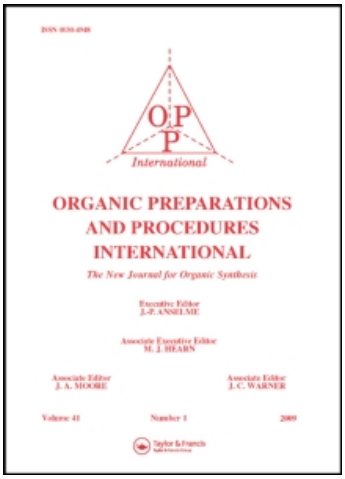

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TAXANE DITERPENE SYNTHESIS STRATEGIES. A REVIEW

Charles S. Swindell[a]
[a] Department of Chemistry, Bryn Mawr College, BrynMawr, PA

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Charles S. Swindell

Department of Chemistry
Bryn Mawr College
Bryn Mawr, PA 19010-2899

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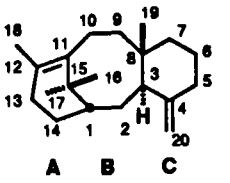
INTRODUCTION. THE TAXANE DITERPENES AND TAXOL

The taxane diterpenes[1] are a group of substances isolated from various yew (*Taxus*) species that, with few exceptions, share the carbon skeleton (**1**) indicated below. Although the naturally



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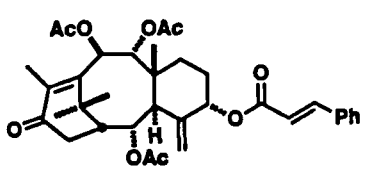
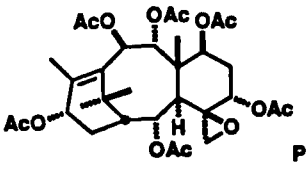
occurring compounds bear differing degrees of oxygenation, some structural subgroups may be discerned. For example, the taxane C-ring functionality increases in complexity from the simple allylic ester characteristic of taxinine,[2] through a more oxidized version represented by baccatin I,[3] to the elaborate 3-oxygenated oxetane incorporated in the C-ring of taxol.[4]

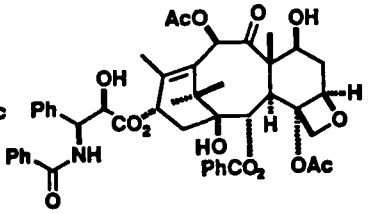
The structural challenge to contemporary organic synthesis methodology offered by these



TAXININE



BACCATIN I



TAXOL

natural products, and the medicinal imperatives that motivate much work in the field converge in the case of taxol.[5] Taxol is the most functionally and stereochemically complex of the taxanes. It exhibits clinically demonstrated activity against ovarian cancer[6] that is mediated almost certainly by its unique interaction with tubulin and tubulin-derived cellular structures.[7]

Although, as of this writing, only modest success in the total synthesis of naturally occurring taxanes has occurred, a vast array of synthesis strategies to the taxane skeleton has been reported. This phase in the development of taxane total synthesis, which has been witnessed over the past

decade or so, seems to be giving way to the application of some of these approaches to the construction of several key natural taxanes. Thus, it is a propitious time for the assessment of strategies for taxane construction. This review focuses on work directed at the tricyclic diterpenoid structure of the taxanes. Partial syntheses and studies directed toward ancillary features such as the taxol A-ring side chain and 3-oxygenated oxetane are not covered. Neither are covered approaches to bicyclo[5.3.1]undecane and bicyclo[6.4.0]dodecane systems that have been developed without regard to their involvement in taxane total synthesis efforts. Furthermore, routes to simple six-membered ring substances for which application to taxane synthesis is mentioned in the report without specification

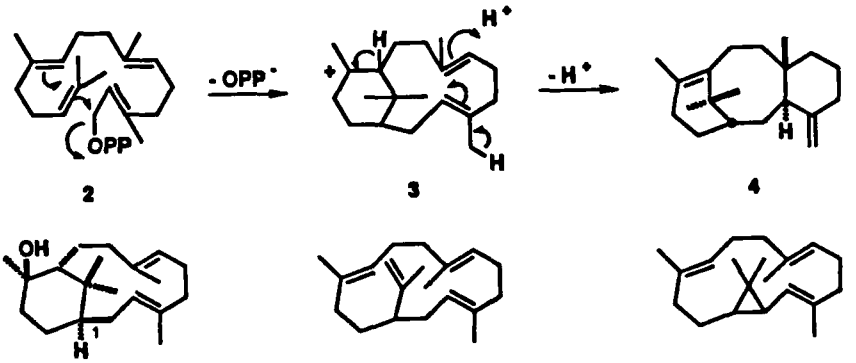


Fig. 1

of a taxane synthesis strategy are not included. Two partial treatments of taxane diterpene synthesis have appeared.[5,8]

I. LINEAR STRATEGIES

The complexity of the naturally occurring taxanes suggests that convergent synthesis strategies would be highly desirable. The fact that about half of the strategies reported to date may be classified as linear attests to the difficulty of developing effective convergent syntheses of the taxane carbon framework.

A. Biogenetically Modeled Strategies

1. A Biogenetic Proposal for the Taxane Skeleton

In 1966, Lythgoe[9] proposed a biogenetic scheme for the taxanes that involves the cyclization of geranylgeranyl pyrophosphate (2) depicted in Fig. 1. No experimental information verifying this proposal for taxane biosynthesis has appeared. Nevertheless, it is clear from Lythgoe's proposal that the taxanes might bear a biogenetic relationship to verticillol,[10] cembrene A,[11] and casbene.[12] However, it is worth pointing out that verticillol does not correlate configurationally with the taxanes at C-1. The suggestion that the taxanes are related to quassin also has been made,[13] and Potier[14] has made a proposal concerning the biogenesis of the taxanes, as well.

2. *Kato's Synthesis of Putative Biogenetic Precursors Possessing a seco-Taxane Skeleton*

Kato recognized that *seco*-taxane intermediates emanating from **3** and related to verticillol might lie along the biosynthetic pathway to the taxanes, and has reported two syntheses of such structures. In the first[15] (Fig. 2), Lewis acid mediated reaction of **5** and **6** furnished **8** as a mixture of two isomers; **7** appeared to be an intermediate in this process. Monocyclic **8**, in which the A-ring had been formed through a process mimicking the initial phase of the Lythgoe biogenetic hypothesis, could be transformed into **10**. Finally, macrocyclization of **10** gave crystalline *seco*-taxane **11** with undefined stereochemistry.

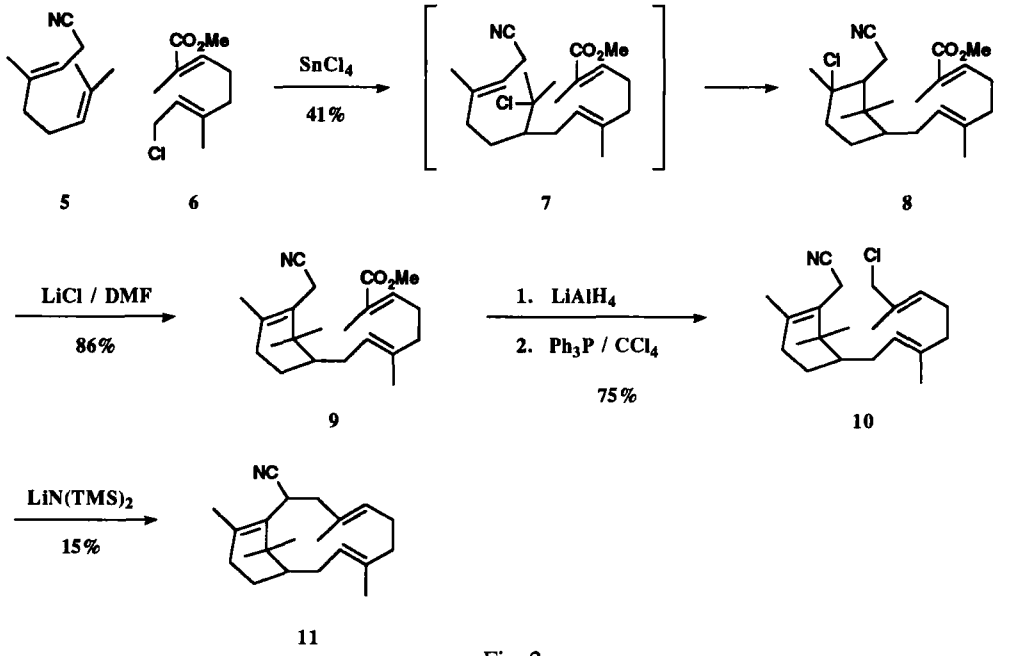


Fig. 2

Kato employed the same strategy in his second *seco*-taxane synthesis[16] (Fig. 3). Neryl sulfone **12** was converted to **14**, which, upon exposure to strong base, underwent allylic bromide double bond isomerization (to give **15**) and subsequent macrocyclization. Presumably, the isomerization of **14** to **15** was mediated by an allylic lithium species derived from the allylic bromide moiety, and occurred because the macrocyclization of **14** is unexpectedly slow. The product **17** was a geometrical isomer of *endo*-anhydroverticillol[10] about the C-7(8) double bond. When geranyl phenyl sulfone (E double bond analogue of **12**) was involved in the same initial two steps, **13** and its *cis*-substituted cyclohexene isomer were formed. The transformation of the latter into **18** was accomplished, but **18** could not be induced to undergo macrocyclization through intramolecular alkylation.

3. *Frejd's Approach: Cyclization to Form the A-Ring*

Frejd has reported[17] a 23-step enantioselective synthesis from L-arabinose of taxane A-ring synthon **40** (Fig. 4). Like the Kato syntheses, the final stage of this sequence is modeled after the

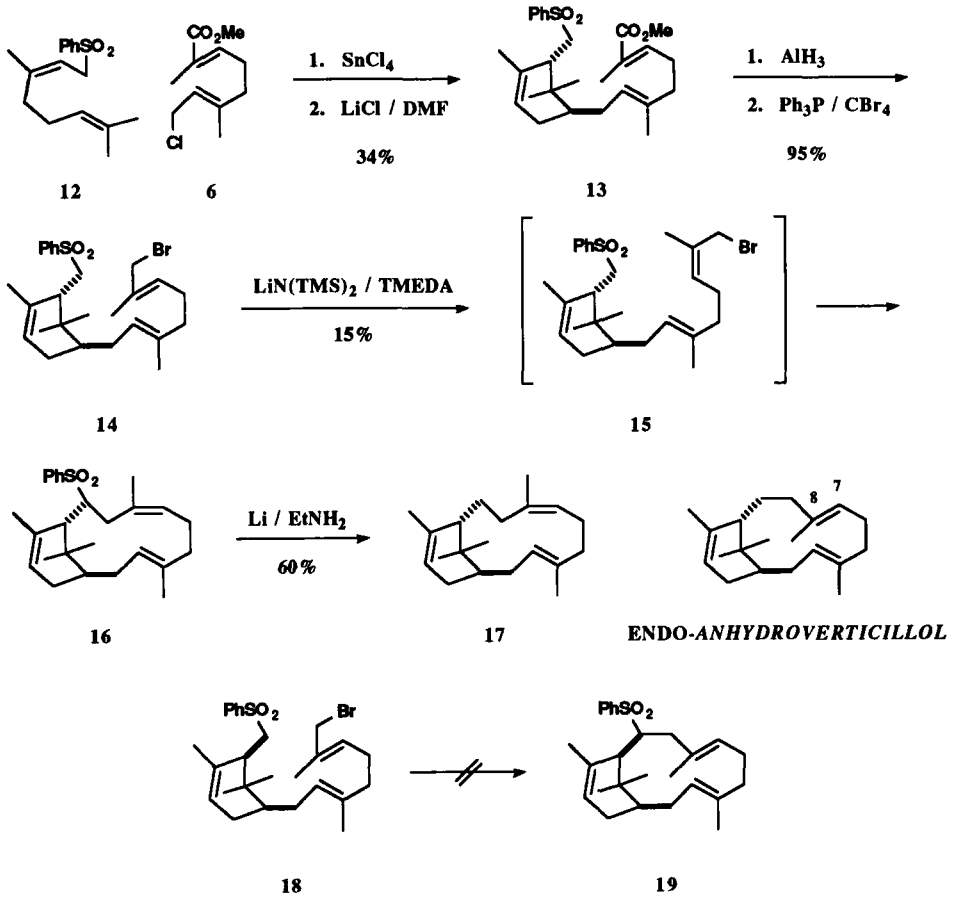


Fig. 3

Lythgoe biogenetic proposal for the taxane A-ring. L-Arabinose was converted to **20** through a known five-step operation. Swern oxidation, reductive epoxide opening, and hydroxyl protection then led to **21**. To install a progenitor of the exocyclic olefin compatible with hydrogenolytic debenzylation, **21** was converted to β-lactone **22**. Deprotection and oxidation of the latter was followed by pyrolytic extrusion of carbon dioxide to furnish the olefin **23**. Intermediate **23** was sequentially transesterified to the ring-opened isopropyl ester, protected, and subjected to a Claisen condensation to deliver **24**. A silylmethyl substituent was incorporated through nickel-catalyzed chemistry. Primary hydroxyl deprotection and Sharpless epoxidation then produced **26**. Finally, the biomimetic ring closure was reached when acid treatment of **26** followed by acetonide formation furnished the exocyclic double bond regioisomer of **27**. Base-induced isomerization then produced **27** itself. Frejd had previously shown[18] that analogues of **26** lacking the trimethylsilyl group and having the alternative double bond geometry failed to cyclize to substances like **27**. Although the Frejd approach has the potential of providing optically active taxanes, the synthetic plan beyond **27** will need to be rather

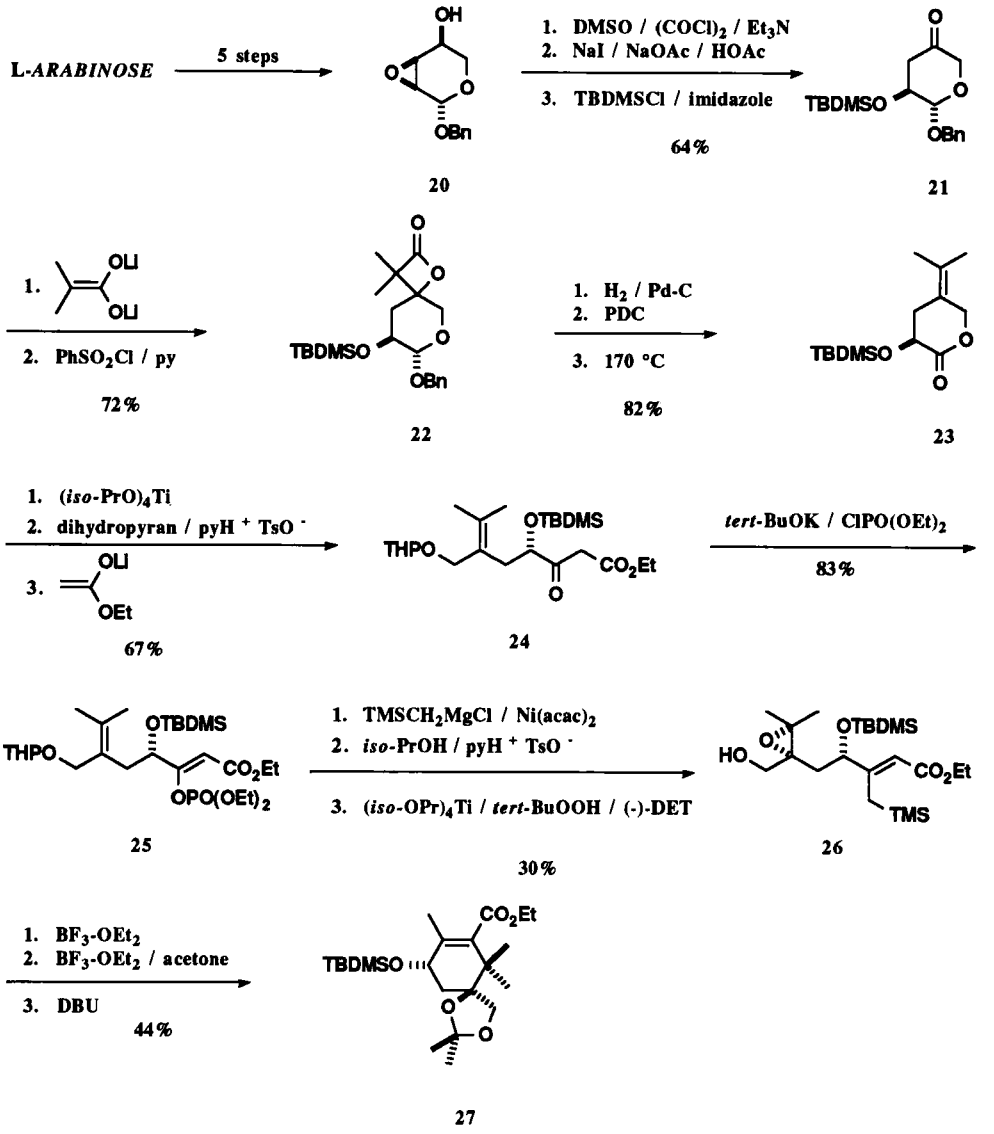


Fig. 4

efficient for it to compete with some of the strategies described below.

4. *Pattenden's Approach: Synthesis of Verticillene and Attempted Transannular Cyclization to Form the C-Ring*

Pattenden has reported a synthesis of verticillene (Fig. 5),[19,20] which, like the targets addressed by Kato, is characterized by a *seco*-taxane skeleton. However, Pattenden's intention was to employ verticillene in a test of the latter phase of the Lythgoe hypothesis, which addresses the formation of the taxane C-ring. Dihydroresorcinol derivative **28** was converted to **29** by enolate alkylation

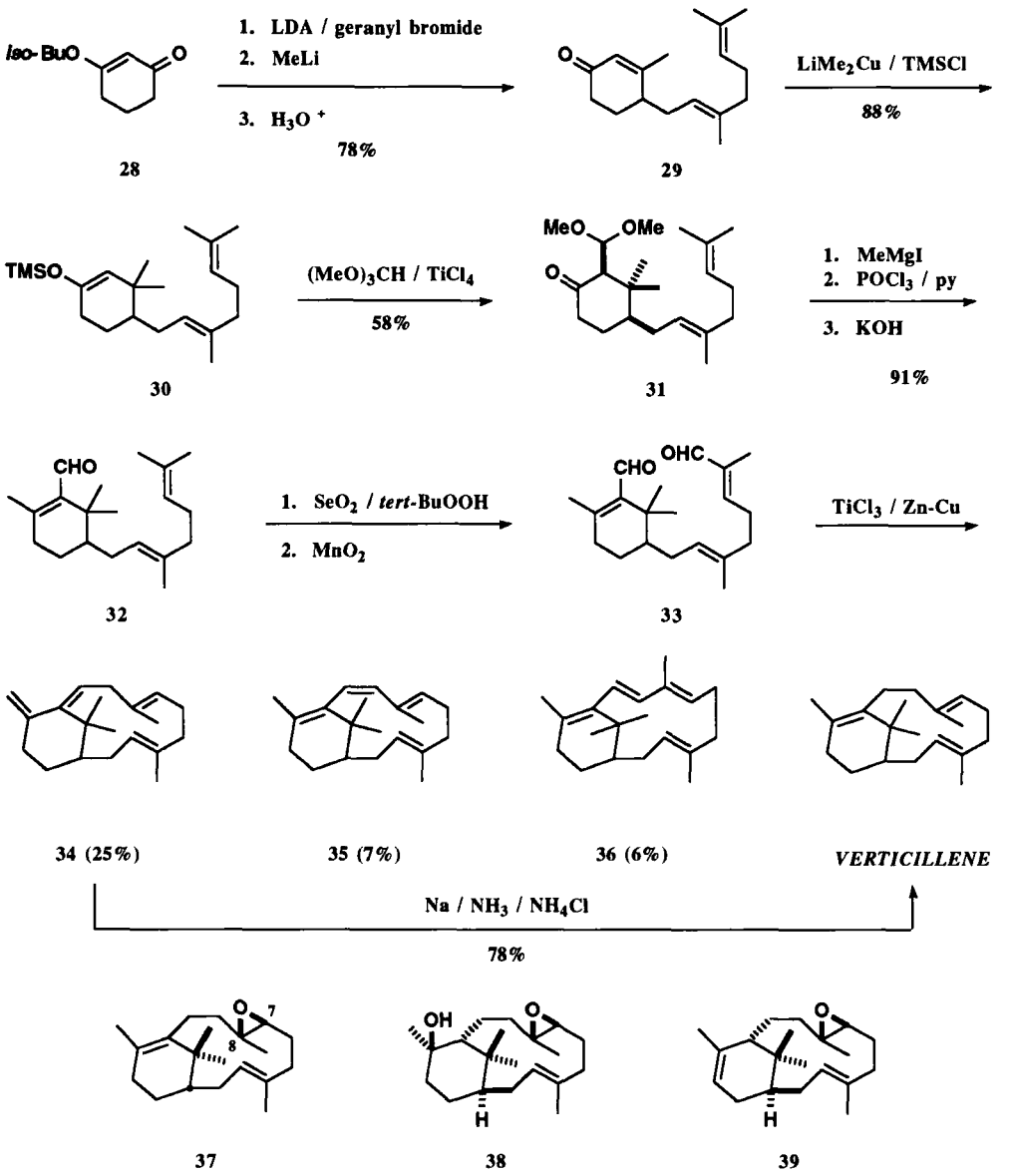


Fig. 5

and application of the Stork β-substituted enone synthesis. Cuprate addition and enolate silylation led subsequently to **30**. Upon exposure to trimethyl orthoformate and a Lewis acid, **30** afforded **31**. The latter intermediate was transformed through a series of conventional operations into critical dialdehyde **33**. Macrocyclization of **33** by means of reductive carbonyl coupling gave hydrocarbons **34-36**. Pattenden suggested that major product **34** was formed through [1,5] sigmatropic shift of hydrogen in primary product **35** driven by migration of the bridgehead double bond into the larger ring. In any case, verticillene could be prepared from **34** by its dissolving metal reduction.

Pattenden reasoned that verticillene was a likely intermediate in the biosynthesis of the taxanes, and that it or a structural relative might undergo transannular cyclization to the taxane skeleton upon treatment with acid.[19,20] However, exposure of verticillene to BF_3-etherate failed to vindicate this notion, and led to decomposition under various conditions. Likewise, epoxides **37-39**, in which the A-ring structural parameters are varied and BF_3 complexation would occur at the C-7(8) locus, would not undergo transannular cyclization. Pattenden concluded that the biosynthesis of the taxanes, if it followed the Lythgoe proposal, was likely to be more subtle than it seemed, since the closure of the C-ring was not predisposed to occur in putative *seco*-taxane intermediates.

B. Intramolecular Diels-Alder Strategies

The occurrence in the taxane skeleton of the six-membered A and C-rings has inspired the development of intramolecular Diels-Alder strategies targeted at either ring.

1. Formation of the A-Ring

The A-ring with its bridgehead olefin is perhaps the most striking structural feature of the taxane diterpenes, and is the more obvious object of intramolecular Diels-Alder chemistry.

a. Shea's Approach

Shea's implementation of this route to the taxanes is an extension of work[21] in which he demonstrated that intramolecular Diels-Alder chemistry provides general access to structures with bridgehead double bonds in six-membered rings. In an early report, Shea described[22] the use of thermal chemistry in the synthesis of **46** and more relevant model **47** (Fig. 6). The synthesis of cycloaddition substrate **44** from **40** began by coupling of the latter with the indicated Grignard reagent. Intermediate **42** was then metalated and condensed with acrolein to provide, after oxidation, **44**.

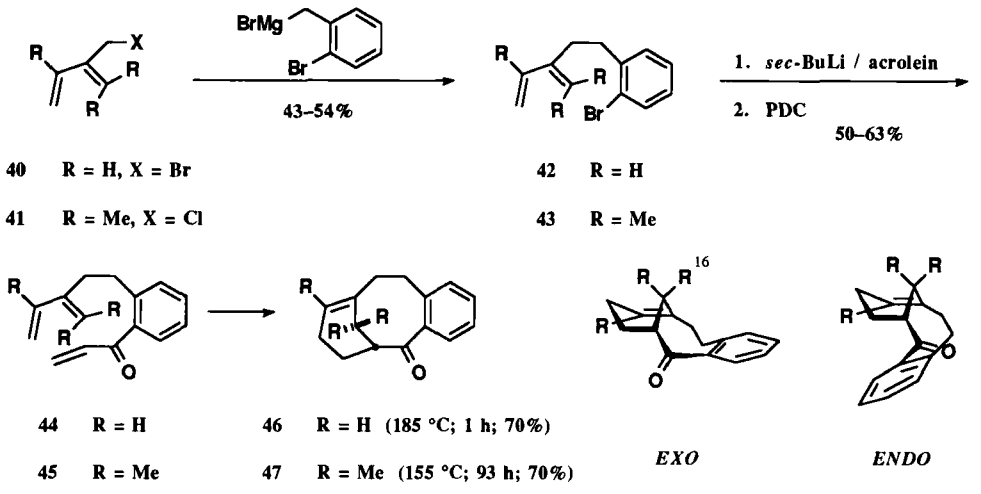


Fig. 6

Trimethylated diene system **41** was prepared from the corresponding allylic alcohol and then carried through the same sequence of operations to give **45**. The thermolysis of **44** succeeded in producing

tricyclic model **46** through the intramolecular Diels-Alder reaction of interest. Not surprisingly, the intramolecular cycloaddition of **45** was considerably slower than in the case of **44**, but proceeded in similar yield to create **47**.

With **46** and **47** in hand, Shea defined their conformational properties through the consideration of molecular models and NMR methods, including saturation transfer spectroscopy.[23] While tricyclic taxane model **46** prefers to exist largely in an exo conformation connected with the alternative, less abundant endo conformation (exo:endo = 88:12) by a barrier of 13.2 kcal mol^{-1}, the incorporation of the three methyl substituents characteristic of **47** reverses the conformational preference (exo:endo = 11:89). Furthermore, the barrier height is raised to 16.5 kcal mol^{-1}. The interaction between Me-16 and the aromatic ring is responsible for the diminished stability of the exo conformation for **47**. Armed with this information, Shea then established[24] that in the Lewis acid catalyzed version of the transformation of **45** into **47** (Et_2AlCl; 90%), which was carried out at temperatures sufficiently low that the conformational mobility of **47** was negligible, there is a pronounced kinetic preference for the formation of the endo conformer (k_{endo}/k_{exo} = 70 at -70°C).

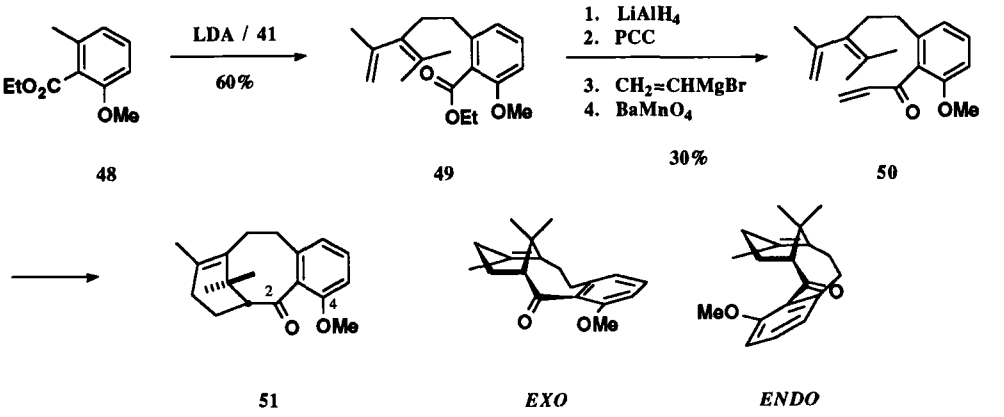


Fig. 7

Thus, the energetic ordering of the intramolecular Diels-Alder reaction transition structures ($\Delta\Delta G^{\neq}_{-70°C}$ = 1.70 kcal mol^{-1}) parallels the energetic ordering of the product ground states ($\Delta\Delta G°_{25°C}$ = 1.24 kcal mol^{-1}). Shea has also reported the catalyzed conversion of **44** to **46** (Et_2AlCl; 71%).[25]

Continuing the above theme, Shea investigated[26] a related series of experiments focused on methoxy-substituted intramolecular Diels-Alder substrate **50** (Fig. 7). Lithiation of the benzylic site in **48** and alkylation with diene chloride **41** produced **49**. A sequence of four adjustments to the original ester carbonyl then led to **50**. Cycloaddition substrate **50** could be transformed in 80% yield into **51** by thermolysis at 150 °C for 70 h. Remarkably, the two atropisomeric products, *exo*-**51** and *endo*-**51**, underwent no detectable interconversion at room temperature. Their independent isolation and characterization, including X-ray crystallographic analyses, were, therefore, possible. Equilibration of the atropisomers of **51** could be effected at 150°C whereupon the *endo*-**51**/*exo*-**51** ratio was

observed to be 2.78 ($\Delta\Delta G°_{150\,°C}$ = 0.86 kcal mol^{-1}). Upon exposure of **50** to $ZnCl_2$ at room temperature, *endo*-**51** was formed with a kinetic selectivity of at least 200:1 ($\Delta\Delta G^{\neq}_{25\,°C}$ > 3.15 kcal mol^{-1}). Although in general terms the behavior of the methoxy aromatic system was similar to that of the simpler one in Fig. 6, the presence of the *ortho*-methoxy substituent leads to a much greater barrier to conformational interconversion. As a consequence, a more effective energetic discrimination between the endo and exo Diels-Alder transition structures occurs. The methoxy group is of interest as an *entrée* to the C-ring functionality of the natural taxanes.

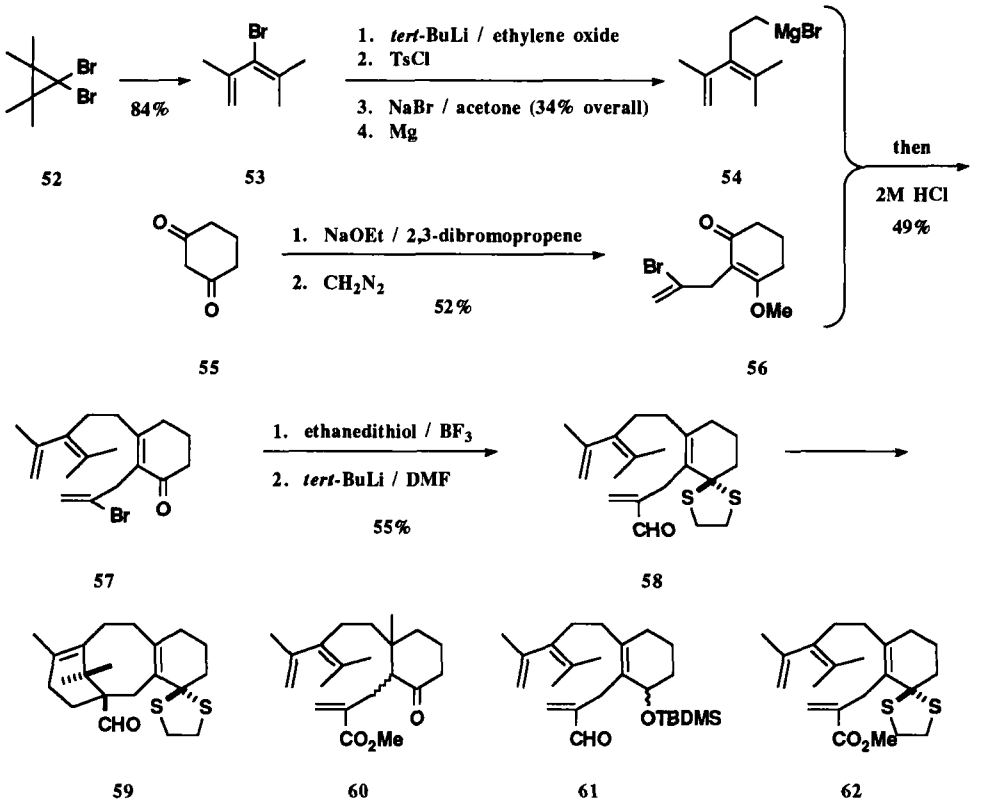


Fig. 8

Shea has explored also the application of intramolecular Diels-Alder chemistry to the construction of a tricyclic taxane ring system with a partially saturated C-ring[27] (Fig. 8). In this modification to his previous work, he abandoned the positioning at C-2 of the dienophile activating functionality. Pyrolysis of **52** gave bromodiene **53**, which, upon metalation, subsequent treatment with ethylene oxide, and functional group manipulation, furnished the bromide precursor to Grignard reagent **54**. In parallel, the alkylation of dihydroresorcinol, **55**, and *O*-methylation of the product afforded **56**. The addition of **54** to **56** followed by hydrolysis provided **57**. Carbonyl protection and attachment of the formyl dienophile activator then led to **58**. This intermediate could be converted to

taxane model **59** thermally (180 °C; 86 h; 12%) or by way of Lewis acid catalysis (Et_2AlCl; 30%). Although these yields are disappointing, the formyl group in **59** is well positioned to allow the incorporation of the bridgehead hydroxyl found in taxol. Systems **60-62** failed to undergo thermal or Lewis acid catalyzed intramolecular Diels-Alder cyclizations. Structure **59** possesses equally energetic exo and endo conformations analogous to those described above and separated by a barrier estimated to lie between 18 and 25 kcal mol^{-1}.

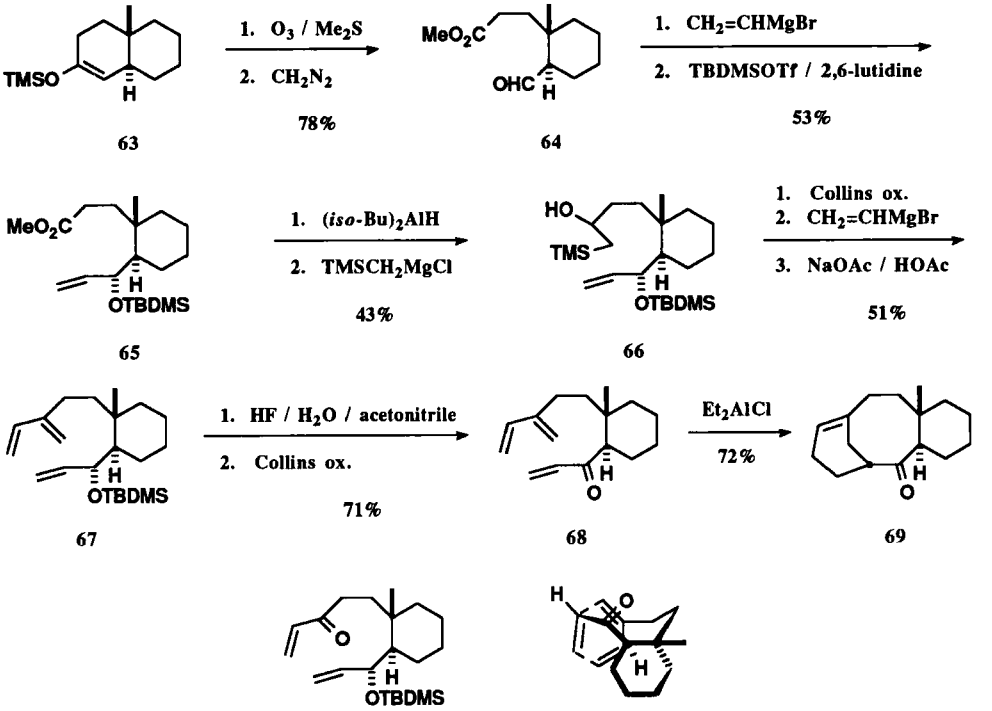


Fig. 9

Shea has investigated[28] the influence of the steric requirements of substituents at C-4 on the stereochemistry of the reduction of the C-2 carbonyl in structures analogous to **51**. The unnatural, β stereochemistry for the resulting C-2 alcohols is favored for small C-4 substituents, especially in $LiAlH_4$ reductions. Large substituents at C-4 lead to increasing amounts of the natural, α alcohols, an effect more pronounced when the reducing agent is (*iso*-Bu)$_2$AlH.

b. Jenkins' Approach

Jenkins has pursued, concurrently with Shea, a very similar strategy. His initial effort[29] was directed toward a tricyclic model devoid of the three methyl groups around the AB substructure, but possessing a saturated C-ring with stereogenic centers at C-3 and C-8. Beginning with known **63** (Fig. 9), ozonolysis and esterification provided **64**. The addition of vinyl Grignard reagent to the aldehyde carbonyl and protection of the resulting alcohol as a silyl ether gave **65**. Although of no

consequence to the outcome of the synthesis, this Grignard addition was highly diastereoselective. Jenkins assumed Cram selectivity in **65** (shown), but was unable to prove the stereochemistry of its precursor. The conversion of **65** to the related aldehyde through a (*iso*-Bu)$_2$AlH reduction set the stage for a sequence of operations designed to elaborate the requisite diene. In this regard, the Jenkins work differs from the Shea syntheses in that the latter involve installation of prefabricated diene units onto the C-ring. Another Grignard addition to the aforementioned aldehyde delivered **66**. Collins oxidation produced the corresponding α-silyl ketone, and a final Grignard addition gave an intermediate silyl alcohol. Exposure of that substance to acetate ion in acetic acid produced **67**, the result of a Peterson olefination. This route to the diene was required by the failure of **70** to enter into standard methylenation reactions. Intermediate **67** was then deprotected and the resulting material oxidized to provide **68**. Finally, the Lewis acid catalyzed Diels-Alder cyclization of **68** furnished **69** and completed the construction of Jenkins's first taxane model. The stereochemistry of **69** was established through X-ray crystallographic analysis, and must arise by way of transition structure **71** for the Diels-Alder reaction. Transition structure **71** is essentially similar to Shea's endo transition structures.

Jenkins next turned his attention to the preparation of a fully methylated model through the same strategy[30] (Fig. 10). Aldehyde **72**, previously synthesized from **65**, was subjected to a Grignard reagent addition–Collins oxidation sequence. Enone **70** had failed previously to undergo methylenation. To address this problem, Jenkins developed methodology for the construction of highly substituted dienes that is exemplified in the conversion of **73** to **74**. Addition to **73** of the indicated selenium-stabilized carbanion gave a hydroxy selenide that underwent elimination of the elements of phenylselenenic acid to give **75**. Trienone **75** then led in good yield to **76** through the key Diels-Alder reaction. Taxane model **76** was obtained as an oil so that NMR methods were relied on for the

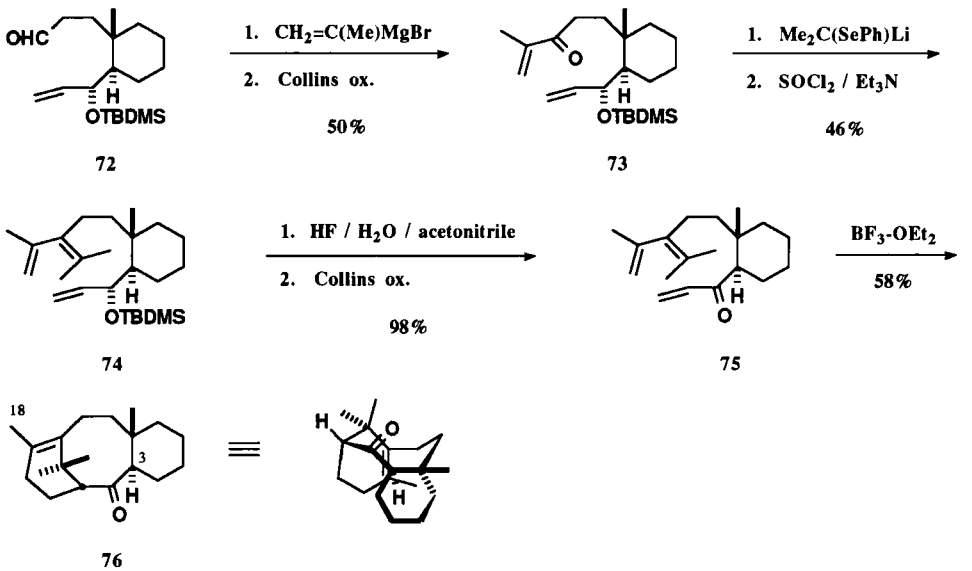


Fig. 10

establishment of its structure. In particular, an NOE enhancement involving Me-18 and the methine proton at C-3 suggested strongly that the stereochemistry of **76** is identical to that of **69**.

In view of Jenkins's and Shea's results, it would seem that the dienophile activating carbonyl is best placed at C-2. This allows it to adopt a favorable endo relationship (conventional Diels-Alder transition structure definition) with respect to its diene reaction partner. Indeed, the modest yields associated with the formation of Shea's model **59**, and the failure of **60-62** to enter into intramolecular Diels-Alder cycloadditions correlate with the inability of their activating carbonyl substituents to assume this orientation. However, it is possible that these results merely reflect the greater degree of substitution about the dienophile substructures, or the poorer activating ability of the formyl and carboxyl carbonyls.

2. *Formation of the C-Ring: Sakan's Approach*

Sakan[31] directed his attention to the formation of the C-ring through intramolecular Diels-Alder chemistry. In this approach, retrosynthetic bond scission was envisioned to occur between C-3 and C-8, and between C-6 and C-7. Thus, as conventionally drawn, the "lower" portion of the C-ring

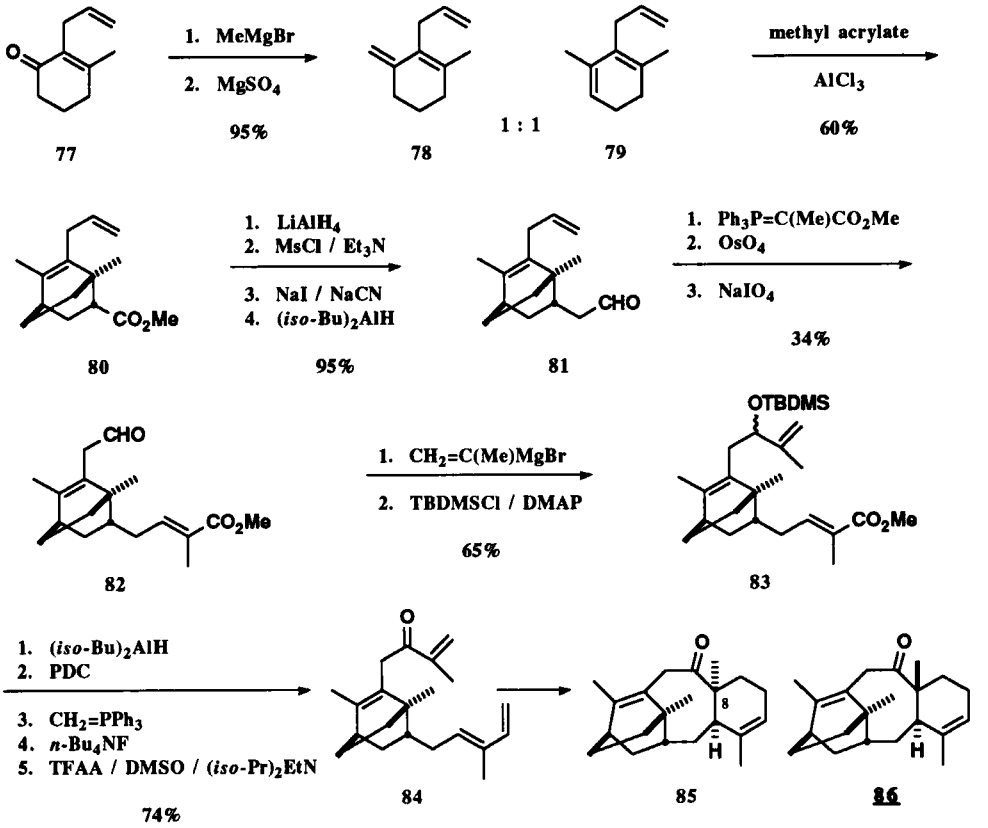


Fig. 11

piece (C-3 through C-6) would provide the diene unit, and the "upper" portion (C-7 and C-8) the

dienophile. A cycloaddition substrate of this kind would have its cyclohexene A-ring biased against the necessary axial orientation of the diene-containing chain. Thus, Sakan investigated a model in which the A-ring formed part of a conformationally immobile bicyclo[2.2.2]octane system. A modification to the two-carbon bridge that includes C-17 might make this strategy applicable to the natural taxanes

Sakan's investigation (Fig. 11) began with **77**, which was converted to a mixture of trienes **78** and **79** by addition of methylmagnesium bromide and subsequent dehydration of the resulting alcohol. Diene **79** was then selected from the mixture by Diels-Alder reaction with methyl acrylate to give **80**. It is not clear whether the 60% yield reported for this transformation was based on the amount of **79** available in the triene mixture, or if it resulted from the $AlCl_3$-induced interconversion of **78** and **79** under the reaction conditions (room temperature). If the former, the actual overall yield of **80** from **77** is half of that indicated. The homologation of **80** by way of a four-step sequence then led to **81**. Dienal **81** was subjected to a Wittig olefination followed by an oxidative cleavage of the less substituted double bond to produce aldehyde **82**. The addition of *iso*-propenyl Grignard reagent to **82** and protection of the allylic alcohol gave **83**. Following the conversion of the ester group into the corresponding aldehyde, Wittig olefination and sequential hydroxyl deprotection and oxidation yielded intramolecular cycloaddition substrate **84**. Sakan found that the Lewis acid catalyzed (Me_2AlCl) Diels-Alder reaction of **84** furnished not the expected taxane model **86**, but instead afforded, in 86% yield, C-8 epimer **85**. However, the uncatalyzed thermal (160 °C) reaction of **84** succeeded in delivering stereochemically correct **86**, in 70% yield. Both **85** and **86** were characterized through X-ray crystallography. Although Sakan offered no explanation for the contrasting stereochemical control under catalyzed and uncatalyzed conditions, presumably **85** arises from an endo transition structure and **86** from an exo one. Lewis acid catalysis of Diels-Alder reactions is known[32] to improve endo selectivity.

C. AB → ABC Strategies

A large number of approaches fit into this category. Not all have yet culminated successfully in syntheses of tricyclic models.

1. Late C-Ring Annulation

The novel taxane AB substructure has stimulated the development of several related strategies that target this part of the taxane skeleton before the more conventional six-membered C-ring is incorporated.

a. Martin's Approach

Martin has described[33] an entry into bicyclo[5.3.1]undec-7-ene AB intermediates that relies upon the anionic oxy-Cope rearrangement. The starting point for this three-step protocol is diketone **87** (Fig. 12). Wittig olefination of **87** led to enones **88**, which underwent organometallic addition to give **89** and **90**. Since only **89** is well suited for the sigmatropic rearrangement to **91**, Martin surveyed several metals, but failed to improve the stereoselectivity of this step. The final Cope rearrangement occurred through the action of KH at room temperature or above, leading to substances

92-95 depending on the substituent pattern in **89**. Tricycle **95** possesses the carbon connectivity of the taxane skeleton, but has its bridgehead double bond incorrectly located in the C-1(14) rather than the C-11(12) position. It is produced as one diastereomer, with the relative stereochemistry at the starred position being undetermined. The remaining relative stereochemistry depicted would be the result of a chair transition structure for the Cope rearrangement. In fact, intermediates like **92-94** are intended to behave as C-ring annulation substrates in Martin's strategy. Both **93** and **94** were isolated as mixtures of diastereomers, the latter mixture arising from the corresponding mixture of geometrical isomers at the stage of **89**.

b. Holton's Synthesis of a Tricyclic Model

Holton described (Fig. 13), in his initial report[34] on his synthesis efforts in the taxane area, a strategy that relies on late AB intermediates. Holton's route to the AB substructure is rather different from Martin's, and proceeds from an optically active starting material. (-)-β-Patchoulene

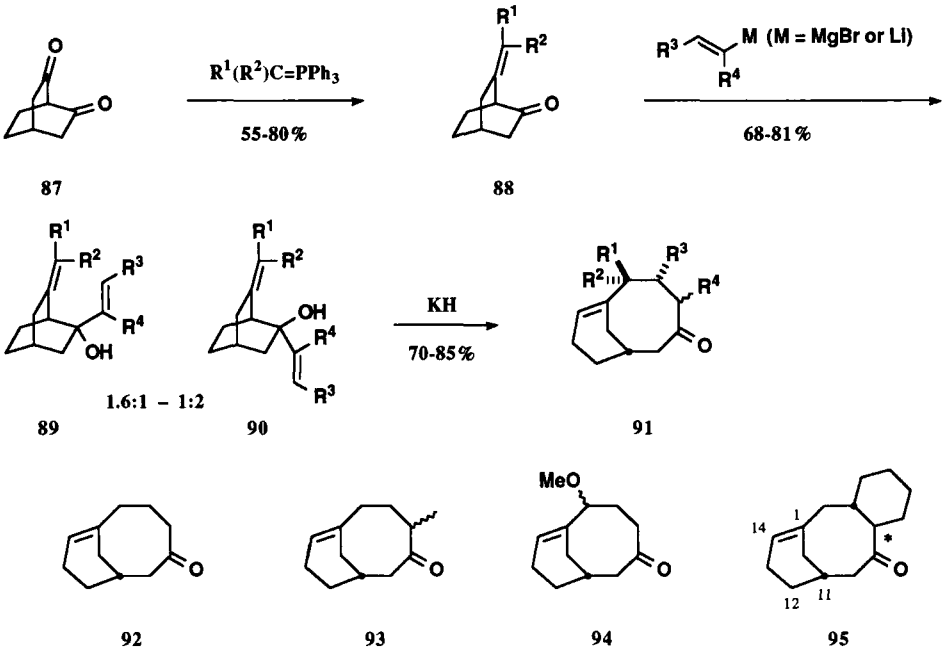


Fig. 12

oxide, available commercially or produced in two steps from naturally occurring patchouli alcohol, was isomerized upon treatment with BF_3-etherate to **96**. Titanium-mediated epoxidation of **96** gave epoxy alcohol **97**, but the latter underwent a fragmentation reaction in situ that completed the bridgehead olefin-containing AB portion of the taxane skeleton. Holton has demonstrated[35] the preference of epoxy alcohol fragmentation reactions like this one for *syn*-periplanar stereochemistry. Bicyclic intermediate **98**, thus obtained in two experimental operations, needed only to be joined with the

remaining C-ring to complete the taxane skeleton. This was effected by sequential hydroxyl protection, silyl enol ether formation, and Michael addition to the methyl vinyl ketone surrogate shown to provide **100**. The structure of **100** rested on an NMR shift reagent study carried out on it and related structures. Finally, **100** underwent aldol cyclization upon exposure to bromomagnesium diisopropylamide or bromomagnesium isopropylcyclohexylamide. Tricyclic taxane model **101** that formed was susceptible to retroaldol reaction, and was converted to more stable tricycle **102** by reduction in situ.

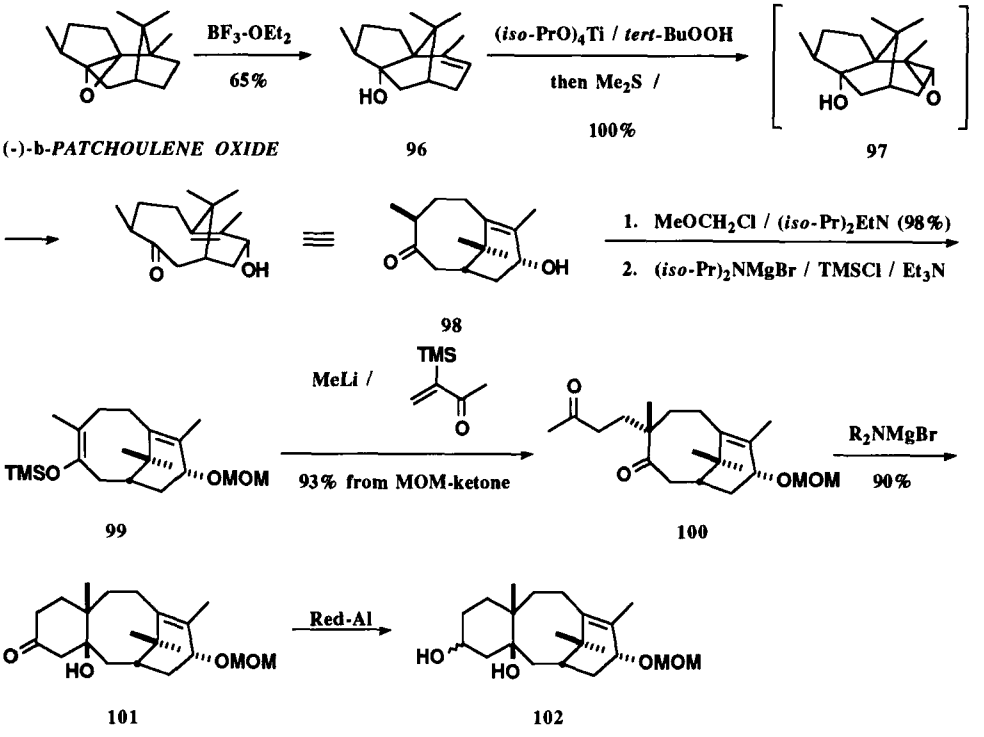


Fig. 13

As may be seen from Fig. 13, the most readily available enantiomer of β-patchoulene oxide leads through Holton's sequence to the *ent*-taxane skeleton. In principle, Holton's synthesis would provide taxanes with the correct absolute stereochemistry if it were carried out from (+)-β-patchoulene oxide. This starting material could be prepared by way of Büchi's route[36] applied to (-)-camphor.

c. Oishi's Approach

The application of new methodology for the formation of medium rings was the focus of Oishi and Ohtsuka's plan for taxane diterpene synthesis. They had previously demonstrated[37] a general strategy for eight to twelve-membered ring construction that relied on the contraction of lactam sulfoxides and sulfones through transannular acylation of their derived sulfur-stabilized carbanions. In its application to the taxane problem, this chemistry was employed in the formation of

the eight-membered rings of AB structures **114**, **126**, and **132**.

Initially, Oishi and Ohtsuka targeted **114**[38] (Fig. 14) as a relevant model for their efforts in the taxane area. β-Ionone could be converted to **103** through three operations on its side chain. The oxidation of **103** led to dienone **104**. Cross conjugated dienone **104** underwent a slow but efficient

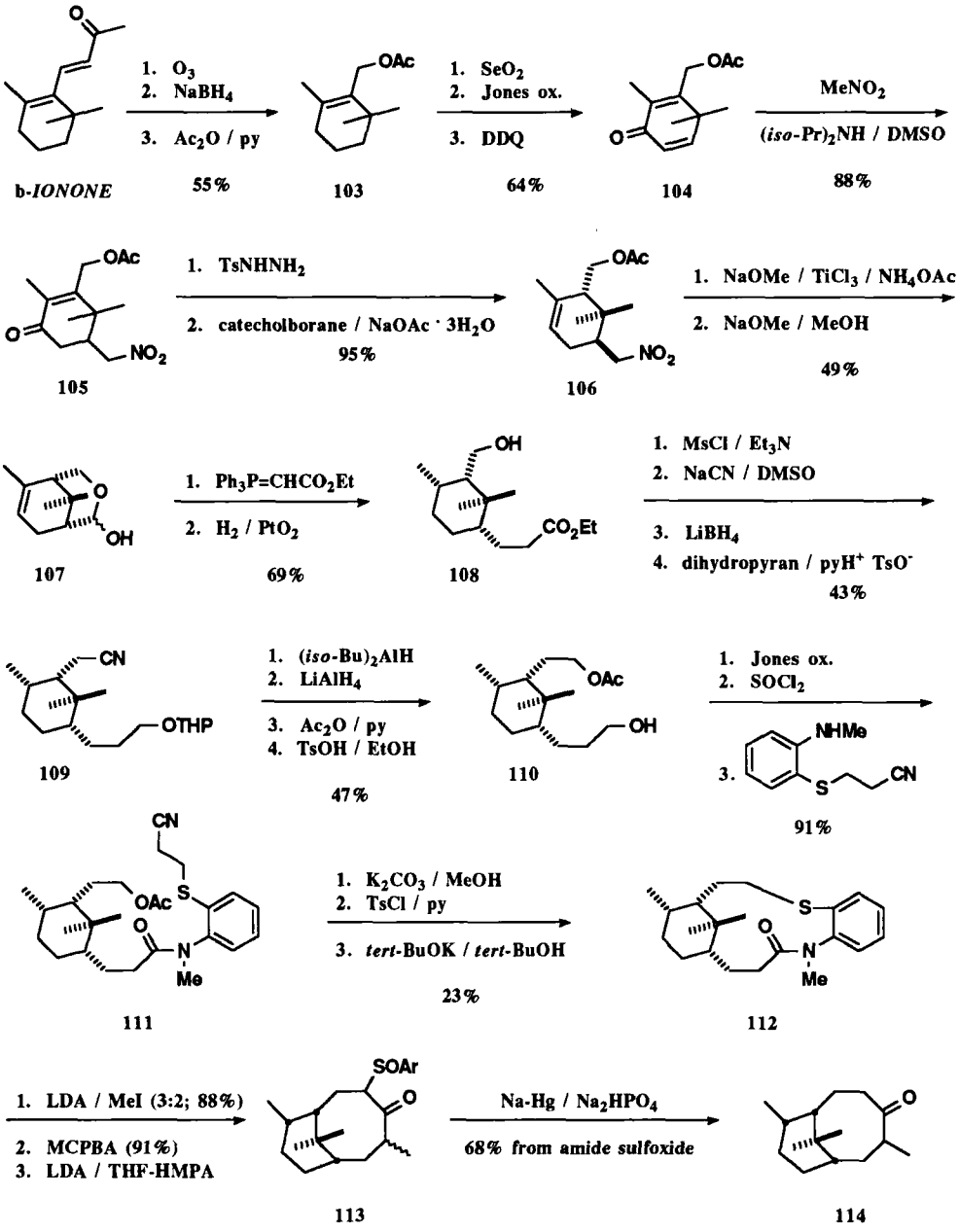


Fig. 14

Michael addition of nitromethane to deliver **105**. Following the conversion of **105** to its tosylhydrazone, catecholborane reduction of that substance installed the *trans*-1,3-relationship of pendent functionalized carbons in **106**. According to Oishi and Ohtsuka, the stereochemistry of this reaction arises from the 1,2-addition of hydride trans to the nitromethyl group. This action creates a cis H-N=N- fragment that delivers hydrogen to the γ-olefinic carbon from the same face of the six-membered ring. The conversion of the nitromethyl substituent to the corresponding aldehyde provided the opportunity to correct that stereochemical relationship to facilitate the intended eight-membered ring closure, but simple base-catalyzed epimerization of the acetate aldehyde that was formed from **106** failed. However, exposure to methoxide succeeded in delivering **107**. Oishi and Ohtsuka reasoned that intramolecular deprotonation α to the aldehyde moiety by the internal alkoxide created upon acetate cleavage was the key feature of this step. A sequence of conventional operations ensued from **107**, which led eventually to **110**. The selective 1,4-reduction of the Wittig product derived from **107** could not be effected, requiring its complete saturation to give **108**. This turn of events was unfortunate since it removed useful functionality from the A-ring.

At the point of intermediate **110**, the Oishi-Ohtsuka medium ring chemistry was staged. Oxidation of the terminal carbon in **110** followed by acid chloride formation and capture by the indicated amine sulfide gave amide **111**. The second operation preliminary to eight-membered ring closure was accomplished when acetate-masked **111** was converted to the corresponding tosylate, and the latter exposed to strong base. In this operation, the arylthiolate was revealed through retro-Michael liberation of acrylonitrile and served to displace tosylate to produce twelve-membered lactam sulfide **112**. Since the ring contraction protocol required that the amide carbonyl possess a greater degree of substitution on its α-carbon,[37] **112** was subjected to enolate methylation to give a mixture of epimers. The oxidation of the mixture of methyl epimers to the lactam sulfoxides preserved the diastereomeric ratio. This observation suggested that sulfur oxidation was stereoselective. Finally, ring contraction occurred upon treatment of the lactam sulfoxides with LDA, which caused deprotonation to occur α to the sulfoxide function and subsequent transannular acylation to produce **113**. Reductive removal of the sulfinyl group from **113** yielded **114** as a single diastereomer with unspecified stereochemistry at the stereogenic carbon α to the carbonyl.

Taxane AB structure **114** provided a model for the assessment of the Oishi-Ohtsuka strategy, but without functionality in the A-ring, it could not be regarded as a viable intermediate for natural taxane synthesis. To remedy this situation, Oishi and Ohtsuka pursued the synthesis of **126** and **132**.[39] The sequence that led to **126** (Fig. 15) began with **115**, available from α-ionone in two steps. Selective 1,4-reduction of **115** created an allylic alcohol that, upon Jones oxidation, gave **116**. Acetalization of this intermediate, and then application of the same dehydrogenation-Michael addition steps used in the construction of **114** produced **117**. Methyl ester **118** was available through a four-step procedure that culminated with reinstallation of the acetal. In order to permit eight-membered ring formation, the *cis*-arrangement of substituents characteristic of **119** was created through catalytic hydrogenation of **118**. Hydride reduction of the intermediate saturated ketone then

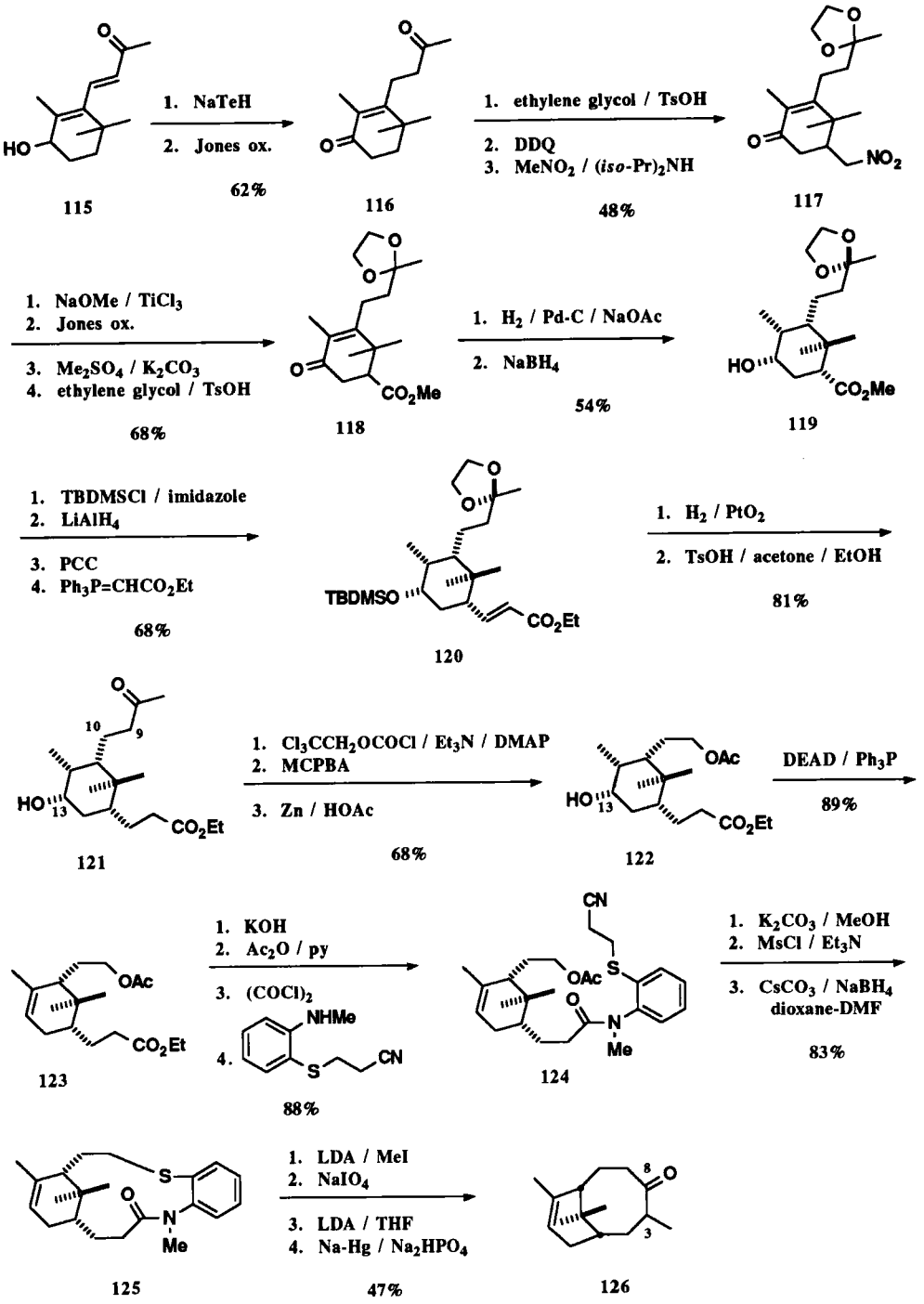


Fig. 15

followed. That **119** possessed an equatorial hydroxyl was evident from the coupling behavior exhibited by the oxygenated methine axial proton in the corresponding acetate. Reportedly, even K-Selectride reduction of the hydrogenation product derived from **118** formed **119**. If a common chair conformation is involved throughout, both borohydride and tri-*sec*-butylborohydride must deliver hydride axially, in these transformations. Straightforward chemistry then led from **119** through **120** to **121**. At this point, the four-carbon side chain was shortened to correspond to C-9 and C-10 in the taxane system. Baeyer-Villiger oxidation of **121** and its TBDMS and MOM derivatives failed to proceed cleanly. However, C-13 (taxane numbering) acyl derivatives of **121** entered into this process efficiently. Thus, the trichloroethyl carbonate of **121** suffered Baeyer-Villiger oxidation to give, after reductive deprotection, acetate **122**. The strategy that Oishi and Ohtsuka intended to follow from **122** now called for the application of their eight-membered ring formation sequence. Unfortunately, the attempted implementation of this plan failed. These workers suggested that the unfavorable but necessary chair inversion of structures such as **122** that would induce three groups on the cyclohexane ring to be *cis*-axial was at play in this failure. An alternative plan required that the configuration of hydroxylated C-13 be inverted to eliminate its interference. However, Oishi and Ohtsuka discovered in implementing this solution that, under Mitsunobu conditions, **122** underwent a facile and highly regioselective dehydration to give **123**. This structural change occurred even in the presence of carboxylic acid nucleophiles, and solved the conformational problem described above. Amide **124** was then prepared from **123**, and the former converted in excellent yield to **125**. Lactam

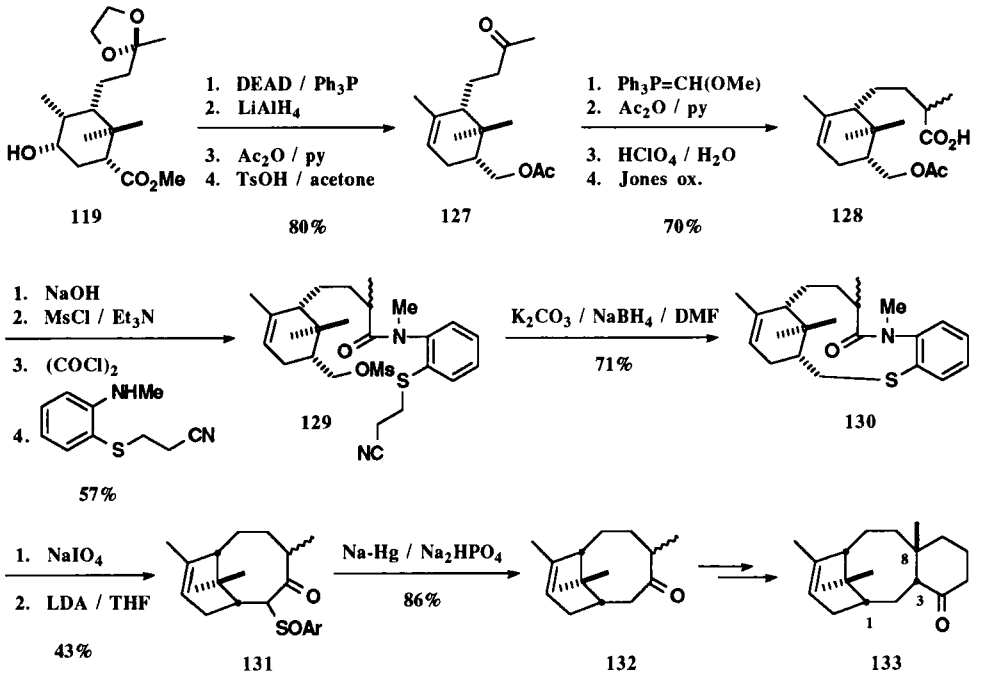


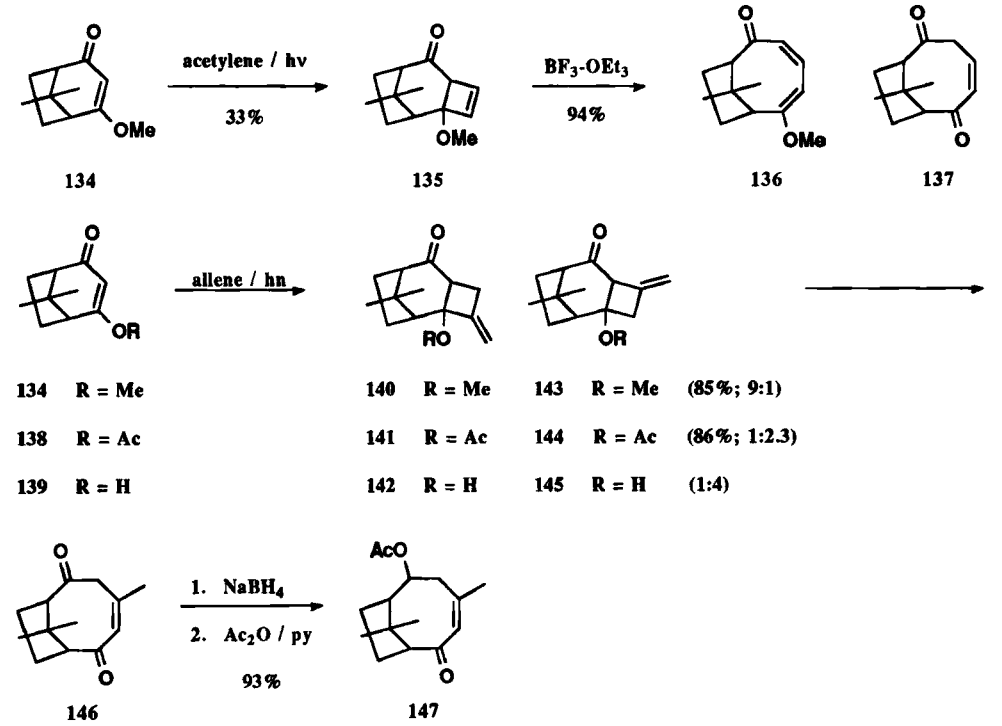
Fig. 16

sulfide **125** was methylated with complete stereoselectivity, and the alkylated product was converted to a mixture of two sulfoxides. Finally, ring contraction and reductive removal of the sulfur substituent gave **126** as a single diastereomer of undetermined relative configuration at C-3.

In completing a synthesis of **126**, Oishi and Ohtsuka had prepared a substance with A-ring functionality, but unfortunately, **126** possessed a methyl group at C-3 rather than C-8 as in the natural taxanes. A solution to this problem – the synthesis of **132** – emanated from previously encountered intermediate **119** (Fig. 16). Beginning with a Mitsunobu dehydration, **119** was converted to **127**. The extension of the top chain in **127** provided carboxylic acid **128**. Amide **129** was then available through steps similar to those employed previously and led ultimately to **130**. Lactam sulfide **130** was produced as a mixture of epimers (2:3), and the oxidation of **130** introduced another stereogenic center that led to the formation of three of the four possible diastereomers: one methyl epimer of **130** gave a single sulfoxide, while the other was oxidized with minimal selectivity (9:4). Separately, these three sulfoxides were subjected to LDA-induced ring contraction to give a total of seven of the eight possible diastereomers of **131** (three stereogenic sites with variable configuration); considerable variation of ring contraction yield with diastereomeric substrate was observed. Taking into account the distribution of isomers intervening between **130** and **131**, and the yields in which they each underwent the reactions involved, the composite yield indicated can be calculated. Finally, the stereochemical issues were greatly simplified with the reductive transformation of **131**, as a pooled mixture of diastereomers, into **132**. The latter was obtained as a 5:3 mixture of separable epimers at the stereogenic site α to the carbonyl, their respective configurations at that site being undetermined. Oishi and Ohtsuka have reported,[8] without specifying the steps involved, that AB intermediate **132** could be converted to **133**, which was characterized by X-ray crystallography. However, they were unable to effect the epimerization of **133** at C-3 that would be necessary to establish the correct taxane relative stereochemistry at C-1, C-3, and C-8.

d. Fétizon's Second Approach

Many of the reported taxane synthesis strategies rely on fragmentation chemistry for the formation of the eight-membered ring. Fétizon employed this tactic in one of his approaches to the taxane skeleton. He investigated first a series of simple model systems with contracted A-rings[40] (Fig. 17). β-Diketone **139** and derivatives **134** and **138** were available from α-fenchol. In the case of **134**, [2+2] photocycloaddition with acetylene provided **135**, which underwent a reaction with BF_3-etherate to deliver retroaldol product **136** accompanied by its hydrolysis product **137** (1:1). As these structures lacked the requisite C-19 methyl group, the [2+2] photocycloadditions of **134**, **138**, and **139** with allene were carried out. Enol ether **134** delivered largely **140**, regioisomerically incorrect for a natural taxane synthesis. Nevertheless, minor photoproduct **143** led in 92% yield to **146** upon treatment with BF_3-etherate. Acetate **138** gave a more favorable mixture of regioisomeric photoproducts **141** and **144** than did **134**. When exposed to ammonia in methanol, the latter underwent competitive conversion to **146** and elimination of acetic acid (latter product not shown; 1:1; 70% combined yield). Finally, in the most efficient process, the photoreaction of **139** with allene gave mainly **145**,



134 135 136 137

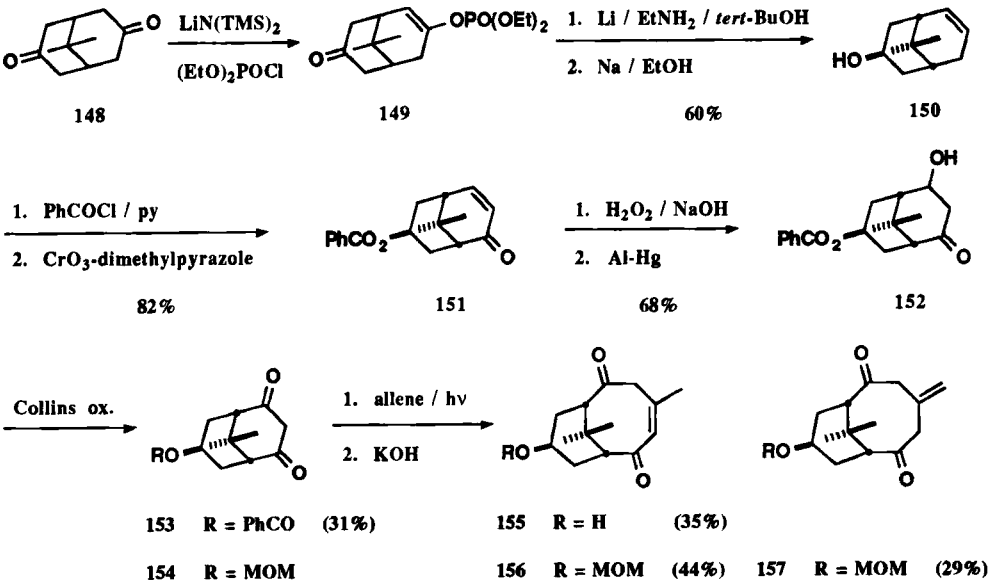
134 R = Me 140 R = Me 143 R = Me (85%; 9:1)

138 R = Ac 141 R = Ac 144 R = Ac (86%; 1:2.3)

139 R = H 142 R = H 145 R = H (1:4)

146 147

Fig. 17



148 149 150 151 152

153 R = PhCO (31%) 155 R = H (35%)

154 R = MOM 156 R = MOM (44%) 157 R = MOM (29%)

Fig. 18

which was converted to **146** by treatment with BF_3-etherate (70%) or with KOH (52%).[41] Fétizon reported[40] that the borohydride reduction of **146** proceeded to give, after acetylation, a single diastereomer of **147**.

A more substituted system was pursued next by Fétizon (Fig. 18). Enol phosphate **149**[42] was produced from bicyclic diketone **148**, and a two-step reductive transformation of **149** led to **150**.[42,43] Benzoylation and allylic oxidation applied to **150** gave **151**. The nucleophilic epoxidation of **151** produced an intermediate epoxy ketone that suffered reductive cleavage α to the carbonyl to yield **152**. Collins oxidation of **152** then gave photosubstrate **153**. When **153**, in the form of its enol tautomer, was subjected to [2+2] photocycloaddition with allene,[41] the resulting cyclobutane aldol was sufficiently stable that hydroxide treatment was required to transform it into **155**. Since the latter operation was accompanied by the saponification of the benzoate ester, Fétizon applied the last two steps to MOM-protected **154**. Double bond regioisomers **156** and **157** resulted in good combined yield, indicating that the regioselectivity of the preceding photoreaction exceeded that with benzoate **153**.

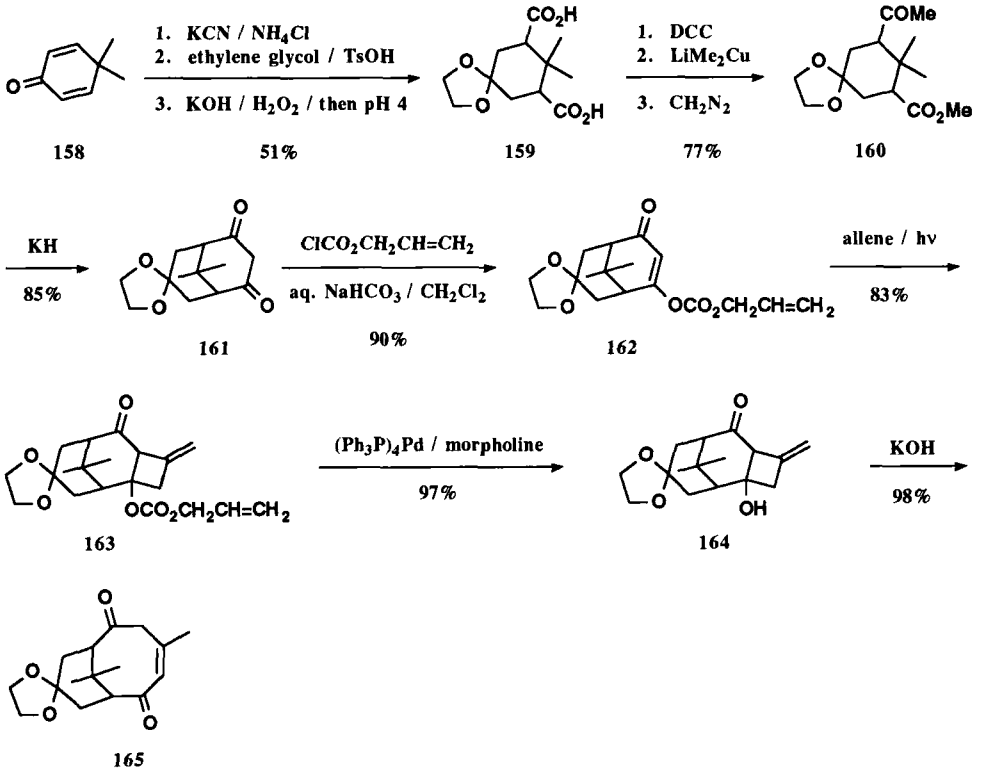


Fig. 19

e. Blechert's Second Approach

Blechert has investigated two chemically related approaches to the taxanes that differ

strategically in the way that the C-ring is incorporated. The failure of Blechert's first approach[44] (section II. B. 3.) to allow the installation of the C-19 angular methyl made necessary a second generation plan[45] that parallels that of Fétizon.[40] Blechert first assembled **161** from **158** through the initial seven-step procedure[44] depicted in Fig. 19. He found[45] that the success of subsequent [2+2] photocycloadditions that involved enol derivatives of **161** depended heavily on the nature of the enol derivative, as well as that of the olefin partner. Thus, the conversion of **161** to allyl carbonate **162** and photoaddition of the latter to allene provided **163** with considerable efficiency. The photoaddition of 1-methylcyclohexene to the benzyl carbonate analogue of **162** failed, while a similar reaction involving allene proceeded in poorer yield than that which produced **163**. The trichloroethyl carbonate derivative of **161** also proved to be unsuitable. The palladium-mediated deprotection of **163** led to aldol **164** whose stability was commensurate with the experience of Fétizon. Finally, hydroxide treatment of **164** produced AB intermediate **165**, structurally close to **155** and **156**. Interestingly, Blechert observed that when the palladium-induced deallylation-deprotection of analogues of **163** created cyclobutanols that fragmented spontaneously (in contrast to the behavior of **164**), the retroaldol enolate intermediates received the allyl unit back from the palladium. In this process, bond reorganization and a net loss of carbon dioxide resulted.

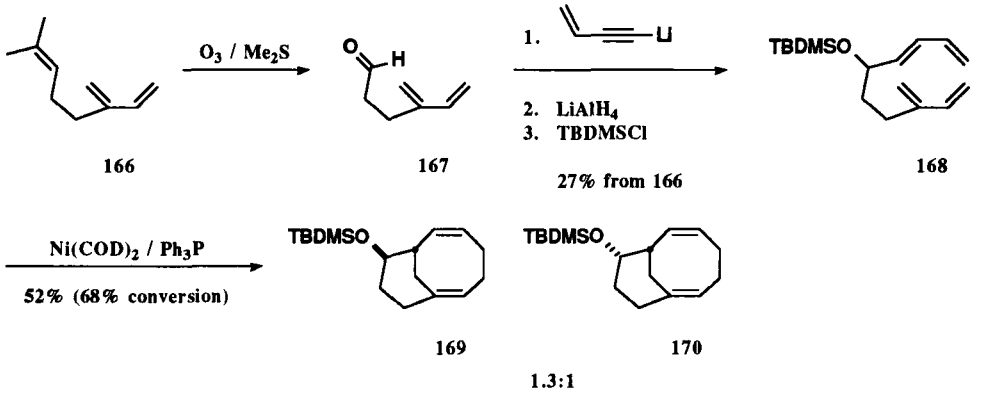


Fig. 20

f. Wender's C-Ring Annulation Approach

Wender has developed a new approach to the construction of polycycles possessing eight-membered rings based on the nickel-catalyzed intramolecular cycloaddition of tethered 1,3-diene units.[46] One attractive feature of this approach is that it may be applied to the formation of AB intermediates,[47] BC intermediates (see section I. D. 2.),[46-48] or, in principle, the one-step formation of the taxane tricycle from a suitable macrocyclic tetraene, although it is not clear that the last, yet unexplored approach would be a viable one. With respect to a route to AB substructures,[47] Wender has investigated the sequence depicted in Fig. 20. Commercially available myrcene (**166**) was transformed through a regioselective ozonolysis into **167**. The addition of the lithium acetylide shown to

167 followed by the hydroalumination of the propargylic alcohol formed in that process gave, after hydroxyl protection, cycloaddition substrate **168**. Treatment of **168** with phosphine-modified nickel(0) then produced a mixture of **169** and **170**. Although these two substances appear rather far

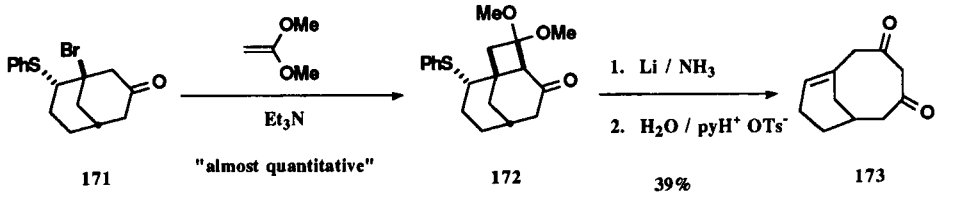


Fig. 21

removed structurally from the natural taxanes, Wender's strategy is especially noteworthy in that it is the only one that addresses the formation of the eight-membered ring through direct cycloaddition.

g. Kraus' Approach

Kraus has demonstrated[49] that in situ generated bridgehead enones can be useful intermediates for the preparation of substances resembling the AB portion of the taxane skeleton (Fig. 21). β-Bromoketone **171**, upon treatment with base, gave the corresponding bridgehead enone, which was intercepted by 1,1-dimethoxyethylene to produce **172**. The reductive fragmentation of **172** then installed the appropriate carbon connectivity for the AB system, and a final deacetalization afforded enedione **173**.

2. Initiation of C-Ring Attachment Prior to the Completion of the AB Substructure

All the strategies outlined in section I. C. 1. have involved or would require the annulation of the C-ring during the terminal phase of the synthesis and after the AB substructure is completed. A related series of strategies, including the only one culminating thus far in the formation of a natural taxane structure,[50] involves the initial attachment of the C-ring carbons before the elaboration of the complete AB substructure.

a. Yamada's Approach

Yamada's strategy[51] for the synthesis of taxinine (Fig. 22) fits into this category, but it has not been reported, as of yet, to proceed past *seco*-intermediate **186**. 5-Methyl-1,3-cyclohexanedione derivative **175**, prepared from parent compound **174** through its treatment with chloromethyl methyl ether and base, reacted by way of its lithium enolate with ethyl crotonate to give bicyclo[2.2.2]octane analogue **176**. As the unsaturated ester provides the C-15 carbon that would bear the geminal methyl substituents common to the taxane A and B-rings, a dimethyl acrylate or related compound would be required for the actual synthesis of taxinine. Functional group manipulation in **176** ensued to provide the related keto aldehyde, which suffered selective addition of allyl Grignard reagent and subsequent benzylation to produce **177**. Nonstereoselective epoxidation of the tethered olefinic group in **177** followed by base-induced ring closure led to **178**, as a mixture of stereoisomers. However, the stereochemical complexity of **178** was of no consequence as its hydroxymethyl group was incorporated in

the exocyclic methylene in intermediate **179**. Hydride reduction of **179**, protection of the resulting alcohol, reductive debenzylation, oxidation of the liberated secondary alcohol, and, finally, alumina-induced double bond isomerization terminated in **180**. The stereochemistry of the hydride reduction

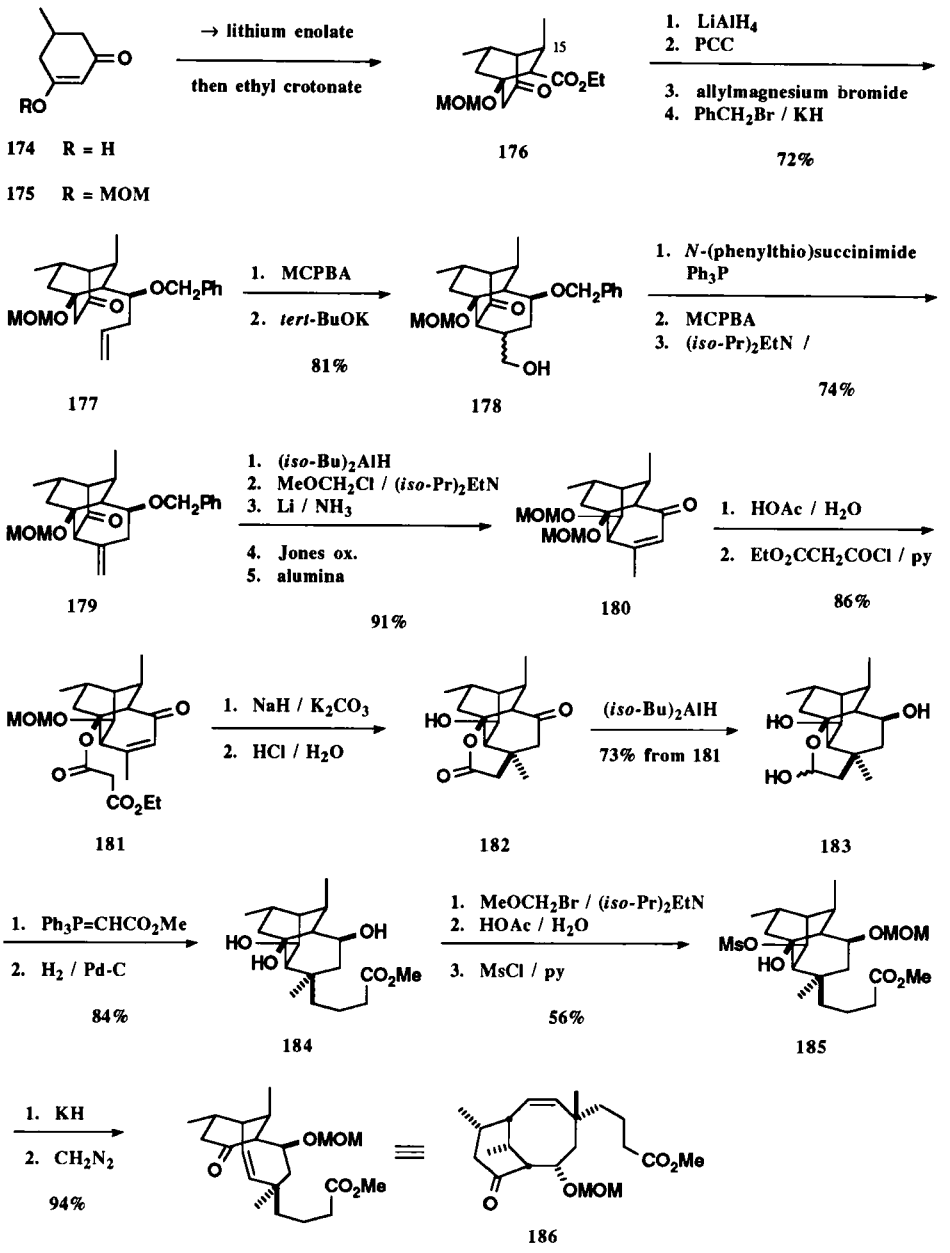


Fig. 22

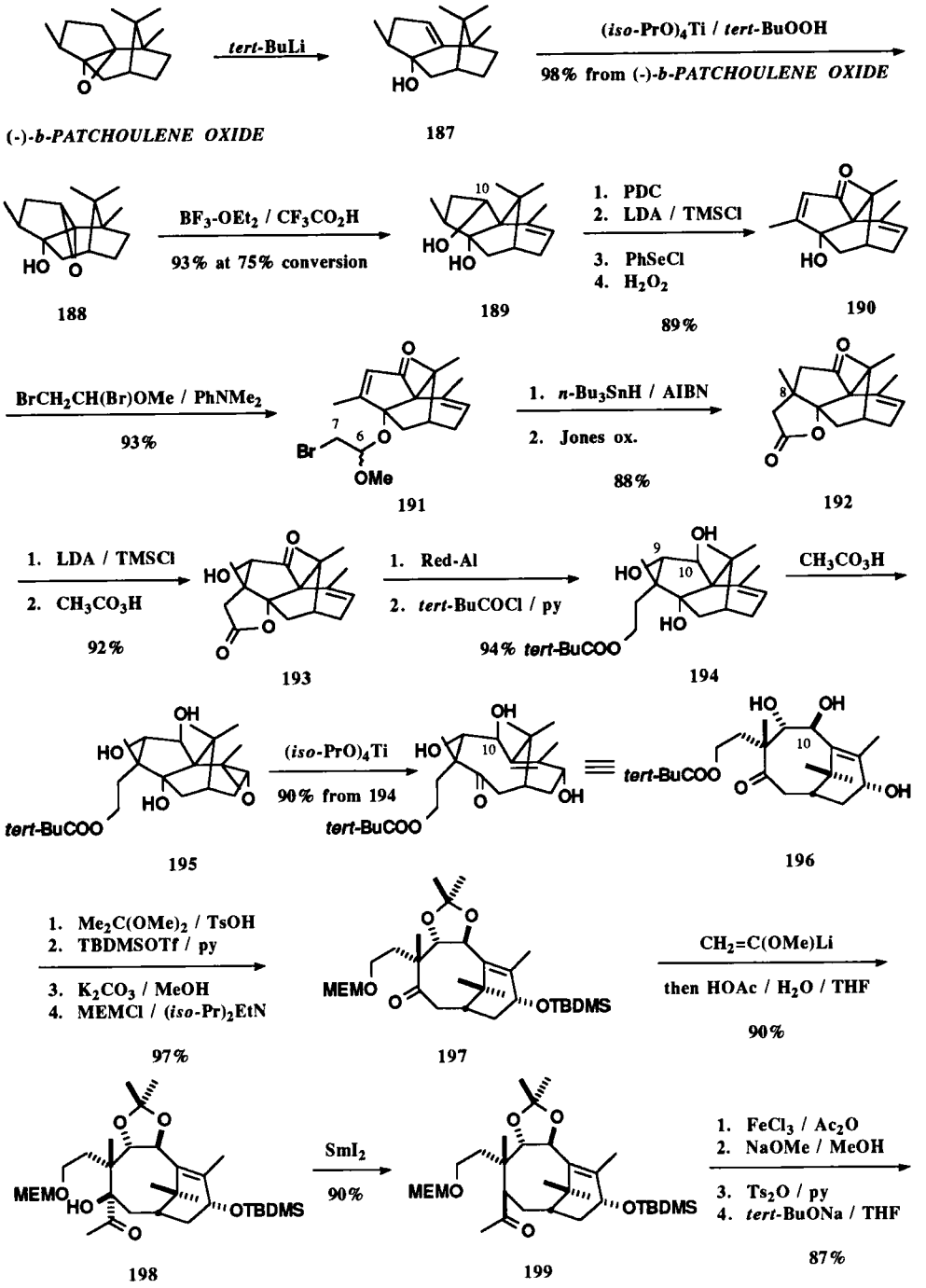


Fig. 23

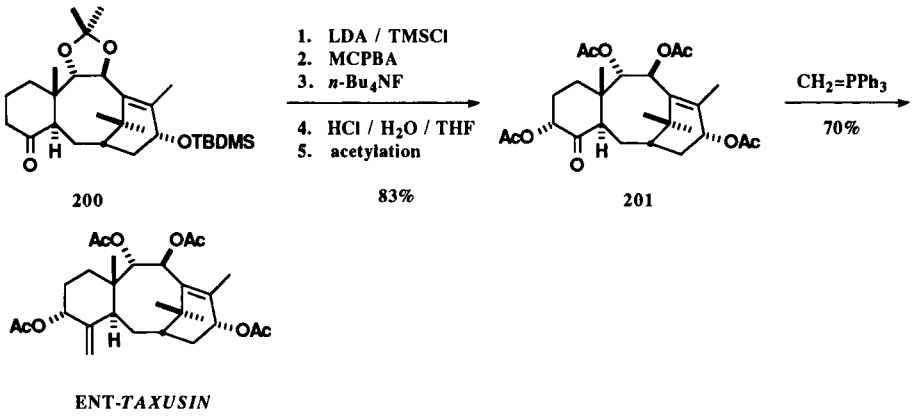


Fig. 23 (cont.)

in this sequence, determined by consideration of ^{1}H NMR data, is surprising given the requirement that it proceeds through hydride delivery within the concave region of tricyclic **179**. With **180** in hand, Yamada found that a selective deprotection of the tertiary hydroxyl masking group could be effected, thus allowing the two-step formation of **181**. An intramolecular Michael process followed to give, after standard hydrolytic decarboxylation, **182**. Hydride reduction of **182** delivered masked aldehyde **183**, which, when exposed to the indicated Wittig reagent and the corresponding product catalytically hydrogenated, led to **184**. Thus, the stage of Yamada's synthesis encompassing the conversion of **180** to **184** was focused on the partial attachment of the taxinine C-ring. Since Yamada intended to employ fragmentation chemistry in his elaboration of the B-ring, the last series of steps was devoted to that operation. Intermediate **184** was doubly protected, selectively deprotected, and exposed to methanesulfonyl chloride and base to yield fragmentation substrate **185**. Finally, **185** was treated with KH at 100 °C for 10 min to give **186**, after reesterification.

The penultimate, fragmentation step is noteworthy for two reasons. First, it would appear to be disfavored on stereoelectronic grounds since there is poor alignment in the relatively rigid carbon cage of **185** of the breaking carbon-carbon and carbon-oxygen bonds.

Second, the stereochemistry of **185** would seem more appropriate for the formation of a *trans*-cyclooctene (note, however, the above comment regarding the hydride reduction of **179**). A nonconcerted mechanism for the fragmentation would alleviate both of these obstacles, although the facility with which it occurs is remarkable.

b. Holton's Synthesis of Taxusin

Holton[50] has extended his strategy for taxane synthesis, previously applied to a very brief construction of the diterpenoid skeleton (section I. C. 1. b.), to the synthesis from readily available (-)-β-patchoulene oxide of *ent*-taxusin[52] (Fig. 23), the enantiomer of one of the simplest natural taxane structures. In this modified approach, two of the five skeletal carbons required by taxusin but missing from (-)-β-patchoulene oxide are appended before the completion of the B-ring. The final stage of Holton's synthesis is devoted then to the full elaboration of the C-ring.

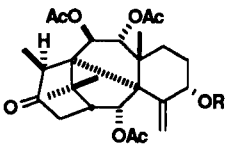
The synthesis of taxusin began with the treatment of (-)-β-patchoulene oxide with *tert*-butyllithium to provide isomer **187**. The epoxidation of **187** gave an intermediate epoxy alcohol, which, when exposed to a mixture of Lewis and protic acids, led to **189**. This latter conversion is similar, though not identical, to the rearrangement involved in Holton's taxane skeleton synthesis that set up the carbon connectivity of the A-ring. However in this case, it was carried out in such a way that critical functionality remained at the carbon destined to become C-10. This feature was immediately exploited in the manipulation of **189** to provide cyclopentenone **190**. The functionalization of **190** at the tertiary hydroxyl then created a substrate (**191**) for a radical-mediated attachment of the C-6–C-7 portion of the C-ring. Following an adjustment of oxidation state, **192** resulted, in which the relative configuration of the C-8 quaternary carbon was well defined. A three-step protocol then completed the essential features of the C-9–C-10 region, and following the protection of the primary hydroxyl, furnished intermediate **194**. The rather severe steric bias afforded by the geminal methyl substituents in this series of intermediates formed the basis of the stereocontrol at C-9 and C-10. With **194** in hand, its epoxidation provided fragmentation substrate **195**, which underwent the key B-ring forming fragmentation through the action of $Ti(O\text{-}iso\text{-}Pr)_4$. Structure **196** possessed a reasonably complete AB substructure, but required the incorporation of the three remaining carbons of the C-ring. The protection of the AB hydroxyl groups, saponification of the pivalate ester, and its replacement with a MEM ether gave **197**. The MEM substituent proved to be essential since its complexation with the indicated lithium reagent *in hexane* formed the basis of the stereoselectivity witnessed in the production of **198**. Although at first glance this result would seem to be insignificant since the deoxygenation of **198** to **199** or its epimer might not be expected to have special stereochemical requirements, in fact only **198** could be induced to undergo the required reduction to **199**. The α-hydroxy ketone epimeric to **198** reacted with SmI_2 to give a rearranged and transannularly cyclized product.[53] The completion of the C-ring proceeded from **199** and began with cleavage of the MEM group to give the corresponding acetate. Following this transformation, saponification of the acetate and tosylation of the primary hydroxyl allowed ring closure to occur through base treatment. These operations gave **200**, in which the *trans*-BC ring fusion stereochemistry was preferred. Finally, α-hydroxylation of **200** by peracid oxidation of its derived silyl enol ether produced, after deprotection and acetylation, **201**. Wittig methylenation completed the synthesis of taxusin. From (-)-β-patchoulene oxide, *ent*-taxusin is prepared in 32 distinct operations with an overall yield of 21% as calculated from the published yield data. Thus, the average yield per step is a remarkable 95%!

c. Hudlicky's Approach through Intermediates Analogous to Taxinines K and L

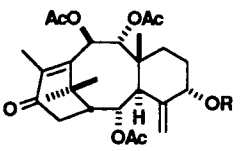
Among the taxanes that possess skeleta that are altered versions of **1** are taxinine K and taxinine L discovered by Nakanishi.[54] Taxinine K was shown by Nakanishi to be the product of the UV irradiation of taxinine A; similar photochemistry would form taxinine L from taxinine H. This in vitro result suggests that taxinines K and L are not products of enzyme-mediated biosynthesis, and that they might be artifacts, although Nakanishi attempted to exclude this possibility.

The authenticity of their natural occurrence notwithstanding, these transannularly cyclized

structures have inspired a unique strategy pursued by Hudlicky[55] (Fig. 24). In Hudlicky's approach, key intermediate **213**, structurally analogous to taxinines K and L, is to be assembled and then fragmented to provide the highly functionalized taxane intermediate **214**. Although the latter phase of the



TAXININE K R = H
TAXININE L R = Ac



TAXININE A R = H
TAXININE H R = Ac

plan has yet to be completed, it rests on a general approach to five-membered ring annulation[56] developed in the Hudlicky group, in addition to the design principle mentioned above.

Beginning with optically active yeast reduction product **202**,[57] which provides quaternary C-8 and oxygenated C-9 of the taxane skeleton in their correct absolute configurations, a series of straightforward transformations led to **204**. Although **204** could be treated with *iso*-butenyl organometallic reagents to give directly **206**, it proved to be more practical to carry out the multistep protocol depicted in Fig. 24. Nazarov cyclization of **206** produced **207**, and its sequential hydroxylation, methylation, and

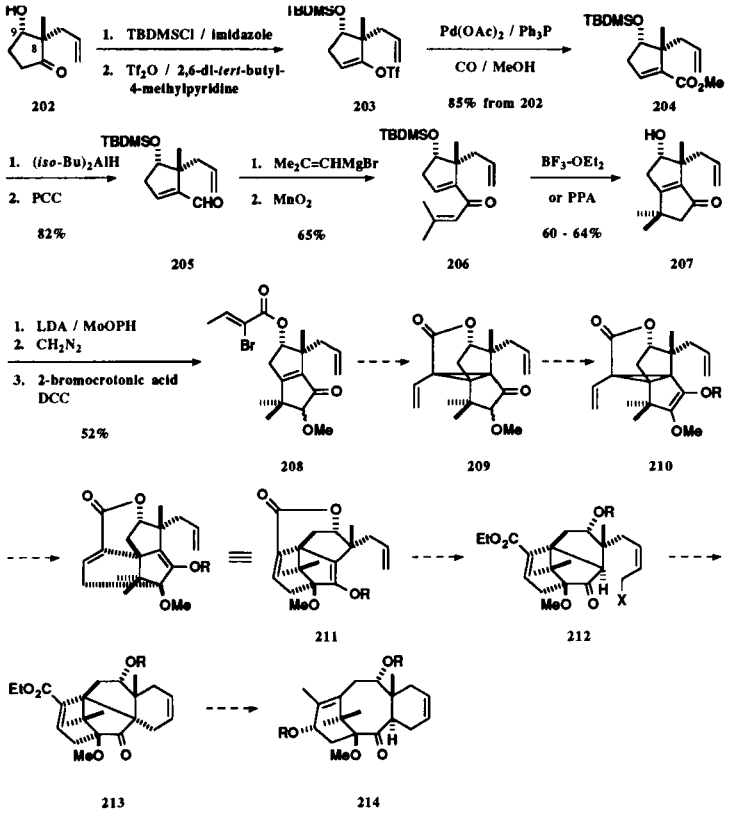


Fig. 24

esterification with 2-bromocrotonic acid provided cyclopentene annulation substrate **208**. According to the general methodology developed by Hudlicky for this purpose, intramolecular Michael addition of an enolate derived from the crotonate moiety and subsequent internal ketone enolate attack at the bromine-bearing carbon would create cyclopropane **209**. The formation of enol derivative **210** would then reveal a *cis*-divinyl cyclopropane that would be expected to undergo Cope rearrangement leading to **211**. The further manipulation of **211** would give the key taxinine K/L analogue **213** whose fragmentation would be expected to complete the carbon connectivity of the taxane skeletal system. A noteworthy feature of the Hudlicky approach to the taxanes is that they would be prepared in the correct absolute stereochemical form.

D. BC → ABC Strategies

Although the vast majority of the linear strategies for taxane synthesis are of the AB → ABC type, two groups have published work that relies on a BC → ABC strategy.

1. Swindell's Approach

Our group published the construction of BC intermediates[58] that require an A-ring annulation approach for their further conversion to the taxanes. Prior to our full investigation of this strategy, a series of molecular mechanics calculations on structures related to the taxanes suggested that the late attachment of the A-ring at both sides of the sterically demanding quaternary C-15 site on the B-ring with direct introduction of the bridgehead olefin would be an energetically viable process.[59] Initially, the route summarized in Fig. 25 was investigated as a general way of accessing appropriately functionalized BC intermediates.[58,60] In this strategy, [2+2] photoaddition chemistry was to be employed in joining the B and C-ring precursors, and fragmentation chemistry was to complete the formation of the eight-membered ring in such a way that functionality required to implement the A-ring annulation

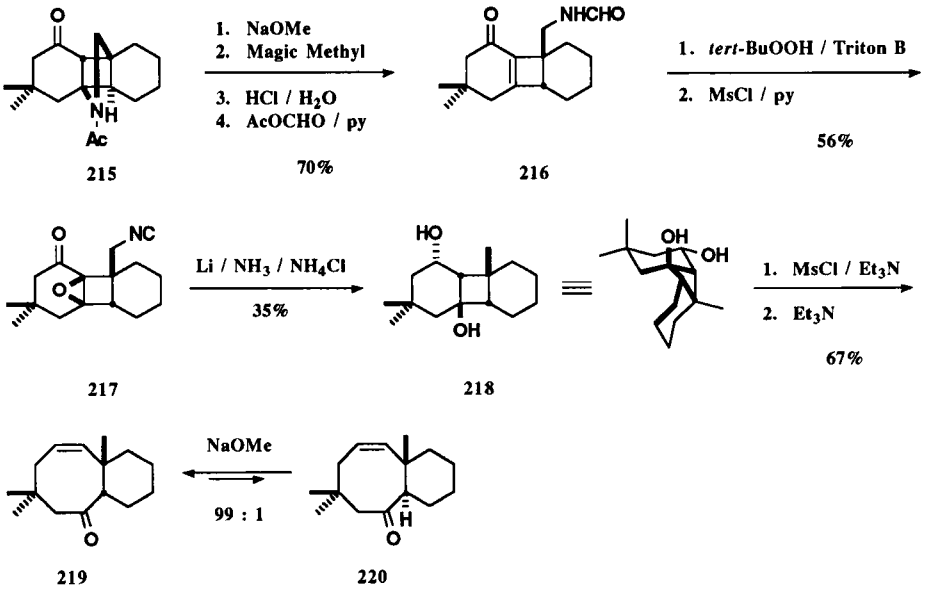
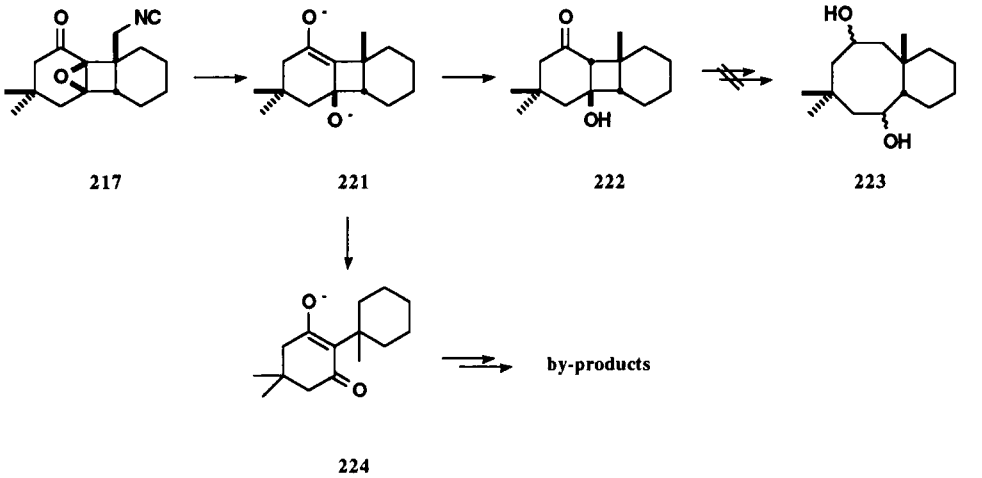


Fig. 25

could be incorporated. Photoproduct **215**,[61] available through five steps in 39% yield from dimedone and cyclohexanone cyanohydrin,[61,62] could be isomerized to the related tricyclic secondary acetamide enone by its treatment with sodium methoxide. A one-pot sequence of amide *O*-methylation, imidate hydrolysis, and primary amine formylation delivered the corresponding formamide analogue **216**. This exchange of formyl for acetyl was required by the plan to use isonitrile reduction chemistry to excise the nitrogen. Although unanticipated at the outset, **216** was demonstrated to possess a cis ring fusion on the basis of an NOE experiment as well as subsequent chemical correlations. Clearly, the basic conditions of the first step caused the epimerization of the product enone methine vinylogously α to the enone carbonyl. Although the ring fusion in question was destined to become the taxane BC-ring fusion, this line of investigation was continued with the hope that a trans ring fusion would be preferred at the bicyclo[6.4.0]dodecane stage. Enone **216** was subjected next to a nucleophilic epoxidation, and dehydration to the isonitrile. Intermediate **217** underwent a dissolving metal reduction that proceeded through reductive cleavage of the epoxide carbon-oxygen bond α to the carbonyl, protonation of the enolate thus produced, and reduction of the carbonyl reinstalled to give the 1,3-diol function found in **218**. A reasonable explanation for the inefficiency of this step (Fig. 26) would be that retroaldolization of β-hydroxy ketone **222** encountered after enolate protonation competes with reduction to the 1,3-diol to give (unsuitably functionalized) bicyclo[6.4.0]dodecane diols **223**. In fact, this was not the case, and considering the stability of β-ketols like **222** observed by the Fétizon and Blechert groups (sections I. C. 1. d. and I. C. 1. e., respectively), this was not surprising. Instead, the lower cyclobutane carbon-carbon bond connecting the two six-membered rings is cleaved at some point along the reductive pathway to give various isolatable byproducts bearing two six-membered rings connected by a single carbon-carbon bond (see the conversion of **221** to **224** in Fig. 26). In any case, **218**, though available in low yield, was well constructed for the fragmentation that occurred upon transformation to its mesylate followed by treatment with base. However, it was **219**,



217 221 222 223

224

Fig. 26

and not its epimer, **220**, that possessed the thermodynamically preferred ring fusion stereochemistry. A number of related bicyclo[6.4.0]dodecane structures have shown a similar preference.[60]

From these results, it was clear that the trans stereochemistry at C-3 and C-8 characteristic of structures such as **215** would have to be preserved. Thus, the sequence depicted in Fig. 27 was developed.[60] Vinylogous imide **226**, prepared from dimedone and cyclohexanone cyanohydrin through three steps and in 85% yield, was converted to **225** by a phase-transfer acylation procedure in 77% yield. The photolysis of **225** gave a photoproduct analogous to **215**, and its L-Selectride reduction followed by mesylation led to fragmentation substrate **228**. Intermediate **228**, in its conventional conformational representation, does not have the classic *anti*-periplanar alignment of fragmenting carbon-carbon and carbon-oxygen bonds. Apparently, it can adopt a boat conformation that solves this stereoelectronic problem since its treatment with zinc caused deacylative fragmentation to occur. Hydrolysis of the intermediate tricyclic bridgehead imine (not shown), and formylation of the angular amino methyl group produced *trans*-fused **229**. A final series of operations, including a dissolving metal reduction procedure for the cleavage of the isonitrile, led to **220**. Thus BC intermediate **220** was obtained through 14 steps in 21% overall yield from commercially available materials.

With a viable route to the BC substructure in hand, the feasibility of annulating the taxane A-ring onto it was tested as shown in Fig. 28.[63] The goal of this work was the construction of a

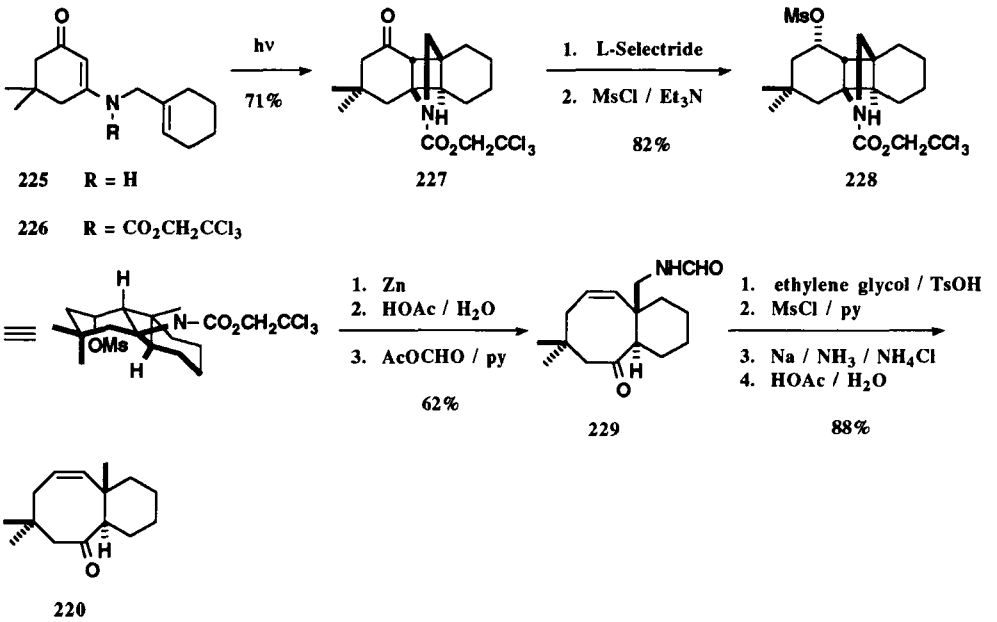


Fig. 27

dihydrotaxane lacking the bridgehead olefin. Beginning with photoproduct **227**, the A-ring progenitor carbons were attached through an alkylation of the anion of the dimethylhydrazone derivative.

Subsequent hydrazone cleavage gave **230**, in which alkylation had occurred axially and on the more exposed convex surface. Since the newly introduced C-11 stereogenic center would induce the configuration of the critical C-1 site upon completion of the A-ring, its configuration was corrected by base-induced epimerization to provide an α-oriented equatorial side chain. Carbonyl reduction and mesylation, as in the previous sequence, led to fragmentation substrate **231**. Next followed a series of transformations modeled after the experience summarized in Fig. 27. This phase culminated in intermediate **232**. As the olefin located in the upper part of the eight-membered B-ring was superfluous to the task at hand, it was removed through catalytic hydrogenation. Carbonyl deprotection, side chain hydroxyl manipulation, and LDA treatment to effect the intramolecular enolate alkylation led without incident to **234**. Tricyclic model **234** was available through this 22-step synthesis in 17% overall yield. Epimerization and NOE difference spectroscopy established that, in contrast to the behavior of bicyclic BC systems like **219/220**, the BC-ring fusion of the (saturated) tricyclic skeleton prefers to be trans.

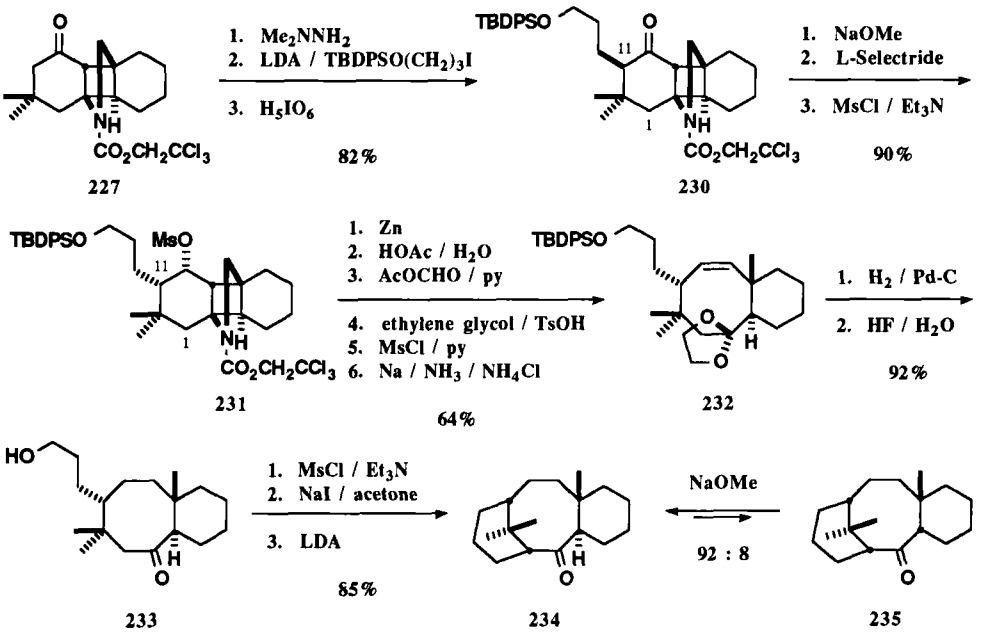


Fig. 28

The most recent report from our group[64] focused on the construction of tricyclic taxane skeletons bearing functionalized B-rings more characteristic of the naturally occurring members of the taxane family, in particular, taxinine (Fig. 29). This work, too, began with photoproduct **227**, which was subjected to a Rubottom oxidation sequence to provide **236**. The standard fragmentation protocol delivered **237**. Deprotonation of **237** at both the ketone and formamide sites produced a lithiated dianion that might have the chelated structure represented by **238**. In any case, the properly

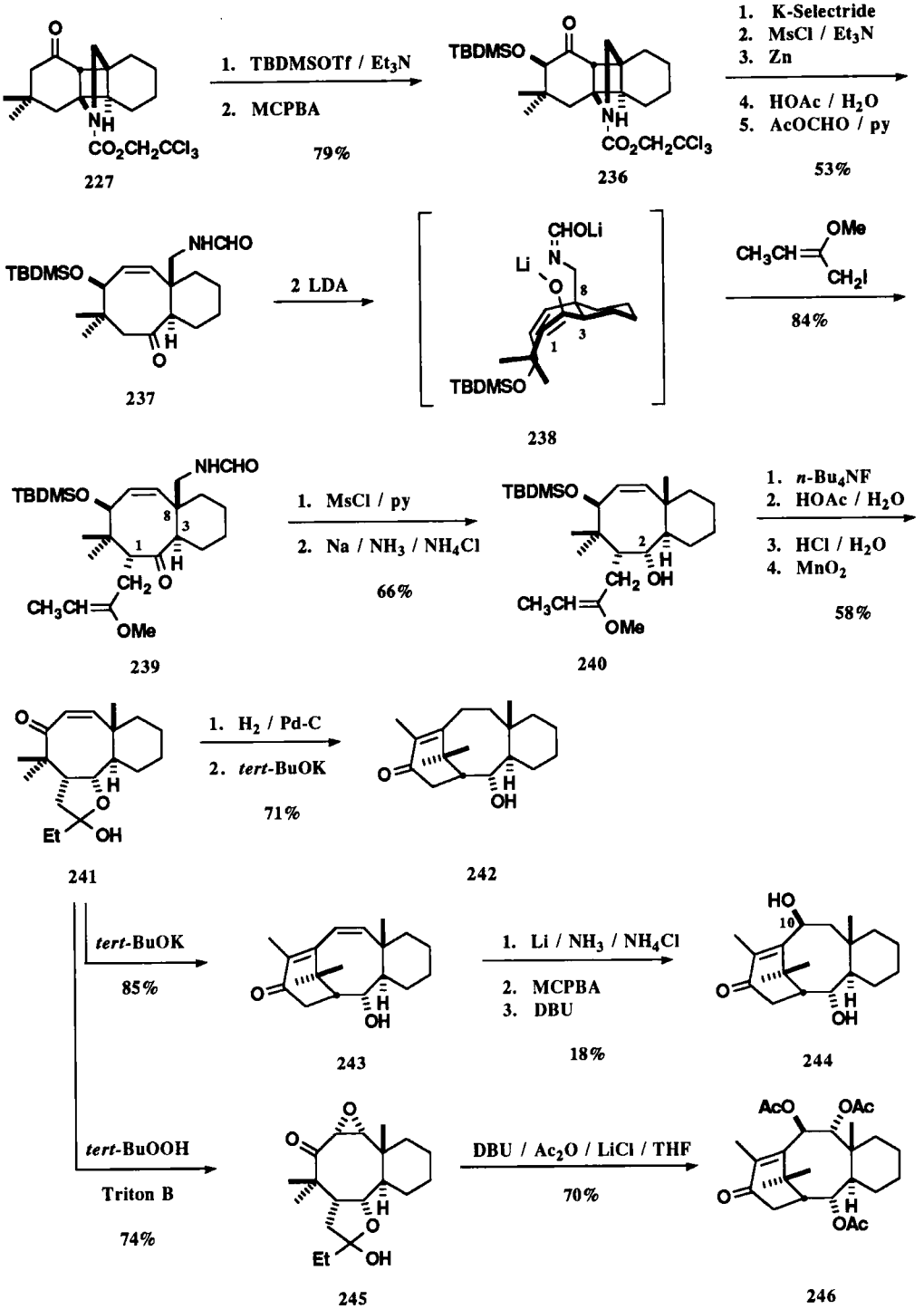
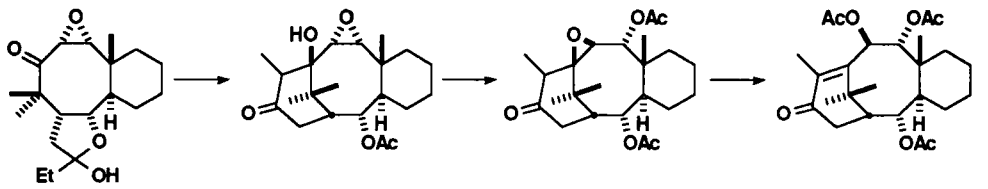


Fig. 29

located sp^2 centers around the cyclooctyl periphery in combination with the trans BC-ring fusion stereochemistry were predicted through a molecular mechanics aided conformational analysis to define the eight-membered ring conformation characteristic of **238**. This was an important strategic concept in our plan since attachment of the A-ring progenitor carbons through enolate alkylation carried out on **238** would be expected to install the appropriate C-1, C-3, C-8 relative stereochemistry. In the event, the formation of **239** was completely stereoselective in the desired fashion. Formation of the isonitrile and dissolving metal reduction produced **240**. Again, stereochemical control, this time at C-2, was predicated on a medium ring conformation similar to that of **238**. It is worth noting that the maintenance of the allylic silyloxy substituent is a good indicator of the facility with which isonitrile reductive cleavage (and ketone reduction) takes place under these conditions. The further conversion of **240** to pivotal intermediate **241** required the indicated three-step deprotection sequence that led through silyl ether cleavage, cyclic acetal closure, and, finally, cyclic acetal hydrolysis. Attempts to combine these steps into a single aqueous acid-induced operation led to complicated product mixtures. Although an annoying feature of the present model syntheses, it is likely that the stability of the cyclic acetal that leads to **241** will allow, at this juncture, the elaboration of the C-ring in a scheme devoted to the preparation of taxinine.

With **241** in hand, three protocols for completing the annulation of the A-ring were investigated. Initially, the question was whether aldol chemistry could be exploited in the required bridgehead double bond closure. To that end, **241** was simplified through hydrogenation, and the product of that reaction treated with base to provide **242**. However, the additional unsaturation incorporated through aldolization of **241** did not prove to be an impediment to taxane skeleton completion as witnessed in the formation of **243**. The availability of **243** then offered the opportunity to probe the stereoselective introduction of oxygenation at the C-10 B-ring site. This was accomplished through reduction of **243** to the related β,γ-unsaturated enone, which underwent epoxidation on its β face. Exposure of the epoxy ketone thus formed to DBU then created **244**, one step closer in functional and stereochemical complexity to taxinine. Finally, **241** could be transformed through a nucleophilic epoxidation process into **245**. Again, stereochemical control in the formation of **245** was derived



245 247 248 246

Fig. 30

from the general conformational principle exemplified in **238**. However, applied to this locus of the B-ring, it was less effective (8:2 diastereomer ratio) than it had been in the previous reactions involving C-1 and C-2. The relevant annulation event applied to **245** took place upon its exposure to non-

aqueous base and an acetylation agent. This one-step procedure created **246**, whose AB substructure is identical to that of taxinine's. In all, the production of **246** required 21 steps and proceeded in 3.2% overall yield.

The conversion of **245** into **246** was expected to occur based on the mechanistic considerations outlined in Fig. 30. In this sequence of steps, aldolization is augmented by an intervening Payne rearrangement and an epoxy ketone isomerization, with acetylation occurring as hydroxyl groups are revealed. In fact, viewed from a structural perspective, the stepwise protocol that leads from **247** through **248** to **246** mimics the structural changes characteristic of the conversion of **243** into **244**. This scheme is patterned after a similar series of double bond migrations within the taxane framework observed by Lythgoe during his pioneering structural studies.[9]

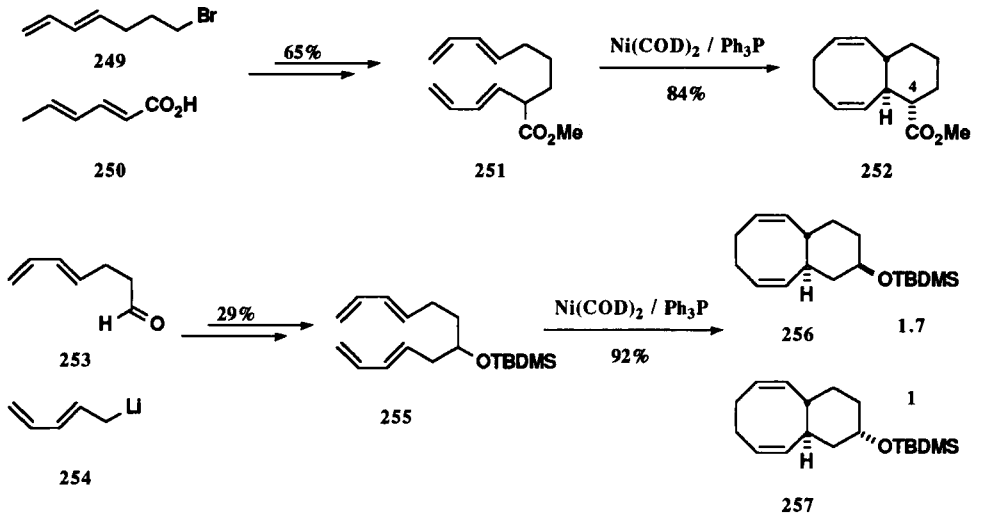
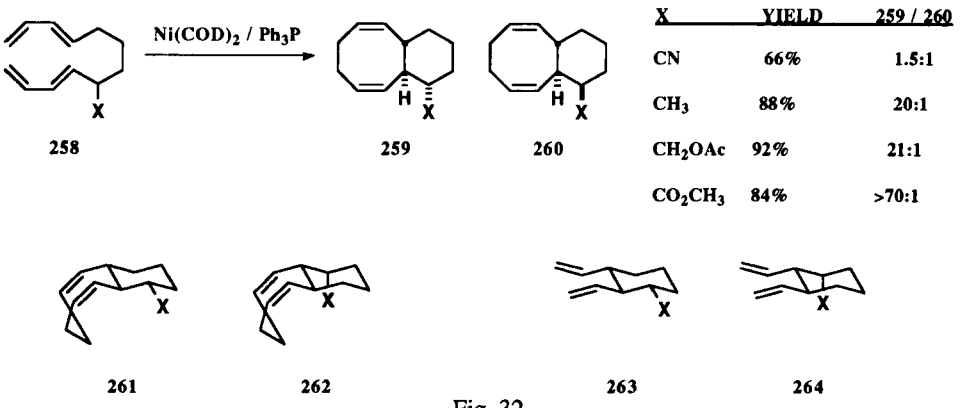


Fig. 31

2. *Wender's A-Ring Annulation Approach*

Wender has employed the nickel-catalyzed eight-membered ring forming chemistry outlined previously in section I. C. 1. f. for the elaboration of various bicyclo[6.4.0]dodecyl systems that maybe viewed as BC intermediates for taxane synthesis. In the initial disclosure[46] of this methodology, Wender reported that tetraene **251** (Fig. 31), available from sorbic acid (**250**) and unsaturated bromide **249**, produced *trans*-fused **252** when treated with the phosphine-nickel(0) catalyst mixture. The stereochemical selectivity with respect to the placement of the C-ring substituent was impressive, and exceeded that involved in the formation of **256** and **257** from tetraene **255**. The issue of stereoselectivity at C-4 in cyclizations like that of **251** to **252** was investigated[48] further as indicated in Fig. 32. Wender prepared from **251** and the corresponding acid a series of three differently substituted cyclization substrates. Their nickel-catalyzed cyclizations, as well as that of **251**, are summarized. Considering the stereoinductive trend associated with the various X groups, Wender suggested that the biases were principally steric in origin. However, the product distributions illustrated in Fig.



X	YIELD	259 / 260
CN	66%	1.5:1
CH_3	88%	20:1
CH_2OAc	92%	21:1
CO_2CH_3	84%	>70:1

Fig. 32

32 could not be modeled by a reversible mechanism wherein stereoisomer ratios would be dictated by the relative stabilities of **259** (see conformer **261**) and **260** (see conformer **262**). Indeed, Wender demonstrated that the reaction was not reversible under the conditions employed in the formation of **259** and **260**. Wender did detect a correlation between the relative strain energies of diastereomeric *syn*-bis-π-allyl mimics **263** and **264**, and the relative rates of the processes that lead to **259** and **260**. On the basis of this preliminary analysis, he suggested that the diastereoselectivity in question could arise from the relative rates of collapse of diastereomeric *syn*-bis-π-allyl intermediates through transition states whose energies are influenced in large part by reactant (bis-π-allyl) strain energies.

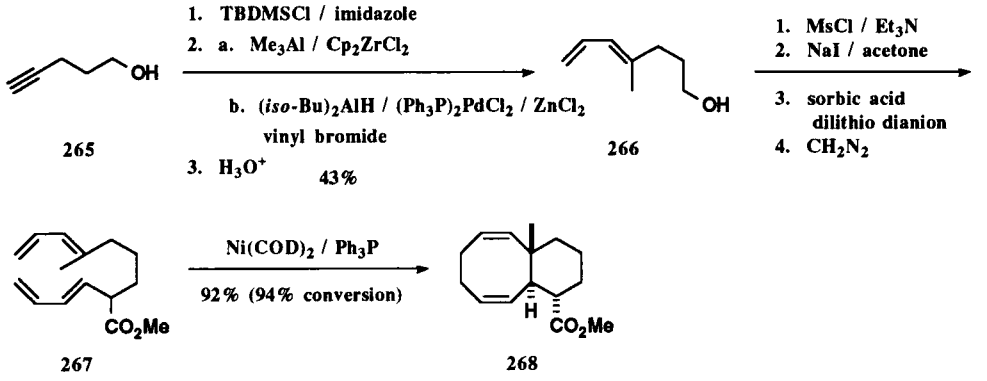


Fig. 33

The application of Wender's tetraene cyclization chemistry to the taxanes would require that it tolerate a heavy degree of alkyl substitution about the developing eight-membered ring framework. To that end, Wender looked at the sequence outlined in Fig. 33,[47] which began with the protection of commercially available **265**. Subsequent carbometalation and coupling with vinyl bromide completed half of the tetraene feature, and installed the methyl group destined to become the angular methyl characteristic of the taxane skeleton. A sequence that involved the alkylation of sorbic acid dianion then culminated in **267**. Finally, nickel-catalyzed cyclization of **267** produced, in a total of

eight operations, **268**, the angularly methylated analogue of **252**.[65]

II. CONVERGENT STRATEGIES

As noted previously, convergent strategies for the synthesis of the taxanes are as attractive as they have been difficult to implement. Nevertheless, several attempts have been made toward this goal, all of which have focused on the formation of the eight-membered B-ring at or after the points of convergence.

A. AC → ABC Strategies

The following reports have described convergent approaches that require more or less direct closure of the B-ring. With two notable exceptions, these plans have been quite limited in their success.

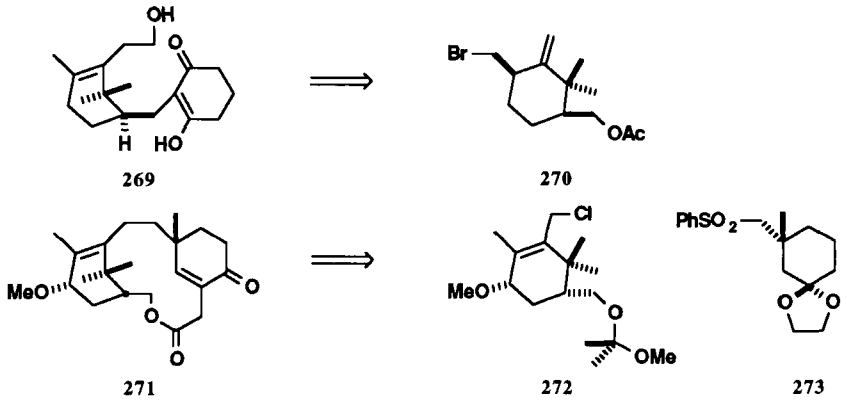


Fig. 34

1. Kitagawa's Approach

Early disclosures from the Kitagawa group centered on strategies that depend on the cyclization of intermediates like **269**[66] and **271**[67] (Fig. 34). While several more accessible publications have reported on the preparation of the A and C-ring intermediates from which these structures presumably have been prepared, no details on the syntheses of **269** and **271** or on attempts to transform them into taxane nuclei are currently available.

The A-ring intermediates related to **270** and **272** in Kitagawa's plan required a 23-step sequence to **272** that begins with d-camphor in Fig. 35.[68] Following the conversion of d-camphor to d-camphoric acid (**274**), the initial phase of the scheme was devoted to the preparation of **277**.[69] Sequential esterification, reduction, and selective acetylation applied to **274** produced monoacetate **275**. Its conversion to the related aldehyde followed by Wittig olefination gave **276**, which underwent bromination-dehydrobromination with rearrangement to deliver **277**. In the rearrangement process, migration of the less substituted homoallylic cyclopentane carbon in **276** creates the carbon skeleton associated with **277**. A short series of straightforward transformations led then to a mixture

of diastereomeric epoxides **279**. Elimination of HBr from **279** gave **280**, and its reductive treatment produced **281**. Next followed a series of steps designed to introduce oxygen onto the site that would become C-13 in the taxane skeleton and to correct the configuration of the C-1 carbon. This sequence culminated in an unfavorable mixture of aldehydes **283** and **284**. Nevertheless, a final

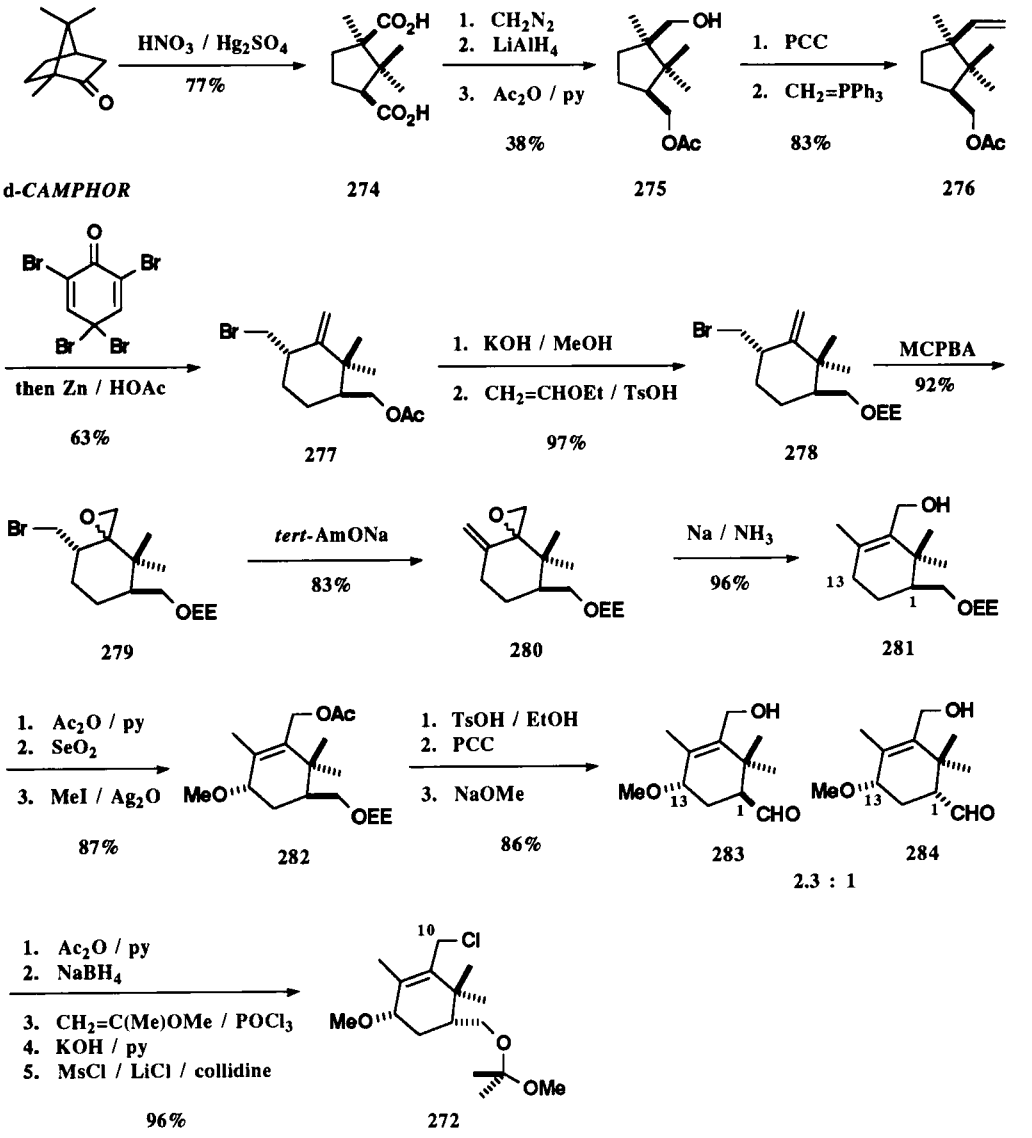


Fig. 35

protocol of conventional functional group and protecting group manipulations led from **284** to **272**. In addition, Kitagawa reported the transformation of **284** into alternative A-ring intermediate **286**, as depicted in Fig. 36.

In parallel with the above efforts to construct the left part of the taxane structure, Kitagawa pursued the synthesis of appropriate C-ring partners.[70] One such synthesis began with 3-methylcyclohex-2-enone (Fig. 37), which suffered sulfur ylide-mediated cyclopropanation, and reaction with

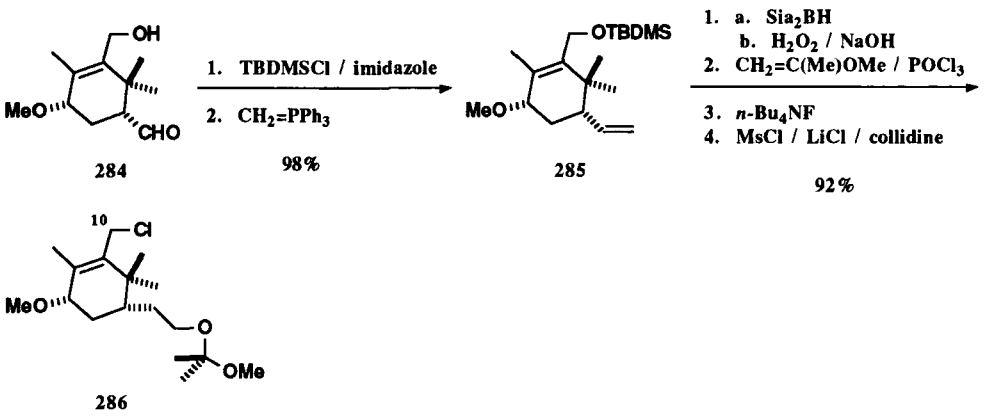


Fig. 36

optically active 2,3-butanediol to deliver a mixture of diastereomeric acetals **288**. Since there was little hope that a kinetic resolution would take place in joining the left and right halves of the taxane skeleton, **288** was resolved and deacetalized to provide **289** and its enantiomer. The assignment of their absolute stereochemistries rested on the application of an octant rule analysis to their circular dichroism spectra. Cyclopropyl ketone **289** was subjected to ring opening with HBr, and the product of that operation was converted to acetal **290**. Finally, a phase-transfer thiolate displacement carried out on **290**, and an ensuing oxidation of the intermediate sulfide yielded sulfone **273**. The latter may be viewed as being well-constructed for C-9–C-10 bond formation when paired with either **272** or **286**.

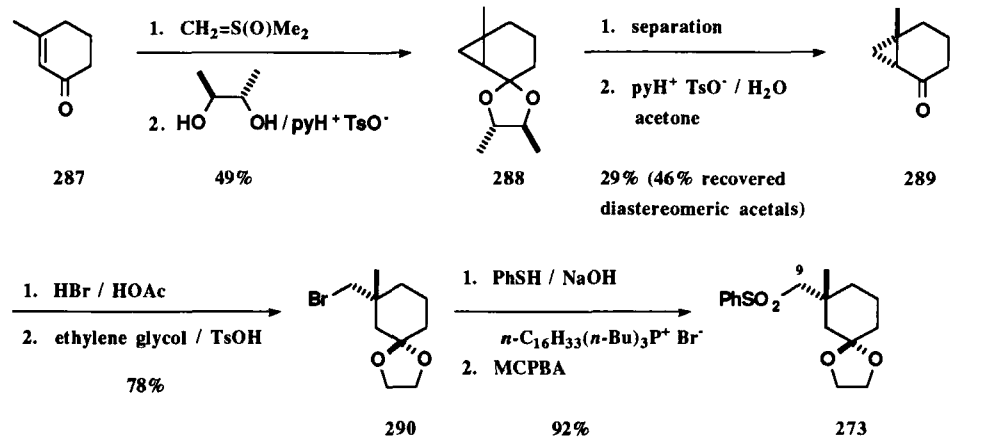


Fig. 37

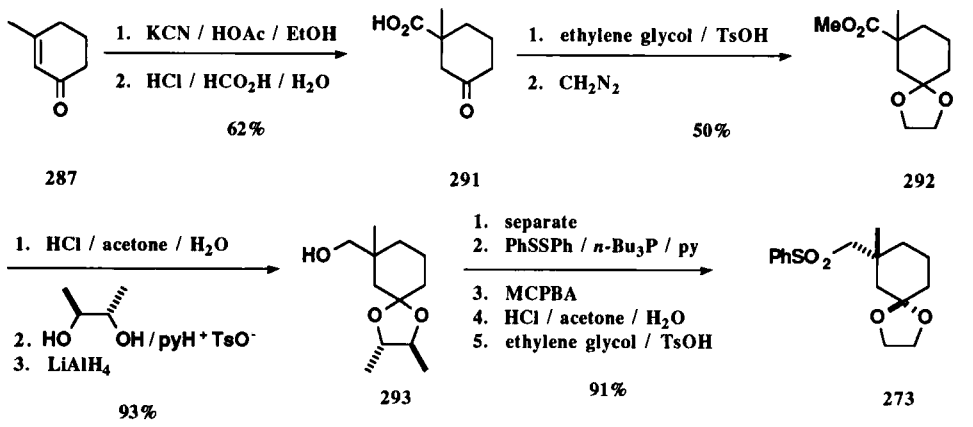


Fig. 38

While the above route was successful, Kitagawa noted that it was not amenable to large scale application. Thus, the chemistry illustrated in Fig. 38 was developed. In this route, **287** was modified

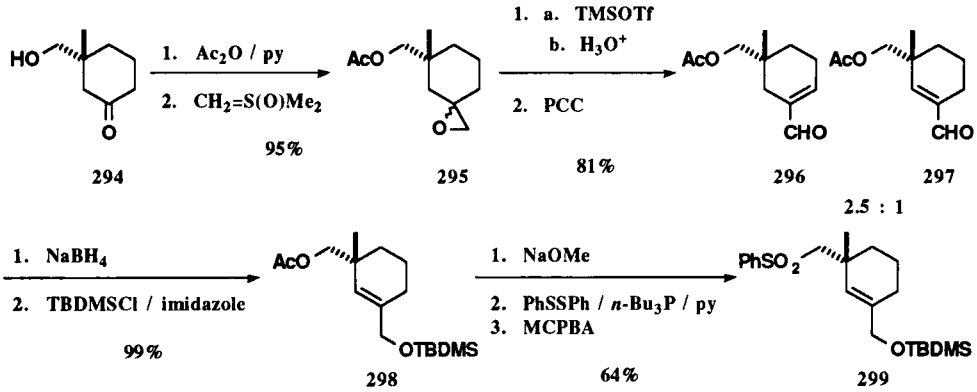


Fig. 39

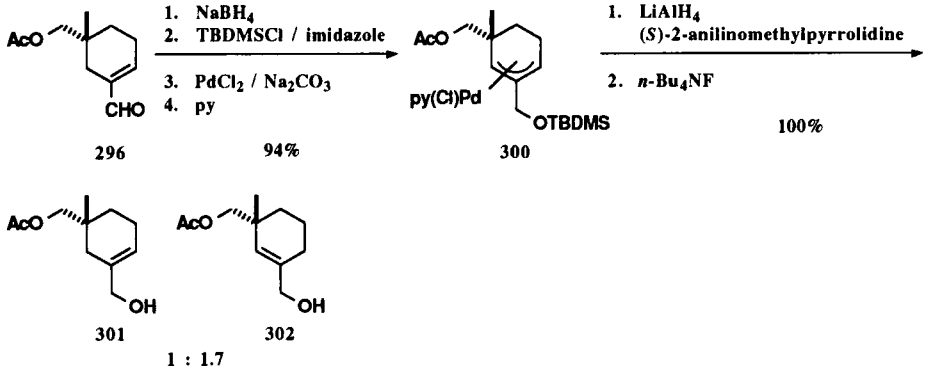


Fig. 40

at the β carbon in such a way that a hydroxymethyl substituent was appended. This part of the sequence ended in diastereomeric acetals **293**, which were resolved and the appropriate enantiomer converted to **273** through a series of steps that involved sulfide formation and acetal exchange. Again, the assignment of absolute stereochemistry to the final intermediates rested on the chiroptical properties of the individual hydroxy ketone enantiomers derived from **293** (see **294**; Fig. 39) by hydrolysis. In the application of the octant rule to these substances, the preferred equatorial orientation of the hydroxymethyl substituents was assumed. Although the route depicted in Fig. 38 was characterized by an overall yield that was less than that of the previous sequence, it met the criterion of large scale application.

Optically active **294**, which had been prepared in the latter route to **273**, was the point of departure for a synthesis by the Kitagawa group of alternative C-ring precursor **299** (Fig. 39). Following the conversion of **294** into diastereomeric epoxides **295**, a mixture of allylic alcohol regioisomers was obtained through the treatment of the epoxide mixture with TMSOTf. The intermediate alcohols were then oxidized to reveal an unfavorable mixture of isomers (**296** and **297**). Aldehyde **297** furnished **299** through a final five-step sequence of operations. To recycle **296**, Kitagawa developed the route shown in Fig. 40, which passed through π-allyl species **300**. Reduction of **300** with a modified $LiAlH_4$ reagent led ultimately to a mixture of allylic alcohol isomers **301** and **302** biased modestly toward **302**. Of course, **302** intervened in the conversion of **297** into **298** discussed above (Fig. 39).

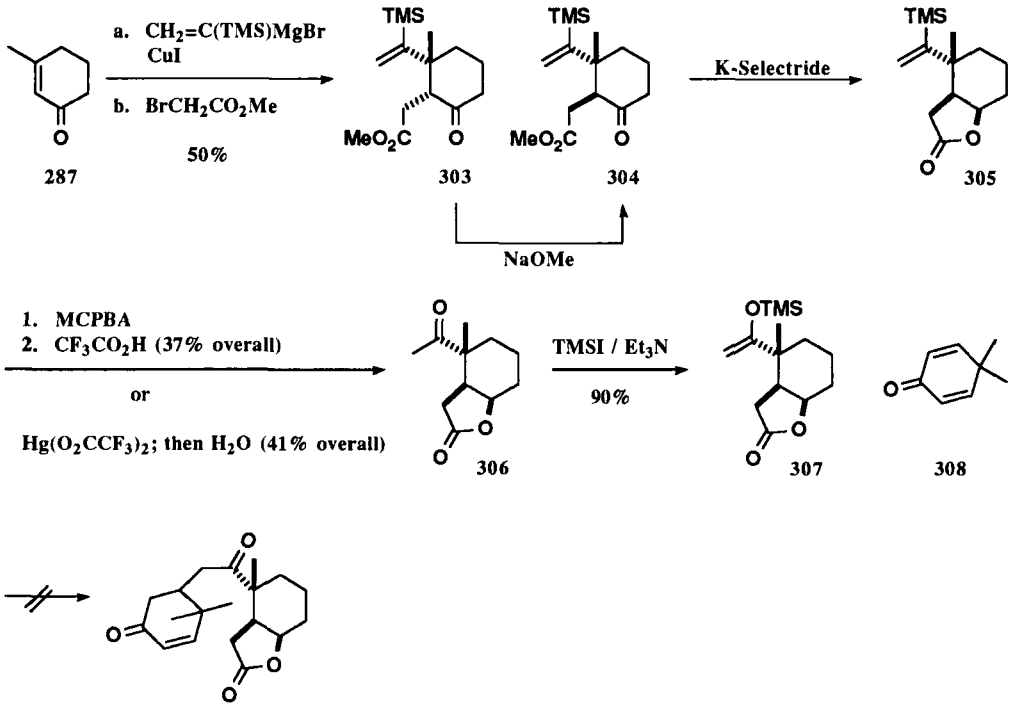


Fig. 41

2. *Fétizon's First Approach*

Fétizon has reported[71] an attempt to develop a taxane synthesis designed to exploit the closure of the taxane B-ring. The first effort to implement this scheme is depicted in Fig. 41. A conjugate addition–alkylation tandem applied to **287** produced a mixture of epimers **303** and **304**, but **303** could be epimerized cleanly to stereochemically appropriate **304** upon exposure to base. Ketone carbonyl reduction and spontaneous lactonization then produced **305**, which was converted into keto lactone **306** through either of the oxidative protocols illustrated. Fétizon had hoped to rely on a Mukaiyama condensation involving enol silyl ether **307** and **308** to establish the C-9–C-10 connection, but a variety of conditions returned **306** and dienone **308**. However, a commendably flexible feature of Fétizon's strategy was that the lactone substructure of intermediates such as **305** could be used to initiate bond formation between C-1 and C-2. Indeed, **305**, through its derived lithium enolate, underwent Michael addition to **308** to establish the lower portion of the B-ring, as represented in structure **310** (Fig. 42). Since a less complicated moiety could serve as progenitor of the C-9–C-10 region of the taxane nucleus in this approach, Fétizon converted **287** into an equilibrium

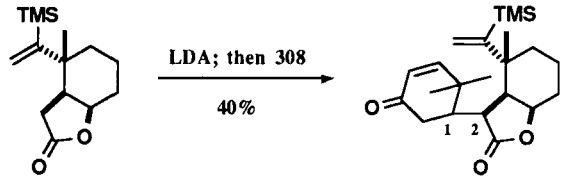


Fig. 42

mixture of vinyl substituted stereoisomers **311** and **312** (Fig. 43) through the same type of chemistry applied in the synthesis of **304**. Reductive lactonization of these keto esters then produced an inseparable mixture of lactones **313** and **314**. LDA treatment of this mixture and subsequent exposure to **308** led with selective involvement of major stereoisomer **314** to Michael addition product **315**.

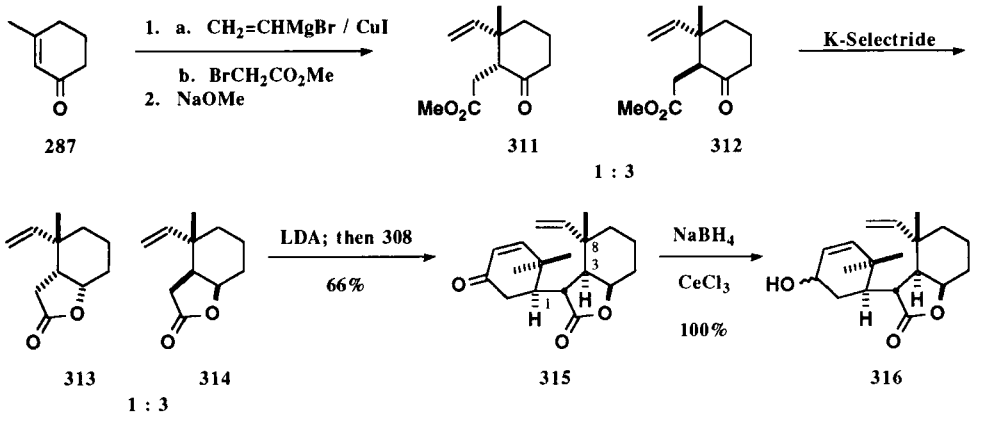


Fig. 43

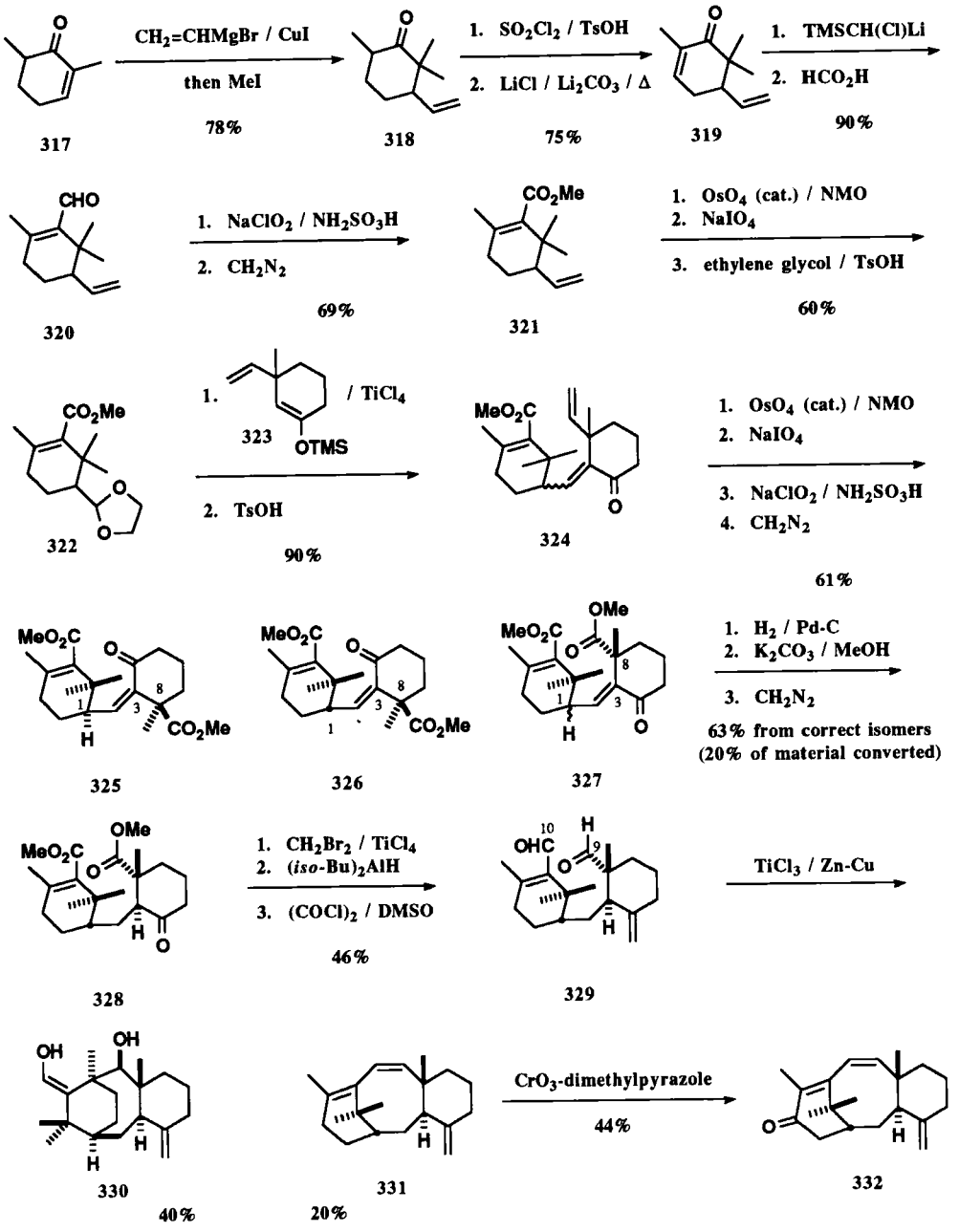


Fig. 44

Unfortunately, X-ray crystallographic analysis demonstrated that **315** possessed the incorrect stereochemical relationship between the C-1 and C-3/C-8 stereogenic sites. Furthermore, neither **315** nor

its 1,2-reduction product, **316**, could be converted by acid-catalyzed macrocyclization into material bearing the taxane skeleton.

3. Kende's Approach

Kende disclosed[72] in 1986 a synthesis of a tricyclic taxane structure through a sequence that is similar in strategy to the above attempted by Fétizon. The initial phase of Kende's synthesis (Fig. 44) was devoted to the preparation of acetal ester **322**. Beginning with enone **317**, conjugate addition of a vinyl nucleophile followed by trapping of the intermediate enolate with methyl iodide produced **318**. Dehydrogenation of **318** through its chlorination-dehydrochlorination led to **319**, which was converted through the related silyl epoxide to enal **320**. After **320** had been transformed into methyl ester **321**, oxidative cleavage of the vinyl group introduced the masked formyl substituent characteristic of **322**.

Acetal **322** was then engaged in a Mukaiyama aldol process with silyl enol ether **323**, and acid treatment of the initial product eliminated ethylene glycol to give **324** as a mixture of four isomers, two Z diastereomers and two E diastereomers in a 2:1 (Z:E) ratio, respectively. A four-step oxidative sequence applied selectively to the vinyl group of **324** gave the corresponding mixture of **325** and **326**, which were separable from each other as well as from the pair of E diastereomers **327**. Kende demonstrated that **325** possessed the incorrect relationship between the C-1 and C-8 configurations by converting it into a substance amenable to X-ray crystallographic analysis. The stereochemistry of **325** was not correctable, and therefore it represented a dead end. On the other hand, isomer **326** had these stereogenic carbons set properly in a relative sense. However, it was assumed by Kende to suffer hydrogenation of its enone double bond to give a dihydro epimer with the incorrect relative configuration at C-3, an outcome predicted on the basis of a similar sequence that was applied to **325**. Fortunately, base-catalyzed epimerization served to correct this problem, leading to a 4:1 ratio of epimers favoring **328**; the structure of **328** was confirmed eventually by its chemical correlation with material subjected to X-ray crystallographic analysis. Likewise, one of the inseparable E isomers possessed the appropriate critical relationship at C-1 and C-8, and could be converted through hydrogenation and base induced equilibration to **328**. In all, approximately one-third of the isomeric **324** material could be carried forward in the synthesis. Lombardo methylenation, hydride reduction, and reoxidation applied to **328** produced key dialdehyde **329**. At this stage, the closure of the C-9–C-10 linkage was to be performed by way of reductive carbonyl coupling mediated by low valent Ti. Indeed, exposure of **329** to the reagent prepared from the Zn-Cu couple reduction of $TiCl_3$ gave the desired **331**, but in quite modest yield. Curiously, the efficiency of the intended macrocyclization was not compromised significantly by intermolecular coupling. Instead, the major product derived from **329** was 1,4-coupling product **330**, which was characterized by a stable enol function.

In a final operation, Kende transformed **331** through allylic oxidation into **332**. At the time of Kende's report, **332** was the most heavily functionalized tricyclic taxane structure that had been prepared, and, in principle, could have been carried forward to taxusin (see Fig. 23). The synthesis of **332** was reasonably efficient as measured by the number of steps involved (24). Unfortunately, the

inefficiencies associated with the convergent strategy and the transformation of **329** into **331** limited the overall yield of **332** to 0.1%.

4. Funk's Approach

Funk[73] has embraced the same strategic plan addressed in the foregoing convergent synthesis attempts, but has implemented it in an ingenious manner that avoids the previously documented difficulty associated with closing the eight-membered ring. Instead, Funk adapted his methodology for carbocycle construction that is based on a Claisen rearrangement ring contraction of macrocyclic

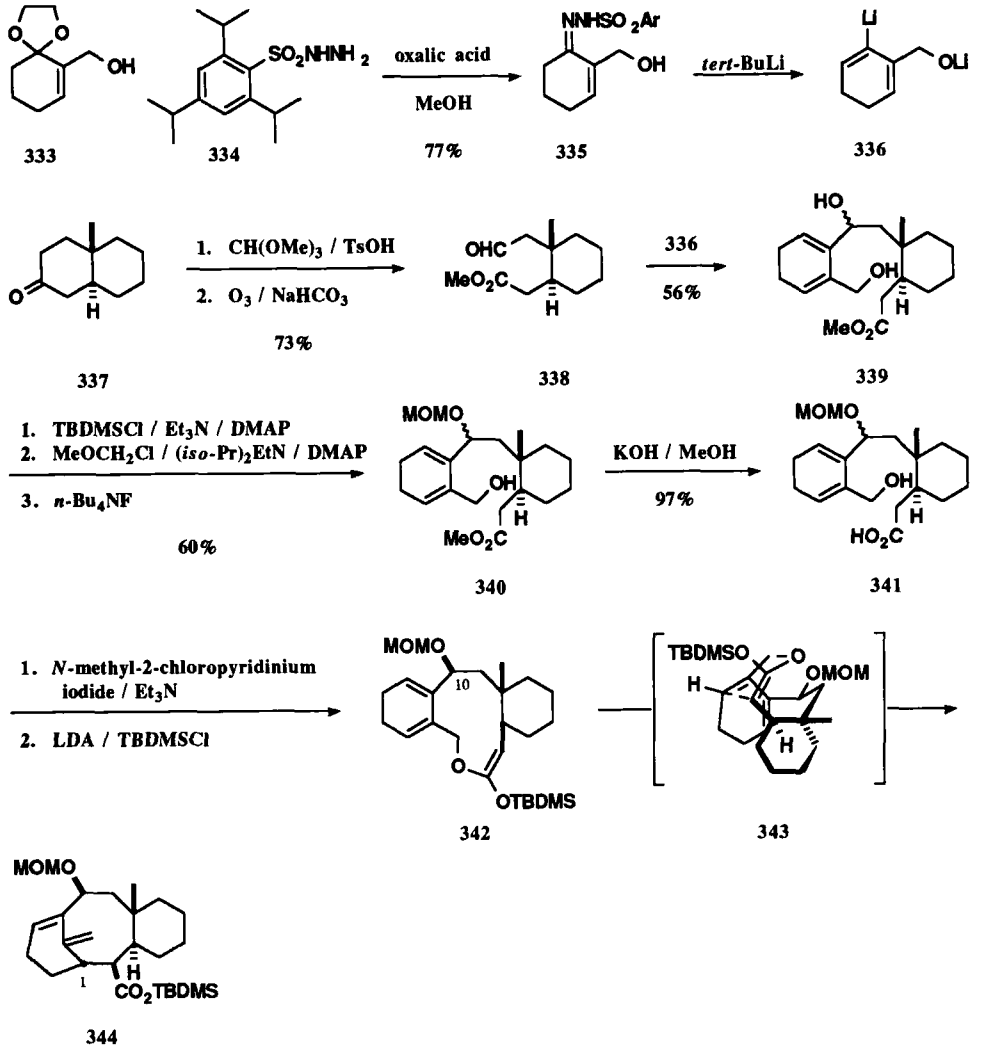


Fig. 45

lactones[74] to the ten-step synthesis of taxane model **344** (Fig. 45). Funk's approach is especially noteworthy because it was the first efficient adaptation of a convergent strategy to the synthesis of a

taxane skeletal model.

Funk's sequence began with ketal alcohol **333**, which represented the A-ring portion of the target. In preparation for the convergent step, **333** was converted to hydrazone **335**, and from there to lithium reagent **336**. The B and C-ring carbons originated in **337**, which was transformed by ozonolysis of the related enol ether into **338**. The interaction of **338** and **336** then created **339** as a mixture of epimers, and there followed a series of adjustments designed to provide hydroxy acid **341**. To transform **341** into the corresponding macrolide required for the key ring contraction step, the Mukaiyama methodology was employed, and a separable mixture of lactone epimers resulted in 63% yield. The stereoisomer having the correct relative configuration at C-10 was carried forward to ketene acetal **342**; Claisen rearrangement of **342** occurred through putative transition structure **343** to establish the taxane carbon skeleton (**344**) in which C-1 relative stereochemistry had been cleanly induced. This was proven by X-ray crystallographic analysis of the carboxylic acid (obtainable in 82% overall yield from the appropriate macrolide epimer) derived from **344**.

Model **344** does not possess the complement of methyl groups about the A-ring required by the natural taxane structures. However, cyclopropanation of the exocyclic methylene moiety followed by hydrogenolysis of a cyclopropyl carbon-carbon bond would serve to introduce the geminal methyl substituents in the adaptation of Funk's route to the preparation of the natural compounds.

5. Kuwajima's Approach

Although Kuwajima's reported model study[75] (Fig. 46) on the synthesis of the taxanes is not convergent, it is of special interest in the context of the present section because it accomplishes the B-ring construction attempted in the earlier work of Kitagawa, Fétizon, and Kende. Kuwajima began with acetal **345**, which, through metalation and copper-induced alkylation by allylic bromide **346**, led to **347**. Following the adjustment of the side-chain oxidation state involved in the conversion of **347** into **348**, the remaining elements of the A-ring were installed through a Michael addition-condensation sequence that created β-diketone **349**. Taking advantage of the known preference of such substituted diketones to undergo silylation at the less hindered oxygen, Kuwajima converted **349** into vinylogous ester **350**. Intermediate **350** was then well suited for its transformation into crucial cyclization substrates **351** and **353-355**. Remarkably, Kuwajima found that **351** underwent an efficient and completely stereoselective transformation with eight-membered ring formation to taxane model **352** upon exposure to a mixture of Lewis acids. Furthermore, similar reactions could be initiated from **353-355**. The products of substrates **354** and **355**, that is, tricyclic systems **356** and **357**, respectively, are created with full and correct control over the relative stereochemistry at C-1, C-9, and C-10. The structure of **356** was confirmed by X-ray crystallographic analysis.

Kuwajima discovered that the origin of the stereochemical control in the formation of **352**, **356**, and **357** was thermodynamic in nature. When low temperature reactions carried out on **354** and **355** were quenched early, cyclized products having a cis disposition of substituents at C-9 and C-10 were detected. However, when these cyclizations were allowed to proceed at higher temperatures, the cis species were found to convert to the single respective diastereomers isolated. Thermodynamic

control is consistent with the observation that double bond geometrical isomer mixtures **354** and **355**

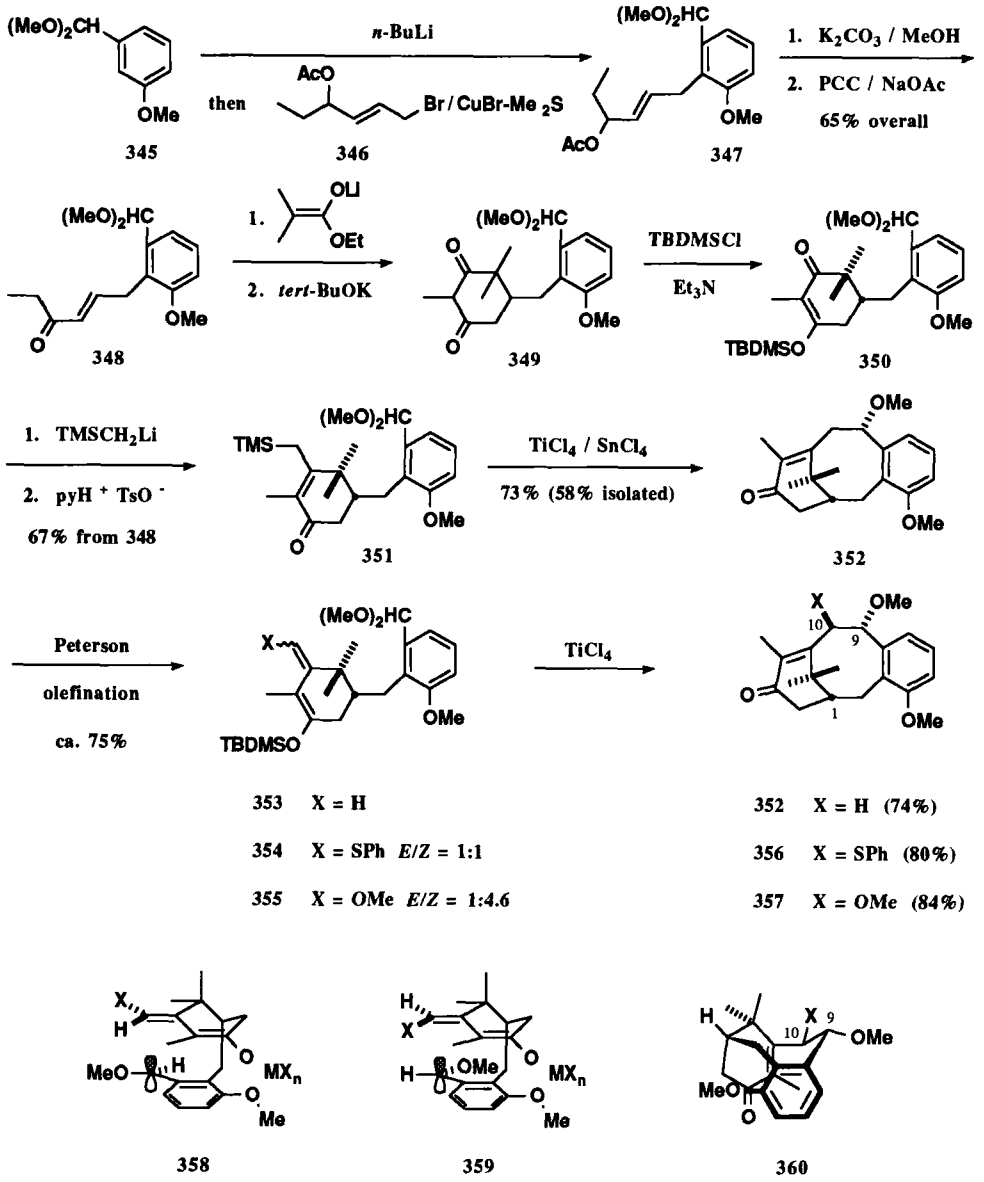


Fig. 46

lead to the corresponding isomerically pure products.

Viewed in somewhat greater detail, it can be seen that Lewis acid induced equilibration of the cyclization steps would allow energetically favored intermediate cation **358** to intervene in the formation of the taxane structures. Cation **358** locates its MeO and X substituents in positions less encumbered than those occupied by the corresponding groups in alternative cation **359**. It is also

clear from product conformational structure **360** that the equatorial orientation of groups at C-9 and C-10 allowed by their (natural taxane relative) stereochemistry would be preferred relative to any alternative. Conformation **360** follows directly from transition structure **358** and is related to the endo conformation observed previously by Shea (section I. B. 1. a.) for very similar materials. Kuwajima suggested that the chelation of the Lewis acid metal center by the ring A and C oxygens depicted in **358** is responsible for bringing the reactive sites in proximity. Considering the limited success witnessed in earlier attempts to implement B-ring closure schemes, this feature might be critical for the success of Kuwajima's approach.

B. Completion of the B-Ring through Bond Cleavage in A[B]C → ABC Strategies

A significant number of approaches that bring together the A and C-rings avoid the direct

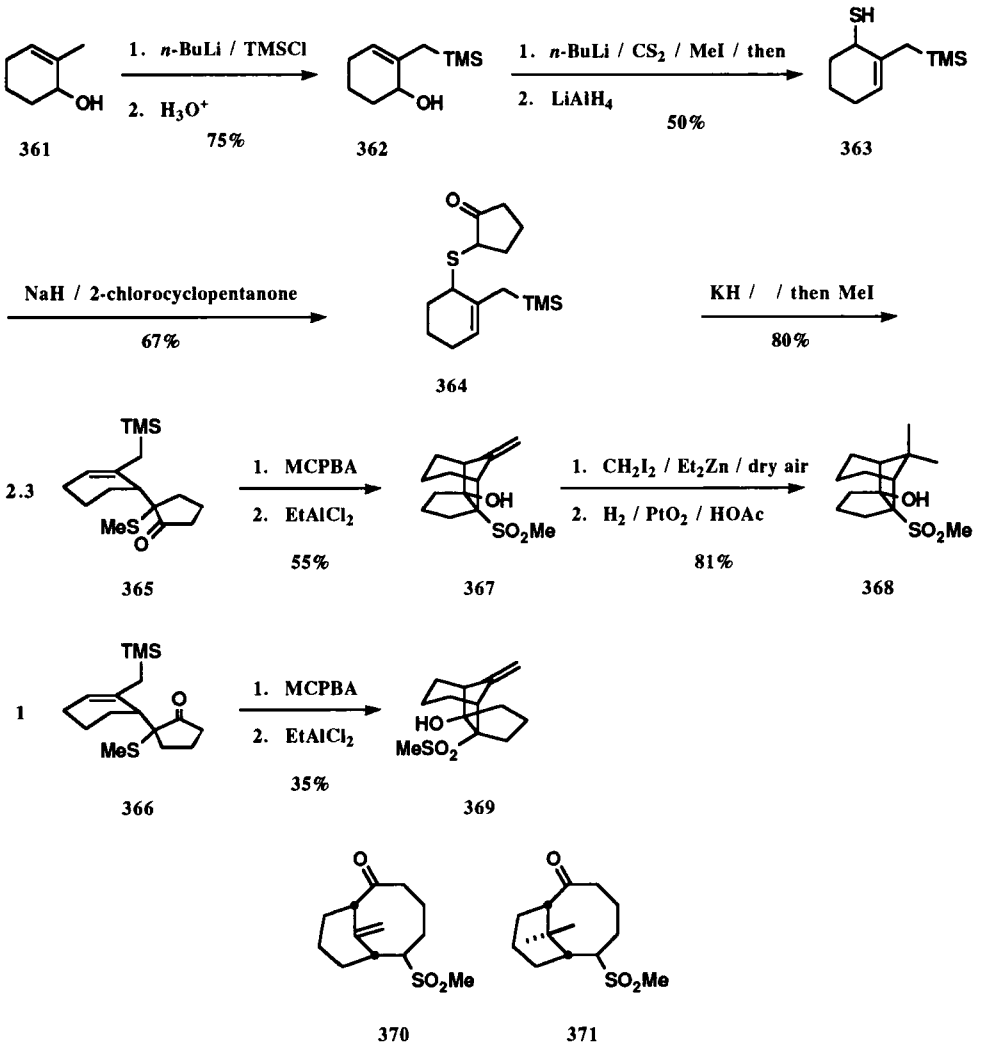


Fig. 47

closure of the B-ring. In these strategies, bond cleavage or reorganization in polycyclic intermediates with masked eight-membered rings completes the tricyclic taxane framework.

1. Trost's Approach

One of the earliest reports on the synthesis of the taxanes was that of Trost,[76] who, in 1982, disclosed an intriguing plan for the assembly of the taxane AB moiety. Beginning with allylic alcohol **361** (Fig. 47), allylic silane **362** was prepared through a lithiation-silylation procedure. [3,3] Sigmatropic transposition of the thiocarbonate derived from **362** followed by reductive cleavage of the product led to allylic thiol **363**. After **363** was alkylated with 2-chlorocyclopentanone to deliver **364**, the latter material was subjected to a second [2,3] sigmatropic rearrangement induced by potassium enolate formation. Work-up of that process with methyl iodide yielded diastereomers **365** and **366**. The four-step conversion of **362** to **365/366** was required by the inability of derivatives of **362** bearing allylic leaving groups to undergo direct displacement (but see Fig. 48). Trost suggested that the success of the sigmatropic reactions resulted from the quasi axial disposition of the allylic groups that is a consequence of A strain involving the (trimethylsilyl)methyl substituent. Further oxidative treatment of **365** and **366** gave the corresponding sulfones, and their exposure to Lewis acid created tricyclic systems **367** and **369**. Intermediate **367** was subjected to the Furukawa version of the Simmons-Smith cyclopropanation, the goal being to produce **368** through cyclopropane hydrogenolysis. Hydroxy sulfones **367**, **368**, and **369** were the basis of Trost's investigation into the fragmentation intended to create the taxane eight-membered B-ring.

When either **367** or **369** were exposed to a stoichiometric amount of KH in DME, there was obtained a 4:1 mixture of **369** and **370** as a single diastereomer. The yield of fragmentation product **370** could be enhanced by adding the potassium ion complexing agents 18-crown-6 or [2.2.2]-cryptand; in the presence of the latter additive, **369** and **370** were produced in a 1:9 ratio, respectively. These results are accommodated by a mechanism that provides for fragmentation and reclosure of alkoxide ion pairs. When the potassium counterion is not sequestered by complexing agent, the closed potassium alkoxide related to **369** is favored because O-K bonding is preferred to the C-K bonding that would apply to the sulfone anion related to **370**. The anion of hydroxy sulfone **369** accumulates in preference to that of **367** because the former is less sterically encumbered. However, Trost argued that [2.2.2]-cryptand "solvates" the potassium cation to such an extent that in naked anion form, the open sulfone carbanion related to **370** is preferred due to its better stabilization through sulfone polarization. In support of this mechanistic picture, Trost observed that reactions emanating from either **367** or **369** induced by a *catalytic* amount of *tert*-BuOK led cleanly to **370** alone. In these experiments, the neutral molecules and not ion pairs are being equilibrated, and the less congested "open" keto sulfone is favored.

Geminal dimethyl structure **368** exhibited analogous behavior, except that its treatment with stoichiometric KH in the absence or presence of cation sequestering agents led only to endo-exo equilibration, as did its exposure to two equivalents of *tert*-BuOK in DMSO. However upon treatment with a catalytic amount of *tert*-BuOK, it, too, underwent fragmentation, in this instance to give

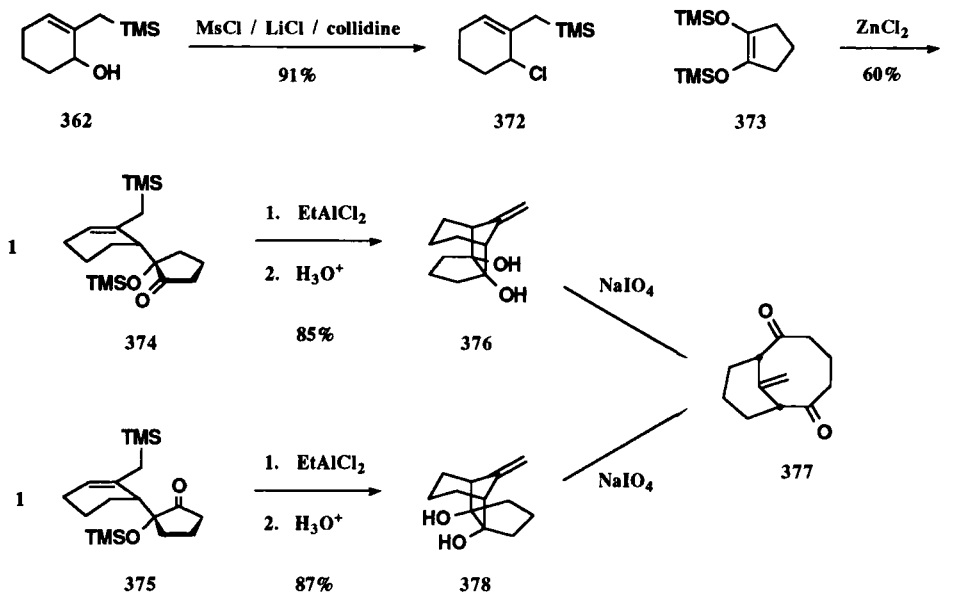


Fig. 48

open structure **371**.

Trost employed the same strategic concept in the construction of taxane AB structure **377**[77] (Fig. 48). In this sequence, allylic chloride **372** underwent a Lewis acid induced condensation with **373** to provide a stereorandom mixture of **374** and **375**. Each of these diastereomers then was led separately through a second Lewis acid induced step that, after silyl ether hydrolysis, gave the respective tricyclic diols **376** and **378**. Of the two allylic silane-ketone condensations, the one leading to more congested **376** was the slower. However, **376**, with its exposed vicinal diol structure, was cleaved by periodate more rapidly than its stereochemical relative **378**. In both cases, diketone **377** resulted.

With the next report[78] from the Trost group, it became clear that the chemistry summarized above was intended to lead to the AB substructure in a convergent synthesis of the taxanes. To implement this plan, an appropriate perhydroindanone incorporating the taxane C-ring would be required as depicted in Fig. 49. Dieckmann condensation of ketal diester **379** with in situ methylation of the β-keto ester enolate created intermediate **380**. A series of classical operations carried **380** to the Robinson annulation product **382** and culminated in *trans*-fused enol ether **383**. The sequential conversion of **383** into its copper enolate and condensation with methyl chloroformate gave *C*-carboxylation and *O*-carboxylation to produce **384**. Hydrolysis yielded β-keto ester **385** with a thermodynamically favored equatorial carbomethoxy group. Equatorial delivery of hydride to the ketone carbonyl of **385** and further reduction of the resulting hydroxy ester formed, after an adjustment of the protection scheme, keto acetonide **387**. The final sequence of operations was designed to contract

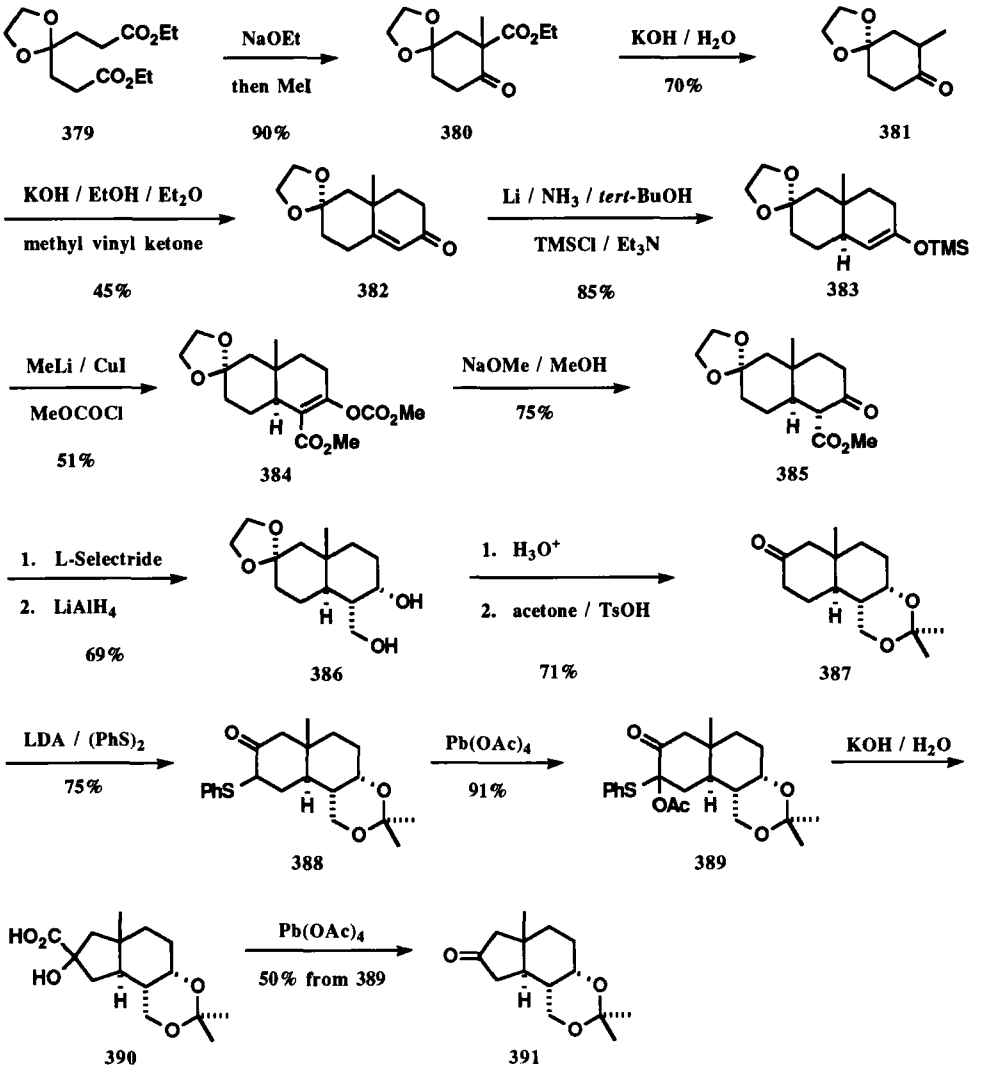


Fig. 49

the cyclohexanone ring of **387** through a modified benzilic acid rearrangement. Thus, sulfenylation and acetoxylation of the site α to the carbonyl of **387** gave **389**. Base treatment of **389** yielded rearrangement product **390**. Finally, oxidative decarboxylation of **390** produced the target perhydroindanone system in the form of **391**. Presumably, **391** will provide, through appropriate manipulation, an analogue of **373** suitable for condensation with **372** and elaboration to the tricyclic taxane skeleton.

The most recent Trost publication[79] in the taxane area has described a related scheme for the elaboration of an optically active and more complex perhydroindanone intermediate (Fig. 50).

Enantiomerically pure hydroxy acetonide **392** was dehydrated to **394**, which allowed the preparation of epoxide **395** in a stereoselective manner. In an imaginative exploitation of the mechanistic features of the Swern oxidation, epoxide **395** was opened by DMSO through acid catalysis to give an intermediate that, upon in situ exposure to base, decomposed to hydroxy ketone **396**. A byproduct of this

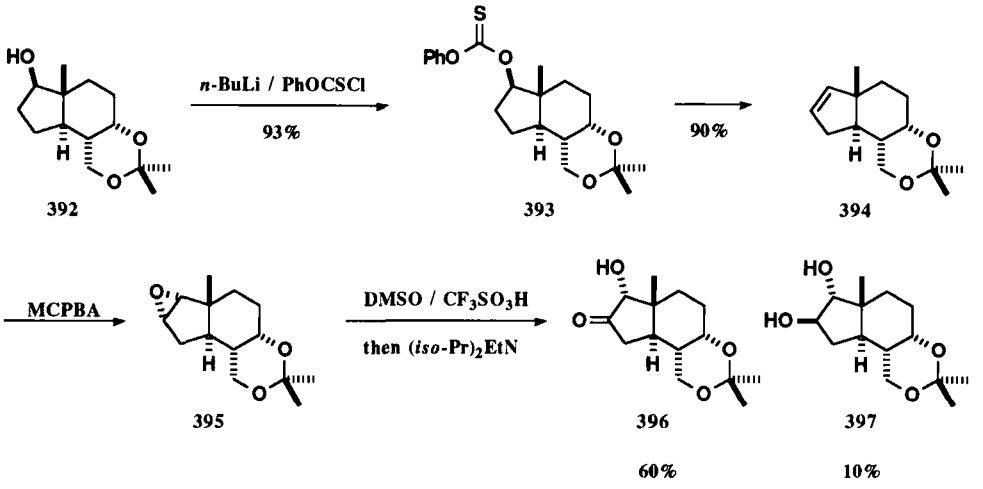


Fig. 50

process, evidently caused by adventitious water, was diol **397**. Several additional examples of this transformation of epoxides were investigated by Trost.

2. *Inouye's First Approach*

Inouye[80] has described a route to the taxanes designed to proceed according to the disconnections illustrated in Fig. 51. This unique strategy was envisaged to involve the bond reorganization implied by arrow A to establish the taxane A-ring, and the annulation implied by arrow B to install the C-ring. Thus starting materials of the homocamphor type would be required. Although Inouye has evidently abandoned this approach, two syntheses of intermediates modeled after **398** in Fig. 51 have been reported by the Inouye group. In the first (Fig. 52), homocamphor quinone (**400**) was converted through fairly conventional operations to keto nitrile **403**. This structure was then transformed into vinyl chloride **405**, which underwent a sulfuric acid mediated hydrolysis to diketone **406**. Aldolization of **406** and subsequent conjugate addition to the resulting tricyclic enone (**407**) produced **408**.

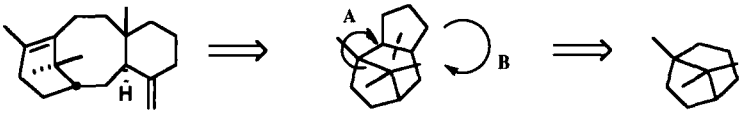


Fig. 51

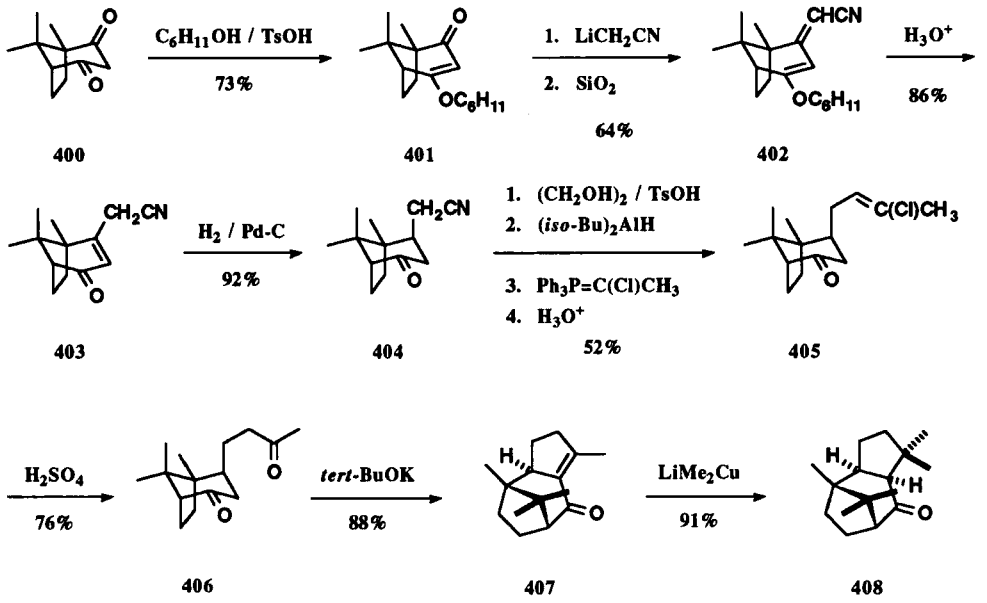


Fig. 52

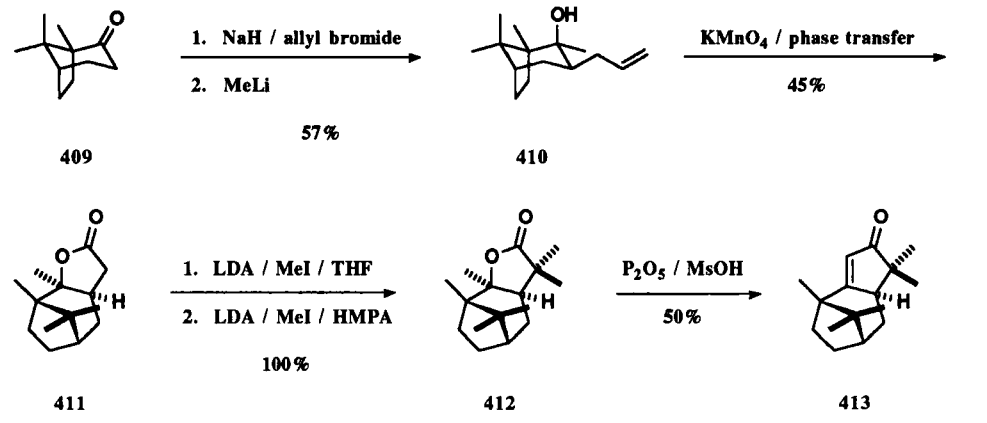


Fig. 53

A second intermediate based on the **398** prototype was **413** (Fig. 53). In this sequence, homocamphor (**409**) was led first to lactone **411** and then to lactone **412**. Strong acid treatment of **412** prompted its conversion to enone **413.**

3. Blechert's First Approach

In section I. C. 1. e., an AB → ABC approach by Blechert was developed as a consequence of the failure of an earlier plan[44] to accommodate the C-8 angular methyl group. For completeness, Blechert's earlier plan is illustrated in Fig. 54. As in his later work, bicyclic diketone **161** figured

prominently in the early phase of the sequence. Its conversion to benzyl carbonate derivative **414** provided a substrate for intermolecular photochemical [2+2] cycloaddition with cyclohexene. That process succeeded in producing cyclobutane **415**, but failed, from a regioselectivity point of view, with 1-methylcyclohexene. Two additional photoaddition types proved to be unproductive, as well. Intermolecular [2+2] cycloaddition of an analogue of **414** bearing a hydroxy group instead of the ketal gave **419** without stereoselectivity at the critical C-8 site. Furthermore, intramolecular photochemical closures of **420** were unsuccessful. Hydrogenolysis of **415** gave a stable ketol intermediate, which, upon reaction with hydroxide, led to cyclooctanedione **416**. The use of the benzyl carbonate masking group was essential since the attempted saponification of the acetate analogue related to **415** gave **421** instead of **416**.

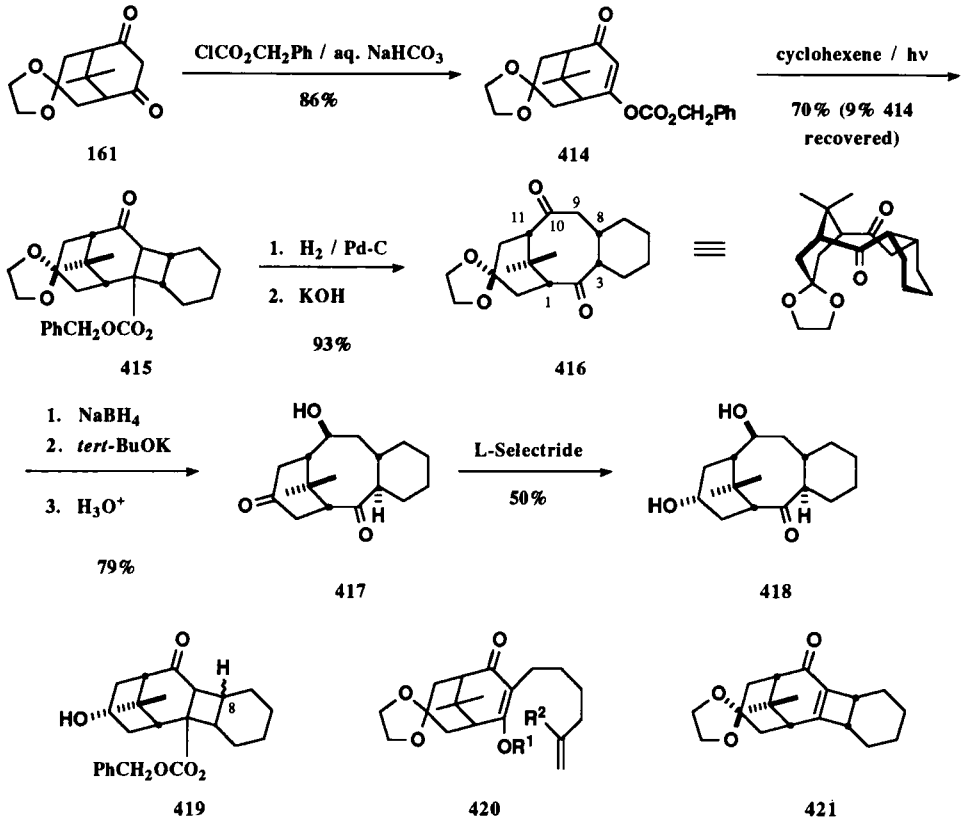


Fig. 54

Tricycle **416** possesses the carbon connectivity of the taxanes but is stereochemically incorrect at C-3. Blechert found through deuterium exchange experiments that **416** underwent base catalyzed enolization toward C-1, C-9, and C-11, but not C-3. While this reactivity has interesting ramifications for functionalization at these sites, it prevented the epimerization at C-3 that was required to establish the correct relative stereochemistry at C-1, C-3, and C-8. Fortunately, Blechert

discovered that reduction of the C-10 carbonyl in **416** allowed the corresponding hydroxy ketone to be epimerized at C-3 quantitatively. The stereochemistry of the reduction of **416** occurs as a consequence of the indicated conformation detected through X-ray crystallographic analysis. Deketalization then gave **417**, which itself could be reduced stereoselectively to **418**.

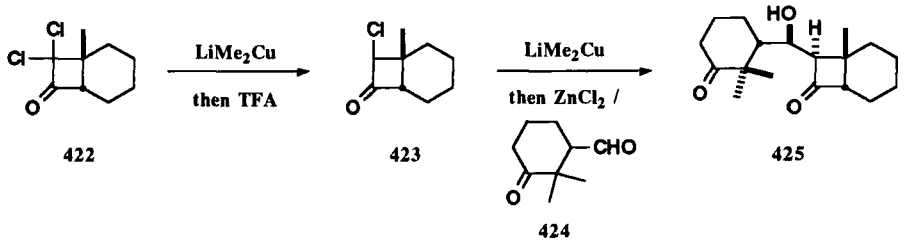


Fig. 55

4. Clark's Approach

In 1984, Clark[81] disclosed the elements of an interesting convergent strategy to the taxanes. In this plan, a racemic C-ring unit is joined with a racemic A-ring partner to provide ultimately the complete tricyclic taxane skeleton. In order for the convergent operation to avoid the formation of a

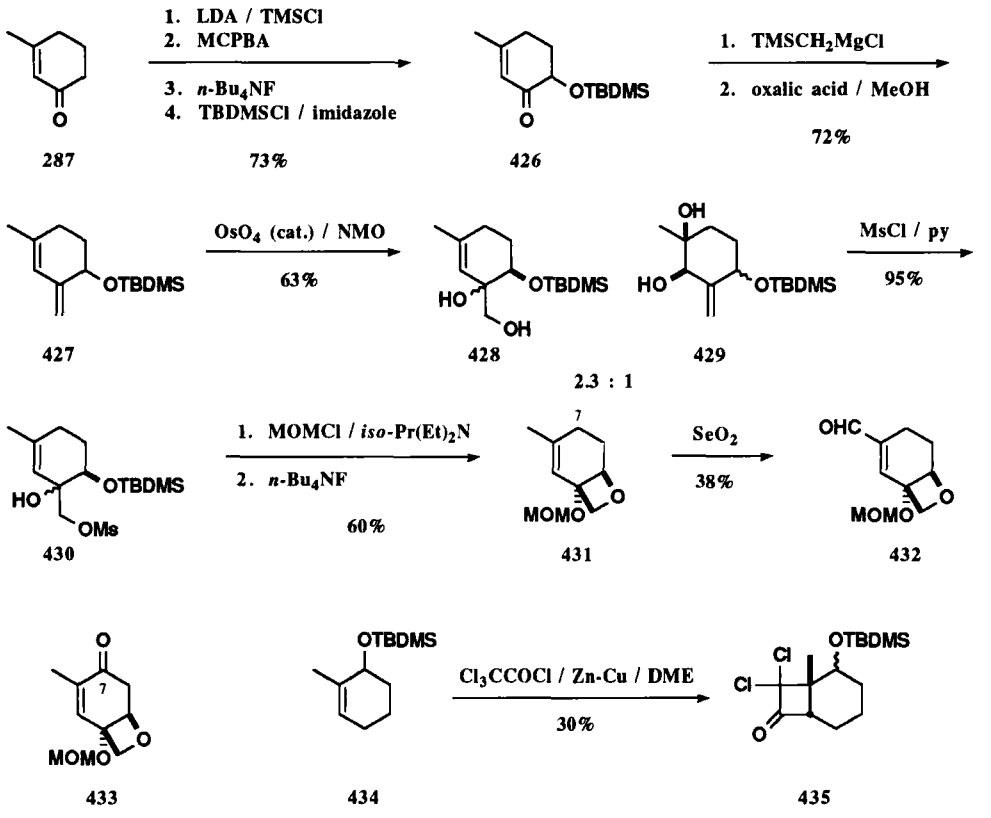


Fig. 56

complicated stereoisomeric mixture, it would have to proceed with mutual resolution of the components involved. Clark demonstrated the feasibility of this feature, as indicated in Fig. 55. Racemic dichloroketene–1-methylcyclohexene adduct **422** was reductively monodechlorinated through exposure to lithium dimethylcuprate. This procedure led to **423**, which underwent its own dechlorination induced by the same cuprate reagent. In this case, however, the intermediate enolate was exposed to racemic **424** to deliver diastereomerically pure aldol product **425**.

With this background, Clark next embarked on syntheses of more realistic A and C-ring precursors.[82] Enone **287** (Fig. 56) underwent a Rubottom oxidation sequence, which gave **426** and was followed by a Peterson olefination that gave **427**. Vicinal hydroxylation of **427** proceeded with modest regio and stereoselectivity in providing a mixture of **428** and **429**. The diastereomers of **428** were carried forward to mesylate stereoisomers **430**, of which one possessed stereochemistry appropriate for the ring closure that yielded oxetane **431**, an obvious candidate for incorporation as the taxol C-ring substructure. For an oxetane of this sort to provide all the functional details of the taxol C-ring, it would have to undergo oxygenation at the C-7 site. However, Clark showed that allylic oxidation of **431** proceeded at the methyl group to give **432**, and not at the endocyclic methylene position (see **433**), as would be expected. Clark did construct a more highly functionalized version of previously encountered **422** in the form of **435**.

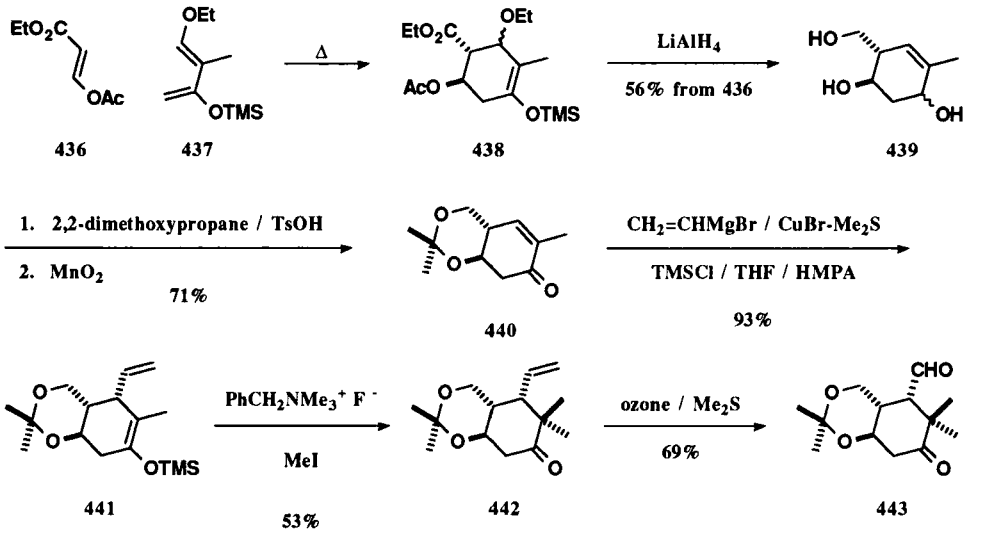
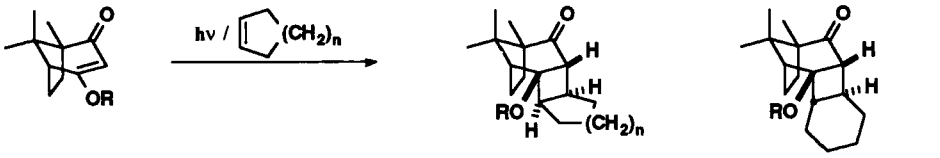


Fig. 57

Clark also investigated the preparation of more elaborate A-ring precursor **443** (Fig. 57). The Diels-Alder cycloaddition of **436** and **437** led to highly functionalized cyclohexene **438**. Further conventional operations then produced enone **440**. Under carefully specified conditions, **440** accepted an axial vinyl group from the corresponding magnesiocuprate reagent to give **441**, after in situ silylation. Finally, fluoride-induced methylation and ozonolysis culminated the synthesis of **443**.



444 R = Me

445 R = Ac

446 R = Me (n = 1) 50%

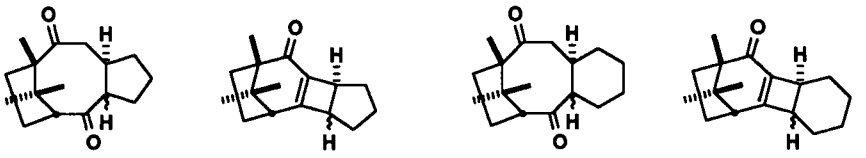
447 R = Ac (n = 1) 55%

448 R = Me (n = 2) 25%

449 R = Ac (n = 2) 28%

450 R = Me 25%

451 R = Ac 28%



452 453 454 455

446 —TMSI→ no reaction

447 —H_2SO_4 / MeOH→ 452 (30%)

447 —K_2CO_3 / MeOH→ 452 (60%) + 453 (20%)

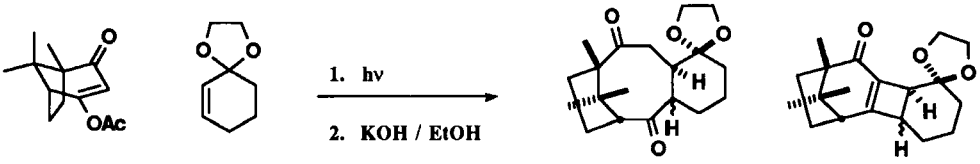
448 —TMSI→ 454 (10%)

449 / 451 —H_2SO_4 / MeOH→ 454 (40%) + 455 (10%)

449 / 451 —KOH / EtOH→ 454 (60%) + 455 (20%)

450 —TMSI→ 454 (90%)

Fig. 58



445 456 457 (40%) 458 (15%)

Fig. 59

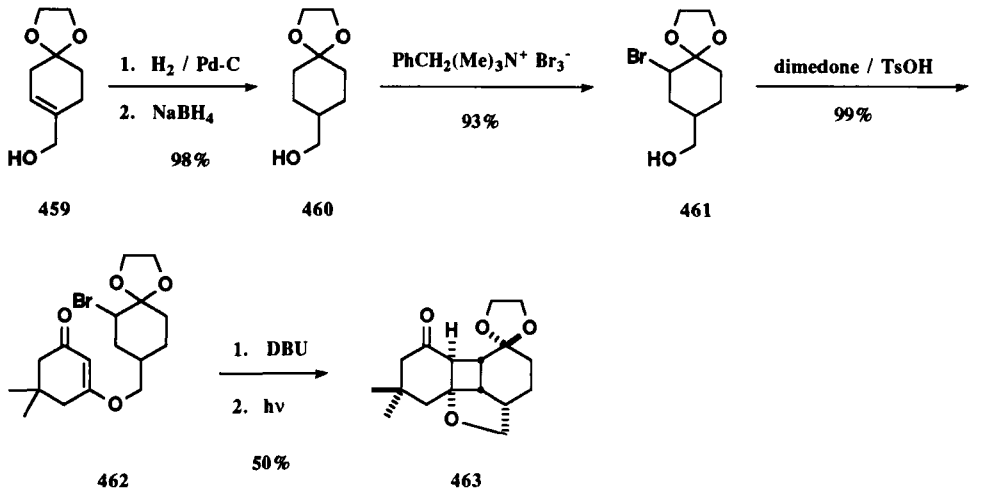


Fig. 60

5. *Berkowitz' Approach*

Berkowitz has reported[83] a strategy, similar to several others, that relies on photochemical [2+2] cycloaddition-fragmentation chemistry for the creation of the eight-membered B-ring. Both intermolecular and intramolecular cycloadditions found their way into Berkowitz's plans. For example, Fig. 58 indicates a series of intermolecular photoadditions between homocamphor derivatives **444** and **445**, and cyclopentene and cyclohexene. The interesting stereochemical feature of these reactions is the facial control imposed by the homocamphor geminal dimethyl moiety. The structures of **446**, **448**, and **450** rest on X-ray crystallographic determinations. Berkowitz subjected **446-451** to

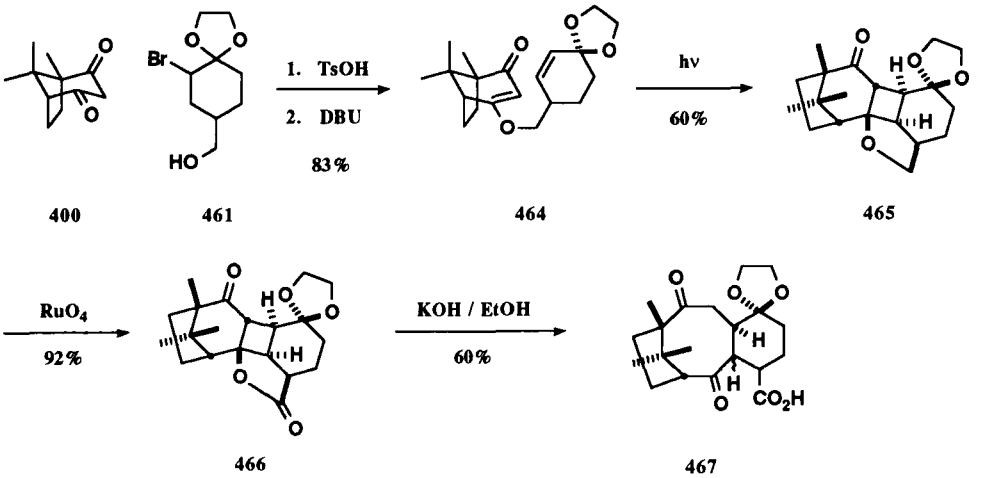


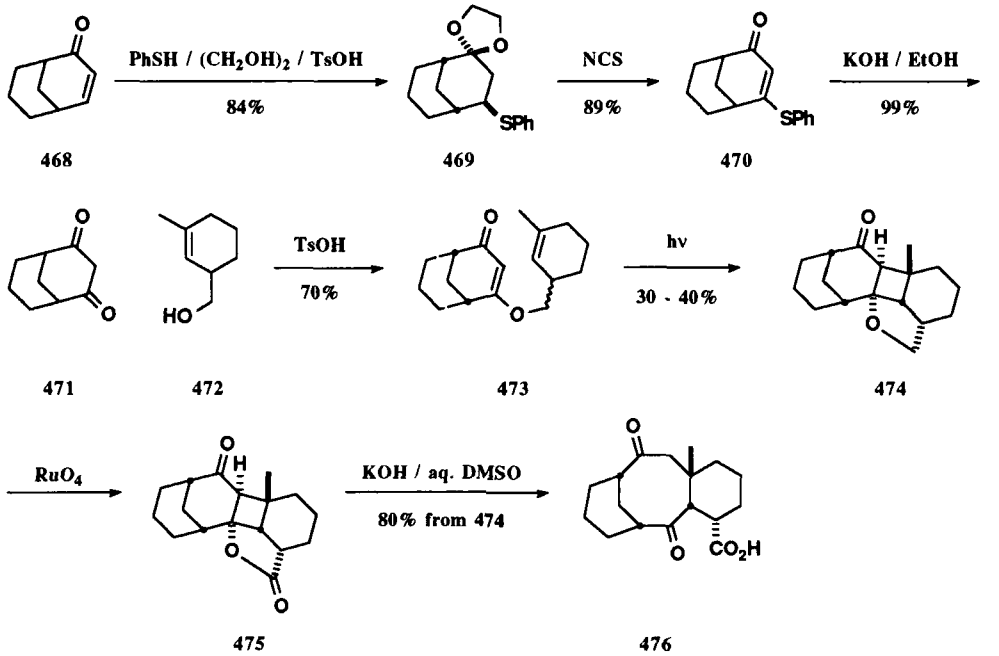
Fig. 61

a variety of fragmentation protocols, which were complicated in some instances by elimination products **453** and **455**. Furthermore, a similar approach was applied by Berkowitz to the preparation of C-ring functionalized **457** (Fig. 59).

Two intramolecular schemes were tested by the Berkowitz group. Fig. 60 illustrates the preparation of a dimedone-derived vinylogous ester that afforded photoproduct **463** upon irradiation. Alcohol **461** led also to homocamphor-derived vinylogous ester **464** (Fig. 61). The latter material underwent a photochemical transformation to **465** whose stereochemical details were postulated by Berkowitz on the basis of his experience with the above intermolecular cycloadditions. To lead **465** through a fragmentation sequence to a tricyclic taxane model, Berkowitz submitted it to a Rylander oxidation that gave lactone **466**. Base treatment of **466** then completed the preparation of taxane model **467**.

6. *Inouye's Second Approach*

Inouye, in an approach unrelated to his first (section II. B. 2.), disclosed a photochemical route[84] very similar to the intramolecular version of Berkowitz's approach. Inouye paired diketone **471** with alcohol **472** in the preparation of vinylogous ester diastereomers **473** (Fig. 62). Since only one of the diastereomers underwent photochemical conversion to **474**, the efficiency of this step was limited. Like Berkowitz, Inouye transformed the tetrahydrofuran photoproduct into the corresponding lactone through a Rylander oxidation, in this case to afford **475**. Saponification then completed the preparation of taxane model **476**.



468 469 470 471 472 473 474 475 476

Fig. 62

7. *Winkler's Approach*

Winkler, too, has developed a [2+2] cycloaddition-fragmentation strategy to the taxanes. However, there are several interesting features of Winkler's plans that distinguish them from some of the apparently similar strategies considered in this review.

The initial and simplest implementation of Winkler's approach[85] is depicted in Fig. 63. The alkylation of the dianion derived from β-keto ester **477** with 4-pentenyl iodide gave **478**, which through a trifluoroacetic anhydride-trifluoroacetic acid mediated reaction with acetone produced dioxenone **479**. Presumably as a consequence of the indicated reactive conformation of **479**, it underwent photochemical conversion to **480** in which the newly formed six and four-membered rings are *trans*-fused. The stereochemistry of **480** then determined the inside-outside stereochemical nature of the bridge in fragmentation product **481**. Keto acid **481**, characterized by X-ray crystallography, was converted through a Barton decarboxylation procedure to taxane AB substructure analogue **482**, which allowed its comparison to the known isomeric and conventionally bridged ketone **483**. At least at the time of Winkler's report, **482** was the smallest inside-outside bicyclic system that had yielded to synthesis.

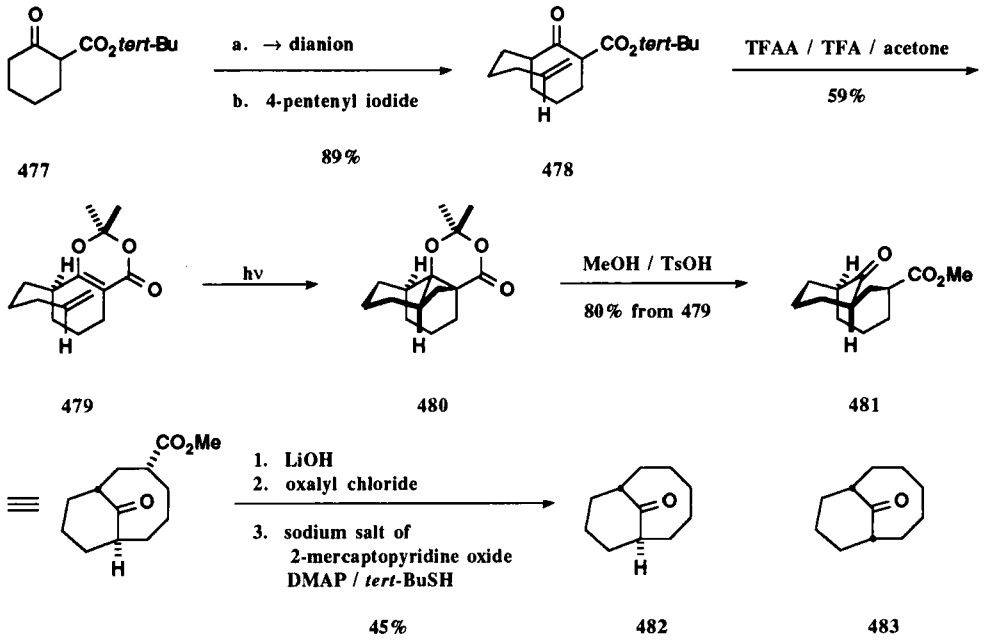


Fig. 63

In order for Winkler's route to the taxane AB substructure to be incorporated into a preparation of a tricyclic taxane system, the carbocyclic ring in photosubstrate **479** would need to be fused to what must become the taxane C-ring. Winkler's initial examination[86] of this modification is shown in Fig. 64. Keto ester **484** was converted to dioxenone **485**, and then to a mixture of epimers **486** and

487. Whereas the irradiation of **486** led to a mixture of products, the irradiation of **487** led cleanly to photoproduct **488** whose structure was established by X-ray crystallography. However at this stage, Winkler's plan went awry because the intended fragmentation of **488** to produce **491** led instead to rearrangement product 490. Evidently, an acid-induced Wagner-Meerwein shift occurs in **488** to produce intermediate **489**, which then closes to isolated lactone **490**. Again, the structure of **490** rests on an X-ray crystallographic determination. Winkler suggested, on the basis of MM2 calculations, that the transformation of **488** into **490** is driven by the relief of strain associated with the conversion of a *trans*-fused bicyclo[4.2.0]octane fragment into the *cis*-fused fragment embedded in **490**.

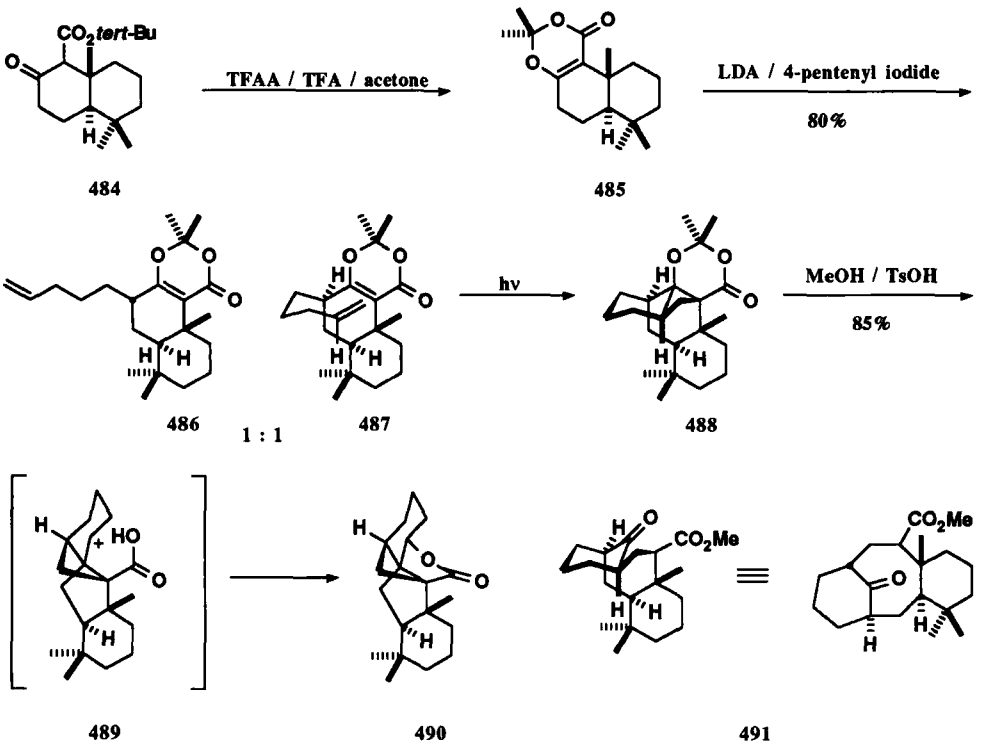
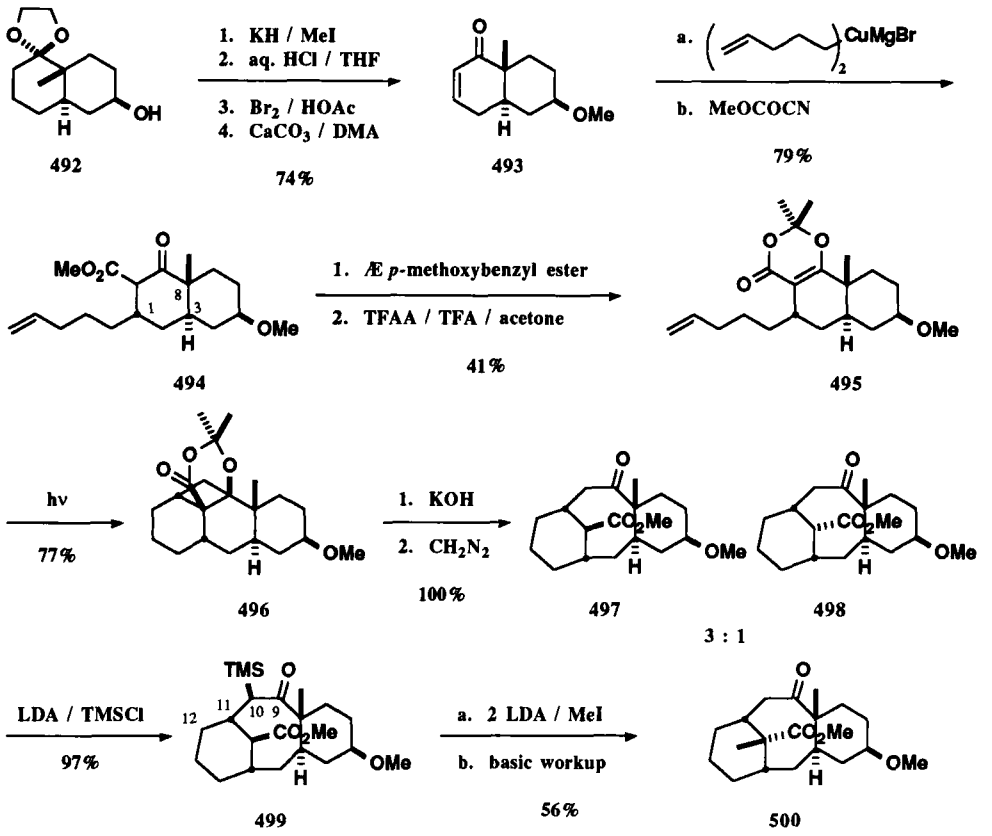


Fig. 64

The most recent disclosure[87] from the Winkler group has described a solution to the problem encountered in Fig. 64. In this work, ketal alcohol **492** was converted to enone **493**, which suffered conjugate addition of a 4-pentenyl group and trapping by methyl cyanoformate to provide **494**. The axial attachment of the 4-pentenyl side chain provided what would become the appropriate C-1, C-3, C-8 stereochemical relationship. Dioxenone formation followed and created photosubstrate **495**. Intermediate **495** differed from **487** above in the stereochemistry of its 4-pentenyl side chain and in the orientation of the dioxenone chromophore. Although the irradiation of **495** led successfully to **496**, photoproduct **496** was dissimilar to those encountered previously by Winkler in that its newly formed six and four-membered rings are *cis*-fused. Nevertheless, **496** served for the purpose at hand

in undergoing transformation upon base-induced fragmentation to a mixture of epimeric tricyclic taxane models **497** and **498**. In a final sequence that emanated from major fragmentation product



492 493 494 495 496 497 498 499 500

Fig. 65

497, this substance was subjected to a ketone enolate silylation reaction whereupon it delivered the remarkable *C*-silylation product **499**. The structure of **499** was secured through X-ray crystallography. Double deprotonation of **499**, and exposure of the dianion to methyl iodide and then to a basic workup to cleave the carbon-silicon bond gave **500**. Winkler suggested that the unusually congested taxane B-ring forced the anomalous *C*-silylation of the enolate derived from **497**. In essence, taxanes that lack the C-11–C-12 bridgehead double bond are unable to accommodate unsaturation at C-9–C-10, as would be required in the expected enol silyl ether isomeric to **499**.

8. A Variation on Fétizon's Second Approach

Previously documented were taxane synthesis strategies that depend on intermolecular photochemical [2+2] cycloaddition-fragmentation chemistry to complete the B-ring. Among them are the sequences reported by Fétizon (section I. C. 1. d.), Blechert (sections I. C. 1. e. and II. B. 3.), and Berkowitz (section II. B. 5.). Fétizon has disclosed[88] a modification of his previously

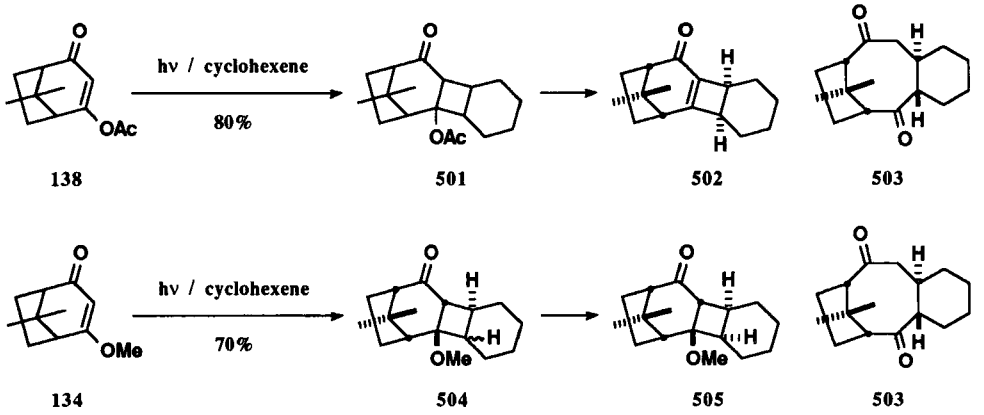


Fig. 66

discussed photochemical route to the taxanes (section I. C. 1. d.) that is very similar in style to those of Blechert and Berkowitz, and differs from his own above photochemical approach more in strategy than in tactics. Bicyclic enol acetate **138**, representing the taxane AB substructure, underwent cycloaddition with cyclohexene to give a 3:1 mixture of unspecified diastereomers **501** (Fig. 66). The stereochemistry of this process may be interpreted in view of Berkowitz's results referred to above. Whereas the treatment of **501** with KOH in anhydrous ethanol afforded **502** in 65% yield, in aqueous ethanol a mixture of **502** (32%) and **503** (48%) resulted. Unfortunately, **503** was shown by X-ray crystallography to possess an incorrectly *trans*-fused C-ring, an observation that is not surprising given the experience of Berkowitz. Fétizon initiated a similar sequence with enol ether **134**. In this case, **504**, again as a 3:1 mixture of isomers, was converted by exposure to methanolic hydrochloric acid to **503** in 55% yield. Less slowly fragmented photoproduct diastereomer **505** could be recovered from this experiment.

At this point, it is instructive to summarize the stereochemical proclivities of the various AB chromophores involved in the photochemical approaches that focus on cyclobutane construction at C-2, C-3, C-8, and C-9. These include all except Swindell's (section I. D. 1.) and Winkler's (section II. B. 7.). The critical issue in these approaches is whether the taxane relative stereochemistry at C-1, C-3, and C-8 is handled properly. Indeed, this is one of the fundamental stereochemical issues that any taxane synthesis strategy must take into account. Blechert succeeded in fixing photochemically the C-1 and C-8 stereocenters, and then adjusted stereochemistry at C-3 through a late epimerization (Fig. 67). The important stereochemical control device in Blechert's approach was the ketal. This may be appreciated by remembering his experience with the formation of **419** in Fig. 54, and by considering the results of Berkowitz and Inouye. Berkowitz found his homocamphor-derived substrates intercepted an olefin in such a way that the C-1–C-8 relative stereochemistry was incorrectly introduced. As noted by Berkowitz,[83] the geminal methyl grouping was presumably at fault. Blechert cleverly solved this problem by using the ketal moiety, which overcame the control imposed by the

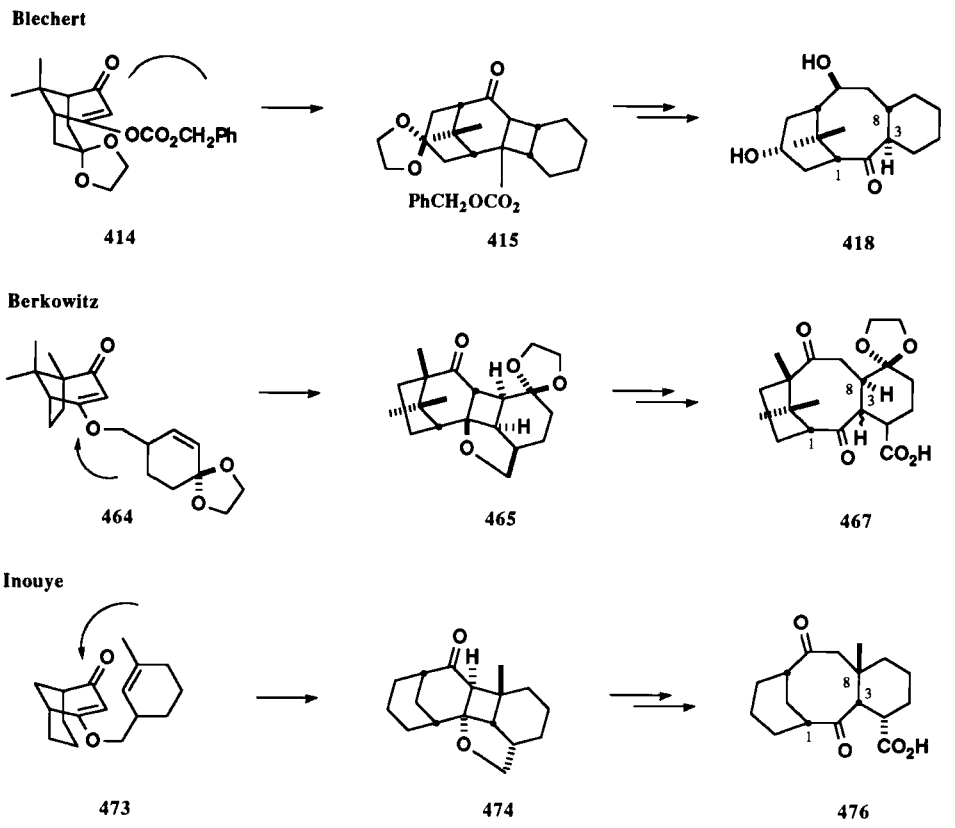


Fig. 67

geminal methyl feature. On the other hand, Inouye's unadorned system underwent cycloaddition on the exo face of the vinylogous ester chromophore through a process that correctly established C-1–C-8 relative stereochemistry.

9. Ghosh's Approach

Ghosh[89] reported quite recently a fragmentation-based strategy for taxane skeleton construction that differs from many such strategies in that a connection between C-2 and C-10 is broken in the formation of the eight-membered B-ring. Unsaturated anhydride **506** (Fig. 68) underwent a Diels-Alder reaction with cyclopentadiene to provide **507**, after two functional group manipulations. In the key step, diester **507** led through reductive bond cleavage to AB analogue **508**. Finally, the five-membered ring of **508** could be enlarged by way of double bond hydration and Jones oxidation followed by ring expansion with ethyl diazoacetate. An analogous sequence initiated by anhydride **511** produced tricyclic model **513**.

10. Paquette's Approach

A limited number of approaches to the taxanes that employ the Cope rearrangement has been reported, such as Martin's that was considered previously in section I. C. 1. a. More recently,

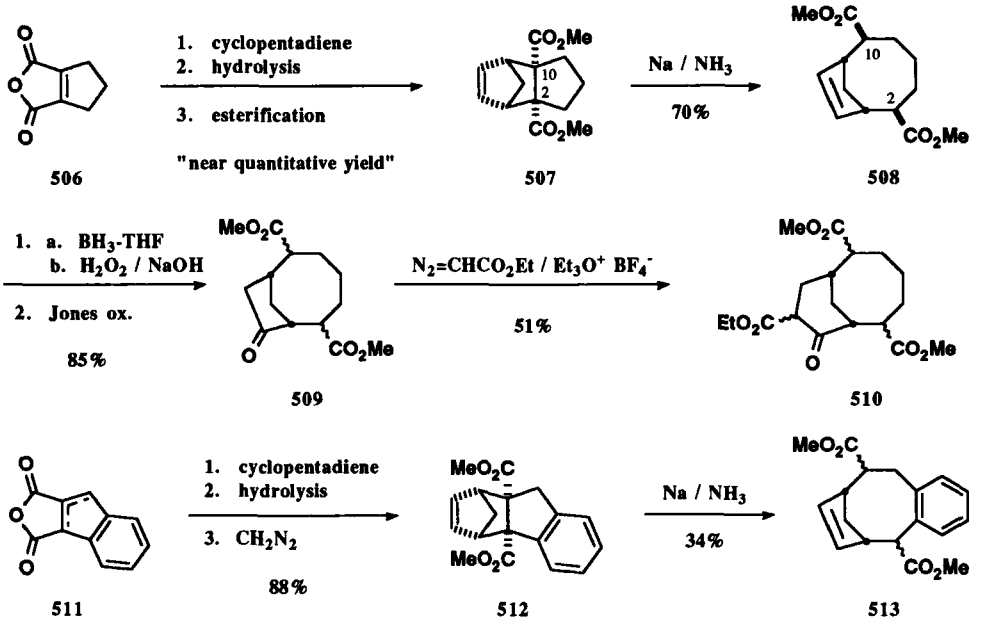


Fig. 68

additional strategies of this kind have been revealed and they make up the remainder of this review. Paquette[90] has explored several intriguing sequences that exploit the Cope rearrangement. While he has not explicitly delineated a complete plan for the preparation of the taxanes, clearly much of his work was initiated with these structures in mind.

Fig. 69 depicts two sequences of some relevance to the synthesis of the taxanes. Optically active **514** suffered the addition of the vinylcerium reagent to provide **515**. When **515** was exposed to KH, an anion-accelerated Cope rearrangement ensued and gave *E*-cyclononene **518**. The conformation of **518** illustrated is a direct consequence of the transition structure associated with the Cope rearrangement, and controls the stereochemistry of the hydride reduction that leads to **519**. In contrast, the epoxidation of **518** allows access to a more stable conformation as indicated by an X-ray crystallographic analysis carried out on product **520**.

Paquette began a more elaborate series of transformations with **521**, whose related cerium reagent added to **514** to yield **522**. In this case, the anionic oxy-Cope process was followed by methylation of the initially produced enolate, thus forming angularly methylated **523**. Paquette demonstrated that the conformational bias imposed by the Cope rearrangement transition structure led to the less stable atropisomer **523** by converting it thermally into more stable atropisomer **524**. Evidently, the activation barrier that separates **523** and **524** is sufficiently high that the mild conditions of the Cope rearrangement allow **523** to accumulate, a situation reminiscent of Shea's atropselective intramolecular Diels-Alder reactions (section I. B. 1. a.). Furthermore, Paquette highlighted

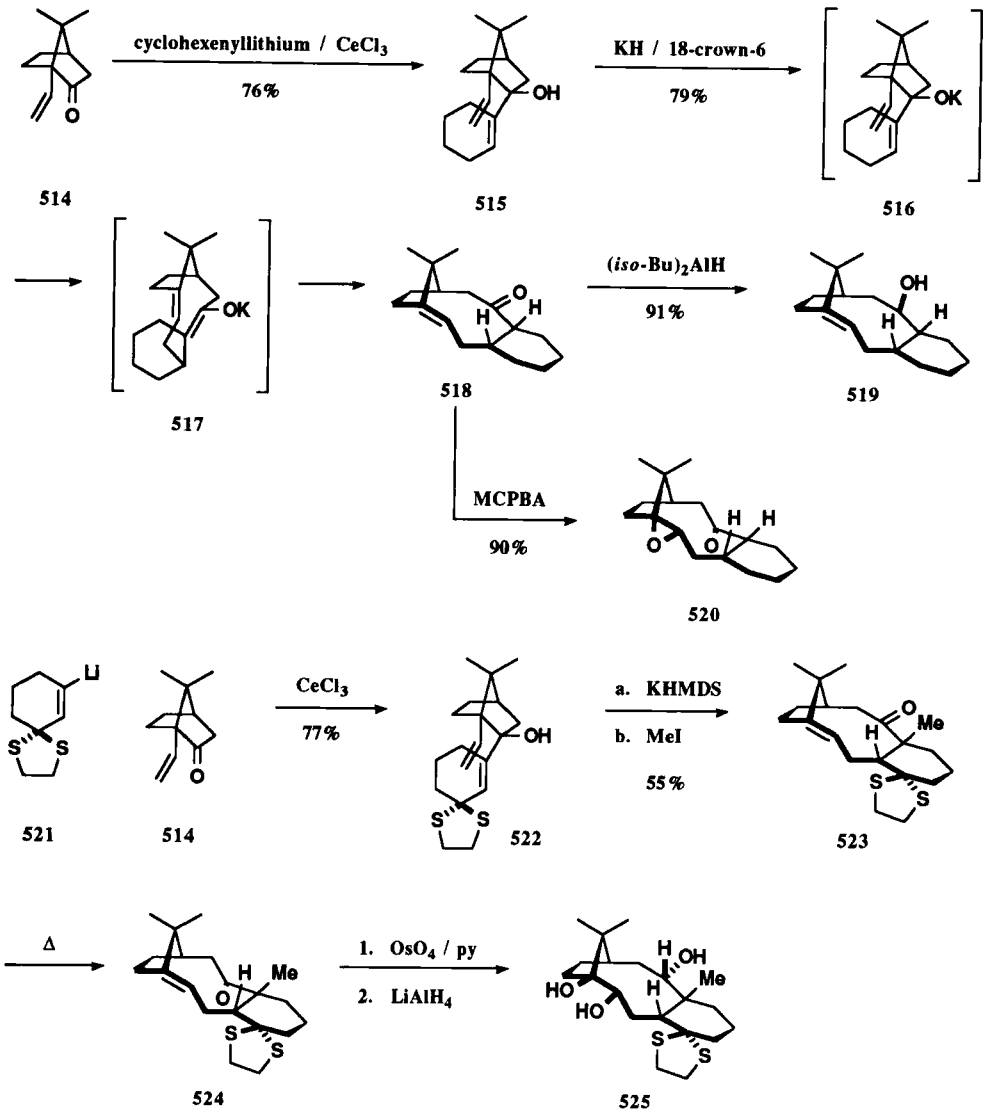


Fig. 69

the dependence of the atropisomer barrier on the bridgehead double bond by converting *both* ***523*** *and* ***524*** into **525**. The conversion of the olefinic sp^2 centers into the hydroxylated sp^3 centers permits the facile adoption of a less energetic conformation like that of **524**. Subsequent hydride reduction of the ketone carbonyl then installed the relative stereochemistry characteristic of **525**. This analysis was suggested also by the formation of epoxide conformer **520**. The carbon skeleton of Paquette's tricycles is not identical to that of the taxanes, but an expansion of the A-ring in concert with contraction of the B-ring would reorganize them appropriately.

11. Zucker's Approach

Zucker[91] employed a route conceptually similar to that of Paquette, but planned it so that the carbon skeleton of the taxane AB system would be configured properly after the Cope rearrangement. Transient ketenes **531** were formed through conventional operations and led, through intramolecular [2+2] cycloadditions, to the required cyclobutanones **534** and **535** (Fig. 70). These processes were complicated by the formation of ene products **532** and **533**. Unfortunately, **535**,

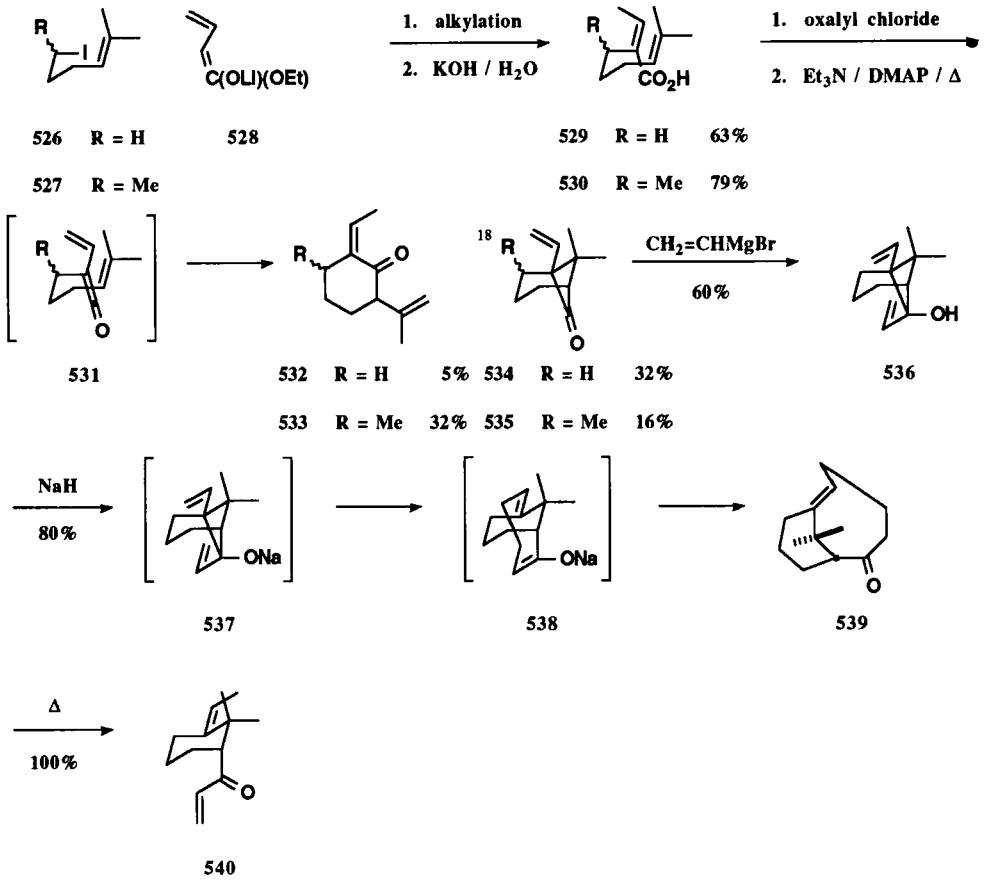


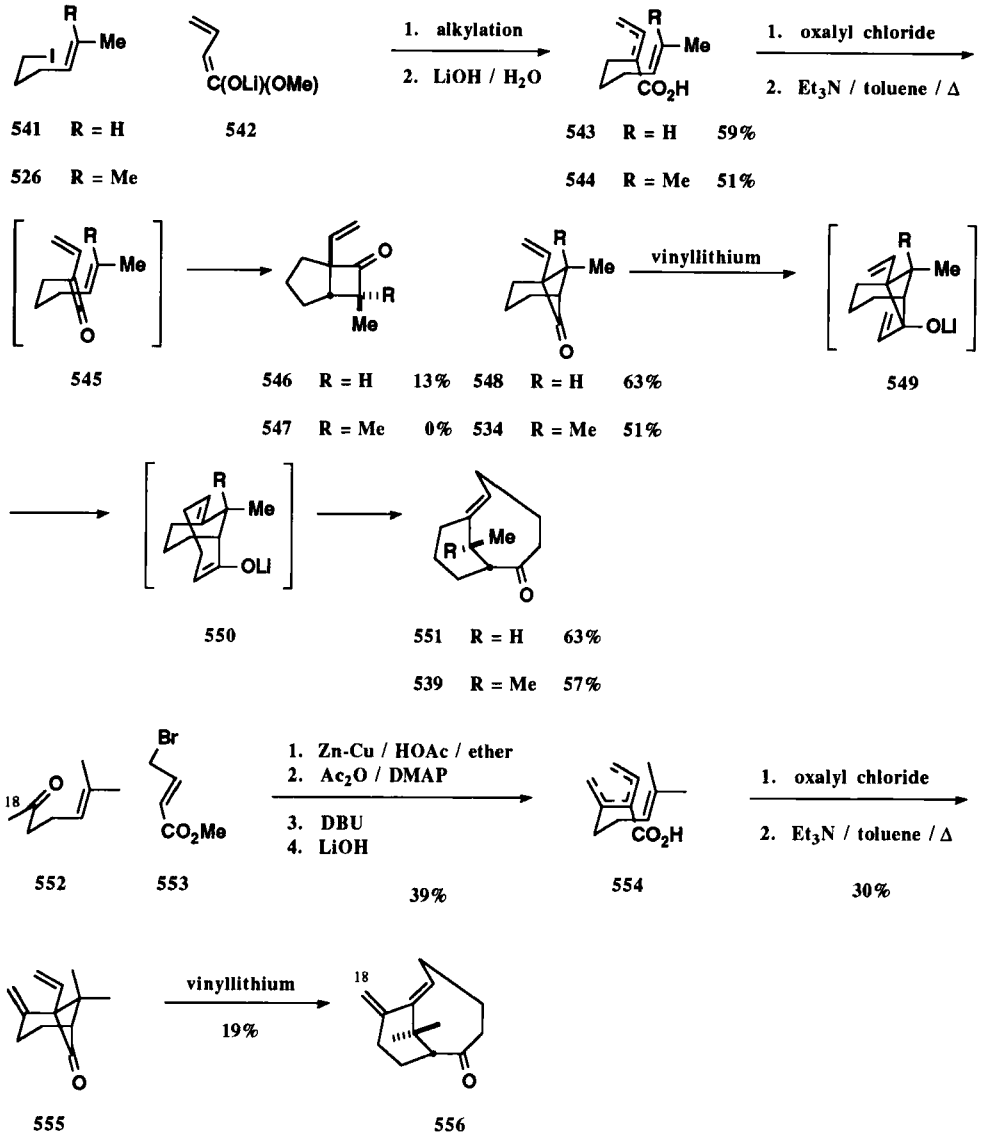
Fig. 70

which possesses the C-18 carbon of the taxanes, was the less abundant product of its corresponding cycloaddition. Extending his investigation with **534**, Zucker transformed that material into Cope substrate **536**. The treatment of **536** with NaH allowed an anion-accelerated oxy-Cope rearrangement to take place, thus delivering **539**. The geometry of the cyclooctene double bond arises from the requirement that the Cope [3,3] sigmatropic reorganization of the *trans*-divinyl cyclobutane substructure take place through a chair transition structure. In contrast, upon subjection of **536** to the conditions that would be required for the thermal oxy-Cope reaction, retro-ene product **540** was produced quantitatively. Zucker had anticipated that the involvement of cyclohexenyl organometallics in addi-

tions to cyclobutanones such as **534** and **535** would provide for convergence in the formation of the tricyclic taxane ring system. However, cyclohexenyllithium failed to engage cleanly in the addition-rearrangement chemistry, thus thwarting this plan.

12. Snider's Approach

Concurrently with Zucker, Snider[92] made a much more detailed investigation of the above taxane synthesis strategy. Snider's work formed part of a broader study of the formation of cyclobutanones by intramolecular ketene [2+2] cycloadditions, and the exploitation of the cyclobutanones



541 R = H 542 543 R = H 59%

526 R = Me 544 R = Me 51%

545 546 R = H 13% 548 R = H 63% 549

547 R = Me 0% 534 R = Me 51%

550 551 R = H 63%

539 R = Me 57%

552 553 39% 554 30%

555 556

Fig. 71

thus formed for complex molecule synthesis.[93] Snider prepared ketenes **545** and observed their transformation into cyclobutanones **548** and **534** (Fig. 71). Better regiochemical control was compromised, however, by lower yields that characterized the cycloaddition leading to **534**. Upon subjection of **548** and **534** to vinyllithium addition, a spontaneous anion-accelerated Cope rearrangement took place to give *E*-cyclooctenones **551** and **539**, respectively. Snider pursued an additional sequence that

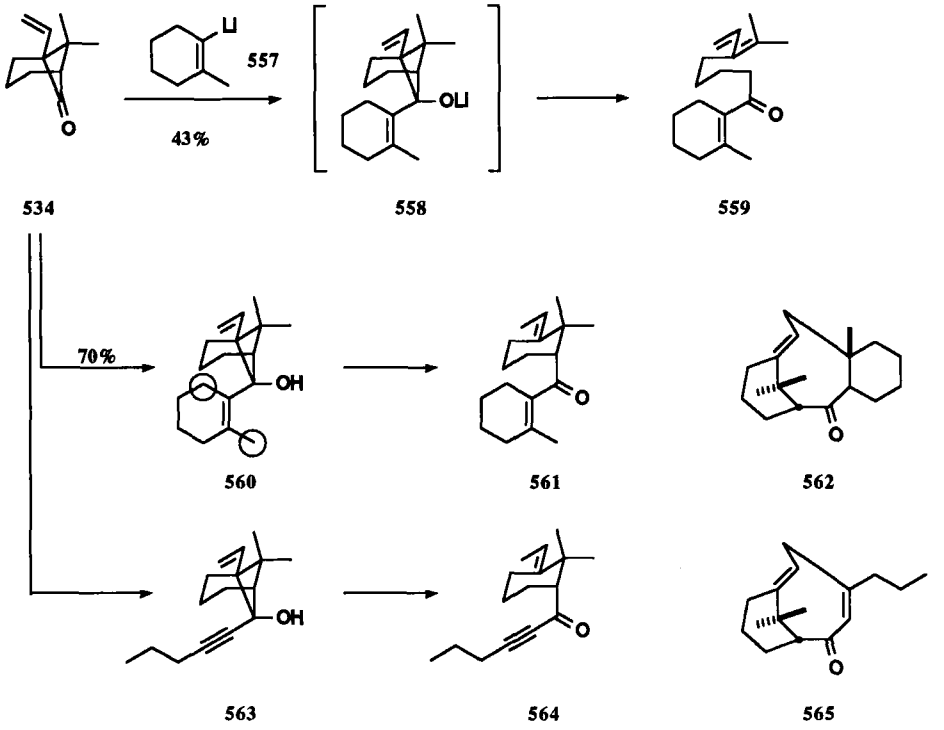


Fig. 72

was designed to incorporate the C-18 carbon that appears on the taxane A-ring. This scheme began with a Reformatsky process involving **552** and **553**, a condensation that, under the conditions employed, occurred selectively at the ester α position. Dehydration and saponification then led to a mixture of diene acid double bond positional isomers **554**. This mixture was converted to a single ketene, which gave cyclobutanone **555**. Vinyllithium addition to **555** produced **556** by way of an in situ Cope rearrangement, although the efficiency of this more complex case was disappointing.

While the above studies culminated in the construction of taxane AB models, Snider's strategy had been conceived to involve the addition of C-ring organometallics that would provide for a convergent preparation of the entire tricyclic taxane skeleton. This aspect of the plan was probed as illustrated in Fig. 72. Exposure of **534** to cyclohexenyllithium **557** produced **558**, but under the conditions anticipated to be necessary for its Cope rearrangement, fragmentation product **559** was

formed instead. That **558** had indeed intervened could be demonstrated by its protonation to provide **560** in 70% yield. However, an attempt to encourage **560** to undergo thermal Cope sigmatropy, a reaction that would give tricyclic **562**, delivered retro-ene product **561**. Likewise, **563** could be prepared, but its derived potassium alkoxide failed to undergo the desired reaction, whereas its thermolysis led to retro-ene structure **564**. Bicycle **565**, well functionalized for C-ring annulation, would have been the product of the successful Cope rearrangement of **563**. Through a series of molecular mechanics calculations and further experimental investigations, Snider identified the reluctance of Cope substrates such as **560** to adopt the necessary reactive conformation due to substitution at the circled sites as the problematic feature of this strategy.

III. CONCLUSION

With the conclusion of this review, which covers work recorded through early 1991, the taxanes continue to be prominent among natural products receiving the attention of the synthesis community.[94] One is struck, however, by the degree of resistance to their total synthesis that has been offered by the structures of these intriguing substances. Despite the efforts of at least thirty research groups, the synthesis of the medicinally active and more structurally complex taxanes remains unsolved. For those who view organic synthesis as a mature field of diminishing interest, clearly it is not yet so mature that it can meet quickly all challenges! On the other hand, there is no reason to believe that the same ingenuity that has solved so many less compelling synthesis problems cannot be brought to bear on this one. Indeed, it does not seem risky to predict that the 1990's should witness the exploitation of the experience just summarized in the discovery of efficient and intellectually appealing preparations of the structurally complex and medicinally significant taxanes.

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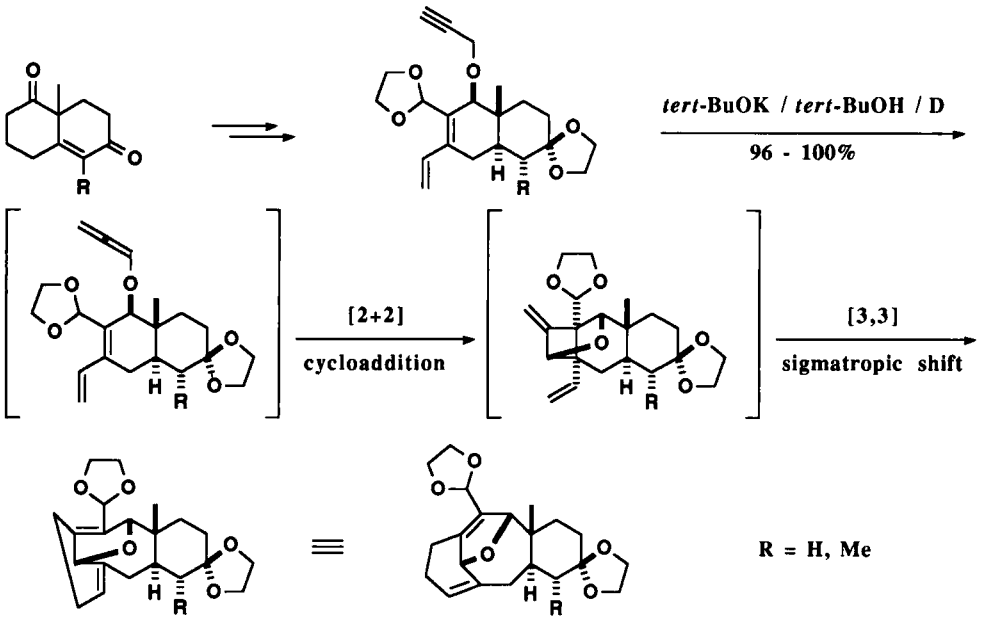

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