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Photocycloaddition in Natural Product Synthesis

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Dedicated to William Motherwell on the occasion of his 60th birthday

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The application of photocycloaddition to natural product synthesis continues to produce innovative and effective strategies for key bond constructions in the complex molecule environment. This Microreview surveys the recent literature for examples that illustrate the power and versatility of photocycloaddition chemistry, drawing from [2+2], [3+2], [4+2], [5+2] and [4+4] reactions. The discussion is confined to natural product syntheses, and will include photocycloaddition key steps in both completed routes and those in progress.

1. Introduction

The photocycloaddition reaction, first observed almost one hundred years ago in classical work by Ciamician and Paternò,[1–3] is now an integral part of modern synthetic methodology. The reaction class is broad, encompassing the synthesis of three- to eight-membered rings in its common implementation and offering tremendous scope for stereocontrol and substrate range. Most importantly, photocycloadditions enable the synthesis of ring systems that are highly strained and/or contain substantial steric hindrance, both features that can be very difficult to access by alternative methods.

Nowhere has the power of photocycloaddition chemistry been better exemplified than in natural product synthesis. Indeed, the requirement for stereoselective C–C bond formation in highly hindered environments is often the defining challenge of the field. As a consequence, it is common to find photocycloadditions used as the key step in a natural product synthesis, e.g. for the construction of a quaternary stereocentre or the installation of a medium ring by tandem cycloaddition/fragmentation. This Microreview will present examples of such key-step photocycloadditions in

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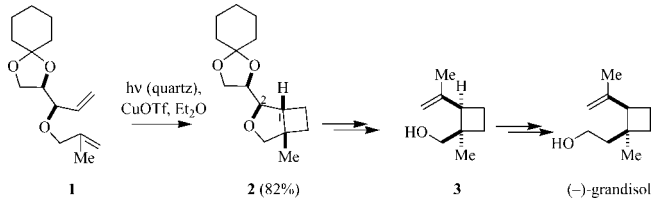
Michael Greaney was born in Liverpool in 1973. He took his undergraduate degree at Oxford, completing his part II research project in the group of Sir Jack Baldwin in 1996. He then moved to London to carry out PhD work with William Motherwell at UCL, completing his thesis on novel fluorinating agents in 1999. He then left the UK on a GlaxoWellcome scholarship to take up a postdoctoral position with Jeffrey Winkler at the University of Pennsylvania, where he worked on the total synthesis of the tumour-promoting diterpene ingenol. He returned to the UK in early 2002, where he is now a lecturer in chemistry at the University of Edinburgh. There, his research interests include the development of novel photocycloadditions as the key steps in natural product syntheses.

natural product synthesis from the recent literature (2000–2006), choosing from the canonical [2+2], [3+2], [4+2], [5+2] and [4+4] reactions. The arene *meta*-photocycloaddition, used to great effect in natural product synthesis, has been the focus of two excellent recent reviews and will not be covered here.[4,5] Extensive review articles and book chapters exist for photocycloaddition chemistry, and the reader is directed to the bibliography for background reading on theory and mechanism.[6–19]

2. [2+2] Photocycloaddition

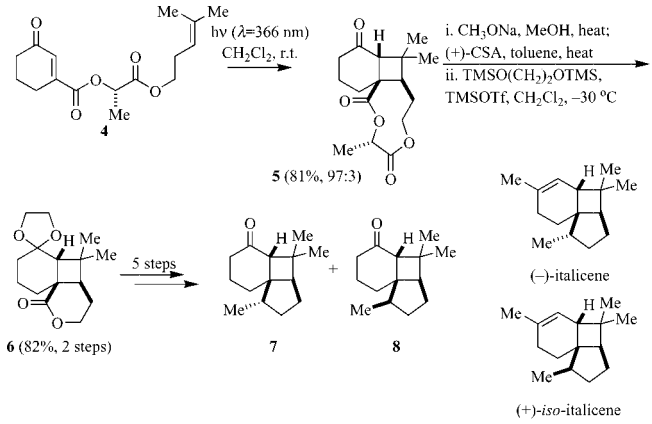
2.1. Cyclobutane-Containing Natural Products

The cyclobutane ring system is found in numerous natural products, and it is therefore not surprising that the photocycloaddition of two alkenes has been widely employed to access such targets. The naturally occurring cyclobutane monoterpene grandisol, an important component in the sexual attracting pheromone of the cotton boll weevil has attracted considerable interest in this regard.[20–29] Ghosh and co-workers' approach towards both enantiomers of grandisol relies on chirality transfer at C2 from the readily available diene **1** to yield the *cis*-1,2-disubstituted cyclobutane **2** (Scheme 1).[30] Irradiation of an ether solution of the diene **1** in the presence of 20–25 mol-% of copper(I) trifluoromethanesulfonate occurred efficiently to furnish **2** in 82% yield. Subsequent anionic fragmentation of the tetrahydrofuran ring provided access to the chiral cyclobutane **3**, a known intermediate in Meyer's synthesis of (–)-grandisol.[26] The approach contrasts with the use of asymmetric catalysis or chiral auxiliaries in the Cu^{I}-catalysed photocycloaddition of non-conjugated alkenes, strategies that have been found to produce low selectivities in previous grandisol syntheses.[29]



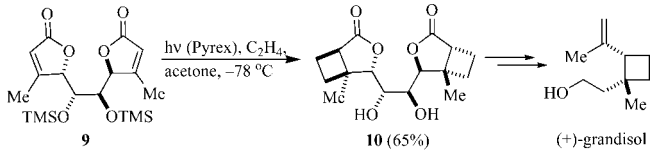
Scheme 1. Alkene–alkene [2+2] photocycloaddition en route to (–)-grandisol.

Asymmetric versions of the [2+2] photocycloaddition using removable chiral auxiliaries for the photocycloaddition between alkenes and enones have, on the other hand, been reported to be highly successful. The construction of the tricyclo[5.4.0.0^{2,5}]undecane skeleton present in (–)-italicene and (+)-isoitalicene involved a [2+2] photocycloaddition as the key step (Scheme 2).[31] The approach made use of (*S*)-lactic acid as a chiral removable tether group, which determined the excellent facial selectivity achieved in the key photoaddition step. Irradiation of oxo ester **4** led to the formation of the straight photoadduct **5** in a very good 81% yield with excellent stereoselectivity (97:3 in favour of the desired diastereoisomer). Removal of the chiral tether group was achieved upon treating **5** with sodium methoxide followed by acid-promoted lactonisation to afford **6**. A further five steps furnished **7** and **8**, potential precursors of (–)-italicene and (+)-isoitalicene, respectively.



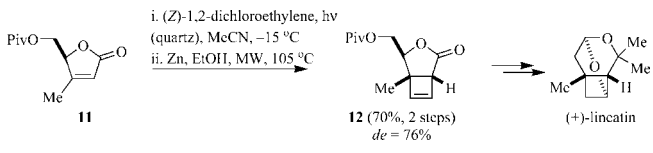
Scheme 2. Tethered [2+2] approach to (–)-italicene and (+)-isoitalicene.

Font and co-workers' investigations[32–34] toward the construction of the cyclobutane ring of grandisol led to improved facial diastereoselectivities in the crucial [2+2] photocycloaddition step using the bis(α,β-butenolide) **9** (available from D-mannitol) as substrate (Scheme 3).[35]



Scheme 3. Synthesis of (+)-grandisol by a C_2-symmetric photosubstrate.

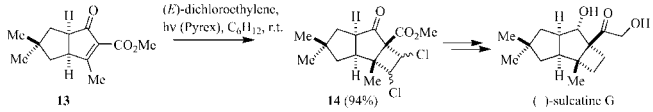
General features of the highly diastereofacial discrimination during the cycloaddition process include the C_2 symmetry of the substrate, which considerably improves the asymmetric induction, and the appropriate protection of the central diol unit. Derivative **9** bearing the bis(trimethylsilyl) protecting group proved to be the most effective substrate exhibiting complete *anti*-facial selectivity. A similar strategy was applied by Font and co-workers to the synthesis of (+)-lineatin (Scheme 4).[36] Photocycloaddition reaction of the 2(5*H*)-furanone **11** with dichloroethylene proceeded with high facial discrimination (9:1), affording the desired diastereomer **12** in 70% yield following reductive elimination of chlorine.



Scheme 4. Intermolecular [2+2] synthesis of lineatin.

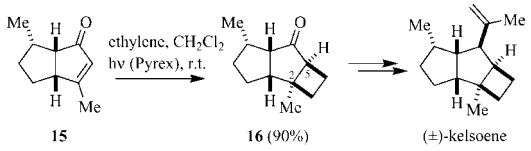
Highly selective intermolecular alkene-enone photocycloaddition constitutes the basis of Mehta and co-workers' novel route towards the synthesis of various terpenoid natu-

ral products bearing the novel tricyclo[6.2.0.0^{2,6}]decane core.[37–39] Photocycloaddition of (*E*)-1,2-dichloroethylene to the diquinane precursor generally occurs from the *exo* face furnishing the desired *cis,anti,cis*-fused 4–5–5 tricyclic motif. Scheme 5 shows the key [2+2] photocycloaddition step in their route towards (–)-sulcatine G.[40] Irradiation of ketone **13** afforded the tricycle **14** in 95% yield, which contains the complete carbon skeleton of the natural product.



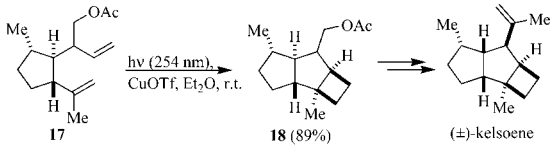
Scheme 5. Alkene-enone [2+2] for the synthesis of (–)-sulcatine G.

Piers and Orellana's approach towards (±)-kelsoene also relies on a [2+2] photocycloaddition of an alkene to a bicyclic enone.[41] The C2 and C5 quaternary centres are installed with excellent stereoselectivity resulting from a selective approach of the alkene from the sterically less hindered face of **15** (Scheme 6).



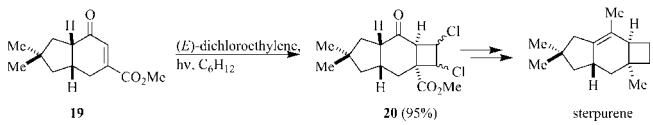
Scheme 6. Pier's intermolecular [2+2] approach to racemic kelsoene.

Bach and co-workers' have presented an alternative approach to racemic kelsoene using a stereoselective Cu^{I}-catalysed intramolecular [2+2] photocycloaddition reaction of two alkenes.[42] Irradiation of compound **17** in the presence of CuOTf afforded the tricycle **18** in 89% yield and with high diastereoselectivity. The required *cis-anti-cis* relative configuration present in kelsoene was achieved by a subsequent elimination/hydrogenation sequence (Scheme 7).



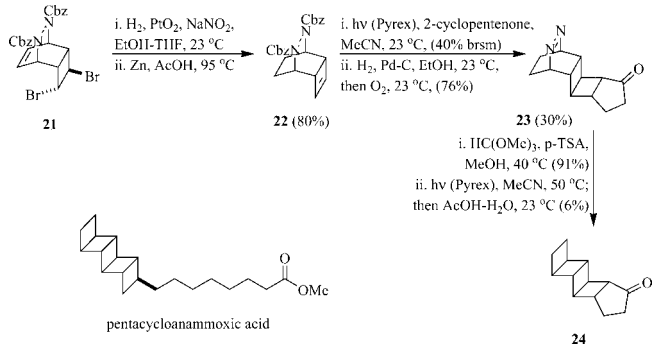
Scheme 7. Bach's intramolecular [2+2] approach to racemic kelsoene.

Mehta and co-workers' approach towards racemic sterpurene illustrates the use of an electron-withdrawing β substituent on the α,β-unsaturated enone moiety to promote the intramolecular [2+2] photocycloaddition, an otherwise challenging transformation when *cis*-fused bicyclic unsaturated enones and olefins are used (Scheme 8).[43]



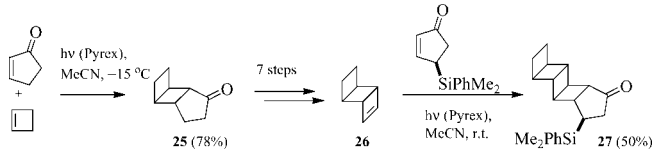
Scheme 8. [2+2] Approach to sterpurene.

Corey and Mascitti have described the first total synthesis of racemic pentacycloanammoxic acid, a 20-carbon fatty acid methyl ester containing the highly strained ladderane[44] pentacyclic motif (Scheme 9).[45] Starting from the tricyclic dibromide **21**, the synthesis of racemic target was completed in 14 steps featuring a number of key photochemical transformations. [2+2] Photocycloaddition between the tricycle **22** and 2-cyclopentenone afforded the pentacyclic azo ketone **23** with exclusive *exo* selectivity in moderate yield. Ketalisation preceded photochemical extrusion of N_2, which took place in a very low 6% yield, presumably owing to the high degree of angle strain in the pentacyclic product **24**.



Scheme 9. Synthesis of racemic pentacycloanammoxic acid.

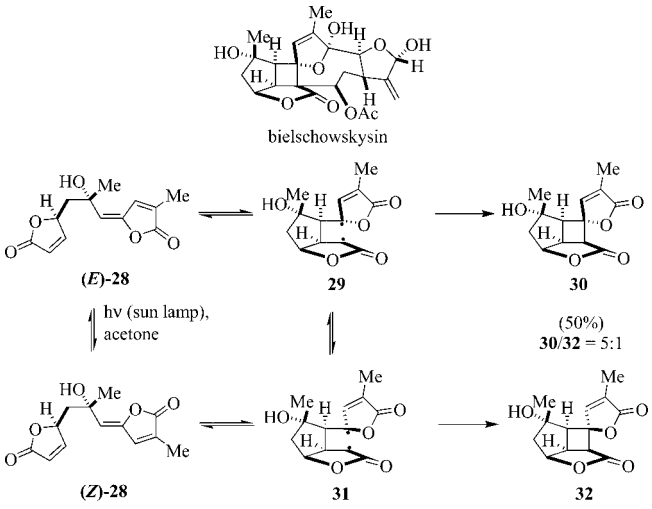
The problem of the inefficient photochemical extrusion step was circumvented through the development of an asymmetric route to pentacycloanammoxic acid (Scheme 10), again involving two key [2+2] photocycloadditions.[46] Step 1 features an *exo*-selective intermolecular alkene-enone [2+2] photocycloaddition, a reaction that is amenable to being carried out on a >30 g scale. Subsequently, the symmetric tricylic olefin **26** undergoes a similar *exo*-selective (7:1) photocycloaddition with a chiral cyclopentenone to form the advanced intermediate **27**, converted into the natural product in a further 11 steps.



Scheme 10. Asymmetric synthesis of pentacycloanammoxic acid.

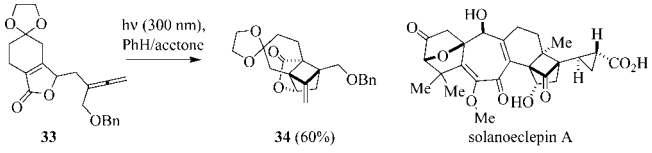
Sulikowski and co-workers identified the tetracyclic cyclobutane **30** as the key intermediate in their work toward the synthesis of bielschowskysin.[47] [2+2] Photocycloaddition of bis(lactone) **28** provides a concise and highly stereocontrolled synthesis of **30** (Scheme 11).

The key photocycloaddition step was dependant on the photosubstrate double-bond geometry and upon irradiation, compound **28** underwent an equilibration-cyclisation sequence affording a 5:1 mixture of [2+2] photoadducts in favour of the desired diastereomer **30**. The preference for the formation of **30** was explained by the development of an unfavourable dipole and/or electrostatic interaction in the alternative closure of the intermediate 1,4-biradical **31**.



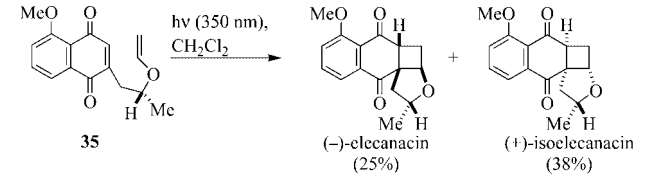
Scheme 11. Intramolecular enoate [2+2] approach to bielschowskyin.

An approach to the bicyclo[2.1.1]hexane substructure of solanoeclepin A features an unusual intramolecular [2+2] photocyclisation of an allene butenolide (Scheme 12).[48] The substrate **33**, designed on the basis of extensive model studies,[49–51] was irradiated to afford the cyclobutane photoadduct **34** as a single diastereomer in 60% yield. The substitution pattern of the pendant alkene dictates the regiochemical outcome of the photocycloaddition. In this particular case, the exclusive formation of the crossed adduct followed the so-called rule of five,[52,53] which explains the regiochemistry by the preferential 1,5-closure during the first step of the cyclisation process.



Scheme 12. Allene-butenolide photocycloaddition.

Wege and Nielsen's approach toward the synthesis of elecanacin involved a [2+2] enol ether/quinine photochemical cycloaddition of **35** as the key step (Scheme 13).[54]



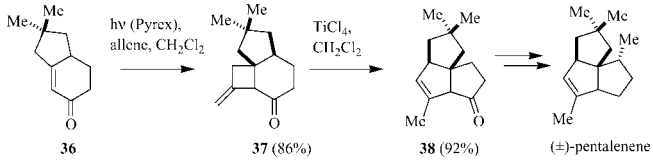
Scheme 13. Elecanacin synthesis.

Addition of the vinyl moiety to the double bond occurred at each of the two diastereotopic faces of the quinone moiety, affording (–)-elecanacin and (+)-isoelecanacin in 25 and 38% yields, respectively.

2.2. Cyclobutane Fragmentation

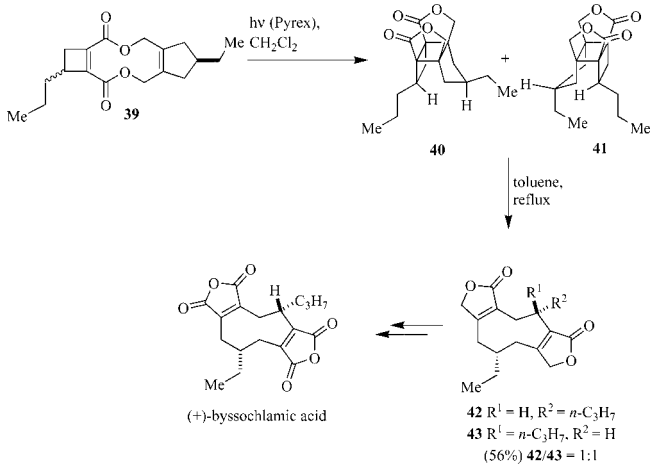
Cyclobutanes are very strained ring systems and consequently susceptible to fragmentation under a variety of conditions. If the cyclobutane ring is fused to one or more rings this progression gives rise to ring-expansion products, making the tandem [2+2] photocycloaddition-fragmentation sequence a powerful complement to typical medium-ring annulation procedures. Following Williams' and Wender's pioneering work in the 1980s on fragmentations of fused cyclobutyl systems for the synthesis of medium-sized rings,[55,56] this strategy has been extensively studied and applied to the syntheses of various natural products.

Kakiuchi and co-workers have reported a formal synthesis of (±)-pentalenene based on their previously developed [2+2] photocycloaddition of cyclohexenone to allene/Lewis acid induced rearrangement sequence.[57] Irradiation of the bicyclic cyclohexenone **36** with allene afforded the tricyclo[6.3.0.0^{1,4}]undecanone **37** in 86% yield (Scheme 14). When the cyclobutane was treated with $TiCl_4$ cleavage of the "fused" cyclobutane bond followed by a 1,2-hydride shift afforded key triquinane intermediate **38**, which has previously been converted to (±)-pentalenene by Paquette and co-workers.[58]



Scheme 14. Allene-enone [2+2] route towards pentalenene.

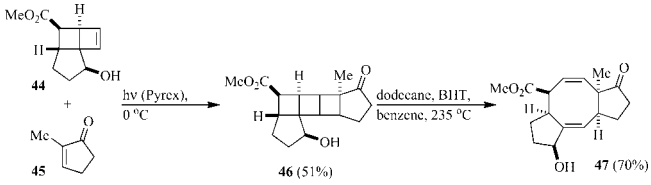
White has applied a photoaddition-cycloreversion strategy to access the nine-membered central ring of (+)-byssochlamic acid (Scheme 15).[59] Irradiation of **39** in CH_2Cl_2 through Pyrex yielded a 1:1 ratio of the stereoisomeric products **40** and **41**. A quantitative thermal fragmentation of the strained central cyclobutene afforded the cyclononadienes **42** and **43**, which were further elaborated to (+)-byssochlamic acid in three steps. Epimerisation of the



Scheme 15. Tandem [2+2] fragmentation strategy for the synthesis of byssochlamic acid.

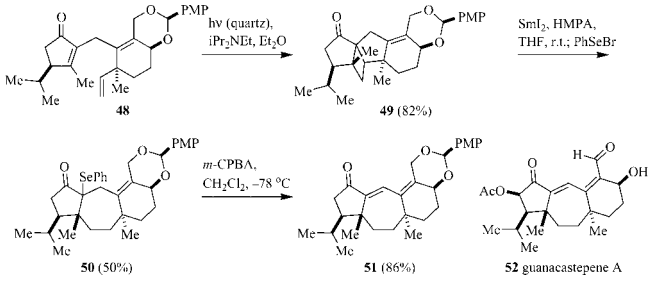
isopropyl substituent in the final step allowed for the formation of the enantiomerically pure natural product.

Snapper and co-workers studied the [2+2] photocycloaddition-thermal fragmentation strategy for the construction of the 5–8–5 ring system, a motif found in several diterpene and sesquiterterpene natural products.[60,61] They demonstrated that functionalised cyclobutenes undergo inter- and intramolecular [2+2] photocycloaddition reactions with cyclopentenones to provide a highly strained photoadduct, which, upon thermal fragmentation, affords a dicyclopenta[*a*,*d*]cyclooctene ring framework (Scheme 16).



Scheme 16. Cyclobutene [2+2]-thermal fragmentation sequence.

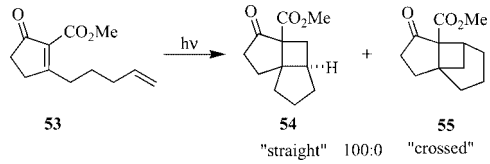
Free radical reactions have also been used successfully in the fragmentation of small rings, often offering a milder alternative to thermal conditions and subsequent high functional group tolerance. Specifically, the cyclobutyl-carbinyl radical has been described in some of the earliest reports of radical fragmentations and has been broadly applied in synthesis. Sorensen and co-workers used an intramolecular [2+2] photocycloaddition and a stereoelectronically controlled reductive fragmentation of a conjugated cyclobutyl ketone for the enantioselective and convergent synthesis of the guanacastepene diterpenes A and E.[62,63] Irradiation of **48** promoted a [2+2] photocycloaddition with complete diastereofacial selectivity to afford **49** in 82% yield. This transformation was followed by the reductive cyclobutane cleavage, upon treatment of photoadduct **49** with SmI_2 (Scheme 17).



Scheme 17. [2+2] Radical fragmentation step in Sorensen's guanacastepene synthesis.

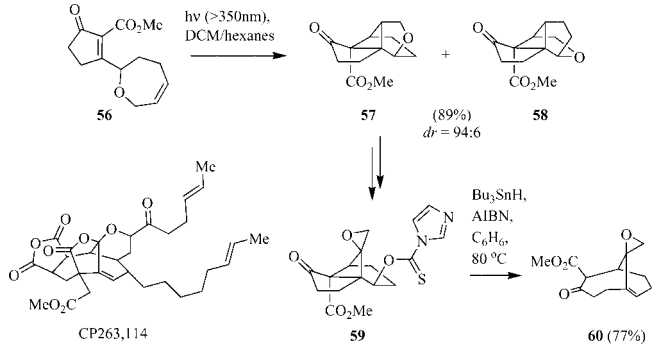
The cyclobutane bond exocyclic to the five-membered ring, parallel to the π-orbital system of the carbonyl group possesses the maximum overlap and is therefore predisposed to fragment. Trapping of the samarium enolate with phenylselenyl bromide afforded the organoselenide **72** as a mixture of diastereomers. Treatment with *m*CPBA then gave rise to the elimination product **73**, the latter containing the complete tricyclic 5–7–6 skeleton of the guanacastepenes.

Intramolecular cycloadditions of cyclohexenones possessing tethered terminal alkene chains have been popular test systems in synthetic photochemistry. Crimmins and coworkers have developed a method that allows selective access to either the "straight" or the "crossed" product in the [2+2] photocycloaddition of cyclopentenones as shown in Scheme 18.[64]



Scheme 18. Straight vs. crossed intramolecular [2+2] photocycloaddition.

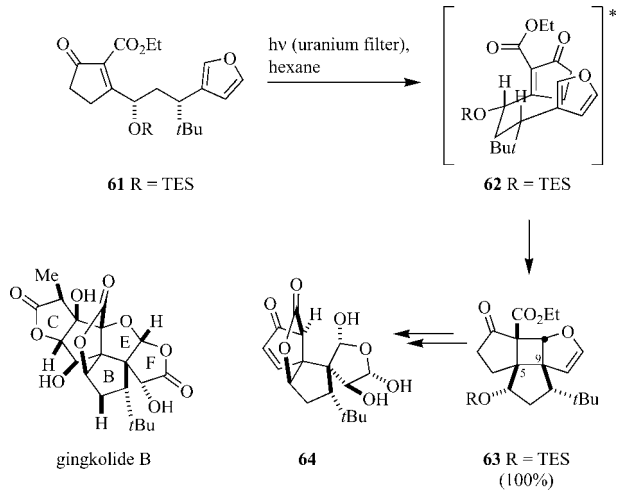
The regioselectivity observed in intramolecular photocycloaddition usually results from both the geometric limitations and the conformation "forced" by the substituents on the tether between the two π bonds involved in the transformation. The formation of the straight photoadduct is favoured as a result of the preference in the initial cyclisation of the triplet excited state to form a five-membered biradical intermediate. On the other hand, the formation of the crossed adduct is relatively disfavoured, as it involves initial cyclisation to form a six-membered ring. Crimmins investigated the incorporation of a temporary tether that would allow the cyclisation to proceed through the formation of a five-membered ring for the production of *either* the crossed or the straight adduct. The cyclic ether **56**, chosen as a substrate on the basis of molecular mechanics calculations, proved effective at reversing regioselectivity in favour of the crossed adduct **57** (Scheme 19). Further elaboration of **57** provided the cyclobutane **59**, which underwent selective fragmentation via the cyclobutyl carbinyl radical to afford the bridged nine-membered ring structure **60**, containing much of the required functionality and all the carbon framework of the core of the CP263,114 natural product.



Scheme 19. Intramolecular crossed [2+2] photocycloaddition for synthesis of the CP263,114 core.

Crimmins and co-workers have used a straight, double diastereoselective [2+2] photocycloaddition in their total synthesis of ginkgolide B. Irradiation of the cyclopentenone **61** afforded the straight photoadduct **63** as a single diastereomer in quantitative yield, establishing the C5 and C9

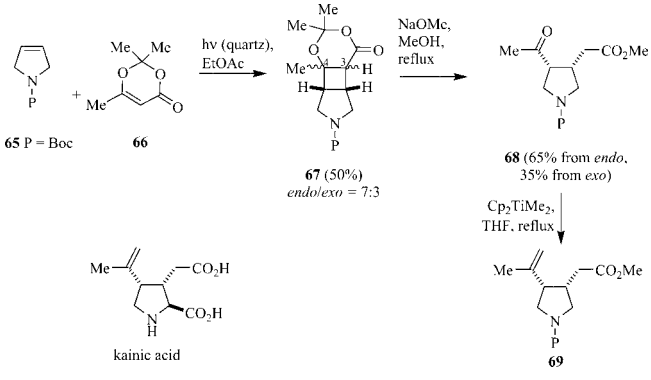
quaternary centres at the heart of the exceedingly complex natural product (Scheme 20).[65]



Scheme 20. Key [2+2] photocycloaddition in Crimmins' total synthesis of ginkgolide B.

The photocycloaddition is postulated to occur through a chair-like transition state in which both the trialkylsilyl ether and the *tert*-butyl group are in pseudo-equatorial orientations, accounting for the stereoselectivity of the transformation. Photoadduct **63** was later subjected to retroaldol fragmentation of the cyclobutane, completing the synthesis of the tetracyclic core of ginkgolide B.

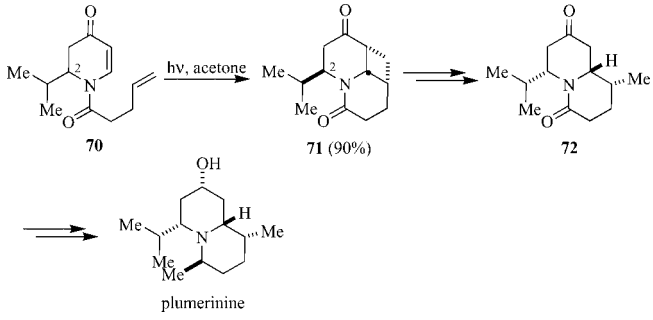
In addition to ring-enlargement products, cyclobutane ring-opening to give acyclic compounds has been applied to the synthesis of natural products. Parsons and co-workers reported studies towards the synthesis of kainic acid based on the [2+2] photocycloaddition/fragmentation sequence shown in Scheme 21.[66] They carried out model studies in which irradiation of a variety of protected pyrroline derivatives **65** in the presence of dioxenone **66** afforded a mixture of readily separable *endo* and *exo* addition products **67** in moderate yields. However, the transformation correctly installed the *cis* stereochemistry at C3 and C4.



Scheme 21. Kainic acid approach involving intramolecular [2+2] photocycloaddition.

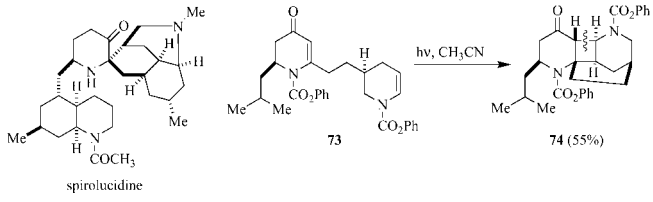
Methoxide-induced fragmentation of the cyclobutane ring led to compound **68** which was further converted to **69**, containing the majority of the kainoid skeleton. In each case, the larger steric hindrance in the *endo* photoadducts produced higher yields in the cyclobutane fragmentation.

Comins and co-workers have developed a tandem vinylogous amide photocycloaddition/reductive fragmentation methodology for the synthesis of alkaloids such as (–)-perhydrohistrionicotoxin.[67] They have adapted this chemistry to the synthesis of the alkaloid plumerinine (Scheme 22).[68] Key [2+2] vinylogous amide photocycloaddition of **70** proceeded with remarkable stereoselectivity to generate exclusively the cycloadduct **71** in 90% yield. Facial selectivity is attributed to the axial orientation of the isopropyl group at C2 shielding one face of the alkene. This crucial step gave access to the construction of the quinolizidine ring as well as setting three of the five stereocentres present in the natural product. The cyclobutane was carried through three steps, then cleaved with SmI_2 to afford the ketone **72**. A further seven steps led to the completion of the synthesis.



Scheme 22. Vinylogous amide [2+2]-fragmentation approach to plumerinine.

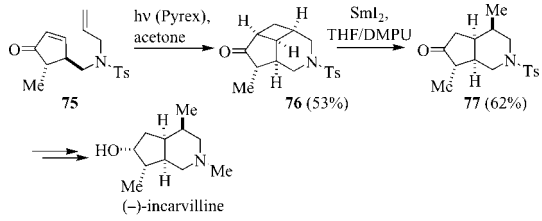
A similar strategy based on [2+2] photocycloaddition was designed for the synthesis of the alkaloid spirolucidine.[69] Scheme 23 shows some model studies of the approach. Upon irradiation, compound **73** underwent a highly stereoselective photocycloaddition to afford tetracyclic ketone **74** as a single product in 55% yield. The observed facial selectivity in the photocycloaddition of **74** was attributed to $A^{(1,3)}$ strain causing the C2 substituent to occupy an axial position, thus directing addition to the opposite alkene face. Cyclobutane reductive ring-opening in compound **74** would afford the central spirocyclic moiety of spirolucidine.



Scheme 23. Vinylogous amide [2+2]-fragmentation approach to spirolucidine.

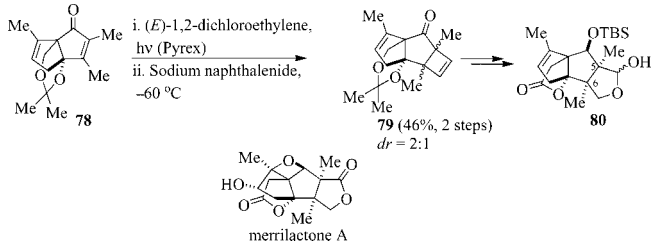
A three-component coupling and an intramolecular enone-olefin [2+2] photocycloaddition followed by an SmI_2-induced cyclobutane ring-opening reaction constituted the key steps in Kibayashi's enantioselective synthesis of (–)-incarvilline (Scheme 24).[70] Enantiomerically pure *N*-allyl

enone **75** underwent an intramolecular enone-olefin photocycloaddition affording a single diastereomer of decahydro-5-azacyclobuta[*cd*]indene skeleton **76** in 53% yield, as well as setting three contiguous stereogenic centres with the correct stereochemical relationship in a single step.



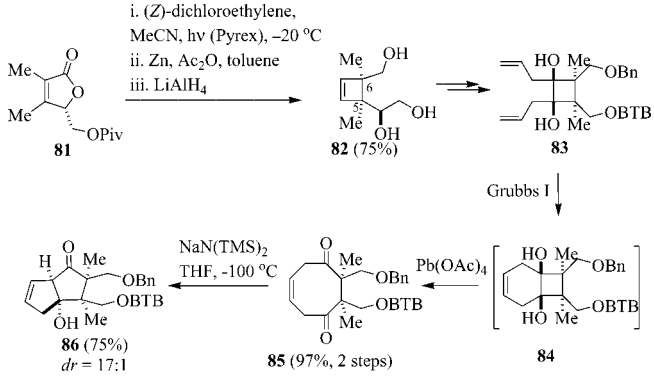
Scheme 24. [2+2]-fragmentation approach to incarvilline.

Mehta and co-workers' total synthesis of the sesquiterpene merrilactone A relies on a [2+2] photocycloaddition for the installment of the C5 and C6 quaternary centres (Scheme 25). Their route involved a photocycloaddition of (*E*)-1,2-dichloroethylene to diquinane **78** in which a moderate degree of β-facial selectivity favoured the formation of the desired diastereomer **79**, produced as a 2:1 mixture of separable diastereomers in 65% yield.[71,72]



Scheme 25. Mehta's route to merrilactone A.

The cyclobutane ring of the major diastereomer was further converted into the γ-lactone ring by ozonolysis and in situ reduction of the double bond, leading to the regioselective formation of lactol **80**. Inoue and Hirama's strategy towards merrilactone A also relied on a [2+2] photocycloaddition reaction to install the C5 and C6 quaternary centres (Scheme 26).[73,74]

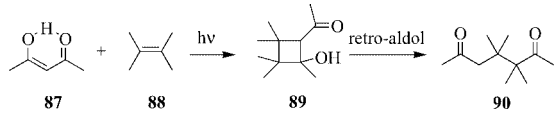


Scheme 26. Inoue and Hirama's [2+2] approach to merrilactone A.

Photocycloaddition reaction between chiral tetrasubstituted olefin **81** and *cis*-1,2-dichloroethylene proceeded with excellent facial diastereoselectivity (9.8:1) affording **82** in 75% yield following dechlorination and reduction. Cyclobutane **82** was advanced to diol **83**, which upon RCM formed cyclohexene **84** which immediately underwent oxidative fragmentation to afford the cyclooctene **85**, precursor for the key transannular aldol reaction to produce advanced intermediate **86**.

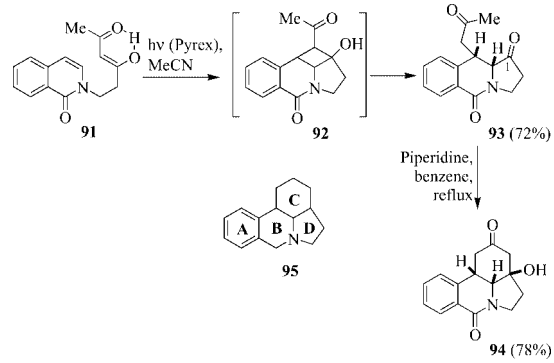
2.3. The de Mayo Reaction

de Mayo and co-workers demonstrated in the 1960s that photocycloaddition of β-diketones and alkenes afforded 1,5-diketones.[75] Tautomerisation of the 1,3-diketone affords the corresponding keto enol which is held in a six-membered ring through intramolecular H-bonding. The keto enol can undergo a [2+2] photocycloaddition to an alkene affording a β-acylcyclobutanol **89** (Scheme 27). Subsequent retro-aldolisation then furnishes the corresponding 1,5-diketone **90**.



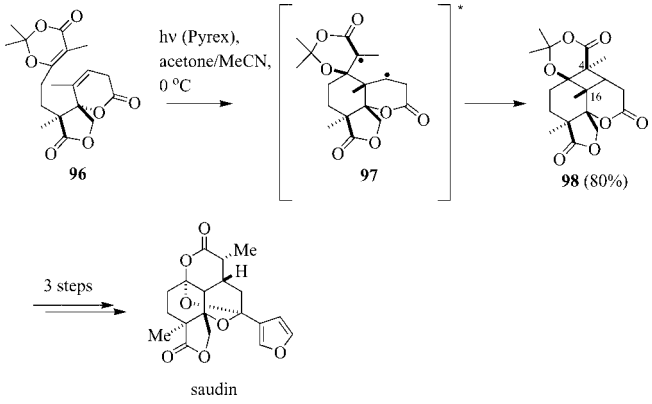
Scheme 27. Generalised de Mayo reaction.

The power of the de Mayo reaction in natural product synthesis, particularly when operated in the intramolecular mode, has been well exemplified, e.g. in syntheses of loganin,[76] longifolene,[77] reserpine,[78] zizaene[79] and hirsutene.[80] More recent work by Minter and co-workers involves an unusual de Mayo reaction developed in an approach toward the galanthan skeleton **95** found in lycorine-type *Amaryllidaceae* alkaloids (Scheme 28).[81] [2+2] Photocycloaddition of isocarbostyril (**91**) proceeded with remarkable regiochemistry to afford the corresponding cyclobutane **92** which upon retro-aldol fragmentation gave **93** in 70% yield. The preference for the formation of the "straight" photoproduct over the "crossed" photoproduct led to the exclusive formation of dione **93** with *cis* stereochemistry of the vicinal tertiary ring protons. Aldol cyclisation furnished the galanthan derivative **94** in 78% yield. The stereoselective formation of **93** was ascribed to limited accessibility to the carbonyl carbon atom at C1 from the *endo* face.



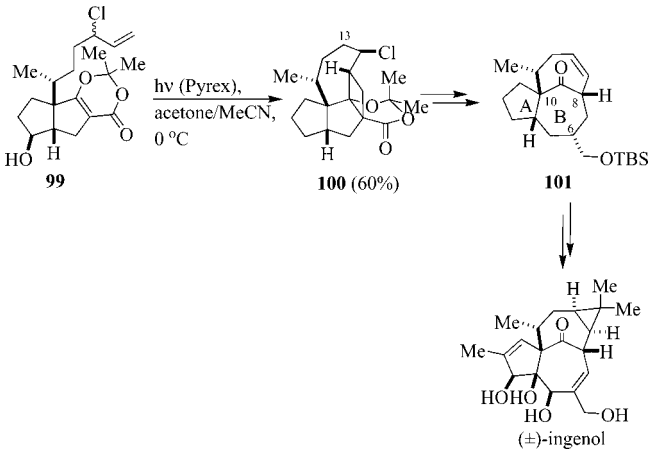
Scheme 28. de Mayo approach to the galanthan ring system.

A notable challenge associated with the classic de Mayo reaction is controlling regioselectivity during the enolisation of the starting β-diketone. The use of a β-keto ester would overcome this regiochemical ambiguity, but in the presence of an alkene the photocycloaddition of a β-keto ester would produce an oxetane by Paternò–Büchi reaction of the ketone carbonyl group instead of the desired cyclobutane. A solution to this problem was reported by Baldwin in 1980 when he described the use of dioxenone heterocycles as covalently locked enol tautomers of β-keto esters.[82] Winkler and co-workers have greatly extended the use of dioxenones in the de Mayo reaction and applied them to a number of complex natural product syntheses.[83,84] Their route for the construction of the labdane natural product saudin is shown in Scheme 29. Model studies indicated that it would be possible to prepare the complex dioxenone **96**, containing a trisubstituted alkene, and implement a late-stage de Mayo reaction.[85] Irradiation produced the desired cyclobutane **98** in 80% yield as a single diastereoisomer, having the correct *trans* relative stereochemistry of the methyl groups at C4 and C16 along with the requisite *cis* fusion between the rings B and C. Three further steps, including the critical retro-aldol fragmentation, afforded the natural product saudin.[86]



Scheme 29. Total synthesis of saudin.

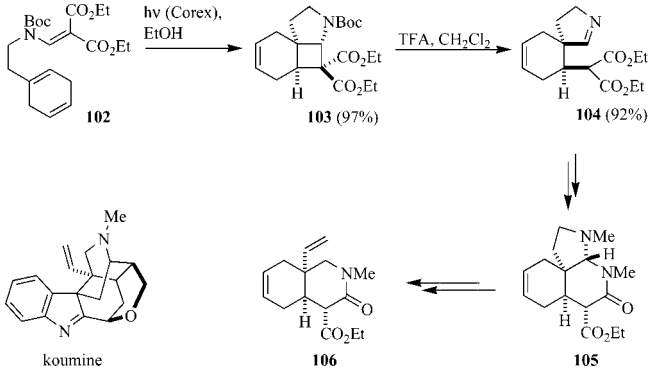
The dioxenone photocycloaddition-fragmentation methodology was the key step in Winkler's synthesis of racemic ingenol (Scheme 30).[87] It was anticipated that the unusual, and highly challenging to synthesise, C8/C10 "inside-outside" carbon framework of **101** could arise from **99** by the dioxenone [2+2] methodology developed within the group. In the event, irradiation of compound **99** afforded photoadduct **100** along with the C13 chloro isomer in 60% yield in a 5:2 ratio. Treatment of **100** with methanolic potassium carbonate promoted cyclobutane fragmentation. Subsequent $LiAlH_4$ reduction of the derived ester, DBU-mediated elimination of the chloride and silylation of the primary alcohol yielded **101** in 35% yield over four steps. The ingenane precursor **101** was then amenable to extensive functionalisation in the lower part of the A and B rings to access the natural product.



Scheme 30. de Mayo reaction in Winkler's total synthesis of ingenol.

2.4. Vinylogous Amide Photoaddition

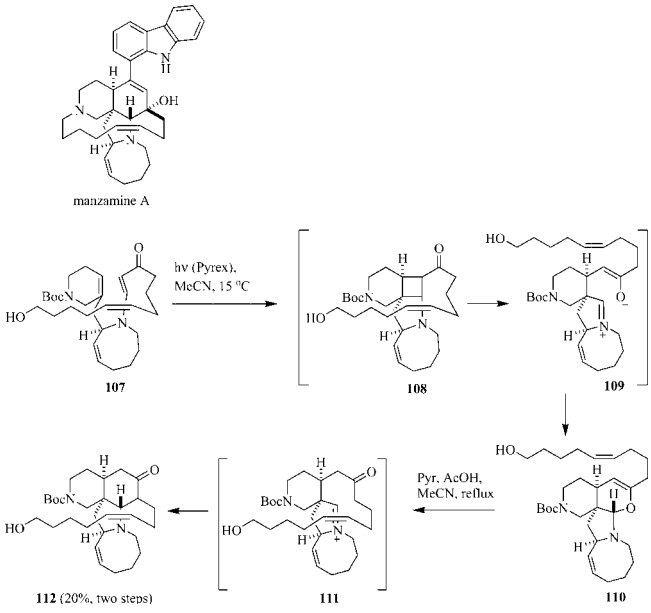
When a vinylogous amide or imide is used as the reaction partner instead of a 1,3-diketone, a photocycloaddition/retro-Mannich fragmentation sequence leads to the formation of N-containing systems. The intramolecular variant of this process, which was first reported by Tamura,[88] produces nitrogen-containing ring systems that have powerful application in natural product synthesis. White and coworkers utilised the nitrogen counterpart of the de Mayo transformation in an approach to the alkaloid koumine.[89] They envisioned a photocycloaddition-retro-Mannich approach for the assembly of the bicyclic octahydroquinoline precursor. Irradiation of **102** led to spiroimine **104** by retro-Mannich fragmentation of the intermediate cyclobutane **103**. The exclusive formation of a single stereoisomer of **104** reflects the uniquely defined configuration around the tetrasubstituted cyclobutane of **103**. Intramolecular cyclisation afforded the γ-lactam **105** which was advanced to a precursor of koumine in a further 4 steps (Scheme 31).



Scheme 31. Vinylogous amide [2+2] photocycloaddition in White's approach to koumine.

Winkler and co-workers have used the vinylogous amide and imide photocycloaddition/retro-Mannich fragmentation in the stereoselective construction of a number of complex alkaloids.[90–92] Their landmark synthesis of manzamine A is particularly noteworthy for the development of a

photocycloaddition-retro-Mannich fragmentation-Mannich closure cascade sequence as the key transformation (Scheme 32).[93]



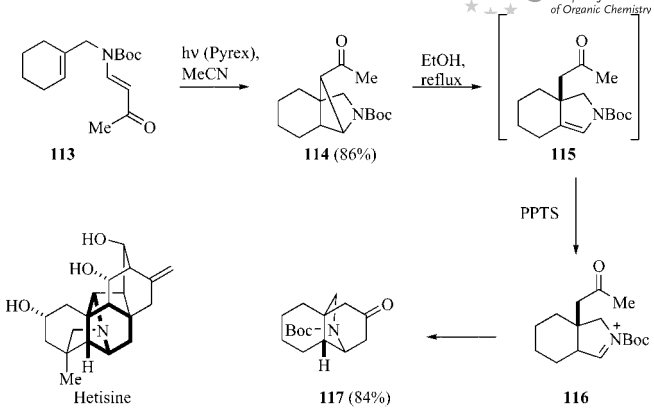
Scheme 32. Photocycloaddition-retro-Mannich fragmentation-Mannich closure cascade sequence in Winkler's synthesis of manzamine A.

Intramolecular photocycloaddition of the complex vinylogous amide **107** yielded cyclobutane-containing intermediate **108**. Retro-Mannich fragmentation and subsequent O-closure of the keto iminium intermediate **109** led to the aminal **110**, which upon isomerisation was converted into the manzamine tetracycle **112**. The remarkable stereochemical control achieved in the photochemical cascade allows for the establishment of all the stereochemical relationships in **112** from a single stereogenic centre. This cascade process led to the first total synthesis of manzamine A, and has been applied to the construction of simplified analogues of the natural product for antimalarial application.[94]

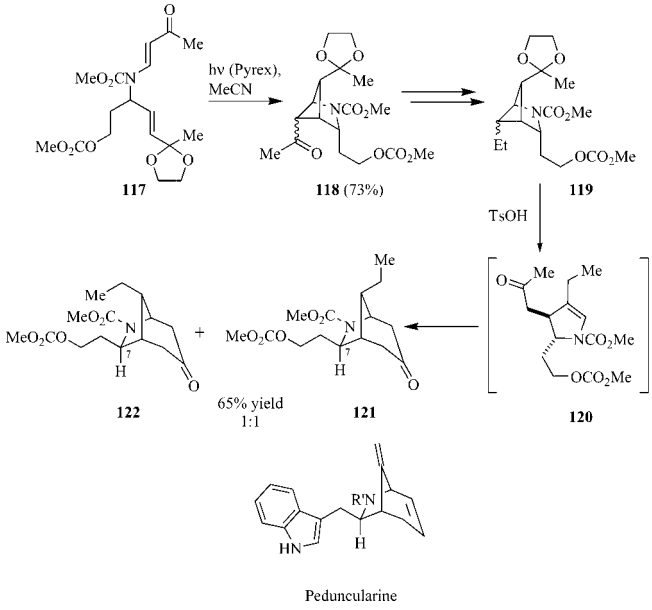
The efficiency of the photocycloaddition-retro-Mannich-Mannich ring closure sequence is again showcased in Winkler and Kwak's synthesis of the azabicyclo[3.2.1]octanone tricyclic core of the hetisine alkaloids (Scheme 33).[95]

Photocycloaddition of **113** afforded the tricyclic photoadduct **114** in 86% yield. The exclusive formation of the "crossed" regioisomer is in accord with the empirical rule of five observed in the intramolecular photocycloaddition of 1,5-dienes. Retro-Mannich fragmentation of compound **114** yielded **115**, which upon treatment with PPTS gave the Mannich product **117** in a high 84% yield and as a single diastereomer. The kinetic protonation from the sterically less hindered convex face of enamine **115**, which leads to the formation of the keto iminium intermediate **116** is the reason for the exclusive formation of **117** in excellent overall yield.

Winkler and Ragains further developed the crossed vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure sequence in a stereoselective construction of the bicyclic core of penduncularine (Scheme 34).[96]



Scheme 33. The photocycloaddition-retro-Mannich-Mannich ring closure sequence in the synthesis of the tricyclic core of the hetisine alkaloids.



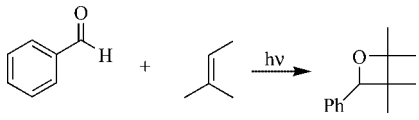
Scheme 34. Approach to peduncularine by photocycloaddition-retro-Mannich fragmentation-Mannich closure cascade.

Irradiation of compound **117** produced the photoadduct **118** as a 5:1 mixture of isomers epimeric at the carbon atom bearing the acetyl group in a good 73% yield. Functional-group interconversions led to **119**, which upon deketalisation underwent retro-Mannich cleavage and subsequent Mannich closure via the keto iminium ion to generate a 1:1 mixture of epimeric azabicycles **121** and **122** with the requisite C7 stereochemistry for the synthesis of penducularine.

2.5. Paternò–Büchi Reaction

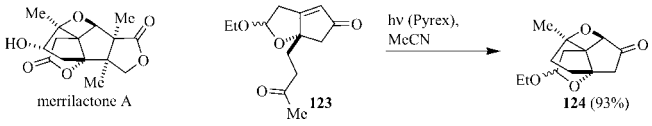
The Paternò–Büchi photocycloaddition constitutes another important example of [2+2] photochemical reaction, in which an aldehyde or ketone reacts with an alkene to

form an oxetane (Scheme 35). Soon after Ciamician's discovery of the [2+2] photocycloaddition in 1908,[1] Paternò disclosed the first example of a [2+2] photocycloaddition of an aldehyde to an alkene to give an oxetane.[2]



Scheme 35. Generalised Paternò–Büchi reaction.

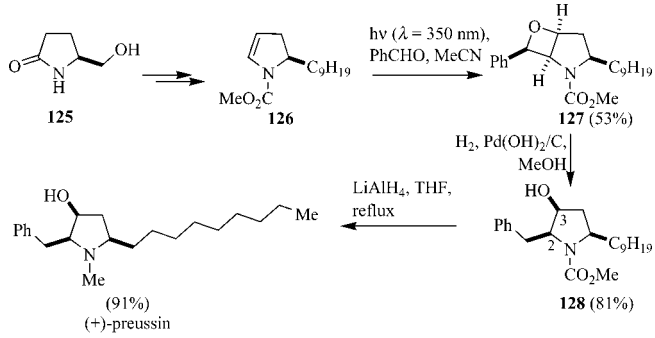
Some years later, Büchi and co-workers' studies confirmed the impressive structural transformations that could be achieved in a single step through irradiation of a suitably unsaturated molecule.[97–99] The Paternò–Büchi reaction has since been skillfully employed in natural product synthesis by a number of groups,[8] although it is less common than [2+2] carbocylisation. In particular, whilst oxetane rings are present in several natural products, the use of the Paternò–Büchi reaction to install these structural motifs in a controlled manner has to date not been widely exploited. A six-step approach to the tetracyclic core of the oxetane-containing sesquiterpene merrilactone A was described by Greaney and co-workers.[100] The strategy uses an intramolecular Paternò–Büchi photoaddition to install the key central oxetane ring (Scheme 36).



Scheme 36. Intramolecular Paternò–Büchi approach to merrilactone A.

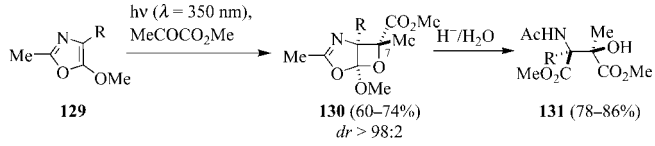
Irradiation of the bicyclic enone **123** produced the tetracyclic oxetane **124** in an excellent 93% yield with complete stereo- and regiocontrol, having the core carbon skeleton of the target compound merrilactone A.

Bach and co-workers' total synthesis of the pyrrolidinol alkaloid (+)-preussin was achieved in nine steps from L-pyroglutaminol in an 11% yield.[101] The key steps of the route included a Paternò–Büchi reaction of benzaldehyde to the dihydropyrrole **126** followed by hydrogenolysis for the efficient carbohydroxylation of the olefin. The strategy takes advantage of the facial diastereoselectivity of the [2+2] reaction, in which benzaldehyde adds to dihydropyrrole in a *syn* fashion. Reduction of the oxetane **127** afforded the key intermediate **128** which contains the required *cis* orientation of the benzyl group at C2 and the hydroxy group at C3 (Scheme 37).



Scheme 37. Intermolecular Paternò–Büchi approach to preussin.

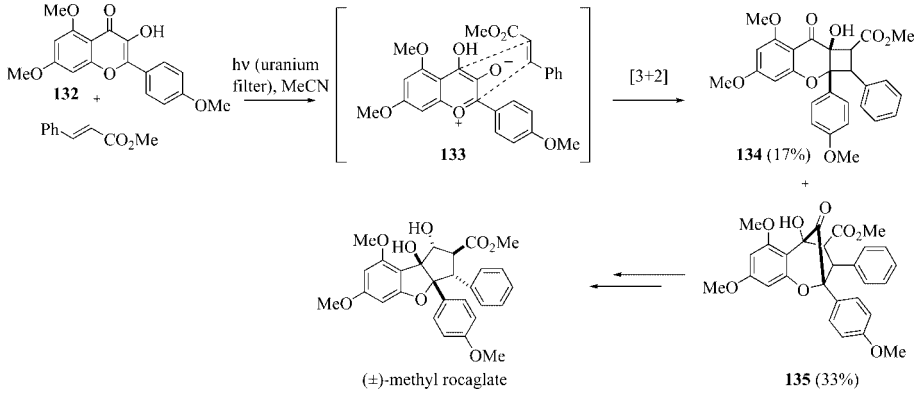
Griesbeck and co-workers presented a similar strategy for the synthesis of various dimethyl *erythro*-β-hydroxyaspartates, which constitute important structural motifs of more complex natural products.[102] Photocycloaddition of methyl pyruvate with various 5-methoxyoxazoles afforded the oxetanes **130** exclusively as *exo* diastereomers. Subsequent hydrolytic ring opening proceeded with retention of configuration at C7 to afford the corresponding *N*-acetyl-β-hydroxyaspartic acid diesters **131** (Scheme 38).



Scheme 38. Paternò–Büchi reaction of methyl pyruvate with oxazoles.

3. [3+2] Photocycloaddition

Aside from the arene *meta*-photoaddition, very recently reviewed elsewhere,[4,5] [3+2] photocycloadditions have been rarely applied to natural product synthesis in recent years.



Scheme 39. Photoexcitory proton transfer in Porco's synthesis of the rocaglamides.

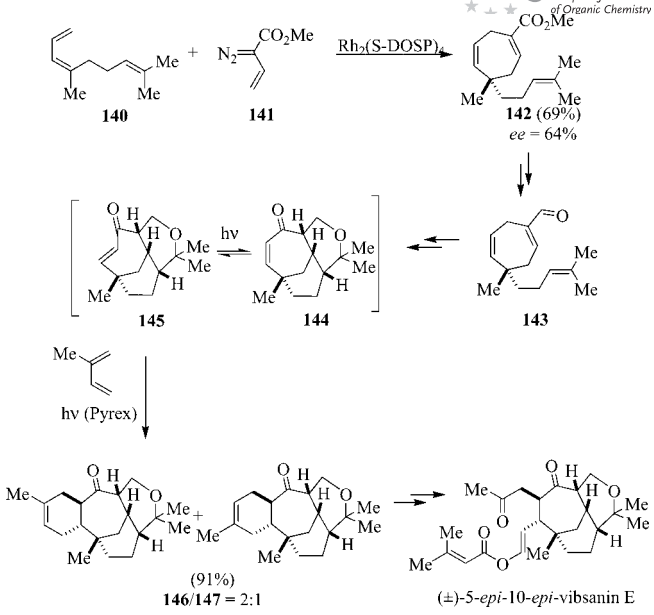
Porco has reported the [3+2] dipolar cycloaddition of an oxidopyrylium betaine, generated through excited state intramolecular proton transfer, in a synthesis of the rocaglamides (Scheme 39).[103] The 3-hydroxyflavone **132** was irradiated at λ >350 nm, generating the required oxidopyrylium ion **133**. [3+2] Dipolar cycloaddition with methyl cinnamate then afforded the aglain cycloadduct **135**, along with a small amount of the [2+2] product **134**. Ketone **135** was then transformed into (±)-methyl rocaglate through α-ketol rearrangement and reduction.

The approach has been developed into an asymmetric synthesis of the rocaglamides, using chiral Brønsted acids as mediators for enantioselective photoaddition.[104]

4. Photochemical [4+2] Cycloaddition

In their studies towards the biomimetic synthesis of the crispatene family of natural products, Baldwin and co-workers suggested an intramolecular photochemical [4+2] cycloaddition for the synthesis of the bicyclo[3.1.0] motif found in this family of compounds.[105] The feasibility of their approach was demonstrated by the synthesis of the (*E*,*E*,*E*,*E*)-tetraene **136** as a model system (Scheme 40). Irradiation of compound **136** afforded the crispatene core **139** in a good 60% yield. The outcome of the reaction was explained as follows: In the presence of UV light compound **136** underwent selective double bond isomerisation affording intermediate **137**, which could be detected by NMR spectroscopy. A second isomerisation of the C6–C7 double bond then set the stage for the symmetry-allowed, and strain-driven, $[_{\pi}4_{s}+_{\pi}2_{a}]$ photocycloaddition furnishing the desired crispatene core **139**.

Davies and co-workers have reported a highly efficient approach to the synthesis of the tricyclic core of the diterpene vibsanin E, which contains a highly functionalised cycloheptane ring.[106] Their approach involved three cycloaddition steps. First, a highly selective rhodium-catalysed [4+3] cycloaddition between **140** and **141** afforded the cycloheptadiene **142**, which was advanced to the aldehyde **143**. Lewis acid catalysed [4+2] cycloaddition then formed the tricycle, which underwent functional-group manipulation to **144** (Scheme 41).

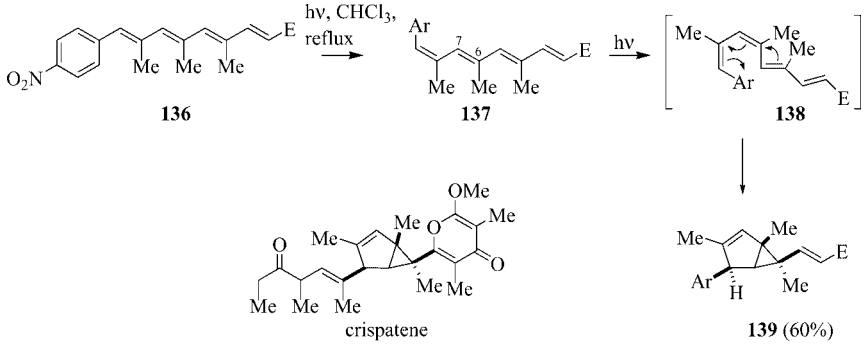


Scheme 41. Multi-cycloaddition approach to vibsanin E.

Photolysis of **144** initially afforded the more reactive *trans*-cycloalkenone **145** by alkene isomerisation, which could then react with isoprene to afford the corresponding photo-Diels–Alder product. The product was formed as a 2:1 mixture of regioisomers in favour of the desired **146**, both containing the requisite *trans* fusion; however, they were epimeric at C5 and C10 to vibsanin E. Compound **146** was further advanced to racemic 5-*epi*-10-*epi*-vibsanin E in 3 further steps.

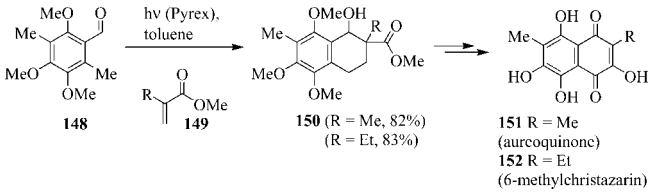
4.1. Photoenolisation/Diels–Alder Reaction (PEDA)

Nicolaou and co-workers have developed novel photoenolisation/Diels–Alder (PEDA) processes and applied them to the synthesis of various natural products. In their synthesis of hybocarpone and analogues, hydroxy-*o*-quinodimethanes are photochemically generated from *o*-alkylbenzaldehydes by irradiation (Scheme 42). Diels–Alder reaction of the reactive species affords the bicycles **150** which can be further advanced to the tetralone monomeric unit.[107] This strategy provided a direct route towards aureoquinone and



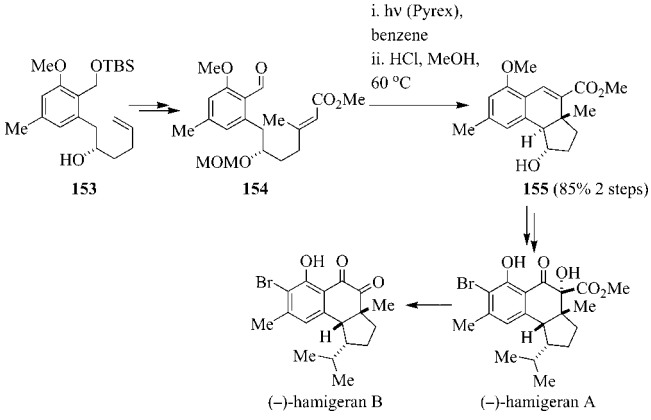
Scheme 40. Photochemical [4+2] reaction in crispatene model study.

6-methylchristazarin. Irradiation of the aldehyde **148** together with **149** (when R = Me) furnished the bicyclic compound **150** as a 2:1 mixture of *syn* and *anti* diastereomers in 82% yield, which was further advanced to aureoquinone (**151**). Similarly, the PEDA product **150** (when R = Et) was converted to another naphthazarin natural product, 6-methylchristazarin (**152**). The hydroxynaphthoquinone **152** (R = Et) is in fact the monomeric subunit of hybocarpone, undergoing radical-induced dimerisation using CAN followed by cleavage of the aryl ethers to afford the pentacyclic natural product.



Scheme 42. PEDA approach to naphthazarin natural products.

Nicolaou and Gray have also reported the first examples of the intramolecular PEDA reaction involving an all-carbon tether between the reacting functionalities, and applied it to the synthesis of the Hamigeran family of natural products (Scheme 43).[107] The method provides an efficient synthesis of both the bicyclo[4.3.0] and -[4.4.0] systems fused onto aromatic nuclei. In their synthetic pathway towards the target molecules, enantioenriched alcohol **153** was advanced to the substrate for the crucial IMPEDA reaction. Photocyclisation of **154** gave a mixture of C10 epimers in high yield. The mixture was inconsequential to the synthesis, as dehydration under acidic conditions and concomitant loss of the MOM group afforded **155** as a single product.

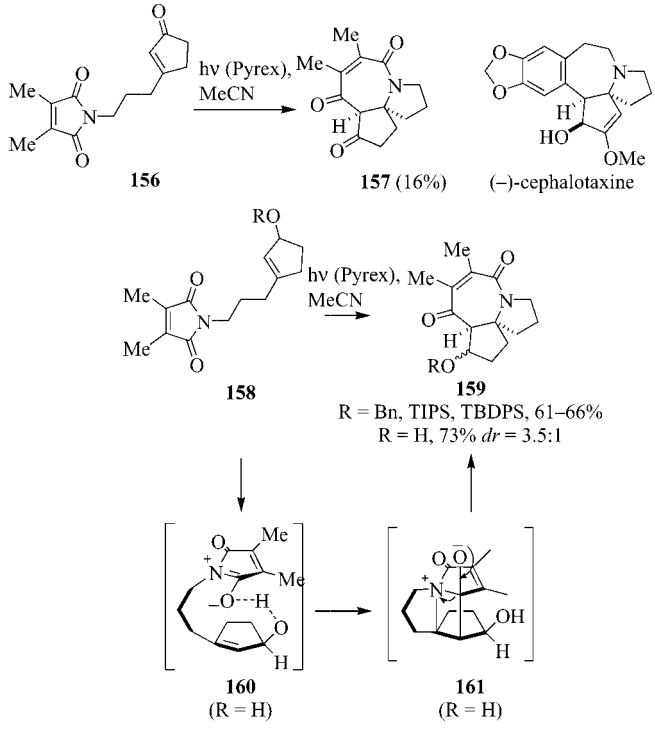


Scheme 43. Nicolaou's IMPEDA approach to the Hamigerans.

The IMPEDA reaction was found to be very fast and highly stereoselective, furnishing the tricyclic moiety exclusively with the *trans* fusion. In addition, the substituents at the contiguous C9, C10 and C11 stereocentres are all *syn* when (*E*) olefins are employed due to an *endo*-selective DA reaction.

5. [5+2] Photocycloaddition

Booker-Milburn and co-workers' approach towards the cephalotaxine CDE ring skeleton relied on a formal intramolecular [5+2] photocycloaddition reaction as the key step (Scheme 44).[108] Their initial efforts involved the irradiation of the cyclopentenyl-substituted maleimide **156**. Initial photocycloadditions afforded the tricyclic product **157** in low yields, attributed to the presence of the cyclopentenone unit, quenching the excited state of the maleimide. As a consequence, the corresponding protected alkenols **158** were synthesised (R = Bn, TIPS, TBDPS). Irradiation afforded the corresponding photoproducts in higher yields but poor diastereoselectivities. Surprisingly, when the unprotected alcohol was submitted to the photocycloaddition conditions in toluene a 73% yield was recorded with a 3.5:1 diastereomeric ratio.



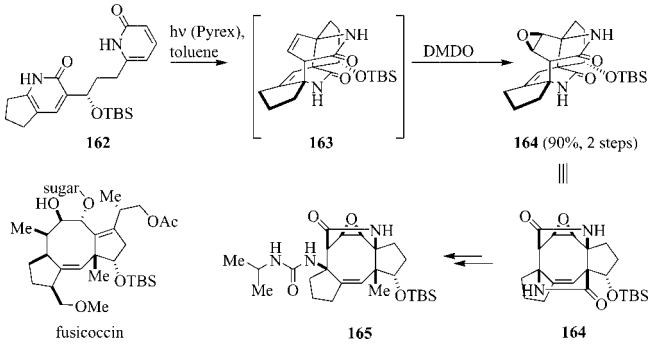
Scheme 44. Booker–Milburn's [5+2] cycloaddition approach to cephalotaxine.

The selectivity was attributed to hydrogen bonding controlling the facial selectivity in the [2+2] photocycloaddition. Subsequent fragmentation of the zwitterionic species affords tricyclic product **159**.

6. [4+4] Photocycloaddition

The groups of Sieburth and West have made extensive studies of the [4+4] photocycloaddition as a method for the construction of cyclooctanoid-containing natural products. Sieburth has reported model studies for the synthesis of fusicoccin A using an intramolecular 2-pyridone [4+4] photocycloaddition.[109,110] Irradiation of the photosubstrate **162** was expected to promote a *cis*-selective cycloaddition that

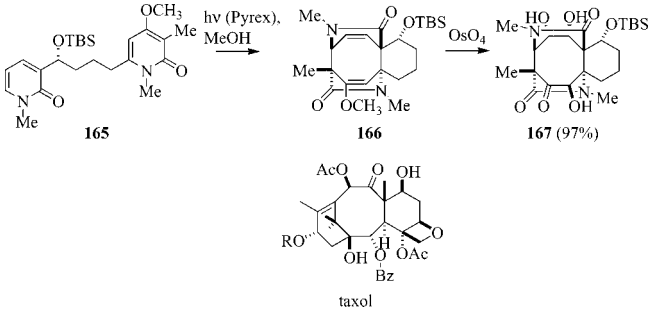
would set the stereochemistry of the methyl groups at C7 and C11. The reaction depended on the presence of two hydrogen-bonding pyridones, intramolecularity and the use of non-polar solvents for success (Scheme 45).



Scheme 45. Synthetic route to fusicoccin using [4+4] photocycloaddition.

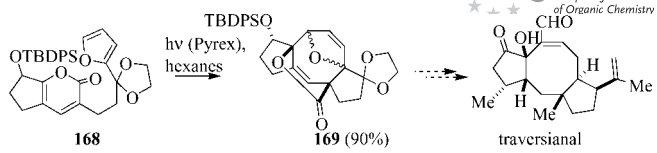
The photoadduct **163** was prone to an unproductive Cope rearrangement, necessitating immediate epoxidation with DMDO. The product epoxide **164** was formed as a single product in 90% overall yield (2 steps) due to selective epoxidation from the least-hindered face. Further steps involving the activation of the amide using isocyanates followed by reduction of the carbonyl group and reduction of the alcohol formed in the previous step afforded the advanced intermediate **165**.

The Sieburth group have also used 2-pyridone [4+4] photocycloadditions in an approach to the anticancer natural product taxol (Scheme 46).[111–113] Smooth photochemical cyclisation of the bis(2-pyridone) **165** afforded compound **166** as a single isomer. The rigidity of the newly formed product allows for further transformations to be carried out selectively, and the selectivity of the synthetic transformation can be easily predicted. In fact, the subsequent dihydroxylation occurred selectively from the two least-hindered faces affording the triol **167** in 97% yield.



Scheme 46. Sieburth's [4+4] photocycloaddition approach to taxol.

West and co-workers' photochemical approach toward the synthesis of cyclooctanoid natural product traversianal relied on the stereoselective [4+4] cycloaddition of fused bicyclic pyran-2-one **168** (Scheme 47).[114] Irradiation of the photosubstrate furnished the adduct **169** as an approximately 1:1 mixture of *endo* and *exo* cycloadducts, both arising from the approach of the furan from the same face as the OTBDPS group.



Scheme 47. Synthetic route to traversianal using [4+4] photocycloaddition.

Minor amounts of the *exo* adduct resulting from approach of the furan from the opposite side to the OTBDPS group were also identified. The outcome of the reaction was explained by assuming a pseudoequatorial position of the silyl ether in the cyclopentene ring, with approach from the opposite side being hindered by the pseudo-axial hydrogen atom.

7. Conclusions

The wide variety of chemistry presented in this review illustrates the enduring power of photocycloaddition in complex molecule synthesis. The range of natural products, and corresponding set of functional groups, amenable to the photocycloaddition approach is vast – spanning relatively simple monoterpenes such as grandisol up to highly complex, polycyclic structures such as manzamine A and ginkgolide A. The total synthesis of these latter examples represents the height of sophistication in the application of photocycloaddition to solve problems of stereocontrol and C–C bond formation in highly hindered environments. A prominent theme of the photocycloaddition strategy found throughout the review is versatility, particularly with respect to the [2+2] manifold of reaction. Initial C–C bond formation can be implemented with high levels of stereocontrol at multiple stereocentres, with the installation of quaternary carbon atoms being particularly effective when compared with alternative methods. A powerful set of fragmentation methods are then available, which have excellent flexibility for incorporation into the overall natural product retrosynthesis. The demonstrated efficacy in relative stereocontrol is now being extended to advances in absolute stereocontrol, and future work will no doubt harness asymmetric photocycloaddition for the creative and effective synthesis of natural products.

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