Invited Review

Recent Advances in the Chemistry of Taxol[1,2]

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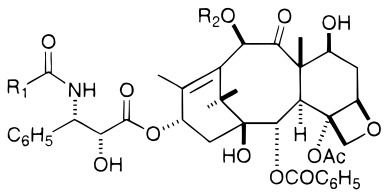
Received February 7, 2000

The history of the development of the important anticancer drug taxol (**1**) is briefly described, and recent studies of its chemistry and tubulin-binding conformation are then presented. Topics discussed include side chain attachment to baccatin III (**3a**), the effect of oxygenation of the taxane ring system on bioactivity, the importance of the oxetane ring for bioactivity, the synthesis of a C-6/C-4 bridged analogue, and the conformation of the side chain when taxol is bound in a complex with polymerized tubulin.

Introduction

The history of the anticancer drug taxol began in 1963−1964 with the discovery that extracts of the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae), showed significant cytotoxic and antileukemic activity.[3] The extract was assigned to Dr. Monroe Wall at the Research Triangle Institute in North Carolina for fractionation, and in 1971 he and Dr. Mansukh Wani and their colleagues announced their discovery that the major active constituent was the novel diterpenoid taxol (**1**).[4]



1 $R_1 = C_6H_5$, R_2 = Ac
2 $R_1 = (CH_3)_3CO$, R_2 = H

Taxol is a member of the class of taxane diterpenoids, which currently has over 300 known members.[5] At the time of its discovery, however, this was a small and relatively unexplored class of natural products, with only a few dozen members. The structure of taxol differed from that of all previously known members in having a complex *β*-phenylisoserine side chain esterifying the C-13 position, and it also contained the unusual oxetane ring. Although its structure was thus clearly unique among known anticancer agents, and although it had very good anticancer activity, its isolation was greeted with underwhelming enthusiasm. This was because it had two serious problems as a candidate for drug development. In the first place, it was only very sparingly soluble in water, and it would thus be a very difficult drug to formulate for administration by the normal route of injection. Second, and more compellingly, it would be a very difficult substance to supply in adequate quantities for clinical use. It was isolated initially in a yield of 0.014% from *T. brevifolia* bark,[3] and this bark is not abundant. Since *T. brevifolia* usually grows as a rather small understory tree and as isolated specimens, it was clear from the very beginning that obtaining an adequate supply of taxol for clinical use would be a herculean task.

Despite these problems the activity of taxol was such that modest additional quantities were procured and additional testing was carried out in some newly developed assays using human xenograft tumors in nude mice. Taxol showed excellent activity in these assays, with particularly promising activity against breast cancer and melanoma, and on this basis the National Cancer Institute took the courageous decision in 1977 to invest in a full-scale preclinical development of taxol as an anticancer agent.

Another important milestone in taxol's development came with the discovery of its unique mechanism of action. In 1978 Fuchs and Johnson reported that it acted as an antimitotic agent,[6] and in 1979 Horwitz reported that it acted to promote the irreversible assembly of tubulin into microtubules.[7] The tubulin−microtubule equilibrium is crucial to the mitotic process,[8] and other antimitotic agents such as the anticancer drugs vinblastine and vincristine, as well as podophyllotoxin and colchicine, act by *preventing* the assembly of tubulin into microtubules.[8] At the time of Horwitz's discovery, however, taxol was the first compound known to act as a promoter of microtubule assembly, and this discovery thus had the effect of enhancing interest in it.

Phase I clinical trials of taxol began in 1981 and were completed successfully after some initial problems due to allergic reactions were solved by premedication and by extending the administration from a bolus injection to a 24 h infusion. Taxol entered Phase II trials in the mid 1980s, and the first report of clinical activity (against ovarian cancer) was published in 1989,[9] followed by reports of activity against breast cancer in 1991.[10] These reports demonstrated unambiguously that taxol had significant activity against solid tumors and fueled an enormous public interest in the drug. Further development of the drug for commercial use was assigned to Bristol-Myers Squibb after a national competition to find the best development partner, and Taxol was approved for treatment of drug-resistant ovarian cancer by the Food and Drug Administration in 1992. Approval for treatment of breast cancer followed in 1994. Clinical use of Taxol has increased steadily since then, and today it is used not only for

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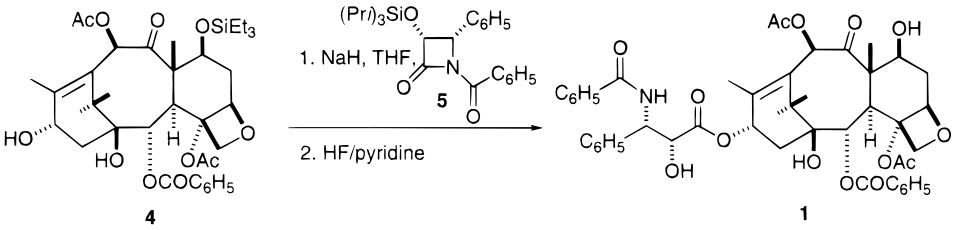
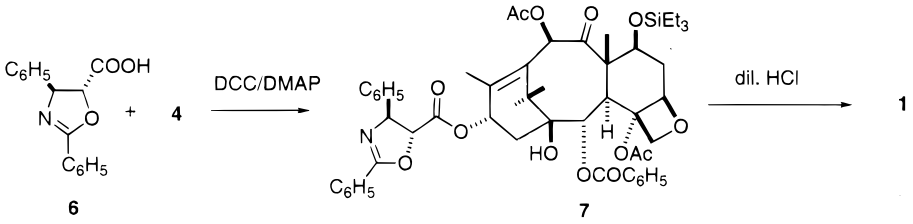
10.1021/pp000064n CCC: $19.00
Published on Web 04/12/2000

Scheme 1



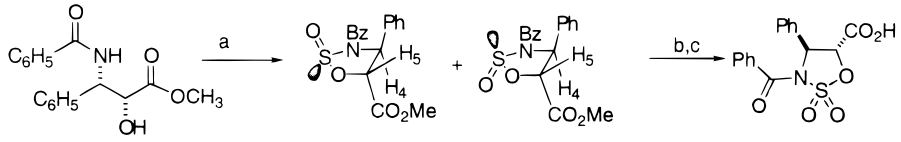
4 **5** **1**

Scheme 2



6 **7**

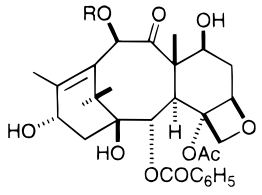
Scheme 3[a]



8 **9a** **9b** **10**

[a] Key: (a) $SOCl_2$, Et_3N, PhH, 0−5 °C; **7**, 68%; **8**, 14%; **9**, 0−3%; (b) $NaIO_4$, $RuCl_3$, CCl_4, CH_3CN, H_2O, 91%; (c) LiOH, H_2O, THF, 92%.

treatment of ovarian and breast cancers but also for treatment of non-small-cell lung cancer, small-cell lung cancer, squamous cancers of the head and neck, and various other cancers.[11] It has become the best-selling anticancer drug in history, with commercial sales of well over $1 billion in 1998. The semisynthetic analogue Taxotere (**2**), developed by Rhone-Poulenc Rorer, has an activity similar to taxol, and it entered clinical practice in the United States in 1996.[12] The supply problem was elegantly solved by a semisynthetic process from the available 10-deacetylbaccatin III (**3b**),[13] which can be converted to taxol in high yield by coupling its acetylated and protected form **4** with an *N*-benzoyl *β*-lactam such as **5** (Scheme 1).[14]



3a R = Ac
3b R = H

The Chemistry of Taxol

We began our investigations into the chemistry of taxol in late 1979 and have focused our attention primarily on the tetracyclic ring system and the effect of structural modifications to this system on the drug's activity. Our early work in this area has been reviewed,[15] and this paper will thus focus on recent and previously unreviewed work from our group.

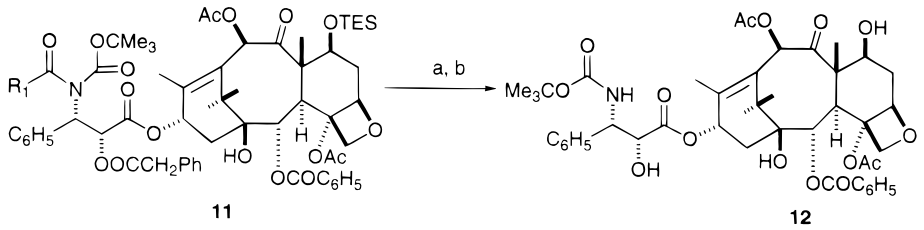
The Side Chain

Although most of our efforts have been directed at modifications of the ring system, we have also investigated alternate ways of coupling the side chain to baccatin III (**3a**) to prepare taxol. The C-13 hydroxyl group of baccatin III is very resistant to acylation, in part because of its hindered location on the underside of the "inverted cup" of the taxane ring system. It is thus important that any side chain acylating agent have a compact structure. Some years ago we introduced the oxazoline derivative **6** as an efficient acylating group for 7-(triethylsilyl)baccatin III; after acylation the resulting oxazoline **7** could be hydrolyzed in high yield to taxol (Scheme 2).[16]

We were interested in finding out whether other cyclic protecting groups could be used, and we thus converted the taxol side chain methyl ester **8** into a mixture of the two epimeric oxo-oxaisothiazoles **9a** and **9b**. Mixture **9a**,**b** was oxidized and then hydrolyzed to the single dioxo-oxaisothiazole carboxylic acid **10** (Scheme 3). Coupling of **10** with 7-(triethylsilyl)baccatin III (**4**) surprisingly gave the oxazoline derivative **7**, previously prepared by the route described above. The formation of **7** from **10** and **4** occurs by rearrangement of **10** into the dihydrooxazole **6**, as proved by exposing **10** to DCC/DMAP in the absence of the baccatin III derivative **4**.[17] This work thus not only led to a new formal synthesis of taxol but also shed a new light on the reactivity of the dioxo-oxaisothiazole ring system.

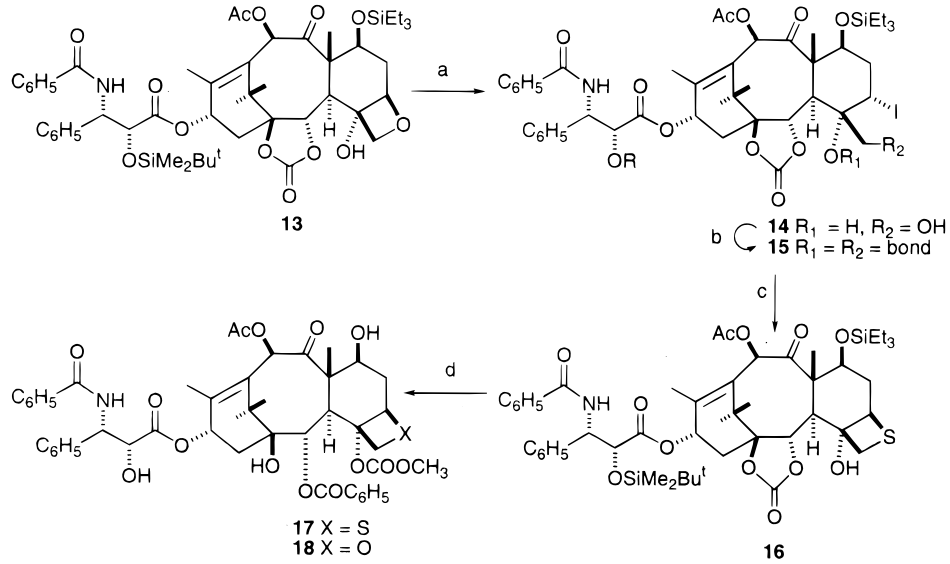
As noted above, there are many methods available for the synthesis of taxol analogues with modified side chains by the attachment of a suitable side chain to a protected baccatin III. Less obviously, it should also be possible to prepare modified taxols by direct modification of an existing side chain. We demonstrated this approach some years go by developing a conversion of cephalomannine to taxol,[18] but taxol itself proved resistant to such manipulations. Recently, however, we found that taxol can be selectively debenzoylated by conversion to its *N*-(*tert*-butyloxycarbonyl) derivative **11**.[19] Reaction of **11** with magnesium methoxide selectively cleaved the benzamide group to give 10-acetyldocetaxel (**12**) in reasonable overall yield. Compound **12** could be converted to docetaxel (**2**) by a published selective deacetylation at C-10.[20]

Scheme 4[a]



[a] Key: (a) $Mg(OMe)_2$, MeOH, rt, 1 h, 75% (b) HF-pyridine, THF, rt, 2 h, 91%.

Scheme 5[a]



[a] Key: (a) Me_3SiI, CH_2CL_2, −78 °C, 45 min, 93%; (b) trifluoromethane sulfonyl chloride/DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 96%; (c) Li_2S, THF, rt, 28 h, then carbonyldiimidazole/imidazole, rt, 12 h, 56%; (d) LHMDS, THF, −78 °C (7 min), rt (1 min), −78 °C (2 min), then methyl chloroformate, −78 °C (10 min), **17** (39%), **16** (41%); (d) PhLi, THF, −78 °C, 3 min, 61%; (e) HF-pyridine, rt, 9 h, 76%.

The Oxetane Ring

The oxetane ring is a unique feature of the structure of taxol, and all analogues prepared to date with an opened oxetane ring have a greatly reduced activity, including the first ring-opened analogues reported by us in 1986.[21] What is less certain is the reason for the importance of the oxetane ring. In principle it could serve at least two functions, since it is a hydrogen-bond acceptor and also serves as a rigid "lock" on the taxoid skeleton. The lock function is illustrated by the fact that ring-opened analogues adopt a different conformation, as indicated, for example, by changes in the ^1H NMR coupling constants of ring A protons on ring-opening.[21b,22]

We felt that a differentiation between the lock function and the hydrogen-bonding function of the oxetane ring could be made by substituting another heteroatom for the oxygen atom. Other workers had prepared nitrogen analogues (azetidine derivatives),[23] but these analogues suffer from the basicity of nitrogen and the likelihood that it would be at least partially protonated under physiological conditions. We thus elected to prepare the sulfetane analogue **17**.

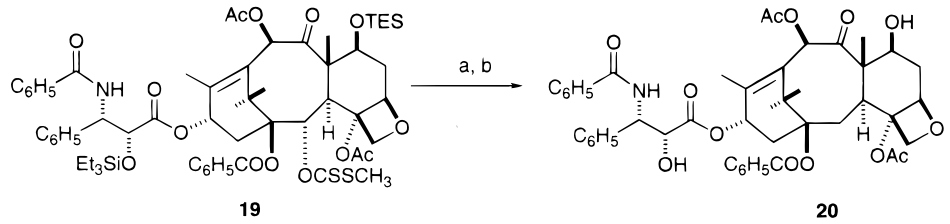
The synthesis of **17** proceeded from the known 4-deacetyl-2-debenzoyl-1,2-dicarbonate derivative **13**, prepared from taxol in four steps. Treatment of **13** with trimethylsilyl iodide gave the iodo-diol **14**, which was converted to the epoxy iodide **15** by treatment with *p*-toluenesulfonyl chloride and DMAP. Reaction of **15** with Li_2S gave the sulfetane derivative **16** in moderate yield once the conditions had been optimized. Acylation of **16** to its 4-acetyl derivative could not be accomplished in acceptable yield, presumably due to the additional steric congestion introduced by the larger sulfur atom, but conversion to its 4-methoxycarbonyl derivative and thence to the taxol analogue **17** was achieved in reasonable yield (Scheme 5).[24]

The bioactivity of the sulfetane analogue **17** was compared directly with that of the corresponding taxol analogue **18**, which was synthesized specifically for comparison purposes. In a tubulin-assembly assay **17** was less active than **18** by a factor of at least 10, and in two different cytotoxicity assays it was at least 2−3 orders of magnitude less active than **18**. These results thus indicate that the substitution of a sulfur for the oxetane oxygen causes significant activity loss and suggests that the hydrogen-bond acceptor ability of the oxetane oxygen is important. Alternatively, the larger size of the sulfur could cause some steric congestion in the binding site on tubulin. This latter concept is supported by a recent theoretical study in which it was shown that the sulfetane analogue **17** did not fit a model of the taxol binding site on tubulin as well as the analogue **18**.[25]

The Hydroxyl Group Question

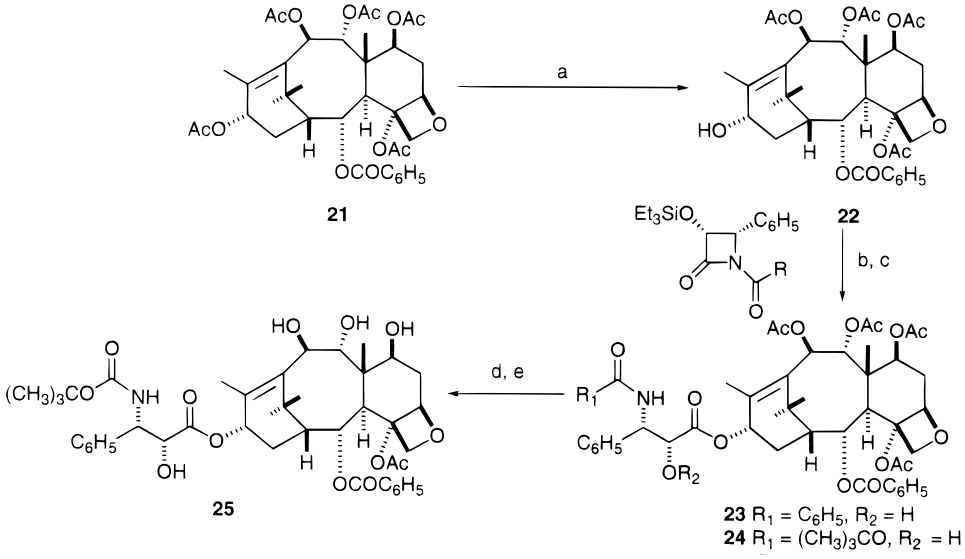
In earlier studies we and others had studied the importance of the various hydroxyl groups of the taxane ring system on the activity of taxol. In these investigations it was shown that both the C-10[26] and C-7[27] positions could be deoxygenated without significant loss of activity, but that deoxygenation of the C-4[28] and C-2[29] positions did result in a significant activity loss. It did not prove possible to prepare 1-deoxy analogues of taxol by these methods, however. In one example of the problems that were

Scheme 6[a]



[a] Key: (a) Tributyltin hydride/AIBN, toluene 90 °C; (b) 5% HCl, MeOH.

Scheme 7[a]

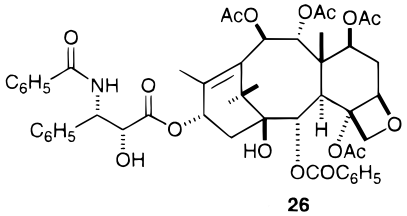


[a] Key: (a) Red Al, THF; 77%; (b) NaH, THF, 0 °C−rt, 77%; (c) TBAF, THF, −20 °C, 96%; (d) **23** (R_2 = $SiEt_3$), KOH, MeOH, 52%; (e) TBAF, THF, −20 °C, 80%.

encountered (Scheme 6), attempted preparation of the 1-(*S*-methylxanthate) of taxol gave instead the 1-benzoyl-2-xanthyltaxol **19**, which could be deoxygenated and deprotected to give 1-benzoyl-2-debenzoyloxytaxol **20**.[30]

A solution to the preparation of 1-deoxytaxol analogues was finally achieved by making use of 1-deoxybaccatin VI (**21**), which was isolated from *Taxus mairei* by collaborators in Taiwan and the People's Republic of China.[31] Treatment of **21** with RedAl at −20 °C gave the 13-deacetyl derivative **22** in good yield, and this could be converted to the corresponding 1-deoxytaxol analogues **23** and **24** by employing the β-lactam chemistry previously described (Scheme 7).[14] Additional analogues such as the 7,9,10-triol analogue **25** could be prepared from **21** by deacetylation of a 2′-protected intermediate with methanolic potassium hydroxide, followed by deprotection at the 2′-position.[32]

Although the 1-deoxytaxols **23**−**25** lacked the 9-keto group of taxol, their bioactivity could be compared directly with the analogue **26**, which differs from **23** only in the presence of the C-1 hydroxyl group. In this comparison compound **23** was approximately half as active as compound **26** in a tubulin-assembly assay and approximately one-tenth as active as **26** in a cytotoxicity assay.[33] It thus appears that the C-1 hydroxyl group does make a small but significant contribution to the overall bioactivity of taxol.

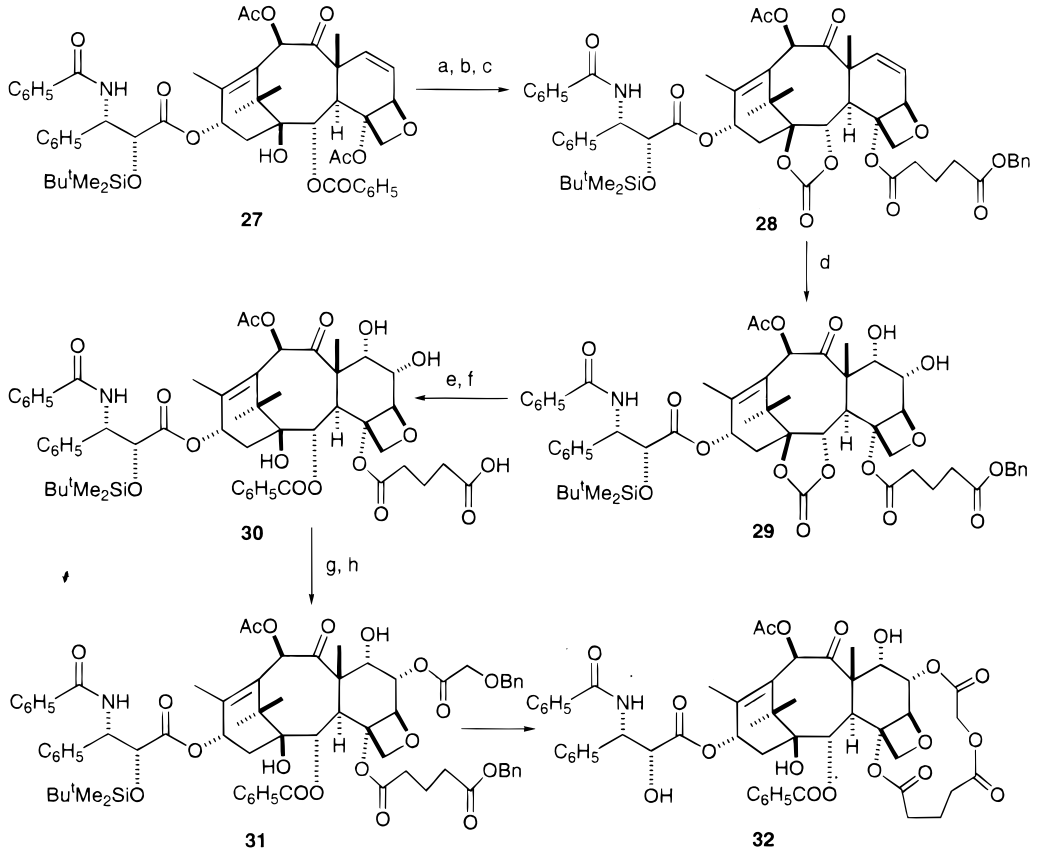


Synthesis of a Bridged Taxol Analogue

One important approach to gleaning information on the nature of the taxol−microtubule interaction is by the synthesis of analogues specifically designed to probe the steric requirements of the binding site. Although our work reported earlier demonstrated the importance of a C-4 acyl group for taxol's activity, little was known about the requirements (if any) for the orientation of this acyl group. We thus designed a bridged analogue (**32**) which would hold the C-4 acyl group in a defined conformation. The analogue would also necessarily introduce significant steric bulk on the underside of the "inverted cup" of the taxane skeleton.

The synthesis of **32** proceeded from the known[34] 6,7-dehydrotaxol **27**. This was selectively hydrolyzed with Triton-B, protected as the cyclic 1,2-carbonate, and then acylated at C-4 to give the analogue **28**. Hydroxylation of **28** gave the 6,7-diol **29**, which was converted to the 2-benzoate **30** by deprotection of the benzyl ester (to prevent organolithium addition to the distal ester site) and reaction with phenyllithium. Reprotection of the carboxyl group and selective acylation of the C-7 hydroxyl group gave the protected hydroxy acid **31**, and deprotection of the two benzyl esters set up the hydroxy acid for cyclization to the lactone. Cyclization proved difficult and was eventually achieved only under high dilution conditions using the Mukaiyama procedure, giving the lactone in 10% yield.[35]

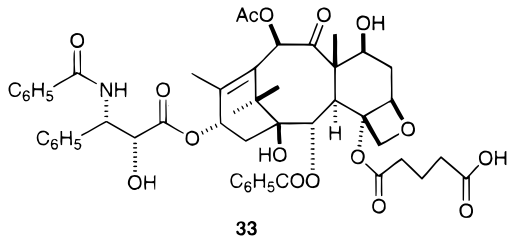
Scheme 8[a]



[a] Key: (a) Triton-B, CH_2Cl_2, −78 to −10°C; (b) CDI, CH_2Cl_2, 40 °C; 56% (2 steps); (c) $PhCH_2OOC(CH_2)_3COOH$, DCC, DMAP, toluene, 86%; (d) OsO_4, NMO, THF/H_2O, 81%; (e) H_2, Pd/C, EtOAc, 87%; (f) PhLi, THF, −78 °C, 78%; (g) $PhCH_2OH$, DCC, DMAP, toluene, 94%; (h) $BnOCH_2COCl$, DMAP, CH_2Cl_2, 85%; (i) H_2, Pd/C, EtOAc, 71%; (j) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_3CN, 80 °C, 10%; (k) HF/pyridine, 64%.

After cleavage of the 2′-silyl ether, the deprotected lactone **32** was obtained (Scheme 8).

The bioactivity of **32** was determined in conjunction with the 4-glutaryl analogue **33**, which was prepared from taxol



33

by standard methods. Both **32** and **33** were essentially inactive in a tubulin-assembly assay. In cytotoxicity assays compound **33** was less active than taxol by at least 2 orders of magnitude, and the lactone **32** was even less active than **33**. These results thus indicate that the binding site cannot accommodate a bulky group at C-4, and especially not one that is held across the "inverted cup" of the tetracyclic taxane ring system.

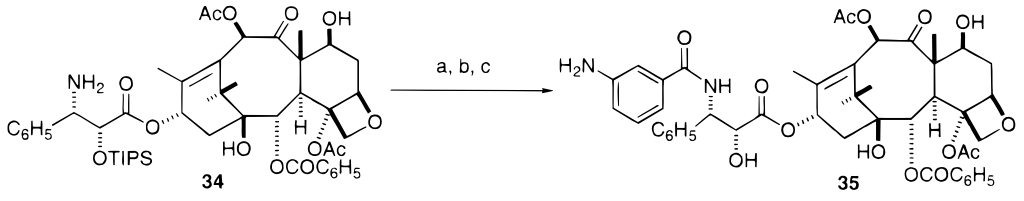
Taxol SAR Summary

The studies described above, together with other studies by ourselves and others, have led to a good general picture of the structure−activity relationships of taxol, and this is summarized in Figure 1. In general, changes to the "southern hemisphere", comprising the C-14 and C-1 to C-5 positions, exert a major effect on taxol's activity. This is the case for changes at C-1 (although here the effects are not large), at C-2, and at C-4. Most changes to the C- and D-rings, including opening of the oxetane ring, almost always lead to loss of activity, although Appendino has found an intriguing example of a C-ring-opened analogue that retains significant activity.[36]

Changes in the "northern hemisphere", comprising the C-6 to C-12 positions, appear to have less impact on taxol's activity, although these changes can still be important therapeutically, and Ojima has developed some interesting taxol analogues modified at C-10 and at C-2 with usefully improved activities.[37]

Changes in the side chain have also been made by several investigators, and it is expected that future "second-

Scheme 9[a]



[a] Key: (a) *m*-$NO_2C_6H_4COCl$, $NaHCO_3$, EtOAc; (b) H_2/Pd-C, MeOH; (c) HF-pyridine, THF, rt.

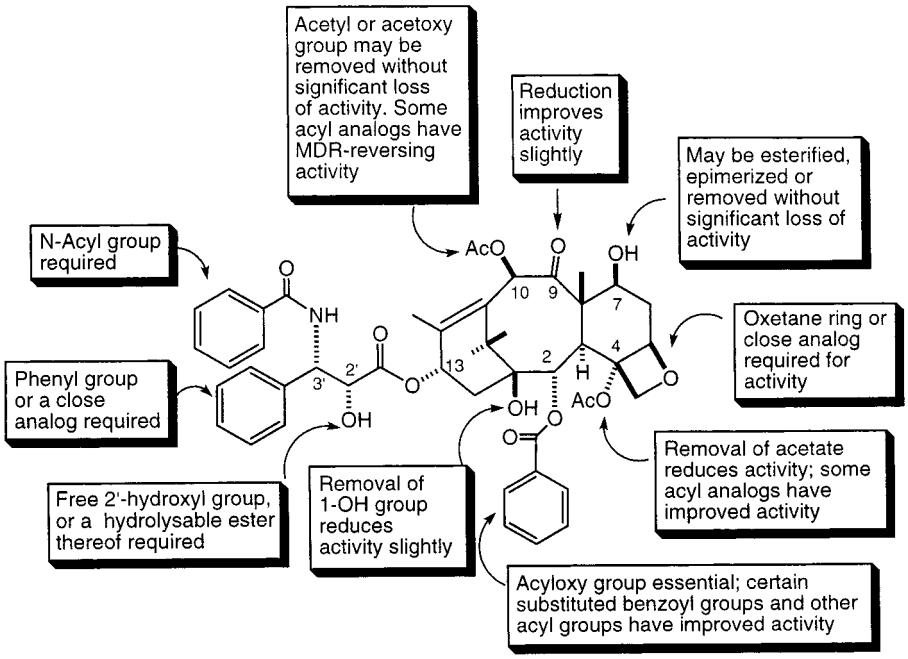


Figure 1. Some structure−activity relationships of taxol.

generation" taxol analogues will have modifications both on the side chain and on the taxane ring system.

The Conformation of Microtubule-Bound Taxol

In addition to the studies of the chemistry of taxol described above we have also been studying the binding of taxol to its tubulin receptor using the tools of fluorescence spectroscopy and REDOR NMR. This work has been done in collaboration with Dr. Susan Bane and her group at SUNY Binghamton, and Dr. Jacob Schaefer and his group at Washington University, St. Louis.[38]

The fluorescence studies were carried out with 3′-*N*-debenzoyl-3′-*N*-(*m*-aminobenzoyl) taxol (**35**), prepared from the aminotaxol **34** by acylation, reduction, and deprotection (Scheme 9).

The fluorescence spectrum of the aminotaxol **35** was found to be very sensitive to its environment. In polar protic solvents the difference between the absorption maximum and the emission maximum in cm^{-1} (the Stokes shift) was found to increase with increasing solvent polarity, as is expected for a *m*-aminobenzamide fluorophore. Surprisingly, however, the Stokes shift was small and essentially invariant in aprotic solvents of varying polarity, even when these solvents had equal or greater polarity than some of the protic solvents (Figure 2). These results suggested that the *m*-aminobenzoyl fluorophore of **35** is somehow "shielded" from the medium in aprotic solvents. This is most readily explained by assuming that taxol **35** adopts a conformation in aprotic solvents in which the 3′-benzamide is under the taxane ring and is thus shielded from solvent effects; this conformation is shown as A in Figure 3. In protic solvents **35** undergoes conversion to the "hydrophobic collapsed" conformation B or C (Figure 3) in which the benzamide fluorophore is extended into the solution. These results are consistent with NMR studies[39,40] that indicate that the conformation of the taxol side chain is dependent on the solvent.

The utility of the fluorescence method becomes apparent from the consideration that it is not possible to obtain simple NMR measurements of taxol in the presence of tubulin, but it is still possible to make fluorescence measurements on the microtubule-bound drug. When this

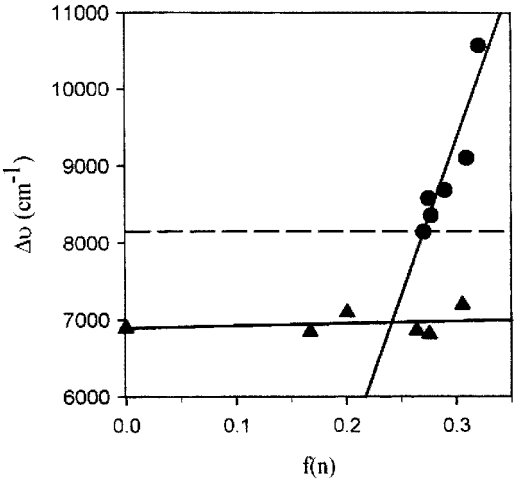
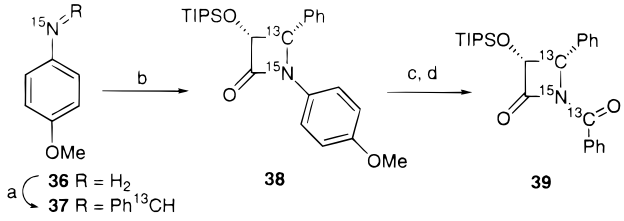


Figure 2. Effect of solvent polarity on the Stokes shift of aminotaxol **35**. The *f(n)* term is a measure of solvent polarity. (▲) Aprotic solvents (from left to right, hexane, diethyl ether, dioxane, ethyl acetate, dimethylformamide, DMSO, and acetonitrile); (●) protic solvents (from left to right, 2-butanol, 2-propanol, 1-propanol, ethanol, methanol, and 2%DMSO/H_2O); and (—) the Stokes shift of microtubule-bound **35**. Reproduced with permission from *Biochemistry* **2000**, *39*, 281−291. Copyright 2000 American Chemical Society.

Scheme 10



was done for the analogue **35**, the Stokes shift was found to correspond with that for **35** in a protic solvent. This result thus suggests that taxol adopts a conformation such as Figure 3 B or C when it is bound to polymerized tubulin.

To distinguish between conformations B and C, we turned to the technique of REDOR NMR spectroscopy. This powerful method can be used on solid samples such as a

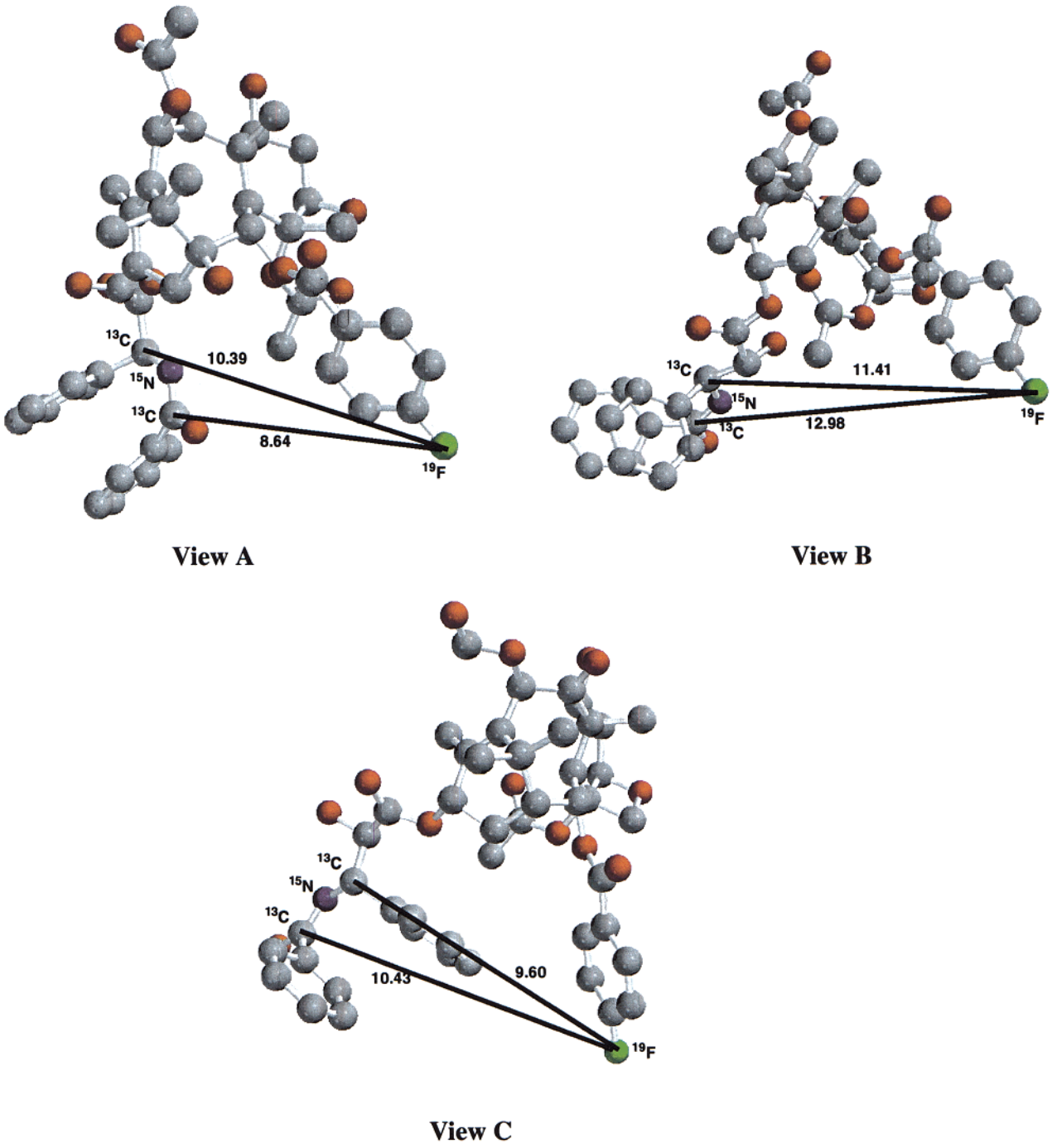


Figure 3. Possible conformations of tubulin-bound taxol. Structure A is taxol based on the docetaxel X-ray coordinates; structures B and C are based on the two different confromations of taxol found in its crystal structure.

lyophilized taxol−tubulin complex, and the intensities of the REDOR peaks provide unambiguous distance measurements between atoms of interest.[41]

The sample used in the REDOR experiments was the quadruply labeled derivative **41**. The labeled *β*-lactam **39** was prepared by reacting [^{15}N]-*p*-anisidine (**36**) and [carbonyl-^{13}C]benzaldehyde) to give the doubly labeled imine **37**, which was then coupled by Ojima's method[42] to give the *β*-lactam **38**. Oxidative cleavage of the *p*-methoxybenzene protective group and reacylation with [carbonyl-^{13}C]-benzoyl chloride gave the triply labeled lactam **39** (Scheme 10).

Coupling of **39** with 2-debenzoyl-2-(*p*-fluorobenzoyl)-7-*O*-(triethylsilyl)baccatin III (**40**), followed by deprotection, gave the quadruply labeled analogue **41** (Scheme 11). Analogue **41** was then used to assemble tubulin in buffer containing polyvinyl pyrrolidine, and the assembled complex was lyophilized.

The double REDOR experiment on the tubulin complex with **41** required 3 months of continuous acquisition to obtain a useful S/N ratio, but this was successfully accomplished. The resulting data gave two independent distance measurements: one of 9.8 Å for the carbonyl-^{13}C/F distance, and one of 10.3 Å for the 3′-^{13}C/F distance.

These distance measurements are clearly incompatible with structure B (Figure 3) but are consistent with structure C. On the basis of this evidence, we were then able to model the taxol−tubulin complex. For this work we used atomic coordinates for the tubulin polymer from work by Nogales et al.[43] and also used data from fluorescence

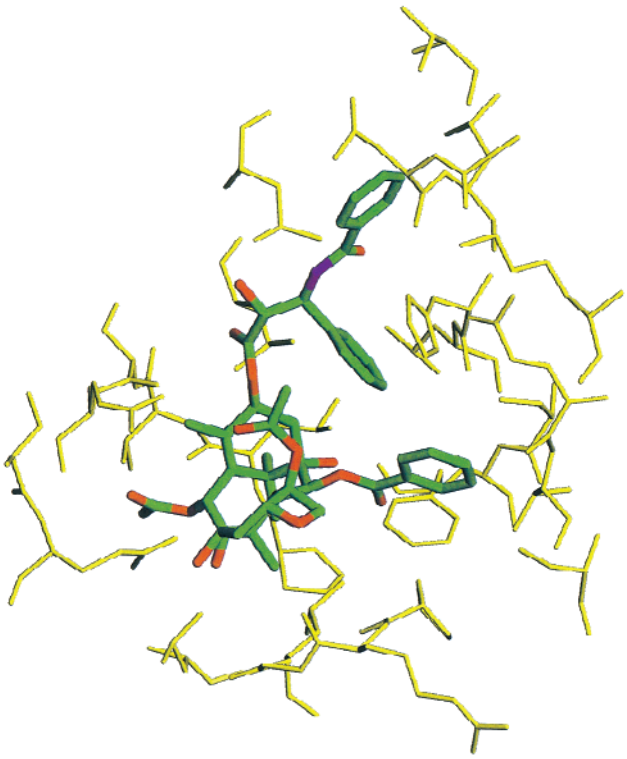
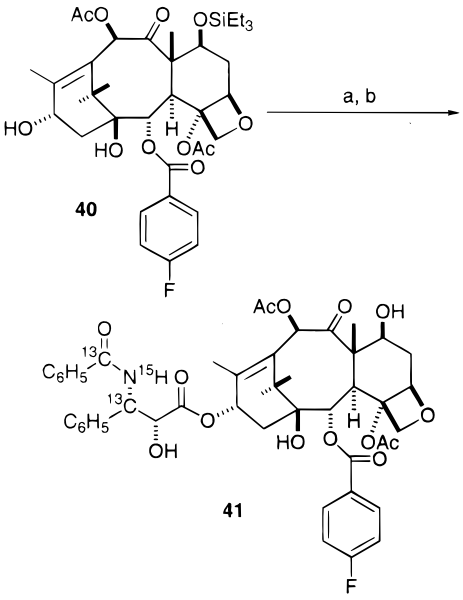


Figure 4. Model of tubulin-bound taxol: (green) taxol; (yellow) protein groups within 4 Å of the ligand. Reproduced with permission from *Biochemistry* **2000**, *39*, 281−291. Copyright 2000 American Chemical Society.

Scheme 11



resonance energy transfer experiments that indicated that the C-2 phenyl ring was closer to the colchicine binding site than the C-3′ benzamide ring. The resulting minimized structure is shown in Figure 4, in which only protein residues with atoms within 4 Å of taxol are shown.

This work has thus demonstrated that a combination of fluorescence spectroscopy and REDOR NMR is a powerful tool for determining the structure of complex ligands on their macromolecular hosts. We are currently using these techniques to develop more precise models for the taxol−tubulin interaction and thus aid in the design and synthesis of ligands that will bind more efficiently to microtubules.

Acknowledgment. The work described above could not have been accomplished without a large group of talented and hard-working colleagues and collaborators. The tubulin and REDOR studies described in the last section were done in collaboration with Dr. Susan Bane (SUNY Binghamton) and Dr. Jacob Schaefer (Washington University, St. Louis), and I am enormously grateful to them and their colleagues for these exciting results. Recent work at Virginia Polytechnic Institute and State University was done by Drs. A. A. L. Gunatilaka, M. H. Sarragiotto, P. G. Jagtap, F. D. Ramdayal, M. D. Chordia, H. Yuan, and E. Baloglu; earlier work was carried out by colleagues whose names are given in the references cited. I would like to pay especial tribute to Dr. Matthew Suffness, who was a leading proponent of research on taxol within the National Cancer Institute and who provided much help and encouragement to the present author. His tragic early death in 1995 deprived the natural products community of a staunch supporter and a good friend. Financial support was provided by the National Cancer Institute from grants CA69571 and CA55731, and I am most grateful for this crucial component of our work.

References and Notes

(1) American Society of Pharmacognosy Research Achievement Award lecture, presented at the Joint Meeting of the American Society of Pharmacognosy, the Association Française pour l'Enseignement et la Recherche en Pharmacognosie, the Gesellschaft für Arzneipflanzenforschung, and the Phytochemical Society of Europe, Amsterdam, The Netherlands, July 27, 1999.
(2) The chemical compound represented by structure **1** was named taxol by its discoverers in 1971, and this name was universally used in the literature for over 20 years until Bristol-Myers Squibb trademarked the name Taxol for its formulation of taxol; the name paclitaxel was then recommended for the chemical substance **1**. Because of the historical nature of this review, the name taxol will be used for the compound of structure **1**. No infringement of the Bristol−Myers Squibb trademark is intended or implied by this usage.
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NP000064N