The Double [3+2] Photocycloaddition Reaction

Jason A. Woolford

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Declaration

I hereby declare that this thesis has not been submitted in whole or in part form for the award of another degree.

Signed

Jason Antony Woolford

UNIVERSITY OF SUSSEX

JASON ANTONY WOOLFORD

DOCTOR OF PHILOSOPHY OF CHEMISTRY

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SUMMARY

One of a synthetic organic chemists' greatest challenges is to create step-efficient routes toward compounds with high molecular complexity. Therefore, reactions such as the *meta* photocycloaddition of an olefin to a benzene derivative, which provide more than one bond in a single step are of significant importance. It this remarkable reaction three new σ bonds, three new rings and up to six new stereocenters are formed simultaneously. Additional complexity can be added by tethering the two reacting partners together and this form of the reaction has found many uses in natural product synthesis.

In this work a remarkable double [3+2] photocycloaddition reaction is reported that results in the formation of a complex *cis, cis, cis, trans*-[5, 5, 5, 5] fenestrane derivative from a simple flat aromatic acetal with two branching alkenes. During this dramatic transformation four carbon-carbon bonds, five new rings and seven new stereocenters are created in a single one-pot process using only UV light. The reaction occurs in a sequential manner from the linear *meta* photocycloadduct, *via* a secondary [3+2] addition of the alkene across the cyclopropane of the adduct. In addition, an angular *meta* photocycloadduct also produced in the initial addition step, undergoes an alternative fragmentation-translocation photoreaction to afford a silphinene-like angular tricyclic compound.

In this work the investigation of this newly discovered process is discussed *via* the synthesis and subsequent irradiation of a series of photosubstrates containing different functional groups in the arene-alkene tether. In addition, attempts toward the synthesis of alternative structures using the same double [3+2] photocycloaddition are reported.

Contents

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A PhD is an interesting experience, a pain and a pleasure in equal measure. It's very much like going on a journey when you don't know the exact route. There are frustrations and disappointments along the way, but also much laugher, camaraderie, encouragement and tremendous excitement and pride when you finally get to the peak. This journey is never travelled alone and words are somewhat inadequate to express my gratitude to all those people who have helped me along the way.

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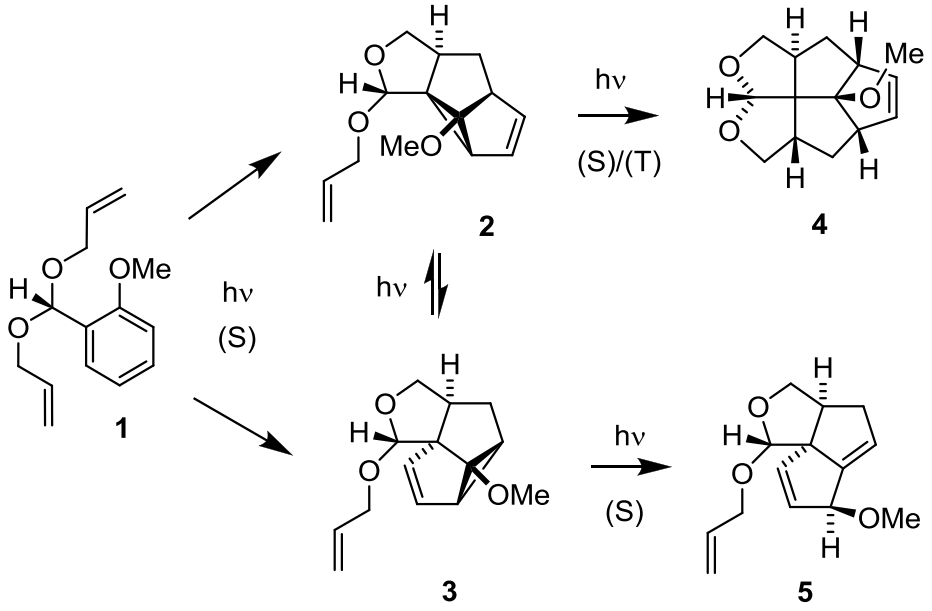
Abstract

In this work a remarkable double [3+2] photocycloaddition reaction is reported, that results in the formation of a complex *cis*, *cis*, *cis*, *trans*-[5, 5, 5, 5] fenestrane derivative **4** from a simple aromatic acetal **1**. During this dramatic transformation, four carbon-carbon bonds, five new rings and seven new stereocenters are created in a single one-pot process. The reaction occurs in a sequential manner from the linear *meta* photocycloadduct **2**, *via* a secondary [3+2] addition of the alkene across the cyclopropane of the adduct. In addition, the angular *meta* photocycloadduct **3** undergoes an alternative fragmentation-translocation photoreaction to afford the silphinene-like angular tricycle **5** (Scheme 1.0).



Scheme 1.0: Example of the photochemical reactions of arenyl-diene photosubstrates, including the double [3+2] photocycloaddition reaction.

This work presents the investigation of this newly discovered process discussed *via* the synthesis and subsequent irradiation of a series of photosubstrates, derived from **1**, containing different functional groups in the arene-alkene tether. Attempts at applying the double [3+2] photocycloaddition to the creation of alterative structures are also discussed by the synthesis of photosubstrates containing different tether positions on the aromatic ring.

Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
br.	Broad
*n*BuLi	*n*-Butyllithium
cat.	Catalyst
CDI	1,1'-Carbonyldiimidazole
CH_2Cl_2	Dichloromethane
COSY	Correlation SpectroscopY
*m*CPBA	*meta* Chloroperbenzoic acid
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*, *N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EDG	Electron Donating Group
ESI	Electron Spray Ionisation
EWG	Electron Withdrawing Group
HBr	Hydrogen Bromide
HCl	Hydrochloric acid
HOMO	Highest Occupied Molecular Orbital
HMBC	Heteronuclear Multi-Bond Coherence
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
hr	Hours
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid

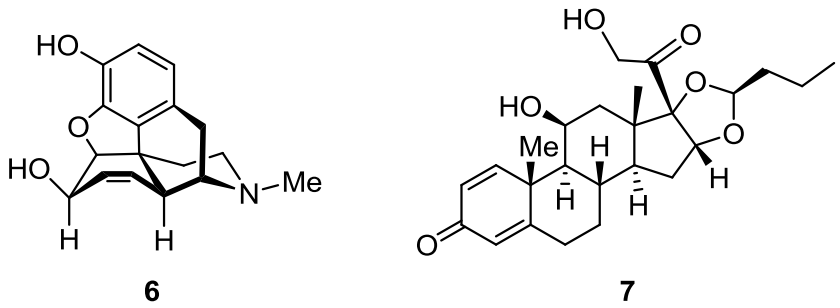
IR	Infra-Red
J	*J* coupling
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mins	Minutes
MPLC	Medium Pressure Liquid Chromatography
NBS	*N*-Bromosuccinimide
nm	Nanometre
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methylmorpholine-*N*-oxide
OMe	Methoxy
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Petrol	Petroleum Ether (40-60)
PT	Phase-Transfer
QUINAP	(*R*)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
ROESY	Rotating frame Overhauser Effect SpectroscopY
RT	Ambient (or Room) Temperature
SM	Starting Material
Temp.	Temperature
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBAHS	Tetrabutylammonium hydrogen sulfate
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-Toluene sulfonyl
UV	Ultra Violet

1 Introduction and background

1.1 The "Step economy"

One of the most important concerns of modern synthetic organic chemistry is that of "step economy".[1] In an ideal world each step of a synthesis would be simple, safe, economical, and environmentally acceptable, in addition to giving complete conversion from starting material to product.[2] However, in practise this is not the case and a synthesis is generally hampered by steps that are deficient in one or often more of these important factors. It is for this reason, that chemical transformations that create more than one bond at a time are so attractive, particularly to the pharmaceutical industry, which has a strong desire to produce libraries of molecules for evaluation as lead compounds in drug discovery.

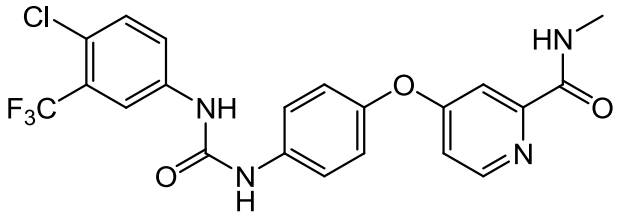
Moreover, the generation of molecular complexity[1g] in these libraries is also important, as the discovery of new chemical entities (NCE's) with useful biological properties is often linked to their base architecture. For example, natural products such as the alkaloid morphine[3] (**6**) and steroid budesonide[4] (**7**) (Figure 1.1) are highly complex three dimensional structures and possess strong biological properties as a result.



6 **7**

Figure 1.1: Examples of structurally complex compounds with biological properties.

Medicinal chemists aim to discover NCE's by screening compounds from combinatorial libraries.[5] However; combinatorial chemistry is predisposed to forming flexible two-dimensional compounds, which has restricted its ability to explore unknown regions of chemical space. In fact, thus far in the two decades of its use, only one purely combinatorial chemistry-synthesised compound has been approved for use as a drug; Sorafenib **8**[6] (Figure 1.2) manufactured by Bayer, although it was turned down for use as a treatment of renal and liver cancers by the NHS due to an unfavourable cost to benefit ratio.[7]

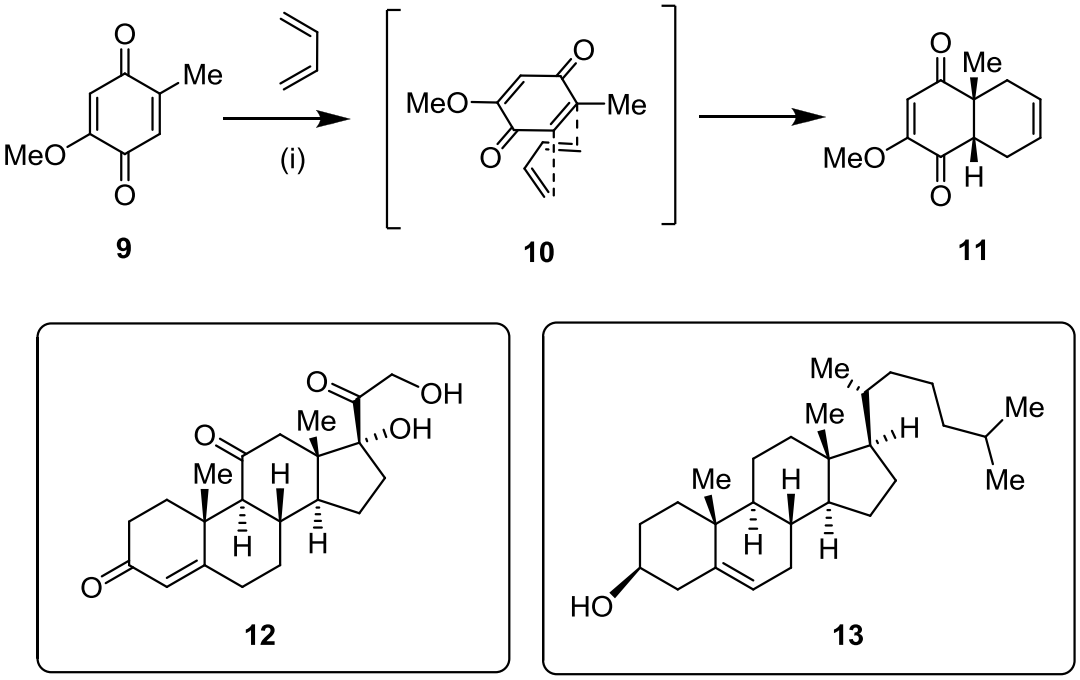


8

Figure 1.2: Structure of Sorafenib: a primary renal and live cancer drug.

With this in mind, a simple step-economical method that could convert a library of simple flat-molecules into a library of structurally complex ones would have great commercial and scientific value to the communities of chemistry and the wider biosciences.

Perhaps the simplest example of a reaction that has addressed the issue of step economy would be a reaction reported in 1928 by Professor Otto Diels and his student Kurt Alder; a reaction that would later bear their names and win them the Nobel Prize.[8] The below example by Woodward *et al.*[9a] from the 1950's is an excellent illustration of how a Diels-Alder reaction can be employed in a synthesis to generate molecular complexity (Scheme 1.1).



Reagents & conditions: (i) benzene, 100 °C, 96 hrs, 86%

Scheme 1.1: The Diels-Alder reaction has been extensively used in steroid synthesis, for example, cortisone (**12**) and cholesterol (**13**) were constructed by R. B. Woodward using this chemistry.

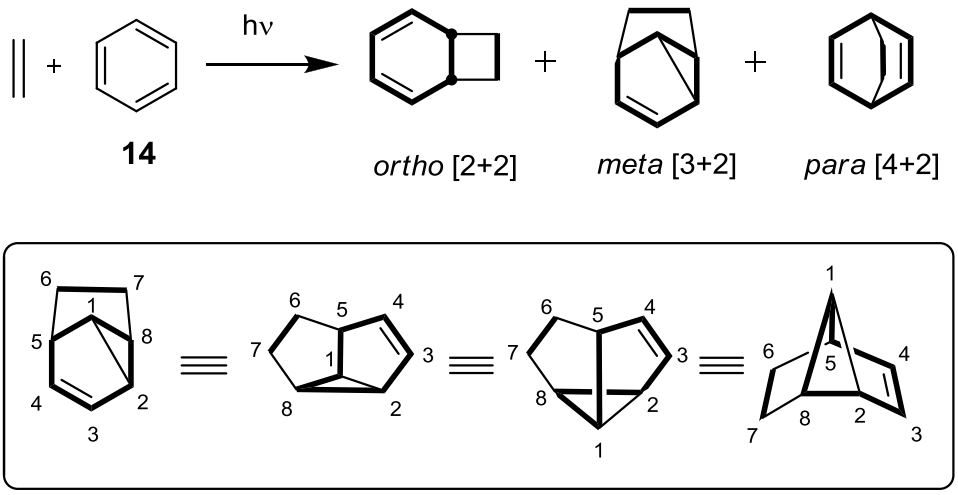
In this case a fused bicyclic ring system **11** is made from a simple diene and dienophile cycloaddition. During the reaction two new carbon-carbon σ bonds are generated in an efficient single step. This is only one part of its appeal, with other advantages including the ability to be affected by many forms of catalysis and performed both inter and intramolecularly.[9] Furthermore, it is stereospecific and regio- and diastereoselective, thanks to the nature of the reaction's highly ordered transition state and Alder's *endo* rule.

Since its discovery the Diels-Alder reaction has stood as one of the most important reactions in the entirety of synthetic organic chemistry, it continues to thrive and be applied to the assembly of complex molecular structures on a daily basis.[9b-d] However, there are reactions that can generate an even greater number of bonds in a single step, such as that mentioned in the following section that form three-bonds in one process: the *meta* photocycloaddition reaction.

1.2 The arene-alkene *meta* photocycloaddition

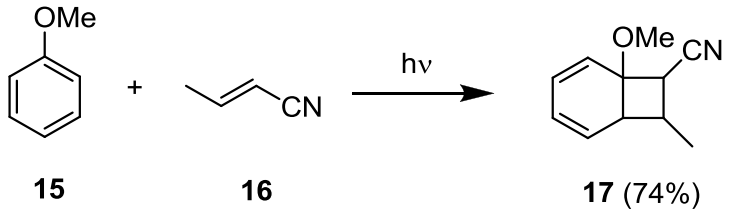
1.2.1 Introduction: photocycloaddition of an alkene to a benzene derivative

The photochemical reactions of benzene and its derivatives have been of great interest to chemists over the last fifty years, particularly with regards to the behaviour of their excited state in the presence of an olefin.[10] When an aromatic ring is directly irradiated with UV light (λ_{max} = 254 nm) it becomes electronically excited and is capable of undergoing a cycloaddition reaction with the double bond, that breaks the aromaticity, leading to the observance of three possible adducts derived from three different modes of addition; *ortho* [2+2], *meta* [3+2] and *para* [4+2] (Scheme 1.2).



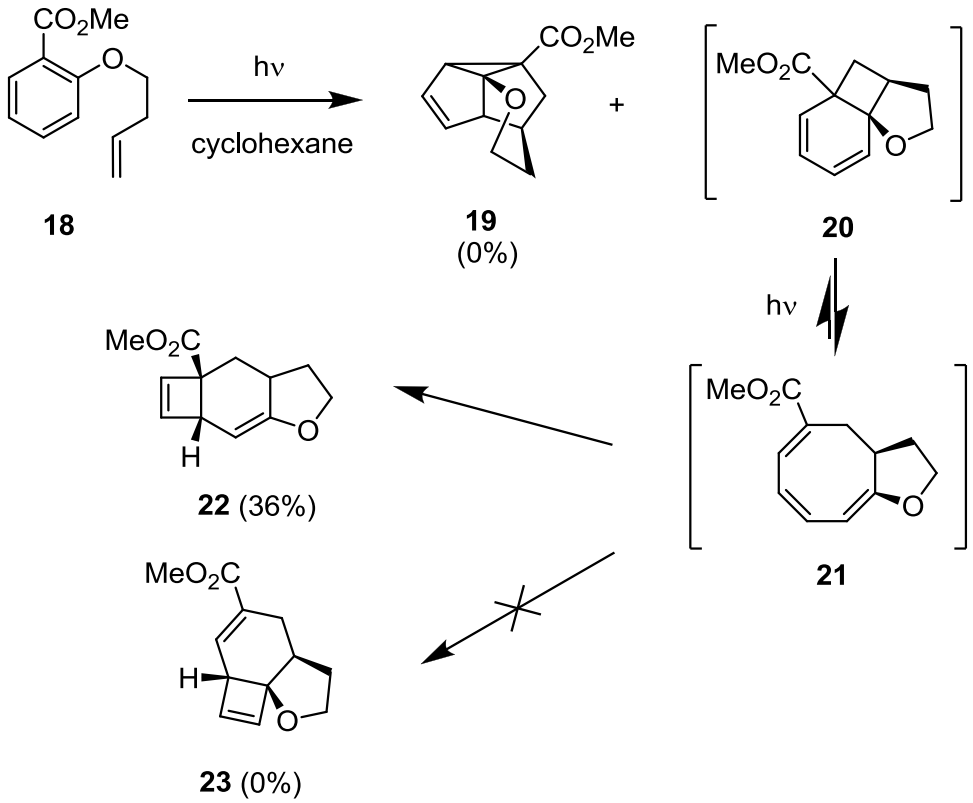
Scheme 1.2: The three modes of photocycloaddition of an olefin to benzene. Note that there are various different ways of representing the central core structure of the adduct derived from *meta* addition.

The [2+2] or *ortho* addition is well documented in the literature and was in fact the first to be reported, in the late 1950's.[11] It is commonly found to be the predominant addition where the alkene has strong electron donor or acceptor properties, for instance, when the alkene is in conjugation with a nitrile group (**15**) such as in Scheme 1.3.[12]



Scheme 1.3: Ortho addition of an electron-deficient alkene.

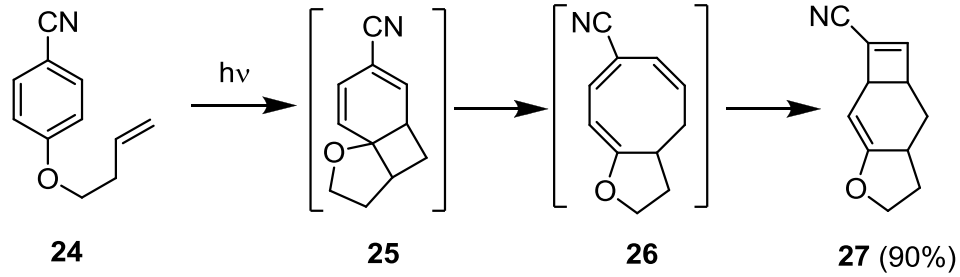
Additionally, studies such as those of Erik Van der Eycken *et al.*[13] who reported on the *meta* photocycloaddition of 4-phenoxybut-1-enes, discovered that *ortho* addition and subsequent rearrangements predominated depending on the placement of groups on the aromatic ring when conducted in an intramolecular fashion. For instance Van de Eycken discovered that having the group *ortho* to the tether as a withdrawing methyl ester (**18**) favoured ortho addition exclusively over *meta* (Scheme 1.4).



Scheme 1.4: Photolysis of 2-But-3-enyloxy-benzoic acid methyl ester.

Generally speaking the primary adduct (**20**) of a [2+2] addition is inherently unstable and tends to undergo thermal and/or photochemical rearrangement to give linear adducts like **22**, rather

than sterically crowded angular form **23.** Another example of this type of rearrangement has been reported with the benzonitrile derivative **24** (Scheme 1.5).[14]



Scheme 1.5: Irradiation of a *para*-hydroxy benzonitrile derivative **24** to give the tricyclic [4.6.5] compound **27**.

The *ortho* addition can be highly competitive with the *meta* addition mode, in part because unlike the *meta* addition, which occurs solely through the π→π* first singlet state (^{1}S) of the aromatic ring. There are several avenues open for the *ortho,* including *via* excitation of the alkene and intersystem crossing of the arene to its triplet state that can equally undergo addition to the alkene.[10]

Attempted prediction of the mode preference has been conducted *via* detailed theoretical studies revolving around the difference in redox potentials of the reactants, the photochemical properties of the excited benzene intermediate and its associated alkene partner.[10,15] For instance the work of Mattay,[16] who noticed limitations in previous methods, focused on calculations of ΔG_{ET} *via* the Rehm-Weller equation[17] (Equation 1.1.) and redox potentials of the donor and acceptor in the system, to create a quantitative prediction model.

$$\Delta G_{\mathrm{ET}} = F\left[E_{\frac{1}{2}}^{Ox}(D) - E_{\frac{1}{2}}^{Red}(A)\right] - \Delta E_{excit} + \frac{e^2 N}{4\pi\varepsilon_0 a}\left[\frac{1}{\varepsilon} - \frac{2}{37.5}\right]$$

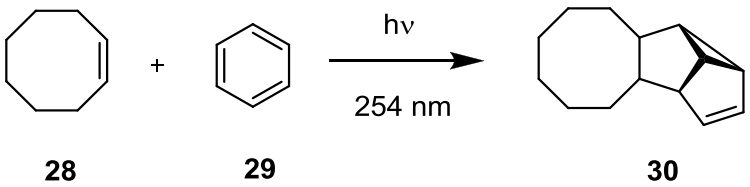
Equation 1.1: The Rehm-Weller equation. Where $E_{\frac{1}{2}}^{Ox}(D)$ and $E_{\frac{1}{2}}^{Red}(A)$ = oxidation and reduction potential of the donor and acceptor in MeCN; E_{excit} = excitation energy; F = 96490 Coulomb.

Through this Mattay discovered a general rule that if the photochemical process had a ΔG_{ET}>1.4-1.6 eV, then the *meta* mode was favoured. Below this value (0<ΔG_{ET}<1.4-1.6 eV), then the *ortho* mode tended to predominate. To date this model has largely been backed up by experimental findings.[10]

It should be briefly mentioned, with regards to the [4+2] or *para* addition that competition from this mode is extremely limited. While it is essentially a photochemical equivalent of the previously highlighted Diels-Alder reaction, unlike its illustrious antecedent it has only been observed in a small number of cases, most notably with allenes and thus hasn't come under much consideration for use in synthesis.[18]

The *meta* form on the other hand clearly stands apart as from the other modes. To begin with, it results in the formation of three new carbon-carbon σ bonds in one operation, the greatest increase in molecular complexity of any single reaction. The intramolecular version therefore can generate tetracyclic sesquiterpenes that contain up to six new stereocenters from simple flat achiral starting materials. Moreover, it has no direct equivalent in thermal chemistry, giving it even greater synthetic utility.

The story of the *meta* photocycloaddition ultimately begins in 1966 when the intermolecular version was discovered almost simultaneously by two groups on opposite sides of the Atlantic; Wilzbach and Kaplan[19] of the Argonne National Laboratory, Illinois and Bryce-Smith, Gilbert and Orger[20] of Reading University.



28 **29** **30**

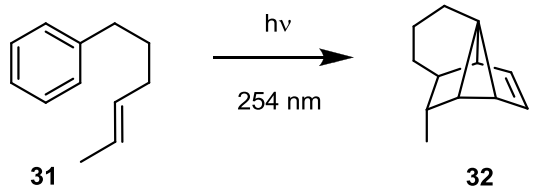
Scheme 1.6: One of the first examples of a *meta* photocycloaddition from Bryce-Smith.

Both groups found that direct irradiation, using 253.7 nm UV light, of a solution containing an olefin (such as cyclooctene **28**) and an aromatic compound like benzene (**29**), resulted in a 1:1 non-aromatic adduct that appeared to contain a vinyl cyclopropane unit at its core (Scheme 1.6). The substituted tricyclo[3.3.0.$0^{2,8}$]oct-3-ene structures (**30**) were characterised through a rigorous study of the then available spectroscopic techniques and a range of typical chemical tests.

Unfortunately, while intermolecular photocycloadditions like that shown in Scheme 1.6 are of interest for studying mechanism, most are intrinsically low yielding.[10b] This is due to the limited lifetime of the excited state in solution and the improbability of such a state coming into contact with an alkene in dilute solution during that period, as opposed to undergoing decay to the ground state or other decomposition processes.

Therefore, synthetic efforts have largely been directed towards intramolecular reactions, which are entropically more favourable and possess fast reaction rates due to the increased chance of the excited state coming into contact with the alkene. Additional constraints in the transition state also lead to better regio- and stereoselectivity.

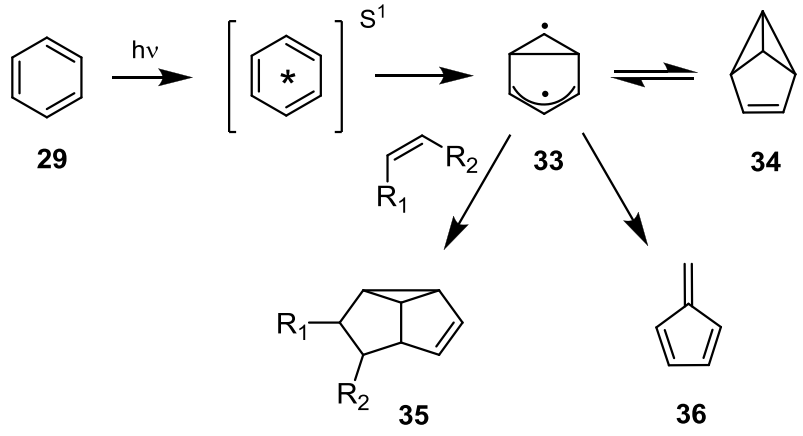
Introduction of the intramolecular variant of the cycloaddition into the chemists' toolbox was made in 1969, when it was reported by Morrison and Ferree working at Purdue University in Indiana.[21] They observed that irradiated 6-phenylhex-2-ene (**31**) underwent an internal [3+2] cycloaddition, although this was not what they had initially anticipated (Scheme 1.7). Their work was actually aimed toward studying the *cis-trans* isomerization reaction of the alkene bond, which had been observed in 1-phenylbut-2-ene the year previously.[2]



Scheme 1.7: Intramolecular *meta* photocycloaddition of 6-phenyl-hex-2-ene **31** showing the major adduct **32**.

The fact that the major products of this photochemical reaction were *meta* photocycloadducts was certainly a fortuitous event, especially, so soon after the initial discovery of the intermolecular version. While preparative separation of the four cycloadducts synthesized was not possible with the technology available at the time, Morrison was able to suggest through experimentation that the internal photoreaction was equivalent to its external counterpart.

The group was unable to make an exact determination of the mechanism of reaction, although they tentatively leaned toward a proposed singlet "exciplex", rather than the diradical "prefulvene" intermediate advocated by Bryce-Smith and colleagues in their original works (Scheme 1.8).[20,23]



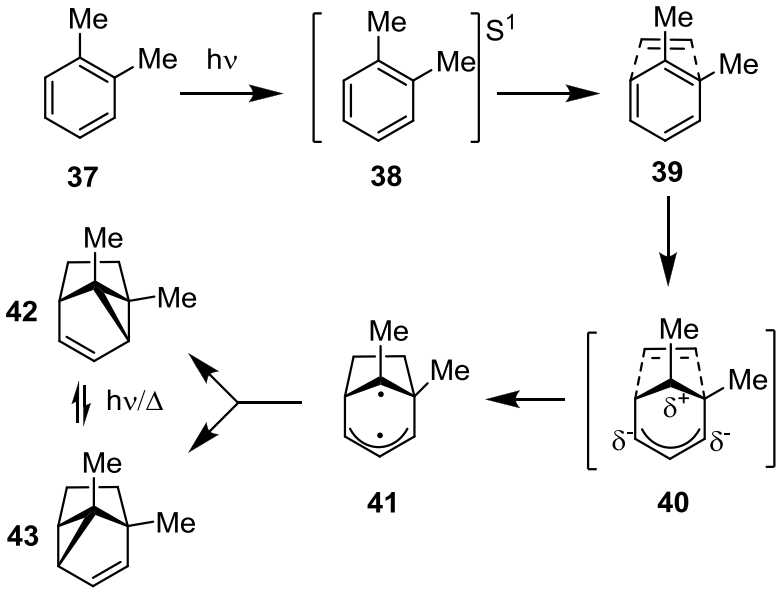
Scheme 1.8: Bryce-Smith's advocated biradical species, called a "prefulvene" **33**, the precedent species to benzvalene (**34**), the *meta* photoadduct (**35**) and fulvene (**36**).

This was only one of several theories put forward to explain the mechanism of the reaction[10a-i] and the idea was still considered relevant as late as 1986.[24] However, through innumerable

research studies employing the use of the *meta* photocycloaddition reaction, the theory was eventually discounted. In particular, a "prefulvene" intermediate could not adequately explain the regio and stereochemical outcomes for additions derived from benzene rings with electron-donating and withdrawing groups such as toluene and cyanobenzene.

1.2.2 Mechanism of the *meta* photocycloaddition reaction.

As mentioned, the mechanism of the *meta* photocycloaddition has been the subject of a great deal of debate.[10,25] Whilst the exact details are still a matter of contention, the pathway illustrated in Scheme 1.9 is generally agreed upon as explaining most of the regio- and stereochemical outcomes of the reaction.



Scheme 1.9: General mechanism of the intermolecular *meta* photocycloaddition

The initial step is the excitation of benzene to its first singlet excited state, which can be stimulated with UV light at approximately 254 nm. The HOMO and LUMO of the excited arene species then interact with the HOMO (π) and LUMO (π^*) of the alkene, creating an "exciplex" (**39**).

The best evidence for this step is the orbital based models created by Houk,[26] who carried out a substantial "qualitative molecular orbital rationalization of the selectivities in *ortho, meta* and *para* cycloadditions" that covered the singlet excited states of a variety of substituted benzenes with alkenes, in particular benzene, *cis*-but-2-ene systems. Houk showed that benzene ^{1}S-π and the A*π* secondary orbital interactions (Figure 1.3) caused a stabilisation of the *endo*-alkene-arene complex and a destabilisation of the *exo* form (in the same sense as Alder's *endo* rule in the Diels-Alder reaction).

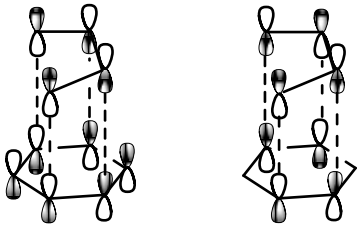
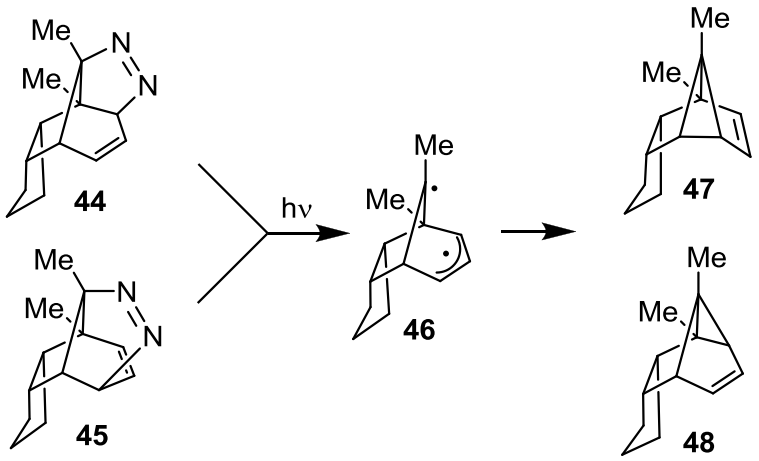


Figure 1.3: Primary and secondary S/A* and the π/π* orbital interactions for benzene and cis-but-2-ene

There are obviously exceptions to every rule, for example, cyclic ene-diol ethers prefer to form the *exo*-photoadduct. In this case it is suggested that the lone pairs on oxygen on the 1,3-dioxole ring are repulsed by the distorted electron cloud that is created during the initial σ-bond formation and thus destabilise the *endo*-exciplex.[27] Such an exciplex has not been definitively proven, however simple observation of the stereo and regio- selectively seen in most intermolecular *meta* photocycloadditions speaks for itself.[28]

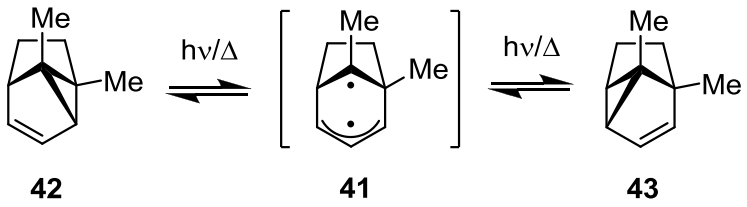
A result of exciplex formation is a distorting of the uniform nature of the aromatic rings electron cloud in such a manner that it becomes a polarised species (**40**) where a partial positive charge can be considered to exist on the "bridgehead", while a partial negative charge is distributed over the allylic positions. During formation of the two arene-alkene carbon σ bonds, this is transformed into a biradical intermediate (**41**) that then prompts cyclopropane ring closure to make the tricyclic core common to all *meta* photoadducts.

Evidence for the theoretical biradical was enhanced by the elegant work of Sheridan and Reedich,[29] (Scheme 1.1.0) who created diazo-compounds **44** and **45**, which decompose under irradiation at 254 nm, to give the same products in a near identical ratio (**44** affords a ratio of **47**:**48** of 1:1.32 while **45** affords a ratio of 1:1.34). The only way to explain such a phenomenon would be to assume that the products are created through the same biradical transition state **46**, although such a state has never been isolated.



Scheme 1.1.0: Evidence for a biradical intermediate **46** in the formation of the cyclopropane ring.

Note in both Scheme 1.1.0 and 1.1.1, that if substituents are present on the aromatic ring, cyclopropane ring closure results in two non-equivalent structures; the behaviour of this closure and therefore the ratio of the two adducts obtained is highly substrate dependent.



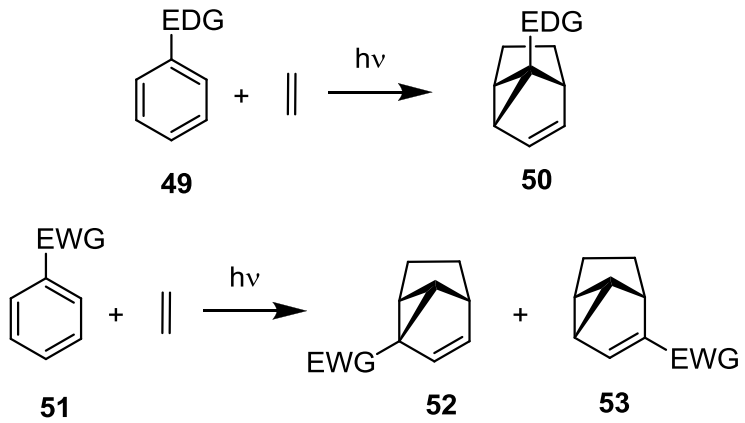
Scheme 1.1.1: Vinylcyclopropane-cyclopentene rearrangement.

It should also be noted that the said ratios from photocycloaddition experiments should be treated with care, as along with decomposition of the strained cyclopropane ring, often reported has been the phenomena of vinylcyclopropane-cyclopentene rearrangement, where essentially

one adduct is converted into the other, either by thermal or photochemical means (Scheme 1.1.1).[10,30] In the photochemical case a photo-stationary state is set up if the rate of conversion is the same in both directions. Generally in practise the absorption is not equal due to side reactions, so one form is predominantly converted to the other.

1.2.3 Regio- and stereoselectivity issues.

The regiochemistry of alkene addition is based on a combination of effects and this changes depending on whether the addition is inter- or intramolecular. However, the first aspect to consider in both cases is the electronic nature of the substituents on the aromatic ring. An electron donating group (EDG) can stabilise the theorised partial positive charge on the bridgehead position, so prefers to sit at that position exclusively. On the other hand, an electron withdrawing group (EWG) is able to stabilise the negative partial charge and thus will be found on one of the allylic positions of the final adduct (Scheme 1.1.2). This evidence itself is enough to suggest that the charged species (**40**) seen in the accepted mechanism may indeed be involved.

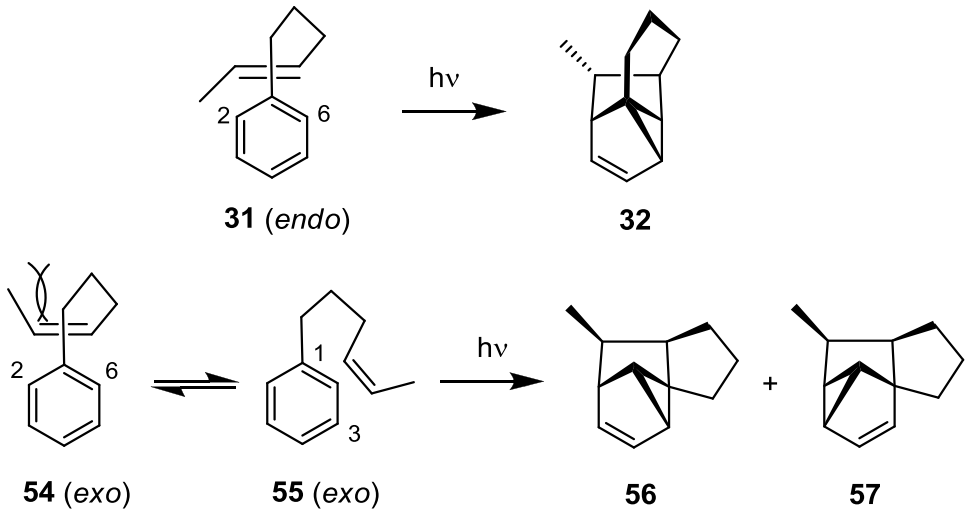


Scheme 1.1.2: Regiochemical control by use of substituents upon the aromatic ring in *meta* photocycloadditions.

The electronic properties of groups connected to the aromatic ring tend to be the overriding effect for the regiochemical outcome, particularly with the intermolecular reaction. It should be

noted that when an aromatic ring is multi-substituted, unless the groups are the same, then directing effects are competitive. For instance, strong π-donors such as methoxy groups tend to dominate, taking up the bridgehead position exclusively and overriding the effect of most other donating groups. When in competition with electron withdrawing substituents the directing effects can be additive resulting in highly selective adduct formation.[10]

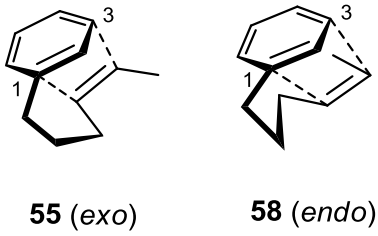
Electronic effects are not enough to explain the finer details of the stereochemistry in the intramolecular reaction. In fact, if controlling aromatic substituents are removed, there are essentially three adducts capable of formation due solely to the properties of the connecting tether. Terminal and *trans*-substituted double bonds lead almost exclusively to 2,6-addition across the tethered position of the ring while *cis*-substituted give rise to 1,3-addition. There is only one type of the former and two of the latter, because cyclopropane ring closure in the 1,3 case leads to non-equivalent structures.



Scheme 1.1.3: Intramolecular 2, 6-addition and 1, 3-additions in *meta* photocycloaddition.

Without strong electronic effects, steric and orbital interactions dictate how the addition of arene to alkene occurs. In the *trans* alkene isomer the *endo* configuration (**31**) is almost exclusively favoured thanks to the best orbital overlap, and so the alkene adds 2,6 across the inductively donating tether.

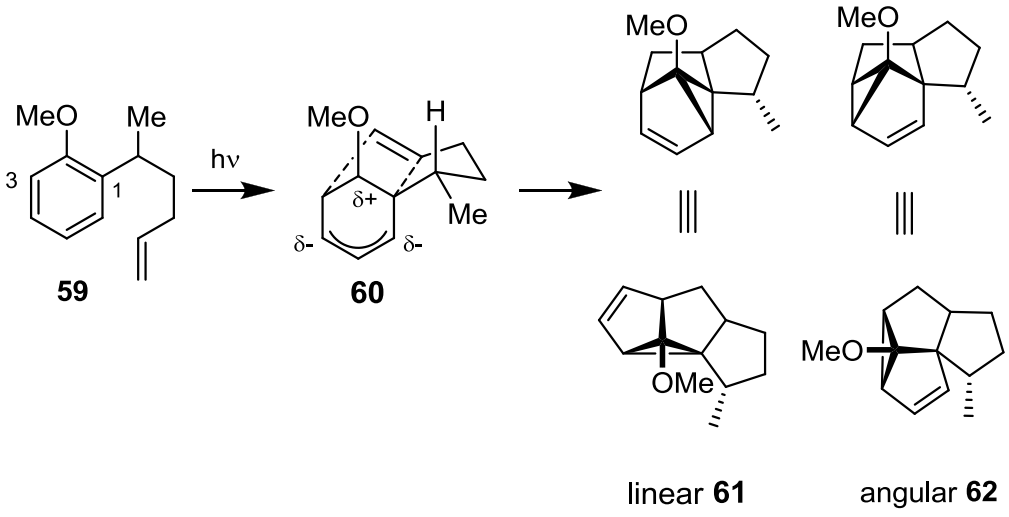
In the *cis* geometry alkene, the *endo* 2,6 configuration cannot be adopted due to inadequate flexibility in the three-atom tether and the *exo* (**54**) is equally disfavoured by steric interactions. As such this leaves the most likely form of addition to be across the 1,3 position in the less strained *exo* conformation (**55**), which also possesses better orbital overlap (Figure 1.4).[31]



55 (*exo*) **58** (*endo*)

Figure 1.4: Representation of 1, 3-addition enforced by steric interactions of the c*is*-alkene and tether together with preferred *exo*-geometry (**55**) due to reduced tension in the carbon chain.

If we were to reintroduce a strong electron donating group to this situation at the *ortho* position to the tethered position where it can have most influence, then the 2,6 route is almost entirely removed from the equation, and 1,3 addition relative to the tether happens exclusively (Scheme 1.1.4).



59 **60** linear **61** angular **62**

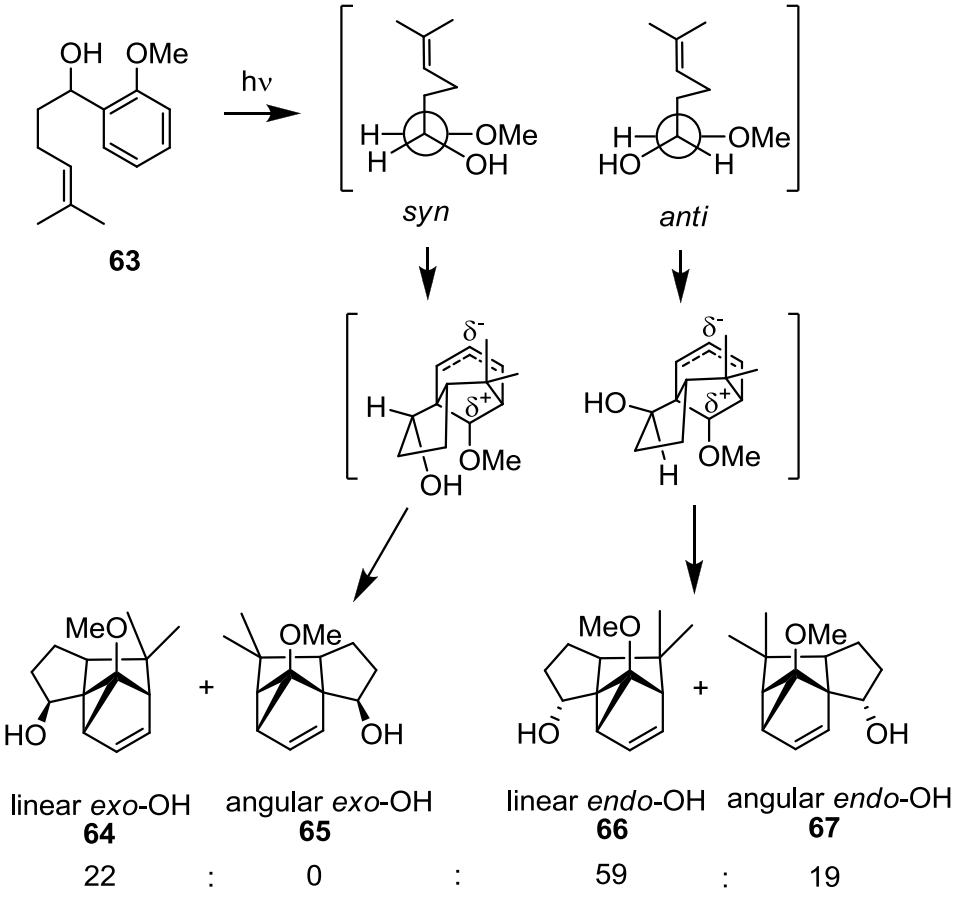
Scheme 1.1.4: Regio- and stereochemical outcome of an intramolecular *meta* photocycloaddition with a methoxy group on the aromatic ring (**59**).

This example highlights two other important aspects of the intramolecular reaction; the first is that the two regioisomers formed are generally described as being of the 'linear' (**61**) or 'angular' (**62**) fused type. The linear was calculated by Wender and Howbert[10g] to be 3.6 $kcalmol^{-1}$ lower in energy than its more sterically crowded isomer, but this is not an infallible indication of which will be preferred. It has been shown that arene and alkene substituents have a high level of control with regard to the direction of the cyclopropane ring closure.[10,32]

For instance, it has been generally noted that intramolecular *meta* photocycloadducts that occur within bichromophores containing an *ortho* group on the aromatic ring and a side chain substituent tend to have a larger ratio in favour of the linear adduct.[33] The reason for this is not straightforward and it should be noted that the ratio can be highly affected by the vinylcyclopropane-cyclopentene rearrangement, which is usually found to convert linear isomers to their angular form rather than vice versa.[34]

The second aspect highlighted in Scheme 1.1.4 is the effect that groups branching off the tether have on the resultant stereochemistry of the products. The methyl sitting in the α-position of the tether prefers to be on the lower *endo* face of the final adducts, because it is favourable for it to sit pseudo-equatorial in the exciplex transition state (**60**) as illustrated (Scheme 1.1.4).

A further illustration of this was conducted by Jan Cornelisse *et al*.[35] in his studies toward "diastereoselective control of intramolecular *meta* photocycloadditions of side-chain-substituted 5-(2-methoxyphenyl)-pent-1-enes". They also reported that when there is an α-substituent attached to the side-chain, the stereochemistry at that centre results in stereoselectivity in the photoadduct, such that the *endo* varieties (**66** and **67**) are predominant (Scheme 1.1.5).



Scheme 1.1.5: *Endo* selectivity due to sterics.

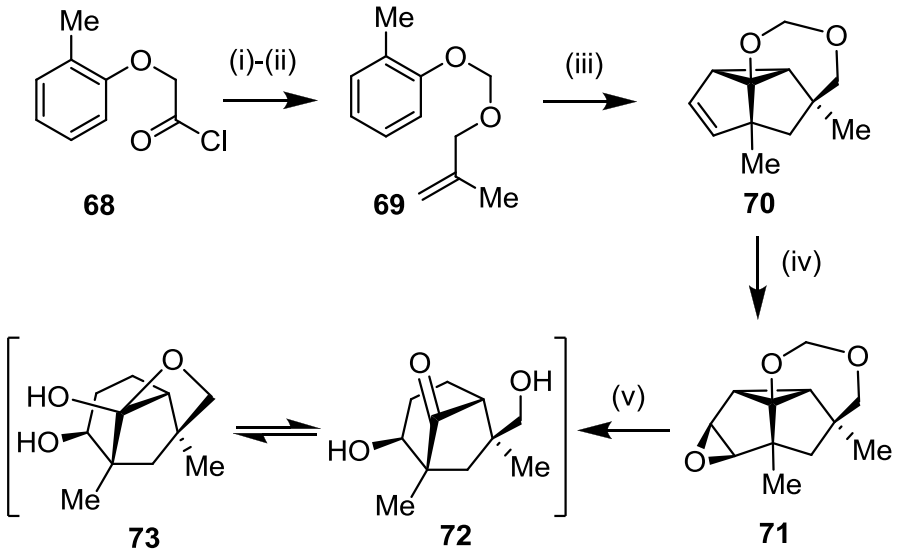
This is thought to occur because of steric hindrance in the *syn* periplanar approach of the alkene bond, in a similar fashion to allylic 1,3-strain.[36] As this force is repulsive it had been theorised that the reverse selectivity might be observed if the substituents attracted one another. This was reported in the earlier chemistry of Zhang and co-workers,[37] who suggested hydrogen bonding as a causal factor. Cornelisse attempted to establish if this were true, by irradiating a series of products with a hydroxy or trimethylsilyloxy group in the α-, β-, or γ-position on the side chain. They discovered that the photoproduct ratios of the TMS-protected versions were practically identical to those formed with the hydroxyl. The *anti* periplanar route seemed to hold true in this case, and hydrogen-bonding was thought to "not play a role in determining the diastereoselectivity of the reaction".[35]

1.2.4 The importance of tether length.

A final major aspect to be considered with tethers is their length. Every intramolecular *meta* photocycloaddition discussed thus far has concerned photosubstrates where the tether between arene and alkene contains the optimum length of three atoms. Separate studies by Morrison,[38] Cornelisse[39] and Gilbert[40] have all reported a significant reduction in the yield of *meta* photocycloaddition reactions for tethers beyond this ideal length presumably due to the increased degrees of freedom. These entropy considerations have therefore largely discouraged the use of longer tethers, particularly in the synthesis of natural products.

Logically, there are some exceptions. In a limited number of cases a longer tether has produced useful results, although there is usually some restriction of the conformational freedom in these instances either by introduction of a heteroatom or steric bulk that allows a suitable conformation to become favoured.[10g]

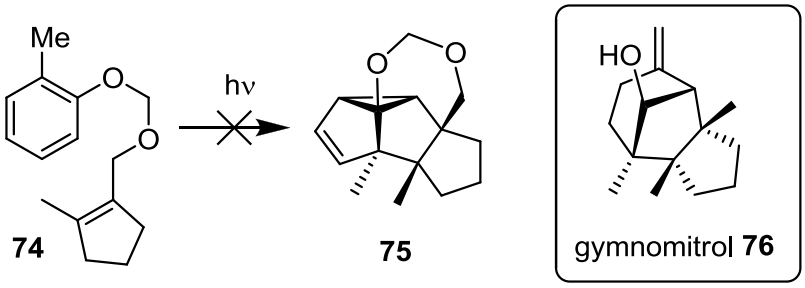
The Penkett group used four atom "temporary" tethers in their attempts to synthesise the cores of gymnomitrol and gelsemine.[41] The idea of using a temporary, easily removable tether was originally proposed by Stork,[42] and can be used to convert an unfavourable intermolecular reaction into a more favourable and selective intramolecular one. The tether can be easily removed afterwards maintaining the adduct structure that was desired from the original intermolecular reaction.



Reagents & conditions: (i) $(Ph_3P)_3RhCl$, 170 °C; (ii) methallyl alcohol, 50% NaOH, benzene, Bu_4NCl, (86%); (iii) hν (254 nm), cyclohexane (17%); (iv) dimethyldioxirane, CH_2Cl_2-acetone (1:1), 0 °C (100%); (v) HCl (aq.), acetone, 0 °C→RT (55%).

Scheme 1.1.6: Studies toward the synthesis of gymnomitrol.

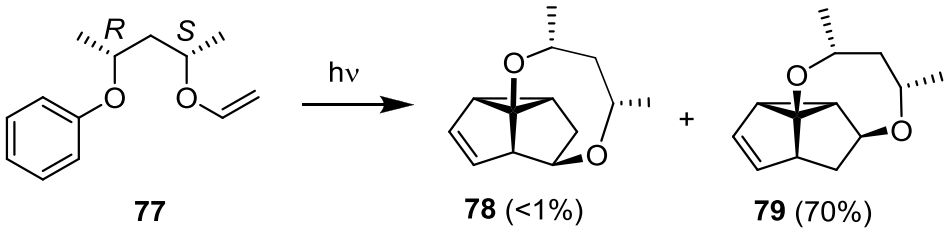
In the study toward gymnomitrol (**76**), the four-atom tether employed to create the basic core structure was an acetal (**69**) and this underwent *meta* photocycloaddition, resulting in a reasonable 17% yield of the *meta* adduct **70** (Scheme 1.1.6). The two oxygen atoms lend the chain the required flexibility to perform the desired addition, something that would not occur in the all-carbon form. Unfortunately a further reaction to fashion the full core of gymnomitrol (**76**) using the sterically more encumbered alkene substrate **74** was regrettably not achieved in the same fashion.[41]



Reagents & conditions: hν (254 nm), cyclohexane, then H_3O^+ (0.1%)

Scheme 1.1.7: Attempted approach to the core gymnomitrol **71**

In the work of Sugimura,[43] a similar type of tether containing two oxygen atoms based on 2,4-pentanediol (**77**) was used to produce the only example of a *meta* photocycloaddition reaction with a five atom tether (Scheme 1.1.8). This reaction is remarkable in part because of its high yields of up to 70%, but also because it occurs in high enantiomeric purity.



77 **78** (<1%) **79** (70%)

Reagents & conditions: (i) hν (254 nm, vycor filter), pentane.

Scheme 1.1.8: Diastereoselective *meta* photocycloaddition with a five-atom tether.

1.2.5 Reactions of *meta* photocycloadducts and their use in natural product synthesis.

The complex architecture of the *meta* photocycloadduct is in itself not a biologically useful entity. However its synthetic strength lies in the one step creation of such complexity and that it possesses an inherently strained cyclopropane ring. By careful selection of reagents this ring can be fragmented to create a variety of common structures found in natural products both from inter- and intramolecular adducts (Scheme 1.5).

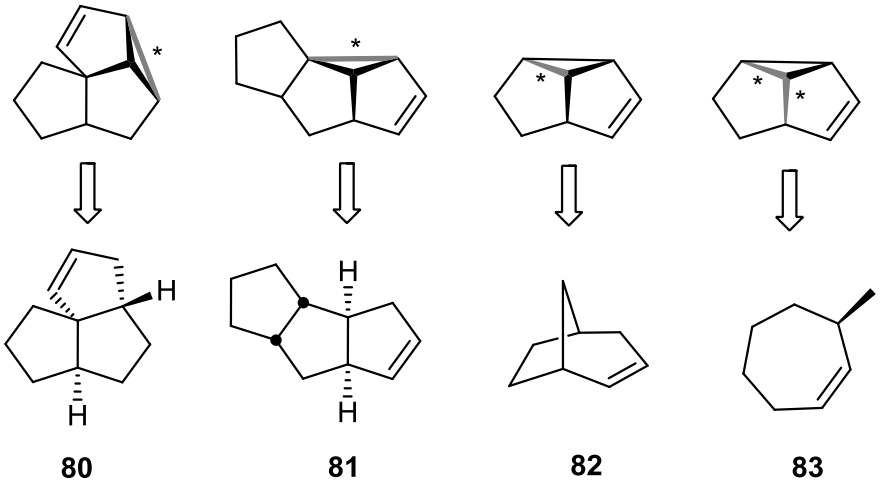
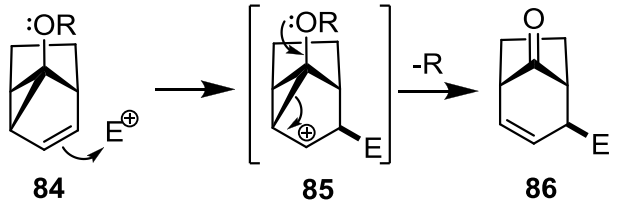


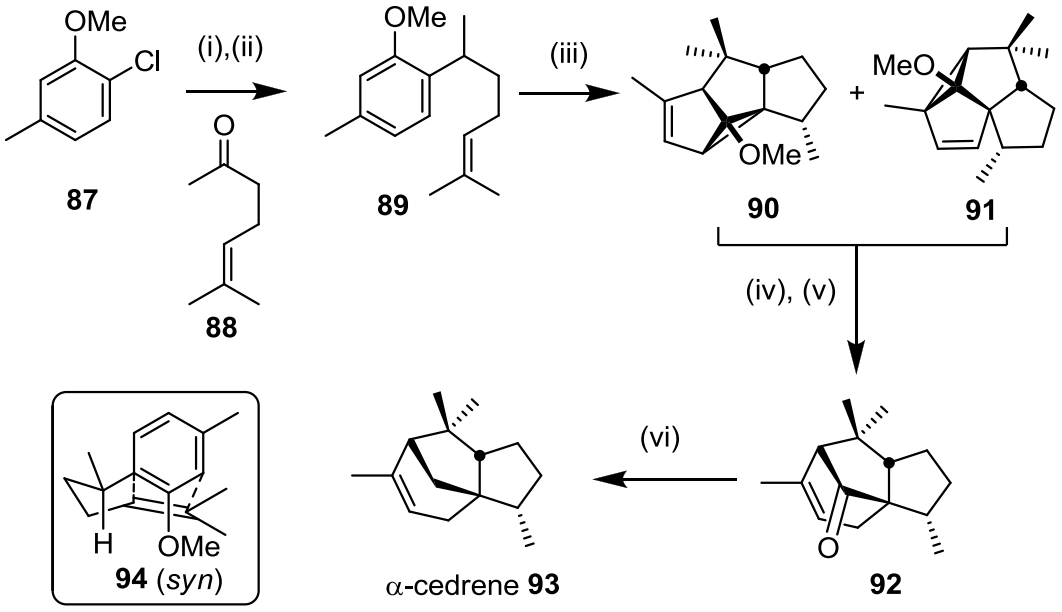
Figure 1.5: Cleavage of one of the cyclopropane bonds on the two intramolecular isomers leads to the angularly fused **80** and linearly fused triquinane **81**. Additionally, cleavage in the intermolecular adducts can lead to bicyclo [3.2.1] octene **82** and double cleavage to a cycloheptene ring **83**.

A variety of methods have been used to achieve the above fragmentations. For example, in the case of an adduct with oxy-functionality at the bridgehead position, the ring can easily be fragmented by addition of an electrophile to the electron-rich alkene to form a cationic intermediate, that then breaks the cyclopropane yielding the bicyclo [3.2.1] octene **86** (Scheme 1.1.9). Examples of electrophiles used for such a reaction had included acid (H^+),[44] bromine (Br^+)[31,45] and *m*CPBA (OH^+).[45]



Scheme 1.1.9: General reaction of a *meta* photoadduct with an electrophile.

Perhaps the best way to illustrate the power of this method toward making natural products is to study Paul Wender's total synthesis of α-cedrene (**93**) published in 1981.[31] This was the first example of a natural product synthesis that made use of the *meta* photocycloaddition. The route is remarkably concise and stereoselective, comprising a total of only five steps (Scheme 1.2.0).

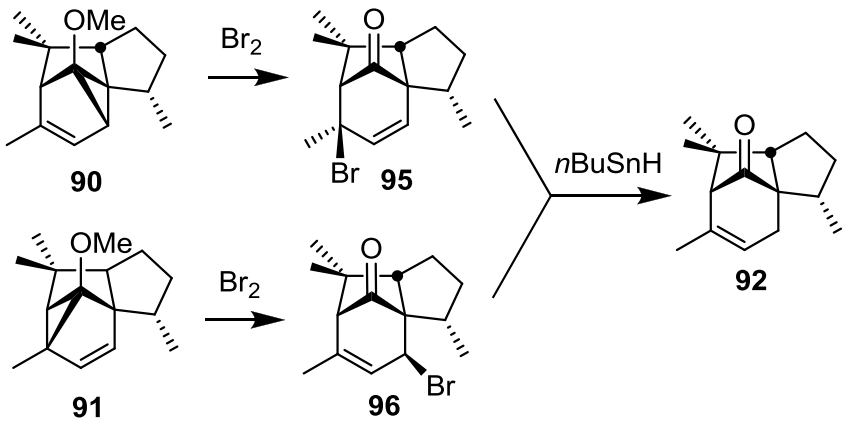


Reagents & conditions: (i) Li, Et_2O, then **88**; (ii) Li, NH_3, then NH_4Cl (74%, two steps); (iii) hν (vycor filter), pentane (65%); (iv) Br_2, CH_2Cl_2; (v) Bu_3SnH (neat) (59%, 2 steps); (vi) NH_2NH_2, KOH, $(HOCH_2CH_2)_2O$, 200 °C (58%).

Scheme 1.2.0: Synthesis of α-cedrene **93**.[31]

Wender's route is an example of great synthetic planning, with the photosubstrate designed to take advantage of all the known methods of controlling the photochemical addition. The methoxy group is a strong π-donor and as such addition occurs exclusively 2,6 across its position on the ring, and 1,3 to the tether. The key stereogenic centre α to the aromatic ring then controls the π-facial selectivity of the exciplex transition state (**94**), forcing the larger methyl group to sit pseudo-equatorial. The tether is therefore forced to adopt a *syn*-pentane conformation, limiting the number of possible products, such that only a 1:1 mixture of the linear and angular *endo* adducts are produced when the photosubstrate is irradiated.

These isomers exist in equilibrium and both can be converted into the same ketone (**92**) *via* reaction with bromine and then elimination of the resultant bromide with tri-*n*-butyltin hydride.



Scheme 1.2.1: Bromine induced fragmentation and subsequent elimination in Wender's synthesis of α-cedrene.

The final step is a simple Wolff-Kishner reduction of the ketone to yield α-cedrene (**93**) in an overall yield of 16% over the five steps.

This remarkable achievement resulted in a flurry of interest in the *meta* photocycloaddition and consequently a great number of natural products have been synthesised based on the reaction (Figure 1.6).

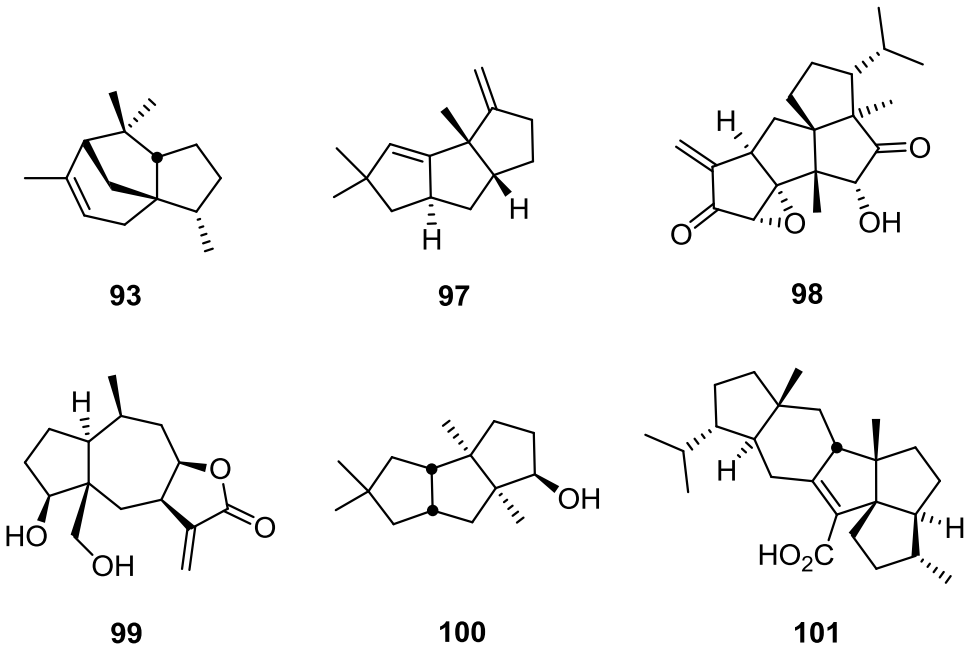
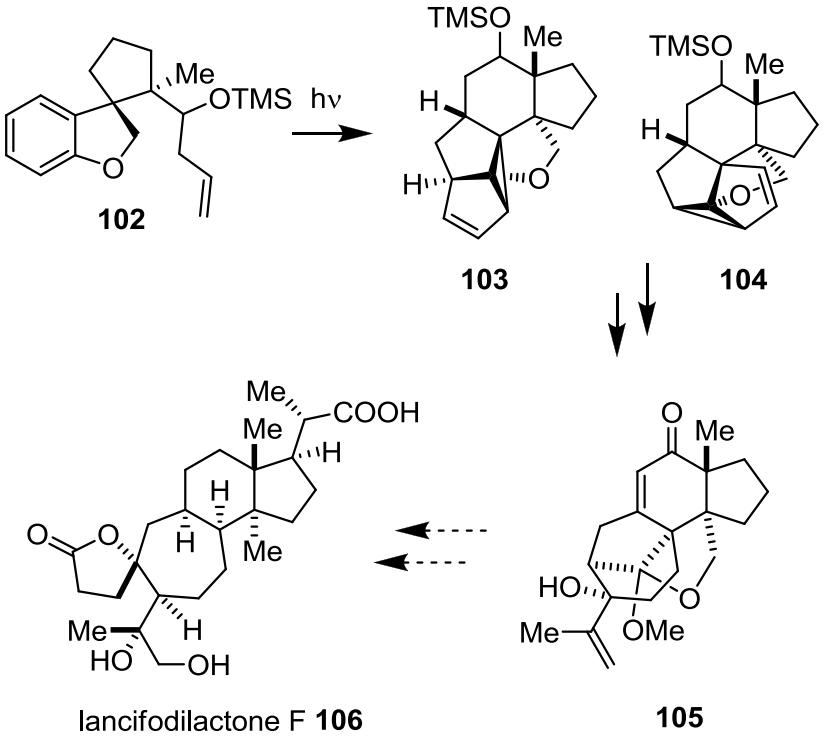


Figure 1.6: A selection of natural products successfully synthesised using a *meta* photocycloaddition.

Most of these natural products contain similar structural motifs. Rudmollin (**99**),[46] much like α-cedrene can be derived from a *meta* photocycloadduct containing oxygen functionality at the bridgehead position that has been subsequently fragmented, however in this case the bridge was reductively cleaved to give a cycloheptene ring. Hirsutene (**97**)[47] and ceratopicanol (**100**)[48] are based on the radically cleaved triquinane core of an intramolecular linear *meta* adduct. Meanwhile, antibiotic crinipellin B (**98**)[49] and retigeranic acid (**101**)[50] derive from the opposite angular counterpart and are sometimes referred to as silphinene type structures.[51]

Wender who published most of the natural product syntheses mentioned above remains the reactions greatest exponent, asserting that the great value of the *meta* photocycloaddition is that often a route occurring *via* this single step tends to "provide one of, if not *the* most concise and step efficient methods to the natural product".[52] For instance, in the case of the Chanon, Baralotto and Julliard[48] synthesis of (±)-ceratopicanol, the cycloaddition helped reduce the number of steps from nineteen using conventional methods[53] to just seven.

Interest still remains high, with the most recent publications directed toward the total synthesis of insecticide Penifulvin A (discussed later in this work) and complex natural terpenoid lancifodilactone F (**106**),[54] of which the key skeletal core has recently been synthesised (Scheme 1.2.2).



Scheme 1.2.2: An approach to the core skeleton of lancifodilactone F, by Wang and Chen.[54]

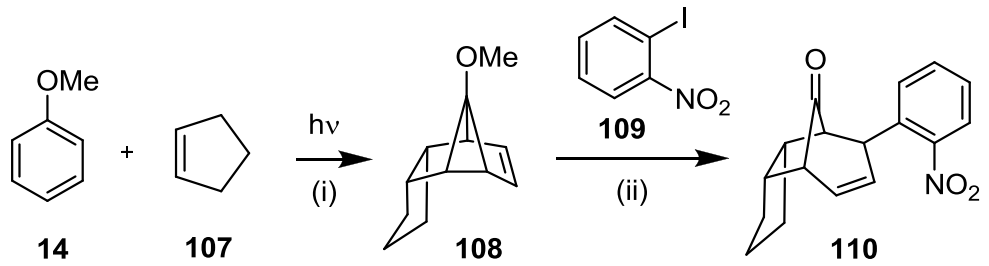
The synthetic utility of the *meta* photocycloaddition does naturally have its limits, being dependent upon certain key factors. First to consider is easy access to the required photosubstrate; secondly, whether this substrate undergoes photocycloaddition in the desired manor (accounting for all the regio- and stereochemical issues already outlined) and in sufficient yield and finally, how easily the cycloadduct can be converted into the desired target with the appropriate functionalities.

While we could feasibly recount further details of the many syntheses that have been completed using a *meta* photocycloaddition step, such information has already been highlighted in a series of excellent reviews on the subject.[10] In particular the recent review by Chappell and Russell[10g] that celebrated the 25th anniversary of Wender's remarkable α-cedrene synthesis is highly recommended.

1.3 Previous Penkett group studies: Palladium catalyzed reactions of *meta* photocycloadducts.

The work of the Penkett group has been, for the past decade, focused on the reactions of *meta* photocycloadducts, with a particular interest in forming carbon-carbon bonds.

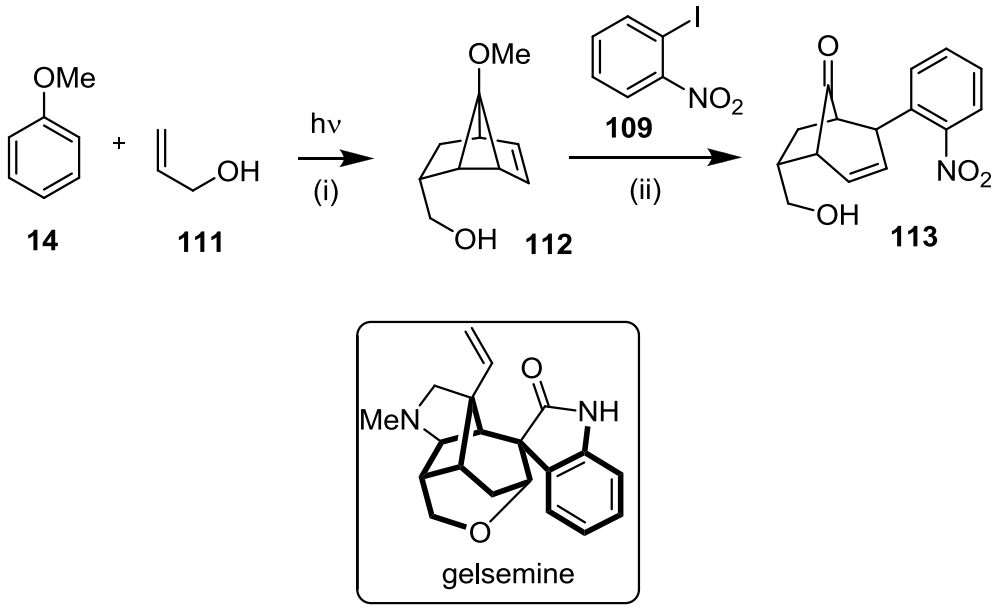
In 2004, Penkett *et al*.[55] described the first examples of this using a Heck reaction. Compound **110** was synthesised in a 27% yield from the *endo meta* adduct of anisole and cyclopentene, which was treated with a mixture of 1-iodo-2-nitrobenzene (**109**), palladium (II) acetate (5 mol %), tri-*o*-tolylphosphine (15 mol %) and triethylamine at 120 °C in DMF for 12 hours.



Reagents & conditions: (i) hν (254 nm), cyclohexane, 19% (ii) **109**, $Pd(OAc)_2$, $P(o\text{-tol})_3$, NEt_3, DMF, 120 °C, 12h, 27%.

Scheme 1.2.3: Heck Arylation of a *meta* photocycloadduct.

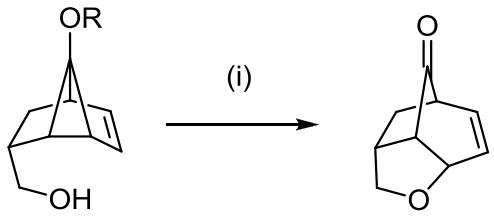
This novel and highly efficient strategy was then used in an attempt towards the construction of the core skeleton of the alkaloid gelsemine.[55] After only two steps 75% of gelsemine's complex carbon framework had been assembled, however a total synthesis for the natural product *via* this promising methodology was never fully realised (Scheme 1.2.4).



Reagents & conditions: (i) hν (254 nm), cyclohexane, 8% (ii) **109**, $Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, DMF, 120 °C, 4h, 37%.

Scheme 1.2.4: First stages of an attempted synthesis of the complex alkaloid gelsemine showing the completed bonds.

From this targeted synthesis project there were a number of other important developments including a palladium catalysed oxidative cyclization process, which resulted in the formation of a new series of complex multi-ring heterocycles.[56]



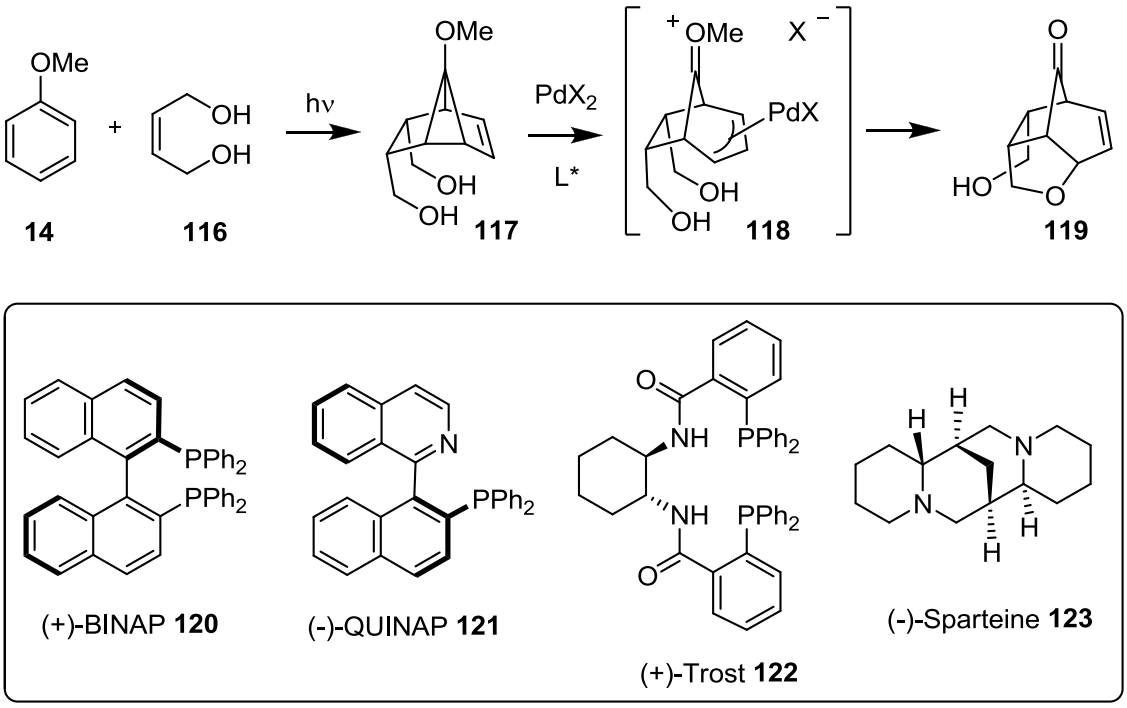
112 R = Me
114 R = $SiMe_3$

115

Reagents & Conditions: (i) $PdCl_2$ (5 mol %), P(o-Tol)$_3$ (10 mol %), NEt_3 (2 eq.) $CuCl_2$ (200 mol %), 20 °C, 48 hr, (69%, when **112**; 62%, when **114**).

Scheme 1.2.5: Intramolecular oxidative cyclization of a *meta* adduct.

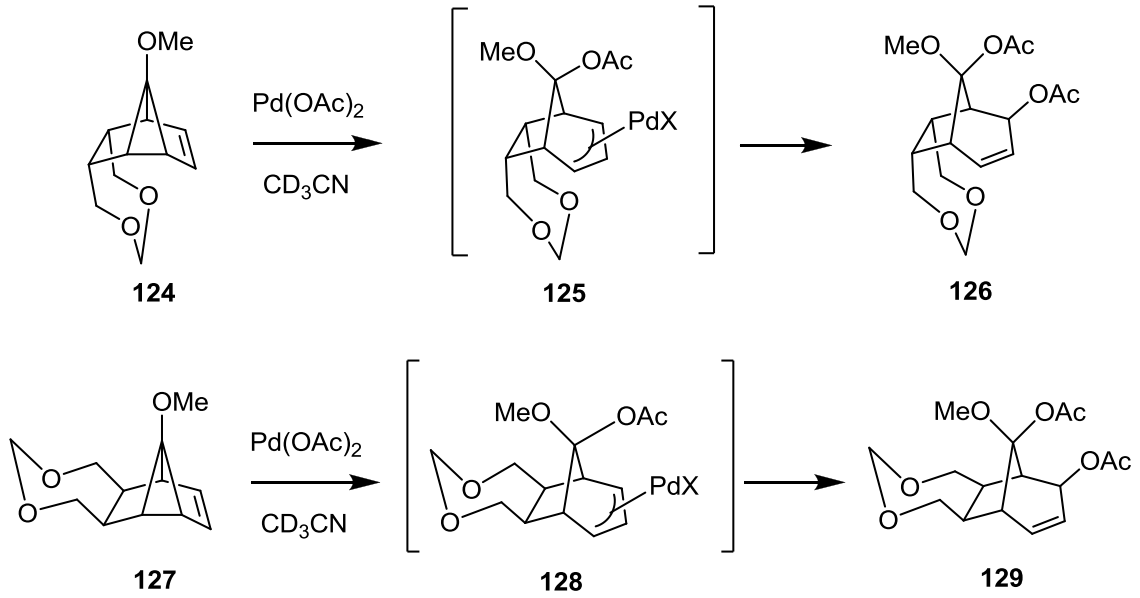
It was believed that this transformation occurred *via* a π-allyl palladium species and hence this led to an investigation towards the formation of an enantio-enriched product by the desymmetrization of a *meso* π-allyl palladium intermediate in the presence of a homochiral ligand.



Scheme 1.2.6: Oxidative cyclisation of the photoadduct derived from anisole and cis-but-2-ene-1,4-diol (**116**), and a series of homochiral ligands used to help promote selectivity.

A variety of ligands commonly used in allylic alkylations were investigated (Scheme 1.2.6). These ligands were mixed with palladium chloride in order to form complexes, which were subsequently reacted in a catalytic amount with the *endo* adduct **117** in MeOH. Oxygen was used as a re-oxidant in conjunction with a substoichiometric amount of copper (II) chloride. Yields of the reactions were low, with (-)-sparteine being the most effective ligand affording a 35% yield. To discover if enantioenrichment had been achieved the free alcohol was converted to a benzoate ester, but it was found that no such enrichment had occurred.

The most recent unpublished work by the Penkett group[57] has focused on the investigation and attempted trapping of the proposed π-allyl palladium intermediate, by use of the *endo* and *exo* acetal adducts derived from anisole and *cis*-4, 7-dihydro-1, 3-dioxepin (Scheme 1.2.7).



Scheme 1.2.7: Investigation of π-allyl palladium intermediates of *meta* adducts.

The reactions were carried out in CD_3CN and carefully observed over the course of the reaction by ^1H NMR spectroscopy. In both cases an intermediate product was clearly noticeable that seemed to conform to the expected π-allyl palladium intermediate and this could be stabilised for several hours by removing the CD_3CN and replacing it with $CDCl_3$.

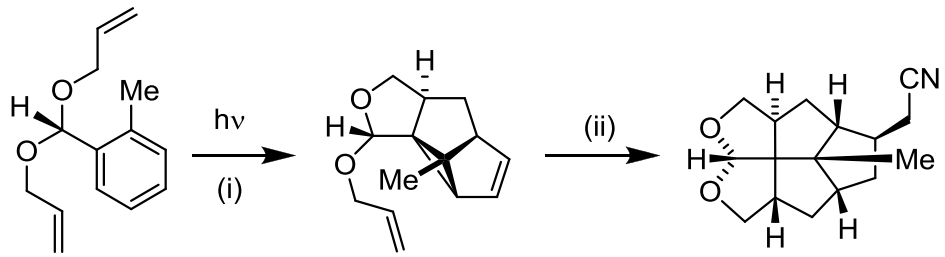
Attachment of a homo-chiral ligand was attempted in the hope that the π-allyl species might be isolated and recrystallized for X-ray analysis. However, no attachment between the *meta* adduct and palladium could be made in the presence of any of the standard ligands shown earlier (Scheme 1.2.6).

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.[55-57] 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).[58]

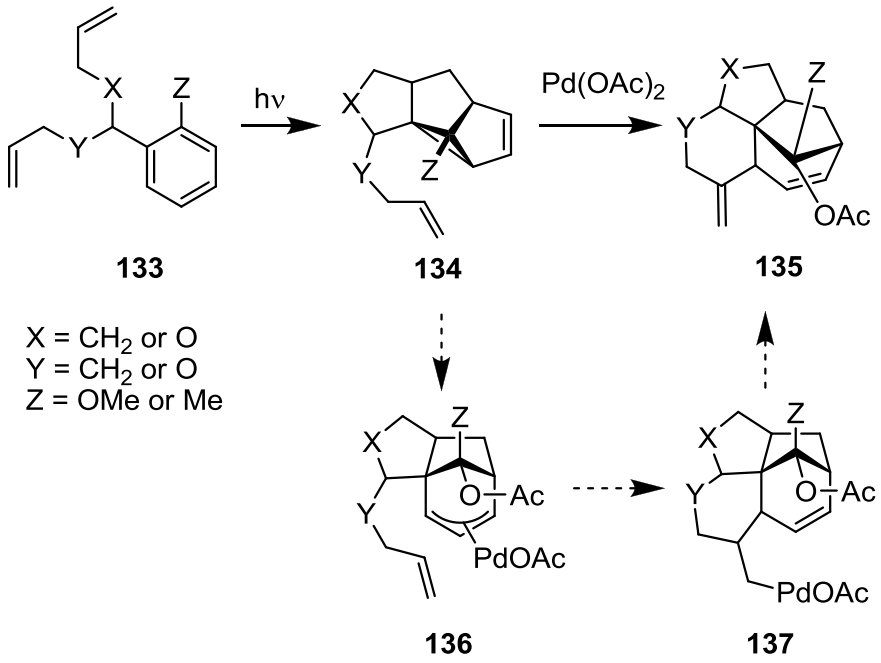


130 **131** **132**

Reagents & conditions: (i) hν (254 nm), cyclohexane, vycor filter, 24%; (ii) $(PhCO_2)2$, MeCN, 90-95 °C, 32%

Scheme 2.1: Wender's synthesis of a *cis, cis, cis, trans*-[5.5.5.5] fenestrane **132**.

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).

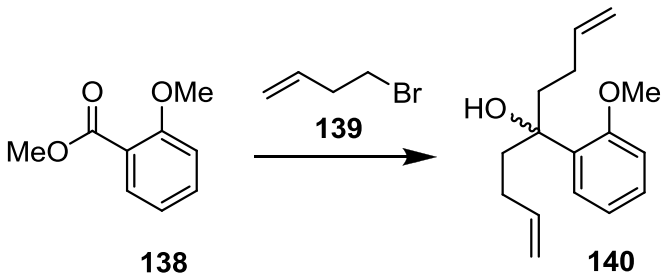


Scheme 2.2: Original synthetic plan using a palladium induced fragmentation.

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.



138 **140**

Reagents & conditions: Mg (2 eq.), butenyl bromide (2.5 eq.), Et_2O, 24 hrs, 75%.

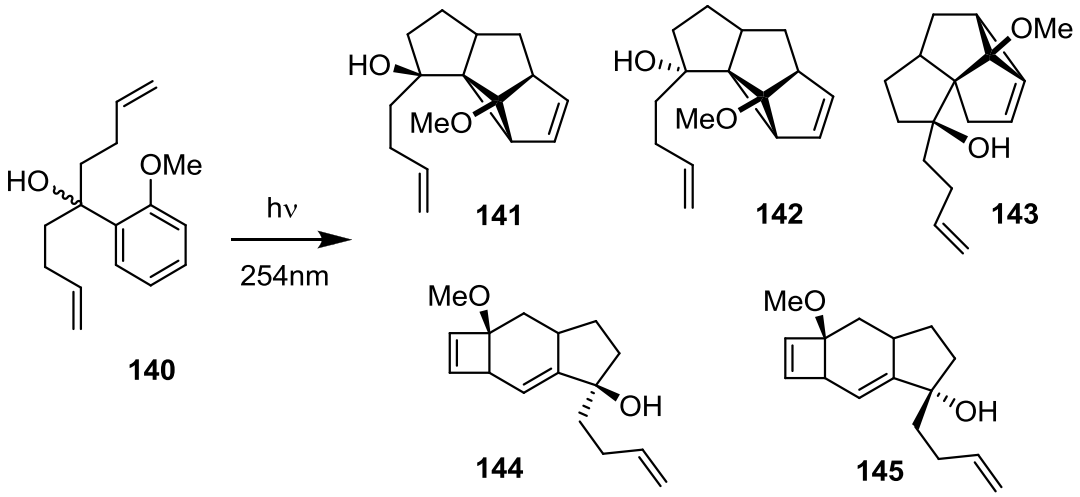
Scheme 2.3: Synthesis of tertiary alcohol photosubstrate **140**.

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"[59] or lead to excitation of the alkene $\pi \rightarrow \pi^*$ in both starting material and products, resulting in their decomposition.[60]

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 ($^3O_2$) undergoes intersystem crossing to form singlet oxygen ($^1O_2$) an extremely reactive species. This can often lead to oxidation reactions with alkenes that interfere with the *meta* photocycloaddition process.[60]

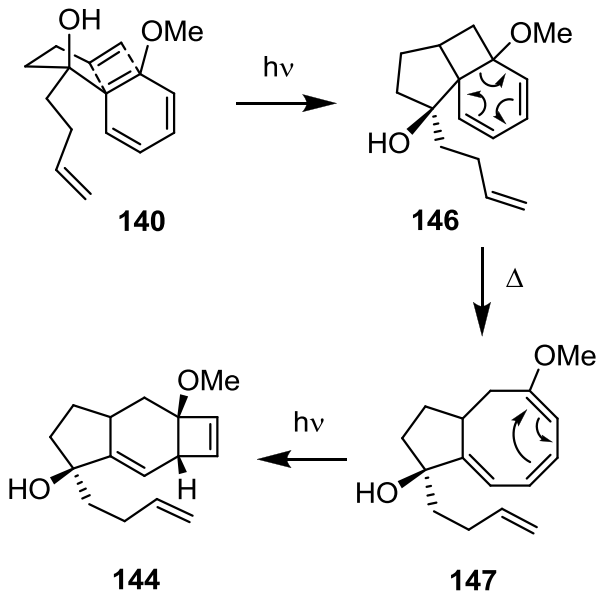
Analysis of the crude photolysis residue by TLC allowed us to identify five major products, which were then separated by flash column chromatography.



Reagents & conditions: 1.84 g, hν (254 nm), cyclohexane, 10 hrs

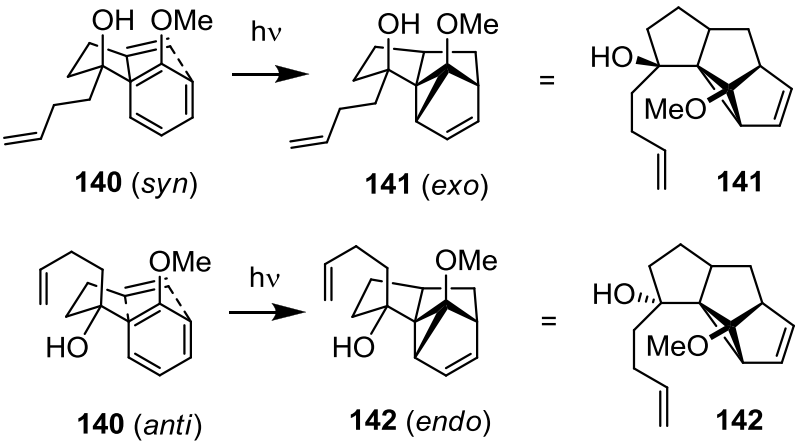
Scheme 2.4: The direct irradiation of photosubstrate **140**.

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 by a thermal disrotatory opening of the labile cyclohexadiene to a tricyclo-octatriene species. An intramolecular [$\pi_{2s}+\pi_{2s}$] photocyclization then recloses the ring to give the compounds seen in the observed mixture of photo-isomers. Such processes have been well documented in the literature (Scheme 2.5).[10b, 61]



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 1.1.5).[34]

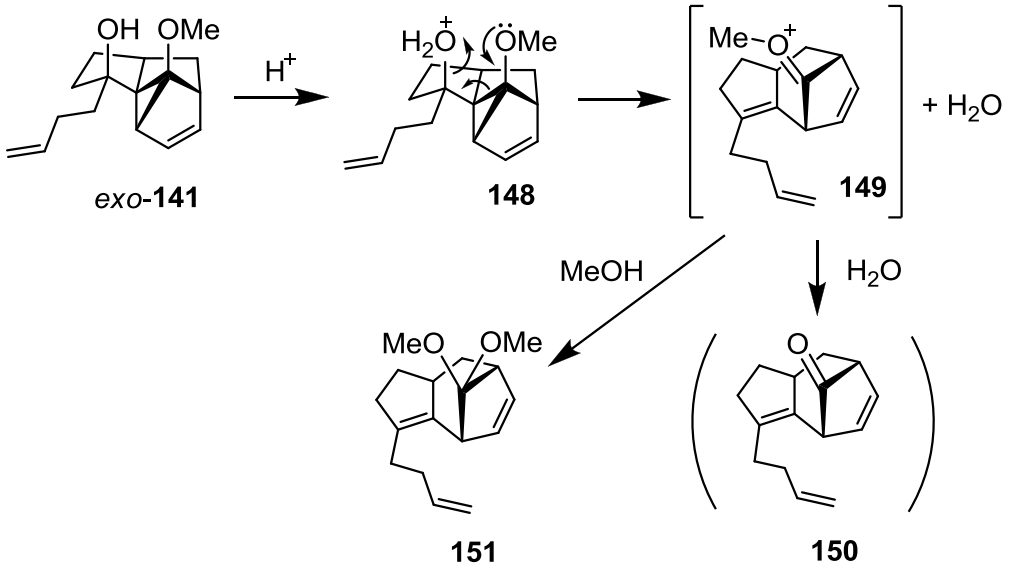
The reason for regioselectivity of the cyclopropane ring closure is less clear cut, with no definitive way of predicting which of the two forms, linear or angular, will predominate. In the case presented here, only one angular *meta* adduct **143** appeared to be formed to a significant degree.

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 hours 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[62] 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.

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

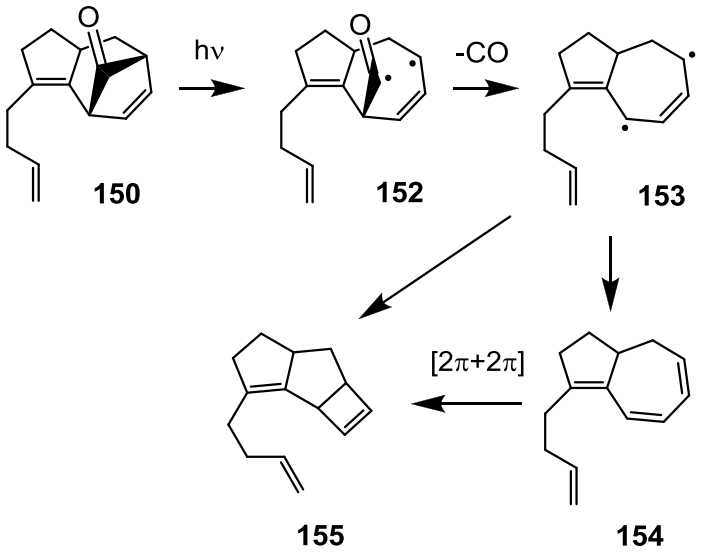
thermally reactive. Irradiation of **140** beyond its total consumption (up to 36 hours) resulted in an increased prevalence of a series of new minor adducts, some of which appeared to be generated during decomposition pathways of the linear *meta* adduct **141** (Scheme 2.7).



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

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.

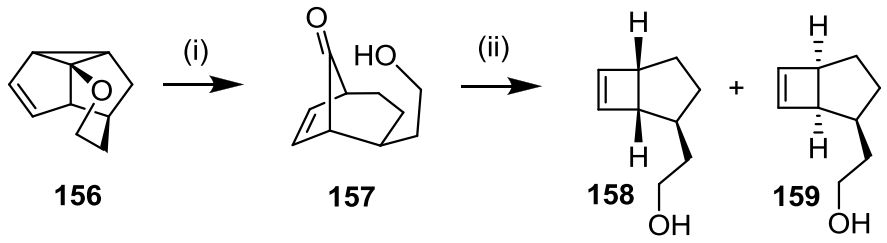
Further to these two adducts, an intriguing tricyclic [4.5.5] ring system (**155**) was also isolated, most likely being derived from a Norrish type I reaction[60] where ketone **150** would be an intermediate (Scheme 2.8).



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→π*) and through intersystem crossing to its triplet state as well. Either form can undergo a radical bond cleavage at either α-carbon to give a diradical.

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).[61]

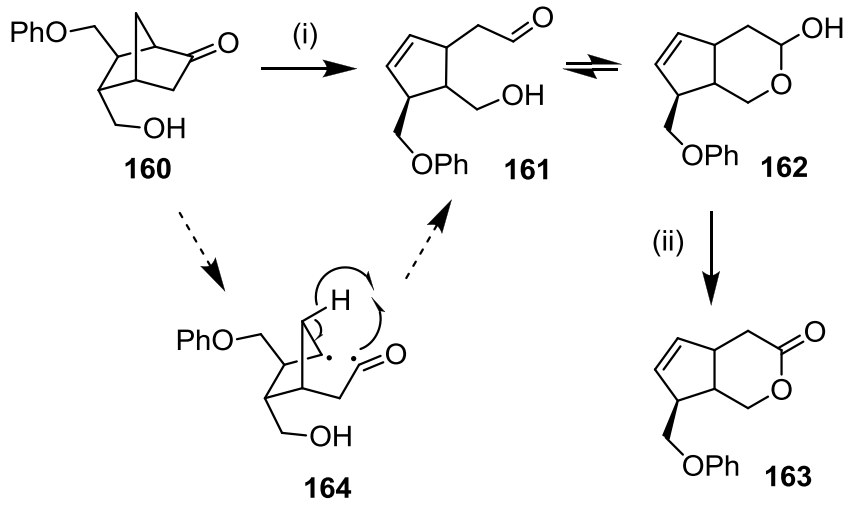


Reagents & conditions: (i) HCl, acetone: H_2O 20:1, RT, 10 min; (ii) hν (300 nm), MeOH, 80%, (1.4:1)

Scheme 2.9: Norrish Type I chemistry on the fragmentation product of a simple *meta* photocycloadduct.

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 [2π+2π] photocyclization of a cyclohepta-1,3-diene intermediate after carbon monoxide extrusion, as seen in our example (Scheme 2.8).

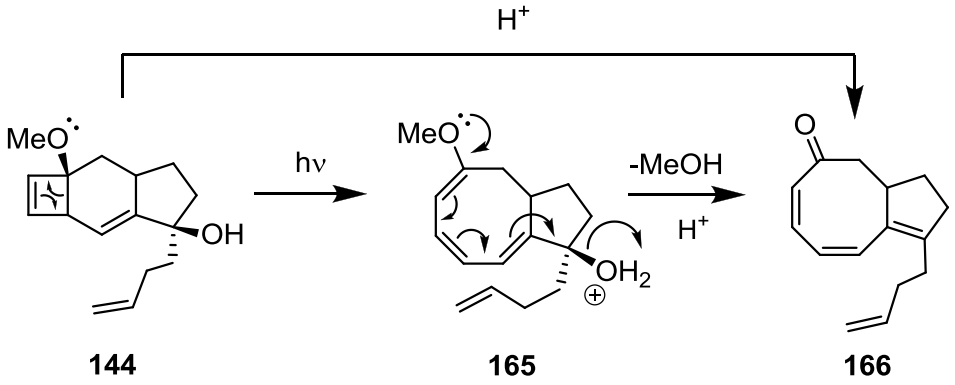
While Norrish type I reactions have been previously observed in competition with photocycloadditions, De Keukeleire and He also produced a notable example in which they studied a Norrish type mechanism toward making lactone photosubstrates for subsequent *meta* photocycloadditions (Scheme 2.1.0).[63]



Reagents & conditions: (i) hν (300 nm), EtOH, 2 hr; (ii) PDC, CH_2Cl_2, 3 hr, 63%.

Scheme 2.1.0: Norrish Type I reaction to make a lactone **163**.

Our final isolated minor adduct was a bicyclic octadieneone 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 2.1.1).



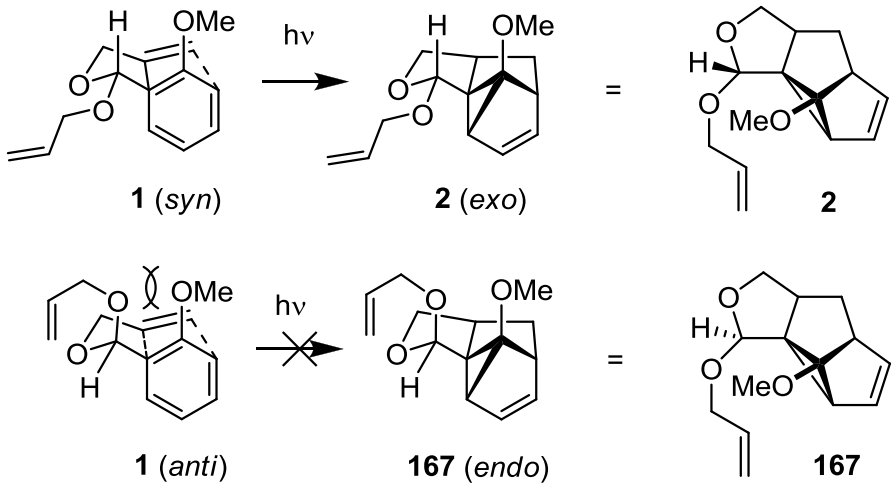
Scheme 2.1.1: Possible mechanism of formation of bicyclo [6.3.0] octatriene **166**

An octene ring had been observed as an intermediate toward the normal *ortho* derived rearrangement products found commonly in photocycloaddition reactions.[10] 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 Eckyren.[64] The isolation of **166** therefore lends further credence to the notion that formation of *ortho* derived tricyclic adducts such as **144** and **145** does 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.

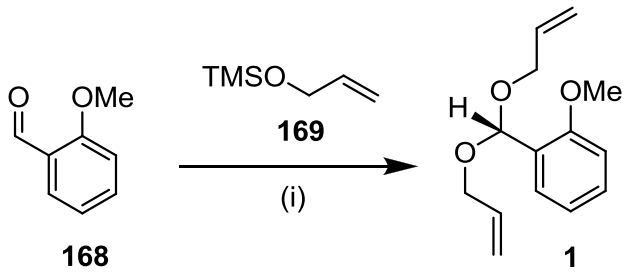
Our attention now turned to the acetal photosubstrate **1**. The photochemistry of this substrate was simplified by the hydrogen being significantly smaller than the oxygen linked tether, which means that it always adopted the *syn*-periplanar orientation in the transition state thus giving fewer potential products (Scheme 2.1.2).



Scheme 2.1.2: Exclusive *syn* configuration of photosubstrate **1**. Note that the terms *syn*, *anti*, *endo* and *exo* refer to the relative position of the hydrogen.

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.[58] In that case the acetal was formed by an acid catalysed condensation with allyl alcohol, using Dean-Stark apparatus.[65] 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 2.1.3).[66]



168 **1**

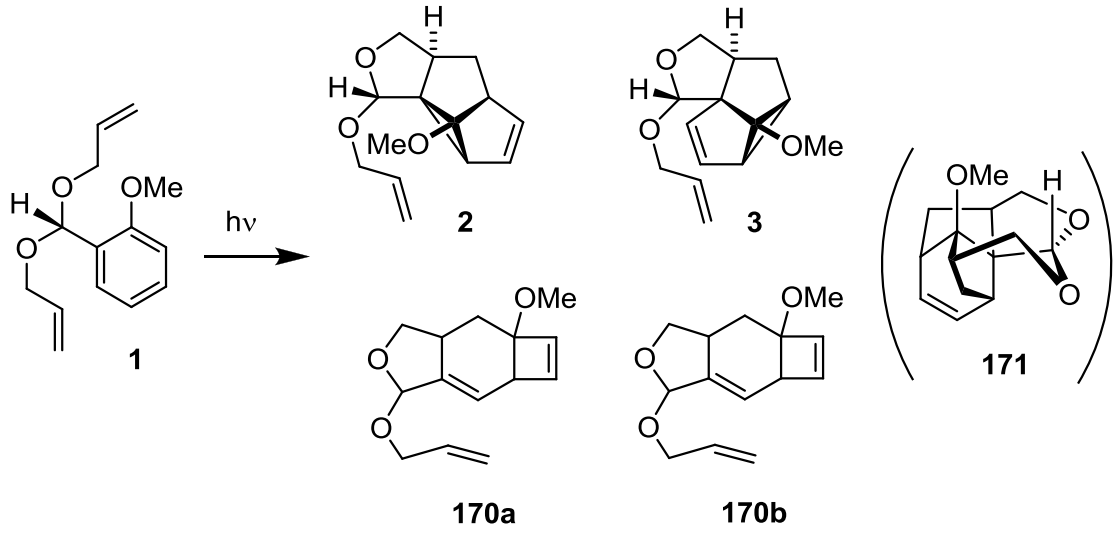
Reagents & conditions: (i) **169** (2.05 eq.), TMSOTf (10 mol %), -78 °C, 2 hr, 36%

Scheme 2.1.3: Synthesis of acetal photosubstrate **1**.

This highly versatile method[67] 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 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 hours following the procedure of Clark-Still.[68] However, purification proved difficult with the available distillation facilities and subsequent Noyori reactions were carried out using material purchased from Sigma-Aldrich® Ltd.

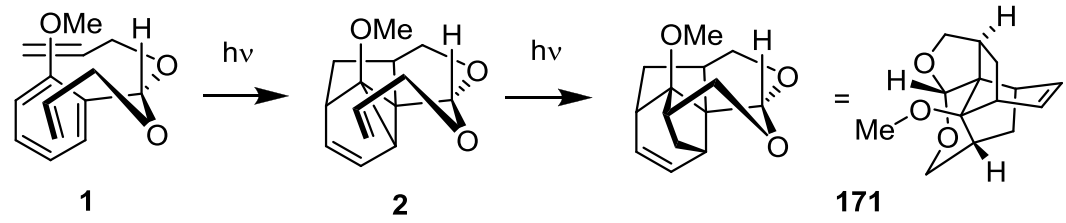
The aromatic acetal photosubstrate **1** was then directly irradiated with 254 nm UV light, as a solution in cyclohexane within a quartz-immersion well photoreactor over an 18 hour period, and five products (Scheme 2.1.4) were isolated from the residue in reasonable yields.



Reagents & conditions: 100 mg, hν (254nm), cyclohexane, 18 hrs

Scheme 2.1.4: Irradiation of photosubstrate **1**. Note the stereochemistry of **170a** and **170b** could not be determined through NMR spectroscopy.

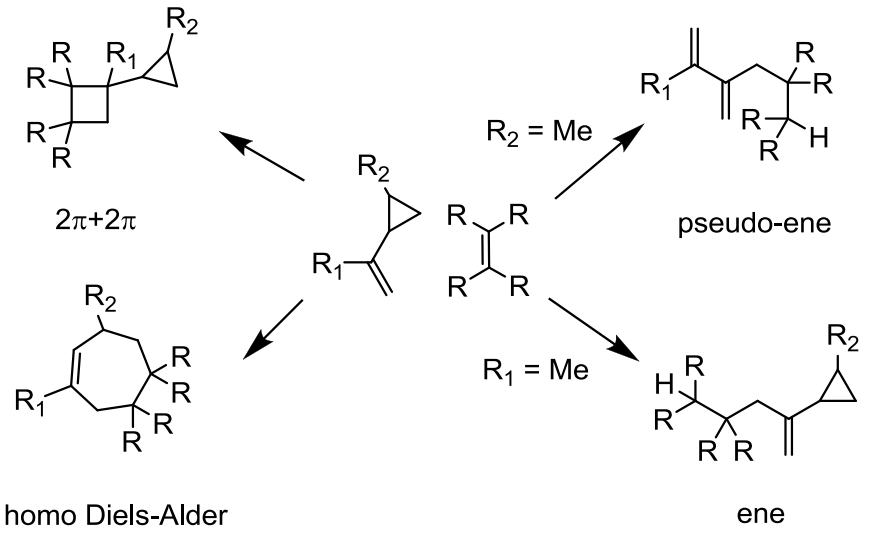
Notably, amongst the expected tetracyclic *meta* and tricylic *ortho* derived adducts was the appearance of an unexpected minor product **171** (in an approximate 8% yield). From detailed NMR analysis (including COSY, HSQC, HMBC and ROESY correlation spectra) this compound was originally postulated to 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 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 2.1.5).



Scheme 2.1.5: Original postulated mechanism of "criss-cross" double [3+2] photocycloaddition, where the alkenes act as a sandwich to the original benzene ring

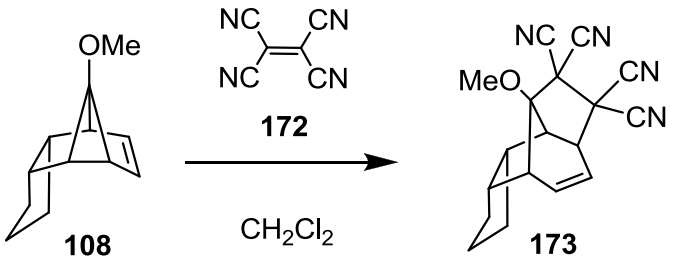
If such a reaction had occurred it would be similar in its effect to the generally overlooked homo Diels-Alder reaction,[69] a thermally induced [4+2] addition between a vinyl cyclopropane and an alkene. However, a notable difference between a homo Diels-Alder product and that formed during the photolysis 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[70] summarised, there were essentially four possible reactions that could occur between the two reacting parties, a standard 2π + 2π addition, an "ene" reaction, a "pseudo-ene" and the homo Diels-Alder (Scheme 2.1.6).



Scheme 2.1.6[70]: Possible reactions between vinyl cyclopropane and an alkene

The latter of these was reported in 1976 by Subrahmanyam,[71] who used exceptionally electron deficient olefins such as tetracyanoethylene (**172**) as the "dienophile" and a *meta* photoadduct derived from anisole and cyclopentene (Scheme 2.1.7).



Scheme 2.1.7: 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 [2π + 2σ + 2π] cycloaddition. However, the author could not rule out the possibility of a non-concerted addition with a polar intermediate.

In 1988, Fenton and Gilbert[70] carried out a similar set of reactions to Subrahmanyan, in which they commented that there was "limited literature concerning the reactions of ethenylcyclopropane systems with dienophiles"[70] 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 1990's, these reactions have vanished off the research radar with only a few exceptions.[72]

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, and 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** (Figure 2.1).

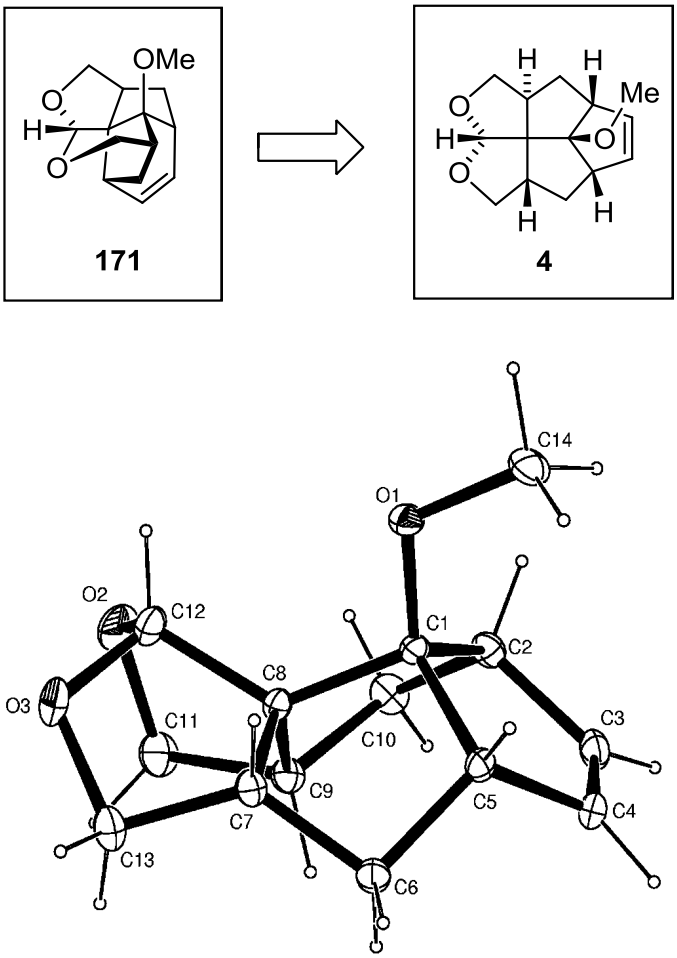
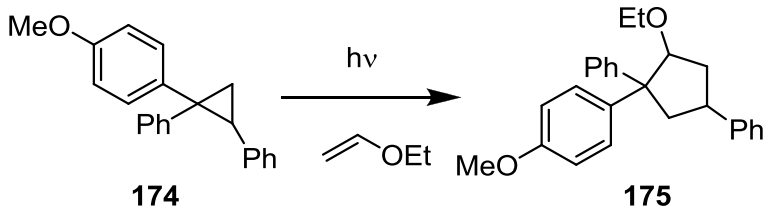


Figure 2.1: Comparison of originally proposed "criss-cross" (**171**) and actual fenestrane (**4**) structures of the secondary photoadduct, with X-ray crystal structure.

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.[58] However, the crucial difference is the method of construction. Wender performed a *meta* photocycloaddition to gain the linear *meta* adduct, 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.[73]



174 **175**

Reagents & Conditions: hν, *p*-dicyanobenzene, MeCN, 62%

Scheme 2.1.8: Photochemical [3+2] addition of an alkene across a cyclopropane ring.

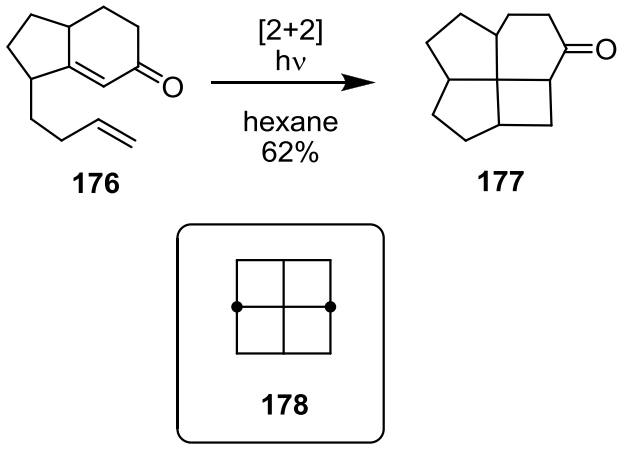
However, Tomioka[74] was able to carry out an intermolecular [3+2] cycloaddition with an alkene to give the cyclopentane compound **175**, which was formed from cyclopropane **174** and ethylvinylether in a 62% yield under electron-transfer sensitized conditions, along with various by products (Scheme 2.1.8).

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"[75] and its wider applicability for making different fenestranes and other complex structures from very simple starting materials.

3 A brief discussion on fenestranes.

3.1 Introduction.

It would seem right at this point in time to highlight exactly what we mean when we refer to the complex structures known as fenestranes. The name is derived from *fenestra*, the Latin for window and was first suggested as a name for this unique series of compounds by Georgian and Saltzman in 1972,[76] when they made the first attempt to form a "flat" geometry at the central quaternary carbon. They synthesised two compounds containing four carbocyclic rings around a central carbon with the intention to provide a model route toward tetracyclo-[3.3.1.$0^{3,9}$.0.$0^{7,9}$]nonane **178**. One of these compounds is illustrated in Scheme 3.1.



Scheme 3.1: Georgian and Saltzmann's model route toward a structure with a planarised carbon.

The existence of the planarised distortion of the central quaternary carbon in fenestranes away from the standard tetrahedral bond angle of 109.5° has been the primary motivation behind their synthesis because they provide a route to studying the fundamental theory of hybridisation in organic chemistry.[77] Unfortunately, the distortion can often be difficult to measure on fenestranes that are unsubstituted such as the ideal situation of compound **178** due to low molecular weight and inability to be easily crystallized.

In the most common [5.5.5.5] fenestranes, deformation can generally be increased by the introduction of double bonds, contraction of one or more of the cyclopentane rings to a cyclobutane or inversion of the configuration at one or more bridgeheads (i.e. a *cis*, *cis*, *cis*, *trans* configured fenestrane has greater distortion in general than a *cis*, *cis*, *cis*, *cis* type.).[77]

In the case of our dioxafenestrane compound **4** (Figure 3.1) the longitudinal bond angle (C_a-C_b-C_c) is 128.5° and the transverse one (C_e-C_b-C_d) is 120.2°.

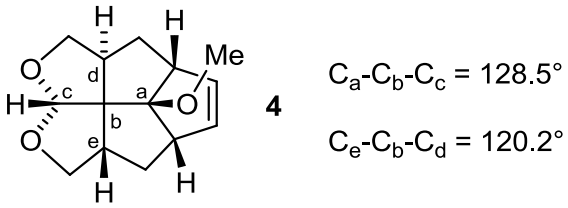


Figure 3.1: Bond angles in the dioxafenestrane **4**.

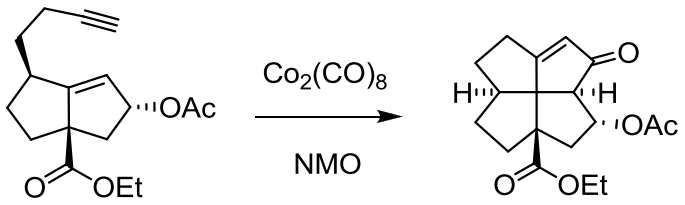
The theoretical issues are not the driving force behind our own interest in fenestranes. We are primarily focused on their untapped potential. In Wender's short, 3-step synthesis of *trans*, *cis*, *cis*, *cis*-[5.5.5.5] fenestrane **132** he suggested that they possess some of the best attributes of steroids, in that they are "both conformationally rigid and chemically robust."[58]

There have been suggestions that potential uses of fenestranes might include the structure serving as the backbone for molecular recognition sites,[78] novel catalysts[79] or chiral auxiliaries.[80] Unfortunately, while these potential uses have been recognised by the wider chemical community, the real road block for fenestranes has been their relative unavailability particularly in comparison to their widely available steroid cousins. This makes our discovered method of formation particularly useful, as fenestranes can be constructed in only two steps where the only reagent is UV light.

3.2 Synthesis of fenestranes.

The rapid and high yielding construction of fenestranes has been greatly challenging. [81] Most traditional methods, including aldol condensations[81] proved to be inefficient and tedious, with some requiring up to 20 steps. Use of the alkene-arene *meta* photocycloaddition in more recent years has improved the efficiency and yield of fenestrane methodologies, although it should be noted that it is by no means the only method currently employed for fenestrane synthesis.

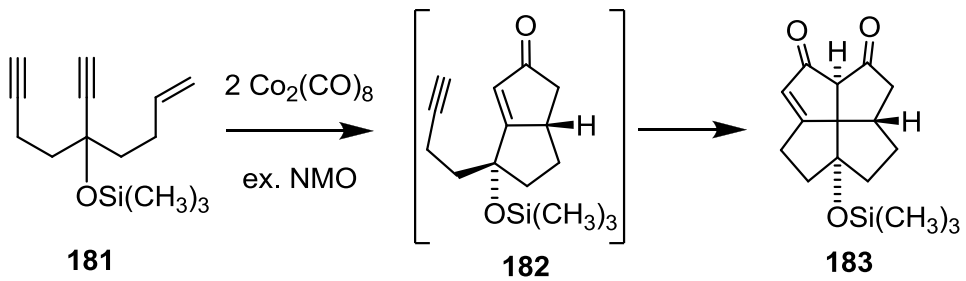
One of the most successful techniques is transition-metal induced, known as the Pauson-Khand[82] reaction; a [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide. The reagent used has generally been the cobalt complex, $Co_2(CO)_8$ although this can often be aided by other reagents such as the example below with *N*-methylmorpholino *N*-oxide (Scheme 3.2).[83]



179 **180**

Scheme 3.2: Pauson-Khand reaction of **179** to form **180**.

The induced Pauson-Khand reaction of **179** with an *exo*-butynyl side chain leads to an all-*cis*-[5.5.5.5] fenestrane **180** in an overall yield of 64%. This type of reaction can even be performed in tandem to create [5.5.5.5] fenestranes such as **183**, from the ene-diyne **181** (Scheme 3.3)

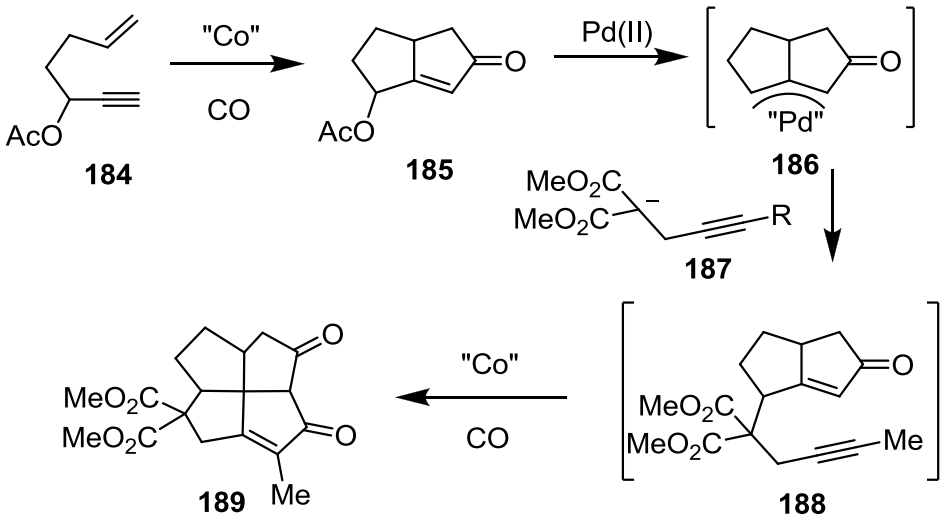


181 **182** **183**

Scheme 3.3: Tandem Pauson-Khand reaction used for the synthesis of highly functionalised [5.5.5.5] fenestrane **183**.

The first carbonylation-cyclization leads to the intermediate bicyclic compound **182** that then proceeds onto the highly functionalised fenestrane **183** by an identical second step. The length of the entire synthetic route, including creation of the ene-diyne, is an impressive five steps with an overall yield of 17%.

Chung, Park and Son[84] recently published another example of a [5.5.5.5] fenestrane synthesised by this method, but using a combination of cobalt nanoparticles and palladium (II) catalysis (Scheme 3.4).



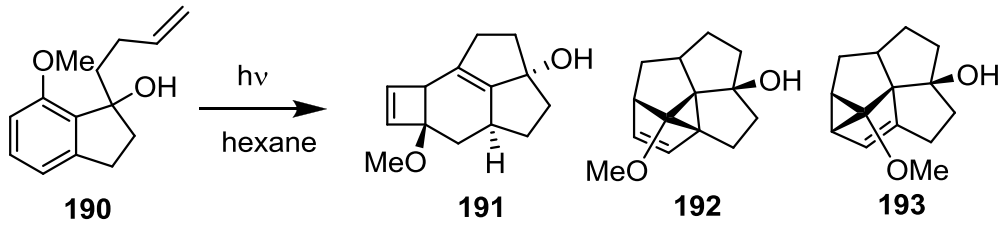
Scheme 3.4: One-pot fenestrane synthesis with cobalt nanoparticles and palladium (II) catalyst.

Highly functionalised fenestrane **189** was constructed from simple ene-yne **184** in a three step one-pot process in 74% yield. However, this was only achieved in two instances and increased steric hindrance resulted in no formation of the π-allyl palladium intermediate (**186**) required.

While these transition metal induced routes are perfectly acceptable, those that have made use of the *meta* photocycloaddition are of more direct relevance to this project. Certainly, Wender was not the first chemist to create fenestrane-type products *via* these tactics; his work was

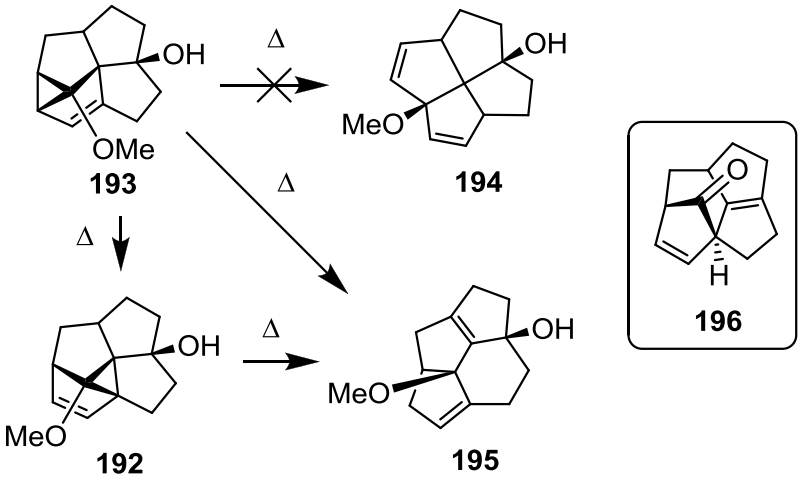
preceded by that of Keese, whose review on recent advances in fenestrane chemistry is highly recommended.[77]

Keese[85] irradiated an indane based chromophore, resulting in the formation of three products with the addition preferentially occurring *via* a [2+2] to give **191** rather than [3+2] cycloaddition (Scheme 3.5).



Scheme 3.5: Photolysis of 5-phenylpentene **193**, where the ratio of products was approximately 4-5: 3-4: 1 (**191**: **192**:**193**).

The two *meta* addition products **192** and **193** are both fenestranes, with **192** being thus far the only known example of a [3.5.5.5] type. Attempts to convert **192** and **193** into other fenestrane compounds were unsuccessful. Thermolysis of pentacyclic [5.5.5.5] fenestrane **193** in toluene at 200 °C led to **195**, rather than to the alternative fenestradiene **194**, which Keese believed would have been observed *via* a predicted [1,5]-hydride shift (Scheme 3.6).

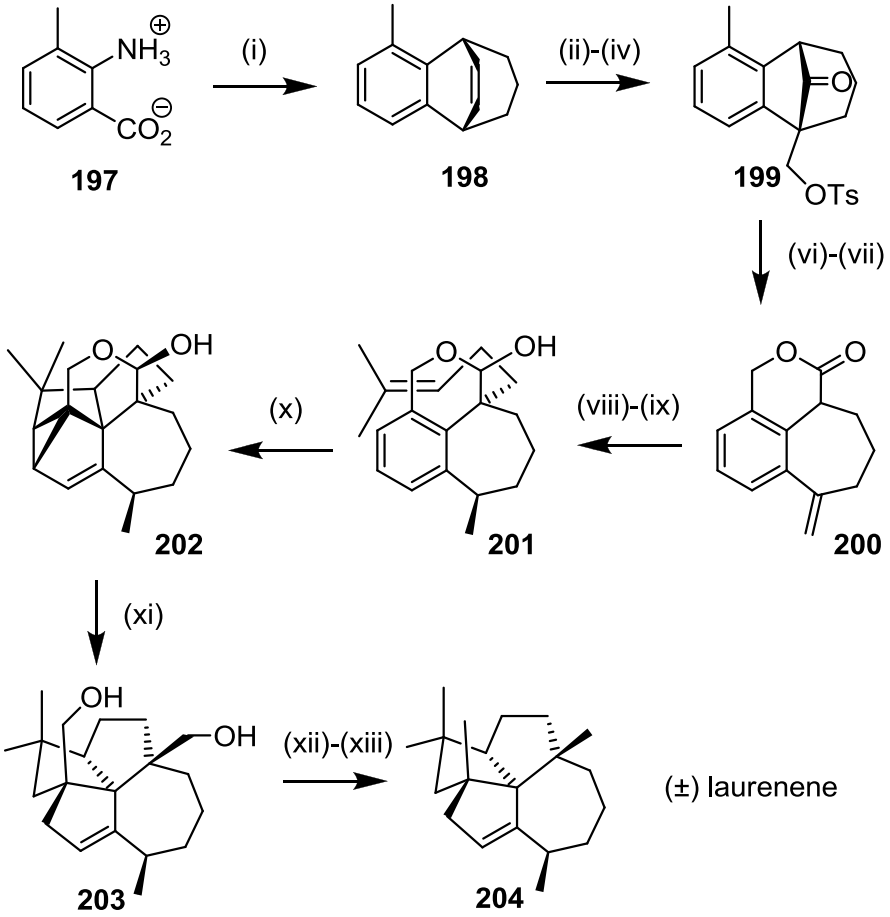


Scheme 3.6: Products from Keese's thermal studies of **192** and **193**.

Thermal reaction of fenestrane **192** gave the same result, suggesting that **193** was converted to **192** first by a forbidden thermal [1,3]-sigmatropic shift (the earlier mentioned vinylcyclopropane-cyclopentene rearrangement). Meanwhile, changing the solvent to DMSO resulted in the formation of **196** instead.

3.3 Naturally occurring fenestranes.

The first of only two naturally occurring fenestrane examples is the diterpene laurenene (**204**); a tetracyclic-[5.5.5.7] fenestrane that was first reported in 1979, but was not synthesised successfully until Wender's concise 13-step route in 1988 (Scheme 3.7).[86]



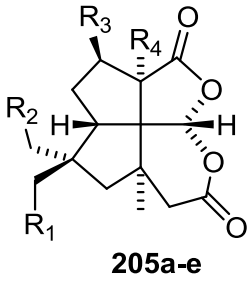
Reagents & conditions: (i) isopentyl nitrite, Cl_3CCO_2H, cycohepta-1,3-diene, CH_2Cl_2 (84%); (ii) O_3, Me_2S, NEt_3 (68%); (iii) $Zn(BH_4)_2$, Et_2O, (98%); (iv) TsCl (72%); (v) PCC (98%); (vi) NBS, AIBN, then KOH (72%); (vii) H_2, Pt (96%); (viii) LDA, DMPU, homoprenyliodide (48%); (ix) $LiAlH_4$, THF (95%); (**201**) hν ($BiCl_3$ filter) (51%); (xi) Li, $MeNH_2$, -6 °C (96%); (xii) KHMDS, HMPA, $CIPO(NMe_2)_2$ (55%); (xiii) Li, $EtNH_2$ (65%).

Scheme 3.7: Wender synthesis of (±) laurenene.[86]

This provides yet another example of the value of the *meta* photocycloaddition for creating different skeletal types in an efficient manner, even those derived from extremely congested photosubstrates such as the lactol **201**. The reaction also makes possible the formation of the

difficult bridgehead double bond. However, while the synthesis of laurenene was an important event in fenestrane chemistry, the compound itself has little biological activity, and has only been subsequently used to make laurenanes for NMR studies and limited functional group manipulation.[87]

The second example of a naturally occurring fenestrane has shown far greater promise and may reveal the true untapped potential for fenestranes to act as high value chemicals such as pharmaceuticals, agrochemicals, ligands or materials.[88]



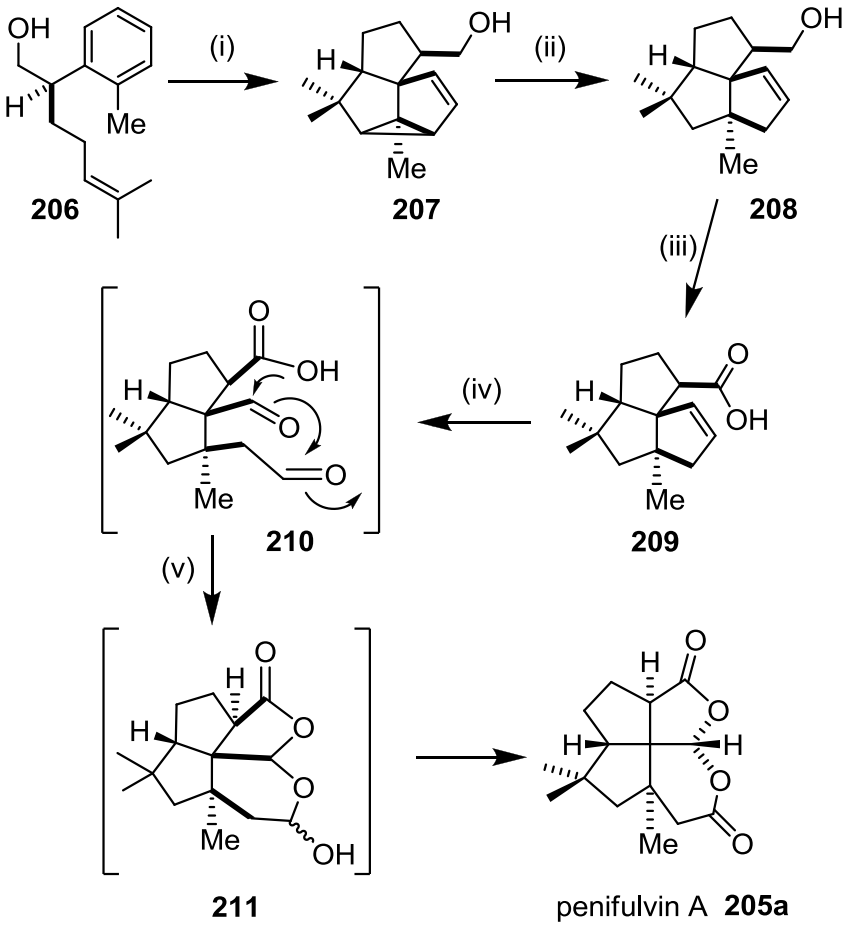
205a-e

A R_1 = H, R_2 = H, R_3 = H, R_4 = H
B R_1 = OH, R_2 = H, R_3 = H, R_4 = H
C R_1 = H, R_2 = OH, R_3 = H, R_4 = H
D R_1 = H, R_2 = H, R_3 = H, R_4 = OH
E R_1 = H, R_2 = H, R_3 = OH, R_4 = H

Figure 3.2: The Penifluvin series

Penifulvin A (Figure 3..2) has shown significant insecticidal activity[89] toward the fall armyworm (*Spodotera frugiperda*), whose larvae cause damage to a large variety of crops across the Americas, with corn in particular being heavily affected

The first total synthesis of Penfulvin A (**205a**) was performed by Gaich and Mulzer[90] in 2009 in both racemic and optically active forms in only 5 steps (Scheme 3.8) from an aromatic photosubstrate (**206**) that acted as a precursor for a *meta* photocycloaddition. This photosubstrate was derived from readily available *o*-tolylacetic acid in three steps and could be made optically active with enantiomeric excess of 95%.



Reagents & conditions: (i) hν, pentane, 2h, 70%; (ii) $EtNH_2$, Li, 72%; (iii) IBX/DMSO, then $NaClO_2$, 92%; (iv) O_3, CH_2Cl_2, thiourea, 78%; (v) PDC 82%

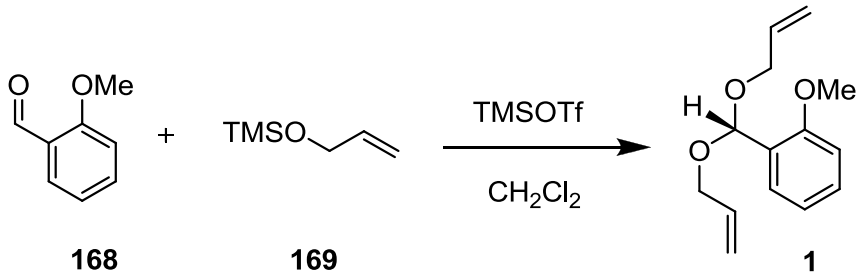
Scheme 3.8: Synthesis of Penifluvin A.

Aside from the separation of the regio-isomers from the *meta* photocycloaddition, one of the most remarkable aspects of this synthesis is that it requires very little purification. In addition, thanks to the oxidative cascade reaction, no protecting groups are required. Since completion of the total synthesis of Penifulvin A, Gaich and Mulzer have also developed enantioselective routes toward Penifulvin B and C, both of which involved only one protecting group step and were comparably concise.[91]

4 Investigation of the double [3+2] photocycloaddition reaction for the synthesis of fenestranes.

4.1 Investigating the synthesis of dioxafenestrane 4.

To begin our investigation into the newly discovered double [3+2] photocycloaddition, we decided to reinvestigate the details of the originally synthesised dioxafenestrane. The first step of this process was optimisation of the simple acetal formation procedure from *o*-anisaldehyde to produce the required photosubstrate (Scheme 4.1 and Table 1).[66]



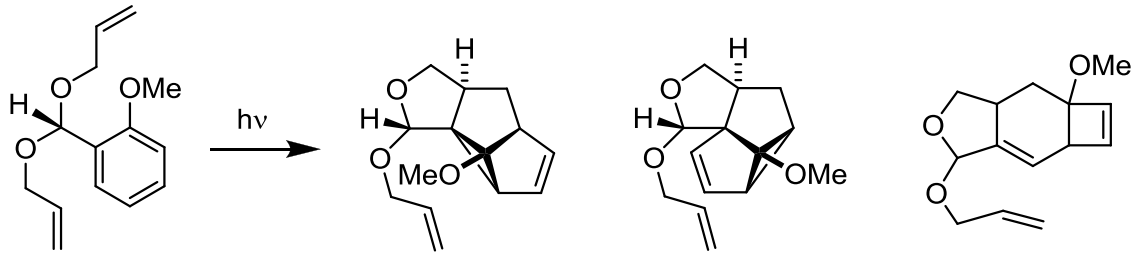
168 **169** **1**

Entry	TMSOTf (mol %)	169 (eq.)	Temp. (°C)	Time (hr)	Yield (%)
1	10	2.1	-78	6	48
2	10	2.1	0	4	0
3	50	2.1	-78	6	0
4	1	2.1	-78	6	63
5	1	2.1	-20	4	23
6	1	2.2	-84	7	68
7	1	2.5	-84	6	83
8	1	2.5	-84 → -60	4	98

Scheme 4.1 and Table 1: Optimisation for the formation of the bis-allyloxy acetal photo substrate **1**.

This was achieved by careful moderation of the reaction temperature, which resulted in an increase of the yield to an excellent 98% from an initial 48% (entry 8).[92] Ensuring good temperature control was crucial to obtaining high yields, so the -78 °C acetone/CO_2 cold bath was replaced with EtOAc/liquid nitrogen, which allowed for temperatures down to -84 °C and overall more stable temperature control during the initial reaction (entries 5 and 6). However, it was discovered that allowing the reaction to warm to -60 °C after initial addition of the aldehyde, by changing to an isopropyl ether/CO_2 bath, resulted in a decrease of the time required without compromising the yield in the way that higher temperature attempts had (entries 2 and 5).[92a]

It should also be noted that increasing the amount of TMSOTf catalyst led to increased product decomposition (entry 3), likely through the presence of an increased amount of triflic acid in the system, to which the acetal is highly sensitive. Avoiding flash column chromatography in the work up was also desirable and resulted in much improved yields.



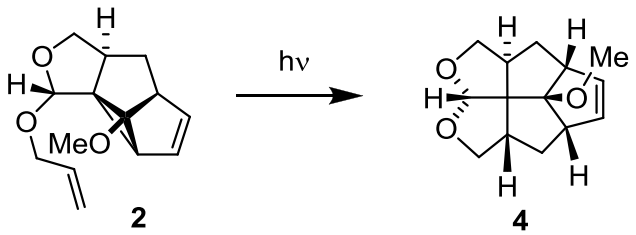
Reagents & conditions: hν (254nm), cyclohexane, 4 hrs

Scheme 4.2: Products from the shorter irradiation of photosubstrate **1**

Attention turned now to the initial *meta* photocycloaddition of photosubstrate **1**. (Scheme 4.2) Careful monitoring of the reaction by NMR showed that if directly irradiated with 254 nm UV light only until total consumption of the starting material (4 hours on a 450 mg scale), then no dioxafenestrane product was observed, only the commonly anticipated products **2**, **3**, **170a**, and **170b**, in yields of 23%, 3.5%, 22% and 11% respectively.

This reaction could be easily scaled up to gram quantities (> 6 g), although each time there were small variations in the ratio of products obtained depending on the effectiveness of chromatographic separation and exact irradiation period. The linear *meta* adduct **2** was generally obtained in yields ranging between 19 and 26%.

A lack of fenestrane suggested that its formation was a non-concerted process that must have arisen from a secondary photoreaction of the linear *meta* adduct. As such, adduct **2** was dissolved in cyclohexane and then irradiated separately under the same photolytic conditions (254 nm, cyclohexane) for 16 hours, to garner the double [3+2] photocycloaddition product **4** in a 38% yield (Table 2, entry 9).



2 **4**

Entry	Scale (mg)	Solvent	Lamp (W)	Time (hr)	Yield (%)
9	50	cyclohexane	16	16	38
10	100	cyclohexane	16	18	36
11	250	cyclohexane	6	47	38
12	200	pentane	6	48	37
13	50	cyclohexane	125*	1	0

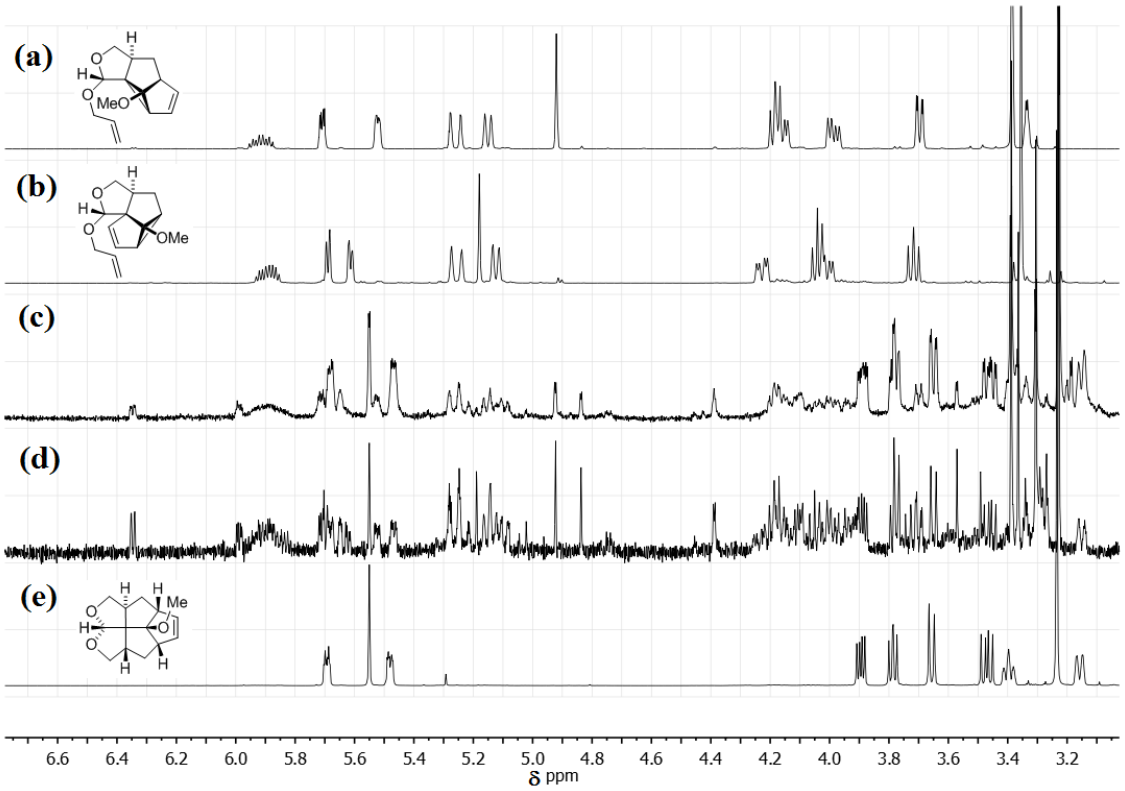
* = Irradiated with a Pyrex filter.

Scheme 4.3 and Table 2: Secondary irradiation of linear *meta* adduct **2**.

The reaction to form fenestrane **4** was also reproducible using the smaller scale quartz immersion well apparatus (holding up to 150 ml of solvent) and the lower flux intensity 6 W Hg vapour lamp. As expected with this lamp, the reaction was considerably slower (entries 11 and 12). Moreover, use of a 125 W lamp (entry 13) was observed to decompose linear adduct **2**

completely with no sign of **4**, despite use of a Pyrex glass filter. Changing the solvent from cyclohexane to *n*-pentane had no discernable effect on the reaction yield or time required (entry 12). In the crude ^{1}H NMR spectrum of these reactions we observed two other minor products present in the residue after photolysis, the first being the angular regioisomer, and the other of an unknown type.

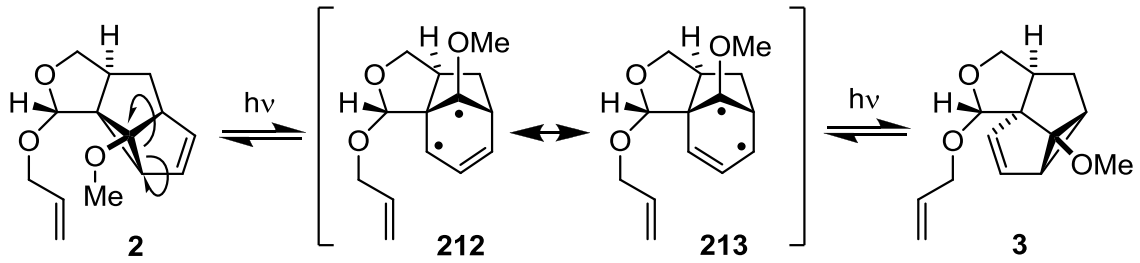
The presence of the angular isomer from pure linear starting material suggested that the two forms were indeed interconvertible as expected.[10] A fact that could be proven further by the direct irradiation of the angular *meta* adduct **3** (see Scheme 4.2), which was conducted on a small 20 mg scale using a 6 W lamp in cyclohexane for 45 hrs. The double [3+2] adduct **4** was again observed, but to a lesser extent than observed with linear adduct **2**. In addition, a comparison of the ^{1}H NMR spectra (Spectra 1) clearly showed the linear *meta* product **2** appearing in the reaction mixture of the angular adducts irradiation and vice versa.



Spectra 1: (a) linear *meta* adduct **2**; (b) angular *meta* adduct **3**.; (c) irradiation of linear adduct **2** crude mixture after 47 hours (6 W, cyclohexane); (d) irradiation of angular adduct **3**: crude mixture after 45 hours (6 W, cyclohexane); (e) double [3+2] photocycloaddition adduct **4**.

These results suggest that the linear and angular isomers "photo-equilibrium" occurs in apparent competition with the second [3+2] addition that results in formation of the fenestrane. Moreover, there is an additional product clearly produced during the secondary irradiation of both adducts, but its identity remained unknown due to an inability to isolated it pure from the linear adduct which possessed an identical retention factor under chromatographic separation.

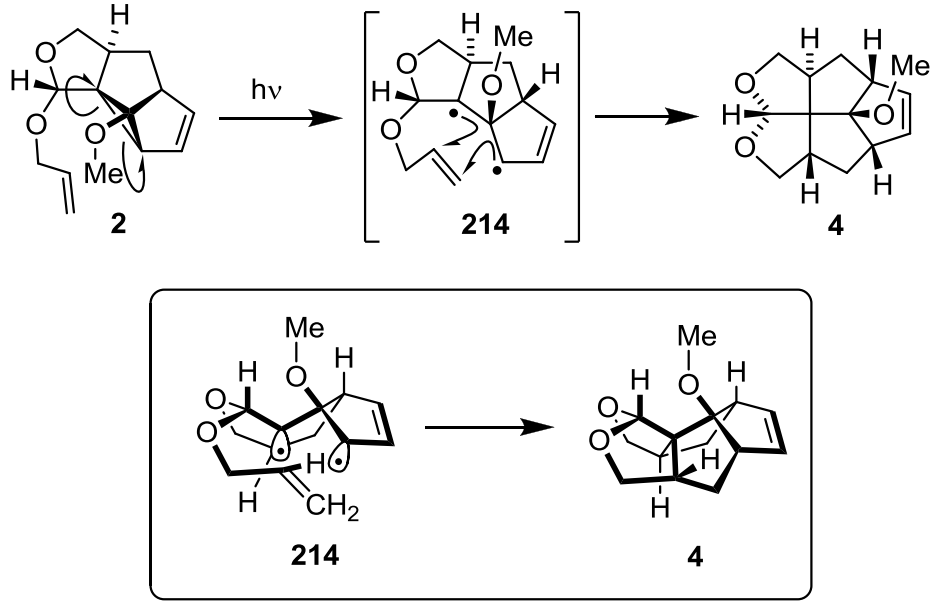
A photochemical vinylcyclopropane-cyclopentene rearrangement is the cause of the conversion between the different *meta* isomers as noted in previous *meta* additions occurring either by heating or irradiation.[31b] It may occur *via* homolytic fission of one of the internal cyclopropyl bonds (Scheme 4.4), which in a substituted *meta* adduct like **2** can reclose to give the opposite isomer.



Scheme 4.4: Proposed interconversion of **2** to **3** *via* photochemical vinylcyclopropane-cyclopentene rearrangement.

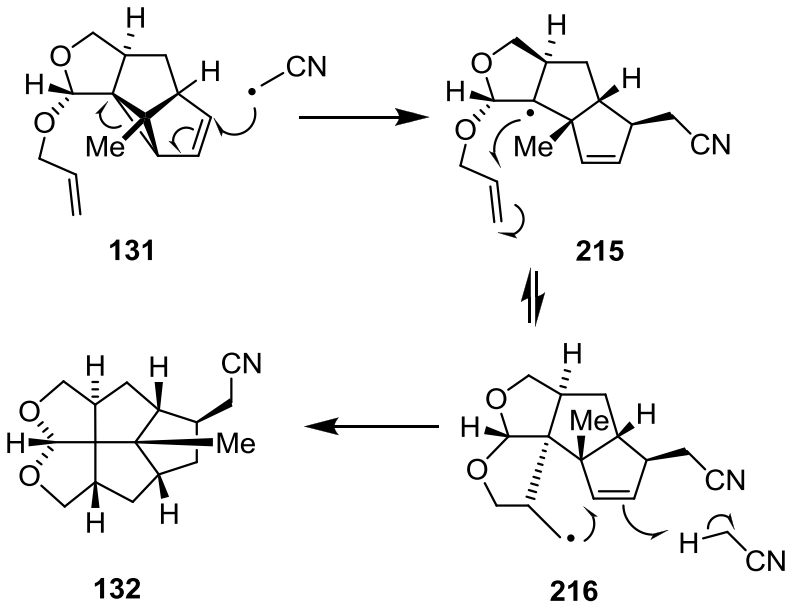
With hindsight it is perhaps unsurprising that our earlier proposed "criss-cross" product did not exist. The insertion of the alkene into the diradical **212** or **213** would have required a conformation, which the tether was highly unlikely to adopt, particularly as the alkenyl chain was not on the adducts *exo* face.

By comparison, in order to transform the linear *meta* adduct **1** to the dioxafenestrane **4** a more feasible mechanism could be suggested in which the external, rather than internal cyclopropane bond underwent homolytic fission and the alkene was subsequently added across the opened face (Scheme 4.5).



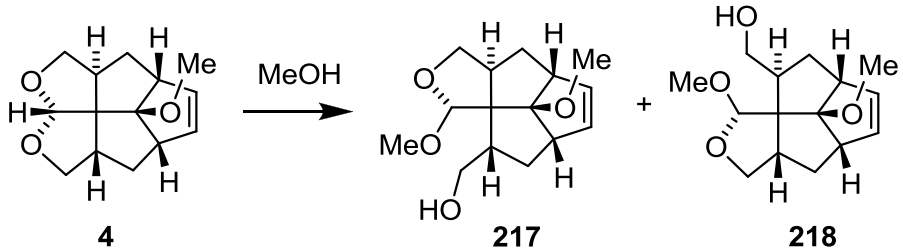
Scheme 4.5: Proposed mechanism for secondary [3+2] addition to form dioxafenestrane **4**.

Such a mechanism compares favourably to that proposed by Wender for the radical cascade reaction in his fenestrane synthesis (Scheme 4.6), where the approach of the alkene is likely *via* a similar conformation of the tether.[58] Wender had previously performed similar radical fragmentations of the cyclopropane in previous work using thiophenol, although not in the presence of an internal alkene (e.g. in the synthesis of hirsutene **97**).[47]



Scheme 4.6: Wender's proposed radical cascade mechanism for the synthesis of dioxafenstrane **132**.

It should be noted that the fenestranes strained acetal was found to be highly sensitive toward protic solvents. For instance, in MeOH it was found to undergo a slow but remarkably clean conversion toward two novel tetracyclic acetal adducts **217** and **218** (Scheme 4.7).



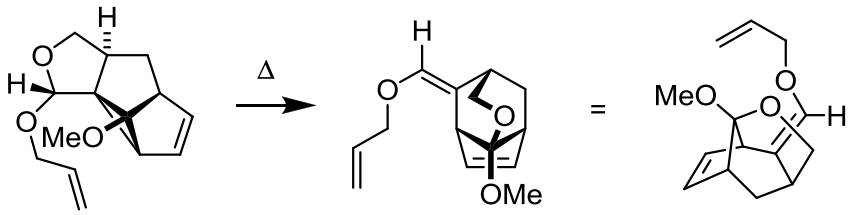
Reagents & conditions: MeOH, 10 days, 54% (**217**) and 5.5% (**218**)

Scheme 4.7: Reaction of fenestrane **4** in MeOH.

The two products were isolated in a ratio of 9.8:1 (**217**:**218**), although the yields were significantly reduced due to separation by flash column chromatography. The reason for this preference is not immediately clear, although is likely due to the conformation of the two different transition states. A simple reaction such as this provides a good illustration of how simple manipulations of this type of fenestrane could lead toward the synthesis of other novel structures

4.2 Thermally induced fragmentation-re-addition of a linear *meta* adduct.

In order to ascertain that the secondary [3+2] addition was truly derived from a photochemical reaction, linear *meta* adduct **2** was subjected to thermolysis to see if the same product could be obtained. The adduct was heated in d_8-toluene at 200 °C for 1 hour 45 minutes until total conversion of the starting material took place. After purification *via* flash column chromatography, the novel tricyclic triene **219** was isolated (Scheme 4.8).



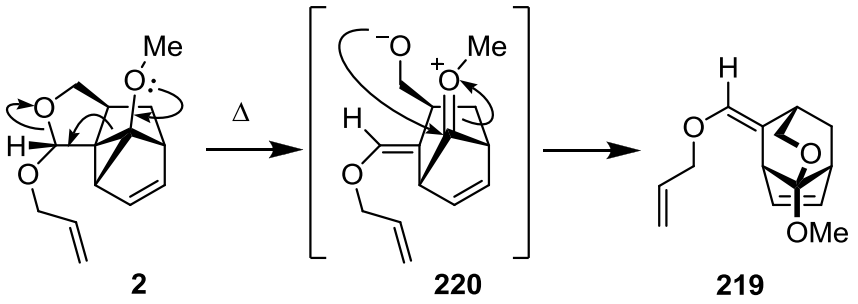
2 **219**

Reagents & conditions: d_8-toluene, 200 °C, 1.75 hr, 59%

Scheme 4.8: Thermolysis of linear *meta* adduct **2** to give tricyclic triene **219**.

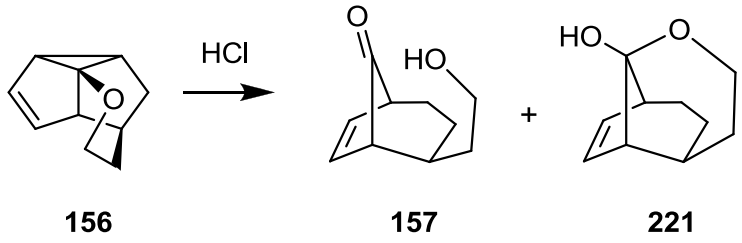
The transformation occurred in a 59% yield and was characterised through NMR spectroscopy, X-ray analysis was not possible, despite attempts to crystallise the product from a variety of solvents. Further to this result, the angular *meta* adduct **3** was treated under the same conditions, but yielded no change even after prolonged thermolysis at 230 °C for 36 hours.

With this in mind, it seemed plausible that the conversion of linear adduct **2** to triene **219** involved a non-concerted fragmentation-re-addition process, triggered by a lone pair on the methoxy group (Scheme 4.9). The cyclopropane ring of the angular *meta* adduct **3** is not aligned correctly and thus cannot perform a similar feat.



Scheme 4.9: Proposed fragmentation-re-addition mechanism for synthesis of triene **45**.

A process such as this has been encountered numerous times, such as with the simple *meta* photocycloadduct **156** whose acid fragmented product **157** was mentioned earlier in regards to its Norrish type photochemical behaviour. The reaction was achieved with dilute HCl in aqueous acetone to give two compounds, **157** and **221**, of which the re-addition product **221** was a minor component in a 6:1 ratio (Scheme 4.1.0).



Reagents & conditions: HCl, acetone: H_2O 20:1, RT, 10 min. 90%

Scheme 4.1.0: Fragmentation re-addition of a simple *meta* photocycloadduct **156**.

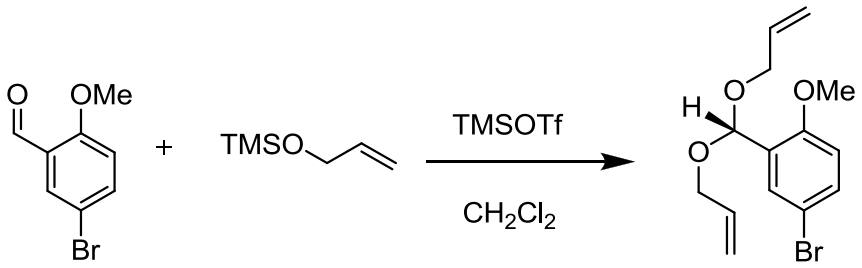
It is feasible to expect that without a source of dilute aqueous acid that the linear *meta* adduct **2** might follow the more minor pathway, as there is less chance for the alkoxy anion to be re-protonated, making it more reactive toward the generated carbonyl intermediate. Another point of interest is that the novel triene formed contains an allyl vinyl ether, and might be expected to undergo a [3,3] sigmatropic Claisen type rearrangement.[93] However, no such rearrangement product derived from **219** was isolated from the reaction mixture. It is likely that the *trans* geometry of the system does not allow for such an occurrence.

4.3 Deuterium study of dioxafenestrane 4 and characterization of the oxasilphinene product 5.

While the structure of the dioxafenestrane adduct was correctly deduced *via* X-ray crystallography, there remained some ambiguity in the assignment of the NMR spectrum. Through HMBC and ROESY correlations it wasn't possible to discern which of the two olefin signals in the spectrum belonged to a particular CH in the structure. This was due to each olefinic methyne having the same type of connectivity, thus making them spectroscopically equivalent. The order from each side proceeds as: =C(H)-C(H)-C(H_2)-C(**H**)-C(H_2)-O-, with the only minor difference being the stereochemistry of the central hydrogen of the sequence.

In order to resolve this issue, it was decided to replace one of the olefinic hydrogen atoms with a deuterium, thus resulting in the spectroscopic "desymmetrization" of the structure and allowing completion of the assignment. In addition, this would allow us to study how different groups, *para* to the methoxy, might affect the formation of the double [3+2] photocycloaddition.

Toward this purpose the brominated acetal **223** was synthesised from the readily available aldehyde **222** using the same Noyori conditions as used previously in the synthesis of the acetal **1**. The reaction was eventually improved (Table 3) to give an 87% yield (entry 18), although this could likely have been further optimized.



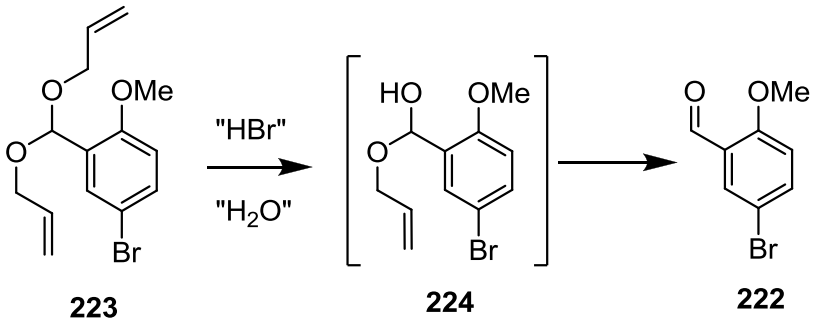
222 **169** **223**

Entry	TMSOTf (mol %)	169 (eq.)	Time (hrs)	Temp. (°C)	Yield (%)
14	1	2.05	5	-78	<79*
15	2	2.05	5	-84	70
16	2	2.10	6	-84	72
17	2	2.10	7	-84	74
18	2	2.20	7	-84	87

*= Only 90% pure by NMR

Scheme 4.1.1 and **Table 3:** Synthesis of brominated acetal **223**.

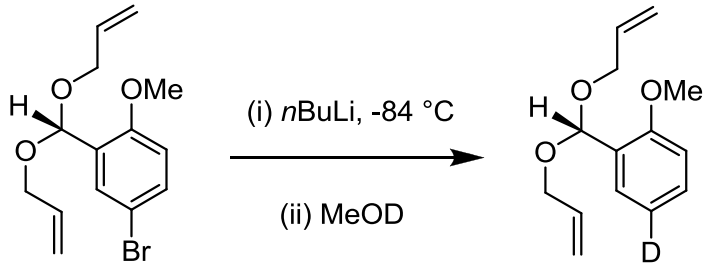
There have been no reported examples of successful *meta* photocycloadditions on photosubstrates containing bromine on the aromatic ring,[10] so we took this opportunity to form the first example, by directly irradiating the brominated acetal photosubstrate **223** with 254 UV light (16 W Hg vapour lamp) in a solution of cyclohexane. Unfortunately, this did not lead to any *meta* or *ortho* adduct formation, but instead gave near total conversion back to the aldehyde after approximately 15 minutes. This was unexpected, but could be due to the generation of HBr under the photolytic conditions (Scheme 4.1.2). This might have been prevented by ensuring that the solvent used was dry and basified.



223 **224** **222**

Scheme 4.1.2: Possible radical decomposition pathway of *p*-bromo photosubstrate **223**.

Unable to obtain the brominated *meta* adduct for subsequent deuteration, we chose instead to deuterate the photo substrate before attempting any irradiation. Addition of *n*-butyllithium to a solution of the bromide in THF at -84 °C resulted in metal-halogen exchange of the bromide with lithium. Subsequent addition of singularly deuterated MeOH (MeOD) eventually gave the desired product in an 82% yield with >85% deuterium incorporation (Scheme 23 and Table 4), which was deemed sufficient for our purposes.



223 **1_D**

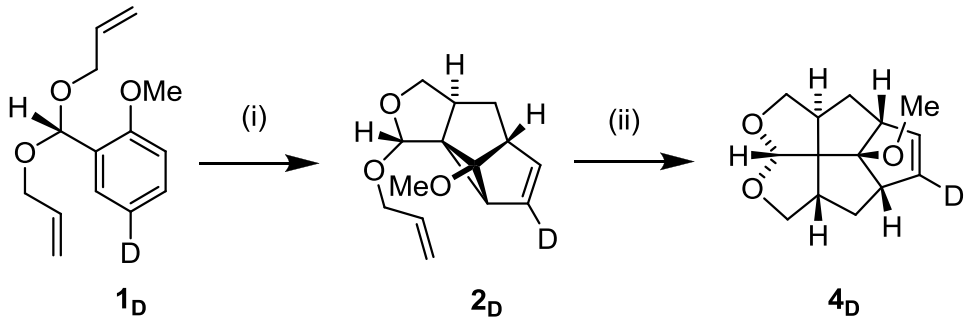
Entry‡	2.5M *n*BuLi (eq.)	MeOD (eq.)	H:D ratio **$1:1_D$**	Yield (%)
19	1.3	excess	1:1.86	70
20	1.5	2	1:16	65
21	1.3	2	1:7	78
22	1.4	3	1:8	82

‡ = Reactions conducted in dry THF

Scheme 4.1.3 and **Table 4**: Deuteration of photosubstrate **223**.

Deuteration was also attempted using D_2O as the deuterium source; however while this resulted in better deuterium incorporation (>90%), the yield was reduced significantly (<11%).

The deuterated acetal was irradiated according to the same procedure as its protonated counterpart **1** at 254 nm using a 16 W Hg vapour lamp, giving the desired linear *meta* adduct $\mathbf{2_D}$ in a 14% yield after flash column chromatography. This was then irradiated again with a 16 W lamp to give the double [3+2] photocycloaddition product $\mathbf{4_D}$ (Scheme 4.1.4).



$\mathbf{1_D}$ $\mathbf{2_D}$ $\mathbf{4_D}$

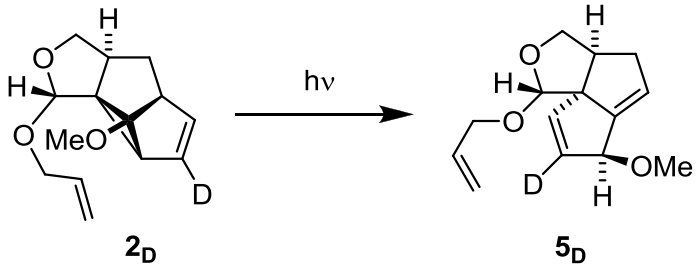
Reagents & conditions: (i) hν (254 nm), cyclohexane, 18 hours, 14%; (ii) hν (254 nm), cyclohexane, 2 days, 11%.

Scheme 4.1.4: Deuterated fenestrane synthesis.

The isolated yield was determined as only 11% and the rate of the second addition was significantly reduced, requiring 2 days compared to only 16-18 hours previously for the protonated version under the same conditions. This might be blamed on the presence of deuterium, but this should not have affected the rate of reaction because deuterium has no involvement in the postulated mechanism.

However it is widely known that the output of any specific lamp can vary with time,[94] particularly if it is switched on and off regularly, which is an unavoidable occurrence with the equipment available to us.

This would seem to be borne out when we attempted the creation of the deuterated dioxafenestrane $\mathbf{4_D}$ using an ageing 16 W mercury vapour lamp, which resulted in none of the desired double [3+2] adduct formation. However, after leaving the reaction to irradiate for 108 hours there was still some notable peaks in the residue. The extended nature of the photolysis meant that the entire original deuterated linear *meta* adduct had been consumed and thus we were able to finally isolate the intriguing tricyclic-[5.5.5] product $\mathbf{5_D}$, that we had previously seen in the photolysis of the protonated *linear* adduct **2**.

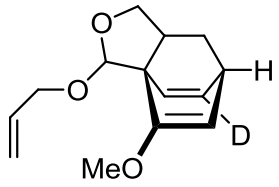


$\mathbf{2_D}$ $\mathbf{5_D}$

Reagents & conditions: hν ('old lamp'), 7 days, 16%

Scheme 4.1.5: Synthesis of tricyclic product $\mathbf{5_D}$.

Our initial interpretation of the NMR led us to thinking that this might be a *para* style adduct (Figure 4.1), created from a rearrangement of the linear *meta* starting material $\mathbf{2_D}$. Such a transformation had been previously claimed by Andrew Gilbert, but never conclusively proven due to the unavailability of modern spectroscopic techniques at the time.[95]



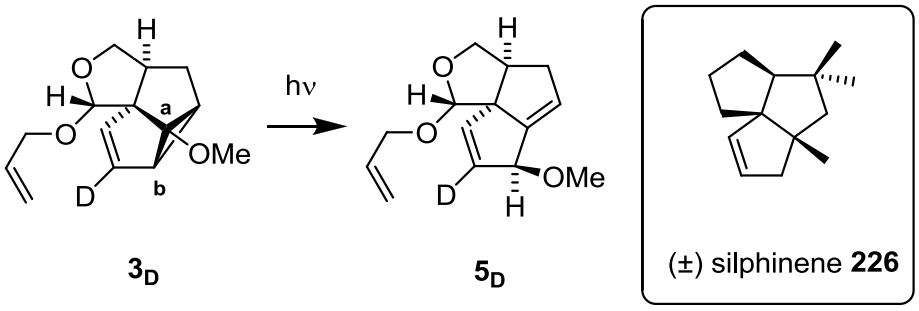
$\mathbf{225_D}$

Figure 4.1: Originally postulated *para* adduct.

However, more careful analysis of the available data and investigation of the product's thermal properties led us to discount this possible structure. Heating at reflux in d_8-toluene at >200 °C

culminated in no reaction, even after 24 hours, suggesting that this was not a *para* structure. Seeing as the *para* adduct is essentially of the Diels-Alder type we might expect it to undergo a retro reaction in a similar fashion at elevated temperatures.[96]

The *angular* fused triquinane structure eventually devised for **5_D** is reminiscent of the silphinene series of compounds (for example crinipellin B **98**) mentioned in the literature section of this work, which have been noted to possess pharmacological properties. The parent compound, silphinene shown in Scheme 4.1.6, had been previously synthesised by Nagarjan and Koteswar Rao[97] in 1989, *via* a radical cyclisation and later by Wender[98] using a *meta* photocycloaddition orientated synthesis that was conducted in only three steps and in multigram quantities.



3_D **5_D**

Scheme 4.1.6: Comparison of the synthesised tricyclic product **5_D** to silphinene **226**.

Structurally speaking the tricyclic core of the product was clearly derived from the angular *meta* adduct and had remained intact at expense of the cyclopropane while the methoxy group had seemingly undergone a 1,2 migration from carbon **a** to **b** (as labelled in Scheme 4.1.6). It should be noted that the ^{1}H NMR of this new oxasilphinene **5_D** also corresponded to that seen in the reaction of protonated meta adducts **2** and **3**, that we had been unable to isolate pure. Returning to this material, purification was attempted by exposing the mixture of the protonated oxasilphinene and the co-eluted linear *meta* adduct **2** to further photolysis, but this proved unsuccessful. In addition, converting the unwanted *meta* adduct *via* thermolysis to **219** also yielded no result, in part because the thermal product co-elutes with a near identical retention factor.

The near exclusive presence of the oxasilphinene product in the reaction using an old lamp would suggest that the UV wavelengths being emitted were shifted in comparison to the younger lamps used previously, eliminating the wavelength that transformed *linear* adduct **2** to dioxafenestrane **4**. This was proven when a new lamp was used to carry out the photolysis instead, yielding 11% of the deuterated fenestrane $\mathbf{4_D}$ product, with very little of $\mathbf{5_D}$ noticeable by NMR.

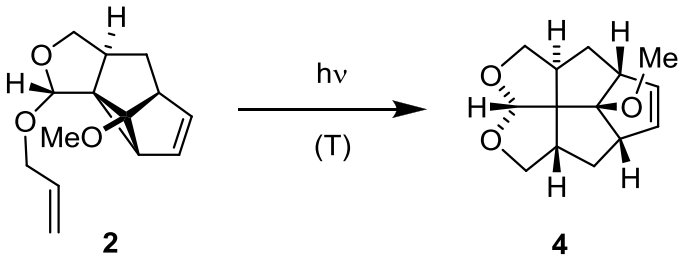
The deuterated dioxafenestrane was used to ensure that the NMR characterisation was correct; however discovery of the lamp dependence issue gave us concern with regard to the reliability of the current method for fenestrane synthesis. If this new chemistry were to be of use in general synthesis it would require a greater degree of reproducibility and control.

4.4 Triplet sensitization and quenching studies: optimisation and mechanistic analysis of the double [3+2] photocycloaddition.

Earlier we proposed that the mechanism for the formation of the dioxafenestrane **4** from the linear *meta* adduct **2** proceeded through a diradical intermediate **214** (see Scheme 4.5). If this were the case it could occur *via* a triplet manifold of the excited state, and would thus be affected by triplet sensitization and quenching.

Triplet sensitization has proven itself as a powerful method for improving the synthesis of triplet state derived photoadducts as it prevents any singlet states of the quencher (in this case linear adduct **2**) from even being generated.[94] The sensitizers used are generally carbonyl compounds and should in theory be regenerated after the energy transfer has taken place and thus be used in a catalytic capacity, although in practise this has not always been the case.[94]

Three well known and readily available triplet sensitizers were used to conduct our experiments; acetone [E_T = 330 kJmol^{-1}], benzophenone [E_T = 287 kJmol^{-1}] and acetophenone [E_T = 309 kJmol^{-1}] (Scheme 4.1.7, Table 5).[99]



2 **4**

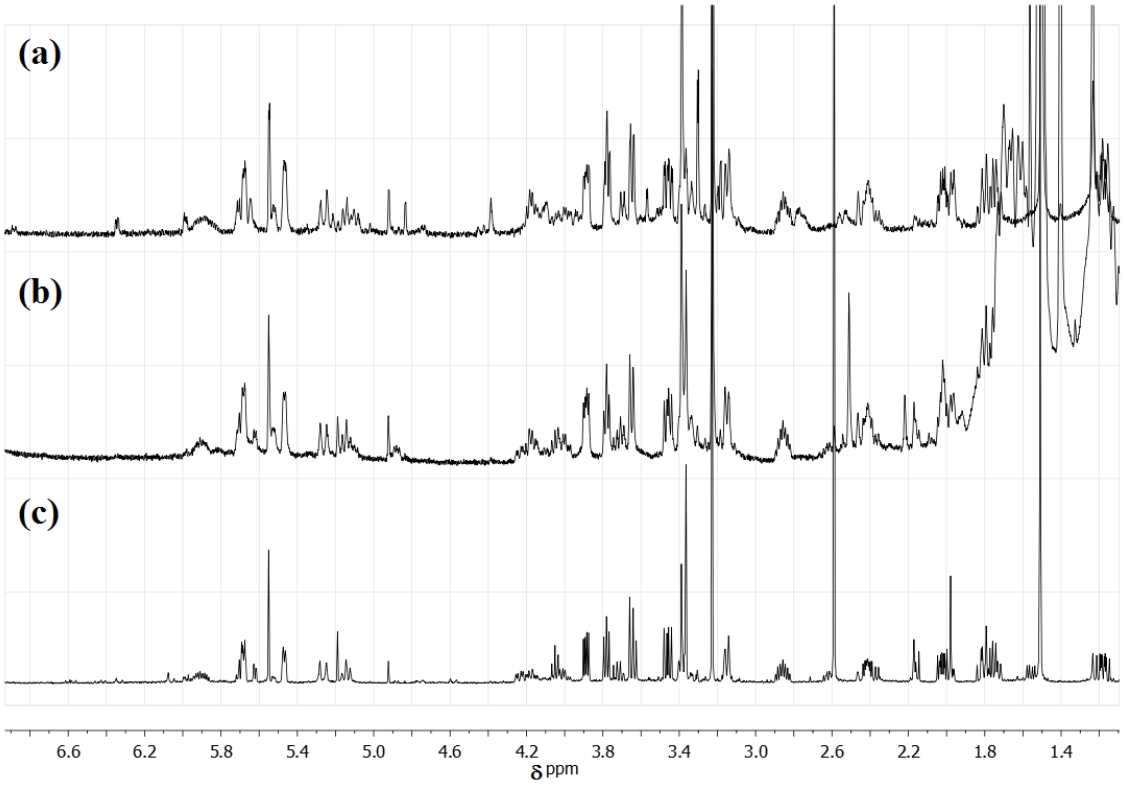
Entry‡	Scale (mg)	Solvent	Triplet Sensitizer (TS)	TS (mol %)	Time (hr)	Yield (%)
23	50	acetone	acetone	-	5	<30
24	50	cyclohexane	benzophenone	200	32	<40
25	110	cyclohexane/acetone (1:1)	acetone	-	4.5	<47
26	110	cyclohexane	benzophenone	500	47	<35
27	100	cyclohexane	acetophenone	200	7	<50
28	100	MeCN	acetophenone	150	2.5	39
29	250	MeCN	acetophenone	100	3.75	50
30	100	MeCN	benzophenone	100	1	0
31	100	MeCN	acetone	500	1	0

‡ = each of these reactions was conducted at 254 nm using a 6 W Hg vapour lamp.

Scheme 4.1.7 and **Table 5**: Triplet sensitized formation of dioxafenestrane **4**.

Initially acetone was tried as the solvent (entry 23), and irradiation at 254 nm resulted in the expected fenestrane, however it was found to contain inseparable contaminants. Subsequent repetition using cyclohexane as the solvent with acetone, benzophenone and acetophenone in various equivalents all had the same outcome (entries 24-27). While the fenestrane was clearly produced in a more reliable fashion, in comparison to the previous non-triplet sensitized reaction, the level of contamination was unacceptably high, making isolation of the pure material impractical even using MPLC techniques.

Acetophenone gave the best result in terms of cleanliness of reaction in cyclohexane, with much reduced reaction times in comparison to benzophenone (entries 26 and 27). The cause of the high level of polymerised material appeared to be degradation of the triplet sensitizer by interaction with the cyclohexane solvent, perhaps *via* hydrogen abstraction and subsequent polymerisation. In the case of benzophenone particularly, the triplet sensitizer was almost completely degraded within the first 8-10 hours. Addition of further equivalents of sensitizer only compounded the problem.



Spectra 2: Comparison for synthesis of dioxafenestrane **4**: (a) original non-sensitized irradiation of linear *meta* adduct **2** in cyclohexane; (b) irradiation of **2** with acetophenone (200 mol %) in cyclohexane; (c) irradiation of **2** with acetophenone (100 mol %) in MeCN.

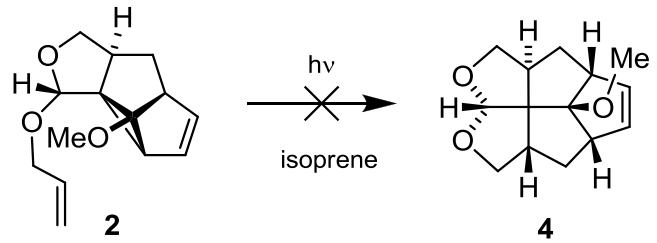
While we were unable to obtain any pure dioxafenestrane **4** in cyclohexane, these studies did allow us to observe that no oxasilphinene was produced under triplet sensitized conditions, despite there still being conversion of the linear adduct to its angular form (Spectra 2). This suggested that the mechanism toward the silphinene might occur *via* a pathway that is either

suppressed under triplet sensitized conditions or simply not as enhanced as the other competing processes.

A change of the solvent to MeCN (entries 28-31), which has been used widely used for photochemistry by groups such as that of Kevin Booker-Milburn,[100] yielded far more favourable results. Pure double [3+2] adduct **4** was obtained in an improved 50% yield, with no degradation of the acetophenone and easy separation *via* flash column chromatography.

Interestingly, in MeCN both benzophenone and acetone proved to be ineffective in producing the desired secondary [3+2] addition, with both reactions leading to decomposition and complex mixtures of polymeric material. Perhaps, the first of these results should not be unexpected as previous literature has shown that benzophenone can undergo a photoreduction *via* hydrogen abstraction from MeCN.[101] The result obtained would appear to suggest that the photoreduction is the preferred route.

A triplet sensitizer can be used to promote the near exclusive formation of the second [3+2] addition so it made logical sense that a triplet quencher should have the opposite effect. Isoprene was chosen as a cheap, readily available quencher[102] and added to the reaction vessel in amounts ranging from 200-1000 mol %. Direct irradiation at 254 nm was run with a 6 W Hg vapour lamp and observed over 6 hrs in both cyclohexane and MeCN (Scheme 4.1.8).

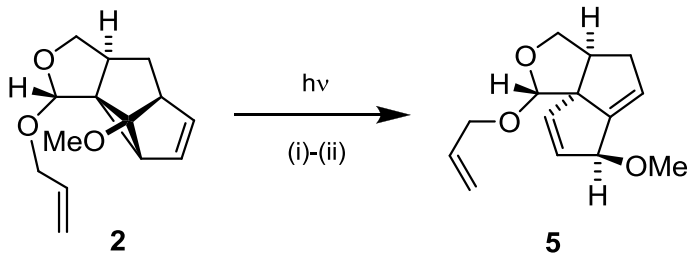


Reagents & conditions: 50 mg, hν (254 nm), cyclohexane/MeCN, isoprene (200-1000 mol %), 6hrs, 0%

Scheme 4.1.8: Triplet quenched reaction of linear *meta* adduct **2**.

Addition of isoprene totally suppressed the formation of the fenestrane product in all cases and additionally, the conversion of linear *meta* adduct **2** to its angular regioisomer, suggesting that both reactions occur *via* triplet manifolds.

Using our new found knowledge concerning the triplet sensitized behaviour of the reaction, we devised a means to isolate the previously difficult oxasilphinene product **5** (Scheme 4.1.9).



2 **5**

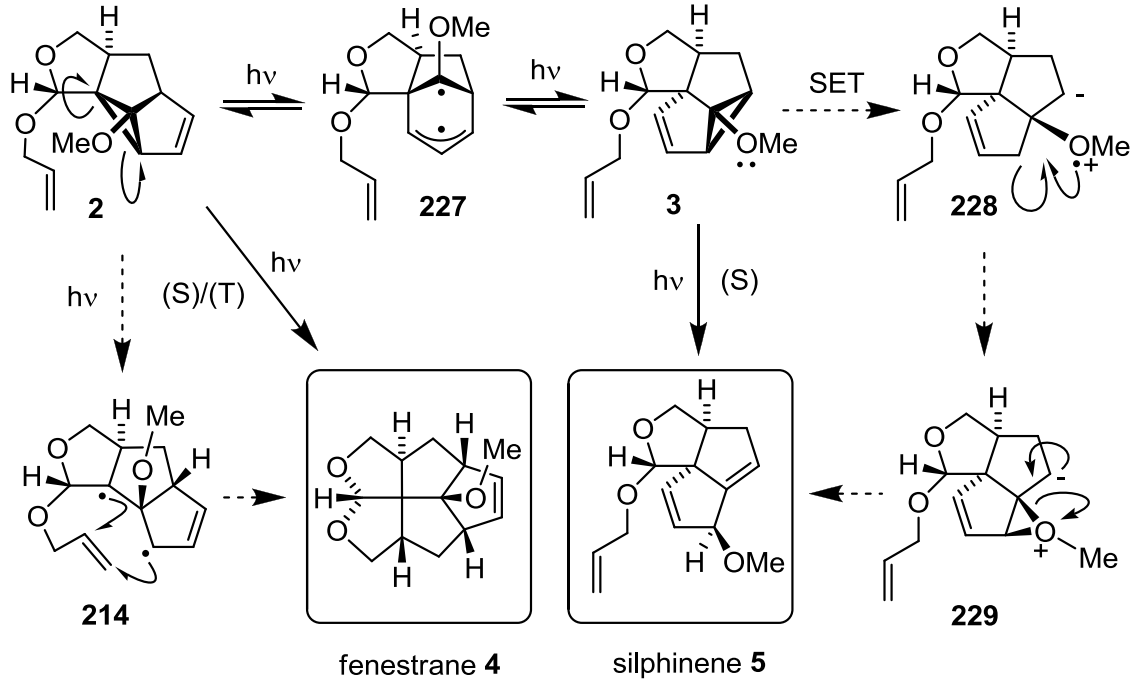
Reagents & conditions: (i) 120mg, hν (254 nm, "old lamp"), cyclohexane, 9hrs; (ii) hν (254 nm), acetone, 1hr, (17%, over two steps).

Scheme 4.1.9: Synthesis of oxasilphinene **5**.

Using an older 16 W Hg vapour lamp we directly irradiated a sample of the linear *meta* adduct in cyclohexane for 9 hours. After this time, there was noticeable formation of the oxasilphinene **5**, but still a small quantity of the linear *meta* starting material. The cyclohexane was removed under reduced pressure and the residue dissolved in pure acetone. This was subjected to a further direct irradiation at 254 nm for an hour, resulting in total consumption of the remaining linear material by conversion to the angular isomer and the dioxafenestrane, thus allowing isolation of the pure oxasilphinene in a 17% yield.

4.5 Mechanistic summary for the irradiation of the acetal photosubstrate 1.

From all of the information gathered the mechanistic rational for the formation of the dioxafenestrane and oxasilphinene products can be summarised in Scheme 4.2.0



Scheme 4.2.0: Suggested mechanistic pathways toward fenestrane **4** and silphinene derivative **5** compounds.

The two *meta* adducts linear and angular can be converted *via* the proposed delocalised triplet diradical **227,** which is formed by the breaking of the internal cyclopropane bond. Both adducts, **2** and **3,** can then undergo a further reaction that involves the breaking of their external cyclopropane bond. The linear **2** is cleaved to a triplet radical intermediate **214** that can then interact with the nearby alkene to afford the pentacyclic dioxafenestrane **4** and thus complete the double [3+2] photocycloaddition reaction.

The mechanism for the formation of the oxasilphinene most likely does not progress *via* a triplet manifold, hence the products' exclusion under triplet sensitized conditions. We proposed that a single electron transfer process may occur involving the lone pair of the proximal methoxy

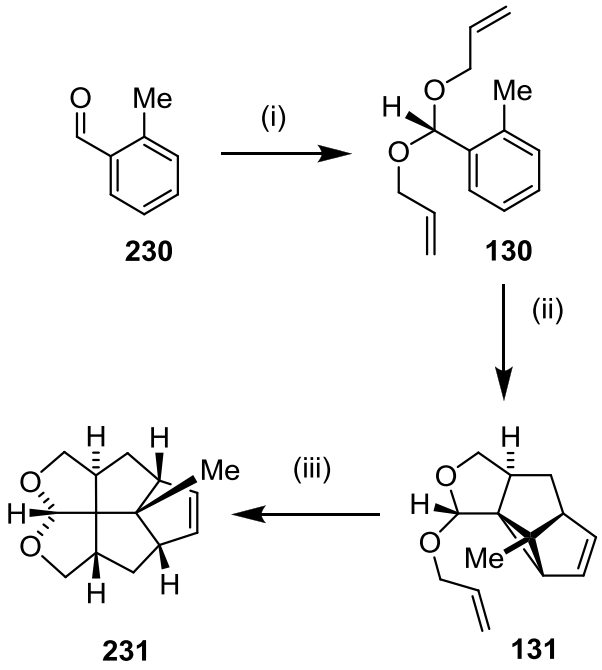
group oxygen. This would generate a radical cation on oxygen (intermediate **228**), which could then recombine to form an oxirane ring (intermediate **229**). Fragmentation of this unstable species would then afford the silphinene adduct **5**, in which the methoxy group has undergone a 1,2- migration and the correct double bond placement is achieved in the process.

Had time allowed, further mechanistic investigation could have been performed using electron-transfer sensitizers such a *para*-dicyanobenzene in the same manner as Tomioka.[74] Theoretically, if our mechanism were correct then such conditions would favour the silphinene route exclusively from angular adduct **3**.

4.6 Synthesis of a methyl dioxafenestrane and confirmation of oxygen's importance in the pathway toward silphinene 5.

The previous investigation into the original double [3+2] photocycloaddition reaction led us to further interesting questions. Firstly, was this reaction unique to a single photosubstrate, or did it have wider applicability? Secondly, if the mechanism of formation for the oxasilphinene relied upon the angular *meta* adduct possessing an oxygen, then could this be, to some extent, proven by removing it? To answer these questions we decided to return to the earlier work of Wender and reinvestigate the photochemistry of the methyl derivative of the acetal photosubstrate.[58]

When previously irradiated the bis-allyloxy acetal **130** yielded the linear *meta* adduct **131** (Scheme 4.2.1) necessary for a secondary [3+2] addition. Subsequently, this addition was completed *via* a radical cascade process as previously shown in Scheme 4.6, but no fenestrane structures were observed or isolated from the initial *meta* photocycloaddition residue.[58] This begged the question of whether the photosubstrate was simply not irradiated long enough to see the second transformation, or if it was unique to our methoxy derivative **1**.



Reagents & conditions: (i) $TMSOCH_2CH{=}CH_2$ (2.5 eq.), TMSOTf (1 mol %), -84 °C to -60 °C, CH_2Cl_2, 6hrs, 99%; (ii) hν (254 nm), cyclohexane, 9.5 hours, 24%; (iii) hν (254 nm), cyclohexane, 8 days, <10%.

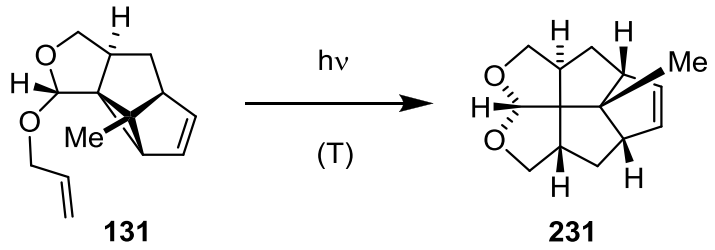
Scheme 4.2.1: Synthesis of methyl dioxafenestrane **231**.

Rather than use the condensation reaction preferred by Wender to construct the acetal **130**, we again relied upon the conditions devised by Noyori which resulted in an initial 75% yield. By use of the previously devised optimised conditions from the methoxy variant, this was eventually increased to 99% and was reproducible on a multigram scale

Direct irradiation of the photosubstrate with 254 nm UV light gave the linear *meta* adduct **131**, which was isolated as best as possible from other unwanted isomers by flash column chromatography in an approximate 24% yield. Immediate dissolution of the adduct in cyclohexane and irradiation using a 16 W Hg vapour lamp for a period of 8 days, gave the dioxafenestrane **231** in a yield of less than 10%. Purification of the product was particularly difficult, requiring the use of neutral silica although some polymeric impurities were irremovable.

From this initial observation, it was not surprising that dioxafenestrane **231** was never reported in the previous study of Wender as the efficiency of the process is exceptionally low. It would also suggest that while oxygen at the bridgehead position of the cyclopropane is not a requirement for the second [3+2] addition to happen, it does enhance the yield and reaction time of the process.

Having previously established that triplet sensitization could be used to improve reaction yield and efficiency, the linear *meta* adduct **131** was subjected to a series of triplet sensitized irradiations (Scheme 4.2.2, Table 6).



131 **231**

Entry	Scale (mg)	Solvent	Triplet Sensitizer (TS)	TS (mol %)	Time (hr)	Yield (%)
32	100	cyclohexane/acetone (1:1)	acetone	-	1.25	<5
33	100	cyclohexane	benzophenone	200	40	0
34	150	cyclohexane	acetophenone	200	6	<40
35	200	MeCN	acetophenone	200	4.5	31

Scheme 4.2.2 and **Table 6**: Triplet sensitized irradiation of methyl linear *meta* adduct **131**.

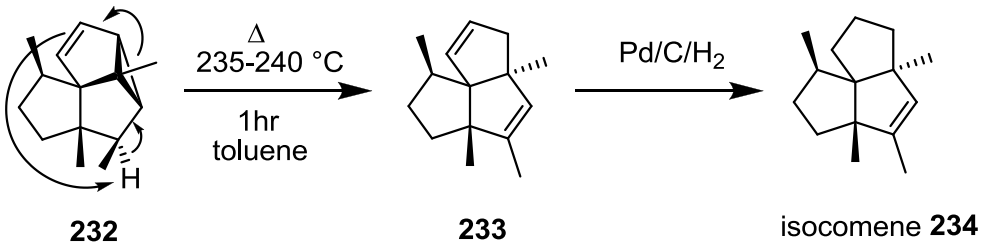
In cyclohexane the reaction was notably improved for acetophenone (entry 34) in terms of reaction time, selectivity and yield. However, the reactions with benzophenone (entry 33) and acetone (entry 32) were overwhelmed by polymeric side products, which negatively influenced the efficiency of the reaction. As before, altering the solvent to MeCN proved to give vastly superior results, resulting in an improved yield of 31%, at a substantially reduced time of only 4 hours and 30 minutes (entry 35).

Notably at no point during our irradiation studies of the linear *meta* adduct **131** was there any observance of the oxasilphinene derived from a 1,2-migration of the methyl group. Such a result lends extra credence to our proposed mechanism for the conversion of the angular adduct and oxygen's involvement.

In addition to the photochemical evidence, the methyl linear adduct **131** gave no thermal rearrangement even when heated above 230 °C in d_8-toluene for up to 72 hrs. This holds with

our earlier postulated fragmentation re-addition mechanism for the thermolysis of the methoxy linear *meta* adduct where an oxygen lone pair was required to assist in the internal decomposition.

Interestingly however, the adduct does not undergo a vinylcyclopropane-cyclopentene rearrangement or a homo 1,5 sigmatropic rearrangement as seen performed during the synthesis of the triquinane compound (±) isocomene (**234**).[103]



Scheme 4.2.3: Homo 1,5 sigmatropic rearrangement to form isocomene.

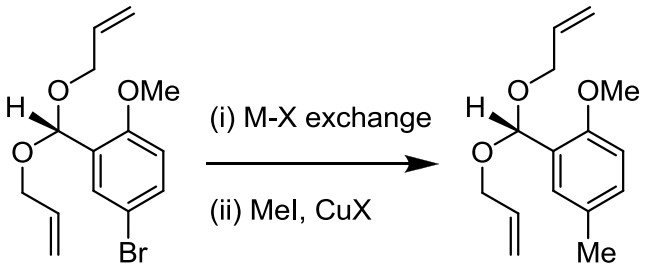
Overall, the study of the methyl photosubstrate demonstrated to us that having the alkoxy group on the aromatic ring has a rather profound influence on the subsequent chemical pathways that are available. The initial findings of the dioxafenestrane work were recently published as a communication in the Journal of the American Chemical Society[75] and can be found after the appendix section of this work. A full paper has been submitted.

4.7 Attempted synthesis of dioxafenestranes from photosubstrates with an additional aromatic *para* substituent.

After the initial discovery of the double [3+2] photocycloaddition reaction, it was thought prudent to study the wider applicability of this sequential photoaddition for making further novel fenestrane cores containing a variety of functionalities.

A simple way to incorporate a new group into the structure would be via the aromatic ring as previously mentioned during the synthesis of the deuterated photosubstrate $\mathbf{1_D}$. We had formed this photosubstrate by utilising the *para*-bromide **223**, which gave us a useful starting material for a series of other possible *para* substituted products by halogen exchange reactions.

We began with perhaps the simplest option, synthesis of the *para* methyl photosubstrate **235**. Generation of the lithiated species was achieved by using *n*-butyllithium, and then methylation was carried out by addition of methyl iodide. The best results are presented in table 7.



223 **235**

Entry	*n*BuLi (eq.)	MeI (eq.)	CuI (eq.)	Crude H:Me ratio 1:235	Yield (%)
36	1.5	1.05	-	2:3	10
37	1.5	3.0	-	3:7	17
38	1.4	1.5	1.5	1:4	46

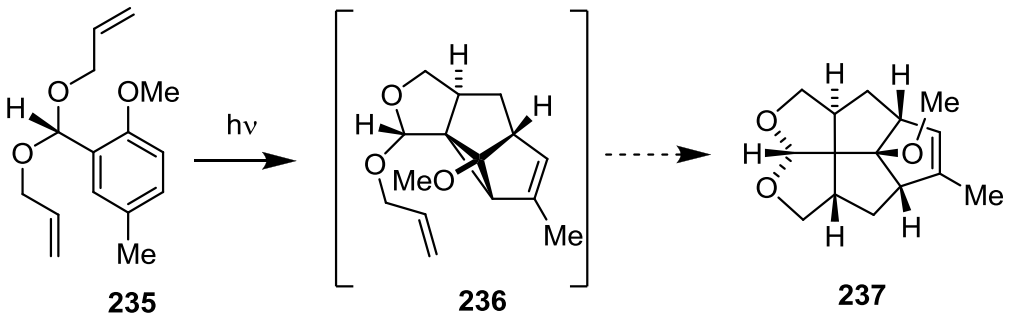
Scheme 4.2.4 and Table 7: Selection of successful attempts toward the synthesis of *para* methyl product **235.**

The degree of methylation *versus* protonation was disappointing and as expected the two forms proved difficult to separate by chromatographic methods. A pentane/CH_2Cl_2 (60:40) mixture gave a small retention factor difference, thus allowing separation by the use of a 100:1 silica/product ratio. While this did afford the *para* methyl material in >90% purity, the isolated yield was low, with the best obtained being only 17% (entry 37). Purification of the methyl iodide and an increased number of equivalents did not improve the ratio any further.

Exchange with lithium generates a reasonably hard anion and iodomethane is a fairly soft electrophile, so copper iodide (1.5 eq.) was added (entry 38) after the initial metal-halogen exchange to generate the softer cuperate. This returned an improved methyl to hydrogen ratio of 4:1, which with subsequent chromatographic afforded a 46% yield of the methylated material in approximate 94% purity.

Further improvement to the initial methylation may have been achieved by replacement of *n*-butyllithium with the more efficient tertiary version or a change of the methylating agent (perhaps to dimethyl sulfate) although time constraints prevented any further optimisation.

Having synthesised some of the required photosubstrate **235**, direct irradiation at 254 nm was carried out using a 16 W Hg vapour lamp in cyclohexane and followed closely *via* ^{1}H NMR spectroscopy (Scheme 4.2.5).

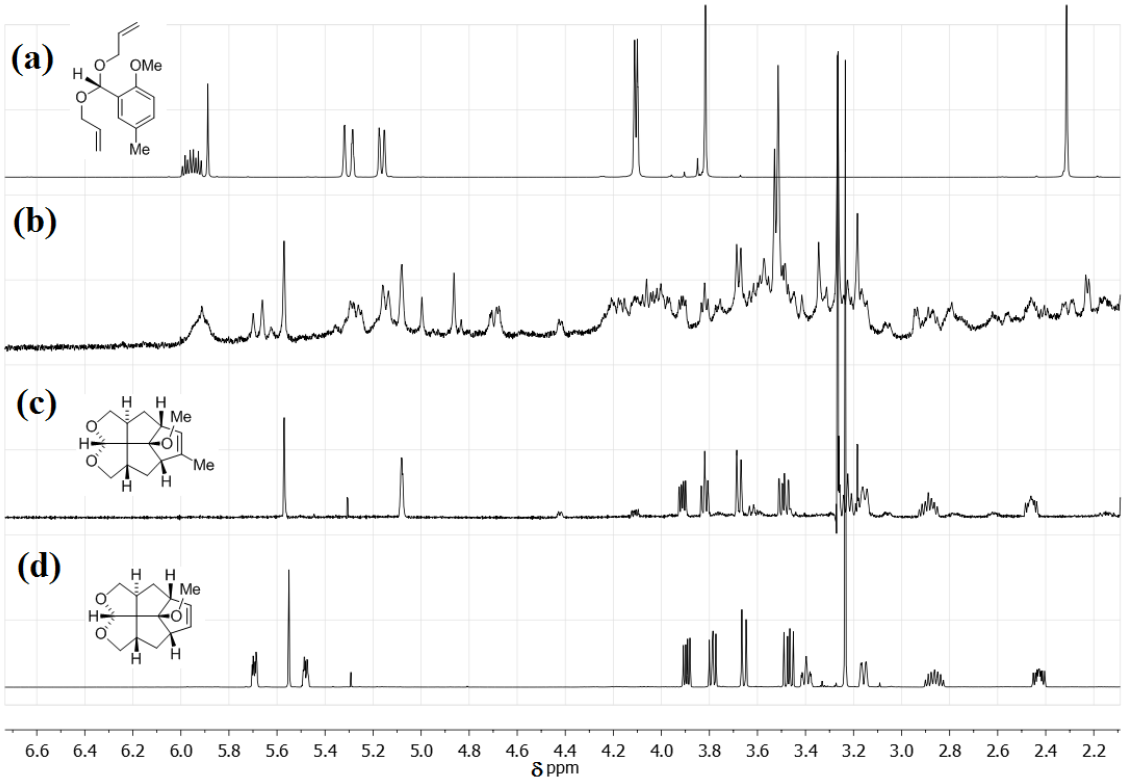


235 **236** **237**

Reagents & conditions: hν (254 nm), cyclohexane, 72 hours, <5%.

Scheme 4.2.5: Irradiation of *para* methyl photosubstrate **235**.

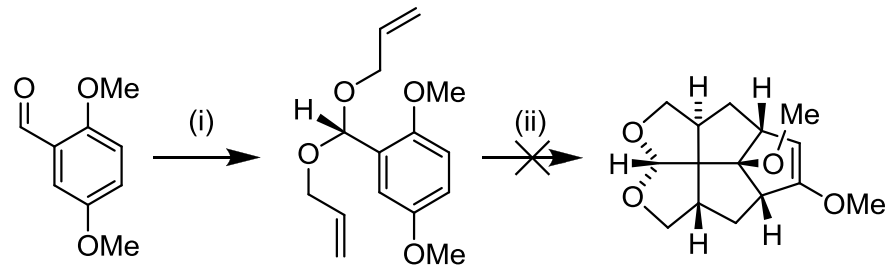
After total consumption of the aromatic material, the resulting mixture of *meta* and *ortho* derived adducts proved to be inseparable. As such it was decided to continue the reaction through the first addition step and onto the second as we were most interested in isolating any of the potential dioxafenestrane **237**.



Spectra 3: Irradiation of *para* methyl photosubstrate **235**: (a) Photosubstrate **235**; (b) crude sample after 72 hours of irradiation; (c) isolated possible dioxafenestrane adduct **237**; (d) dioxafenestrane adduct **4**.

Analysis of the NMR spectrum clearly showed the isolation of an adduct (Spectra 3c), that compared favourably with the original double [3+2] adduct (Spectra 3d). Unfortunately, due to decomposition and inseparable impurities in the same chromatographic region, the isolated yield was less than 5%. The adduct remains unassigned due to rapid decomposition before full analysis could be performed. Subsequent repetition using MeCN and triplet sensitization was planned, but our interests had migrated on to other more productive areas and time constraints meant that this fenestrane regrettably remains uncharacterised.

In addition to the *para* methyl compound, we also attempted to prepare the equivalent *para* methoxy fenestrane compound **240**. The required aldehyde starting material **238**[104] was turned into the acetal **239** under Noyori conditions in a straightforward manner giving a 78% yield of the desired photo substrate, without need for any chromatographic separation (Scheme 4.2.6).



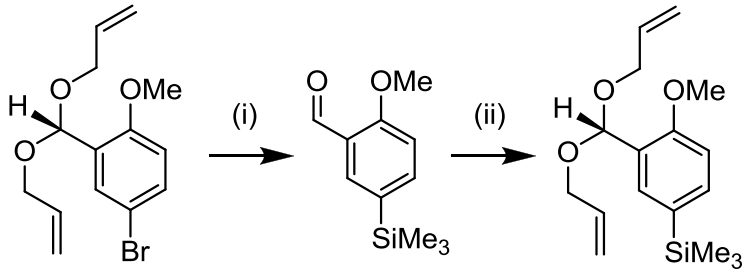
238 **239** **240**

Reagents & conditions: (i) $TMSOCH_2CH{=}CH_2$ (2.5 eq.), TMSOTf (1 mol %), -78 °C, CH_2Cl_2, 6 hr 78%; (ii) hν (254 nm) cyclohexane, 12 hours, 0%.

Scheme 4.2.6: Attempted synthesis of dimethoxy dioxafenestrane **240**.

When irradiated with 254 nm UV light the acetal underwent *meta* photocycloaddition, but unfortunately formed an unintelligible mixture of adducts that were highly labile toward any trace acid and the silica of the chromatography column. This made purification challenging and subsequent further irradiation as in the previous example did not appear to produce any notable fenestrane type adduct for isolation.

Undiscouraged by the previous result we turned our attention to a less electron donating substituent, settling upon the synthesis the *para* trimethylsilyl photosubstrate **242**, with our initial starting point again being the previously used bromide **223** (Scheme 4.2.7).



223 **241** **242**

Reagents & conditions: (i) *n*BuLi (2.5 M, 1.5 eq.), THF, -78 °C, then TMSCl, (3 eq.), 80% (ii) $TMSOCH_2CH{=}CH_2$ (2.1 eq.), TMSOTf (1 mol %), -78 °C, CH_2Cl_2, 33%

Scheme 4.2.7: Attempted synthesis of *para* TMS photosubstrate **242**.

In theory, addition of TMSCl to the lithiated species generates LiCl and not acid, thus addition of a base such as triethylamine should not be necessary. However, the initial metal-halogen exchange resulted in complete cleavage of the acetal; giving the *para* TMS substituted aldehyde **241** in an 80% yield. This result could be ascribed to LiCl acting as a mild Lewis acid catalyst and trace amounts of water in the THF which had not been rigorously dried prior to use.

Noyori conditions were used to restore the acetal functionality, which worked in a high yield, but with co-eluting impurities. These were removed *via* flash column chromatography; however this led to a reduction in the yield of photosubstrate **242** (to 33%), even with the addition of triethylamine (0.1%) to the column.

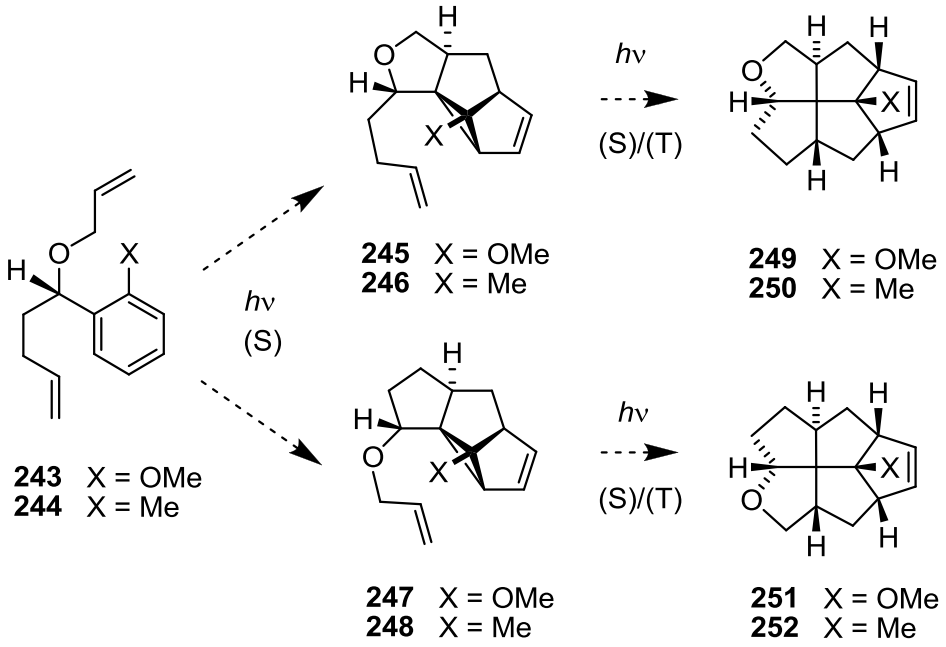
Direct irradiation of photosubstrate **242** with 254 nm UV light was conducted over 12 hours, until total consumption of the starting material had occurred. Analysis of the ^{1}H NMR spectrum implied that *meta* adducts were the primary products, but unfortunately, they turned out to be inseparable and highly labile toward silica.

4.8. Synthesis of oxafenestranes derived from ether photosubstrates.

4.8.1 Introduction.

After the stability issues we faced when adding a third substituent to the aromatic ring we decided to shift focus toward the tether that linked the aromatic ring and the two dienes. The previous fenestranes were both derived from a photosubstrate that contained two identical branched allyloxy tethers, so what would occur if one of them were converted to something else?

Replacement of an oxygen atom with a methylene CH_2 to create an ether would introduce a level of competition into the process and allow us to hopefully furnish two different oxafenestranes from a single ether arenyl-diene photosubstrate (Scheme 4.2.8).



Scheme 4.2.8: Proposed synthesis of oxafenestranes **249-252**.

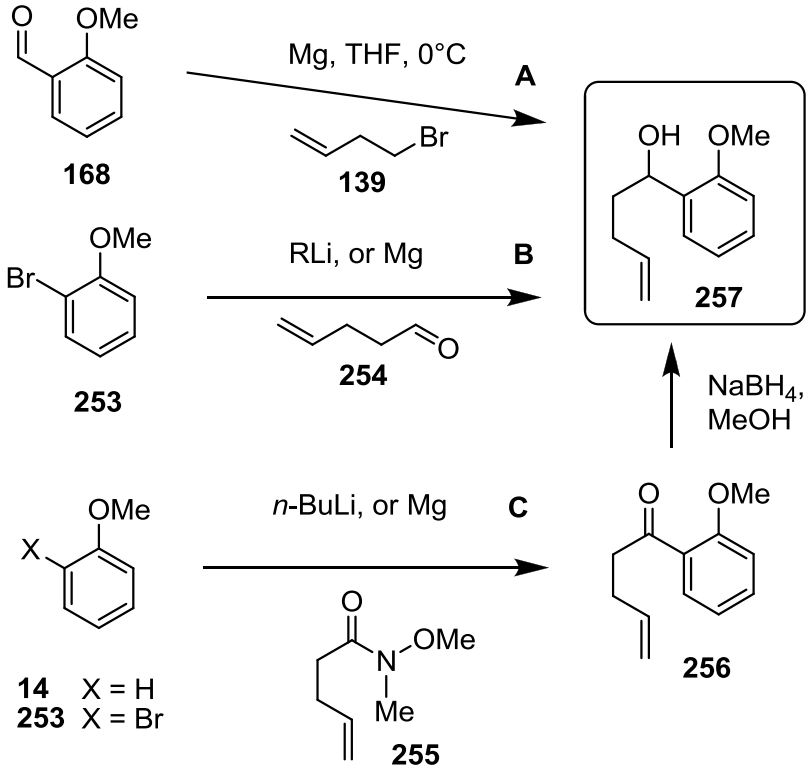
Direct irradiation of an ether photosubstrate such as **243** with 254 nm UV light would result in the production of two linear *meta* adducts **245** and **247**, where the oxygen is either incorporated into the core tetracyclic structure or the "free" alkenyl tether. According to the earlier work of De Keukeliere,[61] the more favourable properties of the C-O-C linkage ought to mean that the

oxygen containing tether is preferentially added to the aromatic ring over the all carbon one. The increased repulsion of the lone pairs on oxygen results in a smaller interior C-O-C angle and the C-O bond is naturally shorter. These factors combine to bring the double bond closer to the excited ring.

The same would also be true for the second [3+2] addition, when oxygen is in the alkenyl tether (as in **247**) it would be expected to preferentially undergo reaction to form the fenestrane over its counterpart **245**.

4.8.2 Synthesis of two methoxy oxafenestranes.

We decided to start with the methoxy derived photosubstrate **243**, which could be easily synthesised from the intermediate alcohol **257** by simple alkylation. In order to create this key alcohol intermediate, several possible routes were envisaged (Scheme 4.2.9).



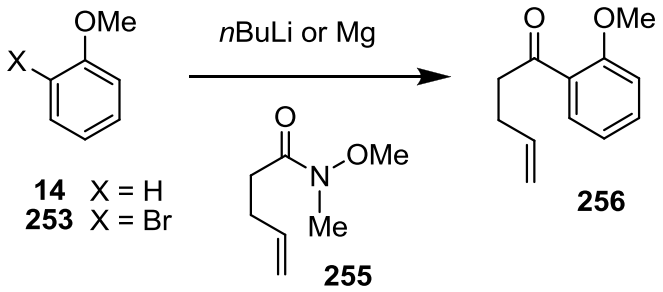
Scheme 4.2.9: Possible routes to key aromatic alcohol **257**.

Eminent photochemist Jan Cornelisse had already synthesised alcohol **257** for a previous study in which he utilised the nucleophilic attack of butenyl magnesium bromide on *o*-anisaldehyde (Scheme 4.2.9, A).[35] However this was only achieved in a disappointing 22% yield and our own repetition of this Grignard reaction resulted in no significant improvement.

The second option (Scheme 4.2.9, B) involved either creation of an organolithium or a Grignard reagent starting from *o*-bromoanisole (**253**). The downside of this potential route was the requirement of 4-pentenal (**254**) as the reacting partner. From previous experience and a study of the relevant literature[105] in which 4-pentenal is often produced *via* the Swern oxidation[106] *in*

situ as a dilute solution, the synthesis of this short chain aldehyde in a usable form can be significantly challenging.

Route C was therefore deemed the most reliable way to achieve the synthesis of **257**, despite the requirement of an additional reduction step through ketone **256** (Table 8). A Weinreb Amide was selected over the potential acid chloride because the amide was easier to form on a large scale and store for later use.

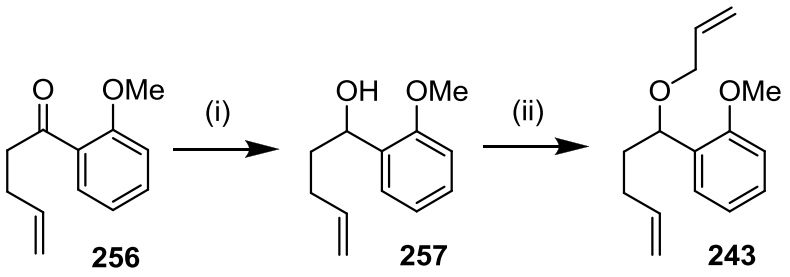


Entry	Sm	Reaction type	Conditions	Temp (°C)	Time (hrs)	Yield (%)
39	**253**	Grignard	Mg (1.05 eq.), Et_2O, then **255** (1 eq.)	RT	16	48
40	**253**	Grignard	Mg (1.05 eq.), Et_2O, then **255** (1 eq.)	RT	16	56
41	**253**	Grignard	Mg (4 eq.), Et_2O, then **255** (3eq.)	0 °C → RT	16	63
42	**253**	Grignard	Mg (4 eq.), THF, then **255** (3eq.)	0 °C → RT	16	24
43[107]	**14**	*o*-lithiation	TMEDA (1.1 eq.), 2.5M *n*BuLi (1.3 eq.), Et_2O, then **255** (2 eq.)	Reflux → RT	16	Trace
44	**14**	*o*-lithiation	*n*BuLi (2.5 M, 1.2 eq.), THF, then **255** (1.1 eq.)	0 °C → RT	16	<10%
45	**14**	*o*-lithiation	*n*BuLi (2.5 M, 1.2 eq.), THF, then **255** (1.2 eq.)	-78 °C → RT	16	0
46	**253**	M-Hal ex.	*n*BuLi (2.5M, 1.4 eq.), Et_2O, then **255** (1.2 eq.)	-78 °C → RT	4	62
47	**253**	M-Hal ex.	*n*BuLi (2.5M, 1.4 eq.), Et_2O, then **255** (1.2 eq.)	-78 °C → RT	7	61

Scheme 4.3.0 and Table 8: Synthesis of ketone **256**.

The necessary Weinreb amide[108] **255** was made in multigram quantities (>15g) and high yield (>94%) from the reaction of 4-pentenoic acid and *N*, *O*-dimethyl-hydroxylamine with CDI acting as an amide coupling agent.[109] The Grignard reaction between *o*-bromoanisole and **255**, resulted in yields of up to 63% on a scale up to 10 grams (entry 41), however total failure was common, as initiation proved to be unreliable even with the addition of an iodine crystal and prolonged heating at reflux.

ortho-Lithiation has been used to achieve acylation of anisole usually with the co-ordinating ligand TMEDA,[110] which breaks the butyllithium hexamer to create a cluster of higher reactivity.[111] However, deprotonation using this method resulted in only a trace amount of the ketone (entry 43). Deprotonation without the TMEDA, at 0 °C gave a slightly improved result (entry 44), although this was abandoned in favour of the metal-halogen exchange of *o*-bromoanisole to create the lithiated species (entries 46 and 47). This gave comparable yields to the Grignard on the same scale, but without the activation issues and as such became the preferred method.

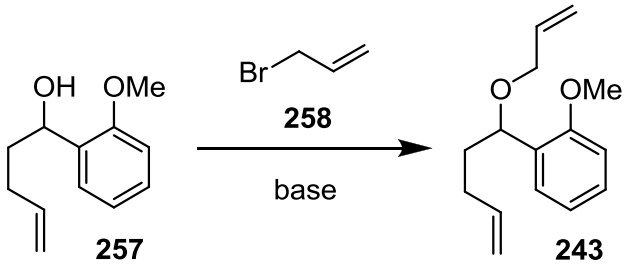


Reagents & conditions: (i) $NaBH_4$ (2.2 eq.), MeOH, 0 °C, 24 hours, 96%; (ii) 50% NaOH (ex.), TBAHS (2 eq.), allyl bromide (5 eq.), CH_2Cl_2, RT, 6 days, 80%.

Scheme 4.3.1: Synthesis of ether **243** from ketone **256**.

From aromatic ketone **256**, the next step was reduction to the alcohol, which was easily achieved in excellent yields (84-96%, on scales up to 4.0 grams) using sodium borohydride in MeOH at 0 °C.

Subsequent transformation to the desired arenyl-diene photosubstrate **243** required the addition of an allyl group, which we hoped to achieve *via* an S_N2 reaction, where the bromine of allyl bromide was substituted for the deprotonated alcohol (Scheme 4.3.2, Table 9).



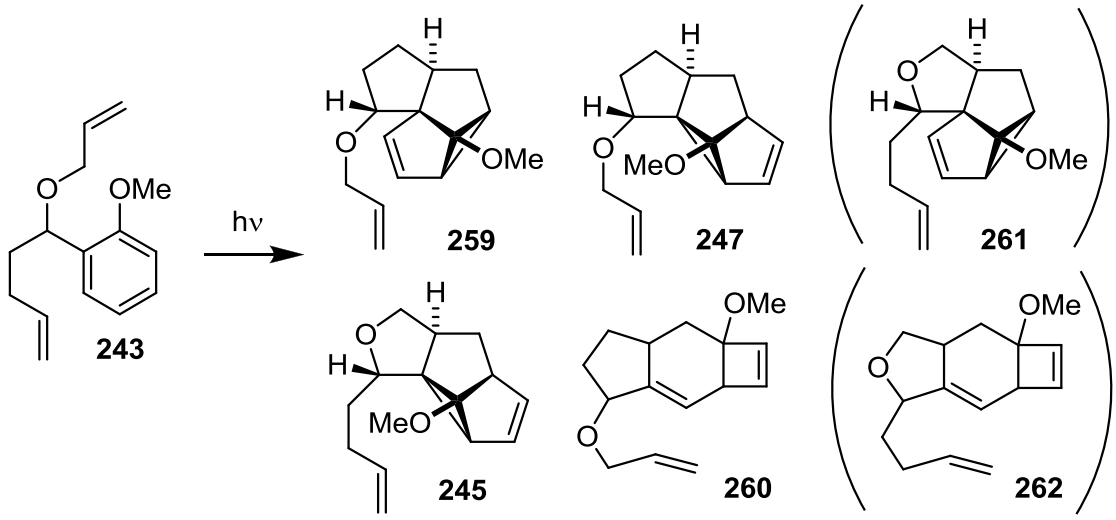
Entry	Base	Solvent	258 (eq.)	PT cat. (eq.)	Temp. (°C)	Time (hrs)	Yield (%)
48	NaH	Et_2O	1.1	-	RT	18	Trace
49	*n*BuLi (2.5 M)	THF	1.2	-	0 °C → RT	20	SM
50	KOH (5M)	CH_2Cl_2	2.0	TBAB (0.1)	RT	72	Trace
51	NaOH	CH_2Cl_2	1.1	TBAI (0.2)	RT	72	Trace
52	NaOH	CH_2Cl_2	1.1	TBAHS (0.2)	RT	72	21
53	NaOH	CH_2Cl_2	1.1	TBAHS (0.5)	RT	144	30
54	NaOH	CH_2Cl_2	1.5	TBAHS (1.0)	RT	72	69
55	NaOH	CH_2Cl_2	2	TBAHS (2.0)	RT	96	69
56	NaOH	CH_2Cl_2	4	TBAHS (2.0)	RT	144	79
57	NaOH	CH_2Cl_2	5	TBAHS (2.0)	RT	144	80

Scheme 4.3.2 and Table 9: Attempts toward synthesis of methoxy photosubstrate **243**.

Initially the deprotonation of the alcohol was attempted with standard bases, NaH (entry 48) and *n*-butyllithium (entry 49) without success. Modification to phase-transfer conditions as recommended by a colleague[112] and subsequent optimisation of the reaction components gave the desired ether in 80% yield (entry 57).

Employment of a phase transfer catalyst[113] is generally a reliable way of facilitating the migration of a reactant between two heterogeneous phases, within only one of which the reaction can occur. In the case of the ether formation conducted here, the ionic sodium salt of the alcohol is soluble in the aqueous phase, but insoluble in the organic (CH_2Cl_2). The catalyst encapsulates the anion, dissipating the charge and thus allowing it to dissolve in the organic phase where it reacts with the allyl bromide. This achieved reasonably fast reactions, with high conversions and fewer by products. It also eliminated the need for large volumes of organic solvent and could be regarded as a "greener" solution to the problem. However in this case the usage of multiple equivalents of toxic allyl bromide perhaps negates the effect.

Methoxy photosubstrate **243** was irradiated with 254 nm UV light on a 600mg scale with complete reaction occurring in 3 hour 30 minutes (Scheme 4.3.3).



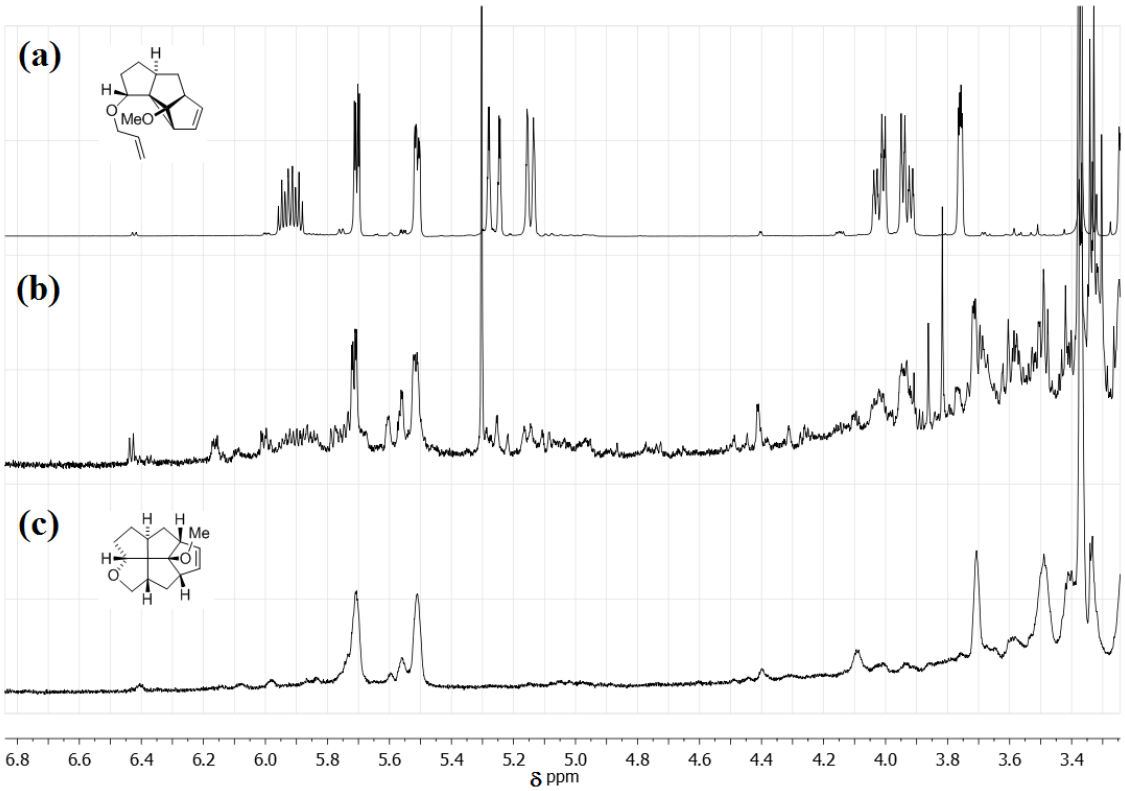
Scheme 4.3.3: Products isolated from the photolysis of ether photosubstrate **243**.

We were only able to isolate four photoadducts free of contamination, with several others observed that contained other co-eluting adducts thus hindering their structural determination. In particular the postulated *ortho* derived rearrangement **262** was a major component, but could not be obtained free from the angular *meta* adduct **261**.

The desired linear *meta* adducts **245** and **247** were only minor components in the crude residue, and interestingly the oxygen containing alkenyl tether appeared to have an insignificant preference for taking part in the *meta* photocycloaddition as opposed to the all carbon chain tether. An exact determination of the product preference ratio wasn't possible due to the previously mentioned difficulty in obtaining the angular adduct with oxygen in its core structure from the *ortho* derived isomer **262**.

Repetition of the reaction on a 3 gram scale using a 6 W Hg vapour lamp over 32 hours (a 16 W was unavailable for use at the time) gave isolated yields of approximately 2, 5, 8 and 18% for **259**, **247**, **245** and **260** respectively. The yield of the linear *meta* adducts **245** and **247** was disappointing with the *ortho* addition being greatly favoured, however there was enough material for us to investigate the secondary [3+2] addition.

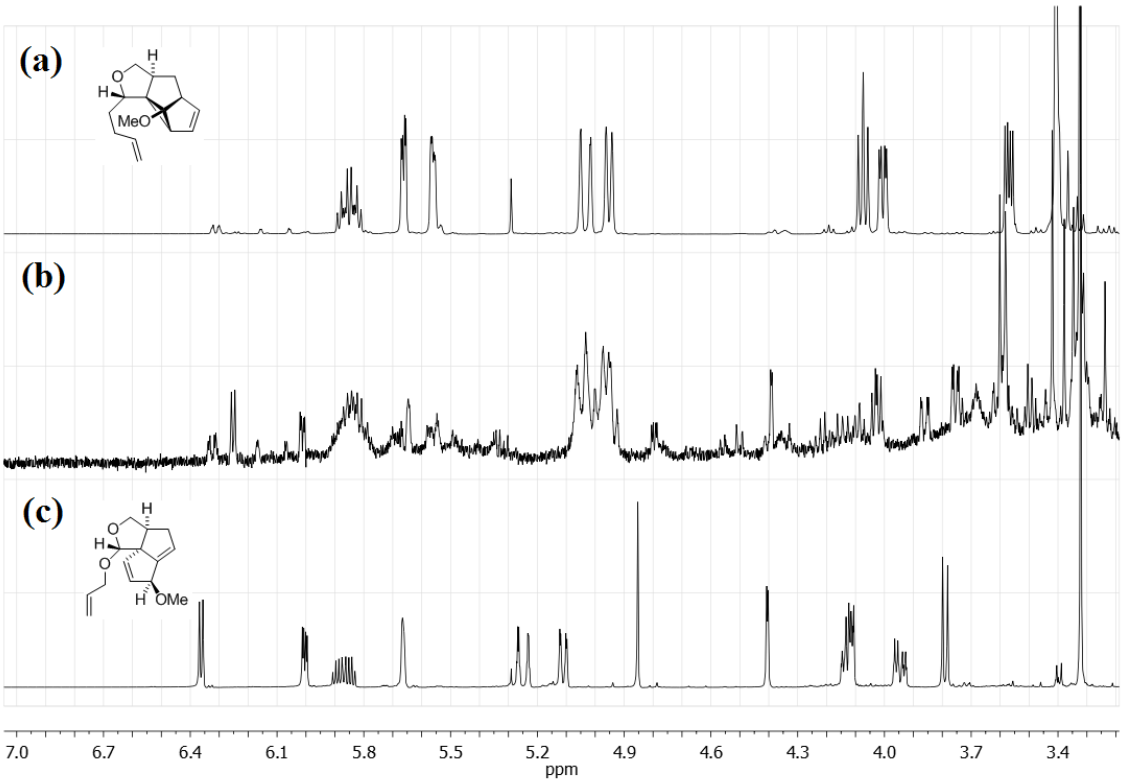
A limited amount of *meta* adduct **247** was irradiated at 254 nm with a 6 W Hg vapour lamp in cyclohexane until complete consumption of the starting material had taken place (Spectra 4).



Spectra 4: Irradiation of *meta* compound **247** (254 nm, 6 W Hg vapour lamp); (a) linear *meta* adduct **247**; (b) after 12 hrs irradiation; (d) possible fenestrane product **251**.

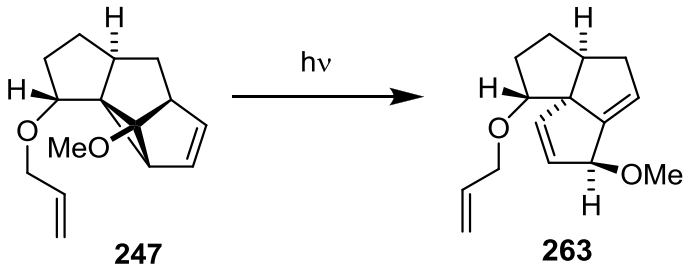
After 12 hours, a product resembling the oxafenestrane **251** had appeared, although it proved impractical to isolate from the surrounding impurities (Spectra 4d).

Linear *meta* adduct **245** was also irradiated in the same manner for 21 hours (Spectra 5), however this showed no obvious formation of its counterpart oxafenestrane **249**. It was interesting to note that the ^{1}H NMR spectrum possessed peaks (Spectra 5b) that resembled those of the oxasilphinene **5** (Spectra 5c), isolated in the earlier acetal work.



Spectra 5: Photolysis of linear *meta* adduct **245**: (a) Linear *meta* adduct **245**; (b) Crude reaction mixture after irradiation for 21 hours; (c) previous dioxasilphinene adduct **5**.

The appearance of a silphinene adduct under these conditions was not unexpected, although purification again proved unfeasible due to the high amounts of polymeric material. Dissatisfied with the result of these secondary irradiations, they were repeated again using a different 6 W Hg vapour lamp. This resulted in neither reaction producing any evidence of the double [3+2] addition, although in the case of linear *meta* adduct **247**, the oxasilphinene product **263** was isolated in an approximate 8% yield with another minor co-eluted impurity.

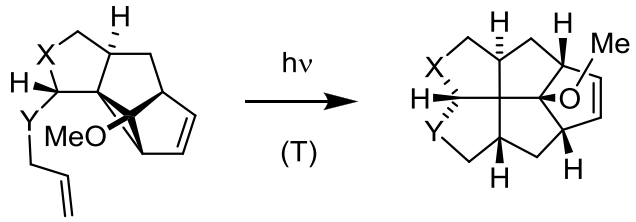


247 **263**

Reagents & conditions: hν (254 nm) cyclohexane, 16 hours, <8%.

Scheme 4.3.4: Synthesis of oxasilphinene **263**.

This unpredictable behaviour again highlighted the fundamental problem of performing irradiations with UV light sources that were subject to fluctuations in output over time. As in the previous dioxafenestrane synthesis examples, direct irradiation at 254 nm UV light under triplet sensitized conditions could be applied in order to overcome the reliability issues. The results of this are displayed in Table 10.



245 X = O, Y = CH_2
247 X = CH_2, Y = O

249 X = O, Y = CH_2
251 X = CH_2, Y = O

Entry	*meta* Adduct	Scale (mg)	Solvent	TS (mol %)	Time (hrs)	Product	Yield (%)
58	**245**	100	cyclohexane	acetophenone (150)	11	**249**	27%
59	**247**	100	cyclohexane	acetophenone (150)	17	**251**	31%

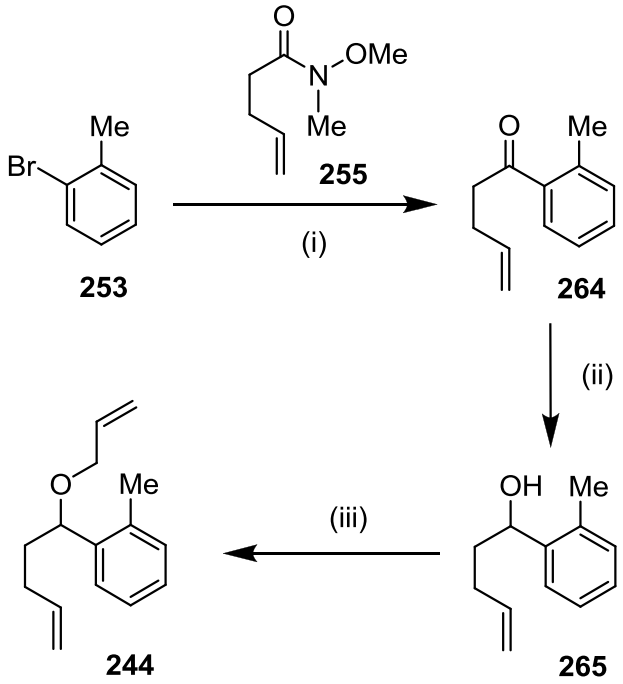
Scheme 4.3.5 and **Table 10**: Triplet sensitized irradiation to form oxafenestranes **249** and **251**

Both adducts smoothly underwent the secondary [3+2] cycloaddition process, giving comparable yields to the previous synthesis of the dioxafenestranes in cyclohexane. While, these isolated yields indicated a slight favouring of the oxygen containing alkenyl tether toward addition, it was not a significant enough effect from which to draw any definitive conclusions.

It would have been prudent to repeat this experiment in MeCN, but regrettably time constraints did not allow for any subsequent repetition of this chemistry and optimisation of the second [3+2] addition step.

4.8.3 Synthesis of two methyl oxafenestranes.

In light of the previous oxafenestrane study, we decided to perform the irradiation of the methyl derivative of ether arenyl-diene photosubstrate **244** where, as before, the synthetic route was conducted *via* aromatic ketone **264**.



Reagents & conditions: (i) Li (2.1 eq.), Et_2O, Ar., 0 °C, **255** (1.1 eq.), 50%; (ii) $NaBH_4$ (2.2 eq.), MeOH, 0 °C, 24 hours, 99%; (ii) 50% NaOH (ex.), TBAHS (1 eq.), allyl bromide (5 eq.), CH_2Cl_2, RT, 24 hrs, 99%.

Scheme 4.3.6: Synthesis of ether **244** from *o*-bromotoluene.

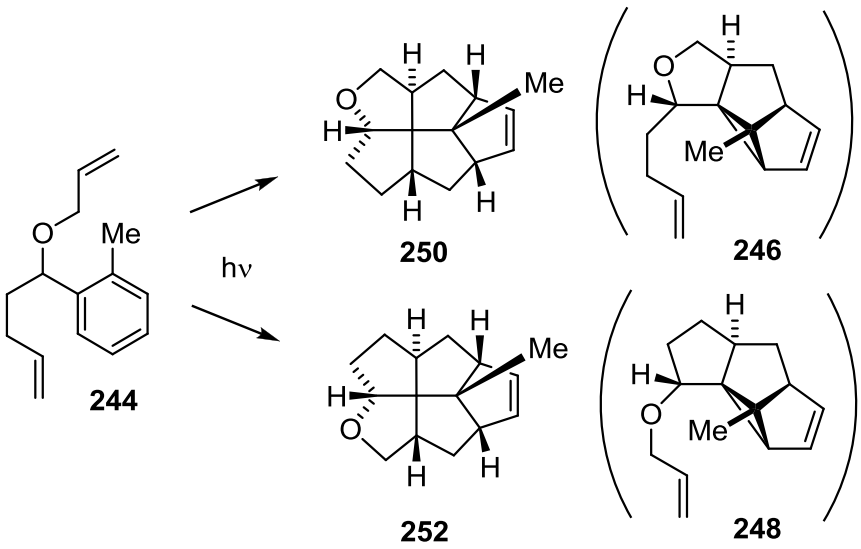
Initially we attempted the Grignard reaction between *o*-tolyl magnesium bromide and Weinreb amide **255**, which turned out to be inefficient with a best obtained yield of 37%. This could be again attributed to the difficulties in initiating and maintaining the Grignard reagent of the aromatic species. Moreover, circumventing the problem to proceed straight through to the aromatic alcohol **265** by using the reaction of butenyl magnesium bromide and *o*-tolualdehyde only resulted in a yield of 28%, despite addition of zinc chloride as a Lewis Acid catalyst.[114]

Returning to the metal-halogen exchange method used in the synthesis of photosubstrate **243** was equally unsuccessful. Despite forming the desired ketone in a reasonable yield, it proved

inseparable from another ketone, non-1-en-5-one, which was formed as a by-product from addition of *n*-butyllithium to the Weinreb amide. This was not an issue in the previous methoxy version because the two ketones had significantly different polarities. Such a problem would likely be avoided by using more reactive *tert*-butyllithium to achieve a more efficient metal-halogen exchange, although this clearly presented a more dangerous option that we were hoping to avoid.

The yield was eventually improved by generating the lithium species *via* addition of the metal to the bromide at 0 °C, and then subsequent exposure to the Weinreb amide. This gave a promising yield of 50% in ether, although a subsequent attempt made in THF resulted in no reaction and there was not time for further optimisation.[143]

The two ensuing steps, reduction and alkylation, required to produce the desired photosubstrate were both conducted using the previously optimized conditions and could be achieved in near quantitative yields (Scheme 4.3.7). This provided some compensation for the lesser yield obtained for the ketone formation.

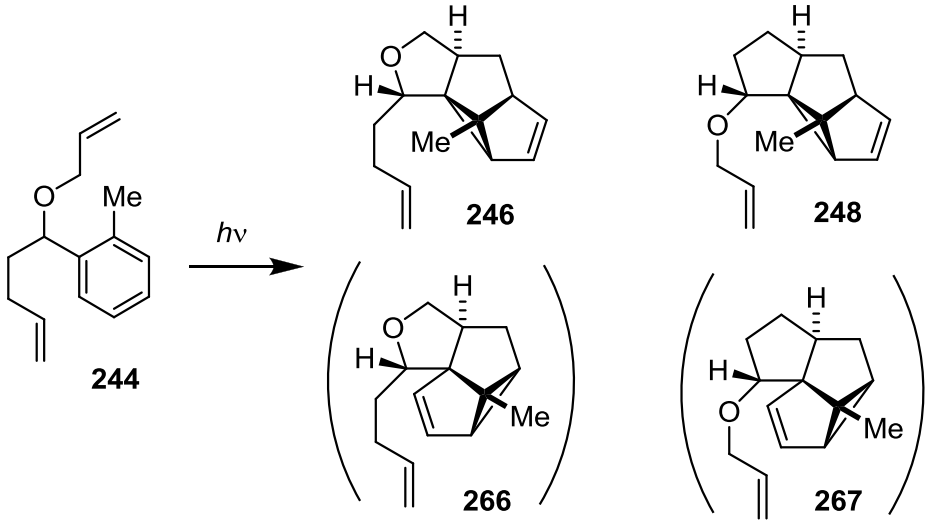


Reagents & conditions: (i) hν (254 nm) cyclohexane, 16 hours, 18% (**250**) and 8% (**252**).

Scheme 4.3.7: Irradiation of photosubstrate **244** leading directly to two oxafenestranes.

The ether photosubstrate **244** was then irradiated with 254 nm UV light on a 1.70 g scale, for 16 hrs using a 16 W Hg vapour lamp in cyclohexane. Rather unexpectedly the products obtained were not the *linear meta* adducts **246** and **248**, but rather their oxafenestranes in yields of approximately 18 and 8% for **250** and **252** respectively. This was an unusual case in which the formation of fenestrane was observed before the consumption of the aromatic material was completed. There was also a trace amount of an apparent angular *meta* adduct isolated from the residue, although which version could not be conclusively proven.

The result of this reaction suggested that significantly more of the oxygen chain was being incorporated into the core structure during the initial *meta* photocycloaddition step. This could be further backed up when the *meta* photocycloaddition was repeated in MeCN. In this case, only the linear *meta* adducts (**246** and **248**) were obtained (Scheme 4.3.8). The ratio between the two linear adducts was approximately 2:1 in favour of the oxygen tether being incorporated into the core structure.



Reagents & conditions: (i) hν (254 nm) MeCN, 26 hours, <30% (**246**) and <15% (**248**)

Scheme 4.3.8: Repeated irradiation of photosubstrate **244** in MeCN.

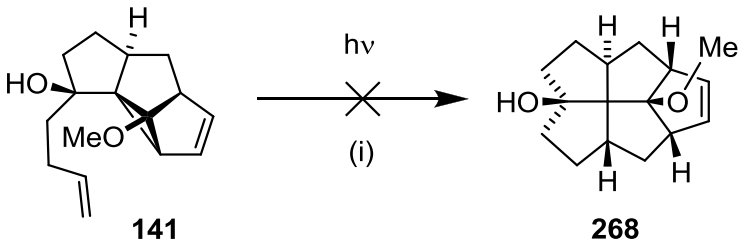
It should be noted that the isolation of the linear *meta* adducts was hampered by the co-elution of their angular regioisomers. Despite this, the result highlighted an interesting contrast to the methoxy derivative, in which the two tethers had shown little difference in their preference

toward *meta* addition (see Scheme 4.3.3). However, during the irradiation of methyl photosubstrate **244** there was a clear inclination for the oxygen tether to be included in the core structure. The reason for this discrepancy may be due to the methoxy derivatives penchant to undergo *ortho* addition instead, where the more flexible oxygen containing tether would be incorporated fastest. Therefore, in the irradiation of methoxy photosubstrate **243** the rates for each different chain to undergo *meta* addition becomes largely similar.

The main conclusion to be drawn from the photochemistry of these ether photosubstrates is that arenyl-diene photosubstrates need not contain oxygen chains in order to undergo the double [3+2] photocycloaddition and that it is certainly not an occurrence unique to the original acetal, thus opening the door for further potential chemistry in this area.

4.9 Attempted formation of an all carbon [5.5.5.5] fenestrane.

Having established that fenestranes could be made using linear *meta* adducts containing a free alkenyl chain with or without oxygen in it, we decided to return to our first tertiary alcohol photosubstrate **140** to attempt to form a fenestrane in the same fashion. The *exo* linear *meta* adduct **141** would be required to perform the transformation, having the correct alkenyl chain orientation in comparison to the *meta* adducts used in the previous fenestrane syntheses.



Reagents & conditions: 100-150 mg, hν (254 nm), acetophenone (100-500 mol %), MeCN, >16 hrs, 0%

Scheme 4.3.9: Failed synthesis of *cis, cis, cis, trans*-[5.5.5.5] fenestrane **268**.

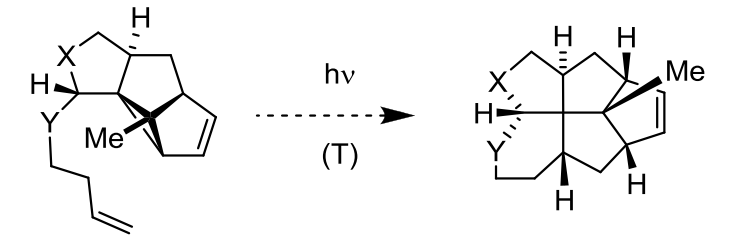
Unfortunately, no fenestrane product was observed despite a variety of attempts using increased amounts of acetophenone. Irradiation led mainly to decomposition of the triplet sensitizer and polymerisation, although there was some minor conversion to the *angular* isomer **143** (<10% in most cases). The reaction was also repeated using both acetone (500 mol %) and benzophenone (500 mol %), with the same result.

Whether this is an indication that an all-carbon variation of the pentacyclic fenestrane cannot be formed by the double [3+2] photocycloaddition remains unclear. The acid labile nature of the *exo* linear adduct may mean that decomposition is preferred over addition. A truer indication of whether an all carbon skeleton could be constructed would likely require the replacement of the hydroxyl with hydrogen like in the previous cases.

4.10 Attempted formation of a [5.5.5.6] fenestrane.

Thus far all the fenestranes reported in this work have incorporated the same pentacyclic *cis, cis, cis, trans*-[5.5.5.5] core structure. It would therefore be a reasonable idea to expand the potential applications of the double [3+2] photocycloaddition by investigating the construction of a different type of fenestrane.

A simple way to do this would be to expand the length of one of the tethers in an ether photosubstrate by an extra methylene, thus potentially giving us one of the [5.5.5.6] oxafenestranes displayed in Scheme 4.4.0.

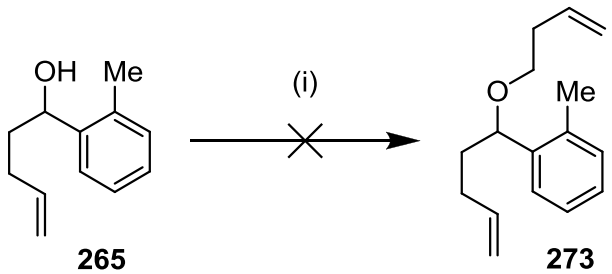


269 X = CH_2; Y = O
270 X = O; Y = CH_2

271 X = CH_2; Y = O
272 X = O; Y = CH_2

Scheme 4.4.0: Proposed synthesis of a [5.5.5.6] oxafenestrane.

Initially, we attempted formation of the photosubstrate **273**, by alkylating the aromatic alcohol **265** using phase transfer conditions, but exchanging allyl bromide for butenyl bromide (Scheme 4.4.1).



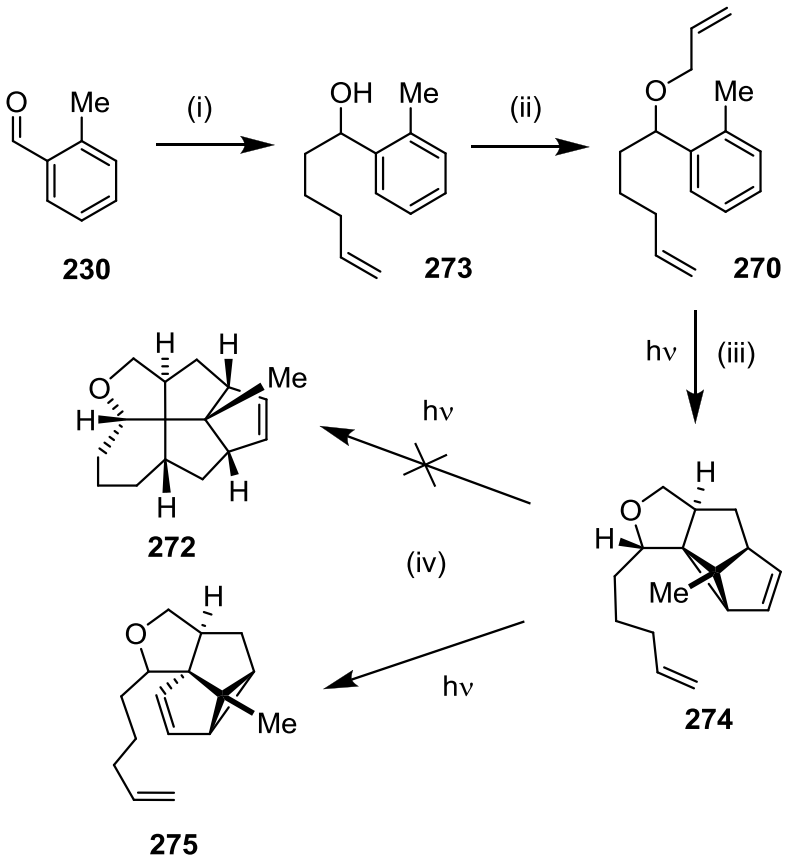
265 **273**

Reagents & conditions: (i) 50% NaOH (ex.), TBAHS (0.5-2.0 eq), butenyl bromide (2.0-4.0 eq), CH_2Cl_2, RT, 1-7 days, <5%.

Scheme 4.4.1: Synthesis of ether **273** from alcohol **265**.

It was decided to use the methyl alcohol in part because this was available at the time, but additionally because as shown in the irradiation of the previous methyl derived ether photosubstrate **244** it leads to a mixture of ether adducts that excludes the *ortho* derived rearrangements that dominate the methoxy case. Unfortunately, despite several attempts the alkylation reaction was found to be ineffective. This could be due to butenyl bromide's inherent lack of reactivity in comparison to allyl bromide, and butenyl bromide's propensity to eliminate HBr and form butadiene.

The cost of butenyl bromide was also rather prohibitive to allow us to use it in a larger excess, so we turned our attention toward extending the all carbon tether instead (Scheme 4.4.2).



Reagents & conditions: (i) Mg (2.5 eq.), pentenyl bromide (1.5 eq.), Et_2O, 81%; (ii) 50% NaOH (20 eq.), TBAHS (1 eq.), allyl bromide (3 eq.), CH_2Cl_2, RT, 24 hrs, 74%; (iii) hν (254 nm), MeCN, 8 hrs, <32%; (iv) hν (254 nm), acetophenone (120 mol %), MeCN, 6 hrs, <11%.

Scheme 4.4.2: Attempted synthesis of [5.5.5.6] oxafenestrane **272**.

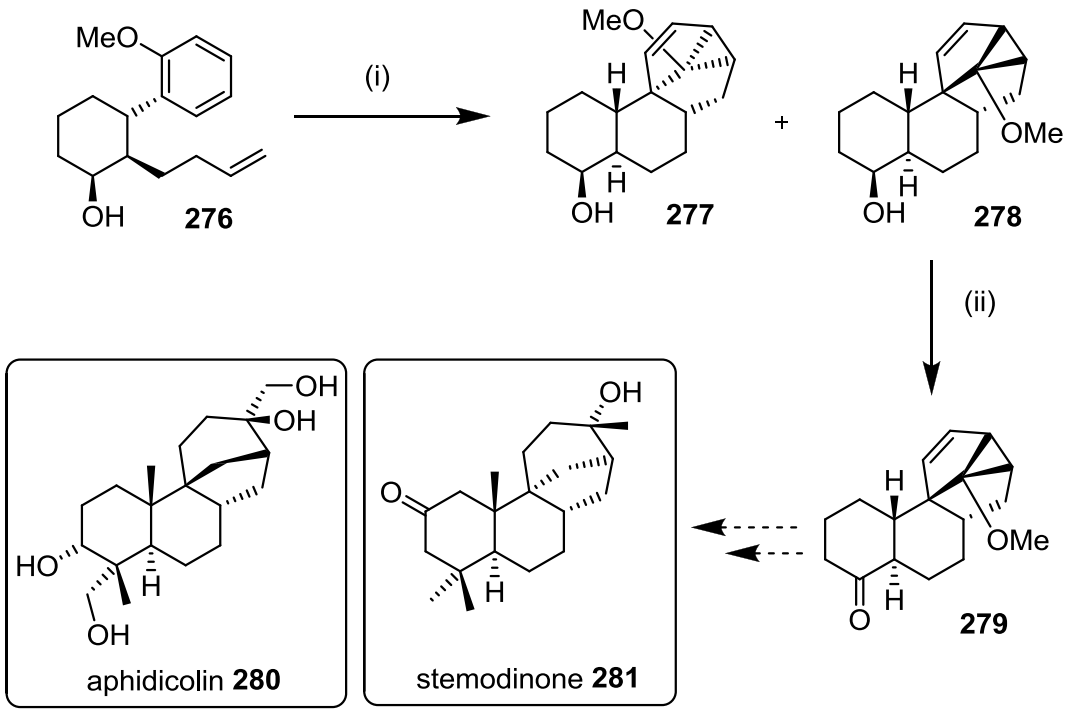
The synthesis of the arenyl-diene photosubstrate **270** proceeded in a straightforward manner starting from the Grignard reaction of *o*-tolualdehyde and pentenyl magnesium bromide in 81% yield. Alkylation of the resultant alcohol (**273**), then direct irradiation of the ether photosubstrate **270** with 254 nm UV light led to the linear *meta* adduct **274** as the major product, although it also contained the angular isomer in a ratio of 3.3:1.

Decades of experimentation has shown a tether containing three carbons between the arenyl and alkene portions is favoured over a four-carbon version for the cycloaddition due to entropy considerations.[10] Therefore the singular linear adduct obtained was what we would expect as competition between the two chains was no longer a relevant issue. Separation of the linear and angular adducts would likely be possible with a higher resolution method like HPLC being employed, but such a facility was not available. Despite the lack of separation, the transformation to the fenestrane should not have been affected because of the capability of the linear and angular isomers to undergo interconversion as proven earlier. Therefore we conducted a direct irradiation of the mixed adducts with 254 nm UV light under conditions of triplet sensitization with acetophenone (120 mol %) for 6 hours

There was significant decomposition during the course of the reaction, and only 11% of a mixture of the linear and angular *meta* photoadducts could be recovered from the crude residue. However, in this case the angular isomer **275** was found to be the major component in a ratio of 5:1.

It would seem that the longer alkene tether in the linear adduct **274** resulted in exclusion of the second [3+2] cycloaddition process. The extra degrees of freedom afforded by the additional methylene, would seem to mean that adoption of the appropriate conformation for the fenestrane occurs too infrequently by comparison to the interconversion between the two isomeric forms and other decomposition processes.

Potentially in the future the fenestrane formation might be induced if the alkene chain were constrained so that it adopted the correct conformation more readily, for instance, by making the tether part of a cyclopentane or hexane ring (Scheme 4.4.3).



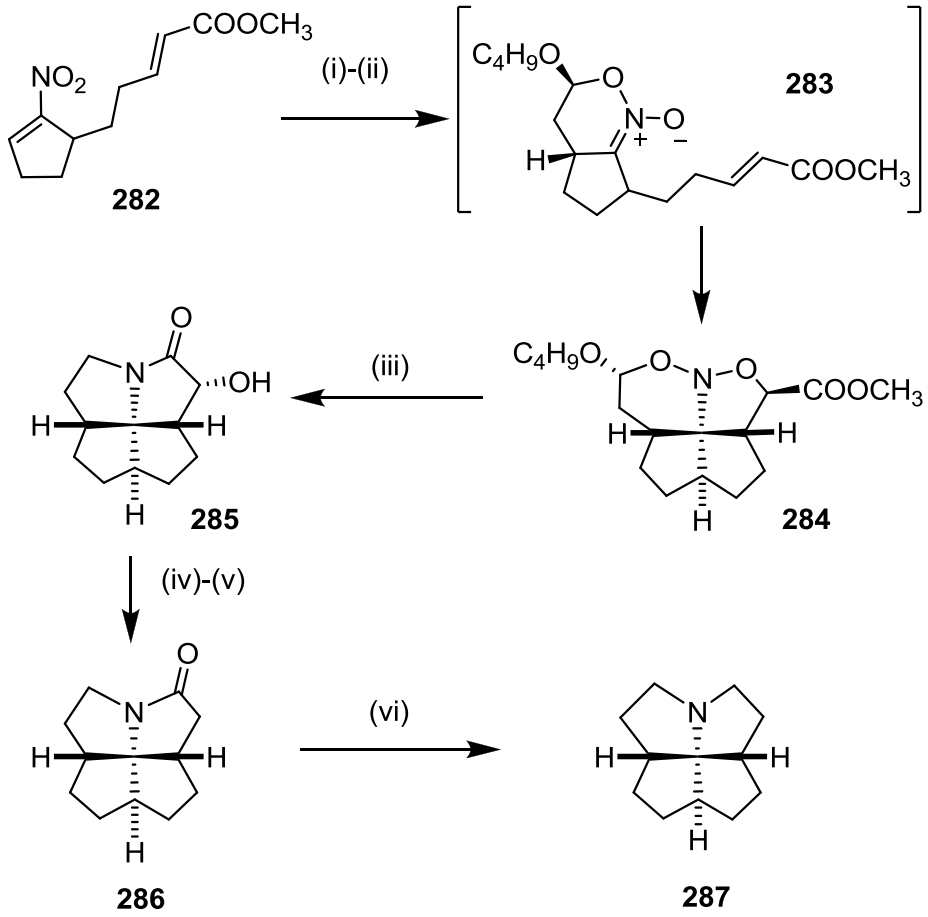
Reagents & conditions: (i) hν (254 nm), cyclohexane, 90% (**277**:**278**, 1.0:1.2); (ii) Dess–Martin periodinane, CH_2Cl_2, 81%.

Scheme 4.4.3: Intramolecular photochemical cycloaddition route toward aphidicolin and stemodinone -

This technique has proven a valid method for improving the efficiency of *meta* photocycloadditions for four-carbon tethers, as shown by Russell, in his work toward the polycyclic ring systems of aphidicolin and stemodinone (Scheme 4.4.3).[115]

4.11 Synthesis of a novel azafenestrane.

In another effort to prove the potential of our newly discovered reaction it was decided to attempt the synthesis of an azafenestrane to further increase the types of useful functionality that could be incorporated in fenestranes using this reaction. Azafenestranes are rare with the best examples arising from the work of Scott Denmark,[116] who reported the first synthesis of *cis, cis, cis, cis*-[5.5.5.5]-1-azafenestranes **285-287**, which were formed *via* a [4+2]/[3+2] tandem cycloaddition from the nitroalkene **282**.[116a]

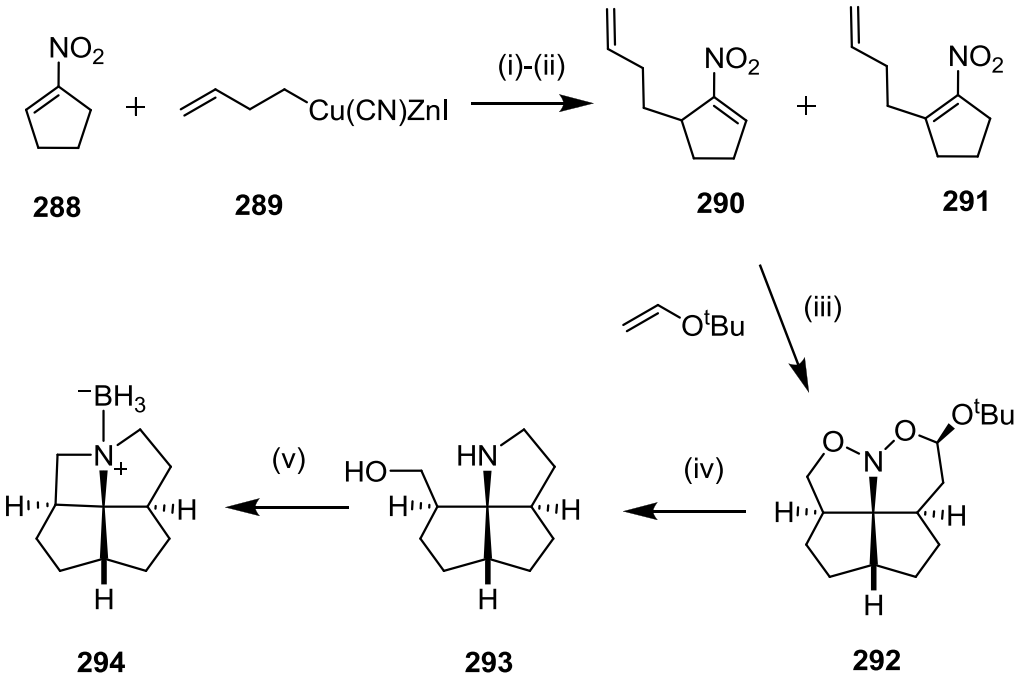


Reagents & conditions: (i) $Al(CH_3)_3$; (ii) $CH_2{=}CHOC_4H_9$; (iii) H_2, Raney-Ni; (iv) C_6H_5OCSCl, pyridine/DMAP; (v) *n*-Bu_3SnH, AIBN; (vi) $LiAlH_4$, THF, reflux

Scheme 4.4.4: Denmark synthesis of an azafenestrane.

While the tandem cycloaddition itself was a concise and rapid method for making the core structure, the formation of the needed nitroalkene was problematic, with the entire synthesis being a long 18 steps, with an overall yield of 0.02%.

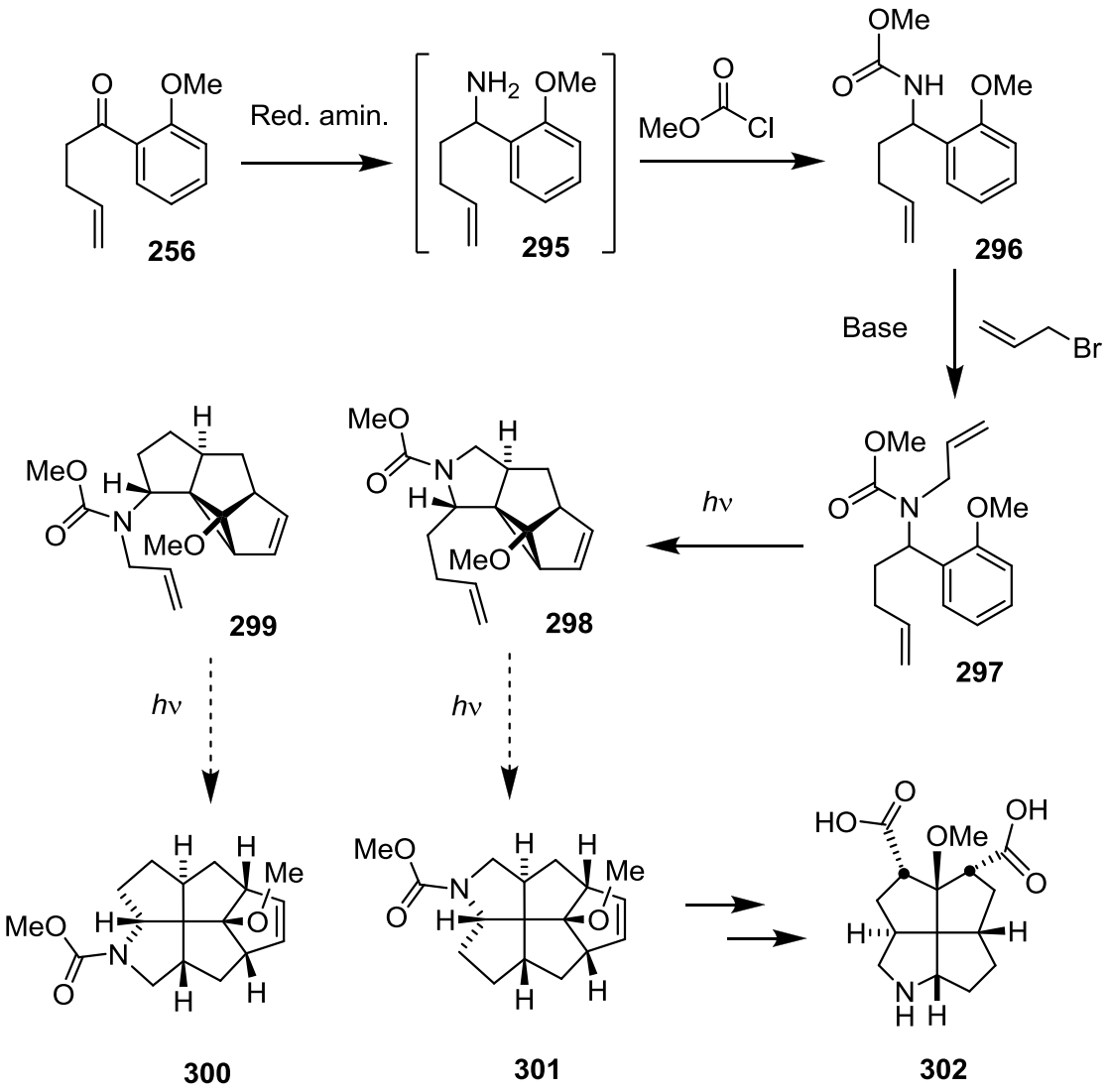
Dissatisfied by the length of the route they originally performed and the rather modest alteration of the bond angles at the central carbon atom, the same group worked on a modification starting from the simple nitroalkene **288**. In this case they created all *cis*-[5.5.5.4] azafenestrane **294**, *via* a route that was only 5 steps in length with an overall yield of 26% (Scheme 4.4.5).[116b]



Reagents & conditions: (i) THF, 0 °C, 1 hr, then PhSeBr, 0 °C→RT, 1 hr; (ii) H_2O_2, THF, 0 °C→RT, 30 min (78% from **288**; **290:291,** 2:1); (iii) $AlMe_3$, CH_2Cl_2, -78 °C, 1 hr, (67%); (iv) H_2 (26 atm), Raney-Ni, 10% H_2O-saturated EtOAc in EtOAc (0.25M), 20 hr, (85%); (v) PPh_3, DIAD, CH_2Cl_2, 0 °C, 40 mins, then BH_3·THF, -78 °C→RT, 1 hr (87%).

Scheme 4.4.5: Synthesis of *cis*, *cis*, *cis*, *cis*-[5.5.5.4]-1-azafenestrane **294**.

From our previous investigations into the double [3+2] photocycloaddition, we could envisage a synthetic route to an azafenestrane structure **301** from the previously synthesised simple aromatic ketone **256** (Scheme 4.4.6).



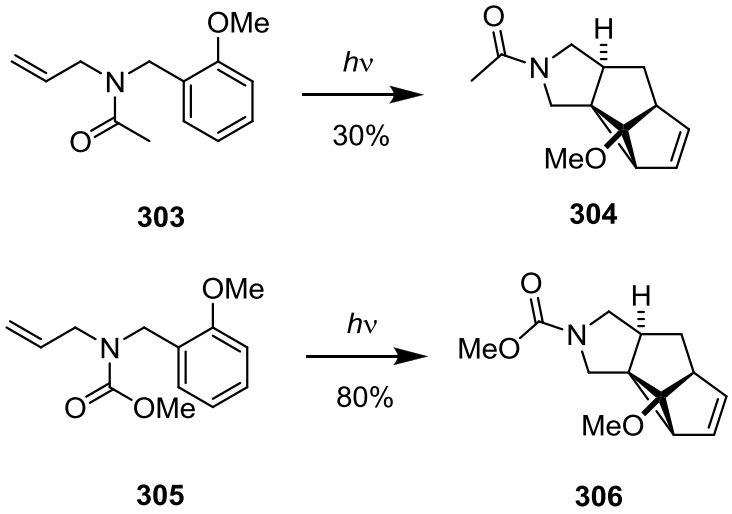
Scheme 4.4.6: Proposed synthetic route to an azafenestrane potentially as a partial route to a conformationally constrained amino acid such as **302**.

The first cycloaddition step would give us a possibility of two linear *meta* adducts (**298** and **299**), the more likely of which being where the shorter nitrogen based tether ends up in the core tetracylic structure. This would then lead to the azafenestrane **301** *via* a secondary [3+2] addition of the all-carbon tether.

Future manipulation of this novel azafenestrane could eventually lead to the formation of new compounds with important biological properties such as the structurally complex and conformationally constrained amino acid (**302**).

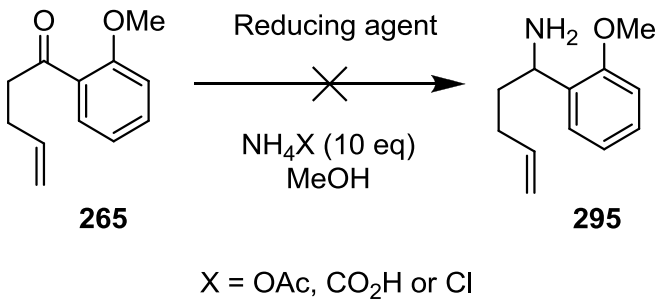
It should be noted that nitrogen photochemistry is often problematic. The intramolecular arene-alkene *meta* photocycloaddition arises from the ^1S state of the benzene ring, however when an amine nitrogen is present in the substrate there is a competing effect of electron transfer from the amine lone pair to the excited benzene.[117] This naturally retards *meta* photocycloaddition reactions, leading to photochemical decomposition.

This problem can be overcome provided that the nitrogen is protected with a suitable electron-withdrawing group. Gilbert and Blakemore, reported that the use of a *N*-carbomethoxy group led to significant *meta* photocycloaddition and that it performed better than the comparable N-acetyl protected compound (Scheme 4.4.7).[117]



Scheme 4.4.7: Intramolecular *meta* photocycloaddition of 3-benzylazoprop-1-enes.

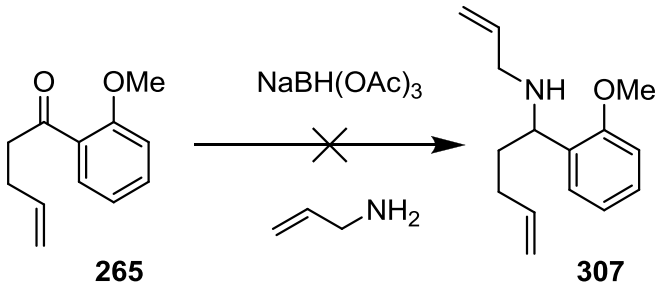
Our initial attempts to make the amine **295**, through direct reductive amination methods[118] were ineffective. Both sodium borohydride and lithium aluminium hydride gave disappointing results.



Scheme 4.4.8: Failed reductive amination of aromatic ketone **265**.

Often these reactions would lead to no reduction or the undesired alcohol. Clearly neither reagent was selective enough to give the desired result, so we switched our focus to using sodium triacetoxyborohydride,[119] which can be made *in situ* from sodium borohydride and acetic acid and has been shown to perform selective reductive aminations as an alternative to the highly toxic sodium cyanoborohydride, which we wished to avoid. These two reagents affect the reduction of the intermediate imine with far greater selectivity than regular hydride reducing agents.

Replacement with triacetoxyborohydride did appear to yield favourable results on a small scale, but this could not be scaled up to usable amounts of material. This failure prompted us to change the source of the nitrogen to allylamine, and attempt the reductive amination below using a method devised by Abdel-Majid *et al*..[118]



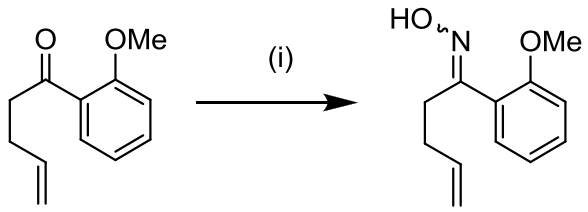
Reagents & conditions: $NaBH(OAc)_3$ (1.5 eq.), allylamine (5.0-10.0 eq.), solvent, <5%

Scheme 4.4.9: Failed reductive amination to form an allyl amine **307**.

Such a change would also have allowed us to shorten the synthetic route, however despite alterations to the number of equivalents of reducing agent, amine and the solvent used (Et_2O,

EtOAc, $CHCl_3$, CH_2Cl_2, THF, MeCN and cyclohexane), the reduction was inefficient and while in some cases the amine may have been formed, the yield was inconsequential.

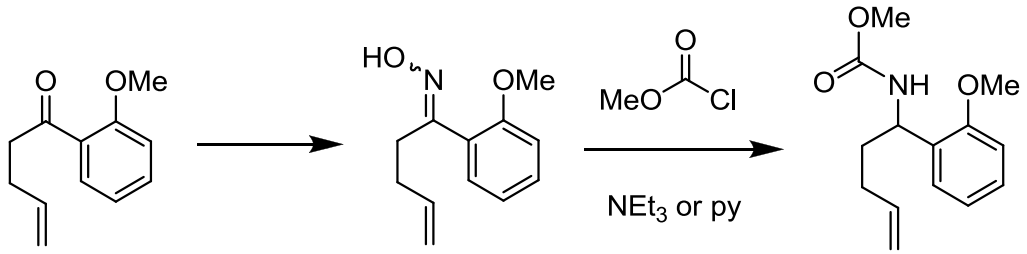
With reductive amination proving difficult we attempted to install the nitrogen by other means, *via* the conversion of ketone **256** to its oxime **105** and subsequent reduction to the required primary amine **295**.



265 **308**

Reagents & conditions: (i) $NH_2OH.HCl$ (3.1 eq.), NaOH (5M, 9.1 eq.), EtOH, reflux, 15 mins, 98%
Scheme 4.5.0: Synthesis of oxime **308**.

Aromatic ketone **265** was rapidly converted to its corresponding oxime in near quantitative yield by heating at reflux in ethanol with 5M sodium hydroxide and hydroxylamine hydrochloride. The product was a crystalline solid, but the yield was improved by extraction with Et_2O in preference to recrystallization from a petrol-EtOAc mixture (from 84% to 98%).



256 **308** **296**

Entry	Reducing agent (eq.)	Scale (g)	Solvent	Temp. (°C)	Time (hrs)	Yield (%)
41[120]	$NaBH_4$ (2.0)	2.0	MeOH	0	24	25%*
42	$LiAlH_4$ (1.1)	0.2	Et_2O	RT	0.5	0%
43	$LiAlH_4$ (1.1)	0.2	THF	RT	24	0%
44	Zinc dust‡ (2.0)	2.0	AcOH†	60	48	<5%
45	Zinc dust (10)	3.0	AcOH	RT	72	24%
46	Zinc dust (10)	4.0	AcOH	RT	72	23%
47[121a]	Zinc dust (2.0), NH_4Cl (4.0)	1.0	MeOH	Reflux	16	SM
48[121b]	Mg (4.0), NH_4CO_2H (3.0)	1.0	MeOH	Reflux	16	SM
49	Zinc dust (10)	0.5	HCl	RT	16	49%
50	$NaBH_4$ (4.0)	0.2	AcOH	RT	24	SM
51	Zinc dust, $NaBH_4$ (4.0)	0.25	AcOH	RT	24	Trace
52	$NaBH_4$ (2.0), NH_4CO_2H (10.0)	1.0	MeOH	RT	72	SM
53	$NaBH_4$ (2.0), NH_4OAc (10.0)	1.0	MeOH	RT	72	SM + (**257**)

* = Unknown product; ǂ = Zinc dust was pre-activated by washing with a 5% solution of HCl † = glacial acetic acid used throughout.

Scheme 4.5.1 and **Table 11:** Synthesis of carbamate **296**.

The reduction of oxime **308** was conducted to afford the free amine, which after an acid-base extraction, was used crude without further purification. Addition of methyl chloroformate (1.1

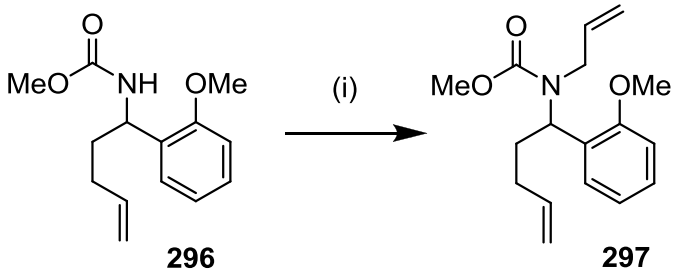
eq.) and an appropriate base (either triethylamine or pyridine) could then hopefully furnish the aromatic carbamate **296.**[122]

A series of reducing agents were tested starting with, sodium borohydride which had no effect on the oxime, yielding 25% of product where the hydroxyl group of the oxime appeared to be protected instead (entry 41). Use of lithium aluminium hydride also resulted in no usable amine product (entry 42).

Zinc dust in acidic media has been successfully used in the literature for the reduction of oximes and also in reductive amination reactions.[10a] Mixtures of zinc in glacial acetic acid gave low yields of desired compound **296** (entries 45 and 46), however the procedure proved unreliable on subsequent attempts, often with ketone **256** appearing as a major product. Zinc-HCl gave a much improved result on a small scale (entry 49), however attempted scaling up led to no reaction. Heating the mixture at reflux resulted in decomposition *via* hydrogenation of the alkene bond.

There were other possible ways to improve the synthetic route, for instance; catalytic hydrogenation is commonly used to perform reductive amination *via* platinum, palladium or nickel catalysts.[123] However, these were not attractive options in this particular case because they commonly result in the destruction of sensitive functionality particularly carbon-carbon multiple bonds.

DIBAL[124] has been employed for the reduction of oximes along with many other more exotic reagents which are also available including $Zn(BH_4)_2/ZnCl_2$,[125] borane-pyridine[126] and $NaBH_4/Mg(ClO_4)_2$.[127] There is also the possibility that optimisation or modification[128] of the conditions for zinc-acetic acid or zinc-HCl may have given the desired result in better yield however it was decided at the time to focus on the forward reactions.



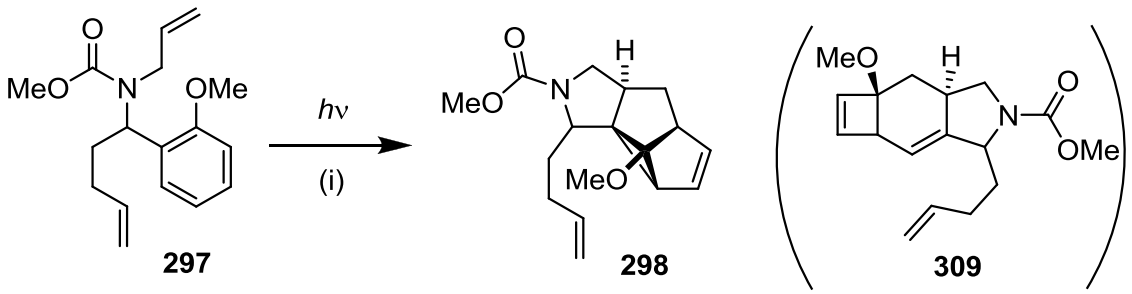
296 **297**

Reagents & conditions: (i) NaH (3 eq.), allyl bromide (2.5 eq.), DMF, 83%.

Scheme 4.5.2: Alkylation of carbamate **296** to yield photosubstrate **297**.

Having formed a small amount of the carbamate **296,** alkylation of the nitrogen proved relatively straightforward, after limited optimisation of reagents, using a method adapted from the work of Hunt, Laurent and Moody.[129] Dry DMF as the solvent proved crucial to the reaction with other solvents such as CH_2Cl_2 yielding only a maximum of 26% of the photosubstrate **297**. This is not entirely surprising as it is known that NaH can combine with DMF to generate $NaNMe_2$ in situ, which is a more effective base for the deprotonation of carbamates[130] than NaH alone.

Photosubstrate **297** was directly irradiated using 254 nm UV light (16 W Hg vapour lamp) until full consumption to give a complex mixture of products. Two major isomers were isolated from the crude reaction mixture (Scheme 4.5.3), with several other isomers observed that could not be satisfactorily purified and characterised.



297 **298** **309**

Reagents & conditions: 1.30 g, hν (254 nm), cyclohexane, 2 hr 50 mins, 16% (**298**); <20% (**309**).

Scheme 4.5.3: Irradiation of photosubstrate **297**.

Linear *meta* adduct **298** could be isolated in yields up to 16%, however this was highly variable due to co-elution of the *ortho* derived adduct **309** and also the lability of both adducts toward the silica used for the chromatography.

It was interesting to note that only the alkene tethered through nitrogen underwent cycloaddition to any significant degree, despite both alkenes of the arenyl-diene photosubstrate **297** being attached by three-atom tethers. A potential reason for this may have been the partial sp^2-hybridization of the protected nitrogen caused by amide resonance (Figure 4.2).

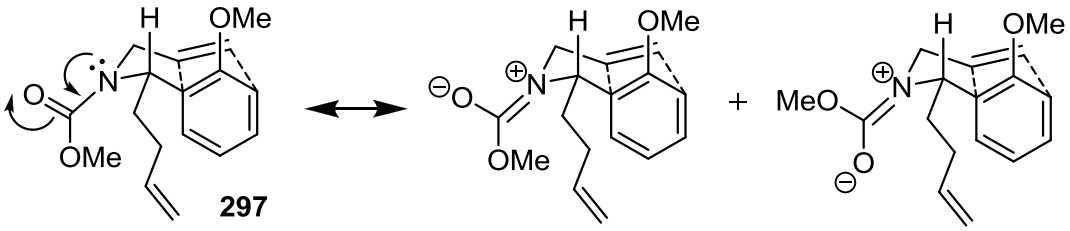
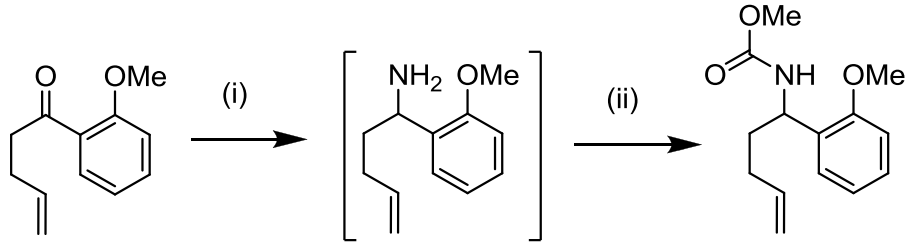


Figure 4.2: Amide resonance of the photosubstrate **297**.

While this would have the negative effect of increasing the C-N-C bond angle, it also results in rotamers where there is no rotation about the nitrogen atom. Therefore, the freedom of the nitrogen tethered alkene is limited, making it more likely to interact with the excited aromatic ring than unconstrained all-carbon tether. An additional drawback however, was that the existence of rotamers increased the complexity of the NMR spectra. In particular, this made the impure *ortho* derived adduct **309** impossible to assign with an acceptable accuracy.

Taking through the linear *meta* adduct synthesised in the previous step, a second direct irradiation under 254 nm UV light was conducted in cyclohexane using a 16 W lamp. Unfortunately, this resulted in only decomposition and gave nothing resembling the desired azafenestrane **301**, after 8 hours.

Unwilling to give up on the synthesis of such a vital product, this project was handed over to a 4th year MChem project student, Timothy Read who proceeded to investigate ways to improve the synthetic route and make the azafenestrane under my supervision.



256 **295** **296**

Reagents & conditions: (i) $NaBH_3CN$ (0.7 eq.), NH_4OAc (10 eq.), abs. MeOH; (ii) $CH_3OC(O)Cl$ (1.1 eq.), NEt_3 (1.2 eq.), Et_2O, (60% over two steps).

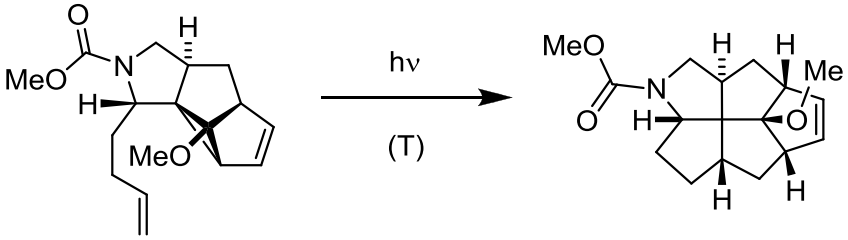
Scheme 4.5.4: Improved synthetic route to carbamate **296**

We decided to accept that sodium cyanoborohydride, whose overt toxicity we had hoped to avoid in our quest to provide a greener route, was the best option for the reductive amination step. As such the aromatic ketone **256** was reliably reduced to the amine, over a period of 3 days.[131]

The fact that the sodium borohydride did not produce any reductive amination under the exact same conditions suggests that sodium cyanoborohydride is more selective towards reductive amination, which has been previously described.[132] The reactivity of sodium cyanoborohydride toward aldehydes or ketones is not particularly good outside of the pH range 3-4. In the generally neutral conditions found in this reaction, reduction to the alcohol is extremely slow, thus allowing the slow coordination of the ammonium species to occur on the ketone leading to the imine intermediate. This is then reduced by the cyanoborohydride to give the amine.

After an acid-base work up, methyl chloroformate was added in the presence of triethylamine to give a 60% yield of the carbamate over two steps, a significant improvement over the previous best synthesis from the oxime and also easily reproducible. Alkylation of the carbamate

nitrogen and direct irradiation of arenyl-diene photosubstrate **297** proceeded as before (see Scheme 4.5.2), allowing repetition of the secondary irradiation (Scheme 4.5.5, Table 12).



298 **301**

Entry	Solvent	acetophenone (mol %)	Lamp (W)	Time (hr)	Yield (%)
54	cyclohexane	200	6	2.25	<13
55	MeCN	120	6	1.15	10

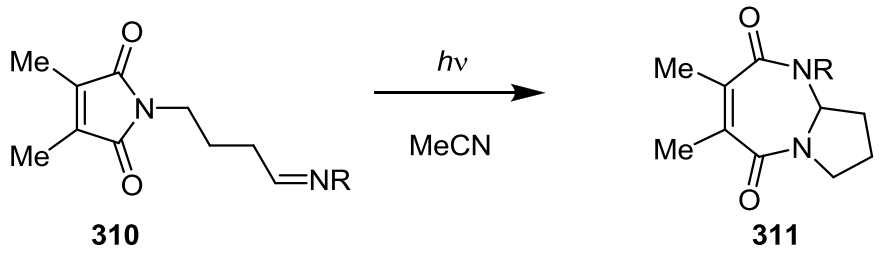
Scheme 4.5.5 and **Table 12**: Triplet sensitized formation of azafenestrane **301**. Note this was conducted with a 6 W Hg vapour lamp.

Acetophenone was employed to promote a triplet sensitized [3+2] addition resulting in a 13% yield of the azafenestrane **301** in cyclohexane (entry 54), although this did contain minor impurities. Repetition in MeCN resulted in a slight reduction of the yield to 10%, although the available linear *meta* adduct used was only about 80% pure. The most worthwhile advantage with MeCN was that of a significantly cleaner process thus allowing the isolation of a pure sample of the novel azafenestrane for full characterisation.

4.12 Attempted double [3+2] photocycloaddition reaction involving a C=N double bond.

The previous section showed us that it was possible to use the double [3+2] photocycloaddition to construct a fenestrane containing a nitrogen atom in the core structure. This synthesis involved the formation of carbon-carbon σ bonds in order to make the relevant structure and while this is certainly the primary goal of most organic synthesis, preparation of a wider variety of heterocycles would be possible if the double [3+2] photocycloaddition reaction could be additionally applied to the synthesis of carbon-heteroatom bonds.

To make a carbon-nitrogen bond, we would need to employ the nitrogen double bond equivalent to an alkene, such as an imine or oxime as the ground state partner to the excited arene. The photochemistry of the carbon-nitrogen double bond is limited, with cycloadditions in particular being relatively rare in comparison to carbon-carbon double bonds.[133] However, Booker-Milburn[100] of Bristol University recently provided the first example of a higher order [5+2] photocycloaddition to maleimides (**311**) using an oxime or hydrazone in exchange for an alkene as the ground state partner.

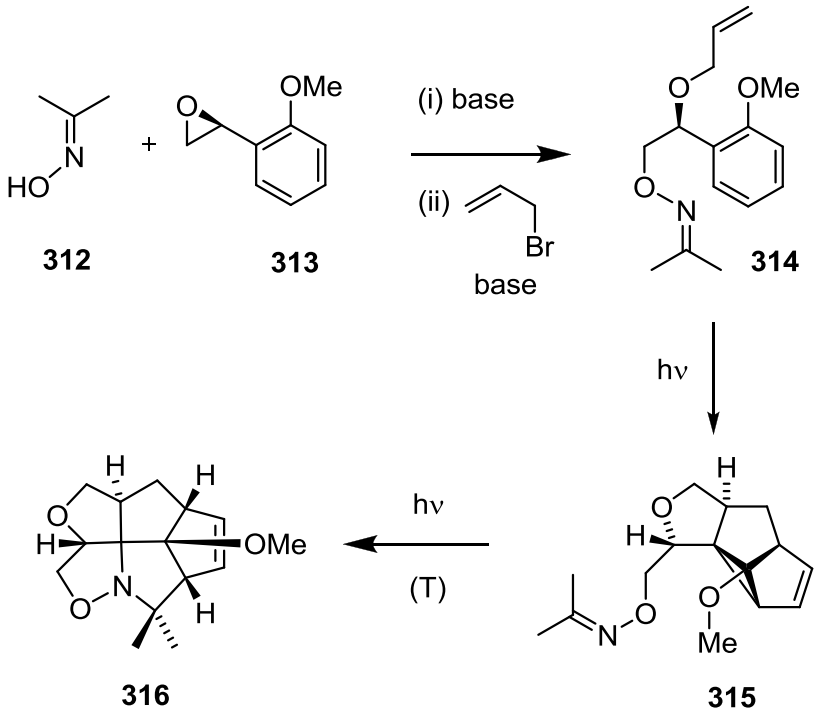


310 **311**

R = OH (78%); OMe (78%); O^{t}Bu (69%); NHTs (60%); NHCOPh (48%)

Scheme 4.5.6: Examples of Booker-Milburn's [5+2] photocycloadditions.

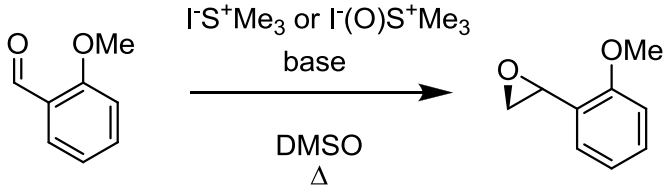
Taking note of this observation we postulated that it might be possible to generate an arenyl-diene photosubstrate **314** where one of the alkenes is exchanged for an oxime. This would then undergo the double [3+2] process proceeding through linear *meta* adduct **315**, to produce a novel poly-heterocyclic fenestrane **316** (Scheme 4.5.7).



Scheme 4.5.7: Proposed synthesis of a novel fenestrane **316** derived from an oxime

The photosubstrate **314** would be prepared by reacting the hydroxy imine **312** with aromatic epoxide **313** derived from *o*-anisaldehyde.[134] The subsequent isolated alcohol would then be alkylated *via* the previously used phase-transfer methods. The *meta* photocycloaddition of an oxime to an aromatic ring is not a known process[10] so the tether containing the alkene should be exclusively incorporated in the core structure to afford the linear *meta* adduct **315**. Secondary irradiation *via* a triplet-sensitised method would hopefully lead to the synthesis of a novel poly-heterocyclic fenestrane **316**.

The oxime chosen for this reaction was that derived from acetone, which could be purchased from commercial sources. However the desired epoxide had to be first synthesised from *o*-anisaldehyde *via* a sulfur ylide, in a process commonly referred to as the Corey-Chaykovsky reaction.[135]



168 **313**

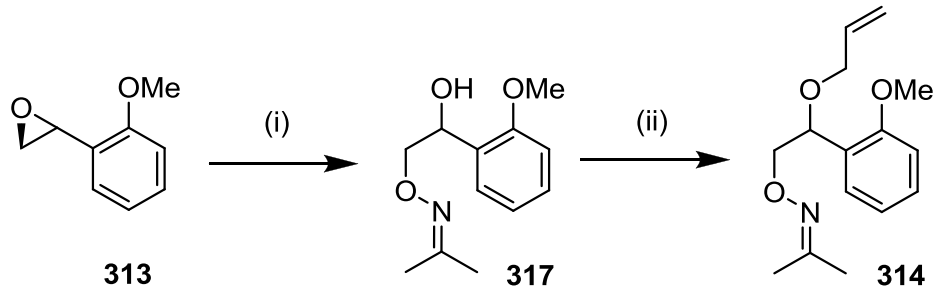
Entry	Scale (g)	Base (eq.)	Ylide precursor	DMSO (ml)	Temp. (°C)	Time (hr)	Crude yield (%)
56	1	KOH (3 eq.)	$I^-S^+Me_3$ (1.2 eq.)	5	80	1	79
57	2	KOH (3 eq.)	$I^-S^+Me_3$ (1.2 eq.)	10	80	1	76
58	4	KOH (3 eq.)	$I^-S^+Me_3$ (1.2 eq.)	20	80	2	polymer
59	4	KOH (2 eq.)	$I^-S^+Me_3$ (1.2 eq.)	20	80	2	polymer
60	4	KOH (3 eq.)	$I^-S^+Me_3$ (1.2 eq.)	40	80	3	polymer
61	4	KOH (3 eq.)	$I^-(O)S^+Me_3$ (1.2 eq.)	30	80	1	36
62	2	KOH (3 eq.)	$I^-(O)S^+Me_3$ (1.2 eq.)	10	60	2.5	polymer
63	2.7	NaH (1.2 eq.)	$I^-(O)S^+Me_3$ (1.2 eq.)	25	50	1	60
64	4	NaH (1.2 eq.)	$I^-(O)S^+Me_3$ (1.2 eq.)	35	50	2	66

Scheme 4.5.8 and **Table 13**: Attempts at the synthesis of epoxide **313**.

Initial attempts using KOH and trimethylsulfonium iodide occurred with good conversion (entries 56 and 57), yielding a reasonably pure epoxide that was used without further purification due to the epoxides tendency to decompose on silica. However, scaling up the reaction resulted in a significant amount of polymerisation (entries 58-60).

Switching to trimethylsulfoxonium iodide initially allowed the reaction to occur on the larger scale (entry 61), but subsequent repetition at a higher concentration resulted in total polymerisation of the reaction mixture (entry 62).

Eventually, the most reliable method found to work at a reasonable scale involved altering the base from KOH to NaH as used in Corey and Chaykovsky's original seminal paper.[135]

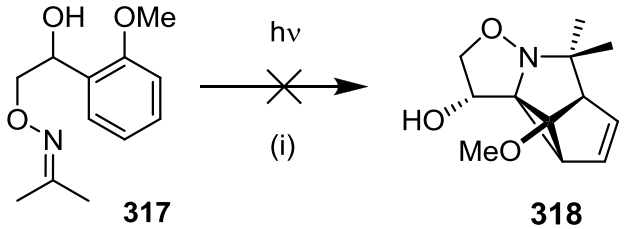


Reagents & conditions: (i) acetone oxime (1.1 eq.), KOH (2 eq.), DMSO, 80 °C for 1 hr; (ii) allyl bromide (5 eq.), NaOH (50%), TBAHS (0.5 eq.), CH_2Cl_2, 0 °C → RT, 24 hrs (75%, two steps).

Scheme 4.5.9: Synthesis of oxime derived photosubstrate **314**.

The remaining two steps to make the photosubstrate proceeded in good yield and were often conducted in tandem. The S_N2 ring opening of the epoxide by deprotonation of acetone oxime usually occurred in excellent yield, although isolation by flash chromatography proved to be difficult, so the alcohol was generally carried through crude in order to preserve yield. The final ether linkage was achieved by phase transfer conditions using TBAHS, as in the previous ether photosubstrate work to give a yield of up to 75% over two steps.

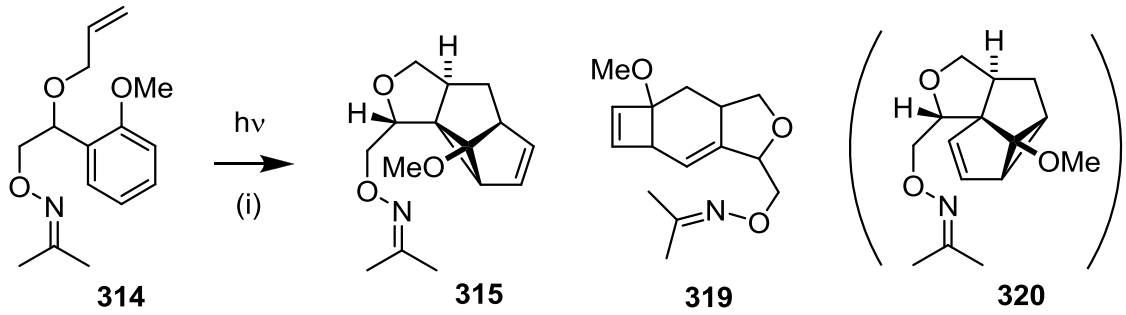
As mentioned there have been no *meta* photocycloaddition adducts reported from the addition of an oxime, so we took this opportunity to irradiate a purified amount of the intermediate alcohol **317**, which contained only the oxime tether (Scheme 4.6.0).



Reagents & conditions: hν (254 nm), cyclohexane, 8hrs, 0%.

Scheme 4.6.0: Attempted formation of an oxime derived *meta* photocycloadduct **318**.

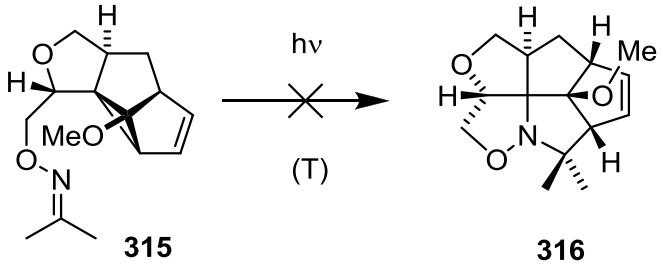
As expected direct irradiation with 254 nm UV light showed no signs of any *meta* addition taking place, only decomposition, thus remaining consistent with the previously observed behaviour of oximes toward benzene derivatives under photolytic conditions.



Reagents & conditions: 1.00 g, hν (254 nm), MeCN, 4 hrs, 19% (**315**), 16% (**319**).

Scheme 4.6.1: Irradiation of oxime derived photosubstrate **314**.

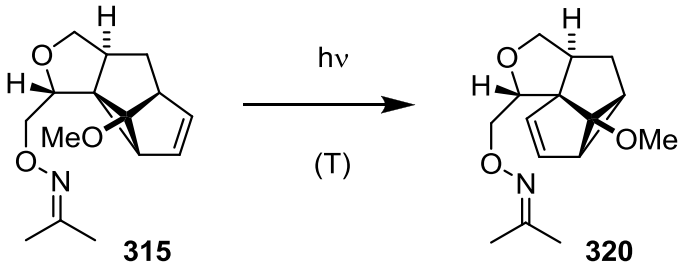
Direct irradiation of photosubstrate **314** using 254 nm UV light (6 W Hg vapour lamp) led to the formation of the linear *meta* photocycloadduct **315** and the *ortho* derived photocycloadduct **319** as the two major products in yields of 19 and 16% respectively (Scheme 4.6.1). A trace amount of an angular *meta* photocycloadduct (**320**) was also observed in the ^{1}H NMR spectrum of the crude residue, but could not be isolated in a satisfactorily pure form.



Reagents & conditions: 40 mg, hν (254 nm), acetophenone (150 mol %), cyclohexane, 3 hrs, 0%

Scheme 4.6.2: Triplet sensitized irradiation of linear *meta* adduct **315** in cyclohexane.

We proceeded onto the second irradiation of the linear *meta* adduct **315**, which was performed in both cyclohexane and MeCN under triplet sensitized conditions using acetophenone (Schemes 4.6.2 and 4.6.3).



Reagents & conditions: 30 mg, hν (254 nm), acetophenone (150 mol %), MeCN, 1 hr 10 mins, 40%

Scheme 4.6.3: Triplet sensitized irradiation of linear *meta* adduct **315** in MeCN.

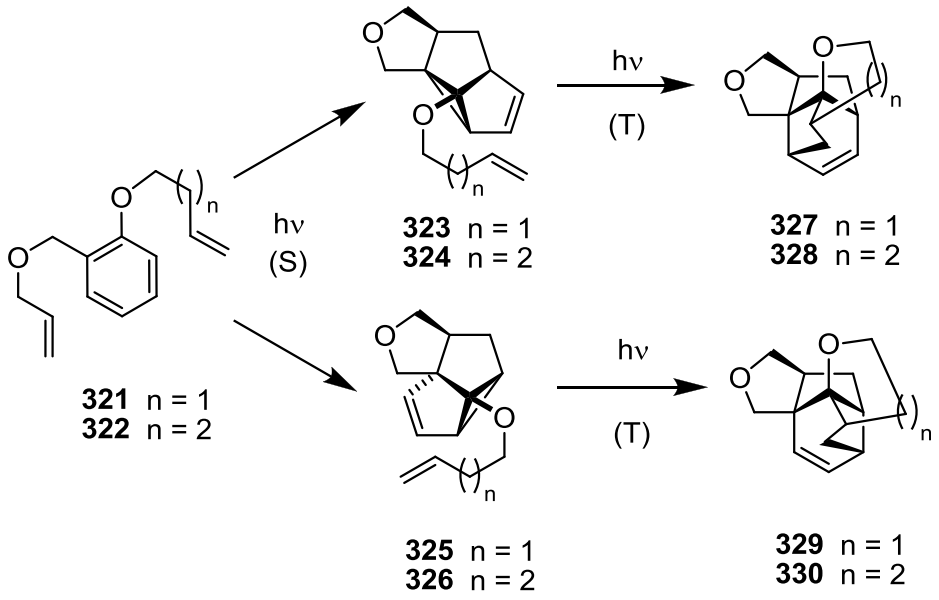
Unfortunately in both reactions, the highly substituted compound did not result in the formation of the desired poly-heterocyclic fenestrane **316**. In cyclohexane the reaction led to large amounts of decomposition *via* polymerisation, whereas in MeCN the linear adduct underwent photo-equilibration by the vinylcyclopropane-cyclopentene rearrangement to the angular isomer **320**, which was returned in a 40% yield.

5 Attempted synthesis of a "criss-cross" double [3+2] photocycloadduct.

5.1 Introduction.

While we have had much success in forming a single type of fenestrane core structure we wished to continue exploring the possibilities of what the double [3+2] photocycloaddition might be capable. Conceivably if an addition could be performed across the external cyclopropane bond of a linear *meta* adduct, then perhaps the same might be true for the internal bond. In this case an alkene would need to be suitably positioned on the upper or *exo* face of the *meta* adduct in order to interact with the formed diradical species and also compete against the photo-equilibration between the linear and angular isomers.

The overall effect would be of a double *meta* photocycloaddition reaction taking place with the two alkenes sandwiching the former aromatic ring from above and beneath in a "criss-cross" fashion; a concept first proposed as a possible identity for dioxafenestrane **4** earlier in this work (see page 47).

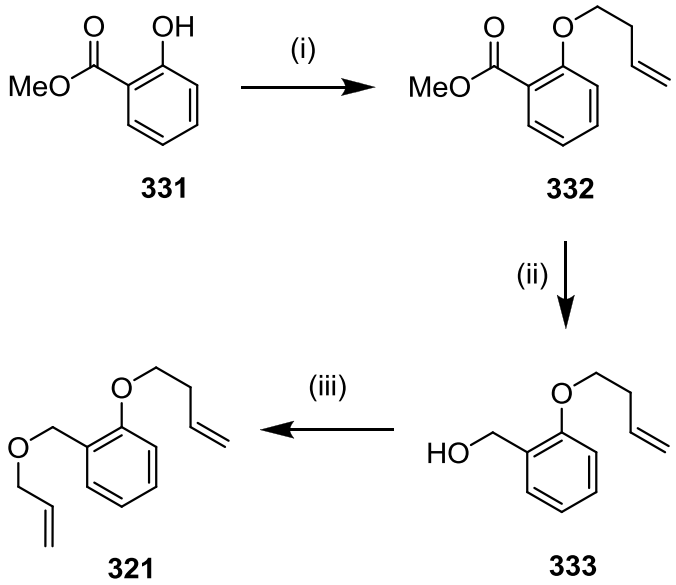


Scheme 5.1: Proposed route toward a novel "criss-cross" double [3+2] photocycloadducts.

In order to make this happen, the two tethered alkenes would be attached from different points on the aromatic ring (Scheme 5.1). One tether would be directly linked to the arene through oxygen, so that its strong electron-donating properties would control the initial *meta* photocycloaddition of the other tether across the ring. The alkoxy chain that drove the initial addition would now be left free and on the *exo* face of the photoadduct, and could be inserted into the internal cyclopropane bond of either regioisomer during a second triplet-sensitised irradiation to afford a criss-cross double *meta* photocycloadduct such as **327-330**.

5.2 Irradiation of butenyl tether photosubstrate 321.

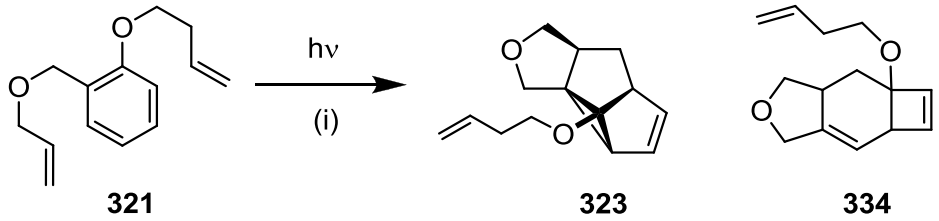
Arenyl-diene photosubstrate **321** was prepared starting from methyl salicylate **331** (oil of wintergreen). The phenolic oxygen was alkylated with butenyl bromide by heating at reflux with K_2CO_3 in butan-2-one, following the procedure of Al-Qaradawi, Cosstick and Gilbert,[14] which resulted in a fairly poor 34% yield.



Reagents & conditions: (i) 4-bromobutene (1 eq.), anhydrous K_2CO_3 (5 eq.), butan-2-one, reflux, 7 days, 34%; (ii) DIBAL (1M, 3 eq.), Et_2O, 0 ºC (84%); (iii) allyl bromide (5 eq.), 50% NaOH (30 eq.), TBAHS (1 eq.), CH_2Cl_2, 0 °C → RT, 24 hrs (96%);

Scheme 5.2: Synthesis of arenyl-diene photosubstrate **321**.

The reduction of the ester was first attempted using $NaBH_4$ in boiling MeOH giving a 21% yield of the alcohol, which then was subsequently improved to 69% by using DME as a higher boiling co-solvent.[136] Further improvement was achieved when a 1M solution of DIBAL was used, resulting in good yields of up to 84% when stirred at 0 °C over several hours. The second tethered alkenyl chain was then attached by converting the primary alcohol to the ether under phase-transfer conditions, in a near quantitative fashion.

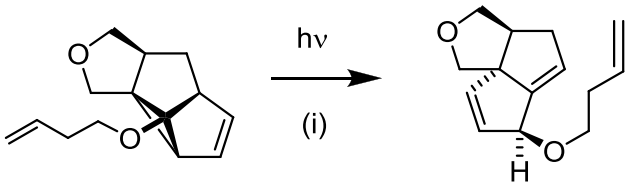


321 **323** **334**

Reagents & conditions: (i) 2.10 g, hν (254 nm), cyclohexane, 16 hrs, 13% and 14%.

Scheme 5.3: Irradiation of photosubstrate **321**.

The synthesised arenyl-diene photosubstrate **321**, was then subjected to irradiation with 254 nm UV light until total consumption, which afforded two major products, the linear *meta* adduct **323** and the *ortho* product **334**, in a ratio of approximately 1:1, with yields of 13% and 14% obtained after flash column chromatography.



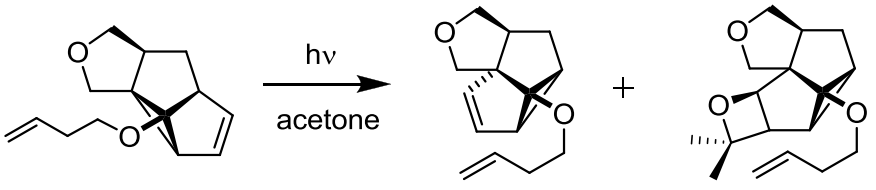
323 **335**

Reagents & conditions: 100 mg, hν (254 nm), cyclohexane, 48 hrs, 12%

Scheme 5.4: Irradiation of linear *meta* adduct **323**.

Secondary irradiation of the linear *meta* adduct **323** without triplet sensitization in cyclohexane led to an observed conversion to the angular *meta* adduct **335**, then through to the oxasilphinene product derived from the 1,2-translocation of the oxygen linked alkenyl chain. This was isolated in a 12% yield, alongside other decomposition adducts, which could not be positively identified.

Triplet sensitized irradiation was attempted in cyclohexane with acetophenone (150 mol %), but this only resulted in a limited conversion from the linear to the angular isomer **336** with no sign of any criss-cross or fenestrane type adducts even after 72 hrs irradiation time.



323 **325** **336**

Reagents & conditions: 50 mg scale; hν (254 nm), acetone, 3 hrs, 18% (**325**), 24% (**336**).

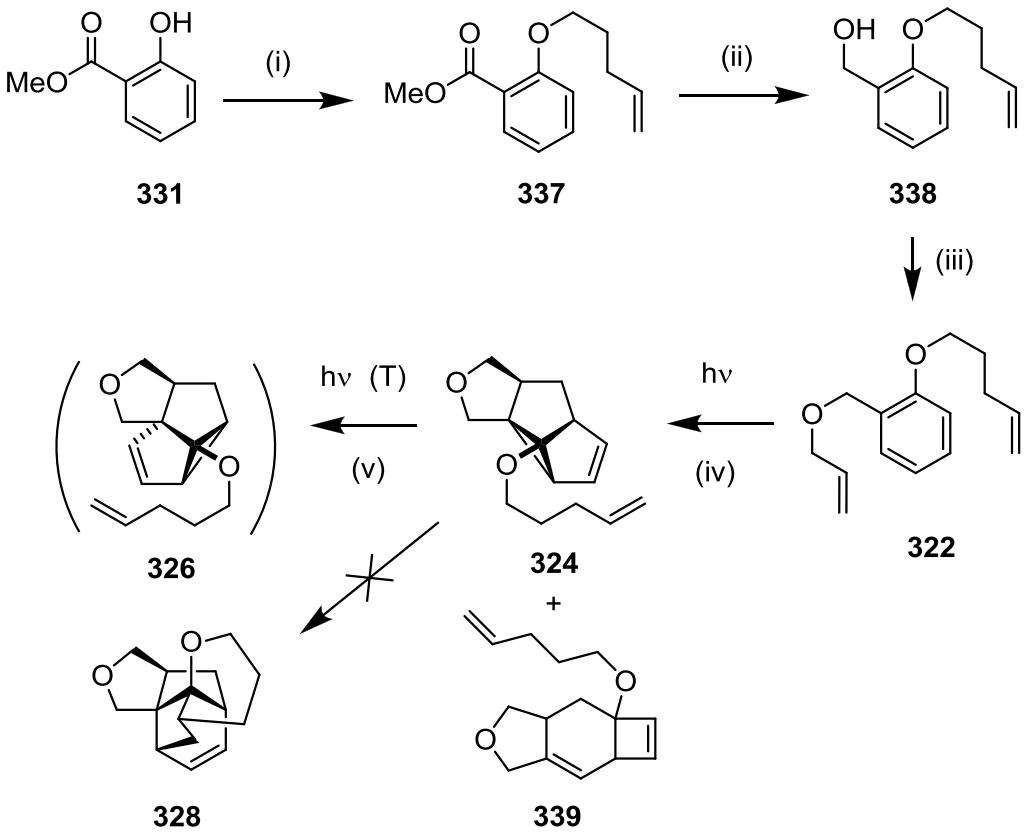
Scheme 5.5: Irradiation of linear *meta* adduct **323** in acetone.

When an irradiation of the linear adduct **323** was conducted using neat acetone as both triplet sensitizer and solvent, conversion to the angular isomer occurred and an additional oxetane

adduct **336** was isolated (Scheme 5.5). This would appear to be derived from a Paterno-Büchi reaction,[137] the [2+2] addition of the acetone carbonyl to the alkene of the core structure. Notably under these triplet sensitized conditions, there was again no 1,2 alkoxy rearrangement and also no Paterno- Büchi adduct from the linear *meta* adduct, implying that this process is slower than the vinylcyclopropane-cyclopentene rearrangement. There was unfortunately no opportunity to attempt this reaction in MeCN.

5.3 Irradiation of pentenyl tether photosubstrate 322.

The failure of the previous butenyl version suggested that the conversion between the linear and angular isomers might simply be quicker than addition of an alkene across the postulated diradical. However, we also postulated that it may be a result of the tether being too inflexible to adopt the necessary conformation for the second [3+2] addition to be favourable. If this latter point were the case then synthesis of a *meta* adduct where the directly linked oxygen tether possessed an additional methylene might lead to the desired double [3+2] product.



Reagents & conditions: (i) Pentenyl bromide (1.05 eq.), anhydrous K_2CO_3 (5 eq.), acetone, reflux, 24 hrs, 83%; (ii) DIBAL (1M, 5 eq.), Et_2O, 0 ºC (78%). (iii) allyl bromide (5 eq.), 50% NaOH (35 eq.), TBAHS (1.1 eq.), CH_2Cl_2, 0 °C → RT, 3 hrs (91%); (iv) 1.50 g, hν (254 nm), cyclohexane, 7 hrs, 9% (**324**) and 17% (**337**); (v) hν (254 nm), acetophenone (150 mol %), MeCN, 32 hrs.

Scheme 5.6: Attempted synthetic route toward criss-cross adduct **328**.

The same procedures as the butenyl case were followed, with some improvement to the initial alkenylation of wintergreen, by using acetone as the solvent and following a method devised by Smith, Morris and Owen[138] that resulted in an improved yield of 83% on a multi-gram scale.

Reduction and ether formation both proceeded in good yields giving the desired photosubstrate **322**, which was then directly irradiated with 254 nm UV light in cyclohexane to give a mixture of two major photoadducts **324** and **339**. These appeared to exist in a 1:1 ratio, although chromatographic resolution was poor and the *meta* adduct **324** was obtained in a 9% yield in comparison to the *ortho* derived adduct **339** at 17%, there was a significant fraction (of which the linear *meta* was the major component) that co-eluted.

Unfortunately, direct secondary irradiation (at 254 nm) of the linear adduct under triplet sensitized conditions for 32 hours with acetophenone (150 mol %) did not lead to any notable product formation except the angular adduct, although this was not isolated in a satisfactorily purified form, due to polymeric impurities. Acetone was also employed and a new product was observed in the ^{1}H NMR spectra although that appeared reminiscent of the previously isolated Paterno-Büchi adduct but this could also not be isolated from the crude residue.

It may still be possible to achieve the goal of creating "criss-cross" adducts. Possibly, the alkene chain taking part in the secondary addition would need to be more constrained so that it could more readily adopt the correct conformation. Despite the failure of this chemistry it should be noted that outside of this work and that of Wender,[58] these are the only examples of arenyl-diene photosubstrate systems undergoing *meta* photocycloaddition. As such they add valuable insight to the already established knowledge gathered about the process.

6 Attempts toward the synthesis of alternative structures via the double [3+2] photocycloaddition.

6.1 Introduction.

Continuing on from the previous section, presented here are further attempts to produce alternative structures to the original fenestrane photoadducts (Figure 6.1, type **I**) described in this work up until now. These fenestranes have been formed from the same kind of simple aromatic starting materials in which both alkenes are attached from a single position on the aromatic ring then branched within the side chain.

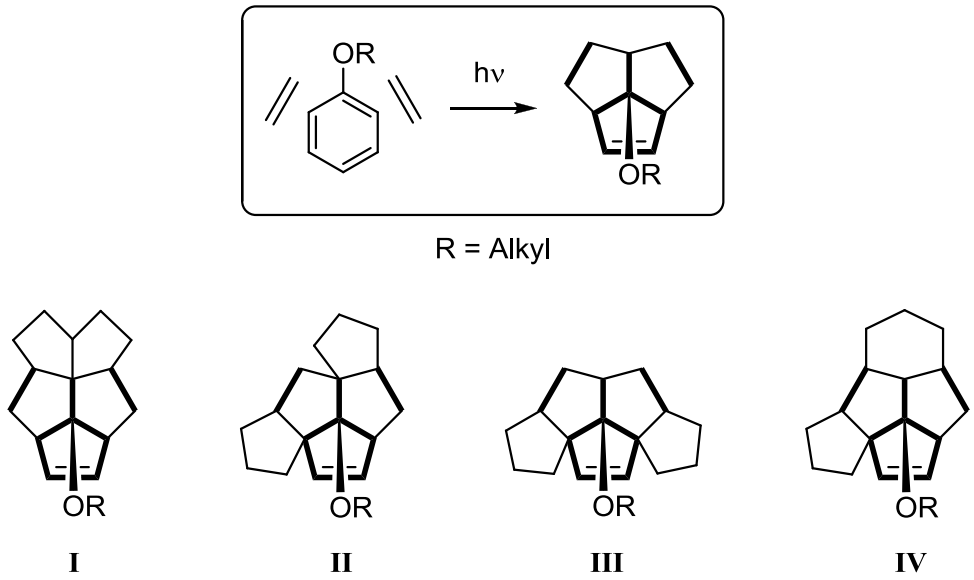
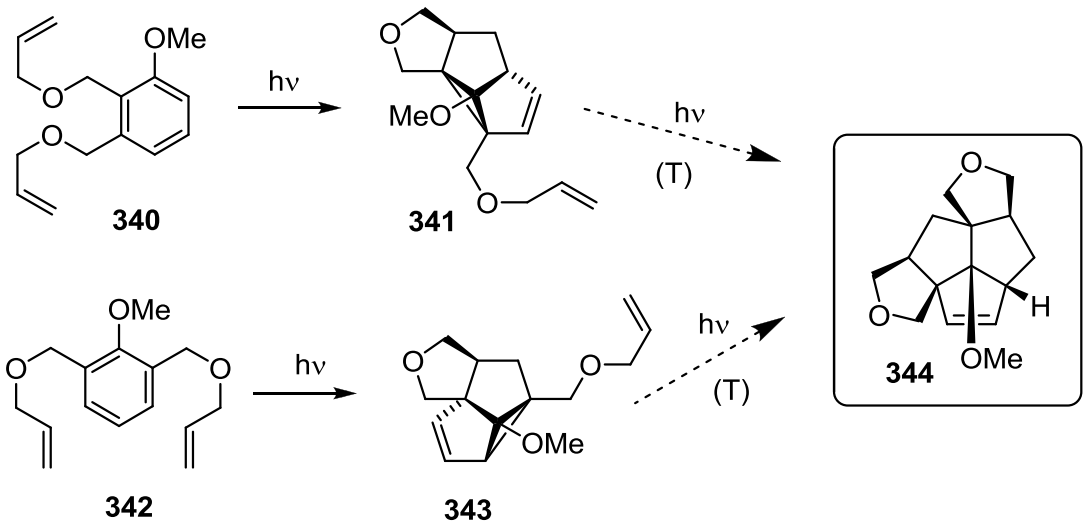


Figure 6.1: Postulated structural motifs.

While the attachment of the alkenyl chains is altered, the core structure of the precursor *meta* photocycloadduct should behave in the same way as the previous examples under the same reactions conditions. Breaking of the external cyclopropane bond then addition of the alkene should fashion structural motifs of the **II**, **III** and **IV** types.

6.2 Attempt toward a Type II motif.

This section focuses on the initial progress that was made toward the formation of type **II** photoadducts as mentioned in the introduction. The type **II** photoadduct **344** could potentially be prepared from either photosubstrate **340** or photosubstrate **342** (Scheme 6.1).

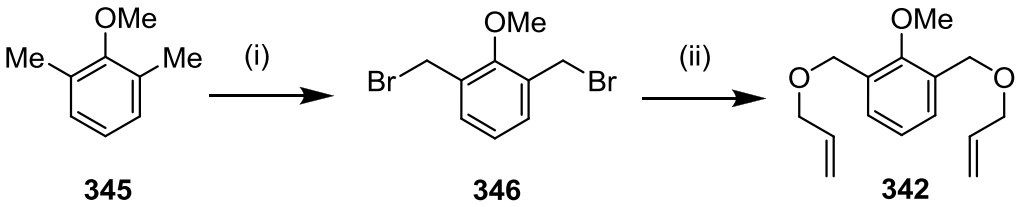


Scheme 6.1: Possible construction of type **II** adduct **344**.

In photosubstrate **340** the electron-donating methoxy group should direct initial *meta* photocycloaddition so that the type **II** photoadduct **344** could be derived from the *linear* isomer **341** following the subsequent second triplet-sensitised photolysis step. In theory, both the linear and angular *meta* photoadduct isomers would then be converted to **344**, as they should photo-equilibrate under the reaction conditions.[31b] The same type **II** adduct should also have been possible to construct from photosubstrate **342** except this time *via* the angular *meta* photoadduct **343**.

Both types of structure could be formed from similar starting materials with the readily available dimethylanisole derivatives acting as a starting point. Due to limited finances the 2,3 dimethyl substituted compound was deemed too expensive to utilise, so the 2,6 substituted version (**345**) was attempted first instead. Our method of choice for synthesising the

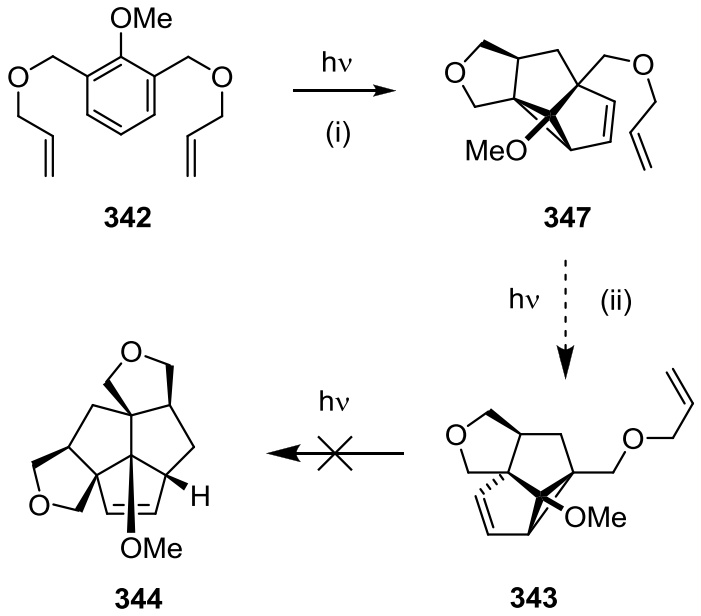
photoadduct involved double bromination of the two methyl groups *via* a Wohl-Zeigler reaction[139] (Scheme 6.2).



Reagents & conditions: (i) NBS (2 eq.), AIBN (5 mol %), 1,2 dichloroethane, reflux, 4 hrs; (ii) allyl alcohol (5 eq.), 50% NaOH (30 eq.), TBAHS (0.5 eq.), CH_2Cl_2, 0 °C → RT, 24 hrs (40%, over two steps).

Scheme 6.2: Synthesis of photosubstrate **342** *via* a Wohl-Ziegler bromination

The dimethylanisole was brominated using *N*-bromosuccinimide[140] *via* radical initiation with AIBN in boiling 1,2- dichloroethane. Due to the severe lachrymator properties of the dibromide, it was used without purification for the alkene attachment, which was carried out under phase-transfer conditions to yield the photosubstrate **342** in a 40% yield over the two steps.



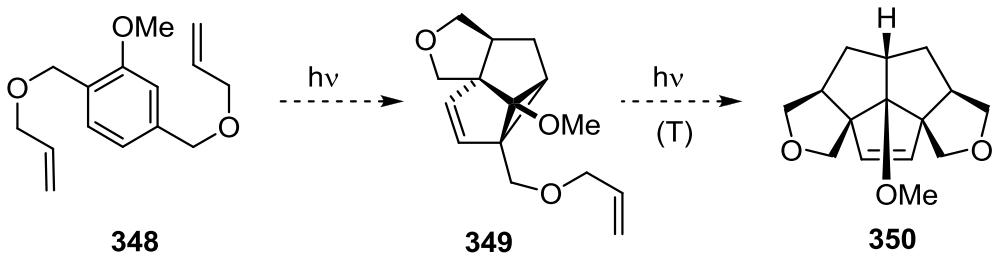
Reagents & conditions: (i) 1.2g, hν (254 nm), cyclohexane, 4 hrs, 49%; (ii) hν (254 nm), acetophenone (150 mol %), MeCN, 13 hrs

Scheme 6.3: Irradiation of photosubstrate **342**.

Irradiation (254 nm) of the photosubstrate gave the linear *meta* adduct in an impressive 49% yield, along with a mixture of angular and an *ortho* derived adduct that could not be separated. Knowing that the linear could undergo photo-equilibration to the required adduct **343**, direct irradiation (254 nm) was conducted in the presence of acetophenone (150 mol %). A limited conversion to the angular was observed, but no subsequent transformation to the type **II** structure **344**.

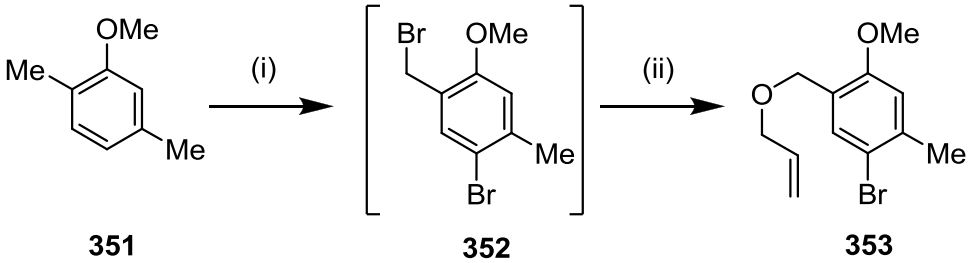
6.3 Attempt toward a Type III motif.

The type **III** photoadduct **350** could be prepared from photosubstrate **348**, but this time starting from 2,5-dimethyl anisole, using the same Wohl-Zeigler reaction as previously mentioned. The methoxy group of **348** would again direct the initial *meta* photocycloaddition to form the angular isomer **349** and its linear partner, through photo-equilibration. Both would then be converted to **350** during a second triplet-sensitised irradiation step (Scheme 6.4).



Scheme 6.4: Postulated synthesis of a type **III** photoadduct **350**.

The Wohl-Zeigler bromination was conducted in the same manner as before using N-bromosuccinimide and AIBN, however due to the positioning of the methyl groups this did not result in the desired photosubstrate (Scheme 6.5).



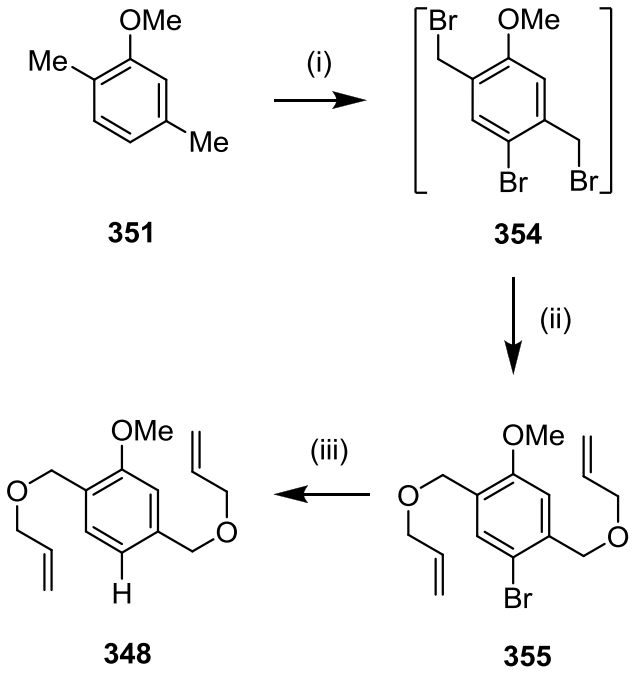
Reagents & conditions: (i) NBS (2 eq.), AIBN (5 mol %), 1, 2 dichloroethane, reflux, 3hrs; (ii) allyl alcohol (5 eq.), 50% NaOH (30 eq.), TBAHS (0.5 eq.), CH_2Cl_2, 0 °C → RT, 3 hrs (25%, over two steps).

Scheme 6.5: Failed synthesis of photosubstrate **348**.

With a methyl in the *meta* position on the aromatic ring it was no longer activated by the strong resonance donation of the methoxy oxygen atom like the methyl group sitting in the *ortho* position. As such the most activated position is that *para* to the methoxy, which is further enhanced by the methyl sitting *ortho* to it. Addition of NBS therefore results first in simple

electrophilic aromatic substitution of the *para* position, before bromination of the more activated *ortho* methyl.

To solve the problem a further equivalent of NBS was used so that the less activated *meta* methyl group was also brominated, before using this trisbrominated species to form the desired ether linkages (Scheme 6.6). Metal-halogen exchange with *n*-butyllithium generated the lithium species, which was then quenched with water to give the desired arenyl-diene photosubstrate **348**, in a respectable 77% yield over three steps.



Reagents & conditions: (i) NBS (3 eq.), AIBN (5 mol %), 1,2 dichloroethane, reflux, 4 hrs; (ii) allyl alcohol (10 eq.), 50% NaOH (30 eq.), TBAHS (0.5 eq.), CH_2Cl_2, 0 °C → RT, 24 hrs (79%, over two steps); (iii) *n*-BuLi (2.5 M, 1.2 eq.), Et_2O, 0 °C, H_2O, 97%.

Scheme 6.6: Synthesis of photosubstrate **348**.

Unfortunately, direct irradiation of photosubstrate **348** using 254 nm UV light over 8 hours, led to a complex mixture of adducts, however separation proved to be impractical *via* column chromatography due to the near identical retention factors of the adducts formed.

Subsequent triplet sensitized irradiation of this crude mixture could not be conducted within the confines of the project timescale. However, there is certainly further scope for investigation into these areas and it would be hoped that the double [3+2] photocycloaddition could be applied to the creation of another structure outside of fenestranes at some time in the future.

7 Conclusion

In this work we have reported a remarkable double [3+2] photocycloaddition reaction that leads from simple aromatic starting materials to a series of complex pentacyclic compounds containing *cis*, *cis*, *cis*, *trans* [5.5.5.5] fenestrane cores (Figure 7.1).

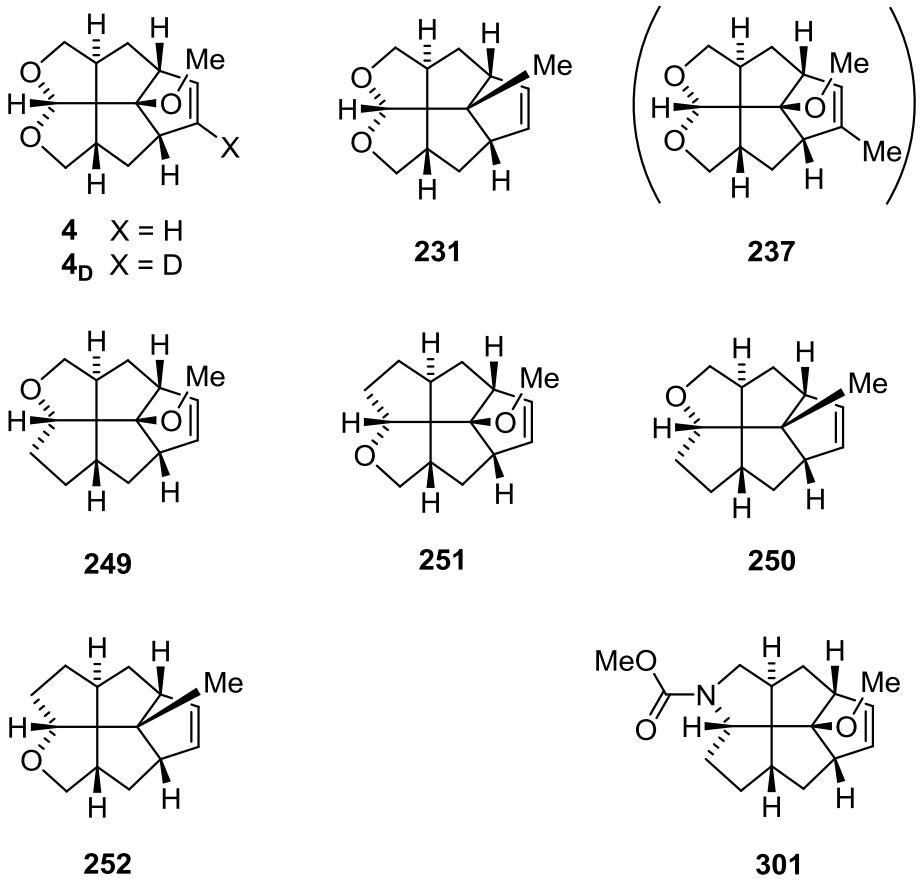


Figure 7.1: A collection of all the *cis*, *cis*, *cis*, *trans*-[5.5.5.5] fenestranes synthesised in this work.

Through this series of compounds we hope to have illustrated that an array of different functionalities can be incorporated using this method, including acetal, ether and nitrogen groups. In addition, we have shown that triplet sensitisation can be used to improve the efficiency of the fenestranes construction to the exclusion of a range of silphinene type adducts, formed by a 1,2 alkoxy rearrangement.

The double [3+2] photocycloaddition was also attempted on a variety of other arenyl-diene photosubstrates with the aim of making alternative structures. While regrettably these initial experiments have met with failure, their photochemistry does add to the noteworthy body of work concerning the *meta* photocycloaddition. Further exploration in this area is warranted as we believe that the simplicity and rapidity of this method for making complex structures has significant unexplored potential.

8 Experimental.

8.1 General procedures.

8.1.1 Reagents and solvents.

All starting materials and reagents were purchased from commercial sources largely, Fisher Scientific UK ltd, Alfa Aesar® and Sigma-Aldrich® Ltd. and were used after verification of purity by NMR. The solvents used in reactions and all forms of chromatography were subjected to rotary evapouration before use to remove impurities, with the exception of halogenated solvents. Petroleum etherused was from the fraction of boiling range 40-60 ºC. Unless stated all solvents used were not rigorously dried.

8.1.2 Spectroscopy and naming.

^{1}H NMR spectra were recorded on Varian VNMRS spectrometers at either 500 or 600 MHz. Chemical shifts (δ) are quoted in ppm using deuterated chloroform ($CDCl_3$)[61] as a reference (δ = 7.26 ppm). Coupling constants (*J*) are quoted in hertz (Hz) and the following abbreviations are used to describe the signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. In some instances dm is used to describe a major doublet signal multiplicity, where the m signifies that other unresolved minor splitting signals are also present in the NMR spectrum. ^{13}C NMR spectra were recorded on the same spectrometers at 125 and 150 MHz respectively, using the same reference solvent ($CDCl_3$ δ = 77.0 ppm). Full proton and carbon assignments have been made using a combination of COSY, DQF-COSY, multiplicity-edited HSQC and standard HMBC correlation spectroscopies.

All stereochemical assignments were performed using rotating-frame Overhauser effect spectroscopy (ROESY). In instances where a signal's identity is ambiguous, a best guess is offered. Selected NMR spectra are included in the appendix section of this thesis. These various

spectra presented were manipulated using MestReNova software version 6.0.0-5344 from Mestrelab Research S.L. © 2009.

Infra-Red (IR) spectra were recorded on a Perkin-Elmer 1710 Fourier-Transform spectrophotometer with frequencies (ν_{max}) quoted in wavenumbers (cm^{-1}). Liquid samples were recorded using sodium chloride plates, while solids were recorded using a KBr disc. Only the significant absorptions are presented in the data, with key stretches identified in brackets.

High Resolution mass spectra were obtained on a Fisons VG Micromass 7070F and a VG AUTOSPEC instrument using Electron Spray Injection (ESI). In all cases spectral data was captured by Dr. A. K. Abdul-Sada of the University of Sussex Mass Spectrometry Centre.

In the case of the photoadducts included in the experimental section below, compound names have been determined using the von Baeyer system for naming polycyclic compounds as approved by IUPAC. All other compound names were determined *via* the automatic naming function of ACD/ChemSketch (Freeware version). All spectra have been compiled in pdf. Format, and can be made available on DVD for viewing by request.

8.1.3 Chromatography.

Where reactions were monitored using TLC, the solvent system and Retention Factor (R_f) are indicated. Chromatography was executed using Partisil® K6F glass backed plates with a 250 μm layer of 60 Å silica gel with fluorescent indicator. Visualization was carried out using ultraviolet light (254 nm); combined with either potassium permanganate ($KMnO_4$), vanillin (4-hydroxy-3-methoxybenzaldehyde) or anisaldehyde dips. Most flash column chromatography was run using Merck Kiesel silica 60 Å (particle size 35 – 70 μm. Specialized Merck Silica gel 60 (particle size 63 - 200 μm) of pH 7.0 (+/- 0.5) was utilized for specific product isolations and is

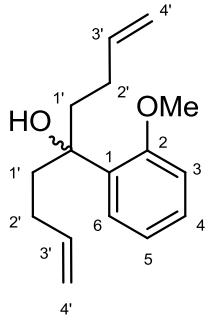
highlighted in the experimental procedures where appropriate. Solvent systems used for chromatographic separations are given for each procedure or product, where applicable.

8.1.4 Photochemistry.

Irradiations were carried out in quartz immersion-well reactors fitted with 6 W or 16 W low pressure mercury vapour lamps or 125 W or 400 W medium pressure mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through a sintered glass tube into the solvent at RT. Experiments were conducted with gentle stirring of the reaction solution under an atmosphere of nitrogen and with cold-water cooling of the lamp and vessel contents throughout.

8.2 Experimental data.

5-(2-Methoxy-phenyl)-nona-1, 8-dien-5-ol **140**.



A flame dried 500 ml three-necked flask was placed under nitrogen then fitted with a reflux condenser, dropping funnel and mechanical stirrer. Dry magnesium turnings (2.31 g, 96.4 mmol) were added to the flask followed by THF (30 ml). The dropping funnel was loaded with a solution of 4-bromo-1-butene (16.3 g, 121 mmol) in THF (20 ml). A small amount of the solution (<5 ml) was added slowly to the magnesium, and the contents heated to reflux. Once Grignard formation was initiated, the solution was cooled to -10 °C and the remaining bromide was added drop wise at a rate that maintained a gentle reflux. After addition, the reaction was stirred until all the magnesium had reacted.

A solution of methyl-2-methoxybenzoate (8.00 g, 48.2 mmol) in THF (50 ml) was loaded into the dropping funnel and added drop wise over 15 mins. After stirring for 6 hrs at ambient temperature, a saturated solution of NH_4Cl (200 ml) was added to quench the reaction and the resulting emulsion was left to stir overnight. The aqueous layer was extracted with Et_2O (3 x 100 ml). Organic layers were combined, washed with H_2O (3 x 100 ml), then brine (2 x 50 ml) and dried over anhydrous $MgSO_4$. The volatile solvents were removed under reduced pressure and the resulting orange residue subjected to flash column chromatography (Et_2O/petrol 10:90) to afford the alcohol **140** (8.03g, 67%) as an orange oil.

R_f 0.37 (Et_2O/petrol 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, d, *J* 7.8, H-3); 7.24 (1H, t, *J* 8.0, H-5); 6.97 (1H, t, *J* 7.5, H-4); 6.91 (1H, d, *J* 8.0, H-6); 5.75-5.85 (2H, m, H-3'); 4.96 (2H,

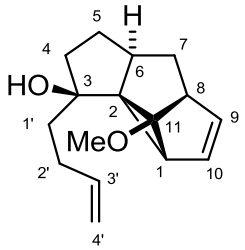
d, *J* 17.2, H-4'); 4.90 (2H, d, *J* 10.3, H-4'); 3.87 (3H, s, -OCH_3); 3.68 (1H, br. s, -OH); 2.10-2.18 (2H, ddm, *J* 2.7, 11.0, H-1'); 1.99-2.09 (2H, m, H-2'); 1.92 (4H, m, H-1'+H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.87 (C-2); 139.24 (C-3'); 132.73 (-C(OH)); 128.02 (C-5); 127.77 (C-3); 120.80 (C-4); 114.11 (C-4'); 111.51 (C-6); 77.55 (C-1); 55.43 (-OCH_3); 39.90 (C-1'); 28.43 (C-2'); IR (thin film, cm^{-1}) 3532 (-OH, stretch), 3076, 2930, 1640 (C=C, vinyl), 1599 (C=C, aromatic), 1582, 1487, 1453, 1436, 1393, 1284, 1233, 1181, 1051, 1027, 995, 907, 751 ; HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512, found 269.1512.

Irradiation of photosubstrate **140** *to yield compounds* **141**, **142**, **143**, **144** and **145**.

Note: All column chromatography on the compounds obtained from this procedure was conducted with silica neutralised via the addition of 0.1% triethylamine during initial slurry formation.

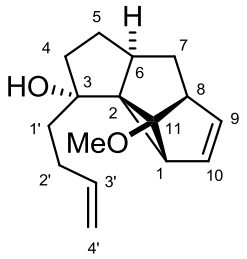
Dry cyclohexane (450 ml) was stirred vigorously over anhydrous K_2CO_3 for 30 minutes, then filtered and added to a quartz immersion-well photoreactor. Alcohol **140** (1.84 g, 7.48 mmol) was then added to the reaction vessel and the mixture was degassed with nitrogen for 20 minutes to remove any dissolved oxygen. The apparatus was cooled with H2O and the solution irradiated for 10 hrs using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis revealed the complete consumption of **140**. The solvent was removed under reduced pressure and the yellow residue was subjected to flash column chromatography (Et_2O/petrol 20:80) to afford a mixture comprised of five photocycloadducts; linear *meta* adduct **142**, suspected angular *meta* adduct **143** (containing an unknown inseparable contaminant); linear *meta* adduct **141**, and *ortho*-derived adducts **144** and **145**. These were obtained in a combined crude yield of approximately 70% with individual isolated yields being 10, <10, 19, 12 and 19% respectively.

rac-(1R, 2S, 3S, 6S, 8S, 11S) 3-Hydroxy-3-(but-3'-enyl)-11-methoxy-tetracyclo [6.2.1.0 ^{2,6}.0 ^{2,11}]undec-9-ene **141**.



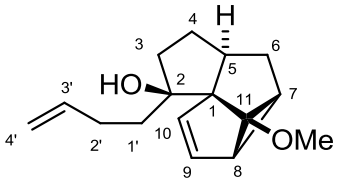
R_f 0.20 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, ddt, *J* 6.6, 10.3, 17.0 H-3'); 5.63 (1H, dd, *J* 2.4, 5.6, H-10); 5.52 (1H, ddd, *J* 1.1, 2.6, 5.7, H-9); 5.04 (1H, dm, *J* 17.1, H-4'); 4.92 (1H, dm, *J* 10.1, H-4'); 3.31 (3H, s, -OCH_3); 3.22 (1H, dd, *J* 2.4, 5.4, H-8); 2.35-2.37 (1H, m, H-1); 2.23-2.31 (2H, m, H-2'/H-6); 2.02-2.17 (1H, m, H-2'/H-5); 1.98 (dd, *J* 7.1, 12.7, H-4); 1.70-1.90 (4H, m, H-4/H-1'/H-7); 1.49 (1H, ddd, *J* 5.2, 11.3, 14.4, H-1'); 1.34-1.39 (1H, m, H-5); 1.34 (1H, s, -OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.63 (C-3'); 132.20 (C-9); 127.96 (C-10); 114.01 (C-4'); 93.06 (C-11); 80.94 (C-3); 60.33 (C-2); 56.46 (-OCH_3); 53.44 (C-8); 44.35 (C-7); 41.12 (C-6); 39.55 (C-4); 35.62 (C-1); 35.15 (C-1'); 28.82 (C-2'); 26.82 (C-5); HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512, found 269.1512.

rac-(1R, 3R, 6S, 8S) 3-Hydroxy-3-(but-3'-enyl)-11-methoxy-tetracyclo[6.2.1.0 ^{2,6}0 ^{2,11}] undec-9-ene **142**.



R_f 0.44 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (1H, ddt, *J* 6.6, 10.2, 17.0, H-3'); 5.64 (1H, ddm, *J* 2.2, 5.6, H-10); 5.50 (1H, dddm, *J* 1.2, 2.5, 5.6, H-9); 5.02 (1H, dm, *J* 17.0, H-4'); 4.94 (1H, dm, *J* 10.2, H-4'); 3.51 (1H, s, -OH); 3.36 (3H, s, -OCH_3); 3.28 (1H, dd, *J* 2.6, 5.1, H-8); 2.46 (1H, br. s, H-1); 2.23-2.32 (1H, m, H-2'); 2.09-216 (1H, m, H-2'); 2.04-2.09 (1H, m, H-6); 1.83-1.95 (4H, m, H-4/H-5); 1.75-1.82 (1H, m, H-7α); 1.62 (1H, ddd, *J* 4.9, 11.7, 13.8, H-13); 1.48-1.56 (2H, m, H-7β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.39 (C-3'); 132.83 (C-9); 127.60 (C-10); 113.95 (C-4'); 92.02 (C-11); 80.27 (C-3); 57.83 (C-2); 57.11 (-OCH_3); 53.49 (C-8); 45.62 (C-5); 41.47 (C-6); 40.69 (C-4); 38.07 (C-1'); 37.05 (C-1); 28.09 (C-2'/C-7); IR (thin film, cm^{-1}) 3522 (-OH, stretch); 3055, 2936, 1676, 1640 (C=C, vinyl); 1597 (C=C, alkene); 1585, 1450, 1397, 1379, 1323, 1233, 1160, 1125, 1100, 1070, 1003, 908, 759, 735 ; HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512, found 269.1512

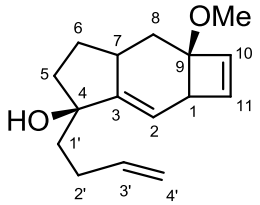
rac-(1S, 2S, 5S, 7R, 8S, 11S)-2-Hydroxy-2-(3'-butenyl)-11-methoxy-3-tetracyclo [5.3.1.$0^{1,5}$.$0^{8,11}$]undec-9-ene **143**.



Alternative method: Linear *meta* adduct **141** (50 mg, 0.20 mmol) and acetophenone (37 mg, 0.31 mmol) were dissolved in MeCN (150 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 4 hrs using a 6 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (Et_2O: pentane 20:80); to yield the angular *meta* adduct **143** (5 mg, 10%) as a colourless oil.

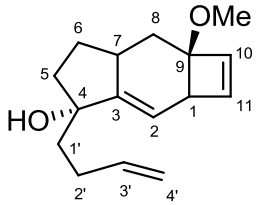
R_f 0.30 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89 (1H, ddt, *J* 6.5, 10.1, 17.0, H-3'); 5.71 (1H, d, *J* 5.7, H-10); 5.58 (1H, dd, *J* 2.5, 5.7, H-9); 5.05 (1H, dm, *J* 17.0, H-4'); 4.94 (1H, dm, *J* 10.1, H-4'); 3.24 (3H, s, -OCH_3); 2.50 (1H, ddd, *J* 6.0, 9.2, 9.2, H-5); 2.26-2.30 (1H, m, H-8); 2.16-2.31 (2H, m, H-2'); 2.07-214 (2H, m, H-3+H-7); 1.93-2.00 (2H, m, H-1'); 1.72-1.80 (1H, m, H-4); 1.71 (1H, dd, *J* 6.4, 13.6, H-6); 1.64-1.71 (1H, m, H-4); 1.49 (1H, dd, *J* 6.1, 13.6, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.68 (C-3'); 133.20 (C-10); 124.16 (C-9); 114.17 (C-4'); 90.41 (C-11); 83.30 (C-2); 76.75 (C-1); 56.13 (C-2); 55.59 (-OCH_3); 39.50 (C-3); 36.20 (C-1'); 36.06 (C-8); 33.91 (C-7); 29.20 (C-2'); 27.37 (C-6); 26.69 (C-4); HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512, found 269.1528

rac-(1R, 4S, 7S, 9S) 4-Hydroxy-4-(but-3'-enyl)-9-methoxytricyclo[7.2.0^{1,9}.0^{3,7}] undec-2,10-ene **144**.



R_f 0.06 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.13 (1H, d, *J* 2.7, H-10); 6.02 (1H, dd, *J* 0.9, 2.7, H-11); 5.78-5.87 (1H, m, H-3'); 5.76 (1H, dd, *J* 2.9, 6.1, H-2); 5.00 (1H, br. d, *J* 17.1, H-4'); 4.92 (1H, br. d, *J* 10.2, H-4'); 3.34 (1H, d, *J* 6.0, H-1); 3.31 (3H, s, -OCH_3); 2.18-2.26 (1H, m, H-7); 2.15 (1H, dd, *J* 5.0, 12.2, H-8); 2.09-2.17 (1H, m, H-2'); 1.99-2.08 (1H, m, H-2'); 1.86-1.93 (1H, m, H-6); 1.73-1.80 (2H, m, H-1'/H-5); 1.51-1.69 (2H, m, H-1'/H-5); 1.47-1.55 (2H, m, H-6/-OH); 1.28 (1H, t, *J* 12.4, H-8); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.73 (C-3); 138.98 (C-3'); 138.16 (C-11); 136.52 (C-10); 117.60 (C-2); 114.16 (C-4'); 85.24 (C-9); 80.56 (C-4) 51.70 (-OCH_3); 46.56 (C-1); 38.89 (C-1'); 38.57 (C-5); 37.35 (C-8); 36.61 (C-7); 28.94 (C-2'/C-6); 28.89 (C-2'/C-6); IR (thin film, cm^{-1}) 3449 (-OH); 2931, 2241, 1821, 1703, 1640 (C=C, vinyl); 1561, (C=C, alkene); 1450, 1296, 1172, 1098, 994, 911, 733; HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512, found 269.1510.

rac-(1R, 4R, 7S, 9S) 4-Hydroxy-4-(but-3'-enyl)-9-methoxytricyclo[7.2.0^{1,9}.0^{3,7}] undec-2,10-ene **145**.



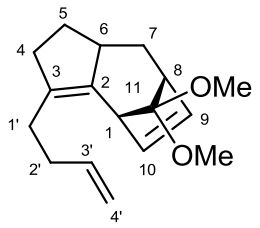
R_f 0.09 (Et_2O/petrol, 20:80); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.12 (1H, d, *J* 2.6, H-10); 6.00 (1H, d, *J* 2.7, H-11); 5.83 (1H, dddd, *J* 6.5, 6.5, 10.3, 16.9, H-3'); 5.71 (1H, dd, *J* 3.0, 6.2, H-2); 5.02 (1H, br. d, *J* 17.0, H-4'); 4.93 (1H, br. d, *J* 10.2, H-4'); 3.33 (1H, d, *J* 6.2, H-1); 3.30 (3H, s, -OCH_3); 2.43-2.50 (1H, m, H-7); 2.18-2.25 (1H, m, H-2'); 2.05-2.13 (2H, m, H-2'/H-8); 1.98 (1H, m, H-6); 1.87 (1H, ddd, *J* 4.6, 7.4, 12.5, H-5); 1.74 (1H, ddd, *J* 5.1, 11.8, 13.9, H-1'); 1.68 (1H, ddd, *J* 7.1, 9.4, 13.0, H-5); 1.59 (1H, ddd, *J* 5.0, 11.7, 13.9, H-1'); 1.55-1.75 (1H, br. s, -OH); 1.25 (1H, dddd, *J* 7.9, 8.6, 8.8, 12.7, H-6); 1.59 (1H, t, *J* 12.5, H-8); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.99 (C-3); 138.91 (C-3'); 137.76 (C-11); 136.39 (C-10); 117.65 (C-2); 114.29 (C-4'); 85.08 (C-9); 80.36 (C-4) 51.69 (-OCH_3); 46.61 (C-1); 39.21 (C-1'); 38.45 (C-5); 36.93 (C-8); 35.72 (C-7); 28.78 (C-2'/C-6); 28.76 (C-2'/C-6); IR (thin film, cm^{-1}) 3434 (-OH, stretch); 2933, 1712, 1665, 1640 (C=C, vinyl); 1562, (C=C, alkene); 1451, 1338, 1299, 1170, 1100, 1025, 910, 830, 766, 730; HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512, found 269.1514.

Decomposition products of **141**, **142**, **143**, **144** *and* **145**.

Note: During the photolytic study of arenyl-diene photosubstrate **140**, many minor products were isolated in a variety of yields dependent upon irradiation time (with reactions being carried out up to 72 hrs) and presence of abstractable hydrogen either in the photoreaction mixture or on the chromatography column. The majority of these minor products could not be isolated in a satisfactorily purified form, however the spectra of those that were are presented as proof of identity.

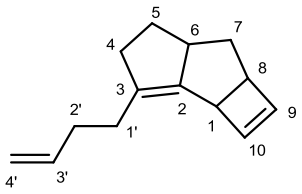
Example procedure: A stirred solution of photosubstrate **140** (2.5 g, 10.16 mmol) in dry cyclohexane (400 ml) was added to a quartz immersion-well photoreactor. The mixture was degassed with nitrogen for 20 minutes to remove any dissolved oxygen. The apparatus was cooled with H_2O and the solution irradiated for 72 hrs using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The yellow residue was subjected to flash column chromatography to afford the major adducts previously reported and **151**, **155** and **166** in approximate yields of 0.4, 0.4 and 1% respectively, along with other inseparable adducts.

rac-(1R, 6S, 8R) 3-(But-3'-enyl)-11,11-dimethoxy-tricyclo[6. 2. 1. $0^{2,6}$] dec-2,9-ene **151**.



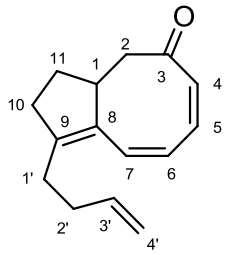
R_f 0.68 (EtOAc/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89-5.92 (1H, m, H-9); 5.76-5.85 (1H, m, H-3'); 5.74-5.77 (1H, m, H-10); 5.01 (1H, br. d, *J* 17.2, H-4'); 4.94 (1H, br. d, *J* 10.2, H-4'); 3.38 (1H, br. d, *J* 2.6, H-1); 3.20 (3H, s, -OCH_3); 3.15 (3H, s, -OCH_3); 2.74-2.78 (1H, m, H-8); 2.49-2.58 (1H, m, H-6); 2.21-2.31 (2H, m, H-1'/H-4); 2.06-2.21 (4H, m, H-4/H-1'/H-2'); 1.99 (1H, ddd, *J* 6.0, 6.9, 11.5, H-5); 2.38 (1H, dddm, *J* 3.5, 7.8, 12.6, H-7); 1.39-1.46 (1H, m, H-7); 1.23-1.33 (1H, m, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.67 (C-3'); 135.14 (C-2); 133.99 (C-3); 131.52 (C-9); 131.16 (C-10); 114.31 (C-4'); 112.04 (C-11); 49.08 (-OCH_3); 49.02 (-OCH_3); 45.79 (C-1); 43.57 (C-8); 40.17 (C-6); 34.92 (C-4); 32.49 (C-2'); 31.37 (C-5); 30.76 (C-7); 27.78 (C-1'); HRMS (ESI) *m/z* calcd. $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 283.1674, found 283.1671

rac-(1S, 6S, 8R) 3-(But-3'-enyl)-tricyclo[6. 2. $0^{1,8}$.$0^{2,6}$]dec-2,9–ene **155**.



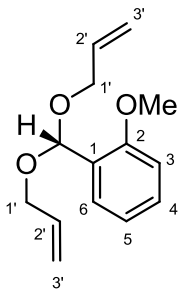
R_f 0.90 (EtOAc/petrol, 10:90); ^{1}H NMR (600 MHz, CD_3CN): δ 6.06 (1H, d, *J* 2.6, H-9); 5.87 (1H, d, *J* 2.6, H-10); 5.78-5.85 (1H, m, H-3'); 5.02 (1H, br. d, *J* 17.1, H-4'); 4.93 (1H, br. d, *J* 10.2, H-4'); 3.56 (1H, dd, *J* 2.9, 7.5, H-8); 3.52 (1H, d, *J* 2.6, H-1); 3.12-3.20 (1H, m, H-6); 2.55-2.62 (1H, m, H-4); 2.36 (1H, dd, *J* 9.1, 15.2, H-4); 2.19-2.24 (1H, m, H-1'); 2.14-2.20 (3H, m, H-1'/H2'); 1.81 (1H, dd, *J* 7.2, 12.4, H-7); 1.35 (1H, ddt, *J* 9.1, 9.3, 12.1, H-5); 0.88 (1H, ddd, *J* 7.5, 10.5, 12.4, H-7); ^{13}C NMR (150 MHz, CD_3CN): δ 144.75 (C-2); 140.67 (C-9); 140.22 (C-3'); 138.17 (C-10); 134.06 (C-3); 115.32 (C-4'); 54.86 (C-8); 49.15 (C-6); 45.94 (C-1); 40.60 (C-4); 34.99 (C-7); 33.65 (C-2'); 32.19 (C-5); 29.95 (C-1'); IR (thin film, cm^{-1}) : 3041, 2925, 2844, 1640 (C=C); 1550, 1442, 1301, 1260, 1094, 1018, 908, 779, 719, 615; LRMS (+EI) *m/z* calcd. $C_{14}H_{18}$ [M+] = 186 found 186 (12%) fragments 145 (100%); 129 (20%); 117 (41%); 105 (17%); 91 (48%); 79 (17%); 67 (14%); 53 (6%).; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}Na$ $[M+Na]^+$ 209.1306, found 209.1301.

rac-(1S)-3-(But-3'-enyl)-bicyclo[6. 3. 0^{1,8}]undec-4,6,8-triene-3-one. **166**.



R_f 0.42 (EtOAc/petrol, 10:90); ^{1}H NMR (500 MHz, C_6D_6): δ 6.15 (1H, d, *J* 12.6, H-7); 5.90 (1H, dd, *J* 13.2, 6.5, H-5); 5.82 (1H, d, *J* 13.2, H-4); 5.69 (1H, ddt, *J* 6.6, 10.0, 16.5, H-3'); 5.49 (1H, dd, *J* 12.6, 6.5, H-6); 5.00 (1H, d, *J* 16.6 C-4'); 4.97 (1H, d, *J* 9.6 C-4'); 3.16-3.24 (1H, m, H-1); 2.56-2.65 (2H, m, C-2); 2.05-2.12 (1H, m, C-10); 2.00-2.05 (3H, m, C-10/C-1'/C-2'); 1.94-1.99 (2H, m, C-1'/C-2'); 1.84-1.92 (1H, m, H-11); 1.38-1.46 (1H, m, H-11); ^{13}C NMR (125 MHz, C_6D_6): δ 202.35 (C-3); 143.84 (C-9); 137.83 (C-3'); 137.36 (C-8); 133.77 (C-5); 130.07 (C-4); 128.84 (C-7); 123.57 (C-6); 114.69 (C-4'); 47.92 (C-2); 46.74 (C-1); 34.50 (C-10); 32.01 (C-1'/C-2'); 30.64 (C-11); 28.33 (C-1'/C-2'); IR (thin film, cm^{-1}) : 2928, 1697, 1655 (C=O, enone); 1626, 1593, 1435, 1415, 1288, 1228, 1137, 994, 909, 823, 784, 733, 661; HRMS (ESI) *m/z* calcd. $C_{15}H_{18}O_1Na$ $[M+Na]^+$ 237.1255, found 237.1252.

1-(Bis(2'-propenyloxy)methyl)-2-methoxybenzene **1**.



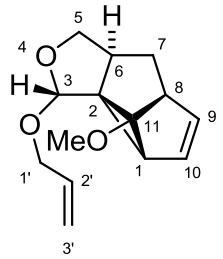
Using a procedure adapted from Noyori, Tsunoda and Suzuki[66] trimethylsilyl trifluoromethanesulfonate (0.170 ml, 0.880 mmol), was added to CH_2Cl_2 (30 ml) under a nitrogen atmosphere at -84 °C, and magnetically stirred for five minutes. Allyloxytrimethylsilane (36.4 ml, 220 mmol) and *o*-anisaldehyde (12.0 g, 88.0 mmol), dissolved in CH_2Cl_2 (25 ml) were added sequentially and drop wise, whilst maintaining the same temperature. The resulting yellow mixture was stirred at -84 °C for three hours, then allowed to warm to -60 °C and stirred for a further hour, the solution turning a deep red. The reaction was quenched with pyridine (15 ml) at the same temperature, and then poured into a saturated solution of $NaHCO_3$ (100 ml). The aqueous layer was extracted with Et_2O (3 x 100 ml); and the combined organic layers dried over anhydrous $MgSO_4$. Excess solvent was removed under reduced pressure and the resulting oil was purified, when required, by flash column chromatography (EtOAc/petrol 2:98); to yield **1** (20.2 g, 98%) as a colourless oil.

R_f 0.45 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (1H, br d, *J* 7.6, H-6); 7.28 (1H, br t, *J* 7.4, H-4); 6.96 (1H, br t, *J* 7.5, H-5); 6.87 (1H, br d, *J* 8.2, H-3); 5.88-5.96 (2H, m, H-2'); 5.88 (1H, s, -C(H)O_2); 5.27 (2H, dm, *J* 17.1, H-3'); 5.12 (2H, dm, *J* 10.5, H-3'); 4.07 (4H, dm, *J* 5.6, H-1'); 3.82 (3H, s, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.10 (C-2); 134.77 (C-2'); 129.63 (C-4); 127.47 (C-6); 126.67 (C-1); 120.30 (C-5); 116.57 (C-3'); 110.68 (C-3); 96.35 (-C(H)O_2); 67.05 (C-1'); 55.55 (-OCH_3); IR (thin film, cm^{-1}) , 3079, 2923, 1647 (C=C, vinyl); 1604 (C=C, aromatic); 1591, 1492, 1464, 1439, 1381, 1286, 1245, 1126, 1033, 924, 756; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1145.

Irradiation of chromophore **1** *to yield compounds* **2**, **3**, **170a** *and* **170b**.

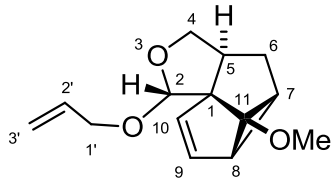
A solution of acetal **1** (450 mg, 1.92 mmol) in dry cyclohexane (350 ml) was degassed with nitrogen for 20 mins in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 4 hrs using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) or until NMR analysis revealed the complete consumption of **1**. The solvent was removed under reduced pressure, and the resulting yellow residue was subjected to flash column chromatography (100:1 silica, triethylamine/Et_2O/petrol, 0.5:20:80) to afford the linear *meta* photocycloadduct **2** (104 mg, 23%); the angular *meta* photocycloadduct **4** (16mg, 3.5%) and a mixture of the rearranged *ortho* photocycloadducts **170a** and **170b**, as colourless to pale yellow oils. Further separation of the *ortho* photocycloadducts **170a** (100 mg, 22%) and **170b** (50 mg, 11%) was carried out using Et_2O/CH_2Cl_2 (5:95).

rac-(1R, 2R, 3R, 6S, 8S, 11S)-3-(2'-Propenyloxy)-11-methoxy-4-oxatetracyclo [6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **2**.



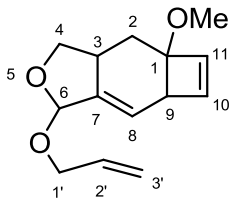
R_f 0.37 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (1H, dddd, *J* 5.4, 6.1, 10.3, 17.2, H-2'); 5.70 (1H, dd, *J* 2.0, 5.6, H-10); 5.52 (1H, dm, *J* 5.6, H-9); 5.26 (1H, dm, *J* 17.2, H-3'); 5.15 (1H, d, *J* 10.3, H-3'); 4.92 (1H, br s, H-3); 4.18 (1H, dd, *J* 7.9, 8.9, H-5α); 4.15 (1H, dd, *J* 5.4, 13.0, H-1'); 3.98 (1H, ddm, *J* 6.1, 13.0, H-1'); 3.69 (1H, ddm, *J* 2.0, 8.9, H-5β); 3.38 (3H, s, -OCH_3); 3.33 (1H, dm, *J* 2.7, H-8); 2.46 (1H, br s, H-1); 2.36 (1H, dddd, *J* 2.0, 7.9, 7.9, 7.9, H-6); 1.96 (2H, dd, *J* 3.0, 8.2, H-7α + H-7β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.79 (C-2'); 132.76 (C-9); 128.59 (C-10); 117.03 (C-3'); 100.50 (C-3); 89.25 (C-11); 71.58 (C-5); 68.03 (C-1'); 56.78 (-OCH_3); 55.79 (C-2); 52.73 (C-8); 46.00 (C-7); 40.40 (C-6); 37.22 (C-1); IR (thin film, cm^{-1}) , 2939, 1647 (C=C, vinyl), 1586 (C=C), 1452, 1413, 1360, 1332, 1245, 1199, 1169, 1134, 1053, 1008, 979, 917, 863, 756; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1145.

rac-(1S, 2R, 5S, 7R, 8S, 11S)-2-(2'-Propenyloxy)-11-methoxy-3-oxatetracyclo [5.3.1.0^{1,5}.0^{8,11}]undec-9-ene **3**.



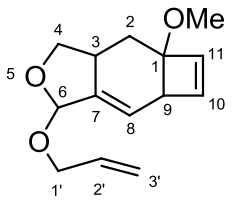
R_f 0.29 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86-5.94 (1H, m, H-2'); 5.69 (1H, dm, *J* 5.7, H-10); 5.62 (1H, ddm, *J* 1.6, 5.7, H-9); 5.26 (1H, dm, *J* 17.2, H-3'); 5.18 (1H, br s, H-2); 5.13 (1H, d, *J* 10.5, H-3'); 4.23 (1H, dd, *J* 5.1, 13.4, H-1'); 4.04 (1H, dd, *J* 8.2, 8.6, H-4); 4.01 (1H, dd, *J* 5.7, 13.4, H-1'); 3.72 (1H, dd, *J* 8.6, 9.5, H-4); 3.36 (3H, s, -OCH_3); 2.61 (1H, ddd, *J* 6.1, 8.8, 9.3, H-5); 2.13-2.19 (2H, m, H-7 + H-8); 1.79 (1H, dd, *J* 5.3, 14.0, H-6*β*); 1.55 (1H, ddm, *J* 6.1, 14.0, H-6*α*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.85 (C-2'); 131.80 (C-10); 125.64 (C-9); 116.14 (C-3'); 101.60 (C-2); 90.01 (C-11); 71.97 (C-1); 70.30 (C-4); 68.34 (C-1'); 56.95 (-OCH_3); 54.52 (C-5); 36.48 (C-7 or 8); 36.33 (C-7 or 8); 25.20 (C-6); IR (thin film, cm^{-1}) , 3037, 2936, 1647 (C=C, vinyl), 1585 (C=C), 1449, 1389, 1305, 1214, 1176, 1115, 1081, 1003, 926, 844, 761, 702; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1147.

1-Methoxy-6-(2'-propenyloxy)-5-oxatricyclo[7.2.0^{1,9}.0^{3,7}]undeca-7,10-diene **170a**.



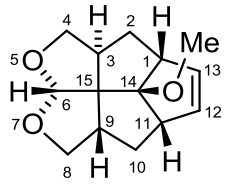
R_f 0.37 (Et_2O/CH_2Cl_2 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.12 (1H, ddd, *J* 0.9. 1.0, 2.9, H-11); 6.08 (1H, dd, *J* 1.0, 2.9, H-10); 5.92-5.94 (1H, m, H-8); 5.86-5.92 (1H, m, H-2'); 5.33 (1H, s, H-6); 5.25 (1H, dddd, *J* 1.6, 1.6, 1.6, 17.2, H-3'); 5.15 (1H, dddd, *J* 1.3, 1.4, 1.6, 10.3, H-3'); 4.31 (1H, dd, *J* 8.6, 8.6, H-4); 4.12 (1H, dddd, *J* 1.4, 1.4, 5.4, 12.8, H-1'); 4.00 (1H, dddd, *J* 1.2, 1.4, 6.1, 12.8, H-1'); 3.66 (1H, dd, *J* 5.8, 8.5, H-4); 3.35 (1H, dm, *J* 6.2, H-9); 3.30 (3H, s, -OCH_3); 2.65-2.73 (1H, m, H-3); 2.11 (1H, dd, *J* 5.4, 12.4, H-2); 1.25 (1H, t, *J* 12.5, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.98 (C-7); 138.60 (C-10); 136.41 (C-11); 134.59 (C-2'); 120.82 (C-8); 117.23 (C-3'); 102.65 (C-6); 83.96 (C-1); 72.23 (C-4); 67.66 (C-1'); 51.83 (-OCH_3); 46.15 (C-9); 35.11 (C-2); 33.53 (C-3); IR (thin film, cm^{-1}) , 3038, 2932, 2246, 1691 (C=C); 1647 (C=C, vinyl); 1563 (C=C, cyclobutene), 1459, 1374, 1343, 1312, 1293, 1172, 1100, 1035, 1003, 920, 831, 767, 730; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1147; LRMS (+EI) *m/z* calcd. $C_{14}H_{18}O_3$ [M+] = 234 found 234 (6%) fragments 207 (63%); 177 (81%); 161 (27%); 147 (89%); 133 (53%); 117 (96%); 105 (69%); 96 (44%); 91 (100%); 77 (72%); 65 (43%); 59 (28%); 51 (38%); 45 (24%); 39 (61%); 28 (56%).

1-Methoxy-6-(2'-propenyloxy)-5-oxatricyclo[7.2.0.0^{3,7}]-undeca-7,10-diene **170b**.



R_f 0.30 (Et_2O/CH_2Cl_2 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (1H, d, *J* 2.9, H-11); 6.03 (1H, dd, *J* 0.9, 2.9, H-10); 5.89-5.97 (2H, m, H-5 + H-2'); 5.41 (1H, br s, H-6); 5.27 (1H, dddd, *J* 1.7, 1.7, 1.7, 17.2, H-3'); 5.15 (1H, dddd, *J* 1.3, 1.3, 1.6, 10.4, H-3'); 4.20 (1H, dddd, *J* 1.4, 1.5, 5.3, 13.0, H-1'); 4.11 (1H, dd, *J* 8.0, 8.1, H-4); 4.04 (1H, dddd, *J* 1.3, 1.4, 6.2, 12.9, H-1'); 3.60 (1H, dd, *J* 8.1, 10.4, H-4); 3.39 (1H, dm, *J* 6.0, H-9); 3.29 (3H, s, -OCH_3); 2.51-2.60 (1H, m, H-3); 2.04 (1H, dd, *J* 5.3, 12.4, H-2); 1.34 (1H, t, *J* 12.4, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.36 (C-7); 138.03 (C-10); 136.79 (C-11); 134.67 (C-2'); 121.51 (C-8); 117.07 (C-3'); 102.34 (C-6); 85.56 (C-1); 71.51 (C-4); 68.53 (C-1'); 51.80 (-OCH_3); 46.56 (C-9); 36.85 (C-3); 32.61 (C-2); IR (thin film, cm^{-1}) , 2931, 1686 (C=C); 1647 (C=C, vinyl); 1564 (C=C, cyclobutene); 1459, 1343, 1293, 1258, 1207, 1158, 1099, 1070, 1003, 928, 818, 768, 724; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1145; LRMS (+EI) *m/z* calcd. $C_{14}H_{18}O_3$ [M+] = 234 found 234 (6%) fragments 233 (10%); 219 (5%); 208 (24%); 193 (10%) 177 (74%); 161 (41%); 147 (100%); 133 (56%); 117 (96%); 105 (60%); 91 (95%); 77 (57%); 65 (32%); 57 (34%); 41 (78%); 28 (48%).

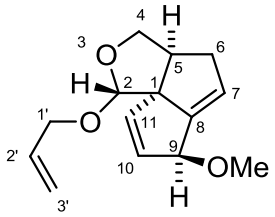
rac-(1R, 3S, 6R, 9S, 11S)-14-Methoxy-5,7-dioxapentacyclo[9.2.1.1^{3,14}.0^{6,15}.0^{9,15}] pentadec-12-ene **4**.



The linear *meta* adduct **2** (250 mg, 1.07 mmol) and acetophenone (192 mg, 1.60 mmol) were dissolved in MeCN (150 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 3.75 hrs using a 6 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (50:1 neutral silica; Et_2O/pentane, 30:70); to yield the double [3+2] cycloadduct **4** as a white to cream coloured solid (112 mg, 50%).

R_f 0.10 (Et_2O/petrol, 20:80); m.p. 85.0-89.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 (1H, ddd, *J* 1.8, 2.4, 6.0, H-12); 5.55 (1H, s, H-6); 5.47 (1H, ddd, *J* 1.5, 2.6, 6.0, H-13); 3.88 (1H, dd, *J* 4.7, 8.9, H-4*α*); 3.78 (1H, dd, *J* 6.1, 7.5, H-8*β*); 3.65 (1H, d, *J* 8.9, H-4*β*); 3.46 (1H, dd, *J* 7.5, 12.0, H-8*α*); 3.38 (1H, dddd, *J* 1.6, 2.5, 8.0, 8.4, H-11); 3.22 (3H, s, -OCH_3); 3.15 (1H, dddd, *J* 1.5, 1.8, 2.6, 9.7, H-1); 2.85 (1H, dddd, *J* 5.6, 6.0, 12.0, 13.7, H-9); 2.41 (1H, ddd, *J* 4.7, 8.1, 10.8, H-3); 2.02 (1H, ddd, *J* 5.4, 7.9, 11.2, H-10*β*); 1.80 (1H, ddd, *J* 9.7, 10.8, 13.2, H-2*β*); 1.74 (1H, ddd, *J* 1.5, 8.1, 13.1, H-2*α*); 1.18 (1H, ddd, *J* 8.4, 11.2, 13.7, H-10*α*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.22 (C-13); 132.17 (C-12); 102.89 (C-14); 102.38 (C-6); 77.38 (C-15); 72.70 (C-4); 68.50 (C-8); 61.44 (C-11); 53.09 (C-9); 52.09 (-OCH_3); 47.90 (C-1); 41.20 (C-3); 36.44 (C-2); 28.95 (C-10); IR (KBr disc, cm^{-1}) 3049, 2952, 1615 (C=C); 1464, 1359, 1290, 1160, 1112, 1020, 992, 934, 891, 862, 812, 783, 722, 686, 576; HRMS (ESI) *m/z* calcd. $C_{14}H_{19}O_3$ $[M+H]^+$ 235.1329, found 235.1328; LRMS (EI+) *m/z* calcd. $C_{14}H_{18}O_3$ [M+] = 234 found 234 (68%) fragments 204 (23%); 189 (11%); 175 (45%); 157 (39%); 144 (40%); 129 (46%); 109 (100%); 91 (66%); 77 (41%); 41 (20%).

rac-(1S, 2R, 5S, 9S)-2-(2'-Propenyloxy)-9-methoxy-3-oxatricyclo[6.3.0^{1,5}.0^{1,8}]undeca-7,10-diene **5**.



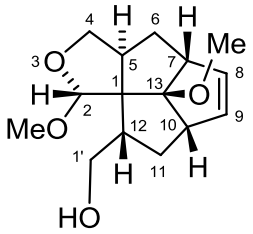
The linear *meta* adduct **2** (120 mg, 0.513 mmol) was dissolved in dry cyclohexane (450 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 9 hrs using an old 16 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting residue was dissolved in acetone (150 ml) and placed in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was irradiated for 1 hr using a 6 W low pressure Hg vapour lamp. The resulting yellow residue was subjected to flash column chromatography (40:1 neutral SiO_2; EtOAc/pentane 18:82) to afford **5** (20.0 mg, 17%) as a pale yellow oil.

R_f 0.38 (Et_2O/pentane, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (1H, d, *J* 6.0, H-11); 5.99 (1H, dd, *J* 2.5, 6.0, H-10); 5.85 (1H, dddd, *J* 5.3, 5.3, 10.5, 17.3, H-2'); 5.65 (1H, dd, *J* 1.7, 3.4, H-7); 5.23 (1H, dm, *J* 17.3, H-3'); 5.09 (1H, dm, *J* 10.5, H-3'); 4.83 (1H, s, H-2); 4.39 (1H, d, *J* 2.5, H-9); 4.08-4.13 (2H, m, H-1' + H-4α); 3.93 (1H, dddd, *J* 1.5, 1.6, 5.4, 13.3, H-1'); 3.77 (1H, d, *J* 8.6, H-4β); 3.30 (3H, s, -OCH_3); 2.81 (1H, ddd, *J* 3.4, 9.8, 16.5, H-6α); 2.77 (1H, ddd, *J* 4.6, 5.0, 9.8, H-5); 2.55 (1H, ddd, *J* 1.7, 5.0, 16.5, H-6β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.54 (C-8); 141.05 (C-11); 134.81 (C-2'); 132.41 (C-10); 126.99 (C-7); 116.05 (C-3'); 108.20 (C-2); 78.38 (C-9); 74.11 (C-1); 72.37 (C-4); 68.06 (C-1'); 56.42 (-OCH_3); 45.20 (C-5); 43.35 (C-6); HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1156, found 257.1153.

Reaction of dioxafenestrane **4** *with methanol to give acetal* **217** *and* **218**.

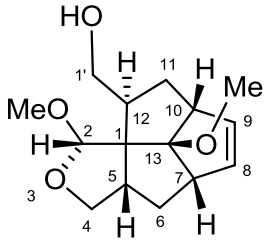
The dioxafenestrane product **4** (80.0 mg, 0.34 mmol) was dissolved in MeOH (2 ml) and allowed to stir under nitrogen for 10 days. The solvent was removed under reduced pressure to afford the crude tetracyclic acetal **217** as a yellow oil with one minor impurity. After chromatographic separation (50:1 silica, NEt_3/Et_2O/pentane 0.1:60:40); the major acetal product **217** was isolated (42 mg, 54%) plus the minor acetal product **218** (5 mg, 5.5%).

rac-(1R, 2R, 5S, 7R, 10S, 12S, 13R) 2,13-Dimethoxy-12-(hydroxymethyl)-3-oxatetracyclo [8.2.1.0^{1,5}.0^{7,13}]dodec-8-ene **217**.



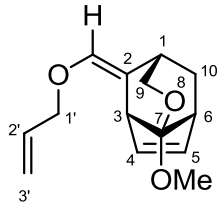
R_f 0.11 (EtOAc/petrol, 50:50); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.61 (1H, dm, *J* 5.8, H-9); 5.45 (1H, dm, *J* 5.8, H-8); 4.93 (1H, s, H-2); 4.03 (1H, dd, *J* 7.8, 8.9, H-4β); 3.79 (1H, dd, *J* 3.2, 8.9, H-4α); 3.73 (1H, dd, *J* 1.8, 11.4, -OH); 3.43-3.51 (1H, m, H-1'); 3.40 (3H, s, acetal -OCH_3); 3.37 (1H, ddd, *J* 2.0, 9.4, 11.7, H-1'); 3.18-3.21 (1H, m, H-7); 3.20 (3H, s, -OCH_3); 3.11 (1H, ddm, *J* 9.0, 9.2, H-10); 2.57 (1H, dddd, *J* 3.6, 6.8, 9.7, 12.8, H-12); 2.47 (1H, dddd, *J* 3.2, 7.8, 8.6, 10.9, H-5); 2.14 (1H, ddd, *J* 9.5, 10.6, 12.4, H-6); 2.04 (1H, ddd, *J* 6.7, 9.2, 12.7, H-11); 1.66 (1H, dd, *J* 8.6, 12.4, H-6); 0.94 (1H, ddd, *J* 9.0, 12.8, 12.8, H-11); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.38 (C-8); 132.50 (C-9); 109.16 (C-2); 106.24 (C-13); 73.43 (C-4); 71.23 (C-1); 63.44 (C-1'); 55.28 (acetal -OCH_3); 53.59 (C-7); 51.57 (-OCH_3); 51.41 (C-10); 49.88 (C-12); 41.95 (C-5); 37.23 (C-6); 33.21 (C-11); HRMS (ESI) *m/z* calcd. $C_{15}H_{22}NaO_4$ $[M+Na]^+$ 289.1410, found 289.1417.

rac-(1R, 2S, 5S, 7S, 10R, 12S, 13S) 2,13-dimethoxy-12-(hydroxymethyl)-3-oxatetracyclo [8.2.1.0^{1,5}.0^{7,13}] dodec-8-ene **218**.



R_f 0.18 (EtOAc/petrol, 50:50); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (1H, dm, *J* 5.7, H-8); 5.50 (1H, dm, *J* 5.7, H-9); 5.31 (1H, s, H-2); 4.09 (1H, dd, *J* 5.0, 8.5, H-4); 3.95 (1H, dd, *J* 2.6, 6.2, -OH); 3.67 (1H, d, *J* 8.4, H-4); 3.58 (1H, ddd, *J* 4.0, 6.3, 10.4, H-1'); 3.52 (3H, s, acetal -OCH_3); 3.47 (1H, dt, *J* 2.5, 10.4, H-1'); 3.19 (3H, s, -OCH_3); 3.13 (1H, br. d, *J* 9.3, H-7); 3.07 (1H, t, *J* 9.1, H-10); 2.69-2.78 (1H, m, H-12); 2.58-2.64 (1H, m, H-5); 2.15 (1H, ddd, *J* 7.1, 9.0, 12.7, H-11); 1.93 (1H, ddd, *J* 9.6, 9.6, H-6); 1.64-1.70 (1H, m, H-6); 0.97 (1H, ddd, *J* 9.3, 12.8, 12.8, H-11); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.43 (C-8); 132.71 (C-9); 108.71 (C-13); 107.01 (C-2); 72.27 (C-4); 69.05 (C-1); 62.47 (C-1'); 56.18 (acetal -OCH_3); 51.72 (-OCH_3); 51.69 (C-7); 50.15 (C-10); 45.39 (C-12); 44.85 (C-5); 35.60 (C-11); 35.51 (C-6); HRMS (ESI) *m/z* calcd. $C_{15}H_{22}NaO_4$ $[M+Na]^+$ 289.1410, found 289.1414.

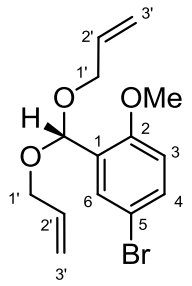
rac-(1S, 3R, 6R, 7R)-2(Z)-(2'-Propenyloxy)methylenyl-7-methoxy-8-oxatricyclo [4.3.1.0^{3,7}]dec-4-ene **219**.



The linear *meta* adduct **2** (50.0 mg) was dissolved in d_8-toluene (0.700 ml) and added to a re-sealable Young's tap NMR tube. This was sealed under a nitrogen atmosphere and heated to 200 °C for approximately 1.75 hrs. The major product was isolated by flash chromatography (40:1 SiO_2; Et_2O/pentane 10:90); yielding triene **219** (30.0 mg, 59%) as a colourless semi-solid.

R_f 0.48 (Et_2O/pentane 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 (1H, d, *J* 2.5, =C(H)O); 5.83-5.92 (1H, m, H-2'); 5.87 (1H, dd, *J* 3.3, 6.4, H-5); 5.78 (1H, dd, *J* 3.1, 6.3, H-4); 5.25 (1H, dm, *J* 17.2, H-3'); 5.09 (1H, dm, *J* 10.3, H-3'); 4.41 (1H, dd, *J* 8.3, 9.4, H-9); 3.93 (2H, dm, *J* 5.4, H-1'); 3.70 (1H, dd, *J* 8.3, 12.9, H-9); 3.33 (1H, d, *J* 3.1, H-3); 3.21 (3H, s, -OCH_3); 2.92 (1H, ddddd, *J* 2.5, 7.7, 9.4, 9.6, 12.9, H-1); 2.73 (1H, ddd, *J* 2.7, 3.3, 3.6, H-6); 1.72 (1H, ddd, *J* 3.6, 7.7, 12.5, H-10α); 1.49 (1H, ddd, *J* 2.7, 9.6, 12.5, H-10β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.07 (=C(H)O-); 134.92 (C-2'); 130.87 (C-5); 130.34 (C-4); 116.16 (C-3'); 114.51 (C-2); 111.35 (C-7); 76.04 (C-9); 63.00 (C-1'); 48.69 (OCH_3); 44.00 (C-3); 43.66 (C-6); 36.86 (C-1); 28.36 (C-10); IR (thin film, cm^{-1}) , 3061, 2941, 2862, 1765, 1667 (C=C) 1646 (C=C, vinyl); 1598 (C=C); 1463, 1368, 1348, 1320, 1288, 1238, 1189, 1126, 1059, 1006, 949, 921, 787, 771, 704; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1150.

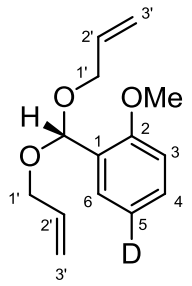
1-(Bis(2'-propenyloxy)methyl)-2-methoxy-5-bromobenzene **223**.



Trimethylsilyl trifluoromethanesulfonate (0.206 ml, 0.93 mmol); was added to CH_2Cl_2 (20 ml) under a nitrogen atmosphere at -84 °C, and magnetically stirred for five minutes. Allyloxytrimethylsilane (19.1 ml, 116 mmol) and 5-bromo-2-anisaldehyde **222** (10.0 g, 46.5mmol) were added sequentially and drop wise, whilst maintaining the same temperature. The resulting pale yellow mixture was stirred at -84 °C for six hours, quenched with pyridine (5 ml) at the same temperature, and then poured into a saturated solution of $NaHCO_3$ (50 ml). The aqueous layer was extracted with Et_2O (3 x 50 ml); and the combined organic layers dried over anhydrous $MgSO_4$. Excess solvent was removed under reduced pressure and the resulting oil was purified, when required, by flash column chromatography (EtOAc/petrol, 2:98); to yield **223** (12.8 g, 87%) as a yellow oil.

R_f 0.34 (Et_2O/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (1H, br s, H-6); 7.38 (1H, br d, *J* 8.7, H-4); 6.74 (1H, br d, *J* 8.7, H-3); 5.85-5.95 (2H, m, H-2'); 5.81 (1H, s, -C(H)O_2); 5.26 (2H, dm, *J* 17.3, H-3'); 5.14 (2H, dm, *J* 10.5, H-3'); 4.06 (4H, dm, *J* 5.5, H-1'); 3.80 (3H, s, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.16 (C-2); 134.46 (C-2'); 132.29 (C-4); 130.47 (C-6); 128.84, 116.88 (C-3'); 112.92, 112.50 (C-3); 95.66 (-C(H)O_2); 67.11 (C-1'); 55.82 (-OCH_3); IR (thin film, cm^{-1}) 3080, 2938, 1647 (C=C, vinyl); 1596 (C=C, aromatic); 1486, 1462, 1377, 1249, 1093, 1020, 921, 807, 754; HRMS (EI) *m/z* calcd. $C_{14}H_{17}Br^{79}NaO_3$ $[M+Na]^+$ 335.0259, found 335.0253.

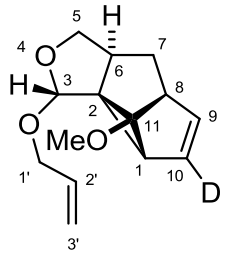
1-(Bis(2'-propenyloxy)methyl)-2-methoxy-5-deuterobenzene $\mathbf{1_D}$.



1-(Bis(2'-propenyloxy)methyl)-2-methoxy-5-bromobenzene **223** (4.00 g, 12.78mmol) in dry THF (12 ml) was cooled to -84 °C under an atmosphere of nitrogen. To this solution was added *n*-butyllithium (2.5 M in hexanes, 6.65 ml, 16.6 mmol) drop wise. Immediately after complete addition, H_3COD (1.04 ml, 25.6 mmol) was added drop wise to the solution. The reaction was warmed to ambient temperature and allowed to stir for 1 hour. Et_2O (20 ml) was added then H_2O (2 x 20 ml) and the separated organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue subjected to flash column chromatography (40:1 silica; Et_2O/petrol, 8:92); to yield the deuterated product $\mathbf{1_D}$ (2.35 g, 78%) as a colourless oil with greater than 80% deuteration at C-5.

R_f 0.22 (Et_2O/petrol, 8:92); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (1H, br. s, H-6); 7.28 (1H, br. d, *J* 8.4, H-4); 6.87 (1H, br. d, *J* 8.4, H-3); 5.88-5.96 (2H, m, H-2'); 5.88 (1H, s, -C(H)O_2); 5.27 (2H, dm, *J* 17.1, H-3'); 5.12 (2H, dm, *J* 10.5, H-3'); 4.07 (4H, dm, *J* 5.6, H-1'); 3.82 (3H, s, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.01 (C-2); 134.69 (C-2'); 129.43 (C-4); 127.27 (C-6); 126.58 (C-1); 119.93 (t, $J_{C\text{-}D}$ 24.6, C-5); 116.44 (C-3'); 110.58 (C-3); 96.26 (-C(H)O_2); 66.94 (C-1'); 55.44 (-OCH_3); HRMS (ESI) *m/z* calcd. $C_{14}H_{17}DNaO_3$ $[M+Na]^+$ 258.1216, found 258.1211.

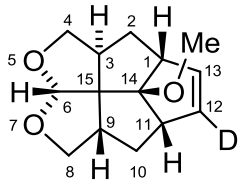
rac-(1R, 2R, 3R, 6S, 8S, 11S)-3-(2'-Propenyloxy)-10-deutero-11-methoxy-4-oxatetracyclo[6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **2$_D$**.



A solution of acetal photosubstrate **1$_D$** (1.00 g, 8.51 mmol) in dry cyclohexane (350 ml) was degassed with nitrogen for 20 mins in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 18 hrs using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The solvent was removed under reduced pressure, and the resulting yellow residue was subjected to flash column chromatography (100:1 silica, triethylamine/Et_2O/petrol, 0.2:20:80) to afford the linear *meta* photocycloadduct **2$_D$** (142 mg, 14%) as a pale yellow oil. Other isomers were observed, but not isolated.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, dddd, *J* 5.4, 6.1, 10.3, 17.2, H-2'); 5.52 (1H, dd, *J* 1.2, 2.8, H-9); 5.26 (1H, dm, *J* 17.2, H-3'); 5.16 (1H, d, *J* 10.3, H-3'); 4.93 (1H, br s, H-3); 4.19 (1H, dd, *J* 7.9, 8.9, H-5α); 4.15 (1H, dd, *J* 5.4, 13.0, H-1'); 3.98 (1H, ddm, *J* 6.1, 13.0, H-1'); 3.70 (1H, ddm, *J* 2.0, 8.9, H-5β); 3.39 (3H, s, -OCH_3); 3.33 (1H, dm, *J* 2.7, H-8); 2.46 (1H, br s, H-1); 2.37 (1H, dddd, *J* 2.0, 7.9, 7.9, 7.9, H-6); 1.97 (2H, dd, *J* 3.0, 8.2, H-7α + H-7β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.80 (C-2'); 132.63 (C-9); 117.06 (C-3'); 100.52 (C-3); 89.27 (C-11); 71.60 (C-5); 68.05 (C-1'); 56.80 (-OCH_3); 55.79 (C-2); 52.73 (C-8); 46.02 (C-7); 40.42 (C-6); 37.14 (C-1) [Note that the C-10 signal was obscured within the spectral noise]; HRMS (ESI) *m/z* calcd. $C_{14}H_{17}DNaO_3$ $[M+Na]^+$ 258.1211, found 258.1208.

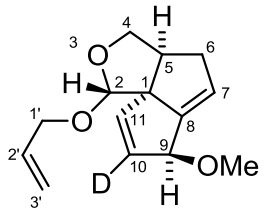
rac-(1R, 3S, 6S, 9S, 11S, 14S, 15R)-14-Methoxy-12-deutero-5,7-dioxapentacyclo [9.2.1.1^{3,14}.0^{6,15}.0^{9,15}] pentadec-12-ene **4$_D$**.



The linear *meta* adduct **2$_D$** (140 mg, 0.595 mmol) was dissolved in dry cyclohexane (350 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 12 hrs using a new 16 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (40:1 neutral silica; EtOAc/pentane 18:82); to yield the deuterated double [3+2] cycloadduct **4$_D$** as a yellow oil (16.0 mg, 11%).

R_f 0.30 (EtOAc/pentane 18:82); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.54 (1H, s, H-6); 5.46 (1H, br s, H-13); 3.88 (1H, dd, *J* 4.7, 8.9, H-4α); 3.77 (1H, dd, *J* 6.1, 7.5, H-8β); 3.64 (1H, d, *J* 8.9, H-4β); 3.45 (1H, dd, *J* 7.5, 12.0, H-8α); 3.38 (1H, ddm, *J* 8.0, 8.4, H-11); 3.22 (3H, s, -OCH_3); 3.14 (1H, dm, *J* 9.7, H-1); 2.85 (1H, dddd, *J* 5.6, 6.0, 12.0, 13.7, H-9); 2.41 (1H, ddd, *J* 4.7, 8.1, 10.8, H-3); 2.02 (1H, ddd, *J* 5.4, 7.9, 11.2, H-10β); 1.80 (1H, ddd, *J* 9.7, 10.8, 13.2, H-2β); 1.73 (1H, ddd, *J* 1.5, 8.1, 13.1, H-2α); 1.17 (1H, ddd, *J* 8.4, 11.2, 13.7, H-10α); ^{13}C NMR (150 MHz, $CDCl_3$): δ 133.16 (C-13); 131.97 (t, $J_{C\text{-}D}$ 25.3, C-12); 102.98 (C-14); 102.47 (C-6); 77.45 (C-15); 72.78 (C-4); 68.58 (C-8); 61.45 (C-11); 53.17 (C-9); 52.18 (-OCH_3); 47.95 (C-1); 41.27 (C-3); 36.51 (C-2); 29.02 (C-10); HRMS (ESI) *m/z* calcd. $C_{14}H_{17}DNaO_3$ $[M+Na]^+$ 258.1216, found 258.1211.

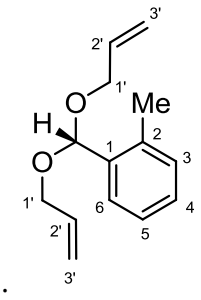
rac-(1S, 2R, 5S, 9S)-2-(2'-Propenyloxy)-9-methoxy-10-deutero-3-oxatricyclo [6.3.0.0^{1,5}]undeca-7,10-diene **5$_D$**.



The linear *meta* adduct **2$_D$** (250 mg, 1.06 mmol) was dissolved in dry cyclohexane (350 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 120 hrs using an old 16 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (40:1 neutral SiO_2; EtOAc/pentane 18:82) to afford 1,2 methoxy migration adduct **5$_D$** (41.0 mg, 16%) as a pale yellow oil.

R_f 0.38 (Et_2O/pentane 20:80); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.34 (1H, s, H-11); 5.84 (1H, dddd, *J* 5.3, 5.3, 10.5, 17.3, H-2'); 5.65 (1H, dd, *J* 1.7, 3.4, H-7); 5.23 (1H, dm, *J* 17.3, H-3'); 5.09 (1H, dm, *J* 10.5, H-3'); 4.83 (1H, s, H-2); 4.38 (1H, s, H-9); 4.08-4.13 (2H, m, H-1' + H-4α); 3.93 (1H, dddd, *J* 1.5, 1.6, 5.4, 13.3, H-1'); 3.77 (1H, d, *J* 8.6, H-4β); 3.30 (3H, s, -OCH_3); 2.81 (1H, ddd, *J* 3.4, 9.8, 16.5, H-6α); 2.77 (1H, ddd, *J* 4.6, 5.0, 9.8, H-5); 2.55 (1H, ddd, *J* 1.7, 5.0, 16.5, H-6β); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.50 (C-8); 140.91 (C-11); 134.77 (C-2'); 132.13 (t, $J_{C\text{-}D}$ 25.6, C-10); 127.01 (C-7); 116.07 (C-3'); 108.17 (C-2); 78.27 (C-9); 74.07 (C-1); 72.36 (C-4); 68.03 (C-1'); 56.42 (-OCH_3); 45.15 (C-5); 43.34 (C-6); HRMS (ESI) *m/z* calcd. $C_{14}H_{17}DNaO_3$ $[M+Na]^+$ 258.1216, found 258.1205.

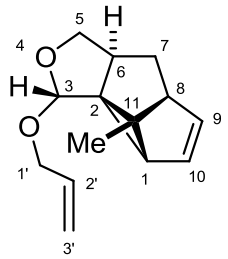
1-(Bis(2'-propenyloxy)methyl)-2-methylbenzene **130**.[58]



This compound had previously been prepared by Wender, Dore and deLong.[58] Trimethylsilyl trifluoromethanesulfonate (0.075 ml, 0.42 mmol); was added to CH_2Cl_2 (20 ml) under a nitrogen atmosphere at -84 °C, and magnetically stirred for five minutes. Allyloxytrimethylsilane (17.2 ml, 104 mmol) and *o*-tolualdehyde **230** (5.00 g, 41.6 mmol) were added sequentially and drop wise, whilst maintaining the same temperature. The resulting pale yellow mixture was allowed to warm to -30 °C and stirred at this temperature for five hrs. The subsequent deep orange-red mixture was then quenched with pyridine (10 ml) at the same temperature, and poured into a saturated solution of $NaHCO_3$ (100 ml). The aqueous layer was extracted with E_2O (3 x 50 ml); and the combined organic layers dried over anhydrous $MgSO_4$. Excess solvent was removed under reduced pressure and the resulting oil was purified by flash column chromatography (Et_2O/petrol 5:95) to yield **130** (8.91 g, 99%) as a colourless oil.

R_f 0.57 (Et_2O/petrol 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, br d, *J* 7.4, H-6); 7.20-7.27 (2H, m, H-4 + H-5); 7.18 (1H, br d, *J* 7.1, H-3); 5.95 (2H, dddd, *J* 4.8, 5.6, 10.5, 17.3, H-2'); 5.72 (1H, s, -C(H)O_2); 5.32 (2H, dm, *J* 17.4, H-3'); 5.18 (2H, dm, *J* 10.5, H-3'); 4.02-4.12 (2H, m, H-1'); 2.41 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.27 (C-2); 136.02 (C-1); 134.56 (C-2'); 130.47 (C-3); 128.35 (C-4); 126.62 (C-6); 125.42 (C-5); 116.68 (C-3'); 98.99 (-C(H)O_2); 66.42 (C-1'); 18.93 (-CH_3).); HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1196.

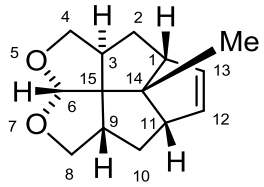
rac-(1S, 2R, 3R, 6S, 8R, 11R)-3-(3'-Propenyloxy)-11-methyl-4-oxatetracyclo [6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **131**.[58]



This compound had previously been prepared by Wender, Dore and deLong.[58] A solution of acetal **130** (2.00 g, 4.59 mmol) in dry cyclohexane (450 ml) was degassed with nitrogen for 20 mins in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 9.5 hrs using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) or until NMR analysis revealed complete consumption of the starting aromatic compound. The solvent was removed under reduced pressure, and the resulting yellow residue was subjected to flash column chromatography (100:1 silica, triethylamine/Et_2O/petrol 0.5:20:80) to afford the linear *meta* photocycloadduct **131** (484 mg, 24%) as a colourless oil. Other isomers were observed, but not isolated.

R_f 0.14; (Et_2O/petrol 2:98); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (1H, dddd, *J* 5.2, 6.3, 10.4, 17.2, H-2'); 5.68 (1H, dd, *J* 2.2, 5.5, H-10); 5.39 (1H, ddd, *J* 0.8, 2.4, 5.5, H-9); 5.23 (1H, dm, *J* 17.3, H-3'); 5.13 (1H, dm, *J* 10.4, H-3'); 4.67 (1H, s, H-3); 4.16 (1H, dd, *J* 7.6, 8.7, H-5α); 4.13 (1H, dddd, *J* 1.5, 1.5, 5.3, 13.1, H-1'); 3.96 (1H, dddd, *J* 1.3, 1.4, 6.3, 13.1, H-1'); 3.65 (1H, dd, *J* 2.4, 8.8, H-5β); 2.90 (1H, dd, *J* 2.4, 5.0, H-8); 2.41-2.47 (1H, m, H-6); 1.94 (1H, br s, H-1); 1.88 (1H, ddm, *J* 6.4, 11.6, H-7β); 1.81 (1H, ddd, *J* 5.1, 9.7, 11.6, H-7α); 1.30 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.84 (C-2'); 132.86 (C-9); 129.13 (C-10); 116.87 (C-3'); 101.64 (C-3); 71.58 (C-5); 67.66 (C-1'); 57.44 (C-8); 53.71 (C-2); 46.53 (C-7); 46.49 (C-11); 40.60 (C-6); 38.58 (C-1); 14.31 (-CH_3); IR (thin film, cm^{-1}) 3052, 2925, 2881, 1647 (C=C, vinyl); 1590, 1448, 1422, 1360, 1340, 1241, 1196, 1173, 1147, 1120, 1090, 1047, 1001, 961, 913, 748; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1196.

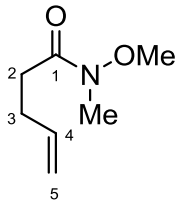
rac-(1R, 3S, 6S, 9S, 11S, 14R, 15R)-14-Methyl-5,7-dioxapentacyclo [9.2.1.1^{3,14}.0^{6,15}.0^{9,15}]pentadec-12-ene **231**.



The linear *meta* adduct **131** (198 mg, 1.01 mmol) and acetophenone (182 mg, 1.51 mmol) were dissolved in MeCN (150 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 mins in order to remove dissolved oxygen. The mixture was then irradiated for 4.5 hrs using a 6 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (100:1 neutral silica, Et_2O/pentane 20:80); to yield the double [3+2] cycloadduct **231** as a pale yellow oil (62.0 mg, 31%).

R_f 0.24 (Et_2O/pentane, 20:80); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.61 (1H, ddd, *J* 2.1, 2.2, 5.8, H-12); 5.40 (1H, ddd, *J* 1.9, 2.3, 5.8, H-13); 5.33 (1H, s, H-6); 3.89 (1H, dd, *J* 5.0, 9.0, H-4α); 3.78 (1H, dd, *J* 6.4, 7.6, H-8β); 3.66 (1H, d, *J* 8.8, H-4β); 3.48 (1H, dd, *J* 7.4, 11.9, H-8α); 2.97 (1H, dddd, *J* 1.9, 2.1, 7.7, 8.5, H-11); 2.70 (1H, dm, *J* 9.8, H-1); 2.66 (1H, dddd, *J* 5.6, 6.4, 11.9, 14.1, H-9); 2.44 (1H, ddd, *J* 4.8, 8.0, 11.0, H-3); 1.95 (1H, ddd, *J* 5.6, 7.7, 11.2, H-10β); 1.78 (1H, dd, *J* 8.2, 13.0, H-2α); 1.70 (1H, ddd, *J* 9.8, 11.0, 13.1, H-2β); 1.27 (3H, s, -CH_3); 1.19 (1H, ddd, *J* 8.5, 11.3, 14.1, H-10α); ^{13}C NMR (150 MHz, $CDCl_3$): δ 132.90 (C-13); 131.96 (C-12); 103.06 (C-6); 78.21 (C-15); 72.71(C-4); 68.82(C-8); 66.74 (C-11); 58.60 (C-14); 56.15 (C-1); 53.24 (C-9); 42.85 (C-3); 37.41 (C-2); 29.92 (C-10); 22.97 (-CH_3); IR (thin film, cm^{-1}) 3039, 2946, 2881, 1686, 1620 (C=C, alkene); 1490, 1454, 1374, 1353, 1330, 1315, 1288, 1253, 1237, 1197, 1167, 1140, 1099, 1076, 1052, 1040, 988, 938, 871, 820, 805, 774, 760, 679; HRMS (ESI) *m/z* calcd. $C_{14}H_{19}O_2$ $[M+H]^+$ 219.1380, found 219.1386. LRMS (+EI) *m/z* calcd. $C_{14}H_{18}O_2$ [MH+] = 219 found 219 (27%) fragments 190 (86%); 172 (46%); 159 (100%); 144 (43%); 131 (87%); 117 (56%); 105 (48%); 91 (69%); 80 (52%); 67 (19%); 43 (22%); 28 (45%).

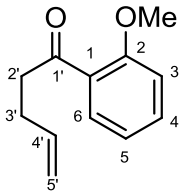
Pent-4-enoic acid methoxy-methyl-amide **255**.



This compound had previously been prepared by Lebreton *et al.*[141] 4-pentenoic acid (10.0 g, 100 mmol) was dissolved in CH_2Cl_2 (200 ml) in a three-necked flask fitted with a thermometer, nitrogen inlet and stopper. The reaction vessel was cooled to 0 ºC and 1,1-carbonyldiimidazole (17.8 g, 110 mmol) was added in portions. This was allowed to stir at 0 ºC for two hours, ensuring that all evolution of CO_2 had ceased. After this time, *N,O*–dimethylhydroxylamine hydrochloride (10.7 g, 110 mmol) was introduced to the reaction via a funnel in portions and the mixture was left to stir overnight. A saturated solution of NH_4Cl (200 ml) was added to the flask and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 ml) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (200 ml); brine (200 ml) and then dried over anhydrous $MgSO_4$. Volatile solvents were removed under vacuum. Dependant on the quality of starting materials, the crude material occasionally required purified by flash column chromatography (EtOAc/petrol 40:60) to afford the amide **255** as a pale yellow and fragrant oil (13.5 g, 94%).

R_f 0.44 (EtOAc/petrol, 40:60); ^{1}H NMR (500 MHz, $CDCl_3$): d 5.78-5.87 (1H, m, H-3'); 5.03 (1H, dm, *J* 17.1, H-4'); 4.95 (1H, dm, *J* 10.2, H-4'); 3.65 (3H, s, -OCH_3); 3.14 (3H, s, CH_3); 2.49 (2H, dd, *J* 7.9, 8.1, H-1'); 2.35 (2H, m, H-2'); 13C NMR (125 MHz, CDCl3): _ 173.74 (C=O); 137.38 (C-3'); 115.00 (C-4'); 61.12 (-OCH3); 32.11 (-CH3); 31.12 (C-1'); 28.47 (C-2'); IR (thin film, cm^{-1}) 2939, 1661 (C=O, amide); 1416, 1384, 1176, 1116, 994, 913, 741, 699, 563 cm^{-1}; HRMS (ESI) *m/z* calculated 166.0844, found 166.0842.

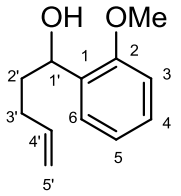
1-(2-Methoxy-phenyl)-pent-4'-en-1-one **256**.



o-Bromoanisole **253** (10.0 g, 53.5 mmol) in dry THF (40 ml) was cooled to -78 °C under an atmosphere of dry nitrogen. To this solution was added *n*-butyllithium (2.5 M in hexanes, 30.0 ml, 74.9 mmol) drop wise over a period of 45 minutes. After complete addition, the mixture was allowed to stir at -78 °C for 15 minutes. Next, pent-4-enoic acid methoxy-methyl-amide (9.18 g, 64.2 mmol) was added drop wise to the solution *via* the dropping funnel. The reaction was warmed to ambient temperature and allowed to stir for 6 hours. The mixture was diluted with Et_2O (100 ml); then washed with saturated NH_4Cl solution (2 x 50 ml); H_2O (2 x 25 ml) and brine (2 x 25 ml). The organic phase was dried over anhydrous $MgSO_4$ and volatile solvents removed under reduced pressure. Purification was conducted using flash column chromatography (EtOAc/petrol 5:95) to yield the ketone **256** (6.25 g, 62%) as an orange oil.

R_f 0.28 (EtOAc/petrol, 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, d, *J* 7.6, H-6); 7.45 (1H, dd, *J* 8.3, 7.4 H-4); 7.00 (1H, dd, *J* 7.5, 7.6 H-5); 6.96 (1H, d, *J* 8.3, H-3); 5.85-5.93 (1H, ddt, *J* 6.7, 10.2, 17.2 H-4'); 5.05 (1H, d, *J* 17.2, H-5'); 4.98 (1H, d, *J* 10.2, H-5') 3.90 (3H, s, -OCH_3); 3.07 (2H, dd, *J* 7.3, 7.5, H-2'); 2.44 (2H, m, H-3'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.88 (C-1', C=O); 158.44 (C-2); 137.78 (C-4'); 133.23 (C-4); 130.21 (C-6); 128.50 (C-1); 120.64 (C-5); 114.77 (C-5'); 111.50 (C-3); 55.46 (-OCH_3); 42.90 (C-2'); 28.41 (C-3'). IR (thin film, cm^{-1}) 3076, 3003, 2976, 2943, 1674 (C=O); 1641 (C=C, vinyl); 1598 (C=C, aromatic); 1485, 1465, 1437, 1360, 1286, 1245, 1181, 1163, 1114, 1023, 985, 913, 757; HRMS (ESI) *m/z* calcd. $C_{12}H_{14}NaO_2$ $[M+Na]^+$ 213.0886, found 213.0887.

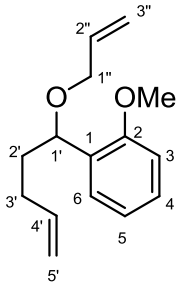
1-(2-Methoxy-phenyl)-pent-4'-en-1'-ol **257**.



This compound had previously been prepared by Cornelisse, Lodder *et al*.[35] A magnetically stirred solution of ketone **256** (3.00 g, 15.8 mmol) in MeOH (20 ml) was cooled to 0 °C. Sodium borohydride (1.25 g, 33.2 mmol) was added cautiously, in portions, over 15 minutes. The reaction was allowed to warm to ambient temperature and stirred for 16 hours. A saturated solution of NH_4Cl (25 ml) was carefully added and the solution was partitioned between Et_2O (50 ml) and H_2O (50 ml). The aqueous layer was further washed with Et_2O (2 x 50 ml). Combined organic layers were collected, dried over $MgSO_4$ and the volatile solvents removed under reduced pressure. Further purification was not required with alcohol **257** (2.92 g, 96%) acquired as a pale yellow oil.

R_f 0.14 (Et_2O/petrol, 10:90); Data previously collected by Cornelisse, Lodder *et al*.[35] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (1H, d, *J* 7.5, H-3); 7.25 (1H, dd, *J* 8.2, 7.6 H-5); 6.96 (1H, dd, *J* 7.5, 7.5 H-4); 6.89 (1H, d, *J* 8.2, H-6); 5.85-5.90 (1H, ddt, *J* 6.6, 10.1, 17.0 H-4'); 5.06 (1H, d, *J* 17.0, H-5'); 4.98 (1H, d, *J* 10.1, H-5'); 4.90 (1H, m, H-1'); 3.86 (3H, s, -OCH_3); 2.57 (1H, s, -OH); 2.23 (1H, m, H-3'); 2.15 (1H, m, H-3'); 1.90 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.58 (C-2); 138.53 (C-4'); 132.39 (C-1); 128.26 (C-5); 126.97 (C-3); 120.74 (C-4); 114.56 (C-5'); 110.54 (C-6); 70.54 (C-1'); 55.24 (-OCH_3); 36.38 (C-2'); 30.28 (C-3'). IR (thin film, cm^{-1}) 3399 (-OH); 2938, 1640 (C=C, vinyl); 1601 (C=C, aromatic); 1588, 1491, 1464, 1287, 1240, 1099, 1050, 1029, 911, 754; HRMS (ESI) *m/z* calcd. $C_{12}H_{16}NaO_2$ $[M+Na]^+$ 215.1042, found 215.1043.

1-(1'-Allyloxy-pent-4'-enyl)-2-methoxy-benzene **243**.



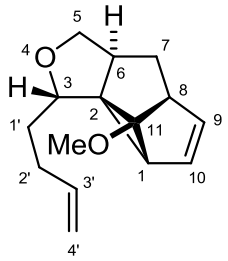
To a stirred solution of alcohol **257** (2.92 g, 15.2 mmol) and allyl bromide (6.58 ml, 76.1 mmol) in CH_2Cl_2 (10 ml) under a nitrogen atmosphere, was added 50% NaOH (25 ml) and TBAHS (10.3 g, 30.4 mmol). This was allowed to stir for 3 days until TLC showed complete conversion of the starting material. The reaction was quenched with saturated NH_4Cl solution (50 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure and the resulting residue purified by flash column chromatography (Et_2O/petrol, 10:90) to yield the ether photosubstrate **243** (2.81 g, 80%) as a yellow oil.

R_f 0.63 (Et_2O/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (1H, br d, *J* 7.4, H-6); 7.24 (1H, br. t, *J* 7.8 H-4); 6.99 (1H, t, *J* 7.4, H-5); 6.87 (1H, br. d, *J* 8.2, H-3); 5.81-5.98 (2H, m, H-4', H-2"); 5.26 (1H, d, *J* 17.2, H-3"); 5.14 (1H, d, *J* 10.4, H-3"); 5.03 (1H, d, *J* 17.2, H-5'); 4.95 (1H, d, *J* 10.2, H-5') 4.80 (1H, dd, *J* 5.1, 7.7, H-1'); 3.93 (1H, dd, *J* 5.2, 12.7, H-1"); 3.82 (3H, s, -OCH_3); 3.79 (1H, dd, *J* 5.9, 12.7, H-1"); 2.09-2.28 (2H, m, H-3'); 1.72-1.85 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.94 (C-2); 138.74 (C-4'); 135.28 (C-2"); 130.92 (C-1); 127.97 (C-4); 126.64 (C-6); 120.69 (C-5); 116.33 (C-3"); 114.22 (C-5'); 110.24 (C-3); 74.38 (C-1'); 69.78 (C-1"); 55.26 (-OCH_3); 36.08 (C-2'); 30.00 (C-3'). IR (thin film, cm^{-1}) 1640 (C=C, vinyl); 1601 (C=C, aromatic); 1598; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1361, found 255.1364.

Direct irradiation of ether photosubstrate **243** *to yield linear meta adducts* **245** *and* **247**, *angular meta adduct* **259** *and ortho derived adduct* **260**.

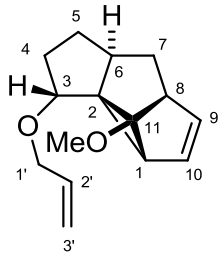
A solution of ether **243** (3.00 g, 12.9 mmol) in dry cyclohexane (150 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 32 hours using a 6 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting yellow residue subjected to flash column chromatography (100:1 silica, EtOAc/petrol, 10:90) to afford *meta* adduct **245** (250 mg, 8.3%). A second separation (Et_2O/pentane 4:94 to 20:80) gave linear *meta* photocycloadduct **247** (145 mg, 4.8%), angular *meta* adduct **259** (55 mg, 1.8%) and *ortho* derived adduct **260** (540 mg, 18%) were also isolated pure from the reaction mixture. Other impure adducts that included further *ortho* derivatives and degradation products from apparent Norrish type reactions also existed in the crude photolysis residue, but could not be obtained in a satisfactorily purified form.

rac-(1R, 2S, 3S, 6S, 8S, 11S)-3-(3'-Butenyl)-11-methoxy-4-oxatetracyclo [6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **245**.



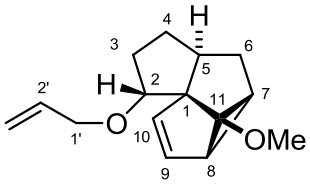
R_f 0.24 (EtOAc/petrol, 10:90) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (1H, dddd, *J* 6.7, 6.7, 10.4, 17.1, H-3'); 5.66 (1H, dd, *J* 2.4, 5.6, H-10); 5.56 (1H, ddd, *J* 1.2, 2.7, 5.6, H-9); 5.03 (1H, d, 17.1, H-4'); 4.95 (1H, d, *J* 10.4, H-4'); 4.07 (1H, dd, *J* 7.7, 8.9, H-5β); 4.00 (1H, dd, *J* 3.3, 9.4, H-3α); 3.57 (1H, dd, *J* 4.7, 9.0, H-5α); 3.41 (3H, s, -OCH_3); 3.40-41 (1H, m, H-8); 2.32-2.38 (1H, m, H-6β); 2.20-2.28 (1H, m, H-2') 2.14-2.16 (1H, m, H-1); 2.07-2.15 (1H, m, H-2'); 1.94 (1H, ddd, *J* 5.4, 9.2, 11.7, H-7α); 1.87 (1H, dd, *J* 6.7, 11.7, H-7β); 1.63 (1H, dddd, *J* 5.1, 9.6, 10.0, 14.1, H-1'); 1.46 (1H, dddd, *J* 3.4, 6.3, 9.9, 14.1, H-1'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.54 (C-3'); 133.06 (C-9); 127.87 (C-10); 114.43 (C-4'); 88.27 (C-11); 75.17 (C-3); 71.91 (C-5); 56.63 (-OCH_3); 56.16 (C-2); 53.61 (C-8); 44.22 (C-7); 43.14 (C-6); 37.04 (C-1) 31.93 (C-1'); 29.92 (C-2'); IR (thin film, cm^{-1}) 3055, 2935, 2855, 1640 (C=C, vinyl); 1586 (C=C, alkene); 1450, 1401, 1356, 1340, 1325, 1305, 1246, 1231, 1193, 1170, 1133, 1097, 1071, 1008, 911, 864, 748, 734; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1347.

rac-(1R, 2S, 3R, 6S, 8S, 11S)-3-(2'-Propenyloxy)-11-methoxy-tetracyclo [6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **247**.



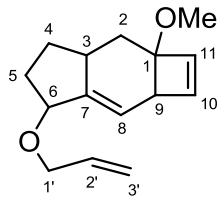
R_f 0.28 (Et_2O/pentane, 4:96) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, dddd, *J* 5.6, 5.7, 10.4, 17.2, H-2'); 5.71 (1H, dd, *J* 2.0, 5.7, H-10); 5.51 (1H, ddd, *J* 1.3, 2.7, 5.6, H-9); 5.26 (1H, dddd, *J* 1.6, 1.7, 1.7, 17.2, H-3'); 5.14 (1H, dddd, *J* 1.4, 1.4, 1.7, 10.4, H-3'); 4.02 (1H, dddd, *J* 1.5, 1.5, 5.5, 12.9, H-1'); 3.93 (1H, dddd, *J* 1.4, 1.5, 5.7, 12.9, H-1'); 3.76 (1H, dd, *J* 2.2, 4.3, H-3); 3.38 (3H, s, -OCH_3); 3.24 (1H, dd, *J* 2.7, 5.6, H-8); 2.47 (1H, m, H-1); 2.20-2.26 (1H, m, H-6α) 2.04-2.11 (1H, m, H-5α); 1.97-2.03 (1H, m, H-4α); 1.82-1.89 (2H, m, H-4β/H-7β); 1.73 (1H, ddd, *J* 5.5, 9.7, 11.7, H-7α); 1.34 (1H, dddd, *J* 2.9, 2.9, 7.5, 12.5, H-5β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.59 (C-2'); 132.55 (C-9); 128.62 (C-10); 116.35 (C-3'); 90.37 (C-11); 78.53 (C-3); 69.70 (C-1'); 56.85 (-OCH_3); 56.15 (C-2); 52.48 (C-8); 45.51 (C-7); 40.14 (C-6); 37.92 (C-1) 33.12 (C-4); 28.49 (C-5); HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1353.

rac-(1S, 2R, 5S, 7R, 8S, 11S)-2-(2'-Propenyloxy)-11-methoxytetracyclo [5.3.1.0^{1,5}.0^{8,11}]undec-9-ene **259**.



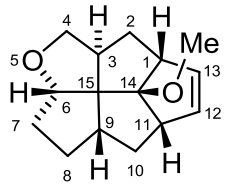
R_f 0.32 (Et_2O/pentane, 4:96) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87-5.94 (1H, m, H-2'); 5.74 (1H, dd, *J* 1.2, 5.7, H-10); 5.55 (1H, dd, *J* 2.4, 5.7, H-9); 5.27 (1H, d, *J* 17.2, H-3'); 5.14, (1H, d, *J* 10.4, H-3'); 4.13 (1H, dd, *J* 4.1, 7.1, H-2); 3.96-4.03 (2H, m, H-1'); 3.32 (3H, s, -OCH_3); 2.24-2.31 (2H, m, H-3*α*/H-5*β*); 2.19 (1H, d, *J* 8.5, H-8); 2.08 (1H, dd, *J* 6.3, 8.5, H-7); 1.71 (1H, dd, *J* 6.1, 8.8, 9.3, H-6*α*); 1.61-1.68 (2H, m, H-4*β*/H-3*β*); 1.52-1.57 (1H, m, H-4*α*); 1.46 (1H, dd, *J* 6.2, 13.6, H-6*β*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.17 (C-2'); 133.70 (C-10); 123.93 (C-9); 116.19 (C-3'); 90.99 (C-11); 78.85 (C-2); 71.63 (C-1); 70.66 (C-1'); 56.96 (C-5); 56.65 (-OCH_3); 37.08 (C-7); 35.92 (C-8); 34.69 (C-3); 28.03 (C-4); 26.82 (C-6); IR (thin film, cm^{-1}) 2935, 1646 (C=C, vinyl); 1584 (C=C); 1448, 1379, 1210, 1157, 1089, 1005, 920, 760, 700; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1354.

rac-(1S, 3S, 6R, 9R)-1-Methoxy-6-(2'-propenyloxy)-tricyclo[7.2.0.0^{3,7}]undeca-7,10-diene **260**.



R_f 0.17 (EtOAc/petrol, 10:90) ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.13 (1H, d, *J* 2.7, H-11); 6.06 (1H, d, *J* 2.7, H-10); 5.91 (1H, dddd, *J* 5.7, 5.7, 10.4, 17.2, H-2'); 5.82 (1H, dd, *J* 2.8, 6.1, H-8); 5.26 (1H, d, *J* 17.2, H-3'); 5.14 (1H, d, *J* 10.4, H-3'); 4.20 (1H, dddd, *J* 5.1, 5.3, H-6); 3.95 (1H, dddd, *J* 1.5, 1.5, 5.6, 12.8, H-1'); 3.91 (1H, dddd, *J* 1.4, 1.5, 5.9, 12.8, H-1'); 3.29-3.36 (1H, m, H-9); 3.32 (3H, s, -OCH_3); 2.33-2.40 (1H, m, H-3); 2.08-2.15 (1H, m, H-4); 2.04 (1H, dd, *J* 5.3, 12.4, H-2); 1.87-1.93 (1H, m, H-5); 1.68 (1H, dddd, *J* 4.8, 7.2, 7.2, 12.2, H-5); 1.30 (1H, dddd , *J* 7.3, 7.3 7.4, 12.6, H-4); 1.15 (1H, t, *J* 12.5, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.46 (C-7); 138.31 (C-10); 136.30 (C-11); 135.33 (C-2'); 121.48 (C-8); 116.65 (C-3'); 84.99 (C-1); 81.30 (C-6); 69.06 (C-1'); 51.71 (-OCH_3); 46.83 (C-9); 37.04 (C-2); 34.39 (C-3); 31.80 (C-5); 29.05 (C-4); IR (thin film, cm^{-1}) 3075, 3043, 2975, 2931, 2846, 2244, 1826, 1679, 1640 (C=C, vinyl); 1586 (C=C, alkene); 1563, 1449, 1377, 1342, 1292, 1257, 1208, 1172, 1098, 1021, 989, 911, 830, 767, 730; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1356.

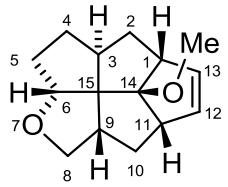
rac-(1R, 3S, 6S, 9S, 11S, 14R, 15R)-14-Methoxy-5-oxapentacyclo[9.2.1.1^{3,14}.0^{6,15}.0^{9,15}] pentadec-12-ene **249**.



The linear *meta* adduct **245** (81.0 mg, 0.349 mmol) and acetophenone (62.8 mg, 0.523 mmol) were dissolved in dry cyclohexane (200 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 11 hours using a 6 W low pressure Hg vapour lamp. Cyclohexane was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (100:1 silica; Et_2O/CH_2Cl_2/pentane 10:5:85); to yield the double [3+2] product **249** as a pale yellow oil (22.0 mg, 27 %).

R_f 0.22 (Et_2O/CH_2Cl_2/pentane, 10:5:85); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (1H, ddd, *J* 1.6, 2.5, 6.0, H-12); 5.46 (1H, ddd, *J* 1.4, 2.6, 6.0, H-13); 4.53 (1H, d, *J* 7.9, H-6), 3.65 (1H, dd, *J* 4.5, 8.8, H-4*β*); 3.52 (1H, d, *J* 8.8, H-4*α*); 3.24 (1H, dddd, *J* 1.4, 2.5, 7.9, 8.5, H-11); 3.21 (3H, s, -OCH_3); 3.11 (1H, dm, *J* 10.1, H-1); 2.29 (1H, ddd, *J* 4.6, 8.1, 11.0, H-3); 2.14-2.26 (2H, m, H-8+H-7*α*); 1.96 (1H, ddd, *J* 5.4, 7.9, 11.2, H-10*α*); 1.87 (2H, dd, *J* 6.9, 14.5, H-7*β*); 1.75 (1H, ddd, *J* 10.2, 10.9, 13.1, H-2*α*); 1.64 (1H, ddd, *J* 1.3, 8.0, 13.0, H-2*β*); 1.51 (1H, ddd, *J* 5.0, 7.3, 11.5, H-8*α*); 1.20 (1H, dddd, *J* 7.1, 11.4, 11.4, 13.5, H-8*β*), 1.06 (1H, ddd, *J* 8.5, 11.2, 13.5, H10-*β*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.35 (C-13); 132.59 (C-12); 102.42 (C-14); 77.34 (C-6); 77.18 (C-15); 72.36 (C-4); 59.96 (C-11); 53.35 (C-9); 51.89 (-OCH_3); 48.15 (C-1); 43.64 (C-3); 39.95 (C-7); 36.60 (C-2); 31.52 (C-10), 23.32 (C-8); HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1356.

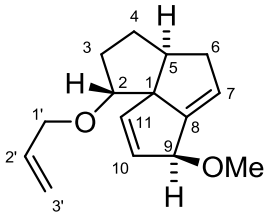
rac-(1R, 3S, 6R, 9S, 11S, 14S, 15S)-14-Methoxy-7-oxapentacyclo[9.2.1.1^{3,14}.0^{6,15}.0^{9,15}] pentadec-12-ene **251**.



The linear *meta* adduct **247** (35.0 mg, 0.151 mmol) and acetophenone (27.2 mg, 0.226 mmol) were dissolved in dry cyclohexane (200 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 17 hours using a 6 W low pressure Hg vapour lamp. Cyclohexane was removed under reduced pressure, and the resulting residue was subjected to flash column chromatography (100:1 silica; Et_2O/pentane, 20:80); to yield the double [3+2] product **251** as a yellow oil (11.0 mg, 31%).

R_f 0.29 (Et_2O/pentane, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (1H, dm, *J* 5.9, H-12); 5.47 (1H, dm, *J* 5.8, H-13); 4.28 (1H, br. s, H-6); 3.67 (1H, t, *J* 6.7, H-8*α*); 3.35 (1H, t, *J* 8.2, H-11); 3.21 (1H, dd, *J* 7.1, 12.1, H-8*β*); 3.19 (3H, s, -OCH_3); 3.10 (1H, dm, *J* 10.0, H-1); 2.81-2.89 (1H, m, H-9); 2.26-2.32 (1H, m, H-3); 1.95 (1H, ddd, *J* 5.3, 7.7, 11.2, H-10*α*); 1.78-1.89 (2H, m, H-5*α*/H-5*β*); 1.68-1.76 (1H, m, H-4α); 1.62 (1H, dd, *J* 8.3, 13.3, H-2β); 1.52-1.57 (1H, m, H-2*α*); 1.42 (1H, dd, *J* 5.7, 12.4, H-4*β*); 1.16 (1H, ddd, *J* 8.9, 11.3, 13.8, H10-β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.66 (C-13); 131.98 (C-12); 103.49 (C-14); 80.32 (C-6); 76.75 (C-15); 66.94 (C-8); 62.06 (C-11); 55.12 (C-9); 52.01 (-OCH_3); 48.62 (C-1); 41.39 (C-3); 36.30 (C-2); 32.62 (C-5); 31.33 (C-4); 28.92 (C-10); HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1356.

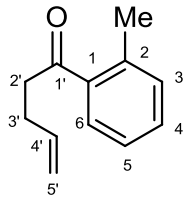
rac-(1R, 2R, 5S, 9S)-2-(2'-Propenyloxy)-9-methoxy-tricyclo[6.3.0^{1,5}.0^{1,8}]undeca-7,10-diene **263**.



The linear *meta* adduct **247** (95.0 mg, 0.410 mmol) was dissolved in dry cyclohexane (150 ml) in a quartz immersion-well photoreactor. Nitrogen was bubbled through the solution for 20 minutes in order to remove dissolved oxygen. The mixture was then irradiated for 18 hrs using a 6 W low pressure Hg vapour lamp. Solvent was removed under reduced pressure, and the resulting yellow residue was subjected to flash column chromatography (Et_2O/pentane 5:95) to afford **263** (8 mg, 8%) as a yellow oil.

R_f 0.27 (Et_2O/pentane, 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 (1H, d, *J* 6.0, H-11); 6.00 (1H, dd, *J* 2.3, 6.0, H-10); 5.82-5.90 (1H, m, H-2'); 5.60 (1H, br. s, H-7); 5.23 (1H, dm, *J* 17.1, H-3'); 5.09 (1H, dm, *J* 10.4, H-3'); 4.41 (1H, d, *J* 2.3, H-9); 3.88-3.98 (2H, m, H-1'); 3.69 (1H, d, *J* 4.3, H-2); 3.32 (3H, s, -OCH_3); 2.66-2.76 (1H, m, H-6α); 2.63-2.70 (1H, m, H-5); 2.23 (1H, ddd, *J* 1.8, 5.3, 16.8, H-6*β*); 2.00-2.09 (1H, m, H-4); 1.88 (1H, dd, *J* 5.9, 13.3, H-3); 1.62-1.70 (1H, m, H-3); 1.54 (1H, dd, *J*. 5.9, 12.0, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.56 (C-8); 144.47 (C-11); 135.63 (C-2'); 131.33 (C-10); 126.75 (C-7); 115.69 (C-3'); 88.84 (C-2); 78.90 (C-9); 73.56 (C-1); 70.70 (C-1'); 56.32 (-OCH_3); 44.70 (C-5); 42.91 (C-6); 31.15 (C-4); 30.61 (C-3); HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1353.

1-(2-Methyl-phenyl)-pent-4'-en-1'-one **264**.

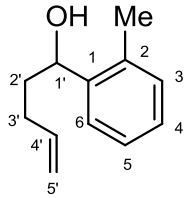


Adapted from Hall and McEnroe.[143] A three necked flask was fitted with a magnetic stirrer and stoppers then evacuated before being flushed with Argon. *o*-Bromotoluene (1.38 ml, 11.5 mmol) in dry Et_2O (20 ml) was introduced *via* syringe, the reaction vessel was cooled to 0 °C, and lithium metal (0.160 g, 22.9 mmol) was carefully added. The reaction was stirred for several hours until total consumption of the lithium metal was observed.

Weinreb amide **255** (1.80 g, 12.6 mmol) was added drop wise via syringe, and the mixture left to stir overnight. H_2O (100 ml) was carefully added, and the two layers separated. The aqueous layer was extracted with Et_2O (3 x 25 ml), and the combined organic layers were dried over anhydrous $MgSO_4$. Volatile solvents were removed under reduced pressure and the resulting orange residue subjected to flash column chromatography (Et_2O/petrol; 10:90) to afford the ketone **264** (0.99 g, 50%) as a yellow oil.

R_f 0.60 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (1H, d, *J* 7.7, H-6); 7.36 (1H, t, *J* 7.4 H-4); 7.22-7.27 (2H, m, H-3/H-5); 5.89 (1H, ddt, *J* 6.5, 10.2, 17.1 H-4'); 5.08 (1H, d, *J* 17.1, H-5'); 5.01 (1H, d, *J* 10.2, H-5'); 2.99 (2H, t, *J* 7.4, H-2'); 2.49 (3H, s, -CH_3); 2.45-2.50 (2H, m, H-3'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.50 (C-1', C=O); 138.03 (C-2); 137.83 (C-1); 137.16 (C-4'); 131.82 (C-3); 128.20 (C-6); 125.55 (C-5); 115.18 (C-5'); 40.59 (C-2'); 28.26 (C-3'); 21.09 (-CH_3). IR (thin film, cm^{-1}) 3075, 2976, 2926, 1686 (C=O); 1641 (C=C, vinyl); 1600 (C=C, aromatic); 1571, 1457, 1353, 1285, 1260, 1211, 1132, 1035, 997, 971, 913, 752; HRMS (ESI) *m/z* calcd. $C_{12}H_{14}NaO_1$ $[M+Na]^+$ 197.0937, found 197.0935.

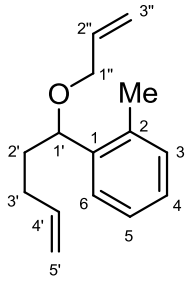
1-(2-Methyl-phenyl)-pent-4'-en-1'-ol **265**.



A magnetically stirred solution of ketone **264** (0.200 g, 1.15 mmol) in MeOH (5 ml) was cooled to 0 °C. Sodium borohydride (87.0 mg, 2.30 mmol) was added carefully to the solution, which was allowed to warm to ambient temperature and stirred for 4 hours. H_2O (10 ml) was added and then Et_2O (20 ml). The aqueous layer was further washed with Et_2O (2 x 20 ml). Combined organic layers were collected, dried over $MgSO_4$ and the volatile solvents removed under reduced pressure. Further purification was not required with alcohol **265** (0.200 g, 99%) acquired as a yellow oil.

R_f 0.25 (Et_2O/petrol, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (1H, d, *J* 7.6, H-6); 7.24 (1H, t, *J* 7.6, H-5); 7.18 (1H, t, *J* 7.5, H-4); 7.14 (1H, d, *J* 7.5, H-3); 5.87 (1H, ddt, *J* 6.7, 10.2, 17.1 H-4'); 5.06 (1H, d, *J* 17.1, H-5'); 5.01 (1H, d, *J* 10.2, H-5'); 4.94-4.98 (1H, m, H-1'); 2.34 (3H, s, -CH_3); 2.29-2.32 (1H, m, H-2'); 2.15-2.23 (1H, m, H-2'); 1.75-1.90 (2H, m, H-3'); 1.82 (1H, br. s, -OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.76 (C-1); 138.20 (C-4'); 134.40 (C-2); 130.37 (C-3); 127.17 (C-4); 126.26 (C-5); 125.14 (C-6); 114.98 (C-5'); 70.13 (C-1'); 37.06 (C-3'); 30.24 (C-2'); 19.00 (-CH_3); IR (thin film, cm^{-1}) 3368 (-OH); 3075, 2939, 1640 (C=C, alkene); 1604 (C=C, aromatic); 1488, 1459, 1381, 1285, 1214, 1180, 1097, 1061, 1006, 911, 758 cm^{-1}; HRMS (ESI) *m/z* calcd. $C_{12}H_{16}NaO_1$ $[M+Na]^+$ 199.1093, found 199.1092.

1-(1'-Allyloxy-pent-4'-enyl)-2-methyl-benzene **244.**



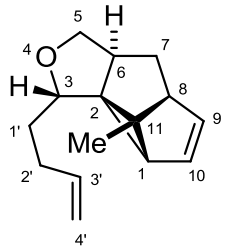
To a stirred solution of alcohol **265** (0.800 g, 4.54 mmol) and allyl bromide (1.96 ml, 22.7 mmol) in CH_2Cl_2 (5 ml) was added 50% NaOH (20 ml) and TBAHS (1.69 g, 4.99 mmol). This was allowed to stir overnight by which time TLC showed complete conversion of the starting material. The reaction was quenched with saturated NH_4Cl solution (50 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure and the resulting residue purified by running the crude mixture through a plug of silica (Et_2O/petrol, 10:90) to yield the ether photosubstrate **244** (0.970 g, 99%) as a pale yellow oil.

R_f 0.85 (Et_2O/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (1H, br. d, *J* 7.6, H-6); 7.23 (1H, br. t, *J* 7.6 H-5); 7.18 (1H, br. t, *J* 7.4, H-4); 7.13 (1H, br. d, *J* 7.4, H-3); 5.89-5.98 (1H, m, H-2"); 5.81-5.89 (1H, m, H-4'); 5.25 (1H, dm, *J* 17.2, H-3"); 5.16 (1H, dm, *J* 10.3, H-3"); 5.05 (1H, dm, *J* 17.2, H-5'); 4.99 (1H, dm, *J* 10.2, H-5'); 4.59 (1H, dd, *J* 4.5, 8.5, H-1'); 3.93 (1H, dd, *J* 5.2, 12.8, H-1"); 3.74 (1H, dd, *J* 6.0, 12.7, H-1"); 2.32 (3H, s, -CH_3); 2.23-2.31 (1H, m, H-3'); 2.13-2.22 (1H, m, H-3'); 1.83-1.92 (1H, m, H-2'); 1.67-1.75 (1H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.61 (C-1); 138.33 (C-4'); 135.23 (C-2"); 135.15 (C-2); 126.96 (C-5); 126.16 (C-4); 126.06 (C-6); 116.56 (C-3"); 114.76 (C-5'); 77.02 (C-1'); 69.49 (C-1"); 36.42 (C-2'); 30.15 (C-3'); 19.01 (-CH_3). IR (thin film, cm^{-1}) 3077, 2927, 1640 (C=C, vinyl); 1600 (C=C, aromatic); 1488, 1458, 1379, 1347, 1280, 1215, 1086, 993, 915, 757; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_1$ $[M+Na]^+$ 239.1406, found 239.1404.

Direct irradiation of ether photosubstrate **244** *to yield linear meta adducts* **246** *and* **248**.

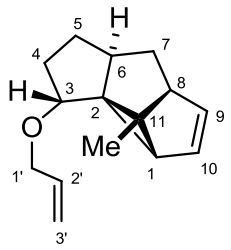
A solution of photosubstrate **244** (1.70 g, 7.87 mmol) in MeCN (350 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 26 hours using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The solvent was removed under reduced pressure, and the resulting orange residue subjected to flash column chromatography (100:1 silica, Et_2O/pentane 3:97) to afford *meta* adducts **246** (515 mg, 30%) and **248** (256 mg, 15%) both containing inseparable regioisomers. For **246** this was estimated to be in an approximate ratio of 8:2 (linear: angular).

rac-(1S, 2S, 3S, 6S, 8S, 11R)-3-(3'-Butenyl)-11-methyl-4-oxatetracyclo[6.2.1.0^{2,6}.0^{2,11}] undec-9-ene **246**.



R_f 0.28 (Et_2O/petrol 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (1H, ddt, *J* 6.7, 10.3, 17.0, H-3'); 5.65 (1H, dd, *J* 2.0, 5.4, H-10); 5.45 (1H, dd, *J* 2.4, 5.4, H-9); 5.04 (1H, dm, 17.0, H-4'); 4.96 (1H, d, *J* 10.3, H-4'); 4.08 (1H, dd, *J* 8.2, 8.8, H-5); 3.77 (1H, dd, *J* 3.3, 9.3, H-3); 3.52 (1H, dd, *J* 5.0, 8.8, H-5); 2.96-3.01 (1H, m, H-8); 2.43-2.50 (1H, m, H-6); 2.20-2.29 (1H, m, H-2') 2.07-2.15 (1H, m, H-2'); 1.78-1.82 (2H, m, H-7); 1.66 (1H, br. d, *J* 2.2, H-1); 1.54-1.62 (1H, m, H-1'); 1.35-1.43 (1H, m, H-1'); 1.29 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.66 (C-3'); 133.34 (C-9); 128.53 (C-10); 114.45 (C-4'); 76.40 (C-3); 72.18 (C-5); 58.55 (C-8); 54.13 (C-2); 45.18 (C-11); 44.86 (C-7); 43.63 (C-6); 38.68 (C-1); 32.03 (C-1'); 29.95 (C-2'); 14.06 (-CH_3); HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO$ $[M+Na]^+$ 239.1406, found 239.1409. Note this compound also contained an inseparable *angular* regioisomer.

rac-(1S, 2R, 3R, 6S, 8S, 11R)-3-(2'-Propenyloxy)-11-methyl-tetracyclo[6.2.1.0^{2,6}.0^{2,11}] undec-9-ene **248**.

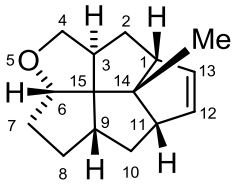


R_f 0.39 (Et_2O/petrol, 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86-5.94 (1H, m, H-3'); 5.69 (1H, dd, *J* 1.9, 5.4, H-10); 5.40 (1H, dd, *J* 2.3, 5.4, H-9); 5.25 (1H, d, 17.3, H-3'); 5.14 (1H, d, *J* 10.4, H-3'); 4.01 (1H, dd, *J* 5.4, 13.1, H-1'); 3.91 (1H, dd, *J* 5.4, 13.1, H-1'); 3.48 (1H, dd, *J* 2.4, 4.3, H-5); 2.83-3.01 (1H, dd *J* 2.3, 5.3, H-8); 2.30-2.37 (1H, m, H-6); 2.04-2.10 (1H, m, H-5); 1.98-1.99 (1H, m, H-1); 1.94-2.00 (1H, m, H-4); 1.77-1.81 (1H, m, H-7); 1.71-1.78 (1H, m, H-4); 1.56-1.62 (1H, m, H-7); 1.27-1.33 (1H, m, H-5); 1.26 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.76 (C-2'); 132.87 (C-9); 129.13 (C-10); 116.29 (C-3'); 80.07 (C-5); 69.45 (C-1'); 57.09 (C-8); 53.11 (C-2); 46.62 (C-11); 46.34 (C-7); 40.14 (C-1); 40.07 (C-6); 32.78 (C-4); 28.50 (C-5); 14.37 (-CH_3); HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO$ $[M+Na]^+$ 239.1406, found 239.1408. Note: this compound also contained inseparable impurities.

Irradiation of ether photosubstrate **244** *to yield oxafenestranes* **250** *and* **252**.

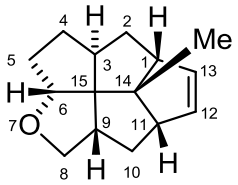
A solution of ether photosubstrate **244** (0.540 g, 2.50 mmol) in dry cyclohexane (450 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 16 hours using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of the aromatic starting material. The solvent was removed under reduced pressure, and the resulting yellow residue subjected to flash column chromatography (100:1 silica, Et_2O/pentane 5:95) to afford double [3+2] adducts **250** (95.0 mg, 18%) and **252** (44.0 mg, 8%).

rac-(1R, 3S, 6S, 9S, 11S, 14S, 15S)-14-Methyl-5-oxapentacyclo[9.2.1.1^{3,14}.0^{6,15}.0^{9,15}] pentadec-12-ene **250**.



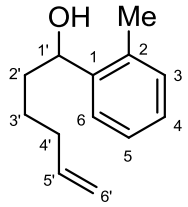
R_f 0.25 (Et_2O/pentane, 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (1H, ddd, *J* 1.9, 2.3, 5.7, H-12); 5.35 (1H, ddd, *J* 1.5, 2.6, 5.7, H-13); 4.24 (1H, d, *J* 7.9, H-6); 3.63 (1H, dd, *J* 4.7, 8.8, H-4*β*); 3.49 (1H, d, *J* 8.8, H-4*α*); 2.78 (1H, dddd, *J* 1.6, 2.4, 7.7, 8.8, H-11); 2.61-2.65 (1H, m, H-1); 2.27 (1H, ddd, *J* 4.7, 8.5, 10.3, H-3); 2.10 (1H, dddd, *J* 7.1, 7.8, 11.4, 14.4, H-7*α*); 2.02 (1H, dddd, *J* 5.0, 5.5, 13.4, 13.4 H-9); 1.87 (2H, dd, *J* 7.2, 14.0, H-7*β*); 1.84 (1H, ddd, *J* 5.5, 7.7, 11.2, H-10*α*); 1.61-1.65 (2H, m, H-2); 1.49 (1H, ddd, *J* 5.0, 7.2, 11.5, H-8*α*); 1.16 (1H, dddd, *J* 7.1, 11.4, 11.5, 13.4, H-8*β*); 1.16 (3H, s, -CH_3); 1.06 (1H, ddd, *J* 8.8, 11.2, 13.4, H10-*β*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.79 (C-13); 132.23 (C-12); 77.87 (C-15); 77.20 (C-6); 72.20 (C-4); 65.78 (C-11); 57.86 (C-14); 56.31 (C-1); 53.54 (C-9); 45.17 (C-3); 40.26 (C-7); 37.64 (C-2); 32.28 (C-10); 26.43 (C-8); 23.56 (-CH_3); HRMS (ESI) *m/z* calcd. $C_{15}H_{21}O_1$ $[M]^+$ 217.1587, found 217.1587.

rac-(1R, 3S, 6R, 9S, 11S, 14R, 15R)-14-Methyl-7-oxapentacyclo[9.2.1.1^{3,14}.0^{6,15}.0^{9,15}] pentadec-12-ene **252**.



R_f 0.29 (Et_2O/pentane, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (1H, ddd, *J* 2.0, 2.4, 5.8, H-12); 5.38 (1H, ddd, *J* 1.5, 2.5, 5.7, H-13); 4.02 (1H, d, *J* 2.3 H-6); 3.65 (1H, t, *J* 6.7, H-8*α*); 3.35 (1H, ddd, *J* 0.6, 7.0, 12.0, H-8*β*); 2.90 (1H, dddd, *J* 1.6, 2.5, 7.5, 8.8, H-11); 2.58-2.66 (1H, m, H-9); 2.62 (1H, dm, *J* 8.1, H-1); 2.29 (1H, ddd, *J* 6.1, 8.7, 11.0, H-3); 1.85 (1H, ddd, *J* 5.4, 7.6, 11.2, H-10α); 1.81-1.84 (1H, m, H-5*α*); 1.66-1.71 (2H, m, H-4*α*/H-5*β*); 1.63 (1H, m, H-2β); 1.37-1.45 (1H, ddd, *J* 8.3, 13.3, H-2α/H-4β); 1.16 (3H, s, -CH_3); 1.15 (1H, dd, *J* 8.9, 11.2, 13.7, H-10β) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.33 (C-13); 131.69 (C-12); 80.95 (C-6); 77.41 (C-15); 67.31 (C-11); 67.20 (C-8); 58.90 (C-14); 56.66 (C-1); 55.10 (C-9); 43.02 (C-3); 37.36 (C-2); 32.79 (C-5); 30.88 (C-4); 29.85 (C-10); 23.23 (-CH_3); HRMS (ESI) *m/z* calcd. $C_{15}H_{21}NaO_1$ $[M+Na]^+$ 239.1406, found 239.1407.

1-(2-Methylphenyl)hex-5-en-1-ol **273**.



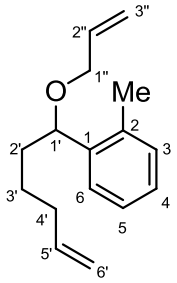
Magnesium turnings (0.805 g, 33.55 mmol) were added to a dry three necked flask, fitted with a reflux condenser, dropping funnel and glass stirrer bar and stirred overnight under a nitrogen atmosphere. Dry Et_2O (5 ml) was then added to the turnings, followed by a small amount of 5-bromo-1-pentene (2.4 ml, 20.13 mmol) in Et_2O (15 ml). The reaction vessel was heated to reflux. Once Grignard formation was initiated, the remaining 5-bromo-1-pentene was added slowly *via* the dropping funnel to ensure a steady reflux. The reaction was stirred until all heat evolution had ceased (approximately 1 hour), then cooled to 0 °C. *o*-Tolualdehyde (1.61 g, 13.4 mmol) was dissolved in Et_2O (10 ml); loaded into the dropping funnel and added drop wise to the reaction.

After complete addition of the aldehyde, the reaction was allowed to warm to ambient temperature and stirred for 2 hours, at which time NMR analysis showed complete consumption of the aldehyde. The reaction was diluted with a saturated solution of NH_4Cl (200 ml); left to stir overnight, then extracted with Et_2O (3 x 100 ml). The combined organic extracts were washed with brine (2 x 100 ml) and dried over anhydrous $MgSO_4$. The resultant orange residue was subjected to flash column chromatography (Et_2O/hexane, 20:80) to give the alcohol **273** (2.05 g, 81%) as a yellow oil.

R_f 0.25 (Et_2O/hexane, 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (1H, d, *J* 7.6, H-6); 7.23 (1H, td, *J* 1.5, 7.6, H-5); 7.17 (1H, td, *J* 7.4, H-4); 7.13 (1H, d, *J* 7.4, H-3); 5.81 (1H, ddt, *J* 6.7, 10.2, 17.0 H-5'); 5.01 (1H, d, *J* 17.0, H-6'); 4.92-4.97 (2H, m, H-6'/H-1'); 2.34 (3H, s, -CH_3); 2.07-2.14 (2H, m, H-4'); 1.68-1.81(3H, m, H-2'/-OH); 1.58-1.65 (1H, m, H-3'); 1.42-1.52 (1H, m, H-3'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.96 (C-1); 138.57 (C-5'); 134.42 (C-2); 130.37 (C-3);

127.14 (C-4); 126.27 (C-5); 125.11 (C-6); 114.67 (C-6'); 70.60 (C-1'); 37.50 (C-2'); 33.59 (C-4'); 25.27 (C-3'); 19.05 (-CH_3); IR (thin film, cm^{-1}) 3368 (-OH); 3074, 3023, 2975, 2935, 1640 (C=C, alkene); 1603 (C=C, aromatic); 1488, 1459, 1438, 1415, 1380, 1285, 1180, 1064, 994, 910, 756; HRMS (ESI) *m/z* calcd. $C_{13}H_{18}NaO_1$ $[M+Na]^+$ 213.1250, found 213.1248.

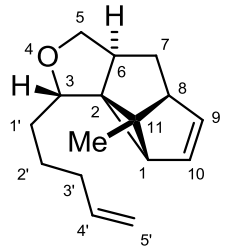
1-(1'-Allyloxy-hex-5'-enyl)-2-methyl-benzene **270**.



To a stirred solution of alcohol **273** (1 g, 5.26 mmol) and allyl bromide (1.4 ml, 15.79 mmol) in CH_2Cl_2 (10 ml) was added 50% NaOH (20 ml) and TBAHS (1.78 g, 5.26 mmol). This was allowed to stir overnight, by which time TLC showed complete consumption of the starting material. The reaction was diluted with saturated NH_4Cl solution (75 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure and the resulting residue purified by running the crude mixture through a plug of silica (Et_2O/petrol, 10:90) to yield the ether **270** (0.900 g, 74%) as a yellow oil.

R_f 0.80 (Et_2O/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (1H, d, *J* 7.6, H-6); 7.21 (1H, td, *J* 1.5, 7.6 H-5); 7.15 (1H, td, *J* 1.5, 7.5, H-4); 7.13 (1H, d, *J* 7.5, H-3); 5.87-5.95 (1H, m, H-2"); 5.75-5.83 (1H, m, H-5'); 5.23 (1H, dm, *J* 17.3, H-3"); 5.15 (1H, dm, *J* 10.3, H-3"); 4.98 (1H, dm, *J* 17.2, H-6'); 4.93 (1H, dm, *J* 10.2, H-6'); 4.56 (1H, dd, *J* 4.0, 8.1, H-1'); 3.91 (1H, dd, *J* 5.0, 12.3, H-1"); 3.72 (1H, dd, *J* 6.2, 12.3, H-1"); 2.31 (3H, s, -CH_3); 2.05-2.10 (2H, m, H-4'); 1.72-1.82 (1H, m, H-2'); 1.58-1.68 (2H, m, H-2'/H-3'); 1.40-1.48 (1H, m, H-3'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.79 (C-1); 138.73 (C-5'); 135.27 (C-2"); 135.15 (C-2); 126.91 (C-3); 126.15 (C-4); 126.06 (C-6); 116.56 (C-3"); 114.51 (C-6'); 77.61 (C-1'); 69.45 (C-1''); 36.82 (C-2'); 33.66 (C-4'); 25.30 (C-3'); 19.06 (-CH_3). IR (thin film, cm^{-1}) 3076, 2976, 2929, 2859, 1641 (C=C, alkene); 1604 (C=C, aromatic); 1488, 1459, 1347, 1284, 1219, 1086, 994, 913, 757; HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_1$ $[M+Na]^+$ 253.1563, found 253.1562.

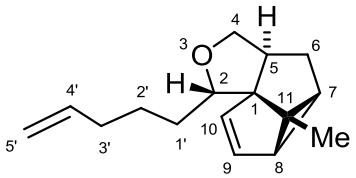
rac-(1S, 2S, 3S, 6S, 8S, 11R)-3-(3'-Pentenyl)-11-methyl-4-oxatetracyclo[6.2.1.0^{2,6}.0^{2,11}] undec-9-ene **274**.



A solution of ether photosubstrate **270** (0.800 g, 2.50 mmol) in dry MeCN (400 ml) was added to a quartz immersion well photoreactor and degassed with nitrogen for 15 minutes. The apparatus was cooled with H_2O and the solution irradiated for 8 hours using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The solvent was removed under reduced pressure, and the resulting orange residue subjected to flash column chromatography (100:1 silica, Et_2O/pentane, 2:98) to afford the linear *meta* adduct **274** (252 mg, 32%); along with a co-spotting impurity identified to be the angular *meta* adduct **275** (in a ratio of 3.3:1), which could not be removed by further chromatographic separation.

R_f 0.30 (Et_2O/pentane, 2:98); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, ddt, *J* 6.7, 10.2, 17.1, H-4'); 5.64 (1H, dd, *J* 2.1, 5.4, H-10); 5.45 (1H, dd, *J* 2.4, 5.4, H-9); 5.01 (1H, dm, 17.1, H-5'); 4.94 (1H, d, *J* 10.2, H-5'); 4.07 (1H, dd, *J* 8.2, 8.5, H-5); 3.75 (1H, dd, *J* 3.4, 8.8, H-3); 3.50 (1H, dd, *J* 5.2, 8.5, H-5); 2.97-3.00 (1H, m, H-8); 2.42-2.49 (1H, m, H-6); 2.04-2.11 (2H, m, H-3') 1.77-1.80 (2H, m, H-7); 1.64-1.65 (1H, m, H-1); 1.54-1.63 (1H, m, H-2'); 1.41-1.51 (2H, m, H-1'/H-2'); 1.29-1.34 (1H, m, H-1'); 1.28 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.85 (C-4'); 133.31 (C-9); 128.55 (C-10); 114.44 (C-5'); 76.84 (C-3); 72.22 (C-5); 58.58 (C-8); 54.19 (C-2); 45.03 (C-11); 44.78 (C-7); 43.71 (C-6); 38.66 (C-1); 33.72 (C-3'); 32.17 (C-1'); 24.98 (C-2'); 14.04 (-CH_3); HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_1$ $[M+Na]^+$ 253.1563, found 253.1564. Note this compound also contained the inseparable *angular* regioisomer.

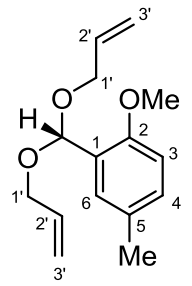
rac-(1S, 2S, 5S, 7R, 8S, 11R)-2-(4'-Butenyl)-11-methyl-3-oxatetracyclo[5.3.1.0^{1,5}.0^{8,11}] undec-9-ene **275**.



A solution of linear *meta* adduct **274** (74.0 mg, 0.320 mmol) and acetophenone (46.0 mg, 0.390 mmol) in dry MeCN (100 ml) was added to a quartz immersion well photoreactor and degassed with nitrogen for 15 minutes. The apparatus was cooled with H_2O and the solution irradiated for 6 hours using a 6 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). MeCN was removed under reduced pressure, and the resulting yellow residue subjected to flash column chromatography (100:1 silica, Et_2O/pentane, 2:98) to afford the angular *meta* adduct **275** (10.0 mg, 11%); along with a co-spotting impurity identified to be the linear *meta* adduct **274** (ratio of 5:1), which could not be removed by further chromatographic separation.

R_f 0.29 (Et_2O/pentane, 2:98); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, ddt, *J* 6.7, 10.2, 17.0, H-4'); 5.65 (1H, dd, *J* 2.1, 5.5, H-9); 5.38 (1H, d, *J* 5.4, H-10); 5.01 (1H, dm, 17.1, H-5'); 4.94 (1H, d, *J* 10.2, H-5'); 4.06 (1H, dd, *J* 3.5, 9.2, H-2); 3.83 (1H, t, *J* 8.1, H-4); 3.59 (1H, dd, *J* 8.1, 10.6, H-4); 2.35-2.41 (1H, m, H-5); 2.05-2.12 (2H, m, H-3'); 1.75 (1H, dd, *J* 6.0, 13.8, H-6) 1.64 (1H, dd, *J* 5.7, 13.8 H-6); 1.58-1.64 (1H, m, H-2'); 1.57-1.60 (1H, m, H-8); 1.55-1.59 (1H, m, H-7); 1.46-1.54 (1H, m, H-1'); 1.42-1.50 (1H, m, H-2'); 1.36 (3H, s, -CH_3); 1.32-1.37 (1H, m, H-1'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.82 (C-4'); 130.73 (C-9); 127.26 (C-10); 114.42 (C-5'); 78.53 (C-2); 71.93 (C-1); 69.64 (C-8); 58.21 (C-5); 46.03 (C-11); 37.96 (C-8); 35.67 (C-7); 34.71 (C-1'); 33.76 (C-3'); 25.50 (C-2'); 24.18 (C-6'); 17.11 (-CH_3); HRMS (ESI) *m/z* calcd. $C_{16}H_{22}NaO_1$ $[M+Na]^+$ 253.1563, found 253.1566. Note this compound also contained the inseparable *linear* regioisomer.

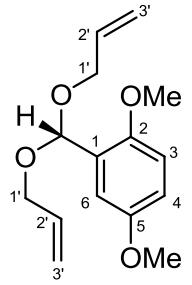
1-(Bis(allyloxy)methyl)-2-methoxy-5-methylbenzene **235**.



Bromide **223** (3.00 g, 9.58 mmol) in dry THF (20 ml) was cooled to -84 °C under an inert atmosphere of nitrogen. To this solution was added *n*-butyllithium (2.5 M in hexanes, 5.36 ml, 13.4 mmol) drop wise. Immediately after complete addition, CuI (2.74 g, 14.4 mmol) was added in portions and the solution was allowed to stir for 1 hour. After this time, Iodomethane (0.890 ml, 14.4 mmol) was added drop wise to the solution. The reaction was warmed to ambient temperature and allowed to stir overnight. It was diluted with Et_2O (50 ml), then washed with H_2O (2 x 25 ml). The organic phase was separated and dried over $MgSO_4$. Solvents were removed under reduced pressure and the residue subjected to flash column chromatography (100:1 silica; CH_2Cl_2/pentane, 40:60); to yield the methylated product **235** (1.1g, 46%) as pale yellow oil.

R_f 0.29 (CH_2Cl_2/pentane, 40:60); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (1H, d, *J* 2.3 H-6); 7.10 (1H, dd, *J* 2.3, 8.4 H-4); 6.79 (1H, d, *J* 8.4, H-3); 5.95 (2H, dddd, *J* 5.6, 5.6 10.4,17.2 H-2'); 5.89 (1H, s, -C(H)O_2); 5.30 (2H, d, *J* 17.2, H-3'); 5.16 (2H, d, *J* 10.4, H-3'); 4.11 (4H, ddd, *J* 1.4, 1.5, 5.6 H-1'); 3.82 (3H, s, -OCH_3); 2.31 (3H, s, -CH_3) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.03 (C-2); 134.80 (C-2'); 129.91 (C-4); 129.55 (C-5); 127.90 (C-6); 126.37 (C-1); 116.60 (C-3'); 110.75 (C-3); 96.39 (-C(H)O_2); 67.14 (C-1'); 55.73 (-OCH_3); 20.59 (-CH_3) ; IR (thin film, cm^{-1}) 2922, 2865, 1683 1647, 1614, 1591, 1501, 1463, 1422, 1383, 1285, 1249, 1182, 1157, 1137, 1076, 1030, 990, 919, 805, 751, 716; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 271.1310, found 271.1305.

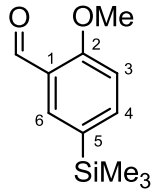
2-(Bis(allyloxy)methyl)-1-methoxy-4-methoxybenzene **239**.



Trimethylsilyl trifluoromethanesulfonate (0.230 ml, 1.26 mmol); was added to CH_2Cl_2 (5 ml) under a nitrogen atmosphere at -84 °C, and magnetically stirred for five minutes. Allyloxytrimethylsilane (5.30 ml, 31.6 mmol) was added drop wise, followed by 2,5-dimethoxybenzaldehyde **238** (2.10 g, 12.7 mmol); whilst maintaining the same temperature. The resultant clear mixture was stirred at -84 °C for six hours, quenched with pyridine (8 ml) at the same temperature, and then poured into a saturated solution of $NaHCO_3$ (50 ml). The aqueous layer was extracted with Et_2O (3 x 25 ml); and the combined organic layers dried over anhydrous $MgSO_4$. Excess solvent was removed under reduced pressure and the resulting oil was purified by a plug of silica (EtOAc/petrol, 10:90) to afford the acetal **239** (2.60 g, 78%) as a colourless oil.

R_f 0.60 (EtOAc/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (1H, br d, *J* 2.7, H-6); 6.85-6.80 (2H, m, H-3 + H-4); 5.90-5.98 (1H, dddd, *J* 4.8, 5.7, 10.4, 17.2 H-2'); 5.86 (1H, s, -C(H)O_2); 5.29 (2H, d, *J* 17.2, H-3'); 5.15 (2H, d, *J* 10.4, H-3'); 4.10 (4H, m, H-1'); 3.79 (3H, s, -OCH_3); 3.78 (3H, s, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.58 (C-2); 151.39 (C-5); 134.67 (C-2'); 127.78 (C-1); 116.63 (C-3'); 114.76 (C-3/C-4); 112.92 (C-6); 112.21 (C-3/C-4); 96.28 (-C(H)O_2); 67.21 (C-1'); 56.32 (-OCH_3); 55.74 (-OCH_3); IR (thin film, cm^{-1}) 3079, 2935, 2835, 1647 (C=C, vinyl), 1592, 1497, 1464, 1422, 1380, 1299, 1277, 1216, 1179, 1161, 1077, 1020, 920, 885, 802, 709. HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1254, found 287.1252.

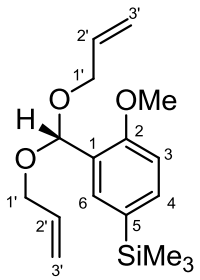
2-Methoxy-5-(trimethylsilyl)benzaldehyde **241**.



Bromide **223** (3.00 g, 9.58 mmol) in dry THF (15 ml) was cooled to -78 °C under an atmosphere of nitrogen. To this solution was added *n*-butyllithium (2.5 M in hexanes, 5.36 ml, 13.4 mmol) drop wise. Immediately after complete addition, TMSCl (4.90 ml, 38.3 mmol) was added drop wise to the solution. The reaction was warmed to ambient temperature and allowed to stir for 4 hours. It was diluted with Et_2O (50 ml), then washed with H_2O (2 x 25 ml). The separated organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure with no further purification required, to afford the aldehyde **241** (1.90 g, 95%) as an orange semi-solid.

R_f 0.10 (EtOAc/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.48 (1H, s, -CHO) 7.97 (1H, d, *J* 1.7 H-6); 7.70 (1H, dd, *J* 1.7, 8.3 H-4); 6.99 (1H, d, *J* 8.3, H-3); 3.93 (3H, s, $-OCH_3$); 0.25 (9H, s, $-Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.08 (-CHO); 162.40 (C-2); 141.00 (C-4); 133.71 (C-6); 131.83 (C-5) 124.24 (C-2); 111.14 (C-3); 55.53 ($-OCH_3$); -1.13 ($-Si(CH_3)_3$); IR (thin film, cm^{-1}) 3012, 2956, 2859, 1682 (C=O, aldehyde); 1591 (C=C, aromatic), 1568, 1464, 1442, 1400, 1383, 1291, 1252, 1194, 1095, 1024, 912, 839, 757; HRMS (ESI) *m/z* calculated $C_{11}H_{16}NaSiO_2$ $[M+Na]^+$ 231.0812, found 231.0815.

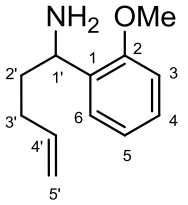
(3-(Bis(allyloxy)methyl)-4-methoxyphenyl)trimethylsilane **242**.



Trimethylsilyl trifluoromethanesulfonate (0.020 ml, 0.110 mmol); was added to CH_2Cl_2 (3 ml) under a nitrogen atmosphere at -84 °C, and magnetically stirred for five minutes. Allyloxytrimethylsilane (2.70 ml, 15.9 mmol) was added drop wise, followed by 2-methoxy-5-(trimethylsilyl)benzaldehyde **241** (1.50 g, 7.21 mmol); whilst maintaining the same temperature. The resulting clear mixture was stirred at -84 °C for six hours, quenched with pyridine (10 ml) at the same temperature, and then poured into a saturated solution of $NaHCO_3$ (25 ml). The aqueous layer was extracted with Et_2O (3 x 25 ml); and the combined organic layers dried over anhydrous $MgSO_4$. Excess solvent was removed under reduced pressure and the resulting oil was purified by a plug of silica (EtOAc/petrol, 10:90) to yield **242** (0.720 g, 33%) as a colourless oil.

R_f 0.20 (EtOAc/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (1H, d, *J* 1.6, H-6); 7.46 (1H, dd, *J* 8.1, 1.6, H-4); 6.89 (1H, d, *J* 8.1, H-3) 5.99-5.92 (2H, dddd, *J* 4.8, 5.6, 10.5, 17.3, H-2'); 5.88 (1H, s, -C(H)O_2); 5.30 (2H, d, *J* 17.2, H-3'); 5.16 (2H, dm, *J* 10.4, H-3'); 4.11 (4H, m, H-1'); 3.84 (3H, s, -OCH_3); 0.25 (3H, s, -Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.89 (C-2); 134.96 (C-4); 134.77 (C-2'); 132.24 (C-6); 130.95 (C-1); 125.95 (C-5); 116.57 (C-3'); 110.17 (C-3); 96.70 (-C(H)O_2); 67.39 (C-1'); 55.40 (-OCH_3); -0.94 (-Si(CH_3)$_3$). IR (thin film, cm^{-1}) 3080, 3015, 2955, 2901, 2840, 2051, 1856, 1647 (C=C, vinyl), 1596 (C=C, aromatic), 1495, 1463, 1409, 1368, 1349, 1293, 1248, 1109, 1034, 919, 839, 812, 758, 692; HRMS (ESI) *m/z* calculated $C_{17}H_{26}NaSiO_3$ $[M+Na]^+$ 329.1543, found 329.1551.

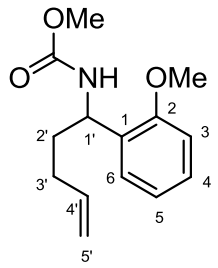
1-(2-Methoxy-phenyl)-pent-4'-enylamine **295**.



Adapted from the procedure used by Gribkov, Hultzsch and Hampel.[131] Ketone **256** (2.56g, 13.5 mmol) and ammonium acetate (10.2 g, 140 mmol) were dissolved in absolute MeOH (40ml) in a 250 ml flask and placed under a nitrogen atmosphere. A magnetic stirrer was added to ensure vigorous mixing. Sodium cyanoborohydride (0.580 g, 9.40 mmol) was then added in one portion, and the solution left to stir at room temperature for approximately 72 hours, when TLC showed all the starting material had been consumed. The solution was acidified with concentrated HCl (pH <2) and the MeOH was removed under reduced pressure. The resulting residue was taken up in H_2O (75ml) and extracted with Et_2O (75ml). While the organic layer was discarded, the aqueous layer was basified with solid KOH (pH >12). This was extracted with Et_2O (3 x 100ml) and the combined organic layers were dried over solid KOH. The solvent was removed under reduced pressure to yield a white oil (3.20 g, <100%).

R_f 0.00 (EtOAc/petrol, 5:95); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (1H, dd, *J* 1.5, 7.5, H-6); 7.21 (1H, td, *J* 1.6, 7.9, H-4); 6.94 (1H, td, *J* 1.0, 7.6, H-5); 6.87 (1H, dd, *J* 1.0, 8.2, H-3); 5.84 (1H, ddt, *J* 6.6, 10.2, 17.1, H-3'); 5.01 (1H, dm, *J* 17.1, H-4'); 4.92 (1H, dm, *J* 10.2, H-4'); 4.12-4.18 (1H, m, H-1'); 3.83 (3H, s, -OCH_3); 2.09-2.16 (1H, m, H-2'); 2.01-2.08 (1H, m, H-2'); 1.81-1.89 (1H, m, H-1'); 1.73-1.81 (1H, m, H-1'); ^{13}C NMR (125 MHz, CDCl3): δ 156.91 (C-2); 138.70 (C-3'); 127.59 (C-4); 126.81 (C-6); 120.61 (C-5); 114.35 (C-4'); 110.58 (C-3); 92.84 (C-1); 55.19 (C-OCH3); 50.62 (C-N); 36.61 (C-1'); 31.04 (C-2'); HRMS (ESI) *m/z* calculated $C_{12}H_{18}NO$ $[M+H]^+$ 192.1383, found 192.1383. LRMS (+EI) *m/z* calcd. $C_{12}H_{17}O_1$ [M+] = 191 found 191 (26%) fragments 178 (16%); 160 (40%); 148 (36%); 136 (100%); 121 (31%); 107 (13%); 91 (7%); 77 (7%); 28 (7%).

[1-(2-Methoxy-phenyl)-pent-4'-enyl]-carbamic acid methyl ester **296**.



Method A: Oxime **308** (4.00 g, 19.5 mmol) was dissolved in glacial acetic acid (20 ml) and stirred under a nitrogen atmosphere. Zinc dust (12.8 g, 195 mmol) was added carefully in portions over 30 minutes. The reaction mixture was left to stir for 72 hours until TLC showed total consumption of the oxime. The crude mixture was carefully added to a solution of 5M NaOH (50 ml); with additional hydroxide added until the mixture was basic (pH >10). Et_2O (3 x 50 ml) was added to extract the crude amine, followed by filtration through celite®. The solvent was removed under reduced pressure, and the resulting yellow residue taken up in Et_2O (20 ml); triethylamine (5.98 ml, 43.0 mmol) was carefully added and the reaction vessel placed under a nitrogen atmosphere. Methyl chloroformate (1.65 ml, 21.5 mmol) was added drop wise over 10 minutes and the reaction mixture was left to stir overnight. The reaction was quenched with saturated $NaHCO_3$ solution (50 ml); and the product extracted with EtOAc (3 x 25 ml). The organic layers were combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was conducted using flash column chromatography (Et_2O/petrol, 20:80) to yield **296** (1.10 g, 23%) as a white solid.

Method B: Amine **295** (3.20 g, 17.6 moles) and triethylamine (2.97 ml, 21.4 moles) were dissolved in Et_2O (70mL) and stirred in a 250mL round bottomed flask at ambient temperature, under a nitrogen atmosphere. Methyl chloroformate (1.65 ml, 21.4 moles) was added drop wise *via* syringe and the mixture was left to stir for 30 minutes.

A saturated solution of $NaHCO_3$ (100mL) was added and the mixture extracted using EtOAc (5 x 50 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to yield **296** (2.01g, 60%, over two steps) as a white solid.

R_f 0.21 (Et_2O/petrol, 20:80); m. p. 96.2 - 97.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (1H, br t, *J* 7.7, H-4); 7.17 (1H, br d, *J* 7.4, H-6); 6.91 (1H, br t, *J* 7.4, H-5); 6.89 (1H, br d, *J* 8.0 H-3); 5.85-5.77 (1H, dddd, *J* 6.4, 6.4, 10.3, 17.2, H-4'); 5.66-5.62 (1H, m, N-H); 5.00 (1H, d, *J* 17.2, H-5'); 4.96 (1H, d, *J* 10.3, H-5'); 4.80-4.86 (1H, m, H-1') 3.85 (3H, s, -OCH_3); 3.64 (3H, s, -C(O) OCH_3) 2.12-1.95 (2H, m, H-2'); 1.94-1.84 (2H, m, H-3'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.03 (C-2); 156.41 (C=O); 137.98 (C-4'); 129.85 (C-1); 128.77 (C-6); 128.41 (C-4); 120.71 (C-5); 114.78 (C-5'); 111.02 (C-3); 55.26 (-OCH_3); 53.67 (C-1'); 51.88 (-C(O)OCH_3); 34.70 (C-2'); 30.70 (C-3').; IR (thin film, cm^{-1}) : 3342 (N-H); 3078, 2947, 1687 (C=O); 1600 (C=C, aromatic); 1539, 1439, 1493, 1460, 1359, 1295, 1239, 1178, 1103, 1054, 1030, 996, 938, 911, 830, 754, 667. HRMS (ESI) *m/z* calcd. $C_{14}H_{19}NNaO_3$ $[M+Na]^+$ 272.1257, found 272.1254.

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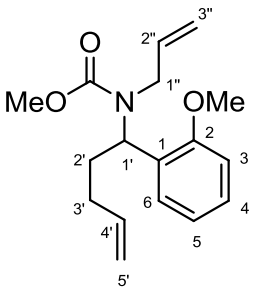
Allyl-[1-(2-methyoxy-phenyl)-pent-4'-enyl]-carbamic acid methyl ester **297**.

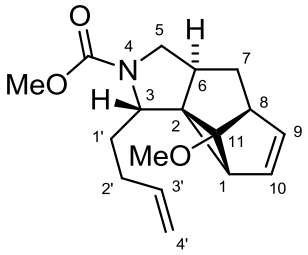


This procedure is adapted from the procedure used by Hunt, Laurent, and Moody.[129] NaH (60% in mineral oil, 0.241 g, 6.02 mmol) was suspended in dry DMF (5 ml) and cooled to 0 °C under an atmosphere of nitrogen. Carbamate **296** (0.500 g, 2.01 mmol) in DMF (1 ml) was added drop wise to the mixture, which was allowed to warm to ambient temperature for 30 minutes, then cooled again to 0 °C. Allyl bromide (0.430 ml, 5.02 mmol) was added drop wise and the mixture stirred at ambient temperature until TLC showed complete consumption of the starting material. The reaction was quenched with saturated NH_4Cl solution (25 ml); extracted with Et_2O (2 x 25 ml) and dried over anhydrous Na_2SO_4. Et_2O was removed under reduced pressure and purification was conducted using flash column chromatography (Et_2O/petrol, 30:70) to yield **297** (0.480 g, 83%) as an orange oil.

R_f 0.29 (Et_2O/petrol, 30:70); ^1H NMR (500 MHz, $CDCl_3$): δ 7.28-7.38 (1H, br s, H-6); 7.26 (1H, br. t, *J* 7.6, H-4); 6.93 (1H, br. t, *J* 7.6, H-5); 6.84 (1H, br. d, *J* 8.2 H-3); 5.86 (1H, dddd, *J* 6.2, 6.2, 10.3, 17.1, H-4'); 5.57 (1H, dddd, *J* 5.9, 5.9, 10.4, 17.0, H-2"); 5.39-5.48 (1H, br s, H-1'); 5.02 (1H, d, *J* 17.1, H-5'); 4.97 (1H, d, *J* 10.3, H-5'); 4.89 (1H, d, *J* 17.0, H-3"); 4.88 (1H, d, *J* 10.4, H-3"); 3.79 (3H, s, $-OCH_3$); 3.74 (3H, s, $-C(O)OCH_3$); 3.62 (2H, d, *J* 6.1, C-1") 2.13-2.07 (2H, m, H-3'); 2.08-1.96 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.10 (C-2); 157.03 (C=O); 138.15 (C-4'); 135.34 (C-2"); 128.71 (C-4); 128.41 (C-1); 127.81 (C-6); 120.03 (C-5); 115.49 (C-3"); 114.65 (C-5'); 110.58 (C-3); 55.40 ($-OCH_3$); 53.60 (C-1'); 52.33 ($-C(O)OCH_3$); 46.51 (C-1"); 30.73 (C-2'/C-3'); 30.69 (C-2'/C-3'). IR (thin film, cm^{-1}) 2938, 2248 (C=N, amide); 1688 (C=O); 1641 (C=C, vinyl); 1601 (C=C, aromatic); 1492, 1457, 1399, 1325,

1287, 1246, 1192, 1143, 1052, 1032, 993, 908, 727, 646; HRMS (ESI) *m/z* calcd. $C_{17}H_{23}NO_3$ $[M+Na]^+$ 312.1570, found 312.1571.

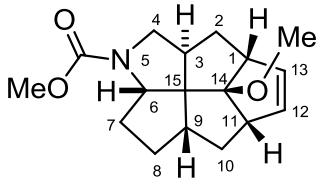
rac-(1R, 2S, 3S, 6S, 8S, 11S)-3-(3'-Propenyl)-11-methoxy-4-carboxymethyl-4-azatetracyclo[6.2.1.0^{2,6}.0^{2,11}]dec-9-ene **298**.



A solution of photosubstrate **297** (1.30 g, 4.30 mmol) was dissolved in dry cyclohexane (400 ml), placed a quartz immersion well photoreactor with a magnetic stirrer and flushed with nitrogen for 20 minutes. The apparatus was cooled with H_2O and the solution irradiated for 2 hrs 10 mins using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The cyclohexane was removed under reduced pressure and purification of the resulting crude residue was conducted using flash column chromatography (100:1 silica, Et_2O/CH_2Cl_2, 6:94) to yield the meta adduct **298** as an orange oil (213 mg, 16%) along with minor impurities.

R_f 0.31 (Et_2O/CH_2Cl_2, 6:94); ^{1}H NMR (600 MHz, CDCl3): δ 5.75-5.84 (1H, m, H-3'); 5.63 (1H, dd, *J* 2.0, 5.4, H-10); 5.53 (1H, dm, *J* 5.4, H-9); 4.99 (1H dm, *J* 17.2, H-4'); 4.89-4.94 (1H, m, H-4'); 4.14-4.17 (0.35H, m, H-3); 4.03 (0.65H, dd, *J* 3.6, 6.7, H-3); 3.67 (2H, s, -(CO)OCH_3); 3.66 (1H, s, -(CO)OCH_3); 3.56 (1H, dd, *J* 9.1, 11.8, H-5); 3.49 (0.65H, dd, *J* 2.7, 11.8, H-5); 3.34-3.38 (0.35H, m, H-5); 3.34 (3H, s, -OCH_3); 3.30-3.33 (1H, m, H-8); 2.24-2.33 (1H, m, 6); 2.10-2.15 (1H, m, H-1); 2.01-2.09 (2H, m , H-2'); 1.95-2.00 (1H, m, H-7); 1.86-1.93 (0.35H, m, H-1'); 1.83-1.89 (1H, m, H-7); 1.70-1.77 (0.65H, m, H-1'); 1.45-1.52 (1H, m, 1'); ^{13}C NMR (150 MHz, CDCl3): δ 1.55 + 154.89 (C=O); 138.54 + 138.37 (C-3'); 132.98 + 132.91 (C-9); 114.43 + 114.22 (C-4'); 90.18 + 90.12 (C-11); 56.71 + 56.66 (-OCH_3); 54.80 + 54.42 (C-3); 52.58 + 52.46 (C-8); 52.27 + 52.16 (-(CO)OCH3); 51.47 (C-5); 46.55 + 46.43 (C-7); 40.63 (C-2); 39.62 (C-6); 37.67 + 37.58 (C-1); 32.63 + 31.92 (C-1'); 29.26 (C-2'); HRMS (ESI) *m/z* calcd. $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1751, found 290.1756.

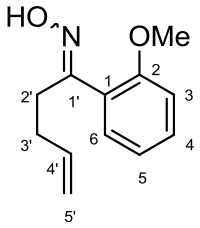
rac-(1R, 3S, 6S, 9S, 11S, 14R, 15R)-14-Methoxy-5-carboxymethyl-5-azapentacyclo [9.2.1.1^{3,14}.0^{6,15}.0^{9,15}]pentadec-12-ene **301**.



A solution of impure linear *meta* adduct **298** (70.0 mg, 0.243 mmol) and acetophenone (35.0 mg, 0.292 mmol) were dissolved in dry, nitrogen flushed MeCN (150 ml) in a quartz immersion well photoreactor fitted with a magnetic stirrer. The apparatus was cooled with H_2O and the solution irradiated for 3 hours using a 6 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The solvent was removed under reduced pressure. Purification was carried out by flash column chromatography (neutral silica, Et_2O/pentane/toluene 10:20:70) to afford the pure double [3+2] product **301** as a pale yellow oil (7 mg, 10%).

R_f 0.24 (Et_2O/pentane/toluene, 10:20:70); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.68 (1H, ddd, *J* 1.9, 2.4, 6.0, H-12); 5.48 (1H, ddd, *J* 1.5, 2.7, 6.0, H-13); 4.47 (0.4H, d, *J* 8.1, H-6); 4.32 (0.6H, d, *J* 8.1, H-6); 3.70 (2H, s, -(CO)OCH_3); 3.67 (1H, s, -(CO)OCH_3); 3.46 (0.6H, d, *J* 11.1, H-4); 3.35 (0.4H, d, *J* 11.1, H-4); 3.22-3.28 (1H, m, H-11); 3.21 (2H, s, - OCH_3); 3.19 (1H, s, -OCH_3); 3.17 (1H, ddd, *J* 5.4, 9.3, 11.1, H-4); 3.04-3.08 (1H, m, H-1); 2.18-2.34 (3H, m, H-3, H-9, H-7); 1.95 (1H, ddd, *J* 5.3, 8.0, 11.3, H-10); 1.82 (0.4H, ddm, *J* 6.6, 14.0, H-7); 1.76 (0.6H, ddm, *J* 6.6, 14.0, H-7); 1.60-1.69 (2H, m, H-2); 1.52-1.57 (1H, m, H-8); 1.18-1.26 (1H, m, H-8); 1.10 (1H, dddd, *J* 8.4, 8.4, 11.4, 13.6, H-10); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.43 + 155.77 (C=O); 133.24 + 133.41 (C-13); 132.50 + 132.59 (C-12); 102.25 + 102.33 (C-14); 75.23 + 76.30 (C-4); 59.36 + 59.86 (C-11); 55.27 + 55.77 (C-6); 54.00 (C-9); 52.13 + 52.33 ((CO)OCH_3); 51.82 + 51.80 (-OCH_3); 51.30 + 51.57 (C-4); 47.37 + 47.62 (C-1); 41.12 + 41.86 (C-3); 40.56 + 40.94 (C-7); 36.95 + 37.00 (C-2); 30.42 + 30.40 (C-10); 25.71 + 25.73 (C-8) ; HRMS (ESI) *m/z* calculated $C_{17}H_{23}NNaO_3$ $[M+Na]^+$ 312.1570, found 312.1579.

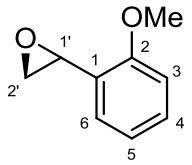
1-(2-Methoxy-phenyl)-pent-4'-en-1'-one oxime **308**.



In a round-bottom flask equipped with reflux condenser ketone **256** (4.00 g, 21.0 mmol) and hydroxylamine hydrochloride (4.54 g, 65.0 mmol) were dissolved in EtOH (80 ml). 5M NaOH (38. 2 ml, 0.191 mol) was added and the mixture was heated at reflux for 15 minutes by which time TLC showed that the reaction was complete. The reaction was cooled to ambient temperature, poured into cold H_2O (200 ml). Ice was added and the mixture acidified using dilute H_2SO_4. The oxime product was extracted with Et_2O (3 x 100 ml); and the combined organic layers dried over $MgSO_4$. Solvent was removed under reduced pressure to give oxime **308** (4.30 g, 99%) as white to sand coloured crystals.

R_f 0.21 (Et_2O/petrol, 20:80); m. p. 65.5 - 66.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (1H, br s, -OH); 7.34 (1H, ddd, *J* 1.8, 7.6, 8.6 H-4); 7.25 (1H, dd, *J* 1.7, 7.6, H-3); 6.96 (1H, ddd, *J* 7.6, 8.6, 1.0 H-5); 6.91 (1H, dd, *J* 8.5, 0.9, H-6); 5.83-5.76 (1H, ddt, *J* 17.0, 10.3, 6.6, H-4'); 5.00 (1H, d, *J* 17.0, H-5'); 4.94 (1H, d, *J* 10.3, H-5'); 3.84 (3H, s, -OCH_3); 2.87 (2H, m, H-2'); 2.23 (2H, m, H-3'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.21 (C-1', C=N); 157.40 (C-2); 137.93 (C-4'); 130.11 (C-3/C-4); 130.08 (C-3/C-4); 125.71 (C-1); 120.56 (C-5); 114.64 (C-5'); 110.89 (C-6); 55.38 (-OCH_3); 29.65 (C-3'); 27.66 (C-2').; IR (KBr disc, cm^{-1}) 3219 (-OH);1642 (C=N); 1598 (C=C, aromatic); LRMS (EI) *m/z* calcd. $C_{12}H_{15}NO_2$ $[M]^+$ 205 found 205; fragments 188 (100%); 174 (48%); 158 (16%); 146 (34%); 134 (55%); 123 (43%); 107 (32%); 91 (41%); 77 (40%); 63 (15%); 55 (35%).

2-(2-Methoxyphenyl)oxirane **313**.

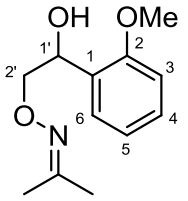


Method A: *o*-Anisaldehyde (1.00 g, 7.34 mmol) was dissolved in DMSO (5 ml) with a magnetic stirrer bar, followed by trimethylsulfonium iodide (1.80 g, 8.81 mmol) in a 25 ml conical flask. To this yellow solution was added freshly ground KOH (1.23 g, 22.0 mmol). The flask was heated at 80 °C for one hour, within which time the solution turned a dark brown. The reaction was diluted with H_2O (15 ml) and the epoxide extracted with Et_2O (3 x 25 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and Et_2O removed under reduced pressure. The resulting crude epoxide was often used without further purification, although the crude material could be passed through a plug of neutral silica (Et_2O/petrol 10:90) to remove any trace impurities. The epoxide **313** was obtained as a colourless to pale yellow oil (0.870 g, 79%)

Method B: This method was adapted from Corey and Chaykovsky.[135] A three-necked round bottom flask was fitted with a magnetic stirrer, reflux condenser, rubber stopper and water aspirator. NaH (60% dispersion in mineral oil, 0.840 g, 0.0350 mmol) and Trimethylsulfoxonium iodide (7.70 g, 0.0350 mmol) were added to the flask and placed under nitrogen, then DMSO (25 ml) was added slowly via syringe, producing vigorous evolution of H_2 gas. This was allowed to stir for 20 mins, yielding a milky precipitate. A solution of *o*-anisaldehyde (2.86 g, 0.0210 mmol) in DMSO (5 ml) was added drop wise *via* syringe ensuring vigorous stirring of the reaction mixture. This was warmed to 60 °C and allowed to stir for 2 hours, then poured into H_2O (100 ml). The product was extracted with Et_2O (3 x 25 ml) and the combined organic layers were dried over anhydrous $MgSO_4$. The volatile solvent was removed under reduced pressure to afford the oxirane **313** (2.90 g, 66%) as a pale yellow oil that was used without further purification.

R_f 0.48 (Et_2O/petrol, 10:90); Previously synthesised by Guy *et al.*[142] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (1H, dt, *J* 1.7, 7.9, H-4); 7.16 (1H, dd, *J* 1.7, 7.6, H-6); 6.95 (1H, t, *J* 7.6, H-5); 6.89 (1H, d, *J* 8.2, H-3); 4.21 (1H, dd, *J* 2.7, 4.2, H-1'); 3.88 (3H, s, -OCH_3); 3.14 (1H, dd, *J* 4.2, 5.7, H-2'); 2.71 (1H, dd, *J* 2.7, 5.7, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.15 (C-2); 128.76 (C-4); 126.15 (C-1); 125.00 (C-6); 120.69 (C-5); 110.15 (C-3); 55.42 (-OCH_3); 50.53 (C-2'); 48.18 (C-1'); IR (thin film, cm^{-1}) 3051, 2916, 2838, 1603 (C=C, aromatic); 1590, 1496, 1464, 1438, 1388, 1310, 1287, 1256, 1237, 1176, 1161, 1130, 1101, 1048, 1027, 988, 878, 753; HRMS (ESI) *m/z* calculated $C_9H_{10}NaO_2$ $[M+Na]^+$ 173.0573, found 173.0577.

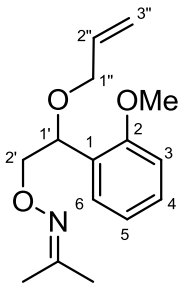
1-(2-Methoxyphenyl)-2-[(propan-2-ylideneamino)oxy]ethanol **317**.



N-Hydroxypropan-2-imine (0.830 g, 11.4 mmol) was dissolved in DMSO (10 ml) in a conical flask fitted with a magnetic stirrer. Freshly ground KOH (1.20 g, 21.3 mmol) was added in portions and the resulting yellow solution was left to stir for 30 minutes. Epoxide **313** dissolved in DMSO (5 ml) was then added drop wise, and the reaction heated at 80 °C for 1 hour, followed by 2 hours stirring at ambient temperature. HCl (2M) was then carefully added until approximately pH 6 and the reaction was diluted with H_2O (50 ml); followed by extraction with Et_2O (3 x 25 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvents removed under reduced pressure. This thick orange oil (2.39g, 94%) was usually used without the need for further purification. For the sake of characterisation the crude material was subjected to flash column chromatography (Et_2O/pentane, 40:60) to yield the pure compound **317** (0.564 g, 22%) as an orange oil.

R_f 0.37 (Et_2O/pentane, 40:60); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (1H, d, *J* 7.5, H-6); 7.28 (1H, dt, *J* 1.5, 8.3, H-4); 6.99 (1H, t, *J* 7.5, H-5); 6.87 (1H, dd, *J* 8.3, H-3); 5.33 (1H, d, *J* 7.6, H-1'); 4.25 (1H, dd, *J* 2.6, 11.8, H-2'); 4.06 (1H, dd, *J* 8.0, 11.8, H-2'); 3.84 (3H, s, -OCH_3); 3.80 (1H, s, -OH); 1.91 (3H, s, -CH_3); 1.89 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.28 (C-2); 155.80 (C=N); 128.60 (C-1); 128.39 (C-4); 127.32 (C-6); 120.64 (C-5); 110.12 (C-3); 76.56 (C-2'); 69.96 (C-1'); 55.23 (-OCH_3); 21.93 (-CH_3); 15.58 (-CH_3); IR (thin film, cm^{-1}) 3435 (-OH); 2918, 1640 (C=N, oxime); 1602 (C=C, aromatic); 1588, 1491, 1464, 1438, 1367, 1240, 1071, 1048, 1027, 915, 826, 754; HRMS (ESI) *m/z* calculated $C_{12}H_{17}NNaO_3$ $[M+Na]^+$ 246.1101, found 246.1103.

1-(2-Methoxyphenyl)-2-[(propan-2'-ylideneamino)oxy]ethanol **314**.



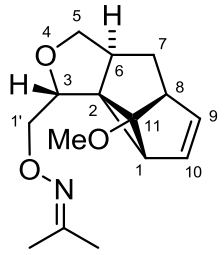
To a magnetically stirred solution of the alcohol **317** (0.350 g, 1.79 mmol) and allyl bromide (0.460 ml, 5.37 mmol) in CH_2Cl_2 (5 ml) was added 50% NaOH (10 ml) and TBAHS (0.610 g, 1.79 mmol). This was allowed to stir overnight by which time TLC showed complete conversion of the starting material. The reaction was diluted with saturated NH_4Cl solution (50 ml); and then extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure to yield the photosubstrate **314** (0.340 g, 83%) as orange coloured oil.

R_f 0.35 (Et_2O/hexane, 20:80); ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (1H, dd, *J* 1.7, 7.5, H-6); 7.28 (1H, ddd, *J* 1.9, 7.3, 8.2, H-4); 6.98 (1H, dt, *J* 1.0, 7.5, H-5); 6.86 (1H, dd, *J* 0.9, 8.3, H-3); 5.92 (1H, dddd, *J* 5.2, 5.8, 10.4, 17.1, H-2''); 5.28 (1H, dm, *J* 17.1, H-3''); 5.13 (1H, dm, *J* 10.4, H-3''); 5.10 (1H, dd, *J* 3.4, 7.7, H-1'); 4.18 (1H, dd, *J* 3.5, 11.3, H-2'); 4.04 (1H, dd, *J* 7.8, 11.8, H-2'); 4.04 (1H, dddd, *J* 1.5, 1.5, 5.2, 13.1, H-1''); 3.91 (1H, dddd, *J* 1.4, 1.4, 5.8, 13.1, H-1''); 3.83 (3H, s, $-OCH_3$); 1.87 (6H, s, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.03 (C-2); 154.61 (C=N); 135.23 (C-2''); 128.51 (C-4); 127.55 (C-6); 127.43 (C-1); 120.57 (C-5); 116.25 (C-3''); 110.20 (C-3); 76.42 (C-2'); 74.09 (C-1'); 70.19 (C-1''); 55.31 ($-OCH_3$); 21.80 ($-CH_3$); 15.69 ($-CH_3$); IR (thin film, cm^{-1}) 2920, 1646 (C=N, oxime); 1601 (C=C, aromatic); 1589, 1491, 1459, 1439, 1368, 1283, 1270, 1241, 1079, 1049, 923, 827, 755; HRMS (ESI) *m/z* calculated $C_{15}H_{21}NNaO_3$ $[M+Na]^+$ 286.1414, found 286.1418.

Direct irradiation of photosubstrate **314** *to yield linear meta adduct* **315** *and ortho derived adduct* **319**.

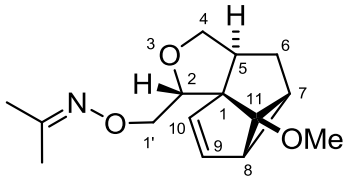
A solution of oxime-derived photosubstrate **314** (1.00 g, 3.80 mmol) in dry MeCN (150 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 4 hours using a 6 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting orange residue subjected to flash column chromatography (100:1 neutral silica, Et_2O/pentane 70:30) to afford *meta* adduct **315** (0.193 mg, 19%) and an *ortho* derived adduct **319** (0.162 mg, <16%), which were isolated from the reaction mixture with inseparable impurities. The *ortho* derived adduct **319** could not be assigned with satisfactory accuracy.

rac-(1R, 2S, 3R, 6S, 8S, 11S)-3-[(Propan-2'-ylideneamino)oxy]-11-methoxy-4-oxatetracyclo[6.2.1.$0^{2,6}$.$0^{2,11}$]undec-9-ene **315**.



R_f 0.25 (Et_2O/hexane, 30:70); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.64 (1H, dd, *J* 2.4, 5.7, H-10); 5.55 (1H, ddd, *J* 1.3, 2.7, 5.6, H-9); 4.21 (1H, dd, *J* 3.9, 5.8, H-3); 4.17 (1H, dd, *J* 7.9, 8.8, H-5β); 4.02-4.10 (2H, m, H-1'); 3.63 (1H, dd, *J* 4.1, 8.8, H-5α); 3.40 (3H, s, -OCH_3); 3.38-3.40 (1H, m, H-8); 2.30-2.37 (1H, m, H-6); 2.26-2.27 (1H, m, H-1); 1.96 (1H, ddd, *J* 5.5, 9.3, 11.7, H-7α); 1.89 (1H, dd, *J* 6.7, 11.7, H-7β); 1.84 (3H, s, -CH_3); 1.83 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.72 (C=N); 133.07 (C-9); 127.93 (C-10); 88.19 (C-11); 74.57 (C-1'); 74.24 (C-3); 73.15 (C-5); 56.64 (-OCH_3); 53.48 (C-2); 53.39 (C-8); 44.94 (C-7); 42.91 (C-6); 36.96 (C-1); 21.77 (-CH_3); 15.67 (-CH_3); IR (thin film, cm^{-1}) 3054, 2935, 2858, 1652 (C=N, oxime); 1641, 1586, 1451, 1405, 1368, 1327, 1299, 1271, 1246, 1241, 1193, 1135, 1096, 1077, 1009, 977, 948, 863, 827, 756, 734, 699; HRMS (ESI) *m/z* calculated $C_{15}H_{22}NO_3$ $[M+H]^+$ 264.1594, found 264.1579.

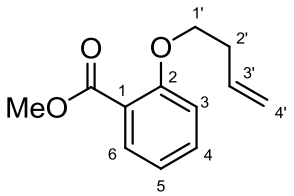
rac-(1R, 2R, 5S, 7R, 8S, 11S)-2-[(Propan-2'-ylideneamino)oxy]-11-methoxy-3-oxatetracyclo[5.3.1.$0^{1,5}$.$0^{8,11}$]undec-9-ene **320**.



A solution of linear *meta* adduct **315** (30.0 mg, 0.11 mmol) and acetophenone (27.0 mg, 0.23 mmol) were dissolved in dry, nitrogen flushed MeCN (150 ml) in a quartz immersion well photoreactor fitted with a magnetic stirrer. The apparatus was cooled with H_2O and the solution irradiated for 1 hour 10 minutes using a 6 W low-pressure Hg vapour lamp (λ_{max} = 254 nm). The solvent was removed under reduced pressure. Purification was carried out by flash column chromatography (neutral silica, Et_2O/pentane, 50:50) to afford the angular adduct **320** (12 mg, 40%) as a yellow oil.

R_f 0.36 (Et_2O/pentane, 60:40); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (1H, dm, *J* 5.6, H-10); 5.62 (1H, dm, *J* 5.6, H-9); 4.54 (1H, dd, *J* 4.4, 5.4, H-2); 4.19 (1H, dd, *J* 4.4, 10.8, H-1'); 4.11 (1H, dd, *J* 4.4, 10.8, H-1'); 3.93 (1H, dd, *J* 7.6, 8.3, H-4β); 3.69 (1H, dd, *J* 7.6, 8.3, H-4α); 3.36 (3H, s, -OCH_3); 2.49 (1H, ddd, *J* 6.3, 7.6, 10.8 H-5); 2.20 (1H, d, *J* 3.4, H-7/H-8); 1.87 (3H, s, -CH_3); 1.86 (3H, s, -CH_3); 1.78 (1H, ddd, *J* 2.8, 3.4, 14.0, H-6α); 1.53 (1H, dd, *J* 6.2, 14.0, H-6β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.01 (C=N); 131.42 (C-9); 126.02 (C-10); 90.53 (C-11); 75.08 (C-1'); 75.05 (C-2); 70.11 (C-1); 69.75 (C-4); 57.26 (C-5); 56.71 (-OCH_3); 36.81 (C-7); 35.82 (C-8); 23.77 (C-6); 21.76 (-CH_3); 15.85 (-CH_3); HRMS (ESI) *m/z* calculated $C_{15}H_{21}NNaO_3$ $[M+Na]^+$ 286.1414, found 286.1401.

2-(But-3'-enyloxy)-benzoic acid methyl ester **332**.

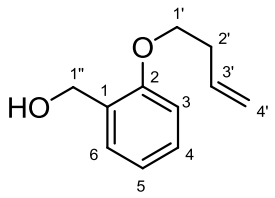


The synthesis of ester **332** was adapted from the method of Al-Qaradawi, Cosstick and Gilbert.[14] Methyl salicylate (7.30 g, 48.1 mmol) was dissolved in butan-2-one (200 ml) and poured into a 500 ml two-necked flask equipped with a reflux condenser, dropping funnel and magnetic stirrer bar. Anhydrous K_2CO_3 (33.0 g, 241 mmol) was added to the flask, ensuring vigorous stirring and the contents brought to reflux. Butenyl bromide (6.50 g, 48.1 mmol) was loaded into the dropping funnel and added drop wise over 2 hours.

The white mixture was left to heat at reflux for 7 days until TLC analysis showed complete consumption of the phenolic starting material. The reaction vessel was cooled to ambient temperature, filtered to remove the K_2CO_3 and other salts and the solvent removed under reduced pressure. The residue was taken up in Et_2O (100 ml); washed with 2M NaOH (2 x 50 ml) and then with H_2O (2 x 50 ml). The organic phase was dried over anhydrous $MgSO_4$, the solvent removed to give **332** as a pale yellow oil 3.40 g (34%) that was used without further purification.

R_f 0.29 (Et_2O/petrol, 10:90). Compound NMR data already determined.[14] IR (thin film, cm^{-1}) 3077, 2949, 1731 (C=O, ester); 1642 (C=C, vinyl); 1601 (C=C, aromatic); 1582, 1492, 1455, 1433, 1386, 1304, 1250, 1190, 1164, 1132, 1084, 1049, 990, 918, 755; HRMS (ESI) *m/z* calcd. $C_{12}H_{14}NaO_3$ $[M+Na]^+$ 229.0835, found 229.0831.

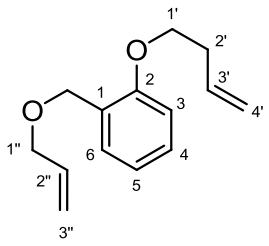
(2-But-3'-enyloxy-phenyl)-methanol **333**.



Ester **332** (2.80 g, 13.6 mmol) was dissolved in Et_2O (50 ml) under a nitrogen atmosphere and cooled to 0 ºC. DIBAL (1M, 40.8 ml, 40.8 mmol) was added drop wise *via* syringe over 30 mins. The reaction was stirred until analysis by TLC showed none of the ester remained. With the temperature maintained at 0 ºC, the reaction was diluted with Et_2O (100 ml) followed cautiously by the addition of H_2O (100 ml). The two layers were partitioned in a separating funnel; the organic layer was washed with brine (2 x 50 ml) and dried over anhydrous $MgSO_4$. Et_2O was removed under reduced pressure to yield alcohol **333** (2.04 g, 84%) as a colourless oil that was used without further purification.

Rf 0.11 (Et_2O/petrol, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.28 (2H, m, H-4/H-6); 6.94 (1H, td, *J* 1.1, 7.4, H-5); 6.88 (1H, dd, *J* 1.0, 8.5, H-3); 5.86-5.95 (1H, ddt, *J* 6.8, 10.2, 17.0, H-3'); 5.22 (1H, dm, *J* 17.0, H-4'); 5.16 (1H, dm, *J* 10.2, H-4'); 4.68 (2H, br. s, H-1''); 4.09 (2H, t, *J* 6.3, H-2'); 2.56-2.61 (2H, m, H-1'); 2.52-2.58 (1H, br. s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.76 (C-2); 134.56 (C-3'); 129.29 (C-1); 128.80 (C-4/C-6); 128.71 (C-4/C-6); 120.65 (C-5); 117.35 (C-4'); 111.00 (C-3); 66.75 (C-1'); 62.28 (C-1''); 33.70 (C-2'); IR (thin film, cm^{-1}) 3392, 3076, 2926, 2873, 1642 (C=C, vinyl); 1603 (C=C, aromatic); 1590, 1492, 1456, 1432, 1389, 1289, 1240, 1196, 1114, 1045, 917, 752; HRMS (ESI) *m/z* calcd. $C_{11}H_{14}NaO_2$ $[M+Na]^+$ 201.0886, found 201.0884.

1-Allyloxymethyl-2-but-3'-enyloxy-benzene **321**.



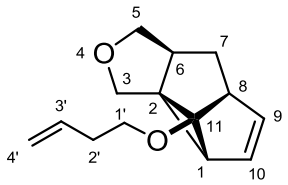
To a stirred solution of alcohol **333** (2.04 g, 11.5 mmol) and allyl bromide (4.96 ml, 57.3 mmol) in CH_2Cl_2 (10 ml) under a nitrogen atmosphere at 0ºC, was added 50% NaOH (30 ml) and TBAHS (3.90 g, 11.5 mmol). This was allowed to warm to ambient temperature and stir for 24 hrs until TLC showed complete conversion of the starting material. The reaction was diluted with saturated NH_4Cl solution (50 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure and the resulting residue purified by flash column chromatography (EtOAc/petrol, 3:97) to yield the ether **321** (2.40 g, 96%) as a pale yellow oil.

Rf 0.39 (Et_2O/hexane, 3:97). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (1H, dd, *J* 1.8, 7.5, H-6); 7.24 (1H, td, *J* 1.8, 7.8, H-4); 6.96 (1H, td, *J* 1.0, 7.4, H-5); 6.85 (1H, dd, *J* 1.0, 8.1, H-3); 5.95-6.04 (1H, ddt, *J* 5.6, 10.5, 17.2, H-2''); 5.88-5.97 (1H, ddt, *J* 6.7, 10.2, 17.0, H-3'); 5.34 (1H, dm, *J* 17.2, H-3''); 5.21 (1H, dm, *J* 10.2, H-3''); 5.18 (1H, dm, *J* 17.1, H-4'); 5.11 (1H, dm, *J* 10.2, H-4'); 4.58 (2H, s, -CH_2-O-); 4.09 (2H, ddd, *J* 1.4, 1.5, 5.6, H-1''); 4.04 (2H, t, *J* 6.6, H-1'); 2.54-2.59 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.36 (C-2); 135-06 (C-2''); 134.58 (C-3'); 128.87 (C-6); 128.45 (C-4); 120.49 (C-5); 116.90 (C-3''); 116.69 (C-4'); 111.24 (C-3); 71.49 (C-1''); 67.32 (C-1'); 66.70 (-CH_2O-) 33.74 (C-2'); IR (thin film, cm^{-1}) 2627, 2849, 1832, 1728, 1641 (C=C, vinyl); 1474, 1433, 1374, 1344, 1292, 1258, 1156, 1096, 1058, 884, 759; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1199.

Irradiation of photosubstrate **321** *to yield linear meta adduct* **323** *and ortho derived adduct* **334**.

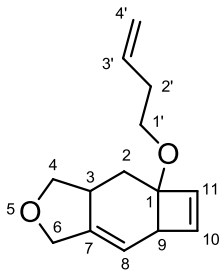
A solution of photosubstrate **321** (2.10 g, 9.63 mmol) in dry cyclohexane (400 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 18 hours using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting orange residue subjected to flash column chromatography (100:1 silica, CH_2Cl_2/Et_2O/petrol, 5:10:85) to afford *meta* adduct **323** (280 mg, 13%) and *ortho* adduct **334** (301 mg, 14%) both with minor co-eluting impurities.

rac-(1R, 2S, 6S, 8S, 11S)-11-(3'-Butenyloxy)-11-methoxy-4-oxatetracyclo [6.2.1.$0^{2,6}$.$0^{2,11}$]undec-9-ene **323**.



R_f 0.39 (CH_2Cl_2/Et_2O/petrol, 5:10:85). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, ddt, *J* 6.7, 10.2, 17.1, H-3'); 5.69 (1H, dd, *J* 2.3, 5.8, H-10); 5.56 (1H, dm, *J* 5.8, H-9); 5.09 (1H, dm, *J* 17.1, H-4'); 5.03 (1H, dm, *J* 10.2, H-4'); 3.90 (1H, d, *J* 9.1, H-3); 3.89 (1H, dd, *J* 7.8, 8.9, H-5); 3.70 (1H, dd, *J* 3.5, 8.9, H-5); 3.69 (1H, d, *J* 9.1, H-1'); 3.63 (1H, dt, *J* 6.8, 9.2, H-1'); 3.57 (1H, dt, *J* 6.8, 9.2, H-1'); 3.37 (1H, dd, *J* 2.7, 5.0,H-8); 2.34 (2H, q, *J* 6.8, H-2'); 2.25-2.31 (1H, m, H-6); 2.21 (1H, br. s, H-1); 1.96 (1H, dd, *J* 5.3, 9.4, H-7); 1.92 (1H, dd, *J* 6.2, 10.6, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.03 (C-3'); 132.81 (C-9); 128.13 (C-10); 116.40 (C-4'); 87.68 (C-11); 73.39 (C-5); 68.67 (C-1'); 66.11 (C-3); 53.75 (C-8); 52.59 (C-2); 44.74 (C-7); 42.38 (C-6); 36.79 (C-1); 34.37 (C-2'); IR (thin film, cm^{-1}) , 3055, 2930, 2851, 1658, (C=C, alkene); 1641 (C=C, vinyl); 1586, 1465, 1456, 1430, 1376, 1330, 1277, 1246, 1188, 1169, 1138, 1077, 1057, 1015, 909, 860, 743; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1198.

1-(3'-butenyloxy)tricyclo[7.2.0.0^{3,7}]undeca-7,10-diene **334**.

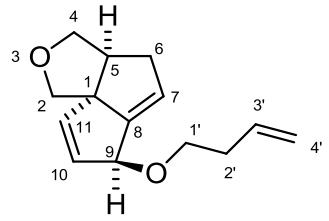


R_f 0.30 (CH_2Cl_2/Et_2O/petrol 5:10:85). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (1H, dm, *J* 1.9, H-11); 6.02 (1H, dm, *J* 1.9, H-10); 5.75-5.84 (1H, m, H-3'); 5.60 (1H, br. s, H-8); 5.06 (1H, dm, *J* 17.1, H-4'); 5.00 (1H, dm, *J* 10.2, H-4'); 4.36 (1H, d, *J* 13.4, H-6); 4.25 (1H, d, *J* 13.4, H-6); 4.18 (1H, t, *J* 8.3, H-4); 3.50 (2H, t, *J* 6.9, H-1'); 3.37 (1H, t, *J* 8.4, H-4); 3.30 (1H, d, *J* 6.0, H-9); 2.47-2.56 (1H, m, H-3); 2.28 (2H, q, *J* 7.0, H-2'); 2.09 (1H, dd, *J* 5.2, 12.3, H-2); 1.25 (1H, t, *J* 12.3,H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.50 (C-7); 138.09 (C-10); 136.58 (C-11); 135.18 (C-3'); 116.16 (C-4'); 115.17 (C-8); 84.67 (C-1); 73.79 (C-4); 63.50 (C-1'); 47.44 (C-9); 36.95 (C-3); 34.93 (C-2'); 33.48 (C-2); IR (thin film, cm^{-1}) 2926, 2847, 1640, (C=C, alkene); 1586, 1459, 1474, 1434, 1374, 1344, 1291, 1157, 1097, 1058, 1029, 994, 918, 821, 785, 760, 721, 693, 652; HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1198.

Irradiation of linear meta adduct **323** *to yield silphinene compound* **335**.

A solution of linear *meta* adduct **323** (0.100 g, 0.460 mmol) in dry cyclohexane (400 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with water and the solution irradiated for 48 hrs using a 16 W low-pressure mercury vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting residue subjected to flash column chromatography (100:1 silica, ether/hexane 20:80) to afford 1,2 alkenyloxy migration adduct **335** (12.0 mg, 12%) alongside other isomers that could not be obtained in a satisfactorily purified form.

rac-(1S, 5S, 9S)-9-(3'-Butenyloxy)-3-oxatricyclo[6.3.0^{1,5}.0^{1,8}]undeca-7,10-diene **335**.

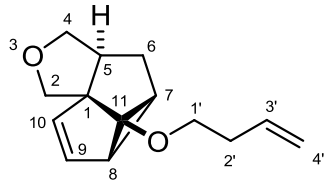


R_f 0.36 (Et_2O/hexane, 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (1H, d, *J* 5.9, H-11); 5.96 (1H, dd, *J* 2.4, 5.9, H-10); 5.78 (1H, dddd, *J* 6.9, 6.9, 10.2, 17.2, H-3'); 5.61 (1H, br. s., H-7); 5.06 (1H, dm, *J* 17.2, H-4'); 5.00 (1H, dm, *J* 10.2, H-4'); 4.49 (1H, d, *J* 2.4, H-9); 3.90 (1H, d, *J* 9.1, H-4α); 3.87 (1H, d, *J* 9.4, H-2α); 3.67 (1H, dd, *J* 4.4, 9.0, H-4β); 3.58 (1H, ddd, *J* 7.1, 7.1, 9.0, H-1'); 3.42-3.47 (1H, m, H-1'); 3.42 (1H, d, *J* 9.4, H-2β); 2.75-2.84 (2H, m, H-5 + H-6α); 2.59 (1H, ddd, *J* 1.7, 5.0, 15.9, H-6β); 2.55 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.67 (C-8); 140.87 (C-11); 135.24 (C-3'); 133.32 (C-10); 125.45 (C-7); 116.31 (C-4'); 76.94 (C-2); 76.85 (C-9); 74.85 (C-4); 70.35 (C-1); 68.31 (C-1'); 47.60 (C-5); 42.82 (C-6) 34.35 (C-2'); HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1198.

Irradiation of linear meta adduct **323** *to yield angular meta adduct* **325** *and oxetane compound* **336**.

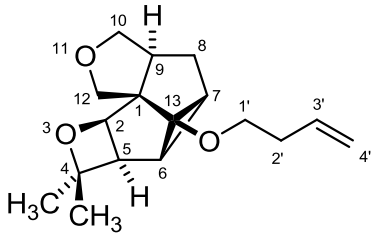
A solution of linear *meta* adduct **323** (50.0 mg, 0.229 mmol) in acetone (150 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with water and the solution irradiated for 3 hrs using a 6 W low-pressure mercury vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting residue subjected to flash column chromatography (Et_2O/hexane, 20:80 to 40:60) to afford angular *meta* adduct **325** (9.0 mg, 18%) and Paterno-Büchi adduct **335** (12.0 mg, 24%) alongside other isomers that could not be obtained in a satisfactorily purified form.

rac-(1R, 5S, 7R, 8S, 11S)-11-(3'-Butenyloxy)-3-oxatetracyclo[5.3.1.0^{1,5}.0^{8,11}]undec-9-ene **325**.



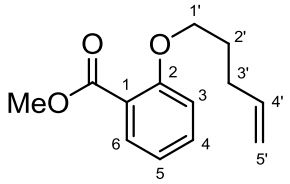
R_f 0.34 (Et_2O/petrol, 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, ddt, *J* 6.9, 10.3, 17.0, H-3'); 5.63 (1H, dd, *J* 2.3, 5.6, H-9); 5.55 (1H, d, *J* 5.6, H-10); 5.08 (1H, dm, *J* 17.0, H-4'); 5.04 (1H, dm, *J* 10.3, H-4'); 4.23 (1H, d, *J* 8.9, H-2); 3.85 (1H, dd, *J* 7.9, 8.0, H-4); 3.81 (1H, d, *J* 8.9, H-2); 3.68 (1H, dd, *J* 8.2, 10.7, H-4); 3.50-3.60 (2H, m, H-1'); 2.42-2.47 (1H, m, H-5); 2.31-2.37 (2H, m, H-2'); 2.16-2.24 (2H, m, H-7 + H-8); 1.81 (1H, dd, *J* 5.8, 14.0, H-6); 1.58 (1H, dd, *J* 6.4, 14.0, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.93 (C-3'); 133.16 (C-10); 125.90 (C-9); 116.57 (C-4'); 89.32 (C-11); 69.98 (C-4); 69.30 (C-1); 68.85 (C-1'); 68.20 (C-2); 58.09 (C-5); 37.37 (C-7/C-8); 36.86 (C-7/C-8); 34.53 (C-2') 23.60 (C-6); HRMS (ESI) *m/z* calcd. $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199, found 241.1197.

rac-(1R, 2R, 5R, 6R, 7R, 9S, 13S)-13-(3'-Butenyloxy)-10,10-dimethyl-3,11–dioxapentacyclo[6.4.1.0^{1,9}.0^{2,5}.0^{7,13}]tridecane **336**.



R_f 0.29 (Et_2O/hexane, 40:60) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (1H, ddt, *J* 6.8, 10.2, 17.2, H-3'), 5.09 (1H, dm, *J* 17.2, H-4'), 5.03 (1H, dm, *J* 10.2, H-4'), 4.69 (1H, dm, *J* 4.2, H-2), 4.26 (1H, d, *J* 9.3, H-12β), 4.01 (1H, t, *J* 8.1, H-10α), 3.83 (1H, d, *J* 9.3, H-12α), 3.76 (1H, ddd, *J* 6.8, 6.8, 8.9, H-1'), 3.64 (1H, ddd, *J* 7.0, 7.0, 8.9, H-1'), 3.47 (1H, dd, *J* 8.3, 10.5, H-10β), 2.48 (1H, d, *J* 4.1, H-5), 2.37 (2H, q, *J* 6.9, H-2'), 2.21 (1H, ddd, *J* 7.3, 7.3, 10.3, H-9), 2.03 (1H, d, *J* 9.8, H-6), 1.97 (1H, dd, *J* 6.0, 9.8, H-7), 1.72 (1H, dd, *J* 6.0, 14.1, H-8β), 1.51 (3H, s, αMe(C-4)), 1.38 (3H, s, βMe(C-4)), 1.37 (1H, ddm, *J* 6.7, 14.1, H-8α); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.06 (C-3'), 116.46 (C-4'), 89.11 (C-2), 83.29 (C-4), 82.13 (C-13), 72.82 (C-10), 69.09 (C-1'), 68.53 (C-1), 68.22 (C-12), 52.99 (C-9), 45.35 (C-5), 34.62 (C-2'), 33.93 (C-6), 31.63 (C-7), 28.89 (αMe), 24.46 (βMe), 23.12 (C-8).HRMS (ESI) *m/z* calcd. $C_{17}H_{24}NaO_3$ $[M+Na]^+$ 299.1618, found 299.1614.

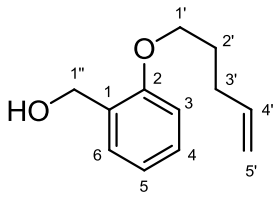
2-Pent-4'-enyloxy-benzoic acid methyl ester **337**.



Procedure adapted from the work of Smith, Morris and Owen.[138] Pentenyl bromide (15.0 g, 101 mmol) and methyl salicylate (14.6 g, 95.9 mmol) together with an excess of K_2CO_3 (66.3 g) were heated to reflux in acetone (500 ml) with vigorous magnetic stirring for 24 hrs. Acetone was removed under reduced pressure and $CHCl_3$ was added to dissolve the organic component. The mixture was then filtered to remove the K_2CO_3, and washed with 2M NaOH (2 x 100 ml). $CHCl_3$ was evaporated to afford the ester **337** (17.6 g, 83%) as a colourless oil.

R_f 0.38 (Et_2O/petrol, 10:90); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (1H, d, *J* 7.7, H-6); 7.43 (1H, dd, *J* 8.4, 8.5, H-4); 6.94-6.98 (2H, m, H-3/H-5); 5.82-5.90 (1H, ddt, *J* 6.7, 10.2, 17.0, H-4'); 5.06 (1H, dm, *J* 17.0, H-5'); 5.00 (1H, dm, *J* 10.2, H-5'); 4.05 (2H, t, *J* 6.4, H-1'); 3.89 (3H, s, -C(O)OCH_3) 2.28 (2H, q, *J* 7.0, H-3'); 1.90-1.96 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.85 (C=O); 158.43 (C-2); 137.70 (C-4'); 133.20 (C-4); 131.48 (C-6); 120.48 (C-1); 120.00 (C-5); 115.09 (C-5'); 113.19 (C-3); 67.98 (C-1'); 51.75 (-C(O)OCH_3); 29.93 (C-3'); 28.29 (C-2'); IR (thin film, cm^{-1}) 3524, 3077, 2949, 2876, 2501, 2331, 2093, 2048, 1920, 1731 (C=O, ester), 1640 (C=C, vinyl); 1601 (C=C, aromatic); 1583, 1492, 1454, 1433, 1389, 1363, 1305, 1252, 1190, 1165, 1132, 1084, 1049, 1014, 915, 837, 755; HRMS (ESI) *m/z* calcd. $C_{13}H_{16}NaO_3$ $[M+Na]^+$ 243.0992, found 243.0990.

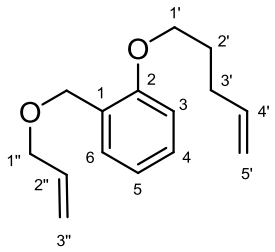
(2-Pent-3-enyloxy-phenyl)-methanol **338**.



Ester **337** (3 g, 13.6 mmol) was dissolved in Et_2O (50 ml) under a nitrogen atmosphere and cooled to 0 ºC. DIBAL (1M, 68.0 ml, 68.0 mmol) was added drop wise *via* a dropping funnel over 1 hr. The reaction was stirred until TLC showed total consumption of the original ester. With the temperature was maintained at 0 ºC, the reaction was diluted with Et_2O (100 ml) followed cautiously by the addition of H_2O (100 ml). The two layers were partitioned in a separating funnel; the organic layer was washed with brine (2 x 50 ml) and dried over anhydrous $MgSO_4$. Et_2O was removed under reduced pressure to yield alcohol **338** (2.05 g, 78%) as a pale yellow oil that was used without further purification.

R_f 0.13 (Et_2O/petrol, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.30 (2H, m, H-4/H-6); 6.94 (1H, t, *J* 7.4, H-5); 6.87 (1H, d, *J* 8.5, H-3); 5.81-5.91 (1H, ddt, *J* 6.7, 10.2, 17.0, H-4'); 5.08 (1H, dm, *J* 17.0, H-5'); 5.02 (1H, dm, *J* 10.2, H-5'); 4.70 (2H, d, *J* 6.5, H-1''); 4.04 (2H, t, *J* 6.4, H-1'); 2.32 (1H, t, *J* 6.5, -OH); 2.26 (2H, q, *J* 7.1, H-3'); 1.89-1.96 (2H, m, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.86 (C-2); 137.58 (C-4'); 129.23 (C-1); 128.87 (C-4/C-6); 128.70 (C-4/C-6); 120.65 (C-5); 117.35 (C-4'); 111.00 (C-3); 66.75 (C-1'); 62.28 (C-1''); 33.70 (C-2'); IR (thin film, cm^{-1}) 3391 (-OH), 3076, 2941, 1641 (C=C, vinyl), 1603 (C=C, aromatic), 1590, 1493, 1455, 1391, 1288, 1240, 1161, 1115, 1047, 955, 914, 835, 752; HRMS (ESI) *m/z* calcd. $C_{12}H_{16}NaO_2$ $[M+Na]^+$ 215.1043, found 215.1041.

1-Allyloxymethyl-2-pent-3-enyloxy-benzene **322**.



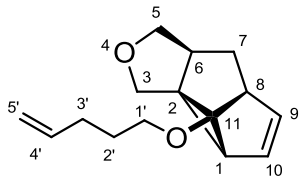
To a stirred solution of alcohol **338** (1.91 g, 9.90 mmol) and allyl bromide (4.31 ml, 49.7 mmol) in CH_2Cl_2 (10 ml) under a nitrogen atmosphere at 0ºC, was added 50% NaOH (30 ml) and TBAHS (3.72 g, 10.9 mmol). This was allowed to warm to ambient temperature and stirred for 3 hrs until TLC showed complete conversion of the starting material. The reaction was diluted with saturated NH_4Cl solution (50 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure and the resulting residue purified by flash column chromatography (Et_2O/petrol, 5:95) to yield the photosubstrate **322** (2.09 g, 91%) as a colourless oil.

R_f 0.56 (Et_2O/petrol, 5:95). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (1H, d, *J* 7.4, H-6); 7.23 (1H, t, *J* 7.9, H-4); 6.95 (1H, t, *J* 7.4, H-5); 6.85 (1H, d, *J* 8.1, H-3); 5.94-6.03 (1H, ddt, *J* 6.7, 10.2, 17.0, H-2’’); 5.82-5.91 (1H, m, H-4’); 5.34 (1H, d, *J* 17.3, H-3’’); 5.20 (1H, d, *J* 10.2, H-3’’); 5.07 (1H, d, *J* 17.1, H-3’’); 5.01 (1H, d, *J* 10.1, H-3’’); 4.59 (2H, s, -CH_2O-); 4.07-4.10 (2H, m, H-1’’); 4.00 (2H, t, *J* 6.3, H-1’); 2.26 (2H, q, *J* 7.0, H-3’); 1.87-1.94 (2H, m, H-2’); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.51 (C-2); 137.86 (C-2’’); 135.07 (C-4’); 128.85 (C-6); 128.47 (C-4); 127.01 (C-1); 120.36 (C-5); 1116.73 (C-3’’); 115.12 (C-5’); 111.16 (C-3); 71.50 (C-1’’); 67.21 (C-1’); 66.97 (-CH_2O-); 30.21 (C-3’); 28.53 (C-2’); IR (thin film, cm^{-1}) 3077, 2924, 1641 (C=C, vinyl), 1603 (C=C, aromatic), 1590, 1493, 1455, 1387, 1286, 1242, 1087, 916, 752; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1353.

Irradiation of photosubstrate **322** *to yield linear meta adduct* **324** *and ortho derived adduct* **339**.

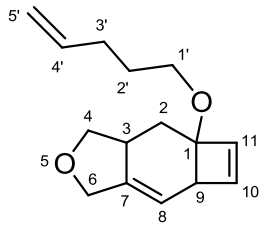
A solution of photosubstrate **322** (1.50 g, 6.46 mmol) in dry cyclohexane (450 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 7 hours using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting residue subjected to flash column chromatography (100:1 silica, CH_2Cl_2/Et_2O/petrol, 5:10:85) to afford *meta* adduct **324** (138 mg, 9%) and *ortho* adduct **339** (257 mg, 17%) both with co-spotting impurities.

rac-(1R, 2S, 6S, 8S, 11S)-11-(3'-Pentenyloxy)-11-methoxy-4-oxatetracyclo [6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **324**.



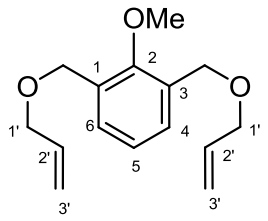
R_f 0.26 (CH_2Cl_2/Et_2O/petrol, 5:10:85). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (1H, dddd, *J* 6.7, 6.7, 10.2, 17.1, H-4'); 5.67 (1H, dd, *J* 2.3, 5.7, H-10); 5.53 (1H, ddd, *J* 1.2, 2.7, 5.8, H-9); 4.99 (1H, dm, *J* 17.1, H-5'); 4.94 (1H, dm, *J* 10.2, H-5'); 3.88 (1H, d, *J* 8.9, H-3); 3.87 (1H, dd, *J* 7.5, 8.9, H-5); 3.68 (1H, d, *J* 8.9, H-5); 3.67 (1H, d, *J* 8.9, H-3); 3.57 (1H, ddd, *J* 6.4, 6.4, 9.2, H-1'); 3.50 (1H, ddd, *J* 6.6, 6.6, 9.2, H-1'); 3.34 (1H, ddm, *J* 2.8, 5.1, H-8); 2.22-2.29 (1H, m, H-6); 2.17-2.18 (1H, m, H-1); 2.10-2.15 (2H, m, H-3'); 1.94 (1H, ddd, *J* 5.3, 9.4, 11.6, H-7); 1.89 (1H, ddm, *J* 6.8, 11.6, H-7); 1.63-1.69 (2H, m, H-2'); ^{13}C NMR (125 MHz; $CDCl_3$): δ 138.15 (C-4'); 132.84 (C-9); 128.18 (C-10); 114.74 (C-5'); 87.68 (C-11); 73.44 (C-5); 68.61 (C-1'); 66.16 (C-3); 53.77 (C-8); 52.59 (C-2); 44.76 (C-7); 42.41 (C-6); 36.75 (C-1); 31.25 (C-3'); 29.11 (C-2'); IR (thin film, cm^{-1}) 3055, 2933, 2849, 1641 (C=C, vinyl); 1586, 1417, 1379, 1361, 1330, 1294, 1246, 1229, 1188, 1169, 1138, 1077, 1057, 1014, 906, 860, 743; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1350.

1-(4'-pentenyloxy)tricyclo[7.2.0.0^{3,7}]undeca-7,10-diene **339**.



R_f 0.18 (CH_2Cl_2/Et_2O/petrol, 5:10:85). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (1H, d, *J* 2.7, H-11); 6.02 (1H, d, *J* 2.7, H-10); 5.79 (1H, ddt, *J* 6.7, 10.3, 17.0, H-4'); 5.59-5.63 (1H, m, H-8); 5.00 (1H, dm, *J* 17.1, H-5'); 4.94 (1H, dm, *J* 10.2, H-5'); 4.37 (1H, d, *J* 13.2, H-6); 4.26 (1H, d, *J* 13.2, H-6); 4.19 (1H, t, *J* 8.1, H-4); 3.46 (2H, t, *J* 6.6, H-1'); 3.38 (1H, dd, *J* 8.3, 9.4, H-4); 3.30 (1H, d, *J* 6.1, H-9); 2.48-2.56 (1H, m, H-3); 2.07-2.12 (3H, m, H-3' + H-2); 1.60-1.66 (2H, m, H-2'); 1.25 (1H, t, *J* 12.6,H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.48 (C-7); 138.29 (C-4'); 138.04 (C-10); 136.71 (C-11); 115.26 (C-8); 114.61 (C-5'); 84.65 (C-1); 73.85 (C-4); 70.13 (C-6); 63.38 (C-1'); 47.50 (C-9); 36.99 (C-3); 33.52 (C-2); 30.17 (C-3'); 29.62 (C-2'); IR (thin film, cm^{-1}) 2928, 2847, 1641, (C=C, alkene); 1444, 1374, 1344, 1290, 1258, 1222, 1157, 1096, 1058, 1028, 993, 911, 821, 785, 753; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found 255.1355.

2-methoxy-1, 3-bis[(prop-2-en-1-yloxy)methyl]benzene **342.**



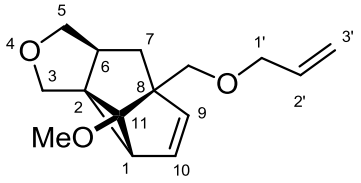
Bromination procedure adapted from that used by Otsuka and Shinkai.[144] 2,6-dimethylanisole (2.00 g, 14.7 mmol) and *N*-bromosuccinimide (5.23 g, 29.4 mmol) were dissolved in 1,2-dichloroethane (25 ml) in a 100 ml, three necked flask, equipped with a nitrogen inlet, condenser and stirring bar. AIBN (0.120 g, 5 mol%) was added, and the opaque yellow mixture was heated to reflux, and left for 4 hours, by which time the solution was clear. The vessel was left to cool slowly and filtered to remove the colourless succinimide that crystallised out. The filtrate was washed with H_2O (3 x 25 ml), dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator to give a yellow oil. This was left in a -20 °C freezer overnight to yield 1,3-bis(bromomethyl)-2-methoxybenzene, as a lachrymating solid.

The dibromide was dissolved in CH_2Cl_2 (20 ml) in a 100 ml two-necked flask equipped with a nitrogen inlet. To this was added, allyl alcohol (2.50 ml, 36.6 mmol), 50% NaOH (45 ml) and TBAHS (2.50 g, 7.32 mmol). This was left to stir overnight until NMR determined that complete conversion of the starting material. The reaction was diluted with saturated NH_4Cl solution (50 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure to yield a dark yellow oil that was purified by flash column chromatography (Et_2O/hexane, 10:90) to yield the diether **342** (1.46 g, 40% over two steps) as an pale yellow oil.

R_f 0.27 (Et_2O/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (2H, d, *J* 7.6, H-4+H-6); 7.13 (1H, t, *J* 7.6, H-5); 5.97 (2H, ddt, *J* 5.6, 10.3, 17.2, H-2'); 5.33 (2H, dq, *J* 1.7, 17.2, H-3'); 5.21 (2H, dm, *J* 10.3, H-3'); 4.59 (4H, s, -CH_2O-); 4.08 (4H, dt, *J* 1.5, 5.6, H-1'); 3.81 (3H, s., -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.72 (C-2); 134.77 (C-2'); 131.47 (C-1+C-3); 129.62

(C-4+C-6); 124.19 (C-5); 117.03 (C-3'); 71.40 (C-1'); 67.04 (-CH_2O-); 62.60 (-OCH_3) ; IR (thin film, cm^{-1}) 3079, 2918, 2851, 2005, 1867, 1647, (C=C, allyl); 1595 (C=C, aromatic); 1465, 1429, 1386, 1355, 1263, 1212, 1166, 1082, 1007, 923, 787; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 271.1305, found 271.1305.

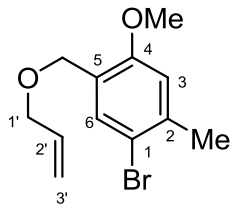
rac-(1R, 2S, 6S, 8S, 11S)-8-(2'-Propenyloxy)-11-methoxy-4-oxatetracyclo [6.2.1.0^{2,6}.0^{2,11}]undec-9-ene **347**.



A solution of photosubstrate **342** (1.20 g, 4.84 mmol) in dry cyclohexane (400 ml) was degassed with nitrogen for 15 minutes in a quartz immersion-well photoreactor. The apparatus was cooled with H_2O and the solution irradiated for 4 hours using a 16 W low-pressure Hg vapour lamp (λ_{max} = 254 nm) until NMR analysis showed the complete consumption of starting material. The solvent was removed under reduced pressure, and the resulting residue subjected to flash column chromatography (100:1 silica, CH_2Cl_2/Et_2O/petrol, 5:20:75) to afford *meta* adduct **347** (590 mg, 49%) as a pale yellow oil.

R_f 0.32 (CH_2Cl_2/Et_2O/petrol, 5:10:85). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (1H, ddt, *J* 6.7, 5.7, 10.4, 17.2, H-2'); 5.74 (1H, dd, *J* 2.6, 5.8, H-10); 5.61 (1H, dd, *J* 1.3, 5.8, H-9); 5.27 (1H, dm, *J* 17.2, H-3'); 5.17 (1H, dm, *J* 10.4, H-3'); 4.02 (2H, dt, *J* 1.5, 5.6, H-1'); 3.89 (1H, dd, *J* 3.9, 9.0, H-5); 3.88 (1H, dd, *J* 3.7, 8.9, H-3); 3.71 (1H, d, *J* 9.5, -CH_2O-); 3.68 (1H, d, *J* 8.9, H-3); 3.66 (1H, dd, *J* 3.2, 9.0, H-5); 3.62 (1H, d, *J* 9.2, -CH_2O-); 3.46 (3H, s, -OCH_3); 2.28-2.29 (1H, m, H-1); 2.17-2.23 (1H, m, H-6); 1.94 (1H, dd, *J* 6.6, 11.5, H-7); 1.85 (1H, dd, *J* 9.7, 11.5, H-7); ^{13}C NMR (125 MHz; $CDCl_3$): δ 134.99 (C-9); 134.85 (C-2'); 127.15 (C-10); 116.88 (C-3'); 87.72 (C-11); 73.60 (C-5); 72.40 (C-1'); 69.96 (-CH_2O-); 66.38 (C-3); 64.99 (C-8); 58.37 (-OCH_3); 54.30 (C-2); 48.29 (C-7); 41.03 (C-6); 36.10 (C-1); HRMS (ESI) *m/z* calculated $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 271.1305, found 271.1307.

1-Bromo-4-methoxy-2-methyl-5-[(prop-2-en-1-yloxy)methyl]benzene **352**.



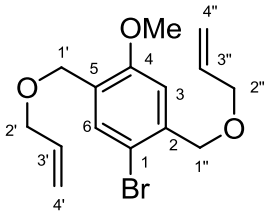
Bromination procedure adapted from that used by Otsuka and Shinkai.[144] 2, 5-dimethylanisole (3.00 g, 22.1 mmol) and N-bromosuccinimide (7.85 g, 44.1 mmol) were dissolved in 1,2-dichloroethane (30 ml) in a 250 ml, three necked flask, equipped with a nitrogen inlet, condenser and stirring bar. AIBN (0.18 g, 5 mol%) was added, and the opaque yellow mixture was heated to reflux, and left for 3 hours, by which time the solution was clear. The vessel was left to cool slowly and filtered to remove the colourless succinimide that crystallised out. The filtrate was washed with H_2O (3 x 25 ml), dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator to give a yellow oil. This was left in a -20 °C freezer overnight.

The dibromide was dissolved in CH_2Cl_2 (20 ml) in a 100 ml two-necked flask equipped with a nitrogen inlet. To this was added, allyl alcohol (3.84 ml, 66.1 mmol), 50% NaOH (45 ml) and TBAHS (3.74 g, 11.0 mmol). This was left to stir overnight until NMR determined that complete conversion of the starting material. The reaction was diluted with saturated NH_4Cl solution (50 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure to yield a yellow oil that was purified by flash column chromatography (Et_2O/hexane, 5:95) to yield the diether **352** (1.50 g, 27% over two steps) as a colourless oil.

R_f 0.38 (Et_2O/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (1H, s, H-6); 6.73 (1H, s, H-3); 5.97 (2H, ddt, *J* 5.6, 10.3, 17.2, H-2'); 5.32 (1H, dm, *J* 17.2, H-3'); 5.21 (1H, dm, *J* 10.3, H-3'); 4.49 (2H, s, -CH_2O-); 4.06 (2H, dt, *J* 1.5, 5.6, H-1'); 3.80 (3H, s., -OCH_3); 2.39 (3H, s., -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.14 (C-4); 137.69 (C-2); 134.83 (C-2'); 132.17 (C-6); 126.36 (C-5); 117.03 (C-3'); 115.16 (C-1); 112.86 (C-3); 71.51 (C-1'); 66.15 (-CH_2O-); 55.58 (-

OCH_3); 23.09 ($-CH_3$). IR (thin film, cm^{-1}) 3078, 2923, 2846, 2003, 2086, 1999, 1849, 1647, (C=C, allyl); 1607 (C=C, aromatic), 1570, 1495, 1462, 1384, 1371, 1302, 1248, 1192, 1159, 1092, 1046, 959, 924, 886, 842, 717; HRMS (ESI) *m/z* calcd. $C_{12}H_{15}Br^{79}NaO_3$ $[M+Na]^+$ 293.0148, found 293.0149.

1-Bromo-4-methoxy-2, 5-bis [(prop-2-en-1-yloxy) methyl] benzene **355**.



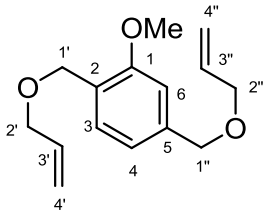
Bromination procedure adapted from that used by Otsuka and Shinkai.[144] 2, 5-Dimethylanisole (3.00 g, 22.1 mmol) and *N*-bromosuccinimide (11.8 g, 66.2 mmol) were dissolved in 1,2-dichloroethane (30 ml) in a 250 ml, three necked flask, equipped with a nitrogen inlet, condenser and stirring bar. AIBN (0.181 g, 5 mol%) was added, and the opaque yellow mixture was heated to reflux, and left for 4 hours, by which time the solution was clear. The vessel was left to cool slowly and filtered to remove the colourless succinimide that crystallised out. The filtrate was washed with H_2O (3 x 25 ml), dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator to give a yellow oil. This was left in a -20 °C freezer overnight.

The dibromide was dissolved in CH_2Cl_2 (25 ml) in a 100 ml two-necked flask equipped with a nitrogen inlet. To this was added, allyl alcohol (6.40 ml, 110 mmol), 50% NaOH (40 ml) and TBAHS (1.87 g, 5.52 mmol). This was left to stir overnight until NMR determined that complete conversion of the starting material. The reaction was diluted with saturated NH_4Cl solution (100 ml); and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, the solvents removed under reduced pressure to yield a yellow oil that was purified by flash column chromatography (Et_2O/hexane, 5:95) to afford the bromide **355** (2.83 g, 39% over two steps) as a colourless oil that froze at -20 °C

R_f 0.20 (Et_2O/hexane, 5:95). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (1H, s, H-6); 7.03 (1H, s, H-3); 5.92-6.03 (2H, m, H-3’ + H-3’’); 5.30-5.37 (2H, m, *trans* H-4’ + H-4’’); 5.20-5.25 (2H, m, *cis* H-4’ + H-4’’); 4.56 (2H, s, H-1’’); 4.51 (2H, s, H-1’); 4.11 (2H, dt, *J* 1.4, 5.6, H-2’’); 4.07 (2H, dt, *J* 1.4, 5.6, H-2’); 3.83 (3H, s., -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.35 (C-4); 137.63 (C-2’); 134.75 (C3’/C-3’’); 134.55 (C3’/C-3’’); 132.01 (C-6); 127.88 (C-5); 117.24 (C-

4’/C-4’’); 117.10 (C-4’/C-4’’); 112.57 (C-1); 110.68 (C-3); 71.67 (C-2’); 71.62 (C-2’’); 71.34 (C-1’’); 66.15 (C-1’); 55.62 (-OCH_3); IR (thin film, cm^{-1}) 3079, 3006, 2913, 2936, 2850, 2086, 2006, 1855, 1647, (C=C, allyl), 1606 (C=C, aromatic), 1571, 1493, 1462, 1381, 1262, 1248, 1157, 1091, 990, 925, 887, 855, 829; HRMS (ESI) *m/z* calcd. $C_{15}H_{19}Br^{79}NaO_3$ $[M+Na]^+$ 349.0410, found 349.0416.

2-methoxy-1, 4-bis [(prop-2-en-1-yloxy) methyl] benzene **348**.



Aromatic bromide **355** (2.63 g, 8.04 mmol) was dissolved in Et_2O (20 ml) in a three-necked flask fitted with a nitrogen inlet and bubbler. The reaction flask was cooled to 0 °C, and *n*-butyllithium (2.5 M, 3.86 ml, 9.65 mmol) was added drop wise over 10 mins, turning the colourless solution yellow. This was left to stir at the same temperature for 30 mins, then H_2O (20 ml) was carefully added *via* a dropping funnel. The now green reaction mixture was partitioned then the aqueous phase was extracted with Et_2O (2 x 25 ml). The organic layers were combined, dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The green residue was subjected to flash column chromatography (Et_2O/hexane, 10:90) to give the title compound **348** (0.800 g, 40%) as a colourless oil

R_f 0.23 (Et_2O/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (1H, d, *J* 7.6, H-3); 6.91 (1H, d, *J* 7.6, H-4); 6.89 (1H, s, H-6); 5.92-6.01 (2H, m, H-3'+ H-3''); 5.28-5.35 (2H, m, *trans* H-4'+ H-4''); 5.18-5.23 (2H, m, *cis* H-4'+ H-4''); 4.56 (2H, s, H-1'); 4.52 (2H, s, H-1''); 4.07 (2H, dt, *J* 1.5, 5.6, H-2'), 4.03 (2H, dt, *J* 1.5, 5.6, H-2''); 3.84 (3H, s, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.29 (C-1); 139.05 (C-5); 135.05 (C-3'/C-3''); 134.76 (C-3'/C-3''); 128.82 (C-3); 126.15 (C-2); 119.67 (C-4); 117.11 (C-4'/C-4''); 116.79 (C-4'/C-4''); 109.55 (C-6); 72.06 (C-1''); 71.39 (C-2'); 71.07 (C-2''), 66.82 (C-1'), 55.39 (-OCH_3); IR (thin film, cm^{-1}) 3079, 2935, 2852, 2073, 1995, 1858, 1646, (C=C, allyl); 1615 (C=C, aromatic); 1586, 1508, 1463, 1419, 1389, 1356, 1261, 1195, 1156, 1127, 1083, 1040, 991, 856, 823, 746; HRMS (ESI) *m/z* calcd. $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 271.1305, found 271.1309

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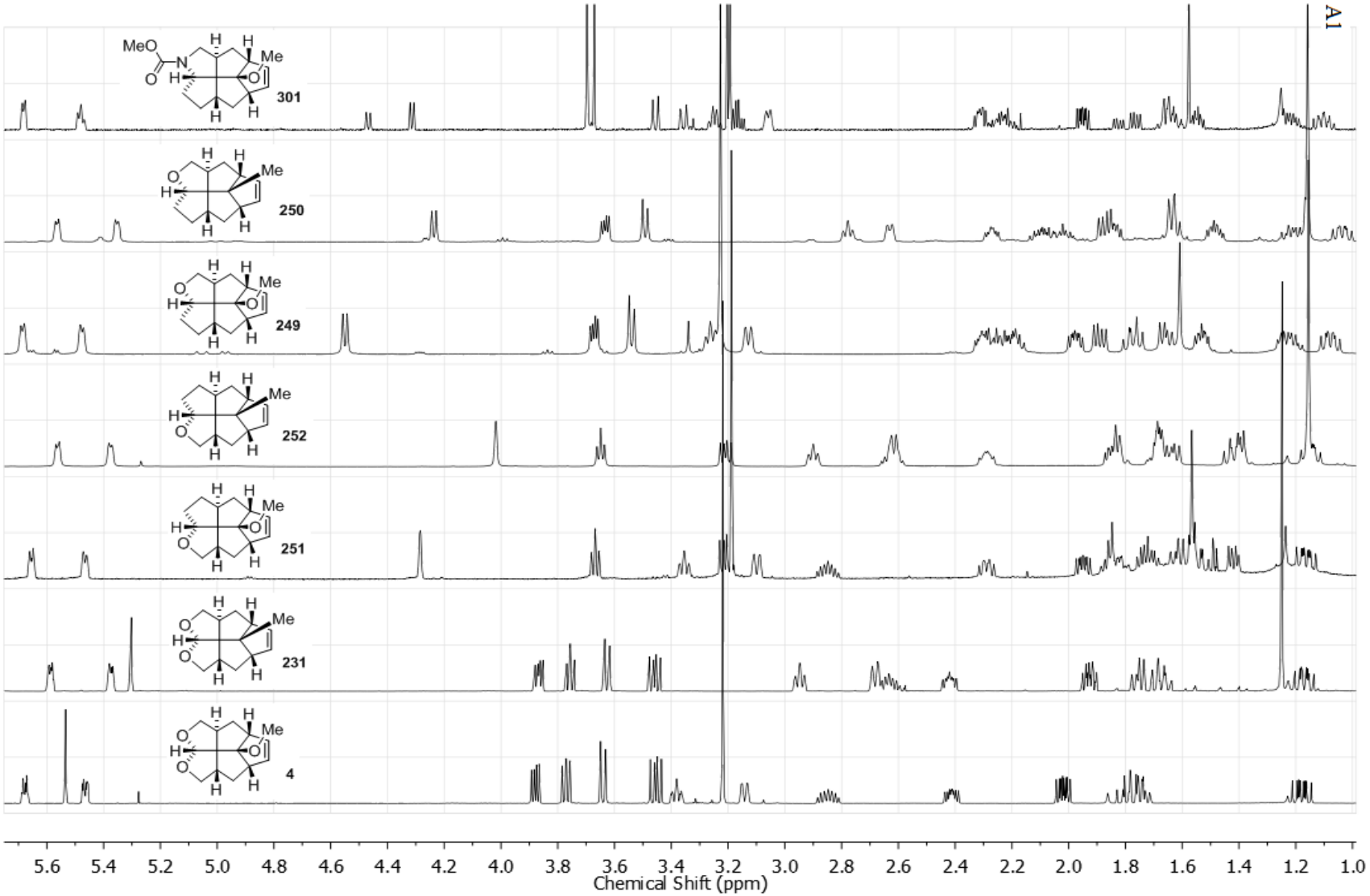
10 Appendix I

The following items are included in this appendix section:

Additional Supporting information:

Communication article from the *Journal of the American Chemical Society* entitled, "The Double [3+2] Photocycloaddition Reaction" can be found online at http://pubs.acs.org/journal/jacsat - Penkett, C. S.; Woolford, J. A.; Day, I. J; Coles, M. P. *J. Am. Chem. Soc.*, **2010**, *123*, 4.

A second appendix that includes a complete collection of the NMR, 7 and Mass spectroscopy data is available on DVD at request to the author.


A1
MeO
N
H
O
Me
301
250
249
252
251
231
4
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
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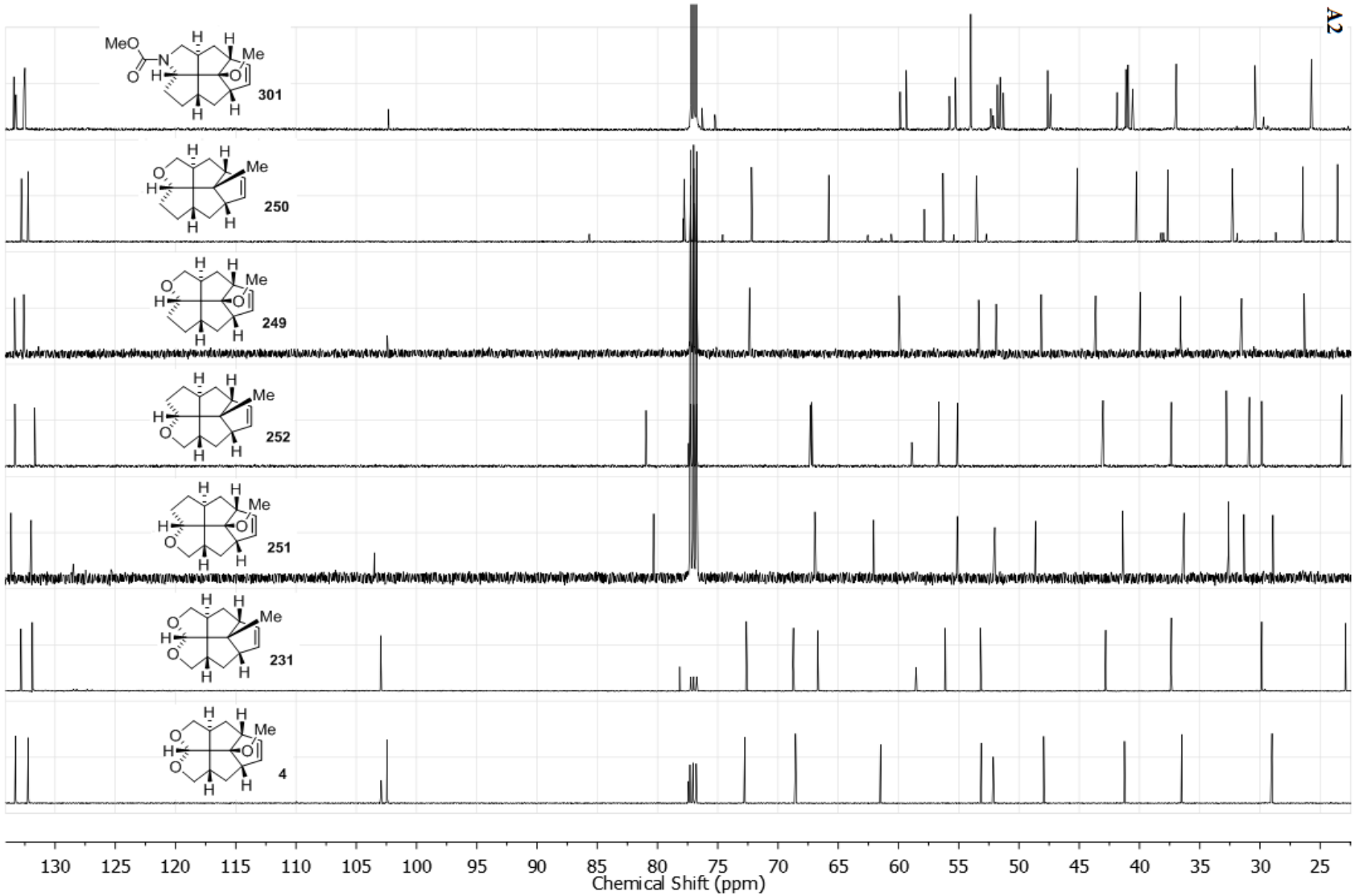
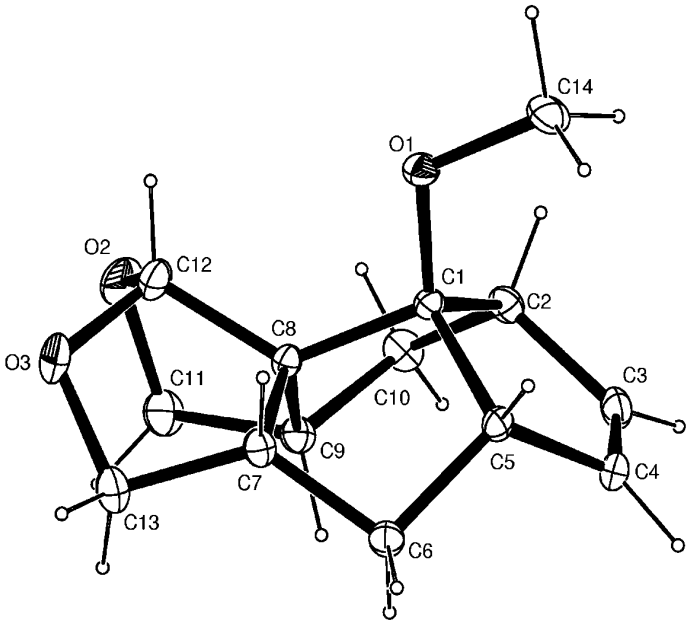
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
Chemical Shift (ppm)


A2
301
250
249
252
251
231
4
130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
Chemical Shift (ppm)

A3 - Crystal structure of dioxafenestrane compound 4.

The crystallographic data for compound **4** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 732415.

View 1



View 2

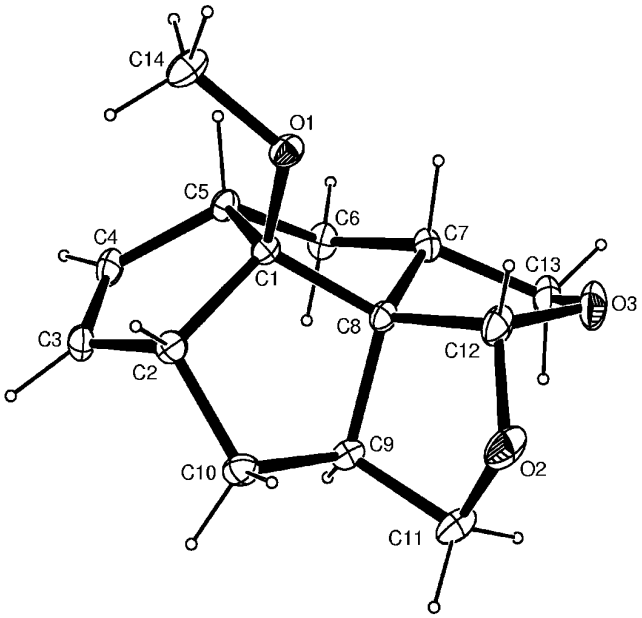


Table 1. Crystal data and structure refinement for apr809.

Identification code	apr809	
Empirical formula	C14 H18 O3	
Formula weight	234.28	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c (No.14)	
Unit cell dimensions	a = 8.6884(2) Å	α= 90°.
	b = 12.1203(3) Å	β= 114.301(1)°.
	c = 11.8457(2) Å	γ = 90°.
Volume	1136.90(4) Å3	
Z	4	
Density (calculated)	1.37 Mg/m3	
Absorption coefficient	0.10 mm-1	
F(000)	504	
Crystal size	0.30 x 0.28 x 0.25 mm3	
Theta range for data collection	3.86 to 27.86°.	
Index ranges	-11<=h<=11, -15<=k<=15, -15<=l<=15	
Reflections collected	17469	
Independent reflections	2652 [R(int) = 0.050]	
Reflections with I>2sigma(I)	2430	
Completeness to theta = 27.86°	98.1 %	
Absorption correction	None	
Tmax. and Tmin.	0.9767 and 0.9721	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	2652 / 0 / 226	
Goodness-of-fit on F2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.039, wR2 = 0.100	
R indices (all data)	R1 = 0.042, wR2 = 0.102	
Largest diff. peak and hole	0.37 and -0.16 e.Å-3	

All hydrogen atoms were located on the difference map and refined

Data collection KappaCCD , Program package WinGX , Abs correction not applied
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for apr809. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2003(1)	1369(1)	3165(1)	23(1)
O(2)	5843(1)	3345(1)	5164(1)	37(1)
O(3)	6609(1)	1583(1)	6000(1)	36(1)
C(1)	1924(1)	1892(1)	4216(1)	17(1)
C(2)	934(1)	2999(1)	3940(1)	21(1)
C(3)	-433(1)	2808(1)	4388(1)	24(1)
C(4)	-346(1)	1828(1)	4907(1)	23(1)
C(5)	1117(1)	1156(1)	4934(1)	18(1)
C(6)	2523(1)	923(1)	6247(1)	22(1)
C(7)	4068(1)	1047(1)	5973(1)	21(1)
C(8)	3727(1)	2098(1)	5199(1)	18(1)
C(9)	3622(1)	3233(1)	5783(1)	22(1)
C(10)	2249(2)	3858(1)	4701(1)	25(1)
C(11)	5350(2)	3752(1)	6111(1)	32(1)
C(12)	5371(1)	2222(1)	5013(1)	28(1)
C(13)	5901(1)	1165(1)	6837(1)	31(1)
C(14)	423(2)	970(1)	2279(1)	31(1)

Table 3. Bond lengths [Å] and angles [°] for apr809.

O(1)-C(1)	1.4242(12)
O(1)-C(14)	1.4262(13)
O(2)-C(12)	1.4115(15)
O(2)-C(11)	1.4413(16)
O(3)-C(12)	1.4452(15)
O(3)-C(13)	1.4559(16)
C(1)-C(8)	1.5401(13)
C(1)-C(2)	1.5537(14)
C(1)-C(5)	1.5819(13)
C(2)-C(3)	1.5042(15)
C(2)-C(10)	1.5348(15)
C(3)-C(4)	1.3247(17)
C(4)-C(5)	1.4991(15)
C(5)-C(6)	1.5585(14)
C(6)-C(7)	1.5134(14)
C(7)-C(13)	1.5042(15)
C(7)-C(8)	1.5255(14)
C(8)-C(12)	1.5396(14)
C(8)-C(9)	1.5589(14)
C(9)-C(11)	1.5237(15)
C(9)-C(10)	1.5431(15)

C(1)-O(1)-C(14)	114.56(8)
C(12)-O(2)-C(11)	105.36(9)
C(12)-O(3)-C(13)	110.83(8)
O(1)-C(1)-C(8)	109.47(8)
O(1)-C(1)-C(2)	115.02(8)
C(8)-C(1)-C(2)	108.78(8)
O(1)-C(1)-C(5)	114.22(8)
C(8)-C(1)-C(5)	102.88(7)
C(2)-C(1)-C(5)	105.67(8)
C(3)-C(2)-C(10)	113.77(9)
C(3)-C(2)-C(1)	104.03(8)
C(10)-C(2)-C(1)	104.37(8)

C(4)-C(3)-C(2)	113.51(10)
C(3)-C(4)-C(5)	112.52(9)
C(4)-C(5)-C(6)	115.41(9)
C(4)-C(5)-C(1)	103.97(8)
C(6)-C(5)-C(1)	107.48(8)
C(7)-C(6)-C(5)	99.65(8)
C(13)-C(7)-C(6)	130.35(10)
C(13)-C(7)-C(8)	102.68(9)
C(6)-C(7)-C(8)	104.01(8)
C(7)-C(8)-C(12)	101.84(9)
C(7)-C(8)-C(1)	101.81(8)
C(12)-C(8)-C(1)	128.51(9)
C(7)-C(8)-C(9)	120.16(8)
C(12)-C(8)-C(9)	101.81(8)
C(1)-C(8)-C(9)	104.56(8)
C(11)-C(9)-C(10)	110.65(9)
C(11)-C(9)-C(8)	104.22(9)
C(10)-C(9)-C(8)	103.35(8)
C(2)-C(10)-C(9)	106.78(8)
O(2)-C(11)-C(9)	103.74(9)
O(2)-C(12)-O(3)	109.50(9)
O(2)-C(12)-C(8)	108.29(9)
O(3)-C(12)-C(8)	104.90(9)
O(3)-C(13)-C(7)	101.24(9)a