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# Harvesting Diels and Alder's Garden: Synthetic Investigations of Intramolecular [4 + 2] Cycloadditions

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## Introduction

The Diels−Alder reaction is firmly entrenched as one of the most versatile synthetic transformations in organic chemistry.[1] Numerous examples attest to its broad utility for the preparation of natural and unnatural products.[2] Seventy years have elapsed since its discovery, and yet investigations into its mechanistic nuances and construction potential continue unabated. Indeed [4 + 2] cycloadditions appear to be the most widely used method of synthesis for simple and complex ring systems. This utility is enhanced by the formation of two $\sigma$ bonds "simultaneously" with the introduction of four new asymmetric centers. Additional selectivity is achieved through the *endo*/*exo* ratio and the number of contiguous stereogenic centers is increased to five, in a single step, if the $\pi$-facial diastereoselectivity is also controlled. The regiochemistry may be controlled by the appropriate choice of substituents in both the diene and dienophile. The topology (*endo* or *exo*) may be influenced by the electronic and functional nature of the groups attached to the dienophile and also render the reaction diasterioselective. Chiral catalysts accomplish the same goal. Frequently, the intramolecular variant offers improved regiochemical and stereochemical control. It also allows the construction of more than one ring simultaneously.[3]

## Background

In common with most students of chemistry, my first exposure to the experimental magic of the Diels−Alder reaction occurred in an undergraduate laboratory. At the time, I did not fully appreciate the universality of this fascinating transformation nor the fact that, subsequently, I would become enamored with its chameleon character and the power it provided for the synthetic chemistry which has formed an integral part of our research. This first experiment involved the reaction of tetraphenylcyclopentadienone (**1**) with dimethylacetylene dicarboxylate (**2**) (Scheme 1). This is a spectacular reaction with many unique features that are now widely recognized. The diene is colored, and the reaction progress may be followed visually, a relatively rare occurrence in most synthetic organic chemistry. In addition, relatively few cyclopentadienones can be isolated at room temperature due to their rapid dimerization. Furthermore, at higher temperature the initial adduct **3** is not isolated and carbon monoxide is expelled to generate a fully substituted benzene ring **4**. This cheleotropic reaction (the name had not yet been invented!) is also more general than was then appreciated. Routes to benzene rings with adjacent functionality are still rather limited due to the *ortho*−*para*-directing influence of various substituents.

Several years ago we developed a strategy for the synthesis of various natural products based on an intramolecular Diels−Alder reaction between cyclopentadiene and a tethered dienophile. This research took advantage of the isomer population of substituted cyclopentadienes, incorporated cleavable blocking groups such as cyclopropanes, or side chain substituents that controlled adduct formation. These investigations led to the total synthesis of cedrene,[4a,b] sinularene,[4c,d] and longifolene.[4e,f] Additional investigations involved model studies for capnellenes[4g] and the preparation of advanced intermediates for gascardic acid[4h,i] and retigeranic acid[4j−l] and studies of $\pi$-facial behavior of cyclopentadienes[4m−o] (Chart 1).

The key elements, which involve the interplay of cyclopentadiene isomerization, tether substituents, and restricted dienophile geometry employed for the total synthesis of (+)-longifolene, are illustrated in Chart 2 and summarize the important features of our intramolecular strategy with cyclopentadienes to bridged ring systems. The spiro-cyclopentadiene aldehyde **A** was condensed with the lithium salt of methyl 3-methylcrotonate, mediated by cadmium chloride, to form the $\gamma$ condensation product which cyclized directly to the lactone **B**. Lewis acid assisted cyclopropane ring opening afforded the cyclopentadiene-tethered lactone **C** as a rapidly equilibrating mixture of isomers from 1,5 sigmatropic rearrangement. In principle, cycloaddition of this material could lead to a complex isomeric mixture, but in reality the single adduct **D** was isolated in 97% yield and converted to (+)-longifolene. This selectivity is a consequence of the restricted geometry imposed by the tether due to the chiral methine center in the lactone dienophile. The other possible adducts from $\mathbf{C^1}$ and $\mathbf{C^2}$ are either Bredt olefins ($\mathbf{D^1}$ and $\mathbf{D^3}$) or are excessively strained ($\mathbf{D^2}$

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**Scheme 1. Classical Cycloaddition**

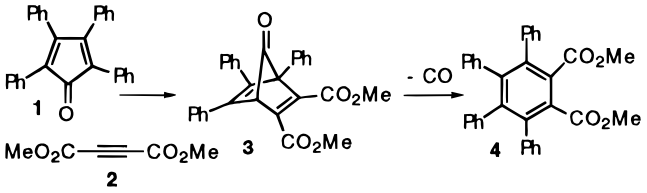


**Chart 1. Previous Studies with Cyclopentadienes**

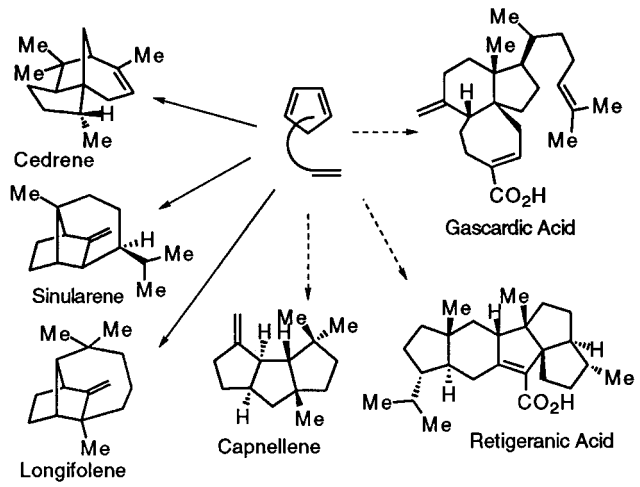
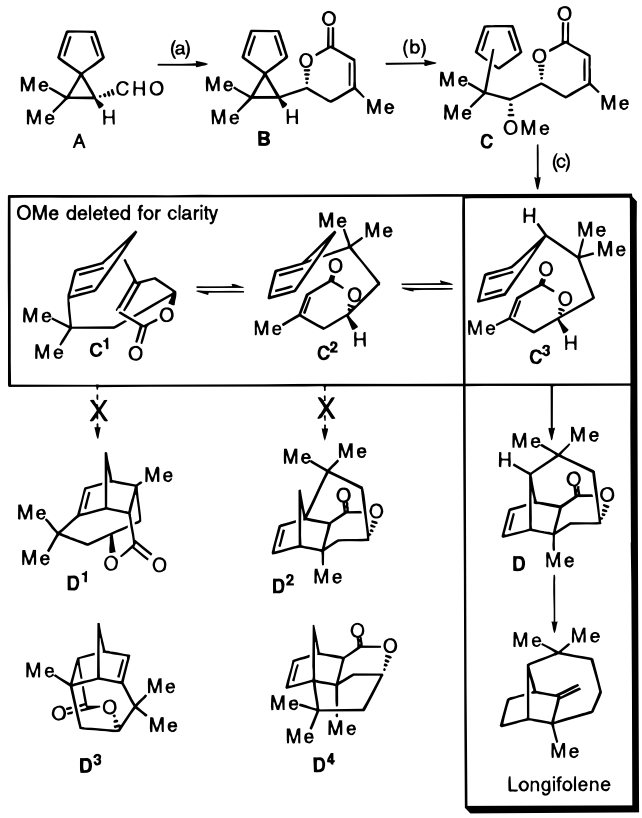


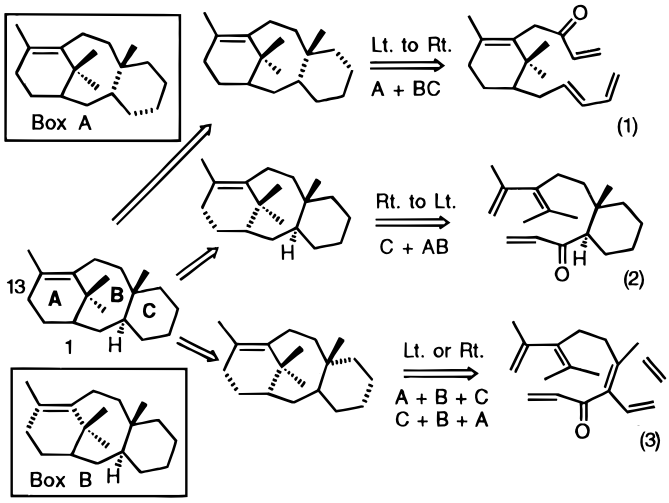

**Chart 2. Key Cycloaddition Elements of (+)-Longifolene Synthesis[a]**




[a] Conditions: (a) LDA, THF, −40 °C, $Me_2C{=}CHCO_2Me$, $CdCl_2$, 20 min; 2 h, 0 °C, 73%. (b) MeOH, $BF_3{\cdot}Et_2O$, 21 °C, 4 h, 83%. (c) Toluene, microwave heating, 2.5 h, 97%.

and **D⁴**). Thus, only the *exo* transition state represented by **C³** can achieve the necessary alignment for efficient orbital overlap. In part, these investigations set the stage

**Scheme 2. Various Cycloadditions for Tricyclo[9.3.1.0$^{3,8}$]pentadecenes**




for our current research in which tether functionality plays a prominent role.

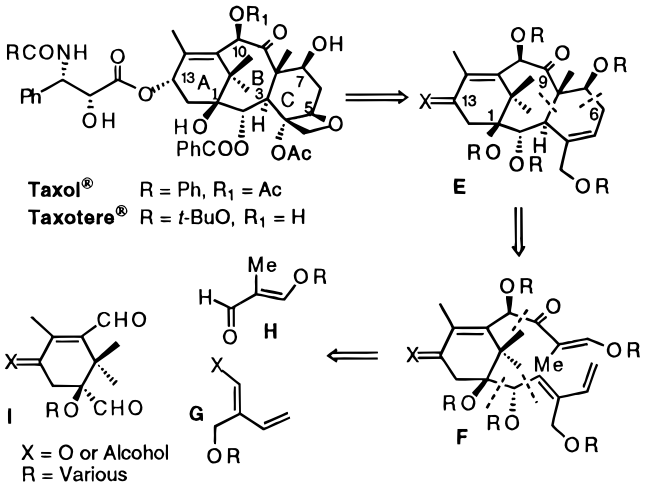
We, in common with others, have been interested in the synthetic challenge presented by the taxoids. In addition to paclitaxel itself, we hope to develop a direct, versatile route to the skeleton amenable for analogues. Thus, the central theme of this Account outlines these efforts. Additional investigations related to ring A building blocks, carbometalation of propargyl alcohols for dienes and furans, the development of tether control groups, and pentadienyl indium additions to trienes for tandem-diene transmissive cycloadditions are described briefly.

## Taxoid Synthesis

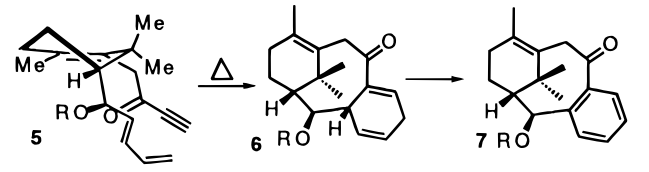
The clinical utility of the antitumor agents paclitaxel[5] and docetaxel for the treatment of ovarian and breast cancer has established these compounds as an important new class of chemotherapeutic agents. These antitumor drugs interfere with the normal microtubule−tubulin polymerization sequence prior to cell division.[6] This novel mode of action, plus the significant synthetic challenge presented by the sterically congested multicyclic structure, has stimulated worldwide interest in these molecules and related analogues.[7] Our initial approach to the tricyclo[9.3.1.0$^{3,8}$]pentadecene nucleus was based on a left to right sequence (ring A to BC)[8] intramolecular Diels−Alder strategy in which ring A cyclohexene building blocks were selected as anchors to facilitate the construction of the B and C rings simultaneously (Scheme 2, eq 1). A very large number of [4 + 2] combinations may be envisioned for the tricyclic nucleus, and our investigations have evolved to encompass aspects of several diverse cycloaddition strategies (eqs 1−3), although other variations, such as the approaches represented in boxes A and B, have not been examined.

A more detailed retrosynthetic analysis requires replacement of the ester side chain by a carbonyl or alcohol and removal of the ring D oxetane to afford the tricyclic

**Scheme 3. Convergent A to BC Intramolecular Diels–Alder Approach**



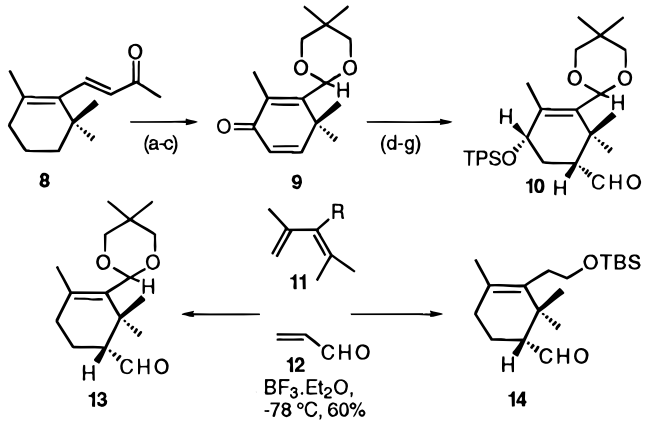

**Scheme 4. Taxoid Model Cycloaddition**



skeleton **E**. Subsequent double disconnection in ring C (retro-Diels–Alder) reveals a precursor related to **F** (Scheme 3). This intermediate could contain the majority of the paclitaxel oxygen substituents, although in practice the use of less substituted systems appeared more prudent. Construction of **F** may be envisaged in a direct manner from further disconnections between $C_1$–$C_2$ or $C_2$–$C_3$ and $C_9$–$C_{10}$. This affords a highly convergent approach to taxanes commencing with a ring A building block as a masked dialdehyde synthon related to **I** followed by attachment of the lower diene and upper dienophile units **G** and **H**, respectively.

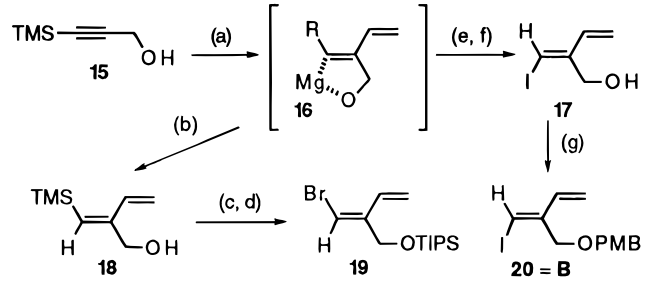
In previous studies, the C ring has been constructed using a bicyclo[2.2.2]octene precursor as a scaffold.[9] It was assumed that this rigid framework was required to hold the diene in an axial orientation to achieve the proper alignment for the cyclization transition state and overcome the entropic difficulties that were believed to be associated with a conformationally mobile ring system such as a cyclohexene. Conformational analysis indicated the transition state geometry for ring C was achievable from suitably substituted cyclohexenes. To further encourage the cycloaddition, the rotational parameters normally encountered with olefinic partners were minimized by selecting an acetylenic dienophile. Model studies led to the successful preparation of the functionalized tricyclo[9.3.1.$0^{3,8}$]pentadecatriene adduct **6** from **5**, and the structure was confirmed by conversion to the aromatic system **7** (Scheme 4).[8] The $C_2$ stereocenter controls the adduct stereochemistry from the transition state illustrated in accord with other studies concerning the $\pi$-facial selectivity of related cycloadditions.[10]

**Scheme 5. Synthesis of Ring A Building Blocks[a]**



[a] Conditions: (a) $O_3$, $Me_2S$; $H^+$, $HOCH_2CMe_2CH_2OH$, 64%. (b) $SeO_2$, PDC, 62%. (c) LDA, PhSeBr, oxidation, 56%. (d) $CH_2$=CHMgBr, CuI, 69%. (e) $NaBH_4$, $CeCl_3$, 96%. (f) TPSCl, imidazole, 96%. (g) $O_3$, $Me_2S$, 99%.

**Scheme 6. Halodiene Syntheses[a]**



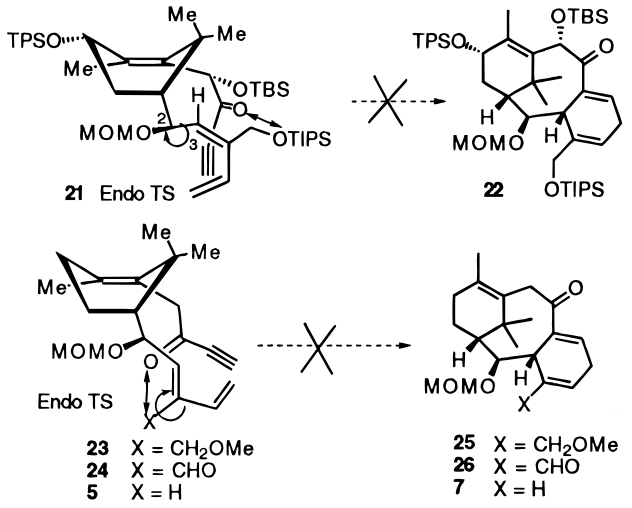
[a] Conditions: (a) $CH_2$=CHMgCl, THF, 0–67 °C, 16 h. (b) Aqueous $NH_4Cl$, 0 °C, 2 min, 75%. (c) TIPSCI, imidazole, $CH_2Cl_2$, 0 °C, 2.3 h, 88%. (d) NBS, DMF, 21 °C, 1 h, 85%. (e) $I_2$, THF, −78 °C, 1.5 h, 53–60%. (f) MeOH, NaOMe, 65 °C, 45 min, 87%. (g) NaH, THF, 0 °C, DMF, 4-MeOBnCl, $Bu_4NI$, 21 °C, 18 h, 97%.

The extension of this chemistry required the introduction of more oxygen functionality and a hydroxymethyl diene substituent (such as **G**) for the eventual introduction of the oxetane. As our research has progressed, the field has advanced rapidly and a better understanding of the factors that must be considered in any synthetic approach to the taxoids has emerged. In particular, it has proven difficult to manipulate many of the required oxygen-containing centers in the intact nucleus. Consequently, it appeared preferable to carry several of these functional groups from an early stage.

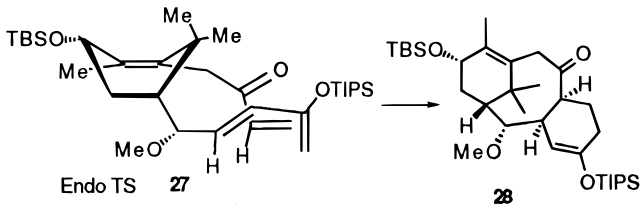
Appropriate ring A building blocks **10**, **13**, and **14** were constructed from $\beta$-ionone (**8**) or, more directly, by the Diels–Alder reaction between an appropriate trimethyl-substituted diene **11** and acrolein (**12**) (Scheme 5).[11]

The required dienes were initially synthesized by palladium-mediated addition, alkene coupling, and halodesilylation.[12] A more versatile route employed the addition of vinylmagnesium chloride to alcohol **15** via the putative magnesium chelate **16** to afford the diene **19** or **20** as required (Scheme 6).[13] Condensation of the derived vinyl anion with the appropriate ring A aldehyde and attachment of the upper acetylenic dienophile afforded the cycloaddition precursors **21**, **23**, and **24** in both the (*E*) and (*Z*) series (Scheme 7).[14]

**Scheme 7. Assorted Attempted Cycloadditions**



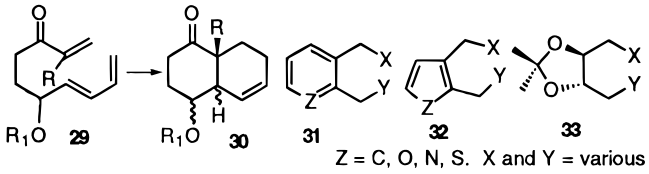

**Scheme 8. Successful Cycloaddition[15]**




It was anticipated that cyclization would provide the desired tricyclic nucleus via an *endo* transition state (**21**, Scheme 7). Despite extensive experimentation, the reaction failed and suggested that one or more of the nonbonded interactions present in the precursor are sufficient to impede cyclization. Initially we suspected the 1,3 interaction between the $C_{13}$ ether and the axial bond connecting the diene side chain was the culprit. However, this is not the case, since after completion of these investigations,[14] Winkler and co-workers[15] reported the successful cyclization of **27** to **28** (Scheme 8) with an *endo* $C_{13}$ ether substituent. Danishefsky and co-workers[16] discovered that an epimeric ether at $C_{10}$ (as contained in **21**) inhibited the Diels–Alder cyclization of ring A in a steroid-based model. This does not seem to be the problem in this case, and the geometric difference between the (*E*) and (*Z*) dienes also did not appear to be critical. However, to ascertain with certainty the factors responsible for the failure of the Diels–Alder cyclization, the (*Z*) series was examined with less substituted systems.

Microwave-assisted heating of **23** (sealed tube) failed to afford significant quantities of **25** as did more activated Diels–Alder precursors.[14] Compound **23** differs from the successful model system **5** only by the inclusion of the methoxymethyl ether diene substituent in place of hydrogen (X = $CH_2OMe$ vs X = H). However, the substituent (X = $CH_2OMe$), due to its rapid free rotation, inhibits the close approach of the dienophile (arrows **21** and **23**), and even aldehyde **24** (X = CHO) did not cyclize to **26**. The fact that the diene in **27** (Scheme 8) both is more reactive and lacks this substituent supports this conclusion. A revision of our approach to the challenging tricyclo[9.3.1.$0^{3,8}$]pentadecene nucleus was required.

**Scheme 9. Tether Control Groups**




## Tether Control Groups

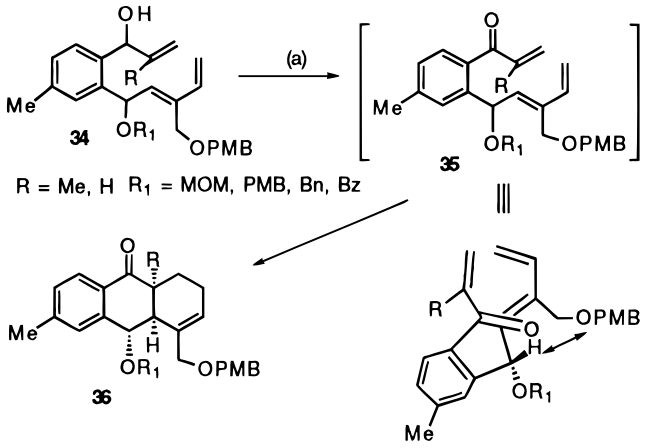
In related research we are developing various "tether control groups" for intramolecular reactions (pericyclic, free radical, dipolar, enolate, metal-mediated, etc.).[17] These constructs are useful as intramolecularity by itself is often insufficient to ensure the best levels of stereoselectivity in complex systems. Functional groups that limit the flexibility of the side chain and impose a restricted geometry on the reactive components will facilitate the achievement of the requisite transition state and lower the activation barrier. When a chiral group is employed, it will induce the desired enantioselectivity to afford chiral nonracemic products. In addition, the group should be selected so the product will contain useful functionality for subsequent synthetic manipulation.

The effect on intramolecular [4 + 2] cycloadditions will be significant, provided the group selected promotes the achievement of a dominant transition state. For example, Diels–Alder cycloaddition of trienes, such as **29**, to generate decalins **30** frequently requires long reaction times and high temperatures, and the selectivity is often disappointing (Scheme 9).[3,18] However, limiting the flexibility in the side chain, through the incorporation of a planar moiety, should enhance the transition state interaction between the reactive components. Thus, appropriate substituents, X and Y, can be incorporated into aromatic (**31**) or heterocyclic (**32**) rings to facilitate a variety of intramolecular reactions. Various examples of this beneficial template effect have appeared in the literature, but a systematic study does not appear to have been reported.[19] Chiral, nonracemic tartrate- and carbohydrate-derived isopropylidene acetals **33** also fulfill the criteria above and can be synthesized easily. In addition, they are usually available in both optical series and supply useful functionality.

Previous strategies to increase the level of regio- and stereochemical control in intramolecular cycloadditions have included the use of cleavable control groups such as silyl acetal tethers[20] and conformationally restricted diester spacers,[21] as well as chiral Lewis acids,[22] chiral auxiliaries,[23] magnesium chelation,[24] and chiral copper complexes.[25] The products from control group cleavage of appropriate adducts constitute an intermolecular cyclohexene synthesis, while the bicyclo[4.4.0] nucleus can be used independently or expanded.

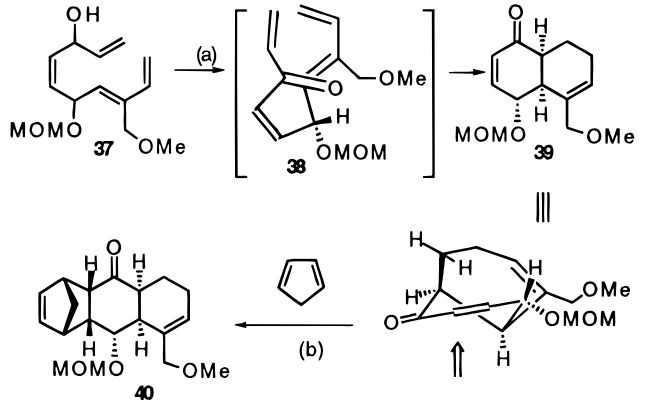
The following examples illustrate the utility of planar control groups. Thus, with a benzene group in the tether the cycloaddition illustrated (**34** to **36**, Scheme 10) oc-

**Scheme 10. Aromatic Tether-Controlled Cycloadditions**[a]




[a] Conditions: (a) Dess–Martin oxidation, $CH_2Cl_2$, 48 °C, 95%.

**Scheme 11. Alkene Tether-Controlled Cycloadditions**[a]

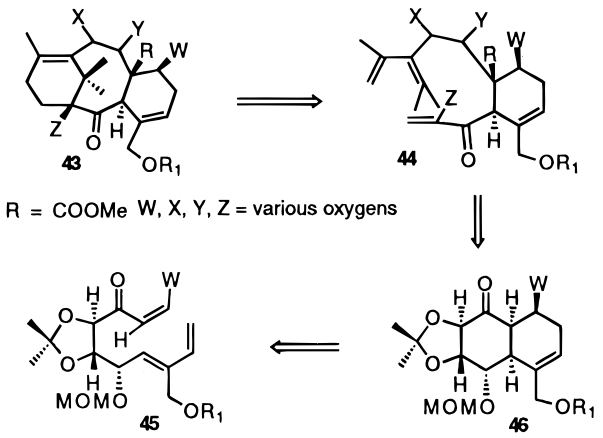



[a] Conditions: (a) Dess–Martin oxidation, $CH_2Cl_2$, 48 °C, 73%. (b) $Et_2AlCl$, $CH_2Cl_2$, 0 °C, 87%.

curred readily during oxidation with Dess–Martin periodinane (2 h, 48 °C, 95% yield) to give a single diastereomer (X-ray).[17] This result illustrated the dramatic improvement that arose from restricting the rotational freedom in the side chain due to the presence of the aromatic ring. Thus, the required diene–dienophile interaction was readily achieved. This adduct arose from preferential addition *anti* to the methoxymethyl ether substituent via an *endo* transition state as illustrated. This orientation places the MOM group in an axial position so it avoids the 1,3-allylic interaction with the bulky group on the diene (arrow) that occurs in the *endo* approach from the opposite face (hydrogen and ether are interchanged). Other ether substituents (PMB, Bn, Bz) in **35** did not alter the $\pi$-facial selectivity observed. This stereochemical preference is consistent with related diene–allylic ether cycloadditions.[10] In a parallel fashion, the ketone **35** (R = H) was synthesized and cyclized to give **36** (R = H) as a single adduct (69%).

The *cis*-olefin present in **37** produced a similar beneficial effect and in refluxing dichloromethane provided the cycloaddition products directly from **38** (73%, ~2:1) (Scheme 11). The major adduct **39** again arose from *endo-anti* addition. The hydroxymethyl protecting group helps determine the $\pi$-facial selectivity. This homoallylic interaction was camouflaged in the aromatic series due to the size of the ether groups. Reduction in the steric demands of this group (Me vs PMB) decreases the *syn* periplanar 1,3 interaction in the transition state for the MOM epimer **38,** and addition may occur from this face as well. Alteration of the size of the diene substituent therefore permits some control of the facial selectivity. A vinyl bromide substituent was employed for this purpose in related studies.[26] Cyclopentadiene reacted readily with the enone **39** (0 °C, $Me_2AlCl$) to generate the ketone **40** (87%, *syn/anti*, 9:1). This adduct arose from addition of the cyclopentadiene *syn* to the methoxymethyl ether substituent in an *endo* manner as illustrated. This convex approach avoids the diaxial interaction with the methylene group in the adjacent ring and is consistent with the pattern observed for 4-(*tert*-butyldimethylsiloxy)cyclohexenone[27] and related systems.[10]

**Scheme 12. Isopropylidene Double, Intramolecular Diels–Alder Approach**



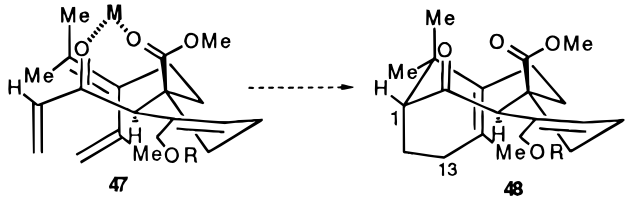

Thus, planar control groups (aromatic rings, *cis* double bonds) in the side chain have a dramatic influence on the ease of cyclization of substituted trienes in intramolecular Diels–Alder reactions. In addition, they supply useful functionality for subsequent synthetic manipulation.

## New Taxoid Approach

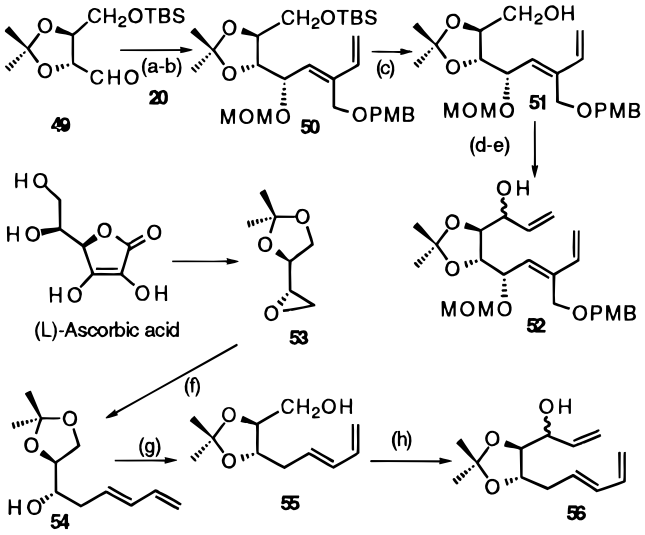
Encouraged by these results, a new convergent, double, intramolecular Diels–Alder strategy for taxoids has been devised that proceeds in a right to left (C to BA) direction (Scheme 2, eq 2).[28] A key feature is the use of a chiral isopropylidene acetal tether control group to impart asymmetry, facilitate the attainment of the requisite transition state for the intramolecular cycloaddition, and introduce latent functionality for subsequent ring cleavage to a substituted cyclohexene.

This approach involves a ring C cycloaddition to give a decalin (**45** to **46**, Scheme 12) followed by ring cleavage. Functional group modification of **46** leads to a second Diels–Alder precursor **44**. An ester group was selected as a surrogate for the $C_{19}$ methyl group in order to facilitate the chelated transition state illustrated (**47**, Scheme 13), in which Lewis acid coordination should occur between this ester and the dienophilic carbonyl to give the adduct

**Scheme 13. Proposed Ring A Cycloaddition**



**Scheme 14. Synthesis of *trans* Acetal Trienols**[a]



[a] Conditions: (a) *sec*-BuLi, **20**, THF, −78 °C, ~2:1, 93%. (b) MOMCl, *i*-$Pr_2EtN$, $CH_2Cl_2$, 77%. (c) *n*-$Bu_4NF$, THF, 94%. (d) $(COCl_2)$ DMSO, $CH_2Cl_2$, −78 °C, 40 min; $Et_3N$, 93%. (e) $CH_2$=CHMgBr, TMF, −78 °C, 97%. (f) *n*-BuLi, THF, $Bu_3SnCH$=CH−CH=$CH_2$, theinylCu(CN)Li, $BF_3$·$Et_2O$, 66%. (g) *p*-TsOH, MeCOMe, 70%. (h) 2 equiv of $(COCl)_2$, $CH_2Cl_2$, 3 equiv of DMSO, −78 °C; 4 equiv of $Et_3N$, 21 °C; 4 equiv of $BrMgCH$=$CH_2$, 0 °C, 82%.

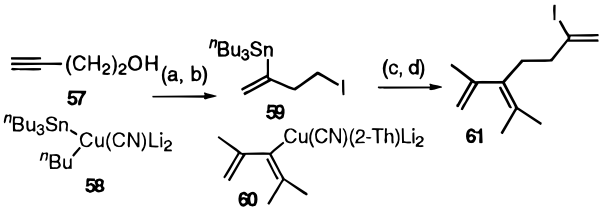
**48**.[28] This should avoid complications encountered with stereocontrol[16] experienced with certain substitution patterns during ring A cycloadditions.[29]

As mentioned above isopropylidene acetals hold promise for the control of many intramolecular reactions, although only a few cases of this beneficial effect have appeared in the literature.[30] In addition, the behavior of 1,7,9-decatrien-3-ones bearing isopropylidene acetals adjacent to the diene has been examined[31] for the synthesis of nargenicin $A_1$. However, as discussed below, placement of the acetonide $\beta$ to both the diene and dienophile improves the stereoselectivity for the synthesis of substituted decalins.

The required trienol precursors related to **52** were prepared from aldehyde **49**[32] as outlined in Scheme 14. Replacement of vinylmagnesium bromide with other haloalkenes generated additional substrates. The vinyl iodide taxoid component **61** was synthesized by copper-mediated tin hydride addition to **57** to give **59** followed by coupling with **60** as illustrated (Scheme 15), and demonstrates the power of modern organometallic chemistry for the facile preparation of these triene systems.

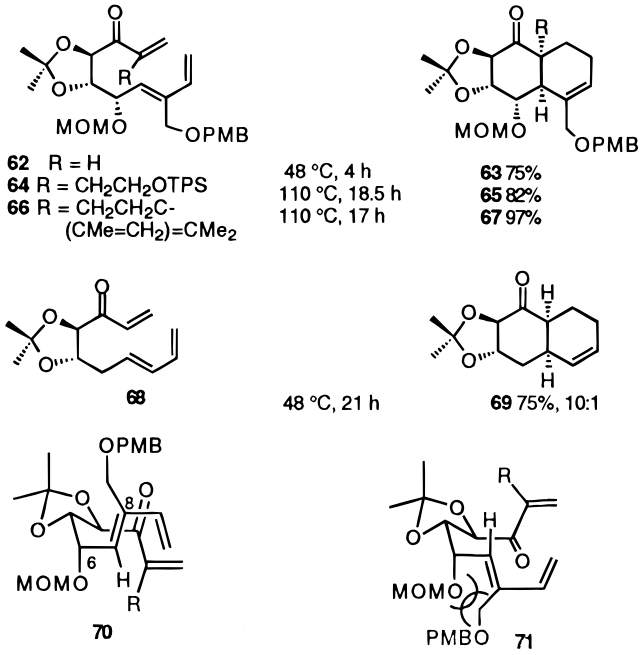
To ascertain the potential influence of the methoxymethyl ether substituent upon the stereoselectivity of the cycloaddition in this *trans* series, the triene alcohol **56** was synthesized from (L)-ascorbic acid (Scheme 14).

**Scheme 15. Synthesis of Vinyl Iodide 61**[a]



[a] Conditions: (a) **58**, THF, −78 °C, 1 h, 49%. (b) $Ph_3$·$I_2$, $Et_3N$, $CH_2Cl_2$, 21 °C, 5 h, 96%. (c) **60**, THF, −78 °C, 15 min, 21 °C, 65 h, 86%. (d) $I_2$ (1 equiv), $CH_2Cl_2$, 21 °C, 10 min, 99%.

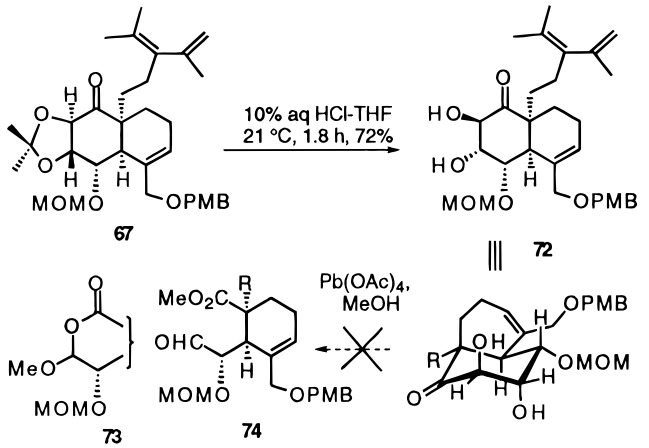
**Chart 3. Tether-Controlled *trans* Acetal Cycloadditions**



The results from the *trans* isopropylidene acetal mediated cycloadditions are listed (Chart 3).[33] In favorable cases the intermediate ketones were cyclized directly to avoid a mixture of adduct and enone. Oxidation of **52** generated the trienone **62** which cyclized directly to **63** in refluxing dichloromethane (75%). The alkyl-substituted dienophiles were less reactive, and the isolated ketones **64** and **66** were cyclized efficiently (82%, 97%). X-ray analysis of **63** confirmed the *cis* ring junction.

The decalin adducts **63**, **65**, **67**, and **69** arose from preferential addition via an *endo* transition state in which the side chain adopted the chairlike conformation **70**. The number of transition states was reduced due to the presence of the isopropylidene unit, which was constrained to a diequatorial conformation. Previous studies[10,17] with planar control groups indicated that the interaction between the $C_6$ and $C_8$ substituents determined the $\pi$-facial selectivity. Thus, for **62**, **64**, and **66**, the preferred orientation **70** placed the MOM group in an axial position to avoid the potential 1,3-allylic interaction that would have occurred in the *endo* approach from the opposite face as illustrated by **71**. For **68**, which lacks both the secondary ether and the vinyl substituent, the stereoselectivity of the cycloaddition might be expected to be reduced. However, these interactions were less important

**Scheme 16. Modification of Adduct 67**



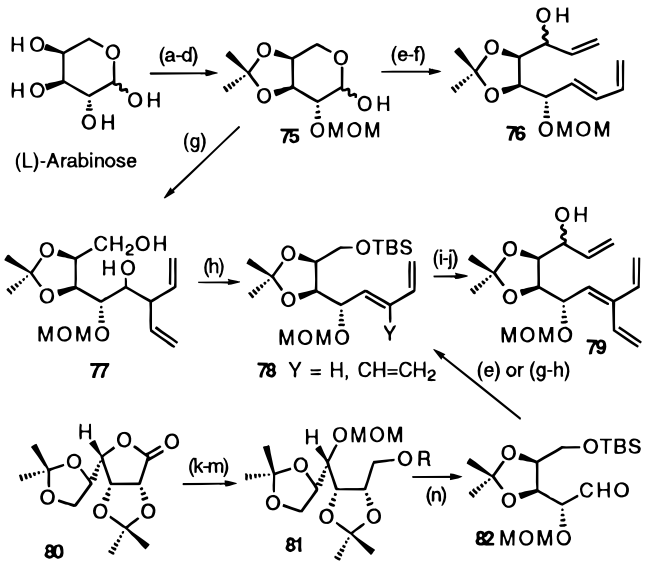

due to the overriding influence of the cyclic acetal, which afforded the same predominant stereochemistry in the adduct **69**.

The efficient preparation of **67** (97%) appeared to set the stage for conversion to the taxane nucleus. Treatment of **67** (Scheme 16) with aqueous acid generated the diol **72**. Unfortunately, in contrast to model studies with **63**, this oxidative cleavage with $Pb(OAc)_4$ did not afford the desired ester−aldehyde **74**, but only a low yield of acetal−lactone **73** from capture of the methoxy hemiacetal. The bulky bridgehead diene substituent inhibited the ease of cleavage and retarded the rate of esterification. This lack of reactivity is a consequence of the preferred conformation of **72** in which the methoxymethyl ether and the diene substituent adopt equatorial positions to minimize their steric interaction. This places the adjacent hydroxyl functions in a diaxial orientation. Thus, reagents that require a cyclic intermediate prior to bond cleavage will not be effective. Consequently, the best alternative, to capitalize on the chemistry we have developed, is to use a "*cis*-tartrate" precursor for the cycloaddition.

The required *cis* substrates for the model studies were synthesized from (L)-arabinose as summarized in Scheme 17. Unfortunately the Horner−Emmons reaction of **75** could not be scaled up efficiently, nor was it possible to selectively protect the primary alcohol due to the preference of **75** to exist in the closed hemiacetal form. Thus, a novel pentadienyl indium synthon has been developed to introduce the triene unit into **75** via the homoallylic alcohol **77** followed by elimination of water to afford triene **78** (Y = CH=$CH_2$). In contrast to most other organometallic pentadienyl anions, addition occurred exclusively at the $\gamma$ rather than the $\alpha$ position. These versatile triene building blocks led to the additional transformations illustrated in Schemes 19 and 20.

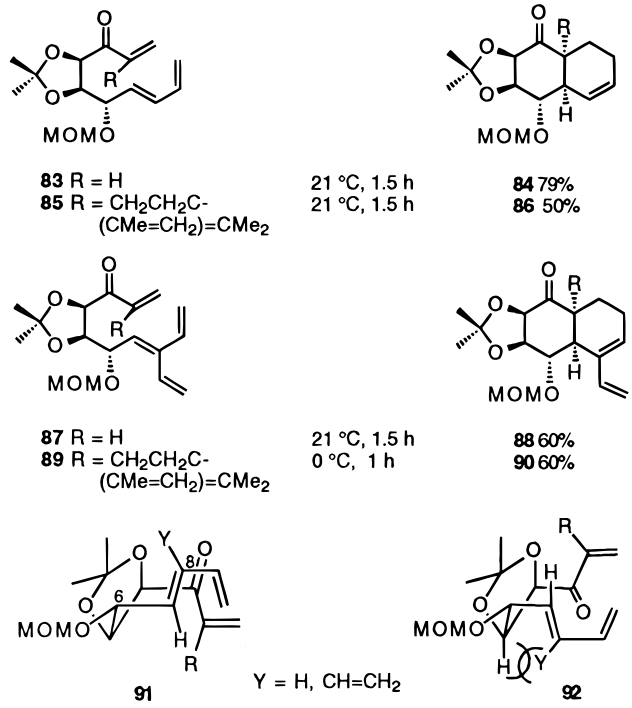
The *cis* isopropylidene acetal **83** cyclized readily at ambient temperature (Chart 4) to afford the single adduct **84** (79%). Thus, epimerization of an acetal center improved the efficiency of the cycloaddition reaction and led to the same stereochemical result. Alcohol **79** was oxidized to ketone **87**, which cyclized spontaneously to decalin **88**. Adducts **86** and **90** arose from the unsaturated

**Scheme 17. Synthesis of *cis* Acetal Trienols[a]**



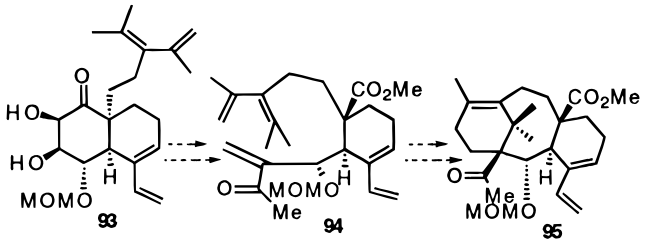

[a] Conditions: (a) BnOH, HCl, 21 °C, 16 h, 88%. (b) $Me_2CO$, $CuSO_4$, $H_2SO_4$, 21 °C, 20 h, 75%. (c) MOMCl, *i*-$Pr_2EtN$, $CH_2Cl_2$, 96%. (d) $Na/NH_3$, $Et_2O$, 97%. (e) 3 equiv of $CH_2$=CH−$CH_2P(O)(OEt)_2$, 3 equiv of *n*-BuLi, THF, −78 to +21 °C, 77%. (f) 1.5 equiv of $(COCl)_2$, $CH_2Cl_2$, 3 equiv of DMSO, −78 °C; 7 equiv of $Et_3N$, 21 °C; 4 equiv of $BrMgCH=CH_2$, 0 °C, 72%. (g) In(s), $BrCH_2CH=CHCH=CH_2$, DMF, 21 °C, 96%. (h) $Et_3N$, DMAP, TBSCl; $Ph_3P$, DEAD, $C_6H_6$, 80 °C, 96%. (i) $Bu_4NF$, THF, 0 °C, 99%. (j) 1.5 equiv of $(COCl)_2$, $CH_2Cl_2$, 3 equiv of DMSO, −78 °C; 7 equiv of $Et_3N$, 21 °C; 4 equiv of $BrMgCH=CH_2$, 0 °C, 93%. (k) $LiAlH_4$, THF, 95%. (l) $Et_3N$, DMAP, TBSCl or BnBr, NaH. (m) MOMCI, NaH, THF, 82%. (n) 3 equiv of $H_5IO_6$, $Et_2O$, 43%.

**Chart 4. Tether-Controlled *cis* Acetal Cycloadditions**

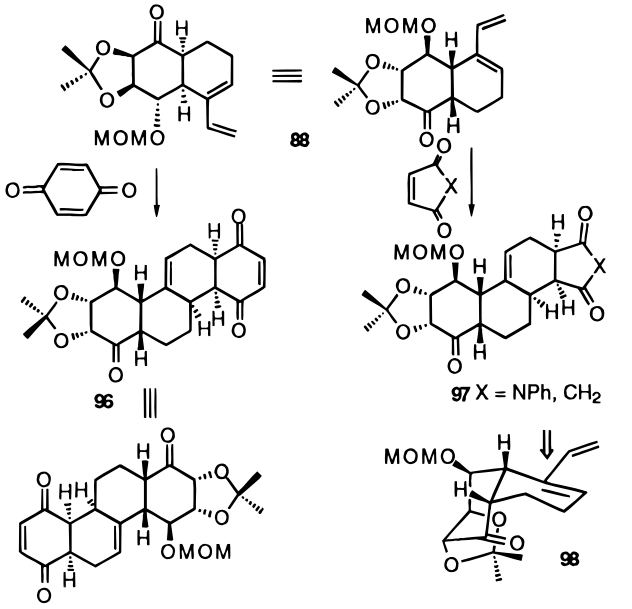



ketones **85** and **89**, respectively. The latter cycloaddition is particularly expedient. In all these cases the preferred *endo* transition state was achieved from the boatlike conformation represented by **91**, which placed the diene and dienophile in close proximity for facile cyclization. Other orientations such as **92** led to the significant nonbonded interactions illustrated.

**Scheme 18. Proposed Ring Cleavage and Ring A Cycloaddition**



**Scheme 19. Route to Highly Oxygenated Nortriterpenes and Steroids**



Hydrolysis of the acetal in **90** afforded the *cis*-diol **93** (Scheme 18), whose conversion to **94** and the tricyclic skeleton **95** are under investigation.

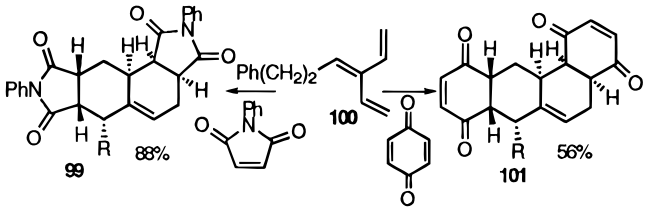
## Tandem Cycloadditions

The versatility of **88** and the pentadienyl indium reagent is further demonstrated by the synthesis of **96** and **97** from **88** via a second cycloaddition. Thus, with either benzoquinone- or cyclopentene-type dienophiles highly oxygenated triterpenoid and steroid skeletons were generated in an enantioselective manner. The new ring added from the most accessible convex face as illustrated (**98**, Scheme 19). The diketone ring in **96** may be viewed as either the A or the D ring component depending upon the synthetic objective. Furthermore, the ring fusions may be adjusted due to the presence of the adjacent ketone functionality. Simple triene units such as **100** underwent diene transmissive cycloadditions (Scheme 20). This allowed the rapid construction of multicyclic skeletons by tandem cycloadditions to afford **99** and the bisquinone **101**. Further reaction of this material with cyclopentadiene generated octacyclic skeletons in a direct manner.

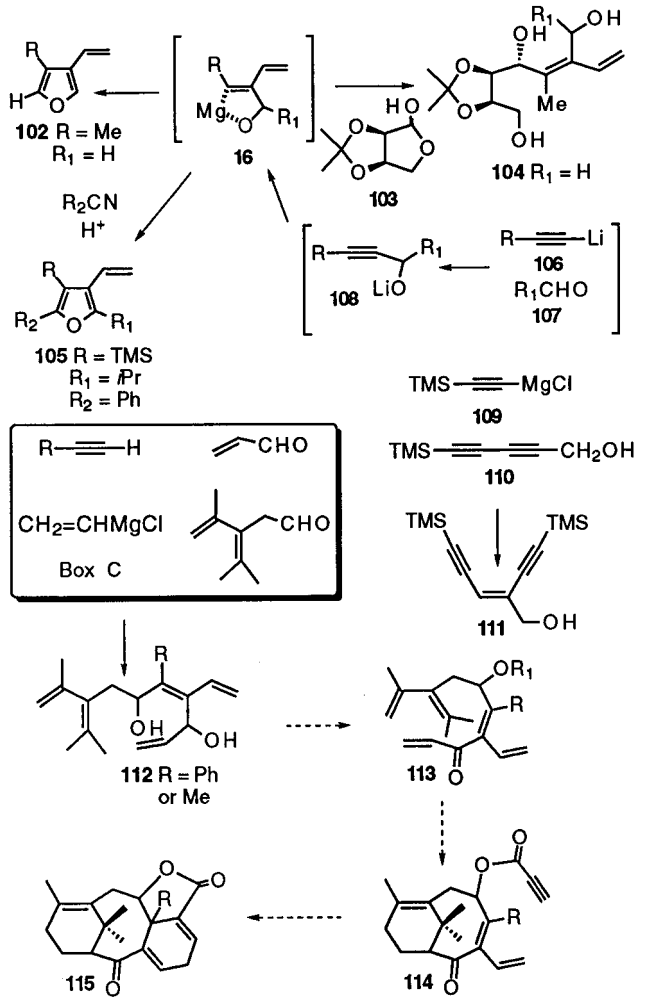
## Carbometalation Studies

We continue to search for short routes to the taxane nucleus that may be adapted to prepare analogues, as well as direct routes to Diels–Alder components. The study

**Scheme 20. Diene-Transmissive Cycloadditions**

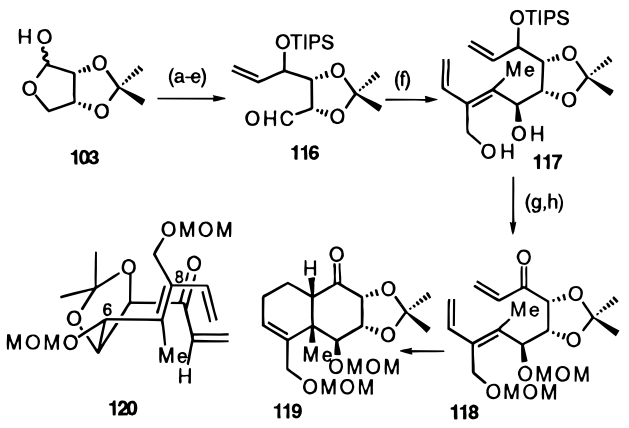


**Scheme 21. Carbometalation Routes to Diols and Furans**



of the magnesium chelates used earlier for the synthesis of our dienes (Scheme 6, **16**)[13] has been expanded. Direct condensation of this intermediate with aldehydes is achieved by conducting the reaction in cyclohexane. Thus, condensation of **16** (Scheme 21) with the hemiacetal **103** afforded a 40% yield (3:1) of the diene triol **104**. Related intermediates may serve as precursors to the *cis* acetal trienes discussed above. If **16** is reacted directly with DMF, the resultant hemiacetal is converted to the furan **102** (90%) upon acidic workup. Alternatively, condensation with a nitrile leads to substituted furans of type **105**. These furans may serve as precursors for double cycloaddition reactions (vinyl group and then furan after isomerization of the exocyclic double bond) and/or natural products by modification of the substitution pattern or oxidation of the side chain. It may be possible to extend these methods for the synthesis of thiophenes and pyrroles.

**Scheme 22. Carbometalation and Cycloaddition of a Hindered Diene**[a]




[a] Conditions: (a) $BrMgCH{=}CH_2$, TMF, −78 to 0 °C, 1.5 h, 80%. (b) TDBMSCl, imidazole, TMF/DMF, 0 °C, 1.5 h, 92%. (c) TIPSTf, collidene, $CH_2Cl_2$, 0−21 °C, 23 h, 99%. (d) PPTS, EtOH, 15 h, 58%. (e) Dess−Martin periodinane, 0−21 °C, 1.5 h, 82%. (f) **16** (R = Me, $R_1$ = H), −78 to +21 °C, 15 h, 43%. (g) MOMCl, *i*-$PrNEt_2$; TBAF, THF, 0−21 °C, 15 h, 52%. (h) Dess−Martin periodinane, 21−48 °C, 4 h, 65%.

A further refinement is to generate the key intermediate **16** in a different manner by commencing with a lithium acetylide **106**. Condensation with aldehyde **107** afforded the lithium alkoxide **108** in situ. Subsequent addition of vinylmagnesium chloride and condensation of **16** with nitriles has allowed the synthesis of tetra-substituted furans (**105**) in one reaction pot, a significant improvement over current routes. If **109** is added to alcohol **110**, the interesting enediyne alcohol **111**[35] can be prepared in a single step.

A potentially short, versatile strategy for synthesis of taxane systems is being developed based on the following combination (Scheme 2, eq 3). Sequential reaction of the components in box C afforded the unsaturated diol **112** (R = Ph). With a methyl group, the corresponding compound **112** (R = Me) has been prepared in a stepwise fashion. After conversion to **113** it is anticipated that the planar tether will facilitate the cycloaddition to **114** and a final ring C cyclization in either an inter- or preferably intramolecular manner may provide **115**. However, these variations and whether the reverse order (C to BA) may be preferable remain to be tested.

Decalins are key components of many biologically active terpenoids, and highly functionalized systems can be prepared directly by an extension of the methods above (Scheme 22). For example, difficult cycloadditions with sterically demanding dienes benefit significantly from incorporation of an isopropylidene control group. The hemiacetal **103**, derived from D-isoascorbic acid, was reacted with vinylmagnesium bromide,[30b] the secondary alcohol protected, and the aldehyde **116** prepared by oxidation. Condensation with **16** (R = Me, $R_1$ = H) afforded **117**. Protection of the allylic alcohols and a second oxidation generated the dienophile−diene **118**, which cyclized spontaneously to **119** (48 °C, 65%). If the order of these reactions is reversed, by initial addition of the diene to **103,** the adduct will be produced in the opposite enantiomeric series. The stereochemistry of the adduct is induced by the *cis* acetonide, which establishes the preferred *endo* transition state in a boat conformation with minimal nonbonded interactions, as depicted in **120**.

## Concluding Remarks

In summary, a synthetic strategy for taxoids based on a sequential intramolecular Diels−Alder approach appears to hold considerable promise. This route has evolved from our initial investigations of related cycloadditions. The principle of using an isopropylidene acetal tether control group has been shown to be particularly advantageous for directing the initial intramolecular cycloaddition for the C ring. In addition, this concept has been applied to the decalin component of steroids and terpenes, and is currently being extended to other intramolecular reactions. The carbometalation and pentadienyl indium protocols hold promise for a variety of synthetic objectives.

Finally, in the discussions above, transition states were provided where appropriate to clarify the results, but additional theory was not dealt with extensively. The orbital aspects of cycloadditions are now well understood, and earlier discussions invoking discrete free radical intermediates have subsided. Thus, it is generally agreed[2,3,36] that [4 + 2] cycloadditions are truly concerted reactions in which the bond-forming steps are synchronous but not necessarily simultaneous in all cases. These special examples are considered asynchronous concerted processes. Irrespective of these nuances, the synthetic power of the Diels−Alder reaction, particularly the intramolecular variant, remains a most versatile synthetic component in the arsenal of organic chemists.

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