents were much less active than taxol (**1**), while analogs with *ortho* and particularly *meta*-substituted aroyl substituents were usually significantly more active than taxol (**1**) (Chaudhary et al., 1994). As one example, the *p*-azido derivative **16** was essentially inactive, while the corresponding *m*-derivative **17** was about sixfold more cytotoxic than taxol (**1**).



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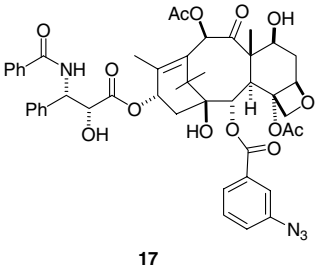

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These and other studies have led to a good understanding of the structure–activity relationships of taxol (**1**); these are summarized in Fig. 1.

These studies and similar studies by others have led to the development of several second generation taxol derivatives that have progressed to clinical use or clinical trials. Taxotere® (docetaxel, **4**, Gueritte-Voegelein et al., 1986) is the only taxol analog to date to enter clinical use, but the analogs BMS-184476 (**18**), BAY-59-8862 (IDN5109, Ortataxel, **19**), TXD-258 (Aventis) (**20**), and RPR-109881 (Aventis) (**21**) have all entered Phase II clinical trials, although development of BAY-59-8862 is in doubt because of toxicity issues (Baumann, 2005).

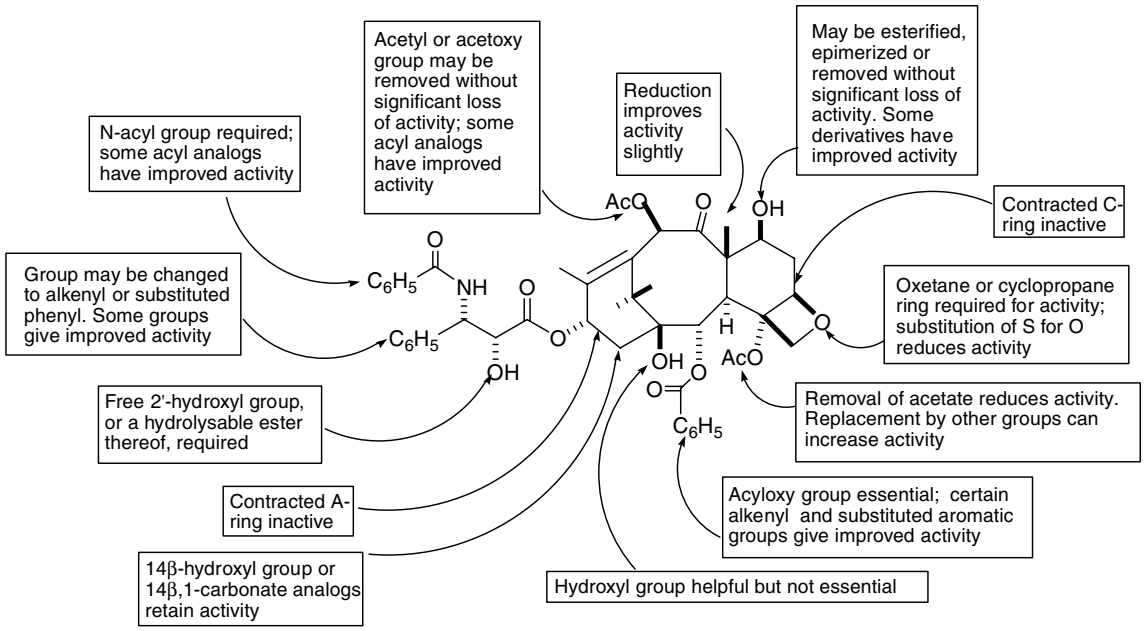
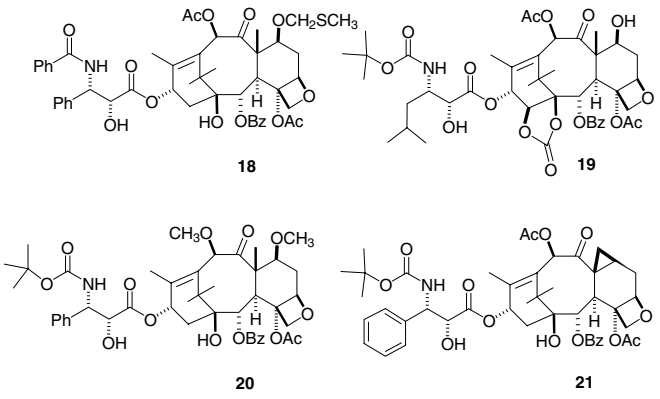


Fig. 1. Structure–activity relationships of taxol.



7. The interaction of taxol with tubulin

As noted earlier, taxol (**1**) acts as an anticancer agent primarily through its interaction with tubulin. An understanding of this interaction, and particularly of taxol's conformation in the binding pocket on tubulin, would provide an insight into the pharmacophore of taxol and why some structural changes are beneficial while others are detrimental to taxol's activity. In addition, if taxol's relatively weak association with tubulin is due in part to the presence of a large number of non-productive conformers, knowledge of the binding conformation(s) could lead to the design of improved analogs. Finally, such an understanding could possibly lead to the design of simpler analogs which retain taxol's tubulin-binding activity. The direct approach to determining this conformation by X-ray crystallography is not available because the taxol–microtubule complex is non-crystalline, so various indirect methods must be used.

Several investigators have studied the NMR spectra of taxol (**1**) in solution to determine the solution conformation. In non-polar solvents, taxol (**1**) exists primarily in a "non-polar" conformation in which the *N*-benzoyl and 2-benzoyl groups are associated (Dubois et al., 1993; Williams et al., 1994). In polar aqueous solvents, it adopts a set of "polar" or "hydrophobic collapsed" conformations in which the 3′-phenyl group is oriented towards the 2-benzoyl group (Vander Velde et al., 1993; Paloma et al., 1994; Ojima et al., 1999). More recently the T-taxol conformation (Fig. 2) was proposed by Snyder et al. (2001) based on the electron crystallographic structure of the tubulin–taxol complex combined with molecular dynamics and NAMFIS NMR analysis of taxol (**1**) in solution. In this conformation the two side chain phenyl groups are approximately equidistant from the C2-benzoyl group, giving the conformer a "T-shaped" appearance.

These studies leave open the question of which conformer best represents the tubulin-bound conformation of taxol (**1**). A direct approach to answering this question is available by the technique of rotational-echo, double resonance (REDOR) NMR spectroscopy. REDOR NMR is a spectroscopic technique for solids spinning at the magic angle, so it can be used for ligand-bound microtubules. It provides a direct measurement of heteronuclear dipolar coupling between pairs of labeled nuclei, and distances of up to 12 Å can be determined with 0.2 Å accuracy. It determines a unique conformational geometry with no assumptions and no models, but it requires the synthesis of labeled ligands. In conjunction with Professors Bane

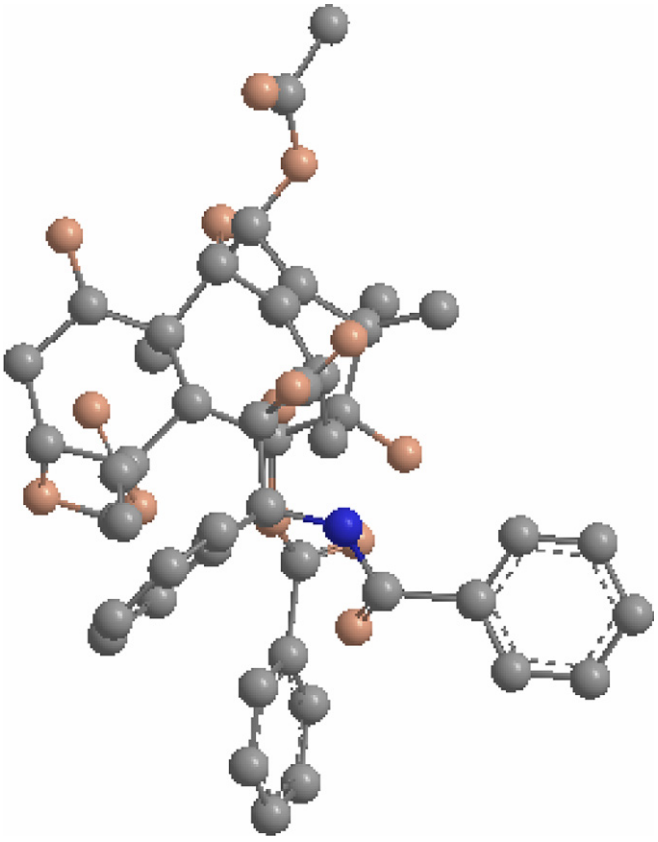


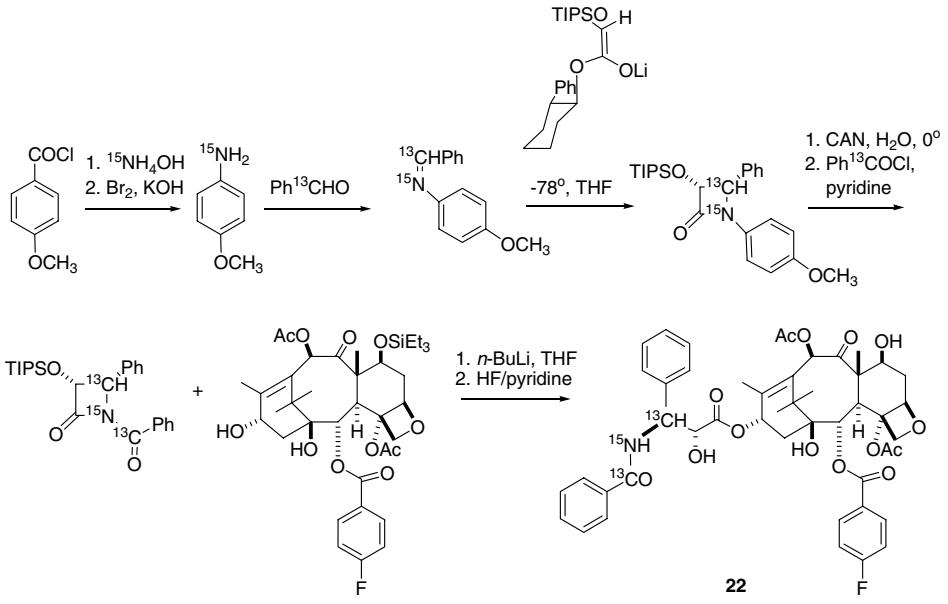
Fig. 2. The T-taxol conformation, showing the C2 benzoyl group positioned between the two side chain phenyl groups.

at SUNY Binghamton and Schaefer at Washington University, we applied this technique to the taxol–tubulin interaction. The labeled taxol **22** was prepared as shown in Scheme 1, and was used to assemble tubulin into microtubules.

This taxol–tubulin complex was then subjected to REDOR NMR spectroscopic analysis. After 8 million scans (three months!) the distances between the fluorine on the C2 benzoyl group and the labeled side chain carbons were determined to be 9.8 and 10.3 Å (Fig. 3; Li et al., 2000). This result has been extended by some recent results with the labeled analog **23**; these results indicated a distance of 6.3 Å between the *p*-fluorine on the C3′-phenyl and the methyl protons of the C4-acetate (Paik et al., 2007). These data are fully consistent with the T-taxol hypothesis, which has a particularly short C3′-phenyl to C4-acetate distance (Fig. 4).

The REDOR NMR studies described above gave strong support for the T-Taxol conformation as being the best descriptor of the tubulin-binding form of taxol (**1**). This hypothesis was also supported by modeling studies of the taxol–tubulin interaction based on the electron crystallographic density of tubulin (Snyder et al., 2001). Although other interpretations of the REDOR NMR spectroscopic data are possible (Geney et al., 2005b), a detailed modeling analysis indicates that the T-taxol model provides the most satisfying fit to the observed electron crystallographic structure (Johnson et al., 2005).

The relatively weak binding of taxol (**1**) to tubulin is presumably caused in part by the existence of many non-productive taxol conformers in solution, leading to the entropic cost of freezing the molecule out into one specific set of binding conformations. If this entropic cost can be paid in advance by the synthesis of a bridged taxol in the right conformation, then the compound's binding to tubulin should be improved and hence its bioactivity should be increased. Several workers have prepared bridged taxol analogs by a variety of elegant approaches with the intention of preparing a more active analog, but most of these approaches were based on the polar or non-polar confor-



Scheme 1. Synthesis of labeled taxol **22**.

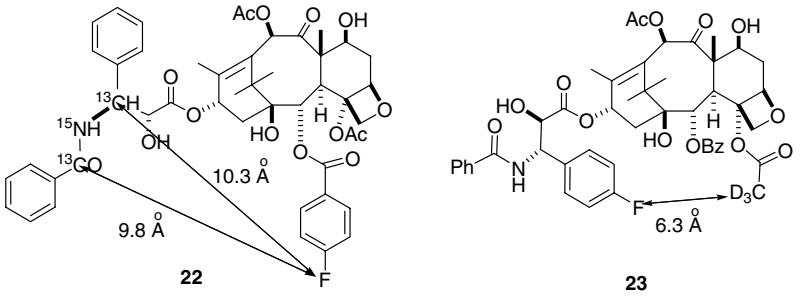


Fig. 3. Internuclear distance determined by REDOR NMR spectroscopy.

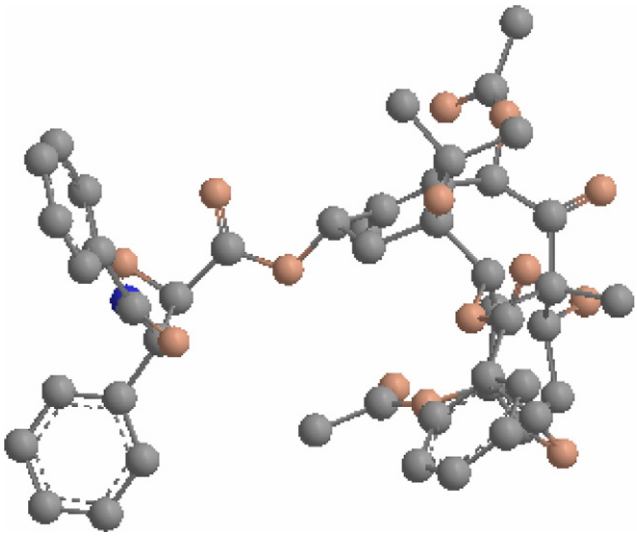


Fig. 4. The T-taxol conformation, showing the close connection between the C4 acetate group and the 3′ phenyl ring.

mations and yielded compounds that were much less active than the parent compound (Kingston et al., 2005).

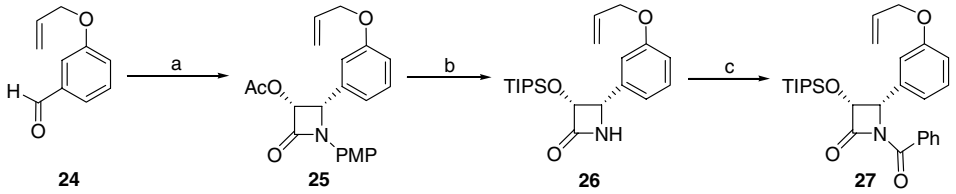
The discovery of the T-taxol conformation opened up a new avenue to explore. If this conformation is the correct one, then it should be possible to test it experimentally by the synthesis of taxol analogs with short bridges between the C4-acetate and the C3′-phenyl positions, since these are in close juxtaposition in T-taxol.

The first synthetic approach was made to the *meta*-phenyl bridged compound **32**, which was prepared by making use of the well-established Grubbs' olefin metathesis reaction. The β-lactam **27** was prepared from substituted benzaldehyde **24** as shown in Scheme 2, using lipase PS to resolve the racemic β-lactams **25**. Deacetylation of **25**, protection of the hydroxyl group as its triisopropylsilyl (TIPS) ether, and oxidative removal of the *p*-methoxyphenyl protective group gave β-lactam **26**, which was benzoylated to give **27**.

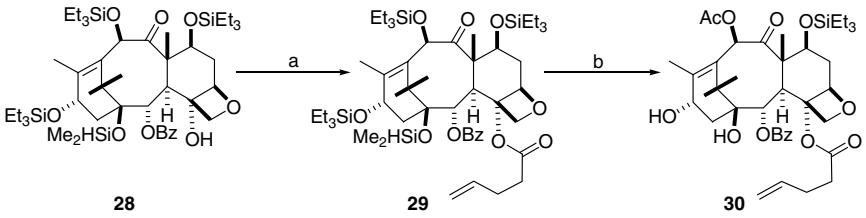
The 4-pentenoyl substituted baccatin III derivative **30** was next prepared from the known derivative **28** as shown in Scheme 3. Acylation at C4 was achieved with 4-pentenoyl chloride and lithium hexamethyldisilazide (LHMDS) to give **29**, and global deprotection of **29** followed by selective acetylation at C10 and selective silylation at C7 gave the product **30**.

Finally, the β-lactam **27** and the baccatin III derivative **30** were coupled to give **31** using the Holton-Ojima protocol, and the bridge was inserted by a Grubbs' ring-closing metathesis reaction. Global deprotection completed the synthesis of **32** (Scheme 4) (Metaferia et al., 2001). Compound **32** can be given the trivial name *m*-britaxel-8, where the suffix 8 designates the number of atoms in the chain between the *meta* position on the C3′ phenyl and the C4 position.

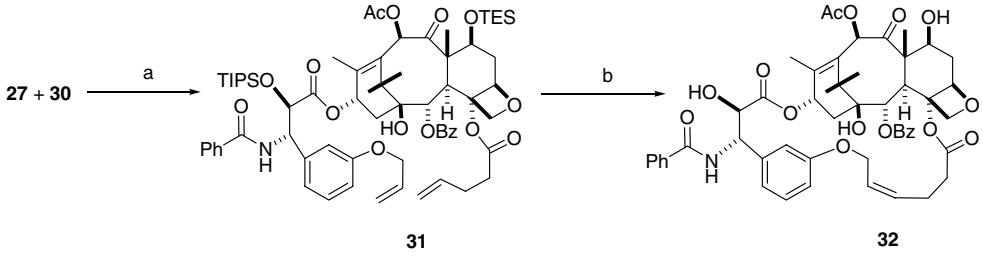
Biological evaluation of compound **32**, together with the related compound *m*-britaxel-6, gave the disappointing result that both compounds were at least tenfold less active than taxol (**1**) in both cytotoxicity and tubulin assembly assays (Metaferia et al., 2001). The reason for this lack of activity became clear from a docking analysis of the compounds' fit into the β-tubulin binding pocket, which showed that the best T-form of compound **32** is seated higher than taxol (**1**) in the pocket as a result of close contact between the propene moiety of the tether and Phe272 of the protein. This analysis also suggested that an *ortho* bridged analog would not encounter this contact, and should thus fit snugly into the pocket.



Scheme 2. Synthesis of β-lactam **27**. a: (i) *p*-$MeOC_6H_4NH_2$, $MgSO_4$, CH_2Cl_2 (100%); (ii) CH_3COOCH_2COCl, Et_3N, −78 °C-room temperature, 12 h (80–85%); (iii) lipase PS (Amano), phosphate buffer, pH 7.2, CH_3CN, 24 h–12 d (95–95%) b: (i) 1 M, KOH, THF, 0 °C (quantitative); (ii) TIPSCl, imidazole, DMF (90–94%); (iii) CAN, CH_3CN, −5 °C (65–92%) c: PhCOCl, Et_3N, DMAP, CH_2Cl_2 (85–95%).

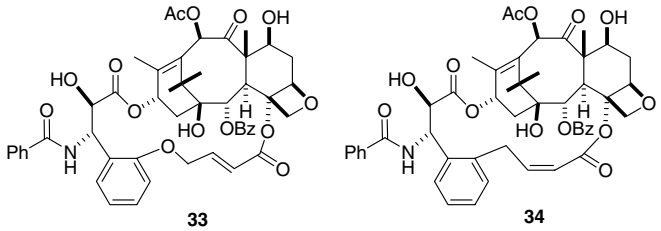


Scheme 3. Synthesis of baccatin III derivative **30**. a: (i) LHMDS, THF, 0 °C, 4-pentenoyl chloride (78%); b: (i) HF · Py, THF (91%); (ii) $CeCl_3$, Ac_2O, THF (92%); (iii) Triethylsilyl chloride, imidazole, DMF (85%).

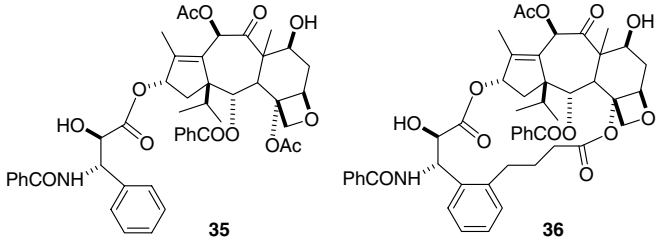


Scheme 4. Synthesis of britaxel derivative **32** a: LHMDS, THF, −40 °C b: (i) $(PCy_3)_2(Cl_2)Ru{=}CHPh$, DCM, room temperature (ii) HF, Py, THF, 0 °C – room temperature.

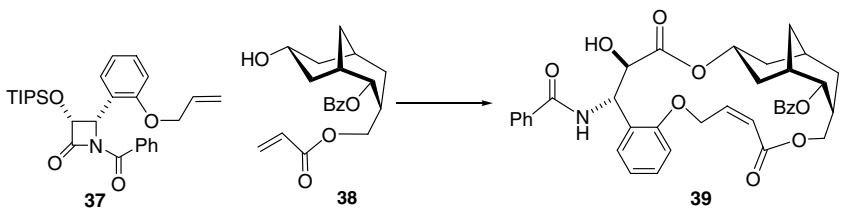
This prediction was dramatically confirmed by the synthesis of the *o*-britaxels-6 (**33**) and -5 (**34**) by simple modifications of the procedures described above (Ganesh et al., 2004). Compound **33** had very similar cytotoxicity and tubulin-assembly activities to those of taxol (**1**), but the big surprise was compound **34**, with a ring size one atom smaller. This compound was up to 20 times more active than taxol (**1**), depending on the assay used (Ganesh et al., 2004), and it was also much more active than taxol (**1**) against two taxol-resistant cell lines and an epothilone-resistant cell line (Ganesh et al., 2007). Molecular modeling of the complex of **34** with β-tubulin showed that the unfavorable interaction with Phe272 of β-tubulin had indeed been removed. These results thus served to confirm the T-taxol conformation as the correct tubulin-binding conformation of taxol (**1**).



Further confirmation of the validity of the T-taxol conformation came from studies of A-*nor* taxols. We had shown several years ago that conversion of taxol (**1**) to its a-*nor* derivative **35** gave a product that was essentially non-cytotoxic (Samaranayake et al., 1991), although it did retain some tubulin-assembly activity. Synthesis of the bridged analog gave a product **36** which was orders of magnitude more cytotoxic than **35**, although it was still less cytotoxic than taxol (**1**). Constraining an inactive compound into the T-taxol conformation thus increased its cytotoxicity many fold (Tang et al., 2006).



A final test of the ability of the T-taxol model to direct the design of bioactive taxol analogs was made by the synthesis of the greatly simplified compound **39** by coupling the β-lactam **37** and the bicyclic compound **38**, followed



Scheme 5. Synthesis of simplified taxol analog **39**.

by Grubbs' olefin metathesis and deprotection (Scheme 5; Ganesh et al., 2006). The analog **39** turned out to be very insoluble in mixed aqueous solvents, and it was thus difficult to obtain reliable bioassay data, but it was at least two orders of magnitude less cytotoxic than taxol to the A2780 ovarian cancer cell line. This result is an encouraging one, since this activity is significantly greater than that of compounds such as **35**, which resemble taxol much more closely, and suggests that refinement of the structure of the target compound may well direct the synthesis of simplified analogs with activity comparable to or even surpassing that of taxol.

8. Conclusion

The preceding review has summarized one small part of the enormous amount of work that has been done on taxol. In addition to the chemical work summarized above and in the reviews previously cited (Wang et al., 2003a,b; Zhang et al., 2005; Geney et al., 2005a; Fang and Liang, 2005; Kingston et al., 2002; Kingston, 2001) extensive studies on the clinical applications of taxol (**1**) and its analog docetaxel, both alone and in combination with other drugs (Ozols, 2003; Piccart and Cardoso, 2003) have indicated that the clinical effectiveness of taxol (**1**) and its sister drugs can still be improved. Taxol (**1**) and its analogs have been called "the most powerful compounds" among the chemotherapeutic drugs introduced in the last decade (Nabholtz et al., 2000). The improved understanding of the way taxol (**1**) binds to tubulin described above and improvements in such areas as drug targeting (Jaracz et al., 2005) suggest that taxol (**1**) and its analogs will continue to be important cancer chemotherapeutic drugs for many years to come.

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