An Efficient Synthesis of Natural Products

Using Singlet Oxygen

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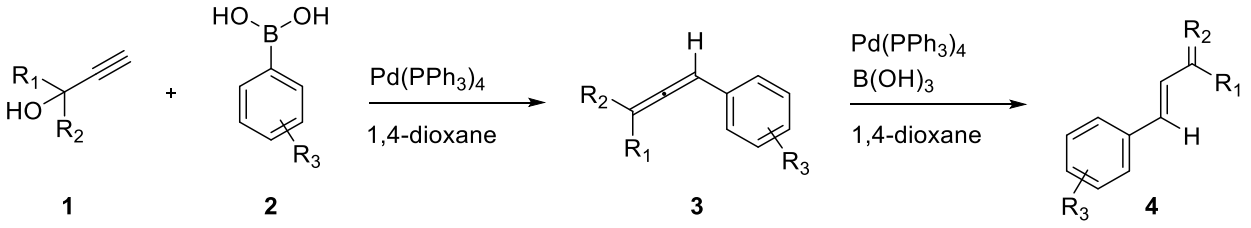
Abstract

The treatment of 1,3-dienes with singlet oxygen ($^1O_2$) to give endoperoxides represents a potent, chemo- and regioselective method for the introduction of oxygen functionality. Additionally, these endoperoxides products can be further utilized in the synthesis of added value compounds, as well as complex natural products. In the thesis a new method for the synthesis of acyclic 1,3-dienes is presented. Furthermore, both acyclic and cyclic 1,3-dienes are used in the synthesis of natural products using singlet oxygen ($^1O_2$) addition as a core strategy.

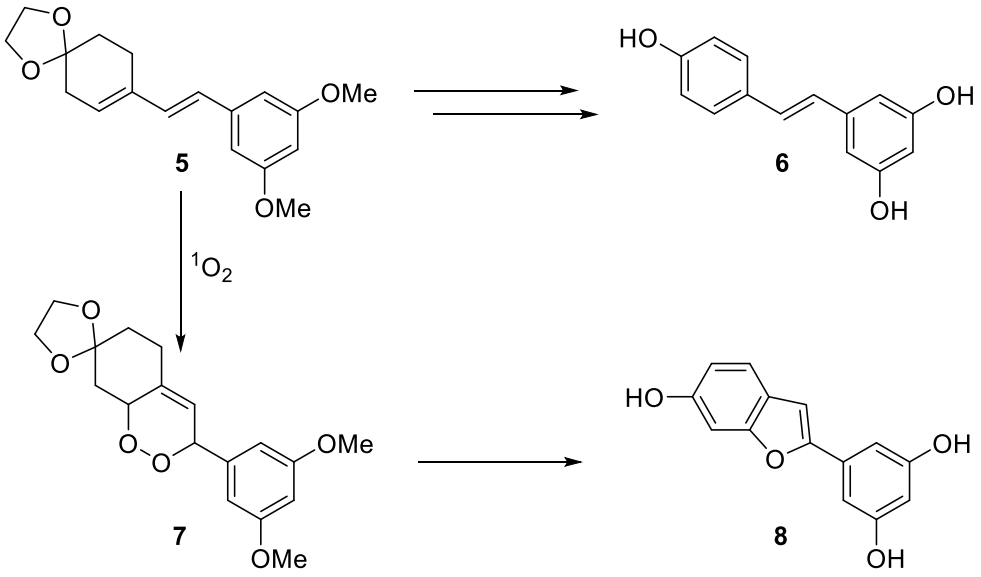
A new approach for the synthesis of range of 1,3-dienes from aryl boronic acids **2** and substituted propargyl alcohols **1** via a palladium catalyzed has been developed. This reaction uses a base-free, Suzuki-Miyaura coupling followed by an unprecedented isomerization sequence and gives a wide range of cyclic and acyclic of 1,3- diene compounds **4** with varying aryl groups in good isolated chemical yields.

This reaction involves initial formation of an allene **3** as intermediate which then undergoes ready rearrangement by way of a palladium hydride intermediate, which results from the interaction of palladium (0) and boric acid. To ascertain mechanistic conformation of this rearrangement the intermediary allenes were isolated and exposed to palladium (0) and boric acid. Additionally, direct injection ESI-MS was utilized to observe an intermediate palladium allyl complex; which can only occur form the addition of palladium-hydride to the allene. Furthermore, a range of stable allenes were then isomerized to 1,3-dienes by using the boric acid and a palladium (0) catalytic system.



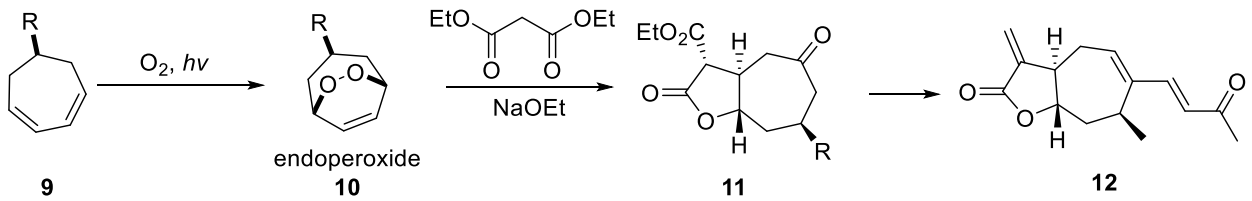
Scheme 1: Synthesis of 1,3-dienes

The synthetic utility of this reaction was applied by developing a convenient route to resveratrol **6** from 1,3-diene **5**. Additionally, we then utilized the addition of singlet oxygen to **5** and were then able to convert the resultant endoperoxide **7** to moracin M (**8)**.



Scheme 2: Synthesis of Natural Products Resveratrol and Moracin M

Additionally, treatment of bicyclic 1,3-dienes **9** with singlet oxygen to give bicyclic endoperoxides **10** was examined as a method to deliver the core structure of the xanthanolide class of natural products. The xanthanolide skeleton, particularly xanthatin which is a potent anti-inflammatory natural product, contain a *trans*-fused ring system and can be obtained from the treatment of **10** with a malonate nucleophile *via* Korn Blum DeLaMare rearrangement. Significant progress toward the total synthesis of xanthatin **12** was made, and we were able to obtain the advanced precursor **11**, which is only 11-steps from **9** to xanthatin **12**.



Scheme 3: Synthesis of natural product xanthanolides.

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Abbreviations

AA	Arachidonic acid
Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
br	Broad
BuLi	Butyllithium
Cat.	Catalytic
COX	Cyclooxygenase
d	Doublet
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarization transfer
DMAP	4-Dimethylaminopyridine
DIBAL (DIBAH)	(DIBAH) Diisobutylaluminum Hydride
DIAD	Diisopropyl azodicarboxylate
Diglime	Bis(2-methoxyethyl) ether
DIPA	Diisopropanolamine
DMP	Dess-Martin periodinan
EI	Electron Ionisation
Et	Ethyl
Equiv.	Equivalents
GC-MS	Gas Chromatography–Mass Spectrometry
H	Hour
HMDS	Hexamethyldisilazide
HMPA, HMP	Hexamethylphosphorictriamide
Hz	Hertz
IR	Infra-red

LAH	Lithium aluminium hydride
LOX	Lipoxygenase
LDA	Lithium Diisopropylamide
J	Coupling Constant
MAPH	Methyl Aluminum bis(2,6- diphenyl phenoxide)
MB	Methyl blue
MCPBA	meta-Chloroperoxybenzoic Acid
min.	Minutes
MOM	Methoxymethyl
m/z	Mass to Charge Ratio
NMR	Nuclear Magnetic Resonance
NMO	N-Methylmorpholine N-oxide
$PdCl_2$(COD)	Dichloro (1,5-cyclooctadiene) palladium(II)
PEG 400	Poly ethylene glycol 400
ppm	Parts per million
PPTS	Pyridinium p-Toluenesulfonate
q	Quartet
r.t.	Room Temperature
s	Singlet
T	Triplet
TBAF	Tetra-n-butylammonium fluoride
TBSOTE	t-Butyldimethylsilyl trifluoromethanesulfonate
TDA-1	Tris[2-(2-methoxyethoxy)ethyl]amine
TBDPS	t-Butyldiphenylsilyl (alcohol protection
TBSCl	t-Butyldimethylsilyl Chloride
TMSCl	Chlorotrimethylsilane
TPAP	Tetra-n-propylammonium Perruthenate
TPP	meso-Tetraphenylporphyrin
TBDPSCl	t-Butyldiphenylsilyl Chloride
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMS	Tetramethylsilane

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1. Introduction

1.1 Singlet Oxygen Background:

Oxygen is one of the most important elements in life, it forms 21% of the air[1] in the atmosphere, 89% of weight of the water of rivers, seas and oceans. In addition, all living organisms utilize oxygen either by respiration or to produce energy. By mass, oxygen is the third most abundant element in the universe, after hydrogen and helium. Oxygen's reactivity come from its unpaired valence electrons in an otherwise stable molecule which make it able to be a strong oxidant and easily reduced.

According to the molecular orbital theory, oxygen can exist in three forms in terms of the configuration of antibonding electrons (figure 1).[2]

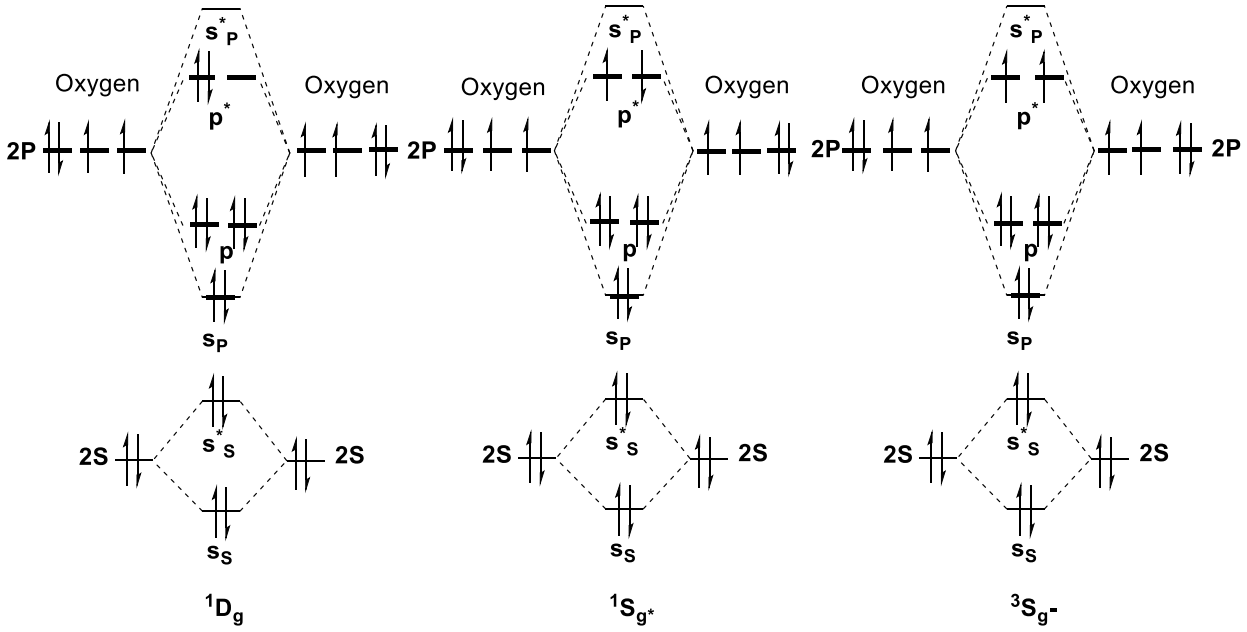


Figure 1: MO diagram of three forms of oxygen.

Figure 1 shows three forms of energy level of the molecule of oxygen, first $^1\Delta_g$ both electrons paired in one orbital leaving other vacant, this oxygen molecule is the more stable singlet state, $^1\Sigma_g^+$ is the second (and less stable) singlet state, $^3\Sigma_g^-$ triplet or regular oxygen state.

The first is the singlet oxygen species $^1\Delta g$ form lies 94.7 kJ (7882 cm^{-1}, 1269 nm) in energy above the triplet ground state. The second state $^1\Sigma g+$ lies 158 kJ (13120 cm^{-1}, 762 nm) in energy above the triplet ground state. Because of the second form state is highest energy than other so, it is less stable, and has very short life time compare with the first form $^1\Delta_g$.,[3] therefore the first form is the important state of singlet oxygen because it has enough time to oxygenate compounds. Also, the diagram shows that the first and second states are diamagnetic while the third is paramagnetic furthermore, they have different chemical properties.

Singlet oxygen was produced by using photosensitization and first reported in 1964 by Foote – Wexler reaction for its ability to oxidize organic and biological compound or to be used in synthesis[4].

Although, singlet oxygen can be produced in different ways, it has become an important reaction in organic synthesis as it can readily undergo addition to alkenes *via* a number of pathways including [4+2]-, [2+2]- and the ene-reaction. Furthermore, because singlet oxygen can be generated biomimetically, the synthetic organic chemist has utilised it to imitate the natural reaction, the analytical chemist to count their effect in the environment, the biochemist because singlet oxygen can be produced from the light-harvesting chlorophyll molecules, and the physics to study the stability of substance and many other branch of sciences.[5]

1.1.1 Singlet oxygen formation and reaction

Singlet oxygen reaction is an oxidation reaction using excited single molecular oxygen to make carbon-oxygen and heteroatom-oxygen bonds.

There are two ways to produce singlet oxygen $^1O_2$ in solution (Scheme 4).

Thermal process or dark singlet oxygenation (Scheme 4A).[6] This route is undertaken without using light to form the singlet molecular of oxygen. Example of this route is using hydrogen peroxide with NaOCl or the use of peroxides [arene endoperoxides; hydrotrioxides; potassium monoperoxysulfate ($KHSO_5$); dimethyldioxirane; ozone/heterocyclic adducts with pyrroles, oxazoles, and imidazoles; or triphenylphosphite ozonide (cyclo-$(PhO)_3PO_3$)].[6]

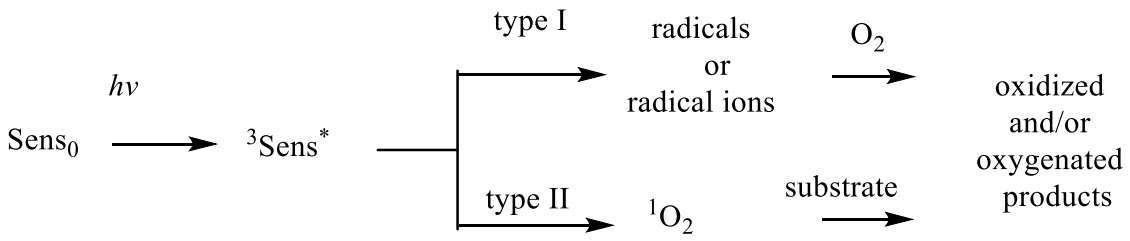
The photosynthesis production of the singlet oxygen (scheme 4B).[4] This route is done by using visible light, oxygen and a sensitizer. Because this route uses natural source of oxygen and readily available visible light it is attractive to the organic chemists, as it is biomimetic as well as green;

A $H_2O_2 + NaOCl \rightarrow {}^1O_2 + NaCl + H_2O$

B $Sens(cat.) + hv \rightarrow Sens^* + {}^3O_2 \rightarrow {}^1O_2 + Sens(cat.)$

Scheme 4: Generation of Singlet Oxygen

A sensitizer is usually an organic dye that has a large de-localized π systems and can be excited by visible light first, this can ionize the oxygen molecule or form singlet oxygen (type II scheme 5).



Scheme 5: Type I and II photosensitized oxidation

The singlet oxygen process is accompanied with trace amount of oxygen radical (type I) which is responsible for photo-bleaching when its exposed for irradiation for extended time periods in a homogeneous solution (scheme 5).

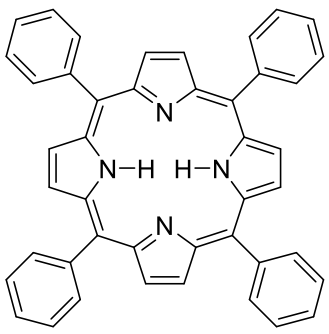
With reference of singlet oxygen reaction experiments, it was noted that the rate of the reaction increases at low temperature whereas, halogenated and deuterated solvents make the reaction slower but with increased yields.[7] Table 1 shows the life time of singlet oxygen in different solvents.

Table 1: life time of singlet oxygen in different solvents[8]

Solvent	$^1O_2$-Lifetime (μs)	Solvent	$^1O_2$-Lifetime (μs)
H_2O	3.1	D_2O	68
CH_3OH	9.1	CD_3OD	270
C_6H_6	30	C_6D_6	681
C_6F_{14}	68000	C_6F_6	21000
$(CH_3)_2CO$	51	$(CD_3)_2CO$	992
$CHCl_3$	229	$CDCl_3$	7000
$C_6H_5CH_3$	29	air	86000
CH_3CN	61	$CFCl_3$	1000
CCl_4	59000	CH_2Cl_2	101

Table 1 gives a comparison between deuterated and non-deuterated solvents and their singlet oxygen life time in addition, fluorinated solvent and CCl_4 are also included. There is a factor called vibrational frequencies related with the electronic transition energy between the singlet oxygen and the solvent. The high value of vibrational frequencies is found in molecules having hydrogen atoms bonded strongly to another atom such as O-H, S-H, N-H, C-H. According to this information H_2O has a high vibrational frequency and very low singlet oxygen life time and is a good quencher. Whereas D_2O has 20 times more life time. The same situation occurs when we exchange C-H with C-F. Also CCl_4 have long life time can be described by the low vibrational frequencies and low quenching rate. [8-9]

There are three common sensitizers used in organic synthesis, tetraphenyl porphyrin (TPP) **13**, rose Bengal (RB) **14** and methylene blue (MB) **15** (figure 2). [5, 10]



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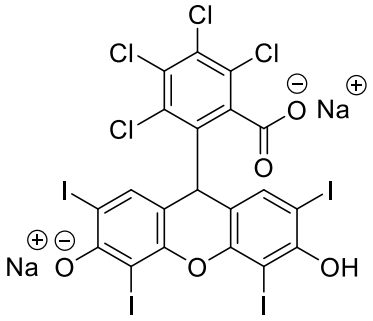

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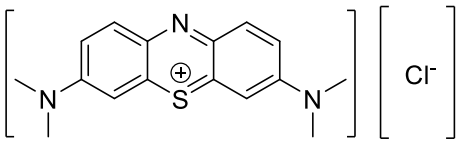

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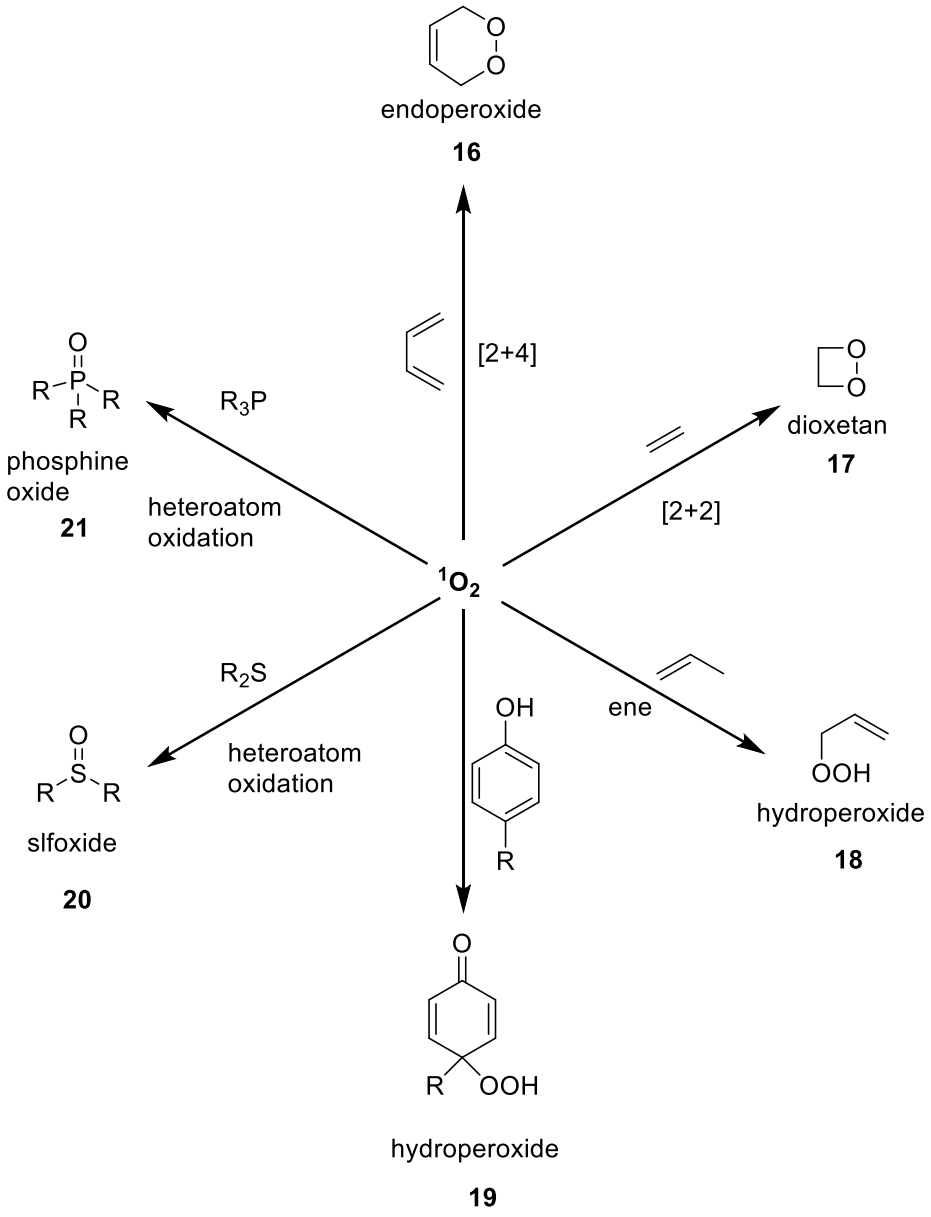
Figure 2: structures of sensitizer

The wavelength range of visible light is between 380 – 750 nm, and every sensitizer dye has a specific range of wavelength in which it can be excited. Methylene blue has strong absorption between 550 – 700 nm, rose Bengal absorbs in the green region of visible light 480 – 550 nm, whereas tetraphenyl porphyrin has the ability to absorb several wavelengths from ultraviolet to visible light.[11]

Singlet oxygen reacts with a range of double bond compounds to give various oxygenated hydrocarbons. Scheme 6[5,12-13] shows that $^1O_2$ can form endoperoxide **16** when added to 1,3-diene via a [2+4]-cycloaddition, dioxetane **17** through a [2+2]-cycloaddition, hydroperoxides **18** and **19** when reacted with alkenes and phenols, sulfoxides **20** when reacted with sulfides and phosphine oxides **21** when reacted with phosphines.



Scheme 6: Synthetic utility of $^1O_2$ for generating oxygenated hydrocarbon[5,12 -13]

Two classes of singlet oxygen reaction are generally important in organic chemistry, firstly addition to alkenes similar to the Alder-Ene reaction, giving allylic hydroperoxides and [2+2]-cycloaddition to form dioxetanes. Secondly, [4+2]-addition to the 1,3-diene giving endoperoxides similar to the Diels-Alder reaction. Other classes of oxidation of certain heteroatoms by singlet oxygen are of somewhat less in generality.

Many reports have been published about study the mechanism of [2+2]-addition concerned about the intermediate and the relation of the stereochemistry of the substance with the rate of the reaction. In addition, the selectivity of the reaction. In general, three intermediates have been proposed per-epoxide **A**, a diradical and zwitterionic intermediates **B**, and transition state **C** (figure 3).

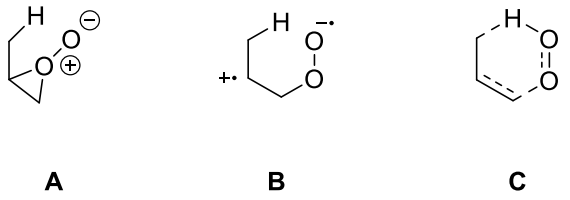
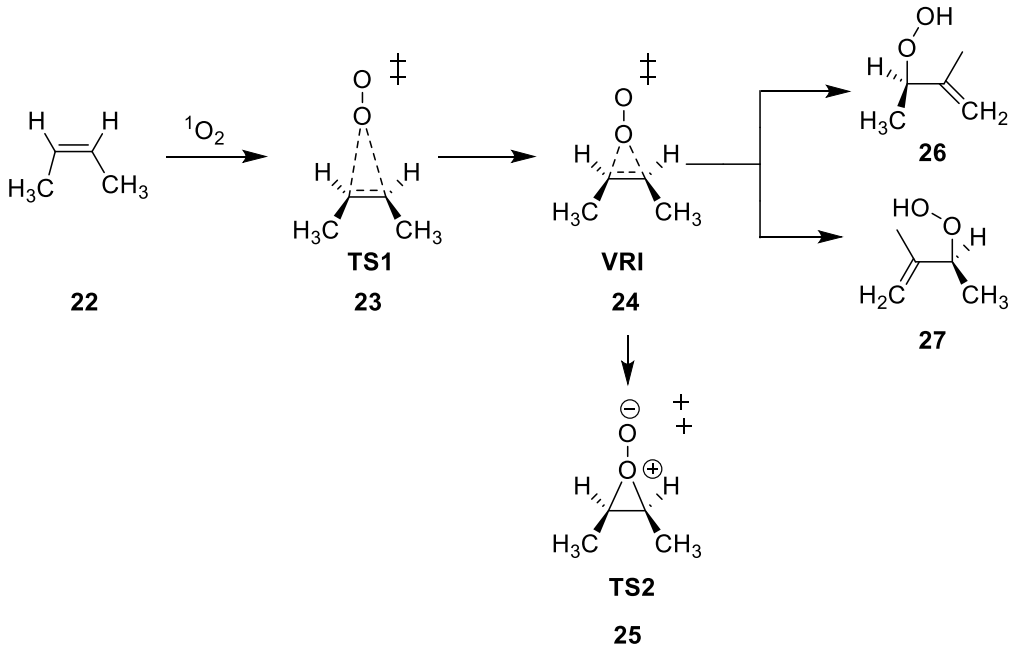


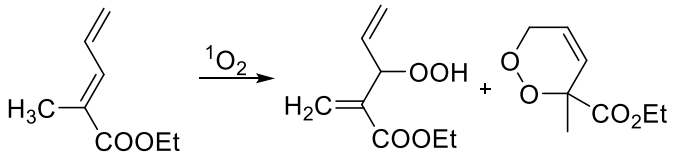
Figure 3: Intermediates of ene reaction mechanism

Using computational and experimental research, one result of B_3LYP study on *cis*-2-butene revealed that the reaction contains a valley–ridge inflection (VRI). Two transition state have a relation with VRI to give allylic hydroperoxide products. The VRI give evidence of the peroxide species (scheme 7**).**[4]



Scheme 7: Mechanism of ene reaction

At this point we can say that ene-addition has polar transition state **23** and **25** and could prefer polar protic solvents compared to the [4+2]-cycloaddition. An investigate done by Griesbeck in 2014 to test the effect of solvent and whether preference for the ene reaction or [4+2]-cycloaddition to substituted 1,3 dienes while he study the gem effect to functionalize dienes.[14]



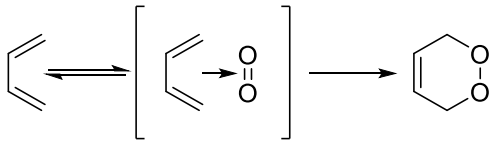
28 **29** **30**

CCl_4	46 : 56
$CHCl_3$	43 : 57
CH_2Cl_2	57 : 43
EtOH	63 :37

Scheme 8: solvent effect

Scheme 8 shows the reaction of singlet oxygen with diene **28** forming hydroperoxide **29** and endoperoxide **30**. When CCl_4 was used as a solvent in the reaction gave 46% of the hydroperoxide **29** and 56% of the endoperoxide **30**. The result show that the best solvent to push the reaction toward **29** was ethanol while the best solvent to form **30** was CCl_4 and $CHCl_3$, respectively. This result can be used as evidence that [4+2]-singlet oxygen cycloaddition prefers a nonpolar solvent whereas the ene-addition prefers polar solvent. Furthermore, it is not only solvent have an effect, the stereochemistry and the substituent groups play a pivotal role in addition of singlet oxygen in the reaction pathway.

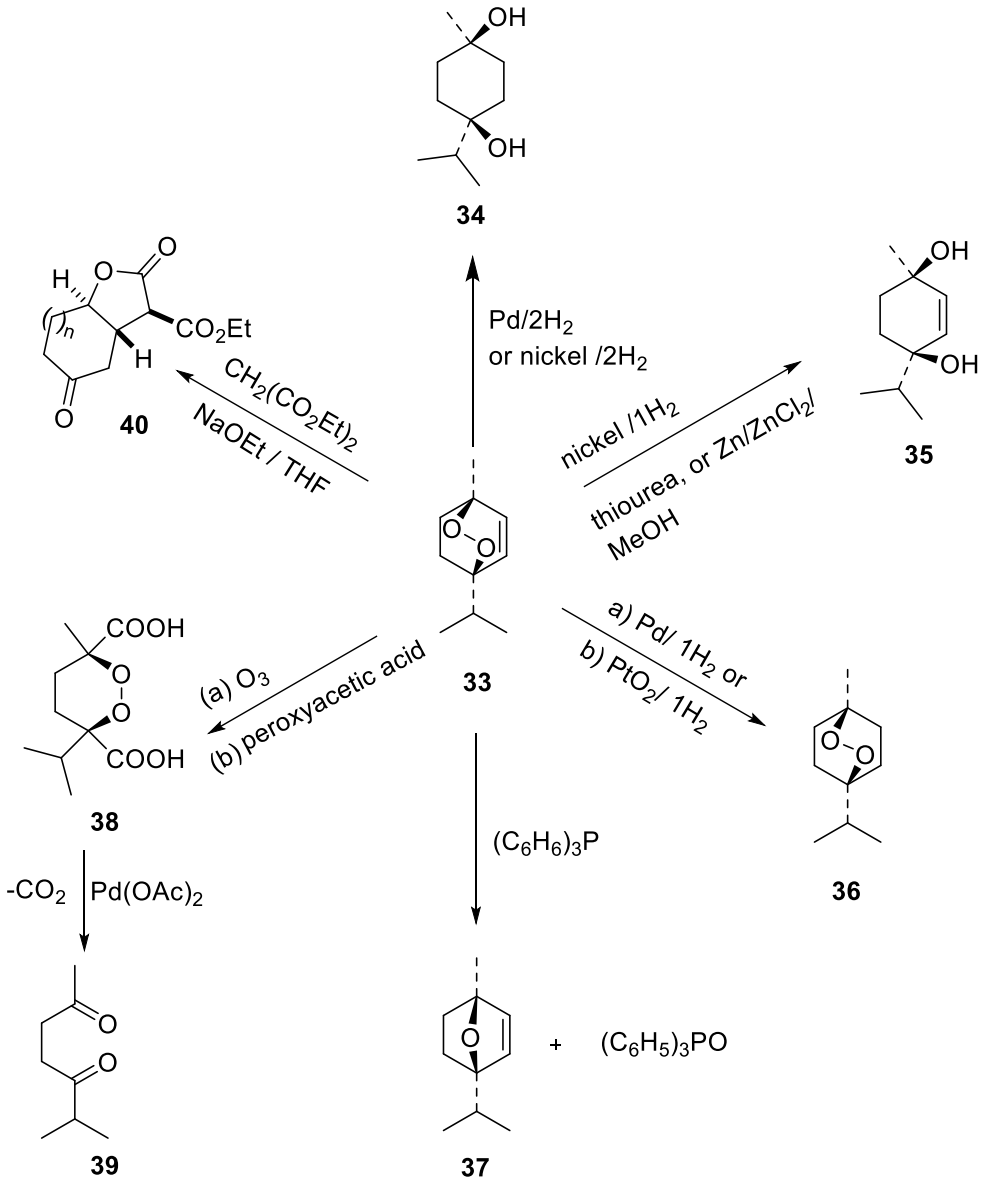
The mechanism of [4+2]-cycloaddition was assumed to follow the classical Diels Alder reaction (scheme 9). The first encounter between the excited singlet oxygen and the *cis*-diene **31** leads to exciplex formation. This mechanism was reversible and the product could undergo retro-[4+2] (scheme 9). This mechanism occurs as a suprafacial process (the bond forming interaction occurs on the same face of a π-system).[14]



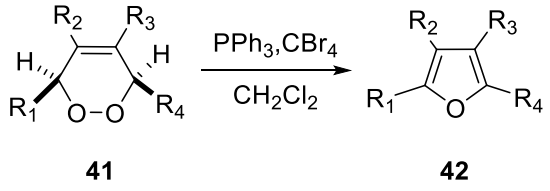
31 **32**

Scheme 9: [4 + 2] Mechanism

Endoperoxide are also known as 1,4-epiperoxides or dioxapropellanes. Endoperoxides are a six-member rings and are one of the most important products of the cycloaddition [4+2]-addition of singlet oxygen to the 1,3-dienes or arenes. These compounds have chemical and biological activity so, it can have reacted easily to give many important compounds natural and unnatural products.[15] Scheme 10 shows some general reaction of endoperoxide **33**. Exposing endoperoxide **33** to reduction conditions (palladium or nickel with two moles of hydrogen) affords 1,4-diols **34** whereas, exposing it to one mole of hydrogen with nickel will give the 1,4-diol with double bond intact **35**. When one mole of hydrogen with palladium is used chemoselectice reduction of the double bond is observed and the endoperoxide stays intact to give **36**. Treatment with ozone and peroxyacetic acid will furnish a peroxidic dicarboxylic acid **38** which decomposes in the presence of palladium acetate to 1,1-dimethylacetonyl acetone **39**.[16] Furthermore, addition of ethyl or methyl malonate in presence of sodium alkoxide to endoperoxide will afford bicyclic butyrolactone **40**, *via* a initial Korn Blum DeLaMare rearrangement by using cyclohepta or cycloocta dienes.[17] In addition, Kimber and co-worker reported in 2018 that dehydration of endoperoxide **41** can be undertaken by applying Appel reaction conditions to afford the furan **42** (scheme 11).[18- 19]



Scheme 10: Reactions of endoperoxides



Scheme 11: Dehydration of endoperoxide

Endoperoxides are formed in various organisms from plants to humans and bacteria. For example, artemisinin **43** is a unique sesquiterpene lactone with an unusual endoperoxide structure extracted from the Chinese medicinal plant *Artemisia annua*, and is used as an effective anti-malarial drug, [20] in addition steperoxide A **44** was recently extracted from higher fungi (mushroom)[21] and reported in 2010 by Liu and co-worker (figure 4).

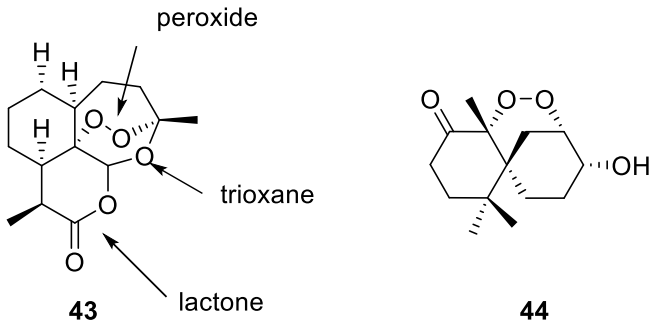


Figure 4: Natural endoperoxide.

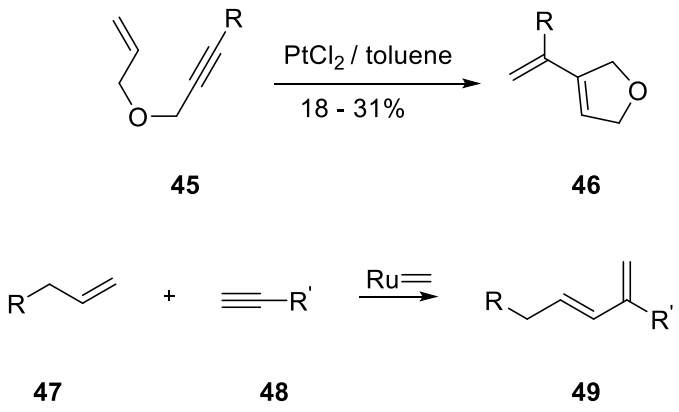
However, the synthesis of suitably substituted endoperoxides is predicated on access to the 1,3-diene precursors. Therefore, in the next section we will cover recent examples of 1,3-diene synthesise from the literature.

1.2. Review of the synthesis of 1,3-Dienes.

Reactions that create a new carbon bonds are an important and vital area of organic synthesis. Of interest within the synthesis of 1,3-dienes, as they are key precursors in a number staple chemical transformation, such as the Diels-Alder reaction and the addition of $^1O_2$ to give endoperoxides. There are a numerous of methods for the synthesis of 1,3-dienes and all could not possibly be covered in full here, and we direct the reader some excellent reviews;[22] however, the next section will catalogue some of the recent advances in their synthesis.

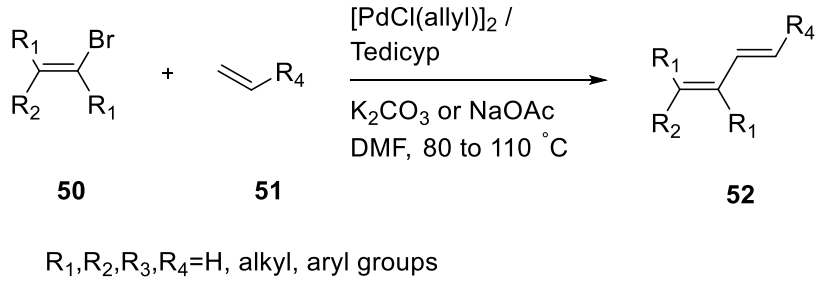
In 1985 Katz and co-worker[23] reported a conjugated diene can be simply prepared by enyne metathesis by bond reorganization[24] of alkene and an alkyne to form 1,3-dienes, and this could be

accomplished in both intra- and intermolecularly (for cycloisomerization can provide five-membered dienes)[25] in presence of metal carbene catalyst (scheme 12).[26]



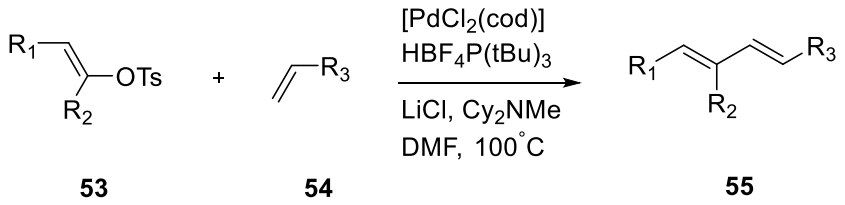
Scheme 12: Enyne metathesis

Conjugated 1,3-dienes can be prepared by cross-coupling reactions. For example, a Heck reaction was used to form range of 1,3-dienes in 2008 by Santelli and co-workers[27] by vinylation of vinyl bromides **50** using [Pd(η^3-C_3H_5) Cl]$_2$ / *cis*,*cis*,*cis*-1,2,3,4-tetrakis [(diphenylphosphino) methyl] cyclopentane (Tedicyp) as the catalyst with a base in DMF (scheme 13).



Scheme 13: Vinylation of vinyl bromides.

In 2006, a Heck reaction was used to prepare 1,3-dienes **55** by cross coupling of nonactive vinyl tosylates or phosphate **53** with an alkene carrying electron-withdrawing groups (electron-deficient alkenes) **54** in the presence of palladium complex [$PdCl_2$(cod)] (scheme 14).[28]

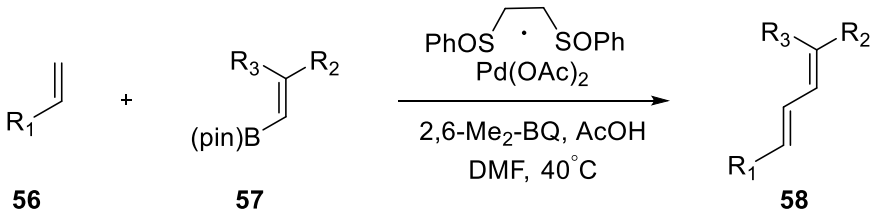


53 **54** **55**

R_1,R_2= H,alkyl : R_3= withdrawing group

Scheme 14: Heck coupling with a nonactivated vinyl tosylate

In 2013, White and co-workers[29] used oxidative Heck reaction (using Pd^{II} instead of Pd^0 and boronic acids or boronic esters instead of halides) for formation of complex 1,3-dienes and polyenes **58** in good yields and excellent selectivity from nonactive terminal olefins **56** with vinyl boronic esters or acids **57** in the presence of Pd^{II}/sulfoxide as a catalyst in DMF and 2,6-Me_2-BQ (scheme 15).



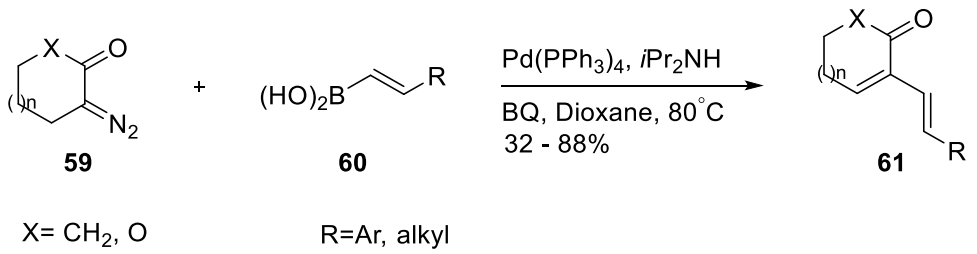
56 **57** **58**

R_1=CH(OMe)-R, CH(NHBoc)-R, CH_2OCOR, COR

R_2= alkyl, R_3=H, Me

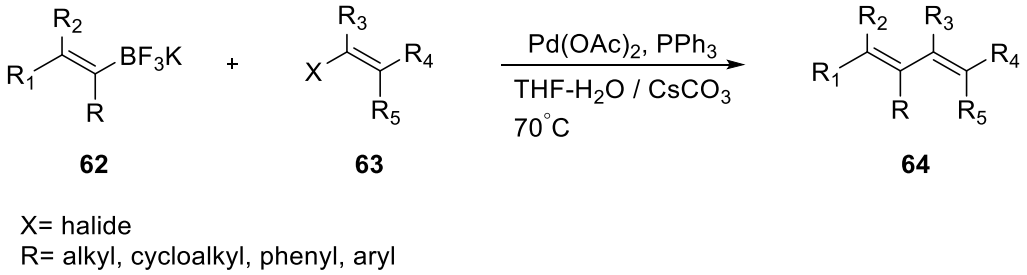
Scheme 15: oxidative Heck reaction to 1,3-dienes

In 2014 Wang and co-workers[30] reported an oxidative cross-coupling palladium-catalyzed of vinyl boronic acids **60** and cyclic α-diazo carbonyl compounds **59** in presence of a base and benzoquinone to furnish a conjugated carbonyl 1,3-dienes such as **61** in poor to good isolated yields (scheme 16).



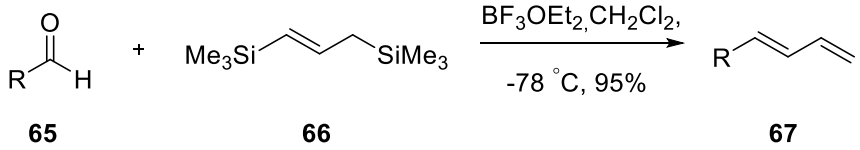
Scheme 16: Oxidative cross-coupling of vinyl boronic acids

In 2005 Molander and co-workers[31] reported a stereoselective synthesis of conjugated 1,3-dienes *via* a Suzuki-Miyaura Cross-Coupling of potassium alkenyl trifluoroborates **62** with alkenyl bromides **63** in presence of palladium catalyst (scheme 17).



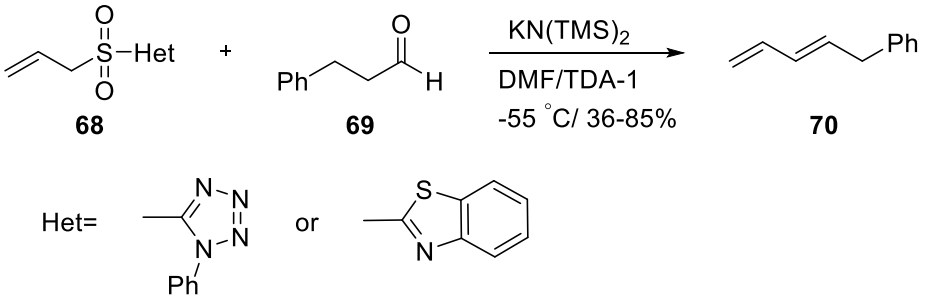
Scheme 17: Synthesis of 1,3-dienes via a Suzuki-Miyaura reaction.

In addition, conjugated 1,3-dienes can be prepared by olefination aldehydes. In 2011 Somfai and co-workers prepared 1,3-dienes from base free addition of 1,3-bis(silyl) propenes to aldehydes in presence of a Lewis Acid as a promoting agent in poor to excellent yield (scheme 18).[32]



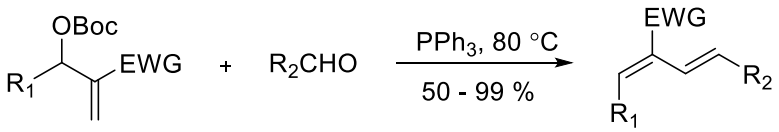
Scheme 18: Olefination of aldehydes to 1,3-dienes

In 2012, Pospisil and co-workers developed a modification of Julia–Kocienski olefination reaction by using cation-specific chelating agents to create a new double bond from the reaction of phenyl sulfones with aldehydes (scheme 19).[33]



Scheme 19: Modification of Julia–Kocienski olefination reaction

Also, He and co-workers in 2010 reported a base free salt Wittig olefination between allylic carbonate and aldehydes in presence of triphenyl or butyl phosphine (scheme 20).[34]



R_1, R_2 = alkyl, aryl, hetro-aryl
EWG = CO_2Et, COMe
Boc = tert-butoxy carbonyl

Scheme 20: Base free salt Wittig olefination

1.3. Synthesis of natural product compounds

1.3.1 Moracin M

1.3.1.1. Background

Moracin M is a benzofuran isolated from the root bark of *Morus alba* also known as white mulberry. It is a fast-growing, small to medium-sized mulberry tree which grows to 10–20 m tall, in the north of China. The root bark of the plant was used widely in traditional Chinese medicine as *anti*-asthmatic and *anti*-tussive.[35]

Moracin M is one of 26 benzofuran compounds (moracin A-Z) extracted from Moraceae family plants. Kyeong Lee[36] in 2015 his review illustrated the structure of the moracins (A – Z) and their structural relationships. In the center of the cycle the structure of 2-phenyl benzofuran compound as the basic scaffold of moracins compounds is shown (figure 5). Also, the figure shows there are four general structure starting from moracin A to moracin D through to moracin M to moracin P.

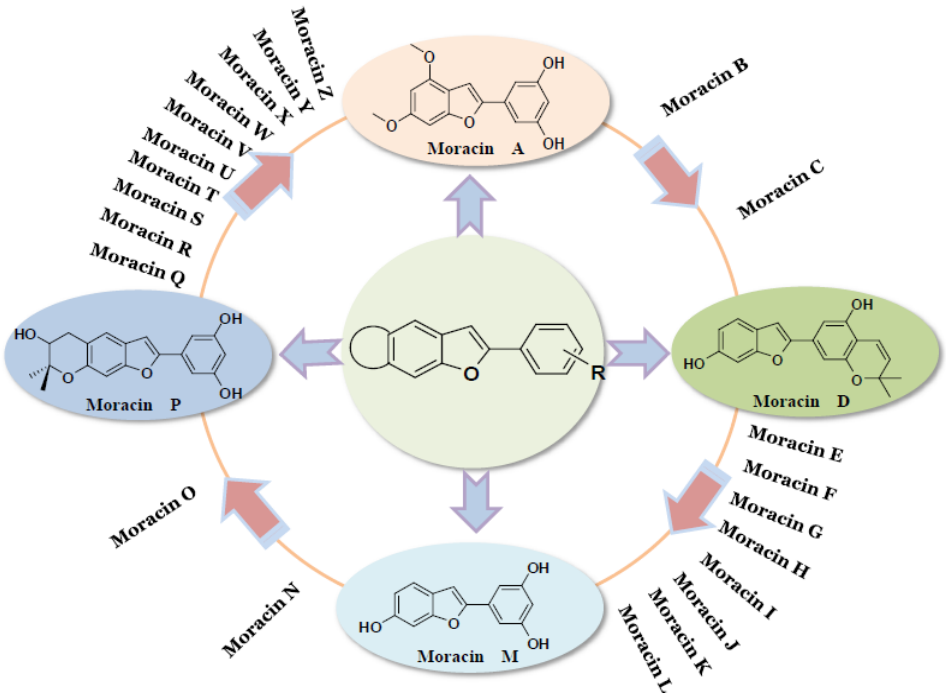
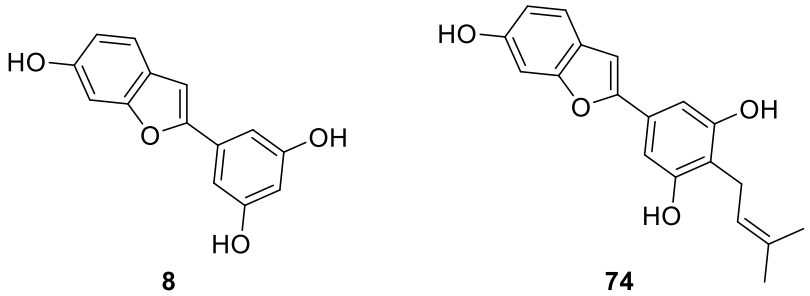


Figure 5: Representation of all the moracin[36]

1.3.1.2. Isolation of Moracin M

Phytoalexins are a large group of chemical compounds including several classes such as terpenoids, glycosteroids and alkaloids. The plants use phytoalexins as a medicine against infection in case of microbial infection. An extraction of infected mulberry (*Morus alba linne*) led to the identification and isolation of moracin A as a first phytoalexin found in the family of Moraceae.[37] There are several reports on the extraction of moracin compounds (A- Z) using different solvents (methanol, acetone, ethanol) to extract different infected or uninfected tissue from diverse mulberry plants.

For example, to extract moracin M, 1 kg of dried powder of root bark of *Morus alba* plant was extracted with 95% ethanol for 48 hours, followed by removal of the solvent under reduced pressure. The residue was then suspended in water and extracted with petroleum ether first then further extracted again with ethyl acetate. Then ethyl acetate layer was dried, the solvent removed under reduced pressure, and finally column chromatography was used to purify the crude, to get just 25 mg of moracin M (**8)** and 10 mg of moracin C (**74) (**figure 6).[38]



8 **74**

moracin M **moracin C**

Figure 6: Chemical structure of moracin M and moracin C

1.3.1.3. Biological activity of Moracin M

Natural product compounds have been used as traditional medicine for the treatment of various diseases and illnesses. Diseases and illnesses can classify more precisely than before, so study of

the biological activity of compounds is important to find a relation between the structure and the biological activity of natural product compounds.

1. Anti-microbial activity

Moracin M has weak activity against nine kinds of bacteria in a study of 2005, where three moracin compounds C, M, and P were examined (table 2).[39]

Table 2: Antimicrobial activity of the compounds 74, 8 and 75 (MIC, µg/ml) *

Comp.	MSSA FDA209	MSSA smith	MRSA K3	MRSA ST28	M. luteus	B. subtilis	E. Coli	K. pneumoniae	P. aeruginosa
74 (C)	6.25	12.5	12.5	12.5	12.5	3.13	>100	25	>100
8 (M)	12.5	25	25	25	25	100	>100	100	>100
75 (P)	50	100	100	100	100	100	>100	100	>100
AMOX	0.10	0.10	25	50	0.025	0.10	3.13	100	N100
VAN	0.39	1.56	1.56	0.78	1.56	0.39	N100	N100	N100

* MRSA is Methicillin resistant *St. aureus*, MSSA is methicillin sensitive *St. aureus* *Micrococcus* (M.), *Bacillus* (B.), *Escherichia* (E.), *Klebsiella* (K.), *Pseudomonas* (P.). Positive controls used were amoxicillin (AMOX) and vancomycin (VAN).

Table 2 shows three moracins compounds (C, M, P) with two antibiotics as a reference against nine kinds of bacteria. The numbers in the table represent the minimum inhibitory concentration (MIC) so, the lowest number is the better inhibiter against bacteria whereas, the highest number is the worst inhibiter. According to this information can easily see that the best inhibiter is moracin C and poorest inhibitor is moracin P; moracin M demonstrated a weak activity with comparisons of other antibiotics. If we compare the structures of these three compounds we can presume that the isopentenyl group in para position of the 2-aryl in moracin C is the significance part for antimicrobial activity.

Later in 2009 there was a study testing six moracin compunds (Q, T, R, U, C and M,) (figure 7) against the antibiotic gentamycin as a reference**.** This study used firstly MIC (minimum inhibition concentration) and secondly MMC (minimum microbial concentration) against three group of microorganisms gram-negative bacteria, gram-positive bacteria and fungi.[40]

In this study, the best inhibition is moracin T showing MIC (5 µg/ml) against *Escherichia coli, Shigella dysenteriae*, *Pseudomonas aeruginosa*, from gram-negative bacteria *and Salmonella typhi, Bacillus cereus* from gram-positive bacteria. If we compare the result of moracin T with the reference antibiotic gentamycin we found that moracin T gave MIC (139 µg/ml) and (39 µg/ml) against: *Citrobacter freundii* and *Klebsiella pneumoniae* respectively while, gentamycin gave MIC (5 and 10 µg/ml) respectively. Furthermore, moracin T performed better than gentamycin against *Candida albicans* and *Microsporum audouinii* fungi. Moracin M showed weak activity against macrobacteria and fungi **(Table 3).**

Table 3: Antimicrobial activity of various moracins in minimal inhibition concentrations (MIC) (µg/ml). *

Comp.	Gram-negative bacteria				Gram- positive bacteria				Fungi		
	Cf	*Ec*	*Sd*	*Pa*	*Kp*	*St*	*Bc*	*Sa*	*Sf*	*Ca*	*Ma*
74 (C)	156	39	5	10	312	10	78	78	39	78	78
8 (M)	312	78	78	156	312	78	-	-	78	-	78
67 (Q)	-	156	-	625	156	-	-	156	-	156	-
77 (R)	-	78	78	10	312	156	156	312	156	-	312
78 (T)	156	5	5	5	39	5	5	10	10	10	39
79 (U)	312	10	78	625	156	39	10	156	20	312	78
Gentamycin	5	5	5	5	10	5	5	10	10	nt	nt

*(-): MIC > (625 µg/ml); (nt) not tested; a Microorganisms: Cf: *Citrobacter freundii*, Ec: *Escherichia coli*, Sd: *Shigella dysenteriae*; Pa: *Pseudomonas aeruginosa*, Kp: *Klebsiella pneumoniae*, St*: Salmonella typhi*, Bc*: Bacillus cereus*, Sa: *Staphylococcus aureus*, Sf: *Streptococcus faecalis*, Ca: *Candida albicans*, Ma: *Microsporum audouinii*.

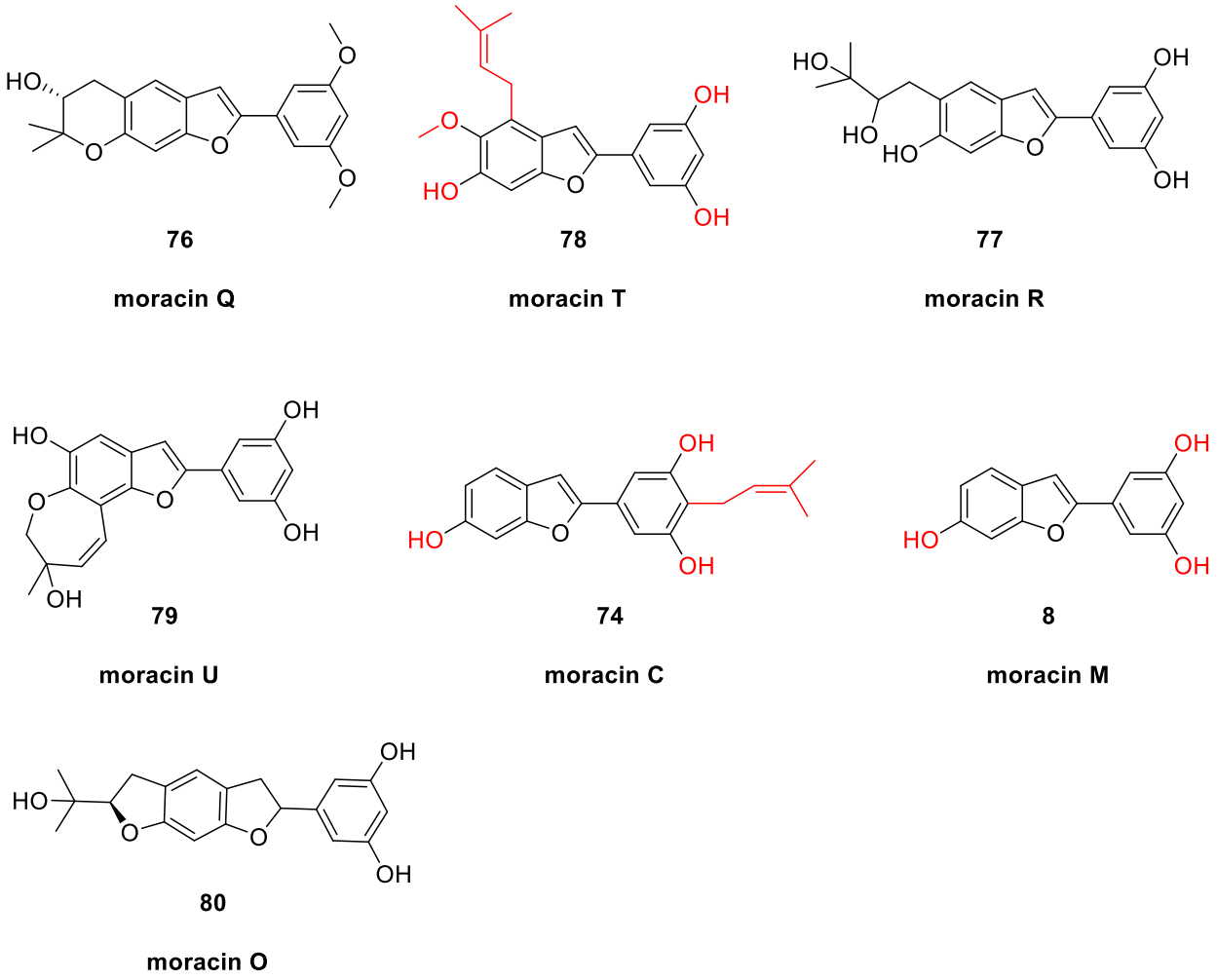


Figure 7: Structure of Moracin Q, T, R, U, C, M, S

To conclude, the relation of activity of moracin T with his structure, moracin T has an additional methoxy groups and isopentenyl group attached to benzofuran unit so, existence of ether and isopentenyl groups in addition of three hydroxyl groups could be make the moracins compounds more active against macrobacteria and fungi. Figure 7 shows three compounds of moracins (M, C, T) their functional groups colored red to illustrate the increase of activity from weak moracin M to medium moracin C to strong moracin T with the relation of their structure against microorganisms.

2. Anticancer Activity

Hypoxia is a low level of oxygen in tissues of human bodies, and this phenomenon can promote tumor progression. There is a factor called hypoxia inducible factor HIF-1, wich is a transcription factor that will respond to a decrease in available oxygen in the cellular environment. In normoxia there are two subunit HIF-1α and HIF-1β whereas under hypoxia condition these two subunits dimerize.[41]

A study in 2009 tested a number of moracins compounds and their *in vitro* inhibition activity against HIF-1 transcriptional activity. Moracin O, P, Q show a potent inhibitor effect as a hypoxia response element HRE (hypoxia response elements) without cytotoxicity, whereas moracin M showed no activity (table 4) **.**[42]

Table 4: IC_{50} Values (μM) of moracins O, P, Q, M on the Inhibition of HIF-1 Activity, VEGF[a] Secretion, and Cell Viability

Compound	HIF-1 IC_{50} nM	VEGF IC_{50} µM	Cell viability
moracin O **(**80**)**	0.14b ± 0.02	7.22 ± 2.13	>30 µM
moracin P **(**75**)**	0.65 ± 0.13	10.6 ± 2.46	>30 µM
moracin Q **(**76**)**	5.88 ± 0.54	9.28 ± 1.34	>30 µM
moracin M **(**8**)**	na[b]	na	>30 µM

a: vascular endothelial growth factor is a part of system to restore the oxygen. b: na = not active.

The three active compounds moracin (O, P and Q) have cyclic oxygen ring fused to benzofuran group with two methyl group while moracin M does not.

3. Anti-diabetes

Hypoglycemic effects (low blood sugar) occurs when the blood sugar (glucose) fall below the normal range level. A study in 2009 extracted moracin M from a natural source (root bark of *Morus alba L.*) and tested in hypoglycemic effects on alloxan-diabetic mice. This study used gliclazide as a reference. This is used to increase the amount of the insulin in the body. Table 5 shows that

moracin M in a dose of 100 mg/kg can make the fasting blood glucose level have a decreasing tendency.[43]

Table 5: Effect of moracin M on plasma glucose of alloxan-diabetic mice.

Comp.	Dose (mg/kg)	Number of mice	Fasting blood glucose levels (mmol/L)
Moracin M (8)	50	10	20.08±5.86
	100	10	18.52±6.61
Gliclazide	50	10	15.63±5.90

4. Phosphodiesterase inhibitors

Phosphodiesterase (PDEs) is an enzyme that breaks a phosphodiester bond that makes up the backbone of the strands of nucleic acid. Inhibitors of PDEs can prolong or enhance the effects of physiological processes mediated by cyclic nucleotides 3,5-adenine monophosphate cAMP or cyclic guanosine monophosphate cGMP by inhibition of their degradation by PDEs. The phosphodiesterase-4 (PDE4) enzymes hydrolyzing cAMP to 5-AMP. It performs as key regulators in many biological processes such as cell division, smooth muscle contractility and platelet aggregation. Phosphodiesterase-4 (PDE4) has been known to be a promising mark for the treatment of asthma.[44- 45]

In 2012 a study tested moracin M (**8)** and moracin C (**74)** against four kinds of PDEs using roflumilast as a reference which is used as a drug that acts as a selective, long-acting inhibitor of the enzyme phosphodiesterase (table 6).[38]

Table 6: Phosphodiesterase inhibitor activity of 74 and 8.

Comp.	IC_{50} in µM			
	PDE4D2	PDE4B2	PDE5A1	PDE9A2
Moracin C (74)	26.0	18.1	>50	>100
Moracin M (8)	2.9	4.5	>40	>100
roflumilast	0.46	0.67		

Table 6 shows *in vitro* inhibition of moracin M are 2.9, 4.5, >40, >100 against PDE4D2, PDE4B2, PDE5A1, PDE9A2, respectively. Comparing these results with the reference roflumilast leads to the conclusion that Moracin M has strong inhibition against PDE4D2 and PDE4B2 while, moracin C gives a moderate inhibition activity.

5. Anti-inflammatory activity

Anti-inflammatory agents have the ability to reduce or remove the swelling of inflammation. Inflammation is a biological response to something harmful or irritating to the body, so inflammation is a part of immunity system trying to heal the body. In general the inflammatory pathways consist of four steps starting with inducers for example tissue damage or infection then, sensors that discover the damage or infection then, mediators that induced by the sensors for example plasma proteases or iNOS production and finally, the target tissues that affected by inflammatory mediators.[46-47]

A study in 2010 tested *anti*-inflammatory activity of moracin M and C against the release of β-glucuronidase from rat PMNs induced by PAF. This study used ginkgolide B as a reference positive control. The result showed that both moracin M and C exhibit a strong activity against the target substance (table 7).[48]

Table 7: anti-inflammatory activity for moracin M and C[a]

Comp.	Inhibition ratios
Moracin C (74)	100%
Moracin M (8)	54%
Ginkgolide B	58%

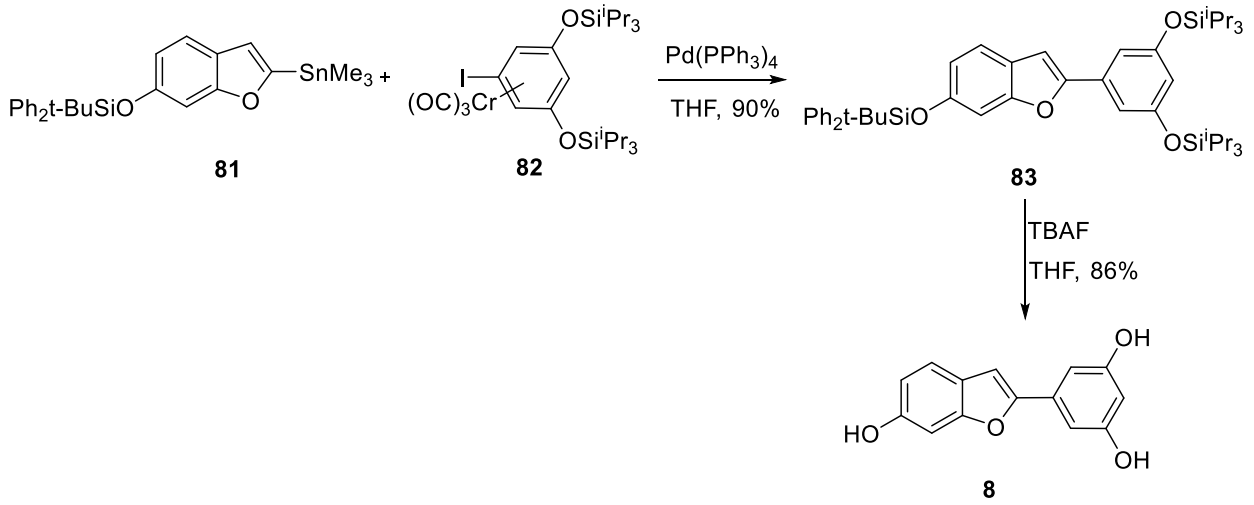
a: Compounds were active with inhibitory ratios more than 50% at a concentration of 10−5 M.

A recent study in 2018 tested the effect of moracin M (**8)** to inhibit the lipopolysaccharide (LPS) by treated nucleus pulposus cell (NPGs) in intervertebral disc. LPS is a large molecule consisting of lipid and poly polysaccharide and is found in the outer membrane of gram negative bacteria and this molecule responsible for inducing inflammation. The study found that moracin M (**8)** can significantly inhibit LPS-induced inflammation at different concentration.[49]

1.3.1.4. Previous Synthesis of Moracin M

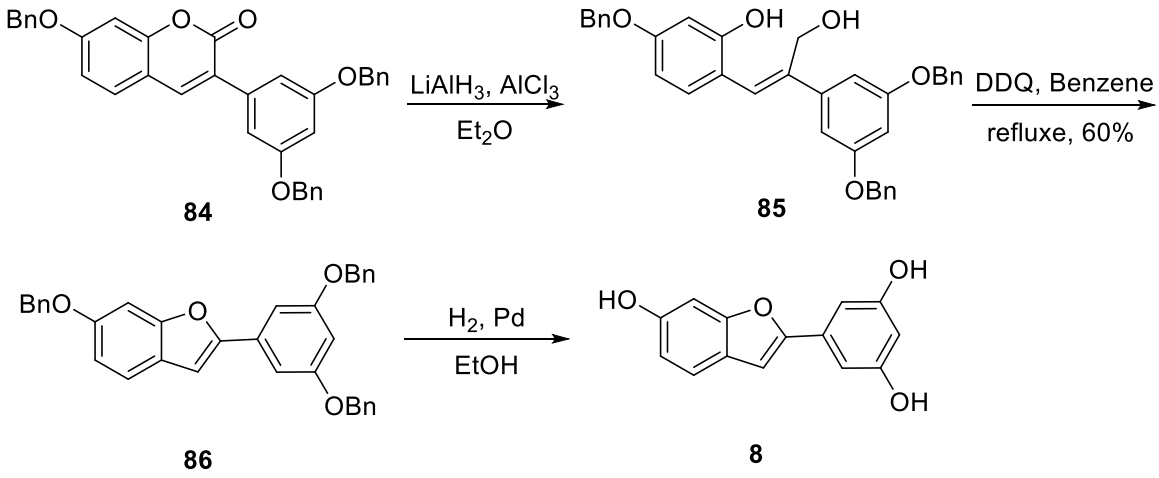
As we know the family of moracins compounds include 26 isolated compounds (A to Z). Moracin M (**8)** structure is regarded as a base for the synthesis of other family compounds, and therefore, there are several reported total synthesise of moracin M.

In 1987 moracin M (**8)** was synthesised as basic skeleton in overall 44%, so it could be readily modified to give another moracin compounds. The key step of this approach was a palladium catalyzed cross coupling reaction between **81** (prepared by 4 steps to form unstable oil used directly without purification) and **82** (prepared by 2 steps in 57%) to give the 2-phenylbenzofuran substituted compound **54** in a good yield. then moracin (M **8**) can be formed by deprotection of **83** with tetra butyl ammonium fluoride in THF (scheme 21).[36,50]



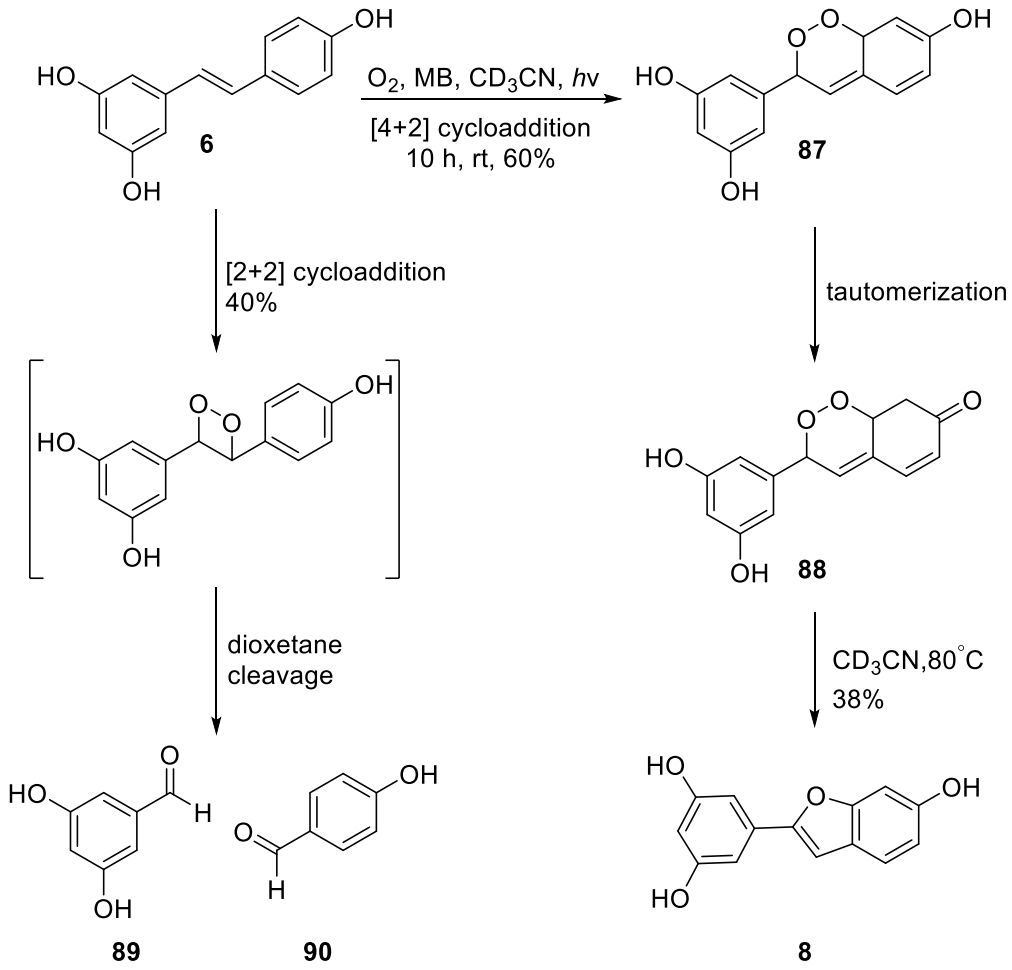
Scheme 21: Synthesis of moracin M (39) by palladium cross coupling reaction

In 2005 moracin M (**8)** was prepared by conversion of 3-phenylcoumarin **84** into 2-phenylbezofuran **86** through the diol compound **85** as a key reaction. The loss of the carbon unit was achieved by reducing the coumarin compound **84** by $LiAlH_4$ to **85** then oxidized it using DDQ to give **86**. The final step was the deprotection of the hydroxy groups to get moracin M (**8)** (scheme 22).[51]



Scheme 22: Synthesis of moracin M in 2005.

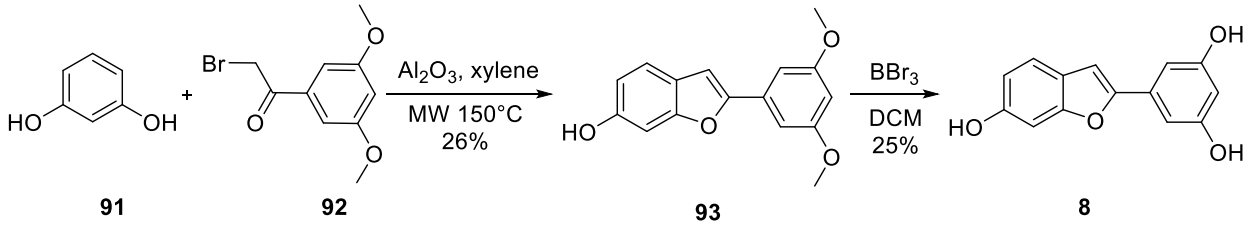
In 2011 moracin M (**8)** was prepared *via* singlet oxygen reaction. In this route *trans*-resveratrol **6** was used as starting material. The oxidation of resveratrol with $^1O_2$ gave the desired endoperoxide **87**, as well as significant amounts of the [2+2]-addition product that subsequently fragmented to give **89** and **90**. This is presumably due to the electron rich double-bond within **6**. The [4+2]-addition product **87** then tautomerize to the observed endoperoxide **88**. Finally dehydration of **88** accomplished by heating in CD_3CN at 80 ºC leading to the formation moracin M (**8)** overall yield 23% (scheme 23).[52]



Scheme 23: Synthesis of moracin M in 2011.

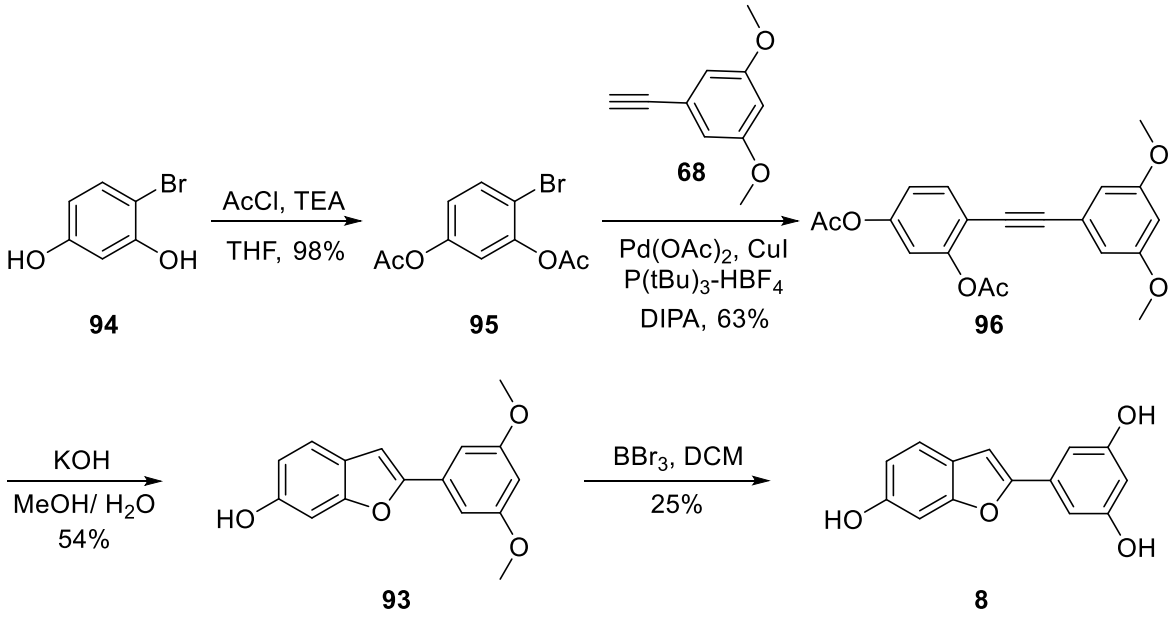
In 2012 moracin M (**8)** was prepared in 2-steps. Firstly, the regioselective reaction between phenol **91** and α-bromoketone **92** in presence of neutral alumina (Al_2O_3 + K_2CO_3) furnished the 2-

substituted benzofuran **93**. Deprotection of the ether groups by BBr_3 then gave moracin M (**8)** overall yield 7% (scheme 24).[53]



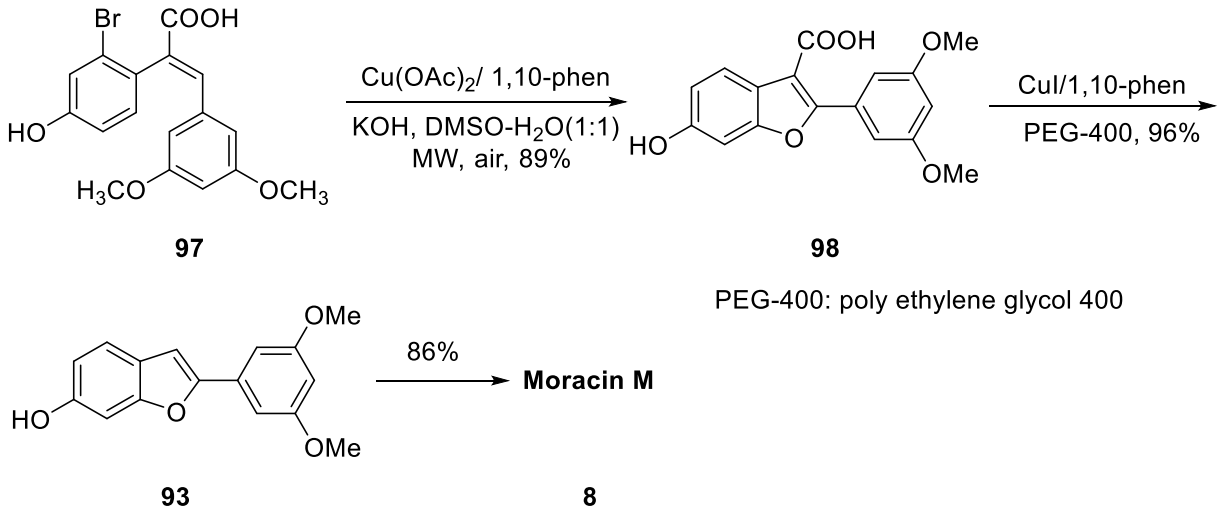
Scheme 24: Synthesis of moracin M (44) in 2012

In 2014 moracin M (**8)** was prepared in overall yield 9% by using a palladium catalyzed Sonogashira cross coupling reaction. The reaction started with acetylation of **94** to reduce the electron density of the halogen in **95** to accelerate the cross-coupling reaction with aryl acetylene **96**, giving **97** in 63%. The deacetylation of **97** under base condition led to the formation of the 2-arylbenzofuran **93**, and then demethylation of the resulting compound gave moracin M (**8)** in 25% (scheme 25).[54]



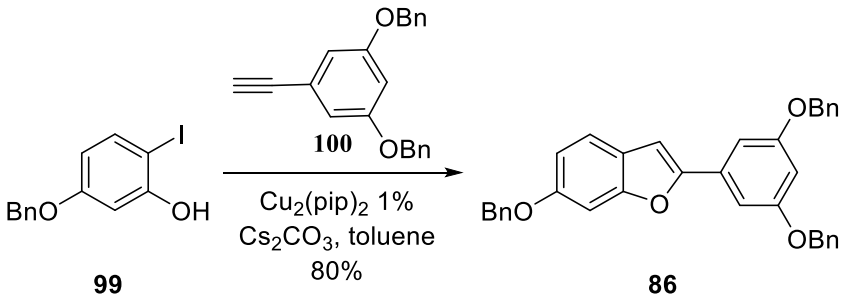
Scheme 25: Using Sonogashira palladium cross coupling in synthesis Moracin M

In 2015 moracin M **(8)** was prepared from 3-carbonyl-2-arylbenzofuran **98** which was prepared from the (*E*)-2-(2-bromophenyl)-3-phenylacrylic acid **97** by reaction with copper acetate catalyst. The decarboxylation of **98** afforded **93** which was demethylated using $AlCl_3$ to give moracin M **(8)** in overall yield 73% (scheme 26).[55]



Scheme 26: Moracin M synthesis from 3-substituted 2 phenylbenzofuran.

In 2016 Chen *et al.* prepared Moracin M **(8)** overall yield 37% by optimized a coupling/cyclization reaction between ortho-indophenols **99** (prepared in 50%) and terminal alkynes **100** with copper (I) as a catalyst to furnish the 2-arylbenzofurans **86** in 80% yield; **86** was subsequently deprotected in 93% to give moracin M **(8)** (scheme 27).[56]



Scheme 27: Synthesis of moracin M

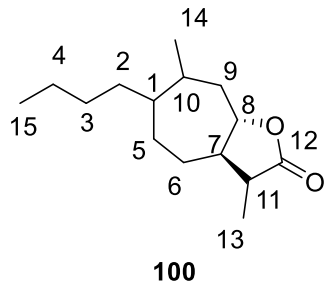
According to the overall yields of previous synthesis ways of moracin M, Yong Zou and co-workers was prepared moracin M in the better overall yields 73%, whereas in 2012 was prepared in 7%, other ways were located between these two percentage.

1.4.Synthesis of Xanthanolides

1.4.1. Introduction

Sesquiterpenoids are a class of terpenes that consist of three isoprene units and often have the molecular formula $C_{15}H_{24}$ and form a major collection of natural terpenoids, that cover thousands of compounds and with over 100 skeletal varieties. Large numbers of sesquiterpenoids exist in plants in their lactonised form. Sesquiterpenoid lactones are mainly specific to the Asteraceae family, but can exist occasionally in other plant families. They have been labeled as the energetic workings of several medicinal plants used in traditional medicine and are known to express a wide variety of biological and pharmacological activities, such as *anti*-inflammatory, cytotoxic, *anti*-proliferative and *anti*-microbial activities, and special effects on the central nervous and cardiovascular systems. Furthermore, some of them have allergenic potency[57,58,59].

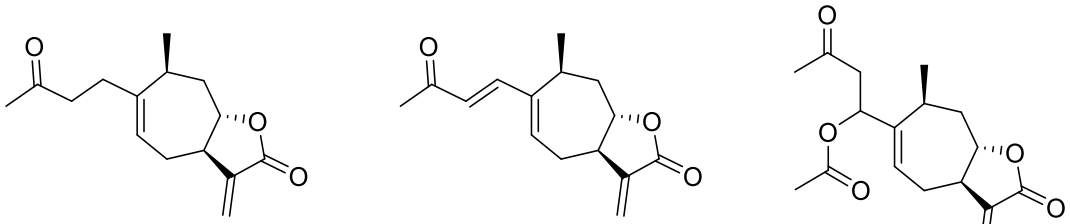
The xanthanolides represent a large class (120+ members) of sesquiterpenoid natural product that display a diverse range of biological profiles and they commonly contain *cis*- or *trans*-fused butyrolactones show in figure 8. Xanthanolides are bicyclic sesquiterpene lactones, in which a five-membered ɤ-butyrolactone ring is fused to a seven membered carbocycle. There are around 101 natural xanthanolides compounds and most of them follow the monomeric form, but dimeric forms do exist.[60] Their structures vary in term of the number and positions of their oxygen functions and the stereochemistry at C-7 and C-8. Large numbers of them have a side chain for four carbons long at C-1, that can be saturated or unsaturated at positions C-2 and C-3. This chain is often substituted with one or two functional groups, mostly keto and/or hydroxyl groups, as well as an acetyl moiety.[60]



100

Figure 8: Xanthanolide skeleton.

Xanthanolides occur in only a few species of the Asteraceae family. In the middle of the last century the first isolation of a xanthanolides resulted in the isolation of xanthatin and xanthainin from the aerial part of *Xanthium pennsylvanicum*[61]. Later, these compounds have successively been isolated by several research groups from diverse plants, e.g. xanthinin from *Xanthium orientale* and *Xanthium italicum* and xanthatin from *Pulicaria crispa*, *Xanthium italicum*, *Xanthium orientale*, *Xanthium spinosum* and *Xanthium strumarium.*[62] The richest source of xanthanolides is Xanthium strumarium; many groups have considered this plant and isolated 26 xanthanolides thus far (figure 9).[60]



101 xanthinosin

12 xanthatin

102 xanthinin

Figure 9: Xanthanolides.

1.4.2.Biological activity of xanthanolides

The structure–activity correlation studies of xanthanolides have shown that the activities are referred chemically by α, β-unsaturated carbonyl structures, for example an α-methylene-ɤ-lactone, an α, β -unsaturated cyclopentenone or a conjugated ester. These kinds of compounds react with nucleophiles, particularly cysteine sulfhydryl groups, by a Michael-addition. The thiol group, for instance cysteine residues in proteins, seem to be the primary targets of sesquiterpene lactones, inhibiting a diversity of cellular functions, which directs the cells into apoptosis. Moreover, DNA has also been shown to be a target molecule of sesquiterpene lactones; therefore, DNA alkylation is a potential molecular basis of cytotoxicity for these compounds.[63] The variances in activity between lactones compounds maybe due to the different numbers of alkylating structural elements. On the other hand, other factors, such as lipophilicity, the molecular geometry

and the chemical environment or the target sulfhydryl, may also effect the activity of xanthanolides.[64]-[65]

1. Anti-inflammatory activity

In 2008, Yoon isolated xanthatin, xanthinosin, obtained from the ethyl acetate extract of *X. strumarium* as inhibitors of NO production in LPS-activated microglial BV-2 cells (this is a type of cell that are the resident macrophages of the brain and spinal cord, and thus act as the first and main form of active immune defense in the central nervous system). The a-methylene–α-lactone ring was recognized as the crucial moiety for their biological activity.

They impact their activity through the inhibition of I-kB-α degradation, NF-jB activation, and subsequent suppression of iNOS and COX-2 expression. These results imply that *X. strumarium* may be useful for the treatment of neuro-inflammatory diseases through reduce regulation of such inflammatory enzymes as iNOS and COX-2.[66]

2. Anti –Cancer activity

Because many herbal medicines are sources of potential drugs for cancer therapy and therefore significant research has been done to find the active substituents. These researches showed that xanthatin (figure 9) had significant inhibitory effects on tumor proliferation and could promote apoptosis in B16-F10 cells (cells used for tumor formation) both *in vitro* and *in vivo* (figure 10). This study used Taxol, the well-known anti-cancer agent, as the positive control Taxol has been commonly known as an antitumor component from the extract of old Chinese medicine, which has great medicinal significance. The stereochemistry of chiral centers for xanthatin 12 was confirmed by using NOESY experiment and ^{1}H NMR spectroscopy data (figure 9).[67]

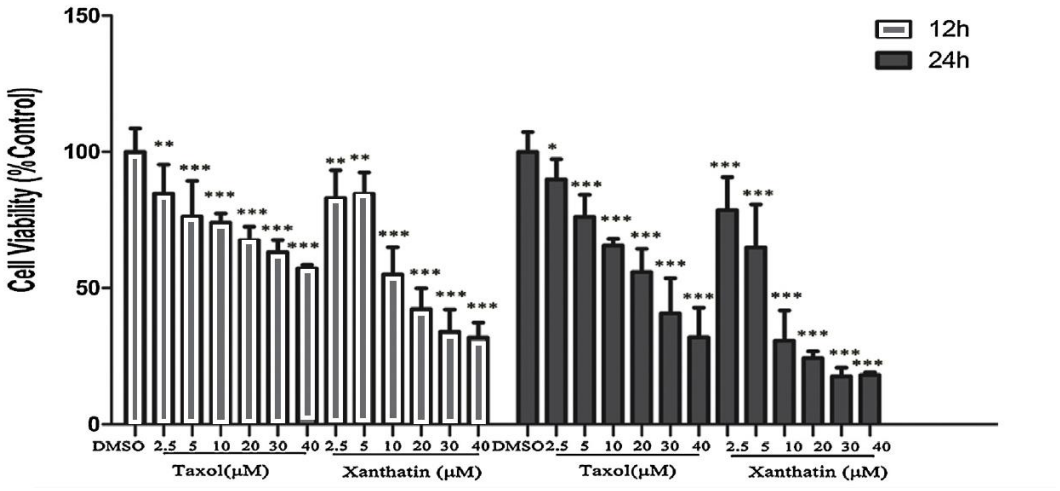


Figure 10. **Cytotoxic effects of xanthatin on melanoma B16-F10 cell proliferation. Data are presented in three independent experiments. Significance: *p < 0.05, **p < 0.01, ***p < 0.001 vs. the negative control**

Figure 10 shows the effect of xanthatin in deferent concentration to reduce the cell viability of melanoma cell after 12 and 24 hours by using Taxol as a reference. The results show that xanthatin gives a more potent activity than Taxol in all concentrations. For example, at (40 μM) of xanthatin the cell viability was 32% after 12 hours and 18% after 24 hours whereas, Taxol shows 35% and 17%, respectively.

3. Antimicrobial activity

Most xanthanolid compounds show significant activity against the Gram-positive Bacterium *Staphylococcus aureus*, *Candida albicans*, *Candida glabrata* and *Aspergillus fumigatus*, antifungal activity. It has also shown *anti*-malarial activity against the chloroquine-resistant *Plasmodium falciparum* strain K1, *Trypanosoma brucei rhodesiense* and *Leishmania donovani*.[68, 60]

4. Antitumor activity

The chloroform extracts of the leaves of *Xanthium italicum* underwent bioassay-guided fractionation and the isolated xanthanolides compounds were then assessed for their

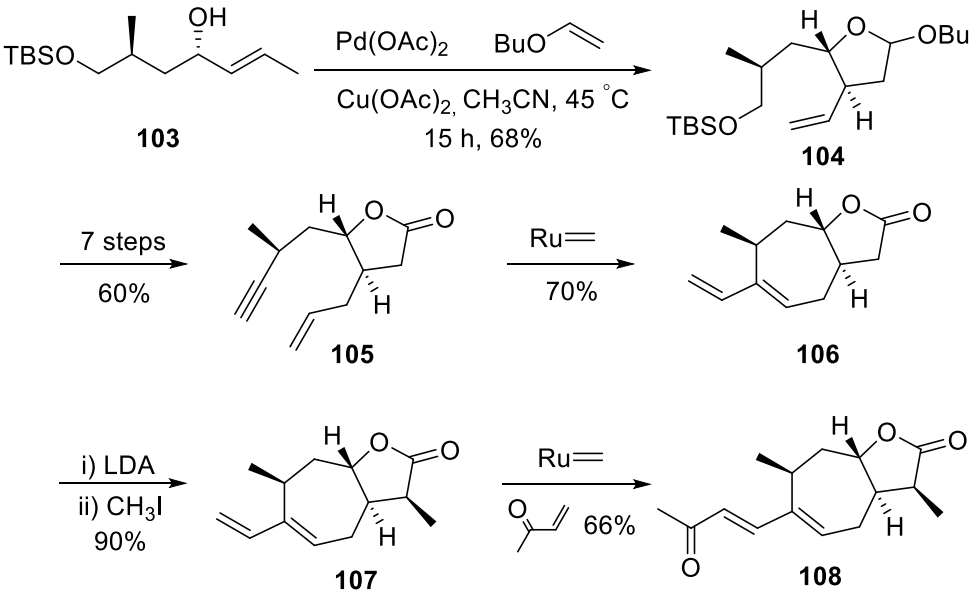
antiproliferative activity against human cervix adenocarcinoma (HeLa), skin carcinoma (A431) and breast adenocarcinoma (MCF7) cells. All of them displayed tumour cell growth-inhibitory activities. These result showed that the most active compound was xanthatin.[69]

1.4.3 Previous Synthesis of Xanthanolides

The amount of research activity concerning α-substituted-γ-butyrolactones and xanthanolides has increased dramatically in recent years. A review of xanthanolides synthesis show that the earliest total synthesis of xanthanolides was by Evans and Morken in 2005[70] when they prepared 11, 13-dihydroxanthatin whereas, sundiversifolide first prepared by Shishido and co-worker 2007.[71] After that Shindo and co-worker in 2010[72] and 2013[73] reported formal synthesis converging with a key intermediate of Shindo and co-workers in 2012.[74] This is a summary of recent routes followed.

1. Asymmetric Synthesis of (-)-Dihydroxanthatin by the Stereoselective Oshima-Utimoto Reaction.

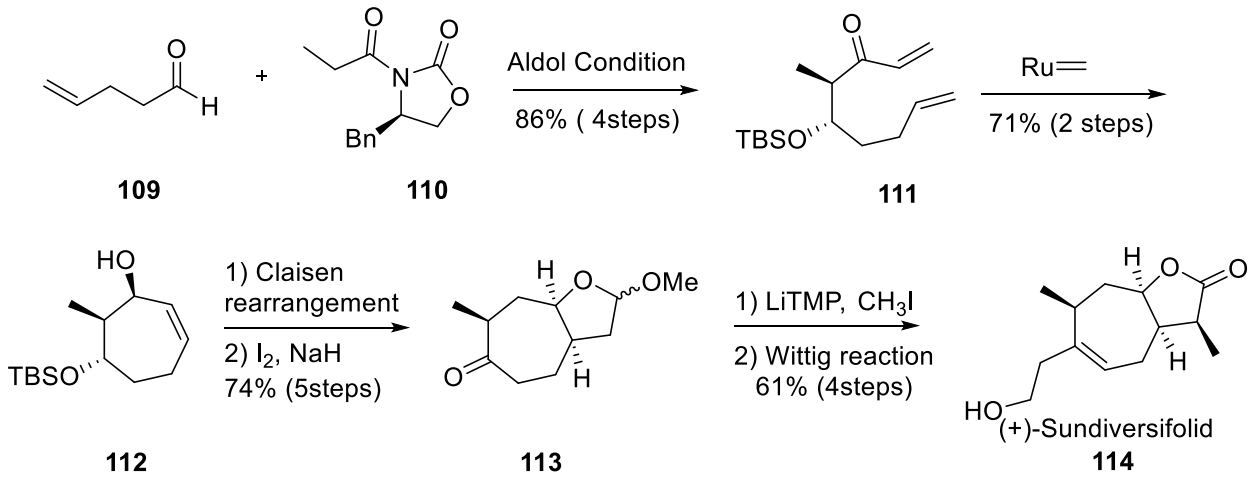
In 2005 Evans and Morken[70] used the catalytic stereoselective Oshima-Utimoto reaction to construct the five-membered oxacycles from simple starting materials and this was employed for the preparation of the lactone group in the asymmetric synthesis of (-)-11α,13-dihydroxanthatin. The allylic alcohol **103** was converted to tetrahydrofuran **104** by the catalytic Oshima-Utimoto reaction (scheme 28). Compound **105** was produced after seven steps includes homologation by a hydroboration/oxidation/olefination sequence. Molecular modeling (MM2) recommended that the favorite alkylation product might be better accessed from a substrate with a minimal dihedral angle between the C-4 and C-5 substituents on the tetrahydrofuran, and consequently, the alkylation was postponed until after ring closing metathesis **107**. Finally, cross metathesis with methyl vinyl ketone completed the synthesis by affording **108** in 66% yield. In this route **108** was prepared by 19 steps in 1% overall yield.



Scheme 28: Synthesis of Xanthanolides.

2. Total Synthesis of (+)-Sundiversifolide.[71]

In 2007 Shindo and his group reported the first enantioselective total synthesis of (+)-sundiversifolide starting with 4-pental **109** to prepare compound **111** by reacting compound **110** under Aldol conditions (scheme 29). The diene **111** was used to constructed **112** through a ring-closing metathesis reaction (RCM). The bicyclic ketone **113** afforded, via Claisen-type [3,3]-sigmatropic rearrangement, **112** followed by an iodo-lactonization reaction. Finally, (+)-sundiversifolide **114** was produced by Wittig-type olefination reduction sequence reaction of ketone **113**. In this route the target **114** was prepared by 15 steps in 41% in overall yield.

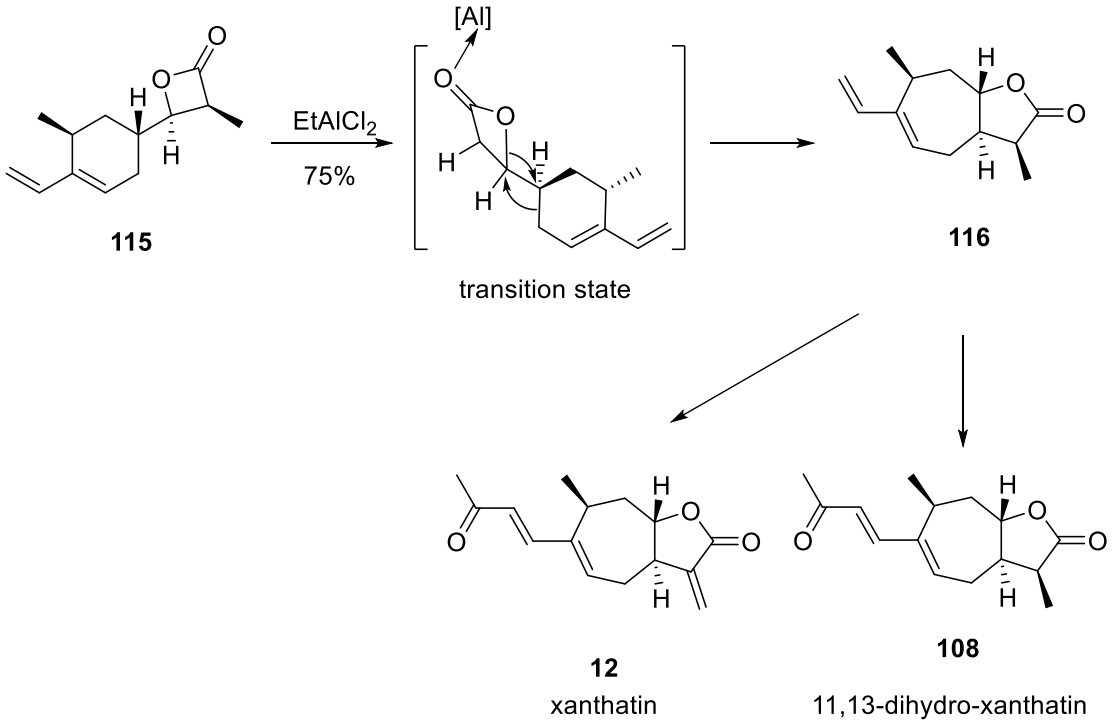


109 **110** **111** **112** **113** **114**

Scheme 29: Synthesis of (+)-Sundiversifolid.

3. By Wagner–Meerwein-type dyotropic rearrangement of β-lactones.[74]

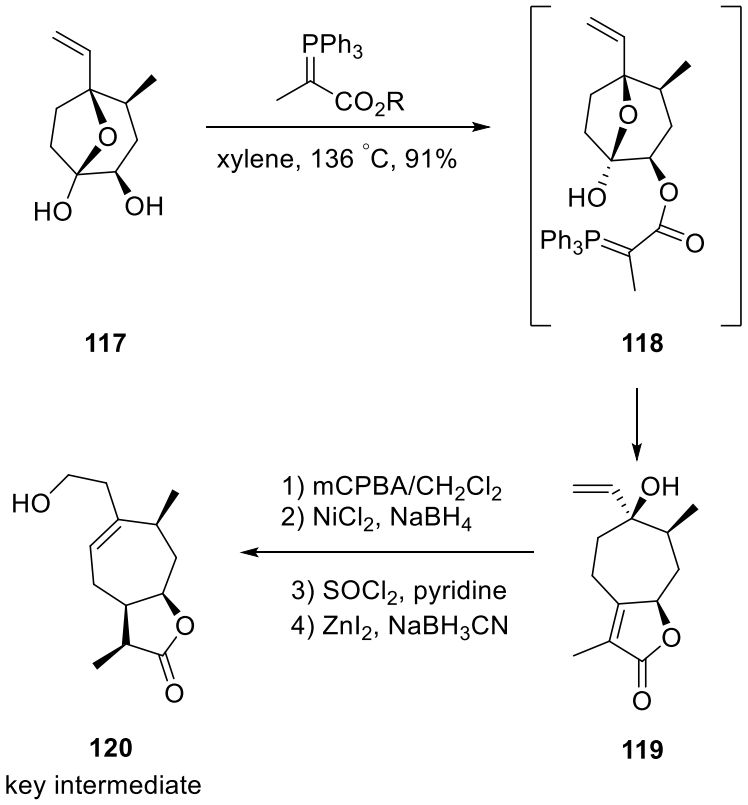
A key step of this suggested preparation was a rearrangement (**115** to **116**), which involves concurrent migration of two vicinal σ-bonds (one C-O bond and one C-C bond), was used to produce the ring enlarged γ-butyrolactones product. This method was applied in a well-organized preparation of many xanthanolide natural products. Scheme 30 shows the synthesis of a number of xanthane-type sesquiterpenoides involving the intermediate **116**. The desired compound was then obtained by the $EtAlCl_2$-mediated dyotropic rearrangement of **115**. The high chemo-, regio- and stereoselectivity of this key transformation can be rationalized by considering the transition state TS-2 (scheme 30). The intermediate was converted to xanthatin **12** and 11,13-dihydroxanthatin **108** in 2- and 3-steps, respectively. It's useful to note that this route of synthesis just delivered **116** in 25% as overall yield in 4 steps without synthesis the target xanthatin.



Scheme 30: Synthesis of the key intermediate.

4. Synthesis via intramolecular acylation and Wittig-lactonization. [72]

In this approach, the seven-membered carbocycle was prepared by an intramolecular acylation and a one-pot Wittig-lactonization as the key steps. This synthesis afforded a useful intermediate having a bicyclic 5,7-fused ring system for the synthesis of the xanthanolides (scheme 31). This scope of synthesis includes 28 steps to xanthatin made the overall yields very low 4% despite the high yield of the key step 91%.

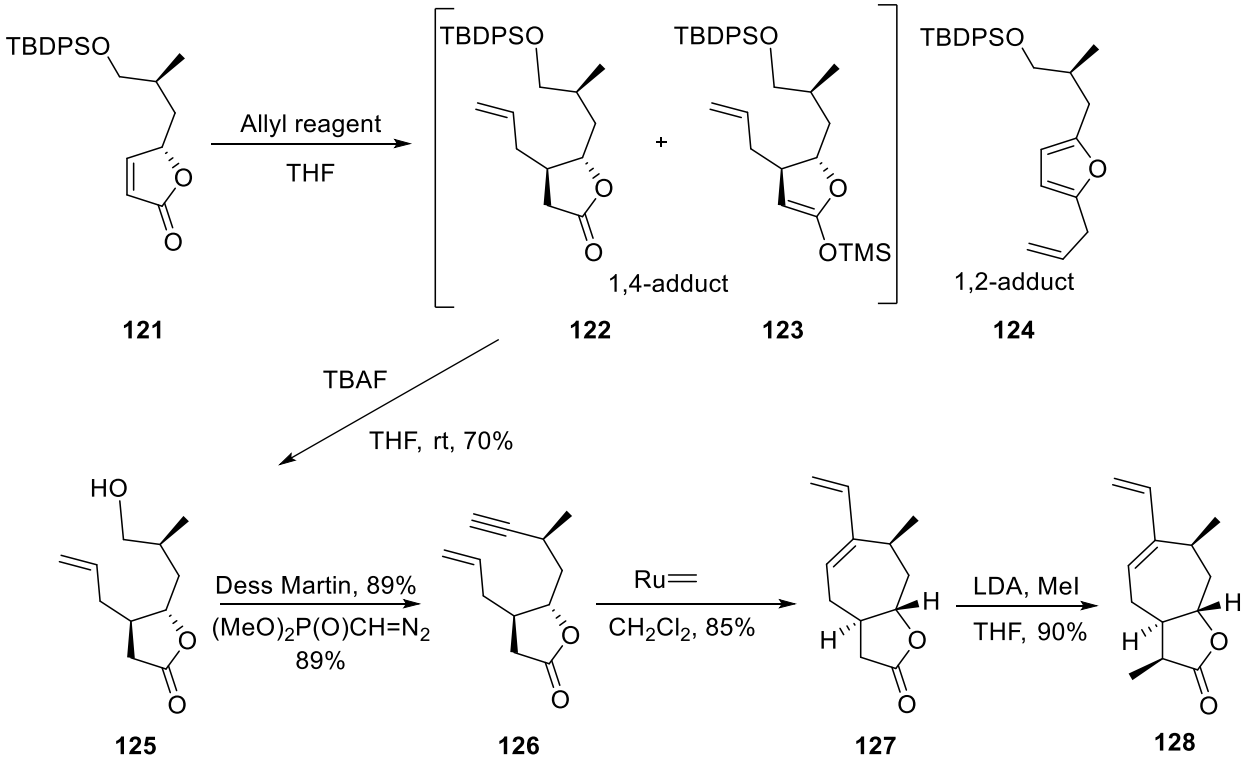


Scheme 31: Synthesis of the key intermediate for the xanthanolides.

5. Asymmetric total syntheses of xanthatin and 11,13-dihydroxanthatin using a stereocontrolled conjugate allylation to γ-butenolide.[73]

Shindo and co-workers improved their previous route for synthesis of xanthanolides from 28-steps to 14-steps. In the earlier work, the cis-fused γ-butyrolactone was used as a common chiral building block, furthermore in the previous route many unrequired steps were necessary to convert the *cis*-fused bicyclic lactone into the *trans*-fused lactone. The key point of this route plan was the improvement of a straight and general synthetic route for the stereoselective manufacture of a series of *trans*-fused xanthanolides. This synthetic route offers a general approach to the xanthanolides and other natural products having the trans-fused γ-butyrolactone (scheme 32). Scheme 8 shows that the γ-butenolide **121** is important to produce **128** (key intermediate) by the conjugate allylation of the optically active γ-butenolide **121**, because this conjugate reaction was expected to proceed from the opposite face of the side chain in **121**. Compound **126** has good

overall yield without any epimerization at the C-10 position. Compound **128** was obtained after ring closing metathesis of the enyne **126** using the Grubbs catalyst to give the seven-membered carbocycle **128** in 85% yields. Finally, by using the Hoveyda catalyst (A), the two products can be easily obtained to create the target compounds**.** The overall yields of this scope were 14%.

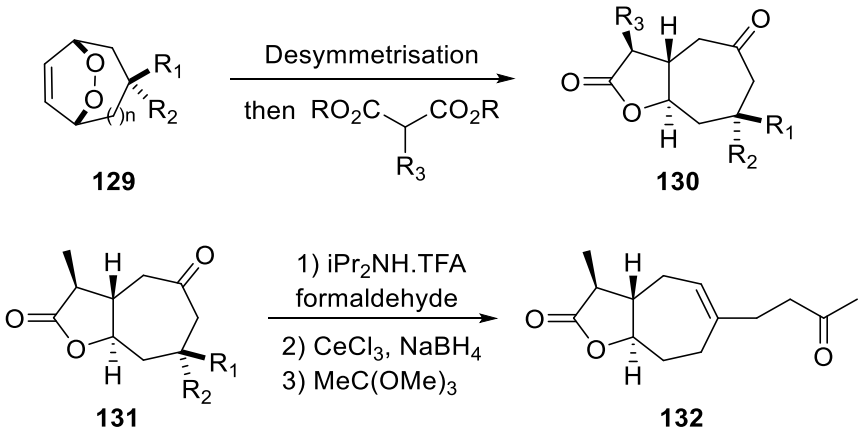


Scheme 32: Total synthesis of Xanthanolides.

2. Aims of the project

The overall aim of this project was to utilise endoperoxides, which can be conveniently accessed by the addition of $^1O_2$ to 1,3-dienes, in the synthesis of natural products, such as the xanthanolides. However, the synthesis of endoperoxides is predicated on access to suitably substituted 1,3-dienes, and as such the first part of the thesis will describe the detection and optimization of a novel allene to acyclic 1,3-diene rearrangement, catalyzed by a unique palladium-hydride complex derived from palladium (0) and boric acid. The rearrangement was discovered serendipitously and warranted investigation within the scope of the project. Furthermore, we will be able to apply this unique rearrangement together with $^1O_2$ oxidation to the synthesis of moracin M.

The second section describes work towards the total synthesis of xanthanolides, once again using endoperoxides derived from cyclic 1,3-dienes. The previous section has already highlighted the importance of xanthanolides, and our own group recently reported an enantioselective approach to *trans*-fused bicyclic butyrolactones, such as **130** and **132** which utilized a desymmetrisation of readily available endoperoxides **129** (Scheme 33). [17] While enantioselective routes toward *cis*-fused butyrolactones exist, general synthetic routes toward *trans*-fused butyrolactones are rarer; e.g. in Shishido's first asymmetric synthesis of the *anti*-inflammatory natural product *xanthatin*,[75] they had to convert a key *cis*-lactone precursor into the *trans*-lactone using a 3-step procedure which included a Mitsunobu inversion of a crucial hydroxyl group.[71]



Scheme 33: Kimber group approach to trans-fused butyrolactones.

In this research programme, intend to utilise this general asymmetric approach to *trans*-fused γ-butyrolactones to synthesise appreciable amounts of the *anti*-inflammatory, xanthatin (figure 11), **12** for biological evaluation. Importantly, the synthetic approach was to be (a) enantioselective; (b) modular, and (c) flexible. This will ultimately allow us to systematically vary the substitution on the *xanthatin* skeleton. Also planned to attempt to access intermediate **133** and synthesise other members of this family of natural products *via* the known key intermediate **134**. The *anti*-inflammatory activity of the synthetic *xanthatin* and its analogues were to be eventually evaluated using the existing collaborators

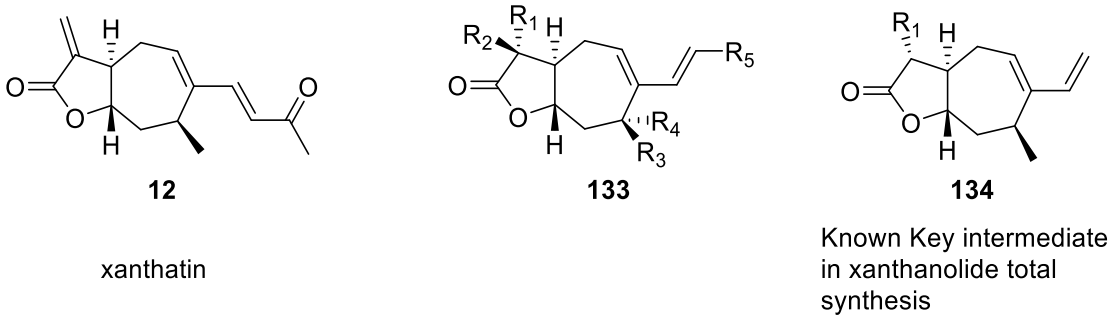


Figure 11. **Targets within this research programme**

3. Result and Discussion

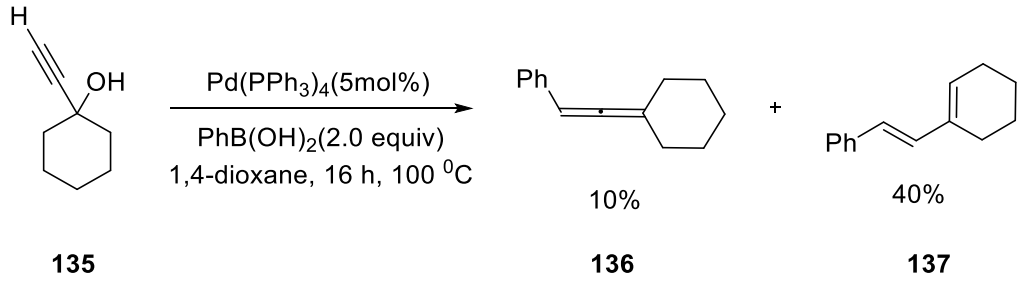
3.1. Synthesis of acyclic 1,3-dienes

3.1.1. Base Free Cross-Coupling Reaction to 1,3-Dienes

One of the more prominent tactics is the use of Pd(0)-catalyzed nucleophilic addition to activated propargylic substrates followed by cross-coupling of the palladium (II) intermediate with an appropriate coupling partner. One of the issues with this approach is the lack of examples within the literature incorporating cross coupling in base free conditions with readily available boronic acids *via* the Suzuki-Miyuara (SM) reaction [76].

With reference to SM-cross coupling reaction, envisaged using propargyl alcohols to react with boronic acid *via* palladium mediated to get the required allenes; however, found that when reaction was performed along with the allene and significant amount of the 1,3-diene was observed.

the initial detection of this transformation occurred when **135** was exposed to the adapted conditions of Yoshida and co-workers[77] (scheme 34) where extended heating of this reaction led the allene **136** as well as significant amounts of the 1,3-diene **137**, in an isolated yield of 40%.



Scheme 34: Unexpected formation of 1,3-diene 137.

In the crude ^{1}H NMR spectrum found three signals that had the same integration instead of one for allene **136** around 6 ppm. After that found that 1,3-diene **137** was the only structure that could fit this spectrum. The purification of the crude product and the isolation of both allene and diene prove that the extending heating of this reaction gives **137** as an additional result. The spectrum

(figure 12) clearly shows the first evidence of **137** with three signals belong to the conjugated double bonds in compound **137**.

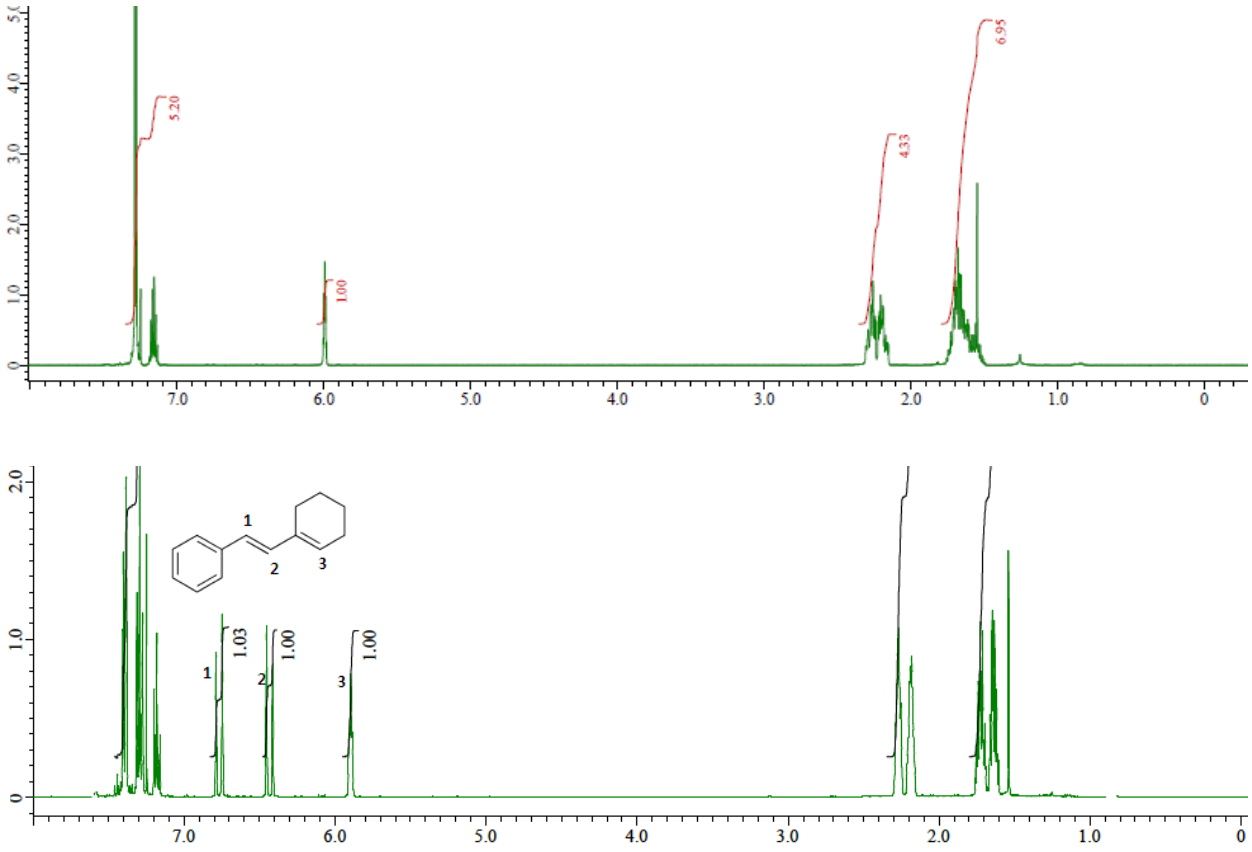


Figure 12: ^{1}HNMR for 136 in the top and 137 in the bottom.

The use of a base free SM-reaction to generate the allene had previously been reported by Yoshida;[77] however, there is no mention of the identification of the 1,3-diene products within this report. Therefore, given this novel transformation, make set out to optimize the formation of the 1,3-diene as shown below in (table 8)**.** Specifically, examined reaction temperature, solvent and equivalent number of boronic acid, and importantly time.

Table 8. Optimization for the formation 1,3-Diene 137 in (scheme 34).[a]

entry	$PhB(OH)_{2.}$ equiv.	Solvent	Temp. [°C]	Conversion[b] [%]
1	3	THF	Reflux	5
2	3	CH_3CN	75	0
3	3	PhMe	75	0
4	3	1,4-dioxane	Reflux	45
5	3	1,4-dioxane	75	85 [78][c]
6	3	1,4-dioxane	66	15
7	2	1,4-dioxane	75	45
8	1	1,4-dioxane	75	20

[a]Reactions were performed under an N_2 atmosphere at 0.5 M for 16 h, unless otherwise stated.

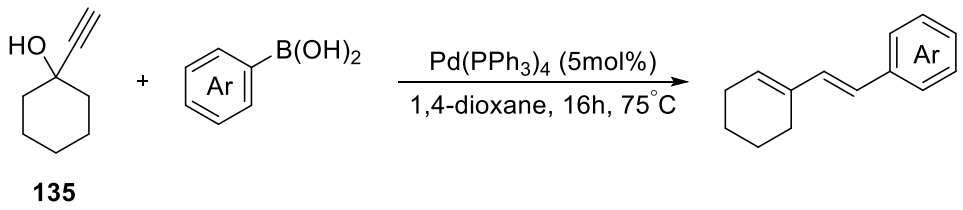
[b]Determined by ^1H NMR spectroscopy.

[c]Isolated yield.

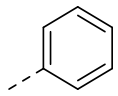
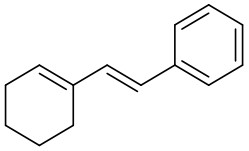
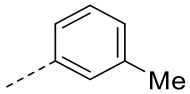
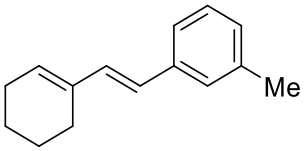
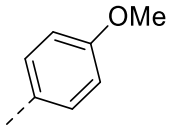
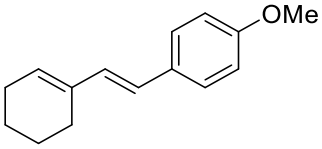
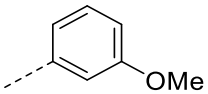
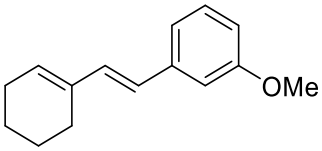
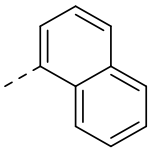
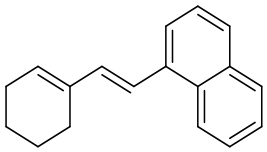
In entry 1, 3.0 equiv. of the boronic acid with THF as the solvent at 66 ˚C gave only minimal amounts of the desired 1,3-diene. In entries 2 and 3 the solvent and temperature changed by using acetonitrile and toluene, respectively, and this gave none of the 1,3-diene. In entries 4-6 we selected 1,4-dioxane as the solvent and varied the temperature. At reflux in dioxane obtained the 1,3-diene in 45% conversion (entry 4); at 75 °C obtained the 1,3-diene in 85% conversion, and in an isolated yield of 78% (entry 5); and at 60 °C only obtained the 1,3-diene in a poor 15% conversion. The number of equivalents of boronic acid was also probed (entry 7 and 8) with 2 equiv giving **137** in get 45% conversion, and 1 equiv. giving **137** in only 20% conversion, this is in constrast to the report of Yoshida and co-workers who found 2 equiv. to be favorable. Therefore, according to the result of the optimization in (Table 7) we found that the ideal condition was in (entry 5) 3 equiv. of boronic acid, 1,4-dioxane as a solvent at 75 ˚C for 16 hours in presence of 5 mol% $Pd(PPh_3)_4$ as a catalyst.

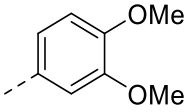
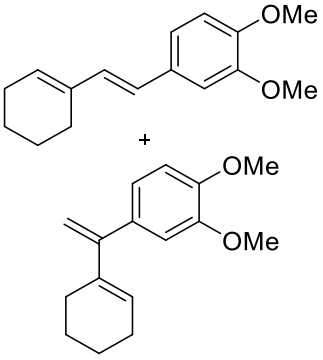
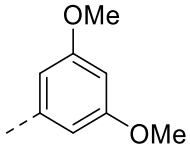
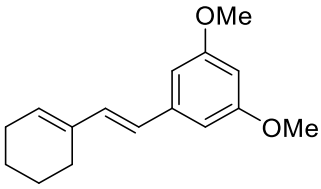
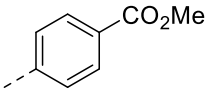
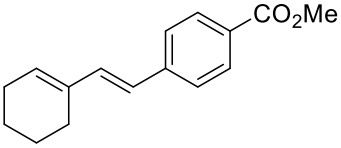
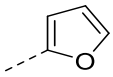
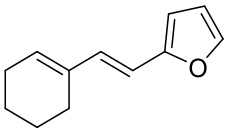
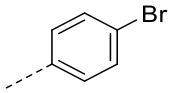
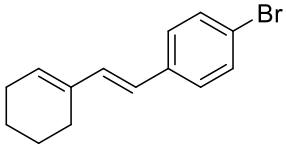
After optimization of the new condition we now applied these to determine the scope of this new transformation, and this was undertaken firstly with several boronic acids and one propargyl alcohol **135** (table 9).

Table 9. Variation of the Arylboronic Acid[a]



135

entry	Ar-B(OH)$_2$	1,3-diene product	Compound number	Yield [%][b]
1			**137**	**78**
2			**138**	**99**
3			**139**	**87**
4			**140**	**60**
5			**141**	**94**

6			**142**	**57**
			143	**29**
7			**144**	**62**
8			**145**	**70**
9			**146**	**66**
10			**147**	**<5[c]**

[a]Reactions were performed under a N_2 atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of $Pd(PPh_3)_4$ for 16 h, unless otherwise stated.

[b]Isolated yields unless otherwise stated.

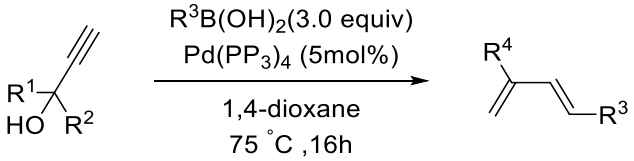
[c]Determined by 1H NMR spectroscopy.

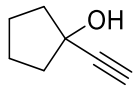
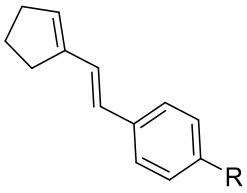
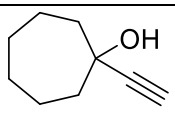
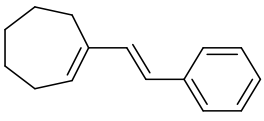
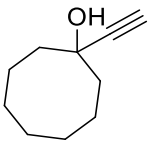
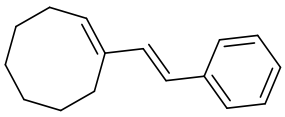
Table 9 shows ten examples cyclic diene prepared from cyclohexyl propargyl alcohol with different aryl boric acids. Entry 1 the diene **137** was prepared from phenyl boronic acid in good yield 78%. Electron-rich boronic acids all participated in the transformation with moderate to high isolated yield (entries 2−4). The sterically bulky 1-naphthylboronic acid perform well, giving the 1,3-diene **141** in an excellent 94% yield (entry 5), as did 3,4-dimethoxyphenylboronic acid, which gave the 1,3-diene **142** in 57% yield with 29% of unpredicted diene **143** (see experimental data)

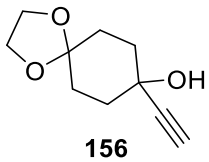
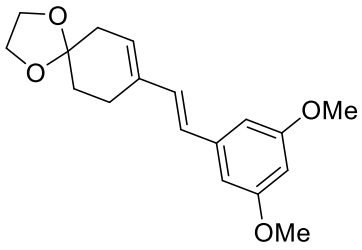
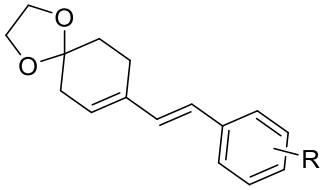
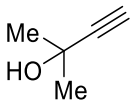
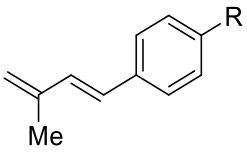
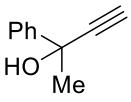
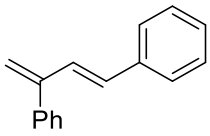
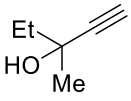
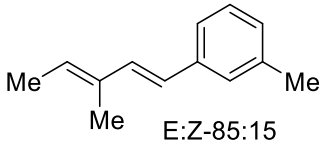
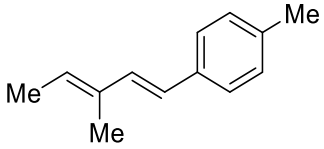
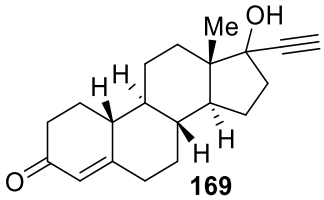
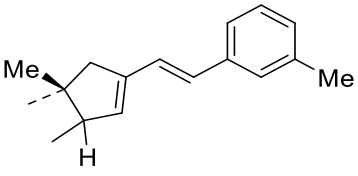
(entry 6). The 3,5-dimethoxyphenylboronic acid gave **144** in 62% isolated yield (entry 7). A boronic acid containing an electron-withdrawing group (CO_2Et) was tolerated under the reaction conditions, giving the 1,3-diene **145** in 70% yield (entry 8). A heterocyclic boronic acid was also acceptable in these reaction conditions, with 2-furanylboronic acid giving **146** in 66% isolated yield (entries 9); however, 4-bromophenylboronic acid gave limited amounts of the 1,3-diene, with a significant amount of starting alkyne and polymeric material being detected (entry 10).

Next, the examination variation of the alkyne coupling partner in this transformation (Table 10).

Table 10. Variation of the Propargyl Alcohol[a]



Entry	Propargyl alcohol	1,3- diene product	Compound number, substitutes	Yield [%][b]
1	 **148**		**149**: R = H	61
2			**150**: R = Me	67
3			**151:** R =OMe	78
4[c]	 **152**		**153**	80
5[c]	 **154**		**155**	75

6[c]	 **156**		**5**	43
7[c]			**158**: R= p-OMe	67
8[c]			**159**: R= m-OMe	80
9	 **160**		**161**: R=H	85
10			**162**: R=Me	47
11			**163**: R=OMe	98
12	 **164**		**165**	74
13	 **166**	 E:Z-85:15	**167**	55
14			**168**	73
15	 **169**		**170**	64

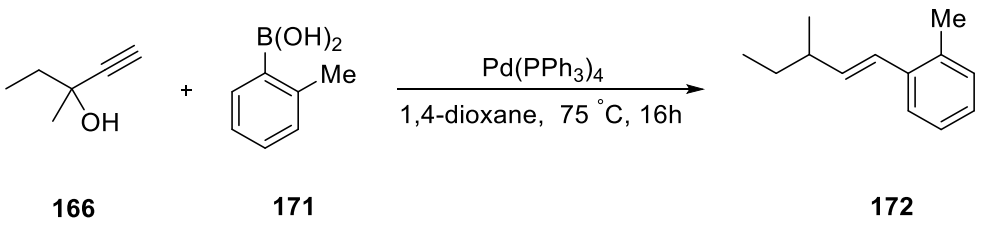
[a]Reactions were performed under a N_2 atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of $Pd(PPh_3)_4$ for 16 h, unless otherwise stated.

[b]Isolated yields unless otherwise stated. c Isolated as a mixture of *E*- and *Z*-isomers in approximately 85:15 ratio.
[c]Propargyl Alcohol prepared under Grignard reaction condition between the cycloketon and ethynyl Magnesium bromide.[78]

Cyclopentyl propargyl alcohol **148** performed well with phenyl, 4-methyl, and 4- methoxyboronic acids giving the 1,3-dienes **149**, **150**, **151** in 61%, 67% and 78% isolated yields, respectively (entries 1−3). Furthermore, cycloheptyl- **152** and cyclooctyl- **154** also participated as expected to give 1,3-dienes **153** and **155**, in yields of 80% and 75%, respectively (entries 4 and 5).

The 1,4-dioxaspiro-protected propargyl alcohol **156**, when coupled with 3,5-dimethoxyphenyl boronic acid, 4- methoxyphenyl boronic acid and 3-methoxyphenyl boronic acid gave the 1,3-dienes **157**, **158** and **159** in a moderate to good yields of 47%, 67% and 80%, respectively demonstrating that the reaction is tolerant of acid sensitive functional groups (entry 6-8). The acyclic propargyl alcohols 2-methyl-3-butyn-2-ol **160**, when exposed to phenylboronic acid, gave 1,3-diene **161** in 85% yield, while 4-tolylboronic acid and 4-methoxyboronic acid gave 1,3-diene **162** and **163** in a modest 47% to high isolated yield 98% (entries 9-11). Similarly, 2-phenyl-3-butyn-2-ol **164** gave the 1,3-diene **165** in 74% isolated yield when exposed to phenylboronic acid (entry 12). In entry 13, we used 3-methyl-1-pentyn-3-ol **166** with 3-methyphenylboronic acid, yielding the 1,3-diene **167** (isolated as a mixture of *E*- and *Z*-isomer in an approximately 85:15 ratio) as the predominant product in 55% yield, while the same propargyl alcohol **166** with 4-tolylboronic acid gave 1,3- diene **168** in 73% isolated yield. The prevalence of this 1,3-diene **168** in this example is presumably due to the formation of the tri-substituted alkene as the thermodynamic product. Finally, 19-norethistrone **169** was exposed to the reaction conditions with 3-methylphenylboronic acid, yielding the 1,3-diene **170** in 64% yield, therefore giving an ideal handle for further functionalization of this important steroid (entry 15).

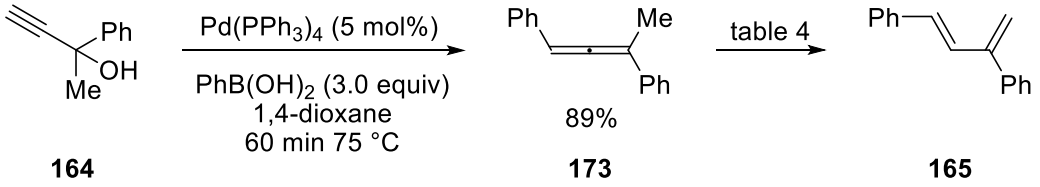
However, when we used ortho-substituted phenylboronic acid, for example reaction of 3-methylpent-1-yn-3-ol **166** with 2-methyl phenylboronic acid **171** under the optimized conditions we obtained compound **172** (Scheme 35). The structure of **172** confirmed by ^{1}HNMR spectrum by miss the signal at 5.9 belong to the second double bond of the diene.



Scheme 35: Unpredictable result of diene synthesis.

After our successful optimization and scope investigation of this the new route for the preparation 1,3-diene, we next investigated the relationship between the allene and 1,3-dienes. Plausibly, the 1,3-diene can result from the rearrangement of an intermediary allene to give the 1,3-diene.

To determine that this process is two-step, i.e. conversion of the propargyl alcohol to the allene followed by rearrangement to its 1,3-diene, the reaction was carried on formation of allene **173**, which was firstly isolated in 89% yield as shown in (Scheme 36).



Scheme 36: The two step of diene synthesis.

With **173** in hand we then exposed it to reaction conditions to promote the formation of 1,3- diene **165** (Table 11). The exposure of **173** to 5 mol % of Pd^0 gave no conversion, with only the starting allene being detected (entry 1). Again, exposure of **173** to phenyboronic acid gave none of the desired 1,3-diene (entry 2). Phenylboronic acid in the presence of Pd^0 did give a small conversion to the diene **165**, but with significant degradation of the allene and addition products[79] being observed (entry 3). In the acid mediated rearrangement of allenes, reported by Sanz and co-workers,[80] pTSA was used to facilitate the rearrangement of the allene. To investigate this, **165** was exposed to 1 equiv of $B(OH)_3$, the only other significantly acidic byproduct of the Suzuki−Miyaura reaction, but this failed to deliver the 1,3-diene (entry 4). This is unsurprising given the pKa of boric acid compared to pTSA. However, when **173** was exposed to Pd^0 and 1

equiv of $B(OH)_3$, conversion to the 1,3- diene was significant, giving **165** in 92% conversion presumably *via* the formation of a $H{-}Pd^{II}$-$OB(OH)_2$ complex (entry 5). Yamamoto and co-workers[79] have reported a similar hydroalkoxylation/isomerization of allenes and alkynes using analogous $H{-}Pd^{II}{-}OBz$ and $H{-}Pd^{II}{-}OAc$ complexes, but with limited selectivity and scope. Therefore, we exposed allene **165** to $H{-}Pd^{II}{-}OBz$, derived from Pd^0 and BzOH, and this gave the 1,3-diene **165**, but with a significant hydroalkoxylation by-product (entry 6).

Table 11 Allene Isomerization

Entry	Additive[b]	Catalyst[c]	Product[d] [%] **173**	product[d][%] **165**
1	-	$Pd(PPh_3)_4$	90	-
2	$PhB(OH)_2$	-	90	-
3	$PhB(OH)_2$	$Pd(PPh_3)_4$	52	15
4	$B(OH)_3$	-	90	-
5	$B(OH)_3$	$Pd(PPh_3)_4$	**>5**	92[86][e]
6	BzOH	$Pd(PPh_3)_4$	**>5**	60[e]

[a]Reactions were performed under an N_2 atmosphere at 0.5 M in 1,4-dioxane for 16 h unless otherwise stated.

[b]100 mol %.

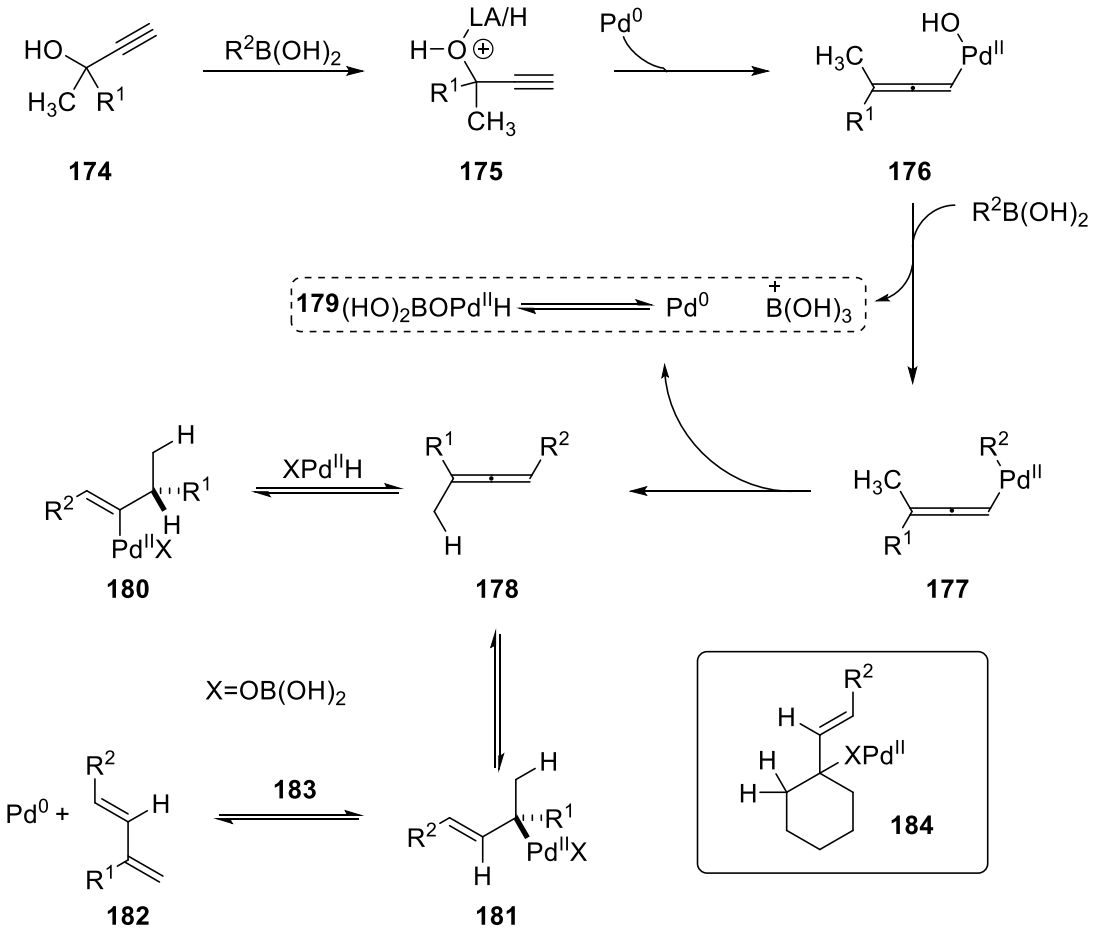
[c]5 mol %.

[d]Determined by ^1H NMR spectrums.

[e]Isolated yield.

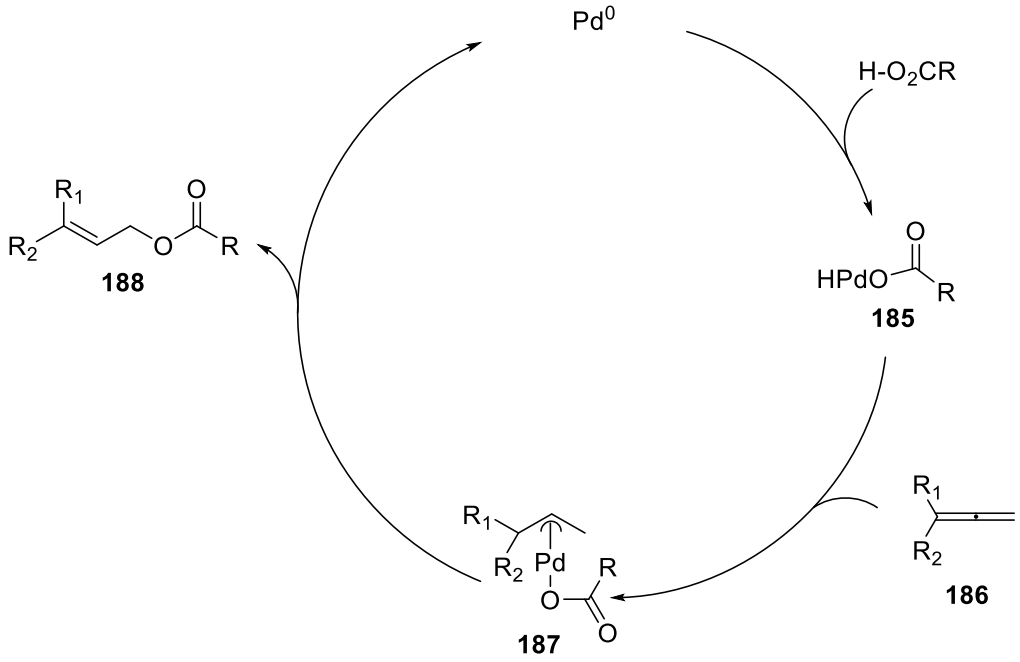
Using the results in (Table 10) together with the well understood mechanism for the formation of the allene[77], leaded to propose a plausible mechanism for the formation of the 1,3-diene (Scheme 37). Activation of **174** *via* a proton or the Lewis acidic boronic acid delivers **175**, which in the presence of Pd^0 undergoes nucleophilic addition to give the allenylpalladium species **176**, followed by a subsequent SM-coupling to deliver the intermediate allene **178**. We then propose, based on the results within (Table 10), that the boric acid oxidizes the resultant Pd^0 to give the Pd^{II} species $H{-}Pd^{II}{-}OB(OH)_2$ **179**. Allene **178** can then undergo hydropalladation with **183** to deliver either **180** or **181** with **180** experiencing a dehydropalladation to regenerate the allene **178**. However,

unlike **180**, **181** can undergo two possible dehydropalladations, either regenerating the allene **178** or, more significantly, delivering the observed 1,3-diene **182**.



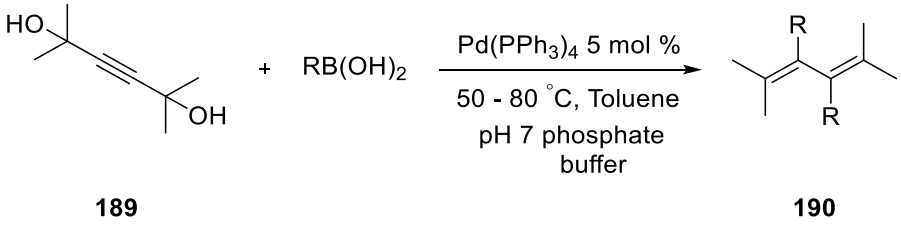
Scheme 37: Proposed Mechanism for the Formation 1,3-Dienes from Propargyl Alcohols and Boronic Acids under Palladium Mediated Catalysis

Our proposed H−Pd^{II}−$OB(OH)_2$ complex parallels the related complexes (e.g., H−Pd^{II}−OBz and H−Pd^{II}−OAc) as reported by Yamamoto (scheme38),[79] but demonstrates a different reactivity. The latter complex when reacted with allenes gives the hydroalkoxylation product, presumably due to the nucleophilicity of the benzoate conjugate base whereas, the former H−Pd^{II}−$OB(OH)_2$ complex gives predominantly the rearranged 1,3-diene product.



Scheme 38: Yamamoto's mechanism

We disclosed these results in July 2016[81], but a similar reaction was subsequently disclosed in September 2016 by Sherburn and co-workers leading to substituted 1,3-dienes by using propargylic diols with boronic acids in presence of palladium zero (Scheme 39).[82]



Scheme 39: Cross-Couplings of Propargylic Diols

3.2. Isomerization of unactivited Allenes to 1,3- Dienes

With reference to our synthesis of natural products using endoperoxides, the convenient starting material should be the cyclo-dienes (seven or eight-member ring) via ring closing diene metathesis. Finding ways to prepare the 1,3-dienes could increase choice in the preparation of different

substitute xanthanolides and in relatively few steps. Ostensibly, the rearrangement of alkyl-substituted allene represents an atom efficient method for the synthesis of dienes *via* a 1,3-hydrogen migratory process. This type of 1,3-hydrogen migration route, either acid catalysed or thermal, is commonly found in activated allenes such as the allenamide series elegantly described by Hsung.[83] However, such transformations on inactivated allenes have been infrequent within the literature, and commonly undertaken at high temperature or under metal catalysed conditions. Allenes and diene have become an increasingly important structural motif in organic synthesis. This is due, in part, to their occurrence in natural products and drug candidates, their unique axially chirality, and their underlying potential in regio- and stereo-specific carbon-carbon and carbon-heteroatom bond forming reactions. As a consequence, concise and technically simple synthetic methods for their construction have been much sought after and have led to various approaches being divulged (Scheme 40).[84]

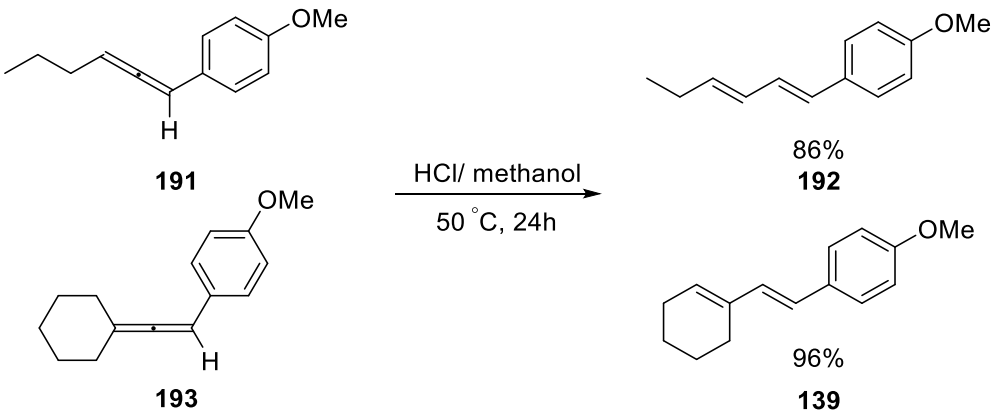
3.2.1 Review of Isomerization of unactivated Allenes to 1,3- Dienes

A limited number of methods have been reported for the successful isomerization of unactivated allenes to 1,3-dienes and these can be grouped into acidic catalyzed, thermal, and finally metal catalyzed methods.

1. Acid catalyzed isomerization.

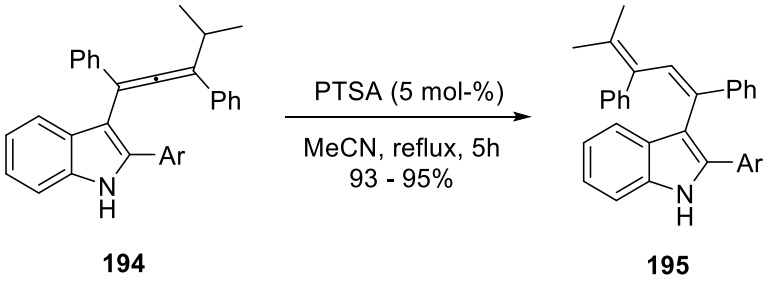
In the presences of an acid unactivated allenes can be isomerization to 1,3 dienes via a series tautomerizations and proton shifts. This was first reported in 1960 by Thomas and co-worker[85] where they studied the orientation of the addition of hydrogen chloride to aliphatic allenic hydrocarbon, and that the addition of hydrogen chloride to 3-methyl-1,2-butadiene at -78 ^{o}C in presence of bismuth trichloride gave the rearranged 1,3-diene.

In 1985 Wenkert and co-workers studied the synthesis of allenes by nickel-catalyzed Grignard reactions with silylpropargyl alcohols and found that when exposed to acid the prepared allenes rearranged to conjugated dienes in high yield (Scheme 40).[86] It is useful to mention that just two example of isomerization were used basic alumina was used in purification.



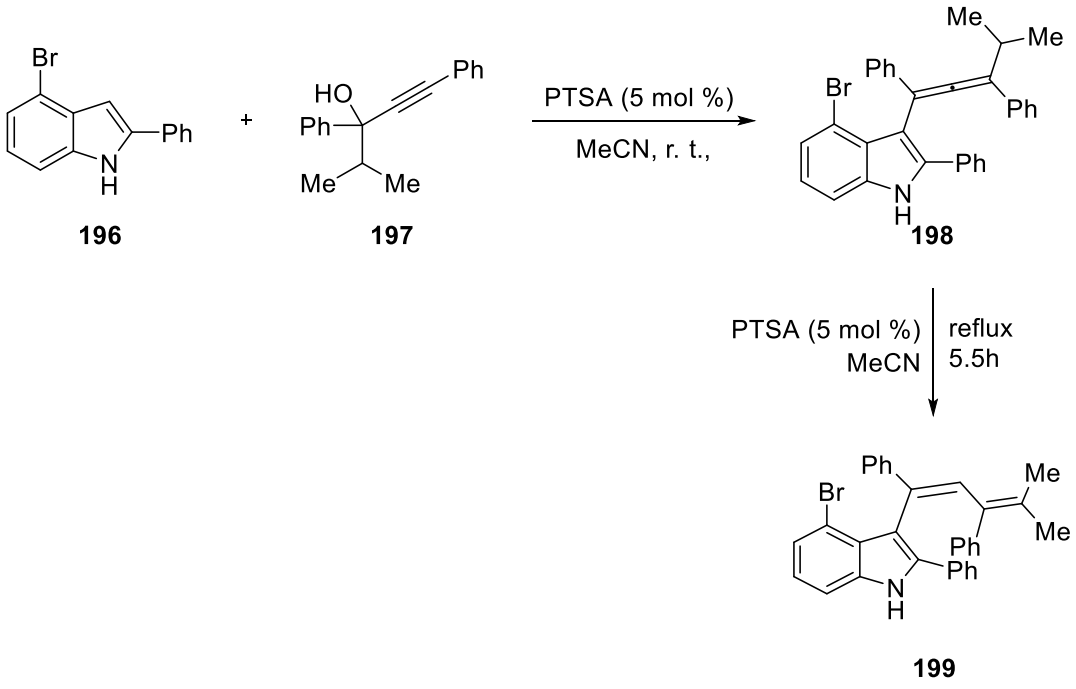
Scheme 40: Hydrochloric acid to isomerization allenes

In 2010 Sanz and co-workers [80] used a Bronsted acid to isomerization allene **194** to diene **195** by using PTSA as acid catalyst in high yield (scheme 41).



Scheme 41: Bronsted acid to isomerization allenes

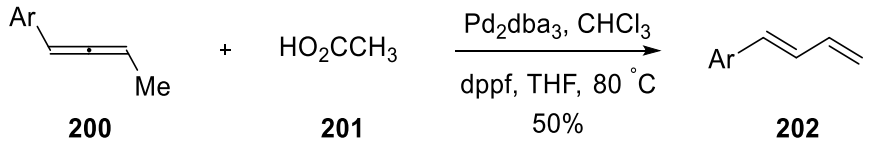
In addition, they found that the diene **199** could be prepared directly in a one pot reaction under the same condition of the preparation of allene **198** by just extending the heating and they proved the suggested mechanism by isolated the intermediate allene **198** (Scheme 42).



Scheme 42: Isomerization of allene.

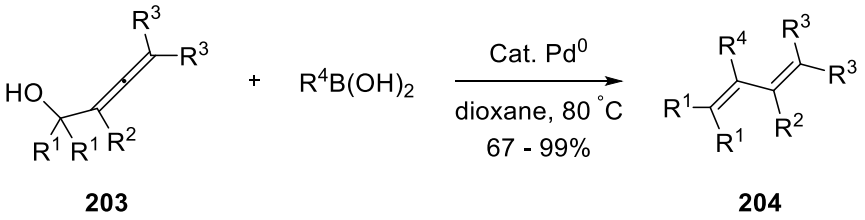
2. Metal Catalyzed Isomerization.

In 1998 Yamamoto[79] found that aliphatic and α-aryl substituted allenes were isomerized to 1,3-dienes in modest yield. This was a by-product of a hydrocarboxylation of allenes in the presences of palladium catalyst and carboxylic acid (scheme 43).



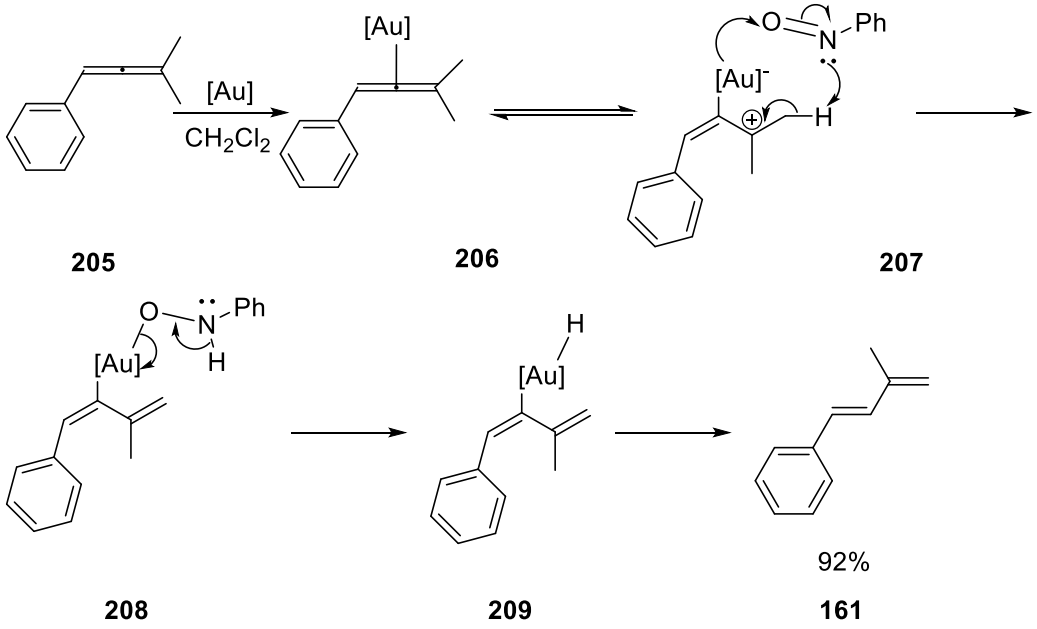
Scheme 43: Formation and isomerization allene with Palladium catalyst

In 2004 Yoshida and Ihara found allenic alcohols with aryl- or alkenyl-boronic acids in the presence of palladium (0) could be coupled with boronic acid aryl or alkenyl groups to give various substituted 1,3-dienes (Scheme 44).[87]



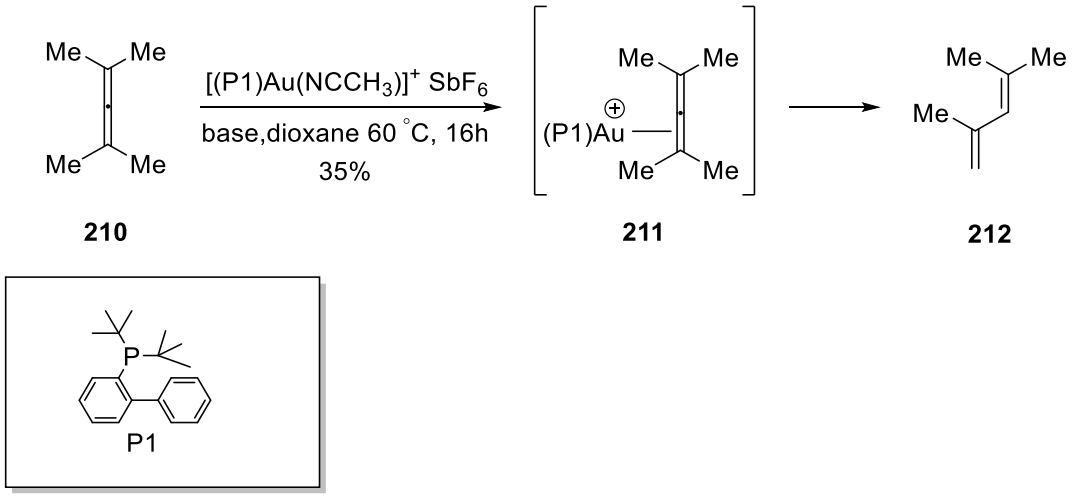
Scheme 44: Rearrangement of allenic alcohols.

In 2012 Liu and co-worker [84] reported a gold catalyzed isomerization of unactivated allenes to 1,3-dienes with nitrosobenzene. The proposed mechanism[84] shows that the role of nitrosobenzene is to facilitate the proton transfer by the electrophilic addition at its nitrogen and this will increase the nucleophilicity of the oxygen (scheme 45).



Scheme 45: Isomerization allene with gold catalyst.

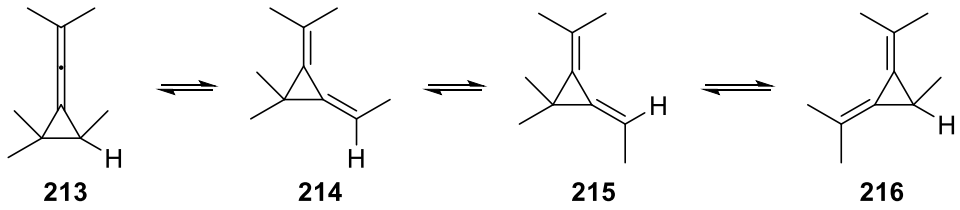
Later in 2014 Widenhoefer and co-worker[88] used a cationic gold (I) complex to form gold π-tetramethylallene complex **211** (scheme 46). Which could be subsequently converted to 1,3-diene **212**.



Scheme 46: Diene from gold π- tetramethylallene complex

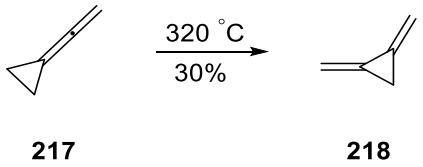
3. Thermal rearrangement of allenes.

In 1966 Paulson and co-worker[89] reported that the cyclopropane allene **213** could be converted to the 1,3-dienes **214** and **216** at a range of different temperature between 360 to 460 ^{0}C. Compounds **214** and **215** were formed at 360 ^{0}C whereas, **216** needed 460 ^{0}C to form (Scheme 47).



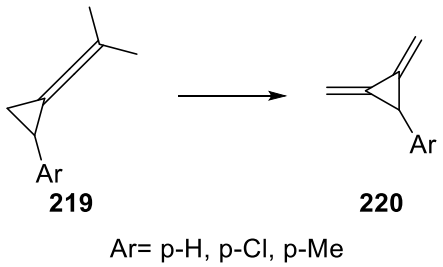
Scheme 47: Thermal rearrangement

In 1970 Bloch and co-worker[90] due to continued interest in cyclopropane allenes reported the conversion of cyclopropane allene **217** to diene **218** at 320 ^{0}C under vacuum in 30% yield in three minutes (Scheme 48).



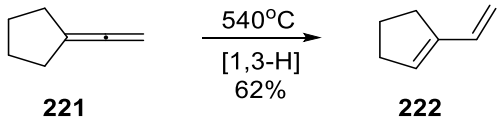
Scheme 48: conversion of cyclopropane allene to diene

In addition, in 1971 Patrick and co-worker[91] reported stereoselective thermal rearrangement of cyclopropane allene **219** to diene **220** at 170 ^{0}C or at 130 ^{0}C in mesitylene solution without mentioned the yield percentage (Scheme 49).



Scheme 49: Rearrangement of cyclopropane allene in mesitylene solution

In 1989 Meier and co-worker[92] reported that when exposed cyclo-allene **221** was exposed to a high temperature, the allene could undergo a facile rearrangement to the 1,3-diene **222** in 62% (scheme 50).



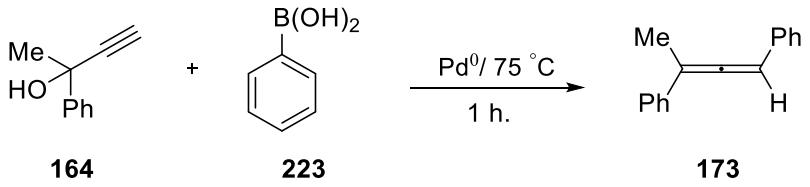
Scheme 50: Thermal rearrangement of allene

3.2.2 Synthesis of Allenes

Having developed a method for the direct conversion of propargyl alcohols to 1,3-dienes, as well as identifying that the 1,3-diene plausibly results from the rearrangement of an intermediary allene, we set about examine further the allene to 1,3-diene transformation. This would be for preparative

purposes as well as a further examination of the mechanism for this rearrangement, Initially this would require the synthesis of a range of inactivated allenes, which would then be exposed to our Pd(0) / $B(OH)_3$ conditions described in section 3.1.1.

Firstly, optimized the allene synthesis using the Yoshida[77] reaction conditions using phenyl boronic acid **223** and propargyl alcohol **164** (scheme 51) and (table 12).



164 **223** **173**

Scheme 51. Synthesis of allene

Table (12) optimization of Allene synthesis reaction

Entry	Partner	Amount equiv.	Catalyst	Amount mol %	Solvent	Conversion[b] [%][c]
1	$PhB(OH)_2$	1.05	$Pd(PPh_3)_4$	5.0	THF	22
2	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	5.0	THF	48
3	$PhB(OH)_2$	2.10	$Pd(PPh_3)_4$	5.0	THF	30
4	$(PhBO)_3$	1.05	$Pd(PPh_3)_4$	5.0	THF	70 [66]
5[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	5.0	THF	91 [78]
6	$PhBF_3K$	1.05	$Pd(PPh_3)_4$	5.0	THF	-
7	$PhB(OH)_2$	3.15	-	-	THF	-
8[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	5.0	PhMe	27
9[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	5.0	DME	30
10[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	5.0	1,4-dioxane	86 [82]
11[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	5.0	DMF	-
12[d]	$PhB(OH)_2$	3.15	$Pd(dba)_2$ + $2PPh_3$	5.0	1,4-dioxane	77

13[d]	$PhB(OH)_2$	3.15	$Pd(dba)_2$ + (±)-BINAP	5.0	1,4-dioxane	75
14[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	2.5	1,4-dioxane	62
15[d]	$PhB(OH)_2$	3.15	$Pd(PPh_3)_4$	10.0	1,4-dioxane	82

[a]All reactions were performed at 70 ˚C on 1.00 mmol of the alkyne at 0.2 mM unless otherwise stated.

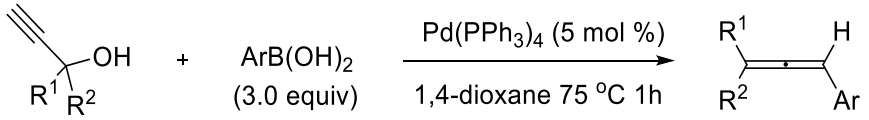
[b]Conversion determined by ^1H NMR using trimethoxybenzene as internal standard.

[c]Isolated yield.

[d]Addition of 4Å molecular sieves.

We began the study by treating alkyne **164** with phenylboronic acid **223** in the presence of a palladium catalyst as shown in (scheme 52) and (table 11). We initially treated **164** with 1.05 equiv. of **223** in refluxing THF with 5 mol% $Pd(PPh_3)_4$ which the yielded in allene **173** in promising 22% conversion (entry 1). Variation of the equivalents of boronic acid was then performed (entries 2 and 3) which indicated that 3.15 equivalents of boronic acid gave a modest increase to 48% conversion. Pleasingly, when 1.05 equivalents of triphenylboroxine was used, in place of boronic acid, this conversion then increased to 70% (entry 4). Therefore, the inclusion of 4Å sieves when using 3.15 equivalents of boronic acid was then trialed which led to an 72% conversion to the desired allene, which was subsequently isolated in 78% yield (entry 5). Potassium trifluorophenylborate failed to yield the desired allene **173** with only starting material being observed (entry 6). A screen of solvents established 1,4-dioxane, in the presence of 4Å sieves, as a superior solvent system to undertake the transformation leading to an improved formation of the allene in 86% conversion and 82% isolated yield (entry 10). Replacing the Pd(0) source from $Pd(PPh_3)_4$ to $Pd.dba_2$ with both PPh_3 and (±)-BINAP resulted in formation of the allene, albeit in slightly reduced conversions (entries 12 and 13). Finally, a variation of the catalysts loading using $Pd(PPh_3)_4$ was performed indicating 5 mol% of Pd(0) to be optimal for this transformation (entries 14 and 15).

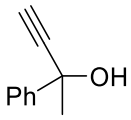
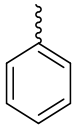
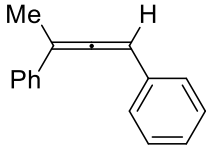
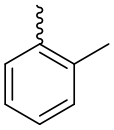
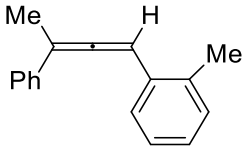
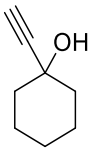
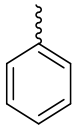
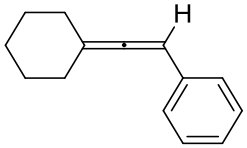
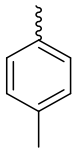
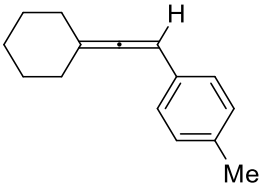
With optimal conditions achieved we were able establish the scope of this transformation and we applied these conditions to different propargyl alcohols with different boronic acids (scheme 52) and (table 13).

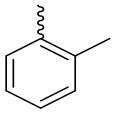
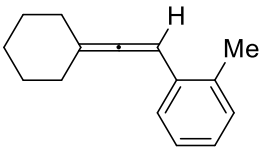
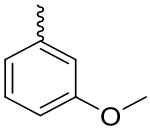
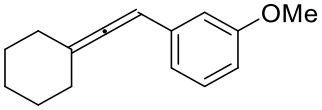
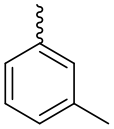
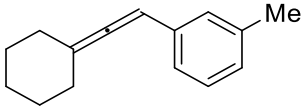
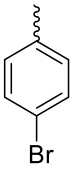
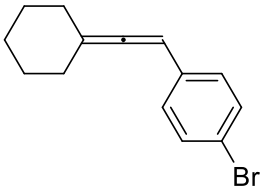
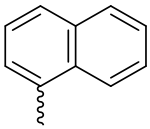
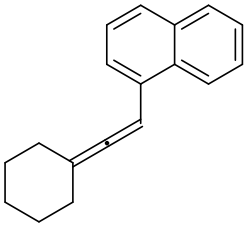
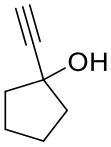
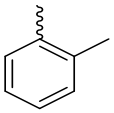
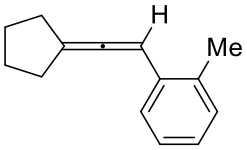
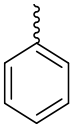
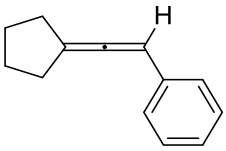
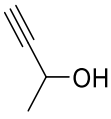
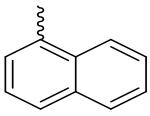
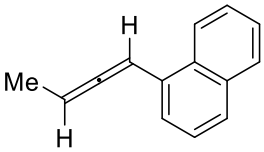


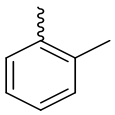
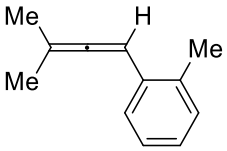
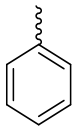
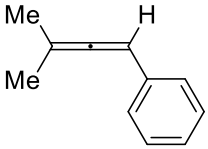
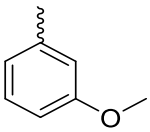
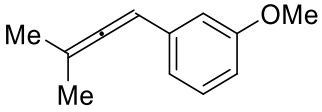
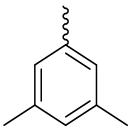
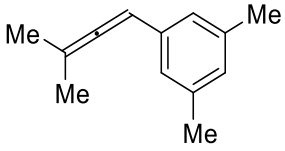
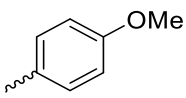
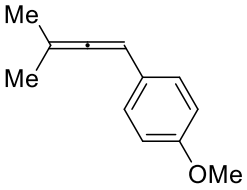
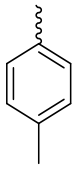
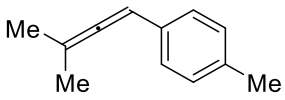
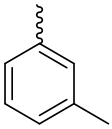
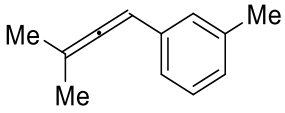
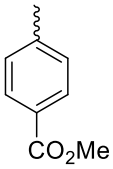
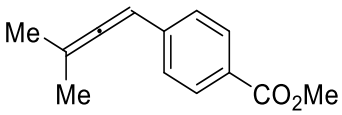
224 **225** **226**

Scheme 52: General condition of allenes synthesis

Table 13 allenes synthesis

Entry	Propargyl alcohol	$ArB(OH)_2$	Allene product	Comp. No.	Yield [%]
1	 **164**			**173**	**91**
2				**226**	**84**
3	 **135**			**136**	**71**
4				**227**	**64**

5				**228**	**60**
6				**229**	**63**
7				**230**	**45**
8				**231**	**19**
9				**232**	**68**
10	 **148**			**233**	**43**
11				**234**	**55**
12	 **235**			**236**	**44**

13	**160**			**237**	**60**
14				**238**	**68**
15				**239**	**38**
16				**240**	**32**
17				**241**	**55**
18				**242**	**72**
19				**243**	**35**
20				**244**	**24**

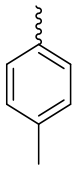
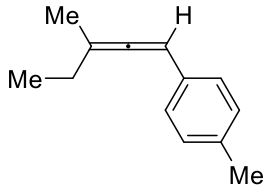
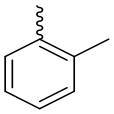
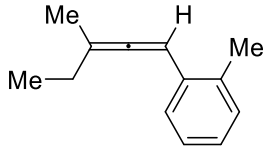
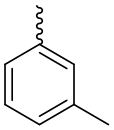
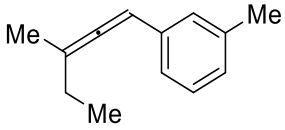
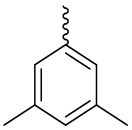
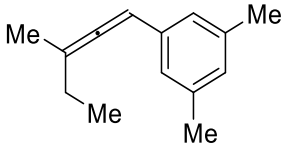
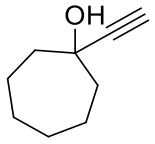
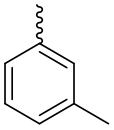
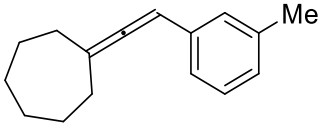
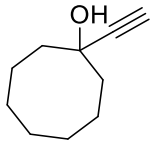
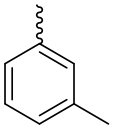
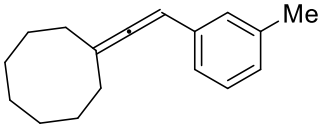
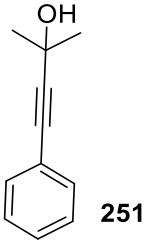
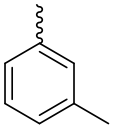
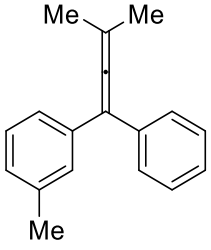
21				**245**	**58**
22				**246**	**62**
23				**247**	**72**
24				**248**	**32**
25				**249**	**45**
26				**250**	**56**
27				**252**	**92**

Table 13 show**s** allenes compounds resulted by the reaction between different propargyl alcohols and various boronic acids. These resultant compounds were confirmed by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR) and by physical properties. Allenes can be recognized by their infrared

spectra by their specific absorption belonging to the bonding with their sp carbon from 1925 to 1980 cm^{-1} depending on the substituent group. Furthermore, most allenes give signals in ^{1}H NMR spectra between (6.80 - 5.80) ppm belong to the hydrogen atom attached to the sp^2-hybridized carbon and a unique ^{13}C NMR signal around 200 belonging to the sp- hybridized carbon of the allene unit.

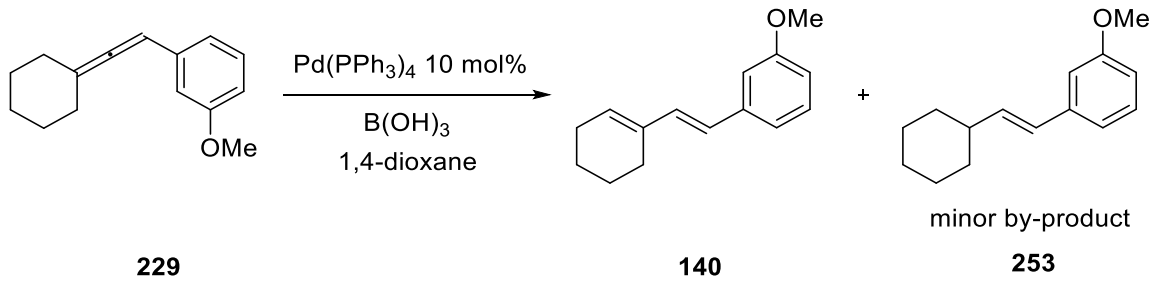
The percentage yield of the resultant compounds varied from 24% to 92%. The percentage varies according to many factors, the pKa of the boronic acids, for example. The phenyl boronic acid[93] is pKa = 8.9, whereas, 2-methyl phenyl boronic acid[94] has pKa = 9.7. This information means the acidity of phenyl boronic acid is larger than others. So, in table 12 the percentage of the result compounds **173** and **238** (entries 1 and 14) were larger than compounds **226** and **237** (entries 2 and 13), same can be said on compound **136** (entries 3) compare with compounds **227** and **228** (entries 4 and 5). But this rule was not all time works for example 4-bromophenyl boronic acid[93] pKa = 8.6 and the percentage of the result was 19% (entry 8).

Furthermore, the ring strain of the cyclic substances also affects the percentage of the result, bonds in cyclopentane offer little conformation flexibility than the ideal bond angles in cyclohexane, cycloheptane and cyclooctane compounds. Ring strain shown in compound **247** (entry 5) has a larger percentage than compound **233** (entry 10) both have same boronic acid also (entry 25 and 26) have 45% and 56% yields respectively.

in addition, internal alkyne **251** give diene **252** in 92% whereas external alkyne **160** give diene **243** in 35% by using same boronic acids

3.2.3 Rearrangement of unactivated allenes to 1,3 dienes

After the initial optimization of isomerization of **173** to diene **165** in section 3.1., the investigation of the allene to 1,3-diene isomerization with regard to temperature and time using allene **229** (scheme 53 and table 14).



Scheme 53: optimization reaction

Table 14. Optimization condition for rearrangement of allene **229** to 1,3-diene **140**

Entry	Temp (°C)	Time (h)	Observed product	
			140	253[f]
1	75	8	66	-
2	75	24	90 [70] [b]	-
3	RT	24	55	-
4	90	24	60[c]	-
5[d]	75	24	35	45
6[e]	75	4.5	>5	40

[a]Reactions were performed under an N_2 or argon atmosphere with the allene (1 equiv), $Pd(PPh_3)_4$ (10 mol%), $B(OH)_3$ (200 mol%) in 1,4-dioxane unless otherwise stated.

[b] Isolated yields.

[c]Degradation.

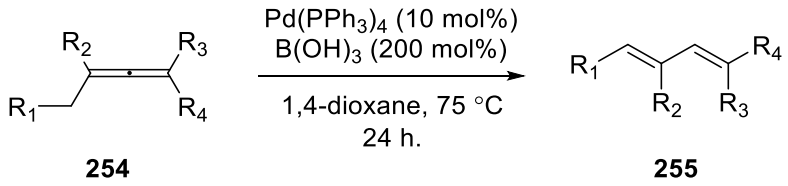
[d]100 mol% $B(OH)_3$.

[e]BzOH (100 mol %) instead of $B(OH)_3$.

[f] determined by HNMR conversion.

Table 14 show six variations of factors of the reaction in (scheme 53), the first one was to leave the reaction for 8 h at 75 ˚C by using 0.1 equivalent of Pd^0 and 2 equivalents of boric acid to get 66% of the desired product (entry 1) whereas, entry 2 had the same condition except leaving the reaction for 24 h to get 90% of the diene **140**. We now fixed the time of the reaction at 24 h and

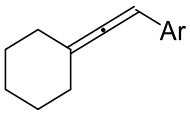
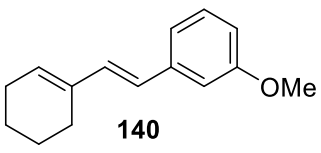
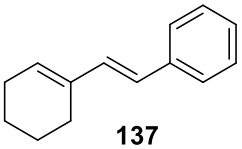
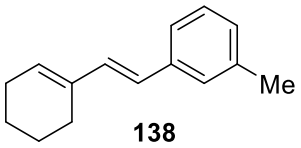
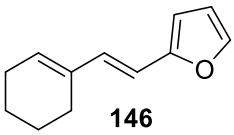
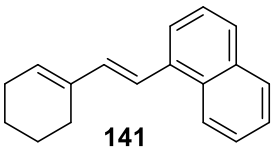
changed the temperature to room temperature (entry 3) and to 90 ^{0}C (entry 4) to get 55% and 60%, respectively of the desired 1,3 dienes. In (entry 5) we decrease the amount of boric acid by half and keep the other conditions as (entry 2), and the amount of the resultant 1,3-diene decrease to 35% and we noticed a new compound **253** in 45% as undesired product. Finally, (entry 6) the boric acid was replaced with one equivalent of benzoic acid because it was used to generate a H-Pd^{II}-OBz complex before,[95] and in this entry we observed a trace amount of the 1,3 dienes (>5) with 40% of the undesired product **253**. Table 13 shows that entry 2 give the best conversion (90%) and therefore, we used these conditions to treat several allenes from (table 13) with (10 mol%) of $Pd(PPh_3)_4$ and 2 equivalents of boric acid in 1,4- dioxane under 75 ˚C for 24 h (scheme 54 and table 15).



254 **255**

Scheme 54: General Conditions of Allene to Diene Rearrangement

Table 15: rearrangement of allenes to 1,3-dienes.

Allenes	1,3- Dienes
	 **140** 76%  **137** 73%  **138** 72%  **146** 62%  **141** 0%

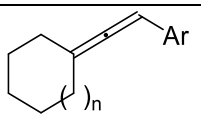
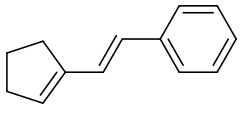
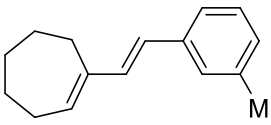
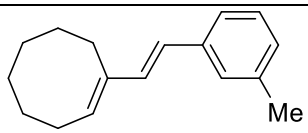
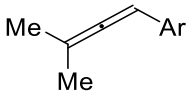
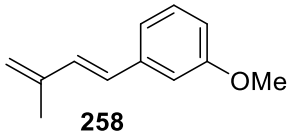
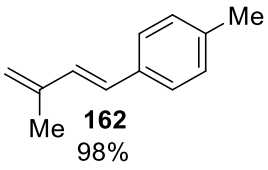
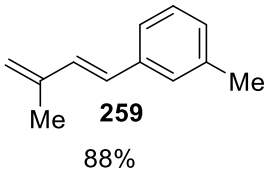
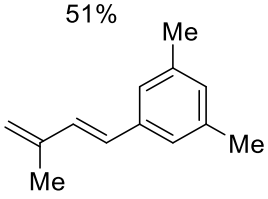
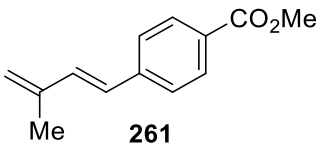
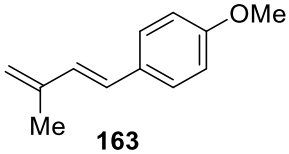
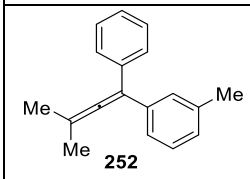
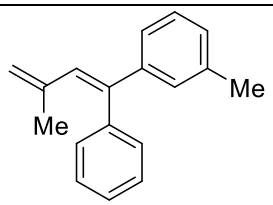
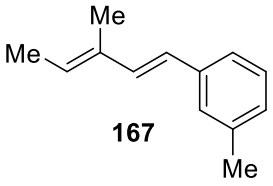
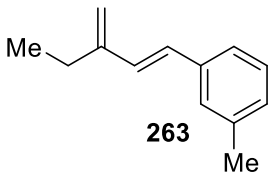
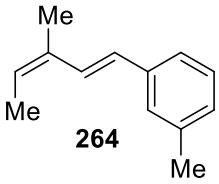
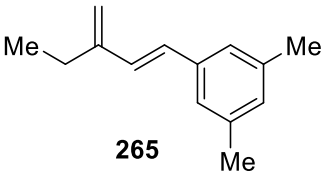
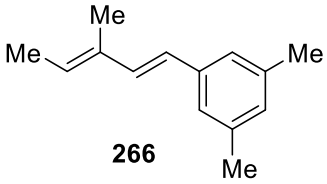
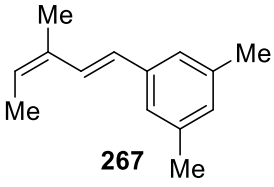
	 **149** 98%  **256** 98%  **257** 89%
	 **258** 51%  **162** 98%  **259** 88%  **260** 85%  **261** 98%  **163** 73%
	 **262** E/Z 1:1 [67%]
247	 **167**  **263**  **264** 94%= [**167** 58%, and 36% for **263** and **264** =4:2:1]
248	 **265** 52%  **266** 24%  **267** 21%

Table 15 shows the scope of the rearrangement with a variety of allenes from (table 12). The cyclohexyl allenes group rearranged to the corresponding dienes in moderate to isolated yields giving the 1,3-dienes products **140**, **137**, **1138**, **146** with one exception of naphthyl allene which was failed to furnish its 1,3-diene **141**. In addition, **146** was prepared in moderate yield by exposing the crude of the allene to the rearrangement condition due to their allenes rapid decomposition upon standing. The cyclopentyl, cycloheptyl and cyclooctyl allenes **149**, **256**, **257** could be rearranged in excellent isolated yields giving 98%, 98%, and 89% repectively. The acyclic allenes could also be rearranged to their 1,3-dienes products **258**, **162**, **259**, **260**, **261**, and **163**, respectively due to their difference of the activity of the aryl groups which was the electron rich corresponding allene gave 51% of diene **258** whereas, the performance of relatively electron poor corresponding allene that gave the anticipated 1,3-diene **261** in 98% yield. This later result suggests to the both electron-rich and electron-deficient aryl allenes perform well in this rearrangement in contrast to the acid mediated processes in direct preparation of 1,3-diene for example product **140** prepared by direct procedure in 60% whereas rearranged in 76% in addition compound **145** prepared in 70% where as a product **261** which is has same aryl group rearranged in 98%. The 1,1-dimethyl diaryl allene **252** could also be rearranged under these conditions, giving its 1,3-diene **262** as a 1:1 mixture of *E*/*Z* geometric isomers and in an isolated yield of 67%.

The 1-aryl-3-methyl-1,2-pentadiene **247** was rearranged to corresponding dienes **167**, **263**, and **264** in excellent yield of 94% as a total percentage of three products. The thermodynamically stable *E*,*E*-1,3-diene **147** formed 58% of the total whereas **263** and **264** was isolated as a mixture (2 : 1) respectively of 36% for both product, the stereochemistry of the compounds was confirmed by the NOE study, in addition the 3,5-dimethyl-1,2-pentadiene **248** was rearranged to the corresponding 1,3-dienes **265**, **266**, and **267** in 97% as a total percentage result and we were able to isolate **265** in 52% yield, whereas the **266** and **267** remained as a mixture in 45% isolated yield.

3.3 Mechanism of the rearrangement

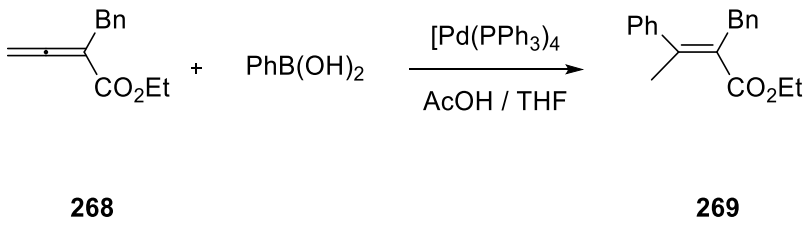
With scope of the rearrangement determined, the mechanism of this rearrangement deserved further attention. In section 3.1.1., we had already demonstrated that Pd(0) and boric acid was vital for the rearrangement. the identification any key palladium allyl intermediates that may provide

further evidence for our mechanism shown in section 3.1.1.

To achieve this, we turned to *in situ* monitoring of the rearrangement by way of ESI-MS and the use of direct sample loop injection. In most cases the organometallic intermediates could appear at different time and be consumed rapidly throughout the chemical reactions. To detect these intermediates mass spectrometry (MS) has been used as a molecule analysis since development of the electrospray ionization (ESI) techniques. ESI-MS (electrospray ionization mass spectrometry) is analytical technique used to find the mass of the compounds according of their mass / charge (m/z) ratio. After injected the compounds of our interest in a continues fluid stream firstly, the ionization part of the devise ionized the compound into positive or negative charge by using high voltage field this technical required a low concentration of the compound in the solution (10^{-3} to 10^{-6} M). At this part the molecules hold same charge of the field are encouraging to migrate to the second part of the device whereas, the different charge molecules are set down. The second step is started when ions reaches to the mass analyzer detector according to their mass and charge. After this step the analyzer generate signals belong to the mass of these ions and these signals recorded by a computer system. The computer has a specific software can convert these signals to useable graph as a mass spectrum showing the relative abundance of the signals versus m/z.[96]

ESI-MS was first reported in 1984 for small molecules ions by John Fenn and co-workers[97] who won the Nobel prize in 2002 for his work in mass spectrometry. This techniques was use as a tool to prove the mechanism for some name reactions since it has been clearly demonstrated used for example in 2004 to probe the intermediates of the mechanisms the Heck[98] and Baylis-Hillman[99] reactions.

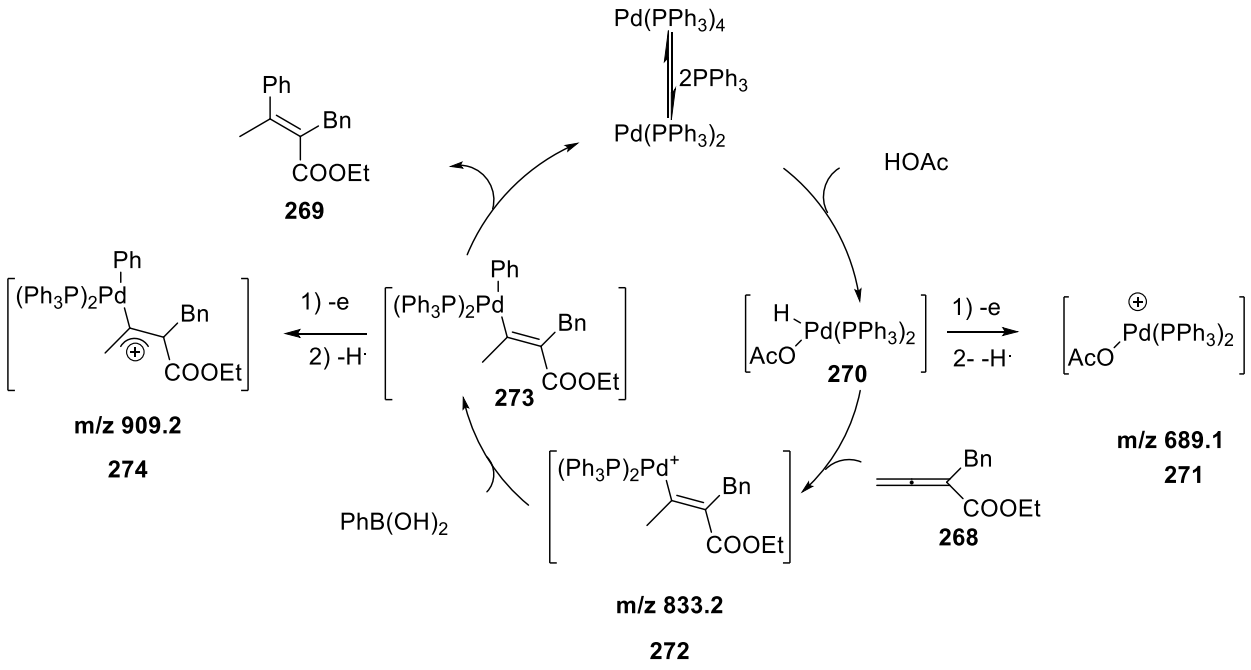
More relevant to our study, in 2005 Ma and co-workers probed the mechanism of the addition of organoboronic acids to terminal allenes in presence of palladium (0) catalyst (scheme 55).[100]



268 **269**

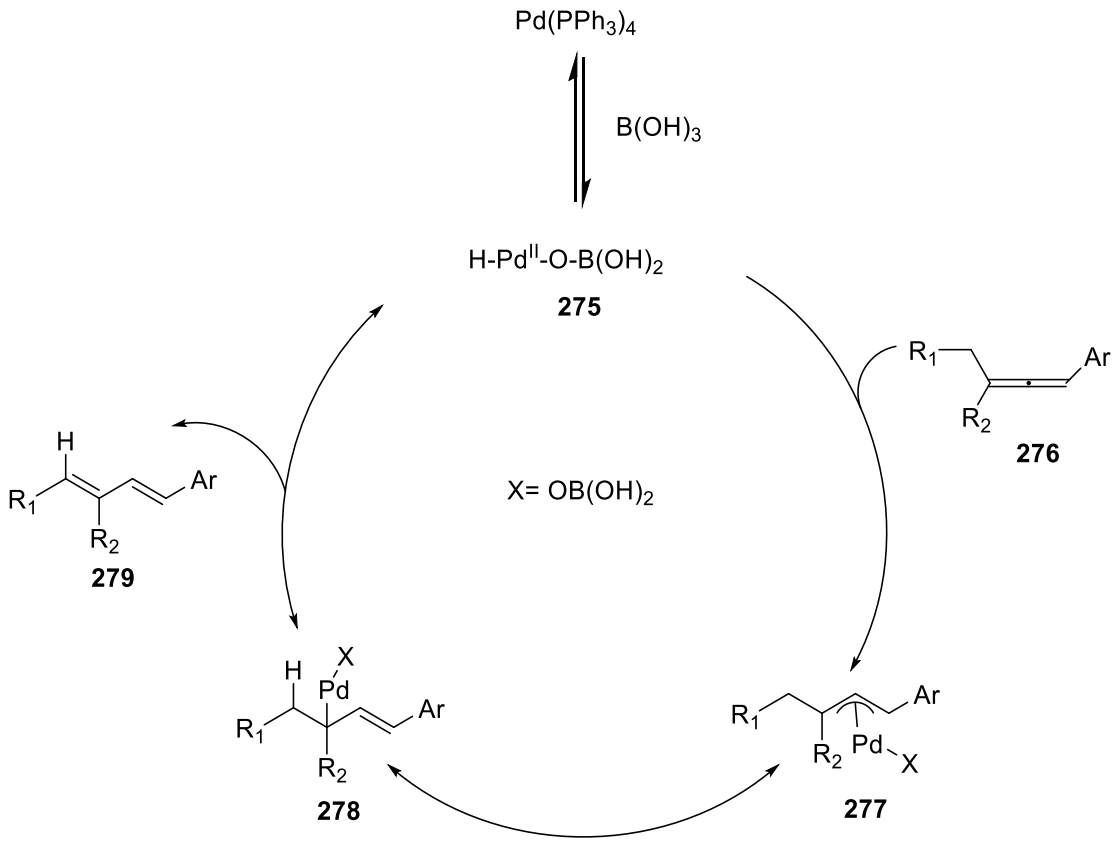
Scheme 55: Addition of organoboronic acids to terminal allene

In thus study they were able to positively identify key complexes supporting their postulated mechanism (scheme 56).[100] After running the reaction, a sample of 20 µL after 3 minutes was diluted with 80 µL of methanol and injected into the ESI unit of the mass spectrometer. The spectra accurately indicated of existence of intermediate ions **271** and **272**. After 2 hours another sample was tested to detect and characterized the ions **271** and **274** which was suggested formed during the ESI process including elimination of H^+.



Scheme 56: Proposed mechanism of palladium catalyzed addition

To probe the mechanism of our rearrangement of inactivated allenes to 1,3- dienes, our general proposed mechanism is illustrated in (scheme 57).

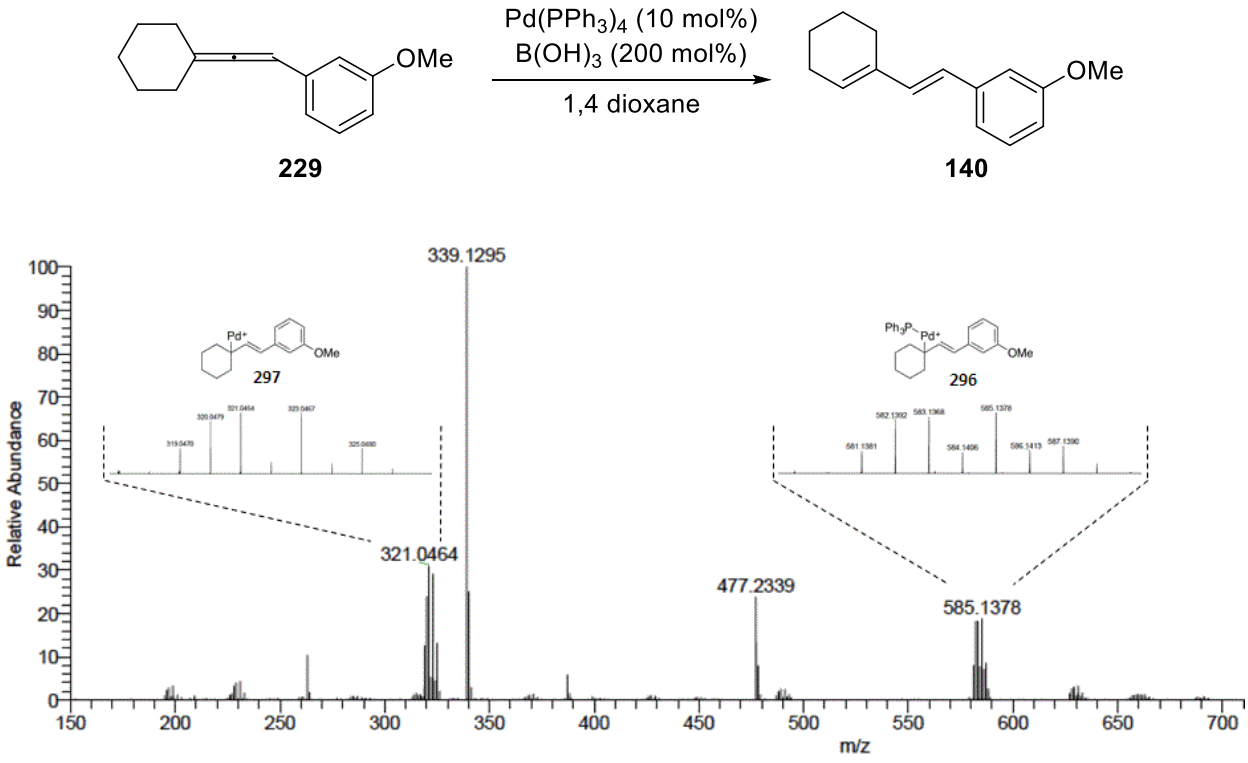


Scheme 57: general plausible mechanism for $Pd^0/B(OH)_3$ mediate allene to 1,3-diene

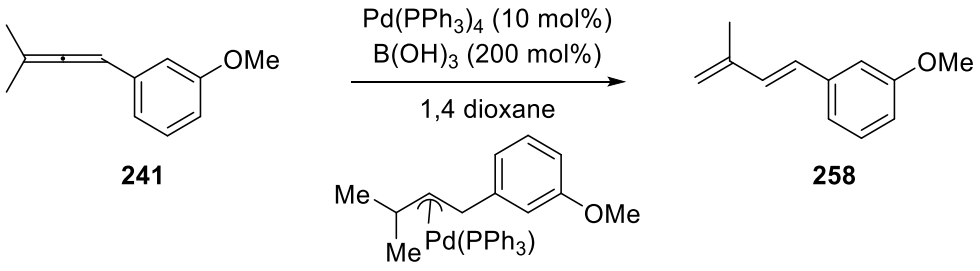
The mechanism started by the reported oxidation of the Pd^0 by boric acid to form hydropalladium species **275** $H\text{-}Pd^{II}\text{-}OB(OH)_2$[81] after that the hydropalladium complex adds to the allene unit **276** to form the π-allylpalladium complex **277,** after that hydropalladium complex **278** undergoes β-hydride elimination to give the 1,3-diene and to form **275** again.[95, 101]

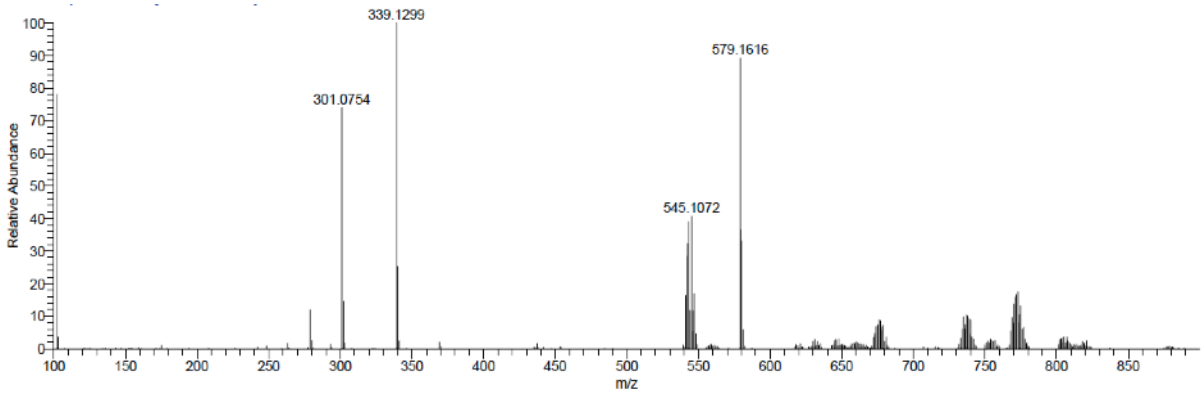
The method we used for ESI-MS analysis was to setup the reaction with a continuous loop injection, as this enabled us to do multiple measurements at nominated times quickly and without diluting the sample with methanol. We selected to two arylallenes **229** and **241** as substrates under the same rearrangement condition, where the substitution on the aryl ring on each allene was selected to ensure adequate ionization, *via* the use of a protonatable group. However, to reduce the electron-donating ability of each allene, and to impede any adventitious protonation, a *meta*-substitution pattern was also selected. Firstly, the rearrangement of allene **229** was monitored by direct sample loop and flow injection analysis by ESI-HRMS. After 10 minutes, we were able to

intercept, detect, and characterize a number of significant palladium complexes. Two distinct complexes can be observed which correspond well to the π-allylpalladium complex **277** described in (Scheme 58), complex **280** where one phosphine is attached to the Pd centre (*m*/*z* 585.1378; calcd for $[C_{33}H_{34}OP^{108}Pd]^+$: *m*/*z* 585.1386) and complex **281** (*m*/*z* 323.0467; calcd for $[C_{15}H_{19}O^{108}Pd]^+$: *m*/*z* 323.0470) where there are no phosphines attached to the Pd centre (Scheme 58). To further support the formation of the π-allylpalladium complex **277** shown in (Scheme 59), allene **24** was also analysed where an ion corresponding to complex **282** where one phosphine is attached to the Pd centre (*m*/*z* 545.1072; calcd for $[C_{30}H_{30}OP^{108}Pd]^+$: *m*/*z* 545.1072) was observed (Scheme 59).



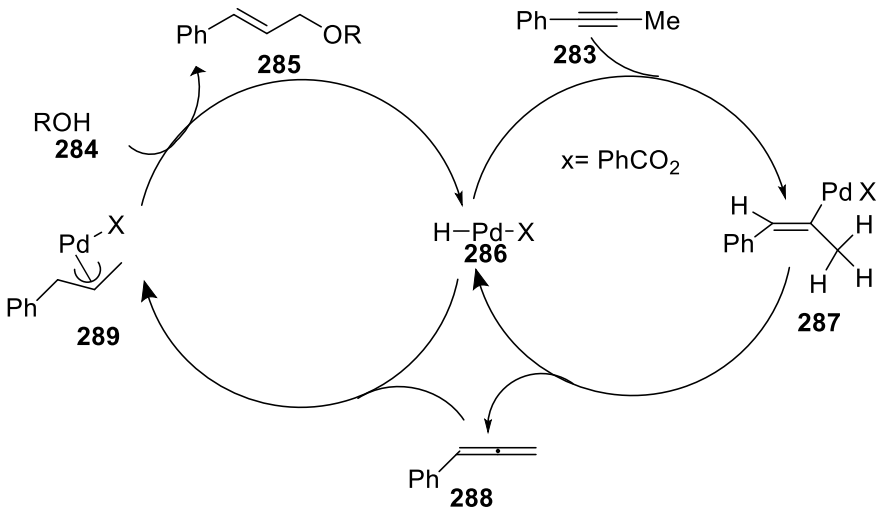
Scheme 58: The detected palladium complexes by direct sample loop





Scheme 59: Further support of detected palladium complexes

The result of MS study gave accurate and strong evidence of formation of π-allylpalladium complex and this can only have resulted from the addition of Pd^{II} to the allene as described by Yamamoto in 2001 (scheme 60),[95] and applied by Ma and co-worker; but in their reactions case they used a terminal allene and proposed the intermediate terminal allene, respectively.



Scheme 60: Yamamotos proposed mechanism

3.4 Synthesis of natural products compounds

Having developed a novel method for the isomerization of unactivated allenes to 1,3-dienes, we next set out to apply this methodology.

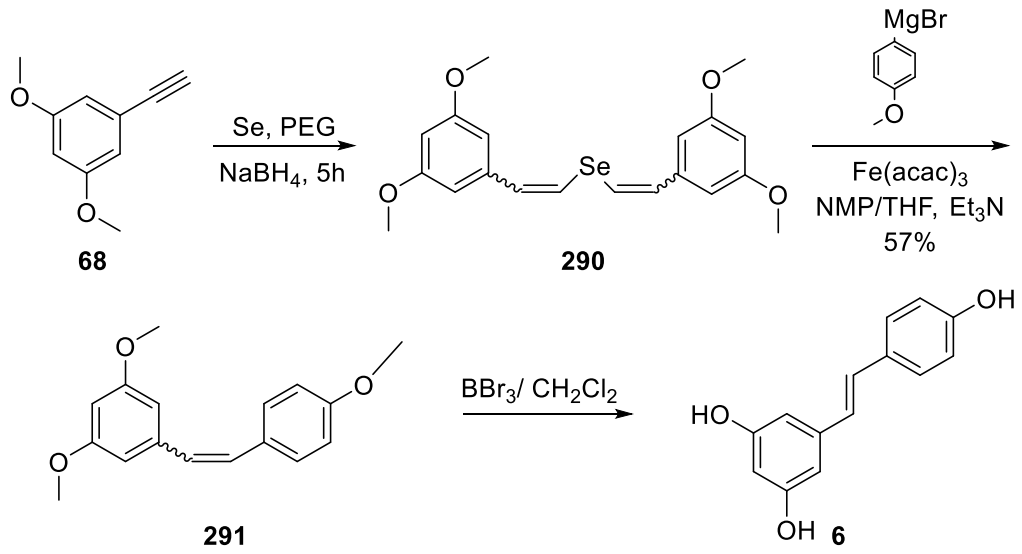
Phytoalexins are class of compounds produced by plants as a reply when the plants is infected. Polyphenols compounds are part of phytoalexins which play a role in the plant defense against fungal and other microbial pathogens. As a result, in recent years there is an increasing interest in preparation of these bioactive compounds.[36]

3.4.1. *Trans*-resveratrol

Resveratrol is a poly-phenol compound produce in the plant as a defence against injury or infection by bacteria or fungi, and is found in the skin grapes, blueberries raspberries and mulberries. Resveratrol is suggested to have many useful health effects, including antioxidant, anti–inflammatory, anti–proliferative, proapoptotic, and anti–angiogenic.[102]

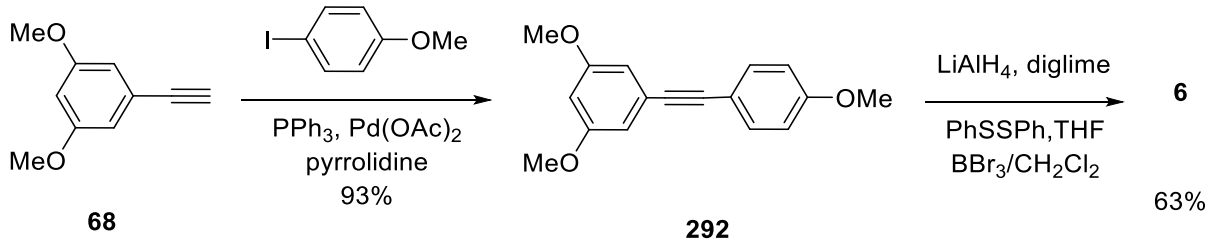
3.4.1.1 Review recent synthesise of trans-resveratrol

In 2017 Perin proposed a simple way to synthesis resveratrol by hydroselenation of dimethoxy phenyl acetylene **68** to form divinyl selenides **290** that was reacted with methoxy phenyl magnesium bromide in the presence of an Fe-catalyst to afford resveratrol trimethyl ether **291** in 57% which can be deprotected of the ether groups to give the target **6** (scheme 61).[103]



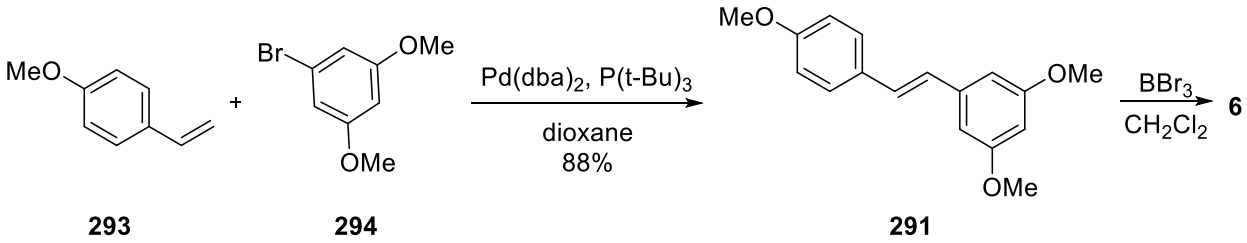
Scheme 61: Synthesis of resveratrol.

In 2015 Francisco prepared resveratrol by using Sonogashira cross coupling of dimethoxy phenyl acetylene **68** with 4-iodoanisole to form **292** then in three steps reduction, isomerization and deprotection to resveratrol **6** in 63% as overall yield (scheme 62).[104]



Scheme 62: Resveratrol by Sonogashira cross coupling

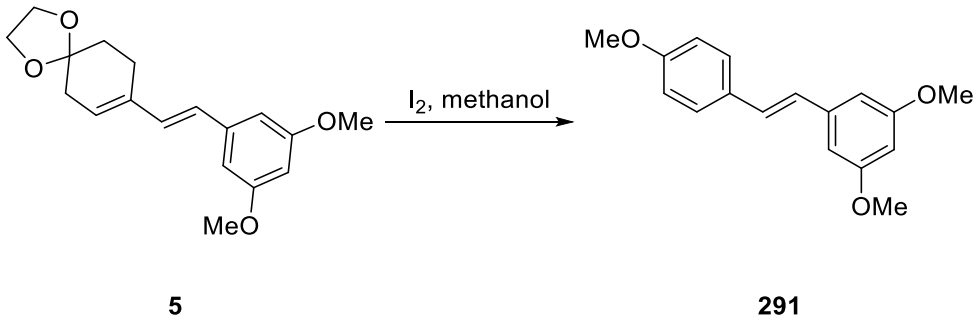
In 2009 Takashi used a Heck reaction to prepared resveratrol from dimethoxy bromobenzene **294** by cross coupling with vinylanisole **293** to form **291** in 88%**,** this was then deprotected to give resveratrol **6** (Scheme 63).[105]



Scheme 63: Heck reaction to resveratrol

3.4.1.2 Synthesis of *trans*-resveratrol

The synthesis of *trans*-resveratrol from one of our 1,3-dienes **5** section (3.1.1.) by aromatization with iodine in methanol to give **291** (Scheme 64); [106] optimisation of this aromatization step is set out in Table 16.



Scheme 64: Aromatization with iodine

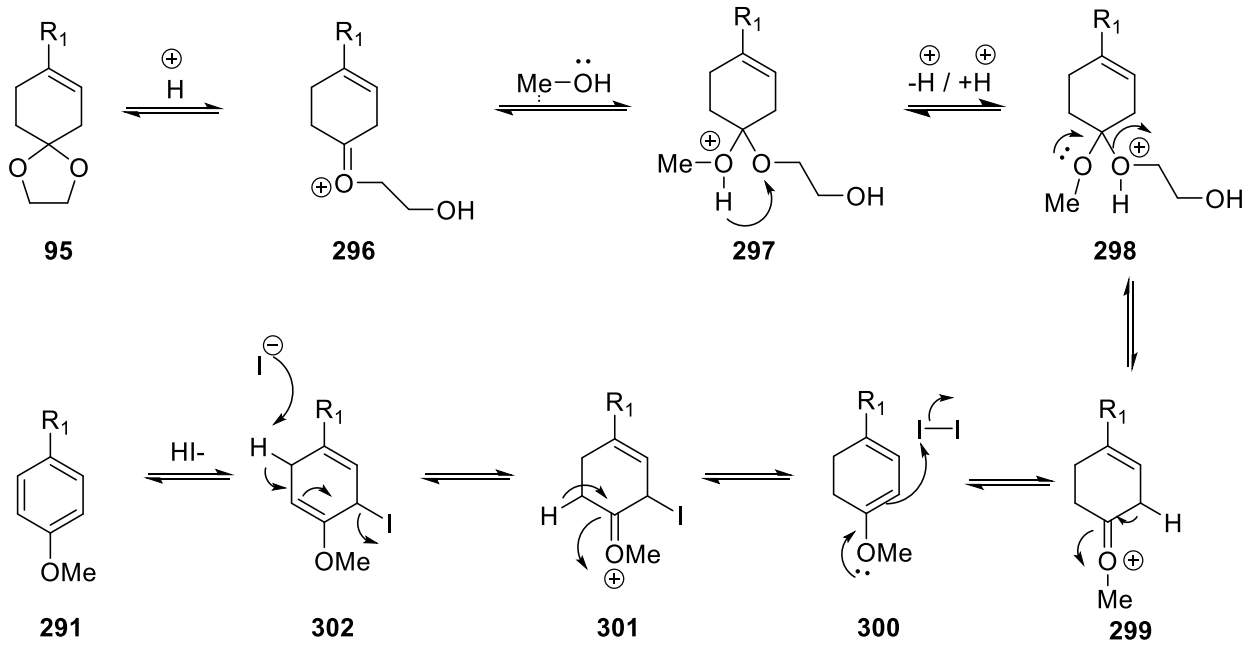
Table 16: Optimizing the aromatizing condition.[a]

Entry	MeOH /mL	Condition	Temperature °C	Time/h	Result (isolated) 291
1	1.5	stirrer	r.t.	4	30%
2	1.5	stirrer	r.t	3	0%
3	1.5	reflux	68	Overnight	0%
4	1.5	reflux	68	40 minutes	0%
5	1	stirrer	r.t.	3.5	44%
6	1	stirrer	r.t.	4.5	13%

[a]The reaction was carried out under a N_2 atmosphere using 50 mg of the diene **5** with one equivalent of iodine.

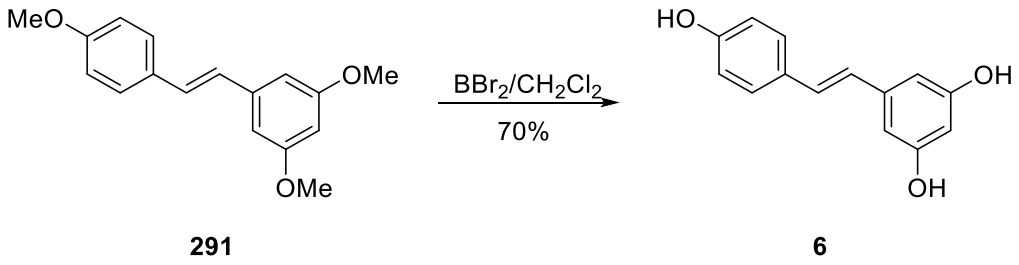
Table 16 shows that by using 1.5 mL of methanol and stirring for 4 hours we obtained **291** in a isolated yield of 30% (entry 1). We reduced the time to 3 hours and this yielded none of the desired compound (entry 2). In entry 3 and 4 we increased the temperature of the reaction and stirred the reaction overnight and for 40 minutes, but this also gave none of **291**. In entry 5 and 6 we used 1.0 mL of methanol and stir the reactions for 3.5 hour and 4.5 hour respectively, to get 44% and 13% yield, respectively, therefore the ideal conditions are described in entry 5.

The proposed mechanism of the reaction[107] is described in (Scheme 65);[108] and shows in general that iodine is able to convert the ketal group to methoxy group and aromatize the cyclohexyl ring due to his ability to generate hydroiodic acid in the reaction condition.



Scheme 65: Proposed mechanism of aromatization.

The last step of resveratrol synthesis was deprotection of **291** by using boron tribromide in dichloromethane to furnish *trans*-resveratrol **6** in 70% yield (scheme 66), the overall yield was 31%. **6** was characterize by ^{1}H NMR with the data in agreement with the literature.[109]

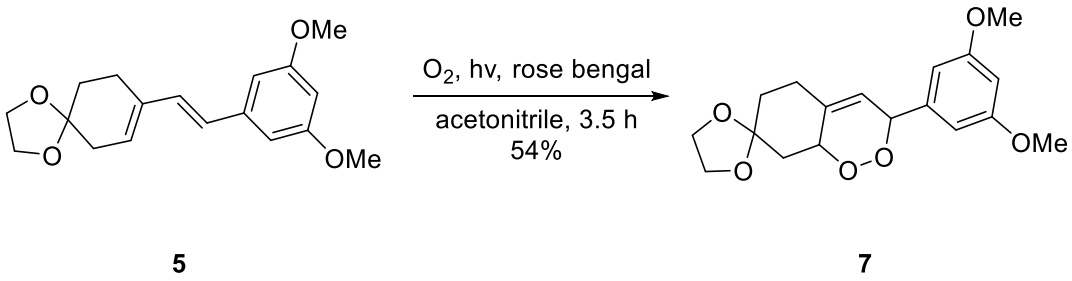


Scheme 66: Deprotection of the methoxy group

3.4.2 Synthesis of Moracin M

The same diene **5** was used to prepare moracin M in four steps starting with a singlet oxygen [2 + 4]-addition to form the endoperoxide **7** which was characterized by ^{1}H NMR with the three signals

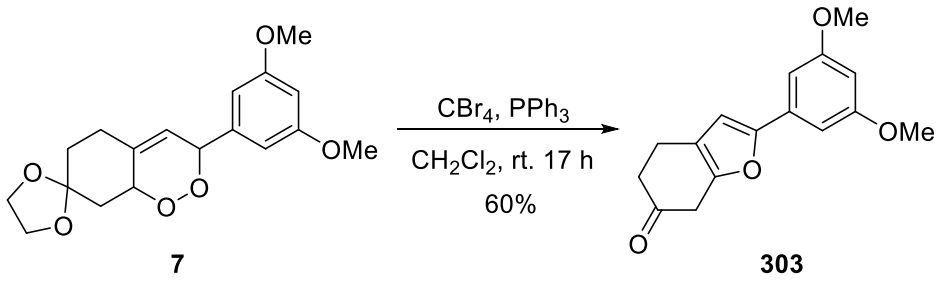
of the diene at 6.39, 6.35 and 5.78 ppm absent and appearance of three new signals at 5.81, 5.31, 4.77 ppm, due to respectively (scheme 67).[110]



5 **7**

Scheme 67: Addition of singlet oxygen

The next step was applying the Appel type dehydration of the endoperoxide to form the furan, that had been successfully optimized by our group.[19] After we applied this reaction we found that the ketal group of compounds **7** had deprotected to reveal the ketone **303** (scheme 68). Fortunately, this product proved crystalline and we were able to get single crystal analysis to definitively assign its structure (figure 13).



7 **303**

Scheme 68: Appel type dehydration

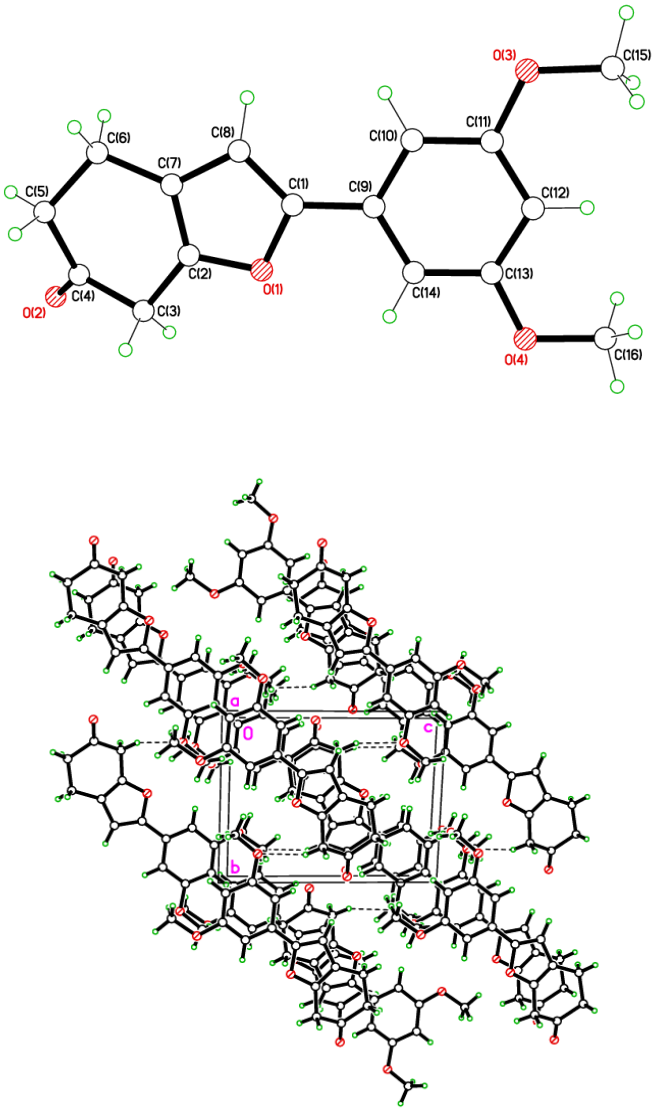
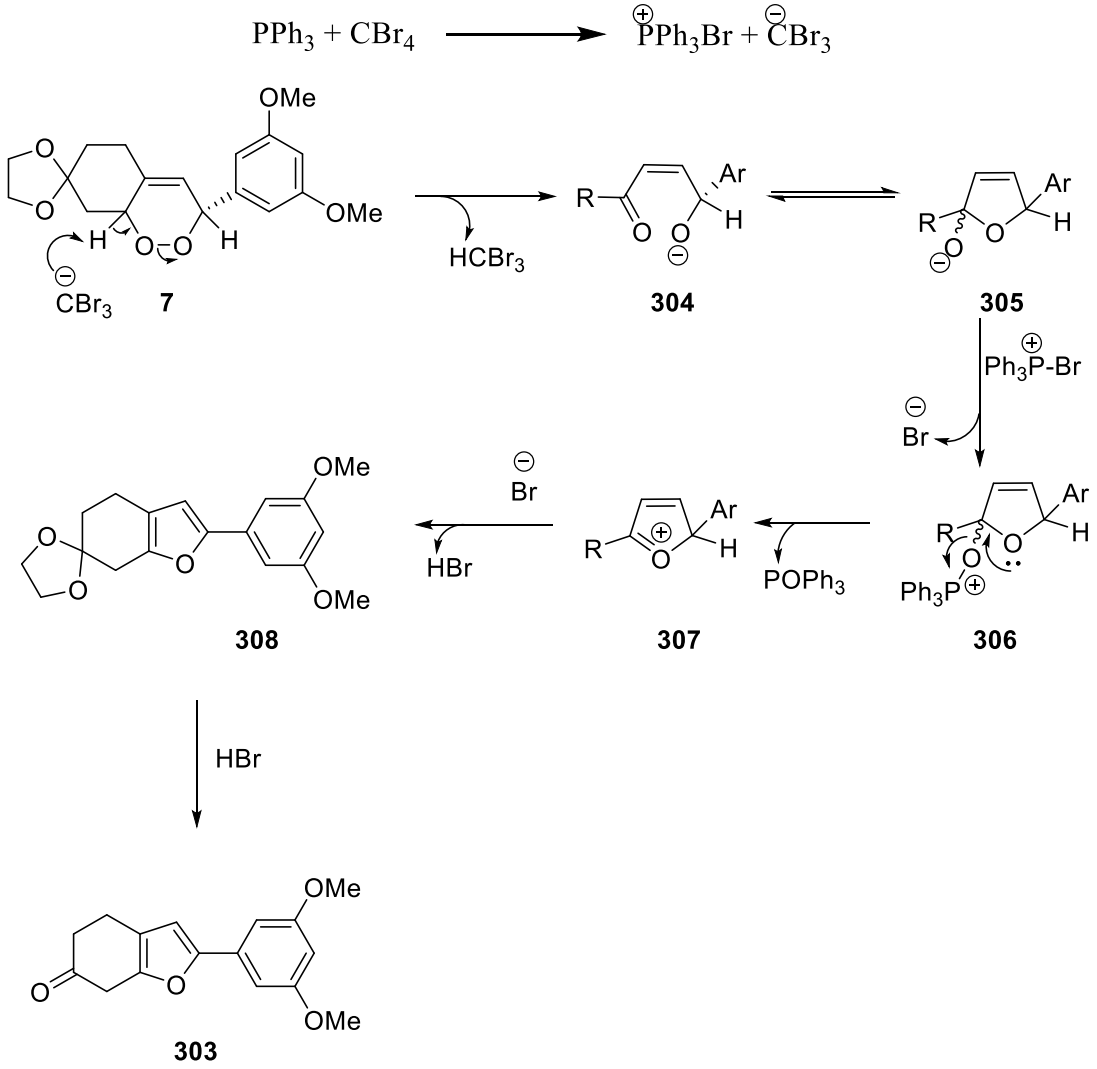


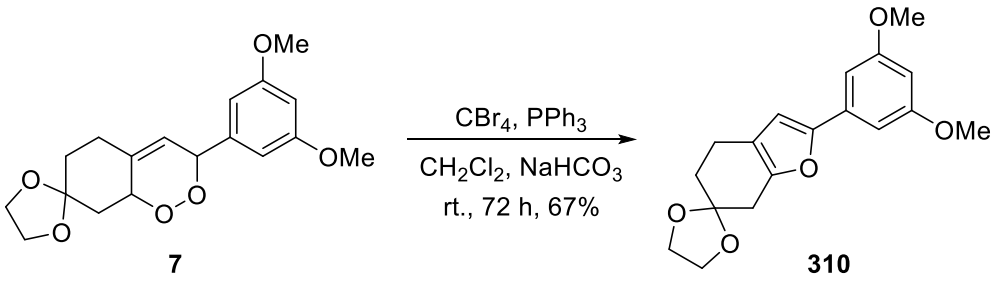
Figure 13: Crystal structure of compound 303

The mechanism of this dehydration is described elsewhere, however its application to the formation of **303** is shown in (Scheme 69).[19] Kornblum De LaMare rearrangement of **304** is promoted by $^{-}CBr_3$, leading to the resonance form **305**. This undergoes PPh_3 mediated dehydration giving **307**, that subsequently aromatises to give **308**. Unfortunately, the residual HBr promotes deprotection of **308**, giving the benzofuran **303**.



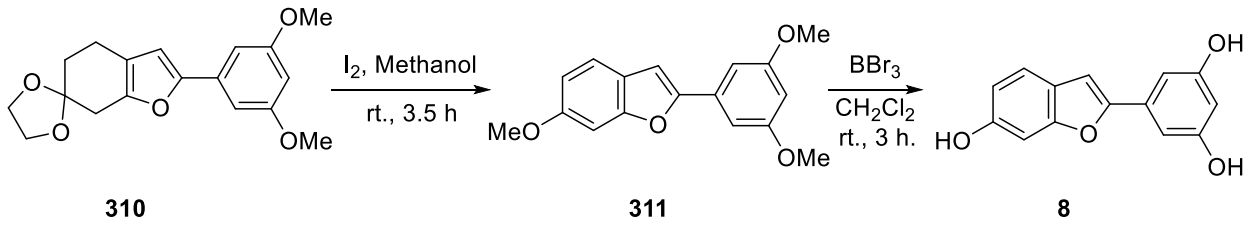
Scheme 69: Mechanism of Appel type reaction

Unfortunately, all attempts to aromatise **303** using the MeOH/I_2 conditions failed, presumably due to the presence of the ketone. Therefore, we modified the dehydration conditions by the introduction of $NaHCO_3$ to neutralize the HBr generated within the Appel reaction. Using these condition, we were able to undertake the dehydration, and keep the acetal intake (scheme 70).



Scheme 70: New applied condition of Apple type reaction

The next step was the aromatization of **310** by iodine in methanol which proceeded well, and the final step was the deprotection of **311** to get Moracin M (**8)** in 75% over these 2-steps (scheme 71)**.**[107] The structure of moracin M was confirmed by ^{1}H NMR spectroscopy with the data corresponding well with those previously reported.

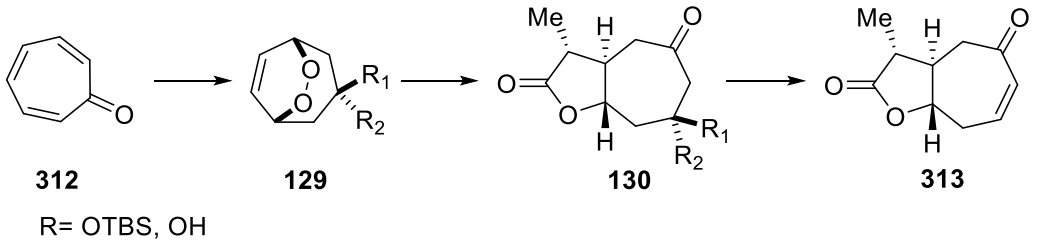


Scheme 71: Aromatization and deprotection

The overall yield of moracin M was 27%, although this percentage seem to be small, but if we compared with previous ways mentioned in review we can found that this percentage better that three of these ways exactly the method of preparation in 2011 used singlet oxygen reaction which has overall percentage 23%.

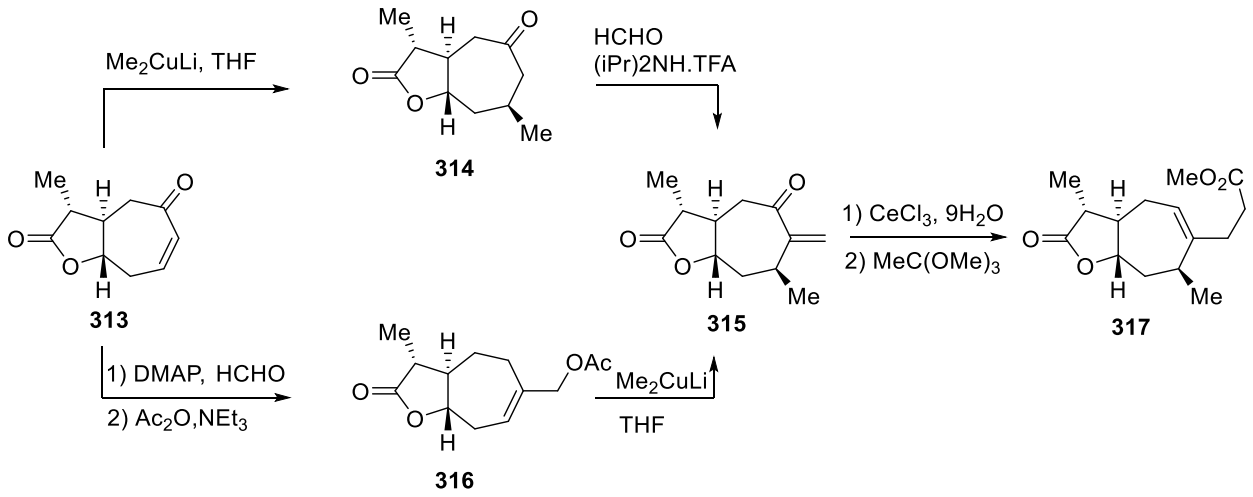
3.5. Synthesis of xanthanolides

The early demonstration of access significant amounts of precursors **130**, in only 5-steps from commercially available sources and in high enantiomeric excess.[17]



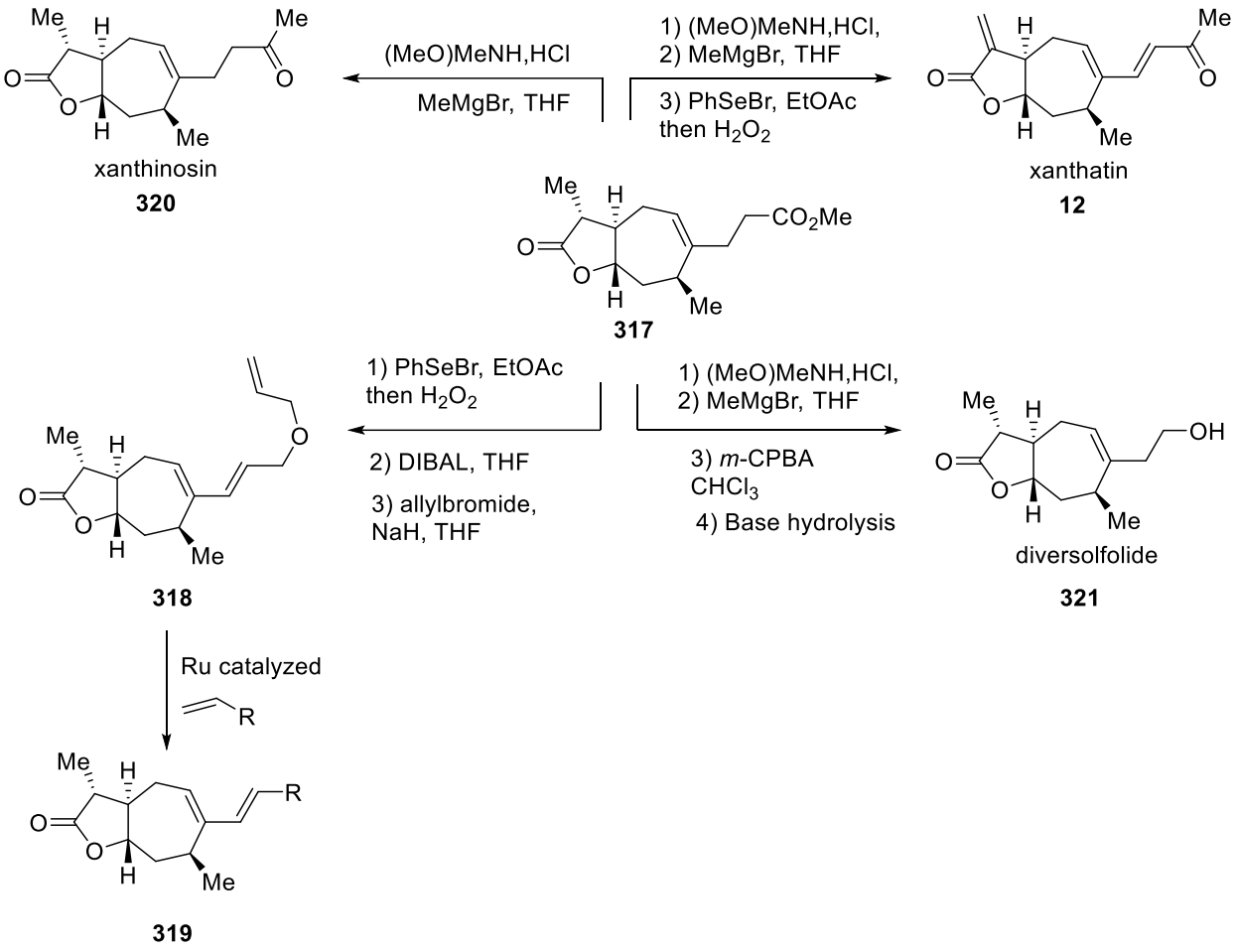
Scheme 72: Synthesis route

Therefore, this part of the project was to complete the synthesis of xanthantin using the approach described below (Scheme 73). the intended to use **130** to deliver the key enone **313**; this was to be achieved by base mediated elimination of OTBS, or by mesylation of the OH group and elimination with base to from **130**.[111] Once in-hand, **313** should be conveniently transformed into the methyl appended exo-methylene enone **315** using two complementary procedures (Scheme 73). Simple treatment of **313** with a methyl cuprate equivalent should deliver **314**, with *ab initio* calculations suggesting that the predominant product should be the diastereoisomer indicated, and subsequent treatment of **314** under the conditions of Connell[112] delivering the exocyclic enone **315**. Alternatively, a Morita-Bayliss-Hillman reaction performed on **313** with formaldehyde,[113] followed by treatment of the product with acetic anhydride should was expected give the acetate **316**, with subsequent treatment with methyl cuprate using the conditions of Yamamoto[114] giving the enone **315**. Unlike previous approaches to this class of compounds our conjugate addition methodology for the introduction of this methyl group allows for other groups (ethyl, propyl, etc.) to be installed therefore allowing the ability to systematically vary this functionality. With enone **315** in hand we could then utilise our existing reported approach to installing the side chain namely, 1,2-reduction under modified Luche reduction conditions giving the allylic alcohol, and treatment with trimethyl giving the ester **317** via a Claisen rearrangement.[115]



Scheme 73: Furnish a side chain at C1.

A total synthesis of xanthatin was to be accomplished *via* functional group manipulation of ester **317**, and installation of the exo-methylene using existing protocols[115] whereas, xanthanosin should be obtained *via* FGI of ester **317** (scheme 74). Alternatively, ester **317** would be transformed into diversifolide *via* chain truncation and a FGI (**317**→ diversifolide) - Target **133**. We also planned also use methyl ester **317** to access other members of this family of natural products. Previous work by the Evans, Shindo, and Tang groups have identified diene target **134** (R = H) also (figure 11) as a key intermediate for synthesising many of the xanthanolide family members.[74,70] Conversion of methyl ester **317** to the **318** can be accomplished by selective reduction, alkylation with allyl bromide generating the relay cross metathesis precursor. Treatment of **318** under ruthenium catalysed metathesis conditions will then give the ruthenium alkylidene intermediate, which in the presence of an external alkene will deliver the cross-metathesis products (**319** and where R = H) - Targets **318** and **319**.[72,116]



Scheme 74: Target products synthesis

3.5.1 Preparation of Cycloendoperoxide :

The approach to the *trans*-xanthanolides required a cyclic 1,3-diene, and with the identified from previous work that three plausible starting 1,3-dienes could be used **322**, **323**, and **324** (figure 14). 1,3-cyclooctadiene **322** is commercially available (and relatively inexpensive) and could be used as a trial substrate; while **323** and **324** can be obtained from relatively cheap tropone.

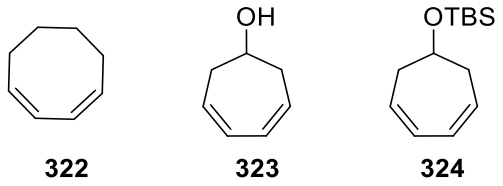
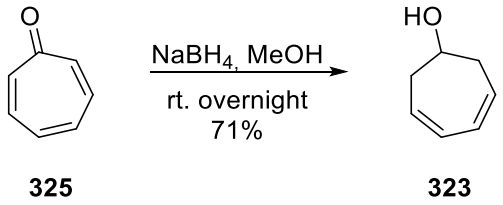


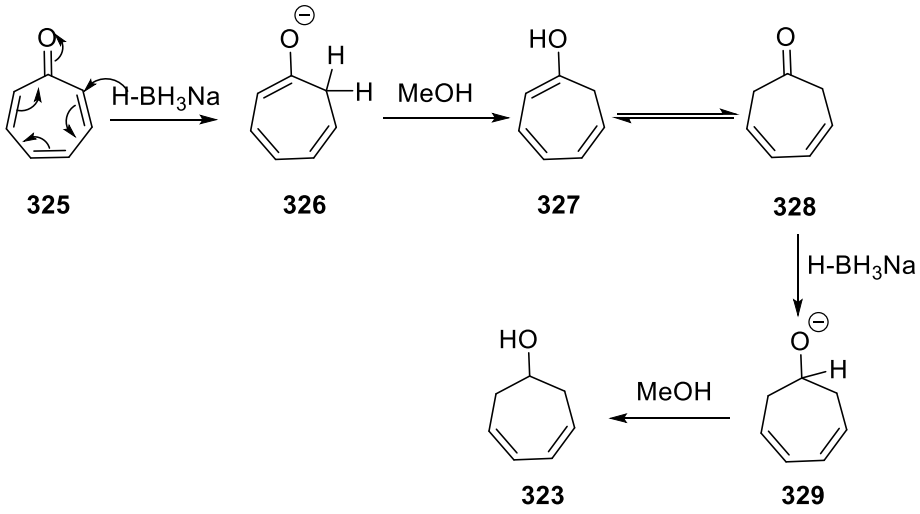
Figure 14: Required 1,3-dienes

To access **325** for the photo oxidation tropone was reduced to 1,3 diene **323** in methanol with $NaBH_4$ (Scheme 75).[117]



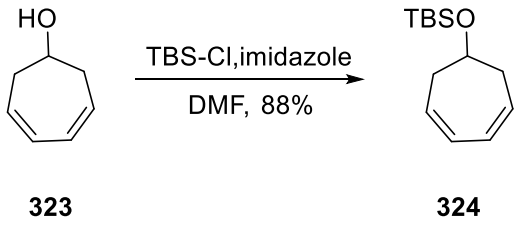
Scheme 75: Reduction of tropone

The mechanism of tropone reduction is described in scheme 74 and utilizes sodium borohydride. Tropone undergoes conjugate reduction to give the ketone **328**, this undergoes further reduction to give the required 1,3-diene **323**.[107]



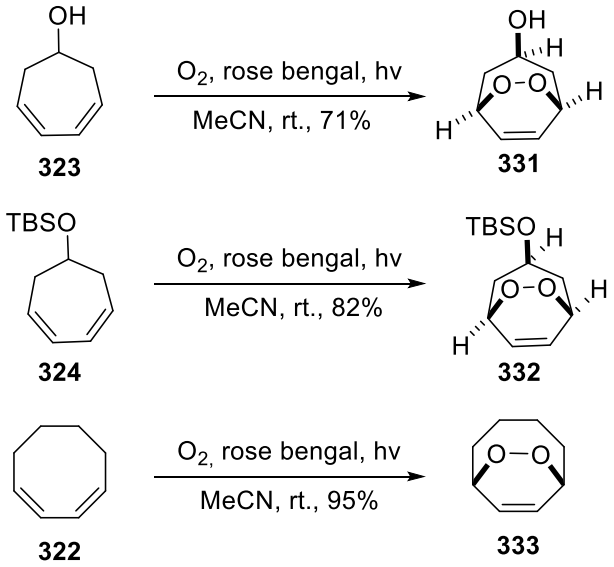
Scheme 76: mechanism of tropone reduction

At this point we kept some of **323** to investigate the preparation of endoperoxide, while the remainder was protected as its TBS-ether using TBSCl, imidazole and DMF to get **324** in 88% (scheme 75). The product was identified by ^{1}H NMR spectra for the two-double bond protons at δ 4.12- 4.01 ppm, respectively and the signals belonging to TBS group at δ 0.09 ppm and 0.07 ppm, respectively.[118]



Scheme 75: protection reaction

All three cyclic 1,3-dienes readily underwent [4+2]-addition using singlet oxygen. The endoperoxide products were formed in good to excellent yields giving **331**, **332**, and **333**, respectively. They were identified by ^{1}H NMR spectroscopy by the appearance of the alkene peaks at δ 6.33 ppm and 6.15 ppm, respectively (scheme 76).[119]

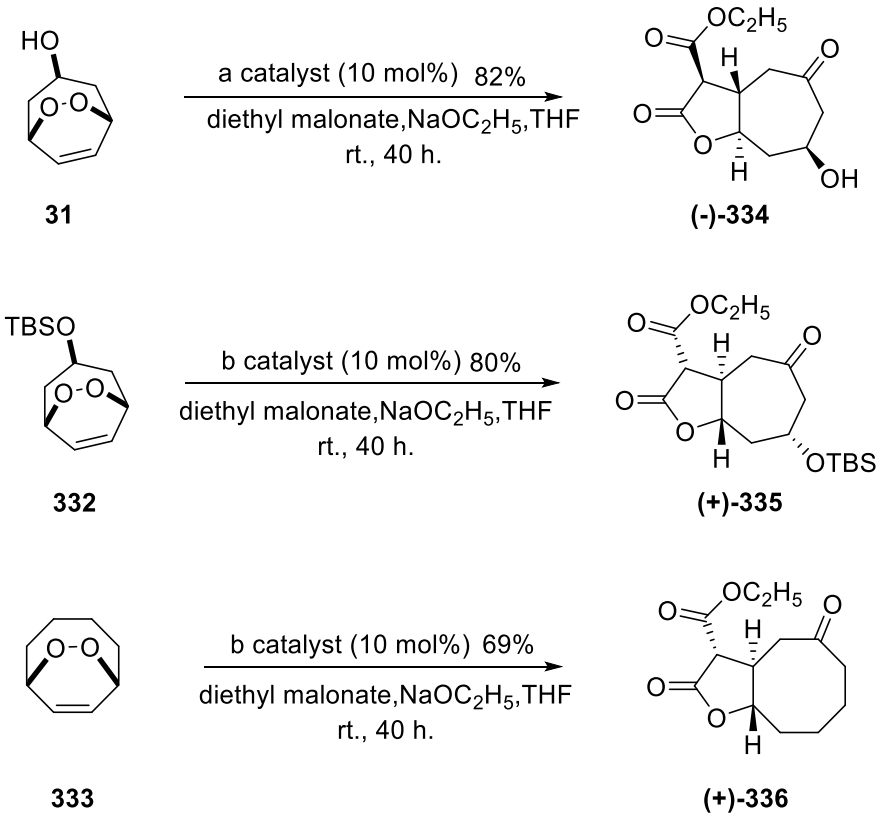


Scheme 76: Preparing endoperoxide

3.5.2 Asymmetric Synthesis of trans-Fused Butyrolactones

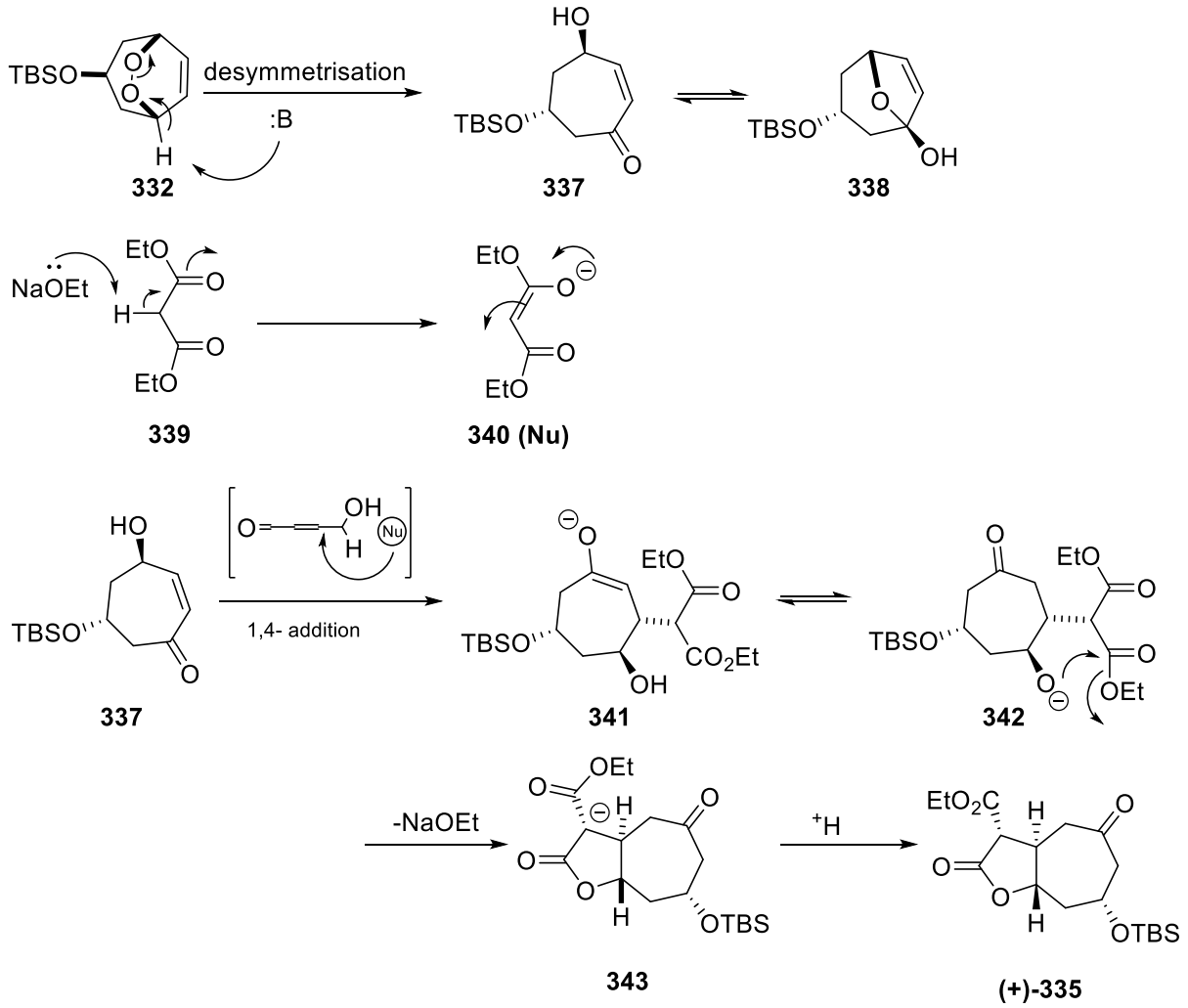
Attention now turned to the desymmetrisation of our endoperoxides to deliver the core *trans*-xanthanolide skeleton shown in (scheme 72). Previous work within the group had delivered a novel desymmetrisation of these cyclicendoperoxides, to give enantioenriched *trans*-fused lactones. This work was based on a previous report by Toste and co-workers,[120] who had used chichona organocatalysts (**A** and **B**)[17] (Scheme 77) to achieve a desymmetrisation of a range of cyclic endoperoxides, furnishing γ-hydroxyenones in high enantionmeric excesses. Our own group were then able to demonstrate that in the presence of a malonate nucleophile, these enones could be converted into their *trans*-lactones in very high yield and acceptable enantiomeric excesses.

Accordingly, endoperoxides **331**, **332** and **333** were each exposed to catalysts **A** or **B** (previously prepared within the group) and sodium diethylmalonate, and this gave enantioenriched *trans*-fused lactones **334**, **335**, and **336** in good isolated yields (scheme 77). The absolute stereochemistry was assigned *via* comparison with our previously disclosed work.[17] The lactones (**334** – **336**), were identified by ^{1}H NMR signals of the proton of the lactone ring at around δ 3.30 ppm and by infrared spectra by the specific absorption belong to carbonyl group of esters at 1735 cm^{-1}; additionally, the physical data matched that already reported.[17]



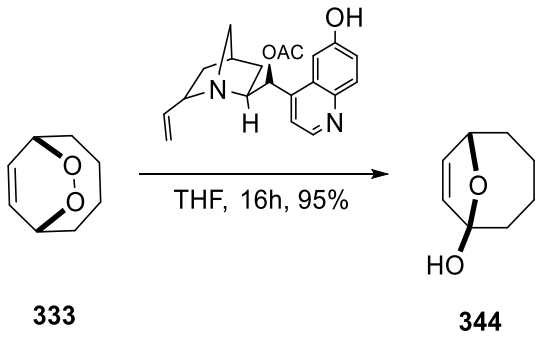
Scheme 77: Synthesis of Butyrolactone

Scheme 78 shows the general mechanism of butyrolactone synthesis. Endoperoxide **332** was desymmetrised *via* Kornblum DeLaMare rearrangement with the cinchona alkaloid to give the hydroxy-enone **337**, the diethyl malonate anion added *anti* to the hydroxyl group to form **340** which was reversible in protic solvent with **342**. The anion **342** then cyclizes to give **343** and finally, the *trans* –fused endoperoxide (+)-**335** was formed by protonation upon work-up.[18]

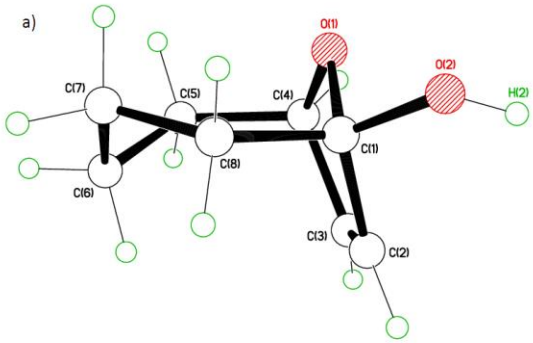


Scheme 78: Mechanism of Butyrolactone Synthesis

To confirm that that the reaction was proceeding through the γ-hydroxy enones we also desymmetrised endoperoxide **333**, in the absence of sodium diethylmalonate (scheme 79). This gave γ-hydroxy enone **344** exclusively, and in high ee. Additionally, **344** proved to be crystalline and suitable crystals for X-ray analysis were obtained, and the structure is shown in (figure 15). Figure 15a clearly shows the structure of **344** and the relative configuration of the two-chiral centers; figure 15b shows the hydrogen bonding of the molecule.



Scheme 79: Desymmetrisation of *meso*-compound 333



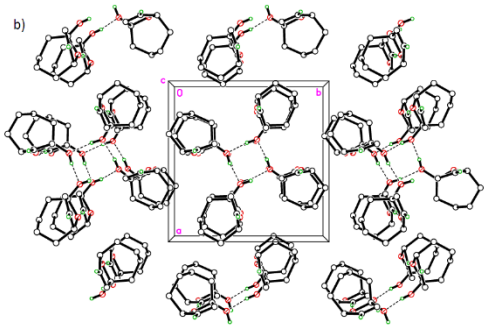
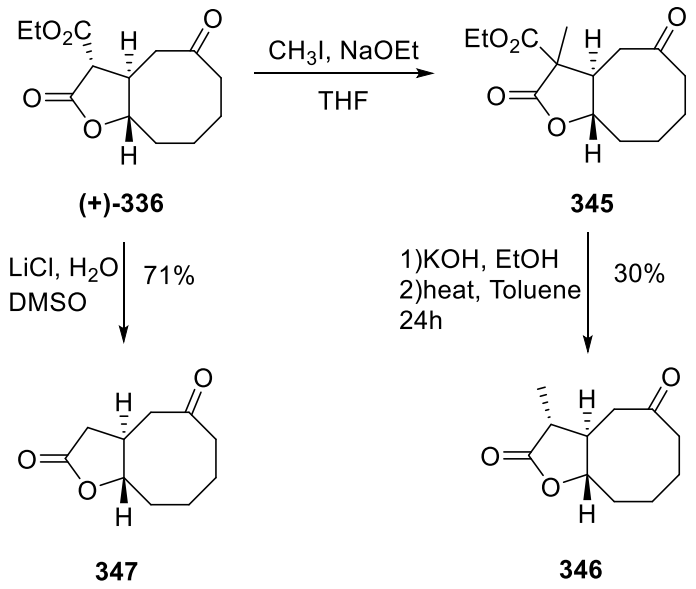


figure 15: Crystal structure of compound (344)

At this point we had three butyrolactones to investigate the total synthesis of the target xanthanolides. Initial work, to establish a viable synthetic route, would be undertaken with **336** due to ease of synthesis, and scalability.

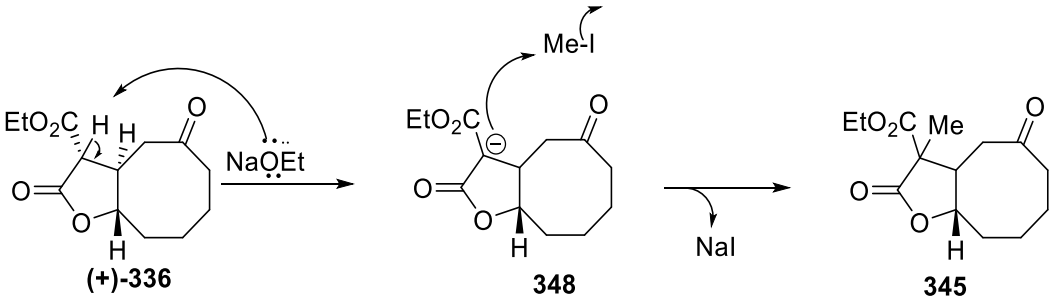
3.5.3 α-Methylation and Decarboxylation of γ- Butyrolactones

After preparation of fused butyrolactone **336** two reactions are needed to give the desired xanthanolides skeleton. Firstly, a methyl group on α-position of the lactone ring is required, and this could be introduced by simple alkyation using methyl iodide with sodium ethoxide in THF. Accordingly, **336** was treated with methyl iodide and sodium methoxide, and this gave **345**, which was subsequently decarboxylated to lactone **346** by saponification of the ester group and then thermal decarboxylation (scheme 80). Unfortunately, the percentage yield of **346** was modest at best, giving **346** in only 30% isolated yield. Additionally, direct Krapcho decarboxylation[121] conditions were applied to **336** giving **347** in 71% isolated yield. The structure of **346** was confirmed by ^{1}H NMR spectroscopy with a methyl group signal at δ 1.30 ppm, whereas compound **347** lacks the signal at δ 3.30 ppm belonging to proton of the lactone ring.



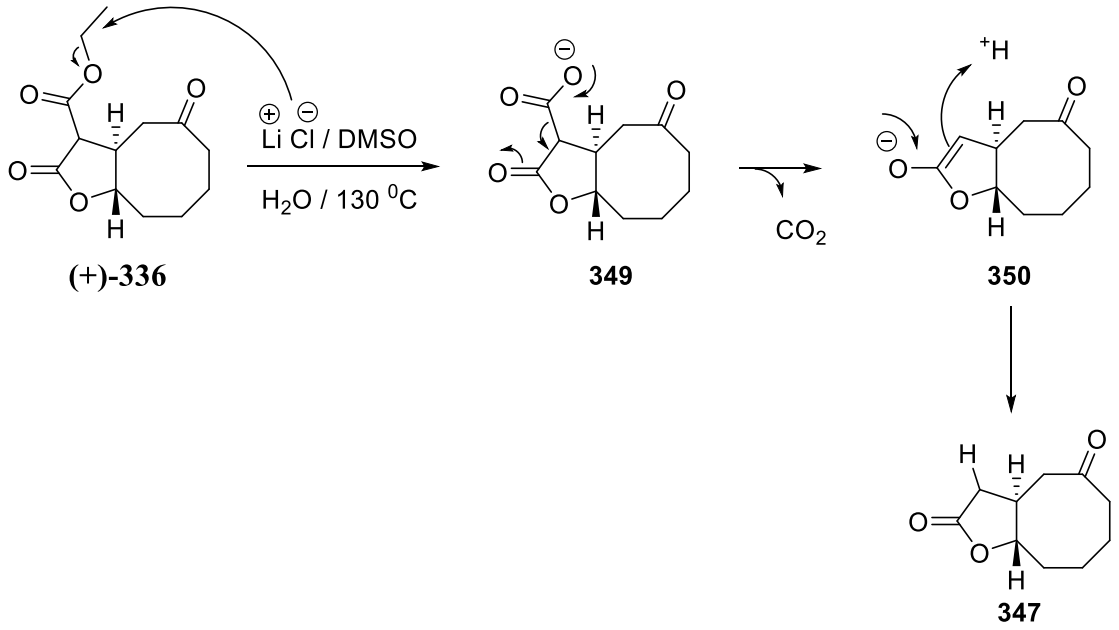
Scheme 80: Decarboxylation of butyrolactone

The mechanism of methylation involved two steps starting with deprotonation of **336** by ethoxide anion to form anion **348**, which is subsequently alkylated with methyl iodide to form **345** (scheme 81).



Scheme 81: mechanism of methylation

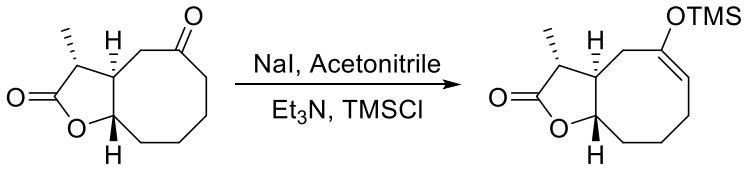
The mechanism of Krapcho decarboxylation [121] involves direct nucleophilic attack of the ethyl group of the ester with chloride ion, followed by decarboxylation to form **350** and finally **347** after protonation (scheme 82)**.**



Scheme 82: Mechanism of Krapcho decarboxylation

3.5.4 Synthesis of butyrolactone α, β-unsaturated ketone.

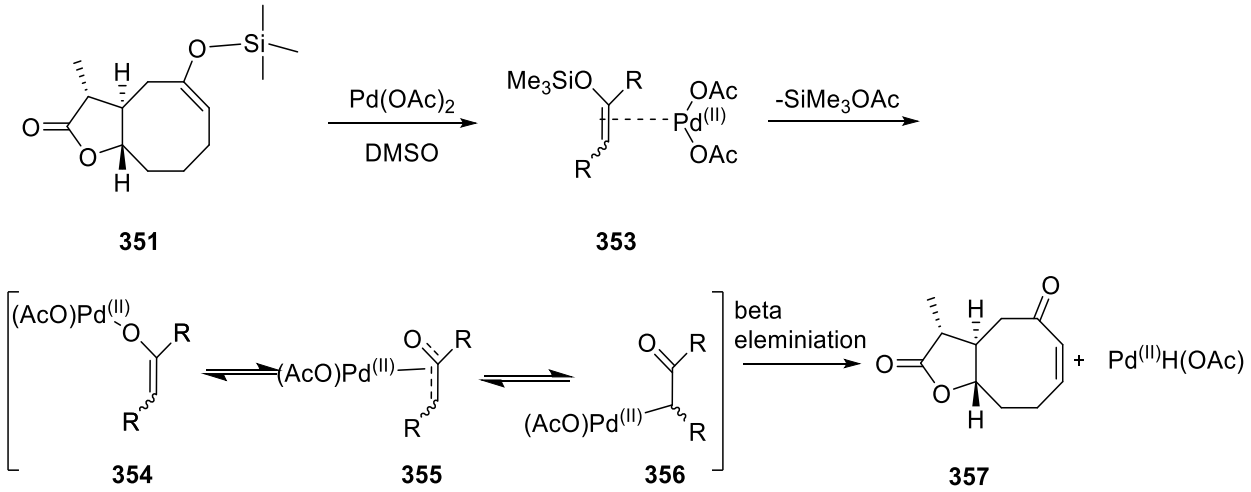
The introduction of the methyl group at C-1, would be accomplished *via* conjugate addition to an enone; and therefore, we needed to prepare an α, β-unsaturated ketone (again we used lactone **346** as is was a readily accessible test substrate). We envisaged this could be introduced by a Saegusa oxidation[122] on a silyl enol ether derived from **346**. Accordingly, **346** was treated under standard enol ether conditions, and this generated the silyl enol ether **351** that was used without purification in the next step (scheme 83).[123]



346 **351**

Scheme 83: Formation of enol ether

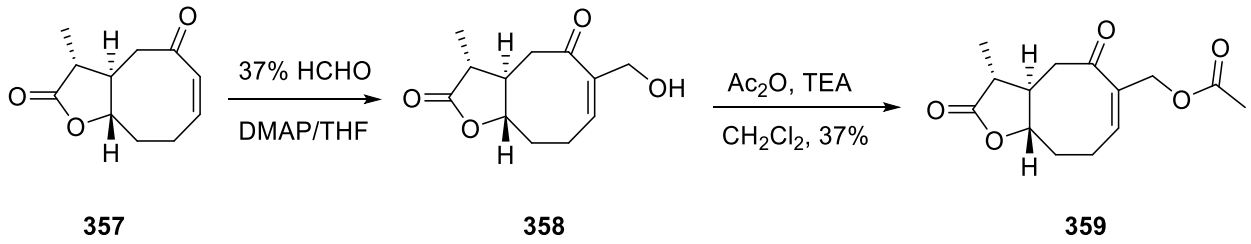
With **351** in hand it was exposed to Saegusa oxidation[122] conditions, the mechanism of which is shown below in (scheme 84)**.** The mechanism of the Saegusa oxidation involves coordination of palladium to the enol olefin **353** followed by loss of the silyl group and formation of an oxoallyl-palladium complex (**354 - 356**). β-hydride elimination to furnish the resultant **357** in 62% over two steps.



Scheme 84: Mechanism of Saegusa oxidation

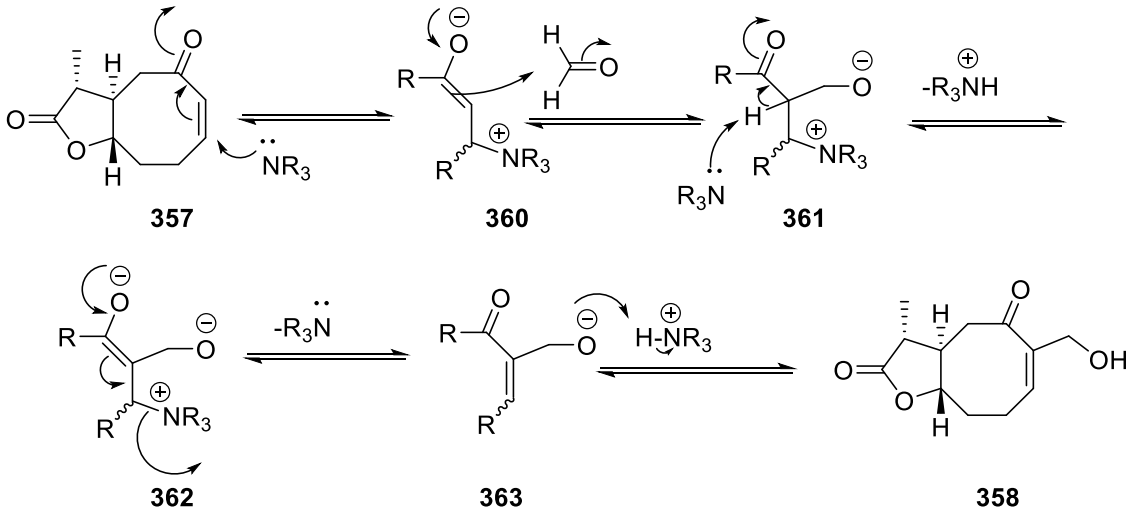
Using these conditions, we were able to obtain **357** in 62% isolated yield, and the product was confirmed by the ^{1}H NMR spectroscopy with enone signals for the new double bond group at δ 6.38 and 6.03 ppm.

As shown in the synthesis plan of xanthanolides in section 2; ideally, we required an exocyclic enone to introduce the side chain at C1. This could, in principle, be introduced *via* a S_N2' reaction of a methyl equivalent to **359**, which in turn can be obtained *via* a Morita-Baylis-Hillman reaction on enone **357**. Consequently, treatment of enone **357** with formaldehyde in presence of DMAP[124] furnished **358** which was subsequently acetylated to give ester **359** in 37% (scheme 85); [125,126] The structure of **359** was confirmed by the ^{1}H NMR spectra with the appearance of a proton signal belonging to the double bond group at δ 5.79 ppm. Unfortunately, due to time constraints, this is as far as the synthesis got with the 8-membered analogue **359**.



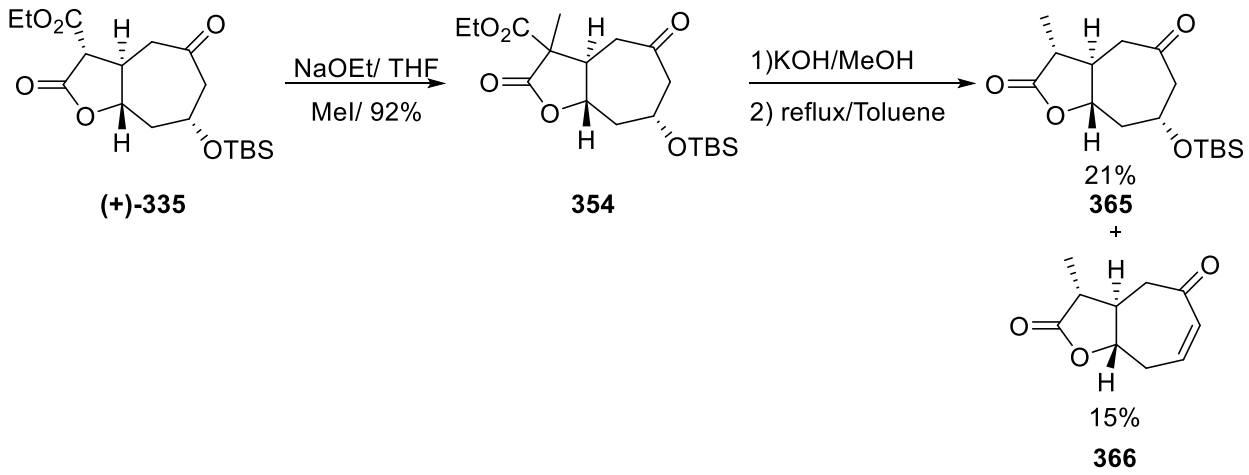
Scheme 85: Baylis Hillman reaction

Scheme 86 describes the mechanism of BH-reaction[124] which starts by the Michael addition of the amine to β-position of the α,β-unsaturated ketone **357** to form zwitterionic enolate **360** which subsequently reacts with the formaldehyde to form another zwitterion **361**. This then subsequently deprotonates to form **362**, which then can eliminate the amine, followed by proton transfer to give **358**.



Scheme 86: Mechanism of Baylis Hillman reaction

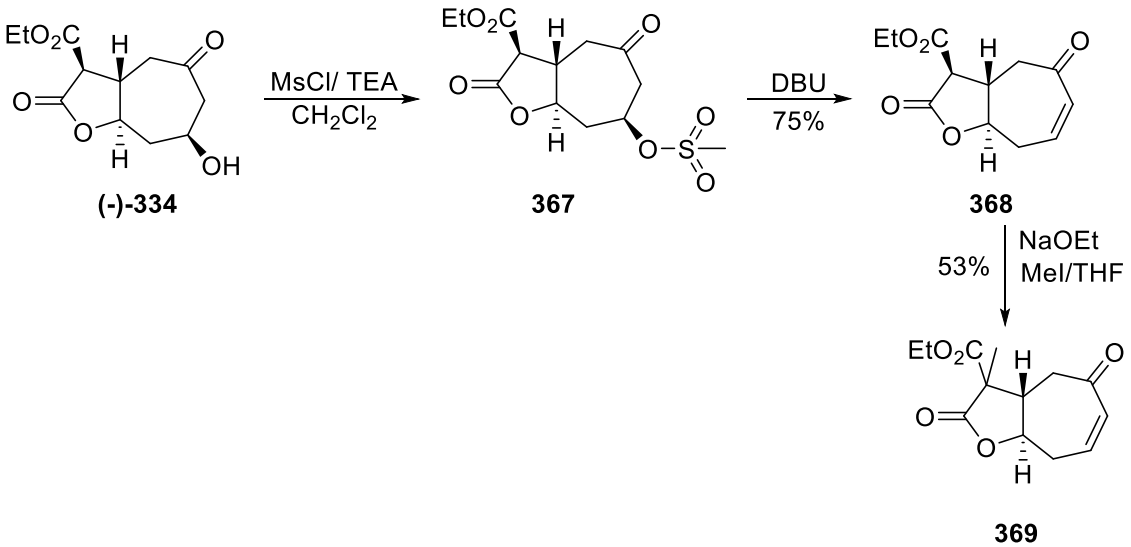
In parallel to the model synthesis work with the 8-membered system, we also explored routes of the synthesis with the 7-membered lactones **334** and **335**. Using the seven-membered OTBS lactone (+)-**335** (scheme 87) we were able to methylate at C-11 using methyl iodide giving **368** in excellent isolated yield of 92%. Decarboxylation of this product was then carried out to give the expected butyrolactone **365** in 21% and as well as the enone **366** in 15% isolated yield. The formation of butyrolactone **366** is a result of base mediated elimination of the OTBS giving the enone. The structure of **366** were confirmed by ^{1}H NMR by the disappearance of the ester group and appearance of the double bond signals at δ 6.34 and 6.09 ppm, respectively. Clearly, this result is significant, as it introduces the methyl group at C-11, as well as the required enone within the 7-memberred ring.



(+)-335 354 365 + 366

Scheme 87: Synthesis of enone 366

In addition, butyrolactone (-)-**334** was converted to α,β-unsaturated ketone **368** in 75% by mesylating of the hydroxyl group in **334** to give **367**,[127] which was simply treated with DBU to give **368**[111] in good isolated yield through an E_1CB mechanism. The next step was the methylation of **368** with methyl iodide to give **369** in 53% which could be simply decarboxylate to give **366**. The structure of **369** was confirmed by the disappearance of the doublet signal belong to one proton at δ 3.35 ppm (Scheme 88).



(-)-334 367 368 369

Scheme 88: Mesylating reaction

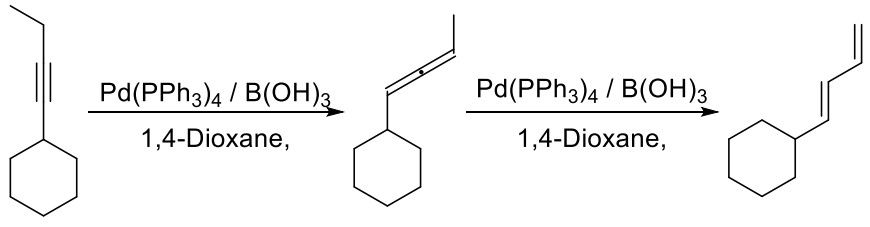
In summary, for the two routes for the 7-membered rings systems we found that **335**, which is formed by three steps in 80% yield, could be converted to **366**, but in a poor 15%, isolated yield. Clearly, this needs further optimization, but does demonstrate that this is a feasible route to deliver the required enone. Alternatively, mesylation and elimination on **334**, does provide the required enone **369**, but further optimization is required to install the methyl group at C-11. Pleasingly, the Bayliss-Hilmann approach for the installation of the methyl group at C-10 looks promising when performed on the 8-membered model system (scheme 85), and it is envisaged this will applied to the 7-membered system once an optimized method has been developed for accessing the desired enone.

4. Conclusion and Future work

In conclusion, a novel approach to construct new and valuable 1,3-dienes from propargyl alcohols using readily available boronic acids in presence of $Pd(PPh_3)_4$ as a catalysis via base-free Suzuki-Miyaura coupling reaction was diveloped. The reaction involves two-steps, firstly the formation of intermediary allene, that is subsequently rearranged *via* a novel Pd(II)-$OB(OH)_2$ complex to give 1,3-dienes. In addition, we optimized a new condition to rearrange unactivated allenes to 1,3-dienes by used of a novel Pd(II)-$OB(OH)_2$. The mechanism of the reactions was proposed that a palladium hydride complex derived from simple $Pd(PPh_3)_4$ and boric acid can rearrange allene to their corresponding 1,3-dienes, and to support this mechanistic hypothesis we proved the existence a key intermediate π-allylpalladium complexes *via* direct sample loop and flow injection analysis by ESI-HRMS.

We prepared 25 1,3-dienes *via* this approach which will increase the store of chemical prepared compounds and it could play an important role in preparation of new compound in the future. Additionally, in-line with the original aims of the thesis, we applied one of our prepared 1,3-diene in a singlet oxygen reaction to synthesise moracin M in only 4-steps.

With reference of the mechanism in (scheme 56)[100] and (scheme 60)[95] we easily found that both of intermediate allenes were terminal or there are no alpha hydrogen and both of them have π-allylpalladium complex. This led us to conclude that the condition of the both reaction are suitable to produce 1,3 diene if we use used another alkyne that can allowed to form 1,3 diene with boric acid, without using alcohol, to let the elimination of β allyl hydropalladium happen instead of coupling reaction in (scheme 60). This conclusion can be used as a future work to optimize a new condition of forming 1,3 dienes from alkynes (Scheme 89).

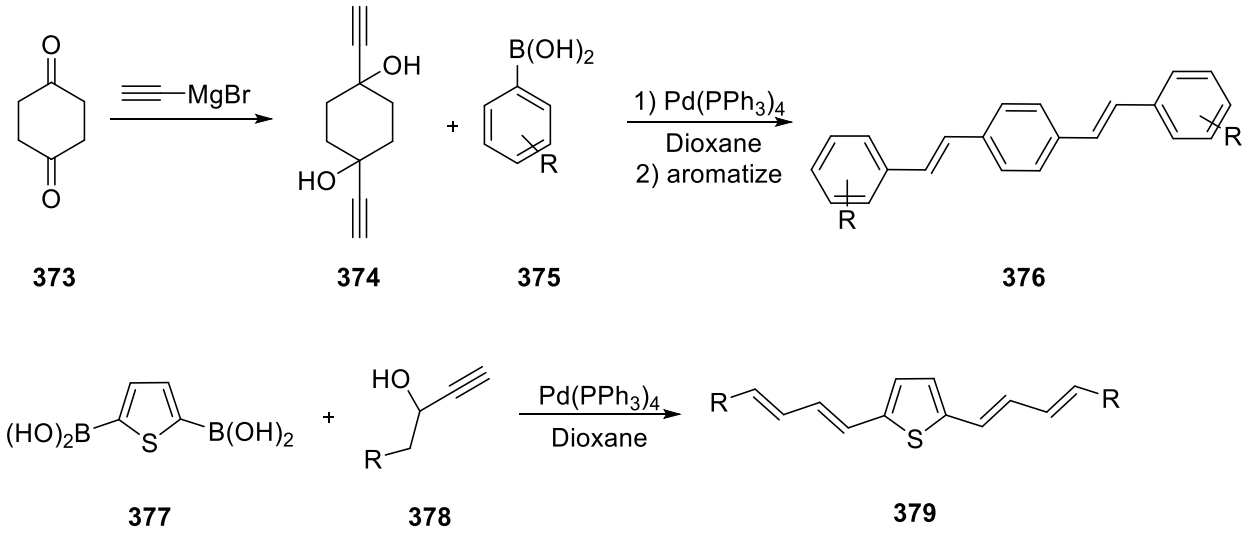


370 **371** **372**

Scheme 89: possible rearrangement reaction

Boronic acid with Pd^0 will form palladium hydride complex H-Pd^{II}-$OB(OH)_2$, which is add to alkyne **370** then eliminate to form allene **371** which is easily rearrange to diene **372** under our optimized condition.[101]

This procedure could also be undertaken in a bi-directional fashion (Scheme 90). Formation of bis-propargyl alcohol **374** from **373**, followed by treatment with an appropriate arylboronic acid under our conditions, which should readily aromatize to **376**. Similarly, treatment of bis arylboronic acids such as **377**, with two equivalents of a propargyl alcohol **378** will yield **379**. Systems such as those depicted below could have very useful physical properties as novel conjugated materials.[81]

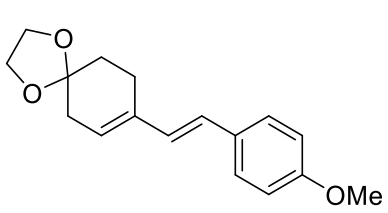


Scheme 90: Suggested future work

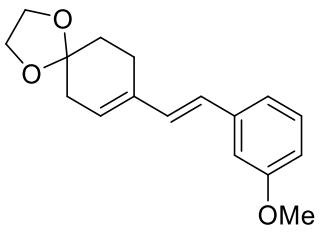
In addition, we could investigate use metals other than palladium, for example nickel or platinum, to perform this allene to 1,3-diene rearrangement as they can also to generate the vital metal-hydride species with boronic acids (or boric acid).

The 1,3-dienes synthesized in section 3.1.1, could also be used to access analogues of resveratrol, as well be used in the total synthesis of other members of the moracin family of natural products.

For example, 1,3-dienes **158** and **159** could be used, via same previous route of synthesis (scheme 91).



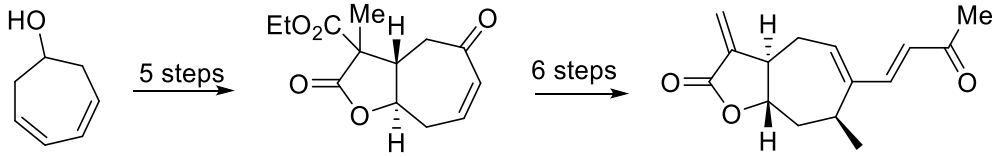
158



159

Scheme 91: Future starting material

We have also made progress on the total synthesis of the xanthanolides. Having accessed key intermediate **369** using the endoperoxide derived from **323**, it is only 6-steps to complete the synthesis. We have demonstrated that the Bayliss-Hilmann approach can be applied to the 8-membered analogue, and this will now be applied to **369** or analogues.



323 **369** **12**

Scheme 92: Future work for xanthatin

5. Experimental

5.1. General

All reagent chemicals were purchased from Sigma-Aldrich Chemical Company Ltd. and Lancaster Chemical Synthesis Ltd. Commercially available reagents were used and without further purification. The palladium reagents were obtained from Sigma-Aldrich Chemical Company Ltd and were handled under argon.

All solvents were directly used commercially except tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. Et_2O was purchased dry from commercial suppliers. Petroleum ether refers to the fractions with a boiling point between 40-60°C. Air-sensitive reactions were carried out using oven-dried glassware under nitrogen atmosphere.

IR spectra were recorded using a Perkin Elmer FTIR spectrometer (Paragon 100) using CH_2Cl_2 as a solvent, unless otherwise stated. Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded at 400MHz and 100MHz respectively using a Bruker Avance 400MHz spectrometer as solutions in deuterated $CDCl_3$. Coupling constants are measured in hertz (Hz) and chemical shifts are quoted as parts per million (ppm).

Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 GF254 aluminium foil backed silica plates. Plates were visualised by Ultra Violet light (254 nm), or vanillin stain. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrix silica 60, with eluent specified.

High and low-resolution mass spectra were carried out on a Thermofisher exactive (orbi) resolution mass spectrometer. Optical rotation measurements were recorded on a polar 2001 polarimeter using chloroform as solvent. Melting point were recorded on a Stuart Scientific apparatus and are uncorrected.

All propargyl alcohols are commercially available unless mentioned.

5.2.Synthetic procedures

A- General procedure to prepare propargyl alcohol compounds.[128]

The corresponding ketone (34.7 mmol) in THF (20 mL) was added dropwise to a solution of ethynylmagnesium bromide (154 mL, 52 mmol, 0.5 M) in THF at 0 °C. The reaction mixture was then stirred for 6 h at room temperature. After addition of saturated aqueous NH_4Cl the mixture was extracted with diethyl ether (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduce pressure. The crude residue was then purified by column chromatography.

B- General procedure to prepare dienes via boronic acid.[81]

Boronic acid (3.15 mmol), and alkyne (1.00 mmol) were dissolved in 1,4-dioxane (5.0 mL) and 4 Å sieves (approx. 400 mg) was added. The resultant mixture was heated to 75 ºC under a N_2 or argon atmosphere for 1 h. To the reaction mixture was added $Pd(PPh_3)_4$ (58 mg. 0.05 mmol, 5.0 mol%) in one portion and the resultant yellow solution heated for a further 20 h. The reaction was cooled, diluted with Et_2O (50 mL) and washed with $NaHCO_3$ (50 mL). Aqueous layer was extracted with Et_2O (50 mL) and the combined organic layers washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed under reduce pressure. The crude residue was purified by column chromatography.

C - General procedure to prepare allenes via boronic acid.222[77]

Boronic acid (3.15 mmol), and alkyne (1.00 mmol) were dissolved in 1,4-dioxane (5.0 mL) and 4 Å sieves (approx. 400 mg) added. The resultant was then heated to 70°C under a N_2 or argon atmosphere for 1 h. and to the reaction mixture was added $Pd(PPh_3)_4$ (58 mg. 0.05 mmol, 5.0 mol%) in one portion and the resultant yellow solution heated for a further 4 h. After this period the reaction was cooled, diluted with Et_2O (50 mL) and transferred to a separating funnel and washed with $NaHCO_3$ (50mL). The aqueous layer was then extracted with Et_2O (50 mL) and the

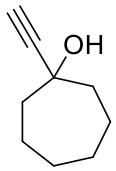
combined organic layers washed with brine (50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was then purified by column chromatography.

D- General procedure for allene to 1,3-diene isomerization.

To a solution of allene (1.00 mmol) in 1,4-dioxane (5.00 mL) was added boric acid (123 mg, 2.00 mmol) and $Pd(PPh_3)_4$ (116 mg. 0.10 mmol, 10 mol%) in one portion. The resultant reaction mixture was stirred and heated at 75°C under a N_2 or argon atmosphere for 24 h. After this period. The reaction was cooled, diluted with Et_2O (50 mL) and transferred to a separating funnel and washed with $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (50 mL), and the combined organic layers washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was purified by column chromatography.

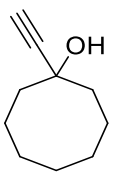
5.3. Products Data

1-Ethynylcycloheptanol. (152)[129]



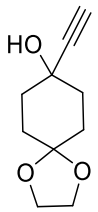
This compound was prepared according to the general procedure A, giving yellow oil (4.55 g, 95%, R_f 0.55 in ethyl acetate /hexane : 1/4); IR (CH_2Cl_2) ν_{max} 3394, 3302, 2931, 2862, 1458, 1126, cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 2.43 (s, 1H), 2.07 (s, 1H), 2.01-1.96 (m, 4H), 1.80 (t, J = 4 Hz, 2H), 1.66-1.54 (m, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 88.9, 71.6, 71.3, 43.1, 28.1, 22.1ppm.

1-Ethynylcyclooctanol. (154)[130]



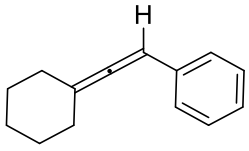
This compound was prepared according to the general procedure A, giving a white solid (4.542 g, 86%) (R_f 0.92 in ethyl acetate /hexane : 1/4); IR (CH_2Cl_2) ν_{max} 3278, 2916, 2854, 1450, 1234 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 2.41 (s, 1H), 2.20 (s, 1H), 2.00-1.82 (m, 4H), 1.62 - 1.52 (m, 7H), 1.51-1.38 (m, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 88.7, 71.1, 71.2, 38.0, 28.1, 24.7, 22.0 ppm.

8-Ethynyl-1,4-dioxaspiro[4.5]decan-8-ol (156)[131]



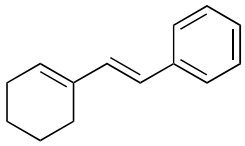
This compound was prepared according to the general procedure A, giving a yellow oil (6.0 g, 95%) (R_f 0.45 in ethyl acetate /hexane: 1/4); IR (CH_2Cl_2) ν_{max} 3586, 3301, 2960, 2306, 1265 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 3.89 (s, 4H), 2.46 (s, 1H), 2.34 (s, 1H), 2.01-1.82 (m, 4H), 1.79 - 1.73 (m, 4H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 107.9, 86.7, 70.0, 67.0, 64.2, 37.0, 31.0 ppm.

(2-cyclohexylideneethenyl) benzene (136) [132]



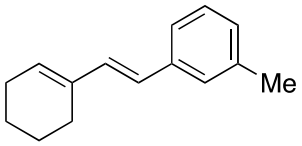
This compound was prepared according to the general procedure C, giving a viscous colourless oil (130 mg, 71%) (R_f 0.45, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2926, 1952, 1459, 1446 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.28 (d, J = 4 Hz, 4H), 7.18-7.13 (m, 1H), 6.00-5.98 (m, 1H), 2.17-2.09 (m, 4H), 2.03-1.96 (m, 4H), 1.70-1.60 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.8, 136.2, 128.6, 126.5, 126.4, 106.6, 92.4, 31.4, 27.8, 26.2 ppm; HRMS [$M+H^+$] calculated for $C_{14}H_{17}$ 185.1325, found 185.1321.

[(*E*)-2-(Cyclohex-1-en-1-yl) ethenyl] benzene (137).[133]



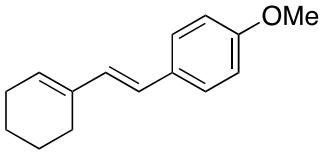
This compound was prepared according to the general procedure B, giving a viscous colourless oil (142mg, 78%) (R_f 0.29, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3082, 2933, 1641, 1493, 739 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.43-7.35 (m, 2H), 7.42-7.32 (m, 2H), 7.21-7.13 (m, 1H), 6.76 (d, *J* = 16.0 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 5.88 (t, *J* = 4.0 Hz, 1H), 2.30-2.22 (m, 2H), 2.21-2.15 (m, 2H), 1.78-1.69 (m, 2H), 1.60-1.67 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.1, 135.9, 132.7, 130.94, 128.8, 128.6, 127.3, 126.9, 126.2, 124.7, 26.2, 24.6, 22.6, 22.6 ppm; HRMS [$M+H^+$] calculated for $C_{14}H_{17}$ 185.1325, found 185.1321.

1-[(*E*)-2-(Cyclohex-1-en-1-yl) ethenyl]-3-methylbenzene (138).[81]



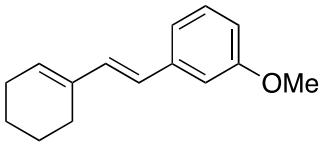
This compound was prepared according to the general procedure, to give a viscous colourless oil (198 mg, 99%) (R_f 0.45, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3045, 2965, 1640, 732 cm-^{1}; H NMR (400 MHz; $CDCl_3$) δ 7.15-7.24 (m, 3H), 6.99-6.97 (m, 1H), 6.75 (d, *J* = 16.0 Hz, 1H), 6.39 (d, *J* = 16.0, Hz 1H), 5.87 (t, *J* = 4.0 Hz, 1H), 2.33 (s, 3H), 2.30-2.21 (m, 2H), 2.21-2.13 (m, 2H), 1.78-1.68 (m, 2H), 1.67-1.59 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.1, 138.0, 136.0, 132.5, 130.7, 128.5, 127.7, 127.0, 124.8, 123.4, 26.2, 24.6, 22.6, 22.6, 21.5 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{19}$ 199.1418, found 199.1487.

1-[(*E*)-2-(Cyclohex-1-en-1-yl) ethenyl]-4-methoxybenzene (139).[134]



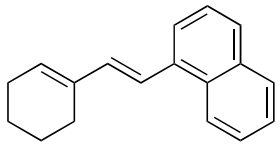
This compound was prepared according to the general procedure, giving a colourless oil (186 mg, 87%) (R_f 0.52, ethyl acetate : petroleum ether / 1:10); IR (CH_2Cl_2) ν_{max} 3054, 2986, 1683, 1512, 739 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.32-7.30 (m, 2H), 6.89-6.85 (m, 2H), 6.65 (d, *J* = 16.4 Hz, 1H), 6.39 (d, *J* = 16.4 Hz, 1H), 5.87 (t, *J* = 3.6 Hz, 1H), 3.80 (s, 3H), 2.30-2.23 (m, 2H), 2.20-2.14 (m. 2H), 1.78-1.68 (m, 2H), 1.67-1.59 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 158.8, 135.5, 131.1, 131.0, 129.7, 127.2, 124.1, 114.2, 55.1, 26.2, 24.5, 22.2, 22.1 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{18}O$ 215.1436, found 215.1448.

1-[(*E*)-2-(Cyclohex-1-en-1-yl)ethenyl]-3-methoxybenzene (140).[81]



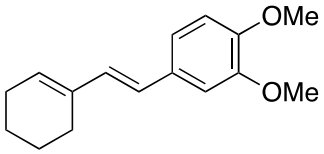
This compound was prepared according to the general procedure, giving a viscous colourless oil (129 mg, 60%) (R_f 0.54, ethyl acetate : petroleum ether / 1:10); IR (CH_2Cl_2) ν_{max} 3010, 2931, 1651, 1157, 771 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.21-7.19 (m, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.92 (s, 1H), 6.79-6.71 (m, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.89 (t, *J* = 4.0 Hz, 1H), 3.81 (s, 3H), 2.30-2.21 (m, 2H), 2.21-2.15 (m. 2H), 1.78-1.68 (m, 2H), 1.67-1.59 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.9, 139.6, 135.9, 133.0, 131.2, 129.5, 124.6, 119.0, 112.6, 111.4, 55.2, 26.2, 24.6, 22.6, 22.6 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{19}O$ 215.1430, found 215.1436.

1-[(*E*)-2-(Cyclohex-1-en-1-yl)ethenyl]naphthalene (141).[81]



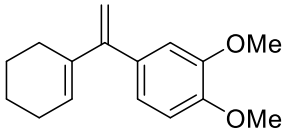
This compound was prepared according to the general procedure, giving a colourless oil (220 mg, 94%) (R_f 0.36, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3027, 2973, 1655, 732 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.82-7.80 (m, 1H), 7.74-7.71 (m, 1H), 7.63-7.61 (m, 1H), 7.53-7.39 (m, 3H), 7.19 (d, *J* = 15.6 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 5.95 (t, *J* = 3.6 Hz, 1H), 2.44-2.38 (m, 2H), 2.27-2.18 (m. 2H), 1.82-1.77 (m, 2H), 1.71-1.63 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 136.3, 135.8, 135.7, 133.8, 131.4, 131.3, 128.6, 127.3, 125.9, 125.8, 125.7, 123.9, 123.2, 121.6, 26.3, 24.8, 22.7, 22.6 ppm; HRMS [$M+H^+$] calculated for $C_{18}H_{19}$ 235.1481, found 235.1486.

4-[(*E*)-2-(Cyclohex-1-en-1-yl)ethenyl]-1,2-dimethoxybenzene (142).[81]



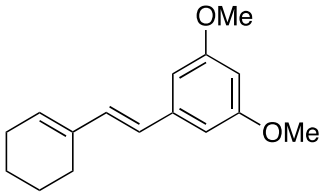
This compound was prepared according to the general procedure B, giving a yellow oil (138 mg, 57%) (R_f 0.59, ethyl acetate : petroleum ether / 15:85); IR (CH_2Cl_2) ν_{max} 3035, 2944, 1589, 1234, 756 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.95-6.86 (m, 2H), 6.80-6.78 (d, 1H), 6.62 (d, *J* = 16.4 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 5.87 (t, *J* = 4.4 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.30-2.22 (m, 2H), 2.12-2.12 (m. 2H), 1.78-1.68 (m, 2H), 1.67-1.58 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 149.1, 148.4, 135.8, 13.97, 130.1, 124.5, 120.9, 119.3, 111.4, 108.6, 56.0, 55.9, 26.2, 24.7, 22.7, 22.6 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{21}O_2$ 245.1536, found 245.1534.

4-(1-(Cyclohex-1-en-1-yl)vinyl)-1,2-dimethoxybenzene (143)



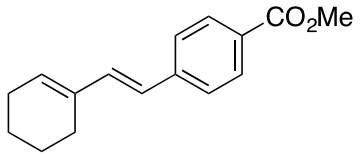
This compound was prepared according to the general procedure B, giving a viscus yellow oil (70 mg, 29%) (R_f 0.69, ethyl acetate:petroleum ether/15:85); IR (CH_2Cl_2) ν_{max} 3045, 2931, 1658, 1249, 758 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.81-6.78 (m, 3H), 5.67 (t, *J* = 4 Hz, 1H), 5.13 (s, 1H), 4.96 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.30-2.21 (m, 2H), 2.15-2.06 (m, 2H), 1.75 - 1.67 (m, 2H), 1.63-1.54 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 151.4,148.3, 148.1, 137.3, 134.8, 128.8, 121.0, 120.9, 112.1, 110.6, 110.4, 55.9, 26.6, 25.9, 22.8, 22.2 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{21}O_2$ 245.1536, found 245.1534.

5-[(*E*)-2-(Cyclohex-1-en-1-yl)ethenyl]-1,3-dimethoxybenzene (144).[81]



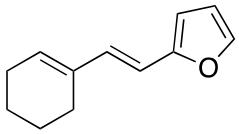
This compound was prepared according to the general procedure B, giving a yellow oil (152 mg, 62%) (R_f 0.58, ethyl acetate : petroleum ether / 15:85); IR (CH_2Cl_2) ν_{max} 2931, 2839, 1589, 1280, 1203, 1049 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.72 (d, *J* = 16.4 Hz, 1H), 6.55 (s, 1H), 6.54 (s, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.32 (m, 1H), 5.89 (m, 1H), 3.79 (s, 6H), 2.30-2.22 (m, 2H), 2.16-2.12 (m, 2H), 1.78-1.68 (m, 2H), 1.68-1.60 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 161.0, 140.2, 135.8, 133.2, 131.3, 128.8, 127.3, 124.7, 104.3, 99.4, 55.4, 26.2, 24.6, 22.6 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{21}O_2$ 245.1536, found 245.1539.

1-[(*E*)-2-(Cyclohex-1-en-1-yl)ethenyl]-4-methyl(carboxy)benzene (145).[81]



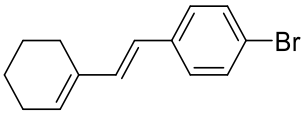
This compound was prepared according to the general procedure B, giving a yellow oil (170 mg, 70%) (R_f 0.36, ethyl acetate : petroleum ether / 15:85); IR (CH_2Cl_2) ν_{max} 2931, 1712, 1604, 1435, 1180, 964 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.45-7.42 (m, 2H), 6.85 (d, *J* = 16.0 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 5.97-5.95 (m, 1H), 3.88 (s, 3H), 2.30-2.16 (m, 4H), 1.74-1.70 (m, 2H), 1.66-1.60 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.1, 142.8, 135.8, 135.2, 133.0, 132.9, 130.0, 126.0, 123.7, 52.1, 26.33, 24.5, 22.5, 22.4 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{18}O_2$ 243.1385, found 243.1379.

2-[(*E*)-2-(Cyclohex-1-en-1-yl)ethenyl]furan (146).[81]



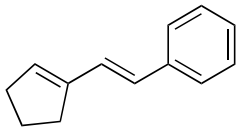
This compound was prepared according to the general procedure, giving a colorless oil (114 mg, 66%) (R_f 0.86, ethyl acetate : petroleum ether / 1:10); IR (CH_2Cl_2) ν_{max} 2953,1728, 1635, 1081, 730 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.31 (d, *J* = 16.0 Hz, 1H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.44-6.42 (m, 1H), 6.20-6.18 (m, 1H), 6.19-6.17 (m, 1H), 5.88 (t, *J* = 3.2 Hz, 1H), 2.15-2.12 (m, 4H), 1.69-1.60 (m, 2H), 1.59-1.55 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 153.9, 141.4, 135.5, 131.2, 131.0, 113.0, 111.4, 106.9, 26.2, 24.2, 22.6, 22.5 ppm; HRMS [$M+H^+$] calculated for $C_{12}H_{13}O$ 173.0961, found 173.0981.

(*E*)-1-Bromo-4-(2-(cyclohex-1-en-1-yl)vinyl)benzene (147)



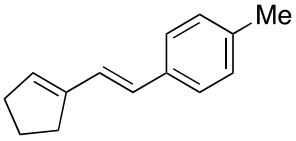
This compound was prepared according to the general procedure B, giving a white solid (<5%, R_f 0.38, 100% petroleum ether); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.55 (d, *J* = 4.4 Hz, 2H), 7.41 (d, *J* = 4.0 Hz, 2H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 5.90 (t, *J* = 3.6 Hz, 1H), 2.22 (t, *J* = 4.0 Hz, 2H), 2.16 (s, 2H), 1.72-1.68 (m, 2H), 1.65-1.60 (m, 2H) ppm.

[(*E*)-2-(Cyclopent-1-en-1-yl)ethenyl]benzene (149).[133]



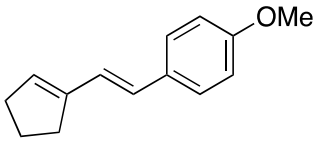
This compound was prepared according to the general procedure, giving a colourless oil (102 mg, 61%) (R_f 0.29, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3054, 2986, 1598, 1420, 738 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.36-7.34 (m, 2H), 7.24-7.22 (m, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 5.89-5.86 (m, 1H), 2.6-2.55 (m, 2H), 2.54-2.49 (m, 2H), 2.05-1.94 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 142.9, 137.9, 132.2, 128.8, 128.6, 127.2, 126.2, 125.9, 33.1, 31.3, 23.23 ppm; HRMS [M+H$^+$] calculated for $C_{13}H_{13}$ 169.1012, found 169.1024.

1-[(*E*)-2-(Cyclopent-1-en-1-yl)ethenyl]-4-methylbenzene (150).[81]



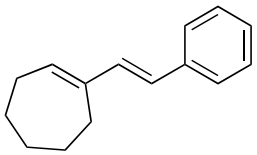
This compound was prepared according to the general procedure, giving a white solid (122 mg, 67%) (R_f 0.33, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3030, 2923, 1605, 1512, 813 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.30-7.28 (m, 2H), 7.12-7.10 (m, 2H), 6.98 (d, *J* = 16.0 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.81 (t, *J* = 4.0 Hz, 1H), 2.59-2.50 (m, 2H), 2.49-2.43 (m, 2H), 2.35 (s, 3H), 2.01-1.91 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.0, 137.0, 135.1, 131.5, 129.8, 129.4, 128.7, 128.4, 126.2, 125.0, 33.1, 31.3, 23.3, 21.3 ppm; HRMS [M+H$^+$] calculated for $C_{14}H_{16}$ 185.1330, found 185.1319.

1-[(*E*)-2-(Cyclopent-1-en-1-yl)ethenyl]-4-methoxybenzene (151).[133]



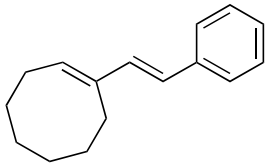
This compound was prepared according to the general procedure, giving a colourless oil (155 mg, 78%) (R_f 0.73, ethyl acetate : petroleum ether / 1:20); IR (CH_2Cl_2) ν_{max} 3035, 2947, 1567, 1465, 1172, 732 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.38-7.34 (m, 2H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.87-6.83 (m, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 5.79 (t, *J* = 2.0 Hz, 1H), 3.80 (s, 3H), 2.57-2.50 (m, 2H), 2.49-2.41 (m, 2H), 2.01-1.91 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.0, 143.0, 130.9, 130.7, 128.3, 127.5, 123.9, 114.1, 55.4, 33.1, 31.3, 23.3 ppm; HRMS [M+H^+] calculated for $C_{14}H_{17}O$ 201.1274, found 201.1286.

1-[(*E*)-2-Phenylethenyl]cycloheptene (153).[133]



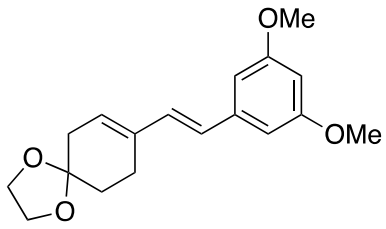
This compound was prepared according to the general procedure, giving a colorless oil (158 mg, 80%) (R_f 0.19, 100% petroleum ether); ; IR (CH_2Cl_2) ν_{max} 3020, 2924, 1618, 1448, 694 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.30-7.28 (m, 2H), 7.16-7.13 (m, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.04 (t, *J* = 6.8 Hz, 1H), 2.45-2.41 (m, 2H), 2.20-2.18 (m, 2H), 1.80-1.76 (m, 2H), 1.53-1.48 (m, 4H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.2, 138.2, 135.6, 133.4, 128.6, 126.9, 126.3, 124.8, 32.4, 28.9, 27.4, 26.9, 26.4 ppm; HRMS [M+H^+] calculated for $C_{15}H_{19}$ 199.1480, found 199.1479.

(1*E*)-1-[(*E*)-2-Phenylethenyl] cyclooctene (155).[135]



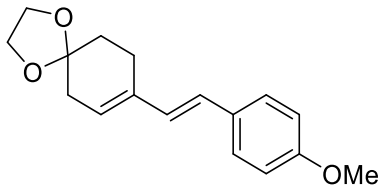
This compound was prepared according to the general procedure, giving a colorless oil (159 mg, 75%) (R_f 0.62, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3013, 2916, 1597, 1450, 745 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.31-7.28 (m, 2H), 7.20-7.17 (m, 1H), 6.74 (d, *J* = 16.4 Hz, 1H), 6.49 (d, *J* = 16.4 Hz, 1H), 5.85 (t, *J* = 4.2 Hz, 1H), 2.51-2.48 (m, 2H), 2.27-2.24 (m, 2H), 1.69-1.45 (m, 8H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 139.4, 138.1, 133.9, 132.4, 128.7, 126.9, 126.5, 125.3, 30.6, 28.7, 27.3, 26.9, 24.5 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{21}$ 213.1638, found 213.1635.

8-[(*E*)-2-(3,5-Dimethoxyphenyl)ethenyl]-1,4-dioxaspiro[4.5]dec-7-ene (5).[81]



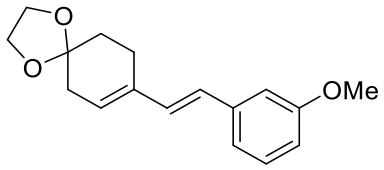
This compound was prepared according to the general procedure B with extending heating to 68 hours, giving a colorless oil (130 mg, 43%) (R_f 0.18, diethyl ether : hexane / 3:7); IR (CH_2Cl_2) ν_{max} 3055, 2939, 1589, 1203, 1149, 702 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.71 (d, *J* = 16.0 Hz, 1H), 6.57-6.55 (m, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.35-6.31 (m, 1H), 5.78 (t, *J* = 4.0 Hz, 1H), 3.98 (s, 4H), 3.78 (s, 6H), 2.50-2.47 (m, 2H), 2.44-2.41 (m, 2H), 1.85-1.83 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.9, 139.9, 135.3, 131.8, 127.4, 126.2, 108.1, 104.4, 99.5, 64.6, 55.4, 36.5, 30.9, 23.8 ppm; HRMS [$M+H^+$] calculated for $C_{18}H_{23}O_4$ 303.1591, found 303.1580.

(*E*)-8-(4-methoxystyryl)-1,4-dioxaspiro[4.5]dec-7-ene (158)



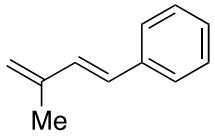
This compound was prepared according to the general procedure B with extending heating to 68 hours, colorless oil, (217 mg, 80%) (R_f 0.36, Et_2O:petroleum ether / 1:3); IR (CH_2Cl_2) ν_{max} 2938, 1595, 1485, 1284, 1111 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 5.72 (t, *J* = 4.0 Hz, 1H), 3.99 (s, 4H), 3.79 (s, 3H), 2.49 (t, *J* = 5.2 Hz, 2H), 2.43 (s, 2H), 1.86 (t, *J* = 6.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 158.9, 135.4, 130.6, 129.3, 127.4, 125.9, 125.7, 114.0, 108.1, 64.5, 55.3, 36.3, 30.9, 23.8 ppm; HRMS [$M+H^+$] calculated for $C_{17}H_{21}O_3$ 273.1485, found 273.1477

(*E*)-8-(3methoxystyryl)-1,4-dioxaspiro[4.5]dec-7-ene (159)



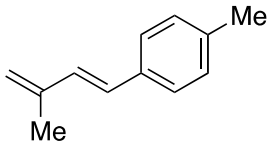
This compound was prepared according to the general procedure B with extending heating to 72 hours, giving a colorless oil (220 mg, 81%) (R_f 0.47, diethyl ether : hexane / 1:3); IR (CH_2Cl_2) ν_{max} 2938, 1595, 1485, 1252, 1111, 773 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.21 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 2.0 Hz, 1H), 6.78-6.74 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.78 (t, *J* = 4.0 Hz, 1H), 3.99 (s, 4H), 3.79 (s, 3H), 2.52-2.49 (m, 2H), 2.44 (s, 2H), 1.88-1.85 (t, *J* = 3.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.8, 139.3, 135.3, 131.5, 129.5, 127.2, 126.1, 119.0, 112.7, 111.6, 108.1, 64.5, 55.2, 36.4, 30.9, 23.8 ppm; HRMS [$M+H^+$] calculated for $C_{17}H_{21}O_3$ 273.1485, found 273.1477.

[(1*E*)-3-Methylbuta-1,3-dien-1-yl]benzene (161).[136]



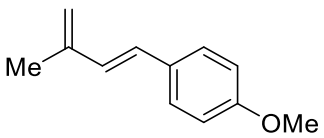
This compound was prepared according to the general procedure B, giving a viscous colorless oil (122 mg, 85%) (R_f 0.31, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3025, 2968, 1645, 1493, 1265, 739 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.37-7.35 (m, 2H), 7.27-7.24 (m, 1H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 2.01 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 142.1, 137.5, 131.8, 128.8, 128.7, 127.5, 126.7, 117.4, 22.8 ppm; HRMS [M+H^+] calculated for $C_{11}H_{13}$ 145.1012, found 145.1021.

1-Methyl-4-[(1*E*)-3-methylbuta-1,3-dien-1-yl]benzene (162).[137]



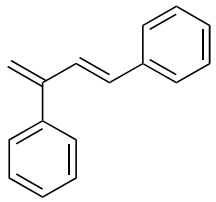
This compound was prepared according to the general procedure B, giving a white solid (74 mg, 47%) (R_f 0.39, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3051, 2986, 1603, 1513, 738 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.17-7.14 (m, 2H), 6.85 (d, *J* = 16.0 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 5.09 (s, 1H) 5.04 (s, 1H), 2.35 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 142.3, 137.4, 134.7, 130.8, 129.4, 128.7, 126.5, 116.9, 21.3, 18.7 ppm; HRMS [M+H^+] calculated for $C_{12}H_{15}$ 159.1168, found 159.1163.

(*E*)-1-methoxy-4-(3-methylbuta-1,3-dien-1-yl)benzene(163).[101]



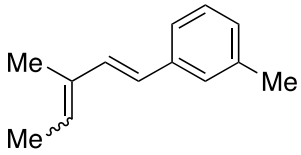
This compound was prepared in overall yield according to the general procedure B, giving a white solid (170 mg, 98%) (R_f 0.78, ethyl acetate:petroleum ether / 1:10); IR (CH_2Cl_2) ν_{max} 3032, 2986, 1640, 1265, 732 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.36 (d, *J* = 6.8 Hz, 2H), 6.86 (d, *J* = 6.8 Hz, 2H), 6.75 (d, *J* = 16.4 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 3.81 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.2, 142.2, 130.2, 129.7, 128.2, 127.7, 116.3, 114.1, 55.3, 18.7 ppm; HRMS [$M+H^+$] calculated for $C_{11}H_{15}O$ 163.1117 found 163.1112.

[(1*E*)-3-Phenylbuta-1,3-dien-1-yl]benzene (165).[136]



This compound was prepared according to the general procedure B, giving a colorless volatile oil that readily degraded upon standing (152 mg, 74%) (R_f 0.28, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3054, 2986, 1642, 1421, 739 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.45-7.23 (m, 10H), 7.11-7.08 (m, 1H), 6.52 (m, 1H), 5.46 (s, 1H), 5.28 (s, 1H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 148.2, 140.2, 137.2, 132.0, 130.8, 128.9, 128.6, 128.3, 127.9, 127.8, 126.5, 117.5 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{15}$ 207.1168, found 207.1165.

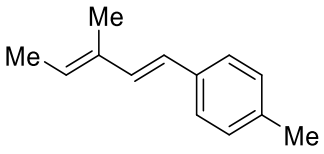
1-Methyl-3-[(1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl]benzene (167).[81]



This compound was prepared according to the general procedure, giving a colorless oil (93 mg, 55%) (R_f 0.41, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3025, 2980, 1640, 1442, 732 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.28-7.17 (m, 3H), 6.98-6.96 (m, 1H), 6.79 (d, *J* = 16.0 Hz, 1H), 6.38 (d, *J* = 16.0, 1H), 5.68 (q, *J* = 6.8 Hz, 1H), 2.31 (s, 3H), 1.81 (s, 3H), 1.78 (d, *J* = 6.8 Hz, 3H)

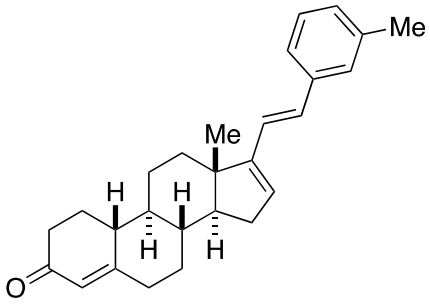
ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.0, 138.4, 134.8, 133.8, 128.3, 128.0, 127.8, 127.0, 125.0, 123.0, 21.8, 14.0, 12.0 ppm; HRMS [M+H$^+$] calculated for $C_{13}H_{17}$ 173.1325, found 173.1323.

1-Methyl-4-[(1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl]benzene(168)



This compound was prepared according to the general procedure B, giving a colorless oil (125 mg, 73%) (R_f 0.42, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3024, 2924, 1602, 1512, 732 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.76 (d, *J* = 16.0 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 5.68 (q, *J* = 7.0 Hz, 1H), 2.32 (s, 3H), 1.86-1.83 (m, 3H), 1.78 (d, *J* = 7.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 136.7, 135.3, 133.0, 129.5, 129.3, 127.6, 127.0, 125.2, 21.2, 14.1, 12.1 ppm; HRMS [M+H$^+$] calculated for $C_{13}H_{17}$ 173.1325 found 173.1317.

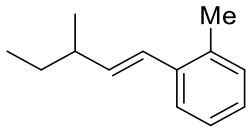
(*E*)-10,13–Dimethyl-17-(3-methylstyryl)-1,2,6,7,8,9.10,11,12,13,14,15–dodecahydro-3H-cyclopenta[a]phenanthren-3-one (170).[81]



This compound was prepared according to the general procedure, to give colorless oil (220 mg, 57%) (R_f 0.11, ethyl acetate : petroleum ether / 1:10); IR (CH_2Cl_2) ν_{max} 3050, 2955, 1675, 1610, 1450, 732 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.21-7.16 (m, 4H), 7.05-7.03 (d, *J* = 5.6 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.69 (s, 1H), 2.40-0.80 (m, 26H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.7, 171.3, 138.3, 137.0, 134.5, 128.6, 128.3, 127.8, 127.1, 124.0,

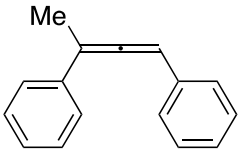
123.7, 84.0, 53.6, 49.8, 47.1, 38.7, 36.4, 35.7, 32.9, 23.7, 21.5, 20.7, 17.5, 14.2 ppm; HRMS [M+H$^+$] calculated for $C_{28}H_{35}O$ 387.2682, found 387.2677.

(*E*)-1-Methyl-2-(3-methylpent-1-ene-1-yl)denzene (172).



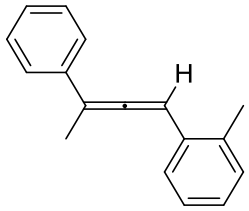
This compound was prepared according to the general procedure B, giving a colorless oil (113 mg, 65%) (R_f 0.42, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3068, 2969, 1485, 1459, 1412 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.21- 7.01 (m, 2H), 6.47 (d, *J* = 16.4 Hz, 1H), 6.32 (d, *J* = 16.8Hz, 1H), 2.41 (s, 3H), 2.19-2.09 (m, 1H), 1.98-1.88 (m, 2H), 1.35 (d, 3H), 0.79 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 141.8, 132.5, 128.7, 128.6, 127.79, 127.7, 125.4, 124.8, 45.2, 32.44, 22.9, 19.8, 9.2; [M+H$^+$], calculated for $C_{13}H_{17}$ 173.1325, found 173.1218.

C. 1,1'-Buta-1,2-diene-1,3-diyldibenzene (173).[95]



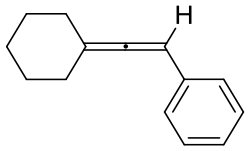
This compound was prepared according to the general procedure C, giving a colourless oil (187 mg, 91%) (R_f 0.45, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3082, 3060, 1935, 1686, 1493 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.68-7.61 (m, 2H), 7.51-7.44 (m, 6H), 7.40-7.32 (m, 2H), 6.52 (q, *J* = 3.2 Hz, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.0, 136.5, 134.7, 128.9, 128.6, 127.2, 127.1, 126.0, 104.7, 96.8, 16.9 ppm; HRMS [M+H$^+$] calculated for $C_{16}H_{14}$ 207.1174, found 207.1168.

1-Methyl-2-(3-phenylbuta-1,2-dien-1-yl)benzene. (226)[77]



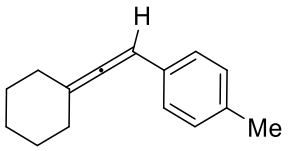
This compound was prepared according to the general procedure C, giving a viscous yellow oil (184 mg, 84%) (R_f 0.41, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3020, 2948, 1933, 1599, 1492 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.53 (d, *J* = 1.6 Hz, 2H),7.52-7.35 (m, 2H), 7.32-7.25 (m, 3H), 7.22-7.14 (m, 2H) 6.72 (t, *J* = 3.2 Hz, 1H), 2.46 (s, 3H), 2.21 (d, *J* = 2.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.5, 140.4 136.5, 135.4, 128.6, 128.1, 127.2, 127.1, 126.3, 125.9, 125.7, 102.2, 92.9, 18.6, 15.7 ppm; HRMS [M-H^+] calculated for $C_{16}H_{15}$ 207.1168, found 207.1181.

(2-Cyclohexylidene ethenyl)-benzene (136).[132, 138]



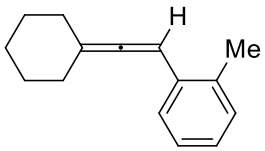
This compound was prepared according to the general procedure C, giving a viscous colourless oil (130 mg, 71%) (R_f 0.45, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2926, 1952, 1459, 1446 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.28-7.26 (m, 4H), 7.17-7.13 (m, 1H), 5.99 (d, *J* = 2.0 Hz, 1H), 2.27-2.24 (m, 2H), 2.21-1.17 (m, 2H), 1.70-1.54 (m, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.8, 136.2, 128.6, 126.5, 126.4, 106.6, 92.4, 31.4, 27.8, 26.2 ppm; HRMS [M+H^+] calculated for $C_{14}H_{17}$ 185.1325, found 185.1336.

1-(2-cyclohexylideneethenyl)-4-methylbenzene (227).[84]



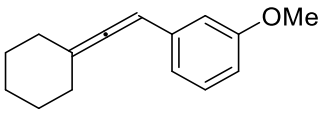
This compound was prepared according to the general procedure C, giving a viscous colourless oil (127 mg, 64%) (R_f 0.25, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2932, 1902, 1513, 1451 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.26 (dd, *J* = 8.0, 8.4 Hz, 2H), 7.10 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.21 (t, *J* = 16.4 Hz, 1H), 2.32 (d, *J* = 5.2 Hz, 3H), 2.08-2.03 (m, 2H), 1.96-1.92 (m, 2H), 1.63-1.52 (m, 4H) 1.44-1.38 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.8, 136.6, 129.2, 127.5, 126.8, 126.0, 36.6, 26.4, 22.7, 21.2 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{19}$, 199.1481 found 199.1479.

1-(2-Cyclohexylideneethenyl)-2-methylbenzene (228).



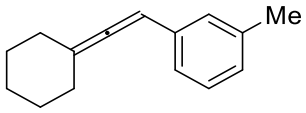
This compound was prepared according to the general procedure C, giving a viscous colourless oil (119 mg, 60%) (R_f 0.44, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3060, 2926, 1951, 1600, 1452 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.34-7.18 (m, 4H), 6.26 (m, 1H), 2.44 (s, 3H), 2.20-2.10, (m, 4H), 1.80-1.70 (m, 4H), 0.97-0.94 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 200.6, 141.6, 135.8, 129.8, 129.6, 127.4, 125.2, 105.0, 89.9, 31.4, 29.4, 26.5, 19.8 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{19}$ 199.1481, found 199.1494.

(2-Cyclohexylidene ethenyl)-3-methoxybenzene (229).[101]



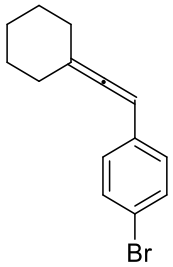
This compound was prepared according to the general procedure C, giving viscous colourless oil (135 mg, 63%) (R_f 0.89, ethyl acetate : petroleum / 5 : 95); IR (CH_2Cl_2) ν_{max} 2924, 1951, 1459, 1442, 1149 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 5.96 (t, *J* = 2.0 Hz, 1H), 3.79 (s, 3H), 2.27-2.24 (m, 2H), 2.20-1.17 (m, 2H), 1.70-1.58 (m, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.8, 159.9, 137.8, 129.5, 119.3, 112.0, 111.8, 106.7, 92.4, 55.2, 31.4, 27.8, 26.2 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{19}O$ 215.1430, found 215.1434.

(2-Cyclohexylidene ethenyl)-3-methylbenzene (230).[101]



This compound was prepared according to the general procedure C, giving a viscous colourless oil (89 mg, 45%) (R_f 0.39, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2924, 1951, 1604, 1442, 1226 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.17 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 2.8 Hz, 2H), 6.98 (d, *J* = 6.8 Hz, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 2.34, (s, 3H), 2.32-2.24 (m, 2H), 2.21-2.18 (m, 2H), 1.70-1.56 (m, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) 199.7, 138.1, 136.1, 128.5, 127.8, 127.2, 123.7, 106.4, 92.4, 31.4, 27.8, 26.2, 21.5 ppm; HRMS [$M+H^+$] calculated for $C_{15}H_{19}$ 199.1481, found 199.1694.

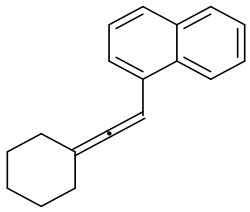
1-Bromo-4-(2-cyclohexylidenevinyl)benzene (231).



This compound was prepared according to the general procedure, giving a viscous oil (50 mg, 19%) (R_f 0.38, 100% petroleum ether); ^1H NMR (400 MHz; $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 6.4 Hz, 2H), 5.91 (t, *J* = 2 Hz, 1H), 2.23-2.16 (m, 2H), 1.68-1.56 (m, 2H), 1.34-1.17

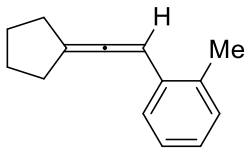
(m, 4H) 0.88-0.84 (m, 2H) ppm; HRMS [M+H$^+$] calculated for $C_{14}H_{16}Br$ 263.0430, found 263.0466.

(2-Cyclohexylidene ethenyl)-naphthalene (232).[101]



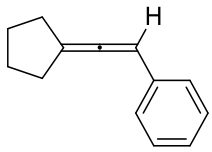
This compound was prepared according to the general procedure C, giving a viscous colourless oil (159 mg, 68%) (R_f 0.44, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3055, 2924, 2854, 1951, 1265, 964 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.28 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.86-7.82 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.53-7.40 (m, 4H), 6.67 (t, *J* = 2.4 Hz, 1H), 2.36-2.29 (m, 4H), 1.72-1.54 (m, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 201.5, 134.0, 132.4, 128.7, 128.0, 126.9,125.9, 125.8, 125.7, 125.6, 125.2, 123.9, 105.0, 89.2, 31.5, 27.5, 26.2 ppm; HRMS [M+H$^+$] calculated for $C_{18}H_{18}$ 235.1487, found 235.1492.

1-(2-cyclopentylideneethenyl)-2-methylbenzene (233) .



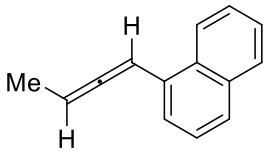
This compound was prepared according to the general procedure C, giving a viscous yellow oil (79 mg, 43%) (R_f 0.45, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3019, 2958, 1949, 1601, 1478 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38 (d, *J* = 4 Hz, 1H), 7.37-7.23 (m, 1H), 7.20-7.09 (m, 2H), 6.33-6.29 (m, 1H), 2.60-2.50 (m, 4H), 2.40 (s, 3H), 1.83-1.77 (m, 4H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 198.6, 141.5, 135.8, 129.8, 129.2, 127.1, 125.5, 106.0, 92.3, 31.4, 27.2, 19.4 ppm; HRMS [M+H$^+$] calculated for $C_{14}H_{17}$ 185.1325, found 185.1337.

(2-Cyclopentylidene ethenyl)-benzene (234).[139]



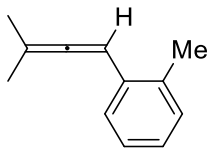
This compound was prepared according to the general procedure C, giving a viscous oil colorless (93 mg, 55%) (R_f 0.87, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3032, 2924, 1951, 1597, 1442 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.31-7.28 (m, 4H), 7.18-7.14 (m, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 2.28-2.26, (m, 2H), 2.22-2.18 (m, 2H), 1.83-1.66 (m, 4H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.8, 136.2, 128.7, 126.60, 126.4, 106.6, 92.4, 31.4, 27.8 ppm; HRMS [$M+H^+$] calculated for $C_{13}H_{15}$ 171.1168, found 171.1172.

1-(Buta-1,2-dien-1-yl)naphthalene. (236)



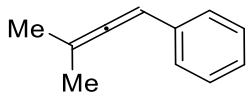
This compound was prepared according to the general procedure C, giving a viscous colourless oil (79 mg, 44%) (R_f 0.45, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3054, 2986, 2055, 1422, 1265 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 8.24 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.52-7.42 (m, 4H), 6.81-6.77 (m, 1H), 5.62-5.55 (m, 1H), 1.85 (dd, *J* = 2.8, 3.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.5, 133.5, 128.7, 127.9, 127.3, 126.0, 125.9, 125.7, 125.7, 125.3, 123.7, 90.6, 88.6, 14.2 ppm; HRMS [$M-H^+$] calculated for $C_{14}H_{11}$ 179.0855, found 179.0865.

1-Methyl-2-(3-methylbuta-1,2-dien-1-yl)benzene. (237)[77]



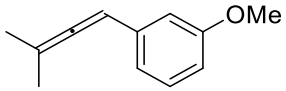
This compound was prepared according to the general procedure C, giving a viscous colourless oil (95 mg, 60%) (R_f 0.47, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3063, 2980, 1952, 1601, 1460 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.37 (d, J = 4 Hz, 1H), 7.20-7.10 (m, 3H), 6.21 (m, 1H), 2.41 (s, 3H), 1.87 (s, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.9, 134.8, 133..9, 132.0, 127.2, 126.2, 129.2, 97.8, 89.9, 20.0, 19.7 ppm; HRMS [$M+H^+$] calculated for $C_{11}H_{13}$ 145.1012, found 145.1021.

(3-Methylbuta-1,2-dien-1-yl)benzene. (238)[84]



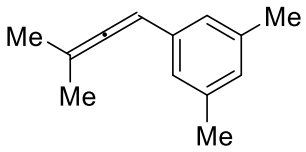
This compound was prepared according to the general procedure C, giving a viscous colourless oil (90 mg, 68%) (R_f 0.46, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3028, 1954, 1598, 1496, 1454. cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.31-7.27 (m, 5H), 6.03-6.00 (m, 1H), 1.86 (s, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.1, 142.0, 131.6, 126.4, 126.3, 99.1, 92.5, 20.2 ppm; HRMS [$M+H^+$] calculated for $C_{11}H_{13}$ 145.1012, found 145.1007.

(3-Methyl-1,2-butadien-1-yl)-3-methoxybenzene (239).[101]



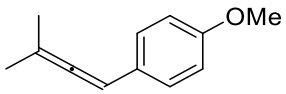
This compound was prepared according to the general procedure C, giving a viscous colourless oil (66 mg, 38%) (R_f 0.56, ethyl acetate : hexane / 5 : 95); IR (neat) 2931, 1950, 1702, 1596, 1259 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.87 (d, *J* = 2.0 Hz, 1H), 6.82 (s, 1H), 6.72 (dd, *J* = 2.0, 2.4 Hz, 1H), 5.98-5.93 (m, 1H) 3.81 (s, 3H),1.82 (s, 3H), 1.81 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.3, 159.9, 137.6, 129.5, 119.4, 112.2, 112.0, 99.3, 92.6, 55.3, 20.4 ppm; HRMS [$M+H^+$] calculated for $C_{12}H_{15}O$ 175.1117, found 175.1119.

(3-Methyl-1,2-butadien-1-yl)-3,5-dimethylbenzene (240).[101]



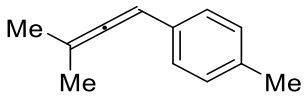
This compound was prepared according to the general procedure C, giving a viscous colourless oil (55 mg, 32%) (R_f 0.58, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2979, 2912, 1954, 1598, 1215 cm^{-1}; ^{1}HNMR (400 MHz; $CDCl_3$) δ 6.87 (s, 2H), 6.80 (s, 1H), 5.93-5.89 (m, 1H), 2.28 (s, 6H), 1.81 (s, 3H), 1.79 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.1, 138.1, 135.9, 128.3, 124.5, 98.9, 92.5, 21.3, 20.4 ppm; HRMS [$M+H^+$] calculated for $C_{13}H_{17}$ 173.1336, found 173.1325.

(*E*)-1-methoxy-4-(3-methylbuta-1,3-dien-1-yl)benzene (241).



This compound was prepared according to the general procedure C, giving a colourless oil (96 mg, 55%) (R_f 0.55, / ethyl acetate:petroleum ether/5:95); IR (CH_2Cl_2) ν_{max} 3057, 3019, 1949, 1494, 1450; ^{1}HNMR (400 MHz; $CDCl_3$) δ 7.21-7.18 (m, 2H), 6.86-6.81 (m, 2H), 5.95 (q, *J* = 2.9 Hz, 1H), 3.79 (s, 3H), 1.81 (d, *J* = 2.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.4, 158.4, 130.2, 127.7, 114.1, 99.1, 92.0, 55.3, 20.5, 18.7 ppm.

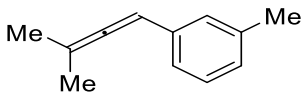
(3-Methyl-1,2-butadien-1-yl)-4-methylbenzene (242).[84]



This compound was prepared according to the general procedure C, giving a viscous colourless oil (113 mg, 72%) (R_f 0.59, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2964, 2918, 1951, 1512, 1454 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.17 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J*= 7.6 Hz,2H), 5.98-5.95 (m, 1H), 2.33 (s, 3H), 1.82 (s, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.9, 136.2,

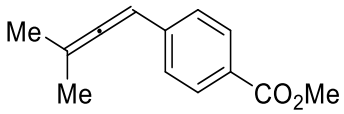
133.1,129.3, 126.6, 99.1, 92.4, 21.3, 20.5 ppm; HRMS [M+H$^+$] calculated for $C_{12}H_{15}$ 159.1168, found 159.1170.

(3-Methyl-1,2-butadien-1-yl)-3-methylbenzene (243).[101]



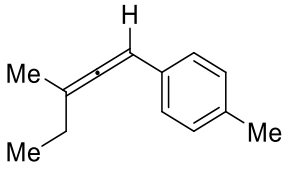
This compound was prepared according to the general procedure C, giving a viscous colourless oil (55 mg, 35%) (R_f 0.58, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3023, 2964, 1944, 1598, 1492 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.16 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 7.2 Hz, 1H), 5.98-5.93 (m, 1H), 2.32 (s, 3H), 1.81 (s, 3H), 1.80 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.2, 138.1, 136.0, 128.5, 127.3, 127.3, 123.9, 99.1, 92.6, 21.5, 20.4 ppm; HRMS [M+H$^+$] calculated for $C_{12}H_{15}$ 159.1168, found 159.1171.

Methyl (3-Methyl-1,2-butadien-1-yl)-4-carboxybenzene (244).[101]



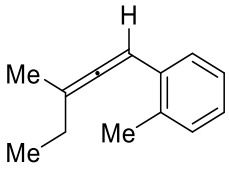
This compound was prepared according to the general procedure C, giving a viscous colorless oil (48 mg, 24%) (R_f 0.63, ethyl acetate:petroleum ether / 5:95); IR (CH_2Cl_2) ν_{max} 3019, 2950, 1952, 1715, 1605, 1453 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.94 (d, *J* = 3.6 Hz, 2H),7.29 (d, *J* = 6.0 Hz, 2H), 6.01-5.99 (m, 1H), 3.90 (s, 3H), 1.87 (s, 6H), 1.85 (s, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 204.5, 167.2, 141.2, 130.0, 129.9, 126.4, 99.8, 92.3, 52.1, 20.2 ppm; HRMS [M+H$^+$] calculated for $C_{13}H_{13}O_2$ 203.1067, found 203.1062.

1-Methyl-4-(3-methylpenta-1,2-dien-1-yl)benzene (245).



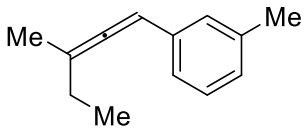
This compound was prepared according to the general procedure C, giving a viscous colourless oil (100 mg, 58%) (R_f 0.7, 100% petroleum ether); IR: 3073, 1949, 1601, 1496, 1150. cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.18 (d, *J* = 4.4 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.08-6.06 (m, 1H), 2.33 (s, 3H), 2.12-2.05 (m, 2H), 1.81 (s, 3H), 1.06 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.0, 136.1, 133.2, 129.3, 126.4, 105.4, 94.3, 27.3, 21.2, 18.9, 12.4 ppm; HRMS [$M+H^+$] calculated for $C_{13}H_{17}$ 173.1325, found 173.1318.

1-Methyl-2-(3-methylpenta-1,2-dien-1-yl)benzene.(246)



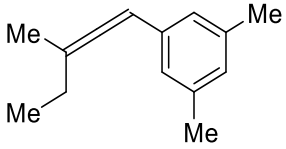
This compound was prepared according to the general procedure C, giving a colourless oil (107 mg, 62%) (R_f 0.67, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3046, 2967, 1951, 1513, 1177 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.19 (d, *J* = 4.8 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.09-6.05 (m, 1H), 2.32 (s, 3H), 2.13-2.06 (m, 2H), 1.81 (d, *J* = 2.4 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.0, 136.1, 133.2, 129.4, 129.3, 126.1, 105.4, 94.3, 27.3, 21.2, 18.9, 12.3 ppm; HRMS [$M+H^+$] calculated for $C_{13}H_{17}$ 173.1325, found 173.1317.

(3-Methyl-1,2-pentadien-1-yl)-3-methylbenzene (247).[101]



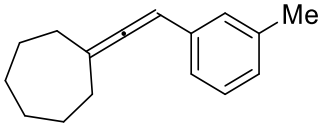
This compound was prepared according to the general procedure, giving a viscous colorless oil (124 mg, 72%) (R_f 0.73, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2575, 2916, 1951, 1604, 1450 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.21-7.19 (m, 1H), 7.13-7.11 (m, 2H), 7.01-7.00 (m 1H), 6.12-6.07 (m, 1H), 2.32 (s, 3H), 2.20 - 2.05 (m, 2H), 1.85 (s, 3H), 1.10 - 1.11 (t, *J* = 4.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.4, 138.2, 136.2, 128.5, 127.3, 123.7, 105.4, 94.6, 27.3, 21.5, 19.0, 15.4, 12.4 ppm; HRMS [M+H^+] calculated for $C_{13}H_{17}$ 173.1325, found 173.1326.

1,3-dimethyl-5-(3-methylpenta-1,2-dien-1-)benzene (248).



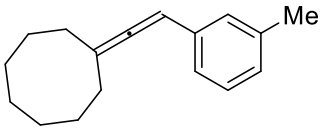
This compound was prepared according to the general procedure, giving a viscous colourless oil (59 mg, 32%) (R_f 0.58, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 2979, 2912, 1954, 1598, 1215 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.91 (s, 2H), 6.84 (s, 1H), 6.05-6.04 (m, 1H), 2.31 (s, 6H), 2.14-2.09 (m, 1H), 1.84 (d, *J* = 3.2 Hz, 3H), 1.08 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 2.203, 138.1, 136.1, 128.3, 124.4, 105.3, 94.5, 27.3, 21.4, 19.0, 12.4 ppm; HRMS [M+H^+] calculated for $C_{14}H_{19}$ 187.1487, found 187.1483.

(2-Cycloheptylidene ethenyl)-3-methylbenzene (249).[101]



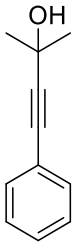
This compound was prepared according to the general procedure C, giving a viscous colourless oil (95 mg, 45%) (R_f 0.48, 100% petroleum ether); IR (neat) 3066, 2924, 1951, 1605, 1458 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.16 (t, *J* = 4.0 Hz, 2H), 7.08 (s, 1H), 6.95 (d, *J* = 6.8 Hz, 1H), 5.94 (m, *J* = 2.4 Hz, 1H), 2.37-2.29, (m, 7H), 1.69-1.61 (m, 8H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.4, 138.1, 136.1, 128.5, 127.3, 127.2, 123.7, 108.4, 92.3, 32.3, 29.5, 28.8, 21.5 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{21}$ 213.1638, found 213.1643.

(2-Cyclooctylidene ethenyl)-3-methylbenzene (250).[101]



This compound was prepared according to the general procedure C, giving a viscous colourless oil (126 mg, 56%) (R_f 0.56, 100% petroleum ether); IR (neat) 3025, 2920, 1941, 1603, 1443, 1219 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.15 (t, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.97 (d, *J* = 2.0 Hz, 1H), 2.32-2.26, (m, 7H), 1.79-1.54 (m, 10H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.6, 138.1, 136.3, 128.5, 127.8, 127.4, 127.2, 123.8, 108.3, 93.0, 31.7, 27.1, 27.1, 26.9, 26.2, 21.5 ppm; HRMS [$M-H^+$] calculated for $C_{17}H_{23}$ 225.1638, found 225.1654.

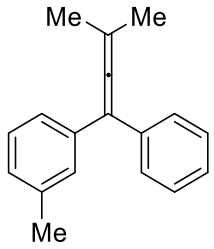
2-Methyl-4-phenylbut-3-yn-2-ol (251)[140]



In small mortar **was** added anhydrous acetone (1.16 g, 20 mmol), ethynyl benzene (2.09 g, 20.00 mmol) and potassium t-butoxide (2.21 g, 20.00 mmol) then use the pestle to mix the mixture for ten minutes after that, the components were left for 30 minutes at room temperature. in 50 ml beaker was added to the mixture 15 ml of 10% aqueous sodium chloride and extracted with dichloromethane then dry the organic layer over $MgSO_4$, filtered and remove the solvent under

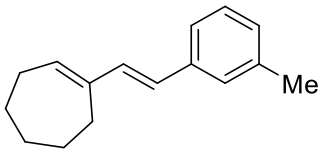
reduce pressure to give a colorless crystal (2.80 g, 87%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.63-7.45 (m, 5H), 5.43 (s, 1H), 1.56 (s, 6H) ppm.

(3-Methyl-1,2-butadien-1-yl)-1-phenyl-1-methylbenzene (252).[101]



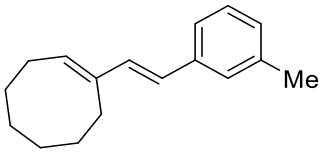
This compound was prepared according to the general procedure C, giving a viscous colorless oil (215 mg, 92%) (R_f 0.35, 100% petroleum ether); IR (neat) 3025, 2917, 1944, 1601, 1443, 880 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34-7.08 (m, 9H), 2.36 (s, 3H), 1.91-1.90 (m, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.8, 143.4, 142.7, 141.7, 137.7, 130.4, 128.2, 128.0, 119.2, 98.4, 22.2, 22.1, 21.6, 20.6 ppm; HRMS [$M+H^+$] calculated for $C_{18}H_{19}$ 235.1481, found 235.1477.

1-[(*E*)-2-(Cyclohept-1-en-1-yl)ethenyl]-3-methylbenzene (256).[101]



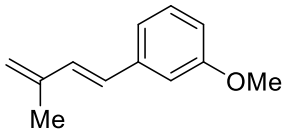
This compound was prepared according to the general procedure D, giving a colourless oil (206 mg, 98%) (R_f 0.46, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3028, 2921, 1603, 1444, 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.17 (m, 3H), 7.00-6.98 (m, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.04-6.01 (m, 1H), 2.44-2.41 (m, 2H), 2.33 (s, 3H), 2.30-2.23 (m, 2H), 1.83-1.76 (m, 2H), 1.57-1.50 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3, 138.1, 135.4, 133.2, 128.5, 127.7, 127.0, 124.9, 123.4, 32.4, 28.8, 27.3, 26.9, 26.4, 21.5 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{20}$ 213.1643, found 2213.1640.

1-[(*E*)-2-(Cycloocta-1-en-1-yl)ethenyl]-3-methylbenzene (257).[101]



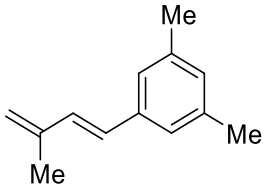
This compound was prepared according to the general procedure D, giving a colourless oil (200 mg, 89%) (R_f 0.46, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3024, 2919, 1702, 1601, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.17 (m, 3H), 7.01-6.99 (m, 1H), 6.74 (d, *J* = 16.4 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 5.86 (t, *J* = 8.8 Hz, 1H), 2.52-2.49 (m, 2H), 2.33 (s, 3H), 2.26-2.23 (m, 2H), 1.62-1.47 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5, 138.1, 138.1, 133.7, 132.1, 128.5, 128.0, 127.0, 125.3, 123.1, 30.6, 28.5, 27.5, 27.1, 26.4, 24.4, 21.5 ppm; HRMS [$M+H^+$] calculated for $C_{17}H_{22}$ 227.1800, found 227.1788.

[(1*E*)-3-Methylbuta-1,3-dien-1-yl]-3-methoxybenzene (258).[101]



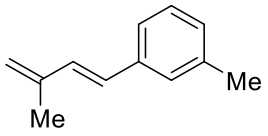
This compound was prepared according to the general procedure D, giving a colourless oil (88 mg, 51%) (R_f 0.55, ethyl acetate : petroleum ether / 5 : 95); IR (CH_2Cl_2) ν_{max} 2939, 1603, 1464, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.21 (m, 1H), 7.04-7.02 (m, 1H), 6.96-6.94 (m, 1H), 6.85 (d, *J* =16.4 Hz, 1H), 6.78-6.76 (m, 1H), 6.49 (d, *J* = 16.4 Hz, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 3.81 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 142.1, 138.9, 132.1, 129.6, 128.7, 119.3, 117.6, 113.3, 111.7, 55.3, 18.7 ppm; HRMS [$M+H^+$] calculated for $C_{12}H_{14}O$ 175.1123, found: 175.1114.

[(1*E*)-3-Methylbuta-1,3-dien-1-yl]-3,5-dimethylbenzene (260).[101]



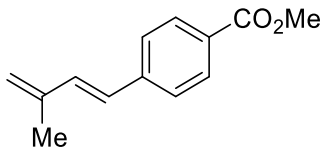
This compound was yield according to the general procedure D, giving a colourless oil (144 mg, 84%) (R_f 0.56, 100% petroleum ether); IR (neat) 2916, 1598, 1445, 1162, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.05 (s, 2H), 6.88 (s, 1H) 6.85 (d, *J* = 16.0 Hz, 2H), 6.48(d, *J* = 16.0 Hz, 1H), 5.10 (s, 1H), 5.04 (s, 1H), 2.30 (s, 6H), 1.95 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.3, 138.1, 137.4, 131.4, 129.3, 128.9, 124.6, 124.5, 117.1, 21.4, 20.4, 18.7 ppm; HRMS [$M+H^+$] calculated for $C_{13}H_{16}$ 173.1330, found 173.1328.

[(1*E*)-3-Methylbuta-1,3-dien-1-yl]-3-methylbenzene (259).[101]



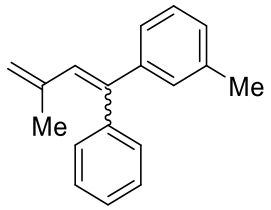
This compound was prepared according to the general procedure D, giving a colourless oil (138 mg, 88%) (R_f 0.56, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3022, 2919, 1605, 1449, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.21 (m, 3H), 7.06-7.05 (m, 1H), 6.87 (d, *J* = 16.0 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.11 (s, 1H), 5.06 (s, 1H), 2.33 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.4, 138.1, 136.1, 128.3, 124.4, 105.3, 94.5, 27.3, 21.4, 19.0, 12.4 ppm; HRMS [$M+H^+$] calculated for $C_{12}H_{14}$ 159.1174, found 159.1171.

Methyl-[(1*E*)-3-methylbuta-1,3-dien-1-yl]-4-carboxybenzene (261).[101]



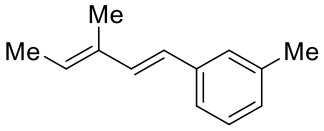
This compound was prepared according to the general procedure D, giving a colourless oil (198 mg, 98% M.P. = 94.5 – 95.5 °C) (R_f 0.61, ethyl acetate:petroleum ether / 5 : 95); IR (CH_2Cl_2) ν_{max} 2947, 1708, 1600, 1455, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, *J* = 6.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 5.18 (s, 1H), 5.12 (s, 1H), 3.89 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 142.0, 141.8, 134.2, 130.0, 128.8, 127.7, 126.4, 119.1, 52.2, 18.6 ppm; HRMS [$M+H^+$] calculated for $C_{13}H_{14}O_2$ 203.1072, found 203.1065.

(3-Methylbuta-1,3-dien-1-yl)-1-phenyl-1-(4-methylbenzene) (262).[101]



This compound was prepared as an approx. 1:1 of *E*/*Z* isomers according to the general procedure D, giving a colourless oil (156 mg, 67%) (R_f 0.37, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3021, 2914, 1599, 1489, 1180, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.01 (m, 9H), 6.67 (s, 1H), 5.04-4.98 (m, 2H), 2.44 (s, 3H), 2.36 (d, *J* = 14 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.7, 141.4, 138.3, 131.0, 130.4, 128.6, 128.2, 128.1, 128.0, 127.8, 127.2, 124.8, 124.3, 119.1, 22.1, 21.6 ppm; HRMS [$M+H^+$] calculated for $C_{18}H_{18}$ 235.1487, found 235.1486.

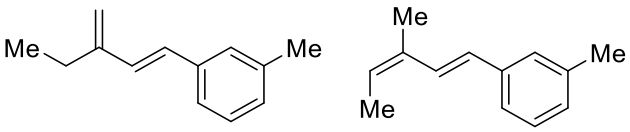
[(2*E*, *4E*)-3-Methylpenta-2,4-dien-1-yl]-3-methylbenzene (167).[101]



This compound was prepared according to the general procedure D, giving a colourless oil (100 mg, 58%) (R_f 0.39, 100% petroleum ether); IR (CH_2Cl_2) ν_{max} 3025, 2980, 1640, 1442, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.18 (m, 3H), 7.01 (d, *J* = 6 Hz, 1H), 6.81 (d, *J* = 16.4 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 5.71 (m, 1H), 2.35 (s, 3H), 1.85 (s, 3H), 1.78 (d, *J* = 6.0 Hz, 3H)

ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0,138.0, 133.8, 128.3, 128.0, 127.8, 127.0, 125.0, 123.0, 21.8, 14.0, 12.0 ppm; HRMS [M+H^+] calculated for $C_{13}H_{17}$ 173.1325, found 173.1323.

[(1*E*)-3-Ethylbuta-1,3-dien-1-yl]-3-methylbenzene (263) and [(2*Z*, *4E*)-3-methylpenta-2,4-dien-1-yl]-3-methylbenzene (264).[101]



These compounds **263** and **264** were isolated as an inseparable mixture in (60 mg, 35%) yield prepared according to general procedure D.

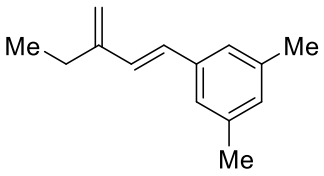
IR (CH_2Cl_2) ν_{max} 3025, 2980, 1640, 1442, 732 cm^{-1};

263 ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.19 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 16.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 5.10 (d, *J* = 2.0 Hz, 2H), 2.36 (q, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 1.16 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.8, 139.9, 128.5, 128.1, 127.1, 125.9, 123.6, 115.0, 24.8, 21.5, 18.8 ppm;

264 ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26 - 7.19 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 1H), (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* =12.0 Hz, 1H), 5.54 (m, 1H), 2.36 (s, 3H), 1.91 (s, 3H), 1.84 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 133.0, 131.2, 128.1, 127.1, 125.6, 123.6, 22.7, 13.3 ppm;

HRMS [M+H^+] calculated for $C_{13}H_{17}$ 173.1325, found: 173.1322.

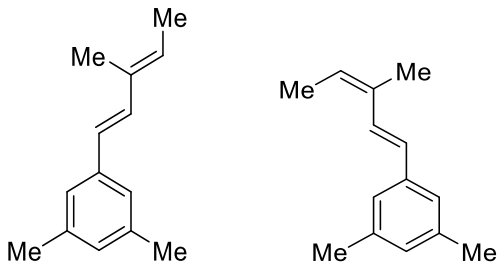
(*E*)-1,3-Dimethyl-5-(3-methylenepent-1-en-1-yl)benzene (265).



Compound **248** was isomerized to three dienes in 97% overall yield according to the general procedure D, this compound isolated from the total result to give a colorless oil (97 mg, 52%) (R_f 0.68, 100% petroleum ether).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.88 (s, 2H), 6.80 (s, 1H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.52 (d, *J* = 16 Hz, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 2.35 (s, 6H), 1.92 (t, *J* = 1.2 Hz, 3H), 1.84 (dd, *J* = 1.2, 1.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 147.9, 138.0, 138.0, 135.9, 133.6, 128.2, 125.5, 124.1, 114.9, 27.2, 21.3, 14.1 ppm; [M+H$^+$] calculated for $C_{14}H_{19}$ 187.1481, found 187.1477.

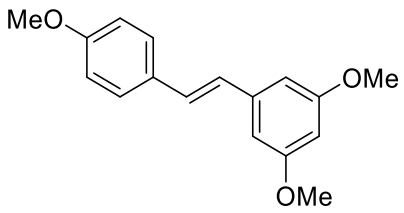
1,3-dimethyl-5-((*1E*,3*E*)-3-methylpenta-1.3-dien-1-yl)benzene (266) and 1,3-dimethyl-5-((*1E,3Z*)-3-methylpnta-1.3-dien-1-yl)benzene (267).



266 and **267** compounds were isomerized in (45 mg, 24%) and (39 mg, 21%) respectively overall yield according to the general procedure, giving a colorless oil (R_f 0.66, 100% petroleum ether). **266** ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.03 (s, 1H), 7.01 (s, 2H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 5.72-5.66 (m, 1H), 2.31 (s, 6H), 1.84 (s, 3H), 1.79 (d, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.0, 134.8, 133.6, 132.9, 129.1, 127.8, 124.3, 124.1, 21.4, 13.8, 12.1 ppm;

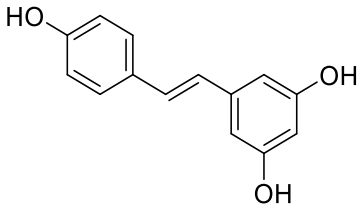
283 ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.20 (d, *J* = 10 Hz, 1H), 6.87 (s, 1H), 6.84 (s, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 5.52-5.50 (m, 1H), 2.38 (d, *J* = 4, 3H), 2.31 (s, 6H), 1.91 (s, 3H), ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.0, 134.8, 133.6, 132.9, 128.7, 125.7, 125.1, 124.1, 21.3, 14.1, 12.8 ppm; HRMS [M+H$^+$] calculated for $C_{14}H_{19}$ 187.1481, found 187.1477.

(*E*)-1,3-Dimethoxy-5-(4-methoxystyryl) benzene (291).



To the solution of diene **5** (0.30 g, 1.00 mmol) in anhydrous methanol (3.00 mL) was added iodine (0.25 g, 1.00 mmol) and the reaction mixture stirred at room temperature for (3.5h). To the solution was added of sat. thiosulfate solution (2.00 mL) and the aqueous layer extracted with ethyl acetate (5 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pet. ether : CH_2Cl_2 : Et_2O / 5:4:1) to furnish **291** (20 mg, 44%) as a yellow solid (MP 55.0-57.0 °C); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45-7.42 (d, *J* = 12.0 Hz, 2H), 7.05 (d, *J* = 16.0 Hz, 1H), 6.91-6.87 (m, 3H), 6.64 (s, 2H), 6.37 (s, 1H), 3.82 (s, 9H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 161.0, 159.5, 139.8, 130.0, 128.8, 127.9, 126.6, 114.2, 104.4, 99.7, 55.5 ppm; HRMS [M+H$^+$] calculated for $C_{17}H_{19}O_3$ 271.1329, found 271.1328.

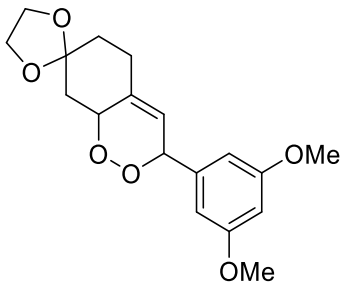
Resveratrol (6).



To a solution of compound **291** (20 mg, 0.087 mmol) in CH_2Cl_2 (2.00 mL) was added a solution of BBr_3 in CH_2Cl_2 (8.00 mL, 1.0 M, 0.78 mmol) drop wise at 0 °C over 30 min. The reaction mixture was stirred at room temperature for 3 h. H_2O (10 mL) was added and the aqueous layer extracted with CH_2Cl_2 (10 mL) and the organic layer combined and dried ($MgSO_4$), filtered the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (R_f 0.7, ethyl acetate:hexane/3:1) to furnish **6** as a yellow solid (12 mg, 70%, MP 240-242 °C); IR (CH_2Cl_2) ν_{max} 3565, 3058, 1415, 1091, 756 cm^{-1}; ^{1}H NMR (400 MHz; d_6-DMSO)

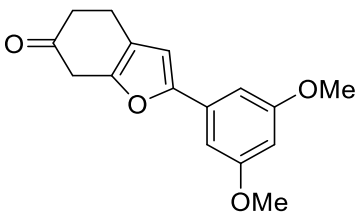
δ 7.35 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.71-6.69 (d, *J* = 8.0 Hz, 2H), 6.33 (s, 2H), 6.06 (s, 1H) ppm; ^{13}C NMR (100 MHz; d_6-DMSO) δ 159.0, 157.7, 139.8, 128.6, 128.4, 126.1, 116.0, 104.8, 102.3 ppm; HRMS [M+H$^+$] calculated for $C_{14}H_{13}O_3$ 229.0870, found 229.0861.

3-(3,5-Dimethoxyphenyl)-5,6,8,8a-tetrahydro-3H-spiro[benzo[c]dioxine-7,2'-[1,3]dioxolane] 12 (7).[141]



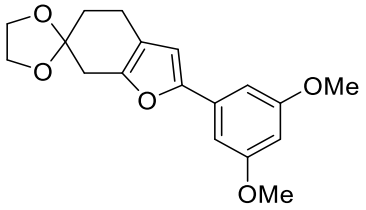
To a solution of compound **5** (151 mg, 0.5 mmol) in CH_2Cl_2 (100 mL) was added methylene blue (50 mg, 0.16 mmol) and the reaction mixture exposed to a slow stream of O_2, and then irradiated with visible light for 3.5 h. The solvent was evaporated under reduce pressure and the residue was purified by flash chromatography (R_f 0.35, ethyl acetate:hexane/1:9) to give **7** as a colorless oil (90 mg, 54%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.54 (s, 2H), 6.41 (s, 1H), 5.81 (s, 1H), 5.31 (s, 1H), 4.78-4.74 (m, 1H), 3.99-3.66 (m, 4H), 3.79 (s, 6H), 2.42 (d, *J* = 8.0 Hz, 2H), 2.12 (m, 1H), 1.83 (m, 1H), 1.61 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.8, 141.1, 137.4, 118.6, 108.8, 106.4, 100.3, 79.9, 64.7, 64.5, 55.4, 38.5, 35.4, 28.2 ppm; HRMS [M+Na$^+$] calculated for $C_{18}H_{22}O_6$ 357.1309, found 357.1308.

2-(3,5-Dimethoxyphenyl)-4,7-dihydrobenzofuran-6(5H)-one (303).[19]



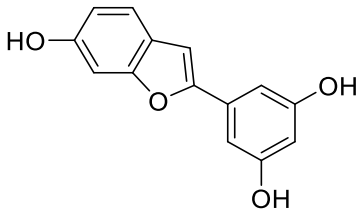
To a solution of CBr_4 (0.092 g, 0.27 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added PPh_3 (0.073 g, 0.27 mmol). The resulting mixture was stirred for 15 min, and then a solution of **7** (75 mg, 0.22 mmol) in CH_2Cl_2 (1.0 mL) was added. The reaction mixture was brought to room temperature and stirred for a further 17 h. After this period, the solvent was removed *in vacuo* and the crude product purified by column chromatography (R_f = 0.56, pet. ether:CH_2Cl_2:Et_2O/5:4:1) to give the furan (**303**) as a white crystalline solid (37 mg, 60%, MP = 146–148 °C); IR (CH_2Cl_2) ν_{max} 3019, 1713, 1597, 1216 cm^{-1}; ^1H NMR (400 MHz; CDCl3) δ 6.77 (s, 2H), 6.52 (s, 1H), 6.37 (s, 1H,), 3.82 (s, 6H), 3.58 (s, 2H), 2.77 (t, *J* = 6.4 Hz, 2H,), 2.66 (t, J = 6.4 Hz, 2H,) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.1, 161.1, 153.8, 146.1, 132.5, 118.7, 105.8, 101.6, 99.8, 64.8, 55.5, 39.4, 19.8 ppm; HRMS [$M+H^+$] calculated for $C_{16}H_{17}O_4$ 273.1121, found 273.1131.

2-(3,5-Dimethoxyphenyl)-4,7-dihydro-5H-spiro[benzofuran-6,2'-[1,3]dioxolane] (310).



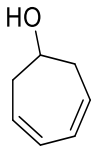
To a solution of CBr_4 (0.092 g, 0.27 mmol) in CH_2Cl_2 (1.0 mL) cooled to 0 °C was added PPh_3 (0.073 g, 0.27 mmol). The resulting mixture was stirred for 15 min. followed by a solution of $NaHCO_3$ (0.022 g, 0.27 mmol), then a solution of **7** (0.075 g, 0.22 mmol in CH_2Cl_2 (1.0 mL) was added. The solution was brought to RT and stirred for a further 72h. After this period, solvents were removed *in vacuo* and the crude product purified by column chromatography (R_f 0.58, pet. ether:CH_2Cl_2:Et_2O/5:4:1) to give the furan **310** as a colourless oil (211 mg, 67%); ^1H NMR (400 MHz; $CDCl_3$) δ: 6.75 (d, *J* = 2.4 Hz, 2H), 6.46 (s, 1H), 6.33 (t, *J* = 4.0 Hz, 1H), 4.04 – 4.01 (m, 4H), 3.80 (s, 6H), 2.92 (s, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 1.91 (t, *J* = 6.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 161.0, 152.9, 148.0, 133.0, 118.1, 109.0, 106.1, 101.7, 99.4, 64.8, 55.4, 34.9, 32.2, 19.3 ppm; HRMS [$M+H^+$] calculated for $C_{18}H_{21}O_5$ 17.1384, found 317.1394.

Moracin M (8).[107]



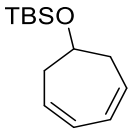
To the solution of compound **310** (25 mg, 0.08 mmol) in anhydrous methanol (1.00 mL) was added iodine (20 mg, 0.08 mmol) and the reaction mixture stirred at room temperature until the starting material was consumed (3.5h). To the solution was added (2.00 mL) of sat. soln. of sodium thiosulfate pentahydrate and the aqueous layer extracted with ethyl acetate (5 mL) The organic extracts were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. The residue crude (24 mg) was directly entered to the next step by dissolving in CH_2Cl_2 (2 mL) and a solution of BBr_3 in CH_2Cl_2 (8 mL, 1.0 M, 0.80 mmol) added drop wise at 0°C over 30 min under N_2. The reaction mixture was then stirred at room temperature for 3 hours. After this period H_2O (10 mL) was added and the aqueous layer extracted with CH_2Cl_2 (10 mL) and the organic layer combined and dried with magnesium sulfate, filtered the solvent removed under reduced pressure. Purification by silica gel column chromatography (R_f 0.31, hexane:ethyl acetate/1:1) gave moracin M (**8)** as a white solid (17 mg, 90%) yield over 2-steps, m.p. 280-282 °C (lit. 271-271 °C); ^{1}H NMR (400 MHz; d_6-DMSO) δ 7.34 (d, *J* = 8.0 Hz, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 2H), 6.18 (s, 1H) ppm; ^{13}C NMR (100 MHz; d_6-DMSO) δ 159.3, 156.2, 155.7, 154.4, 132.2, 121.6, 121.3, 112.9, 103.1, 102.8, 102.1, 97.9 ppm; ^{1}H NMR (400 MHz; d_4-methanol) δ: 7.33 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 2H), 6.76 (s, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.26 (s, 1H) ppm; ^{13}C NMR (100 MHz; d_4-methanol) δ 158.5, 155.8, 155.3, 154.7, 132.5, 121.7, 120.8, 111.9, 102.7, 102.2, 101.0, 97.2 ppm; HRMS [M+H$^+$] calculated for $C_{14}H_{11}O_4$ 243.0652, found 243.0661.

3,5-Heptadienol (323).[117]



To a solution of (1.00 g, 10.0 mmol) of tropone in methanol 20 mL was added sodium borohydride (0.50 g, 13.2 mmol). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and diethyl ether 25 mL was added to the crude and washed with water (10 mL) and brine (2 x 10mL). The organic layer was extracted, dried over $MgSO_4$, filtered and the solvent was removed under reduce pressure, gave **323** as a yellow oil (0.85 g, 77%). (R_f 0.6, 1:1/EtOAc:hexane) IR (CH_2Cl_2) ν_{max} 3325, 2915, 1430 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.71-5.67 (m, 2H), 5.61-5.57 (m, 2H), 4.33 (s, 1H), 3.85-3.80 (m, 1H), 2.46-2.38 (m, 2H), 2.28-2.19 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 128.8, 126.1, 69.4, 40.6 ppm.

((ᵗButyldimethylsily)oxy)-l,3-cycloheptadiene(324).[118]

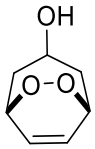


A mixture of dimethylformamide (4 mL), 3,5-cycloheptadienol **323,** (850 mg, 7.7 mmol), tert-butyldimethylsilyl chloride (1.5 g, 10 mmol), and imidazole (1.3 g, 15.8 mmol) was stirred for 20 h at room temperature. The reaction mixture was then decanted into dichloromethane (35 mL) and was washed with water (5 mL), saturated ammonium chloride (5 mL) and then with brine (2 x 5 mL). The organic layers were dried with $MgSO_4$, filtered and evaporated. The crude oil was purified by column chromatography (hexane), to give **324** as a yellow oil (1.28 mg, 75%) (R_f 0.9, hexane); IR (CH_2Cl_2) ν_{max} 3054, 1680, 1422, 1259, 1084 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.77 (t, J = 8.4 Hz, 2 H), 5.66-5.62 (m, 2 H), 4.06-4.00 (m, 1H), 2.51-2.39 (m, 4 H), 0.87 (s, 9 H), 0.05

(s, 6 H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 128.0, 126.0, 71.4, 41.0, 25.7, -2.8 ppm; HRMS [M+H$^+$] calculated for $C_{13}H_{25}OSi$ 225.1669, found 225.1662.

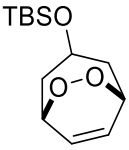
E. General synthesis of endoperoxide.[142] To a stirred solution diene (14 mmol) in CCl_4 80 mL was added rose Bengal (R.B.) 35 mg. The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was passed through the solution and the mixture was stirred at room temperature for 24 h.. The solvent was removed under pressure (30°C, 20 mmHg), giving an oil, which was purified by a silica gel column chromatography (ethyl acetate:hexane/2:3).

6,7-Dioxabicyclo[3.2.2]non-8-en-3-ol (331).



This compound was prepared according to the general procedure E, giving a colorless oil (1.41 g, 71%) (R_f 0.31, ethyl acetate:hexane/1:9); IR (CH_2Cl_2) ν_{max} 3599, 3055, 2987, 1668, 1262cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.35 (dd, *J* = 3.2, 3.6 Hz, 2H), 4.99 (q, *J* = 4.0 Hz, 2H), 3.74-3.65 (m, 1H), 2.56 (s, 1H), 2.33-2.26 (m, 2H), 1.99-1.93 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 128.7, 73.5, 65.7, 40.6 ppm; HRMS [M+Na$^+$] calculated for $C_7H_{10}O_3Na$ 165.0533, found 165.0533.

((6,7-Dioxabicyclo[3.2.2]non-8-en-3-yl)oxy)(tert-butyl)dimrthylsilane (332).[117]



This compound was prepared according to the general procedure E, giving a white solid (2.94 g, 82%, MP 75-77 ^{0}C) (R_f 0.24, ethyl acetate:hexane/5:95); IR (CH_2Cl_2) ν_{max} 3054, 2968, 1471, 1264, 1145 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.37 (dd, *J* = 2.0, 3.2 Hz. 2H), 4.64 (t, *J* = 3.6 Hz, 2H),

3.73-3.68 (m, 1H), 2.22-2.15 (m, 2H), 2.07-2.01 (m, 2H) 0.84 (s, 9H), 0.00 (s, 6H) ppm; HRMS [M+Na^+] calculated for $C_{13}H_{24}SiO_3Na$ 279.1387, found 279.1387.

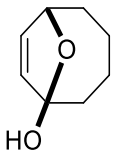
7,8-Dioxabicyclo[4.2.2]dec-9-ene (333)[143]

This compound was prepared according to the general procedure E, giving a white solid powder (1.86 g, 95%, MP 55-56 ^{0}C (literature[143] 53-55 ^{0}C)) (R_f 0.68, diethyl ether:hexane/2:3); IR (CH_2Cl_2) ν_{max} 2953, 1463, 1271 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.14 (dd, *J* = 2.0, 2.0 Hz, 2H), 4.77-4.72 (m, 2H), 2.13-2.06 (m, 2H), 1.89-1.80 (m, 2H), 1.78-1.69 (m, 2H), 1.62-1.55 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 128.2, 76.6, 33.2, 24.0 ppm; HRMS [M+H^+] calculated for $C_8H_{13}O_2$ 141.0910, found 141.0909.

F. General procedure of enantio-enrich lactone formation. [119]

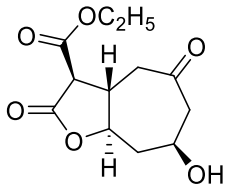
To a solution of the endoperoxide (1.0 mmol) in dry THF (5 mL) was added (0.1 mmol) catalyst a or b. The resultant mixture was stirred for 16 h. at room temperature After this period a solution of ethyl malonate (1.0 mmol) [prepared in THF (3.0 mL) by the addition of NaOEt (2.2 mL, 0.5 M, 1.1 mmol) to the malonate (1.0 mmol)] was added dropwise at 0 °C, and the resultant solution allowed to warm to room temperature and stirred. After 1-2 h an additional tetrahydrofuran (15 mL) was added to help the solubility then the reaction kept stirred 24 h. The reaction mixture was then cooled to 0 °C and quenched by the addition of 1 M HCl (10 mL) after which it was partitioned between ethyl acetate (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with further portions of ethyl acetate (2 × 20 mL). The organic layers were then combined, washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed under pressure. The crude products were then purified by chromatography column eluting with (hexane:ethyl acetate/2:3). The following products were obtained.

(*Z*)-4-Hydroxycyclooct-2-en-1-one (344)[143]



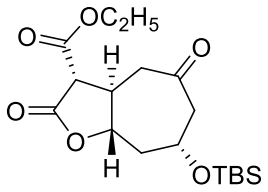
This compound was isolated through the lactonization formation general procedure F using the b catalyst before added the malonate giving a white solid crystal (133 mg, 95%, MP 107 – 109 ^{0}C(in literature[143] 93-94 ^{0}C)) (R_f 0.53, ethyl acetate:hexane/2:3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.00 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.78 (d, *J* = 5.6 Hz, 1H), 4.98 (d, *J* = 6.8 Hz, 1H), 2.73 (s, 1H), 2.00-1.85 (m, 2H), 1.69-1.50 (m, 4H), 1.48-1.44 (m, 2H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 134.5, 132.6, 11.4, 81.6, 39.0, 33.5, 23.8, 23.0 ppm; HRMS [M+H$^+$] calculated for $C_8H_{13}O_2$ 141.0910, found 141.0911.

(-)Ethyl(3R,3aS,7S,8aR)-7-Hydroxy-2,5-dioxooctahydro-2H-cyclohepta[b]furan-3-carboxylate (334).



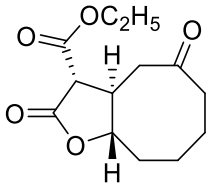
This compound was prepared according to the general procedure F using the a catalyst, giving a colourless oil (210 mg, 82%) (R_f 0.17, petroleum ether:ethyl acetate/1:1); $[\alpha]^{24}_D$ = -29.0 ($_c$ 1.00, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3596, 3055, 1788, 1736, 1709, 1180 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.30-4.24 (m, 2H), 3.93 (ddd, *J* = 2.8, 2.4, 1.6 Hz, 1H), 3.34 (d, *J* = 12.4 Hz, 1H), 3.23-3.16 (m, 1H), 3.06 (t, *J* = 11.6 Hz, 1H), 2.87 (dd, *J* = 5.4, 4.8 Hz, 1H), 2.80-2.71 (m, 2H), 2.32 (dd, *J* = 11.6, 11.6 Hz, 1H), 1.98-1.89 (m, 1H), 1.31 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 205.7, 169.6, 166.4, 78.9, 65.4, 62.7, 53.1, 53.1, 44.4, 43.0, 41.7, 14.1 ppm; HRMS [M+Na$^+$] calculated for $C_{12}H_{16}O_6Na$ 279.0836, found 279.0839.

(+)-ethyl(*3S,3aR,7R,8aS*)-7-((tert-butyldimethylsilyl)oxy)-2,5-dioxooctahydro-2H-cyclohepta[b]furan-3-carboxylate (335).[17]



This compound was prepared according to the general procedure F using the b catalyst , giving a yellow viscous oil (296 mg, 80%) (R_f 0.55, hexane:ethyl acetate/3:2); $[\alpha]^{22}_D$ = +7.4 ($_c$ 1.00, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1787, 1737, 1709, 1256 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 4.23 (dq, *J* = 2.0, 2.4 Hz, 2H), 4.17-4.10 (m, 1H), 3.89-3.83 (m, 1H), 3.30 (t, *J* = 6.4 Hz, 1H), 3.19-3.15 (m, 1H), 2.99 (dd, *J* = 10.8, 10.8 Hz, 1H), 2.80 (dd, *J* = 5.2, 4.8 Hz, 1H), 2.62-2.57 (m, 2H), 2.27 (dd, *J* = 11.4, 12 Hz, 1H), 1.98-1.89 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 205.8, 169.6, 166.4, 79.0, 66.0, 62.5, 53.2, 44.7, 43.7, 41.4, 25.8, 25.6, 17.9, 14.0, -4.8 ppm; HRMS [$M+Na^+$] calculated for $C_{18}H_{30}O_6SiNa$ 393.1704, found 393.1693.

(+) Ethyl (*3S,3aR,9as*)-2,5-dioxodecahydrocycloota[b]furan-3-carboxylate(336).[17]

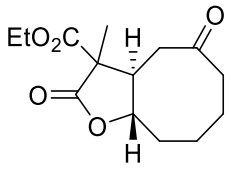


This compound was prepared according to the general procedure F catalyst b, giving a viscous colorless oil (175 mg, 69%) (R_f 0.50, 6:4 hexane : ethyl acetate); $[\alpha]^{22}_D$ = +65 ($_c$ 1.00, CH_2Cl_2); ^1H NMR (400 MHz; $CDCl_3$) δ 4.33-4.20 (m, 2H), 4.19-4.10 (m, 1H), 3.37 (d, *J* = 12.4 Hz, 1H), 3.23-3.10 (m, 1H), 2.78-2.67 (m, 2H), 2.42 (dd, *J* = 14.4, 11.5 Hz, 1H), 2.33 (dt, *J* = 12.7, 5.6 Hz, 1H), 2.24-2.12 (m, 1H), 1.92-1.69 (m, 4H), 1.50-1.37 (m, 1H), 1.35-1.27 (m, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 211.6, 169.4, 166.6, 84.1, 62.5, 53.9, 45.5, 43.9, 39.0, 31.1, 26.0, 22.1, 14.1 ppm; HRMS [$M-H^+$] calculated for $C_{13}H_{17}O_5$ 253.1071 found 253.1066.

G. General procedure of α-Methylation of Lactone.[119]

To a solution of sodium ethoxide in ethanol (0.5 M, 2.2 mL) and THF (4 mL) was added lactone (1.00 mmol) while holding the reaction under N_2. After 10 min. of stirring the mixture became a sludge. At this period, methyl iodide (149 mg,1.05 mmol) was added and the reaction mixture stirred overnight (16 h) at room temperature. The reaction was quenched by the addition of 1 M HCl (2 mL) and the mixture partitioned between dichloromethane (50 mL) and 1 M HCl (50 mL). The aqueous layer was then extracted, the subsequent organic layers were ($MgSO_4$) dried and filtered, and the solvent was removed under reduced pressure. The TLC test gives one spot of the crude (R_f=0.61 hexane: ethyl acetate 6:4) and this was it used without further purification due to one spot in tlc.

(+)-ethyl (*3R,3aR,9aS*)-3-methyl-2,5-dioxodecahydrocycloocta[b]furan-3-carboxylate (345).[17]



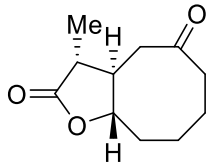
This compound was prepared according to the general procedure G, giving a viscose colorless oil (255 mg, 95%); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1780, 1739, 1707, 1265 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 4.29-4.22 (m, 2H), 4.22-4.17 (m, 1H), 3.26-3.16 (m, 1H), 2.70-2.60 (m, 1H), 2.52-2.43 (m, 1H), 2.42-2.32 (m, 2H), 2.13 (dtd, *J* = 15.2, 5.6, 2.7 Hz, 1H), 1.91-1.71 (m, 4H), 1.58-1.48 (m, 1H), 1.40-1.37 (s, 3H), 1.29 (t, J = 7.1, 2.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 212.1, 173.9, 169.7, 82.6, 62.5, 55.1, 47.7, 40.8, 40.1, 30.8, 26.1, 22.7, 14.1, 13.9 ppm; HRMS [$M+Na^+$] calculated for $C_{14}H_{20}O_5Na$ 291.1203 found 291.1203.

H. General hydrolysis Decarboxylation of the lactones.[119]

To a solution of KOH (2 M, 15 mL) and ethanol (15 mL) was added the lactone (1.4 mmol) and the reaction miture stirred for 16 h. at room temperature. After this period, the mixture was acidified, the aqueous layer extracted with dichloromethane (2 x 20 mL), the resultant organic layer dried with $MgSO_4$ and filtered, and the solvent removed under pressure. The residue was

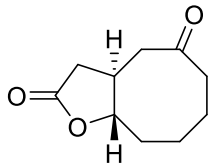
then dissolved in toluene (10 mL) and refluxed overnight. The toluene was then removed under pressure and the residue purified by silica column chromatography eluting with hexane:ethyl acetate 3:2.

(3R,3a,9aS)-3-Methylhexahydrocycloocta[b]furan-2,5(3H,4H)-dione(346).[17]



This compound was prepared according to the general procedure H, giving a viscous colorless oil (59 mg, 30%) (R_f 0.22, hexane:ethyl acetate/3:2); IR (CH_2Cl_2) ν_{max} 3055, 2986, 1765, 1703, 996 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 4.14 (dt, *J* = 3.2, 3.2, 2.8 Hz, 1H), 2.64-2.55 (m, 2H), 2.46-2.26 (m, 3H), 2.23-2.09 (m, 2H), 1.91-1.65 (m, 3H), 1.64-1.51 (m, 1H), 1.50-1.37 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 212.7, 177.0, 83.9, 48.9, 45.2, 42.6, 39.8, 31.4, 25.7, 22.9, 12.8 ppm; HRMS [$M+H^+$] calculated for $C_{11}H_{17}O_3$ 197.1172, found 197.1172.

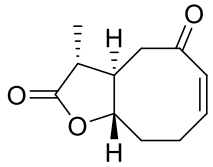
(3aR,9aS)-Hexahydrocycloocta[b]furan-2,5(3H,4H)-dione (347)[17,121]



In a round flask was placed lactone (348) (0.254 g, 1.00 mmol), LiCl (0.084g, 2.00 mmol), H_20 (0.036g, 2.00 mmol), and 5 mL of anhydrous DMSO. After refluxed the mixture at 135°C under nitrogen atmosphere for 20 h, the reaction mixture was cooled to room temperature and quenched with (20 mL) of water and extracted with (50 mL) of ethyl acetate, washed with brine, dried with $MgSO_4$ then filtered. The solvent was removed under reduce pressure. The resultant crude purified with silica column chromatography eluting with (petroleum ether:ethyl acetate/3:2), giving a white solid (130 mg, 71%) (R_f 0.2, petroleum ether:ethyl acetate/3:2). ^1H NMR (400 MHz; $CDCl_3$) δ 4.18 (td, *J* = 9.1, 3.1 Hz, 1H), 2.77-2.57 (m, 4H), 2.45 (dd, *J* = 13.9, 11.3 Hz, 1H), 2.41-2.29 (m,

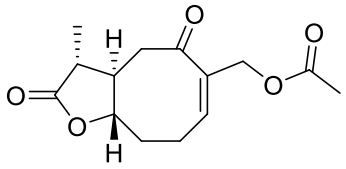
2H), 2.25-2.14 (m, 1H), 1.94-1.69 (m, 3H), 1.68-1.57 (m, 1H), 1.52-1.39 (m, 1H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 212.4, 174.4, 86.0, 46.4, 41.1, 39.7, 37.1, 31.6, 25.7, 22.8 ppm.

(3*R*,3*aR*,9*aS*,Z)-3-Methyl-3a,8,9,9a-tetrahydrocycloota[b]furan-2,5(3H,4H)-dione (357).[144,145]



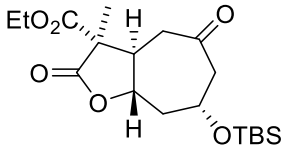
In a suitable flask lactone **346** (1.17 g, 5.0 mmol) was mixed with (900 mg, 6 mmol) of pre-dried sodium iodide in (5 ml) acetonitrile. After this period triethylamine, (607 mg, 0.85 mL, 6 mmol) was added followed by TMSCl, (652 mg, 0.77 mL, 6 mmol) drop wise. The reaction mixture left overnight. At this point (10 mL) of cold hexane then (10 mL) of cold water were added. The resultant mixture extracted with dichloromethane (2 X 10 mL). The combined organic layers dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to give the (1.25 g) which was proceed to the next step without further purification. The crude product was dissolved in DMSO (100 mL) then, $Pd(OAc)_2$ (112 mg, 0.5 mmol) was added and the reaction mixture stirred vigorously at 80 ^{0}C under oxygen atmosphere for 42 h. After $NaHCO_3$(50 mL) was added and the resultant solution extract with diethyl ether (3 X 100 mL). The combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resultant crude was purified by flash column chromatography (ethylacetate : petroleum ether/4:1, R_f 0.57), to give a colorless oil (602 mg, 62%); IR (CH_2Cl_2) ν_{max} 3055, 2985, 1776, 1705, 1665 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.47-6.31 (m, 1H), 6.00 (t, *J* = 12.6 Hz, 1H), 4.17 (td, *J* = 10.2, 5.1 Hz, 1H), 2.91 (dd, *J* = 15.7, 4.9 Hz, 1H), 2.73-2.62 (m, 2H), 2.27-2.19 (m, 2H), 1.96-1.85 (m, 1H), 1.85-1.72 (m, 2H), 1.25 (t, *J* = 2.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 177.1, 177.0, 139.8, 132.7, 84.0, 45.3, 42.7, 39.9, 31.5, 25.8, 12.8 ppm; HRMS [M+Na$^+$] calculated for $C_{11}H_{14}O_3Na$ 217.0835, found 217.0833.

((*3R.3aR,9aS,Z*)-3-Methyl-2,5-dioxo-2,3,3a,4,5,8,9,9a-octahydrocycloota[b]furan-6-yl)methyl acetate (359).[125,113]



To a solution on lactone **357** (291 mg, 1.5 mmol) in THF (0.75 mL) was added (0.3 mL) formaldehyde in water 37% and DMAP (30 mg, 0.24 mmol). The resultant mixture stirred slowly for 10 days at room temperature, after this period the mixture quenched with (5 mL) of 5% HCl at 0^0C then, the mixture extracted with dichloromethane (2 X 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The resultant crude product was purified by flash column chromatography with (ethyl acetate:hexane/1:1) (R_f 0.57), giving a colorless oil (147 mg, 62%); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1776, 1743, 1708 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.79 (d, *J* = 3.6 Hz, 1H), 4.39 (t, *J* = 9.6 Hz, 1H), 4.32 (t, *J* = 5.8 Hz, 1H), 4.25 -4.14 (m, 1H), 4.10-3.99 (m, 1H), 2.92-2.72 (m, 2H), 2.64-2.43 (m, 2H), 2.41-2.27 (m, 2H), 2.06 (s, 3H), 1.40-1.36 (m, 1H), 1.26 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 210.8, 177.0, 170.5, 130.9, 130.2, 82.0, 63.8, 46.9, 41.4, 40.8, 26.1, 23.1, 21.1, 12.6 ppm; HRMS [M+Na^+] calculated for $C_{14}H_{18}O_5Na$ 289.1046 found 289.1044.

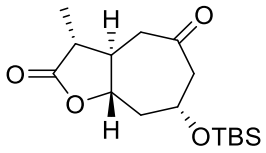
Ethyl(*3R,3aR,7R,8aS*)-7-((tert-butyldimethylsilyl)oxy)-3-methyl-2,5-dioxootahydro-2H-cyclohepta[b]furan-3-carboxylate (354).



This compound was prepared according to the general procedure G, giving a viscous colorless oil (353 mg, 92%) (R_f 0.69, petroleum ether:ethyl acetate/1:1); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1781, 1738, 1708, 1157 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.22 (q, *J* = 2.5 Hz, 2H), 3.95-3.82 (m, 1H), 3.35 - 3.21 (m, 1H), 3.15-3.05 (m, 1H), 2.99 (dd, *J* = 12.4, 10.7 Hz, 1H), 2.37-2.24 (m, 1H), 2.04-

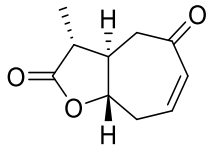
1.89 (m, 1H), 1.90-1.79 (m, 1H), 1.60 (d, *J* = 11.9 Hz, 3H), 1.36 (d, J = 9.1 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 205.8, 174.3, 171.0, 79.3, 62.5, 53.3, 45.2, 41.6, 40.5, 39.2, 25.6, 14.0, 13.8, -4.8 ppm; HRMS [M+Na^+] calculated for $C_{19}H_{32}O_6NaSi$ 407.1860, found 407.1861.

(*3R,3aR,7R,8aS*)-7-((tert-Butyldimethylsilyl)oxy)-3-methylhexahydro-2H-cyclohepta[b]furan-2,5(3H)-dione (365).



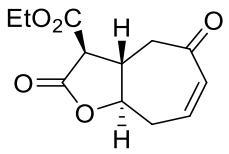
This compound was prepared according to the general procedure H, giving a colorless oil (66 mg, 21%) (R_f 0.54, hexane:ethyl acetate/1:1); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1778, 1707, 1186 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.47-4.38 (m, 1H), 4.34 (dd, *J* = 6.6, 4.9 Hz, 1H), 2.87-2.76 (m, 2H), 2.70 (dd, *J* = 18.3, 2.7 Hz, 1H), 2.62 (td, *J* = 8.9, 4.4 Hz, 1H), 2.39-2.24 (m, 2H), 2.20-2.08 (m, 1H), 1.82 - 1.71 (m, 1H), 1.28-1.23 (3H), 0.83 (d, *J* = 2.9 Hz, 9H), 0.06 (d, *J* = 2.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.3, 177.7, 80.4, 65.4, 51.0, 46.5, 42.9, 41.8, 25.8, 18.0, 12.7, -5.0 ppm; HRMS [M+Na^+] calculated for $C_{16}H_{28}O_4NaSi$ 335.1649, found 335.1650.

(*3R,3a,8aS*)-3-methyl-3a,4,8,8a-tetrahydro-2H-cyclohepta[b]furan-2,5(3H)-dione (366).



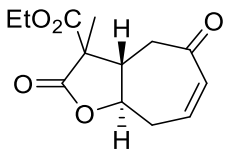
This compound was prepared according to the general procedure H, giving a yellow oil (27 mg, 15%) (R_f 0.53, hexane:ethyl acetate/1:1); IR (CH_2Cl_2) ν_{max} 3054, 2986, 1777, 1706, 1660 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.34 (q, *J* = 3.0 Hz, 1H), 6.09 (d, *J* = 2.9 Hz, 1H), 4.39 (q, *J* = 5.2 Hz, 1H), 3.60-3.41 (m, 1H), 3.26-3.10 (m, 2H), 2.94-2.89 (m, 1H), 2.26-2.15 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 198.7, 177.3, 137.7, 132.5, 80.4, 44.8, 43.4, 42.1, 37.0, 12.8 ppm; HRMS [M+H^+] calculated for $C_{10}H_{13}O_3$ 181.0859,found 181.0855.

Ethyl((*3R,3aS,8aR*)-2,5-dioxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-3-carboxylate (368).[111]



The lactone **334** (256 mg, 1mmol) was dissolved in (5 mL) of dry dichloromethane then triethyl amine was added (0.35 mL, 2 mmol). The resultant reaction mixture was cooled in ice bath to 0 ^{0}C and MsCl (0.15 mL, 1.5 mmol) added dropwise with stirring. After 1 hour the reaction mixture was warmed to RT and stirred overnight until all starting material was consumed indicated by TLC plate. At this point the mixture was cooled to 0 ^{0}C then DBU (0.21 mL, 2 mmol) was added wisely and after one hour leaved to stirred at room temperature for overnight. The reaction mixture diluted with dichloromethane and (10 mL), water (10 mL), the organic layer was separated, and the aqueous layer extracted with dichloromethane (2 X 10 mL). The combined organic layers dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The resultant crude purified by flash column chromatography with (ethyl acetate:hexane/3:7 to 6:4) (R_f 0.71), giving a colorless oil (178mg, 75%); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1784, 1737, 1708, 1604 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.35-6.25 (m, 1H), 6.06 (dd, *J* = 13.2, 2.9 Hz, 1H), 5.04 (td, J = 10.4, 4.7 Hz, 1H), 4.41-4.32 (m, 2H), 3.69-3.60 (1H), 3.27-3.22 (m, 1H), 3.22-3.15 (m, 1H), 2.60-2.48 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 197.3, 165.3, 161.7, 136.4, 132.6, 80.6, 64.6, 44.5, 42.2, 38.7, 36.8, 13.8 ppm; HRMS [M+H$^+$] calculated for $C_{12}H_{15}O_5$ 239.0914, found 139.0914.

Ethyl(*3S, 3aS, 8aR*)-3-methyl-2,5-dioxo-3, 3a, 4, 5, 8, 8a-hexahydro-2H-cyclohepta[b]furan-3-carboxylate (369).



This compound was prepared according to the general procedure G, giving a viscous colorless oil (134 mg, 53%) (R_f 0.26, petroleum ether:ethyl acetate/1:1); IR (CH_2Cl_2) ν_{max} 3054, 2987, 1783, 1738, 1710, 1661, 1185 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.32 (qd, *J* = 6.6, 2.9 Hz, 1H), 6.11-6.02 (m, 1H), 4.48 (td, *J* = 10.3, 4.5 Hz, 1H), 4.30-4.17 (m, 2H), 3.23-3.09 (m, 2H), 2.71-2.58 (m, 2H), 2.51 (dd, *J* = 17.5, 13.0 Hz, 1H), 1.42 (s, 3H), 1.27 (t, *J* = 7.2, Hz, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 198.1, 174.1, 169.4, 137.4, 132.5, 79.4, 62.6, 43.6, 40.2, 39.5, 36.7, 14.3, 14.0 ppm; HRMS [$M+Na^+$] calculated for $C_{13}H_{16}O_5Na$ 275.0890, found 275.0890.

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7. Appendix:

2-(3,5-Dimethoxyphenyl)-4,7-dihydrobenzofuran-6(5H)-one (303) X-Ray data

Formula.

$C_{16}H_{16}O_4$. One molecule in the asymmetric unit. The ring C(2) > C(7) is distorted with C(4)–O(2) lying out of the plane as might be expected with a significant aliphatic proportion in the ring.

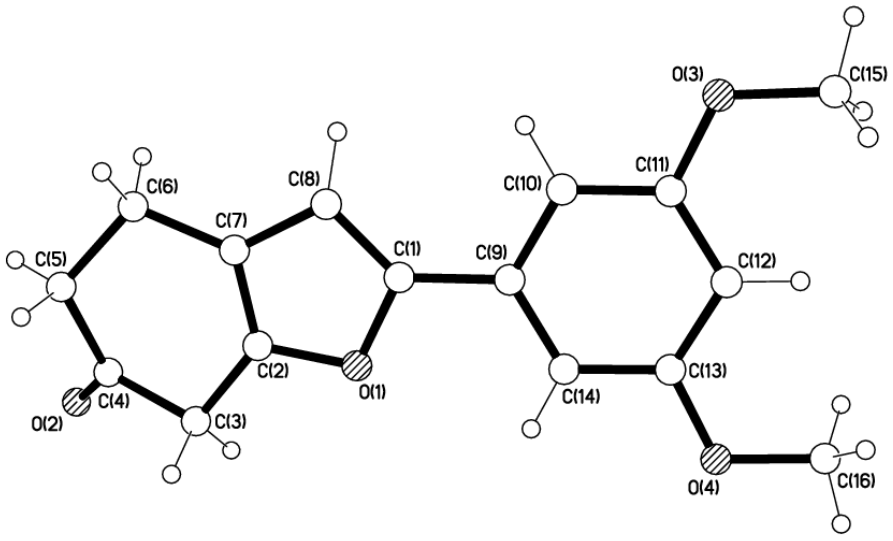
Disorder & Solvent of Crystallisation.

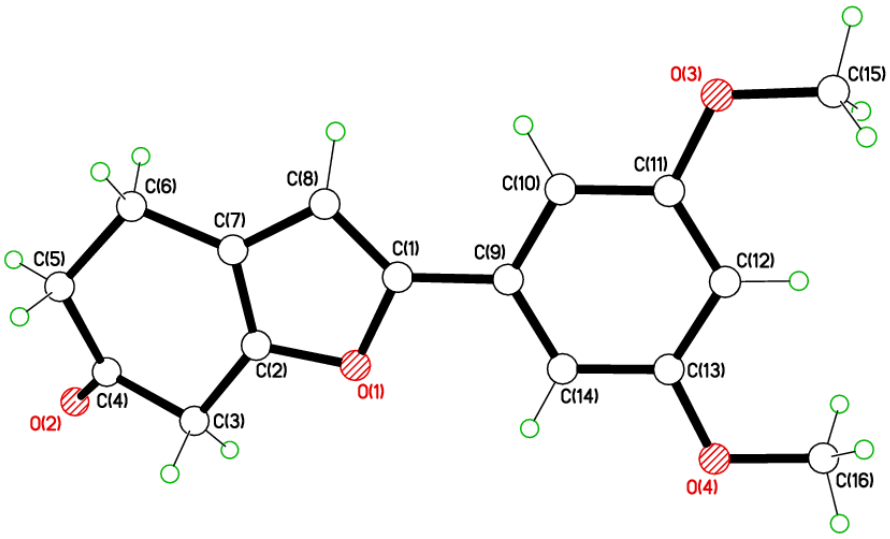
No disorder or solvent of crystallisation.

Packing.

Molecules pack in layers with some weak (aliphatic)C–H···O intermolecular interactions within sheets. Only van der Waals forces between layers.

Author for all publications, posters, etc.: Dr. Mark R.J. Elsegood.

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C(11)
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C(8)
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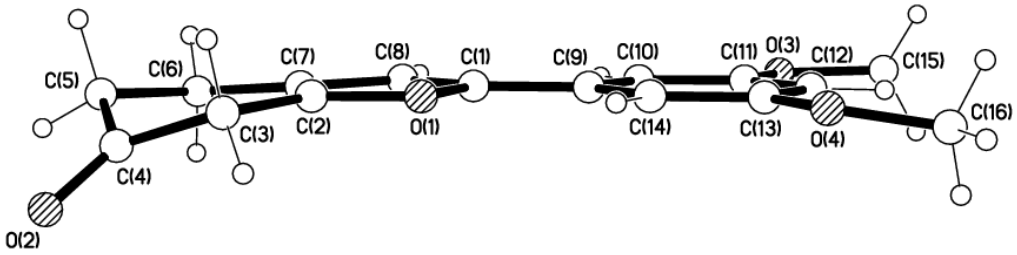
O(4)
C(16)


C(7)
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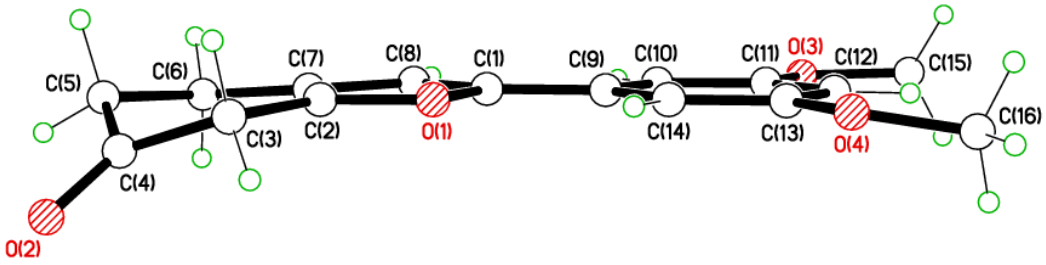
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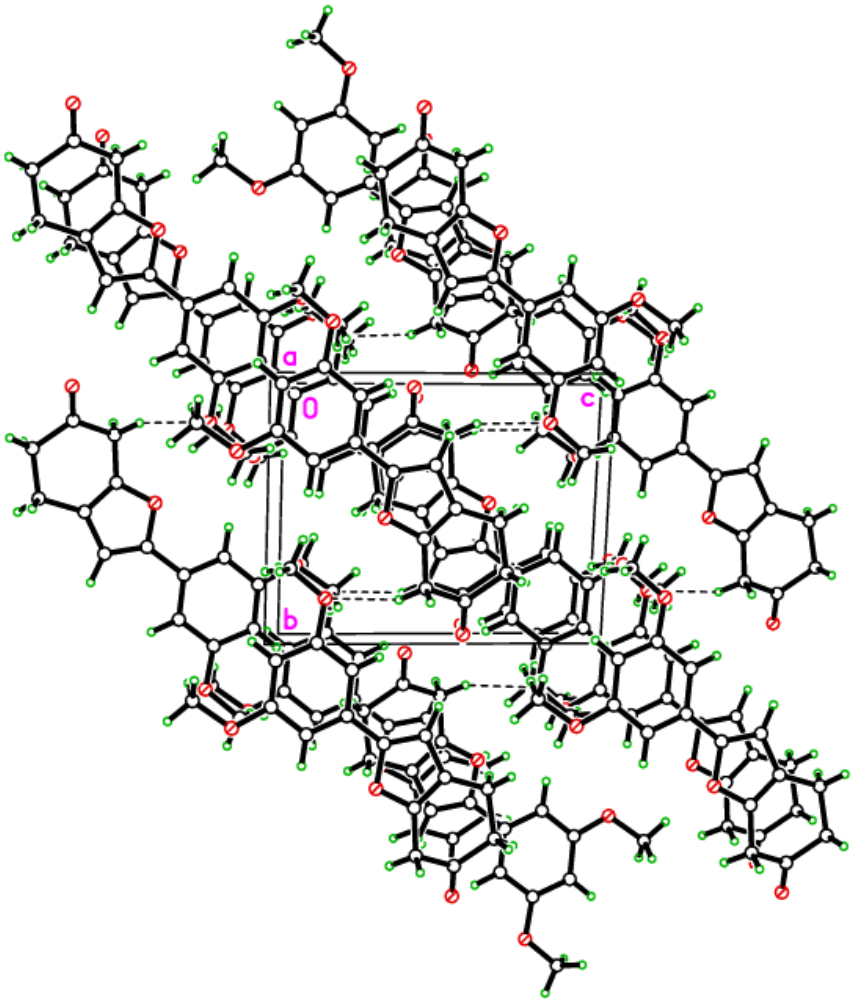
C(4)
O(2)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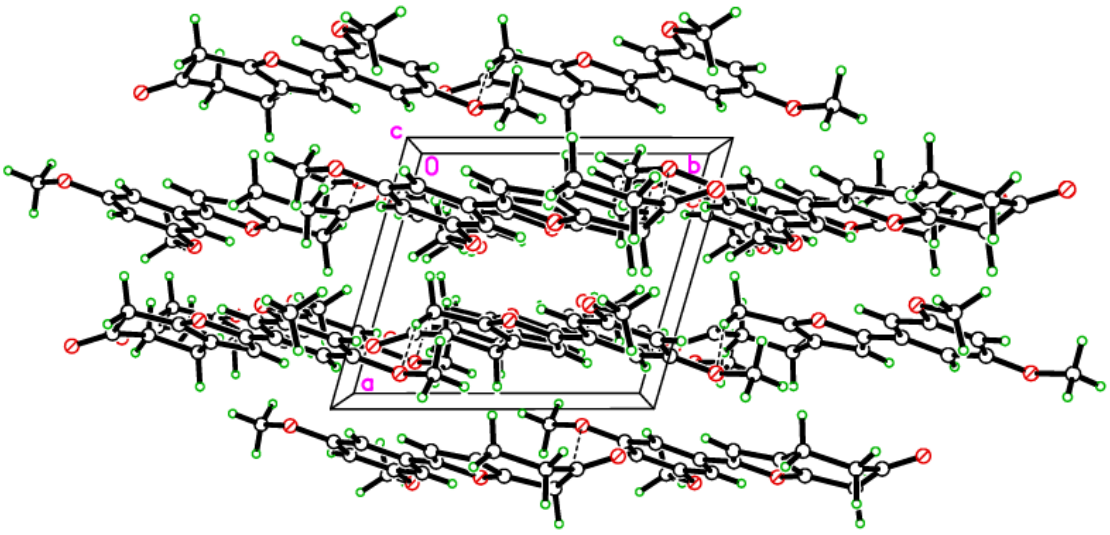


Crystal data

$C_{16}H_{16}O_4$	Z = 2
M_r = 272.29	F(000) = 288
Triclinic, $P\bar{1}$	D_x = 1.416 Mg m^{-3}
a = 7.48034 (16) Å	Cu $K\alpha$ radiation, λ = 1.54184 Å
b = 8.57141 (19) Å	Cell parameters from 7623 reflections
c = 10.4014 (2) Å	θ = 4.3–70.3°
α = 90.8603 (17)°	μ = 0.83 mm^{-1}
β = 94.6762 (18)°	T = 100 K
γ = 105.8774 (19)°	Block, colourless
V = 638.84 (2) Å^3	0.13 × 0.08 × 0.04 mm^3

Data collection

Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000 detector diffractometer.	2324 independent reflections
Radiation source: Rotating anode	2143 reflections with $I > 2\sigma(I)$
Detector resolution: 10 pixels mm^{-1}	R_{int} = 0.031
profile data from ω–scans	θ_{max} = 68.2°, θ_{min} = 4.3°
Absorption correction: multi-scan *CrysAlis PRO* 1.171.39.34b (Rigaku Oxford	h = -8→8

Diffraction, 2017) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	
T_{min} = 0.806, T_{max} = 1.000	k = -10→10
11720 measured reflections	l = -12→12

Refinement

Refinement on F^2	Primary atom site location: iterative
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.032	All H-atom parameters refined
$wR(F^2)$ = 0.085	$w = 1/[\sigma^2(F_o^2) + (0.0388P)^2 + 0.2134P]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 1.07	$(\Delta/\sigma)_{max}$ = 0.001
2324 reflections	$\Delta\rangle_{max}$ = 0.22 e Å^{-3}
245 parameters	$\Delta\rangle_{min}$ = -0.19 e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²) for (mck40)

	x	y	z	U_{iso}*/U_{eq}
C1	0.74475 (17)	0.63752 (14)	0.63340 (11)	0.0227 (3)
O1	0.68007 (12)	0.47270 (10)	0.65125 (8)	0.0235 (2)
C2	0.69736 (17)	0.39693 (14)	0.53759 (11)	0.0229 (3)
C3	0.64839 (19)	0.21786 (15)	0.52724 (12)	0.0265 (3)
H3A	0.695 (2)	0.1750 (18)	0.6040 (15)	0.033 (4)*
H3B	0.509 (2)	0.1700 (19)	0.5121 (15)	0.036 (4)*
C4	0.73635 (17)	0.16745 (14)	0.41293 (11)	0.0238 (3)
O2	0.78693 (13)	0.04451 (10)	0.41461 (8)	0.0294 (2)
C5	0.74718 (19)	0.27102 (15)	0.29558 (12)	0.0258 (3)
H5A	0.820 (2)	0.2344 (17)	0.2376 (14)	0.028 (4)*
H5B	0.617 (2)	0.2425 (18)	0.2547 (15)	0.034 (4)*
C6	0.81535 (19)	0.45662 (15)	0.32061 (11)	0.0245 (3)
H6A	0.954 (2)	0.4945 (18)	0.3155 (14)	0.030 (4)*
H6B	0.761 (2)	0.5069 (17)	0.2533 (14)	0.026 (3)*
C7	0.76920 (16)	0.50602 (14)	0.45032 (11)	0.0222 (3)

C8	0.79919 (17)	0.66262 (15)	0.51211 (11)	0.0231 (3)
H8	0.852 (2)	0.7694 (18)	0.4763 (14)	0.029 (4)*
C9	0.74438 (16)	0.74355 (14)	0.74436 (11)	0.0227 (3)
C10	0.81133 (17)	0.91158 (14)	0.73493 (11)	0.0241 (3)
H10	0.860 (2)	0.9570 (17)	0.6573 (14)	0.029 (4)*
C11	0.80990 (17)	1.01267 (14)	0.83991 (12)	0.0242 (3)
C12	0.74471 (17)	0.95067 (15)	0.95574 (12)	0.0247 (3)
H12	0.7476 (18)	1.0213 (17)	1.0256 (14)	0.024 (3)*
C13	0.68003 (17)	0.78257 (15)	0.96373 (11)	0.0238 (3)
C14	0.67830 (17)	0.67856 (15)	0.85960 (12)	0.0238 (3)
H14	0.633 (2)	0.5644 (19)	0.8694 (14)	0.030 (4)*
O3	0.87717 (13)	1.17582 (10)	0.82132 (8)	0.0294 (2)
C15	0.8749 (2)	1.28634 (16)	0.92497 (13)	0.0290 (3)
H15A	0.750 (2)	1.2772 (18)	0.9497 (15)	0.035 (4)*
H15B	0.957 (2)	1.2731 (18)	1.0008 (16)	0.033 (4)*
H15C	0.923 (2)	1.392 (2)	0.8914 (15)	0.041 (4)*
O4	0.61433 (13)	0.70844 (10)	1.07288 (8)	0.0288 (2)
C16	0.6394 (2)	0.80924 (16)	1.18787 (12)	0.0280 (3)
H16A	0.594 (2)	0.7364 (18)	1.2551 (14)	0.028 (4)*
H16B	0.565 (2)	0.8867 (17)	1.1789 (13)	0.027 (3)*
H16C	0.775 (2)	0.8673 (19)	1.2087 (15)	0.036 (4)*

Geometric parameters (Å, º) for (mck40)

C1—C8	1.3593 (17)	C9—C10	1.3973 (17)
C1—O1	1.3830 (14)	C9—C14	1.3991 (17)
C1—C9	1.4589 (16)	C10—C11	1.3863 (17)
O1—C2	1.3725 (14)	C10—H10	0.957 (15)
C2—C7	1.3481 (17)	C11—O3	1.3730 (14)
C2—C3	1.4773 (17)	C11—C12	1.3946 (17)
C3—C4	1.5169 (16)	C12—C13	1.3950 (17)
C3—H3A	0.964 (16)	C12—H12	0.934 (14)
C3—H3B	1.007 (16)	C13—O4	1.3696 (14)
C4—O2	1.2131 (15)	C13—C14	1.3894 (17)
C4—C5	1.5145 (17)	C14—H14	0.954 (15)
C5—C6	1.5430 (17)	O3—C15	1.4288 (15)
C5—H5A	0.949 (15)	C15—H15A	0.969 (16)

C5—H5B	0.997 (16)	C15—H15B	0.985 (16)
C6—C7	1.5025 (16)	C15—H15C	0.959 (17)
C6—H6A	1.006 (15)	O4—C16	1.4339 (15)
C6—H6B	0.950 (15)	C16—H16A	0.965 (15)
C7—C8	1.4322 (17)	C16—H16B	0.980 (14)
C8—H8	0.984 (15)	C16—H16C	1.005 (17)
C8—C1—O1	109.66 (10)	C7—C8—H8	127.7 (8)
C8—C1—C9	134.41 (11)	C10—C9—C14	119.95 (11)
O1—C1—C9	115.91 (10)	C10—C9—C1	119.38 (11)
C2—O1—C1	106.14 (9)	C14—C9—C1	120.67 (11)
C7—C2—O1	111.13 (10)	C11—C10—C9	119.50 (11)
C7—C2—C3	129.13 (11)	C11—C10—H10	119.9 (9)
O1—C2—C3	119.66 (10)	C9—C10—H10	120.5 (9)
C2—C3—C4	108.89 (10)	O3—C11—C10	115.34 (10)
C2—C3—H3A	110.8 (9)	O3—C11—C12	123.10 (11)
C4—C3—H3A	108.4 (9)	C10—C11—C12	121.56 (11)
C2—C3—H3B	110.9 (9)	C11—C12—C13	118.11 (11)
C4—C3—H3B	107.9 (9)	C11—C12—H12	119.9 (9)
H3A—C3—H3B	109.8 (13)	C13—C12—H12	122.0 (8)
O2—C4—C5	122.11 (11)	O4—C13—C14	115.40 (11)
O2—C4—C3	120.54 (11)	O4—C13—C12	123.10 (11)
C5—C4—C3	117.25 (10)	C14—C13—C12	121.50 (11)
C4—C5—C6	116.74 (10)	C13—C14—C9	119.36 (11)
C4—C5—H5A	107.7 (9)	C13—C14—H14	118.7 (9)
C6—C5—H5A	111.8 (9)	C9—C14—H14	122.0 (9)
C4—C5—H5B	104.3 (9)	C11—O3—C15	117.95 (9)
C6—C5—H5B	108.5 (9)	O3—C15—H15A	113.0 (9)
H5A—C5—H5B	107.2 (12)	O3—C15—H15B	111.3 (9)
C7—C6—C5	111.70 (10)	H15A—C15—H15B	109.8 (12)
C7—C6—H6A	109.5 (8)	O3—C15—H15C	104.5 (10)
C5—C6—H6A	109.4 (8)	H15A—C15—H15C	108.4 (13)
C7—C6—H6B	111.0 (8)	H15B—C15—H15C	109.6 (13)
C5—C6—H6B	108.5 (9)	C13—O4—C16	117.03 (10)
H6A—C6—H6B	106.6 (12)	O4—C16—H16A	105.6 (9)
C2—C7—C8	106.09 (10)	O4—C16—H16B	110.9 (8)

C2—C7—C6	122.43 (11)	H16A—C16—H16B	108.6 (12)
C8—C7—C6	131.33 (11)	O4—C16—H16C	110.3 (9)
C1—C8—C7	106.97 (11)	H16A—C16—H16C	110.6 (12)
C1—C8—H8	125.3 (8)	H16B—C16—H16C	110.8 (12)
C8—C1—O1—C2	0.37 (13)	C8—C1—C9—C10	0.3 (2)
C9—C1—O1—C2	-178.38 (10)	O1—C1—C9—C10	178.66 (10)
C1—O1—C2—C7	-0.03 (13)	C8—C1—C9—C14	-179.53 (13)
C1—O1—C2—C3	176.91 (11)	O1—C1—C9—C14	-1.18 (17)
C7—C2—C3—C4	14.46 (19)	C14—C9—C10—C11	-0.62 (18)
O1—C2—C3—C4	-161.85 (10)	C1—C9—C10—C11	179.54 (11)
C2—C3—C4—O2	147.96 (12)	C9—C10—C11—O3	-179.58 (11)
C2—C3—C4—C5	-35.51 (15)	C9—C10—C11—C12	0.63 (19)
O2—C4—C5—C6	-138.11 (13)	O3—C11—C12—C13	-179.81 (11)
C3—C4—C5—C6	45.42 (16)	C10—C11—C12—C13	-0.04 (19)
C4—C5—C6—C7	-28.67 (16)	C11—C12—C13—O4	179.47 (11)
O1—C2—C7—C8	-0.30 (14)	C11—C12—C13—C14	-0.57 (19)
C3—C2—C7—C8	-176.87 (13)	O4—C13—C14—C9	-179.46 (11)
O1—C2—C7—C6	175.72 (10)	C12—C13—C14—C9	0.57 (19)
C3—C2—C7—C6	-0.8 (2)	C10—C9—C14—C13	0.03 (18)
C5—C6—C7—C2	7.35 (17)	C1—C9—C14—C13	179.87 (11)
C5—C6—C7—C8	-177.74 (12)	C10—C11—O3—C15	178.45 (11)
O1—C1—C8—C7	-0.55 (14)	C12—C11—O3—C15	-1.77 (18)
C9—C1—C8—C7	177.88 (13)	C14—C13—O4—C16	170.94 (11)
C2—C7—C8—C1	0.52 (14)	C12—C13—O4—C16	-9.10 (18)
C6—C7—C8—C1	-175.01 (13)		

Document origin: *publCIF* [Westrip, S. P. (2010). *J. Apply. Cryst.*, **43**, 920-925].

Computing details

Data collection: *CrysAlis PRO* 1.171.39.34b (Rigaku OD, 2017); cell refinement: *CrysAlis PRO* 1.171.39.34b (Rigaku OD, 2017); data reduction: *CrysAlis PRO* 1.171.39.34b (Rigaku OD, 2017); program(s) used to solve structure: SHELXT 2014/5 (Sheldrick, 2014); program(s) used to refine structure: *SHELXL2018*/1 (Sheldrick, 2018); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table 1

Experimental details

Crystal data	
Chemical formula	$C_{16}H_{16}O_4$
M_r	272.29
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	100
a, *b*, *c* (Å)	7.48034 (16), 8.57141 (19), 10.4014 (2)
α, β, γ (°)	90.8603 (17), 94.6762 (18), 105.8774 (19)
V (Å^3)	638.84 (2)
Z	2
Radiation type	Cu *K*α
μ (mm^{-1})	0.83
Crystal size (mm^3)	0.13 × 0.08 × 0.04
Data collection	
Diffractometer	Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000 detector diffractometer.
Absorption correction	Multi-scan *CrysAlis PRO* 1.171.39.34b (Rigaku Oxford Diffraction, 2017) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.806, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	11720, 2324, 2143
R_{int}	0.031
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.602
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.032, 0.085, 1.07
No. of reflections	2324
No. of parameters	245
H-atom treatment	All H-atom parameters refined
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.22, -0.19

Computer programs: *CrysAlis PRO* 1.171.39.34b (Rigaku OD, 2017), SHELXT 2014/5 (Sheldrick, 2014), *SHELXL2018*/1 (Sheldrick, 2018), Bruker *SHELXTL*.

(*Z*)-4-Hydroxycyclooct-2-en-1-one (344) X-Ray Data

MCKALS8 Figures & Description.

Data collected at the ALS synchrotron. Note authors and acknowledgement below.

Formula.

$C_8H_{12}O_2$. One molecule in the asymmetric unit.

Disorder & Solvent of Crystallisation.

No disorder or solvent of crystallisation.

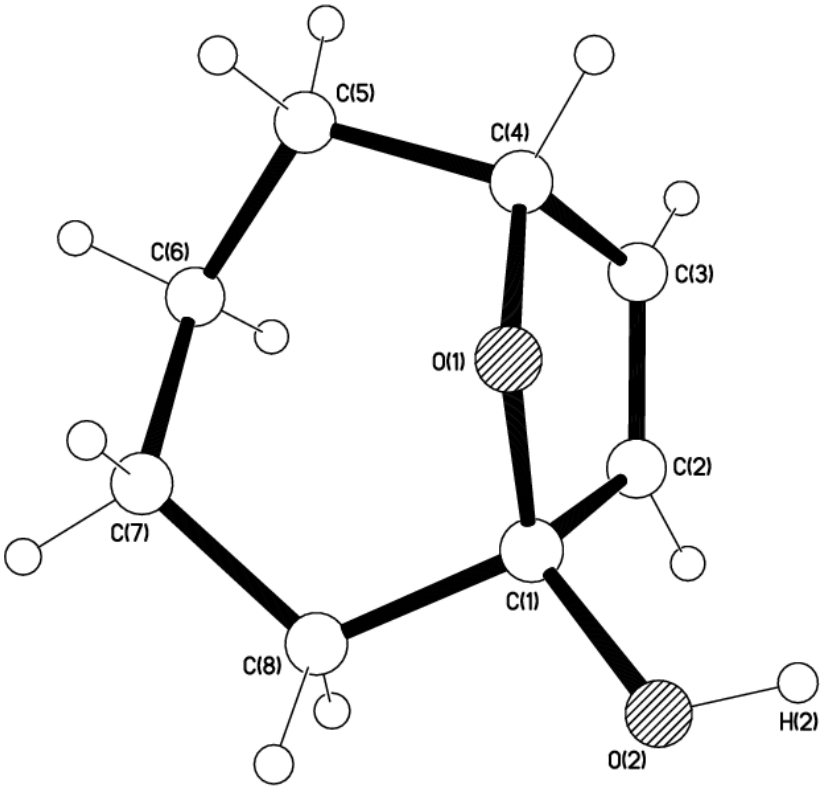
Packing.

Molecules pack via strong O(2)–H(2)···O(2) H-bonds into spiral chains along the 4-fold *c* axis via the hydroxyl groups. There are also weaker C(3)–H(3)···O(1) H-bonds in this direction. See tables for H-bond geometry.

Authors for all publications, posters, etc.: Dr. Mark R.J. Elsegood & Dr. Simon J. Teat.

ALS Acknowledgement, which MUST be used in all publications, seminars, poster, etc.:

This research used resources of the Advanced Light Source, which is a DOE Office of Science User Facility under contract no. DE-AC02-05CH11231.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C(2)
C(7)
C(1)
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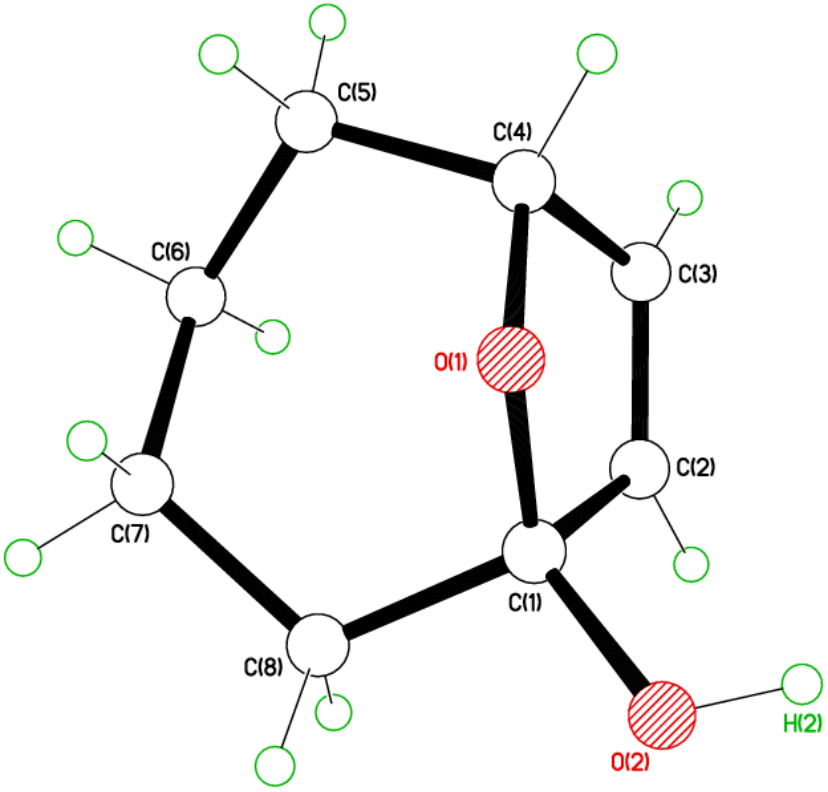
H(2)
O(2)


C(5)
C(4)
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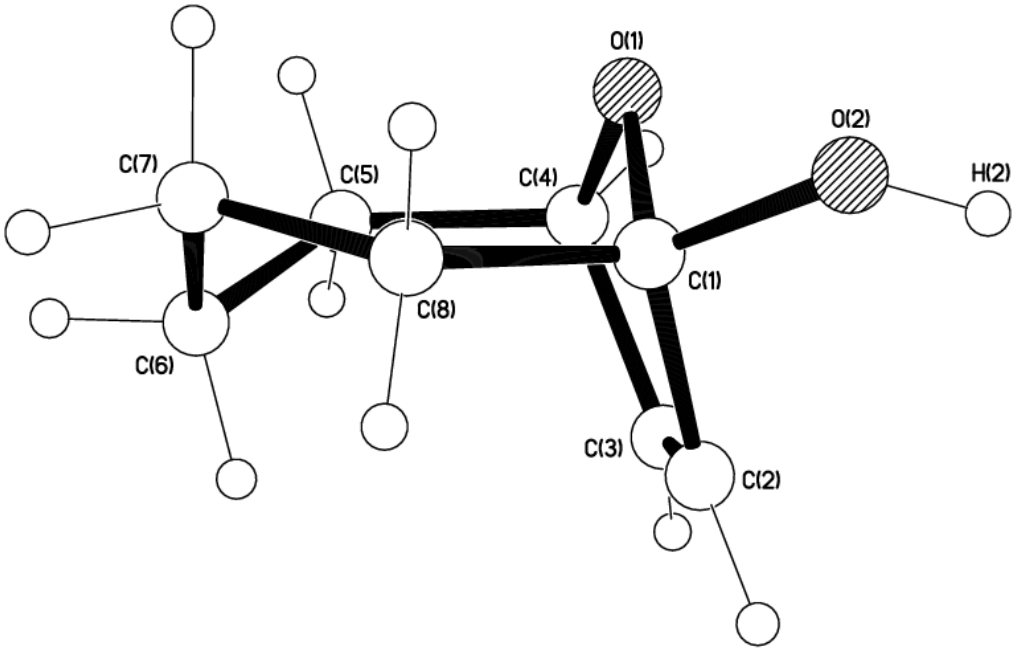
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C(3)
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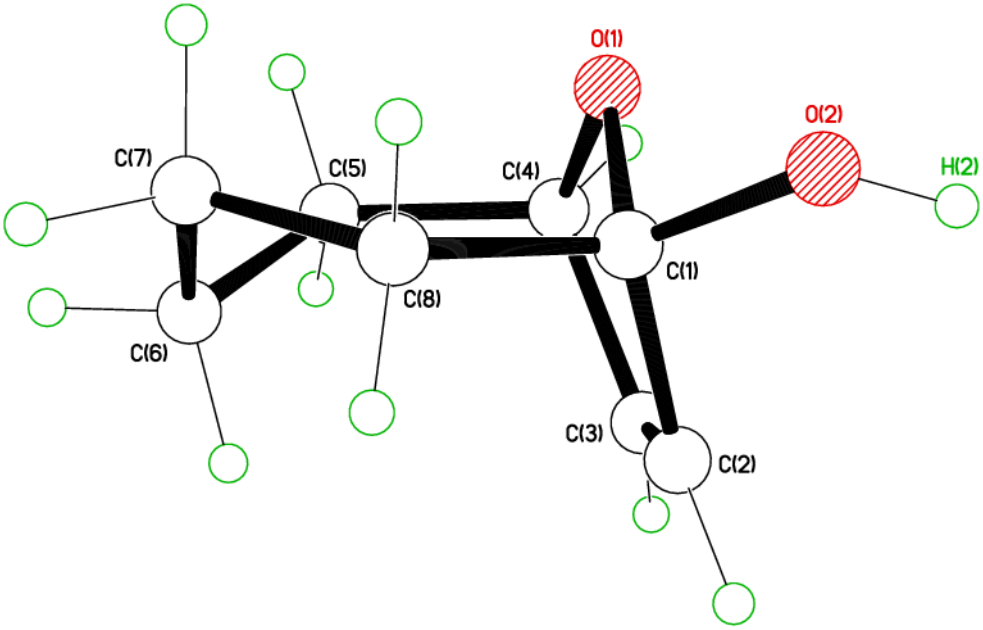
O(1)
O(2)
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C(7)
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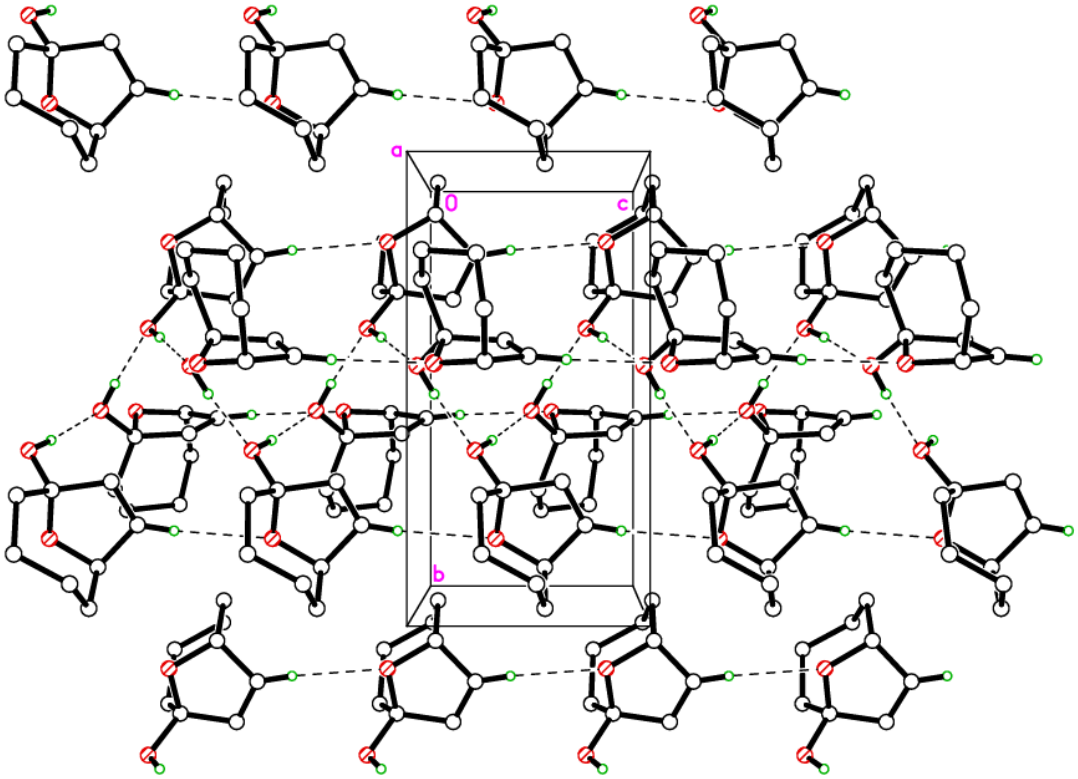
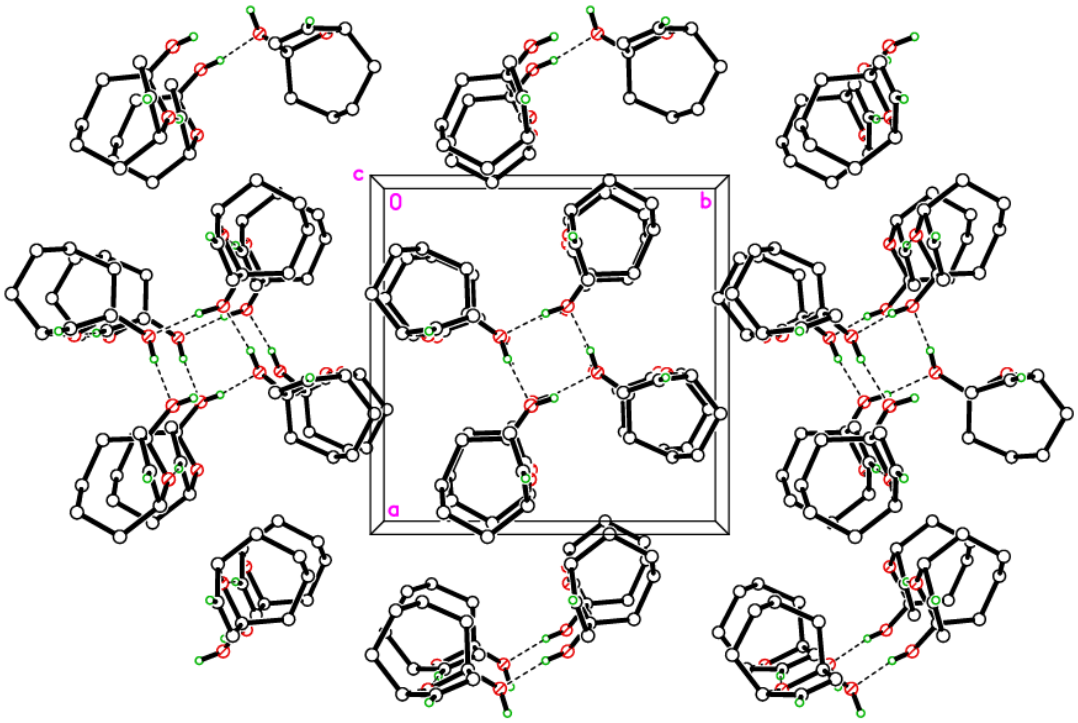
C(6)
C(3)
C(2)


a
0
c
b



Crystal data

$C_8H_{12}O_2$	D_x = 1.325 Mg m^{-3}
M_r = 140.18	Synchrotron radiation, λ = 0.7749 Å
Tetragonal, $P4_1$	Cell parameters from 9079 reflections
a = 11.1057 (7) Å	θ = 2.8–30.7°
c = 5.6962 (4) Å	μ = 0.11 mm^{-1}
V = 702.55 (10) Å^3	T = 100 K
Z = 4	Needle, colourless
F(000) = 304	0.30 × 0.01 × 0.01 mm^3

Data collection

Bruker D8 with PHOTON 100 detector diffractometer	1679 independent reflections
Radiation source: Advanced Light Source station 11.3.1	1603 reflections with $I > 2\sigma(I)$
Silicon 111 monochromator	R_{int} = 0.051
Detector resolution: 10.42 pixels mm^{-1}	θ_{max} = 30.7°, θ_{min} = 2.0°

ω/θ shutterless scans	h = -14→14
Absorption correction: multi-scan *SADABS* v2016/2, Sheldrick, G.M., (2012)	k = -14→14
T_{min} = 0.967, T_{max} = 0.999	l = -7→7
9782 measured reflections	

Refinement

Refinement on F^2	All H-atom parameters refined
Least-squares matrix: full	$w = 1/[\sigma^2(F_o^2) + (0.0323P)^2 + 0.1154P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.029$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.069$	$\Delta\rangle_{max} = 0.22$ e Å^{-3}
$S = 1.06$	$\Delta\rangle_{min} = -0.18$ e Å^{-3}
1679 reflections	Extinction correction: *SHELXL2017*/1 (Sheldrick 2017), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
140 parameters	Extinction coefficient: 0.041 (10)
1 restraint	Absolute structure: Flack x determined using 689 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Primary atom site location: iterative	Absolute structure parameter: -0.2 (4)
Hydrogen site location: difference Fourier map	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for (mckals8)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.55573 (10)	0.84379 (10)	0.34622 (19)	0.0124 (3)
C1	0.61513 (14)	0.73031 (14)	0.3807 (3)	0.0124 (3)
O2	0.55209 (10)	0.64158 (10)	0.2532 (2)	0.0138 (3)
H2	0.488 (3)	0.620 (2)	0.326 (6)	0.038 (7)*
C2	0.60777 (14)	0.71150 (15)	0.6421 (3)	0.0139 (3)
H2A	0.628 (2)	0.630 (2)	0.709 (4)	0.021 (6)*
C3	0.57195 (15)	0.81162 (15)	0.7465 (3)	0.0149 (3)
H3	0.5638 (18)	0.826 (2)	0.907 (5)	0.017 (5)*
C4	0.56012 (14)	0.90902 (14)	0.5650 (3)	0.0135 (3)
H4	0.4852 (17)	0.9565 (16)	0.580 (4)	0.010 (4)*

C5	0.66936 (15)	0.99339 (15)	0.5667 (3)	0.0169 (4)
H5A	0.656 (2)	1.056 (2)	0.442 (4)	0.023 (6)*
H5B	0.6709 (18)	1.0329 (19)	0.716 (4)	0.016 (5)*
C6	0.78970 (15)	0.92867 (15)	0.5305 (4)	0.0183 (4)
H6A	0.8516 (17)	0.9922 (18)	0.541 (4)	0.016 (5)*
H6B	0.804 (2)	0.873 (2)	0.661 (4)	0.022 (6)*
C7	0.80068 (15)	0.86186 (15)	0.2962 (4)	0.0185 (4)
H7A	0.765 (2)	0.912 (2)	0.172 (4)	0.019 (6)*
H7B	0.890 (2)	0.853 (2)	0.253 (5)	0.030 (6)*
C8	0.74392 (14)	0.73626 (14)	0.2838 (3)	0.0153 (3)
H8A	0.743 (2)	0.709 (2)	0.114 (5)	0.024 (6)*
H8B	0.7934 (18)	0.6774 (19)	0.366 (4)	0.016 (5)*

Geometric parameters (Å, º) for (mckals8)

O1—C1	1.4360 (18)	C5—C6	1.531 (2)
O1—C4	1.442 (2)	C5—H5A	1.01 (2)
C1—O2	1.4103 (19)	C5—H5B	0.96 (2)
C1—C2	1.506 (2)	C6—C7	1.532 (3)
C1—C8	1.535 (2)	C6—H6A	0.99 (2)
O2—H2	0.86 (3)	C6—H6B	0.98 (2)
C2—C3	1.322 (2)	C7—C8	1.532 (2)
C2—H2A	1.01 (2)	C7—H7A	0.98 (2)
C3—C4	1.502 (2)	C7—H7B	1.03 (2)
C3—H3	0.93 (3)	C8—H8A	1.01 (3)
C4—C5	1.533 (2)	C8—H8B	0.97 (2)
C4—H4	0.989 (19)		
C1—O1—C4	107.89 (12)	C4—C5—H5A	107.8 (13)
O2—C1—O1	108.34 (12)	C6—C5—H5B	108.6 (12)
O2—C1—C2	112.67 (13)	C4—C5—H5B	107.5 (13)
O1—C1—C2	103.42 (13)	H5A—C5—H5B	108.2 (17)
O2—C1—C8	107.91 (13)	C5—C6—C7	114.46 (14)
O1—C1—C8	109.95 (13)	C5—C6—H6A	105.3 (11)
C2—C1—C8	114.35 (14)	C7—C6—H6A	110.0 (13)
C1—O2—H2	111.1 (19)	C5—C6—H6B	109.3 (14)
C3—C2—C1	110.15 (15)	C7—C6—H6B	110.2 (13)

C3—C2—H2A	131.0 (13)	H6A—C6—H6B	107 (2)
C1—C2—H2A	118.9 (13)	C6—C7—C8	116.63 (15)
C2—C3—C4	108.79 (16)	C6—C7—H7A	108.6 (13)
C2—C3—H3	127.6 (14)	C8—C7—H7A	108.6 (13)
C4—C3—H3	123.2 (14)	C6—C7—H7B	109.4 (15)
O1—C4—C3	103.66 (13)	C8—C7—H7B	107.3 (13)
O1—C4—C5	109.85 (13)	H7A—C7—H7B	105.8 (19)
C3—C4—C5	111.49 (14)	C7—C8—C1	113.95 (13)
O1—C4—H4	108.4 (12)	C7—C8—H8A	108.7 (13)
C3—C4—H4	113.3 (12)	C1—C8—H8A	108.9 (13)
C5—C4—H4	109.9 (10)	C7—C8—H8B	110.9 (12)
C6—C5—C4	113.76 (13)	C1—C8—H8B	109.0 (13)
C6—C5—H5A	110.8 (13)	H8A—C8—H8B	105 (2)
C4—O1—C1—O2	142.45 (13)	C2—C3—C4—C5	-100.52 (17)
C4—O1—C1—C2	22.68 (16)	O1—C4—C5—C6	-57.75 (19)
C4—O1—C1—C8	-99.85 (15)	C3—C4—C5—C6	56.57 (19)
O2—C1—C2—C3	-128.32 (15)	C4—C5—C6—C7	60.9 (2)
O1—C1—C2—C3	-11.56 (18)	C5—C6—C7—C8	-82.15 (19)
C8—C1—C2—C3	107.98 (16)	C6—C7—C8—C1	47.8 (2)
C1—C2—C3—C4	-3.76 (19)	O2—C1—C8—C7	148.22 (14)
C1—O1—C4—C3	-24.90 (15)	O1—C1—C8—C7	30.2 (2)
C1—O1—C4—C5	94.33 (14)	C2—C1—C8—C7	-85.57 (18)
C2—C3—C4—O1	17.58 (17)		

Hydrogen-bond geometry (Å, º) for (mckals8)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2···O2^{i}	0.86 (3)	1.91 (3)	2.7644 (14)	172 (3)
C2—H2*A*···O2^{ii}	1.01 (2)	2.63 (2)	3.597 (2)	160.4 (18)
C3—H3···O1^{iii}	0.93 (3)	2.51 (3)	3.439 (2)	174.0 (19)

Symmetry codes: (i) -*y*+1, *x*, *z*+1/4; (ii) *y*, -*x*+1, *z*+3/4; (iii) *x*, *y*, *z*+1.

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Computing details

Data collection: Bruker *APEX* 2; cell refinement: Bruker *SAINT* v8.38a; data reduction: Bruker *SAINT*

v8.38a; program(s) used to solve structure: SHELXT 2014/5 (Sheldrick, 2014); program(s) used to refine structure: *SHELXL2017*/1 (Sheldrick, 2017); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table 1

Experimental details

Crystal data	
Chemical formula	$C_8H_{12}O_2$
M_r	140.18
Crystal system, space group	Tetragonal, $P4_1$
Temperature (K)	100
a, c (Å)	11.1057 (7), 5.6962 (4)
V (Å^3)	702.55 (10)
Z	4
Radiation type	Synchrotron, λ = 0.7749 Å
μ (mm^{-1})	0.11
Crystal size (mm^3)	0.30 × 0.01 × 0.01
Data collection	
Diffractometer	Bruker D8 with PHOTON 100 detector diffractometer
Absorption correction	Multi-scan *SADABS* v2016/2, Sheldrick, G.M., (2012)
T_{min}, T_{max}	0.967, 0.999
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	9782, 1679, 1603
R_{int}	0.051
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.658
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.029, 0.069, 1.06

No. of reflections	1679
No. of parameters	140
No. of restraints	1
H-atom treatment	All H-atom parameters refined
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.22, -0.18
Absolute structure	Flack x determined using 689 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.2 (4)

Computer programs: Bruker *APEX* 2, Bruker *SAINT* v8.38a, SHELXT 2014/5 (Sheldrick, 2014), *SHELXL2017*/1 (Sheldrick, 2017), Bruker *SHELXTL*.

Table 2

Hydrogen-bond geometry (Å, º) for (mckals8)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2···O2^{i}	0.86 (3)	1.91 (3)	2.7644 (14)	172 (3)
C2—H2*A*···O2^{ii}	1.01 (2)	2.63 (2)	3.597 (2)	160.4 (18)
C3—H3···O1^{iii}	0.93 (3)	2.51 (3)	3.439 (2)	174.0 (19)

Symmetry codes: (i) -*y*+1, *x*, *z*+1/4; (ii) *y*, -*x*+1, *z*+3/4; (iii) *x*, *y*, *z*+1.