Photochemical Strategies for the Construction of Polycyclic Molecules

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I. Introduction

During the past decade photochemistry has profoundly affected organic synthesis as proved by the many successful synthetic routes that currently involve a photochemical reaction as a key step. Light is clearly manifesting itself as a unique reagent. The understanding of the photochemical behavior of various chromophores indeed provides a firm basis for diverse synthetic applications. In addition, new concepts and novel reactions, which exclusively proceed from excited states, have considerably widened the scope of light-induced synthesis. To date it is generally recognized that photochemical activation may account for a high degree of control on the chemo-, regio-, and stereoselectivity of reactions, which otherwise might be elusive. Photochemical processes are therefore especially promising for the synthesis of complex polycyclic molecules.

In recent years a number of excellent monographs, reviews, and chapters on different aspects of photochemical organic synthesis have appeared. It is obviously not the purpose of this review to present an exhaustive list of all contributions.[1] Rather, we would like to focus on photochemical strategies for the construction of polycyclic and heterocyclic molecules. Our intention is to survey the latest and most promising concepts. Wherever it is felt necessary for the clarity of the presentation, essential functional group manipulations to obtain a particular synthon or target molecule are included. Yields are only mentioned when clearly determined. In many reports it is not sufficiently established whether the quoted yields are for isolated reaction products or based on consumed substrate.

II. Arene–Alkene Photocycloadditions

Arenes in the presence of alkenes undergo 1,2 or ortho, 1,3 or meta, and 1,4 or para cycloadditions upon irradiation at 254 nm.[2] From the synthetic viewpoint the arene–alkene photocycloadditions offer great opportunities. Thus, intermolecular reaction of benzene (1) and a 1,2-disubstituted ethylene (2) may lead,


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depending on the nature of the substituents, to bicyclo-[4.2.0]octa-2,4-dienes **3** (ortho addition), tricyclo-[3.3.0.0^{4,6}]oct-2-enes **4** (meta addition), or bicyclo-[2.2.2]octa-2,5-dienes **5** (para addition) (eq 1). These photoadducts may contain up to six (meta addition) contiguous stereocenters. Due to the formation of small rings, the retention of alkene geometry, and the pronounced regioselectivity, the number of stereomers actually observed is restricted. By subsequent cleavage of any bond in the photoadducts a number of cyclic systems can be accessed.

$$(1)$$
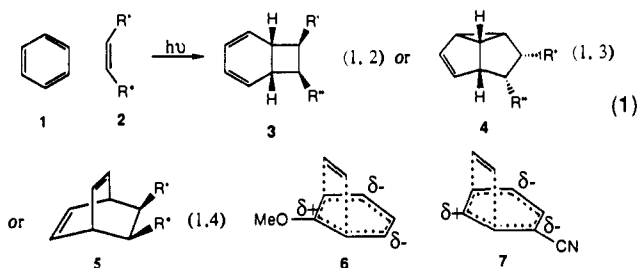
In intramolecular reactions the excited-state interactions of the bichromophores and the reaction efficiencies are greatest for molecules which have three units (usually methylene groups) in the connecting chain. Among others, steric constraints generally allow for high selectivities.

A. Arene–Alkene Meta Photocycloadditions

The meta photocycloaddition of alkenes having simple, nonpolar substituents to arenes appears to be quite facile and general.[3] The course of the reaction has been investigated in detail.[4] Through the extensive bond reorganization occurring in the meta photocycloaddition, the greatest increase in molecular complexity of any general reaction is achieved.[5] Detailed structural analysis of the meta cycloadducts from numerous systems shows that the addition occurs exclusively at the 2,6-positions of benzenes having electron-donor substituents (e.g., OMe; 6) and at the 2,4-positions when the substituent is an electron-acceptor group (e.g., CN; 7) (eq 1).[6] The resulting cycloadducts may subsequently be manipulated to a number of both common and unusual cyclic structures via cleavage of the three-membered ring or of other principal bonds. The recognition of this versatility has led to the development of very elegant synthetic approaches to a wide variety of natural products, in particular by the group of Wender.[7]

The efficacy of the arene–alkene cycloaddition in polycyclopentanoid synthesis is highlighted by the two-step synthesis of the angularly fused triquinane (±)-silphinene (11) (eq 2).[7,8] Photolysis of the readily

$$(2)$$
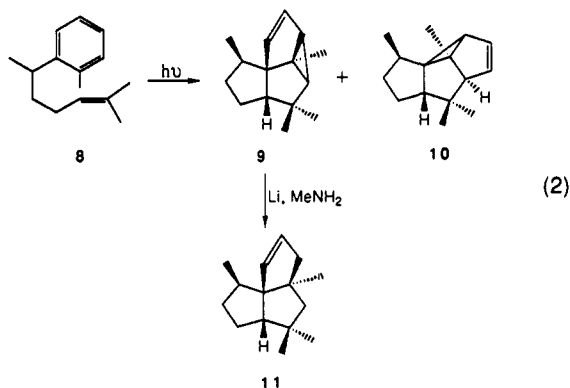
available precursor 8 affords the cycloadducts 9 and 10 (1:1, 70%). The ortho methyl group on the arene 8 dictates the regioselectivity (2',6'-positions), while orbital overlap accounts for the less-sterically congested exo selective process. Furthermore, minimization of the interaction of the benzylic methyl group and the directing arene methyl group regulates the stereoinduction. The natural product is obtained from 9 by

reduction with lithium and methylamine. This provokes opening of the cyclopropane bond which better overlaps with the alkene radical anion. A shorter and more efficient entry into this skeletal class is hardly conceivable.

An intramolecular meta-cycloaddition-based strategy is also quite appropriate to synthesize linear triquinanes, such as (±)-coriolin (15) (eq 3).[9] Following meta

LAH = lithium aluminum hydride

$$(3)$$
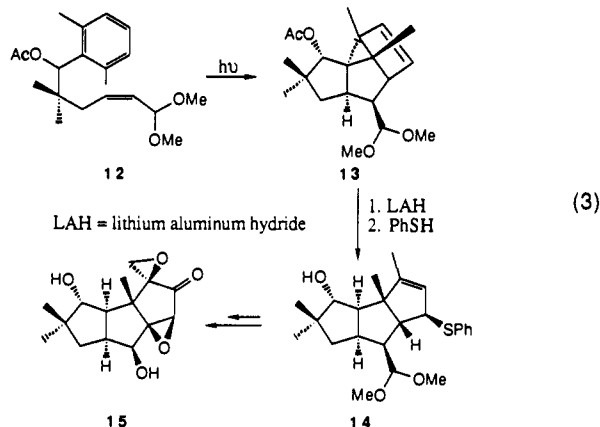
photocycloaddition of the substrate 12 to the photocycloadduct 13 (15%), the linearly fused triquinane skeleton of coriolin is elaborated by reduction of 13 and treatment with thiophenol, leading to preferential cleavage of one of the allylic three-membered ring bonds. The resulting triquinane 14 is subsequently converted to coriolin (15) through a series of straightforward steps.

The use of polycyclic arene–alkene systems may lead to quite complex structures, such as (±)-laurenene (19), a naturally occurring fenestrane (eq 4).[10] The com-

$$(4)$$
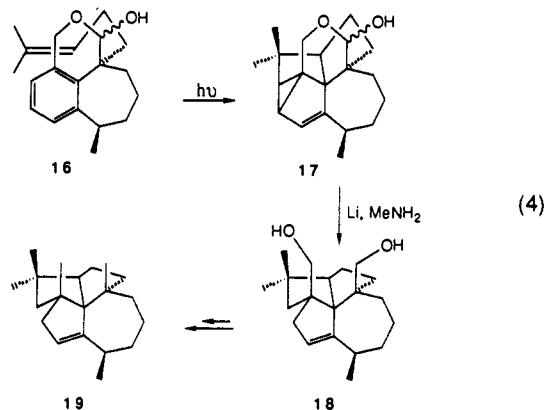
plexity increase attending the arene–alkene meta photocycloaddition shortens the synthesis of this tetracyclic molecule, which requires approximately 30–40 steps, to only 13 steps. The key photochemical reaction is the photolysis of lactol 16, yielding only cycloadduct 17 (51%). In this connection it is important to note that the factors influencing the preferential formation of only one vinyl cyclopropane isomer have not been systematically investigated. Several studies suggested that the major isomer is the one in which strain is minimized.[3e] Treatment of 17 with lithium and methylamine afforded diol 18, which after deoxygenation led to the natural product 19.

In the preceding examples addition is preferentially directed by a donor group positioned ortho to the alkene tether. The donor effect of the chain may be offset by

steric effects introduced for example by Z-alkenes. Addition across the tether is possible for E-alkenes,[3e,4a,11] as illustrated by the construction of ($\pm$)-desdimethylquadrone (23) (eq 5).[7a] Irradiation of compound 20

$$(5)$$
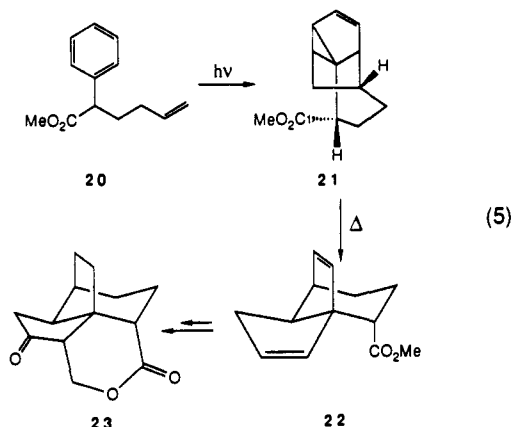
provided the expected adduct 21, which was however accompanied by isomeric compounds. The modest regio- and stereoselectivity indicates that the 2′,6′-addition is difficult to achieve, even with sterically unencumbered alkenes. The absence of the vinylcyclopropane isomer of 21 can be explained by the fact that a highly strained trans-fused bicyclo[4.1.0]heptane subunit would be involved.[3e] Deconvolution of cycloadduct 21 was achieved by a homo 1,5-sigmatropic rearrangement to the diene 22, from which desdimethylquadrone (23) was readily prepared.

Another asset of the intramolecular arene–alkene meta-photocycloaddition methodology is the entry to the synthesis of cycloheptanoids such as ($\pm$)-rudmollin (30) (eq 6).[12] Photolysis of 24 afforded the two meta


$$(6)$$
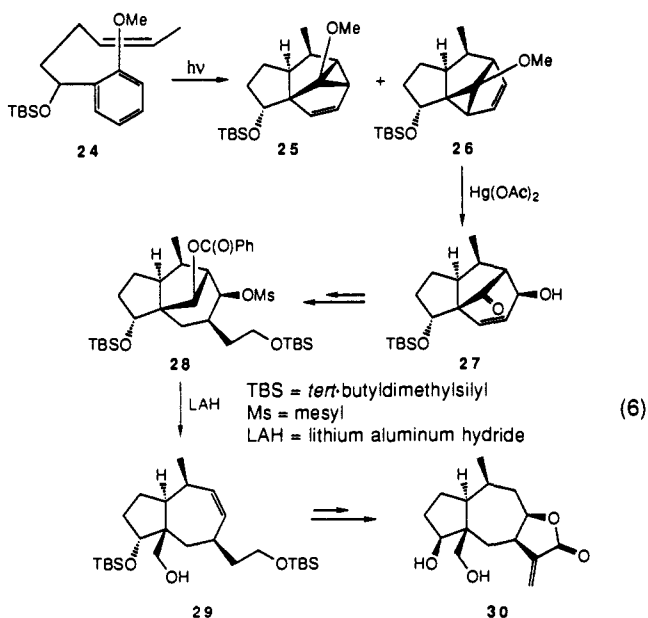
adducts 25 and 26 (2:1, 62%). Formation of the cycloheptane subunit was accomplished in a series of steps, the first of which was cleavage of the internal cyclopropane bond by treatment of the adducts with mercuric acetate. The resulting ketone 27 is then converted to the mesylate 28, which underwent a hydride-promoted Grob fragmentation, thereby un-

masking the cycloheptane subunit. Rudmollin (30) is produced by further elaboration of the intermediate 29.

Introduction of a heteroatom, such as oxygen, in the connecting chain alters the mode selectivity markedly, depending on its location. Thus, vinyl ether 31 gave predominant addition to the 1′,4′-positions, while benzyl allyl ether (32) exhibited 1′,3′-regioselectivity.[3c] The directing effect of the alkoxy group leading to 2′,6′-photocycloaddition was confirmed for (2-phenoxyethyl)ethylene (33) and derivatives 34–39 (yields varying between 21% and 51%) and for (2-phenoxyethyl)cyclopentene (40). On the other hand, irradiation of (2-phenoxyethyl)cyclohexene (41) only led to a complex reaction mixture (eq 7).[3g,3h,13]

33 : $R^1 = R^2 = R^3 = R^4 = R^5 = H$
34 : $R^1 = Me$; $R^2 = R^3 = R^4 = R^5 = H$
35 : $R^2 = Me$; $R^1 = R^3 = R^4 = R^5 = H$
36 : $R^3 = Me$; $R^1 = R^2 = R^4 = R^5 = H$
37 : $R^1 = R^2 = R^3 = R^4 = R^5 = D$
38 : $R^1 = R^4 = Me$; $R^2 = R^3 = R^5 = H$
39 : $R^1 = CF_3$; $R^2 = R^3 = R^4 = R^5 = H$

$$(7)$$
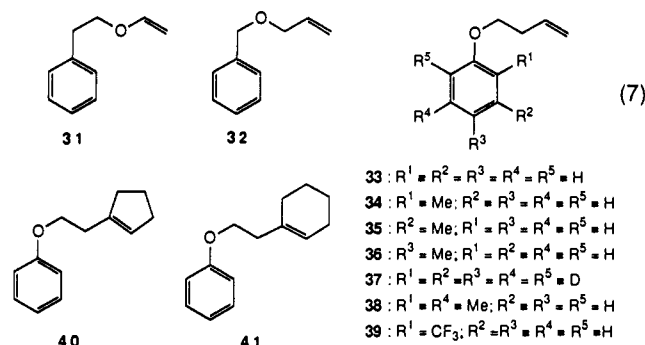
We have investigated the photochemistry of the bicyclic lactones 48 and 49, derived from Norrish type I cleavage of the aryl-substituted norbornan-2-ones 42 and 43 (eq 8) (see also section V). Regioselective Norrish

42,44,46,48 : Y = CH_2Ph
43,45,47,49 : Y = Ph

$$(8)$$
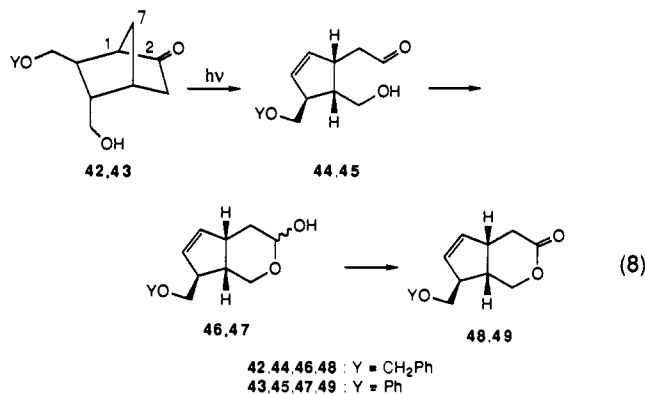
type I photofragmentation of the C(1)–C(2) bond, followed by abstraction of the endo-oriented hydrogen atom from C(7) led to the γ,δ-unsaturated aldehydes 44 and 45, respectively. These unstable compounds were not isolated, but oxidation in situ of the corresponding lactols 46 and 47 gave the lactones 48 and 49, respectively.

Irradiation of 48 in cyclohexane/ethyl acetate (5:1) afforded the vinylcyclopropane isomers 50 and 51 (3:2, 25%) resulting from meta photocycloaddition of the alkene at positions 1′ and 3′ of the phenyl ring (eq 9).[14] The structures were fully elucidated by a detailed NMR investigation.[3f,15] It is quite intriguing that the meta photocycloaddition still takes place when four atoms including an oxygen atom intervene between the arene and the alkene. If the tether contains more than four carbon atoms, no meta photocycloaddition occurs.[3c,16] We examined further the effect of methoxy and

$$(9)$$
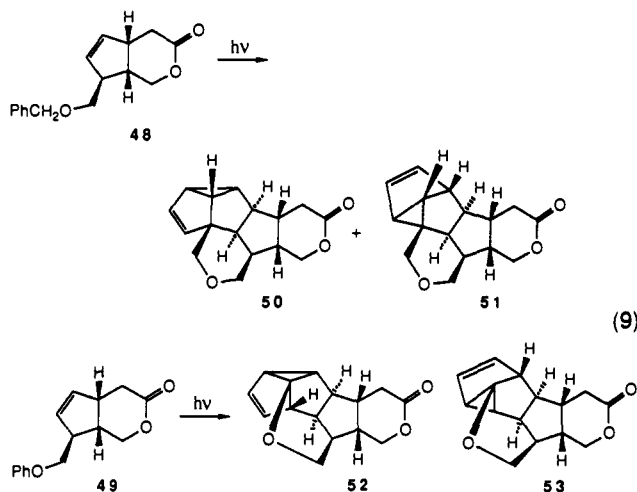
trifluoromethyl substituents at different positions.[17] All results were in accord with the polarized models (see 6 and 7).[6,13] The highest yield (64%) was observed for the trifluoromethyl group in the ortho position.

Direct irradiation of norbornan-2-one 42 and oxidation of the reaction mixture in situ gave the lactones 50 and 51 (21%), which were obtained also from irradiation of 48. Thus, generation of lactol 46 has evidently been sequenced by a meta photocycloaddition of the alkene to the phenyl group. This tandem Norrish type I reaction and intramolecular arene–alkene meta photocycloaddition result in a completely stereoselective isomerization of the aryl-substituted norbornan-2-one 42 to the triquinanes 50 and 51 containing nine contiguous stereocenters.

Irradiation of either lactone 49, a lower homologue of 48 (two-step process, 35% overall), or norbornan-2-one 43 (one-step process, 34%) afforded a single photocycloadduct 52 (35%), since the formation of the vinylcyclopropane isomer 53 is prohibited (eq 9).[3e] As expected the addition occurred at the positions 2' and 6'.[6]

The photoadduct containing a cyclopropyloxy function proved to be unstable. Treatment of 52 with dilute acetic acid provoked opening of the nonallylic bond in the three-membered ring to the lactol 54 and the corresponding acetate 55 (eq 10).[15] Lactol 54 was

$$(10)$$
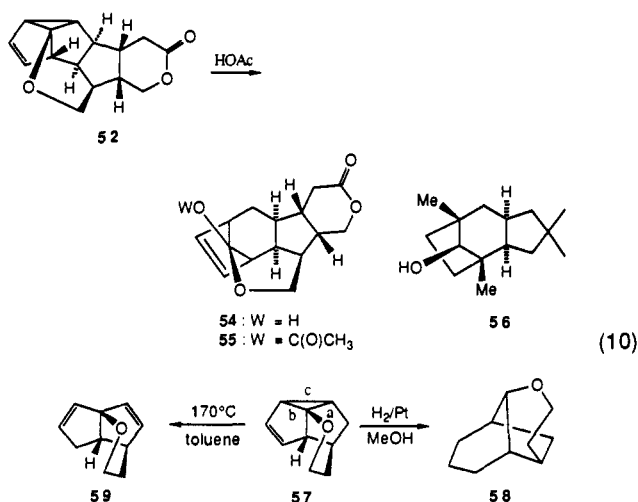
obtained in almost quantitative yield by reaction with hydrogen chloride. Such a conversion gives direct access

to the recently discovered bullerane skeleton represented by (+)-cerapicol (56).[18]

It is of interest that both allylic cyclopropane bonds could be cleaved selectively.[17] Catalytic hydrogenation of the model compound 57 afforded the tricyclic ether 58 (51%) via hydrogenolysis of bond b (eq 10). Ether cleavage would give access to 6,8-disubstituted bicyclo[3.2.1]octanes. On the other hand, thermolysis led to the bridged diquinane 59 (72%) as the result of cleavage of bond c concomitant with a 1,5-hydrogen shift.

This rearrangement occurred even in normal reaction conditions, as illustrated by the photobehavior of compounds 60 and 63 (eq 11).[17] Thus, irradiation of

$$(11)$$
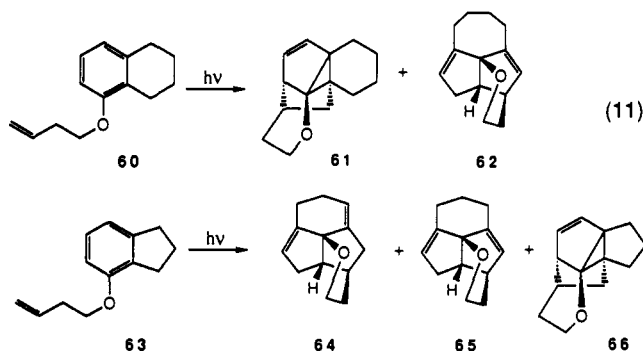
tetralin 60 gave a mixture of the cycloadduct 61 and the diene 62 (1.5:1; 30%). Upon thermolysis, 61 was converted to 62 (52%). Similarly, photolysis of indan 63 furnished the dienes 64 and 65 next to the expected cycloadduct 66 (4.1:1.0:2.2, 50%). The synthetic interest resides in the smooth conversion of a readily accessible tetralin or indan, containing a but-3-enyloxy group at C(1), to tricyclo[5.4.1.0^{4,12}]dodecane and tricyclo[5.3.1.0^{4,11}]undecane systems, respectively.

A study of 1-substituted indans demonstrated that the chemoselectivity as well as the regioselectivity is primarily controlled by donor substituents on the indan moiety.[19] Thus, the presence of a methoxy group at C(7), such as in 67 and 68, led to photoproducts 69–70, 71–72, and 73–74, respectively (ratio 69:71:73 of 4–5: 3–4:1, 45%; ratio 70:72:74 of 3.5:1.5:1, 47%) (eq 12).


$$(12)$$
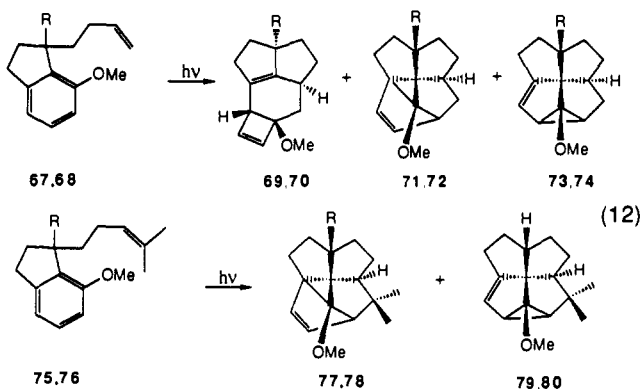
67,69, 71,73, 75,77, 79 : R = OH
68,70, 72,74, 76,78, 80 : R = H

The formation of ortho cycloadducts could be prevented by introduction of methyl groups at the terminal C-atom of the double bond. Irradiation of 75 gave 77, albeit in low yield, as the exclusive product (compound 79 not detected) arising from an initial meta cycloaddition at

C(6) and C(7a). When **76** was irradiated, a mixture of **78** and **80** was obtained.

In the absence of a methoxy group, the meta photocycloaddition occurred across C(4) and C(7a), as evidenced by the formation of compounds **84–86** and **87–89** from the respective substrates **81–83** (ratio 84:87 of 1:2, 65%; ratio 85:88 of 1:1.2, 52%; ratio 86:89 of 1:2.5, 42%) (eq 13). Thermolysis of **74** (toluene, 240

$$81,84,87 : R^1 = R^2 = H$$
$$82,85,88 : R^1 = H; R^2 = Me$$
$$83,86,89 : R^1 = Me; R^2 = H$$
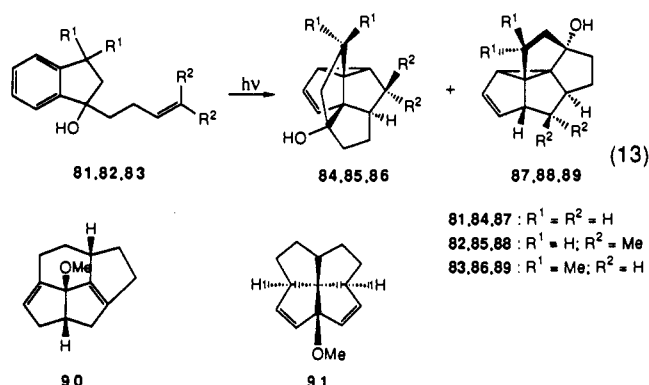
°C) led to a single product **90**. The [5.5.5.5]fenestrane **91** was not detected.[19]

Intermolecular meta photocycloadditions offer less control over selectivity compared to the intramolecular process. Photolysis of indan **92** in the presence of vinyl acetate (**93**) provided a convenient route to the endo cycloadduct **94**. Solvolysis led to the alcohol **95**, from which the dimethyl analogue **96** was derived. Rearrangement gave the tricyclic ketone **97**, possessing the ring system of quadrone (eq 14).[20]
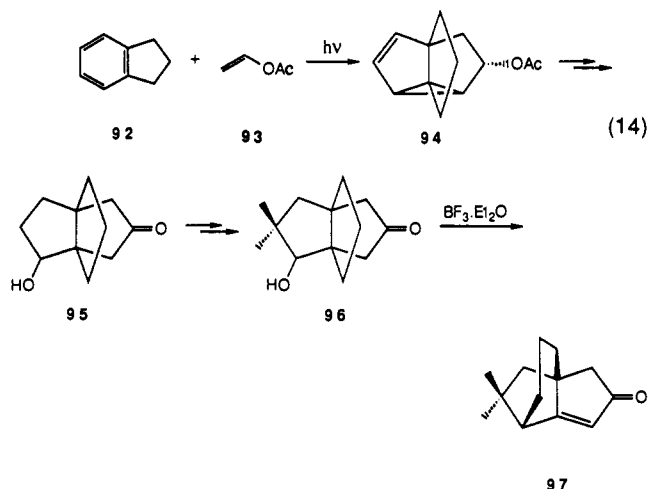
In contrast to the success of meta photocycloadditions to benzenes, polynuclear arenes are in general reluctant to coupling with alkenes. An exception is the reaction between anthracene and *cis*-cyclooctene.[3b] Noteworthy is the fact that the great synthetic potential of meta photocycloadditions involving heterocyclic aromatic compounds has not been exploited yet.

B. Arene–Alkene Ortho Photocycloadditions

When naphthalenes are irradiated, photocycloaddition to the 1,2-positions is a general reaction.[2h,4,21] Photocycloaddition of 2-naphthol (**98**) with acrylonitrile (**99**) afforded the head-to-head cyclobutanol derivative **100** (36%), which underwent retro-aldol reaction in

basic medium to 1-(2-cyanoethyl)-2-naphthol (**101**) (76%) (eq 15).[22] Irradiation of **100** in benzene in the
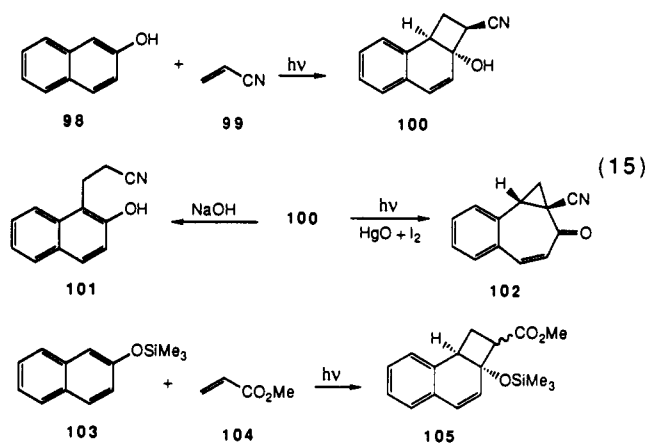
presence of mercuric oxide and iodine led to ring enlargement (**102**).[23] Remarkably, the photocycloaddition of 2-naphthol and methyl acrylate did not proceed, while **105** was obtained as a mixture of endo and exo adducts (57%) from the reaction of 2-naphthyl trimethylsilyl ether (**103**) and methyl acrylate (**104**) (eq 15).[24]

Methyl 1-naphthoate (**106**) was successfully reacted with acetylacetone (**107**) to the β-hydroxy ketone derivative **108** (eq 16). Retro-aldol reaction readily
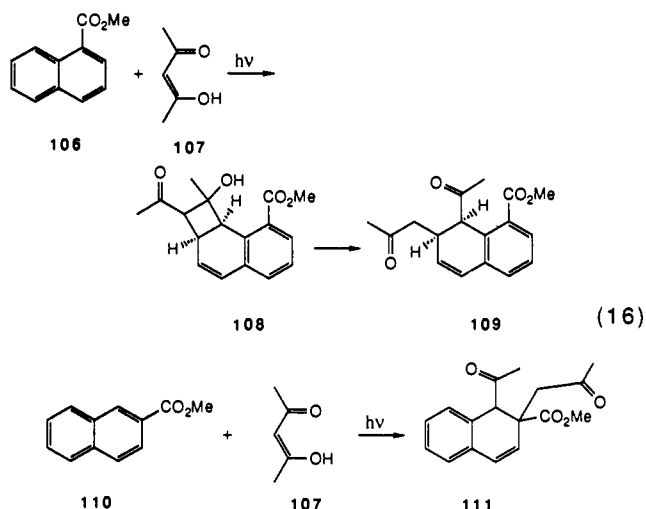

occurred whereby diketone **109** was formed. However, the similar reaction involving methyl 2-naphthoate (**110**) proceeded regioselectively at positions 1 and 2 to give diketone **111** as the major adduct (eq 16).[25]

Photocycloadditions of a number of phenols,[26] in particular fluorinated derivatives,[27] with a variety of alkenes have been investigated to probe substituent effects on the regio- and stereoselectivity. Ortho addition of substituted phenols, e.g. **112** and benzonitrile (**113**), followed by rearrangement of the cycloadduct **114**, proved to be a facile access to azacyclooctatetraenes, such as **115** (eq 17), albeit in low yields (15–20%).[28] Improvements were realized by using para-substituted benzonitriles and a polar solvent (acetonitrile).[29] It was furthermore possible to apply the photocycloaddition-rearrangement process to naphthonitriles and phenols.[30]

Intramolecular ortho photocycloadditions have occasionally been reported, e.g., conversion of enamide

(17)
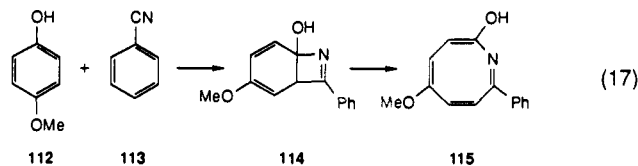
116 to the tricyclic amide 117 (95%)[31] and rearrangement of meta-substituted 4-(but-3-enyloxy)acetophenones to 4-acetyl-11-oxatricyclo[6.3.0^{1,6}]undeca-2,4-dienes.[32] Wagner has shown that the nature of the meta substituent imparts complete regioselectivity to the reaction. Thus, compound 118 gave exclusive cycloaddition at the unsubstituted meta carbon atom (photoproduct 119) (eq 18). When the methoxy group was

(18)
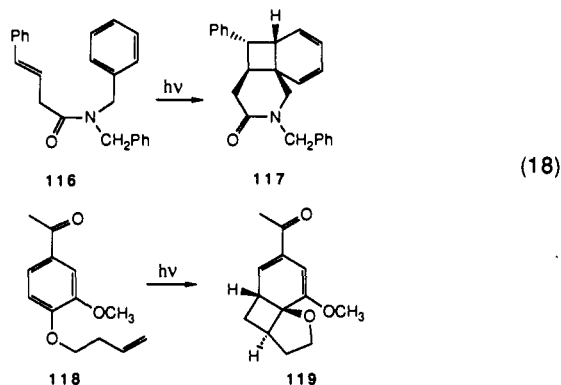
replaced by a methyl or a cyano group, cycloaddition took place at the meta carbon atom bearing the substituent.

Ortho reaction is almost exclusively observed in arene photocycloadditions involving alkynes. The initial cycloadducts rearrange directly to cyclooctatetraenes. Irradiation of a mixture of benzene (1) and dimethyl acetylenedicarboxylate (120) led via the ortho cycloadduct 121 to the cyclooctatetraene 122 (eq 19).[7a]

(19)

TMS = trimethylsilyl
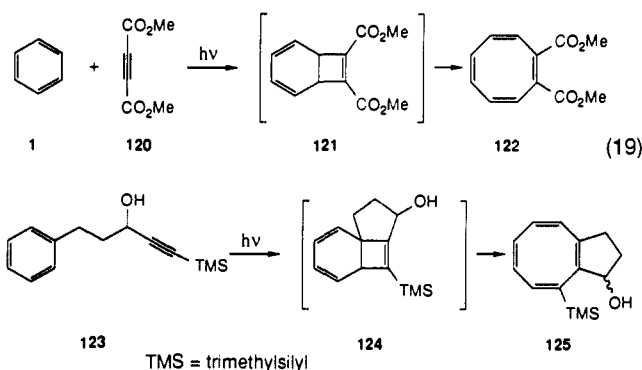
The intramolecular variants of this reaction have not proved to be efficient, yet placement of trialkylstannyl or trialkylsilyl groups on the alkyne, such as in 123, gave efficient formation of cyclooctatetraene 125 via the intermediate tricyclic 124 (eq 19).[33]

C. Arene–Alkene Para Photocycloadditions

Para photocycloadditions have been found to occur primarily when arenes are photolyzed in the presence of dienes and allenes.[34] Also, irradiation of enol ether 126 furnished the bicyclic ether 127 (eq 20).[35]

(20)
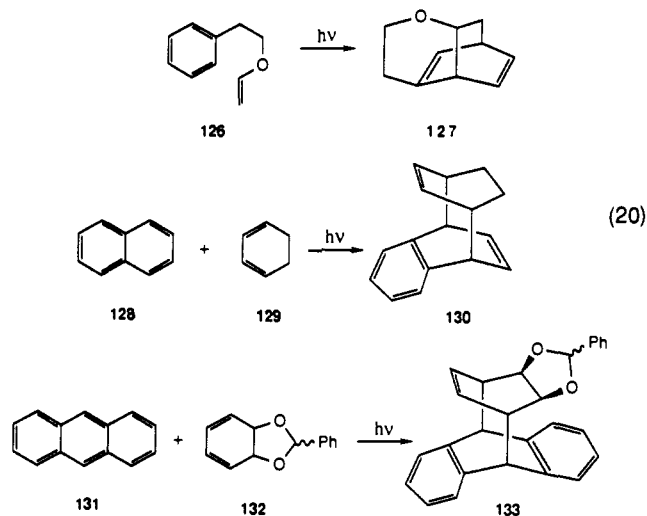
It appears furthermore that para photocycloaddition is a common pathway in the photochemistry of extended aromatic systems, such as naphthalene and anthracene.[36] Cyclohexa-1,3-diene (129) added to naphthalene (128) in the para mode with formation of the tetracyclic compound 130, while cycloaddition of anthracene (131) and acetal 132 led to adduct 133 (eq 20). These photoadducts enable construction of hexaprismanes.

III. Di-π-methane-Type Rearrangements

A. Di-π-methane Rearrangements
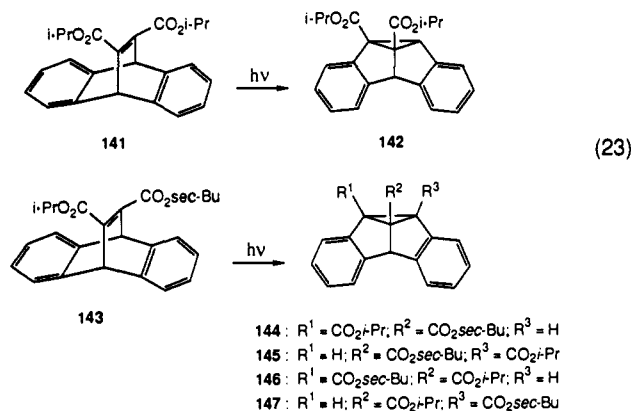
The mechanistic features of the di-π-methane (DPM) rearrangement, called the Zimmerman rearrangement after the principal researcher of the process, have thoroughly been studied and are well-established now.[37] The intriguing transformation of a sp^3-hybridized carbon atom substituted with two π bonds (di-π-methane system) to an ethenylcyclopropane is not well-documented in organic synthesis. An exception is the total synthesis of (±)-desoxytaylorione (136), which involved the DPM rearrangement of the 2-substituted cyclopent-2-en-1-one 134 to the bicyclic compound 135 (eq 21).[38]

(21)
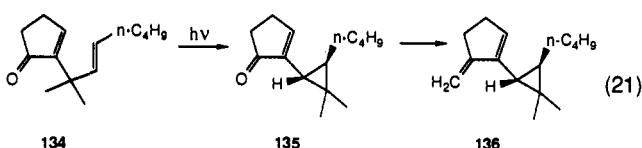
Of interest is the assembly of the highly strained compound 140 via a tandem photo-Diels–Alder addition of diene 137 and dienophile 138 and DPM rearrangement of the resulting cycloadduct 139 (eq 22).[39]


(22)
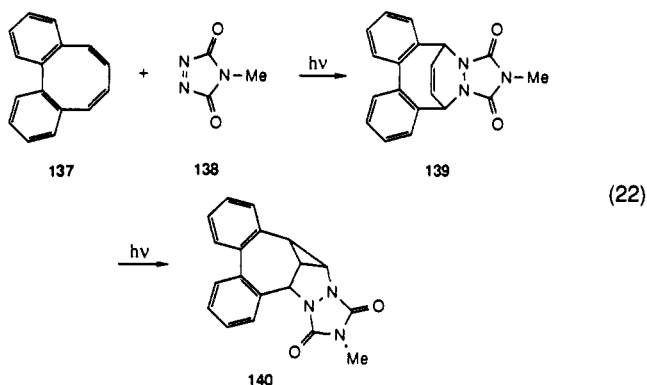
Much attention has been devoted to DPM rearrangements in the solid state.[40] Photolysis of chiral single crystals of the diisopropyl ester **141** led to the optically pure dibenzosemibullvalene **142** (eq 23).[41] The

(23)

144 : $R^1 = CO_2i\text{-}Pr; R^2 = CO_2sec\text{-}Bu; R^3 = H$
145 : $R^1 = H; R^2 = CO_2sec\text{-}Bu; R^3 = CO_2i\text{-}Pr$
146 : $R^1 = CO_2sec\text{-}Bu; R^2 = CO_2i\text{-}Pr; R^3 = H$
147 : $R^1 = H; R^2 = CO_2i\text{-}Pr; R^3 = CO_2sec\text{-}Bu$

racemic mixed diester **143** underwent DPM rearrangement to give four diastereomeric reaction products **144–147**, both in solution and in the solid state.[42] Whereas no chiral discrimination occurred in solution for both racemic and optically active **143**, in the solid state, dibenzosemibullvalene **144** (80% ee) prevailed (eq 23).

It was shown for other dibenzobarrelene diesters that the nature of the ester groups controls the diastereoselectivity.[43] In optically active esters, e.g., derived from (1R,2S,5R)-(-)-menthol, the asymmetric induction was furthermore dependent on the location of the chiral handle.[44] These and many other examples show that solid-state DPM rearrangements can provide suitable synthons for the asymmetric synthesis of particular polycyclic systems.

Deviating reaction pathways have also been noted. While **148** and **149** gave the expected DPM rearrangement in solution, a [2 + 2] photocycloaddition reaction was observed in the solid state, leading to adducts **150** and **151**, respectively (eq 24).[45]

(24)

148,150 : R = Ph
149,151 : R = i-Pr
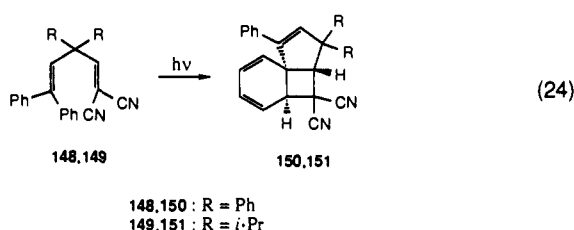
B. Oxadi-π-methane Rearrangements

Triplet-state activation of β,γ-unsaturated carbonyl compounds triggers a 1,2-acyl shift with formation of an acylcyclopropane. This oxadi-π-methane (ODPM) rearrangement competes in the appropriate conditions with a 1,3-acyl shift occurring from the lowest excited singlet state.[46] Thus, the reaction route can judiciously be selected by irradiating either directly or under sensitized conditions.

A very useful ODPM rearrangement is the conversion of bicyclo[2.2.2]oct-5-en-2-one (**152**) to tricyclo[3.3.0.0²,⁸]-octan-3-one (**153**) (eq 25).[47] This key reaction opened new avenues to the synthesis of assemblies of fused five-membered rings as elegantly demonstrated for a number of natural products by Demuth and Schaffner.[48]

(25)
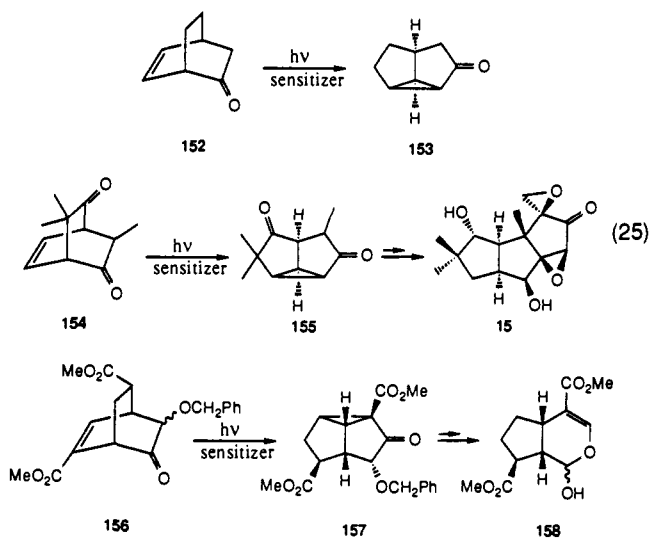
The triquinane (±)-coriolin (**15**) was synthesized via the ODPM rearrangement of **154**, leading to the tricyclic diketone **155** as the key step (eq 25).[49] The versatility of the method is illustrated by the synthesis of the iridoid (±)-forsythide aglucon dimethyl ester (**158**). The short reaction route is focused on the acetone-sensitized ODPM rearrangement of **156** to the diquinane **157** (60%) (eq 25).[50]

A different approach to the synthesis of polyquinanes addressed by Schultz involved the ODPM rearrangement of strained tricyclic ketones, as represented by the transformation of **159** to **160** (eq 26).[51]


(26)
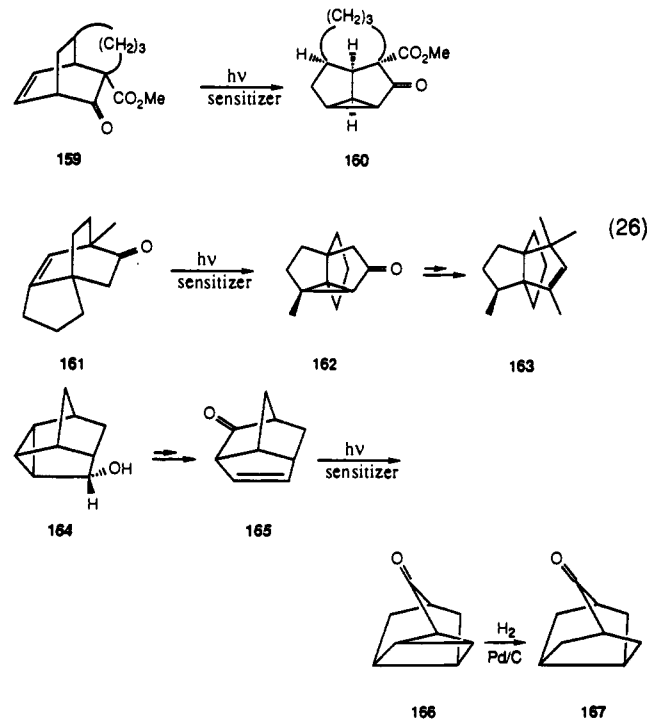
Two other ODPM rearrangements of polycyclic β,γ-unsaturated ketones are worth mentioning. (±)-Modephene (**163**) was synthesized by elaboration of the tetracyclic ketone **162**, which itself was accessible by ODPM rearrangement of **161** (50%) (eq 26).[52] The synthesis of 2,8-didehydronoradamantan-9-one (**167**) was performed starting from brend-4-en-2-one (**164**)

via ODPM rearrangement of compound 165 (25%) and reductive cleavage of the cyclopropane ring in 166 (eq 26).[53]

The enantiospecific ODPM transformation of bridged β,γ-unsaturated ketones has paved the way to a ready access to enantiomeric target compounds.[48c]

C. Azadi-π-methane Rearrangements

Horspool and colleagues have studied in great detail the effect of substituents with respect to the formation of cyclopropylimines from α,β-unsaturated imines or azadi-π-methane (ADPM) systems.[54] It was found that electron-withdrawing groups located on the nitrogen atom have a beneficial influence on the ADPM rearrangement. Thus, the acetoxy-substituted imine 168 afforded compound 169 in the presence of suitable sensitizers.[55] The similar ADPM system 170 led to the cyclopropylimine 171, while the compound lacking the methyl group only gave cis–trans isomerization thereby indicating the importance of the functionality pattern (eq 27).[56]

(27)
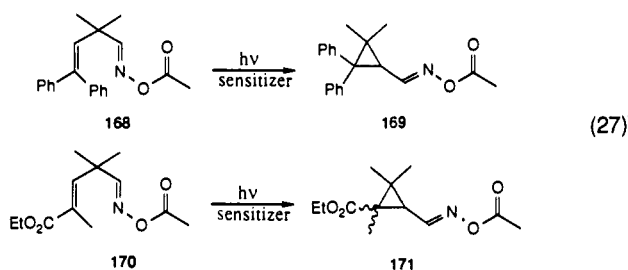
The ADPM rearrangement of cyclopropyl derivatives of β,γ-unsaturated aldehydes can be applied to obtain intermediates for the synthesis of pyrethroids.[57]

IV. Photocyclizations

The formation of polycyclic systems by intramolecular photocyclization is a common process for several types of aromatic compounds. A variety of synthetic pathways are based on this reaction as a key step.

A. Intramolecular Coupling of Arenes

Numerous examples of Ar—X—Ar (X = —CH= CH—, —O—, —S—, —NR—, —C(O)NR—) systems are known to undergo intramolecular coupling of the arenes. The cyclic photoproducts are readily converted to polynuclear aromatic compounds by oxidation[58] or elimination, as exemplified for the common stilbene–phenanthrene type conversion (eq 28). Photoinduced trans to cis isomerization in 172 and 173 initiates electrocyclization, while aromatization to phenanthrene (176) occurs readily either by oxidation of 174 or by methanol elimination in 175.

Much attention has been given to regioselectivity control. The photocyclization of the stilbene derivative 177 in tert-butyl alcohol containing a catalytic amount of sulfuric acid gave preferential formation of 178, which led via elimination to the 2-substituted phenanthrene 179 (74%) (eq 28).[59] Usually, oxidative photocyclization of meta-substituted stilbenes furnishes approximately equal mixtures of 2-substituted and 4-substituted phenanthrenes.

(28)

172,174 : R = H
173,175 : R = OMe
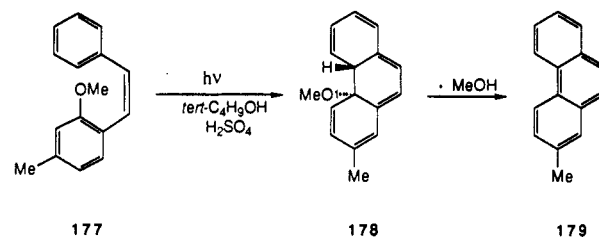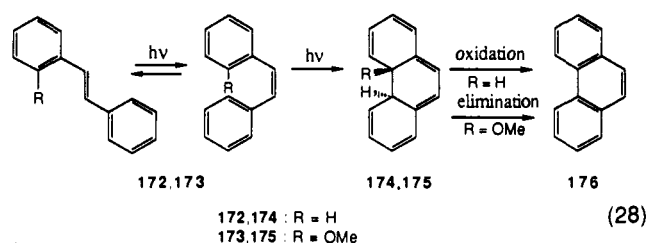
The effect of suitably positioned methoxy groups has also been exploited in the double photocyclization of 180–182. Thus, the dimethoxylated derivative 180 led exclusively to 183 (49%). The influence of methoxy groups on the central benzene unit is particularly striking, as 181 afforded a mixture of 185 and 184 (97:3; 35%), while the polycyclic aromatic quinone 186 was the sole photoproduct obtained from 182 (34%) (eq 29).[60]

(29)

180,183 : R¹ = R² = R⁴ = H; R³ = OMe
181,184 : R¹ = R³ = R⁴ = OMe; R² = H
182 : R¹ = H; R² = R³ = R⁴ = OMe
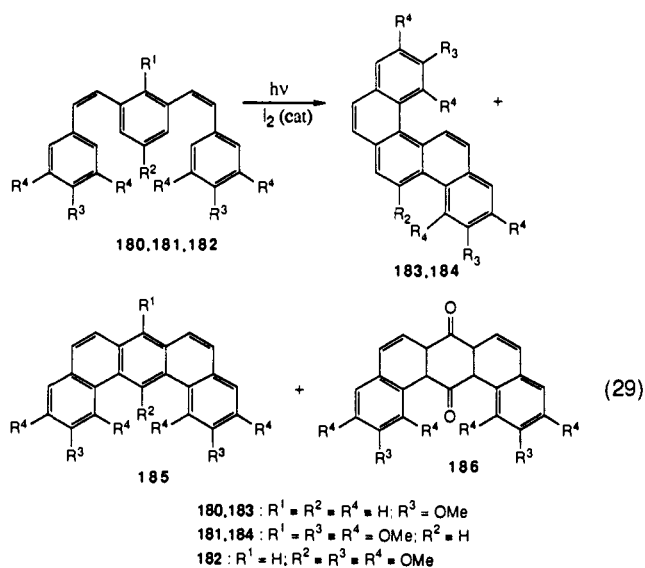
The abovementioned examples illustrate that stilbene-type molecules have been used as precursors for a variety of polycyclic aromatic hydrocarbons. In many cases the cyclization followed divergent reaction pathways depending on the particular reaction conditions. Thus, dihydrohexahelicene 188, formed by photocyclization of 187, could either be isomerized via hydrogen shifts or oxidized to hexahelicene (189) (eq 30).[61]


(30)
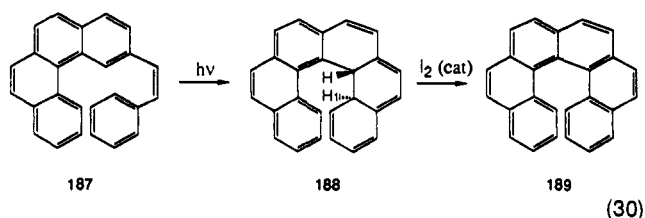
1,4-Phenanthrenequinones, e.g., **191**, have been synthesized starting from suitably functionalized stilbenes, e.g., **190** (eq 31).[62] A useful variant for the synthesis of


(31)
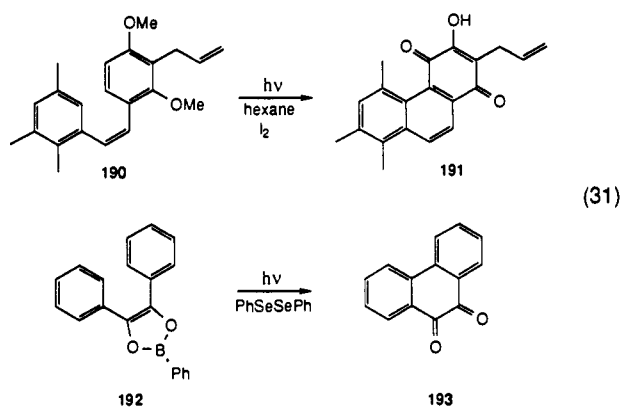
9,10-phenanthrenequinone (**193**) implied photocyclization of 2,4,5-triphenyl-1,3-dioxoborole (**192**) in the presence of diphenyldiselenide (54%) (eq 31).[63]

The [2.2]paracyclophane-containing stilbene **194** has been cyclized to the bridged phenanthrene **195** (46%), which may be considered as a model for the investigation of electronic interactions between orthogonal π-systems (eq 32).[64]

(32)
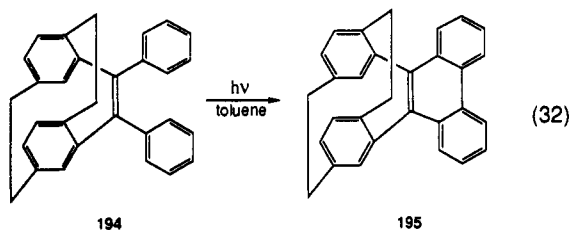
Azastilbenes, such as **196** and **197**, failed to undergo photocyclization under the usual conditions. However, addition of sulfuric acid or Lewis acids dramatically promoted the formation of heterocyclic aromatic compounds, such as **198** (42%) or **199** (40%) (eq 33).[65]

(33)

196,198 : R = Me; X = CH
197,199 : R = Me; X = N
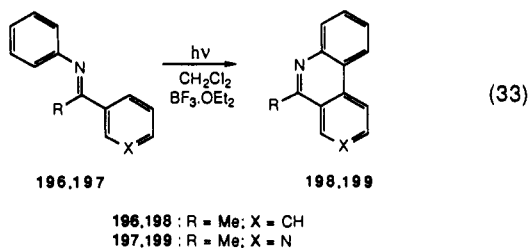
An interesting extension of the stilbene oxidative photocyclization method led to azonia derivatives of polycyclic aromatic hydrocarbons. Examples are the azonia derivatives of hexahelicene **201** (from **200**)[66] and of the polycyclic aromatic hydrocarbon **203** (from **202**)[67] as well as the pyrrolophenanthridizinium salt **205** (from **204**) (eq 34).[68]

B. Photocyclodehydrohalogenation

Intramolecular photocyclization of aromatic compounds involving the overall elimination of hydrogen halide has been applied in many studies.[69] The scope of the photocyclodehydrohalogenation is quite broad

(34)
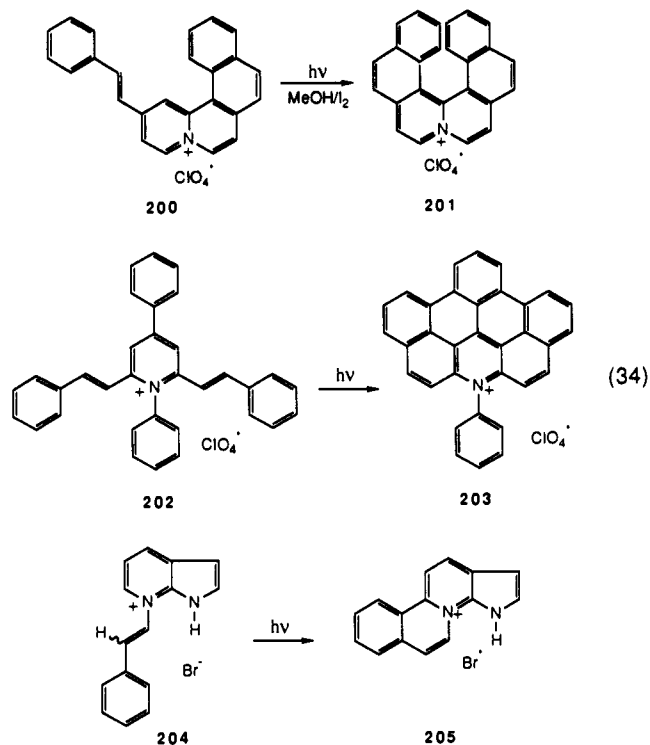
since the arenes may be heterocyclic and the two-carbon unit between the reacting arenes may be replaced by other atoms belonging to a cyclic system.

The great potential in the synthesis of novel heterocycles has frequently been demonstrated.[70] Tetrahydroisoquinolines have been converted readily to naturally occurring aporphines, such as (±)-bulbocapnine (**207**) (from **206**) and (±)-cassythicine (**209**) (from **208**) (eq 35).[71]


(35)
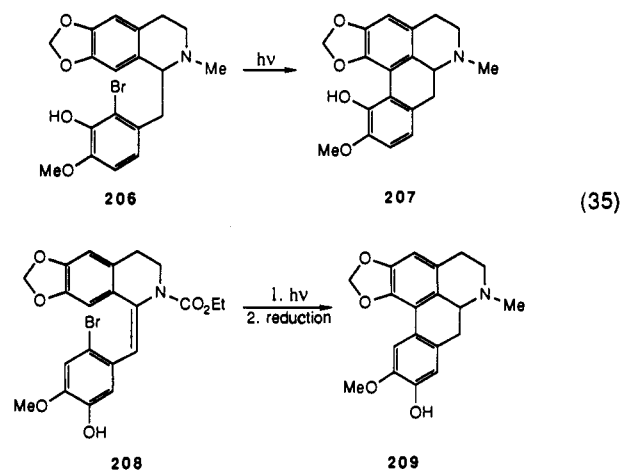
A wide variety of halogen-substituted heterocycles are prone to undergo photocyclodehydrohalogenation. Examples are the photolysis of the triazolone **210** to **211**,[72] while the pyridinium salt **212** was cyclized to **213** by formation of a five-membered ring (eq 36).[73]

Photocyclodehydrohalogenations often occur in high yield and with marked regioselectivity.[74] Thus, conversion of **214** in benzene containing triethylamine proceeded solely to the pentacyclic **215** (83%) (eq 37).[75] It should be added that, in contrast to known methods,[76] the photocyclization route to benzo[c]acridine derivatives is both efficient and versatile.[77]

(36)

(37)
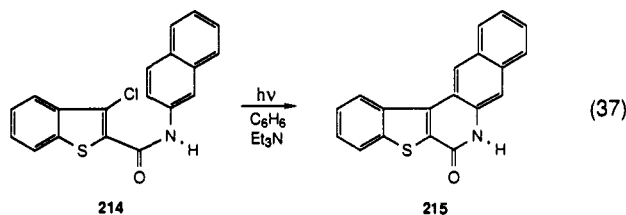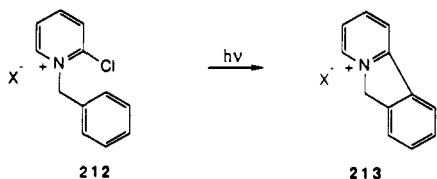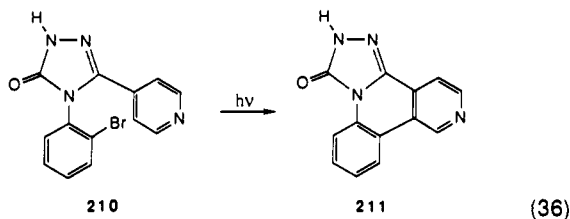
Variants involving sulfur-containing compounds present new opportunities for the preparation of benzothiazoles, such as **217** (from **216**),[78] and indoloquinolizines, such as **219** (from **218**) (eq 38).[79]

(38)
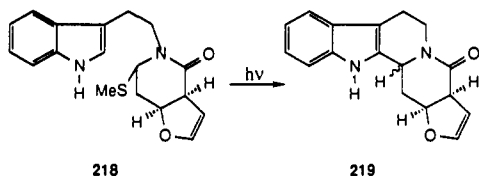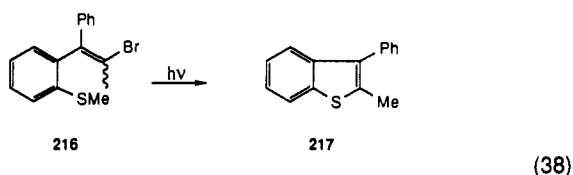
Photocyclodehydrohalogenations in molecules possessing aliphatic halogens have been reported occasionally. The chlorine-containing indole **220** gave azepinoindole **221** (48%) on irradiation in the presence of sodium acetate (eq 39).[80] Similar reactions were


(39)
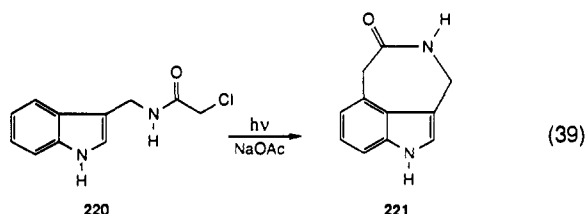
observed for geminal dichloro and trichloro derivatives.[81]

C. Photocyclization of Arenes and Alkenes

The photocyclizations of Ar—X—CH=CH₂ systems (X = heteroatom, carbonyl group, amide group, alkene) or suitable variants are analogous to the corresponding diaryl compounds (see section IV.A). The photocyclization of arenes and alkenes is a conceptually

interesting key reaction in the construction of polycyclic molecules.[82]

If hydrogen shifts occur in the intermediates to give stable products, the overall reaction is nonoxidative. In particular, cyclizations of enamides to tetrahydroisoquinolines have been studied thoroughly. Irradiation of the simple enamide **222** led via intermediate **223** to the lactam **224** (eq 40).[83]

(40)
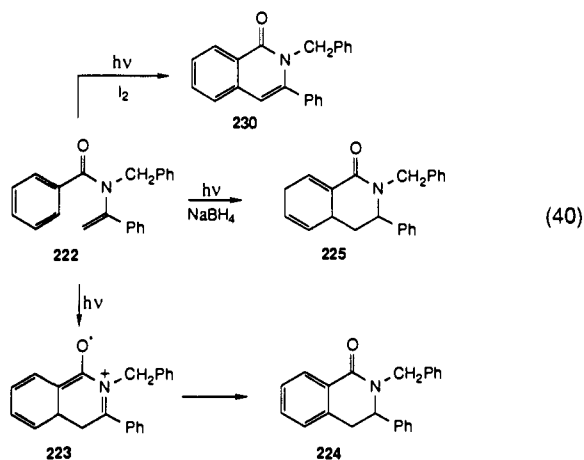
Reductive photocyclization of enamides has gained widespread acceptance as it enables straightforward assembly of a variety of heterocyclic compounds. Thus, enamide **222** may under reductive conditions (acetonitrile/methanol (9:1), sodium borohydride) be transformed to the versatile diene synthon **225** (eq 40).[84]

The same conditions were used in connection with the synthesis of (±)-yohimbine and derivatives. The key intermediate **227**, obtained from enamide **226** (90%) (eq 41),[85] was subsequently elaborated to (±)-agrocla-

(41)

MPS = *p*-methoxyphenylsulfonyl
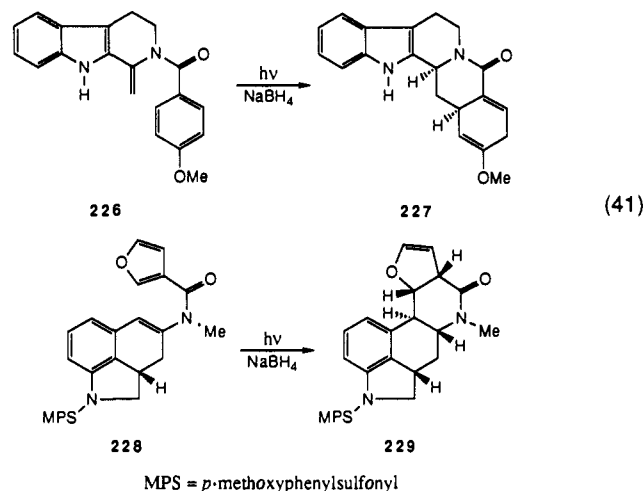
vine, (±)-fumigaclavine B, and (±)-lysergene.[85c]

Among the many alkaloids that recently were accessed by this technique are heteroyohimbine alkaloids,[85a] the corynanthe alkaloids corynantheline, hirsuteine, and isositsirikine,[86] ergot alkaloids,[87] (±)-deserpidine,[88] *B*-homo-5-thiaprotoberberines,[89] (±)-quinine, and (±)-ajmalicine.[90] The versatility of the procedure is nicely illustrated by the photogeneration of **229** (53%) by reductive photocyclization of the enamide **228** (eq 41).

Few photocyclizations of enamides under oxidative conditions, i.e., irradiation in the presence of an oxidant such as iodine, have been reported. The reaction may

be regarded as a simple transformation of an acyclic enamide (222) to the corresponding oxidized cyclic enamide 230 (> 90%) (eq 40).[83]

A different approach to the construction of polycyclic systems involves electron-transfer processes. In this connection the photochemistry of phthalimides has been extensively investigated.[91] It has been shown that photochemical electron transfer (PET) from donor partners, either inter- or intramolecularly, to phthalimide as electron acceptor is a single decisive step in product formation.[92] Photocyclization of phthalimide derivatives has been applied to the synthesis of a number of natural products, the berberine alkaloid chilinene (232) being a representative example (seven steps from phthalimide 231, 17.7% overall) (eq 42).[93]

231   232

(42)

233   234   235

E = electrofugal group
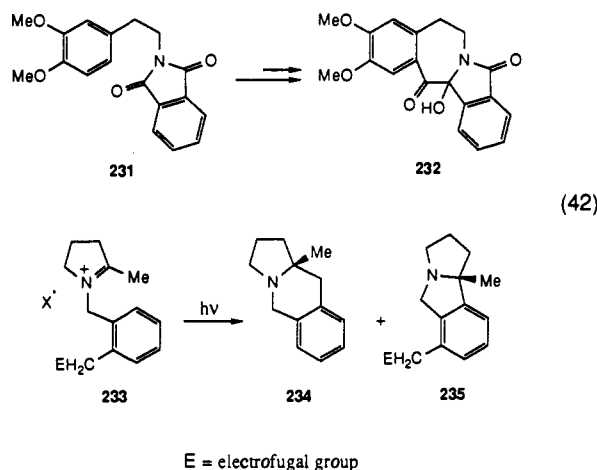
Single electron transfer (SET) of iminium salts has been elaborated by Mariano.[94] Depending on structural factors and reaction conditions, SET photocyclization of pyrrolinium salt 233 afforded compounds 234 and 235 in varying ratios (eq 42).

V. Hydrogen Abstractions

An excited carbonyl group can undergo a number of competitive reactions as many detailed studies have revealed.[95] Hydrogen abstraction, particularly the intramolecular version, is a very valuable process for the obtention of polycyclic molecules.[96] The present discussion will therefore be limited to intramolecular hydrogen abstractions.

It is now accepted that hydrogen abstraction in nonpolar solvents occurs from the (n,π^*) triplet state of the carbonyl group. The hydrogen atom may be delivered intermolecularly by a suitable donor molecule, or it may be abstracted intramolecularly from a CH unit which is spatially close to the excited carbonyl group.[97] The preferred reaction mode obviously is the abstraction of a γ-hydrogen atom, possibly followed by fragmentation (Norrish type II process). Weiss, Eaton, Ramamurthy, and others have investigated special features of this reaction in ordered systems.[98]

A representative example of photochemical hydrogen abstraction is the transformation of the norbornyl ketone 236 to the 1,4-biradical 237, which cyclized to cyclobutanol 238 (eq 43).[99]

Readily accessible norbornan-2-ones may be converted to cyclopentenes containing a γ,δ-unsaturated aldehyde functionality via regioselective Norrish type I photofragmentation of the C(1)–C(2) bond, followed

236   237   238   (43)
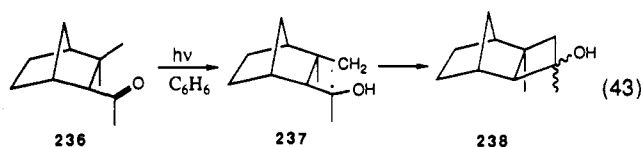
by hydrogen transfer from C(7). This efficient conversion (yields usually >60%) provides a versatile clue for the synthesis of various cyclopentanoids. By a proper choice of the alkene utilized in the Diels–Alder type assembly of the norbornan-2-one skeleton, the resulting cyclopentene may be fully functionalized whereby the configuration at three contiguous stereocenters is established. This feature is nicely demonstrated by the conversion of the norbornan-2-ones 42 and 43 to the γ,δ-unsaturated aldehydes 44 and 45, which cyclized spontaneously to the lactols 46 and 47, respectively (eq 8). The formation of the cyclopentene double bond triggered a meta photocycloaddition, as discussed before (see section II.A).

The iridoids are particularly suitable target molecules for this photochemical approach.[100] The present route constitutes the first synthesis of (±)-brasoside O-acetyl aglucon (242), an iridoid lactone derivative.[101] Norrish type I reaction of 239 followed by hydrogen abstraction from the one-carbon bridge and reduction in situ afforded the diquinane 240 (76%). Manipulation of 240 by straightforward reactions furnished the intermediate diol 241, which could readily be converted to lactone 242 (eq 44). Slight modifications of the synthetic sequence were used to synthesize the O-methyl aglucons of verbenaline (243) and hastatoside (244), respectively (eq 44).[102]

239   240   241

TBS = tert-butyldimethylsilyl

242   243   244   (44)

245,246   247,248   245,247 : Y = O
                              246,248 : Y = OMe
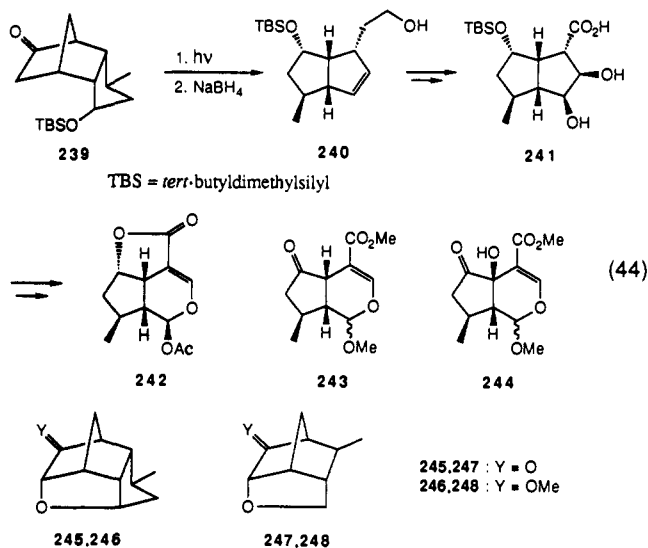
Interestingly, the α-alkoxynorbornan-2-one derivatives 245 and 247 were photostable. Prolonged irradiation in methanol only afforded the corresponding acetals 246 and 248 (eq 44).[103]

If no γ-hydrogen is available, abstraction of remote hydrogen atoms is feasible. This occurs also when special conformational effects and particular geometries guide the reactivity in cyclic systems. Several δ-hydrogen abstractions by cyclopentanone units are key steps in the synthesis of dodecahedrane,[104] while the same strategy was pursued in the synthesis of punctain.[105] Another example is the construction of the aflatoxin skeleton, which was based on the δ-hydrogen

abstraction in 249 leading to benzfuranol 250 (eq 45).[106]

249   250

MOM = methoxymethyl

(45)

251   252
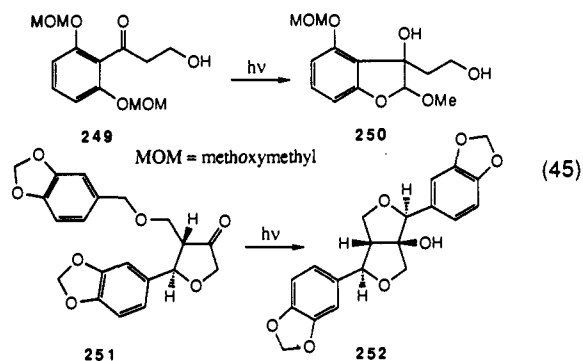
A similar application was presented in the synthesis of paulownin involving conversion of furan-3-one 251 to furan-3-ol 252 (eq 45).[107]

In ortho-substituted aromatic ketones, such as 253 and 255, similar reactions give rise to benzfuranols, e.g., 254, and indanols, e.g., 256, respectively (eq 46).[96b,108]


253   254

255   256   (46)

OMe O

257,258   259,260   +   261

257,259 : n = 1
258,260 : n = 2
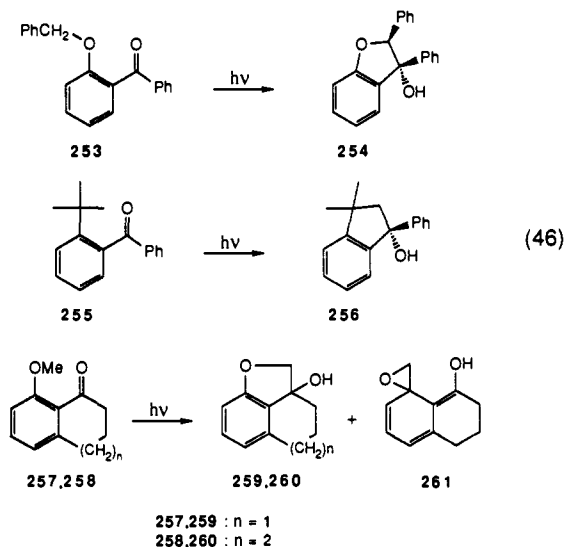
The reaction may be steered by conformational factors. Whereas the indanol 259 was the major reaction product on irradiation of the bicyclic aromatic ketone 257, compound 260 was observed as a byproduct in the reaction mixture of the tetralone 258, which mainly contained spiroenol 261 (eq 46).[109]

Of special interest is the Norrish type II reaction of pyrrolidin-2-ones. Irradiation of 262 in tert-butyl alcohol gave the strained 1-azabicyclo[3.2.0]heptan-2-one derivative 263 (50%), accompanied by its epimer 264 (34%). Acid treatment led to the functionalized azetidines 265 and 266 (eq 47).[110]

262

263   264

HCl, EtOH   (47)

265   266
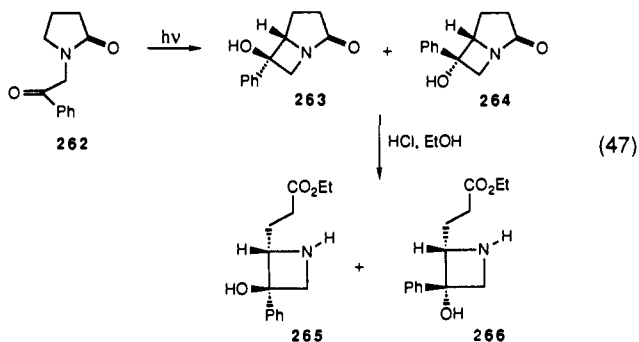
The transformation was also applied to six- and seven-membered ring substrates. Furthermore, δ- and ε-hydrogen abstractions were realized in model compounds, such as 267 and 269, giving rise to 268 and 270, respectively (eq 48).[111]

267   268

(48)

269   270
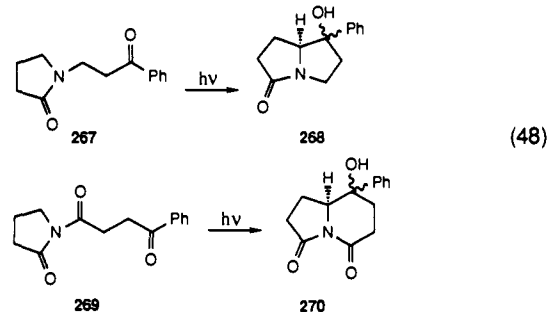
A very useful application in sugar chemistry involved the abstraction of a δ-benzylic hydrogen atom in 271 to yield an epimeric mixture of 272 and 273 with a clear preference for the less polar epimer 272 (eq 49).[112]

271

(49)

272   273
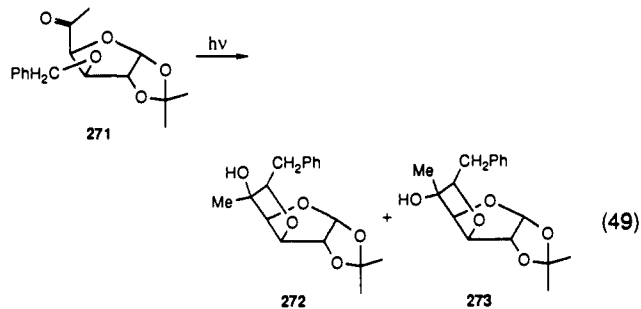
Chemoselectivity was noted in diketones in favor of benzylic γ-hydrogen abstraction. It was reported that the aromatic ketones 274 and 276 led to the benzocyclobutenols 275 and 277, respectively (eq 50), on irradiation in hexane.[113] In contrast, irradiation of the 1,3-diketone 278 and various substituted analogues in methanol afforded tetralones, such as 279 (48%) (eq 50). Dehydration gave the α-naphthol derivative 280.[114]

274   275

276

(50)

hv | hexane

277

278   279   280
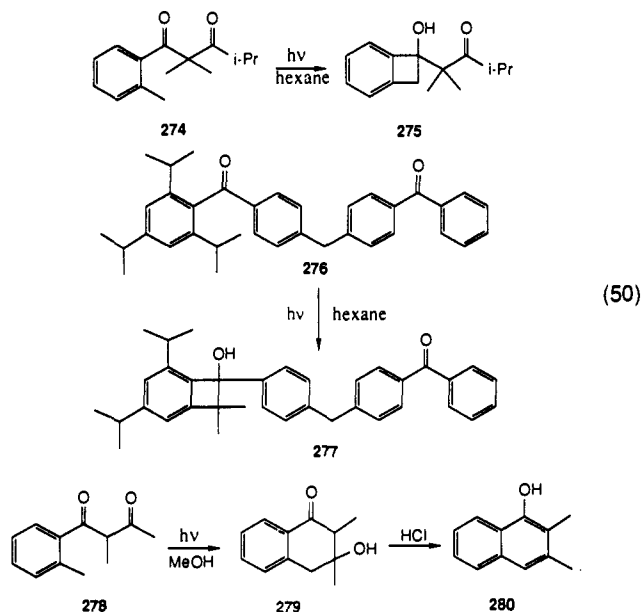
Substantial progress has been made in the photochemistry of cyclic thioimides.[115] Benzylic hydrogen abstraction by the thiocarbonyl group in N-(ω-phenylalkyl)thiophthalimides, such as **281**, furnished the epimeric thiols **283** and **284**, respectively, in varying ratios (eq 51).[116] Dithiophthalimide **282**, however, gave

281 : Y = O
282 : Y = S

(51)
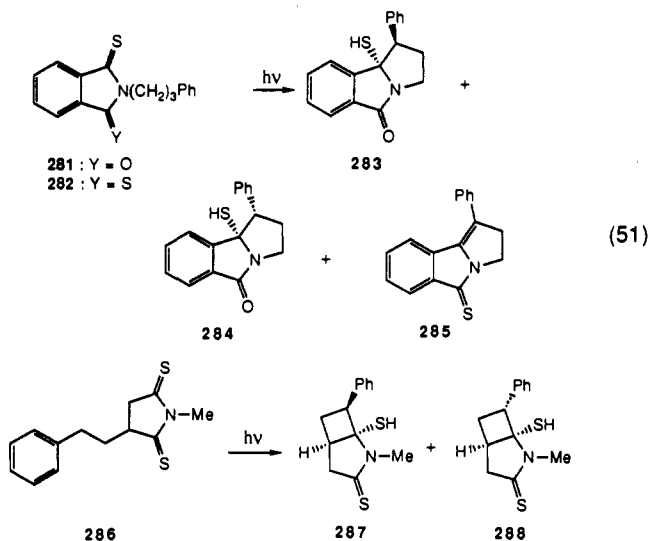
the conjugated heterocyclic compound **285** (82%) (eq 51). Similarly, irradiation of dithioglutarimide **286** led to the cyclized compounds **287** and **288** by benzylic hydrogen abstraction (> 60%) (eq 51).[117] The reaction efficiency decreased when the benzylic methylene group was not in the γ-position.

VI. [n + 2] Photocycloadditions

The present discussion of photochemical cycloadditions is restricted to systems in which one of the reagents contains a 2π-electron entity. Higher-order cycloadditions, which play a significant role in synthetic endeavors, have already been described in detail.[118]

A. [1 + 2] Photocycloadditions

An efficient methodology to affect [1 + 2] photocycloaddition involves pyrazoline formation followed by nitrogen expulsion. An intramolecular example described by Schultz deals with the conversion of cyclohexa-2,4-dien-1-one **289** to pyrazoline **290**, which was photolyzed to vinylcyclopropane **291** (eq 52).[119]

(52)
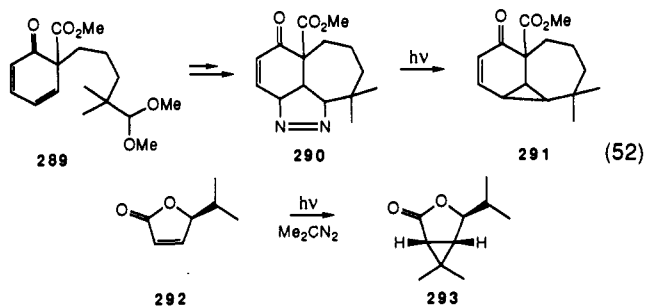
This tricyclic photoproduct was an important intermediate in the total synthesis of racemic and optically pure (−)-longifolene.

A convenient method to convert α,β-unsaturated esters to the corresponding cyclopropane derivatives

by photolysis in the presence of dimethyldiazomethane and concomitant pyrazoline decomposition was reported by Franck-Neumann.[120] Thus, transformation of the unsaturated lactone **292** to the bicyclic lactone **293** may be regarded as an overall intermolecular [1 + 2] photocycloaddition (eq 52).[121]

B. [2 + 2] Photocycloadditions

The [2 + 2] photocycloaddition between two 2π-electron-containing entities giving rise to four-membered-ring structures is by far the most successful contribution of photochemistry to organic synthesis. During the last two decades, numerous studies have focused on the mechanism as well as on the synthetic approaches to natural products based on a [2 + 2] photocycloaddition as a key step.[122] As this is particularly true for photocycloadditions to unsaturated enones, many reviews and relevant papers have been published in this area.[123] It appears that the regio- and stereoselectivity for [2 + 2] photocycloaddition reactions can be controlled very well.

It should be stressed that, in general, donor–acceptor interactions involving photochemical electron transfer (PET) and radical–ion intermediates provide important controls on the chemo-, regio-, and stereoselectivity for many reactions, including cycloadditions.[124] In particular vinyl ether-type alkenes are prone to undergo intra- and intermolecular [2 + 2] cycloadditions under PET conditions. The selectivity is often quite pronounced and mixed cycloadditions are feasible, as exemplified by the formation of the cyclobutane derivative **296** (50%) from the respective vinyl ethers **294** and **295** (eq 53).[125]

a: 1,4-dicyanobenzene

Tf = triflate

(53)
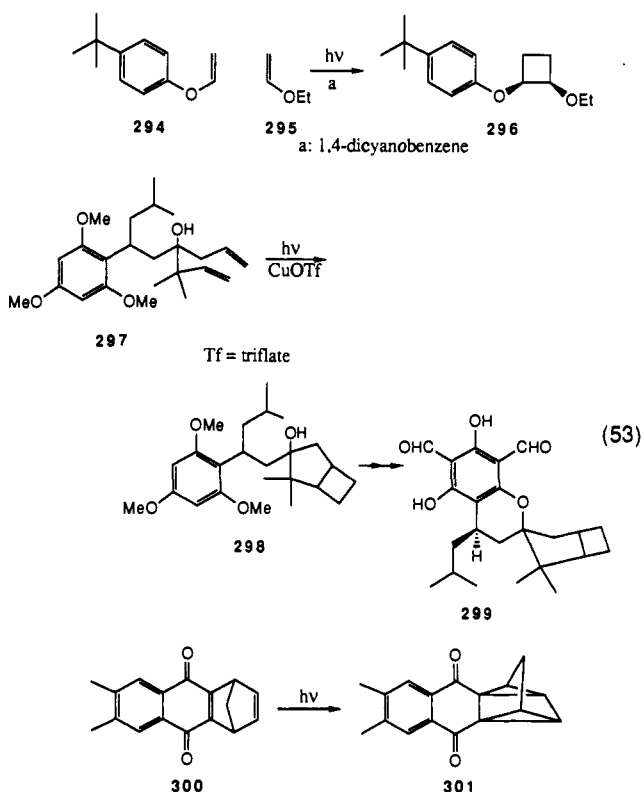
Alternatively, photocycloaddition of alkenes can be affected by copper(I) catalysis. In the synthesis of (±)-robustadial A (**299**), the transformation of diene **297** to

the cyclobutane derivative **298** (80%) in the presence of copper(I) triflate served as the key step (eq 53).[126]

The well-known conversion of norbornadienes to quadricyclane systems has been proposed for chemical energy storage.[127] A variant using visible light for activation is the quantitative isomerization of naphthoquinone **300** to quadricyclane **301** (eq 53).[128]

When the reaction is applied to molecules containing two identical or similar units, remarkable polycyclic arrays can readily be obtained. For example, the cytosinyl part in **302** gave cycloaddition to the 5-methoxyuracil moiety if the irradiation was conducted at wavelengths above 290 nm. The unstable dimer **303** led in aqueous solution to the uracil derivative **304**, which was available directly from **305**. It is of interest to note that these cycloadditions could be reversed at 254 nm (eq 54).[129]

(54)
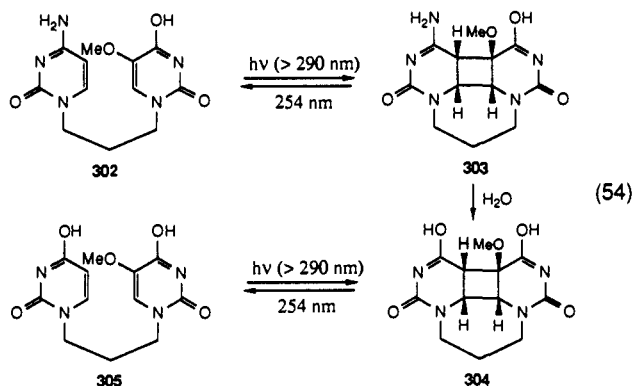
Photocyclodimerization of styrene-type systems have been developed for the synthesis of cyclophanes.[130] Irradiation of a series of α,ω-bis(p-vinylphenyl)alkanes afforded the corresponding cyclophanes, e.g., **307** derived from **306**. Subsequent Birch reduction led to cyclophane **308** (eq 55).[131] Heterocyclophanes are

(55)
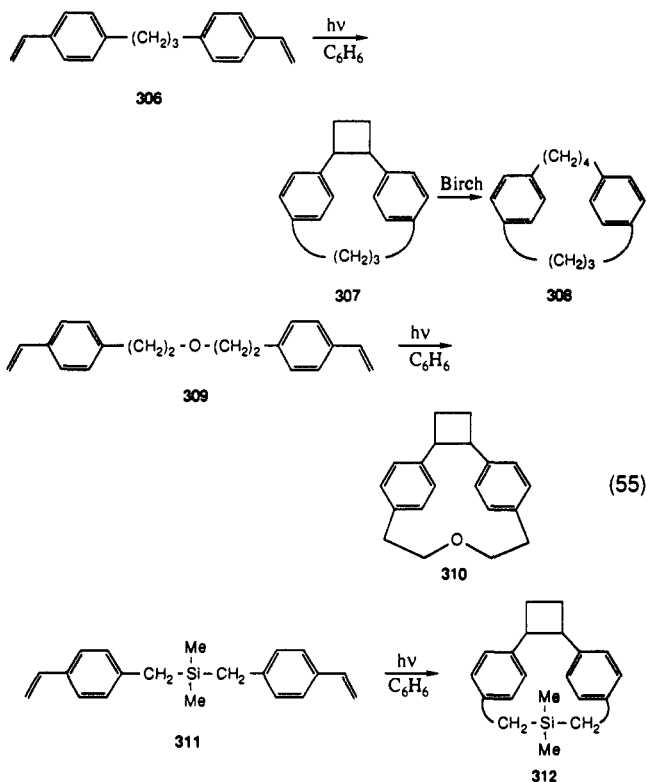
accessed by inclusion of heteroatoms in the chain linking the aromatic nuclei.[132] In this respect the highly efficient formation of photocycloadduct **310** (85%) from the stilbene-type dimer **309** is worth mentioning. Even silicon-containing analogues, such as **311**, can conveniently be cyclized in benzene to the cyclobutane derivative **312** (eq 55).[133]

The major regioisomer in intramolecular cycloadditions of substituted cyclohex-2-en-1-ones appears to be that formed by closure of the biradical intermediate in which a five-membered ring has been formed ("rule of five").[134] Examples abound in which the alkene part has been modified differently. Head-to-head cycloadducts **314, 316**, and **318** were derived from the cyclopropyl-containing cyclohex-2-en-1-one **313**,[135] the 3-substituted cyclohex-2-en-1-one **315**, and the 2-substituted cyclohex-2-en-1-one **317**, respectively (eq 56).[136]

(56)
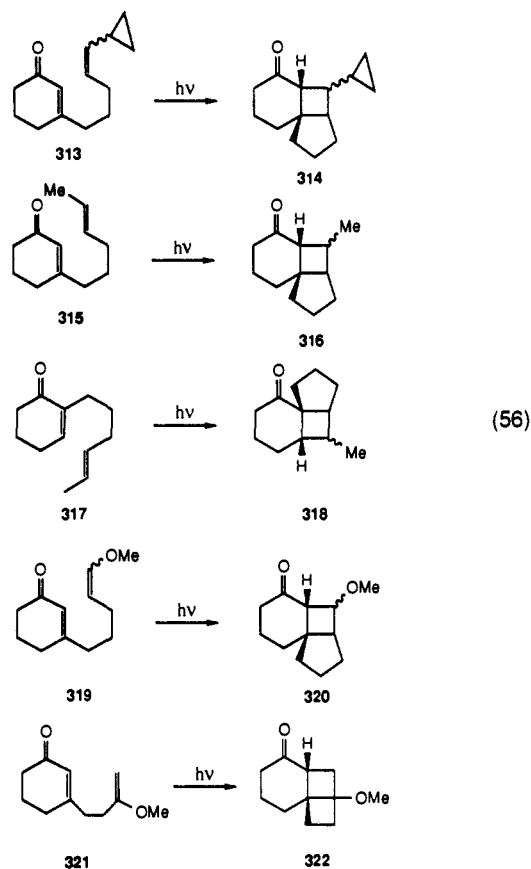
The reaction mode in cyclohex-2-en-1-ones having a vinyl ether group as second chromophore depends on the number of intervening units between the two chromophores. Thus, three methylene groups in **319** are required to give the head-to-head cycloadduct **320**. However, if only two methylene units in the connecting chain are present, head-to-head conversion of **321** to **322** was observed (eq 56).[137]

[2 + 2] photocycloadditions of cyclohexa-2,5-dien-1-ones have been examined in detail by Schultz.[138] Both **323** and **324** underwent photocyclization to **326**, preferably under sensitized conditions (64% for **323**, 46% for **324**). The reaction occurred very efficiently when the 3-methoxy substituent was absent, e.g., conversion of **325** to **327** (84%) (eq 57). Apparently, the styrene chromophore detracts from type A photoreactivity, which is observed in similar systems carrying a methoxy

(57)
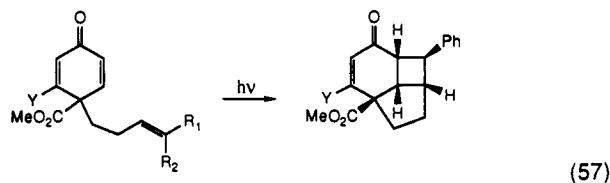
323 R$_1$ = H; R$_2$ = Ph; Y = OMe
324 R$_1$ = Ph; R$_2$ = H; Y = OMe
325 R$_1$ = H; R$_2$ = Ph; Y = H

326 Y = OMe
327 Y = H

328

329
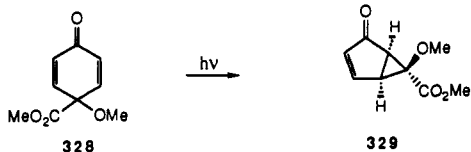
group at C(4) instead of an alkyl chain. Thus, cyclohexa-2,5-dien-1-one 328 furnished the bicyclic compound 329 with complete diastereoselectivity (81%).[139]

Interesting studies have appeared in which the double bond of an α,β-enone system as photoactive unit in intramolecular [2 + 2] photocycloadditions is incorporated in a five-membered ring. This concept was applied in the total synthesis of the marine metabolite isoamijiol (332) (eq 58).[140] Among the seven carbon-

330   331   332

333   334   335

(58)

336   337   338

339   340

341   342
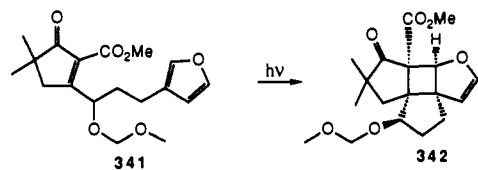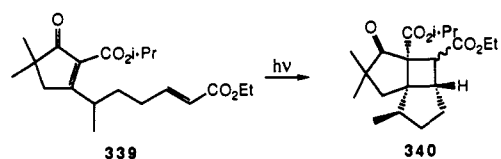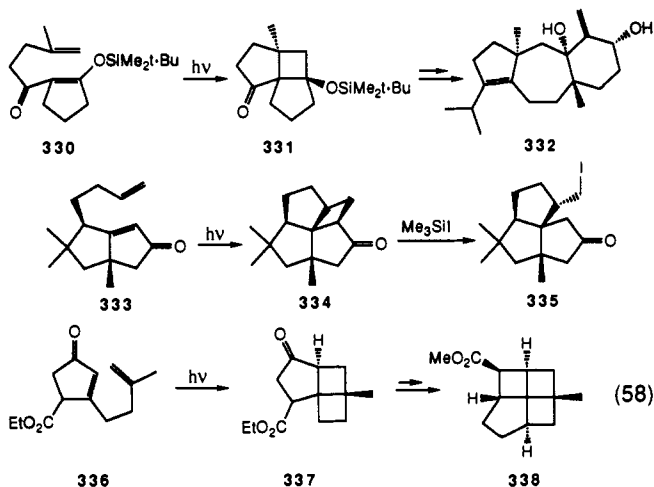
carbon bond forming reactions the formation of a single photoadduct 331 from compound 330 was prominent.[141]

Already quite elaborate cyclopent-2-en-1-one systems were utilized to form sterically congested fenestranes.[142] The triquinane silphinene (11) was synthesized by Crimmins using the intramolecular photocycloaddition of 333 to the fenestrane 334 followed by trimethylsilyl iodide-induced cyclobutane cleavage as the key steps (eq 58). Iodide 335 was further developed to 11 by straightforward manipulations.[143]

Photocycloaddition of 1,5-dienes as an approach to fenestranes was pursued by Wolff and Agosta.[144] An

appropriate combination of substituent and steric effects resulted in exclusive 1,6-cyclization as demonstrated by the intramolecular reaction of enone 336 to a single regioisomer 337 (2:1 in favor of β-carbethoxy, 84%). Further transformations yielded the [4.4.4.5]-fenestrane 338 (eq 58).

Related reactions of α-(alkoxycarbonyl)cyclopent-2-en-1-ones occurred with almost complete stereoselectivity.[145] The β-keto esters 340 (80%) and 342 (74%) were obtained from 339 and 341, respectively, on irradiation at wavelengths above 350 nm (eq 58).[146]

Intramolecular photocycloaddition of acyclic vinylogous amides, followed by retro-Mannich fragmentation, provides an entry to N-heterocycles.[147] A short synthetic route to (±)-vindorosine (346) using this method has been reported.[148] Irradiation of the substituted indole 343 led to spiroindoline 345 after retro-Mannich reaction of cycloadduct 344. Further elaboration afforded vindorosine (346) (eq 59).

343   344

(59)

345   346

R =

R' = carbobenzyloxy
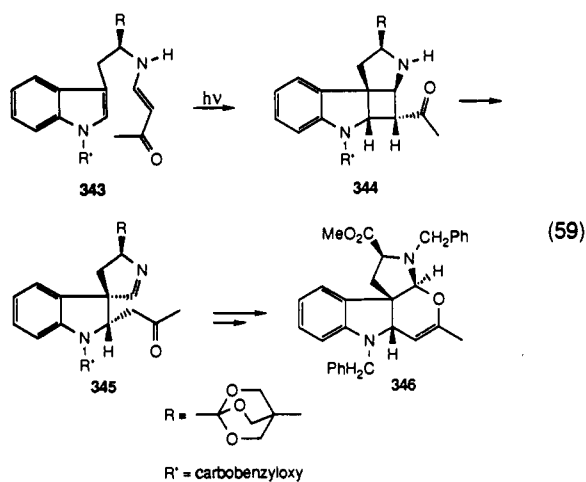
Another example is encountered in the total synthesis of (−)-perhydrohistrionicotoxin (349).[149] Intramolecular photocycloaddition of 347 led to the tetracyclic compound 348, which was further converted to 349 by straightforward reactions (eq 60).

347

(60)

348   349
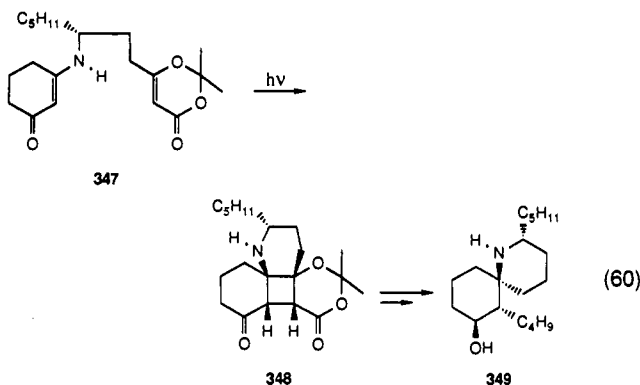
The intermolecular [2 + 2] photocycloaddition of cyclohex-2-en-1-ones to 1,2-bis(trimethylsiloxy)cyclobutene (350) proved to be a conceptually interesting and versatile method to stereocontrolled total synthesis of various sesquiterpenes and diterpenes.[150] The essential feature in this approach is based on the fact that alkene 350 serves as a latent cyclohexa-1,4-dione unit obtainable on hydrolysis of the cycloadducts and oxidative cleavage of the resulting 1,2-diol.[151] Thus,

3-cyano-2-methylcyclohex-2-en-1-one (351) gave cycloaddition to 352 (96%), which eventually led to the functionalized decalane 353 (eq 61). 1-Oxygenated

354 : R = Me
355 : R = CO₂H

356

(61)
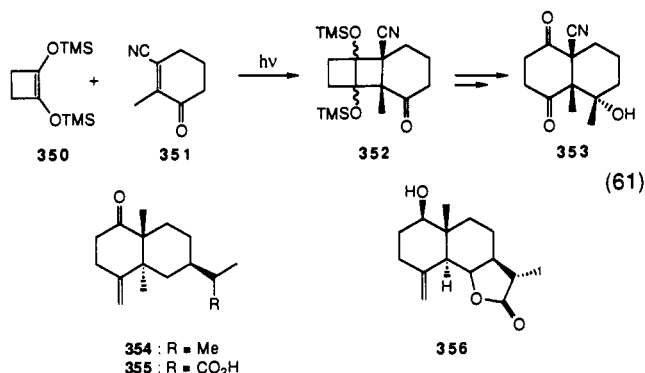
eudesmane sesquiterpenes, such as (±)-dihydrodictyopterone (354),[152] (±)-oxocostic acid (355),[153] and (±)-dihydroreynosin (356)[154] were smoothly accessed (eq 61).

Entry to the perhydroazulenic or 7,5-ring system is a further opportunity offered by the current approach. The key compound 358, obtained from irradiation of the C(6)-alkylated 3-methylcyclohex-2-en-1-one 357 and 350, could be transformed in several reaction steps to the 1-(tosyloxy)eudesmane derivative 359, which after solvolysis and side-chain modification yielded the guaiane sesquiterpene (±)-α-bulnesene (360) (eq 62).[150]

(62)
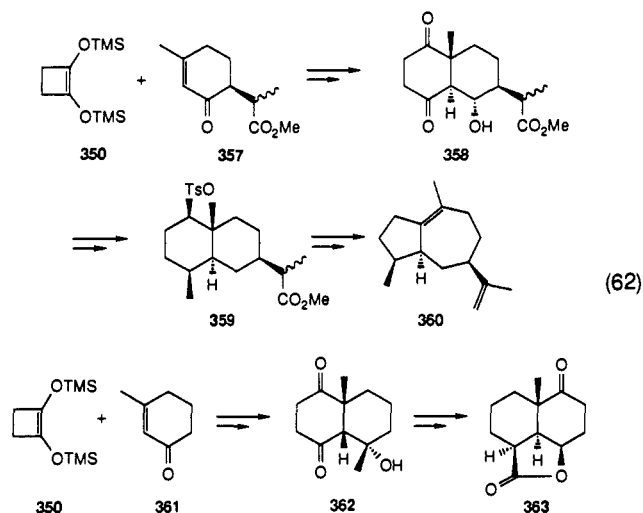
The method also opened a new and efficient route to polycyclic diterpenes.[155] The synthetic plan centers around the tricyclic lactone 363 (eight reaction steps from 361 via 362, 18% overall) (eq 62).

Thermal cycloreversion of a [2 + 2] photocycloadduct was applied in the total synthesis of the carotane sesquiterpene (+)-daucene (368), which was obtained in a three-step sequence from the naturally occurring (−)-piperitone (364).[156] Cycloadduct 365 (85%) underwent, via metathesis to 366, a transannular reaction involving oxygen to oxygen migration of a silyl group (ene-type reaction). Subsequent acid treatment led to diketone 367. Further manipulation afforded daucene (368) with high overall chirality transfer (eq 63).

The utilization of a variety of substituted cyclobutenes as well as other cycloalkenes has considerably widened the synthetic scope of the intermolecular

(63)
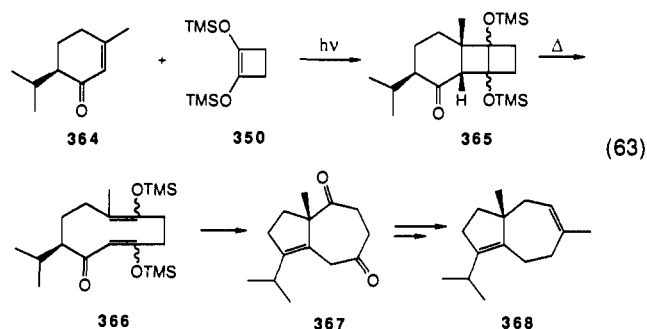
[2 + 2] photocycloaddition process. Photoaddition of enone 370 with excess cyclopentene (369) led to the adducts 371 and 372, respectively (87:13, 91%) (eq 64).[157]

(64)

Ts : tosylate
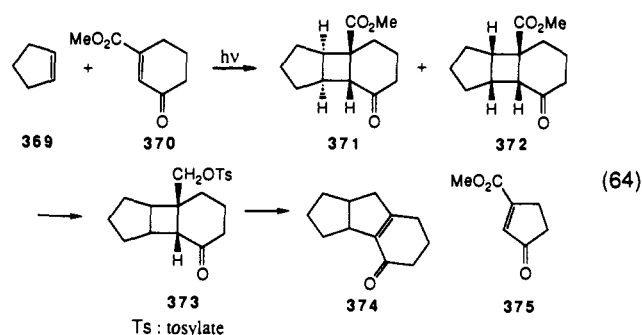
Rearrangement of the strained cyclobutane ring following suitable functionalization as in 373 furnished the ring-expanded tricyclo[6.4.0.0³,⁷]dodec-Δ¹,⁸-en-9-one (374).[158] According to Lange, the sequence starting with enone 375 constitutes an approach to the triquinane and taxol carbon skeletons.

A short synthesis of the fungal metabolite hirsutene (382) containing the cis-anti-cis-tricyclo[6.3.0.0⁴,⁸]-undecane ring system was reported by Weedon.[159] The skeleton was assembled by a de Mayo reaction of 2-methylcyclopent-2-en-1-ol (376), an 5,5-dimethyl-cyclohexane-1,3-dione (377) (eq 65). The bicyclic

(65)
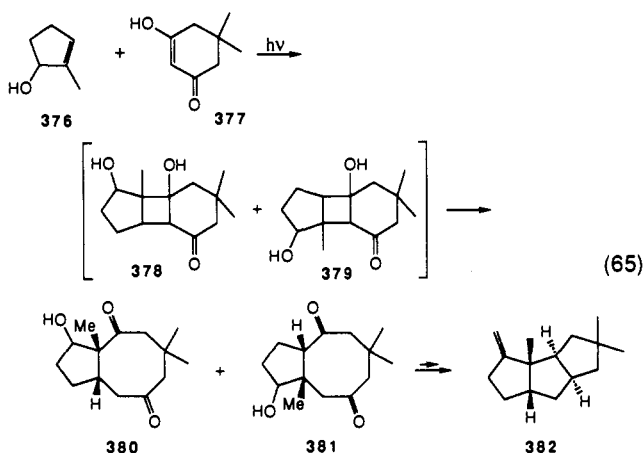
compounds 380 and 381 (1:2) were generated from the initially formed cyclobutanes 378 and 379, respectively, (86%) by spontaneous retro-aldol ring opening.

The stereoselective synthesis of acyclic 1,5-dienes was achieved using 2,5-dihydrothiophene 1,1-dioxols (sulfolenes) as 1,2-divinyl synthons. This concept was applied by Williams in the synthesis of 10-hydroxyge-raniol (386) involving the photocycloaddition between

2,5-dihydro-3-methylthiophene 1,1-dioxide (**383**) and citraconic anhydride (**384**) leading to photoadduct **385** (80%) (eq 66).[160]

$$(66)$$
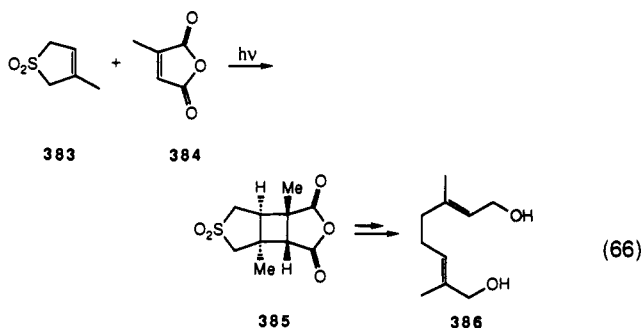
Heterocyclic enones, such as dioxopyrroline **388**, showed peculiar photoreactivity when irradiated in the presence of alkenes, e.g., propene (**387**). While the cis-fused dioxopyrrolidine **389** was stable under the reaction conditions, the trans-fused adduct rearranged to dihydropyridone **390** with concomitant loss of carbon monoxide (eq 67).[161] This feature was observed also in the presence of cyclic dienes.[162]

$$(67)$$
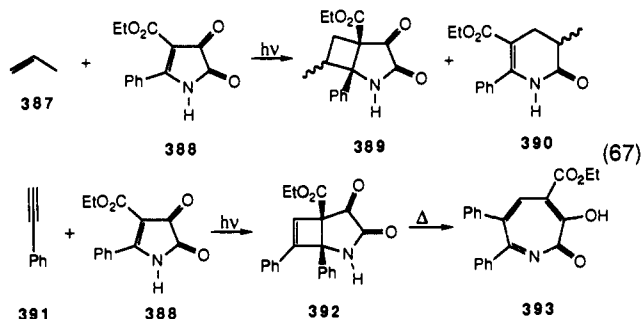
The [2 + 2] photocycloaddition involving the same dioxopyrroline **388** and 1-phenylethyne (**391**) opened a new avenue to the azatropolone skeleton. Cycloadduct **392** could be treated in a number of ways to give ring expansion, e.g., thermolysis induced electrocyclic ring opening to the azotropolone derivative **393** (eq 67).[163]

N-Acylindoles, such as **394**, show a propensity to yield head-to-tail adducts, such as **396**, in the presence of alkenes, e.g., vinylcyclopropane (**395**).[164] The regioselectivity could be reversed by tethering the alkene to the indole. As a result, *N*-acylindole **397** afforded the tetracyclic compound **398** (eq 68).[165]

$$(68)$$
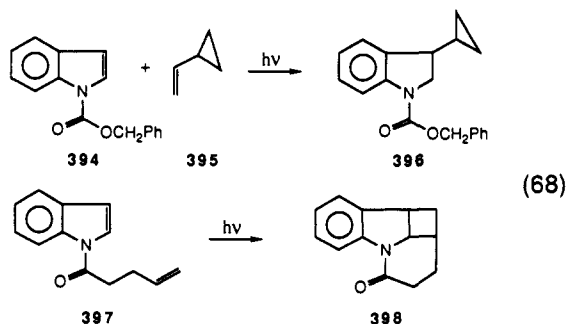
α,β-Unsaturated γ-lactones also give photocycloaddition to alkenes. Irradiation of **399** and cyclopentene (**369**) afforded the diastereomeric cycloadducts **400** and **401** with a preference for **400** (eq 69). The ratio varied

$$(69)$$

R = CH$_2$OC(O)*tert*-Bu

R' = O(CH$_2$)$_2$O
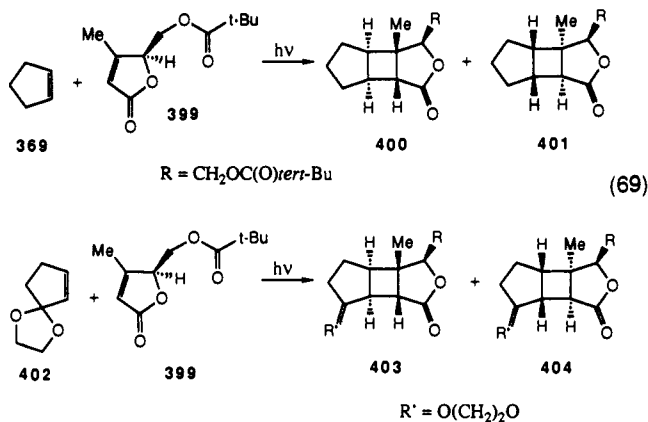
according to the substitution pattern at C(5). In order to get access to a key intermediate for the synthesis of (−)-bourbonene, irradiation of compound **399** was conducted in the presence of the cyclopentene derivative **402**. The reaction proceeded regioselectively to the cis-anti-cis stereomers **403** and **404** (eq 69).[166]

B. Paterno–Büchi Reactions

The photocycloaddition of a carbonyl group and an alkene, known as the Paterno–Büchi reaction, gives rise to an oxetane.[167] It was shown by Turro that the reaction is pressure-dependent.[168] Simple cyclohex-2-en-1-ones, such as **405**, underwent photocycloaddition to tetramethoxyethylene (**406**) in benzene to afford 1-oxaspiro[5,3]non-5-enes, such as **407** (> 90%) (eq 70).[169] Irradiation in acetonitrile, on the contrary, led

$$(70)$$
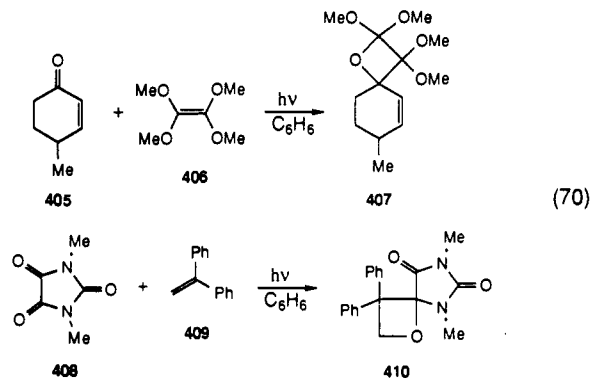
predominantly to cyclobutane-type adducts. The Paterno–Büchi reaction may be extended to the synthesis of heterocyclic systems as exemplified by the formation of oxetane **410** from coupling of compound **408** with 1,1-diphenylethylene (**409**) (eq 70).[170]

The formation of thietanes from thiones and alkenes displays intriguing features as highlighted by the reactions of thiobarbiturates **411–413** and tetramethylethylene (**414**).[171] While the monothio derivative **411** afforded a mixture of thietane **415** (51%) and its cleavage product **416** (47%), dithiobarbiturate **412** and trithiobarbiturate **413** gave chemoselective cycloaddition at the 4-thiocarbonyl group to thietanes **417** (91%) and **418** (51%), respectively (eq 71).

The Paterno–Büchi photocycloaddition of carbonyl compounds to furans affords cis-2,7-dioxabicyclo[3.2.0]-hept-3-ene ring systems with high exo relative face selectivity.[172] The relationship of this reaction to the aldol condensation has been noted by Schreiber.[173] The

411 : X = Y = O
412 : X = O, Y = S
413 : X = Y = S

417 : X = O
418 : X = S

(71)
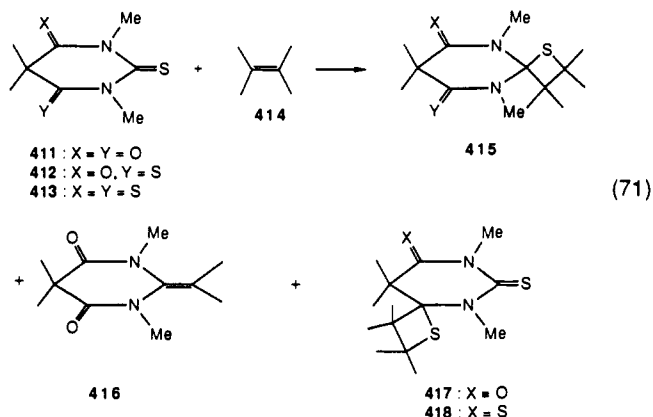
furan is equivalent to a Z-enolate and hydrolytic unmasking of the "photoaldol" adducts affords threo aldols of 1,4-dicarbonyl compounds.[174] The cup-shaped skeleton of the photoproducts lends control to a variety of reactions wherein electrophilic reagents add to the enol ether on its convex face. Thus, hydroboration-oxidation of the "photoaldol" 421 obtained from 2,4-dimethylfuran (419) and benzaldehyde (420) gave the 1,3-diol 422 (82%), resulting in total stereocontrol over five chiral centers in a two-step procedure (eq 72).

a : BF₃.THF: H₂O₂/NaOH

(72)
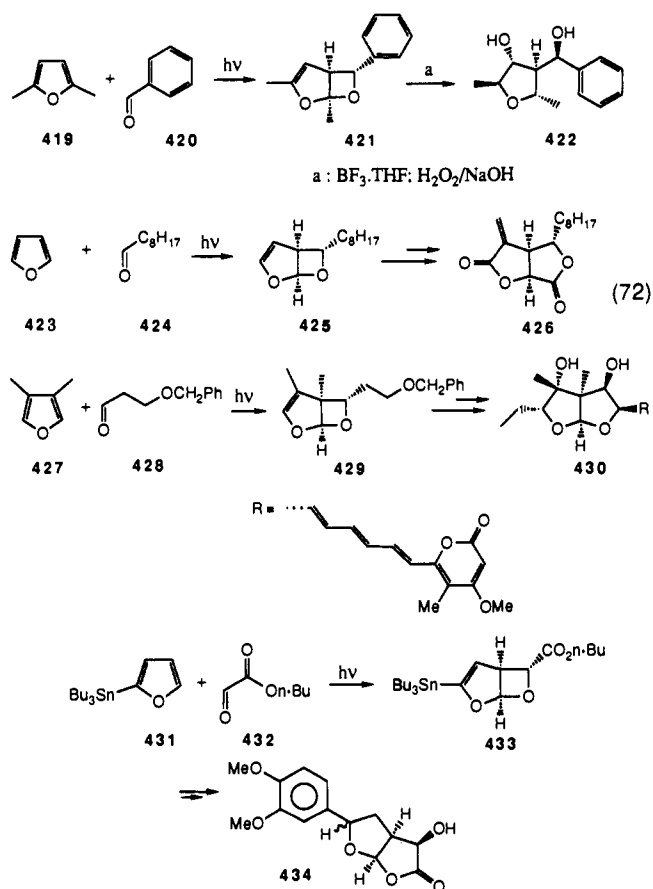
The furan–carbonyl photocycloaddition has been applied to the synthesis of the antifungal metabolite (±)-avenaciolide (426)[175] and the mycotoxin asteltoxin (430)[176] involving as the first step the photocycloaddition of nonanal (424) to furan (423) yielding acetal 425 and of 2-benzyloxypropanal (428) to 3,4-dimethylfuran (427), respectively (eq 72).

The inherent lack of chemoselectivity of photochemically excited aldehydes in their addition to unsym-

metrical furans can be overcome by using a main-group metal to direct the site of addition and to participate in a metal-catalyzed coupling reaction. Application of silyl- and stannyl-substituted furans has resulted in a four-step synthesis of a ginkgolide B-kadsurenone hybrid, potential antagonists of the platelet activating factor (PAF).[177] Photoaddition of 2-tributylstannyl-furan (431) and n-butyl glyoxylate (432) afforded a single photoproduct, 433 (35%), which was further manipulated to a separable mixture of epimers 434.

C. [n + 2] Photocycloadditions

Irradiation of the alkynylcyclohex-2-en-1-one 435 in the presence of tetramethylethylene (414) gave rise to the bicyclic compound 436 as the result of a [3 + 2] cycloaddition (eq 73).[178] Modification of this process

(73)

permitted construction of unusual tricyclic systems in a single reaction step, such as 438, derived from 435 and 1,1-dimethoxy-2-methylprop-1-ene (437).[179]

In photoreactions of dienes or dienones and alkenes, [4 + 2] photocycloadditions may compete with [2 + 2] photocycloadditions, depending on the structural features of the substrates and the reaction conditions. Sensitized irradiation of the 2-pyrone 439 with acrylonitrile (99) gave mainly the [2 + 2] cycloadduct 440, while methyl 2-pyrone-5-carboxylate 441 afforded the [4 + 2] cycloadduct 442 as the major reaction product (eq 74).[180] In connection with this result, the various

(74)

factors influencing the coupling of 2-pyrone derivatives and a series of vinyl compounds have been thoroughly investigated.[181]

In particular, naphthoquinones show a pronounced tendency to react in the [4 + 2] fashion, e.g., 1,4-naphthoquinone 443 and allene 444 gave in benzene the spiro adduct 445 (85%)[182] and 1,2-naphthoquinone 446 afforded an epimeric mixture of 448 and 449 (63: 37, 62%) on irradiation in the presence of trans-but-2-ene (447) (eq 75).[183] The role of the solvent in these reactions was particularly stressed.[184]

(75)
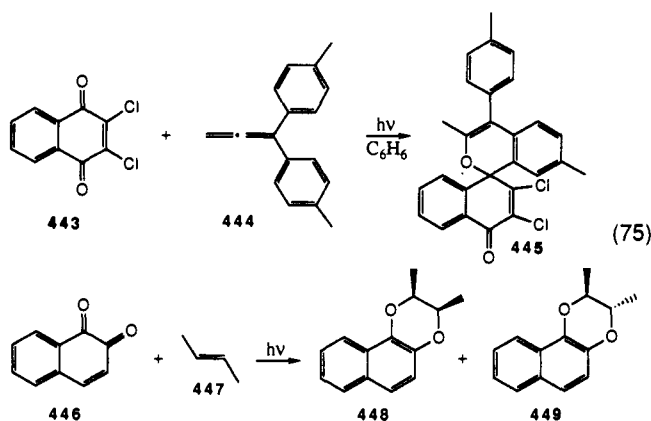
Tropones are prone to undergo [6 + 2] photocycloadditions, particularly at low temperature or in acidic medium.[185] (±)-Dactylol (453) was synthesized starting from the tropone 450, which was converted photochemically (–60 °C, chloroform) to the [6 + 2] adduct 451 (41%) and its epimer 452 (11:1) (eq 76).[186]

(76)
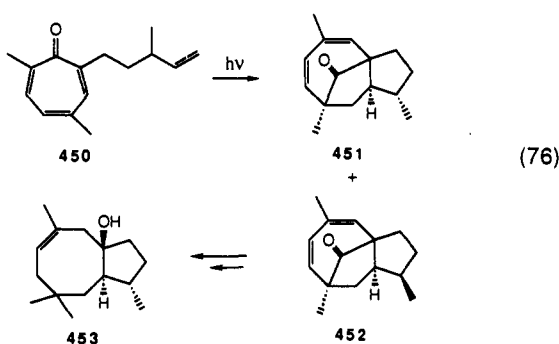
Cyclohexa-2,5-dien-1-ones, such as 455, generated from Birch reduction–alkylation of methyl benzoate (454) gave on irradiation di-π-methane rearrangement to the cyclopropane derivative 456. Under the reaction conditions 456 was converted to the oxyallyl zwitterion intermediate 457, which furnished bridged polycyclic molecules, such as 458 and 459, resulting from [3 + 2] and [5 + 2] photocycloadditions, respectively. The partitioning of the reaction pathways appears to be governed by steric and electronic factors (eq 77).[187]

(77)
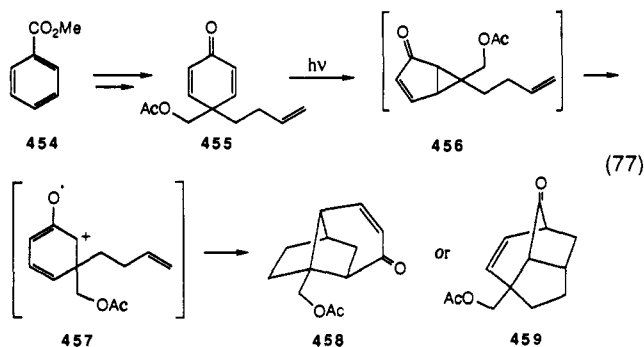
VII. Conclusion

Photochemical reactions are extremely valuable processes in synthetic strategies. As illustrated in this review, a wide variety of both intermolecular and intramolecular photoactive systems have great potential with respect to the construction of polycyclic molecules. Numerous studies have shown that through an appro-

priate choice of substrates and conditions photoconversions can be highly selective and efficient. While more traditional synthetic procedures often require elaborate manipulations for controlled introduction of substituents, the mild conditions and the formation of strained molecules commonly encountered in photoreactions allow for more rigid control of the stereo-, regio-, and chemoselectivity. Consequently, multistep synthetic sequences can be shortened dramatically, as complicated polycyclic skeletons may be assembled in a key photochemical reaction. It is anticipated that these very special features will promote further penetration of photochemical methods in organic synthesis.

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