Novel [2+2] Photocycloadditions of Vinylogous Amides and Imides

Andrew James Amin Roupany

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Supervisor: Dr. James Baker

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Department of Chemistry
20 Gordon Street
London
WC1H 0AJ

Declaration

I, Andrew James Amin Roupany confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

This thesis describes investigations into the [2+2] photocycloaddition reaction of vinylogous amides and imides contained within five membered rings with alkenes; the aim of this being the synthesis of aminocyclobutanes. The initial focus is towards intramolecular reactions, synthesising vinylogous amides with a tethered alkene. Irradiation of these compounds leads to a [2+2] photocycloaddition followed by a spontaneous retro-Mannich fragmentation, affording keto-imines. Upon addition of a Boc group to these vinylogous amides, and irradiation of the resultant vinylogous imides, the retro-Mannich fragmentation is prevented and aminocyclobutanes are isolable.

Attention is then turned to the intermolecular [2+2] photocycloaddition reaction which does not occur at all with vinylogous amides. However, upon adding an acetyl or Boc group to the vinylogous amides, the intermolecular reaction does take place with certain alkenes. This reaction affords aminocyclobutanes, often as a mixture of regio- and diastereo-isomers. Removal of the Boc group again leads to the retro-Mannich fragmentation taking place. The resultant imine is hydrolysed under the reaction conditions, and 1,5-diketones are obtained in an analogous manner to the de Mayo reaction. If the alkene used in the irradiation has a leaving group connected to the double bond, then this is eliminated after the retro-Mannich fragmentation. In this case, the products are novel conjugated enaminones. The chemistry of these compounds is then investigated. They undergo a Diels-Alder reaction with maleimide and are transformed into aminotropones upon heating or *via* a bromination-elimination reaction.

The work described in this thesis has been published, and the full paper is attached in the appendix at the end of the thesis.

Contents

Abbreviations:

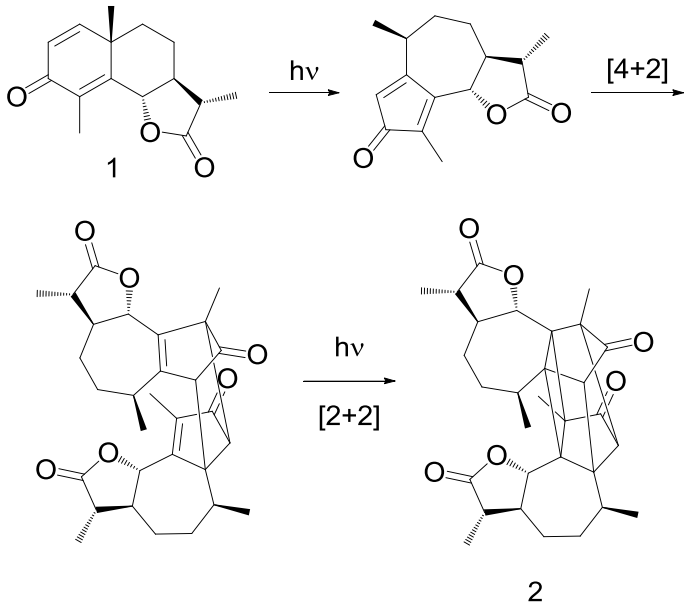
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Bn	Benzyl
Boc	Di-*tert*-butyl carbonate
Bu	Butyl
Bz	Benzoyl
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
Et	Ethyl
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
IBX	2-iodoxybenzoic acid
IC	Internal conversion
IR	Infrared
ISC	Intersystems crossing
LED	Light emitting diode
LUMO	Lowest unoccupied molecular orbital
m.p.	Melting point
M.S	Mass spectrometry
Me	Methyl
MEM	2-methoxyethoxymethyl ether
MS	Molecular sieves
µW	Microwave
n	Integer number
n-	Normal
NBS	N-bromosuccinimide
NMR	Nuclear magnetic resonance
NOe	Nuclear Overhauser effect
NOeSY	Nuclear Overhauser effect spectroscopy
p	Para
Ph	Phenyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Py	Pyridine
RT	Room temperature (19 – 22 °C)
SES	2-trimethylsilylethanesulfonyl

t or *Tert*	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	Tolyl
TTBAL-H	Tritertiarybutylaluminium
UCL	University College London
UV	Ultraviolet
VR	Vibrational relaxation

1. Introduction

1.1. History of photochemistry

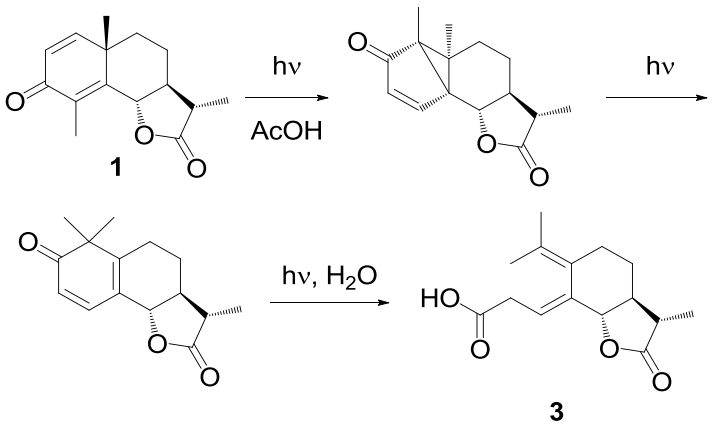
Photochemistry is defined as "*the branch of chemistry concerned with the chemical effects of light (far UV to near IR)".*[1] It is prevalent in nature; for example both photosynthesis in plants and the synthesis of vitamin D in the body are light-dependant processes.[2] However, it was not until the mid-nineteenth century that it was described in pure chemistry terms. Believed to be the first organic photochemical reaction carried out, Hermann Trommsdorff described the effects of sunlight on crystals of santonin **1**, noticing that upon irradiation the crystals turned from white to yellow and burst.[3] Although he was unable to characterise the newly formed product he did note that it was identical in composition to the starting material. Indeed when the structure was finally published over a hundred years later it was shown to arise from an initial photochemical rearrangement, followed by a Diels-Alder type reaction and finally a photochemical [2+2] cycloaddition to give caged product **2** (**Scheme 1**).[4]



Scheme 1

Following this observation, Sestini irradiated santonin in an 80% acetic acid solution in one of the very first planned photochemical reactions. He discovered that photosantonic acid **3** is formed in this reaction,[5] although again the

structure was not elucidated until 1958, over one hundred years later[6] and the intermediates not identified for a further five years (**Scheme 2**).[7]



Scheme 2

From these early beginnings, the field of synthetic organic photochemistry was born.

In this thesis introduction, the fundamentals of organic photochemistry will be discussed along with an outline of practical considerations. Following this, common photochemical reactions of carbonyl compounds and alkenes will be discussed, followed by a review of the literature in the area of [2+2] photocycloadditions.

1.2. Fundamentals of organic photochemistry

The Grotthus-Draper law states that, in order for a molecule to undergo a photochemical change, it must first absorb a photon of light.[8] In doing this, an electron is excited from one molecular orbital to another (**Figure 1**). This usually takes place from the highest occupied molecular orbital (HOMO) as it is the highest in energy. The unoccupied orbital into which this is excited depends on the energy, and hence wavelength of the photon. However, the ultimate destination of this electron is generally the lowest occupied molecular orbital (LUMO) as an electron promoted to a higher orbital will very quickly drop back down in energy to the LUMO *via* a number of photophysical processes.[9] **Figure**

1 shows the excitation of an electron from the HOMO to the LUMO in a simplified, stylised molecular orbital diagram.

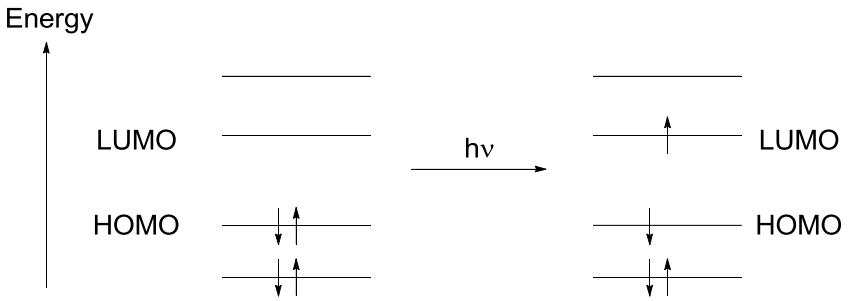


Figure 1

The excited state shown in **Figure 1** is termed a singlet state as the spins of the electrons are still opposed. As the electrons no longer reside in the same molecular orbital they are no longer required to have opposing spins, and as such there is a corresponding triplet state where the electrons have parallel spins. The triplet state is lower in energy, but as the transition from the singlet ground state to a triplet excited state is strongly forbidden as the spin angular momentum must be conserved, almost all absorptions will be singlet-singlet absorptions.[10] Once an electron has been excited, there are a number of processes that can occur; these can be shown diagrammatically in the form of a Jablonski diagram (**Figure 2**)[9].

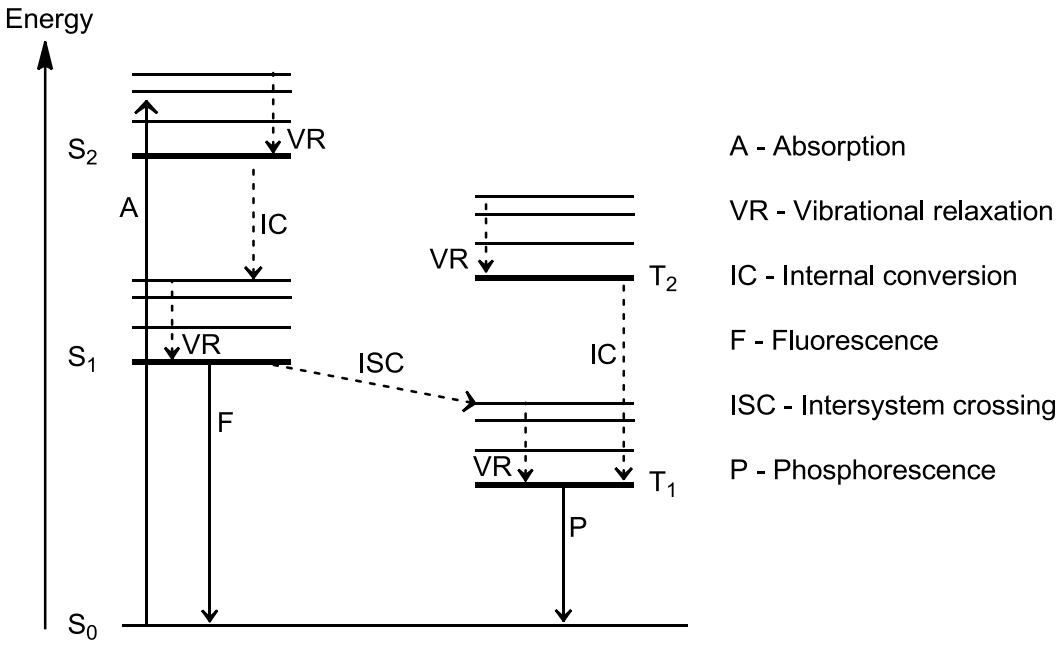


Figure 2

Absorption of a photon of light (A, **Figure 2**) will result in an electron being excited to a higher energy level, known as a singlet excited state (S_1 and S_2). Within each of these electronic levels are a series of vibrational and rotational energy sub-levels. Absorption of a photon does not lead directly to the lowest vibrational state as the geometry of the molecule is retained upon excitation. This is not the most stable geometry for the new electronic distribution, and thus the molecule does not have the lowest vibrational energy for the given electronic level. This is an expression of the Frank-Condon principle.[9] The molecule will quickly lose energy *via* a process called vibrational relaxation (VR, **Figure 2**), dropping down in energy to the lowest vibrational state within the electronic state and adopting the most stable geometry. If there are lower electronically excited states available for the electron, it can further fall in energy to these by a process called internal conversion (IC). It is also possible for the electron to drop down in energy all the way back to the singlet ground state (S_0) *via* this process. However, the electron can also drop back down to the singlet ground state by another process called fluorescence (F). In order to lose the energy from the system it is released in the form of a photon of light, thus this conversion is known as radiative decay, as opposed to non-radiative decay, such as internal conversion and vibrational relaxation, which lose their energy in the form of heat. If the electron has undergone vibrational relaxation and internal conversion prior to fluorescence, the photon emitted will be of lower energy, hence longer wavelength than the initially absorbed photon. This phenomenon is known as a Stokes shift.[8]

An electron in an excited singlet state can also undergo another non-radiative decay process called intersystem crossing (ISC, **Figure 2**) to give an excited triplet state (T_1 and T_2). This process is 'spin forbidden' as it breaks the law of the conservation of spin angular momentum and as such is a much slower process, despite being thermodynamically favoured. It can therefore only occur if fluorescence or internal conversion back to the singlet ground state do not take place quickly. Once in the triplet state, the molecule can undergo vibrational relaxation as before to a lower rotational and vibrational energy level, or drop back down to the ground state, either *via* a second intersystem crossing

or by phosphorescence (P). Phosphorescence is a radiative decay process similar to that of fluorescence in that the energy released is in the form of a photon of light. However, as this process is spin-forbidden, it is a much slower process than fluorescence. T_1 will be lower in energy than S_1 meaning that the photon released by phosphorescence will be of a longer wavelength than both the absorbed photon and those released *via* fluorescence.[9] In all cases it is generally the lowest electronic energy level of each multiplicity from which radiative emissions takes place, thus emission will normally take place from S_1 or T_1 only. This is known as Kasha's rule and occurs as the energy gaps between higher electronically excited states are relatively small, allowing internal conversion to take place very quickly. The gap between S_1 and S_0, or T_1 and S_0 is much larger, and thus radiative decay occurs more readily as internal conversion is significantly slower.[11,12]

There is one last process which can occur from either the singlet or triplet electronically excited state, and that is a photochemical reaction. Due to the change in orbital occupancies from the singlet ground state, some reactions require photochemical conditions rather than standard thermal conditions. An example of a reaction which readily occurs under photochemical conditions but not thermal conditions is the [2+2] cycloaddition of two isolated alkenes. To understand why this is the case, the HOMO and LUMO of a two electron π system, as found in an alkene, must be considered (**Figure 3**).

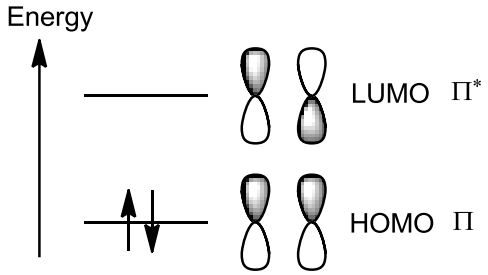


Figure 3

Under thermal conditions the orbital overlap of the HOMO and LUMO form one bonding and one antibonding interaction when they approach *via* a suprafacial orbital overlap (**Figure 4**). Furthermore, the alkene moieties are too small to

twist into a geometry which would allow a symmetry allowed, antarafacial overlap. As an antibonding interaction is higher in energy than the bonding interaction, the overall effect is that no bond can be formed. This is summarised by the Woodward-Hoffman rules which state that under thermal conditions 4n electron processes are forbidden *via* suprafacial overlap.[9,13,14]

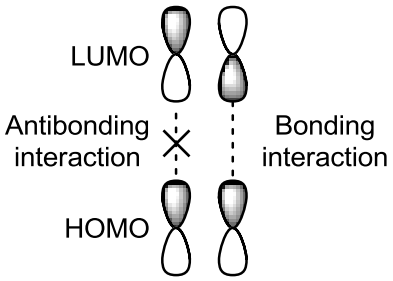


Figure 4

Upon irradiation and absorption of a photon by an alkene, an electron is promoted from the HOMO to the LUMO which corresponds to the molecule being excited from the ground state (S_0) to the first excited singlet state (S_1). This change of orbital occupancy creates a new HOMO and LUMO (HOMO* and LUMO*) (**Figure 5**). It should be noted that the HOMO* and LUMO* are not the actual HOMO and LUMO in the excited molecule, but instead the names correspond to the molecular orbitals found in the ground state.

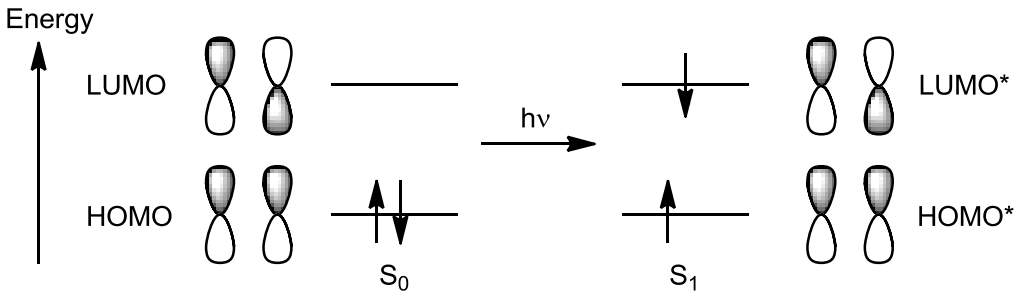


Figure 5

The HOMO* of one alkene now has a favourable orbital interaction with the HOMO of the other alkene upon suprafacial approach, and the same is true of the LUMO* with the other LUMO. The means that the reaction is symmetry allowed, and shows that for photochemical reactions, the Woodward-Hoffman rules are reversed (**Figure 6**).[13]

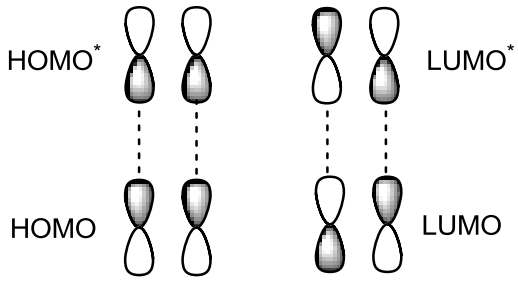


Figure 6

Furthermore, when a molecule in the ground state reacts with a molecule in the excited state, a reaction is now energetically favourable as the overall change in energy is negative (**Figure 7**).[15]

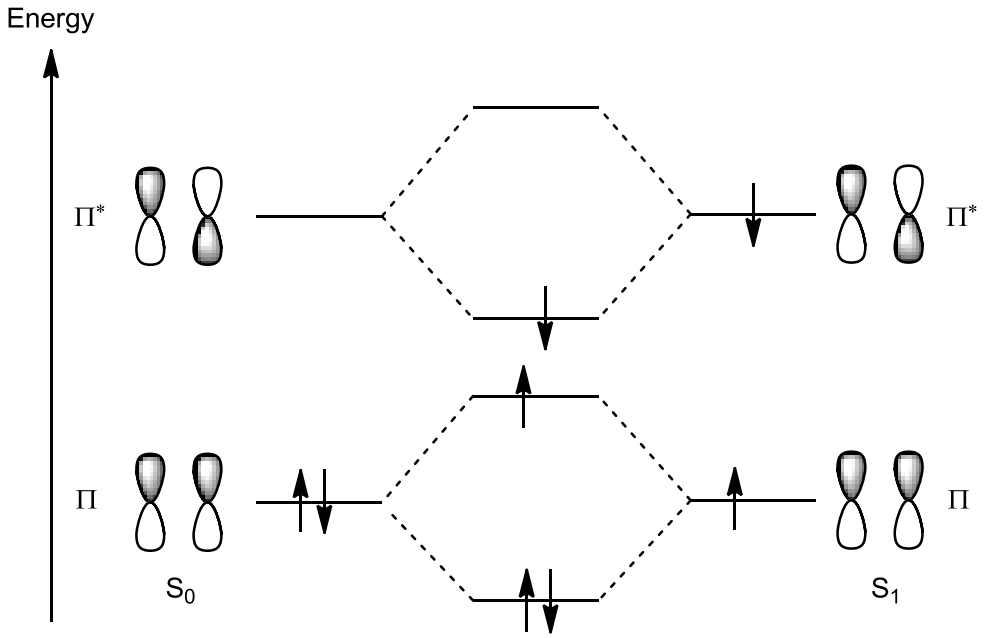
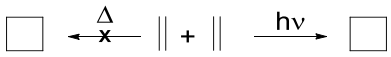


Figure 7

The overall reaction is shown in **Scheme 3** as the dimerisation of the simplest alkene, ethene, to give cyclobutane under photochemical conditions. This is a reaction which does not take place under thermal conditions.



Scheme 3

A photochemical reaction can take place from either the singlet excited state, or the triplet excited state depending on the mechanism. However, the triplet state of a molecule is not always easily accessible due to a large energy gap between the singlet and triplet states which acts as a barrier against ISC (a,

Figure 8). To get around this, triplet sensitisers can be used. These are molecules which have a very small energy gap between the singlet and triplet excited states (b) and thus ISC is a more facile process. Once in the triplet state, it can transfer its energy to the other molecule (c), but only if the other molecule has a triplet excited state of lower energy. Overall, this process allows access to the triplet state of the compound which may not be achieved by direct irradiation.

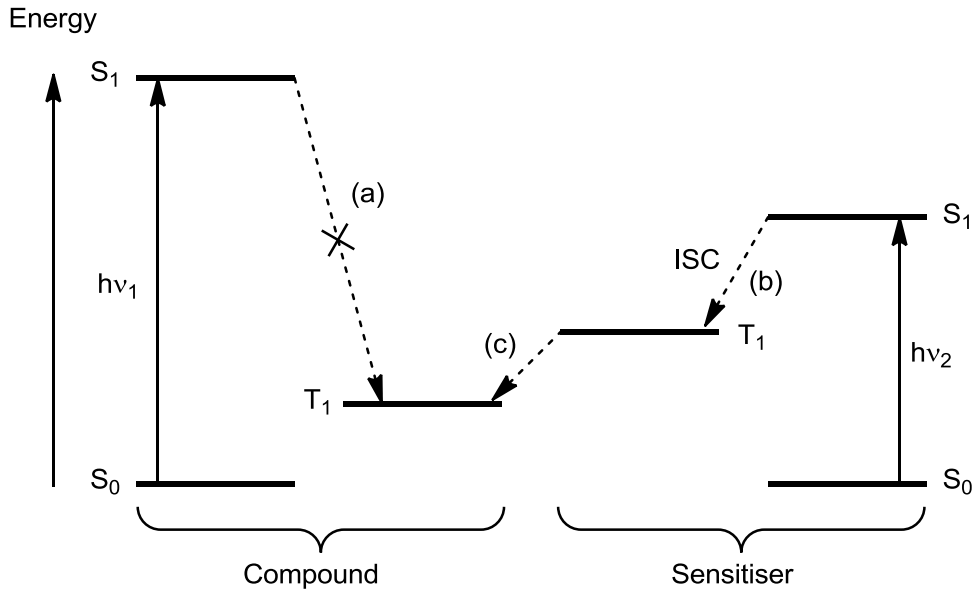


Figure 8

1.3. Practical considerations in organic photochemistry

There are many practical considerations which need to be taken into account before a photochemical reaction can be carried out. The first of these is the choice of light source. Historically this would have been sunlight, however nowadays there is a choice between three main methods. The most common of these methods is the mercury discharge lamp which emits a wide range of wavelengths of light. Of these lamps, the medium pressure lamp is probably the most commonly used, which, although it has a continuous spectral output in the electromagnetic region of 200 nm to above 700 nm, has spikes at certain wavelengths. The important spikes for UV irradiation are at 254 nm, 297-302 nm, 313 nm, 334 nm, 365 nm, 405-408 nm and 436 nm.[8] As a result of this, the absorption by a molecule may not be very efficient unless the λ_{max} coincides

with one of these spikes. The inefficiency of the mercury lamp is another drawback; a lot of the power is lost as heat. Not only is this a problem in terms of energy usage, but it is a fire risk too. To circumvent this, special immersion wells must be used during irradiations. These are wells in which the lamp sits surrounded by a glass jacket, through which cold water is constantly pumped to keep the apparatus as cool as possible. The immersion wells also serve a second purpose, as a light filter; depending on the type of glass they are made from, only certain wavelengths of light will be able to pass through. This is important as very high energy light will most likely degrade the substrate, and thus the filters generally act as a short wavelength cut off. Pyrex® glass filters are the most commonly used with a lower cut off of about 275 nm, although Corex® (260 nm cut off), Vycor® (220 nm cut off) and quartz glass filters (170 nm cut off) can all also be employed.[8]

A second option for the light source is the use of light emitting diodes (LEDs). These are narrow-band wavelength light sources with the advantage that no filter is required. Furthermore, they require very little energy relative to the mercury lamps and can be placed in close proximity to the reaction mixture in order to maximise efficiency.[16] As they use little energy, constant cooling is not needed, however the current drawback is that they do not provide a large amount of light. Often, to get enough radiation for a preparative scale reaction to proceed at a reasonable rate, a large array of LEDs is needed and currently UV-LEDs are expensive. However, for small scale reactions, such as those used in biological chemistry, these LEDs are ideal.[17] Additionally, the lack of heat production means there is no chance of thermal degradation, which can be a problem for protein systems.[18] Cheaper visible light LEDs have found use in synthesis recently, especially in arrays, and in conjunction with photoredox catalysts.[19,20]

A final option for the light source is to use lasers.[21,22] These, as with LEDs, have the advantage of being monochromatic but are also tuneable. This means that irradiation of a single desired wavelength can be achieved. However, they are

very rarely used in synthesis as they are very expensive and can only be used in very small scale reactions due to the limited width of the beam.

Another practical consideration to take into account is the solvent for the reaction. The solvent choice is important as the substrates need to be soluble to ensure an efficient reaction, but can also act as a secondary light filter, absorbing certain wavelengths of light. Acetonitrile is regularly used as are water and hydrocarbons such as pentane and hexane. All of these are transparent to radiation above 190 nm and, as such, will not absorb any of the photons which make it through the filter, allowing maximum efficiency. Methanol, ethanol, THF and diethyl ether are all transparent above 215 nm and can therefore also be used as the filter will cut out any radiation below this wavelength anyway. Ethyl acetate (256 nm), DMF (268 nm), DMSO (268 nm) and toluene (284 nm) are less commonly used due to their high UV cut offs or their photochemical reactivity, but again they can be used if these are not issues. Acetone has an even higher cut off of 330 nm,[23] but it regularly finds use in photochemical reactions as it is a triplet sensitiser. Chlorinated solvents are very rarely used as the weak C-Cl bond can break during photolysis giving rise to chlorine radicals that may react undesirably with the substrate.[24]

A final practical consideration is whether to use a batch reactor or a continuous flow reactor. In a batch reactor, the lamp, contained in an immersion well, sits inside a specially designed piece of glassware in which is a solution of the substrate. This is the standard way of carrying out photochemical reactions. However, the transmission of light through a solution decreases exponentially as the distance from the lamp increases, the solution nearest the lamp shielding the rest of the mixture from the light. This issue is exacerbated upon scaling up a reaction. Furthermore, scaling up of a reaction requires bigger glassware, which is expensive. More recently, continuous flow reactors have been used. This idea was pioneered by the Booker-Milburn group who wrapped tubing made from a UV-transparent material, fluorinated ethylenepropylene, around an immersion well containing a medium pressure mercury lamp (**Figure 9**). The

tubing was connected at one end to a reservoir containing the starting materials and at the other to a second reservoir where the product would be collected. The solution was pumped through the tubing using an HPLC pump and the irradiation time could be specified by changing the flow rate.[25] Flow reactors allow for easy scale-up as they can simply be run for longer. Furthermore, they give a more uniform irradiation, as all of the solution effectively experiences the same amount of radiation. They also limit the amount of time which the product of the reaction is left exposed to the light. This is important as extended irradiation could lead to degradation of the product. The major drawback of flow reactors is that they can be difficult to set up and require more equipment.

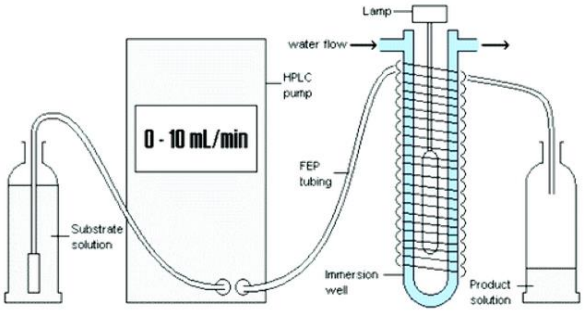


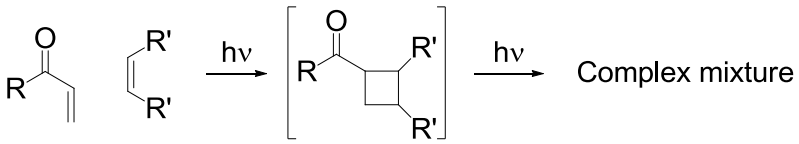
Figure 9[25]

Before starting most photochemical reactions it is important to remove as much oxygen from the reaction mixture as possible. This is important as molecular oxygen itself contains a chromophore and, upon irradiation, forms the highly reactive species singlet oxygen. This can then react with the substrates[26] giving rise to degradation and unwanted products, thus lowering the yield of the desired product. Removal of oxygen is achieved *via* a process called degassing, in which an inert gas, usually nitrogen or argon, is bubbled through the solution which is sealed from the air.

1.4. Secondary photoreactions

A problem which is regularly encountered in organic photochemistry is that once a product molecule is formed, it is still exposed to the light. As a result, it can undergo further photochemical reactions, leading to the degradation of the desired product and cause a reduction in the yield. Often this limits the utility of photochemistry.[27] This is particularly a problem when a chromophore, such as a

carbonyl group, is still present in the product. A common example of this is photochemical transformations of α,β-unsaturated carbonyl compounds such as enones. The majority of desired reactions of these compounds will take place at the carbon-carbon alkene bond. However, once the alkene has reacted, the product still retains the chromophoric carbonyl group and can absorb further photons and undergo further photochemical reactions. **Scheme 4** shows a general [2+2] photocycloaddition reaction in which the carbonyl group in the product can undergo further excitation.[28] These undesired secondary reactions lead to significant, and sometimes complete, breakdown of the product.[29] In order to obtain better yields in these reactions, making them more viable in synthesis, these secondary reactions have to be avoided.



Scheme 4

Often secondary reactions are reduced by limiting the amount of time in which the reaction mixture is exposed to the UV light. Reactions can proceed in high yields by stopping the reaction after about 30% conversion, recovering the unreacted starting material and submitting this again to irradiation to access more of the product.[30] The downside of this method is that it vastly increases the time taken to run the reaction and is heavily labour intensive; on a large scale this method is not viable. In a similar manner, a continuous flow setup can reduce secondary photoreactions as the product is removed from the light source quickly after reacting, which means it does not have a chance to absorb again and react further.[25] Although this can be effective, it may not always work. Diffusion can still take place within the solution or some of the substrate may react immediately upon irradiation. In both of these cases, the product will be irradiated for a significant amount of time, which can still lead to secondary photoreactions.

Another common way of limiting secondary reactions is to filter out the higher frequencies of the incident radiation by using appropriate filters. If the

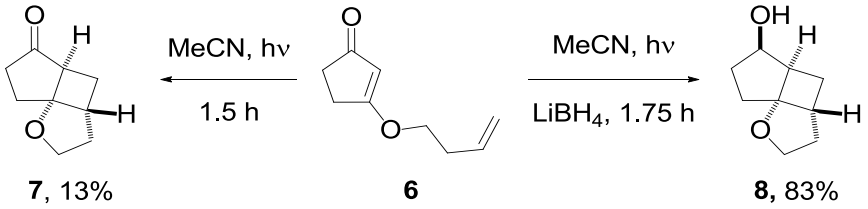
frequency, and hence wavelength, of light required to excite the desired product is not available to it, then further reactions are prevented.[31] However, this is not always a viable option. Often the absorption maxima of the product is very close in energy to that of the starting material and filtering out that energy would stop the initial reaction from taking place. For example, the absorption maxima of a cyclopentanone product **4** is around 300 nm[32] whilst that for the cyclopentenone starting material **5** is around 304 nm (**Scheme 5**).[33] Thus filtering the light would not be viable in any reaction where the π-bond is transformed into σ- bonds.

5 λ_{max} = 304 nm **4** λ_{max} = 300 nm

Scheme 5

Previous work within our research group pioneered the idea of removing the chromophore from the product before it could undergo secondary photoreactions. This was exemplified in the intramolecular enone-alkene [2+2] photocycloaddition of **6**. If the carbonyl group is removed before any secondary reactions can occur then the product should be photochemically stable. Therefore, in order for this idea to work effectively, a reaction was sought that would remove the carbonyl group faster than any secondary photoreactions could occur. Furthermore, the reaction to remove the carbonyl must be selective for the product only and not the starting material. In order to fulfil these criteria, a reaction was needed which would occur quickly with ketones, but not at all with enones. The initial approach was to use a reducing agent which would reduce the ketone of the product to the corresponding alcohol but not reduce the starting material. The resulting alcohol could be oxidised back to the ketone after the irradiation was complete, which can be easily achieved using Swern or Dess-Martin oxidations.[34] The [2+2] photocycloaddition of vinylogous ester **6** proceeds with complete consumption of starting material after 1.5 hours. However, the desired product **7** could only be isolated in a 13% yield. When the same reaction was attempted in the presence of the reducing agents sodium borohydride or lithium borohydride, the cyclobutane product **8** was formed in

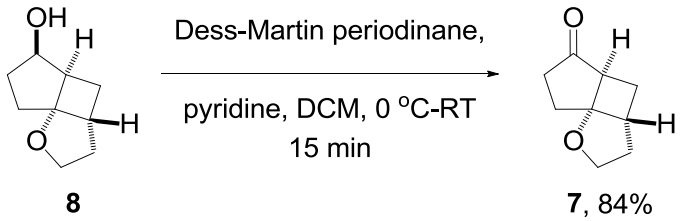
moderate to high yields of 45% with sodium borohydride and 83% with the more reactive lithium borohydride (**Scheme 6**).[34]



7, 13% **6** **8,** 83%

Scheme 6

Cyclobutane **7** can then be accessed if required *via* an oxidation of alcohol **8** in good yield by using Dess-Martin conditions (**Scheme 7**).



8 **7**, 84%

Scheme 7

It was then shown that this methodology could be extended to give a series of more complex cyclobutanes (**Table 1**). In all cases the yield of the alcohol formed using the *in situ* reduction method exceeded the yield of the ketone formed *via* direct irradiation of the vinylogous ester; in some cases the ketones were not isolated at all.

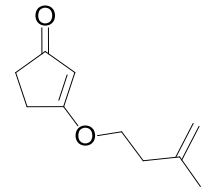
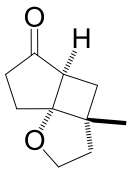
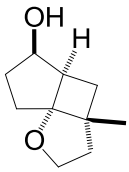
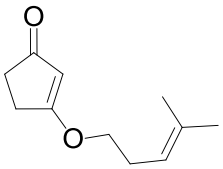
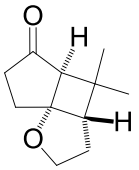
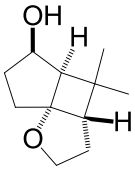
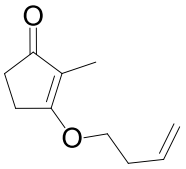
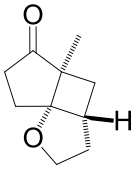
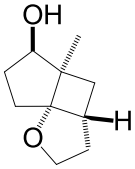
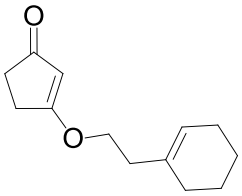
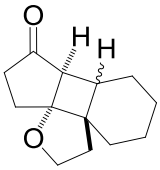
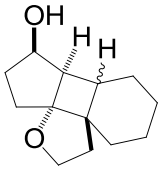
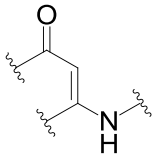
Vinylogous ester	Ketone *via* direct irradiation	Alcohol *via in situ* reduction method
	 0%	 71%
	 0%	 78%
	 50%	 72%
	 13%	 72% (1:1 mixture of diastereomers)

Table 1

This method of preventing secondary photoreactions, and its application in the photochemistry of vinylogous amides, was the starting point for the work described in this thesis.

1.5. Photochemical reactions

This project is concerned with the photochemistry of vinylogous amides. These are compounds with a nitrogen atom directly conjugated to an enone (**Scheme 8**). To understand the photochemistry of such systems it is important to appreciate the photochemistry of compounds containing isolated carbonyls and alkenes. Outlined below are some of the more common photochemical reactions of the carbonyl group and the alkene group. This is then followed by a review of the enone-alkene [2+2] photocycloaddition reaction with particular focus on vinylogous amides, upon which this project is based.

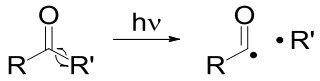


Scheme 8

1.5.1. Photochemical reactions of the carbonyl group

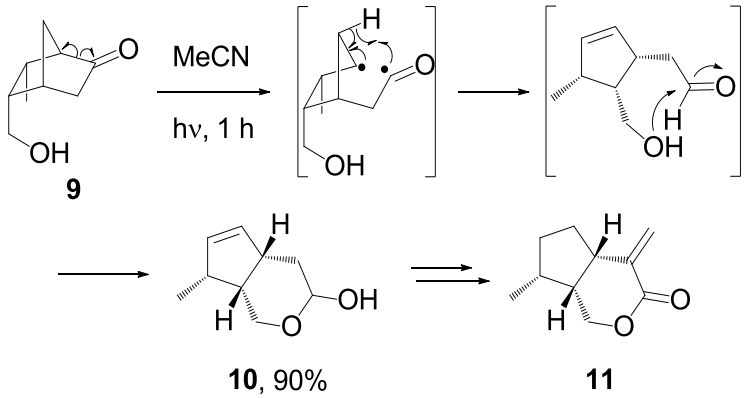
Once a carbonyl group is photochemically excited it can undergo many different reactions, most of which are impossible under thermal conditions as they would be energetically unfavourable. However, due to the high energy intermediates formed under photochemical conditions, these reactions are spontaneous. Furthermore, the differences in occupancy of the frontier molecular orbitals upon irradiation allow other reactions to occur which are forbidden under thermal conditions as the orbitals do not match up favourably.

The simplest reaction of the carbonyl group is α-fission to form a pair of radicals, a reaction known as a Norrish type I reaction (**Scheme 9**).[35,36,37]



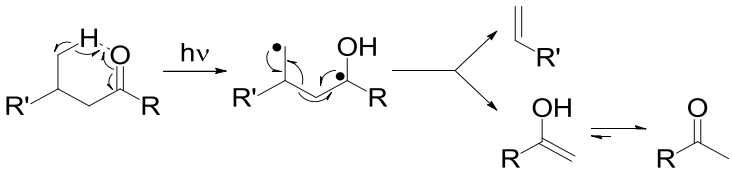
Scheme 9

Often these radicals will recombine or react in an uncontrolled manner which limits the synthetic usefulness of this reaction. However, a few examples do exist in the literature of harnessing this reaction towards total syntheses.[38,39,40] Callant *et al.* showed that the Norrish type I reaction could be used in the total synthesis of a number of compounds in the natural product family of iridoids. Irradiation of ketone **9** leads to the α-fission of the carbonyl group to produce a pair of radicals. The radicals seek to form more stable products, in this case an alkene and an aldehyde *via* a disproportionation reaction. The aldehyde then takes part in an intramolecular cyclisation to form a lactol **10** which can be further transformed into the natural product boschnialactone **11** (**Scheme 10**).[41]



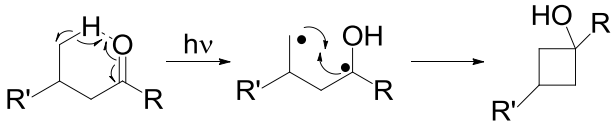
Scheme 10

In a similar reaction, the excited carbonyl group can abstract a hydrogen atom from a carbon in the γ-position *via* a six membered transition state, again forming a pair of radicals. These can then lead to the fission of the β-carbon bond and the formation of an alkene and an enol, the latter of which will tautomerize to its ketone form (**Scheme 11**). This reaction is known as a Norrish type II fragmentation.[35,36,37]



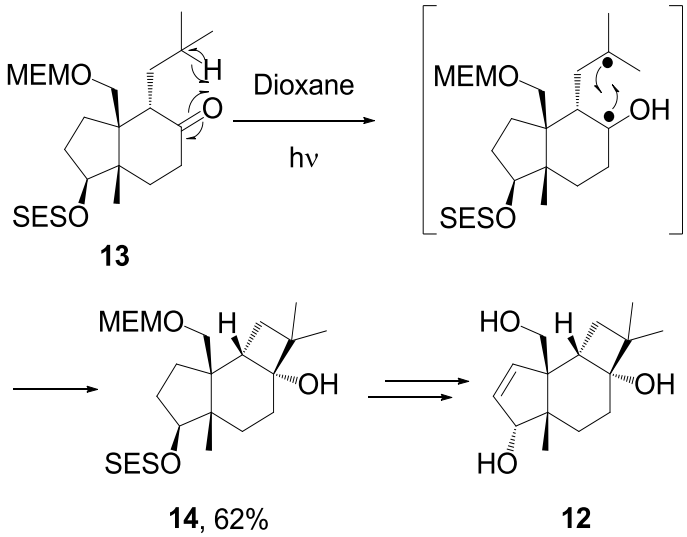
Scheme 11

These radicals can also recombine to form a cyclobutane in a process known as a Yang cyclization or the Yang reaction (**Scheme 12**).[37,42]



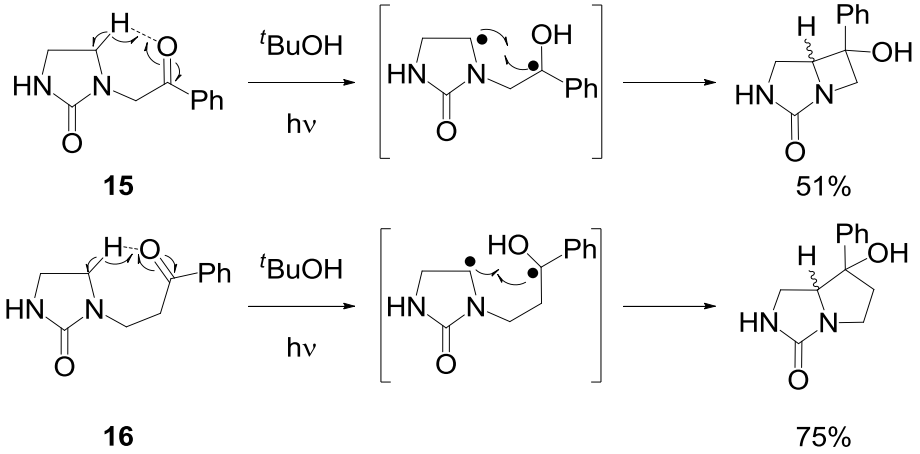
Scheme 12

This is a synthetically more useful reaction and has been exploited by Paquette *et al.* in their total synthesis of the antibacterial natural product (-)-Punctatin A **12**. Irradiation of ketone **13** gives rise to a pair of radicals *via* a Norrish type II hydrogen abstraction which then recombine to form a *trans*-fused cyclobutane **14**. Further transformations of this intermediate led to the natural product (**Scheme 13**).[43]



Scheme 13

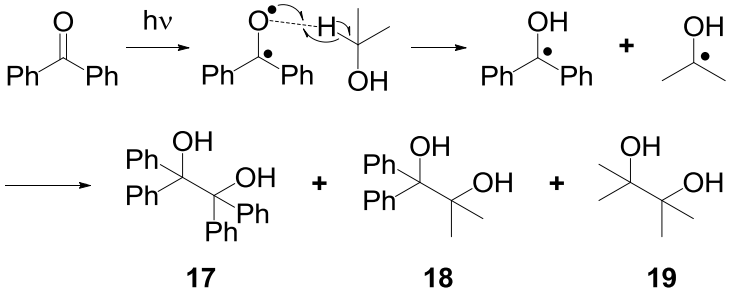
If there is no hydrogen atom present on the γ-carbon, a hydrogen on the δ-carbon can be abstracted instead. This is illustrated by Bach *et al.* in their studies of imidazolidinones, where irradiation of **15** with a γ-hydrogen leads to the formation of a four-membered ring, whereas irradiation of **16** without one leads to the formation of a five membered ring (**Scheme 14**).[44]



Scheme 14

If the irradiation of a ketone takes place in the presence of a hydrogen donor, such as an alcohol, the excited carbonyl species can abstract a hydrogen atom from the donor affording a tertiary radical, which can dimerise to form a symmetrical pinacol. An example of this is the formation of benzopinacol **17** from the photoreduction of benzophenone in 2-propanol. However, the alcohol also forms a tertiary radical which can lead to the formation of a mixed pinacol **18** and a symmetrical pinacol **19** (**Scheme 15**)[45] which often limits the use of

this reaction synthetically and complicates purification. Furthermore, there are many other ways of achieving this transformation under thermal conditions.[46,47,48]



17 **18** **19**

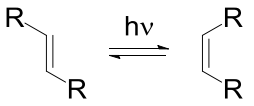
Scheme 15

Another reaction which can take place with an isolated carbonyl group is the Paternò-Büchi reaction. This will be covered later (**Chapter 1.5.3**) within the context of [2+2] photocycloaddition reactions. Although there are many other reactions which an isolated carbonyl group can undergo, these are the most common. Bach *et al*. and Hoffmann have produced more comprehensive reviews of these reactions among other photochemical reactions.[49,50]

1.5.2. Photochemical reactions of alkenes

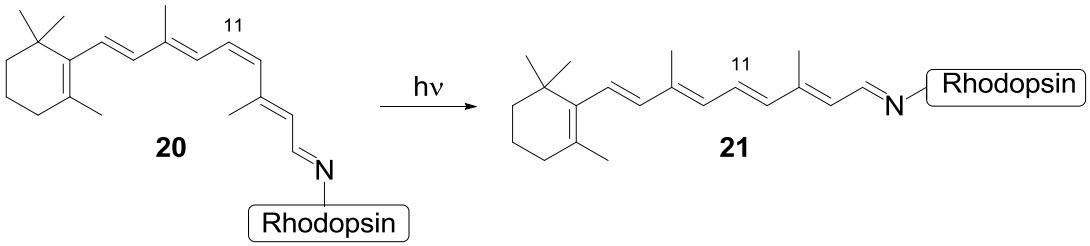
Another common chromophore in organic photochemistry is the carbon-carbon double bond. Again, multiple different photochemical reactions have been reported with isolated alkenes, but only the most common reactions will be discussed here.

One of the most important photochemical reactions of alkenes is geometric isomerisation. Once in its excited state, the π-bonding orbital is only half filled with the π*-antibonding orbital also half filled. This means that the π-bond which holds the molecule in a locked geometry no longer exists and free rotation around the carbon-carbon bond is possible. As a result it is possible to interconvert between the E and Z isomers of an alkene by UV irradiation (**Scheme 16**).[8]



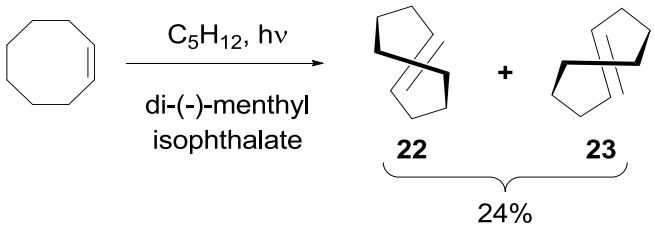
Scheme 16

The *cis-trans* photoisomerisation reaction is the basis of sight in humans. When a photon hits the protein rhodopsin, a molecule of the prosthetic group 11-*cis*-retinal **20** is excited and undergoes *cis-trans* isomerisation to form the all *trans*-retinal **21** (**Scheme 17**). This changes the tertiary structure of the rhodopsin protein, initiating a series of connected pathways which terminate in the brain and result in us being able to see. The all *trans*-retinal is then converted back enzymatically to the 11-*cis*-retinal allowing the reaction to occur again.[51] The geometric isomerisation reaction occurs within 200 fs in healthy eyes, a speed necessary for accurate sight.[52]



Scheme 17

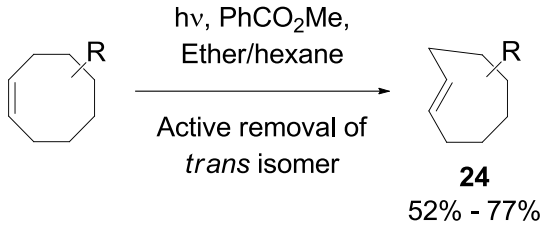
This reaction also allows access to highly strained *trans*-cycloalkenes such as *trans*-cyclooctene. Inoue *et al.* show that the sensitized irradiation of *cis*-cyclooctene affords a mixture of R-(-)-*trans*-cyclooctene **22** and S-(+)-*trans*-cyclooctene **23**, the ratio of which can be affected by the use of different chiral sensitisers (**Scheme 18**).[53]



Scheme 18

Often, the products have very similar photochemical properties to the starting materials, which means they easily undergo the reverse reaction and an equilibrium is reached whereupon a photostationary state is obtained. The proportion of each product in the mixture formed depends upon the relative

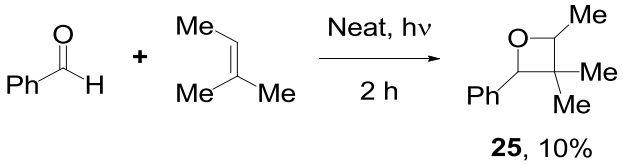
absorptivity of each. A separation step is almost always required and yields are lowered as a result. Royzen *et al.* have used a setup where the reaction mixture is constantly pumped through a column containing $AgNO_3$ impregnated silica gel during the irradiation of *cis*-cyclooctene. The *cis* isomer elutes freely and is returned back to the reaction mixture whilst the *trans* isomer **24** is retained on the silica gel which is then recovered by extraction after the reaction. *Via* this method they were able to achieve good yields (up to 77 %) of various *trans*-cyclooctenes on up to gram scales (**Scheme 19**, R=OH, alkyl or carbamate).[54]



Scheme 19

1.5.3. [2+2] photocycloaddition reactions

Another important reaction of both alkenes and carbonyl compounds is the [2+2] photocycloaddition; this is an electrocyclic reaction between two π-bonds, forming two new σ-bonds in a four-membered ring. The reaction was pioneered by Paternò *et al.* who showed that a reaction takes place between an aldehyde or ketone and a substituted olefin to form a four-membered ring upon irradiation. For example, irradiation of a mixture of benzaldehyde and 2-methylbut-2-ene affords cyclobutane **25** (**Scheme 20**).[55] This reaction was further elaborated by Büchi *et al.* nearly fifty years later and has since become known as the Paternò-Büchi reaction.[56]



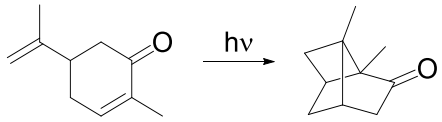
Scheme 20

Two isolated alkenes are rarely used together in [2+2] photocycloadditions however as often they are unreactive. In many cases the λ_{max} is at too low a wavelength to allow excitation of an alkene. Furthermore, upon excitation the

excited state is often quenched by *cis-trans* isomerisation. To make the alkene undergo a [2+2] photocycloaddition reaction, a carbonyl group is usually conjugated to the alkene, to form an enone. This shifts the λ_{max} to a more accessible wavelength, allowing the reaction to take place efficiently. The enone-alkene [2+2] photocycloaddition is the basis of this project, and will be discussed now in much more detail.

1.5.3.1. Enone-alkene [2+2] photocycloaddition reactions

The [2+2] photocycloaddition reaction between an enone and an alkene is probably the most widely used photochemical reaction in organic chemistry. It was first discovered in 1908 by Ciamician *et al.* who showed that carvone **26** is converted to carvone camphor **27** upon irradiation in sunlight for many months (**Scheme 21**).[57,58] Although the structure was only confirmed later,[59] they correctly speculated that a four-membered ring was being formed by a reaction between the enone and alkene.



26 **27**

Scheme 21

Since this early report, many other enone-alkene [2+2] photocycloadditions have been published, including both intermolecular and intramolecular versions.

1.5.3.2. Enone-alkene intermolecular [2+2] photocycloadditions

The enone-alkene [2+2] photocycloaddition reaction normally takes place from the n-π* triplet excited state. This is a state where one of the electrons from the oxygen lone pair is excited to the π* orbital of the enone, forming the singlet state (S_1), followed by ISC to the triplet n-π* state (T_1) (**Figure 10**). Once in the n-π* triplet state, the enone can form an exiplex with the alkene. An exciplex is the name given to a complex of an excited state molecule with the molecule with which it is reacting. One σ-bond then forms between the enone and the alkene leaving a diradical, which quickly combines to give a second σ-bond forming the new cyclobutane (**Figure 10**).[8,10]

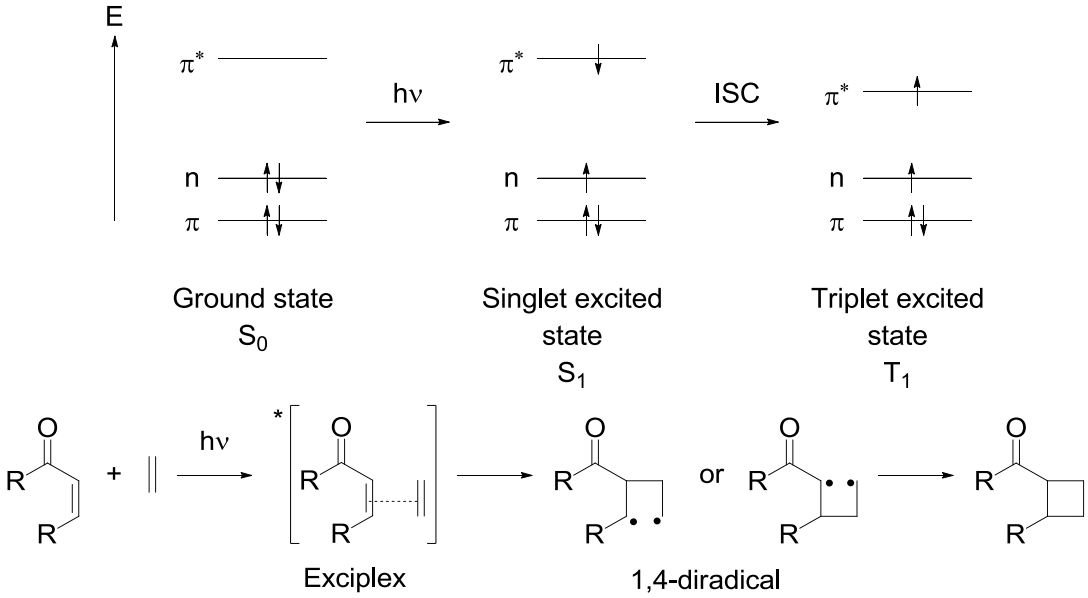
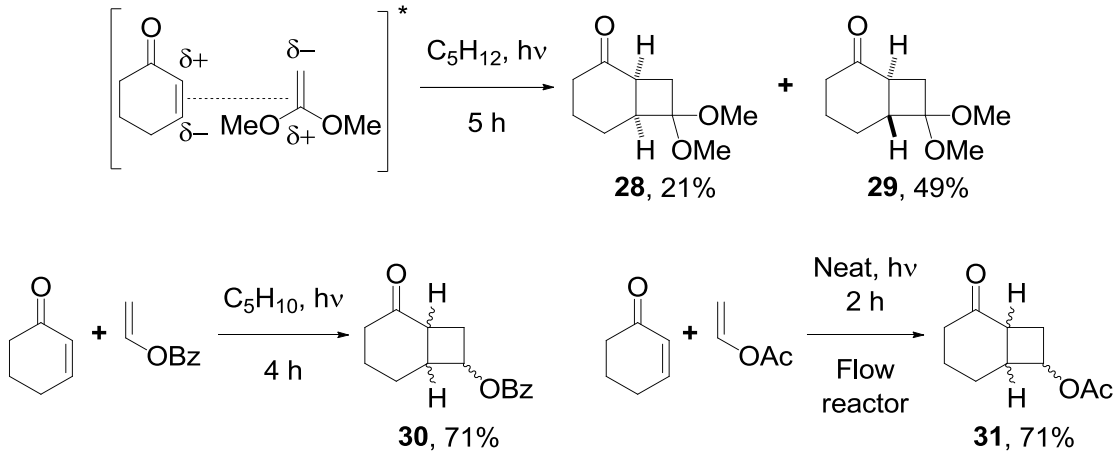


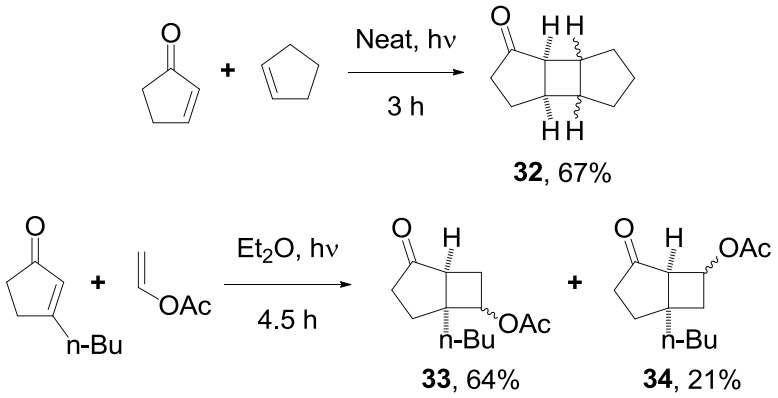
Figure 10

The intermolecular [2+2] photocycloaddition between enones and alkenes has been studied extensively. In particular the stereochemistry and regiochemistry of these reactions have been studied in an attempt to control these factors. Corey *et al.* investigated the reaction with unsymmetrical alkenes in an attempt to rationalise the regioselectivity observed in these reactions. They found that irradiation of cyclohexenone with 1,1-dimethoxyethylene gave a mixture of two diastereomeric cyclobutanes **28** and **29**. The regioselectivity was rationalised by saying that the dipoles had aligned during the exciplex formation and hence, after the reaction, the more electronegative end of the olefin would be in closer proximity to the carbonyl. They report that calculations of the charge distribution in the n-π* excited state show that the ß-carbon is more negatively charged than the α-carbon (**Scheme 22**). In other cases too, with highly polarised alkenes, this regioselectivity can be so good as to produce a single regioisomer, such as the formation of cyclobutanes **30** and **31** (**Scheme 22**).[60,61]



Scheme 22

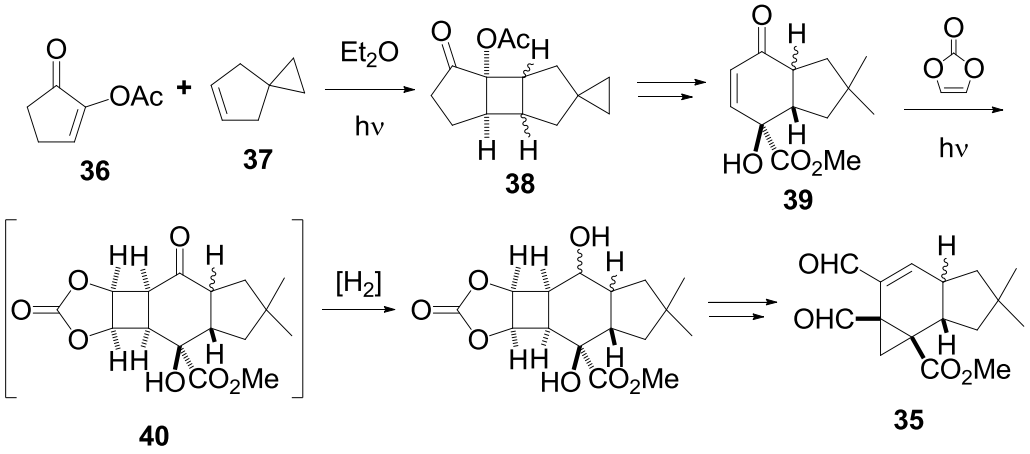
The enone is generally contained within a ring as this slows down *cis-trans* isomerism of the alkene, limiting the quenching of the excited state *via* this reaction. As well as using enones in six membered rings, as discussed above, the enone-alkene [2+2] photocycloaddition can be carried out with enones contained in five membered rings. Eaton published the intermolecular [2+2] photocycloaddition between cyclopentene and cyclopentenone to give cyclobutane **32** (**Scheme 22**).[62] Again, the regiochemistry of [2+2] photocycloadditions between cyclopentenones and alkenes can be controlled to an extent by using polarised alkenes, such as vinyl acetate to form cyclobutanes **33** and **34** with some regioselectivity (**Scheme 23**).[63]



Scheme 23

The power of this reaction has been shown by Helmlinger *et al.* in their synthesis of methyl isomarasmate **35**, an antibiotic derivative. Irradiation of enone **36** with alkene **37** gives cyclobutane **38** which undergoes further transformations to yield enone **39**. This was then irradiated in the presence of vinylene carbonate to yield the unstable cyclobutane **40** which was

subsequently hydrogenated. Further transformations yielded the antibiotic product **35** (**Scheme 24**).[64]

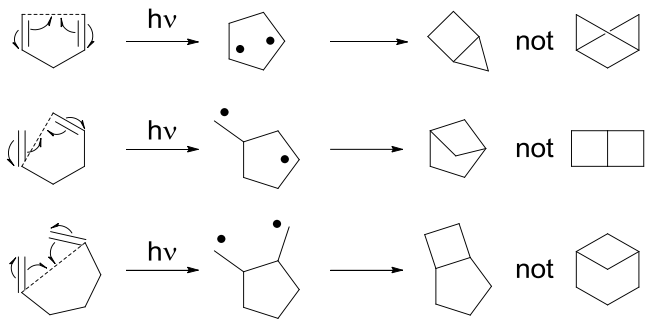


Scheme 24

The above reactions are only a few examples of intermolecular [2+2] enone-alkene photocycloadditions which represent a large area of study. Crimmins *et al.* have produced a more comprehensive review of the literature in this area.[65]

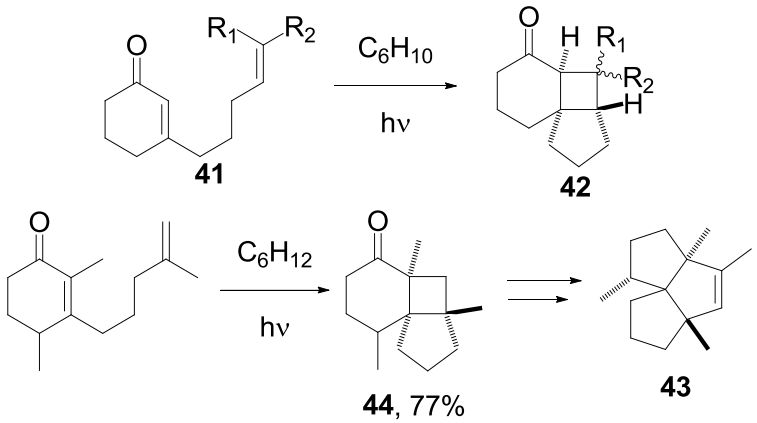
1.5.3.3. Enone-alkene intramolecular [2+2] photocycloadditions

The scope of the intermolecular [2+2] photocycloaddition is limited. This is due to the lack of regiochemical control in many reactions. In contrast to this, intramolecular photocycloadditions generally have very predictable regiochemistry, especially when the enone and alkene are separated by one, two or three atoms. This result was rationalised by Srinivasan *et al.* and Liu *et al.* independently by saying that the reaction must go *via* a diradical species where one new σ-bond has formed but the other has not. The results can then be explained by saying that the first σ-bond will form in a five-membered ring wherever possible, before the diradical combines to form the cyclobutane (**Scheme 25**).[66, 67] This is known as the rule of five.



Scheme 25

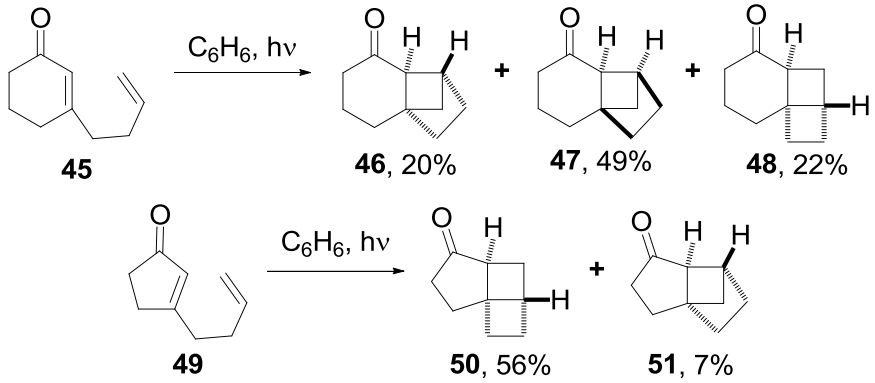
As with the intermolecular [2+2] photocycloaddition, the enone is often part of a ring; generally cyclopentenones and cyclohexenones are used and the alkene tethered to the ring by a chain. Becker e*t al.* showed that this reaction can be carried out with a cyclohexenone with a variety of tethered alkenes **41** affording cyclobutanes **42** (**Scheme 25**, R_1 = H, Me or ^{i}Pr; R_2 = H or Me).[68] Pirrung carried out a similar reaction in a key step of his synthesis of the natural product (±)-isocomene **43** *via* cyclobutane **44** (**Scheme 26**).[69] The single regioisomeric products of these reactions show the power of the rule of five.



Scheme 26

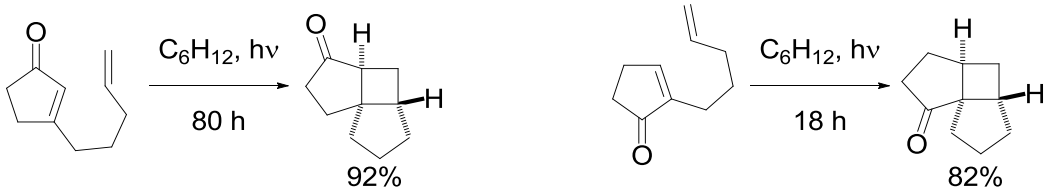
Systems with a two carbon tether between the enone and pendant alkene have also been studied in both cyclohexenones and cyclopentenone. In the case of enone **45**, the major irradiation products are the two diastereomers of the 'crossed' cyclobutanes **46** and **47**, whilst the minor product is the 'straight' cyclobutane **48**. However, surprisingly, upon irradiation of enone **49** the 'straight' adduct **50** is the major product, over the expected 'crossed' product **51** (**Scheme 27**).[70] The report suggests that this change in regiochemistry is due to the excited enone not being able to twist into the necessary conformation for the

crossed product to form as well in the five membered ring system as it does in the six membered ring system.



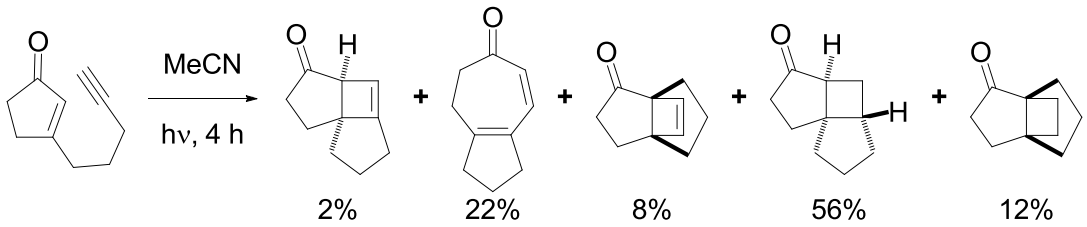
Scheme 27

Matlin *et al.* have shown that similar reactions also proceed well with a cyclopentenone containing a five carbon tether at the 2- and 3-positions of the enone (**Scheme 28**).[71]



Scheme 28

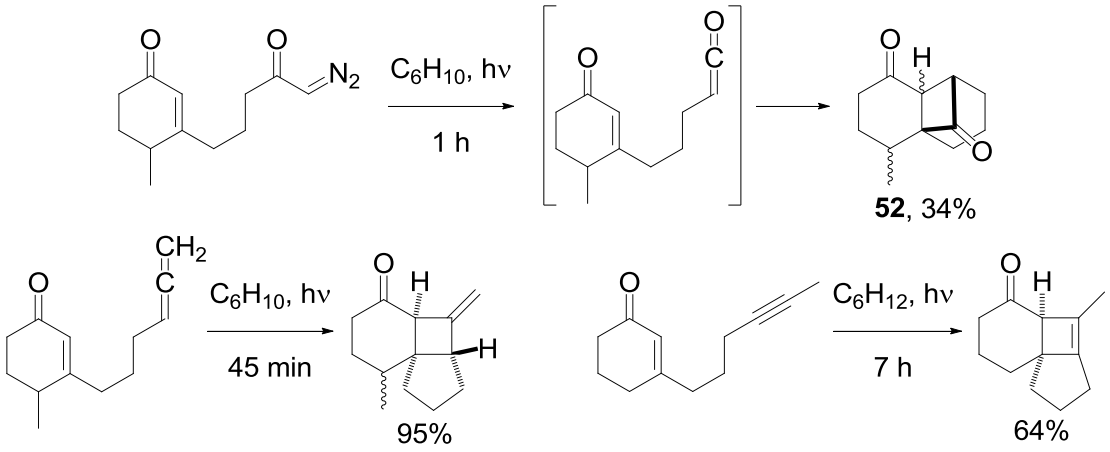
Mancini *et al.* have shown that, although a similar reaction with a tethered alkyne is possible, it leads to a mixture of products (**Scheme 29**). These products arise from secondary photoreactions, the initial cyclobutene product being broken down into a variety of other products.[72]



Scheme 29

Analogous reactions with cyclohexenones have been carried out with tethered ketenes (synthesised *in situ* from the diazoketone),[73] allenes[74] and alkynes[75] (**Scheme 30**). It is interesting to note the regiochemistry in the reaction with ketene to form cyclobutane **52**, which is the opposite of that seen in all other enone-alkene [2+2] photocycloadditions. The proposed rational for this is that

the olefin unit in the ketene is sufficiently polarised that the electronic effects in this reaction govern the regiochemical outcome rather than the rules of five.



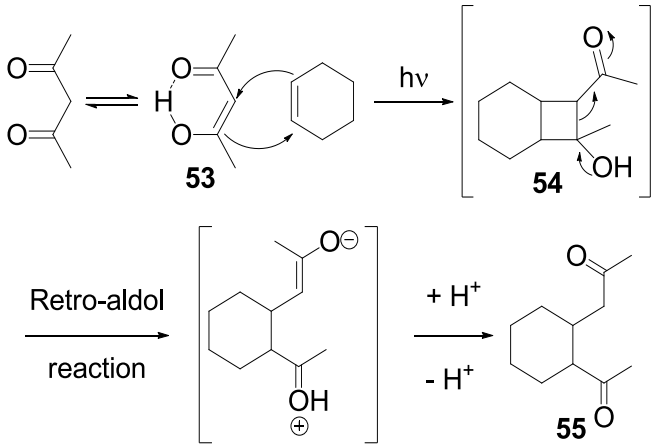
Scheme 30

Once more, these reactions are only a small number of the intramolecular [2+2] photocycloadditions found in the literature. More comprehensive reviews have been published in this area.[65,76]

In a similar reaction to those described above, the transient enone formed by tautomerisation of a 1,3-diketone can also undergo a [2+2] photocycloaddition with an alkene. This reaction is known as the de Mayo reaction and will now be discussed in detail.

1.5.4. The de Mayo reaction

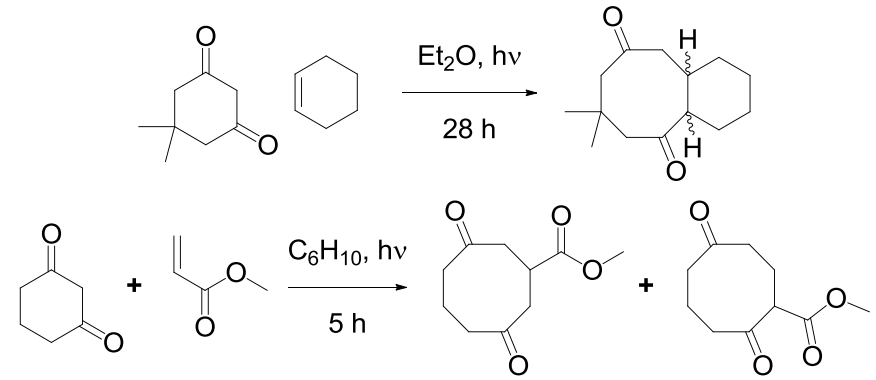
It was discovered that upon irradiation of a 1,3-diketone in the presence of an olefin, a 1,5-diketone was formed with the olefin unit inserted between the carbonyl groups (**Scheme 31**). The reaction proceeds *via* a [2+2] photocycloaddition between the alkene and the enol form of the diketone **53**, which is stabilised by hydrogen bonding in a six-membered ring. The reaction affords a transient hydroxycyclobutane **54**, which undergoes a retro-aldol fragmentation to yield the 1,5-diketone **55**. This reaction has since become known as the de Mayo reaction in honour of its pioneer.[77]



Scheme 31

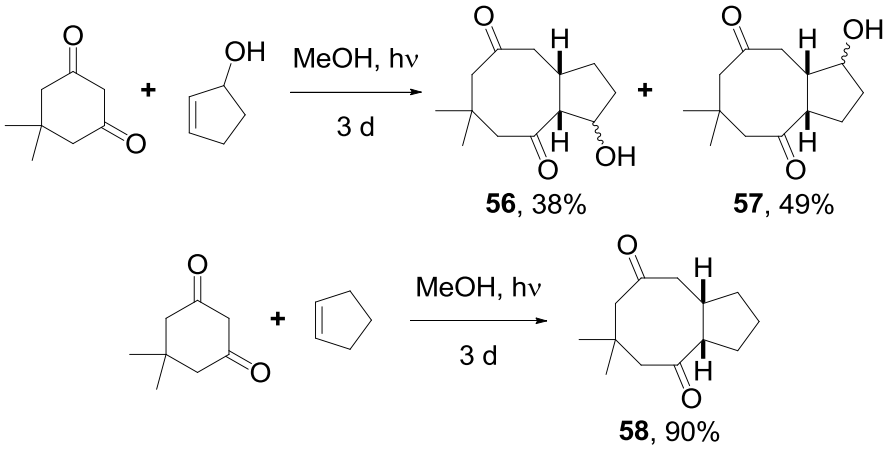
The synthesis of 1,5-diketones is important as these compounds are useful building blocks, in particular in the synthesis of heterocyclic compounds such as pyridines;[78,79] indeed they are intermediates in the Hantzsch pyridine synthesis.[80] Although these compounds can be synthesised *via* other means, of particular note *via* an enol or enolate addition to a Michael acceptor,[81,82] this often requires a strong acid or base to which the compound may be sensitive. Furthermore, the products may then undergo Robinson cyclisation.[15] Other syntheses do exist, but often require toxic reagents[83] or expensive catalysts.[84] In contrast to these, the de Mayo reaction can be carried out under neutral conditions.

Following on from the initial publication, the de Mayo reaction was later extended to using dimedone and cyclohexadione as the 1,3-diketones, with cyclohexene and methyl acrylate as the alkenes respectively (**Scheme 32**).[85] It should be noted that the yield for these reactions are not reported, thus comparison of these reactions to others is difficult as well as commenting on the regioselectivity.



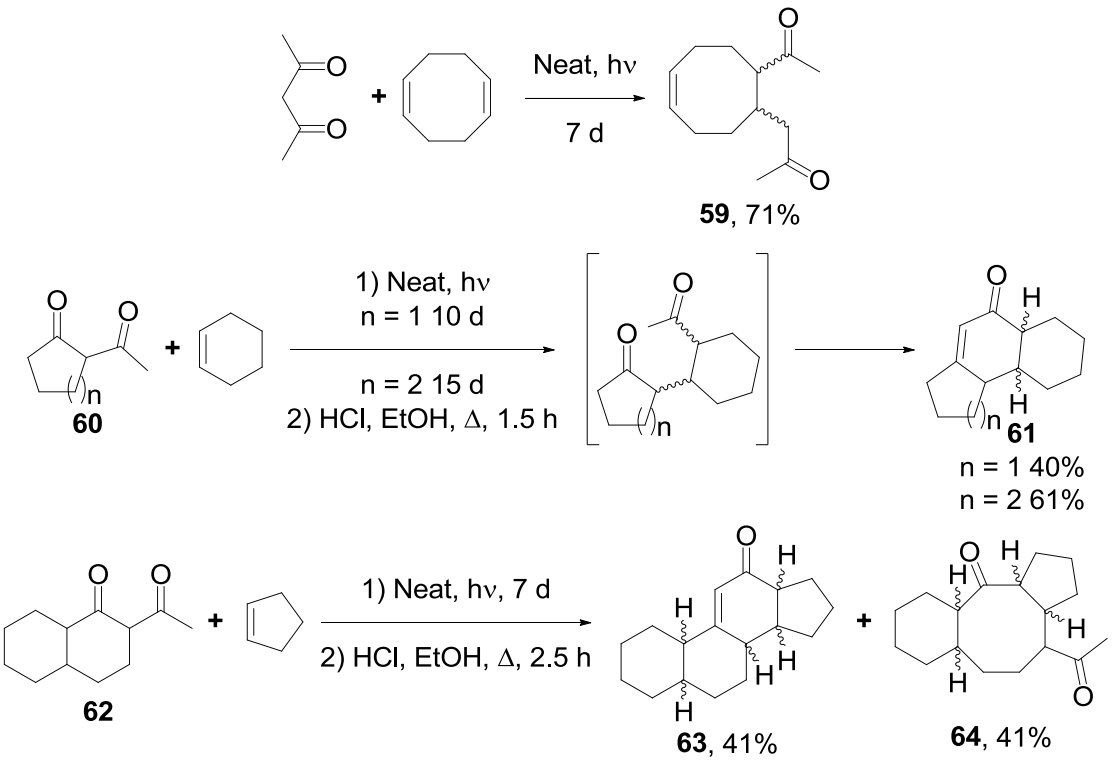
Scheme 32

Weedon *et al.* investigated this reaction further, using dimedone as the diketone with a series of cyclopentenes. They isolated diketones **56** and **57** from the reaction with 2-cyclopentenol and **58** from the reaction with cyclopentene (**Scheme 33**).[86,87]



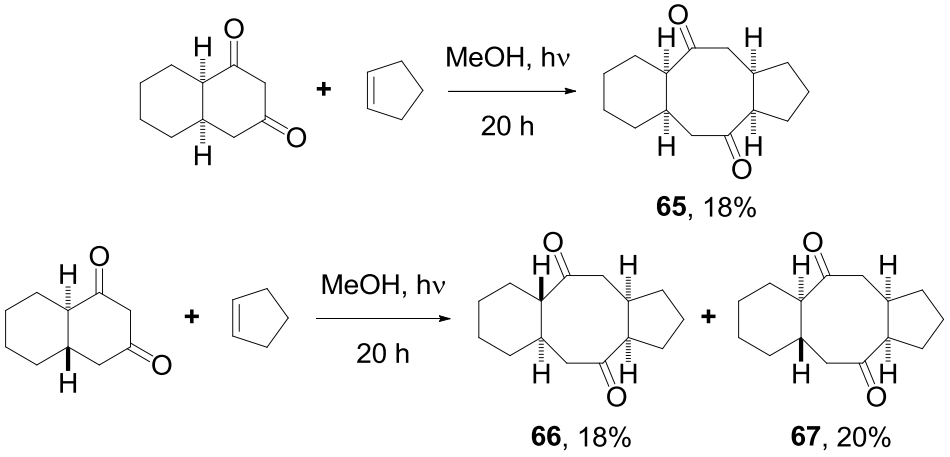
Scheme 33

Nozaki *et al.* further extended the de Mayo reaction by using alkenes contained in larger rings (**Scheme 33**); irradiation of acetylacetone with cyclooctadiene affording diketone **59** They also used unsymmetrical diketone **60** with cyclohexene, although in this case they were unable to isolate the 1,5-diketones. Upon treatment of the crude mixture with hydrochloric acid, one of the diketones underwent an aldol condensation to give enone **61**, the other not being able to be isolated pure (**Scheme 34**). Furthermore, using diketone **62** in a de Mayo reaction with cyclopentene followed by treatment with acid, they obtained enone **63** and diketone **64** (**Scheme 34**).[88]



Scheme 34

Umehara *et al.* have also investigated the de Mayo reaction; using both *cis*- and *trans*-decalin-1,3-dione in a de Mayo reaction with cyclopentene to investigate the diastereoselectivity of this reaction. Although the resultant mixture was a complex one, they were able to show that the major product from the *cis*-isomer was diketone **65** whilst the major components from the *trans*-isomer were diketones **66** and **67** (**Scheme 35**).[89] In both cases the stereochemistry comes about presumably *via* an *exo* approach of the alkene from the least hindered face in order to minimise all steric interactions.

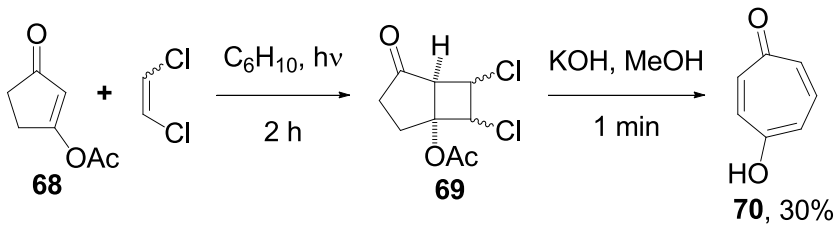


Scheme 35

In reality 1,3-diketones are rarely used in the de Mayo reaction; the above reactions comprising all of the reported literature examples in this area according to the literature review carried out here. One reason for this may be due to the inefficiency of the reaction. Indeed, many of the above reactions take at least a day, some up to 2 weeks. It is likely that the presence of such a small number of these reactions in the literature is due to their apparent lack of reactivity. Another reason that 1,3-diketones may not have been widely used in the de Mayo reaction is that the cyclobutane may be the actual product of interest. These problems have been overcome by trapping the enone form out as the enol acetate, or as a carbonate group. Now follows a summary of these reactions.

1.5.4.1. Intermolecular de Mayo reactions with trapped 1,3-diketones

Challand *et al.* trapped out the enone of 1,3-cyclopentadione using ketene to form enol acetate **68**. Whilst the irradiation of the parent diketone in the presence of a number of alkenes gave no reaction, the irradiation of 1,3-cyclopentadione enol acetate **68** in the presence of these alkenes afforded the desired cyclobutanes. This is exemplified by the reaction with 1,2-dichloroethylene, affording the cyclobutane **69**, which does not undergo fragmentation. This is most likely due to the oxygen lone pair being tied up in the acetate group. Upon removal of the acetate group with base however, the fragmentation does takes place along with elimination of HCl to give γ-tropolone **70** (**Scheme 36**).[85]

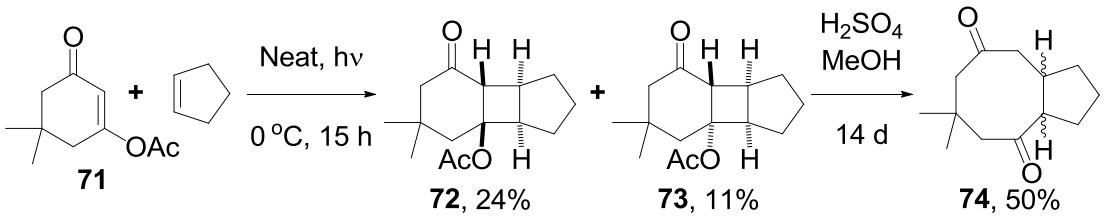


Scheme 36

One possible explanation for the reaction with enone acetates being significantly faster than the diketones is that the enone functionality is always available in these cases. There is no need for the compound to undergo

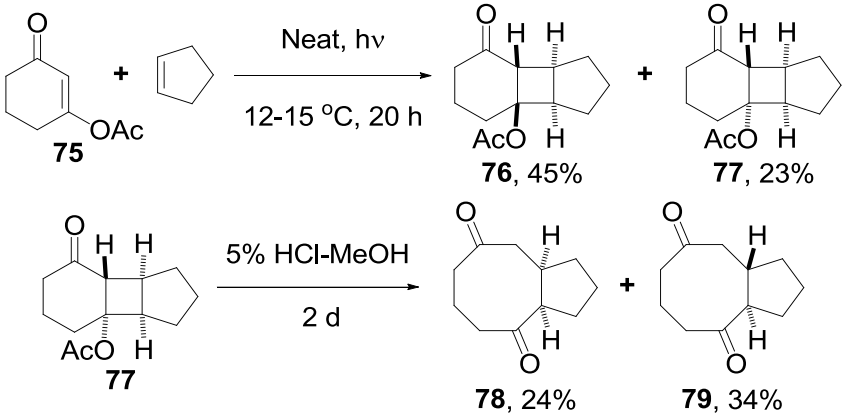
tautomerisation which would limit the amount of the compound in the enol form at any given time. Another possibility for the difference in the rate of reaction could be due to the difference in their solubility. Whereas the diketones are sparingly soluble, especially in hydrocarbon solvents, the acetates are much more soluble, speeding up the rate of reaction.[85] In contrast to the de Mayo reaction with 1,3-diketones, this method also has the benefit of allowing isolation of the cyclobutane.

This difference in the rate of the reaction is exemplified by the reaction of cyclopentene with the enone acetate of dimedone **71** compared to that with the parent diketone. The reaction with the diketone takes three days (**Scheme 33** above),[86] whereas reaction with the enone acetate **71** goes to completion in 15 hours, affording cyclobutanes **72** and **73**. These undergo retro-aldol fragmentation upon acid catalysed removal of the acetyl group, affording diketone **74** as a mixture of diastereomers, which comes about due to acid catalysed epimerisation *via* the enol form (**Scheme 37**). [90]



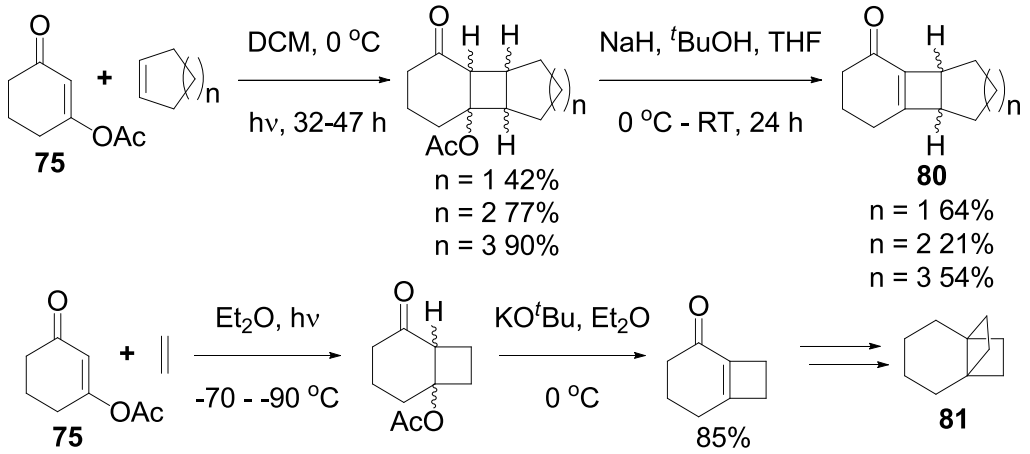
Scheme 37

Umehara *et al*. have shown that irradiation of enone acetate **75** in the presence of cyclopentene affords cyclobutanes **76** and **77**. Removal of the acetate groups from either of the regioisomers under acidic conditions, led to the formation of diastereomeric diketones **78** and **79** (**Scheme 38**).[91]



Scheme 38

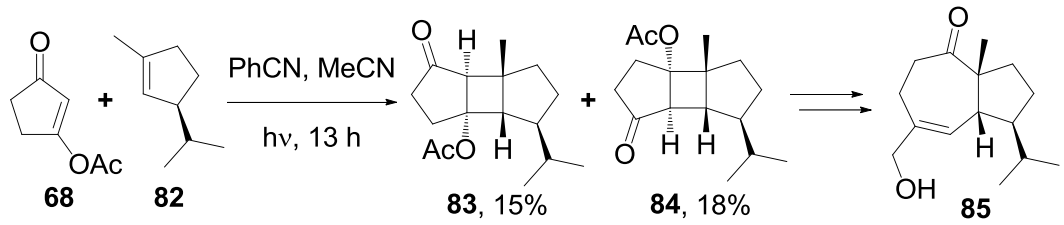
Cantrell *et al.* showed that reaction of the cyclobutanes **76** and **77** with a strong base, potassium *t*ert-butoxide leads to ß-elimination of acetic acid to form cyclobutene **80** (**Scheme 39**, n=1). They showed that this reaction can be carried out on a variety of cyclobutanes synthesised from **75**.[92] Galatsis *et al.* further developed this reaction, extending the reaction to a variety of cyclic alkenes (**Scheme 39**, n = 1, 2 or 3). They report that this is a general reaction for cyclobutanes formed from the de Mayo reaction of six membered ring enones with a disubstituted alkene.[93] Eaton *et al.* used this method in their synthesis of propellanes, for example **81** (**Scheme 39**).[94]



Scheme 39

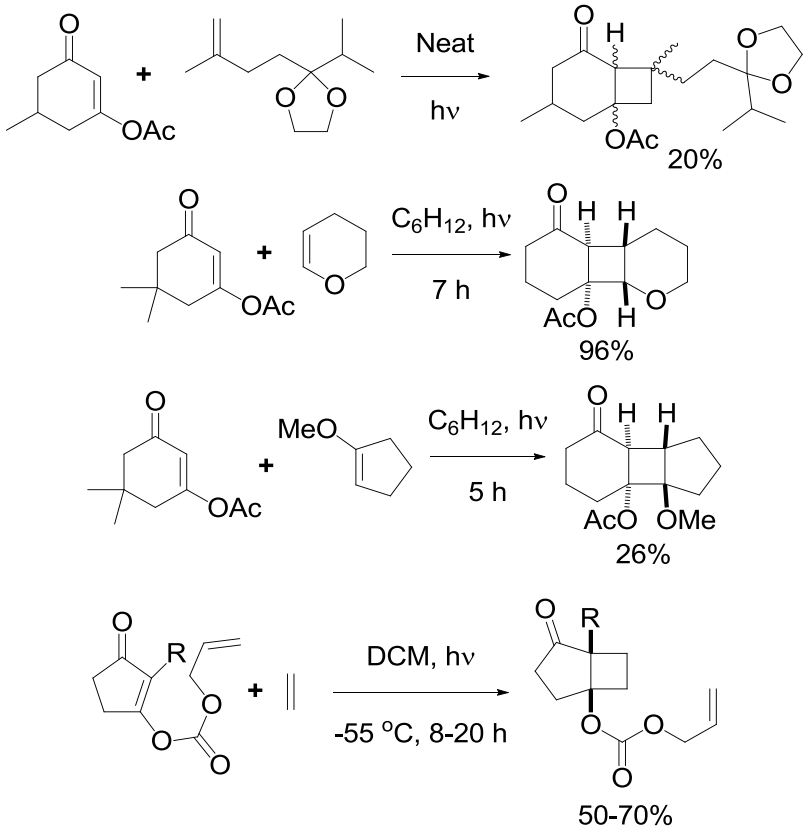
Using an enantiopure alkene, the [2+2] photocycloaddition of an alkene with a trapped 1,3-diketone can be carried out asymmetrically. This has been shown by Hansson *et al.* in their synthesis of the natural product (+)-Aphanamol I, reacting alkene **82** with enone **68** to afford a pair of regioisomeric cyclobutanes

83 and **84**. Further reactions on **84** yielded the natural product (+)-Aphanamol I **85** (**Scheme 40**).[95]



Scheme 40

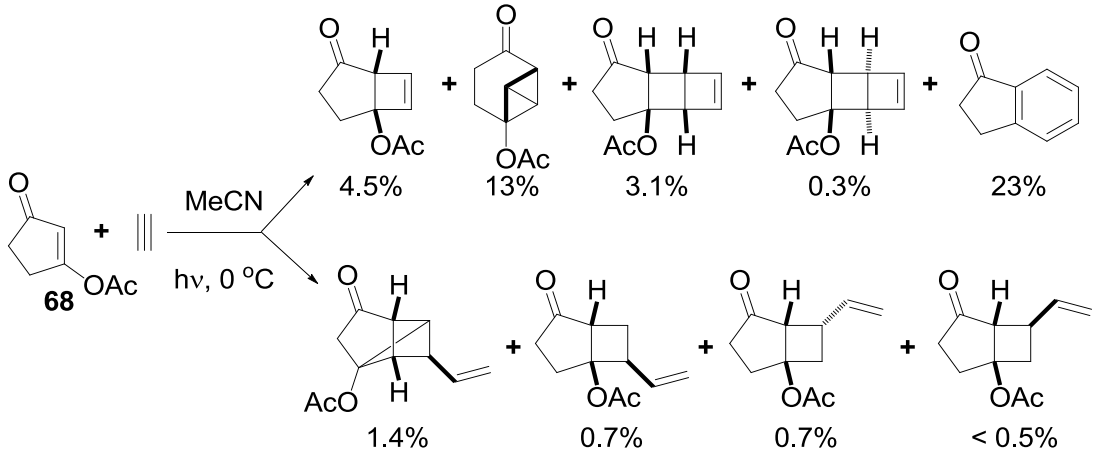
A few other uses of the de Mayo reaction with trapped 1,3-diketones have been reported by Grayson *et al.* (**Scheme 41**),[96] Barker *et al.* (**Scheme 41**)[97] and Schulz *et al*. (**Scheme 41**, R = alkyl).[98] In all of these cases the cyclobutanes isolated were the desired products. This shows the power of this reaction to form cyclobutanes which are important groups and difficult to synthesise *via* thermal means.



Scheme 41

Although alkynes can also be used in the de Mayo reaction with trapped 1,3-diketones, Cavazza *et al.* have shown that the reaction of **68** with acetylene leads to a mixture of multiple products (**Scheme 42**). These products mostly

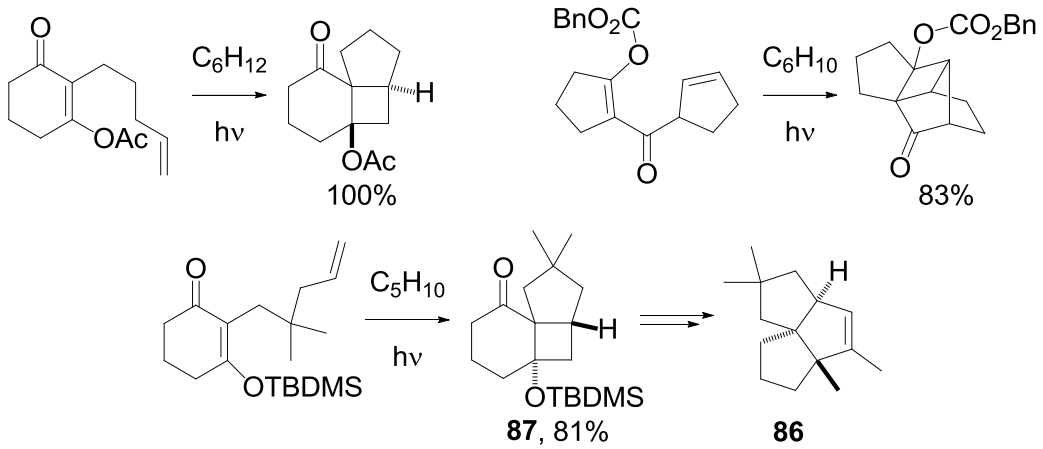
arise from photochemical rearrangements and secondary photoreactions, the initial photoproducts undergoing a second reaction with acetylene.[99]



Scheme 42

1.5.4.2. Intramolecular de Mayo reactions with trapped 1,3-diketones

There are very few reports in the literature regarding intramolecular de Mayo reactions with 1,3-diketones. However, enol acetates,[100] enol carbonates[101] and silyl enol ethers have all been employed successfully in these reactions, the last of which was used in the total synthesis of the antibiotic natural product (±)-pentalenene **86**, going *via* cyclobutane **87** (**Scheme 43**).[102]



Scheme 43

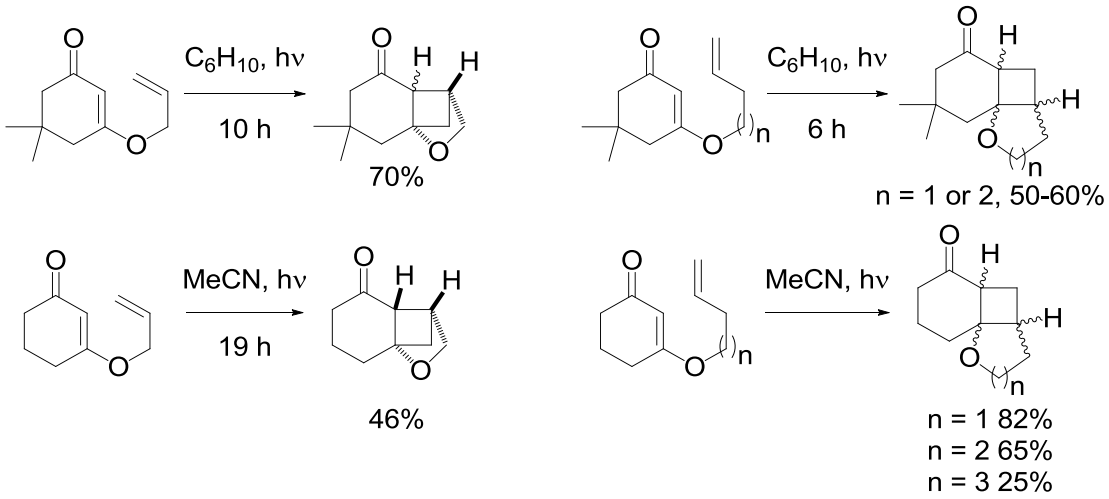
A natural progression from using the trapped 1,3-diketones in the enone-alkene [2+2] photocycloaddition, is to use vinylogous esters, containing an ether linkage in conjugation with the enone instead of the ester linkages outlined above. Similar compounds can also be used with a nitrogen atom (vinylogous

amides) or a sulfur atom (vinylogous thioester). This would allow access to a number of heterocycles and a number of heteroatom adorned cyclobutanes. With the exception of one example that makes use of a sulfur atom,[103] these take the form of vinylogous esters and vinylogous amides, the photochemistry of which will now be discussed.

1.5.5. [2+2] photocycloadditions of vinylogous esters

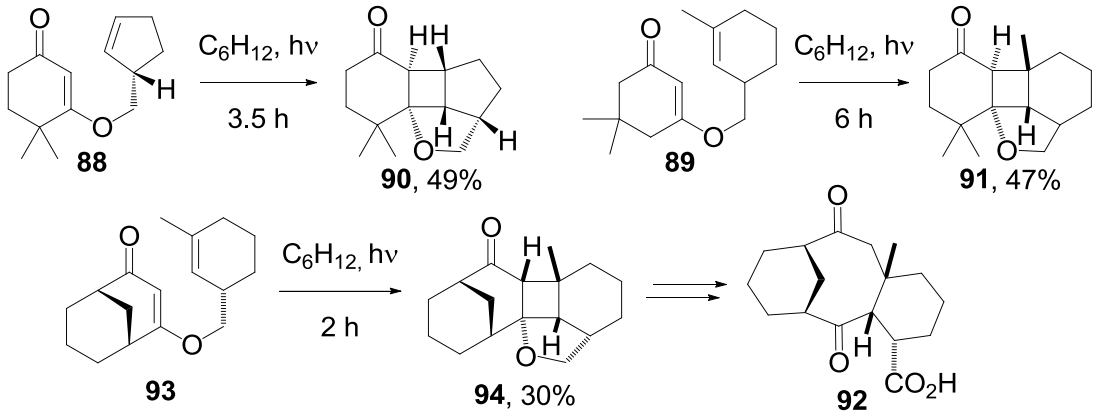
1.5.5.1. Intramolecular [2+2] photocycloadditions of vinylogous esters

Tamura *et al*. and Mattay *et al.* both showed that vinylogous esters with tethered alkenes undergo analogous reactions to those of the all carbon chains (**Chapter 1.5.3.3**) with similar regioselectivities (**Scheme 44**).[104,105,106]



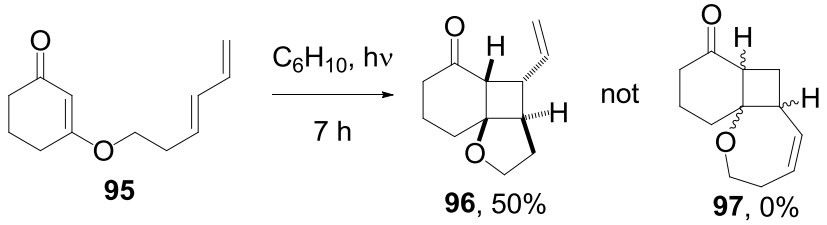
Scheme 44

It has also been shown that the tethered alkene can be cyclic in nature. Inouye *et al.* have shown that irradiation of vinylogous esters **88** and **89** lead to cyclobutanes **90** and **91** respectively (**Scheme 45**).[107] The same group demonstrated the use of this reaction in an initial step towards a model system of the taxane core **92**. Irradiation of vinylogous ester **93** affords cyclobutane **94**, which is further transformed into **92** (**Scheme 45**).[108]



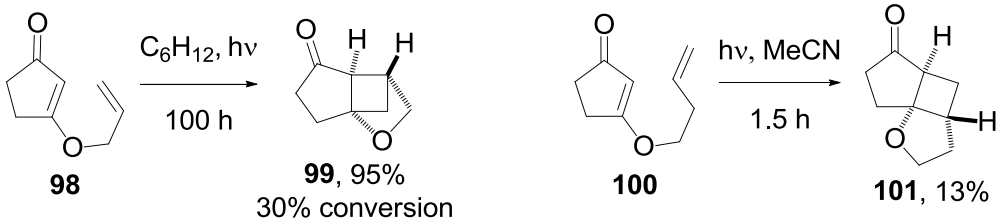
Scheme 45

Further to these reactions, Pirrung *et al.* demonstrated excellent regioselectivity in the [2+2] photocycloaddition of vinylogous ester **95** containing a pendant diene; the 5,4 system **96** forming over the 7,4 system **97** (**Scheme 46**)[109]



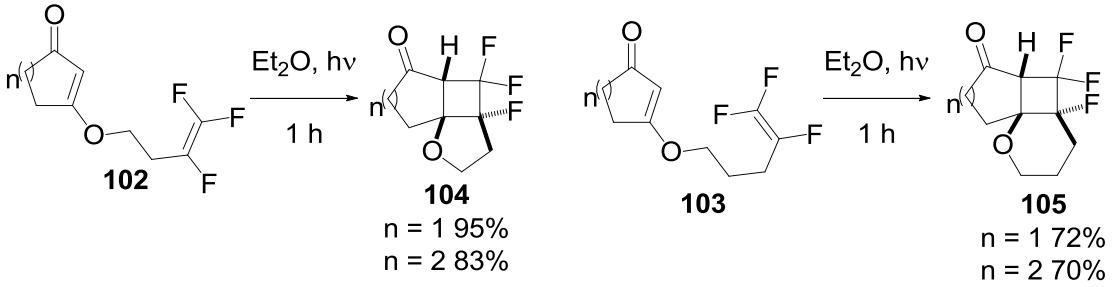
Scheme 46

It has been shown that the vinylogous ester can also be incorporated into a five membered ring, and the [2+2] photocycloaddition proceeds with various degrees of success. An intramolecular [2+2] photocycloaddition reaction takes place with vinylogous ester **98** affording cyclobutane **99** in excellent yield, but only at 30% conversion after 100 hours.[30,110] In contrast to this, the analogous reaction of vinylogous ester **100** to afford cyclobutane **101** is significantly quicker, but has been shown to be very low yielding by previous work in our group (**Scheme 47**).[34] The low yield for this reaction was shown to be due to extensive secondary photoreactions taking place.



Scheme 47

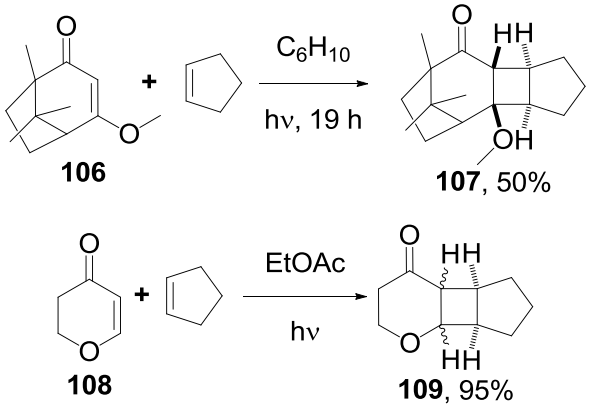
Bach *et al.* have shown that irradiation of vinylogous esters **102** and **103**, with tethered fluorinated alkenes, leads to intramolecular [2+2] photocycloadditions to give cyclobutanes **104** and **105** respectively (**Scheme 48**).[111] Fluorinated compounds are found in many drug molecules, as are heterocycles and cyclobutanes, thus having access to fluorinated heterocyclic cyclobutanes in a single step could be very useful in the context of drug discovery.[112]



Scheme 48

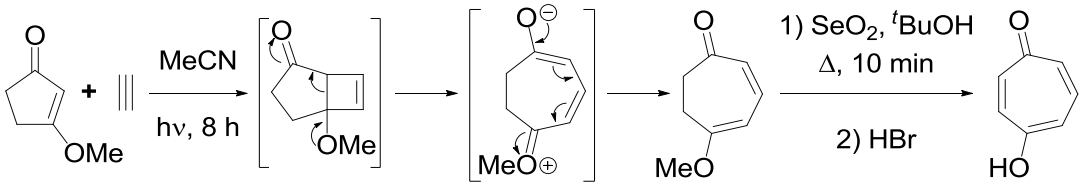
1.5.5.2. Intermolecular enone-alkene [2+2] Photocycloadditions of vinylogous esters

Although very few, some intermolecular reactions with vinylogous esters have also been reported. In their route towards taxanes, Berkowitz *et al*. carried out the intermolecular [2+2] photocycloaddition of vinylogous ester **106** with cyclopentene, affording cyclobutane **107** (**Scheme 49**).[113] Sato *et al.* report the reaction of vinylogous ester **108**, with the oxygen atom contained within the ring, undergoing an intermolecular [2+2] photocycloaddition with cyclopentene, affording cyclobutane **109** as a mixture of diastereomers (**Scheme 49**).[114]



Scheme 49

Cavazza *et al.* used acetylene in a de Mayo type reaction with vinylogous ester **110** to give dieneone **111** after a retro-aldol reaction. Oxidation followed by cleavage of the methoxy group gave γ-tropolone **70** (**Scheme 50**)[115] in a different way from that of Challand *et al.* mentioned earlier (**Chapter 1.5.4.1**). The photochemical step in this reaction was only carried out to 19% conversion, presumably as significant secondary photoreactions took place otherwise. This may also explain why there are no other reports of alkyne-vinylogous ester [2+2] photocycloaddition reactions in the literature according to this literature review.



110 **111**, 57% 19% conversion **70**, 38%

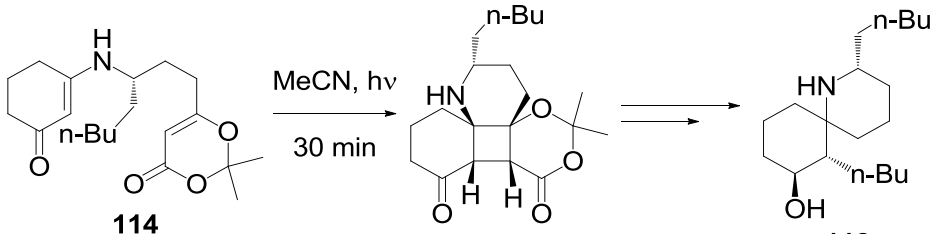
Scheme 50

1.5.6. [2+2] photocycloadditions of vinylogous amides and imides

The [2+2] photocycloaddition of vinylogous esters provides a useful route to complex, often polycyclic, systems in a single step which may not be accessible *via* thermal reactions. Furthermore, these systems contain cyclobutane rings which can be found in a number of natural and bioactive molecules[116] and are difficult to access under standard conditions. They are also useful intermediate towards other molecules; facile cleavage of the ring giving access to a wide variety of derivatives.[117] By using vinylogous amides instead of vinylogous esters, changing the oxygen atom for a nitrogen atom, cyclobutanes containing a pendant amine, upon which further substitutions could be carried out, are accessible. Outlined below is a review of the literature in the area of both intramolecular and intermolecular [2+2] photocycloadditions of vinylogous amides.

1.5.6.1. Intramolecular [2+2] photocycloadditions of vinylogous amides

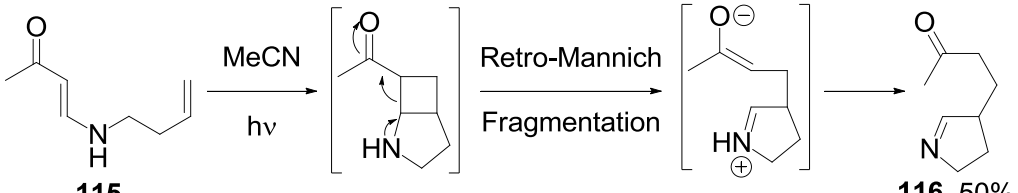
The intramolecular vinylogous amide-alkene [2+2] photocycloaddition has been demonstrated by Winkler *et al.* The natural product (-)-perhydrohistrionicotoxin **112** was synthesised from cyclobutane **113**, which in turn was synthesised by the intramolecular [2+2] photocycloaddition of vinylogous amide **114** containing a dioxinone substituent (**Scheme 51**).[118]



114 **113**, 95% **112**

Scheme 51

The power of vinylogous amide-alkene [2+2] photocycloadditions is that they can allow access to aminocyclobutanes. However, it has been found that often when vinylogous amides with tethered alkenes are irradiated, they undergo the desired [2+2] photocycloaddition to form the cyclobutanes, but then spontaneously collapse to form imines. This reaction occurs *via* a retro-Mannich fragmentation in an analogous fashion to the de Mayo reaction undergoing a retro-aldol fragmentation.[119] For example, irradiation of vinylogous amide **115** affords keto-imine **116**, the intermediate cyclobutane **117** undergoing a retro-Mannich fragmentation (**Scheme 52**).[120,121,122,123]

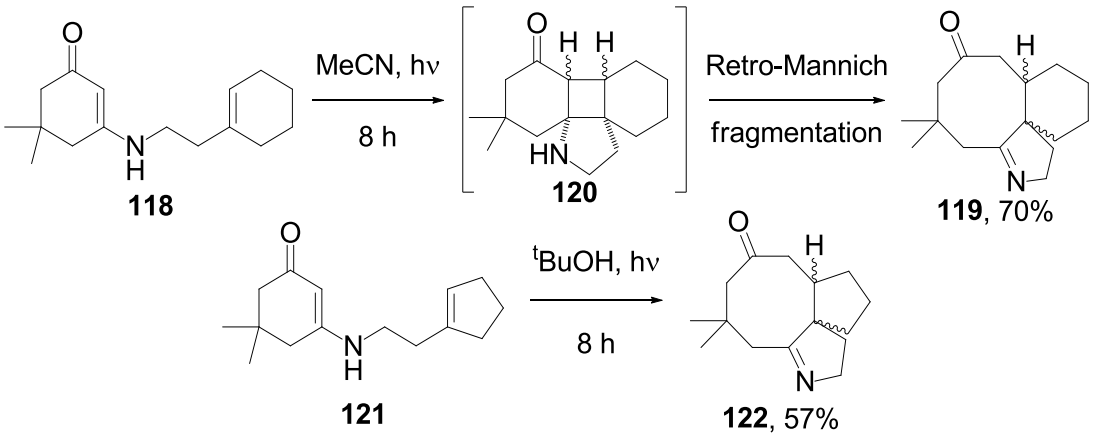


115 **117** **116**, 50%

Scheme 52

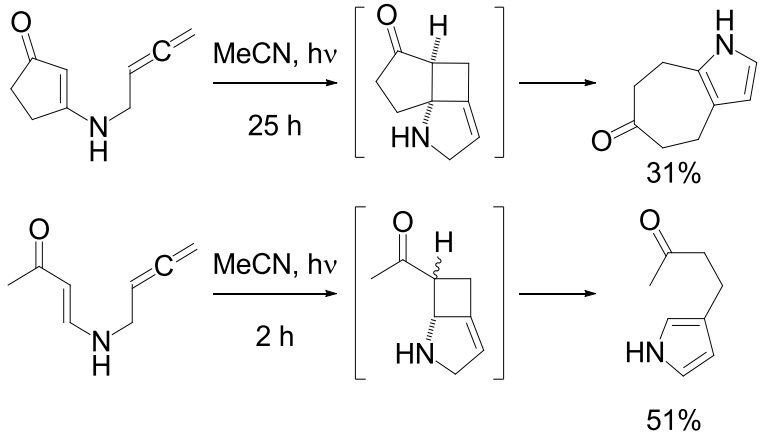
In a similar manner to the vinylogous esters, in most examples in the literature the vinylogous amide is cyclic in nature. For example, irradiation of vinylogous amide **118** affords keto-imine **119**, again *via* a retro-Mannich fragmentation of the cyclobutane intermediate **120** (**Scheme 53**).[124] Similarly, Vogler *et al.* showed that the irradiation of a series of substituted vinylogous amides with different length tethers containing different sized cycloalkenes afford keto-

imines. This is exemplified by the transformation of vinylogous amide **121** into keto-imine **122** (**Scheme 53**).[125]



Scheme 53

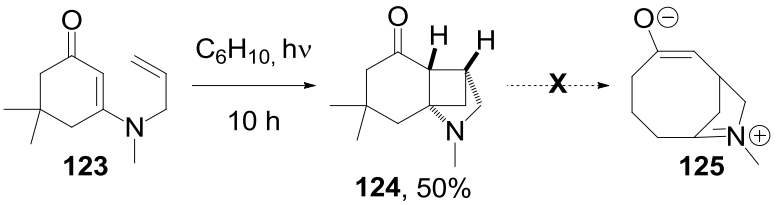
This cyclisation-retro-Mannich sequence also occurs with both cyclic and acyclic vinylogous amides containing a pendant allene unit and has found use in the synthesis of pyrroles (**Scheme 54**).[126,127]



Scheme 54

In contrast to the previous reactions, Tamura *et al.* showed that tertiary vinylogous amides do not undergo the retro-Mannich reaction; irradiation of vinylogous amide **123** gives aminocyclobutane **124**.[128] It is likely that this does not undergo the retro-Mannich fragmentation as the product would be an iminium species, **125**, which is significantly less stable than the imines formed previously (**Scheme 55**). If the retro-Mannich fragmentation were to take place, a proton transfer could not take place to give a stable, neutral species. Furthermore, the resultant carbon-nitrogen double bond would form to a

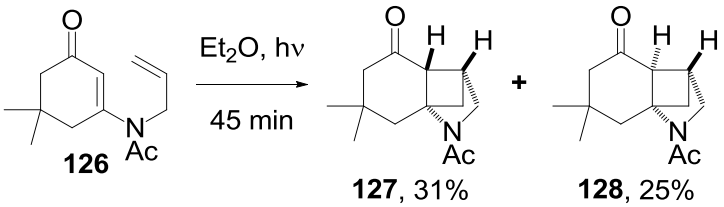
bridgehead carbon, which due to the ring strain introduced would be very high in energy.



Scheme 55

1.5.6.2. Intramolecular [2+2] photocycloadditions of vinylogous imides

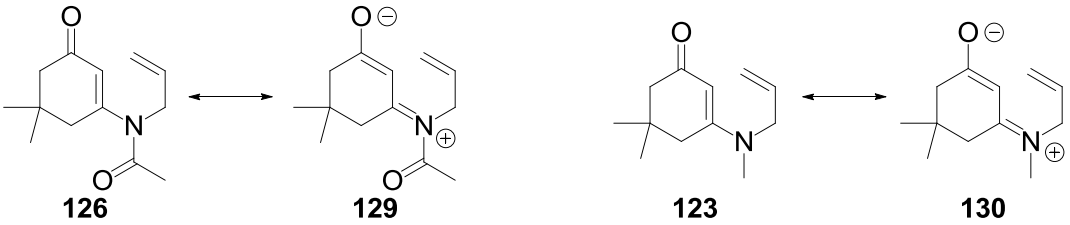
In many cases, these tertiary vinylogous amides take the form of vinylogous imides; that is where the amine portion is substituted for an amide moiety. Tamura *et al.* again showed that irradiation of vinylogous imide **126** gives diastereomeric cyclobutanes **127** and **128**, which are stable to the retro-Mannich fragmentation (**Scheme 56**).[128]



Scheme 56

The difference between the intramolecular [2+2] photocycloaddition reactions of vinylogous amide **123** and vinylogous imide **126** demonstrates the importance of the vinylogous imide functionality over that of the vinylogous amide. In both cases there is a tertiary nitrogen atom, however with vinylogous amide **123** the reaction takes 10 hours, whereas with vinylogous imide **126**, containing the acetyl group, the reaction is complete within 45 minutes. A possible explanation for this is that the electron withdrawing nature of the acetyl group decreases the electron density at the enone. By tying up the nitrogen lone pair in an acetyl group, the contribution from resonance form **129** to the overall structure of vinylogous imide **126** will be lower than the contribution of resonance form **130** to vinylogous amide **123** (**Scheme 57**). This means that that there will be overall greater enone character in the vinylogous imide, favouring the chances of a reaction taking place as it does so at the enone. This would result in an

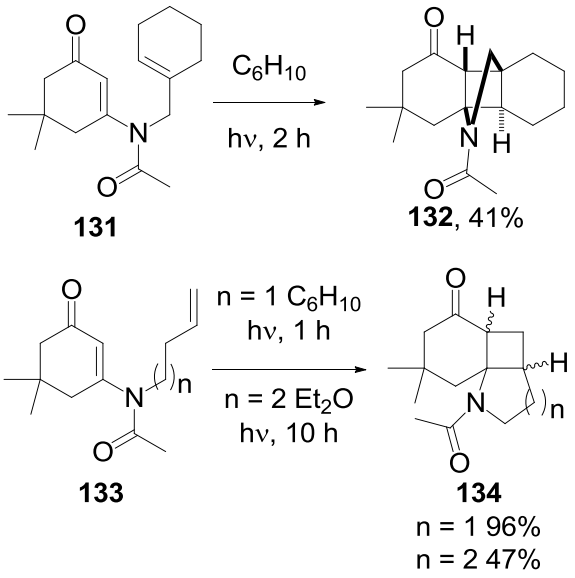
increase in the rate of reaction. In contrast to this, vinylogous amide **123** will have more imine character than **126**, thus the reaction which takes place at the enone will be disfavoured. In cases where the reaction is so slow that it appears not be taking place at all, this method could be a useful way of making the reaction viable.



126 **129** **123** **130**

Scheme 57

Schell *et al.* later further developed the intramolecular vinylogous imide-alkene [2+2] photocycloaddition reaction. Irradiation of vinylogous imide **131** affords cyclobutane **132** (**Scheme 58**).[129] Tamura *et al*. then showed that similar reactions take place with vinylogous imides **133**, containing tethered alkenes on four or five carbon chains, forming aminocyclobutanes **134** (**Scheme 58**).[130]

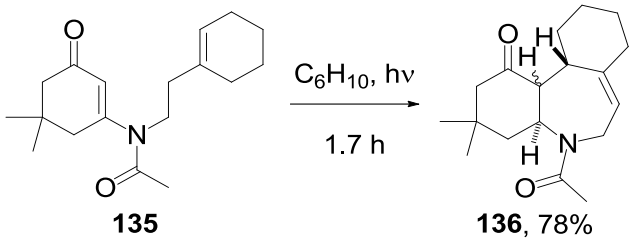


131 **132**, 41%

133 **134**
n = 1 96%
n = 2 47%

Scheme 58

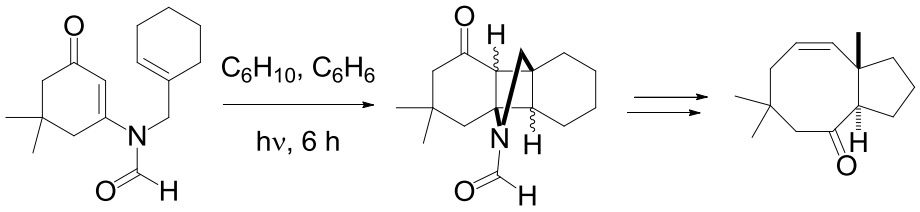
It interesting to note that, in contrast to these reactions, upon irradiation of vinylogous imide **135**, it undergoes an ene reaction to form keto-amide **136** rather than a [2+2] photocycloaddition (**Scheme 59**).[131] The reason for this is unclear, although it is possible that the conformation of the molecule prevents the [2+2] photocycloaddition taking place efficiently.



135 **136**, 78%

Scheme 59

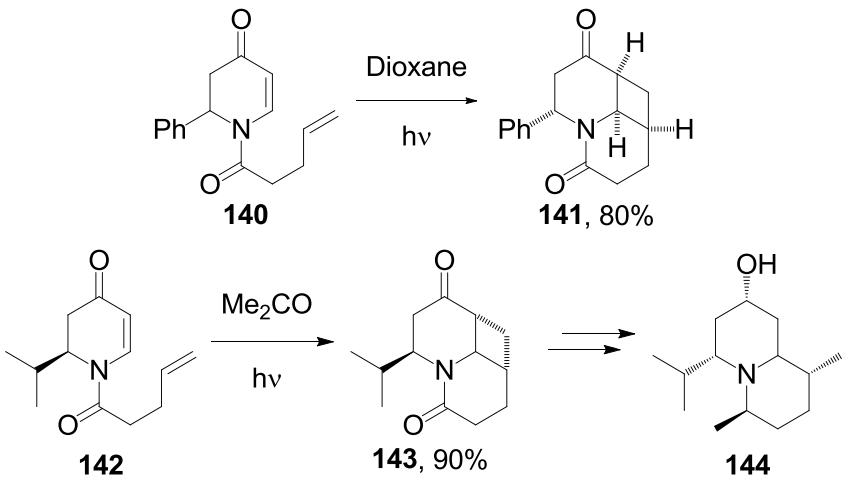
It has been shown that the imide functionality does not have to be comprised of an acetyl group. Swindell *et al.* used an N-formyl group in the synthesis of the core of the natural product taxane **137** starting from vinylogous imide **138** *via* cyclobutane **139** (**Scheme 60**).[132,133]



138 **139**, 69% **137**

Scheme 60

Adamson *et al.* and Comins *et al.* report similar reactions, in this case with the nitrogen atom of the vinylogous imide contained within a ring and the alkene tethered directly to the vinylogous imide functionality. Irradiation of vinylogous imide **140** affords tricycle **141** (**Scheme 61**),[134] whilst irradiation of vinylogous imide **142** affords cyclobutane **143**. Further transformations of **143** afforded the putative structure of the alkaloid, Plumerinine **144** (**Scheme 61**).[135]

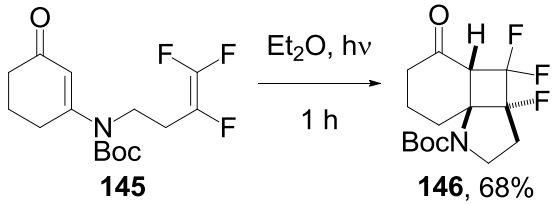


140 **141**, 80%

142 **143**, 90% **144**

Scheme 61

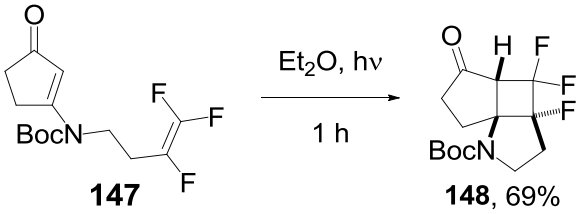
Bach *et al.* have shown that an N-Boc vinylogous imide with a trifluoro-substituted alkene tether **145** undergoes an intramolecular [2+2] photocycloaddition to afford the trifluorinated N-Boc-aminocyclobutane **146** (**Scheme 62**).[111]



145 **146**, 68%

Scheme 62

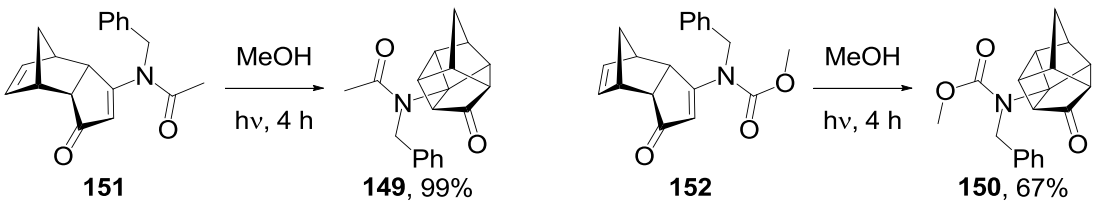
The same group also showed that the intramolecular [2+2] photocycloaddition reaction of vinylogous imides can be further extended to those within five membered rings; irradiation of vinylogous imide **147** affording aminocyclobutane **148** (**Scheme 63**).[111]



147 **148**, 69%

Scheme 63

Bakkeren *et al.* have used a [2+2] photocycloaddition method to synthesise caged products **149** and **150** from vinylogous imides **151** and **152** respectively (**Scheme 64**).[136] These products would be very difficult to synthesise under thermal conditions due to their very highly strained nature.

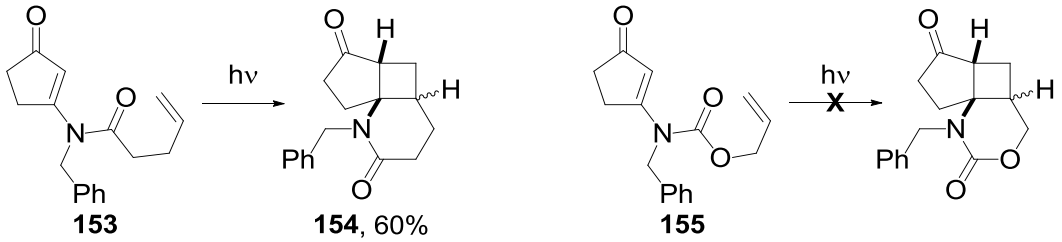


151 **149**, 99% **152** **150**, 67%

Scheme 64

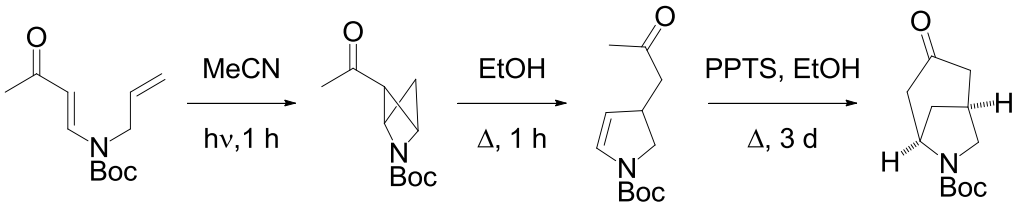
It has been reported that the alkene unit and amide moiety can be combined into a single tether with vinylogous imides contained in five membered rings. Piva *et al.* report that irradiation of vinylogous imide **153** affords cyclobutane **154** as a mixture of diastereomers. However, upon irradiation of vinylogous

imide **155**, where one of the carbon atoms has been replaced by an oxygen atom, no reaction is observed (**Scheme 65**). This is reported to be due to the decreased flexibility of the pendant chain introduced by the inclusion of an oxygen atom. This means that the molecule cannot get into a conformation from which a reaction is possible.[137]



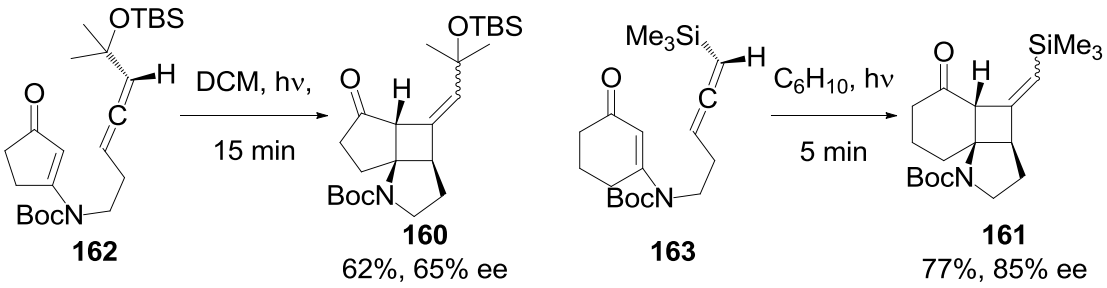
Scheme 65

As with the [2+2] photocycloaddition reactions with vinylogous amides, an open chain variant has been reported. Using a vinylogous imide with one carbon between the nitrogen and a tethered alkene, along with a Boc-protected nitrogen **156**, the 'crossed' cyclobutane **157** is formed which does not undergo the retro-Mannich fragmentation. Instead fragmentation is achieved under thermal conditions to give enamine **158**. Mannich cyclisation of this enamine can be carried out under acid catalysis using pyridinium *p*-toluenesulfonate, affording the bicycle **159** (**Scheme 66**).[138]



Scheme 66

Shepard *et al.* have shown that the [2+2] photocycloaddition of vinylogous imides is also possible with tethered allenes. Furthermore, using an optically active allene, the cycloaddition can be made enantioselective; cyclobutanes **160** and **161** being synthesised upon irradiation of vinylogous imides **162** and **163** respectively in good enantioselectivities (**Scheme 67**).[103,139]

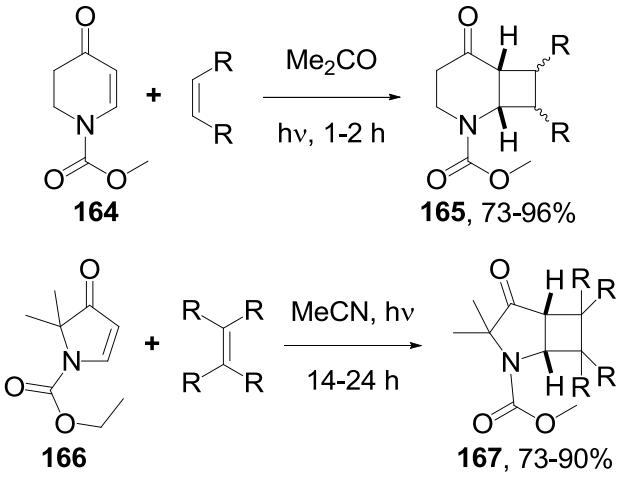


Scheme 67

1.5.6.3. Intermolecular [2+2] photocycloadditions of vinylogous imides

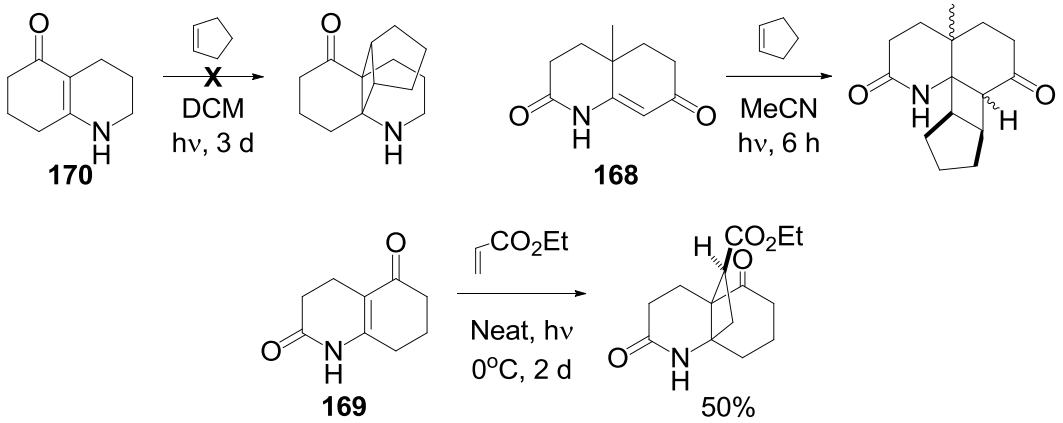
Reports of the intermolecular enone-alkene [2+2] photocycloadditions of vinylogous amides appear to be entirely absent from the literature. Although the reason for this is unknown, it is likely that this is due to the excited state of the vinylogous amide being short lived. If this is the case then only alkenes in close proximity to the enone would undergo any reaction, thus intermolecular reactions are possibly too slow to be observed. This is in contrast to intramolecular reactions, where the relative local concentration of the alkene is significantly higher.

There are also very limited reports of the intermolecular reaction with vinylogous imides. Guerry *et al.* report the intermolecular [2+2] photocycloaddition of vinylogous imide **164** with a series of alkenes to give cyclobutanes **165** (**Scheme 68**).[140] Patjens *et al.* report a similar reaction with a five membered ring vinylogous imide **166** and various alkenes to give give similar cyclobutanes **167** (**Scheme 68**, R=H, Me or OMe).[141] These reactions are useful as they allow the synthesis of cyclobutanes without the necessity of it being tethered to the amine.



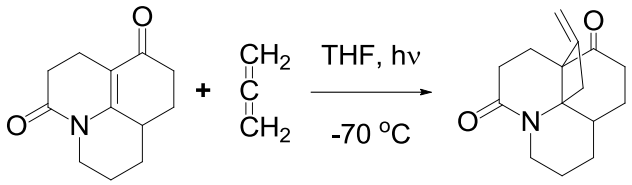
Scheme 68

Cantrell[142] and Wiesner *et al.*[143] describe intermolecular reactions of vinylogous imides **168** with cyclopentene and **169** with ethyl acrylate respectively (**Scheme 69**). Cantrell, however, reports that a similar vinylogous amide **170** does not undergo any reaction with cyclopentene, suggesting that the conjugated carbonyl group is vital for the reaction to take place (**Scheme 69**). Further to the argument of lifetimes of excited states outlined above, the reason for this could be the same as the difference in rates between intramolecular [2+2] photocycloadditions of vinylogous amides and vinylogous imides with alkenes. The electron withdrawing group serves to increase the double bond character at the enone, speeding up the reaction. In the intermolecular reaction however, the reactions of vinylogous amides are so slow that no reaction takes place.



Scheme 69

Finally, Wiesner *et al.* also describe a similar intermolecular photocycloaddition of vinylogous imide **171**, this time with an allene (**Scheme 70**).[144]



Scheme 70

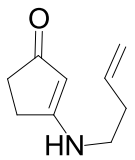
According to the literature review carried out here, these are the only examples of intermolecular [2+2] photocycloadditions of vinylogous amides or imides in the literature. It would be useful to further extend this mode of reactivity in order to synthesise a variety of different aminocyclobutanes. This extension is one of the aims of this project.

2. Results and discussion

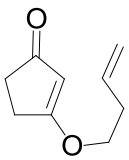
2.1 Aims

This project aims to broaden the scope of viable photochemical reactions, in particular vinylogous amide-alkene [2+2] photocycloadditions. This is an important class of reactions as it allows for the rapid construction of aminocyclobutanes which may be inaccessible *via* standard thermal means. As mentioned previously, these are not only interesting structures in their own right, for example as possible drug candidates, but the release of the ring strain associated with cyclobutanes can be utilised to drive further reactions. Although a number of [2+2] photocycloadditions of vinylogous amides and imides with alkenes have been reported, they are primarily directed towards acyclic vinylogous amides,[120-123,138] and those contained in six membered ring systems[111,118,124,125,128-130,132-135,140,142,143] as outlined in the introduction (**Chapter 1.5.6**). Notably only four examples of the [2+2] photocycloaddition of vinylogous amides and imides contained in five membered rings exist in the literature.[111,136,137,141] It is postulated that this relative lack of literature reports may have been due to secondary photoreactions occurring upon irradiation. Previous work within the group developed a solution to this problem in the case of vinylogous esters by using reducing agents to remove the chromophore from the product by an *in situ* reduction (**Chapter 1.4**).[34] The initial aim of this project is to see if this methodology is viable with vinylogous amides.

The system chosen to test this hypothesis was vinylogous amide **172**, an analogous system of the vinylogous ester **6** used previously, and a system notably absent from the literature (**Figure 11**).



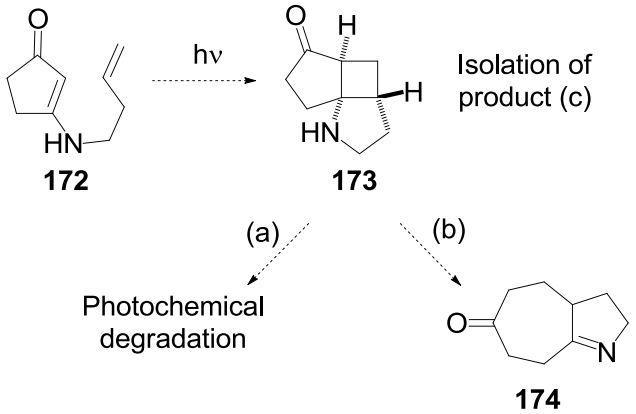
172



6

Figure 11

If a [2+2] photocycloaddition did take place with **172**, one of three things would occur: The aminocyclobutane product **173** could undergo secondary photoreactions and degrade (a, **Scheme 71**); a retro-Mannich fragmentation to give an imine **174** could take place, as has been found with other vinylogous amides in the literature (b);[120-127] or **173** would be stable to both secondary photoreactions and retro-Mannich fragmentation (c).

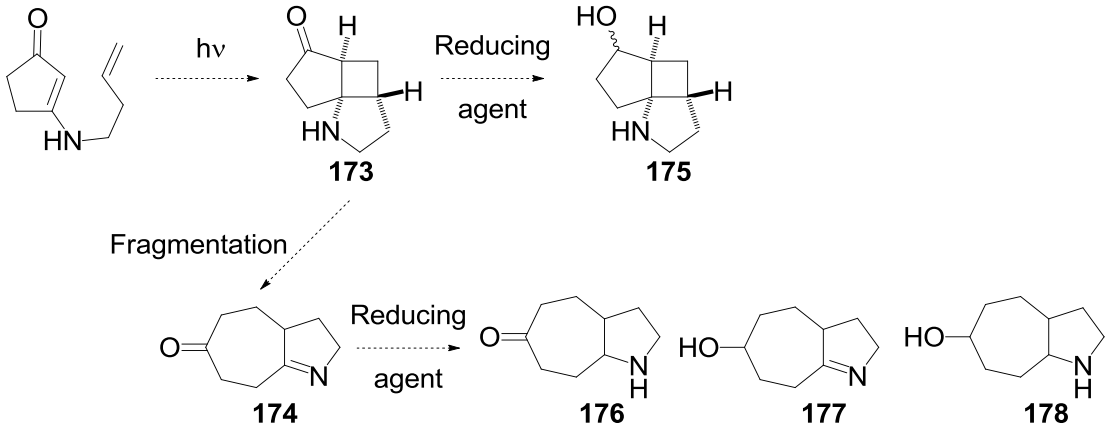


172 **173** **174**

Scheme 71

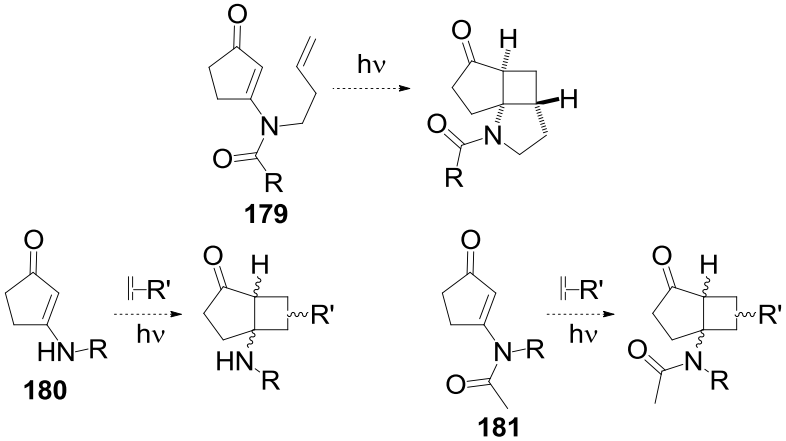
It should be noted that the stereochemistry in **173** is set by the 5,4,5 ring system. It is impossible for the ring junction between a five membered ring and a four membered ring to be *trans* fused, thus the two protons at the ring junctions must be on opposite faces.

Imine **174** still retains a chromophore, so it is possible that this would also undergo secondary photoreactions if it were to form. If it was found that secondary photoreactions were to occur from either product, the next aim would be to employ the *in situ* trapping strategy using hydride reducing reagents to circumvent this.[34] Furthermore, this strategy could possibly prevent the retro-Mannich fragmentation occurring as the ketone is necessary for the fragmentation to take place. If the reduction is quicker than the fragmentation, cyclobutane **175** could be isolated, whereas if the fragmentation took place faster than the reduction of the ketone in **173**, fragmentation would still take place. In this case, reduction would likely take place at the imine, the ketone or possibly both to give **176**, **177** or **178** respectively (**Scheme 72**).



Scheme 72

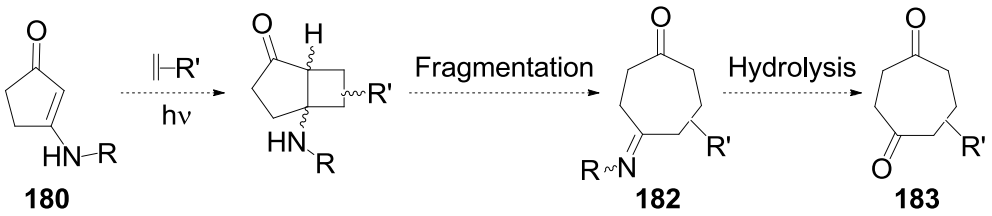
If secondary photoreactions were not observed to be a problem with this vinylogous amide, the next step would be to synthesise a series of other vinylogous amides to test the scope of this reaction. An acetylated, or Boc protected vinylogous amide, vinylogous imide **179** could be used to stop the retro-Mannich reaction if it were to take place.[128] Other vinylogous amides **180**, and related, Boc protected and acetylated vinylogous imides **181** could be synthesised in order to test the intermolecular [2+2] photocycloadditions of these compounds with alkenes (**Scheme 73**). It could be hypothesised from the work of Cantrell and Wiesner *et al*. that, whilst the intermolecular [2+2] photocycloaddition of vinylogous amides with alkenes may not work, using the related vinylogous imides, a reaction may well take place.[142,143]



Scheme 73

If the intermolecular reaction was found to work, then it is again possible that a retro-Mannich fragmentation would occur to give imine **182**. Hydrolysis of this would give access to de Mayo products, diketones **183** (**Scheme 74**). There are

few literature reports of de Mayo products, especially in seven membered ring systems, which suggests that in many cases, the de Mayo reaction does not work well. Therefore this method may be a useful alternative to the classic de Mayo reaction.

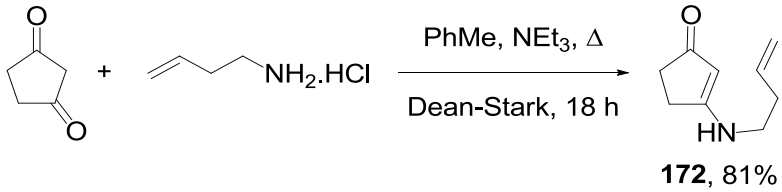


Scheme 74

2.2 Results and Discussion

2.2.1 Intramolecular [2+2] photocycloadditions of vinylogous amides

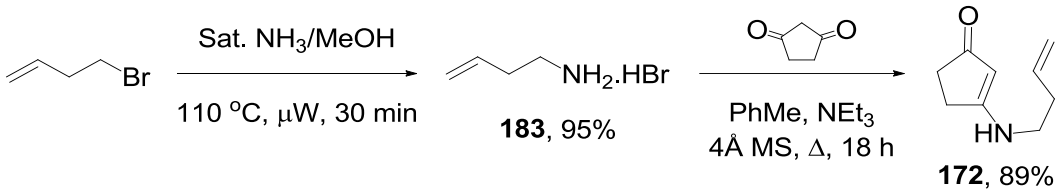
The initial synthesis of the first vinylogous amide for this project, vinylogous amide **172**, was carried out *via* a condensation reaction between 1,3-cyclopentadione and 3-buten-1-amine hydrochloride using triethylamine as a base (**Scheme 75**). In order to push this condensation reaction to completion, a Dean-Stark apparatus was used to actively remove water from the reaction mixture. The reaction proceeded in 81% yield.



Scheme 75

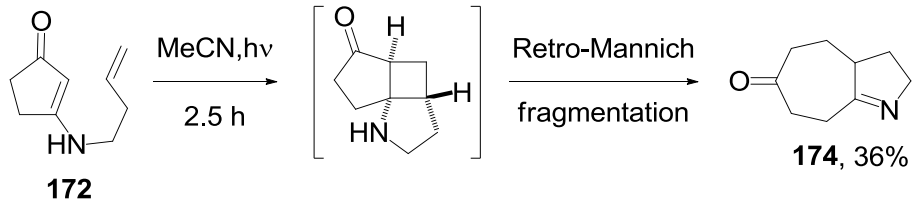
Although this reaction proved successful, an alternative way of synthesising this vinylogous amide was investigated as the amine hydrochloride is very expensive. Using the method of Dieltiens *et al.*[145] and Saulnier *et al.*[146] which utilise an alkyl bromide, in this case 3-bromo-1-butene, under microwave heating in saturated ammonia in methanol, a nucleophilic substitution to form amine **183** was achieved in 95% yield. **183** was used without further purification in the condensation reaction with 1,3-cyclopentadione, giving a slightly higher

yield (89%) than using the hydrochloride salt. Molecular sieves (MS) were used in this reaction to actively remove the forming water as they are more efficient than Dean-Stark apparatus on a small scale. This too may account for the slightly elevated yield (**Scheme 76**).



Scheme 76

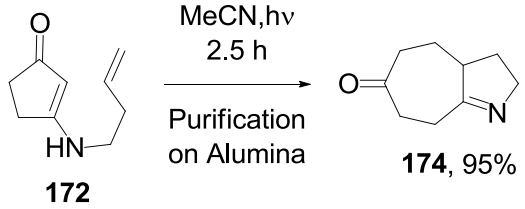
Before irradiation of this vinylogous amide was carried out, a general procedure was decided upon for all irradiations in this project. In all cases, irradiation was carried out in acetonitrile through Pyrex® glassware using a 125 W medium pressure lamp, unless otherwise stated. Upon irradiation of vinylogous amide **172**, all of the starting material was consumed within 2.5 hours, and upon column chromatography, the keto-imine **174** was isolated in 36% yield. This suggests that the [2+2] photocycloaddition had taken place and, as expected, was followed by a spontaneous retro-Mannich fragmentation (**Scheme 77**).



Scheme 77

Due to the low yield of the reaction, it was decided that the reaction should be attempted again, using the triplet sensitiser acetone as the solvent. This change led to a lowering of the yield to 19%, although the reaction was significantly faster, requiring only 45 minutes to go to completion. It is presumed that this decrease in yield is down to the triplet sensitiser allowing access to different reaction pathways. In the reactions using either acetonitrile or acetone, the purification by column chromatography was particularly difficult, postulated to be due to the product degrading on silica gel. This hypothesis is supported by the returned mass-balance from the column being significantly lower than that loaded onto the column. To avoid this, purification was attempted using basic

aluminium oxide (alumina) in place of silica gel. Returning to using acetonitrile as the solvent in the irradiation and using alumina in the purification, the yield was increased to 95% (**Scheme 78**).

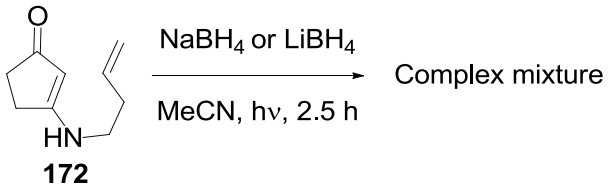


172 **174**, 95%

Scheme 78

It was clear from this result that secondary photoreactions were not an issue in this reaction. There are two possible reasons for this. First, the intermediate cyclobutane might not absorb efficiently enough for secondary photoreactions to take place. This is unlikely as the analogous vinylogous ester was shown to undergo secondary photoreactions[34] and, as the heteroatom is no longer in conjugation with the ketone, the difference in electronics between the aminocyclobutane and alkoxycyclobutanes would be minimal. More likely is that the retro-Mannich fragmentation takes place significantly faster than any secondary photoreactions do, and the resultant keto-imine does not undergo secondary photoreactions itself.

Whilst this synthesis of these 7,5-keto-imines is novel and interesting, finding a way to isolate the more structurally complex aminocyclobutanes was considered important given their potential applications. Thus having ascertained that the [2+2] photocycloaddition of vinylogous amide **172** did indeed work, attention was turned to attempting to stop the retro-Mannich reaction from occurring. It was hypothesised that this could be achieved by using *in situ* trapping reagents, as pioneered previously in the group.[34] Without the carbonyl moiety, the retro-Mannich fragmentation cannot take place. To this end, irradiation of vinylogous amide **172** was carried out in the presence of two equivalents of the reducing agents sodium borohydride or lithium borohydride (**Scheme 79**). However, both irradiations led to a complex mixture of products, and, despite numerous attempts at purification, no identifiable products could be isolated.

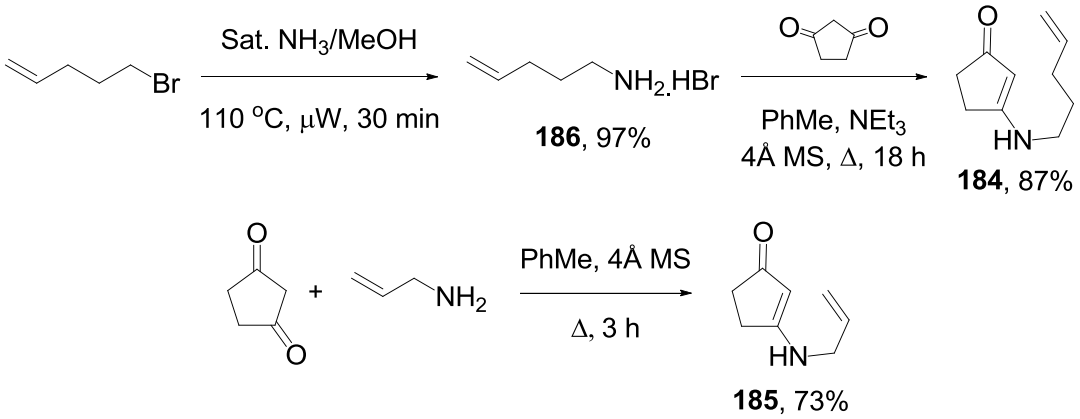


172

Scheme 79

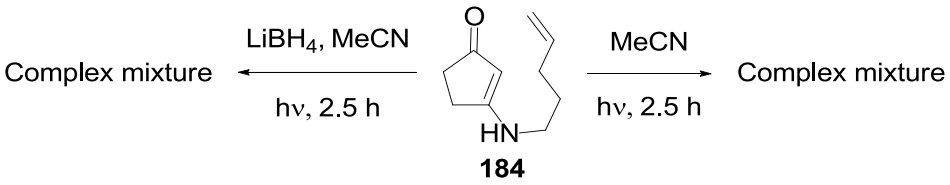
Given these complications, it was decided that this approach may not be viable. Instead it was decided to adopt the precedented approach of incorporating a group onto the nitrogen to prevent the retro-Mannich fragmentation taking place.[128] Results from the resultant study will be discussed later (**Chapter 2.2.2**), following a discussion of the results of an investigation into the scope of the [2+2] photocycloaddition-retro-Mannich fragmentation cascade reaction.

To test the scope of the cycloaddition-fragmentation reaction, vinylogous amides **184** and **185** were synthesised. These contain three and one carbon atoms between the enaminone nitrogen and the alkene respectively. 4-penten-1-amine is not commercially available, and had to be synthesised as the hydrobromide salt **186** from 5-bromo-1-pentene using the microwave conditions described before, in this case in 97% yield. Once again this was used in the condensation reaction with 1,3-cyclopentadione and triethylamine, affording **184** in 87% yield (**Scheme 80**). The synthesis of **185** was simplified as allylamine is commercially available. This condensation reaction did not require a base and was significantly quicker, complete conversion took place in three hours, affording **185** in 73% yield (**Scheme 80**).



Scheme 80

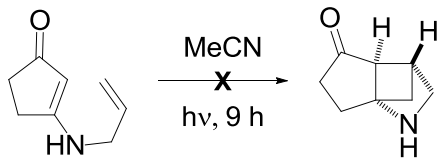
Irradiation of **184** for 2.5 hours led to complete consumption of starting material and a very complex mixture by crude ^{1}H NMR spectroscopy and TLC analysis (**Scheme 81**). Attempts to isolate any products from this mixture were fruitless. It is possible that the retro-Mannich fragmentation is not occurring in this reaction, and that this complex mixture is at least in part due to secondary photoreactions. Upon irradiation of this vinylogous amide in the presence of lithium borohydride, in the hope of possibly preventing any secondary photoreactions, a complex mixture was once more obtained from which again, no products could be isolated (**Scheme 81**). It is possible that in this case, the reduction of the ketone was slower than the secondary photoreactions. Due to these outcomes, this reaction was not taken further.



184

Scheme 81

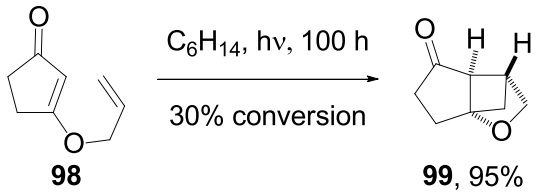
Attention was next turned to the photochemistry of vinylogous amide **185**. It was hypothesised from the rule of five[66,67] that the [2+2] photocycloaddition of **185** would most likely give the crossed product **187**. However, upon irradiation of **185** no reaction was observed after 9 hours other than slight degradation of the starting material, as monitored by TLC and crude ^{1}H NMR spectroscopic analysis. Increasing the concentration from 0.02 M to 0.10 M had no effect on the reaction (**Scheme 82**). It is likely that the rigidity of this system holds the molecule in an unfavourable conformation for the [2+2] photocycloaddition to take place. Indeed, construction of a 3D molecular model shows that overlap of the alkene with the enone is very difficult to achieve. This would slow the reaction significantly to the point where no reaction is observable.



185 **187**

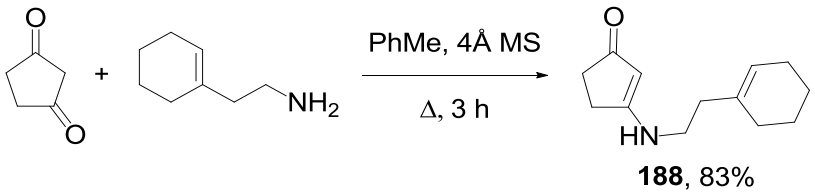
Scheme 82

This finding is in agreement with the findings for the corresponding vinylogous ester system published by Matlin *et al.*[30,147] As outlined in **Chapter 1.5.5.1**, they report that the intramolecular [2+2] photocycloaddition of **98** to give the crossed cyclobutane **99** takes 100 hours to reach 30% conversion (**Scheme 83**). With these results in mind it was decided not to further investigate this reaction.



Scheme 83

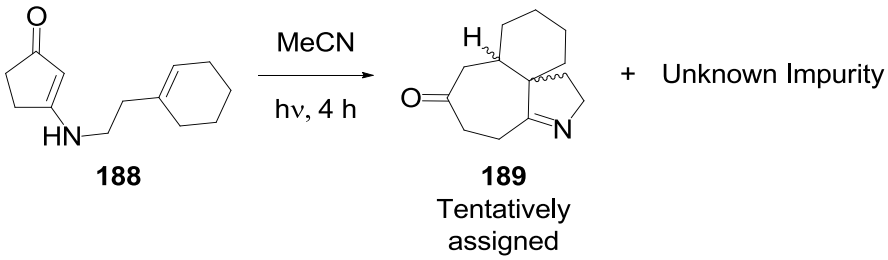
Given these results, and the positive result upon irradiation of vinylogous amide **172** with two carbons between the nitrogen and alkene, it was decided that the focus of the intramolecular [2+2] photocycloaddition reactions should be on other vinylogous amides with two carbons between the nitrogen and the alkene. To this end, attention was turned to the synthesis of **188**, as similar vinylogous amides, albeit in six membered rings, have been used previously in the literature.[125,131] The condensation reaction was carried under the conditions employed previously, in this case with 2-(1-cyclohexenyl)ethylamine, and **188** was afforded in 83% yield (**Scheme 84**).



Scheme 84

Irradiation of vinylogous amide **188** for four hours led to complete consumption of starting material by TLC analysis and a mixture of products. Purification of this mixture proved very difficult due to its complex nature. Although it could not be fully purified, an impure product was obtained which has tentatively been assigned as **189** as a mixture of diastereomers by careful examination of the ^{1}H and ^{13}C NMR spectra. This assignment comes from two peaks in the ^{13}C NMR spectrum at 213 ppm and 209 ppm corresponding to the two ketones from the different diastereomers, as well as peaks at 183 ppm and 182 ppm for the

imines. Furthermore, comparison of these NMR spectra with the ones obtained for the previously formed keto-imine **174** further supports this assertion. Keto-imine **189** is formed from the [2+2] photocycloaddition, followed by the retro-Mannich fragmentation pathway as before (**Scheme 85**). Despite numerous attempts to separate this product from the other impurities, it proved impossible to get it clean enough to unequivocally confirm its structure. Furthermore, due to extensive overlap of peaks in the ^{1}H NMR spectrum of this mixture, especially at chemical shifts between 0 and 3 ppm, the nature of this impurity could not be speculated upon.



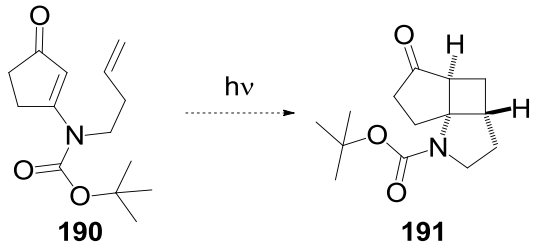
188 **189** Tentatively assigned

Scheme 85

Given the problems with other vinylogous amides, it was decided that attention should focus on the reaction with vinylogous amide **172** and an attempt to circumvent the retro-Mannich fragmentation in order to access the desired aminocyclobutane.

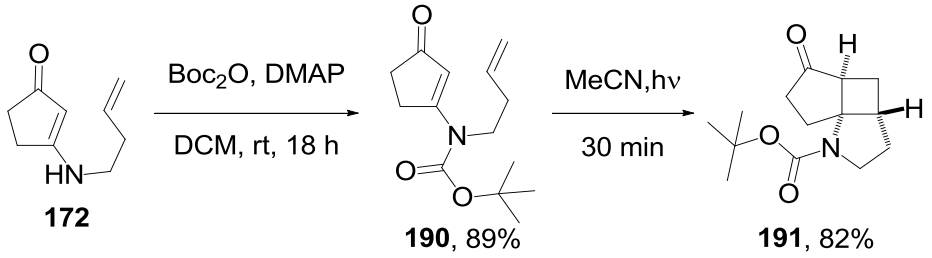
2.2.2 Intramolecular [2+2] photocycloadditions of vinylogous imides

Given the literature reports suggesting that tertiary vinylogous amides and vinylogous imides do not undergo the retro-Mannich fragmentation,[128-130,132-144] it was decided that this would be the starting point for the investigation to circumvent this fragmentation. The majority of these reports are concerned with intramolecular [2+2] photocycloadditions of vinylogous imides containing an N-acetyl group. However, as the free aminocyclobutanes were desired, but cyclobutanes can be sensitive to harsh conditions such as those used in acetyl deprotection, the Boc group was chosen as it can be removed easily at room temperature. Given these considerations, it was hypothesised that irradiation of vinylogous imide **190** would afford aminocyclobutane **191** which should be stable to retro-Mannich fragmentation (**Scheme 86**).



Scheme 86

Vinylogous imide **190** was synthesised by treatment of **172** with Boc anhydride (Boc_2O) and N,N-dimethylaminopyridine (DMAP) in DCM overnight at room temperature in 89% yield (**Scheme 87**). Irradiation of **190** for half an hour led to complete consumption of the starting material and the formation of aminocyclobutane **191** in an excellent 82% yield (**Scheme 86**). As expected, this aminocyclobutane did not undergo retro-Mannich fragmentation. The ^{1}H and ^{13}C NMR spectra of **191** show the presence of rotamers, presumably due to the limited rotation around the carbamate bonds of the Boc group. However, these resolve into a single species upon running the NMR experiments at 330 K.



Scheme 87

This reaction is significantly quicker than the corresponding reaction of the free vinylogous amide. This can be rationalised in part by considering the relative enone characters contained within the two compounds. Due to the delocalisation of the nitrogen lone pair of vinylogous amide **172** into the enone, there will be a significant contribution to the overall structure from resonance form **192** (**Figure 12**). This results in vinylogous amide **172** having greater imine character and less enone character, and as the [2+2] photocycloaddition requires an enone, the reaction is slowed. In contrast to this however, the lone pair in vinylogous imide **190** is partially delocalised into the Boc group as well as the enone, thus there will be a smaller contribution to the overall structure from

resonance form **193**. This results in a greater enone character in the vinylogous imide, increasing the rate of the [2+2] photocycloaddition reaction.

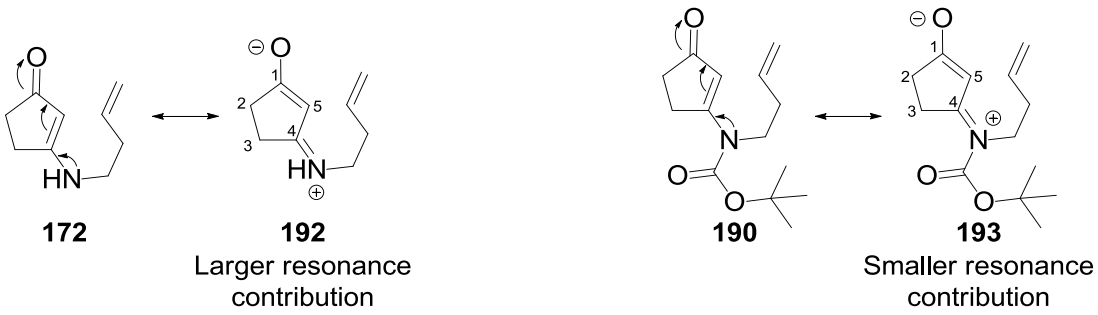
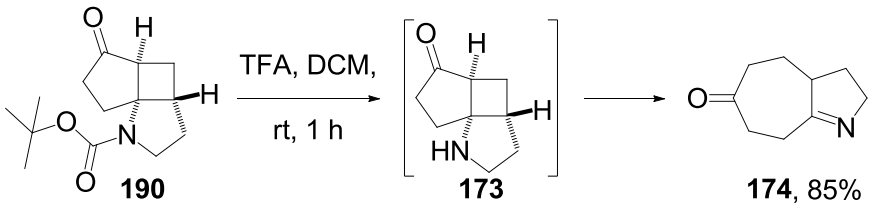


Figure 12

This can also be visualised as the relative electron density at C-5 which can be shown quantitatively by looking at both the ^{13}C NMR chemical shift of C-5 and the ^{1}H NMR chemical shift of the corresponding proton. The more shielded the carbon nucleus is, the greater the electron density is, suggesting that the nitrogen lone pair is more delocalised into the enone. These shifts are 5.00 ppm for the proton and 99.3 ppm for the carbon in **172**, whereas in **190** they are 5.62 ppm and 112.4 ppm respectively. These chemical shifts show that the carbon, and hence the enone moiety in **172**, is more shielded thus has greater electron density due to more extensive delocalisation of the nitrogen lone pair.

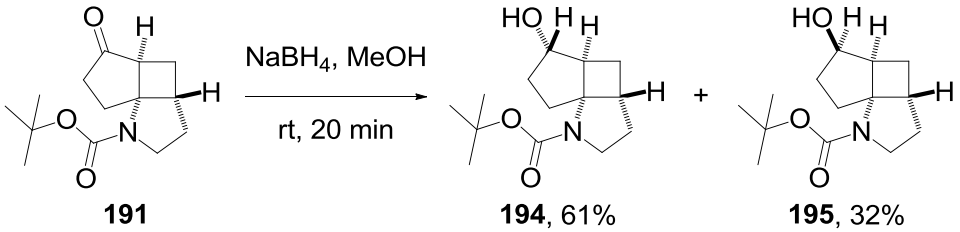
In order to demonstrate that the free aminocyclobutane **173** was highly labile to fragmentation, and that the retro-Mannich reaction was occurring thermally and not photochemically, the Boc group was removed from cyclobutane **191**. As expected the only product isolated was keto-imine **174** in 85% yield and none of the aminocyclobutane **173** was observed (**Scheme 88**).



Scheme 88

Given the interest in aminocyclobutanes, it was important to find a way of removing the Boc group without the retro-Mannich fragmentation taking place.

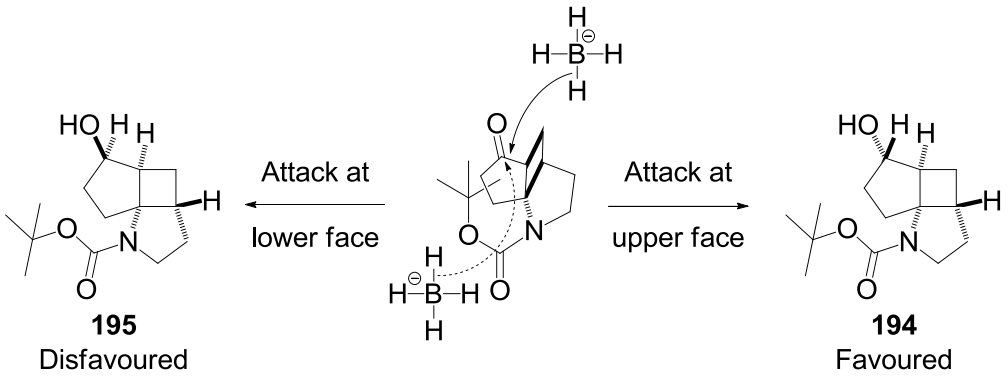
Given the mechanism of the retro-Mannich reaction, it was postulated that removal of the ketone moiety would stop the fragmentation from occurring. It was felt that reduction of the ketone would be the easiest method to achieve this. Cyclobutane **191** was thus treated with two equivalents of sodium borohydride in methanol to afford alcohols **194** and **195** in 61% and 32% yield respectively (**Scheme 89**). Although it proved impossible to distinguish between the major and minor isomers at this stage due to significant overlap of the peaks in the ^{1}H NMR spectra, the relative stereochemistry could be inferred after the Boc group was removed (*vide infra*).



191 **194**, 61% **195**, 32%

Scheme 89

The major isomer was that from which the hydride attack takes place from the top face as drawn. It is postulated that the selectivity of this reduction is due to the lower face of the ketone being partially blocked by the other five-membered ring and in particular the Boc group which is fixed almost directly below the ketone. The top face however is relatively less hindered, with only the much smaller four-membered ring causing any steric hindrance (**Figure 13)**.



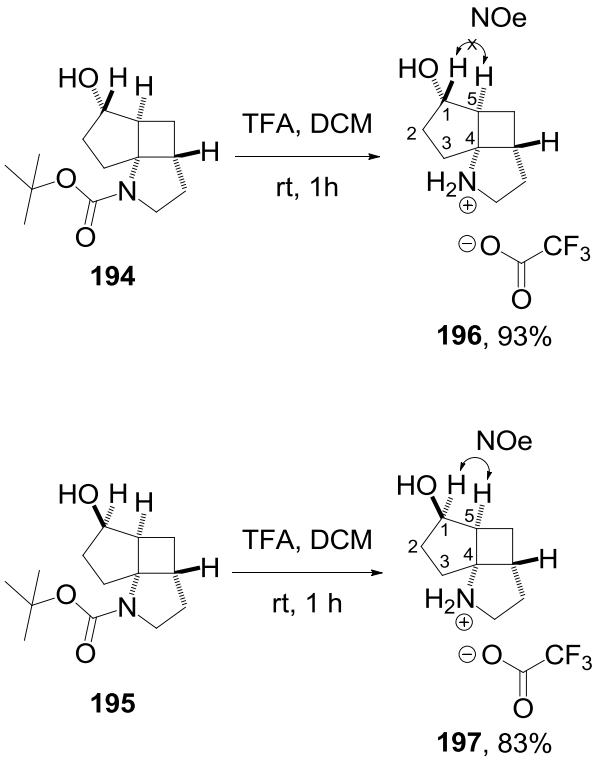
195
Disfavoured

194
Favoured

Figure 13

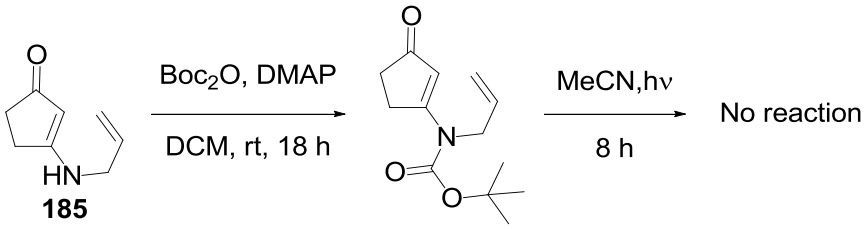
Having separated the two alcohols **194** and **195**, they were individually treated with a 1:1 mixture of TFA and DCM to remove the Boc groups. As hypothesised, without the ketone in place, the retro-Mannich fragmentation

could not take place, and the TFA salts of aminocyclobutanes **196** and **197** were isolated in 93% and 83% yield respectively (**Scheme 90**). The relative stereochemistry of each cyclobutane could be identified at this stage by a NOeSY NMR experiment, which showed an NOe between H-1 and H-5 in **197** which was not present in **196**.



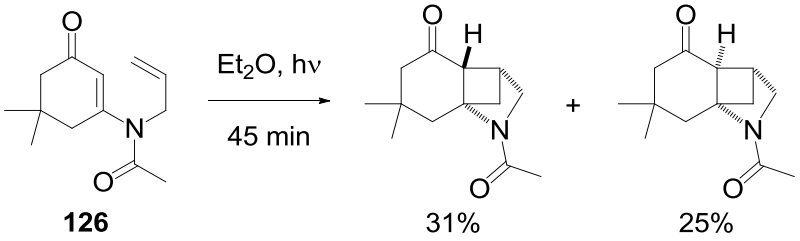
Scheme 90

With this success in mind, attention was turned to the reaction of vinylogous imide **198**, with one carbon between the vinylogous imide nitrogen and the alkene. The free vinylogous amide was unreactive upon irradiation (**Chapter 2.2.1**), and it was hoped that the increase in the rate of reaction seen previously with the vinylogous imides would lead to an observable reaction. Synthesis of **198** was achieved *via* a Boc protection as before in 88% yield from vinylogous amide **185** (**Scheme 91**). However, irradiation of vinylogous imide **198** led to no observable reaction by TLC analysis or ^{1}H NMR spectroscopy, even after 8 hours of irradiation (**Scheme 91**).



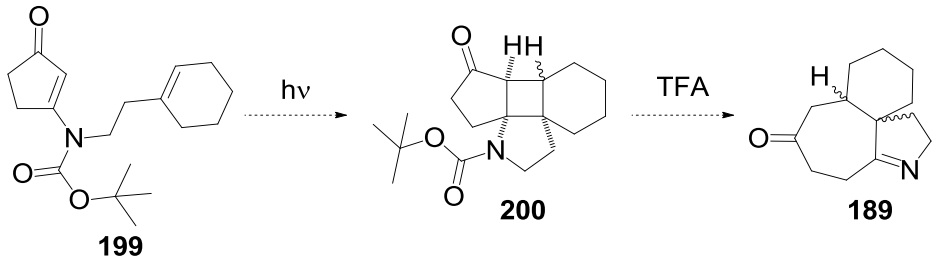
Scheme 91

This lack of reactivity is in agreement with the rigid structure of the compound not allowing sufficient overlap of the enone and the alkene to allow the reaction to take place, as was seen with the free vinylogous amide **185**. However, this is in contrast to an analogous six-membered ring system described by Tamura *et al.* (**Scheme 92**) where the reaction of vinylogous imide **126** takes place in just 45 minutes as mentioned previously in **Chapter 1.5.6.2**.[128] Evidently however, the difference in the structure between the five and six membered rings gives rise to this significant difference in reactivity.



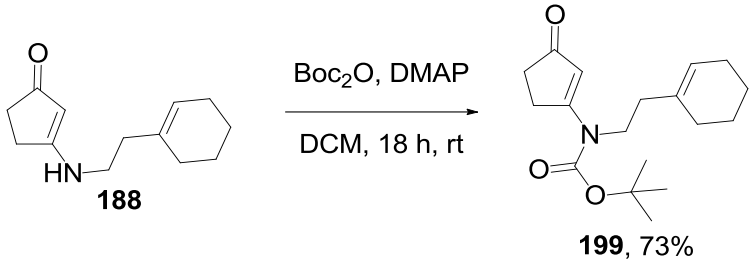
Scheme 92

Returning to vinylogous imides with two carbons between the nitrogen and the alkene, it was hoped that the Boc protection method could be used with vinylogous amide **188**. Boc protection of **188** would afford vinylogous imide **199**, irradiation of which could be carried out to obtain aminocyclobutane **200** (**Scheme 93**). Furthermore, this method could also allow access to keto-imine **189**, since it could not be isolated cleanly by direct irradiation (**Scheme 84**, above).



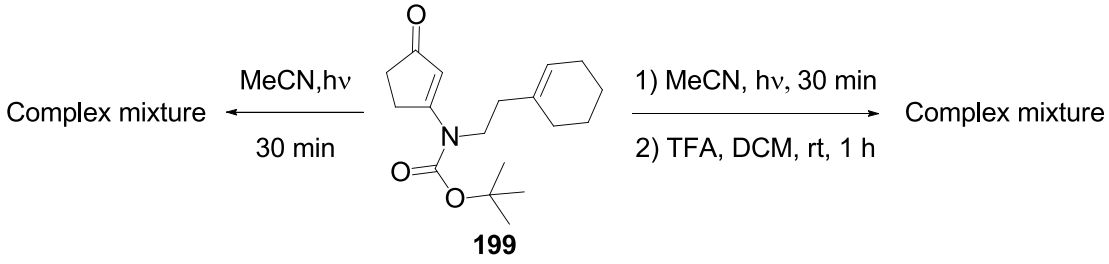
Scheme 93

To this end vinylogous amide **188** was Boc protected *via* the standard conditions, affording vinylogous imide **199** in 73% yield (**Scheme 94**).



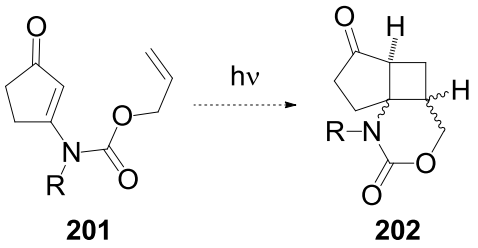
Scheme 94

Irradiation of vinylogous imide **199** led to complete consumption of starting material in 30 minutes. Unfortunately the resulting mixture was highly complex, comprising multiple compounds from which none of the desired cyclobutanes could be isolated (**Scheme 95**). Furthermore, it could not be established if the cyclobutanes were present in the mixture due to the complex nature of the crude ^{1}H NMR spectrum. Treatment of this crude mixture with TFA led to another complex mixture from which no clean products could be isolated (**Scheme 95**). However, inspection of the crude ^{13}C NMR spectrum and comparison with the spectrum taken for the impure sample of keto-imine **189** previously obtained, suggested that none of the keto-imine was present. It is believed that this irradiation suffers from significant side reactions or that the cyclobutanes are degrading, precluding isolation.



Scheme 95

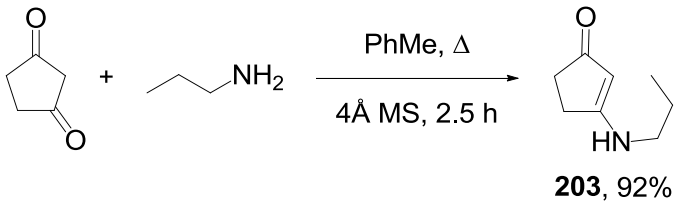
Attention was next turned to attempting to combinine both the alkene and the carbamate moieties into a single tether, such as in vinylogous imide **201**. It was felt that these substrates would give interesting photoproducts and that the R group on the amine could be varied to furnish a series of cyclobutanes containing a cyclic carbamate **202** (**Scheme 96**).



201 **202**

Scheme 96

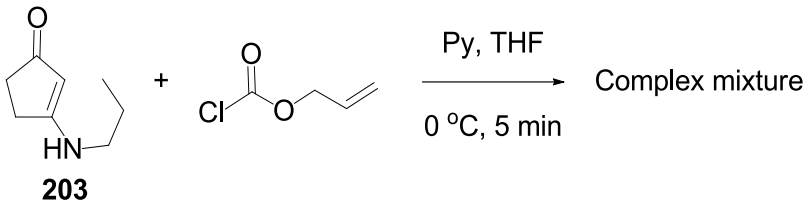
The most direct way to these vinylogous imides was envisaged to be *via* the reaction of a vinylogous amide with allyl chloroformate. For this reaction however, a different vinylogous amide without a tethered alkene had to be synthesised. To this end, vinylogous amide **203** was synthesised from 1,3-cyclopentadione and propylamine using 4 Å molecular sieves in 92% yield (**Scheme 97**).



203, 92%

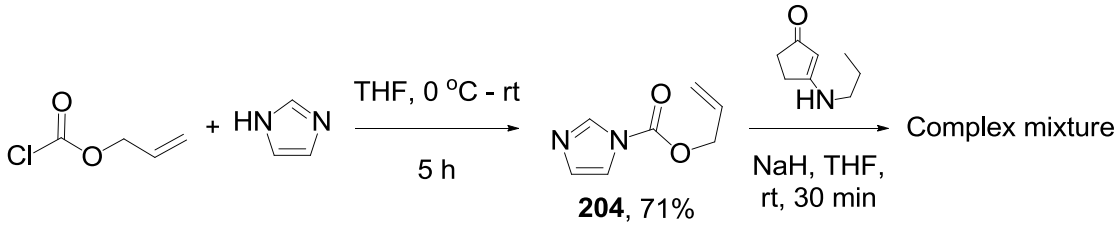
Scheme 97

Using modified conditions to those reported by Meggers *et al.*, allyl chloroformate was added to a solution of vinylogous amide **203** and pyridine.[148] The mixture immediately changed colour from a clear solution to red and then black, TLC analysis showing that multiple products had formed (**Scheme 98**). Attempts at purifying this mixture were unsuccessful, and the crude ^{1}H NMR spectrum showed no peaks for the enone alkene proton suggesting that the vinylogous amide had degraded or that addition had taken place at the carbon.



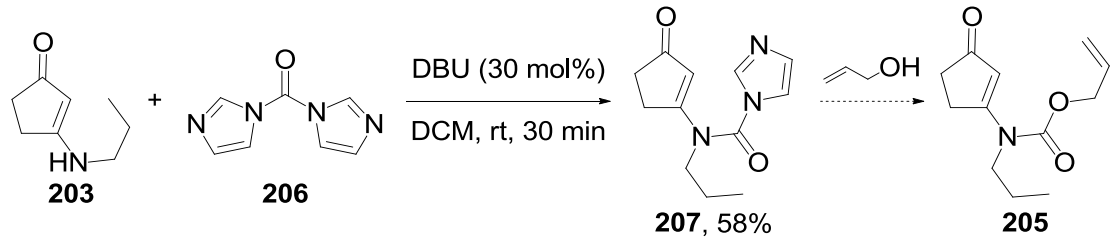
Scheme 98

It was thought that the chloroformate might be too reactive for this reaction to proceed cleanly. To avoid this, it was hoped that the imidazole amide **204**, synthesised *via* the method of Sarpong *et al.*,[149] would undergo the desired reaction more cleanly. **204** was synthesised in 71% yield, however the reaction with vinylogous amide **203** was unsuccessful, again a complex mixture was obtained (**Scheme 99**).



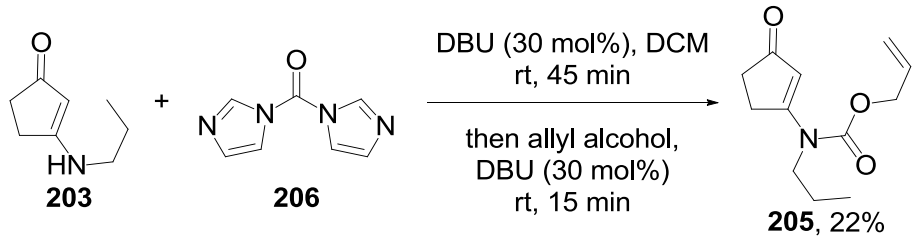
Scheme 99

An alternative strategy was then devised. A leaving group was connected to vinylogous amide **203** *via* a carbonyl linker, which could be substituted with allyl alcohol to furnish the desired product, vinylogous imide **205** (**Scheme 99**). To this end, **203** was reacted with 1,1'-carbonyldiimidazole **206** using DBU as a base to afford vinylogous imide **207** in 58% yield (**Scheme 100**). The DBU was used in a sub-stoichiometric amount since the liberated imidazole can also act as a base in the reaction. It should be noted that **207** degrades on standing in air, and it is believed that the yield was lowered due to the instability of the product to purification.



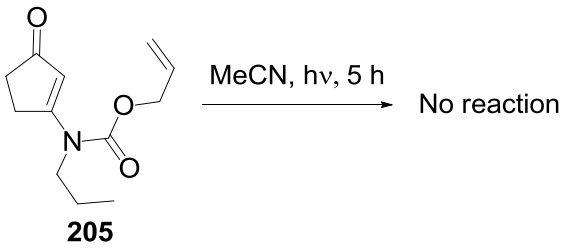
Scheme 100

Due to the instability of this product, it was decided that the best method for synthesising **205** was *via* a one-pot reaction, adding allyl alcohol directly after the first reaction. This would ensure that the yield would not be lowered due to the intermediate degrading upon isolation. To ensure that the reaction mixture was still basic enough, a further 30 mol% of DBU was added along with the allyl alcohol. The reaction was complete within 15 minutes and afforded vinylogous imide **205**, in an overall 22% yield (**Scheme 101**).



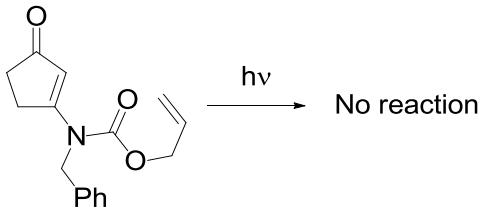
Scheme 101

Although this yield is low, enough of the clean product was obtained in order to attempt the photochemistry; with optimisation, this yield could be improved upon. Irradiation of vinylogous imide **205** under the standard conditions led to no reaction being observed, just slow degradation of the starting material over 5 hours (**Scheme 102**).



Scheme 102

This lack of reactivity is consistent with results reported by Piva *et al.* who state that vinylogous imide **155** does not undergo an intramolecular [2+2] photocycloaddition (**Scheme 103**).[137] They postulate that this is due to the rigid conformation of the carbamate group not allowing the molecule to rotate into the necessary arrangement. Simply, the enone and the alkene are too far away to react. This appears to be true too with vinylogous imide **205**; a 3D model reveals that the molecule is too rigid to allow overlap of the enone and alkene moieties, assuming there is restricted rotation around the amide bond.[137]



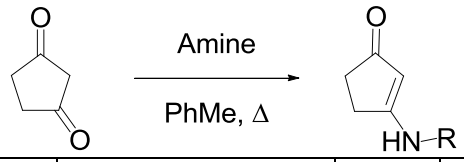
155

Scheme 103

Having attempted a number of intramolecular [2+2] photocycloaddition reactions with vinylogous amides and imides with varying success, attention was next turned to the intermolecular [2+2] photocycloaddition reactions of these compound classes with alkenes and alkynes.

2.2.3 Intermolecular [2+2] photocycloadditions of vinylogous amides with alkenes

In order to test the reactivity of vinylogous amides in the intermolecular [2+2] photocycloaddition reaction with alkenes, a series of vinylogous amides **203** (described previously), **208**, **209** and **210** were synthesised in good yields (**Table 2**). It should be noted that in this synthesis of vinylogous amide **203** (entry 1), a Dean-Stark apparatus was used to remove the water as it was on a significantly larger scale than before.



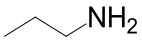
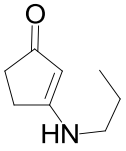
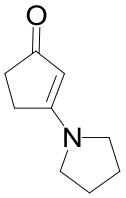
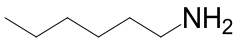
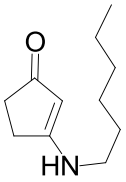
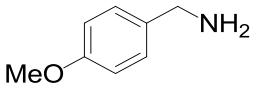
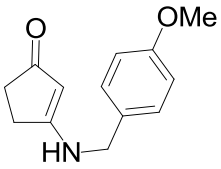
Entry	Amine	Water removal method	Time (h)	Vinylogous amide	Yield
1		Dean-Stark apparatus	2.5	 **203**	99%
2		4 Å Molecular Sieves	3.5	 **208**	81%
3		4 Å Molecular Sieves	3.5	 **209**	80%
4		4 Å Molecular Sieves	2.5	 **210**	65%

Table 2

These vinylogous amides were irradiated in the presence of different alkenes, including both electron rich and electron poor ones and in both acetonitrile and the triplet sensitiser acetone (**Table 3**). However, upon irradiation, no reaction was seen as monitored by TLC and ^{1}H NMR spectroscopic analysis other than slight degradation of the starting material upon prolonged exposure to the UV light. Furthermore, increasing the relative concentration of the alkene, and the reaction time to up to 10 hours, had no effect on the outcome of the reaction.

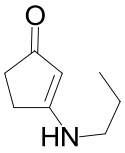
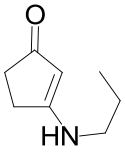
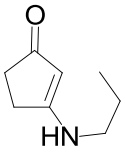
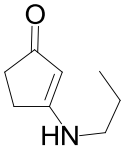
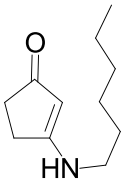
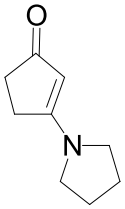
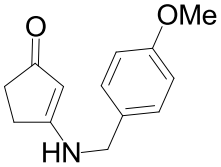
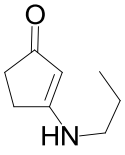
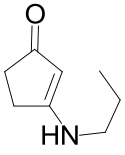
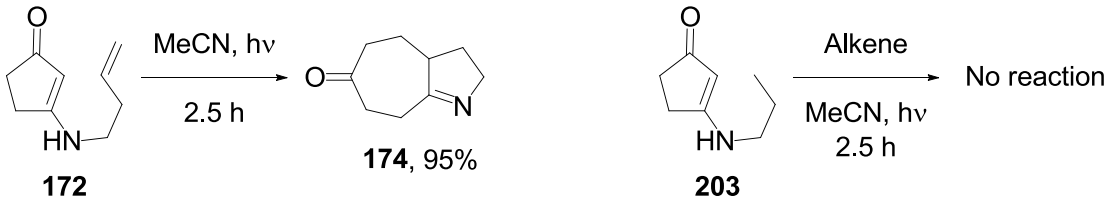
Entry	Vinylogous amide	Alkene	Solvent	Ratio of alkene:solvent	Time (h)
1		Cyclopentene	MeCN	3:1	9.0
2		1-hexene	MeCN	3:1	9.0
3		1-hexene	Acetone	5:1	5.5
4		1-nonene	Acetone	5:1	9.0
5		1-nonene	MeCN	9:1	7.0
6		1-nonene	MeCN	9:1	10.0
7		1-hexene	MeCN	3:1	9.0
8		Vinyl acetate	MeCN	3:1	6.0
9		Acrylonitrile	MeCN	3:1	6.0

Table 3

It was concluded from these results, and the previous literature reports,[142] that the intermolecular [2+2] photocycloaddition of these vinylogous amides was not possible. Given the planar nature of the enone portion of these vinylogous amides, it is unlikely that this lack of reactivity is due to steric reasons, especially when using vinylogous amide **203**, with a short alkyl chain. Furthermore, as previously mentioned, Cantrell found that whilst a vinylogous amide would not undergo an intermolecular [2+2] photocycloaddition, a very similar vinylogous imide would.[142] This suggests that the reason for vinylogous amides not undergoing intermolecular [2+2] photocycloadditions is due to the electronics of the system. However comparing vinylogous amide **203** with vinylogous amide **172**, which underwent a successful intramolecular [2+2] photocycloaddition, it is clear that the electronics of these systems are almost identical, thus it is not simply just down to electronics (**Scheme 104**). It is hypothesised that the lifetime of the excited state is very short, thus if there is an alkene in close proximity, such as the one held in place by the tether in **172**, then a reaction can take place. If there is not an alkene in close proximity, then the vinylogous amide will drop back down to the ground state. In the intermolecular reaction, the effective concentration of the alkene in proximity to the excited vinylogous amide will be very low. This means that a reaction is very unlikely to take place before the vinylogous amide drops back to the ground state.



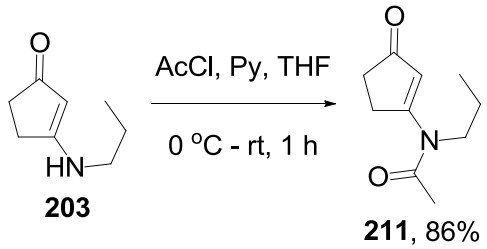
172 **174**, 95% **203**

Scheme 104

2.2.4 Intermolecular [2+2] photocycloadditions of vinylogous imides with alkenes

Given these results, and those reported by Cantrell,[142] attention was turned to the photochemistry of vinylogous imides in the hope that these would undergo intermolecular [2+2] photocycloadditions with alkenes. Although the Boc group

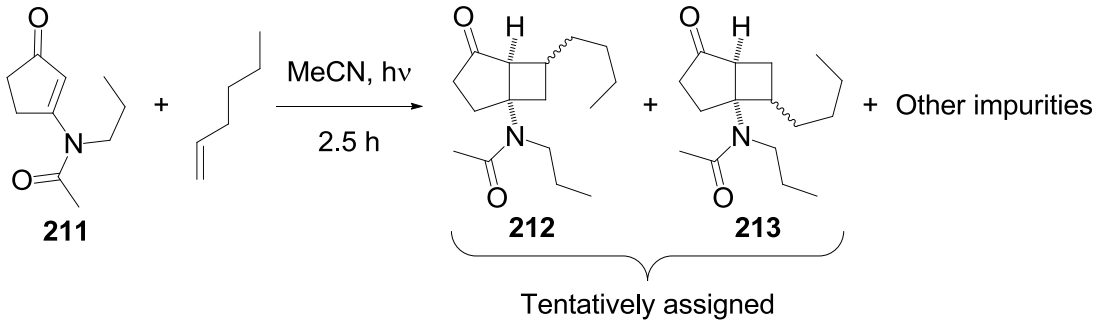
was used for the intramolecular [2+2] photocycloadditions of vinylogous imides in this project, the majority of literature reports on vinylogous imides use the acetyl group.[128-131,136] As a result of this, the acetyl group was the starting point for the investigation into the intermolecular reaction. It should be noted however, that whilst intramolecular [2+2] photocycloadditions of alkenes with vinylogous imides with an acetyl group have been reported in the literature, no examples of the intermolecular reaction have been. Acetylation of vinylogous amide **203** was achieved under literature conditions, using acetyl chloride with pyridine as a base, affording vinylogous imide **211** in 86% yield (**Scheme 105**).[131]



203 **211**, 86%

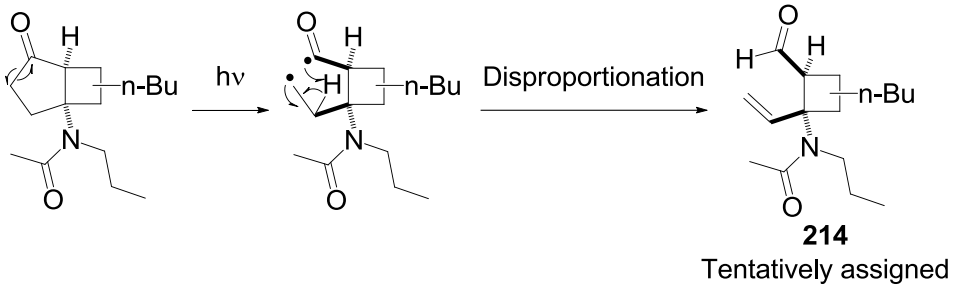
Scheme 105

The first alkene partner chosen for the intermolecular [2+2] photocycloaddition reaction with vinylogous imide **211** was 1-hexene. Irradiation of vinylogous imide **211** in a 3:1 mixture of acetonitrile and 1-hexene led to complete consumption of starting material in 2.5 hours as seen by TLC analysis. However, ^{1}H NMR spectroscopy showed that a complex mixture had formed. Nevertheless, purification of this mixture was embarked upon. By flash column chromatography, impure samples of what are believed to be cyclobutanes **212** and **213** as mixtures of the two diastereoisomers were obtained (**Scheme 106**). Unfortunately, despite numerous attempts, these mixtures could not be obtained pure; impurities remained in both samples.



Scheme 106

The tentative assignment of these cyclobutane products comes from the ^{1}H and ^{13}C NMR shifts, in particular a 1H proton shift just above 3 ppm in both samples, with a corresponding carbon shift around 50 ppm. This is indicative of the cyclobutane proton next to the ketone as seen by comparison of other cyclobutanes synthesised in this project (*vide infra*). Furthermore, the loss of the enone functionality from the starting material, as shown by the ^{13}C NMR spectrum, suggests a reaction is taking place at the enone whilst the product also appears to contain a butyl group, presumably from the 1-hexene. One of the impurities has tentatively been assigned as alkene **214**. This could have formed *via* a Norrish fragmentation at the ketone of one of the products, followed by a disproportionation reaction (**Scheme 107**). The assignment for this product came from inspection of the ^{1}H NMR spectrum. A doublet at a chemical shift of 9.92 ppm suggested the presence of an aldehyde; whilst a double doublet at a chemical shift of 6.08 ppm coupling to two doublets at chemical shifts of 5.19 and 5.08 ppm suggested the presence of a terminal alkene. Due to the complex nature of the ^{1}H NMR spectrum, it is impossible to tell which isomer of **214** was identified, although it is likely that both did form. This type of Norrish fragmentation-disproportionation reaction is a known reaction in the literature[150,151,152,153,154,155,156] and was seen in the vinylogous ester system used in previous work within the group.[34]



214

Tentatively assigned

Scheme 107

In an attempt to minimise any possible secondary photoreactions, the use of the *in situ* reduction protocol was considered once more, whereby a reducing agent is added to the reaction mixture. To test if this idea was viable and that the vinylogous imide itself would not be reduced, **211** was subjected to the conditions which would be used in this reaction, but in the dark. **211** was thus stirred in acetonitrile in the presence of two equivalents of lithium borohydride for three hours. TLC analysis showed that a reaction was taking place, with a complex mixture forming from which nothing could be identified. This, coupled with the lack of success of this methodology in the intramolecular vinylogous amide [2+2] photocycloadditions, suggested that this method would not be viable for vinylogous amides and imides.

Having found that the *in situ* reduction strategy would not be feasible, attention was turned to trying to reduce the number of possible cyclobutane products formed in the intermolecular [2+2] photocycloaddition of vinylogous imide **211**. Any prochiral alkene would lead to two possible diastereoisomers due the possibilities of both an *exo* approach of the alkene to the enone, leading to the *syn*-cyclobutane **215**; and an *endo* approach of the alkene, leading to the *anti*-cyclobutane **216** (**Figure 14**).

215

exo approach

Syn-cyclobutane

216

endo approach

Anti-cyclobutane

Figure 14

Furthermore, any unsymmetrical alkene would lead to a mixture of regioisomers. The 'head-to-head' isomer **217** will be formed from the approach of the alkene with the R groups pointing in the same direction as the enone ketone; whereas the 'head-to-tail' isomer **218** will be formed when the alkene approaches in the other direction (**Figure 15**).

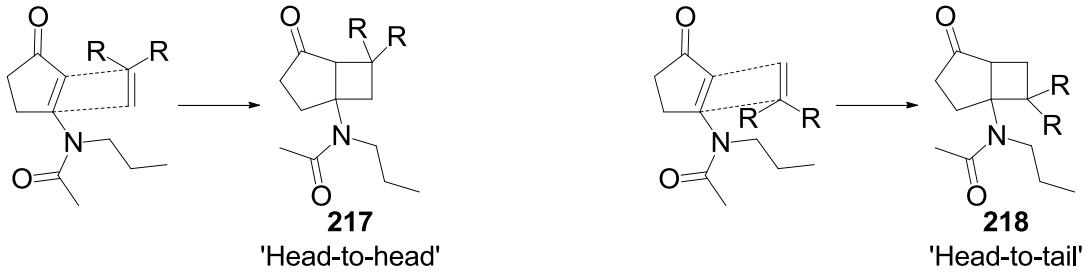
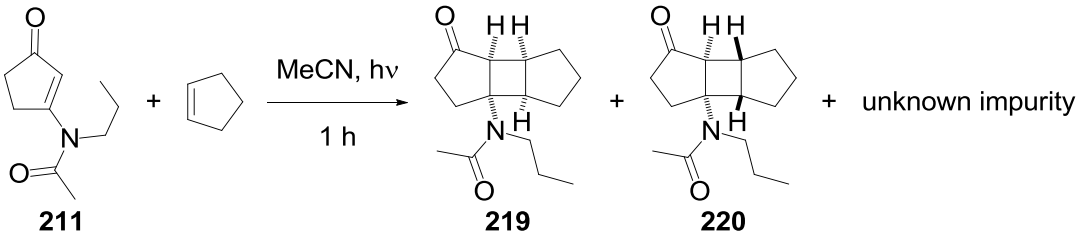


Figure 15

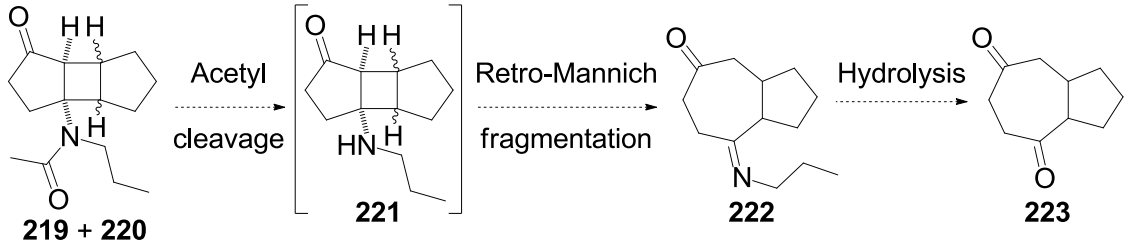
In order to reduce the number of cyclobutanes to a single isomer, a tetra-substituted, symmetrical alkene would have to be used. However, tetra-substituted alkenes are often very slow in [2+2] photocycloaddition reactions. Thus it was decided that cyclopentene, a simple, commercially available symmetrical alkene would be used as the partner to vinylogous imide **211** to at least avoid the issue of regioisomers. Irradiation of **211** in a 3:1 mixture of acetonitrile and cyclopentene for one hour led to complete consumption of the starting material. Although TLC and ^{1}H NMR spectroscopic analysis showed a somewhat complex mixture of products, a slightly impure mixture of what is believed to be cyclobutanes **219** and **220** was still able to be obtained (**Scheme 108**). However, despite numerous attempts by crystallisation and chromatography, it proved impossible to separate these two diastereoisomers from other minor impurities and from each other. By comparing the relative integrations of the peaks in the ^{1}H NMR spectrum, it was possible to tell that the two diastereoisomers existed in an approximate 4:1 ratio. Unfortunately, due to significant overlap of the peaks it proved impossible to tell which diastereoisomer was the major product.



Scheme 108

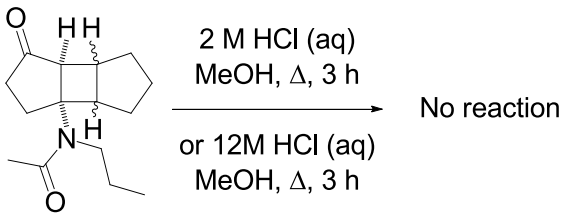
The assignment of these products was again made by examination of the NMR spectra of the mixture. In a similar manner to cyclobutanes **212** and **213** (**Scheme 106**), the presence of a 1H proton shift at 3 ppm with a corresponding carbon shift at 53 ppm suggests that a cyclobutane is present, supported by the loss of the enone functionality. Furthermore, the products contain the correct number of carbon atoms by ^{13}C NMR spectroscopy and appear to contain a new cyclopentane unit in each product.

This reaction, and the one with 1-hexene, suggested that the addition of an acetyl group did indeed facilitate the intermolecular [2+2] photocycloadditions of vinylogous amides. Furthermore, it was evident that this group precluded the retro-Mannich fragmentation from taking place. It was hoped that removal of the acetyl group would allow the fragmentation to take place, and, following hydrolysis, give access to de Mayo type products which may not be accessible *via* the classic de Mayo reaction.[77] Removal of the acetyl group from the diastereoisomeric mixture of **219** and **220** would give the aminocyclobutane **221**, which should fragment to afford keto-imine **222**. This could then be hydrolysed to give diketone **223**, if it did not occur spontaneously under the reaction conditions (**Scheme 109**).



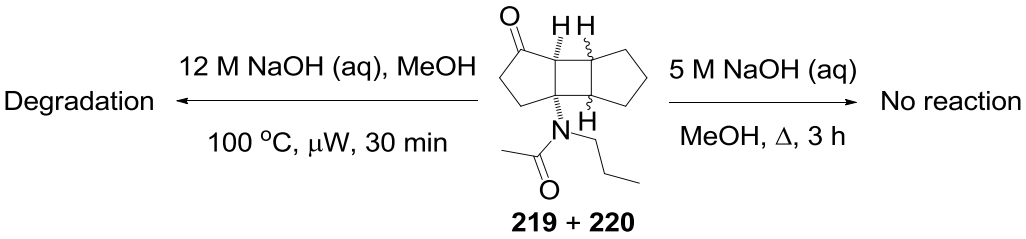
Scheme 109

To this end the cleavage of the acetyl group was attempted under standard conditions, using both acid catalysed hydrolysis and base catalysed hydrolysis. Upon heating a solution of **219** and **220** in a 5:1 mixture of 2 M aqueous hydrochloric acid and methanol, used to aid dissolution, for three hours at reflux, no reaction occurred. Increasing the acidity of the solution by using 12 M hydrochloric acid in place of 2 M had no effect (**Scheme 110**).



Scheme 110

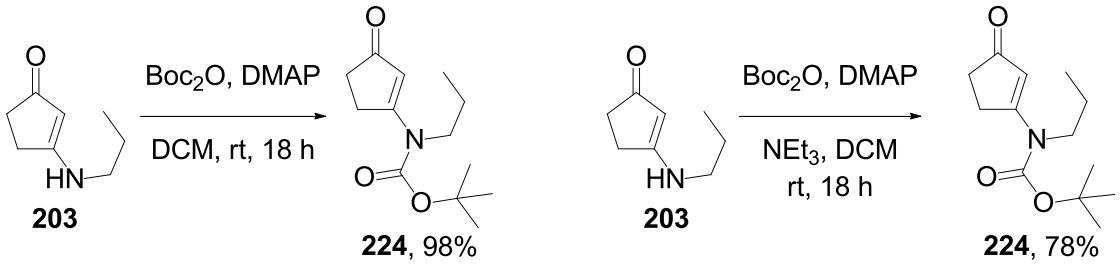
Attempts to use base catalysed hydrolysis for this reaction were also unsuccessful. An initial attempt to use 5 M aqueous sodium hydroxide in a 5:1 mixture with methanol at reflux for three hours led to no reaction at all (**Scheme 111**). However, upon using more forcing conditions of 12 M aqueous sodium hydroxide at 100 °C under microwave heating for half an hour, none of the product was seen, only degradation of starting material (**Scheme 111**).



Scheme 111

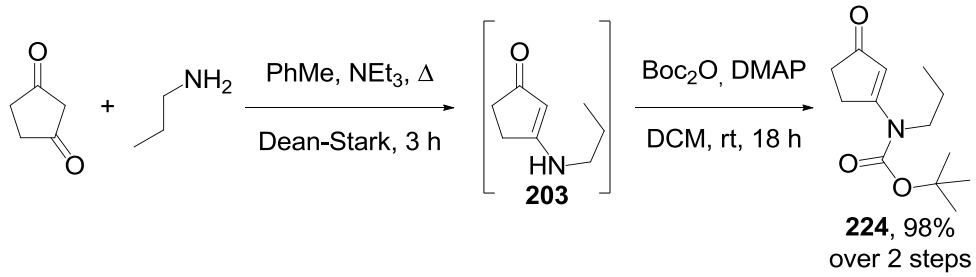
Due to the difficulties in removing the acetyl group, and the success of using N-Boc-vinylogous imide **190** in the intramolecular [2+2] photocycloaddition reaction, attention was turned to the use of N-Boc vinylogous imides in the intermolecular [2+2] photocycloaddition reaction with alkenes. Boc addition to vinylogous amide **203** was carried out as before, affording vinylogous imide **224** in 98% yield (**Scheme 112**). It should be noted that employing more standard conditions, using triethylamine as a base in the reaction, lowered the yield to

78% (**Scheme 112**), possibly due to the triethylamine being wet and this water hydrolysing the vinylogous imide.



Scheme 112

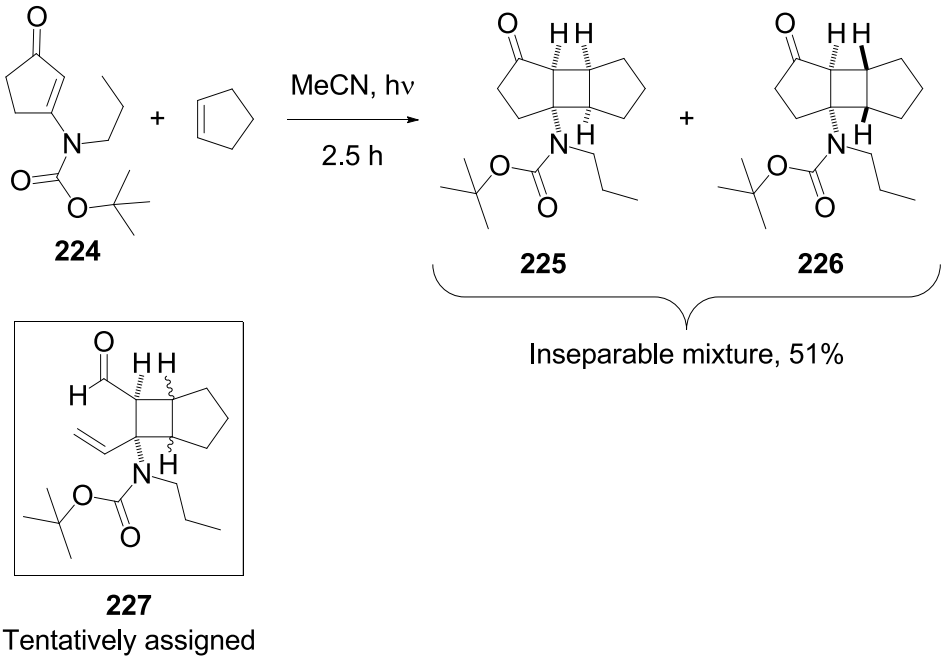
Given that the vinylogous amide synthesis is almost quantitative in yield, as is the Boc protection, it was hypothesised that these two steps could be carried out without an intermediate purification step. This would simplify the vinylogous imide synthesis, making the reaction more attractive. To this end, the vinylogous amide was synthesised as before and subjected to the Boc protection conditions without purification. The vinylogous imide was obtained in an excellent 98% yield over the two steps from commercially available starting materials on a gram sclae *via* this route (**Scheme 113**).



Scheme 113

With vinylogous imide **224** in hand, the intermolecular [2+2] photocycloaddition could be attempted. Cyclopentene was once more used as the alkene in order to avoid the issue of regioisomers and it was used in a 1:3 ratio with acetonitrile as the solvent. Complete consumption of the starting material took 2.5 hours and the crude ^{1}H NMR spectrum showed that cyclobutanes **225** and **226**, as a mixture of diastereoisomers, were present and were the major component of the mixture. Flash chromatographic purification once more proved to be very difficult with **225** and **226** co-eluting with an impurity. Although this impurity was not isolated, it was tentatively assigned as the Norrish fragmentation product **227** from the ^{1}H NMR spectral shifts. This assignment was made by the

presence of a doublet at a chemical shift of 9.70 ppm suggesting an aldehyde and two single proton doublets at 5.63 ppm and 5.55 ppm, along with a multiplet at 5.33 ppm suggesting the presence of a terminal alkene. These co-eluted in all solvent systems tested in chromatography when using silica gel as the stationary phase, and were also inseparable by crystallisation. However, they were finally separated using alumina as the stationary phase, and diastereomeric cyclobutanes **225** and **226** were isolated in 51% yield as an inseparable mixture (**Scheme 114**). It is worth noting that the first purification step using silica gel is necessary as chromatography on alumina alone does not afford the product clean either.



Scheme 114

Using the relative integration between peaks in the ^{1}H NMR spectrum it is possible to tell that this reaction has some diastereoselectivity, affording approximately a 3:1 mixture of diastereoisomers. Unfortunately, due to extensive overlap of the peaks in the ^{1}H NMR spectrum, it was impossible to tell which of the diastereoisomers was the major component of the mixture. As mentioned before (**Figure 14**), the two diastereoisomers arise from different approaches of the alkene to the enone portion of the vinylogous amide. It could be postulated that the steric influence of the amine and Boc groups could potentially cause some steric hindrance to an *exo* approach of the alkene. This

would not hinder an *endo* approach, thus it is postulated that the major diastereoisomer would be cyclobutane **225** rather than **226** (**Figure 16**).

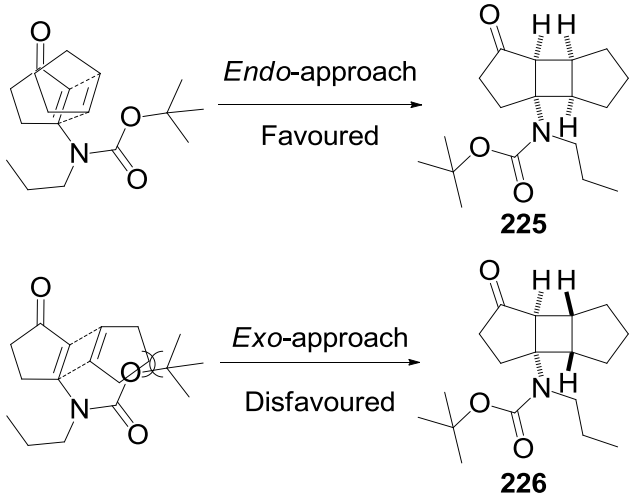
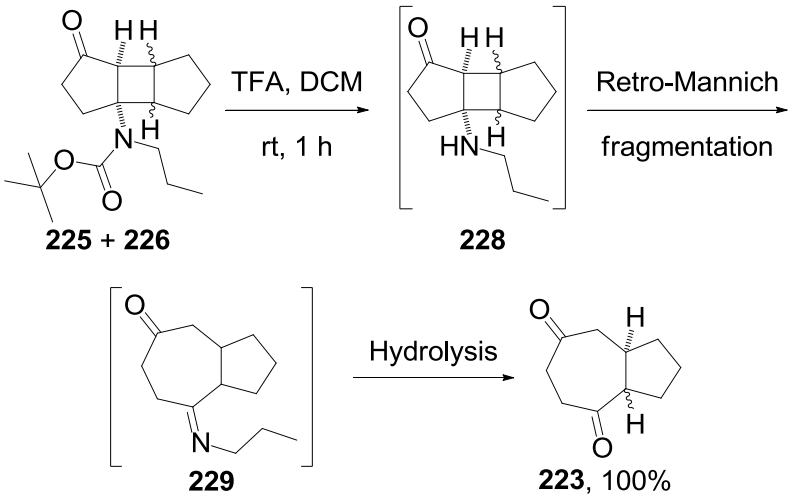


Figure 16

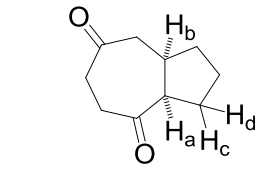
In contrast to the acetyl group, the Boc group was easy to remove. Treatment of the mixture of **225** and **226** with a 1:1 mixture of TFA and DCM led to clean removal of the Boc group. As expected the aminocyclobutane **228** was not isolated, instead the reaction afforded known diketone **223**,[85,157] presumably *via* hydrolysis of imine **229**, in quantitative yield as an inseparable mixture of diastereoisomers in a 10:1 ratio (**Scheme 115**).



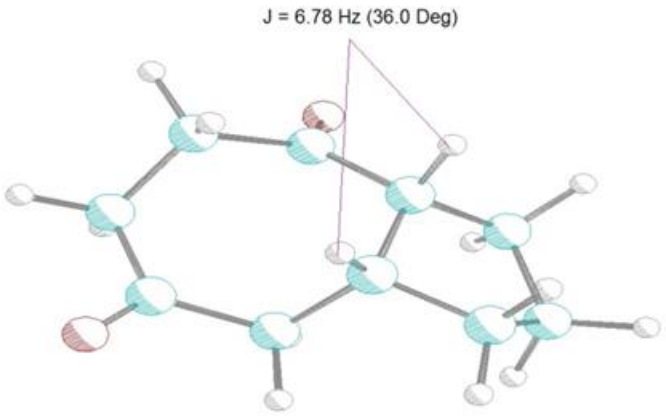
Scheme 115

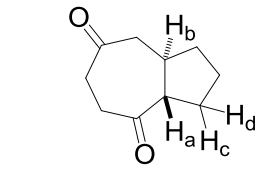
To assign the relative stereochemistry of the major component of the mixture, a NOeSY NMR experiment was run to see if there was any interaction between the two ring junction protons. Unfortunately due to extensive overlap between

the signals for these protons with others in the compound, the experiment proved inconclusive. It was possible however to work out the structure of the major component by using a homonuclear decoupling NMR experiment with help from Dr. Abil Aliev (UCL chemistry). This experiment works by selectively saturating one of the peaks in the ^{1}H NMR spectrum during acquisition using a radio frequency (RF) pulse at the correct frequency and monitoring the effect on the overall spectrum. By doing this, the coupling caused by this proton is removed from all other peaks, and by comparing the new multiplet for a proton to the original one, the coupling value for the interaction between this and the proton corresponding to the saturated peak can be confirmed. It was possible to measure the J-values experienced by H_a as 10.3, 8.1 and 6.4 Hz directly from the original ^{1}H NMR spectrum, which corresponded to coupling to H_b, H_c and H_d (**Figure 17**). These proton peaks however were part of different multiplets caused by overlap with the signals for other protons in the compound, and as such it was impossible to tell which of these coupling values corresponded to the coupling of H_a to H_b. By removing the coupling caused by H_b as described above, it was possible to tell that the coupling of H_a to H_b had a J-value of 10.3 Hz as this is the one that disappeared. It is important to note that this could not have been the coupling of H_a to H_c or H_d as the signals for these protons were not affected by the decoupling RF pulse. With this knowledge in hand, a computer program (PcModel version 8.50.00 by Serena Software) was used, again with help from Dr. Abil Aliev (UCL chemistry) which models the structures and predicts the J-values after an energy minimisation calculation. It was found that for *cis*-**223** the J-value was predicted to be 6.8 Hz, whilst the J-value for *trans*-**223** was predicted to be 10.8 Hz (**Figure 17**). From this data, the major isomer was proposed to be *trans*-**223**.



Cis-**223**
Predicted J-value 6.8 Hz





Trans-**223**
Predicted J-value 10.8 Hz

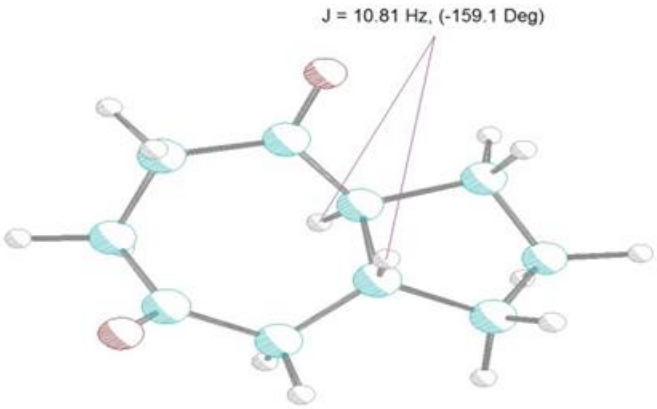


Figure 17

This result is further supported by comparison with the literature. The ^{13}C NMR data from this reaction suggests that the major product is the same as that reported by House *et al.* who presume to have obtained the *trans* isomer *via* a different method, although they do not give any experimental evidence for their presumption.[157]

It is believed that the *cis* isomer is the first to form upon removal of the Boc group from cyclobutanes **225** and **226** as the stereochemistry is set in the cyclobutane as *cis* due to the 5,4 ring system. However, under the acidic reaction conditions, H_a can epimerise *via* the enol form (or the enamine form if it occurs prior to hydrolysis), followed by reprotonation at the ring junction to form *trans*-**223**. The *trans* isomer is presumably more thermodynamically favourable as it puts both of the bonds to the seven-membered ring in a pseudo-equatorial conformation rather than one pseudo-equatorial and one pseudo-axial as in *cis*-**223** (**Figure 18**). This is supported by literature findings, suggesting that the

trans isomer of a 7,5-ring system is generally thermodynamically favoured over the *cis* isomer.[158,159,160]

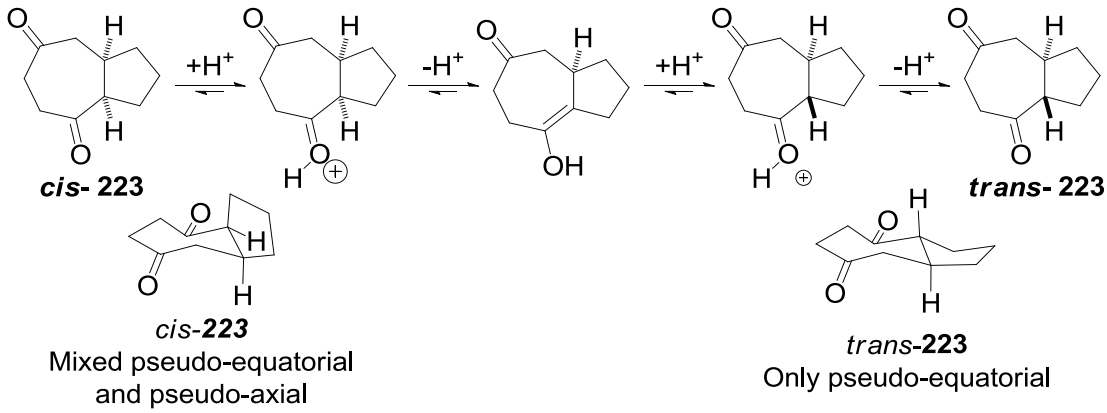
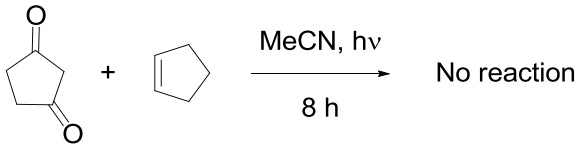


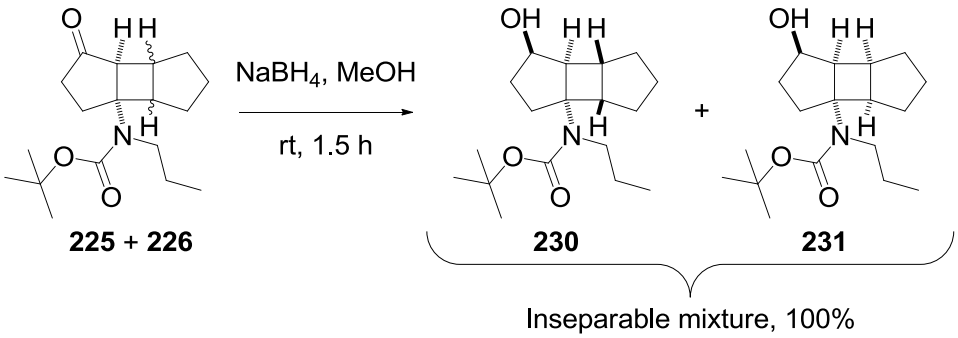
Figure 18

This cycloaddition-fragmentation reaction allows access to de Mayo type products which may not be accessible *via* direct irradiation of the parent 1,3-diketone. Indeed, there are no reports in the literature of a direct de Mayo reaction between 1,3-cyclopentadione and any alkene, possibly due to the reaction not taking place. To support this, 1,3-cyclopentadione was irradiated in a 3:1 mixture of acetonitrile and cyclopentene and no reaction was observed by TLC or ^{1}H NMR spectroscopic analysis (**Scheme 116**).



Scheme 116

As with the intramolecular [2+2] photocycloaddition, the free aminocyclobutanes were desired from cyclobutanes **225** and **226**. To this end, reduction of the diastereomeric mixture of cyclobutanes **225** and **226** was carried out using sodium borohydride in methanol to afford alcohols **230** and **231** as a mixture of diastereomers in quantitative yield (**Scheme 117**). Once more separation of the diastereoisomers proved impossible despite numerous attempts by flash column chromatography on both silica gel and alumina.



Scheme 117

Although they were inseparable, the NMR spectra showed that the mixture comprised just two different diastereoisomers, rather than the possible four. Furthermore, these were still in an approximate 3:1 ratio as measured by the relative peak integrations in the ^{1}H NMR spectrum. This suggests that the reduction takes place in a highly stereoselective manner, each diastereoisomer of the starting material affording a single diastereoisomer upon reduction. However, it was still impossible to tell which two diastereoisomers were present due to extensive overlap of signals in the ^{1}H NMR spectrum again. It is postulated that the reduction would have taken place at the least hindered face of the ketone (the lower face as drawn in **Figure 19**), thus the diastereoisomeric mixture of **230** and **231** would be more likely to have been formed than the mixture of **232** and **233** (**Figure 19**). It should be noted that this effect will be less pronounced in cyclobutane **226** but the result suggests that this effect is pronounced enough to give a single product.

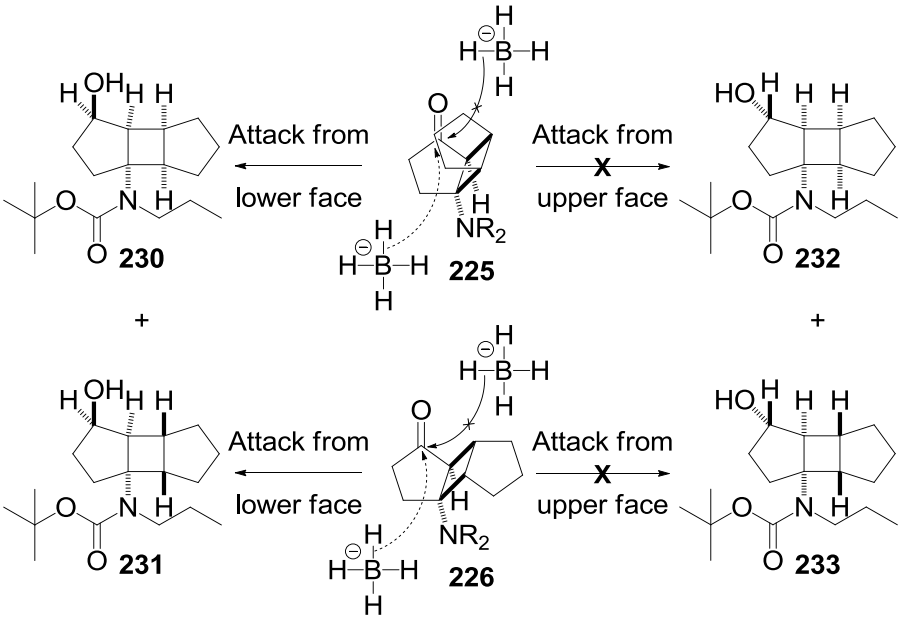
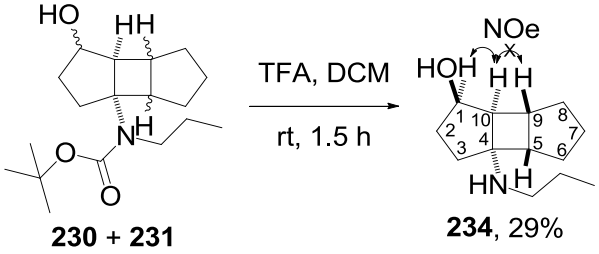


Figure 19

The postulated attack from the lower face is the opposite to that postulated in the reduction of the ketone in cyclobutane **191**, formed by an intramolecular [2+2] photocycloaddition (**Chapter 2.2.2**). The reason for this is that the Boc group in that case was fixed in a position directly beneath the ketone; however in this case there is enough flexibility in the molecule for the Boc group not to be situated below the ketone.

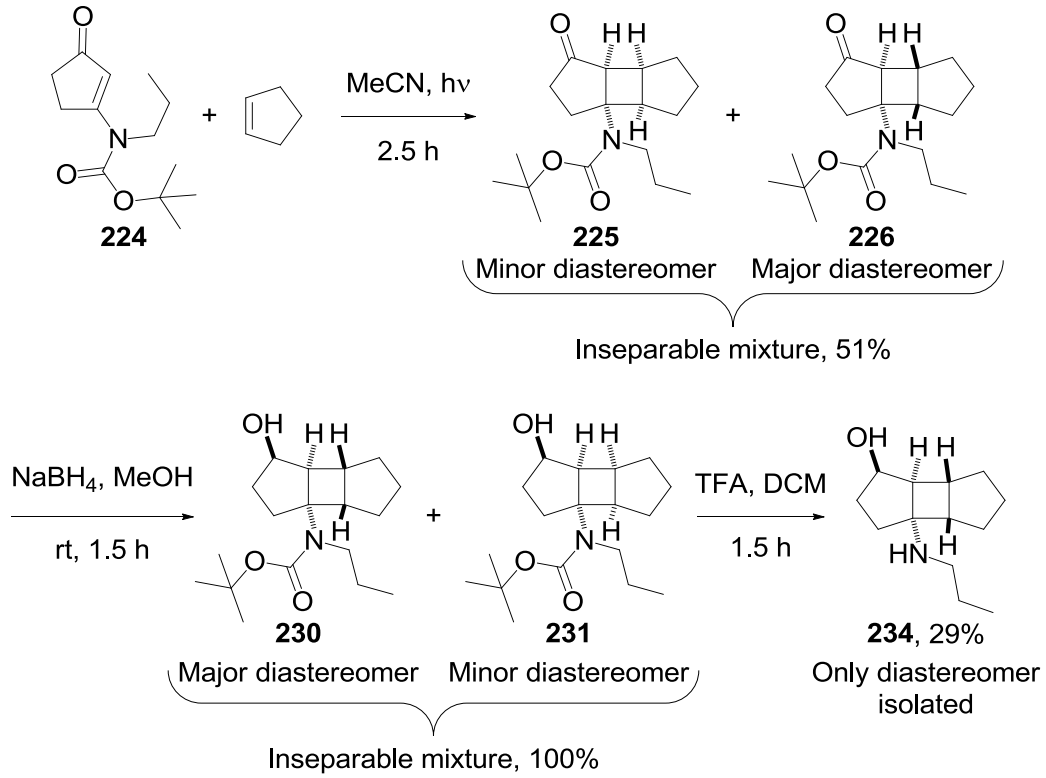
Having reduced the ketone, it was again possible to remove the Boc group without the retro-Mannich fragmentation taking place. Treatment of the mixture of **230** and **231** with a 1:1 mixture of TFA and DCM led to the cleavage of the Boc group. After neutralisation of the TFA and purification, the product of this reaction was a single diastereoisomer of aminocyclobutane **234** in a 29% yield (**Scheme 118**).



Scheme 118

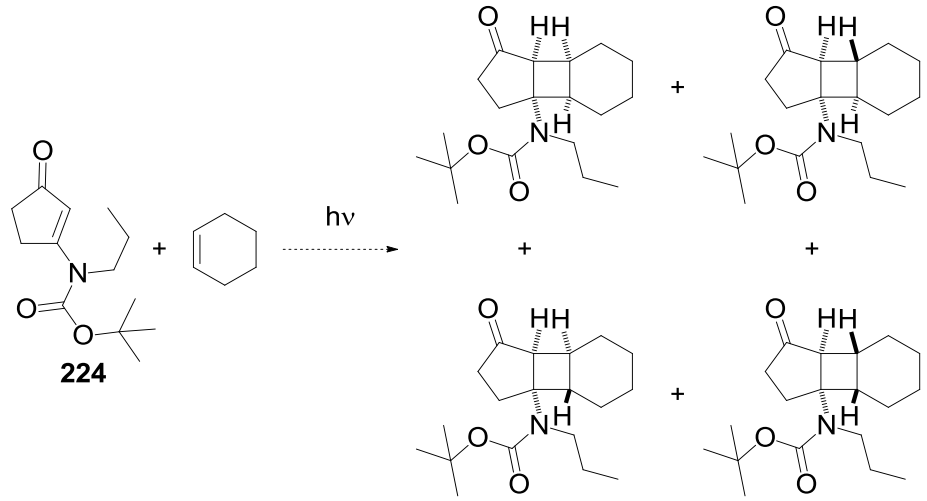
It is believed that this low yield is due to the instability of the product to purification by flash column chromatography. The product was not isolated from the column using standard solvent systems; instead it had to be recovered from the silica gel using neat methanol. Everything that was obtained *via* this method was pure product; however despite a large volume of methanol being passed through the silica, no more than 29% could be recovered. This suggests that the product crystallises on the silica gel or that it is highly insoluble. It should be noted that the product of this reaction was a single diastereoisomer, despite the starting material being a mixture of two. A NOeSY NMR experiment revealed that there was a NOe interaction between proton 10 and proton 1 but not between proton 10 and proton 9 (**Scheme 118**), suggesting that the product is as drawn above.

This product must be derived from the major diastereomer present in the starting material as the absolute maximum yield the minor diastereomer could have afforded was 25%. This is because the diastereomers existed in a 3:1 ratio in the starting alcohol. This fact, coupled with the NOeSY data from aminocyclobutane **234** suggests that reduction of the ketones in cyclobutanes **225** and **226** occurred from the top face of both as hypothesised, affording alcohols **230** and **231** (**Scheme 119**). However, it also suggests that the major component of the diastereoisomeric mixture of **225** and **226** formed in the initial [2+2] photocycloaddition reaction was **226** rather than **225** as hypothesised. This hypothesis was made based on steric interactions. This result, however, suggests that the outcome is likely not based on steric interaction, but based on electronic properties of the vinylogous imide or secondary orbital interactions. The electronic and orbital properties of a molecule are very difficult to predict, and without a much more detailed investigation, it is impossible to rationalise the outcome of this reaction based on these properties.



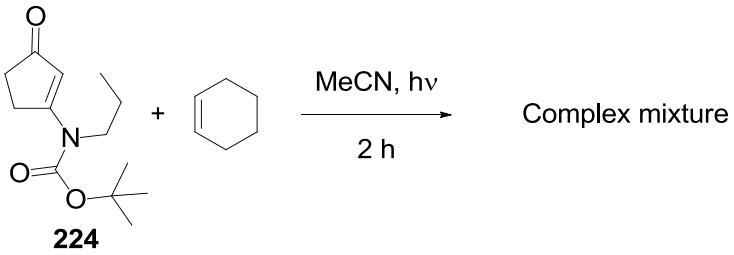
Scheme 119

Having shown that the intermolecular [2+2] photocycloaddition of vinylogous imide **224** works with cyclopentene, the scope of this reaction could be tested by using different alkenes. Given the success of cyclopentene, the next logical alkene to attempt was cyclohexene. In contrast to the [2+2] photocycloaddition with cyclopentene from which only two possible diastereomers were possible, the reaction with cyclohexene could lead to four possible diastereomers (**Scheme 120**). This is because a 6,4 ring junction has enough flexibility to exist in either the *cis* or *trans* form, in contrast to a 5,4 ring junction which can only be *cis*-fused.



Scheme 120

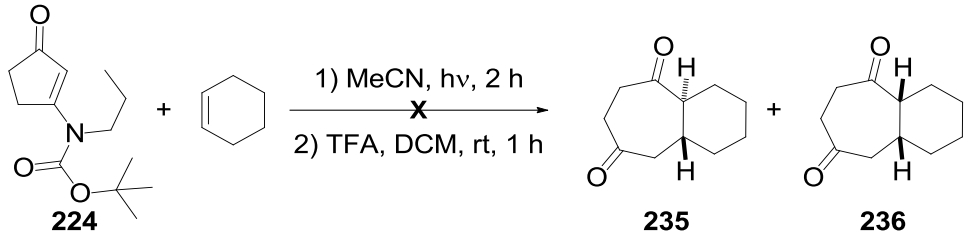
Upon irradiation of vinylogous imide **224** in a 3:1 mixture of acetonitrile and the cyclohexene, the starting material was consumed in two hours. Unfortunately the resultant mixture was comprised of a highly complex mixture of compounds, TLC analysis showing nine overlapping spots. Furthermore, the crude ^{1}H NMR spectrum was very messy. It is believed that this is partly due to there being four different diastereoisomers of the cyclobutane, and partly due it being a messy reaction, possibly undergoing unwanted side-reactions (**Scheme 121**).



Scheme 121

All attempts by chromatography to get any of the products clean individually or as a mixture of isomers were unsuccessful. It was hypothesised that upon removal of the Boc group from these cyclobutanes, the retro-Mannich fragmentation should take place. Due to the destruction of two of the stereocenters in the molecules this would then afford just two diastereoisomeric products, diketone **235** and **236** (**Scheme 122**). The crude photochemical mixture was treated with a 1:1 mixture of TFA and DCM for one hour. However, instead of making the mixture less complex by the convergence of the four cyclobutanes into two diketones, the reaction mixture was even more complex

by TLC and ^{1}H NMR spectroscopic analysis. Despite numerous attempts, neither of the diketones could be isolated from this complex mixture (**Scheme 122**). Due to these problems, this reaction was not pursued further.

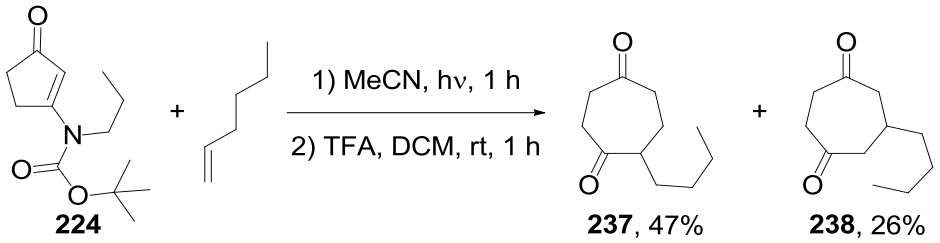


224 **235** **236**

Scheme 122

Given that the various regioisomers and diastereoisomers of the cyclobutanes in the previous reactions proved impossible to separate, it was decided that a different standard protocol was required for unsymmetrical alkenes. Given that the diketones would be more readily separable than the cyclobutanes, as there would be just two regioisomers, it was decided that the crude photochemical mixture should be treated directly with the Boc removal conditions and the diketones obtained without an intermediate purification step. Although this would preclude the isolation of the aminocyclobutanes, it would still show the power of the vinylogous imide-alkene [2+2] photocycloaddition and allow access to a variety of novel 1,4-diketones which may not be accessible *via* the de Mayo reaction.

The first unsymmetrical alkene tested in this way was 1-hexene. Irradiation of vinylogous imide **224** in a 3:1 mixture of acetonitrile and 1-hexene led to complete consumption of the starting material in one hour. The excess alkene was removed *in vacuo* and the crude mixture was then treated with a 1:1 mixture of TFA and DCM for one hour. As expected purification was simplified compared to previous reactions, and diketones **237** and **238** were afforded in 47% and 26% yield respectively over two steps (**Scheme 123**). A further 5% was isolated as a mixture of the two diketones.



Scheme 123

It is hypothesised that the regioselectivity observed in this reaction arises due to a favourable dipole-dipole interaction in the exciplex formed during the photochemical reaction. This rationale was suggested by Corey *et al*. who report that the ß-carbon of an enone is more negative than the α-carbon in the n-π* excited state.[60] Upon approach of an olefin and exciplex formation, the dipoles of the olefin will align preferentially with those in the enone (see **Chapter 1.5.3.2**).[60] Thus, in this reaction, cyclobutane **239** is favoured as the dipoles in 1-hexene align with those in the enone, and hence diketone **237** is the major product upon fragmentation (**Figure 20**). Cyclobutane **240**, which leads to diketone **238**, on the other hand, has an unfavourable interaction between the dipoles in the exciplex formed during the photochemical reaction and thus is disfavoured (**Figure 20**).

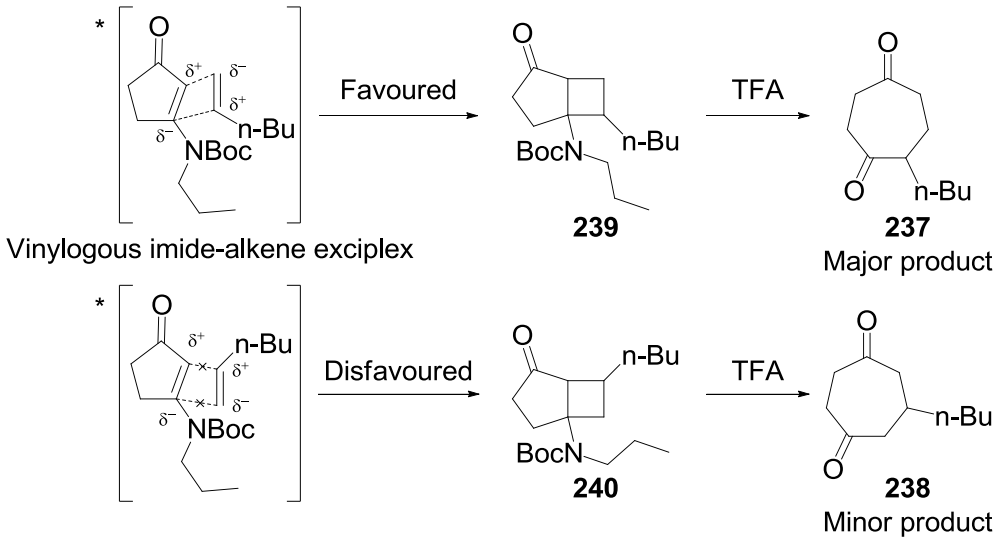


Figure 20

Another explanation for this regioselectivity is from an orbital point of view. In the excited state, the molecular orbitals in the new LUMO (LUMO*) of the enone are significantly more polarised than the HOMO*. This results in the LUMO*-LUMO interaction being the dominant effect in controlling the regiochemistry

over the HOMO*-HOMO. Furthermore, in the LUMO*-LUMO case, a favourable bonding interaction will take place in a head-to-tail manner, as this is the large-large orbital overlap, favouring the formation of cyclobutane **239** (**Figure 21**).[13]

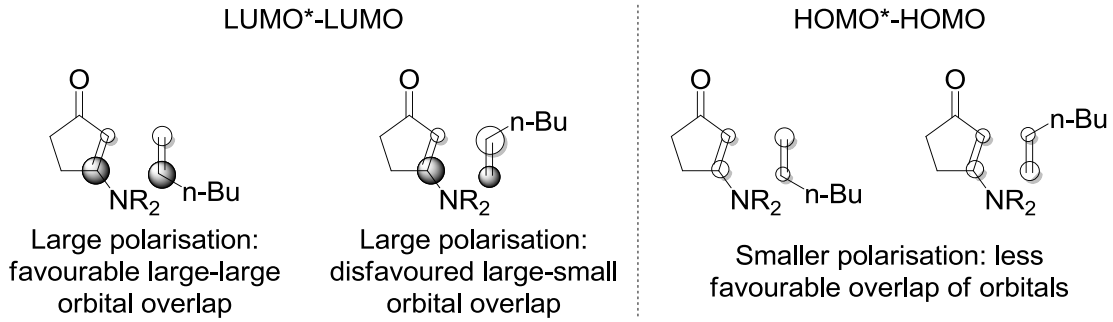
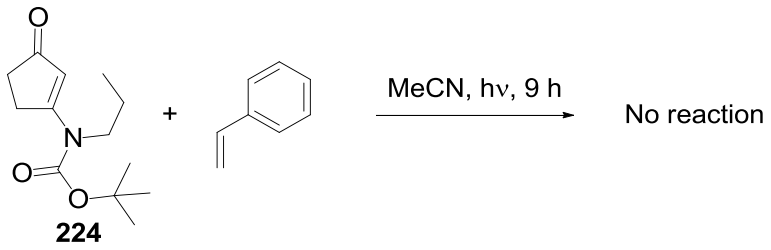


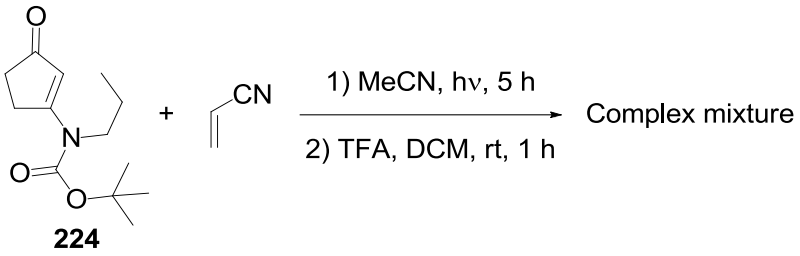
Figure 21

Attention was next turned to [2+2] photocycloaddition reactions of vinylogous imide **224** with conjugated olefin partners. Styrene was chosen first as it is readily available, cheap, has found use in photochemical reactions previously[161,162] and has been shown to exhibit good diastereoselectivity in some reactions.[163] However, in this case it did not take part at all in the photochemical reaction; after nine hours all that was seen was mild degradation of vinylogous imide **224** and nothing else (**Scheme 124**).



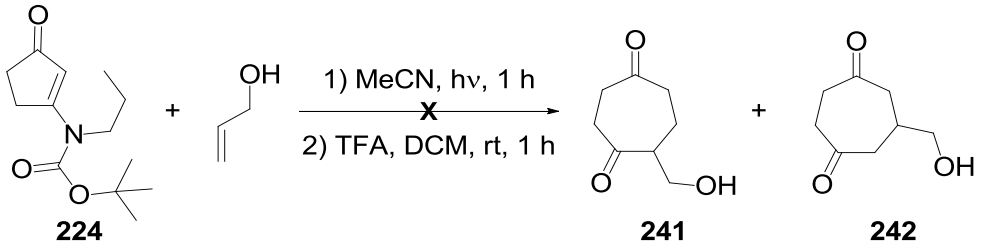
Scheme 124

Irradiation of vinylogous imide **224** in a 3:1 mixture of acetonitrile and acrylonitrile lead to complete consumption of the starting material within 5 hours. The crude mixture was then treated with a 1:1 mixture of TFA and DCM for an hour. The reaction mixture was comprised of a number of different products as seen by TLC analysis, suggesting that the photochemical reaction is not a particularly clean one. Attempts to isolate either of the diketones clean proved impossible due to this problem (**Scheme 125**).



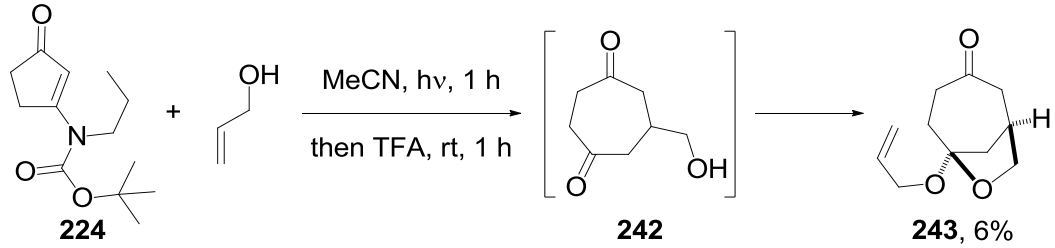
Scheme 125

Upon irradiation of vinylogous imide **224** in a 3:1 mixture of acetonitrile and allyl alcohol, the starting material was consumed in one hour as shown by TLC analysis. Boc removal was carried out under the standard conditions but no products could be isolated upon flash column chromatography. It is believed that either the polarity of the diketones **241** and **242** (**Scheme 126**) precluded isolation from the silica gel, or that they were degrading on the column.



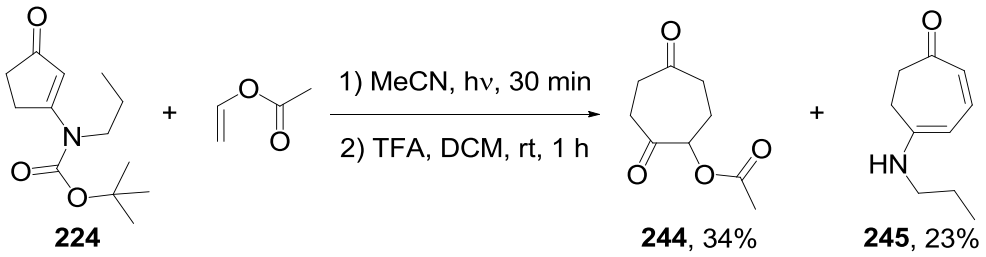
Scheme 126

Interestingly, treatment of the crude photochemical mixture with the Boc cleavage conditions without removal of the excess allyl alcohol led to the formation and isolation of acetal **243** in 6% yield (**Scheme 127**). This finding suggests that diketone **242** is being formed in this reaction, but it could not be isolated. The low yield of this acetal may be due to the diketone only being formed in a very small amount, or possibly that this acetal is sensitive to degradation.



Scheme 127

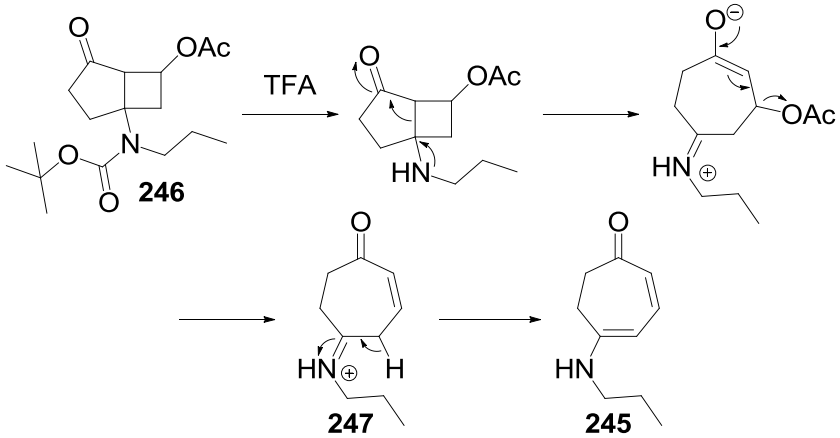
Irradiation of vinylogous imide **224** with vinyl acetate for half an hour, followed by Boc cleavage of the crude mixture afforded two products. The first product was the expected diketone **244** in 34% yield (**Scheme 128**). As seen by ^{1}H and ^{13}C NMR spectroscopy, the second product contained three olefinic protons and still maintained the propyl group. Thus from this data, this product was assigned as conjugated enaminone **245** and was isolated in 23% yield (**Scheme 128**).



224 **244**, 34% **245**, 23%

Scheme 128

It is believed that this conjugated enaminone is the product of the retro-Mannich fragmentation of cyclobutane **246**, followed by elimination of the acetate group to give enone **247**. In contrast to previous imines formed *via* this retro-Mannich fragmentation, the iminium ion in **247** tautomerises into the more stable enamine form in conjugation with the enone in **245** (**Figure 22**).



246 **247** **245**

Figure 22

This elimination-tautomerisation process occurring with cyclobutane **246** is in contrast to the other regioisomer, cyclobutane **248**, which cannot eliminate the acetate group. Instead, this undergoes protonation followed by hydrolysis (**Figure 23**) which has been seen in all previous retro-Mannich fragmentations from cyclobutanes formed *via* the intermolecular [2+2] vinylogous imide-alkene photocycloaddition.

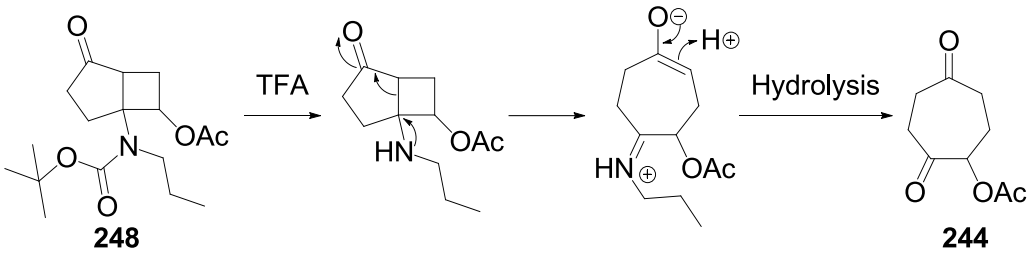


Figure 23

Up to this point the standard conditions for the intermolecular [2+2] photocycloaddition were to use the alkene as a co-solvent in a 1:3 ratio with acetonitrile. With the cheap, commercially available alkenes used previously this was viable; however if using an expensive or non-commercially available alkene it is important to use as little as possible. Given the success of the reaction with vinyl acetate, it was decided to use this reaction to optimise the conditions.

Table 4 shows the results of this optimisation study. Running the reaction with 11 equivalents of the alkene (1 mL of vinyl acetate in the 30 mL reaction mixture), it took slightly longer to go to completion, but actually served to slightly increase the yield of the reaction (entry 2). Reducing the amount of alkene to 5 equivalents had no effect on the time for the reaction to take place, but led to a significantly lowered yield (entry 3). In an attempt to see how far this reaction could be pushed, it was attempted with just 2 equivalents of vinyl acetate. In this case the reaction took longer and was significantly messier; **245** could not be isolated clean, a new, unknown impurity co-eluting with **245** upon chromatography (entry 4). It is thought that side-reactions took place instead of the desired [2+2] photocycloaddition, or degradation occurred during the increased reaction time. From this sampling of alkene equivalents, the best outcome was obtained with 11 equivalents.

Entry	Equivalents of alkene	Irradiation time /min	Yield of **244**	Yield of **245**
1	150	30	34%	23%
2	11	45	47%	26%
3	5	45	22%	19%
4	2	75	15%	Not isolated

Table 4

It is again interesting to note the regioselectivity in this intermolecular [2+2] photocycloaddition. In the best reaction, the ratio of **244** to **245** is exactly the same as for the reaction with 1-hexene (above). The major product from this reaction is **244**, which arises from the fragmentation of cyclobutane **248**. This head-to-tail isomer in turn arises from a favourable dipole-dipole interaction of the enone with the alkene as with 1-hexene (**Figure 24**).[60] Again, this is also favoured by the difference in the polarisation of the HOMO* and LUMO* states, outlined previously.[13]

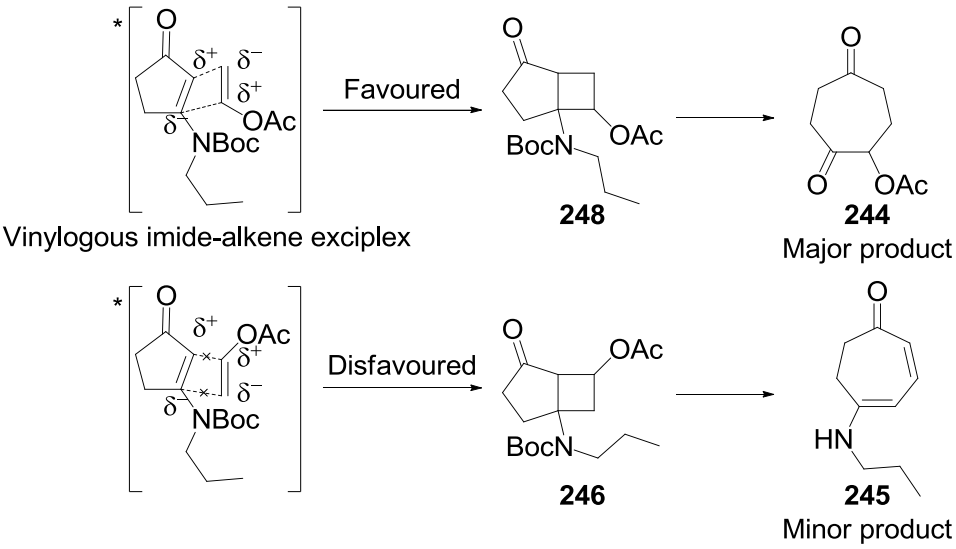


Figure 24

The formation of the conjugated enaminone **245** is interesting as such conjugated enaminones contained in seven membered rings have not been

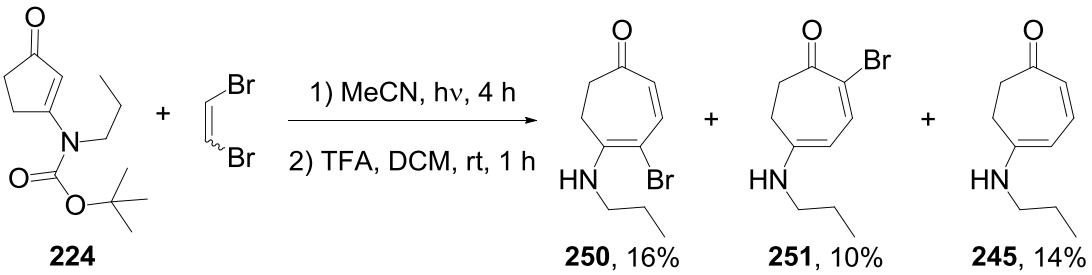
reported before in the literature. It was postulated that any alkene with a connected leaving group would yield similar products in this photocycloaddition-fragmentation sequence. Furthermore, if the alkene was symmetrical, only one product should be formed; thus 1,2-dichloroethylene seemed the perfect fit for this reaction. Although commercially available, this alkene is expensive and it was decided that the initial trial should use just 5 equivalents of the alkene. It was found that irradiation of vinylogous imide **224** with 1,2-dichloroethylene followed immediately by Boc cleavage, afforded conjugated enaminone **249** in 64% yield. It was noticed during the course of this reaction and purification that the product was prone to degradation. Standing in the air for a week led to complete degradation into multiple unknown products, most likely due to the action of moisture in the air. It was felt that this could be taking place during the work up as well, thus it was decided that avoiding a basic wash could increase the yield. Instead the neutralisation of any residual TFA and formation of the free base was achieved by stirring the crude mixture, after removal of most of the TFA *in vacuo*, in neat triethylamine for five minutes. This was then removed *in vacuo* and the resulting mixture subjected to flash column chromatography. By this method, the yield of conjugated enaminone **249** was increased from 64% to 77% (**Scheme 129**).

224 **249**, 77%

Scheme 129

It should be noted that a mixture of *cis* and *trans* 1,2-dichloroethylene was used in these reactions as this was all that was commercially available. However, it was felt that both isomers would yield the same final product and that they may well isomerise under the photochemical conditions anyway, reaching an equilibrium mixture. Finally, it was hoped that the amount of the alkene could be reduced; however, upon running the reaction with 2 equivalents, a disappointing 20% yield was obtained.

Attention was next turned to using 1,2-dibromoethylene as the alkene partner in the intermolecular [2+2] photocycloaddition. Using the same conditions as with 1,2-dichloroethylene, full consumption of the starting material was achieved in four hours. This increased reaction time could be put down to the increase in steric bulk around the alkene moiety from the two bromides compared to two chlorides. Removal of the Boc group from the crude photochemical mixture afforded a complex mixture, from which three products were isolated. The expected conjugated enaminone **250** was isolated, although in a disappointing 16% yield. After careful inspection of the ^{1}H and ^{13}C NMR spectra, the second product was assigned as conjugated enaminone **251**, where the bromide appears to have moved to a different carbon atom and this was isolated in a 10% yield. The final product was conjugated enaminone **245**, which was isolated in a 14% yield (**Scheme 130**). This is the same product as that formed in the reaction with vinyl acetate, in this case presumably *via* debromination of **250** or **251**.



Scheme 130

It is proposed that **251** and **245** both arise in this reaction from **250** as this must be the initial product of the reaction. One possible mechanism for the formation of these two products is outlined below (**Figure 25**). Protonation of conjugated enaminone **250** by TFA gives the iminium ion **252**, from which both products are accessible *via* attack of bromide. If the bromide attacks at C-2 in an S_N2' reaction, intermediate **253** will be formed, which upon loss of a proton would afford conjugated enaminone **251**. However, the liberated bromide could also directly attack the bromide at C-4, affording molecular bromine and debrominated conjugated enaminone **245**. Electrophilic bromination of **245** could also take place to afford **251** in a different manner, again *via* intermediate

253. It is believed that these side reactions do not occur in the reaction with 1,2-dichloroethylene as a chloride is a poorer nucleophile and leaving group than a bromide.

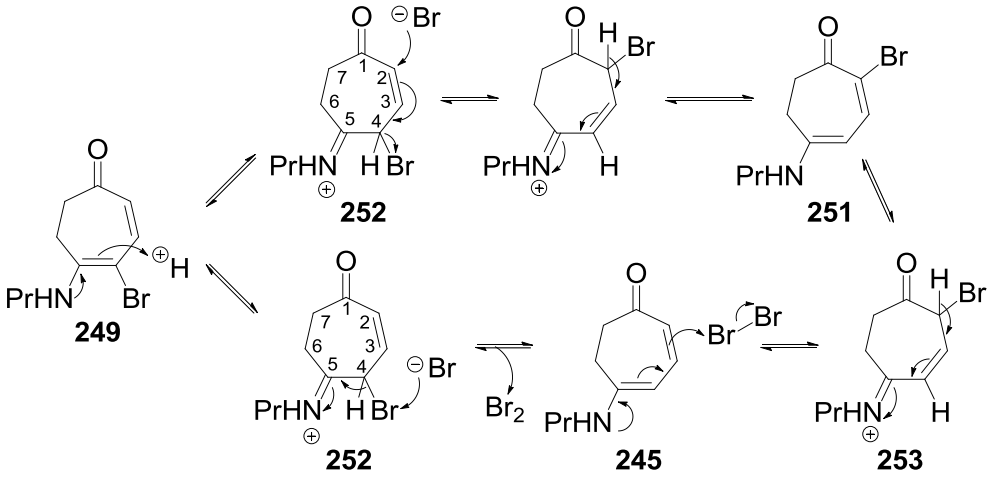
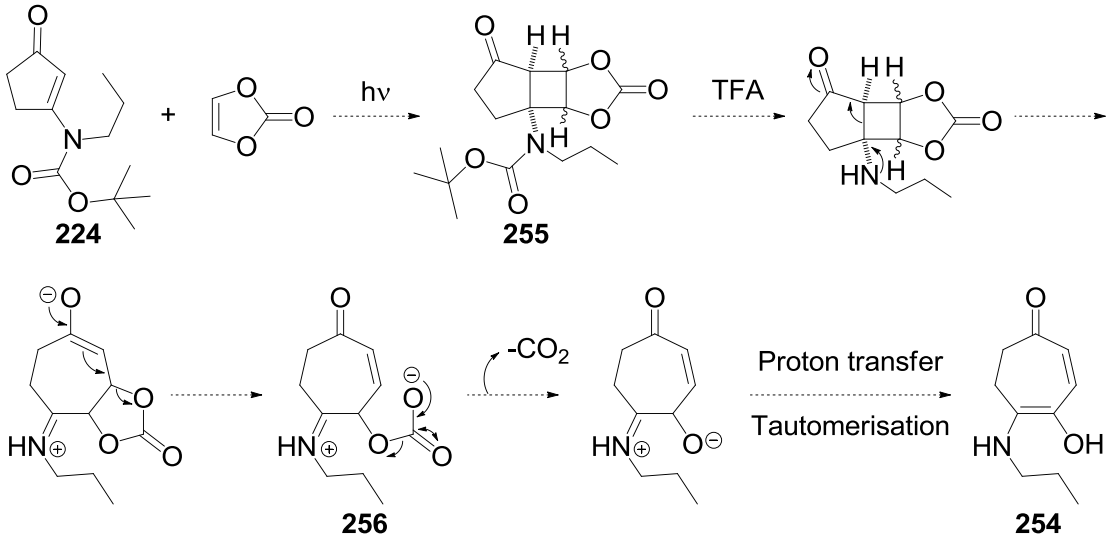


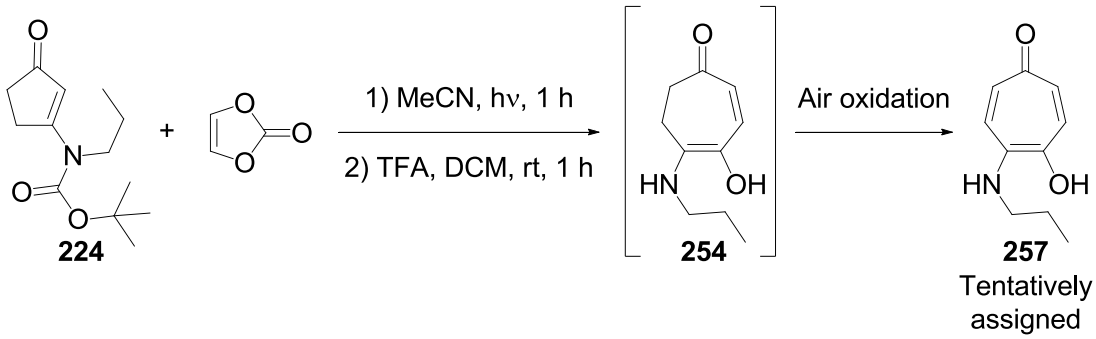
Figure 25

The next alkene chosen in the [2+2] photocycloaddition reaction with vinylogous imide **224** was vinylene carbonate. This was chosen as it is another symmetrical alkene which contained a leaving group. Due to the nature of this leaving group, it was hoped that the hydroxylated conjugated enaminone **254** could be isolated upon Boc removal. It was hypothesised that upon fragmentation of cyclobutane **255**, the cyclic carbonate moiety would open to give intermediate **256**, which would decarboxylate affording **254** (**Scheme 131**).



Scheme 131

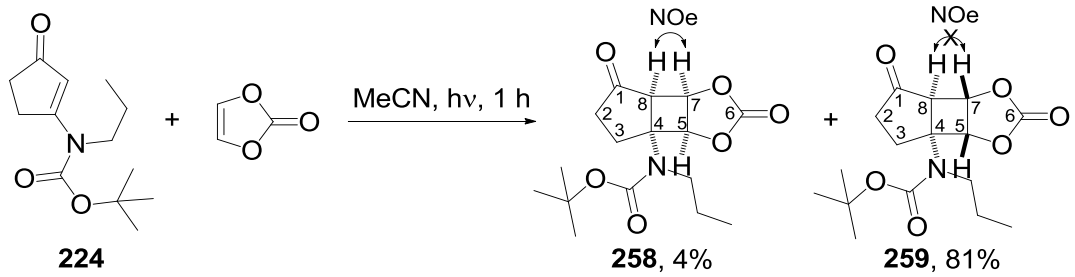
Irradiation of vinylogous imide **224** in the presence of 5 equivalents of vinylene carbonate took one hour to go to completion and the crude ^{1}H NMR spectrum suggested that the [2+2] photocycloaddition had taken place and was fairly clean. Boc cleavage of this crude mixture led to a complex mixture from which only one product was obtained. Unfortunately this was not clean, some minor impurities remained, and a second attempt to purify it led to complete loss of the product suggesting that it is unstable, particularly to flash chromatography. However, careful inspection of the ^{1}H and ^{13}C NMR spectra of this impure product suggested that it could be the oxidised form of the conjugated enaminone **254**, aminotropone **257** (**Scheme 132**). This structure is supported by four single proton doublets between 6.67 and 7.10 ppm in the ^{1}H NMR spectrum and their corresponding carbon peaks between 113.7 and 129.9 ppm. These peaks correspond closely with related aminotropones synthesised later in this project (*vide infra*). Unfortunately this cannot be fully confirmed due to the impure nature of the compound and the impurities could not be identified. It is believed that this oxidation takes place in the air during the reaction or upon work-up. The yield for this reaction could not be accurately measured without knowing the identity of the impurities, but it must be less than 12% due to the mass balance returned.



Scheme 132

Although this is an interesting transformation, the low yield and instability of the product were problematic. However, the crude ^{1}H NMR spectrum of the irradiation products suggested that the cyclobutanes were fairly clean and thus an attempt to separate and purify the two cyclobutanes was carried out. In contrast to all previous diastereoisomeric mixtures of cyclobutanes, it was possible to separate these two, isolating cyclobutane **258** in 4% yield and

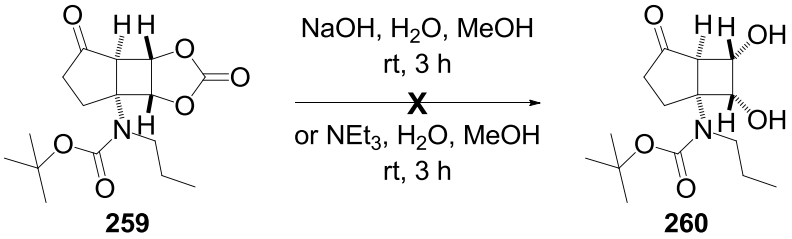
cyclobutane **259** in 81% yield. The assignment of the two cyclobutanes was made by a NOeSY NMR experiment which showed an NOe between H-7 and H-8 in **258**, but not in **259** (**Scheme 133**).



224 **258**, 4% **259**, 81%

Scheme 133

Attempts to hydrolyse the carbonate in **259** to afford a 1,2-diol **260** by the methods of Sharpless *et al.*[164] or Nicolaou *et al*.[165] were unsuccessful, affording a complex mixture (**Scheme 134**). The crude NMR spectra of this reaction suggests that none of the 1,2-diol was present, and it could be envisaged that such a compound would be sensitive to cyclobutane fragmentation.



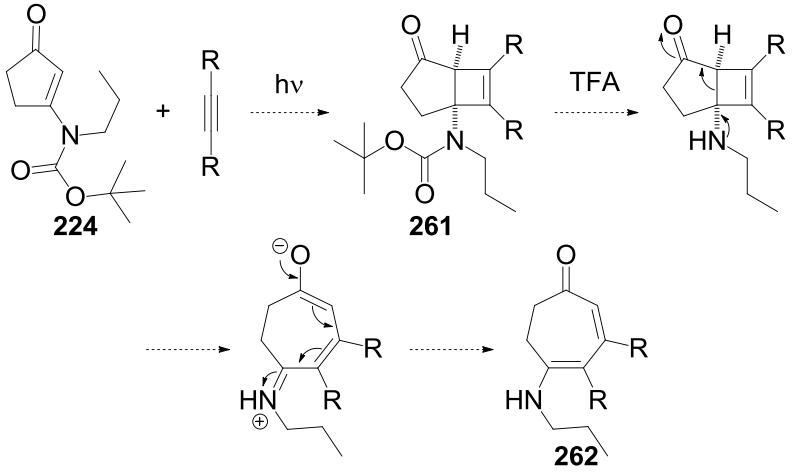
259 **260**

Scheme 134

2.2.5 Intermolecular [2+2] photocycloadditions of vinylogous imides with alkynes

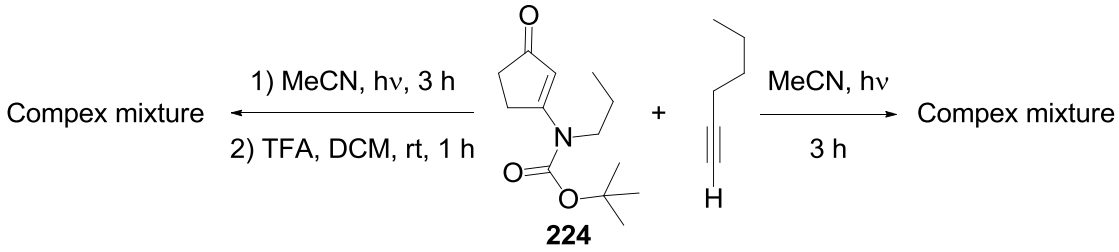
Given the success of the intermolecular [2+2] photocycloaddition of vinylogous imides with alkenes, an investigation into the reaction with alkynes was undertaken. Currently there are no examples of [2+2] photocycloadditions between vinylogous amides or imides and alkynes in the literature. If successful, this would give access to cyclobutenes **261**. Furthermore, it was hypothesised that removal of the Boc group would lead to the retro-Mannich fragmentation, and given the presence of the alkene moiety within the seven

membered ring, most likely form the conjugated enaminones **262**, similar to those seen before (**Scheme 135**).



Scheme 135

To test this reaction, 1-hexyne was used as the first alkyne. Irradiation of vinylogous imide **224** in a 3:1 mixture of acetonitrile and 1-hexyne led to complete consumption of the starting material in three hours. However, the result was a complex mixture as seen by TLC analysis and crude ^{1}H NMR spectroscopy. Purification *via* flash chromatography afforded nothing that could be identified (**Scheme 136**). Removing the Boc group immediately after the reaction did not aid the purification, in fact it served only to make the mixture more complex (**Scheme 136**).



Scheme 136

The reaction was then attempted with 3-hexyne in the hope that this would reduce the complexity of the reaction mixture by yielding a single possible cyclobutene product. The starting material was consumed in five hours, however again purification proved difficult, and nothing was isolated that could be identified. Once more, treatment with TFA after the reaction led to a more complex mixture which contained no olefinic protons in the crude ^{1}H NMR

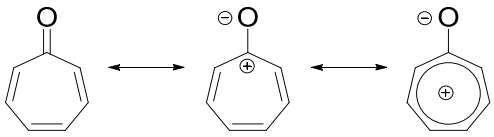
spectrum. This suggests that none of the desired product was formed. It is believed that either this reaction suffers from secondary photoreactions, or the cyclobutene product is too unstable, degrading under the reaction conditions. This is consistent with work on the vinylogous ester system previously investigated in work within our group,[166] and also with work reported by Cavazza *et al.* The latter investigation suggests that cyclobutene ring systems similar to the one which would form in this reaction have a high propensity to undergo secondary photoreactions as mentioned previously in **Chapter 1.5.4.1**.[99] In summary the use of alkynes in the [2+2] photocycloaddition with this vinylogous imide system was deemed not to be viable.

2.2.6 Reactions of conjugated enaminones

Conjugated enaminones **245** and **249** within seven membered rings represent a novel system. It was therefore decided to investigate the chemistry of these conjugated enaminones. Of particular interest was their use in the synthesis of tropones, in particular aminotropones.

2.2.6.1 Reactions towards the synthesis of aminotropones

The tropone moiety **263** is a seven membered ring containing three conjugated alkenes and a ketone. In its extreme resonance form, **264**, it can be seen as being aromatic as it is a fully conjugated, six electron (4n+2) ring system (**Figure 26**).

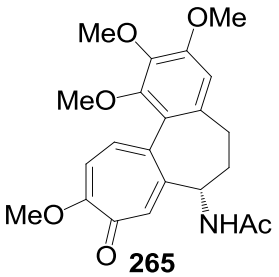


263 **264**

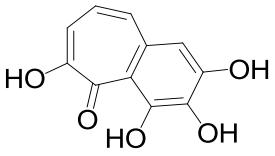
Figure 26

The tropone, tropolone (hydroxytropones) and benzotropone moieties are found in many drugs and natural products. These include colchicine **265** used as a treatment for gout and with supposed anti-tumor properties,[167] purpurogalline **266** a biological pigment,[168] and Hinokitiol **267** a natural product with anti-

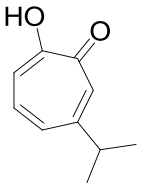
microbial and anti-fungal properties (**Figure 27**).[169] Due to the presence of these moieties in drugs and natural products, easy installation of the tropone ring into a structure is an important synthetic challenge.



265
Colchicine



266
Purpurogalline



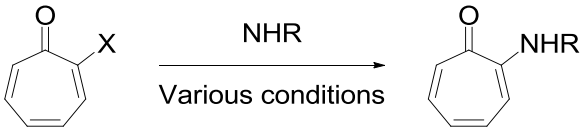
267
Hinokitiol

Figure 27

One of the most common routes for the synthesis of the tropone ring is *via* a cyclopropanation of a six membered ring followed by cleavage of the high energy cyclopropane to give a seven membered ring.[170,171,172,173,174,175,176,177,178,179] An alternative method is to use a cycloaddition reaction; [4+3],[180,181,182,183] [5+2],[184] [4+2][185,186] and [2+2] cycloadditions[115,187] have all been used to synthesise seven membered rings or intermediates which can be transformed into the tropone core. Other methods of tropone synthesis include starting with a seven membered ring and employing an oxidation or elimination reaction using the appropriate leaving groups to install the double bonds. This is often facile due to the drive towards aromatisation. This has been achieved using hydrogen bromide and acetic acid,[188] 10% palladium on charcoal,[189] bromine in acetic acid,[190,191] selenium dioxide,[192,193] DDQ[194] and the hydrolysis of dimethoxytropinone methobromide.[195]

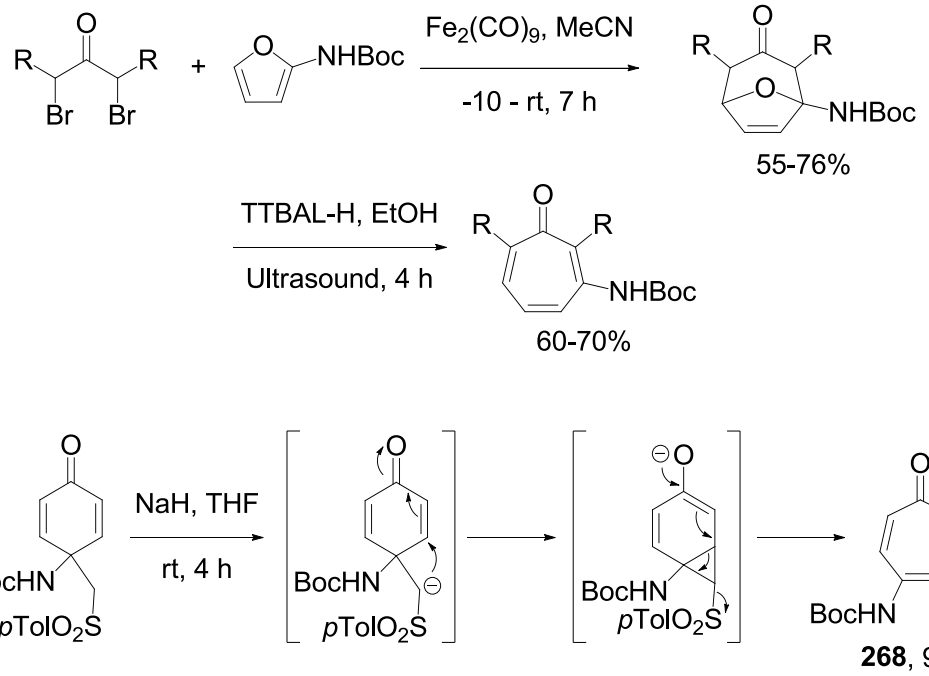
Although significantly fewer in number, there are some reports of the synthesis of aminotropones. These are often *via* the substitution of other tropones (**Scheme 137**) including: the substitution of 2-methoxytropolone with ammonia in methanol,[196] 2-tosyloxytropone using neat amines[197] and 2-((trifluoromethyl)sulfonyl)tropone in a Buchwald-Hartwig amination with a variety of anilines.[198] Catalytic hydrogenation of 3- and 4-azidotropone have been used to synthesise 3- and 4-aminotropone respectively.[199] The removal of the tosyl

group from 2-tosyl-5-aminotropone *via* catalytic hydrogenation has also been used to synthesise 4-aminotropone.[200]



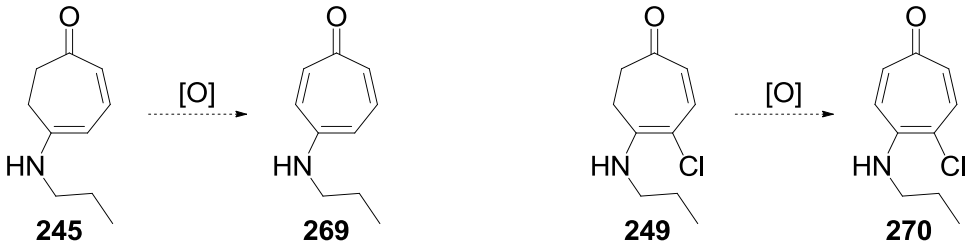
Scheme 137

Montaña *et al*. have shown that 3-aminotropones can be synthesised by a [5+2] cycloaddition between a 2-aminofuran and dibromoacetones with an $Fe_2(CO)_9$ catalyst, followed by basic fragmentation of the intermediate (**Scheme 138**, R=Me or Et).[201] 4-aminotropones have also been synthesised *via* an intramolecular cyclopropanation-fragmentation-elimination reaction starting from *p*-tosylquinamines (**Scheme 138**).[202] This latter route described by Carreño *et al.* gives 4-aminotropones such as **268**. These are very similar to those that would be formed from conjugated enaminones synthesised in this project.



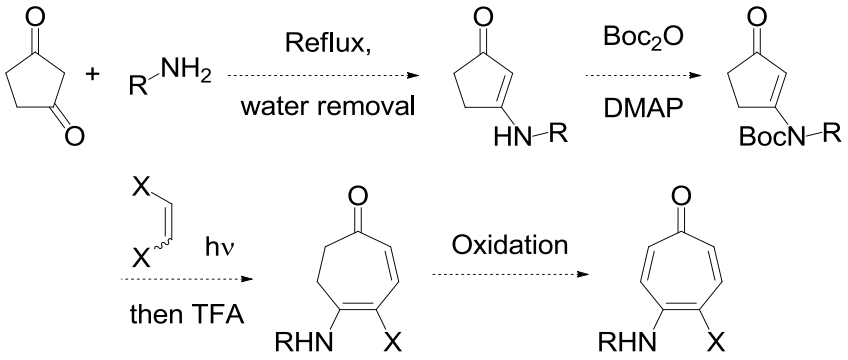
Scheme 138

Given the oxidation state of the conjugated enaminones **245** and **249** compared to those of the corresponding aminotropones **269** and **270,** it was thought that a simple oxidation could afford the desired products (**Scheme 139**).



Scheme 139

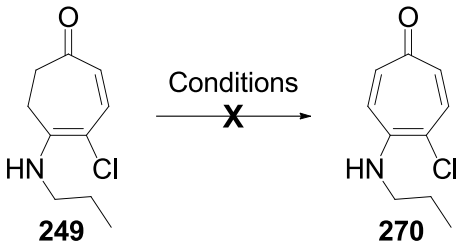
The reaction sequence to aminotropones by Carreño *et al.* (outline above) requires five steps from commercially available starting materials to aminotropones, whereas this proposed route would only require four steps from the 1,3-dione and amine (**Scheme 140**). Furthermore, by varying the amine in the condensation step, a wide variety of aminotropones could be synthesised which would be more difficult *via* other methods. All of the other reactions in the literature for the synthesis of 4-aminotropones require an existing tropone core which has to be synthesised first. Another advantage of this proposed methodology is that the oxidised form of conjugated enaminone **249** still has the chloride in place which could be used for further reactions such as coupling or substitution reactions.



Scheme 140

Initial attempts to oxidise **245** in air were unsuccessful. Stirring **245** in deuterated chloroform or methanol for six days in air led to no oxidation as monitored by ^{1}H NMR spectroscopy. Furthermore, stirring **245** in deuterated water in the presence of sodium hydroxide for six days open to the air also led to no oxidation. In all cases the only reaction noted was slight degradation of the conjugated enaminone into unknown products. Exposing conjugated enaminone **249** to these conditions led to complete degradation of the starting material within two days.

Given these results, stronger oxidation conditions were attempted, all using conjugated enaminone **249**. A number of conditions previously used in tropone syntheses were employed;[115,192-194,203,204,205] however, in all cases, none of the desired aminotropone could be isolated, or even seen in the crude NMR spectra (**Table 5**).

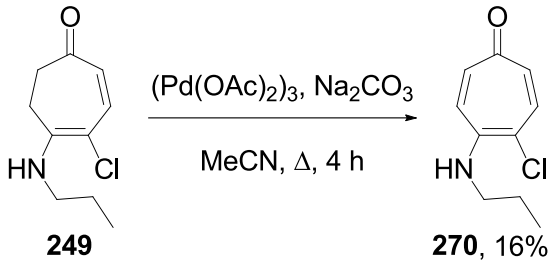


249 **270**

Entry	Oxidant	Solvent	Time	Temperature	Outcome
1	DDQ	DCM	5 min	RT	Complete degradation
2	DDQ	DCM	5 min	0 °C	Complete degradation
3	Br_2	$CHCl_3$	18 h	0 °C – reflux	Complex mixture
4	SeO_2	^tBuOH	3 h	RT	Complex mixture
5	IBX	DMSO	1 h	70 °C	Complex mixture

Table 5

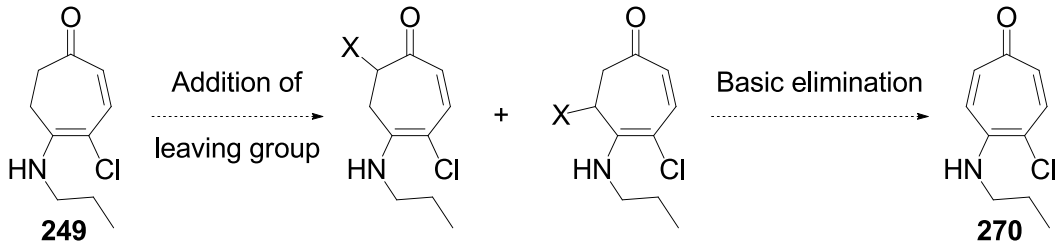
Murahashi *et al.* have used a palladium catalyst to oxidise ß-amino ketones to vinylogous amides.[206] It was hoped that this could be used to achieve the desired oxidation of conjugated enaminone **249**. The reaction went to completion in four hours, and upon purification aminotropone **270** was isolated in 16% yield (**Scheme 141**). It should be noted that this product is highly unstable. Degradation in air occurred after one week and, it is believed, occurs quickly during flash chromatography, hence the low yield. Indeed Carreño *et al.* report that aminotropones are highly unstable even in air.[202]



249 **270**, 16%

Scheme 141

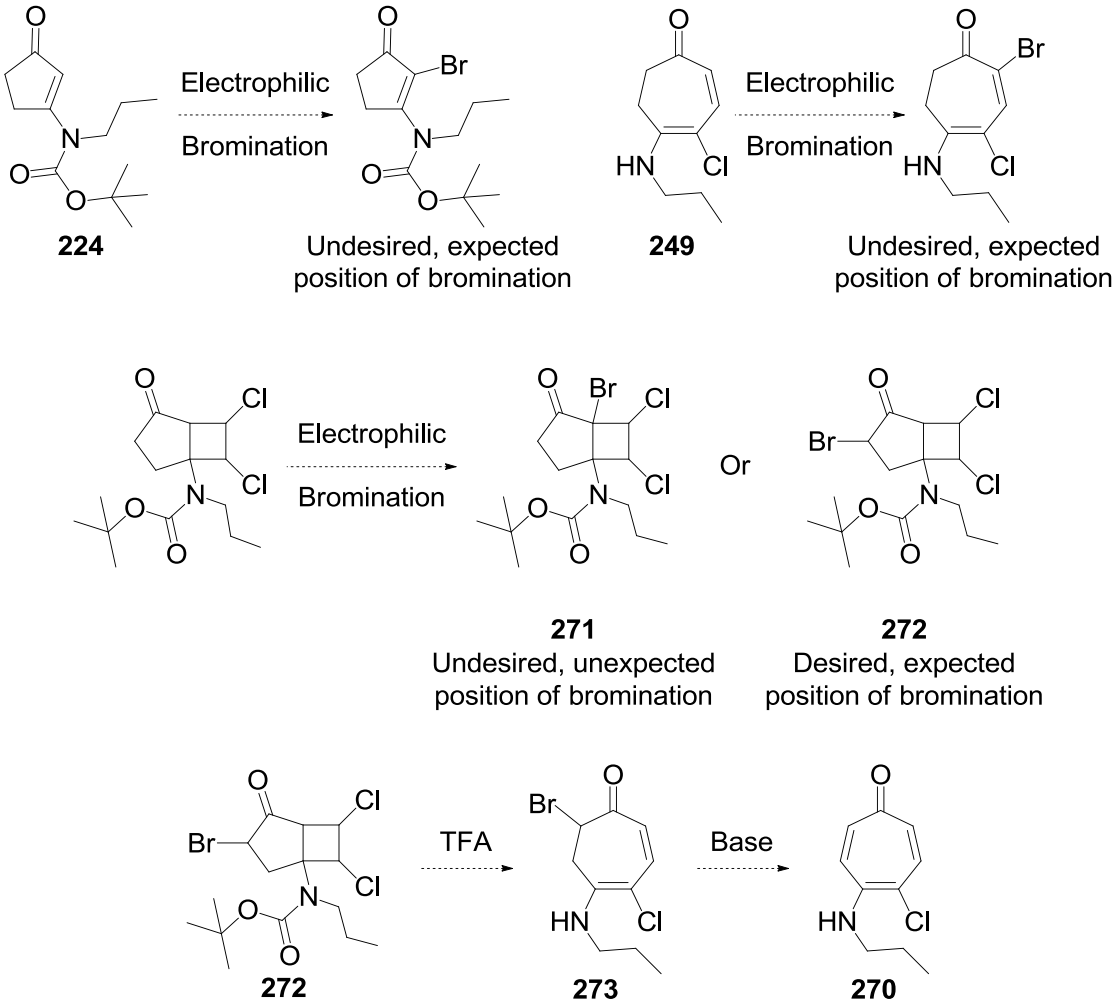
As oxidation attempts had not worked well, introduction of a leaving group onto one of the sp^3 hybridised carbon atoms followed by elimination was the next strategy attempted. It was thought that, aided by the drive towards aromatisation, this approach would afford the desired aminotropones (**Scheme 142**).



249 **270**

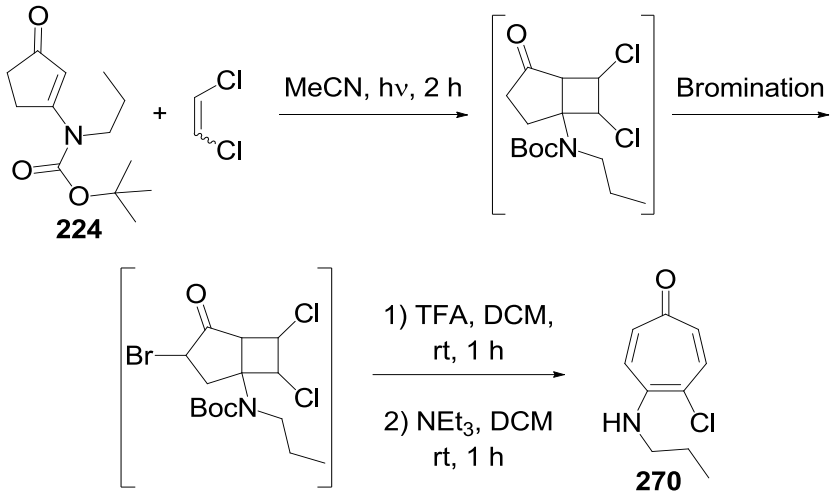
Scheme 142

The first choice of leaving group was a bromide. However, there was a concern that attempting an electrophilic bromination on either vinylogous imide **224** before the [2+2] photocycloaddition, or conjugated enaminone **249** after the [2+2] photocycloaddition, would likely lead to bromination at the wrong position. Subsequent elimination would then not be able to take place (**Scheme 143**). It was thus decided that an electrophilic bromination should be carried out on the cyclobutanes, as this is more likely to occur at the desired position. The reason for this is that electrophilic brominations go *via* an enol or enolate form of the carbonyl. However, if the double bond of the enol or enolate were to form between carbons 1 and 5, which upon bromination would yield cyclobutane **271**, a very high energy intermediate would form due to the excessive ring strain introduced. In contrast to this, a double bond between carbons 1 and 2 would be relatively unstrained, and as such should form more readily. This means that electrophilic bromination should take place at carbon 2, affording cyclobutane **272** which should afford aminotropone **270** upon basic elimination of HBr from intermediate conjugated enaminone **273** (**Scheme 143**).



Scheme 143

To test this, the cyclobutane obtained by photocycloaddition of vinylogous imide **224** with 1,2-dichloroethylene was used as it would give a single regioisomeric product. Initial tests were carried out on the crude photochemical mixture which was then subjected to the standard Boc removal conditions. This was followed by treatment with triethylamine to eliminate the installed bromide. **Table 6** outlines the conditions and outcomes of these reactions.



224 **270**

Entry	Brominating agent	Catalyst	Temperature	Solvent(s)	Time (h)	Yield[a]
1	NBS	NH_4OAc	room temperature	CCl_4	6	0%
2	NBS	$NaHSO_4$ on SiO_2	room temperature	CCl_4	6	0%
3	$CuBr_2$	None	70 °C	EtOAc $CHCl_3$	5	0%
4	$TBABr_3$	None	room temperature	DCM MeOH	18	27%
5	NBS	AIBN	80 °C	C_6H_6	3	8%

Notes: a) Isolated yield over the four steps

Table 6

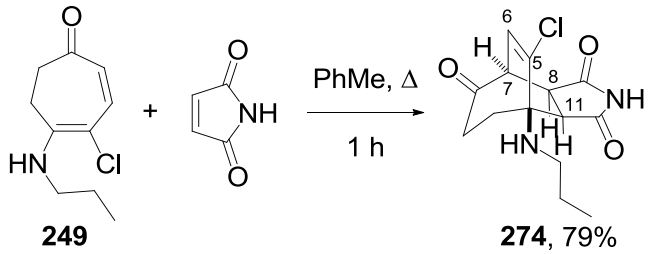
A literature investigation suggested the best reagents for this reaction would be N-bromosuccinimide (NBS), copper bromide or tetrabutylammonium tribromide ($TBABr_3$). The first attempt (entry 1) utilised ammonium acetate with NBS to form small amounts of molecular bromine *in situ*, whilst the acidic ammonium acetate would catalyse enolisation.[207] Unfortunately no product was isolated and so the acidic catalyst was changed. The use of sodium bisulfate immobilised on silica gel (entry 2) again gave no success though.[208] Attention was then turned to the use of copper (II) bromide as the brominating regent (entry 3), but this also failed to afford any of the aminotropone.[209] The use of $TBABr_3$ in a 5:2 mixture of DCM and methanol,[210] however, afforded a 27% yield of the desired amimotropone **270** (entry 4). Finally, it was hoped that a

radical bromination might yield the desired product. However, whilst using NBS with the radical initiator AIBN did afford an 8% yield of aminotropone **270,** it did not improve upon the previous yield. It is possible that part of the problem encountered with these reactions is due to the instability of the aminotropone. This is exemplified by the fact that it degrades on standing in the air or in chloroform in under 12 hours.

Due to these problems, it was decided that attention should be turned away from the synthesis of aminotropones and towards the Diels-Alder reactions of these conjugated enaminones. However, during this investigation, a serendipitous route to aminotropones was discovered in excellent yield as outlined below (*vide infra*).

2.2.6.2 Diels-Alder reactions with conjugated enaminones and a new route to aminotropones

There was particular interest in the use of the conjugated enaminones in the Diels-Alder reaction as this would yield interesting polycyclic products. It was found that the Diels-Alder reaction between conjugated enaminone **249** and maleimide, a commonly used dienophile in the Diels-Alder reaction,[211,212,213] afforded Diels-Alder adduct **274** as a single diastereoisomer in good yield (**Scheme 144**).



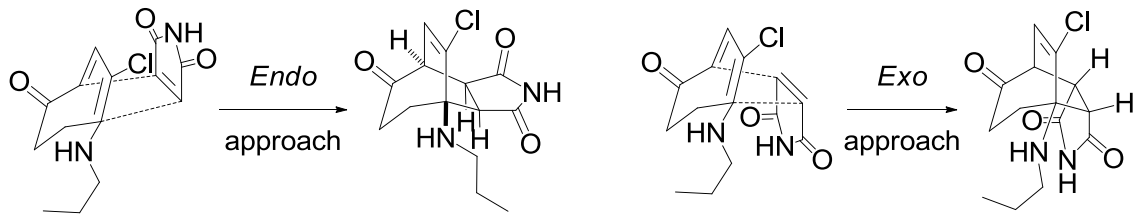
249 **274**, 79%

Scheme 144

This reaction displays excellent diastereoselectivity, affording a single product, **274**. The structure of this product was assigned by careful measurement of J-coupling values and a NOeSY NMR experiment. Construction of a 3D model of **274** shows that the torsional angle between protons H-7 and H-8 is

approximately 90°. When this is the case there will be no 3-bond J-coupling between these two protons, and indeed this is what is seen in the ^{1}H NMR spectrum of **274.** Both of the peaks for H-7 and H-8 are sharp doublets, corresponding to their coupling with H-6 and H-11 respectively as seen by a COSY NMR experiment. Although the other diastereomer was not formed for comparison, a molecular model can be made and the dihedral angle for the corresponding H-7 and H-8 protons can be estimated. By this method, the angle would be approximately 20-30°, which would give rise to significant J-coupling in the ^{1}H NMR spectrum providing further evidence for the isolated product being **274**. Furthermore, a NOeSY NMR experiment suggests that there is no NOe between H-7 and H-8, as expected for this product.

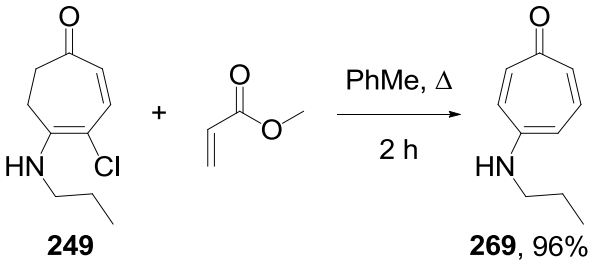
Diels-Alder adduct **274** is formed by the *endo* approach of the maleimide to the conjugated enaminone **249**. In theory, a second product **275**, could be formed *via* an *exo* approach of the maleimide to **249**. **Figure 28** shows both possible reactions. Generally the product from the *endo* approach will be favoured due to favourable secondary orbital interactions in the transition state. In the case of the Diels-Alder reaction between conjugated enaminone **249** and maleimide, this is presumably favoured to such an extent that a single product is formed.



274 **275**

Figure 28

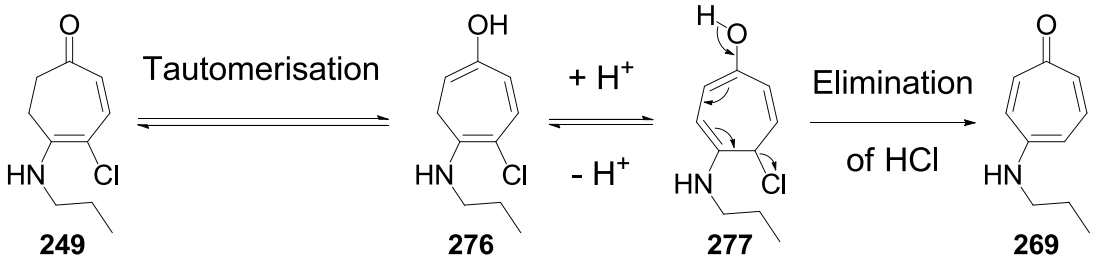
Interested in broadening the scope of this reaction, the Diels-Alder reaction of conjugated enaminone **249** with methyl acrylate, another commonly used dienophile in Diels-Alder reactions,[214,215,216] was then attempted. However, in this case no Diels-Alder reaction occurred. Instead, surprisingly, aminotropone **269** was isolated in an excellent 96% yield (**Scheme 145**).



249 **269**, 96%

Scheme 145

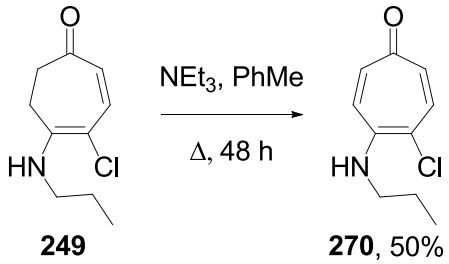
It is postulated that this aminotropone is formed *via* a tautomerisation of conjugated enaminone **249** to give enol **276**, followed by a rearrangement to **277**, from which elimination of HCl can take place to afford the aminotropone **269**. The eliminated HCl can then catalyse further tautomerisation (**Figure 29**).



249 **276** **277** **269**

Figure 29

The role of methyl acrylate in this reaction was investigated by running the reaction again without any dienophile present. As with the reaction containing methyl acrylate, the starting material was consumed within two hours and aminotropone **269** was formed in 96% yield showing that it plays no part in the reaction. Interested in whether this reaction was catalysed by trace amounts of acid in the solvent or from the starting material, the reaction was run in the presence of five equivalents of triethylamine; any acid in this case would be neutralised by the base. After two hours, starting material predominated, but another product was present by TLC analysis which did not correspond to **269**. Leaving the reaction for two days, the starting material had been fully consumed and purification afforded aminotropone **270** in 50% yield (**Scheme 146**).

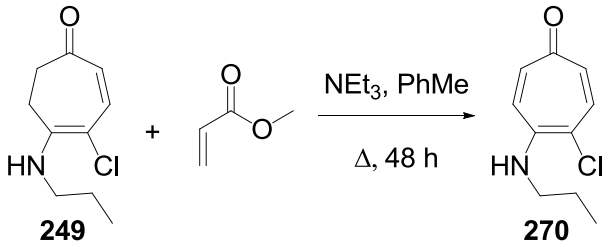


249 **270**, 50%

Scheme 146

This outcome supports the hypothesis that the formation of **269** from **249** is catalysed by trace amounts of acid in the reaction mixture as addition of the base stops this transformation. It is believed that the formation of aminotropone **270** is due instead to the oxidative action of the air. Indeed, running the reaction in degassed solvent under a blanket of argon led to significantly slower conversion, the starting material only being consumed after four days. It is likely that this conversion is due to small amounts of air entering the system over the long time course. In this case, **270** was formed in a lower 39% yield, most likely due to the instability of aminotropones,[202] as over time the product can degrade more. Furthermore this is likely to be the reason for the lower yield of the reaction in air to form **270,** compared to that without the base present to form **269**.

Despite finding a route to aminotropones, there was still interest in the Diels-Alder reactions of conjugated enaminone **249**. It was noted that the reaction with maleimide led to the Diels-Alder adduct **274** within an hour and showed no signs of the aminotropone **269** in the crude ^{1}H NMR spectrum. This is in stark contrast to the reaction with methyl acrylate which led to aminotropone **269** after two hours with no sign of the Diels-Alder adduct. This suggested that the elimination of HCl was occurring quicker than the Diels-Alder reaction with methyl acrylate. It was thus postulated that stopping the elimination by adding a base might allow the Diels-Alder reaction to take place. However, upon repeating the reaction in the presence of triethylamine, only slow conversion to the aminotropone **270** took place, as it did with no methyl acrylate (**Scheme 147**). It is likely that this Diels-Alder reaction is too slow for any conversion to take place before elimination or oxidation.

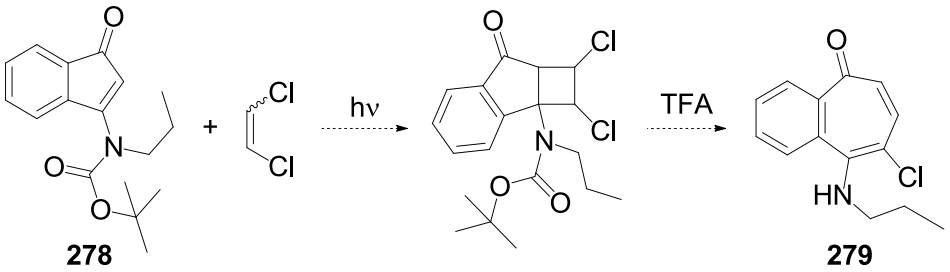


Scheme 147

It was evident that heating **249** led to elimination of HCl and the formation of the aminotropone. It was thus decided to attempt a Lewis acid catalysed Diels-Alder reaction which could be carried out at room temperature, thereby circumventing the aminotropone formation. Furthermore, it was hoped that this would speed up the reaction enough to see a noticeable conversion. A series of Lewis acids which had previously been used in Diels-Alder reactions were tested with methyl acrylate as the dienophile. However none of the reactions afforded the desired Diels-Alder adducts. Reactions with $FeCl_3$[217] and $AlCl_3$[218] gave no reaction, whilst reactions with $CuCl_2$,[219] $SnCl_4$[220] and $Ti(O^iPr)_4$[218] led to degradation of the starting material. Given the sensitivity of the conjugated enaminone **249**, and the above results, it was decided that this method would not be viable as the starting material is likely too unstable.

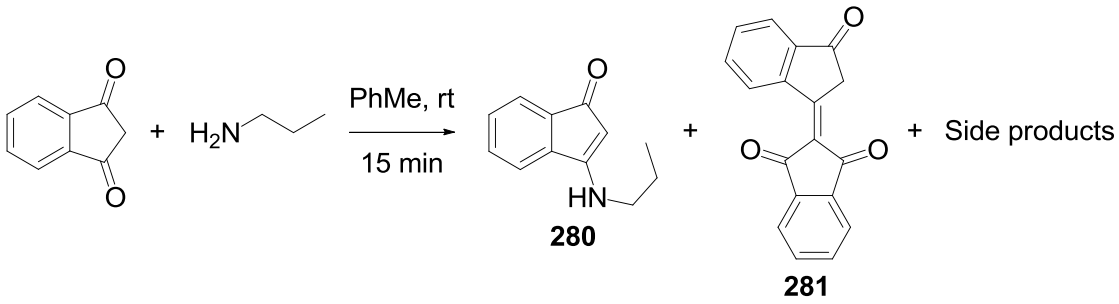
2.2.7 Reactions towards the synthesis of amino-benzotropones

As well as tropones, benzotropones are also found in a variety of natural products and have also been synthesised in a multitude of ways.[221,222, 223,224] It was envisaged that using the photocycloaddition-fragmentation protocol that had been developed in this project, amino-benzotropones could be accessed. If the [2+2] photocycloaddition of benzovinylogous imide **278** and 1,2-dichloroethylene with subsequent Boc removal, followed the same path as that with vinylogous imide **224**, then the resulting product would be amino-benzotropone **279** (**Scheme 148**). In this case no final oxidation step would be required to access the tropone core.



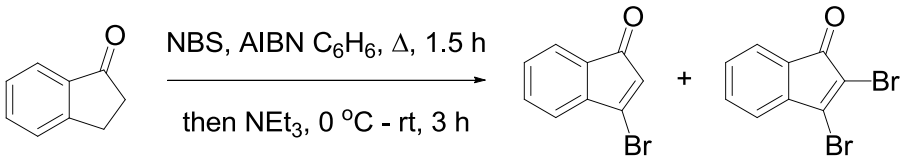
Scheme 148

The first step in this synthesis was to make benzovinylogous amide **280**. It was hoped that this could be made in the same way as previous vinylogous amides, in this case using 1,3-indandione as the starting material rather than 1,3-cyclopentadione. However, upon the addition of propylamine to a solution of the dione at room temperature, the solution immediately changed colour and TLC analysis showed that the starting material was fully consumed within 15 minutes affording a complex mixture. Isolation of these products clean proved impossible, but impure samples were obtained of what is believed to be vinylogous amide **280** and known trione **281**[225,226] by careful inspection of the NMR spectra (**Scheme 149**). It is postulated that **281** is formed *via* a base catalysed self-condensation as reported by Würthner *et al.*[225,226]



Scheme 149

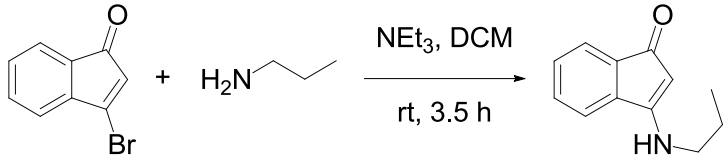
Given this problem, it was decided to attempt this synthesis *via* the protocol of Sheridan *et al.* for the synthesis of a similar benzovinylogous amide.[227] This involved a double radical bromination of 1-indanone with N-bromosuccinimide (NBS) using the radical initiator 2,2'-azobis(2-methylpropionitrile) (AIBN), followed by the *in situ* elimination of HBr with triethylamine. The reaction afforded bromoindenone **282** in 64% yield over the two steps, along with a 4% yield of the known, doubly brominated indenone **283** (**Scheme 150**).[228]



282, 64% **283**, 4%

Scheme 150

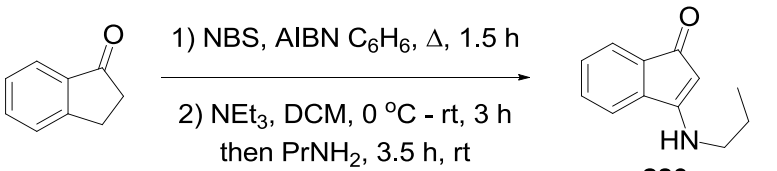
Still following the protocol of Sheridan *et al.*[227] the bromide was displaced with propylamine, using triethylamine as a base, affording benzovinylogous amide **280** in 55% yield (**Scheme 151**). It is worth noting that **280** slowly degrades in air and upon purification; this is likely to account for the moderate yield.



282 **280**, 55%

Scheme 151

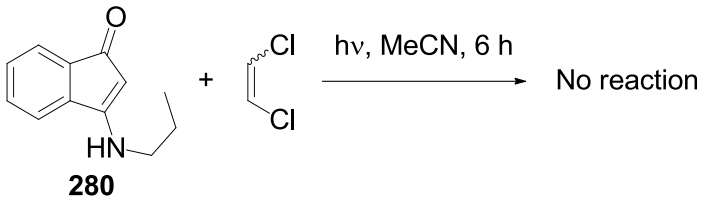
It was noted that this step could theoretically be combined with the step before to make the synthesis more convenient. However, running this reaction without an intermediate purification step led to a reduction in the overall yield from 35% to 20% over the three steps (**Scheme 152**).



280
20% over 3 steps

Scheme 152

With benzovinylogous amide **280** in hand, the intermolecular [2+2] photocycloaddition with 1,2-dichloroethylene could be tested to see if it would take place. However, even after six hours of irradiation, TLC analysis suggested that no reaction had taken place at all (**Scheme 153**).

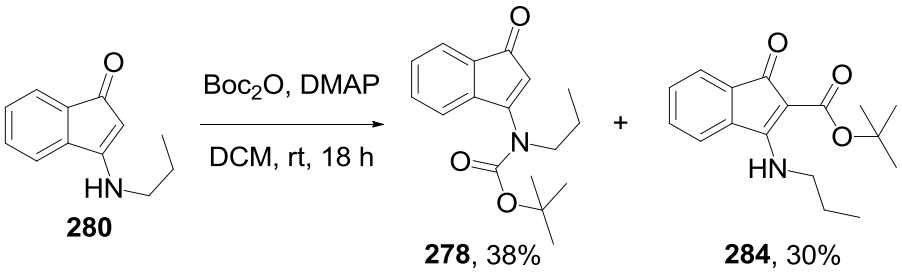


280

Scheme 153

The reason for this is unclear. It is possible that as before the enone does not contain sufficient double bond character for the reaction to take place. The double bond of the enone will be partially delocalised into the aromatic ring as well as the ketone which supports this argument. Another possibility is that the aromatic ring could be quenching the excited state of the enone, stopping it from being able to react with the alkene.

With this in mind, it was hoped that addition of the Boc group would facilitate the intermolecular [2+2] photocycloaddition reaction as it has done previously. Boc addition to benzovinylogous amide **280** under the standard conditions, using 1.2 equivalents of Boc anhydride and a catalytic amount of DMAP, afforded the desired benzovinylogous imide **278** in a disappointing 38% yield. This low yield was a consequence of the additional formation of benzovinylogous amide **284** in 30% yield where the Boc addition had taken place at the α-carbon (**Scheme 154**). Furthermore 30% of the starting material was recovered.



280

278, 38%

284, 30%

Scheme 154

Disappointed with the low yield, the reaction was attempted in different solvents. Changing to THF, acetonitrile or chloroform did not improve the yield. It should be noted that during the reaction using chloroform, no **284** was seen by TLC analysis after one hour, only starting material and **278**. However, upon leaving the reaction for a day, TLC analysis revealed that starting material was still

present and the major product was now **284** with no **278** present. This therefore suggests that **278** was being converted into **284** or being broken down reforming the starting material. Furthermore, heating the reaction only seemed to increase this conversion, some **284** being seen after just an hour. These results suggest that benzovinylogous imide **278** is the kinetic product from this Boc addition reaction, whereas benzovinylogous amide **284** is the thermodynamic product. Increasing the amount of Boc anhydride to two, three or five equivalents gave the same results. Adding triethylamine to the reaction mixture did not improve the yield of the desired product, nor did changing the amounts of DMAP from 5 mol% down to 2 mol%, or increasing it to 50 mol% or one equivalent. Removing the DMAP entirely led to no reaction taking place.

Before attempting to optimise the Boc protection further, it was important to test the photoreactivity of benzovinylogous imide **278**. To this end, **278** was irradiated in the presence of 10 equivalents of 1,2-dichloroethylene. The starting material was fully consumed within two hours; however, the result was a complex mixture of products from which no identifiable products could be isolated clean. The mixture was treated with TFA to see if any of the desired amino-benzotropone could be isolated. Unfortunately this led to an even more complex mixture of products, from which nothing was cleanly isolated (**Scheme 155**). However, it was evident from the ^{1}H NMR spectrum of the fractions from flash column chromatography that the desired amino-benzotropone was not present.

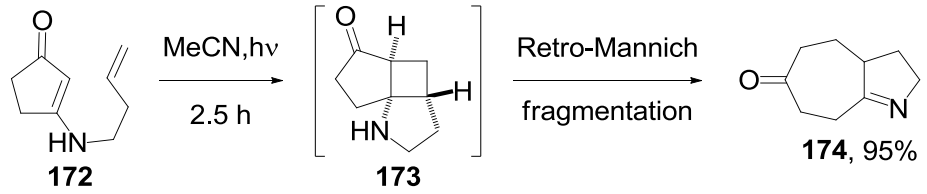
Scheme 155

The reason for this complex mixture could be twofold. In the case that the product does form, it is possible that the electronics of the resultant cyclobutane compared to those synthesised previously, result in it undergoing secondary

photoreactions. Alternatively, the desired [2+2] photocycloaddition does not take place, and instead the photoactive indenone may undergo other photochemical reactions. Without being able to isolate any of the products from this reaction, it is not possible to tell which of these pathways occurred. As a result of these problems, this reaction was deemed not to be a viable route towards amino-benzotropones.

2.3 Summary and future work

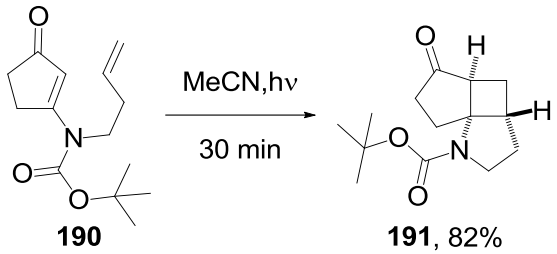
Work to date has shown that a number of interesting structures are accessible starting from [2+2] photocycloadditions of vinylogous amides and vinylogous imides. To test these reactions, a number of these starting compounds were synthesised in moderate to excellent yields. Irradiation of vinylogous amide **172** led to a [2+2] photocycloaddition followed by a spontaneous retro-Mannich fragmentation, forming keto-imine **174** in excellent yield (**Scheme 156**).



172 **173** **174**, 95%

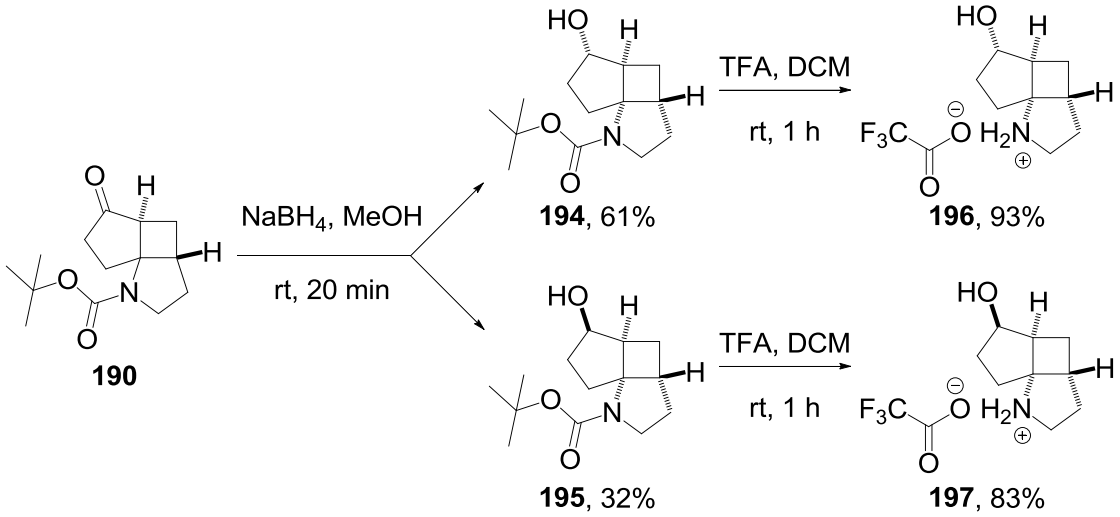
Scheme 156

The addition of a Boc group onto the nitrogen not only significantly increased the rate of the [2+2] photocycloaddition, but circumvented the retro-Mannich fragmentation. This enabled access to aminocyclobutane **191**, again in a very good yield (**Scheme 157**). The synthesis of aminocyclobutanes was one of the main aims of this project as they are commonly found in natural product and drug molecules. As a result of this the synthesis of cyclobutanes, in particular with a heteroatom handle, is an important synthetic tool.



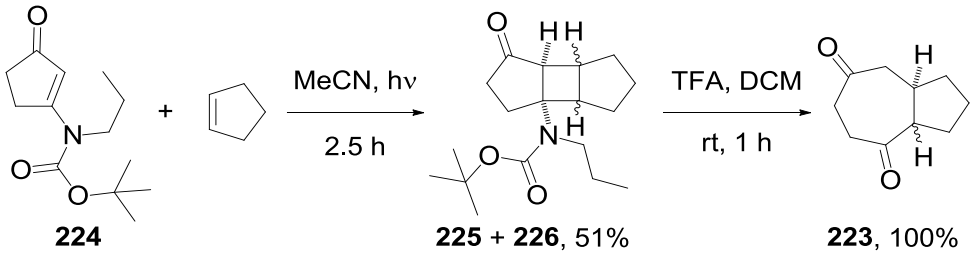
Scheme 157

Reduction of the ketone gave two separable diastereoisomers **194** and **195**, which did not undergo fragmentation upon removal of the Boc group. Instead, free aminocyclobutanes **196** and **197** were isolated (**Scheme 158**). The overall yields for these reactions were very good, **196** being formed in 47% yield over the three steps, and **197** in 22% yield over the three steps.



Scheme 158

The intermolecular [2+2] photocycloaddition between various vinylogous amides and various alkenes led to no reaction at all. However, by the addition of a Boc group on to the nitrogen, the photocycloaddition could take place. Removal of the Boc group was facile and the resulting products were of the de Mayo type, 1,5-diketones. This reaction was exemplified by the reaction between vinylogous imide **224** and cyclopentene, followed by removal of the Boc group to give diketone **223** in 51% yield over two steps as a 10:1 mixture of diastereoisomers (**Scheme 159**).

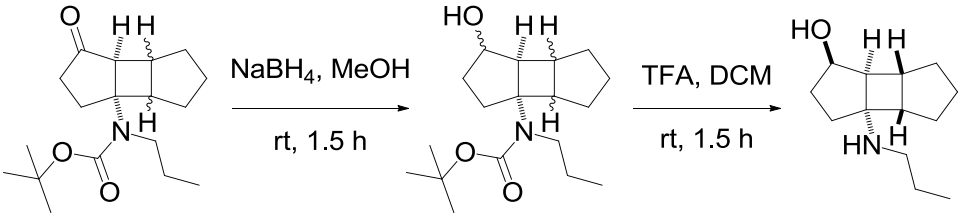


224 **225** + **226**, 51% **223**, 100%

Scheme 159

This diketone is not accessible *via* the classic de Mayo reaction, thus this reaction represents an alternative approach to the de Mayo reaction in such cases. Indeed, the lack of literature reports in the area suggests that the de Mayo reaction is limited in its scope. A chiral de Mayo reaction could also be envisaged from this finding by using a vinylogous imide with a chiral amine portion in the photocycloaddition. Due to the nature of the classic de Mayo reaction, this would otherwise be impossible. These findings are therefore an important step towards a useful, asymmetric photochemical reaction.

Again it was shown that reduction of the ketone allowed removal of the Boc group without the retro-Mannich fragmentation taking place. This was exemplified by the reduction and subsequent Boc removal from cyclobutanes **225** and **226**, affording aminocyclobutane **234** in 29% yield over two steps (**Scheme 160**).

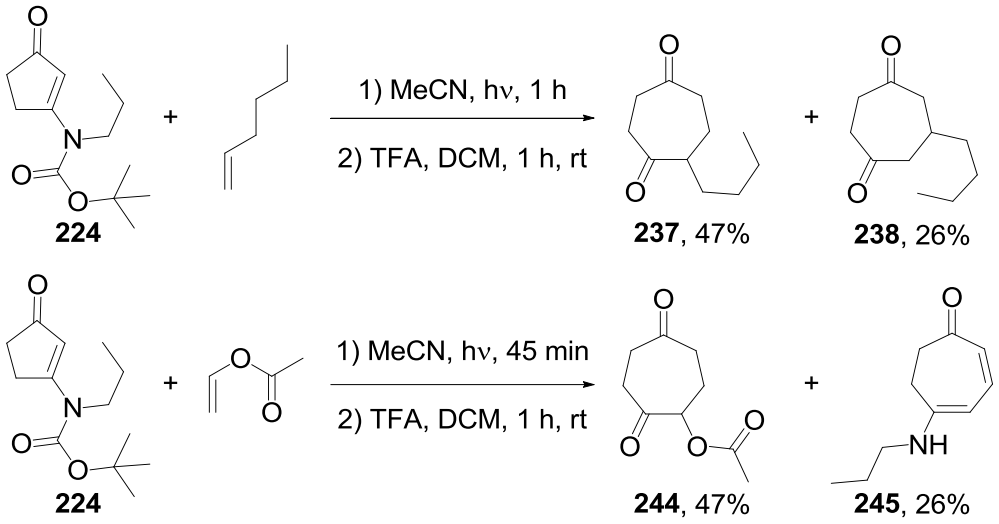


225 + **226** **230** + **231**, 100% **234**, 29%

Scheme 160

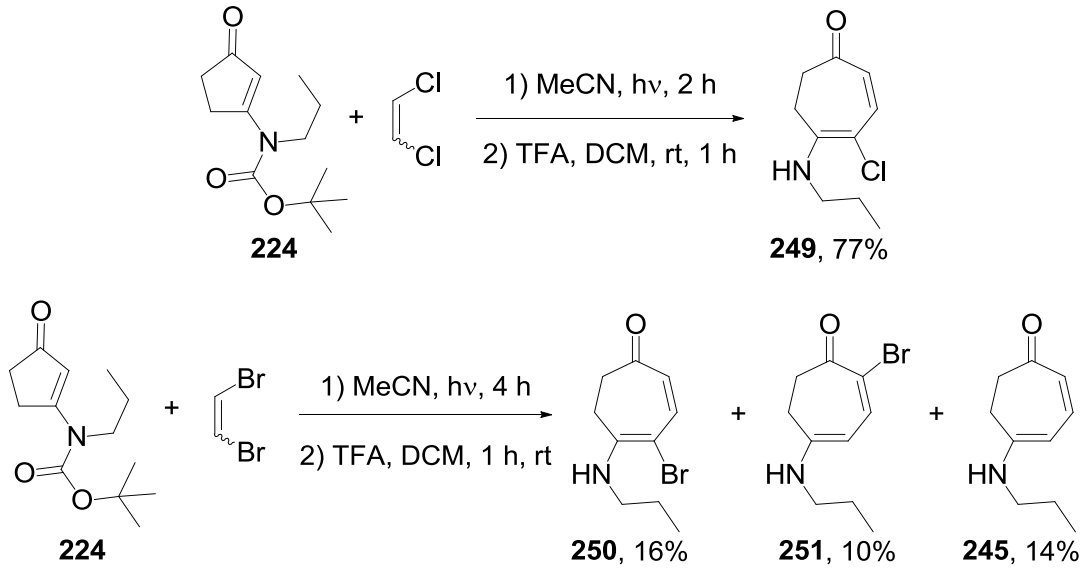
The scope of this photocycloaddition-fragmentation reaction was investigated by using a variety of alkenes. The cyclobutanes were not isolated, as they existed as a number of regioisomers and diastereoisomers; instead the crude photochemical mixture was treated directly with TFA. The reaction between vinylogous imide **224** and 1-hexene yielded the expected diketones **237** and **238**. However, upon repeating the same sequence using vinyl acetate as the

alkene led to one expected product, diketone **244** and one unexpected product, conjugated enaminone **245** (**Scheme 161**).



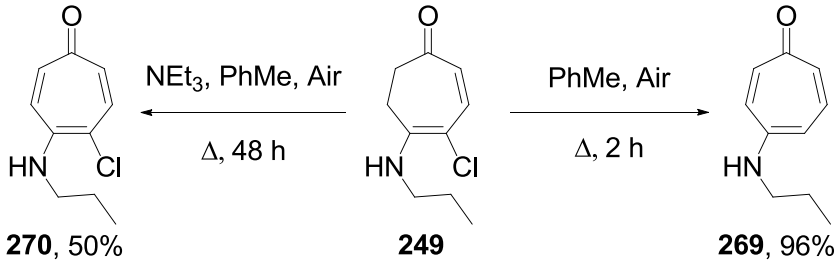
Scheme 161

It was found that using an alkene with at least one leaving group attached, in the intermolecular [2+2] photocycloadditions with vinylogous imide **224**, followed by immediate Boc removal, allowed access to a number of these conjugated enaminones (**Scheme 162**). Such conjugated enaminones within a seven membered ring are entirely absent from the literature. In the reaction with 1,2-dichloroethylene, only one product was isolated, conjugated enaminone **249** in 77% yield. However, using 1,2-dibromoethylene the expected product, conjugated enaminone **250**, was isolated alongside conjugated enaminone **251** where the bromide is situated on a different carbon, and the debrominated conjugated enaminone **245**.



Scheme 162

It was found that conjugated enaminone **249** could be transformed into aminotropone **269** by heating it in air. By adding triethylamine into this reaction, aminotropone **270** was isolated instead of **269** (**Scheme 163**).

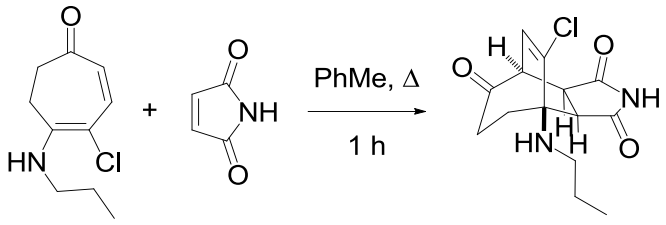


Scheme 163

Like cyclobutanes, the tropone core is found in a number of natural products and drug molecules, thus access to this system is an important tool. Furthermore, it is hypothesised that these aminotropones could also find use in the field of therapeutics. This method could allow access to a number of substituted aminotropones which could not be accessed previously by existing literature methods.

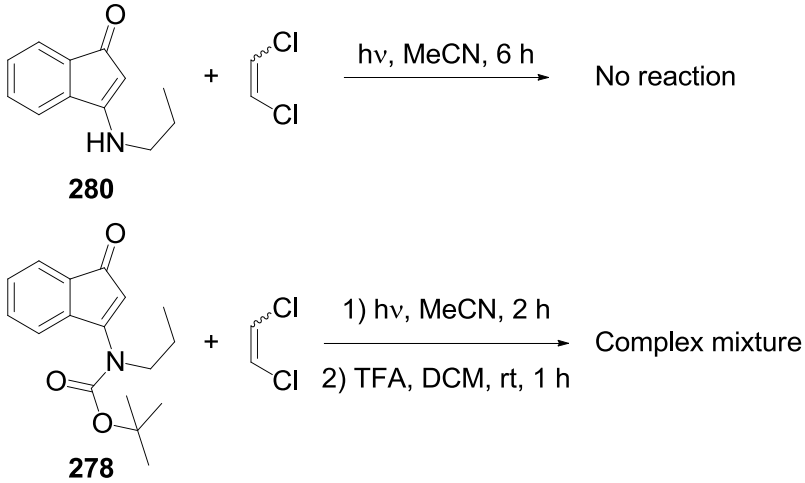
It was found that conjugated enaminone **249** undergoes a Diels-Alder reaction with maleimide, affording Diels-Alder adduct **274** as a single diastereoisomer in a good yield (**Scheme 164**). This reaction, and the transformation to

aminotropones, demonstrates well some of the chemistry of these novel conjugated enaminones.



Scheme 164

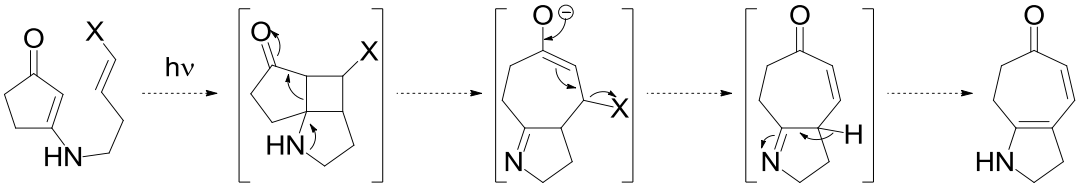
Finally attempts were made to synthesise amino-benzotropones *via* the developed methodology. Benzovinylogous amide **280** was synthesised, which failed to undergo any photochemical reaction with 1,2-dichloroethylene. However, upon photolysis of benzovinylogous imide **278** in the presence of the same alkene, a complex mixture was obtained. Upon treatment with TFA, ^{1}H NMR spectroscopy suggested that none of the desired amino-benzotropone had formed (**Scheme 165**).



Scheme 165

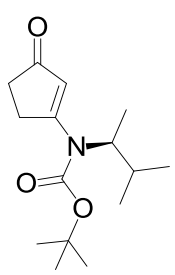
Future work on this project would be to further develop the scope of these reactions. Although a number of alkenes have been studied in this project, there remain others to be tested, in particular alkenes with leaving groups attached. This would increase the number of conjugated enaminones which are accessible *via* this methodology. Finding a way to tether this kind of alkene to the cyclopentenone core would also be valuable given the success of the intramolecular [2+2] photocycloaddition and might avoid the need to add a Boc

group to the vinylogous amide (**Scheme 166**). Further investigation into the reactions of the conjugated enaminones would also be an interesting avenue of future work.

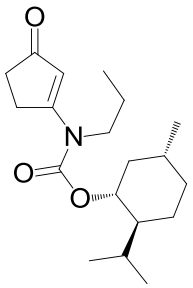


Scheme 166

Development of the scope of this methodology could also focus on different vinylogous imides, formed from different amines. Of particular interest would be the use of chiral amines in the synthesis of chiral vinylogous imides such as **285**, or the use of chiral carbamates to make chiral vinylogous imides such as **286** (**Figure 30**). The chiral nature of these compounds could lead to asymmetric photochemical reactions, an area of chemistry which is currently very limited. Of particular interest would be their use towards chiral de Mayo products, which cannot be accessed *via* the classic de Mayo reaction.



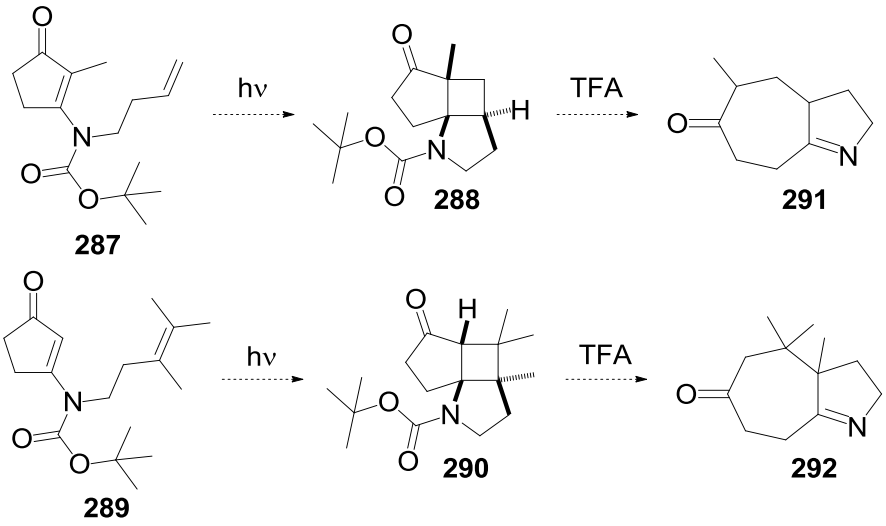
285



286

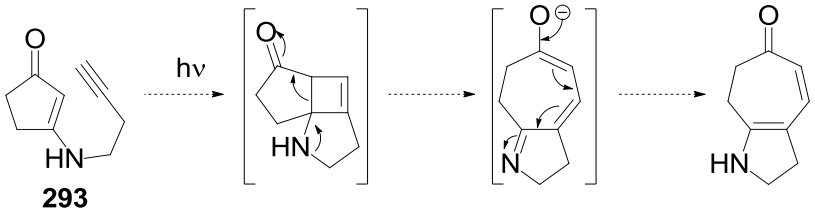
Figure 30

Other vinylogous imides which could be investigated could be based on the ones used in this project; in particular more highly substituted vinylogous imides could be used. For example vinylogous amides with methyl groups at the α-position such as vinylogous imide **287** which would likely yield cyclobutane **288**; or those with more complex tethered alkenes such as vinylogous imide **289**, irradiation of which would give cyclobutane **290**. Furthermore, removal of the Boc group from these aminocyclobutanes, or irradiation of the corresponding vinylogous amides before the Boc group was added could yield ketoimines **291** and **292** (**Scheme 167**).



Scheme 167

A final area of development in this methodology would be to further explore the [2+2] photocycloadditions of these vinylogous amides and imides with alkynes. Of particular interest would be the synthesis and irradiation of a vinylogous amide with a tethered alkyne, such as vinylogous amide **293**. Given the difficulties encountered using alkynes in the intermolecular [2+2] photocycloaddition, and their propensity to undergo secondary photoreactions,[99] carrying out an intramolecular reaction would preclude the need to isolate the cyclobutenes. Furthermore, the resulting products would likely be conjugated enaminones, again allowing access to more of these interesting, novel compounds (**Scheme 168**).



Scheme 168

3. Experimental section

3.1 General Information

All reactions were carried out at atmospheric pressure, under argon unless otherwise stated. Solvents and reagents were purchased from suppliers (Alfa Aesar and Aldrich) and used without any further purification. Normal phase silica gel (BDH) and sand (VWR) were used for flash chromatography unless otherwise stated. All reactions were monitored by thin layer chromatography (TLC) unless otherwise stated. TLC plates pre-coated with silica gel 60 F254 on aluminium (Merck KGaA) were used, detection was by UV (254 nm) or chemical stain ($KMnO_4$ or vanillin). Mass Spectrometry was performed using a VG70 SE operating in EI, CI (+ or -) or ES (+ or -) modes depending on the sample. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz, 500 MHz or 600 MHz and ^{13}C NMR at 100 MHz, 125 MHz or 150 MHz on a Bruker AMX300, AMX400, AMX500 or AMX600 at ambient temperature unless otherwise stated. Chemical shifts (δ) are quoted in ppm. The multiplicity of the signal is indicated as: s-singlet, d-doublet, t-triplet, q-quartet, sext-sextet, dd-doublet of doublets, dt-doublet of triplets, td-triplet of doublet, qd-quartet of doublets, ddd-doublet of doublet of doublets, dtd-doublet of triplet of doublets, ddt-doublet of doublet of triplets, dddd-doublet of doublet of doublet of doublets, br-broad, m-multiplet defined as all multipeak signals where overlap or complex coupling of signals makes definitive descriptions of peaks difficult. All peaks should be taken as sharp unless otherwise described. Coupling constants are quoted in Hz to one decimal place. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected.

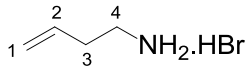
3.2 Abbreviations

Within this text, room temperature is defined as between 19 ºC - 22 ºC. The term *in vacuo* is used to describe solvent removal by Büchi rotary evaporation between 17 ºC and 60 ºC, at approx. 10 mmHg. The term ‘degassed’ refers to

the process of removing O_2 from a solution by bubbling argon through a sealed vessel containing the solution. Irradiations were carried out using a medium pressure 125 W mercury lamp, cooled via a water well. For NMR experiments, $CDCl_3$ is fully deuterated (D_3) chloroform, DMSO is fully deuterated (D_6) dimethylsulfoxide, and MeOD is fully deuterated (D_4) methanol. Solvents were chosen according to the position of solvent peak in the spectra and solubility of the substrate. Petroleum ether is petroleum ether (40-60 ºC), EtOAc is ethyl acetate, DCM is dichloromethane, MeOH is methanol, Et_2O is diethyl ether, MeCN is acetonitrile, PhMe is toluene, NEt_3 is triethylamine and TFA is trifluoroacetic acid.

3.3 Experimental procedures

But-3-enylamine hydrobromide[145,146] (183)

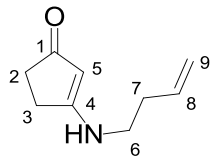


183

4-bromo-1-butene (133 mg, 0.100 mL, 0.985 mmol) was dissolved in a saturated solution of ammonia in methanol (4.5 mL) in a microwave vial. The mixture was stirred at 110 ^oC for 30 min in the microwave. The solvent was removed *in vacuo*, affording amine **183** as a white solid (143 mg, 0.941 mmol) in 95% yield. m.p. dec. >150 °C.

^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (br, 3H, NH_3), 5.79 (ddt, 1H, *J* = 17.1, 11.5 and 6.9, H-2), 5.29-5.19 (m, 2H, H-1), 3.14 (sext, 2H, *J* = 7.0, H-4), 2.58 (q, 2H, *J* = 7.0, H-3); ^{13}C NMR (125 MHz, 1:1 $CDCl_3/CD_3OD$) 133.7 (CH), 120.2 (CH_2), 40.2 (CH_2), 32.7 (CH_2); IR (solid, cm^{-1}) 3097 (s), 3007 (s), 1968 (w); MS (EI) *m/z* (relative intensity): 138 (M^+ -HBr, 27), 86 (71), 84 (100), 82 (20), 80 (19), 55 (40), 51 (45), HBr salt not seen, exact mass could not be measured due to small size.

3-(But-3-en-1-ylamino)cyclopent-2-enone (172)



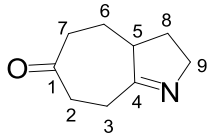
172

Method 1: To a suspension of 1,3-cyclopentadione (181 mg, 1.85 mmol) in dry PhMe (6 mL) was added 3-buten-1-amine hydrochloride (199 mg, 1.85 mmol) and NEt_3 (256 µL, 187 mg, 1.85 mmol). The mixture was stirred at reflux under Dean-Stark conditions for 18 h. The solvent was removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAc) afforded vinylogous amide **172** as a white solid (226 mg, 1.50 mmol) in 81% yield.

Method 2: To a solution of amine **183** (497 mg, 3.25 mmol) in dry PhMe (7 mL) was added 1,3-cyclopentadione (322 mg, 3.29 mmol), NEt_3 (332 mg, 440 µL, 3.29 mmol) and 4 Å molecular sieves. The solution was stirred at reflux for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAC) afforded vinylogous amide **172** as a white solid (442 mg, 2.89 mmol) in 89% yield. m.p. 123-124 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddt, 1H, *J* = 17.0, 10.2 and 6.8, H-8), 5.57 (br, 1H, NH), 5.13-5.08 (m, 2H, H-9), 5.00 (s, 1H, H-5), 3.19 (q, *J* = 6.4, 2H, H-6), 2.52 (m, 2H, H-3), 2.39-2.34 (m, 4H, H-2 and H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (C), 176.5 (C), 134.6 (CH), 117.1 (CH_2), 99.3 (CH), 44.0 (CH_2), 33.7 (CH_2), 32.9 (CH_2), 28.1 (CH_2); IR (solid, cm^{-1}) 3193 (w), 2977 (w), 2929 (w), 2861 (w), 1634 (m), 1568 (s), 1525 (s); MS (EI) *m*/z (relative intensity): 151 (M^+, 17), 144 (13), 110 (54), 88 (16), 86 (100); Exact mass calculated for [$C_9H_{13}NO$] requires *m/z* 151.09917, found 151.09966 (EI).

3,3a,4,5,7,8-Hexahydrocyclohepta[b]pyrrol-6(2H)-one (174)



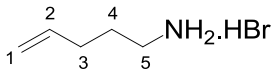
174

Method 1: A solution of vinylogous amide **172** (180 mg, 1.20 mmol) in MeCN (60 mL) was degassed for 20 min and irradiated for 2.5 h. The solvents were removed *in vacuo* and purification by flash chromatography on alumina (DCM) afforded keto-imine **174** as a light yellow oil (171 mg, 1.14 mmol) in 95% yield.

Method 2: To a solution of Boc protected aminocyclobutane **191** (20 mg, 0.080 mmol) in DCM (2 mL) was added TFA (2 mL) and the mixture stirred for 1 h. The solvents were removed *in vacuo* and purification by flash chromatography on alumina (DCM) afforded keto-imine **174** as a light yellow oil (10 mg, 0.068 mmol) in 85% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91-3.81 (m, 1H, *H*H-9), 3.73-3.64 (m, 1H, H*H*-9), 2.89-2.77 (m, 2H, *H*H-3 and H-5), 2.68-2.57 (m, 4H, H-2 and H-7), 2.55-2.46 (m, 1H, *H*H-3), 2.27 (dtd, *J* = 13.0, 8.8, 4.1, 1H, *H*H-8), 2.05-1.99 (m, 1H, *H*H-6), 1.69-1.53 (m, 2H, H*H*-6 and H*H*-8); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.6 (C), 178.4 (C), 58.8 (CH_2), 51.1 (CH), 42.5 (CH_2), 39.6 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 28.2 (CH_2); IR (solid, cm^{-1}) 3008 (w), 2970 (m), 2941 (m), 2864 (w), 1740 (s), 1633 (m), 1572 (w); MS (CI) *m*/z (relative intensity): 152 ($M^+ + H^+$, 100), 123 (13), 110 (7); Exact mass calculated for $[C_9H_{13}NO]+H^+$ requires *m/z* 152.10754, found 152.10802 (CI).

Pent-4-enylamine hydrobromide (186)

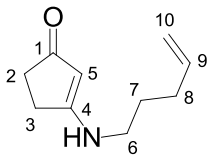


186

5-bromo-1-pentene (503 mg, 400 µL, 3.38 mmol) was dissolved in saturated solution of ammonia in methanol (4.5 mL) in a microwave vial. The mixture was stirred at 110 ^{o}C for 30 min in the microwave. The solvent was removed *in vacuo*, affording amine **186** as a white solid (545 mg, 3.28 mmol) in 97% yield. m.p. dec. >150 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, br, 3H, NH), 5.69 (ddt, *J* = 16.9, 10.1, 6.6, 1H, H-2), 5.05-4.95 (m, 1H, H-1), 2.95 (m, 2H, H-5), 2.13-2.09 (m, 2H, H-3), 1.91-1.81 (m, 2H, H-3); ^{13}C NMR (125 MHz, 1:1 $CDCl_3$/CD_3OD) δ 136.3 (CH), 116.3 (CH_2), 39.5 (CH_2), 30.5 (CH_2), 26.3 (CH_2); IR (solid, cm^{-1}) 3411 (m, br), 2976 (s), 2937 (s), 1641 (m), 1600 (m); MS (EI) *m*/z (relative intensity): 139 (M^+-HBr, 6), 105 (6), 91 (6), 88 (11), 86 (68), 84 (100), 69 (10), 57 (9), HBr salt not seen, exact mass could not be measured due to small size.

3-Pent-4-enylamino-cyclopent-2-enone (184)

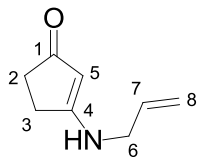


184

To a solution of amine **186** (530 mg, 3.19 mmol) in dry PhMe (7 mL) was added cyclopentadione (313 mg, 3.19 mmol), triethylamine (483 mg, 662 µL, 4.79 mmol) and 4 Å molecular sieves. The solution was stirred at reflux for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAC) afforded vinylogous amide **184** as an off-white solid (460 mg, 2.79 mmol) in 87% yield. m.p. 125-126 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.2, 10.3, 6.8, 1H, H-9), 5.23 (s, br, 1H, NH), 5.07-5.02 (m, 2H, H-10), 5.00 (s, 1H, H-5), 3.17 (t, *J* = 6.1, 2H, H-6), 2.56 (m, 2H, H-3), 2.39 (dt, *J* = 7.0, 5.4, 2H, H-8), 2.14-2.06 (m, 2H, H-2), 1.73-1.67 (m, 2H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5 (C), 176.4 (C), 137.2 (CH), 115.8 (CH_2), 99.4 (CH), 44.6 (CH_2), 33.7 (CH_2), 30.9 (CH_2), 28.2 (CH_2,), 27.8 (CH_2); IR (solid, cm^{-1}) 3191 (w), 3076(w), 2933 (m), 2861 (m), 1633 (m), 1569 (s); MS (CI) *m*/z (relative intensity): 166 (M^+ +H^+, 29), 151 (100), 139 (19), 87 (25); Exact mass calculated for [$C_{10}H_{15}NO$]+H^+ requires *m/z* 166.12319, found 166.12322 (CI).

3-Allylamino-cyclopent-2-enone (185)



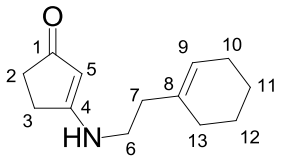
185

To a suspension of 1,3-cyclopentadione (300 mg, 3.06 mmol) in dry PhMe (5 mL) was added allylamine (230 µL, 175 mg, 3.06 mmol) and 4 Å molecular sieves and the mixture stirred at reflux for 3 h. The solvent was removed *in vacuo* and purification by flash chromatography (5% MeOH in EtOAc to 10% MeOH in EtOAc) afforded vinylogous amide **185** as an off-white solid (307 mg, 2.24 mmol) in 73% yield. m.p. 116-117 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, br, 1H, NH), 5.82 (ddt, *J* = 16.4, 11.2, 5.8, 1H, H-7), 5.35-5.17 (m, 2H, H-8), 5.03 (s, 1H, H-5), 3.77-7.73 (m, 2H, H-6), 2.62-2.58 (m, 2H, H-3), 2.37-2.33 (m, 2H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7 (C), 176.6 (C), 132.6 (CH), 117.7 (CH_2), 99.8 (CH), 47.5 (CH_2), 33.8 (CH_2), 28.2 (CH_2); IR (solid, cm^{-1}) 3239 (m), 3061 (m), 2927 (w), 1638 (m), 1554 (s); MS (CI) *m*/z (relative intensity): 275 (15), 138 (M^+ +H^+, 100), 109 (4), 94 (4);

Exact mass calculated for $[C_9H_{13}NO]+H^+$ requires *m/z* 138.09189, found 138.09213 (CI).

3-((2-(Cyclohex-1-en-1-yl)ethyl)amino)cyclopent-2-enone (188)

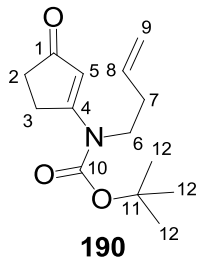


188

To a suspension of 1,3-cyclopentadione (294 mg, 3.00 mmol) in dry PhMe (5 mL) was added 2-(1-cyclohexenyl)ethylamine (459 µL, 412 mg, 3.30 mmol) and 4 Å molecular sieves and the mixture was stirred at reflux for 3 h. The solvent was removed *in vacuo* and purification by flash chromatography (5% MeOH in $CHCl_3$) afforded vinylogous amide **188** as a white solid (510 mg, 2.49 mmol) in 83% yield. m.p. 136 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.50 (s, 1H, H-9), 5.24 (br, 1H, NH), 5.05 (s, 1H, H-5), 3.20 (dt, *J* = 6.4, 5.8, 2H, H-6), 2.59-2.55 (m, 2H, H-3), 2.44-2.39 (m, 2H, H-2), 2.23 (t, *J* = 6.5, 2H, H-7), 2.03-1.98 (m, 2H, H-10), 1.93-1.89 (m, 2H, H-13), 1.65-1.60 (m, 2H, H-12), 1.58-1.53 (m, 2H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5 (C), 176.5 (C), 134.0 (C), 124.3 (CH), 99.5 (CH), 42.7 (CH_2), 36.9 (CH_2), 33.7 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 22.4 (CH_2); IR (solid, cm^{-1}) 3195 (w), 2927 (w), 2835 (w), 1634 (w), 1578 (s), 1527 (m); MS (CI) *m*/z (relative intensity): 206 ($M^+ + H^+$, 100), 205 (56), 204 (25), 111 (23), 110 (46), 85 (13); Exact mass calculated for $[C_{13}H_{18}NO]+H^+$ requires *m/z* 206.15394, found 206.15316 (CI)

tert-Butyl but-3-en-1-yl(3-oxocyclopent-1-en-1-yl)carbamate (190)

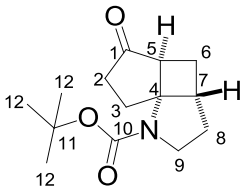


190

To a solution of vinylogous amide **172** (500 mg, 3.31 mmol) in DCM (12 mL) was added a solution of di-*tert*-butyl dicarbonate (865 mg, 3.97 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in DCM (3 mL) and the solution stirred at room temperature for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (Et_2O) afforded Boc-protected vinylogous amide **190** as an orange-brown oil (739 mg, 2.95 mmol) in 89% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.3, 10.2, 7.1, 1H, H-8), 5.62 (s, 1H, H-5), 5.10-5.06 (m, 2H, H-9), 3.68 (t, *J* = 7.4, 2H, H-6), 3.13 (t, *J* = 4.7, 2H, H-3), 2.44-2.42 (m, 2H, H-2), 2.35 (q, *J* = 7.3, 2H, H-7), 1.53 (s, 9H, H-12); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.8 (C), 173.6 (C), 151.9 (C), 134.1 (CH), 117.8 (CH_2), 112.4 (CH), 83.6 (C), 48.3 (CH_2), 34.6 (CH_2), 32.0 (CH_2), 30.9 (CH_2), 28.2 (CH_3); IR (oil, cm^{-1}) 2978 (m), 2933 (m), 1728 (s), 1703 (w), 1680 (s), 1578 (s); MS (ES-) *m*/z (relative intensity): 250 (M^+ - H^+, 100), 188 (38), 171 (56), 157 (50), 146 (88); Exact mass calculated for [$C_{14}H_{21}NO_3$]-H^+ requires *m/z* 250.1443, found 250.1443 (ES-).

(3aR,4aS)-t*ert*-Butyl 5-oxooctahydro-1H-cyclopenta[1,4]cyclobuta[1,2-b]pyrrole-1-carboxylate (191)



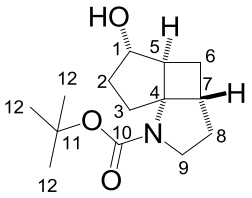
191

A solution of Boc-protected vinylogous amide **190** (275 mg, 1.49 mmol) in MeCN (90 mL) was degassed for 30 min and irradiated for 30 min. The solvent was removed *in vacuo* and purification by flash chromatography (25% Et_2O in petroleum ether with 2% NEt_3) afforded Boc-protected aminocyclobutane **191** as a yellow oil (307 mg, 1.22 mmol) in 82% yield.

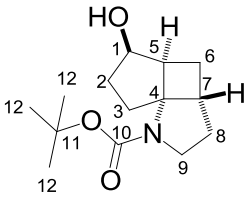
^{1}H NMR (400 MHz, $CDCl_3$, 330 K*) δ 3.78-3.71 (m, 1H, *H*H-9), 3.62 (ddd, *J* = 8.2, 6.3, 4.9, 1H, H*H*-9), 2.80 (qd, *J* = 7.6, 3.2, 1H, H-7), 2.73-2.57 (m, 4H, H-2, *H*H-3 and *H*H-5), 2.12 (ddd, *J* = 8.1, 7.6, 5.2, 1H, *H*H-8), 2.05-2.01 (m, 2H, H-6), 1.93-1.87 (m, 1H, H*H*-3), 1.76 (dddd, *J* = 7.9, 7.6, 4.8, 3.3, 1H, H*H*-8), 1.45 (s, 9H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K*) δ 218.7 (C), 154.3 (C), 80.2 (C), 69.5 (C), 48.8 (CH_2), 46.0 (CH), 43.5 (CH), 38.5 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 28.7 (CH_3), 25.6 (CH_2); IR (oil, cm^{-1}) 2973 (w), 2938 (w), 2872 (w), 1735 (s), 1693 (s); MS (ES-) *m*/z (relative intensity): 501 (100), 250 (M^+ -H^+, 25), 212 (22), 194 (24); Exact mass calculated for [$C_{14}H_{21}NO_3$]-H^+ requires *m/z* 250.1443, found 250.1145 (ES-).

* NMR at ambient temperature showed the presence of rotamers which resolved upon heating to 330 K.

(3aR,4aS,5S)-tert-Butyl 5-hydroxyoctahydro-1H-cyclopenta[1,4]cyclobuta[1,2-b]pyrrole-1-carboxylate (194) and **(3aR,4aS,5R)-tert-Butyl 5-hydroxyoctahydro-1H-cyclopenta[1,4]cyclobuta[1,2-b]pyrrole-1-carboxylate (195)**



194



195

To a solution of Boc-protected aminocyclobutane **191** (71 mg, 0.28 mmol) in MeOH (5 mL) was added sodium borohydride (22 mg, 0.57 mmol) and the mixture stirred for 20 min. The solvent was removed *in vacuo* and the white solid was dissolved in aqueous HCl (2M, 2 mL), extracted with DCM (3 x 5 mL) and the combined organic layers dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and purification by flash chromatography (50% Et_2O in petroleum ether with 2% NEt_3) afforded alcohol **194** as a colourless oil (44 mg, 0.17 mmol) in 61% yield and alcohol **195** as a colourless oil (23 mg, 0.091 mmol) in 32% yield.

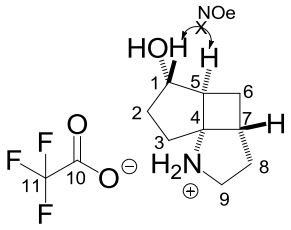
194: ^{1}H NMR (400 MHz, $CDCl_3$, 330 K*) δ 4.25 (br, 1H, OH), 3.92 (m, 1H, H-1), 3.76 (ddd, *J* = 11.1, 8.1, 3.8, 1H, H*H*-9), 3.37 (ddd, *J* = 11.2, 8.9, 7.0, 1H, *H*H-9), 2.55-2.39 (m, 3H, H*H*-3, H-5 and H-7), 2.22 (dddd, *J* = 12.8, 9.0, 7.0, 3.9, 1H, H*H*-8), 2.06-1.97 (m, 2H, H-2), 1.82-1.69 (m, 2H, , H*H*-6 and *H*H-8), 1.57 (ddd, *J* = 13.0, 8.3, 6.3, 1H, *H*H-6), 1.50-1.46 (m, 10H, *H*H-3 and H-12); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K*) δ 154.0 (C), 80.0 (C), 76.2 (CH), 71.8 (C), 49.1 (CH_2), 48.7 (CH), 40.5 (CH), 33.4 (CH_2), 32.7 (CH_2), 30.1 (CH_2), 28.5 (CH_3), 24.9 (CH_2); IR (oil, cm^{-1}) 3420 (br, m), 2966 (m), 2933 (m), 2869 (w), 1664 (s); MS (ES+) *m*/z (relative intensity): 276 (M^+ +Na, 76), 261 (100), 245 (30), 220 (68), 180 (46), 136 (29); Exact mass calculated for $[C_{14}H_{23}NO_3]$+Na, requires *m/z* 276.1576 found 276.1571 (ES+).

195: ^{1}H NMR (400 MHz, $CDCl_3$, 330 K*) δ 4.52 (ddd, *J* = 10.3, 7.7, 6.3, 1H, H-1), 3.76 (ddd, *J* = 11.1, 7.8, 6.4, 1H, H*H*-9), 3.47 (ddd, *J* = 11.2, 7.7, 6.5, 1H, *H*H-9), 2.60-2.48 (m, 2H, H-5 and H-7), 2.35 (ddd, *J* = 13.4, 11.7, 7.1, 1H, H*H*-3), 2.20-2.08 (m, 3H, H-2 and , H*H*-8), 1.84-1.69 (m, 2H, H*H*-6 and *H*H-8), 1.54 (ddd, *J* = 13.1, 9.3, 5.5, 1H, *H*H-6), 1.49-1.43 (m, 10H, *H*H-3 and H-12); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K*) δ 154.2 (C), 79.3 (C), 72.9 (CH), 70.8 (C), 48.7 (CH_2), 42.5 (CH), 42.4 (CH), 32.9 (CH_2), 31.3 (CH_2), 31.0 (CH_2), 28.6 (CH_3), 20.0 (CH_2); IR (oil, cm^{-1}) 3416 (br, w), 2944 (m), 2964 (m), 2869 (m), 1693 (s), 1672 (s); MS (ES+) *m*/z (relative intensity): 276 (M^+ +Na, 16), 261 (19), 239 (30), 220 (27), 198 (50), 180 (67), 136 (100); Exact mass calculated for $[C_{14}H_{23}NO_3]$+Na requires *m/z* 276.1576, found 276.1566 (ES+).

* NMR at ambient temperature showed the presence of rotamers which resolved upon heating to 330 K.

N.B. Stereochemistry inferred from NOESY data after Boc removal (**#244** and **#245**).

(3aR,4aS,5S)-5-Hydroxyoctahydro-1H-cyclopenta[1,4]cyclobuta[1,2-b]pyrrol-1-ium 2,2,2-trifluoroacetate (196)

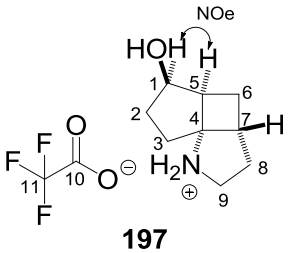


196

To a solution of alcohol **194** (165 mg, 0.652 mmol) in DCM (3 mL) was added TFA (3 mL) and the mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting oil was dissolved in MeOH (2 mL) and the solid removed by filtration. The solvent was removed *in vacuo* affording aminocyclobutane **196** as a yellow oil (162 mg, 0.607 mmol) in 93% yield.

^{1}H NMR (600 MHz, MeOD) δ 4.02 (m, 1H, H-1), 3.62-3.54 (m, 2H, H-9), 2.61 (ddd, *J* = 9.2, 8.0, 4.7, 1H, H-7), 2.59-2.56 (m, 1H, H-5), 2.22-2.08 (m, 3H, H*H*-2, H*H*-3 and H*H*-8), 2.06-2.00 (m, 1H, *H*H-3), 1.96-1.92 (m, 2H, *H*H-2 and *H*H-8), 1.83-1.78 (m, 1H, H*H*-6), 1.75-1.70 (m, 1H, *H*H-6); ^{13}C NMR (150 MHz, MeOD) δ 163.1 (q, $^{2}J_{CF}$ = 34.5, C), 118.2 (q, $^{1}J_{CF}$ = 291, CF_3), 76.6 (CH), 75.3 (C), 47.4 (CH), 47.1 (CH_2), 38.5 (CH), 34.0 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 24.5 (CH_2); IR (oil, cm^{-1}) 3362 (br, w), 2962 (m), 2951 (m), 2873 (w), 2763 (w), 2502 (w), 1669 (s); MS (EI) *m*/z (relative intensity): 153 (M^+, 15), 136 (26), 108 (15), 95 (16), 84 (35), 83 (100), 82 (23), 80 (17), 69 (29); Exact mass calculated for [$C_9H_{15}NO$] requires *m/z* 153.11482, found 153.11541 (EI).

(3aR,4aS,5R)-5-Hydroxyoctahydro-1H-cyclopenta[1,4]cyclobuta[1,2-b]pyrrol-1-ium 2,2,2-trifluoroacetate (197)



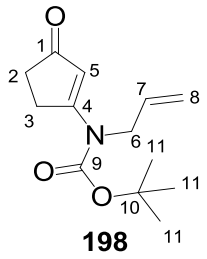
197

To a solution of alcohol **195** (97 mg, 0.38 mmol) in DCM (3 mL) was added TFA (3 mL) and the mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting oil was dissolved in MeOH (2 mL) and the solid removed by filtration. The solvent was removed *in vacuo* affording aminocyclobutane **197** as a yellow oil (85 mg, 0.32 mmol) in 83% yield.

^{1}H NMR (600 MHz, MeOD) δ 4.28 (ddd, *J* = 10.0, 8.1, 6.5, 1H, H-1), 3.64-3.54 (m, 2H, H-9), 2.69 (ddd, *J* = 9.7, 8.2, 5.4, 1H, H-5), 2.64 (ddd, *J* = 9.2, 7.7, 4.8, 1H, H-7), 2.27 (ddd, 13.4, 9.1, 5.3, 1H, H*H*-6), 2.19-2.06 (m, 2H, H*H*-2 and H*H*-8), 1.98-1.89 (m, 3H, *H*H-2, H*H*-3 and *H*H-8), 1.87-1.81 (m, 1H, *H*H-3), 1.55 (ddd, *J* = 13.4, 9.8, 4.8, 1H, *H*H-6); ^{13}C NMR (150 MHz, MeOD) δ 163.0 (q, $^{2}J_{CF}$ = 34.5, C), 118.1 (q, $^{1}J_{CF}$ = 290, CF_3), 73.5 (C), 72.3 (CH), 47.0 (CH_2), 41.7 (CH), 39.8 (CH), 32.7 (CH_2), 31.4 (CH_2), 30.0 (CH_2), 19.9 (CH_2); IR (oil, cm^{-1})

3368 (br, m), 2962 (m), 2950 (m), 2874 (w), 2764 (w), 2502 (w), 1667 (s); MS (EI) *m*/z (relative intensity): 153 (M^+, 11), 136 (22), 108 (14), 95 (16), 84 (34), 83 (100), 82 (25), 80 (19), 69 (34); Exact mass calculated for [$C_9H_{15}NO$] requires *m/z* 153.11482, found 153.11523 (EI).

tert-Butyl allyl(3-oxocyclopent-1-en-1-yl)carbamate (198)

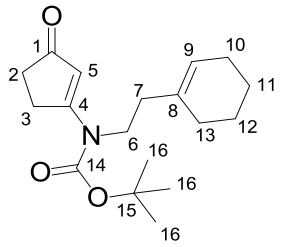


198

To a solution of vinylogous amide **185** (460 mg, 3.36 mmol) in DCM (12 mL) was added a solution of di-*tert*-butyl dicarbonate (878 mg, 4.03 mmol) and 4-dimethylaminopyridine (21 mg, 0.17 mmol) in DCM (3 mL) and the solution stirred at room temperature for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (Et_2O) afforded Boc-protected vinylogous amide **198** as an orange-brown oil (698 mg, 2.95 mmol) in 88% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.3, 10.4, 5.2, 1H, H-7), 5.69 (s, 1H, H-5), 5.21 (d, J = 10.4, 1H, H-8_{cis}), 5.15 (d, J = 17.4, 1H, H-8_{trans}), 4.26 (dt, J = 5.1, 1.6, 2H, H-6), 3.13-3.11 (m, 2H, H-3), 2.43-2.42 (m, 2H, H-2), 1.52 (s, 9H, H-11); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.8 (C), 173.8 (C), 151.9 (C), 131.8 (CH), 117.3 (CH_2), 113.1 (CH), 83.8 (C), 51.1 (CH_2), 34.5 (CH_2), 30.7 (CH_2), 28.1 (CH_3); IR (oil, cm^{-1}) 2977 (w), 2932 (w), 1724 (s), 1677 (s), 1564 (s); MS (CI) *m/z* (relative intensity): 238 (40, $M^+ + H^+$), 210 (24), 182 (100), 138 (57); Exact mass calculated for [$C_{13}H_{19}NO_3$]+H^+ requires *m/z* 238.1443, found 238.1441 (CI).

tert-Butyl (2-(cyclohex-1-en-1-yl)ethyl)(3-oxocyclopent-1-en-1-yl)carbamate (199)

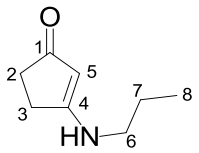


199

To a solution of vinylogous amide **188** (148 mg, 0.722 mmol) in DCM (3 mL) was added a solution of di-*tert*-butyl dicarbonate (189 mg, 0.866 mmol) and 4-dimethylaminopyridine (4 mg, 0.04 mmol) in DCM (2 mL) and the solution stirred at room temperature for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (50% petroleum ether in Et_2O) afforded Boc-protected vinylogous amide **199** as an orange-brown oil (161 mg, 0.528 mmol) in 73% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.62 (s, 1H, H-5), 5.44 (s, 1H, H-9), 3.66 (t, J = 8.0, 2H, H-6), 3.12 (t, J = 4.7, 2H, H-2), 2.43-2.41 (m, 2H, H-3), 2.19 (t, J = 7.9, 2H, H-7), 1.97-1.94 (m, 4H, H-10 and H-13), 1.63-1.58 (m, 2H, H-11), 1.55-1.51 (m, 11H, H-12 and H-16); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.8 (C), 173.8 (C), 151.9 (C), 134.1 (C), 124.1 (CH), 112.3 (CH), 83.5 (C), 48.1 (CH_2), 35.9 (CH_2), 34.6 (CH_2), 31.0 (CH_2), 28.5 (CH_2), 28.2 (CH_3), 25.3 (CH_2), 22.9 (CH_2), 22.3 (CH_2); IR (oil, cm^{-1}) 2975 (w), 2928 (m), 2836 (w), 1727 (s), 1703 (m), 1679 (s), 1566 (s); MS (ES-) *m*/z (relative intensity): 304 (100), 283 (33), 282 (38), 281 (22), 255 (63), 233 (23), 204 (80), 188 (39); Exact mass calculated for $[C_{18}H_{27}NO_3]$-H^+ requires *m/z* 304.1913, found 304.1922 (ES-).

3-(Propylamino)cyclopent-2-enone (203)



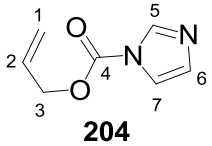
203

Method 1: To a suspension of 1,3-cyclopentadione (432 mg, 4.41 mmol) in dry PhMe (10 mL) was added propylamine (912 µL, 781 mg, 11.0 mmol) and 4 Å molecular sieves and the mixture stirred at reflux for 3 h. The solvent was removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAc) afforded vinylogous amide **203** as a white solid (562 mg, 4.04 mmol) in 92% yield.

Method 2: To a suspension of 1,3-cyclopentadione (1.30 g, 13.3 mmol) in dry PhMe (20 mL) was added propylamine (2.70 mL, 1.94 g, 33.3 mmol) and the mixture stirred at reflux under Dean-Stark conditions for 2.5 h. The solvent was removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAc) afforded vinylogous amide **203** as a white solid (1.83 g, 13.2 mmol) in 99% yield. m.p. 113-114 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (br, 1H, NH), 5.01 (s, 1H, H-5), 3.10 (q, *J* = 7.0, 2H, H-6), 2.59 (t, *J* = 5.5, 2H, H-3), 2.38 (t, *J* = 5.5, 2H, H-2), 1.62 (sext, *J* = 7.3, 2H, H-7), 0.95 (t, *J* = 7.4, 3H, H-8); ^{13}C NMR (125 MHz, 1:1 $CDCl_3$/CD_3OD) δ 205.7 (C), 178.7 (C), 97.9 (CH), 46.8 (CH_2), 33.3 (CH_2), 27.8 (CH_2), 21.8 (CH_2), 11.2 (CH_3); IR (solid, cm^{-1}) 3192 (w), 2958 (m), 2929 (m), 2873 (m), 1643 (m), 1571 (s), 1523 (s); MS (EI) *m*/z (relative intensity): 139 (M^+, 60), 111 (17), 110 (32), 96 (13), 88 (16), 86 (100); Exact mass calculated for [$C_8H_{13}NO$] requires *m/z* 139.09917, found 139.09923 (EI).

Allyl 1H-imidazole-1-carboxylate (204)[149]

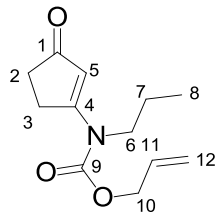


204

To a solution of imidazole (1.25 g, 18.3 mmol) in dry THF (17 mL) at 0 °C was added allyl chloroformate (1.00 mL, 1.13 g, 9.45 mmol) dropwise over 15 min and the white suspension was stirred at 0 °C for 1 h. The mixture was allowed to warm to room temperature and stirred for a further 4 h. The mixture was filtered and the white solid washed with Et_2O (25 mL). The filtrate and washings were combined and the solvents removed *in vacuo*. The resulting oil was dissolved in Et_2O (25 mL), washed with water (2 x 25 mL) and the organic layer dried ($MgSO_4$) and the solvent removed *in vacuo* affording imidazole amide **204** as a clear oil (995 mg, 6.55 mmol) in 69% yield which degrades on standing in air.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H, H-5), 7.44 (s, 1H, H-6), 7.08 (s, 1H, H-7), 6.02 (ddt, *J* = 17.2, 10.5, 6.0, 1H, H-2), 5.46 (dq, *J* = 17.2, 1.3, 1H, H_{trans}-1), 5.39 (dq, *J* = 10.4, 1.1, 1H, H_{cis}-1), 4.90 (dq, *J* = 6.0, 1.2, 2H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5 (C), 137.2 (CH), 130.8 (CH), 130.5 (CH), 120.5 (CH_2), 117.2 (CH), 68.7 (CH_2); IR (oil, cm^{-1}) 3133 (w), 2953 (w), 1759 (s), 1650 (w), 1527 (w); MS could not be obtained due to the instability of the product. Spectra agree with literature values.[149]

Allyl (3-oxocyclopent-1-en-1-yl)(propyl)carbamate (205)

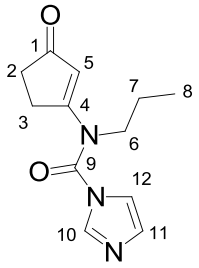


205

To a solution of vinylogous amide **203** (300 mg, 2.16 mmol) in dry DCM (10 mL) was added 1,1'-carbonyldiimidazole (315 mg, 1.94 mmol) and DBU (97 µL, 98 mg, 0.65 mmol). The mixture was stirred at room temperature for 45 min before allyl alcohol (145 mg, 170 µL, 2.50 mmol) and more DBU (97 µL, 98 mg, 0.65 mmol) were added. The mixture was stirred for a further 15 min at room temperature. The solvents were removed *in vacuo* and purification by flash chromatography (50% petroleum ether in Et_2O to 100% Et_2O) afforded a 4:1 mixture of vinylogous imide **205** and imidazole amide **204** which was further purified by flash chromatography on alumnia (Et_2O) to afford vinylogous imide **205** as a clear oil (93.4 mg, 0.419 mmol) in 22% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddt, *J* = 17.2, 10.5, 5.8, 1H, H-11), 5.69 (t, *J* = 1.3, 1H, H-5), 5.39 (dq, *J* = 17.2, 1.4, 1H, H_{trans}-12), 5.33 (dq, *J* = 10.5, 1.2, 1H, H_{cis}-12), 4.73 (dt, *J* = 5.8, 1.3, 2H, H-10), 3.67 (t, *J* = 7.9, 2H, H-6), 3.17-3.19 (m, 2H, H-3), 2.48-2.45 (m, 2H, H-2), 1.73-1.65 (m, 2H, H-7), 0.95 (t, *J* = 7.5, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6 (C), 173.3 (C), 153.1 (C), 131.4 (CH), 119.3 (CH_2), 113.0 (CH), 67.6 (CH_2), 50.4 (CH_2), 34.5 (CH_2), 30.6 (CH_2), 20.8 (CH_2), 11.1 (CH_3); IR (oil, cm^{-1}) 2961 (m), 2930 (m), 2876 (m), 1729 (s), 1679 (s), 1567 (s); MS (ES+) *m*/z (relative intensity): 224 ($M^+ + H^+$, 52), 208 (25), 181 (30), 180 (100), 138 (42); Exact mass calculated for $[C_{12}H_{17}NO_3]+H^+$ requires *m/z* 224.1287, found 224.1286 (ES+).

N-(3-Oxocyclopent-1-en-1-yl)-N-propyl-1H-imidazole-1-carboxamide (207)

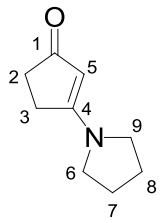


207

To a solution of 1,1'-carbonyldiimidazole (256 mg, 1.58 mmol) in dry DCM (10 mL) was added vinylogous amide **203** (200 mg, 1.44 mmol) and DBU (65 µL, 66 mg, 0.43 mmol) and the mixture stirred at room temperature for 30 min. The mixture was washed with saturated aqueous ammonium chloride (2 x 10 mL), water (2 x 10 mL) and brine (10 mL). The organic layers dried ($MgSO_4$) and the solvent was removed *in vacuo* affording vinylogous imide **207** as a slightly yellow oil (194 mg, 0.83 mmol) in 58% yield which degrades on standing in air.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H, H-10), 7.27 (s, 1H, H-11), 7.15 (s, 1H, H-12), 5.66 (t, *J* = 1.3, 1H, H-5), 3.78 (t, *J* = 7.5, 2H, H-6), 2.66-2.63 (m, 2H, H-3), 2.48-2.45 (m, 2H, H-2), 1.78 (sext. *J* = 7.5, 2H, H-7), 0.98 (t, *J* = 7.5, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0 (C), 171.9 (C), 150.1 (C), 137.2 (CH), 131.2 (CH), 117.7 (CH), 116.9 (CH), 53.3 (CH_2), 34.4 (CH_2), 29.1 (CH_2), 21.3 (CH_2), 11.1 (CH_2); IR (oil, cm^{-1}) 3115 (w), 2966 (w), 2934 (w), 2877 (w), 1705 (s), 1680 (s), 1580 (s); MS (ES-) *m*/z (relative intensity): 232 (M^+ - H^+, 38), 212 (100), 191 (24), 180 (25), 175 (85), 158 (21), 157 (28), 138 (70), 113 (29); Exact mass calculated for [$C_{12}H_{15}N_3O_2$]-H^+ requires *m/z* 232.1086, found 232.1092 (ES-).

3-(Pyrrolidin-1-yl)cyclopent-2-enone (208)

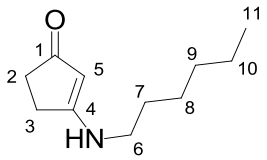


208

To a suspension of 1,3-cyclopentadione (300 mg, 3.06 mmol) in dry PhMe (8 mL) was added pyrrolidine (627 µL, 543 mg, 7.65 mmol) and 4 Å molecular sieves and the mixture stirred at reflux for 3.5 h. The solvent was removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAc) afforded vinylogous amide **208** as a white solid (376 mg, 2.49 mmol) in 81% yield. m.p. 103-104 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1H, H-5), 3.47 (t, 2H, H-6 or H-9), 3.30 (t, 2H, H-6 or H-9), 2.66-2.63 (m, 2H, H-3), 2.45-2.43 (m, 2H, H-2), 2.07-1.99 (m, 4H, H-7 and H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2 (C), 174.9 (C), 100.2 (CH), 49.3 (CH_2), 47.8 (CH_2), 34.3 (CH_2), 28.1 (CH_2), 25.6 (CH_2), 25.1 (CH_2); IR (solid, cm^{-1}) 2960 (m), 2922 (m), 2874 (m), 1726 (w), 1648 (m), 1561 (s); MS (EI) *m*/z (relative intensity): 151 (M^+, 100), 123 (12), 122 (81), 108 (24), 95 (33), 94 (15), 88 (15), 86 (93); Exact mass calculated for [$C_9H_{13}NO$] requires *m/z* 151.09917, found 151.09966 (EI).

3-(Hexylamino)cyclopent-2-enone (209)

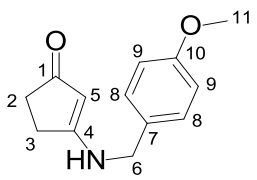


209

To a suspension of 1,3-cyclopentadione (196 mg, 2.00 mmol) in dry PhMe (5 mL) was added n-hexylamine (264 µL, 202 mg, 2.00 mmol) and 4 Å molecular sieves and the mixture stirred at reflux for 3.5 h. The solvent was removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAc) afforded vinylogous amide **209** as a white solid (290 mg, 1.60 mmol) in 80% yield. m.p. 118-120 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, br, 1H, NH), 5.10 (s, 1H, H-5), 3.16 (dt, *J* = 6.8, 6.3, 2H, H-6), 2.63 (t, *J* = 5.4, 2H, H-3), 2.44 (t, *J* = 5.4, 2H, H-2), 1.63-1.58 (m, 2H, H-7), 1.37-1.24 (m, 6H, H-8, H-9 and H-10), 0.88 (t, *J* = 6.6, 3H, H-11); ^{13}C NMR (125 MHz, 1:1 $CDCl_3$/MeOD) δ 206.9 (C), 178.4 (C) 99.0 (CH), 46.4 (CH_2), 34.5 (CH_2), 32.7 (CH_2), 29.8 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 23.8 (CH_2), 15.1 (CH_3); IR (solid, cm^{-1}) 3194 (w), 2956 (m), 2923 (m), 2852 (m), 1634 (m), 1574 (s), 1517 (s); MS (EI) *m*/z (relative intensity): 181 (M^+, 13), 166 (4), 152 (5), 144 (4), 124 (5), 110 (6), 88 (14), 86 (100); Exact mass calculated for [$C_{11}H_{19}NO$] requires *m/z* 181.14612, found 181.14576 (EI).

3-((4-Methoxybenzyl)amino)cyclopent-2-enone (210)



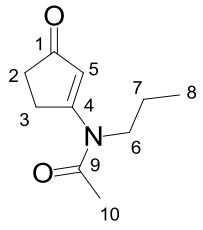
210

To a suspension of 1,3-cyclopentadione (196 mg, 2.00 mmol) in dry PhMe (5 mL) was added 4-methoxybenzylamine (261 µL, 274 mg, 2.00 mmol) and 4 Å

molecular sieves and the mixture stirred at reflux for 2.5 h. The solvent was removed *in vacuo* and purification by flash chromatography (10% MeOH in EtOAc) afforded vinylogous amide **210** as a white solid (281 mg, 1.29 mmol) in 65% yield. m.p. 125-126 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5, 2H, H-9), 6.87 (d, *J* = 8.5, 2H, H-8) 5.35 (s, br, 1H, NH), 5.09 (s, 1H, H-5), 4.23 (d, *J* = 4.5, 2H, H-6), 3.80 (s, 3H, H-11), 2.58 (t, *J* = 5.1, 2H, H-3), 2.38 (t, *J* = 5.2, 2H, H-2); ^{13}C NMR δ (125 MHz, $CDCl_3$) 204.7 (C), 175.9 (C), 159.4 (C), 129.2 (2x CH), 128.7 (C), 114.3 (2x CH), 100.1 (CH), 55.4 (CH_3), 48.8 (CH_2), 33.8 (CH_2), 28.2 (CH_2); IR (solid, cm^{-1}) 3211 (w), 3034 (w), 2929 (w), 2865 (w), 1644 (w), 1545 (s), 1508 (s); MS (EI) *m*/z (relative intensity): 217 (M^+, 14), 134 (6), 122 (9), 121 (100), 91 (6), 86 (9); Exact mass calculated for [$C_{13}H_{15}NO_2$] requires *m/z* 217.10973 found 217.11031 (EI).

N-(3-Oxo-cyclopent-1-enyl)-N-propyl-acetamide (211)



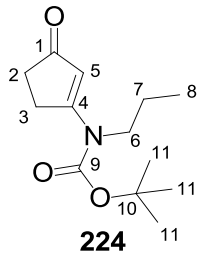
211

To a stirring solution of vinylogous amide **#3** (360 mg, 2.59 mmol) in dry THF (4 mL) was added a solution of pyridine (833 µL, 818 mg, 10.4 mmol) in dry THF (4 mL) dropwise over 10 min. The mixture was cooled to 0 ^{o}C and a solution of acetyl chloride (368 µL, 406 mg, 5.18 mmol) in dry THF (2 mL) added over 2 min. The mixture was then allowed to warm to room temperature and stirred for 1 h. The solvents were removed *in vacuo* and the resulting oil redissolved in DCM (10 mL) and washed with HCl (1 M, 2 x 10 mL) and water (20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* affording

acetylated vinylogous amide **211** as a red-brown oil (403 mg, 2.23 mmol) in 86% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (s, 1H, H-5), 3.58 (t, *J* = 7.7, 2H, H-6), 3.18 (t, *J* = 5.0, 2H, H-3), 2.45 (t, *J* = 4.9, 2H, H-2), 2.33 (s, 3H, H-10), 1.68 (sext, *J* = 7.5, 2H, H-7), 0.97 (t, *J* = 7.5, 3H, H-8); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1 (C), 173.1 (C), 171.2 (C), 114.9 (CH), 50.7 (CH_2), 34.5 (CH_2), 30.9 (CH_2), 24.7 (CH_3), 21.6 (CH_2), 11.2 (CH_3); IR (oil, cm^{-1}) 2964 (m), 2935 (m), 2878 (m), 1671 (s), 1554 (s); MS (EI) *m*/z (relative intensity): 182 (M^+, 100), 140 (11), 113 (6); Exact mass calculated for $[C_{10}H_{16}NO_2]$+ requires *m/z* 182.11810, found 182.11756 (EI).

tert-Butyl (3-Oxocyclopent-1-en-1-yl)(propyl)carbamate (224)



224

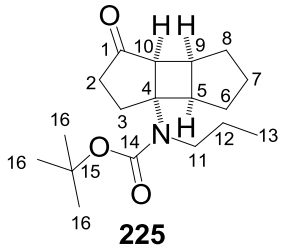
Method 1: To a solution of vinylogous amide **203** (1.83 g, 13.2 mmol) in DCM (20 mL) was added a solution of di-*tert*-butyl dicarbonate (3.47 g, 15.9 mmol) and 4-dimethylaminopyridine (81 mg, 0.66 mmol) in DCM (10 mL) and the solution stirred at room temperature for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (Et_2O) afforded Boc-protected vinylogous amide **224** as an orange oil (3.08 g, 12.9 mmol) in 98% yield.

Method 2: To a suspension of 1,3-cyclopentadione (1.30 g, 13.3 mmol) in dry PhMe (20 mL) was added propylamine (2.70 mL, 1.94 g, 33.3 mmol) and the mixture stirred at reflux under Dean-Stark conditions for 2.5 h. The solvent was removed *in vacuo* and the resulting tan solid dissolved in DCM (20 mL). To this solution was added a solution of di-*tert*-butyl dicarbonate (3.48 g, 16.0 mmol)

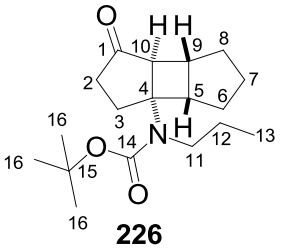
and 4-dimethylaminopyridine (81 mg, 0.66 mmol) in DCM (10 mL) and the solution stirred at room temperature for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (Et_2O) afforded Boc-protected vinylogous amide **224** as an orange oil (3.12 g, 13.0 mmol) in 98% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 (s, 1H, H-5), 3.57 (t, *J* = 7.6, 2H, H-6), 3.13 (t, *J* = 4.9, 2H, H-3), 2.44-2.43 (m, 2H, H-2), 1.62 (sext, *J* = 7.4, 2H, H-7), 1.52 (s, 9H, H-11), 0.91 (t, *J* = 7.4, 3H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9 (C), 174.3 (C), 152.0 (C), 112.2 (CH), 83.6 (C), 50.6 (CH_2), 34.6 (CH_2), 31.0 (CH_2), 28.2 (CH_3), 20.9 (CH_2), 11.3 (CH_3); IR (oil, cm^{-1}) 2971 (m), 2878 (m), 1725 (s), 1677 (s), 1563 (s); MS (CI) *m*/z (relative intensity): 240 ($M^+ + H^+$, 100), 212 (19), 184 (86), 168 (27), 130 (42); Exact mass calculated for $[C_{13}H_{21}NO_3]+H^+$ requires *m/z* 240.1522, found 240.1903 (CI).

***tert*-Butyl ((3aS,3bR,6aS,6bS)-1-oxodecahydrocyclobuta[1,2:3,4]di[5]annulen-3a-yl)(propyl)carbamate (225)** and **t*ert*-Butyl ((3aS,3bS,6aR,6bS)-1-oxodecahydrocyclobuta[1,2:3,4]di[5]annulen-3a-yl)(propyl)carbamate (226)**



225



226

A solution of Boc protected vinylogous amide **224** (360 mg, 1.50 mmol) in a 3:1 mixture of MeCN and cyclopentene (75 mL) was degassed for 30 min and irradiated for 2.5 h. The solvents were removed *in vacuo* and the resulting oil was purified by flash chromatography (gradient elution from 10% EtOAc in petroleum ether (1% NEt_3) to 20% EtOAc in petroleum ether (1% NEt_3)). The still impure product was further purified by flash chromatography on alumina (gradient elution from 25% Et_2O in petroleum ether to 33% Et_2O in petroleum

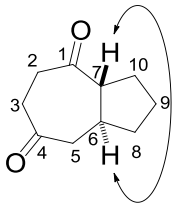
ether) to afford Boc protected aminocyclobutanes **225** and **226** as a white solid (237 mg, 0.772 mmol) in 51% yield as 3:1 ratio of **226** to **225** in an inseparable mixture diastereoisomers (measured by integration of ^{1}H NMR spectrum). m.p. Dec. >150 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.19-3.14 (m, $1H_a$, H*H*-11), 3.01-2.96 (m, $1H_a$, *H*H-11 and $2H_b$), 2.80-2.78 (m, $1H_a$, H-10) 2.64-2.58 (m, $1H_a$, H*H*-3 and $2H_b$), 2.54-2.49 (m, $1H_a$, H*H*-2), 2.45-2.36 (m, $3H_a$, *H*H-3, H-5 and H-9 and $2H_b$), 2.28-2.20 (m, $1H_a$, *H*H-2 and $1H_b$), 1.80-1.67 (m, $3H_a$, H*H*-6, H*H*-7 and H*H*-8 and $3H_b$), 1.63-1.52 (m, $3H_a$, *H*H-6, *H*H-7, *H*H-8 and $5H_b$) 1.46-1.32 (m, $11H_a$, H-12 and H-16 and $11H_b$), 0.89-0.81 (m, $3H_a$, H-13 and $3H_b$); ^{13}C NMR shows two sets of peaks - ^{13}C NMR (150 MHz, $CDCl_3$) δ – Major diastereoisomer – 219.1 (C), 155.2 (C), 79.9 (C), 61.4 (C), 52.0 (CH), 50.8 (CH), 46.5 (CH_2), 39.1 (CH_2), 38.2 (CH), 37.1 (CH_2), 33.4 (CH_2), 28.6 (CH_3), 28.5 (CH_2), 25.3 (CH_2), 24.0 (CH_2), 11.3 (CH_3). Minor diastereoisomer – 219.5 (C), 154.6 (C), 79.5 (C), 62.1 (C), 52.9 (CH), 49.7 (CH), 46.7 (CH_2), 38.3 (CH_2), 37.9 (CH), 37.5 (CH_2), 33.4 (CH_2), 28.4 (CH_3), 27.8 (CH_2), 25.6 (CH_2), 24.5 (CH_2), 11.5 (CH_3); IR (solid, cm^{-1}) 2957 (m), 2876 (w), 1726 (s), 1679 (s); MS (CI) *m*/*z* (relative intensity): 308 ($M^+ + H^+$, 82), 240 (21), 208 (100); Exact mass calculated for $[C_{18}H_{29}NO_3]+H^+$ requires *m/z* 308.22257, found 308.22311 (CI).

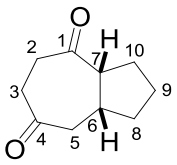
N.B. Stereochemistry inferred from NOESY data after reduction and Boc removal (**234**).

Proton NMR spectrum for the minor diastereomer (**225**) could not be assigned due to extensive peak overlap and the signals being too weak to get 2D NMR data.

Octahydroazulene-4,7-dione (223)



trans-**233**



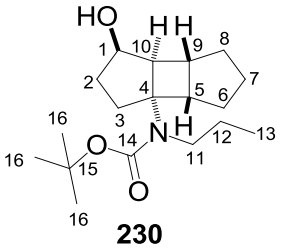
cis-**233**

To a solution of Boc protected aminocyclobutanes **225** and **226** (as a 3:1 ratio of diastereomers) (42 mg, 0.14 mmol) in DCM (3 mL) was added TFA (3 mL) and the mixture was stirred at room temperature for 1 h. The solution was neutralised with aqueous saturated $NaHCO_3$ (20 mL) and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash chromatography (Et_2O) afforded diketones cis-**233** and *trans*-**233** as a white solid (23 mg, 0.14 mmol) in quantitative yield as a 10:1 ratio of *trans*-**233** to *cis*-**233** in an inseparable mixture of diastereomers (measured by integration of ^1H NMR spectrum). m.p. 69-70 °C.

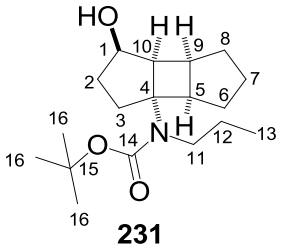
^1H NMR (600 MHz, $CDCl_3$) δ 3.32 (ddd, *J* = 10.3, 8.1, 6.4, $1H_a$, H-7), 2.91-2.82 (m, $1H_a$, H*H*-2 and $1H_b$), 2.77-2.73 (m, $1H_b$), 2.70-2.62 (m, $1H_a$, H*H*-3 and $2H_b$), 2.60-2.48 (m, $4H_a$, *H*H-2, H-5 and H-6 and $2H_b$), 2.34-2.24 (m, $2H_a$, *H*H-3 and H*H*-8 and $1H_b$), 2.09-1.99 (m, $2H_b$), 1.88 (dtd, *J* = 12.3, 6.4, 2.8, $1H_a$, H*H*-10), 1.83-1.73 (m, $1H_a$, H*H*-9 and $2H_b$), 1.71-1.66 (m, $1H_a$, *H*H-8 and $1H_b$), 1.53-1.45 (m, $1H_a$, *H*H-9 and $1H_b$), 1.40-1.35 (m, $1H_b$), 1.20-1.13 (m, $1H_a$, *H*H-10); ^{13}C NMR shows two sets of peaks - ^{13}C NMR (150 MHz, $CDCl_3$) δ – Major diastereoisomer – 210.5 (C), 209.9 (C), 52.8 (CH), 46.4 (CH_2), 38.6 (CH), 38.5 (CH_2), 38.2 (CH_2), 34.3 (CH_2), 25.6 (CH_2), 25.1 (CH_2). Minor diastereoisomer – 210.9 (C), 209.3 (C), 58.0 (CH), 50.1 (CH_2), 40.7 (CH), 39.8 (CH_2), 38.0 (CH_2), 35.5 (CH_2), 25.8 (CH_2), 24.3 (CH_2); IR (solid, cm^{-1}) 2947 (m), 2879 (m), 1699 (s); MS (CI) *m*/z (relative intensity): 168 ($M^+ + H^+$, 73), 149 (37), 149 (38) Exact mass calculated for $[C_{10}H_{14}NO_2]+H^+$ requires *m/z* 167.10720, found 167.10674 (CI). Spectroscopic data is consistent with the literature[157]

N.B. A homonuclear decoupling experiment and computational *J* value prediction were employed (using PcModel version 8.50.00 by Serena Software) to determine that the major diastereomer present was the *trans* product. Upon decoupling of H-7, the *J* value of 10.3 Hz experienced by H-6 disappears. This proves that this *J* value is caused by the coupling of H-7 to H-8. The *cis*-fused and *trans*-fused ring systems were modelled to predict the *J*-values; J_{cis} was predicted to be 6.8 Hz and J_{trans} predicted to be 10.8 Hz. Thus the 10.3 Hz coupling of H-7 to H-8 observed for the major diasteomer is consistent with the prediction for the *trans* product.

tert-Butyl ((1R,3aS,3bR,6aS,6bS)-1-hydroxydecahydrocyclobuta[1,2:3,4]di[5]annulen-3a-yl)(propyl)carbamate (230) and **_tert_-Butyl ((1R,3aS,3bS,6aR,6bS)-1-hydroxydecahydrocyclobuta[1,2:3,4]di[5]annulen-3a-yl)(propyl)carbamate (231)**



230



231

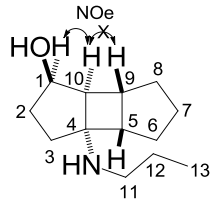
To a solution of Boc protected aminocyclobutanes **225** and **226** (as a 3:1 ratio of diastereomers) (104 mg, 0.339 mmol) in MeOH (5 mL) was added sodium borohydride (26 mg, 0.68 mmol) and the mixture stirred for 1.5 h. Aqueous HCl (2M, 5 mL) was added and the aqueous layer was extracted with DCM (3 x 10 mL), the combined organic layers dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and purification by flash chromatography on basic alumina (gradient elution from 50% Et_2O in petroleum ether to 70% Et_2O in petroleum ether) afforded alcohols **230** and **231** as a colourless oil (105 mg, 0.339 mmol) in quantitative yield as a 3:1 ratio of **230** to **231** in an inseparable mixture diastereoisomers (measured by integration of ^1H NMR spectrum).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36-4.29 (m, 1H_a, H-1 and 1H_b), 3.09-3.00 (m, 2H_a, H-11 and 1H_b), 2.97-2.92 (m, 1H_b), 2.62-2.59 (m, 1H_b), 2.52-2.45 (m, 1H_a, H-5 and 1H_b), 2.40-2.37 (m, 1H_a, H-9 and 1H_b), 2.31-2.26 (m, 1H_a, H*H*-3), 2.22-2.16 (m, 1H_a, H-10 and 1H_b), 2.01-1.97 (m, 1H_a, H*H*-2 and 1H_b), 1.85-1.78 (m, 1H_a, *H*H-2 and 1H_b), 1.69-1.66 (m, 2H_a, H-7 and 2H_b), 1.58-1.49 (m, 7H_a, *H*H-3, H-6, H-8 and H-12 and 7H_b), 1.44-1.42 (m, 9H_a, H-16 and 9H_b), 0.88-0.84 (m, 3H_a, H-13 and 3H_b); ^{13}C NMR shows two sets of peaks - ^{13}C NMR (150 MHz, $CDCl_3$) δ Major diastereoisomer – 155.9 (C), 79.4 (C), 74.8 (CH), 64.3 (C), 49.3 (CH), 48.4 (CH), 46.9 (CH_2), 38.7 (CH_2), 33.7 (CH_2), 31.3 (CH_2), 30.2 (CH), 29.5 (CH_2), 28.6 (CH_3), 25.8 (CH_2), 23.6 (CH_2), 11.5 (CH_3). Minor diastereoisomer – 150.0 (C), 78.9 (C), 75.0 (CH), 65.1 (C), 48.9 (CH), 47.3 (CH), 46.9 (CH_2), 37.6 (CH_2), 34.3 (CH_2), 31.4 (CH_2), 30.4 (CH), 29.5 (CH_2), 28.8 (CH_3), 26.1 (CH_2), 24.1 (CH_2), 11.6 (CH_3); IR (oil, cm^{-1}) 3305 (br), 2928 (s), 2861 (m), 1730 (m), 1692 (s); MS (CI) *m*/z (relative intensity): 310 ($M^+ + H^+$, 76), 252 (100), 208 (90); Exact mass calculated for $[C_{18}H_{31}NO_3]+H^+$ requires *m/z* 310.2377, found 310.2354 (CI).

N.B. Stereochemistry inferred from NOESY data after reduction and Boc removal (**234**).

Proton NMR spectrum for the minor diastereomer (**231**) could not be assigned due to extensive peak overlap and the signals being too weak to get 2D NMR data.

(1R,3aS,3bS,6aR,6bS)-3a-(Propylamino)decahydrocyclobuta[1,2:3,4]di[5]annulen-1-ol (234)

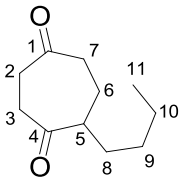


234

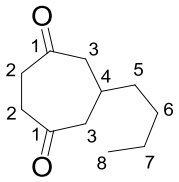
To a solution of alcohols **230** and **231** (as a 3:1 mixture of diastereomers) (73 mg, 0.24 mmol) in DCM (5 mL) was added TFA (5 mL) and the mixture was stirred at room temperature for 1.5 h. The solution was neutralised with aqueous NaOH (5 mL) and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (10% MeOH in EtOAc to 100% MeOH) afforded a white powder which was dissolved in DCM (2 mL) and the solid removed by filtration. The solvent was removed *in vacuo* affording aminocyclobutane **234** as a colourless oil (14 mg, 0.067 mmol) in 29% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.30 (dt, *J* = 10.9, 6.4, 1H, H-1), 2.44-2.38 (m, 2H, H-5 and H-9), 2.36 (t, *J* = 7.2, 2H, H-11), 2.06-1.96 (m, 1H, H*H*-2), 1.92-1.79 (m, 4H, *H*H-2, H*H*-3, H*H*-7 and H-10), 1.79-1.67 (m, 2H, *H*H-3 and *H*H-7), 1.58-1.43 (m, 6H, H-6, H-8 and H-12), 0.92 (t, *J* = 7.5, 3H, H-13); ^{13}C NMR (150 MHz, $CDCl_3$) δ 74.5 (CH), 61.8 (C), 52.5 (CH), 46.3 (CH), 45.1 (CH_2), 35.0 (CH_2), 32.9 (CH_2), 32.1 (CH_2), 30.2 (CH), 27.5 (CH_2), 27.0 (CH_2), 23.8 (CH_2), 12.1 (CH_3); IR (oil, cm^{-1}) 3308 (br), 2940 (s), 2858 (m); MS (CI) *m*/z (relative intensity): 210 ($M^+ + H^+$, 100), 151 (70), 133 (64); Exact mass calculated for $[C_{13}H_{23}NO]+H^+$ requires *m/z* 210.1850, found 210.1858 (CI).

5-Butylcycloheptane-1,4-dione (237) and **6-Butylcycloheptane-1,4-dione (238)**



237



238

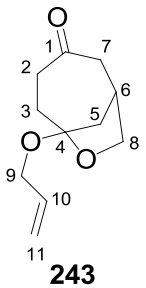
A solution of Boc-protected vinylogous amide **224** (360 mg, 1.50 mmol) in a 3:1 mixture of MeCN and 1-hexene (50 mL) was degassed for 30 min and irradiated for 1 h. The solvents were removed *in vacuo* and the resulting oil was dissolved in DCM (10 mL) and TFA (10 mL) was added slowly. The mixture was stirred for 1 h before the solvents were removed *in vacuo*. The resulting oil was purified by flash chromatography (50% Et_2O in hexane) affording diketone **237** as a colourless oil (129 mg, 0.709 mmol) in 47% yield and diketone **238** as a colourless oil (71 mg, 0.39 mmol) in 26% yield as well as a mixture of **237** and **238** as a colourless oil (15 mg, 0.083 mmol) in 6% yield.

237: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.69-2.53 (m, 7H, H-2, H-3, H-5 and H-7), 2.06-2.01 (m, 1H, H*H*-6), 1.79-1.73 (m, 1H, H*H*-8), 1.65-1.58 (m, 1H, *H*H-6), 1.38-1.21 (m, 5H, *H*H-8, H-9 and H-10), 0.88 (t, *J* = 7.2, 3H, H-11); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.6 (C), 210.9 (C), 52.4 (CH), 41.9 (CH_2), 38.2 (CH_2), 37.4 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 27.0 (CH_2), 22.8 (CH_2), 14.0 (CH_3); IR (oil, cm^{-1}) 2955 (m), 2930 (m), 2860 (m), 1703 (s); MS (ES-) *m*/z (relative intensity): 181 (M^+ -H^+, 16), 174 (47), 171 (37), 169 (100), 161 (18), 143 (15); Exact mass calculated for [$C_{11}H_{18}O_2$]-H^+ requires *m/z* 181.1229, found 181.1511 (ES-).

238: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 13.5, 4.0, 2H, *H*H-3), 2.68-2.58 (m, 4H, H-2), 2.53 (dd, *J* = 13.5, 9.3, 2H, H*H*-3), 2.08-2.02 (m, 1H, H-4), 1.36-1.27 (m, 6H, H-5, H-6 and H-7), 0.88 (t, *J* = 7.1, 3H, H-8); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.3 (C), 49.4 (CH_2), 38.3 (CH_2), 36.1 (CH_2), 32.5 (CH), 29.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (oil, cm^{-1}) 2956 (m), 2929 (m), 2860 (m), 1700 (s);

MS (ES-) *m*/z (relative intensity): 181 (M^+ -H^+, 22), 174 (50), 171 (35), 169 (100), 161 (15); Exact mass calculated for [$C_{11}H_{18}O_2$]-H^+ requires *m/z* 181.1229, found 181.1522 (ES-).

8a-Allylhexahydro-2H-cyclohepta[b]furan-6(7H)-one (243)

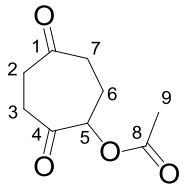


243

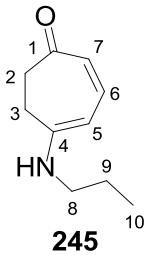
A solution of Boc-protected vinylogous amide **224** (239 mg, 1.00 mmol) in a 3:1 mixture of MeCN and allyl alcohol (50 mL) was degassed for 30 min and irradiated for 1 h. To this solution was added TFA (10 mL) and the mixture stirred for a further hour at room temperature. The solvents were removed *in vacuo* and the resulting oil dissolved in DCM (20 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 15 mL) and water (2 x 15 mL). The combined organic layers dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. Purification by flash chromatography (50% Et_2O in hexane to 5% MeOH in Et_2O) afforded keto-acetal **243** as a clear oil (12 mg, 0.060 mmol) in 6% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.1, 10.4, 5.5, 1H, H-10), 5.27 (dq, *J* = 17.1, 1.6, 1H, H_{trans}-11), 5.17 (dq, *J* =10.4, 1.5, 1H, H_{cis}-11), 4.12 (ddq, *J* = 12.4, 5.4, 1.5, 1H, H*H*-9), 4.05 (ddq, *J* = 12.4, 5.6, 1.5, 1H, *H*H-9), 3.96 (ddd, *J* =8.5, 3.8, 1.0, 1H, H*H*-8), 3.69 (dd, *J* = 8.5, 1.0, 1H, *H*H-8), 2.64-2.61 (m, 1H, H-6), 2.60-2.57 (m, 1H, H*H*-3), 2.49 (dd, *J* = 12.9, 5.0, 1H, H*H*-7), 2.47-2.43 (m, 1H, *H*H-3), 2.40-2.37 (m, 1H, *H*H-7), 2.33-2.30 (m, 2H, H-5), 2.29-2.25 (m, 1H, H*H*-2), 1.99 (ddd, *J* = 13.2, 7.7, 3.2, 1H, *H*H-2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.1 (C), 135.3 (CH), 116.5 (CH_2), 109.6 (C), 72.7 (CH_2), 63.5 (CH_2), 49.5 (CH_2), 39.2 (CH_2), 38.0 (CH_2), 36.9 (CH), 35.0 (CH_2); IR (oil, cm^{-1}) 2933 (s), 2855 (m), 1784 (m), 1715 (m); Mass ion not found.

2,5-Dioxocycloheptyl acetate (244) and **5-(Propylamino)cyclohepta-2,4-dienone (245)**



244



245

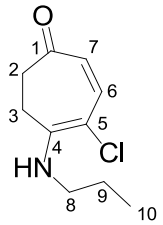
A solution of Boc protected vinylogous amide **224** (239 mg, 1.00 mmol) in MeCN (29 mL) and vinyl acetate (1 mL) was degassed for 15 min and irradiated for 45 min. The solvents were removed *in vacuo* and the resulting oil was dissolved in DCM (10 mL) and TFA (10 mL) was added slowly. The mixture was stirred for 1 h before the solvents were removed *in vacuo*. The resulting oil was dissolved in DCM (10 mL), washed with aqueous $NaHCO_3$ (1 M, 2 x 20 mL) and water (20 mL) and the organic layer dried (Na_2SO_4), filtered and the solvents were removed *in vacuo*. The resulting oil was purified by flash chromatography (Et_2O to 5% MeOH in Et_2O) to afford diketone **244** as a clear oil (86 mg, 0.47 mmol) in 47% yield and conjugated enaminone **245** as a yellow solid (42 mg, 0.26 mmol) in 26% yield. m.p. 102-103 °C.

244: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (dd, *J* = 10.1, 4.8, 1H, H-5), 2.79-2.63 (m, 5H, H-2, H*H*-3 and H-7), 2.57-2.53 (m, 1H, *H*H-3), 2.20 (dddd, *J* = 14.7, 7.5, 4.5, 4.2, 1H, H*H*-6), 2.15 (s, 3H, H-9), 2.04-1.97 (m, 1H, *H*H-6); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.1 (C), 204.2 (C), 170.1 (C), 78.0 (CH), 39.0 (CH_2), 37.4 (CH_2), 35.2 (CH_2), 26.0 (CH_2), 20.7 (CH_3); IR (oil, cm^{-1}) 2941 (w), 1741 (s), 1712 (s), 1703 (s); MS (CI) *m*/z (relative intensity): 185 ($M^+ + H^+$, 32), 143 (25), 141 (10), 125 (100), 98 (12), 97 (13); Exact mass calculated for $[C_9H_{11}O_4]+H^+$ requires *m/z* 185.08138, found 185.08099 (CI).

245: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 11.9, 8.9, 1H, H-6), 5.60 (d, *J* = 11.9, 1H, H-7), 4.86 (d, *J* = 9.0, 1H, H-5), 4.50 (br, 1H, NH), 3.02 (td, *J* = 7.2,

5.5, 2H, H-8), 2.60-2.58 (m, 2H, H-2), 2.45-2.43 (m, 2H, H-3), 1.63 (sext, *J* = 7.3, 2H, H-9), 0.98 (t, *J* = 7.4, 3H, H-10); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.0 (C), 160.0 (C), 144.2 (CH), 117.9 (CH), 92.0 (CH), 45.3 (CH_2), 39.0 (CH_2), 30.1 (CH_2), 21.9 (CH_2), 11.7 (CH_3); IR (solid, cm^{-1}) 3287 (br, w), 3078 (w), 2961 (w), 2933 (w), 2875 (w), 1736 (w), 1617 (m), 1586 (w), 1504 (s); MS (EI) *m*/z (relative intensity): 165 (M^+, 100), 137 (42), 136 (40), 122 (42), 108 (71), 94 (31); Exact mass calculated for $[C_{10}H_{15}NO]$+ requires *m/z* 165.11481, found 165.11488 (EI).

4-Chloro-5-(propylamino)cyclohepta-2,4-dienone (249)



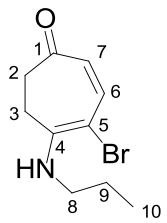
249

To a solution of Boc protected vinylogous amide **224** (239 mg, 1.00 mmol) in MeCN (50 mL) was added *trans* 1,2-dichloroethylene (385 µL, 485 mg, 5.00 mmol) and the mixture degassed for 15 min and irradiated for 2 h. The solvents were removed *in vacuo* and the resulting oil was dissolved in DCM (10 mL) and TFA (10 mL) was added slowly. The mixture was stirred for 1 h before the solvents were removed *in vacuo*. NEt_3 (5 mL) was added and the mixture stirred for a further 5 min before the solvent was removed *in vacuo*. The resulting oil was purified by flash chromatography (25% Et_2O in hexane) to afford conjugated enamine **249** as a yellow solid (153 mg, 0.769 mmol) in 77% yield. m.p. 97-98 °C.

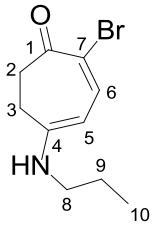
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 12.6, 1H, H-6), 5.62 (d, *J* = 12.6, 1H, H-7), 5.30 (br, 1H, NH), 3.25 (td, *J* = 7.2, 6.1, 2H, H-8), 2.69-2.66 (m, 2H, H-2), 2.62-2.59 (m, 2H, H-3), 1.63 (sext, *J* = 7.3, 2H, H-9), 1.01 (t, *J* = 7.4, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 154.3 (C), 143.1 (CH), 117.2 (CH),

100.2 (C), 45.6 (CH_2), 38.5 (CH_2), 24.0 (CH_2), 21.9 (CH_2), 11.2 (CH_3); IR (solid, cm^{-1}) 3316 (br, w), 2964 (w), 2932 (w), 2872 (w), 1724 (m), 1638 (m), 1591 (s), 1530 (s); MS (ES+) *m*/z (relative intensity): 202 (^{37}Cl M^+ $+H^+$, 21), 200 (^{35}Cl M^+ $+H^+$, 62) 174 (33), 164 (32), 129 (21), 105 (64); Exact mass calculated for $[C_{10}H_{14}NO^{35}Cl]+H^+$ requires *m/z* 200.0842, found 200.0841 (ES+).

4-Bromo-5-(propylamino)cyclohepta-2,4-dienone (250) and 2-Bromo-5-(propylamino)cyclohepta-2,4-dienone (251)



250



251

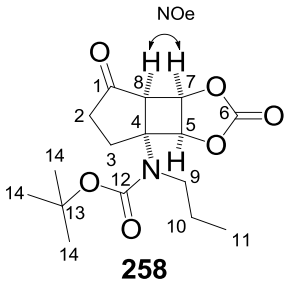
To a solution of Boc-protected vinylogous amide **224** (120 mg, 0.502 mmol) in MeCN (25 mL) was added 1,2-dibromoethylene (mixture of *cis* and *trans*, 207 µL, 465 mg, 2.50 mmol) and the mixture degassed for 15 min and irradiated for 4 h. The solvents were removed *in vacuo* and the resulting oil was dissolved in DCM (5 mL) and TFA (5 mL) was added slowly. The mixture was stirred for 1 h before the solvents were removed *in vacuo*. NEt_3 (5 mL) was added and the mixture stirred for a further 5 min before the solvent was removed *in vacuo*. The resulting oil was purified by flash chromatography (100% Et_2O to 2% MeOH in Et_2O) affording conjugated enamine **250** as a yellow solid (20 mg, 0.081 mmol) in 16% yield, m.p. 111-112 °C, conjugated enamine **251** as a yellow solid (12 mg, 0.048 mmol) in 10% yield, m.p. 113-114 °C and conjugated enamine **245** as a yellow solid (17 mg, 0.10 mmol) in 21% yield.

250: ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 12.5, 1H, H-6), 5.55 (d, *J* = 12.5, 1H, H-7), 5.32 (br, 1H, NH), 3.22 (td, *J* = 7.2, 6.2, 2H, H-8), 2.69-2.67 (m, 2H, H-3), 2.59-2.57 (m, 2H, H-2), 1.61 (sext. *J* = 7.3, 2H, H-9), 0.99 (t, *J* = 7.4, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0 (C), 155.7 (C), 145.2 (CH), 117.9 (CH), 90.3 (C), 46.0 (CH_2), 38.7 (CH_2), 24.0 (CH_2), 22.3 (CH_2), 11.3 (CH_3); IR

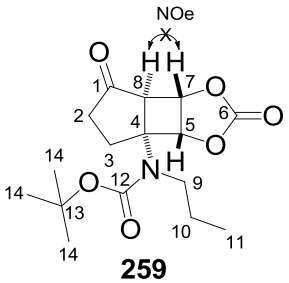
(solid, cm^{-1}) 3288 (br, m), 2961 (m), 2925 (m), 2854 (m), 1735 (w), 1614 (m), 1579 (m), 1498 (s); MS (EI) *m*/z (relative intensity): 245 (^{81}Br M^+, 100), 243 (^{79}Br M^+, 98), 202 (25), 200 (27), 188 (31), 186 (30), 136 (55), 122 (21), 94 (21); Exact mass calculated for [$C_{10}H_{14}NO^{79}Br$] requires *m/z* 243.02533, found 243.02589 (EI).

251: ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 9.9, 1H, H-6), 4.82 (d, *J* = 9.9, 1H, H-5), 4.43 (br, 1H, NH), 3.05 (td, *J* = 7.3, 5.6, 2H, H-8), 2.79-2.77 (m, 2H, H-2), 2.46-2.44 (m, 2H, H-3), 1.66 (sext. *J* = 7.4, 2H, H-9), 1.00 (t, *J* = 7.4, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (C) 160.7 (C), 146.2 (CH), 112.3 (C), 92.1 (CH), 45.4 (CH_2), 37.7 (CH_2), 29.9 (CH_2), 21.9 (CH_2), 11.7 (CH_3); IR (solid, cm^{-1}) 3274 (br, w), 2962 (m), 2930 (m), 2870 (w), 1734 (w), 1610 (s), 1562 (s), 1508 (s); MS (EI) *m*/z (relative intensity): 245 (^{81}Br M^+, 72), 243 (^{79}Br M^+, 75), 136 (100), 122 (47) 112 (48), 110 (24); Exact mass calculated for [$C_{10}H_{14}NO^{79}Br$] requires *m/z* 243.02533, found 243.02571 (EI).

***tert*-Butyl ((3aS,3bR,6aR,6bR)-2,6-dioxohexahydro-3aH-cyclopenta[3,4]cyclobuta[1,2-d][1,3]dioxol-3b-yl)(propyl)carbamate (258)** and **t*ert*-Butyl ((3aR,3bR,6aR,6bS)-2,6-dioxohexahydro-3aH-cyclopenta[3,4]cyclobuta[1,2-d][1,3]dioxol-3b-yl)(propyl)carbamate (259)**



258



259

To a solution of Boc protected vinylogous amide **224** (200 mg, 0.840 mmol) in MeCN (40 mL) was added vinylene carbonate (266 µL, 360 mg, 4.18 mmol) and the mixture degassed for 15 min and irradiated for 1 h. The solvents were removed *in vacuo* and the resulting oil was purified by flash chromatography (33% EtOAc in petroleum ether to 50% EtOAc in petroleum ether) to afford Boc

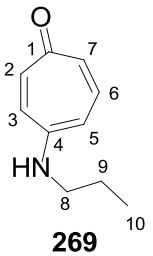
protected aminocyclobutane **258** as a colourless oil (11 mg, 0.033 mmol) in 4% yield and Boc protected aminocyclobutane **259** as a colourless oil (221 mg, 0.680 mmol) in 81% yield.

258: ^{1}H NMR (400 MHz, $CDCl_3$ 330 K*) δ 5.21-5.19 (m, 2H, H-5 and H-7), 3.40-3.37 (m, 1H, H-8), 3.30-3.10 (m, 2H, H-9), 2.87 (ddd, *J* = 15.0, 10.9, 5.1, 1H, *H*H-3), 2.69 (dddd, *J* = 19.7, 11.5, 5.1, 1.5, 1H, *H*H-2), 2.47 (dddd, *J* = 19.7, 10.8, 8.3, 0.7, 1H, H*H*-2), 2.01 (ddd, *J* = 15.0, 11.5, 8.3, 1H, H*H*-3), 1.59-1.46 (m, 11H, H-10 and H-14), 0.93 (t, *J* = 7.4, 3H, H-11); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K*) δ 209.9 (C), 154.7 (C), 154.6 (C), 81.6 (C), 77.6 (CH), 72.0 (CH), 69.0 (C), 52.9 (CH), 46.8 (CH_2), 39.8 (CH_2), 29.0 (CH_2), 28.3 (CH_3), 23.4 (CH_2), 11.1 (CH_3); IR (oil, cm^{-1}) 2971 (m), 2934 (w), 2877 (w), 1828 (s), 1808 (s), 1744 (s), 1688 (s); MS (ES+) *m*/z (relative intensity): 324 ($M^+ + H^+$, 22), 280 (85), 252 (100), 206 (39), 178 (18); Exact mass calculated for $[C_{16}H_{21}NO_6]+H^+$ requires *m/z* 324.1447, found 324.1450 (ES+).

259: ^{1}H NMR (400 MHz, $CDCl_3$, 330 K*) δ 5.03 (d, *J* = 5.1, 1H, H-5), 4.77 (dd, *J* = 5.1, 2.2, 1H, H-7), 3.26-3.18 (m, 2H, H-8 and *H*H-9), 3.01 (ddd, *J* = 14.9, 9.7, 5.9, 1H, H*H*-9), 2.55 (dddd, *J* = 18.4, 11.0, 9.0, 1.4, 1H, *H*H-2), 2.45-2.28 (m, 3H, H*H*-2, H-3), 1.57-1.38 (m, 11H, H-10 and H-14), 0.85 (t, *J* = 7.4, 3H, H-11); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K*) δ 210.4 (C), 154.4 (C), 154.3 (C), 81.0 (C), 80.3 (CH), 72.7 (CH), 66.0 (C), 56.8 (CH), 47.2 (CH_2), 38.1 (CH_2), 33.4 (CH_2), 28.2 (CH_3), 23.5 (CH_2), 10.9 (CH_3); IR (oil, cm^{-1}) 2974 (m), 2935 (w), 2875 (w), 1717 (s), 1620 (m), 1594 (m); MS (ES+) *m*/z (relative intensity): 324 ($M^+ + H^+$, 25), 280 (82), 252 (100), 206 (33), 178 (19); Exact mass calculated for $[C_{16}H_{21}NO_6]+H^+$ requires *m/z* 324.1447, found 324.1458 (ES+).

* NMR at ambient temperature showed the presence of rotamers which resolved upon heating to 330 K.

4-(Propylamino)cyclohepta-2,4,6-trienone (269)

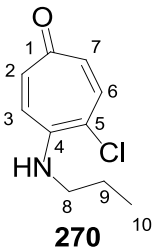


269

A solution of conjugated enaminone **249** (50 mg, 0.25 mmol) in PhMe (3 mL) was heated to reflux for 3 h. The solvent was removed *in vacuo* and purification by flash chromatography (EtOAc) afforded aminotropone **269** as a yellow solid (39 mg, 0.24 mmol) in 96% yield. m.p. dec. >150 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 11.7, 10.3, 1H, H-6), 6.93 (dd, *J* = 12.9, 2.6, 1H, H-2), 6.87 (dd, *J* = 13.0, 2.3, 1H, H-3), 6.40 (dd, *J* = 11.7, 2.6, 1H, H-7), 6.13 (br, 1H, NH), 5.84 (dd, *J* = 10.3, 2.1, 1H, H-5), 3.07-3.04 (m, 2H, H-8), 1.67 (sext, *J* = 7.3, 2H, H-9), 0.98 (t, *J* = 7.4, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9 (C), 155.0 (C), 142.2 (CH), 140.3 (CH), 133.2 (CH), 126.2 (CH), 105.1 (CH), 45.4 (CH_2), 21.6 (CH_2), 11.8 (CH_3); IR (solid, cm^{-1}) 3247 (br, m), 3058 (m), 2961 (m), 2932 (m), 2874 (m), 1636 (m), 1587 (s), 1492 (s); MS (ES+) *m*/z (relative intensity): 164 (M^+ +H^+, 100), 135 (12); Exact mass calculated for [$C_{10}H_{13}NO$]+H^+ requires *m/z* 164.0997, found 164.0936 (ES+).

4-Chloro-5-(propylamino)cyclohepta-2,4,6-trienone (270)



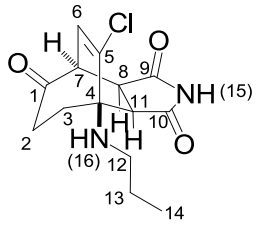
270

A solution of conjugated enamine **249** (30 mg, 0.15 mmol) and NEt_3 (105 µL, 76.0 mg, 0.750 mmol) in PhMe (2 mL) was heated to reflux for 48 h open to air.

The solvents were removed *in vacuo* and purification by flash chromatography (EtOAc) afforded aminochlorotropone **270** as a yellow solid (15 mg, 0.076 mmol) in 50% yield. m.p. dec. >165 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 12.8, 1H, H-6), 7.14 (dd, *J* = 13.3, 2.8, 1H, H-2), 7.04 (d, *J* = 13.3, 1H, H-3), 6.48 (dd, *J* = 12.8, 2.8. 1H, H-7), 5.37 (br, 1H, NH), 3.35 (td, *J* = 7.1, 5.6, 2H, H-8), 1.74 (sext, *J* = 7.3, 2H, H-9), 1.06 (t, *J* = 7.4, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4 (C), 148.5 (C), 141.8 (CH), 139.7 (CH), 126.3 (CH), 124.7 (CH), 116.1 (C), 45.8 (CH_2), 22.9 (CH_2), 11.3 (CH_3); IR (solid, cm^{-1}) 3405 (w), 3290 (br, w), 2963 (w), 2932 (w), 2875 (w), 1632 (m), 1577 (m), 1544 (s), 1509 (s); MS (EI) *m*/z (relative intensity): 199 (^{37}Cl M^+, 6), 197 (^{35}Cl M^+, 16), 162 (17), 142 (29), 140 (100), 105 (18); Exact mass calculated for $[C_{10}H_{12}NO^{35}Cl]$-H^+ requires *m/z* 196.0529, found 196.0522 (ES-).

(3aS,4R,8R,8aS)-9-Chloro-8-(propylamino)-3a,4,6,7,8,8a-hexahydro-4,8-ethenocyclohepta[c]pyrrole-1,3,5(2H)-trione (274)

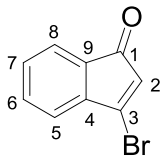


274

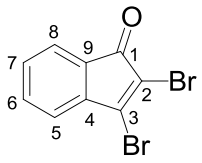
To a solution of conjugated enamine **249** (70 mg, 0.35 mmol) in PhMe (4 mL) was added maleimide (68 mg, 0.70 mmol) and the mixture was stirred at reflux for 1 h. The solvent was removed *in vacuo* and purification by flash chromatography (50% Et_2O in petroleum ether to 100% Et_2O) afforded Diels-Alder adduct **274** as a white powder (83 mg, 0.28 mmol) in 79% yield. m.p. dec. >210 °C.

^{1}H NMR (600 MHz, DMSO) δ 11.57 (s, 1H, NH-15), 6.25 (d, *J* = 8.1, 1H, H-6), 3.76 (d, *J* = 8.5, 1H, H-11), 3.38 (d, *J* = 8.5, 1H, H-8), 3.22 (d, *J* = 8.1, 1H, H-7), 2.78-2.73 (m, 1H, H*H*-12), 2.58-2.50 (m, 3H, H-2 and *H*H-12), 2.34 (dd, *J* = 9.9, 3.9, 1H, NH-16), 2.13 (dt, *J* = 14.1, 7.0, 1H, H*H-3*), 1.93 (dt, *J* = 14.1, 7.0, 1H, *H*H-3), 1.47 (sext, *J* = 7.3, 2H, H-13), 0.93 (t, *J* = 7.3, 3H, H-14); ^{13}C NMR (150 MHz, DMSO) δ 204.3 (C), 178.4 (C), 178.1 (C), 140.9 (C), 122.4 (CH), 60.6 (C), 51.1 (CH), 47.4 (CH), 43.7 (CH), 43.6 (CH_2), 37.7 (CH_2), 33.7 (CH_2), 23.5 (CH_2), 11.9 (CH_3); IR (solid, cm^{-1}) 3204 (m), 3096 (w), 2964 (w), 2932 (w), 2871 (w), 1777 (m), 1717 (s), 1686 (s), 1625 (m); MS (ES+) *m*/z (relative intensity): 299 (^{37}Cl M^+ +H^+ 100), 297 (^{35}Cl M^+ +H^+, 43), 202 (29), 200 (83); Exact mass calculated for [$C_{14}H_{17}N_2O_3{}^{35}Cl$]+$H^+$ requires *m/z* 297.1006, found 297.1003 (ES+).

3-Bromo-1H-inden-1-one (282)[227] and **2,3-Bibromo-1H-inden-1-one (283)**[228]



282



283

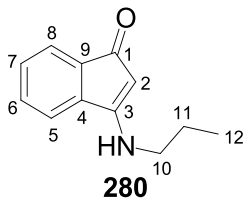
To a solution of 1-Indanone (200 mg, 1.52 mmol) and NBS (563 mg, 3.18 mmol) in benzene (10 mL) was added AIBN (52 mg, 0.32 mmol). The solution was stirred at reflux for 1.5 h before being allowed to cool to room temperature and then cooled further to 0 °C. NEt_3 (634 µL, 461 mg, 4.56 mmol) was added and the solution allowed to warm to room temperature and stirred for 3 h. The solvents were removed *in vacuo* and purification by flash chromatography (25% DCM in petroleum ether to 100% DCM) afforded indenone **282** as an orange solid (202 mg, 0.967 mmol) in 64% yield, m.p. 56-58 °C and indenone **283** as a yellow solid (17 mg, 0.058 mmol) in 4% yield m.p. 121-122 °C.

282: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.43 (m, 2H, H-5 and H-6), 7.36 (t, *J* = 7.4, 1H, H-7), 7.23 (d, *J* = 7.3, 1H, H-8), 6.23 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9 (C), 148.7 (C), 143.0 (C), 133.7 (CH), 130.5 (C), 130.4 (CH),

127.4 (CH), 121.9 (CH), 121.4 (CH); IR (solid, cm^{-1}) 3112 (w), 3020 (w), 1712 (s), 1599 (m), 1539 (m); MS (EI) *m*/z (relative intensity): 210 (^{81}Br M^+, 34), 208 (^{79}Br M^+, 34), 129 (100), 101 (47), 75 (23), 74 (23); Exact mass calculated for [$C_9H_5O^{79}Br$] requires *m/z* 207.95183, found 207.95195 (EI). Spectroscopic data is consistent with the literature.[228]

283: ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.47 (m, 2H, H-5 and H-6), 7.33 (td, *J* = 7.5, 1.0, 1H, H-7), 7.23 (dd, *J* = 7.6, 1.0, 1H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7 (C), 146.4 (C), 142.6 (C), 134.5 (CH), 129.9 (CH), 129.2 (C), 123.0 (CH), 122.5 (C), 121.2 (CH);); IR (solid, cm^{-1}) 3112 (w), 3020 (w), 1712 (s), 1599 (m), 1539 (m); 3101 (w), 1714 (s), 1544 (m); Mass ion not found. Spectroscopic data is consistent with the literature.[228]

3-(Propylamino)-1H-inden-1-one (280)



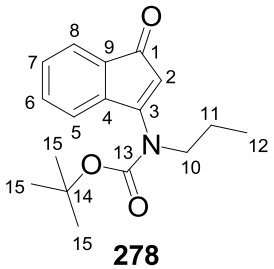
280

To a solution of indenone **282** (100 mg, 0.478 mmol) in DCM (5 mL) was added triethylamine (199 µL, 145 mg, 1.43 mmol) and propylamine (30 µL, 42 mg, 0.72 mmol) and the mixture stirred for 3.5 h. The solvents were removed *in vacuo* and purification by flash chromatography (2% MeOH in DCM) afforded benzo-vinylogous amide **280** as a brown solid (49 mg, 0.26 mmol) in 55% yield. m.p. 142-143 °C.

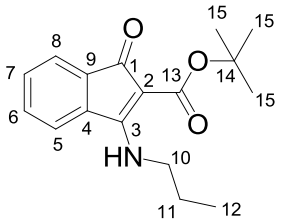
^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 6.3, 1.8, 1H, H-5), 7.38-7.31 (m, 2H, H-6 and H-7), 7.23 (dd, *J* = 6.2, 1.8, 1H, H-8), 5.97 (br, 1H, NH), 4.93 (s, 1H, H-2), 3.35 (td, *J* = 7.2, 6.1, 2H, H-10), 1.77 (sext, *J* = 7.3, 2H, H-11), 1.04 (t, *J* = 7.3, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5 (C), 165.5 (C), 138.3 (C), 136.1 (C), 130.4 (2 X CH), 120.5 (CH), 116.5 (CH), 91.6 (CH), 46.9 (CH_2), 22.3

(CH_2), 11.5. (CH_3); IR (solid, cm^{-1}) 3256 (m), 3046 (w), 2964 (m), 2875 (w), 1722 (w), 1660 (m), 1614 (s), 1567 (s); MS (EI) *m*/z (relative intensity): 187 (M^+, 97), 159 (70), 158 (100), 145 (70), 130 (67); Exact mass calculated for [$C_{12}H_{13}NO$] requires *m/z* 187.09917, found 187.09933 (EI).

***tert*-Butyl (1-oxo-1H-inden-3-yl)(propyl)carbamate (278)** and **t*ert*-Butyl 1-oxo-3-(propylamino)-1H-indene-2-carboxylate (284)**



278



284

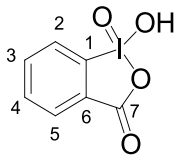
To a solution of benzo-vinylogous amide **280** (140 mg, 0.749 mmol) in DCM (5 mL) was added a solution of di-*tert*-butyl dicarbonate (196 mg, 0.899 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in DCM (5 mL) and the solution stirred at room temperature for 18 h. The solvents were removed *in vacuo* and purification by flash chromatography (50% Et_2O in hexane to 100% Et_2O) afforded Boc-protected benzo-vinylogous amide **278** as a brown oil (81 mg, 0.28 mmol) in 38% yield and Boc-protected benzo-vinylogous amide **284** as a brown solid (65 mg, 0.23 mmol) in 30% yield. m.p. Dec. >180 °C

278: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.1, 1H, H-5), 7.36 (td, *J* = 7.5, 1.3, 1H, H-7), 7.27 (td, *J* = 7.3, 0.9, 1H, H-6), 7.15 (dt, *J* = 7.4, 0.9, 1H, H-8), 5.60 (s, 1H, H-2), 3.67 (t, *J* = 7.5, 2H, H-10), 1.71 (sext. *J* = 7.4, 2H, H-11), 1.51 (s, 9H, H-15), 0.94 (t, *J* = 7.4, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (C), 164.3 (C), 152.5 (C), 141.8 (C), 132.3 (C), 132.2 (CH), 129.2 (CH), 122.1 (CH), 121.3 (CH), 113.1 (CH), 82.7 (C), 52.2 (CH_2), 28.0 (CH_3), 21.9 (CH_2), 11.2 (CH_3); IR (oil, cm^{-1}) 2971 (m), 2934 (w), 2876 (w), 1699 (s), 1606 (m), 1557 (m); MS (ES+) *m*/z (relative intensity): 310 (M^+ +Na, 34), 254 (21), 232 (100),

214 (22) 190 (33); Exact mass calculated for $[C_{17}H_{21}NO_3]$+Na requires *m/z* 310.1419, found 310.1421 (ES+).

284: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (br, 1H, NH), 7.64 (d, *J* = 7.2, 1H, H-5), 7.57 (d, *J* = 7.5, 1H, H-8), 7.52 (td, *J* = 7.3, 0.7, H-7), 7.43 (td, *J* = 7.5, 1.2, 1H, H-6), 3.84 (td, *J* = 7.2, 6.2, 2H, H-10), 1.90 (sext, *J* = 7.3, 2H, H-11), 1.60 (s, 9H, H-15), 1.13 (t, *J* = 7.4, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2 (C), 171.5 (C), 167.3 (C), 137.8 (C), 134.1 (C), 132.8 (CH), 131.3 (CH), 123.6 (CH), 122.2 (CH), 96.0 (C), 80.2 (C), 47.4 (CH_2), 28.6 (CH_3), 23.4 (CH_2), 11.4 (CH_3); IR (solid, cm^{-1}) 2968 (w), 2931 (w), 2878 (w), 1719 (w), 1687 (m), 1633 (s), 1615 (s), 1576 (s); MS (ES+) *m*/z (relative intensity): 318 (42), 232 (44), 188 (100), 169 (31), 146 (51); Mass ion peak not found.

2-Iodoxybenzoic acid[229]



To a solution of oxone (37.2 g, 60.5 mmol) in distilled water (200 mL) was added 2-Iodobenzoic acid (5.00 g, 20.2 mmol) and the mixture stirred at 70 °C for 2 h. The solid was filtered off and the filtrate allowed to cool to room temperature and stirred for a further 30 min. The precipitate was filtered and washed with water (4 x 25 mL) then acetone (2 x 50 mL) and dried under vacuum to afforded IBX as a white, crystalline solid (1.00 g, 3.57 mmol) in 18% yield.

^{1}H NMR (500 MHz, DMSO) δ 8.13 (d, *J* = 8.0, 1H, Ar-H), 8.02 (dd, 1H, *J* = 7.5, 1.2, 1H, Ar-H), 7.99 (td, *J* = 7.6, 1.4, 1H, Ar-H), 7.83 (td, *J* = 7.4, 0.9, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO) δ 167.5 (C), 146.5 (C), 133.4 (CH), 133.1 (CH),

131.5 (C), 130.1 (CH), 125.0 (CH); Mass ion not found. Spectroscopic data is consistent with the literature[230].

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5. Appendix