From α-cedrene to crinipellin B and onward: 25 years of the alkene–arene *meta*-photocycloaddition reaction in natural product synthesis

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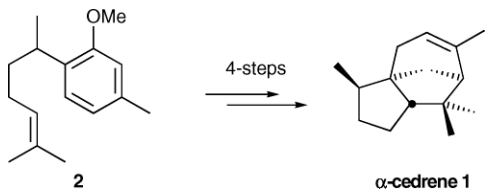
Wender and Howbert's remarkable synthesis of α-cedrene in 1981 brought the attention of the synthetic community to the alkene–arene *meta*-photocycloaddition reaction. Here we review the natural product syntheses that have been achieved, over the last 25 years, utilising this strategic level reaction.

Introduction

This year is the 25th anniversary of the publication of the remarkable synthesis by Wender and Howbert of α-cedrene **1** and with it the introduction of the alkene–arene *meta*-photocycloaddition reaction into the canon of synthetic chemistry (Scheme 1).[1]



Scheme 1 Wender's approach to α-cedrene **1**.

The remarkable brevity of this route, beginning as it does from a simple aromatic compound **2** with one stereogenic centre, completes the synthesis of α-cedrene **1** in four further steps. To reach this tricyclic sesquiterpene so rapidly, with the correct relative stereochemistry at each of its four chiral centres, is truly impressive and suggests that the key *meta*-photocycloaddition step should be a standard, strategic-level reaction in the arsenal of synthetic chemists. In this perspective, by reviewing the literature of its use in natural product synthesis up to July 2006, we hope to demonstrate not only the impressive achievements to date but, by understanding the features that control the outcome of these powerful reactions, to suggest that many opportunities exist to further develop the application of this reaction in synthesis. The fundamental discovery, mechanistic and theoretical aspects of this reaction have been thoroughly and expertly reviewed elsewhere and will only be discussed in so far as is necessary to understand the synthetic chemistry that follows; many of these reviews also deal with synthetic aspects of this area.[2]

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The *meta*-photocycloaddition reaction—observed selectivities

Mode selectivity. Photochemically mediated cycloaddition of an alkene to an arene ring requires excitation of the aromatic

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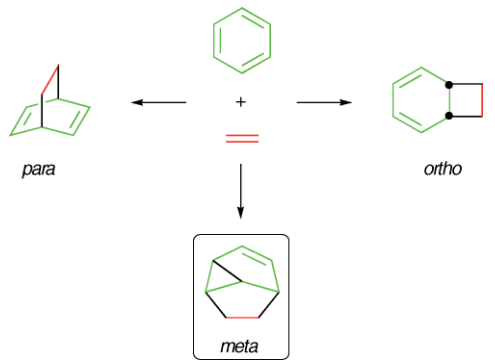
moiety to its first singlet excited state with 253.7 nm light. This can occur to give *ortho*-, *meta*- or *para*-adducts (Scheme 2). The latter class is only rarely observed and no synthetic work has been reported.[3] The *ortho*- and *meta*-adducts are more frequently encountered and much work has been reported regarding a predictive model to delineate which is favoured in a given situation.[2] Mattay and Meuller have developed a satisfying empirical method based on an assessment of the free energy for electron transfer (ΔG_{ET}), estimated by the Rehm–Weller equation, for the two reacting groups.[4] For the purposes of this review we will focus exclusively on the *meta*-photocycloaddition, a mode favoured for alkene–arene pairs with a $\Delta G_{ET} > 1.5$ eV.

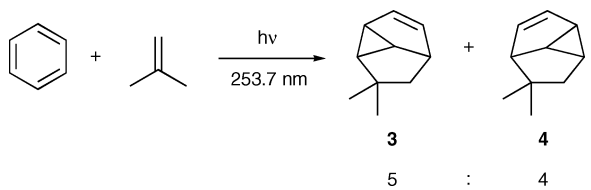


Scheme 2 Three modes of the photocycloaddition of an alkene to a benzene ring.

The first examples of a *meta*-photocycloaddition reaction were reported contemporaneously by Bryce-Smith *et al.* at Reading[5] and Wilzbach and Kaplan at Illinois in 1966.[6] Morrison and Ferree reported the first intramolecular example just three years later in 1969.[7]

Intermolecular reactions

a. Regioselectivity issues. A representative example of a *meta*-photocycloaddition, illustrating the commonly observed two regioisomeric cyclopropane products **3** and **4**, is shown in Scheme 3.[8]

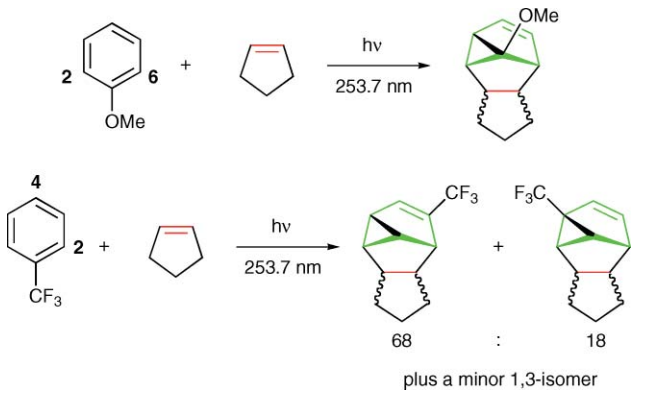


Scheme 3 Regioselective cyclopropane formation in the *meta*-photocycloaddition reaction.

In addition, if the benzene ring bears substituents then there is potential for the cycloaddition to occur with varying regioselectivity. In general it is observed that addition of the alkene takes place, preferentially, 2,6 across electron donor groups, *e.g.* methyl or methoxy, whilst electron-withdrawing groups such as cyanide or trifluoromethyl groups favour 2,4-addition (Scheme 4).[2,9]

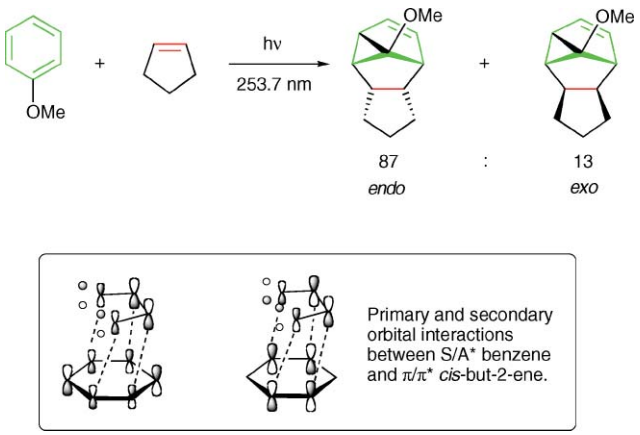
b. Stereoselectivity issues.

(i) exo–endo-Selectivity. Closer examination of the products in Scheme 4 reveals a characteristic preference for the formation



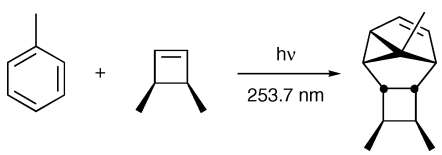
Scheme 4 Regiochemical preferences in the *meta*-photocycloaddition with substituted benzenes.

of the *endo*-isomer in many intermolecular reactions.[2] The case for anisole and cyclopentene is shown in Scheme 5.[10] The observed *endo*-selectivity can be explained in the same way as the *exo*/*endo*-selectivity in the Diels–Alder reaction; on the basis of favourable secondary orbital interactions. Houk has discussed this in terms of frontier molecular orbitals for benzene and *cis*-but-2-ene.[11] Details of the key primary and secondary interactions are shown in Scheme 5.



Scheme 5 *endo*-Selectivity in the intermolecular *meta*-cycloaddition reaction.

(ii) π-Facial selectivity in the alkene component. The degree of π-facial selectivity in the attack on the alkene, as might be expected, varies considerably with the alkene structure but the example shown in Scheme 6 illustrates that essentially complete selectivity is possible.[12]



Scheme 6 π-Facial selectivity in attack on the alkene component.

Intramolecular reactions

a. Regio-/stereoselectivity issues. In intramolecular reactions regio- and stereochemical issues become intertwined. The

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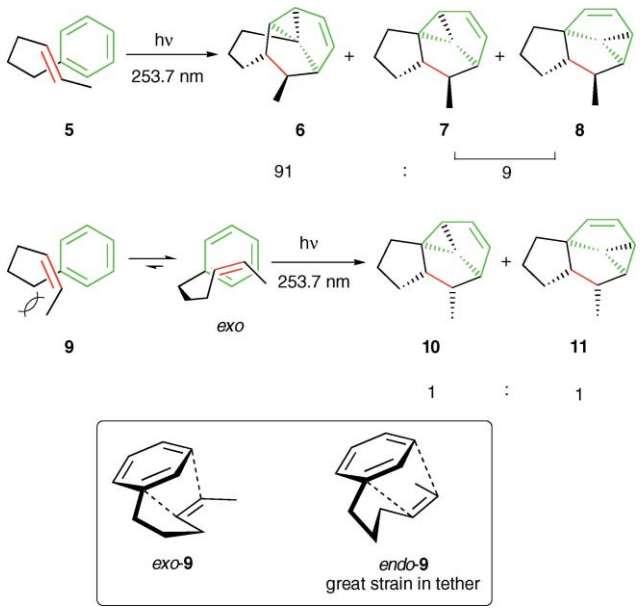
majority of studies have used substrates with a three-atom tether connecting the arene and alkene moieties. It might be anticipated from the forgoing discussion that if the tether were the only substituent on the benzene ring then cycloaddition would occur across that tether. For terminal and *E*-disubstituted double bonds this regiochemistry of addition is often found to furnish the major product *e.g.* **5** to **6** (Scheme 7)[13] and has found an application in the approach by Wender *et al.* toward desdimethylquadrone (Scheme 25).[2b,14] Interestingly, the presence of a *Z*-double bond leads to a strong preference for 1,3-addition *e.g.* **9** to **10/11**. This has been rationalised on the basis of steric interactions of the vinyl methyl group with hydrogens in the linking tether.[1,7,13,15] An overwhelming preference for the *exo*-isomer is found in nearly all cases, dictated by the need to minimise strain in the tether whilst maximising orbital overlap of the relevant alkene and arene orbitals (Scheme 7).[2b] Implicit in these results is that alkene geometry is retained during *meta*-photocycloaddition reactions.



Scheme 7 Regio- and stereochemical preferences in intramolecular *meta*-photocycloaddition reactions.

Generally, when an *ortho*-donor group is present this can significantly direct the regioselectivity of addition in favour of the 1,3-mode (*e.g.* Chanon *et al.*'s ceratopicanol synthesis,[16] Scheme 43).

Asymmetric induction from stereogenic centres on the tether has been proven to be effective in a number of studies,[2a] not least in the α-cedrene synthesis, and will be discussed in the course of the synthetic work reported below.

In the context of intramolecular reactions with a three-carbon tether the relationship of the two regioisomeric cyclopropane products to linear and angular triquinanes has led to their being named as shown in Fig. 1. When MM2 calculations were performed on this prototypical case by Wender and Howbert the 'linear' isomer was found to be 3.6 kcal mol^{-1} lower in energy than the 'angular' isomer.[14,17] In applying this result in a predictive manner, the difference between the position of equilibrium under photochemical and thermal conditions must be considered in conjunction with the influence of the substituents. Nonetheless,

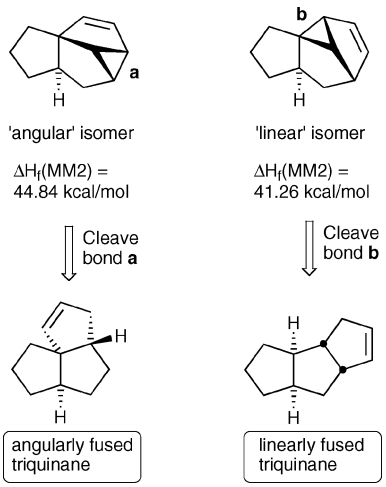


Fig. 1 Calculated relative energies of 'angular' and 'linear' isomers.

calculations of product stability have proved useful in rationalising the outcome of these reactions *e.g.* Wender *et al.*'s laurenene synthesis (Scheme 34).[18]

Consideration of the structure of these cycloadducts reveals the general truth that it is not these compounds that are likely to be of use in synthesis but rather what they may be converted into. As with any reaction that significantly increases molecular complexity it is a key issue whether that complexity is relevant to the target molecule. In the case of the *meta*-photocycloaddition the adducts are usually too complex as the cyclopropanes so-formed are frequently not required in the target molecule. Thus any method that couples the fragmentation of the cyclopropane to a transformation that further advances the synthesis is of significant value, *e.g.* the formate solvolysis during Mehta *et al.*'s descarboxyquadrone synthesis (Scheme 58).[19] Some exemplar ring systems that might be prepared from a *meta*-photocycloadduct are shown in Fig. 2.

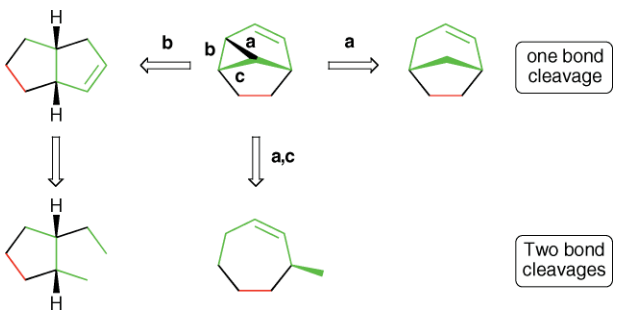
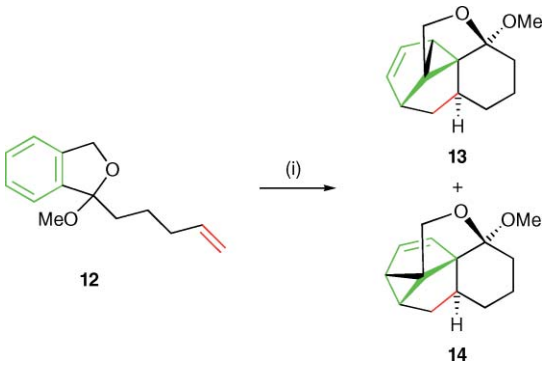


Fig. 2 Some potential ring systems accessible from a *meta*-photocycloadduct.

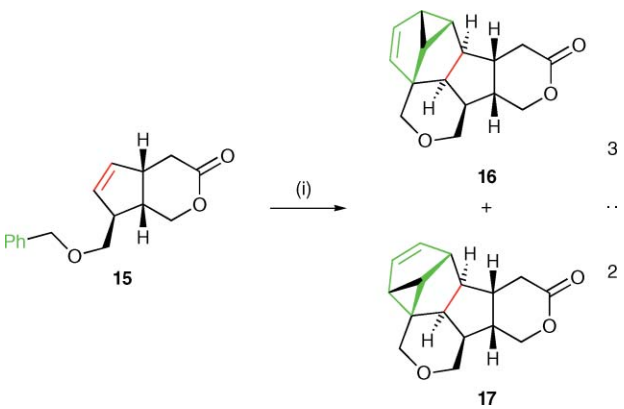
b. The significance of tether length. Fundamental studies on intramolecular *meta*-photocycloaddition reactions identified a significant difference in quantum yields dependent on whether there were three or four atoms in the tether linking the alkene and arene moieties, *e.g.* for 6-phenylhex-1-ene, $\phi < 0.005$,[20] whereas for the isomeric *Z*-6-phenylhex-2-ene $\phi = 0.26$.[7,13,15] This appears to have discouraged the use of longer linking tethers in natural product synthesis. However, a limited number of studies appear to indicate that if the conformational freedom of the tether is restricted or

if a suitable conformation for cycloaddition is favoured in any way then greater than three atoms may be workable. Wender and deLong studied photolysis of **12**, in which a cyclic acetal offers some conformational restriction, and obtained an impressive 68% yield of **13** and **14** at 60% conversion (Scheme 8).[21]



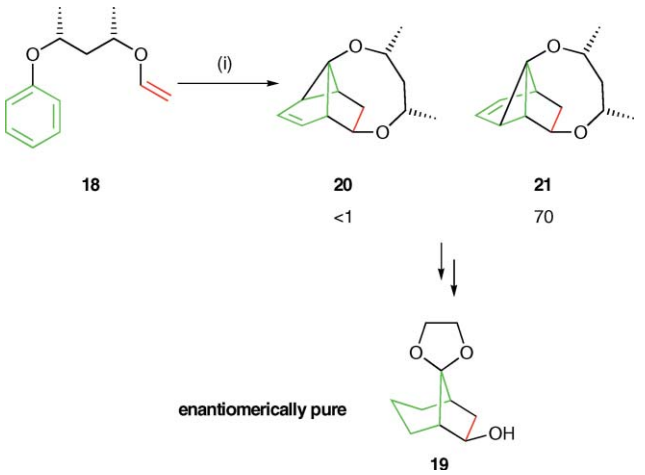
Scheme 8 Wender and deLong's study of four atom tethers. *Reagents and conditions*: (i) *hv* (Vycor filter) (68% yield at 60% conversion).

As part of a wider study on tandem Norrish type I–alkene–arene *meta*-photocycloaddition reactions De Keukeleire and He found that compound **15** underwent photolysis to deliver a 3 : 2 mixture of **16** and **17** in a significant 42% yield (Scheme 9).[22] The usual *exo*-selectivity was found with 1,3-addition to the benzene ring driven by the *Z*-double bond as previously discussed (*cf.* synthetic studies on cerapicol,[22] Scheme 49).



Scheme 9 De Keukeleire's study on four atom tethers. *Reagents and conditions*: (i) *hv* (254 nm), Rayonet reactor (42%).

Still longer tethers are rare, however, Sugimura *et al.* have reported an impressive example of a compound (**18**) with a five-atom tether. In this case the cleavable tether also functions as a very effective chiral auxiliary to deliver enantiomerically pure **19** *via* **20** and **21** (Scheme 10).[23] The high yield noted was reported to reduce noticeably in more substituted derivatives *e.g.* tolyl analogues. In view of the problems with chemical yields in the intramolecular photocycloaddition of enol ethers/acetates noted in some synthetic studies, albeit on very challenging substrates, this is not unexpected (Scheme 27 and 30). The particular advantages of this tether, toward a number of reactions, has been analysed by Sugimura *et al.* and the importance of the entropy term in explaining its ability to deliver very high asymmetric induction

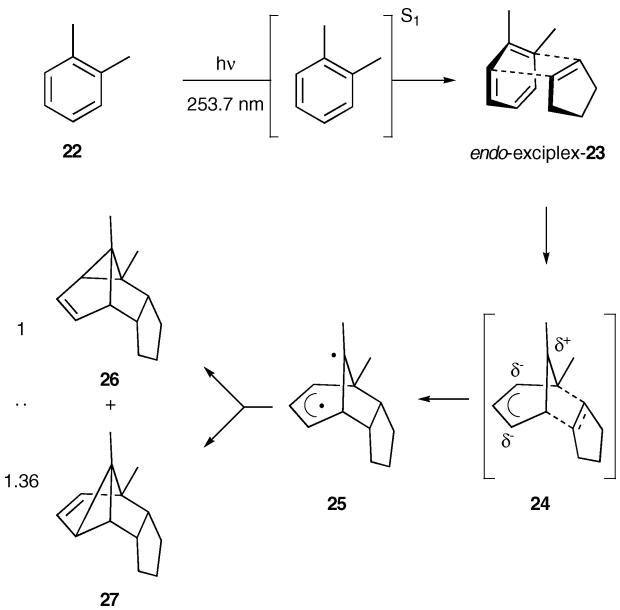


Scheme 10 Sugimura *et al.*'s study of a diastereoselective *meta*-photocycloaddition with a five-atom tether. *Reagents and conditions*: (i) *hv* (low pressure mercury vapour lamp, Vycor filter), pentane (**21**: 70%).

has been emphasised.[23c,d] Interestingly, the tether contains two oxygen atoms. De Keukeleire has noted the paradoxical influence of incorporating an oxygen atom in substrates featuring a tether of greater than three atoms (Scheme 9).[22b]

Mechanistic rationalisation

Extensive mechanistic and theoretical studies have been conducted to rationalise the results from the many studies on the *meta*-photocycloaddition reaction and, although the precise detail of the pathway followed is still the subject of debate,[24] that outlined in Scheme 11 appears to be in accord with the facts.[25]



Scheme 11 A possible mechanism for the *meta*-photocycloaddition illustrated for the case of *ortho*-xylene and cyclopentene.

The reaction begins with excitation of the benzene ring to its first singlet excited state, which requires 253.7 nm light, and it is then thought to form an *endo*-exciplex **23** with the alkene reaction

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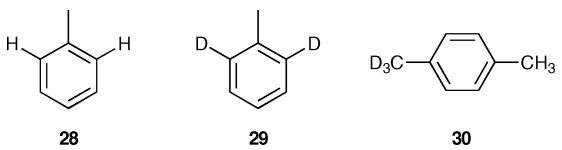
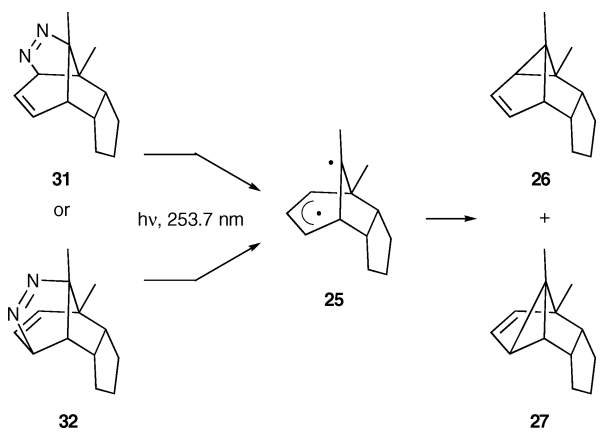
partner.[7,26] The detection of such exciplexes and experiments performed to demonstrate that such exciplexes precede the product, rather than forming in competition with it, have been limited to a small number of particularly favourable and informative cases.[27] Nevertheless, the observation that the stereo- and regiochemical outcomes of the *meta*-photocycloadditions discussed below, and those encountered in more general cases, can be interpreted on this basis offers considerable circumstantial support for exciplex formation prior to generation of the product. The exciplex is then thought to develop *via* a rate-limiting addition step, with formation of two C–C bonds between the alkene and arene, as evidenced by an inverse α-secondary deuterium isotope effect ($k_H/k_D = 0.93$) in intermolecular competition experiments between substrates such as **28**/**29** and cyclopentene (Fig. 3).[28] As the addition proceeds, a polarised species **24** is implicated with a small positive charge on the one carbon bridge and a negative charge, allylically distributed, on the three-carbon bridge. Related studies on the addition of cyclopentene to, *inter alia*, photo-excited α,α,α-trideutero-*para*-xylene **30** lead to the observation of preferential addition across the CH_3 group. The positive β-secondary deuterium isotope ($k_H/k_D = 1.06$) measured is in accord with the preference of alkenes to add 2,6 across donor groups.[25]



28 **29** **30**

Fig. 3 Substrates used in deuterium isotope effect studies.

A biradical intermediate such as **25** has been proposed as the species that immediately precedes the products. An elegant experiment in support of this was carried out by Sheridan and Reedich in which diazo compounds **31** and **32**, on photolysis with 253.7 nm radiation, each extrude nitrogen and afford the same two compounds **26** and **27** in almost the same ratio (**31** gives **26** : **27** 1 : 1.32; **32** gives **26** : **27** 1 : 1.34, Scheme 12) as is obtained by direct photolysis of *ortho*-xylene and cyclopentene (Scheme 11).[29] Whether such a compound is a true intermediate or a species with a fleeting existence on a descending energy curve is not clear. All attempts to trap the species **24** and **25** discussed above have been unsuccessful.[2a]



Scheme 12 Sheridan and Reedich's photolysis of diazo compounds **31** and **32**.

At a practical level, the light required for the photoexcitation of the benzene ring is normally supplied by a mercury discharge tube. Whilst low pressure tubes emit the majority of their output at 253.7 nm (some emission occurs at 185 nm), medium and high pressure lamps emit several other lines or a continuum of radiation respectively. Light in the region 170–200 nm can excite the benzene ring to its second singlet excited state and produce Dewar benzenes. In addition, it can lead to excitation of the alkene in the starting material or product (π–π*) resulting in degradation of both. Thus filters such as Vycor glass are employed to significantly reduce the amount of light below 210 nm reaching the reaction mixture.

Natural product synthesis utilising the *meta*-photocycloaddition

Overall, the synthetic utility of these reactions is dependent on the three phases of the synthesis set-out below all being efficient:

(i) access to the photocycloaddition substrate,

(ii) the photocycloaddition itself,

(iii) the conversion of the photocycloadduct to the target.

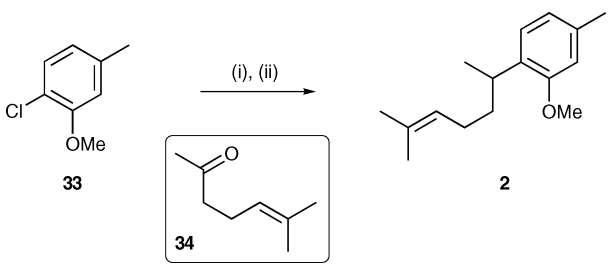
Consideration of the key *meta*-photocycloaddition step raises many of the key issues that must be addressed in the application of this reaction in synthesis. Accepting that, for the purposes of this review, we are discussing the *meta*-mode of addition there are four issues of selectivity that will be discussed in the context of the syntheses that follow: (i) the ratio of regioisomeric cyclopropanes and whether both are viable intermediates to continue the synthesis, (ii) for intramolecular examples, the number of atoms in the tether, (iii) the regiochemistry of cycloaddition, (iv) the stereochemistry, including asymmetric induction from pre-existing stereogenic centres, *exo*/*endo*-selectivity in the cycloaddition step and conservation of alkene geometry. In addition, we will evaluate the yields associated with these reactions and assess the increase in complexity that accompanies the transformation.

Insofar as published results allow we shall address each of them in turn in the following survey.

Natural product syntheses

Synthesis of α-cedrene[1]

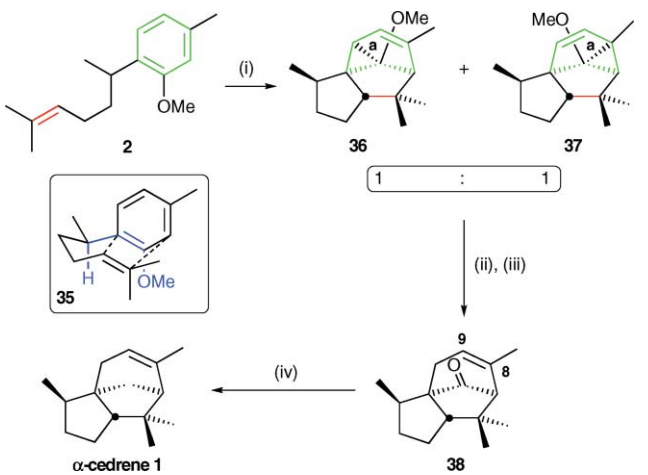
The bichromophore, from which the synthesis begins, is straightforward to prepare and takes advantage of a one-pot, two-step, reductive coupling developed by Hall and McEnroe,[30] in this instance utilising chlorocresol **33** and ketone **34** (Scheme 13).



Scheme 13 Synthesis of α-cedrene; preparation of the photocycloaddition precursor. *Reagents and conditions*: (i) Li, Et_2O then **34**; (ii) Li, NH_3 then NH_4Cl (74%).

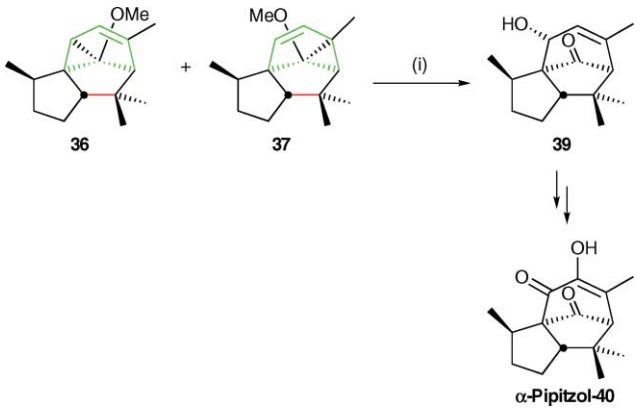
Photochemical transformations typically involve high energy intermediates and thus it is commonly observed that selectivity can be a problem, both in terms of multiple reaction types, *e.g.* Norrish type I and type II reactions from a single carbonyl precursor, and concerning issues such as stereoselectivity. Examination of the structure of **2** reveals that a number of control features, some required by the target, have been incorporated into its architecture to address some of the regio- and stereochemical issues raised in the introduction (*vide infra*).

As in the vast majority of synthetic studies involving the *meta*-photocycloaddition reaction, the alkene and arene moieties are separated by a tether of three atoms in length, leading to the formation of a new five-membered ring upon cycloaddition. This takes advantage of the typically high quantum yields that attend this length of tether (Schemes 8 and 9). Of the regiochemistries of *meta*-photocycloadditions that are permitted by this length of tether, the preference for addition across the strongest π-donor group explains, in part, the presence of the methoxy group. This directing effect is augmented by the influence of the *Z*-double bond. That this effect is probably of secondary importance may be judged from the outcome of the cycloaddition step in the synthesis of a number of compounds, *e.g.* hirsutene, subergorgic acid and ceratopicanol (Schemes 27, 41 and 43 respectively), but particularly De Keukeleire and He's studies on cerapicol[22] (Scheme 49). The stereogenic centre adjacent to the benzene ring allows control of π-facial selectivity. A formal allylic strain motif in **2** (blue in **35**, Scheme 14) favours the local conformation shown that leads to the most stable *exo*-exciplex **35**, with the tether adopting a distorted *syn*-pentane conformation with a pseudo-equatorial methyl group. Thus, irradiation of **2** with light from a Vycor-filtered medium pressure mercury lamp[31] delivers two cycloadducts **36** and **37**, distinguished by regioisomeric cyclopropanes in a 1 : 1 ratio at photochemical equilibrium (65% yield). At thermal equilibrium **36**, the 'linear isomer', is formed exclusively. Regioselective cleavage of the internal cyclopropane bonds, **a** in **36** and **37**, renders these two isomers synthetically equivalent. However, the means by which this is achieved is critical and by no means general. In the present case, regiocontrol is exerted by a push–pull effect in which electrophilic activation of the substrate is coupled with a 'push' from an oxygen lone pair. There is some ambiguity as to whether the electrophile reacts at the double bond or the cyclopropane and differences have been reported (Schemes 50 and 51). Thus treatment of **36** and **37** with 4 N HCl affords the desired tricyclic skeleton but as a regioisomeric mixture of Δ8 and Δ9 alkenes. A two-step cleavage with electrophilic activation by bromine preceding radical debromination with tri-*n*-butyltin hydride gave **38** as a single alkene in 59% yield.[32] It is interesting to contrast these outcomes with cyclopropane cleavage in De Keukeleire's[22] and Penkett's[60] work toward the synthesis of cerapicol and gelsemine respectively (Schemes 49 and 50). The final step of the synthesis is a straightforward Wolff–Kishner reduction to deliver α-cedrene in 58% yield. Thus, a full assessment of this synthesis makes manifest the erudition in its design.



Scheme 14 Synthesis of α-cedrene **1**. *Reagents and conditions*: (i) *hν* (Vycor filter), pentane (65%); (ii) Br_2, CH_2Cl_2; (iii) Bu_3SnH (neat) (59%, 2 steps); (iv) NH_2NH_2, KOH, $(HOCH_2CH_2)_2O$, 200 °C (58%).

By exploiting alternative post-cycloaddition functional group manipulations, Wender and Howbert carried out a synthesis of pipitzol **40** as outlined in Scheme 15.[17,33]



Scheme 15 Synthesis of pipitzol. *Reagents and conditions*: (i) I_2, THF, H_2O.

The synthesis of α-cedrene opened the door to a considerable number of natural product syntheses, each advancing our understanding of the key structural factors controlling the outcome of these interesting and powerful *meta*-photocycloaddition reactions. These are now examined in turn.

Syntheses based on intramolecular *meta*-photocycloaddition reactions

Rudmollin, isocomene and silphinene. A group of structurally similar *ortho*-disubstituted aromatic substrates has been studied in relation to the synthesis of rudmollin **41**, isocomene **42** and silphinene **43** (Fig. 4). The subtle differences in the structures of isocomene and silphinene present an interesting challenge in the way that related photocycloadducts are converted into their respective targets. Rudmollin, which appears distinctly different from the other natural products discussed so far, has much in its synthesis that relates to the route to α-cedrene and as such is examined first.

Synthesis of rudmollin[34]. The synthesis of rudmollin *via* a *meta*-photocycloaddition requires the cleavage of two of the bonds present in the photocycloadduct to reveal a seven-membered ring, a necessarily more involved procedure. However, careful planning

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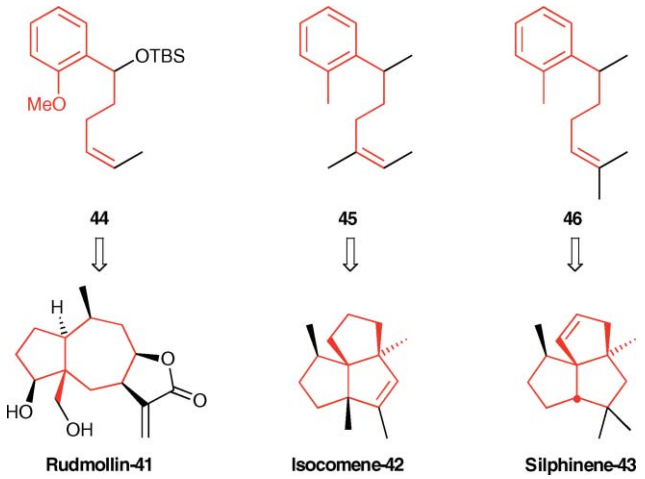
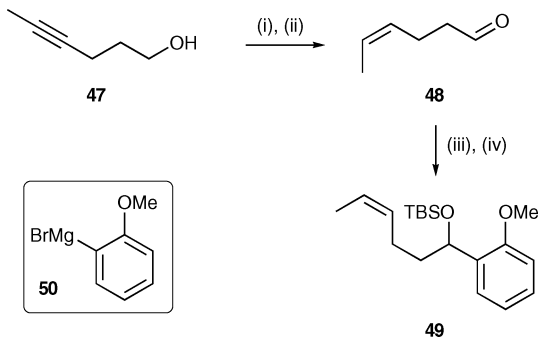


Fig. 4 *ortho*-Disubstituted aromatic substrates for the synthesis of isocomene, rudmollin and silphinene.

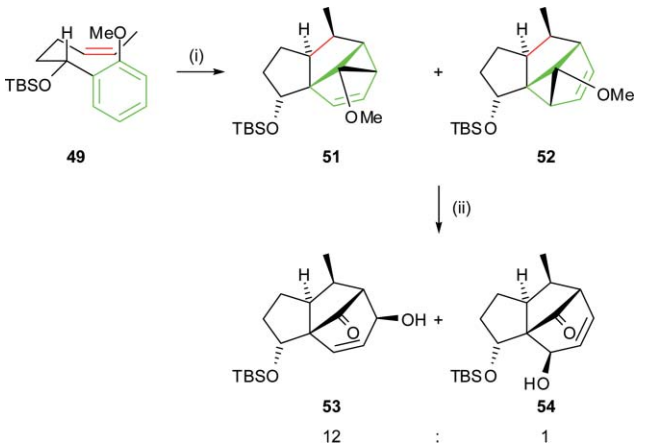
ensured that all of the carbons are used in the final compound and most of the stereochemical information is retained. Preparation of the photocycloaddition precursor is straightforward with control over the double bond geometry being exercised by a Lindlar reduction (Scheme 16).



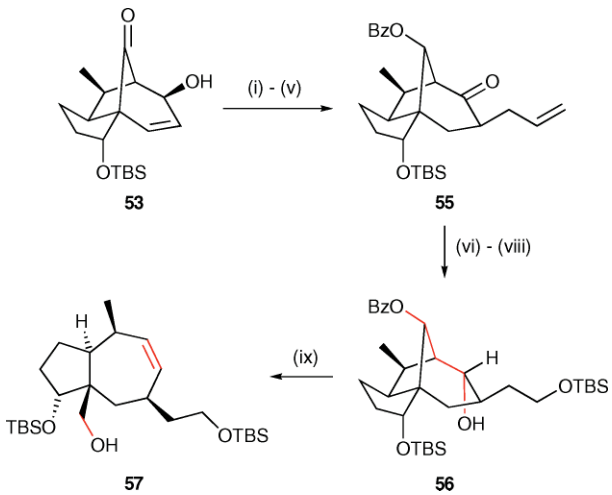
Scheme 16 Synthesis of rudmollin; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) H_2 (10–40 psi), $Pd/CaCO_3$ (Lindlar), quinoline, pentane (94%); (ii) PCC, CH_2Cl_2, 0–25 °C (54%); (iii) **50**, THF, 0 °C (98%); (iv) TBSCl, DMAP, NEt_3, DMF (97%).

Unsurprisingly, the photocycloaddition of **49** closely parallels that encountered in the α-cedrene synthesis with good asymmetric induction from the stereogenic centre adjacent to the aromatic ring, the expected *exo*-selectivity, retention of alkene stereochemistry in the product and a 2.3 : 1 ratio of regioisomeric cyclopropanes **51** and **52** favouring the 'angular' isomer. As with α-cedrene, accessing a bicyclo[3.2.1]octane ring system in the first fragmentation of the photoadduct renders both isomers synthetically equivalent. In this instance the equivalence is realised by treatment with mercuric acetate that affords, from **52**, a 71% yield of allylic alcohol **53** accompanied by 6% of the allylic isomer **54**. Subjecting **51** to the same reaction conditions affords **53** in 58% yield accompanied by less than 7% of **54** (Scheme 17).

The second phase of the ring-fragmentation process reveals the desired *trans*-fused bicyclo[5.7.0]decane ring system, this being carried out by a Grob-type ring-fragmentation (Scheme 18). Thus, following a series of functional group interconversions, two of the remaining three carbons were introduced by a stereoselective



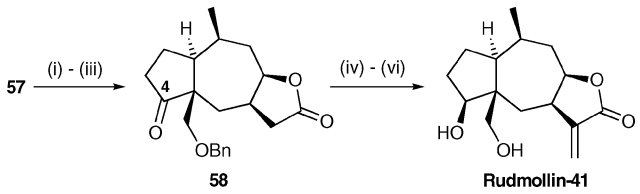
Scheme 17 Synthesis of rudmollin; photocycloaddition of **49**. *Reagents and conditions*: (i) *hv* (Vycor filter), pentane (63%); (ii) $Hg(OAc)_2$, THF, H_2O (71% + 6% allylic isomer from **52**).



Scheme 18 Synthesis of rudmollin; Grob-type fragmentation to reveal seven-membered ring. *Reagents and conditions*: (i) $NaBH_4$, MeOH (94%); (ii) MnO_2, CH_2Cl_2 (93%); (iii) H_2, 5% Pd/C, Et_2O (99%); (iv) $(PhCO)_2O$, DMAP, NEt_3, DMF, 46–50 °C (95%); (v) $KN(TMS)_2$, DME, 0 °C then BEt_3, THF, allyl iodide (75% at 75% conversion); (vi) $NaBH_4$, $CeCl_3$, MeOH (72%, 3 : 1 α : β); (vii) O_3, MeOH, CH_2Cl_2, −78 °C then $NaBH_4$, −78–25 °C (98%); (viii) TBSCl, imidazole, DMF (97%); (ix) MsCl, pyridine then $LiAlH_4$, DME, 0–25 °C (84%).

enolate allylation to give **55**. Stereoselective reduction of the ketone establishes the correct geometry for the Grob-type fragmentation (red in **56**) that, after functional group manipulation of the double bond, was triggered by sequential mesylation of the alcohol then $LiAlH_4$ cleavage of the benzoate ester, the resulting aldehyde being reduced *in situ* to afford **57**.

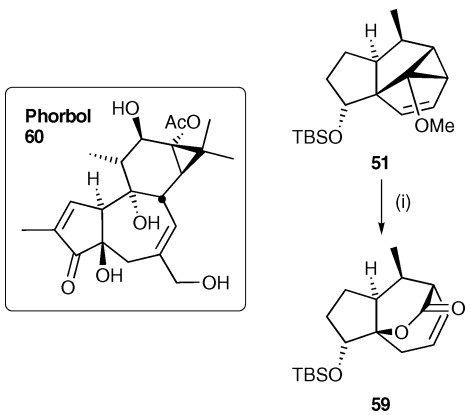
The synthesis was completed in a relatively straightforward fashion in which, following cleavage of the silicon protecting groups from **57**, a double oxidation with Jones' reagent accessed the corresponding keto-acid to set-up an iodolactonisation to establish the final ring of rudmollin (Scheme 19). Reductive removal of the iodide under radical conditions gave **58**. Stereoselective reduction of the ketone at C4 followed by hydrogenolysis of the benzyl protecting group delivered desmethylene rudmollin. The synthesis was then completed by introduction of the final



Scheme 19 Synthesis of rudmollin. *Reagents and conditions*: (i) KH, THF, BnBr (96%); (ii) HF–H_2O, CH_3CN, THF then Jones' reagent, acetone, 0–25 °C (82%); (iii) I_2, 2,4,6-collidine, CH_3CN then Bu_3SnH, AIBN, PhH, 80 °C (53%); (iv) $NaBH_4$, MeOH, −78–25 °C (92%); (v) H_2 (40 psi), 10% Pd/C, 70% $HClO_4$ (cat.), MeOH (82%); (vi) $(Me_2N)_3CH$, 90 °C then DIBAL, THF, 0 °C (54%).

methylene group using a method developed by Wasserman and Ives, and Ziegler and Fang.[35]

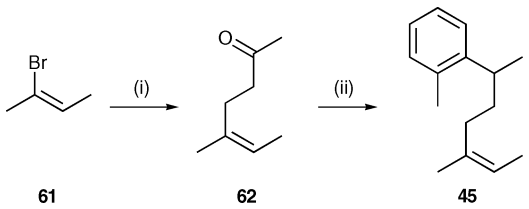
Returning to the selective fragmentation of the photocycloadducts, an alternative double fragmentation of **51** was examined (Scheme 20). Recognising the relationship of **51** to phorbol (**60**) an acid-catalysed cleavage, similar to that explored during the studies on α-cedrene, delivered a bicyclo[3.2.1]octane that, after reprotection, allowed a regioselective Baeyer–Villiger reaction to complete the sequence. This sequence neatly encapsulates the issues of processing of the cycloadducts by demonstrating the diversity of structures that might be accessed. Yet, in this latter case, the need to have the correct regioisomer of cyclopropane (unless photoequilibration is effective) is paramount.



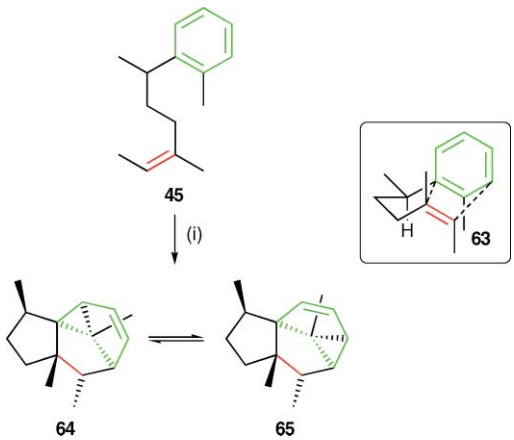
Scheme 20 Synthetic intermediate toward phorbol. *Reagents and conditions*: (i) H_2SO_4, H_2O, acetone, reflux then TBSCl, NEt_3, DMAP, DMF then TMSTf, $(TMSO)_2$, CH_2Cl_2, −30 °C.

Synthesis of isocomene[36]. Wender and Dreyer's synthesis of isocomene further develops some of the themes introduced in the α-cedrene work, but emphasises the importance of the methodology of cleaving the cyclopropane ring. Contrasting the results with those obtained in the silphinene synthesis below is instructive, particularly the position of its *gem*-dimethyl group (Scheme 24). The key bond construction in the synthesis of the photocycloaddition substrate **45** is again carried out according to the Hall protocol[30] with the additional consideration of alkene geometry addressed by use of *Z*-2-bromobut-2-ene as a starting material (Scheme 21).

Exposure of **45** to Vycor-filtered light from a medium pressure mercury lamp afforded, presumably *via* exciplex **63**, the two regioisomeric cyclopropanes **64** and **65** in 72% yield (Scheme 22).



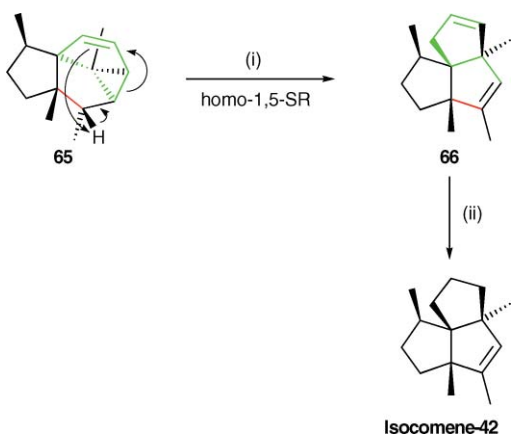
Scheme 21 Synthesis of isocomene; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) Li, Et_2O then CuI, −65 °C then methyl vinyl ketone (56%); (ii) *ortho*-bromotoluene, Li, Et_2O, room temperature, then **62** then NH_3, −78 °C (78%).



Scheme 22 Synthesis of isocomene; photocycloaddition of **45**. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (72%).

The tether adopts the now familiar distorted *syn*-pentane conformation bearing a pseudo-equatorial methyl group, and π-facial selectivity is controlled in the same way as for α-cedrene. An overriding preference for *exo*-selectivity is again observed and the stereochemistry of the alkene is retained during the cycloaddition process.

The ratio of **64** and **65** is interesting, being 4.5 : 1 after 10 minutes but 1 : 1 after 4 hours irradiation. Separation and re-subjection to photolysis demonstrated that these photoisomers could indeed be equilibrated, albeit with some decomposition. Given that, in this instance, both isomers were not equally suitable for conversion to isocomene (Scheme 23) *via* a homo-1,5-sigmatropic



Scheme 23 Synthesis of isocomene. *Reagents and conditions*: (i) 235–240 °C (69%); (ii) H_2, 5% Pd/C, hexane (98%).

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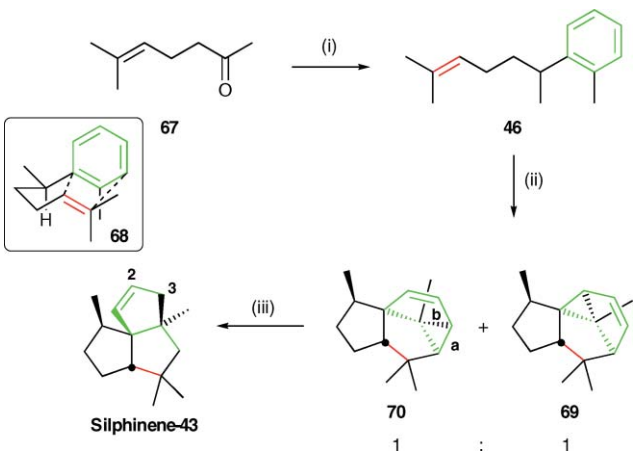
rearrangement, the ability to separate and photoequilibrate the isomers was potentially of synthetic value.

In the event, separation of **64** and **65** proved difficult on a large scale and it proved more efficient to thermolyse the mixture of the regioisomeric cyclopropanes to afford dehydroisocomene in 57% yield with thermal rearrangement of **64** to **65** preceding the homo-1,5-rearrangement.[37] As an aside, it may be noted that fragmentation to give an angular isomer results in the six carbons of the original benzene ring being converted into a linear chain forming part of the bicyclo[3.3.0]octane unit that arises from the alkene and arene moieties of the substrate.

Synthesis of silphinene[38]. Perhaps the most remarkable example of this group of *meta*-photocycloaddition reactions is that which leads to the synthesis of silphinene (Scheme 24). This angularly fused triquinane that features three quaternary carbons and four stereogenic centres has been synthesised in three synthetic operations in multigram quantities.



Scheme 24 Synthesis of silphinene. *Reagents and conditions*: (i) *o*-bromotoluene, Li (1% Na), Et_2O then NH_3, −78 to −33 °C, NH_4Cl (87%); (ii) *hν* (Vycor filter), pentane (70%); (iii) Li, $MeNH_2$, −78 °C (74%; 9 : 1 alkene isomers).

Application of Hall and McEnroe's procedure[30] to commercially available ketone **67** and lithiated *ortho*-bromotoluene afforded substrate **46** in 87% yield. Photolysis of **46** with Vycor-filtered light from a medium pressure mercury lamp gave a 1 : 1 mixture of regioisomeric cyclopropanes from an exciplex **68** whose conformation is dictated by previously discussed considerations. Only the 'angular' isomer **70** is suitable for conversion to silphinene[39] and its treatment with lithium in methylamine results in selective cleavage of bond **a** over **b**, on the basis of better orbital overlap with the intermediate alkene-derived radical anion, to afford silphinene **43** in a 9 : 1 ratio with the Δ2,3 isomer (74% yield). Consistent with this observation, the major isomer was calculated (MM2) to be the more stable alkene by 2.6 kcal mol^{-1}. The remarkable brevity of this route suggests that the *meta*-photocycloaddition is indeed a valuable strategic-level reaction.

Synthesis of desdimethylquadrone[40]

Quadrone is a tetracyclic sesquiterpene with interesting anticancer properties (Fig. 5).[41] Two synthetic studies on simplified versions of this structure have been carried out utilising the *meta*-photocycloaddition.

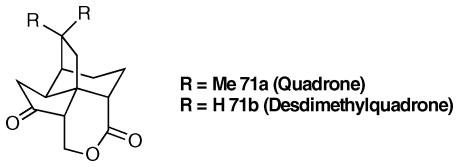
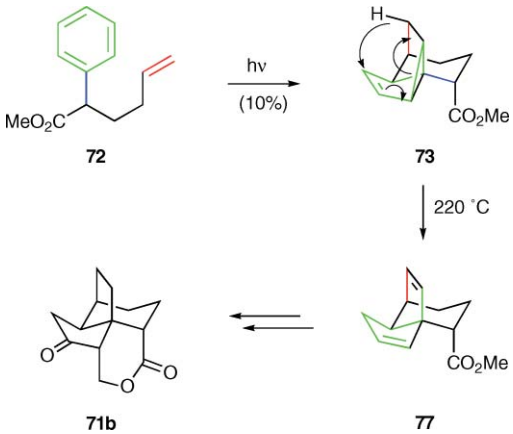


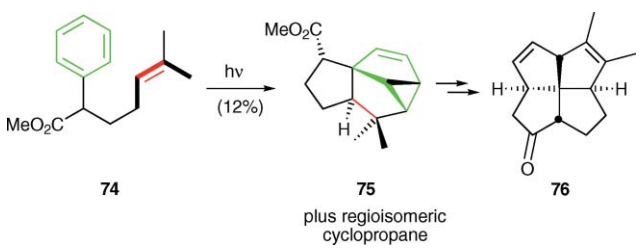
Fig. 5 Structure of quadrone.

Mehta's study on descarboxyquadrone[19] is based on an intermolecular *meta*-photocycloaddition and will be discussed in a later section (Scheme 61) whereas the study by Wender and Wolanin, directed toward desdimethylquadrone **71b**, is an example of a synthesis that employs an intramolecular *meta*-photocycloaddition (Scheme 25).[40]



Scheme 25 Synthetic study toward desdimethylquadrone.

Photolysis of **72**, although low yielding, afforded, as the main product, a single regioisomer of cyclopropane resulting from addition across the tether. That one cyclopropane is formed is understood in terms of the much higher energy of the alternative compound. Having obtained **73** the same homo-1,5-sigmatropic rearrangement deployed during the isocomene synthesis successfully afforded **77** that has three of the four rings of desdimethylquadrone **71b**. Addition across the tether (**72** to **73**) fits the pattern of adding across the strongest donor group unless sterics dictate otherwise, *e.g.* the presence of a *Z*-double bond. This latter point is illustrated by a parallel example (**74** to **75**) reported by Keese *et al.* during their work on the theoretically interesting fenestranes such as **76** (Scheme 26).[42]



Scheme 26 Keese and coworkers' approach to fenestranes.

Hirsutene, coriolin and laurenene

The following group of syntheses utilises photocycloadditions involving the 1,2,3-trisubstituted aromatics **78**, **79**/**80** and **81** with the tether positioned centrally (Fig. 6). Photocycloadditions in such substrates represent an increase in the complexity of the starting material and will deliver more hindered photoadducts, thereby testing the ability of the excited state of these molecules to overcome this increased barrier to reaction. The close structural relationship of hirsutene **82** and coriolin **83** suggested that a common strategy should be possible. The more complex fenestrane, laurenene **84**, has also proved accessible from a substrate of this class.

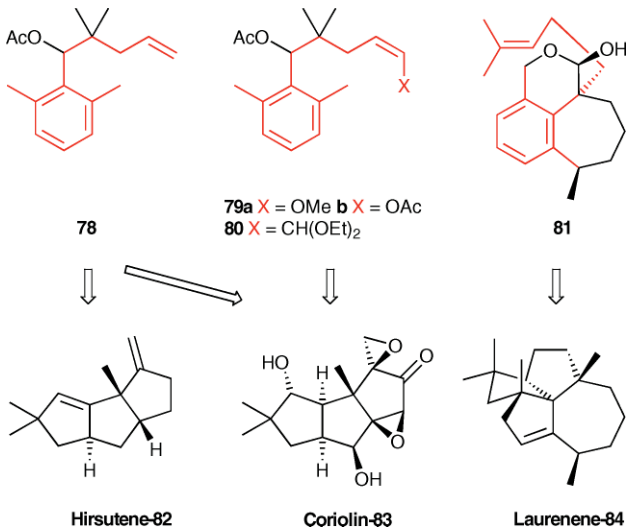
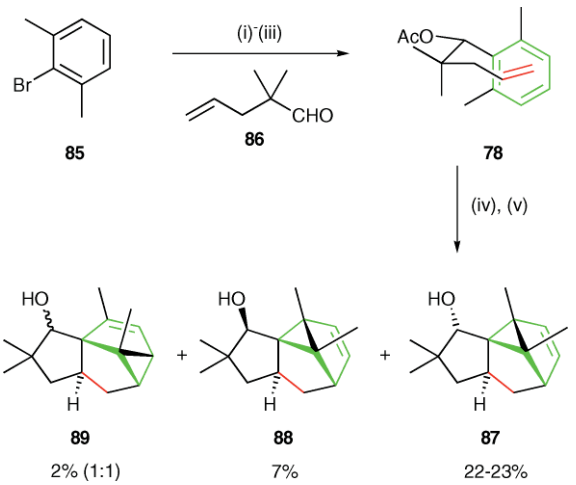


Fig. 6 1,2,3-Trisubstituted substrates leading to hirsutene, coriolin and laurenene.

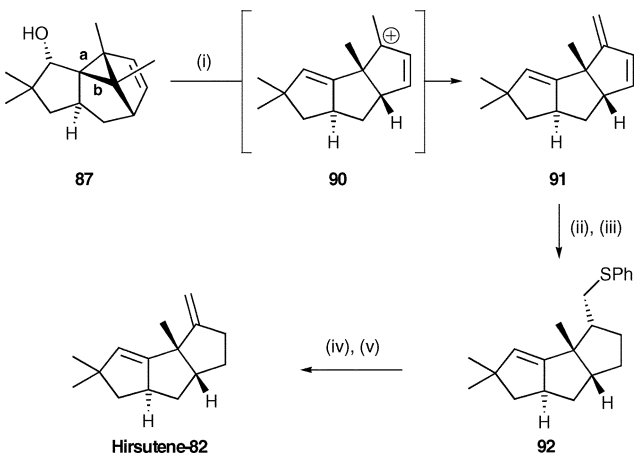
Synthesis of hirsutene[43] and coriolin[44]. Wender and Howbert prepared the substrate **78** in a straightforward manner by addition of the Grignard reagent derived from **85** to aldehyde **86**. Acetylation prior to photolysis, although not influential with regard to stereoselection, was found to raise the yield of this challenging cycloaddition. Photolysis under the previously described conditions delivered a mixture of four adducts **87**, **88** and two diastereoisomers of **89** with **87** predominating (Scheme 27). Though the yields are clearly lower than in the previous examples the steric hindrance (each of the carbons in the cyclopropanes of **87** and **88** are quaternary) is such that it is remarkable that the reaction proceeds at all. In addition, as Cornelisse has observed, polarisation of the electron cloud in the transition state would lead to one of the electron donating methyl groups sitting at a site that is polarised with negative charge (Scheme 11).[2a] It is tempting to conclude that the C–O bond is less effective at controlling asymmetric induction than the C–C bonds in the α-cedrene and isocomene examples. However, the high levels of induction seen in the synthesis of rudmollin suggest that it is more likely a consequence of steric interactions between the pseudo-equatorial C–O bond and the adjacent *gem*-dimethyl group in **78** making the corresponding pseudo-axial conformer less unfavourable. The familiar *exo*-selectivity is observed and despite the absence of a *Z*-double bond, 1,3-addition across the *ortho*-donor group is



Scheme 27 Synthesis of hirsutene; photocycloaddition of **78**. *Reagents and conditions*: (i) Mg, Et_2O; (ii) **86**; (iii) Ac_2O, DMAP (79% overall); (iv) *hν* (Vycor filter), cyclohexane; (v) $LiAlH_4$, Et_2O.

preferred to 2,6-addition since 2,6-addition would involve a very hindered transition state.

Cyclopropane ring-opening was initiated by treatment of **87** with camphorsulfonic acid (Scheme 28). Although the two bonds labelled **a** and **b** were judged to offer approximately equal overlap with the putative cation that develops on acid treatment, cleavage of **a** proceeds *via* a transition state leading to a tertiary allylic cation **90** that was neutralised by an E1 elimination to give **91**. Radical addition of thiophenol to the terminal double bond of **91** allows selective hydrogenation of the disubstituted double bond, mediated by Crabtree's catalyst, to afford **92**. Restoration of the terminal double bond by pyrolysis of the sulfoxide corresponding to **92** yielded hirsutene **82** in *ca.* 60% yield.



Scheme 28 Synthesis of hirsutene. *Reagents and conditions*: (i) 10-camphorsulfonic acid, C_6H_6 (71%); (ii) PhSH, 100 °C (78%); (iii) H_2, CH_2Cl_2, $[Ir(cod)PyPCy_3]PF_6$; (iv) $NaIO_4$, MeOH (86%); (v) 170 °C, $P(OMe)_3$ (60%).

Building on the successful preparation of hirsutene, two approaches to coriolin were described, the first developed from the photoadduct **87** prepared in the hirsutene synthesis (again underlining the vital aspect of how the cyclopropane of the

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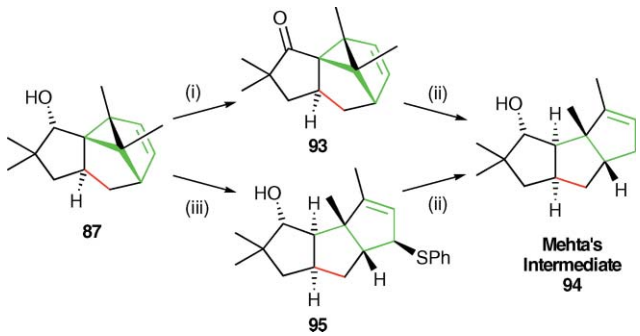
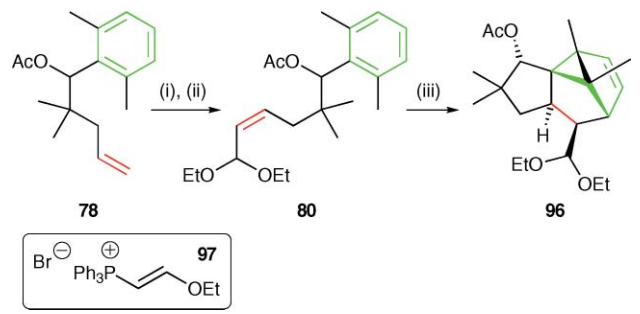
cycloadduct is cleaved) while the second begins from a more highly substituted precursor for the photocycloaddition.

Oxidation of alcohol **87** to give ketone **93** affords a means to introduce electrons into the molecule and the ketyl that results from treatment with lithium in liquid ammonia creates a radical adjacent to the cyclopropane with ring-opening controlled by the ability to access a tertiary allylic radical. Further reduction *in situ* affords Mehta and coworkers' intermediate toward coriolin **94**.[45] Alternatively, the aforementioned radical addition of thiophenol was employed to give **95** with the regiochemistry of ring-opening presumably being dictated by consideration of effective orbital overlap. Reductive cleavage of the C–S bond with lithium in liquid ammonia followed by protonation to give the more substituted double bond again delivers Mehta's intermediate **94** (Scheme 29).



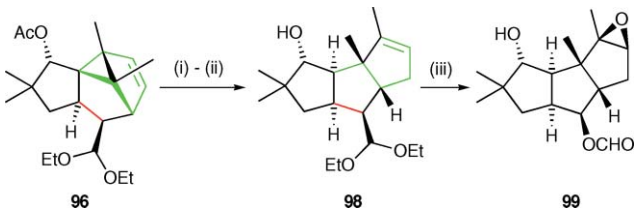
Scheme 29 First formal synthesis of coriolin. *Reagents and conditions*: (i) PDC (74%); (ii) Li, NH_3, Et_2O, EtOH (92%); (iii) PhSH (1 equiv.) (quant.).

In an attempt to provide a more direct route to coriolin, photolysis of substrates bearing various *Z*-disubstituted double bonds were examined. Interestingly **79a/b** proved very poor substrates, a situation that parallels the relatively inefficient intermolecular cycloaddition of vinylacetates to aromatic compounds *en route* to isoiridomyrmecin, modhephene and descarboxyquadrone (Schemes 56 and 58). By contrast, photolysis of **80** was relatively successful and the modest 15% yield of **96** obtained must be judged against the extreme steric hindrance that develops in the transition state of the photocycloaddition reaction and the significant increase in useful complexity that is introduced into the product (Scheme 30).



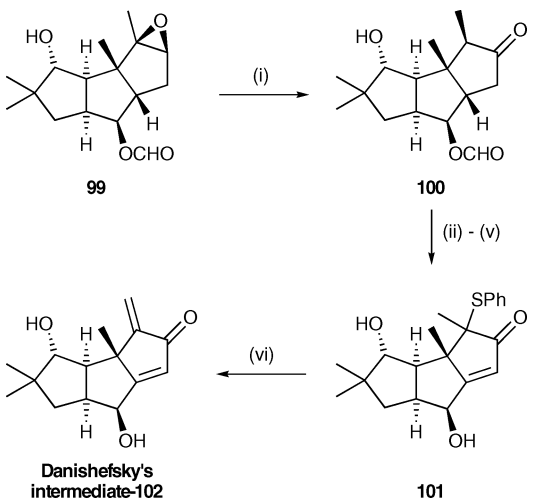
Scheme 30 Second formal synthesis of coriolin; a new photolysis substrate. *Reagents and conditions*: (i) O_3, MeOH, −78 °C (61%); (ii) **97**, NaOEt, CH_2Cl_2 (55%); (iii) *hv* (Vycor filter), cyclohexane (~15%).

Application of the thiophenol ring-opening tactic followed by a dissolving metal reduction establishes the required linear triquinane ring system (**98**) then treatment with *m*-CPBA in moist dichloromethane epoxidises the double bond and allows acid-catalysed hydrolysis of the diethylacetal with concomitant Baeyer–Villiger reaction to afford formate **99** (Scheme 31). The ease of the latter reactions partially compensates for the disappointing yield from photolysis of **80**.



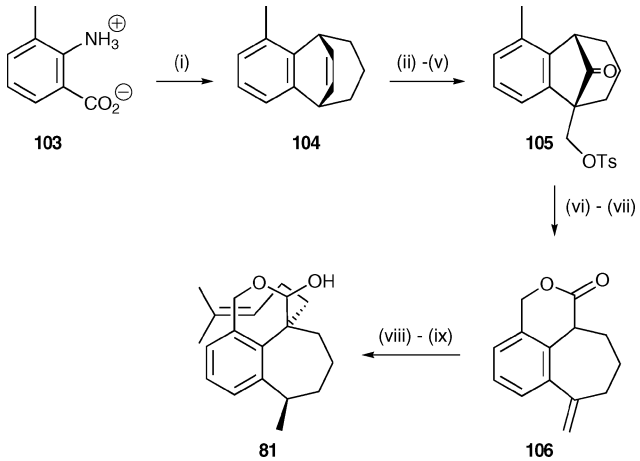
Scheme 31 Second formal synthesis of coriolin; establishing the linear triquinane framework. *Reagents and conditions*: (i) PhSH (1 equiv.), 100 °C (72%); (ii) Li, NH_3, Et_2O (80%); (iii) *m*-CPBA, CH_2Cl_2, H_2O (67%).

From **99**, Lewis acid-catalysed rearrangement of the epoxide gave ketone **100** which, following unsaturation using Saegusa *et al.*'s methodology,[46] required only introduction of a thiophenoxide α to the carbonyl group (**101**) to complete a formal total synthesis. Further elimination of the corresponding sulfoxide to afford diene **102** permitted correlation with Danishefsky's late-stage intermediate to coriolin (Scheme 32). The succinctness of this sequence emphasises the utility of the photocycloadduct in the preparation of these terpenoid compounds.



Scheme 32 Second formal synthesis of coriolin. *Reagents and conditions*: (i) BF_3, C_6H_6; (ii) LDA, Me_3SiCl; (iii) $Pd(OAc)_2$, CH_3CN; (iv) LDA, $PhSSO_2Ph$ (42% over 4 steps); (v) HOAc, H_2O, THF (3 : 1 : 1) (100%); (vi) *m*-CPBA, EtOAc, heat.[47]

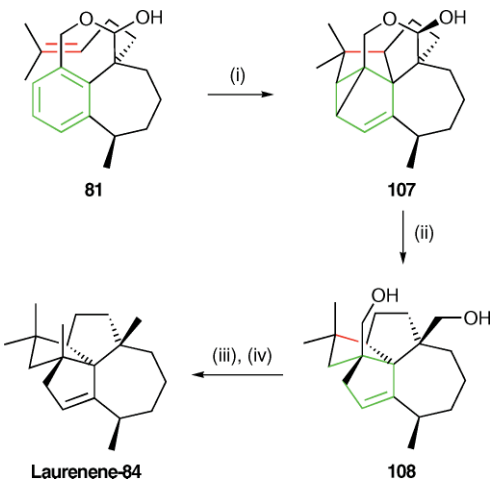
Synthesis of laurenene[18]. Preparation of the naturally occurring fenestrane, laurenene, represents one of the most complex molecules prepared using the alkene–arene *meta*-photocycloaddition reaction. The substrate **81** was synthesised by an elegant route that employed a Diels–Alder reaction of a benzyne to cycloheptadiene to fuse on the seven-membered ring in **104** (Scheme 33). After cleavage of the alkene by ozonolysis, a regioselective aldol reaction, with enolisation controlled by the aromatic methyl group, set up a Grob-type fragmentation of the



Scheme 33 Synthesis of laurenene; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) isopentyl nitrite, Cl_3CCO_2H, cyclohepta-1,3-diene, CH_2Cl_2 (84% based on recovered starting material); (ii) O_3, Me_2S, NEt_3 (68%); (iii) $Zn(BH_4)_2$, Et_2O (98%); (iv) TsCl (72%); (v) PCC (98%); (vi) NBS, AIBN then KOH (72%); (vii) H_2, Pt (96%); (viii) LDA, DMPU, homoprenyliodide (48%); (ix) $LiAlH_4$, THF (95%).

derived keto-tosylate **105**. Prior to hydroxide treatment the methyl group was brominated with *N*-bromosuccinimide (NBS) to deliver lactone **106** concomitant with fragmentation. Hydrogenation of the alkene prepared the compound for stereoselective homoprenylation of the lactone enolate with good (8 : 1) 1,4-asymmetric induction. Finally, reduction to lactol **81** completed the synthesis of the photocycloaddition substrate.

Photocycloaddition of **81** proceeded to a single 'angular' regioisomer of cyclopropane **107** in 51% yield with the expected *exo*-selectivity (Scheme 34). This relatively unusual occurrence (*cf.* studies on aphidicolin and stemodin, Scheme 55) was rationalised by Macromodel calculations that suggest that the alternative 'linear' regioisomer is significantly less stable. Contrasting this outcome with the prototypical case, discussed in the introduction (Fig. 1), highlights the importance of calculating each case individually to take account of the effect of substituents and fused rings. Of particular note was the improved yield obtained



Scheme 34 Synthesis of laurenene. *Reagents and conditions*: (i) *hv* ($BiCl_3$ filter) (51%); (ii) Li, $MeNH_2$, −6 °C (96%); (iii) KHMDS, HMPA, $ClPO(NMe_2)_2$ (55%); (iv) Li, $EtNH_2$ (65%).

in this challenging substrate when the incident light is filtered through $BiCl_3$ solution (21% higher than with a Vycor filter), the problem being traced, in part, to product absorbance and subsequent degradation. In the authors' experience, when a cycloaddition is slow other processes often compete. In contrast to the studies on hirsutene and coriolin the aromatic moiety is not symmetrical; that addition does not occur across the tether is unsurprising but addition across just one of the two *ortho*-substituents is worthy of comment, particularly as this is probably the worst donor of the two. Presumably, this selectivity is based on steric grounds. Orbital overlap controlled reductive cleavage of the cyclopropane with concomitant reduction of the lactol to a diol **108** leaves only reductive removal of the hydroxyls *via* their phosphordiamidates[48] to complete an elegant solution to this complex problem (Scheme 34).

Silphiperfolenes, retigeranic acid and subergorgic acid

In a further series of syntheses Wender,[49] Singh[51] and deLong[52] have explored the potential of a second pattern of trisubstituted benzenes of general structure **109** (Fig. 7). They served to examine an alternative allylic strain element to control π-facial selectivity and introduced an interesting group of radical based methods for opening of the cyclopropanes with concomitant formation of a C–C bond.

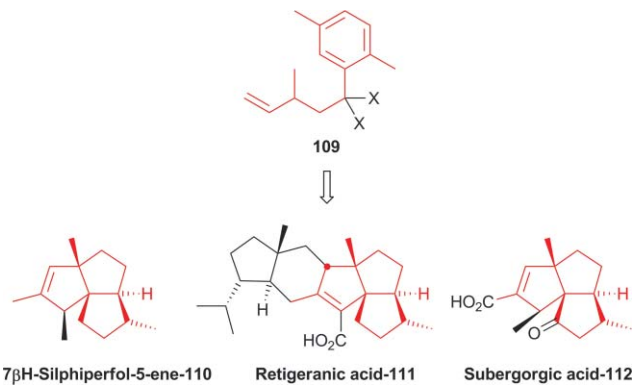
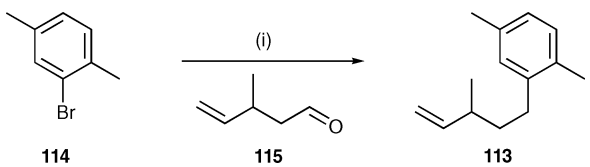


Fig. 7 A common substrate motif for the synthesis of the silphiperfolenes, retigeranic acid and subergorgic acid.

Synthesis of the silphiperfolenes[49]. The substrate **113** is prepared in a straightforward manner using the procedure by Hall and McEnroe in 92% yield (Scheme 35).[30]



Scheme 35 Synthesis of the silphiperfolenes; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) Li, Et_2O, **115** then NH_3 (92%).

The photocycloaddition of **113** is typical in proceeding from the conformer shown (Scheme 36) with *exo*-selectivity. However, in this instance, π-facial selectivity is controlled by the allylic strain element (highlighted in blue) that develops into a situation where

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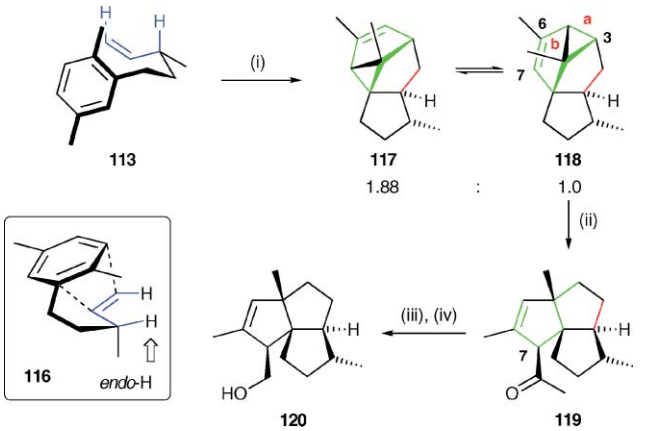
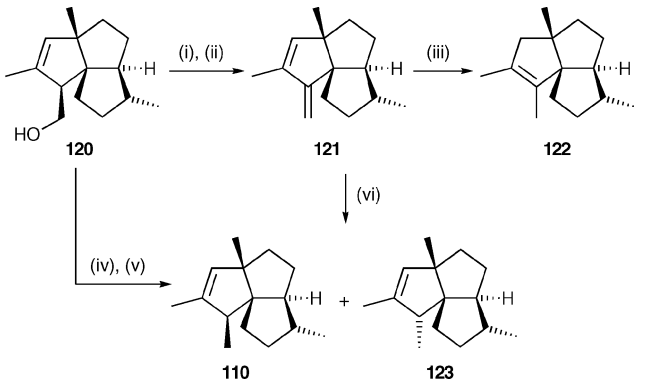


Scheme 36 Synthesis of the silphiperfolenes; preparation of a common intermediate. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (72%); (ii) *hv* (Pyrex filter), CH_3CHO, 0 °C (60%); (iii) Br_2, NaOH, H_2O, dioxane, reflux (95%); (iv) $LiAlH_4$, THF, reflux (91%).



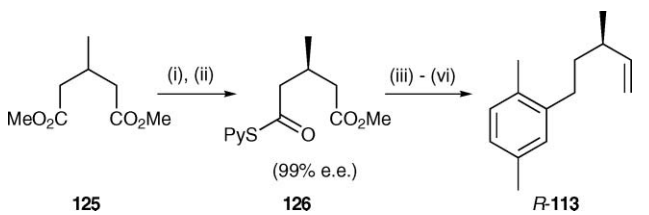
Scheme 37 Synthesis of silphiperfol-6-ene, 7αH-silphiperfol-5-ene and 7βH-silphiperfol-5-ene. *Reagents and conditions*: (i) $PhNO_2SeCN$, *n*-Bu_3P, THF (99%); (ii) H_2O_2, THF (78%); (iii) Li, NH_3, Et_2O, −33 °C (91%); (iv) *n*-BuLi, $(EtO)_2POCl$, THF–TMEDA (4 : 1) (76%); (v) Li, *t*-BuOH, $EtNH_2$, THF, 0 °C (55%; **110** : **123**, 1 : 0); (vi) $(Ph_3P)_3RhCl/H_2$, C_6H_6–EtOH (3 : 1) (89%; **110** : **123**, 1 : 2.8).

the exciplex **116**, that precedes cycloaddition, has the hydrogen and not the methyl in an *endo*-position. Again, it may be noted that, despite the terminal alkene, addition takes place across the donor methyl group not across the tether. Two photocycloadducts **117** and **118** are obtained in a 1.88 : 1 ratio favouring the 'linear' isomer in 72% yield, clearly superior to the more sterically congested 1,2,3-trisubstituted aromatics discussed previously. Given that it is the minor regioisomer that is required to complete the synthesis, the ability to photoequilibrate **117** and **118** is significant. However, as is often the case, some degree of degradation accompanies this procedure (*cf.* isocomene (Scheme 22), subergorgic acid (Scheme 41) and crinipellin B (Scheme 46)).

Having obtained the angular isomer **118** the cyclopropane is then regioselectively cleaved with concomitant formation of the required C–C bond at C7. This second photochemical step, in which acetaldehyde is added to **118**, is noteworthy for its highly stereoselective addition to the convex face and regioselective cleavage of the cyclopropane *via* a secondary rather than the apparently available tertiary radical. This is presumably explained by a more favourable alignment of the intermediate radical formed at C6 with bond **a** than bond **b** and the reaction being under kinetic control. The method is based upon a report by Kharasch *et al.* in which, following n–π* photoexcitation of the acetaldehyde, Norrish type I fragmentation can give an acyl radical (note the use of a Pyrex filter to cut off shorter wavelength radiation that can lead to direct extrusion of CO without radical generation).[50] This species begins a radical chain process by adding to the alkene in **118**. Following fragmentation of the cyclopropane with concomitant generation of a secondary radical at C3, hydrogen abstraction from acetaldehyde completes the chain. The two carbon atoms so added were reduced to the required single carbon atom in **120** by bromoform reaction and then treatment with $LiAlH_4$ (Scheme 36).

From the common intermediate **120** elimination of the alcohol to give diene **121** followed by reduction of the diene with lithium in liquid ammonia gave silphiperfol-6-ene **122** (Scheme 37). By contrast, selective reduction of the terminal alkene with Wilkinson's catalyst provided a 2.8 : 1 mixture of 7αH-silphiperfol-5-ene **123** to 7βH-silphiperfol-5-ene **110**. A highly stereoselective route to 7βH-silphiperfol-5-ene **110** was afforded by conversion of the alcohol of **120** to a diethyl phosphate followed by reduction with lithium in ethylamine (Scheme 37).

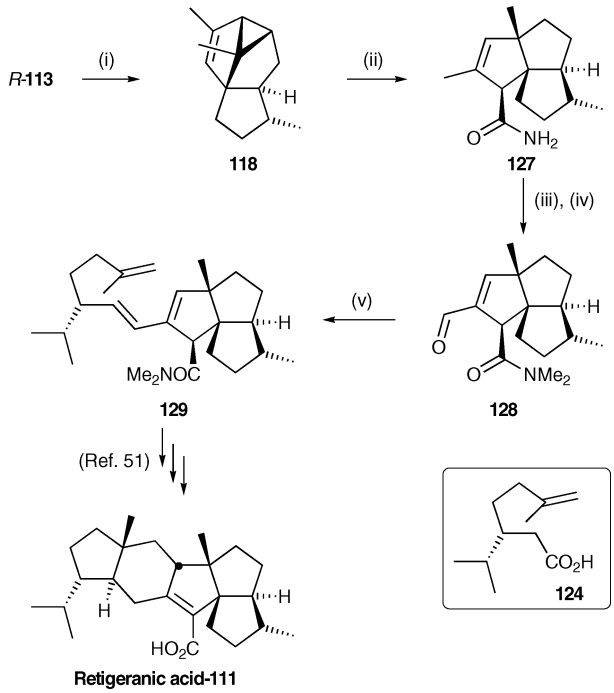
Synthesis of retigeranic acid[51]. Developing the work on the silphiperfolenes to approach the significantly more complex compound retigeranic acid **111** mandated a convergent approach in which the angularly fused triquinane portion would be combined, at a late stage of the synthesis, with chiral fragment **124** (Scheme 39). To remove the inevitable problems with separation of diastereoisomers, **113** would be required in homochiral form. Thus the straightforward Hall procedure is replaced by a route based on enzymatic desymmetrisation (Scheme 38).



Scheme 38 Synthesis of retigeranic acid; preparation of optically active **113**. *Reagents and conditions*: (i) pig liver esterase; (ii) dipyridyl disulfide, Ph_3P, CH_2Cl_2 (96%); (iii) *p*-xylyl bromide, Li, Et_2O, CuI, −78 °C to 0 °C then **126**, −78 °C (90%); (iv) $LiAlH_4$, Et_2O; (v) H_2, 10% Pd/C, EtOH–$HClO_4$ (100 : 1) (93%, 2 steps); (vi) *n*-Bu_3P, *o*-nitrophenylSeCN then 30% H_2O_2 (84%).

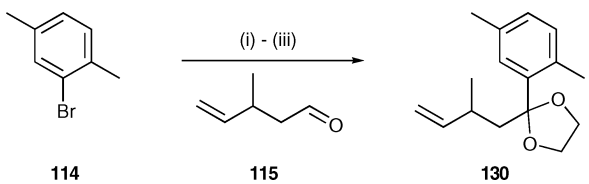
R-**113** was then photocyclised as in Scheme 36 but on this occasion cyclopropane ring-opening was initiated using a one-carbon radical generated by photolysis of formamide in the presence of **118** (Scheme 39). Following dimethylation of the nitrogen of **127** the allylic methyl group is oxidised with SeO_2 to set up an enolate-mediated coupling with **124**. The final steps of the synthesis were based around a key intramolecular Diels–Alder reaction of **129**.[51]

Synthesis of subergorgic acid[52]. The final synthesis of this group, subergorgic acid, explores the influence of more significant



Scheme 39 Synthesis of retigeranic acid. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (72%); (ii) *hv* (Pyrex filter), $HCONH_2$, acetone, *t*-BuOH; (iii) KOH, DMSO, MeI (80%); (iv) SeO_2, *t*-BuOOH, $(CH_2Cl)_2$, reflux (53%); (v) **124**, LDA, THF, 50 °C to 0 °C then add to **128** (−78 °C), warm to 25 °C; AcOH then *N*,*N*-dimethylformamide dimethyl acetal, reflux (65%).

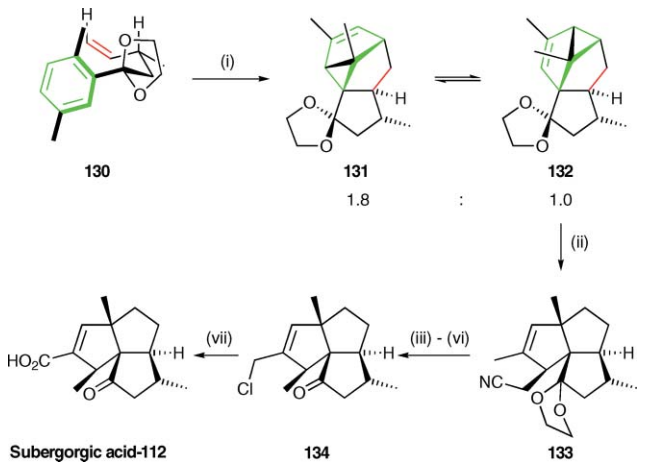
steric hindrance adjacent to the aromatic ring, specifically a cyclic ketal. The synthesis of the precursor to the photocycloaddition requires only a slight modification from that described for **113** (Scheme 40).



Scheme 40 Synthesis of subergorgic acid; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) Li, Et_2O, then **115**; (ii) PCC, CH_2Cl_2; (iii) $(CH_2OH)_2$, 10-camphorsulfonic acid, C_6H_6, reflux.

Photolysis of **130**, resulting in the formation of two regiosomeric cyclopropanes, each with three contiguous quaternary centres, represents a demanding reaction (*cf.* studies on the synthesis of grayanotoxin-II (Scheme 48)). The reaction was found to require stringent exclusion of the corresponding ketone to avoid complex mixtures and even with this precaution the reaction was only run to *ca.* 66% completion to give a 42% yield (61% based on recovered starting material) as a result of photolability of the product. Interestingly, despite the influence of the ketal on the photolysis conditions, the ratio of cyclopropane isomers was largely unaffected compared to those formed from **113** (Scheme 41).

The 'angular' isomer **132** was ring-opened using the same radical-based tactic discussed previously but this time initiated by thermal fragmentation of dibenzoyl peroxide. Reductive cleavage



Scheme 41 Synthesis of subergorgic acid. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (42%); (ii) dibenzoyl peroxide, CH_3CN, reflux (67%); (iii) K, 18-crown-6, toluene (90%); (iv) *m*-CPBA (80%); (v) *N*-cyclohexyl,*N*-isopropylamine, MeMgBr (70%); (vi) $SOCl_2$, pyridine (85%); (vii) DMSO, $AgBF_4$ then NEt_3 (85%) then $NaClO_2$.

of the cyano group in **133** by the method by Oishi *et al.*[53] was followed by a three-step activation of the allylic methyl group with the ketal being lost during the thionyl chloride treatment to afford **134**. The final oxidation was effected in two stages with a silver-mediated Kornblum oxidation followed by treatment with sodium chlorite (Scheme 41).

Ceratopicanol, crinipellin B and grayanotoxin-II

The final group of three trisubstituted aromatic compounds **135**, **136** and **137** that have been used in natural product synthesis display the difficult 1,2,3-trisubstituted pattern of substitution discussed earlier but with the tether positioned terminally not centrally (Fig. 8). Thus, if photocycloaddition was to occur in the normal way, across the donor group, it would necessarily deliver adducts with at least three contiguous quaternary centres.

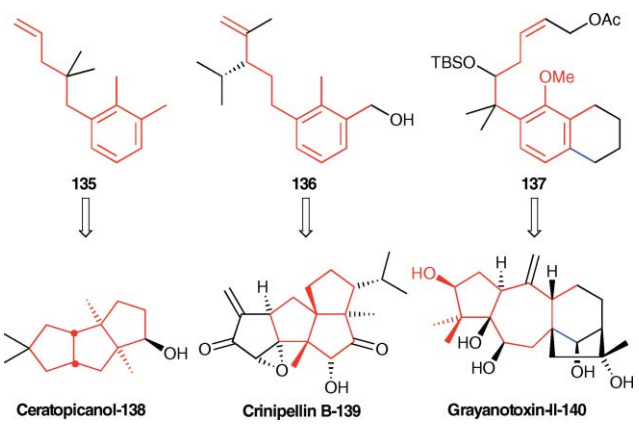


Fig. 8 1,2,3-trisubstituted aromatic subunits studied for the synthesis of ceratopicanol, crinipellin B, and grayanotoxin-II (tetrasubstituted aromatic).

Synthesis of ceratopicanol[16]. Chanon *et al.* have described a short and efficient synthesis of ceratopicanol based around an intramolecular arene *meta*-photocycloaddition as part of their

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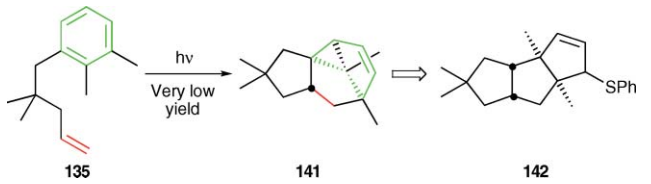
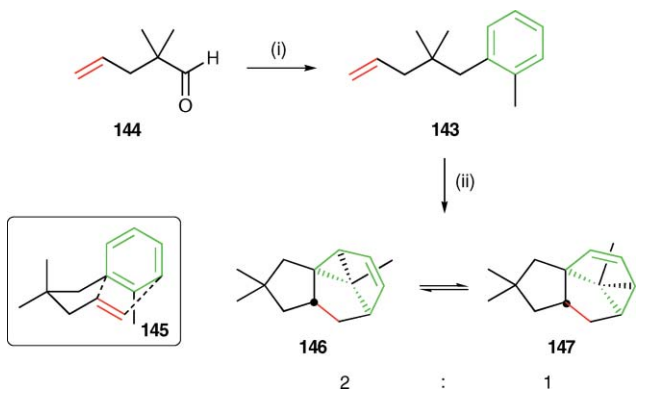
interest in holosynthons.[54] However, they reported only very low yields for the transformation of **135** into **141**, despite the kinetic advantage that often attends the presence of a *gem*-dimethyl group in the tether of a ring-closing process, indicating the great difficulty that these substrates present (Scheme 42).



Scheme 42 Synthesis of ceratopicanol; attempted photocycloaddition of **135**.

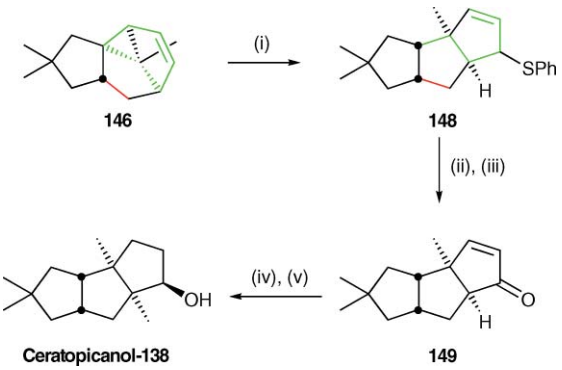
Based on this result the synthetic plan was adapted to begin with a less substituted aromatic **143** that was readily prepared by the Hall procedure in 98% yield from **144** (Scheme 43).[30] The photolysis proceeded according to plan, through an *exo*-oriented exciplex **145**, with addition across the donor methyl group, in a much improved 72% yield (again we note that in the absence of a *Z*-substituted double bond the preference is to avoid addition across the tether). The 'linear' isomer **146** was found to be the major isomer whilst the 'angular' isomer **147** was recycled by photoequilibration.



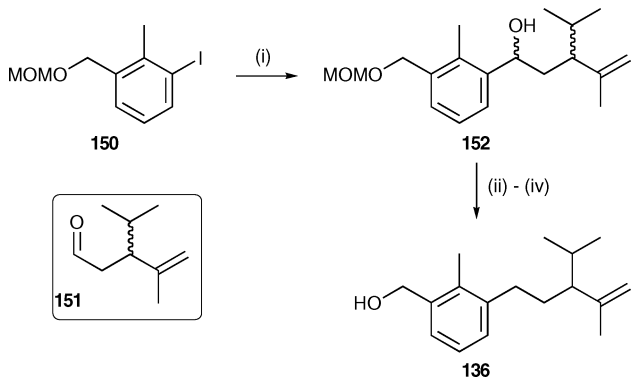
Scheme 43 Synthesis of ceratopicanol; photocycloaddition of **143**. *Reagents and conditions*: (i) Li, *o*-bromotoluene then Li, NH_3, NH_4Cl (98%); (ii) *hv* (254 nm), cyclohexane (72%).

Radical addition of thiophenol to **146** according to Wender and Howbert's method[44] (though with the additional use of ultrasound) afforded the nor-ceratopicanol skeleton **148** (Scheme 44). Reductive cleavage of the C–S bond followed by oxidation to the corresponding ketone gave **149**. The ketone allowed introduction of the troublesome extra methyl group stereoselectively and in excellent (97%) yield. The synthesis was completed by a tandem conjugate reduction–1,2-reduction of the enone moiety by $NaBH_4$ to deliver the correct diastereoisomer of ceratopicanol **138**.

Synthesis of crinipellin B[55]. Wender and Dore's synthesis of crinipellin B **139** required access to a relatively complex photocycloaddition substrate **136**. The aromatic portion **150** was prepared from 3-nitro-2-methyl benzoic acid in three pots then, after halogen–lithium exchange, coupled to aldehyde **151**, itself available in three steps from isobutyraldehyde, to give **152** (Scheme 45). Oxidation to the ketone allowed deoxygenation



Scheme 44 Synthesis of ceratopicanol. *Reagents and conditions*: (i) PhSH, 100 °C, ultrasound (97%); (ii) Li, NH_3, −78 °C (80%); (iii) CrO_3-3,5-dimethylpyrazole (60%); (iv) LDA, −78 °C, MeI (97%); (v) $NaBH_4$, EtOH (60%).

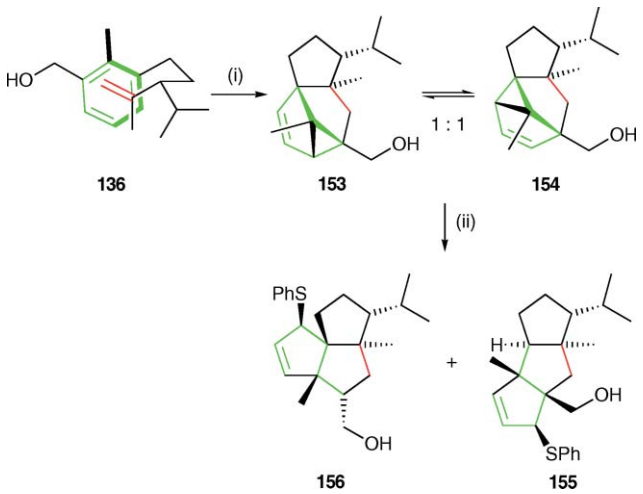


Scheme 45 Synthesis of crinipellin B; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) *t*-BuLi, THF, −78 °C then **151**; (ii) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 0–22 °C (78%; 2 steps); (iii) H_2NNH_2, KOH, diethylene glycol, 118–122 °C then 230–232 °C (92%); (iv) 3 M HCl, THF, reflux (93%).

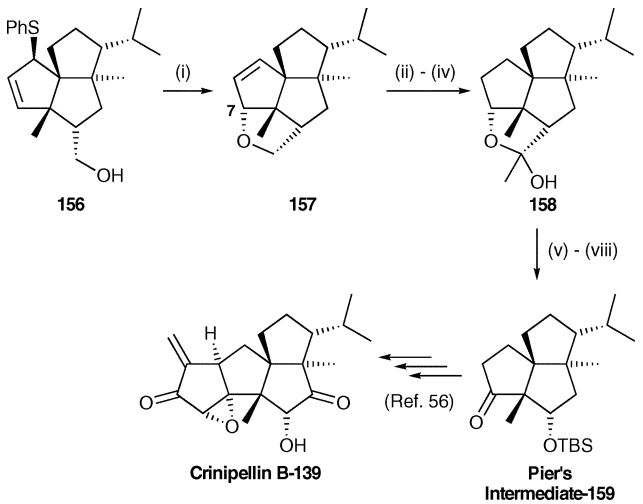
via a Wolff–Kishner reduction and cleavage of the MOM group afforded the substrate **136**.

Despite the significant steric hindrance of this substrate and the four contiguous quaternary asymmetric centres formed in each of the products a 33% yield of the two regioisomeric cyclopropanes **153** and **154** was obtained. As with the isocomene synthesis it was observed that short irradiation times gave a mixture with a preponderance of the linear isomer **154**, whereas more prolonged irradiations delivered an equal mixture. As observed in other cases, *e.g.* subergorgic acid, the adducts proved photolytically labile. In practice, the crude was treated with thiophenol under radical conditions[44] to afford an easily separable mixture of linear and angular triquinanes **155** and **156** (Scheme 46).

The particular value of the thiophenol mediated cyclopropane ring-opening is evident as it facilitates the required oxygenation at C7. Thus the sulfonium ion formed by methylation of **156** with Meerwein's salt induces an S_N2' tetrahydrofuran ring-closure to give **157** (Scheme 47). The process of fragmenting the cyclopropane has thereby significantly advanced the synthesis. The double bond, having served its purpose was then removed by hydrogenation rendering the methylene group adjacent to the oxygen the most readily oxidisable, the latter being realised by treatment with ruthenium tetraoxide. Addition of methyl



Scheme 46 Synthesis of crinipellin B; photocycloaddition and fragmentation of **136**. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (33%); (ii) PhSH, 95–105 °C (68%).

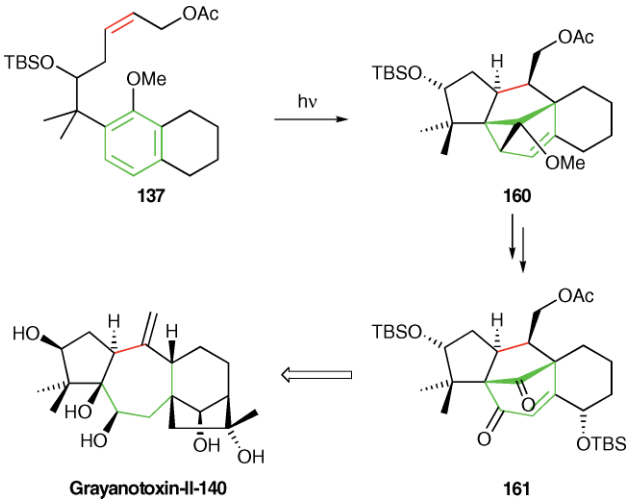


Scheme 47 Synthesis of Piers' intermediate for crinipellin B. *Reagents and conditions*: (i) Me_3OBF_4, CH_2Cl_2, reflux (74%); (ii) H_2 (49 psi), 10% Pd/C, EtOAc (97%); (iii) $RuCl_3$, $NaIO_4$, 2 : 2 : 3 CCl_4–CH_3CN–H_2O (72%); (iv) MeLi, THF, −78 °C (95%); (v) *m*-CPBA, $CHCl_3$ (55%); (vi) Dess–Martin periodinane, CH_2Cl_2 (87%); (vii) $Ba(OH)_2$, MeOH, 0 °C (80%); (viii) TBSOTf, Et_3N, CH_2Cl_2, −78 °C (86%).

lithium leads to hemi-acetal **158** from which the equilibrium keto-alcohol form was oxidised under Baeyer–Villiger conditions. The corresponding differentially-protected diol allows selective oxidation to afford Piers' intermediate **159** and hence complete a formal total synthesis of crinipellin B.[56]

Synthetic studies toward grayanotoxin-II[2b,57]. A final example of this type of substrate arose from studies by Wender and Olivero toward grayanotoxin-II **140** in which, in addition to the difficult 1,2,3-substitution pattern, is present a fourth substituent in **137**. Despite these apparent steric issues the reaction was successful and at least one compound examined in this series gave a yield as high as 50% (Scheme 48).[14]

Overall, these substrates are on the limit of what is possible with this reaction but impressive syntheses are still achievable.



Scheme 48 Synthetic studies toward grayanotoxin-II.

Cleaveable tethers

The use of cleavable tethers has not been widely explored but three published studies have served to indicate the potential value of this tactic. In addition, Stork has reported the synthesis of 3-oxosilphinine **162** using a silicon-tethered *meta*-photocycloaddition (Fig. 9).[58]

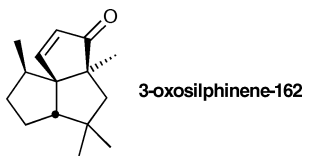


Fig. 9 Structure of 3-oxosilphinine.

Synthetic studies on cerapicol[22]. As part of a study on tandem Norrish type I-*meta*-photocycloaddition reactions De Keukeleire obtained **165**, upon irradiation of **163**, *via* lactols **164** (Scheme 49). Interestingly, the photocycloaddition takes place across the donor group in **164** despite the presence of a *Z*-double bond to give **165**. Alkene π-facial selectivity was imposed by the tether and the usual *exo*-stereoselectivity was found. As with the previously discussed studies on desdimethylquadrone (Scheme 25) only a single regioisomer of product was obtained. The cleavage of the cyclopropane in the δ-lactone corresponding to **165** is interesting and contrasts with the fragmentation of both the α-cedrene and rudmollin intermediates, **36/37** and **51/52** respectively, in not cleaving the bond adjacent to the alkene (*cf.* gelsemine, Scheme 50 and 51) but rather undergoes protonation to afford hemi-acetal **166**. The authors note that the observed mode of cleavage leads to the more stable product as judged by calculation using a combined SCA–MacroModel approach. The lone pairs on the ether oxygen may also align favourably to assist cleavage of this C–C bond. The clear relationship of **166** to compounds with a bullerane skeleton, *e.g.* cerapicol **167**, suggests a possible application of this type of *meta*-photocycloaddition. Srinivasin and Hoye and others noted that intermolecular photocycloadditions to 2-methylanisole were slow and low yielding, though Hoye was able to isolate an 11% yield of photoadducts, after acid hydrolysis, following a 7 day irradiation. This in turn suggests a possible worth of this cleavable

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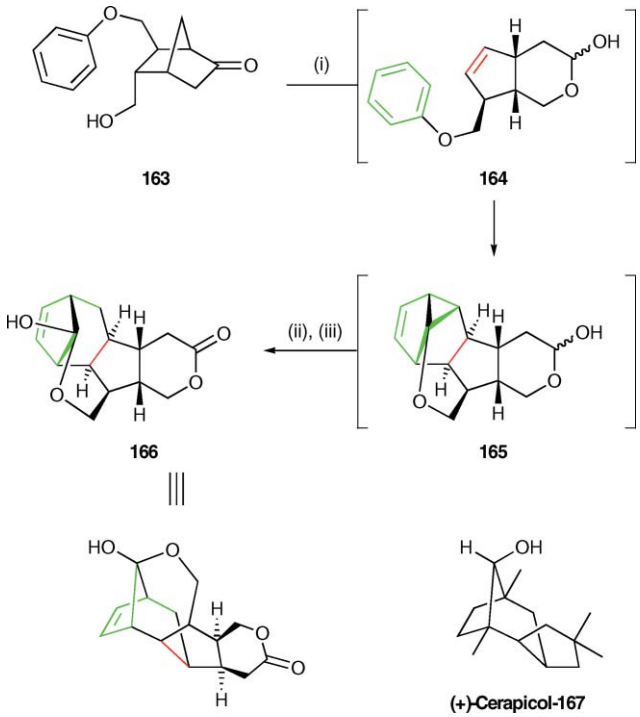


Scheme 49 Synthetic studies toward cerapicol. *Reagents and conditions*: (i) *hv*, cyclohexane–EtOAc (5 : 1); (ii) PDC, CH_2Cl_2 (34% overall); (iii) dil. HCl (quant.).

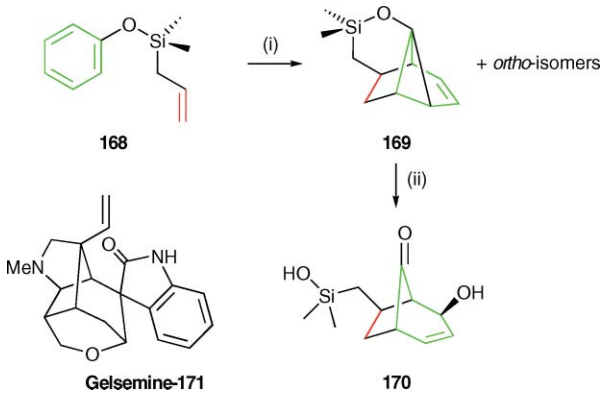
tether when the more hindered substrate required to prepare cerapicol is used, a point noted by Wender and Howbert in the context of the α-cedrene synthesis.[1,59]

Synthetic studies toward gelsemine[60]. Penkett *et al.*, following earlier work by Fleming *et al.*,[61] carried out a study of the utility of a silicon-linked tether. The photocycloaddition of **168** led to addition across the tether, as seen in the studies on desdimethylquadrone (Scheme 25) and cerapicol (Scheme 49), and gave rise to the same, single, regioisomer of *meta*-photocycloaddition product **169** in 38% yield (accompanied by 16% of products arising from initial *ortho*-addition). The potential value of the tether, as opposed to an equivalent intermolecular reaction, resides in the formation of this single regioisomeric cyclopropane (and with *exo*- rather than *endo*-stereoselectivity). Thus, treatment of **169** with *m*-CPBA gives epoxidation with concomitant fragmentation to afford a single regioisomer of allylic alcohol **170** containing the bicyclo[3.2.1]octane skeleton found in gelsemine **171** (Scheme 50).

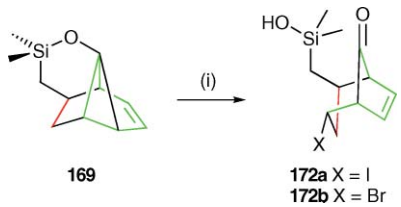
The fragmentation of cycloadduct **169** under alternative conditions flags up the subtlety in the preferred mode of reactivity. Thus, in the same manner as observed with protonation of the lactone corresponding to **165** (Scheme 49), treatment of **169** with either *N*-iodosuccinimide (NIS) or NBS leads to reaction at the cyclopropyl bond distal to, rather than proximal to, the alkene to afford **172a/b** (Scheme 51).

Studies on Heck reaction-induced fragmentation of such vinylcyclopropanes have lead to further developments in the application of *meta*-photocycloadducts toward a synthesis of gelsemine.[60c,d]

Additional functionality was introduced into the core of the molecule by photolysis of substrate **173**. Following fragmentation of the initial photocycloadduct a single regioisomer of allylic

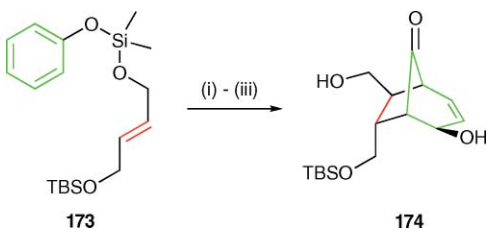


Scheme 50 Synthetic studies toward gelsemine. *Reagents and conditions*: (i) *hv*, hexane (38%); (ii) *m*-CPBA (56%).



Scheme 51 Fragmentation of *meta*-photocycloaddition product **169**. *Reagents and conditions*: (i) NIS, X = I (57%) or NBS, X = Br (51%).

alcohol **174** was obtained and it may be inferred from this result that a single regioisomer of photocycloadduct was generated (Scheme 52). Of particular interest is the presence of a four-atom tether in **173**. A relatively modest yield of **174** was obtained indicating that, in this instance, the presence of oxygen atoms in the tether was not as effective in improving yields as, say, in the examples in Schemes 9 and 10. This may imply that other features, *e.g.* rings that limit the conformational freedom of a tether, are more significant in raising yields in substrates with four-atom tethers in accordance with the paradoxical nature of including oxygen in the tether, *vide supra.*

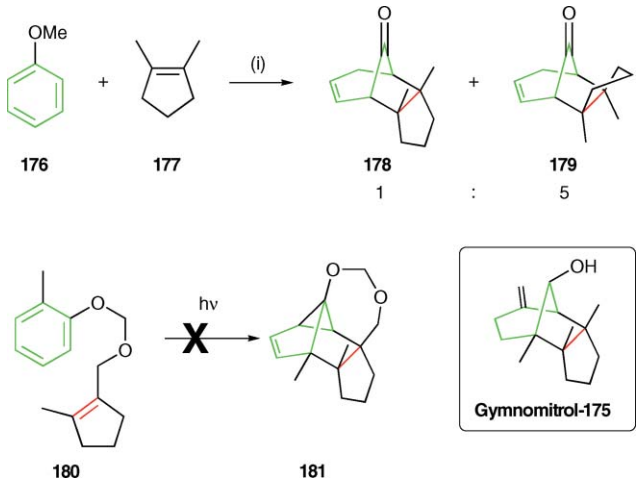


Scheme 52 Synthetic studies toward gelsemine. *Reagents and conditions*: (i) *hv* (low pressure Hg lamp), cyclohexane, 4 h; (ii) *m*-CPBA, CH_2Cl_2; (iii) MeOH, pyridinium *para*-toluene sulfonate, 4 days (11% overall).

In addition to the above studies Penkett *et al.* have also examined an approach toward gymnomitrol **175** that is considered in the next section (Scheme 53).[60b]

Four-atom tethers—gymnomitrol,[59a,60b] aphidicolin and stemodin[62]. As discussed in the introduction, studies on substrates in which there is a four-atom tether are sparse. The critical feature to achieve higher yields appears to be some bias of the conformational freedom of the tether toward the reactive conformation. To date, only three studies directed toward

a natural product have been reported, each of which raises interesting points, with Penkett's studies on gelsemine having been discussed above (Scheme 52). Building on their previous work, Penkett's group utilised a four atom cleavable tether in an approach to gymnomitrol **175**. An earlier attempt by Hoye to employ an intermolecular *meta*-photocycloaddition approach to **175**, had proved unsuccessful, presumably due to the significant steric hindrance associated with adding 1,2-dimethylcyclopentene to 2,5-dimethyl anisole.[59a] Indeed the addition of **176** to **177** furnished only a 0.1% yield of a 1 : 5 mixture of **178** to **179** (Scheme 53). Seeking to take advantage of an intramolecular reaction, a series of substrates were prepared and photolysed. Unfortunately, the steric encumbrance of **180** still proved too much to allow the photocycloaddition to **181** to take place (Scheme 53).



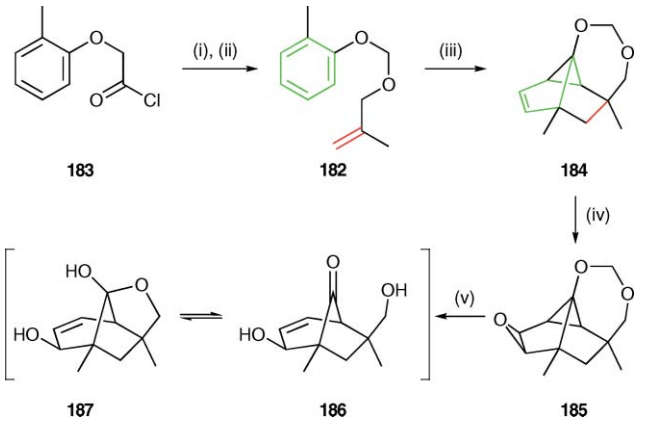
Scheme 53 Attempted photocycloaddition approaches to gymnomitrol. *Reagents and conditions*: (i) *hv* (253.7 nm), cyclohexane then H_3O^+ (0.1%).

However, the less hindered substrates examined, *e.g.* **182** (prepared in two steps from **183**) did undergo the desired reaction to give 17% of isomerically clean **184**, illustrating the use of this type of acetal tether in a *meta*-photocycloaddition reaction. Facile fragmentation of the derived epoxide, **185**, to deliver **186**/**187**, regio- and stereoisomerically clean, suggests the potential of the method (Scheme 54).

A final study in this area attempted to access the aphidicolin **188** and stemodinone **189** ring systems (Fig. 10). This approach uses the A-ring of these structures to impose a gauche conformation to one part of the tether.

Photocycloaddition of **190** proceeded in high yield to afford a 1.2 : 1 mixture of **191** and **192** (Scheme 55). Unusually, these are not regioisomeric cyclopropanes but diastereoisomers originating from two distinct cycloadditions proceeding *via endo*- and *exo*-transition states respectively.

Access to the *endo*-transition state is permissible in this case as there is no additional strain in obtaining the correct orbital alignment, unlike with a three-atom tether (Fig. 11). This is the first example of a predominantly *endo*-selective intramolecular *meta*-photocycloaddition, albeit modestly so. As expected the electron donating methoxy group controls the regiochemistry of the photocycloaddition.



Scheme 54 Studies toward the synthesis of gymnomitrol. *Reagents and conditions*: (i) $(Ph_3P)_3RhCl$, 170 °C; (ii) methallyl alcohol, 50% NaOH, benzene, Bu_4NCl (86%); (iii) *hv* (253.7 nm), cyclohexane (17%); (iv) dimethyldioxirane, CH_2Cl_2–acetone (1 : 1), 0 °C (100%); (v) HCl (aq.), acetone, 0 °C–room temperature (55%).

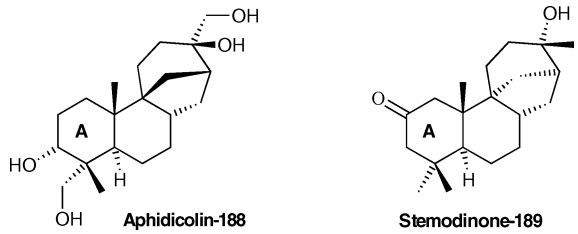
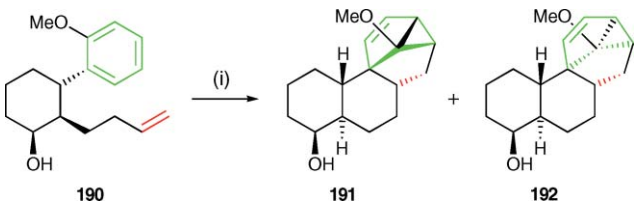


Fig. 10 Structures of aphidicolin and stemodinone.



Scheme 55 An approach to the aphidicolin and stemodinone ring systems. *Reagents and conditions*: (i) *hv* (low pressure mercury vapour lamp), cyclohexane (**191** : **192**, 1.2 : 1) (90%).

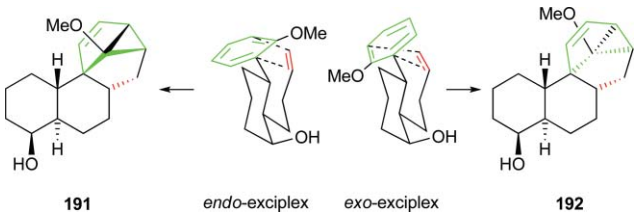


Fig. 11 Possible exciplexes preceding the photocycloaddition of **190**.

Intermolecular examples

Whilst most effort in the use of the *meta*-photocycloaddition in natural product synthesis has utilised the intramolecular reaction there has been some very interesting work originating from intermolecular photocycloadditions.

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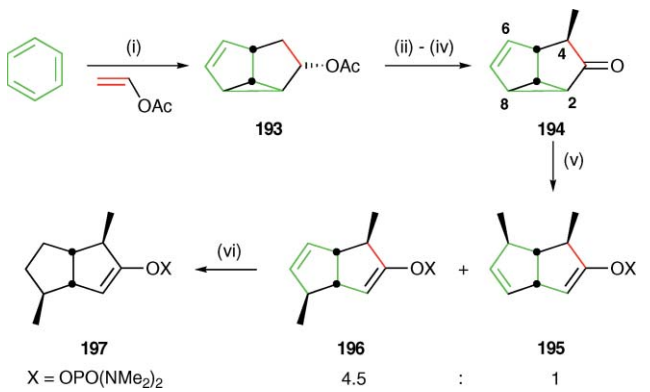
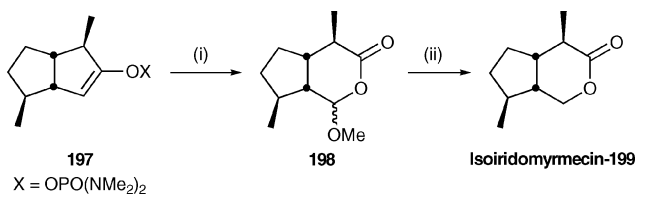
Synthesis of isoiridomyrmecin[63]. Photolysis of vinyl acetate in benzene produced a low yield of **193**.[64] This is not too surprising in light of the difficulties encountered with this type of alkene (*cf.* **79a** and **79b**) in Wender's studies on coriolin synthesis,[44] however, the cheapness of the starting materials and ease of the reaction compensates for this. In contrast to the intramolecular cases, and in keeping with fundamental studies on this reaction, *endo*-selectivity is observed (Scheme 56). The shape of the ring system is then utilised to control first the regioselective enolate formation then a subsequent *exo*-face alkylation to give **194**. Fragmentation of the cyclopropane is coupled with addition of a methyl group *via* a Gilman cuprate to afford **195** and **196**. The regioselectivity of this addition is controlled by unfavourable interactions with the methyl group at C4 (*cf.* Scheme 60) and the stereochemistry by approach from the least hindered face with inversion of configuration at C8. The enolate resulting from this addition was trapped as a phosphordiamidate. Selective hydrogenation of the least hindered double bond in **196** was carried out over Adam's catalyst to give **197**.



Scheme 56 Synthesis of isoiridomyrmecin; photocycloaddition and cyclopropane cleavage. *Reagents and conditions*: (i) *hv* (Vycor filter); (ii) $LiAlH_4$ (89%); (iii) MnO_2 (95%); (iv) LDA, −78 °C, MeI (75%); (v) Me_2CuLi, THF, −78 °C then $Cl_2PO(NMe_2)$ then Me_2NH (100%); (vi) H_2, PtO_2 (90%).

Having obtained **197**, ozonolysis in MeOH coupled with a reductive work-up gave the diastereoisomeric psuedolactones **198**. The synthesis was subsequently completed by reduction with sodium cyanoborohydride to give isoiridomyrmecin **199** in 68% yield (Scheme 57).



Scheme 57 Synthesis of isoiridomyrmecin. *Reagents and conditions*: (i) O_3, MeOH, CH_2Cl_2, −78 °C then $NaBH_4$ (92%; 1 : 1 epimers); (ii) $NaBH_3CN$, H_2O, THF, H_2SO_4 (68%).

Wender and Dreyer described a related photocycloadduct, **200**, arising from addition of vinyl acetate to indane, that has formed the key starting material for two syntheses: modhephene **201** and descarboxyquadrone **202** (Figure 12).

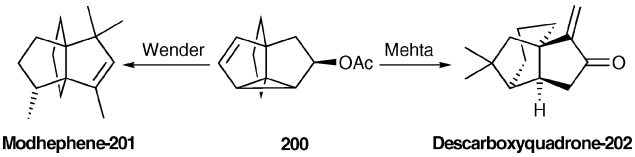
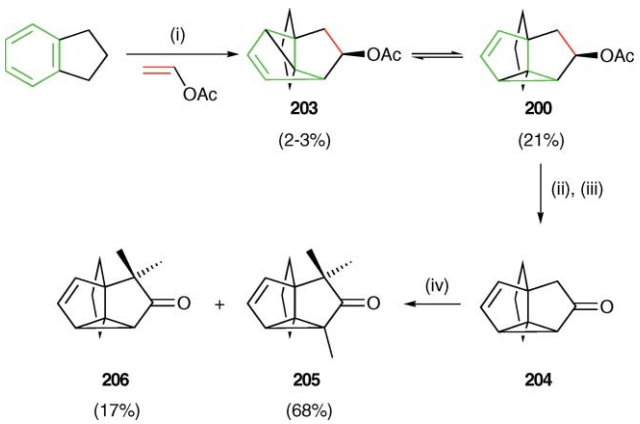


Fig. 12 A common intermediate for modhephene and descarboxyquadrone.

Synthesis of modhephene[65]. The synthesis of this [3.3.3]propellane **201**, whilst not the most complex molecule made with a *meta*-photocycloaddition reaction, is, in the view of the present authors, the one that best exploits its various assets and represents a truly remarkable achievement in synthesis.

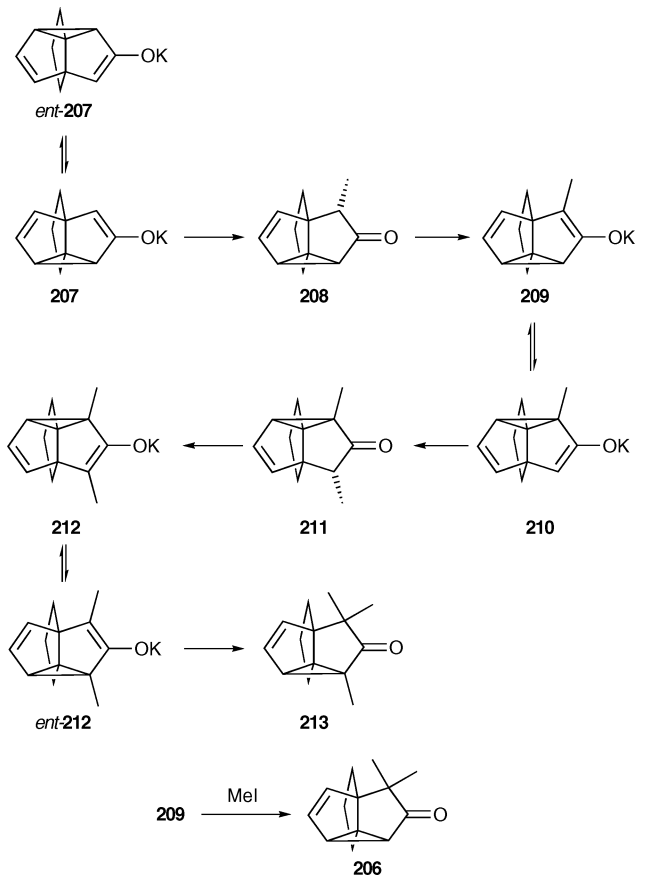
The photoadduct **200**, as with **193**, is formed in a modest 21% yield but again proceeds from readily available starting materials to allow multigram quantities to be prepared (Scheme 58). As expected the reaction is *endo*-selective with addition taking place across a donor substituent. The two isomers **200** and **203** are formed in *ca.* 10 : 1 ratio and are photoequilibrated under the reaction conditions.



Scheme 58 Synthesis of modhephene; photocycloaddition and alkylation. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (21%); (ii) KOH, MeOH (86%); (iii) $Ba(MnO_4)_2$ (95%); (iv) *t*-BuOK (15 eq.), MeI (10 eq.), THF (68% of **205**).

Hydrolysis of **200** was followed by oxidation to the corresponding ketone **204**. With the ring system in place there is a need to selectively introduce four methyl groups. Remarkably, treatment of **204** with methyl iodide in the presence of potassium *tert*-butoxide results in the formation of two compounds **205** and **206** the major one being trimethylated.

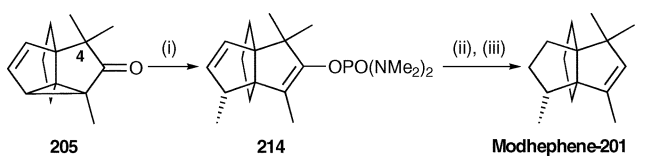
This apparently surprising reaction is readily rationalised when it is recognised that the enolate derived from **204** is a semibullvalene and hence susceptible to facile Cope rearrangement. The consequences of this rearrangement are set out in Scheme 59. Two subtleties arise at this point: firstly the rate of alkylation of **209** needs to be slower than rearrangement to **210** then alkylation, otherwise the 'cul-de-sac' compound **206** will predominate. Indeed studies on an enol phosphate derived from **207** indicated facile Cope rearrangement at temperatures as low as −100 °C.[65] Secondly, Cope rearrangement of either **207** or **212** generates enantiomeric compounds and hence, if any attempt were made to turn this into an enantioselective synthesis, it must either happen



Scheme 59 Synthesis of modhephene; details of the enolate alkylation.

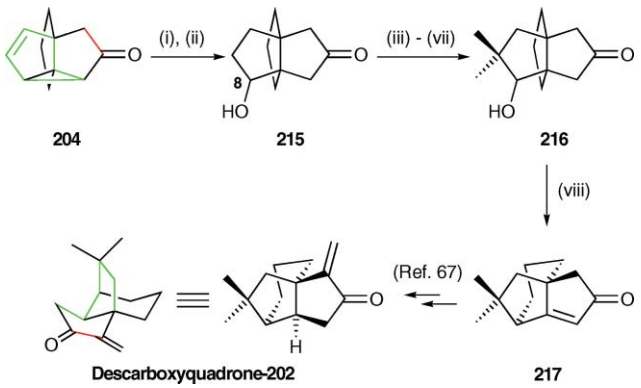
post trimethylation or the alkylation itself could be conducted in the presence of, say, a chiral counterion.

Finally, fragmentation of the cyclopropane is tied to introduction of the fourth methyl group by a highly stereo and regioselective cuprate-mediated addition reaction akin to that discussed in the isoiridomyrmecin synthesis (Scheme 56). However, in this case, the greater steric hindrance presented by the *gem*-dimethyl group at C4 of **205** prevents the side product arising from 1,7-addition that was seen in the previous case. The resultant enolate is trapped as its phosphordiamidate **214**. Thus the cyclopropane, often the unnecessary element of the complexity introduced in the *meta*-photocycloaddition reaction, is used to remarkable effect. To complete the synthesis all that was required was a dissolving metal reduction of the phosphordiamidate in **214** followed by a selective hydrogenation of the least hindered double bond (Scheme 60).



Scheme 60 Synthesis of modhephene. *Reagents and conditions*: (i) Me_2CuLi (5 equiv.), THF, −78 °C, $Cl_2PO(NMe_2)$ then Me_2NH (76%); (ii) Li, $EtNH_2$, THF, *t*-BuOH, 0 °C (93%); (iii) H_2, PtO_2 (100%).

Synthesis of descarboxyquadrone[19]. The final synthesis examined is Mehta's preparation of descarboxyquadrone. One approach to a quadrone derivative was set-out above (Scheme 25) but this is a distinctively different strategy. This approach explores the strategy of rearrangement of the skeleton, post cyclopropane cleavage, and thus suggests a wider range of targets that could be approached using the *meta*-photocycloaddition reaction. Beginning from **204**, careful hydrogenation of the double bond in the presence of the strained cyclopropane allows a key oxygenation at C8, concomitant with its cleavage, in a second step to give **215**. Following protection of the ketone, oxidation of the hydroxy group facilitates first, the introduction of the *gem*-dimethyl group then, after re-conversion to the alcohol and deprotection of the ketone, the critical Lewis acid mediated Wagner–Meerwein rearrangement of **216** to afford **217**.[66] This rearrangement, although not high yielding, is the first such rearrangement of this ring system and completes a formal synthesis of descarboxyquadrone (Scheme 61).[67]



Scheme 61 Synthesis of descarboxyquadrone. *Reagents and conditions*: (i) Cat. reduction; (ii) HCO_2H, heat then KOH, MeOH (95%); (iii) $HOCH_2CH_2OH$, PPTS, C_6H_6, 80 °C (95%); (iv) PCC, CH_2Cl_2 (82%); (v) *t*-BuOK, MeI, THF (71%); (vi) $LiAlH_4$, Et_2O (95%); (vii) acetone, PPTS, H_2O, 60 °C (95%); (viii) $BF_3{\cdot}OEt_2$, C_6H_6, 80 °C (20–25%).

Conclusions and prospects

In conclusion, we can see how the α-cedrene synthesis has set in train a series of studies that have demonstrated the immense power of this strategic level reaction. A number of sophisticated and frequently brief synthetic routes to a range of terpenoid natural products have been described. Much of the understanding of the factors that control the regio- and stereoselectivity issues associated with these reactions was determined during the course of fundamental mechanistic and theoretical studies but the synthetic work has capitalised on and further advanced this knowledge. In particular, the discipline of target molecule synthesis has greatly enhanced our understanding of how to manipulate the photocycloadducts. However, it is clear that much remains to be done and further advances are to be expected. For example the studies of Sugimura *et al.*[23] highlight the potential of chiral auxiliaries in controlling the absolute stereochemistry of these reactions while recent work, by Van der Eycken *et al.*, on the use of cyclodextrins suggest the potential for supramolecular complexes in this role.[68] The work of Stork and Lambert,[58] Penkett *et al.*[60] and Sugimura *et al.*[23] indicates that use of cleavable tethers has potential, in particular circumstances, to control the regiochemistry of photocycloaddition, which of

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two regioisomeric cyclopropanes is formed (which has proved a difficult issue) and to override the inherent *endo* preference seen in the corresponding intermolecular photocycloadditions. The use of tethers longer than three atoms has been clearly established as practical in recent years and their application to target synthesis is expected to follow.[21,22a,23,60b,62] New methods for the cleavage of the cyclopropane moiety, concomitant with a significant advance in the synthetic route, continue to emerge. The recent example from Penkett and coworkers' studies toward gelsemine, wherein the Heck reaction of an aromatic halide is deployed, is an interesting example of such work.[60c,d] Target synthesis of non-terpenoid structures would also represent a departure from past efforts. Perhaps the most tantalising but difficult challenge would be to achieve absolute asymmetric induction with circularly polarised light.[69]

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