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Synthetic Applications of Intramolecular Enone–Olefin Photocycloadditions

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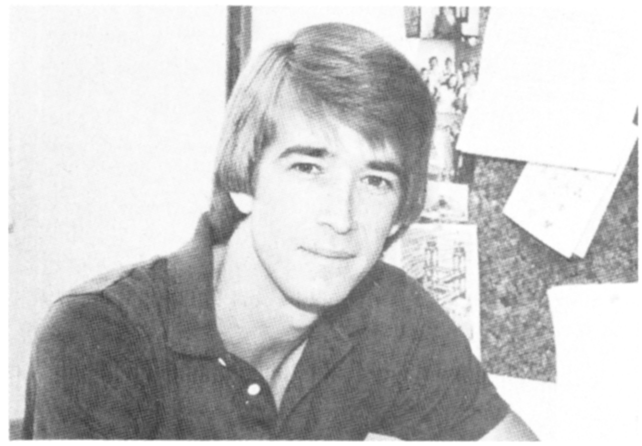
I. Introduction

The intramolecular enone–olefin photocycloaddition, the light-induced [2+2] cycloaddition of a ground-state olefin tethered to an excited-state enone to form a cyclobutane, was first reported by Ciamician in 1908 when he observed the formation of carvone camphor on prolonged exposure of carvone to "Italian sunlight"[1] (Figure 1).

Buchi's reinvestigation of this process confirmed the isomerization and sparked new interest in the reaction.[2] The rapidity with which complex systems could be constructed by this method was recognized by Cookson[3] who irradiated the Diels–Alder adduct of quinone and cyclopentadiene and by Eaton[4] who utilized a similar intramolecular photocycloaddition in his synthesis of cubane. This reaction was first applied to the total synthesis of a natural product by Wiesner who prepared 12-epilycopodine utilizing an intramolecular photocycloaddition[5] (Figure 2).

Corey,[6] Eaton,[7] and de Mayo,[8,9] among others, subsequently began to investigate the *inter*molecular enone–olefin photocycloaddition, and these studies culminated in several successful synthetic applications, including the synthesis of caryophyllene[10] and bourbonene,[11] as well as a proposed mechanistic rationale for the reaction. While the major disadvantage of the *inter*molecular photocycloaddition is its low regioselectivity in some systems, this problem can be substantially overcome by incorporating the olefin and the enone in the same molecule. Although many of the early examples of the reaction *were intra*molecular, this variation saw only limited use until the late 1970s when its potential for the rapid construction of systems of seemingly intractable complexity was recognized by Oppolzer, Pattenden, and others.



Michael T. Crimmins, currently Associate Professor of Chemistry at the University of North Carolina at Chapel Hill, received his undergraduate degree at Hendrix College in Conway, AK, in 1976 and his Ph.D. from Duke University in 1980 under the direction of Steven W. Baldwin. After postdoctoral studies as an NIH Postdoctoral Fellow at the California Institute of Technology working with Professor David A. Evans, he joined the faculty at the University of North Carolina in 1981. He is currently a Fellow of the Alfred P. Sloan Foundation. Professor Crimmins' research interests are in the areas of synthetic methodology and total synthesis of natural products.

II. Mechanism

While there is still much that is not well understood about the photocycloaddition process, several points concerning the proposed mechanistic scheme[6,8–10] (Figure 3) are worthy of note and serve as a basis for the discussion that follows.

The initial excitation of the enone is probably $n \rightarrow \pi^*$ followed by intersystem crossing to either an $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ triplet state T_1.[12] Schuster has recently presented evidence indicating that a twisted $\pi \rightarrow \pi^*$ triplet is the reactive species in the photocycloaddition of at least some cyclohexenones and may be responsible for the formation of trans 6,4 systems in some instances.[13] If the singlet S_1 can undergo rotation, energy-wasting cis–trans isomerization competes with intersystem crossing and subsequent photocycloaddition.[14] This occurs in acyclic systems that are not held rigidly by hydrogen bonding and in cyclic systems where the enone is in a ring larger than six members. Intersystem crossing is sufficiently rapid in cyclopentenones and cyclohexenones and when the double bond of the enone is held in a five-membered ring to give reasonable quantum efficiencies for photoaddition.[15] An exception to the general rule that medium-

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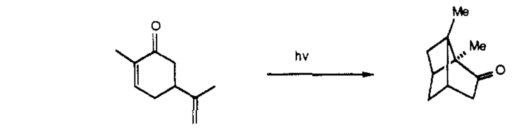

Figure 1.

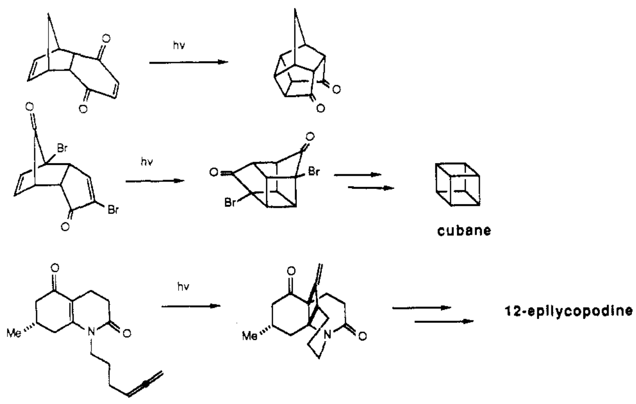

Figure 2.

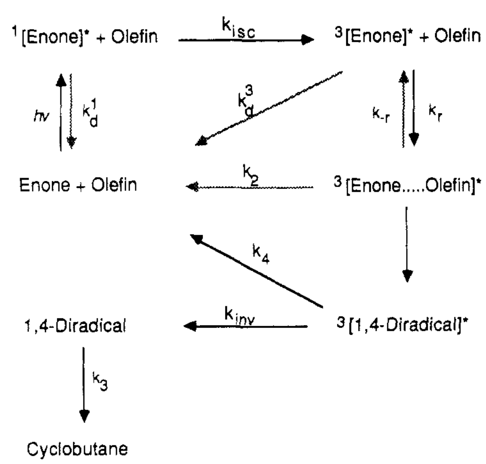

Figure 3.

ring enones do not undergo photocycloaddition was recently reported by Pirrung who has carried out intramolecular photocycloadditions on cyclooctenones with oxygen substituents at the enone β-carbon[16] (Figure 4).

The next step is the complexation of the triplet state T_1 with the olefin to form an exciplex. Although it has not been directly observed, this complex has been invoked to explain the regioselectivity of some intermolecular photocycloadditions and to rationalize the observation that the rates for photocycloaddition are much higher than those of normal radical additions to olefins.[8,9] The collapse of the exciplex to a 1,4-diradical may proceed through initial bond formation at either C_α or C_β of the enone (or both in some cases). Formation of products derived from intramolecular hydrogen atom abstraction lends credence to both the diradical nature of the reaction as well as initial bond formation at both C_α and C_β. Additionally, the integrity of the olefin geometry is lost during the cycloaddition; cis and trans olefins give mixtures of all possible stereoisomers.[6] Cleavage of the diradical to the enone and olefin may be competitive with ring closure to the cyclobutane as evidenced by recovery of isomerized starting olefin,[17] but Becker has provided experimental evidence to indicate that there is no radical reversion

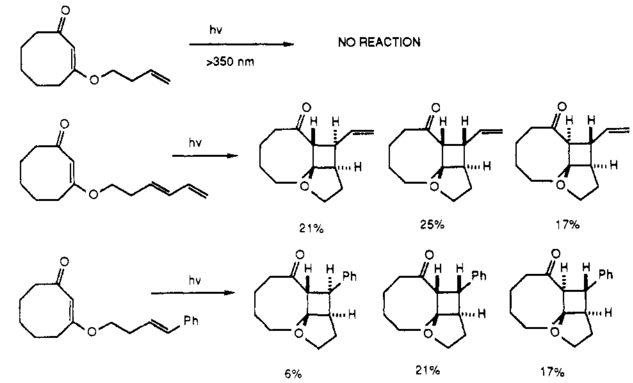

Figure 4.

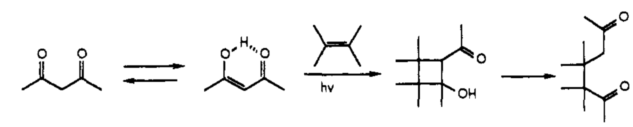

Figure 5.

in some systems.[18] Lastly, spin inversion of the triplet diradical to the singlet diradical is followed by ring closure to form the cyclobutane.

The regioselectivity of the intramolecular photocycloaddition is generally quite high in systems where the two double bonds are connected by two, three, or four atoms. The general trend is for favored formation of five-membered rings, if possible, in the initial radical addition of the excited state to the olefin and for the formation of six-membered rings if a five-membered ring cannot be formed. This observation was termed the "Rule of Fives" by Hammond and Srinivasan[19] and is similar to the observation by Beckwith[20] that 5-hexenyl radical undergoes cyclization to the cyclopentylmethyl radical 75 times faster than to the cyclohexyl radical. While it is tempting to utilize the analogy of the Rule of fives with the 5-hexenyl radical cyclization, it should be noted that the kinetic versus thermodynamic basis for this result has not been established in most cases.

III. Intramolecular de Mayo Reactions

A. Enol Esters of β-Diketones

An early, ingenious application of the *inter*molecular enone–olefin photocycloaddition was developed by de Mayo who irradiated β-diketones in the presence of olefins to produce 1,5-diketones.[21] The reaction proceeds through the enol of the 1,3-diketone, which is held rigidly in a six-membered ring by an intramolecular hydrogen bond. Photoaddition of an olefin to this enol results in a β-hydroxy ketone that generally undergoes spontaneous retroaldolization to give the 1,5-diketone (Figure 5).

One of the most widely utilized and synthetically useful applications of the *intra*molecular photocycloaddition reaction has been in the addition of olefins to enol esters and enol ethers of β-diketones, also known as the intramolecular de Mayo reaction. In the earliest reported example of this variation of the reaction, Oppolzer irradiated the enol carbonate 1 through Pyrex and obtained cyclobutane 2 in 92% yield.[22] The exclusive formation of the "crossed" adduct is typical of systems with two atoms separating the two double

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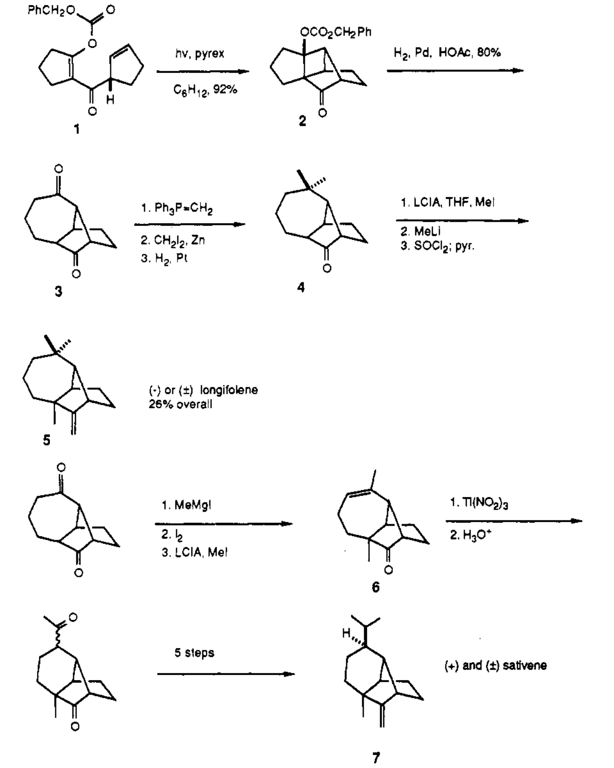

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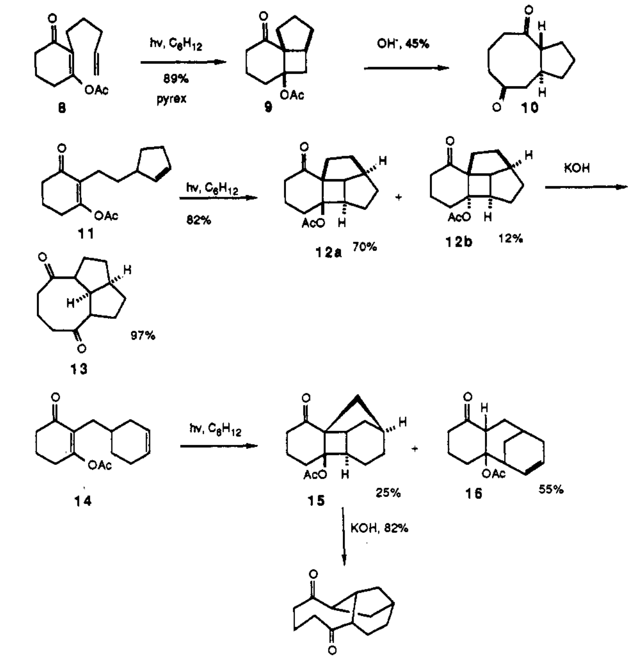
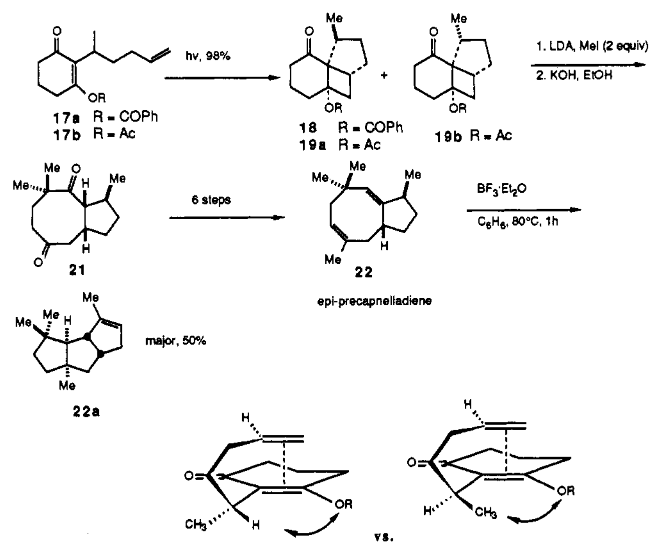


SCHEME 3

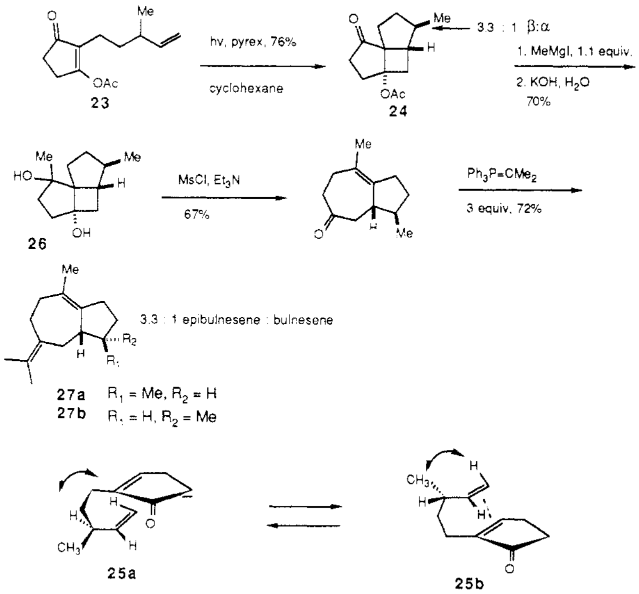


bonds and exemplifies the Rule of Fives. Hydrogenolysis of the benzyl carbonate in acetic acid also resulted in retroaldolization to give the diketone **3** in 80% yield. Selective olefination of the cycloheptanone followed by introduction of the *gem*-dimethyl gave **4**, which was readily converted to longifolene (**5**) in three steps. Diketone **3** has also been elaborated to the tricyclic sesquiterpene sativene (**7**) by a thallium-mediated ring contraction of cycloheptene **6**. These syntheses have been carried out on both racemic and optically active material (Scheme 1).

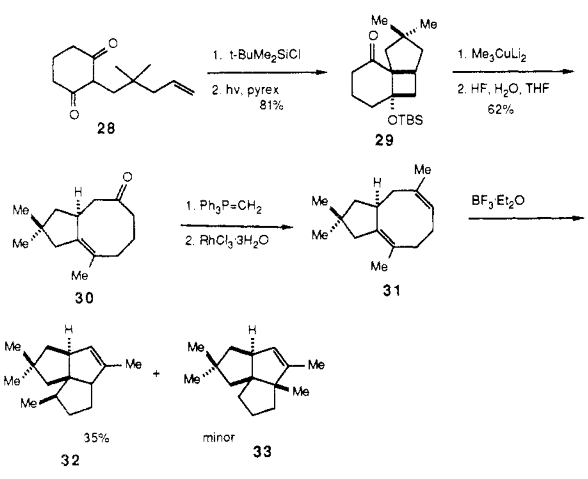
Both Oppolzer[23] and Pattenden[24] have studied the photoaddition of enol acetate **8**, which produces the "straight" adduct **9** in high yield. This regiochemistry results due to the general preference for the formation of five-membered rings when possible. Tricyclic system **9** can be fragmented by treatment with base to produce the diketone **10** in good yield. Oppolzer[23] has also shown that the cyclopentenyl derivative **11** gives the same regiochemistry, although 12% of the trans cyclobutane is produced. Fragmentation destroys the mixed stereogenic center and gives a single diketone **13** in excellent yield. In contrast to **11**, irradiation of the cyclohexenyl system **14** produced only 25% of the cycloadduct **15**, while the major product **16** was the result of hydrogen atom abstraction in the 1,4-diradical. There is obviously considerable geometric strain in the transition state for the initial cyclization, which would generate **15** resulting in the generation of **16** by the alternate initial cyclization (Scheme 2).

Pattenden[25] has utilized this approach to 5,8 systems in a synthesis of epiprecapnelladiene and $\Delta^{8,9}$-capnellene from the enol benzoate **17a**. Photocycloaddition of **17a** gave 98% of a single diastereomer **18**. When the corresponding enol acetate **17b** is irradiated, a 92:8 mixture of **19a** to **19b** is obtained. This excellent level of stereoselectivity can be rationalized as a kinetic preference for formation of the exciplex **20a** due to nonbonded interactions between the secondary methyl and the benzoate (or acetate) in the alternative transition-state model **20b**. The smaller acetate has a less pronounced steric interaction with the methyl than the benzoate. Alternatively, cleavage of the 1,4-diradical derived from **20b** may be more rapid than from **20a** due to these nonbonded interactions during the final cyclobutane closure. Thus, the stereoselectivity may be attributable to radical reversion of the minor isomer. This question could be resolved if it were known whether these systems undergo radical cleavage. As noted above, Becker has observed cases where radical reversion is not operative, but there is also evidence for radical cleavage in some systems. Dialkylation of ketone **18** followed by base-induced fragmentation generated diketone **21**, which could be converted to epiprecapnelladiene **22** in six steps. Conversion of epiprecapnelladiene to $\Delta^{8,9}$-capnellene (**22a**) was accomplished with $BF_3{\cdot}Et_2O$ in benzene[26] (Scheme 3).

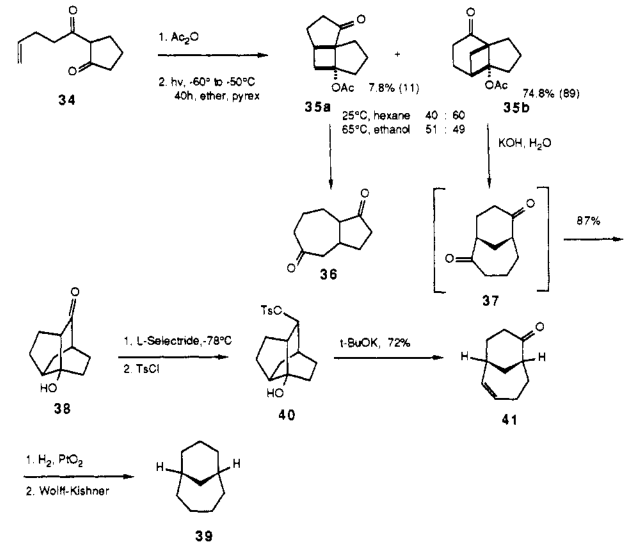
SCHEME 4



SCHEME 5



SCHEME 6



The stereoselective photocycloaddition of enol acetate **23** to cyclobutane **24** (Pyrex, 76%) in the synthesis of bulnesene and epibulnesene produced a 3.3:1 mixture of the β to α isomers.[27] The lower stereoselectivity in this case is a result of the secondary methyl interacting with the smaller hydrogen in **25b** (relative to the benzoate or acetate in **20b**). A thermodynamic preference for the formation of **24**β via a radical fragmentation pathway cannot be excluded. Conversion of **24** to tertiary alcohol **26** followed by fragmentation and Wittig olefination gave a 3.3:1 mixture of epibulnesene (**27a**) and bulnesene (**27b**) in 34% overall yield (Scheme 4).

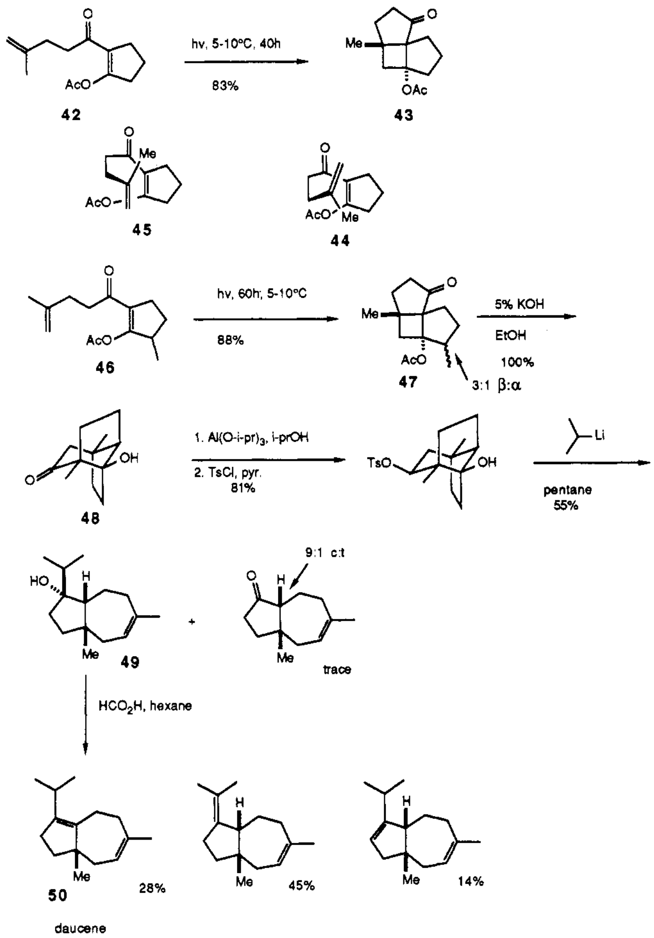
In a synthesis of pentalenene by Pattenden, β-diketone **28** was converted to its silylenol ether and irradiated through Pyrex to produce **29** in 81% yield.[28] Treatment of the ketone with Me_3CuLi_2 and subsequent fragmentation with HF produced the cyclooctenone **30**, which gave cyclooctadiene **31** after olefination and isomerization of the double bond. Pentalenene (**32**), along with the minor component **33**, was then generated by exposure of **31** to $BF_3{\cdot}Et_2O$ (Scheme 5).

Seto[29] and Pattenden[30] have studied the photoaddition of the enol acetate of **34**. Pattenden reported a regiochemical ratio of 2:3 (93% yield) for the products **35a** and **35b** when the reaction was carried out at 25 °C in hexane. Seto found that the regiochemical outcome was temperature dependent and that the ratio of **35a** to **35b** ranged from 11:89 at −70 °C in ether to 51:49 at 65 °C in ethanol. It is noteworthy that the acetylation of **34** is not regiospecific but the two enol acetates interconvert via a photo-Fries process. Only the enol acetate leading to **35a,b** participates in the photocycloaddition. Base hydrolysis of **35a** and **35b** gave the diketone **36** and the aldol **38** (via diketone **37**), respectively. Further elaboration of aldol **38** to bicyclo[4.3.1]decane (**39**) was achieved by reduction of the ketone followed by Grob fragmentation of the secondary tosylate **40** and sequential reduction of the enone **41** to hydrocarbon **39** (Scheme 6).

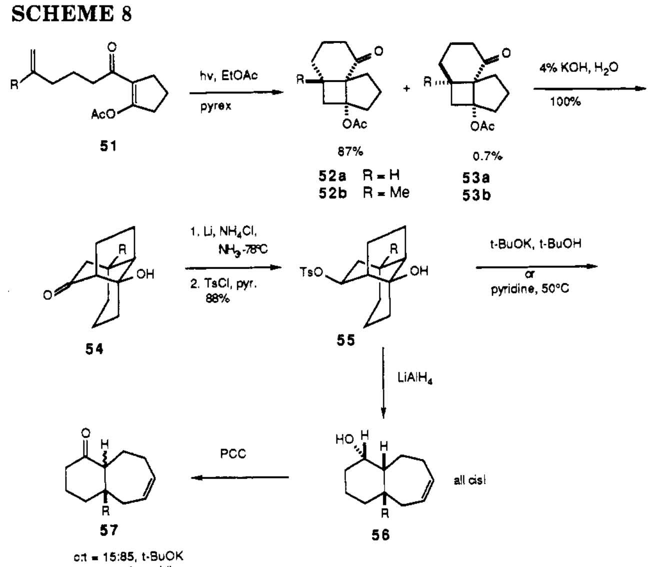
Interestingly, enone **42**, the methyl-substituted variant of **34**, undergoes photocycloaddition to give exclusively the straight adduct **43**.[31] This has been rationalized as a steric interaction between the methyl group and the cyclopentane methylenes in the exciplex **44**, which would be much reduced in **45**. This regiochemical reversal when a methyl is introduced at this position has been noted in other systems by Wolf and Agosta (see section VI). Enol acetate **46** has been irradiated to produce a 3:1 mixture of methyl epimers of the exclusive straight adduct **47**. In this case production of the alternative regioisomer would require that a serious interaction between the vinyl methyl and the secondary methyl be overcome. Fragmentation and subsequent spontaneous retroaldolization–realdolization produced **48**, which was converted to the 5,7 system **49**, a daucene (**50**) precursor (Scheme 7).

The 1,7-diene **51** underwent highly regioselective cycloaddition to **52** whether R was H or Me, although a small amount of the trans 6,4 adduct **53** was detected.[32] Both substrates gave the straight adduct exclusively, the general tendency for 1,7-dienes, since a six-membered ring is formed in preference to a seven-membered ring. Treatment of **52** with aqueous KOH gave the tricyclic aldol **54**, the result of retroaldolization followed by an intramolecular aldol. Fragmentation of **55** with lithium aluminum hydride gave the all-cis 6,7 alcohol **56**, which could be oxidized to cis ketone **57** (Scheme 8).

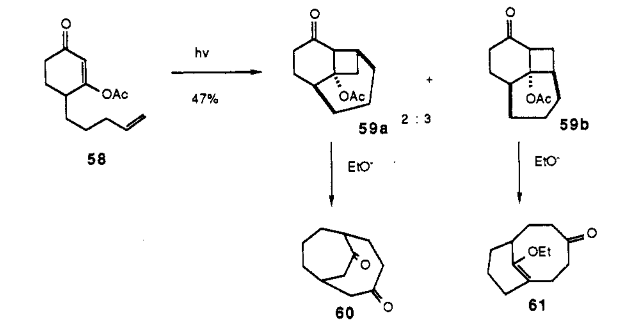
SCHEME 7



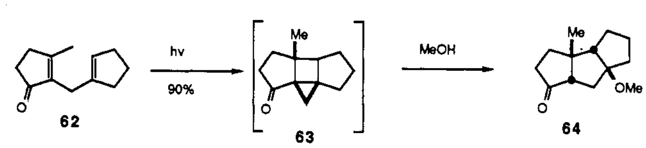
SCHEME 8



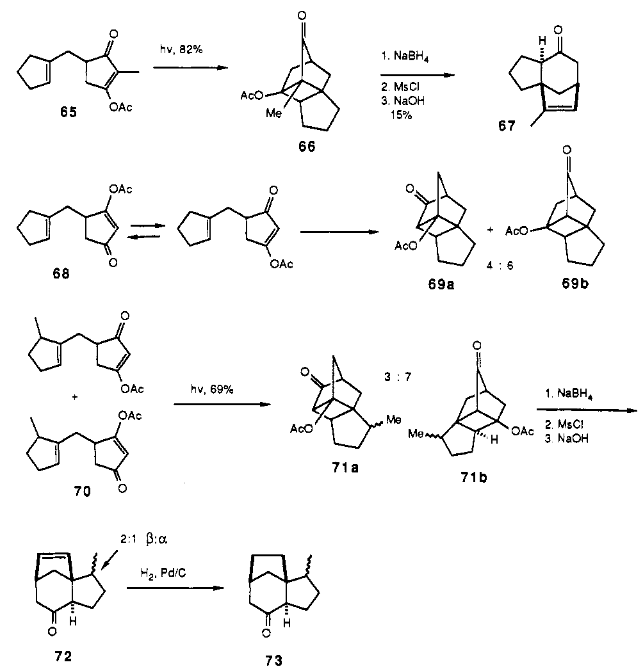
SCHEME 9



SCHEME 10



SCHEME 11

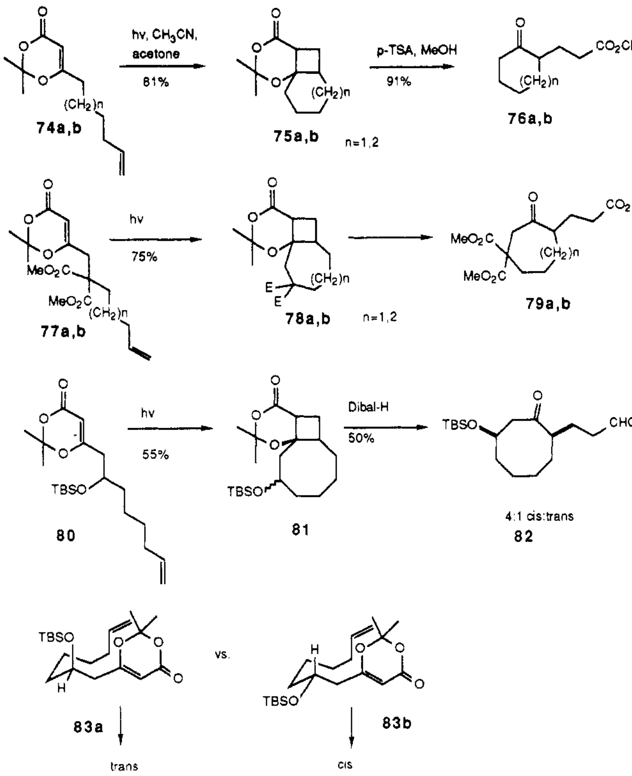


An unusually nonselective regiochemical result was obtained when 1,7-diene **58** was irradiated: A 2:3 mixture of **59a** to **59b** was obtained.[24,30] These were fragmented to the bicyclic systems **60** and **61**, respectively (Scheme 9).

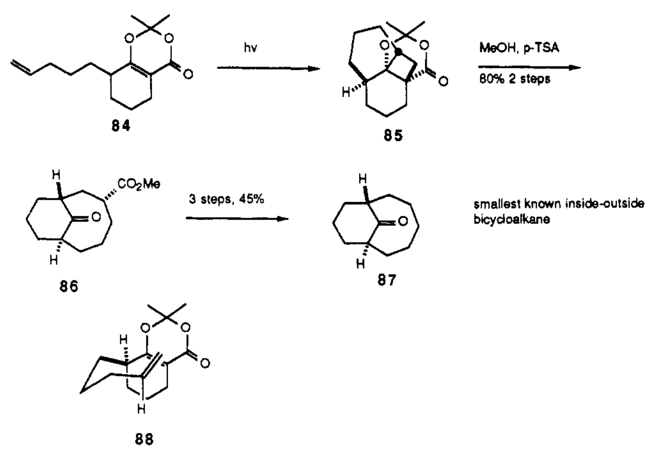
In an unusual approach, Pattenden prepared the cis-syn-cis linear triquinane **64** via irradiation of the 1,4-diene **62** in methanol.[33] It would appear in this system that initial radical cyclization occurs at the enone β-carbon, forming a five-membered ring containing radical centers at carbons 1 and 4. The intermediate **63** then results from collapse of the diradical to form a cyclopropane. The product then presumably arises from the attack of solvent on the intermediate cyclopropane **63** (Scheme 10).

When enol acetate **65** was irradiated in hexane through Pyrex, an 82% yield of a single diastereomer **66** was obtained.[34,35] This ketone could be reduced and fragmented to the tricyclic ketone **67**. Alternatively, the corresponding system without the methyl group gave a 40:60 ratio of the two possible diastereomers **69a** and **69b**, both of which arise in accordance with the Rule of Fives, indicating that any selectivity in these systems is likely controlled by electronic factors. Enol acetates **70** produced (69% yield) a mixture of both diastereomers and regioisomers upon photocycloaddition. The major regioisomer **71b**, a 2:1 mixture of methyl epimers, was reduced and cleaved to the tricyclic ketones **72**, which upon hydrogenation produced a mixture of two methyl isomers. The minor isomer had been previously converted to zizaene by Coates and Sowerby (Scheme 11).

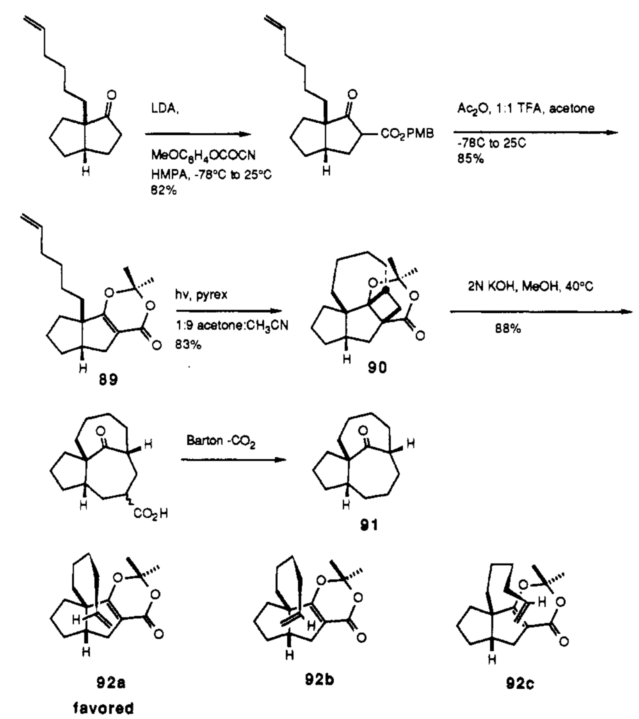
SCHEME 12



SCHEME 13



SCHEME 14



B. Dioxolenones as β-Keto Ester Equivalents

Recently, Winkler has studied the intramolecular photocycloadditions of dioxolenones (which are β-keto ester equivalents) tethered to olefins. This work has allowed rapid access to a variety of ring systems, particularly medium rings.[36] Irradiation of dioxolenones **74a**, **74b**, **77a**, and **77b** in acetone–acetonitrile through Pyrex gave exclusively the straight cycloadducts **75a**, **75b**, **78a**, and **78b**, respectively in 75–81% yields. Methanolysis of the cycloadducts also resulted in retroaldolization to produce keto esters **76a**, **76b**, **79a**, and **79b** in excellent yields. Dioxolenone **80** produced 55% of a mixture of cycloadducts **81**, which upon reductive cleavage with Dibal-H yielded a 4:1 cis to trans mixture of cyclooctanones **82**. This stereoselectivity can be rationalized due to the unfavorable steric interaction of the "axial" TBS ether with the dioxolenone ring in exciplex **83a**, which is higher in energy than **83b** with an equatorial TBS ether. A thermodynamic explanation based on cleavage of the intermediate diradical as discussed for the formation of **18** and **19** is also possible. There appears to be a significant electronic preference for the "straight" adduct in these systems. The intermolecular version, which has been extensively investigated by Baldwin, also shows remarkable regioselectivity[37] (Scheme 12).

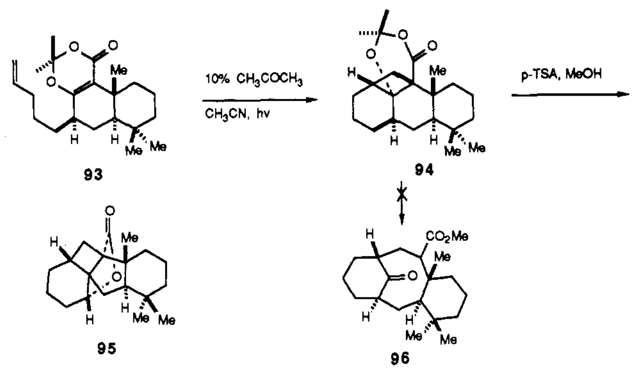
This method has been applied in a rapid synthesis of an inside–outside bicycloalkanone **87**.[38] Photoadduct **85**, the only photoproduct of the irradiation of **84**, was treated with methanol and acid to provide the keto ester **86**, which was readily decarboxylated to give the smallest known inside–outside bicycloalkanone **87**. Ketone **87** displayed 11 distinct resonances in its ^{13}C NMR spectrum, and its structure was further confirmed by X-ray analysis of the intermediate keto acid. The stereochemical result of the cycloaddition apparently arises from cyclization to the diradical via the lowest energy chair conformation **88** of the exciplex. Alternative conformations result in significant interactions between the tether and the cyclohexenyl ring (Scheme 13).

A synthesis of the carbon skeleton of the unusual natural product ingenol has also been accomplished by this approach.[39] Photocycloaddition of dioxolenone **89** (Pyrex, acetone, acetonitrile) generated a single photoadduct **90**, which after methanolysis and decarboxylation gave the ingenane skeleton **91**. This inside–outside bicyclic system results from the exciplex **92a** with the fewest transannular interactions in comparison to **92b** and **92c** (Scheme 14).

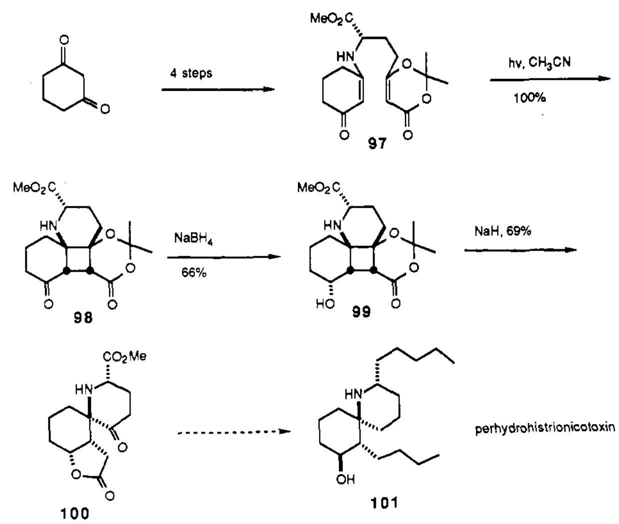
Winkler has attempted to make use of this protocol in a synthesis of the taxane skeleton **96**; however, the product **94** of the photocycloaddition of 1,7-diene **93** does not undergo the normal ring-opening sequence upon methanolysis. An unusual rearrangement to lactone **95** was observed instead of the desired product **96**[40] (Scheme 15).

The final example of this variation of the intramolecular de Mayo reaction is its application to the

SCHEME 15



SCHEME 16

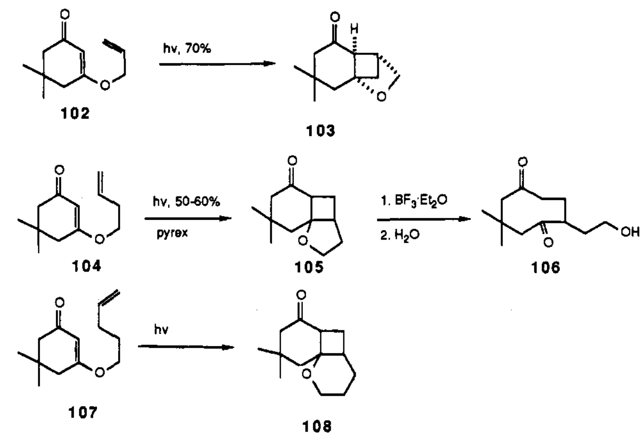


preparation of a key intermediate for the synthesis of perhydrohistrionicotoxin (**101**).[41] The vinylogous amide **97** was irradiated through Pyrex in acetonitrile to give the cis,syn,cis adduct **98** quantitatively. Reduction of the ketone produced the alcohol **99**, which was deprotonated to effect an intramolecular alcoholysis of the dioxolanone and generate lactone **100**, with appropriate functionality and stereochemistry for elaboration to perhydrohistrionicotoxin (**101**) (Scheme 16).

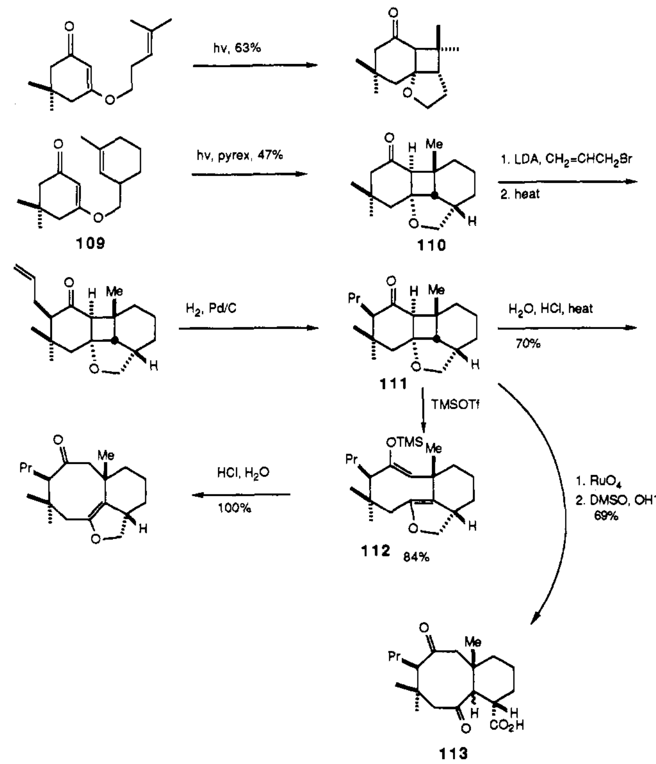
C. Vinylogous Esters and Amides as β-Diketone Equivalents

Another approach to the intramolecular de Mayo reaction has utilized vinylogous esters and amides of cyclic 1,3-diketones where the alkyl group of the amine or the alcohol contains a site of unsaturation so that the ether oxygen of the ester or the nitrogen of the amide becomes part of the tether between the two olefins. These systems can be induced to undergo retroaldol reactions if treated under the proper conditions. The earliest example of this approach was reported by Tamura who irradiated the vinylogous ester **102** and obtained a 70% yield of the crossed adduct **103**.[42] Similarly, 1,6-diene **104** gave the straight adduct **105**, which like **102** underwent cycloaddition in accord with the Rule of Fives. When the ether **105** was treated with $BF_3 \cdot Et_2O$ followed by aqueous workup, the cyclooctanedione **106** was isolated. The homologous 1,7-diene **107** also provided the straight adduct **108**[43] (Scheme 17).

SCHEME 17



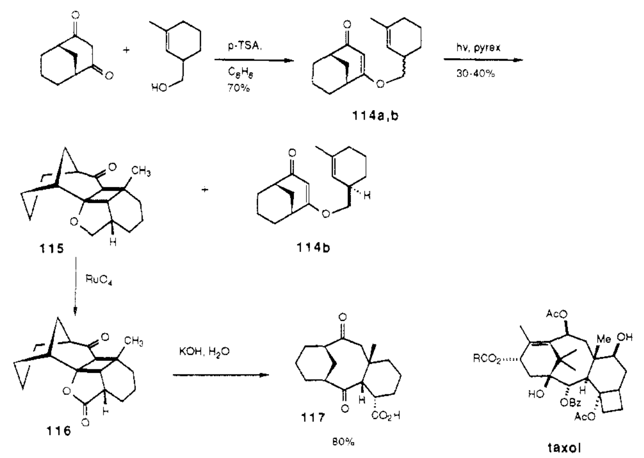
SCHEME 18



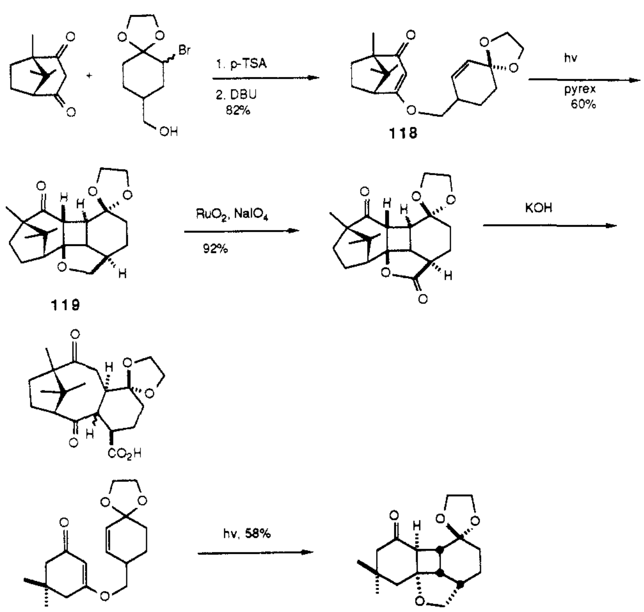
Inouye and Kakisawa,[44,45] as well as Berkowitz,[46,47] have investigated the application of this basic approach to the synthesis of the taxane skeleton. Photocycloaddition of **109** produced 47% of the single diastereomer **110**, which after conversion to **111** was cleaved with trimethylsilyl triflate to give the enol silyl ether **112**.[45] Alternatively, the tetrahydrofuran could be oxidized with RuO_4 to the lactone, which was saponified with concomitant cyclobutane cleavage to the diketone **113**. A system more analogous to the taxanes was also investigated by Inouye and Kakisawa.[48] Irradiation of the mixture of diastereomers **114a** and **114b** resulted in cycloaddition of one diastereomer to **115** and recovery of the other. The cycloadduct **115** was treated as before with RuO_4 followed by base hydrolysis to provide the diketone **117** in good yield (Schemes 18 and 19).

A similar system, **118**, studied by Berkowitz produced a different stereochemical result in photoadduct **119** due to the steric bias induced by the *gem*-dimethyl group on the bridging methylene.[46] The *gem*-dimethyl apparently forces the olefin to approach from the endo

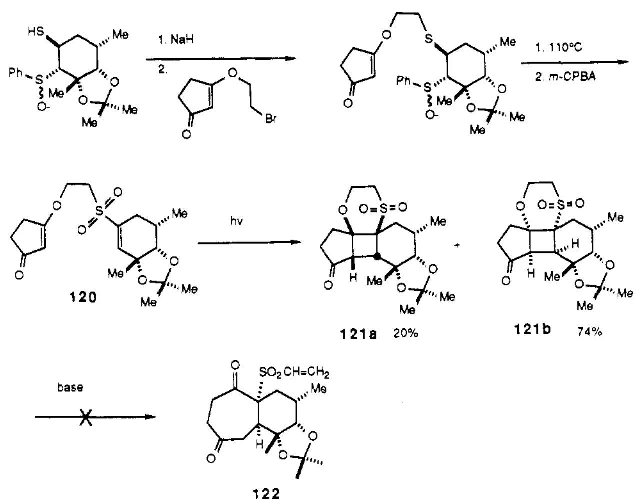
SCHEME 19



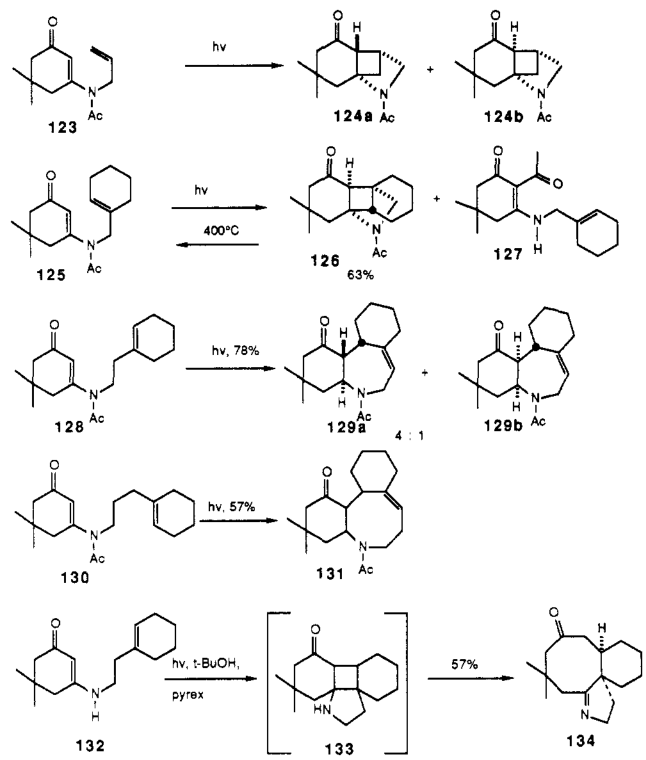
SCHEME 20



SCHEME 21



SCHEME 22



face of the bicyclic enone. The adduct **119** was oxidized and cleaved as above (Scheme 20).

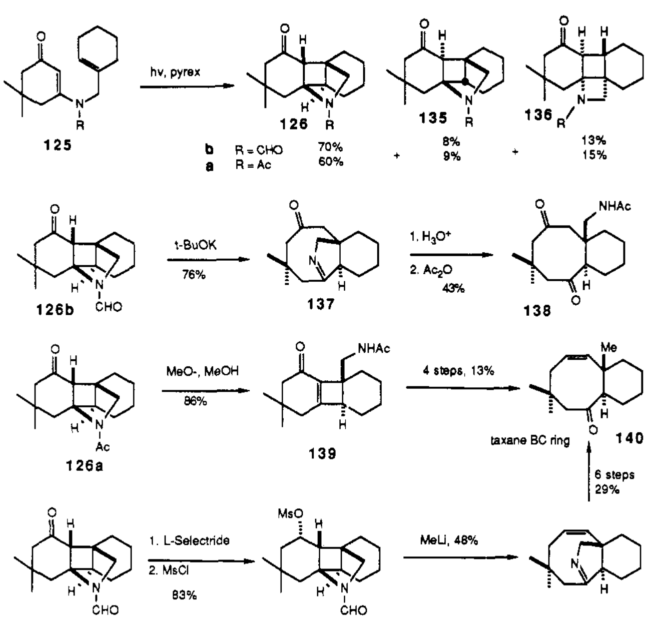
Fuchs attempted to utilize an intramolecular photocycloaddition–cyclobutane fragmentation of vinylogous ester **120** in an approach to cytochalasin C.[49] The vinyl sulfone **120** underwent cycloaddition in excellent yield, producing a 3.7:1 mixture of the two diastereomers **121b** and **121a**; however, attempted fragmentation by deprotonation of the sulfone to induce elimination of the alkoxide and subsequent retroaldolization to **122** was unsuccessful. This example does demonstrate the wide variety of functionality that can be tolerated by the photocycloaddition reaction (Scheme 21).

Tamura noted the first example of the photocycloaddition of a vinylogous amide when he carried out of the intramolecular photocycloaddition of **123** to generate the isomeric cyclobutanes **124a** and **124b**.[50] As seen in the vinylogous ester system, a tether of two atoms results in the production of the crossed adduct. Similarly, Schell irradiated the cyclohexenyl analogue **125** and obtained 63% of the cyclobutane **126** in addition to some of the product of Fries rearrangement **127**.[51] The homologue **128**, as well as the bis homologue **130**, did not yield any cyclobutane but produced the products **129** and **131**, respectively, which result from intramolecular hydrogen atom abstraction in the intermediate diradical.[52] In contrast to the imides, the NH derivative **132** produced the imine **134**, which apparently arises from the intermediate aminocyclobutane **133** by a retroaldol of the β-amino ketone[53] (Scheme 22).

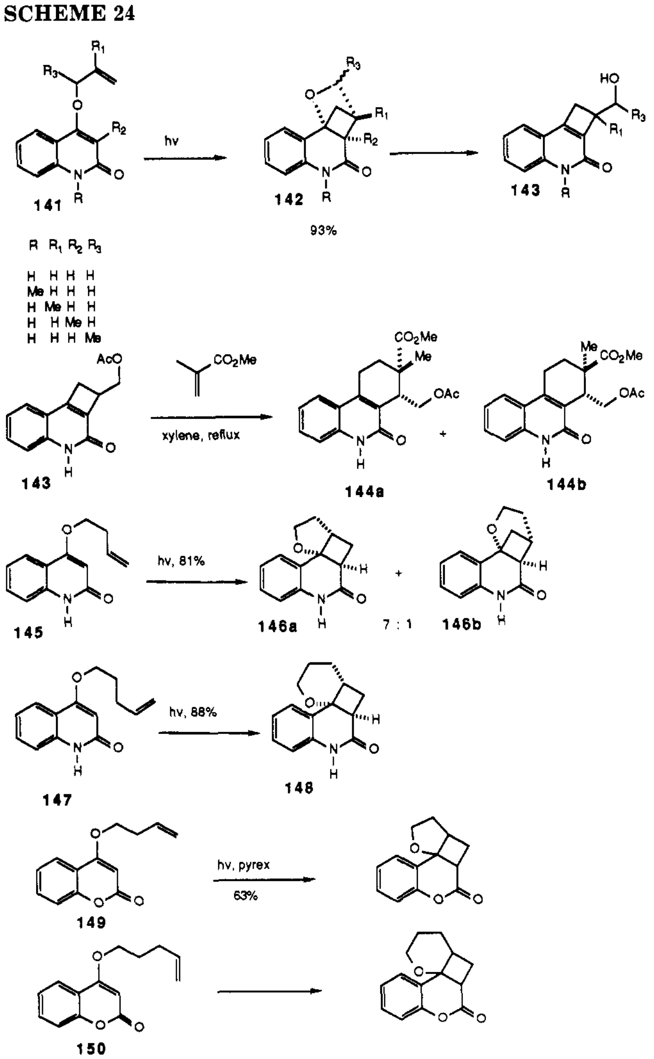
The photoaddition of vinylogous amide **125** was reinvestigated by Swindell who found that small amounts of the other cycloadducts **135** and **136** are also produced.[54] The major product **126b** of the formyl system was readily cleaved with *t*-BuOK to imine **137**, which could be hydrolyzed to the diketone **138** which is similar to the taxane ring systems noted earlier. Alternatively, the acetyl derivative **126a** could be eliminated to the enone **139** and transformed to the cyclooctane **140** in low yield (Scheme 23).

Kaneko and Sato have studied the photochemistry of 4-(ω-alkenyloxy)-2-quinolones **141** and have shown that the substitution on both the olefin and the enone have no effect on the regiochemical results of this sys-

SCHEME 23

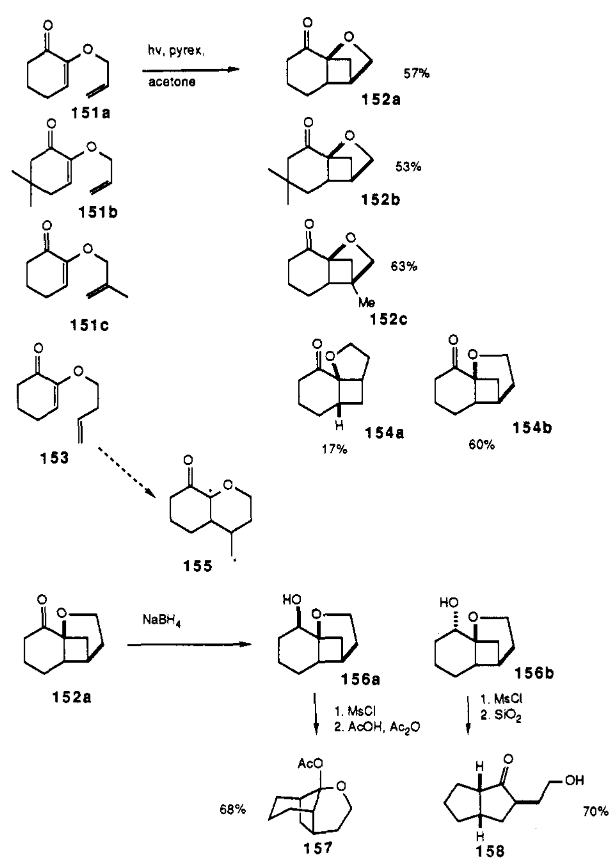


SCHEME 24



tem if two atoms separate the two olefins.[55] All the cases they studied gave the crossed adduct 142 in accord with the Rule of Fives. The cyclobutyl ethers 142 can be treated with base to generate the cyclobutenes 143, which can be heated in the presence of dienophiles such as methyl methacrylate to give Diels–Alder adducts

SCHEME 25



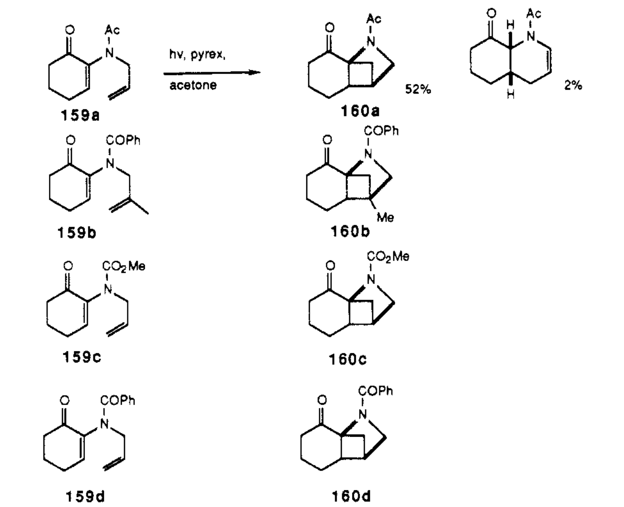
such as 144a and 144b. The three-atom tether in 145 resulted in a 7:1 mixture of the straight to crossed products 146a and 146b, while the four-atom-tethered 147 gave exclusively the parallel product 148. These photoadditions all proceed in excellent yields. The benzopyranones 149 and 150 gave similar results[56] (Scheme 24).

IV. Other Examples with Heteroatom-Containing Tethers

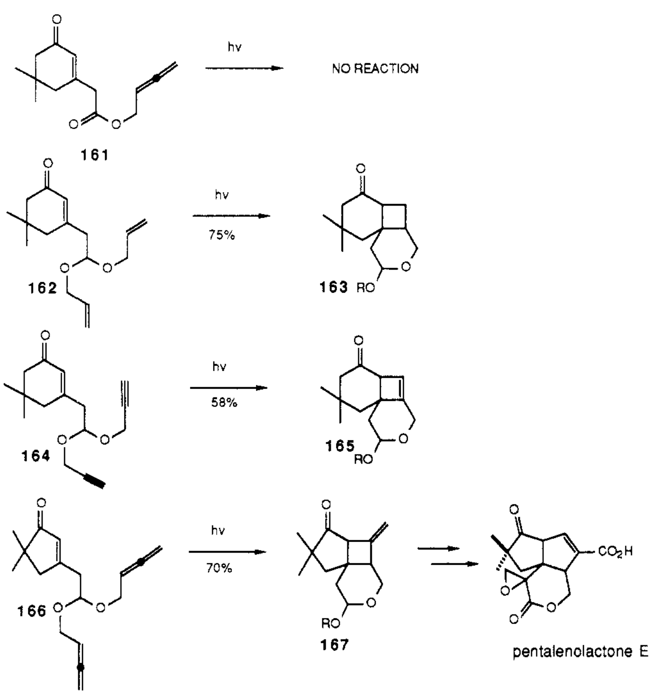
Several other examples of synthetic applications of the intramolecular photocycloaddition of enones tethered to olefins via an oxygen or nitrogen have been investigated recently. Tamura and co-workers have irradiated a series of 2-(alkenyloxy)cyclohexenones and demonstrated that they give predominantly crossed products even when the double bonds are separated by three atoms.[57] Enones 151a–c gave exclusively the crossed adduces 152a–c, respectively, in yields of 53–63%. The homologous enone 153 produced a 1:3.5 mixture of the straight to crossed cyclobutanes 154a and 154b in 77% yield. This unexpected result has been rationalized by invoking the unusually high stability of the intermediate diradical 155 whose formation presumably directs the cyclization to override the normal kinetic preference for formation of a five-membered ring. The cyclobutane 152a was reduced to a mixture of alcohols 156a and 156b, which after mesylation underwent rapid cationic rearrangement to form the acylal 157 and the keto alcohol 158, respectively (Scheme 25).

The corresponding nitrogen analogues 159a–d also gave good yields of the expected crossed cyclobutanes 160a–d[58] (Scheme 26).

SCHEME 26



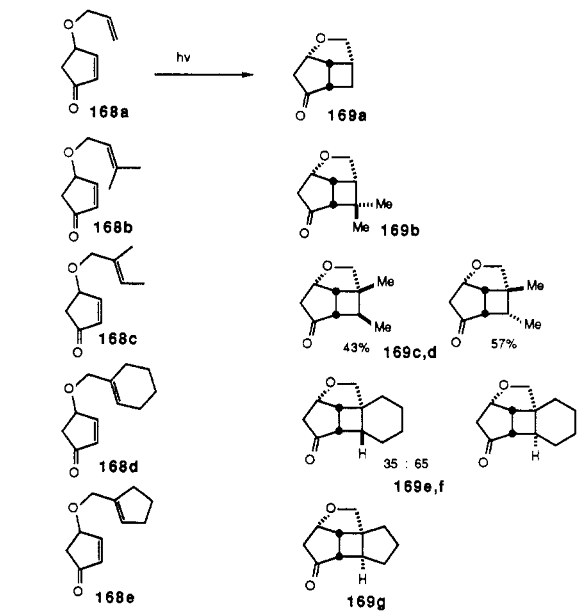
SCHEME 27



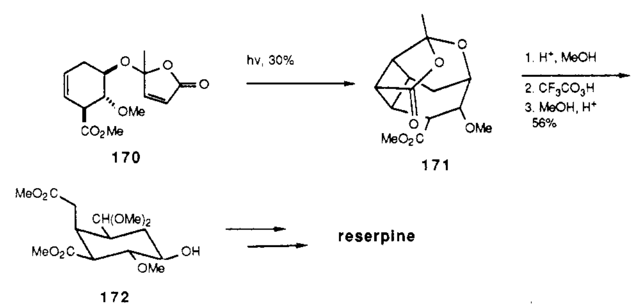
Pirrung had initially attempted to carry out the photocycloaddition of the enone ester 161 in an approach to the synthesis of pentalenolactone E, but 161 failed to cyclize presumably due to an unfavorable conformational preference of esters.[59] This same effect had been observed by Boeckman in intramolecular Diels–Alder reactions. As a clever solution to this problem, the corresponding bis(alkenyloxy)acetals were prepared and irradiated. The cycloadditions occurred readily with the olefin **162**, producing cyclobutane **163** in 75% yield. The acetylene **164** also readily cyclized to the cyclobutene **165**, a rare example of the acetylene in intramolecular photocycloadditions. Cyclopentene **166** with the bis(allenyloxy)acetal proved to be the most synthetically useful as it was converted to cyclobutane **167** in 70% yield, and the desired pentalenolactone E was available through this manifold after a series of transformations[60] (Scheme 27).

The 4-(allyloxy)cyclopentenone **168a** was shown to produce the cyclobutane **169a** by Gariboldi who photocyclized a series of 4-(allyloxy)cyclopentenones, all of

SCHEME 28



SCHEME 29



which gave the straight adducts[61] (Scheme 28).

Pearlman has utilized an intramolecular photoaddition of lactone **170** in the preparation of reserpine.[62,63] The photoadduct **171** was hydrolyzed, subjected to Baeyer–Villiger oxidation, and hydrolyzed to produce the highly substituted cyclohexane **172**. The photocycloaddition effectively adds a vicinal aldehyde–acetic acid moiety to a cyclohexene in a regio- and stereospecific manner (Scheme 29).

Another lactone, **173**, was subjected to internal photoaddition by Koga to construct an intermediate **175** for the synthesis of stoechospermol (**175**). The cycloaddition produces exclusively the cis,anti,cis products **174a** and **174b**[64] (Scheme 30).

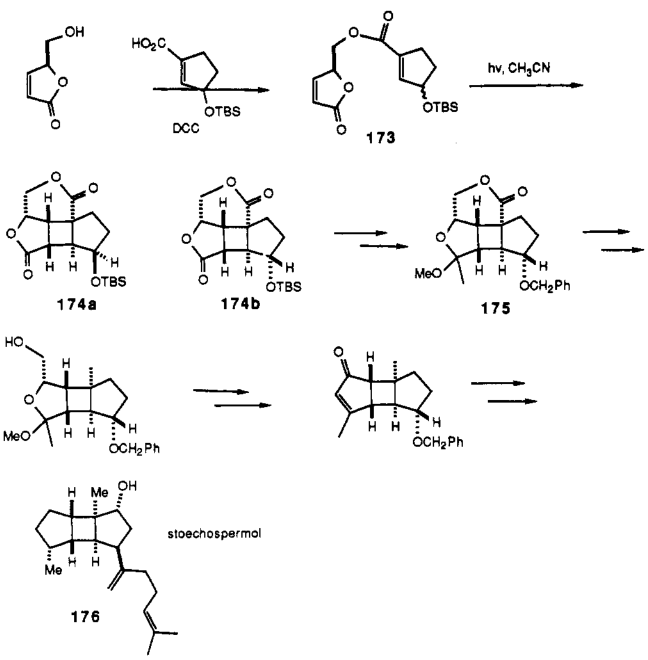
As final examples of oxygen-tethered dienes, diesters **177** and **179** were irradiated to generate the crown ethers **178** and **180** in modest yields[65] (Scheme 31).

V. Cyclic Enones Tethered to Olefins by All-Carbon Chains

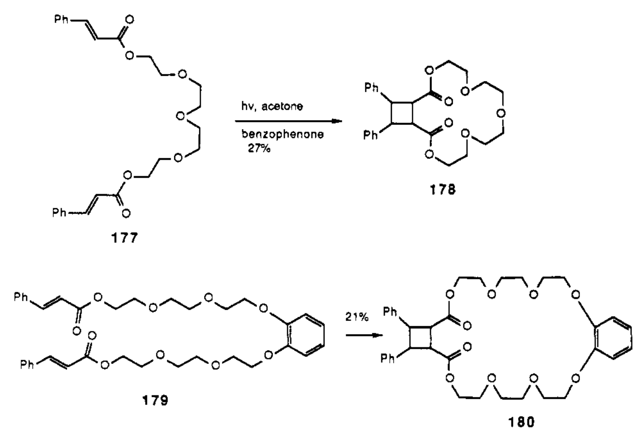
A. 2-Alkenylcyclohexenones

Enol esters of cyclic 1,3-diketones with an alkenyl chain attached at the 2-position have been widely used in the intramolecular de Mayo reaction (see section III), but simple 2-alkenylcyclohexenones have also been utilized in the intramolecular photocycloaddition reaction. Cargill subjected enone **181** to irradiation and obtained an 83% yield of the straight adduct **182**.[69] Much later Becker made a careful investigation of the

SCHEME 30



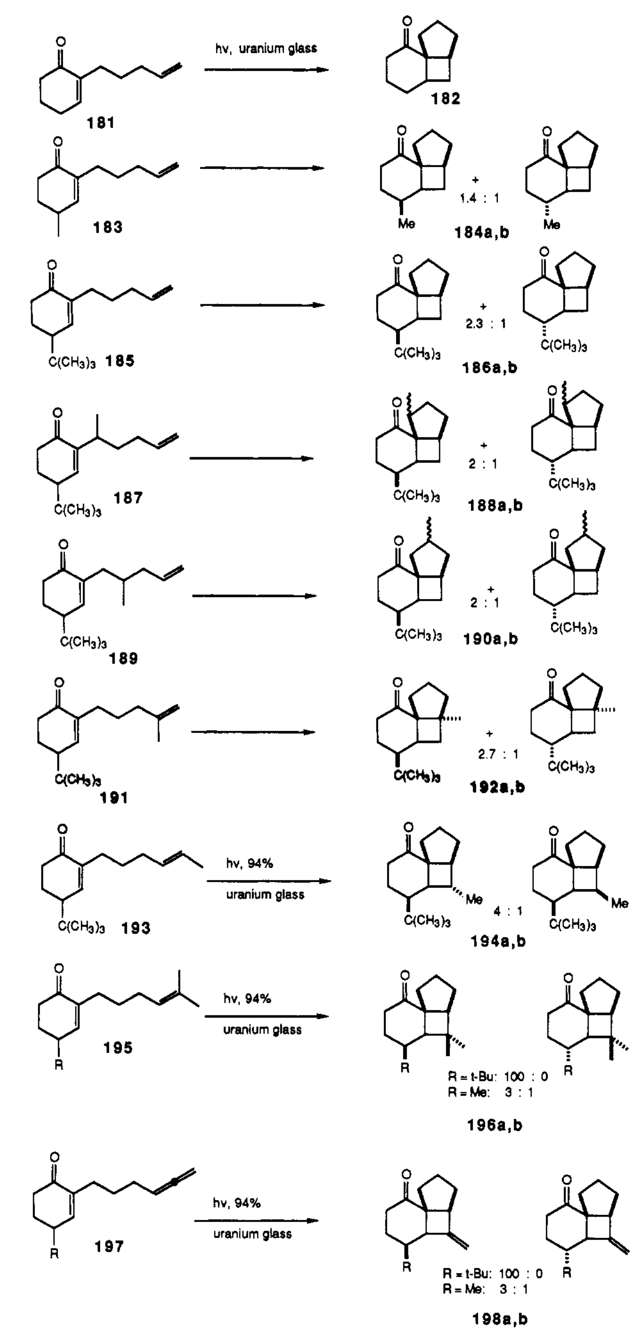
SCHEME 31



stereochemical influence of an alkyl substituent at the 4-position of these systems.[66] He found that substitution at the 4-position generally influenced the olefin to approach the enone from the face opposite the alkyl group (183 → 184a,b) and that increasing the size of the alkyl group at the 4-position resulted in a modest increase in stereoselectivity (185 ≥ 186a,b). Substitution on the tethering methylenes seemed to have little or no effect on the stereoselectivity (187 → 188a,b; 189 → 190a,b), but additional substitution on the olefinic carbons could have a significant impact on the selectivity. The selectivity increases from 2.3:1 to 2.7:1 when a methyl group is incorporated on the internal carbon of the olefin (185 vs 191), but the improvement is most notable when first one (193 → 194a,b) and then two (195 → 196a,b) methyl groups are added to the terminal carbon of the olefin. These results are not surprising since the methyl groups on the terminal olefin carbon are much closer to the 4-*tert*-butyl substituent (193 and 195) than the methyl group in 191 (Scheme 32).

These results can be rationalized by comparing the stabilities of the two stereoisomeric exciplexes (199 is of lower energy than 200) or by invoking a thermodynamically based radical reversion explanation. The diradical 201 that proceeds to the minor product should

SCHEME 32

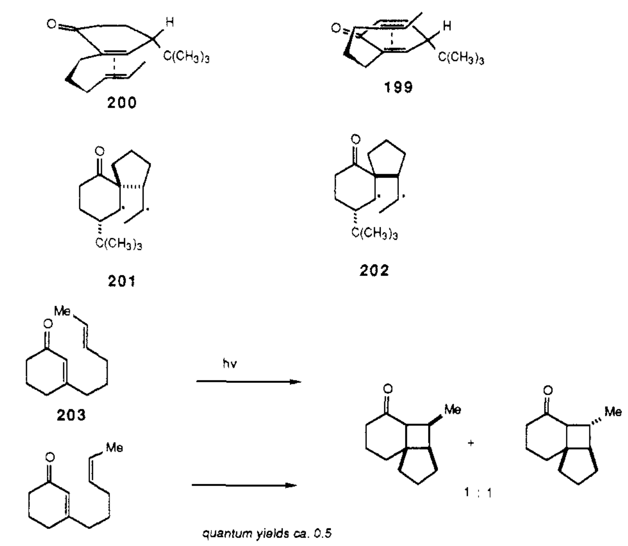


experience a more severe steric interaction during the cyclobutane closure than should 202; therefore, 201 should proceed more slowly to product and have a greater opportunity to cleave back to the starting enone. It should be noted, however, that in very closely related systems 203 and 204 Becker has presented convincing evidence that no radical reversion is operative, since the quantum yields are quite high and no olefin isomerization can be detected in unreacted starting material[18] (Scheme 33).

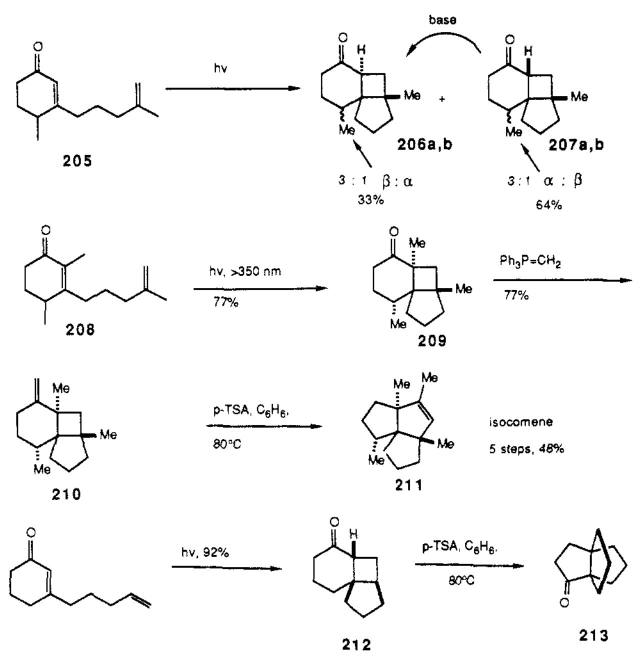
B. 3-Alkenylcyclohexenones

A similar result to Becker's study had been noted earlier by Pirrung who had irradiated the 3-alkenylcyclohexenone 205 to provide a mixture of cis- and trans-fused photoadducts 206a,b and 207a,b.[67,68] In surprising contrast, the 2-methyl analogue 208 produced a single diastereomer 209. The adduct 209 was treated

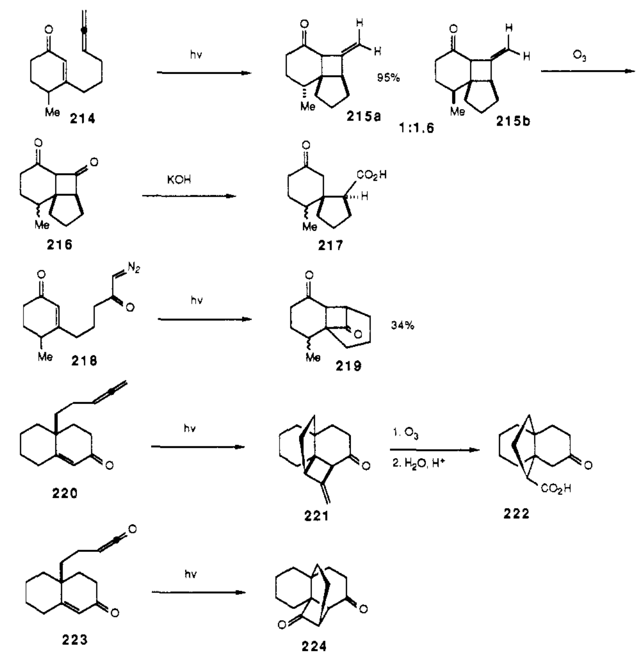
SCHEME 33



SCHEME 34



SCHEME 35



with methylenetriphenylphosphorane to give the exocyclic olefin **210**, which was rearranged to the triquinane isocomene **211** with *p*-toluenesulfonic acid. An alternative mode of migration had been previously observed by Cargill in the acid-catalyzed rearrangement of cyclobutane **212** to the propellane **213**[69] (Scheme 34).

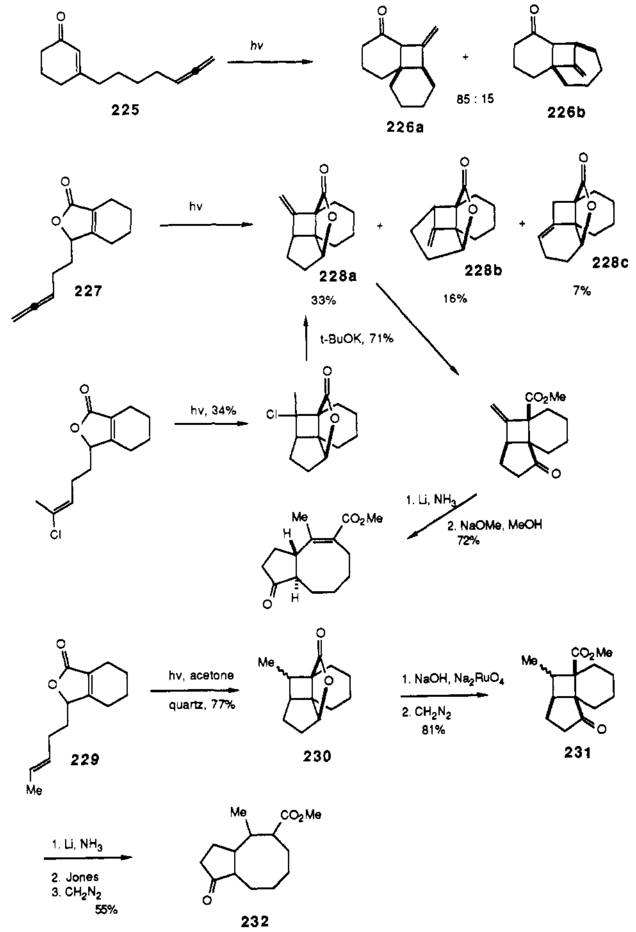
The 3-allenylcyclohexenone **214** again gave a predponderence of the anti addition product **215b**, although not with the high selectivity of **210**.[70] The olefin of the photoadduct was oxidatively cleaved, and the resultant cyclobutanone **216** was opened to the keto acid **217** with aqueous potassium hydroxide. In sharp contrast to the allene **214**, which cyclized exclusively to the straight adduct, the ketene generated from diazo ketone **218** gave the crossed adduct **219** as the only isolable product.[71] Similarly, allene **220** produced the single diastereomer **221** as evidenced by its two-step conversion to **222**, while the ketene **223** provided the alternative regioisomer **224**. The complete reversal of the ketene photocycloadditions is due to a strong electronic preference for the head to tail adduct in the ketenes that has been noted in the intermolecular photocycloadditions of ketenes (Scheme 35).

Another interesting example is that of the enone **225**, which is tethered to the allene by four carbons. While the straight adduct **226a** is the major product, 15% of the crossed adduct **226b** is observed.[72] This is somewhat surprising due to the notable regioselectivity of the intermolecular photocycloaddition of allenes to enones. However, Coates has observed small amounts of the crossed adduct **228b** in the irradiation of allene **227**, while no crossed adducts were noted in the photocycloaddition of olefin **229** to **230**.[73] The lactone **230** has been converted to keto ester **231**, which could be reductively opened to the 5,8 system **232**[74] (Scheme 36).

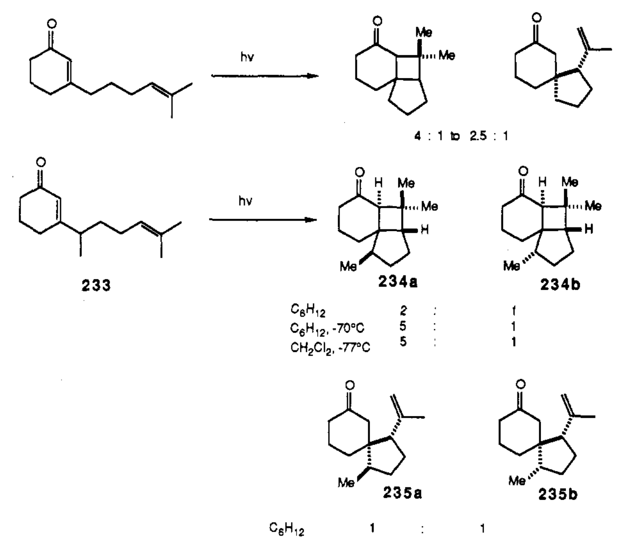
The photocycloaddition of cyclohexenone **233** was originally reported by Fetizon who irradiated **233** at −77 °C in dichloromethane and noted a 3:1 mixture of photoadducts. He assigned the major product the structure **234a** but incorrectly assigned the minor adduct as the crossed photoadduct.[75] Hoye later clarified the results and confirmed the structure of the minor isomer as the methyl epimer **234b** by X-ray analysis.[76] Hoye also noted that the photoaddition was temperature dependent; the ratio of **234a** to **234b** ranged from 2:1 in cyclohexane at 25 °C to 5:1 in frozen cyclohexane or in dichloromethane at −70 °C. This temperature dependence is most likely a simple reflection of the dependence on temperature of the difference in the two free energies of activation ($\Delta\Delta G^{\ddagger}$). Additionally, minor components **235a** and **235b** were also isolated and identified; however, the proportion of these products remained essentially constant with temperature and solvent. In an attempt to utilize this photocycloaddition in a synthesis of some spirocyclic sesquiterpenes, Hoye tried various thermal and catalytic methods to convert **234a** and **234b** into the isopropenyl systems **235a** and **235b**. These attempts were ultimately unsuccessful (Scheme 37).

A solution to the cleavage problem encountered by Hoye was developed by Oppolzer who used the allylic

SCHEME 36



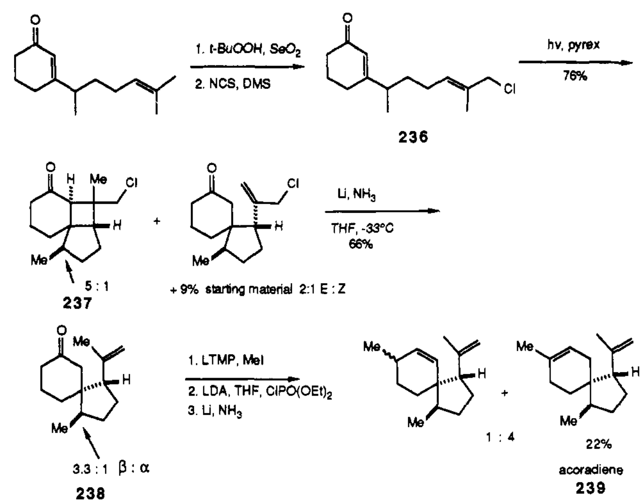
SCHEME 37



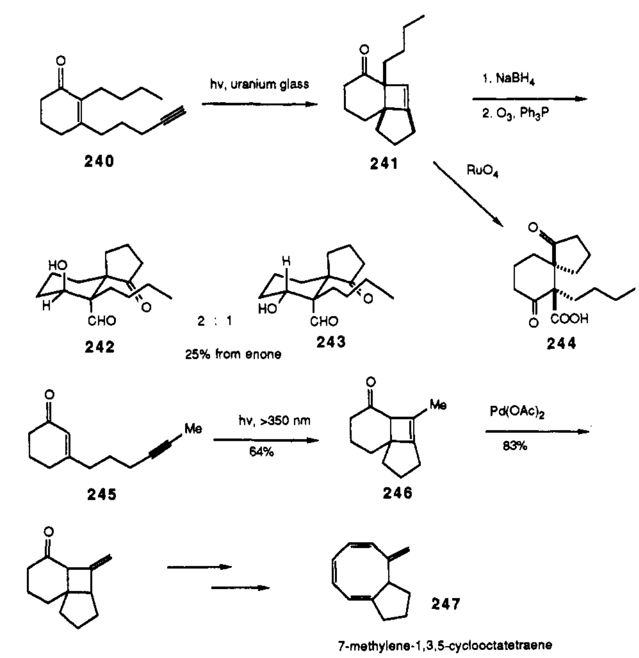
chloride **236** to prepare the cyclobutane **237** as a 5:1 mixture of methyl epimers.[77] Since a small amount of starting material containing isomerized olefin was recovered in the reaction, the stereoselectivity in this reaction was attributed to radical reversion. The chloro ketone **237** was exposed to lithium and ammonia to cleave the cyclobutane to **238**, which was readily converted to acoradiene (**239**) (Scheme 38).

Smith has carried out the photocycloaddition of acetylene **240** to **241** in an attempt to prepare a key intermediate for the synthesis of perhydrohistrionicotoxin.[78] Reduction of the ketone of **241**

SCHEME 38



SCHEME 39

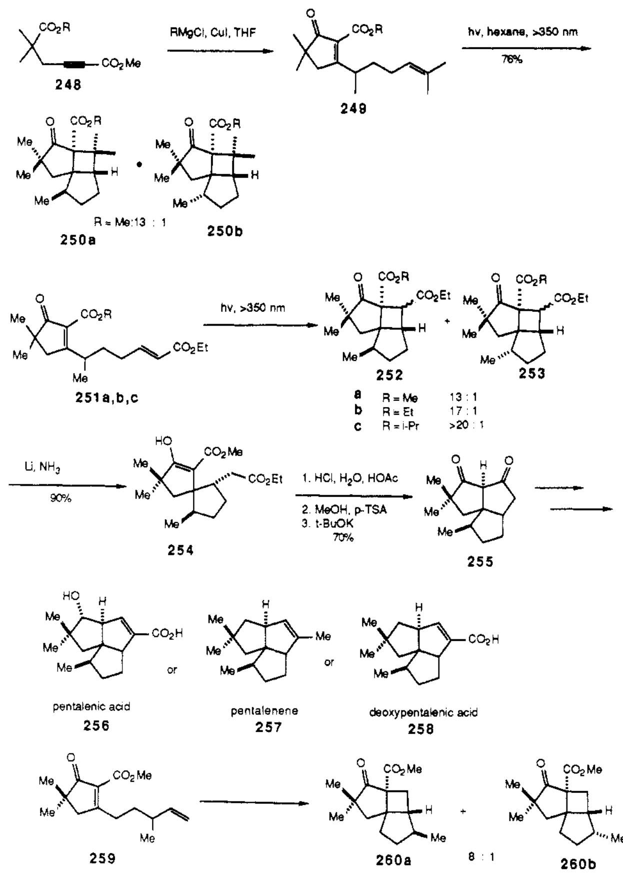


followed by ozonolysis of the alkene gave a 2:1 mixture of **242** and **243** that unfortunately could not be decarbonylated to the desired intermediate. Ruthenium tetroxide oxidation of **241** to **244** also failed to give the desired spirocyclic system on attempted decarboxylation. A similar acetylene photoaddition was utilized by Paquette who accomplished the synthesis of 7-methylene-1,3,5-cyclooctatetraene **247** by isomerization of **246** and further manipulations[79] (Scheme 39).

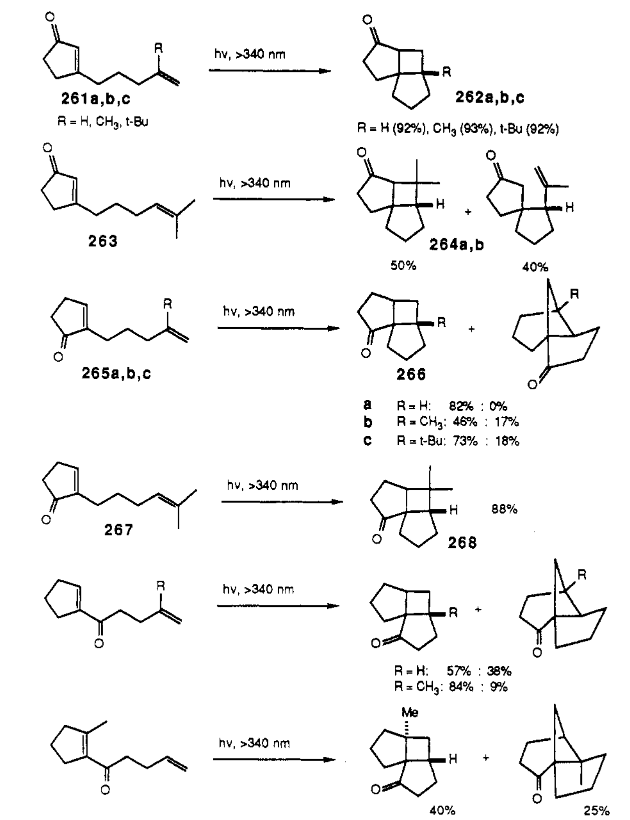
C. Alkenylcyclopentenones

Until fairly recently cyclopentenones, in contrast to cyclohexenones, had not been widely employed in intramolecular photocycloaddition reactions. Recently, Crimmins prepared several 2-carboalkoxy-3-alkenylcyclopentenones and subjected them to intramolecular photocycloadditions.[80] Cyclopentenone **249** was synthesized from the acetylenic diester **248** in a single step and then irradiated to give a 76% yield of the methyl epimers **250a** and **250b** in a ratio of 13:1. Likewise, the esters **251** (prepared by ozonolysis of **249** followed by

SCHEME 40



SCHEME 41



Wittig condensation) were irradiated to give a mixture of diastereomers **252** and **253**. Notably, the diastereoselectivity increases as the size of the ester alkyl group increases.[81] All three examples are significantly more selective than the case of the cyclohexenyl systems where the 2-position bears a hydrogen, e.g. **232** and **236**. This is consistent with the argument that some type of steric interaction between the secondary methyl group and the 2-substituent is present either in the exciplex (if the effect is a kinetic one) or during the final cyclobutane ring closure (if radical reversion is operative and the effect is more thermodynamic). Similarly, cyclopentenone **259**, with the methyl group at the alternative allylic position, produced an 8:1 mixture of diastereomers **260a** and **260b**. Keto diester **252** was reductively cleaved to **254** with lithium in ammonia followed by decarboxylation, reesterification, and cyclization to form the triquinane diketone **255**, which was carried on to pentalenic acid (**256**), pentalenene (**257**), and deoxypentalenic acid (**258**) separately (Scheme 40).

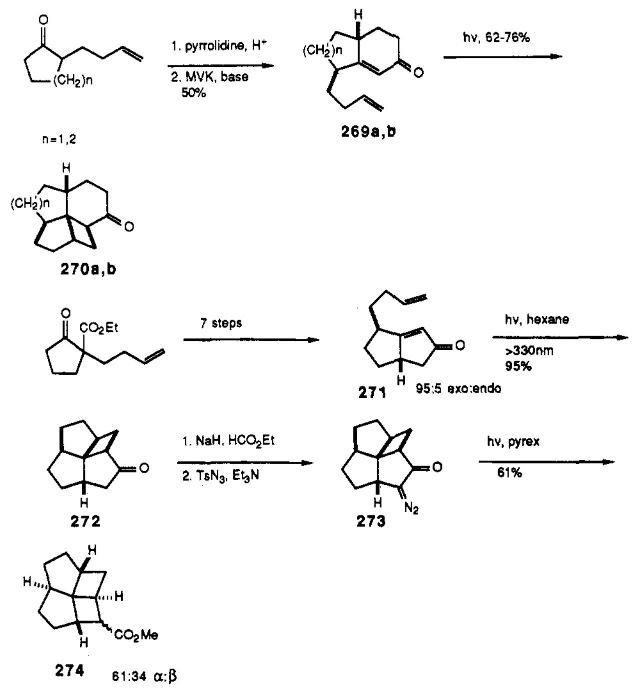
Wolff and Agosta have investigated the regioselectivity of a number of cyclopentenones differing in their substitution on the olefin moiety.[82] The 3-alkenylcyclopentenones **261a–c** and **263** all gave exclusively the straight adducts **262a–c** and **264a,b** in agreement with the Rule of Fives regardless of the substitution pattern on the olefin. The 2-alkenylcyclopentenones, however, produced exclusively the straight adduct only if the substituent on the internal carbon of the olefin is H (**265a** → **266a**, **267** → **268**). If the substituent on the internal carbon of the olefin is an alkyl group, a significant amount of the crossed adduct is formed (**265b,c** → **266b,c**). Possible reasons for this effect will be discussed in section VI (Scheme 41).

A very interesting aspect of the photocycloaddition of cyclopentenones has been in the application of these photocycloadditions to the synthesis of fenestranes (organic compounds with four rings fused to a central quaternary carbon atom). The original case reported by Georgian and Saltzman does not employ a cyclopentenone but is included here for completeness.[83] The enones **269a,b**, prepared via a Robinson annelation, were photocyclized to the [6.5.5.4]- and the [6.6.5.4]-fenestranes (**270a,b** respectively) in 62 and 76% yields. Later, the [5.5.5.4]- and the [5.5.4.4]fenestranes were constructed by Dauben.[84] Irradiation of enone **271** at >330 nm gave the expected straight adduct **272**, which is a [5.5.5.4]fenestrane, in 95% yield. Diazotization of the ketone followed by a photochemical Wolff rearrangement gave a mixture of the [5.5.4.4]fenestrane esters **274** in 61% yield (Scheme 42).

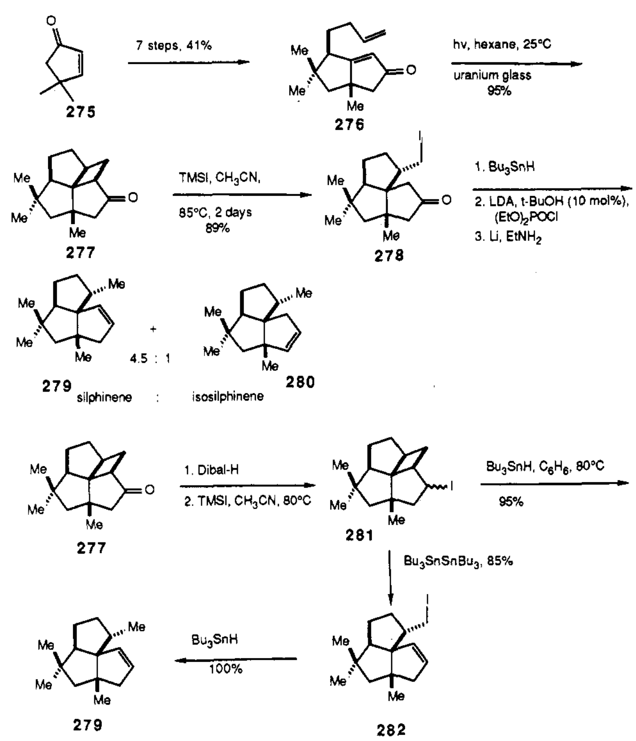
Crimmins has further elaborated fenestranes prepared via intramolecular photocycloadditions as a means of controlling the stereochemistry of substituents in triquinane systems. The diquinane enone **276**, which was readily available from 4,4-dimethylcyclopentenone **275**, was irradiated (hexane, 25 °C, >350 nm, 95%) to give the [5.5.5.4]fenestrane **277**,[85] which was treated with TMSI in acetonitrile, producing the iodo ketone **278**. The iodine was reductively removed, and the ketone was selectively converted (4.5:1) to a mixture of silphinene (**279**) and isosilphinene (**280**).[86] Alternatively, the ketone **277** was transformed to the iodide **281**, which was reductively cleaved directly to silphinene with Bu_3SnH, or isomerized to the iodide **282**, which was quantitatively reduced to silphinene[87] (Scheme 43).

The enone **283**, which incorporates an additional methyl group on the internal olefinic carbon, could *not* be induced to undergo photocycloaddition under the same conditions used for the enone **276** (25 °C, hexane,

SCHEME 42

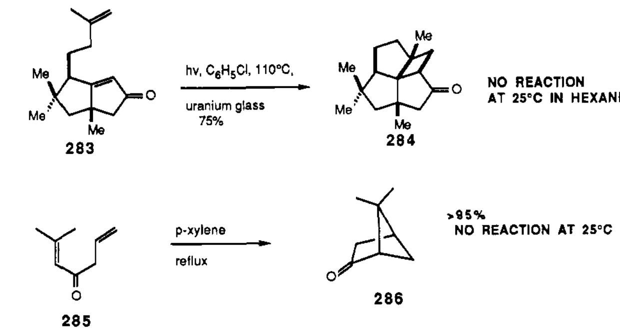


SCHEME 43

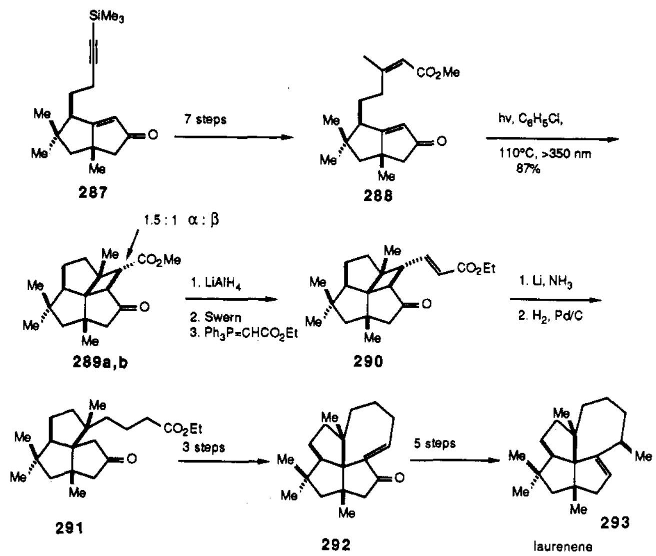


>350 nm).[85] However, if the reaction was carried out at 110 °C in chlorobenzene, a 75% yield of the fenestrane 284 was obtained. This fenestrane contains methyl groups at opposing ring junctures and creates a highly sterically crowded system. The failure of the enone to cyclize at 25 °C is presumably due to an unfavorable interaction between these two methyl groups, but the temperature dependence could reflect a thermal barrier between two excited states of different reactivity. Wolff and Agosta have seen a similar temperature dependence in the photocycloaddition of acyclic enone **285** to **286**[88,89] (Scheme 44).

SCHEME 44



SCHEME 45

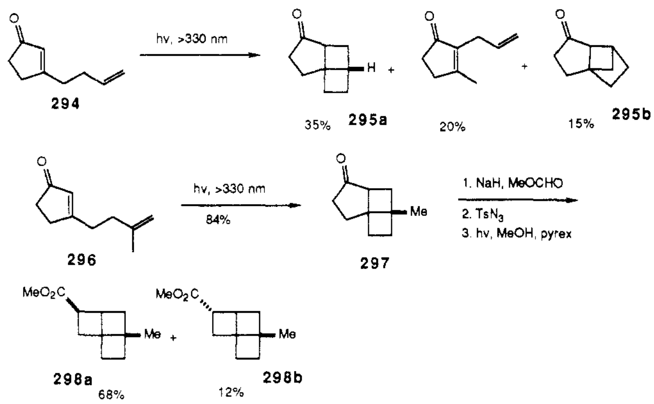


The unusual diterpene laurenene has been synthesized by taking advantage of this approach to highly substituted fenestranes.[90] The silyl acetylene **287** was readily available from 4,4-dimethylcyclopentenone and could be converted in high yield to the unsaturated ester **288**. Irradiation of **288** at 110 °C in chlorobenzene produced a 1.5:1 mixture of diastereomers **289a** and **289b** in 87% yield. This mixture was converted to the unsaturated esters **290**, which were reductively cleaved and then hydrogenated to generate the keto ester **291**. Closure of the seven-membered ring gave **292**, and incorporation of the secondary methyl group completed the synthesis of laurenene (**293**) (Scheme 45).

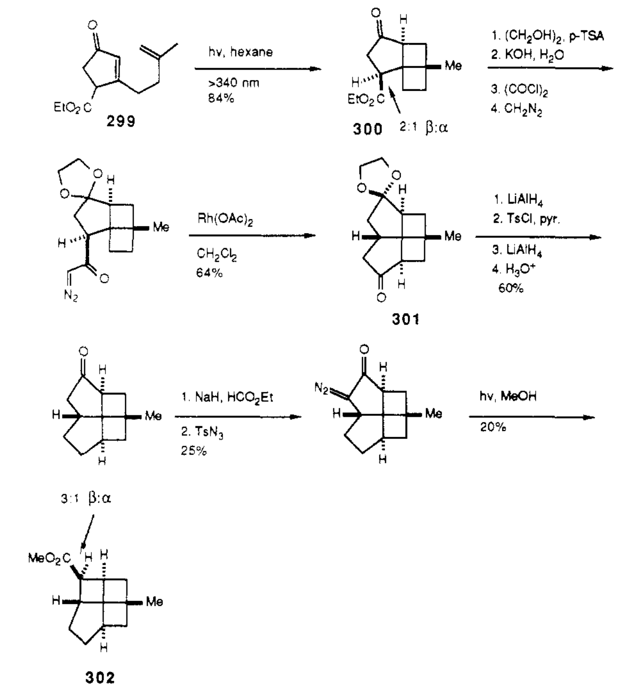
Wolff and Agosta have taken advantage of the observation that an alkyl substituent on the internal carbon of the olefin of 1,5-dienes such as **294** dramatically increases the amount of straight adduct obtained upon photocyclization to prepare some unusual fenestranes. The normal case **294** gave 35% of the straight adduct **295a** and 15% of the crossed product **295b**.[91,95] In contrast, the methyl-substituted olefin **296** cyclized exclusively to the straight system **297** in 84% yield. The [5.4.4]fenestrane was then contracted to the [4.4.4]-fenestranes **298a** and **298b** through a Wolff rearrangement (Scheme 46).

In a similar manner, the ester derivative **299** was converted to a 2:1 mixture of epimers **300** in 84% yield whereupon the ester was transformed to a diazo ketone and the fourth ring of the fenestrane was closed via a carbene insertion to give **301**.[93,94] Removal of one of the carbonyls and contraction of the remaining cyclo-

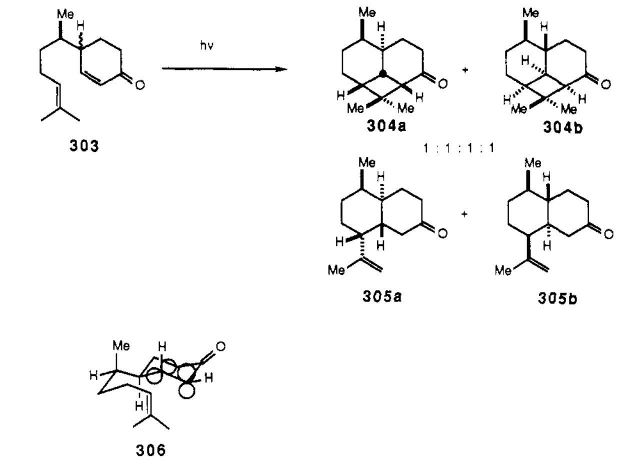
SCHEME 46



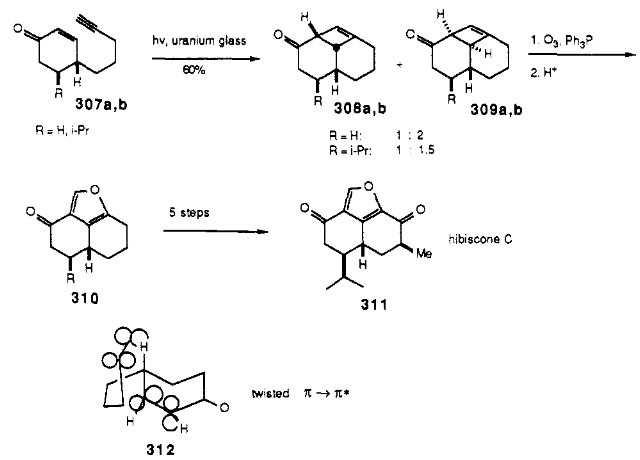
SCHEME 47



SCHEME 48



SCHEME 49



pentanone allowed the preparation of the first [5.4.4.4]fenestrane **302** (Scheme 47).

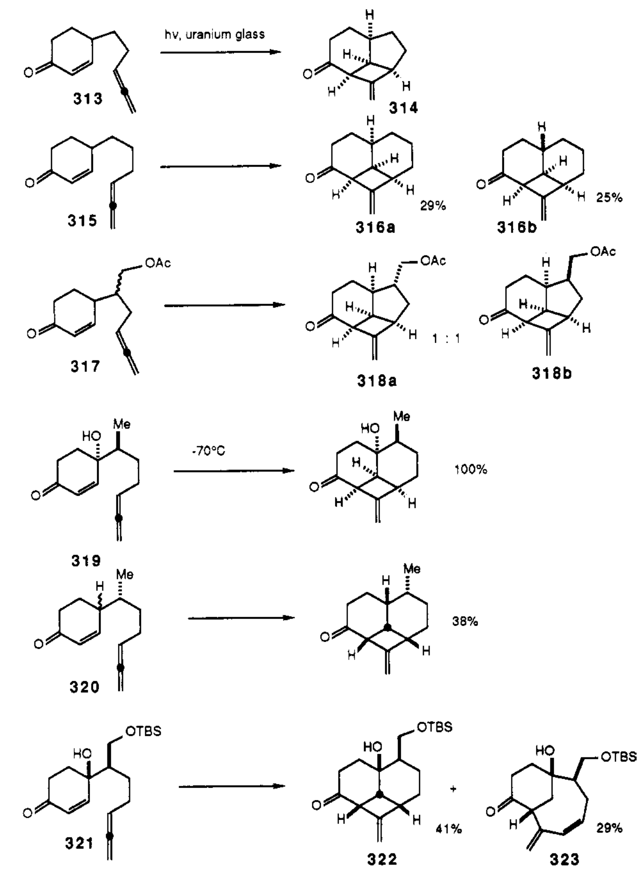
D. 4-Alkenylcycloalkenones

Cycloalkenones with alkenyl substituents at the 4-position have not been widely applied in photocycloadditions as have the 2-alkenyl and 3-alkenyl derivatives. In fact, only recently have examples of the photocycloadditions of 4-alkenylcycloalkenones been reported. Croft and Jeffries studied the photoaddition of diastereomeric enones **303** with the intention of exploiting a similar reaction in the synthesis of the decipiane diterpenes.[95] A solution of enone **303** was irradiated at 300 nm and produced four products: **304a** and **304b**, the result of [2+2] cycloaddition, plus **305a** and **305b**, products of intramolecular hydrogen atom abstraction, in approximately equal amounts. All four products possess a trans relationship at the decalin ring juncture, which can be rationalized by invoking the model proposed by Wiesner.[96] This states that if the β-carbon of the triplet state of the enone is assumed to be somewhat pyramidalized (resulting in a twisted π → π*) and the resultant radical is allowed to adopt the most favorable conformation (e.g., **306**), the initial cyclization will proceed through this conformation. This interpretation indeed leads to the observed *trans*-decalin systems (Scheme 48).

While the system above gave the *trans*-decalins as opposed to the cis systems needed for the decipiane diterpenes, it served as an impetus for the further investigation of 4-alkenylcyclohexenones. Smith photocyclized the acetylene **307a** and obtained a 1:2 mixture of the diastereomeric cyclobutenes **308a** and **309a**.[97,98] Here the *trans*-decalin predominates, but a substantial amount of the cis is also observed. The isopropyl-substituted **307b** gave even more of the cis product. This can also be rationalized via a twisted π → π* triplet **312** in which the 4-substituent is equatorial. The fewer degrees of freedom in the acetylene make it more difficult for the chain to reach around to the opposite face to form the trans product as opposed to the alkene case. The photoadducts **309** were cleaved with ozone, and the resultant formyl ketones were treated with acid to produce the furan **310**, which was readily converted to hibiscone C (**311**) in five steps (Scheme 49).

Dauben has studied a variety of allene-containing 4-substituted cycloalkenones shown below.[99,100] The 1,6-diene **313** gave the expected straight adduct **314** as a single diastereomer with a cis ring fusion while the 1,7-diene **315** produced both the cis and trans products **316a** and **316b**. Similarly, photocycloaddition of the 1,6-dienes **317** resulted in formation of only the straight, cis products **318**. The cis adducts are also the only

SCHEME 50

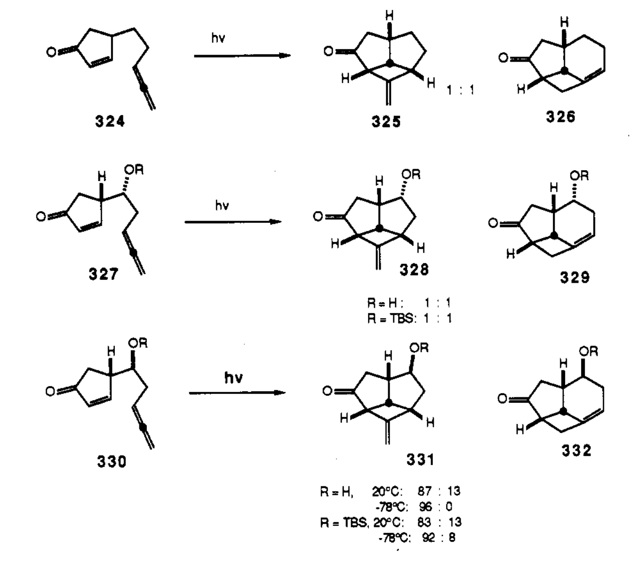


products obtained upon irradiation of **319** and **320**. This sharply contrasts the results of Jeffries in the irradiation of **303**. A possible explanation has been proposed by Dauben based on the observation that enone **321** produces not only the cis adduct **322** but also the diene **323**, which is apparently the result of intramolecular hydrogen atom abstraction from the diradical resulting from initial bond formation at C2 of the enone. Dauben suggests that on the basis of hydrogen atom abstraction products in the Jeffries case (**305a,b**) the cycloaddition occurs via initial bond formation at C3 when an olefin is involved in the cyclization, while initial bond formation occurs at C2 when an allene is tethered to the enone. This could also explain the different stereochemical result since a *trans*-decalin would appear to be favored if initial bond formation occurs at C3, but the cis product would seem more likely if the C2 bond formed first[100] (Scheme 50).

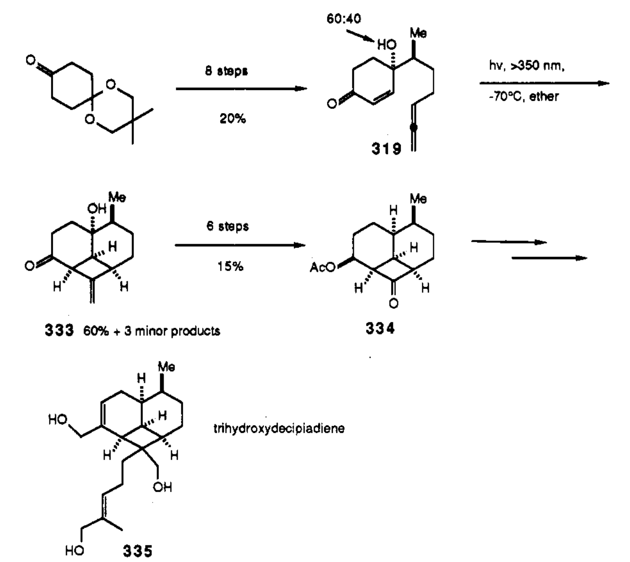
The cyclopentenone analogue **324** resulted in formation of not only the straight adduct **325** but also the bridgehead olefin **326**, the result of photoaddition to the terminal π-bond of the allene, clearly demonstrating that the structure of the enone, the length of the tethering chain, and the nature of the olefin (allene) all play a role in determining the products and the stereochemistry.[101] This same effect was also observed in the enones **327** and **330**, and the ratio of **331** to **332** was found to be temperature dependent (Scheme 51).

A previously prepared intermediate in the synthesis of trihydroxydecipiadiene has been constructed through the use of these photocycloadditions.[102] Irradiation of hydroxy enone **319** (a 60:40 mixture of diastereomers) produced the desired *cis*-decalin **333** (60%) plus three minor products. Conversion of **333** to cyclobutanone

SCHEME 51



SCHEME 52



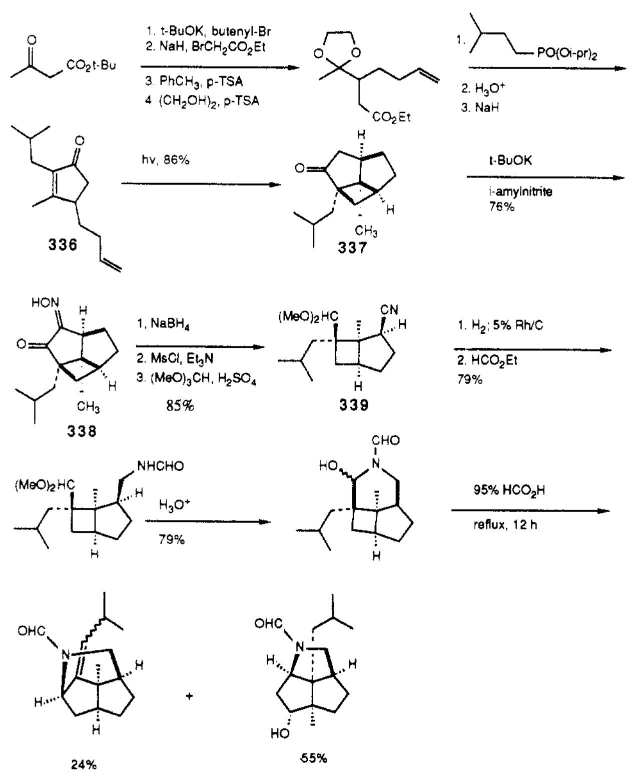
334, an intermediate previously transformed into trihydroxydecipiadiene **335**, was accomplished in six steps in 15% overall yield (Scheme 52).

An approach to the total synthesis of the alkaloid dendrobine by Heathcock employed an intramolecular photocycloaddition of enone **336**, which gave a single photoadduct **337**.[103] Treatment of **337** with base and isoamyl nitrite produced **338**, which was cleaved to the cyclobutane **339**. Further elaborations resulted in the formation of intermediates that might be useful in the preparation of alkaloid systems (Scheme 53).

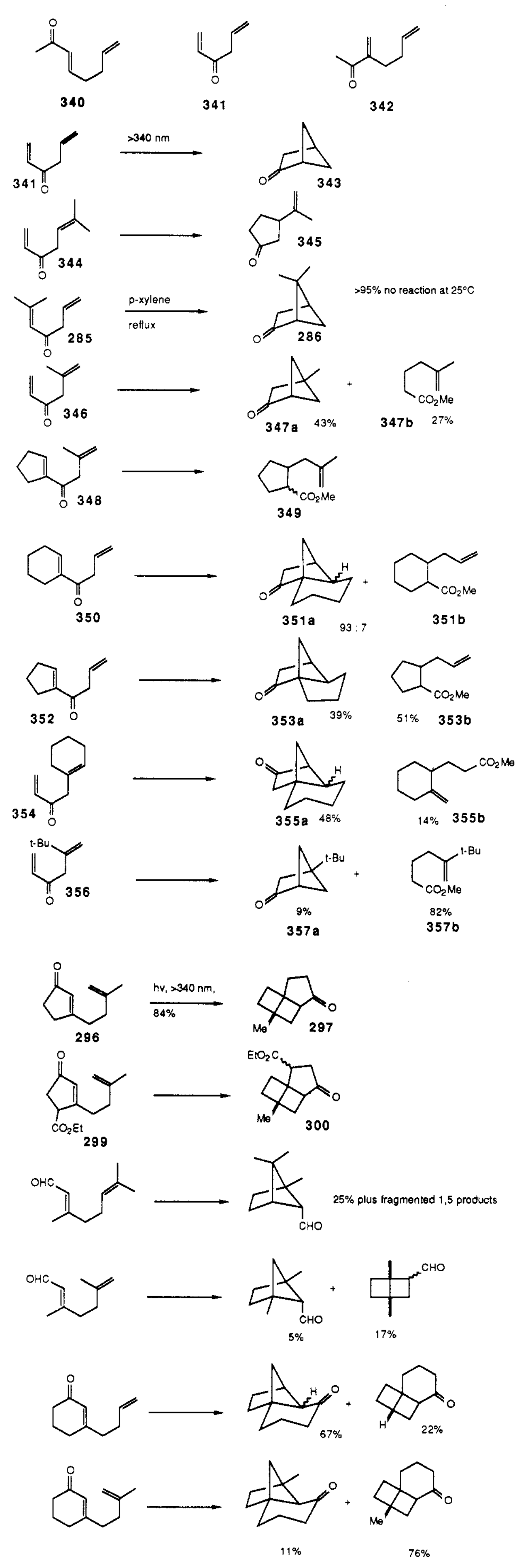
VI. Photocycloadditions of 1,5-Hexadienes

While a few selected examples of the intramolecular photocycloadditions of 1,5-hexadienes have been noted above, a more general discussion of these systems seems warranted. Three general systems, 1-acyl-1,5-hexadienes **340**, 1,5-hexadiene-3-ones **341**, and 2-acyl-1,5-hexadienes **342**, have been carefully investigated by Wolff and Agosta.[88,89,104] A common trend has been observed for the first two cases (1-acyl-1,5-hexadienes **340** and 1,5-hexadiene-3-ones **341**) while the third case (2-acyl-1,5-hexadienes **342**) behaves somewhat differ-

SCHEME 53



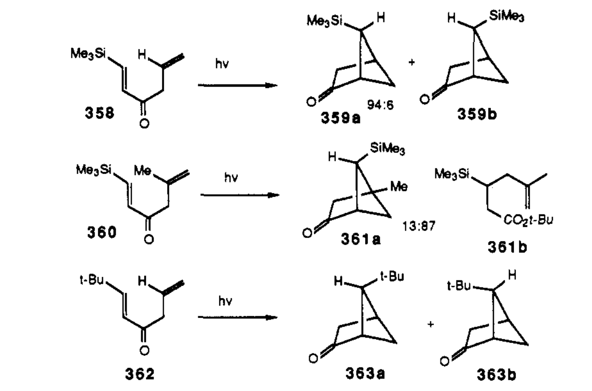
SCHEME 54



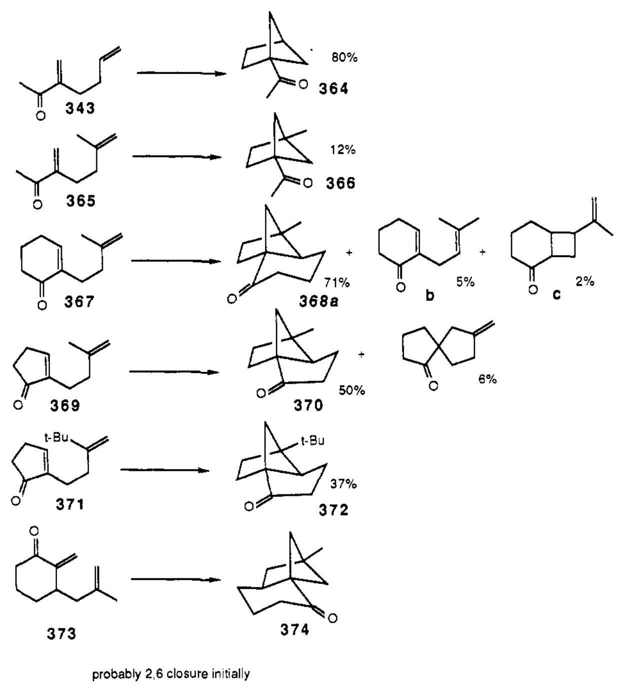
ently. Generally, the 1-acyl-1,5-hexadienes **340** and the 1,5-hexadiene-3-ones **341** undergo photocyclization to give predominantly the crossed products resulting from initial 1,5-cyclization of the triplet species in accordance with the Rule of Fives.[89] Substitution at C1, C2, C4, or C6 does not appear to significantly alter the course of the cyclization. Two structural changes that do appear to affect the ratio of 1,5:1,6 cyclization are substitution at C5 of the diene and incorporation of the conjugated double bond into a ring. The first of these two effects can be observed in the comparison of the unsubstituted case (**341** → **343**) with the methyl derivative (**346** → **347**) and the *tert*-butyl derivative (**356** → **357**) in which a progressive increase in the amount of 1,6-cyclization is seen. This is very similar to the steric effect noted in the cyclization of 5-substituted 5-hexenyl radicals, which show a depressed rate for formation of the cyclopentylmethyl radical and an increase in the rate for the formation of the cyclohexyl radical. This also seems to indicate that cyclization proceeds from C1 to C5 rather than from C2 to C6 relative to the unsubstituted case. Incorporation of the conjugated double bond into a ring has a similar effect, with the five-membered ring being more effective for promotion of 1,6-cyclization than the six-membered ring. This effect is most likely related to the observation that enone triplets are twisted about the carbon–carbon double bond and that incorporation of this double bond into a ring can severely alter the geometry of the excited state. When both effects are combined, the result is exclusive 1,6-cyclization (**348** → **349**, **296** → **297**, and **299** → **300**) (Scheme 54).

It interesting to note that substitution of the C1 of 1,5-hexadien-3-ones with a trimethylsilyl group has approximately the same effect as incorporating the conjugated double bond into a six-membered ring (**358** → **359** vs **350** → **351**). The reasons for this effect are

SCHEME 55



SCHEME 56



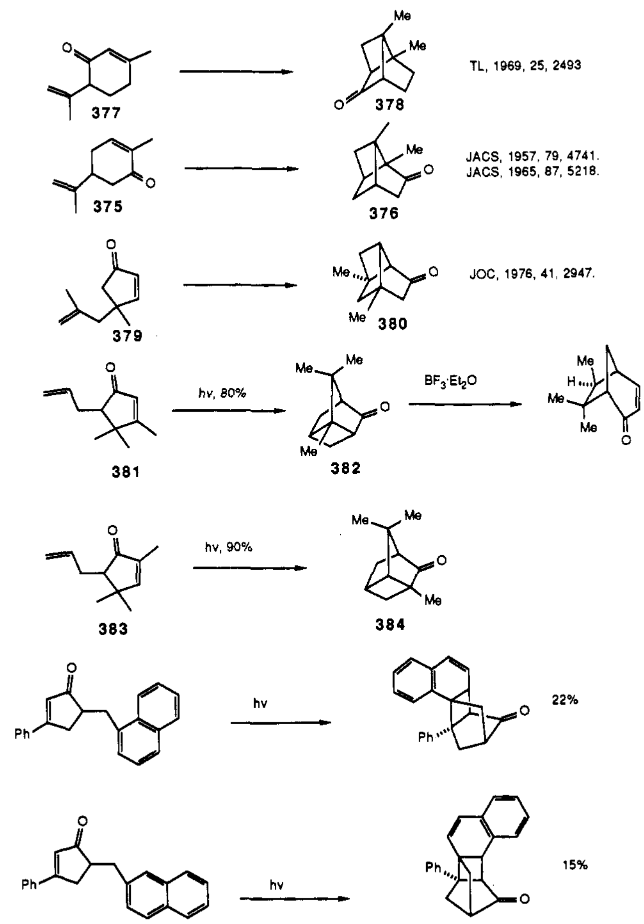
not clear; however, they would not appear to be of steric origin[105] (Scheme 55).

The case of 2-acyl-1,5-hexadienes is quite different from the two discussed above in that there seems to be no effect on the outcome of the photocycloaddition whenever structural changes are introduced.[104] Substitution at C5 (**365** → **366**) yields exclusively the crossed adduct as does the simplest case (**343** → **364**). Introduction of the conjugated double bond into a ring in conjunction with substitution at C5 (**369** → **370**, **371** → **372**) has no effect on the regiochemistry. The case of enone **369** is particularly interesting since it has a carbon skeleton identical with that of **296** and differs only in the location of the carbonyl group. These observations led Wolff and Agosta to the conclusion that the 2-acyl-1,5-hexadienes must be profoundly different mechanistically and that they likely undergo cyclization from C2 to C6 rather than from C1 to C5 as postulated for the other two systems (Scheme 56).

VII. Cross-Ring Photocycloadditions

The first intramolecular photocycloaddition recorded was one in which the olefin was attached to a carbon across the ring from the enone double bond.[1,2] The

SCHEME 57



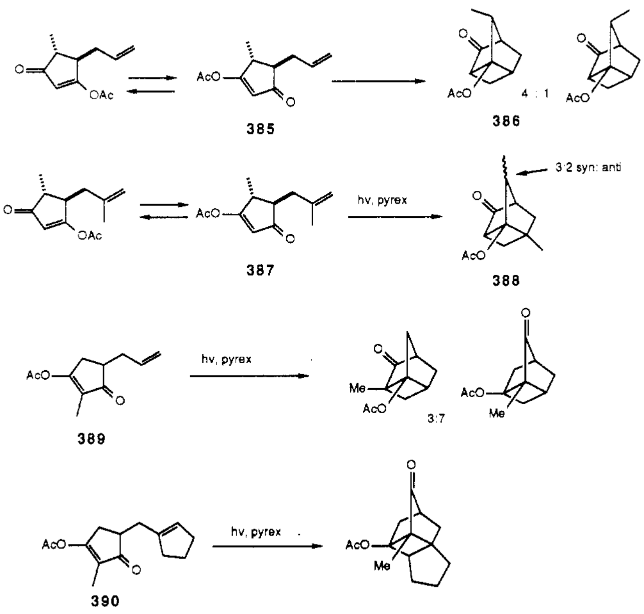
result was a photoaddition that produced a skeleton containing a bridged bicyclic system (**375** → **376**). A number of other systems of this type have been investigated, although there is still a great deal that is not understood about the regiochemistry of these photoadditions.[106-108] While in most cases either regioisomeric photoadduct could be produced in accordance with the Rule of Fives, the major and usually exclusive product is the one derived from bonding of the β-carbon of the enone to the more internal carbon of the olefin (i.e., the α-carbon of the enone becomes bonded to the distal olefin carbon). An exception to this observation is enone **379**, which gives **380** wherein the alternative regioisomer would result from a violation of the Rule of Fives[106] (Scheme 57).

Increasing the substitution on the enone β-carbon as well as on the internal carbon of the olefin had no effect in enone **387** as compared to **385**.[108] The one noteworthy exception to this general trend is the enone **390**, in which the enone is substituted at C2 and the olefin is contained in a five-membered ring. In this case the opposite regioisomer is obtained exclusively (Scheme 58).

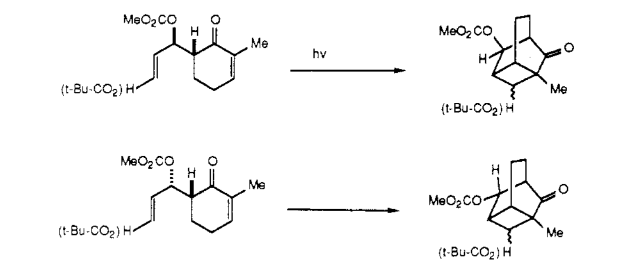
An attempt by Martin to override the normal regiochemical preference of systems of this type by significantly changing the electronic nature of the olefin by incorporating an oxygen substituent provided no improvement as the usual products were obtained[109] (Scheme 59).

Sternbach has recently completed a synthesis of (+)-methylenomycin from carvone utilizing the original photocycloaddition observed by Ciamician. When the

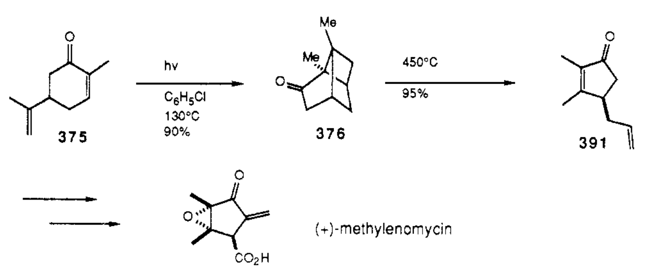
SCHEME 58



SCHEME 59



SCHEME 60

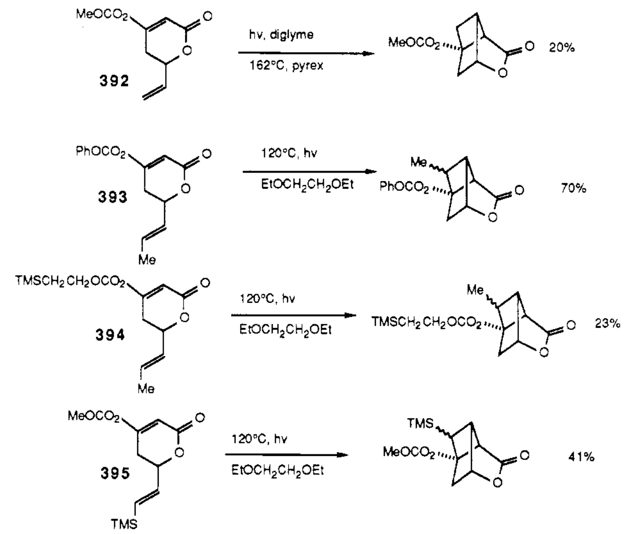


photocycloaddition of carvone **375** is carried out in chlorobenzene at 130 °C, a 90% yield of carvone camphor **376** is obtained. Pyrolysis of the cyclobutane provides a 95% yield of enone **391**, which was converted to methylenomycin in six steps in good yield[110] (Scheme 60).

Similar elevated temperature photocycloadditions of lactones **392–395** have also been successful[110] (Scheme 61).

There is still much that is not well understood about the mechanistic aspects of the intramolecular photocycloaddition, and while broad generalizations with regard to selectivity in a reaction whose mechanism is not totally understood is dangerous, there are a few simple trends worthy of note. None of the trends to be listed are universal: All have significant exceptions. Regiochemistry generally seems to be controlled by the number of atoms in the chain connecting the two carbon–carbon double bonds (particularly in cases where the connecting atoms are all carbon). Two-atom bridges yield crossed adducts while bridges with three or more

SCHEME 61



atoms generally produce straight adducts. Stereochemical control seems to be governed primarily by nonbonded interactions such as $A^{1,3}$ strain and transannular interactions of the tethering chain as well as interactions between the substituents on the tethered olefin with substituents elsewhere in the molecule. The stereochemistry of the ring fusions produced in photocycloadditions is typically the result of geometric constraints generated by the length of the tether between the two olefins. Finally, systems containing allenes tethered to conjugated enones appear to proceed through a different mechanistic manifold and require individual evaluation. Although much has been accomplished with regard to establishing trends for predicting the regio- and stereochemical outcome of these reactions, much work remains.

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