**Taxol**

### 34.1 Introduction

The story of taxol (1), a molecule that received much publicity in the early 1990s, goes back to ancient times. Julius Caesar mentions in his “Gallic Wars” that Catuvolcus, a chieftain of the Eburones, committed suicide by taking extracts from the yew tree.\(^1\) Several other accounts report more recent uses of such extracts as poison or as a cancer-healing folk medicine. The modern history of this natural product began in 1962, when A. Barclay collected bark from *Taxus brevifolia*, the Pacific Yew tree, from forests in the northwestern United States, as part of a joint project between the U.S. Department of Agriculture and the National Cancer Institute aimed at the discovery of new anticancer agents.\(^2\) An intense search for the cytotoxic principle led to the isolation of taxol in minute quantities. It has been estimated that the sacrifice of one 100-year-old yew tree would result in approximately only 300 mg of taxol, just about enough for one single dose for a cancer patient. In a seminal paper published in 1971,\(^3\) Wall, Wani, and coworkers reported the molecular structure of taxol on the basis of an X-ray crystallographic analysis.

Taxol’s journey to the clinic was slow and arduous. Initial difficulties with aqueous solubility and lack of knowledge regarding its mechanism of action delayed its development until 1979 when, in another seminal paper in the field, S. B. Horwitz and her collaborators disclosed their findings on the interaction of taxol with microtubules.\(^4\) Taxol’s unique biological action, which includes promotion of microtubule formation and microtubule stabilization, stimulated a renewed interest in taxol as a potential drug candidate. The problem of procuring adequate supplies of taxol became even
more acute when environmentalists, concerned about the endan-
gered spotted owl that lives in the northwestern United States,
raised objections to the destruction of the ancient forests. A poten-
tial solution was found when 10-deacetylbaccatin III, a precursor of
taxol lacking the C-10 acetoxy group and the C-13 side chain, was
discovered in the needles and twigs of *Taxus baccata*, the Eu-
ropean Yew tree. Harvesting this renewable source, followed by
semisynthesis,6 allows the production of taxol on a relatively large
scale. In the meantime, synthetic chemists around the world
embarked on different schemes to synthesize taxol. In 1992, taxol
was approved for the treatment of ovarian cancer by the U.S. Food
and Drug Administration, and it held promise for the treatment of
several other types of cancer including breast, lung, and melanoma.
By the fall of 1995, three distinct total syntheses of taxol had been
disclosed.7,8 In this chapter, we discuss the synthesis developed in
the Nicolaou laboratories, which was reported first in the journal
*Nature*.

### 34.2 Retrosynthetic Analysis and Strategy

Although taxol’s unique mode of action and potential as an anti-
cancer agent underlie much of the intense interest in this cele-
brated diterpene, synthetic chemists were most impressed with
taxol’s structure. The taxol molecule (1) is distinguished by a
6-8-6 tricyclic carbon framework, by a characteristic ester side
chain, and by a dense pattern of oxygenated functionality. Inspec-
tion of 1 reveals that of the fourteen carbon atoms defining the
boundary of the molecule, nine are asymmetric and seven of these
bear some form of oxygenation. Taxol’s saturated six-membered
C-ring is the site of an unusually heavy concentration of asymm-
etry; this imposing substructure contains five contiguous stereogenic
centers, and it supports the unusual and potentially electrophilic
oxetane ring.

Interestingly, the stereochemical challenge that would beset any
synthetic approach is matched, and perhaps eclipsed, by the poten-
tially serious problem presented by the central eight-membered
carbocycle. On the basis of unfavorable entropy, bond angle de-
formations, and destabilizing transannular interactions, the eight-mem-
bered ring has traditionally been regarded as one of the most diffi-
cult to construct.92 and the development of general methods for its
synthesis has received a great deal of attention.9b The powerful
combination of the eight-membered ring and the array of oxy-
genated functionality decorating the periphery of the molecule make
taxol an extremely challenging target for synthesis.

Not surprisingly, taxol has motivated the development of many
synthetic strategies, and much fascinating science has emerged
from research in this area.2,10 Attracted by the formidable challenge
posed by the structural complexity of taxol (1) and by the need for a synthetic entry into the taxoid class of compounds, the Nicolaou group embarked, in early 1992, on a total synthesis of this molecule.

Scheme 1 shows the structure of taxol (1) and the strategic bonds identified for retrosynthetic disconnection. Taking advantage of precedent in the field regarding the attachment of the ester side chain to the taxoid framework, the ester bond is first disconnected to provide, after suitable protections, the baccatin III derivative 2 and the β-lactam derivative 3 as potential precursors. The union of compounds 2 and 3, followed by elaboration to the target molecule is a matter of following published protocols. To further simplify the taxoid skeleton, the C-13 oxygen is excised retrosynthetically from structure 2, giving compound 4 as the precursor. At this point, serious consideration was given to the selection of a cyclic carbonate to protect the C1–C2 diol system. In addition to its role as a protecting group, the carbonate ring could conceivably provide the preorganization necessary to facilitate a projected ring closure to form taxol’s eight-membered ring (see below). Moreover, it was anticipated that a cyclic carbonate could serve as a potential precursor to the desired C1-hydroxy, C2-benzoate system of taxol (see Figure 1). Thus, compound 5 presented itself as a key intermediate in the synthesis. In the synthetic direction, it was our hope that phenyllithium would react chemoselectively with the carbonate carbonyl in 5 to give 4 upon collapse of the tetrahedral intermediate (see Figure 1). As attractive as this transformation seemed, we were not unaware of the presence of several other electrophilic functional groups in addition to the carbonate carbonyl in 5. Indeed, the carbon framework of 5 supports a variety of electrophilic groups and each could, in principle, react with a strong nucleophile such as phenyllithium. Nevertheless, this simple transformation was found to be feasible during the course of our taxol degradation/reconstitution studies.11

Proceeding with the retrosynthetic analysis, it is now timely to address the issue of the rather sensitive oxetane ring. Disconnection of the C5–O bond as indicated in structure 5 and engagement of

![Figure 1. The cyclic carbonate → hydroxybenzoate transformation.](image-url)
Scheme 1. Strategic bond disconnections and retrosynthetic analysis of taxol (1).
the tertiary and primary hydroxyl groups extending from C-4 in a five-membered acetonide ring, reveals olefin 6 as a potential precursor. In the synthetic direction, introduction of an oxygen atom at C-5 to the desired face of the double bond in 6, followed by an S_N2-type displacement, or a direct ring closure of the primary hydroxyl on the double bond could accomplish the desired goal of forming the oxetane ring. The issue of constructing the C9–C10 functionality could conceivably be addressed from a C9–C10 diol system. As shown in Figure 2, the regio- and stereochemical outcome of manipulating the C9–C10 diol system to the desired C-9 keto, C-10 β-acetoxy system of taxol is left open, but with the possibility of correction via the indicated mechanism in the event that the wrong isomer is formed initially. Specifically, it was hoped that the presumed greater thermodynamic stability of the natural isomer would drive the equilibrium in the desired direction. With this expectation in mind, the eight-membered ring of compound 6 can be disassembled by a retro-pinacol coupling, providing dialdehyde 7 as a possible progenitor.

A conspicuous and valuable structural feature of 7 is the five-membered cyclic carbonate ring bridging the vicinal oxygen atoms attached to C-1 and C-2 (taxol numbering). An analysis of molecular models of compound 7 revealed that this cyclic protecting group might influence the projected pinacol coupling reaction in a favorable way by restricting rotational freedom. In fact, this analysis seemed to suggest that a cyclic protecting group bridging the C-1 and C-2 oxygen atoms would favor the adoption of a conformation

![Figure 2. The C9–C10 regiochemistry problem.](image-url)
in which the two aldehyde functions are positioned in neighboring regions of space, which would clearly facilitate any process leading to their union. Although a host of cyclic protecting groups could conceivably provide the preorganization necessary to induce the crucial ring closure reaction, we were particularly interested in the cyclic carbonate because it can serve as a direct precursor to the C-1 hydroxy, C-2 benzoate system of the natural product (see Figure 1).

Removal of the carbonate ring from 7 (Scheme 1) and further functional group manipulations lead to allylic alcohol 8 which can be dissected, as shown, via a retro-Shapiro reaction to give vinyl-lithium 9 and aldehyde 10 as precursors. Vinyl-lithium 9 can be derived from sulfonyl hydrazone 11, which in turn can be traced back to unsaturated compounds 13 and 14 via a retro-Diels–Alder reaction. In keeping with the Diels–Alder theme, the cyclohexene aldehyde 10 can be traced to compounds 16 and 17 via sequential retrosynthetic manipulations which defined compounds 12 and 15 as possible key intermediates. In both Diels–Alder reactions, the regiochemical outcome is important, and special considerations had to be taken into account for the desired outcome to prevail. These and other regio- and stereochemical issues will be discussed in more detail in the following section.

34.3 Total Synthesis

The general strategy outlined in Scheme 1 is predicated on the convergent union of two prefabricated building blocks representing rings A and C, followed by the execution of an intramolecular bond-forming process to complete the tricyclic carbon framework of taxol. You will note that key intermediates 10 and 11 are simply functionalized cyclohexene rings. It, therefore, seemed prudent to devise a strategy for the construction of these two intermediates based on the powerful and predictable Diels–Alder reaction.12

The synthesis of hydrazone 11 commences with an intermolecular Diels–Alder reaction between diene 13 and the commercially available ketene equivalent, 2-chloroacrylonitrile (14) (see Scheme 2).13 When these simple starting materials are confined to a sealed tube and heated at 130°C for three days, crystalline cyclohexene 18 is produced in 85% yield. Interestingly, and perhaps somewhat surprisingly, 18 is the only regiosomer formed in this reaction. On the basis of the substitution pattern of diene 13, it was anticipated that 19 ought to be the major product formed in this process. However, considering that the Diels–Alder reaction is susceptible to steric effects, we were concerned that destabilizing nonbonding interactions in the transition state leading to the desired regiosomer 18 might prohibit, or at least hinder its formation. Nonetheless,
34.3 Total Synthesis

Scheme 2. Synthesis of hydrazone 11.

Compounds 13 and 14 combine smoothly under the indicated conditions to give, after silica gel chromatography, the desired adduct 18. It was not possible to establish the structure of 18 by \(^1\)H NMR spectroscopy because the chemical shifts for the two sets of ring methylene hydrogens are coincident. Compound 18 is, however, a beautifully crystalline solid, and its constitution could be confirmed by X-ray crystallography. It is instructive to note that the product from this easily executed Diels–Alder reaction already has much in common with the targeted A-ring intermediate 11.

It was recognized at an early stage that a C-1 keto function would permit an evaluation of a number of possibilities for joining A- and C-ring intermediates. At this stage in the synthesis, it was therefore necessary to address the problem of achieving the hydrolysis of the chloronitrile moiety in 18 to the corresponding ketone. Although several methods, including Evans’s sodium sulfide method,\(^{14}\) were examined for this purpose, Shiner’s protocol\(^{15}\) was found to be the most satisfactory. Thus, subjecting 18 to the action of five equivalents of potassium hydroxide in tert-butyl alcohol at 70 °C results in the formation of hydroxyketone 19 in 65% yield. Under these conditions, the hydrolysis of the chloronitrile moiety is accompanied by cleavage of the primary acetate group. Although the yield for this transformation is somewhat low and occasionally capricious, multigram quantities of hydroxyketone 19 can be prepared via this straightforward two-step sequence.
A digression is in order at this point. A fruitful by-product of research in organic synthesis has been the development of reagents that are synthetically equivalent\footnote{16} to chemical species that are either inaccessible or are susceptible to undesirable reaction pathways. For example, a particularly direct approach to the synthesis of unsaturated ketone 20 would feature an intermolecular [4+2] cycloaddition reaction between a suitably protected diene and ketene. Unfortunately, however, ketene itself is not a viable dienophile in Diels–Alder reactions, because instead it participates in [2+2] cycloaddition reactions with 1,3-dienes to give substituted cyclobutanones. Thus, the identification of reagents that can serve as synthetic equivalents of ketene\footnote{17} and can participate in Diels–Alder reactions with 1,3-dienes has significantly expanded the repertoire of organic synthesis. The ketene equivalent featured in Scheme 2 is 2-chloroacrylonitrile (14). This substance was selected for use in this synthesis because it has been shown to undergo highly regioselective cycloadditions with 1,3-dienes\footnote{14,17,18} and because it is commercially available. Compound 14 is synthetically equivalent to ketene because the carbonyl group can be unveiled upon hydrolysis of the chloronitrile adduct (see 18→19). It is as if ketene were employed in the Diels–Alder reaction.

Ketone 20, derived in one uneventful step from hydroxyketone 19 (see Scheme 2), is a versatile synthetic intermediate. By virtue of its keto group, compound 20 could, in principle, serve as an electrophile in conventional carbonyl addition reactions with various C-ring nucleophiles. On the other hand, the keto function in 20 could provide a convenient handle for the elaboration of an A-ring nucleophile that could subsequently be joined with C-ring electrophiles. As matters transpired, many attempts to utilize 20 as an electrophile were thwarted by its pronounced tendency to enolize in the presence of nucleophilic (and basic) organometallic reagents. The latter option (A-ring as a nucleophile) was, however, found to be feasible. Despite its highly hindered (neopentyl) nature, the ketone carbonyl group in 20 reacts smoothly with 2,4,6-triisopropylbenzenesulfonylhydrazine\footnote{19} to give crystalline hydrazone 11. This substance is particularly interesting because it could conceivably be converted into vinyllithium reagent 9 (see Scheme 1) via a Shapiro reaction.\footnote{20} Indeed, during the course of relevant model studies,\footnote{21} it was found that putative vinyllithium reagent 9, derived from the action of n-butyllithium on hydrazone 11, can be intercepted by model C-ring aldehydes.

Of the two cyclohexenoic sectors of taxol, C-ring intermediate 10 is clearly the more complex (see Scheme 1). The cyclohexene ring in 10 includes four contiguous asymmetric carbon atoms, one of which is quaternary.\footnote{22} When confronted with a highly stereodefined six-membered ring, one should be mindful of opportunities afforded by the powerful Diels–Alder reaction. Indeed, an important virtue of the Diels–Alder reaction is that it can create, in a single stereospecific step, a cyclohexene ring containing up to four contiguous stereogenic centers.\footnote{12} The Diels–Alder reaction is
considered stereospecific because relative stereochemical relationships contained within the diene and/or the dienophile are reflected in the [4+2] adduct; this is the familiar cis principle. In addition to its stereospecificity, the Diels–Alder reaction, in many instances, can be highly regio- and stereoselective.

A careful assessment of the constitution of compound 10 led to the development of a rather efficient strategy featuring the Diels–Alder reaction (see Scheme 3). Although the unassisted intermolecular reaction between 3-hydroxy-2-pyrone (16) and α,β-unsaturated ester 17 is unacceptable in terms of both regioselectivity and chemical yield, compounds 16 and 17 combine smoothly in refluxing benzene and in the presence of phenylboronic acid to give fused bicyclic lactone 12 (61% yield) after workup with 2,2-

![Scheme 3. Synthesis of aldehyde 10.](image-url)
dimethyl-1,3-propanediol. In this most productive reaction, which is based on the brilliant work of Narasaka, these two simple achiral starting materials become linked to the boron atom of phenylboronic acid to give mixed boronate ester 21 after expulsion of two water molecules. The boron atom thus serves as a template and brings the diene and dienophilic components together to enable an intramolecular Diels–Alder reaction, thereby allowing the regiochemical course of the cycloaddition to be rigorously controlled. This transformation is among a diverse collection of reactions that are facilitated and controlled through the use of a disposable tether or atom. Interestingly, bicyclo[2.2.2]lactone 15, the expected product from this reaction, participates in a lactone migration reaction to give bicyclo[4.3.0]lactone 12. It is noteworthy that Narasaka's boron template methodology enforces the union of compounds 16 and 17 and permits the construction of a molecule already possessing four of the requisite five contiguous stereogenic centers. In addition, the cycloaddition process exhibits complete endo stereoselectivity. Although 12 is prepared in racemic form, it possesses all the desired relative stereochemical relationships.

Bis(silylation) of 12 with excess tert-butyltrimethylsilyl triflate (see Scheme 3), followed by a chemoselective reduction with lithium aluminum hydride (LiAlH4) unexpectedly affords alcohol 22 in 89% overall yield. Exposure of 22 to a catalytic amount of camphorsulfonic acid (CSA) in methanol–CH2Cl2 selectively cleaves one the tert-butyltrimethylsilyl ethers, providing a γ-lactone 1,3-diol in 94% yield. Sequential protection of the primary hydroxyl group as a tert-butylidiphenylsilyl ether (92% yield) and the secondary hydroxyl group as a benzyl ether (88% yield) proceeds smoothly under standard conditions without complications to furnish γ-lactone 23. Reduction of the γ-lactone function in 23 with LiAlH4 is accompanied by cleavage of the tertiary tert-butyltrimethylsilyl ether to give the corresponding triol which can subsequently be converted to 24 on treatment with 2,2-dimethoxypropane and a catalytic amount of CSA (66% overall yield). Finally, oxidation of primary alcohol 24 with tetrapropylammonium perruthenate (TPAP)/N-methylmorpholine-N-oxide (NMO) takes place smoothly to give the desired C-ring aldehyde 10 (95% yield).

The development of the efficient reaction sequences summarized in Schemes 2 and 3 accomplished the first goal of the project. With appropriately functionalized and differentiated surrogates of taxol's A- and C-rings in hand, it was then necessary to contend with the potentially difficult task of effecting their union. You will note that compounds 10 and 11 are complementary with respect to reactivity. By virtue of the Shapiro reaction, A-ring hydrazone 11 can be regarded as a latent carbon nucleophile. It was anticipated at the outset that the action of n-butyllithium on 11 would furnish vinyl-lithium reagent 9 (see Scheme 1), and that this reactive carbon nucleophile might then participate in a carbonyl addition reaction with aldehyde 10. If successful, this convergent coupling reaction would accomplish the formation of the C1–C2 bond of taxol. In the
event, treatment of a solution of hydrazone 11 in THF with 2.1 equivalents of n-butyllithium at -78 °C produces, after warming to 25 °C, putative vinyl lithium reagent 9 (see Scheme 4). Exposure of this reactive species to C-ring aldehyde 10 then results in the formation of allylic alcohol 9 (82% yield). Remarkably, compound 8 is the only stereoisomer observed in this reaction. This most gratifying result certainly was not predicted. The exclusive production of 8 in this manner is consistent with the addition of nucleophile 9 to the less hindered Re face of a chelated aldehyde carbonyl (see 25); presumably the disposition of the C-8 methyl group would significantly hinder an addition to the Si diastereoface.

This coupling reaction is noteworthy for two reasons. First, it permits the union of the two sectors of taxol through a carbon–carbon bond between positions 1 and 2. Second, it affords an allylic alcohol, the hydroxyl group of which provides a convenient opportunity to selectively functionalize the $\Delta^{14,1}$ double bond. Treatment of a solution of 8 in benzene at 25°C with tert-butyl hydroperoxide and a catalytic amount of VO(acac)$_2$ affords, as the sole product, epoxy alcohol 26 (87% yield). In this successful Sharpless oxidation reaction, the C-2 hydroxyl group in 8 directs, via a conformation that minimizes destabilizing nonbonding interactions between the two heavily substituted six-membered rings, a completely regio- and stereoselective epoxidation of the C14–C1 double bond. The subsequent reductive opening of the oxirane ring in 26 with lithium aluminum hydride is also regioselective, affording vicinal diol 27 in 76% yield. It is important to note that this three-step reaction sequence (i.e. coupling, oxidation, reduction) permits the construction of a key carbon–carbon bond and allows the vicinal oxygens at carbons 1 and 2 to be correctly positioned in space.

As discussed previously, the use of a cyclic protecting group bridging the vicinal hydroxyls at C-1 and C-2 is an important feature of this synthesis. It was hoped that this device would facilitate the pending pinacol coupling reaction by conferring conformational rigidity to the cyclization precursor (see intermediate 7, Scheme 1). This tactic, together with the discovery that the C-1 hydroxy, C-2 benzoate system of the natural product can be unveiled in one step upon treatment of a simple cyclic carbonate with phenyllithium (see Figure 1), led to the selection of a carbonate as the cyclic protecting group. Treatment of a solution of diol 27 in HMPA–Et$_2$O at 25°C with potassium hydride and phosphine results in the formation of carbonate 28 (77% yield). Cleavage of both silicon protecting groups with excess tetra-$n$-butylammonium fluoride then furnishes a diol that can be easily oxidized to key intermediate 7 with TPAP–NMO$^{37}$ (74% overall yield).

A critical stage in the synthesis has been reached. The constitution of dialdehyde 7 would seem to lend itself to a reductive carbon–carbon coupling reaction. If feasible, such a process would accomplish the construction of taxol’s strained eight-membered ring, and it was hoped that carbons 9 and 10 would not, at any stage during the course of their union, be deprived of their valuable oxygen atoms. A Ti$^0$-mediated pinacol coupling, also known as the McMurry coupling reaction, appeared particularly attractive. It is appropriate at this point to acknowledge important precedent that encouraged the selection of this particular cyclization reaction. In 1986, Kende and his collaborators disclosed a convergent synthesis of a rather advanced tricyclic taxane triene via a strategy that features a McMurry coupling reaction.$^{31}$ Although the yield for the crucial cyclization step was modest (23% yield), it was encouraging that the congested taxane carbon framework could be assembled through direct closure of the eight-membered B-ring. Moreover, refinements of and further insights into the McMurry coupling reaction were
reported after Kende's disclosure, including several exciting uses of low valent Ti-induced ring closures in the context of natural product syntheses. For example, the final step in Dauben's elegant synthesis of (+)-kempene-233 is a McMurry cyclization of a keto aldehyde that possesses other potentially reducible functional groups. In retrospect, the successful applications of the McMurry coupling reaction for the construction of a taxane derivative by Kende31 and in numerous natural product total syntheses32,33 reinforced the decision to utilize the McMurry cyclization in this synthesis.

Through the reaction sequences described, gram quantities of dialdehyde 7 could be procured. As a result, the crucial McMurry pinacol coupling could be evaluated carefully so that optimum conditions for ring closure could be defined. After a good deal of systematic study, it was found that addition of dialdehyde 7 (in DME) by syringe pump to a solution of TiCl3•(DME)1.5 (11 equivalents) and Zn–Cu couple (26 equivalents) in DME at 70°C results in the formation of cis-diol (±)-29 in 23% yield. The rather low yield in this reaction reflects the inherent difficulties in forming highly functionalized and strained medium rings. Fortunately, sufficient quantities of (±)-29 could be accumulated so that the synthesis could continue.

Although the diastereoselective transformations summarized in Scheme 4 have secured correct relative stereochemical relationships, all of the chiral intermediates described thus far are racemic. We were cognizant of the possibility that our racemic synthetic material could be resolved after the introduction of an enantiomerically pure taxol side chain. Nonetheless, the vicinal hydroxyl groups in (±)-29 presented a very convenient opportunity to carry out a resolution at this stage of the synthesis. To this end, addition of (1S)-(−)-camphamic chloride (30)21b,34 to a solution of (±)-29 and triethylamine in CH2Cl2 affords an equimolar mixture of C-9 camphanate diastereomers (31 + diastereoisomer, 86% total yield) (see Scheme 5). The selective derivatization of the apparently more hindered C-9 hydroxyl in this reaction is somewhat surprising. Gratifyingly, the 1:1 mixture of monocamphanate diastereoisomers can be resolved chromatographically and, on the basis of an X-ray crystallographic analysis, it was possible to assign absolute stereochemistry to both isomers. The action of basic methanol on camphanate ester 31 cleaves the ester linkage and liberates stereoisomerically pure diol (+)-29 (90% yield).

Whereas treatment of (±)-29 with camphamic chloride achieves the selective esterification of the hindered C-9 hydroxyl group, the action of acetic anhydride on (±)-29 results in the equally selective acetylation of the C-10 hydroxyl group! It is not clear to what this discrepancy should be attributed, so we will not offer a rationalization here. This unexpected result is, however, most gratifying because TPAP–NMO oxidation27 of the remaining C-9 hydroxyl furnishes keto acetate 6 (88% overall yield). You will note that the contiguous keto and acetate functions in 6 are both expressed in the natural product.
Scheme 5. Resolution of intermediate (±)-29 and synthesis of intermediate 33.

With an adequate solution to the B-ring problem, the unresolved issues associated with ring C can now be addressed. Intermediate 6, containing an appropriately placed double bond, seems poised for the requisite oxetane annulation. As it turns out, the C-ring problem was approached from many different vantage points, and many unsuccessful experiments were performed. Nonetheless, it was eventually found that intermediate 6 could be converted into 32 through an intermolecular hydroboration/oxidation reaction (see Scheme 5). In the event, treatment of 6 with excess BH₃·THF, followed by a standard oxidative workup, furnishes a 3:1 mixture of C-5 and C-6 alcohol regioisomers in favor of the desired alcohol 32 (55% total yield + recovered starting material). While the stereochemistry of the C-6 regioisomer remains unassigned, that of
the C-5 α isomer was established by conversion to and correlation with a degradation product. From intermediate 32, the construction of the oxetane ring only requires a few functional group manipulations. Cleavage of the isopropylidene ketal in 32 with HCl in methanol, followed by selective acetylation of the primary hydroxyl group, furnishes intermediate 33 in 76% overall yield.

Hydrogenolysis of the C-7 benzyl ether, followed sequentially by selective triethylsilylation of the newly liberated C-7 hydroxyl and mesylation of the C-5 secondary hydroxyl, provides compound 34 in 60% overall yield (see 33 → 34, Scheme 6). On the basis of Potier’s studies, it was hoped that the C-20 hydroxyl group,

Scheme 6. Synthesis of taxol (1).
derived from cleavage of the C-20 acetate in 34, could be induced to displace the proximal C-5 mesylate in an intramolecular fashion. To this end, selective cleavage of the C-20 acetate in 34 can be brought about with basic methanol at 0°C to give the desired diol mesylate. When a solution of the latter substance and excess tetra-n-butylammonium acetate in butanone is heated to reflux, the desired intramolecular etherification reaction takes place, with inversion of configuration at C-5, to give hydroxy oxetane 35 in 72% yield. Despite its hindered nature, the C-4 tertiary hydroxyl group in 35 can be acetylated smoothly with acetic anhydride and 4-dimethylaminopyridine (4-DMAP) to give compound 5 (see Scheme 1) in 94% yield.

Throughout the course of this synthesis, the five-membered carbonate ring has served several important functions. In addition to its passive role as a protecting group, the carbonate ring confers rigidity to pinacol cyclization precursor 7 and forces the two aldehyde carbonyls into reasonably close proximity; although an examination of molecular models suggested that this should have a very favorable effect on the cyclization event, there is certainly room for improvement in this most crucial stage. It was also anticipated, on the basis of chemical degradation/reconstitution studies, that the carbonate ring could also serve as a direct precursor to taxol’s C-1 hydroxy and C-2 benzoate functions (see Figure 1). Indeed, treatment of compound 5 with phenyllithium at −78°C in THF furnishes, in 80% yield, the desired hydroxybenzoate ester 4 (Scheme 6). It is certainly noteworthy that the other three carbonyl groups and the oxetane ring are impervious to the action of phenyllithium under these conditions. The compatibility of the C-9 keto function, the two acetate esters, and the oxetane ring with this transformation presumably reflects the highly effective steric shielding that these groups experience within the crowded taxoid framework.

All that remains before the final destination is reached is the introduction of the C-13 oxygen and attachment of the side chain. A simple oxidation of compound 4 with pyridinium chlorochromate (PCC) provides the desired A-ring enone in 75% yield via a regioselective allylic oxidation. Sodium borohydride reduction of the latter compound then leads to the desired 13α-hydroxy compound 2 (83% yield). Sequential treatment of 2 with sodium bis(trimethylsilyl)amide and β-lactam 3 according to the Ojima–Holton method provides taxol bis(triethylsilyl ether) (86% yield, based on 89% conversion) from which taxol (1) can be liberated, in 80% yield, by exposure to HF-pyridine in THF at room temperature. Thus the total synthesis of (−)-taxol (1) was accomplished.
34.4 Conclusion

Taxol stood for more than two decades as a challenge to synthetic chemists, pointing out the weakness of the science of organic synthesis to construct highly oxygenated and congested polycyclic frameworks. With this synthesis and those reported by the Holton\textsuperscript{7} and Danishefsky\textsuperscript{8} groups a major barrier has been overcome and new vistas opened. A large number of designed taxol analogs were synthesized through application of the technology developed in this synthesis, and new strategies and tactics for chemical synthesis were established. Amongst the most interesting features of this route to taxol are: (a) the boron-mediated Diels–Alder reaction to provide an entry into the highly functionalized C-ring framework; (b) application of Shapiro and McMurry reactions to couple the two ring systems and effect closure of the eight-membered ring; and (c) the regio- and stereocontrolled incorporation of the oxygen functionalities in the eight-membered ring of taxol.

Of course, one should realize that, while the approach described above appears to have proceeded smoothly, much unsuccessful but often interesting work remains untold in this chapter. For a number of unsuccessful attempts, the reader is referred to the original papers,\textsuperscript{5,11,13,21a,b,24} but even there much of the drama and excitement remains obscure. Only those who were there at the time will ever know the entire story.

References

1117.


17. For a review of ketene equivalents, see: (a) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. Synthesis 1977, 289; (b) See also, De Lucchi, O.; Pasquato, L. Tetrahedron 1988, 44, 6755.


22. For some excellent reviews of methodology for the construction of quaternary carbon centers, see: (a) Martin, S. F. Tetrahedron 1980, 36, 419; (b) Fuji. K. Chem. Rev. 1993, 93, 2037.


