

Photochemistry of cyclopentenones : Beyond [2+2] photocycloaddition reactions

Hendrik Eijsberg

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By

Hendrik EIJSBERG

Subject: Photochemistry of cyclopentenones: Beyond [2+2] photocycloaddition reactions

Presented the 2nd of May 2012 before the review board:

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Summary

The aim of this project was to explore the scope and limitations of a tandem photochemical process, consisting of a [2+2] cycloaddition between cyclopentenones and alkenes followed by a Norrish I/γ-hydrogen transfer reaction of the initial bicyclic adduct is formed. Using standard synthetic procedures, a small library of cyclopentenone substrates was prepared. The development of new methods to access substituted cyclopentenones, using organocatalyzed aldolisation conditions, was considered; however, these efforts were unfruitful.

The photochemical studies showed that a selection of cyclopentenones and alkenes could react together to furnish cyclobutene aldehydes with average to good yields. The reaction conditions were optimized for the formation of this specific compound type, and some of the limitations as regards substrate diversity were determined. In some cases, control of the regioselectivity of the Norrish-I process was problematic.

In course of the study, it was discovered that some of these cyclobutene aldehydes could themselves react photochemically, via an intramolecular Paternò–Büchi reaction, to form hitherto unknown tricyclic oxetanes. This constitutes a one-pot triple photochemical reaction sequence between the starting cyclopenenones and alkenes. Conditions were optimized for this transformation and several examples prepared. The tricyclic core structure was studied in detail, in both solution and the solid state, revealing that the formation had been highly diastereoselective in some examples. Some limitations, arising from steric hindrance and/or use of electron rich alkenes, constituted a limitation of the scope of the process.

Résumé

L'objectif de ce projet a été d'explorer les limites et les possibilités d'une réaction tandem photochimique, composée d'une cycloaddition [2+2] entre des cyclopentenones et des alcènes, suivie d'une Norrish I/transfert du γ-hydrogen si l'adduit bicyclique se forme.En utilisant des procédures de la littérature, une petite bibliothèque de cyclopentenones fut préparée. Le developpement de méthodes permettant l'accès à des cyclopentenones substituées, par des réactions d'aldolisation organocatalysées, fut explorée sans succès.

Des études photochimiques menées sur une selection de cyclopentenones et d'alcènes ont montré qu'ils pouvaient réagir ensemble pour fournir des cyclobutène aldehydes avec des moyens à bons rendements. Les conditions réactionnelles furent optimisées pour la formation de ce composé et quelques unes des limites en termes de susbtrat furent déterminées. Dans certains cas, un problème de régiosélectivité de la réaction de Norrish I furent constatés.

Durant le cette étude, il fut découvert que certains de ces cyclobutène aldéhydes pouvaient eux-mêmes réagir photochimiquement par une réaction de Paternò–Büchi intramoléculaire pour mener à des oxétanes tricycliques totalement inédits. Ceci représente une séquence *one-pot* de trois réactions photochimiques entre la cyclopentenone de départ et l'alcène. Les conditions opératoires furent optimisées pour cette transformation et plusieurs exemples furent préparés. La structure centrale tricyclique fut étudiée en détail, en solution et dans l'état solide, montrant que la formation de ces oxétanes était hautement diastéréoselective dans certains exemples. Certaines limitations, découlant de gène stérique et/ou l'utilisation d'alcènes électroniquement riches, constituent une limite à la portée de cette réaction.

Riassunto

Questo progetto è nato con l'obiettivo di sviluppare un processo tandem fotochimico, costituito da una cicloaddizione [2+2] tra olefine e substrati ciclopentenonici, seguita da una reazione di Norrish-I / trasferimento di γ-idrogeno sul prodotto biciclico ottenuto. Usando procedure standard, è stata preparata una libreria di substrati ciclopentenonici da testare in questo processo. Lo studio di nuove metodologie organocatalitiche per la sintesi di tali substrati è stato inoltre intrapreso, sfortunatamente senza buoni risultati.

Lo studio di questo processo ha mostrato come una serie di ciclopentenoni sia effettivamente in grado di reagire con doppi legami olefinici, portando alla formazione di derivati aldeidici ciclobutenici, con discrete o buone rese. Le condizioni di reazione sono state ottimizzate per la formazione di questa classe di composti, e alcune limitazioni relative alla struttura del substrato sono emerse da questi studi. In alcuni casi, infatti, il controllo della regioselettività della reazione di Norrish-I si è rivelato problematico.

Durante tale studio, è apparso che alcune delle aldeidi ciclobuteniche ottenute si sono rivelate in grado di reagire ulteriormente in condizioni fotochimiche, attraverso una reazione di Paternò–Büchi intramolecolare, portando alla formazione di ossetani triciclici finora sconosciuti. Ciò costituisce in ultima analisi un triplo processo fotochimico one-pot a partire da ciclopentenoni e alcheni.

Anche le condizioni di reazione per questa sequenza sono state ottimizzate e alcuni esempi sono stati preparati e isolati. La struttura triciclica di questi nuovi composti e stata caratterizzata nel dettaglio, sia in soluzione che allo stato solido, rivelando un'elevata diastereoselettività in diversi casi. La presenza di gruppi stericamente ingombranti, o l'uso di olefine elettronricche, si sono dimostrati tuttavia una limitazione alla sintesi di queste interessanti strutture.

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List of abbreviations

CI	Chemical Ionisation
COSY	COrrelation SpectroscopY
DBU	1,8-diazabicyclo[5.4.0]- undec-7-ene
DMAP	4-(DiMethylAmino)Pyridine
EI	Electronic Ionisation
EM	ElectroMagnetic
GCMS	Gas Chromatography Mass Spectroscopy
HMBC	Heteronuclear Multiple-Bond Correlation
HMQC	Heteronuclear Multiple-Quantum Correlation
HSQC	Heteronuclear Single Quantum Correlation
ISC	InterSystem Crossing
J-MOD	J-MODulated spin echo
JRES	J-RESolved 2D experiment
LDA	Lithium Diisopropyl Amidure
NMR	Nuclear Magnetic Resonance
nOeSY	nuclear Overhauser effect SpectroscopY
ppm	Parts per million
SM	Starting Material
TBS, TBDMS	Terbutyldimethylsilyl
TLC	Thin Layer Chromatography
TME	Tetramethylethylene / 2,3-dimethylbutene
UV	UltraViolet

General introduction

Photochemistry is the science of the interaction of light with matter, leading chemical species to undergo chemical transformations. Irradiation of chemical species with the appropriate light source results in the target molecule absorbing a photon and thus increasing its internal energy. The crucial point of photochemical transformations is that the resulting molecule or atom (R in figure 1), when carried to an excited energy state (R*), has a reactivity that is different from the ground state. In all physical systems, a photoexcited system will return to the ground state by releasing the energy as heat (kinetic energy), reemitting a photon or by reacting within itself or with another system.

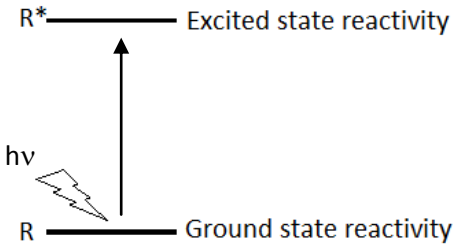


Figure 1

Photochemistry is often included in the arsenal of "green chemical transformations".[1] Indeed, photochemical reactions are induced by a photon, the cheapest reagent available, since it's provided freely by the sun and in effectively unlimited quantity. In practice, intense irradiation can be carried out with readily available lamps and is sufficient for laboratory purposes. Photochemistry is also used in some industrial scale applications.[2–4]

This general introduction will explain some of the basic tenets of photochemistry and outline the principal photochemical transformations of organic compounds that are relevant to this research project.

The basics of organic photochemistry

A photochemical reaction begins by the absorption of a photon by a molecule.[5,6] Two laws have been established for this process: absorption of a photon is necessary to initiate a photochemical transformation (Grotthuss-Draper law) and one photon activates one molecule (Stark-Einstein law). Absorption is a selective process: a molecular species will only be able to absorb photons from finite, discrete spectral ranges. These wavelengths, related to quanta of energy ($E=h\nu$), correspond to transitions in the electronic, vibrational and rotational configuration of the species. For a given transition (thus, a given wavelength), a molar absorption coefficient (ε, in m^2/mol) can be measured which represents the propensity of the species to absorb photons at that wavelength. This coefficient can be correlated to the electronic structure of the chromophore.
Electronic transitions are usually in the UV-visible range of electro-magnetic (EM) radiation. These are the transitions that are relevant to organic photochemistry and involve transitions between molecular orbital energy levels. Due to the necessity of conserving symmetry and spin, only certain transitions are "allowed". In contrast with"forbidden" transitions, the probability of the transition occurring is high. The molecular orbitals and allowed transitions of a carbonyl group are illustrated in scheme 2.

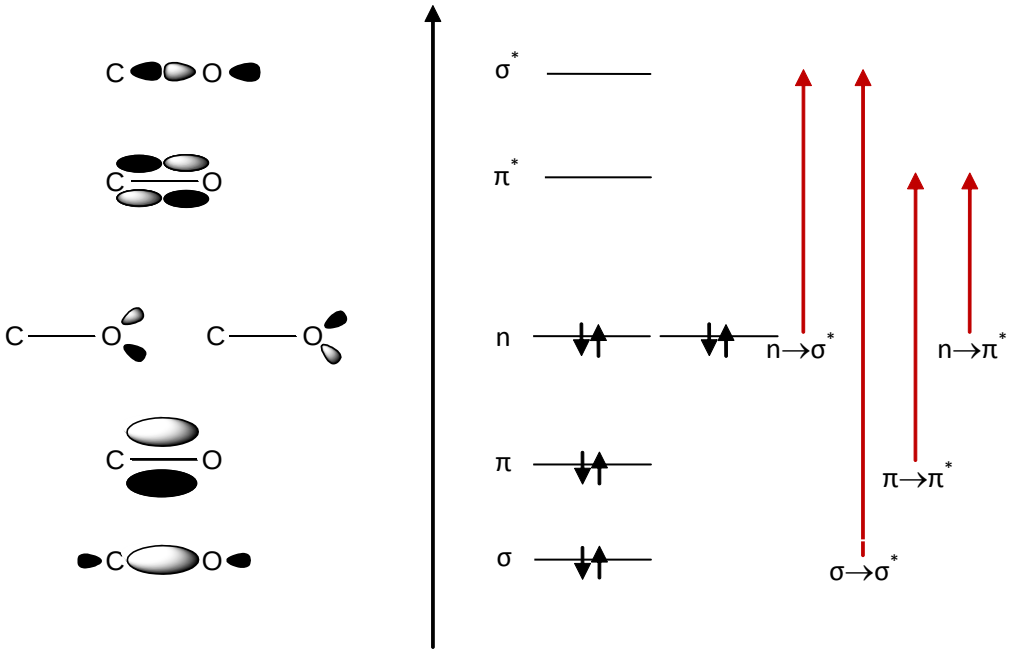


Figure 2

All molecules have an electronic configuration comprised of discrete energy levels: molecular orbitals. They are combinations of the atomic orbitals of the component atoms and are filled by the valence electrons of these same atoms. The ground state is the minimum energy configuration: molecular orbitals are filled by paired electrons with opposite spins (Pauli principle) occupying the lower energy orbitals first (Klechkowski or Aufbau principle). The ground state is the energy minimum and has a total spin S=0, therefore it is has a multiplicity of 1 (=2S+1) and is therefore a singlet state.

Excited states are energy levels of the molecule higher than the ground state. They can be reached by absorbing the appropriate photon (or for vibrationnal levels, kinetic energy). Absorption of a photon allows for promotion of an electron to another molecular orbital. The total spin of the system is conserved after such a transition: it is an excited singlet state. These transitions do not break symmetry or change the overall spin and can therefore occur readily. The lifetime of the excited states is limited, the de-excitation by emission of a photon (resonance fluorescence) being an equally easy process. However, excited singlet states can undergo ISC (Inter-System Crossing), which involves the slight stabilization of the molecule by increasing the overall spin (Hund rule). This is achieved by inverting the spin of the higher energy electron: the overall spin S is no longer nil, but 1. The multiplicity (2S+1) is now 3, hence a triplet state. The lifetime of this triplet state is greater than the singlet state, since the return to the ground state (the transition is called phosphorescence) is forbidden because of the spin change. The energy levels and transitions can be represented in a Jablonski diagram (figure 3).

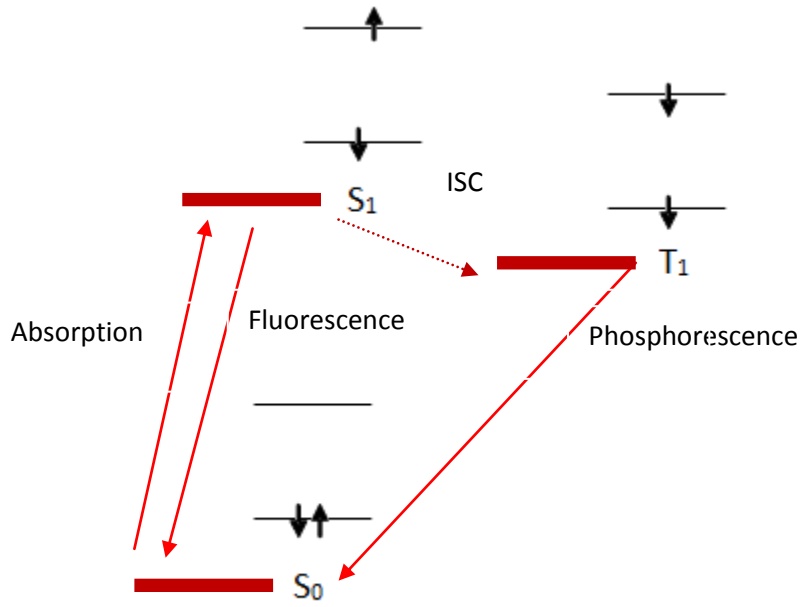


Figure 3

To complicate matters, the previous energy levels are themselves degenerated into vibrational energy levels (scheme 4). The former are linked to the electronic deployment in the molecular orbitals, the latter are linked to nuclear motion (rotation,vibration, stretching, etc…). While both are components of the internal energy of the molecule, they can be described separately (Born–Oppenheimer approximation). Vibrational transitions account for variations of the transition energy: atoms have monochromatic peaks in their spectra, molecules have bands . Transitions between vibrational levels are also subject to laws: transitions are allowed if there is sufficient overlap between the associated wave functions (Franck–Condon rule).

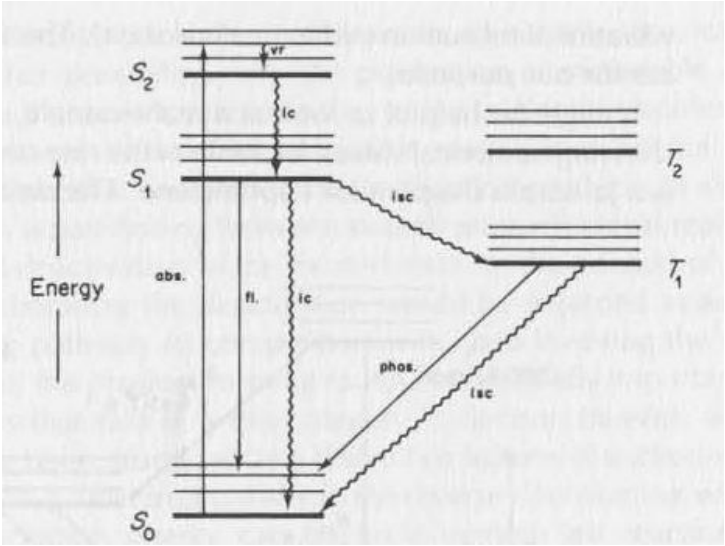


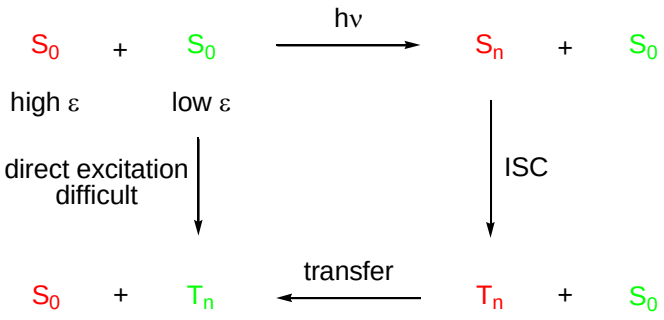
Figure 4

Excited states are the "natural"reactive states in photochemistry. These excited states must have sufficient lifetimes to react: the longer-lasting triplet states are usually the reactive states. Sometimes, the excited levels are difficult to reach: poor quantum yield (ratio of photons absorbed leading to a reaction to total number of absorbed photons), etc… In these cases, photosensitizers can be used.

Photosensitizers are species that absorb photons and transfer the excitations to species by non-photochemical interaction. They have the following characteristics:

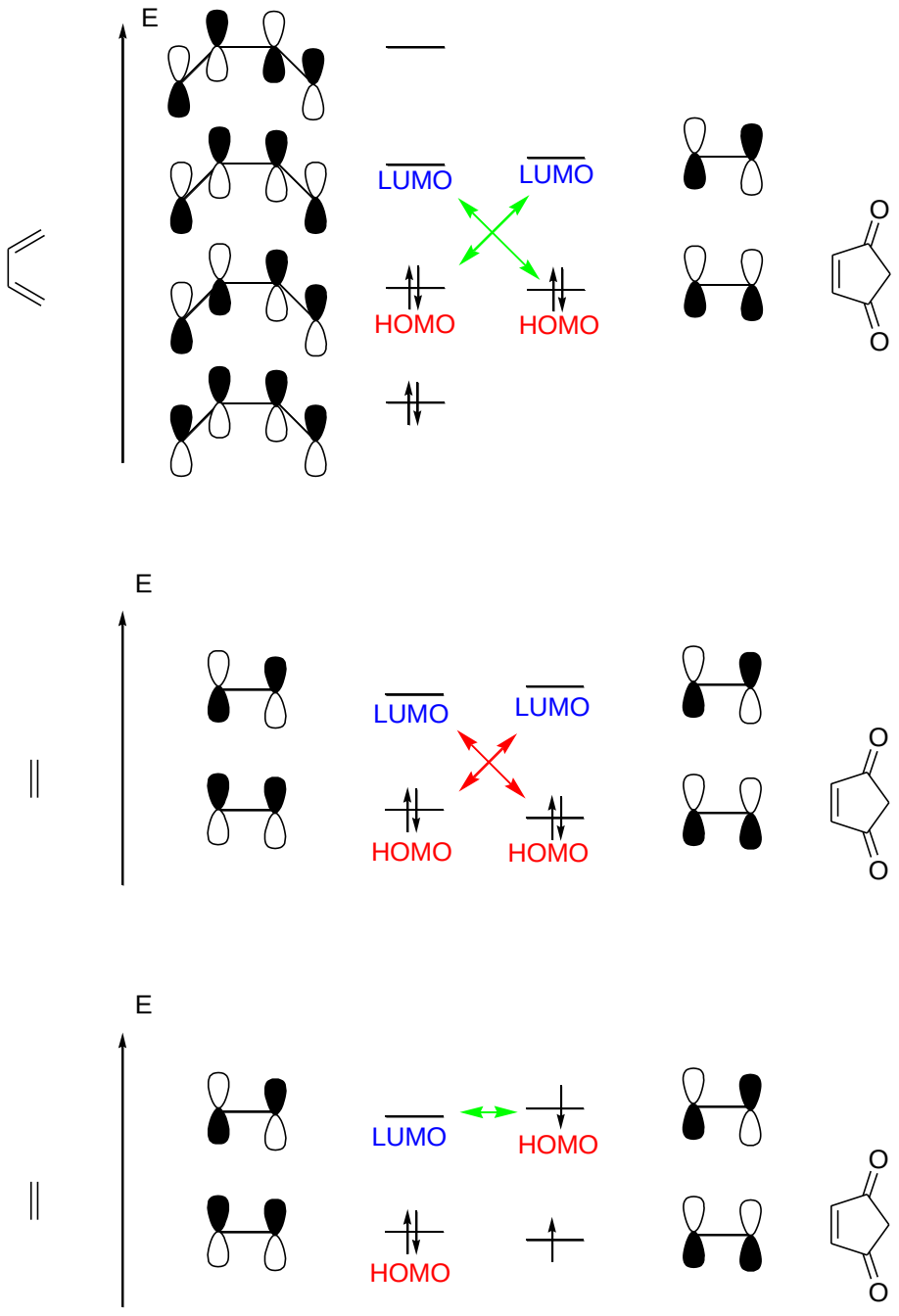
- They can absorb incident photons very easily: they have a high ε, molar absorption, at an easily accessible wavelength. They should also be able to shift to a triplet state easily if that is the sensitization required.
- The excited states have a long (in terms of photochemical transformation, this means 10^{-4} / 10^{-5} seconds compared to 10^{-10} seconds) lifetime. This means the species in the excited has limited reactivity other than transferring the spin and excitation to the target molecule).
- The excited state of the photosensitizer must be higher in energy that the target excited state.

The action of a photosensitizer in regards to the target molecule can be summarized thus:



Scheme 1

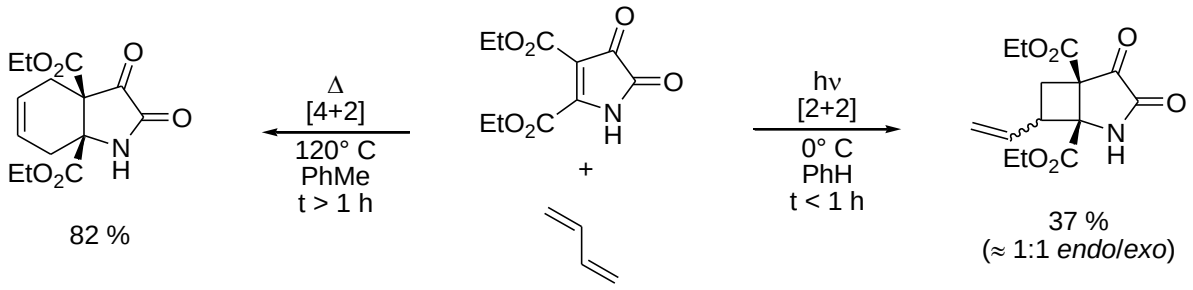
Amongst the laws of chemistry, the Woodward-Hoffmann rules are of particular interest in intermolecular photochemical reaction. These rules govern the feasibility of pericylic reactions, reactions that have a cyclic transition state and involve displacements of π and σ bonds. The physical phenomena behind them are the selection rules describing the interactions between molecular orbitals. Excited states react differently from the ground state and leads to different reaction products. Frontier orbital theory, developed first by Fukui[7] and then Woodward and Hoffmann[8], suggests that the electrocyclic reactions are only possible if the reactant molecular orbitals are symmetrical, meaning the addition of the orbitals leads to bonding, and not anti-bonding, orbitals.



Scheme 2

The reactivity of enone systems with alkenes and dienes can be switched with photochemistry (figure 2): dienes can react with an enone in the ground state (Diels-Alder), a simple alkene cannot but it can with an enone in its excited state.

A good example of the orthogonal nature of photochemical versus non-photochemical reactivity is the following work on dioxopyrolines. Sano and Isobe have described the reactions of a highly reactive enone and butadiene to yield [3.2.0] bicyclocarbocycles under photochemical conditions[9] or [4.3.0] bicyclocarbocycles under thermal conditions[10].



Scheme 3

The photoexcited dioxopyroline reacts differently with the diene because the excited state HOMO can now react with a single double bond instead of the whole conjugated system (Diels Alder).

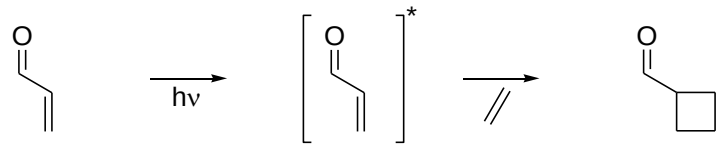
As demonstrated in the above intermolecular example, photochemistry allows for otherwise impossible reactivity of chromophores by accessing excited states. Several of these original reactivities are described below.

Basic transformations through organic photochemistry

All molecules can absorb photons at certain wavelengths. Organic photochemistry is usually limited to UV-visible, photons whose absorption leads to electronic transitions. Typical organic photochemistry is usually limited to radiation of wavelengths 100 – 600 nm and can be limited further depending on the light source and the reaction glassware.

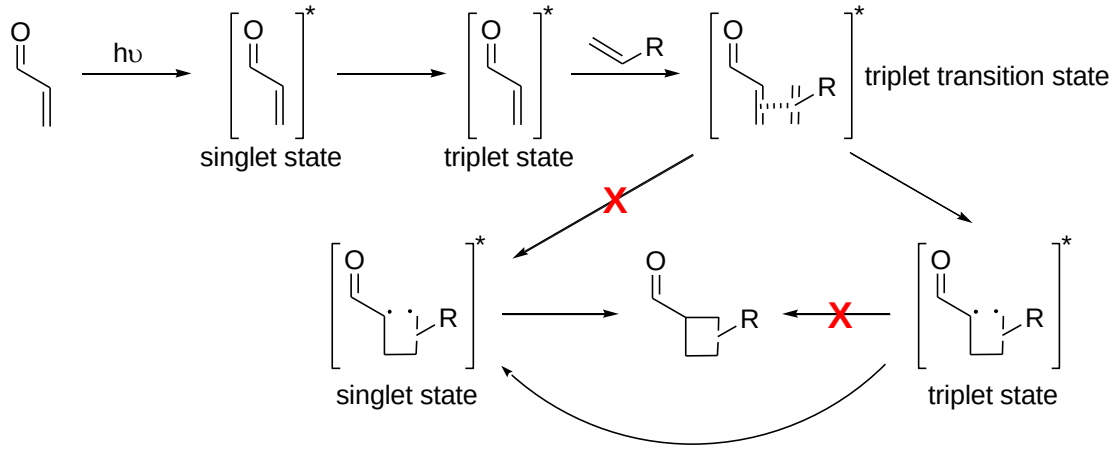
[2+2] photocycloaddition.

The most important photochemical transformation in solution is, arguably, the [2+2] photocycloaddition between a an excited alkene and a non-excited alkene, most particularly the addition of α,β unsaturated carbonyl species to double bonds . [11–18] It is the principal method for the preparation of cyclobutane structures. The reaction has been extensively studied[11,13,14,19–25] and has been used in several syntheses of natural products.[12,15–18,21,26–33] Unconjugated alkenes, such as the ferulic acid derivatives,[34] can undergo photodimerization to form complex bioactive structures around cyclobutane cores.



Scheme 4

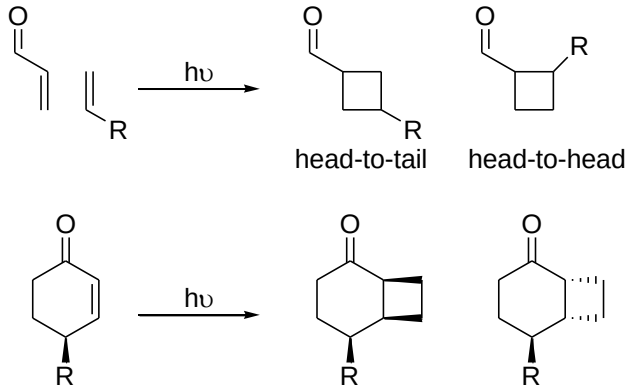
Enones, unsaturated carbonyl species, can react very easily photochemically under UV-visible light irradiation. [35] The mechanism of this reaction is complex, because of many possible reaction pathways studied by Crimmins[11]. The following simplified mechanism is commonly accepted (scheme 5). This simplified mechanism does not cover all possible regioisomers.



Scheme 5

Figure 1 explains the main steps of the reaction: the enone absorbs a photon in the 280-340 nm region (corresponding to the n → π* transition) and moves from the singlet to the triplet state (ISC) and then adds to the alkene via a triplet transition state. The resulting biradical is in a triplet state, since the spin cannot change during the reaction. The resulting triplet state cannot form the final σ C-C bond since the two unpaired electrons cannot form a molecular orbital due to having the same spin. The biradical flips to the singlet state, by undergoing ISC, which can the form the cyclobutane.

Additional issues are regioselectivity and diastereoselectivity (scheme 6):[24] head-to-tail and head-to-head distribution is governed by various electronic effects (based on the stability of the biradical intermediates). Diastereoselectivity can be influenced by steric effects during the approach of the enone on the alkene partner.



Scheme 6

The reaction can be carried intramolecularly which yields higher stereoselectivities than the intermolecular reaction which is notoriously unselective.[19,36–40]
This reaction has been used extensively in organic synthesis[15,21,27–29,32,41–43] such as the synthesis of (-)-Grandisol[44] **1**, (-)-Echinosporin **2** [45], Littoralisone[46] or Silphinene[36]. All these molecules contained functionalized cyclobutanes that would otherwise be difficult to prepare or cyclobutane intermediate in their synthesis. [47]

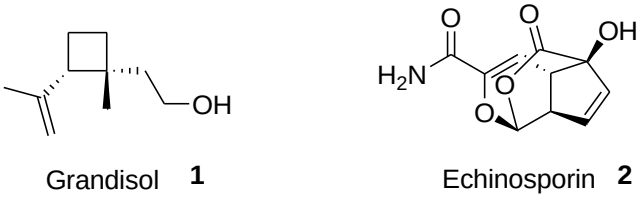
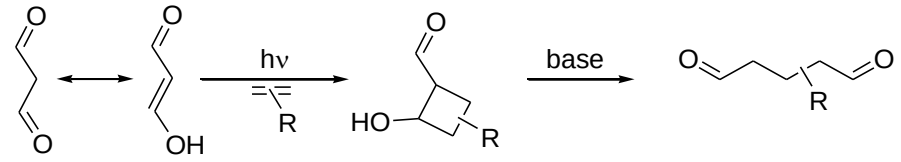


Figure 5

A variant of this reaction, the De Mayo reaction, exists for derivatives of 1,3 ketones.[48] [2+2] photoaddition to an alkene leads to a motif that is formally an intramolecular aldol. Bases can promote the retro-aldolisation of this structure.

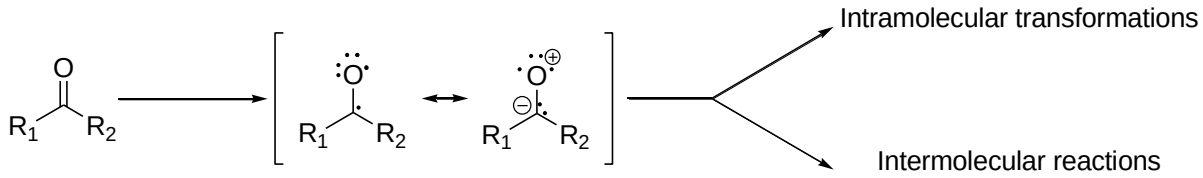


Scheme 7

This method has been used for the synthesis of tropolones and several natural products such as himachalene derivatives.[48–50]

Carbonyl photochemistry

The carbonyl function is a chromophore that can absorb photons in the UV-visible spectra, which leads to a triplet species, reacting as a biradical.

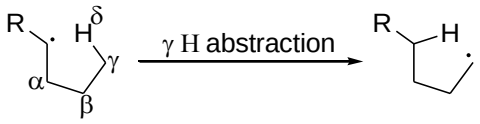


Scheme 8

The major basic photochemical transformations of carbonyl species are:[5,6,51–54]

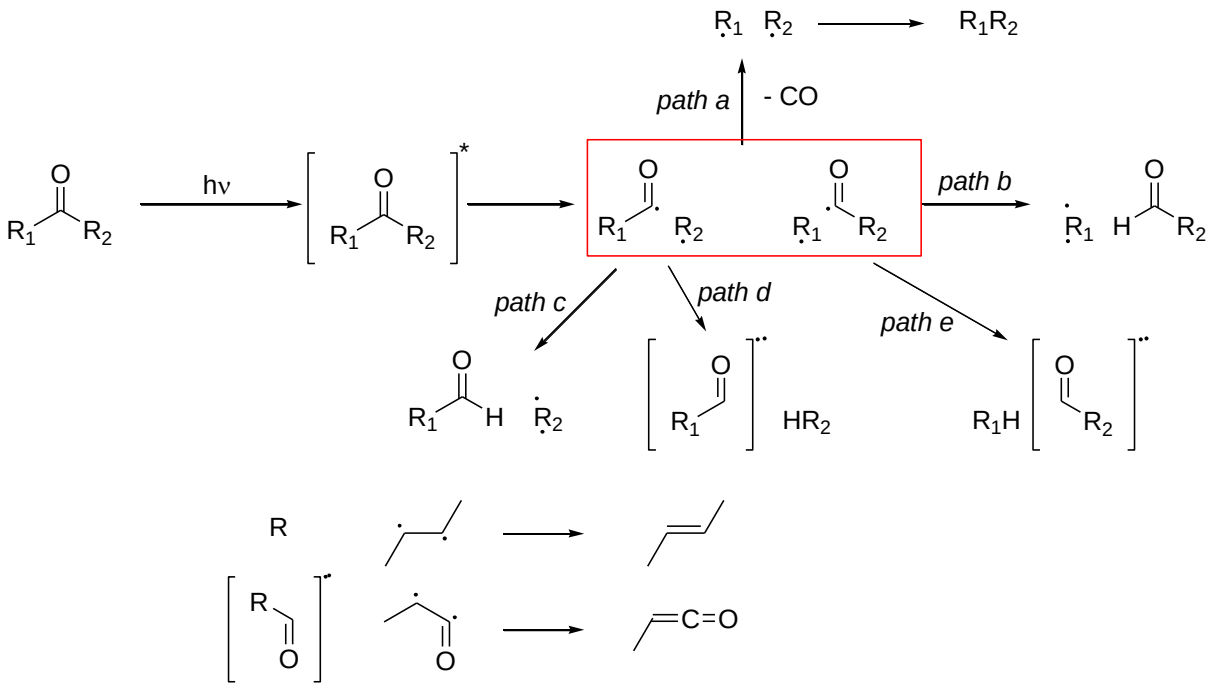
- The Norrish I process

This reaction is the homolytic rupture of the single bonds connecting a carbonyl iniated by light. This reaction concerns aldehydes and ketones[55–58], acids and derivatives[59].
Upon being excited to the triplet state, the carbonyl species can break one or both of the α bonds (depending on the species), leading to two possible sets of an acyl radical and a alkyl radical (two species in the red rectangle). The most likely reaction is the recombination of the two radical centers, yielding the initial ketone (however epimerization may occur due to the radical centers being flat and therefore losing any chiral information). Alternatively, an acyl radical or an alkyl radical may abstract a γ hydrogen and form, respectively, a ketene or an alkene. The radical center may be shifted by abstraction of a hydrogen borne at the γ position (scheme 9).



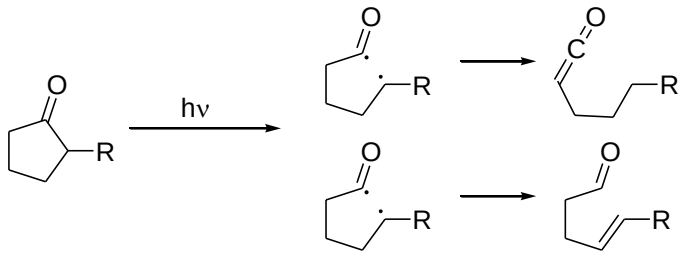
Scheme 9

The acyl radical may extrude carbon monoxide, leading to two alkyl radicals (path a) that may either react with each other, form symmetrical compounds (R_1R_1) or abstract a proton from another molecule.
The acyl radical can abstract a proton from the other radical and yield an aldehyde (pathways b and c). The alkyl biradical can undergo intramolecular transformations; mostly notably leading to alkene should the two radical centers be on vicinal carbons. Similarly, the alkyl radical can abstract a proton from the acyl species (pathways d and e), leading to an alkane (in regard to the previous radical center). The biradical acyl species can also undergo intramolecular reactions, mostly notably the formation of a ketene if the two radical centers be on vicinal carbons.



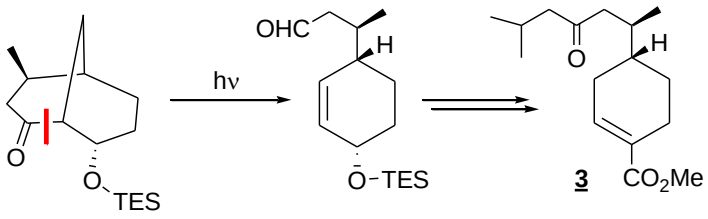
Scheme 10

Radical species react until they have formed non-radical products. Cyclic carbonyl species give particular products by proton abstraction for example here with a cyclopentane ring:



Scheme 11

The Norrish I process of cyclopentanones is central to this research project and will be developed further in this thesis, especially as regards the regioselectivity issues. The reaction is a synthetic transformation and has been applied in various syntheses such as that of (+)-Juvabione **3**.[60]

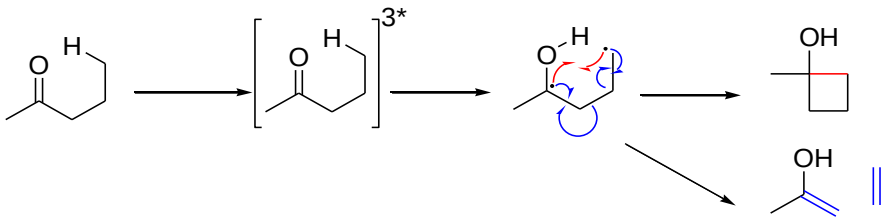


Scheme 12

Other examples of synthetic uses of Norrish I type reactions include the preparation of the Fusicoccane A–B ring fragment.[61] The reaction also appears in the synthesis of (±)-Coriolin allowing in which it facilitates the isomerisation of a key intermediate.[62]

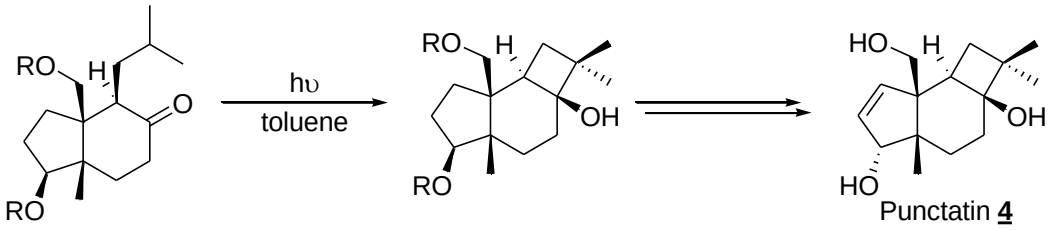
➢ The Norrish II reaction

A carbonyl species that bears a hydrogen atom on the γ position that is spatially accessible (a pseudo-six membered ring transition state is possible) may undergo transfer of the hydrogen to the oxygen atom of the carbonyl. The excitedcarbonyl (reacting in the triplet state) reacts as a biradical. Transfer of the hydrogen to the carbonyl biradical leads to a highly reactive biradical species that can undergo various transformations.[63–65]



Scheme 13

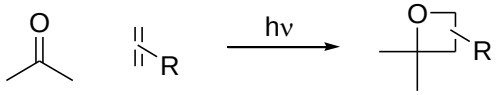
The alcohol biradical species can most notably cyclize to a cyclobutanol (Norrish-Yang) or fragment to a two alkenes, formally a retro-[2+2] of the above cyclobutane. This reaction has also been employed in total synthesis, mostly to prepare cyclobutanols: Punctatin **4**[66,67] is a biologically active molecule prepared by the group of Pr Paquette using a Norrish II step:



Scheme 14

➢ The Paternò–Büchi reaction[17,53,68–70]

Carbonyls, forming biradicals upon irradiation, can react with alkenes by trapping the biradicals to form oxetanes: four membered cyclic ethers. This reaction is the foremost method to prepare this structure.



Scheme 15

Oxetanes are an uncommon motif in organic synthesis and medicinal chemistry.[71–77] Perhaps the most commonly known oxetane ring in a natural product is that of Taxol **5**.[78,79] It is also present in a number of taxane derivatives.[80–86] Oxetanes are also present in inhibitors of HMG CoA synthase[87], Renin[88], HIV[89] and other biomolecules such as ent-trachylobane diterpenoids[90], Docetaxel [91], neoclerodane diterpenoids[92], Oxetanocin derivatives[93], Oxetin[94] and Merrilactone A **6**.[95] Some degradation of DNA by light can be attributed to the formation of oxetane and subsequent transformation.[96]

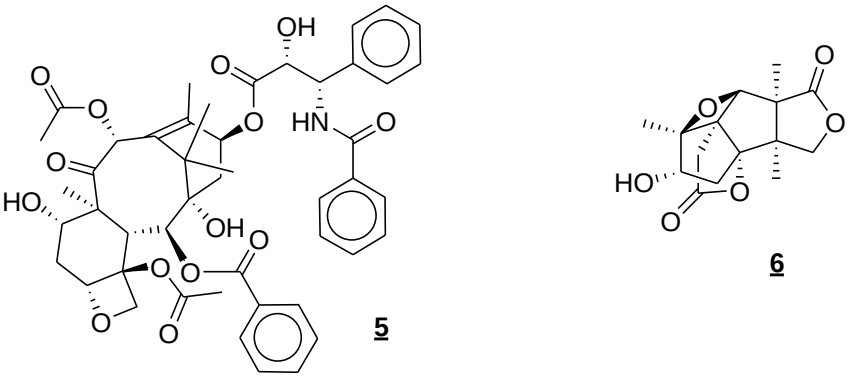


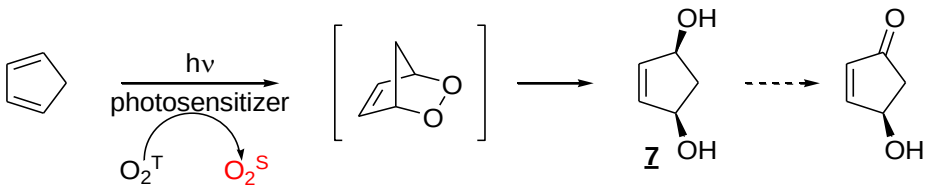
Figure 6

Other described examples of oxetanes include but are not limited to DNA oligomer derivatives[97], polymers[98] and crown ethers[99].

Oxetanes appear as synthetic intermediates in a number of syntheses. They can undergo retro-Paternö–Buchi (formally a metathesis between an alkene and a carbonyl).[100,101] They can be considered as homologues of epoxides in terms of strain and reactivity for various ring opening reactions with nucleophiles.[102,103] They can also react with carbon dioxide in presence of strong Lewis acids to lead to cyclic carbonates.[104] A number of 3-substituted oxetane derivatives such as 3-oxetanone, are useful building blocks in synthesis, often undergoing rearrangements to complex heterocycles.[76,105–112]
This reaction works best with electron rich alkenes. Numerous stereoselectivity issues exist with this reaction, due to steric and electronic factors. [113–118] Several isomers arise from this reaction.

Other photochemical transformations

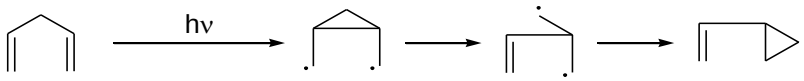
Photooxidation is oxidation of organic compounds induced by light. Oxygen has a triplet ground state which means that is unable to react easily with most species (due to the Pauli exclusion principle). However, the two singlet states (the π electrons have antiparallel spins) are close in terms of energy to the triplet ground state and can be easily be reached by irradiation in presence of the appropriate photosensitizers.[119] The singlet state is able to react with a wide variety of functions: alkenes[120,121], dienes[122], indoles[123] and azides[124,125] for example. The photo-oxidation of cyclopentadiene[122,126] leads to *cis*-cyclopent-2-en-1,4-diol **7** which provides an entry to the rich chemistry of 4-hydroxycyclopentenone. [127]



Scheme 16

The singlet oxygen is promoted by a photosensitizer, Rose Bengal being the most popular one.[128] Total synthesis examples include (+)-artemisinin and (+)-deoxoartemisinin, both molecules include the peroxo bridge.[129]

The di-π-methane rearrangement concerns 1,4 diunsaturated species. Such species that have two double bonds having one common carbon neighbour can undergo photochemical rearrangement to a vinyl cyclopropyl species. [130,131] The reaction is controlled by various electronic and steric factors.[22,130,132]



Scheme 17

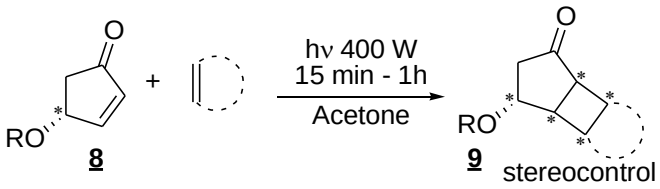
This reaction has been involved in the synthesis of Hirsutene, a triquinane sesquiterpene.[133]

Photoreduction is also a notable photochemical transformation, especially the amine-initiated photoreduction.[134] Amines, acting as electron donor, have been used to reduce various carbonyl species.

Photochemistry is a powerful tool in organic synthesis, transforming even the simplest molecules into highly reactive species that can lead to complex reactions yielding otherwise difficult to prepare structures. However, photochemical transformations are susceptible to over-reactions and competing transformations. This research project aims to explore the vagrancies of irradiated solutions of cyclopentenones and alkenes and this manuscript will describe an exploration of how, past the safe confines of the [2+2] photocycloaddition, new and interesting challenges appear.

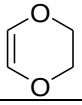
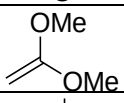
Chapter 1 Presentation of research project

Organic photochemistry is of interest in the host research group in Orsay: one study focuses on [3.2.0] bicycloheptanones: in previous work, Dr Matthieu Le Liepvre studied the synthesis of various 4-hydroxybicyclo[3.2.0]heptan-2-one derivatives **9** via a [2+2] photocycloaddition reaction between 4-hydroxycyclopentenones **8** and alkenes.[126,135,136] A selection of the target compounds were obtained starting from enantiomerically enriched cyclopentenones with moderate diastereoselectivites.



Scheme 18

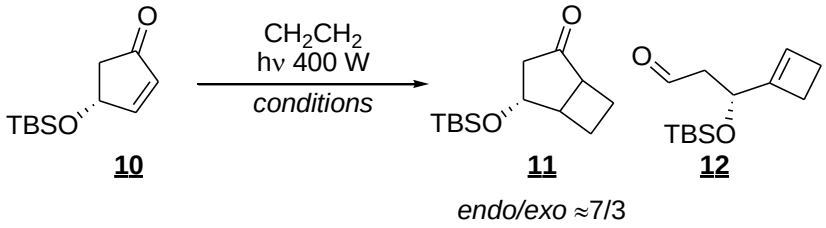
Tableau 1

R =	Alkene	Yield
H		49
Ac		43
Boc		49
MOM		48
TBS		50
		45
		41
		41
		49
		33
		40
		38

The reactions conditions were optimized for the [2+2] photochemical cycloaddition reaction between the 4-OTBS enone **10** and ethylene: acetone proved to be the most convenient solvent. Acetone is very common for this transformation as it behaves both a solvent and a sensitizer.

Various hydroxyl protecting groups were examined. These studies were a stepping stone for the developpement of an intramolecular version of this [2+2] photocycloaddition carried out successfully under similar conditions. [136]

In the course of the optimization of the [2+2] reaction, various solvents were tested. In most cases for short irradiation times, the expected [2+2] adduct **11** was the major product. However, in a few cases, a second product was detected and in one case it could be isolated as the major component in 49 % yield. The compound was identified as cyclobutene aldehyde **12**.

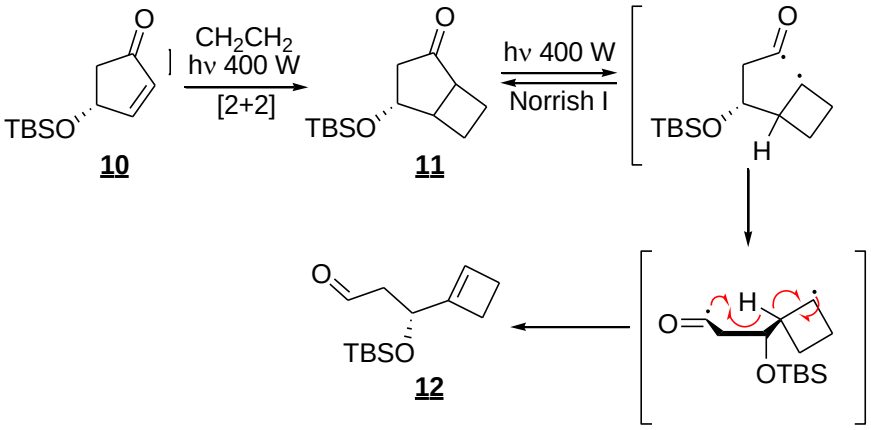


Scheme 19

Table 1

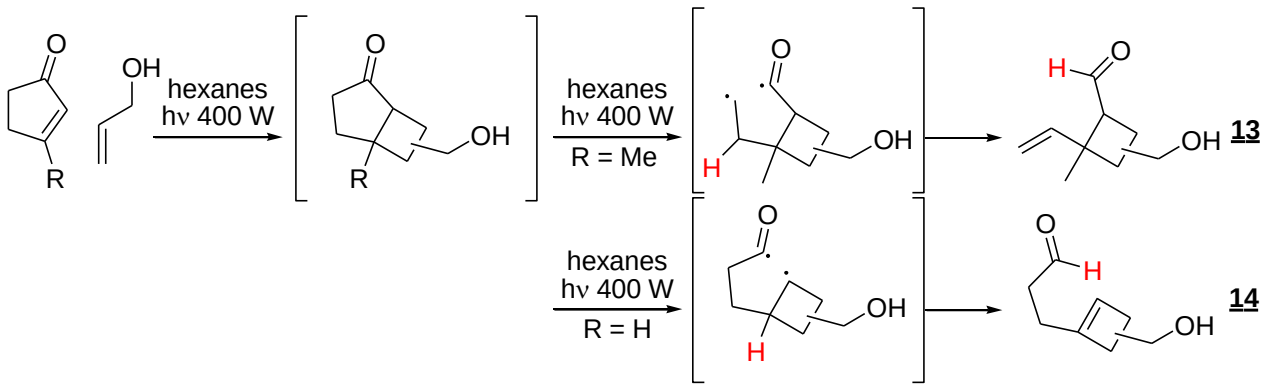
Time (min)	Solvant	Major product
50	CH_2Cl_2	**11** (41 %)
50	Acetonitrile	**11** (46 %)
25	Methanol	**11** (13 %)
270	Toluene	**12** (49 %)

The cyclobutene aldehydes have been known to be formed as side-products to [2+2] photocycloaddition reactions but were seldom investigated, often discarded as the result of parasite reactions. It is obtained by a Norrish I fragmentation of the [2+2] adduct followed by a γ hydrogen transfer.[13,137–139] The sequential [2+2]/Norrish I/γ-hydrogen abstraction reaction hasn't attracted much interest: the few studies concerning it regard it mostly as a unwanted side reaction.[140–149]



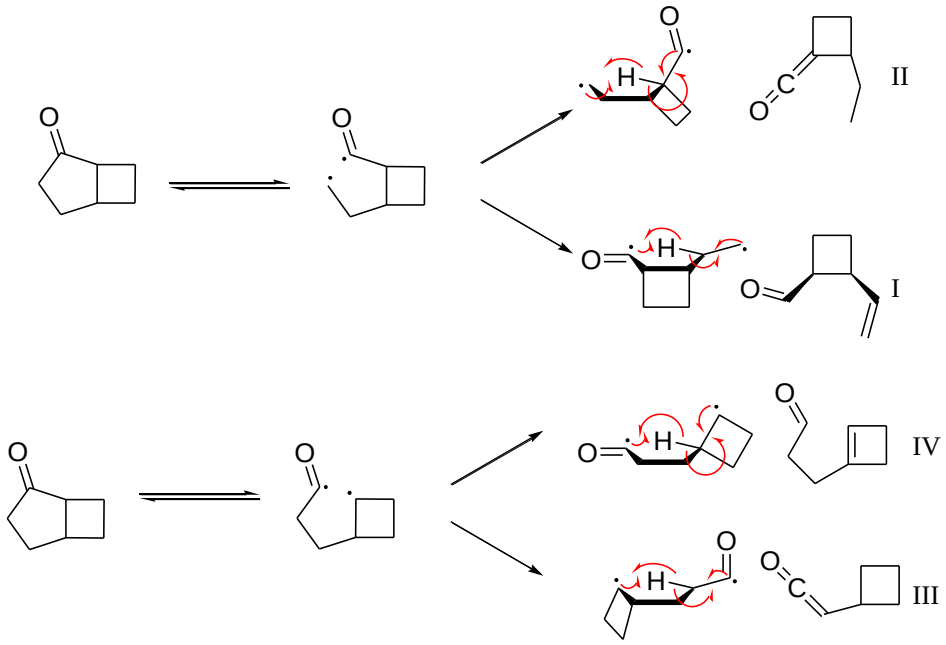
Scheme 20

During the course of this research project, the group of Sydnes published results involving an analogous tandem photochemical reaction between cyclopentenone and allyl alcohol yielding aldehyde **13**.[140] Their results revealed an important point concerning the formation of the cyclobutene aldehyde: a hydrogen must be present in the 3 position with a cyclopentenone. With a substrate bearing a methyl in the 3 position: the reaction was directed via the alternative γ hydrogen reaction pathway, yielding structural isomer **14**.



Two parallel Norrish I fragmentations pathways therefore exist.

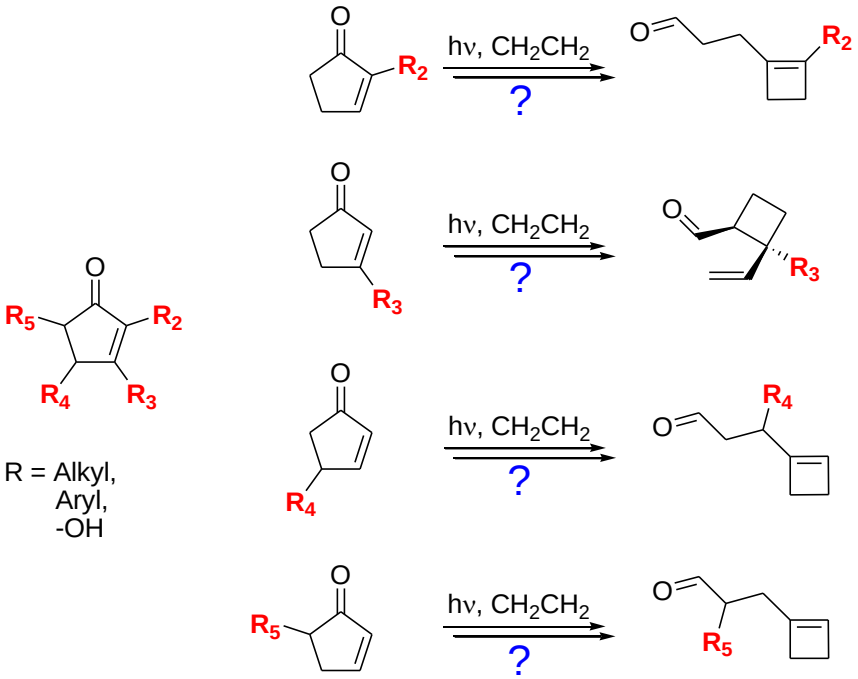
Scheme 21



Scheme 22

Of the above four Norrish I initiated rearrangements, only IV was observed in the previous reaction carried out by Le Liepvre. This is consistent with literature studies of Norrish I fragmentations of 5-membered rings: fragmentation occurs on the cyclobutane side (furnishing the most stable biradical species, I/II < III/IV) and the cyclobutene aldehyde is favored over the ketene (IV > III).[55,138] Depending on the relative stabilities of the biradical intermediate species, the outcome of the reaction can vary. We could suppose that substitution on the 5 position of the cyclopentenone would diminish the difference in stability between the possible biradical species arising from Norrish I fragmentation. Therefore, a shift towards the other fragmentation pattern may be observed. Other factors might shift the relative stabilities of the biradical species such as steric hindrance, which might lead to different reaction outcomes.

Based on these observations, the following reactivity can be expected and will be examined:



Scheme 23

As an interesting parallel, cyclohexenenones are also common reactants in photochemistry[11,24,144] and their syntheses are often similar to those of cyclopentenones reviewed in chapter 2. [150–152] However, Norrish I fragmentation of a cyclohexanone is known to favor the ketene over the aldehyde (III>IV equivalents of the 6 membered ring).[55,138] The expected outcome of the tandem photochemical transformation falls outside of the objectives of this research project (since no cyclobutene aldehydes are formed) and is therefore of no interest to us at this juncture.

The cyclobutene aldehyde core structure represents considerable synthetic potential. The aldehyde and cyclobutene functions are both highly reactive. Additional chemical "handles" can be created by increasing the functionalities of the reactants: substituted cyclopentenones and alkenes.

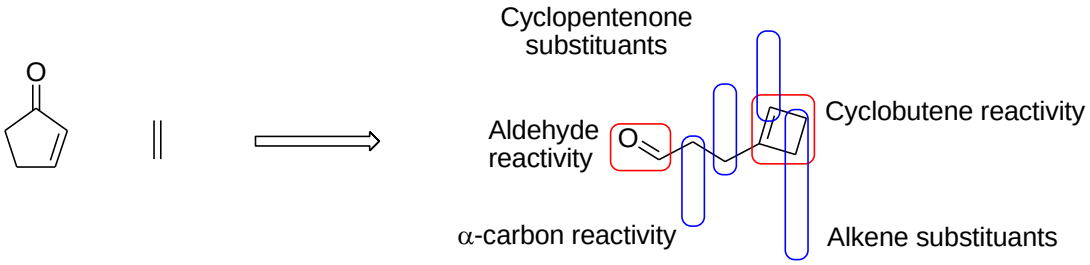


Figure 7

Aldehydes are notoriously reactive compounds and are amenable to a large variety of reactivity patterns including but not limited to:

- Nucleophilic addition: organometallics, carbanions, …[153,154]
- Oxidation to acids, esters.[155]
- Olefination reactions: Wittig and derivatives.[156–160]
- Reduction to alcohols or alkanes.[161]

- Reactivity of the α position: first and foremost the aldol reaction.[162–171]

Cyclobutenes are equally reactive, they are an uncommon building block in synthesis[47,172,173] and quite difficult to prepare.[174–176] They are basically cycloalkenes that have an enchanced reactivity due to high ring strain. Possible transformations include:

-Oxidation of the double bond: epoxidation is often followed by ring opening and rearrangement.[177]

-Oxidative cleavage of the double bond to form diols.[178]

-Metathesis: ring opening, polymerization,.. .[179–182]

It should be noted that specific substitution could lead to interesting functional groups on the target cyclobutene aldehyde:

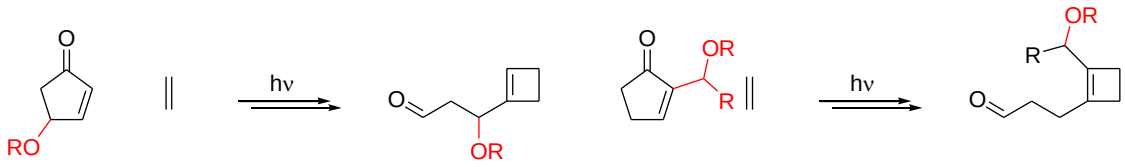
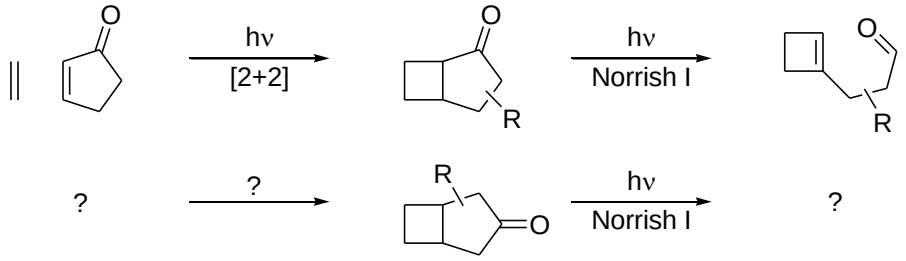


Figure 8

Allylic systems can be obtained by starting from 4-hydroxycyclopentenones derivatives, a common class of building bricks[127], and Baylis-Hillman adducts derived from cyclopentenones.[183–185] Allylic alcohol derivatives are reactive positions for example for the Tsuji-Trost reaction in presence of metal catalysts or SN_2'-type transformations.[186–191]

In tune with the current trend of "green chemistry"[192], this tandem transformation leading to cyclobutene aldehydes, and photochemical transformations in the broader sense,[32,193,194] are interesting and powerful synthetic methods of simple reactants leading to valuable structures: the atom efficiency is total, no other reagents apart from the two partners (alkene and cyclopentenone) and the solvent is necessary. To extend this idea of a "green" method to access highly functionalized molecules, a similarly "green" synthesis of substituted cyclopentenones is a logical extension. Cyclopentenones are known substrates for the Baylis-Hillman transformations and they naturally fit into the family of organocatalyzed reactions. Additionally, aldolisation of cyclopentenones has been described in similar organocatalyzed conditions.[195]

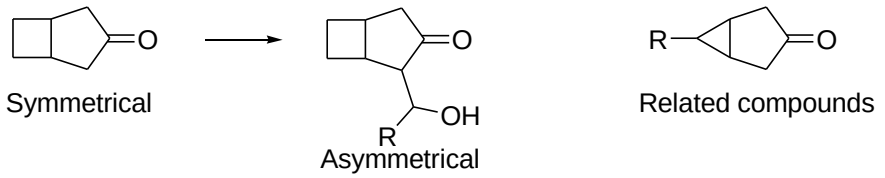
Furthermore, this tandem reaction rests on the intermediate bicyclo[3.2.0]heptan-2-one. The isomeric bicyclo[3.2.0]heptan-3-ones are also compounds of interest.[196,197] The photochemical behavior of these compounds has never been studied but represents an interesting challenge to pursue alongside our main objective.



Scheme 24

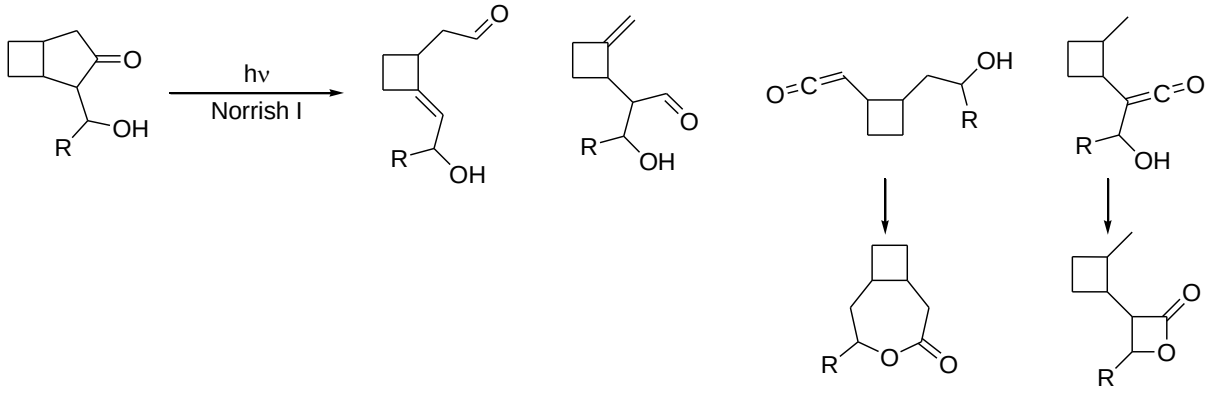
Substituted bicyclo[3.2.0]heptan-2-ones can also be prepared by organocatalyzed reactions of unsymmetrical bicyclo[3.2.0]heptan-2-one. Indeed, cyclopentenones are a very common substrates for organocatalyzed aldolisation.

The host group in Sardinia maintains several research programs including the synthesis of highly functionalized carbocycles.[198–207] Ongoing projects that are relevant to this project include organocatalyzed functionalization of small carbocycles[199,201] and acid catalyzed ring expansions.[205,207]



Scheme 25

Based on the ongoing research on related bicyclic compounds and their use as aldolisation donors, the heptanone seems an interesting candidate for organocatalyzed reactions. These substituted heptanones are not substrates for [2+2] photocycloaddition, since there is no enone. However Norrish-I fragmentation of these bicyclic structures is, in theory, possible and could lead to interesting rearrangements: cyclobutylidene aldehydes with an allylic alcohol branch (if this compound would fragment in a similar fashion to [2+2] photoadduct of cyclopentenones and alkenes) or more complicated rearrangements (opening of the cyclobutane, displacement of the hydroxyl group).



Scheme 26

If Aldol XX were to undergo Norrish I in a similar fashion to the [2+2] bicyclic adducts, the expected products would be two isomeric cyclobutylidene aldehydes and two isomeric ketenes that are likely to undergo intramolecular addition of the alcohol, forming lactones.

Thus we conceived a “green” synthesis of highly functionalized cyclobutene aldehydes by combining the two methodologies giving us our initial project: SPOC (Synthesis by Photochemistry and Organo Catalysis). We would aim to investigate the tandem photochemical transformation of cyclopentenones to cyclobutene aldehydes and prepare said cyclopentenones by organocatalytic methods.

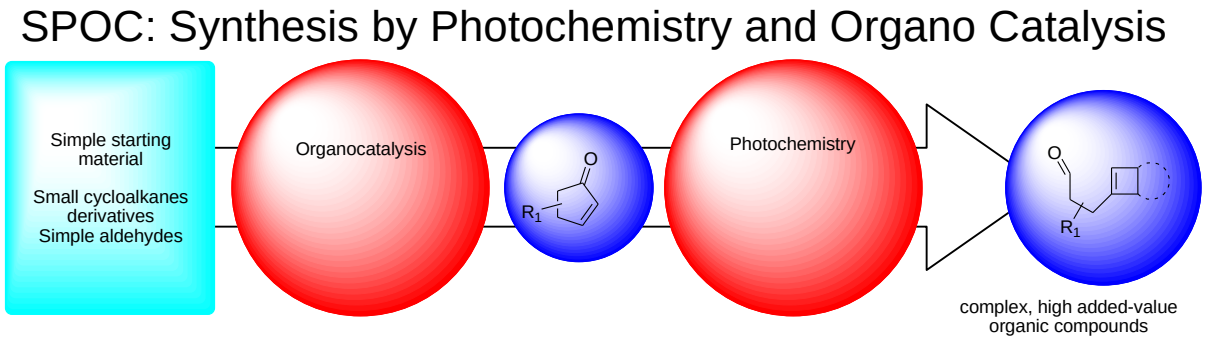


Figure 9

This was the premise of this research project at the outset: the exploration of the synthetic potential of the tandem photochemical transformation and its development as a viable tool for the organic chemist.

The research project was therefore conceived as follows:

- The synthesis of cyclopentenones for the photochemical transformations must be simple and compatible with the overall objective of developing “sustainable chemistry” of which photochemistry is a part of. Consequently, the developpement of clean, organocatalytic methods is much preferable to metal based strategies that generate large amounts of waste material and employ costly reagents.

- While the [2+2] reaction is an extensively studied transformation and the Norrish I reaction a well established reaction in the organic chemist’s toolbox, the tandem reaction is mostly a to-be-avoided side reaction. Conditions that favor the tandem reaction must be identified and the the scope and limitations of this transformation are to be identified.

- The tandem reaction, once mastered, will be applied to the preparation of highly functionalized synthons for total synthesis.

Chapter 2 Preparation of cyclopentenones

Cyclopentenones are a common class of cyclic enones. They feature in many areas in organic chemistry and unsubstituted cyclopentenone serves as benchmark substrate for many reactions such as conjugate addition, Baylis-Hillman or Diels-Alder reactions. In the rest of this manuscript, cyclopentenone will always refer to the conjugated cyclopent-2-enone, not the unconjugated one.



Figure 10 Cyclopent-2-enone and cyclopent-3-enone

This chapter will briefly review the reactivity and the synthesis of cyclopentenones, and will continue with details of the preparation of the cyclopentenones that used in the course of this project.

Reactivity of cyclopentenones

Cyclopentenones are readily available reagents for chemical synthesis, starting with basic cyclopentenone that is a cheap, commercially available compound. The core structure is highly reactive, with methods existing to modify every position.

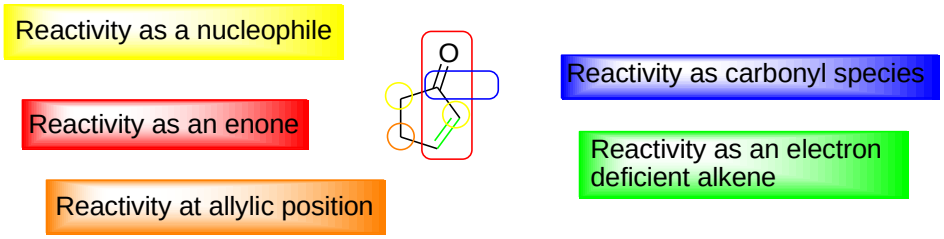
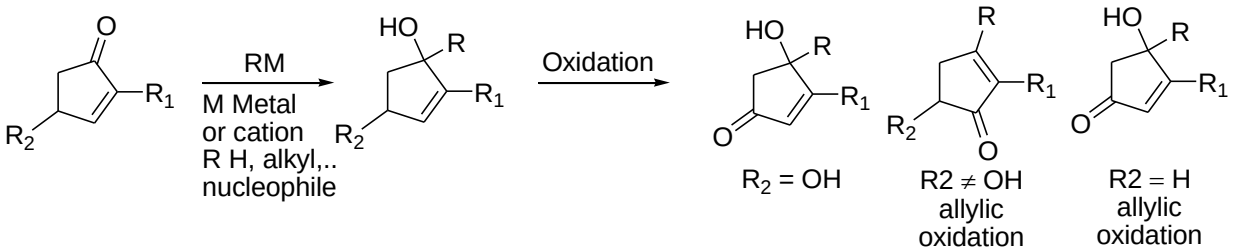


Figure 11

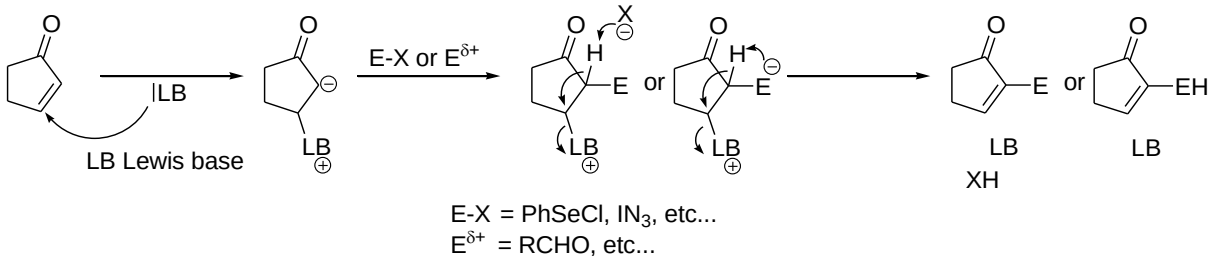
The 1 position (the carbonyl carbon) can react as any carbonyl function.[153,154,208–211] This chemistry is too far reaching to go into details, but the main point to make is that it is an electrophilic position that can react with a wide variety of inorganic, organic and organometallic species.

Of particular pertinence in this research project is the synthesis of cyclopentenones for use as substrates for photochemical transformations. Enones are required in the tandem transformation and therefore the enone function should be preserved in this application. The products of addition to the carbonyl, allylic alcohols, are of interest (in this regard, they are otherwise always interesting) only if they can lead to enones. Allylic oxidation is the oxidation of the allylic position of a simple alkene[212–214] (R_2 = H) or the 1,3 transfer of oxygen of allylic alcohols ($R_2 \neq$ OH).[215,216] Allylic oxidation can furnish enones.



Scheme 27

The 2-position can be reacted in multiple ways. The most common way is the addition of a weak nucleophile (Lewis base) to the 3-position (Michael addition) thus creating an enolate (or oxa-π-allyl) nucleophile which can react with a broad variety of electrophiles[217]: aldehydes and ketones (Baylis-Hillman)[185,218–221], imines (aza-Baylis-Hillman)[222], triarylbismuth(V) dichlorides (leading to 2-aryl enones)[223], iodine azide (leading to 2-iodo compounds)[224], phenylselenium chloride [225],etc… To the author's best knowledge, no examples of direct alkylation of the double bond in the 2-position have been described with Heck type reactions.



Scheme 28

2-Halocyclopentenones can be prepared by a bromination-elimination sequence[226] and then coupled to various organometallic species for further reactions.[227–230] Alternatively, 2-boronic cyclopentenone acids can be prepared for the cross-coupling coupling by protection-borylation-deprotection sequences of the appropriate 2-bromocyclopentenones. [231] In this case, the cyclopentenone is the boron partner in the Suzuki transformation.

The 3-position can easily be functionalized with the conjugate addition of various nucleophiles: organometallics[232–236], sulfur compounds[237], silyloxy compounds[238], inorganic nucleophiles, alcohols in an intramolecular fashion[136]…The reaction can be catalyzed by metal complexes[239–246], organocatalysts[247], etc… The photochemical alkylation of the 3-position has also been described.[248] This field of organic chemistry is wide and in constant expansion and is beyond the scope of this research project. As previously mentioned, cyclopentenones are common acceptors for this kind of reactivity.
Heck reactions can also be carried on this position.[249]

The 4 position can be functionalized by radical reactions such as bromination with N-bromosuccinimide (NBS), promoted by AIBN.[250] This opens the way to further functionalization on this position.

Finally, the 5 position can react as a typical α carbon to a carbonyl function. Aldolisation of cyclopentenones has been described in a limited number of examples. [251–255] One example of an organocatalyzed aldolisation has been described.[195]

The enone has a whole can react as a typical enone for photochemical reaction (see introduction) and numerous cycloaddition reactions have been described such as the Diels-Alder reaction[256–260], cyclopropanation[160,261–263], aziridination[264,265], epoxidation[265–268], …

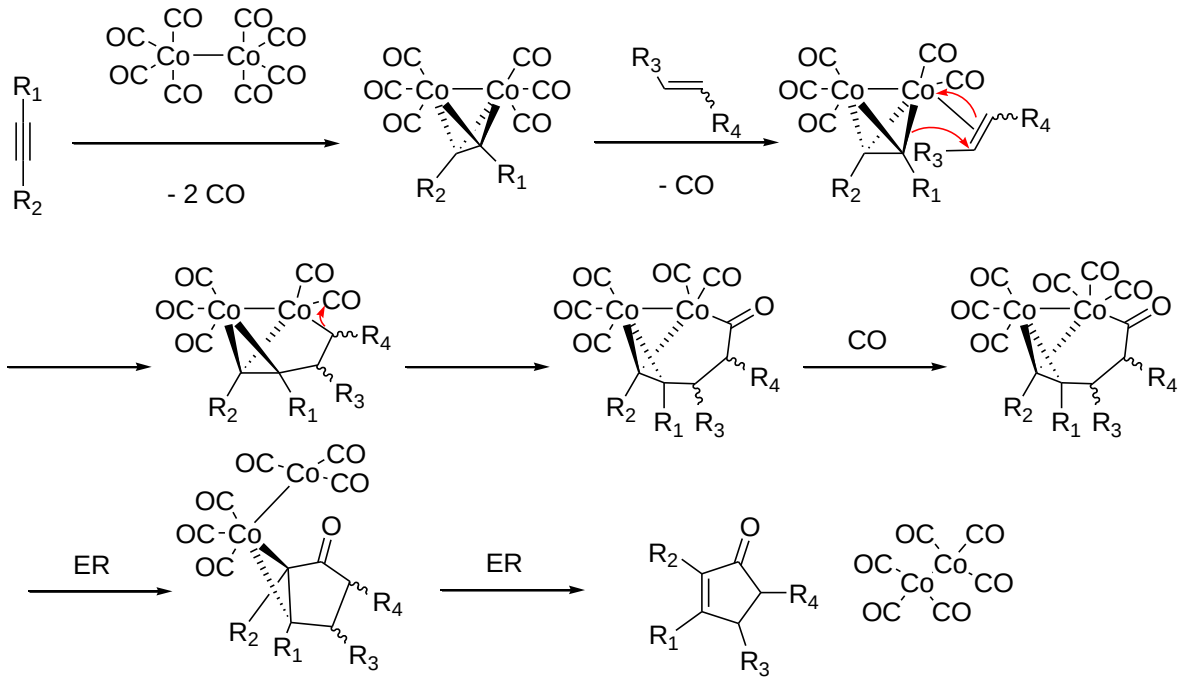
Methods for the synthesis of cyclopentenones

Due to the interest of cyclopentenones as reagents in total synthesis, many methods have been established for the preparation of these compounds. [127,269,270] Typical targets in synthesis where cyclopentenones are involved include prostaglandins[271–274] and jasmonates[275]. Cyclopentenones also have a interest as pharmacophores themselves.[276] These transformations can be classified in the following categories.

Total ring construction

Cyclopentenones can be prepared from two or three partners by forming two or three new σ bonds between them in a sequential, domino fashion. This is usually considered the most efficient method to construct these rings, as it usually is a one-pot transformation and is atom efficient. Due to entropic concerns (three component reactions are slow), metal catalysts are necessary.

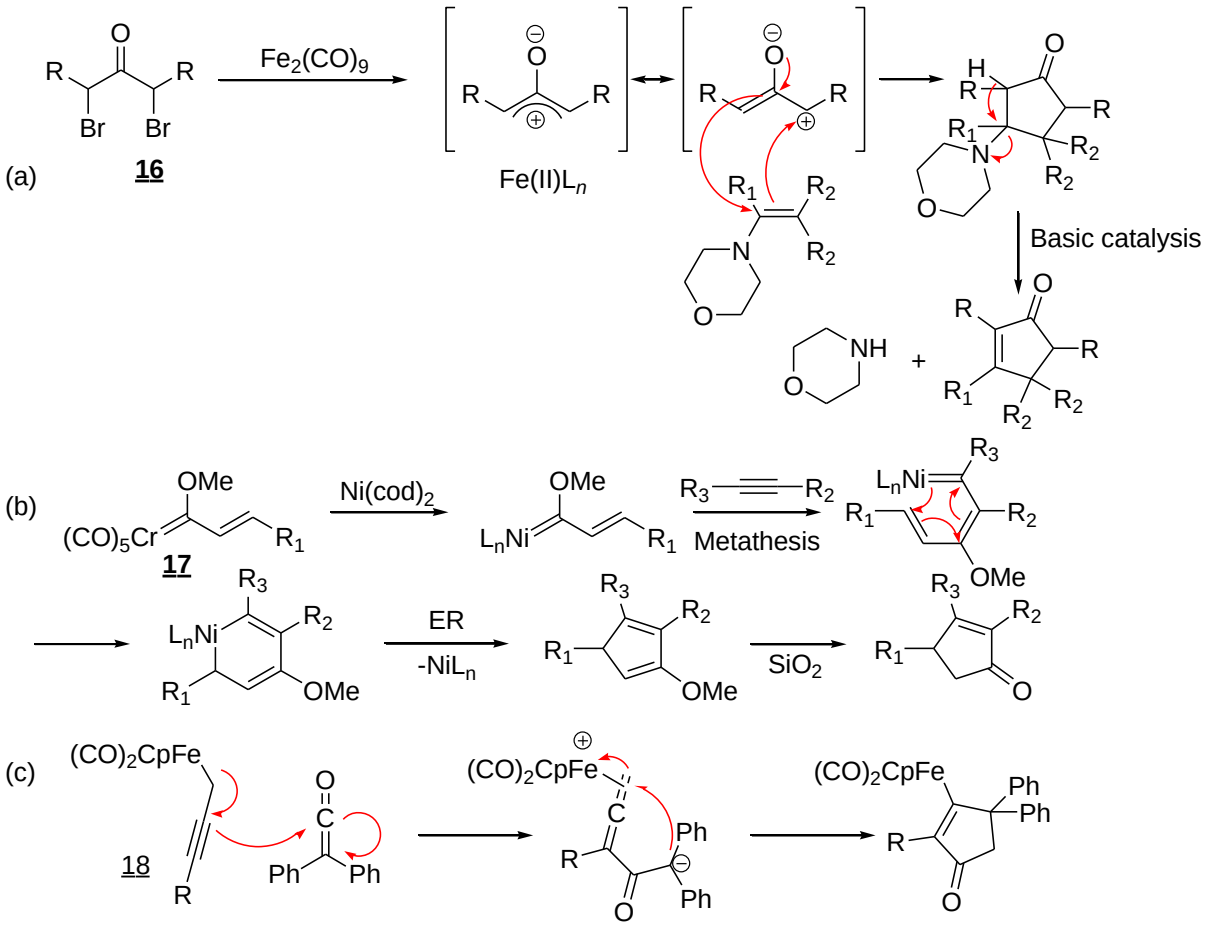
The prime example of this type of transformations is the Pauson-Khand reaction (PKR). Pauson and Khand described the cobalt-mediated synthesis of polycyclic cyclopentenones from norbornene derivatives, acetylene complexes of dicobalt octacarbonyl and carbon monoxide.[277] Since this method was first reported, it has been extended to a wide variety of substrates. [278–284]The common mechanism for this transformation involves formation of the triple bond – dicobalt complex. Insertion of the alkene into the C-Co bond occurs on the least hindered side (R1<R2) of the dicobalt complex. A CO inserts itself in the newly formed C-Co bond. Eliminative reduction of the dicobalt species generates the new cyclopentenone.



Scheme 29

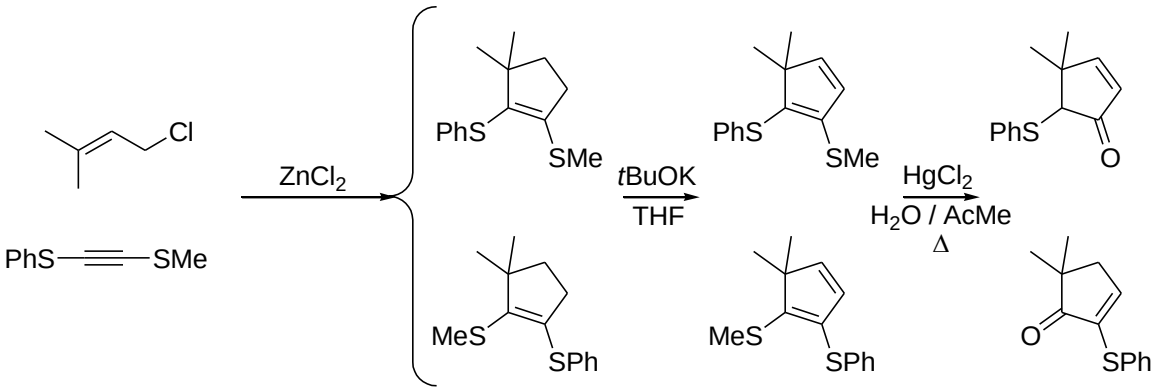
Various improvements to the PKR have been made: rhodium and iridium can be used as catalysts (the mechanism is the same), metallocenes are also available as catalysts (the zirconium for example forms a zirconacycle with the alkene and the alkyne),[285,286] aldehydes can be used as CO sources.[287,288] A variation of the zirconium-catalyzed PKR exists where the carbonyl source is an isocyanate.[289] The PKR can lead to 4 regioisomers (R1/R2 and R3/R4 can swap). The regioselectivity for the insertion of the alkene is dependent on steric factors (usually R2 is larger than R1), complex effects (steric, solvent, temperature) control the relative positions of R3/R4 however in the intermolecular reaction the regioselectivity is still not completely understood or controlled.[290] This reaction was been used successfully in the total synthesis of Epoxydictymene.[291]
A related transformation involves replacing the alkyne by a π–allylic precursor. The metallo π–allyl species adds to the alkene, a CO ligand is inserted and a cyclopentenone is generated after eliminative reduction. This was described with ruthenium [292], nickel [293,294] and palladium[295] .

[3+2] Cyclization allows for generation of a cyclopentenone by reacting an unsaturated species with a zwitterionic species. Examples of this include the reaction of α,α'-dibromoketones **16** (precursors of enolic cations) with enamines[296] (scheme 23 a), chromium alkenylcarbene complexes **17** adding to internal alkynes[297] (scheme 23 b) or vinyl lithium species reacting to chromium alkynylcarbenes[298] and 2-alkynyl iron complexes **18** reacting with ketenes[299](scheme 23 c).



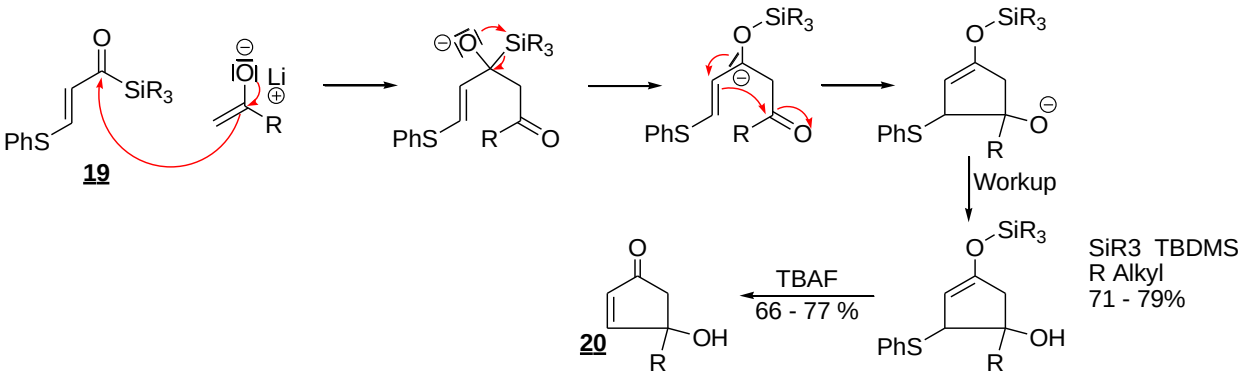
Scheme 30

Zinc chloride promotes a similar reaction between allyl chlorides and thiomethylthiophenylethyne resulting in cyclopentylthioethers. They can be transformed into cyclopentenones in two steps.



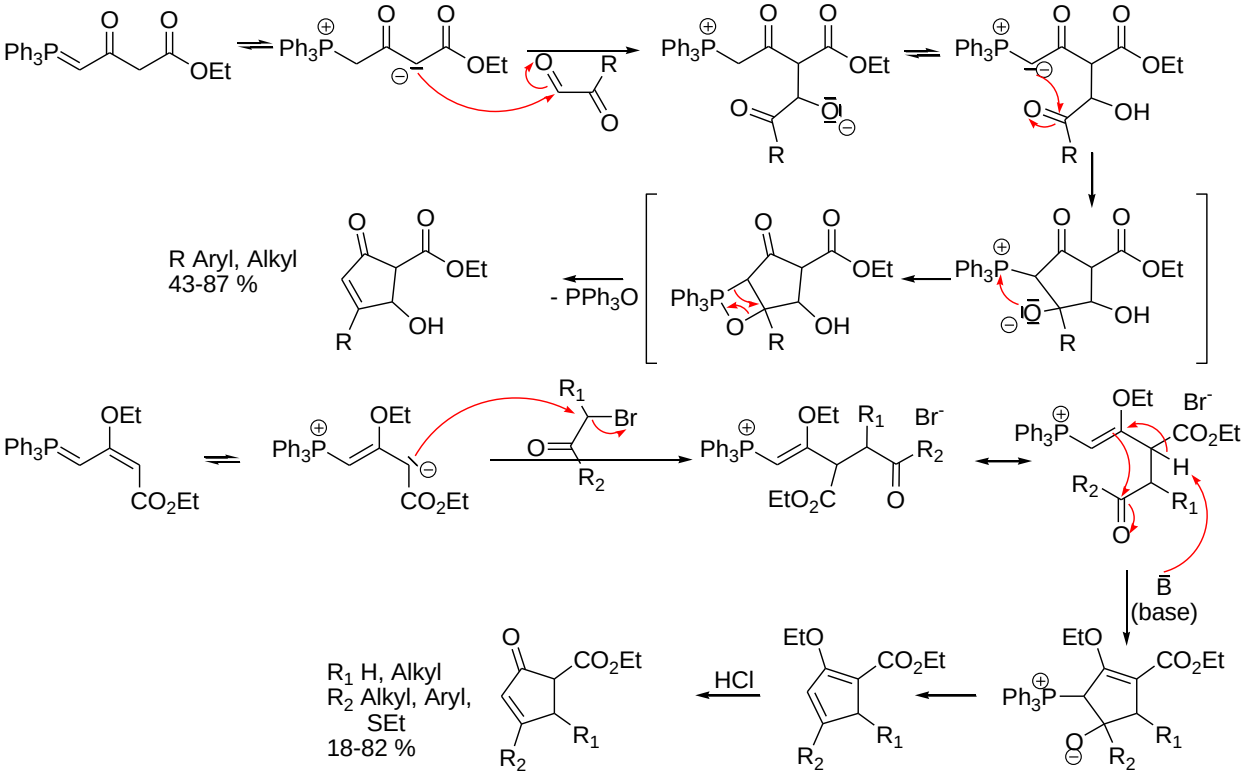
Scheme 31

Another type of non-metal catalyzed [3+2] is the condensation of lithium enolate to acryolyltrimethylsilanes **19**. A Brook rearrangement of the resulting *gem*-silyl enolate leads to an allyl carbanion that rearranges to a cyclopentane derivative. Appropriate substitution of the starting sila-enone allows for a tandem desilylation and β-elimination, yielding the 4-alkyl-4-hydroxy cyclopentenone **20**. [300]



Scheme 32

Tandem Condensation-Wittig reactions between Wittig reagents and ketones represent another [3+2] type cyclization leading to cyclopentenones in an efficient manner. Hatanaka's group has developed several methodologies around those basic ideas.[301–303]

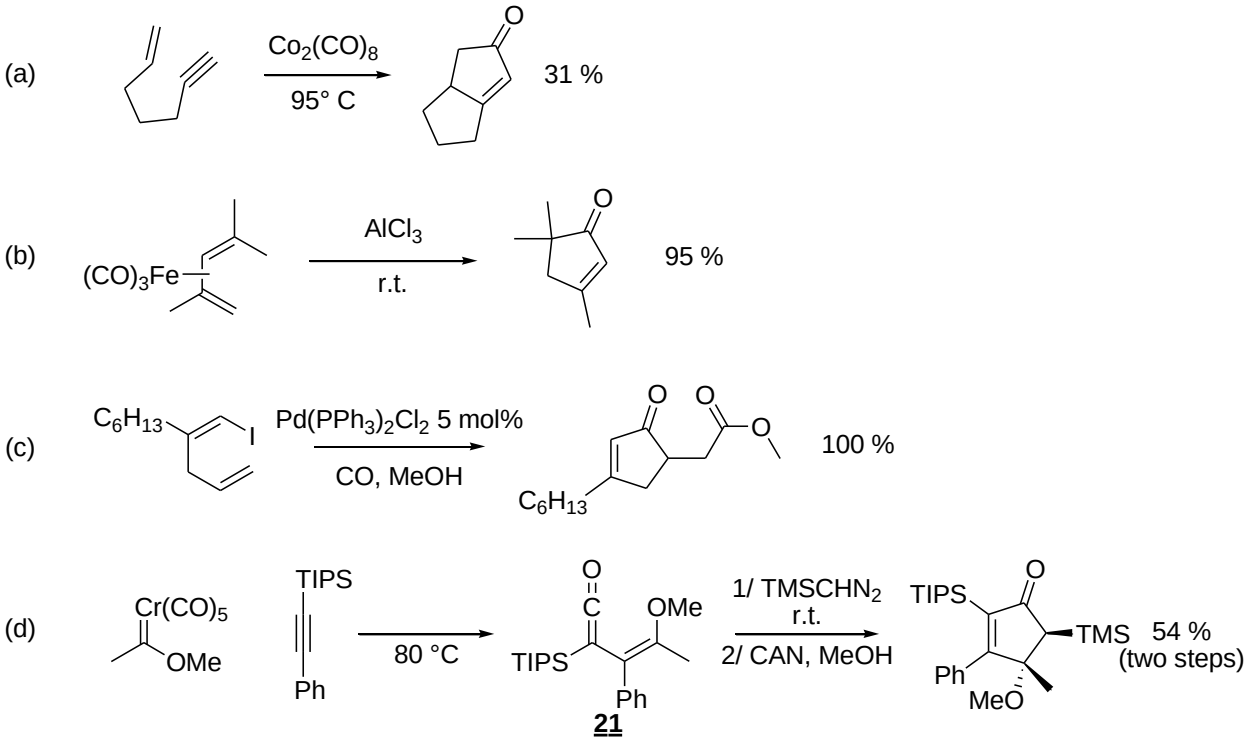


Scheme 33

Various related methods exist for the synthesis of cyclopentane or cyclopentene derivatives.[285,301–308]

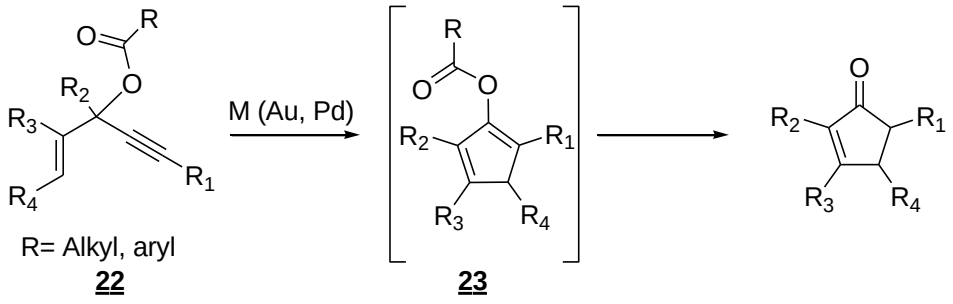
Another related transformation is the [4+1] cyclization. They can be Pauson-Khand transformations (this can be called, though it merits discussion, a intramolecular reaction) where the alkene and alkyne are joint (an enyne)[309], carbonylative cyclization of 1,3 butadiene derivatives in presence of diiron nonacarbonyl and aluminium halides[310,311] or the carbonylative cyclization of dienyl halides (or

triflates) by a palladium catalyst under an atmospheric pressure of carbon monoxide[312,313]. In these transformations, the one carbon partner is carbon monoxide. However, [4+1] transformations have also been described with silyl vinylketenes **21** reacting with derivatives of diazomethane. The silyl vinylketenes are generated from Fischer carbene complexes reacting with silyl substituted acetylenes.



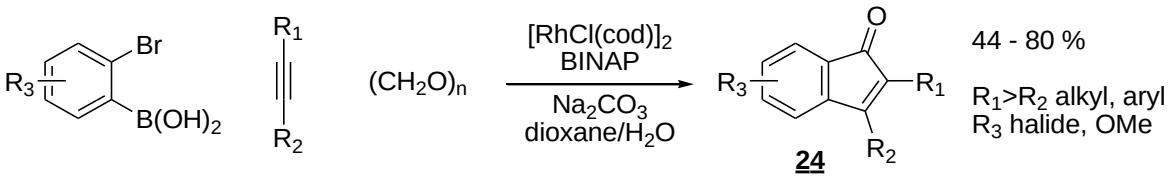
Scheme 34

Another type of [4+1] cyclization is the Rautenstrauch rearrangement,[314] through which 3-acyloxy-1,4 enynes **22** can be transformed into cyclopentadienol esters **23**. Palladium catalysts[314] (proceeding through a palladium carbene mechanism) and gold catalysts[315] (proceeding through cationic gold (I) species) have been described for this transformation.



Scheme 35

Indenones **24**, cyclopentenones concatenated with a benzene ring can be constructed in a domino sequence involving a 2-bromophenylboronic acid, a substituted acetylene, formaldehyde (as a CO source) and a rhodium(I) catalyst. [316] The method is effective for a small range of common substituents. The method can be extend to various indane derivatives.[317]



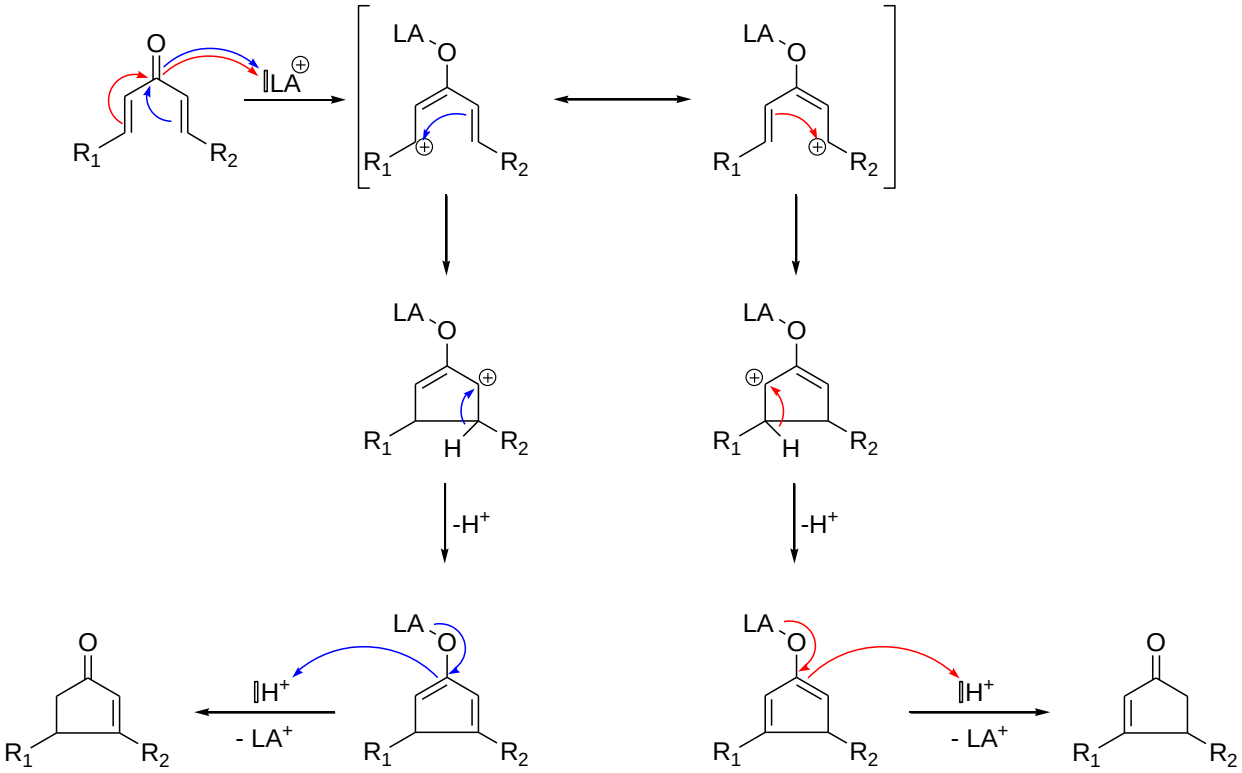
Scheme 36

Organocatalysis is also an interesting tool for the preparation of cyclopentenones. Jørgensen described the dual organocatalyzed and carbene catalyzed the two step addition of β-keto phenyltetrazolesulfones to α,β-unsaturated aldehydes.[318]

Cyclization

In this manuscript, cyclization refers to the formation of a new cyclic structure from an acyclic molecule, or fraction thereof, by the formation of one new σ bond. It differs from the previous one where more than one such bond is formed. This definition includes cases where a σ bond is created and subsequently, a new π bond is generated (often parallel to the newly created σ bond).

The first and foremost method is the Nazarov cyclization,[319] a pericyclic rearrangement reaction where a divinyl ketone is transformed into a cyclopentenone. It's importance in the toolbox of the modern synthetic chemist has been documented in several reviews.[320–327]



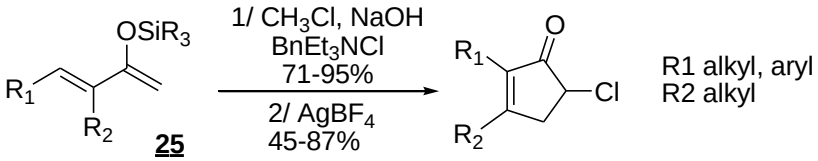
Scheme 37

The reaction proceeds by activation by a Lewis acid of the ketone. The cationic species then rearranges into a cyclopentadienolate, yielding the cyclopentenones after protonation and tautomerisation to the enone. [328,329] The reaction is stereoselective: the formation of a particular cyclopentenone is dependent on the steric and electronic properties of the reacting dienone.[320,330] The following points have been established:

- α substitution improves reactivity of the dienone (due to the Thorpe–Ingold effect)
- the more substituted the final double-bond is, the more favored its formation is.
- polarization of the double bonds (donating/withdrawing substituents) influence the outcome of the reaction by stabilizing the carbocation intermediates.[331]
- regioselectivity can be controlled with various removable substituents : silicon groups[332,333], tin[334], fluorine[335].
- Various metal complexes can catalyze this reaction: Palladium[336], Iridium[337], Copper[338], Scandium[339],… have been described. The advantage of metal catalysts is that tandem transformation can be carried, such as iridium catalyzed Nazarov/Michael sequences.[340]
- Organocatalysts are also available as potential catalysts.[341]
- Enantioselective Nazarov are possible by using chiral metal complexes, chiral organocatalysts, chiral auxiliaries.[342]

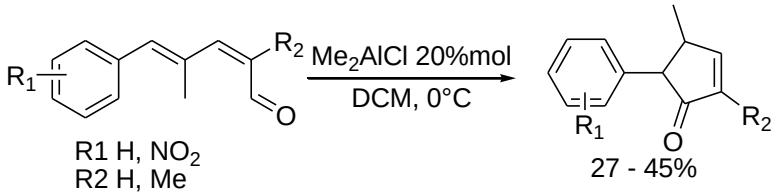
One of the problems of the Nazarov transformation is the reactant, the vinyl ketone, being a highly reactive species. Matsuo *et al.* have described the synthesis of a divinyl ketone by double elimination of a β-hydroxy,β'-chloro ketone obtained from the ring opening of a cyclobutanone.[343]

While the Nazarov reaction starts from divinyl ketones and proceeds through diene cation intermediates, Nazarov-type pentadienyl systems can also be generated from dichlorocyclopropanol silyl ethers, themselves deriving from butadienol silyl ethers **25** undergoing cyclopropanation. [344] The dichlorocyclopropanol silyl ethers can be isolated as such or reacted further in a one pot procedure where they react as divinyl ketone equivalents. Various substituents can be accommodated with good yields.



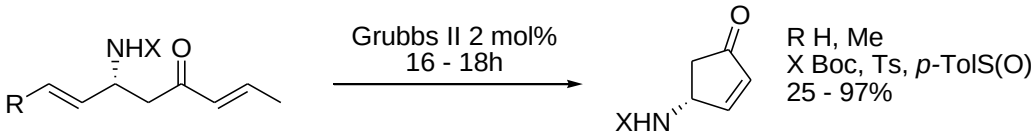
Scheme 38

2,4-dienals can be activated by Lewis acids such as dimethyl aluminum chloride to cyclize to cyclopentenones.[345]



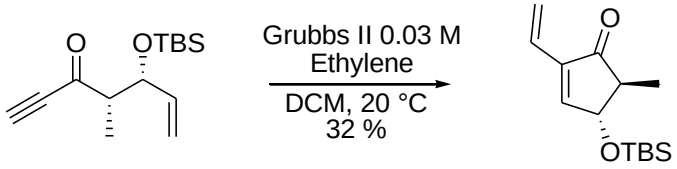
Scheme 39

Ring Closing Metathesis (RCM) is a common tool for the cyclization of macromolecules.[181] Cyclopentenones can be prepared from hept-1,6-dien-3-one core structures (two extra carbons that are eliminated). The 5 membered enone is difficult to prepare this way, but there are examples such as the preparation of these enantiomericaly pure 4-aminocyclopentenones derivatives.[346,347]



Scheme 40

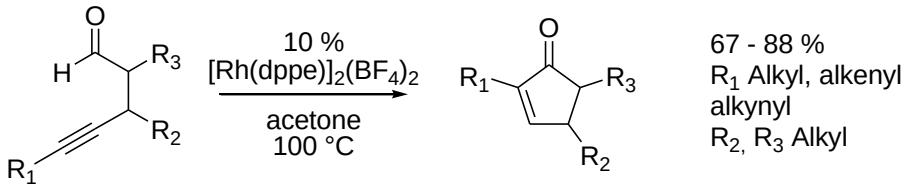
Hept-6-en-1-yn-3-ones can also be cyclized into vinyl-substituted cyclopentenones. [347] This is refered to as "ring closing enyne metathesis".[348]



Scheme 41

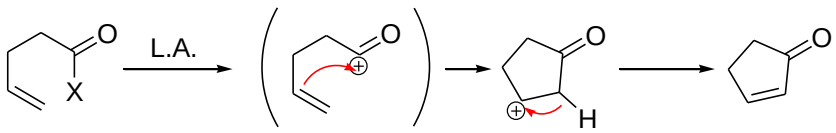
Cyclopentenols and cyclopentenes can also be prepared by RCM and oxidized to the desired cyclopentenones. [349–352]

Pent-4-ynals can be efficiently converted to cyclopentenones.[353] This isomerization is catalyzed by rhodium complexes. The method is compatible with several types of substrates (alkyl, alkenyl, etc…).[354]



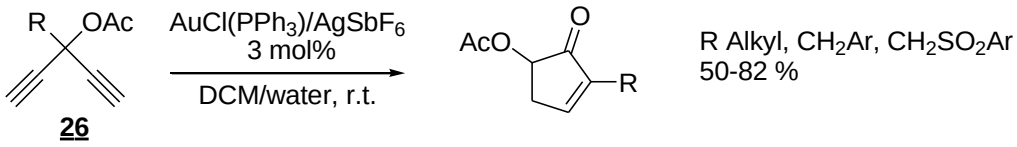
Scheme 42

Similar to this, α-allyl electrophilic carbonyl species (aldehydes and acyl chlorides) can cyclize to cyclopentenones in presence of Lewis acids to activate them.[355]



Scheme 43

The cyclization of 1,1-diethynyl- carbinol acetates **26** into cyclopentenones can be achieved with Gold(I) catalyst. The diethynyl acetates undergo Gold-mediated displacement of the acetate to yield allenyne acetate (the product obtained for short reaction times) which then react further with the Gold catalyst and yields the except cyclopentenone in good yields.[356]

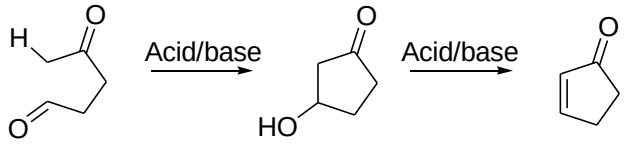


26

Scheme 44

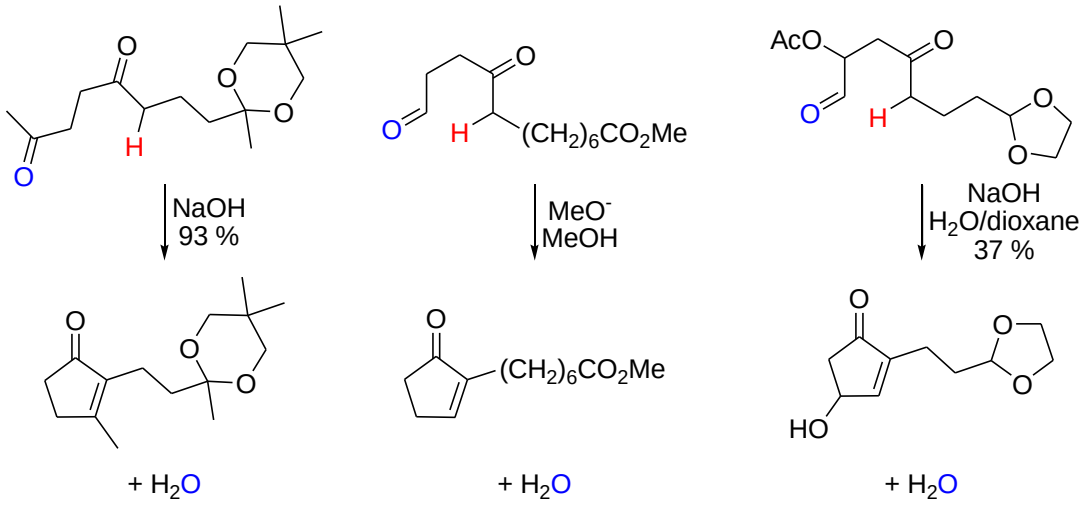
A related transformation catalyzed by Gold(I) complexes, with a similar displacement of a acyloxy group on a 4-en-1-yne framework has also been described as leading to cyclopentenones.[357]

Various syntheses of cyclopentenones involve the intramolecular aldolisation of a 4-oxopentanal moiety into a 3-hydroxycyclopentanone. β-elimination (crotonisation) leads to the cyclopentenone. 1,4 Ketones are common precursors to cyclopentenones.[270]



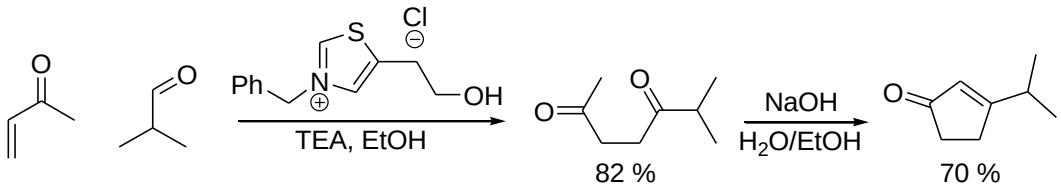
Scheme 45

Intramolecular aldolisation has been described by numerous research groups. Some examples are mentioned here:[358–361]



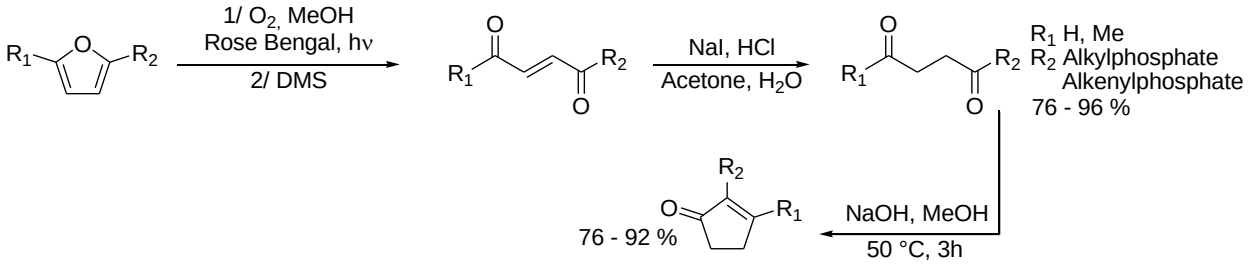
Scheme 46

The synthesis of these dicarbonyl species can be carried for example by condensation of aldehydes on acroleins.



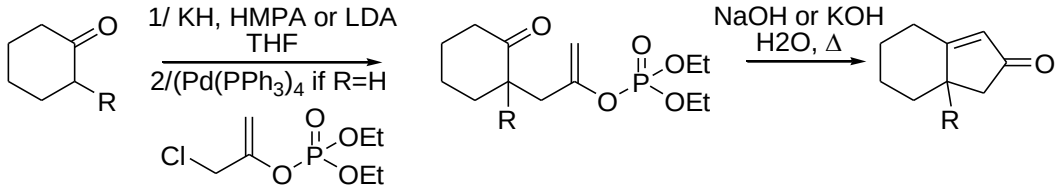
Scheme 47

Another method to generate these dicarbonyl species is the photochemical oxidation of furans followed by a selective reduction of the C=C double bond.[362] The condensation is again promoted by sodium hydroxide.



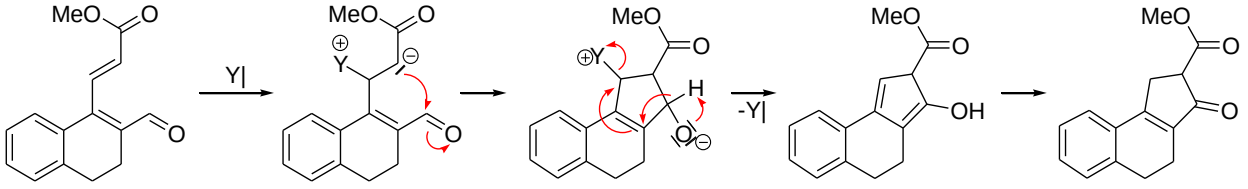
Scheme 48

Procedures not very different from the Robinson annulation between cyclohexanones and acetone enolate derivatives have been described.[363]



Scheme 49

A "tandem Michael-aldol" reaction has been described as a route to fused cyclopentenones. [364] The reaction is in essence an intramolecular Baylis-Hillman reaction: a nucleophile (thiols or phosphines have been described) add to the unsaturated ester chain of the bicyclic system. Condensation of the carbanion on the aldehyde, followed by elimination of the nucleophile and prototropy gives the polycyclic cyclopentenone.

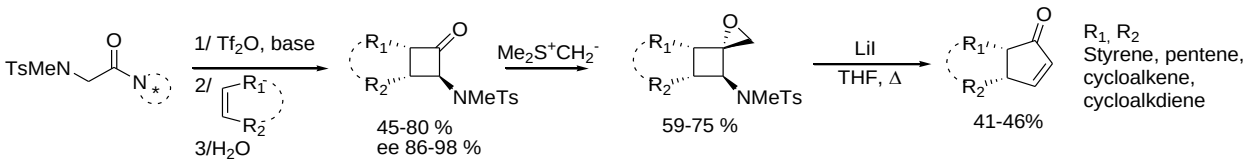


Scheme 50

Rearrangements of small carbocycles

Cyclopropanes and cyclobutanes have higher ring strain that cyclopentanes[365], thus rearrangements from the former to the latter are energetically favored.

α-(N-methyl-N-tosyl)-amino-cyclobutanones, prepared from α-aminoamides and alkenes, can be reacted with methylene carbenes to yield methylenecyclobutane epoxides derivatives. These compounds can be rearranged in presence of lithium iodide to cyclopentenones.[366]



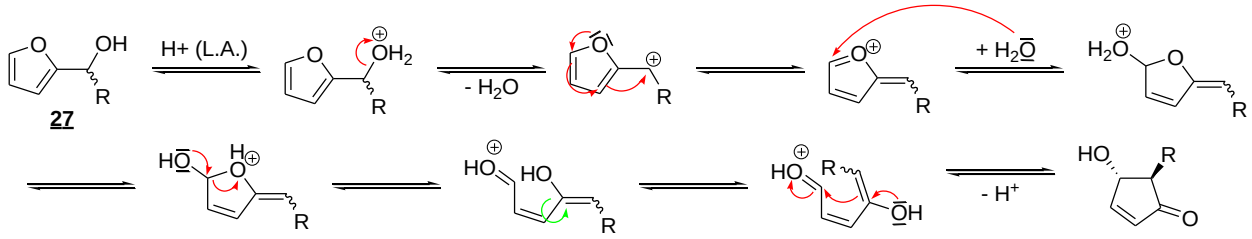
Scheme 51

Lithium iodide has been described for ring expasion of many spiroepoxides.[367–371]

Rearrangements and transformations of larger sized rings.

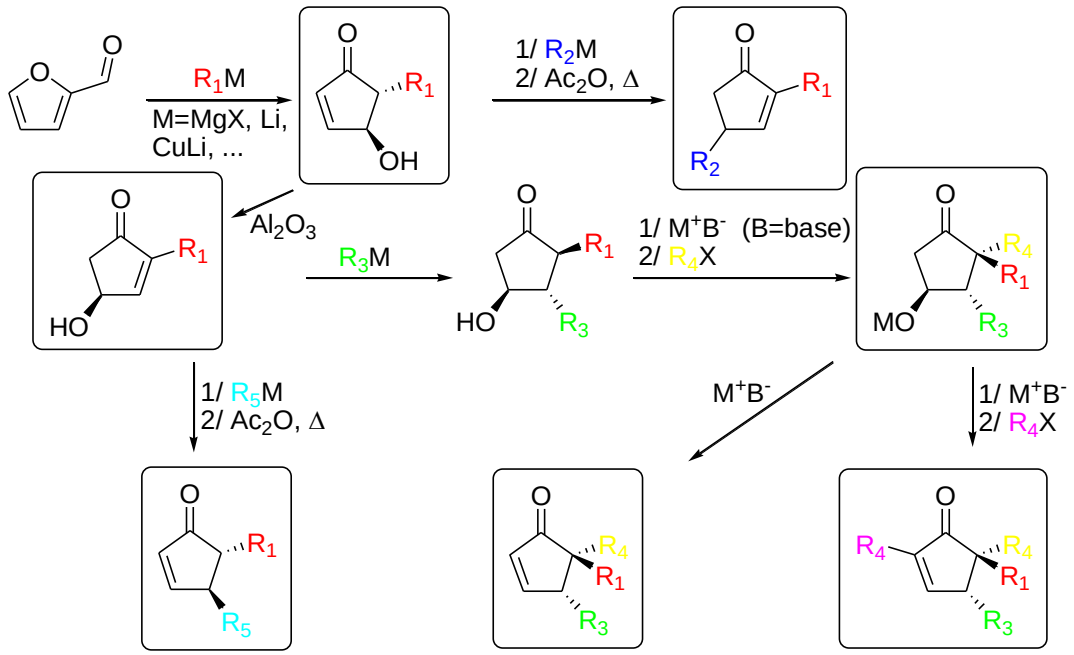
This section refers to all forms of transformations of cyclopentane derivatives and any larger cycle into cyclopentenones. Synthetic methods that include ring opening/closure, any rearrangement that is subsequent to a transformation or isomerisation are developed here.

Furan derivatives can be rearranged to cyclopentenones (Achmatowicz reaction) [372] through various cationic rearrangements. This reaction has been used extensively to obtain cyclopentenones with varied substitution. [373–376] The mechanism varies depending on the substituents: O-substitution cannot follow the classical pathway and the reaction must promoted differently[377], the classical Achmatowicz reaction mechanism from α-substituted furfuryl alcohol **27** has been well explored.[378]



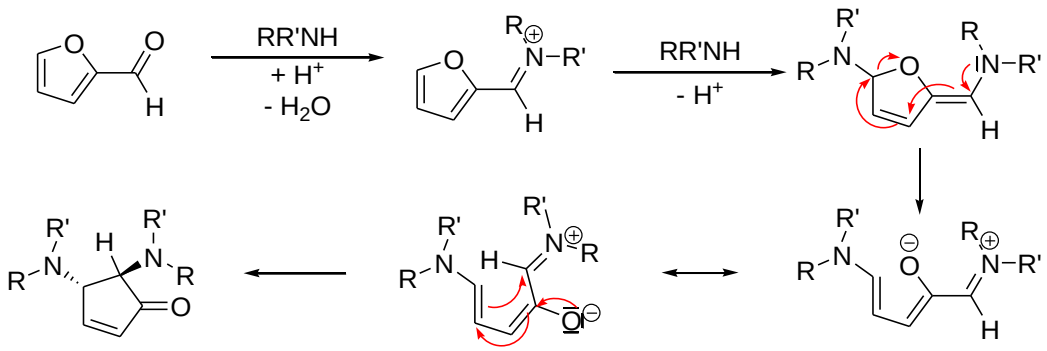
Scheme 52

This method is of considerable instead in the synthesis of 2-substituted 4-hydroxycyclopentenones. α-substituted furfuryl alcohols are easily accessible from furfural and transformed into enones.[379] Common reagents to promote this transformation are mineral acids (such as KH_2PO_4)[380,381], acetic acid[379] or Lewis salts (such as $ZnCl_2$)[373].The usefulness of this has been extended by group of Csàkÿ, working on the synthesis of cyclopentadienyl ligands[382], by functionalizing the 4-hydroxy cyclopentenone further: addition of organometallics followed by elimination of the hydroxyl yields 4,5-disubstitution and 2,3-disubstitution by rearrangement[373,383] or alkylation of the 5-position[374].



Scheme 53

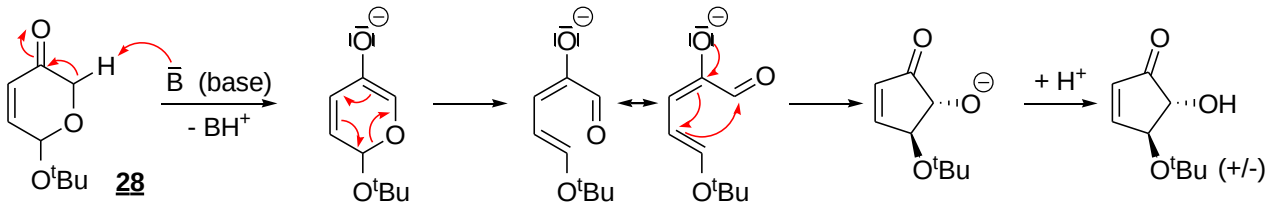
Furfuryl alcohols with hydroxyl-bearing side chains can have intramolecular reactions where the attack of the water molecule is replaced by intramolecular addition of the hydroxyl, leading to bicyclic cyclopentenones.[384] 2-furaldehyde can also react with a variety of amines to yield disubstituted cyclopentenones through a similar mechanism.[385–387]



Scheme 54

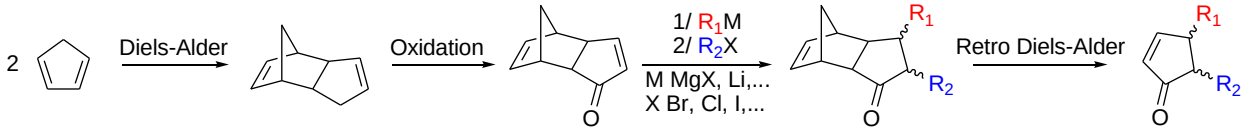
This method has been described successfully with several amines: amino acids, morpholine, alkyl and aryl amines.[385,386,388] 4-hydroxy cyclopentenones can be converted to 4-amino cyclopentenones by reacting the former with isocyanates.[389]

A related transformation is the base-catalyzed rearrangement of pyranones **28** into cyclopentenones.[390–392] Conversely, these pyranones can be prepared from furfuryl alcohols.[393]



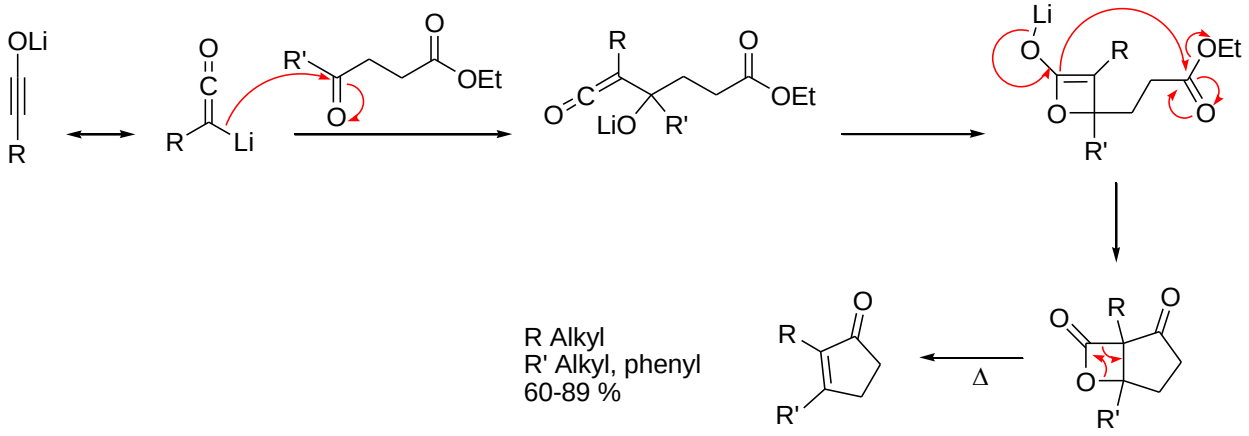
Scheme 55

Retro-Diels-Alder strategies have been developped for the synthesis of cyclopentenones. Oxidation of the dimer of cyclopentadiene yields a enone that is formally a D-A adduct of cyclopentadiene and cyclopentadienone. The enone side can be functionalized and the cyclopentenone can be obtained by deprotecting the alkene by removing cyclopentadiene.[394]



Scheme 56

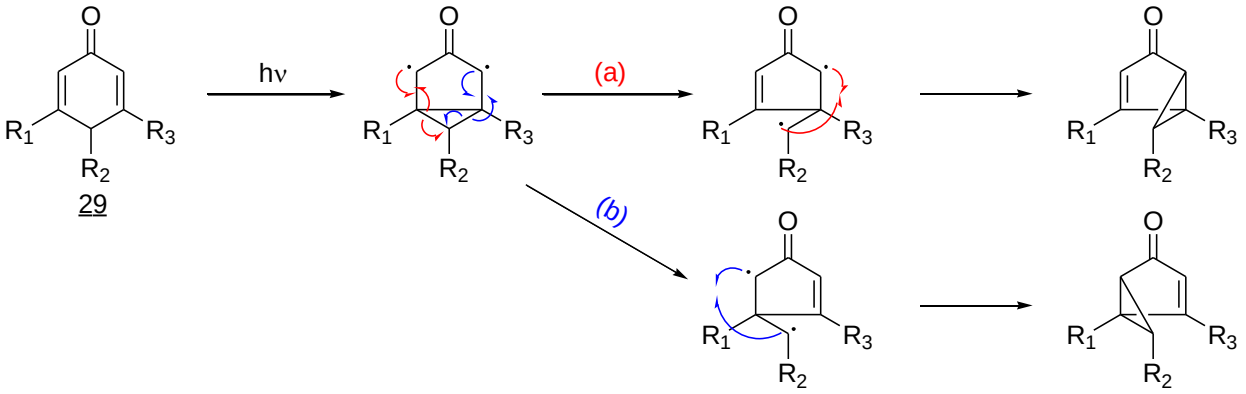
An interesting method involving the elimination of carbon dioxide from bicyclic β-lactones has been described by Shindo *et al.* [395].



Scheme 57

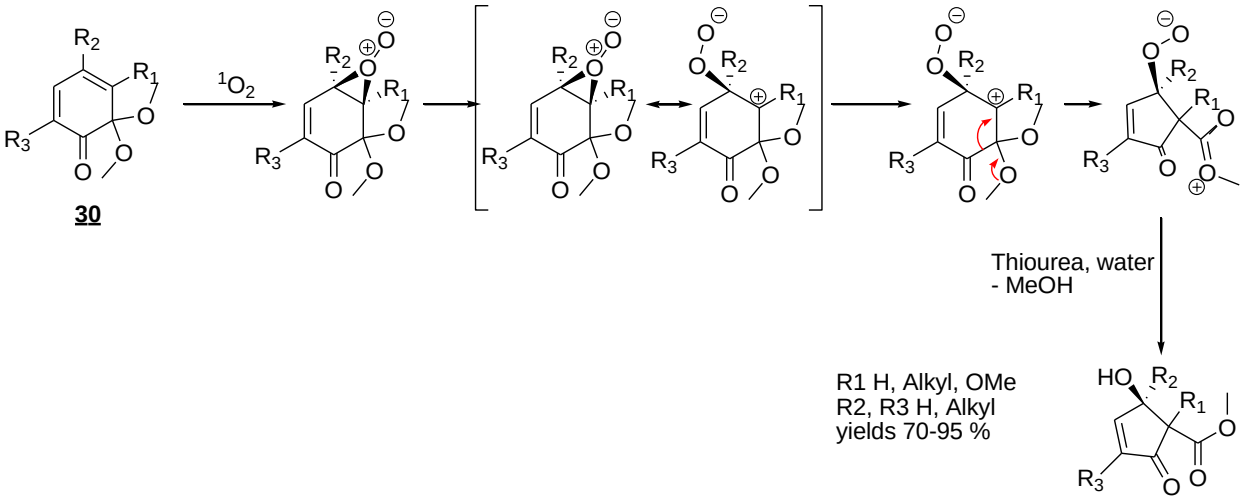
These bicyclic β-lactames are prepared from the tandem addition-intramolecular condensation of a lithium ethynolate to a 3-ketoester. The ketolactone then undergoes retro [2+2] yielding 2,3 disubstituted cyclopentenones in good yields.

Cyclopentenones can be generated photochemically from cyclohexa-2,5-dienones **29**, for example monoketal quinones.[396,397] Cyclohex-2,4-dienones (o-benzoquinones)can also be transformed to cyclopentenones.[398–400] The reaction is a di-π-methane isomerisation.[131,401] The mechanism is known and well-studied.[22,130,131,401] The regioselectivity of the reaction (path a *vs* b) is based on the mobility of the π systems: the least conjugated double bond is the least reactive, the cyclopropyl is opened on the least substituted side.



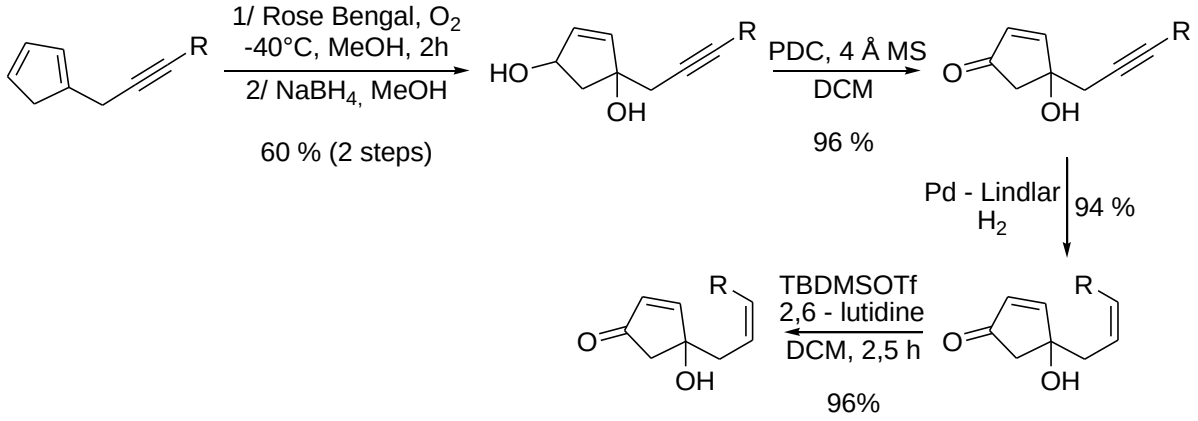
Scheme 58

o-Benzoquinones **30** can converted to cyclopentenones by reacting them with singlet oxygen (obtained by bubbling oxygen through a solution containing Bengal Rose, a photosensitizer). [2+1] addition of the dioxygen leads to a rearrangement of the six membered ring to a five membered ring with high yields and stereoselectivities.[402]



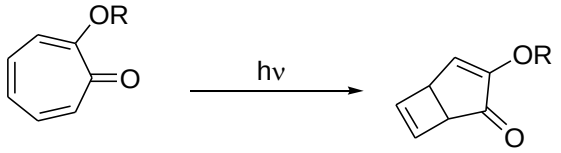
Scheme 59

Bengal Rose is also a common photosensitizer for the photooxygenation of cyclopentadienes.[403,404] The latter has been applied to the synthesis of cyclopentenone. Corey describes the transformation of a cyclopentandiene derivative to a diol that leads to several functionalized cyclopentenones.[405]



Scheme 60

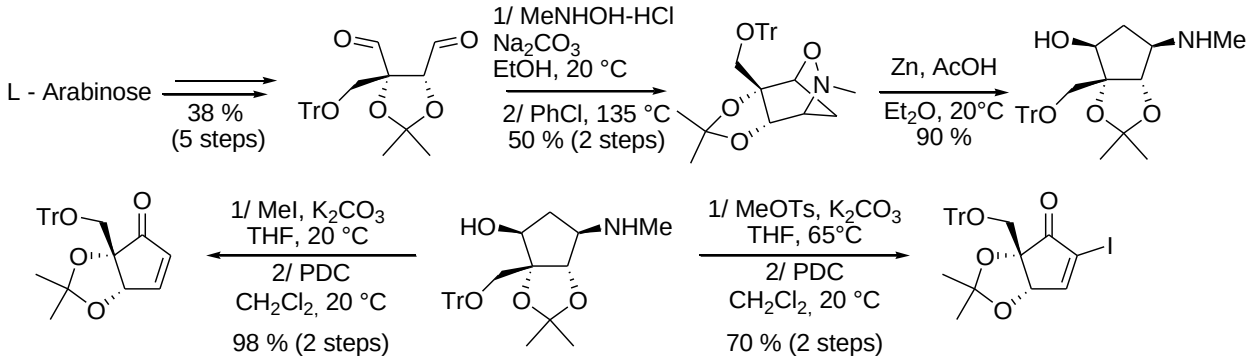
Another photochemical method is the intramolecular cyclization of tropone ethers. The cyclopentenone bicycle is obtained by the [2+2] photocycloaddition of the least electron rich (the one without the alkoxy) α,β double bond to the γ,δ double bond.[406,407]



Scheme 61

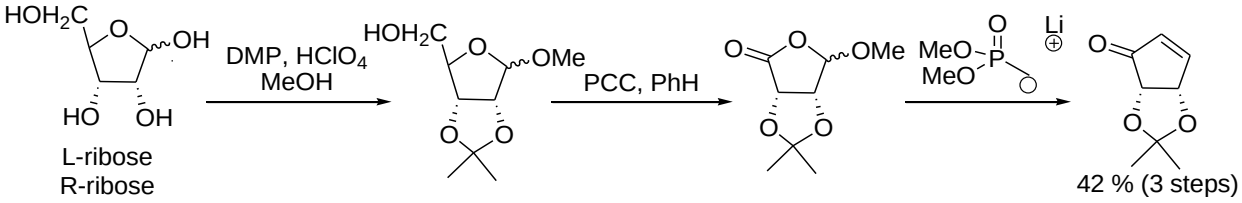
Enantioselective versions have been developed (using chiral induction from natural chiral molecules).[408]

Bicyclic nitrones prepared from chiral sugar derivatives can be opened by zinc-catalyzed cleavage of the N-O bond. Oxydation of the alcohol gives a substituted ketone. Retro-Michael (or specifically the Hofmann elimination in this case) of the ammonium group furnishes the enone.[409]



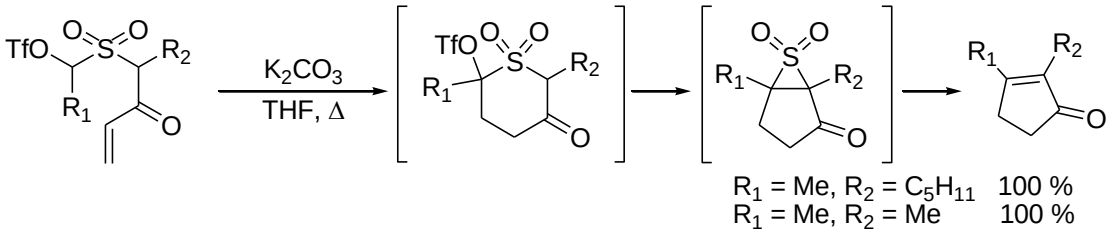
Scheme 62

Ribose can also be converted to cyclopentenones through lactones that are hidden 1,4 aldehydes that react with lithium dimethyl methylphosphonate. Olefination is followed by oxidation. The method works for both available enantiomers of ribose.[410]



Scheme 63

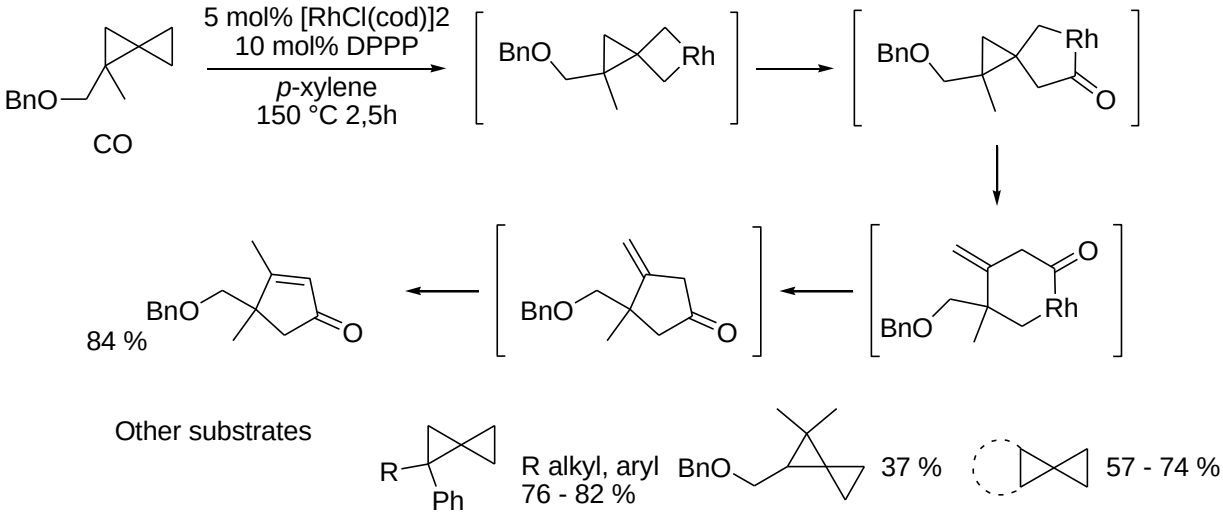
Ramberg-Bäcklund reactions, formation of alkenes from α–halogeno sulfones that undergo base-promoted cyclization and subsequent extrusion of sulfur dioxide, can be applied to the synthesis of cyclopentenones.[411]



Scheme 64

While the last step is highly efficient, the synthesis of the starting sulfone is somewhat lengthy and the yield are barely average.

Finaly, spiropentanes (two cyclopropanes joined at the tips) can be converted to cyclopentenones under pressure of carbon monoxide and in presence of rhodium catalysts as described by Matsuda *et al*.[412]



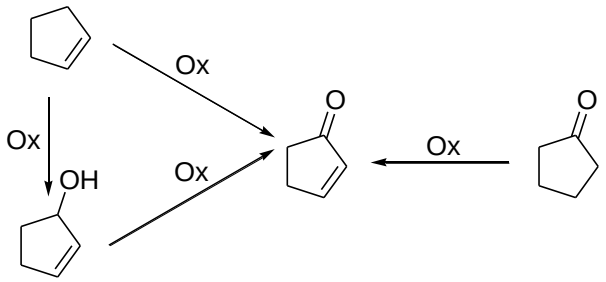
Scheme 65

The spiropentanes can be prepared with typical carbene chemistry to yield cyclopropanes.

Misc. transformations

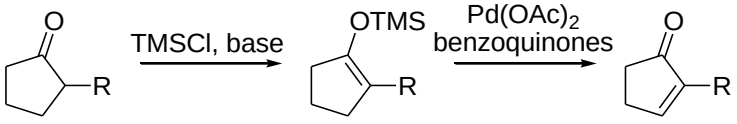
Many chemical transformations that yield cyclopentenones cannot be easily classified in the above categories.

Cyclopentanes, cyclopentenols and cyclopentanones can be oxidized into cyclopentenones. One of the major pitfalls for cyclopentenols is the danger of allylic oxidation. The synthesis of cyclopentenes and cyclopentenols is a large topic by itself and therefore has no place in this manuscript, however it is necessary to mention that such procedures exist.



Scheme 66

Of note however, is the oxidation of cyclopentanones to the enone. Various methods have been developed to carry out this transformation, most notably the Saegusa strategy, involving the synthesis of a silyl enol ether and subsequent oxidation by palladium complexes in presence of oxidants. [413] Interestingly, direct oxidation has been reported in presence of amine cocatalysts.[414]

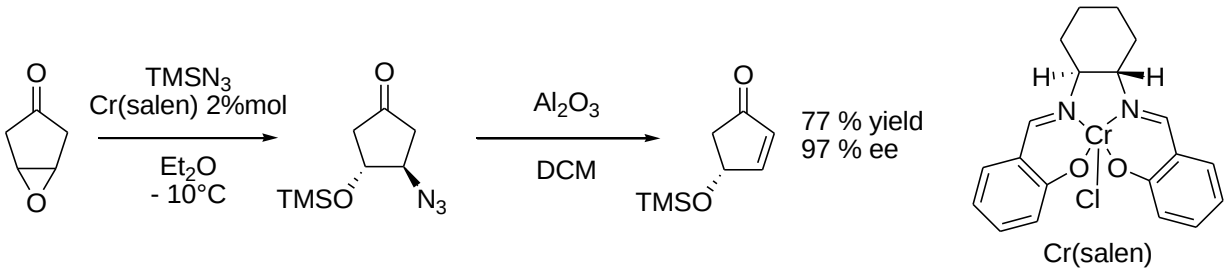


Scheme 67

In addition to this palladium chemistry, alternatives have been described using IBX[415] and the older and less friendly phenylselenium chemistry.[416]

A tetrahydrofuryl bearing 4-alkoxy-5-bromoalk-2-en-1-ol has been described to undergo a sequence of intramolecular transformations yielding a cyclopentenone after 5 days of stirring at room temperature.[417]

Desymmetrization of cyclopent-3-enone oxide can be carried out by opening the epoxide with $TMSN_3$ in presence of a chiral chromium salen complex. Subsequent treatment in basic conditions yields 4-trimethylsilylcyclopentenone in good yields.



Scheme 68

As this extensive presentation of synthetic methodologies shows, the tools for the synthesis of cyclopentenones are numerous and can be employed with great efficient to create variedly substituted cyclopentenones. While we have limited our synthesis of cyclopentenones to a few simple compounds through simple methods, we must be mindful that the tandem photochemical reaction can be applied to many more cyclopentenones then described in this manuscript and that a rationale exists to combine any of the methods mentioned here to the photochemical transformation presented here.

Cyclopentenones prepared in this work

As stated in the introduction, our research project aims to explore the scope and limitations of the tandem photochemical transformation. Towards this, we sought to prepare variously substituted cyclopentenones.

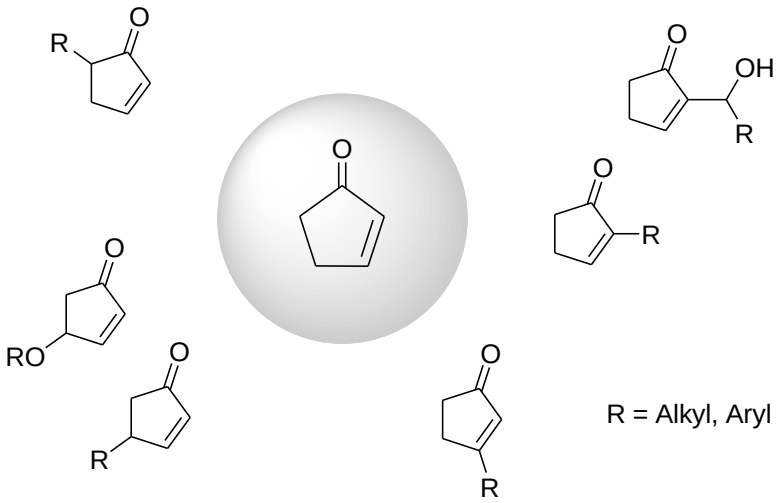


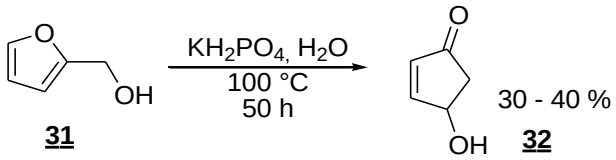
Figure 12

To probe the possibilities of this reaction, each position must be studied with various components. In the context of our stated objective to develop atom-efficient, « green » methods for organic transformations. Synthetic methods involving metals, chiral complexes, expensive solvents (ionic liquids), etc… are therefore avoided if possible. We were most interested in organocatalytic transformations leading to complex molecular structures with highly functionalized products.

4-substituted cyclopentenones

The Orsay group has studied the on the regioselectivity of the [2+2] photocycloaddition of 2-oxysubstituted cyclopentenones.[126] We naturally sought to study 4-hydroxy derivatives of cyclopentenone in the context of the tandem photochemical reaction.

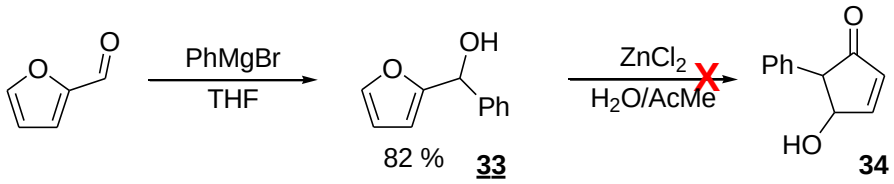
The transformation of furfuryl alcohols to cyclopentenones (Achmatowicz reaction) represents an easy, if lengthy and inefficient, access to 4-hydroxycyclopentenone.[418] Furfuryl alcohol **31** was boiled in water over several days yielding the 4-hydroxycyclopentenone **32** in low yield (30-40 %).



Scheme 69

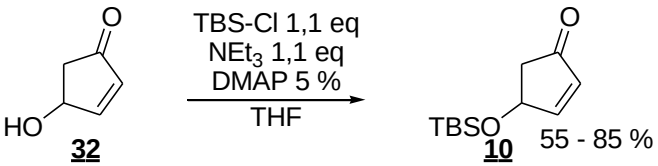
For subsequent synthetic use of **32**, extensive purification was unnecessary given that the product was clean by NMR standards, although a brown colour persists. For use as a photochemical substrate, we needed spectroscopically pure and not merely analytically pure cyclopentenones. Distillation was carried out to obtain sufficiently pure material for irradiation.
Attempts to carry out the isomerisation of furfuryl alcohol with microwave irradiation[419] in water, instead of boiling water with mineral acids, were unsuccessful. Similar tests with polyphosphoric acid were equally unsuccessful.

Attempts to explore the use of this rearrangement further were carried out: furfuryl alcohol derivative **33** was prepared from furfural by a Grignard addition reaction in 82 % yield. Zinc chloride rearrangement[374,420] to **34** was attempted but was unsuccessful for reasons unknown and the attempts were abandonned.



Scheme 70

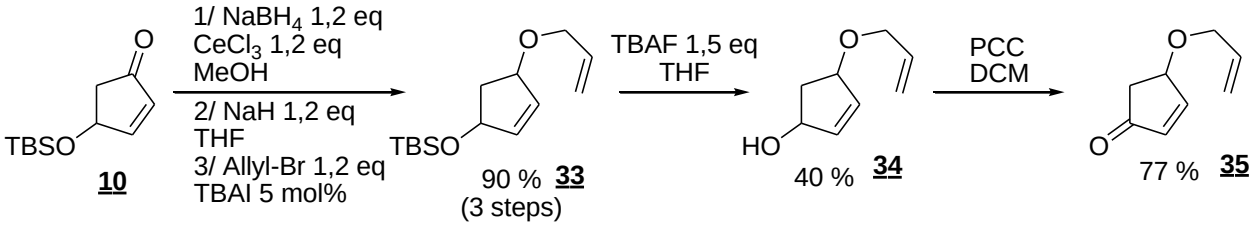
Alcohol **32** was easily converted into its tertbutyldimethylsilyl ether **10** by treatement with TBS chloride in presence of trietyhlamine and DMAP furnishing cyclopentenone **10**.[126] Yields varied considerably from one to the next next, covering a range of 55 – 85 %.



Scheme 71

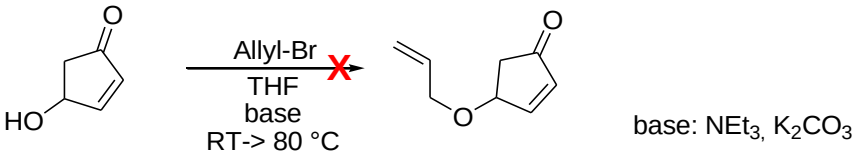
As with **32**, **10** was distilled before use as a photochemical substrate.

Compound **10** was used to prepare 4-allyloxycyclopentenone XX for tests as intramolecular reactions. The protected cyclopentenone was reduced in Luche conditions[421] and the resultant alcohol was allylated to yield **33** in 90 % overall yield. Removal of the protecting group and oxidation furnished the allyloxy cyclopentenone **35**.



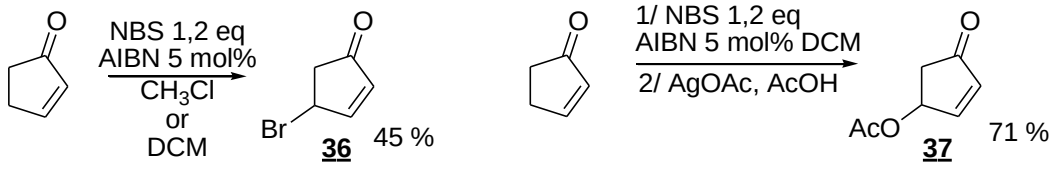
Scheme 72

This sequence provided the cyclopentenones **35** with an average overall yield (28 % from **10**). However it was not a very atom efficient synthesis and lengthy (5 steps). Unfortunatly, the more direct synthesis, direct allylation of 4-hydroxycyclopentenone, failed both with triethylamine and potassium carbonate, in THF, with or without heating.



Scheme 73

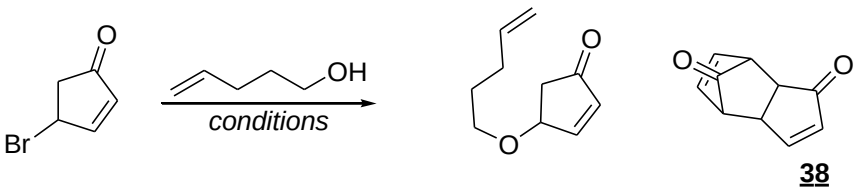
The lengthy synthesis of silyl ether **10** from furfuryl alcohol **32** led us to consider an alternative synthetic route to the 4-alkoxy cyclopentenones.
4-bromocyclopentenone **36** seemed was very easily prepared from cyclopentenone in radical bromination conditions (NBS, AIBN, yield 45 %).[250] We hoped to use it as a electrophile reacting a nucleophilic alcohol. However, the brominated compound was quite unstable: immediately after workup, it was obtained as a slightly yellow oil, but in less than 5 days in the dark, or 24h on the bench without argon, it turned to a brown thick paste. The compound was most conveniently converted to 4-acetoxycyclopentenone in a sequential bromination-substitution reaction using silver (I) acetate and acetic acid[422] to yield the more stable 4-acetoxy compound **37** in 71 % (combined yield over two steps).



Scheme 74

An attempt to carry out a nucleophilic substitution reaction on a freshly prepared sample of the bromine of **36** using pent-4-en-1-ol proved to be unsuccessful in all the conditions attempted (scheme 82). The only identified product formed was the dimer of cyclopentadienone **38**. It is likely

that cyclopentadienone forms due to the basic conditions and reacts with **36** and then undergoing elimination.



38

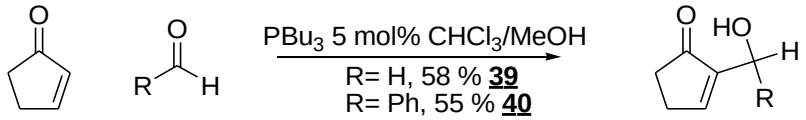
LiH, THF, -78°C to RT	degradation	
DMAP, THF, RT	none	37 %
NEt3, THF, RT	none	XX %

Scheme 75

2-substituted cyclopentenones

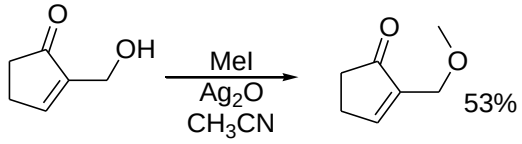
The 2-methyl compound was obtained commercially. Other compounds were prepared with relative ease.

Two Baylis-Hillman dducts of cyclopentenones were prepared from benzaldehyde and formaldehyde using conditions developed by Iguchi *et al.* using tributylphopshine as the organocatalyst[423].



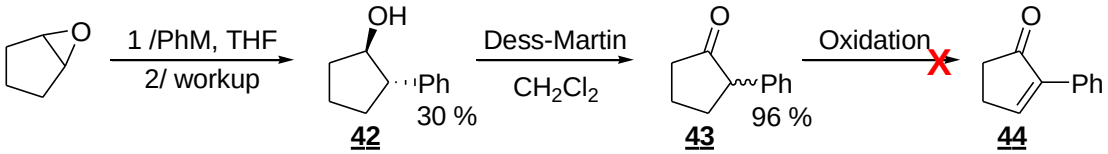
Scheme 76

The 2-hydroxymethylcyclopentenone **39** was converted into its methyl ether **41** by reaction with methyl iodide and silver oxide in acetonitrile, with 53 % yield.



39 **41**

Another method explored was the synthesis of 2-phenylcyclopentenone with the following sequence: cyclopentene oxide was opened with a phenyl metal species (magnesium halide or lithium) to yield **42**, oxidized to ketone **43** and then oxidized further to enone **44** (through a bromination-elimination sequence).



42 **43** **44**

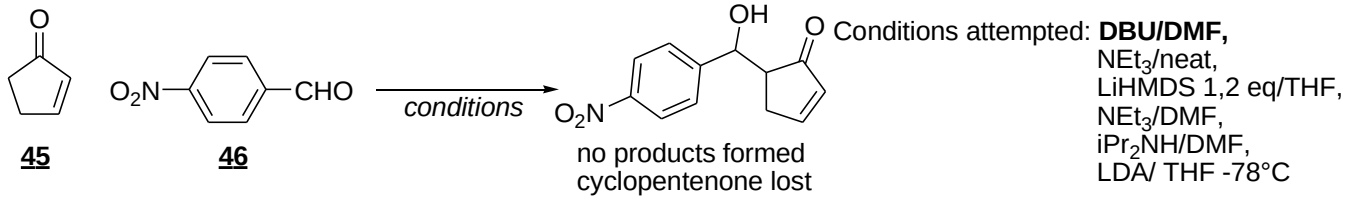
Scheme 77

The synthesis of the phenylcyclopentanol **42** was carried out by nucleophilic ring opening with various (and readily available) reagents: phenyl magnesium bromide and chloride worked at 30 %, Oxidation of the alcohol was carried out with high yields when using DMP (96 %). The final dehydrogenation could be perfomed with the conditions described by Ohta *et al*. using NBS to generate α-bromo ketones that would eliminate and rearrange to give the target enone **44**.[424] Unfortunately, while the product was detected in the crude reaction mixture, distillation of the latter failed to provide the expected product.

5-substituted cyclopentenones

We first tried to react the 5-position as we would an α position on a non-conjugated carbonyl, despite only a few examples that indicate such a similar reactivity.

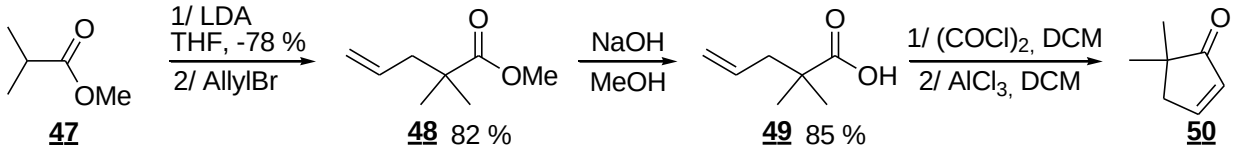
Attempts to perform aldolisation of the simple cyclopentenone **45** with **46** were carried out. We were particularly interested in the conditions developed by Zhang using simple organocatalysts.[195]



Scheme 78

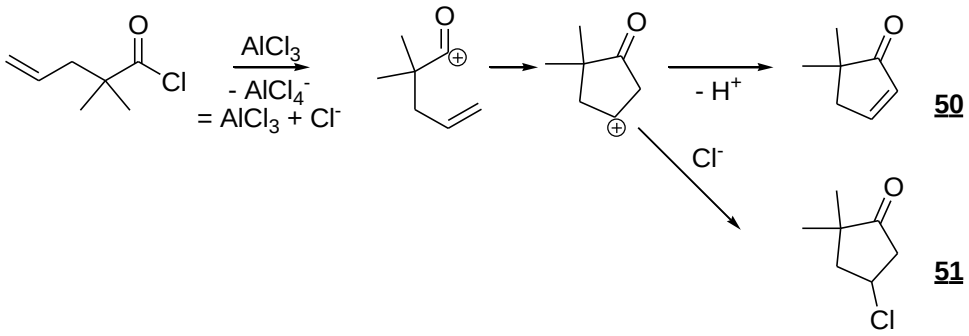
The conditions developed by Zhang (DBU, DMF) failed to provide the expected aldol. Various simple conditions were attempted but all failed. Similarly, attempts to alkylation the position with LDA or NaH and MeI were a failure, no alkylated products were observed and almost all of the starting material (cyclopentenone) was lost.

We envisaged the preparation of 5-substituted cyclopentenones following a Friedel-Crafts cyclization sequence (Scheme 85). A α substituted acetate can be be allylated, the acid function uncovered and converted to the acyl chloride to induce a Friedel-Crafts like cyclization.



Scheme 79

LDA deprotonation/alkylation conditions were used to achieve the allylation of methyl dimethylacetate XX, providing 82 % of the C-allylated compound XX. Saponification with sodium hydroxide gave the acid XX in 85 % yield. Cyclization of the acid was carried out by forming the acyl chloride *in situ* and followed by treatment with aluminium chloride.[355] The expected 5,5-dimethyl-cyclopentenone was formed but a chloro compound was also present in the isolate product. It was identified as 3-chloro, 5,5-dimethyl-cyclopentanone XX.

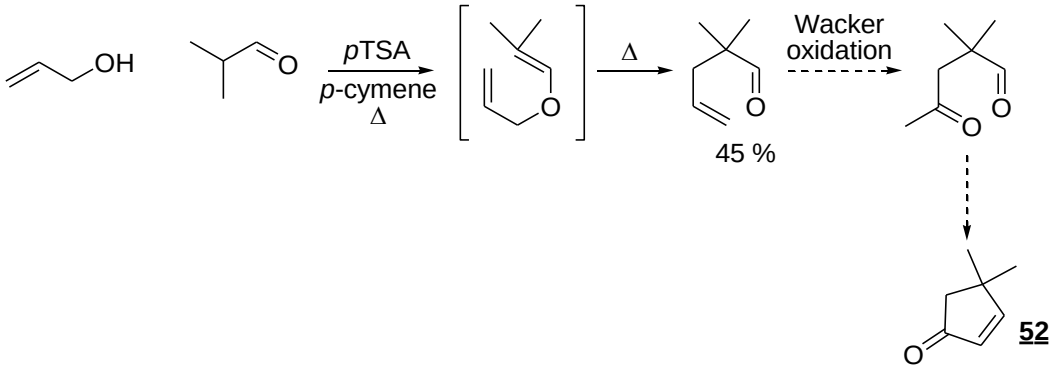


Scheme 80

This chloro compound may have arisen from trapping of the intermediate carbocation XX by a chloride ion. We reasoned that this side product should be transformed into XX by treatment with bases, but these attempts to achieve this were unsuccessful. Attempts to prevent the formation of XX by diluting the reaction mixture thus hoping to favoring the intramolecular elimination over the intermolecular reaction with the chlorine ion) were unproductive.

4-substituted cyclopentenones

We attempted the preparation of 4,4-dimethylcyclopentenones **52** as follows (scheme 87). α-Allylaldehyde that could be prepared in one step from allyl alcohol and isovaleraldehyde[425] and could serve as a possible intermediate to 4,4-dimethylcyclopentenone **52**.

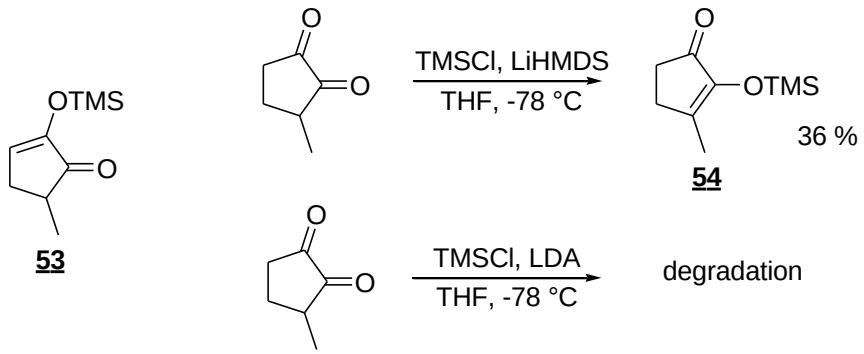


Scheme 81

A Claisen rearrangement of the allyl enol leads to the aldehydes in 45 % yield at best. The transformation was a liability because the reproductability was poor. Furthermore, the Wacker oxidation conditions that were attempted ($PdCl_2$/CuCl/O_2/DME) failed to yield the ketoaldehyde.

Polysubstituted cyclopentenones

Functionalisation of commercially available 3-methylcyclopenta-1,2-dione was attempted in an attempt to prepare cyclopentenone **53**.



Scheme 82

We sought to prepare the trimethylsilyl enol of the kinetic enolate by deprotonating the dione in kinetic conditions. This was unsuccesfull with LDA. Attempts with LiHMDS, a more selective hindered base, were also unsuccessful, but yielded the unwanted (the thermodynamic) silyl enol ether **54** in 36 %. This is unfortunate because this cyclopentenones, being 3-substituted, is unlikely to lead to cyclobutene aldehydes. In the case of LDA, we believe the workup might have compromised the reaction and it may also have affected the LiHMDS reaction by leading to rearrangement of the kinetic enol (which should arise in our conditions) to the observed one.

Conclusion

The literature convering the synthesis of cyclopentenones is rich and wide. We selected a few methods that seemed easy and compatible with our stated goal of preparing variously substituted cyclopentenones. We prepared a selection of substrates to be used to probe the scope and limitations of the tandem photochemical [2+2]/Norrish I transformations:

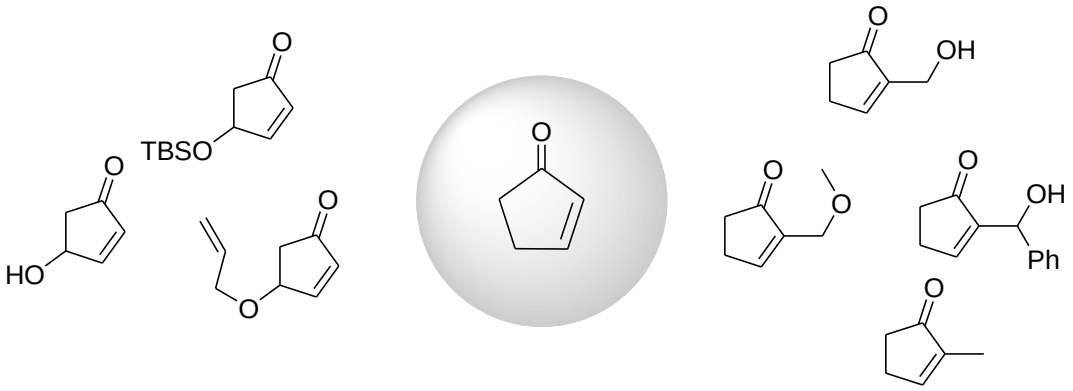


Figure 13

Chapter 3 Preparation of substrates by organocatalysis

Catalysis is the use of a, in the course of the reaction, substoechiometric species to promote a reaction that otherwise occurs unsatisfactorily. Catalysts can influence various parameters of a reaction: yields, reaction speed, chemo-, regio- and stereoselectivity.

Commonly used catalysts are metallic species, often coordinated with ligands which may provide the stereocontrol. On the other hand, organocatalysis is catalysis promoted by a non-metallic, organic molecule. These types of catalyst operate by bonding covalently to the reactants, leading to highly reactive species. Heterogenous catalysts and phase transfer catalysts draw upon non-bonding interactions and ionic interactions respectively.
Organocatalysis appeared in the middle of the 20th century. Some quote the work of Pracejus on the diasteroselective addition of chiral amines to asymmetric ketenes as the first examples of organocatalysis[426,427], but the work of Hajos and Parrish[428] on one hand and Eder, Sauer and Wiechert on the other[429] on Proline catalyzed Robinson annelation is the first widely recognized example of organocatalysis. The field would develop slowly at first but has known exponential developpement in the last 20-30 years, having become a common tool in modern total synthesis strategies.[430]

Introduction: organocatalysis, a brief overview

Organocatalysis is an attractive approach to chemical transformations since it doesn't have some of the main drawbacks of metal-based catalysis: no metal contamination, facile recovery and ease of availability of the catalytic species. However, just as the highly competitive science of ligand design has known the developpement of increasingly expensive ligands in a quest for higher yields and selectivities, organocatalysts have undergone a "space race" to design more and more efficient (and expensive) organocatalysts. Simple organocatalysts are available from the natural chiral pool: amino acids, chiral alkaloids such quinine and cinchonine, chiral terpenoids, etc…

Organocatalysts have been extensively studied and reviewed by the scientific community.[431–440] They are spread widely over the field of chemistry, they can take several forms: chiral amines are by far the more numerous.
Their chemical reactivity can also be sorted out in several categories not limited to:

- Lewis bases, which act as nucleophiles, adding to non-, poorly or wrongly reacting species to promote a certain reactivity pattern.[441] These include the most important class of organocatalysts, the chiral amines, which are known to promote reactions by forming reactive species such as iminiums or enamines. [442–445]

- Lewis acids, which are similar to their metallic counterparts, increasing the reactivity of electrophilic species and inducing chirality by forming chiral transition states due to conformational preferences. [446]

- Carbenes, most notably NHC-carbenes that can have complex reactivities.[447,448]

- Phase transfer catalysts are water-soluble, usually ionic, complex hydrocarbons that locally create the ideal conditions for a reaction to take place by forming substrate-catalyst adducts that are surrounded by reactive species. The local structuration enforces chiral selectivity. [449,450]

- Bronsted acid and bases which facilitate deprotonation and protonation are made to happen in a stereocontrolled manner by controlling the chiral environment of the protons.[451,452]

- Hydrogen bond donor/acceptors. These species selectively stabilize certain reaction intermediate conformers, which induces stereoselectivity.[438,453]

While the concept of organocatalysis was initially limited to amine-activated reactions of carbonyls, the field has grown to include many types of reaction. A large portion of the literature is still dedicated to carbonyl chemistry: aldolisation (the cornerstone of organocatalysis)[442,454–464],Mannich reactions,[442,465,466] alpha-heterofunctionalisation[467] and additions to carbonyls[468]. Ventures have also been in made in the fields of Michael additions,[469–477] Diels-Alder reactions,[260,442,478] epoxydation,[266,267,479–481] cyclization reactions,[263] transfer hydrogenation,[482–485] cyclopropanation reaction[261,262] and more. Organocatalysis has even been described in reactions where transition metals were once thought absolutely necessary such as a the recent report of metal-free conjugate addition of an organotrifluoroborate to a enone promoted by organocatalysis.[486]
Concurrently, organocatalysts have evolved past proline. Proline does remain a benchmark catalyst[487,488] and is the forerunner to a vast library of pyrrolidine derivatives[466,489–494]. Many of the more simple (but surprisingly occasionally the more efficient) organocatalysts come the chiral pool of amino-acids, peptides and naturally occurring chiral alkaloids.[462,495] Other classes of organocatalysts include phosphines,[496] phosphonium salts,[497] phosphoric acids,[498] thioureas,[499,500] cinchona derivatives,[261,499,501–503] quaternary chiral ammonium fluorides,[504] imidazolidinones[505] to name but the most recurrent ones.

All this points to the obvious conclusion that organocatalysis is a fully fledged approach to the science of organic synthesis. Its importance increases with our society's increasing demand for the developpement of eco-friendly and cheap methods for the construction of any substances from polymers to pharmaceutical compounds.

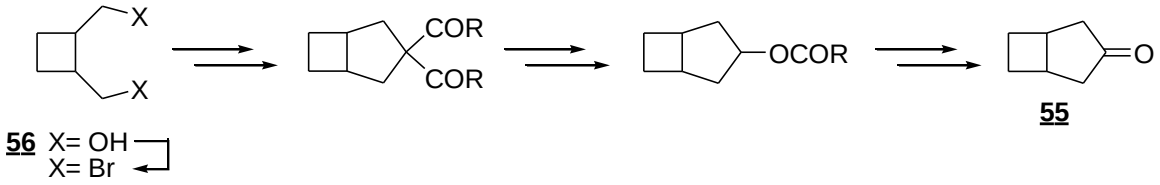
Preparation of photochemistry substrates

The objective of this part of the whole project is to prepare molecules to carry out our photochemical transformation on. We seek to prepare carbonyl species: enones for the whole transformation are our primary concern, but we have an interest in ketones that could undergo Norrish I types processes.

Preparation of symmetrical bicyclic ketones

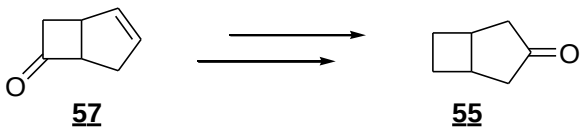
The objective of this particular research project was the preparation of bicyclo[3,2,0]hept-6-anone **55**, a symmetrical ketone that is related to other ongoing research projects in Cagliari.

The synthesis of this heptanone has been described in the literature starting from 1,2-di(hydroxymethyl)cyclobutane **56** which involves malonic synthesis and subsequent decarboxylation, followed by Baeyer-Villiger and final oxidation as key steps (Scheme 3).[506]



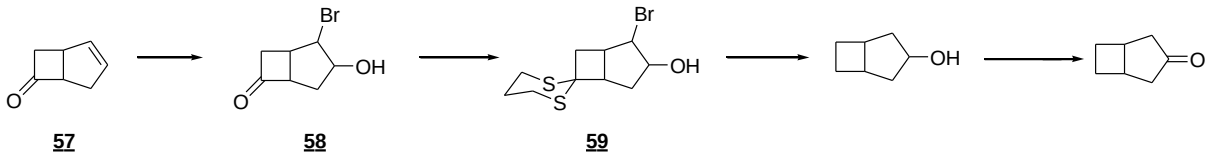
Scheme 83

This synthetic path, while simple on paper, is long and involves toxic compounds such chromic acid and $Pb(OAc)_4$. Therefore an alternative synthesis was devised starting from readily available starting materials such as the following commercially available bicycloheptenone **57** (Scheme 4):



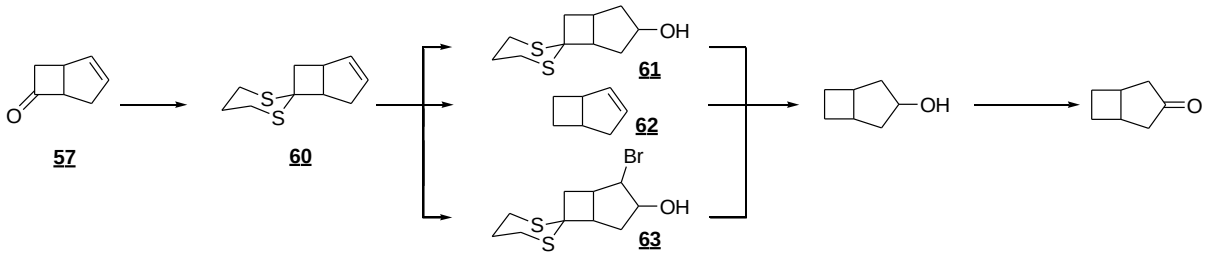
Scheme 84

The transformation of the above bicycle would involve total reduction of the carbonyl and oxidation of the double bond. Since these reactions are generally incompatible, protection reactions may be necessary. Several synthetic paths were imagined and tested (Scheme 5).



Scheme 85

We first explored the hydrobromation of the heptenone and subsequent debromination which has been described.[507,508] Hydrobromination of the bicycloheptenones **57** lead to **58** in good yields (81 %). The debromination involved a tin catalyst that was unavailable and postponed the attempts indefinitely.

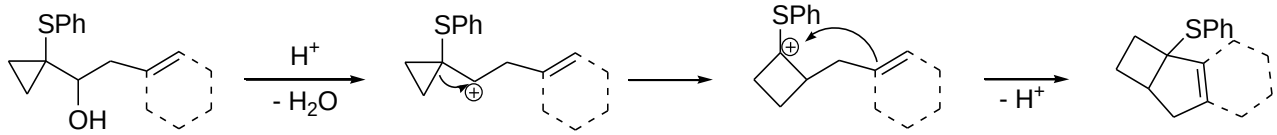


Scheme 86

The formation of the dithiane **60** and its subsequent reduction into an alkane appeared to be the next best solution for our compound. Catalytic APTS and standard silica in refluxing dichloromethane allowed for quantitative transformation of **57** into **60**. However, subsequent attempts to oxidize 2 failed to give the expected products: Brown hydroboration (BH_3 / H_2O_2, NaOH) gave none of the expected product **61** (or a regioisomer) but GC-MS indicated that the major products were mono- (M+16) or di-oxidized (M+32) starting material (oxidation of the sulfurs is likely). Direct reduction of **60** into bicycloheptene **62** was not attempted since the resultant alkene may have been too volatile. Hydrobromation of **60** into **63** was not successful either, only degraded starting material was recovered.

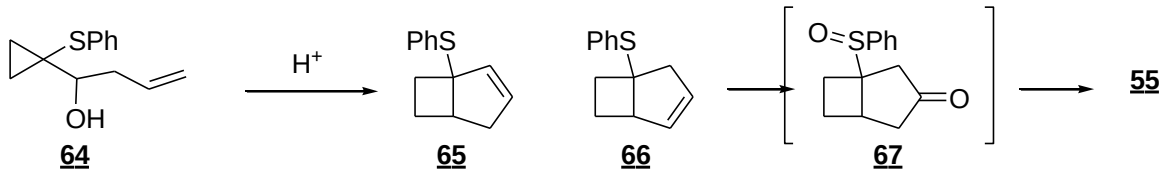
Direct Brown hydroboration of **57** into the triol was equally unsuccessful and yielded only the enol (reduction of the carbonyl). Attempts to brominate the alcohol into a bromoalkene with PPh_3 and CBr_4 only yield an unusable black tar.

Another approach, based on previous research of the Piras group[202,204,206], involves the rearrangement of 1-thiophenyl, 2-(1-hydroxy)alk-3-enyl into thiophenyl bicycloheptenes. [203]



Scheme 87

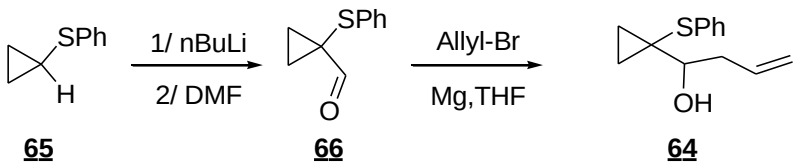
Applied to the synthesis of bicycloheptanones, the following sequence was devised (Scheme 6):



Scheme 88

Rearrangement of the easily available compound **64** would generate the bicycloheptenone structure, which upon oxidation would introduce the carbonyl functionality and generate the sulfoxide or the sulfone, which can be easily removed to generate the symmetrical ketone **57**. Previous described examples of this rearrangement did not involve a simple non-conjugated alkene but aromatic rings.

Cyclopropyl thioether **64** was prepared in two steps from simple cyclopropylphenyl thioether (Scheme 7):

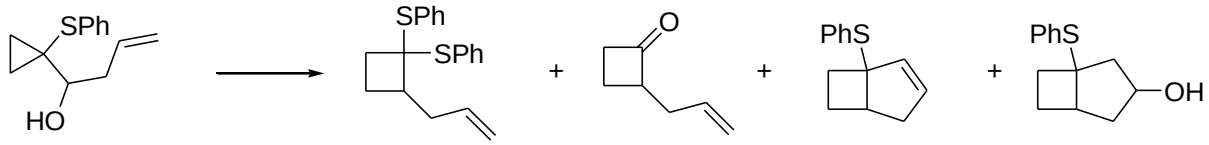


65 **66** **64**

Scheme 89

The cyclopropylphenyl thioether **65** was treated with nBuLi at -78°C and reacted with DMF to generate the cyclopropyl thiophenyl aldehyde **66**. The first attempted involved slow addition of the n-butyl lithium to the thioether at -78°C in THF, one hour stirring and then slow addition of a substoechiometric amount of DMF gave 25 % of the expected product and 47 % of unreacted starting material **65**. Longer deprotonation time (4h at 0°C instead of 1h at -78°C) gave 33 % yield and 33% recovered SM.
Grignard addition of allyl magnesium bromide to aldehyde **66** gave 75-83 % yield of **64** with the crude mixture showing no traces of the starting material; simple filtration of the crude reaction mixture yielded the pure product **64**.

In order to attempt the acid-catalyzed transformation of allyl alcohol **64** to bicyclic alkene **65**, the alcohol was submitted to various conditions based on the previously described conditions for this rearrangement: APTS as a catalyst and refluxing benzene.[203] The results are summarized in the following table:



64 **67** **68** **65** **69**

Scheme 90

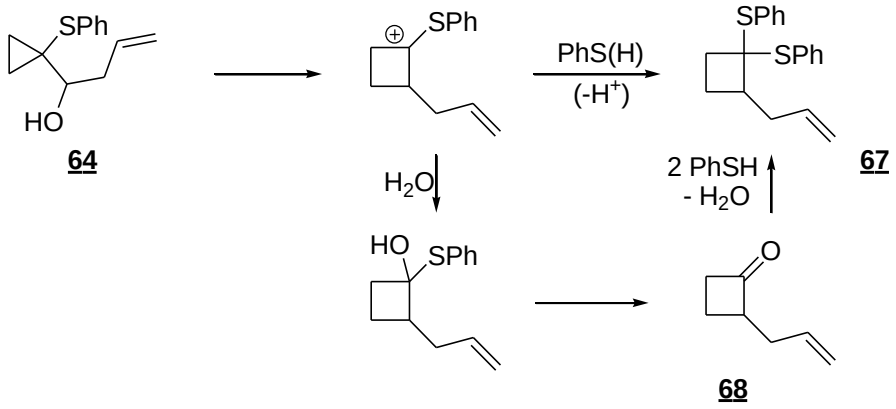
Entry	Conditions	Results
1	TsOH 10 %, THF, 5 days reflux	**65** detected, very low conversion. SM major component.
2	TsOH 20 %, THF, 10 days of reflux	**65** detected, 15-20 % conv. SM major component.
3	TsOH 10 %, PhMe, 5 days reflux	Total conv. of the SM into **65** and **67**, 1:1 inseparable mixture.
4	TsOH 10 %, PhMe, 4 Å MS, 5 days reflux	High conversion into mostly 17 compound

5	TsOH 10 %, THF, Ac_2O 2 eq, reflux 3 days	Conversion into **64**-acetate and various unidentified compounds, none of the **65** or **69**.
6	TsOH 20 %, PhMe, reflux with Dean-Stark	Low conversion, chrom. frac. could not be identified. None of the **65** or **69** products.

Table 2

While benzene was the solvent used in the literature, the less dangerous toluene was chosen as solvent. THF was tried as it would be better suited for the expected reaction which involves carbocations.

One major problem that was encountered was the formation of a compound detected and tentatively identified in GCMS as **67**. This compound could arise from one of the following paths (Scheme 95):

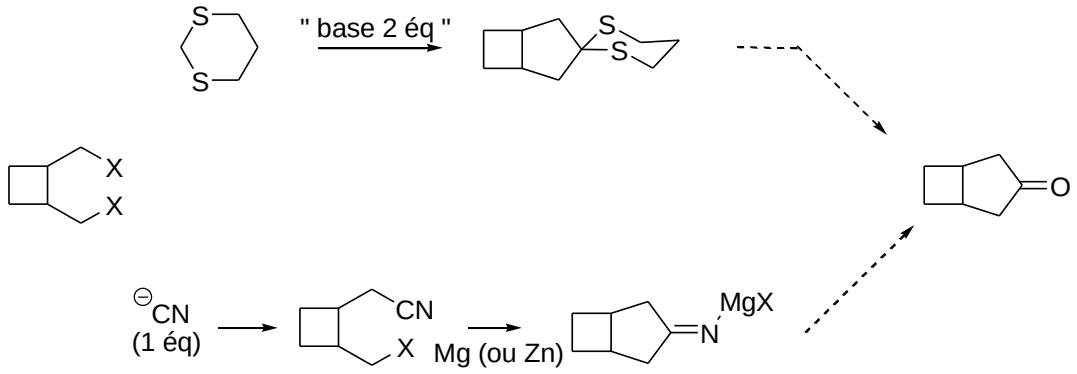


Scheme 91 Possible mecanisms for formation of dithiane 67

The formation of **67** could be attributed to a too high concentration of water (either from the rearrangement or traces in the solvent). Attempts to trap the water with molecular sieves (entry 4), acetic anhydride (entry 5) or a Dean-Stark apparatus (entry 6) failed to give any worthwhile results.

The best conditions tried were entry 2, which gave roughly 15-20 % conversion of the starting material 12 into an isomer of **65**(as per GC-MS). However, this conversion was obtained after 10 days of refluxing in THF and deemed to be insufficient for a continued effort in this direction. The rearrangement not being very efficient, it was decided to stop pursuing this pathway.

The bicyclic substrate being difficult to prepare and the fact that similar substrates have been proven to be quite unreactive led to this pathway being abandoned in favor of other projects. However, the following synthetic proposal may warrant investigation should the project be revived.



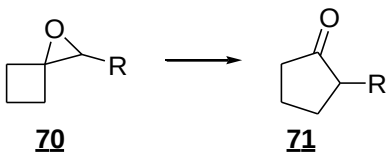
Scheme 92

The cyclobutandiol (X=OH) is commerical. Bromination, mesylation or tosylation would lead a cyclobutane with the appropriate leaving groups. Reacting this species with one equivalent of cyanide and subsequent intramolecular condensation of a metallic species, leading to a imine, then to the ketone. This sequence is possible if X=Br, but this can be alleviatedby reacting a tosylate, for exemple, with a iodide solution that would insert an iodide, allowing for the metal iodide reaction. Another possibility is a double dithiane reaction, generating the protected ketone in a tandem sequence. The ketone can be regenerated by removing the protecting group.

Rearrangement of cyclobutylidene epoxides

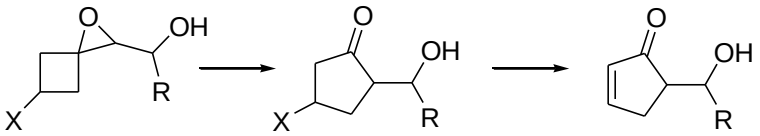
Our lack of success in the preparation of the bicyclic ketone led to focus on the preparation of cyclopentenones.

Rearrangement reactions of oxaspirocarbocycles into cycloalkanones have been described for cyclopropylidene and cyclobutylidene epoxides. [509,510] In our present case, oxaspirocyclohexanes **70** could be prepared from cyclobutanones, a known research topic here. They could be transformed into cyclopentanones **71** (Scheme 9):



Scheme 93

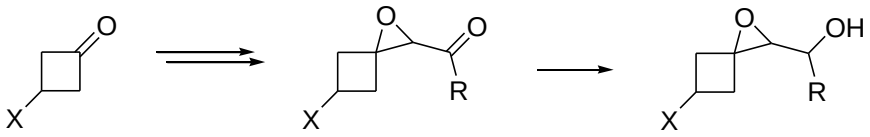
In the present case, the objective is to prepare cyclopentenone-aldol **74**. These could be prepared by elimination of leaving group X from cyclopentanone **73** which could be obtained by the ring expansion rearrangement starting from hydroxyl oxaspirocyclohexane **72** (Scheme 10).



72 **73** **74**

Scheme 94

Spiro compound **72** could be prepared from the following spiro epoxyketone, that we felt could be prepared from the appropriate 3-substituted cyclobutanone:



22

Scheme 95

Two reaction pathways were imagined to obtain the oxaspiro compound from the cyclobutanone, either a Wittig-epoxydation sequence or a Darzens condensation reaction. Bother the epoxydation and the Darzens condensation could theoretically be performed with organocatalysts (Scheme 12):

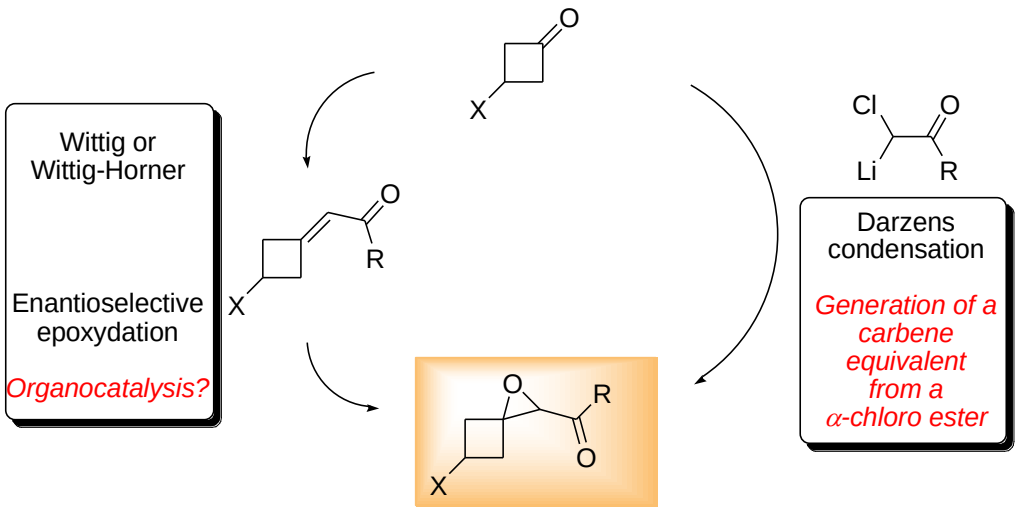
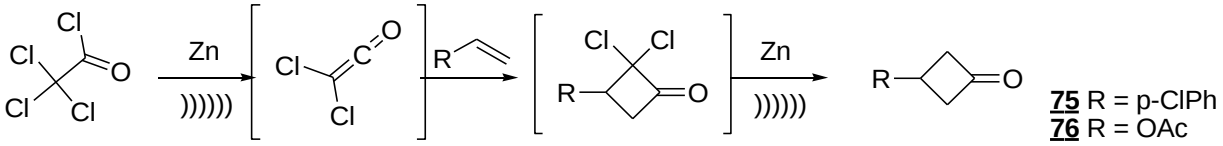


Figure 14

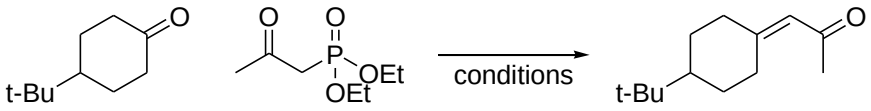
The cyclobutanones can be prepared by numerous methods but the only being used currently for related projects is the zinc mediated [2+2] cycloaddition between alkenes and *in situ* generated ketenes.[511] Trichloroacetyl chloride is treated with zinc in a sonic bath to generate the dichloroketene that adds to the alkene with sonication. The chlorine is then reduced again with zinc. Both reactions are performed successively in a *one pot* procedure (Scheme 11).



Scheme 96 Synthesis of cyclobutanones

In the course of this study, only 3-(*para*-chlorophenyl) cyclobutanone **75** was prepared but the methodology has been used to prepare other compounds. The objective was to prepare **76** (to access **73**, X= OAc) in a later stage of this project.
Compound **75** was prepared with 80 % yield using the aforementioned procedure. However this compound was not used at first, due to the cost of preparing it. Instead, cheap 4-*tert*butylcyclohexanone **77** was used instead.

We first attempted the Wittig methodology. The olefination was performed with Wittig-Horner reagent **28** and the various attempts are summarized in the following table:



27 **28** **29**

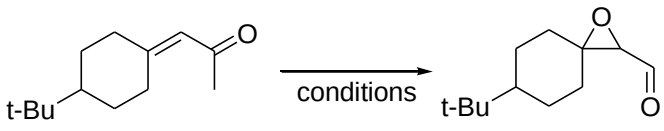
Scheme 97

Entry	Conditions	Results
1	K_2CO_3, H_2O, r.t.	No reaction
2	NaH, THF, r.t.	No reaction
3	KOH, H_2O/EtOH	450 mg (42%) pure product fraction + 440 mg fraction of product & SM

Table 3

Standard conditions were tried until a suitable method was found (KOH in an ethanol/water mixture).

Epoxidation of **79** to obtain **80** was then attempted with standard conditions:



79 **80**

Scheme 98

Entry	Conditions	Results

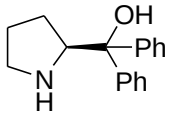
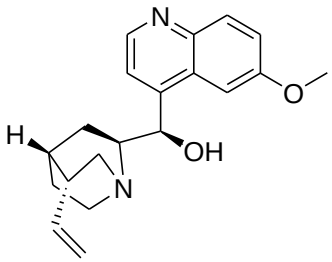
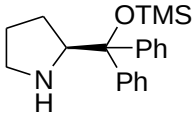
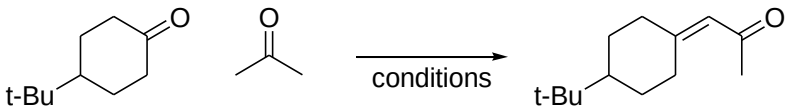
1	H_2O_2 / NaOH MeOH 0°C	50 % yield after one night. White solid
2	^{t}BuOOH, / LiOH EtOH r.t.	33 %
3	 ^{t}BuOOH, hexane	No reaction (week at r.t., week at reflux)
4	 ^{t}BuOOH, hexane, r.t.	No reaction (week at r.t.)
5	 (Jorgensen catalyst) H_2O_2, CH2CL2, r.t.	No reaction (2 weeks, oxidant reload after 1 week)

Table 4

On a side note, the formal synthesis of **79** could also be made from the aldol condensation and subsequent elimination reaction of acetone on ketone **77**. This was attempted with several bases (KOH in acetone/H_2O solution, ^{t}BuOK in THF) without success.



77 **79**

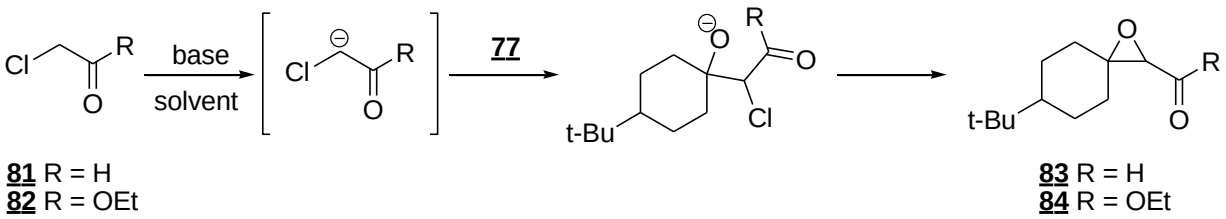
Scheme 99

The epoxydation route seemed to be a dead end and was abandoned. However, a few solutions were not tried at the time. For exemple, the Wittig-Horner reagent could have been different: an aldehyde for exemple instead of a ketone, which might have made the enone more reactive to the organocatalyzed epoxydation reagents. Alternatively, epoxidation with mCPBA could have been done and the rest of the project continued with racemic compounds.

The second approach, the Darzens condensation, was then attempted. On one hand, this method is more interesting because it is more atom-efficient: here the only by product is HCl (plus any base related compounds) compared to a phosphonate for the W-H route. On the other hand,

organocatalytic Darzens reactions are rare and usually the electrophile is a highly reactive aldehyde.[512–514]

Again, initial tests were performed on 4-*tert*butylcyclohexanone **77** before attempting to carry suitable conditions over to the cyclobutanone (Scheme 13):

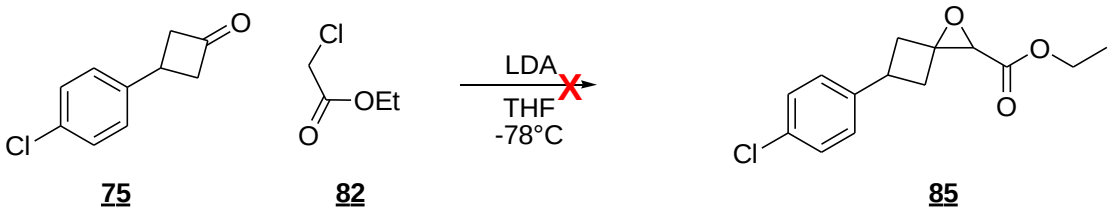


Scheme 100

At first, cheap chloroethanal **31** aqueous solutions were used. Being an aqueous solution, strong bases were obviously out of the question. The choice of the base was pondered along the following lines: the ketone isn't soluble in water and the chloroethanal is highly soluble. If a water soluble base was used, deprotonation and polymerization might occur in the aqueous phase. Therefore, it seemed that a biphasic media with a base more soluble in the organic fraction might be a good idea. Piperidine was tried for several days but to no avail. Triethylamine also gave no result over several days. It should be noted that GCMS of crude products gave no sign of chloroethanal which might indicate that polymerization and/or degradation has occurred. Attempts at extracting the chloroethanal with diethyl ether and then treating it with ^{t}BuOK were also unsuccessful.

Ethyl chloroacetate **82** was then tried since Darzens condensations with this compound have been described on cycloalkanones (by Darzens himself, a hundred years ago). Sodium ethoxide in ethanol, potassium tertbutanolate in tertbutanol both failed to react, however LDA at -78°C allowed for formation of **84** with a 77% yield. Two isomers were obtained (possibly cis and trans isomers) but only one could be obtained pure (the second one was in the same chromatography fraction as a part of the first isomer).

Once this method was established, the synthesis of **85** was attempted (Scheme 14):



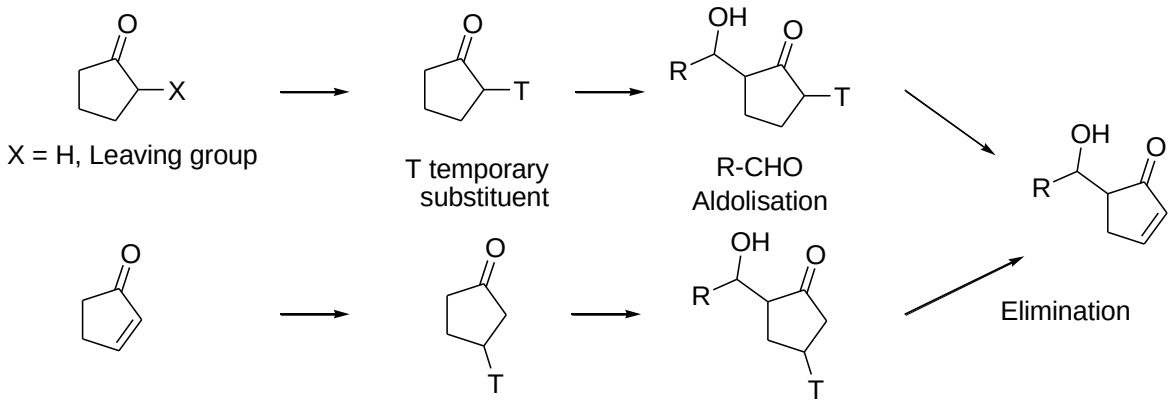
Scheme 101 Failed synthesis of 85

The reaction failed, product **85** was not found in the crude, a complex mixture of several products. It is possible that the product might be unstable and prone to various ring opening reactions. The starting material is stable, having stayed on the bench for two months without degrading.

This second chapter was also abandoned due to a lack of encouraging results; however the concept may be worth reactivating since not all possibilities were explored.

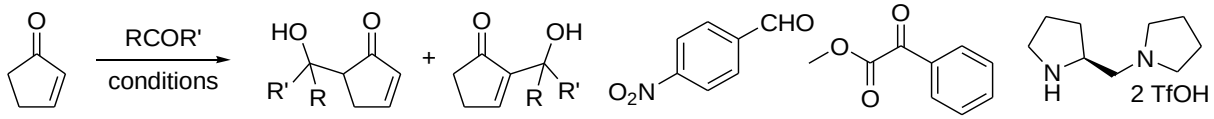
Reactions of heterosubstituted cyclopentanones

Our previous experiments showed that organocatalyzed aldolisation of cyclopentenone were unsuccessful. Since this was studied, Rouden *et al.* have described the use phosphoric acids for this transformation and have stated that enamine catalysis could not achieve what we intended.[455] Our object is to prepare appropriately substituted cyclopentanones, whereupon aldolisation could be regioselective and by a simple transformation, the substituent would be removed and the enone would be generated. The most simple solutions are the preparation of 2-substituted cyclopentanones (α halogenation, nucleophilic substitution,…) and 3-substituted cyclopentanones (Michael addition, …) which (in theory) should be easy to convert to enones (Scheme 15).



Scheme 102 Use of heterosubstituted cyclopentanones

Cyclopentenone **45** itself is a very poor substrate for aldolisation. Very few methods have been described to prepare 86; one involving DBU could not be reproduced. [195] Other methods involve expensive rhodium catalysts for example[515] or the previously mentioned phosphoric acids.[455] Nevertheless a few attempts were made with cyclopentenone (Scheme 107):



45 **86** **46** **87** **88**

Scheme 103

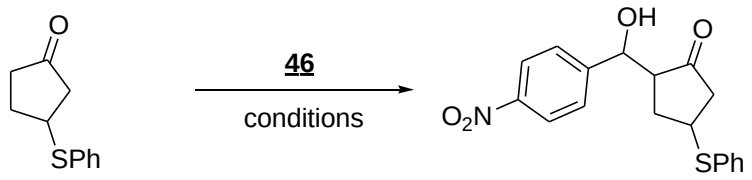
DBU failed to allow cyclopentenone to react with *para*-nitrobenzaldehyde **46** or methyl benzoylformate **87** contrary to results indicated in the literature. Quinidine also failed to promote the reaction. Diamine **88** was also tried, since it has been described as an organocatalyst for the Diels-Alder reaction of cyclopentenone (the mechanism necessarily passes by a dienamine so with

this catalyst we were “certain” that the species was formed, therefore the problem isn’t one of non-formation of the catalytic species).

The first attempt at using such heterosubstituted cyclopentanones was made with 3-thiophenyl cyclopentanone **89** (Scheme 108) which was prepared easily from cyclopentenone, thiophenol and a base. Triethylamine was used successfully in Et_2O and H_2O. L-proline in THF also furnished the expected product but as a racemic mixture. However, in all cases, the product would never be 100 % pure after chromatography due to an easy retro-Michael reaction. The thiophenol easily forms diphenyldisulphide (PhSSPh) in basic conditions. Both sulfur compounds are also prone to oxidation.

This is a problem because it means that unless the aldolisation reaction is very fast, retro Michael would keep the ketone from reacting as a donor. Furthermore it also means that the starting material would eventually degrade.

The reaction was attempted in various different conditions without success:



89 **90**

Scheme 104

Entry	Ketone (mmol)	Aldehyde (mmol)	Catalyst	Solvent	Conditions
1	1	1,1	L-proline 20 %	DMSO	r.t. 5 days
2	1	1,1	L-proline 20 %	THF/H_2O 4:1	r.t. 10 days
3	1	1,1	L-proline 20 %	DMF	r.t. 5 days
4	1	1,1	L-proline 20 %	THF/H_2O 4:1	r.t. 5 days
5	1	1,1	L-proline 20 % APTS 20 %	THF/H_2O 4:1	r.t. 5 days
6	3,5	0,7	L-proline 20 %	DMSO	r.t. 5 days
7	5	1	L-proline 20 %	DMSO	Slow add of ald. R.t. 2 d
8	5	1	L-proline 20 %	THF/H_2O 4:1→ 7:1	Slow add of ald. R.t. 2 d

9	1	1,5	TEA 2 eq	$MeOH/CH_2Cl_2$	r.t. 2 days
10	1		L-proline 1 eq, APTS cat.	$MeOH/CH_2Cl_2$	Aldehyde added after an hour
11	6,8	3,1	L-tryptophan 20 %	H_2O	r.t. 5 days
12	6,8	3,1	L-tryptophan 20 %	DMF	r.t. 5 days
13	6,8	3,1	L-tryptophan 20 %	neat	r.t. 5 days

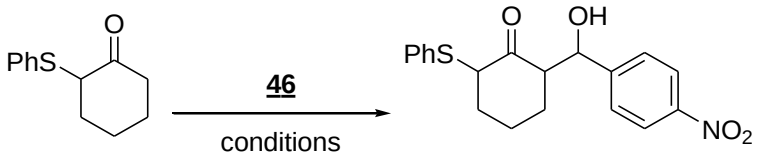
Table 5

Entry 9 led to the formation of the Baylis-Hillman adduct. Otherwise none of the conditions tried gave any sign of aldolisation.

This substrate was chosen in part because of likeliness to induce aldolisation on the other alpha carbon. However this substrate didn't work so research efforts moved to 2-thiophenyl compounds.

Such compounds could be prepared by nucleophilic substitution of α-halogenocycloalkanones. Initialy, 2-chlorocyclopentanone was not available so attempts were made to prepare 2-chloro and 2-bromocyclopentanone from the basic cyclopentanone with various halogenations methods (NBS, etc…). While the product was in each case detected, purification led to formation of 2-halogeno and simple cyclopentenone. Therefore, in the meanwhile, 2-chlorocyclohexanone was used and the 2-thiophenylcyclohexanone **91** could be obtained in 70-90 % yields when treated with KOH in EtOH.

This new substrate was then subjected to a battery of tests reactions to determine its scope. The results are summarized below:



91 **92**

Scheme 105

Entry	Ketone (mmol)	Aldehyde (mmol)	Catalyst	Solvent	Conditions
1	1,5	0,5	GONG 20 %	CH2CL2	6 days r.t.
2	1,5	0,5	L-proline 20 %	CH2CL2	6 days r.t.
3	2,5	0,5	L-tryptophan	H_2O	6 days r.t.

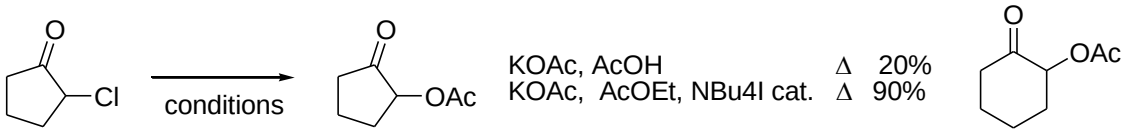
4	1,5	0,5	quinidine 20 %	CH2CL2 (water added day 8)	5 days r.t. + 4 days reflux
5	2	3	^{t}BuOK 2,2 eq	THF	- 20°C 1 hour
6	2,5	0,5	Gong catalyst 20 %	CH_2Cl_2	4 days -40°C .
7	2,5	0,5	L-proline 20 % CSA 10 %	H_2O	8 days r.t.
8	2,5	0,5	L-proline 20 %	DMSO	8 days r.t.
9	2,5	0,5	L-alanine 20 %	DMSO/H_2O	8 days r.t.
10	2,5	0,5	L-proline-tetrazole 20 %	CH_2Cl_2	7 days r.t.

Table 6

While some of the attempts appeared to give some traces products visible on TLC, nothing was ever detected by GCMS and the limiting aldehyde was never completely consumed.

This behavior could possibly be explained by a too great steric hindrance: the enamine could be not form or, being formed, could not react.

Based on earlier research on α-acetoxy ketones was shown that is could react as a donor for organocatalyzed reactions. The preparation of 2-acetoxycyclopentanone **94** is described from the chloro compound **93** but the conditions work poorly (refluxing in acetic acid gives 20 % yield). Several classic solvents were tried (EtOH, AcOEt) unsatisfactorily until a phase transfer agent (NBu_4I) was added in catalytic amounts. Typical yields with these conditions are around 85-90% (Scheme 17):

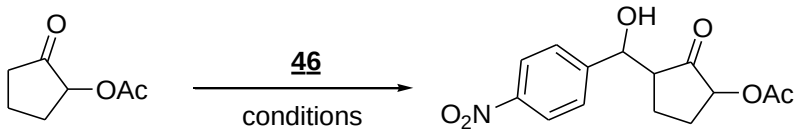


93 **94** **95**

Scheme 106

The method gave the same results with the 6 membered ring **95**.

With enough of this ketone, tests were performed and are summarized below:



94 **96**

Scheme 107

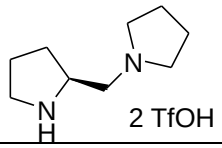
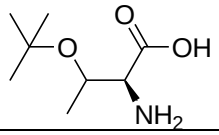
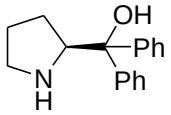
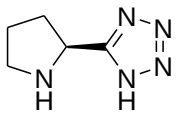
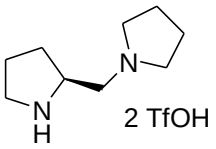
Entry	Ketone (mmol)	Aldehyde (mmol)	Catalyst (20 %)	Solvent	Time	Result
1	1.5	0.5	L-proline	CH2CL2	20 days	0 %
2	2	0.5		THF	5 days	0 %
3	2	0.5	L-proline	neat	1 day	48 %
4	2	1,5	L-proline	neat	2 days	89 %
5	2	0.5	L-tryptophan	neat	4 days	78 %
6	2	0.5	Quinidine	neat	1 day	60 %
7	2	0.5		neat	2 days	86 %
8	4	3	DL proline	neat	2 days	63 %
9	2	1		neat	5 days	0 %
10	2	0.5		neat	1 days	63 %
11	2	1	L-tyrosine	Neat	5 days	No reaction
12	2	0.5		Neat	2 days	81 %

Table 7

Most entries give positive if not interesting results. Entry 1 and 2 are coherent with past results that having neat conditions is a necessity for the reaction to occur. The proline and tryptophan entries show that these catalysts are usually good.

The problem in determining the use of these various catalysts is the high number of possible stereoisomers. To best of available knowledge, the compound formed is solely the α,α' aldol, so in a first approximation we can discard the α,α aldol isomers. That still leaves 3 stereocenters so 8 possible isomers. HPLC indicates that there are two major isomers (TLC also shows two spots) which have not been identified. HPLC also shows enones forming. In one experiment, a recristilization of the product was performed in EtOH/PeEther and the solid fraction was a mixture of aldol and

Mannich compound. At this point, nothing certain can be said about whether the enones are Mannich enones or cyclopentenone aldols, although the former seems more likely judging by the NMR (shifting in the aromatic peaks has been seen and the CH-OAc proton is always present).

This would not be a very serious problem if the stereochemical question could be postponed until the enone is formed (one stereocenter being removed). However many conditions have been tried on both the starting material (Al_2O_3, pyridine, DBU, Mg/THF, $ZnCl_2$, ^tBuOK, SiO_2/Δ) and aldol mixtures (Al_2O_3, NEt_3/KI, refluxing in toluene).

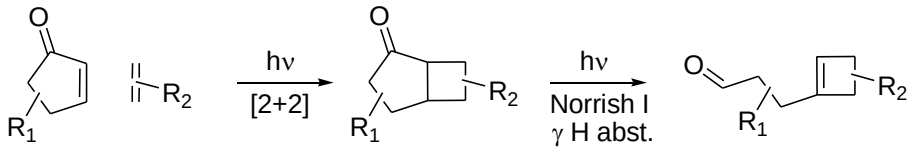
The alumina was a particular interesting solution because it is described as being able to transform a 2-acetoxycyclopentanone into the according enone in a steroid structure. It is possible however that the alumina used was the wrong type or needed some form of activation.

Conclusions and perspectives

This chapter concerned the work performed during the Cagliari mission of the SPOC project thesis work and aimed at providing the SPOC project with cyclopentenone aldols for photochemical applications. Unfortunately, none of the various projects bore any fruitful results. While the final project, using acetoxy cyclopentanones allows for formation of the aldol, the elimination has yet to succeed. A few things remain to be tried to remove the acetoxy, such as flash pyrolysis or possibly some form of palladium catalyzed elimination. It may be necessary to either find another ketone substrate (halogeno ketones could possibly be easier to react but their regioselectivity is expected to be on the wrong side). One important step is also the isolation of the various aldol isomers. Since satisfactory conditions have been found in HPLC, preparative HPLC is the logical step.

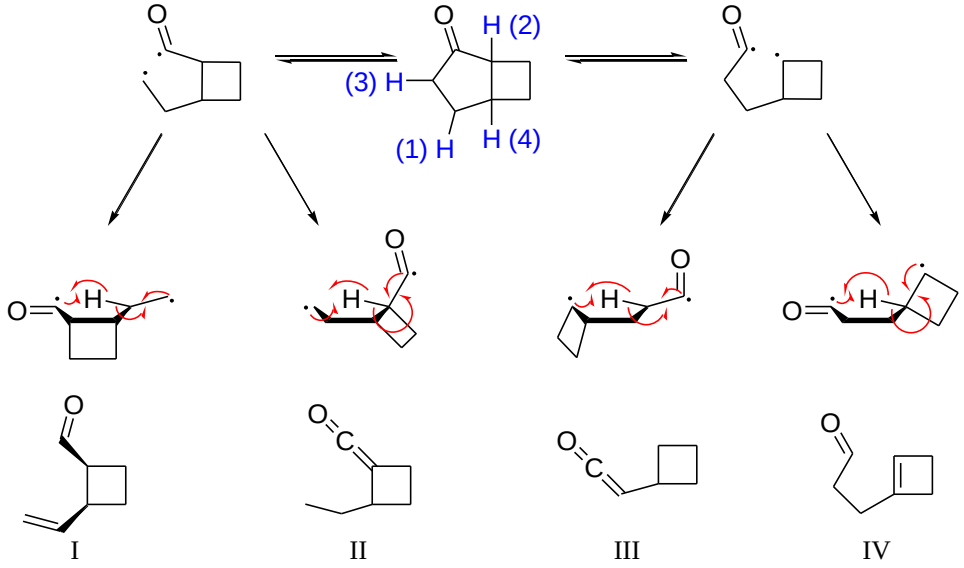
Chapter 4 Synthesis of cyclobutene aldehydes

As indicated in the introduction, the main obejective of this research project was the study of the hitherto unexplored tandem photochemical reaction of between cyclopentenones and alkenes leading to cyclobutene aldehydes. These species arise from two sequential photochemical processes: [2+2] photocycloaddition followed by Norrish I cleavage and then γ-hydrogen abstraction.



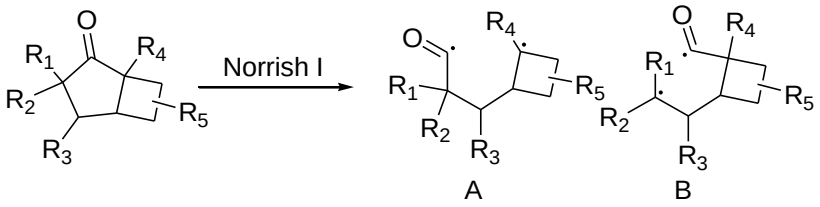
Scheme 108

As a standalone method, the tandem photochemical transformation remains largely unexplored and mostly unstudied. We embarked on a study of the scope and limitations of the transformation to establish whether it can be considered as a plausible tool in organic synthesis.
As previously mentionned, the fragmentation of the bicyclic ketone can go several ways in terms of Norrish I fragmentation.



Scheme 109

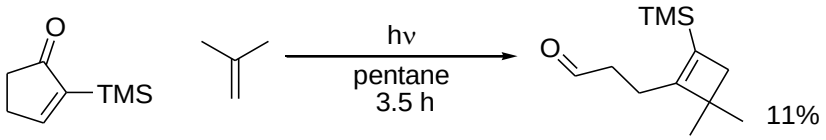
We focused our research project on cyclopentenones. This means that ketenes (II and III) are disfavored. This leaves the two aldehydes compounds:



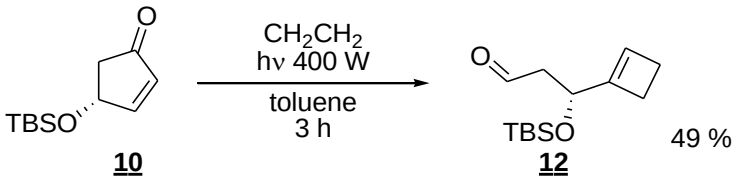
Scheme 110

Efficient photochemical processes along the desired reaction pathway (leading to the cyclobutene aldehydes) require that the regioselectivity of the Norrish I fragmentation of the initially formed bicyclic [2+2] adduct be towards the cyclobutene aldehyde. The regioselectivity of the Norrish I fragmentation is linked to the relative stabilities of the biradical species being formed.

Examing some of the results of the results in the literature, such as the irradiation of 2-trimethylsilylcyclopentenone XX and isobutylene decribed by Swenton[146,516], and the the previously discussed example (chapter 1, R_3=OTBS other R=H), the only observed product was the cyclobutene aldehyde deriving from biradal A.



Scheme 111



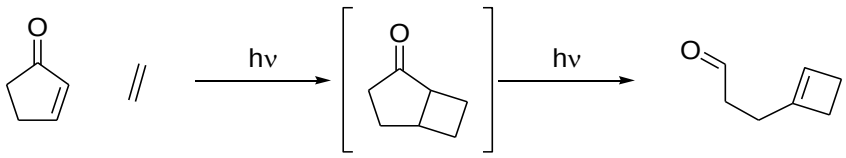
Scheme 112

This is logical in that methylene radical is less unstable than the cyclobutyl radical. However, should R1 and R2 be groups that might stabilize radicals (scheme 114), then a change in the regioselectivity might be observed, leading to products that would not be cyclobutene aldehydes. This raises the issue of 5-substitution for the cyclopentenones.

Our first objective was to **determine standard conditions for the tandem photochemical transformation** by optimizing various experimental parameters.

Initial investigations

For our first experiments, we decided to work with the simplest combination: cyclopentenone **45** and ethylene. The expected product was the simplest cyclobutene aldehyde.

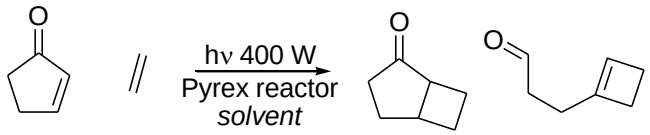


Scheme 113

Various solvents were used to conduct the following model reaction: 5 mmol of cyclopentenone are placed in 220 mL of solvent in the Pyrex photochemical reactor (details in the experimental section) and irradiation by a 400 W medium Mercury pressure light. The reaction was monitored by GC. The initial reaction mixture was sampled for reference before irradiation began and shows only one compound, cyclopentenone.

GC monitoring indicated that cyclopentenone is consumed upon irradiation. A new compound appeared rapidly: detected from 5 minutes irradiation time onwards. This is tentatively attributed to the bicyclic adduct XX. The relative proportion of this compound increases over the following hour (30-45 minutes in acetone, 1h in acetonitrile). During this time, a new compound, apparently more volatile than the bicyclic adduct (due to lower retention time), was detected. Barely present after 3h in acetone, but becoming the major component after 1h30 and then the only remaining compound in acetonitrile between 5h and 6h. The intermediate compound was confirmed as the [2+2] adduct based on GCMS analysis, proton NMR of crude mixtures and observed behavior (appearance and subsequent consumption). The final compound detected was identified as the cyclobutene aldehyde based on isolated samples: NMR, GCMS and injections of samples in the monitoring GC.

Quantitatively, the results are represented in the following table:

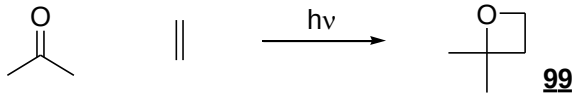


45 **97** **98**

Entry	Solvent	Time	Results
1	Toluene	1 h	Complete conversion. Cyclobutene aldehyde detected, but more volatile then solvant
2	Acetone	40m	Incomplete conversion. Ketone (≈ 90 %), SM, SM dimers
3	Acetone	3h	Complete conversion. Ketone XX and Päterno-Buchi adduct.
4	Diethyl Ether	3h	Complete conversion. Traces of cyclobutene aldehyde.
5	Cyclohexane	18h	Complete conversion. Degradation, no cyclobutene aldehyde detected
6	Acetonitrile	6h	Complete conversion. Aldehyde (82 %)

Table 8

Toluene (entry 1) proved to be an unsuitable solvent for this reaction in preparative mode due to difficulties in removing the solvent without simultaneously removing the cyclobutene aldehyde or degrading it. Distillation of the aldehyde out of the solvent was not possible due to a too small concentration of products (0.02 mol/L). In acetone (entries 2 and 3), the reaction conversion of the cyclopentenone to the bicyclic adduct was successful but the cyclobutene aldehyde was not observed unless irradiation is prolonged. In this case, the cyclopentenone was consumed entirely, but the recovered mass was well in excess of the maximum theoretical mass (several grams instead of 700 mg) and the analysis of the crude mixture (proton NMR and GCMS) suggested that the major reaction product in acetone is a Paterno-Büchi oxetane adduct **99** arising from the reaction between acetone and ethylene being bubbled. [114,517]



Scheme 114

Diethyl ether and cyclohexane (entries 4 and 5) proved to be poor solvents for this reaction: cyclobutene aldehyde could never be detected as a major compound, even with prolonged irradiation. Acetonitrile, described by Carless in his work with cyclobutene aldehydes arising from photochemical reactions[518], and proved to be successful, yielding 82% with careful evaporation of the solvent and without further purification.
In his experiments, Carless carried out his reactions in a Quartz reactor vessel, however our tests in acetonitrile with such reactors yielded similar results to our experiments in the Pyrex reaction. We decided to carry out all experiments in the Pyrex reactor. The addition of photosenstizers (acetophenone, benzophenone) in acetonitrile was investigated but the results were again similar. We deemed photosensitizers unnecessary and only complications for the purification of the final reaction mixture. Therefore, they were never used for the tandem transformations.

Further experiments were carried out in these conditions: 6h of irradiation in acetonitrile with 10 equivalents of alkene partner.

Two simple alkenes were then investigated: tetramethylethylene (TME, also 2,3-dimethylbutene) and cyclopentene.

Our first experiments with TME were carried out in the above mentioned conditions. GC monitoring identified one intermediate compound detected during the first hour of irradiation, assumed to be the [2+2] adduct of the cyclopentenone and TME. However, prolonged irradiation gave a mixture of several newcompounds. The crude mixture contained, based on the proton NMR, two aldehydes : the expected one (as indicated by a triplet proton signal for the aldehyde proton) and another (a doublet for the aldehyde proton).

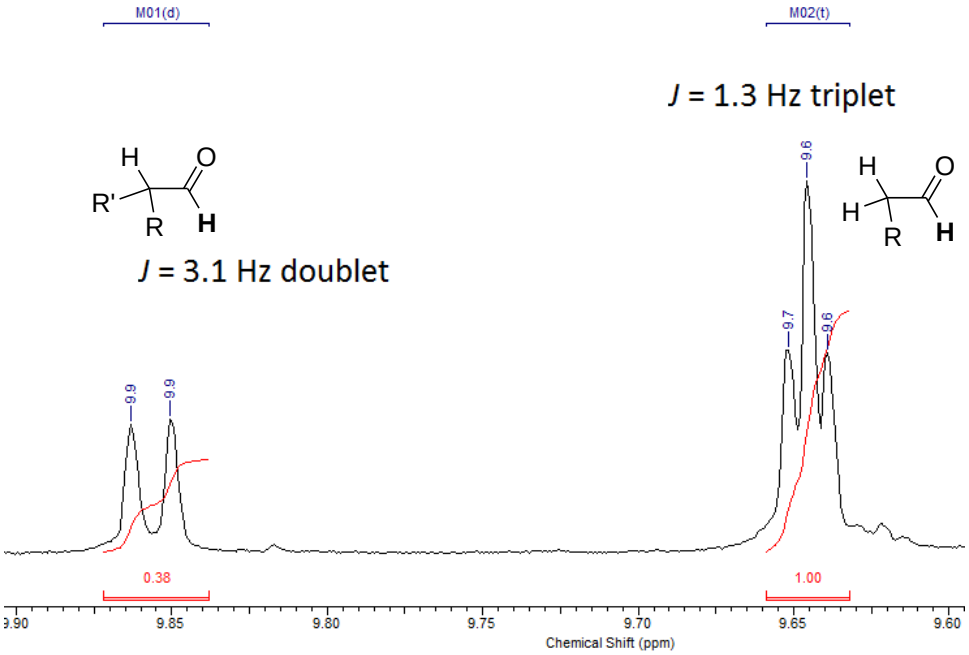
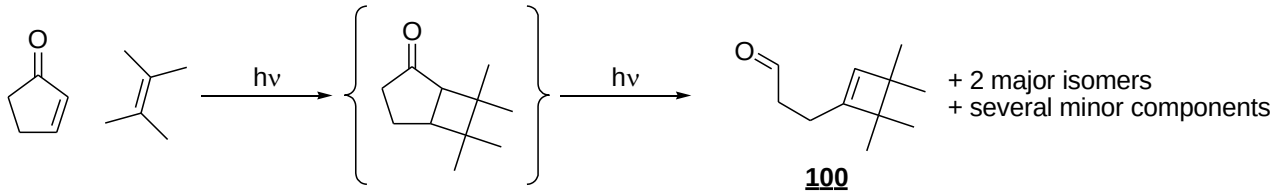


Figure 15

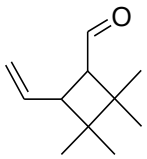
Several other compounds are also present: a total of 3 major [1:1] compounds (including the expected aldehyde) and several smaller components (a mixture of [1:1] and [1:2]). The recovered mass was close to the expected mass, indicating very little loss of material. The mixture proved to be inseperable by chromatography or distillation. GCMS identified the major compound as a [1:1] adduct, NMR identified it as the expected aldehyde.



100

Scheme 115

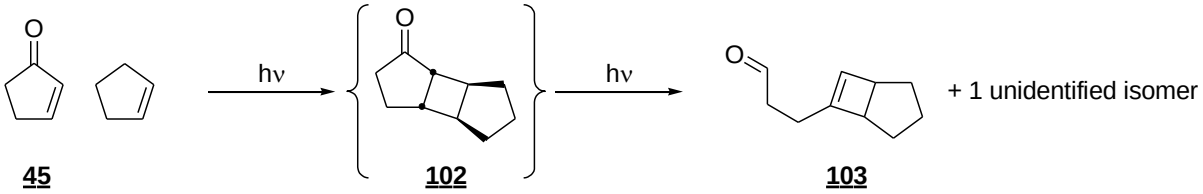
Proton NMR of the crude reaction mixture showed two aldehyde signals (figure 7): one was the expected triplet ($CH_2C\mathbf{H}O$) but the second was a doublet that was consistent with a C**H**CHO. GCMS suggested this compound be a structural isomer. The structure was tentatively proposed to be the regioisomeric alkene-aldehyde **101**, resulting from α cleavage pathB (scheme 114).
While the extant standard conditions provided the expected aldehyde, it was contaminated by several inseparable and unidentified compounds.



101

Figure 16

We investigated the reaction between cyclopentenone and cyclopentene, also carried out in the following conditions: 6h of irradiation in acetonitrile, monitored by GC.



45 **102** **103**

Scheme 116

Initially, we thought we had succeeded in replicating the success of the reaction with ethylene: the [2+2] adduct **102** formed in the first hour (it was identified by GCMS and NMR) and its disappearance was monitored by GC and the same time as a new component appeared by prolonged irradiation. It appeared that one major compound was formed based on GC and TLC analyses and NMR seemed to indicate this compound was the cyclobutene aldehyde. The ^{1}H NMR spectra showed a series of signals appropriate for the structure of cyclobutene aldehyde **103**: an aldehyde carbonyl at 200 ppm and two sp^{2} carbons at 150 and 130 ppm consistent with a cyclobutene. Other compounds appear as a few signals in the 4-5 ppm (CH-heteroatom) and a slightly higher integration in the alkyl peak region. This would have been consistent with a product tainted with slight degradation products. However, GCMS indicated that only isomers of [1:1] adducts were present: two major products and one minor product in roughly 5:4:1 proportions. The cyclobutene aldehyde seems to be the major product: almost 60 % based on the GC and GCMS. Furthermore, the ^{13}C NMR is revealing: the cyclobutene aldehyde was indeed present but was accompanied by another major compound. It could not be identified at the time (see the following chapter). Attempts to purify the cyclobutene aldehyde by chromatography failed. Bisulfite purification was unsuccessful. Distillation was only partially successful: only small amounts of the cyclobutene aldehyde could be recuperated. The other compounds degraded.

It is important to note at this point that two sets of diagnostic ^{13}C signals can be identified here: the cyclobutene aldehyde can be detected with a CHO at 200 ppm, a quaternary sp^{2} carbon at 150 ppm and a CH sp^{2} carbon at 130 ppm. The second compound can be detected by the presence of CH-heteroatom sp^{3} carbons around 90 ppm. The integration of the 4-5 ppm signals allows for quantification of the second compound. The minor compound was visible in the NMR spectra, with diagnostic peaks in the same areas as the major non-cyclobutene aldehyde product (87.7 ppm and 87.6 ppm for the latter, 88.3 ppm and 77.8 ppm for the former).

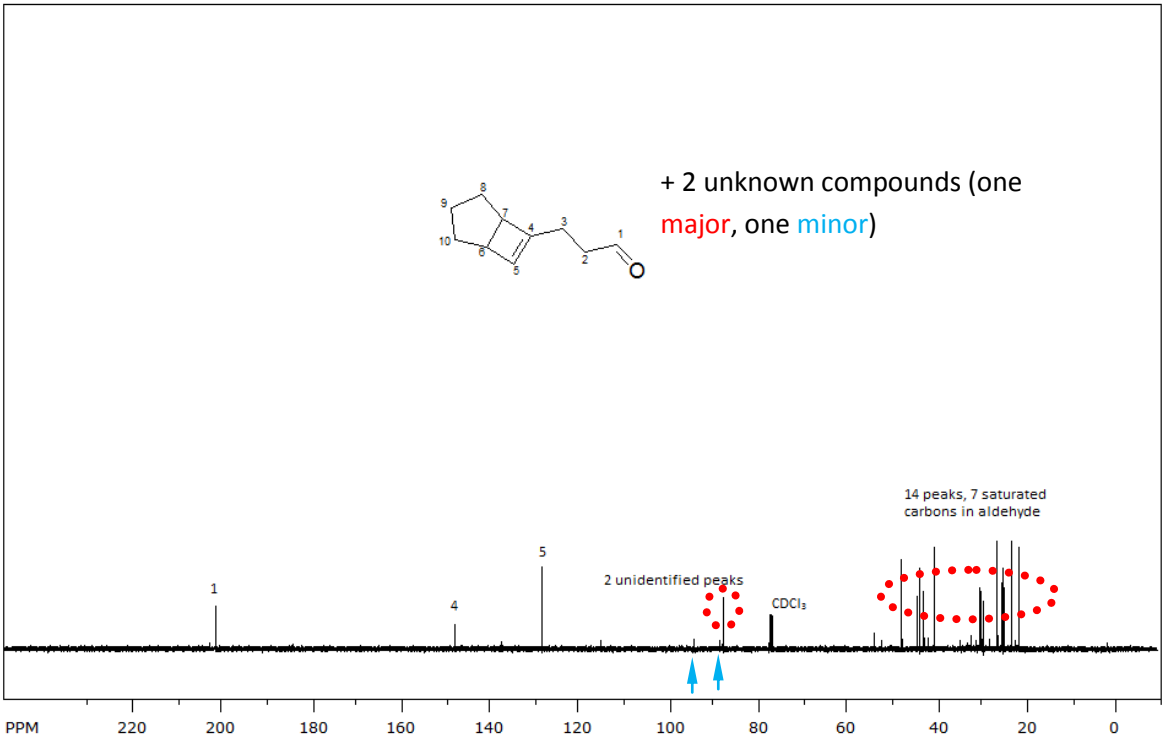


Figure 17

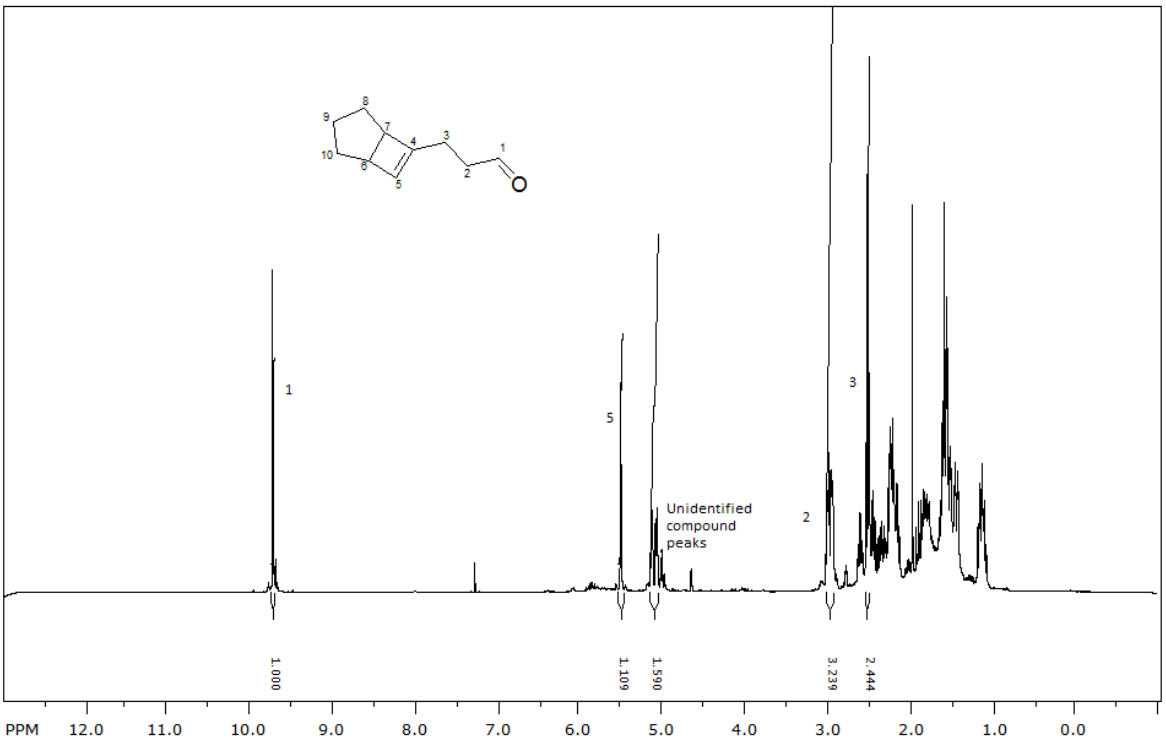


Figure 18

After this first set of experiments, we concluded that the presence of both these secondary products was reproducible and unavoidable. Our first experiments with ethylene as the alkene partner had led us to excessive optimism as regards to the simplicity of the tandem photochemical transformation. The reaction with TME proved more complex than the one with cyclopentene and we therefore decided to reinvestigate the reaction conditions, this time working with cyclopentene and cyclopentenone as reference compounds. This was expected to make product isolation simpler, since the cyclobutene aldehydes are volatile species.

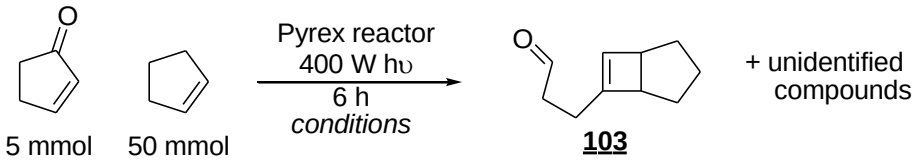
Optimization of the reaction conditions

Without knowing the identity the secondary compounds, we explored various parameters with a view to increase the yield and purity of the cyclobutene aldehyde **103**. Several options were considered in the photochemical reaction of cyclopentene and cyclopentenone:

- Modification of the reaction conditions: change of solvent and/or presence of additives to inhibit further reactions or degradation of the cyclobutene aldehyde
- The cyclobutene aldehyde could be transformed *in situ* to a derivative, possibly altering reaction patterns.

The first objective required better optimization of the solvent conditions. As previously mentioned, extensive NMR analyses of mixture indicated that the unidentified signals can be attributed to CH-Heteroatom protons and allows for quantification. By comparing the average integration of the aldehyde proton and alkene proton peaks, and the average integration of the unidentified peaks, a close relative proportion of each compound could be determined. The following standard reaction was run in various solvents: 5 mmol of cyclopentenone and 50 mmol of cyclopentene (10 equivalents) were placed in 220 mL degassed solvent in the Pyrex photochemical reactor. After 6 hours of irradiation with the 400 W medium-pressure Mercury lamp, the solvent was removed by careful evaporation and the crude mixture examined by proton NMR.

The results of these investigations are summarized in the following table.



103

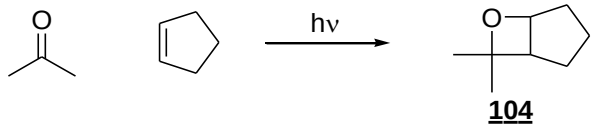
Entry	Solvent	% Aldehyde	% Unknown Compounds
1	Dichloromethane [a]	50	50
2	Toluene [a]	50	50
3	Cyclohexane [a]	47	53
4	Acetonitrile [a]	54	46

5	Acetone [b]	n/a	
6	Methanol [a]	82	18

a Recovered mass was >95% of expected mass for 5 mmol of cyclobutene aldehyde ***b*** Recovered mass was well in excess of expected mass, with an estimated 80 % being products of photochemical reactions of the solvent

Table 9

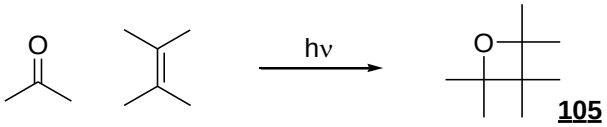
Reactions performed in dichloromethane, toluene, hexane and acetonitrile (entries 1 to 4) gave roughly equal proportions of cyclobutene aldehyde and other products. Acetone (entry 5) was a poor choice solvent, for the same reasons mentioned previously: a Paterno-Buchi side reaction occurs between acetone and cyclopentene.



104

Scheme 117

While the crude reaction mixture showed evidence of compound **104**, we experienced difficulties in obtaining an analytically pure sample of the oxetane contaminant. However, comparable experiments carried out with TME furnishing a crude mixture containing the hexamethyloxetane **105**. We were able to obtain an analytically pure sample of the latter.

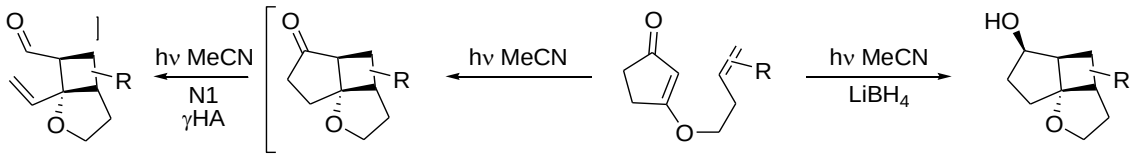


105

Scheme 118

Significantly and to our delight, methanol proved to be a notably better solvent for the clean formation of the cyclobutene aldehyde. Indeed the relative proportion of target compound was notably higher, yielding a mixture comprised of 82 % cyclobutene aldehyde. It was conluded that methanol is a better solvent for the tandem photochemical transformation and should be retained for the improved standard conditions.

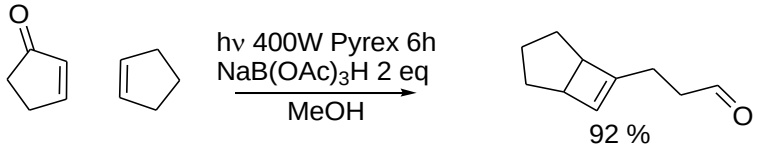
At this point, the other products are still present and the problem of separation remains. Reduction of the aldehyde to the alcohol would increase the polarity of the species and hopefully allow for separation. While reduction of the cyclobutene aldehyde is possible working on the crude, we felt that *in situ* reduction would be more efficient. Reducing the cyclobutene aldehyde as soon as it forms could possibly limit or even stop the formation of the other products.
The trapping of photochemical transformation products to avoid extraneous reactions is a time-tested strategy.[40,147,519] Of particular interest is the work of Baker *et al*. concerning the reduction of [2+2]-adduct ketones to alcohols to avoid Norrish I processes.[520]



Scheme 119

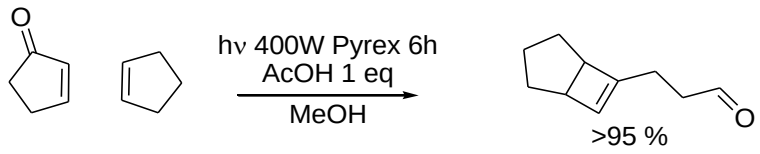
We decided to attempt the reduction of the cyclobutene aldehyde as it was being formed during the photochemical transformation. However, the required reducing agent should reduce the cyclobutene aldehyde without reacting with cyclopentenone or the bicyclic ketone. Selective reduction is a major tool in modern organic synthesis[161,521–524] and sodium borohydride ($NaBH_4$) was described as being efficient to reduce the bicyclic ketones used by Baker *et al* without affecting the cyclopentenone. However, we require a selective reduction of the more reactive aldehyde rather than the ketone species: candidates for such a smooth reduction include 9-borabicyclo[3.3.1]nonane-pyridine[525], sodium cyanoborohydride[526–529] and sodium triacetoxyborohydride.[530–532]

The two borohydride reagents were investigated. The photochemical reaction was set up normally (5 mmol cyclopentenone and 50 mmol of cyclopentenone in methanol or acetonitrile) with 2 equivalents of reducing agent that were added to the photochemical reactor prior to irradiation. The reaction was run for 6 hours, worked up and the crude reaction mixture analyzed.
We ran our first tests in aceonitrile, with the twin objective of obtaining enough of the unknown compound for analysis (see chapter 5) and having a sufficient proportion of unwanted compound to observe the effects of the reducing agents on the product distribution.
In acetonitrile, treatement after irradiation consisted in removing the solvent by rotator evaporation, taking up the crude in diethyl ether and removing boron salts by filtration.
While the use of sodium cyanoborohydride led to complex and unidentifiable mixtures, sodium triacetoxyborohydride gave us an interesting result: cyclobutene alcohol was obtained in roughly 45 % proportion of the crude and the other compounds were obtained in roughly 55 % total. Furthermore, the component mixture was easy to separate by TLC (7/3 pet. ether/diethyl ether): 0.17 Rf for the alcohol, and 0.6 and 0.63 for the two other compounds. We then performed the tandem photochemical transformation/reduction sequence in methanol with sodium triacetoxyborohydride as the reduction agent. For this reaction, workup consisted in removing most of the solvent after the reaction, adding water to quench, extracting with diethyl ether, drying with magnesium sulfate and evaporation. We were most surprised to find that the crude seemed to contain only cyclobutene aldehyde, traces of acetic acid and very limited traces of the unknown side product, based on NMR analysis. This slightly impure material nonetheless represented a 92 % isolated yield of cyclobutene aldehyde.



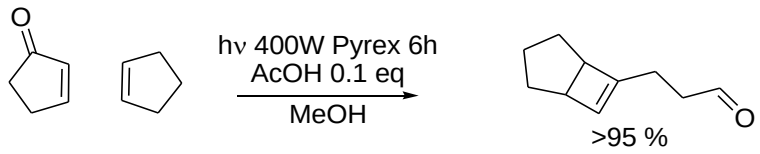
Scheme 120

On a first assessment, it seemed that the borohydride reagent had not had any effect at all. However this was not quite true, since the yield of isolated aldehyde had actually increased with respect to the previous reactions run in the absence of reducing agent. The presence of acetic acid in the crude product mixture (and a slight smell of acetic acid in the bottle of reducing agent) moved us to investigate a possible role of acetic acid during the photochemical reaction. The reference reaction was run with 1 equivalent of acetic acid in methanol. The acetic acid was added with the methanol, degassed together and removed by evaporation. The crude reaction mixture was then analyzed by NMR.



Scheme 121

Traces of acetic are still present, but the crude reaction mixture was otherwise pure cyclobutene aldehyde, with infinitesimal traces of the other products. The recovered yield was almost quantitative. We sought to optimize the amount of acetic acid: the less acetic acid added, the less will have to be removed. The excess acetic acid was removed by dissolving the crude mixture in diethyl ether and stirring it with sodium hydrogenocarbonate.
The standard reaction (5 mmol cyclopentenone, tenfold cyclopentene) was run once again but with 0.1 equivalent of acetic acid. This procedure proved to be highly successful, which allowed for easier removal of the acid. Indeed, at such low concentrations, the acid was removed with the methanol by evaporation.



Scheme 122

The same experiment was run with 24 hours of irradiation but the product distribution in the crude material appeared not to change. We were satisfied with 6 hours of irradiation and deemed longer irradiation time to be unnecessary.

Our optimized conditions are **6h of irradiation in methanol with 0.1 equivalents of acetic acid and lead to almost quantitative yields of pure cyclobutene aldehyde without any purification**.

In order to study the origins of the favorable role played by acetic acid, we performed some NMR experiments. The cyclobutene aldehyde **103** was studied in deuterated chloroform and in deuterated methanol.

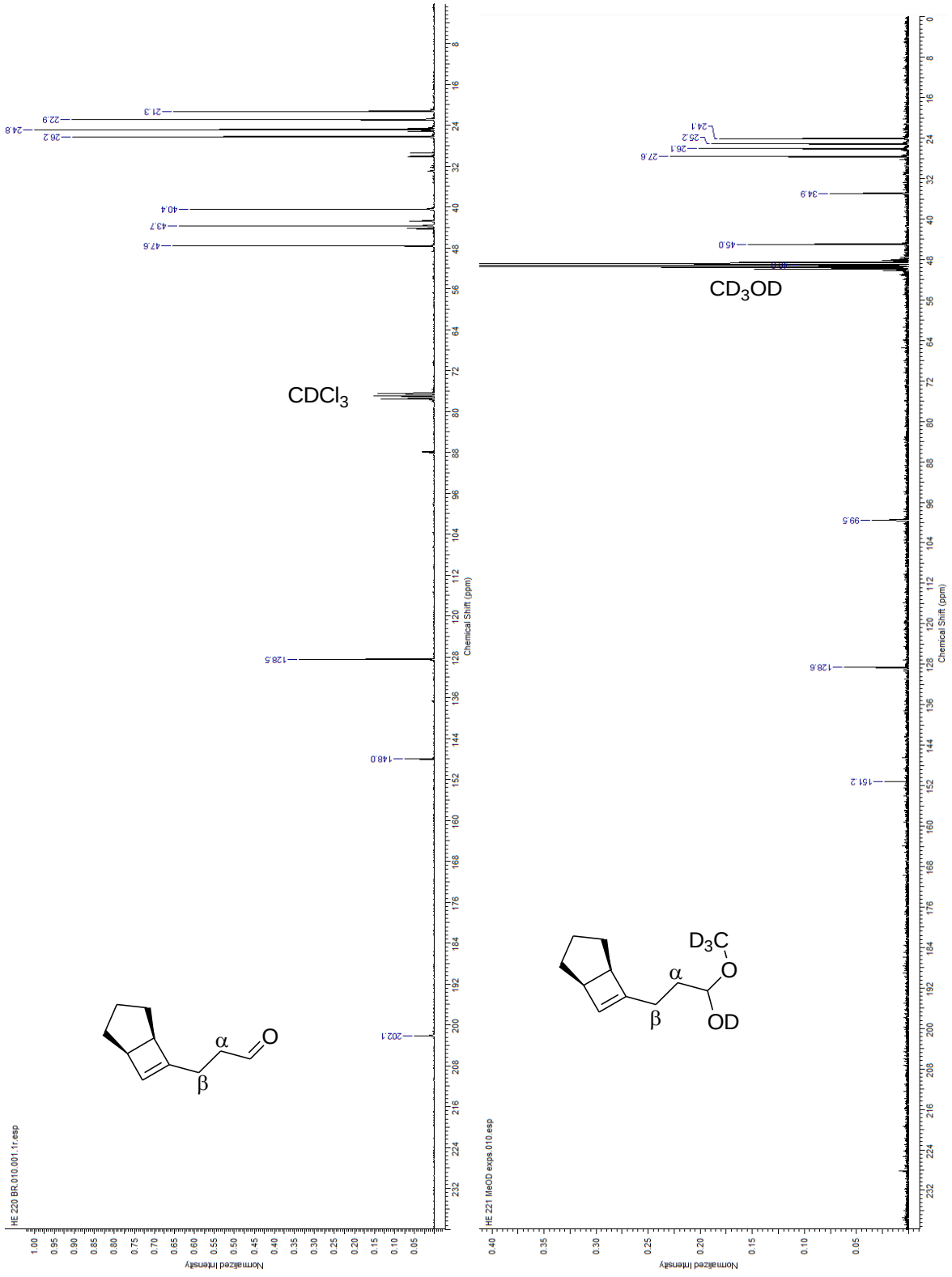
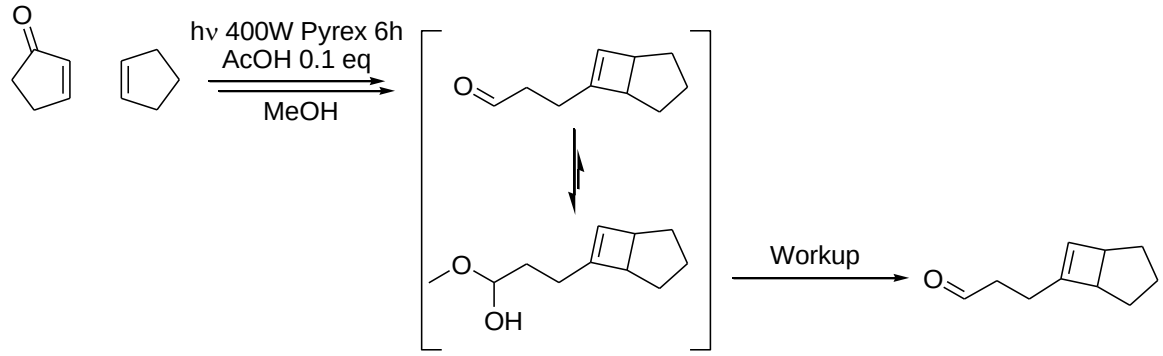


Figure 19

In $CDCl_3$, the signal of the aldehyde carbon of **103** appeared around 200 ppm. In CD_3OD, the signal disappears and was replaced by a signal at 99.5 ppm, consistent with a hemiacetal. J-MOD experiments confirmed the new peak as a CH. The displacement of the α- carbon also shifted: the α carbon went from 40.5 ppm to 34.9 ppm, consistent with a lessened electronic pull. Therefore, it is likely that in methanol, the cyclobutene aldehyde exists largely as a hemiacetal. The hemiacetal is a

less reactive function than an aldehyde and has no low energy chromophore. In methanol, the tandem photochemical reaction of cyclopentene and cyclopentenone leads to the cyclobutene hemiacetal which then reverts to the cyclobutene aldehyde when the methanol is removed. The reaction in presence of triacetoxyborohydride yielded the cyclobutene aldehyde after work-up, because the hemiacetal does not react with the borohydride: the traces of acetic acid may facilitate the hemiacetal formation.



Scheme 123

Tandem reactions are of interest if the one pot transformation is more efficient than two separate transformations performed back-to-back. We prepared the [2+2] adduct of cyclopentenone and cyclopentene by a short irradiation in acetone[126]: 3 hours of irradiation were necessary in the large photochemical reactor (all other reactions are run in a small photochemical reactor, 3 hours would equate to roughly 45 minutes or 1 hour) working with acetone to react 40 mmols of cyclopentenone with cyclopentene to obtain the bicyclic adduct **102**. The latter was isolate by chromatography to give a final yield of 54 %. It should be noted at this point that only one diastereoisomer is obtained, the *cis-anti-cis* or *exo* adduct. This selectivity is due to the formation of only one triplet transition state during the reaction (chapter 1, figure 1):

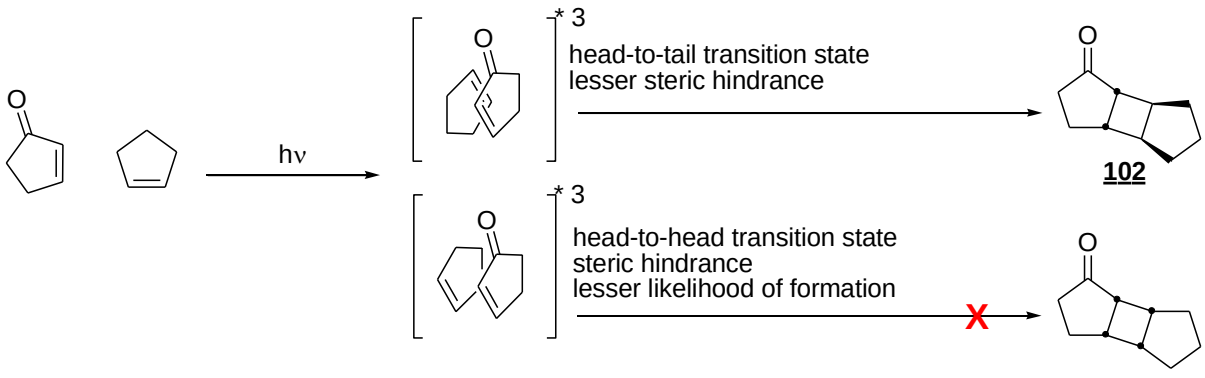
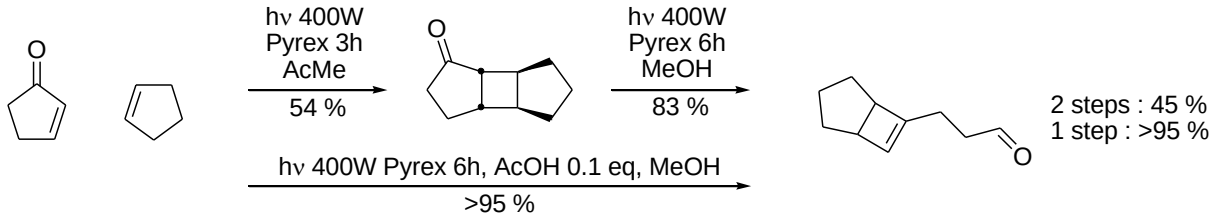


Figure 20

The isolation of the ketone is inefficient, the yield is moderate at best. This can be explained by pollution of the crude reaction mixture by Paternò–Büchi products between acetone and cyclopentene and further (and unwanted at this point) reactions of the ketone. Chromatography was necessary at the end of the first reaction to obtain a pure sample of ketone **102**. The bicyclic ketone was then irradiated in methanol for 6 hours, yielding 83 % of highly pure cyclobutene aldehyde **103**.

On the whole, the total reaction time is longer, the whole process is much less efficient in a sequential fashion than in a tandem sequence.



Scheme 124

At this point, we have considered that **the best way to prepare cyclobutene aldehyde was the 6 h hour irradiation of cyclopentenone and alkene in methanol, with the possibility of including 0.1 equivalents of acetic acid in the reaction mixture to increase selectivity.**

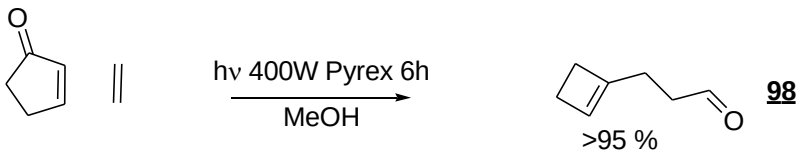
Extension to other substrates

We next sought to apply the tandem photochemical reaction to other substrate combinations in order to assess the broader scope and limitations of the reaction.

First trials

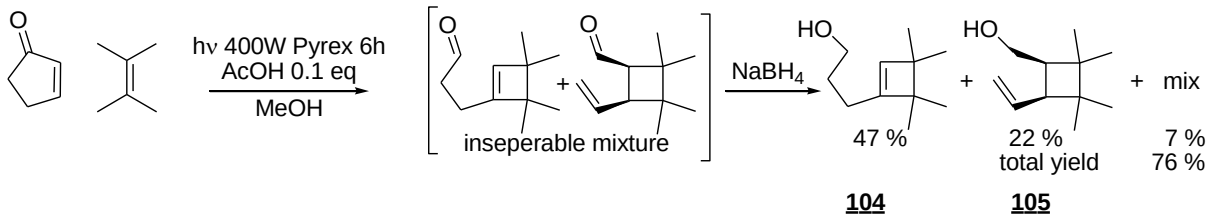
With these conditions in hand, we turned to the most two previous reactions involving two basic alkenes: ethylene and TME.

The reaction with ethylene was run first in the presence of 0.5 mmol acetic acid in the extant standard conditions: ethylene was bubbled through a methanol solution of 5 mmol of cyclopentenone and irradiated for 6 hours. Acetic acid proved to be a difficulty since its removal by evaporation also induced evaporation of the volatile cyclobutene aldehyde. The reaction was run successfully in methanol (without acetic acid) and did not appear to generate a secondary product. The pure product **98** was obtained with an excellent yield (> 95 %). No chromatography was necessary.



Scheme 125

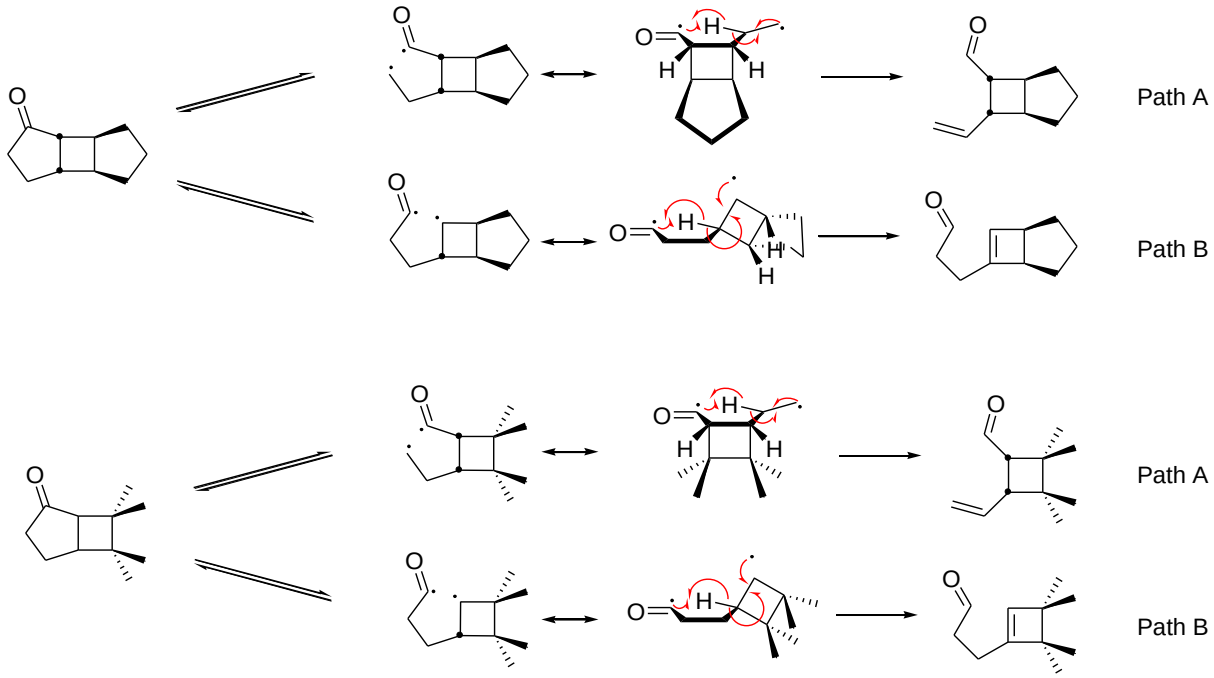
The reaction was next conducted with cyclopentenone and a tenfold excess of TME.



Scheme 126

Tetramethyethylene reacted with cyclopentenone in methanol in the presence of acetic acid (10 %) to give a mixture of two aldehydes, identical those previously obtained in obtained in reactions run in acetonitrile (see scheme 119). The crude yield was close to 100%, but the aldehydes proved to be inseparable by chromatography, while distillation degraded the compounds.
However, when the reaction was repeated and 2 equivalents of sodium borohydride were added to the reaction mixture after the end of the irradiation period, two partially separable alcohols were obtained. One, **104**, was the reduction product of the expected cyclobutene aldehyde. The other, **105**, was a structural isomer deriving from an alternate Norrish I fragmentation pathway leading to a 2-vinyl cyclobutylcarboxaldehye, thus confirming the structure presented in figure 8.

The difference in the reactivity observed for cyclopentene and TME can be explained by considering the intermediate biradicals.



Scheme 127

After Norrish I fragmentation of the [2+2] adduct, the biradical undergoes γ-hydrogen abstraction to yield the cyclobutene aldehydes. According to the literature, the biradical species reacts through a five-centered intermediate state.[56,138,533] Five membered rings are also described to generally not lead to ketenes, therefore only the two aldehydes paths (noted A & B here) are considered. For the

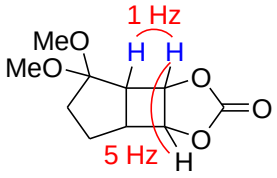
cyclopentene adducts: there is only one [2+2] adduct, the *cis-anti-cis* tricyclic ketone, and only one aldehyde is detected. The chain (either the alkyl radical or the acyl radical chain) is therefore always *trans* to the the cyclopentane ring. There is little steric hindrance in either intermediate of pathways A or B for cyclopentene. The relative stabilities of the radical species (pathway A is a primary radical, pathway B is a cyclobutyl secondary radical) favor the cyclobutene aldehyde. However, with TME, both intermediates have non-negligible steric hindrance between the methyl groups and the chains and the carbonyls. This adds to the instability of the radical species, rendering the relative energy difference between the two pathways lower, and thus allowing for both products to be obtained. The cyclobutene aldehyde is still favored, due to a more stable intermediate.

This first round of extensions have comforted us in our selected conditions for the tandem photochemical [2+2]/Norrish I/ γ-hydrogen reaction with simple substrates. **6 hours of irradiation in methanol appeared to give the best results** in terms of isolated cyclobutene aldehydes (or derivatives thereor). However another problem has been identified: the regioselectivity of the Norrish I fragmentation in the region between cyclopentenone and TME is not as onesided as for ethylene and cyclopentene.

Variations on the alkene partners

Unsubstituted cyclopentenone was retained the evaluation of the tandem photochemical transformation with a selection of simple alkenes. These alkenes were selected amongst those reviewed as being established partners for the [2+2] photocycloaddition.[11] We selected alkenes which should lead to multifuctionnal cyclobutene aldehydes.

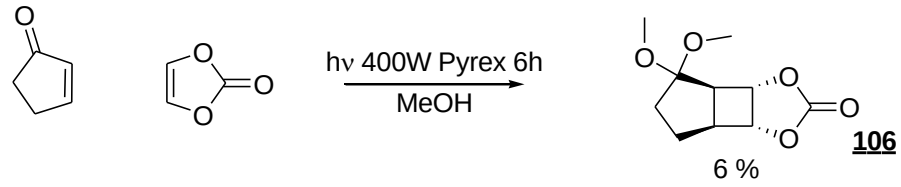
Vinylene carbonate is commonly used in photochemical reactions.[534,535] We irradiated 5 mmol of cyclopentenone in methanol for 6 hours in presence of 50 mmol of vinylene carbonate. We did not observe any indication of a cyclobutene aldehyde. However our experiments exposed a problem with vinylene carbonate: a reaction did occur but at an substantially lower reaction rate. Furthermore, only the dimethyl acetal of the [2+2] adduct **106** was isolated (6 % yield) by chromatography from the crude reaction mixture that was unfortunately clouded by unreacted alkene that could not removed by evaporation. The presence of two methoxy groups and the *cis-anti-cis* configuration is supported by ^{1}H NMR: a J = 1 Hz coupling between the bridgehead protons on different five membered rings and J = 5 Hz for the others. nOe experiments were also carried out, they showed no spatial coupling between the two hydrogen blue in the scheme below. However, the absence of interaction is unconclusive in nOe experiments.



Scheme 128

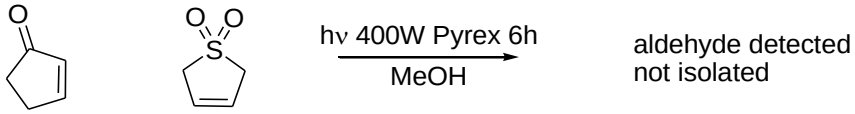
We attribute the slow reaction to a concurrent absorption of the incident irradiation to the cyclopentenone by the carbonate. Prolonged irradiation (more than 16h) degraded the reaction

products. This is unsurprising considering that carbonate can undergo photochemical extrusion of carbon dioxide.[536–538] Acetic acid was not employed at this point because none of the secondary products (identifiable by the 80-85 ppm CH signals in ^{13}C) was detected.

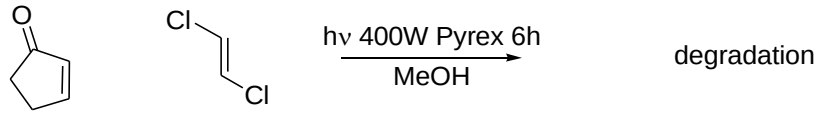


Scheme 129

Sulfolene (50 mmol) was reacted with 5 mmol cyclopentenone in the standard methanol conditions, an aldehyde could be detected (CH=O signal detected around 200 ppm in the ^{13}C NMR spectra of the crude reaction mixture) but the large amount of unreacted sulfolene could not separated from the cyclobutene aldehyde. The problem of alkene removal encouraged us to abandon the use of this alkene.

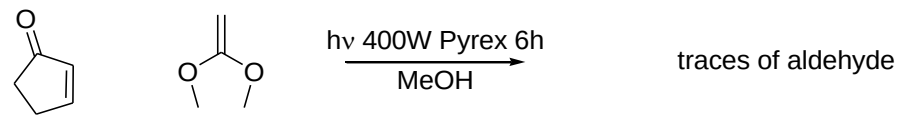


Irradiation of 5 mmol of cyclopentenone with 50 mmol of 1,2-dicholoroethylene failed to give a cyclobutene aldehyde. Analysis of the crude reaction mixture showed a plethora of signals in the alkyl region but no signals that were characteristic of an aldehyde or an alkene. The data would have been consistent a [2+2] adduct, however no carbonyl signals were detected upon ^{13}C analysis. The [2+2] reaction was been described, therefore it possible that the crude reaction mixture is composed of degradation products of the [2+2] bicyclic ketone. Since no aldehyde was detected, acetic acid was not investigated as an additive.



Scheme 130

Finally, DME (dimethyl ketene acetal or 1,1-dimethoxyethylene) and cyclopentenone irradiated in methanol with a tenfold excess of alkene for 6h. Aldehydes were detected: ^{13}C and ^{1}H analyses of the crude reaction mixture showed that the cyclobutene aldehyde was being formed, albeit in trace amounts. Alkene signals were also present indicating that a cyclobutene aldehyde was likely present. Acetic acid was not employed at this point because none of the signals attributed to the unknown compound (identifiable by the 80-85 ppm CH signals in ^{13}C) were detected.



Scheme 131

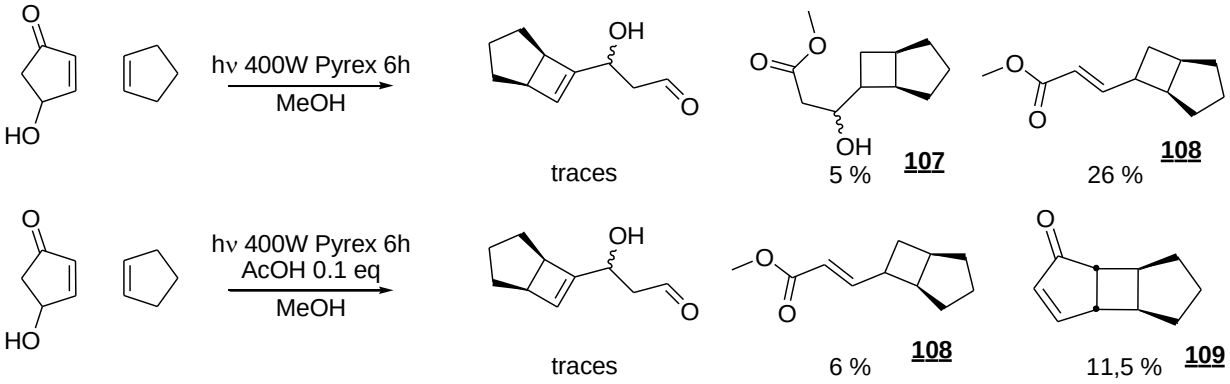
To conclude these first experiments with our selected standard conditions (5 mmol cyclopentenone, 10 equivalents of alkene, 6 hours of irradiation in methanol), we were disappointed to observe that no cyclobutene aldehydes were being formed in large proportions when functionalized alkenes were employed on substrates. We therefore decided to retain simple alkenes as reaction partners and investigated the scope of functionality on the cyclopentenone partner instead.

Variations on the cyclopentenone

Cyclopentenone have an extensive chemistry that was reviewed in chapter 2. We sought to explore the scope and limitations relative to the cyclopentenone partner. The three simple alkenes, first and foremost, cyclopentene, were reacted with the substituted cyclopentenones in the selected conditions: 6 hours of irradiation in methanol. Acetic acid remains a potential additive.

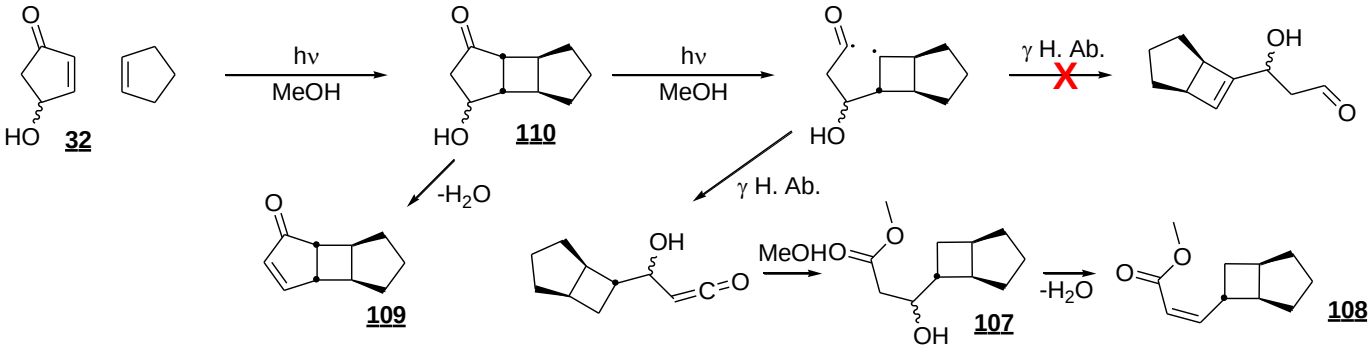
4-hydroxy cyclopentenone and its tertbutyldimethylsilyl ether cyclopentenone were readily available for tests. Furthermore, the prior experiments uncovering the tandem transformation carried out by Dr Le Liepvre[135] were with cyclopentenone **10** (see scheme 22).

4-hydroxycyclopentenone **32** was irradiation in presence of cyclopentene (tenfold excess) in methanol for 6 hours. The reaction was carried out both and without acetic acid.



Scheme 132

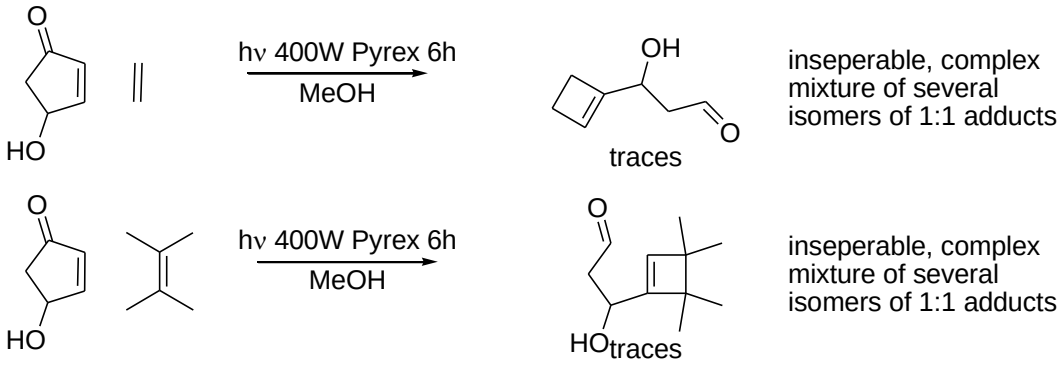
In each case, the results were disappointing: only traces of cyclobutene aldehyde could be detected. Analysis of the crude mixtures (NMR, GCMS) indicated that the cyclobutene aldehyde was present along with several other 1:1 adducts. More seriously, several ester compounds, **107** and **108**, were isolated by chromatography. These compounds can arise from the same Norrish I fragmentation as for the cyclobutene aldehyde, but with a different γ hydrogen abstraction which leads to the ketene. This ketene is trapped by the solvent, methanol, leading to the methyl esters. The hydroxyl group can undergo elimination (either in the reactor, during evaporation of the solvent or more likely the chromatography) leading to the unsaturated ester. Enone **109** was formed when acetic acid was employed: its formation can be rationalized by the [2+2] adduct **110** undergoing elimination. Furthermore, this example shows that acetic acid can have deleterious effects.



Scheme 133

This result is disturbing since it indicates reactivity which differs to that observed with unsubstituted cyclopentenone. While Carless had described that irradiation of [2+2] adducts of cyclopentenone and TME could lead to ketene (and then ester) formation in methanol[518], but no evidence for the formation of ketenes had been previously noted before now. Compared to the excellent results in the reaction between bare cyclopentenone and cyclopentene, we can only assume at this point that the hydroxyl group impedes the tandem photochemical reaction towards the cyclobutene aldehyde.

Results for the reaction between 4-hydroxy cyclopentenone on one hand, and ethylene or TME on the other proved equally inconclusive.

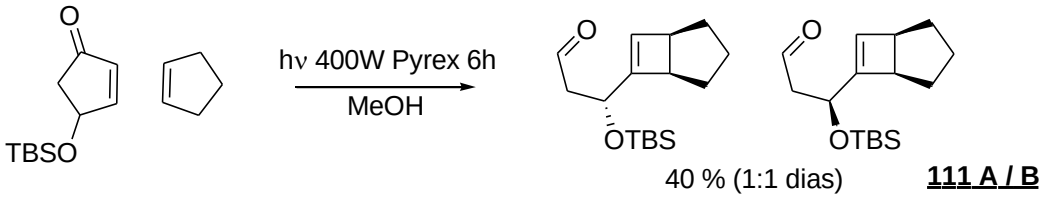


Scheme 134

In both cases, we determined that some of the target cyclobutene aldehyde was being formed under our conditions, due to aldehyde (≈ 9.6 ppm) and alkene (≈ 5.6 ppm) signals being present in the ^{1}H NMR of the crude reaction mixtures. However, they represented a small fraction that could not be separated from the crude reaction mixtures. Once again, GCMS detected several isomers of the 1:1 adducts.

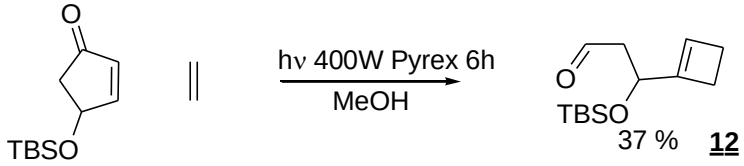
The 4-hydroxycyclopentenone proved to be a tricky substrate. While it appears that the reaction is, at least partially, affording the expected cyclobutene aldehydes, several side-reactions yield dozens of other products. At this point, we concluded that the hydroxyl substituent in the 4 position hinders the formation of the cyclobutene aldehyde. Furthermore, we did not notice any positive effect of acetic acid in the reaction with cyclopentene, which leads us to believe the reactivity problems exposed here with the 4-hydroxycyclopentenone are different from those first noticed with unsubstiuted cyclopentenone.

We next examined 4-*tert*-butyldimethylsilyloxycyclopentenone **10** (referred to as 4-OTBS cyclopentenone), the substrate in the initial discovery of the tandem reaction. In each case, we applied our chosen methanol conditions to this cyclopentenone in combination with the three simples alkenes: 5 mmol cyclopentenone XX with 50 mmol alkene, irradiated for 6 hours in methanol with no acetic acid.



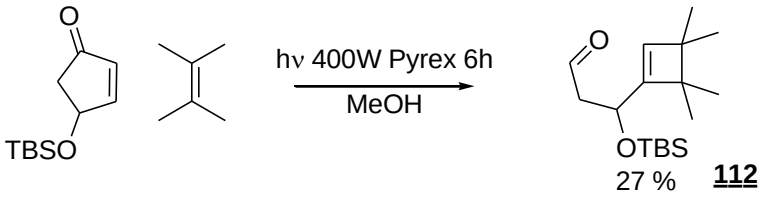
Scheme 135

Cyclopentene worked in these conditions without giving any major side products. Two diasteroisomeric aldehydes were isolated by chromatography in an inseperatable mixture in equal proportions, with a total yield of 40%.



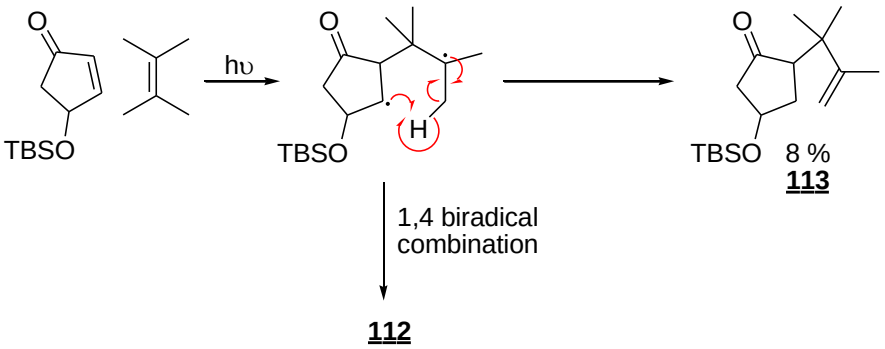
Scheme 136

Consistent with Scheme 22, ethylene proved to be an equally successful alkene partner. The cyclobutene aldehyde could be easily isolated by chromatography, yielding 37 % pure compound. Another compound was also isolated and its NMR spectra were consistent with the class of unknown secondary products previously detected (signals in the 5-6 ppm region in ^{1}H and two signals in the 85-80 ppm region in the ^{13}C).



Scheme 137

Tetramethylethylene was then employed as an alkene partner in those conditions and chromatography yielded 27 % of the target cyclobutene aldehyde. Several side products were also formed that, thankfully, could be separated easily but not identified except for ketone XX (8% yield), which arises from an incomplete [2+2] photocycloaddition.

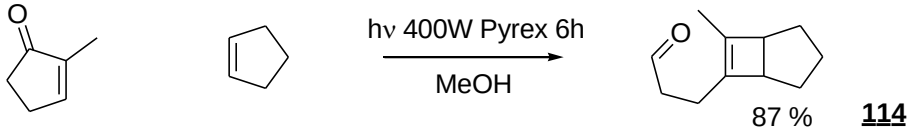


Scheme 138

4-OTBS cyclopentenone gives good results with the three basic alkenes. This expected reactivity can be compared to that of the 4-OH cyclopentenone. We believe that the lack of reactivity observed for the latter is due to the hydroxyl group and not due to a general limitation of 4-substitution of the substrate.

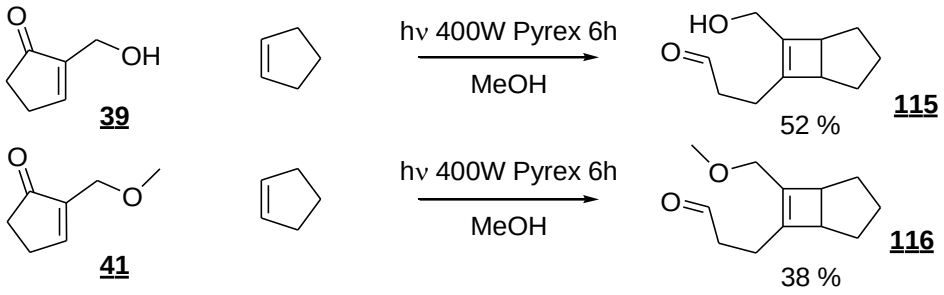
A few 2-substituted cyclopentenones were then examined for the tandem photochemical reaction to examine the effects of the 2-substitution. The Baylis-Hillman adducts of cyclopentenone are the most important of these substrates. The previously used conditions were once again used: 5 mmol of cyclopentenone and 50 mmol of cyclopentene were irradiated in methanol for 6 hours.

The most simple 2-substituted compound, 2-methylcyclopentenone is a commercially available substrate that was successfully transformed into the expected cyclobutene aldehyde **114** after 6 hours of irradiation in methanol without any purification (chromatography). The high yield, 87 %, was very similar to the reaction with unsubstituted cyclopentenone.

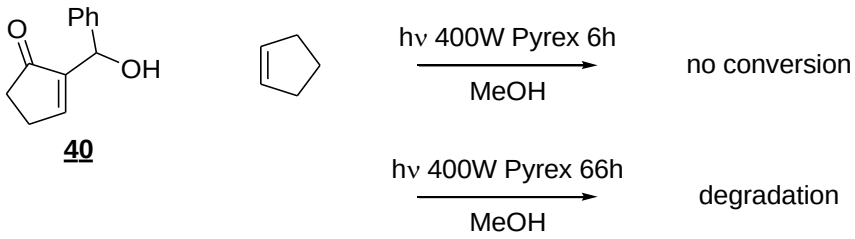


Scheme 139

Cyclopentenone **39** and the related O-methylated ether **41** were reacted in methanol with cyclopentene and yielded the expected cyclobutene aldehydes in average yields, respectively 52 % and 38 % after chromatography. Chromatography removed unidentified polar material that was not determined to be obviously structurally related to the photoproducts. None of the previously detected side products were detectable in the crude reaction mixture by NMR. The O-methylated ether was prepared out of concern that the alcohol functionality would be the cause of the observed lower yields. It appears that this is not the case.



Scheme 140



Scheme 141

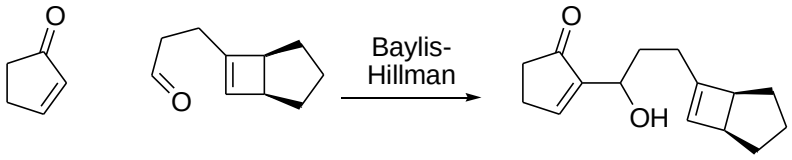
The adduct of cyclopentenone and benzaldehyde, the benzylic alcohol cyclopentenone **40** proved to be a difficult substrate. It failed to react as expected with cyclopentene. 6h of irradiation afforded no conversion and long term irradiation failed to produce any meaningful results. This can be explained by the high absorbance of the phenyl group which "drains" the irradiation.

The question of 2-substitution has been partially answered by these experiments. While a methyl substituent barely affected the reaction with cyclopentene. However, more complex substrates such as the Baylis-Hillman lead to lower yields. The issue seems to stem from steric hindrance, since all four substituents give lower yields the more the substituents are cumbersome. The alcohol seems to be a non-issue here (contrary to the 4 position).

Future avenues of interest

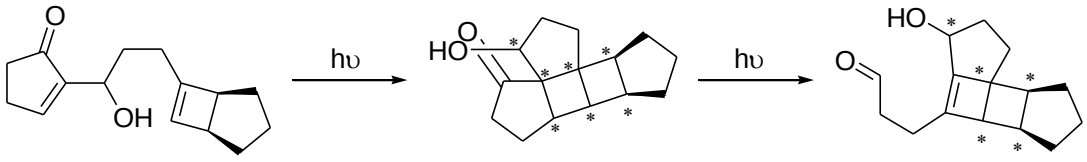
The 5 position of the cyclopentenone remains unstudied due to the lack of appropriately prepared substrates. Substituents in this position will shift the regioselectivity towards the vinyl cyclobutane carboxaldehyde structure deriving from the "alternate" Norrish I fragmentation described at the beginning of this chapter. However, the question remains as to whether cyclobutene aldehydes will still be formed as the major compound: the regioselectivity seems to also be dependent on the alkene partner.

There seems to be some potential for the development of the tandem photochemical reaction applied to Baylis-Hillman compounds. While only two substrates were mentioned in this manuscript, several others were prepared and used in our exploratory experiments and suggested that cyclobutene aldehydes could be formed in those cases. Furthermore, it may be interesting to use the cyclobutene aldehydes themselves as reagents for the Baylis-Hillman transformation:



Scheme 142

This substrate could undergo an intramolecular tandem photochemical transformation, which could lead to structurally complex cyclobutene aldehydes:



Scheme 143

Cyclopentene has consistently given good results in the tandem reaction which leads us to believe there is a good chance that other alkene partners with cyclopentene structures may also perform adequately. There are several commercially available ones, for example: Norbornene, 3-Cyclopentene-1-carboxylic acid and 2-Azabicyclo[2.2.1]hept-5-en-3-one.

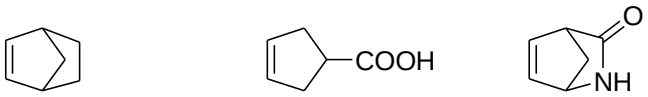


Figure 21

Conclusion on the tandem transformation

While the transformation yielding cyclobutene aldehyde is one amongst several reaction pathways available to irradiated mixtures of cyclopentenones and alkenes, conditions have been established that consistently favor this product: 6h of irradiation in methanol. Acetic acid is a possible additive that can diminish side reactions, but can promote others. We conclude that we have established the first set of specific conditions for the tandem transformations, but that the scope and limitations remain incompletely studied. Now that the first exploratory studies have concluded, further complementary studies are called for.

The most important point is however that conditions have now been established to lead to the cyclobutene aldehyde in average to high yields.

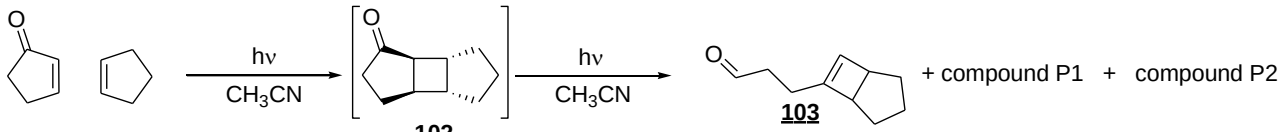
Chapter 5 Preparation of polycyclic oxetanes

In the previous chapter, we showed how a tandem photochemical reaction between a cyclopentenone and an alkene may lead to a cyclobutene aldehyde. From time to time, the formation of secondary products was observed. GCMS analysis had suggested that these compounds have a molecular weight corresponding to [1:1] adducts. In this chapter, these unknown side-products are examined, leading to the discovery of an unprecedented polycyclic oxetane molecular skeleton.
It should be noted at this point that all reactions in this chapter are carried out in a Pyrex reactor.

The secondary compounds

During the course of our optimizations on the tandem photochemical transformation, it was observed that unidentified [1:1] secondary products would consistently be formed in certain reactions, notably the tandem reaction carried out with cyclopentenone and cyclopentene. In this reaction, two unknown compounds could be detected after 6 hours of irradiation in acetonitrile. These compounds, both constitutional isomers of the cyclobutene aldehyde (MW = 150 g/mol), although, somewhat enigmatically, no unsaturations were detected (C=O or C=C) and each bore two CH-heteroatom carbons (detectable in the ^{13}C NMR spectrum of the crude reaction mixture in the 80-85 ppm region). The hydrogens on these carbons were detectable in the ^{1}H NMR spectrum in as two methane-type hydrogen signals per compound in the 4-5 ppm region. This allowed for quantitative analysis of the reaction mixture. The two secondary compounds were consistently present in a 0.8 to 0.87 ratio (5/1) between the two compounds respectively named P1 and P2.

In an attempt to identify these compounds, we first sought to increase the proportion of their formation in the photochemical reaction. We noticed that increasing the irradiation time in acetonitrile from 6 h to 16 h increased the proportion of these secondary products from 46% to 79 %. Extending the irradiation time to 24 h total did not change the ratio of compounds in the reaction mixture.



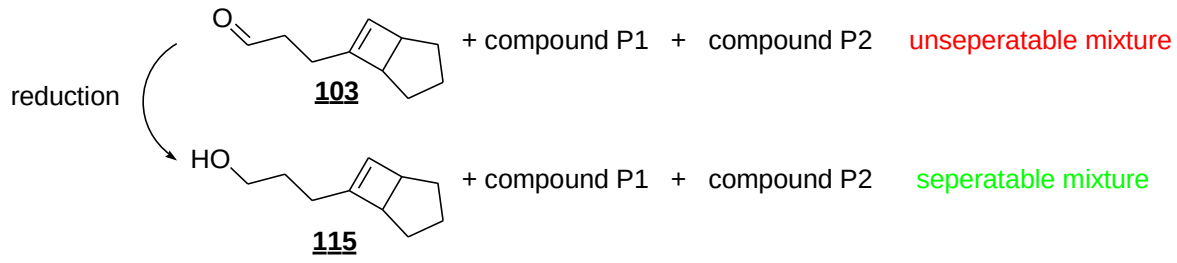
102 **103**

6 hours irradiation:	54 %	38 %	8 %
16h hours irradiation:	21 %	70 %	9 %
24h hours irradiation:	21 %	70 %	9 %

Scheme 144

Based on our experience in the separation of the cyclobutene aldehyde from other products in the crude reaction mixture of the tandem photochemical reactions described in chapter 4, we envisaged to remove the cyclobutene aldehyde by transforming it to the corresponding cyclobutene alcohol and should facilitate the isolation of compounds P1 and P2 from the product mixtures described in Scheme 148.

Since P1 and P2 bore no unsaturated functions, we assumed that reduction should not affect these compounds.



Scheme 145

We decided to treat the crude reaction mixture obtained after 16 h of irradiation of a mixture of 5 mmol of cyclopentenone and 50 mmol of cyclopentene in acetonitrile with two equivalents of sodium borohydride. The reaction mixture was untouched after the irradiation, but simply transferred to a flask for the reduction. The latter was carried out at room temperature for 4 to 5 hours. We were delighted to notice the following separation on the TLC (petroleum ether/diethyl ether 7:3):

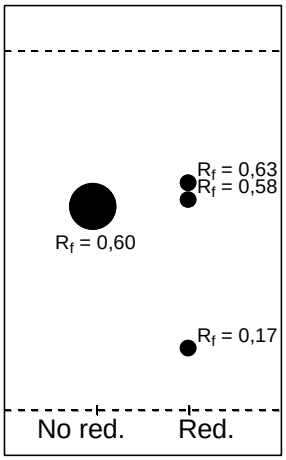


Figure 22

We determined that the new high polarity spot (Rf = 0.17) corresponded to the cyclobutene alcohol, leaving two spots corresponding to P1 and P2. We noticed a similar phenomenon in the GC analysis of the product mixture following reduction: where we previously had observed one large peak, two very distinct peaks could be detected. The above TLC summarizes the situation: previously the cyclobutene aldehyde, P1 and P2 would appear as one large coalesced spot, but reduction allows for resolution of the mixture in the three components.

We were able to isolate P1 and P2, with one (P1, the major compound) being isolated as the least polar compound (Rf = 0.63) and the second, the minor, slightly more polar (Rf = 0.58). At this point, we observed that both compounds had very similar NMR spectral data: same number of signals, same multiplicities of the carbons (CH, CH_2, CH_3, C_q). The only differences were slight variations in the chemical shifts of some signals and variations in coupling constants of the ^1H NMR signals. We hypothesised that P1 and P2 were diastereoisomers.

We carried out extensive analysis on the major compound P1 and will detail the determination of the structure here. Presented here are the ^1H (360 MHz) spectra and ^{13}C J-MOD (90 MHz) spectra:

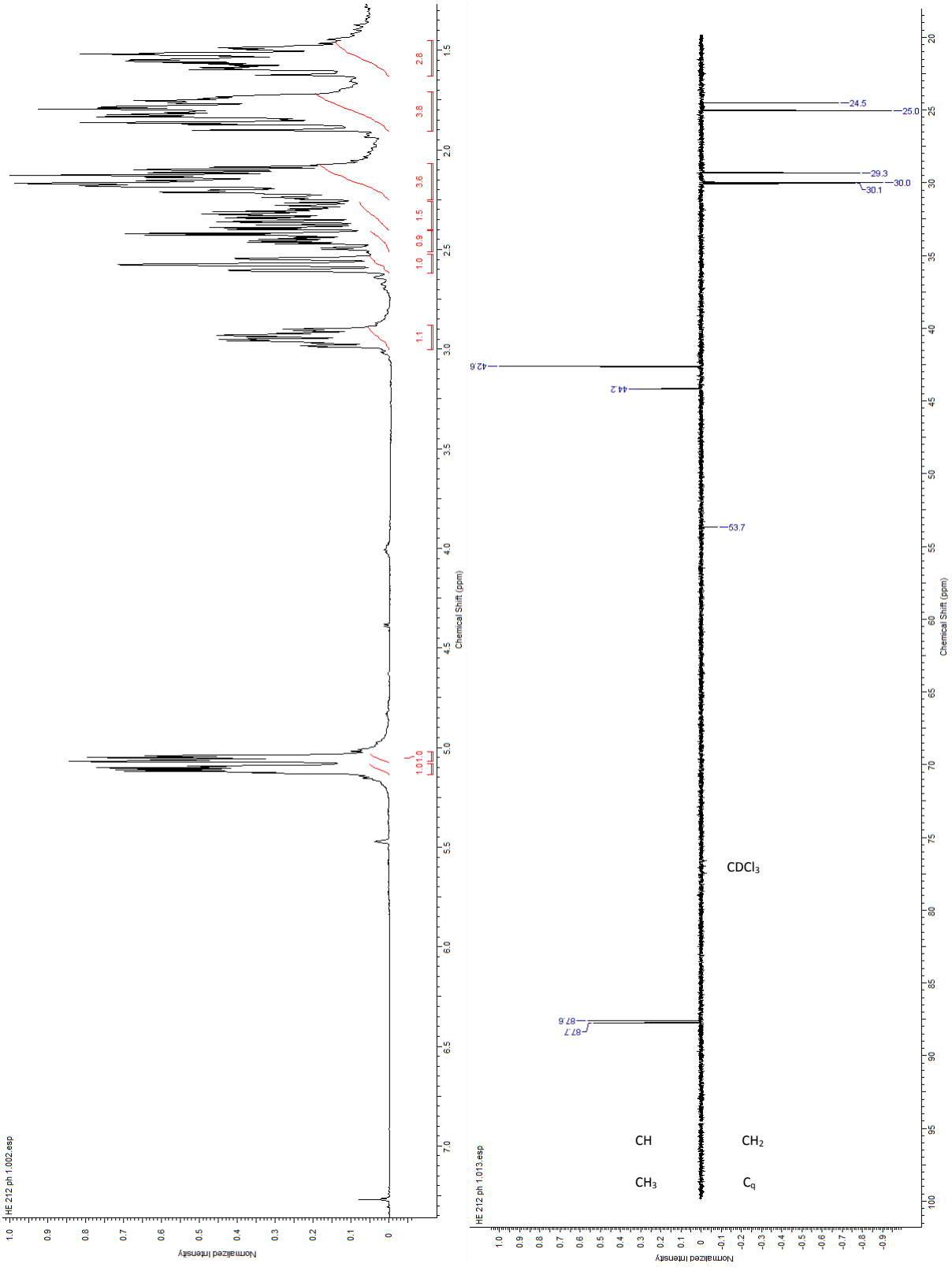


Figure 23

Further NMR experiments performed on P1 were HSQC (C – H correlation) and COSY (H –H correlation), they are not included here but they contribute to the determination of the structure.

A brief analysis of the data is presented at this point:

The molecular weight of the structure (150 g/mol) corresponds to $C_{10}H_{14}O$. This corresponds to a degree of unsaturation of 4. However, no multiple bonded carons were detected in the ^{13}C spectra: no sp^2 or sp carbons, only sp^3. Therefore, the structure is tetracyclic. GCMS indicated no M-18 ions (indicative of the loss of a protonated hydroxyl substituent) and the IR showed no hydroxyl group absorbtion band. Therefore, the molecule was not an alcohol (which is consistent with the low polarity observed on the TLC) amongst the four cycles, one is a cyclic ether.

Furthermore, detailed analysis of the HSQC, ^{13}C J-MOD and ^{1}H spectra indicated that the molecule contained no methyl carbons, only CH and CH_2 carbons that are listed below:

Carbon displacement	Mult.	Hydrogens borne	Neighbouring carbons[a]	Comments
87.7	CH	5.10	30.1	CH-heteroatom
87.6	CH	5.05	44.2	CH-heteroatom
53.7	Cq	quaternary		
44.2	CH	2.98	87.2; 42.6; 25.0	Consistent with C-H bridgehead carbons from cyclobutene aldehyde[b].
42.6	CH	2.60	44.2; 30.0	
30.1	CH_2	2.45; 2.35	87.7; 24.5	Cyclopentane ring
30.0	CH_2	1.75; 1.55	42.6; 29.3	
29.3	CH_2	2.10; 1.85	30.0; 25.0	
25.0	CH_2	2.18; 1.50	44.2; 29.3	
24.5	CH_2	2.15; 1.80	30.1	

a immediate neighbours, based on HSQC and COSY ***b*** Cyclobutene aldehyde from reaction between cyclopentenone and cyclopentene.

Table 10

This spectroscopic data can be attributed to the following **tetracyclic oxetane structure** (for simplicity's sake only the carbon shifts are included):

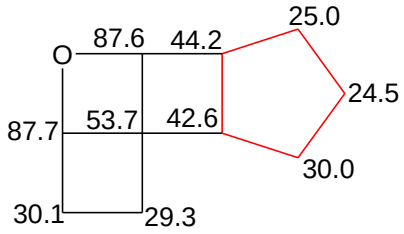


Figure 24

The major oxetane P1 was extensively studied with J-RES experiments[539] to extract a maximum of proton-proton coupling constants. Supplementary SERF (selective J-RES) experiments were necessary to resolve the more complex signals. The complete and extensive NMR data is included in the experimental section.
The minor oxetane P2 was also studied and the data is consistent with a structure identical to the one above. The precise attribution is redundant here but is also present in the experimental section.

Both P1 and P2 are diastereoisomers of this tetracyclic oxetane structure. We can derive certain facts from the coupling constants and the structure of the cyclobutene aldehyde, such as the fact that the cyclobutane – cyclopentane ring junction is *cis*, as imposed by the cyclobutene aldehyde.
Furthermore, comparison of the signals of the oxetane ring hydrogens between the two P1 and P2

products reveals the only change in the multiplicity patterns between the two spectras (the other signals are almost the same):

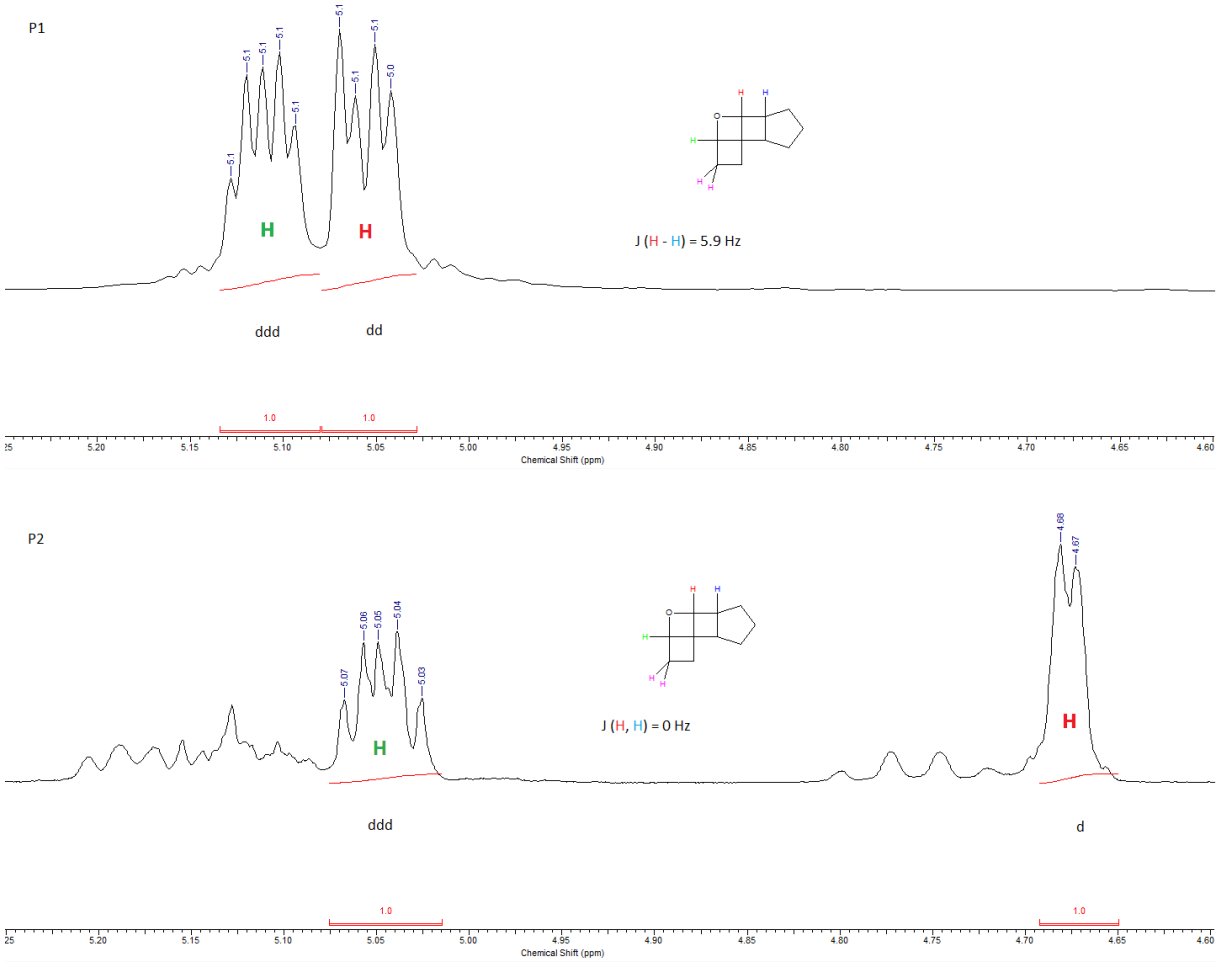


Figure 25

In both cases, the leftmost proton signal corresponds to the green hydrogen on the oxetane ring. It is a ddd, being coupled with the neighboring CH_2 and having a W-coupling with the other oxetane ring hydrogen. However, the other hydrogen (in red) is either a doublet or a doublet-doublet. Bearing in mind, that the W-coupling is always present, the other coupling is the ^3J coupling between the red and blue hydrogens. We infer from its presence in P1 (J = 5.9 Hz) and absence in P2 that in the first case, the hydrogens are *cis* relatively to each other and *trans* in P2. We therefore have the following structures:

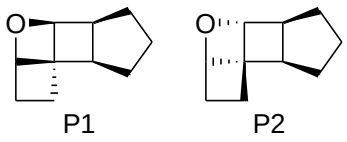
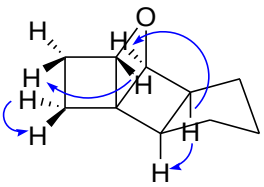


Figure 26

nOe experiments carried out on P1 allowed us to confirm the relative positions of the hydrogens and distinguish the protons from some of the CH_2.



nOe interactions
of *endo* compound

Figure 27

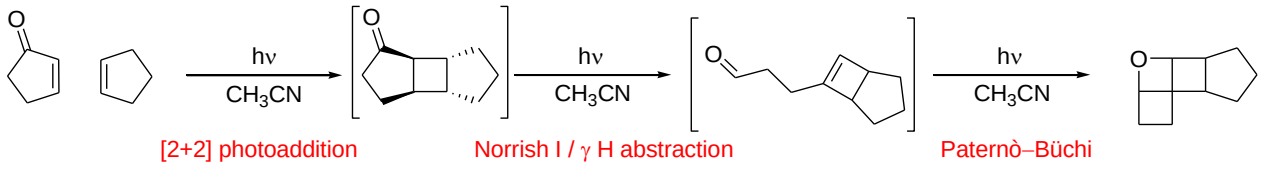
We can summarize the results of this reaction in the following:



Scheme 146

The two tetracyclic oxetane diastereoisomers are isolated in a 5/1 ratio, consistent with the ratio observed in the crude reaction mixture. A total yield of oxetanes is 60 % which is an interesting start at this point.

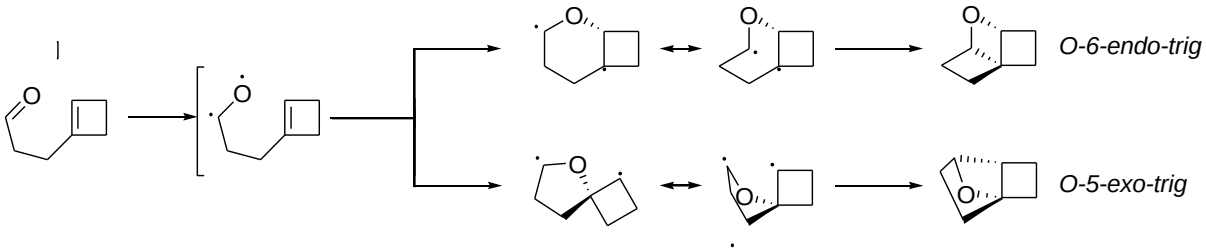
The formation of this species can be explained by an intramolecular Paternò–Büchi (PB) reaction[17,100,114–116,118,268,535,540] of the cyclobutene aldehyde formed in the tandem photochemical reaction.



Scheme 147

This means that these newly identified compounds are side-products formed by a photochemical transformation happening subsequently to the tandem process leading to the cyclobutene aldehyde the other reactions as soon as the cyclobutene aldehyde begins to form. Intramolecular Paternò–Büchi reactions are known[541,542], but never for so strained a structure.

As we have stated, these oxetanes derive from the cyclobutene aldehyde XX by an intramolecular Paternò–Büchi reaction. It can be assumed that the reaction follows the typical PB reaction pathway (the cyclopentene ring is omitted for clarity):



Scheme 148

Irradiation of the cyclobutene aldehyde generates an excited species that, reacting in the triplet state, will react with the double bond by addition of one of the radical centers and subsequent ring closure. The regioselectivity derives from the primary oxygen radical that can reasonably be assumed to react first, the competing C attacks has been documented as possible but less likely.[543] The regioselectivity of the addition is straightforward in the case of the trisubstituted double bond and proceeds by the *O-6-endo-trig* pathway to form the tertiary cyclobutyl radical. The competing *O-5-exo-trig* would only be possible should the double bond be tetrasubstituted. Twisted cyclobutanes being unstable, no pathways including them were considered.

In this case, with cyclopentene, there is a diastereoselectivity issue. The two oxetanes can be refered to as *endo* (or *cis-anti-cis*) and *exo* (or *cis-syn-cis*), referring to the relative positions of the oxetane and cyclopentane rings.

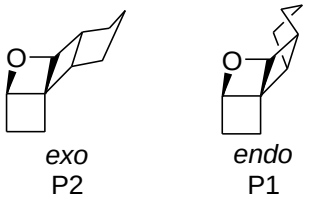
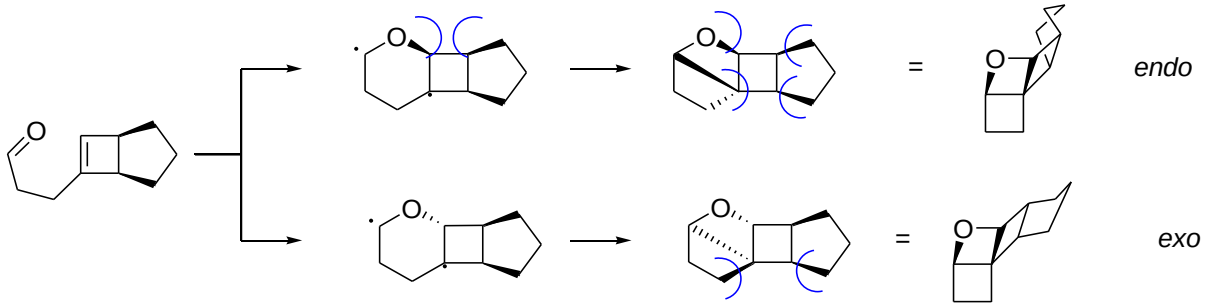


Figure 28

Identification was possible by nOe experiments and coupling (or absence thereof) between bridgehead hydrogens. The ratios always favored the *endo* isomer by at least a 2:1 ratio but never more than 5:1. This is a quite surprising, given that this is the isomer with the most steric stress.

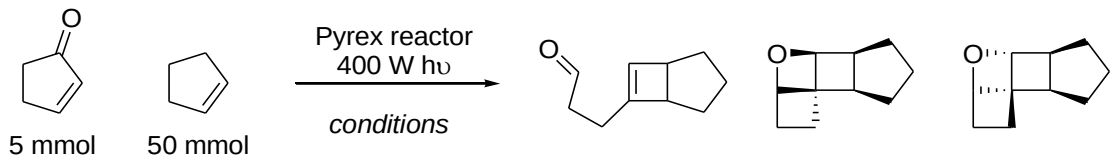


Scheme 149

At this point, we had identified the unknown products which were arising in the tandem processes described in chapter 4. They are the result of a **triple photochemical reaction between cyclopentene and cyclopentenone and have a polycyclic oxetane structure centered on the 5-oxatricyclo[4.2.0.0^{1,4}]octane core, which is unprecedented**. We decided to further explore this triple photochemical reaction by attempting to optimize the process and explore its scope and limitations.

Optimization of the reaction conditions.

Following the above discovery of the formation of the two polycyclic oxetanes in the reaction between cyclopentenone and cyclopentene, we decided to try to the optimize on the reaction. On the basis of this new compound identification, and some new experiments described below, the previous table concerning the outcome of the irradiation of cyclopentenone in presence of a tenfold excess of cyclopentenone can be completed and amended thus:



5 mmol 50 mmol

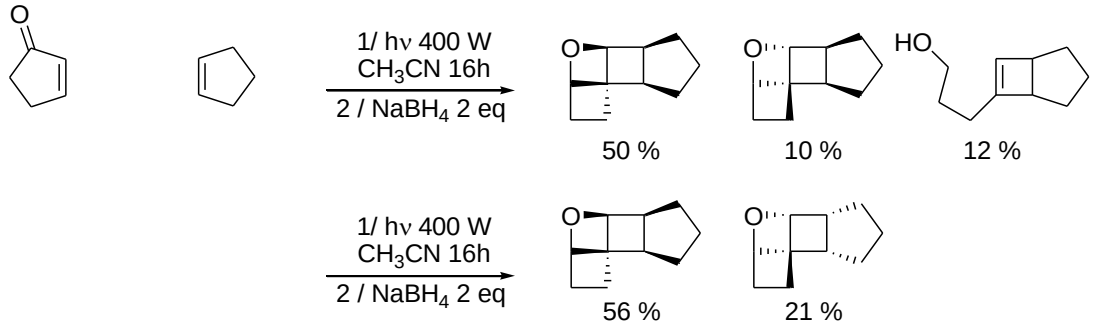
Entry	Solvent	Time	Additives	Relative proportions [c]		
1	Dichloromethane [a]	6 h	none	50	42	8
2	Toluene [a]	6 h	none	50	40	10
3	*c*-C_6H_{12} [a]	6 h	none	47	45	8
4	CH_3CN [a]	6 h	none	54	38	8
5	Acetone [b]	6 h	none	n/a		
6	MeOH [a]	6 h	none	82	12	6
7	MeOH [a]	6 h	1 eq AcOH	99	1	0
8	MeOH [a]	6 h	0,1 eq AcOH	99	1	0
9	CH_3CN [a]	6 h	0,1 eq AcOH	67	28	5
10	*c*-C_6H_{12} [a]	16 h	none	16	71	13
11	*c*-C_6H_{12} [a]	24 h	none	18	69	13
12	CH_3CN [a]	16 h	none	21	70	9
13	CH_3CN [a]	24 h	none	21	70	9

a Isolated mass was >95% of expected mass ***b*** Recovered mass was well in excess of expected mass, with an estimated 80 % being products of photochemical reactions of the solvent ***c*** Based on ^{1}H NMR data of the crude reaction mixture

Table 11

This completed table shows that acetonitrile and areboth reasonable solvents for the 16 h irradiation of the cyclopentenone-cyclopentene mixture. At 16 h, a cap in the conversion in reached, meaning further irradiation is at best unnecessary. Remarkably, conversion of the cyclobutene aldehyde to the oxetane was capped and and seemed to reach a plateau past a certain irradiation time. Acetontrile seemed a more prudent choice than cyclohexane for several reasons: it is a better solvent (cyclohexane might be problematic with more polar reagents) and addition of sodium borohydride to remove unreacted aldehyde might be difficult.

We also noticed that we could slightly improve the overall yields of oxetane by modifying the workup.



Scheme 150

As previously mentioned, cyclopentene and cyclopentenone yield two diastereoisomeric tetracyclic oxetanes. Separation of the oxetanes from the cyclobutene aldehyde requires reduction of the aldehyde to the more polar alcohol **115**. Previously, the crude reaction mixture after the 16 h irradiation in acetonitrile was reduced with added $NaBH_4$.The reaction was then quenched, worked up and then chromatographied. Quenched reduction crude mixtures allow for recuperation of the three products: cyclobutene alcohol (12 % recovered yield), *endo* oxetane (50 %) and *exo* oxetane (10 %). It is possible to increase the yield in oxetanes by not quenching the reaction mixture after the reduction reaction, but simply evaporating the solvent and chromatographying this reaction mixture. In this case, only *endo* oxetane (56 %) and *exo* oxetane (21 %) were isolated. The increase in yield could be explained by less loss of mass during the workup and chromatographic conditions focused on the oxetanes.

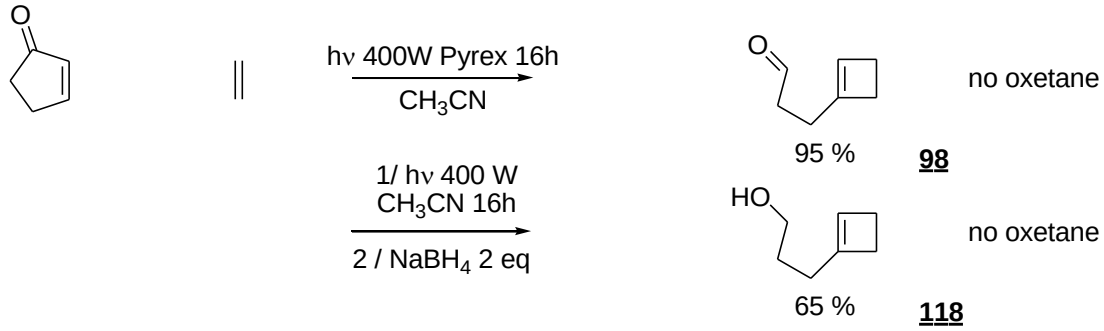
In the light of these observations, **16h of irradiation in acetonitrile will be considered the standard conditions for the triple photochemical transformation of a cyclopentenone and an alkene to the oxetanes.** Separation of the crude mixture should be carried out by chromatography, with prior $NaBH_4$ reduction of the cyclobutene aldehyde if necessary. The resulting alcohol can then be more easily separated from the polycyclic oxetanes.

Application of the triple photochemical reaction

As was the case with the tandem photochemical process leading to cyclobutene aldehyde, we wished to explore the scope and limitations of this reaction. The reaction conditions established above, 16h of irradiation in acetonitrile, were applied to a selection of available substrates.

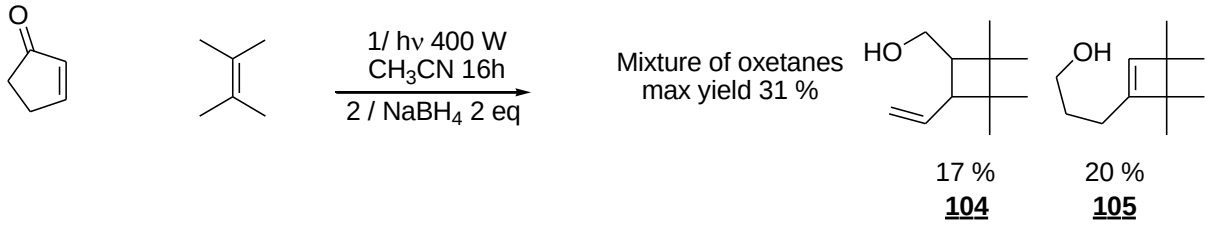
Unsubstituted cyclopentenone and simple alkenes

Unsubstituted cyclopentenone was reacted first with two other simple erence alkenes: ethylene and TME. We also tried vinylene carbonate, sulfolene and DMK as alkene partners.



Scheme 151

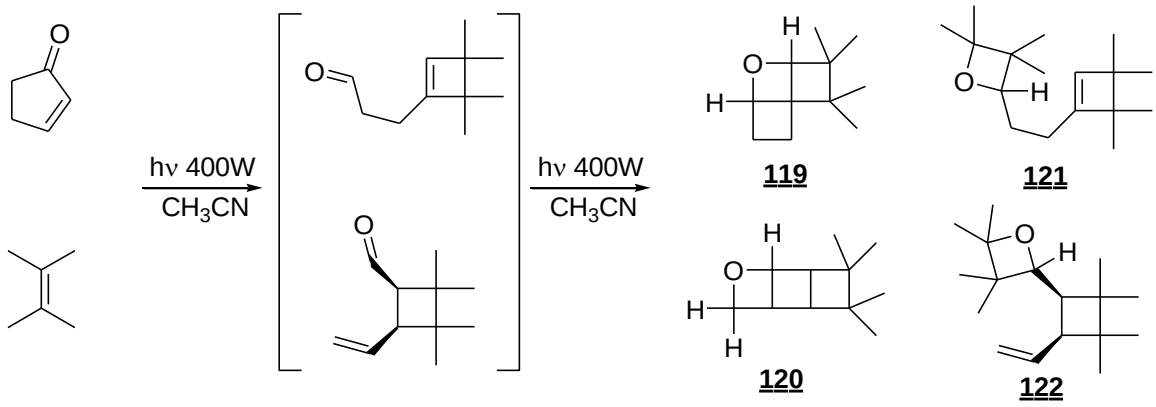
When irradiated for 16 h in acetonitrile, ethylene failed to react in an analogous fashion with cyclopentenone. No oxetane was detected (no signals in the ^{13}C in the 80-85 ppm region), whilst almost all of the material was recovered as aldehyde. This is unsurprising, considering that our initial apparent success with the tandem reaction involving ethylene was due to the absence of a triple photochemical reaction with ethylene. The corresponding oxetane fails to form.No explanation for the lack of reactivity can been proposed at this point. In effect, these reaction conditions constitute another excellent means for the preparation of the cyclobutene aldehyde. Tandem photochemical/reduction conditions gave the cyclobutene alcohol **118** in 65 %.



Scheme 152

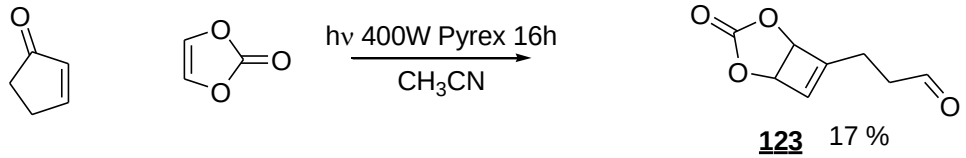
Once again, Tetramethylethylene proved to be problematic. The crude mixture showed several NMR signals attributable to oxetanes: proton signals in the 4-5 ppm area and many signals in the 80-100 ppm area of the ^{13}C spectra. Separation of the mixture was aided by reduction of the crude, allowing for the more polar alcohols to be separated. The least polar fractions contained several oxetanes that could be the expected oxetane **119** and also 2:1 adducts, cyclobutene oxetanes such as **121** and **122**, resulting from Paternö–Büchi reactions between the cyclobutene aldehyde and the excess TME. None of expected tricyclic oxetane could be isolated pure. This disappointing result can be explained

by the previously observed regioselectivity problem in the tandem reaction in which two aldehydes are obtained and a further issue of large concentrations of TME, an electron rich alkene, that favor intermolecular Paternò–Büchi reactions.



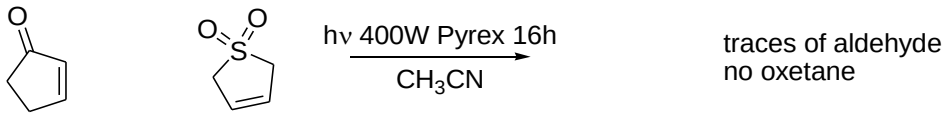
Scheme 153

Oxetanes diagnostic signals could be detected in the crude reaction mixture: a series of signals in the ^{13}C in the 75-95 ppm region. Several were identified as C-H, no C-H_2 were detected but it is possible that C_q were present. The target oxetane **119** was likely present, but one or two of the [2:1] oxetanes **121** and **122** was likely present. It seems **120** was not present.



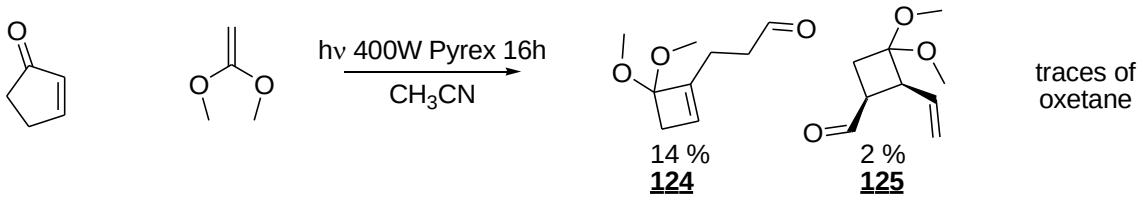
Scheme 154

Vinylene carbonate was reacted in acetonitrile. Irradiation of 5 mmol of cyclopentenone and 50 mmol alkene for 16 hours. We expected that it would work better than in methanol where a ketal was formed. Vinylene carbonate reacted sluggishly and only yielded the cyclobutene aldehyde **123** in 17 %yield after the chromatography. As previously, we attribute this to absorption of irradiation by the alkene and the possible photodegradation of any carbonate.



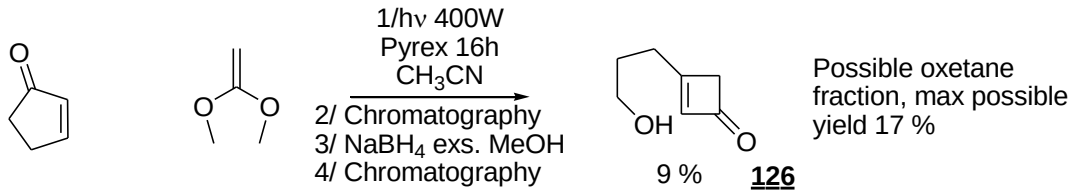
Scheme 155

Sulfolene proved as poor a reagent in acetonitrile as in methanol, though we had hoped that separation might be easier. Cyclopentenone (5 mmol) and sulfolene (50 mmol) were irradiation for 16 hours in acetonitrile without giving rise to any detectable oxetane compounds, although aldehyde signals were detected in the crude material by NMR. Separation was not possible by chromatography.



Scheme 156

Dimethyl ketene acetal (50 mmol) was irradiated in presence of cyclopentenone (5 mmol) in acetonitrile for 16 hours but a the same regioselectivity issues as with TME were found here in the formation of the aldehyde species: cyclobutene aldehyde **124** was obtained with 14 % yield and a small fraction of regioisomer **125** was also isolated (2 %) after chromatography. Chromatography of the crude reaction mixture also gave one collection of fractions that was identified as a mixture of oxetanes (signals were detected in the 85-80 ppm reigon in the ^{13}C spectra) and aldehydes. Subsequent reduction of this fraction with sodium borohydride and further chromatography gave impure samples of oxetane, that could not be isolated in analytically pure form (only the diagnostic signals were clearly identified), and substituted cyclobutenone **126**.



Scheme 157

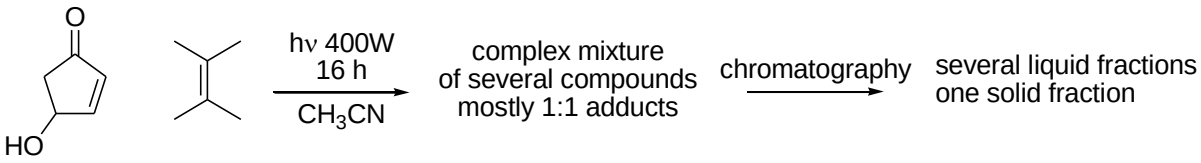
This cyclobutenone probably arises from cyclobutene aldehyde **124** undergoing a reduction of the carbonyl to the alcohol and hydrolysis of the dimethylacetal on the cyclobutene moiety. The hydrolysis occurs after the first chromatography, either during the reduction, its workup or atfer.

Once again, unsubstituted cyclopentenone fails to react as hoped with the selected alkenes except for cyclopentene. We therefore turned our attention to reactions involving substituted cyclopentenone substrates.

Variations on the cyclopentenone partner

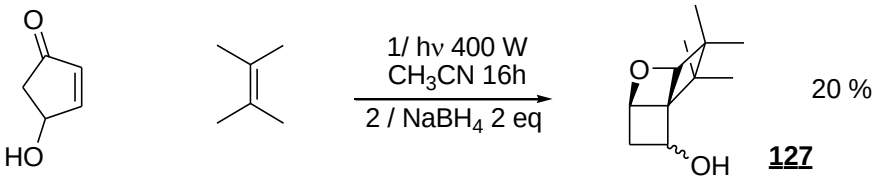
In the course of the study of the tandem photochemical transformation, 4-substituted cyclopentenone often reacted to give mixtures of compounds containing the cyclobutene aldehydes but also exhibiting signals that could possibly be attributed to polycyclic oxetanes structures. With the conditions optimized for the triple photochemical transformation yielding oxetanes, we proceeded to reexamine the reactions of 4-hydroxycyclopentenone XX and the related TBS ether XX with the three simple alkenes: ethylene, TME and cyclopentene.

We began by reacting 4-hydroxycyclopentenone and TME: after 16 hours of irradiation in acetonitrile, the reaction gave a complex crude reaction mixture which, after chromatography, furnished one solid which was identified as the tricyclic oxetane **127**.



Scheme 158

The one solid compound, the oxetane, was one pure 1:1 adduct of 4-hydroxycyclopentenone and TME and attributed the following structure to it:



Scheme 159

We studied this compound in detail because the hydroxyl substituant raised a stereoselectivity issue, since no other oxetane-type compound could be detected in the crude reaction mixture. Therefore, we sought to determine the stereochemistry.

Extensive NMR analysis confirmed the tricyclic oxetane structure above. Elements of note are the oxetane ring signals: 77.8 and 88.3 ppm for the CH-heteroatom signals in the ^{13}C spectrum, bearing hydrogens detected as ^{1}H signals at 4.87 and 4.72 ppm.

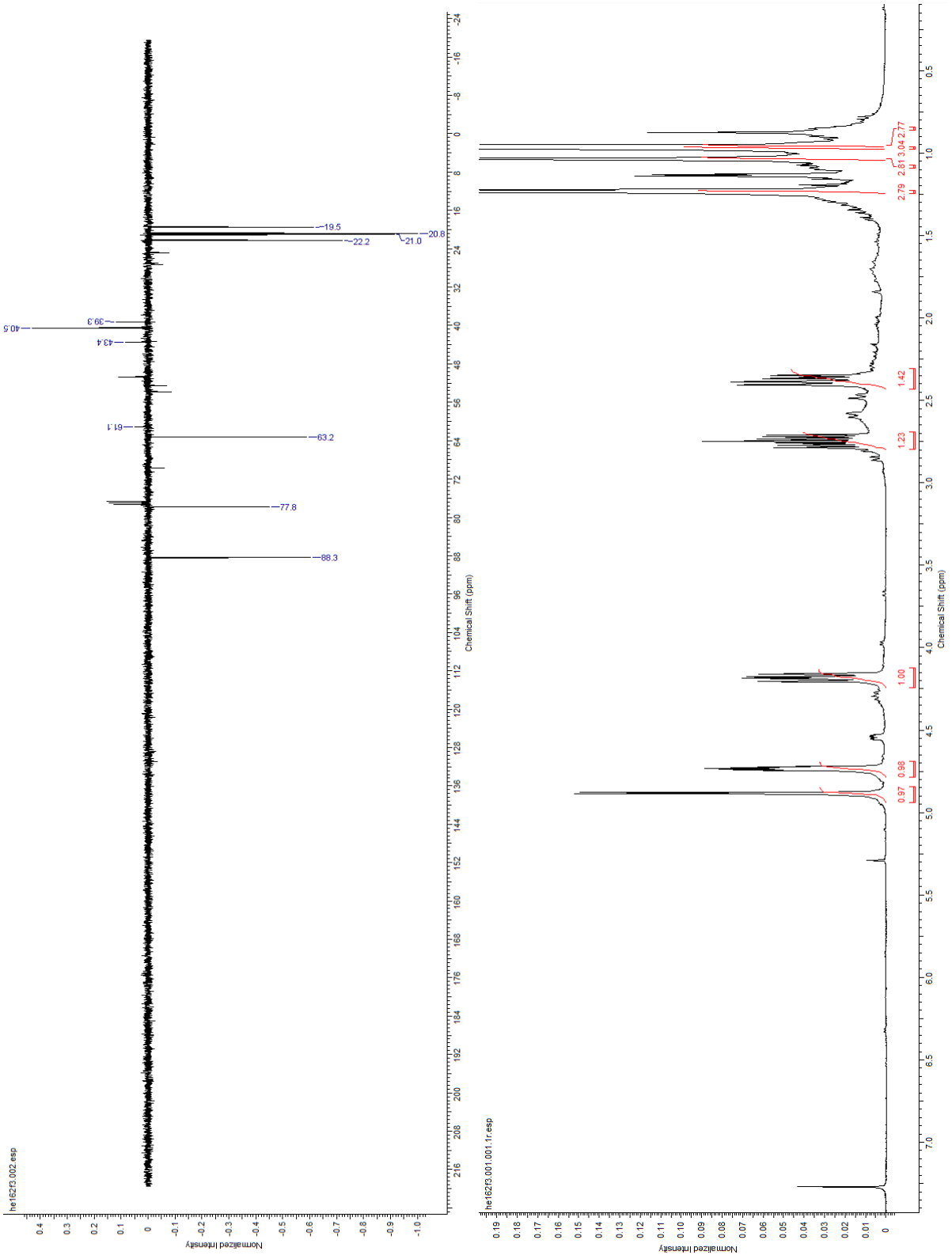


Figure 29

We were able to obtain X-Ray diffraction data on the oxetane compound:

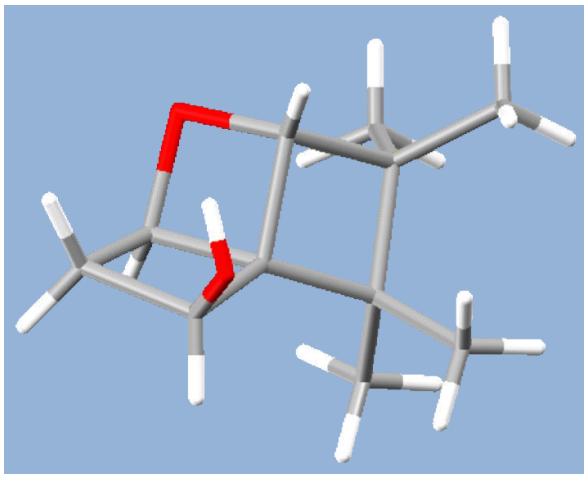
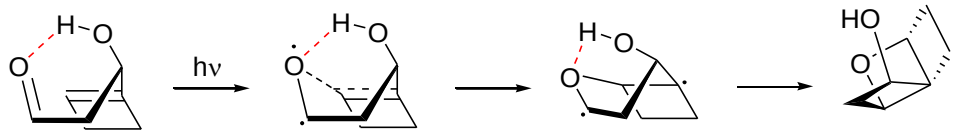


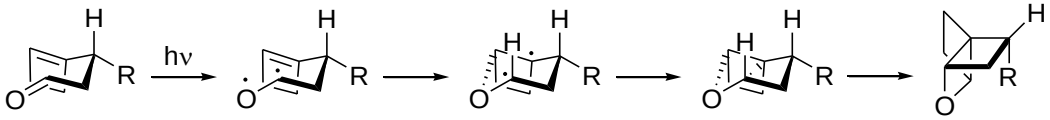
Figure 30

Unsurprisingly, the 4:4 ring junctions are all *cis*. The *cis* arrangement (or *endo* configuration of the substituent) of the two oxygens is surprising however: XX is less stable than then the equivalent *trans* compound, due to the repulsion between the hydroxyl in the above structure and the oxetane ring. The observed stereochemistry can be explained by hydrogen bonds orientating the reactive intermediates. Similar interactions have been suggested to explain diasteroselectivity in allyl alcohol systems reacting with ketones.[113,544]



Scheme 160

Another possible mechanistic explanation is a pseudo-cyclohexane “chair” conformation that would promote the most stable pseudo-cyclohexane with a maximum of substituents in the equatorial position.



Scheme 161

This particular configuration of the ring bearing the two oxygens could be characterized by the coupling constants of the neighbouring hydrogens.

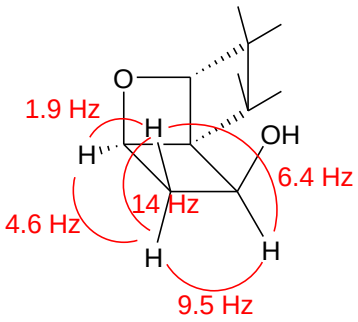
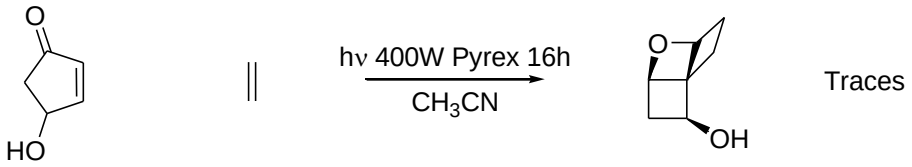


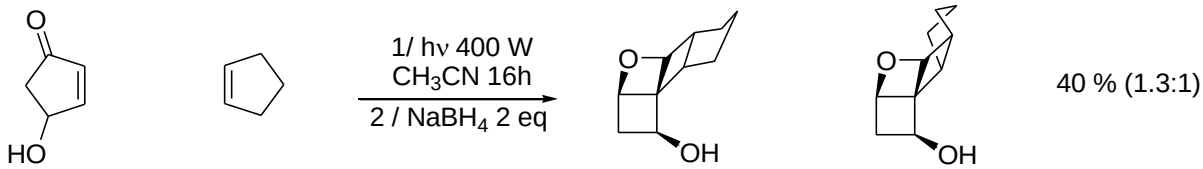
Figure 31

These coupling constant values were useful for the structural attribution of the configuration of the tricyclic oxetane cores present in other oxetanes derived from 4-hydroxy cyclopentenone derivatives.



Scheme 162

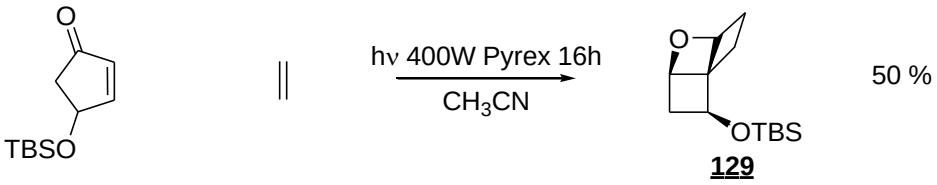
Next, we reacted 5 mmol of **32** in acetonitrile under irradiation for 16 hours with bubbling ethylene. Once again, ethylene proved to be a disappointment. Only faint signals attributable to the expected oxetane could be detected. The crude reaction product was a complex mixture of unidentifiable components.



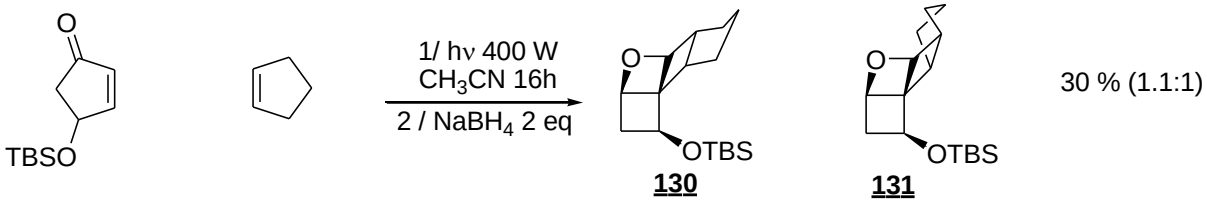
128 X / N

4-hydroxycyclopentenone was irradiated for 16 hours in acetonitrile in presence of cyclopentene. Subsequent reduction of the crude reaction mixture provded a mixture of tetracyclic hydroxyoxetanes in 40 % yield. The oxetanes both had the *cis* oxygen relationship (based on the coupling constants of the hydrogens closest to the two oxygens) and the isomers were *endo* and *exo* similar to the unsubstituted oxetanes.

We next turned our attention to the TBS ether **10** of 4-hydroxycyclopentenone as a substrate. Surprisingly, this compound reacted with ethylene in acetonitrile (16 hours of irradiation) to yield a single oxetane **129** in 50 % yield contrary to the previously tested cyclopentenones. Analysis of the coupling constants of the hydrogens of methylene between the two carbons bearing the oxygens indicated that the oxygens were *cis*. The silyl ether function was therefore in the *endo* configuration Reduction was not necessary to separate the oxetane from the cyclobutene aldehyde **12**.

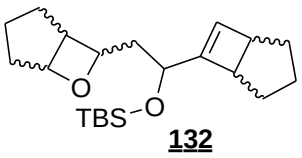


Scheme 163



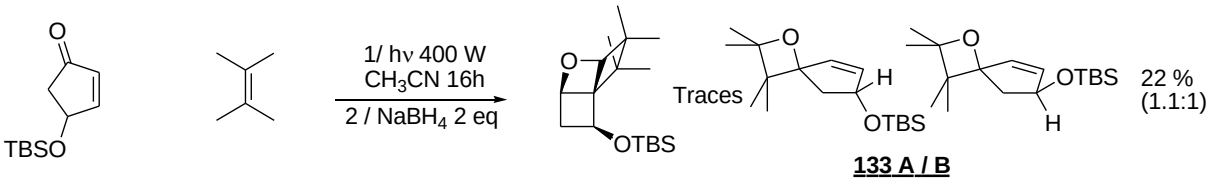
Scheme 164

Cyclopentenone **10** and cyclopentene reacted satisfactorily in the 16 hour acetonitrile conditions. A mixture of two oxetanes was isolated after reduction of the crude reaction mixture and chromatography. The recovery of the alcohols was not attempted. The oxetanes were *endo* and *exo*, in roughly equimolar proportions and were once again in a *cis* oxygen relationship. The total yield was 30 %. In addition, a smalll proportion of 2:1 adduct **132** was detected in the crude reaction mixture by GCMS and NMR, a cyclobutene oxetane resulting from a Paternò–Büchi between the cyclobutene aldehyde and excess cyclopentene, were detected.



Scheme 165

The formation of a 2:1 adduct has previously been observed with TME; However, this is the first time such a reaction had been observed with cyclopentene. Difficulty, leading to sluggishness, in forming the oxetane due to steric congestion may explain that alternate reaction pathways such as, in this case, having the cyclobutene aldehyde react intermolecularly.

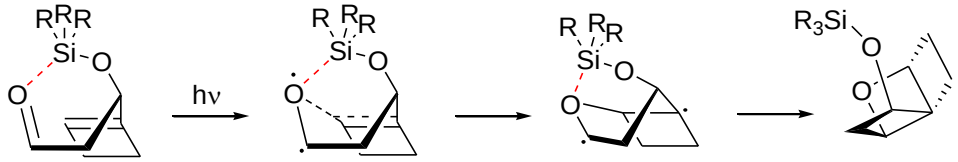


Scheme 166

TME was reacted with cyclopentenone XX in the 16 h acetonitrile conditions but difficulties arose as numerous products were formed. Signals consistent with the target tricyclic oxetane were detected but the major products were a mixture of spiro cyclopentenyloxetanes XX and XX. These products arose from an intermolecular Paternò–Büchi between the cyclopentenone and TME. This would

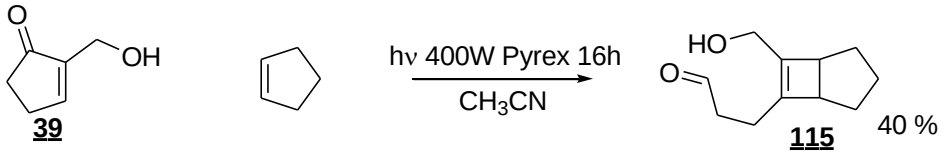
support the idea that the 4-OTBS does limit addition of the enone in a [2+2] photocycloaddition, again possibly due to steric bulk, instead leaving the P-B to be the major reaction by default.

While our success with 4-hydroxycyclopentenone were either varied, the silyl ether performed well. Further the same *endo* configuration of the oxygenated substituent was to found in all isolated oxetanes. A literature supported theory was proposed for the hydroxyl group forming a hydrogen bond with the carbonyl species and thus locking the molecule in a particular conformer during the reaction.We can also propose the following model for the silyl ether:



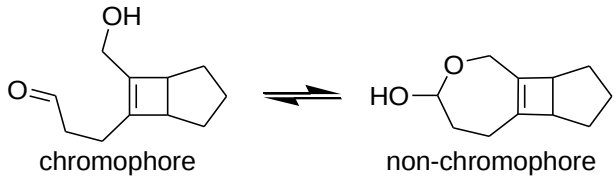
Similarly to Scheme 116, the TBS group can act as a Lewis acid and stabilize some of the reactive conformers.

2-substituted cyclopentenones were then subjected to our conditions: 5 mmols of cyclopentenonen tenfold excess of alkene in acetonitrile and 16 hours of irradiation.



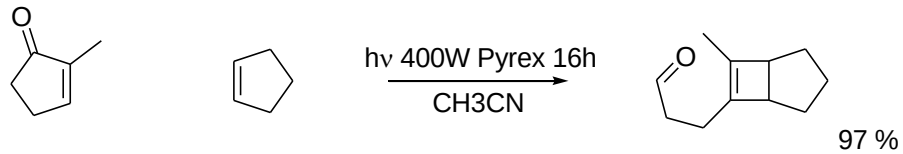
Scheme 167

When the Baylis-Hillman adduct **39** and cyclopentene were irradiated in acetonitrile for 16 h, the reaction progressed to the tandem transformation stage but no further. The cyclobutene aldehyde **115** was isolated in 40 % yield. At this point, a concern was raised about the possibility of an intramolecular hydroxyaldehyde/hemiacetal equilibrium:



Scheme 168

Our previous experiments suggest that the cyclobutene aldehyde forms hemiacetals in methanol rendering the former unreactive in photochemical conditions. It is possible that a similar phenomenon impedes formation of the oxetane. To explore this possibility, we utilized 2-methylcyclopentenone XX. Irradiation in acetonitrile for 16 hours furnished only the cyclobutene aldehyde in 97 % yield. Only very limited traces of signals consistent with the oxetane ring signals were detectable.

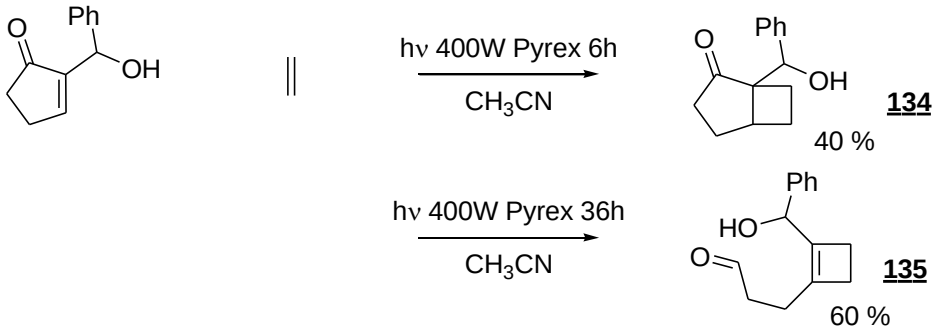


114

Scheme 169

This suggests that the problem is the tetrasubstituted double bond, due to 2-substitution of the cyclopentenone. Paternò–Büchi reactions have been described between ketones and tetrasubstituted alkenes, so it isn't fundamentally impossible.[545]
In both cases, no oxetane material was detected, meaning that the problem is overall non-reactivity and not a branching towards alternate reactivity, since the aldehyde is not consumed.

The Baylis-Hillman phenyl cyclopentenone **40** was reacted with ethylene to see whether a less cumbersome alkene than cyclopentene would react more easily.



134

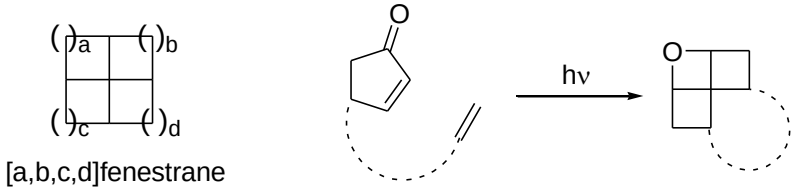
135

Scheme 170

Irradiation in acetonitrile of XX with ethylene bubbling through did yield the [2+2] adduct after 6 hours but the cyclobutene aldehyde compound could only be isolated after prolonged irradiation (36 h). The influence of the alkene partner is limited here, but the substrate appears to be less reactive than others.

Extension of the method towards the synthesis of fenestranes

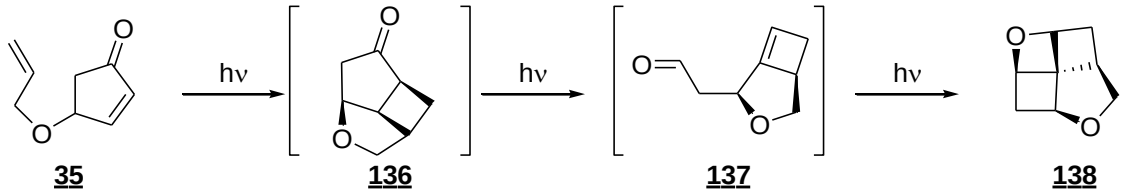
Inspired by the considerable interest in the synthesis of fenestranes[546–548], polycyclic molecules with a central spiro carbon, we investigated the possibility of preparing oxafenestranes using the triple, sequential photochemical transformation.



Scheme 171

Fenestranes are an curiosity, a topic of interest to modern organic chemists[549], but some recent research papers document their successful use as pharmalogical compounds.[550–553] A few examples of naturally occurring fenestranes have been described, such as Laurenene, a diterpene from the essential oil of *Dacrydium cupressinum* with a [5.5.5.7]fenestrane core .[554,555] Its synthesis has been described by several groups.[556–558] One of the core interests of fenestranes is the study of the central carbon and its geometry.[548,559,560] The smallest fenestrane to date is [4,4,4,5] fenestrane.

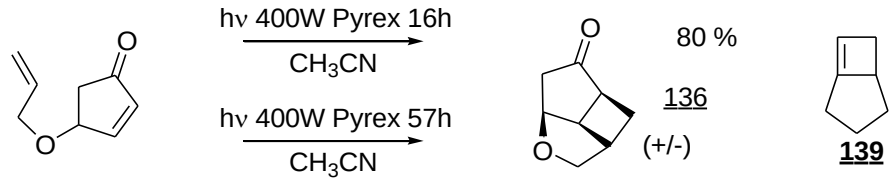
We decided to try our conditions (acetonitrile 16h) with 4-allylcyclopentenone **35** hoping to go past the [2+2] photocycloaddition. The irradiation of this compound was described by Jommi *et al.* leading to the [2+2] adduct **136**.[422] We hope that prolonged irradiation would induce Norrish I fragmentation and hydrogen abstraction furnishing **137**, which would undergo Paternò–Büchi photocycloaddition to oxetane **138**, the target oxa-fenestrane.



35 **136** **137** **138**

Scheme 172

Irradiation of cyclopentenone **35** for 16h was however disappointing: only the [2+2] adduct **136** was obtained without further conversion to the cyclobutene aldehyde, much less the oxetane.

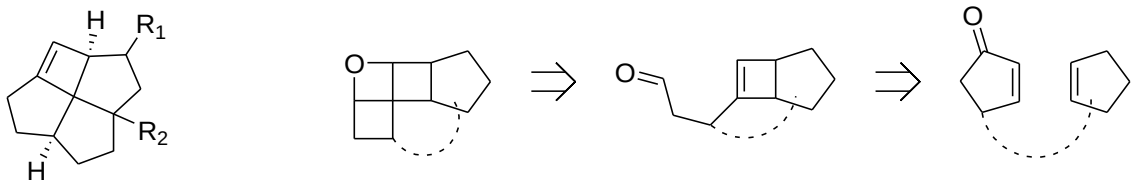


139

Scheme 173

This can be explained by the high structual instability of aldehyde **137**, which would be a severely bent alkene due to the XX core.[561] Another possible problem, more general to intramolecular tandem reactions, is that the γ hydrogen abstraction transition state (the *pseudo* 5-memebered ring) is inaccessible due to geometrical constraints (no rotation possible for example). This could be alleviated by having longer side chains to allow for greater rotational freedom.

The only described molecules (therefore stable, obtainable species) comprising an **139** core have further substituents that may allay the instability of the bridgehead double bond. For example, Keese *et al.* have described several fenestranes of general structure **140**.[562] Therefore, performing the intramolecular photochemical sequence with cyclopentene bearing a cycloalkenyl chain such as **142** might allow for formation of the cyclobutene aldehyde, paving the way for a **141**-type oxetane.



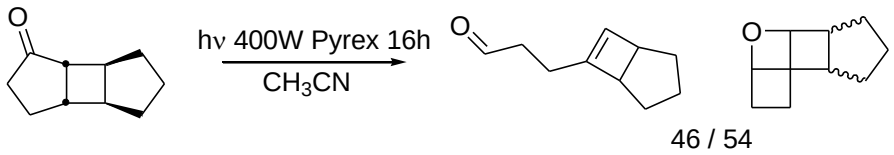
140 **141** **142**

Scheme 174

On the question of alkenyl side chains, our efforts to prepare O-homoallyl 4-hydroxycyclopentenone were unsuccessful but deserve testing. While the resultant cyclobutene aldehyde would still be a anti-Bredt alkene, the larger ring might be stable.

Irradiation of ketones

We tested the irradiation of the bicyclic ketones in acetonitrile and found that conversion to the oxetane was poor, giving a roughly 1:1 mixture after 16h of irradiation. This again shows the use of working in *one pot* conditions.



Scheme 175

This suggests that the reactions are interdependant. As previously noted, conversion to the oxetane slows to a halt between 10 and 16h of irradiation. It is possible that cyclopentenone for exemple acts as a photosensitizer for the Paternò–Büchi reaction and its consumption halts the latter reaction.

While some limitations to the reaction were uncovered, it is most important to recognize that several structures have been prepared with average to good yields, all containing the previously undescribed tricyclic oxetane core.

Future ventures of interest

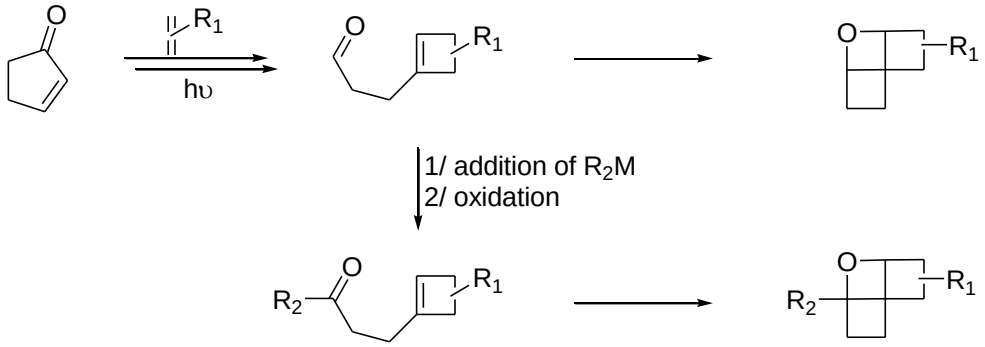
As we have stated, the tricyclic oxetane core is totally original. There is an extensive chemistry to be developed on the potential uses of these oxetanes: reactions with nucleophiles, etc…

The avenue of fenestrane synthesis deserves further interest: extending the length of the linker might allow for the tandem reaction to occur and then the synthesis of the oxetane becomes more feasible.

In any case, the synthesis of cyclopentenones (reviewed in chapter 2) is very rich and numerous methods exist to prepare enantiomerically enriched cyclopentenones. These could then be subjected to the apparently highly diastereoselective triple photochemical reaction and yield

complex oxetane structures with high enantiopurity. Assemblies of these chiral oxetanes could be used to prepare chiral pockets for the purpose of performing enantioselective transformations.

Finally, the intermediate aldehydes could be isolated and the final intramolecular reaction studied in greater detail. It could also be possible at this point to transform the aldehydes into a ketone in an addition-oxidation sequence. Should the ketone react as the aldehyde in the PB reaction, wecould access tricyclic oxetanes substituted in a position that cannot be reached starting from cyclopentenone (the R2 substituent is formally a 1-substituent).



Conclusion

The triple photochemical reaction was an unexpected discovery made in the course of the study of the tandem photochemical reaction. We managed to uncover conditions that allowed for the synthesis of polycyclic oxetanes containing a oxatricyclo[4.2.0.01,4]octane in an easy *one-pot* sequential transformation starting from a variety of cyclopentenones and alkenes.

The transformation appears to show great diastereoselectivity when a oxygenated 4-substituent is present, however 2-substituents completely stop the reaction.

Conclusion

This project has undoubtedly expanded our knowledge of the photochemistry of cyclopentenones and alkenes, strengthened the case for the developpement of the photochemical synthesis of cyclobutene aldehydes and uncovered a route to previously unknown tricyclic oxetane derivatives. However, while the road is now open, the road is not yet clear.
Several limitations have been exposed for both reactions: certain alkenes induce regioselectivity and chemocselectivity issues and substituents on the 2 position of the cyclopentenone hinder the formation of the oxetane. The question of substituents in the 5 position remains unanswered.

The situation can be summarized thus:

- For the cyclobutene aldehyde:
    - 2-substitution is possible and has been explored with simple alkyl groups: methyl and substituted methanol (derived from Baylis-Hillman adducts).
    - 3-substitution is impossible due to mechanistic constraints, a hydrogen is necessary.
    - 4-substituion is possible and has been explored successfully with hydroxyl derivatives
    - 5-substitution hasn't been attempted but may increase regioselectivity problems.

- For the polycyclic oxetane:
    - 2-substitution is impossible due to apparent non-formation of the oxetane in these cases.
    - 3-substitution is impossible due to mechanistic constraints, a hydrogen is necessary.
    - 4-substituion is possible and has been explored successfully with hydroxyl derivatives and yielding the *cis* diastereoisomer (relative to the oxetane oxygen and the substituent).
    - 5-substitution hasn't been attempted but may cause diasteroselectivity problems.

Concurrently, our organocatalysis experiments have yielded nothing of value, except perhaps to demonstrate the non-feasabilility of the cyclopentenone aldols by enamine catalysis.

However difficult and unrewarding this exploration of the extended photochemistry of cyclopentenones and alkenes may have been, the door is nevertheless wide open for a more comprehensive exploration of the synthetic possibilities of both the double and triple reactions. Blundering through the unknown, we have achieved the synthesis of oxetanes of a totally original structure. Our two methods (methanol 6h and acetontrile 16h) complement the already established conditions for the preparation of the bicyclic ketone.

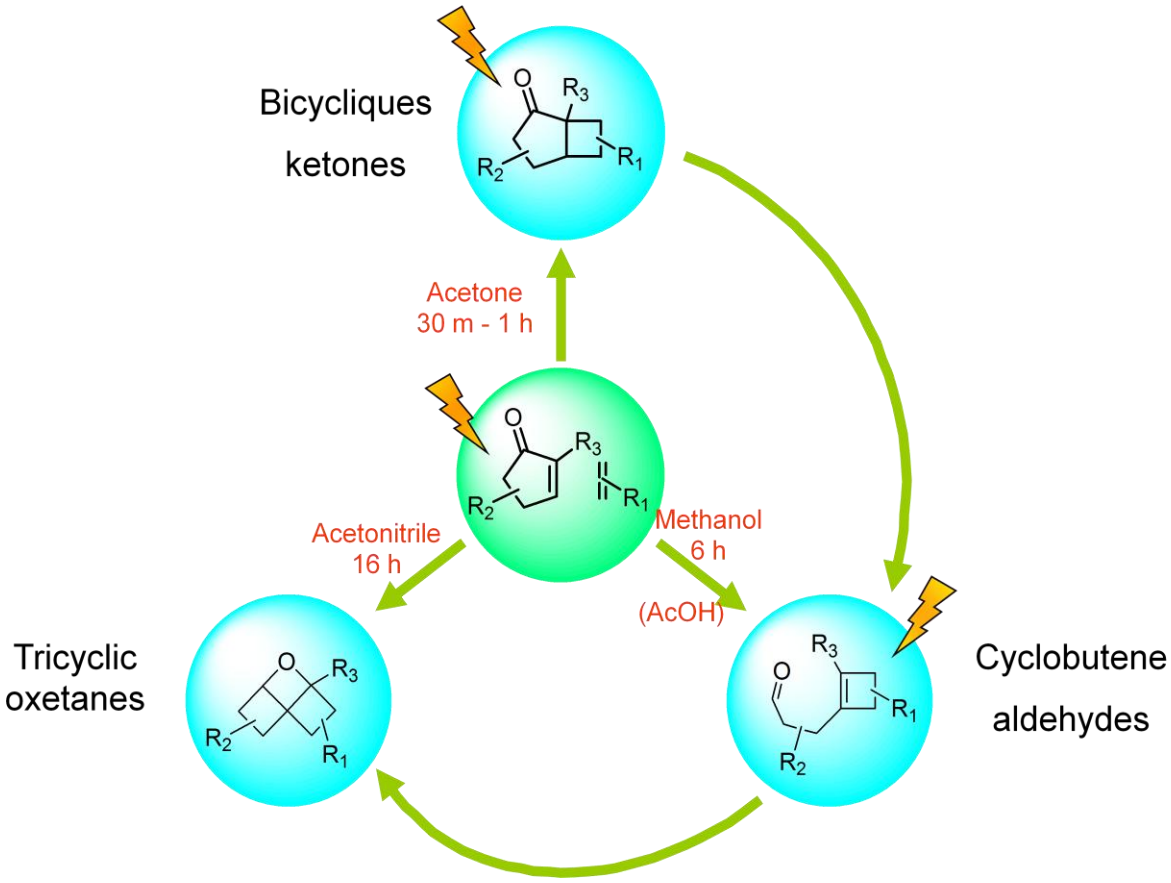

Bicycliques
ketones
Acetone
30 m - 1 h
Acetonitrile
16 h
Methanol
6 h
(AcOH)
Tricyclic
oxetanes
Cyclobutene
aldehydes

Figure 32

Experimental section

General remarks

All the experimental data gathered in this project (expect for chapter 3) was collected at the ICMMO research group (Université Paris-Sud, Orsay). NMR data was collected with the available spectrometers : Bruker AC 250 (250 MHz), AM 300 (300 MHz), AV 360 (360 MHz) and the research spectrometer, a Bruker 600 MHz, for advanced experiments. Chemical shifts are expressed with respect to residual protonated solvent (δ = 7.27 ppm for $CHCl_3$), which served as an internal standard. 13C NMR spectra were recorded with a the same spectrometers; chemical shifts are expressed with respect to the deuterated solvent (δ = 77.0 ppm for $CDCl_3$). Signals are identified with the standard nomenclatura (m multiplet, s singlet, d doublet, dd doublet of doublets, etc…).

Fourier transform IR spectra were recorded with a Perkin–Elmer Spectrum One spectrophotometer.

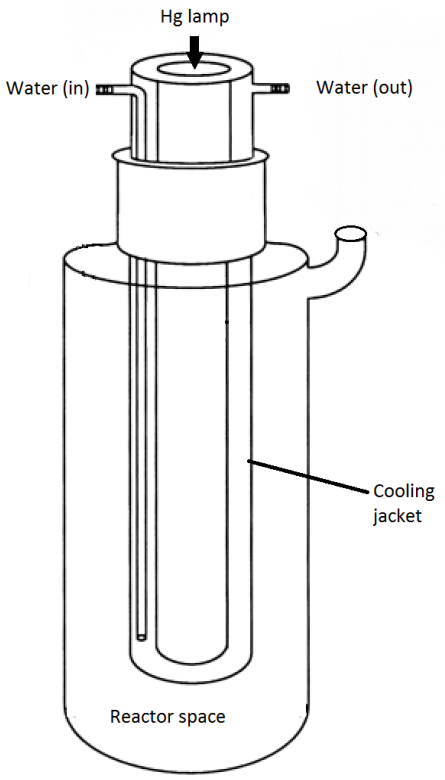
Reactions were monitored, reactants permitting, by GC with a CE Instruments GC 900 Series apparatus bearing a BP 10 30 m x 0.25 mm column (semi polar) slaved to a control computer.

MS and HRMS experiments were carried out at the ICMMO research group (Université Paris-Sud, Orsay) by the Mass Spectroscopy unit. Mass spectra were measured at 70eV (EI) or with ionized NH_3 (CI) with a Trace DSQ Thermo Electron spectrometer. High resolution mass spectra were measured with a Perkin-Elmer FINNIGAN MAT 95 S spectrometer.

TLC were carried out of a silica-coated glass plates (Merck 60F254) and chromatographies are run on (35-70 mesh) SDS silica gel.

All products mentionned in chapter 3 were characterized at Cagliari University : Varian 300 Mhz spectrometer and Agilent 5973N (Cpsil 32m) GCMS apparatus working in IE mode with 70 eV strength.

The photochemical reaction were carried out either in a small (reactor volume 250 mL) or large reactor (reactor volume 1 L) of general construction as follows:



The glassware is Pyrex and cooled by running tap water to maintain the reactor at near room temperature. A medium pressure Mercury 400 W lamp was used for all reactions. Unless mentioned otherwise, all reactions are run in the small reactor. The large reactor is used for more than 10 mmol cyclopentenone reactions and requires longer irradiation times (with respect to the small reactor) because of reactor geometry.

Solvents are purified in the traditional fashion: THF with sodium/benzophenone and dichloromethane with a purification apparatus. Methanol and acetonitrile are HPLC quality commercial qualities. Toluene is distilled over sodium.

Standard procedures

Standard photochemical reaction A:

80 % to 100 % of the designated solvent (200-250 mL for the small reactor) is placed in the open photochemical reactor (cooling jacket and light not yet inserted) and the apparatus is placed in the sonic bath for at least 15 minutes. The sonic bath is then removed, reagents are added (cyclopentenone 5 mmol and alkene 50 mmol), the volume of designated solvent is completed, any additives (such as acetic acid) are added at this point, the central cooling system and light are added and argon is bubbled for a maximum of 5 minutes. An aliquot is collected and injected in GC as a reference sample. Bubbling is stopped and the reactor is partially sealed allowing only for a small flow of argon at the top of the reactor (needles for entry and exit of gas).

Once the reactor is sealed, irradiation is carried out for the designated amount of time. The reaction is followed by GC.

At the end of the reaction, the medium is transferred into a flask and the solvent carefully removed with a rotatory evaporator. Crude material is analyzed by NMR and is purified by flash chromatography.

Standard photochemical reaction B:

80 % to 100 % of the designated solvent (200-250 mL for the small reactor) is placed in the open photochemical reactor (cooling jacket and light not yet inserted) and the apparatus is placed in the sonic bath for at least 15 minutes. The sonic bath is then removed, reagents are added (cyclopentenone 5 mmol) and the volume of designated solvent is completed, any additives (such as acetic acid) are added at this point, the central cooling system and light are added and ethylene is bubbled for at least 30 minutes. In the meantime, an aliquot is collected and injected in GC as a reference sample. The reactor is partially sealed allowing only for a small flow of argon at the top of the reactor (needles for entry and exit of gas).

Once the reactor is sealed, irradiation is carried out for the designated amount of time. The reaction is followed by GC.

At the end of the reaction, the medium is transferred into a flask and the solvent carefully removed with a rotatory evaporator. Crude material is analyzed by NMR and is purified by flash chromatography.

Standard photochemical reaction C:

80 % to 100 % of the designated solvent (200-250 mL for the small reactor) is placed in the open photochemical reactor (cooling jacket and light not yet inserted) and the apparatus is placed in the sonic bath for at least 15 minutes. The sonic bath is then removed, reagents are added

(cyclopentenone 5 mmol and alkene 50 mmol), the volume of designated solvent is completed, any additives (such as acetic acid) are added at this point, the central cooling system and light are added and argon is bubbled for a maximum of 5 minutes. An aliquot is collected and injected in GC as a reference sample. Bubbling is stopped and the reactor is partially sealed allowing only for a small flow of argon at the top of the reactor (needles for entry and exit of gas).

Once the reactor is sealed, irradiation is carried out for the designated amount of time. The reaction is followed by GC.

The irradiated solution is transferred into a flask and 2 eq (in respect to initial proportions of enone, 37.83 g/mol) of $NaBH_4$ and a stirring bar are added. The reaction is stirred for 4-5 h at room temperature and followed by TLC.

When the reaction is finished, the solvent is partially removed and the reaction quenched with a small volume of water (10-20 mL). Extraction by diethyl ether, drying and evaporation of the organic fractions yields the crude that can then be chromatographied.

Standard organocatalytic transformation:

The cyclopentanone derivative, such as 2-acetoxycyclopentanone (284 mg, 2 mmol) is placed in a small container/flask. The aldehyde, such as 4-nitrobenzaldehyde (75.7 mg, 0.5 mmol), an organocatalyst (0.1 mmol, 5% mmol) and a small stirring device are added. The reaction is stirred until the reaction is complete which is visible when the the media is no longer heterogenous.

Standard Baylis-Hillman transformation:

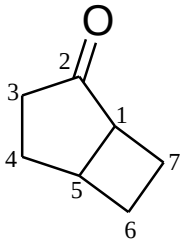
In a 100 mL flask with a stirring bar: cyclopenten-1-one (20 mmol) is placed in 50 mL $CHCl_3$/MeOH (3:2) and the aldehyde (25 mmol) is added at ambient temperature. Tributylphosphine (1 mmol, 0.24 mL) was added by syringe and the mixture was stirred overnight. The solvent was then removed by rotator evaporation

and the resulting mixture was purified by flash chromatography.

Irradiation of cyclopentenone and ethylene

Standard procedure B: 25 min in acetone with 410 mg (5 mmol) cyclopentenone and ethylene gas gives 582 mg of crude material that was mostly the following compound (near quantitative yield). A analytically pure sample could be obtained by a difficult bulb-to-bulb distillation (300 mg gives 35 mg at 45-50 °C / 2 mbar).

Bicyclo[3.2.0]heptan-2-one **97**



$C_7H_{10}O$ (110,15 g/mol)

Yellowish oil

R_f = 0.3 (petroleum ether/diethyl ether 9:1)

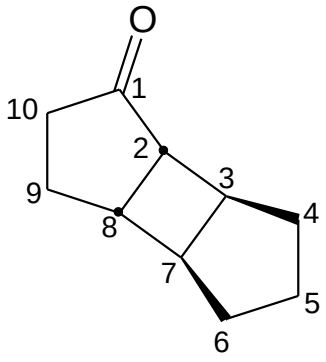
^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.07 - 2.95 (m, 1 H, H_1), 2.75 - 2.59 (m, 2 H, H_5, H_7), 2.44 - 2.26 (m, 3 H, H_3, H_4, H_7), 2.17 - 1.96 (m, 1 H, H_6), 1.91 - 1.75 (m, 3 H, H_3, H_4, H_6)

^{13}C NMR (91 MHz, $CDCl_3$, δ): 223.1 (C_2), 44.9 (C_1), 36.7 (C_3), 35.3 (C_5), 27.9 (C_4), 24.9 (C_6), 22.1 (C_7).

Irradiation of cyclopentenone and cyclopentene

Standard procedure A in the large reactor: 3h in acetone with 3.28 g (40 mmol) cyclopentenone and 20 mL mmol (200 mmol) cyclopentene gives 7 g crude material, 3.278 g (54 % yield) after chromatography (petroleum ether/diethyl ether 9:1) of the following compound:

Tricyclo[5.3.0.$0^{2,6}$]decan-3-one **<u>102</u>**



$C_{10}H_{14}O$ (150,22 g/mol)

Transparent liquid

R_f = 0.4 (pentane/diethyl ether 9:1)

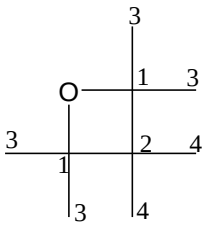
^{1}H NMR (360 MHz, $CDCl_3$, δ): 2.67 (ddd, J = 9.4 Hz, 12.1 Hz, 17.7 Hz, 1H, H_2), 2.52-2.39 (m, 2H, H_3, H_8), 2.32-1.36 (m, 11H).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 222.1 (C_1), 48.7 (C_2), 43.0 (C_7), 40.3 (C_3), 38.5 (C_8), 36.1 (C_{10}), 33.0 ($C_{4/6}$), 32.9 ($C_{4/6}$), 28.1 (C_9), 24.5 (C_5).

Irradiation of tetramethylethylene

Standard procedure A without cyclopentene, but simply 6 mL tetramethylethylene and 6 h in acetone.

Hexamethyloxetane **105**



$C_9H_{18}O$ (142,23 g/mol)

Yellowish liquid

Impurity observed in photochemical reaction involving TME in acetone.

^{1}H NMR (250 MHz, $CDCl_3$, δ): 1.26 (s, 12H), 1.07 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 110.1 (C_1, 2C), 47.7 (C_2), 26.6 (C_3, 4C), 20.5 (C_4, 2C).

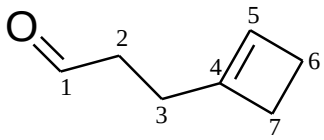
Photochemical transformations in methanol

Unless otherwise stated in this section, all reactions in methanol yield crude reaction mixtures near the expected mass for full conversion to 1:1 adducts of the starting materials.

Irradiation of cyclopentenone and ethylene

Standard procedure B: 6h in methanol with 410 mg (5 mmol) cyclopentenone and ethylene gas gives 515 mg (93 % yield) of the following compound:

3-Cyclobut-1-enyl-propionaldehyde **98**



$C_7H_{10}O$ (110,15 g/mol)

Yellowish oil

R_f = 0.4 (petroleum ether/diethyl ether 9:1)

^{1}H NMR (250 MHz, $CDCl_3$, δ): 9.72 (t, *J* = 1.4 Hz, 1H, H_1), 5.63 (br s, 1H, H_5), 2.50 (td, *J* = 1.4 Hz, 6.6 Hz, 2 H, H_2), 2.35-2.36 (m, 2 H, H_3), 2.25-2.30 (m, 4H, H_7, H_6, H_7, H_6)

^{13}C NMR (62 MHz, $CDCl_3$, δ): 202.0 (C_1), 147.9 (C_4), 127.8 (C_5), 40.6 (C_2), 30.9 (C_3), 26.3 (C_7), 23.4 (C_6).

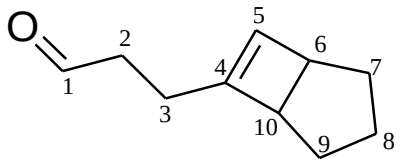
IR (film, NaCl): 2934.7 cm^{-1}, 2872.5 cm^{-1}, 1723.8 cm^{-1}, 1632.8 cm^{-1}, 1442.9 cm^{-1}.

MS (CI, *m/z*): 128.3 ($[M+NH_4]^+$), 110.0 (MH^+)

Irradiation of cyclopentenone and cyclopentene

Standard procedure A: 6h in methanol with 30 µL (0.5 mmol) acetic acid with 410 mg (5 mmol) cyclopentenone and cyclopentene 5 mL (50 mmol) gives 745 mg (near quantitative) yield of the following compound.

3-Bicyclo[3.2.0]hept-6-en-6-yl-propionaldehyde **103**



$C_{10}H_{14}O$ (150,22 g/mol)

Yellowish oil

R_f = 0.6 (Petroleum ether/diethyl ether 7:3)

^{1}H NMR (250 MHz, $CDCl_3$, δ): 9.72 (t, *J* = 1.8 Hz, 1H, H_1), 5.51 (br s, 1H, H_5), 2.97-3.0 (m, 1 H, H_{10}), 2.92-2.94 (m, 1 H, H_6), 2.50 (td, *J* = 1.8 Hz, 7.3 Hz, 2 H, H_2, H_2), 2.30-2.13 (m, 2H, H_3), 1.60-1.39 (m, 4H, H_7, H_8, H_8, H_9), 1.16-1.05 (m, 2H, H_7, H_9).

^{13}C NMR (62 MHz, $CDCl_3$, δ): 201.9 (C_1), 148.1 (C_4), 128.6 (C_5), 47.8 (C_{10}), 43.8 (C_6), 40.5 (C_2), 26.3 ($C_{7/9}$), 25.0($C_{7/9}$), 23.0(C_8), 21.4 (C_3).

IR (film, NaCl): 2936.6 cm^{-1}, 2852.7 cm^{-1}, 1726.7 cm^{-1}, 1630.3 cm^{-1}, 1442.8 cm^{-1}.

MS (CI, *m/z*): 168.0 ($[M+NH_4]^+$), 151.0 (MH^+).

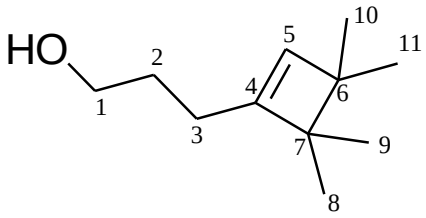
MS (IE, *m/z*): 149.0, 121.0, 107.0, 94.0, 93.0, 91.0, 79.0 (major), 77.0, 67.0.

HRMS (APCI, H^+): 151.1118 ($C_{10}H_{15}O$, expected 151.1117).

Irradiation of cyclopentenone and tetramethylethylene and subsequent reduction

Standard procedure C: 6h in methanol with 30 µL (0.5 mmol) acetic acid with 410 mg (5 mmol) cyclopentenone and tetramethylethylene gives respectively 395 mg (47 % yield) and 185 mg (22 % yield) of the following alcohols.

3-(3,3,4,4-Tetramethyl-cyclobut-1-enyl)-propanol **104**



$C_{11}H_{20}O$ (168,28 g/mol)

Transparent oil

R_f = 0.16 (pentane/diethyl ether 3:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.64 (t, *J* = 1.6 Hz, 1H, H_5), 3.67 (t, *J* = 6.7 Hz, 2H, H_1), 1.96 (dt, *J* = 1.6, 7.8 Hz, 2H, H_3), 1.70 (m, 2H, H_3), 1.00 (s, 12 H, H_8, H_9, H_{10}, H_{11})

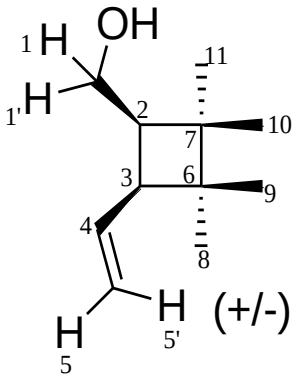
^{13}C NMR (90 MHz, $CDCl_3$, δ): 154.5 (C_4), 133.1 (C_5), 62.9 (C_1), 47.2 (C_6, C_7), 44.8 (C_6, C_7), 29.5 (C_2), 24.3 (C_3), 23.5 ($C_{8/9/10/11}$), 22.2 ($C_{8/9/10/11}$).

IR (film, NaCl): 3346.7 (broad) cm^{-1}, 2946.4 cm^{-1}, 1636.7 cm^{-1}, 1450.3 cm^{-1}.

MS (CI, *m/z*): 169.3 (MH^+), 186.4 ($[M+NH_4]^+$).

HRMS (ESI, H^-): 167.1073 ($C_{11}H_{19}O$, expected 167.1441).

cis-(2,2,3,3-tetramethyl-4-vinylcyclobutyl)methanol **105**



$C_{10}H_{20}O$ (168,28 g/mol)

Transparent oil

R_f = 0.21 (pentane/diethyl ether 3:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.05 (ddd, *J* = 16.5 Hz, 10.8 Hz, 10.3 Hz, 1H, H_4), 5.05 (dd, *J* =10.3 Hz, 2.4 Hz, 1H, H_5), 5.02 (ddd, *J* = 16.5 Hz, 2.4 Hz, 0.66 Hz, 1H, $H_{5'}$), 3.80 (dd, *J* = 11.1 Hz, 8.7 Hz, 1H, H_1), 3.74 (dd, *J* = 11.1 Hz, 7.3 Hz, 1H, $H_{1'}$), 2.62 (dd, *J* = 10.8 Hz, 9.4 Hz, 1H, H_3), 2.34 (ddd, *J* = 9.4, 8.7, 7.3 Hz, 1H, H_2), 1.025 (s, 3H, H_8), 1.019 (s, 3H, H_{11}), 0.98 (s, 3H, H_9), 0.86 (s, 3H, H_{10}).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 136.6 (C_4), 117.4 (C_5), 61.2 (C_1), 48.4 (C_3), 46.7 (C_2), 40.1 ($C_{6/7}$), 38.6 ($C_{6/7}$), 26.3 (2C, $C_{8/11}$), 20.5 (C_{10}), 20.2 (C_9).

IR (film, NaCl): 3375.6 (broad) cm^{-1}, 2956.2 cm^{-1}, 1633.9 cm^{-1}, 1458.7 cm^{-1}, 1368.2 cm^{-1}.

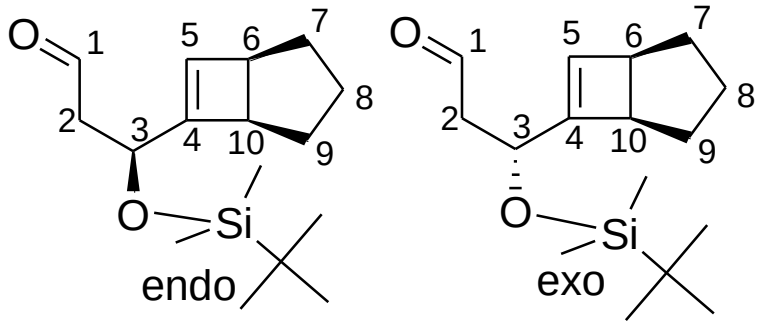
MS (CI, *m/z*): 186.2 ($[M+NH_4]^+$).

Irradiation of 4-tertbutyldimethylsilylcyclopentenone and cyclopentene

Standard procedure A: 6h in methnaol with 1.05 g (5 mmol) 4-OTBS-cyclopentenone and cyclopentene 5 mL (50 mmol) gives 40 % combined yield of the following mixture.

The two isomers could not be separated chromatographically or spectrographically. They are identified as A and B, A being very slightly major (55/45).

Mixture of *endo*- and *exo*-bicyclo[3.2.0]hept-6-en-6-yl)-3-tertbutyldimethylsilyloxypropanal. **<u>111</u>**



$C_{16}H_{28}O_2Si$ (280,48 g/mol)

Yellowish oil

R_f = 0.30 (petroleum ether/diethyl ether 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.79 (t, J = 2.5 Hz, 2.5 Hz, 1H, H_{1A}), 9.77 (t, J = 2.5 Hz, 2.5 Hz, 1H, H_{1B}), 5.70 (s, 1H, $H_{5A/B}$), 4.61-4.54 (m, 1H, H_{3A}), 4.56-4.49 (m, 1H, H_{3B}), 3.14 (dd, J = 7.10, 3.22 Hz, 1H, H_{6B}), 3.07 (dd, J = 7.25, 3.08 Hz, 1H, H_{6A}), 3.02-2.91 (m, 2H, $H_{10A/B}$), 2.63-2.49 (m, 2H, $H_{2A/B}$), 1.69-1.56 (m, 2H, $H_{7/9A/B,}$ $H_{7/9A/B}$), 1.55-1.44 (m, 2H, $H_{8A/B,}$ $H_{8A/B}$), 1.24-1.07 (m, 2H, $H_{7/9A/B,}$ $H_{7/9A/B}$), 0.87 (s, 9H, Si*t*Bu$_A$), 0.86 (s, 9H, Si*t*Bu$_B$), 0.04 (s, 3H, $SiMe_A$), 0.05 (s, 3H, $SiMe_A$, $SiMe_B$), 0.06 (s, 3H, $SiMe_B$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 201.8 (C_{1A}, C_{1B}), 149.6 (C_{4A}), 149.3 (C_{4B}), 130.2 (C_{5B}), 129.4 (C_{5A}), 65.6 (C_{3A}), 65.4 (C_{3B}), 49.3 (C_{2A}), 49.1 (C_{2B}), 46.2 (C_{6B}), 46.1 (C_{6A}), 43.6 (C_{10B}), 43.4 (C_{10A}), 26.2 ($C_{7/9A}$, 2C),, 25.6 ($C_{7/9B}$, TBS, 4C), 25.5 ($C_{7/9B}$), 23.1 (C_{8A}), 23.0 (C_{8B}), 18.0 (TBS C_q), -4.5 ($SiMe_B$), -4.6 ($SiMe_A$), -5.0 ($SiMe_A$), -5.2 ($SiMe_B$).

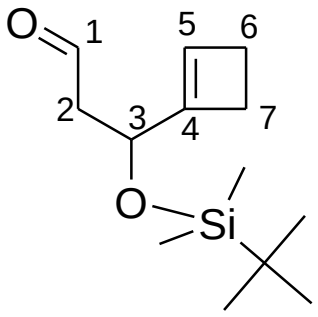
MS (CI, *m/z*): 298.1 ($[M+NH_4]^+$), 149.0 ($[MH\text{-}TBDMSOH]^+$).

HRMS (APCI, H^+): 281.1920 ($C_{16}H_{29}O_2Si$, expected 281.1931).

Irradiation of cyclopentenone and ethylene

Standard procedure A: 6h in methnaol with 1.05 g (5 mmol) 4-OTBS-cyclopentenone and ethylene gas gives 445 mg (37 % yield).

3-cyclobutenyl-3-tertbutyldimethylsilyloxypropanal **12**



$C_{13}H_{24}O_2Si$ (240,41 g/mol)

Transparent oil

R_f = 0.37 (petroleum ether/diethyl ether 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.79 (t, *J* = 2.3 Hz, 2.6 Hz, 1H, H_1), 5.84 (d, *J* = 0.9 Hz, 1H, H_5), 4.63-4.56 (m, 1H, H_3), 2.61 (ddd, *J* = 2.6 Hz, 6.5 Hz, 15.8 Hz, 1H), 2.52 (ddd, *J* = 2.3 Hz, 5.1 Hz, 15.8 Hz, 1H), 2.47-2.43 (m, 2H, $H_{6/7}$, $H_{6/7}$), 2.37-2.31 (m, 2H, $H_{6/7}$, $H_{6/7}$), 0.87 (s, 9H, Si*t*Bu), 0.05 (s, 6H, $SiMe_2$).

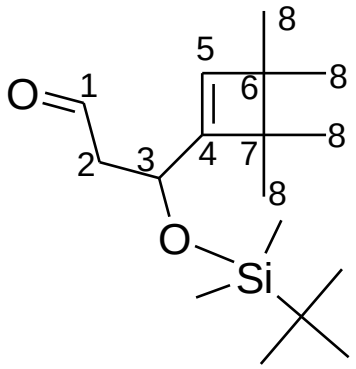
^{13}C NMR (75 MHz, $CDCl_3$, δ): 201.7 (C_1), 149.7 (C_4), 128.9 (C_5), 66.2 (C_3), 49.2 (C_2), 28.7 ($C_{6/7}$), 26.2($C_{6/7}$), 25.6 (Si_tBu), 18.1 (TBS C_q), -4.6 (SiMe), -5.1 (SiMe).

HRMS (APCI, H^+): 241.1603 ($C_{13}H_{25}O_2Si$, expected 241.1618).

Irradiation of cyclopentenone and tetramethylene

Standard procedure A: 6h in methanol with 1.05 g (5 mmol) 4-OTBS-cyclopentenone and 50 mmol TME (6 mL) gives several fractions after chromatography (petroleum ether/diethyl ether, gradiant from 95/5 to 8/2) including the two following compounds with respectively 400mg (27 % yield) and 133 mg (8% yield).

3-(3,3,4,4-Tetramethyl-cyclobut-1-enyl)-3-tertbutyldimethylsilyloxy propanol **112**



$C_{17}H_{32}O_2Si$ (296,52 g/mol)

Transparent oil

R_f = 0.4 (pentane/diethyl ether 9:1)

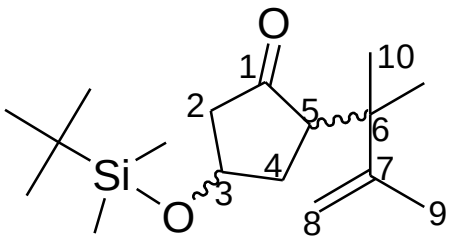
^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.78 (t, J = 2.6 Hz, 2.6 Hz, 1H, H_1), 5.86 (d, J = 1.3 Hz, 1H, H_5), 4.61 (ddd, J = 1.3 Hz, 5.3 Hz, 6.2 Hz, 1H, H_3), 2.54 (m, 2H, H_2), 1.10 (s, 3H, Me_8), 1.06 (s, 3H, Me_8), 1.02 (s, 3H, Me_8), 0.91 (s, 3H, Me_8), 0.87 (s, 9H, Si*t*Bu), 1.07 (s, 1H, SiMe),0.06 (s, 1H, SiMe).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 201.9 (C_1), 154.1 (C_4), 135.9 (C_5), 65.0 (C_3), 49.8 (C_2), 47.1 ($C_{6/7}$), 44.8 ($C_{6/7}$), 25.7 (TBS, 3C), 23.3 (C_8), 23.1 (C_8), 22.9 (C_8), 22.9 (C_8), 18.0 (TBS C_q), -4.4 (SiMe), -5.1 (SiMe).

MS (CI, *m/z*): 182.1 ([M+NH_4-TBDMSOH]$^+$), 165.1 ([MH-TBDMSOH]$^+$), 314.2 ([M+NH_4]$^+$).

4- tertbutyldimethylsilyloxy-2-(2,3-dimethylbut-3-en-2-yl)cyclopentenone **113**

There is apparently one diastereoisomer, since only one set of signals was visible and one “spot” was detected by TLC.



$C_{17}H_{32}O_2Si$ (296,52 g/mol)

Transparent liquid

R_f = 0.65 (pentane/diethyl ether 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.79-4.71 (m, 2H, H_8, H_8), 4.50 (t, J = 3.08, 3.08 Hz, 1H, H_3), 3.73-3.66 (m, 1H, H_5), 2.42-1.96 (m, 4H, H_2, H_2, H_4, H_4), 1.70 (s, 3H, Me_9), 1.17 (s, 3H, Me_{10}), 1.09 (s, 3H, Me_{10}), 0.81 (s, 9H, Si*t*Bu), 0.03 (s, 3H, SiMe), 0.00 (s, 3H, SiMe).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 217.4 (C_1), 151.3 (C_7), 110.5 (C_8), 71.9 (C_3), 50.7 (C_2), 49.2 (C_5), 39.5 (C_6), 36.7 (C_4), 25.7 (Si*t*Bu, 3C), 25.2 (C_{10}), 23.6 (C_{10}), 19.5 (C_9), 17.7 (TBS C_q), -4.3 ($SiMe_2$, 2C).

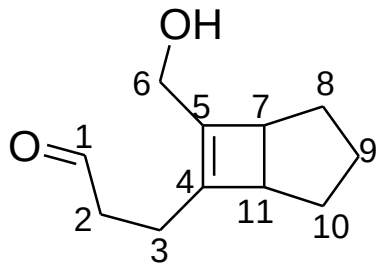
MS (CI, *m/z*): 182.1 ($[M+NH_4\text{-TBDMSOH}]^+$), 314.3 ($[M+NH_4]^+$).

HRMS (ESI, Na+): 319.2055 ($C_{17}H_{32}NaO_2Si$, expected 319.2064).

Irradiation of cyclopentenone 39 and cyclopentene

Standard procedure A: 6h in methnaol with 560 mg (5 mmol) cyclopentenone **39** and cyclopentene 5 mL (50 mmol) gives 468 mg (52 % yield).

3-(7-(hydroxymethyl)bicyclo[3.2.0]hept-6-en-6-yl)propanal **<u>115</u>**



$C_{11}H_{16}O_2$ (180,24 g/mol)

Transparent oil

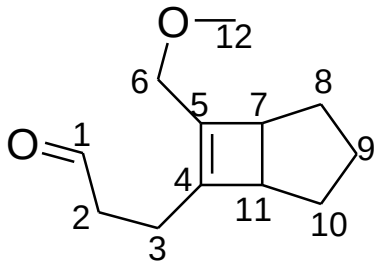
^{1}H NMR (360 MHz, $CDCl_3$, δ): 9.63 (s, 1H, H_1), 4.03-3.75 (m, 2H, H_6, H_6), 2.95-2.75 (m, 2H, H7, H_{11}), 2.47 (t, J = 7.1 Hz, 7.1 Hz, 2H, H_2, H_2), 2.38-2.26 (m, 1H, H_3), 2.22-2.08 (m, 1H, H_3), 1.60-1.32 (m, 4H, H_8, H_9, H_9, H_{10}), 1.11-0.90 (m, 2H, H_8, H_{10}).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 202.4 (C_1), 139.9 (C_5), 139.8 (C_4), 57.1 (C_6), 44.6 (C_{11}), 43.5 (C_7), 41.2 (C_2), 24.6 ($C_{8/10}$), 24.6 ($C_{8/10}$), 22.7 (C_9), 19.1 (C_3).

Irradiation of cyclopentenone 41 and cyclopentene

Standard procedure A: 6h in methnaol with 350 mg (2.7 mmol) cyclopentenone **41** and cyclopentene 2.7 mL (27 mmol) gives 369 mg (38 % yield).

3-(7-(methoxymethyl)bicyclo[3.2.0]hept-6-en-6-yl)propanal **116**



$C_{12}H_{18}O_2$ (194,27 g/mol)

Yellowish oil

R_f = 0.77 (petroleum ether/diethyl ether 1:1)

^{1}H NMR (360 MHz, $CDCl_3$, δ): 9.73 (s, 1H, H_1), 3.79 (s, 2H, H_6), 3.27 (s, 3H, H_{12}), 2.94 (m, 2H, H_7, H_{11}), 2.51 (dd, J = 7.1 Hz, 7.2 Hz, 2H, H_2, H_2), 2.38 (ddd, J = 7.2 Hz, 7.2 Hz, 14.6 Hz, 1H, H_3), 2.26 (ddd, J = 7.1 Hz, 7.1 Hz, 14.6 Hz, 1H, H_3), 1.65-1.42 (m, 4H, H_8, H_9, H_9, H_{10}), 1.20-1.02 (m, 2H, H_8, H_{10}).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 201.8 (C_1), 142.2 (C_5), 137.8 (C_4), 66.9 (C_6), 58.1 (C_{12}), 45.3 (C_{11}), 44.4 (C_7), 41.5 (C_2), 24.9 ($C_{8/10}$), 24.8 ($C_{8/10}$), 23.1 (C_9), 19.5 (C_3).

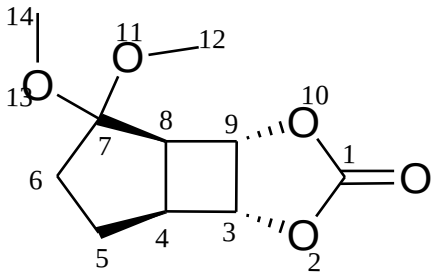
MS (CI, *m/z*): 180.0 ($[M+NH_4\text{-MeOH}]^+$), 212.0 ($[M+NH_4]^+$).

HRMS (APCI, H^+): 195.1022 ($C_{21}H_{19}O_2$, expected 195.1395).

Irradiation of cyclopentenone and vinylene carbonate

Standard procedure A: 6h in methanol with 5 mmol (410 g) cyclopentenone and 4.3 g (50 mmol) vinylene carbonate gives 60 mg (5.6 %yield) after chromatography (petroleum ether/diethyl ether 5/1).

Cis-anti-cis-8,8-dimethoxy-3,5-dioxatricyclo[5.3.0.$0^{2,6}$]decan-4-one **<u>106</u>**



(+/-)

$C_{10}H_{14}O_5$ (214,22 g/mol)

Transparent liquid

R_f = 0.55 (pentane/diethyl ether 3:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.79 (dd, J = 1.4 Hz, 5.6 Hz, 1H, H_3), 4.64 (dd, J = 0.9 Hz, 5.6 Hz, 1H, H_9), 3.19 (s, 3H, $H_{12/14}$), 3.12 (s, 3H, $H_{12/14}$), 3.00-2.86 (m, 2H, H_8, H_4), 2.12 (ddd, J = 13.4, 6.6, 1.0 Hz, 2H, H_6), 1.67 (dd, J = 13.4, 7.0 Hz, 2H, H_5)

^{13}C NMR (90 MHz, $CDCl_3$, δ): 155.7 (C_1), 109.8 (C_7), 79.7 (C_9), 75.1 (C_3), 50.6 (C_{12}), 49.6 (C_{14}), 48.1 (C_8), 43.8 (C_4), 31.9 (C_6), 25.8 (C_5).

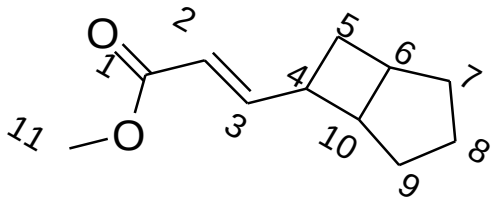
nOe (600 MHz, $CDCl_3$, δ): non-conclusive, no transfer detected between bridgehead protons.

MS (CI, *m/z*): 232.1 ($[M+NH_4]^+$).

Irradiation of 4-hydroxycyclopentenone and cyclopentene

Standard procedure C: 6h in methanol with 30 µL (0.5 mmol) acetic acid with 490 mg (5 mmol) 4-hydroxy-cyclopentenone and 5 mL (50 mmol) cyclopentenone gives 54 mg (6 %) of ester and 85 mg (11.4 %) enone.

(Z)-methyl 3-(bicyclo[3.2.0]heptan-6-yl)acrylate**108**



$C_{11}H_{16}O_2$ (180,24g/mol)

Yellowish liquid

R_f = 0.55 (pentane/diethyl ether 9:1)

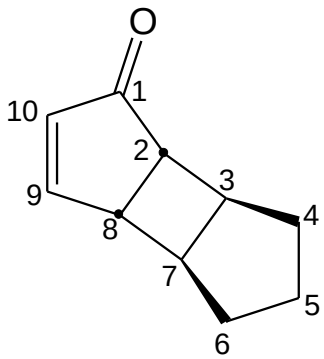
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.11 (dd, *J* = 15.58, 7.59 Hz, 1H), 5.71 (d, *J* = 15.6 Hz, 1H), 3.71 (s, 3H, H_{11}) , 2.73-2.62 (m, 1H, H_6), 2.64-2.54 (td, *J* = 6.4 Hz, 6.4 Hz, 12.5 Hz, 1H, H_{10}), 2.47 (m, 1H, H_4), 2.12-1.97 (m, 1H, H_5), 1.87-1.77 (m, 2H, H_8, H_8), 1.69 (ddd, *J* = 4.0 Hz, 9.0 Hz, 12.9 Hz,1H, H_5), 1.62-1.37 (m, 4H, H_7, H_7, H_9, H_9).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 167.5 (C_1), 153.7 (C_3), 117.7 (C_2), 51.3 (C_{11}), 43.9 (C_{10}), 39.4 (C_4), 34.1 (C_6), 32.9 ($C_{7/9}$), 32.6 ($C_{7/9}$), 29.4 (C_5), 24.8 (C_8).

IR (film, NaCl) : 2949.0 cm^{-1}, 1724.4 cm^{-1}, 1650.8 cm^{-1}, 1650.8 cm^{-1}.

MS (CI, *m/z*): 198.1 ($[M+NH_4]^+$).

Tricyclo[5.3.0.$0^{2,6}$]dec-4-en-3-one**109**



$C_{10}H_{12}O$ (148,2 g/mol)

Yellowish liquid

R_f = 0.50 (pentane/diethyl ether 9:1)

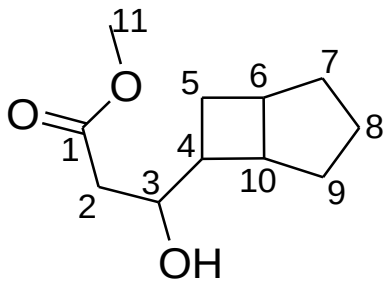
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.73 (dd, J = 3.7 Hz, 5.4 Hz, 1H, H_9), 6.25 (d, J = 5.4 Hz, 1H, H_{10}), 2.76 (d, J = 2.1 Hz, 1H, H_2), 2.52-2.32 (m, 2H, H_3, H_7), 2.27 (dd, J = 2.1 Hz, 3.7, Hz, 1H, H_8), 1.93-1.63 (m, 4H, H_4, H_4, H_6, H_6), 1.61-1.36 (m, 2H, H_5, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 212.8 (C_1), 166.5 (C_9), 134.8 (C_{10}), 47.5 (C_2), 45.0 (C_7), 43.1 (C_3), 38.7 (C_8), 32.7 (C_3), 32.1 (C_7), 24.6 (C_5).

HRMS (ESI, Na^+): 171.0779 ($C_{10}H_{12}NaO$, expected 171.0780).

Standard procedure A: 6h in methanol with 490 mg (5 mmol) 4-hydroxycyclopentenone and cyclopentene 5 mL (50 mmol) gives 237 mg (26 % yield) of the previous unsaturated ester and 50 mg (5 %) of the following ester:

Methyl 3-(bicyclo[3.2.0]heptan-6-yl)-3-hydroxypropanoate**<u>107</u>**



$C_{11}H_{18}O_3$ (198,26 g/mol)

Yellowish liquid

R_f = 0.4 (pentane/diethyl ether 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.01-3.88 (m, 1H, H_3), 3.67 (s, 3H, H_{11}), 2.66-2.51 (m, 2H, H_4, H_6), 2.44 (ddd, *J* = 2.8 Hz, 13.6 Hz, 16.2 Hz, 1H, H_2), 2.26 (dd, *J* = 9.3 Hz, 16.2 Hz, 1H, H_2), 1.85-1.70 (m, 2H, H_5, H_5), 1.53-1.39 (m, 6H, H_7, H_7, H_8, H_8, H_9, H_9).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 173.4 (C_1), 72.0 (C_3), 51.6 (C_{11}), 42.4 (C_{10}), 40.4 (C_6), 38.4 (C_2), 34.0 (C_4), 33.0 ($C_{7/9}$), 32.9 ($C_{7/9}$), 26.4 (C_8), 24.8 (C_5).

MS (CI, *m/z*): 216.1 ($[M+NH_4]^+$), 199.1 (MH^+).

HRMS (APCI, H^+): 199.1482 ($C_{11}H_{19}O_3$, expected 199.1329).

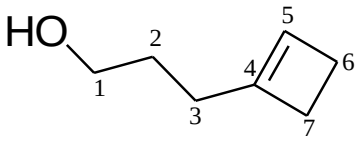
Photochemical transformations in acetonitrile

Unless otherwise stated in this section, all reactions in methanol yield crude reaction mixtures near the expected mass for full conversion to 1:1 adducts of the starting materials.

Irradiation of cyclopentenone and ethylene and subsequent reduction

Standard procedure C: 16h in acetonitrile with 410 mg (5 mmol) cyclopentenone and ethylene gas gives 365 mg (65 % yield) of the following compound:

3-Cyclobutenylpropan-1-ol **118**



$C_7H_{12}O$ (112,17 g/mol)

Transparent oil

^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.64 (br s, 1H, H_5), 3.57 (t, *J* = 6.7 Hz, 2H, H_1, H_1), 2.36 (m, 2H, H_6, H_6), 2.27 (m, 2H, H_7, H_7), 2.01 (m, 2H, H_3, H_3), 1.64 (m, 2H, H_2, H_2).

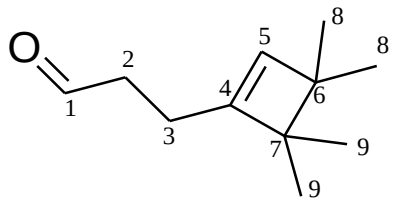
^{13}C NMR (75 MHz, $CDCl_3$, δ): 149.8 (C_4), 126.9 (C_5), 62.2 (C_1), 30.9 (C_3), 29.5 (C_2), 27.2 (C_7), 26.3 (C_6).

HRMS unsuccessful (ESI+, ESI-, APCI-, APCI+).

Irradiation of cyclopentenone and tetramethylethylene

Standard procedure C: 16h in acetonitrile with 410 mg (5 mmol) cyclopentenone and tetramethylethylene gives a crude mixture from which the following analytical data can be extracted:

3-(3,3,4,4-Tetramethyl-cyclobut-1-enyl)-propionaldehyde **100**



$C_{10}H_{18}O$ (166,26 g/mol)

Yellowish oil

R_f = 0.55 (petroleum ether/diethyl ether 9:1)

^{1}H NMR (250 MHz, $CDCl_3$, δ): 9.78 (t, *J* = 1.3 Hz, 1H, H_1), 5.63 (t, *J* = 1.7 Hz, 1H, H_5), 2.57 (td, *J* = 1.3 Hz, 7.4 Hz, 2 H, H_2), 2.22 (td, *J* = 1.7 Hz, 7.4 Hz, 2 H, H_3), 1.02 (s, 6H, H_8, H_9), 1.01(s, 6H, H_8, H_9).

^{13}C NMR (62 MHz, $CDCl_3$, δ): 202.1 (C_1), 152.9 (C_4), 133.1 (C_5), 30.8 (C_2), 28.9 (C_3), 23.2 ($C_{8/9}$), 21.9 ($C_{8/9}$), 21.1 ($C_{6/7}$), 21.0 ($C_{6/7}$).

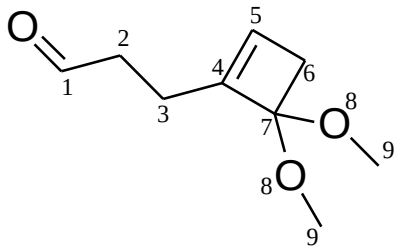
IR (film, NaCl): 2974.6 cm^{-1}, 2949.2 cm^{-1}, 2922.1 cm^{-1}, 2885.1 cm^{-1}, 1730.3 cm^{-1}, 1714.4 cm^{-1}, 1450.3 cm^{-1}, 1368.5 cm^{-1}.

MS (CI, *m/z*): 184.3 ($[M+NH_4]^+$), 167.1 (MH^+).

Irradiation of cyclopentenone and 1.1-dimethoxyethylene

Standard proecedure A: 16h in acetonitrile with 410 mg (5 mmol) cyclopentenone and 1,1-dimethoxyethylene 5 g (50 mmol) gives respectively 119 mg (14 % yield) and 17 mg (2 % yield) of the following compounds:

3-(4,4-dimethoxycyclobut-1-en-1-yl)propanal **124**



$C_9H_{14}O_3$ (170,21 g/mol)

Yellowish oil

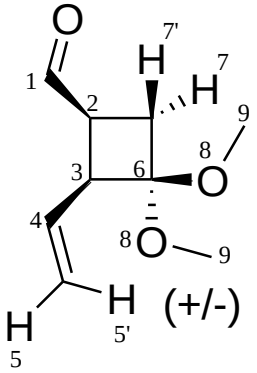
R_f = 0.4 (pentane/diethyl ether 3:1)

Standard procedure A: 16h in acetonitrile with 410 mg (5 mmol) cyclopentenone and 1,1-dimethoxyethylene 5 g (50 mmol) gives 14 % yield.

^{1}H NMR (360 MHz, $CDCl_3$, δ): 9.77 - 9.61 (m, 1 H, H_1), 5.98 (s, 1 H, H_5), 3.31 - 3.21 (m, 6 H, H_9), 2.64 - 2.51 (m, 2 H, H_2, H_2), 2.45 - 2.30 (m, 4 H, H_3, H_3, H_6, H_6).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 201.2 (C_1), 149.0 (C_4), 130.5 (C_5), 103.9 (C_7), 50.8 (2C, C_9), 40.2 (C_2), 38.8 (C_6), 20.3 (C_3).

cis-3,3-dimethoxy-2-vinylcyclobutane-1-carbaldehyde **125**



$C_9H_{14}O_3$ (170,21 g/mol)

Yellowish oil

R_f = 0.5 (pentane/diethyl ether 3:1)

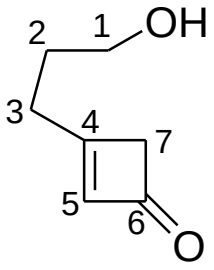
^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.74 (d, *J* = 2.0 Hz, 1H, H_1), 5.92 (ddd, *J* = 10.0 Hz, 10.2 Hz, 17.2 Hz, 1H, H_4), 5.23 (ddd, *J* = 0.7 Hz, 1.9 Hz, 17.2 Hz, 1H, $H_{5'}$), 5.16 (ddd, *J* = 0.7 Hz, 1.9 Hz, 10.2 Hz, 1H, H_5), 3.51 (dddddd, *J* = 0.7 Hz, 0.7 Hz, 0.8 Hz, 2.0 Hz, 10.0 Hz, 10.0 Hz, 1H, H3), 3.19 (s, 6H, H_9), 3.07 (dddd, *J* = 2.0 Hz, 6.4 Hz, 8.8 Hz, 10.0 Hz, 1H, H_2), 2.65 (ddd, *J* = 0.8 Hz, 6.4 Hz, 12.8 Hz, 1H, H_7), 2.15 (ddd, *J* = 2.0 Hz, 8.8 Hz, 12.8 Hz, 1H, $H_{7'}$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 202.7 (C_1), 132.7 (C_4), 118.6 (C_5), 101.3 (C_6), 52.6 (C_3), 48.9 (C_9), 48.7 (C_9), 41.4 (C_2), 29.5 (C_7).

Irradiation of cyclopentenone and 1.1-dimethoxyethylene

Dimethyl ketene acetal (5 g, 50 mmol) and cyclopentenone (40 mg, 5 mmol) were irradiated 16 h in acetonitrile (standard procedure B). Chromatography yields several fraction, the most polar containing oxetanes/aldehydes is reduced with $NaBH_4$ (10 mmol, , re-chromatographied and the most polar fraction is this species: 58 mg (9 % yield).

3-(3-hydroxypropyl)cyclobut-2-enone **126**



$C_7H_{10}O_2$ (126,15 g/mol)

Yellowish liquid

R_f = 0.35 (pentane/diethyl ether 9:1)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.83 (s, 1H, H_5), 3.59 (t, *J* = 6.5 Hz, 6.5 Hz, 2H, H_1), 3.14 (t, *J* = 2.2 Hz, 2.2 Hz, 2H, H_7), 2.47-2.30 (m, 2H, H_3), 1.72 (td, *J* = 6.5 Hz, 6.5 Hz, 13.8 Hz, 2H, H_2).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 197.1 (C_6), 192.2 (C_4), 154.9 (C_5), 61.5 (C_1), 47.9 (C_7), 29.4 (C_3), 21.0 (C_2).

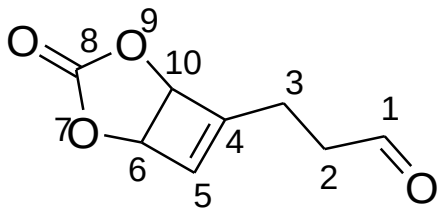
MS (CI, *m/z*): 144.0 ($[M+NH_4]^+$).

HRMS (ESI, H^+): 127.0754 ($C_7H_{11}O_2$, expected 127.0754).

Irradiation of cyclopentenone and vinylene carbonate

Standard procedure A: 16h in acetonitrile with 410 mg (5 mmol) cyclopentenone and 4.2 g (50 mmol) vinylene carbonate gives 143 mg (17 % yield) after chromatography (petroleum ether/diethyl ether 9/1).

3-(3-oxo-2,4-dioxa-bicyclo[3.2.0]hept-6-en-6-yl)propanal **123**



$C_8H_8O_4$ (168,15 g/mol)

Greyish liquid

R_f = 0.4 (pentane/diethyl ether 3:1)

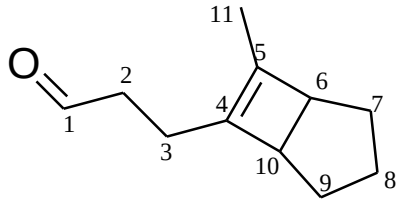
^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.73 (s, 1H), 6.32 (td, *J* = 1.8 Hz, 1.8 Hz, 3.4 Hz, 1H, H_5), 5.29-5.22 (m, 2H, H_6, H_{10}), 2.68 (t, *J* = 7.0 Hz, 7.0 Hz, 2H, H_2, H_2), 2.51-2.43 (m, 2H, H_3, H_3).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 199.9 (C_1), 158.8 (C_4), 155.9 (C_8), 137.3 (C_5), 78.3 (C_{10}), 75.2 (C_6), 39.7 (C_2), 20.5 (C_1).

Irradiation of 2-methylcyclopentenone and cyclopentene

Standard procedure A: 16h in acetonitrile with 480 mg (5 mmol) 2-methylcyclopentenone and cyclopentene 5 mL (50 mmol) gives 815 mg (97 % yield).

3-(3-Methyl)-bicyclo[3.2.0]hept-6-en-6-yl-propionaldehyde **<u>114</u>**



$C_{11}H_{16}O$ (164,24 g/mol)

Slightly yellowish clear liquid

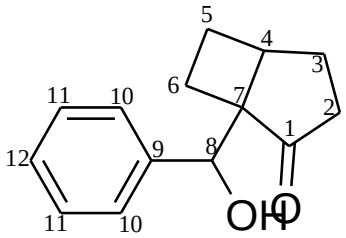
(6 mL) gives 22 % yield.^{1}H NMR (360 MHz, $CDCl_3$, δ): 9.77 (t, *J* = 1.8 Hz, 1 H, H_1), 2.93 - 2.87 (m, 1 H, $H_{6/10}$), 2.87 - 2.80 (m, 1 H, $H_{6/10}$), 2.52 (dt, *J* = 1.8 Hz, 7.5 Hz, 2 H, H_2, H_2), 2.38 - 2.17 (m, 2 H, H_3, H_3), 1.65 - 1.45 (m, 4H, H_7, H_8, H_8, H_9), 1.52 (s, 3 H, Me_{11}), 1.16 - 1.03 (m, 2 H, H_7, H_9).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 202.4 (C_1), 137.8 (C_5), 137.6 (C_4), 46.3 (C_6), 44.9 (C_{10}), 41.6 (C_2), 25.0 ($C_{7/9}$), 24.3 ($C_{7/9}$), 23.1 (C_8), 19.3 (C_3), 11.3 (C_{11}).

Irradiation of cyclopentenone 40 and ethylene

Standard procedure A: 36h in acetonitrile with 940 mg (5 mmol) cyclopentenone **40** and ethylene gas gives 432 mg (40 % yield) product after chromatography.

3-[2-[hydroxy(phenyl)methy]cyclobut-1-en-1-yl]propanal **<u>135</u>**



$C_{14}H_{16}O_2$ (216,27 g/mol)

Yellowish oil

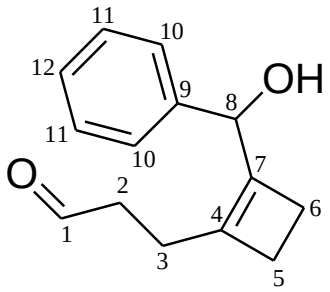
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.24 - 7.42 (m, 5H, Ph), 4.91 (s, 1H, H_8), 2.84 - 3.07 (m, 1H, H_4), 2.53 - 2.74 (m, 1H, H_2), 1.89 - 2.29 (m, 4H, H_2, H_5, H_5, H_6), 1.49 - 1.73 (m, 3H, H_3, H_3, H_6)

^{13}C NMR (75 MHz, $CDCl_3$, δ): 226.3 (C_1), 141.0 (C_9), 128.1 (C_{11}), 127.6 (C_{11}), 127.1 (C_{12}), 126.5 (2C, C_{10}), 77.1 (C_8), 56.7 (C_7), 37.8 (C_2), 37.4 (C_4), 26.3 (C_3), 26.2 (C_5), 21.1 (C_6).

Irradiation of cyclopentenone 40 and ethylene

Standard procedure A: 36h in acetonitrile with 940 mg (5 mmol) cyclopentenone **40** and ethylene gas gives 432 mg (40 % yield) product after chromatography.

3-[2-[hydroxy(phenyl)methy]cyclobut-1-en-1-yl]propanal **135**



$C_{14}H_{16}O_2$ (216,27 g/mol)

Yellowish oil

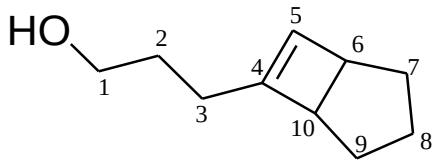
^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.74 (t, J= 1.0 Hz, 1H, H_1), 7.27 - 7.41 (m, 5H, Ph), 5.30 (s, 1H, H_8), 2.56 (dt, J= 1.0 Hz, 6.8 Hz, 2H, H_2, H_2), 2.41 (t, J= 6.8 Hz, 2H, H_3, H_3), 2.18 - 2.29 (m, 4H, H_5, H_5, H_6, H_6).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 202.2 (C_1), 142.2 (C_7), 141.8 (C_4), 140.3 (C_9), 128.3 (2C,C_{11}), 127.4 (C_{12}), 126.2 (2C,C_{10}), 71.5 (C_8), 41.4 (C_2), 27.2 (C_5), 25.4 (C_3), 21.1 (C_6).

Irradiation of cyclopentenone and cyclopentene and subsequent reduction

Standard procedure C: 24h in acetonitrile with 410 mg (5 mmol) cyclopentenone and cyclopentene gives three following compound with respectively 94 mg (12 % yield), 374 mg (50 %) and 78 mg (10 %) of the following compounds:

3-(bicyclo[3.2.0]hept-6-en-6-yl)propan-1-ol **115**



$C_{10}H_{16}O$ (152,23 g/mol)

Transparent oil

R_f = 0.17 (Petroleum ether/diethyl ether 7:3)

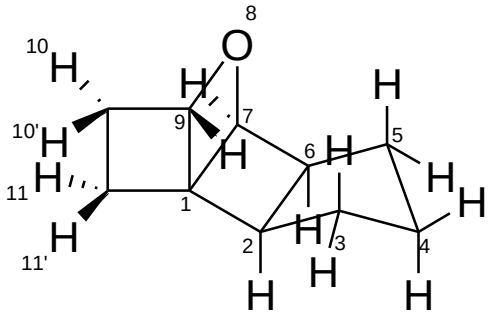
^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.52 (s, 1 H, H_5), 3.63 (t, *J* = 6.7 Hz, 2 H, H_1), 3.02-2.99 (m, 1 H, H_6), 2.97-2.94 (m, 1 H, H_{10}), 2.0-1.9 (m, 2H, $H_{7/9}$), 1.68 (t, *J* = 6.7, 2 H, H_2), 1.64-1.55 (m, 2 H, H_3), 1.52-1.42 (m, 2H, H_8), 1.17-1.07 (m, 2H, $H_{7/9}$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 149.7 (C_4), 127.8 (C_5), 62.7 (C_1), 47.7 (C_{10}), 43.7 (C_6), 29.5(C_2), 26.4 (C_8), 25.0 (2C, $C_{7/9}$), 23.1 (C_3).

IR (film, NaCl): 3325.7 (broad) cm^{-1}, 3027.4 cm^{-1},, 2931.9 cm^{-1}, 1630.5 cm^{-1}, 1442.7 cm^{-1}, 1323.2 cm^{-1}.

HRMS not successful

endo-8-oxatetracyclo[5.4.0.0^{1,9}.0$^{2.6}$]undecane**116**



$C_{10}H_{14}O$ (150,22 g/mol)

Transparent liquid

R_f = 0.63 (Petroleum ether/diethyl ether 7:3)

^{1}H NMR (600 MHz, $CDCl_3$, δ): 5.10 (ddd, *J* = 5.5 Hz, 2.6 Hz, 2.4 Hz, 1H, H_9), 5.05 (dd, *J* = 5.9 Hz, 2.6 Hz, 1H, H_7), 2.98 (dddd, *J* = 5.9 Hz, 7.5 Hz, 9.4 Hz, 9.4 Hz, 1H, H_6), 2.60 (ddd, *J* = 6.2 Hz, 8.1 Hz, 9.4 Hz, 1H, H_2), 2.45 (dddd, *J* = 2.4 Hz, 8.4 Hz, 8.6 Hz, 13.3 Hz, 1H, H_{10}), 2.35 (dddd, *J* = 3.8 Hz, 5.5 Hz, 11.3 Hz, 13.3 Hz, 1H, $H_{10'}$), 2.18 (dddd, *J* = 1.7 Hz, 3.4 Hz, 7.5 Hz, 8.2 Hz, 1H, H_5), 2.15 (dddd, *J* = 1 Hz, 3.8 Hz, 8.4 Hz, 12 Hz, 1H, H_{11}), 2.10 (dddd, *J* = 1 Hz, 8.9 Hz, 9.8 Hz, 12.4 Hz, 1H, H_4), 1.85 (ddddd, *J* = 0.7 Hz, 3 Hz, 4Hz, 7.9 Hz, 12.4 Hz, 1H, H_4), 1.80 (dddd, *J* = 0.7 Hz, 8.6 Hz, 11.3 Hz, 12 Hz, 1H, $H_{11'}$), 1.75 (dddddd, *J* = 1.7 Hz, 3 Hz, 4 Hz, 6.2 Hz, 8.9 Hz, 10.2 Hz, 1H, H_3), 1.55 (ddddd, *J* = 4 Hz, 8.1 Hz, 8.2 Hz, 9.8 Hz, 10.2 Hz, 1H, H_3), 1.50 (ddddd, *J* = 3.4 Hz, 4 Hz, 7.9 Hz, 9.4 Hz, 1H, H_5).

^{13}C NMR (110 MHz, $CDCl_3$, δ): 87.7 (C_9), 87.6 (C_7), 52 (C_1), 44.2 (C_6), 42.6 (C_2), 30.0 (C_{10}), 29.9 (C_3), 29.3 (C_4), 25.0 (C_5), 24.5 (C_{11}).

nOe (600 MHz, $CDCl_3$, δ): H_{11}-$H_{11'}$ (++), H_7-H_6 (++), H_9-$H_{10'}$ (+), H_2-H_6 (+).

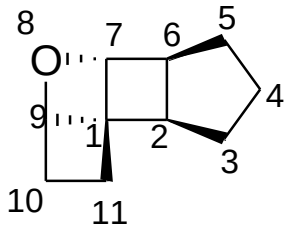
IR (film, NaCl): 2939.8 cm^{-1}, 996.7 cm^{-1}, 979.9 cm^{-1}, 853 cm^{-1}.

MS (CI, *m/z*): 168.0 ($[M+NH_4]^+$), 150.1 (M^+), 185.0 ($[MN_2H_5]^+$).

MS (IE, *m/z*): 150.1, 117.0, 108.0, 91.0 (majot), 79.0.

HRMS (APCI, H^+): 151.1112 ($C_{10}H_{15}O$, expected 151.1117).

exo-8-oxatetracyclo[5.4.0.0^{1,9}.0^{2,6}]undecane **117**



$C_{10}H_{14}O$ (150,22 g/mol)

Transparent oil

R_f = 0.63 (Petroleum ether/diethyl ether 7:3)

^{1}H NMR (250 MHz, $CDCl_3$, δ): 5.07 (ddd, *J* = 5.4, 2.3, 2.7 Hz, 1H, H_9), 4.70 (d, *J* = 2.3 Hz, 1H, H_7), 3.01 (dt, *J* = 5.9 Hz, 6.4 Hz, 1H, H_6), 2.94 (dt, *J* = 5.9 Hz, 6.3 Hz, 1H, H_2), 2.56-2.41 (m, 2H, H_{10}), 2.11-1.98 (m, 1H, H_{11}), 1.91-1.37 (m, 7H, H_{11}, H_5, H_5, H_4, H_4, H_3, H_3)

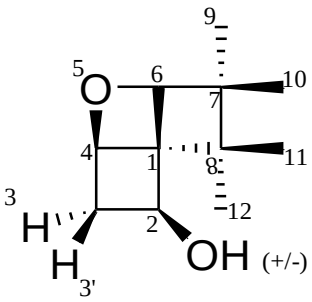
^{13}C NMR (75 MHz, $CDCl_3$, δ): 94.3 (C_7), 88.78 (C_9), 50.1, 47.8 (C_6), 42.6 (C_2), 30.9 (C_5), 29.8 (C_{10}), 28.0 (C_3), 26.1 (C_4), 22.1 (C_{11}).

MS (CI, *m/z*): 170.1 ($[M+NH_4]^+$), 153.0 (MH^+).

Irradiation of 4-hydroxycyclopentenone and tetramethylene

Standard procedure A: 16h in acetonitrile with 490 mg (5 mmol) 4-OH-cyclopentenone and TME 6 mL (50 mmol) gives 120mg (13 % yield) of the following compound after chromatography

7,7,8,8-tetramethyl-5-oxatricyclo[4.2.0.0^{1,4}]octan-2-ol **127**



$C_{11}H_{18}O_2$ (182,26 g/mol)

White solid

R_f = 0.48 (pentane/AcOEt 1:1)

^{1}H NMR (360 MHz, $CDCl_3$, δ): 4.87 (d, *J* = 2.3 Hz, 1 H, H_6), 4.73 (ddd, *J* = 4.6 Hz, 2.3 Hz, 1.9 Hz, 1H, H_4), 4.17 (dd, *J* = 9.5 Hz, 6.4 Hz, 1 H, H_2), 2.74 (ddd, *J* = 14.0 Hz, 9.5 Hz, 4.6 Hz, 1H, H_3), 2.37 (ddd, *J* = 14.0 Hz, 6.4 Hz, 1.9 Hz, 1H, $H_{3'}$), 1.22 (s, 3H, H_{12}), 1.02 (s, 3H, H_9), 0.96 (s, 3H, H_{10}), 0.94 (s, 3H, H_{11}).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 88.3 (C_6), 77.8 (C_4), 63.2 (C_2), 61.1 (C_1), 43.4 (C_8), 40.5 (C_3), 39.3 (C_7), 22.2 (C_{10}), 21.0 (C_9), 20.7 (C_{11}), 19.4 (C_{12}).

nOe (400 MHz, $CDCl_3$, δ): H_2-H_3 (++), H_2-H_4 (++), H_2-H_{11} (++), H_2-H_{12} (+), H_6-H_{10} (++).

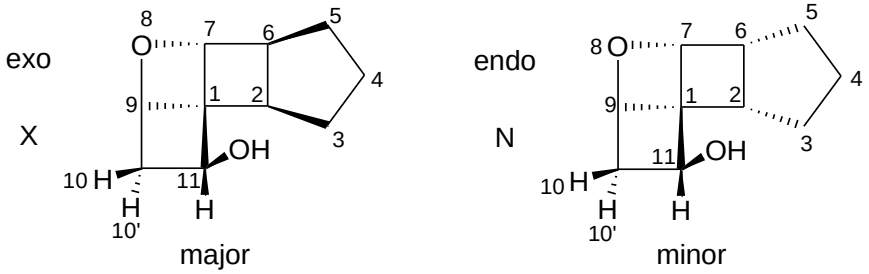
IR (film, NaCl): 3388.7 cm^{-1}, 2925.7 cm^{-1}, 1731.7 cm^{-1}, 1461.7 cm^{-1}.

HRMS (ESI, Na^+): 205.1199 ($C_{11}H_{18}NaO_2$, expected 205.1204).

Irradiation of 4-hydroxycyclopentenone and cyclopentene

Standard procedure A: 16h in acetonitrile with 490 mg (5 mmol) 4-OH-cyclopentenone and cyclopentene 5 mL (50 mmol) gives 332 mg in (40 % combined yield) of a mixture of two isomers after chromatography (petroleum ether/diethyl ether 3:1 to 1:1).

Mixture of *endo*-11-hydroxy-8-oxatetracyclo[5.4.0.$0^{1,9}$.$0^{2,6}$]undecane and *exo*-11-hydroxy-8-oxatetracyclo[5.4.0.$0^{1,9}$.$0^{2,6}$]undecane **128**



$C_{10}H_{14}O_2$ (166,22 g/mol)

Yellowish liquid

R_f = 0.4 (petroleum ether/diethyl ether 1:1)

^{1}H NMR (360 MHz, $CDCl_3$, δ): 5.28 (dd, *J* = 5.6 Hz, 2.3 Hz, 1H, H_{9N}), 4.92 (d, *J* = 2.1 Hz, 1H, H_{7X}), 4.74 (dd, *J* = 2.5 Hz, 2.5 Hz, 5.8 Hz, 1H, H_{7N}), 4.63 (td, *J* = 2.1 Hz, 2.3 Hz, 4.7 Hz, 1H, H_{9X}), 4.02 (dd, *J* = 8.90, 7.14 Hz, 1H, H_{11X}), 3.93 (dd, *J* = 8.94, 7.22 Hz, 1H, H_{11N}), 3.02-2.91 (m, 3H, H_{6N}, H_{6X}, H_{2X}), 2.86-2.61 (m, 3H, H_{2N}, $H_{10'X}$, $H_{10'N}$), 2.40-2.06 (m, 4H, H_{5N}, H_{5X}, H_{10X}, H_{10N}), 1.90-1.33 (m, 10H, H_{3N}, H_{3N}, H_{4N},H_{4N}, $H_{5N,}$ H_{3X}, H_{3X}, H_{4X},H_{4X}, H_{5X}).

^{1}H NMR (360 MHz, CDC_3OD, δ): 5.34 (dd, *J* = 2.5 Hz, 5.2 Hz, 1H, H_{9N}), 4.99 (d, *J* = 2.0 Hz, 1H, H_{7X}), 4.82 (m, 1H, H_{7N}), 4.67 (ddd, *J* = 2.0 Hz, 2.3 Hz, 4.8 Hz, 1H, H_{9X}), 4.04 (dd, *J* = 7.0 Hz, 9.3 Hz, 1H, H_{11X}), 3.96 (dd, *J* = 7.0 Hz, 9.3 Hz, 1H, H_{11N}), 3.06-3.00 (m, 2H, H_{6X}, H_{2X}), 2.98 (dd, *J* = 5.8 Hz, 11.5, Hz 1H, H_{6N}), 2.91-2.83 (m, 1H, H_{2N}), 2.79 (ddd, *J* = 4.8 Hz, 9.3 Hz, 12.5 Hz, 1H, $H_{10'X}$), 2.72 (ddd, *J* = 5.2 Hz, 9.30 Hz, 12.3 Hz, 1H, $H_{10'N}$), 2.35 (ddd, *J* = 6.95, 2.1 Hz, 7.0 Hz, 12.3 Hz, 1H, H_{10N}), 2.31 (ddd, *J* = 2.0 Hz, 7.0 Hz, 12.5 Hz, 1H, H_{10X}), 2.28-2.18 (m, 2H, H_{5N}, H_{5X}), 1.77-1.47 (m, 10H, H_{3N}, H_{3N}, H_{4N},H_{4N}, $H_{5N,}$ H_{3X}, H_{3X}, H_{4X},H_{4X}, H_{5X}).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 88.9 (C_{7X}), 82.3 (C_{9N}), 79.6 (C_{9X}), 78.5 (C_{7N}), 64.5 (C_{11N}), 64.4 (C_{11X}), 59.5 (C_{1N}), 55.8 (C_{1X}), 47.2 (C_{6X}), 43.9 (C_{6N}), 41.4 (C_{2X}), 40.35 (C_{2N}), 40.3 (2C, C_{10X}, C_{10N}) , 31.1 (C_{5X}), 30.2 (C_{3N}), 29.4 (C_{4N}), 28.0 (C_{3X}), 25.8 (C_{4X}), 25.3 (C_{5N}).

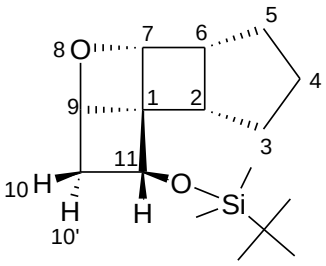
^{13}C NMR (90 MHz, CD_3OD, δ): 90.9 (C_{7X}), 84.3 (C_{9N}), 81.4 (C_{9X}), 80.4 (C_{7N}), 65.2 (C_{11N}), 65.1 (C_{11X}), 60.9 (C_{1N}), 57.4 (C_{1X}), 48.5 (C_{6X}), 45.3 (C_{6N}), 43.0 (C_{2X}), 41.8 (C_{2N}), 41.0 (2C, C_{10X}, C_{10N}), 32.2 (C_{5X}), 31.2 (C_{3N}), 30.5 (C_{4N}), 29. 0 (C_{3X}), 26.8 (C_{4X}), 26.4 (C_{5N}).

HRMS (ESI, H^+): 189.1061 ($C_{10}H_{14}NaO_2$, expected 189.0892).

Irradiation of 4-tertbutyldimethylsilylcyclopentenone and cyclopentene

Standard procedure A: 16h in acetonirile with 1.05 g (5 mmol) 4-OTBS-cyclopentenone and cyclopentene 5 mL (50 mmol) gives 22 % combined yield of the two following oxetanes in separate fractions. Aldehyde XX was also isolated: 213 mg (15 %). Chromatography was carried out with petroleum ether/diethyl ether gradient from 100:1 to 90:10.

endo-11- tertbutyldimethylsilyloxy-8-oxatetracyclo[5.4.0.0^{1,9}.0$^{2.6}$]undecane **131**



$C_{16}H_{28}O_2Si$ (280,48 g/mol)

Yellowish liquid

R_f = 0.5 (petroleum ether/diethyl ether 9:1)

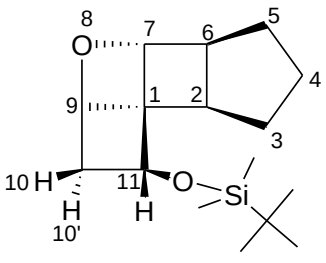
^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.27 (dd, *J* = 2.4 Hz, 5.77 Hz, 1H, H_7), 4.73 (ddd, *J* = 2.2 Hz, 2.4 Hz, 4.8 Hz, 1H, H_9), 3.97 (dd, *J* = 6.6 Hz, 9.0 Hz, 1H, H_{11}), 3.02-2.91 (m, 1H, H_6), 2.81-2.74 (m, 1H, H_2), 2.64 (ddd, *J* = 4.8 Hz, 9.0 Hz, 13.2 Hz, 1H, $H_{10'}$), 2.38 (ddd, *J* = 2.2 Hz, 6.6 Hz, 13.2 Hz, 1H, H_{10}), 1.91-1.72 (m, 3H, H_5, H_4, H_3), 1.66-1.53 (m, 3H, H_5, H_4, H_3), 0.89 (s, 9H, Si*t*Bu), 0.04 (s, 6H, $SiMe_2$),

^{13}C NMR (63 MHz, $CDCl_3$, δ): 82.3 (C_9), 78.6 (C_7), 64.8 (C_{11}), 59.6 (C_1), 44.1 (C_6), 41.0 (C_2), 40.4 (C_{10}), 30.4 (C_3), 29.5 (C_4), 25.8 (Si*t*Bu, 3C), 25.5 (C_5) 18.0 (SiC_q), -4.7 ($SiMe_2$).

MS (CI, *m/z*): 298.1 ([M+NH_4]$^+$), 166.0 ([M+NH_4-TBDMSOH]$^+$).

HRMS (APCI, H^+): 281.1920 ($C_{16}H_{29}O_2Si$, expected 281.1931).

exo-11- tertbutyldimethylsilyloxy-8-oxatetracyclo[5.4.0.0^{1,9}.0$^{2.6}$]undecane. **130**



$C_{16}H_{28}O_2Si$ (280,48 g/mol)

Yellowish liquid

R_f = 0.55 (petroleum ether/diethyl ether 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.93 (d, J = 2.3 Hz, 1H, H_7), 4.64 (ddd, *J* = 2.2 Hz, 2.3 Hz, 4.8 Hz, 1H, H_9), 4.05 (dd, J = 6.5 Hz, 8.7 Hz, 1H, H_{11}), 3.0-3.94 (m, 2H, H_6, H_2), 2.66 (ddd, *J* = 4.8 Hz, 8.7 Hz, 13.4 Hz 1H, $H_{10'}$), 2.33 (ddd, *J* = 2.2 Hz, 6.5 Hz, 13.4 Hz, 1H, H_{10}), 1.77-1.41 (m, 6H, H_3, H_3, H_4, H_4, H_5, H_5), 0.88 (s, 9H, Si*t*Bu), 0.03 (s, 3H, SiMe), 0.02 (s, 3H, SiMe)

^{13}C NMR (63 MHz, $CDCl_3$, δ): 89.1 (C_7), 79.9 (C_9), 64.3 (C_{11}), 55.7 (C_1), 47.4 (C_6), 41.5 (C_2), 41.1 (C_{10}), 31.3 (C_3), 28.1 (C_4), 25.6 (Si*t*Bu, 3C), 25.5 (C_5), 18.1 (SiC_q), -4.6 (SiMe), -5.2 (SiMe).

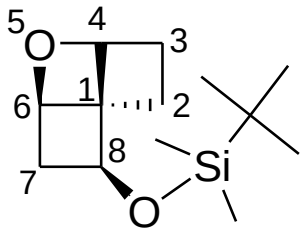
MS (CI, *m/z*): 298.1 ($[M+NH_4]^+$), 166.0 ($[M+NH_4\text{-TBDMSOH}]^+$).

HRMS (APCI, H^+): 281.1919 ($C_{16}H_{29}O_2Si$, expected 281.1931).

Irradiation of 4-tertbutyldimethylsilylcyclopentenone and ethylene

Standard procedure B: 16h in acetonirile with 1.05 g (5 mmol) 4-OTBS-cyclopentenone and ethylene gas gives 50 after chromatography (petroleum ether/diethyl ether 99:1).

2-tertbutyldimethylsilyloxy-5-oxatricyclo[4.2.0.01,4]octane **<u>129</u>**



$C_{13}H_{24}O_2Si$ (240,41 g/mol)

Transparent oil

R_f = 0.29 (petroleum ether/diethyl ether 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.40 (ddd, *J* = 2.4 Hz, 2.6 Hz, 5.1 Hz, 1H, H_4), 4.81 (ddd, *J* = 2.1 Hz, 2.4 Hz, 4.7, 1H, H_6), 4.04 (dd, *J* = 6.8 Hz, 9.2 Hz, 1H, H_8), 2.72 (ddd, *J* = 4.7 Hz, 9.2 Hz, 13.7 Hz, 1H, H_7), 2.49-2.43 (m, 2H, $H_{2/3,}$ $H_{2/3}$), 2.38 (ddd, *J* = 2.1 Hz, 6.8 Hz, 13.7 Hz, 1H, $H_{7'}$), 2.30-2.12 (m, 2H, $H_{2/3,}$ $H_{2/3}$), 0.90 (s, 1H, Si*t*Bu), 0.04 (s, 3H, SiMe), 0.03 (s, 3H, SiMe).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 84.7 (C_6), 80.7 (C_4), 65.6 (C_8), 57.4 (C_1), 41.0 (C_7), 29.5 (C_3), 29.0 (C_2), 25.8 (Si*t*Bu, 3C), 18.0 (TBS C_q), -4.7 (SiMe), -4.8 (SiMe).

IR (film, NaCl): 2954.0 cm^{-1}, 2857.4 cm^{-1}, 1731.6 cm^{-1}, 1472.1 cm^{-1}, 1257.6 cm^{-1}.

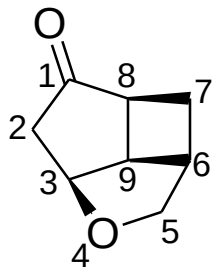
HRMS (APCI, H^+): 241.1611 ($C_{13}H_{25}O_2Si$, expected 241.1618).

HRMS (ESI, H^+): 181.1220 ($C_{11}H_{17}NaO_2$, expected 181.1223).

Irradiation of 4-allyloxycyclopentenone

Standard procedure A: 16h in acetonitrile with 3 mmol (408 mg) cyclopentenone **35** gives 328 mg (80 % yield) without chromatography. 57h of irradiation gives 371 mg, but slightly deteriorated.

5-oxatricyclo[4.2.1.$0^{3,9}$]nonan-8-one.



$C_8H_{10}O_2$ (138,16 g/mol)

Transparent liquid

^{1}H NMR (360 MHz, $CDCl_3$, δ): 4.46 (dd, J = 5.3 Hz, 6.0 Hz, 1 H, H_3), 3.68 (d, J = 9.3 Hz, 1 H, H_5), 3.54 (dd, J = 4.1 Hz, 9.3 Hz, 1 H, H_5), 3.27 (ddd, J = 2.6 Hz, 5.0 Hz, 6.0 Hz, 1 H, H_9), 2.93 (dddd, J = 4.1 Hz, 4.3 Hz, 5.0 Hz, 8.0 Hz, 1 H, H_6), 2.54 - 2.63 (m, 2 H, H, H_8, H_7), 2.47 - 2.54 (m, 1 H, H_2), 2.37 (dd, J = 5.3 Hz, 18.0 Hz, 1 H, H_2), 1.50 - 1.80 (m, 1 H, H_7).

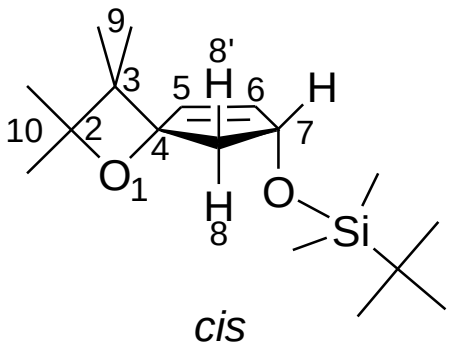
^{13}C NMR (90 MHz, $CDCl_3$, δ): 219.5 (C_1), 78.7 (C_3), 74.0 (C_5), 47.2 (C_2), 44.6 (C_9), 38.5 (C_8), 36.2 (C_6), 27.0 (C_7).

HRMS (ESI, Na^+): 161.0572 ($C_8H_{10}NaO_2$, expected 161.0573).

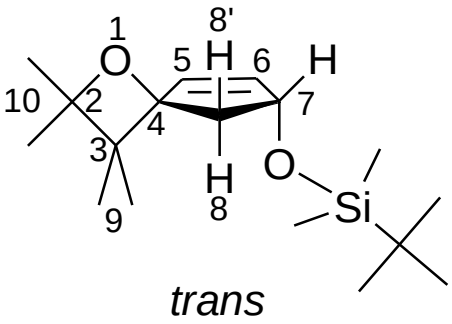
Irradiation of 4-tertbutyldimethylsilylcyclopentenone and tetramethylethylene

Standard procedure A: 16h in acetonirile with 1.05 g (5 mmol) 4-OTBS-cyclopentenone and 50 mmol cyclopentene (5 mL) gives 22 % combined yield with the following diastereoisomer.

Mixture of *cis*- and *anti*-7- tertbutyldimethylsilyloxy-2,2,3,3-tetramethyl-1-oxaspiro[3.4]oct-5-ene



cis



trans

$C_{17}H_{32}O_2Si$ (296,52 g/mol)

Transparent liquid

R_f = 0.53 (pentane/diethyl ether 9:1)

The two isomers could not be separated chromatographically or spectrographically. They are identified as A and B, in a 1:2 ratio. Studying the shifts of the C_7HH protons shows that the difference between both protons is greater in B than A. This means that the electronic environment of the two protons is more different in B than A. This could be interpretated as B being the *cis* isomer. This would be consistent with the latter being the kinetic product.

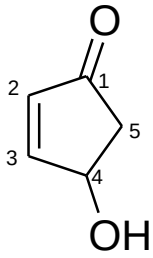
^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.12 (dd, J = 1.2 Hz, 5.7 Hz, 1H, H_{5A}), 6.04 (dd, J = 1.4 Hz, 5.7 Hz, 1H, H_{5B}), 5.91 (dd, J = 2.0 Hz, 5.7 Hz, 1H, H_{6A}), 5.83 (dd, J = 1.6 Hz, 5.7 Hz, 1H, H_{6B}), 4.91-4.85 (m, 1H, H_{7A}), 4.54 (tdd, J = 1.4 Hz, 1.6 Hz, 5.5 Hz, 6.6 Hz 1H, H_{7B}), 2.82 (dd, J = 6.6 Hz, 13.8 Hz, 1H, $H_{8'B}$), 2.30 (dd, J = 6.2 Hz, 13.9 Hz, 1H, $H_{8'A}$), 1.91 (dd, J = 4.3 Hz, 13.9 Hz, 1H, H_{8A}), 1.71 (dd, J = 5.5 Hz, 13.8 Hz, 1H, H_{8B}), 1.34 (s, 1H, H_{10A}, 3H),1.30 (s, 1H, H_{10B}, 6H), 1.29 (s, 1H, H_{10A}, 3H), 1.13 (s, 1H, H_{9A}, 3H), 1.09 (s, 1H, H_{9B}, 3H), 1.07 (s, 1H, H_{9A}, 3H), 1.01 (s, 1H, H_{9B}, 3H), 0.88 (s, 9H, Si*t*Bu_A), 0.87 (s, 9H, Si*t*Bu_B), 0.06 (s, 6H, $SiMe_{2A}$), 0.06 (s, 6H, $SiMe_{2B}$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 139.3 (C_{6A}), 137.8 (C_{6B}), 135.6 (C_{5B}), 134.9 (C_{5A}), 95.6 (C_{4A}), 94.3 (C_{4B}), 83.6 (C_{2A}), 83.0 (C_{2B}), 75.1 (C_{7A}), 74.2 (C_{7B}), 50.7 (C_{3B}), 49.2 (C_{3A}), 45.3 (C_{2B}), 45.0 (C_{2A}), 26.1 (C_{10B}, 2C), 25.8 (C_{10A}), 25.6 (TBS_A, 3C), 25.6 (TBS_B, 3C), 3C, , 23.9 (C_{10A}), 21.4 (C_{9B}), 21.3 (C_{9B}), 21.2 (C_{9A}), 20.5 (C_{9A}), 18.1 (TBS C_{qA}), 18.0 (TBS C_{qB}), -4.67 ($SiMe_B$), -4.60 ($SiMe_B$), -4.75 ($SiMe_A$), -4.74 ($SiMe_A$).

HRMS (ESI, H^+): 297.2241 ($C_{17}H_{33}NaO_2$, expected 297.2244).

Preparation of substrates

4-hydroxycyclopent-2-enone **32**[418]



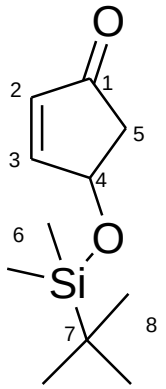
$C_5H_6O_2$ (98,1 g/mol)
Slightly yellow liquid

R_f = 0.15 (pentane/diethyl ether 3:1)

^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.55 (dd, *J* = 5.6 Hz, 1.9 Hz, 1H, H_3), 6.15 (ddd, *J* = 5.6 Hz, 2.9 Hz, 1.2 Hz, 1H, H_2), 5.07-4.87 (m, 1H, H_4), 2.70 (ddd, *J* = 18.5 Hz, 6.0 Hz, 2.9 Hz, 1H, H_5), 2.21 (td, *J* = 18.5 Hz, 2.5 Hz, 2.5 Hz, 1H, H_5).

Distilled furfuryl alcohol (10 mL, 11.28 g, 115 mmol), KH_2PO_4 (1,1 g, 8 mmol) and a magnetic stirring bar are placed in 700 mL of distilled water. At least 48 hours of reflux boiling in the appropriate reflux apparatus (flask, condenser) yields a dark brown liquid with occasional brown polymeric material. The liquid is filitered through Cellite to remove the solids and then carefully evaporated to remove 95 % of the water. Filtration can be replaced by dichloromethane washing (30 mL) at the cost of slightly lower yields. Extraction of the aqueous phase is carried out with 5 x 40 mL AcOEt followed by drying ($MgSO_4$) and removal of the solvent. The crude material is slightly colored, but is pure in NMR and acceptable for synthetical purposes. Distillation (90-95°C at 10-15 mbar) is necessary for use as a photochemical reactant. Yields were consistently poor and between 30 % and 40 %.

4-(tertbutyldimethylsilyloxy)-cyclopent-2-enone**10**[126]



$C_{11}H_{20}O_2Si$ (212.36 g/mol)

White solid (T < 10 °C)

R_f = 0.49 (petroleum ether/diethyl ether 9:1)

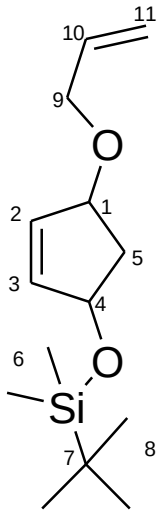
^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.56 (dd, *J* = 5.6 Hz, 2.2 Hz, 1H, H_3), 6.19 (dd, *J* = 5.6 Hz, 0.5 Hz, 1H, H_2), 5.13-4.80 (m, 1H, H_4), 2.72 (dd, *J* = 18.2 Hz, 6.0 Hz, 1H, H_5), 2.25 (dd, *J* = 18.2 Hz, 2.1 Hz, 1H, H_5) , 0.92 (s, 9H, H_8), 0.14 (s, 1H, H_6), 0.13 (s, 1H, H_6).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 206.5 (C_1), 163.8 (C_3), 134.4 (C_2), 70.8 (C_4), 44.9 (C_5), 25.7 (C_8), 18.0 (C_7), -3.6 (C_6), -4.8 (C_6).

In a two-necked 250 mL flask equipped with a thermometer and a magnetic stirring bar, the following were added: 80 mL distilled THF, 4-hydroxycyclopentenone (5.7g, 58 mmol) and triethylamine (13 mL, 93 mmol).The flask were cooled to -5°C with a NaCl/ice bath. DMAP (146 mg) was added followed by a slow addition of TBSCl (8.17 g, 94 mmol). After 30m-1h at -5°C, the cold bath is substituted for a cold (tap) water bath and allowed to stir overnight.

The reaction mixture is then poured into a 50 mL 0.5 N solution of HCl and stirred for 30 minutes. The acqeuous phase was extracted by 4 x 50 mL PE. The combined organic fractions are washed with 2 x 40 mL 0.5 M HCl, 2 x 40 mL sat. NaHCO3 and 2 x 40 mL brine. The organic solution is dried ($MgSO_4$), filtered and the solvent evaporated. A brown liquid that becomes solid under 0°C (with a little remnant liquid) is obtained. NMR shows it is the expected product. Observed contaminants are TBS species, probably TBSOH. The yield at this point is usually 80 % but can be anywhere from 50 to 92 %. The variation in yield has not been explored or determined. The compound is usable as such for non-photochemical purposes.
Distillation with a Kugelrohr (100°C, 4 mbar) apparatus is necessary to obtain white crystals (at less than 10 °C) or transparent liquid (at room temperature) sufficiently pure for photochemical purposes.

O-Allyl, O-(tertbutyldimethylsilyl)-cyclopent-2-en-1,4-diol **33**



$C_{14}H_{26}O_2Si$ (254,44 g/mol)

Transparent liquid

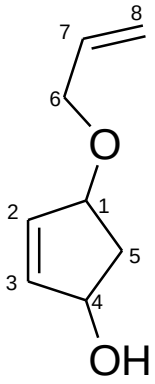
^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.99-5.82 (m, 2H, H_{11}), 5.28 (ddd, J = 1.3 Hz, 3.2 Hz, 17.2 Hz, 1H, H_3), 5.16 (ddd, J = 1.2 Hz, 3.2 Hz, 10.3 Hz, 1.1 Hz, 1H, H_2), 4.66 (ddd, J = 1.3 Hz, 5.6 Hz, 7.0 Hz, 1H, H_4), 4.38 (ddd, J = 1.1 Hz, 5.6 Hz, 7.0 Hz, 1H, H_1), 4.01 (d, J = 5.7 Hz, 2H, H_9), 2.66 (td, J = 13.3, 7.0, 7.0 Hz, 1H, H_5), 1.58 (td, J = 13.3, 5.6, 5.6 Hz, 1H, H_5), 0.89 (s, 9H, H_8), 0.07 (s, 6H, H_6)

^{13}C NMR (90 MHz, $CDCl_3$, δ): 137.4 (C_2), 135.2 (C_{10}), 132.8 (C_2), 116.6 (C_{11}), 81.3 (C_1), 74.8 (C_4), 69.3 (C_9), 41.5 (C_5), 25.9 (C_8), 18.0 (C_7), -4.6 (C_6), -4.7 (C_6).

TBS silyl ether XX (265 mg, 1.4 mmol), MeOH (HPLC quality, 10 mL) and a stirring bar are placed in a 50 mL flask. Heptahydrate cerium chloride (III) (0.64 g, 1.73 mmol) is added at room temperature and the mixture is stirred thus for 20-30 minutes. The media is brought down to -78°C with a dry ice/acetone bath and sodium borohydride (61 mg, 1,4 mmol) is added. The flask is stirred overnight and allowed to warm slowly to room temperature. The reaction is quenched by means of a small volume (5 mL) of saturated NH_4Cl solution. Extraction by AcOEt (3 x 10 mL), washing with brine (15 mL), drying ($MgSO_4$) and evaporation of the solvent furnishes a clear liquid. The former is placed in a 50 mL flask with 10 mL THF and a stirrer and cooled to -5°C/0°C with an NaCl/ice bath. After 20 minutes stirring, NaH is added (68 mg) and stirred further for 30 m/1 h. Allyl bromide (0.17 mL, 1.7 mmol) and TBAI (84,3 mg) are then added. The reaction is stirred overnight and allowed to return to room temperature. The transparent media becomes yellow and thick with floating particles. The reaction is quenched with saturated NH_4Cl (5 mL), extracted by Et_2O (4 x 10 mL), washed with brine (15 mL), dried ($MgSO_4$) and evaporated to yield clear liquid that appeared as two spots in TLC

(Petroleum ether/ Et_2O 1:1) that could be *cis* and *anti* isomers. Chromatography failed to separate them completely but both compounds had very similar NMR structures (the major is described here), both consistent with the described structure. All the fractions were gathered and used as a mixture. Yields were 56 % for these proportions after chromatography and 90 % without chromatography (but for 19.7 mmol starting enone).

O-Allyl-cyclopent-2-en-1,4-diol **34**[563]



$C_8H_{12}O_2$ (140,18 g/mol)

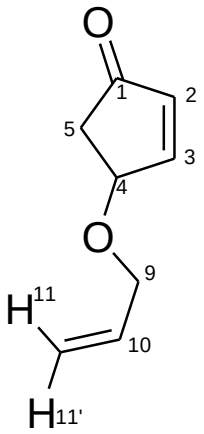
Transparent liquid

^{13}C NMR (75 MHz, $CDCl_3$, δ): 137.6 (C_2), 134.7 (C_3), 132.7 (C_8), 116.4 (C_7), 81.3 (C_1), 73.8 (C_4), 69.4 (C_6), 40.5 (C_5).

The silyl ether (XX, 4.55 g, 17.9 mmol) is placed in distilled THF (30 mL) in a 100 mL flask under Ar. TBAF is added (1M solution in THF, 30 mL, 30 mmol) and the reaction is stirred overnight at room temperature. The reaction is quenched with NH_4Cl saturated solution (30 mL), extracted with EtOAc (3 x 40 mL), dried ($MgSO_4$) and the solvent removed.

The cyclopentenol is obtained pure (1 g, 7.2 mmol, 40 %) after removal of traces of tetrabutylammonium species by dissolving the crude material in diethyl ether and filtering it through a thin slab of Cellite.

4-allyloxy-cyclopent-2-enone**35**



$C_8H_{10}O_2$ (138,16 g/mol)

Transparent liquid

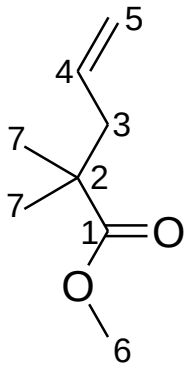
^{1}H NMR (250 MHz, $CDCl_3$, δ): 7.58 (dd, J = 2.3 Hz, 5.7 Hz, 1H, H_3), 6.21 (dd, J = 1.4 Hz, 5.7 Hz, 1H, H_2), 5.27 (ddd, J = 1.3 Hz, 1.3 Hz, 1.4 Hz, 17.2 Hz, 1H, H_{11}), 5.18 (dddd, J = 1.4 Hz, 1.5 Hz, 1.5 Hz, 10.3 Hz, 1H, $H_{11'}$), 5.89 (dddd, J = 5.6 Hz, 5.6 Hz, 10.3 Hz, 17.2 Hz, 1H, H_{10}), 4.69 (dddd, J = 1.4 Hz, 2.2 Hz, 2.3 Hz, 5.9 Hz 1H, H_4), 4.05 (tdd, J = 2.65, 1.3 Hz, 1.5 Hz, 5.6 Hz, 2H, H_9, H_9), 2.64 (dd, J = 5.9 Hz, 18.3 Hz, 1H, H_5), 2.27 (dd, J = 2.2 Hz, 18.3 Hz, 1H, H_5).

^{13}C NMR (62 MHz, $CDCl_3$, δ): 205.7 (C_1), 161.0 (C_3), 135.5 (C_2), 134.0 (C_{10}), 117.6 (C_{11}), 76.6 (C_4), 70.5 (C_9), 41.5 (C_5)

IR (film, NaCl) : 2861.3 cm^{-1}, 1721 cm^{-1}, 1349 cm^{-1}, 1184.8 cm^{-1}.

The cyclopentenol (3.58g, 25.9 mmol) is disolved in distilled DCM (40 mL) in a 100 mL flask. PCC (12 g) dispersed in cellite is pourred slowly in the flask. The reaction in monitored by TLC (a UV visible, less polar spot appears). Once the reaction is complete, the contents of the flask is filtered through Cellite, washed with water, brine, dried ($MgSO_4$) and the solvent removed affording pure ketone in 2.8 g (20 mmo; 77 %).

Methyl 2,2-dimethylpent-4-oate[564]



$C_8H_{14}O_2$ (142,2 g/mol)

Yellowish liquid

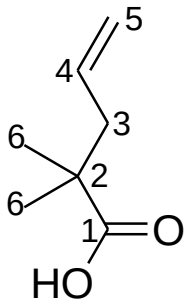
^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.18-4.85 (m, 1H, H_4), 5.90-5.50 (m, 2H, H_5), 3.65 (s, 3H, H_6), 2.26 (d, *J* = 7.4 Hz, 2H, H_3), 1.16 (s, 6H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 177.7 (C_1), 134.0 (C_4), 117.7 (C_5), 51.4 (C_6), 44.6 (C_3), 42.1 (C_2), 24.6 (2C, C_7).

To a 500 mL two-necked flask equipped with a stirring bar and a dropping funnel, under constant pressure of argon, 30 mL of freshly distilled THF are added. After 5-10 minutes of passing argon through the system, freshly distilled diisopropylamine (14 mL, 90 mmol) is added with a syringe. The flask is cooled to -78°C with an acetone/dry ice bath. After 10-15 minutes of stirring at -78°C, *n*-butyl lithium (51.5 mL, 1.6M solution in hexanes, 85 mmol) is added slowly with the dropping funnel. The media becomes yellowish. Stirring continues for 30 minutes. Methyl isobutyrate (8 mL, 70 mmol) is placed in the funnel with 40 mL of distilled THF. The above solution is added slowly over 30-45 minutes and stirred further at least 1 hour. Freshly distilled allyl bromide (7,2 mL, 77 mmol) is placed in the funnel with 30 mL distilled THF. The above solution is added slowly over 30-45 minutes and stirred further at least 1 hour. The media loses its yellow tinge.

The reaction is quenched with a 30 mL saturated NH_4Cl solution at -78° C, stirred for 20 minutes and allowed to return to room temperature. The reactor is emptied in a flask containing 50 mL diethyl ether for dilution. The organic fraction is washed with 70 mL brine. The aqueous fraction is extracted with 3 x 40 mL diethyl ether. The organic fractions are consolidated, dried ($MgSO_4$) and the solvent evaporated.
The resultant liquid is distilled (60 ± 1 mbar, 70 °C) yielding 8.182 g (82%) of pure allyl ester.

2,2-dimethylpent-4-enoic acid



$C_7H_{12}O_2$ (128.17 g/mol)

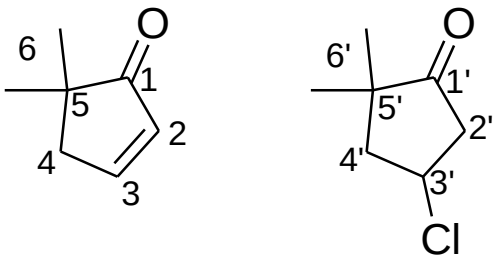
Transparent liquid

^{1}H NMR (360 MHz, $CDCl_3$, δ): 11.13 (br s, 1H, acid proton), 5.78 (tdd, *J* = 7.4 Hz, 7.4 Hz, 9.5 Hz, 21.0 Hz, 1H, H_4), 5.12-5.02 (m, 2H, H_5), 1.20 (s, 6H, H_6), 2.30 (d, *J* = 7.4 Hz, 2H, H_3).

^{13}C NMR (91 MHz, $CDCl_3$, δ): 184.3 (C_1), 133.9 (C_4), 118.1 (C_5), 44.4 (C_3), 42.1 (C_2), 24.6 (C_6)

In a 1 L flask, MeOH (HPLC grade, 300 mL), distilled water (150 mL) and a stirring bar were added. The allyl ester (6.09 g, 42.8 mmol) is added with a pipette. The flask is placed in a cold oil bath and a reflux setup prepared. Sodium hydroxide (3.5 g) is added slowly and without stirring. After 5 minutes of stirring, the bath is heated to 80 °C and stirred overnight. The next day, the flask is cooled and the solvent evaporated. HCl 1M is added until pH < 1. Extraction with 5 x 50 mL DCM is carried out. Drying ($MgSO_4$) and evaporation of the solvent yields pure acid (4.675 g, 85 %, 36.5 mmol). With smaller proportions, distillation (80 mbar, 125 °C) is necessary to achieve purity.

Mixture of 5,5-dimethylcyclopent-2-enone **50** and 2-chloro-5,5-dimethylcyclopentanone **51**[355]



$C_7H_{10}O$ (110,15 g/mol)

$C_7H_{11}ClO$ (146,61 g/mol)

Yellow liquid (mixture)

R_f = 0.5 (pentane/diethyl ether 3:1)

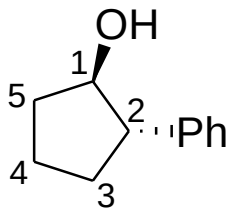
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.57 (td, *J* = 2.6 Hz, 2.6 Hz, 5.4 Hz, 1H, H_3), 6.07 (ddd, J = 1.8 Hz, 3.7 Hz, 5.4 Hz, 1H, H_2), 4.16-4.11 (m, $H_{3'}$), 2.54-2.48 (m, 2H, H_4), 2.48-2.17 (m, 4H, $H_{2'}$, $H_{4'}$), 1.05 (s, 12H, H_6, $H_{6'}$).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 217.7 ($C_{1'}$), 214.7 (C_1), 161.8 (C_3), 131.7 (C_2), 66.8 ($C_{3'}$), 53.3 ($C_{5'}$), 50.4 (C_5), 45.4 (C_4), 42.5 ($C_{2'}$), 34.5 ($C_{4'}$), 29.2 ($C_{6'}$), 24.7 (2C, C_6), 22.0 ($C_{6'}$).

A 25 mL flask containing 5 mL of distilled DCM and a stirring bar under argon is cooled to 0°C. Acid XX (720 mg, 5.6 mmol) is dissolved in a few mL DCM and added with a syringe. After 10 min stirring at 0°C, distilled $(COCl)_2$ (0.5 mL, 5.6 mmol) is added under argon with a syringe. The reactor is stirred for 4 h at 0°C/5 °C.
A suspension of $AlCl_3$ (0.75 g) in DCM (10 mL) at 0°C is prepared under argon in a 50 mL flask. The media is yellow. The contents of the former flask are transferred into the latter slowly with a cannula. The yellow color becomes orange overnight, allowing for the reactor to warm up to room termpature. Quenching is performed with ice first and then cold, distilled water (100 mL).

The original procedure was carried out thus: The organic fraction is discarded and the aqueous phase was acidified until pH = 1 with 2M HCl and extracted with diethyl ether (4 x 100 ml). The combined organic fractions were washed with $NaHC0_3$ and then dried ($MgSO_4$). Evaporation of the solvent yielded nothing.
However, evaporation of the solvent from the “discarded” fraction contained the mixture of ketones. Various basic treatements and chromatography failed to yield a pure sample of the desired cyclopentenone.

2-phenyl-cyclopentanol **<u>42</u>**



(+/-)

$C_{11}H_{14}O$ (162,23 g/mol)

Transparent liquid

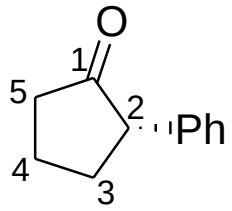
R_f = 0.25 (pentane/diethyl ether 3:1)

^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.40-7.21 (m, 5H, Ph), 4.15 (q, *J* = 7.1 Hz, 7.1 Hz, 7.4 Hz, 1H, H_1), 2.89 (q, *J* = 7.4 Hz, 7.9 Hz, 7.9 Hz, 1H, H_2), 1.96-1.65 (m, 2H), 2.18-2.05 (m, 4H).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 143.3 (quat. Ph), 128.4 (Ph, 2C), 127.3 (Ph, 2C), 126.2 (Ph), 80.2 (C_1), 54.3 (C_2), 33.8 (C_5), 31.8 (C_3), 21.7 (C_4).

Commercial PhMgBr solution (33 mL, 1.8 M, 60 mmol) is added to 50 mL distilled THFin a 250 mL flask under argon equipped with a stirring bar. After 10 minutes stirring, cyclopentene oxide (4.35 mL, 50 mmol) in 10 mL THF was added slowly at room temperature. The reaction mixture becomes brown and turpid. The reaction mixture is stirred until the epoxide has disappeared from the CCM. The reaction was quenched with 50 mL NH_4Cl. The reaction mixture was diluted with 100 mL diethyl ether and extracted with 3 x 50 mL diethyl ether. The combined organic fraction are dried ($MgSO_4$), the solvent removed . The crude product (5.06g) was purified by chromatography (petroleum ether/diethyl ether 9/1 to 3/1) to yield 2.4g (30 %) of phenyl alcohol.

2-phenylcyclopentanone **43**



(+/-)

$C_{11}H_{12}O$ (160,21 g/mol)

Yellow liquid

R_f = 0.55 (pentane/diethyl ether 3:1)

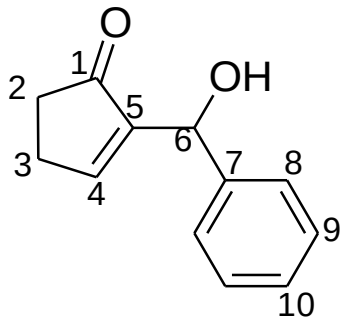
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.42-7.19 (m, 5H, Ph), 3.35 (t, *J* = 9.8 Hz, 1H, H_2), 2.63-2.44 (m, 2H), 2.39-2.26 (m, 1H), 2.25-2.06 (m, 2H), 2.03-1.89 (m, 1H).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 218.1 (C_1), 138.3 (quat. Ph), 128.5 (Ph, 2C), 128.0 (Ph, 2C), 126.8 (Ph), 55.2 (C_2), 38.3 (C_5), 31.6 (C_4), 20.7 (C_3).

In a 25 mL flask, alcohol XX (422 mg, 2.6 mmol) and 10 mL of distilled DCM are stirred with a stirring bar for a few minutes. Dess-Martin periodoidane (1.28 g, 3 mmol) is added slowly. The transparent medium becomes white and opaque. The reaction can be followed by TLC (a less polar spot appears).

Once the SM has disappeared, the reaction is quenched with 20 mL $Na_2S_2O_3$. The media changes from white to a biphasic transparent/yellow. The media is extracted with 2 x 20 mL Et_2O and the whole is washed with 10 mL saturated $NaHCO_3$. The organic phase is dried ($MgSO_4$) and the solvent removed. The crude material is pure product (401 mg, 2.5 mmol, 96 %).

2-(hydroxy(phenyl)methyl)cyclopent-2-enone **40**



$C_{12}H_{12}O_2$ (188,22 g/mol)

Yellowish solid

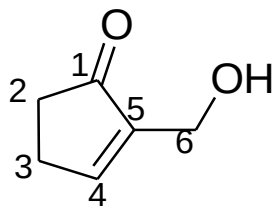
Standard BH procedure : cyclopentenone

^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.62-7.17 (m, 6H, Ph, H_4), 5.56 (s, 1H, H_6), 2.60-2.56 (m, 2H, H_2, H_2) 2.48-2.42 (m, 2H, H_3, H_3).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 209.4 (C_1), 159.2 (C_4), 147.7 (C_5), 141.3 (C_7), 128.4 (2C, C_9), 127.7 (C_{10}), 126.2 (2C, C_8), 69.7 (C_6), 35.1 (C_2), 26.5 (C_3).

Standard Baylis-Hillman procedure.

2-(hydroxymethyl)cyclopent-2-enone **39**



$C_6H_8O_2$ (112,13 g/mol)

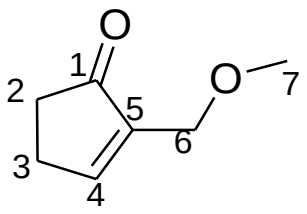
White solid

^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.58-7.51 (m, 1H, H_4), 4.45-4.35 (m, 2H, H_6, H_6), 2.54-2.43 (m, 2H, H_2, H_2), 2.71-2.61 (m, 2H, H_3, H_3).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 200.8 (C_1), 158.8 (C_4), 134.6 (C_5), 57.6 (C_6), 35.0 (C_2), 26.8 (C_3).

Standard Baylis-Hillman procedure.

2-(methyloxymethyl)cyclopent-2-enone **41**



$C_7H_{10}O_2$ (126,15 g/mol)

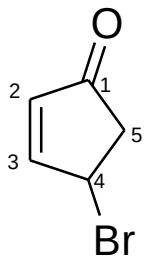
Transparent liquid

^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.52 (d, J = 1.1 Hz, 1H, H_4), 4.03 (dd, J = 2.1 Hz, 3.7 Hz, 2H, H_6, H_6), 3.33 (s, 3H, Me_7), 2.37 (td, J = 2.1 Hz, 2.1 Hz, 7.1 Hz, 2H, H_2, H_2), 2.62-2.53 (m, 2H, H_3, H_3).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 208.2 (C_1), 159.6 (C_4), 142.9 (C_5), 66.0 (C_6), 58.6 (C_7), 34.6 (C_2), 26.6 (C_3),

A 50 mL flask containing 2-(hydroxymethyl)cyclopent-2-enone (576 mg, 5.1mmol), methyl iodide (3.23 mL, 51 mmol), silver oxide (I) (1.3g, 5.6mmol) and a stirring bar are placed in 20 mL acetonitrile (HPLC quality). Overnight stirring, dilution with Et_2O, filtration through silica, drying ($MgSO_4$) and removal of the solvent yields the ether in 53 % yield.

4-bromocyclopent-2-enone[250] **36**



C_5H_5BrO (161,45 g/mol)

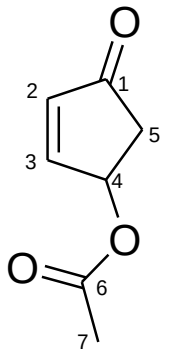
Yellowish liquid

^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.65 (ddd, *J* = 3.0 Hz, 3.1 Hz, 5.5 Hz, 1H, H_3), 6.24 (ddd, *J* = 1.5 Hz, 2.9 Hz, 5.5 Hz, 1H, H_2), 5.13 (ddd, *J* = 1.5 Hz, 2.2 Hz, 5.7 Hz, 1 H, H_4), 3.00 (ddd, *J* = 3.0 Hz, 5.7 Hz, 19.3 Hz, 1 H, H_5), 2.68 (ddd, *J* = 2.2 Hz, 3.1 Hz, 19.3 Hz 1 H, H_5)

^{13}C NMR (90 MHz, $CDCl_3$, δ) : 204.5 (C_1), 162.3 (C_3), 134.6 (C_2), 44.8 (C_5), 42.6 (C_4).

50 mL DCM (or CCl_4) are placed in a 100 mL flask mounted with a reflux apparatus at room temperature followed by cyclopent-2-enone (2.5 g, 30 mmol) and N-bromosuccinimide (6 g, 37 mmol). AIBN (0.125 g) is added slowly. After 5 minutes stirring at room temperature, the reaction is stirred at 70°C overnight. The reaction media is then allow to cool and filtered through Celite, washed with water (2 x 20 mL) and $Na_2S_2O_3$ (1M, 3 x 20 mL), dried ($MgSO_4$) and the solvent is removed. The crude oil is transparent with a yellow tinge. The crude is pure brominated compound (2.1g, 43%) but rapidly degrades to a brown paste.

4-acetoxycyclopent-2-enone **37**



$C_7H_8O_3$ (140.14 g/mol)

Transparent liquid

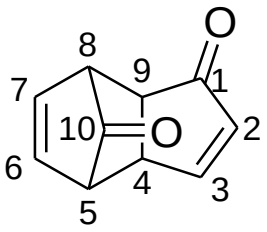
^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.54 (dd, *J* = 2.4 Hz, 5.8 Hz, 1 H, H_3), 6.29 (dd, *J* = 1.3 Hz, 5.8 Hz, 1 H, H_2), 5.73 - 5.88 (m, 1 H, H_4), 2.79 (dd, *J* = 6.3 Hz, 18.8 Hz, 1 H, H_5), 2.28 (dd, *J* = 2.4 Hz, 18.8 Hz, 1 H, H_5), 2.04 (s, 3 H, Me_7).

^{13}C NMR (90 MHz, $CDCl_3$, δ): 204.7 (C_1), 170.3 (C_6), 158.9 (C_3), 136.8 (C_2), 71.8 (C_4), 40.8 (C_5), 20.7 (C_7)

50 mL DCM (or CCl_4) are placed in a 100 mL flask mounted with a reflux apparatus at room temperature followed by cyclopent-2-enone (2.5 g, 30 mmol) and N-bromosuccinimide (6 g, 37 mmol). AIBN (0.125 g) is added slowly. After 5 minutes stirring at room temperature, the reaction is stirred at 70°C overnight. The reaction media is then allow to cool and filtered through Celite and the solvent is removed.

The yellow oil is dissolved in glacial acetic acid (10-20 mL) with a stirring bar. Silver acetate (7g, 45 mmol) is added. The reaction is stirred for at least 48h at 100 °C (reflux). Removal of the acetic acid and chromatography gives the expected acetoxycyclopentenone (3g, 71 %).

tricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene-3,10-dione **38**



$C_{10}H_8O_2$ (160,17 g/mol)

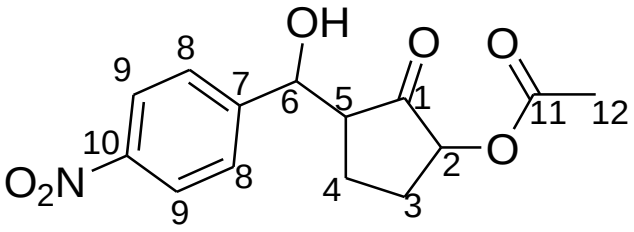
Transparent liquid

Degradation product of 4-bromocyclopentenone in basic media.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.36 (ddd, J = 0.5 Hz, 2.7 Hz, 5.7 Hz 1H, H_3), 6.33 (dd, J = 1.6 Hz, 5.7 Hz, 1H, H_2), 6.27 (ddddd, J = 0.4 Hz, 0.5 Hz, 1.2 Hz, 3.5 Hz, 6.8 Hz, 1H, H_7), 6.14 (ddddd, J = 0.4 Hz, 0.4 Hz, 1.2 Hz, 3.6 Hz, 6.8 Hz 1H, H_6), 3.49 (dddd, J = 0.4, 0.5 Hz, 1.6 Hz, 2.7 Hz, 4.5 Hz, 6.0 Hz, 1H, H_4), 3.36 (ddddd, J = 0.5 Hz, 1.1 Hz, 1.2 Hz, 3.5 Hz, 4.8 Hz, 1H, H_8), 3.18 (dddd, J = 1.1 Hz, 1.2 Hz, 3.6 Hz, 4.5 Hz 1H, H_5), 2.87 (dddd, J = 0.4 Hz, 0.4 Hz, 4.8 Hz, 6.0 Hz, 1H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 206.4 (C_{10}), 199.5 (C_1), 161.3 (C_3), 141.1 (C_2), 129.5 (C_7), 129.0 (C_6), 49.9 (C_8), 49.0 (C_5), 43.1 (C_9), 41.4 (C_4).

3-[hydroxy(4-nitrophenyl)methyl]-2-oxocyclopentyl acetate **96**



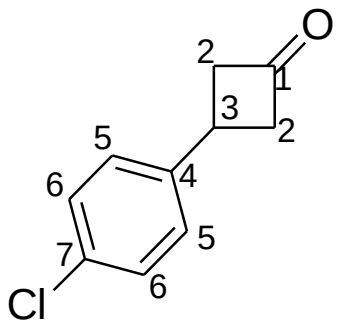
$C_{14}H_{15}NO_6$ (293,272g/mol)

Yellow liquid

^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.19 (d, *J* = 8.0 Hz, 2 H, H_9), 7.52 (d, *J* = 8.0 Hz, 2H, H_8), 5.43 (m, 1H, H_6), 4.98 (m, 1H, H_2), 2.62-1.67 (m, 5H, H_3, H_3, H_4, H_4, H_5), 2.10 (s, 3H, Me_{12}).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 212.0 (C_1), 170.1 (C_{11}), 149.5 (C_{10}), 147.3 (C_7), 126.3 (2C, C_9), 123.7 (2C, C_8), 76.5 (C_2), 70.3 (C_6), 53.1 (C_5), 26.5 (C_3), 20.2 (C_{12}), 17.5 (C_4).

3-(4-chlorophenyl)cyclobutanone **75**[511]



$C_{10}H_9ClO$ (180,63 g/mol)

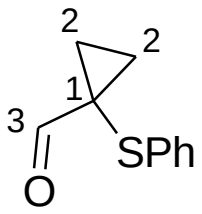
Transparent liquid

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.29-7.18 (m, 4H, Ph), 3.60 (q, *J* = 8.1 Hz, 1H, H_3), 3.47-3.43 (m, 2H, H_2, H_2), 3.20-3.11 (m, 2H, H_2, H_2).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 206.1 (C_1), 142.0 (C_4), 128.7 (2C, C_6), 127.8 (2C, C_5), 54.6 (2C, C_2), 27.9 (C_3).

A 250 mL flask containing a mixture of Zn powder (2g, 30 mmol), *para*-chlorostyrene (2.1g, 15 mmol) and 50 mL of distilled diethyl ether under Ar was placed in an ultrasonic water bath maintained at 15-20 °C. With sonication, a solution of trichloroacetyl chloride (4.02 g, 22 mmol) in 50 mL of distilled diethyl ether was added dropwise over 1 h and sonication was continued for an additional 30 min. The reaction mixture was treated with 10 mL of H_2O and filtered through Celite. The filtrate was extracted with ether and washed with H_2O, saturated $NaHCO_3$ and brine. After the solvent was dried (Na_2SO_4) and removed. The crude oild was diluted with HOAc (20 mL) in a 100 mL flash and added dropwise to a Zn dust suspension (6 g, 31 mmol) in HOAc (30 mL). After complete addition, the mixture was stirred at 80 °C for 2 h and then cooled and 5 mL of H_2O were added. The mixture was filtered through Celite, thefiltrate was then washed with water, saturated $NaHCO_3$ and brine and then dried, and the solvent was removed. The cyclobutanone was obtained pure after chromatography (31 %).

1-(phenylthio)cyclopropanecarbaldehyde[565]



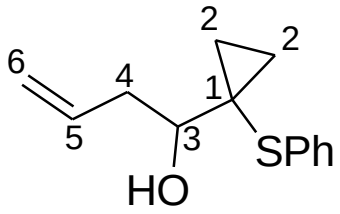
$C_{10}H_{10}OS$ (178,25 g/mol)

Transparent liquid

^1H NMR (300 MHz, $CDCl_3$, δ): 9.81 (s, 1H, H_3), 7.31 – 7.1 (Ph, 5H), 1.15-1.05 (m, 4H, H_2, H_2, H_2, H_2).

Litterature procedure : In a 250 mL flask, cyclopropyl phenyl thioether (6g, 40 mmol) were soluted in 100 mL distilled THF. A stirring bar was added and the flask was stirred at 0°C for 10 minutes. BuLi is added slowly with a syringe (1.6 M sol. in hexanes, 25 mL, 40 mmol). The transparent media becomes clouded as addition proceeds. The reaction is stirred for 1 hour at 0°C and then cooled to -78°C. Distilled DMF (3.0 mL, 28 mL) is added with a syringe. After addition, the reaction is stirred for 2 hours. Distilled water is added (40 mL) to quench the reaction. Once the flask has returned to r.t., it is poured in a beaker containing 100 mL petroleum ether. The aqueous fraction is extracted several times with diethyl ether. The various organic fractions are consolidated, washed brine, dried (Na_2SO_4) and the solvent removed. Chromatography of the crude mixture yields 25 % expected aldehyde (1.84 g, 10 mmol) and 47 % unreacted starting material (2.82 g, 19 mmol). Longer stirring at 0°C after addition of BuLi (4h instead of 2h), addition of DMF carried out at -78°C overnight and quenching/workup in the morning allowed for decreased recovered SM (2.01 g, 13 mmol, 33%) but increased product (2.39 g, 13 mmol, 33 %).
Alternative procedure : Reverse addition, preparation of the salt of butyl lithium and cyclopropyl phenyl thioether and its addition to a solution of DMF yields 28% product and no unreacted thioether.

1-(1-(phenylthio)cyclopropyl)but-3-en-1-ol **64**



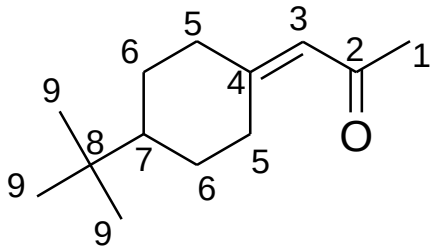
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.46-7.44 (m, 2H, SPh), 7.28-7.15 (m, 3H, SPh), 5.9-5.7 (m, 1H, H_5), 5.13-5.07 (m, 2H, H_6, H_6), 3.5-3.3 (m, 1H, H_3), 2.64-2.52 (m, 1H, H_4), 2.4-2.27 (m, 1H, H_4), 1.90 (br s, 1H, OH), 1.13-1.00 (m, 4H, H_2, H_2, H_2, H_2).

All glassware was dried in the oven prior to the reaction. Mg flakes were also placed in the oven beforehand. Stirrer and Mg cuttings (1.5 g) were placed in a two-funneled 100 mL flask. A reflux device, an addition device and a $CaCl_2$ stopper were mounted. The whole apparatus was fully purged with Ar.

Distilled (20 mL) Et_2O was added to the addition device. Mg was barely immerged in solvent. Allyl bromide drops were added and a touch of I_2 was added until a reaction was observed. Allyl bromide (1.54 mL, 30 mmol) and distilled Et_2O (20 mL) were added with the addition device dropwise. The reaction was stirred for 40 minutes with occasional heating with a heatgun to maintain the reaction.

1-(phenylthio)cyclopropanecarbaldehyde (1.84 g, 10 mmol) in 15 mL distilled Et_2O were added dropwise with the addition device. Addition generates bubbles, local heating and dispersed the dark, tepid aspect of the reaction flask. After 1.5 h of refluxing, water was added to quench the reaction. After allowing the flask to cool, the contents was transfered to an extraction apparatus. The aqueous fraction was extracted with diethyl ether several times. The combined organic fractions were washed with water, dried (Na_2SO_4) and the solvent removed. Only the expected product is present in the crude (GCMS). Chromatography yields pure product (1.65 g, 7.5 mmol, 75 %).

1-(4-tert-butylcyclohexylidene)propan-2-one **79**

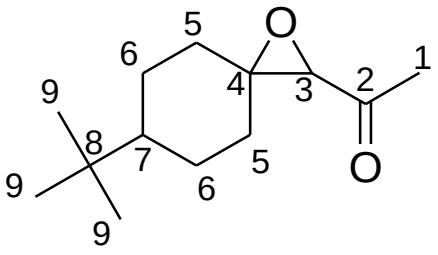


^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.96 (s, 1H, H_3), 3.79 (d, *J* =12.6 Hz, H_5, H1), 2.02 (s, Me_1), 2.0-1.6 (cycle, 4H), 1.24-1.06 (cycle, 4H), 0.82 (s, *t*Bu, 9H).

$C_{13}H_{22}O$ (194,31 g/mol)

Diethyl 2-oxopropylphosphonate (1.64 g, 8.45 mmol), ethanol (10 mL) and stirring bar are placed in a 50 mL flask. 5 mL 10 % KOH solution (8.45 mmol) in water are added. Media becomes yellow after a few minutes. 4-terbutylcyclohexanone (847 mg, 5.5 mmol) in 10 mL ethanol is added with a syringe. The reaction is followed by TLC. Once the reaction is complete, the solvent is removed and the crude mixture is chromatographied. Product can be seperated from unreacted starting material : 450 mg, 42 %. The crude contained traces of the unconjugated cyclohexenylacetone.

1-(6-tertbutyl-1-oxapiro[2.5]octan-2-yl)ethan-1-one **83**



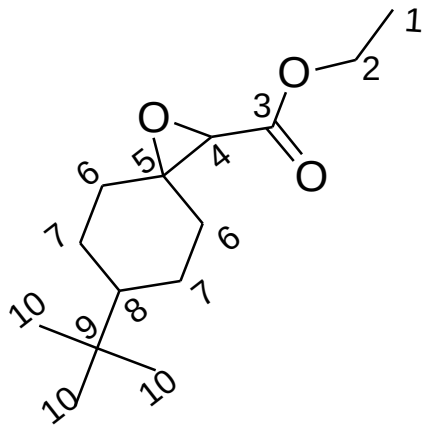
$C_{13}H_{22}O_2$ (210,31 g/mol)

White solid

^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.56(s, 1H, H_3), 2.42 (s, 3H, H_1), 2.21-1.14 (m, 9H, $H_{5\text{-}7}$), 1.04 (s, 9H, H_9).

Cyclohexylidene compound XX (388 mg 2 mmol) and a stirring bar are placed in a 50 mL flask under Ar. 10 mL methanol are added and the flask is cooled to 0°C. Hydrogen peroxide (30 % weight, 0.6 mL, 6 mmol). After 10 minutes stirring at 0°C, NaOH (10 % in water, 0.1 mL, 0.25 mmol) is added. The reaction is stirred at 0°C for two hours. After the end of the reaction (followed by TLC), the reactor contents is pourred into 50 mL of brine and the whole is repeatedly extracted with DCM. The organic fractions are combined, dried (Na_2SO_4) and the solvent removed. Chromatography yields the spiro-epoxide in 50 % yield (210 mg).

ethyl 6-tertbutyl-1-oxapiro[2.5]octane2-carboxylate **84**



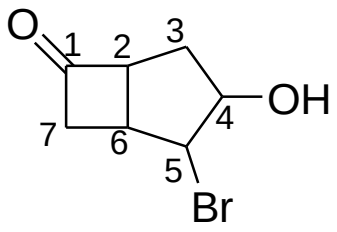
$C_{14}H_{24}O_3$ (240,34 g/mol)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.11 (t, *J* = 6.4 Hz, 6.4 Hz, 2H, H_2), 3.28 (s, 1H, H_4), 1.90-0.90(m, 11H, H_2, H_2, H_6, H_6, H_6, H_6, H_7, H_7, H_7, H_7, H_8), 0.81 (s, 9H, *t*Bu).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 169.0 (C_3), 65.7 (C_2), 64.8 (C_5), 59.9 (C_4), 47.8 (C_8), 34.1 (2C, C_6), 33.0 (C_9), 28.1 (3, C_{10}), 25.9 (2C, C_7), 14.2 (C_1).

Distilled amine (0.85 mL, 6 mmol), distilled THF (20 mL) and a stirring bar are placed in a flask and cooled to -78/-80 °C. After 20 minutes stirring, BuLi was added (solution in hexanes, 5.5 mmol). After 30 minutes stirring, ethyl chloroacetate (1.2 g, 6 mmol) in 10 mL THF was added slowly at -78/80 °C After 20 minutes stirring, 4-terbutylcyclohexanone (770 mg, 5 mmol) in 10 mL THF was added slowly. The reaction was stirred overnight and allow to return to room temperature. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (3x30 mL). The organic fractions were combined, dried (Na_2SO_4) and the solvent removed. Chromatography yields 77 % epoxide (930 mg).

4-bromo-3-hydroxybicyclo[3.2.0]heptan-6-one **58**[566]



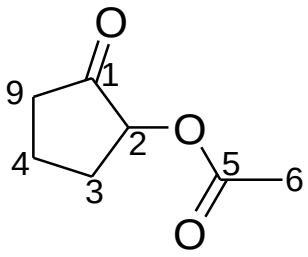
$C_7H_9BrO_2$ (205,05 g/mol)

White powder

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.62 (s, lH), 4.28 (s, lH), 3.79 (m, lH), 3.31-3.16 (m, 4H), 2.50 (ddd, *J* = 4.2 Hz, 9.6 Hz, 14.2 Hz, 1H), 2.21 (d, *J* = 14.2 Hz, lH).

Bicyclo[3.2.0]hept-2-en-6-one (270 mg, 2.5 mmol), a stirrer , 5 mL H_2O and 15 mL acetone are placed in a 50 mL flask. Vigourous stirring is underway when freshly recristalized NBS is slowly added (534 mg, 3 mmol) and the reaction is stirred overnight. Once the reaction is complete, diethyl ether is added. The aqeuous fractions are repeatedly extracted with diethyl ether. The organic fractions are combined, washed ($NaHCO_3$ sat.), dried (Na_2SO_4) and the solvent removed. Yield is 415 mg (81 %).

2-acetoxycyclopentanone **94**

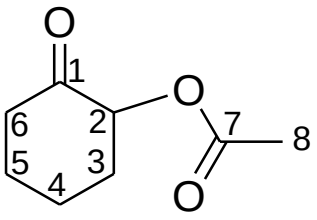


^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.94 (t, *J* = 9.0 Hz, 9.0 Hz, 1H, H_2), 2.33-2.17 (m, 4H, H_3, H_3, H_6, H_6), 2.00(s, 3H, Me_6), 1.76-1.69 (m, 2H, H_4, H_4).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 212.8 (C_1), 170.6 (C_6), 76.1 (C_2), 35.3 (C_5), 28.8 (C_4), 21.2 (C_7), 17.6 (C_3).

In a 50 mL flask equipped with a stirring bar, α-chlorocyclopentanone (4.8 g, 40 mmol) and potassium acetate (6.4 g, 60 mmol) are stirred in 30 mL ethyl acetate (standard quality). Tetrabutylammonium iodide (555 mg, 1.5 mmol) is added, a reflux device added and the reaction is stirred for 12-48h. Visible precipitation of KB is visible after a time and the media becomes orange-brown. The flask is cooled, emptied into a beaker of 100 mL Et_2O and filtered through silica to remove the solid products. Removal of the solvent yields pure acetoxycyclopentanone (5.1 g, 90 %).

2-acetoxycyclohexanone **95**



^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.12 (t, *J* = 6.15 Hz, 6.15 Hz,1H, H_2), 2.50-2.17 (m, 4H, H_3, H_3, H_6 H_6), 2.10 (s, 3H, Me_8), 2.00-1.68 (m, 4H, H_4, H_4, H_5, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 205.2 (C_1), 170.6 (C_7), 77.2 (C_2), 41.3 (C_6), 33.7 (C_4), 27.7 (C_5), 24.7 (C_8), 21.3 (C_3).

The same procedure as above is used with α-chlorocyclohexanone with the same results.

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