CHEMICAL REVIEWS

Review

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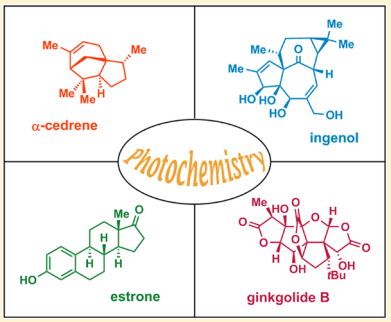
Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis

Markus D. Kärkäs,[†] John A. Porco, Jr.,[*,‡] and Corey R. J. Stephenson[*,†]

[†]Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

[‡]Department of Chemistry, Center for Molecular Discovery (BU-CMD), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

ABSTRACT: The use of photochemical transformations is a powerful strategy that allows for the formation of a high degree of molecular complexity from relatively simple building blocks in a single step. A central feature of all light-promoted transformations is the involvement of electronically excited states, generated upon absorption of photons. This produces transient reactive intermediates and significantly alters the reactivity of a chemical compound. The input of energy provided by light thus offers a means to produce strained and unique target compounds that cannot be assembled using thermal protocols. This review aims at highlighting photochemical transformations as a tool for rapidly accessing structurally and stereochemically diverse scaffolds. Synthetic designs based on photochemical transformations have the potential to afford complex polycyclic carbon skeletons with impressive efficiency, which are of high value in total synthesis.



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1. INTRODUCTION

The synthesis of natural products defines the frontier of synthetic chemistry as it offers the practitioners the challenge of constructing complex and structurally diverse molecular frameworks. This wealth of synthetic challenges has been a valuable platform for expanding state-of-the-art synthetic methodology and discovering fundamentally new chemical protocols that can subsequently be implemented by the whole chemical community.[1−12]

Natural products that display biological activity often serve as vital targets for novel drug lead candidates.[13−17] Access to these complex and structurally diverse assemblies constitutes a multifaceted challenge for chemists, which requires efficient and powerful synthetic strategies.[18−20] The use of small-molecule libraries inspired by bioactive natural products is an essential part of drug discovery and is an attractive aspect of the early stages of drug development. Here, the transition from planar structures with a sp^2-rich character to more structurally complex libraries that contain multiple sp^3 centers may

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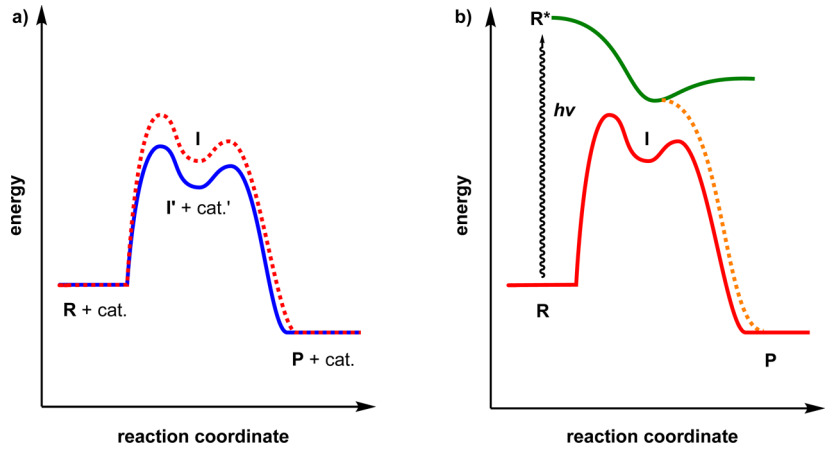

Figure 1. Reaction pathways in (a) a thermal reaction with reagent R yielding product P catalyzed by a catalyst (cat.) via intermediate I′ and (b) in a photochemically induced reaction where the chemical reaction commences from the excited state of the reagent (R*).

yield a higher probability of displaying selective biological activity.[21]

The increased attention to environmentally related issues has also led to the reassessment of several existing technologies, requiring the scientific community to devise novel and "green" methods. These processes should be energy-efficient, reduce the consumption of raw materials, and ultimately produce minimal amounts of waste.[22−25] Ideal methods would provide the opportunity to transform simple feedstocks into highly functionalized and complex molecules. An attractive approach would be to explore the potential of photochemical reactions, as they only involve the absorption of photons. In this sense, photoinduced reactions offer powerful and efficient strategies for designing diverse organic frameworks that might otherwise be difficult to access.[26,27]

A central feature of all light-promoted transformations is the involvement of electronically excited states, formed upon the absorption of photons. This excitation leads to the generation of transient reactive intermediates and significantly alters the reactivity of a chemical compound (Figure 1), a process that can be controlled to generate the intended product in high yield and with excellent selectivity.[28,29] Compared to thermal reactions, a majority of the prevailing photochemical reactions do not require additional reagents for activation, such as metal catalysts, Brønsted acids, or bases. The selective input of energy provided by light offers a means to produce strained and unique target molecules that cannot be assembled using thermal protocols, thus allowing for the production of immense molecular complexity in a single chemical step. Rational and efficient synthetic methodologies can thereby be designed as a rapid entry to diverse molecular scaffolds containing various functional groups, often in shorter synthetic sequences with respect to alternative multistep procedures.[30,31]

As previously mentioned, the use of photochemistry is appealing for generating molecular complexity that may not be accessible by conventional methods. As a result, a number of fascinating total syntheses of natural products have been achieved, which highlight the remarkable power of UV light for constructing advanced polycyclic carbon skeletons.[27,32,33] The use of UV light for bond assembly has been known for a long period of time. Trommsdorff found in the early 19th century that crystals of the sesquiterpene santonin reacted upon exposure to sunlight, which may be considered the birth of photochemistry.[34,35] From the mid-20th century, myriad

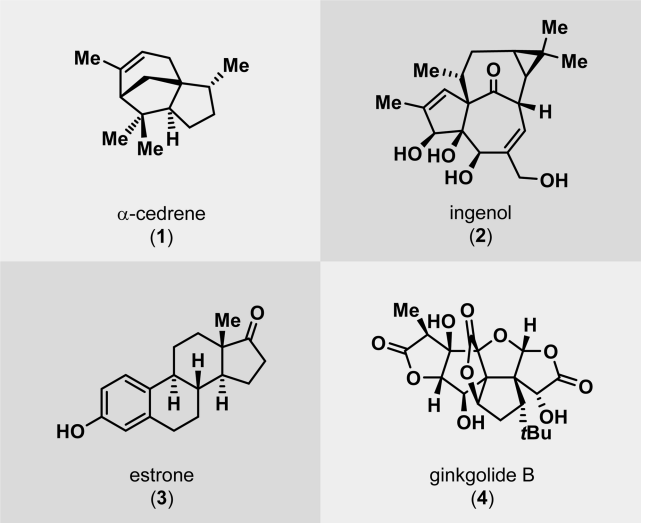

Figure 2. Representative examples where photochemical reactions have been exploited for construction of complex natural products with polycyclic frameworks.

examples have been reported where photochemistry has been exploited for remarkable rearrangements and construction of complex molecular scaffolds.[27,36] Figure 2 depicts some of the outstanding and now classic examples of natural product synthesis where photochemical reactions have been applied in key steps. These include the synthesis of α-cedrene (**1**),[37] ingenol (**2**),[38] estrone (**3**),[39−41] and ginkgolide B (**4**),[42] among others.

This review aims to demonstrate the importance of photochemical approaches for accessing complex chemotypes and its key role in the synthesis of advanced structures with relevance to biological systems. The review is organized by the different types of photochemical reactions, beginning with various [n + 2] photocycloadditions and then describing various photochemical rearrangements that can be achieved. The broader chemistry community has recently become well-aware of the virtues of photoredox catalysis to engage in an array of single-electron transfer (SET) events that have previously been elusive. The final chapter of this review therefore highlights the use of photoredox catalysis to trigger unique catalytic processes in natural product synthesis.

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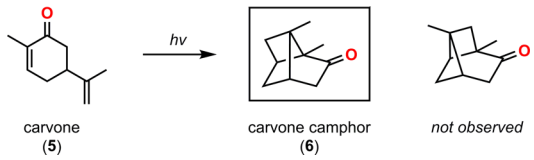
2. [2 + 2] PHOTOCYCLOADDITIONS

2.1. [2 + 2] Photocycloadditions of Olefins—A Versatile Method for Accessing Cyclobutanes

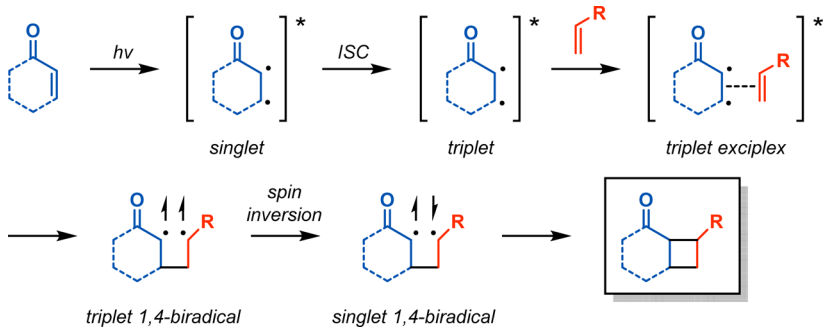
Ciamician and Silber reported on the [2 + 2] photocycloaddition in 1908 when they observed the formation of carvone camphor (**6**) when carvone (**5**) was exposed to light for 1 year (Scheme 1).[43] In the [2 + 2] photocycloaddition of alkenes, α,β-unsaturated carbonyl compounds are generally employed, as they are more easily photoexcited. This produces an initial short-lived singlet state that decays by intersystem crossing (ISC) to produce a triplet state. The triplet exciplex that is formed with the ground state alkene moiety results in a triplet 1,4-biradical that undergoes spin inversion to the singlet biradical, thus allowing for generation of the desired cyclobutane (Scheme 2).[44−46] The [2 + 2] photocycloaddition has the possibility of generating two different regioisomers, which are referred to as the head-to-tail and head-to-head products (Scheme 3, top). In general, head-to-tail products are formed when the R group is electron-donating, while head-to-head products are produced when the R group is electron-withdrawing (Scheme 3, bottom).[47−50]

[2 + 2] Photocycloaddition affords cyclobutanes, an important and common structural motif in a variety of natural products (Figure 3). This makes the [2 + 2] photocycloaddition of two alkene units a powerful method in natural product synthesis for constructing precursors to either acyclic or cyclic systems, including carbo-, heterobi-, and oligocyclic structures. The utilization of the [2 + 2] photocycloaddition of olefins has, for example, been exploited in the total synthesis of (−)-biyouyanagin A (**17**, Scheme 4),[51−53] (−)-littoralisone (**20**, Scheme 5),[54] (−)-paeoniflorin (**23**, Scheme 6),[55] (±)-punctaporonin C (**26**, Scheme 7),[56,57] and (+)-solanascone (**29**, Scheme 8).[58] Recent examples for use of the [2 + 2] photocycloadditions include the total syntheses of aquatolide (**32**, Scheme 9)[59] and an

Scheme 1. Ciamician and Silber's early [2 + 2] Photocycloaddition of Carvone (5)

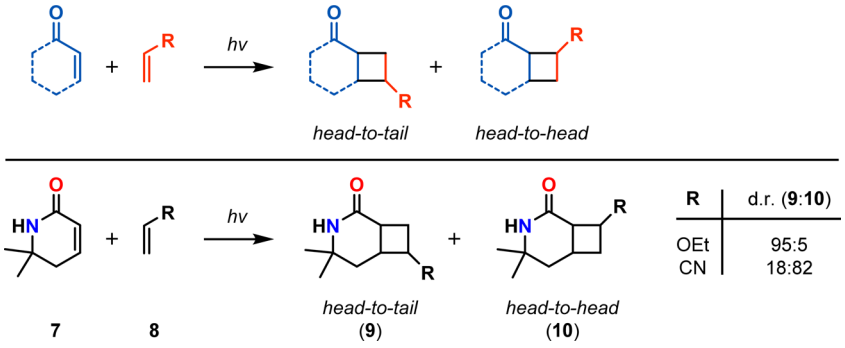


Scheme 2. Photoexcitation of Enones[a]



[a]ISC = intersystem crossing.

Scheme 3. Regioselectivity in [2 + 2] Photocycloadditions



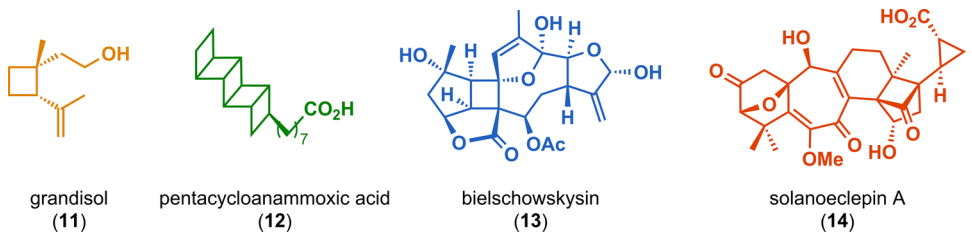


Figure 3. Examples of natural products containing the cyclobutane scaffold.

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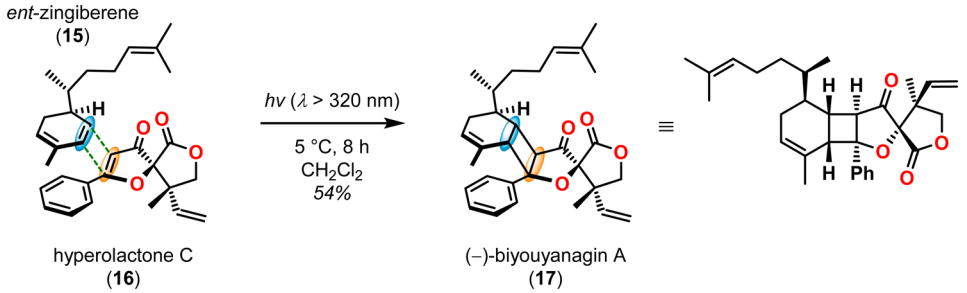
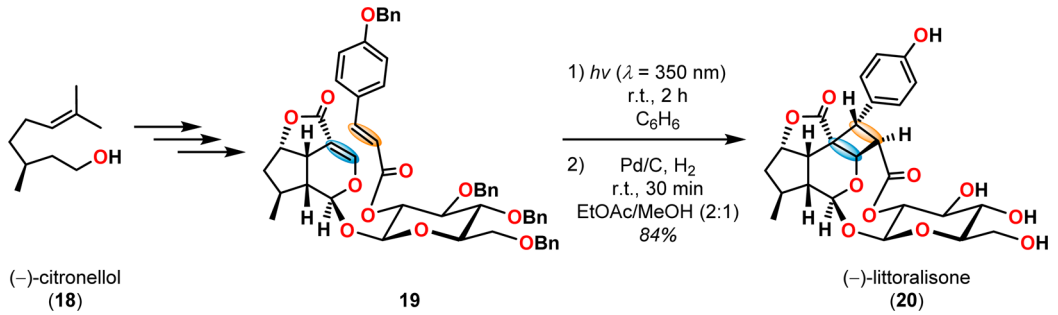
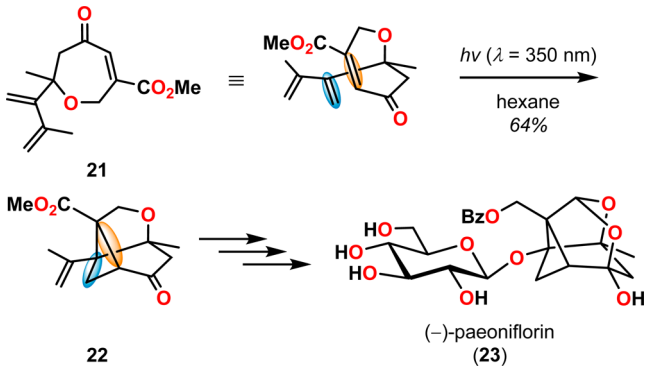
Scheme 4. Intermolecular [2 + 2] Photocycloaddition in the Synthesis of (−)-Biyouyanagin A (17)



Scheme 5. Application of the Intramolecular [2 + 2] Photocycloaddition in the Total Synthesis of (−)-Littoralisone (20)



Scheme 6. [2 + 2] Photocycloaddition of Enone 21 in the Total Synthesis of (−)-Paeoniflorin (23)

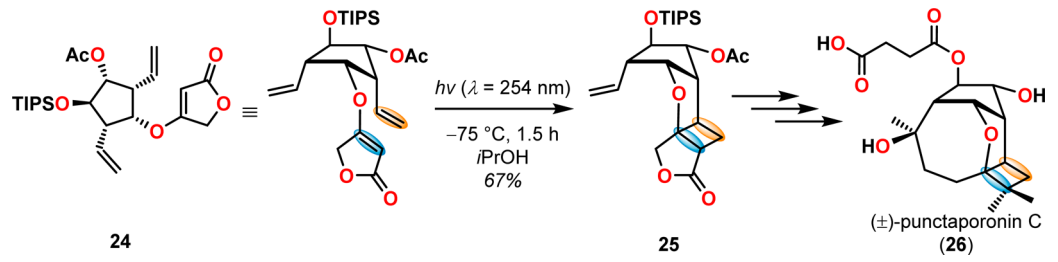


intramolecular [2 + 2] photocycloaddition for construction of the tricyclic core of solanoeclepin A (**14**, Scheme 10).[60]

Optically active allenes appended to enones have also been shown to afford the cyclobutane photoadducts with high levels of asymmetric induction, thus providing access to optically active fused polycyclic structures that might otherwise be difficult to access (Scheme 11).[61,62] A remarkable example for generation of molecular complexity from simple precursors can be encountered in the photocycloaddition/rearrangement sequence that converts pyrroles to aziridines (Scheme 12).[63] Booker-Milburn and co-workers discovered that irradiation of pyrroles such as **37** could facilitate rearrangement from the initially produced [2 + 2] photocycloaddition adduct **38** to produce aziridine **39**. This constitutes a novel photochemical sequence for conversion of substituted pyrroles into intricate tricyclic aziridines and was shown to be general for a variety of substituted pyrroles, ranging from mono- to tetrasubstituted.

From the aforementioned example it is obvious that the inherent ring strain in the cyclobutane ring system renders it amenable to strain-releasing reactions, making the cyclobutane products versatile substrates for further reactions. If the generated cyclobutane is fused to one or several rings, a tandem [2 + 2] photocycloaddition−fragmentation sequence offers powerful routes for accessing ring-expansion products and can thus be used as an intermediate for constructing more complex medium-sized ring systems (Scheme 13). Typical fragmentation pathways for the generated [2 + 2] photoadducts include Grob fragmentations (Figure 4, top), radical fragmentations (Figure 4, middle), or De Mayo reactions (Figure 4, bottom). The robust and sterically tolerant nature of the [2 + 2] photocycloaddition makes it well-suited for constructing C−C bonds in a plethora of contexts.[64−66]

Scheme 7. Intramolecular [2 + 2] Photocycloaddition for Synthesis of the (±)-Punctaporonin C (26) Core[a]



[a]TIPS = triisopropylsilyl.

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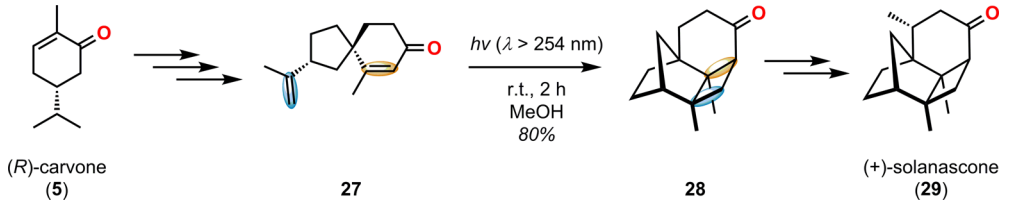
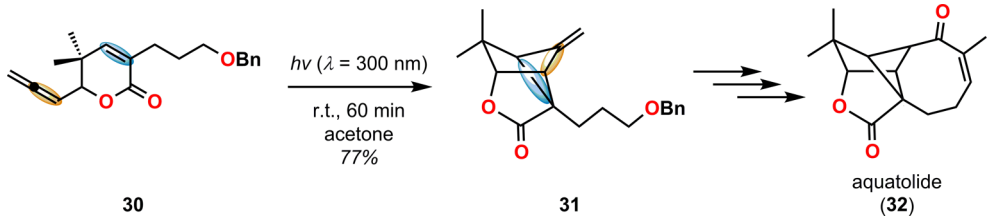
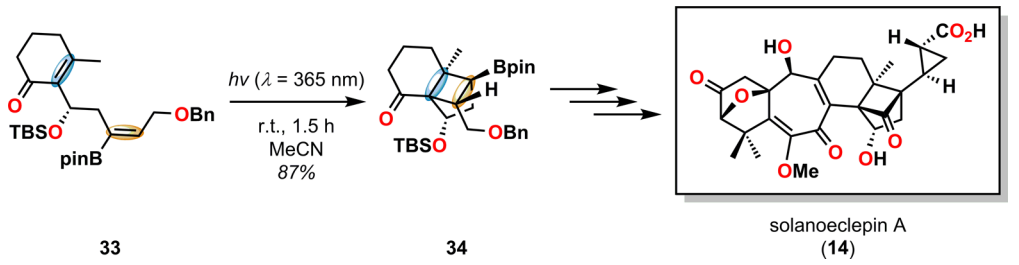
Scheme 8. Intramolecular [2 + 2] Photocycloaddition in the Synthesis of (+)-Solanascone (29)



Scheme 9. Photochemical [2 + 2] Cycloaddition in the Total Synthesis of Aquatolide (32)

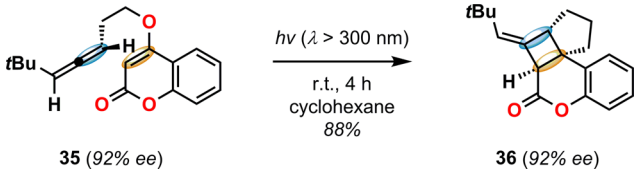


Scheme 10. Intramolecular [2 + 2] Photocycloaddition for Construction of the Tricyclo[5.2.1.0^{1,6}]decane Core of Solanoeclepin A (14)[a]



[a]Bpin = (pinacolato)boron. TBS = *tert*-butyldimethylsilyl.

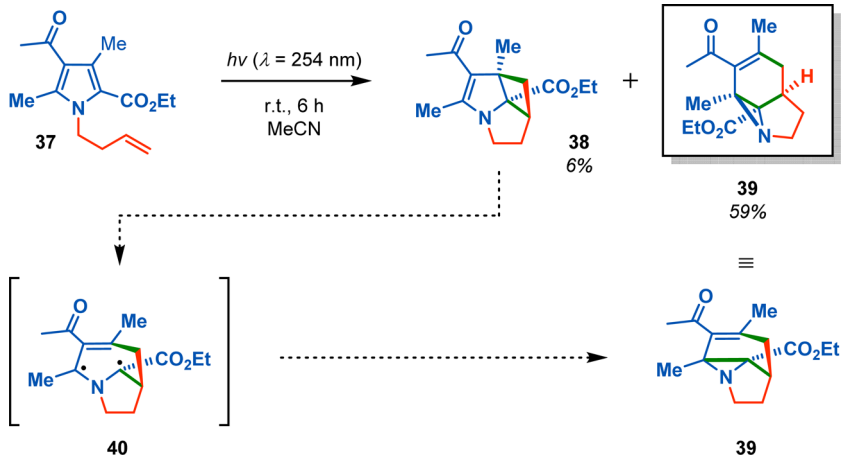
Scheme 11. Intramolecular [2 + 2] Photocycloaddition of Optically Active Allene 35



The use of the [2 + 2] photocycloaddition for the chemoselective annulation of larger ring systems is a powerful concept and was utilized in the total synthesis of (±)-gibberellic acid (**46**, Scheme 14),[67] (±)-pentalenene (**53**, Scheme 15),[68,69] and linderol A (**56**, Scheme 16).[70−72] The [2 + 2] photocycloaddition in combination with a retro-aldol reaction is known as the De Mayo reaction and will be discussed in detail in section 2.3.

A Grob fragmentation[73] was employed in the synthesis of (±)-epikessane (**62**) to construct the hydroazulene skeleton via ring expansion.[74] Cyclobutane **60**, produced from [2 + 2] photocycloaddition of 4-acetoxy-2-cyclopentenone (**57**) and 1-acetoxy-2-carbo-methoxycyclopentene (**58**), treated with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine, thereby triggering Grob fragmentation to afford ketone **61** bearing the

Scheme 12. Photocycloaddition/Rearrangement of Pyrroles to Aziridines



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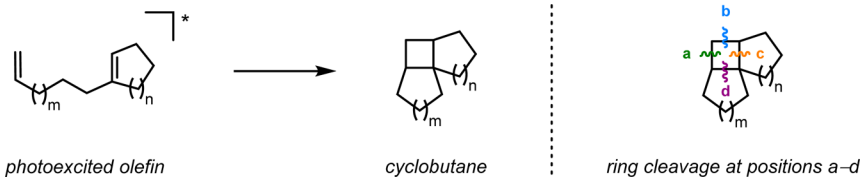
Scheme 13. Formation of Cyclobutanes via [2 + 2] Photocycloaddition, Followed by Ring-Opening To Generate Medium-Sized Rings



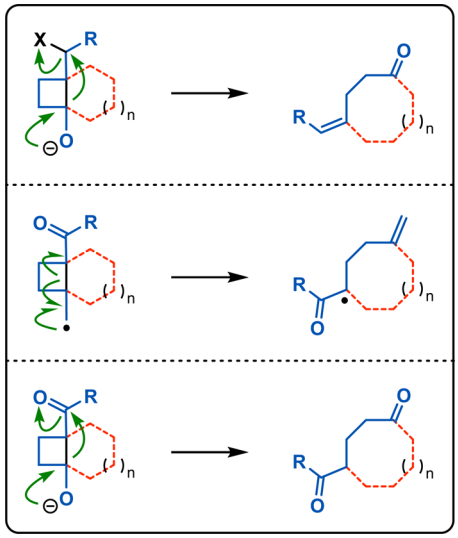


Figure 4. Fragmentation strategies for [2 + 2] photocycloaddition adducts: (top) Grob fragmentation, (middle) radical fragmentation, and (bottom) De Mayo reaction.

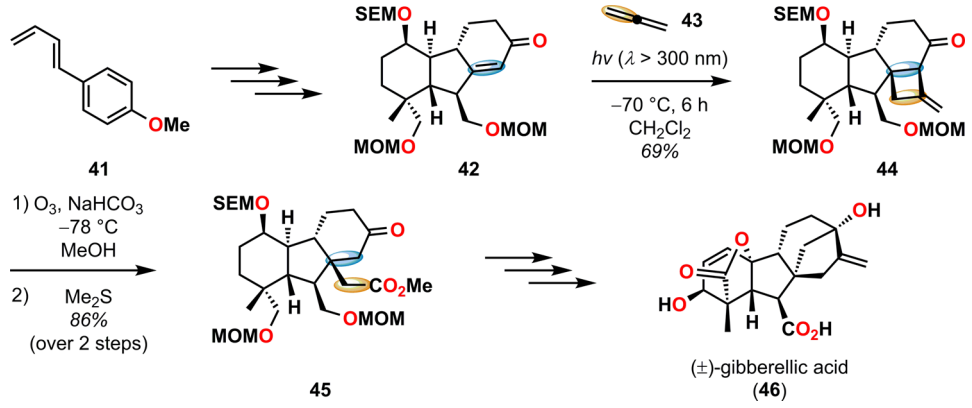
hydroazulene core of epikessane (**62**) (Scheme 17). Epoxides can also be used as functional groups to achieve ring expansion through a Grob-type fragmentation and were utilized in the total synthesis of the hydroazulene sesquiterpene (+)-aphanamol I (see Scheme 50).[75]

Isocomene (**63**) is a sesquiterpene that belongs to a family of tricyclic angular triquinane sesquiterpenes, initially isolated from the plant *Isocoma wrigthii*.[76,77] Tobe and co-workers used a [2 + 2] photocycloaddition approach using enone **66** to generate the tricyclic adduct **67**.[78] Subjecting enone **66** to an excess of 1,2-propadiene (**43**) in CH_2Cl_2 at −78 °C (λ = 300 nm) successfully gave the desired head-to-head product **67** in high yield and excellent selectivity (Scheme 18). Compound **67** was subsequently converted in two steps to epoxide **69**, which under Lewis acid-mediated epoxide−carbonyl rearrangement conditions[79] afforded the triquinane core. Further manipulations of triquinane **70** resulted in (±)-β-isocomene (**64**, Figure 5), which could undergo acid-catalyzed isomerization to furnish (±)-isocomene (**63**). A related ring expansion route by use of the epoxide-carbonyl rearrangement was also employed by Tobe and co-workers in the synthesis of (±)-modhephene (**65**).[80]

Free radical fragmentations of the generated cyclobutanes to produce medium-sized ring systems represent a second class of essential cleavage reactions that have been widely exploited in organic synthesis.[81−86] Shipe and Sorensen employed an intramolecular [2 + 2] photocycloaddition/radical SmI_2-mediated fragmentation sequence in the convergent enantioselective syntheses of both natural (+)- and unnatural (−)-guanacastepene E (**73**) and formal total syntheses of (+)- and (−)-guanacastepene A (**71**, Figure 6).[87,88] Initial π-allyl Stille cross-coupling afforded photosubstrate **76**, which underwent intramolecular [2 + 2] photocycloaddition to furnish cyclobutane **77** in 82% yield. The selective ring opening of the cyclobutane (**77**) was accomplished using SmI_2-mediated ketyl radical formation and radical fragmentation. Subsequent trapping of the samarium enolate with phenylselenenyl bromide gave organoselenide **78**. Selenoxide elimination with *m*CPBA produced the tricyclic compound **79**, which could be elaborated to (+)-guanacastepene A (**71**) and (+)-guanacastepene E (**73**) (Scheme 19).

The radical fragmentation of [2 + 2] photocycloadducts involving Sn reagents has also been exploited in natural product synthesis. Lange and Gottardo utilized Bu_3SnH in combination with azobis(isobutyronitrile) (AIBN) to affect the ring expansion of cyclobutylcarbinyl iodide **83** in the formal synthesis of pentalenene (**53**) (Scheme 20).[89] A related radical

Scheme 14. Application of the [2 + 2] Photocycloaddition/Ozonolysis/Retro-Dieckmann Reaction Sequence in the Synthesis of (±)-Gibberellic Acid (46)[a]



[a]MOM = methoxymethyl. SEM = 2-(trimethylsilyl)ethoxymethyl.

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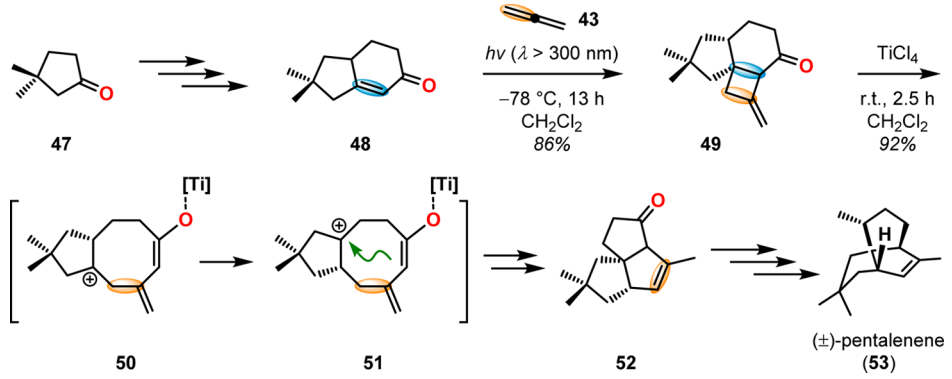
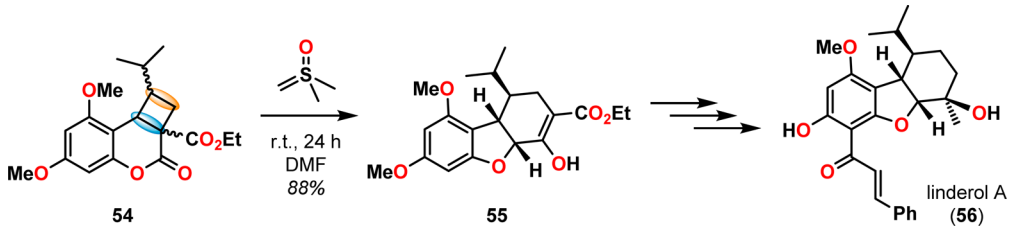
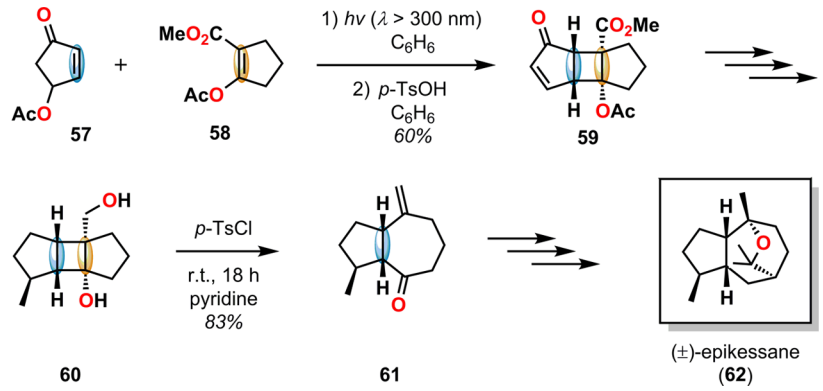
Scheme 15. Allene–Enone [2 + 2] Photocycloaddition with Subsequent Lewis Acid-Catalyzed Rearrangement in the Synthesis of (±)-Pentalenene (53)



Scheme 16. Dimethylsulfoxonium Methylide Mediated Rearrangement of Cyclobutane 54 in the Synthesis of Linderol A (56)



Scheme 17. Grob Fragmentation for Generation of the Hydroazulene Skeleton in the Synthesis of (±)-Epikessane (62)[a]



[a] *p*-TsOH = *p*-toluenesulfonic acid; *p*-TsCl = *p*-toluenesulfonyl chloride.

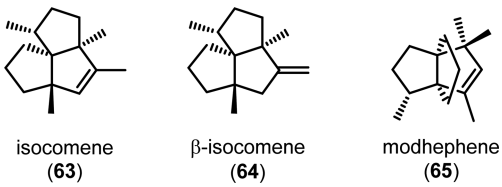


Figure 5. Structures of isocomene (**63**), *β*-isocomene (**64**), and modhephene (**65**).

fragmentation/elimination sequence has also been applied in the total synthesis of the sesquiterpenoid alismol (**92**) to afford the bicyclo[5.3.0]decane ring system **90** using a Bu_3SnH/AIBN reagent combination (Scheme 21).[90,91]

Laurenene (**99**) is a diterpene initially isolated by Corbett and co-workers in 1979 from *Dacrydium cupressinum* and contains the unique fenestrane motif (see Figure 30). The tetracyclic [5.5.5.7]fenestrane core was seen as a challenge that photocycloaddition chemistry was suited to address.[92,93] To generate the sterically crowded quaternary carbon center, a [2 + 2] photocycloaddition of enone **94** furnished the essential cyclobutane intermediate **95** in 87% yield and established the three contiguous quaternary centers required for the central core of laurenene (**99**). Further manipulations transformed cyclobutane **95** to the unsaturated keto ester **96**, where the cyclobutane underwent reductive ring opening under Birch reduction conditions (Na/NH_3) at −33 °C, followed by hydrogenation using Pd/C to afford keto ester **97**. A reduction–oxidation sequence generated the keto–aldehyde containing substrate, which underwent an intramolecular aldol condensation to give enone **98** containing the essential cycloheptane ring and core structure of (±)-laurenene (**99**) (Scheme 22).[94] A related [2 + 2] photocycloaddition approach has also been reported for the synthesis of the sesquiterpene (±)-silphinene (**105**) (Scheme 23).[95]

Merrilactone A (**106**, Figure 7) is a sesquiterpene containing a bicyclo[3.3.0]octane core, two lactone moieties, an oxetane ring, and seven contiguous stereogenic centers, making it an alluring synthetic target.[96,97] Originally isolated from the pericarps of

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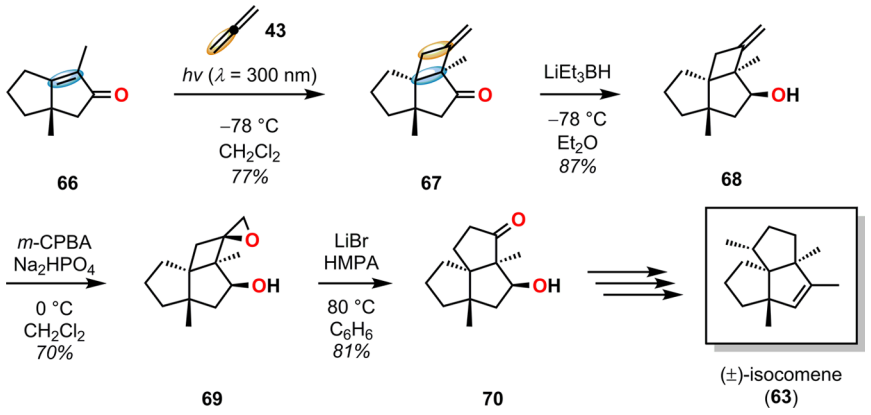
Scheme 18. Tobe's Approach for Construction of the Tricyclic Core of (±)-Isocomene (63)[a]



[a]HMPA = hexamethylphosphoric triamide. *m*-CPBA = *m*-chloroperoxybenzoic acid.

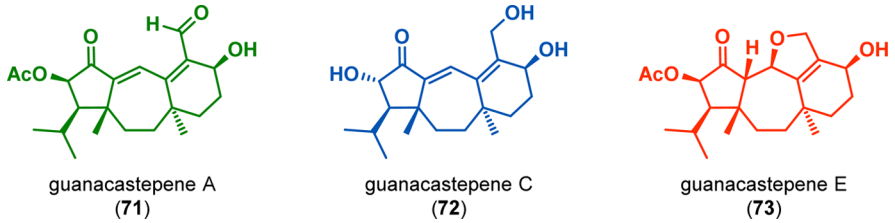
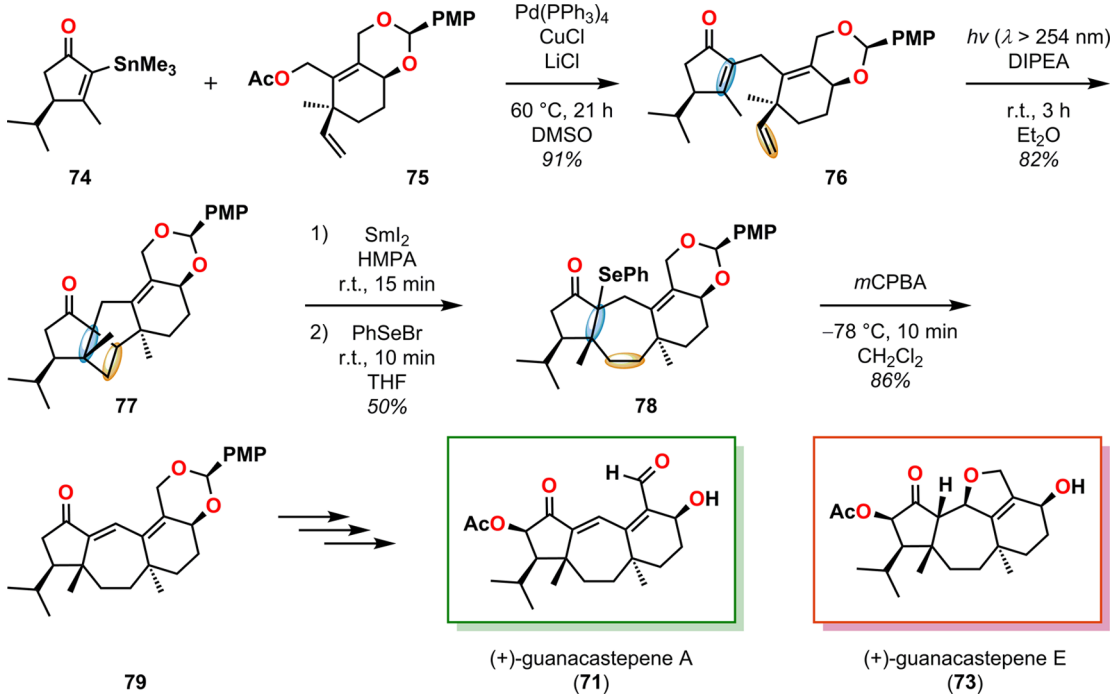


Figure 6. Structures of guanacastepenes A (**71**), C (**72**), and E (**73**).

Scheme 19. Use of the Intramolecular Enone−Olefin [2 + 2] Photocycloaddition and Stereoelectronically Controlled, Reductive, SmI_2-Mediated Fragmentation in the Syntheses of (+)-Guanacastepene A (71) and (+)-Guanacastepene E (73)[a]



[a]*m*CPBA = *m*-chloroperoxybenzoic acid. DIPEA = diisopropylethylamine. HMPA = hexamethylphosphoric triamide. PMP = *p*-methoxyphenyl.

Illicium merrillianum, merrilactone A (**106**) displays neurotrophic activity in cultures of fetal rat cortical neurons[98,99] and is a promising potential therapeutic agent for the neurodegeneration associated with Alzheimer's and Parkinson's diseases.[100−106] Several total syntheses of merrilactone A (**106**) have been reported following its isolation. The groups of Mehta[107] and Inoue[108] both employed a [2 + 2] photocycloaddition of the acetylene surrogate 1,2-dichloroethylene in the synthesis of (±)-merrilactone A and in the asymmetric synthesis of (−)-merrilactone A, respectively. In addition to the two syntheses by Mehta and Inoue, Greaney and co-workers have also reported on the total synthesis of (±)-merrilactone A, which

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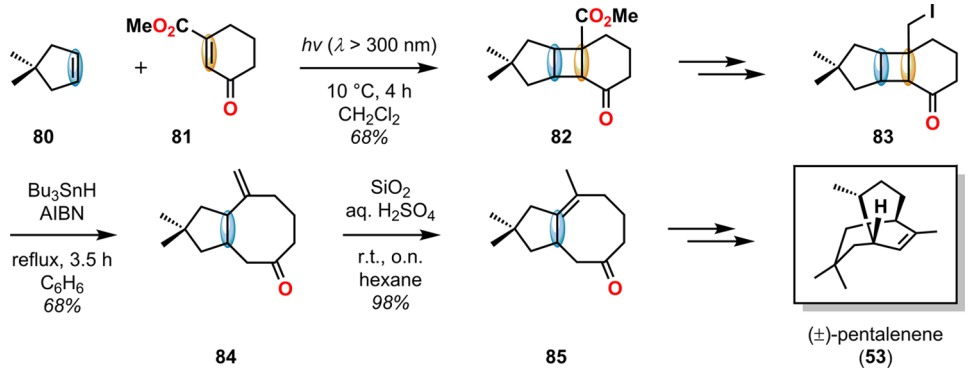
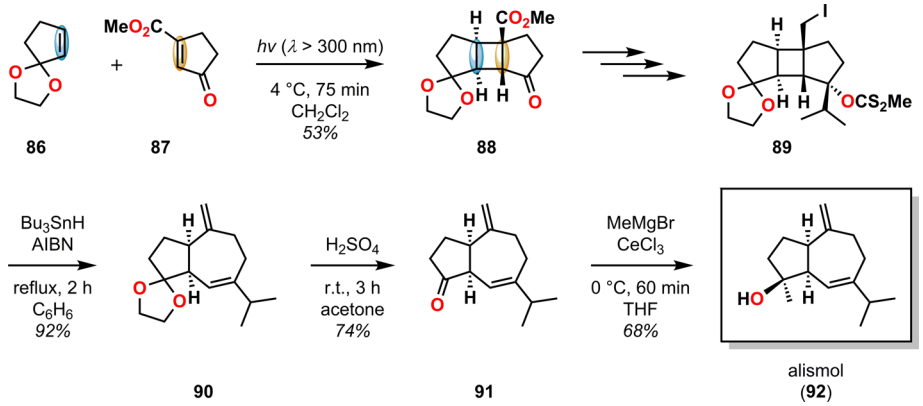
Scheme 20. Bu_3SnH-Mediated Fragmentation of Cyclobutane 83 in the Formal Synthesis of (±)-Pentalenene (53)[a]



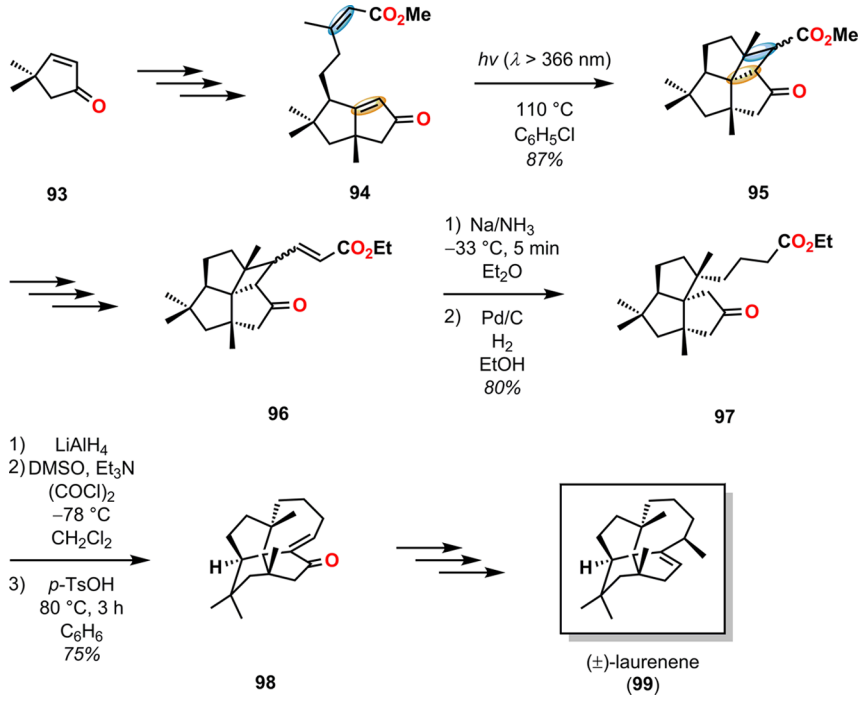
[a]AIBN = azobis(isobutyronitrile).

Scheme 21. [2 + 2] Photocycloaddition with Subsequent Bu_3SnH-Mediated Fragmentation in the Total Synthesis of Alismol (92)[a]



[a]AIBN = azobis(isobutyronitrile).

Scheme 22. Synthesis of (±)-Laurenene (99) via Intramolecular [2 + 2] Photocycloaddition Followed by Reductive Cleavage[a]



[a]*p*-TsOH = *p*-toluenesulfonic acid.

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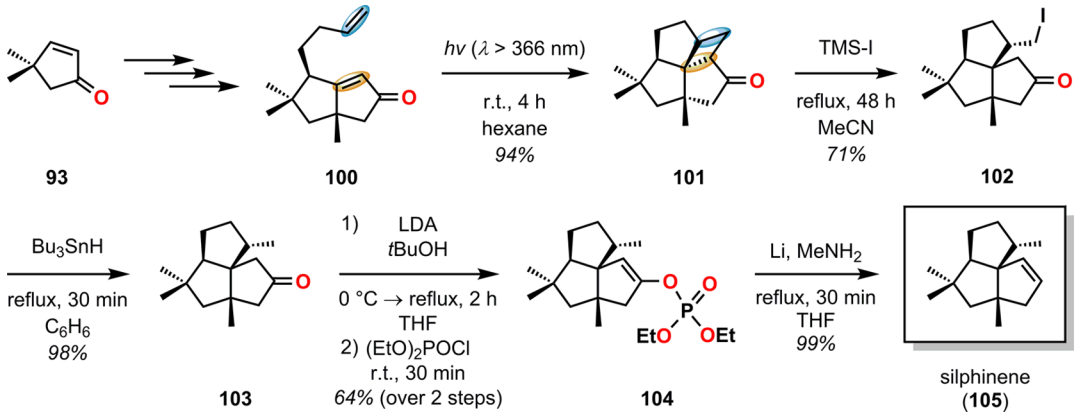
Scheme 23. Construction of the Core in Silphinene (105) By [2 + 2] Photocycloaddition[a]



[a]LDA = lithium diisopropylamide.

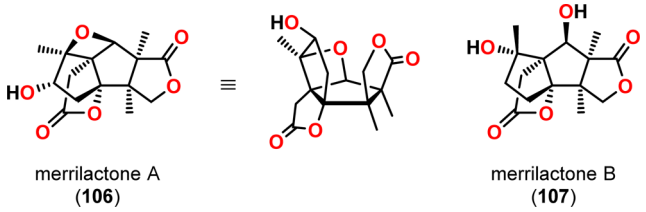


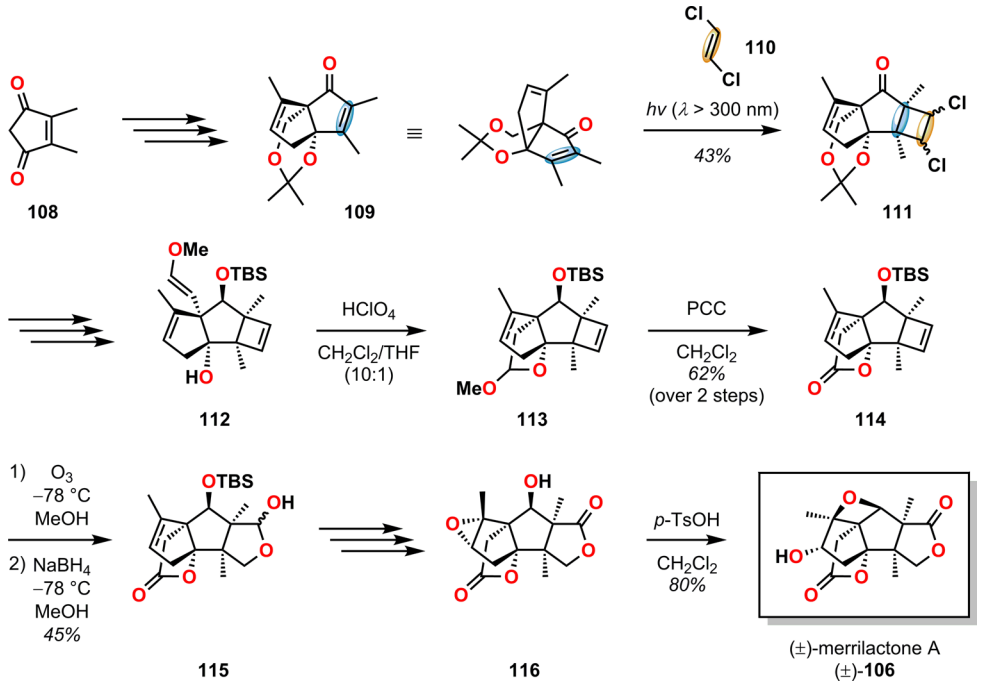
Figure 7. Structures of merrilactones A (**106**) and B (**107**).

relied on an initial [2 + 2] photocycloaddition of 4,5-dimethylmaleic anhydride and dimethylketene acetal.[109] The photocycloaddition was chosen to produce the challenging syn angular methyl groups given the reactions robust nature in sterically encumbered environments.

In Mehta and Singh's approach[107] toward the synthesis of (±)-merrilactone A (Scheme 24), photochemical [2 + 2] cycloaddition of enone **109** and *trans*-1,2-dichloroethylene (**110**) afforded cyclobutane (**111**) in 43% yield, which was subsequently converted to enol ether **112** through a four-step procedure involving eliminative dehalogenation, acetonide deprotection, oxidation, and homologation. Acid-mediated intramolecular hemiacetal formation and oxidation furnished lactone **114**. Ozonolysis and in situ reduction of the fused cyclobutene produced lactol **115**, which was further elaborated into epoxide **116**. Exposure of epoxide **116** to *p*-TsOH allowed for the homo-Payne rearrangement, yielding the target compound (±)-merrilactone A (**106**).

For the asymmetric total synthesis of (−)-merrilactone A (**106**), Inoue and co-workers utilized the [2 + 2] photocycloaddition of the enantiomerically pure lactone **117** and *cis*-1,2-dichloroethylene (**118**) to afford cyclobutene **120** after Zn-promoted dehalogenation and $LiAlH_4$ reduction. Cyclobutene **120** was subsequently converted into diene **121**, which

Scheme 24. Mehta and Singh's Approach to (±)-Merrilactone A (106)[a]



[a]PCC = pyridinium chlorochromate. TBS = *tert*-butyldimethylsilyl. *p*-TsOH = *p*-toluenesulfonic acid.

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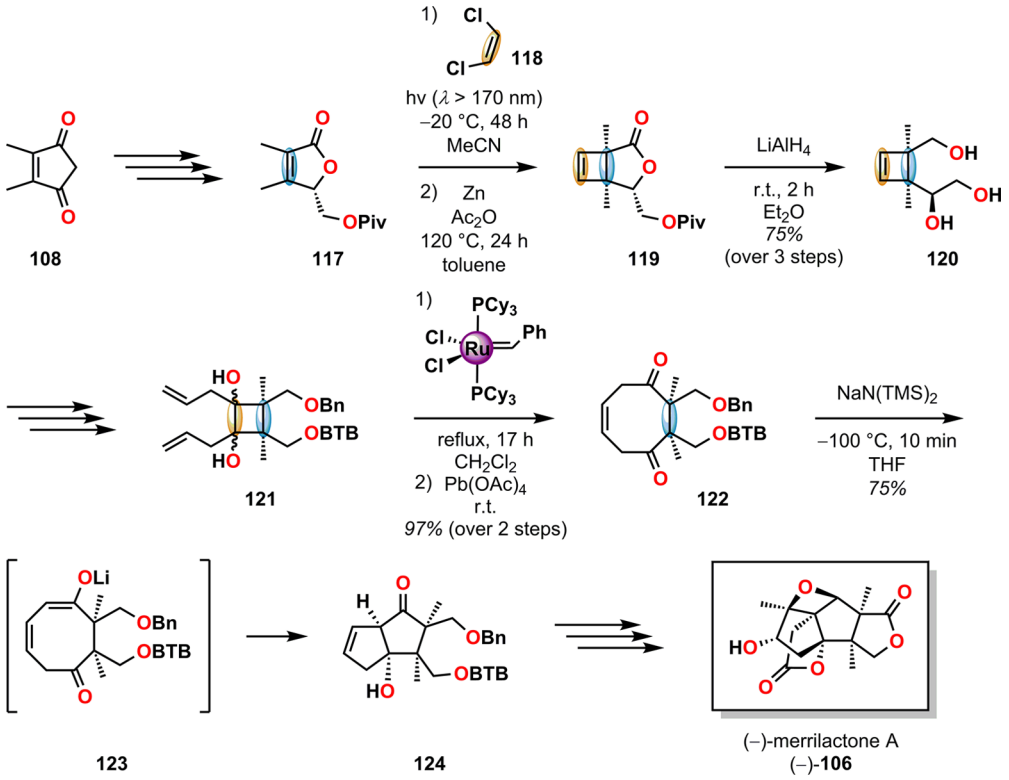
Scheme 25. Inoue and Co-Workers' Approach toward (−)-Merrilactone A (106)[a]



[a]BTB = 2,6-bis(trifluoromethyl)benzyl.

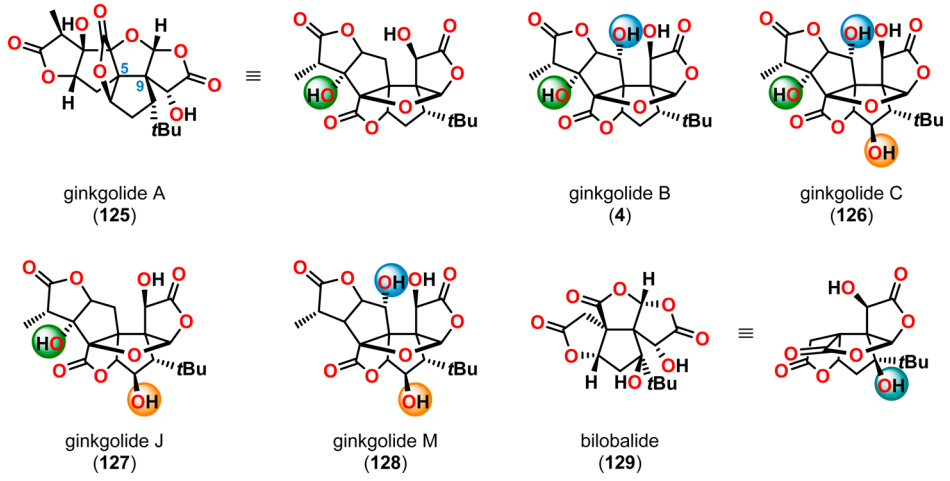


Figure 8. Structures of ginkgolides A, B, C, M, and J (**125**, **4**, **126**−**128**) and bilobalide (**129**).

underwent ring-closing metathesis to yield a bicyclo[4.2.0]-octane system that upon subjection to $Pb(OAc)_4$ underwent oxidative ring expansion to give the cyclooctanedione **122**. After some optimization, it was found that reacting cyclo-octanedione **122** with $NaN(TMS)_2$ allowed for site-selective deprotonation and diastereoselective C−C bond formation through a transannular aldol reaction, producing the desired bicyclo[3.3.0]octane system **124** with only small amounts of the other diastereomers. Further manipulations completed the asymmetric synthesis of (−)-merrilactone (**106**) in 31 steps with an overall yield of 1.1% (Scheme 25).

The ginkgolides are a family of polycyclic oxygenated compounds obtained from the ginkgo tree (*Ginkgo biloba*). Extracts from the ginkgo tree have been used as herbal medicines for 5000 years for alleviating disorders such as coughs, bronchitis, and asthma.[110−113] These therapeutic effects were shown to originate from five different compounds, called the ginkgolides, which differ only in the number and position of the hydroxyl groups (Figure 8). The ginkgolides were originally isolated by Furukawa[114−116] in 1932, but their structures were not established until 1967, when X-ray crystallography studies confirmed the structure and absolute stereochemistry of the ginkgolides.[117−121] Bilobalide (**129**)[122] and ginkgolide J (**127**)[123] were subsequently discovered and added as members of the ginkgolide family. The five ginkgolides (A, B, C, J, and M) all share an identical carbon skeleton, consisting of 6 rings,

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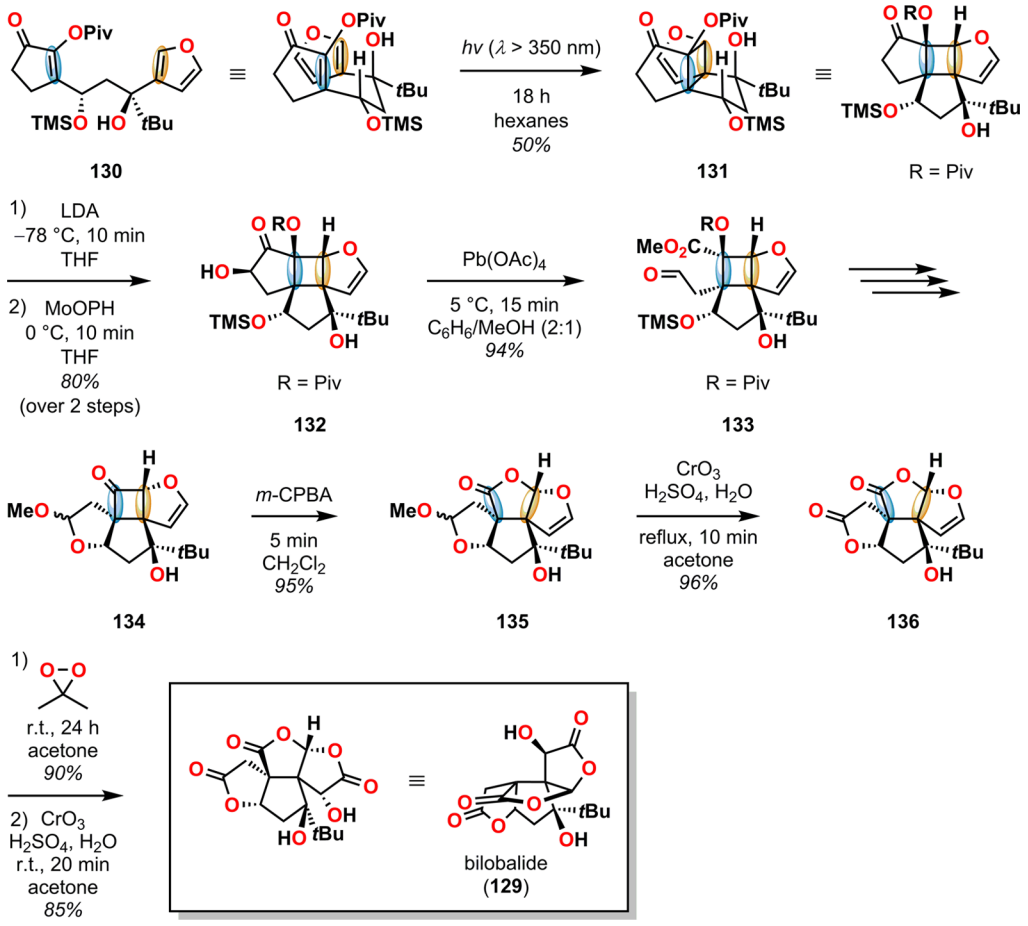
Scheme 26. Use of Intramolecular [2 + 2] Photocycloaddition in the Synthesis of Bilobalide (129)[a]



[a] *m*-CPBA = *m*-chloroperoxybenzoic acid. LDA = lithium diisopropylamide. MoOPH = (hexamethylphosphoric triamide)oxodiperoxy(pyridine)-molybdenum(VI) (MoO_5·pyr·HMPA). Piv = pivaloyl.

11 stereogenic centers, and an uncommon *tert*-butyl moiety. The syntheses of ginkgolides A (**125**)[124] and B (**4**)[125] as well as bilobalide (**129**)[126,127] were initially accomplished by Corey and co-workers.[128]

A remarkable example where [2 + 2] photocycloaddition has been employed to access complex polycyclic carbon skeletons is the total synthesis of ginkgolide B (**4**) reported by Crimmins and co-workers, where they made use of a [2 + 2] photocycloaddition in order to establish the two vicinal quaternary stereocenters.[42,129] Previously, the same group reported the synthesis of the structurally related compound bilobalide (**129**) using a stereoselective, intramolecular [2 + 2] photocycloaddition as the key step for assembling the core of bilobalide (**129**) (Scheme 26).[130,131] Here the [2 + 2] photocycloaddition of photosubstrate **130** gave the desired photoadduct **131** in 50% yield where both the (trimethylsilyl)oxy and the *tert*-butyl groups occupy pseudoequatorial positions on the generated five-membered ring. Hydroxylation of photoadduct **131** with MoOPH {(hexamethylphosphoric triamide)oxodiperoxy-(pyridine)molybdenum(VI) [MoO_5·pyr·HMPA][132,133]} produced hydroxy ketone **132** in 80% yield. Oxidative cleavage of hydroxy ketone **132** afforded aldehyde **133** in 94% yield, which could subsequently be converted into acetal **134** in three steps. A regioselective Baeyer−Villiger oxidation of cyclobutanone **134** furnished lactone **135** in 95% yield. After construction of the basic skeleton of bilobalide, a three-step oxidation sequence involving Jones' reagent[134]/dimethyldioxirane/Jones' reagent furnished the target compound bilobalide (**129**) in excellent yield.

As previously shown for the ginkgolides, the introduction of the functional groups and the correct orchestration of the C5 and C9 quaternary carbon centers have been recognized as the crucial steps and certainly constitute a significant challenge for synthetic chemists. A resourceful synthetic approach was taken by Crimmins and co-workers, who made use of the enone−furan **138** as the key building block in the total synthesis of ginkgolide B (**4**, Scheme 27).[42,129] The important photocycloaddition substrate **138** was prepared using a previously established homoenolate approach for the construction of carboalkoxycyclopentenones.[135,136] Reacting the acetylenic ester **137** with the appropriate zinc−copper homoenolate gave the photosubstrate **138** in 82% yield. Subsequent irradiation of enone **138** in hexanes resulted in the formation of the tetracyclic photoadduct **139** in quantitative yield and in >98:2 diastereoselectivity, thus establishing the two quaternary centers of the ginkgolide skeleton. Conversion of cyclobutane **139** to the bridged lactone **140**, accompanied by treatment with dimethyldioxirane, provided bis-hemiacetal **141**, which was further transformed to lactone **142**. Acid-catalyzed methanolysis of lactone **142** facilitated ring closure to construct the E ring of the ginkgolides, affording the pentacyclic lactone **143** in 88% yield. Finally, ring closure and additional functionalization of the F ring provided ginkgolide B (**4**).[42,129]

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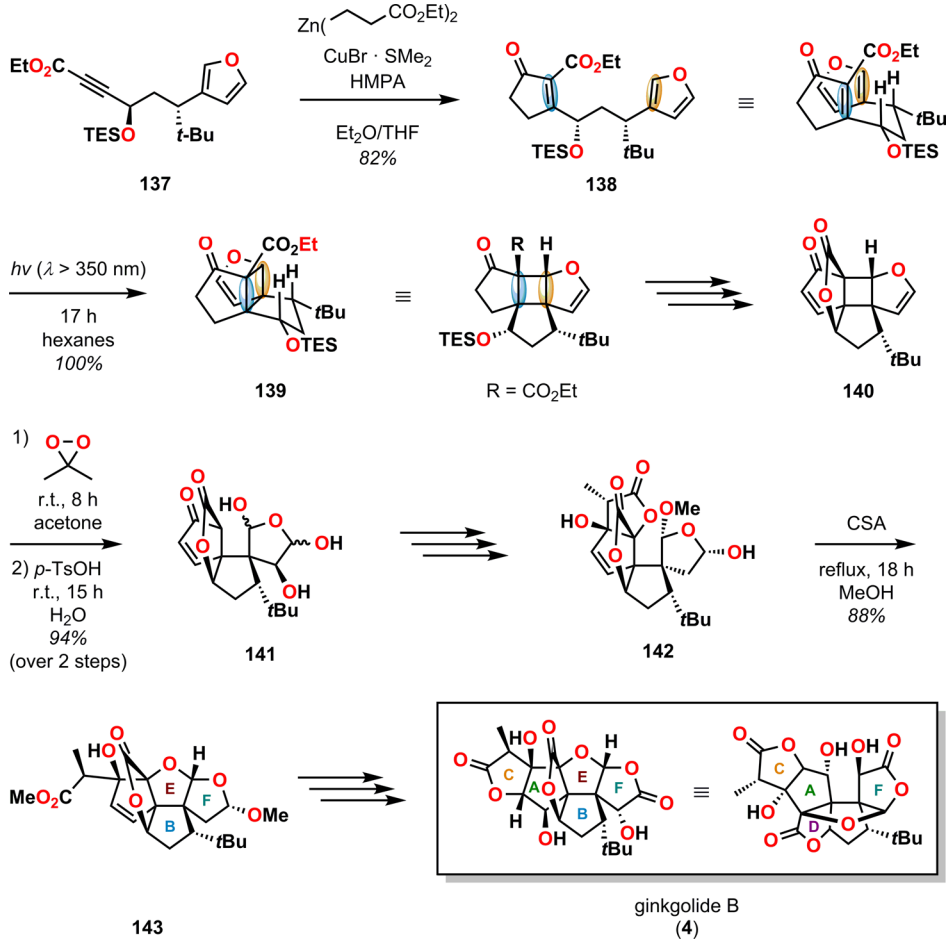
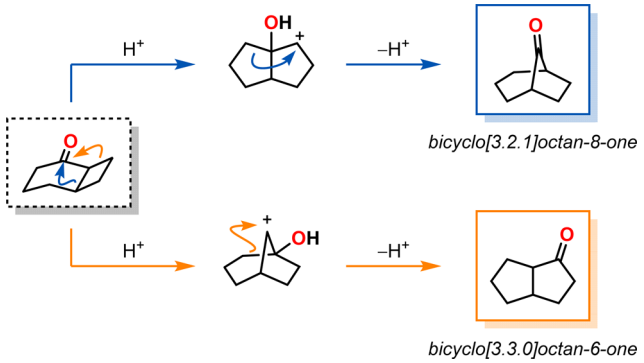
Scheme 27. Total Synthesis of Ginkgolide B (4) via Stereoselective Intramolecular [2 + 2] Photocycloaddition and Cyclobutane Ring-Opening Methodology[a]



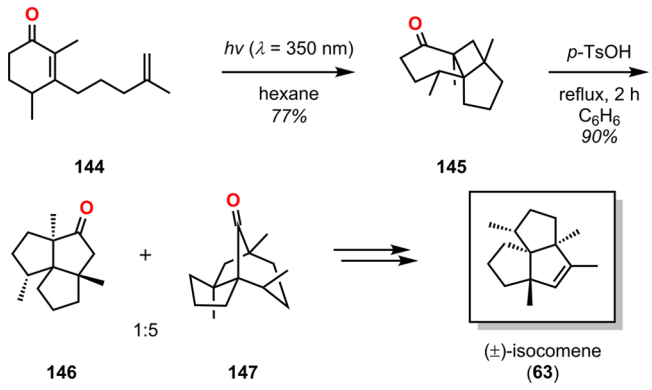
[a]CSA = camphorsulfonic acid. TES = triethylsilyl. *p*-TsOH = *p*-toluenesulfonic acid; HMPA = hexamethylphosphoric triamide.

Ring expansion by use of the Cargill rearrangement[137−141] is an attractive way to produce bridged ketones from cyclobutenyl ketones (Scheme 28). Pirrung took advantage of this rearrangement in the synthesis of (±)-isocomene (**63**) (Scheme 29). Intramolecular [2 + 2] photocycloaddition of **144** generated tricyclo[6.3.0.0^{1,6}]undecanone **145**. Subsequent Cargill rearrangement of cycloadduct **145** afforded the two bicyclo[3.3.0]-octane and bicyclo[3.2.1]octane products **146** and **147** in a 1:5 ratio. Finally, bicyclo[3.2.1]octane **147** was transformed to (±)-isocomene via acid-catalyzed rearrangement.[142,143] Additional routes to (±)-isocomene (**63**) include the use of the Paternò−Büchi reaction,[144,145] the meta-photocycloaddition,[146] and the oxa-di-π-rearrangement,[147] and they will be discussed in more detail in the upcoming sections.

Scheme 28. Ring Expansion of Cyclobutanes via Cargill Rearrangement



Scheme 29. Pirrung's Approach to (±)-Isocomene (63)[a]



[a]*p*-TsOH = *p*-toluenesulfonic acid.

The [2 + 2] photocycloaddition can also be accompanied by a thermally induced ring opening. This route was exploited by Schreiber and Santini in the synthesis of the sex pheromone

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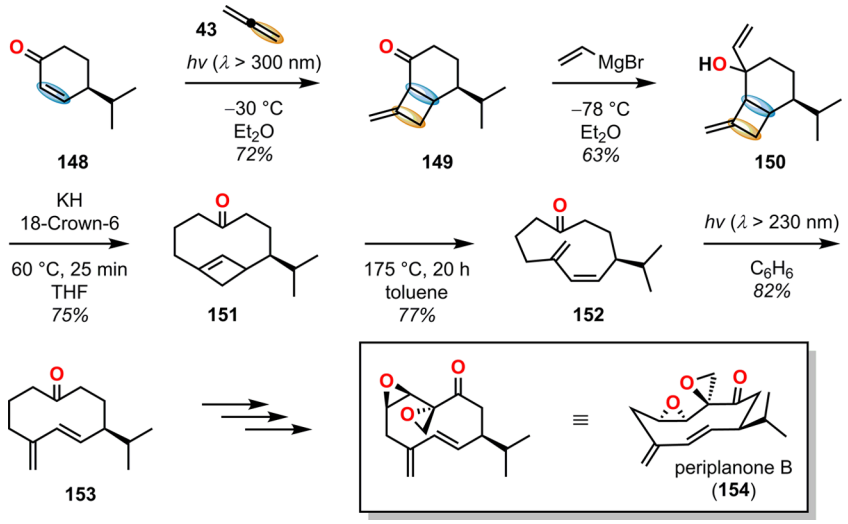
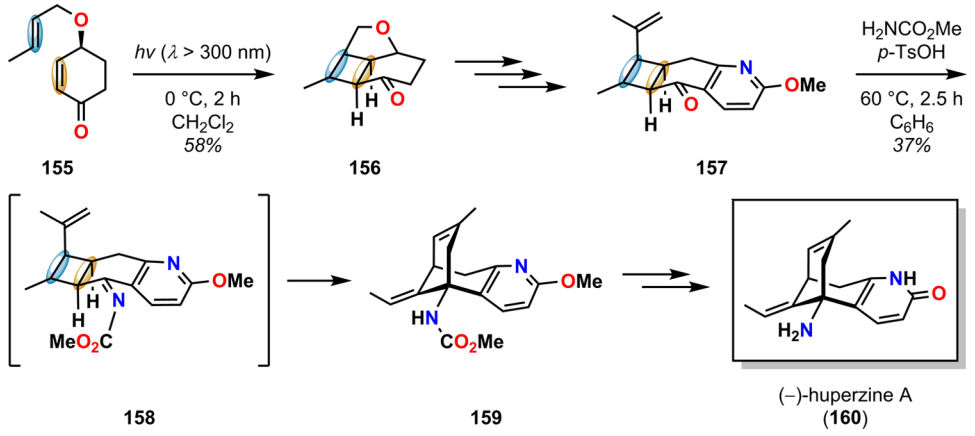
Scheme 30. [2 + 2] Photocycloaddition with Subsequent Thermal Ring Opening in the Synthesis of Periplanone B (154)



Scheme 31. Synthesis of the Nootropic Alkaloid (−)-Huperzine A (160) Using a [2 + 2] Photocycloaddition/Cyclobutane Fragmentation Sequence through an Aza-Prins Reaction[a]



[a] *p*-TsOH = *p*-toluenesulfonic acid.

periplanone-B (**154**, Scheme 30).[148−150] The synthesis commenced with a [2 + 2] photocycloaddition of allene (**43**) and alkene **148** to afford a mixture of the syn and anti head-to-head photoproduct **149**. It was revealed that the diastereomeric mixture converged to the same end product; thus, addition of vinylmagnesium bromide provided a mixture of allyl carbinols **150**. Subsequent anion-accelerated oxy-Cope rearrangement followed by electrocyclic ring opening produced a mixture of *s*-cis diene **152** and *s*-trans diene **153**. Cis/trans photoisomerization of the dienes showed a photostationary equilibrium in a 15:1 ratio with the *s*-trans isomer **153** being favored, which could be converted to periplanone B (**154**).

An intramolecular aza-Prins reaction with a guided fragmentation of a cyclobutylcarbinyl cation was used as the key step for assembling the bicyclo[3.3.1]nonene core of the nootropic alkaloid (−)-huperzine A (**160**).[151] Here, the necessary photoadduct **156**, generated from intramolecular [2 + 2] photocycloaddition in 58% yield from **155**, was converted to cyclohexanone **157**. Condensation of ketone **157** with NH_2CO_2Me in the presence of *p*-TsOH initiated the aza-Prins reation sequence, presumably via carbamate **158**, to afford the desired fragmentation product **159**, which is a known precursor to (−)-huperzine A (**160**) (Scheme 31).

It is clear that the wide range of natural products that can be accessed by the [2 + 2] photocycloaddition makes the reaction a highly useful tool in total synthesis. The prominent structures that have successfully been accessed utilizing a [2 + 2] photocycloaddition strategy are frameworks with multiple stereocenters and quaternary carbon centers. The ability to create several C−C bonds in hindered environments, in a single transformation, highlights the powerful features of the [2 + 2] photocycloaddition. The accessible fragmentation strategies that can subsequently be used allow for creative and effective construction of a multitude of complex natural products and their derivatives.

2.2. [2 + 2] Photocycloadditions between Olefins and Carbonyls—Oxetane Synthesis through the Paternò−Büchi Reaction

The [2 + 2] photocycloaddition of an alkene and a carbonyl compound—the Paternò−Büchi reaction—is a powerful method for construction of oxetanes, which are versatile intermediates in organic synthesis and occurring motifs in pharmaceutical compounds as well as in natural products (Figure 9).[152,153] In these reactions the carbonyl motif usually serves as the light-absorbing species. Excitation of the nπ^* state thus results in a

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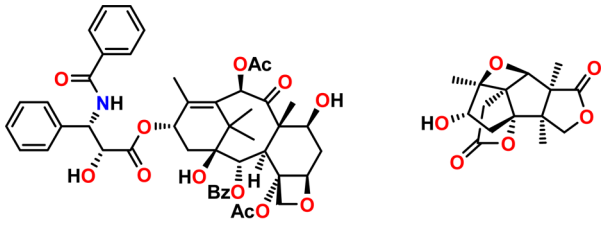
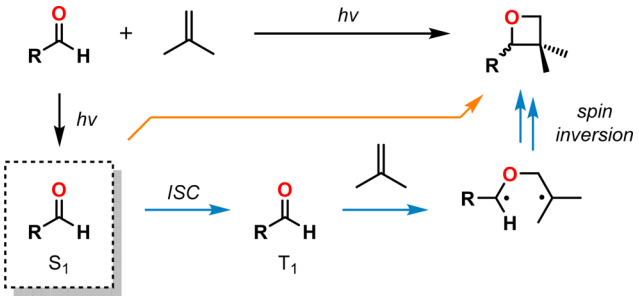


Figure 9. Compounds containing the oxetane motif.

singlet state that readily undergoes ISC to the triplet state, from which a majority of the Paternò–Büchi reactions occur. The diastereoselectivity is dictated by the lifetimes of the generated triplet 1,4-biradicals, as a consequence of the stepwise mechanism, and is connected with the mode of spin inversion events that allows for closed-shell products to be formed (Scheme 32). The regioselectivity can usually be predicted by

Scheme 32. Illustration of the Paternò–Büchi Reaction[a]

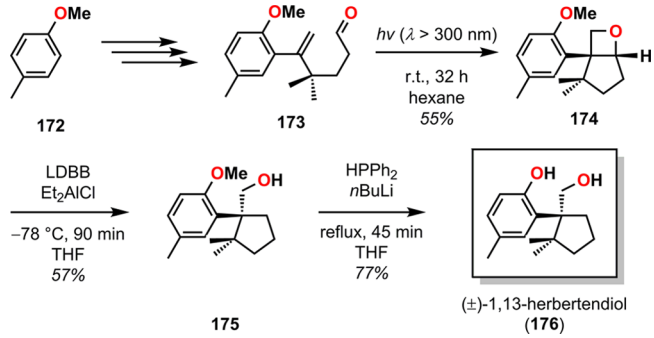


[a]ISC = intersystem crossing.

formation of the most stable biradical upon addition of the carbonyl compound to the alkene moiety.[154−159] A requirement for the Paternò–Büchi reaction to occur is that the alkene cannot have a lower triplet energy state than the carbonyl entity; if this would be the case, energy transfer is the major reaction pathway, with oxetane formation occurring slowly.[160−165]

Although the Paternò–Büchi reaction has been less frequently employed in natural product synthesis than the cyclobutane [2 + 2] photocycloaddition reaction, it has for example been utilized in the synthesis of (+)-preussin (**167**, Scheme 33),[166] (±)-oxetanocin (**171**, Scheme 34),[167] and (±)-1,13-herbertendiol (**176**, Scheme 35).[168]

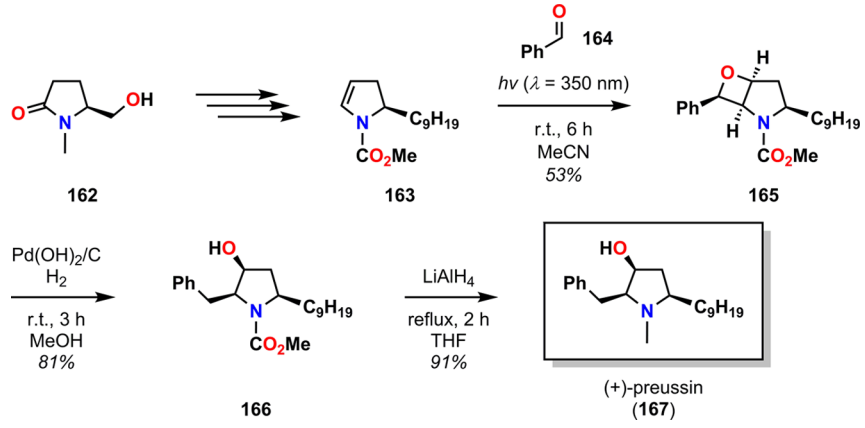
Scheme 35. Synthesis of (±)-1,13-Herbertendiol (176)[a]



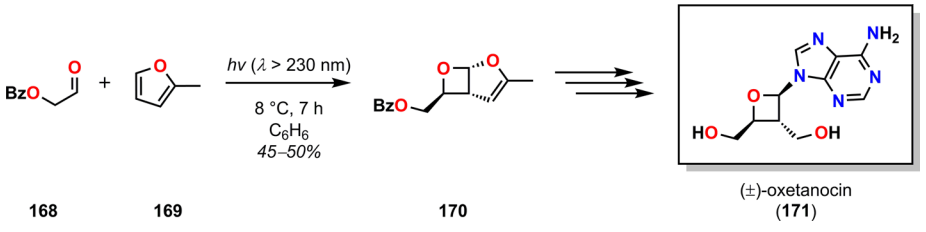
[a]LDBB = lithium di-*tert*-butylbiphenylide.

An intramolecular version of the Paternò–Büchi reaction was applied by Greaney and co-workers in a six-step approach to the tetracyclic core intermediate **184** of merrilactone A (**106**).[169] Starting from TBS-protected 3-hydroxycyclopentenone (**177**), nucleophilic addition of **178** afforded alcohol **179**, which was subsequently desilylated and oxidized to generate hydroxy enone **180**. A domino oxy/carbopalladation reaction with $Pd(OAc)_2$ produced the bicyclic acetal **182** as a 1:1 mixture of diastereoisomers. Oxidative cleavage of alkene **182** gave ketone **183**,

Scheme 33. Total Synthesis of the Pyrrolidinol Alkaloid (+)-Preussin (167) by a Diastereoselective Paternò–Büchi Approach



Scheme 34. Synthesis of (±)-Oxetanocin (171) Using the Paternò–Büchi Reaction



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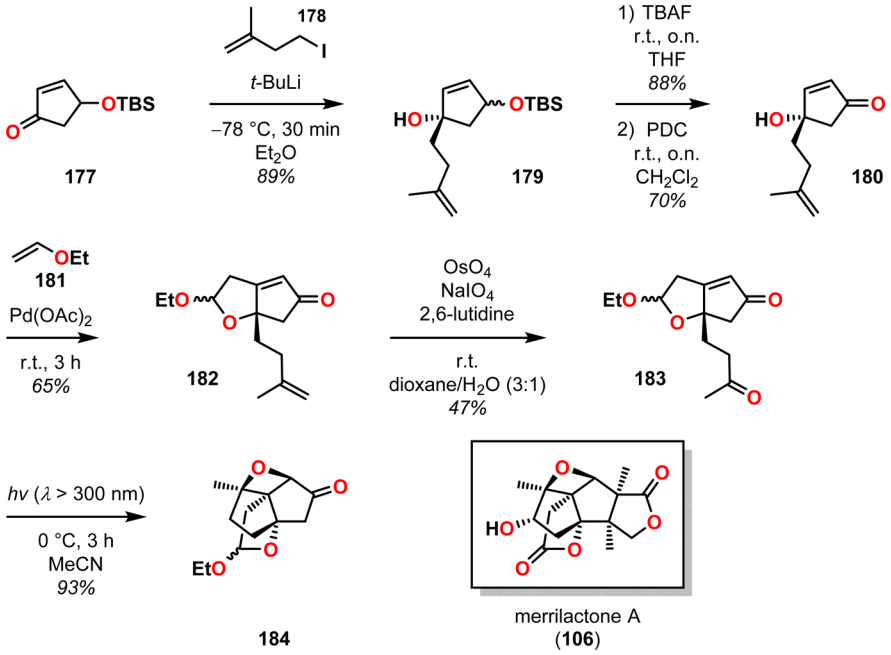
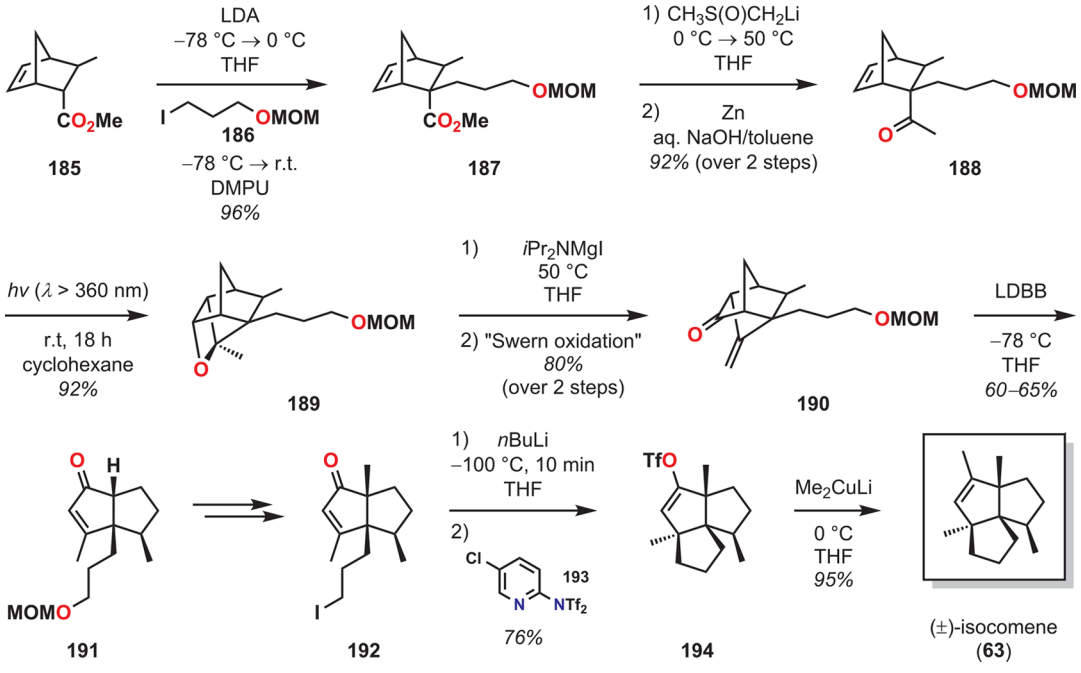
Scheme 36. Intramolecular Paternò–Büchi Reaction To Produce Oxetane 184 Bearing the Tetracyclic Core of Merrilactone A (106)[a]



[a]PDC = pyridinium dichromate. TBAF = tetra-*n*-butylammonium fluoride.

Scheme 37. Rawal's Synthesis of (±)-Isocomene (63) By an Intramolecular Paternò–Büchi Reaction[a]



[a]LDA = lithium diisopropylamide. LDBB = lithium 4,4′-di-*tert*-butylbiphenylide. MOM = methoxymethyl. DMPU = *N*,*N*′-dimethylpropyleneurea.

which upon irradiation underwent [2 + 2] photocycloaddition to the tetracyclic oxetane **184** in 93% yield (Scheme 36). In addition to creating two new rings, the intramolecular Paternò–Büchi reaction also establishes three stereocenters, thus forming the oxa[3.3.3]propellane motif present in merrilactone A (**106**).

Rawal and co-workers also utilized an intramolecular Paternò–Büchi reaction as the key step in the stereocontrolled syntheses of the angular triquinane (±)-isocomene (**63**).[144,145] It was envisioned that diquinane enone **192**, which has three of the stereocenters correctly in place, would be a key intermediate in the synthesis. The synthesis of the desired methyl ketone substrate **188** for the Paternò–Büchi reaction was synthesized from norbornene **185** by alkylation with the methoxymethyl (MOM) ether of 3-iodopropan-1-ol (**186**) followed by reaction with dimsyl lithium and Zn. Irradiation of methyl ketone **188** produced the desired oxetane **189** in 92% yield, which was subsequently cleaved using an excess of iPr$_2$NMgI. Oxidation of the resulting homoallylic alcohol under Swern conditions[170]

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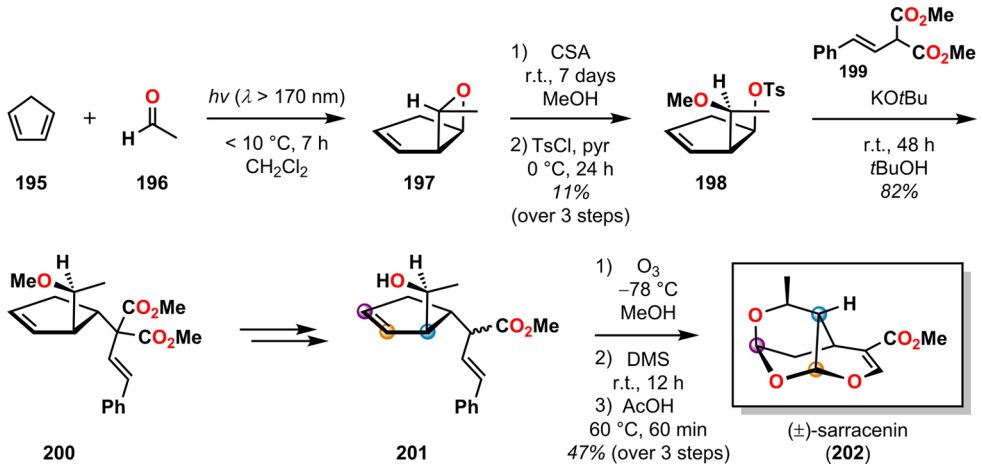
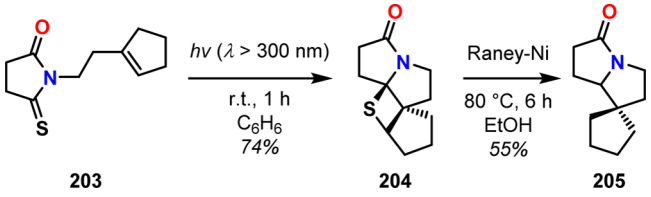
Scheme 38. Access to (±)-Sarracenin (202) Using a Paternò–Büchi Reaction[a]



[a]CSA = camphorsulfonic acid. DMS = dimethyl sulfide. TsCl = *p*-toluenesulfonyl chloride.

Scheme 39. Intramolecular Paternò–Büchi Reaction of Thiocarbonyl 203



provided fragmentation precursor **190**. Treatment of ketone **190** with lithium di-*tert*-butylbiphenylide (LDBB)[171,172] as a one-electron reducing agent yielded the desired reductive fragmentation product **191**, which was subsequently methylated at the bridgehead position and converted to diquinane **192**. Treatment of iodide **192** with nBuLi allowed for anionic cyclization and in situ trapping of the resulting enolate to afford enol triflate **194**, which upon treatment with Me_2CuLi gave (±)-isocomene (**63**) (Scheme 37). The synthesis of (±)-isocomene (**63**) illustrates the advantages of the Paternò–Büchi photocycloaddition–reductive fragmentation strategy for access to intricate triquinane-based natural products.

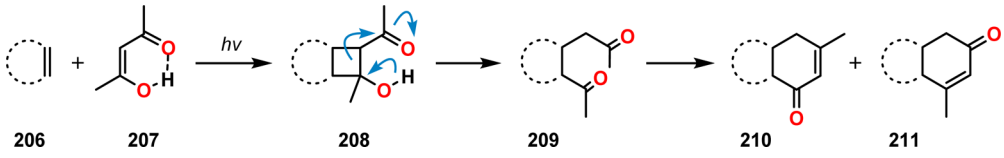
(−)-Sarracenin (**202**) is a tricyclic highly oxygenated monoterpene originally isolated from *Sarracenia flava*.[173] In the synthesis of (±)-sarracenin, Hoye and Richardson employed the Paternò–Büchi photocycloaddition of cyclopentadiene (**195**) and acetaldehyde (**196**) to access the *exo* diastereomeric oxetane **197**. Acid-catalyzed methanolysis followed by exposure to TsCl in pyridine allowed for oxetane opening and formation of tosylate **198**. Treating tosylate **198** with KO*t*Bu and dimethyl *β*-styrenylmalonate (**199**) provided malonate **200**, which underwent decarbomethoxylation followed by demethylation to yield alcohol **201**. Methanolic ozonolysis followed by reductive workup with dimethyl sulfide (DMS) and subsequent acetic acid treatment produced (±)-sarracenin (**202**) in a nine-step sequence in an overall yield of 2% (Scheme 38).[174]

The Paternò–Büchi reaction can also be carried out with thiocarbonyl compounds.[175] An intramolecular Paternò–Büchi reaction has for example been reported for the synthesis of spirocyclic pyrrolizinone **205**.[176] Here, irradiation of thioxasuccinimide system **203** afforded the tetracyclic thietane **204** as the major photoproduct in 74% yield. Reduction of photoproduct **204** with Raney-Ni gave the spiro pyrrolizinone **205** in 55% yield (Scheme 39), showing that carrying out the Paternò–Büchi with thiocarbonyl compounds can be used to access complex assemblies.

2.3. [2 + 2] Photocycloadditions Followed by Retro-Aldol Reaction—The De Mayo Reaction

An important contribution to the field of photochemistry was made in 1962 by De Mayo and co-workers when they observed that irradiation of alkenes with acetylacetone afforded 1,5-diketones in good yields. Subjecting the produced 1,5-diketones to catalytic amounts of acid or base subsequently led to cyclization to give cyclohexenones (Scheme 40).[177] The first step in the De Mayo reaction involves tautomerization of the 1,3-dicarbonyl compound to the enol. For *β*-diketone **212** this affords the corresponding keto enol **213**, which allows for [2 + 2] photocycloaddition with alkene **214** and thus generates a *β*-acylcyclobutanol (**215**). Subsequent retro-aldol condensation of the formed cyclobutanols produces the 1,5-dicarbonyl species **216** (Scheme 41), which can be further transformed into cyclooctadiones (see Scheme 42) and cyclohexenones.[178,179] The poor regioselectivity that is sometimes observed in the De Mayo reaction can be explained by formation of a triplet 1,4-biradical from the keto enol reaction partner, which needs to undergo spin inversion to a singlet biradical for cyclobutane formation to occur (cf. Schemes 2 and 32).[180,181]

Scheme 40. Initial Photochemical Experiments Performed by De Mayo and Co-Workers



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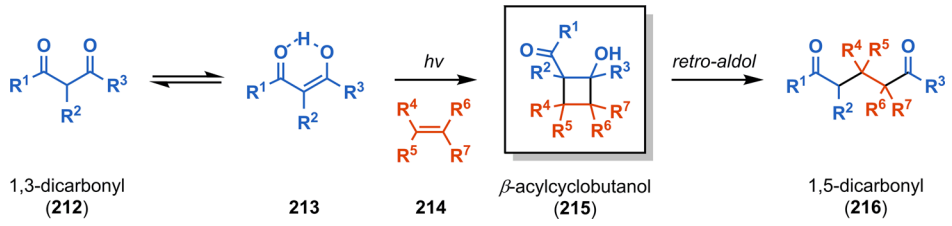
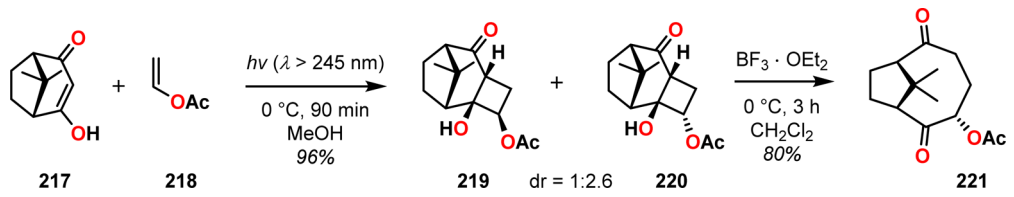
Scheme 41. Depiction of the De Mayo Reaction



Scheme 42. Formation of 1,5-Cyclooctadione 221 Using the De Mayo Reaction[182]



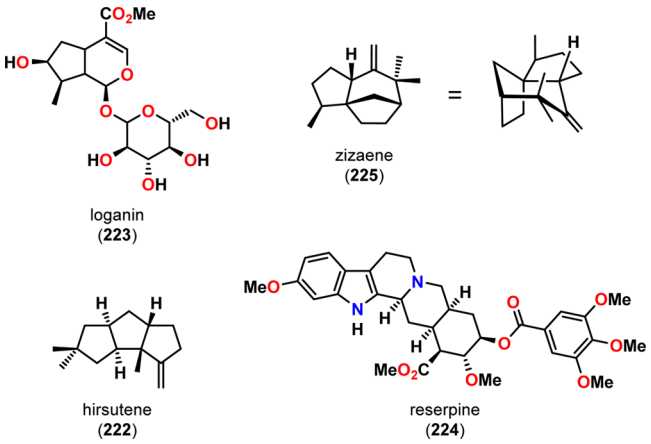
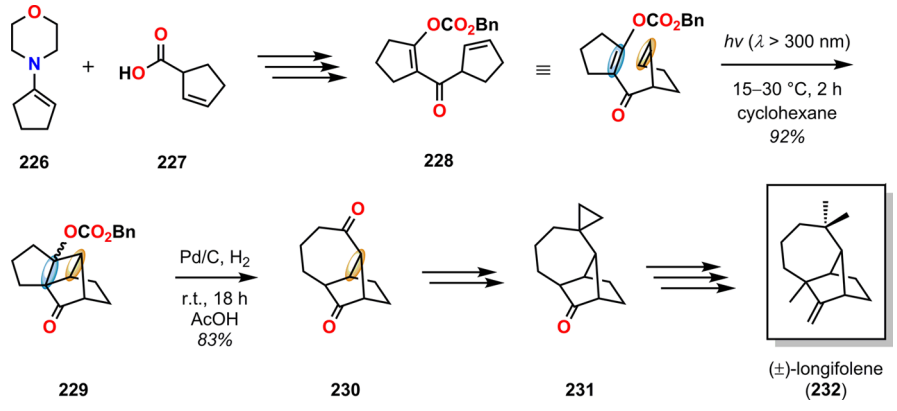


Figure 10. Examples of natural products accessed using the De Mayo reaction.

The synthetic utility of the De Mayo reaction in natural product synthesis has been readily explored and early examples include hirsutene (**222**),[183,184] loganin (**223**),[185−187] reserpine (**224**),[188,189] and zizaene (**225**) (Figure 10).[190,191] Another classical example employing an intramolecular [2 + 2] photocycloaddition followed by a retro-aldol reaction was reported in the total synthesis of (±)-longifolene (**232**),[192,193] a tricyclic sesquiterpene containing a bicyclo[5.4.0]undecane scaffold.[194−201] Here, the design of the complex carbon skeleton of this sesquiterpene was centered on a photoaddition/retro-aldolization sequence. Irradiation of benzyloxycarbonyl derivative **228** afforded cyclobutane **229** regioselectively, which upon hydrogenolysis underwent retro-aldol cleavage to give the bicyclo[5.4.0]undecane core. Subsequent functionalization of bicyclo[5.4.0]undecane **230** through a regioselective Wittig reaction/Simmons−Smith cyclopropanation sequence, followed by additional manipulations, produced (±)-longifolene (**232**) in ∼25% overall yield (Scheme 43).[192,193] The expedient construction of the sesquiterpene (±)-longifolene (**232**) exemplifies the synthetic utility of the intramolecular De Mayo reaction in natural product synthesis.

Daucene (**233**) is a member of the carotane-type sesquiterpenes and has an unusual hydroazulene skeleton. The daucane (carotane) sesquiterpenes all share a bicyclo[5.3.0]decane core with diverse functionality and varied degrees of oxidation (Figure 11) and have been shown to exhibit diverse biological activities.[202−205] During the years, several total syntheses of daucene (**233**) have been reported.[206−211] Seto and co-workers employed a highly regioselective intramolecular [2 + 2] photocycloaddition followed by a retro-aldol reaction to access a variety of carotane-type terpenes, including (±)-daucene.[212] Irradiation of enone **239** resulted in efficient and regioselective photocyclization to afford photoproduct **240** in 88% yield (Scheme 44). Subsequent alkaline hydrolysis of the acetate group in photoproduct **240** resulted in retro-aldolization and ring expansion to provide the tricyclic ketol **242**, which was

Scheme 43. Use of a Photocycloaddition/Retro-Aldol Sequence (De Mayo Reaction) in the Total Synthesis of (±)-Longifolene (232)



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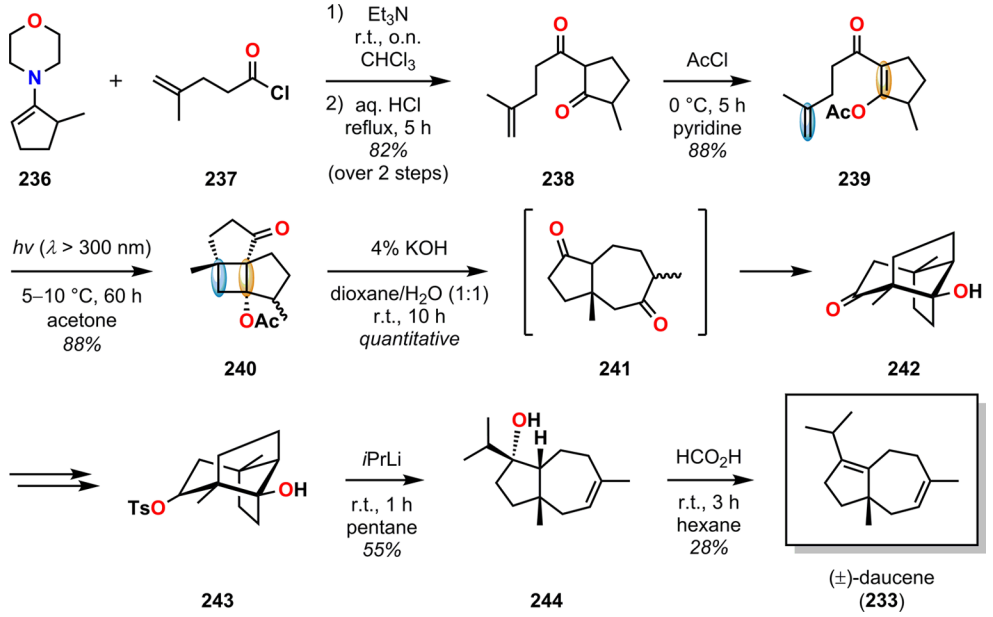
Scheme 44. Synthesis of (±)-Daucene (233) by Use of the De Mayo Reaction



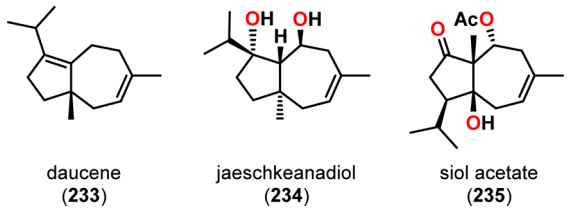


Figure 11. Representative examples of daucane (carotane) sesquiterpenes.

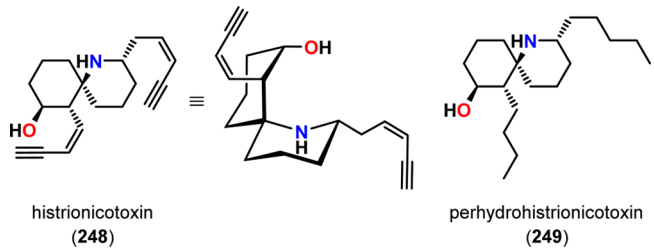


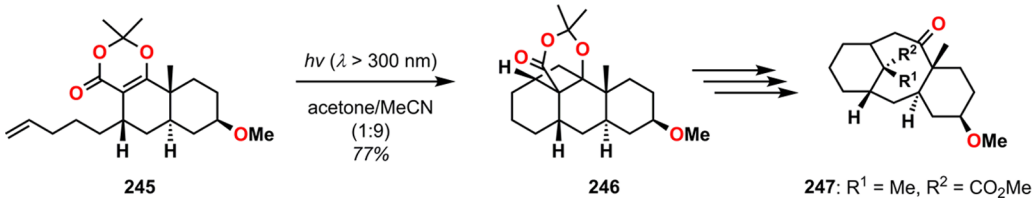
Figure 12. Structures of histrionicotoxin (**248**) and perhydrohistrionicotoxin (**249**).

subsequently transformed to monotosylate **243**. Treating **243** with *i*PrLi initiated Grob fragmentation, followed by alkylation of the produced ketone to furnish the tertiary alcohol **244**. Subjecting alcohol **244** to HCO_2H at room temperature provided the dehydrated product (±)-daucene (**233**) in 28% yield together with two other regioisomeric products.

The direct use of *β*-keto esters and *β*-keto acids in photocycloadditions can generate oxetanes through the Paternò–Büchi reaction (vide infra) instead of the desired cyclobutane. However, the use of dioxenones as *β*-keto ester and *β*-keto acid surrogates circumvents this problem by covalently locking the 1,3-dicarbonyl compound in the enol form and was originally reported by Baldwin and Wilkinson.[213] Dioxenones have, after this observation, been applied to a number of natural product syntheses, such as the tricyclic skeleton of taxane diterpenes (Scheme 45).[214,215]

Another example of employing dioxenones can be found in the synthesis of perhydrohistrionicotoxin (**249**). Histrionicotoxin (**248**) and its derivatives (Figure 12) are powerful neurotoxic alkaloids initially isolated from the Columbian frog *Dendrobates histrionicus*.[216−218] Initial attempts of synthesizing perhydrohistrionicotoxin (**249**) by Smith and Koft employed a [2 + 2] photocycloaddition methodology as the key step for assembling the core of perhydrohistrionicotoxin (**249**).[219] Here, the cyclobutene fragment **251** was recognized as a potential intermediate in the synthesis of the natural product. Unfortunately, the outlined synthetic approach by the authors was not viable for converting the generated cyclobutene photoproduct **251** to perhydrohistrionicotoxin (**249**) (Scheme 46). However, a few years later, Winkler and co-workers reported the total synthesis of (−)-perhydrohistrionicotoxin, where the absolute configuration was derived from L-glutamic acid (**253**).[220] For establishing the relative configuration, the authors employed an intramolecular De Mayo reaction between a vinylogous amide and a dioxenone to afford the necessary keto-lactone

Scheme 45. Construction of the Taxane Skeleton (247) by Use of an Intramolecular Dioxenone Photocycloaddition–Fragmentation Strategy



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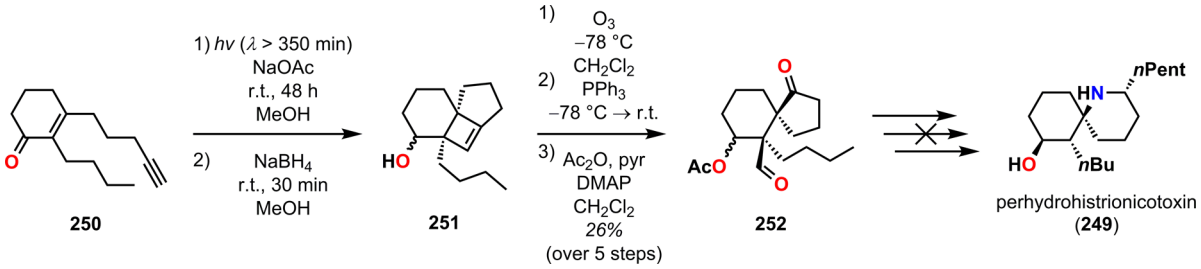
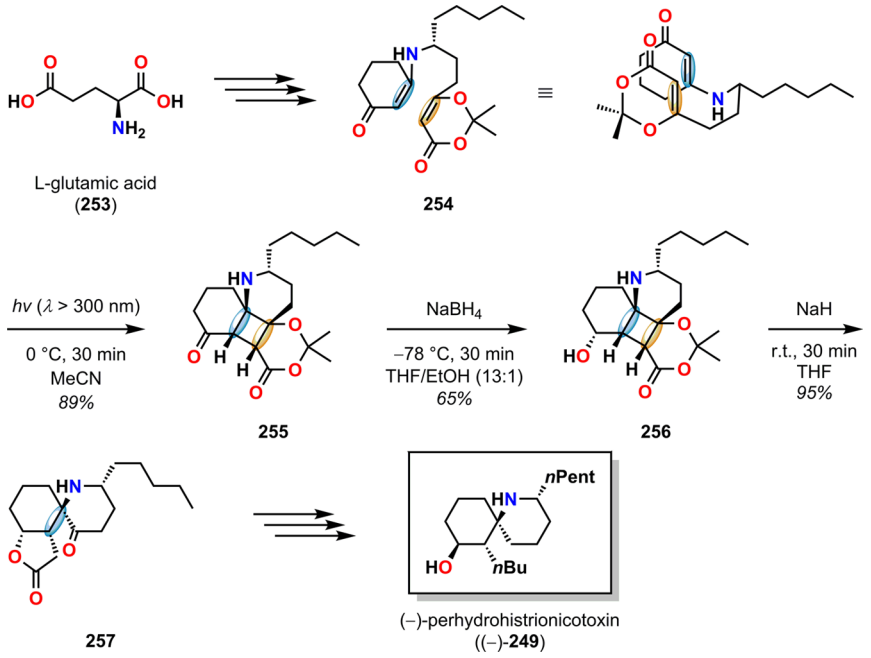
Scheme 46. Unsuccessful Approach toward the Synthesis of Perhydrohistrionicotoxin (249) via Cyclobutene Intermediate 251[a]



[a]DMAP = 4-dimethylaminopyridine.

Scheme 47. Fragmentation of Photoproduct 255 en Route to the Total Synthesis of (−)-Perhydrohistrionicotoxin (249)



intermediate **257**, which could be converted to (−)-perhydrohistrionicotoxin (**249**) (Scheme 47).

A related fragmentation strategy employing dioxenones has also been employed in the total synthesis of (±)-saudin (**267**, Scheme 48).[221,222] Here, irradiation of dioxenone **261** afforded photoadduct **262** as a single diastereomer in 80% yield. Introduction of the furan motif was accomplished in a two-step sequence by first reacting **262** with *n*BuLi and Tf_2O in the presence of TMEDA to produce enol triflate **263**. Subsequent Stille coupling of enol triflate **263** with 3-furyltributylstannane (**264**) gave the furyl enol ether **265** in almost quantitative yield, which upon exposure to LiOH resulted in fragmentation. Cyclization to (±)-saudin (**267**) was carried out by treating the fragmented product with pyridinium tosylate. This 15-step route afforded (±)-saudin (**267**) in 5% overall yield and illustrates the potential of the intramolecular dioxenone photocycloaddition for the efficient construction of complex carbocyclic motifs.

A related retro-aldol approach was also utilized by Winkler and co-workers in the first total synthesis of (±)-ingenol (**2**, Figure 14).[38] Ingenol (**2**) is a complex diterpenoid originally isolated from *Euphorbia ingens* in 1968 by Hecker.[223] However, its structure was not determined until 1970, when the crystal structure of the triacetate compound was derived.[224] The *Euphorbia* species contains a variety of diterpenoids with complex carbon skeletons, some of which are shown in Figure 13.[225−229] Of the various diterpenoids, the ingenanes display several interesting biological activities, such as anti-leukemic and anti-HIV.[230−233] In particular, ingenol 3-angelate (ingenol mebutate, **274**, Figure 14) has received a great deal of attention since its approval by the Food and Drug Administration (FDA) in 2012 for treatment of actinic keratosis, a precancerous skin condition.[234−236]

The biological activity and the structural complexity of ingenol (**2**) have motivated interest from synthetic organic chemists for several decades. The polyoxygenated tetracyclic core of ingenol (**2**) features several challenges, including the stereogenic triol unit of the A and B rings and a quaternary carbon stereocenter. However, the unusual *in/out* stereochemistry,[237] or trans intrabridgehead stereochemical configuration, of the bicyclo[4.4.1]undecane motif represents a particularly daunting difficulty.[238−250] In light of these challenges, a number of total syntheses of ingenol (**2**) have been reported.[38,251−261]

In the first total synthesis of ingenol (**2**),[38] Winkler and co-workers established the rare and challenging trans intrabridgehead configuration of the BC ring system by employing inside−outside stereoisomerism methodologies previously developed in their laboratory.[262] Initial attempts to use the De Mayo reaction on allylic alcohol **279**, obtained from the bicyclic enone **275**, resulted in a low yield (16%) of the desired photoadduct.

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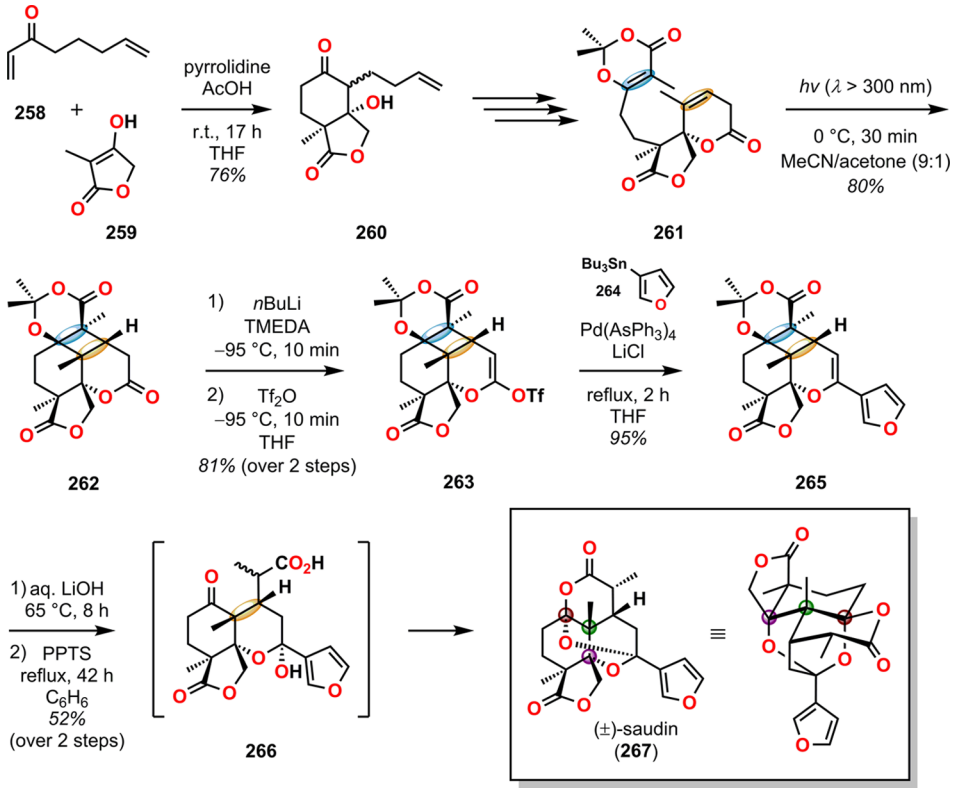
Scheme 48. Access to (±)-Saudin (267) by Means of a [2 + 2] Photocycloaddition and Subsequent Retro-Aldol Reaction[a]



[a]PPTS = pyridinium *p*-toluenesulfonate. Tf_2O = trifluoromethanesulfonic anhydride. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

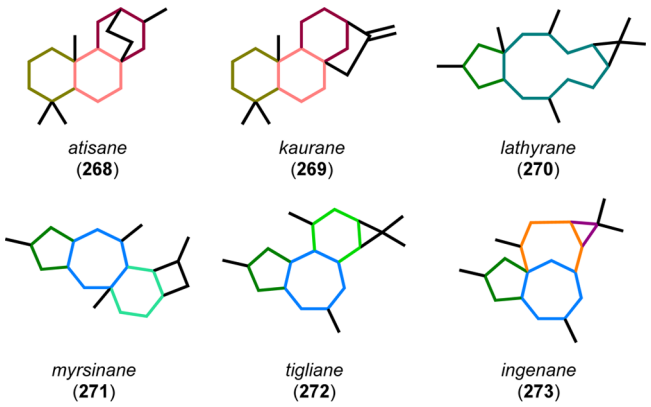


Figure 13. Skeletal types of *Euphorbia* diterpenes.

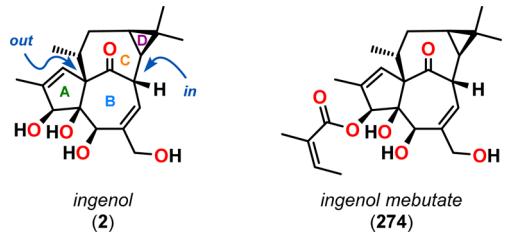


Figure 14. Structures of ingenol (2) and FDA approved ingenol mebutate (274).

However, irradiation of the corresponding allylic chloride (**280**) afforded photoadduct **281** with the important bicyclo[5.3.0]-decane motif in 60% yield. Fragmentation of cyclobutane **281** with methanolic potassium carbonate followed by $LiAlH_4$ reduction, chloride elimination, and silylation of the primary alcohol gave bicyclo[4.4.1]undecanone **282** in 35% yield over four steps. Cyclopropanation and reductive methylation subsequently produced cyclopropane **283**, which allowed for further manipulations into (±)-ingenol (**2**) (Scheme 49).[38]

Modifications of the De Mayo reaction have also been developed and have for example been utilized in the synthesis of (+)-aphanamol I (**291**)[75] and for constructing the 3,12-dioxatricyclo[8.2.1.$0^{6,13}$]tridecane skeleton of terpenoid natural products.[263] Hansson and Wickberg's strategy for accessing (+)-aphanamol I (**291**) depended upon a De Mayo-type sequence where the opening of the generated cyclobutane ring was achieved through a base-induced opening with concomitant *β*-elimination of a properly oriented oxirane.[75] Here, the essential photosubstrate **286** was derived from (+)-(*R*)-limonene (**284**). Irradiation of photosubstrate **286** and cyclopentenone **287** afforded a 1:1 mixture of the regioisomeric photoadducts **288** and **289**. Reacting photoadduct **289** with dimethyloxosulfonium methylide yielded the *endo*-epoxide **290**, which upon alkaline hydrolysis by refluxing with LiOMe in MeOH produced (+)-aphanamol I (**291**) in 70% yield through fragmentation of the intermediate *γ,δ*-epoxy alcohol (Scheme 50).

Bach and co-workers explored an unusual fragmentation pathway for constructing 3,12-dioxatricyclo[8.2.1.$0^{6,13}$]tridecane skeletons.[263] [2 + 2] Photocycloadditions of tetronate **292** gave photoproduct **293** in 65% yield as a single diastereoisomer. Facile ring expansion occurred upon treatment with KOH in aqueous MeOH to give the seven-membered ketolactone **295** via the intermediate tricyclic hemiacetal **294** (Scheme 51). The ring strain present in the tetracyclic compound **293** apparently facilitates nucleophilic substitution by hydroxide, thus resulting in cleavage of the cyclobutane ring.

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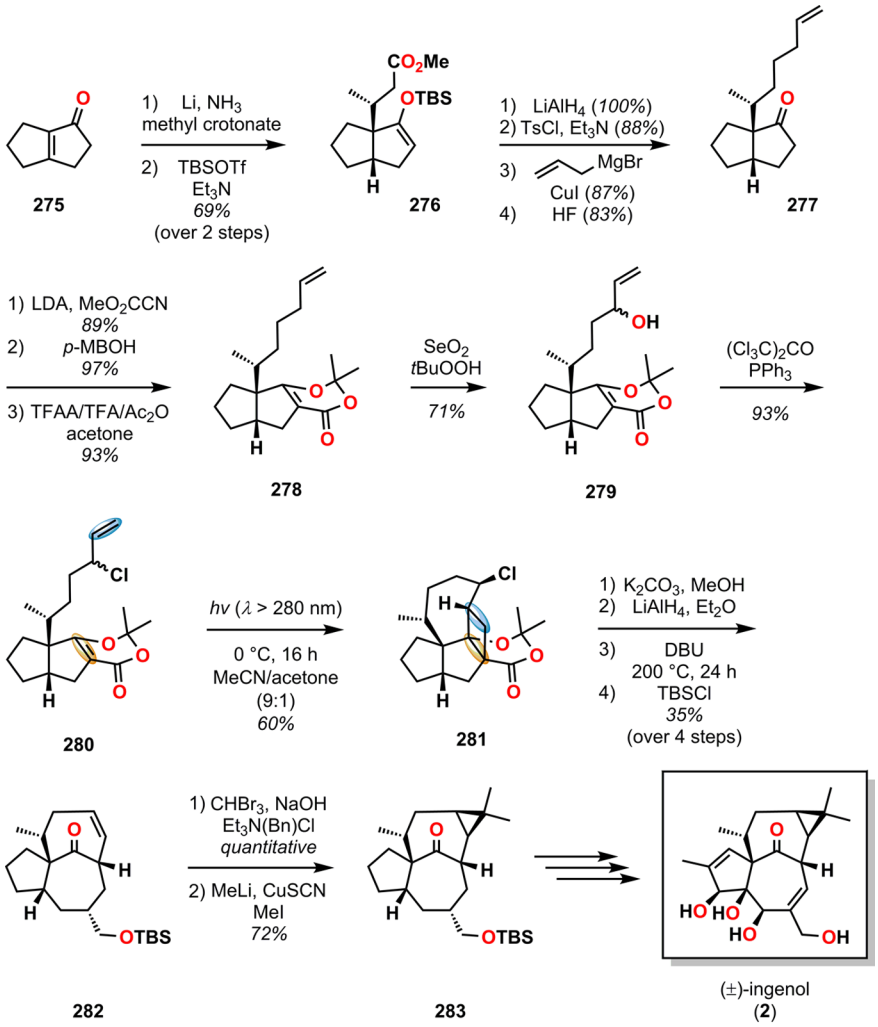
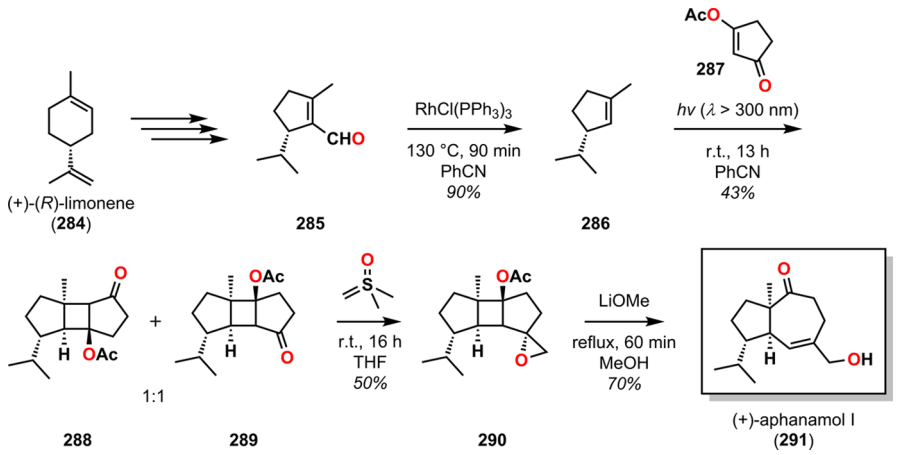
Scheme 49. Application of the De Mayo Reaction in the First Total Synthesis of (±)-Ingenol (2)[a]



[a]LDA = lithium diisopropylamide. *p*-MBOH = *p*-methoxybenzyl alcohol. TFA = trifluoroacetic acid. TFAA = trifluoroacetic anhydride. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Scheme 50. Synthesis of (+)-Aphanamol I (291) by Use of a Modified De Mayo Sequence



Recent work by Minter and Winslow involves the use of an unusual De Mayo approach for constructing the tetracyclic galanthan ring system (**296**, Figure 15),[264] which is the core of the lycorine-type *Amaryllidaceae* alkaloids.[265,266] Minter and Winslow utilized photosubstrate **305**, synthesized in three steps from isocarbostyril (**300**), as the precursor to the galanthan skeleton. Irradiation of the De Mayo substrate **305** afforded a single product, which was shown to be photoproduct **307** with the correct *cis* stereochemistry of the vicinal tertiary ring protons. Subsequent ring closure was achieved under basic conditions

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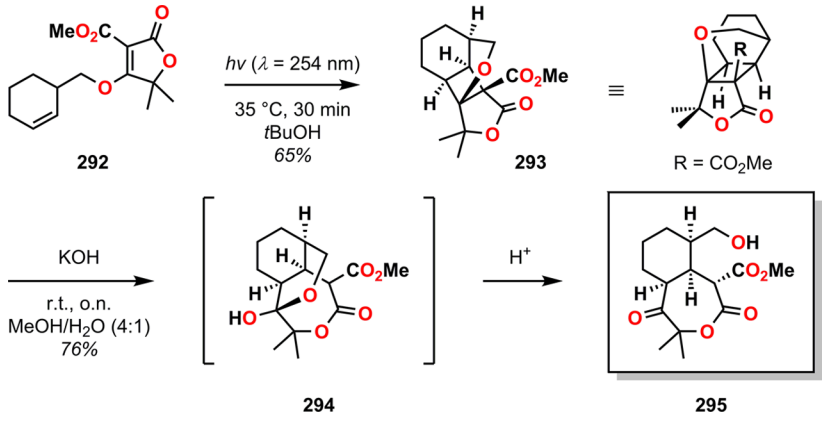
Scheme 51. Hydroxide-Mediated Ring Expansion of [2 + 2] Photocycloaddition Product 293



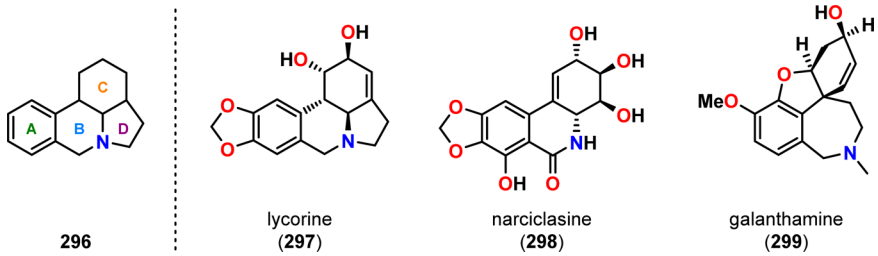
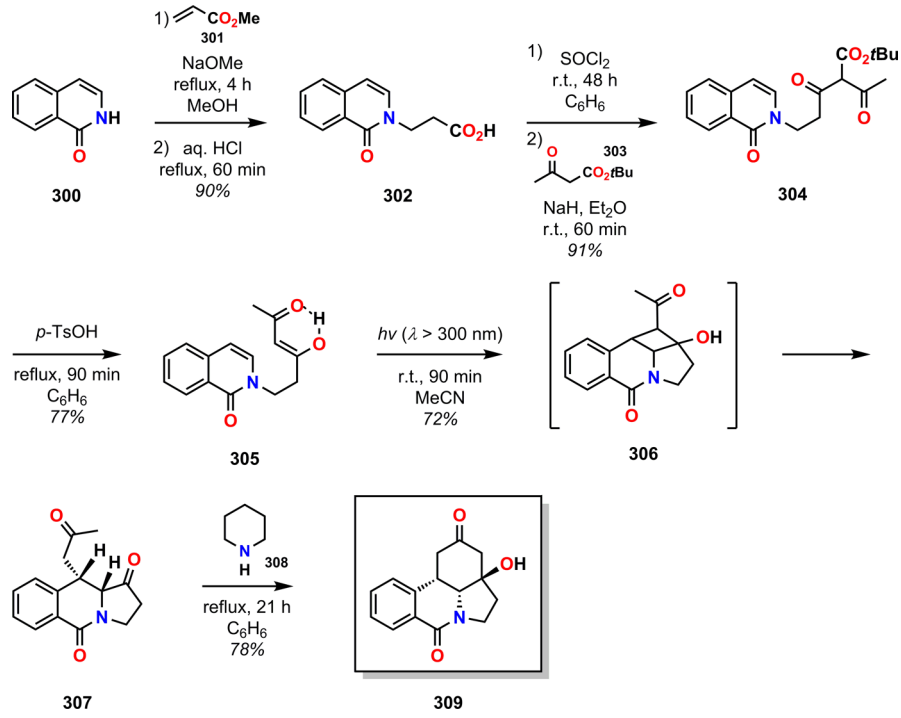


Figure 15. Structure of the galanthan skeleton (**296**) and examples of *Amaryllidaceae* alkaloids.

Scheme 52. Synthesis of Tetracyclic Compound 309 Bearing the Galanthan Skeleton[a]



[a] *p*-TsOH = *p*-toluenesulfonic acid.

using piperidine in refluxing benzene to afford the galanthan derivative **309** in five steps with 35% overall yield (Scheme 52).

2.4. [2 + 2] Photocycloadditions of Vinylogous Amides—Formation of Nitrogen-Containing Ring Systems

In analogy to the De Mayo reaction, which utilizes 1,3-dicarbonyl compounds, [2 + 2] photocycloaddition adducts of vinylogous amides (enaminones) can undergo subsequent fragmentation. The fragmentation gives ketoimines or ketoiminium ions, which can be recyclized in a domino sequence. This photocycloaddition/retro-Mannich fragmentation sequence provides a powerful route for the construction of nitrogen-containing ring systems and has since its initial observation by Tamura and co-workers[267] (Scheme 53) been exploited in natural product synthesis.[268]

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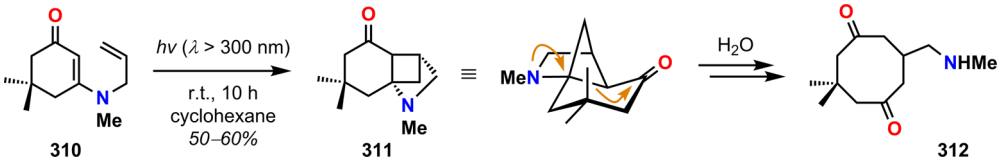
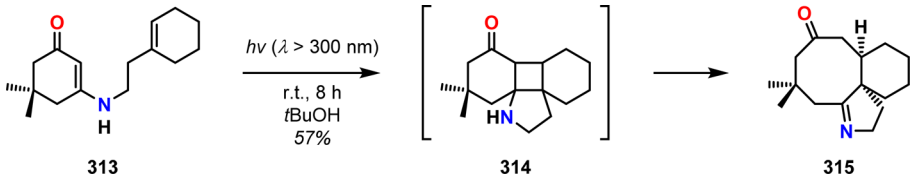
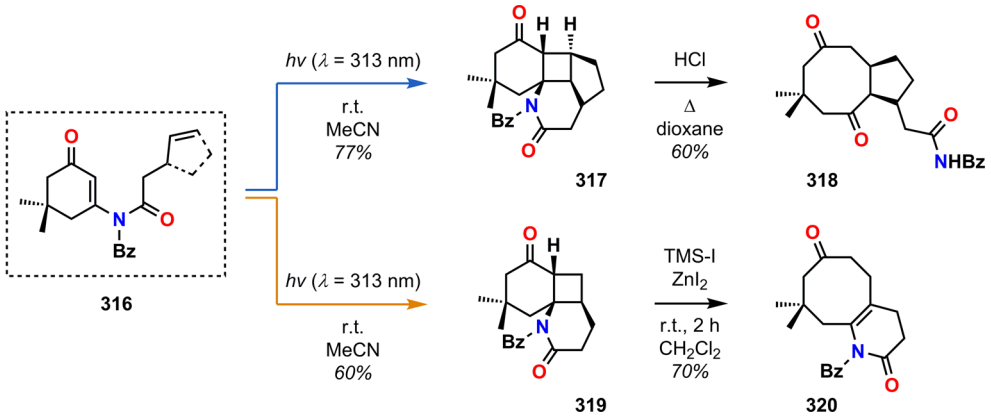
Scheme 53. Tamura and Co-Workers' Initial Observation of the Intramolecular Photocycloaddition/Retro-Mannich Fragmentation Sequence of Vinylogous Amides



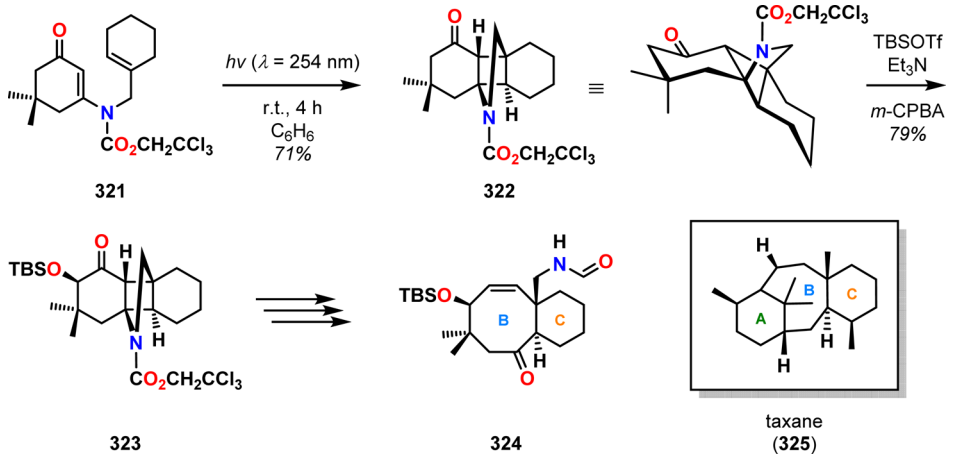
Scheme 54. Intramolecular Photocycloaddition/Retro-Mannich Fragmentation of Secondary Vinylogous Amide 313



Scheme 55. Intramolecular [2 + 2] Photocycloaddition of *N*-Alkenoyl *β*-Enaminones with Subsequent Acid- or Trimethylsilyl Iodide-Catalyzed Cyclobutane Ring Opening



Scheme 56. Use of the Photocycloaddition/Retro-Mannich Sequence for the Construction of the BC Substructure of Taxanes[a]



[a]TBS = *tert*-butyldimethylsilyl. *m*-CPBA = *m*-chloroperoxybenzoic acid.

Similarly to Tamura and co-workers' initial work, Schell and Cook investigated the use of secondary vinylogous amides. Irradiation of the secondary vinylogous amide **313** afforded ketoimine **315**, which is presumably generated from cyclobutane intermediate **314** upon retro-Mannich fragmentation (Scheme 54).[269] Pete and co-workers employed the intramolecular [2 + 2] photocycloaddition of *N*-alkenoyl *β*-enaminones to produce valuable synthons for synthesis of triquinanes or various sesquiterpenes (Scheme 55).[270] Related photocycloaddition/retro-Mannich sequences have also been reported for 3-aminocyclopentenones[271] and for the synthesis of 6-aza-bicyclo[3,2,1]-octan-3-ones[272] and pyrroles.[273,274]

Examples of the application of the photocycloaddition/retro-Mannich reaction can be found in studies toward the synthesis of taxane skeletons by Swindell and co-workers.[275−278] Photocycloaddition of vinylogous amide **321** generated

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photoproduct **322**, which was converted to silyloxy ketone **323** through a Rubottom-type oxidation. Subsequent fragmentation and additional manipulations converted silyloxy ketone **323** to enone **324** having the basic BC subunit of the taxane diterpenoids (Scheme 56).

The intramolecular photocycloaddition of vinylogous amides has also been exploited in the *Sceletium* alkaloid[279] mesembrine (**328**) by Winkler and co-workers.[280] Similarly to the alkaloids pretazettine (**326**) and sceletium A-4 (**327**), mesembrine (**328**) also features a functionalized *cis*-3a-aryloctahydroindole core (Figure 16). The desired photosubstrate **330** was accessible from

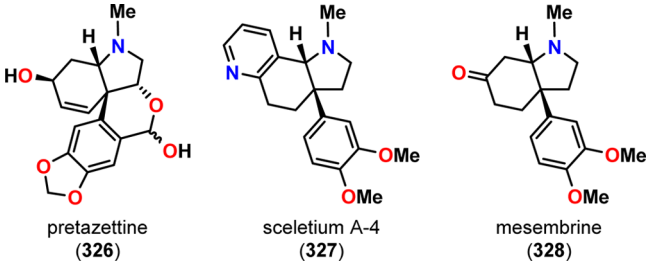
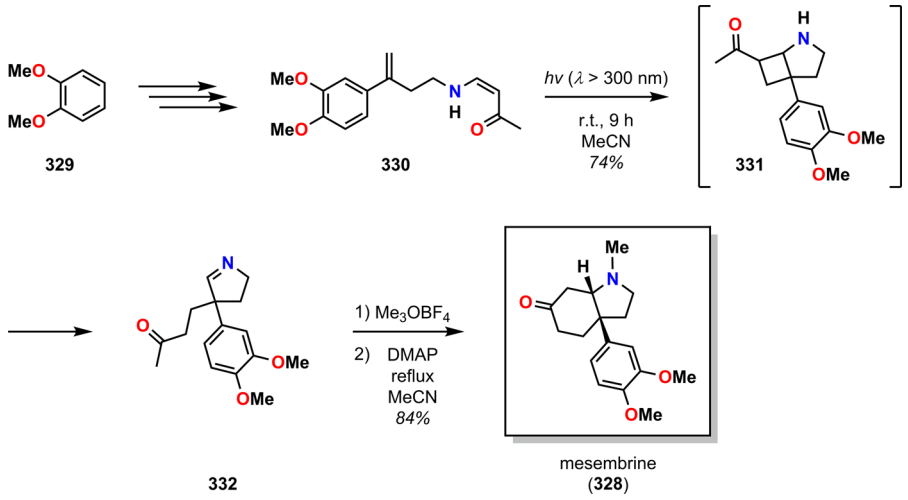


Figure 16. Examples of alkaloids containing the *cis*-3a-aryloctahydroindole motif.

veratrole (**329**) in four steps. Intramolecular photocycloaddition of **330** led to the photocycloaddition/reto-Mannich product **332** in 74% yield. Subsequent methylation using Me_3OBF_4 followed by treatment with DMAP facilitated ring closure, affording mesembrine (**328**) in 84% yield (Scheme 57).[280] The efficient access to the alkaloid mesembrine (**328**) in merely seven steps with an overall yield of 33% from veratrole (**329**) illustrates the power of the synthetic utility of the photocycloaddition/retro-Mannich fragmentation/Mannich closure cascade sequence.

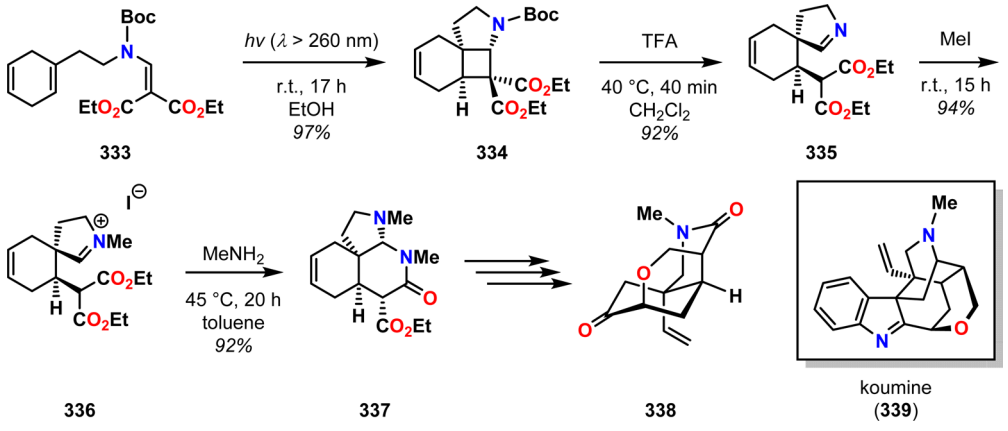
White and Ihle have employed β-aminoalkylidene malonates for accessing spiropyrrolines and the tetracyclic core of the indolenine alkaloid koumine (**339**).[281] The strategy for assembling the nonindolenine fragment **338** of koumine (**339**) was believed to be accessible through a photocycloaddition/retro-Mannich approach from β-aminoalkylidene malonate **333**. Irradiation of malonate **333** indeed furnished cyclobutane **334**, which upon removal of the Boc group caused spontaneous retro-Mannich fragmentation to spiroimine **335**. Methylation of the imine nitrogen and subsequent treatment with $MeNH_2$ triggered initial aminal formation, followed by intramolecular acylation to give lactam **337**, which could be converted to ketone **338**, a precursor for koumine (**339**) (Scheme 58). A related [2 + 2] photocycloaddition/retro-Mannich fission approach for tryptamine-based

Scheme 57. Synthesis of Mesembrine (328) via the Intramolecular Photocycloaddition of Vinylogous Amide 330[a]



[a]DMAP = 4-dimethylaminopyridine.

Scheme 58. Photocycloaddition/Retro-Mannich Approach for Construction of the Koumine Core[a]



[a]Boc = *tert*-butyloxycarbonyl. TFA = trifluoroacetic acid.

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vinylogous amides was also employed by White and co-workers in the total syntheses of (±)-coerulescine (**340**), (±)-horsfiline (**341**), and (±)-elacomine (**342**) (Figure 17).[282]

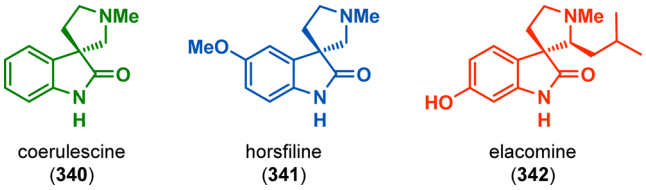
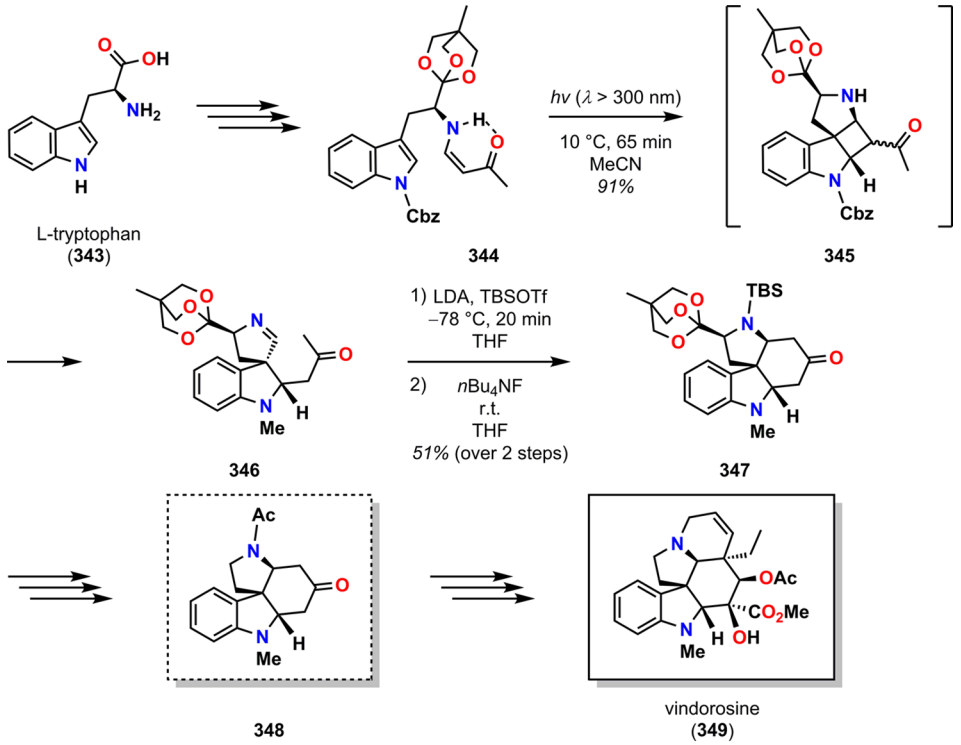


Figure 17. Synthesis of the spiro[pyrrolidine-3,3′-oxindole] alkaloids coerulescine (**340**), horsfiline (**341**), and elacomine (**342**) by use of the [2 + 2] photocycloaddition/retro-Mannich fragmentation process.

The formal synthesis of vindorosine (**349**), starting from L-tryptophan (**343**), is another example where the intramolecular vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure sequence has been applied for construction of nitrogen-containing ring systems (Scheme 59).[283] By starting from L-tryptophan (**343**), Winkler and co-workers showed that photosubstrate **344** afforded the highest stereoselectivity in photocycloaddition, providing photoproduct **346** in 91% yield as a single diastereomer. Treatment of keto imine **346** with LDA followed by TBSOTf and nBu$_4$NF produced the desired tetracyclic ketone **347** in 51% yield. The latter intermediate could be converted to **348**, a precursor to vindorosine (**349**), highlighting the efficiency of the vinylogous amide photocycloaddition approach to the synthesis of the aspidosperma alkaloids.

The application of this methodology to the construction of more complex alkaloids is exemplified by Winkler and co-workers in the syntheses of the marine alkaloids ircinol (**350**), ircinal (**351**), manzamine A (**352**), and manzamine D (**353**) (Figure 18).[284,285] [2 + 2] Photocycloaddition of vinylogous amide **354** afforded aminal **357**. Exposure of aminal **357** to pyridinium acetate produced manzamine tetracycle **358** in 20% yield as a single

Scheme 59. Formal Synthesis of the Aspidosperma Alkaloid Vindorosine (349) by Photocycloaddition/Retro-Mannich Fragmentation[a]



[a]Cbz = carboxybenzyl. LDA = lithium diisopropylamide. TBS = *tert*-butyldimethylsilyl.

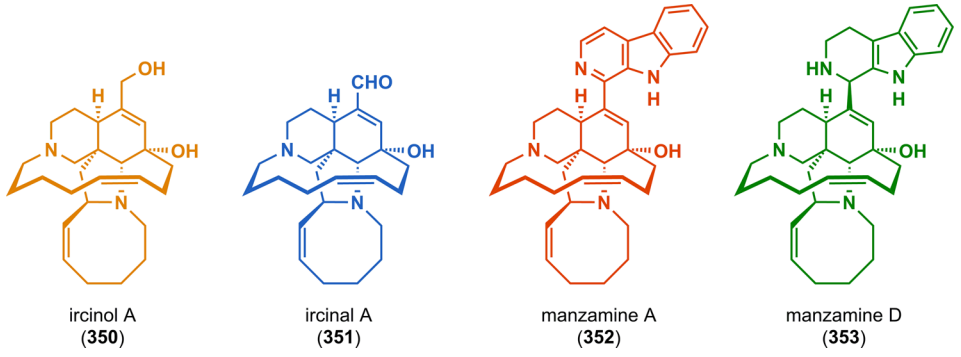


Figure 18. Structures of the marine alkaloids ircinol A (**350**), ircinal A (**351**), manzamine A (**352**), and manzamine D (**353**).

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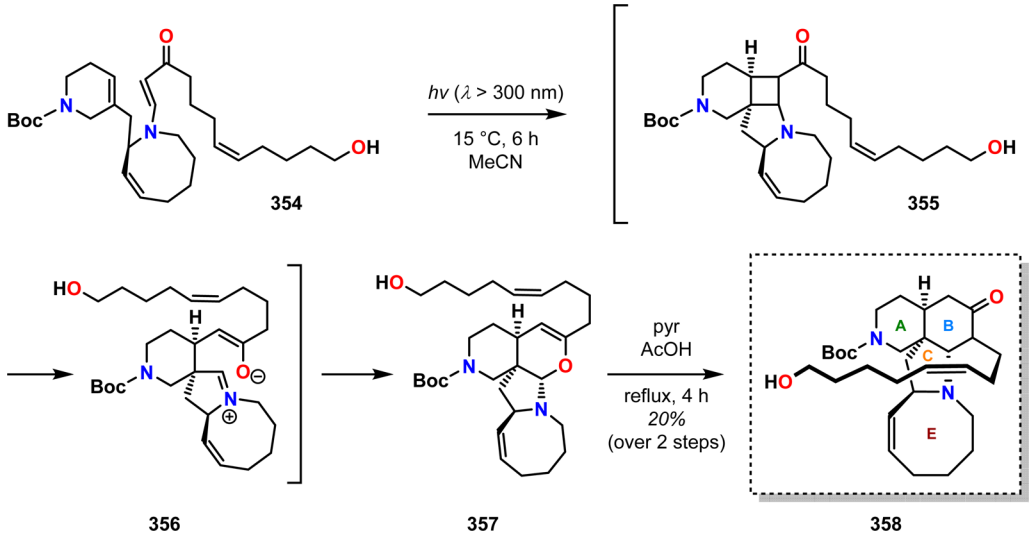
Scheme 60. Photocycloaddition/Fragmentation/Mannich Closure to Ketone 358, a Precursor to Ircinol A (350), Ircinal A (351), Manzamine A (352), and Manzamine D (353)[a]



[a]Boc = *tert*-butyloxycarbonyl.

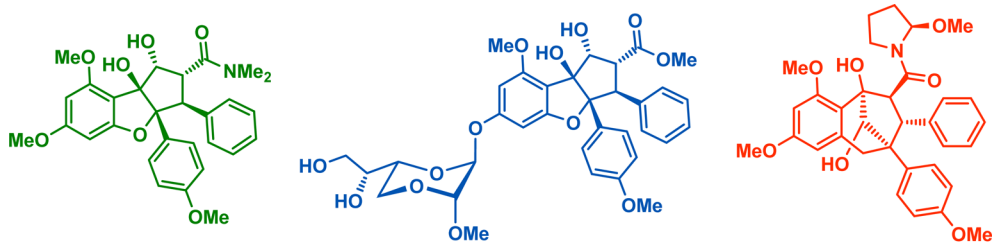


Figure 19. Examples of natural products produced by the plant genus *Aglaia*.

stereoisomer from photosubstrate **354**. Macrocyclization to produce the 13-membered D ring and subsequent manipulations allowed for conversion of precursor **358** to the four marine alkaloids ircinol (**350**), ircinal (**351**), manzamine A (**352**), and manzamine D (**353**) (Scheme 60). The establishment of all of the stereogenic centers in the manzamine skeleton from the single stereogenic center present in photosubstrate **354** validates the remarkable levels of stereochemical control that are possible using the photocycloaddition/fragmentation/Mannich closure cascade sequence in organic synthesis.

3. [3 + 2] PHOTOCYCLOADDITIONS

Apart from the meta-photocycloaddition reaction that is discussed in section 7, [3 + 2] photocycloadditions have been rarely applied in natural product synthesis. Several structurally interesting natural products have been isolated from the plant genus *Aglaia* (Figure 19).[286−289] Porco and co-workers developed a biomimetic approach involving a [3 + 2] photocycloaddition/ketol shift rearrangement/reduction sequence using 3-hydroxyflavone and methyl cinnamate derivatives to access (−)-rocaglamide and related natural products.[290−293] In the synthesis of methyl rocaglate (**366**), irradiation of 3-hydroxyflavone **362** produced oxidopyrylium intermediate **364**, which undergoes a [3 + 2] photocycloaddition with methyl cinnamate (**363**) to furnish aglain core structure **365**. Subsequent treatment with NaOMe/$Me_4NBH(OAc)_3$ was the basis for a ketol rearrangement/reduction sequence to provide methyl rocaglate (**366**) (Scheme 61).[290,292] A related approach has also been employed to accomplish enantioselective photocycloaddition and was used in the asymmetric synthesis of rocaglamides.[291,293]

The groups of Porco and Stephenson have also reported a tandem dienone photorearrangement−cycloaddition reaction of cyclohexadienones tethered with various 2π and 4π functional groups that afforded polycyclic, bridged scaffolds.[294] Photoirradiation of alkenyl ether-tethered cyclohexadienones, such as **367**, resulted in the bridged tricyclic ketone **371**, presumably via the photorearranged oxyallyl intermediate **368**, which upon [3 + 2] photocycloaddition resulted in the observed product (Scheme 62). Using cyclohexadienone **372** containing a furfuryl alkyne ether tether led to the production of the polycyclic ketone **374** (Scheme 63). This tandem dienone photorearrangement/cycloaddition/[4 + 2] cycloaddition sequence generates four new bonds where the final hexacyclic framework **374** contains seven stereogenic centers, thus highlighting the complex architectures that can be created in this tandem process.

4. PHOTOCHEMICAL [4 + 2] CYCLOADDITIONS IN NATURAL PRODUCT SYNTHESIS

4.1. Photochemical Generation of Dienes—Combining Photoenolization with [4 + 2] Cycloadditions

o-Quinodimethanes are fundamental intermediates in total synthesis and are in general produced from *o*-alkyl-substituted

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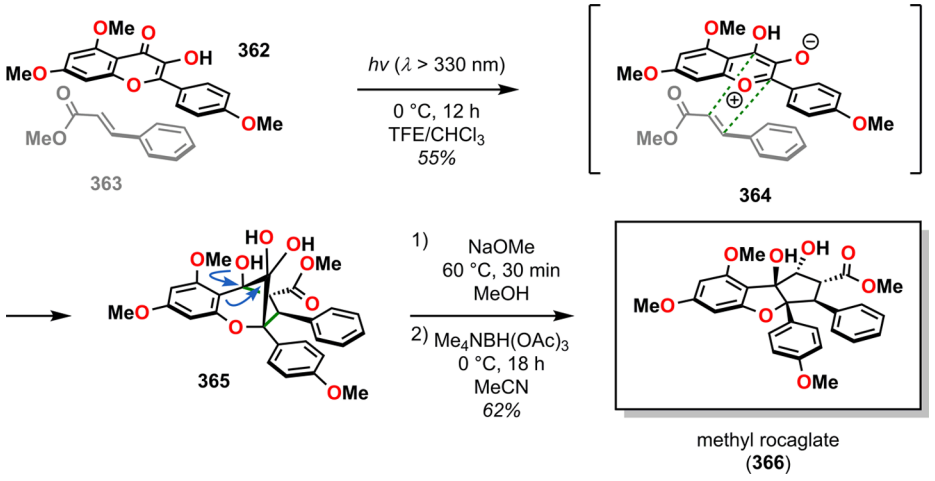
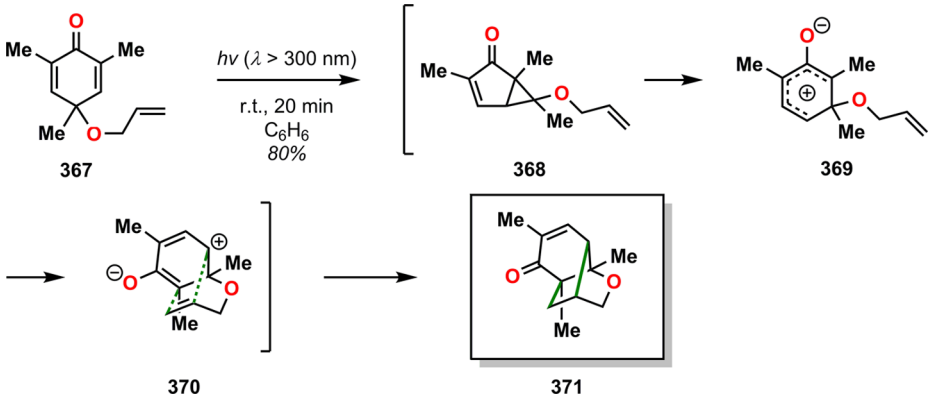
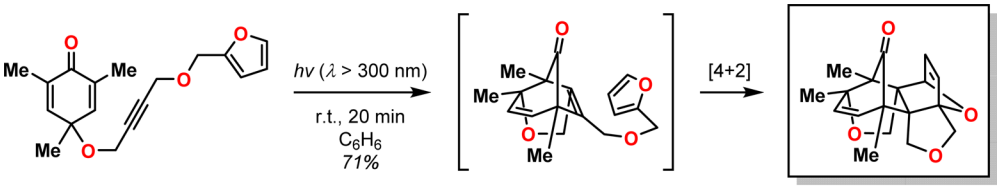
Scheme 61. Synthesis of Methyl Rocaglate (366) Using a [3 + 2] Photocycloaddition/Ketol Shift Rearrangement/Reduction Sequence



Scheme 62. Tandem Dienone Photorearrangement−Cycloaddition of Cyclohexadienone 367



Scheme 63. Tandem Dienone Photorearrangement/Cycloaddition/[4 + 2] Cycloaddition To Afford Polycyclic Ketone 374



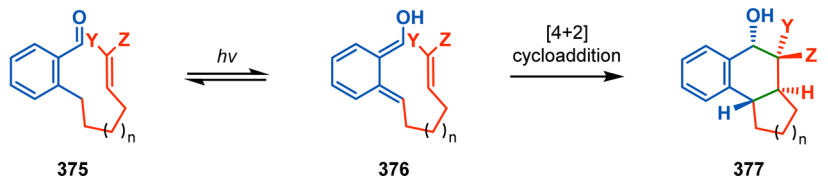


Figure 20. Schematic depiction of the photoenolization/[4 + 2] cycloaddition sequence.

aromatic carbonyl compounds.[295−299] The high reactivity associated with the photochemically generated *o*-quinodimethanes can be utilized by subsequently trapping them in a Diels−Alder reaction (Figure 20).[300−302]

A classic example where the photochemically produced *o*-quinodimethanes subsequently underwent [4 + 2] cycloaddition can be found in the total synthesis of (+)-estrone (**3**) by Quinkert and co-workers. Here, photochemically triggered formation of dienol **380** from precursor **379** allowed for [4 + 2] cycloaddition to afford alcohol **381**, which could subsequently be converted to estrone (**3**) via already known transformations (Scheme 64).[303−305] Other early examples where the photoenolization/[4 + 2] cycloaddition sequence had been employed include the formal total synthesis of podophyllotoxin

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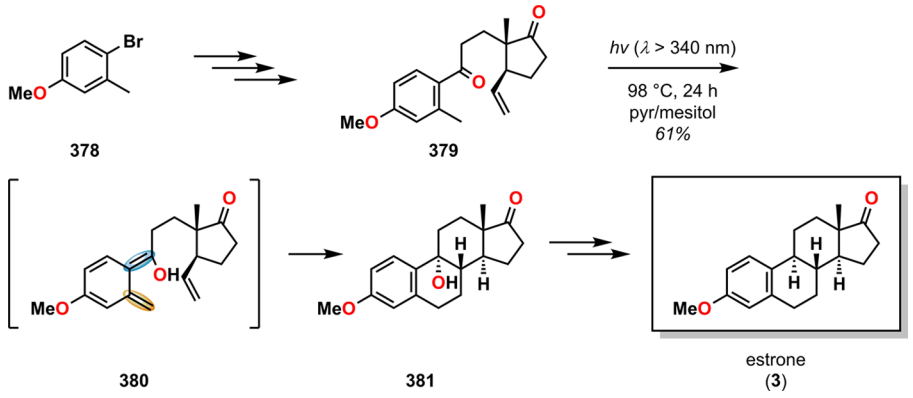
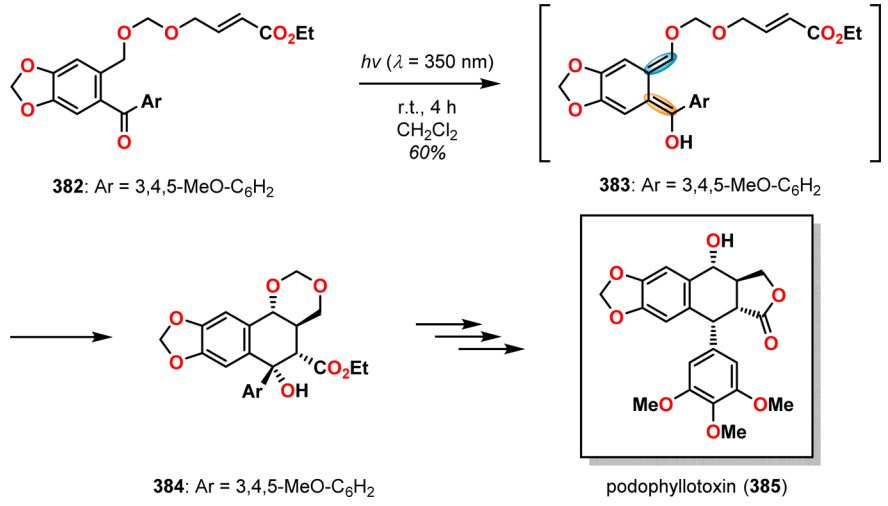
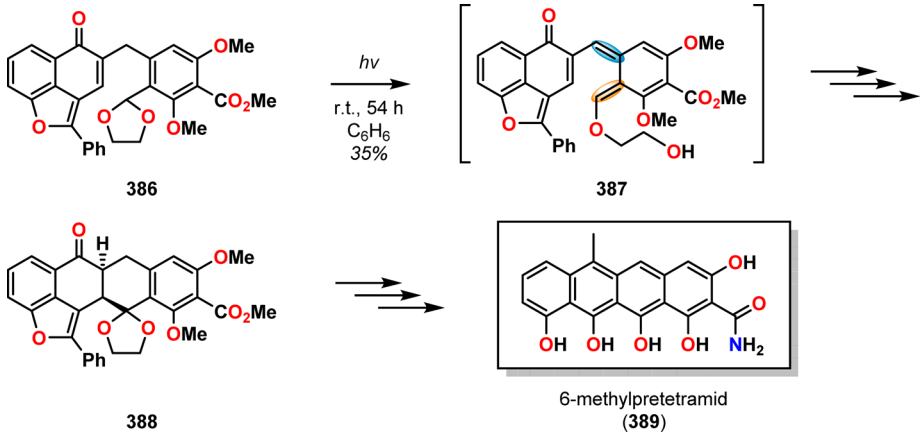
Scheme 64. Application of the Photoenolization/[4 + 2] Cycloaddition Sequence in the Total Synthesis of Estrone (3)



Scheme 65. Tandem Photoenolization/Diels–Alder Reaction in the Synthesis of Podophyllotoxin (385)



Scheme 66. Photocyclization in the Total Synthesis of 6-Methylpretetramid (389)



(**385**, Scheme 65)[306] and the synthesis of 6-methylpretetramid (**389**, Scheme 66).[307,308]

The hamigerans are a family of natural products isolated from the poecilosclerid sponge *Hamigera tarangaensis*. The framework of hamigerans A–C (**390**–**392**) contains a substituted benzenoid core fused onto either a [4.3.0] or a [5.3.0] bicyclic ring system, three or four contiguous stereogenic centers, and an isopropyl group (Figure 21).[309,310] In the total syntheses of hamigerans A (**390**) and B (**391**), Nicolaou and co-workers

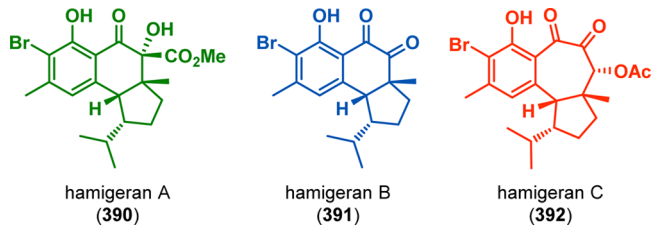


Figure 21. Structures of hamigerans A–C (**390**–**392**).

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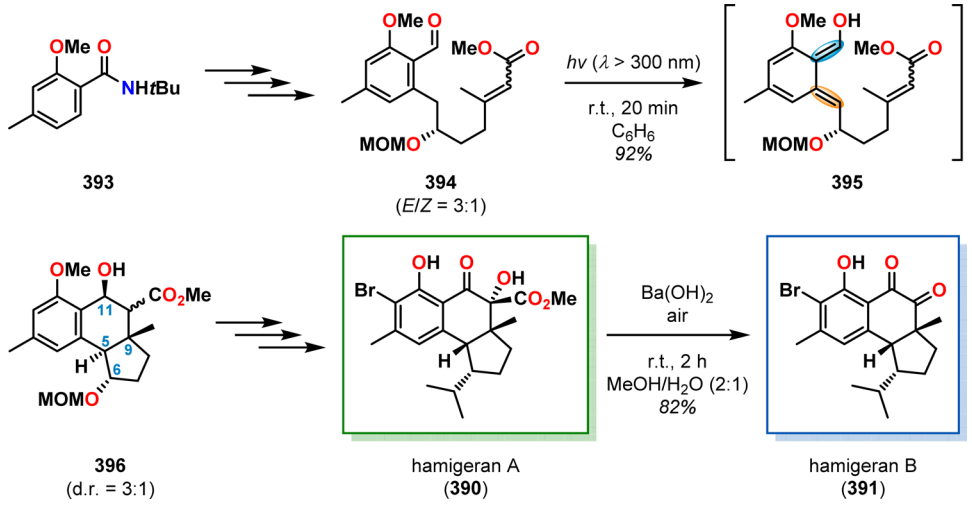
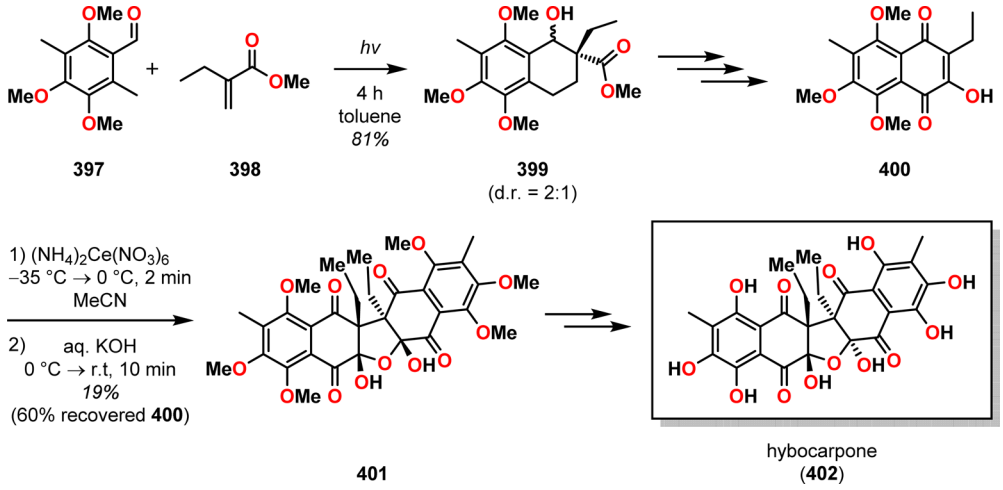
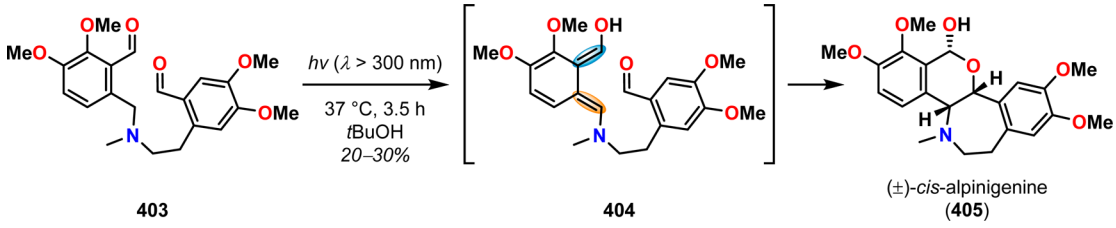
Scheme 67. Photochemical Generation and Diels–Alder Trapping of *o*-Quinodimethane 395 in the Total Synthesis of Hamigerans A (390) and B (391)



Scheme 68. Photoenolization/[4 + 2] Cycloaddition in the Total Synthesis of Hybocarpone (402)



Scheme 69. Photolysis of Bis-aldehyde 403 for Generation of (±)-*cis*-Alpinigenine (405)



employed the photoinitiated [4 + 2] cycloaddition as the key step for assembling the hamigeran core.[311−313] It was envisioned that incorporating an oxygen functionality at C6 would allow for the enantioselective synthesis of the targeted compounds. Irradiation of photosubstrate **394**, derived from benzamide **393** as a 3:1 *E*/*Z* mixture, indeed triggered *o*-quinodimethane formation and afforded the tricyclic hydroxyl ester **396** in 92% yield as a mixture of C10 epimers (~3:1; see Scheme 67). Subsequent epimerization at C5 and additional manipulations produced hamigeran A (**390**), which could be expediently converted to hamigeran B (**391**) in 82% yield through a $Ba(OH)_2$-mediated cascade reaction involving saponification, decarboxylation, and auto-oxidation. A related photoenolization/Diels–Alder strategy was also applied by Nicolaou and Gray in the total synthesis of the lichen-derived antitumor agent hybocarpone (**402**) (Scheme 68) and analogues thereof.[314]

A hetero-Diels–Alder reaction with the photochemically produced dienol **404** was utilized by Prabhakar and co-workers in the total synthesis of the alkaloid (±)-*cis*-alpinigenine (**405**).[315,316] Here, photolysis of bis-aldehyde **403** led to the formation of at least seven photoproducts. The desired tetracyclic (±)-*cis*-alpinigenine (**405**) was presumably formed from *o*-quinodimethane intermediate **404**, affording **405** in 20–30% yield (Scheme 69).

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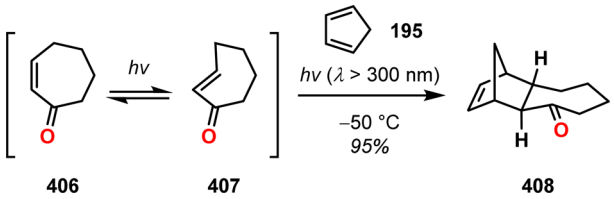
4.2. Photoisomerization Approaches for Triggering [4 + 2] Cycloadditions

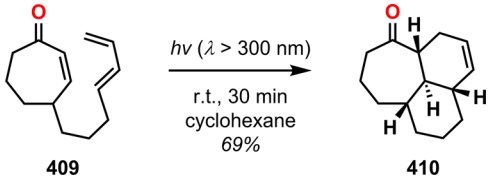
The photoisomerization of *cis*-cycloalkenones to *trans*-cycloalkenones is a well-established procedure.[317−323] An early example of this effect can be found in the photoisomerization of *cis*-2-cycloheptenone (**406**) to *trans*-2-cycloheptenone (**407**), where irradiation of a mixture of *cis*-2-cycloheptenone and excess cyclopentadiene (**195**) at −50 °C gave a single adduct (**408**) in 95% yield (Scheme 70).[324] Intramolecular Diels−Alder trapping

Scheme 70. Photoisomerization of *cis*-2-Cycloheptenone (406)



of photochemically generated *trans*-cyclic enones have also been reported as a rapid entry to complex polycyclic structures (Scheme 71).[325]

Scheme 71. Intramolecular Diels−Alder Reaction of Photochemically Generated *trans*-Cycloheptenone



The diterpene vibsanin E (**413**) was initially isolated by Kawazu from the Japanese fish poison plant *Viburnum odoratissimum* and was among the first vibsane natural products to be isolated (Figure 22).[326] Its highly oxygenated cycloheptane ring and the 3-oxatricyclo[6.3.2.0^{5,10}]tridecane core make vibsanin E (**413**) a considerable synthetic challenge.[327,328] Davies and co-workers' approach to (±)-5-epi-10-epivibsanin E (**423**) centered on three different cycloaddition steps: a Rh-catalyzed [4 + 3] cycloaddition, a heteronuclear [4 + 2] cycloaddition, and a photochemically induced [4 + 2] cycloaddition.[329,330] The synthesis commenced with Rh-catalyzed [4 + 3] cycloaddition between diene **414** and vinyldiazoacetate **415** to afford cycloheptadiene **416** in 69% yield. The subsequent step involved reduction of ester **416** and oxidation of the resulting alcohol under Swern conditions to furnish aldehyde **417** in 90% yield. $BF_3{\cdot}OEt_2$-assisted heteronuclear [4 + 2] cycloaddition of aldehyde **417** constructed the tricyclic vibsanin E core with the desired relative configuration. Further manipulations of tricycle **418** gave the conjugated ketone **419**, which was shown to be resistant to a tandem conjugate addition/alkylation strategy that would have completed the synthesis of vibsanin E (**413**). Furthermore, thermal Diels−Alder reactions were also conducted but failed to give any product, highlighting the limited reactivity of **419** due to the sterically encumbered environment. An alternate strategy therefore had to be examined that increased the reactivity of enone **419**. Intrigued by the possibility of exploiting a tandem photoisomerization/[4 + 2] cycloaddition sequence, the authors irradiated enone **419** in the presence of isoprene (**421**) to efficiently generate alkene **422** in 61% yield with the desired anti fusion across the enone moiety. This was further advanced to (±)-5-epi-10-epivibsanin E (**423**) (Scheme 72).

Baldwin and co-workers employed the photoisomerization of (*E*,*E*,*E*,*E*)-tetraene **424** to produce the (*E*,*E*,*E*,*Z*)-tetraene intermediate **425**. Tetraene **425** undergoes a radical cascade, ultimately revealing compound **427** (Scheme 73), which contains the crispatene core,[331] similar to that reported by Padwa and co-workers in their studies of 1,3,5-hexatrienes.[332,333] A recent example of the use of photoisomerization is encountered in Tang and co-workers' synthesis of xanthanolide dimers.[334] Xanthanolides are sesquiterpenoids with over a hundred members having been identified to date. A majority of the members in the xanthanolide family feature a butyrolactone moiety that is *trans*- or *cis*-fused to a seven-membered carbocycle, as in xanthatin (**429**, Figure 23).[335−339] Although Tang and co-workers were not initially attempting to access dimeric products, they discovered that irradiation of xanthatin (**429**) under a N_2 atmosphere led to a mixture of 3-epimogolide A (**435**) and mogolide A (**436**) in a combined yield of 74% (Scheme 74). The authors proposed that the reaction proceeded via photoinduced C1−C5 double bond isomerization to generate *trans*-cycloheptene **432**, which rapidly undergoes Diels−Alder dimerization via **433** to produce the pentacyclic product **434**. From intermediate **434**, a subsequent [2 + 2] photocycloaddition gives the two dimerization products, 3-epimogolide A (**435**) and mogolide A (**436**).[334] Although the photoisomerization strategy has not received significant attention in natural product synthesis, the examples discussed in this section highlight the synthetic utility of the photoisomerization of *cis*-cycloalkenes to *trans*-cycloalkenes to trigger subsequent reactions.

5. NORRISH-TYPE PHOTOREACTIONS

The Norrish type I reaction refers to a photochemical reaction where the C−C bond between a carbonyl group and an α-carbon is homolytically cleaved. Several reaction modes are available for the generated 1,4-diradical and are dependent on the exact nature of the molecule (Scheme 75). One pathway involves decarbonylation with subsequent cyclization to furnish interesting cyclic products. Alternative pathways include formation of ketenes or

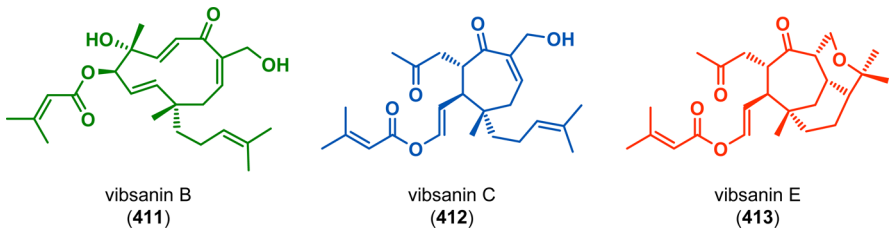


Figure 22. Structures of vibsanin B (**411**), C (**412**), and E (**413**).

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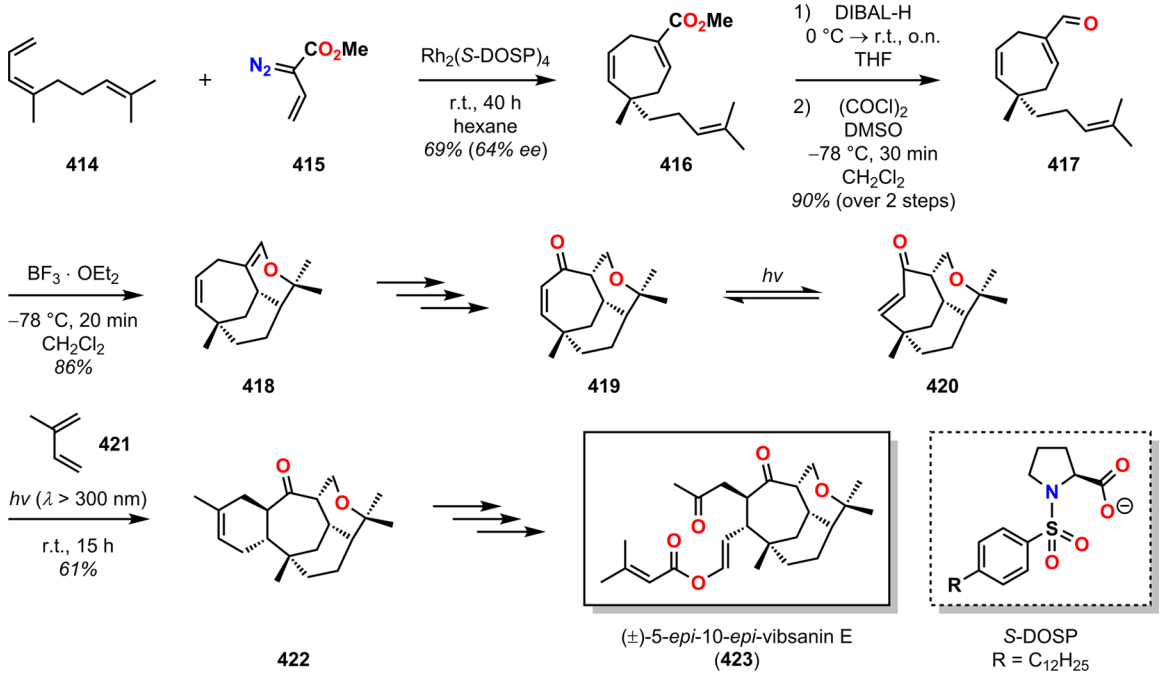
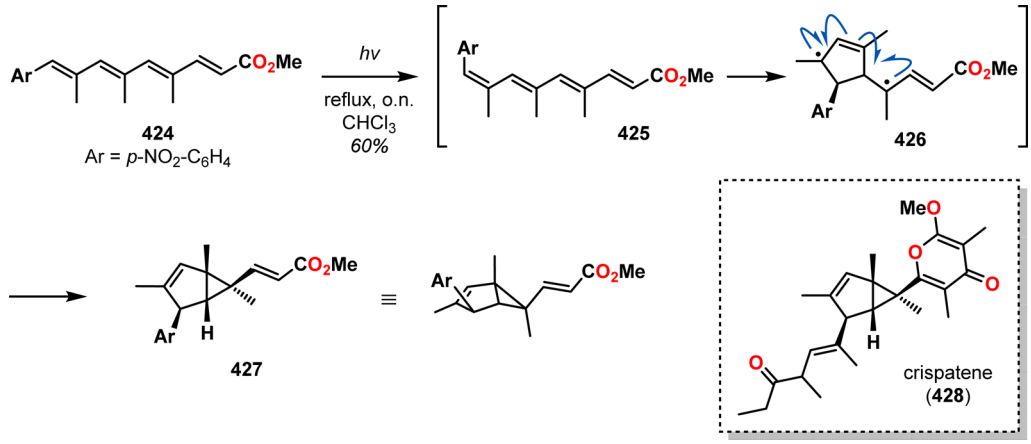
Scheme 72. Application of a Tandem Photochemical Isomerization/[4 + 2] Cycloaddition Sequence in the Total Synthesis of (±)-5-Epi-10-epivibsanin E (423)[a]



[a]DIBAL-H = diisobutylaluminum hydride.

Scheme 73. Photoisomerization of (*E,E,E,E*)-Tetraene 424



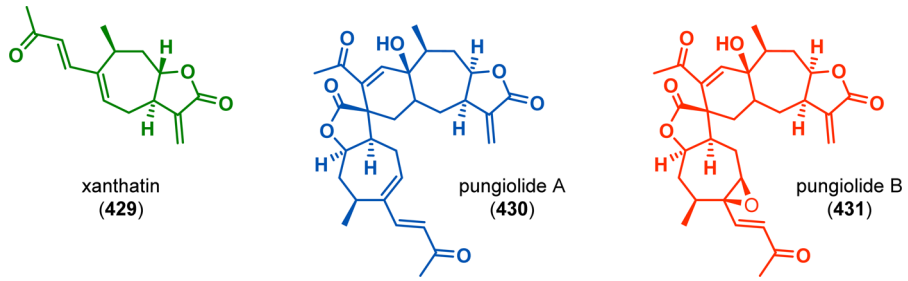


Figure 23. Examples of monomeric and dimeric xanthanolides.

aldehydes or a simple recombination of the 1,4-diradical, resulting in racemization of the α-carbon center.[340−343]

The Norrish type II photoreaction involves an intramolecular γ-hydrogen abstraction of an excited carbonyl compound and was first reported by Ronald Norrish in the early 1930s.[344−347] The primary 1,4-diradical that is formed can subsequently undergo further cleavage to produce alkenes and enols as the initial products (pathway A in Scheme 76). Alternatively, the produced 1,4-diradical can recombine to form cyclobutanols, a process that is called Norrish−Yang cyclization (pathway B in Scheme 76).[348,349]

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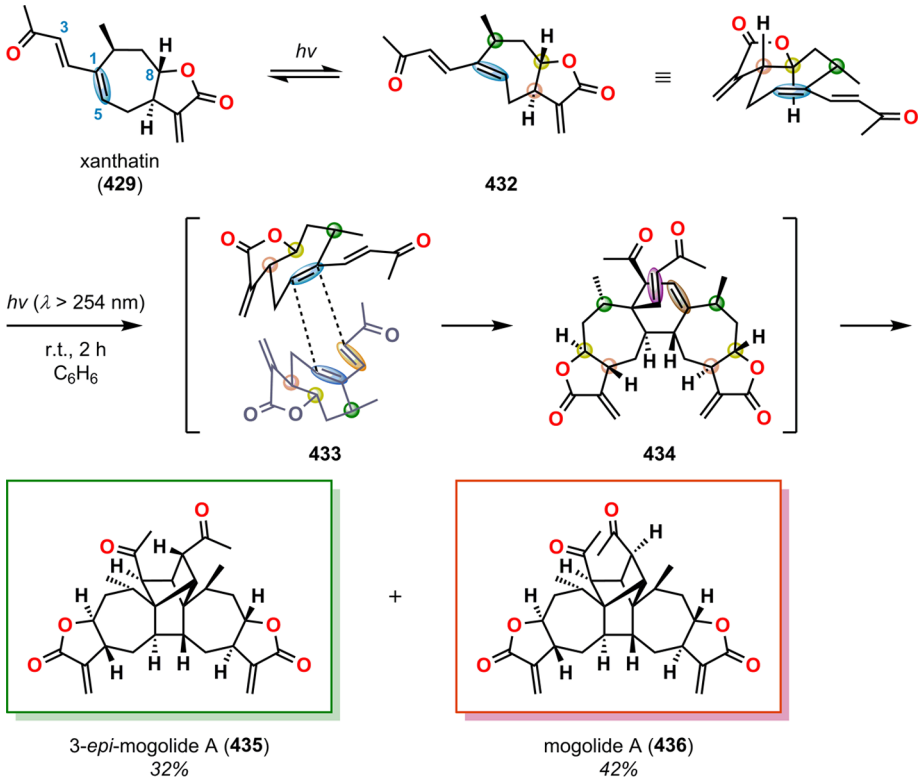
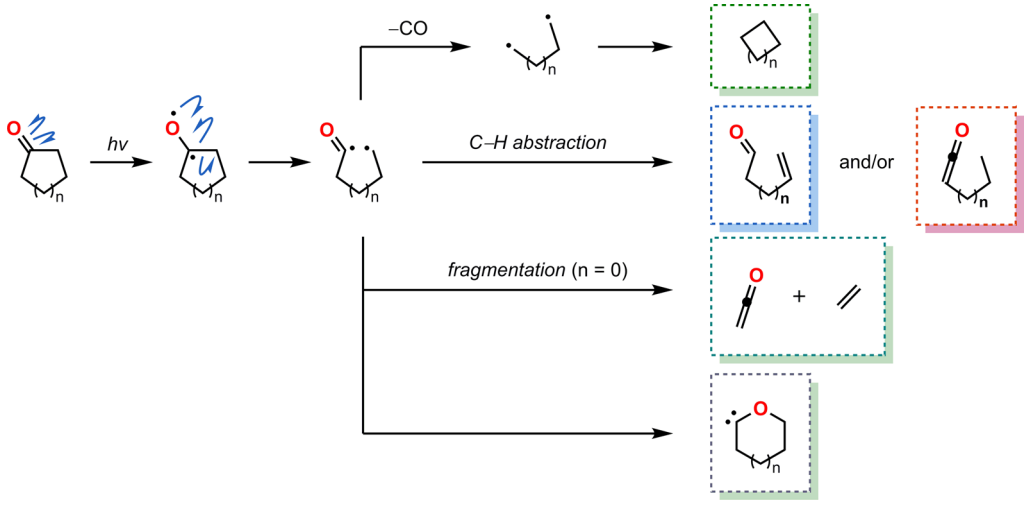
Scheme 74. Synthesis of 3-Epimogolide A (435) and Mogolide A (436)



Scheme 75. Depiction of the Norrish Type I Reaction and the Possible Photoproducts That Can Be Generated



The competition between fragmentation and cyclization is strongly dependent on the nature of the substituents.

5.1. Norrish Type I Photoreactions

The utilization of the Norrish type I reaction can be found in the synthesis of α-cuparenone (**439**). Here, irradiation of diketone **438** produced α-cuparenone (**439**) in 85% yield via a decarbonylation/cyclization sequence (Scheme 77).[350] A related approach was also used by the authors in the total synthesis of the sesquiterpene (±)-herbertenolide (**442**), where a Norrish type I reaction was employed to produce the essential cyclopentane core (Scheme 78).[351]

In Nicolaou and co-workers' studies on the hamigerans, a Norrish type I homolysis reaction was observed for hydroxy ketoester **443**. Irradiation of a benzene solution containing hydroxy ketoester **443** produced an equilibrium mixture of C10 epimers. The authors speculated that this equilibration originates from a Norrish type I cleavage reaction of the C10−C11 bond, resulting in diradical **444**. This diradical can either reclose, regenerating the hydroxyl ketoester **443**, or undergo inversion prior to recombination to produce the C10 epimer **445** (Scheme 79). Furthermore, peculiar ring-contracted products were also derived from diketone **446**. These ring-contraction products presumably proceed through a Norrish type I fragmentation, generating diradical **447**. Subsequent expulsion of CO and intramolecular recombination of diradical **448** produces the observed ring-contracted product **449** (Scheme 80).[312,313]

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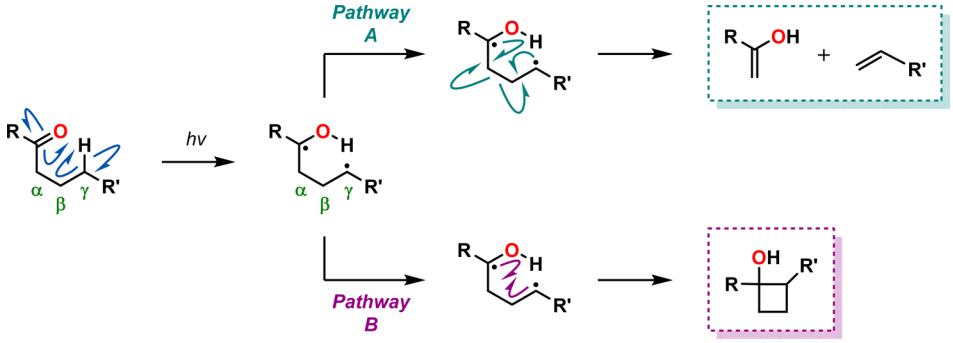
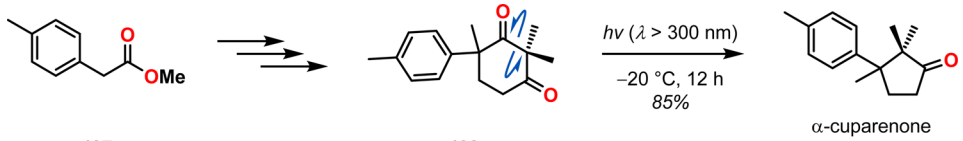
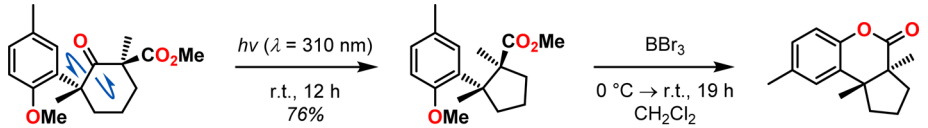
Scheme 76. Depiction of the Norrish Type II Reaction Involving γ-Hydrogen Abstraction



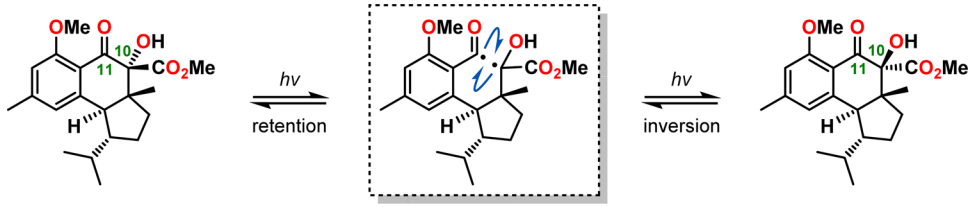
Scheme 77. Use of the Norrish Type I Reaction in the Synthesis of α-Cuparenone (439)



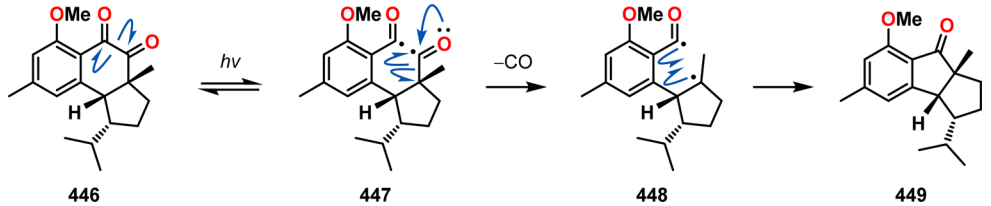
Scheme 78. Decarbonylation/Cyclization Sequence in the Total Synthesis of (±)-Herbertenolide (442)



Scheme 79. Photoinduced Epimerization of Hydroxy Ketoester 443 at C10 through Norrish Type I Fragmentation–Recombination



Scheme 80. Norrish Type I Fragmentation of Diketone 446 Observed in the Total Syntheses of the Hamigerans



Bicyclo[2.2.1]heptanones and related derivatives are prone to undergo Norrish type I cleavage. The resulting acyl radicals can subsequently abstract a hydrogen atom, leading to the formation of γ,δ-unsaturated aldehydes. Vandewalle and co-workers employed such an approach in the synthesis of (±)-boschnialactone (**454**).[352] Irradiation of bicyclo[2.2.1]heptanone **450** promoted Norrish type I photoinduced α-cleavage to afford the 1,5-diradical **451**. Subsequent hydrogen atom abstraction by the produced acyl radical gave the γ,δ-unsaturated aldehyde **452**, which underwent facile ring closure to form lactol **453** in 90% yield. Oxidation with PCC followed by double bond hydrogenation using Pd/C gave (±)-boschnialactone **454** in 75% yield (Scheme 81). Additional applications of this photoinduced α-cleavage/hydrogen abstraction sequence can be found in the synthesis of (+)-juvabione (**459**, Scheme 82)[353] and (±)-hop ether.[354]

The formation of tetrahydrofuryl ethers upon irradiation of cyclobutanones in the presence of alcohols or other protic solvents is believed to proceed via initial formation of an oxacarbene species, which is subsequently inserted into the O–H bond.[355−357] Molander and co-workers utilized this oxacarbene/insertion

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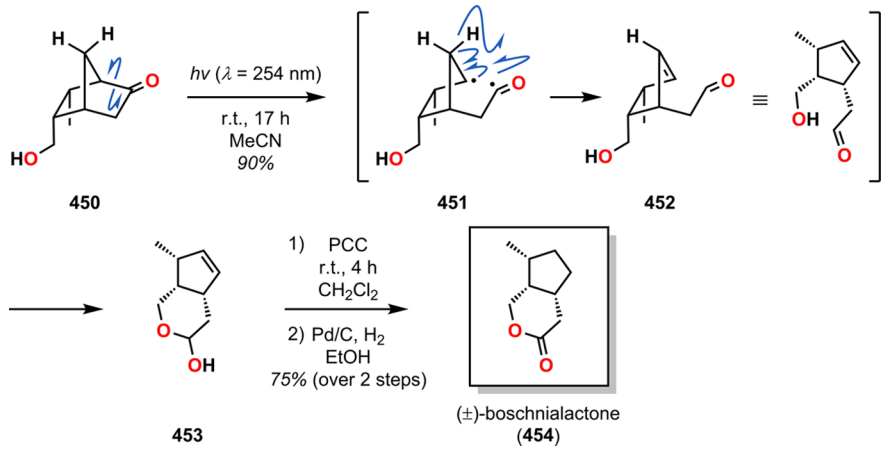
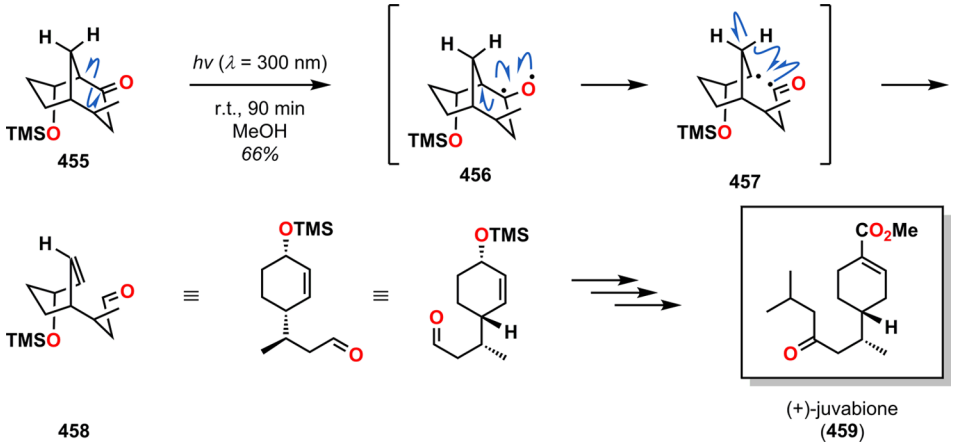
Scheme 81. Norrish Type I Cleavage with Subsequent γ-Hydrogen Abstraction in Bicyclo[2.2.1]Heptanone 450[a]

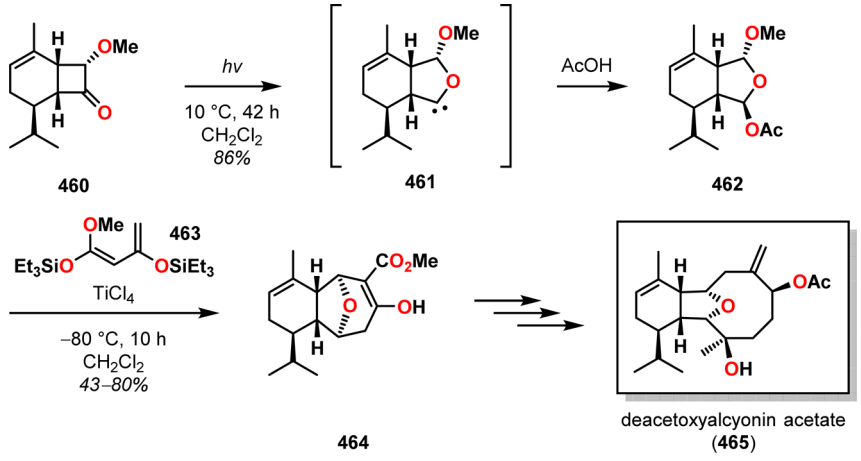


[a]PCC = pyridinium chlorochromate.

Scheme 82. Synthesis of (+)-Juvabione (459) through a Norrish Type I Fragmentation Methodology



Scheme 83. Norrish Type I Cleavage with Subsequent Oxacarbene Trapping in the Total Synthesis of Deacetoxyalcyonin Acetate (465)



sequence in the synthesis of deacetoxyalcyonin acetate (**465**).[358] The photochemical rearrangement of cyclobutanone **460** generated oxacarbene **461**, which could be trapped with AcOH to afford the mixed acetal ring expansion product **462** in high yield and with complete retention of the stereocenter adjacent to the carbonyl. The mixed acetal **462** subsequently underwent a $TiCl_4$-mediated [4 + 3] annulation at −80 °C to give the ester **464**, which could be advanced to deacetoxyalcyonin acetate (**465**) (Scheme 83).

5.2. Norrish–Yang Cyclizations

(−)-Punctaporonin A (**470**), originally isolated from the fungus *Poronia punctata*, is a trihydroxylated tricyclic sesquiterpene

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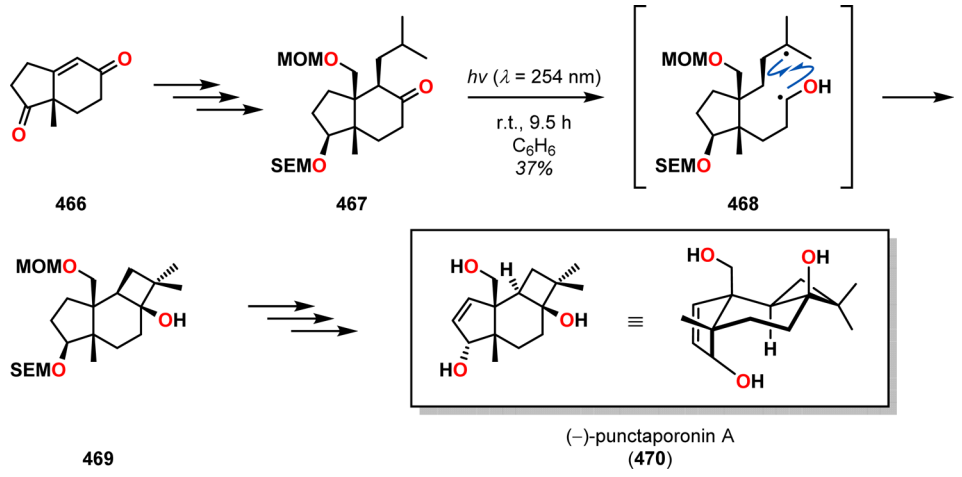
Scheme 84. Norrish–Yang Cyclization of Ketone 467 in the Total Synthesis of (−)-Punctaporonin A (470)[a]



[a]MOM = methoxymethyl. SEM = 2-(trimethylsilyl)ethoxymethyl.

containing a *trans*-cyclobutanol unit.[359,360] For construction of the strained four-membered cyclobutanol scaffold, Sugimura and Paquette applied Norrish type II photochemistry.[361] The synthesis commenced with diketone **466**, which was converted to the essential photosubstrate **467**. Irradiation of a benzene solution of ketone **467** generated diradical **468** via γ-hydrogen abstraction from the proximal isopropyl moiety, which produced the desired key Norrish–Yang cyclized product **469** in 49% yield along with approximately 20% of the Norrish β-fragmentation product (cf. Scheme 76). Removal of the SEM group and subsequent manipulations completed the synthesis and afforded (−)-punctaporonin A (**470**) (Scheme 84).

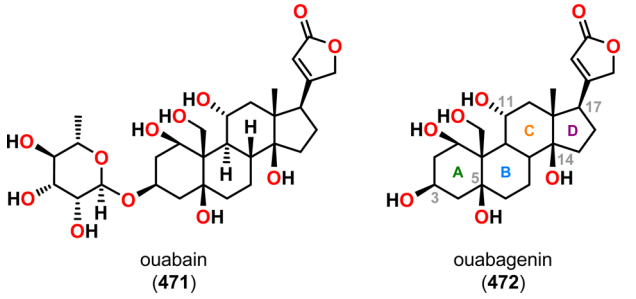
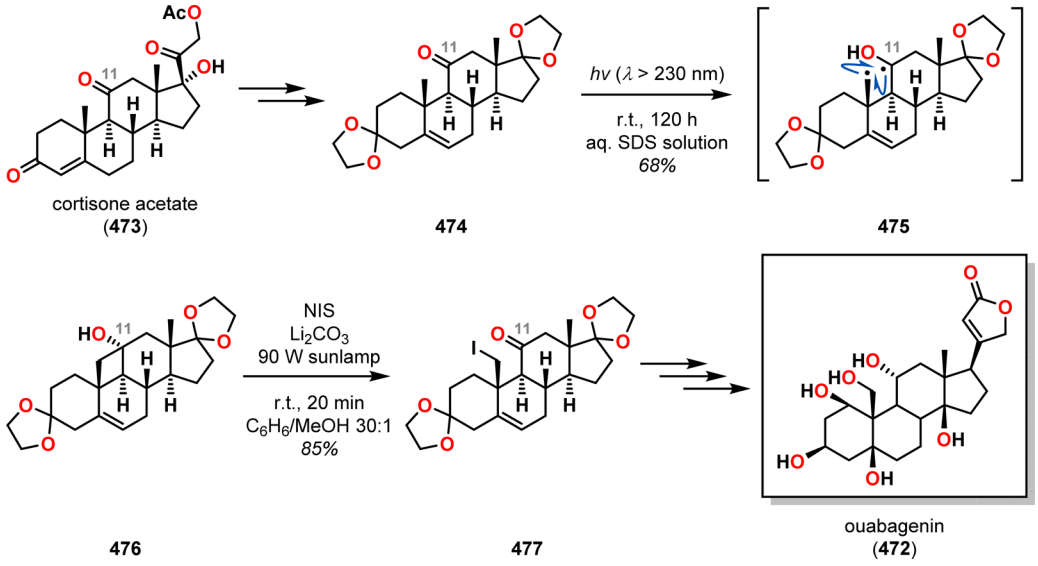


Figure 24. Structures of ouabain (**471**) and ouabagenin (**472**).

Ouabain (**471**) and ouabagenin (**472**) belong to a class of steroids known as cardenolides and exhibit positive inotropic acitivity (Figure 24).[362−364] The steroidal skeleton of ouabagenin (**472**), an aglycon of ouabain (**471**), possesses several characteristic features, such as *cis*-fused A/B and C/D rings, an angular hydroxyl unit at the C14 position, and a β-oriented butenolide group at C17, and poses a formidable synthetic challenge. In light of the need for a scalable and economically viable route to the cardenolides and derivatives thereof, Baran and co-workers' synthesis commenced with cortisone acetate (**473**).[365,366] Conversion of cortisone acetate (**473**) to adrenosterone with subsequent ketalization afforded ketone **474**. Functionalization of the angular C19 methyl group was realized through a Norrish type II photochemical event (Scheme 85). Precedent for such a

Scheme 85. Photoinduced Norrish–Yang Cyclization in the Synthesis of Ouabagenin (472)[a]



[a]NIS = *N*-iodosuccinimide. SDS = sodium dodecyl sulfate.

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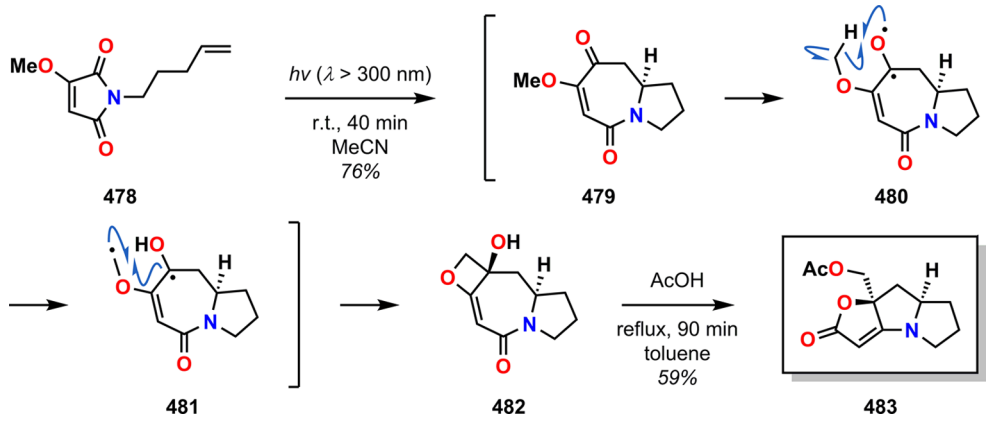
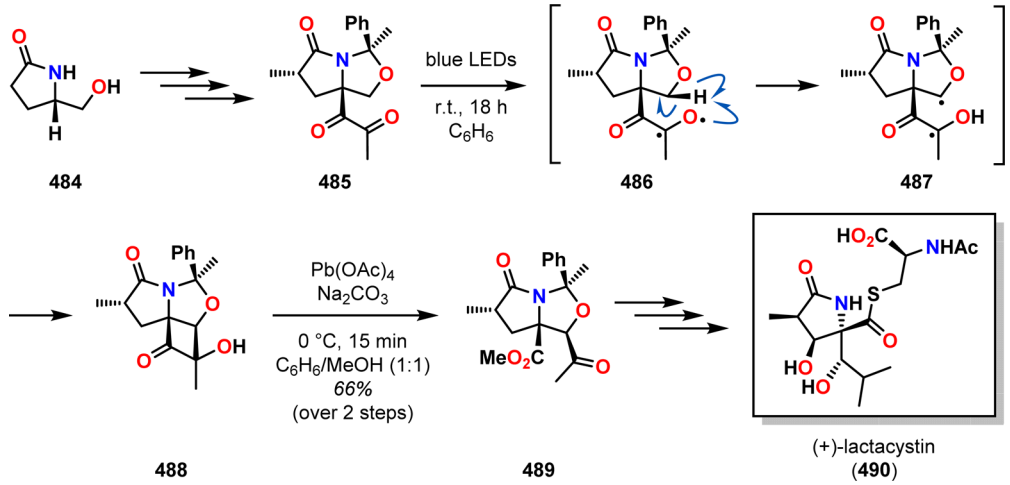
Scheme 86. Maleimide [5 + 2] Photocycloaddition/Norrish Type II Cascade for Synthesis of Tricyclic Lactone 483



Scheme 87. Application of the Norrish−Yang Cyclization in the Total Synthesis of (+)-Lactacystin (490)



strategy can be found in the work of Jeger's[367] and Thomson's[368] groups on C19 functionalization of steroid scaffolds. Irradiation of ketone **474** efficiently provided the desired cyclobutanol **476** in 68% yield on a multigram scale after ring closure of diradical **475**. Subsequent oxidative fragmentation employing *N*-iodosuccinimide as oxidant gave iodide **477**. This process presumably proceeds via a transient hypoiodite species, which undergoes a chemoselective homolysis of the C11−C19 bond followed by recombination with an iodine radical to furnish the fragmentation product **477**, which could be further transformed into ouabagenin (**472**).

Booker-Milburn and co-workers recently applied the Norrish−Yang cyclization for the synthesis of aza-fuzed tricyclic lactones.[369,370] It was realized that alkoxy-substituted maleimides such as **478** underwent a [5 + 2] cycloaddition/Norrish−Yang cyclization cascade sequence of the major initial photoadduct **479** to provide the complex azepine-fused alkylidene-oxetanol **482** in a single photochemical operation. The produced oxetane derivatives, such as **482**, were shown to afford the tricyclic lactone **483**, a result of acid-catalyzed rearrangement (Scheme 86). The rearrangement was proposed to proceed via initial oxetane ring-opening, followed by transannular amide cleavage. The resulting amine cyclizes to produce an aminol, which upon elimination of water forms the tricyclic lactone **483**.

A recent application of the Norrish−Yang cyclization can be found in Inoue and co-workers' synthesis of (+)-lactacystin (**490**).[371] The C5−C9 core skeleton of (+)-lactacystin (**490**) was provided by commercially available (*S*)-pyroglutaminol (**484**), which was converted to diketone **485**. Subjecting diketone **485** to UV light (λ < 360 nm) gave a complex product mixture, presumably due to unselective photoexcitation. As an alternative, the authors turned their attention to blue LEDs ($\lambda \approx$ 460 nm). Using the longer-wavelength-emitting blue LEDs led to smooth conversion to the *cis*-fused cyclobutanone **488**. The observed chemoselective hydrogen abstraction in the Norrish type II reaction is presumed to originate from the more electron-rich nature of the ethereal C(sp^3)−H bond in comparison to the aliphatic C−H bond. Subsequent oxidative ring-opening using $Pb(OAc)_4$ generated ketoester **489** as a single isomer in 66% yield over two steps (Scheme 87), which could be converted to (+)-lactacystin (**490**) through homologation at C10, construction of C6 and C7 stereocenters, and attachment of the cysteine moiety.

Substrates lacking γ-hydrogens are also prone to undergo Norrish-Yang cyclization. Examples of this type have been applied in the synthesis of (±)-paulownin (**493**, Scheme 88)[372] and the structurally related (+)-phrymarin I and (+)-phrymarin II.[373]

6. THE OXA-DI-π-METHANE REARRANGEMENT—ACCESS TO COMPLEX MOLECULAR FRAMEWORKS

Substrates housing β,γ-unsaturated ketone motifs are generally competent in undergoing the oxa-di-π-methane rearrangement. The reaction involves triplet-sensitized irradiation and is the

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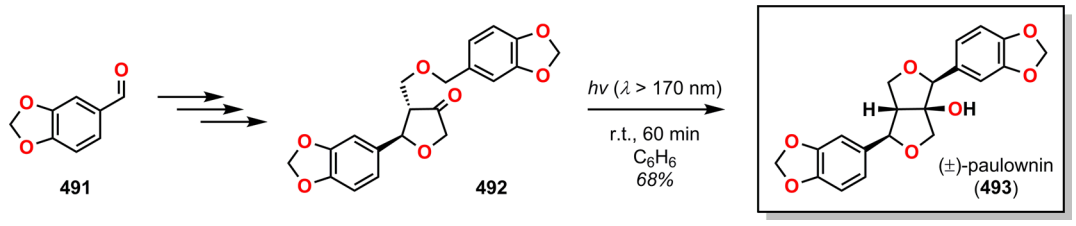
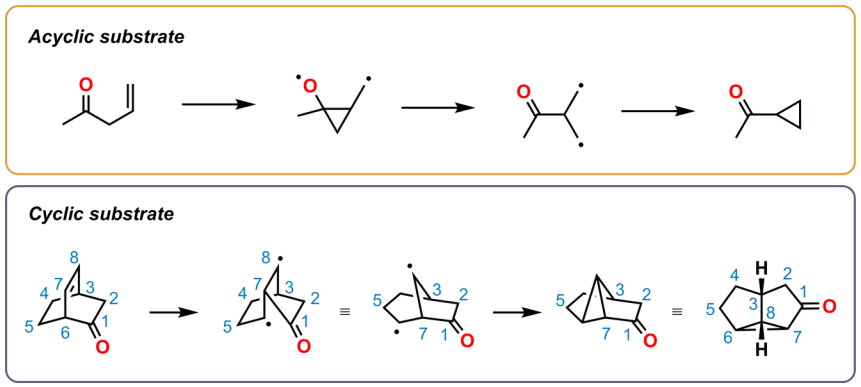
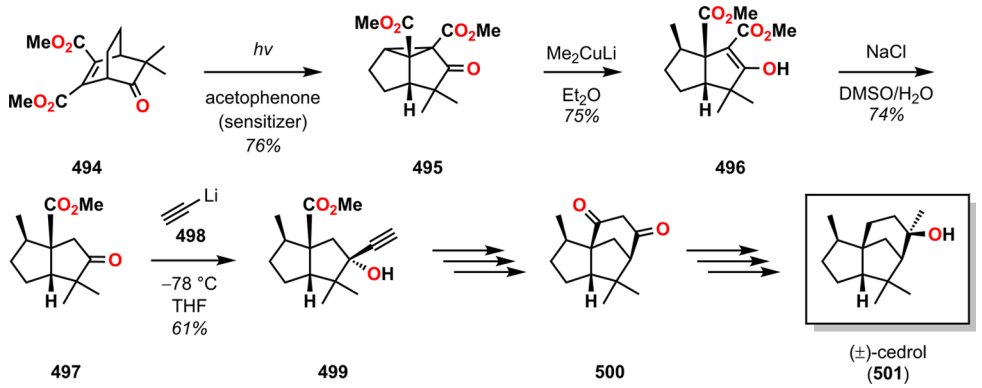
Scheme 88. Use of the Norrish−Yang Cyclization in the Total Synthesis of (±)-Paulownin (493)



Scheme 89. Illustrative Examples of the Oxa-di-π-methane Rearrangement for (top) an Acyclic and (bottom) a Cyclic β,γ-Unsaturated Ketone



Scheme 90. Use of the Oxa-di-π-methane Rearrangement in the Formal Total Synthesis of (±)-Cedrol (501)



reason why the reaction is conducted in the presence of a sensitizer, usually by employing acetone as the solvent. The oxa-di-π-methane rearrangement ultimately furnishes an α-cyclopropyl ketone, where photochemical excitation brings about a 1,2-acyl migration, resulting in bond formation between what were formerly the α and γ atoms.[374] Scheme 89 depicts typical cyclic and acyclic substrates that undergo the oxa-di-π-methane rearrangement.

The first reported example of the oxa-di-π-methane rearrangement dates back as far as 1966. Here, the authors discovered that a β,γ-unsaturated ketone underwent rearrangement to afford a cyclopropyl ketone.[375] After this initial report, there have been a multitude of synthetic examples that address the photochemistry of substrates containing β,γ-unsaturated ketone scaffolds.[376] The synthetic advantages of using the oxa-di-π-methane rearrangement as a tool in synthesis can be attributed to its feature of accessing molecular frameworks with significantly increased structural complexity that might be difficult to obtain via other routes. The relatively easily accessed starting materials, β,γ-unsaturated ketones, and the high tolerance of functional groups certainly increase the synthetic potential of the photochemical rearrangement.[377]

Stevens and Yates reported one of the initial applications of the oxa-di-π-methane rearrangement in total synthesis. The authors employed the oxa-di-π-methane rearrangement of bicyclo[2.2.2]-octenone derivatives for the synthesis of cedrenoid sesquiterpenes.[378] Acetophenone-sensitized irradiation of the Diels−Alder adduct **494** afforded the oxa-di-π-methane rearranged product **495**. The strained tricyclic compound **495** was subsequently subjected to Me_2CuLi to give compound **496**, which underwent Krapcho decarbomethoxylation to ketoester **497** in 74% yield. The introduction of the functionalized two-carbon substituent was carried out by treating **497** with lithium acetylide (**498**). This afforded the propargylic alcohol **499**, where attack of the acetylide occurs at the β-face of **497**. Propargylic alcohol **499** was subsequently transformed into the Stork−Clarke β-diketone **500** (Scheme 90),[378,379] which had previously been reported as a key intermediate in the synthesis of (±)-cedrol (**501**).[436,380]

Another example of employing the bicyclo[2.2.2]octenone skeleton for rearrangement into viable building blocks in total

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synthesis can be found in the synthesis of (±)-modhephene (**65**), which contains a carbocyclic [3.3.3]propellane framework (see Figure 25).[381−394] Here, Mehta and Subrahmanyam applied a photochemical approach that involved the oxa-di-π-methane rearrangement for constructing the sesquiterpene hydrocarbon (±)-modhephene (**65**). In this route, diene **506** was converted to bicyclo[2.2.2]octenone **508** through a Diels−Alder cycloaddition. Irradiation of β,γ-unsaturated ketone **508**, in the presence of acetone, afforded the tetracyclic strained cyclopropyl ketone **509** housing three quaternary carbon centers through a oxa-di-π-methane rearrangement. Conventional synthetic manipulations then converted the tetracyclic ketone **509** into the sesquiterpene (±)-modhephene (**65**) (Scheme 91).[395,396]

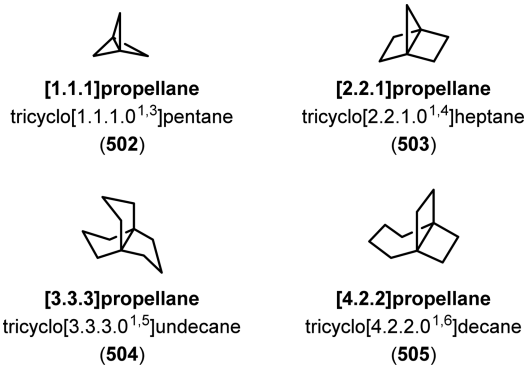


Figure 25. Examples of carbocyclic propellanes.

Uyehara and co-workers have also utilized the oxa-di-π-methane rearrangement in the synthesis of (±)-modhephene (**65**) and (±)-isocomene (**63**).[147] Here, oxa-di-π-rearrangement of bicyclo[2.2.2]oct-5-en-2-ones **512** and **514** afforded ketones **513** and **515**, which could be further elaborated to (±)-modhephene (**65**) and (±)-isocomene (**63**), respectively (Scheme 92).

The structurally related magellanine (**516**),[397−399] magellaninone (**517**),[397−399] and paniculatine (**518**)[400] are members of the *Lycopodium* alkaloids, which are a family of natural products

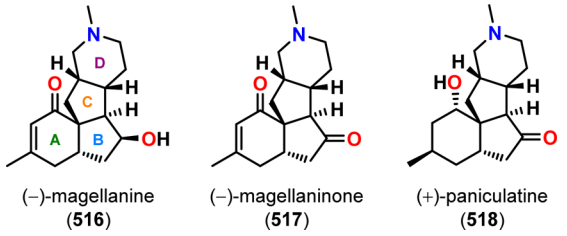
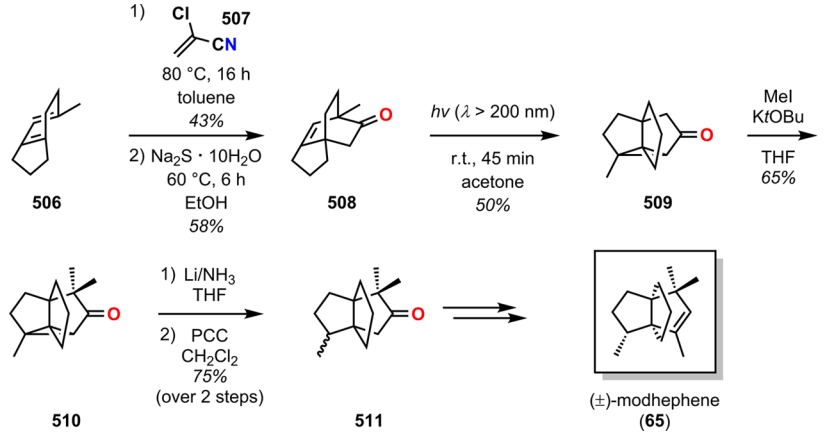


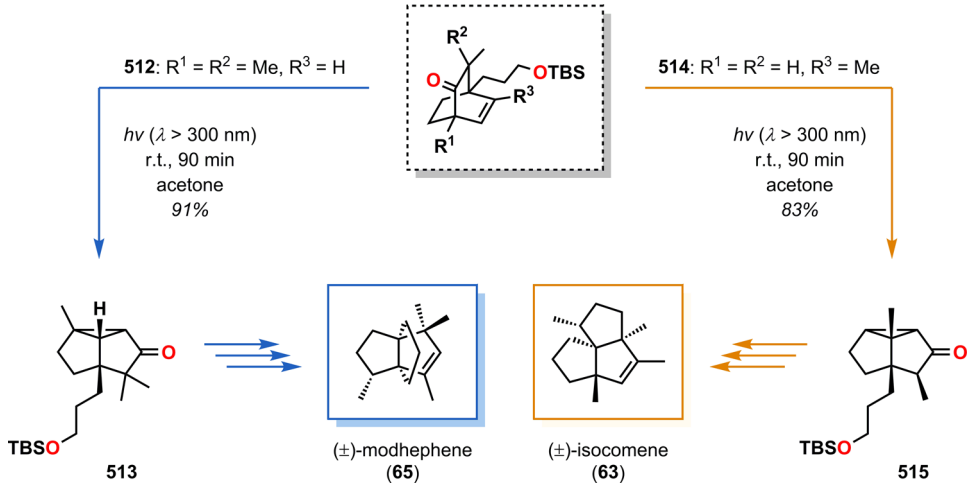
Figure 26. Structures of the *Lycopodium* alkaloids (−)-magellanine (**516**), (−)-magellaninone (**517**), and (+)-paniculatine (**518**).

Scheme 91. Construction of the Carbocyclic Framework of (±)-Modhephene (65) by Use of the Oxa-di-π-methane Rearrangement[a]



[a]PCC = pyridinium chlorochromate.

Scheme 92. Uyehara's Approach to (±)-Modhephene (65) and (±)-Isocomene (63)



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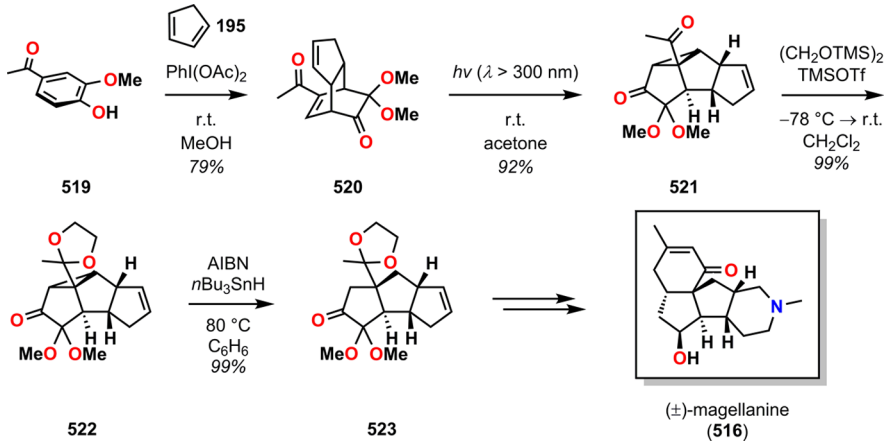
Scheme 93. Synthesis of the Tetracyclic (±)-Magellanine (516) by Use of the Oxa-di-π-methane Rearrangement[a]



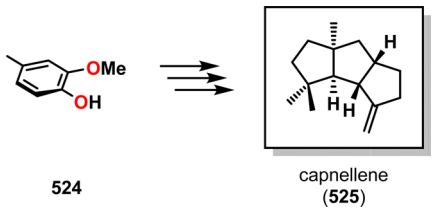
[a]AIBN = azobis(isobutyronitrile). TMSOTf = trimethylsilyl trifluoromethanesulfonate.

that have attracted considerable interest from the synthetic community since their isolation in the 1970s due to their intriguing polycyclic skeleton and biological activity (Figure 26).[401−404] These alkaloids share a diquinane core that is fused to a cyclohexenone or cyclohexanol and piperidine unit. Construction of the tetracyclic scaffolds of these alkaloids and also controlling the stereochemistry at a multitude of the carbon centers of the bicyclo[3.3.0]octane core certainly represent daunting synthetic challenges.[405−409]

The tetracyclic magellanine (**516**) with six contiguous stereogenic centers, one of which is a quaternary carbon center, was efficiently synthesized from commercially available acetovanillone **519** using the oxa-di-π-methane rearrangement as a key step.[410] Liao and co-workers found that irradiation of Diels−Alder cycloadduct **520** yielded the tetracyclic diketone **521** through the oxa-di-π-methane rearrangement. Cyclopropyl ring-opening resulted in a linear triquinane (**523**), which was subsequently transformed into (±)-magellanine (**516**) (Scheme 93).

A similar approach by Liao and co-workers was also applied in the synthesis of (±)-$\Delta^{9(12)}$-capnellene (**525**), which was accessed in nine steps with 20% overall yield from 2-methoxy-4-methylphenol (**524**) (Scheme 94).[411] Additional

Scheme 94. Synthesis of (±)-$\Delta^{9(12)}$-Capnellene (525) from 2-Methoxy-4-methylphenol (524)



examples of linear triquinanes that have been assembled utilizing the oxa-di-π-methane rearrangement are (−)-complicatic acid (**526**),[412,413] (−)-coriolin (**527**),[414−418] (−)-hirsutene (**222**),[419−422] (+)-hirsutic acid (**528**),[412,413,423,424] and (−)-phellodonic acid (**529**) (Figure 27).[425]

The examples highlighted here illustrate the power of the oxa-di-π-methane rearrangement for the elaborate functionalization of simple scaffolds into highly condensed skeletons for use in the total synthesis of natural products.

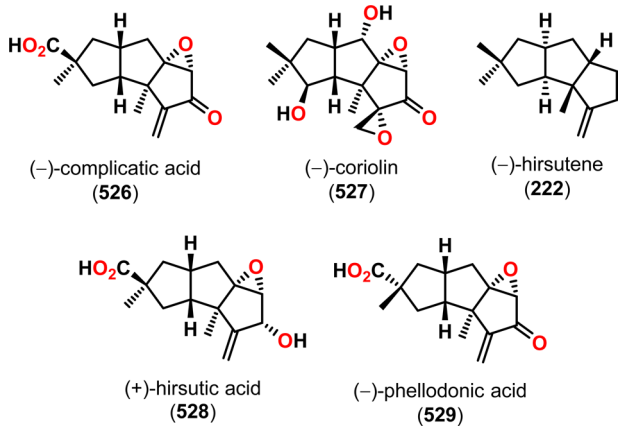


Figure 27. Examples of linear triquinanes that have been synthesized via the oxa-di-π-methane rearrangement.

7. THE META-PHOTOCYCLOADDITION REACTION—A POWERFUL METHOD FOR ACCESSING POLYCYCLIC SKELETONS

Aromatic compounds are known for their robustness; however, upon electronic excitation the aromatic ring can be activated and engaged in reaction pathways that are generally not possible from the ground state. Scheme 95a depicts the cycloaddition between an alkene (ethylene) and an arene (benzene) and the three pathways, ortho-, meta-, and para-photocycloaddition, that can be observed.[426] Ortho- and meta-photocycloadditions are the most frequently encountered outcomes, while para-photocycloaddition is rarely observed. The meta-photocycloaddition (Scheme 95b) is perhaps the most remarkable photochemical reaction, as it allows for the formation of three single bonds and up to six stereogenic centers in one step.[427,428] The reaction proceeds via the formation of a tricyclic scaffold from which fragmentation of the three-membered ring can produce several products (Scheme 95c). Cleavage of the C2−C8 bond is considered as the most common pathway and generates a bicyclo[3.3.0]octane framework. On the other hand, cleavage of the C1−C2 bond or the bond between C1 and C8 furnishes a bicyclo[3.2.1]octane skeleton. The extensive bond reorganization associated with the meta-photocycloaddition reaction makes it a powerful method for generating significant molecular complexity in a single synthetic step, and it lacks a thermal

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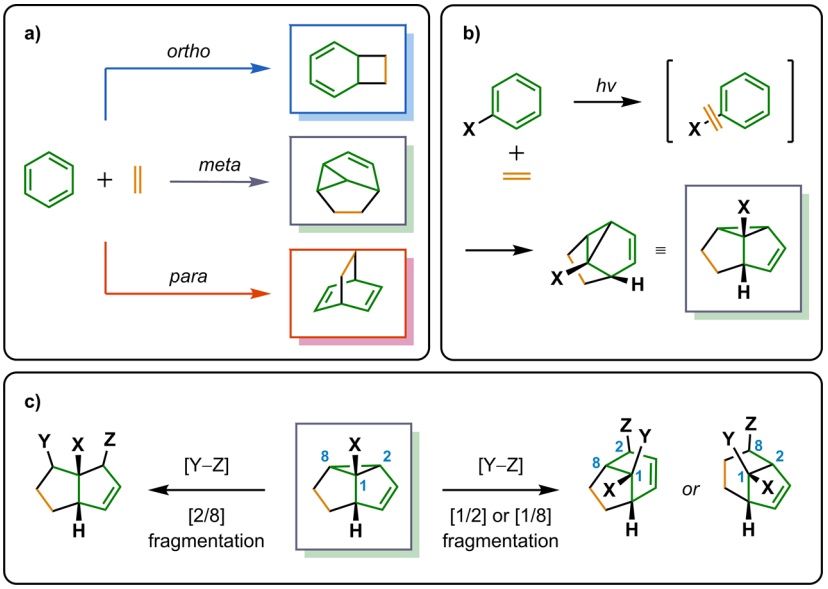
Scheme 95. (a) Three Modes of Photocycloadditions of an Alkene to a Benzene Ring, (b) Pathway for the Meta-Photocycloaddition, and (c) Key Bond Fragmentations for the Meta-Photocycloaddition Adduct for Accessing Complex Cyclic Frameworks



counterpart. The versatility of the different fragmentation routes creates various exotic frameworks and it is this feature that has rendered the meta-photocycloaddition a widely used tool in a number of synthetic routes for accessing natural products.[429,430]

Although Wilzbach and Kaplan reported the first example of a meta-photocycloaddition reaction in 1966,[431] it was Wender's successful implementation of the meta-photocycloaddition in the total synthesis of a variety of natural products that began to attract significant attention.[432] In particular, Wender's synthesis of α-cedrene (**1**) expanded the concept of the alkene–arene meta-photocycloaddition reaction and extended the chemical toolbox (Figure 28).[37] The tricyclic α-cedrene (**1**) belongs to a family of naturally occurring sesquiterpenes. It was isolated[433,434] from *Juniperus cedrus* and *Juniperus thurifera* in 1841; however, its structure and the tricycle undecane skeleton were not verified until 1953 by Stork and Breslow.[435] The intriguing [5.3.1.0^{1,5}] tricyclic structure found in the cedranoids has attracted considerable interest among the synthetic community.[436−447]

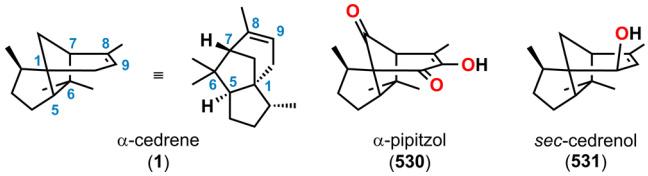
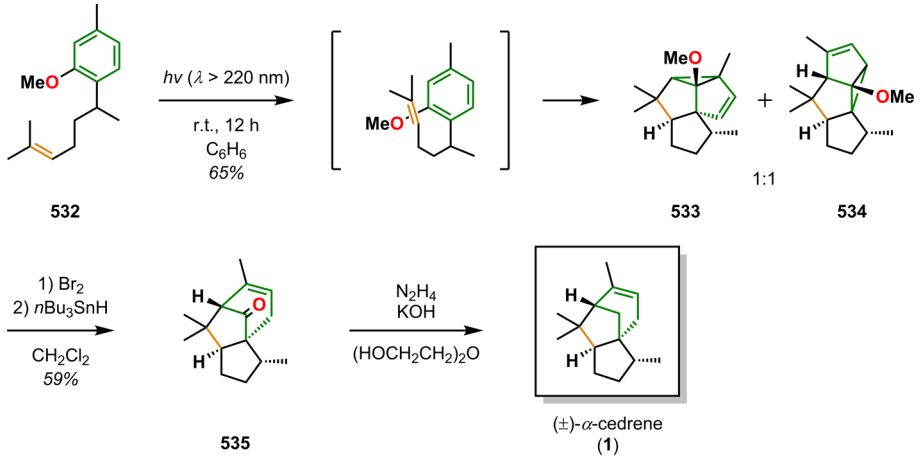


Figure 28. Examples of cedranoids.

Wender's concise synthesis of (±)-α-cedrene (**1**) in merely four steps (Scheme 96) exemplified the ability of the meta-photocycloaddition reaction to provide the tricyclic sesquiterpene with the correct configuration at all four stereogenic centers. The high diastereo- and regioselectivity is dictated by 1,3-allylic (A^{1,3}) strain between the aryl methoxy and the methyl group in **532**. This favors a conformation for the ring closure step that gives the two products **533** and **534** in a 1:1 ratio. Subsequent fragmentation of the cyclopropane ring upon treatment with Br_2, followed by reductive dehalogenation with nBu$_3$SnH, provided convergent access to ketone **535** from the two cycloaddition products **533** and **534**. Wolff–Kishner reduction of ketone **535** generated (±)-α-cedrene (**1**) in merely four steps.[37]

Scheme 96. Total Synthesis of (±)-α-Cedrene (1) Using Meta-Photocycloaddition



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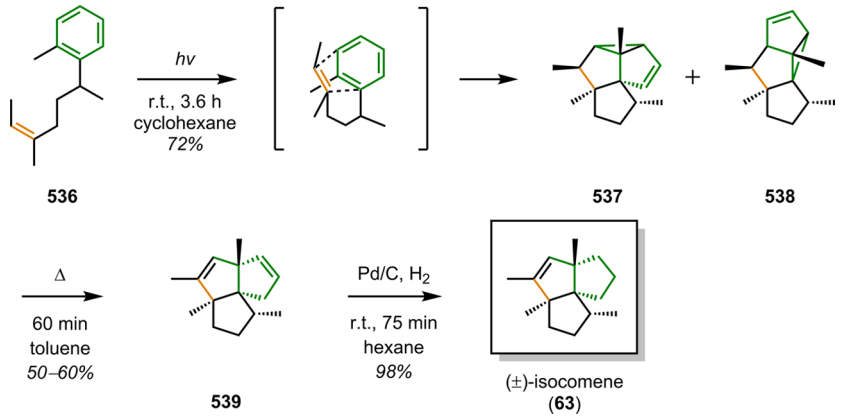
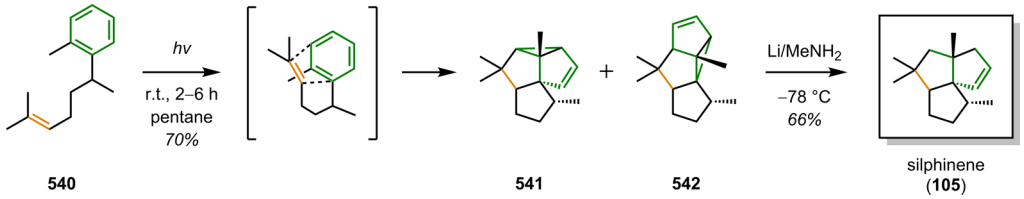
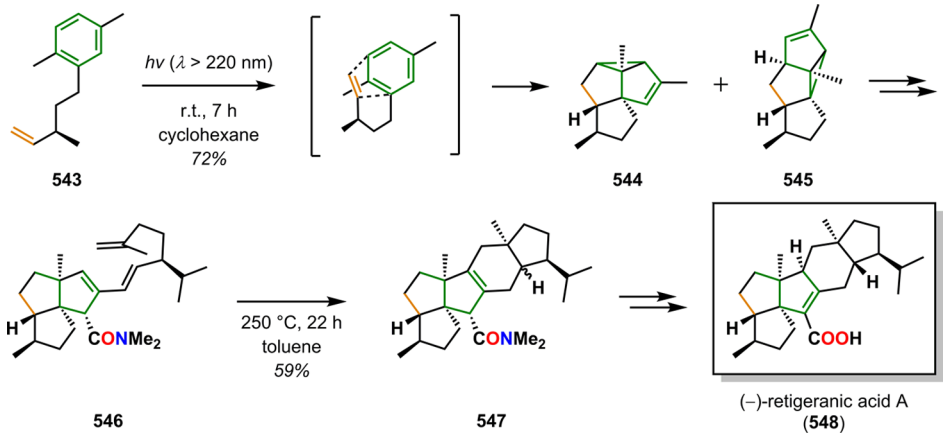
Scheme 97. Photochemical Approach for Synthesis of (±)-Isocomene (63)



Scheme 98. Route to Silphinene (105) Using Meta-Photocycloaddition



Scheme 99. Synthesis of (−)-Retigeranic Acid A (548)



As previously discussed in section 2.1, both (±)-isocomene (**63**)[78] and silphinene (**105**)[95] have been synthesized using the [2 + 2] photocycloaddition. However, the tricyclic cores of (±)-isocomene (**63**)[146] and silphinene (**105**)[448] can also be accessed by using a meta-photocycloaddition strategy and are depicted in Schemes 97 and 98, respectively.

Pentacyclic (−)-retigeranic acid A (**548**), a structurally related natural product, was initially isolated from Himalayan lichen and is reported to have antibacterial activity.[449,450] It is a structurally unique member of the class of sesterterpene natural products and houses a triquinane subunit and eight stereocenters.[451,452] Due to retigeranic acid's intriguing structure, several research groups have pursued its synthesis and related sesterterpenoids.[453−455] Early examples of the total synthesis of retigeranic acid include reports by the groups of Corey,[456] Hudlicky,[457−460] and Paquette.[461−463]

Wender and Singh's convergent approach to (−)-retigeranic acid A (Scheme 99) commenced with the preparation of the enantiomerically pure arene−alkene derivative **543** from commercially available 3-methylglutaric acid. Photolysis of the arene−alkene fragment **543** afforded a 1:2 mixture of photoadducts **544** and **545**, which were found to be interconvertible vinylcyclopropane isomers, allowing them each to be converted to the Diels−Alder precursor **546**. This precursor was then allowed to undergo an intramolecular Diels−Alder reaction to furnish the pentacyclic compound **547**, which could be further transformed into (−)-retigeranic acid (**548**).[464]

Subsequently, the Wender group reported on the total synthesis of rudmollin (**554**).[465] The pseudoguaianolide rudmollin (**554**) was initially isolated from a coneflower by Herz and co-workers and exhibits antileukemic activity.[466] It was realized by Wender and co-workers that the *trans*-fused perhydroazulene core of rudmollin (**554**) could be accessed through the use of an arene−olefin cycloaddition strategy. Their approach thus centered on accessing a seven-membered cyclic compound via intramolecular meta-photocycloaddition of substrate **549**, which would establish the trans relationship between carbons C1 and C5. Furthermore, since these photocycloadditions

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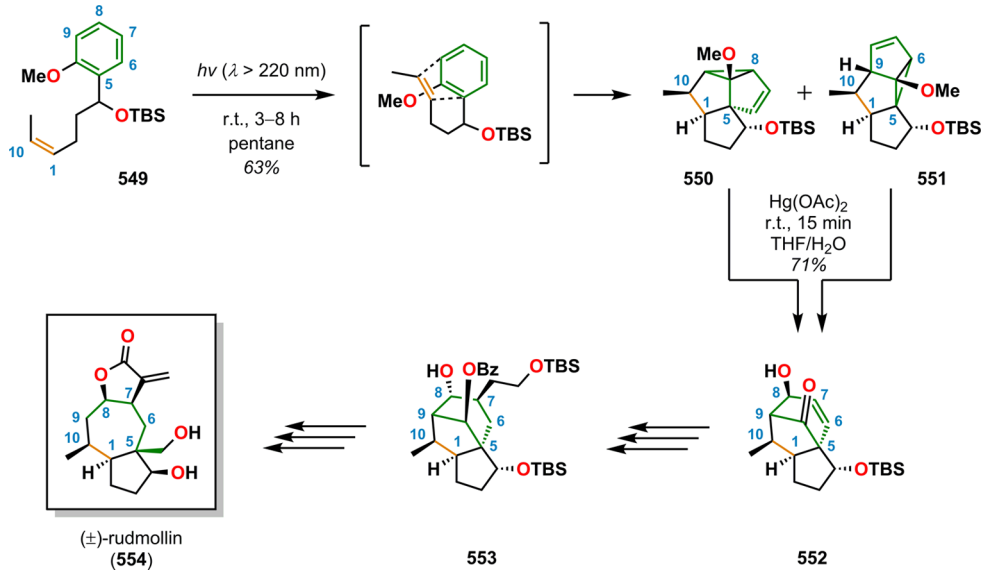
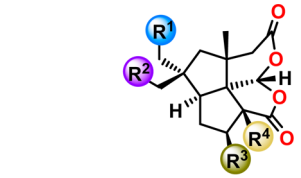
Scheme 100. Total Synthesis of (±)-Rudmollin (554) Using an Intramolecular Meta-Photocycloaddition Approach



generally preserve the geometry of the olefin moiety, this would also set the relative configuration between carbons C1 and C10 in the photocycloadduct. Performing the meta-photocycloaddition on substrate **549** afforded the two photocycloadducts **550** and **551** in a 7:3 ratio and hence established the relative configuration at the three carbon centers C1, C5, and C10. Here, the cyclopropane isomers **550** and **551** could be converted into a common product by employing a similar technique as with (±)-α-cedrene (**1**); see Scheme 96. However, instead of using Br_2-induced cleavage of the cyclopropane bond, $Hg(OAc)_2$-catalyzed hydrolysis was shown to convergently transform the cycloadducts **550** and **551** into compound **552**, which could subsequently be used to access (±)-rudmollin (**554**) (see Scheme 100).[465,467]

Penifulvin A (**555**), an antiinsectan sesquiterpenoid, was originially isolated by Gloer and co-workers in 2006 from *Penicillium griseofulvum*.[468,469] The penifulvins (Figure 29)



penifulvin A (**555**): R^1, R^2, R^3, R^4 = H
penifulvin B (**556**): R^1 = OH, R^2, R^3, R^4 = H
penifulvin C (**557**): R^1 = H, R^2 = OH, R^3, R^4 = H
penifulvin D (**558**): R^1, R^2, R^3 = H, R^4 = OH
penifulvin E (**559**): R^1, R^2 = H, R^3 = OH, R^4 = H

Figure 29. Structure of penifulvins A–E.

contain an intricate dioxa[5.5.5.6]fenestrane skeleton where four rings are joined at a central quaternary carbon atom (Figure 30). In addition to the two vicinal quaternary stereocenters, a total of five stereogenic centers exist within the 15-carbon atom framework.[470,471] The unique and complex molecular scaffold of penifulvins has made them an attractive target for total synthesis.[472−474]

Recently, the Mulzer group used the arene olefin meta-photocycloaddition to access the sesquiterpene (−)-penifulvin A (**555**).[475−477] The asymmetric synthesis of compound **566** was

Figure 30. Numbering of the fenestrane framework.

carried out by using Myers' alkylation strategy (Scheme 101).[478] Photoreaction of compound **566** resulted in a mixture of the two allylic regioisomers **569** and **570** in a 1:1 ratio. Subsequent cyclopropane ring opening using Birch-like reductive conditions afforded alcohol **571**. This was followed by an oxidative cascade sequence to complete the concise synthesis of (−)-penifulvin A (**555**) (Scheme 102). In addition to the photocyclization event, which furnishes separable regioisomers, the synthesis did not require any protecting groups.[475] The total syntheses of penifulvins B (**556**) and C (**557**) were subsequently accomplished using a similar meta-photocycloaddition approach as the key step to rapidly access the fenestrane-type carboskeletons.[476] Wender and co-workers have also disclosed a method for synthesizing *cis,cis,cis,trans*-[5.5.5.5]fenestranes using the meta-photocycloaddition.[479]

Laurenene (**99**) is another natural product containing the fenestrane framework that has been synthesized using meta-photocycloaddition.[480] Wender and co-workers started with a Diels–Alder reaction of commercially available **575** and cyclohepta-1,3-diene (**576**) to afford the tricyclic arene **577**, which was subsequently elaborated to give lactone **579** upon Grob fragmentation of keto tosylate **578**. Hydrogenation of lactone **579** and alkylation with homoprenyl iodide furnished the desired stereoisomer **581** with a 8:1 preference. Photolysis of lactol **582**, prepared by $LiAlH_4$ reduction of lactone **581**, through a $BiCl_3$ filter solution allowed for 80% conversion and isolation of a single hexacyclic product (**583**) in 51% yield. Completion of the synthesis was then accomplished in three steps to afford (±)-laurenene (**99**) in 5% overall yield (Scheme 103).

Additional examples of natural products that have been accessed using the meta-photocycloaddition reaction as the key step are shown in Figure 31 and include (±)-coriolin (**527**),[481]

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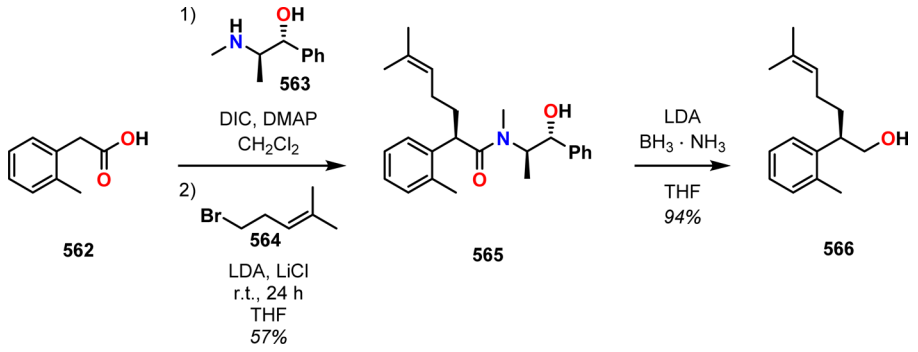
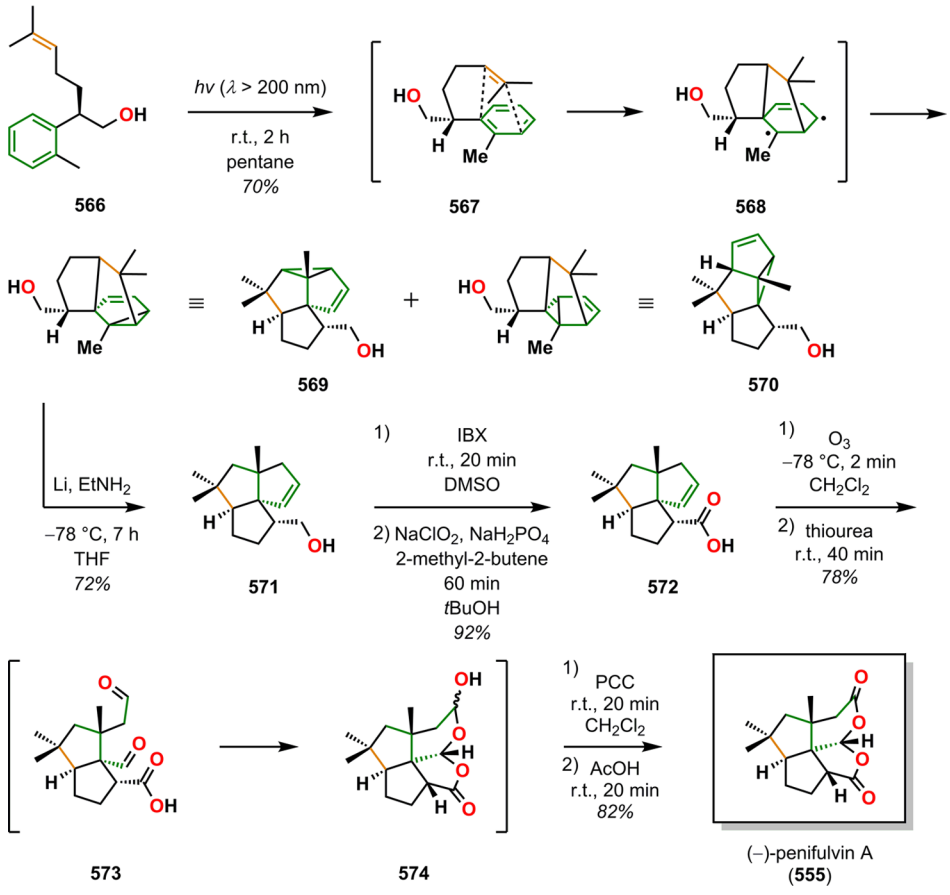
Scheme 101. Synthesis of Enantiomerically Enriched Alcohol 566 Using Pseudoephedrine as a Chiral Auxiliary[a]



[a]DIC = diisopropylcarbodiimide. DMAP = 4-dimethylaminopyridine. LDA = lithium diisopropylamide.

Scheme 102. Use of the Arene Olefin Meta-Photocycloaddition in the Total Synthesis of (−)-Penifulvin A (555)[a]



[a]IBX = 2-iodoxybenzoic acid. PCC = pyridinium chlorochromate.

(±)-hirsutene (**222**),[482] (±)-isoiridomyrmecin (**586**),[483] (±)-modhephene (**65**),[484] (±)-silphiperfol-6-ene (**588**),[485] subergorgic acid (**590**),[486] and crinipellin B (**592**).[487]

8. VISIBLE-LIGHT PHOTOREDOX CATALYSIS—SINGLE-ELECTRON TRANSFER APPROACHES IN NATURAL PRODUCT SYNTHESIS

A central theme in photoinduced reactions is the excitation of an electron from an occupied molecular orbital to an antibonding orbital to generate a neutral $\pi-\pi^*$ excited state. A fundamentally different approach would be to use photosensitizer compounds for activation of organic compounds. Upon absorption of visible light, these photosensitizers form excited states that can function both as powerful oxidants and reductants, which would allow for the generation of radical cations or radical anions under remarkably mild reaction conditions.[488] Photoredox catalysis offers selective excitation of the organic compound, avoiding excitation of the whole organic network and decomposition, as can be the case with UV-light excitation. Visible-light photoredox catalysis is a rapidly emerging field that offers an attractive alternative to conventional methods of producing radical ion intermediates that are capable of engaging in a multitude of different pathways. This powerful method has enabled the development of novel reaction schemes and approaches for the controlled engineering of structurally complex and diverse

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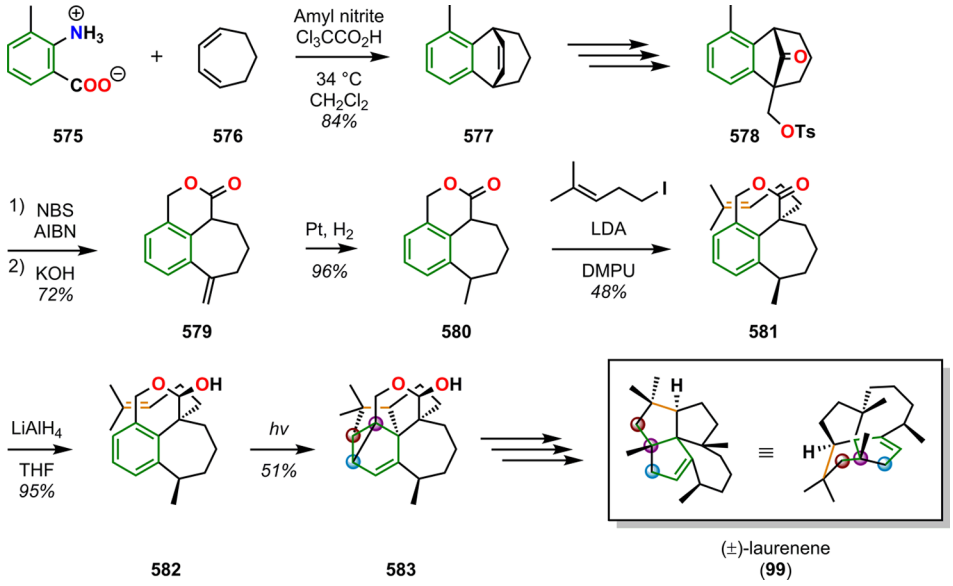
Scheme 103. Total Synthesis of (±)-Laurenene (99)[a]



[a]AIBN = azobis(isobutyronitrile). DMPU = *N,N′*-dimethylpropyleneurea. LDA = lithium diisopropylamide. NBS = *N*-bromosuccinimide.

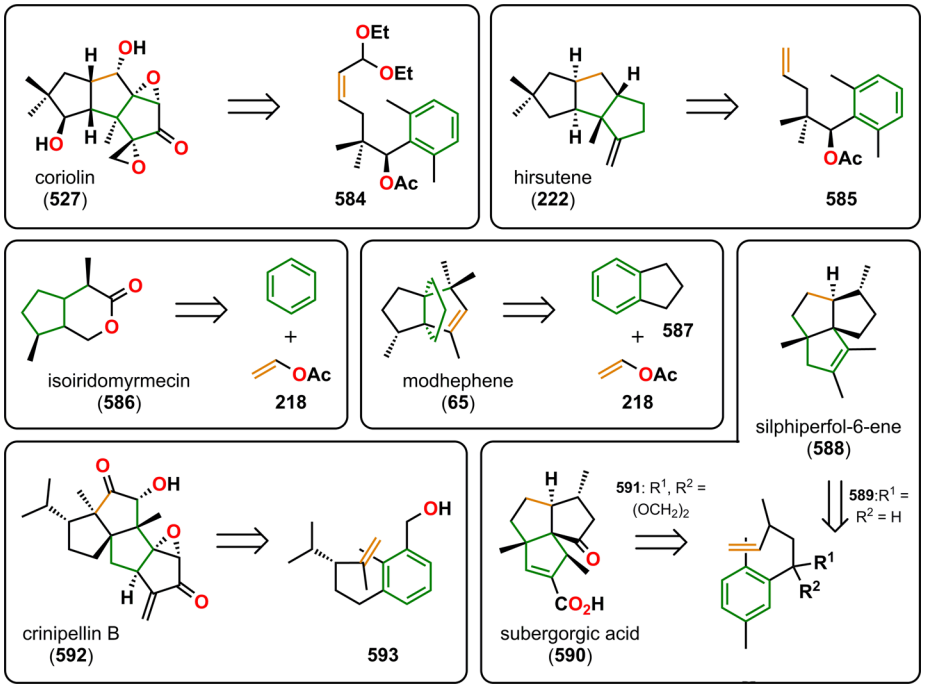


Figure 31. Representative examples of natural products accessed by the meta-photocycloaddition reaction.

frameworks through single-electron transfer (SET) reactions. In particular, transition-metal polypyridyl complexes based on Ru and Ir have proven to afford unique chemical reactivities when excited by visible light (Figure 32). These photocatalysts are chemically robust, afford long-lived excited state lifetimes, and possess favorable redox properties that can be conveniently fine-tuned by modifying the polypyridyl ancillary ligands (Figure 33).[489−493] These properties allow overall redox-neutral reactions to be carried out as both reductants and oxidants that can be transiently generated during different stages in the catalytic process. This reactivity pattern is beneficial since it might allow for the exploration of alternative pathways under benign reaction conditions.[494−504]

A variety of cyclobutane-containing natural products have been accessed via photoinduced SET. The use of visible-light photoredox catalysis can, for example, be found in the synthesis of magnosalin (**599**, Scheme 104),[505] *ent*-sceptrin (**606**, Scheme 105),[506] (±)-epiraikovenal (**614**, Scheme 106),[507] and (±)-cannabiorcicyclolic acid (**619**, Scheme 107).[508] The synthesis of γ-butyrolactones from simple alkenes and unsaturated acids via polar radical crossover cycloaddition (PRCC) reactions was recently reported by Nicewicz and co-workers.[509] The mechanism was proposed to involve single-electron oxidation of the alkene (**621**) by the excited acridinium photocatalyst (**620**$^{+*}$), which produces an electrophilic alkene cation radical (**622**). The carboxylic acid (**623**) can subsequently add to the

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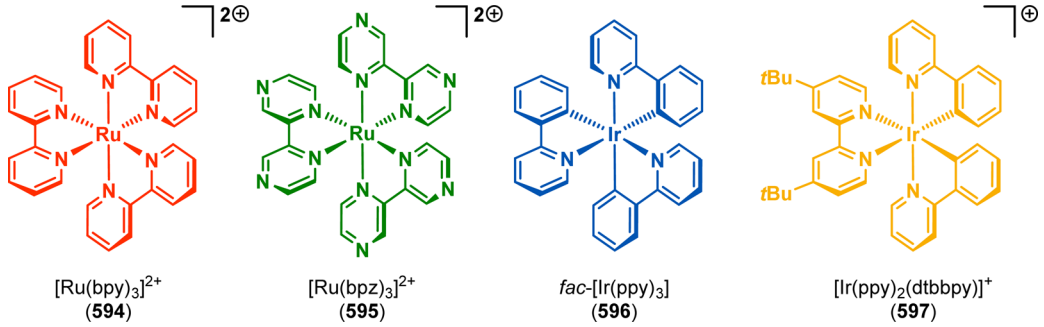


Figure 32. Examples of Ru- and Ir-based photosensitizers (bpy = 2,2′-bipyridine, bpz = 2,2′-bipyrazine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridine).

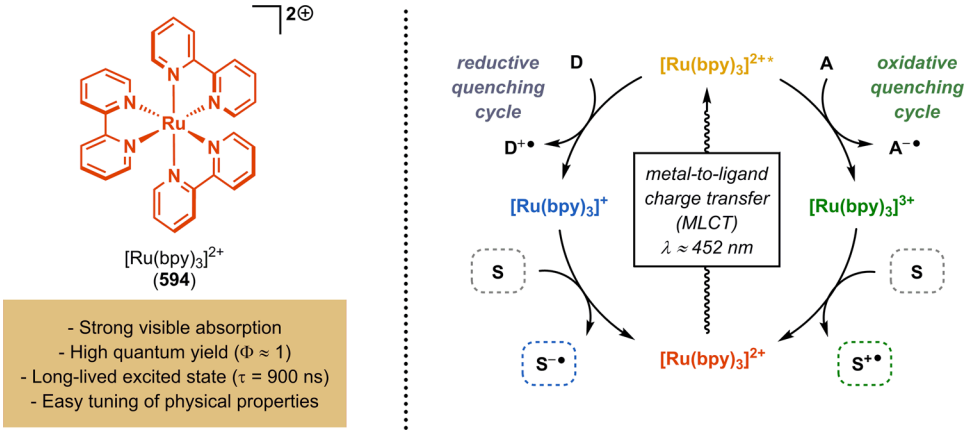
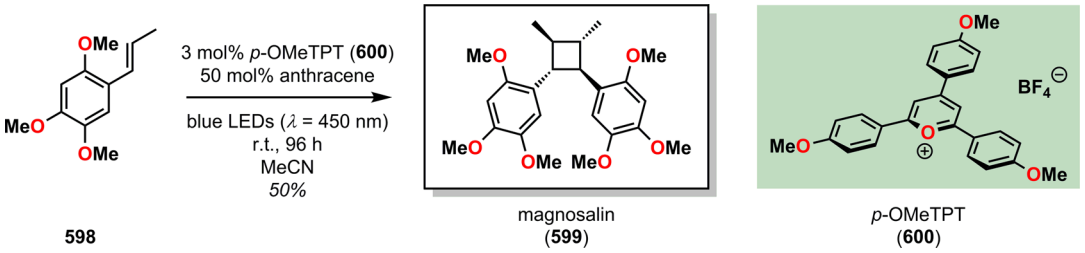


Figure 33. Properties of the $[Ru(bpy)_3]^{2+}$ photocatalyst (**594**) (bpy = 2,2′-bipyridine, MLCT = metal-to-ligand charge transfer, A = sacrificial electron acceptor, D = sacrificial electron donor, S = substrate).

Scheme 104. Synthesis of Magnosalin (599) via Photoinduced Electron Transfer[a]



[a] *p*-OMeTPT = 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate.

generated radical cation **622** to furnish radical **624**, which undergoes 5-*exo*-trig radical cyclization to give **625**. Hydrogen atom transfer (HAT) to radical **625** produces the desired γ-butyrolactone (**626**) and completes the catalytic cycle (Scheme 108, top). The authors subsequently applied the PRCC method to the synthesis of protolichesterinic acid (**630**). Irradiation of styrene **627** and β-haloacrylic acid (**628**) in the presence of 2.5 mol% of acridinium photocatalyst **620**(BF_4) and substoichiometric quantities (25 mol%) of the redox-active cocatalyst PhSSPh afforded lactone **629** in 69% yield, which upon treatment with $RuCl_3/NaIO_4$ followed by K_2CO_3 produced protolichesterinic acid (**630**) as a single isomer in 54% yield (Scheme 108, bottom).

The use of two electron-rich components in Diels–Alder cycloadditions typically requires harsher reaction conditions and prolonged reaction times as a result of the electronic mismatching. In contrast, radical cations generated from electron-rich olefins have been documented to react rapidly with electron-rich dienes in [4 + 2] cycloadditions, and the reactions typically occur with high chemo-, stereo-, and regioselectivity with rates that can be several orders of magnitude higher than the corresponding thermal process with the neutral species.[510−513] The essential radical cations are usually produced using high loadings of one-electron oxidants, such as aminium salts,[514] or photoinitiated electron transfer initiated by an organic photosensitizer.[515]

The Yoon group utilized visible-light photocatalysis as a means for the efficient generation of the vital radical cations.[516−518] This allowed for an operationally simple protocol for radical cation Diels–Alder cycloadditions that employed low loadings (0.5 mol%) of $[Ru(bpz)_3]^{2+}$ (**595**[519]) as photosensitizer.[516] Given the broad scope of this reaction, the authors became interested in heitziamide A (**635**), a natural product isolated as a racemate from the medicinal shrub *Fagara heitzii*.[520] Irradiation of styrene **631** and myrcene (**632**) in the presence of 2 mol% $[Ru(bpz)_3]^{2+}$

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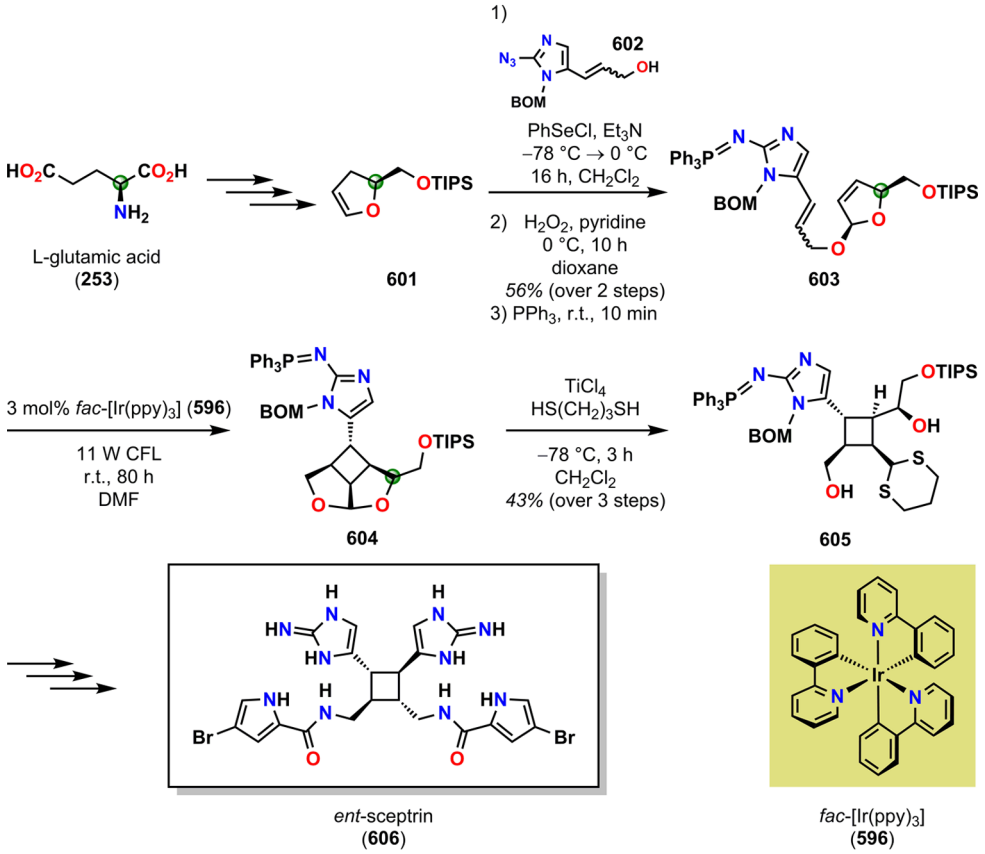
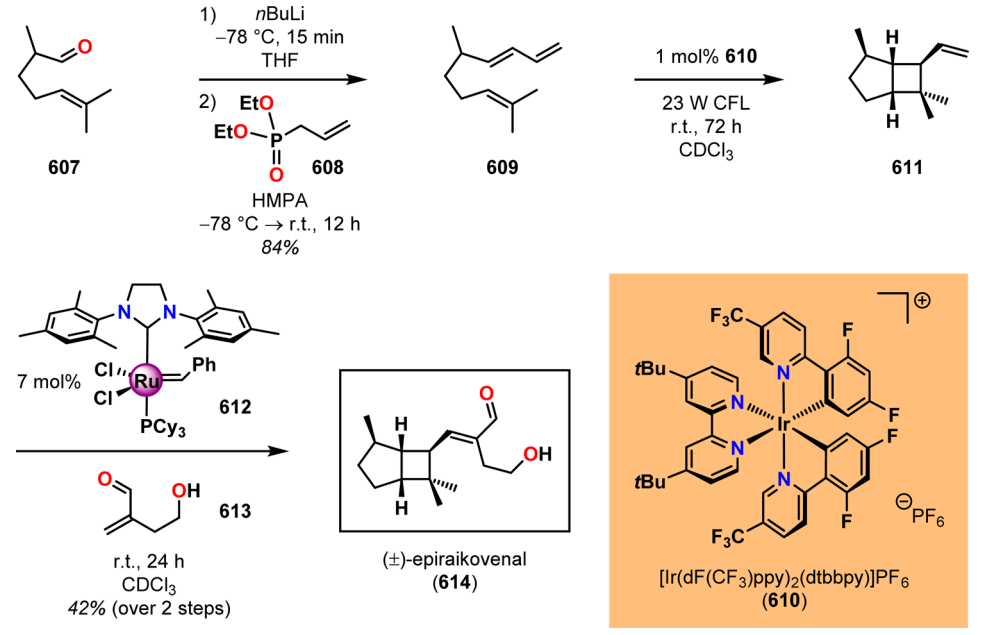
Scheme 105. Visible-Light Photoredox Catalysis in the Synthesis of *ent*-Sceptrin (606)[a]



[a]BOM = benzyloxymethyl. TIPS = triisopropylsilyl. ppy = 2-phenylpyridine. *fac* = facial.

Scheme 106. Visible-Light-Promoted [2 + 2] Cycloaddition of 1,3-Diene 609 in the Synthesis of (±)-Epiraikovenal (614)[a]



[a]dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine. dtbbpy = 4,4′-di-tert-butyl-2,2′-bipyridine. HMPA = hexamethylphosphoric triamide.

(**595**) produced [4 + 2] adduct **633** in 80% yield. This process can be best described as an umpolung process that reverses the intrinsic electronic character of the electron-rich olefin, thus producing the cycloadduct with the natural regiochemistry of heitziamide A (**635**). As a comparison, the thermal Diels−Alder reaction furnished the unnatural isomeric cycloadduct without

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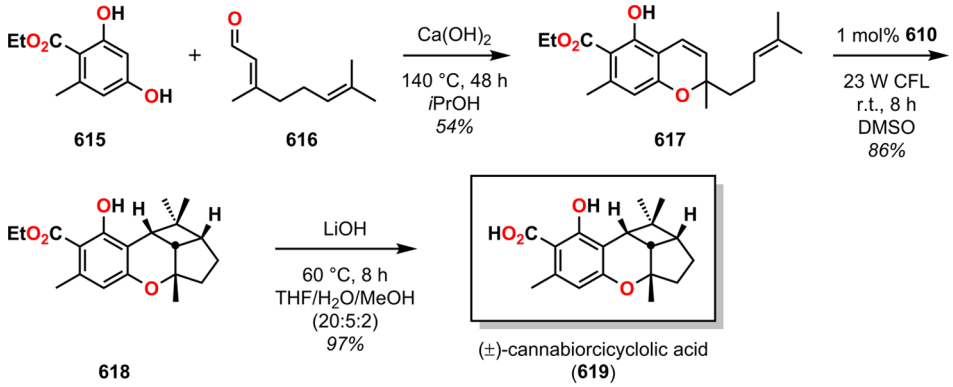
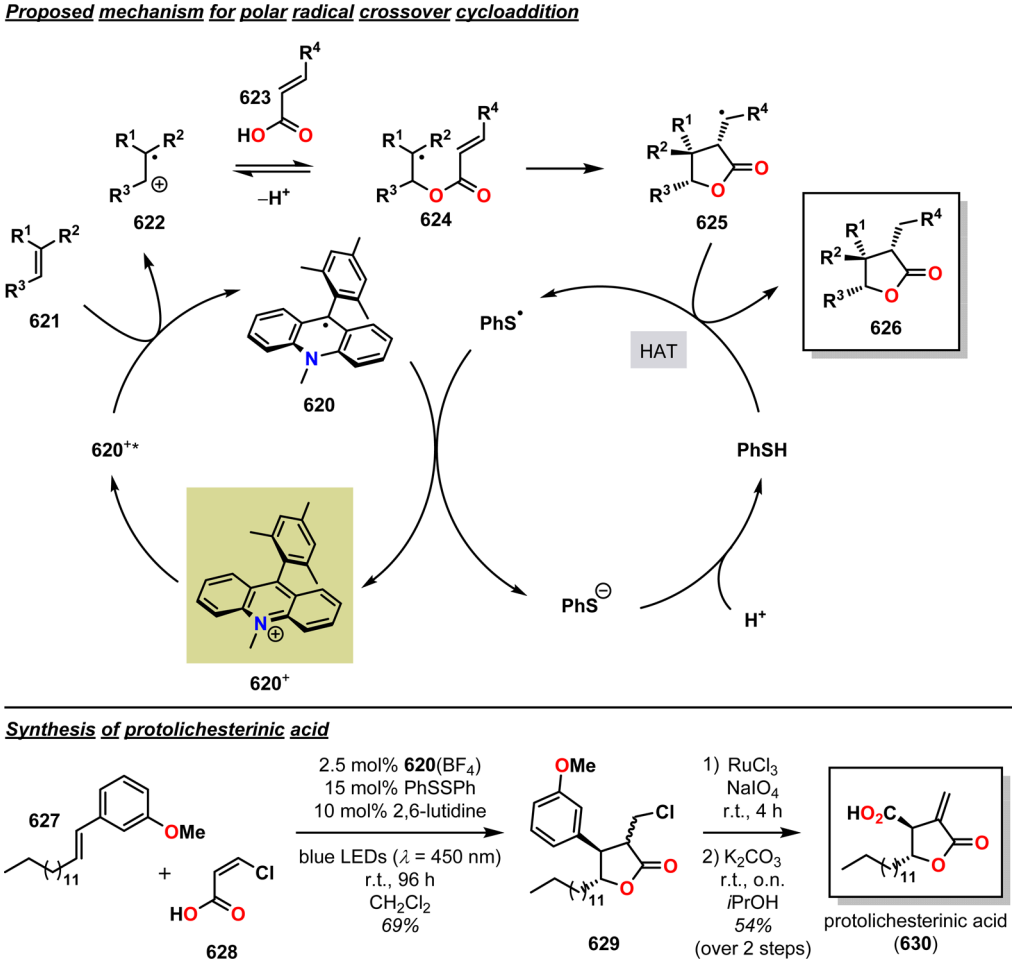
Scheme 107. Visible-Light-Sensitized [2 + 2] Cycloaddition of Olefin 617 in the Synthesis of (±)-Cannabiorcicyclolic Acid (619)[a]



[a]CFL = compact fluorescent light.

Scheme 108. (Top) Proposed Mechanism for Polar Radical Crossover Cycloaddition (PRCC) of Alkenes and Unsaturated Acids and (Bottom) Its Application in the Synthesis of Protolichesterinic Acid (630)[a]



[a]HAT = hydrogen atom transfer.

any trace of **633**. Deprotection of the TBS protecting group and subsequent oxidation afforded carboxylic acid **634**, which could be converted to heitziamide A (**635**) by EDC coupling with isobutylamine (Scheme 109).

Given the high oxidation potential of the $[Ru(bpz)_3]^{2+}$ photosensitizer (1.4 V vs SCE), the visible-light-mediated radical cation Diels–Alder reaction is believed to proceed via reductive quenching of the excited state of the photosensitizer $\{[Ru(bpz)_3]^{2+\bullet}\}$ by the electron-rich olefin moiety **631**. This results in a radical cation (**631**$^{+\bullet}$) that undergoes the [4 + 2] cycloaddition to generate a radical cycloadduct, which can either be reduced by the reduced photosensitizer $\{[Ru(bpz)_3]^{+}\}$ or abstract an electron from another olefin molecule to initiate radical chain processes.[503,516,521] A related radical cation Diels–Alder approach has also been utilized in the synthesis of (±)-kingianic acid E (**639**) (Scheme 110).[522]

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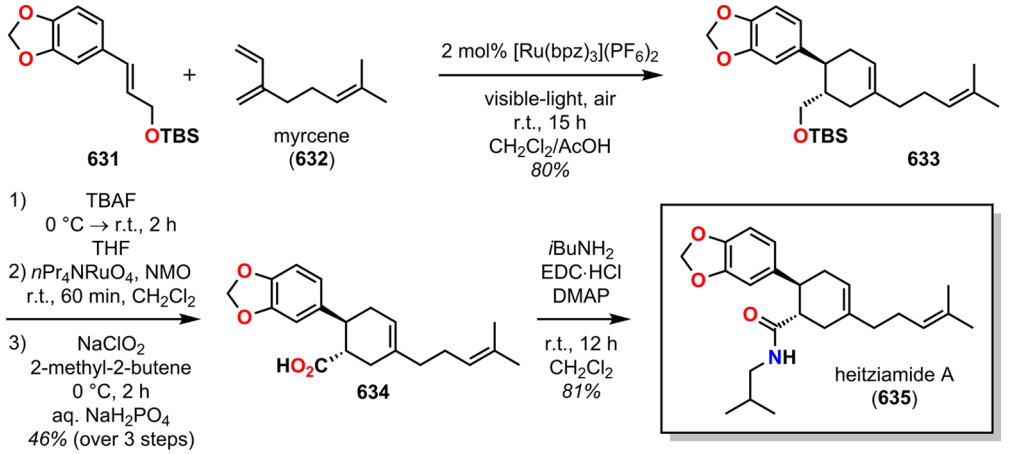
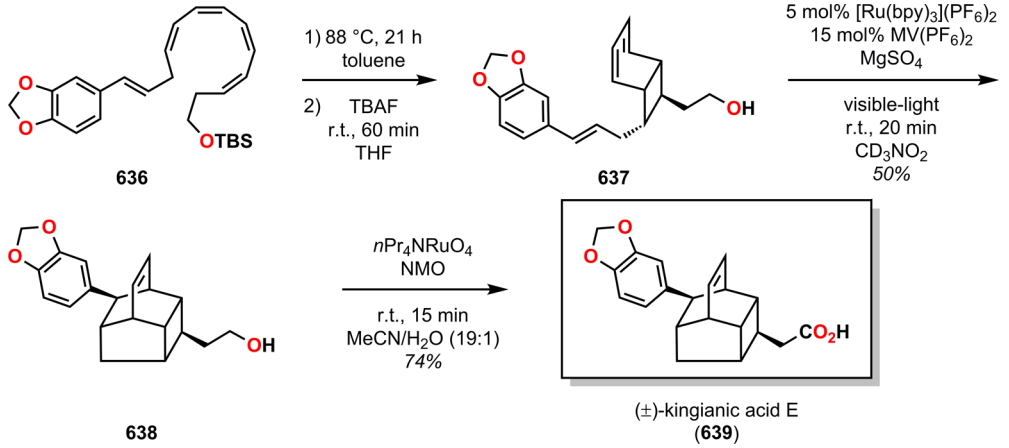
Scheme 109. Visible-Light Photocatalytic Radical Cation Diels–Alder Cycloaddition in the Synthesis of Heitziamide A (635)[a]



[a]EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. TBAF = tetra-*n*-butylammonium fluoride. TBS = *tert*-butyldimethylsilyl. NMO = *N*-methylmorpholine N-oxide. bpz = 2,2′-bipyrazine. DMAP = 4-dimethylaminopyridine.

Scheme 110. Synthesis of (±)-Kingianic Acid (639) via a Radical Cation Diels–Alder Approach[a]



[a]NMO = *N*-methylmorpholine *N*-oxide. TBAF = tetra-*n*-butylammonium fluoride. bpy = 2,2′-bipyridine. MV = methyl viologen.

Aplyviolene (**646**) belongs to a class of spongian diterpene natural products and contains a *cis*-perhydroazulene unit.[523−525] For aplyviolene (**646**), formation of the bicyclic lactone subunit and the C8−C14 bond has been recognized as particularly challenging. In Schnermann and Overman's synthesis of (−)-aplyviolene (**646**), the key step involved a photoredox-mediated fragmentation strategy, which allowed construction of the crucial C8−C14 bond.[526] The synthesis commenced with (+)-fenchone (**640**), which was converted to *N*-(acyloxy)-phthalimide **641**. Irradiation of cyclopentenone **642** and *N*-(acyloxy)phthalimide **641** in the presence of 1 mol% $[Ru(bpy)_3]^{2+}$ (**594**), Hantsch ester **643**, and DIPEA efficiently provided the coupled product **644** in 61% yield with <5% of the reductively dechlorinated analogue. Reductive enol silylation of coupled product **644** using $Me_2CuCNLi_2$ in the presence of TBS-Cl at −20 °C delivered the tricyclic enol ether **645**, which had previously been converted to (−)-aplyviolene (**646**) (Scheme 111). The use of the photoredox-mediated fragmentation strategy thus allowed the construction of the C8−C14 bond and highlights the utility of using photoredox catalysis for generation of tertiary carbon radicals in the construction of quaternary stereocenters in a stereoselective fashion. A related strategy was also employed by Overman and co-workers in the synthesis of *trans*-clerodane natural products.[527]

Pyrroloindoline alkaloids are a class of natural products that are formally derived from two molecules of tryptophan and have been shown to exhibit a broad range of biological activities. As a result of their structural complexity and broad biological activity, pyrroloindoline alkaloids have attracted attention from several research groups.[528−530] In the synthesis of (+)-gliocladin C (**652**), Stephenson and co-workers utilized a photoredox-mediated indole coupling reaction as the key step to access the C3−C3′ bisindole motif. Irradiation of bromopyrrolindoline **648**, derived from Boc-D-tryptophan methyl ester (**647**), and aldehyde **649** using 1 mol% $[Ru(bpy)_3]Cl_2$ and Bu_3N as reductive quencher successfully provided the C3−C3′ coupling product **650** in 82% yield. Subsequent decarbonylation of the aldehyde at the C2′ position using a combination of $Rh(CO)(PPh_3)_3Cl$, dppp, and DPPA in xylenes afforded the decarbonylated product **651** in 85% yield, which could be further advanced to (+)-gliocladin C (**652**) in merely 10 steps from Boc-D-tryptophan methyl ester (**647**) and in 30% overall yield (Scheme 112).[531]

Beatty and Stephenson identified (+)-catharanthine (**653**) as an entry point for the synthesis of a number of structurally related

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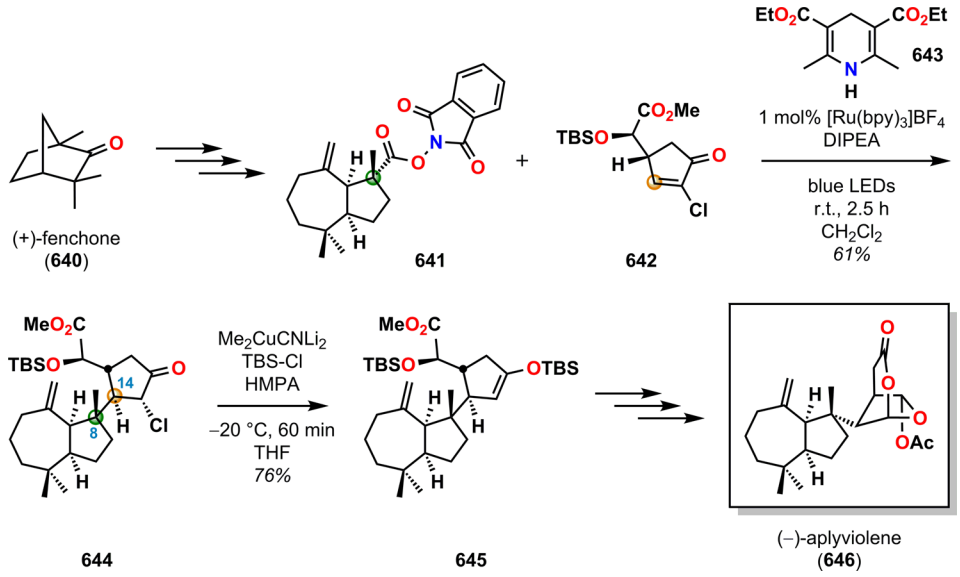
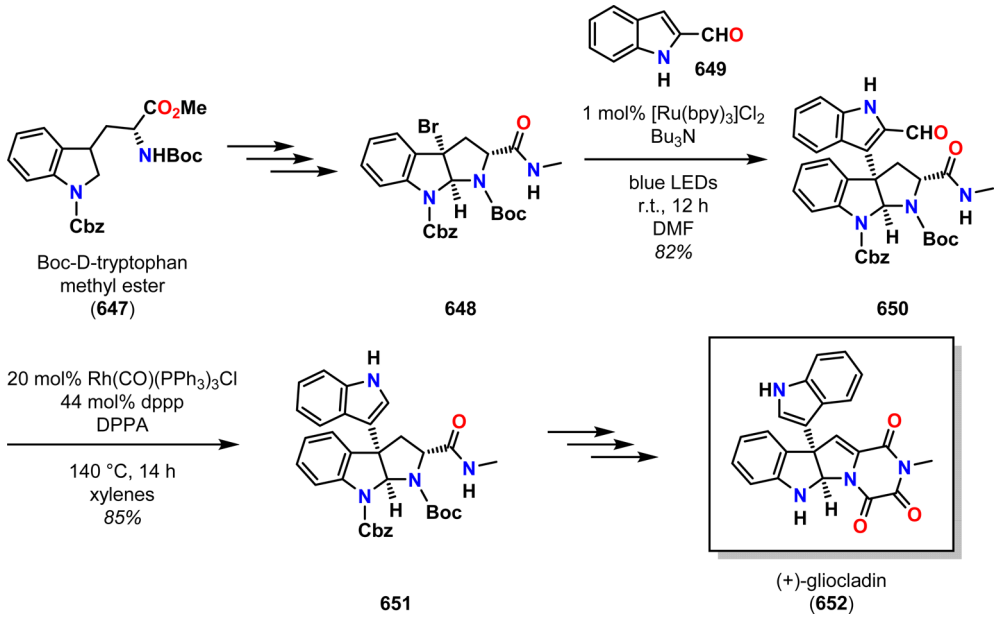
Scheme 111. Photoredox-Mediated Tertiary Radical Generation in the Synthesis of (−)-Aplyviolene (646)[a]



[a]DIPEA = diisopropylethylamine. TBS = *tert*-butyldimethylsilyl. HMPA = hexamethylphosphoric triamide. bpy = 2,2′-bipyridine.

Scheme 112. Photoredox-Enabled Synthesis of (+)-Gliocladin (652)[a]



[a]Boc = *tert*-butyloxycarbonyl. Cbz = carboxybenzyl. DPPA = diphenylphosphoryl azide. dppp = 1,3-bis(diphenylphosphino)propane. bpy = 2,2′-bipyridine.

alkaloids.[532] Catharanthine has been reported to undergo a unique fragmentation of its C16−C21 bond[533,534] and it was envisioned that such an oxidative fragmentation could be exploited to produce a common α-aminonitrile intermediate (**654**), which could subsequently be converted to a variety of analogous alkaloids. Visible-light irradiation of catharanthine (**653**) in the presence of the fluorinated photocatalyst **610** and TMSCN indeed produced an α-aminonitrile fragmentation product (**654**) in 93% yield. Performing the reaction in a photochemical flow reactor[535−540] allowed for improved scalability, decreased reaction time, and the controlled generation of HCN, affording intermediate **654** in 96% yield. Refluxing a MeOH solution containing α-aminonitrile intermediate **654** and 1 equiv. of trifluoroacetic acid for 3 h gave (−)-pseudotabersonine (**655**) as the only observed product in 90% yield. Hydrogenation of the aminonitrile fragmentation product **654** followed by reflux in the presence of 1 equiv. of trifluoroacetic acid was anticipated to produce (−)-pseudovincadifformine (**660**). However, this yielded the natural product (+)-coronaridine (**657**) as the sole product in 48% yield over two steps and represents the highest yielding preparation of coronaridine from catharanthine reported thus far. An alternative approach to (−)-pseudovincadifformine (**660**) was therefore investigated and involved initial hydrogenation over Pd/C, followed by $NaBH_4$ reduction to give **658**. Exposing amine **658** to oxidative photoredox conditions employing malonate **659** as the terminal oxidant

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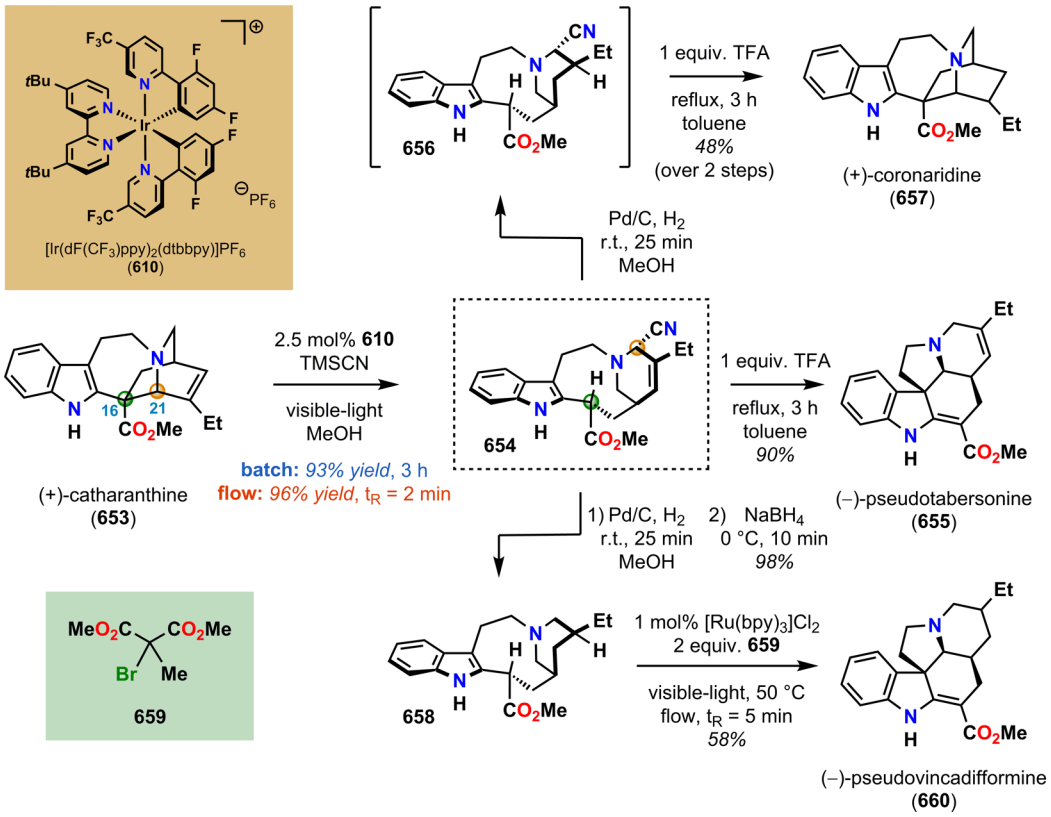
Scheme 113. Synthesis of Alkaloid Natural Products Enabled by Photoredox Catalysis in Flow[a]



[a]TFA = trifluoroacetic acid. dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine. dtbbpy = 4,4′-di-tert-butyl-2,2′-bipyridine. bpy = 2,2′-bipyridine. TMS = trimethylsilyl.

subsequently yielded (−)-pseudovincadifformine (**660**) in 58% yield (Scheme 113).[532] This work demonstrates the synthetic utility of photoredox catalysis in natural product synthesis and the rapid access to structurally related alkaloid motifs from a common advanced intermediate.

The examples described in this section highlight photoredox catalysis as a robust tool for the mild generation of radical species for potential access to a wide variety of complex molecular scaffolds, thus expanding the use of photochemistry en route to natural product targets.

9. CONCLUSIONS AND OUTLOOK

The purpose of this review has been to highlight some of the accomplishments that have been presented in natural product total synthesis using photochemistry. Photochemically mediated reactions have proven to be highly useful for construction of highly strained and complex molecular frameworks that can otherwise be challenging to access via conventional, thermal processes. However, the use of specialized equipment for performing these photochemical reactions could serve as a significant impediment for possible practitioners looking to implement these techniques. Although this may impede the advancement of photochemical transformations, continued triumphs in the total synthesis of natural products and biologically active compounds, along with further mechanistic studies to elucidate the general chemical reactivity of the electronically generated excited intermediates, will continue to inspire the development and application of photochemistry in organic synthesis.

The recent emergence of photoredox catalysis as a means to generate radical species in a controlled and mild fashion has further increased the ability of accessing complex molecular scaffolds. It is believed that such controlled redox manipulations will allow for chemoselective access to a wide array of novel structural motifs. Another important direction in modern photochemistry is its application to continuous flow processing. Compared to normal batch reactors, carrying out photochemical reactions in flow reactors can greatly improve the yields and selectivities due to the avoidance of unproductive reaction pathways.

On the whole, photochemistry serves as a useful tool for mastering new and environmentally benign transformations. In the future, it can also be used to expand our classical chemical toolbox by offering improved reaction conditions and can facilitate the discovery of new transformations for efficient bond construction. Thus, in combination with flow chemistry and other advanced techniques, photochemistry will continue to serve as an attractive option for accessing intricate chemotypes of biological and medicinal importance.

AUTHOR INFORMATION

Corresponding Authors

*J.A.P. e-mail: porco@bu.edu.
*C.R.J.S. e-mail: crjsteph@umich.edu.

Notes

The authors declare no competing financial interest.

Biographies

Markus D. Kärkäs obtained his Ph.D. degree in 2013 from Stockholm University, under the supervision of Prof. Björn Åkermark. His research

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focused on the development and mechanistic insight of artificial water oxidation catalysts. After completing his Ph.D. studies he continued to work as a researcher in the group of Prof. Åkermark and was involved in studying and developing homogeneous as well as heterogeneous water oxidation catalysts. He is currently a Swedish Research Council (Vetenskapsrådet) postdoctoral fellow in the research group of Prof. Corey Stephenson at the University of Michigan, where his research is directed toward the development of novel synthetic transformations involving visible-light photoredox catalysis.

John A. Porco, Jr. received his Ph.D. degree in 1992 from Harvard University under the direction of Prof. Stuart Schreiber. He did postdoctoral studies with Chi-Huey Wong at the Scripps Research Institute. After a period in industry, John joined the Department of Chemistry at Boston University in 1999 as assistant professor and was promoted to professor of chemistry in September 2004. From 2002 to 2013 he was director of the NIH-funded Center for Chemical Methodology and Library Development (CMLD-BU) and since 2013 has directed the BU Center for Molecular Discovery (BU-CMD). His research is focused in two major areas: the development of new synthetic methodologies for efficient chemical synthesis of complex molecules and the synthesis of complex chemical libraries.

Corey R. J. Stephenson received an Honours B.Sc. degree in 1998 from the University of Waterloo and a Ph.D. degree in 2005 from the University of Pittsburgh, where he worked under the direction of Prof. Peter Wipf. After carrying out postdoctoral research in the laboratory of Prof. Erick M. Carreira at ETH Zürich, Switzerland, he joined the Department of Chemistry at Boston University in 2007 as assistant professor and co-principal investigator in the Center for Chemical Methodology and Library Development (CMLD-BU). He was granted tenure and promoted to associate professor in February 2013. In July 2013, he joined the Department of Chemistry at the University of Michigan, Ann Arbor, as an associate professor and was promoted to professor in September 2015. His research interests include photoredox catalysis, natural product synthesis, and continuous flow chemistry.

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ABBREVIATIONS USED

AIBN	azobis(isobutyronitrile)
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
Bpin	(pinacolato)boron
bpy	2,2′-bipyridine
bpz	2,2′-bipyrazine
BTB	2,6-bis(trifluoromethyl)benzyl
Cbz	carboxybenzyl
m-CPBA	*m*-chloroperoxybenzoic acid
CFL	compact fluorescent light
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dF(CF_3)ppy	2-(2,4-difluorophenyl)-5-trifluoromethylpyridine
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMPU	*N*,*N*′-dimethylpropyleneurea
DMS	dimethyl sulfide
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
dtbbpy	4,4′-di-*tert*-butyl-2,2′-bipyridine
EDC	1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide
fac	facial
FDA	Food and Drug Administration
HAT	hydrogen atom transfer
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoric triamide
IBX	2-iodoxybenzoic acid
ISC	intersystem crossing
LDA	lithium diisopropylamide
LDBB	lithium 4,4′-di-*tert*-butylbiphenylide
p-MBOH	*p*-methoxybenzyl alcohol
MLCT	metal-to-ligand charge transfer
MOM	methoxymethyl
MoOPH	(hexamethylphosphoric triamide)oxodiperoxy-(pyridine)molybdenum(VI) (MoO_5·pyr·HMPA)
MV	methyl viologen
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
ppy	2-phenylpyridine
PRCC	polar radical crossover cycloaddition
SCE	saturated calomel electrode
SDS	sodium dodecyl sulfate
SEM	2-(trimethylsilyl)ethoxymethyl
SET	single-electron transfer
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
p-OMeTPT	2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate
p-TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluenesulfonic acid

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