

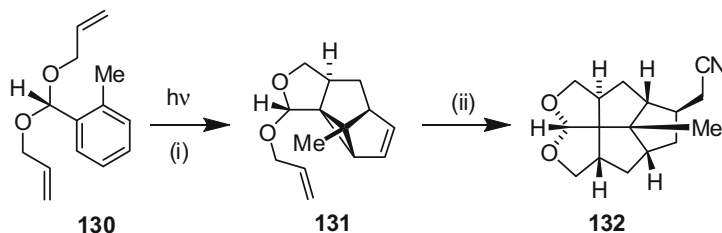
Chapter 2

Discovery of the Double [3+2] Photocycloaddition

2.1 Introduction: Original Aim

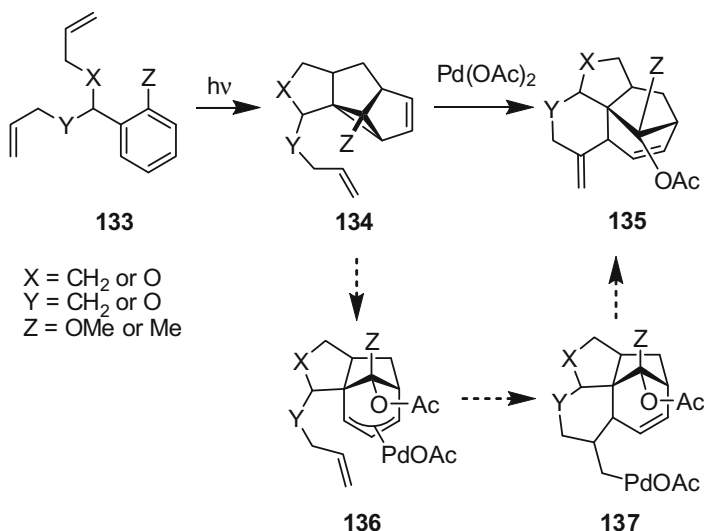
As mentioned the Penkett group has performed a wide range of intramolecular palladium induced fragmentation-cyclizations on *meta* photocycloadducts with the aim of generating molecular complexity in a rapid, simple fashion with sights firmly set toward forming carbon–carbon bonds in natural products [1–4]. Our aim was to extend this investigation to the creation of novel architecturally complex compounds not found in nature. The previous fragmentations had been conducted on the tricyclic adduct of intermolecular *meta* photocycloadditions, so we thought it prudent to see if the same process could be applied to the tetracyclic product of the intramolecular form of the reaction.

Paul Wender had already demonstrated that the exploitation of an arenyl-diene (or arene bis-alkene) photosubstrate could result in a *meta* photocycloadduct with a free alkenyl chain and that this could be reacted further under radical conditions to form a pentacyclic ring system derived from a *cis, cis, cis, trans* [5.5.5.5] fenestrane (**132**) (Scheme 2.1) [5].



Scheme 2.1 Wender's synthesis of a *cis, cis, cis, trans*-[5.5.5.5] fenestrane **132**. *Reagents & conditions:* (i) $h\nu$ (254 nm), cyclohexane, vycor filter, 24%; (ii) $(\text{PhCO}_2)_2$, MeCN, 90–95 °C, 32%

Therefore we concluded that coupling of the free double bond of a *meta* adduct derived from a similar photosubstrate, onto the core might be achievable via a palladium induced fragmentation of the cyclopropane ring to produce a novel tetracyclic-[6.6.5.5] fenestrane **135** (Scheme 2.2).



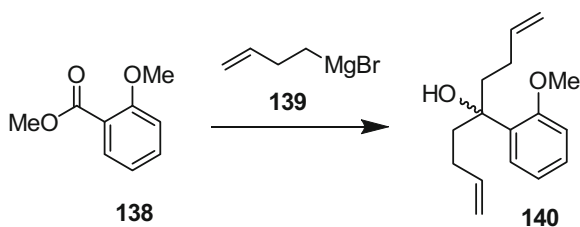
Scheme 2.2 Original synthetic plan using a palladium induced fragmentation

Potentially the incorporation of additional functionality could then be made through the remaining alkene bonds in this novel structure. Moreover, it would be anticipated that this process could be conducted in a substoichiometric manner by implementation of a re-oxidant such as copper (II) chloride.

2.2 Preliminary Studies

A primary focus for our chemistry was to take cheap, readily available starting materials and through simple, step efficient means, make architecturally complex structures. As such, our first choice was to synthesise the arenyl-diene photosubstrate **140** (Scheme 2.3), which could be made in an uncomplicated manner from aromatic benzoate **138**, via a Grignard reaction involving two equivalents of butenyl magnesium bromide.

Scheme 2.3 Synthesis of tertiary alcohol photosubstrate **140**. *Reagents & conditions:* Mg (2 eq.), butenyl bromide (2.5 eq.), Et₂O, 24 hrs, 75%

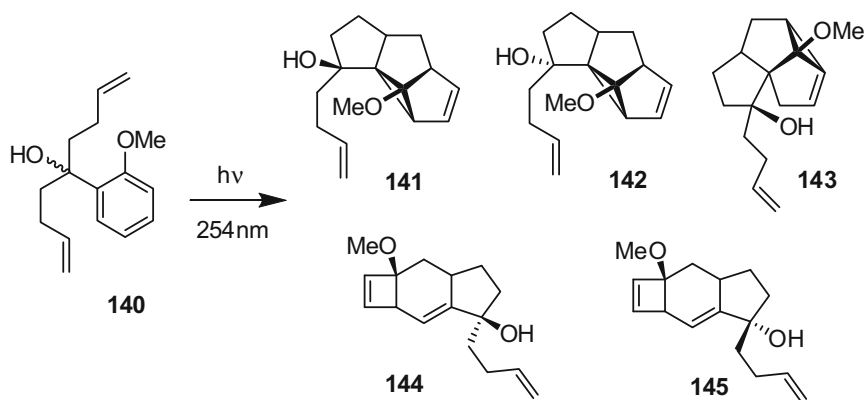


The reaction was completed in 75% yield on a multiple gram scale and the resultant tertiary alcohol **140** was then directly irradiated with 254 nm UV light, using a 16 W low-pressure Hg vapour lamp in a solution of cyclohexane until the aromatic starting material was consumed. The reaction was conducted in a quartz immersion well apparatus, double walled to allow for water cooling and in which the lamp is effectively surrounded by the solution (up to 450 ml) that is being irradiated.

The quartz is required to block radiation below 200 nm. UV radiation below this limit can excite the benzene ring to its second singlet excited state resulting in the production of “Dewar Benzenes” [6] or lead to excitation of the alkene $\pi \rightarrow \pi^*$ in both starting material and products, resulting in their decomposition [7].

The reaction vessel was also purged of dissolved oxygen by bubbling nitrogen through the solvent. Removal of oxygen is paramount because under photolytic conditions the normal triplet ground state ($^3\text{O}_2$) undergoes intersystem crossing to form singlet oxygen ($^1\text{O}_2$) an extremely reactive species. This can often lead to oxidation reactions with alkenes that interfere with the *meta* photocycloaddition process [7].

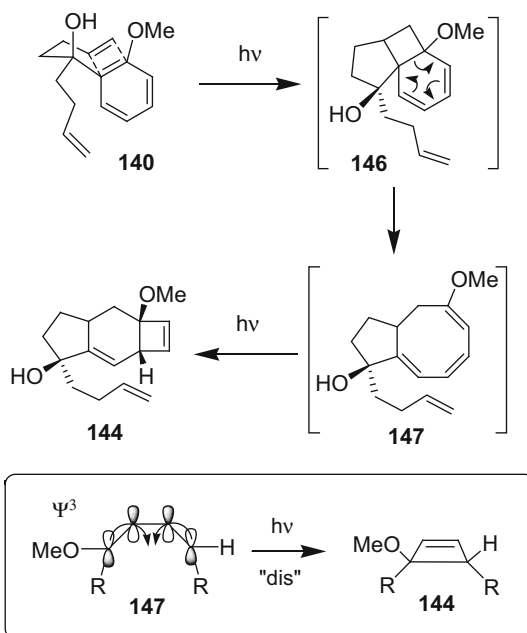
Analysis of the crude photolysis residue by TLC allowed us to identify five major products, which were then separated by flash column chromatography (Scheme 2.4).



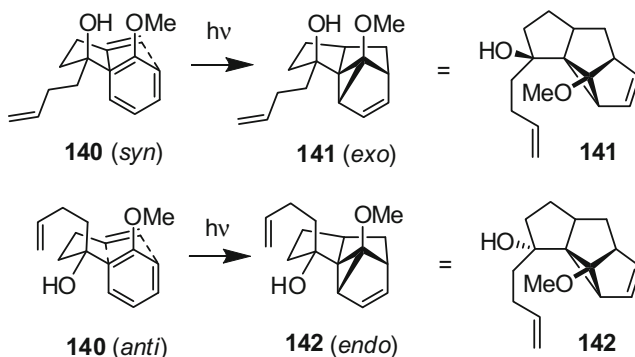
Scheme 2.4 The direct irradiation of photosubstrate **140**. *Reagents & conditions:* **140** (1.84 g), $h\nu$ (254 nm), cyclohexane, 10 hrs

Tetracyclic products **141** and **142**, described as *linear* adducts and **143**, described as *angular*, can be deduced as having arisen from *meta* addition across the methoxy position as expected. The tricyclic-[4.6.5] structures **144** and **145** are derived from an initial *ortho* addition at the 1,2 position of the aromatic ring followed a rapid opening of the strained cyclobutane containing diene **146** to yield a tricyclo-octatriene species (**147**). Whilst still in the presence of UV light, an intra-molecular $[2\pi + 2\pi]$ photocyclization recloses the ring in a disrotatory fashion to give the tricyclic compounds seen in the observed mixture of photo-isomers. Such processes have been well documented in the literature (Scheme 2.5) [8, 9].

Scheme 2.5 Mechanism for the formation of *ortho* addition derived adduct **144**



Due to the 1,3 allylic style arrangement and comparable steric bulk of the hydroxyl and alkenyl groups to the methoxy on the aromatic ring, there is competition between two possible exciplex configurations for the *meta* photocycloaddition (Scheme 2.6).



Scheme 2.6 Possible exciplexes and subsequent linear adducts. Note *endo* and *exo* refer to the position of the hydroxyl group in the adduct

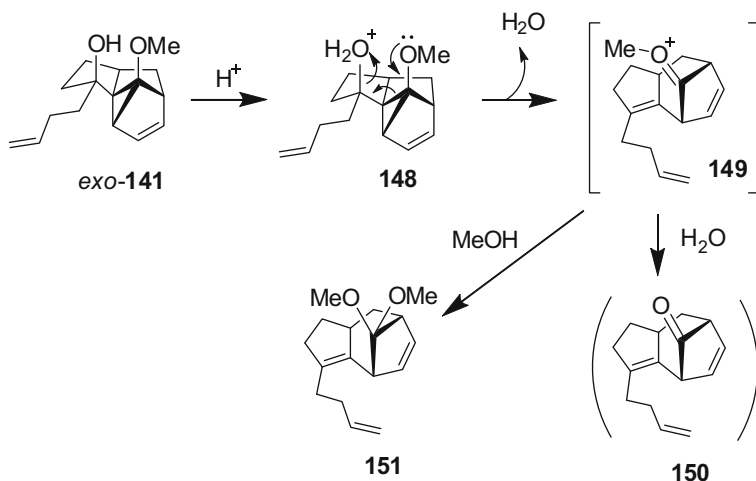
Exo adduct **141** is more prevalent due to the hydroxyl's smaller size, so that the bulkier alkenyl chain prefers to be *anti*-periplanar, rather than *syn*-periplanar to the methoxy in the exciplex (the same is true for the angular isomer). It is not the result of any potential hydrogen bonding, an effect between the hydroxyl and

methoxy, which was studied in greater detail and discounted by Jan Cornelisse in his study on 5-(2-methoxyphenyl) pent-1-enes previously discussed in the literature section of this work (Scheme 1.15) [10].

The reason for regioselectivity of the cyclopropane ring closure is less clear cut, with no definitive way of predicting which of the two forms, linear or angular, will predominate. In the case presented here, only one angular *meta* adduct **143** appeared to be formed to a significant degree.

Initially yields were difficult to establish due to a high number of impurities, most of which were seemingly derived from the instability of the linear *meta* adducts toward acid induced fragmentation of the cyclopropane ring. This complicated flash column chromatography particularly on a larger scale, although this could be combated using 0.1% triethylamine in the initial silica slurry formation. Subsequently, yields were eventually determined to be 19, 10, 10, 12 and 19% for **141**, **142**, **143**, **144** and **145** respectively after a reaction time of approximately 10 h on a 1.84 g scale.

During the study of this reaction it was noted that the yield of the *exo*-linear adduct appeared to be more affected by an increase in acidity than its *endo* counterpart. For instance, it was noted that the *exo* form, underwent degradation at an accelerated rate when taken up in CDCl_3 that had not been neutralised [11] for NMR analysis. This increased instability could only be attributable to the orientation of the hydroxyl moiety. In **141**, the orbital alignment between the breaking hydroxyl C–O and cyclopropane C–C bonds would appear to be more favourable; therefore when the hydroxyl is protonated, this led to an enhanced rate of elimination due to cyclopropane fragmentation (Scheme 2.7). This notably cannot occur in the angular case where the cyclopropane is on the opposite side and thus unavailable to participate in such a process.

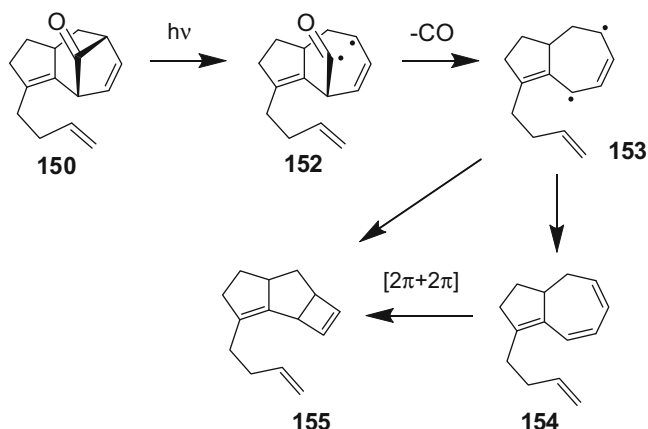


Scheme 2.7 An acid induced fragmentation decomposition pathway for linear *meta* adduct **141**

One of the key challenges often facing synthetic organic photochemistry is that a single photochemical reaction can lead to multiple products that are in themselves photochemically or thermally reactive. Irradiation of **140** beyond its total consumption (up to 36 h) resulted in an increased prevalence of a series of new minor adducts, some of which appeared to be generated during decomposition pathways of the linear *meta* adduct **141** (Scheme 2.7).

A tricyclic compound **150** possessing a ketone was observed, although never isolated in acceptable purity. It was clearly the product of the acid induced fragmentation of the cyclopropane ring, resulting in the elimination of an equivalent of MeOH. Evidence of MeOH generation is further backed by the observation and isolation of the dimethyl acetal **151** from the reaction mixture.

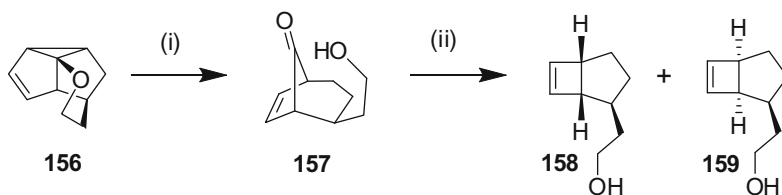
Further to these two adducts, an intriguing tricyclic [4.5.5] ring system (**155**) was also isolated, most likely being derived from a Norrish Type I reaction [7] where ketone **150** would be an intermediate (Scheme 2.8).



Scheme 2.8 Possible mechanism for the formation of Norrish product **155**

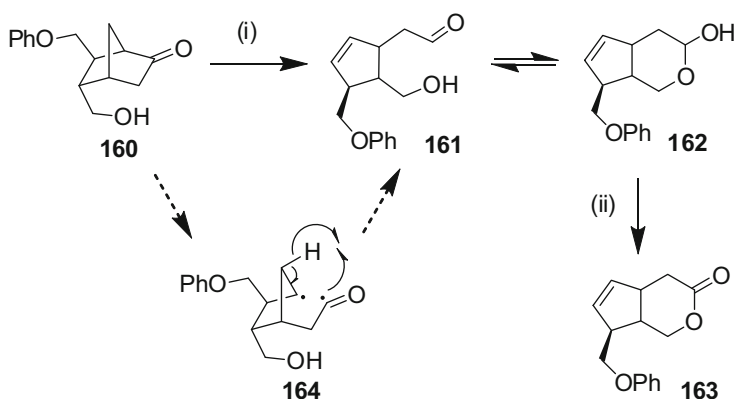
Essentially, photochemical fission occurs at the ketone when the carbonyl accepts a photon and is excited to its first singlet excited state ($n \rightarrow \pi^*$) and through rapid intersystem crossing to its triplet state as well. Either form can undergo a radical bond cleavage at either α -carbon to give a diradical species (**152**). From this point the diradical can recombine, undergo rearrangements or, as in the case of compound **150**, extrude carbon monoxide from the carbonyl fragment followed by a re-addition of the two remnants. A comparable example of this Norrish chemistry can be found in the irradiation of the acid fragmented product of simple *meta* photocycloadduct **156** (Scheme 2.9) [9].

Irradiation of **157** at 300 nm in MeOH gave two bicyclo [3.2.0] hept-6-enes, which were predicted to be formed *via* the $[2\pi + 2\pi]$ photocyclization of a cyclohepta-1,3-diene intermediate after carbon monoxide extrusion, as seen in our example (Scheme 2.8).



Scheme 2.9 Norrish Type I chemistry on the fragmentation product of a simple *meta* photocycloadduct. *Reagents & conditions:* (i) HCl, acetone: H₂O 20:1, RT, 10 min; (ii) *hν* (300 nm), MeOH, 80%, (1.4:1)

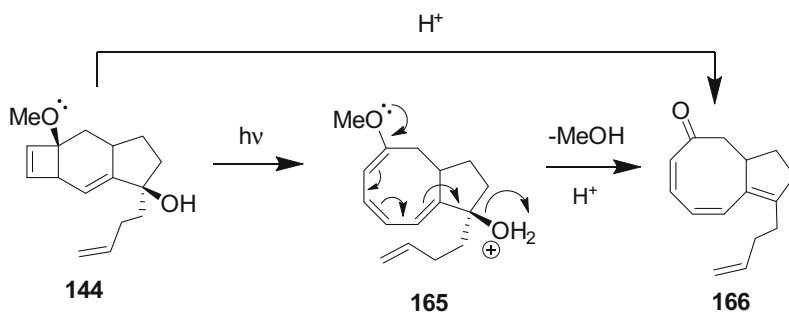
While Norrish Type I reactions have been previously observed in competition with photocycloadditions, De Keukeleire and He also produced a notable example in which they studied a Norrish Type mechanism toward making lactone photo-substrates for subsequent *meta* photocycloadditions (Scheme 2.10) [12].



Scheme 2.10 Norrish Type I reaction to make a lactone **163**. *Reagents & conditions:* (i) *hν* (300 nm), EtOH, 2 hr; (ii) PDC, CH₂Cl₂, 3 hr, 63%

Our final isolated minor adduct was the bicyclic octadienone compound, **166**, which was likely the product of a decomposition pathway from the *ortho* addition derived tricyclic compounds. Both adducts **144** and **145** were heated at 200 °C for several hours, but showed limited thermal decomposition. This suggested that the process was occurring through a photolytic re-opening of the cyclobutene ring followed by elimination of the alcohol via utilisation of the lone pair on the methoxy group to yield the observed structure (Scheme 2.11).

An eight-membered ring had been observed as an intermediate toward the normal *ortho* derived rearrangement products found commonly in photocycloaddition reactions [8, 13–21]. However, isolation of such structures isn't possible in photosubstrates that do not possess a leaving group in the appropriate position for elimination, a fact highlighted by both De Keukeleire and Van der Ecken [22, 23]. The isolation of **166** therefore lends further credence to the notion that



Scheme 2.11 Possible mechanism of formation of bicyclo[6.3.0]undecatrieneone **166**

formation of *ortho* derived tricyclic adducts such as **144** and **145** does in fact proceed *via* an octatriene intermediate (**165**).

In total there were in excess of ten unique minor products isolated in the reaction mixture, most of which remain uncharacterised due to an inability to separate each from the polymeric materials commonly produced. The difficulties presented by the instability of the linear *meta* adduct in particular made this substrate a less attractive option for taking forward for further study. As such, it was decided to use a photosubstrate without the troublesome hydroxyl group.

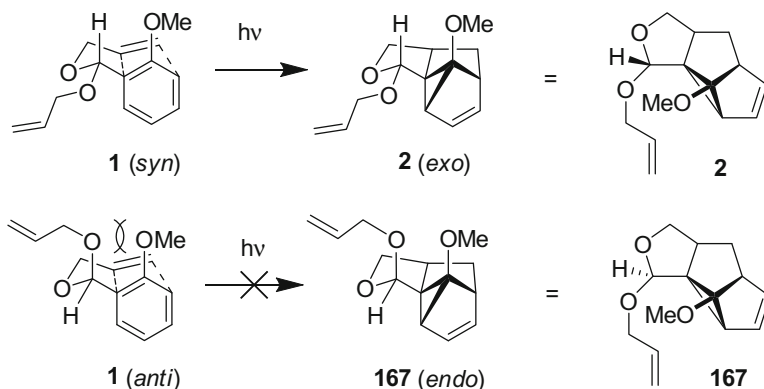
2.3 Discovery of the Double [3+2] Photocycloaddition and Structural Elucidation

Our attention now turned to the acetal photosubstrate **1**. The photochemistry of this substrate was simplified by the hydrogen being significantly smaller than the oxygen linked tether, which means that it always adopted the *syn*-periplanar orientation in the transition state thus giving fewer potential products (Scheme 2.12).

In addition, the hydrogen on the *exo* face would not be as susceptible to elimination as the hydroxyl group in the previously irradiated photosubstrate **140**.

The methyl derivative of acetal photosubstrate **1** had been previously synthesised by Wender in 1996 for use in a *meta* photocycloaddition to make “fenestrane” type structures [5]. In that case the acetal was formed by an acid catalysed condensation with allyl alcohol, using Dean-Stark apparatus [24]. However in the methoxy case this failed to give a reliable result. Therefore as an alternative, we turned to the acetal formation procedure reported by Noyori, which allowed photosubstrate **1** to be synthesised in an initial 36% yield from *o*-anisaldehyde (Scheme 2.13) [25].

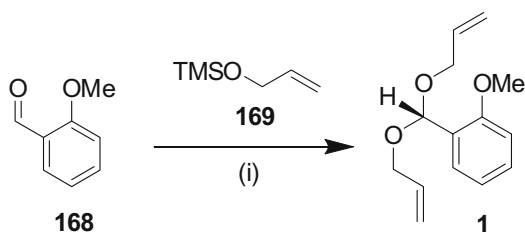
This highly versatile method [26] is achieved under mild, aprotic conditions using alkoxytrimethylsilane as an acetal-forming agent and TMSOTf as a catalyst. Unlike the traditional acid catalysed method (which is reversible without the



Scheme 2.12 Favoured *syn* pentane configuration of photosubstrate **1**. Note that the terms *syn*, *anti*, *endo* and *exo* refer to the relative position of the hydrogen at the α -position of the tether

Scheme 2.13 Synthesis of acetal photosubstrate **1**.

Reagents & conditions: (i) **169** (2.05 eq.), TMSOTf (10 mol %), $-78\text{ }^{\circ}\text{C}$, 2 hr, 36%

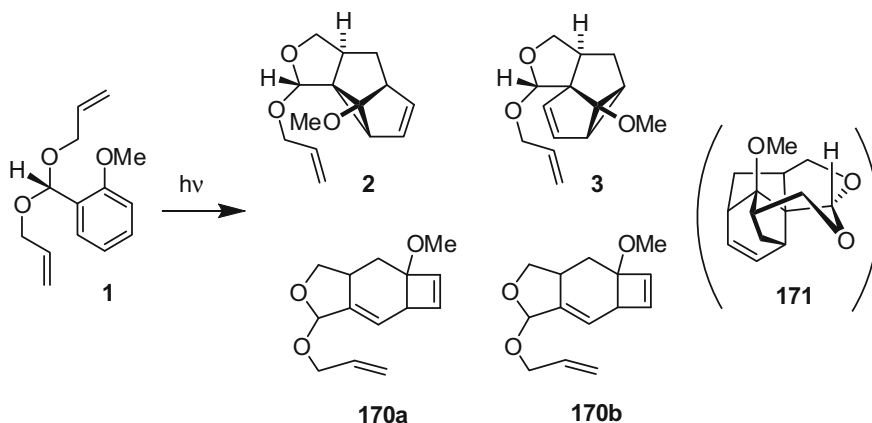


rigorous removal of water) the equilibrium in this acetal forming process lies greatly toward the products due to the high stability of the hexamethyl siloxane by-product generated.

The required allyloxytrimethylsilane could be produced *via* the reaction of allyl alcohol, NaH and TMSCl in boiling Et_2O over 24 h following the procedure of Clark-Still [27]. However, purification proved difficult with the available distillation facilities and subsequent Noyori reactions were carried out using material purchased from Sigma-Aldrich® Ltd.

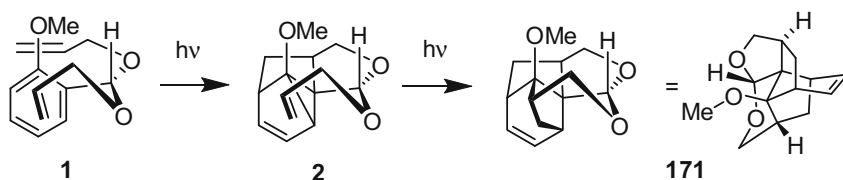
The aromatic acetal photosubstrate **1** was then directly irradiated with 254 nm UV light, as a solution in cyclohexane within a quartz-immersion well photoreactor over an 18 h period, and five products (Scheme 2.14) were isolated from the residue in reasonable yields.

Notably, amongst the expected tetracyclic *meta* and tricyclic *ortho* derived adducts was the appearance of an unexpected minor product **171** (in an approximate 8% yield). From detailed NMR analysis (including COSY, HSQC, HMBC and ROESY correlation spectra) this compound was originally postulated to be the result of a double *meta* photocycloaddition process. The key feature of the transformation would be the retention of the original 6-membered ring of the benzene in the final product. In essence, two sequential *meta* photocycloadditions



Scheme 2.14 Irradiation of photosubstrate **1**. Note the stereochemistry of **170a** and **170b** could not be determined through NMR spectroscopy. *Reagents & conditions:* **1** (100 mg), $h\nu$ (254nm), cyclohexane, 18 hrs

would have occurred resulting in the former aromatic ring being sandwiched between the two alkenes, in a “criss-cross” manner, one from above and the other below (Scheme 2.15).

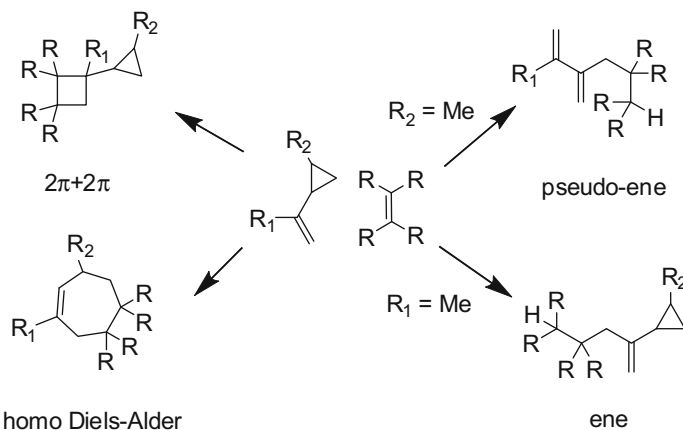


Scheme 2.15 Original postulated mechanism of “criss-cross” double [3+2] photocycloaddition, where the alkenes act as a sandwich to the original benzene ring

If such a reaction had occurred it would be similar in its effect to the generally overlooked homo Diels–Alder reaction [28, 29], a thermally induced [4 + 2] addition between a vinyl cyclopropane and an alkene. However, a notable difference between a homo Diels–Alder product and that formed during the photolysis of the acetal photo substrate **1**, is that the former would involve the *meta* adduct double bond, whereas in the “criss-cross” adduct this would not be the case.

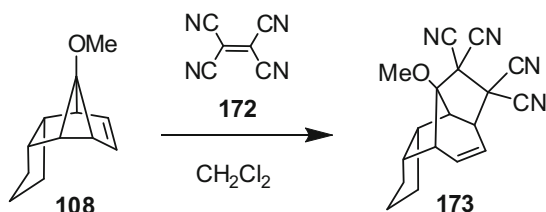
As Gilbert [30] summarised, there were essentially four possible reactions that could occur between the two reacting parties, a standard $2\pi + 2\pi$ addition, an “ene” reaction, a “pseudo-ene” and the homo Diels–Alder (Scheme 2.16).

The latter of these was reported in 1976 by Subrahmanyam [31], who used exceptionally electron deficient olefins such as tetracyanoethylene (**172**) as the “dienophile” and a *meta* photoadduct derived from anisole to cyclopentene (Scheme 2.17).



Scheme 2.16 [30] Possible reactions between vinyl cyclopropane and an alkene

Scheme 2.17 An example of the homo Diels–Alder reaction between TCNE and a *meta* adduct



The reactions occurred thermally at ambient temperature in a near quantitative yield simply by mixing the two components in CH_2Cl_2 . Subrahmanyam observed that the dihydro derivative of the adduct did not react with the incoming alkene and thus postulated that the mechanism might be a concerted $[2\pi + 2\sigma + 2\pi]$ cycloaddition. However, the author could not rule out the possibility of a non-concerted addition with a polar intermediate.

In 1988, Fenton and Gilbert [30] carried out a similar set of reactions to Subrahmanyam, in which they commented that there was “limited literature concerning the reactions of ethenylcyclopropane systems with dienophiles” [30] and that despite the inherent ease with which suitable *meta* photocycloadducts could be constructed, that interest in the field was poor. In fact largely since the early 1990s, these reactions have vanished off the research radar with only a few exceptions [32, 33].

While our original supposition was acceptable according to study of the NMR data, it ultimately proved incorrect. Crystalline material was obtained by slow recrystallization from benzene, to subsequent X-ray analysis unambiguously confirmed the identity of our proposed “criss-cross” product as a pentacyclic compound based on the energetically disfavoured *cis, cis, cis, trans*-[5.5.5.5] fenestrane core **4** (Fig. 2.1).

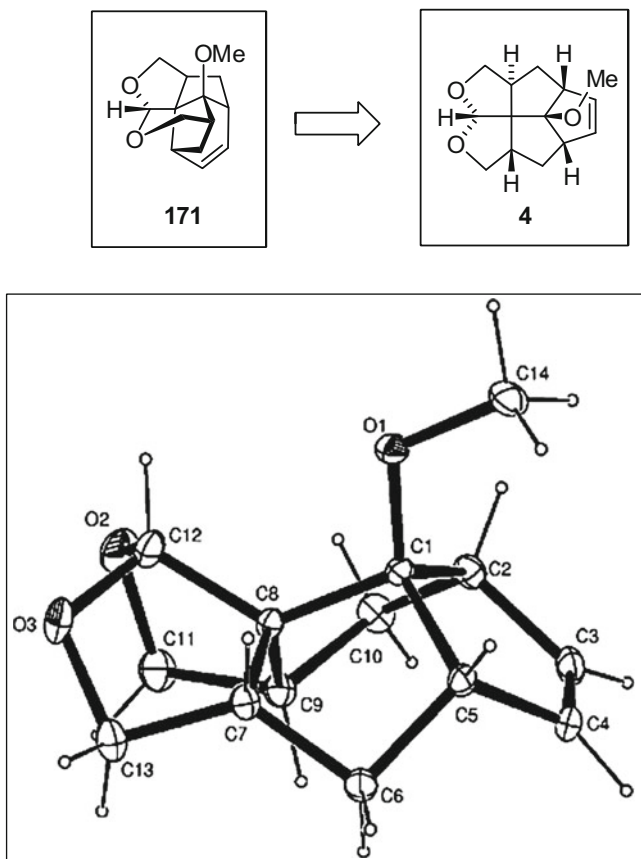
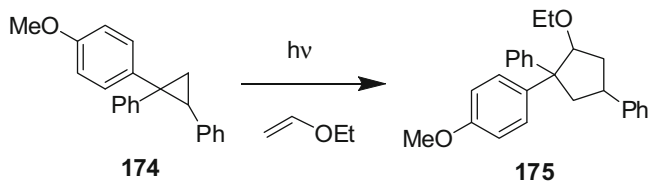


Fig. 2.1 Comparison of originally proposed “criss-cross” (**171**) and actual fenestrane (**4**) structures of the secondary photoadduct, with X-ray crystal structure

This complex dioxafenestrane, although novel, is a member of the same family that was the focus of the previously mentioned work of Wender, Dore and de Long [5]. However, the crucial difference is the method of construction. Wender performed a *meta* photocycloaddition to gain the linear *meta* adduct **2**, then synthesised the fenestrane through a radical cascade process (refer to Scheme 2.1), whereas at first glance, we would seem to have produced a similar result in a one-pot process using only UV light.

The dioxafenestrane **4** would seem to be derived from a second photochemical [3+2] addition of the free alkenyl tether of the linear *meta* adduct **2** onto the core structure across the cyclopropane. A study of the literature shows that additions of this type to cyclopropanes are rare, in part because it is not possible to form a 1,3 dipole species with a cyclopropane and thus ring opening under photochemical conditions tends to occur only under highly strained circumstances [34].

However, Tomioka [35] was able to carry out an intermolecular [3+2] cycloaddition with an alkene to give the cyclopentane compound **175**, which was formed from cyclopropane **174** and ethylvinylether in a 62% yield under electron-transfer sensitized conditions, along with various by products (Scheme 2.18).



Scheme 2.18 Photochemical [3+2] addition of an alkene across a cyclopropane ring. *Reagents & Conditions:* hv, p-dicyanobenzene, MeCN, 62%

The sheer simplicity of constructing such a complex fenestrane with nothing other than UV light was a remarkable and exciting occurrence. Therefore, with this result in hand, it was deemed prudent to abandon the original palladium approach in order to investigate the finer details of what we dubbed the “double [3+2] photocycloaddition” [36, 37] and its wider applicability for making different fenestrans and other complex structures from very simple starting materials.

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