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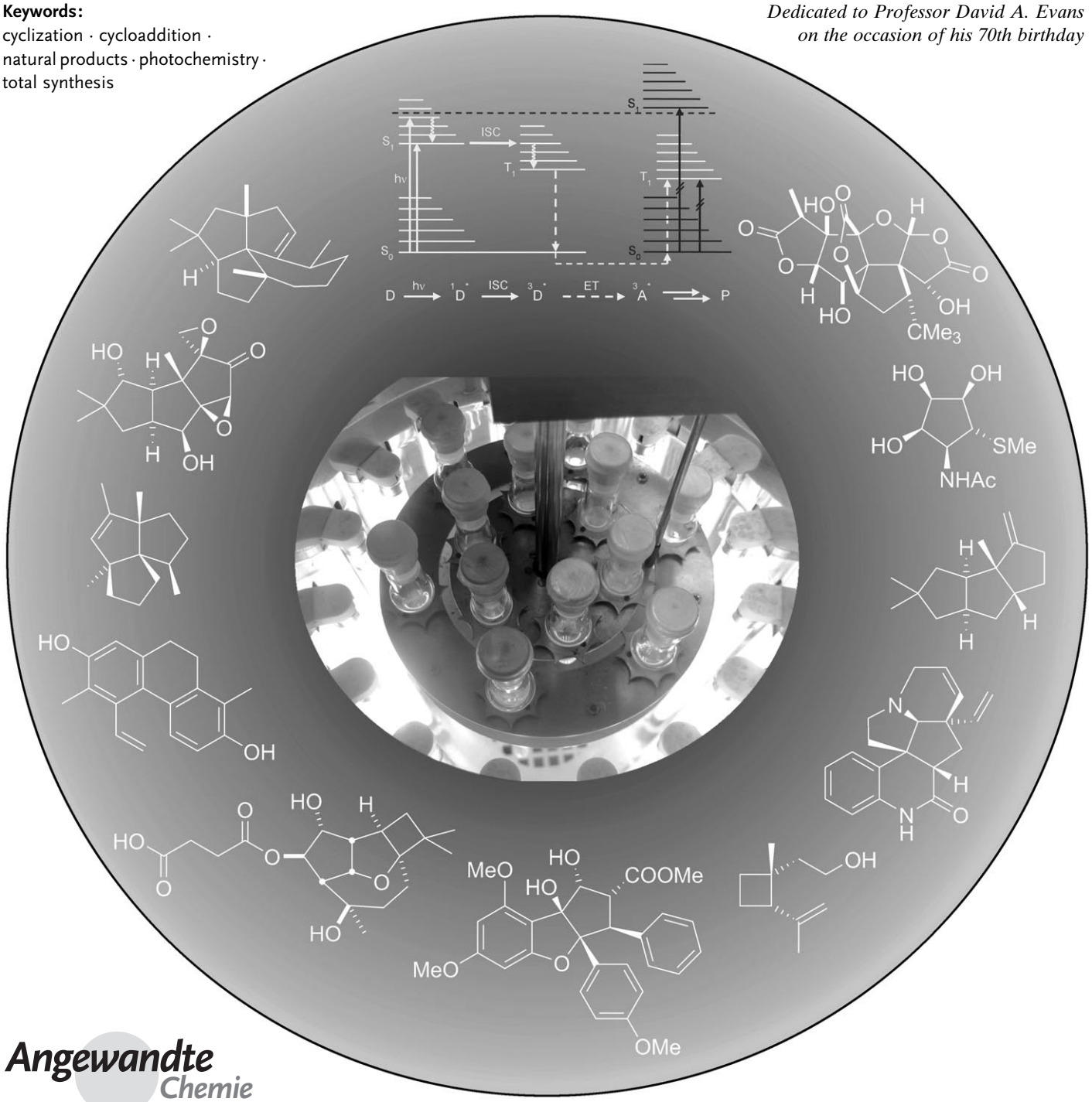
Synthetic Methods

# Photochemical Reactions as Key Steps in Natural Product Synthesis

*Thorsten Bach* and Jörg P. Hehn*

**Keywords:**
cyclization · cycloaddition · natural products · photochemistry · total synthesis

*Dedicated to Professor David A. Evans on the occasion of his 70th birthday*



*Photochemical reactions contribute in a significant way to the existing repertoire of carbon–carbon bond-forming reactions by allowing access to exceptional molecular structures that cannot be obtained by conventional means. In this Review, the most important photochemical transformations that have been employed in natural product synthesis are presented. Selected total syntheses are discussed as examples, with particular attention given to the photochemical key step and its stereoselectivity. The structural relationship between the photochemically generated molecule and the natural product is shown, and, where necessary, the consecutive reactions in the synthesis are illustrated and classified.*

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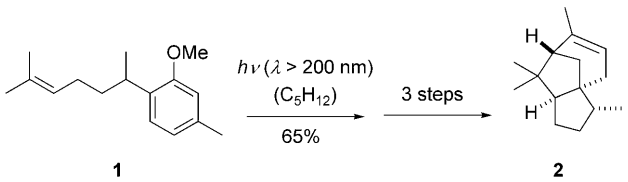
## 1. Introduction

Is there anything that hasn't already been said or written about natural product synthesis?[1] Great art has been seen in it,[2] and attempts have been made to establish it as a handcraft. Economical rules have been assigned to it,[3] and it has been fitted into logical schemes.[4] Some people view natural product synthesis as a mature area of science without new impetus, others consider it to be the supreme discipline of organic chemistry, if not chemistry in general. It always was and still is a reflection of the times, because it scrutinizes new methods and reflects the development of the chemical sciences. Subjectivity adds zest to the assessment of a natural product synthesis, which involves evaluation and analysis of the route to a particular synthetic target. These analyses are the culmination of many points of view, some of which are described above and which are not always rational. With that said, photochemical reactions possess an exotic charm and are particularly fascinating because of their unconventional nature. The high energy that is transferred to a molecule by absorption of light facilitates reaction pathways that cannot be accessed by conventional methods. As a result, astonishing transformations occur that result in the formation of remarkable molecular structures, which barely resemble their precursor molecules.[5] The synthesis of racemic[6] (±)-cedrene (**2**) from precursor **1** serves as an example.[7] By using a photochemical reaction as a key step, an entirely different molecular skeleton, possessing an equal number of carbon atoms, was generated in only four steps (Scheme 1).

There is frequently a thin line between diverse photochemical reaction pathways, and slight changes in the structure of the substrate can lead to an entirely different outcome. In combination with the unfamiliar photochemical equipment, this has resulted in many synthetic chemists being reluctant to use photochemical reactions.[8] This reserve is not justified, and one of the objectives of this Review is to show that photochemistry can play an important role both in general synthesis and, in particular, in natural product synthesis.




***Scheme 1.*** Efficient synthesis of (±)-cedrene (**2**) by a photochemical key step.

As a consequence of space restriction, emphasis is placed in this Review on C–C bond-forming reactions, and they are grouped into relevant subchapters. Model studies related to natural product synthesis, photochemically initiated radical reactions, and single-electron transfer (SET) processes have been omitted. A wavelength or wavelength range for the irradiation is given in the depicted examples, provided this information was reported in the reference material. The temperature of a reaction is only mentioned if it was not carried out at room temperature.

## 2. Photocyclizations

While the term photocyclization refers to light-induced pericyclic ring closing reactions, conrotatory [6π] cyclizations[9] and disrotatory [4π] cyclizations are the most impor-

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tant reactions of this type.[10] These reactions occur mostly on the singlet hypersurface and deliver the respective photoproducts stereospecifically.

### 2.1. [6π] Photocyclizations

[6π] Photocyclizations can be classified according to the type of substrate that is employed. The majority of these reactions involve 1,3,5-trienes (**A**) to generate carbocycles, or enamides (**B**) to afford heterocyclic products (Figure 1).

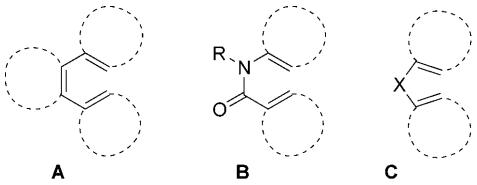
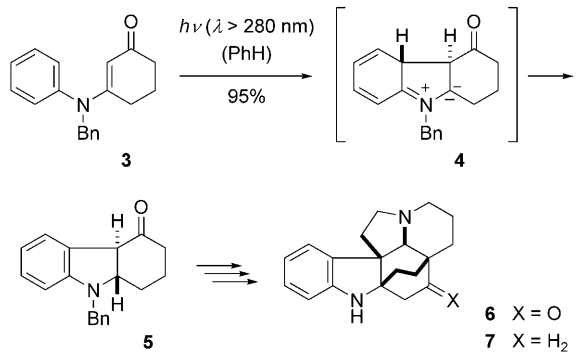



***Figure 1.*** General representation of substrates **A**–**C** for the [6π] photocyclization.

Substrates of type **C** (X = O, NR)[11] are less common and, in the case of X = NR, can be used for the synthesis of pyrrolines, dihydroindoles, and hexahydrocarbazoles. One example of this type of reaction is the cyclization of tertiary enaminone **3** to generate tricyclic *trans*-hexahydro-4-carbazolone **5**.[12] Conrotatory [6π] ring closure results in the formation of zwitterion **4** as an intermediate, which then undergoes a suprafacial 1,4-H shift to afford the product. This reaction has been exploited in the synthesis of indole alkaloids. In the present case, the photoproduct was converted in twelve steps into (±)-19-oxoaspidofractinine (**6**),[13] the reduction of which is known to generate (±)-aspidofractinine (**7**) (Scheme 2).[14]

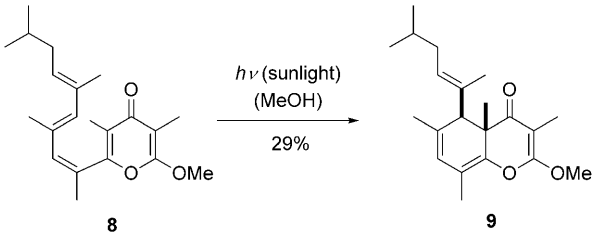
Another application of the cyclization of a substrate of class **C** can be found in the synthesis of (±)-lycoramine.[15] In this example, a vinyl aryl ether (Figure 1; structure **C**, X = O) rather than an amine served as the substrate for the photoreaction.




***Scheme 2.*** The initial [6π] photocyclization of enaminone **3** used in the formal synthesis of (±)-aspidofractinine (**7**). Bn = benzyl.

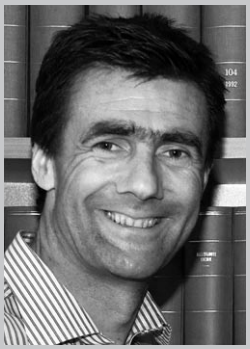
#### 2.1.1. [6π] Photocyclization of Trienes

A recent synthesis by Moses and co-workers nicely illustrates the stereochemical course of the [6π] cyclization.[16] The natural product (±)-tridachiahydropyrone (**9**) was obtained from γ-pyrone **8**, in what is believed to be a biomimetic reaction (Scheme 3).




***Scheme 3.*** Sunlight-induced [6π] cyclization to afford (±)-tridachiahydropyrone (**9**).

The correct relative configuration of the two adjacent stereogenic centers was established by a conrotatory ring closure. The synthesis of substrate **8** was achieved by a Suzuki cross-coupling reaction of a dienylboronate and an alkenyl bromide attached to a γ-pyrone. (±)-Photodeoxytridachione and (±)-iso-9,10-deoxytridachione were also synthesized by a biomimetic photocyclization from an analogous tetraene



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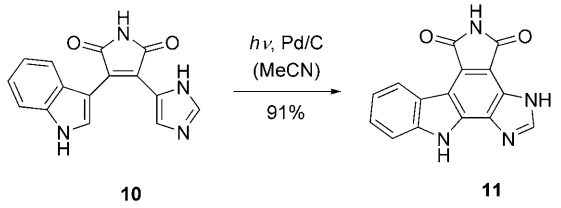
substituted γ-pyrone. However, the yields were lower in this case.[17] While aromatization is not possible in the case of compound **9**, this reaction pathway often follows the photocyclization to generate a central benzene ring. The biomimetic synthesis of granulatimide (**11**) from didemnimide A (**10**) by Andersen and co-workers (Scheme 4) serves as an




***Scheme 4.*** Synthesis of granulatimide (**11**) from didemnimide A (**10**).

example.[18] This reaction was carried out in the laboratory using a medium-pressure Hg lamp, a quartz apparatus, and catalytic amounts of Pd/C. The authors describe that irradiation with sunlight in the presence of atmospheric oxygen also results in rapid ring formation and oxidation. Clearly, excitation with light of long wavelength is sufficient to trigger the [6π] cyclization.

The heterocyclic skeletons of many natural products have been constructed by [6π] photocyclizations and their structures are depicted in Figure 2. The gray shading indicates the bond that was formed in the photochemical step. The natural products that have been synthesized in this way include (+)-

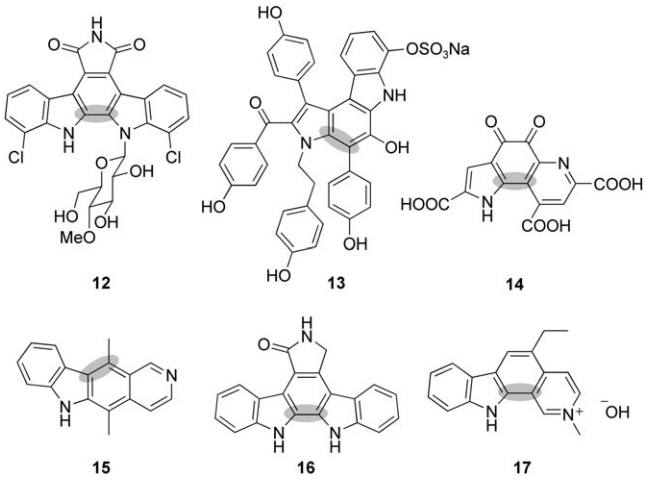
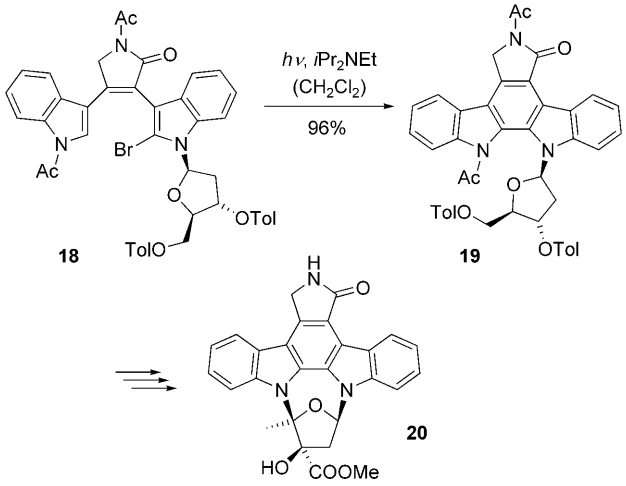



***Figure 2.*** Structures of (+)-rebeccamycin (**12**), dictyodendrin B (**13**), methoxatin (**14**), ellipticine (**15**), the staurosporine aglycon (**16**). and the indole alkaloid **17** isolated from *Aspidosperma gilbertii*. The bond that was formed by [6π] cyclization is highlighted in gray.

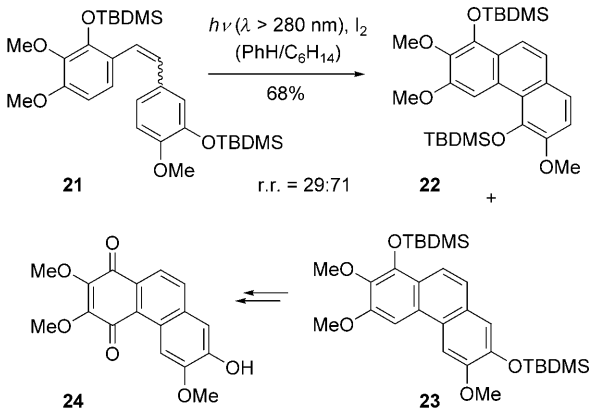
rebeccamycin (**12**),[19] dictyodendrins B (**13**), C, and E,[20] methoxatin (**14**),[21] ellipticine (**15**),[22] the staurosporine aglycon (staurosporinone or K252c, **16**),[23] (+)-staurosporine,[24] (+)-RK286c,[24] (+)-MLR-52,[24] (−)-TAN-1030a,[24f] urostifoline,[25] and the indole alkaloid **17**, which was isolated from *Aspidosperma gilbertii*.[26] The essential oxidation of the intermediate cyclohexadiene occurred either by exposure to atmospheric oxygen or by addition of an oxidant such as $I_2$ or diphenyl diselenide.

If non-oxidative conditions are required, a halogenated substrate can be used to achieve aromatization by elimination following the [6π] cyclization. Fukuyama and co-workers employed this reaction in the total synthesis of (+)-K252a (**20**), where dihydroindolocarbazole **19** was generated from 2-bromoindole **18** (Scheme 5).[27] The authors attributed the high yield of the reaction to the selected reaction conditions, which, for these indolecarbazole alkaloids, are superior to the oxidative cyclizations.




***Scheme 5.*** Total synthesis of (+)-K252a (**20**) by [6π] photocyclization of bromoindole **18**. Ac = Acetyl; Tol = *para*-toluoyl.

The [6π] photocyclization of stilbenes is one of the shortest and most effective routes to phenanthrenes; hence, this reaction plays an important role in the synthesis of phenanthrene-type natural products. *E*/*Z* isomerization of the stilbene precursor and pericyclic ring opening are possible nonproductive reaction pathways, so it is advisable to use either oxidative conditions or halogenated substrates to shift the equilibrium in favor of the product by irreversible formation of the phenanthrene. As depicted in Scheme 6, combretastatin C-1 (**24**) was obtained from stilbene **21** in this

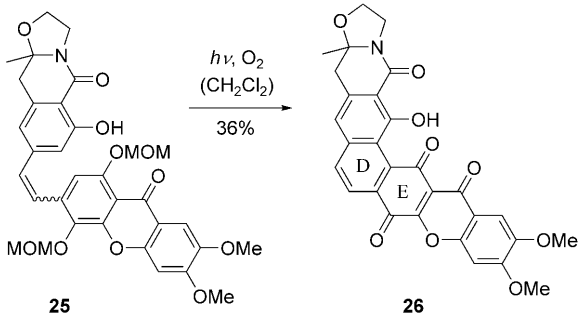



***Scheme 6.*** [6π] Photocyclization of stilbene **21** as a key step in the synthesis of combretastatin C-1 (**24**). TBDMS = *tert*-butyldimethylsilyl.

way.[28] As seen in this example, the regioselectivity of the [6π] photocyclization favors the sterically less hindered product. Regioisomers **22** and **23** were formed in a regioisomeric ratio (r.r.) of **22**/**23** = 29:71. The major regioisomer **23** was transformed into natural product **24** in two steps (deprotection, oxidation).

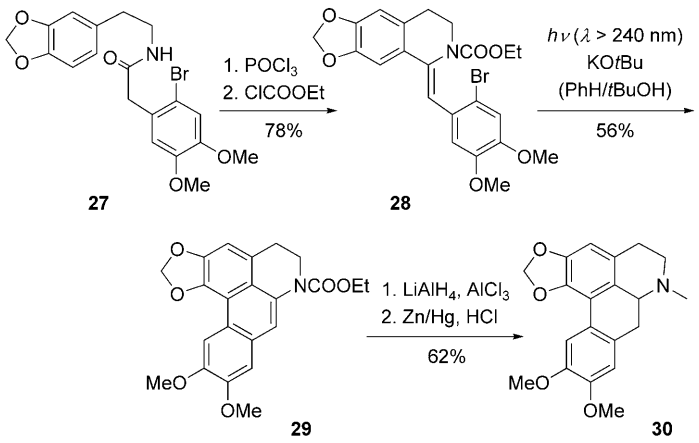
Other simple phenanthrene natural products that were made by means of a [6π] cyclization include the plectranthones,[29] aristolochic acid,[30] (±)-tylophorine,[31] the phenanthrenes TaIV and TaVIII,[32] and the diterpenoid quinone (±)-danshexinkun A.[33] The [6π] cyclization can even be used effectively in the final stages of the synthesis of complex phenanthrenes. This was demonstrated by both Kelly and Jagoe[34] and Mehta et al.[35] in the total synthesis of (±)-cervinomycin $A_2$ (**26**) and the closely related E-ring hydroquinone (±)-cervinomycin $A_1$. In the synthesis by Kelly and Jagoe (Scheme 7), regioselective ring closure of substrate **25** resulted in formation of the D ring, which was accompanied by simultaneous deprotection and oxidation of the E ring to the quinone.




***Scheme 7.*** Completion of the synthesis of (±)-cervinomycin $A_2$ (**26**) by a [6π] photocyclization. MOM = methoxymethyl.

Numerous alkaloids contain a phenanthrene or dihydrophenanthrene skeleton that can be formed by [6π] photocyclization. This disconnection leads, once again, to easily accessible stilbene precursors and consequently to a method for convergent assembly of the molecule. The synthesis of aporphine alkaloids by [6π] photocyclization is one of the earliest and best studied syntheses of this kind.[36] One example is the synthesis of (±)-dicentrine (**30**) by Cava et al. (Scheme 8).[37] A Bischler–Napieralski reaction of amide **27** afforded an aromatic imine, which was then directly acylated with ethyl chloroformate to generate enamide **28**. Non-oxidative [6π] photocyclization gave the desired phenanthrene **29**, which was reductively converted into natural product **30**. Other aporphines that have been synthesized by using a [6π] photocyclization as the key step are cassameridine,[37] (±)-aporphine,[38] (±)-nuciferine,[38,39] (±)-glaucine,[39] (±)-cassamedine,[40] (±)-sinomendine,[41] (±)-elmerrillicine,[42] pontevedrine,[43] cepharadione B,[44] and (±)-goudotianine.[45]

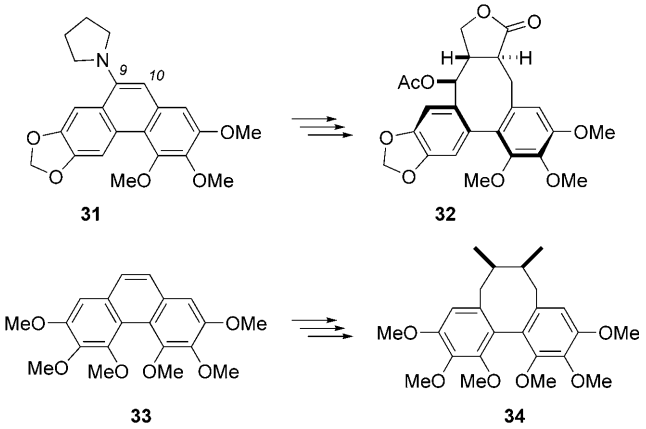
Alkaloids possessing nitrogen atoms that are not incorporated into the stilbene chromophore can be prepared in a similar fashion. Successful routes to atherosperminine and




***Scheme 8.*** Final steps of Cava's synthesis of (±)-dicentrine (**30**).

related phenanthrene alkaloids,[46] annoretine,[47] litebamine,[48] (±)-julandine,[49] (±)-cryptoleurine,[49] and *N*-methylsecoglaucine[50] have been reported in this context.

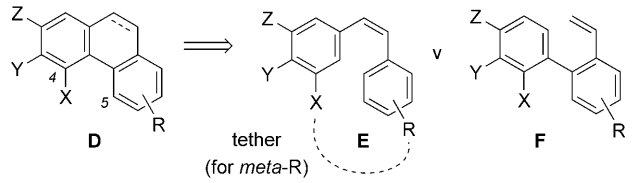
The double bond between C9 and C10 in the phenanthrene may not only be reduced, as described above, but can also be manipulated by using other types of synthetic transformations (Scheme 9). For example, phenanthrene **31**, which was obtained by [6π] photocyclization, was converted into the lignan natural product (±)-steganacin (**32**),[51] while (±)-desoxyschizandrin (**34**) could be synthesized from phenanthrene **33** by oxidative cleavage, Grignard addition, and reductive ring closure.[52]




***Scheme 9.*** Modifications of the central phenanthrene ring in the total syntheses of (±)-steganacin (**32**) and (±)-desoxyschizandrin (**34**).

The regioselectivity of the reaction becomes a problem if 4- and 5-substituted phenanthrene or dihydrophenanthrene scaffolds of type **D** are required (Scheme 10). If the substituents X and Z are different, conventional ring closure leads to the formation of regioisomers. Most notably, if Z is a hydrogen atom, the unwanted regioisomer clearly predominates. One possible solution for this problem is to tether the rings with a suitable chain, as shown schematically in structure **E**. This strategy is particularly attractive if the R substituent is

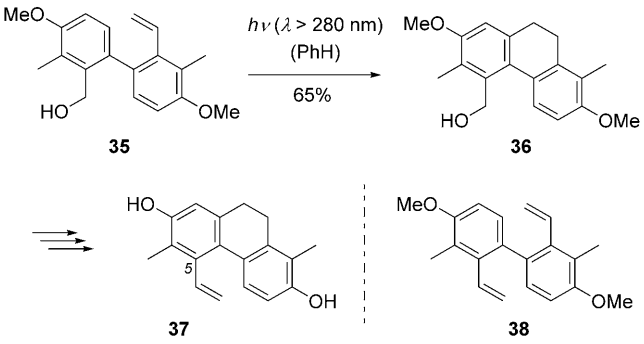
  




***Scheme 10.*** Solving the problem of regioselectivity in the photochemical synthesis of phenanthrenes of type **D** by tethering both phenyl rings (**E**) or by using a vinylbenzene of type **F**.

located in the *meta* position, which corresponds to the 5-position of the phenanthrene product. By using an *ortho*-dibenzylidene unit as a tether, Castedo et al. elegantly established the 4,5-*O*-substitution required for the natural product cannithrene-II.[53]

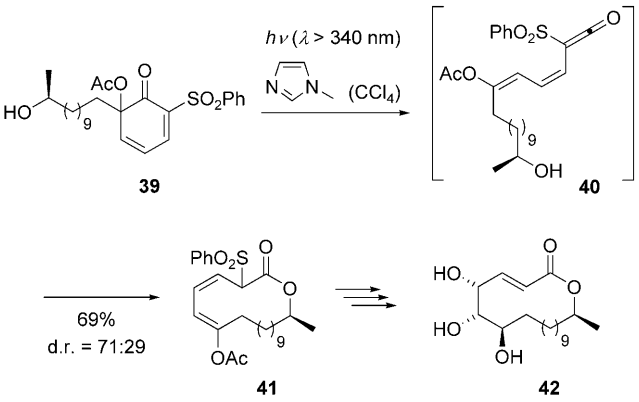
Alternatively, a vinyl-substituted benzene of type **F** can be used as a precursor for the cyclization (Scheme 10). In this case the [6π] photocyclization can only occur at the position that is not blocked by the X substituent. Kende and Curran used the reaction for the regioselective formation of juncusol (**37**), a cytotoxic phytoalexin.[54] Irradiation of vinyl benzene **35** under a nitrogen atmosphere delivered the desired dihydrophenanthrene **36**, which was subsequently converted into the natural product **37**. Attempts to install the vinyl group at C5 prior to the cyclization failed because of the fact that substrate **38** rapidly underwent an additional cyclization to the tetrahydropyrene following the first ring closure (Scheme 11). At almost exactly the same time, McDonald and Martin reported another synthesis of juncusol that employed a virtually identical [6π] photocyclization as the key step.[55]




***Scheme 11.*** Irradiation of vinylbenzene **35** in the total synthesis of juncusol (**37**).

The [6π] photocyclization of a vinylbenzene was first employed in the syntheses of the alkaloids sanguinarine and chelerythrine.[56] More recently, Kelly and co-workers applied the [6π] photocyclization of an *ortho*-pyridinylstyrene to the synthesis of the alkaloid santiagonamine.[57] A heteroatom variant of the [6π] photocyclization, namely the reaction of an α,β,γ,δ-unsaturated carboxylic acid to an β,γ-unsaturated lactone, was utilized in a synthesis of nagilactone F.[58]

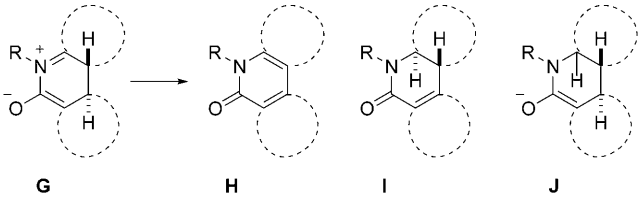
Reversal of the [6π] photocyclization, that is to say the conrotatory ring opening of a 1,3-cyclohexadiene, leads to the cleavage of a six-membered ring.[59,60] The photolactonization step in Quinkert's total synthesis of the lichen macrolide (+)-aspicilin (**42**) may mechanistically follow this pathway, but it may also be interpreted as an α-cleavage reaction (see Section 4). As shown in Scheme 12, irradiation of *ortho*-quinolacetate **39** initially led to the formation of the intermediate seco-isomeric dieneketene **40**, which then underwent nucleophilic attack by the secondary alcohol to generate the 18-membered macrolactone **41**.[61]




***Scheme 12.*** Synthesis of (+)-aspicilin (**42**) by photolactonization starting from quinolacetate **39**. Ac = acetyl.

### 2.1.2. *[6π] Photocyclizations of Enamides*

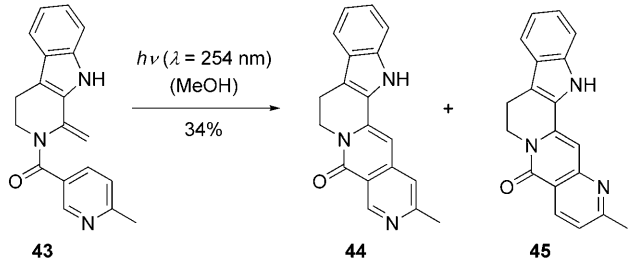
Enamide [6π] photocyclizations in natural product synthesis have been studied in depth by Ninomiya and Naito.[62] Three feasible reaction products are shown in Scheme 13 that can be generated from the zwitterion **G**, which is formed by conrotatory ring closure of enamide **B** (Figure 1). Pyridone **H** can be formed under oxidative conditions. In the absence of an oxidant, a suprafacial 1,5-H shift affords dihydropyridones of type **I** under thermal conditions, in analogy to the transformation **4**→**5** (Scheme 2). The direction of the H shift is often determined by the fact that enamides of aromatic carboxylic acids are used and that the aromaticity is restored during the formation of **I**. Lastly, the [6π] photocyclization can also be conducted under reductive conditions (for example, $NaBH_4$ in MeOH), so that the enolate **J** is generated, which then undergoes subsequent protonation. If enamides of benzoic acid are used as substrates the protonation takes place to form 1,3-hexadienes.




***Scheme 13.*** Possible consecutive reactions of zwitterion **G**, which was formed by conrotatory ring closure.

In each of these cases, the [6π] photocyclization of enamides offers an excellent approach to isoquinoline alkaloids. One of the first alkaloids synthesized in this manner was the corianthé alkaloid angustidine (**44**).[63] Irradiation of enamide **43** with a low-pressure Hg lamp resulted in [6π] photocyclization to generate both the natural product and the corresponding regioisomer **45** (**44**/**45** = 60:40, Scheme 14). Similarly, the pyridine-containing alkaloids nauclétine,[63b] (±)-angustoline,[63,64] alamarine,[65] and nauclefine (parvine)[66] were also synthesized by using this reaction.

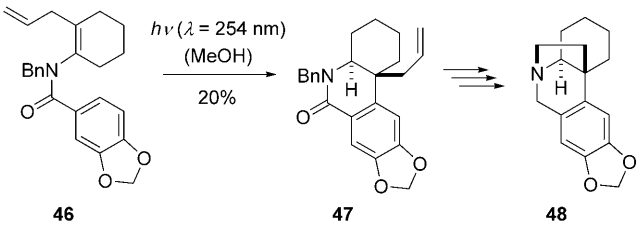



***Scheme 14.*** Enamide [6π] photocyclization with subsequent oxidation by atmospheric oxygen in the synthesis of angustidine (**44**) and its regioisomer **45**.

As mentioned previously for the stilbene substrates, the oxidative reaction pathway can be predetermined if a nucleophilic leaving group is located on the aromatic ring. In the case of enamide cyclizations, however, this is not limited to halogen substituents, but methoxy groups are also capable of undergoing elimination. For this reason, caution has to be exercised if *ortho*-substituted benzoic acid derivatives are irradiated. Application of the elimination can be found in the syntheses of naucleficine[67] and oxogambirtannine[68] as well as in the formal total syntheses of fagaronine,[69] nitidine, and avicine.[70] Kametani et al. used the elimination of HBr to suppress the competing elimination of methanol in their syntheses of several protoberberine alkaloids.[71]

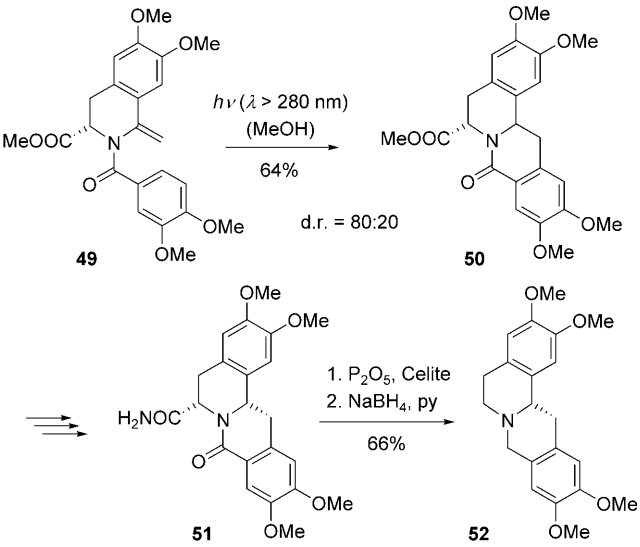
In some cases, the oxidatively formed pyridone ring has been converted into a saturated derivative by subsequent reduction with $LiAlH_4$, $NaBH_4$, or Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride]. The strategy was employed in the syntheses of the alkaloids (±)-xylopinine (**52**),[72–74] (±)-tetrahydropalmatine,[73] (±)-sinactine,[73,75] (±)-cavidine,[75,76] yohimbine,[77] bharatamine,[78] homochelidonine,[79] chelirubine,[80] (±)-α-anhydrodihydrocaranine,[81] and (±)-γ-lycorane.[81] The non-oxidative cyclization, according to the transformation **G**→**I** in Scheme 13, affords *trans*-configured substituents, which can be synthetically useful. This reaction was used by Ninomiya et al. in an early synthesis of (±)-crinan (**48**).[82] The [6π] photocyclization of benzoic amide **46** delivered the expected *trans* product, albeit in low yield, which could be separated from small amounts of the regioisomeric product by chromatography. To complete the synthesis the bridging pyrrolidine ring was established by oxidative cleavage of the double bond, reduction, and debenzylation (Scheme 15).

Among the numerous examples of the application of this reaction one can find the syntheses of (±)-berbine,[72] (±)-




***Scheme 15.*** Synthesis of (±)-crinan (**48**) by a non-oxidative [6π] photocyclization of benzoic amide **46**.

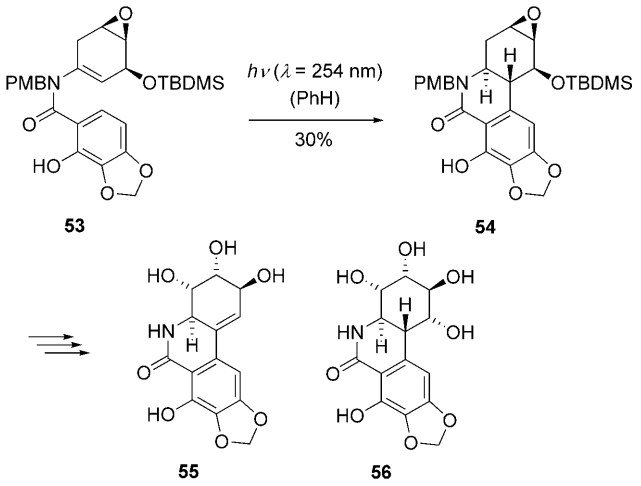
xylopinine (**52**),[83] (±)-corynoline,[84] (±)-bharatamine,[78] mappicine ketone (nothapodytine B),[85] flavopereirine,[86] and the formal total synthesis of (±)-vindorosine.[87] Kametani et al. demonstrated in the synthesis of (−)-xylopinine (**52**) that the facial diastereoselectivity of the reaction can be used for the formation of enantiopure alkaloids (Scheme 16).[88] Enamide **49** was synthesized from enantiomerically pure 3,4-dimethoxyphenylalanine and then subjected to [6π] photocyclization to afford photoproduct **50** as an inseparable mixture of diastereoisomers (d.r. = 80:20). Following conversion of the methoxycarbonyl group into the corresponding amide, the two diastereoisomers could be separated and the major diastereoisomer **51** was converted into the natural product by dehydration and subsequent hydrodecyanation.




***Scheme 16.*** Diastereoselective [6π] photocyclization of enamide **49** in Kametani's synthesis of (−)-xylopinine (**52**).

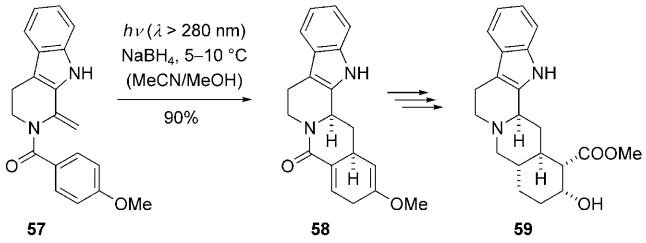
Enamide **53** was also found to undergo diastereoselective cyclization, with the attack on the enamide double bond being controlled by the adjacent stereogenic center. Rigby et al. employed the photoproduct **54** for the enantioselective synthesis of the amaryllidaceae alkaloids (−)-narciclasine (**55**) and (+)-pancratistatin (**56**).[89] Despite substantial attempts, it was not possible to improve the conversion or the yield of the [6π] photocyclization step (Scheme 17).




***Scheme 17.*** Synthesis of the common precursor **54** through diastereoselective [6π] photocyclization of enamide **53** in total syntheses of (−)-narciclasine (**55**) and (+)-pancratistatin (**56**). PMB = *para*-methoxybenzyl.

The synthesis of (±)-yohimbine (**59**) by Ninomiya and co-workers serves as an example of reductive enamide cyclizations of the type **G**→**J** (Scheme 13).[90] The reductive enamide cyclization of precursor **57** proceeded smoothly to generate the product **58** in excellent yield. In a five-step reaction sequence this intermediate was converted into yohimbinone (Scheme 18), the reduction of which is known to deliver the

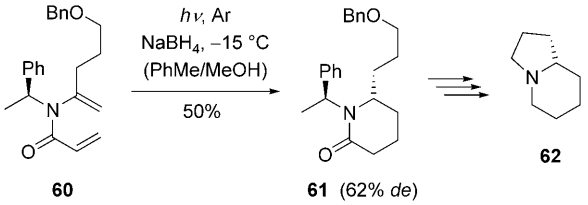



***Scheme 18.*** Reductive [6π]-photocyclization of enamide **57** in the formal total synthesis of (±)-yohimbine (**59**) by Ninomiya et al.

target natural product.[91] Another application of this strategy can be found in the formal total synthesis of (±)-deserpidine.[92] By employing a chiral lithium aluminium hydride/quinine complex, Ninomiya and co-workers achieved an enantioselective reductive [6π] photocyclization with 37% *ee*, which was used for the synthesis of optically active (−)-xylopinine (**52**).[93]

The use of heteroaromatic carboxylic acids (for example, furan-2-carboxylic acid, 2-phenyloxazole-4-carboxylic acid) as precursors for the enamides significantly extends the options for further functionalization after a [6π] photocyclization. The reduced heterocycle can be cleaved in a variety of ways to provide access to a number of different types of alkaloids. Some examples include (±)-emetine,[94] (±)-eburnamine,[95] (±)-ajmalicine,[96,97] (±)-quinine,[97] (±)-akuammigine,[97] (±)-tetrahydroalstonine,[97] (±)-pseudodistomins A and B,[98] (±)-lysergic acid,[99,100] (±)-isofumigaclavine,[100] (±)-hirsuteine,[101,102] (±)-corynantheline,[102] (±)-isositsirikine,[102] (±)-agroclavine,[103] (±)-fumigaclavine B,[103] (±)-lysergene,[103] (±)-lysergol,[104] (±)-isolysergol,[104] (±)-elymoclavine,[104] (±)-chanoclavine-I,[105] and (±)-isochanoclavine-I.[105]

The [6π] photocyclization can be controlled by using a chiral auxiliary, as demonstrated in the reaction of substrate **60** during the synthesis of (+)-coniceine (**62**) by Aitken and co-workers (Scheme 19).[106] (*S*)-α-Methylbenzylamine acts as




***Scheme 19.*** Auxiliary-controlled enamide cyclization of substrate **60** for the enantioselective synthesis of (+)-coniceine (**62**).

an auxiliary to control the diastereoselectivity of the reduction step. The best diastereomeric excess (*de*) in favor of compound **61** was obtained at a reaction temperature of −15 °C in a toluene/methanol (9:1) mixture. After reduction of the lactam and hydrogenolytic cleavage of the auxiliary and the benzyl group, ring closure was achieved by nucleophilic substitution of the bromide, which had been generated from the corresponding alcohol.

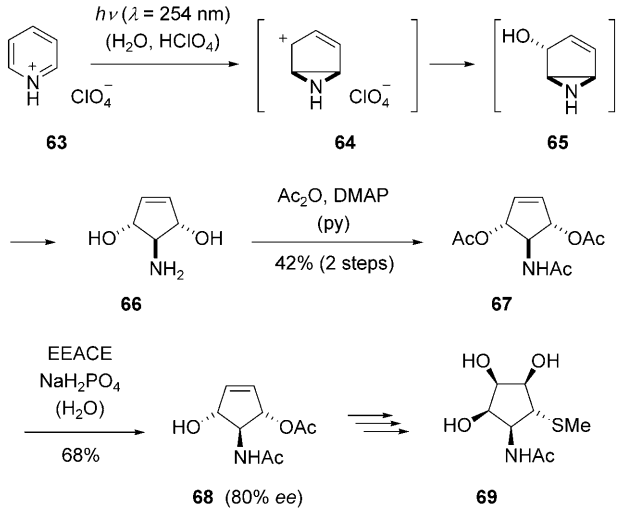
Prior to this report, Gramain and co-workers had detailed the use of (*S*)-α-methylbenzylamine as an auxiliary for reductive photocyclization and had applied the reductive [6π] photocyclization to the asymmetric syntheses of (+)-pipecoline and (+)-coniine.[107] As part of a synthesis of (±)-corytenchirine, Kametani et al. reported an acid-catalyzed [6π] photocyclization of an acetylated enamide that proceeded reductively to afford a quinolizinylium salt, which was subsequently reduced.[108]

### 2.2. [4π] Photocyclizations

[4π] Photocyclizations occur by disrotatory ring closure. Relevant applications in natural product synthesis are based either on the use of pyridinium salts as substrates[109] or on the [4π] cyclization of cycloheptadienones and cycloheptatrienones.

As depicted in Scheme 20, irradiation of the N-unsubstituted pyridinium salt **63** initiates a cationic [4π] cyclization to yield an aziridine, which then undergoes nucleophilic ring opening by a solvent molecule, by an $S_N2$-substitution mechanism, to afford the respective cyclobutane. Thus, product **66**, which can be isolated as the corresponding *meso*-diacetate **67**, is formed in acidic aqueous solution via intermediates **64** and **65**.[110] After enzymatic desymmetrization with an acetylcholine esterase (EEACE), monoacetate **68** served as a key intermediate in Mariano's total syntheses

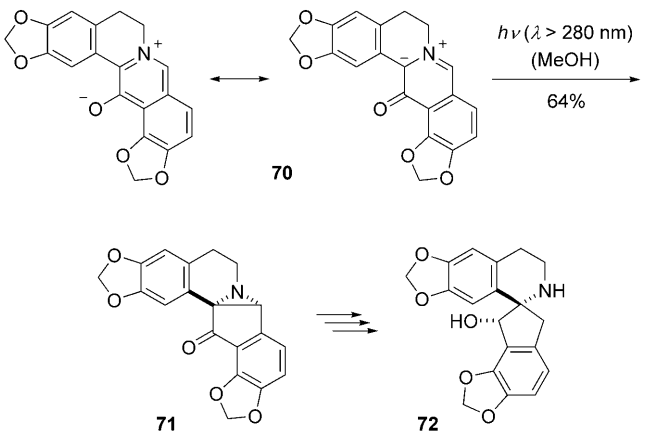



***Scheme 20.*** Total synthesis of (+)-mannostatin (**69**) based on a cationic [4π] cyclization of pyridinium salt **63**. DMAP = 4-(dimethylamino)pyridine; py = pyridine.

of (+)-mannostatin (**69**),[111] (−)-allosamizoline,[112] (−)-swainsonine,[113] and (+)-castanospermine.[114]

Alternatively, direct enantioselective synthesis of intermediates of type **68** can be achieved using N-substituted pyridinium salts, whereby the substituent acts as a chiral auxiliary.[115] This approach was employed in the formal synthesis of hexaacylated (+)-trehazolamine,[116] a known intermediate in the synthesis of (+)-trehazolin.[117] An N-alkylated pyridinium salt was also used as a precursor in a formal total synthesis of (−)-cephalotaxine.[118]

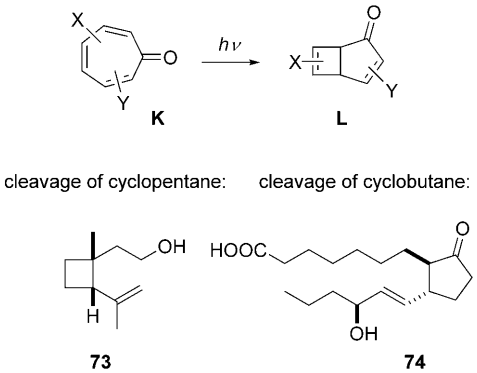
Prior to the syntheses mentioned above, a mechanistically related valence tautomerization of a 3-hydroxypyridine was reported by Hanaoka et al. in the synthesis of (±)-dihydrofumariline-1 (**72**).[119] In this case, phenolbetaine **70** was photochemically converted into aziridine **71**. Diastereoselective reduction of the resultant ketone with $NaBH_4$ delivered the desired relative configuration at the secondary alcohol prior to reductive opening of the aziridine ring (Scheme 21).




***Scheme 21.*** [4π] Cyclization of phenolbetaine **70** to yield aziridine **71** in the total synthesis of (±)-dihydrofumariline-1 (**72**).

A [4π] cyclization product that is closely related to aziridine **71** was employed as an intermediate in the formal total syntheses of the benzindenoazepines (±)-*cis*-alpinigenine (**161**, Scheme 45) and (±)-*cis*-alpinine (**162**, Scheme 45).[120]

[4π] Cyclization of a seven-membered ring system, with the general structure **K**, generates a bicyclic [3.2.0]cycloheptane skeleton **L**, which has been so far utilized in total syntheses by consecutive cleavage of either the four- or the five-membered ring (Scheme 22). This stereospecific ring




***Scheme 22.*** Synthesis of bicyclo[3.2.0]heptadienones **L** by [4π] photocyclization of tropones **K**; structures of (±)-grandisol (**73**) and (±)-11-deoxyprostaglandin $E_1$ (**74**).

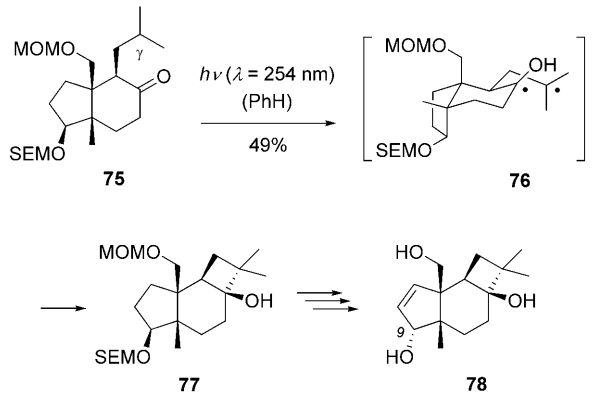
closure was employed in a racemic synthesis of (±)-grandisol (**73**) as a way to establish the correct relative configuration of the two stereogenic centers.[121] A synthesis of (±)-11-deoxyprostaglandin $E_1$ (**74**) was achieved using readily available tropolone methyl ether as the starting material. The [4π] cyclization occurred regioselectively, at the unsubstituted diene, and the resultant methoxycyclobutane was easily opened under oxidative conditions.[122]

## 3. Norrish–Yang Cyclizations

The classic Norrish–Yang cyclization[123] affords cyclobutanes, oxetanes, or azetidines by γ-hydrogen abstraction of a photoexcited carbonyl group to generate a 1,4-diradical. The synthesis of punctaporonins A and D[124] by Paquette and Sugimura (Scheme 23) is a very nice example of the application of this reaction in total synthesis.[125] Irradiation of cyclohexanone **75** delivered the cyclization product **77** via the short-lived intermediate **76**. The relative configuration of the product is determined by the chairlike structure of the diradical **76**. Thus obtained, cyclobutanol **77** was converted into (−)-punctaporonin A (**78**) and its C9 epimer (+)-punctaporonin D.

Following γ-hydrogen abstraction, Norrish type II cleavage may occur in competition with the desired cyclization. In the case of the reaction **75**→**77**, the respective cleavage product was also observed (ca. 20%). If γ-hydrogen abstraction is impossible, a five-membered ring can be formed by

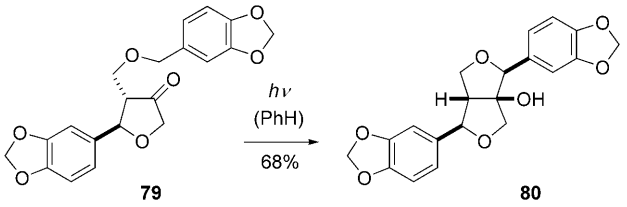
  




***Scheme 23.*** Norrish–Yang cyclization of cyclohexanone **75** to cyclobutane **77** in the synthesis of (−)-punctaporonin A (**78**). SEM = 2-(trimethylsilyl)ethoxymethyl.

abstraction of a δ-hydrogen atom. Clearly, Norrish type II cleavage is not a competing reaction in this case.

An illustrative example of the application of the Norrish–Yang cyclization to generate five-membered rings is the synthesis of (±)-paulownin (**80**).[126] This natural product was obtained directly by irradiation of precursor **79** (Scheme 24).




***Scheme 24.*** Synthesis of (±)-paulownin (**80**) from precursor **79**.

Starting from an enantiomerically pure 3-hydroxybutanolide, the same key reaction was used in the synthesis of (+)-paulownin (**80**) and the closely related lignanes (+)-phrymarin I and II.[127] Further natural products that were synthesized using Norrish–Yang cyclization to form the five-membered ring are depicted in Figure 3. Among these are (±)-cuparene (**81**),[128] the racemic pheromone **82**,[82,129] and (±)-isoretronecanol (**83**).[130] The alcohol resulting from the Norrish–Yang cyclization was reduced in all cases and the newly formed C–C bond is marked in gray.

The synthesis of (±)-cuparene is noteworthy because the thio variant of the Norrish–Yang cyclization was employed, which affords a five-membered ring even in the presence of a

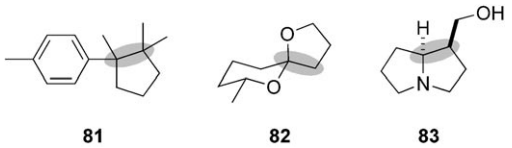
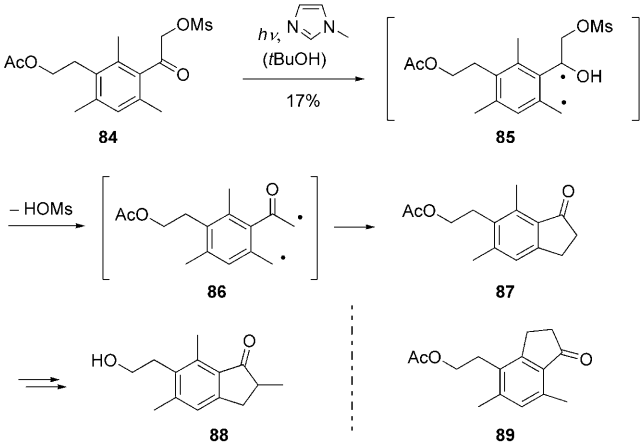



***Figure 3.*** Structures of (±)-cuparene (**81**), pheromone **82**, and (±)-isoretronecanol (**83**).

γ-hydrogen atom.[131] The formation of a six-membered ring by abstraction of an ε-hydrogen atom in the presence of γ- and δ-hydrogen atoms was observed during the photochemical conversion of the secosteroid physalin B into physalin R.[132] Presumably, the spatial positioning of the carbonyl group is responsible for the regioselectivity in this case. It has not been determined if physalin R is a natural product or simply an artifact.

A more recent variation of the Norrish–Yang cyclization was used by Wessig and Teubner for the synthesis of (±)-pterosines B (**88**) and C.[133] Starting from ketone **84**, the photochemically generated 1,4-diradical **85** underwent a spin-center shift[134] to afford 1,5-diradical **86**, which led to the observed products.[135] The crucial step is the elimination of the leaving group in the α position. Unfortunately, the hydrogen abstraction was not regioselective and the unwanted isomer, **89**, was formed in the same yield as the desired product **87** (Scheme 25).




***Scheme 25.*** Spin-center shift as a variant of the Norrish–Yang reaction in the synthesis of pterosin B (**88**).

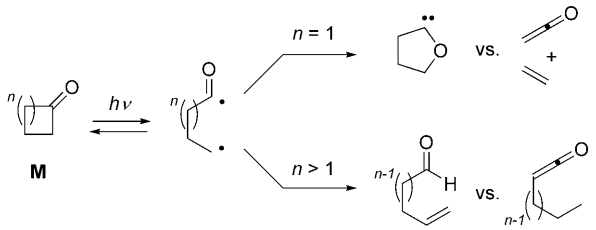
Moreover, it is also likely that other reaction pathways can compete with the elimination. As discussed in Section 6.1, the triplet intermediate **85** might also afford a dienol that has extensive synthetic potential.

In analogy to the classic Norrish–Yang cyclization, α,β-unsaturated γ-ketoamides can be transformed into *N*-alkyl pyrrolidinones.[136] This reaction was employed in the total synthesis of (±)-jatropham.[137]

## 4. Norrish Type I Cleavage Reactions

As indicated by the name, the α cleavage of photoexcited carbonyl compounds, the so-called Norrish type I cleavage,[138] leads to the cleavage of C–C bonds and only rarely to the formation of C–C bonds. Thus, this reaction plays only a minor role in the context of this Review. Nonetheless, the most important synthetically relevant processes are briefly discussed and the relevance of these reactions will be illustrated with the aid of examples. Scheme 26 gives a




***Scheme 26.*** Reaction pathways of ketone **M** after fragmentation by a Norrish type I cleavage.

simplified view of the possible pathways accessible by this reaction starting from the generic cyclic carbonyl compound **M** (which may of course also be substituted) to explain the different products that are observed.

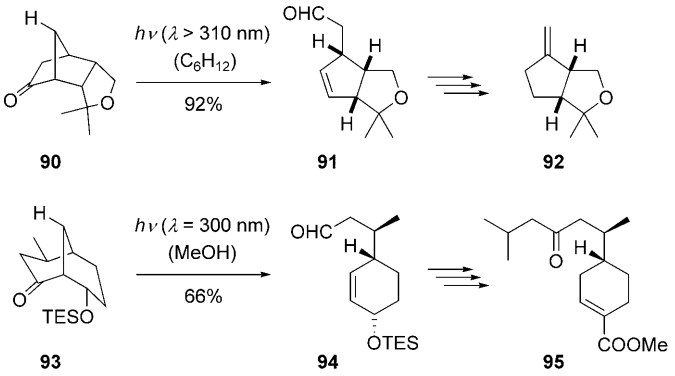
Irradiation of cyclobutanones ($n=1$) generates the corresponding oxacarbene species via a singlet 1,4-diradical, in a reversible reaction. While this species is normally trapped by the solvent, bond cleavage to afford a ketene and an olefin, or decarbonylation/cyclization to generate a cyclopropane (not depicted) are competing pathways in the absence of a trapping agent.

For higher cycloalkanones ($n>1$) recombination of the intermediate cleavage product is possible, which leads to epimerization, or an intramolecular hydrogen abstraction may take place, thus generating an unsaturated aldehyde or a ketene. Alternatively, decarbonylation/cyclization is also possible, one example of which is the synthesis of the cyclopentane ring of (+)- and (−)-α-cuparenone, which was achieved in a nanocrystalline suspension.[139] (±)-Herbertenolide was also synthesized by using a solid-state decarbonylation reaction.[140,141]

### 4.1. Ring Opening To Yield Unsaturated Aldehydes

This reaction generates an unsaturated aldehyde from a cyclic ketone. Generally bicyclo[2.2.1]heptanones, and homologues thereof, are employed as substrates, so the products of this reaction are recognizable (in a retrosynthetic sense) as exocyclic aldehydes that are tethered to the 3-position of a cycloalkene through a methylene or ethylene bridge. For example, aldehyde **91** was produced by irradiation of precursor **90**.[142] After α cleavage, the resulting acyl radical abstracted the depicted hydrogen atom of the substrate and thus delivered the product. γ,δ-Unsaturated aldehyde **91** was subsequently used in the synthesis of (±)-hop ether (**92**; Scheme 27). Further applications of this reaction using bicyclo[2.2.1]heptanones as substrates can be found in the total and formal total syntheses of the iridoids (±)-specionin,[143] (±)-loganin,[144] (±)-teucriumlactone C,[144] (±)-boschnialactone,[144] and (±)-dimethyl secologanoside.[145]

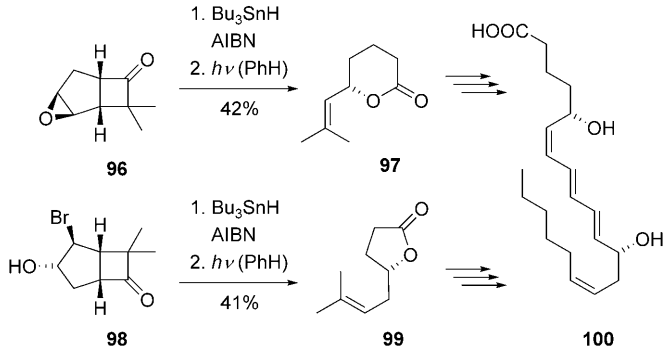
In an analogous reaction, irradiation of enantiopure bicyclo[3.3.1]nonanone **93** afforded unsaturated aldehyde **94**, which was converted into the sesquiterpene (+)-juvabione (**95**).[146]




***Scheme 27.*** Application of the Norrish type I cleavage in the synthesis of (±)-hop ether (**92**) and (+)-juvabione (**95**). TES = triethylsilyl.

### 4.2. Cleavage of Cyclobutanones to Ketenes

This reaction is useful if both the fragments pictured in Scheme 26—the ketene and olefin—are tethered together so that an acyclic compound with defined configuration is obtained after addition of a nucleophile. In this context, Wakefield and co-workers investigated the reaction of bicyclo[3.2.0]heptanones that also carry a suitable group to trap the ketene.[147] Solvents that are capable of trapping the oxacarbene intermediate should be avoided, thus these reactions are carried out in nonpolar solvents, such as pentane or benzene. As shown in Scheme 28, the two stereogenic




***Scheme 28.*** Norrish type I cleavage with nucleophilic trapping of the resultant ketene for the synthesis of both fragments of leukotriene-$B_4$ (**100**).

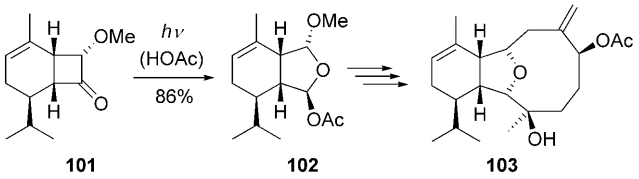
centers of leukotriene-$B_4$ (**100**) can be sourced from both antipodes of dimethylbicyclo[3.2.0]hept-2-en-6-one. One enantiomer was converted into epoxide **96**, the other one into the bromohydrin **98**. After reductive conversion into the respective secondary alcohols, a photochemical rearrangement, via a ketene intermediate, afforded δ-lactone **97** in the former case and γ-lactone **99** in the latter case. After further manipulation, the two parts were joined to afford the target molecule.[148]

Other natural products that were successfully synthesized based on this strategy include (±)-goniothalamin,[149] (±)-argentilactone,[149] the (±)-*Streptomyces* L-factor,[149] and (+)-eldanolide.[147,150] The low yields of the photoreactions in

Scheme 28 (42% for **96**, 41% for **98**) are due to the undesired formation of the oxacarbene species, which can also be trapped in an intramolecular fashion by the tethered nucleophile.

### 4.3. Formation of Oxacarbenes from Cyclobutanones

If irradiation of a cyclobutanone substrate is carried out in a protic solvent the solvent can effectively trap the oxacarbene intermediate. For example, irradiation of cyclobutane **101**, which is easily obtained from α-phellandrene, with a low-pressure Hg lamp in the presence of acetic acid, generated the mixed bisacetal **102**. This compound was subsequently used for the synthesis of deacetoxyalcyonin acetate (**103**), an eunicellin diterpene (Scheme 29).[151]




101 102 103

***Scheme 29.*** Total synthesis of (−)-deacetoxyalcyonin acetate (**103**) by a Norrish type I cleavage with trapping of the intermediate oxacarbene.

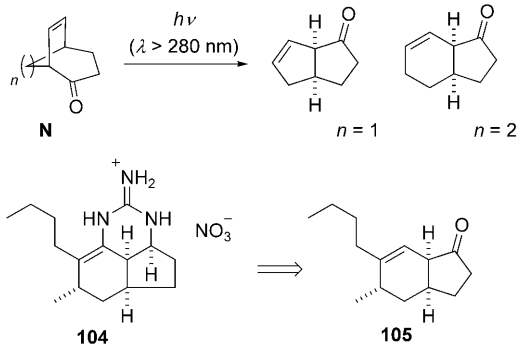
The formation of the oxacarbene is a singlet reaction and thus proceeds, as in the case described above, with retention of configuration of the cleaved bond. Further applications of this rearrangement can be found in the syntheses of (±)-prostaglandin-$F_{2\alpha}$[152] and the fungal metabolites (±)-muscarine,[153] and (±)-*allo*-muscarine.[153]

## 5. Photochemical Rearrangements

Closely related to the Norrish type I cleavage reactions are the two photochemical acyl rearrangements of β,γ-unsaturated carbonyl compounds, namely the 1,3-acyl shift (Section 5.1) and the 1,2-acyl migration (Section 5.2). The latter is commonly referred to as oxa-di-π-methane rearrangement. In both cases the bond in the α position relative to the photoexcited carbonyl group is broken and the acyl group migrates onto the neighboring C=C bond. The 1,3-acyl shift takes place on the singlet hypersurface as a $[_{\sigma}2_s+_{\pi}2_s]$ reaction. The oxa-di-π-methane rearrangement is a triplet process that is carried out in the presence of a sensitizer, usually using acetone as the solvent. The photo-Fries rearrangement (Section 5.3) also involves an acyl migration. Further photochemical rearrangements, including those of cross-conjugated cyclohexadienones (Section 5.4) are also discussed here (Section 5.5).

### 5.1. 1,3-Acyl Migration

The photochemical 1,3-acyl shift is a reversible reaction, thus a synthetic application is only feasible if a distinct thermodynamic force exists, typically in the form of a reduction of ring strain.[154] For example, bicyclo-[3.2.1]octenones (**N**, $n=1$) deliver bicyclo[3.3.0]octenones, while bicyclo[3.2.2]nonenones (**N**, $n=2$) afford the respective bicyclo[4.3.0]nonenones (Scheme 30). A typical target mole-



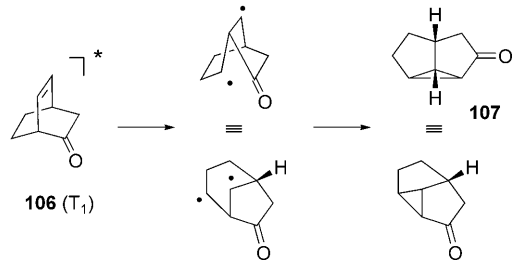

***Scheme 30.*** Synthesis of bicyclo[3.3.0]octenones or bicyclo-[4.3.0]nonenones by photochemical 1,3-acyl migration starting from substrate **N**; 1,3-acyl migration product **105** as a starting point of the synthesis of (±)-ptilocaulin (**104**).

cule for the 1,3-acyl shift is (±)-ptilocaulin (**104**), the bicyclo[4.3.0]nonene core of which can be traced back to ketone **105**.[155] Other syntheses that include these types of photochemically derived compounds as key intermediates are (±)-pinguisone,[156] (±)-deoxopinguisone,[156] and (±)-$\Delta^{9(12)}$-capnellene.[157]

The formal total syntheses of (±)-mussaenoside and (±)-8-epiloganin aglycon both serve to illustrate the use of bicyclo[3.2.1]octenone as a precursor for the synthesis of cyclopentanoid natural products.[158]

### 5.2. Oxa-di-π-Methane Rearrangement

The accessibility of the starting materials and the significant increase in complexity achieved has made the oxa-di-π-methane rearrangement one the most commonly used photochemical rearrangements.[159] Scheme 31 depicts a prototyp-

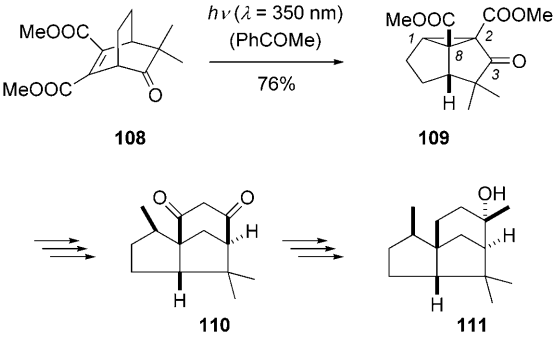



***Scheme 31.*** Simplified mechanism of the oxa-di-π-methane rearrangement, using photochemically excited ketone **106** as an example.

ical substrate for this reaction, bicyclo[2.2.2]octenone (**106**), which undergoes rearrangement to afford the corresponding tricyclo[3.3.0.0$^{2,8}$]octan-3-one (**107**). The C=C bond in this bicyclic system possesses a relatively low triplet energy so, in the presence of an appropriate sensitizer, the molecule is excited into the triplet state ($T_1$). The subsequent stepwise reaction pathway can be understood as a 1,2-acyl shift followed by radical recombination of the resultant 1,3-diradical to afford a cyclopropane. Starting from enantiomerically pure substrate **106**, the tricyclic ketone **107** is obtained as a single enantiomer.

One of the first applications of the oxa-di-π-methane rearrangement in a total synthesis was the formal total synthesis of (±)-cedrol (**111**) by Yates and Stevens.[160] Substrate **108**, obtained by a Diels–Alder reaction, was irradiated in the presence of acetophenone as the sensitizer to afford product **109** (Scheme 32). Ring opening between C1

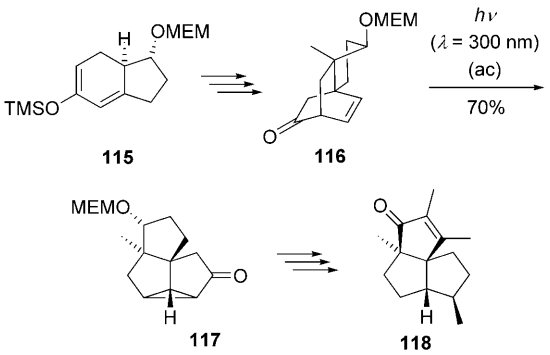



***Scheme 32.*** Formal total synthesis of (±)-cedrol (**111**) by using an oxa-di-π-methane rearrangement of bicyclic precursor **108**.

and C2 of the strained tricyclo[3.3.0.0$^{2,8}$]octane-3-one was achieved by substitution with lithium dimethylcuprate. Thus, the necessary methyl group for the Stork–Clarke diketone (**110**) was introduced stereospecifically and with the required configuration. Conversion of diketone **110** into (±)-cedrol had been reported by Stork and Clarke previously.[161]

In the 1980s Demuth et al. intensively studied the use of the oxa-di-π-methane rearrangement in natural product synthesis.[162] Among others, enantiopure ketone **107**, which was obtained in greater than 85% yield by an oxa-di-π-methane rearrangement, was used as the starting material for the syntheses of (+)-loganin aglycon 6-acetate (**112**)[163] and iridodial (Figure 4).[164,165] A diketone related to **106** was triply methylated and served as the starting material in a synthesis of (−)-coriolin (**113**).[166] Further routes to (±)-coriolin (**113**) starting from trimethylated bicyclo[2.2.2]octenediones were reported by Singh et al.[167a,b,h] Other linear triquinanes that have been synthesized using an oxa-di-π-methane rearrangement as the key step are (±)-Δ$^{9(12)}$-capnellene,[167c,168] (−)-phellodonic acid,[169a] (±)-[167d,e] and (−)-hirsutene,[169b,c] (±)-[167f] and (−)-complicatic acid,[169d,e] and finally (±)-[167f,g] and (+)-hirsutic acid (**114**),[169d,e] which will be discussed later in this section.

Angular triquinanes and triquinanes with a propellane structure are similarly accessible by an oxa-di-π-methane rearrangement. Demuth and Hinsken employed the Hajos–Sauer–Wiechert reaction[170] for the synthesis of bicyclic starting material **115**, which was then converted in a few steps into compound **116**, the substrate for an oxa-di-π-methane rearrangement.[171] The efficient rearrangement of this substrate provides proof that even sterically demanding substrates can be employed without problems. In this example, only 4% of the side product resulting from the 1,3-acyl shift was isolated. Bond cleavage of the cyclopropane ring in photoproduct **117** was carried out reductively (Li, *t*BuOH), and the resulting enolate was α methylated. Eight subsequent steps afforded the sesquiterpene (−)-silphiperfol-6-en-5-one (**118**, Scheme 33).




***Scheme 33.*** Construction of the carbocyclic skeleton of (−)-silphiperfol-6-en-5-one (**118**) by using an oxa-di-π-methane rearrangement. MEM = 2-(methoxyethoxy)methyl; ac = acetone.

Mehta and Subrahmanyam used an indenone that was produced by a Robinson annulation for the synthesis of the [3.3.3]propellane (±)-modhephene (**121**).[172] The indenone was converted into compound **119**, the substrate for the key reaction, and upon irradiation, product **120** was obtained in 50% yield. The product resulting from a 1,3-acyl shift was also observed in minor quantities and was possibly formed in an unsensitized reaction. After α,α-dimethylation and reductive cleavage (Li, $NH_3$) of ketone **120**, the target molecule was generated in three further steps (scheme 34).

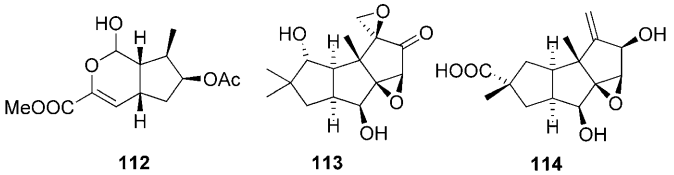
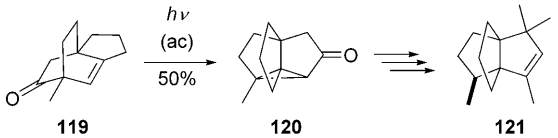



***Figure 4.*** Structures of (+)-loganin aglycon 6-acetate (**112**), (−)-coriolin (**113**), and (+)-hirsutic acid (**114**).

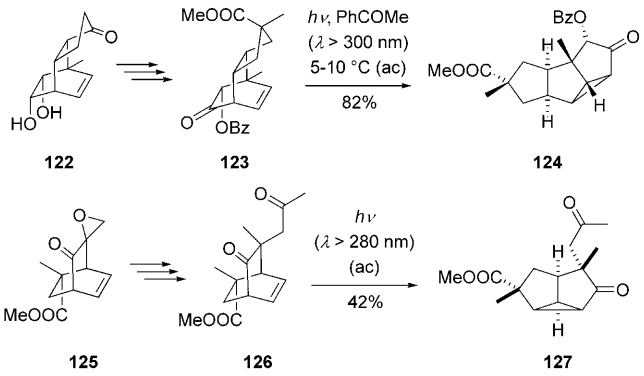



***Scheme 34.*** Oxa-di-π-methane rearrangement of tricyclic substrate **119** as a key step in a synthesis of (±)-modhephene (**121**).

A similar route to both (±)-modhephene (**121**) and the related sesquiterpene (±)-isocomene (**191**, Scheme 52) were reported by Uyehara et al.[173]

The Diels–Alder reaction is often used for the synthesis of the bicyclo[2.2.2]octenones that serve as substrates for the oxa-di-π-methane rearrangement. Although the required cyclohexadiene starting materials can be made in a variety of ways, the recent studies by Singh et al.[167] and Banwell and co-workers[169] are the most noteworthy in this context. While Singh et al. used reactive dienes that were generated by the Adler reaction of salicyl alcohols, Banwell and co-workers employed enantiomerically pure dienes, which were obtained by microbial dihydroxylation of toluene. To allow comparison, some of the intermediates that were produced during the total syntheses of (+)-[169d,e] and (±)-hirsutic acid[167f,g] (**114**, Figure 4) are depicted in Scheme 35, namely the primary Diels–Alder cycloaddition products **122** and **125**, as well as the substrates (**123** and **126**) and products (**124** and **127**) of the oxa-di-π-methane rearrangement.

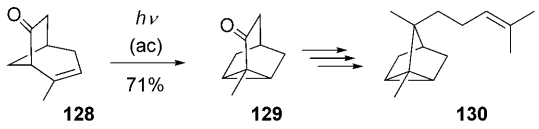



***Scheme 35.*** Comparison between the oxa-di-π-methane rearrangement of ketones **123** and **126** in two syntheses of hirsutic acid (**114**, Figure 4).

Further applications of this synthetic strategy can be found in the triquinane syntheses mentioned above and in the syntheses of the cedranoids (±)-α- and (±)-β-biotol.[174]

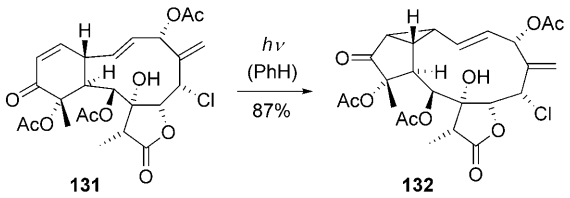
Liao and co-workers also used the oxa-di-π-methane rearrangement of an bicyclo[2.2.2]octenone that was obtained by a Diels–Alder reaction for the syntheses of (±)-$\Delta^{9(12)}$-capnellene[175] and the *Lycopodium* alkaloid (±)-magellanine.[176]

Although less common than the bicyclo[2.2.2]octenones, other bicyclic alkenones can also be used as substrates for the oxa-di-π-methane rearrangement. Scheme 36 shows an early example of the application of a bicyclo[3.2.1]octenone in the synthesis of (±)-α-santalene (**130**).[177] Irradiation of a solution of ketone **128** in acetone with a high-pressure Hg lamp afforded tricyclooctanone **129**. A ring contraction via the diazoketone then generated the tricyclo[2.2.1.$0^{2,6}$]heptane core of the tricyclene terpenoid. The natural product (±)-teresantalic acid was produced as an intermediate in the subsequent synthesis.




***Scheme 36.*** Unusual substrate **128**, which underwent oxa-di-π-methane rearrangement in the synthesis of (±)-α-santalene (**130**).

Synthetically related to the oxa-di-π-methane rearrangement are the di-π-methane rearrangement and the aza-di-π-methane rearrangement.[178] Both rearrangements play a much less important role in natural product synthesis than the oxa-di-π-methane rearrangement. The di-π-methane rearrangement typically occurs by a singlet process, whereas the aza-di-π-methane rearrangement is carried out in the presence of a sensitizer. Clardy, Fenical and co-workers reported that the diterpene erythrolide A (**132**) is most probably formed in nature by a di-π-methane rearrangement of erythrolide B (**131**), and showed they could generate erythrolide A synthetically by using this reaction pathway (Scheme 37).[179] The rearrangement of (±)-9,10-deoxytridachione to (±)-photodeoxytridachione is also thought to be a di-π-methane rearrangement but proceeds through a stepwise mechanism involving a 1,2-migration and subsequent formation of a 1,3-diradical.[180]




***Scheme 37.*** Biomimetic di-π-methane rearrangement of erythrolide B (**131**) to furnish erythrolide A (**132**).

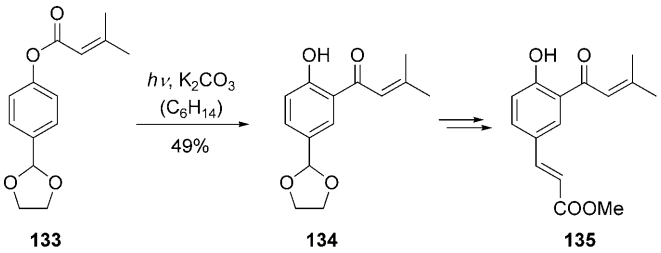
Both the di-π-methane rearrangement[181] and the aza-di-π-methane rearrangement[182] have been employed for the formation of the cyclopropyl ring in pyrethroids, such as chrysanthemic acid.

### *5.3. Photo-Fries Rearrangements*

As opposed to the thermal Fries rearrangement the photo-Fries rearrangement does not require strong Lewis acids, and thus offers a mild synthetic alternative.[183] Irradiation of phenolic esters with light of short wavelength (commonly $\lambda = 254$ nm) brings about homolytic cleavage of the ester bond, which results in the formation of a phenoxyl radical and an acyl radical.[184] Radical recombination can then occur in either the *ortho* or the *para* position. The presence of substituents at the respective positions results in perfect regioselectivity often being achieved.

An illustrative example of a photo-Fries rearrangement can be found in the total synthesis of capillarol (**135**) by Yokota and co-workers (Scheme 38). While rearrangement of ester **133** to furnish the *ortho*-acylated phenol **134** was not successful using Lewis acids such as $AlCl_3$, $TiCl_4$, or poly-




***Scheme 38.*** Total synthesis of capillarol (**135**) involving a photo-Fries rearrangement of ester **133** to afford phenol **134**.

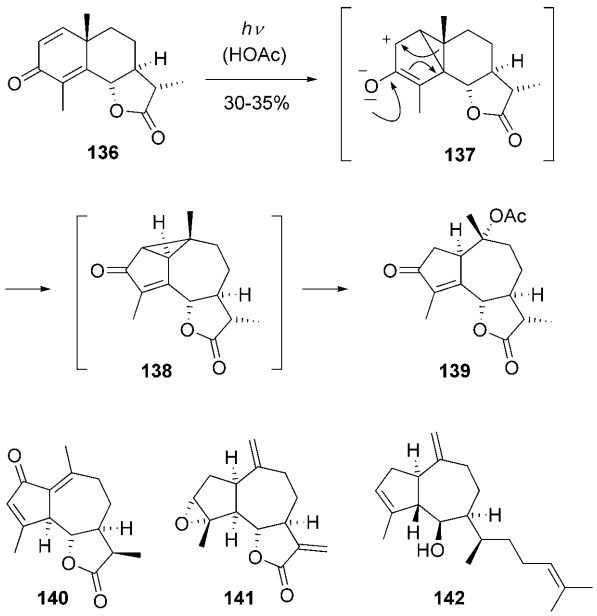
phosphoric acid, the desired product could be obtained in 49% yield by irradiation with a high-pressure Hg lamp.[185]

A recent total synthesis of the antibiotic (−)-kendomycin by Mulzer and co-workers demonstrates that complex macrolactones can also be excellent substrates for the photo-Fries rearrangement.[186] The photo-Fries rearrangement has been used several times for the synthesis of polycyclic hydroxyquinones, for example (±)-griseofulvin,[187] islandicin,[188] bikaverin,[189] and spinochrome A.[190] Furthermore, the photo-Fries rearrangement can be found in syntheses of the benzopyran natural products precocene I and II[191] as well as the alkaloids arizonine[192] and (±)-caseadine.[192] An extended form of the photo-Fries rearrangement was employed in the syntheses of the monoterpenoid indole alkaloids (±)-tubotaiwine[193] and (±)-deethylibophyllidine.[194] In both cases, the last step of the synthesis involved irradiation of an aminoacrylate to afford the desired *N*-methoxycarbonyl enamine product. A formal photo-Fries product can also be obtained by a photo-Friedel–Crafts reaction,[195] which was employed in the synthesis of α- and β-lapachone.[196]

### 5.4. Rearrangements of Cross-Conjugated Cyclohexadienones

As early as 1834 Trommsdorff observed a photochemical reaction of solid (−)-α-santonin.[197] The mechanism of the rearrangement, whereby the cross-conjugated cyclohexadienone[198] (−)-α-santonin (**136**) is converted into (+)-*O*-acetyl isophotosantonic acid (**139**) upon irradiation in acetic acid, is depicted in Scheme 39.[199] Initially, through a triplet reaction, the tricyclic cyclopropane **137** is formed, which then rearranges by way of a 1,4-migration to form intermediate **138**. Subsequent nucleophilic attack of acetic acid results in C–C bond cleavage and formation of *O*-acetylisophotosantonic acid.[200] This rearrangement served as the starting point for several natural product syntheses. Among these are the guaianes (+)-achillin (**140**),[201] (−)-estafiatin (**141**),[202] (+)-pachydictyol A (**142**),[203] (−)-oxoisodehydroleucodin,[204] (+)-jalcaguaianolide,[205] 1α,7α,10α*H*-guaian-4,11-dien-3-one,[206] hydrocolorenone,[206] plagiochiline N,[207] and both epimers of the iso-*seco*-tanapartholides.[208]

The photochemical rearrangements of santonin derivatives proceeded in distinctly better yields if the lactone moiety had first been opened. The syntheses of several 4α-hydroxy-8,12-guaianolides,[209] of (+)-podoandin, and of (+)-zedolac-




***Scheme 39.*** Mechanistic course of the rearrangement of (−)-α-santonin (**136**) to yield (+)-*O*-acetyl isophotosantonic acid (**139**); structures of the natural products (+)-achillin (**140**), (−)-estafiatin (**141**), and (+)-pachydictyol A (**142**).

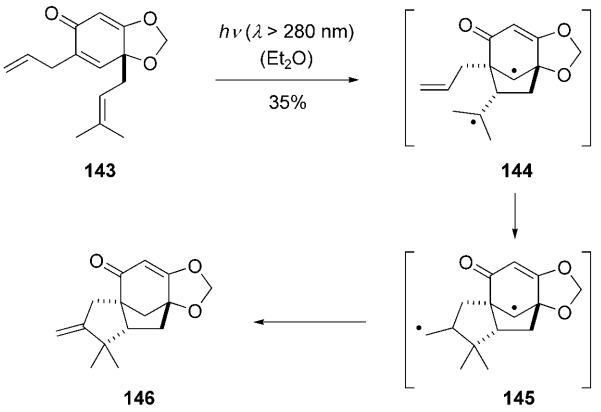
tone A were achieved in this manner.[210] Additional natural products that have been generated by photochemical rearrangement of a cyclohexane-annulated cyclohexadienone include (±)-β-vetivone,[211] (−)-cyclocolorenone,[212] and (−)-axisonitrile-3.[213] The analogous reaction, utilizing a cyclopentane-annulated cyclohexadienone, was employed as the key step in the syntheses of the sesquiterpenes (±)-oplopanone,[214] (±)-α-cadinol, and (±)-3-oxo-α-cadinol.[215]

The photochemical properties of the phytoquinoid cyclohexadienone (−)-illicinone A (**143**) were studied intensively after its isolation. It was found that (±)-illicinone A (**143**) can be synthesized by photochemical rearrangement of the prenyl phenyl ether illicinol and that irradiation of (−)-illicinone A (**143**) results in formation of (−)-tricycloillicinone (**146**).[216] This reaction clearly does not follow the pathway shown in Scheme 39, but rather takes place via the diradical intermediates **144** and **145**. These observations were recently exploited in a biomimetic total synthesis of (±)-tricycloillicinone (**146**) (Scheme 40).[217]

### 5.5. Other Rearrangements

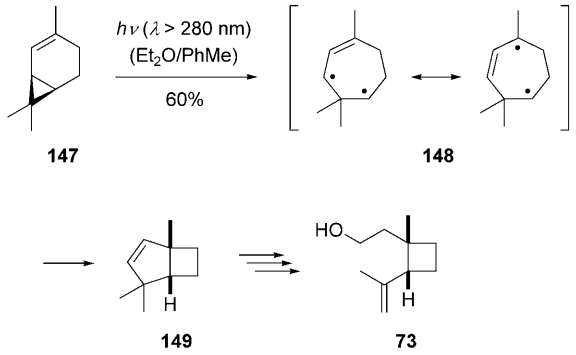
It was already observed 50 years ago that, upon irradiation with a mercury lamp, the monoterpene (+)-verbenone undergoes a [1,3]-shift to generate (+)-chrysanthenone.[218] Additionally, the sesquiterpene (+)-vulgarone A, a homologue of (+)-verbenone, also undergoes a photoinduced [1,3]-shift to afford (+)-vulgarone B.[219] A number of total syntheses have been achieved by using the photoinduced rearrangement of a vinylcyclopropane, for example, the synthesis of (+)-α- and (+)-β-cyperone starting from (−)-epimaalienone,[220] and the syntheses of (±)-grandisol (**73**)[221]




***Scheme 40.*** Synthesis of (±)-tricycloillicinone (**146**) starting from (±)-illicinone A (**143**).

and (−)-$\Delta^{9(12)}$-capnellene.[221b] (+)-$\Delta^2$-Carene (**147**) served as the starting material in the formal total synthesis of (±)-grandisol (**73**).[221] Irradiation of **147** generated bicyclo-[3.2.0]heptene **149** via diradical **148** (Scheme 41).




***Scheme 41.*** Formal total synthesis of (±)-grandisol (**73**) by photo-induced vinylcyclopropyl rearrangement of (+)-$\Delta^2$-carene (**147**).

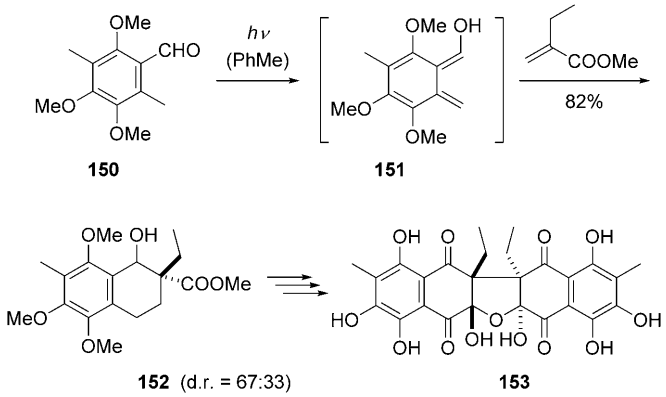
A [3,3] migration of a bicyclo[3.2.2]nonadienone allowed (±)-sesquicarene to be obtained.[222] A quinone served as the chromophore for the photochemical isomerization of (+)-komaroviquinone to (+)-komarovispirone, a reaction that is though to be part of the biosynthetic pathway.[223] In another biomimetic reaction, the photoinduced skeletal rearrangement of (−)-thebaine proceeded under basic conditions to afford neodihydrothebaine and bractazonine.[224]

## 6. Reactions via Dienol Intermediates

Two kinds of dienols play important roles as intermediates for structures of relevance to total synthesis. These are the *ortho*-quinodimethanes[225] (Section 6.1), which are derived from *ortho*-alkyl-substituted aromatic ketones or aldehydes, and the photodienols (Section 6.2), which are obtained from α,β-unsaturated esters and amides by γ-hydrogen abstraction. In the former case the photochemically generated intermediate is usually trapped in a Diels–Alder reaction,[226] whereas in the latter case stereoselective protonation generates a β,γ-unsaturated product with a stereogenic center in the α position.

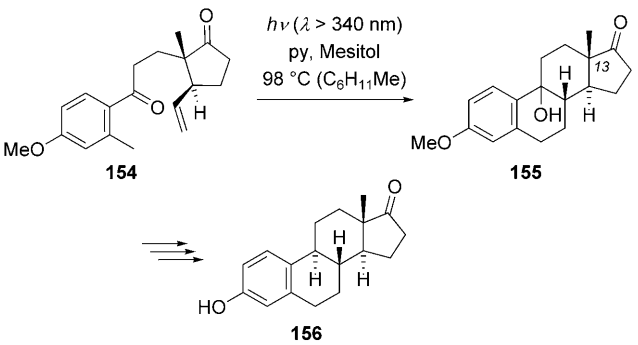
### 6.1. [4+2] Cycloadditions of ortho-Quinodimethanes

In a reaction that is analogous to the initial step of a Norrish–Yang cyclization, a hydrogen atom can be abstracted from the alkyl substituent of an aromatic carbonyl compound. As this reaction takes places via a triplet intermediate, both the *E*- and the *Z*-configured products are formed. In the case of an intermolecular reaction, the longer lived (*E*)-dienol is trapped almost exclusively. The first steps in the total synthesis of (±)-hybocarpone (**153**) provide an example of a reaction of this type. Irradiation of aromatic aldehyde **150** resulted in the formation of dienol **151**, which subsequently underwent [4+2] cycloaddition to generate tetrahydronaphthalene **152** (*exo*/*endo* = 67:33; Scheme 42).[227]




***Scheme 42.*** Synthesis of (±)-hybocarpone (**153**) by Diels–Alder reaction of the photochemically generated dienol **151**.

One of the classic total syntheses discussed in this Review is the synthesis of (+)-estrone (**156**) by Quinkert et al., in which an intramolecular Diels–Alder reaction of a photochemically generated *ortho*-quinodimethane is employed as the key step (Scheme 43).[228] Cycloaddition of precursor **154**

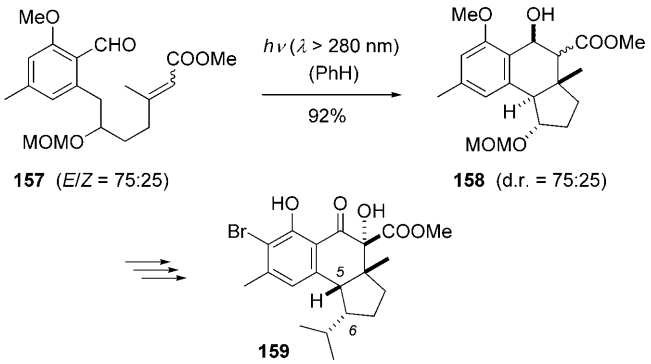



***Scheme 43.*** Application of the photodienol/Diels–Alder sequence in the synthesis of (+)-estrone (**156**).

afforded the epimeric alcohols **155**, which could be converted into the target molecule (**156**) by dehydration and further literature-known transformations.[229] Careful optimization of the reaction conditions resulted in epimerization at C13 of the estrone skeleton, by Norrish type I cleavage, as well as other side reactions being avoided.

One of the key steps in the syntheses of the hamigerans by Nicolaou et al. is the intramolecular Diels–Alder reaction of an *ortho*-quinodimethane. This intermediate was generated photochemically from precursor **157** (Scheme 44) and afforded the tricyclic product **158**.[230] In addition to the depicted methoxymethyloxy-substituted starting material, the corresponding isopropyl-substituted compound could also be used in the photochemical step. In this case, however, the necessary epimerization at C5 was unsuccessful. Besides the depicted (±)-hamigeran A (**159**), hamigerans B and E were also synthesized in this way.

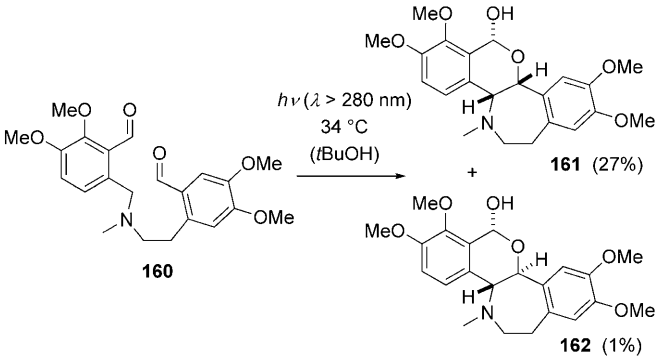



**157** (*E*/*Z* = 75:25) **158** (d.r. = 75:25) **159**

***Scheme 44.*** Total synthesis of (±)-hamigeran A (**159**) by intramolecular [4+2] cycloaddition of a photochemically generated *ortho*-quinodimethane.

A putative application of the [4+2] cycloaddition of a photochemically generated *ortho*-quinodimethane is found in the synthesis of the B ring of the tetracyclin 6-methylpretetramide,[231] although the authors suggest a different reaction mechanism.[232] A further example is the formal total synthesis of (±)-podophyllotoxin by Kraus and Wu.[233]

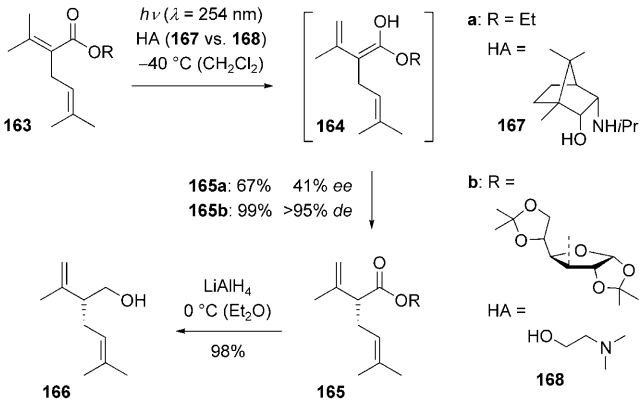
The *ortho*-quinodimethane that is formed upon irradiation of *ortho*-alkylated aromatic aldehydes can also be trapped by an aldehyde in a hetero-Diels–Alder reaction. Irradiation of dialdehyde **160** afforded a complex mixture of reaction products, from which the *endo* cyclization product (±)-*cis*-alpinigenine (**161**) and the *exo* cyclization product (±)-alpinigenine (**162**) could be isolated (Scheme 45).[234]




***Scheme 45.*** Hetero-Diels–Alder reaction of a photodienol in the synthesis of the natural products (±)-*cis*-alpinigenine (**161**) and (±)-alpinigenine (**162**).

### 6.2. Deconjugation of α,β-Unsaturated Carbonyl Derivatives

α,β-Unsaturated esters and amides can be converted into the respective dienols by using light of short wavelength ($\lambda$ = 254 nm). The reaction is a singlet process and occurs through γ-hydrogen abstraction. As *E*/*Z* isomerization of the photoexcited intermediate can also take place, it is sensible to use substrates that are symmetrically substituted in the β position. During the reaction, protonation of the dienol at the α position by an external proton source results in deconjugation of the double bond. The configuration of the newly formed stereogenic center can be controlled either by a chiral proton source, which represents an enantioselective reaction, or by a chiral auxiliary in the presence of an achiral acid, which represents a diastereoselective reaction.[235] Both cases are illustrated in Scheme 46 for the synthesis of (−)-lavandulol (**166**), which was described by Piva.[236] The camphor-derived amino alcohol **167** was employed as a chiral acid in the case of the prochiral ethyl ester **163a**. This resulted in enantioselective protonation of intermediate dienol **164a**, albeit in only 41% *ee*. The low selectivity was attributed to the substituent in the α position, as other examples employing similar substrates afforded much higher *ee* values.[237] The target molecule was subsequently obtained by reduction of ester **165a**.




**163** **164** **167** **168** **166** **165**

***Scheme 46.*** Enantioselective or diastereoselective syntheses of (−)-lavandulol (**166**) by protonation of a photochemically deconjugated ester.

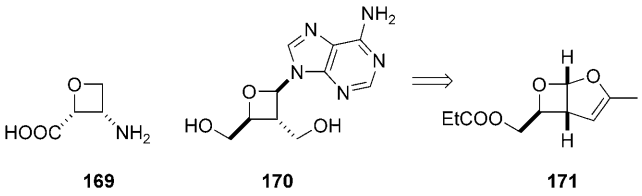
As an alternative method, diacetonglucose can be used as a chiral auxiliary, as in ester **163b.** Diastereoselective protonation of enol **164b** with *N*,*N*-dimethylaminoethanol (**168**) delivered the corresponding β,γ-unsaturated ester with per-

fect facial diastereoselectivity. Needless to say, the deconjugation can also be carried out racemically, as seen in the syntheses of a San José scale pheromone,[238] (±)-anhydrobisfarnesol,[239] and (±)-amphiasterin B4.[240]

## 7. Paternò–Büchi Reaction

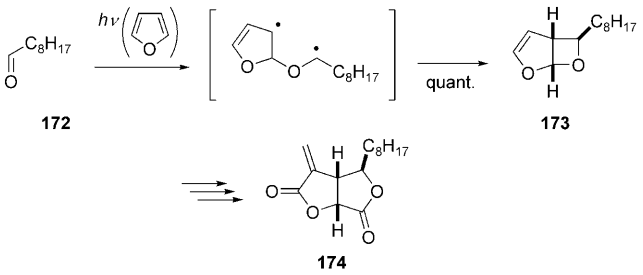
In this long-known photocycloaddition,[241] photoexcited carbonyl compounds react with olefins to yield oxetanes.[242] Electron-rich olefins are most commonly used as substrates, and the reaction normally takes place via triplet intermediates. The reaction is, therefore, not concerted but proceeds via a 1,4-diradical intermediate, which must undergo a spin flip—an intersystem crossing (ISC)—prior to cyclization. The number of naturally occurring oxetanes is limited so it is not surprising that most applications of Paternò–Büchi reactions in natural product synthesis include a cleavage of the oxetane ring. Among the naturally occurring oxetanes the two simple natural products (±)-oxetine (**169**) and (±)-oxetanocin (**170**) were generated with the help of a Paternò–Büchi reaction (Scheme 47). Butylglyoxylate and a suitably protected enamine served as substrates in the synthesis of (±)-oxetin (**169**),[243] while for (±)-oxetanocin (**170**) propionyloxyacetaldehyde was treated with a furan to yield product **171**, which was subsequently transformed into the natural product.[244]




***Scheme 47.*** Structures of (±)-oxetine (**169**) and (±)-oxetanocin (**170**), which were synthesized by using a Paternò–Büchi reaction.

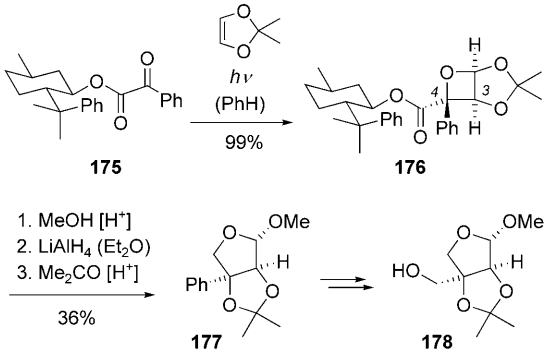
The Paternò–Büchi reaction of furans[245] has been studied intensively by Schreiber et al., and was used in the syntheses of the natural products (±)-avenaciolide[245a,246] and (±)-asteltoxin.[245a,247] These syntheses exploited the fact that the bicyclic products, such as **173**, are formal *anti*-aldol products because of their inherent 1,3-difunctionality. Racemic (±)-avenaciolide (**174**) was synthesized from bicycle **173**, which is the product of a Paternò–Büchi reaction between nonanal (**172**) and furan. The relative configuration of the three stereogenic centers generated during the Paternò–Büchi reaction remained intact in the natural product. The stepwise mechanism of the Paternò–Büchi reaction is also depicted in Scheme 48. The simple diastereoselectivity of the reaction is governed by a preference for the thermodynamically more stable product. There are exceptions, however, for reactions, in which the preferred ISC geometry favors the opposite product.[248]

2(4)-Alkoxy-substituted oxetanes can generally be viewed as latent carbonyl compounds. Oxetanes with 1,2,3-trifunctionality are generated when 1,3-dioxoles are employed as the




***Scheme 48.*** Stepwise formation of the Paternò–Büchi product **173**, which led to the natural product (±)-avenaciolide (**174**).

olefin component of the Paternò–Büchi reaction. This reaction was exploited in the enantioselective synthesis of (+)-β-L-apio-L-furanoside (**178**) by Scharf and co-workers.[249] By using an auxiliary approach,[250] oxetane **176** was obtained with high diastereoselectivity by photocycloaddition of phenylglyoxylate **175** with 2,2-dimethyl-1,3-dioxole. Tetrahydrofuran **177** was generated with retention of the stereochemistry at C3 and C4, and was subsequently converted into the desired product by exhaustive aromatic oxidation and reduction of the resulting carboxylic acid (Scheme 49).

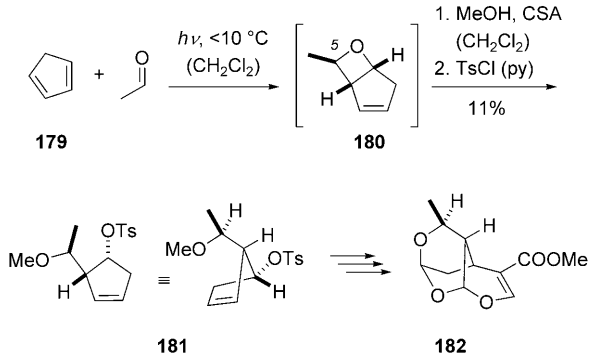



***Scheme 49.*** Diastereoselective Paternò–Büchi reaction en route to (+)-β-L-apio-L-furanoside (**178**).

In cases where the oxetane products do not possess an acetal moiety, ring opening can be achieved by nucleophilic substitution or hydrogenolysis. In the synthesis of (±)-sarracenin (**182**) by Hoye and Richardson (Scheme 50), the Paternò–Büchi product **180**, which was obtained from cyclopentadiene and acetaldehyde, was opened at C5 by methanolysis, which resulted in inversion of the configuration at this center.[251] The resultant secondary alcohol was subsequently tosylated. The correct relative stereochemistry required for the natural product (**182**) was established by nucleophilic substitution of tosylate **181** with an appropriate enolate.

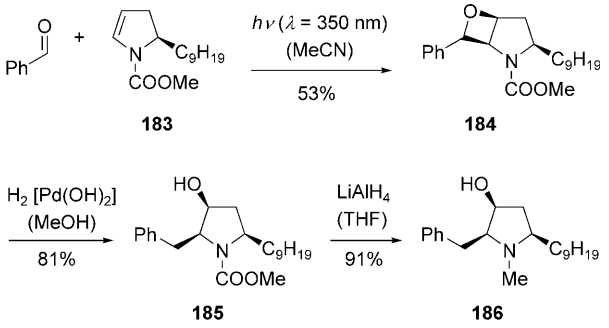
If the C2- or C4-position of a monocyclic oxetane is unsubstituted, substitution usually follows an $S_N2$ mechanism. A simple example is the synthesis of (±)-pseudoephedrine from a photochemically generated aminooxetane.[252] Aromatic aldehydes and ketones readily react as the carbonyl




***Scheme 50.*** Access to (±)-sarracenin (**182**) by a Paternò–Büchi reaction. CSA = camphorsulfonic acid, Ts = toluenesulfonyl.

component in the Paternò–Büchi reaction, and subsequent ring opening of the resulting 2-aryl-substituted oxetanes can easily be achieved by hydrogenolysis. The regioselectivity and the simple diastereoselectivity of the photocycloaddition is generally high, thus the Paternò–Büchi reaction/hydrogenolysis sequence is an attractive method to achieve a carbohydroxylation of an alkene.[253] This concept was applied in the synthesis of (+)-preussin (**186**, Scheme 51). Enamine **183**,

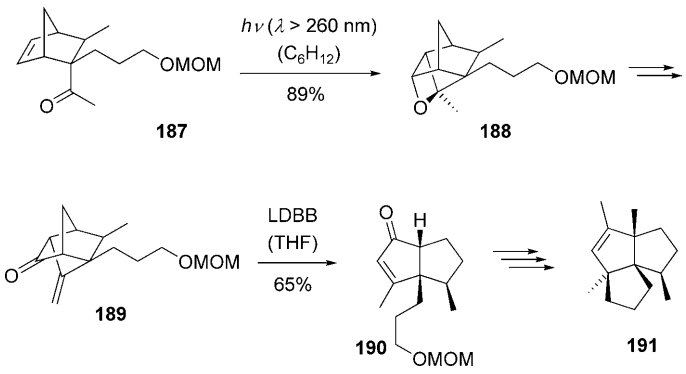



***Scheme 51.*** Construction of two stereogenic centers by a Paternò–Büchi reaction in the synthesis of (+)-preussin (**186**).

which is readily accessible from L-pyroglutamic acid, was treated with benzaldehyde to afford oxetane **184** in 53% yield. Hydrogenolysis afforded alcohol **185**, and subsequent reduction of the methoxycarbonyl group afforded the enantiomerically pure natural product, which turned out to be a potent CDK2 inhibitor.[254]

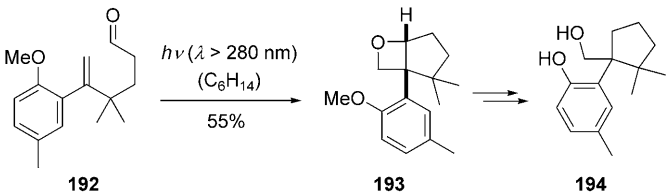
The Paternò–Büchi reaction can be viewed as a step in metathesis if combined with a subsequent thermolysis. However, applications have so far been limited to the synthesis of simple pheromones.[255]

An elegant use of the intramolecular Paternò–Büchi reaction in natural product synthesis was described by Rawal and Dufour.[256] In a first step, bicyclic acetyl norbornenes such as compound **187** were photochemically converted into their respective oxetanes (such as **188**). Subsequent base-catalyzed elimination resulted in opening of the four-membered ring to form the corresponding homoallylic alcohols, which were then converted into ketones, such as **189**, by oxidation. Finally, reductive cleavage of the tricyclic skeleton with lithium di-*tert*-butylbiphenylide (LDBB) gave stereoselective access to the diquinane skeleton. In the present case, diquinane **190** was converted into the triquinane natural product (−)-isocomene (**191**, Scheme 52).[257] Further applications can be found in the syntheses of (±)-hirsutene,[258] (±)-modhephene (**121**, Scheme 34),[259] (±)-5-oxosilphiperfol-6-ene,[260] and (±)-silphiperfol-6-ene.[260]




***Scheme 52.*** Synthesis of (−)-isocomene (**191**) by intramolecular Paternò–Büchi reaction of ketone **187** and reductive cleavage of tricyclic compound **189**.

Even oxetanes can be opened reductively with LDBB. Grainger and co-workers employed the reductive ring opening of oxetane **193**, which was synthesized from δ,ε-unsaturated aldehyde **192** by an intramolecular Paternò–Büchi reaction, in the synthesis of (±)-herbertendiol (**194**). The more-substituted bond is cleaved preferentially under reductive conditions (LDBB, $Et_2AlCl$), thus the natural product was obtained in two steps (including deprotection) from intermediate **193** (Scheme 53).[261]




***Scheme 53.*** Oxetane **193**, formed by a Paternò–Büchi reaction, as precursor for the synthesis of (±)-herbertendiol (**194**).

## 8. [2+2] Photocycloadditions of Olefins

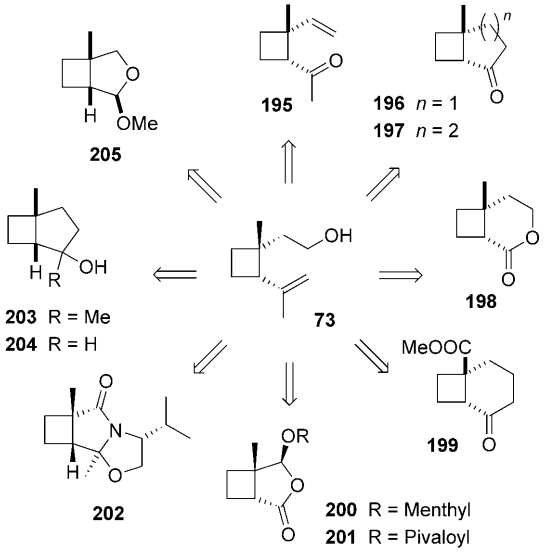
No other photochemical reaction has had such a large impact on natural product synthesis as the [2+2] photocycloaddition of olefins.[262] The [2+2] photocycloadditions that are typically used in total synthesis can be classified according to three reaction pathways. The most important substrates are α,β-unsaturated, mostly cyclic, carbonyl compounds that upon direct excitation reach a comparatively stable ππ* triplet state via a short-lived singlet state. In a

manner similar to the Paternò–Büchi reaction, formation of the cyclobutane ring takes place by ring closure of a 1,4-diradical.[263] Population of the triplet state can also be achieved by sensitization. This is the second important reaction pathway and such reactions can be identified by the addition of triplet sensitizers to the reaction mixture. Acetone (often as the solvent), benzophenone, or acetophenone are typical examples. By this means it is also possible to excite other olefins that possess a low triplet energy, for example, dienes or styrenes. Lastly, copper salts can be employed as catalysts. By excitation of the charge-transfer band of the respective copper(I)-alkene complex at $\lambda \approx 250$ nm a direct [2+2] photocycloaddition is possible.[264] Preparatively, this reaction is only useful for 1,6-dienes, which afford bicyclo[3.2.0]heptanes or the corresponding heterocycles if there is a heteroatom present in the chain.

### 8.1. Synthesis of Cyclobutanes

In principle, retrosynthetic analysis of naturally occurring cyclobutanes is facile and the substrates that are required for the appropriate [2+2] photocycloaddition are readily identified. Apart from considering the parameters that govern the regio- and stereoselectivity, the key issue is to select starting materials that can be photochemically excited in a feasible manner, as demonstrated in the syntheses of grandisol (**73**), a sex pheromone of the boll weevil. The naturally occurring form is (+)-grandisol (**73**), which possesses the depicted absolute and relative configuration, and this natural product probably holds the record for the most photochemical approaches to its synthesis (see Schemes 22, 41, and 67). Scheme 54 shows various routes to grandisol, all of which involve the use of a [2+2] photocycloaddition for the construction of the cyclobutane ring.[265] The research group that discovered grandisol (**73**) was the first to complete its synthesis by a photochemical approach, by using a very




***Scheme 54.*** Retrosynthetic disconnection of (±)- and (+)- grandisol (**73**) into reported [2+2] photocycloaddition products.

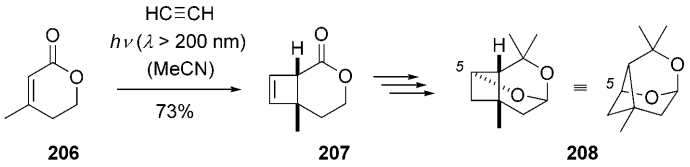
unselective intermolecular [2+2] photocycloaddition to generate intermediate **195**.[266] The enone photocycloadditions of ethylene to 3-methylcyclopent-2-enone[267] or 3-methylcyclohex-2-enone[268] proceeded more efficiently to afford cyclobutanes **196** or **197**. The racemic intermediate **196** was also used to achieve an enantioselective synthesis of (+)-grandisol (**73**) by kinetic resolution.[269] Products **198**[270] and **199**[271] were generated from the appropriate lactone (acetophenone as a sensitizer) and ketoester precursors. While 5-substituted 4-methyl-2(5*H*)-furanones (butenolides) could be prepared in an enantiopure form, they exhibited poor selectivities when treated with ethylene. Nonetheless, after separation of the diastereomers, enantiomerically pure (+)-grandisol (**73**) could be obtained via intermediates **200**[272] or **201**.[273] It was possible to improve the selectivity by the use of $C_2$-symmetric bis-butenolides.[274]

(*S*)-Valinol was employed as a chiral auxiliary to generate (−)-grandisol (*ent*-**73**) via intermediate *ent*-**202**.[275] Accordingly, (*R*)-valinol could be used to access (+)-grandisol (**73**), via intermediate **202**. Bicyclo[3.2.0]heptan-4-oles **203**[276] and **204**[277] and 3-oxabicyclo[3.2.0]heptane **205**[278] were synthesized by using an intramolecular copper-catalyzed [2+2] photocycloaddition. The relative configuration of the newly formed ring was controlled by the hydroxy-substituted stereogenic center. In this manner,[279,280] or alternatively by the use of a chiral auxiliary[279] in the chain, the products **203** or **204** were also obtained as single enantiomers.

(+)-Lineatin (**208**), an aggregation pheromone from certain bark beetles, is structurally related to grandisol (**73**). It possesses an internal acetal, the opening of which leads to the identification of a simple cyclobutane as a possible intermediate for its synthesis. As a result, strategies for a photochemical approach to enantiomerically pure (+)-lineatin (**208**),[281] as well as racemic (±)-lineatin (**208**),[282] focused on the use of an intermolecular [2+2] photocycloaddition. Rather than using ethylene as the olefinic component of the reaction, olefins in higher oxidation states were used that either possessed a hydroxy group at C3 or could be converted into a cyclobutene after the photocycloaddition. Particularly noteworthy is the synthesis by White et al.,[283] in which the rarely used [2+2] photocycloaddition of acetylene was employed as the key step. Irradiation in Vycor glass, which has a high transparency for short wavelengths, allowed excitation of α,β-unsaturated lactone **206** and delivered cyclobutene **207** in a good yield. Further functionalization was performed after introduction of the methyl groups by a regio- and diastereoselective hydroboration, and the ring closure at C5 was achieved by nucleophilic substitution of a tosylate with inversion of configuration (Scheme 55).

The most common approach to the synthesis of grandisol (**73**) involves formation of the non-annulated cyclobutane via annulated intermediates, and this strategy has been known for a long time. It was first utilized in the synthesis of (±)-caryophyllene (**209**) and (±)-isocaryophyllene (**210**) by Corey et al. in 1964.[284] In this case, the product of a photocycloaddition between cyclohexenone and isobutene was used as the starting material. More recent applications include the syntheses of (±)-, (+)-, and (−)-sceptrin (**211**), by employing either a [2+2] photocycloaddition of maleic anhy-




***Scheme 55.*** [2+2] Photocycloaddition of lactone **206** with acetylene in the synthesis of (±)-lineatin (**208**).

dride and 1,4-dichloro-2-butene,[285] or an intramolecular [2+2] photocycloaddition of an oxabicyclo[2.2.1]heptadiene at the beginning of the synthesis (Figure 5).[286]

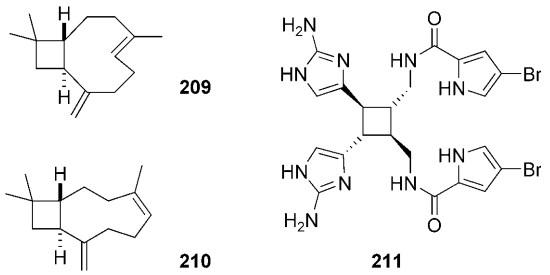
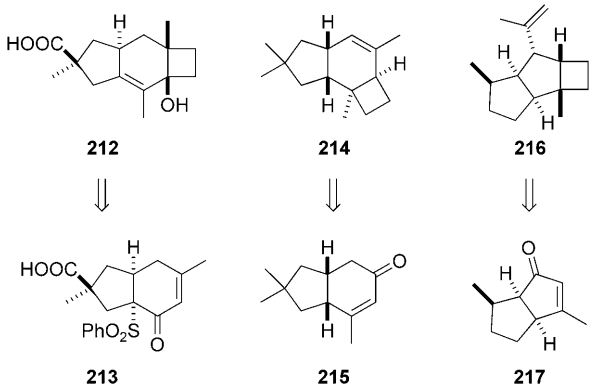



***Figure 5.*** Structures of (±)-caryophyllene (**209**), (±)-isocaryophyllene (**210**), and (−)-sceptrin (**211**).

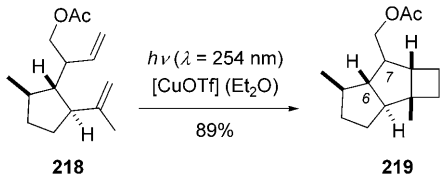
Cyclobutane annulations of existing ring systems are usually achieved by photocycloaddition of ethylene, or ethylene surrogates (for example, 1,2-dichloroethylene), with an endocyclic olefin. This is illustrated in Scheme 56 for the natural products (±)-sterpuric acid (**212**),[287] (±)-protoillud-7-ene (**214**),[288] and (±)-kelsoene (**216**),[289] wherein cyclic intermediates **213**, **215**, and **217** served as the enone component of the [2+2] photocycloaddition, respectively. Other natural products that possess a sterpurane skeleton and were synthesized in an analogous fashion include (±)-sterpurene,[290] (±)-sterpurene-3,12,14-triol,[291] and (±)- and (+)-cerapicol.[290c,292] Allene can be employed as a synthetic equivalent for propylene or ketene, and has been used in this way in the syntheses of (±)-atisine,[293] (−)-




***Scheme 56.*** Retrosynthetic analysis of (±)-sterpuric acid (**212**), (±)-protillud-7-ene (**214**), and (±)-kelsoene (**216**).

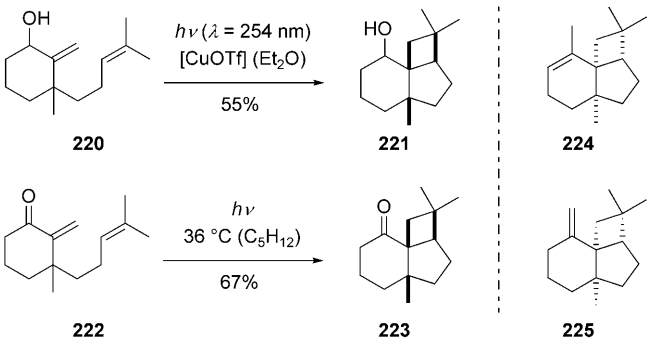
annotinine,[294] (±)-allocyathin $B_3$,[295] (−)-cyathin $A_3$,[296] (±)-heliannuol D,[297] and (±)-pentalenene.[298]

Other intermolecular approaches to racemic and enantiopure kelsoene (**216**)[299] have been reported. A synthesis of the structurally related natural product (−)-sulcatine G[300] was achieved by using a strategy that parallels the one that has just been described. An alternative route to (±)-kelsoene (**216**) made use of an intramolecular copper-catalyzed [2+2] photocycloaddition (Scheme 57).[289a,301] By using this reaction, product **219** could be obtained in high yield and with good diastereoselectivity from the *trans*-substituted cyclopentane **218**, which, in turn, was accessible in eight steps from β-citronellene. The desired control of both stereogenic centers on the cyclobutane ring was not possible when using a *cis*-substituted cyclopentane as the substrate, so subsequent inversion at C6 was necessary for the synthesis of (±)-kelsoene (**216**). During this process, the configuration at C7 was also adjusted.




***Scheme 57.*** Intramolecular copper-catalyzed [2+2] photocycloaddition of diene **218** in a synthesis of (±)-kelsoene (**216**). Tf = trifluoromethanesulfonyl.

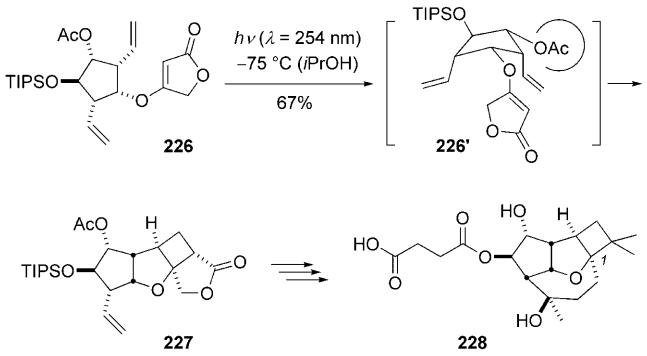
The ginseng sesquiterpenes (±)-α- (**224**) and (±)-β-panasinsene (**225**) were also synthesized by an intramolecular [2+2] photocycloaddition (Scheme 58). Both the copper-catalyzed reaction of substrate **220** to yield the primary product **221** (which was subsequently oxidized to ketone **223**)[302] and the enone photocycloaddition of substrate **222**[303] afforded the desired tricyclic skeleton. The racemic ketone was, in one example, transformed into a racemic mixture of panasinsenes, while in another case it was converted into enantiomerically pure (−)-β-panasinsene (**225**) by a kinetic resolution.




***Scheme 58.*** Approaches toward (±)-α- (**224**) and (±)-β- panasinsene (**225**).

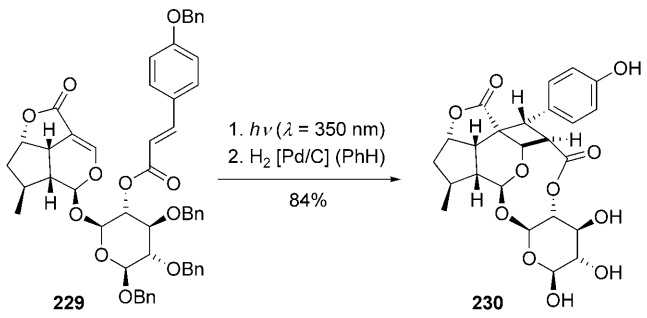
To date, all attempts to synthesize the panasinsenes by using an intermolecular [2+2] photocycloaddition have failed.[302] As a result, photochemical formation of the cyclobutane ring has only been possible by using the intramolecular variant. The same problem was encountered in the synthesis of (±)-punctaporonin C (**228**), because annulation of a cyclobutane ring onto a dihydrofuran is impossible by photochemical means. The intramolecular [2+2] photocycloaddition of tetronate **226** was used as an alternative and proceeded, presumably via conformation **226′**, with good regioselectivity and perfect diastereoselectivity to yield product **227**.[304] The isomer shown in Scheme 59 was isolated




***Scheme 59.*** Intramolecular regio- and diastereoselective [2+2] photocycloaddition of tetronate **226** in the total synthesis of (±)-punctaporonin C (**228**). TIPS = triisopropylsilyl.

in 67% yield. The tetronate moiety subsequently provided a synthetic handle at the carbon atom C1, so that the fourth ring of the rare oxatetracyclo[6.3.2.0$^{1,4}$.0$^{5,12}$]tridecane could be closed by an intramolecular aldol reaction. The vinyl group that did not participate in the photochemical reaction was converted into an acetyl group by Wacker oxidation.

An intramolecular [2+2] photocycloaddition often represents the best method for the synthesis of annulated cyclobutanes because of its high regio- and stereocontrol. The impressive, selective synthesis of (−)-littoralisone (**230**) from precursor **229** (Scheme 60) supports the hypothesis that biochemical formation of this iridoid also involves a photochemical reaction.[305]




***Scheme 60.*** Final steps of a synthesis of (−)-littoralisone (**230**) by an intramolecular [2+2] photocycloaddition and deprotection.

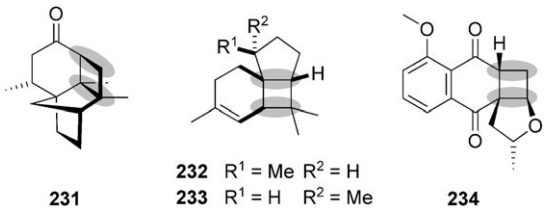
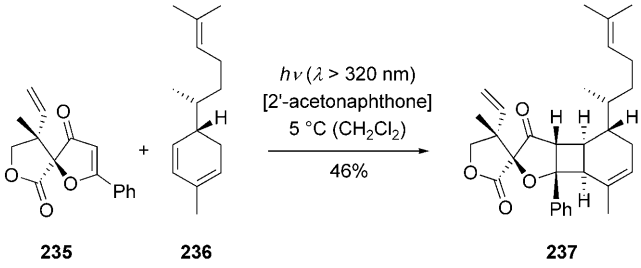



***Figure 6.*** The naturally occurring cyclobutanes (+)-solanascone (**231**), (±)-italicene (**232**), (±)-isoitalicene (**233**), and (−)-elecanacin (**234**), which where synthesized by intramolecular [2+2] photocycloadditions.

As shown in Figure 6, a range of naturally occurring cyclobutanes have been synthesized by using intramolecular [2+2] photocycloaddition. One such example is (+)-solanascone (**231**),[306] the biosynthesis of which [from (−)-solavetivone] is thought to occur photochemically.[307] Further examples include (±)-italicene (**232**),[308] (±)-isoitalicene (**233**),[308] (−)-elecanacin (**234**),[309] (±)-trihydroxydecipiadiene,[310] and (+)-dehydrosolanascone.[306]

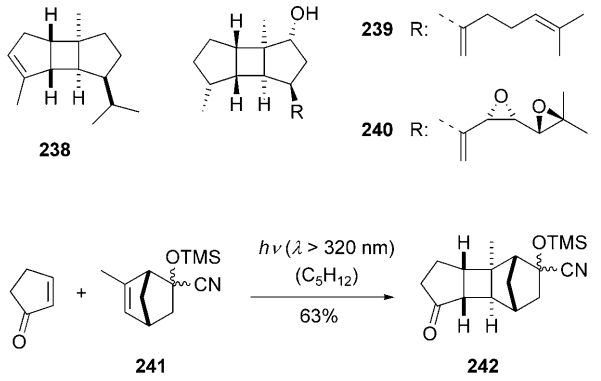
For natural products that possess a cyclobutane ring as the central element of an at least tricyclic skeleton, the intermolecular [2+2] photocycloaddition can immediately be recognized as an attractive method to join the two parts of the molecule. This strategy does not necessarily work as well as in the case of (−)-biyouyanagin A (**237**), where the natural product was obtained in remarkably high selectivity from substrates **235** and **236** (Scheme 61).[311]




***Scheme 61.*** Intermolecular regio- and diastereoselective [2+2] photocycloaddition of substrates **235** and **236** at the end of the synthesis of (−)-biyouyanagin A (**237**).

The tricyclo[5.3.0.0$^{2,6}$]decane core of the bourbonene sesquiterpenes and the spatane diterpenes invites the use of a [2+2] photocycloaddition for the formation of the central ring (Scheme 62). Indeed, there are a number of syntheses that approach the target molecule in this way. The first synthesis of (±)-α- (**238**) and (±)-β-bourbonene by White and Gupta follows the above-mentioned intermolecular [2+2] photocycloaddition strategy. However, the regioselectivity of the reaction, in which cyclopentenone was employed as the enone component and 1-methyl-3-isopropylcyclopentene as the left fragment, was low.[312] Subsequent approaches circumvented this problem by using different alkene components or by temporarily tethering the reaction partners.[313] The spatane diterpenes (+)-stoechospermol (**239**)[314] and (+)-spatol (**240**)[315] were synthesized in an analogous manner. In the syntheses of (±)-stoechospermol (**239**) and (+)-spatol

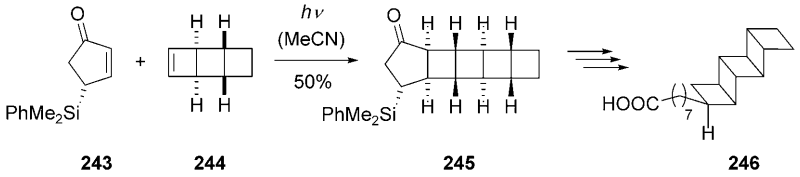
  




***Scheme 62.*** Structures of (±)-α-bourbonene (**238**), (+)-stoechospermol (**239**), and (+)-spatol (**240**); intermolecular [2+2] photocycloaddition of cyclopentenone and olefin **241** as key step in the syntheses of **239** and **240**.

(**240**) by Salomon et al. the [2+2] photocycloaddition of cyclopentenone and alkene **241** proceeded with acceptable regioselectivity to afford product **242** in 63% yield as a mixture of diastereomers.[316]

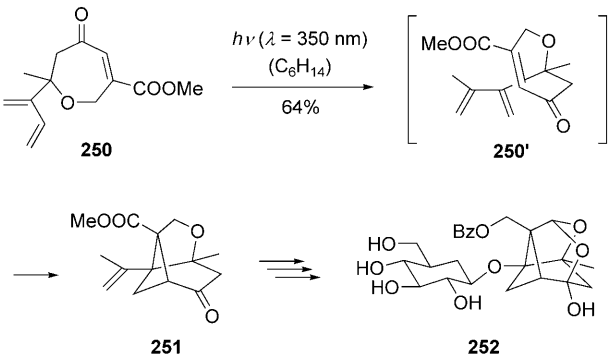
Further examples of intermolecular [2+2] photocycloadditions can be found in the syntheses of (±)- and (+)-pentacycloanammoxic acid (**246**).[317] As depicted in Scheme 63, the synthesis of enantiomerically pure acid **246** was achieved by using enantiopure chiral cyclopentenone **243** to control the configuration so that the reaction with alkene **244** afforded the pentacyclic product **245**. Natural product **246** was obtained after further synthetic manipulations.




***Scheme 63.*** Diastereoselective [2+2] photocycloaddition of silyl-substituted cyclopentenone **243** with *meso*-tricyclo[4.2.0.0$^{2,5}$]oct-3-ene (**244**) for the synthesis of (+)-pentacycloanammoxic acid (**246**).

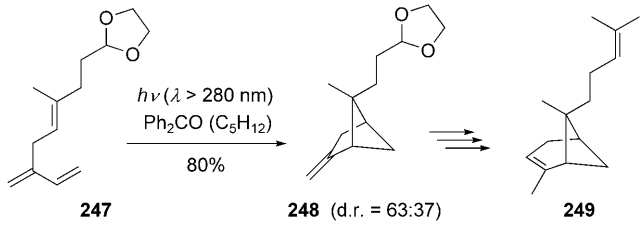
The use of 1,5-dienes in intramolecular [2+2] photocycloadditions results in crossed regioselectivity, and thus leads to the formation of 1,3-bridged cyclobutanes. In this way, sensitized irradiation of diene **247** (Scheme 64) afforded product **248** in high yield, which was subsequently used in the synthesis of (±)-α-*trans*-bergamotene (**249**).[318] The depicted major *trans* diastereoisomer was transformed into the target molecule in a number of steps, one of which was a ring expansion.

A similar strategy was applied by Miyashita and Yoshikoshi in the total synthesis of (±)-longipinene.[319] The heteroanalogous [2+2] photocycloaddition of N-acylated α-(*N*-allylamino)acrylates was used for the synthesis of the unusual naturally occurring cyclobutane amino acids 2,4-methanoproline and 2,4-methanoglutamic acid.[320] Another example that resembles the reactions mentioned above can be found in the synthesis of (−)-paeoniflorin (**252**).[321] In this case, the racemic enone **250** was converted into product **251**, which has an oxatricyclo[4.3.0.0$^{4,7}$]nonane structure, by an intramolecular [2+2] photocycloaddition (Scheme 65). The relative configuration can be explained on the basis of the depicted conformation **250′**. After the photoreaction and ketone reduction ($NaBH_4$, MeOH), the enantiomers were separated by classical resolution of the resulting secondary alcohol. Eight additional synthetic steps delivered the target molecule **252** in enantiomerically pure form.

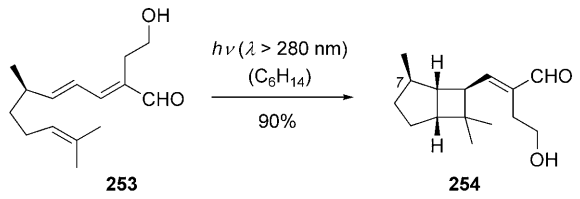



***Scheme 65.*** Construction of the carbocyclic core of (−)-paeoniflorin (**252**) by intramolecular [2+2] photocycloaddition.

The rare natural product preraikovenal (**253**), an acyclic α,β,γ,δ-unsaturated aldehyde, served as the precursor for the synthesis of (+)-epiraikovenal (**254**).[322] The [2+2] photocycloaddition of the olefin to the γ,δ-double bond took place with formation of a five-membered ring (Scheme 66). Naturally occurring epiraikovenal exists as the (−) enantiomer, so the authors speculate that it might be formed from *ent*-**253**, while (−)-raikovenal,




***Scheme 64.*** Sensitized [2+2] photocycloaddition of 1,5-diene **247** in a synthesis of (±)-α-*trans*-bergamotene (**249**).



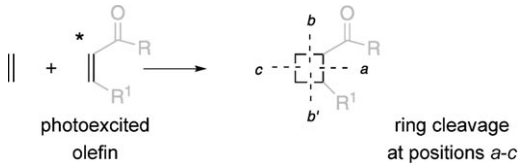

***Scheme 66.*** Synthesis of (+)-epiraikovenal (**254**) starting from preraikovenal (**253**).

the C7 epimer of (−)-epiraikovenal (*ent*-**254**) which is also found in nature, could be formed from **253** via a boatlike transition state. Indeed, irradiation of **253** also yielded small amounts (5%) of (−)-raikovenal.

### 8.2. Cyclobutane Cleavage Following Intermolecular [2+2] Photocycloaddition

As two olefin components are involved in any [2+2] photocycloaddition reaction, the fragmentation of the resultant cyclobutane and the outcome of a photocycloaddition/ring-cleavage sequence can be viewed from the perspective of either reaction partner. When cyclic enones are used as one of the photoactive components, one tends to classify this enone as the essential olefin. To establish a clear vocabulary according to which ring-cleavage reactions of cyclobutanes will be discussed, each of the bonds that can be cleaved have been designated a Latin lowercase letter (*a*–*c*) in Scheme 67.




***Scheme 67.*** Convention for the nomenclature of the cleaved bonds of intermolecularly generated cyclobutanes.

Compared to the intramolecular [2+2] photocycloaddition, the intermolecular variant offers greater convergence, but has the disadvantage of lower regio- and stereoselectivity in most cases. The rule of thumb for predicting the regioselectivity for enone substrates is that donor-substituted olefins give the head-to-tail product (donor and carbonyl group in the 1,3-position) while acceptor-substituted olefins form the head-to-head product (acceptor and carbonyl group in the 1,2-position).[262] Ring cleavage of intermolecular [2+2] photocycloaddition products has already been extensively discussed in a previous review,[242g] so we confine the examples to ones that were not covered there or that have been reported more recently.

When an α,β-unsaturated carbonyl compound is employed as the photoexcited olefin in a [2+2] photocycloaddition, one of the undeniably most important fragmentations occurs along the bond *a*. Typical fragmentation patterns for the generic cycloaddition products **I**–**III** are summarized in Figure 7. A [2+2] photocycloaddition in combination with a retro-aldol reaction of type **I** is called the de Mayo reaction.[323] This fragmentation takes place spontaneously if unprotected 1,3-dicarbonyl compounds, which react as β-hydroxy enones, are used and it affords products with 1,5-diketo functional groups. By using open-chain 1,3-dicarbonyl substrates the natural products (±)-isolaurene[324] and (±)-cuparene,[324] (−)-sarracenin,[325] (±)-hinesol,[326] (±)-agarospirol,[326] sollasin A and B,[327] and (±)-loganin[328,329] were synthesized by this photoannulation. The same fragmentation can be found in the synthesis of the secologanin aglucon *O*-methyl ether.[330]

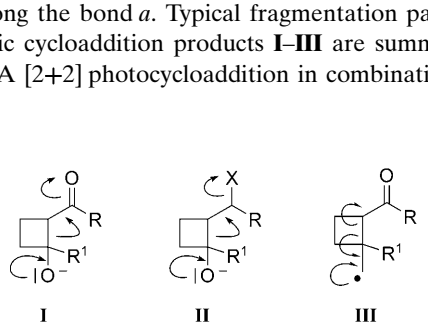
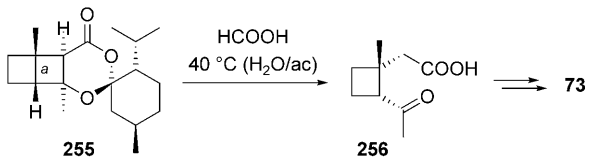


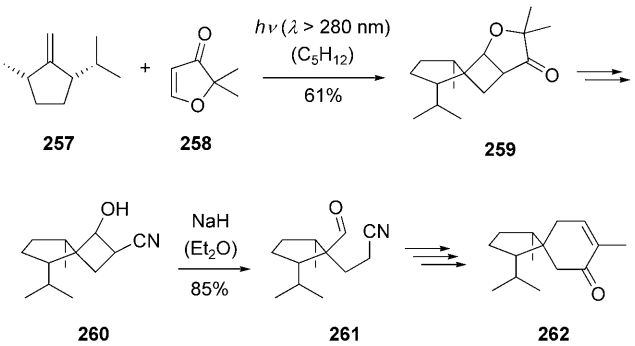

***Figure 7.*** Cleavage of bond *a* by retro-aldol reaction (type **I**), Grob fragmentation (type **II**), and radical fragmentation (type **III**).

1,3-Dioxin-4-ones often serve as surrogates for β-ketocarboxylic acids. δ-Ketocarboxylic acids are generated after [2+2] photocycloaddition, hydrolysis, and fragmentation. One example is given in Scheme 68 and begins with compound **255**, which is the photocycloaddition product of 1-methylcyclobutene and a chiral 1,3-dioxinone. Hydrolysis afforded carboxylic acid **256**, which was subjected to Peterson olefination and reduction to provide the already extensively discussed (+)-grandisol (**73**, Scheme 22).[331] Further applications of 1,3-dioxinones in this context can be found in the syntheses of (+)-elemol[332] and (+)-valeranone.[333]




***Scheme 68.*** De Mayo reaction to furnish the δ-ketocarboxylic acid **256** by hydrolysis of the acetal in the photocycloaddition product **255**.

3(2*H*)-Furanones are also latent 1,3-dicarbonyl building blocks and consequently have been used in natural product synthesis as part of a [2+2] photocycloaddition/fragmentation sequence. Baldwin and Fredericks commenced their synthesis of the sesquiterpene (−)-acorenone (**262**) with the reaction of olefin **257** with furanone **258** (Scheme 69).[334] Cyclobutane **259** was formed, by a head-to-tail reaction, in high regio- and diastereoselectivity. The simple diastereoselectivity of the reaction was irrelevant, as during subsequent bond cleavage to **261** (upon formation of the β-hydroxy nitrile to **260**) the



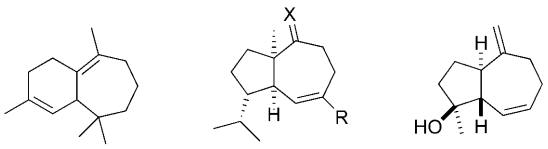

***Scheme 69.*** Total synthesis of (−)-acorenone (**262**) through [2+2] photocycloaddition of 3(2*H*)-furanone **258** and base-induced cleavage of the β-hydroxynitrile **260**.

newly created stereogenic centers—except for the quaternary center at the cyclopentane ring—were lost. A 3(2*H*)-furanone was also used as the starting material for the total synthesis of (±)-occidentalol.[335]

The de Mayo reaction has been used extensively for the ring expansion of cyclic 1,3-diketones and derivatives thereof. By using this reaction, five-membered rings can be converted into seven-membered rings, and six-membered rings to eight-membered rings. (±)-Precapnelladiene was synthesized in this way.[336] Tropones can be obtained by retro-aldol reactions of 5-hydroxy-3,6-bicyclo[3.2.0]heptadiene-2-ones or by thermolysis of the parent compounds. In this manner, syntheses of the natural products stipitotanic acid[337] and nezukone were achieved.[338]

Halides or pseudohalides can be used as the leaving group (X) in the Grob fragmentation of compounds of type **II**. Once again, this reaction is predominantly used to achieve ring expansion, as seen, for example, in the synthesis of the sesquiterpene (±)-β-himachalene (**263**).[337b,339] In the case of epoxides the leaving group can also be an oxido group. Synthesis of the hydroazulene sesquiterpenes (+)-aphanamol I (**264**) and II (**265**, Figure 8) was achieved in this way by application of a [2+2] photocycloaddition/fragmentation sequence.[340]

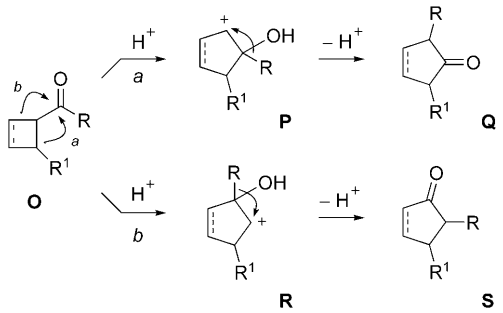



**263** **264** X = O; R = $CH_2OH$ **266**
**265** X = α-OH, β-H; R = CHO

***Figure 8.*** Structures of (±)-β-himachalene (**263**), (+)-aphanamol I (**264**) and II (**265**), and (±)-dictamnol (**266**).

Radical fragmentations of substrates of type **III** have been employed successfully for the synthesis of natural products by Lange et al. By using this strategy, the trinorguaiane sesquiterpene (±)-dictamnol (**266**)[341,342] and the sesquiterpene (±)-alismol[342] were synthesized, and a formal total synthesis of (±)-pentalenene was accomplished.[343]

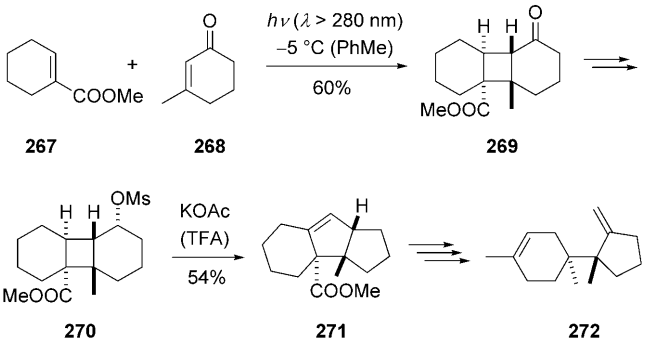
The carbonyl carbon atom of the former enone can easily be converted into a strongly electrophilic center, and this technique has been applied in a range of rearrangements, which aim to cleave bond *a*. The simplest means of activation is protonation or activation with a Lewis acid, which can result in a double rearrangement through the reaction cascade described below. Starting from **O**, cleavage of bond *a* leads, via intermediate **P**, to the 1,3-disubstituted (mostly bridged) ketone **Q**, while cleavage of bond *b* leads, via cation **R**, to the annulated cyclopentanone or cyclopentenone **S** (Scheme 70). The acid-catalyzed rearrangement of a strained β,γ-unsaturated ketone is known as the Cargill rearrangement.[344] Examples of the use of the first reaction sequence can be found in the total synthesis of (−)-hibaene[345] and in the formal total synthesis of (±)-verrucarol.[346] In the latter example, no 1,2-alkyl migration took




***Scheme 70.*** Ring expansion of cyclobutanes by a Cargill rearrangement.

place, because the intermediate cation was trapped intramolecularly by a methoxycarbonyl group.

Diquinane-like bicyclo[3.3.0]octanes can be generated from the bicyclo[4.2.0]octane substructure by a simple cationic cyclobutylmethyl/cyclopentyl rearrangement. Examples of the use of this rearrangement can be found in the syntheses of (±)-hirsutene,[347] (±)-debromoaplysin and (±)-aplysin,[348] and (±)-trichodiene (**272**).[349] The strategy used for the synthesis of trichodiene is depicted in Scheme 71. The [2+2] photocycloaddition of compounds **267** and **268** unexpectedly afforded head-to-tail product **269**, which was then



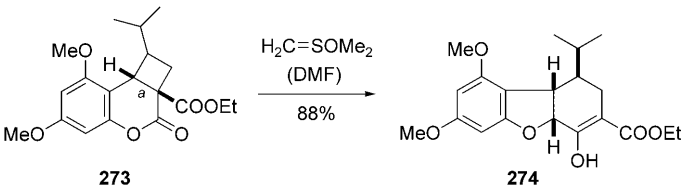

**267** **268** **269**
**270** **271** **272**

***Scheme 71.*** Cationic rearrangement of cyclobutane **270** in the formal total synthesis of (±)-trichodiene (**272**).

converted into the substrate for the rearrangement (**270**) by reduction and mesylation. The rearrangement worked best in trifluoroacetic acid (TFA) to afford olefin **271**, which, in additional steps, was converted into a relay compound for the formal total synthesis of (±)-trichodiene (**272**).

Mechanistically different, but resulting in the same skeletal rearrangement of a bicyclo[4.2.0]octane substructure to a bicyclo[3.3.0]octane substructure, 5,6-disubstituted bicyclo[4.2.0]octan-2-ones can be rearranged in the presence of $AlCl_3$, as demonstrated in the syntheses of (±)-5-oxosilphiperfol-6-ene, (±)-silphiperfol-6-ene,[350] and (±)-3-oxosilphinene.[351] Another noteworthy rearrangement is the reaction of coumarin photoadduct **273**, which underwent rearrangement following attack of the dimethylsulfoxonium methylide at the lactone carbonyl group (Scheme 72). Intermediate **274** served as the precursor for the synthesis of (±)-linderol A.[352] An enantioselective variant of this synthesis,



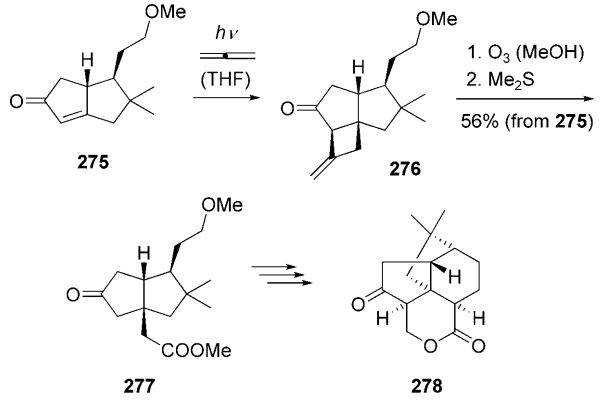

273 274

***Scheme 72.*** Rearrangement of a cyclobutanone in the synthesis of (±)-linderol A.

which is based on the use of a chiral alcohol as an ester auxiliary, has also been reported.[353]

In the simplest case of a subsequent bond cleavage at *b* or *b′* (Scheme 67) the [2+2] photocycloaddition reaction delivers formal addition products at the α or β position of the photoexcited olefin. If appropriate substituents are chosen, this cleavage can take place in a similar manner to the bond cleavage at *a*. The retro-aldol reaction (type **I**, Figure 7) was applied in the synthesis of (±)-norketotrichodiene,[354] the Grob fragmentation (type **II**, Figure 7) in the synthesis of (±)-edulinine,[355] and the radical fragmentation (type **III**, Figure 7) in another synthesis of (±)-trichodiene (**272**).[356] Typical cleavage reactions that sometimes result in rearrangements commence with cyclobutanones as starting materials. In the [2+2] photocycloaddition of enones, allene serves as a synthetic equivalent for ketene and reacts to afford head-to-head products. The simplest consecutive reaction is the retro-Dieckmann reaction, which formally generates the product of a Michael addition of an acetic acid enolate to the enone. A synthetic handle to allow for intramolecular enolate alkylation was introduced in this way in the synthesis of (−)-quadrone (**278**).[357] The [2+2] photocycloaddition of enone **275** afforded the expected head-to-head product **276**, which was immediately subjected to ozonolysis and spontaneously generated δ-ketoester **277** during the work-up. The overall yield for the steps that have just been described ( Scheme 73) was 56%.

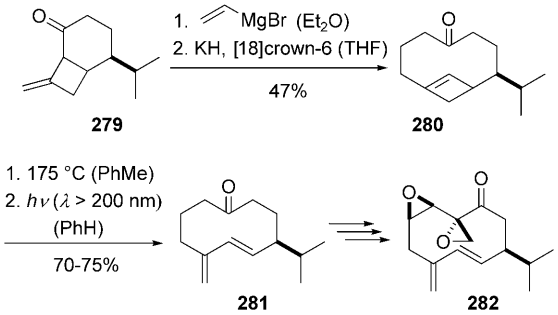
Further applications of the [2+2] photocycloaddition/fragmentation sequence can be found in the synthesis of (±)-gibberellic acid[358] and, as modified versions, in syntheses of (+)-3-deoxyaphidicolin[359] and (±)-subergorgic acid.[360]




275 276 277 278

***Scheme 73.*** Formation of a quaternary carbon atom, by using a sequence involving photocycloaddition with allene and subsequent ozonolysis, in the synthesis of (−)-quadrone (**278**).

The direct use of an allene/[2+2] photocycloaddition product was described by Schreiber and Santini in the synthesis of (±)-periplanone B (**282**).[245,361] Starting with a diastereomeric mixture of compound **279**, which was generated by regioselective [2+2] photocycloaddition, the addition of vinylmagnesium bromide and a subsequent oxy-Cope rearrangement afforded cyclobutene **280**. Thermal ring opening followed by *Z*/*E* isomerization yielded the ten-membered ketone **281**, which served as a precursor to the target molecule **282** (Scheme 74).



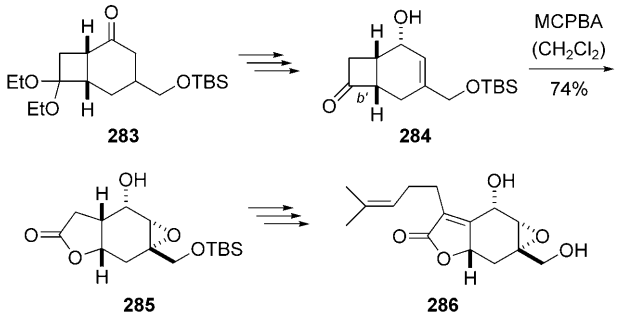

279 280 281 282

***Scheme 74.*** Synthesis of (±)-periplanone B (**282**) by an oxy-Cope rearrangement of a photocycloaddition product followed by fragmentation of the resultant cyclobutene **280**.

In contrast to allenes, [2+2] photocycloadditions of 1,1-dialkoxyalkenes give head-to-tail products. In this way, latent cyclobutanones with inverted regioselectivity can be generated. Cleavage of the formal *b′* bond (Scheme 67) of cyclobutanone **284** was used by Smith and Richmond in the syntheses of (±)-paniculides A, B (**286**), and C.[362] A Baeyer–Villiger oxidation with *meta*-chloroperoxybenzoic acid (MCPBA) furnished epoxylactone **285** as the major product. The synthesis commenced with the formation of the epimeric cyclobutanes **283** by an intermolecular [2+2] photocycloaddition (Scheme 75).

Five-membered carbocyclic rings can be obtained from cyclobutanones by ring expansion with ethyl diazoacetate in the presence of $BF_3$. Liu and Chan employed this reaction in the syntheses of (±)-$\Delta^{9(12)}$-capnellene,[363] (−)-khusimone,[364] (+)-zizanonic acid,[364] and (−)-epizizanonic acid.[364]

Using a retro-benzilic acid rearrangement ring expansion of a four-membered ring to a five-membered ring was

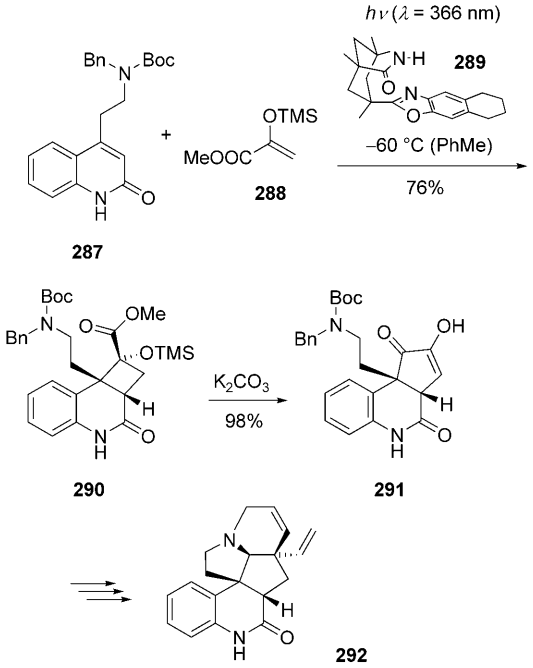



283 284 285 286

***Scheme 75.*** Baeyer–Villiger reaction for the ring expansion of cyclobutanone **284** to yield butyrolactone **285** in the synthesis of (±)-paniculide B (**286**).

achieved in the total synthesis of the *Melodinus* alkaloid (+)-meloscine (**292**).[365] The synthesis commenced with an enantioselective intermolecular [2+2] photocycloaddition of silyl enol ether **288** with quinolone **287** in the presence of the chiral complexing agent **289**.[366] Enantiomerically pure **290**, which was obtained in 76% yield, was treated with base to generate the rearrangement product **291** (Scheme 76). The two stereogenic centers that were formed in the photoreaction provided the steric bias to establish the two additional stereogenic centers in the central cyclopentane ring during the subsequent reductive amination and Claisen rearrangement steps.



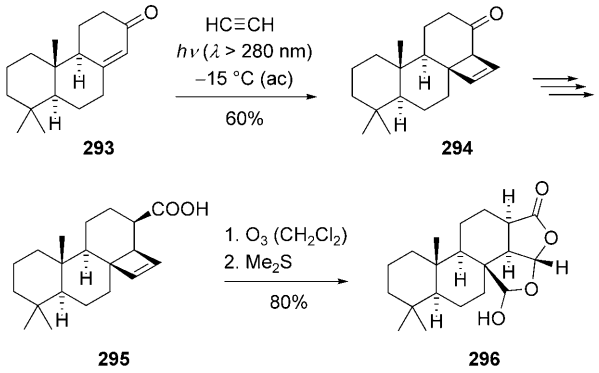

***Scheme 76.*** Template-controlled enantioselective [2+2] photocycloaddition of quinolone **287** with silyl enol ether **288** and subsequent retro-benzilic acid rearrangement as key steps in the total synthesis of (+)-meloscine (**292**).

The ring expansion of a four-membered ring to generate a six-membered ring by a formal 1,3-migration of a vinyl cylcobutane was used in the syntheses of the erythrina and homoerythrina alkaloids erysotrine,[367] (±)-schelhammericine,[368] and (±)-3-epischelhammericine.[368]

If the rearrangement proceeds by bond cleavage followed by bond formation within a ring system, then the topology of the system changes. A Cargill rearrangement of a bicyclo[4.2.0]octenone formed by [2+2] photocycloaddition of a cyclohexenone resulted in the formation of a bicyclo[3.3.0]octenone (Scheme 70), which was subsequently used in an elegant synthesis of (±)-modhephene (**121**, Scheme 34) by Smith and Jerris.[369]

Bicyclo[4.2.0]octanes can undergo a 1,2-shift of bond *b* to form a bicyclo[3.2.1]octane skeleton. This rearrangement has been applied in the syntheses of (±)-quadrone (**278**, Scheme 73) by Yoshii and co-workers,[370] (+)-quadrone (**278**, Scheme 73) by Smith and Konopelski,[371] and (−)-erythroxylol B,[372] (−)-erythroxydiol A,[372] and (−)-benuol by Abad et al.[372]

The twofold C–C bond connectivity at both ends of the photoexcited alkene is manifested upon cleavage of bond *c* (Scheme 67). Oxidative cleavage of this bond generates 1,4-difunctionality, which can then be used in a variety of ways. In the synthesis of (−)-dendrillol-1 (**296**), photocycloaddition of enone **293** and acetylene afforded product **294** as a single diastereomer.[373] The final step in the synthesis involved cleavage of the ensuing double bond by ozonolysis, which resulted in direct formation of the target molecule from carboxylic acid **295** (Scheme 77).




***Scheme 77.*** Total synthesis of (−)-dendrillol-1 (**296**) by ozonolysis of a photochemically generated cyclobutene.

The reaction of alkynes with maleic anhydride was likewise used for the synthesis of (±)-methylenomycin A,[374] (±)-xanthocidin,[375] and (±)-dedihydroxy-4,5-dihydroxanthocidin.[375] 1,2-Dichloroethene or vinylene carbonate can be used as a surrogate for acetylene, while enol ethers possessing a labile protecting group at the oxygen atom can be used as surrogates for other alkynes. In the first case, bond *c* can be cleaved with ozone, periodate, or lead acetate, as utilized, for example, in the syntheses of (±)- and (−)-merrilactone A[376,377] and (+)-halimedatrial.[378] In the second case, after deprotection of the oxygen atom, cleavage of bond *c* can be achieved oxidatively in the presence of a ruthenium catalyst, as used in the synthesis of (±)-biotin.[379]

Needless to say, in addition to oxidative cleavage, the classic methods of fragmentation, which have been extensively discussed for bond *a* (Figure 7), are also possible. Some uses of this reaction sequence in natural product synthesis are depicted in Figure 9. For each example the photocycloaddition product, the precursor for the fragmentation, and the respective natural product are pictured in a single row. (−)-Echinosporin (**299**) was synthesized from the [2+2] photocycloaddition product **297** via a retro-aldol reaction of intermediate **298**.[380] Tosylate **301**, which was generated from the tricyclic photoproduct **300**, was the substrate for a Grob fragmentation that was used in the synthesis of the sesquiterpenes (±)-5-epikessane (**302**) and (±)-dehydrokessane. This conversion involved an elimination step to give the corresponding enone, thus the relative configuration at the acetate bearing carbon atom of compound **300** was irrelevant.[381] Oxidative cleavage of a cyclobutane was used in the

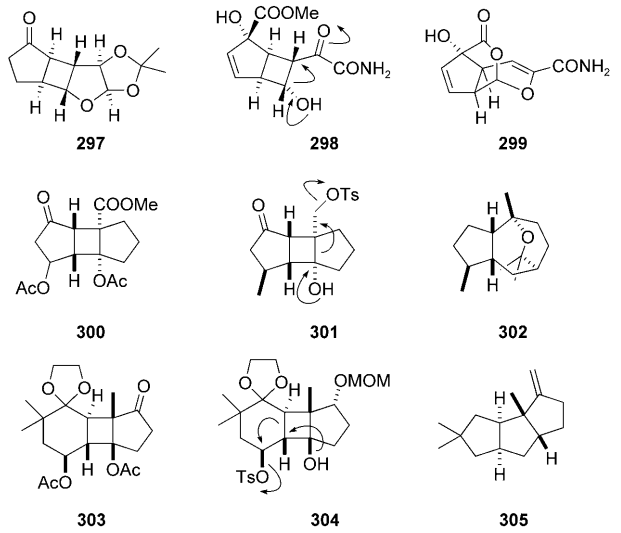
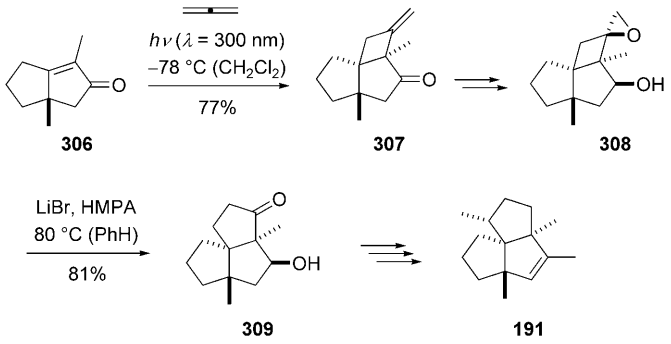



***Figure 9.*** Products of the photocycloaddition and precursors for the ring cleavage in the syntheses of (−)-echinosporin (**299**), (±)-5-epikessane (**302**), and (±)-hirsutene (**305**).

synthesis of (±)-α-himachalene.[382] At first glance, the photoproduct **303** (35% yield) seems unusual as it bears a *cis-anti-trans* configuration. However, this arrangement is possible when cyclohexenes are used in the [2+2] photocyloaddition, and provides the driving force for the subsequent rearrangement of the tosylate **304**, which results in formation of the triquinane structure of (±)-hirsutene (**305**).[383] (±)-Coriolin (**113**, Figure 4) was also synthesized in this way.[384]

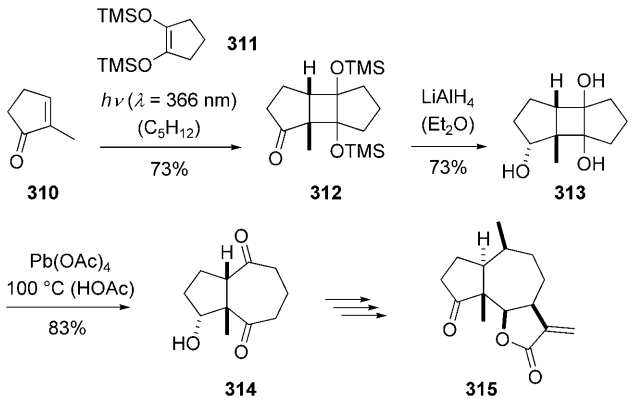
The annulation of larger rings is possible by cleavage of bond *c* (Scheme 67) of an annulated four-membered ring, which in turn is formed by intermolecular [2+2] photocycloaddition to an enone. Annulation of a five-membered ring can be achieved by 1,2-migration onto an exocyclic carbon atom. Tobe et al. used the epoxide/carbonyl rearrangement to synthesize various triquinanes. To illustrate, Scheme 78 depicts a synthesis of (±)-isocomene (**191**, Scheme 52), which started with the [2+2] photocycloaddition of allene to enone **306**.[385] The head-to-head product **307** was formed diastereoselectivly and was converted in two steps into epoxide **308**, the substrate for the desired rearrangement.




***Scheme 78.*** Synthesis of oxaspiro[2.3]hexane **308** followed by ring expansion in an approach towards (±)-isocomene (**191**). HMPA = hexamethylphosphoramide.

Presumably, the epoxide is firstly opened by LiBr in an $S_N2$ fashion and then rearrangement takes place, by a 1,2-migration, to afford triquinane **309**. (±)-β-Isocomene[385] and (±)-modhephene (**121**, Scheme 34)[386] were also synthesized in this manner.

Annulation of a six-membered ring can be achieved by [2+2] photocycloaddition of 1,2-bis(trimethylsilyloxy)cyclobutene followed by oxidative cleavage. This strategy has been used for the synthesis of, in particular, the eudesmanolides and eudesmanes. Natural products which have been synthesized in this manner are (±)-oxocostic acid,[387] (±)-dihydroreynosin,[387,388] (±)-1-oxo-dihydromagnolialide,[388] (±)-maritimin,[388] (±)-dihydromagnolialide,[388] (±)-magnolialide,[388] (±)-dihydrosantamarine,[388] and (±)-α-santonin,[388] as well as (+)-balanitol[389] and (+)-selin-4-(15)-ene-1β,11-diol.[389] An analogous reaction can be carried out using 1,2-bis(trimethylsilyloxy)cyclopentene (**311**) and results in annulation of a seven-membered ring. Intermolecular [2+2] photocycloaddition of 2-methyl-2-cyclopentenone (**310**) afforded the photoproduct **312** in 73% yield, which was subsequently subjected to reduction and deprotection to generate triol **313**.[390] Cleavage of the cyclobutane ring furnished compound **314**, which has been utilized in numerous natural product syntheses. One example is the sesquiterpene lactone (±)-damsin (**315**, Scheme 79).[391] Other pseudoguaianolides that



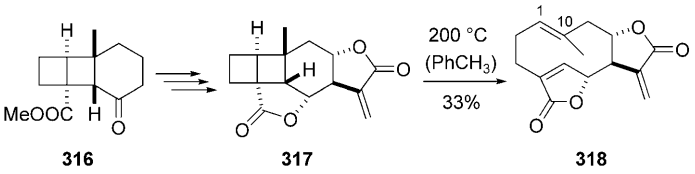

***Scheme 79.*** Ring extension of diol **313** by oxidative diol cleavage en route to the total synthesis of (±)-damsin (**315**).

were synthesized in this manner are (±)-neoambrosin,[392] (±)-parthenin,[392] (±)-hymenin,[392] (±)-carpesiolin,[393] and (±)-hysterin.[394] Starting from 1,2-bis(trimethylsilyloxy)cyclopentene and cylopentenone,[390] the equivalent reaction sequence facilitated the synthesis of the guaianolides (±)-compressanolide[395,396] and (±)-estafiatin.[396,397] A similar formal total synthesis of (±)-compressanolide employed, after removal of the acetyl protecting groups, an oxidative diol cleavage of the [2+2] photocycloaddition product of 1,2-diacetoxycyclopentene and 3-methoxycarbonylcyclopent-2-enone.[398]

Cleavage of both the *a* and *c* bonds (Scheme 67) gives the formal products of a cross-metathesis. This can be achieved thermally if the central cyclobutane ring is highly strained. Most syntheses that take advantage of this strategy use a

cyclobutene as one of the reaction partners in the [2+2] photocycloaddition. In this case, cycloaddition with an enone followed by thermolysis affords a ten-membered ring. The reaction was used by Wender and Lechleiter in the synthesis of the germacrane sesquiterpene (±)-isabelin (**318**) (Scheme 80).[399] The photocycloaddition product **316** was converted, in several steps, into pentacycle **317**, pyrolysis of which generated a 33:67 mixture of the target molecule **318** and its 1,10-(*Z*) isomer in quantitative yield.

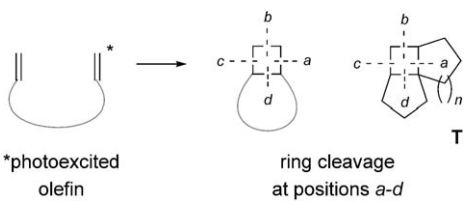



***Scheme 80.*** Total synthesis of (±)-isabelin (**318**) by thermal rearrangement of pentacycle **317**.

Ten-membered rings that are formed in this manner can undergo a transannular ring closure to generate either hydronaphthalenes or hydroazulenes. Synthetic applications of the bicyclo[4.4.0]decane scaffold can be found for the target molecules (±)-calameon,[400] (±)-atractylon,[401] (±)-isoalantolactone,[401] (+)-isocalamendiol,[402] (±)-warburganal[403] and (−)-zonarene,[404] and for the bicyclo[5.3.0]decane scaffold in the synthesis of (+)-daucene.[405] 2,3-Divinylcyclohexanes can be formed as a side product of the thermal decomposition of tricyclo[4.4.0.$0^{2,5}$]decanones (fission of bond *c*), and this was exploited by Williams and Callahan in the synthesis of (−)-shyobunone.[406] The [2+2] photocycloaddition product of maleic anhydride and 3-methyl-3-sulfolene was converted into 10-hydroxygeraniol by cleavage of bonds *a* and *c* by flash vacuum pyrolysis and subsequent reduction.[407]

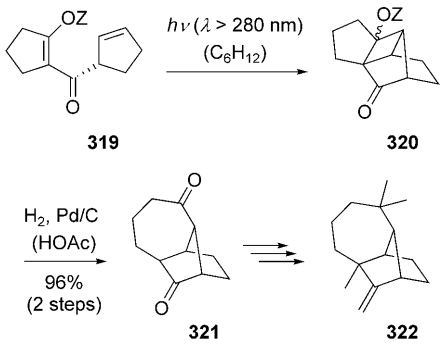
### 8.3. Cyclobutane Cleavage after Intramolecular [2+2] Photocycloaddition

There are many variants of the intramolecular [2+2] photocycloaddition because the linking chain does not necessarily need to be attached directly at the olefin (although it is pictured this way in Scheme 81). As a result of this fact, there are a large number of ring-opening reactions and they are not easy to classify. With this said, in the following examples positions *a–d* (Scheme 81) have been referred to where possible so as to allow these reactions to be roughly categorized. A scaffold that is frequently obtained by intramolecular [2+2] photocycloaddition is the tricyclic skeleton **T** that has ring sizes $n=1$ or $n=2$ for the ring derived from the cyclic enone component. In terms of the ring that results from the tether, the formation of a five-membered ring is particularly facile[408] by a so-called straight [2+2] photocycloaddition. Cleavage of bond *a* or *d* (Scheme 81) in this framework delivers bicyclo[5.3.0]decanes (*a* or *d* for $n=1$) and bicyclo[6.3.0]undecanes (*a* for $n=2$) or bicyclo[5.4.0]undecanes (*d* for $n=2$).




***Scheme 81.*** Convention for the nomenclature of the cleaved bonds of intramolecularly generated cyclobutanes.

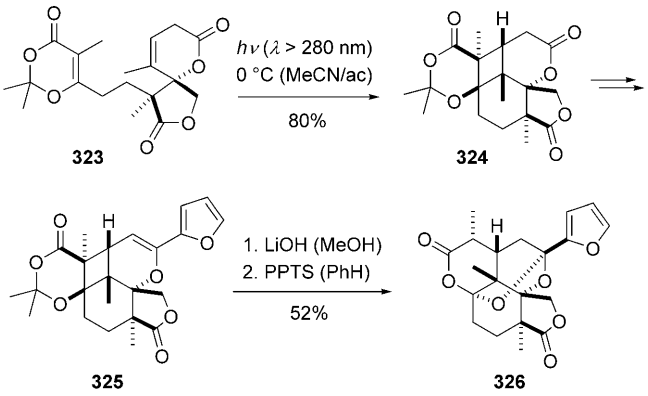
The classic syntheses of (±)- and (+)-longifolene (**322**) as well as (+)-sativene by Oppolzer and Godel utilize the de Mayo reaction as access to a bicyclo[5.4.0]undecane skeleton.[409] Photocycloaddition of benzyloxycarbonyl-protected (Z) substrate **319** delivered cyclobutane **320**. Hydrogenolysis of the protecting group initiated the desired fragmentation reaction. Cleavage of bond *a* (Scheme 81) generated diketone **321**, which possesses the tricyclic core required for the target molecule (Scheme 82).




***Scheme 82.*** Construction of the skeleton of (+)-longifolene (**322**) by intramolecular [2+2] photocycloaddition followed by retro-aldol reaction.

Many natural products containing the frameworks mentioned above have been synthesized in a similar way. Another example of a cleavage of type *a* (Scheme 81), by a retro-aldol reaction can be found in the synthesis of (±)-daucene.[410] Other related fragmentations delivered the hydroazulene sesquiterpene (±)-β-bulnesene[411] and the dolastane (±)-isoamijiol.[412] In the synthesis of (±)-ingenol by Winkler et al., a retro-aldol reaction was used to establish a bridged bicyclo[5.3.0]decane subunit.[413] In this example, a 1,3-dioxin-4-one was employed as the enone component of the cycloaddition reaction and this ring subsequently disappears entirely following hydrolysis and a retro-aldol reaction. In Scheme 83 the use of a 1,3-dioxin-4-one in Winkler's synthesis of (±)-saudin (**326**) is shown.[414] The intramolecular [2+2] photocycloaddition of dioxinone **323** afforded compound **324** with high stereo- and regioselectivity. Installation of the furan ring by a cross-coupling reaction, followed by fragmentation of substrate **325** afforded compound **326**, which is readily recognizable as the product of this sequence on account of its 1,5-difunctionality. Another example of this




***Scheme 83.*** Application of a [2+2] photocycloaddition/de Mayo reaction sequence at the end of a synthesis of (±)-saudin (**326**).

strategy can be found in the synthesis of (−)-perhydrohistrionicotoxin.[415]

Further applications of the intramolecular [2+2] photocycloaddition with subsequent cleavage of bond *a* (Scheme 81) can be found in the formal total synthesis of (±)-reserpine[416] and in the synthesis of the sesquiterpene (±)-zizaene (**332**, Figure 10).[417]

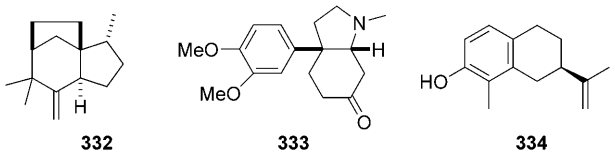


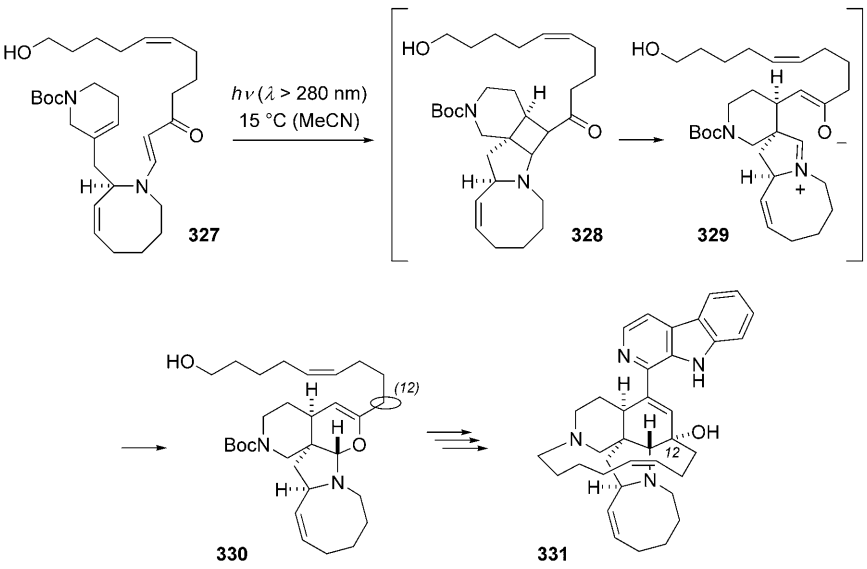

***Figure 10.*** Structures of the natural products (±)-zizaene (**332**), (±)-mesembrine (**333**), and (+)-ligudentatol (**334**), which were formed by intramolecular [2+2] photocycloaddition followed by cleavage of bond *a*.

In an analogous fashion to β-hydroxycarbonyl compounds, β-aminocarbonyl compounds can also undergo fragmentation. Accordingly, if vinylogous amides (enaminones) are employed in [2+2] photocycloadditions, the products undergo spontaneous fragmentation to yield ketoimines or ketoiminium ions, which can then recyclize in a domino reaction. In this manner, Winkler and Axten synthesized the manzamine alkaloids (−)-ircinol A, (+)-ircinal A, (+)-manzamine A (**331**), and (+)-manzamine D.[418] As shown in Scheme 84 for the synthesis of (+)-manzamine A (**331**), vinylogous amide **327** was converted into product **330** using an intramolecular [2+2] photocycloaddition, to give cyclobutane **328**, followed by a ring opening/ring closure cascade that proceeded via zwitterion **329**. Subsequently, a second ring opening was initiated with pyridinium acetate, which resulted in stereoselective formation of the bond between the circled C12 carbon atom and the carbon atom of the iminium ion by way of a Mannich reaction. The whole sequence proceeded in a yield of 20%.

The application of a retro-Mannich reaction with subsequent ring closure allowed straightforward access to the alkaloid (±)-mesembrine (**333**),[419] and was also used in an enantioselective formal total synthesis of (−)-vindorosine.[420] The combination of an intramolecular photocycloaddition involving an indole substituted in the 3-position with β-aminoalkylidene malonate and a retro-Mannich reaction, was recently used by White et al. in the syntheses of the alkaloids (±)-coerulescine, (±)-horsfiline, (±)-elacomine, and of a β-carboline alkaloid.[421]

The Lewis acid catalyzed retro-aldol fragmentation of dihydropyrane photoadducts yields oxygenated products that can be condensed to give benzoid arenes. An application of this inventive sequence can be found in the synthesis of (+)-ligudentatol (**334**).[422]

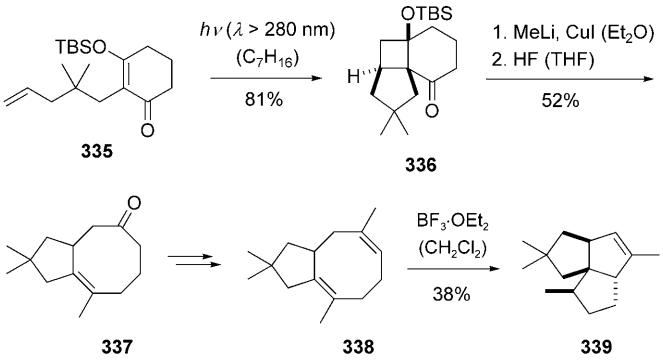
Following cleavage of bond *a* (Scheme 81) in a product of type **T** ($n=2$), the resulting bicyclo[6.3.0]undecane skeleton can be converted into the tricyclo[6.3.0.$0^{4,8}$]undecane core of angularly fused sesquiterpenes or the tricyclo[6.3.0.$0^{2,6}$]undecane core of linearly fused sesquiterpenes. Studies by Pattenden and co-workers have shown that this biosynthetic pathway is also possible in the laboratory. The latter transformation was employed in a synthesis of (±)-$\Delta^{8(9)}$-capnellene—and thus in a formal total synthesis of (±)-$\Delta^{9(12)}$-capnellene—from (±)-*epi*-precapnelladiene,[423] while an example of the former transformation is shown below. The angularly fused sesquiterpene (±)-pentalenene (**339**) was synthesized from enone **335**. A highly selective intramolecular [2+2] photocycloaddition of enone **335** afforded intermediate **336** that, after methyl addition, underwent Grob fragmentation to yield bicyclo[6.3.0]undecenone **337**. A Wittig reaction and rhodium-catalyzed isomerization gener-




***Scheme 84.*** Total synthesis of manzamine A (**331**) by application of a [2+2] photocycloaddition/retro-Mannich reaction sequence followed by ring closure to afford tetracycle **330** from vinylogous amide **327**.

ated diene **338**, which was converted into the target molecule **339** on addition of acid (Scheme 85).[424]



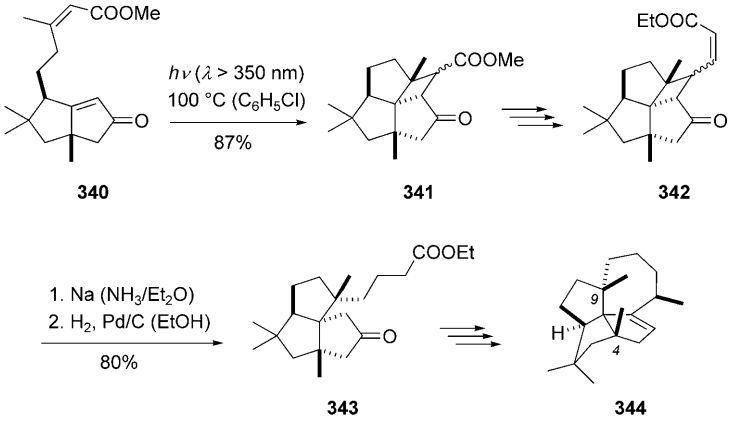

***Scheme 85.*** Access to (±)-pentalenene (**339**) by means of a [2+2] photocycloaddition of enone **335** and subsequent Grob fragmentation.

Another elegant way to access the tricyclo[6.3.0.0$^{4,8}$]undecane skeleton of angular triquinanes is the 1,2-shift of bond *a* in skeleton **T** (Scheme 81). An ideal application of this strategy was reported by Pirrung in the synthesis of (±)-isocomene (**191**, Scheme 52) by using a cyclobutylmethyl/cyclopentyl rearrangement.[425]

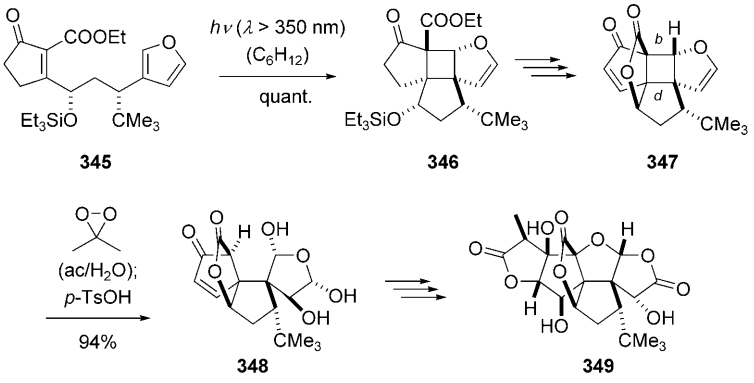
A third approach to the tricyclo[6.3.0.0$^{4,8}$]undecane skeleton from the core structure **T**, but this time for cases when $n=1$, is to cleave bond *b* then close it again with an accompanying ring expansion. Crimmins and DeLoach synthesized (±)-pentalenic acid, (±)-deoxypentalenic acid, and (±)-pentalenene (**339**) in this manner.[426] The same research group reported the use of this strategy, starting from an already bicyclic enone and with closure of a larger ring, in the synthesis of the naturally occurring fenestrane (±)-laurenene (**344**).[427] The intramolecular [2+2] photocycloaddition of enone **340** had to be carried out at higher temperatures (in chlorobenzene as solvent), presumably because the methyl groups at carbons C4 and C9 are subject to considerable steric repulsion. Photoproduct **341** was obtained as a mixture of diastereomers and was subsequently, either as a mixture or separated, converted into ester **342** in three steps through the addition of two carbon atoms. As seen in Scheme 86, reductive fragmentation of bond *b* (Scheme 81) followed by reduction of the β,γ-unsaturated ester afforded intermediate **343**. The final ring closure to generate the fenestrane scaffold was achieved by an acid-catalyzed aldol condensation.

It is clear from structure **341** that a tricyclo[6.3.0.0$^{4,8}$]undecane skeleton can also be generated by this reaction pathway, as shown in the syntheses of the sesquiterpene (±)-silphinene. In this example, the cleavage of bond *b* (Scheme 81) was achieved either by nucleophilic substitution[428] or by radical fragmentation.[429] Further examples, mostly involving a reductive cleavage of type *b* (Scheme 81) for the construction of spirocyclic or annulated ring systems, can be found in the synthesis of (±)-α-acoradiene by Oppolzer et al.,[430] (−)-perhydrohistrionicotoxin by Comins et al.,[431] and (−)-incarvilline by Kibayashi et al.[432] Crimmins et al. also used a [2+2] photocycloaddition/fragmentation sequence for the synthesis of the ginkgo components (±)-bilobalide[433] and (±)-ginkgolide B (**349**).[434] Scheme 87 shows their impressive route to (±)-ginkgolide B (**349**), which commenced with an intramolecular cycloaddition of a furan. Photoproduct **346** was obtained, in quantitative yield, from precursor **345** via a transition state in which both the silyloxy and the *tert*-butyl group were in a pseudoequatorial position. Further transformations afforded the pentacyclic intermediate **347**, which underwent cleavage of bond *b* by an $S_N1$ substitution reaction. Without prior epoxidation of the double bond, undesired cleavage of bond *d* occurred under acidic conditions resulting in regeneration of the furan moiety. The cleavage product **348** was then converted into the target molecule **349**.

Compared to the extensively discussed cleavage reaction of bonds *a* or *b*, there are few examples of syntheses where




***Scheme 86.*** Synthesis of (±)-laurenene (**344**) by intramolecular [2+2] photocycloaddition of enone **340** and reductive cleavage of the cyclobutane moiety in ketone **342**.




***Scheme 87.*** Diastereoselective [2+2] photocycloaddition of furan **345** and nucleophilic ring opening of cyclobutane **347** in Crimmins' synthesis of (±)-ginkgolide B (**349**).

bond *c* (Scheme 81) is cleaved following an intramolecular [2+2] photocycloaddition. Three examples of the application of this type of cleavage will be mentioned (Figure 11).

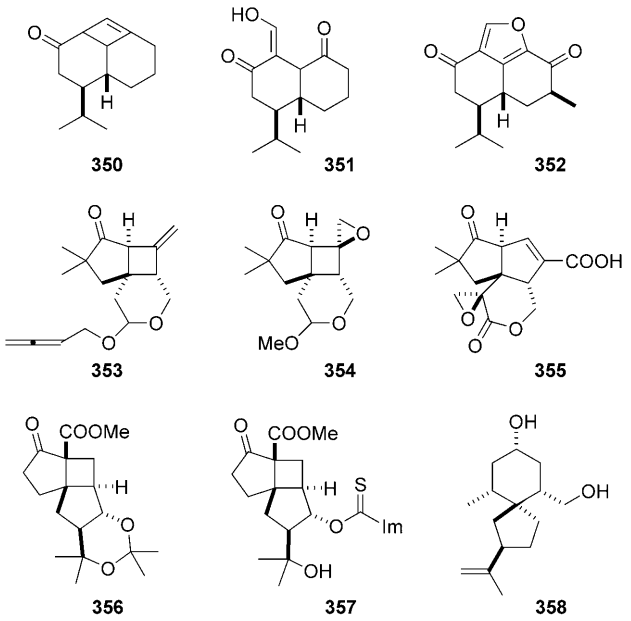
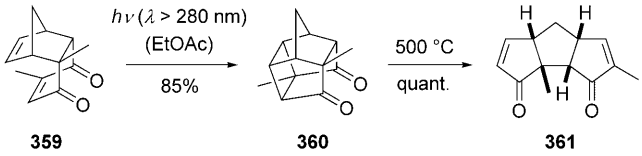



***Figure 11.*** Products of the photocycloaddition and precursors for the fragmentation in the syntheses of (±)-hibiscone C (gmelofuran) (**352**), (±)-pentalenolactone G (**355**), and (±)-lubiminol (**358**). Im = *N*-imidazolyl.

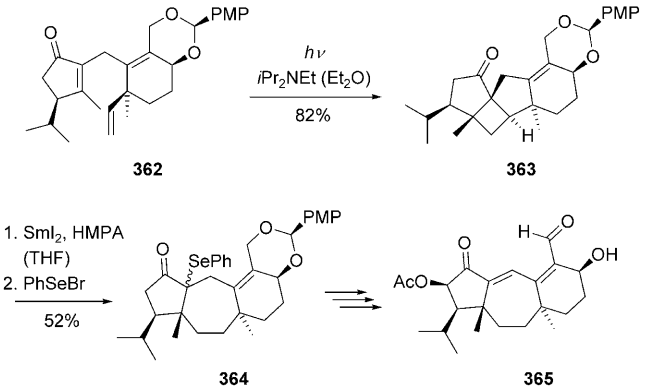
Intramolecular [2+2] photocycloaddition of an alkyne afforded compound **350** as a mixture of diastereomers. Oxidative cleavage delivered product **351** with 1,4-difunctionality, which was subsequently used for the synthesis of the furan ring of (±)-hibiscone C (gmelofuran; **352**).[435] A diallene was the starting material for cyclobutane **353**, which was also synthesized by intramolecular [2+2] photocycloaddition. Ring expansion, from a four- to a five-membered ring, was achieved by the previously discussed rearrangement of an epoxide, thus allowing access to the methyl ester of (±)-pentalenolactone G (**355**) from epoxide **354**.[436] In the last example, while a conventional [2+2] photocycloaddition was used to obtain product **356**, this was later followed by an unconventional radical fragmentation of thiocarbamate **357**. After ring opening of the cyclobutane under cleavage of bond *c* (Scheme 81), the intermediate primary radical initiated a rearrangement that generated a six-membered ring. This presumably proceeded by addition to the carbonyl group of the ketone followed by ring opening. In this way, a synthesis of the phytoalexin (±)-lubiminol (**358**) was achieved.[437]

Sequences that involve the cleavage of several cyclobutane bonds resemble a metathesis reaction. One application can be found in the synthesis of (±)-byssochlamic acid in which a strained tricyclononane skeleton was cleaved thermally, in a similar reaction to the one depicted in Scheme 80, to give the monocyclic nine-membered ring of the natural product.[438] Mehta et al. elegantly used the Diels–Alder products of cyclopentadiene and *para*-benzoquinones for the synthesis of various linearly fused triquinanes such as (±)-hirsutene (**305**, Figure 9),[439,440] (±)-coriolin (**113**, Figure 4),[440] (±)-$\Delta^{9(12)}$-capnellene,[440,441] and (±)-cucumin E.[442] Scheme 88 shows a route towards (±)-hirsutene (**305**) as an example. In this approach the Diels–Alder adduct of 2,5-dimethyl-*para*-benzoquinone and cyclopentadiene, compound **359**, was photolyzed. Intramolecular [2+2] photocycloaddition furnished the pentacyclic dione **360** in very good yield, which was thermally converted into the expected product **361**. Upon further heating (reflux in benzyl benzoate), the *cis-syn-cis* scaffold of compound **361** was transformed into the *cis-anti-cis* scaffold of hirsutene, which could then be obtained in nine additional steps.




***Scheme 88.*** Synthesis of hirsutene precursor **361** by [2+2] photocycloaddition followed by thermal fragmentation.

A more recent example of ring cleavage at bond *d* (Scheme 81), which results in the formation of a bicyclo-




***Scheme 89.*** Formation of the cycloheptane ring in (+)-guanacastepene A (**365**) by [2+2] photocycloaddition of enone **362** and subsequent radical fragmentation.

[5.3.0]decane substructure is depicted in Scheme 89. Cyclobutane **363**, which was obtained stereoselectively from precursor **362**, was converted into product **364** by reductive bond cleavage. The samarium enolate was trapped with PhSeBr, thereby allowing subsequent elimination to afford the conjugated ring system of (+)-guanacastepene A (**365**).[443] (+)-Guanacastepene E was also synthesized in an analogous approach.

The products of a copper-catalyzed [2+2] photocycloaddition were rearranged, by cleavage of bond *d* (Scheme 81) and 1,2-migration, to cyclopentanones by Ghosh and co-

workers. These cyclopentanones served as starting materials in the syntheses of (±)-α-cedrene,[444] (±)-$\Delta^{9(12)}$-capnellene,[445] and (±)-β-necrodol.[446]

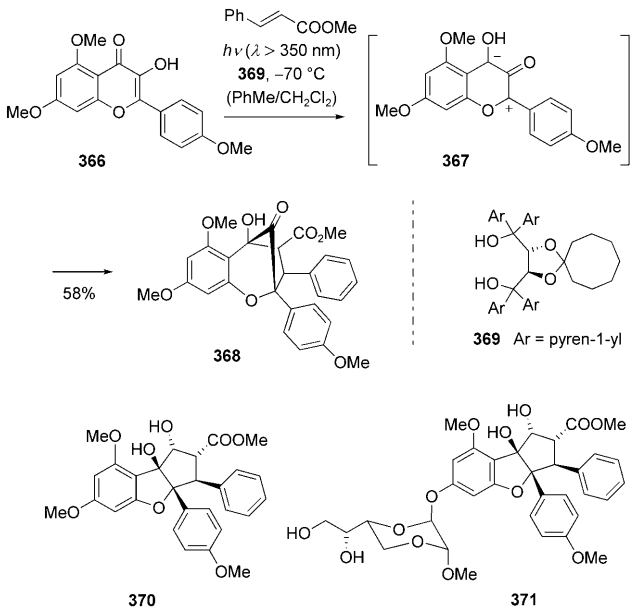
## 9. Further Photocycloadditions

The fact that other cycloadditions can also be initiated photochemically is often overlooked because of the predominance of the [2+2] photocycloaddition. However, some of these reactions have found their way into natural product synthesis. These include (in addition to the [4+2] cycloadditions that have already been mentioned in Section 6.1) the [3+2], [5+2], and [6+2] cycloadditions as well as the *meta*-photocycloaddition. The [3+2] cycloaddition can occur by a proton transfer to generate the reactive intermediate in the same manner as previously described for the [4+2] cycloaddition. The [5+2] cycloaddition possibly involves an α cleavage that is related to the Norrish type I fragmentation which was discussed in Section 4. Presumably, the [6+2] cycloaddition takes place by a stepwise mechanism involving biradical intermediates.[447]

### 9.1. [3+2] Photocycloaddition

Construction of the tetrahydrocyclopenta[*b*]benzofuran core of the rocaglates and rocaglamides was achieved by the research groups of Porco and Rizzacasa by using a photochemically induced [3+2] cycloaddition. As shown in Scheme 90, hydroxyflavone **366** undergoes a photoinduced intramolecular proton transfer that results in the formation of the oxidopyryliumbetaine intermediate **367**, which is—as indicated by the depicted resonance structure—a reactive 1,3 dipole. Trapping by a dipolarophile, in the present case cinammic acid methyl ester, affords the bridged product **368**, which readily undergoes base induced rearrangement to furnish the desired scaffold.[448] By using a chiral Brønsted acid Porco and co-workers were able to perform an enantioselective 1,3-dipolar cycloaddition. The best selectivity (82% *ee*) was obtained with the shown taddol **369** under the given conditions. The *ee* value could be increased significantly by recrystallization. In this way, (−)-methylrocaglate (**370**), (−)-rocaglamide, and (−)-rocaglaol were synthesized.[449] Syntheses of the more complex rocaglates (−)-silvestrol[450] (**371**) and (−)-episilvestrol[450b] were achieved by using the same key step.

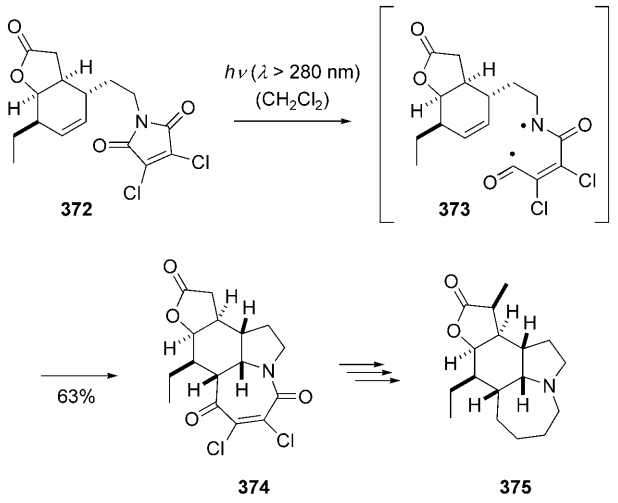
An azomethine ylide, which was generated photochemically by aziridine opening (reversal of a [4π] cyclization; see Section 2.2), served as the substrate for a diastereoselective 1,3-dipolar cycloaddition en route to the isoquinoline alkaloid (−)-quinocarcin.[451]




***Scheme 90.*** Enantioselective [3+2] photocycloaddition of hydroxyflavone **366** to afford adduct **368**, which served as the starting material for the synthesis of (−)-methylrocaglate (**370**) and (−)-silvestrol (**371**).

### 9.2. [5+2] Photocycloaddition

For the synthesis of the stemona alkaloid (±)-neostenine (**375**), Booker-Milburn and co-workers used the unusual intramolecular [5+2] photocycloaddition of maleimide **372**.[452] Irradiation of the substrate in a continuous flow reactor[453] afforded the tetracyclic product **374** in 63% yield (Scheme 91). Mechanistic investigations suggest that the 1,5-singlet diradical **373** is formed as an intermediate, which facilitates the formal cycloaddition by addition to the olefin.



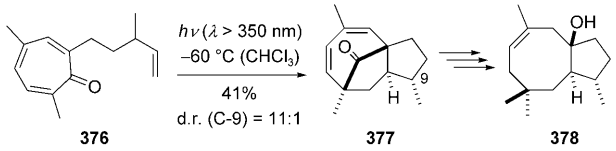

***Scheme 91.*** Total synthesis of (±)-neostenine (**375**) by using a formal [5+2] photocycloaddition of maleimide **372**.

It was important to carry out this reaction in a flow reactor as the discontinuous process afforded only low yields (<20%) when more than 100 mg of substrate was used. In contrast, significant amounts (>1 g) of product could be easily obtained in a single run under the optimized conditions.

### 9.3. [6+2] Photocycloaddition

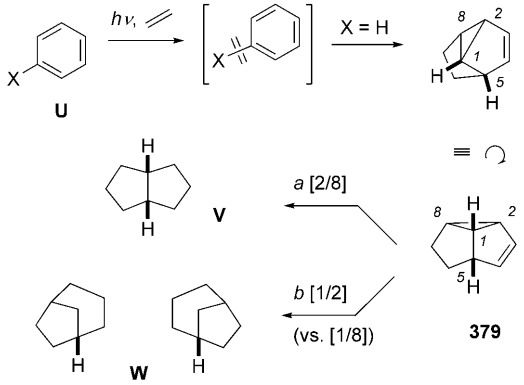
In a total synthesis reported by Feldman et al., the eight-membered ring of the sesquiterpene (±)-dactylol (**378**) was formed by an intramolecular [6+2] photocycloaddition of tropone **376** to afford cyclooctadiene **377** (Scheme 92). After five additional steps, which included a regioselective Baeyer–Villiger oxidation of bis-neopentylketone **377** and chemoselective 1,4-reduction of the cycloocta-1,3-diene unit, the target molecule **378** was obtained.[454]




***Scheme 92.*** Synthesis of the eight-membered ring of (±)-dactylol (**378**) by [6+2] photocycloaddition of tropone **376**.

### 9.4. meta-Photocycloaddition

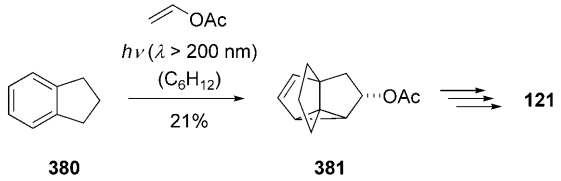
The *meta*-photocycloaddition[455] is among the most fascinating of the photochemical reactions. During the course of the reaction three single bonds are formed and up to six stereogenic centers are created. In Scheme 93 the simplest




***Scheme 93.*** Schematic representation of the *meta*-photocycloaddition and bond fragmentations useful for the synthesis of natural products.

*meta*-photocycloaddition, the reaction of benzene (**U**, X = H) and ethylene, is depicted. The reaction proceeds on the singlet hypersurface with an exciplex and another intermediate (written as a 1,3-diradical or zwitterion) being formed during the reaction. The reaction results in the formation of a tricyclo[3.3.0.$0^{2,8}$]oct-3-ene, in this example compound **379**. In terms of synthetic application of this reaction it is important to note that donor-substituted arenes (**U**, X = donor) preferably give products where the donor resides in the 1-position of the tricyclo[3.3.0.$0^{2,8}$]oct-3-ene scaffold. Fragmentation of the resultant three-membered ring is the most important consecutive process of the *meta*-photocycloaddition. Cleavage of the bond between C2 and C8 (pathway *a*) furnishes the bicyclo[3.3.0]octane skeleton **V**, while cleavage of the bond between C1 and C2, and less frequently between C1 and C8, generates the bicyclo-[3.2.1]octane skeleton **W** (Scheme 93). Both scaffolds are present as subunits of numerous natural products of isoprenoid origin, the syntheses of which are often achieved using *meta*-photocycloadditions. It was Paul Wender who first introduced, in a range of inspiring examples, the *meta*-photocycloaddition reaction into natural product synthesis.[456]

Intermolecular *meta*-photocycloaddition is a reaction that rarely proceeds in good yield. Nevertheless, it is an attractive reaction for synthetic applications because it provides a simple means to generate large quantities of products with high molecular complexity, which can serve as a basis for further manipulations. For example, irradiation of a mixture of indane (**380**) and vinyl acetate with a 450 W lamp through a Vycor filter afforded product **381** in 21% yield (Scheme 94).

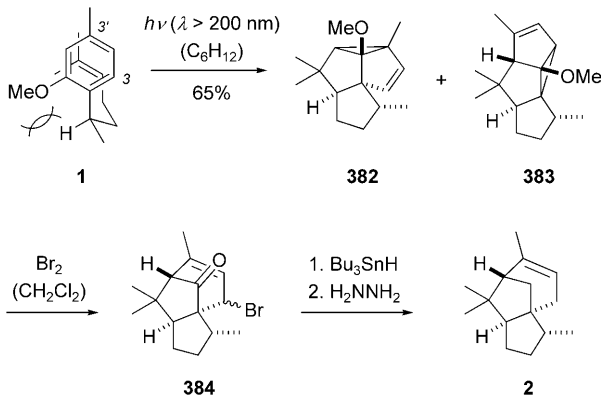



***Scheme 94.*** *meta*-Photocycloaddition of indane (**380**) and vinyl acetate as the starting point for Wender's synthesis of (±)-modhephene (**121**, Scheme 34).

In this specific case, 4.2 g of product **381** were generated from 82 g of starting material **380**. In this product, the [3.3.3]propellane skeleton of the sesquiterpene (±)-modhephene (**121**, Scheme 34) can be readily identified and this natural product was readily synthesized following bond cleavage of type *a* (Scheme 93).[457] Another application of the intermolecular *meta*-photocycloaddition can be found in the synthesis of (±)-isoiridomyrmecin.[458]

The substrates for intramolecular *meta*-photocycloadditions are almost always donor-substituted arenes with an alkenyl chain attached in the *ortho* position. Chains that react with formation of a five-membered ring are preferred, so that the product is formed via a chairlike transition state. Controlling the relative configuration is possible, particularly if the alkenyl carbon atom that is attached to the arene is a stereogenic center. As shown in Scheme 95, 1,3-allylic strain favors a particular conformation for the ring closure.[459] Thus, the facial diastereoselectivity and regioselectivity can be determined unambiguously. The only question that cannot usually be answered explicitly is whether the cyclopropane is formed at the C3- or C3′-position of the arene. Mixtures of products are often obtained: in the depicted example products **382** and **383** are generated in a 1:1 ratio. Compounds of type **382** are precursors for angular triquinanes after type *a* bond cleavage (Scheme 93), while compounds of type **383** afford linear triquinanes (see below). In the specific example of Scheme 95 however, bond *b* was cleaved upon exposure to bromine to afford bromide **384**, as an epimeric mixture at C10, thus providing convergent access to this compound from

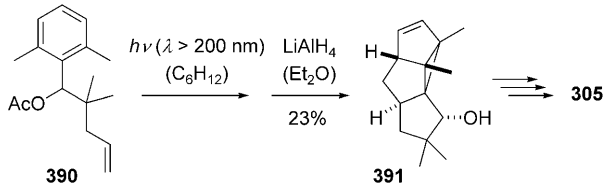



***Scheme 95.*** Total synthesis of (±)-cedrene (**2**) by Wender et al.

a mixture of **382** and **383**. After reductive removal of the bromine atom, the corresponding ketone was obtained in a yield of 59% and was subsequently converted into the product (±)-cedrene (**2**) by a Wolff–Kishner reduction. The fascinating transformation that starting material **1** undergoes in the course of this four-step sequence was also mentioned briefly in the introduction.[7]

*meta*-Photocycloaddition products can also undergo bond cleavages of type *b* (Scheme 93), of which there are two options, both of which result in the formation a seven-membered ring. In the synthesis of (±)-rudmollin (**389**) products **386** and **387** were obtained in a 70:30 ratio from the alkenyl-substituted anisole **385**.[460] In a similar manner to the previous example, type *b* bond cleavage, through mercury-catalyzed hydrolysis, afforded convergent access to a single structure so that the benzoyl-protected β-hydroxy mesylate **388** was obtained after further transformations. Subsequent fragmentation generated the hydroazulene core of the pseudoguaianolides (Scheme 96).

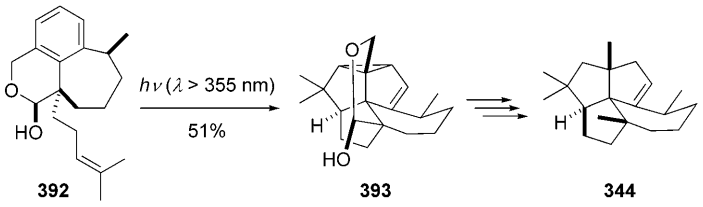
Although ring opening of type *b* (Scheme 93) is very attractive due to its convergency, bond cleavage of type *a* is used much more frequently. Unfortunately, in this case the regioisomers produced during the *meta*-photocycloaddition must be separated. Linear triquinanes are synthesized from regioisomers of type **391** (Scheme 97), which was readily



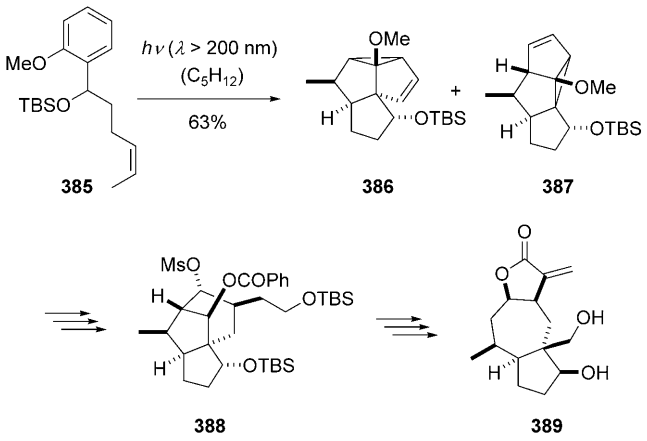

***Scheme 97.*** *meta*-Photocycloaddition of substrate **390** at the start of a total synthesis of (±)-hirsutene (**305**, Figure 9).

produced by diastereoselective photocycloaddition of substrate **390** followed by deprotection. Cleavage of type *a* was achieved under acid catalysis to deliver (±)-hirsutene (**305**, Figure 9) after further transformations.[461] Other linear triquinanes have been synthesized by using similar strategies that involve *meta*-photocycloadditions including (±)-coriolin (**113**, Figure 4)[462] and (±)-ceratopicanol.[463]

The other regioisomer produced in the *meta*-photocycloaddition affords, as already implied above, angular triquinanes. The synthesis of the isoprenoid fenestrane (±)-laurenene (**344**) by Wender et al.[464] (Scheme 98) is a rare example in which the angular skeleton is produced exclusively in the *meta*-photocycloaddition. The tricyclic starting material




***Scheme 98.*** Total synthesis of (±)-laurenene (**344**) by *meta*-photocycloaddition of precursor **396**.



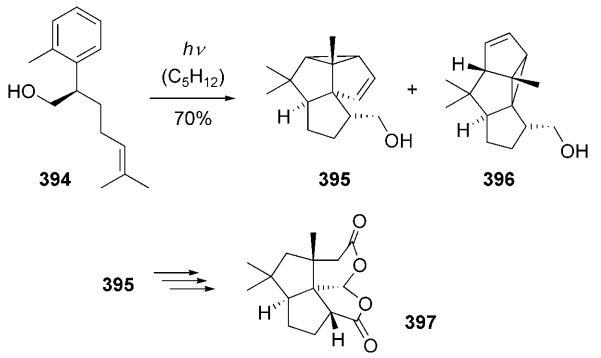

***Scheme 96.*** Total synthesis of (±)-rudmollin (**389**) by *meta*-photocycloaddition of anisole **385**.

**392** furnished, upon irradiation through a $BiCl_3$ filter solution, only the desired regioisomer **393**. Presumably, the much greater steric hindrance of the other regioisomer prevents its formation.

A recent study by Mulzer and Gaich addresses natural products with a dioxafenestrane skeleton, namely the insecticide sesquiterpene (−)-penifulvin A (**397**)[465] and related penifulvins. The dioxa[5.5.5.6]fenestrane scaffold of these compounds could be generated from the angular triquinane precursor **395** (cleavage of type *a* according to Scheme 93) by oxidation of the double bond. Unfortunately, the preceding *meta*-photocycloaddition of substrate **394** afforded both regioisomers, **395** and **396**, in a ratio of 55:45 (Scheme 99). (−)-Penifulvin B and (−)-penifulvin C were also synthesized by using this strategy.[466]

Angular triquinanes that have been synthesized by using a *meta*-photocycloaddition include (±)-isocomene (**191**,




***Scheme 99.*** Application of *meta*-photocycloaddition in the total synthesis of (−)-penifulvin A (**397**).

Scheme 52),[467] (±)-silphinene,[468] (±)-silphiperfol-6-ene,[469] (±)-7β*H*-silphiperfol-5-ene,[469] (±)-retigeranic acid,[470] (±)-subergorgic acid,[471] and (±)-crinipellin B.[472]

## 10. Outlook

Considering the highly complex target molecules and the fairly straightforward synthetic sequences that have been presented in the previous sections, the questions arise as to where the future of photochemistry in natural product syntheses lies and what improvements are possible. A subjective answer to this question comprises, in short, of three main points. The first is that almost no enantioselective reactions have been introduced into organic photochemistry.[473] There are only a few reactions in which an external reagent has been employed, either stoichiometrically or catalytically,[474] to achieve significant asymmetric induction. If one compares the present state of synthetic photochemistry to that of conventional synthetic chemistry, it is lagging behind in its development because of the fact that highly enantioselective catalytic processes have not yet been established. Herein lies enormous potential for further development. Second, the range of natural products that can be synthesized photochemically is limited. Many target molecules are isoprenoid or aromatic natural products. Expanding the product scope requires, among other things, optimization of the irradiation conditions, application of novel light sources, modification of the irradiation conditions by using an in-depth knowledge of the photophysical processes, the use of suitable sensitizers, and, last but not least, the courage to plan a synthesis that requires a novel photochemical reaction as a key step.[475] Third—and in relation to the second point—in the future, new photochemical reactions or photochemical reactions in combination with new (enantioselective) consecutive reactions are necessary, and these still need to be developed. The enantioselective modification of achiral, photochemically generated scaffolds has not been studied intensively.[476] However, this deserves considerable attention as photochemically accessible molecular structures are often unique or difficult to access by other means. Additionally, if the photoreactions leading to this scaffold are catalytic and proceed with visible light,[477] this is even more advantageous. If the ideas mentioned above can be addressed, and if enough researchers focus on these topics, then the future of photochemistry in natural product synthesis is bright.[478]

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[475] No other total synthesis supports this statement presumably any better than the landmark synthesis of vitamin $B_{12}$ by Eschenmoser et al. The construction of the corrin scaffold was successfully performed by employing a novel photochemical

  

cycloisomerization of a seco-corrinoid cadmium complex: a) Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Löllinger, R. Keese, K. Müller, A. Eschenmoser, *Angew. Chem.* **1969**, *81*, 301 – 306; *Angew. Chem. Int. Ed.* **1969**, *8*, 343 – 348; b) A. Eschenmoser, C. E. Wintner, *Science* **1977**, *196*, 1410 – 1420.

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[478] After completion of the work related to this Review, further natural product syntheses were published, which we list chronologically with reference to the respective Section: a) (+)-Deoxypseudopterolide: Z. Yang, Y. Li, G. Pattenden, *Tetrahedron* **2010**, *66*, 6546 – 6549 (see Section 5); b) (+)-Connatusin B: D. J.-Y. D. Bon, M. G. Banwell, A. C. Willis, *Tetrahedron* **2010**, *66*, 7807 – 7814 (see Section 5); c) (±)-Biyouyanagin B: K. C. Nicolaou, S. Sanchini, T. R. Wu, D. Sarlah, *Chem. Eur. J.* **2010**, *16*, 7678 – 7682 (see Section 8).



  