Pergamon

*Tetrahedron*, Vol. 52, No. 18, pp. 6251-6282, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01077-7

# TETRAHEDRON REPORT NUMBER 398

---

# The [4 + 4] Cycloaddition and its Strategic Application in Natural Product Synthesis

Scott McN. Sieburth* and Nicholas T. Cunard

Department of Chemistry, State University of New York at Stony Brook
Stony Brook, New York 11794-3400

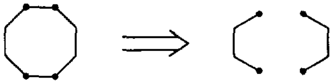
## Contents

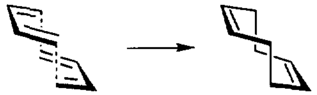
1. Introduction and Definitions 6252
2. Targets and Strategy 6252
3. Survey of [4 + 4] Reactions 6253
    3.1. Aromatics 6254
    3.2. Heteroaromatics 6257
    3.3. Orthoquinodimethanes and diyls 6260
    3.4. 1,3-Dienes 6262
    3.5. Catalyzed reactions 6264
    3.6. By [4 + 3] cycloaddition 6266
    3.7. Other processes 6267
4. Syntheses via [4 + 4] Reactions 6269
    4.1. Fused 5–8 rings: model systems 6270
    4.2. Fused 5–8 rings: total synthesis 6272
5. Syntheses via [4 + 4] Cycloaddition—Taxol 6272
    5.1. Bicyclic model systems 6272
    5.2. Tricyclic model systems 6274
    5.3. Total synthesis 6275
6. Conclusions 6276

## 1. Introduction and definitions

Cycloaddition reactions[1] are counted among the strategic disconnections,[2] and are frequently deployed as key transformations in total synthesis. On the most fundamental level, a cycloaddition results in the formation of two new bonds, at least one new ring, and often as many as four new stereogenic centers. The [4π+2π] Diels-Alder is typical in this regard and is the most frequently used cycloaddition, in part because of its predictable regioselectivity and stereoselectivity.[3]

Higher-order cycloadditions[4]—reactions that form rings larger than six-membered—are receiving increased attention, in concert with the growing number of biologically active natural products containing a medium ring. Compounds with an eight-membered ring have figured greatly here, with prominent examples such as pleuromutilin[5] (**1**) and taxol (**15**).[6] Comparisons of ring closure reactions as a function of ring size[7] have found cyclooctane to be the ring most difficult to form. Of the four two-component cycloadditions leading to an eight-membered ring, only the [4+4] divides the skeleton into fragments of equal size. This review considers the many versions of the [4+4] reaction[8] and the application of the [4+4] synthetic strategy in the pursuit of total synthesis.[9]





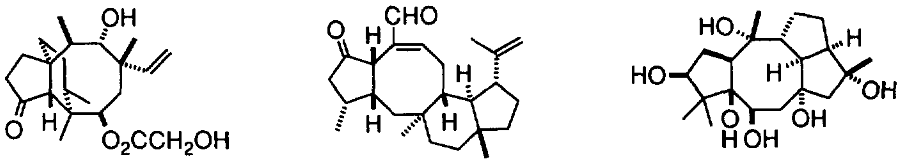
First a comment about definitions. The close association of orbital symmetry rules[10] with the Diels-Alder cycloaddition has given rise to a strong mechanistic connotation for the term cycloaddition. While cycloadditions are an important subset of the pericyclic reactions,[11] the term cycloaddition need not be restricted to pericyclic processes. In the context of synthetic strategy, a mechanism-based definition for cycloadditions is both counterproductive and impractical, as detailed reaction mechanisms are often not known. Huisgen's mechanism-neutral enumeration[1] essentially defines cycloaddition as any process that forms two bonds to make a ring, including pathways that clearly involve one or more intermediates. For the purposes of this review, we consider all of the synthetic approaches that bring together two four-carbon fragments to form an eight-membered ring and syntheses in which [4+4] is a strategic disconnection.

## 2. Targets and Strategy

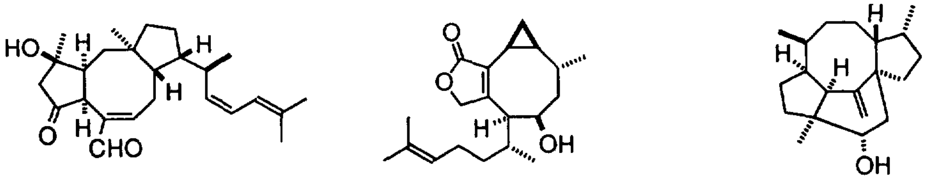
A variety of cyclooctanoid natural products have been described that combine intriguing structural complexity with important biological activity. While taxol has received the most attention (see Section 5), several other examples are given in Figure 1. Historically, the important antibiotic pleuromutilin[5] has been the subject of several synthetic studies.[12] More recently, polycyclic molecules such as variecolin,[13] kalmanol,[14] longipenol,[15] and crenulide[16] present the cyclooctane unit in other challenging ring fusions. The ophiobolins,[17] other dicyclopenta[a,d]cyclooctenes such as the fusicoccins and ceroplastol, and related structures, have also received significant attention from the synthetic community.[18,19]

A cyclooctanoid can also be an intermediate en route to a [3.3.0] ring system present in compounds such as pentalenene (**7**) and modhephene (**8**). Transannular ring closure of cyclooctenes with both cationic[20] and radical mechanisms[21] has been amply demonstrated. Equation 1 illustrates a pivotal cyclization in Mehta's synthesis of pentalenene;[22] and the radical cyclization of tertiary radical **12** (equation 2) found use in Curran's synthesis of modhephene.[21]

Dissection of a cyclooctane through a retro-[4+4] reaction strategically divides this challenging ring into two fragments of equal size. When the cyclooctane target is unsymmetrically substituted, as is often the case, four of these disconnections are possible. Figure 3 illustrates this process for the taxol skeleton. Interestingly, all of these approaches have been studied (see Section 5.1).

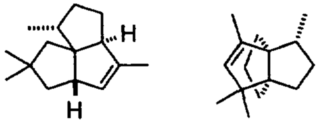


**1** pleuromutilin (antibiotic)   **2** variecolin (angiotensin II antagonist)   **3** kalmanol (cardiotoxic)

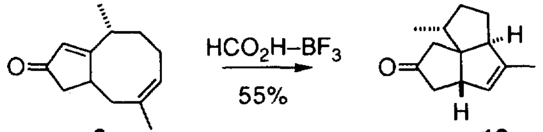


**4** ophiobolin K (nematocide)   **5** crenulide (icthyotoxic)   **6** longipenol (termite defense secretion)

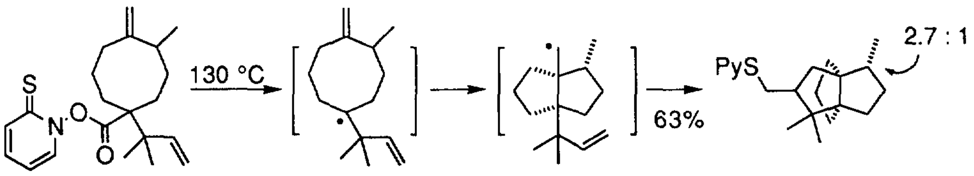
**Figure 1.** Some biologically active natural products containing an eight-member ring.



**7** pentalenene   **8** modhephene



**9** **10** (1)

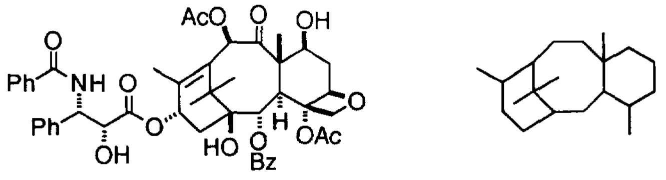


**11** **12** **13** **14** (2)

**Figure 2.** Transannular cyclization of a cyclooctene can produce the [3.3.0] bicyclic system.

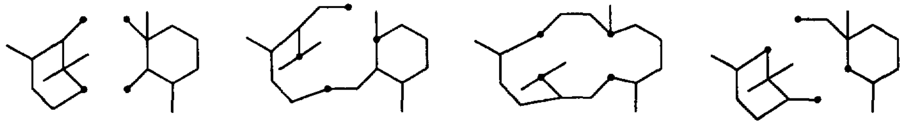
## 3. Survey of [4+4] Reactions

The [4+4] cycloaddition is generally less known than the cycloadditions leading to smaller rings. The following survey gives examples of this transformation, organized by a hierarchy of reactant type: aromatics, orthoquinodimethanes, 1,3-dienes, and miscellaneous examples. This survey is followed by a discussion of synthetic methods directed toward harnessing this type of transformation and a summary of total syntheses that use a [4+4] disconnection.



**15** taxol

taxol skeleton

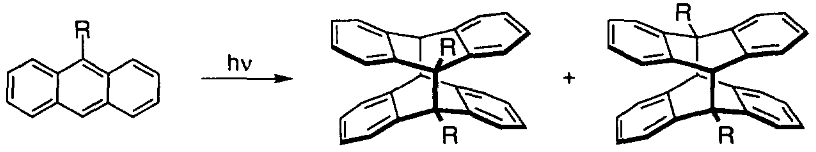


I II III IV

**Figure 3.** Four different [4+4] dissections of the cyclooctane ring of taxol.

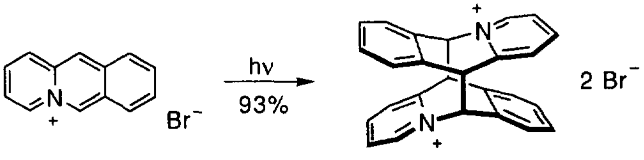
## 3.1 Aromatics.[23]

**Anthracene.** The earliest example of a [4+4] cycloaddition was the photodimerization of anthracene,[24] initially described by Fritzsche,[25] with a correct structure proposed before the turn of the century.[26] This reaction remains one of the most reliable photocycloadditions and is the basis of continuing investigation. Both head-to-head (**17**) and head-to-tail (**18**) products are often produced;[27] however the former dimer is less stable and frequently has not been reported. Other polycyclic aromatics undergo anthracene-like photocycloaddition, an interesting example being acridizinium salts such as **19**.[28]



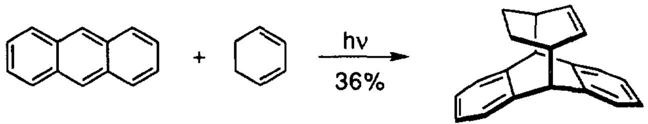
**16** **17** **18** (3)

| | | | |
|---|---|---|---|
| **a** | R = $CH_3$ | 96% | 40 : 60 |
| **b** | R = $OCH_3$ | 93% | 45 : 55 |



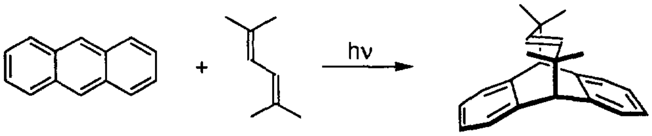
**19** **20** (4)

Anthracene participates in [4+4] photocycloadditions with simple 1,3-dienes, such as cyclohexadiene[29] and cyclopentadiene.[30] Even substrates that appear unsuitable for cycloaddition, such as *s*-trans 1,3-dienes[29] and 1,3-diynes,[31] can afford [4+4] products. In many cases, the initially formed and highly strained products are not characterized but are inferred from trapping experiments. An unusual case is the 1,2,3-triene intermediate **26**, which has been characterized spectroscopically.[32]



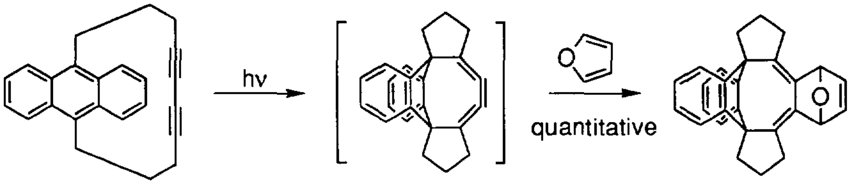
**21** **22**

(5)



**21** **23** **24** unstable

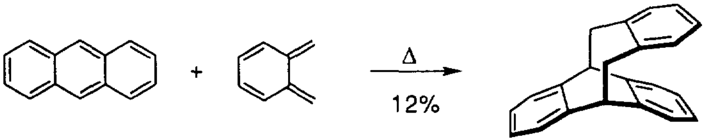
(6)



**25** **26** **27**

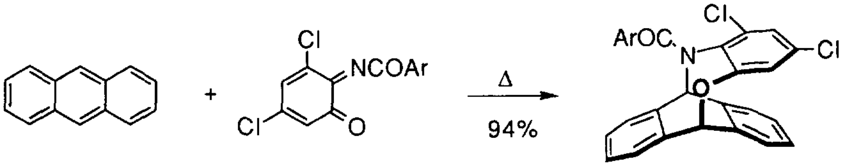
(7)

Reactive species like orthoquinodimethane **28** can react thermally with anthracene to produce the [4+4] cycloadduct.[33] Heteroatom analogs of **28**, such as **30**, also participate in this type of cycloaddition.[34]



**21** **28** **29**

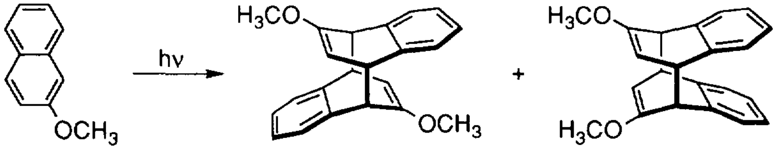
(8)



**21** **30** **31**

(9)

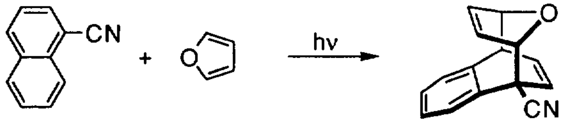
**Naphthalene and Benzene.** The smaller aromatics benzene and naphthalene are more parsimonious than anthracene in their [4+4] reactivity. Neither of the parent compounds photodimerize. The first example of a naphthalene photodimerization involved the 2-methoxy analog **32**.[35] In this case, only the substituted ring participates, and both the anti and the syn isomers are formed.



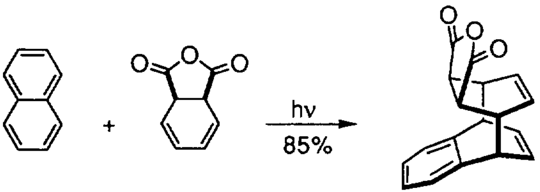
**32** **33** up to 90% **34** unstable

(10)

Furan will undergo photocycloaddition with 1-cyanonaphthalene;[36] and photocycloaddition of naphthalene with 1,3-dienes can be quite efficient, as illustrated for cyclohexadiene **37**.[37] In both of these cases, only a single product isomer was reported.

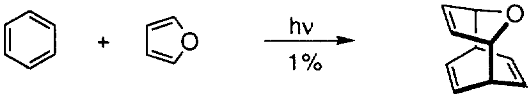


**35** **36** (11)

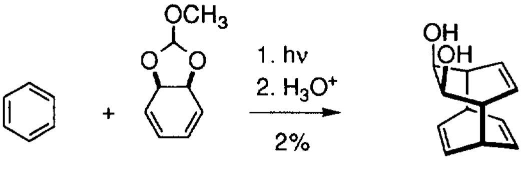


**37** **38** (12)

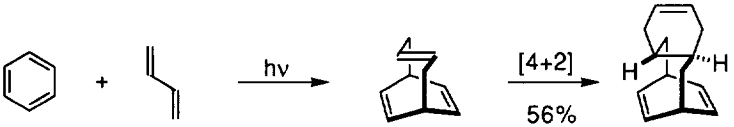
Like its polycyclic homologs naphthalene and anthracene, benzene will undergo [4+4] photocycloaddition with furan[38] (eq 13) and 1,3-dienes[39] (eq 14), a process often referred to as "para-cycloaddition." As found for reactions of acyclic 1,3-dienes with anthracenes (eq 6) and 2-pyridones (see Section 3.2), the [4+4] product often reflects the primary conformation of the diene: *s*-cis or *s*-trans. In the case of 1,3-butadiene, the trans cycloadduct **42** is highly reactive and undergoes a subsequent Diels-Alder reaction to give tricyclic **43**.



**39** (13)

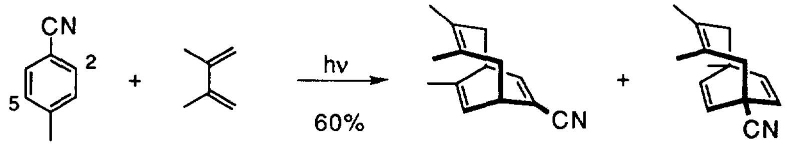


**40** **41** (14)



**42** **43** (15)

A noteworthy recent finding is the dominating effect of a nitrile on the regioselectivity of benzene–1,3-diene [4+4] photocycloaddition (eq 16).[40]

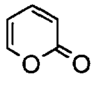


**44** **45** **46** 6 : 1 **47**

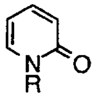
(16)

## 3.2 Heteroaromatics.

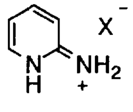
The heteroaromatic structures **48-54** all undergo [4+4] photocycloaddition reactions.



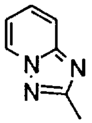
**48**



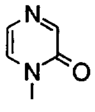
**49**



**50**



**51**

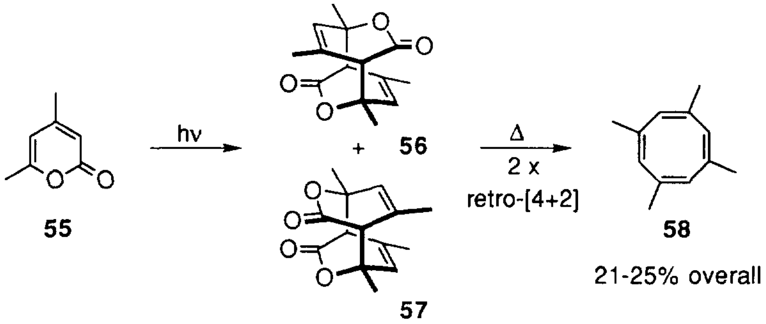


**52**

**53**

**54**

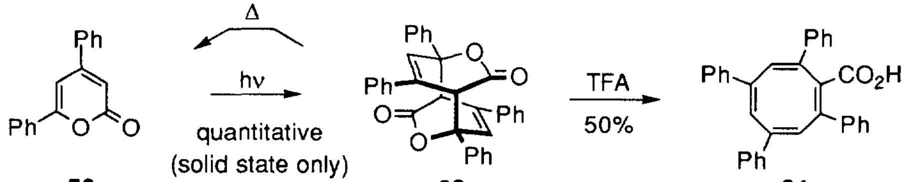
**2-Pyrone.** Photodimerization of 2-pyrones proceeds with a high head-to-tail regioselectivity. The mixture of cis and trans products derived from 4,6-dimethyl-2-pyrone (**55**) thermally extrudes two equivalents of carbon dioxide in a double retro-[4+2] reaction to produce the symmetric 1,3,5,7-tetramethylcyclooctatetraene **58**.[41]



**55** **56** **57** **58**

(17)

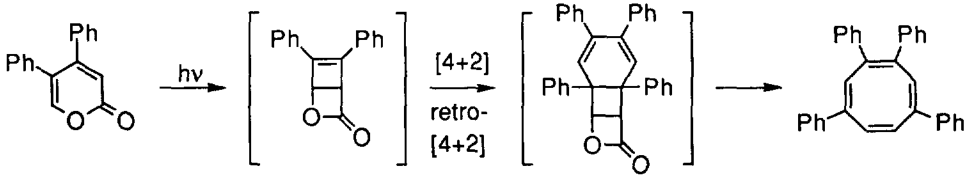
Substitution of 2-pyrone with other groups is compatible with [4+4] chemistry but can result in surprises. With phenyl groups at C4 and C6 (**59**), a trans [4+4] photoproduct is formed, but only in the solid state.[42] Thermolysis of **60** does not give the cyclooctatetraene but instead induces a retro-[4+4] reaction and returns the starting 2-pyrone **59**. However, treatment of **60** with acid does provide the cyclooctatetraene **61**.



**59** **60** **61**

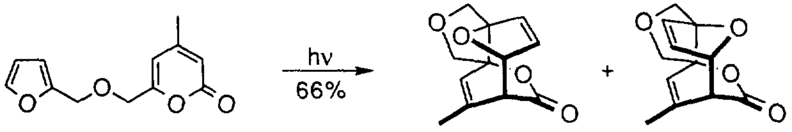
(18)

In contrast to **59**, when the phenyls are located at C4 and C5 (**62**), only 1,2,4,7-tetraphenylcyclooctatetraene **65** is observed.[43] Formation of **65** is rationalized by a multistep mechanism (eq 19) involving photoisomerization, Diels-Alder and retro-Diels-Alder reactions, electrocyclic ring opening, and expulsion of carbon dioxide (see also the similar transformation, eq 65).



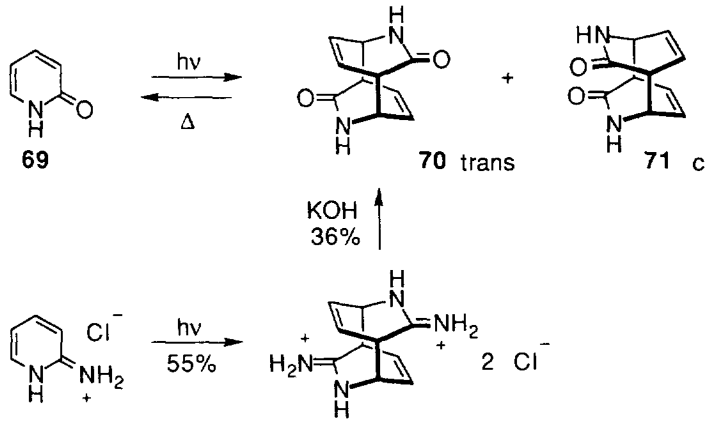
**62** **63** **64** 24% at **65** 48% conversion (19)

The only example of a [4+4] reaction of a 2-pyrone with a furan has been the intramolecular cycloaddition of **66**. This reaction afforded a mixture of endo and exo products in good yield.[44]



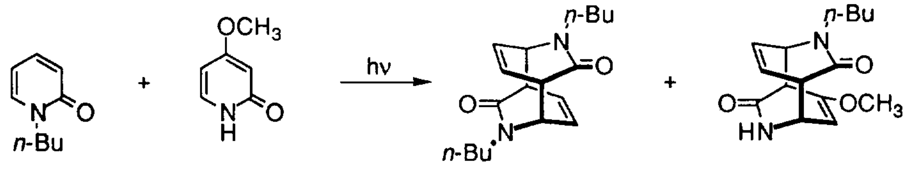
**66** **67** 1 : 1.5 **68** (20)

**2-Pyridone and related azaheterocycles.** The most heavily studied of the heterocyclic [4+4] photocycloadditions is that of the 2-pyridones (**49**).[45] As in the case of 2-pyrone **55**, the dimerization of **69** is highly regiospecific and gives only head-to-tail products.[46] Trans isomers dominate and are more stable than the cis isomers.[46] Unlike the 2-pyrone photodimers (eq 17), pyridone dimers undergo thermal cleavage and revert to 2-pyridones.[47] 2-Aminopyridinium salts (e.g., **50**) also photodimerize, producing trans [4+4] products such as **72** that can be hydrolyzed to the trans 2-pyridone photodimers **70**.[48]



**69** **70** trans **71** cis **50** **72** (21)

Photodimerization of 2-pyridones tolerates alkyl[49] and chlorine[50] substitution at nearly all positions; however, alkoxy substitution at C4 (viz. **74**) shuts down the [4+4] dimerization pathway.[51] These 4-methoxy-2-pyridones have recently been found to give cross product **76** with 2-pyridone **73** in a process that is very concentration dependent.[52]



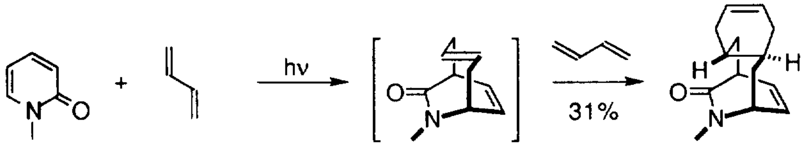
**73** **74** **75** dimer **76** cross product

1 : 1 1.8 : 1

1 : 4 1 : 7.2

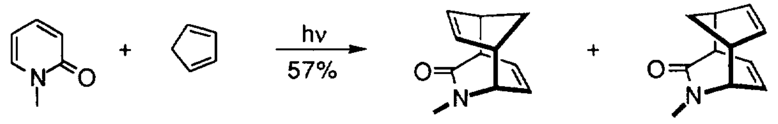
(22)

2-Pyridones undergo [4+4] photocycloaddition with simple 1,3-dienes.[53] Once again (see equations 6 and 15), the dominant ground state conformation of the diene is reflected in the products, and the highly strained initial photoproduct **78** (containing a trans alkene) finds relief in a second, but thermal, [4+2] cycloaddition.



**77** **78** **79**

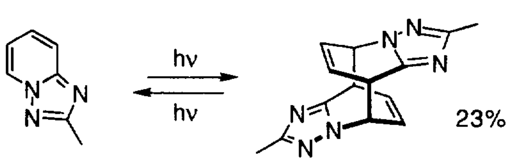
(23)



**77** **80** 8 : 3 **81**

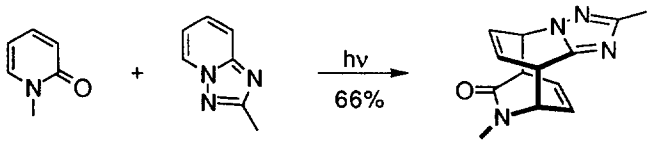
(24)

Triazolopyridines, with some structural similarity to 2-pyridones, undergo a photo-reversible [4+4] cycloaddition (eq 25).[54] The triazolopyridine was found to give a [4+4] cross product with 2-pyridone (eq 26).[55]



**51** **82**

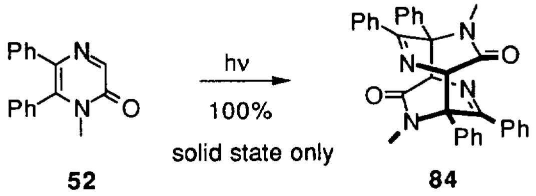
(25)



**77** **51** **83**

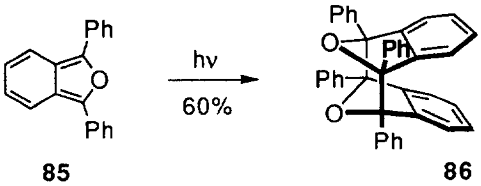
(26)

Of the many six-membered rings with two heteroatoms, only the pyrazinone derivative **52** has been found to undergo a [4+4] photodimerization, and this reaction occurs only in the solid state.[56]



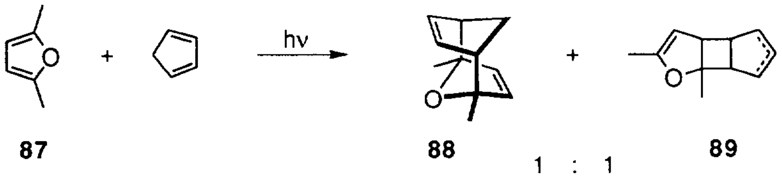
(27)

**Furans.** 1,3-Diphenylisobenzofuran (**85**) undergoes a photo-[4+4] dimerization, giving only the syn product.[57] This is the only reported example of photodimerization of an isobenzofuran.



(28)

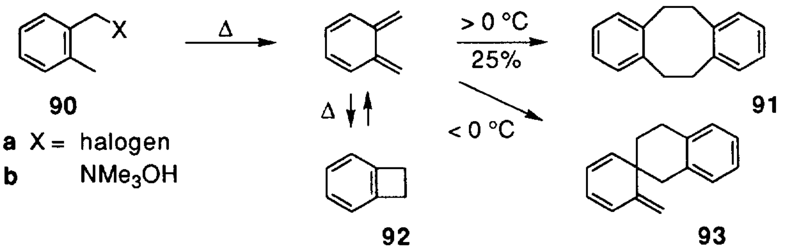
Although furan itself does not photodimerize,[58] many examples of its [4+4] reactivity with other aromatic substrates are known, including benzene,[38] naphthalene,[36] and anthracene.[59] Further, 2,5-dimethylfuran **87** has also been reported to undergo [4+4] photocycloaddition with cyclopentadiene to give two products (eq 29).[38] Cyclobutane **89** (structure not fully characterized) may derive from a Cope rearrangement of the cis [4+4] product.



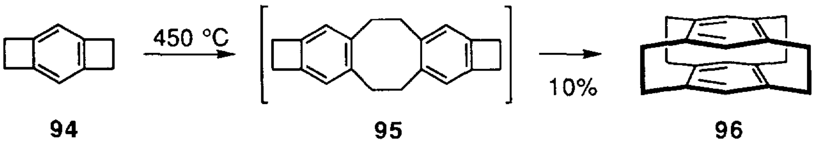
(29)

## 3.3 Orthoquinodimethanes and diyls.

Several important examples of thermal [4+4] cycloadditions involve orthoquinodimethanes.[60] In the competition between [4+4] and [4+2] pathways (among others), higher temperatures favored the former.[61] This version of the [4+4] cycloaddition has provided an efficient route to [a,e]dibenzocyclooctanes (e.g., **91**), and to a number of cyclophanes such as **96**.[62]

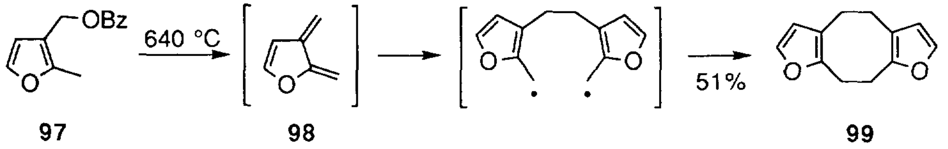


(30)

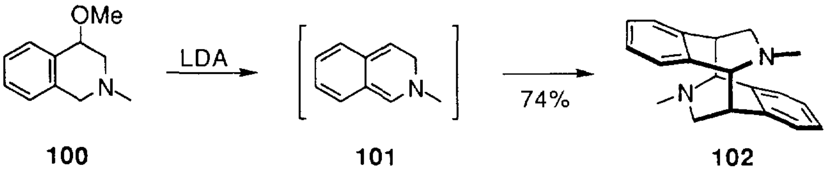


(31)

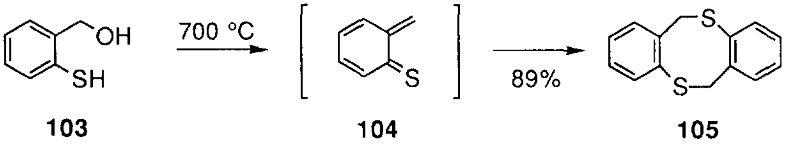
Heteroaromatic analogs of the orthoquinodimethanes have been studied, and the heteroatom can substantially influence the regiochemistry of the reaction. Pyrolytic generation of the reactive furan derivative **98** results in the head-to-head [4+4] product **99**, without forming the head-to-tail alternative.[63-65] In contrast, nitrogen analog **101** gives only head-to-tail union.[66] Heteroatom substitution of a terminal methylene carbon in an orthoquinodimethane can also lead to [4+4] products, as with sulfur analog **104** (eq 34).[67]



(32)

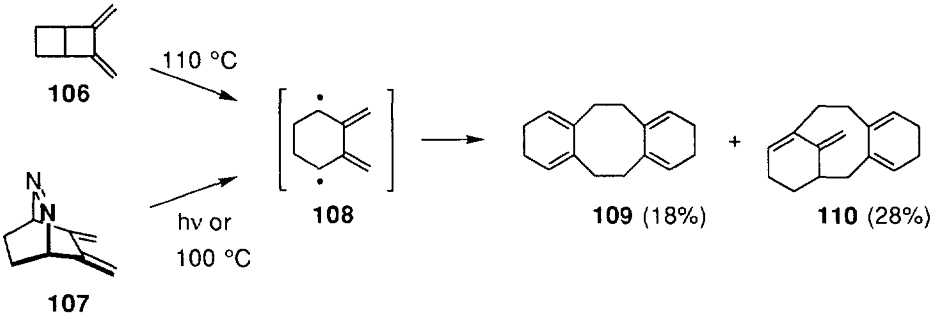


(33)



(34)

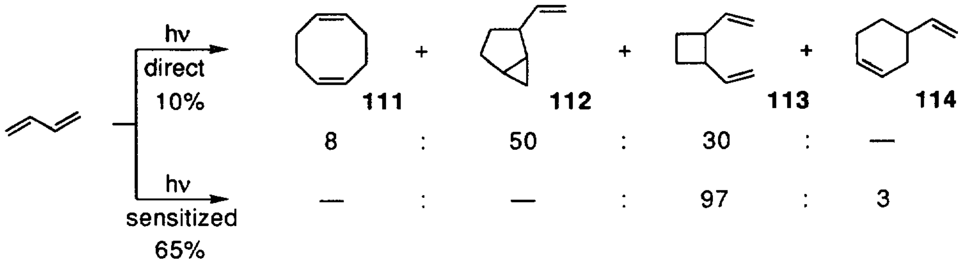
An aromatic ring is not necessary for this type of reaction; thermal or photochemical generation of the diyl **108** leads to cyclooctanes **109** and **110** in reasonable yield, along with other products.[68] The efficiency of this approach (e.g., formation of **110**) to the taxol skeleton has been noted.[69]



(35)

### 3.4 1,3-Dienes.

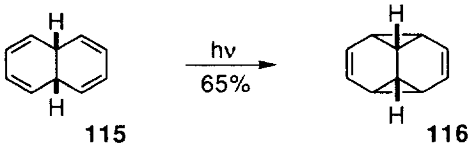
Direct irradiation of 1,3-butadiene leads to a large number of products, with 1,5-cyclooctadiene formed in low yield.[70] When photosensitization is employed, the triplet diene affords largely [2+2] products and no cyclooctadiene.[71]



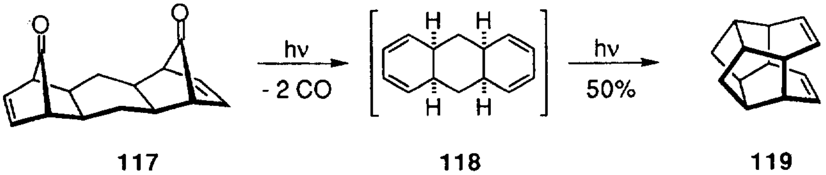
(36)

(37)

Nonetheless, the potential for [4+4] photocycloaddition of simple dienes, if held in the proper proximity and conformation, is clearly seen in the formation of **115** from tetraene **116**.[72] More recently, it has been found that photoexpulsion of carbon monoxide from the cis-syn-cis **117** generates **119** via [4+4] reaction of tetraene **118**.[73]

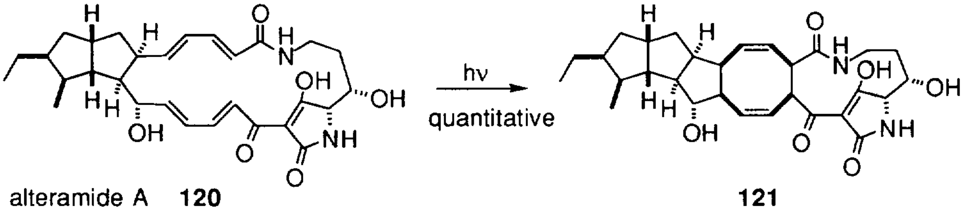


(38)



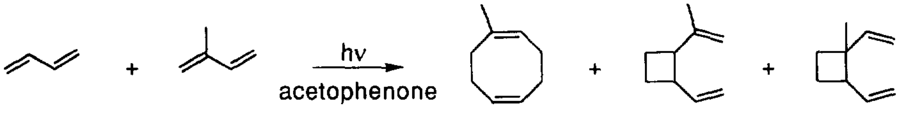
(39)

One of the best examples of a [4+4] photocycloaddition of two 1,3-dienes involves the natural product alteramide A **120**. Irradiation of this compound transforms it quantitatively to the [4+4] product **121**.[74]

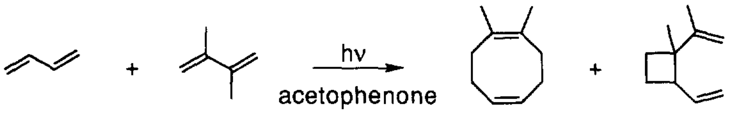


(40)

Whereas photosensitized irradiation of 1,3-butadiene does not lead to 1,5-cyclooctadiene (eq 37),[71] when 1,3-butadiene is irradiated as a mixture with isoprene (**122**) or 2,3-dimethyl-1,3-butadiene (**45**), a cyclooctadiene derived from both 1,3-dienes is isolated.[75] Substitution at the central positions of the 1,3-diene increases the amount of the *s*-cis conformer, and this steric effect is reflected in the yields of the cyclooctadiene product.

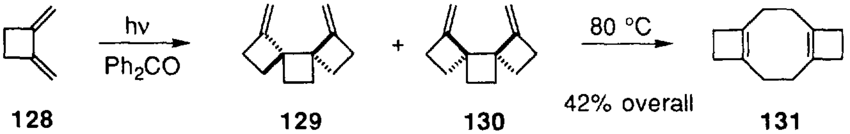


**122** **123** (2%) **124** (17%) **125** (36%) (41)

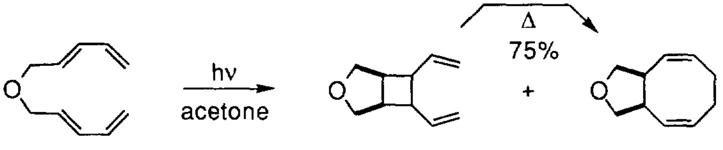


**45** **126** (15%) **127** (58%) (42)

The facile Cope rearrangement of *cis*-1,2-divinylcyclobutane to 1,5-cyclooctadiene[76] makes a two step sequence of [2+2] cycloaddition and thermal rearrangement an effective net [4+4] transformation for 1,3-dienes. This type of sequence was employed by Borden and Reich in the synthesis of tricyclic **131**.[77] An intramolecular variation was shown by Wender to be efficient overall for construction of cis-fused 5-8 rings.[78,79] Both the cis and trans divinyl isomers of **133** rearrange to **134**; the cis isomer isomerizes more efficiently and at a lower temperature.

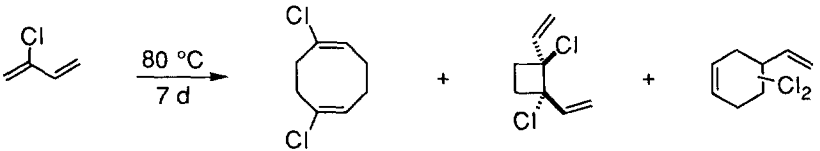


**128** **129** **130** **131** (43)



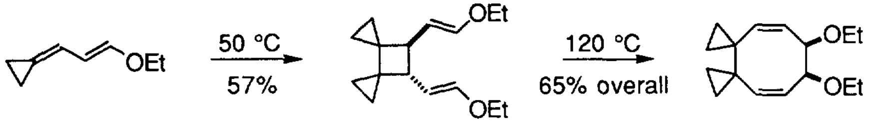
**132** **133** (84%) three isomers **134** (4%) (44)

One of the earliest indications of a thermal [4+4] reaction between two simple 1,3-dienes was the discovery of a high boiling fraction in samples of chloroprene (**135**),[80] shown to be exclusively the head-to-head isomer **136**.[81] This reaction has proven to be general for 1,3-dienes, but is usually slow and gives poor yields.[82] The mechanism of this [4+4] cycloaddition involves via an initial [2+2] reaction followed by Cope rearrangement. In the case of isoprene (**122**), the selectivity for head-to-head product is low.[83]



**135** **136** (14%) **137** **138** (45)

Enhancement of the [2+2] step, such as the case of cyclopropane **139**, leads to an efficient overall transformation to the cyclooctadiene **141**.[84]

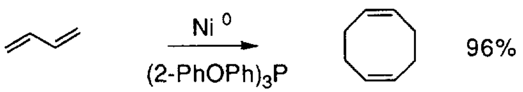


**139** **140** **141**

(46)

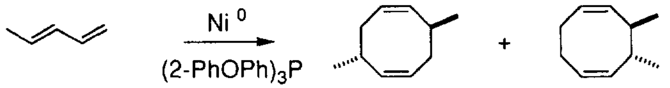
## 3.5 Catalyzed Reactions.

Polymerization of 1,3-dienes by transition metals can be optimized for a variety of products, and the dimerization of 1,3-butadiene to form cyclooctadiene with a nickel catalyst can be highly efficient (eq 47).[85,86] Use of substituted dienes introduces issues of regiochemistry and stereochemistry (and sometimes efficiency) and often leads to a mixture of products, as shown for piperylene (**142**).[85a]



**111**

(47)

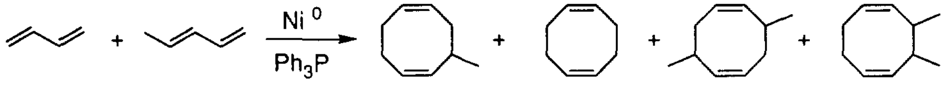


**142** **143** **144**

major isomers

(48)

Furthermore, the reaction rates are often attenuated by substitution of the diene. This outcome can be used to advantage, as with the cross-reaction of 1,3-butadiene and piperylene (equation 49).[87]

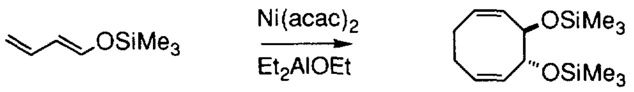


**142** 73% **145** **111** **143** **144**

1 : 2.5 60 : 20 : 9 : 2

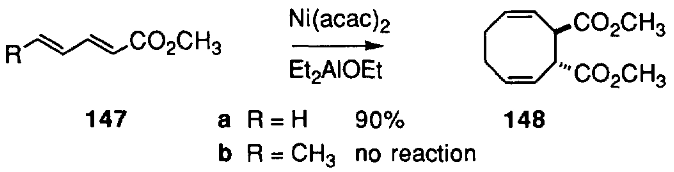
(49)

Efficient and highly selective nickel-catalyzed [4+4] dimerizations with functionalized 1,3-dienes have been demonstrated, including examples **145** and **147a**.[88] When the diene is substituted on both termini, for example **147b**, the dienes are inert to the reaction conditions.[88] For intramolecular examples, see equations 82-84.



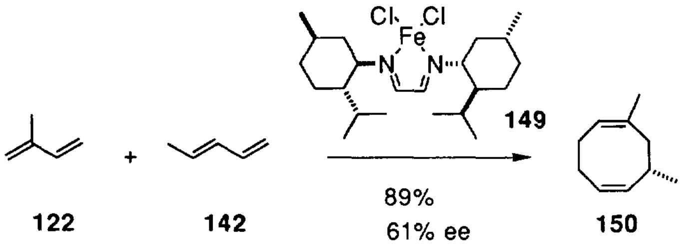
**145** 83% **146**

(50)



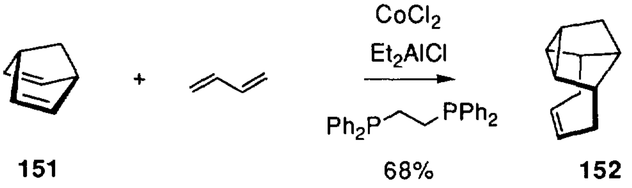
(51)

Other transition metals such as cobalt and iron can also be used. With the asymmetric iron catalyst **149**, the cross reaction of isoprene and piperylene can be achieved in high yield and with reasonable enantioselectivity.[89]



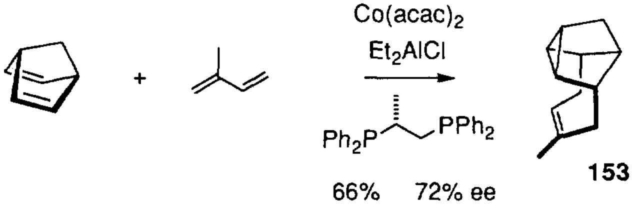
(52)

Investigations of Ziegler-Natta catalysts led to the discovery of a catalytic homo-[4+4] cycloaddition reaction of norbornadiene **151** with 1,3-dienes, providing the polycyclic product **152**.[90]

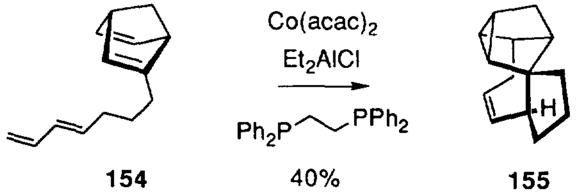


(53)

Lautens has explored the use of asymmetric phosphine ligands to produce enantiomerically enriched products (eq 54) and extended this reaction to the intramolecular case (eq 55).[91]



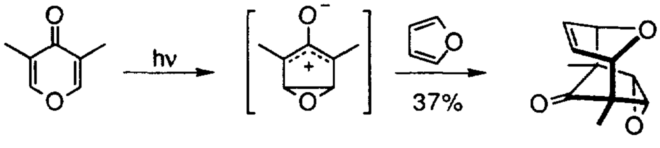
(54)



(55)

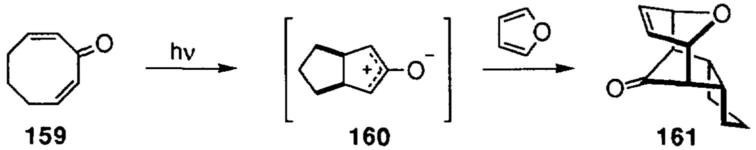
### 3.6 By [4+3] Cycloaddition.

Cycloadditions of 1,3-dienes with oxyallyl cations, or their equivalent,[92] can provide entry to cyclooctanoids if the zwitterion is part of a five-membered ring. Examples have been reported with the reactive species formed both photochemically and thermally. Cross-conjugated dienones **156**[93] and **159**[94] photoisomerize and undergo [4+3] cycloaddition with furan. In both cases a single endo product was reported. With 4-pyrone **156**, only a [2+2] cycloaddition was observed with cyclopentadiene.[93]



**156** **157** **158**

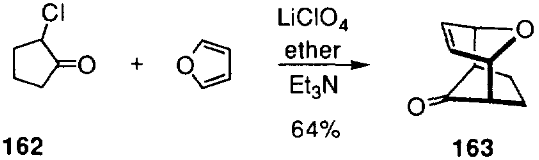
(56)



**159** **160** **161**

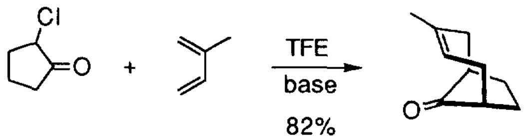
(57)

Solvolytic generation of the zwitterion from an α-chloroketone or enamine, in the presence of furan or a 1,3-diene, generates the cyclooctanoid product. As found for the photochemically derived species, a high degree of stereoselectivity was observed (eq 58 and 60).[95]



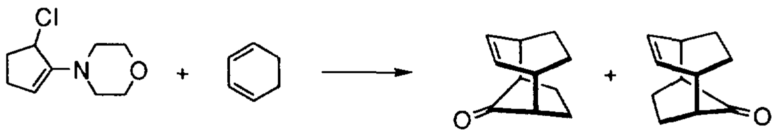
**162** **163**

(58)



**162** **164**

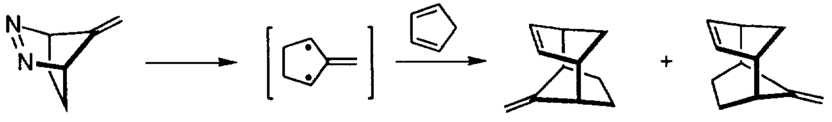
(59)



**165** **166** 93 : 7 **167**

(60)

Ethano-bridged trimethylenemethane (**169**), in the presence of a cyclic 1,3-diene, produces doubly bridged cyclooctenes (eq 61).[96] In this case the method used to generate the diyl does affect the yields, and in all cases the cycloadducts **170** and **171** are accompanied by significant amounts of other products.



(61)

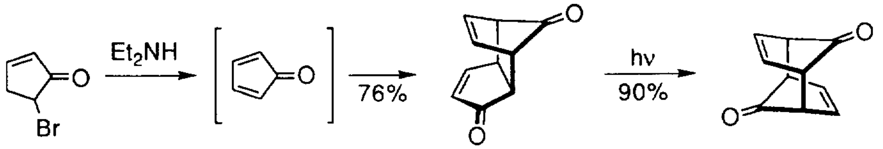
**168** **169** **170** **171**

| conditions | 170 | | 171 |
|---|---|---|---|
| 60 °C | 14% | : | 2% |
| hv | 36% | : | 2% |

### 3.7 Other Processes.

Some [4+4] reactions, particularly those involving discrete (isolable) intermediates, fall outside of the classifications used above. Examples of these are described below.

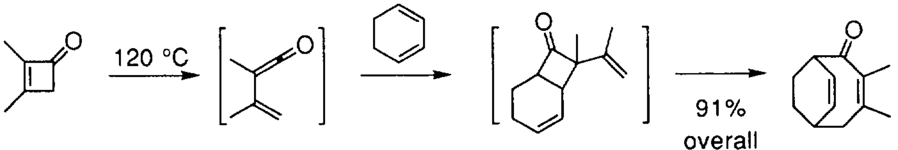
Transient formation of cyclopentadienone gives rise to the [4+2] Diels-Alder product **174**.[97] This dimer contains a conjugated pi-system and can be efficiently photoisomerized into [4+4] product **175**.[98]



(62)

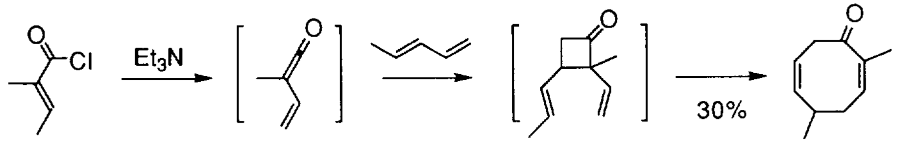
**172** **173** **174** **175**

Danheiser has developed a [4+4] cycloaddition that proceeds through a cascade of thermal pericyclic reactions for which the key step is a [2+2] cycloaddition to give a cyclobutanone such as **178** or **182**. Despite the number of bond reorganizations involved, the overall yield can be excellent.[99]



(63)

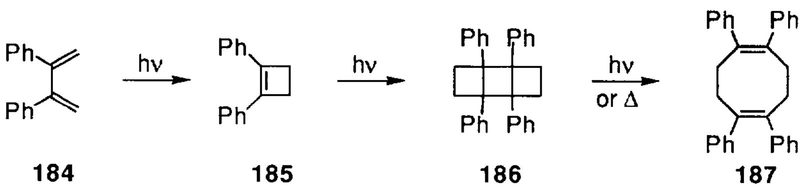
**176** **177** **178** **179**



(64)

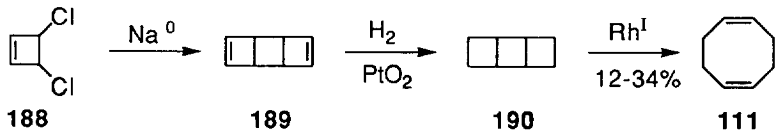
**180** **181** **182** **183**

Two versions of a metathesis-type of [4+4] cycloaddition have been reported, and these also involve cyclobutyl intermediates (eqs 65 and 66). Irradiation of either 2,3-diphenyl-1,3-butadiene **184** or 1,2-diphenylcyclobutene **185** generates the strained [2+2] photodimer **186** as well as 1,2,5,6-tetraphenyl-1,5-cyclooctadiene (**187**). Dimer **186** is converted to cyclooctadiene **187** by further irradiation or by thermolysis.[100]



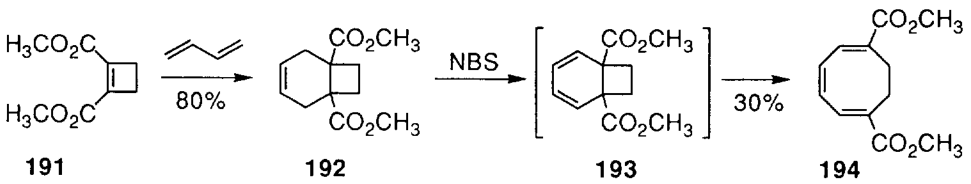
(65)

A similar tricyclic intermediate **189** is formed by sodium-mediated dehalogenation of dichloride **188**, to give the apparent [4+2] dimerization product (**189**) of cyclobutadiene. Reduction of the alkenes followed by rhodium-catalyzed isomerization gave 1,5-cyclooctadiene in modest yield.[101]

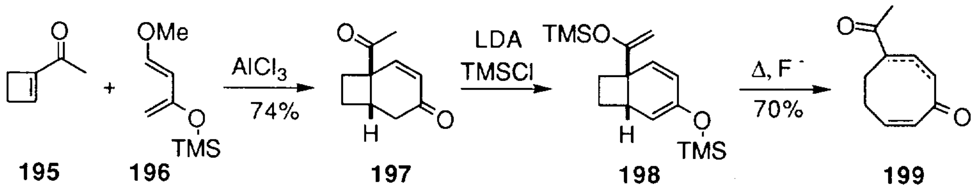


(66)

An alternative to the metathesis approach is the use of a Diels-Alder reaction with a cyclobutene. Transformation of the initial cyclohexene product **192** to a cyclohexadiene **193** allows for thermal isomerization to a cyclooctatriene.[102] Two variations of this sequence have been reported (eqs 67, 68).[103,104]

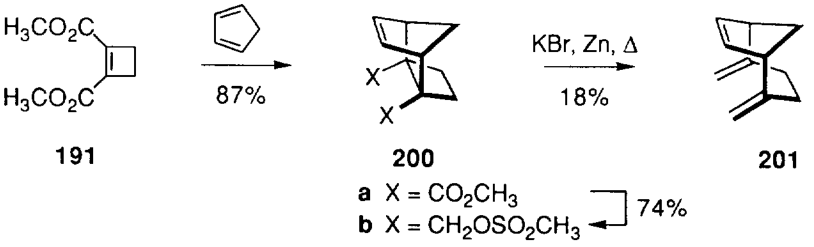


(67)



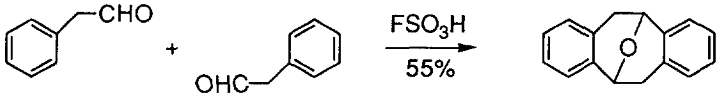
(68)

An alternative cyclobutane fragmentation also using diester **191** as the starting cyclobutene is shown in equation 69 (compare to equation 67).[105] Following Diels-Alder reaction and manipulation of the ester functionality, generation of the bromide under reducing conditions produced the unstable triene **201**.



(69)

An interesting example of eight-membered ring synthesis can also be found in the dimerization of phenylacetaldehyde under Friedel-Crafts conditions.[106]

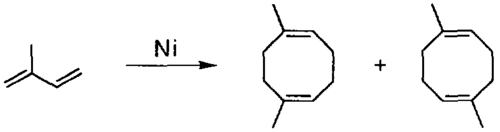


**202** **202** **203**

(70)

## 4. Syntheses via [4+4] Reactions

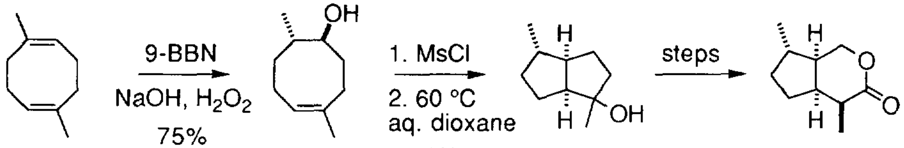
In principle, any synthesis that begins with the commercially available 1,5-cyclooctadiene (eq 47) or with dimethyl-1,5-cyclooctadienes **204** or **205** (eq 71) takes advantage of the efficient, catalytic [4+4] cyclodimerization of 1,3-butadiene or isoprene (**119**).[85] Two examples can be found in Figure 2 and three more examples are given in equations 72, 73, and 74.



**119** **204** **205**

(71)

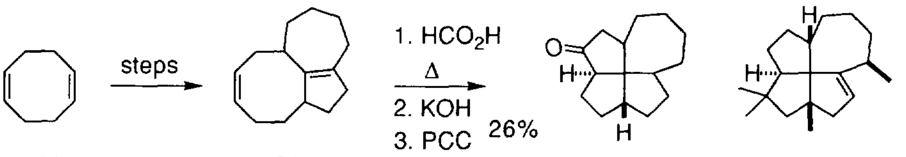
Whitesell's succinct preparation of iridomyrmecin (**208**) began with hydroboration of the isoprene dimer **205**.[107] Solvolysis of the mesylate derivative gave the [3.3.0] product **207** with control of three stereogenic centers.



**205** **206** **207** **208** iridomyrmecin

(72)

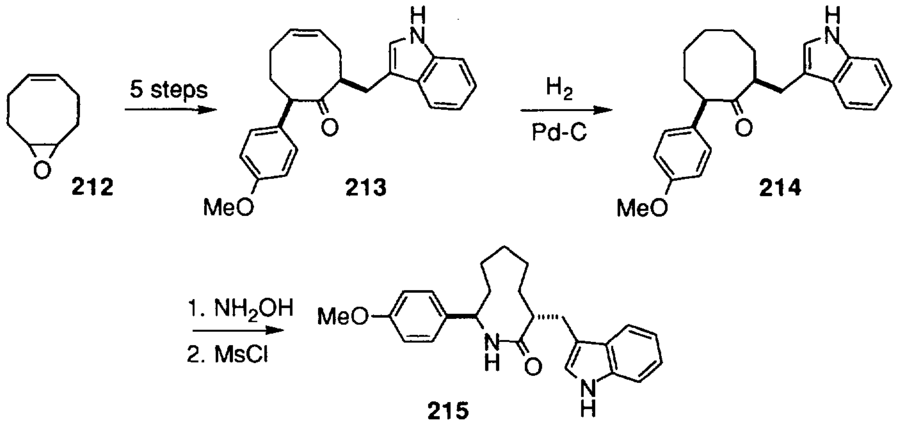
Mehta's assembly of the framework of laurenene **211** began with 1,5-cyclooctadiene.[108] Elaboration into the tricyclic diene **209** as a mixture of diastereomers was followed by acidic transannular ring closure to give a tetracyclic formate ester product. Hydrolysis and oxidation led to the isolation of ketone **210**.



**111** **209** **210** **211** laurenene

(73)

The monoepoxide of 1,5-cyclooctadiene was the starting point for Kahn's synthesis of the nine-membered lactam **215**, a designed mimic of jaspamide.[109] Beckman rearrangement of the oxime of ketone **214** gave the amide linkage, as well as epimerizing one stereocenter of **214** to the desired trans relationship in the product. Anticipated use of the double bond in **213** to prepare additional analogs was frustrated as this ketone proved to be inert under Beckman rearrangement conditions.



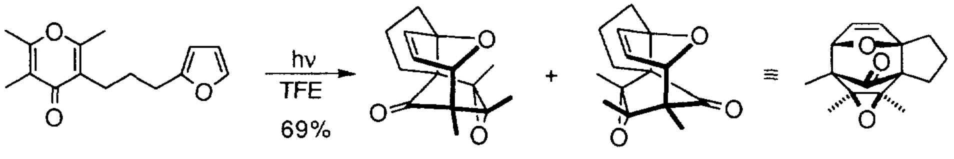
212 213 214 215

(74)

## 4.1 Fused 5-8 Rings: Model Systems

One common feature of naturally occurring eight-membered rings is a fusion to a five-membered ring. Thus, the 5-8 ring system has been a primary target in the development of [4+4] cycloadditions, and it can be produced from two reactive species tethered with a three-carbon chain.

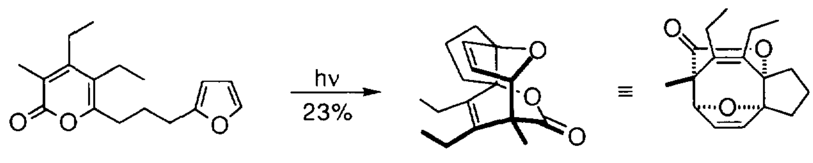
West has described use of the mixed 4-pyranone–furan system, which efficiently undergoes photocycloaddition to give largely two [4+4] isomers (eq 75).[110] Interestingly, the endo/exo ratio is reversed from that reported for the intermolecular case[93] (eq 56).



216 217 1 : 3 218

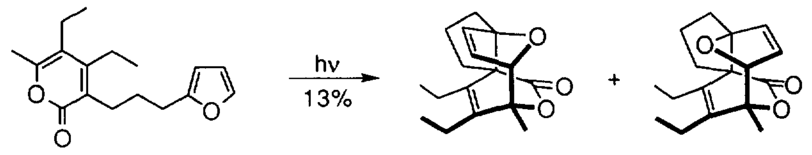
(75)

West has also examined the intramolecular reaction of 2-pyrones and a furan tethered at both the 6- (eq 76) and 3- (eq 77) positions of the 2-pyrone.[110] Cycloaddition products were found for both of these isomers, and the former case was both more selective and more efficient. The full substitution of the pyrone ring may have adversely affected these yields as related examples (see equation 20) have been much more efficient.



219 220

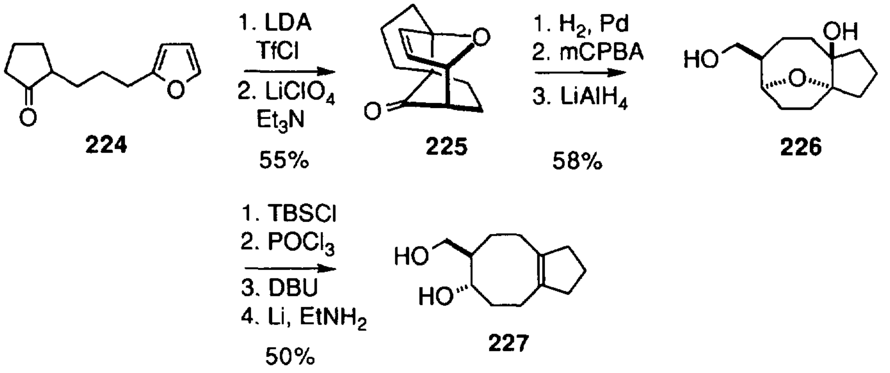
(76)



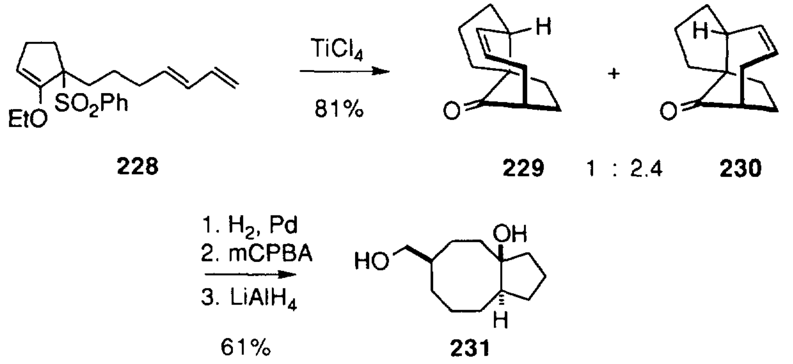
221 222 2 : 1 223

(77)

Harmata's solvolytic cycloaddition of a chloroketone and a furan generates a single isomeric product **225** in good yield and as essentially one stereoisomer.[111] Cleavage of the bridging ketone and ether led to **227**. In related work, solvolysis of sulfone **228** initiates a cycloaddition with the tethered 1,3-diene to give a very good yield of the cycloadducts **229** and **230**.[111]

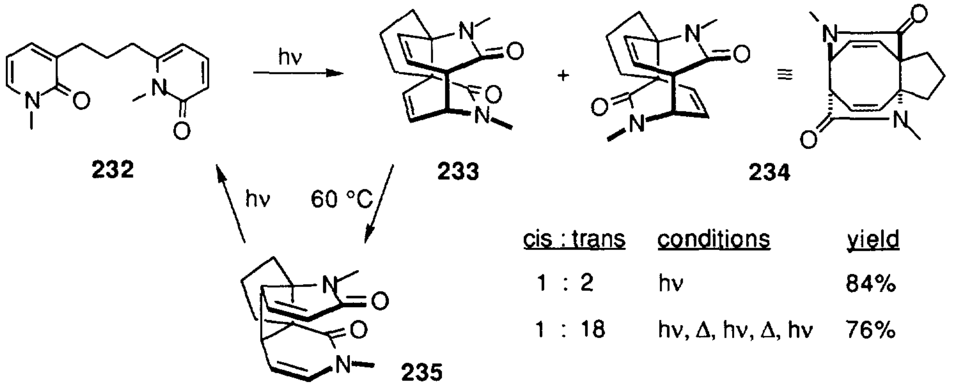


(78)



(79)

Unsymmetrically tethered 2-pyridones (viz. **232**) photoisomerize efficiently to the [4+4] adducts, favoring the trans isomer.[112] The cis isomer **233** has been found to convert to the trans isomer **234** through a Cope rearrangement (to **235**) followed by a photocleavage/recombination pathway that leads to greatly enhanced yields of the trans [4+4] product.[113]

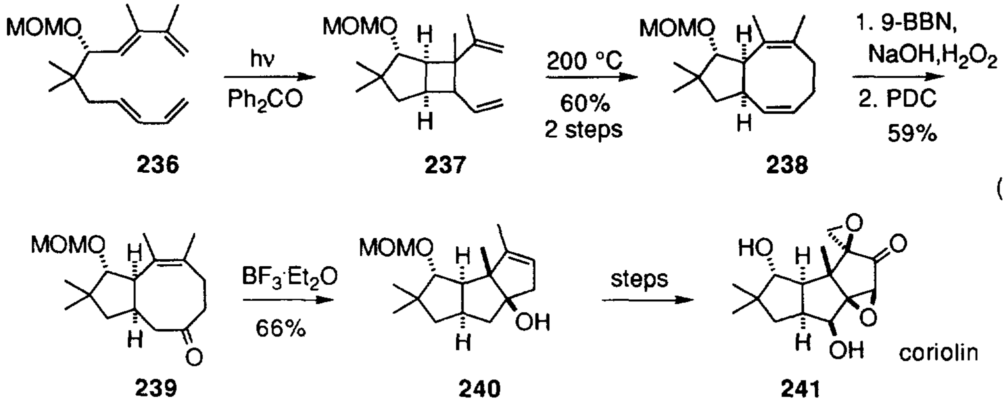


| cis : trans | conditions | yield |
|---|---|---|
| 1 : 2 | hv | 84% |
| 1 : 18 | hv, Δ, hv, Δ, hv | 76% |

(80)

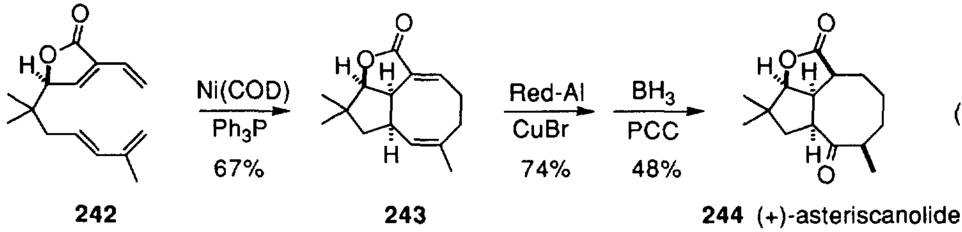
### 4.2 Fused 5-8 Rings: Total Synthesis

Intramolecular, two-stage cycloaddition of the tethered 1,3-dienes in **236** to give the [6.3.0] product **238** was a central component of Wender's synthesis of coriolin.[79] Stereogenesis during benzophenone sensitized [2+2] cycloaddition is controlled by the protected alcohol on the tether, setting three contiguous centers. Subsequent thermolysis of the mixture of cis and trans divinylcyclobutanes gave the cis-fused cyclooctadiene **238** in good overall yield from the starting tetraene. Hydroboration-oxidation and transannular ring closure provided the linear triquinane framework (**240**) with the correct relative stereochemistry for coriolin.



(81)

Wender's nickel catalyzed intramolecular [4+4] chemistry was deployed in an exceptionally short synthesis of the natural product asteriscanolide (**244**), in enantiomerically pure form.[114] The nickel catalyzed cycloaddition of **242** gave product **243** in good yield. Completion of the synthesis entailed chemoselective reduction of the conjugated alkene followed by hydroboration of the remaining trisubstituted olefin from the convex face. Oxidative workup then gave the natural product.

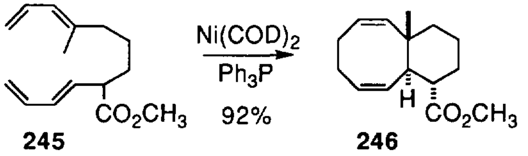


(82)

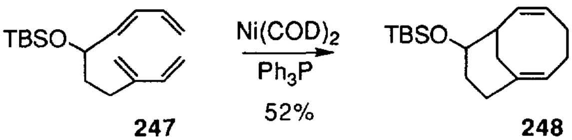
## 5. Syntheses via [4+4] Cycloaddition - Taxol

### 5.1 Bicyclic Model Systems.

The most intensively studied natural product with an eight-membered ring is taxol.[6] Among the many synthetic strategies, several [4+4]-based approaches to the ring system have been developed (See Figure 3 in Section 2). Wender's nickel catalyzed cycloaddition (see eqs 82, 83, and 84) was found to be suitable for preparation of either of the 8-6 ring fusions: the trans [6.4.0] BC ring system **246** with a quaternary carbon, or the [5.3.1] AB ring system **248** of taxol.[115] In the former case, the tether substituent exerts substantial control over the stereochemistry of the cycloaddition, whereas the silyloxy group on the three-carbon tether of **247** had little stereogenic influence. Note that equation 84 can be considered as a Type II or Type III dissection of the eight-membered ring (Figure 3). A transannular combination of equations 83 and 84 has not been reported.

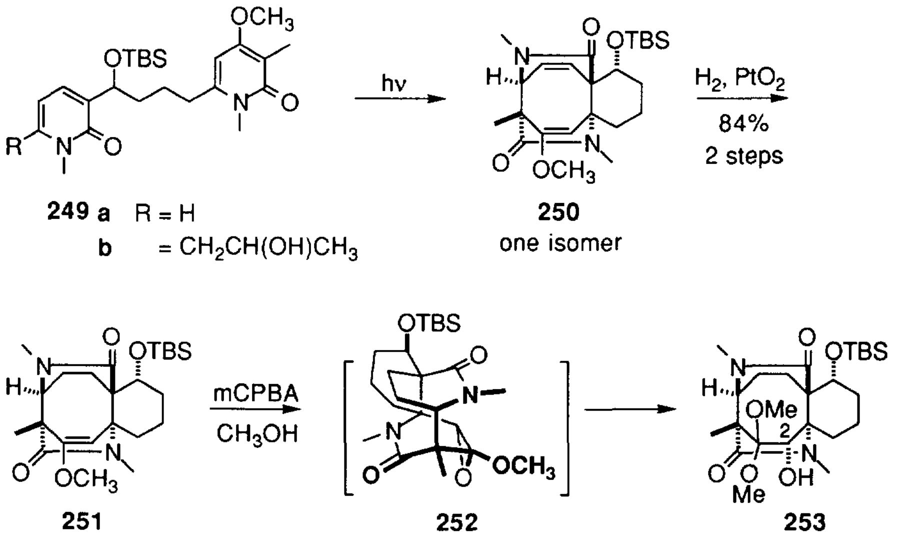


(83)



(84)

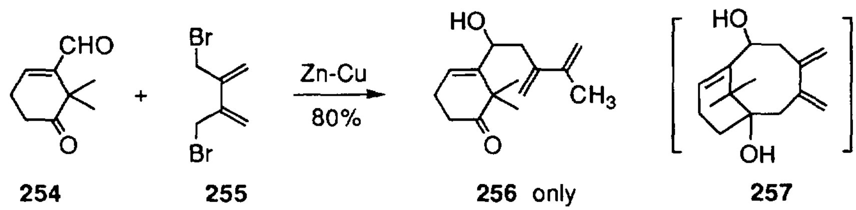
Intramolecular 2-pyridone photocycloaddition with **249** has been utilized in a model system for the BC rings of taxol.[116] The silyloxy group of **249a** has a significant (presumably steric) influence and leads to photoproduct **250** as a single diastereomer. This product is quite strained, due in part to a boat conformation of the cyclohexane ring,[117] and undergoes a retro-[4+4] reaction on exposure to silica gel. Hydrogenation of one alkene bond prevents reversion to aromatic **249a**, and the structure of **251** was confirmed by X-ray crystallography. Epoxidation of the enol ether of **251** in methanol[118] evidently proceeds from the least hindered face because the product was a single hydroxy ketal **253** presumably derived from acid catalyzed opening of **252**.[119] In contrast to **249a**, substrate **249b** does not undergo [4+4] photocycloaddition, perhaps because simultaneous formation of four tetrasubstituted carbons presents too great a steric impediment.[120]



(85)

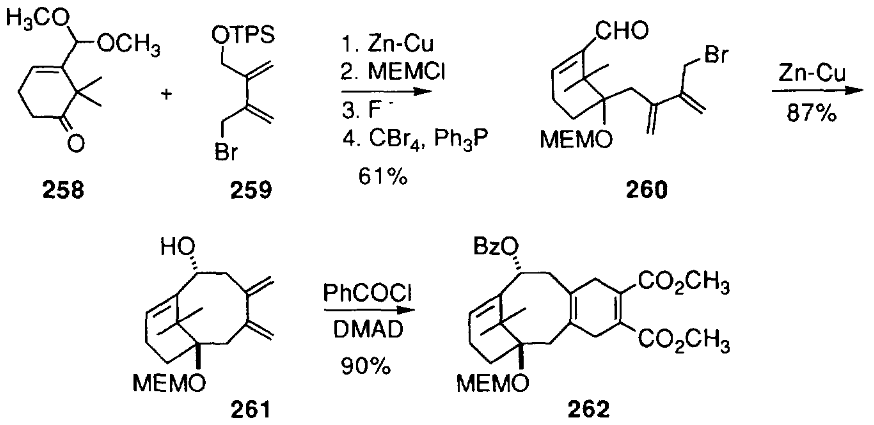
## 5.2 Tricyclic Model Systems.

A combination of [4+4] (Type I, Figure 3) and [4+2] cycloadditions has been used by Wang to prepare the three carbocyclic rings of taxol.[121] While in principle a double alkylation of **254** with dibromide **255** would yield **257**, this single-step operation gave only the monoalkylation product **256**.



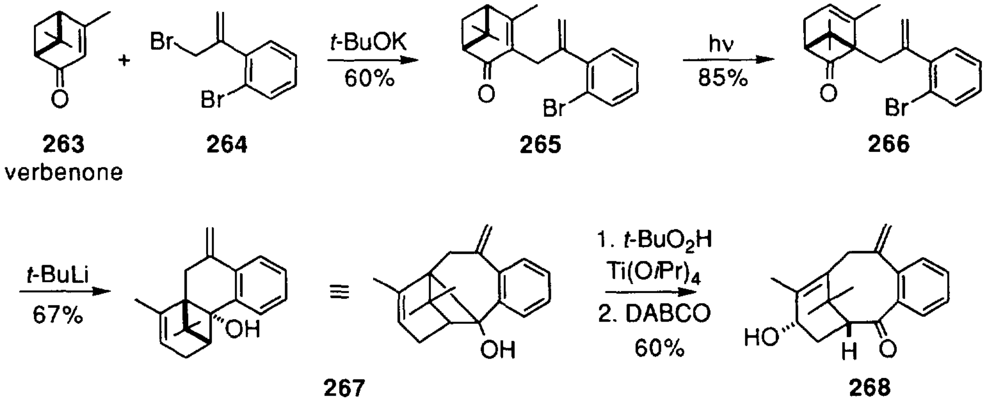
(86)

In the case of **258** and **259**, forming both new bonds stepwise makes the transformation a very effective overall process. Treatment of the resulting 1,3-diene **261** with benzoyl chloride and dimethyl acetylenedicarboxylate forms the taxol C ring in high yield (eq 87).



(87)

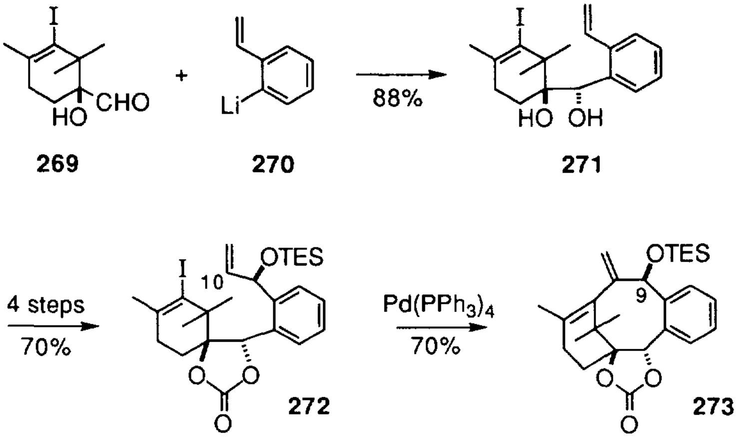
A [4+4] route to taxol, with one of the four-carbon units masked, is the centerpiece of Wender's pinene-based approach to taxol (Type IV, Figure 3).[122] Verbenone (**263**), derived from pinene, is alkylated by the



(88)

four-carbon component **264**. Subsequent 1,3-photorearrangement of the verbenone component assembles the second four-carbon cyclobutanone unit. The next ring closure is a six-membered ring-forming process. Hydroxyl-directed epoxidation of the trisubstituted alkene bond arms the system for a base-promoted fragmentation to generate the eight-membered ring product **268** in enantiomerically pure form.

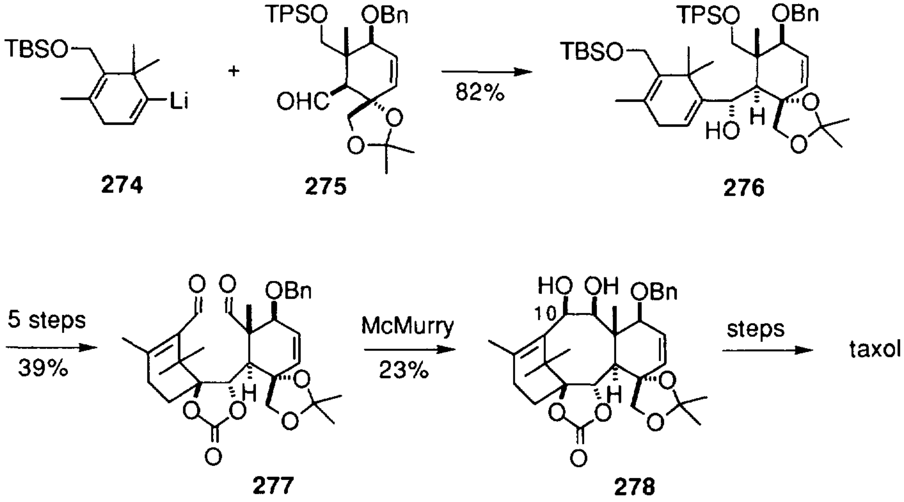
A recent Danishefsky approach[123] to the taxanes (eq 89) is fundamentally a Type IV [4+4] sequence. Late introduction of C10 allows a stereogenic center at C9 to be set selectively. Closure of the eight-membered ring using the Heck reaction efficiently completes the [4+4] sequence.



(89)

## 5.3 Total Synthesis.[124]

Nicolaou's landmark synthesis of taxol (Type I, Figure 3) was also based on the coupling of two four-carbon components.[125] Vinyllithium reagent **274** and aldehyde **275** gave alcohol **276**. After adjustment of the functionality, a McMurry pinacol coupling of dialdehyde **277** closed the second bond of the eight-membered ring in modest yield but with the correct stereochemistry at C10. Diol **278** was successfully converted into taxol.



(90)

## 6. Conclusions

Construction of cyclooctanoids using a [4+4] strategy has produced outstanding solutions to the challenges of eight-membered ring synthesis, including one of the first total syntheses of taxol (eq 90) and an exceptionally short route to (+)-asteriscanolide (eq 82).

Among the methodologies outlined in this review, a number of provocative examples warrant further investigation. These include the photoreactions of suitably aligned 1,3-dienes (eqs 38-40), the photoreaction of 1,3-dienes with benzene (eqs 13-16) and also with heteroaromatics (eqs 23, 24, and 29), the catalyzed reactions of 1,3-dienes intermolecularly (eqs 50-52) and intramolecularly (eqs 83 and 84), and the Diels-Alder/photoisomerization chemistry of cyclopentadienone (eq 62).

Continuing interest in medium ring structures, both designed and naturally occurring, can be expected to stimulate further development of [4+4] pathways.

## 7. Acknowledgment

The authors thank Professor Frederick G. West and Professor Frank E. McDonald for reviewing the manuscript and for supplying additional examples.

## 8. References

1 Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 321-328.

2 Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, CT, 1993; Vol. 2; pp 27-66. Bertz, S. H.; Sommer, T. J. *ibid.* pp 67-92.

3 Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon: New York, 1991; Vol. 5; pp 315-399.

4 Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579-585. Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382-1396. and references therein.

5 Arigoni, D. *Pure Appl. Chem.* **1968**, *17*, 331-348.

6 Reviews: **a)** *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Ed.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. **b)** Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47-75. **c)** Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1-192. **d)** Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465-543.

7 Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95-102.

8 For reviews discussing [4+4] cycloadditions see: Lablache-Combier, A. *Bull. Soc. Chem Fr.* **1972**, 4791-4837. Kaupp, G. *Liebigs Ann. Chem.* **1973**, 844-878. Schönberg, A. *Preparative Organic Photochemistry*; Springer-Verlag: New York, 1968, Chapter 9. Trecker, D. J. *Org. Photochem.* **1969**, *2*, 63-116. Bouas-Laurent, H.; Desvergne, J.-P. In *Photochromism: Molecules and Systems*; Dürr, H.; Bouas-Laurent, H., Ed.; Elsevier: New York, 1990; pp 561-630. see also reference 4.

9 For a general review of eight-membered ring synthesis see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757-5821.

10 Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781-853.

11 *Pericyclic Reactions*; Marchand, A. P.; Lehr, R. E., Ed.; Academic: New York, 1977.

12 Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767-1769. Boeckman, R. K., Jr.; Springer, D. M.; Alessi, T. R. *J. Am. Chem. Soc.* **1989**, *111*, 8284-8286. Boeckman, R. K., Jr. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic: New York, 1991; Vol. 3; pp 37-87.

13 Hensens, O. D.; Zink, D.; Williamson, J. M.; Lotti, V. J.; Chang, R. S. L.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 3399-3403.

14 Burke, J. W.; Doskotch, R. W.; Ni, C.-Z.; Clardy, J. *J. Am. Chem. Soc.* **1989**, *111*, 5831-5833.

15 Prestwich, G. D.; Tempesta, M. S.; Turner, C. *Tetrahedron Lett.* **1984**, *25*, 1531-1532.

16 Sun, H. H.; McEnroe, F. J.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 1903-1906.

17 Ophiobolin K: Singh, S. B.; Smith, J. L.; Sabnis, G. S.; Dombrowski, A. W.; Schaeffer, J. M.; Goetz, M. A.; Bills, G. F. *Tetrahedron* **1991**, *47*, 6931-6938. For a summary of this class of structures see reference 9.

18 Total synthesis: Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354-356. Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735-2737. Kato, N.; Wu, X.; Tanaka, S.; Takeshita, H. *Chem. Lett.* **1989**, 91-94. Kato, N.; Takeshita, H.; Kataoka, H.; Ohbuchi, S.; Tanaka, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 165-174. Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737-2739. Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676-1683.

19 For recent work and lead references see: Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M.-J. *J. Org. Chem.* **1989**, *54*, 592-601. Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075-3087. Paquette, L. A.; Liang, S.; Galatsis, P. *Synlett* **1990**, 663-665. Sieburth, S. McN.; Chen, J.-l. *J. Am. Chem. Soc.* **1991**, *113*, 8163-8164. Jommi, G.; Orsini, F.; Resmini, M.; Sisti, M. *Tetrahedron Lett.* **1991**, *32*, 6969-6972. Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615-3626. Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676-1683. Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931-5943. Inouye, Y.; Shirai, M.; Michino, T.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 324-326. Umehara, M.; Honnami, H.; Hishida, S.; Kawata, T.; Ohba, S.; Zen, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 562-567. Kato, N.; Wu, X.; Nishikawa, H.; Takeshita, H. *Synlett* **1993**, 293-295. Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057-3083. Rigby, J. H.; McGuire, T.; Senanayake, C.; Khemani, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3449-3457.

20 Review: Harrowven, D. C.; Pattenden, G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon: New York, 1991; Vol. 3; pp 379-411.

21 Curran, D. P.; Shen, W. *Tetrahedron* **1993**, *49*, 755-770.

22 Mehta, G.; Rao, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 8015-8021.

23 Reviews and discussions of aromatic photocycloaddition reactions: Bryce-Smith, D. *Pure Appl. Chem.* **1973**, *34*, 193-212. Mattay, J. *Tetrahedron* **1985**, *41*, 2405-2417. McCullough, J. J. *Chem. Rev.* **1987**, *87*, 811-860. see also reference 8.

24 Reviews: Becker, H.-D. *Adv. Photochem.* **1990**, *15*, 139-227. Becker, H.-D. *Chem. Rev.* **1993**, *93*, 145-172.

25 Fritzsche, J. *J. Prakt. Chem.* **1867**, *101*, 333.

26 Orndorff, W. R.; Cameron, F. K. *Amer. Chem. J.* **1895**, *17*, 658-681.

27 Kaupp, G.; Teufel, E. *Chem. Ber.* **1980**, *113*, 3669-3674. Becker, H.-D.; Langer, V. *J. Org. Chem.* **1993**, *58*, 4703-4708.

28 Bradsher, C. K.; Beavers, L. E.; Jones, J. H. *J. Org. Chem.* **1957**, *22*, 1740-1741. Wagner, J.; Bendig, J.; Felber, A.; Sommerer, A.; Kreysig, D. *Z. Chem.* **1985**, *25*, 64.

29 Yang, N. C.; Libman, J. *J. Am. Chem. Soc.* **1972**, *94*, 1405-1406. Yang, N. C.; Masnovi, J.; Chiang, W.-L.; Wang, T.; Shou, H.; Yang, D.-D. H. *Tetrahedron* **1981**, *37*, 3285-3300. Saltiel, J.; Dabestani, R.; Schanze, K. S.; Trojan, D.; Townsend, D. E.; Goedken, V. L. *J. Am. Chem. Soc.* **1986**, *108*, 2674-2687.

30 Kaupp, G. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 718-719.

31 Inoue, T.; Kaneda, T.; Misumi, S. *Tetrahedron Lett.* **1974**, 2969-2972.

32 Hayashi, T.; Mataga, N.; Inoue, T.; Kaneda, T.; Irie, M.; Misumi, S. *J. Am. Chem. Soc.* **1977**, *99*, 523-526.

33 Sisido, K.; Udô, Y.; Nozaki, H. *J. Org. Chem.* **1961**, *26*, 584-585.

34 Heine, H. W.; Suriano, J. A.; Winkel, C.; Burik, A.; Taylor, C. M.; Williams, E. A. *J. Org. Chem.* **1989**, *54*, 5926-5930.

35 Bradshaw, J. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1963**, *85*, 3953-3955. Teitei, T.; Wells, D.; Sasse, W. H. F. *Tetrahedron Lett.* **1974**, 367-370.

36 Pac, C.; Sugioka, T.; Sakurai, H. *Chem. Lett.* **1972**, 39-42. Kan, K.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1634-1636.

37 Mak, K. T.; Srinivasachar, K.; Yang, N. C. *J. Chem. Soc., Chem. Commun.* **1979**, 1038-1040.

38 **a)** Garcia, H.; Gilbert, A.; Griffiths, O. *J. Chem. Soc., Perkin Trans 2* **1994**, 247-252. **b)** Berridge, J. C.; Gilbert, A.; Taylor, G. N. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2174-2178. **c)** Cantrell, T. S. *J. Org. Chem.* **1981**, *46*, 2674-2679.

39 Kraft, K.; Koltzenburg, G. *Tetrahedron Lett.* **1967**, 4357-4362. Yang, N. C.; Horner, M. G. *Tetrahedron Lett.* **1986**, *27*, 543-546.

40 Gilbert, A.; Griffiths, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1379-1384. See also reference 38a.

41 de Mayo, P.; Yip, R. W. *Proc. Chem. Soc.* **1964**, 84. de Mayo, P.; McIntosh, C. L.; Yip, R. W. *Org. Photochem. Synth.* **1971**, *1*, 99-100.

42 Rieke, R. D.; Copenhafer, R. A. *Tetrahedron Lett.* **1971**, 879-882.

43 Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1964**, *86*, 4212-4213.

44 West, F. G.; Chase, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 3794-3795.

45 Sharp, L. J., IV; Hammond, G. S. *Mol. Photochem.* **1970**, *2*, 225-250.

46 Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187-1191.

47 Taylor, E. C.; Paudler, W. W. *Tetrahedron Lett.* **1960,** *No. 25*, 1-3.

48 Taylor, E. C.; Kan, R. O. *J. Am. Chem. Soc.* **1963,** *85*, 776-784. Taylor, E. C.; Spence, G. G. *Org. Photochem. Synth.* **1971**, *1*, 46-48.

49 Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans 2* **1985**, 1445-1448.

50 Dilling, W. L.; Tefertiller, N. B.; Mitchell, A. B. *Mol. Photochem.* **1973,** *5*, 371-409.

51 Kaneko, C.; Shiba, K.; Fujii, H.; Momose, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 1177-1178.

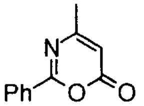
52 Chao-Hsiung Lin, Research Notes, SUNY Stony Brook.

53 Sato, E.; Ikeda, Y.; Kanaoka, Y. *Liebigs Ann. Chem.* **1989**, 781-788.

54 Nagano, T.; Hirobe, M.; Itoh, M.; Okamoto, T. *Tetrahedron Lett.* **1975**, 3815-3818.

55 Nagano, T.; Hirobe, M.; Okamoto, T. *Tetrahedron Lett.* **1977**, 3891-3894.

56 Solution photochemistry of 1,3-oxazin-6-one **279** does not yield [4+4] products: de Mayo, P.; Weedon, A. C.; Zabel, R. W. *Can. J. Chem.* **1981**, *59*, 2328-2333. Nishio, T.; Nakajima, N.; Omote, Y. *Tetrahedron Lett.* **1980**, *21*, 2529-2530.



**279**

57 Guyot, A.; Catel, J. *Bull. Soc. Chem Fr.* **1906,** *35*, 1124-1135. Courtot, P.; Sachs, D. H. *Bull. Soc. Chem Fr.* **1965**, 2259-2262.

58 Padwa, A. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 3; pp 501-547.

59 Mizuno, K.; Pac, C.; Sakurai, H. *Chem. Lett.* **1973**, 309-310.

60 Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987,** *43*, 2873-2889. Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proced. Int.* **1991,** *23*, 239-272.

61 Errede, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 949-954. For a higher yielding approach to dibenzocyclooctane see: Boudjouk, P.; Sooriyakumaran, R.; Han, B.-H. *J. Org. Chem.* **1986,** *51*, 2818-2819.

62 Eaton, B. E.; Laganis, E. D.; Boekelheide, V. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 6564-6566. Boekelheide, V. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic: New York, 1984; Vol. 1; pp 1-19.

63 Trahanovsky, W. S.; Cassady, T. J.; Woods, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 6691-6695. Leung, M.-k.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1995,** *117*, 841-851.

64 For the alternative furan substitution see: Stone, K. J.; Greenberg, M. M.; Blackstock, S. C.; Berson, J. A. *J. Am. Chem. Soc.* **1989,** *111*, 3659-3671.

65 For a pyrrole and other heterocycle analogs see: Chou, T.-s.; Chang, R.-C. *J. Chem. Soc., Chem. Commun.* **1992**, 549-551. and references therein.

66 Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1994,** *35*, 3081-3082.

67 Mao, Y.-l.; Boekelheide, V. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1732-1735. For a study of the nitrogen analog see: Mao, Y.-l.; Boekelheide, V. *J. Org. Chem.* **1980**, *45*, 1547-1548.

68 Roth, W. R.; Biermann, M.; Erker, G.; Jelich, K.; Gerhartz, W.; Görner, H. *Chem. Ber.* **1980**, *113*, 586-597. Roth, W. R.; Scholz, B. P. *Chem. Ber.* **1982**, *115*, 1197-1208. Roth, W. R.; Kowalczik, U.; Maier, G.; Reisenauer, H. P.; Sustmann, R.; Müller, W. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1285-1287. and references therein.

69 Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Ohkuma, T.; Peschke, B.; Rawlins, D. B.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K.; Wessjohann, L. A. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Ed.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; pp 326-339.

70 Srinivasan, R.; Sonntag, F. I. *J. Am. Chem. Soc.* **1965**, *87*, 3778-3779.

71 DeBoer, C. D.; Turro, N. J.; Hammond, G. S. *Org. Synth.* **1973**, *C. V. 5*, 528-532.

72 Masamune, S.; Seidner, R. T.; Zenda, H.; Wiesel, M.; Nakatsuka, N.; Bigam, G. *J. Am. Chem. Soc.* **1968**, *90*, 5286-5288.

73 Srikrishna, A.; Sunderbabu, G. *J. Org. Chem.* **1987**, *52*, 5037-5039.

74 Shigemori, H.; Bae, M.-A.; Yazawa, K.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 4317-4320.

75 Sartori, G.; Turba, V.; Valvassori, A.; Riva, M. *Tetrahedron Lett.* **1966**, 211-218.

76 Vogel, E. *Liebigs Ann. Chem.* **1958**, *615*, 1-14.

77 Borden, W. T.; Reich, I. L.; Sharpe, L. A.; Weinberg, R. B.; Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2438-2442.

78 Hertel, R.; Mattay, J.; Runsink, J. *J. Am. Chem. Soc.* **1991**, *113*, 657-665.

79 Wender, P. A.; Correia, C. R. D. *J. Am. Chem. Soc.* **1987**, *109*, 2523-2525.

80 Carothers, W. H.; Williams, I.; Collins, A. M.; Kirby, J. E. *J. Am. Chem. Soc.* **1931**, *53*, 4203-4225.

81 Cope, A. C.; Schmitz, W. R. *J. Am. Chem. Soc.* **1950**, *72*, 3056-3062.

82 For a recent study and lead reference see: Klärner, F.-G.; Krawczyk, B.; Ruster, V.; Deiters, U. K. *J. Am. Chem. Soc.* **1994**, *116*, 7646-7657.

83 Walling, C.; Peisach, J. *J. Am. Chem. Soc.* **1958**, *80*, 5819-5824. Binder, J. L.; Eberly, K. C.; Smith, G. E. P., Jr. *J. Polymer Sci.* **1959**, *38*, 229-239.

84 Stadlwieser, J.; Kienzle, F.; Arnold, W.; Gubernator, K.; Schönholzer, P. *Helv. Chim. Acta* **1993**, *76*, 178-186.

85 Reviews: **a)** Heimbach, P.; Jolly, P. W.; Wilke, G. *Adv. Organomet. Chem.* **1970**, *8*, 29-86. **b)** Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, 1975; Vol. 2. **c)** Keim, W.; Behr, A.; Röper, M. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Ed.; Pergamon: New York, 1982; Vol. 8; pp 371-462. **d)** Jolly, P. W. *Ibid.* pp 671-711.

86 Brenner, W.; Heimbach, P.; Hey, H.; Müller, E. W.; Wilke, G. *Liebigs Ann. Chem.* **1969**, *727*, 161-182.

87 Tolstikov, G. A.; Dzhemilev, U. M.; Ivanov, G. E. *Zh. Org. Khim.* **1975**, *11*, 984-989. See also reference 85a-c.

88 Tenaglia, A.; Brun, P.; Waegell, B. *J. Organomet. Chem.* **1985**, *285*, 343-357.

89 Baldenius, K.-U.; tom Dieck, H.; König, W. A.; Icheln, D.; Runge, T. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 305-307.

90 Carbonaro, A.; Cambisi, F.; Dall'Asta, G. *J. Org. Chem.* **1971**, *36*, 1443-1445.

91 Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863-6879.

92 Reviews: Noyori, R.; Hayakawa, Y. *Org. React. (N.Y.)* **1983**, *29*, 163-344. Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1-19. Mann, J. *Tetrahedron* **1986**, *42*, 4611-4659. Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon: New York, 1991; Vol. 5; pp 593-615.

93 Barltrop, J. A.; Day, A. C.; Samuel, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 7521-7528.

94 Crandall, J. K.; Haseltine, R. P. *J. Am. Chem. Soc.* **1968**, *90*, 6251-6253.

95 Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976-979. Ernst, B.; Ganter, C. *Helv. Chim. Acta* **1978**, *61*, 1775-1777. Föhlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951-1960.

96 Siemionko, R. K.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 3870-3882.

97 Hafner, K.; Goliasch, K. *Chem. Ber.* **1961**, *94*, 2909-2921.

98 Klinsmann, U.; Gauthier, J.; Schaffner, K.; Pasternak, M.; Fuchs, B. *Helv. Chim. Acta* **1972**, *55*, 2643-2659.

99 Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670-7672.

100 White, E. H.; Anhalt, J. P. *Tetrahedron Lett.* **1965**, 3937-3945. DeBoer, C. D.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 803-804.

101 Sohn, M.; Blum, J.; Halpern, J. *J. Am. Chem. Soc.* **1979**, *101*, 2694-2698.

102 Fray, G. I.; Saxton, R. G. *The Chemistry of Cyclo-octatetraene and its Derivatives*; Cambridge University: New York, 1978.

103 Vogel, E.; Roos, O.; Disch, K.-H. *Liebigs Ann. Chem.* **1962**, *653*, 55-66.

104 Fujiwara, T.; Ohsaka, T.; Inoue, T.; Takeda, T. *Tetrahedron Lett.* **1988**, *29*, 6283-6286.

105 Martin, H.-D.; Heller, C.; Mayer, B.; Beckhaus, H.-D. *Chem. Ber.* **1980**, *113*, 2589-2600.

106 Kagan, J.; Chen, S.-Y.; Agdeppa, D. A., Jr.; Watson, W. H.; Zabel, V. *Tetrahedron Lett.* **1977**, 4469-4470. See also: Harmata, M.; Murray, T. *J. Org. Chem.* **1989**, *54*, 3761-3763.

107 Matthews, R. S.; Whitesell, J. K. *J. Org. Chem.* **1975**, *40*, 3312-3313.

108 Mehta, G.; Rao, K. S. *J. Org. Chem.* **1988**, *53*, 425-427.

109 Kahn, M.; Nakanishi, H.; Su, T.; Lee, J. Y.-H.; Johnson, M. E. *Int. J. Peptide Protein Res.* **1991**, *38*, 324-334.

110 West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795-6803. See also reference 44.

111 Harmata, M.; Elahmad, S.; Barnes, C. L. *J. Org. Chem.* **1994**, *59*, 1241-1242. For a related study see: Harmata, M.; Elahmad, S. *Tetrahedron Lett.* **1993**, *34*, 789-792.

112 Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80-87.

113 Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597-3599.

114 Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904-5906.

115 Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678-4679. Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221-2224. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089-1094. For molecular modeling studies of this reaction see: Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451-2454. Gugelchuk, M. M.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 330-339.

116 Sieburth, S. McN.; Ravindran, K. *Tetrahedron Lett.* **1994**, *35*, 3861-3864.

117 Sieburth, S. McN. *J. Chem. Soc., Chem. Commun.* **1994**, 1663-1664.

118 Frimer, A. A. *Synthesis* **1977**, 578-579.

119 Jainhao Chen, Research Notes, SUNY Stony Brook.

120 Jian-long Chen, Research Notes, SUNY Stony Brook.

121 Wang, Z.; Warder, S. E.; Perrier, H.; Grimm, E. L.; Bernstein, M. A.; Ball, R. G. *J. Org. Chem.* **1993**, *58*, 2931-2932.

122 Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878-5879. See also reference 69.

123 Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J.; de Gala, S. *Tetrahedron Lett.* **1993**, *34*, 7253-7256. Young, W. B.; Masters, J. J.; Danishefsky, S. *J. Am. Chem. Soc.* **1995**, *117*, 5228-5234. For completion of the synthesis see: Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723-1726.

124 For a recent discussion see: Wender, P. A.; Marquess, D. G.; McGrane, P. L.; Taylor, R. E. *Chemtracts-Org. Chem.* **1994**, *7*, 160-171.

125 Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature (London)* **1994**, *367*, 630-634. Nicolaou, K. C.; Guy, R. K. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Ed.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; pp 302-312. Nicolaou, K. C.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2079-2090. see also reference 123.

126 Examples: **a)** Dowbenko, R. *Tetrahedron* **1964**, *20*, 1843-1858. **b)** Friedman, L. *J. Am. Chem. Soc.* **1964**, *86*, 1885-1886. **c)** Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201-205. **d)** Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708-1709. **e)** Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051-6059.

(*Received* 3 *July* 1995)