Studies Toward the Synthesis of Stemodinone

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Abstract

Stemodinone **1**, the principal target of the work in this thesis, is a naturally occurring tetracyclic diterpene isolated from the leaves of *Stemodia maritima* L. (Schrophulariaceae) and used for the treatment of venereal disease. The reported medicinal properties of stemodinone and its analogous compounds such as aphidicolin **2** attracted the attention of organic chemists to the investigation of the complex structure of the compound. The recently described trigoheterone A **3** (Figure **1**) has shown significant inhibitory effect towards five cancer cell lines (SW480, HL-60, A549, SMMC-7721 and MCF-7) with IC_{50} values similar to the cisplatin.

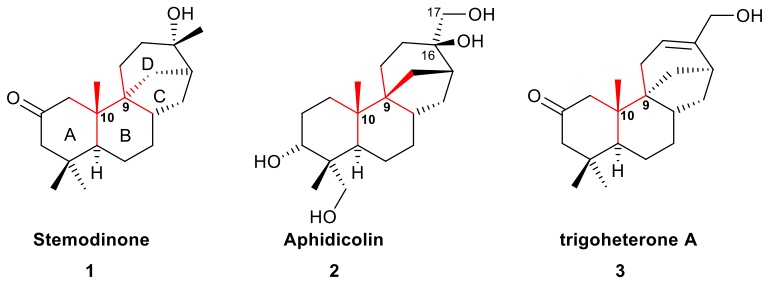
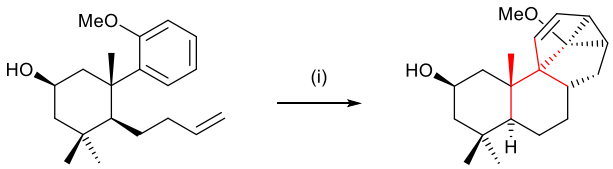


Figure 1: Structures of stemodinone **1** and aphidicolin **2** and trigoheterone A **3**.

From a synthetic viewpoint, preparing the quaternary spiro centre at C9 is complicated by it being adjacent to a second quaternary carbon: a very hindered environment (Figure 1): carbons 9 and 10, highlighted in red).

The present work is part of a programme to develop a synthesis of stemodinone **1** that is based upon an intramolecular alkene-arene *meta*-photocycloaddition. The most advanced example of this type being the conversion of **4** into synthetic intermediate **5**. In particular, the adjacent quaternary centres in **5** (highlighted in red) have been formed by the cycloaddition of sp^2 hybridised carbon atoms, one component of which is a benzene ring excited to its first singlet excited state (S_1).

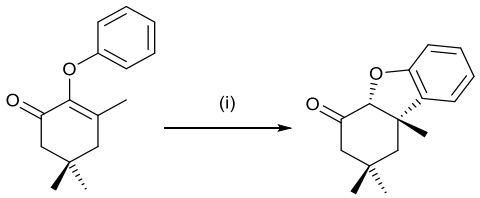


4 5

Scheme 1: an alkene-arene *meta*-photocycloaddition reaction of **4** to give **5**, toward a synthesis of stemodinone **1**. *Reagents and conditions*: (i) hν (254 nm), cyclohexane (56%).

Previous work by Boyd and Chappell established a synthetic route for the preparation of the photocycloaddition precursor **4**, beginning from the commercially available starting material dimedone, which has the *gem*-dimethyl group present on the A-ring of stemodinone **1**. However, the synthesis of **4** contains a conjugate addition of an aryl cuprate that proceeds in, at best, 15% yield.

Described in the present work is an effort to address an improved synthesis of **4** utilising a Schultz heteroatom-directed photoarylation *e.g.* **6** to **7** (Scheme 2). Specifically, with the aim of improving the preparation of the quaternary centre in **4** adjacent to the aromatic ring.

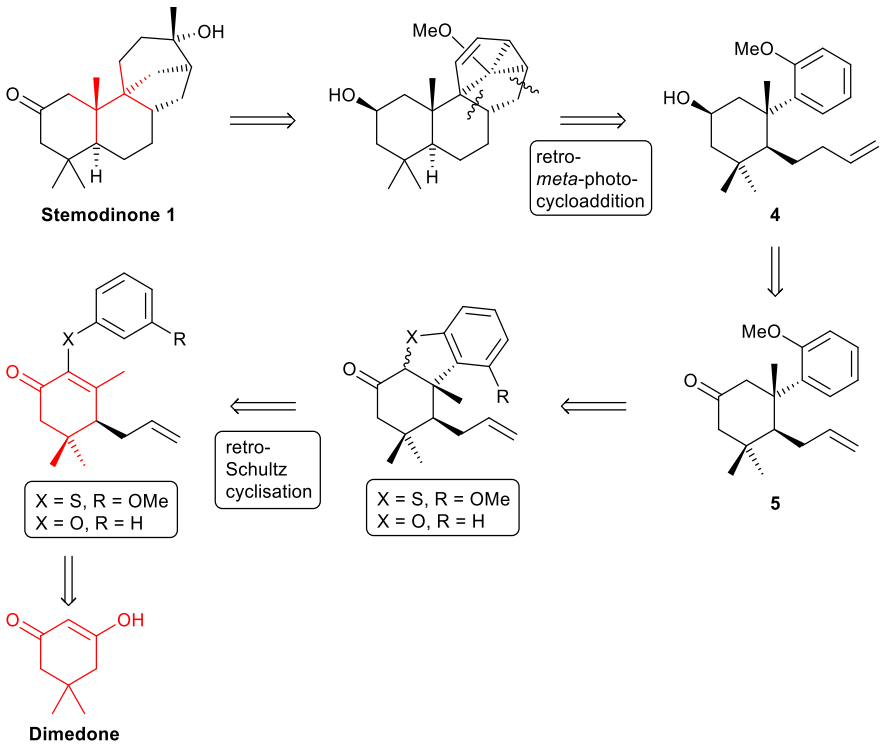


6 7

Scheme 2: exemplar case of a Schultz photoarylation. *Reagents and conditions:* (i) hν (~300 nm), MeOH (97%).

The general value of generating highly hindered quaternary carbons by the combination of sp^2 carbons via their π-faces has been illustrated above. Schultz has demonstrated that this class of photoarylation is able to facilitate the synthesis of quaternary centres in the lycoramine and morphine skeletons.

Set out below is a disconnection of stemodinone **1** that uses both the arene-alkene *meta*-photocycloaddition and a Schultz heteroatom-directed photoarylation, leading back to dimedone (Scheme 3).



Scheme 3: disconnection of stemodinone to facilitate incorporation of an arene-alkene *meta*-photocycloaddition and a Schultz photoarylation.

In this thesis, an examination of the Schultz cyclisation toward stemodinone is reported, with both sulfur and oxygen linking atoms. The potential value of flow photochemistry methods, as compared to batch photolysis, is also examined.

Declaration

I confirm that this is my own work and the use of all material from other sources has been properly and fully acknowledged.

Candidate name: Abubakar Sani

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A Ph.D. research program has been a truly life-changing, frustrating, painful, and rewarding experience of my life and it would not have been possible to do without the support and guidance that I received from many people.

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I am also very grateful to Dr Chris Smith for his valuable scientific advice and many insightful discussions and suggestions. Many thanks also to the members of my PhD committee, Professor Laurence Harwood and Dr John McKendrick for encouragement and supervisory role. I would also like to thank, Dr Geoff Brown and CAF Lab. Technical NMR specialist Dr. Radek for always being available to help with NMR problems, Prof Ann Chippindale for the X-ray crystallography, and Mr Nicolas Michael for the mass spectroscopic analysis.

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Table of Contents

Abbreviations

°C	degree centigrade
^{1}H	proton
^{13}C	carbon thirteen
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2'-azo *bis*isobutyronitrile
App.	apparent
Ar	aryl (substituted aromatic ring)
atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
bp	boiling point
br.	broad
nBu	*normal*-butyl
tBu	*tertiary*-butyl
ca	circa (approximately)
cat.	catalytic
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
cm	centimetres
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
DBPO	dibenzoyl peroxide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e	diastereomeric excess
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DIH	1,3-diiodo-5,5-dimethylhydantoin
dil.	Dilute
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydo-2(1*H*)-pyrimidone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
e.e.	enantiomeric excess
equiv.	equivalents
Et	ethyl
EtOAc	ethyl acetate
EI	electron impact
ESI	electrospray ionization
eV	electron volts
FMO	frontier molecular orbital
FT	Fourier Transform
g	grams
G	Gaussian
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide

HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
h	hours (length of reaction time)
hν	irradiation with light
Hz	Hertz
IC	internal conversion
IR	infra-red
$Ir(Fppy)_3$	Tris[2-(2,4-difluorophenyl)pyridine]iridium
ISC	intersystem crossing
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
KHMDS	potassium *bis*(trimethylsilyl)amide
LC_{50}	Lethal Concentration
LAH	lithium aluminium hydride
LHMDS	lithium *bis*(trimethylsilyl)amide
LDA	lithium diisopropylamide
Lit.	literature
L-selectride	lithium tri-*sec*-butylborohydride
LTMP	lithium 2,2,6,6-tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
m	*meta*
m	multiplet
M	molarity
Me	methyl
MEM	2-methoxyethoxymethyl
mg	milligrams

mL	millilitres
mM	millimolar
MOM	methoxymethyl
mp	melting point
MPM	*p*-methoxybenzyl
MS	mass spectrometry
MVK	methyl vinyl ketone
m/z	mass to charge ratio
NaHMDS	sodium *bis*(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
nm	nanometre
NMR	nuclear magnetic resonance
^{1}H-NMR	proton- nuclear magnetic resonance
^{13}C-NMR	carbon thirteen- nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
NPMI	*N*-phenylmaleimide
o	*ortho*
OAc	acetoxy
OMe	methoxy
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
P.E.	petroleum ether (40°-60°C)
PG	protecting group
Ph	phenyl
ppm	part per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
^{i}Pr	*iso*-propyl

psi	pounds per square inch
q	quartet
R_f	retention factor
r.t.	room temperature
R_t	retention time
s	singlet
S_1	singlet excited state
t	triplet
T_1	triplet excited state
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDMSOTf	*tert*-butyldimethylsilyltrifluoromethanesulfonate
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBSCl	*tert*-butyldimethylsilyl chloride
TBDPOTf	*tert*-butyldiphenylsilyltrifluoromethanesulfonate
TBTH	tributyltin hydride
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane
TMSTf	trimethylsilyltrifluoromethanesulfonate
Tol	*p*-tolyl
p-TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluenesulfonic acid
UV	ultra-violet
VR	vibrational relaxation

Chapter 1.

1.1 Introduction

Stemodinone **1**, the principle target of the work in this thesis, is a naturally occurring tetracyclic diterpene isolated from the leaves of *Stemodia maritima* L. (Schrophulariaceae) and used for the treatment of venereal disease (Figure 1).[1] The reported medicinal properties of stemodinone attracted the attention of organic chemists to the investigation of the complex structure of the compound. In 1973, Manchand and co-workers reported the phytochemical screening, isolation, and characterisation of two unique tetracyclic diterpenes, stemodinone **1** and stemodin **2**, their structures being confirmed by x-ray crystallography of **1** together with oxidation of **2** to give **1** using Jones reagent.[2] These naturally occurring compounds have a fused spiro and bridged ring arrangement between rings B, C and D (Figure 1).

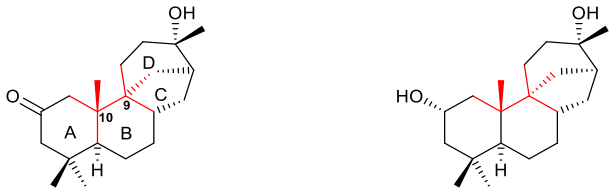
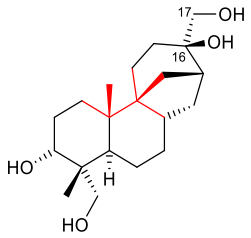


Figure 1 Structures of stemodinone **1** and stemodin **2**.

From a synthetic viewpoint, preparing this spiro centre is complicated by it being adjacent to a second quaternary carbon: a very hindered environment (Figure 1: carbons 9 and 10, highlighted in red).[3]

In 1972, the isolation of aphidicolin **3** was reported by Hesp and co-workers as a novel diterpene metabolite from the Fungus *Cephalosporium aphidicola* petch[4,5] and later found to occur in *Nigrosporum sphaerica* (Figure 2).[6]

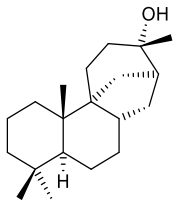


Aphidicolin
3

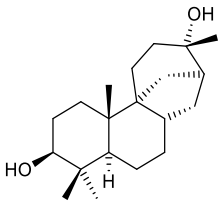
Figure 2 Structure of aphidicolin **3**.

Aphidicolin **3** was found to have a similar tetracyclic skeleton to stemodinone **1** but with a different, diastereomeric, stereochemical relationship of the C and D rings. Aphidicolin **3** and its prodrugs, 17-glycinate.HCl and 16-fluoroaphidicolin, have shown interesting antiviral and antitumor activity, and the use of aphidicolin and its hydroxylated analogues against *leishmanial* parasites has been reported.[7,8] The biological properties are presumably due to the ability of aphidicolin to act as a reversible enzyme inhibitor of DNA polymerase α, even though the mechanism of this activity was not established.[9] It has also been reported to possess antibiotic properties.[4]

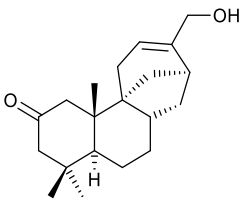
Other naturally occurring diterpenoids with the same stemodane-type skeleton structure including 2-desoxystemodinone **4**, maritimol **5** and trigoheterone A **6** have been reported in the literature, as shown in Figure 3.[4] The recently described trigoheterone A **6** has shown significant inhibitory effects toward five cancer cell lines (SW480, HL-60, A549, SMMC-7721 and MCF-7) with LC_{50} values similar to cisplatin.[4b]



2-desoxystemodinone
4



Maritimol
5



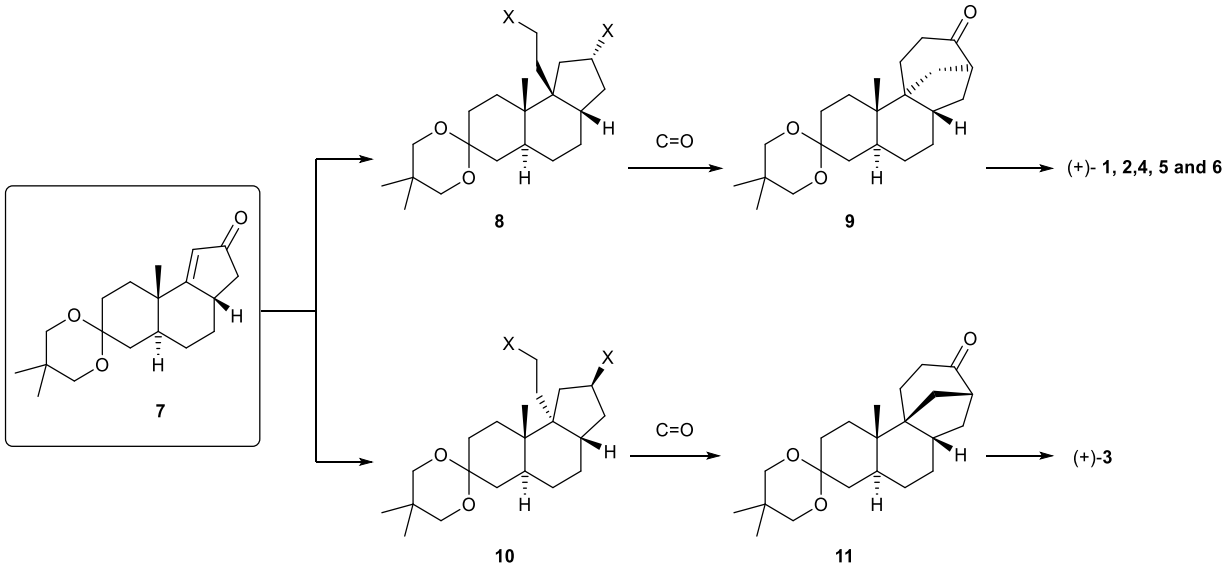
trigoheterone A
6

Figure 3: Structures of 2-desoxystemodinone **4** and maritimol **5** and trigoheterone A **6**.

1.2 Two exemplar total syntheses of a stemodane-type and aphidicolin diterpenoids

The total syntheses of stemodin and aphidicolin have been reviewed by Toyota and Ihara in 1999 and Bettolo in 2016.[3a] In addition, some further syntheses have been reported.[3b,3c, 3d] However, one synthesis of each framework is considered below to emphasise the challenges inherent to their synthesis and to frame the approach taken in the present work.

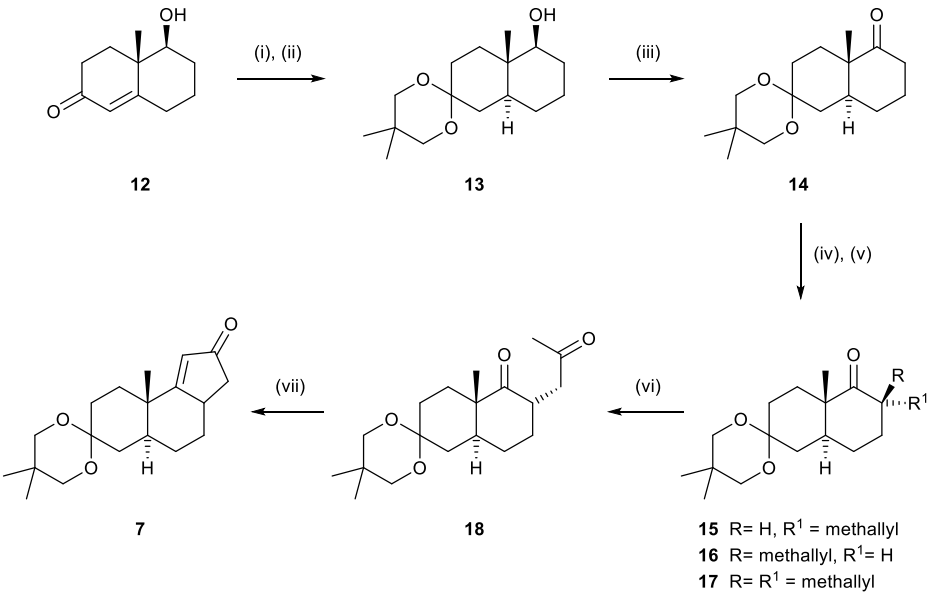
Synthetic organic chemists have been faced with a great challenge in the construction of the novel BCD ring system found in the structures of stemodane-type diterpenoids (**1, 2, 4, 5** and **6**) as well as in aphidicolin **3**. The most demanding part of these challenges involves setting up the quaternary centres at C-9 and C-10 with the desired stereochemistry, which may lead to the construction of either the stemodane or aphidicolane ring system. First considered is an approach toward the stemodane class by Piers. This discussion largely focuses on how the BCD ring system was built up and how the stereochemistry at the C-9 quaternary centre was achieved, so that they may be contrasted with the approach adopted in our group; specifically, utilising an intramolecular *meta*-photocycloaddition reaction. Disconnection of the skeletal structure of **1**-**5** by Piers *et al*., indicates that it should be possible to synthesize all these diterpenoids from a common precursor even though the nature, position and arrangement of functional groups contained on the ring A of these substances varies significantly. Since the basic carbon skeleton of the A, B, and C rings are common to compounds **1**-**5 (**Figure 3), the Piers group suggested that an intermediate such as **7** could serve as a suitable synthetic precursor to the protected tetracyclic diketones **9** and **11**, viable precursors for the stemodane and aphidicolane diterpenes, respectively.[10]



Scheme 1: Piers synthetic plan for the stemodanes and aphidacolanes from tricyclic enone precursor **7**.

Piers and his co-workers have achieved the stereoselective syntheses of stemodinone **1**, stemodin **2**, 2-desoxystemodinone **4**, maritimol **5,** and trigoheterone A **6** from this common precursor **7**.[10] The two key reactions of the syntheses are the photocycloaddition of allene to **7**, and a Thorpe-Ziegler cyclisation to generate ring D (Schemes 3 and 4). The photocycloaddition introduces the second of the adjacent quaternary carbons at C-10 and C-9 and the so-formed *exo*-methylene cyclobutane was subsequently developed into the cyano-alkyl side chain, present in **28**, that facilitates the Thorpe-Ziegler ring formation. Starting from the known ketol **12** allows C-9 to be incorporated from the outset. Ketalization of **12** with *gem*-dimethyl-1,3-propanediol produced the ketal alcohol **13**, followed by oxidation with pyridinium chlorochromate in the presence of sodium acetate gave rise to the keto ketal **14** (Scheme 2). Thus, alkylation of ketone **14**, gave a mixture of compounds that included the desired monoalkylation product **15**, the corresponding epimer **16**, and a small amount of the dialkylation product **17**. Since **16** (axial methallyl group) would be expected to be considerably less stable than **15**, the resulting stereoisomeric mixture was treated with sodium methoxide in methanol to yield the major isomer **15** (equatorial methallyl group) and **17** in a ratio of (95: 5)

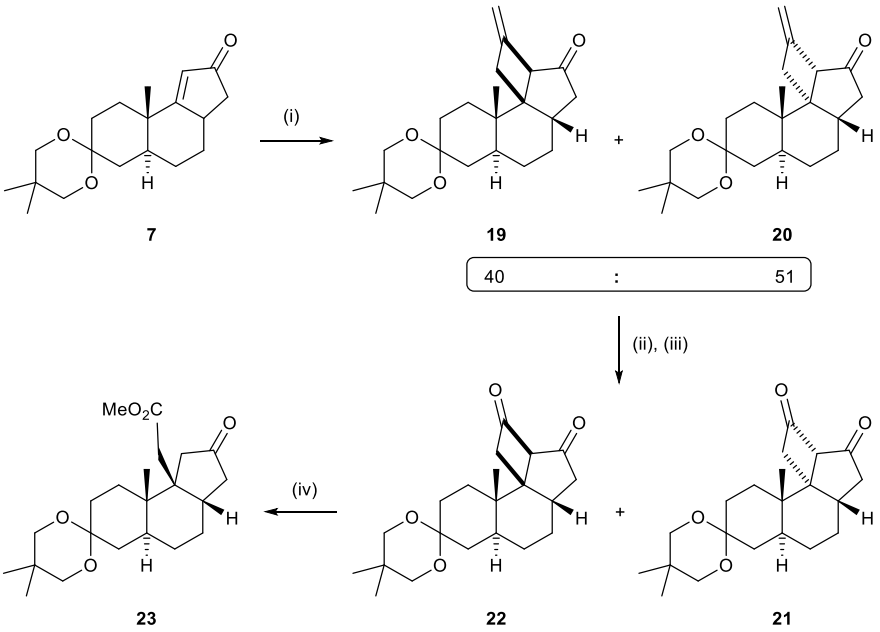
respectively. However, these two diastereoisomers could be separated by column chromatography. The methyl ketone **18** was produced *via* a Lemieux-Johnson oxidation upon treatment of *exo*-olefin **15**, with a catalytic amount of osmium tetraoxide and excess of sodium metaperiodate.[11] The crucial conversion of the diketone **18** into the tricyclic enone **7** as the major product, involved base-promoted intramolecular aldol condensation of the diketone **18** (Scheme 1).[3]



Scheme 2: Synthesis of tricyclic enone **7**. *Reagents and conditions*: (i) $OHCH_2C(CH_3)_2CH_2OH$, TsOH, (ii) Li/liq.NH_3; (iii) PCC, NaOAc; (iv) LDA, THF, 0 °C, methallyl iodide, -78 °C; (v) NaOMe (epimerization); (vi) OsO_4, $NaIO_4$; (vii) NaH.

The photocycloaddition of allene to tricyclic enone **7** conducted in order to introduce a functionalized two-carbon side chain at C-9 position, provided a mixture of four isomeric products in 96% yield, in a ratio of [40:51:6:3]. After separation, the two major photoadducts **19** and **20** were obtained in a ratio of 1:1. The synthetic equivalence of **19** and **20** is demonstrated below. The use of a photoexcited state of **7** to overcome the significant steric hindrance associated with preparing adjacent quaternary centres is instructive and informed our own investigation (*vide infra*). That this reaction involves the combination of sp^2 carbons

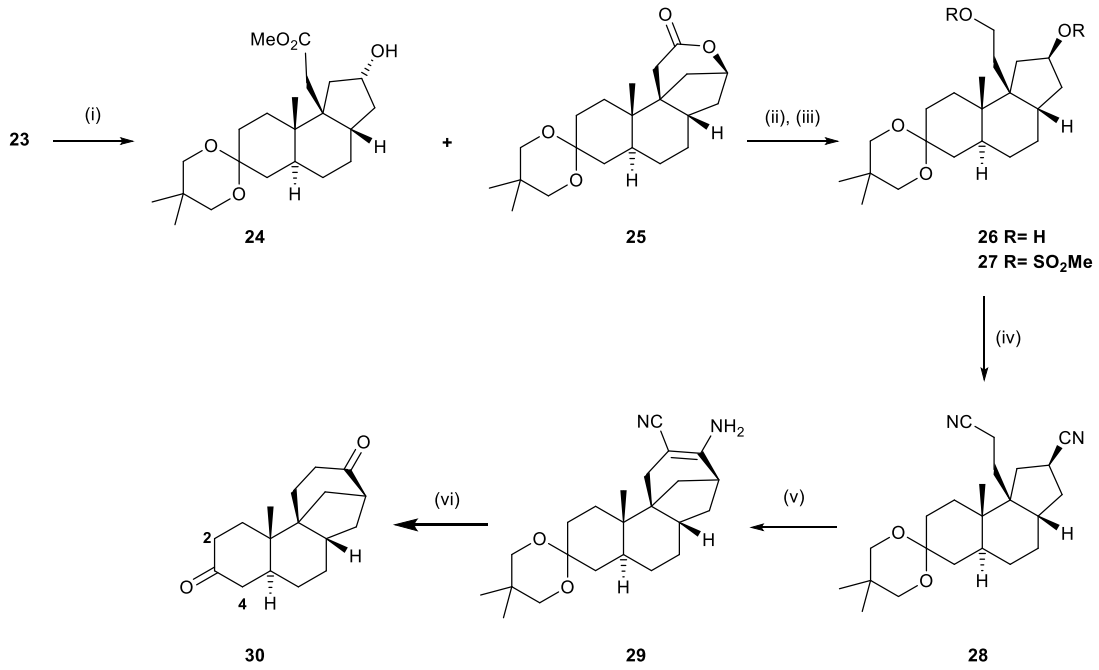
is not coincidental from a steric perspective. The regioselectivity could be anticipated by consideration of the work of Wiesner on such cycloadditions and may well be a consequence of sterics, with insignificant frontier orbital effects being likely.[12a,12b] Treatment of the photoadduct **19** with ozone, followed by reduction of the ozonide with dimethylsulfide, gave the rather unstable dione **22**. Further treatment of **22** with sodium methoxide in dry methanol produced keto ester **23** in high yield (Scheme 3).[13a] Implicit in this observation is the equivalence of the two $CH_2C(O)$ moieties arising from cleavage of the cyclobutanone in either **21** or **22**. These have been proposed to interconvert by aldol/Claisen ester-type condensation/cleavage, leading to the thermodynamically stable product.[13a]



Scheme 3: Piers approached towards the synthesis of ketone ester, a promising stemodane precursor. *Reagents and conditions*: (i) $H_2C{=}C{=}CH_2$, tetrahydrofuran, hν, -78 °C; (ii) O_3, CH_2Cl_2, MeOH (1.5 equiv.), -78 °C; (iii) Me_2S; (iv) NaOMe, MeOH, rt., 2.5 h.

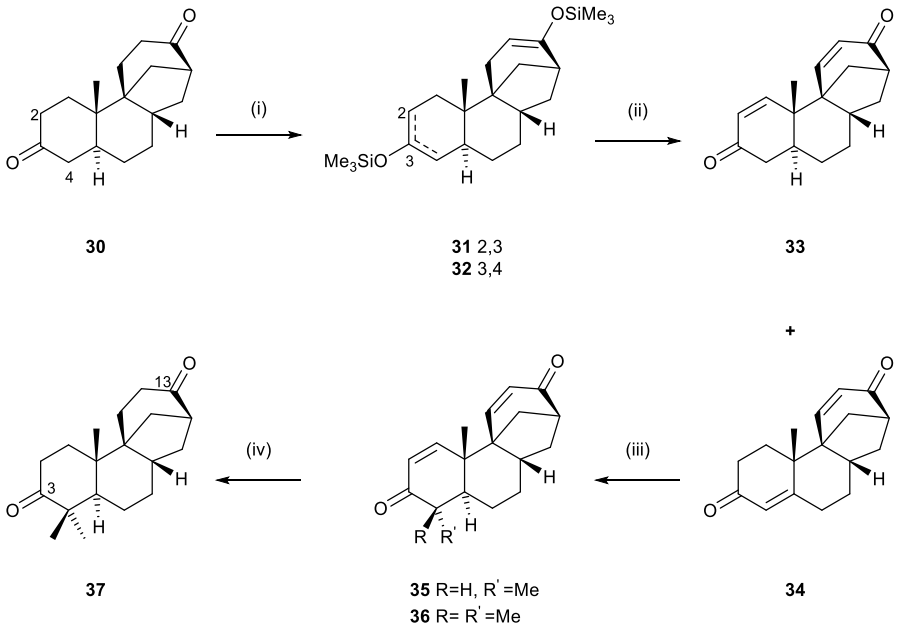
However, reduction of **23** with sodium borohydride in methanol gave a 1:1 mixture of alcohol **24** and lactone **25** (Scheme 4). To increase the ratio of diastereomeric alkoxides formed, treatment of **24** with the bulky reducing agent, lithium tri *sec*-butylborohydride in ether, was carried out and afforded **24** in 74% yield. Presumably, attack from the *exo*-face of the *cis*-

hydrindane moiety was favoured on grounds of a less hindered approach of the nucleophile at the Bürgi-Dunitz angle.[14] The ester was then reduced with $LiAlH_4$ followed by reaction of the resultant diol **26** with methanesulfonyl chloride in pyridine, gave the dimesylate **27**. Testament to the hindered approach to the back of the secondary mesylate in **27**, its further treatment with excess sodium cyanide required hexamethylphosphoramide as solvent but produced crystalline dinitrile **28** in 60% yield. When compound **28** was treated with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, the key Thorpe-Ziegler condensation was effected to afford the enaminonitrile **29** in 90% yield. Acid hydrolysis of **29** with phosphoric acid in reflux aqueous acetic acid afforded in 80% yield the crystalline diketone which possesses the tetracyclic stemodane skeleton **30** (Scheme 4).[10]



Scheme 4: Piers approached towards the synthesis of tetracyclic diketone. *Reagents and conditions*: (i) $LiBH(s\text{-}Bu)_3$, tetrahydrofuran, -78 °C; (ii) $LiAlH_4$, ether, rt.; (iii) $MeSO_2Cl$, pyridine, r.t.; (iv) NaCN, HMPA, 60 °C; (v) *t*-BuOK, *t*-BuOH, reflux; (vi) H_3PO_4, AcOH, H_2O, reflux.

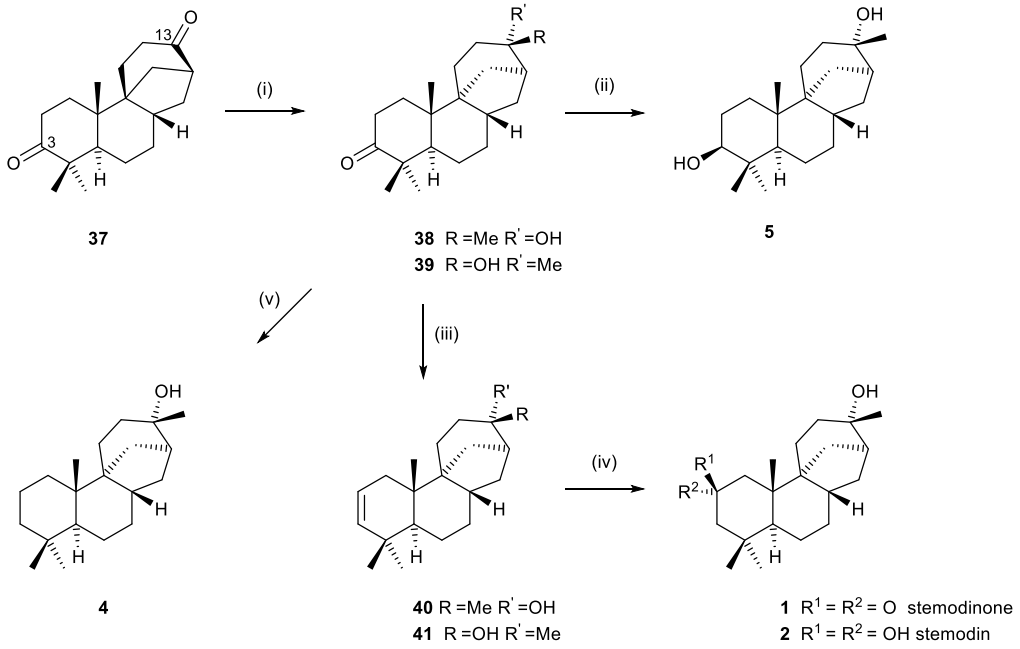
To execute a double Saegusa oxidation,[15] **30** was treated with excess of freshly prepared trimethylsilyl iodide in the presence of triethylamine in dichloromethane for 1 hour to produce a mixture of bis-enol ethers **31** and **32** in a ratio of about 4.5:1, respectively. Oxidation of this mixture with palladium(II) acetate in acetonitrile followed by separation of the resultant products, gave the crystalline bis-enones **33** (67%) and **34** (19%). Rapid treatment of the enolate anion (lithium bis(trimethylsilyl)-amide, dimethoxyethane, 0 °C) of **33** with a large excess of methyl iodide gave the monomethylated product **34** nearly exclusively (95%). The stereochemistry at C-4 of this compound was shown by a proton-NMR decoupling experiment. Irradiation at δ 1.17 (3-proton doublet due to C-4 methyl group) causes collapse of the doublet of quartets at δ 2.38 (C-4 proton) to a clean doublet with J = 13 Hz (geminal *trans*-diaxial coupling). The second methyl group was introduced after treatment of **35** via a similar procedure giving the required bis-enone **36** in 77% yield. The crystalline dione **37** was generated by catalytic hydrogenation of compound **36** in quantitative yield.[13a] Thus, Piers and co-workers had succeeded in the conversion of **30** to **37** with regioselective alkylation of the ketone at C-3 by taking advantage of three key points of selectivity. First, the regioselective introduction of the double bond into the A-ring at position 2, on grounds of preferential enolization toward this carbon. Second, the double bond at C-2 directed enolate formation toward C-4 and thus selective methylation. Third, enolization in the D-ring would have required the formation of an anti-Bredt alkene, preventing such a reaction (Scheme 5).[13a,13b,13c,13d,13e, 13f,13g]



Scheme 5: Synthesis of tetracyclic *gem*-dimethyl dione **37**. *Reagents and conditions*: (i) TMSI, Et_3N, -95 °C, DCM, 1h; (ii) $Pd(OAc)_2$, CH_3CN; (iii) **33**, two cycles of treatment with $LiN(SiMe_3)_2$, DME, 0 °C, MeI, 77%, (then separate); (iv) H_2/10% Pd-C.

According to the literature of the syntheses of stemodane-type diterpenoids, the chiral centre at C-13 was introduced in a variety of ways. [16a,16b,16c,16d] However, the ketone at C-13 of **37** is relatively unhindered compared to that at C-3, and since the methyl group of the desired *tert*-alcohol **38** is equatorially oriented, then the desired transformation **37** to **38** could be accomplished by treatment of the resulting alkylated dione **37** with methyltriisopropoxytitanium. This reaction afforded the keto alcohol **38**, admixed with its C-13 epimer **39** in the ratio of 6:1 respectively, in 82% yield. Reduction of the keto alcohol **38** with sodium borohydride in methanol, followed by purification of the crude product gave (±)-maritimol **5**, in 73% yield.[17a, 17b, 17c, 17d] Treatment of the epimeric mixture of keto alcohols **38** and **39** with 1.3 equiv. of *p*-toluenesulfonylhydrazide in hot ethanol gave a mixture of the crude *p*-toluenesulfonylhydrazones which further reacted with sodium hydride in reflux toluene to give a Shapiro reaction affording (±) stemod-2-en-13α-ol **40** (58%) and (±) stemod-2-en-13β **41** (12%). Subsequently, compound **40** was regioselectively hydroborated in THF with excess

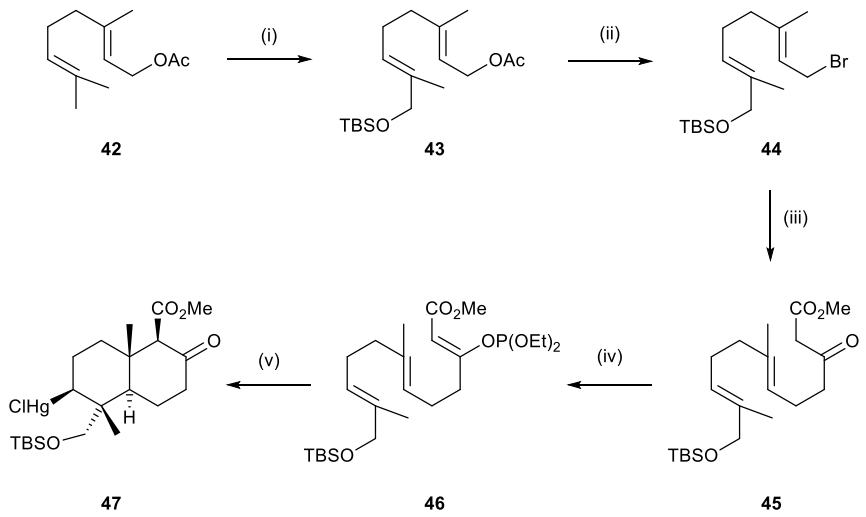
9-borabicyclo[3.3.1]nonane, after oxidation of the resultant organoborane mixture with alkaline hydrogen peroxide, (±) stemodin **2** was obtained in 88% yield.[18] Alternatively, racemic keto alcohol **37** has been transformed into (±) 2-desoxystemodinone **4** (via a Caglioti reaction),[18] while alkene **39** has been converted into stemodinone **1** (Scheme 5).[16c]

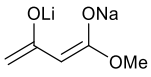


Scheme 6: Piers approach toward the synthesis of stemodinone **1**, stemodin **2**, 2-desoxystemodinone **4**, and maritimol **5**. *Reagents and conditions*: (i) $MeTi(i\text{-}prO)_3$, (then separate); (ii) $NaBH_4$ (iii) NH_2NHTs, NaH (iv) 9-BBN, 30% H_2O_2, NaOH; (v) NH_2NHTs then $NaBH_3CN$.

In 1980, Corey and co-workers reported the synthesis of aphidicolin **3**. The two critical reactions in Corey's approach to the synthesis of aphidicolin are the formation of bicyclic keto ester **47** in a stereoselective manner from a mercuric trifluoroacetate-promoted polyene cyclisation reaction of enol phosphonate **46** and the introduction of formyl group at C-8 position of the ketone **52** utilising a novel reaction developed in Corey's laboratory.[19] The route begins with allylic oxidation of geraniol acetate **42** followed by $NaBH_4$ reduction of the resulting aldehyde and subsequent protection of the alcohol as its silyl ether, providing the compound **43**, which in turn was subjected to hydrolysis of acetate moiety, mesylation of the

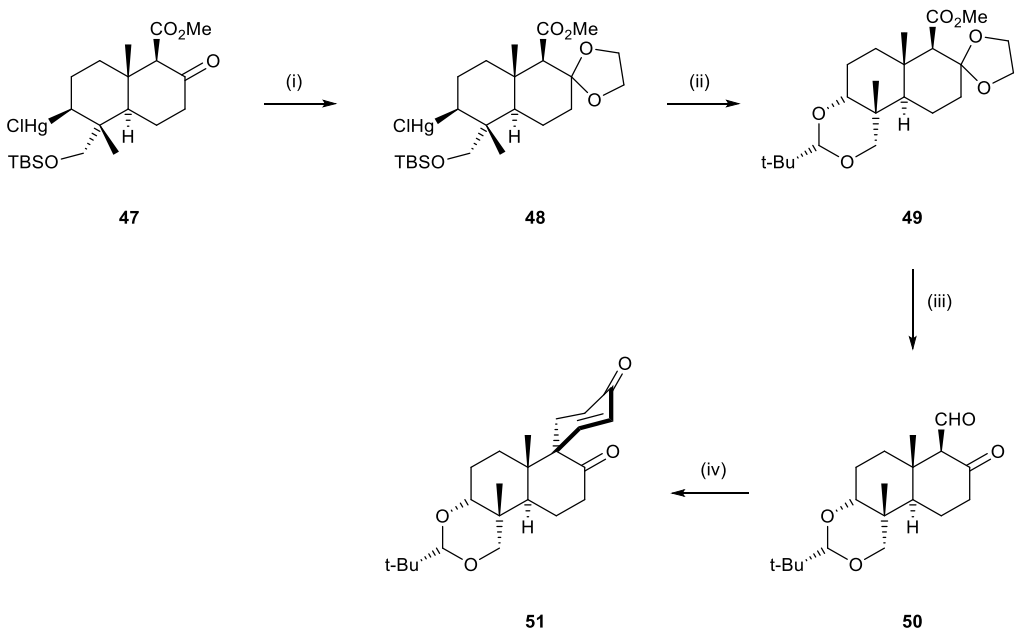
resulting primary alcohol, and bromination with LiBr to give rise to **44**. The unstable allylic bromide **44** was further treated with lithio-sodio dienolate of methyl acetoacetate, reacting at the least hindered/stable enolate, to furnish the β-keto ester **45**. In turn, this was then transformed into the enol phosphonate ester **46** by deprotonation at the most acidic position of **45** then quenching the resultant enolate on oxygen with the hard, oxyphilic electrophile $(EtO)_2POCl$. Polyene cyclisation reaction of **46**, in a manner anticipated by the Stork-Eschenmoser hypothesis,[20a,20b] was conducted with mercuric trifluoroacetate to give the corresponding bicyclic product, which upon treatment with NaCl yielded the mercurated keto ester **47** with the relative stereochemistry of three contiguous stereocentres correctly set (Scheme 7).[19] It is instructive that two quaternary carbons and the 1,3-diaxial methyl groups form readily by reaction of two sp^2 centres (see also Scheme 3).



Scheme 7: Synthesis of bicyclo keto ester **47**. *Reagents and conditions*: (i) SeO_2, $NaBH_4$, TBSCl; (ii) K_2CO_3, MsCl, Et_3N, then LiBr; (iii) 

; (iv) NaH, $(EtO)_2POCl$; (v) $Hg(OCOCF_3)_2$, $MeNO_2$, 0 °C, NaCl, H_2O.

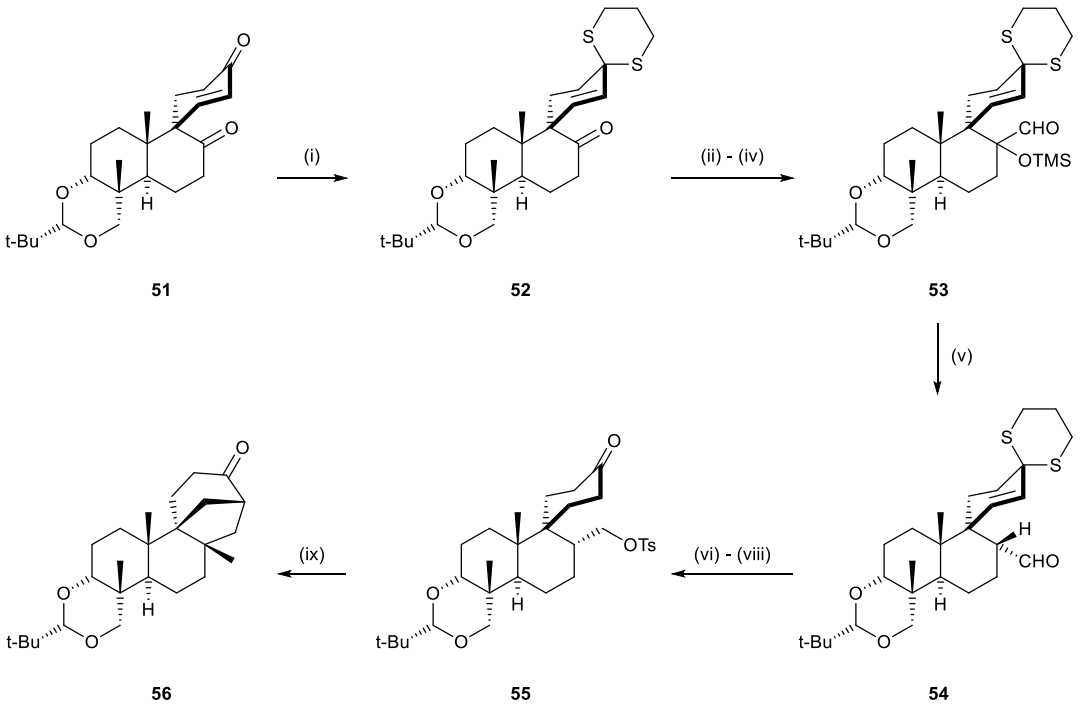
After ketalization of **47**, the compound **48** was converted to the acetonide **49** in 5 steps. In particular, the generation of a secondary radical from the C-Hg bond, via an intermediate Hg-H species, allows oxidative trapping to give a ketone. As noted in the Piers synthesis (Scheme 4), use of the bulky reagent L-selectride afforded stereoselective reduction of the ketone, in this case affording an equatorial OH, ready for stereoselective acetal formation with an equatorial *tert*-Butyl group. After transformation of the ester group of **49** into the formyl group of **50** in 3-steps, then the introduction of the spiro ring at the C-9 position of **50** was performed. This requires the adjacent quaternary carbon centres to be formed and again a combination of two sp^2 carbons was found successful, in this case an enolate and an α,β-unsaturated ketone. Specifically, a Michael reaction of the enolate with methyl vinyl ketone in the presence of K_2CO_3 and DBU, followed by Robinson spiroannulation reaction of the resulting Michael product with pyrrolidinium acetate to afford **51**, presumably via an enamine (Scheme 8).[19] Of considerable importance to the later adaptation of this route to stemodinone, the reaction is diastereoselective with the MVK approaching from the axial direction but *anti* to the angular methyl group.[19] This places the α,β-unsaturation in the correct position to control formation of the C/D ring system in stemodinone, a synthetic device not dissimilar to that employed by Piers in alkylation of ring A (Scheme 5).

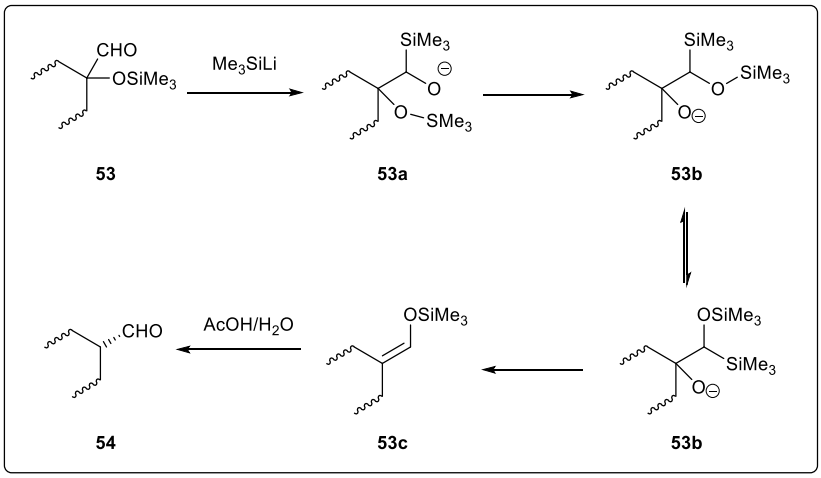


Scheme 8: Synthesis of spiro diketone **34**. *Reagents and conditions*: (i) $HOCH_2CH_2OH$, TsOH; (ii) $NaBH_4$, PDC/O_2, $(n\text{-}Bu)_4NF$, L-Selectride, *t*-BuCHO, TsOH; (iii) LAH then PCC then H_3O^+; (iv) (a) MVK, DBU, K_2CO_3, (b) $(CH_2)_4NH$, AcOH.

Chemoselective thioketalization of the enone **51** afforded the compound **52**, presumably on grounds of lower steric hindrance. In order to introduce a formyl group at C-8 position of **52**, a new method, which offers a solution to the problem of attaching carbon to very hindered ketone that favoured enolization, was developed by Corey and his co-workers. Accordingly, a silicon-enhanced cyanohydrin formation afforded the C-C bond, by treatment of the ketone **52** with TMSCN in the presence of ZnI_2, whose cyano group is reduced with DIBAL giving the corresponding aldehyde **53**. Deoxygenation of the tertiary C-O bond was effected by an unusual Peterson reaction; thus, after addition of trimethylsilyllithium to the aldehyde carbon and transfer of the OTMS from the tertiary to the secondary alkoxide, the reaction was worked up and purified [**53** to **54** via **53a** to **53c** (scheme 9)]. The resulting bistrimethylsilyl compound was treated with LDA to facilitate the Peterson reaction and yield a silyl enol ether that was hydrolysed to the aldehyde **54**. The relative difficulty of this strategy for preparing aphidicolin then becomes apparent, in contrast to the better flow of similar intermediates towards

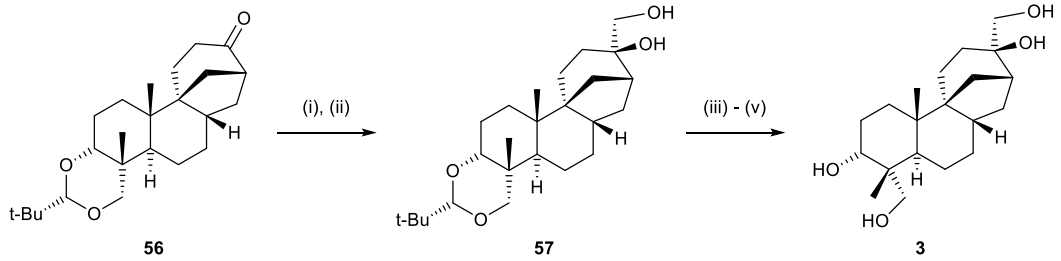
stemodinone. Thus obtained, the aldehyde was then further transformed into **55** in six steps. Following initial reduction with $NaBH_4$ then protection as the corresponding TBS ether, deprotection of the dithioketal using an oxidative hydrolysis procedure, mediated by l,3-diiodo-5,5-dimethylhydantoin revealed the ketone **55**. (Scheme 9).[19] Following hydrogenation of the double bond, the silyl ether was then cleaved back to the alcohol and converted to a tosylate leaving group to afford **55**. Regioselective enolate formation, to facilitate closure of the final ring proved challenging; fortunately, access to the kinetic enolate proved possible with a very hindered base at -120 °C and this alkylated internally to give **56** as shown in scheme 9.





Scheme 9: Corey's approached towards the synthesis of tetracyclic ketone **55**. *Reagents and conditions*: (i) TMSS–⌒–STMS, ZnI_2; (ii) TMSCN, ZnI_2; (iii) DIBAL 0 °C; (iv) TMSLi; (v) LDA then $AcOH/H_2O$; (vi) $NaBH_4$, (vii) TBSCl, DMAP, (viii) l,3-diiodo-5,5-dimethylhydantoin/H_2O, (ix) H_2/Pd-C, (x) TBAF, (xi) TsCl, DMAP, (xii) $LiN(t\text{-}Bu)_2$, -120 °C.

Finally, the hydroxymethyl group at C-16 position of **57** was introduced with 1-ethoxyethoxymethyllithium to give rise to (±)-3 after acidic treatment. In order to separate a 1:1 mixture of (±)-**3** and the epimer at C-16, the mixture is converted to the corresponding mixture of diacetonides, separated then rehydrolysed to give diastereomerically pure (±)-**3** (Scheme 10).[19]



Scheme 10: Corey's approach toward the synthesis of aphidicolin **3**. *Reagents and conditions*: (i) O, Li, OEt; (ii) AcOH, $MeOH/H_2O$; (iii) OMe, PPTS; (vi) separation; (v) H_3O^+.

However, the pathway for Corey's synthesis of aphidicolin **3** is also applicable to the synthesis of stemodinone **1** and stemodin **2** through a common intermediate **55**. Moreover, Corey and co-worker considered the part of structure **55** and realized that if intramolecular alkylation was to occur between C-12 and CH_2OTs group would lead to an aphidicolane-type skeleton. However, internal alkylation involving C-15 and the CH_2OTs function would produce a stemodane-type skeleton as shown in Figure 4.

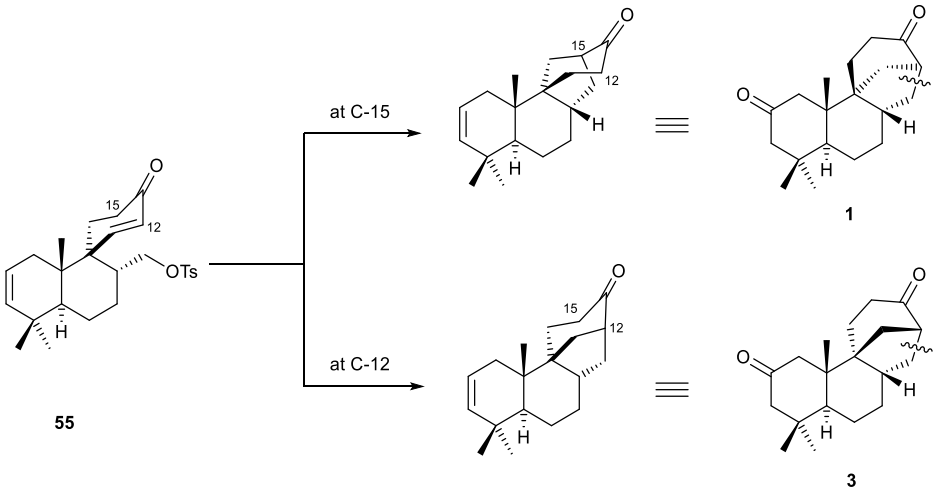
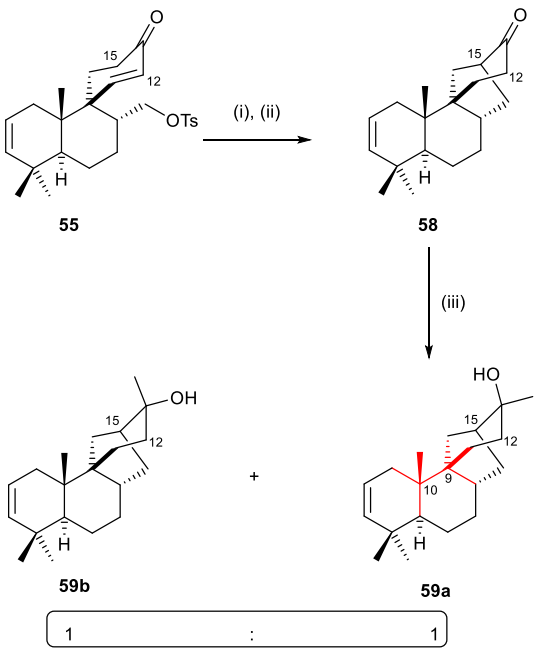


Figure 4: Intermediate **55** for Corey's synthesis of stemodinone **1** and aphidicolin **3**

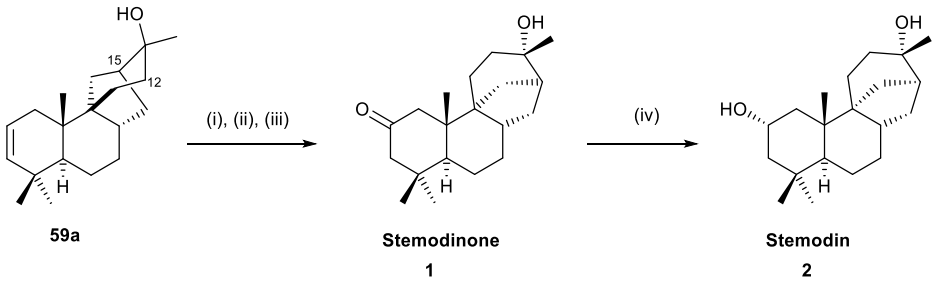
In order to construct the tetracyclic skeleton of stemodinone, one more cyclization was achieved by Corey and co-workers upon treatment of tricyclic enone tosylate **55** with 1.1 equivalent of potassium *tert*-butoxide in tetrahydrofuran at 23 °C, then followed by reduction of the enone with lithium in liquid ammonia at -78 °C to afford **58** in 50% overall yield from aldehyde **54** after purification. Upon reaction of **58** with methyllithium in ether at 0 °C a mixture of *tert*-alcohol **59a** and **59b** (~ 1:1) respectively was afforded.[16c] However, reaction of **58** with methylmagnesium bromide in ether at 23 °C furnished *tert*-alcohols **59a** and **59b** (2.4:1) in 85% yield.[21]

The isomeric spiro epoxides were reported to be reduced with lithium triethylborohydride[22] in tetrahydrofuran at 23 °C affording a mixture of **59a** and **59b** (5:1).



Scheme 11: Assembly of the C/D-rings during Corey's approach to stemodinone **2**. *Reagents and conditions*: (i) *t*-BuOK/THF; (ii) Li in Liq. NH_3, -78 °C; (iii) MeLi/Et_2O, 0 °C.

Furthermore, treatment of **59a** (scheme 12) in acetone at 23 °C with 7.6 equivalents of *N*-bromoacetamide solution in water[23], then followed by work up with methylene chloride gave a single bromohydrin which oxidized upon treatment with pyridinium chlorochromate in CH_2Cl_2 to the corresponding α-bromo ketone which underwent debromination when treated with zinc dust in ether-aqueous ammonium chloride at 23 °C to afford stemodinone **1**. However, reduction of stemodinone **1** with sodium in tetrahydrofuran-ethanol at 0 °C afforded Stemodin **2** in 43% overall yield from **59a**[24] as shown in Scheme 12.

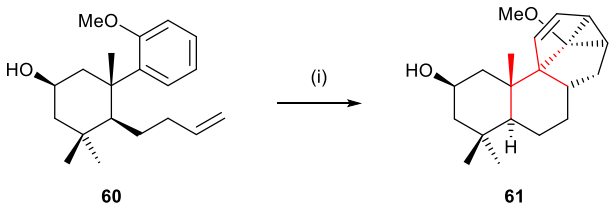


Scheme 12: Corey's approach to stemodinone **2** and stemodin **1**. *Reagents and conditions*: (i) $(CH_3)_2CO$, 23 °C, $CH_3CONHBr/H_2O$; (ii) Work up with CH_2Cl_2; (iii) PCC/ CH_2Cl_2; (iv) Zn in Et_2O-aq. NH_4Cl, 23 °C; (v) Na/THF-EtOH, 0 °C.

Corey's synthesis of stemodinone **1** from **55**, establishing two adjacent quaternary centres at C-9 and C-10 (Scheme 11), by the successive combination of sp^2 hybridised carbons, correlates with our main objective with regard to the construction of **1** by employing a *meta*-photocycloaddition reaction from precursor **60** (Scheme 13), itself prepared from a Schultz heteroatom photoarylation reaction (*vide infra*) and both combination of sp^2 hybridised carbons.

1.3 The *meta*-photocycloaddition reaction

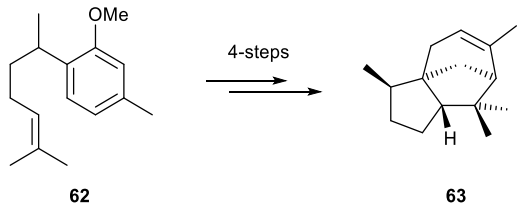
The approach to the stemodinone ring system adopted in our group is based around the alkene-arene *meta*-photocycloaddition of substrates of the type shown in Scheme 13. In particular, the adjacent quaternary centres in **61** (highlighted in red) have been formed by the cycloaddition of sp^2 hybridised carbon atoms, one component of which is a benzene ring excited to its first singlet excited state (S_1). This key aspect of the approach can be seen to relate to the previous syntheses reviewed above (*e.g.* Scheme 3) and indeed a number of others.



Scheme 13: An alkene-arene *meta*-photocycloaddition reaction toward a synthesis of stemodinone **1**. *Reagents and conditions*: (i) hν (254 nm), cyclohexane (56%).

Because of the central importance of this reaction in our approach, its application in synthesis is summarised below.

In 1981, Wender and co-workers reported the first total synthesis of the secondary metabolite α-cedrene **63** utilizing a *meta*-photocycloaddition reaction. The simple aromatic compound **62**, with its asymmetric carbon centre, served as the starting point followed by four further steps to achieve the total synthesis of α-cedrene **63** (Scheme 14).[25] This work marked the transition of this reaction from the discovery/mechanistic investigation phase into its application in synthesis.



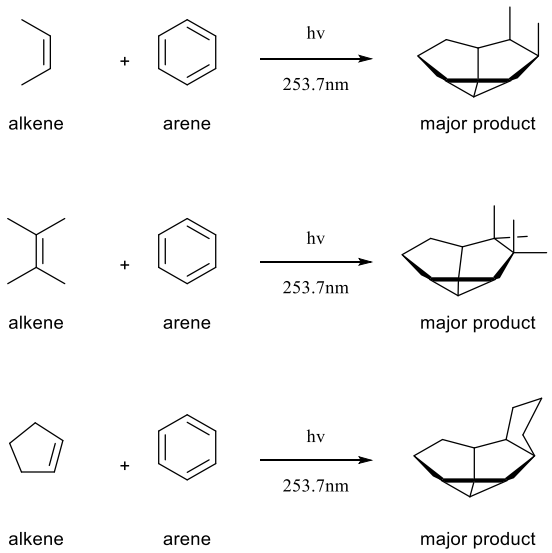
Scheme 14: Wender's approach toward the synthesis of α-cedrene **63**.

Thus, this phytochemical compound can be synthesized rapidly and with the correct relative stereochemistry at each of its four stereogenic centres, demonstrating the power of the key *meta*-photocycloaddition step. This suggested that the *meta*-photocycloaddition should become a standard, strategic-level reaction in organic synthesis.[26] Subsequently, a series of reports on the use of the alkene-arene *meta*-photocycloaddition have been documented in the chemical literature, fully supporting this conjecture. The work described in the present report seeks to further develop the synthetic application of this reaction.

The *ortho*-and particularly the *para*-photocycloadditions have not received detailed attention since they occur rarely and usually with low quantum yield.[27] However, the complexity of the *ortho/para* products is considerably increased with respect to that of the reactants, as a new ring and up to four new stereocentres are formed.[28] Primary attention will be given to the *meta*-photocycloaddition reaction due to its more extensive development and use in synthesis. As a result of the obvious relationship between synthesis and mechanism, this report will start with a brief historical perspective as well as mechanistic aspect of *meta*-photocycloaddition.

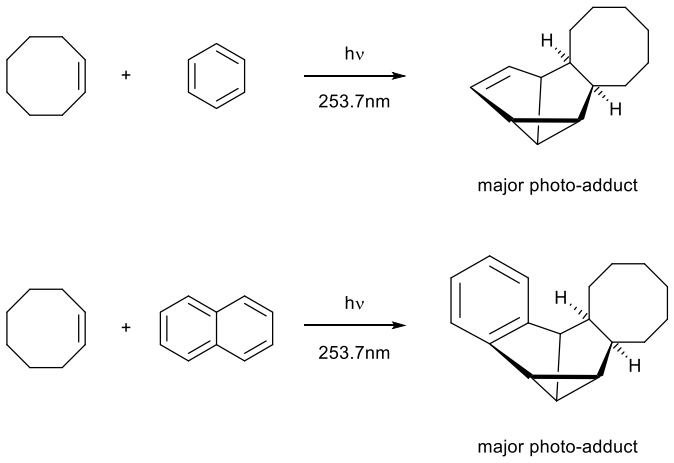
1.4 Discovery of the *meta*-photocycloaddition reaction

In 1966, Wilzbach and Kaplan at Illinois, and Bryce-Smith, Gilbert and Orger at Reading concurrently reported the first documented examples of the *meta*-photocycloaddition reaction. Experimental evidence reported by Wilzbach and Kaplan reveals that, irradiation of an approximately 10% solution of either (i) *cis*-but-2-ene, (ii) 2,3-dimethylbut-2-ene or (iii) cyclopentene in benzene with light of wavelength 254nm, under a nitrogen atmosphere and at ambient temperature yielded 1:1 adducts of the alkene and benzene as shown in Scheme 15. [28]



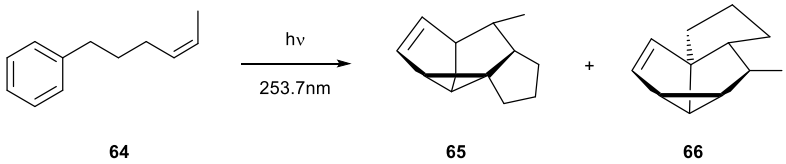
Scheme 15: The first *meta*-photocycloaddition reaction reported by Wilzbach and Kaplan.

Similarly, Bryce-Smith, Gilbert and Orger reported that treatment of an equimolar mixture of *cis*-cyclooctene and benzene afford a mixture of 1:1 adducts as indicated in Scheme 16.[29] At a practical level, from determination of the structure of the *cis*-but-2-ene adduct, a useful general rule emerged for the assignment of the configuration of carbons C-6 and C-7 by ^{1}H NMR spectroscopy. A strong coupling was observed by Wilzbach and Kaplan between H-5 and H-6 (J = 5 Hz) and H-7 and H-8 (J = 6 Hz) that was only consistent with the configuration of the methyl groups as 6-*endo* and 7-*endo*; however, this coupling was found to be absent in the *exo*-orientation. This general rule has helped in the assignment of stereochemistry of *meta*-cycloadducts in many subsequent studies. To ascertain if the reaction was limited to benzenoid aromatics, Bryce-Smith *et al.* repeated the experiment but using *cis*-cyclooctene and naphthalene instead of benzene and achieved the formation of several 1:1 *meta*-photocycloadducts. Each adduct was found to contain a single double bond that was deduced to form part of a vinylcyclopropane chromophore via analysis of the frequency and coupling of olefinic protons in the ^{1}H-NMR spectra. The NMR spectra suggested that the photoadducts were derivatives of tricyclo[3.3.0.0]oct-3-ene, since all the 6-protons derived from benzene were not alike (Scheme 16).



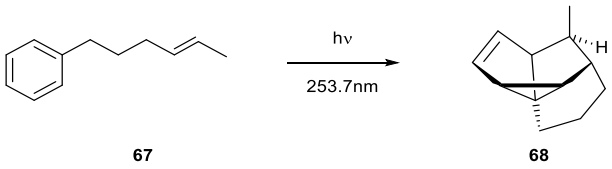
Scheme 16: The *meta*-photocycloaddition reaction reported by Bryce-Smith, Gilbert and Orger.

However, the first example of the intramolecular variant of *meta*-photocycloaddition was reported in 1969 by Morrison and Ferree.[30] Initially, they proposed that irradiation of solution of *cis*-6-phenylhex-2-ene **64** in cyclopentene with light from a Vycor-enclosed low-pressure mercury arc lamp would cause excitation of the phenyl group to its first singlet excited state, followed by intersystem crossing to the first triplet excited state. Subsequent internal energy transfer to the disubstituted alkene moiety should result in some degree of *cis/trans*-isomerisation. However, the major products were determined to be a mixture of isomers **65** and **66** were obtained from intramolecular *meta*-photocycloaddition (Scheme 17).[30]



Scheme 17: Regioselectivities observed in the *meta*-photocycloaddition of *cis*-6-phenylhex-2-ene.

Conversely, irradiation of *trans*-6-phenylhex-2-ene **67** produced a single major 2,6-*meta*-photocycloadduct **68** (Scheme 18).

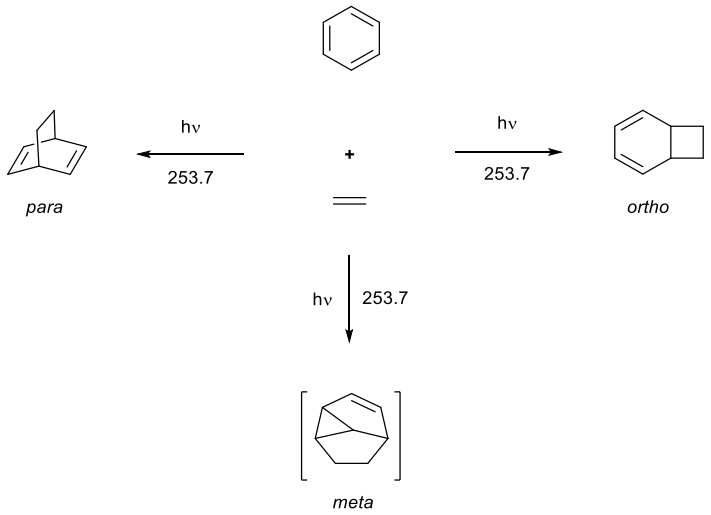


Scheme 18: Regioselectivities observed in the *meta*-photocycloaddition of *trans*-6-phenylhex-2-ene.

1.5 The *meta*-photocycloaddition reaction-observed selectivity

1.5.1 Mode selectivity

Photocycloaddition of an alkene to an arene ring requires excitation of the aromatic moiety to its first singlet excited state with light of 253.7nm to afford *ortho*-, *meta*- or *para*-adducts (Scheme 19).



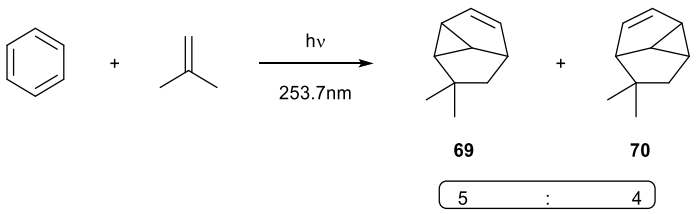
Scheme 19: The modes of the photocycloaddition reaction of alkene to a benzene moiety.

Much work has been reported regarding *ortho*- and *meta*-adducts and also a predictive model to describe which one is favoured in a given situation.[31] The *para*-adduct is only rarely observed and no application in synthesis has been documented.[32] A satisfactory empirical method based on assessment of free energy for electron transfer (ΔG_{ET}) for the two reacting groups, estimated by the Rehm-Weller equation, was developed by Mattay and Meuller.[33] This report will exclusively focus on the *meta*-photocycloaddition, a mode favoured for alkene-arene pairs with a ΔG_{ET}>1.7eV.

1.5.2 Intermolecular reactions

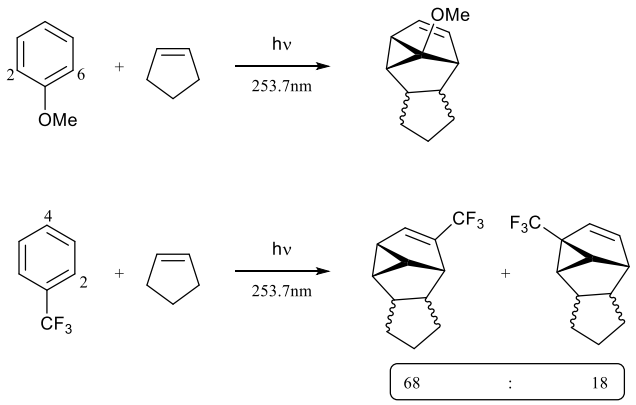
1.5.2.1 Regioselectivity issues

The commonly observed two regioisomeric cyclopropane products **69** and **70**, formed by a *meta*-photocycloaddition reaction are shown in Scheme 20.[34]



Scheme 20: Regioisomer formation during a*meta*-photocycloaddition reaction.

However, there is potential for the cycloaddition to occur with varying regioselectivity if the benzene ring bears substituents. It is generally observed that, addition of the alkene takes place, preferentially, 2,6-across electron donor groups, such as methyl (or methoxy), while electron-withdrawing groups such as cyanide (or trifluoromethyl) favour 2,4-addition (Scheme 21).[35]



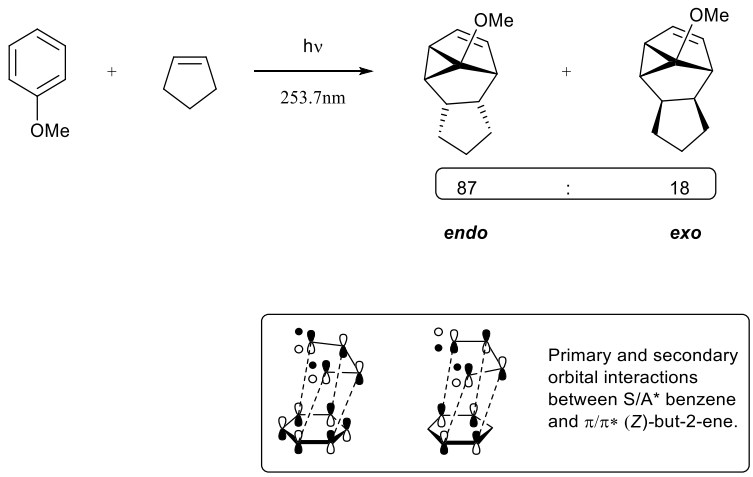
Scheme 21: Regiochemical preference in the *meta*-photocycloaddition with substituted benzene.

1.5.2.2 Stereoselectivity issues

(i) *exo/endo* selectivity:

Upon thorough inspection of the products in Scheme 21 preferentially the formation of *endo-isomer* is indicated, and this is common in many intermolecular reactions.[31] The reaction of anisole and cyclopentene is shown in Scheme 22[36] as an example. The *endo*-selectivity observed in this case followed a similar pattern to the *exo/endo*-selectivity in the Diels-Alder reaction based upon secondary orbital interaction. This has been explained by Houk for

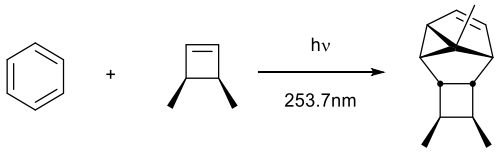
benzene and cis-but-2-ene in terms of frontier molecular orbital theory.[37] The key primary and secondary orbital interactions are shown in Scheme 22.



Scheme 22: *Endo*-selectivity in the intermolecular *meta*-photocycloaddition reaction.

(ii) *π-facial selectivity* in the alkene component:

The structure of the alkene determines the degree of the π-facial selectivity in attack on the arene, but the essentially complete selectivity is possible as shown in Scheme 23.[38]

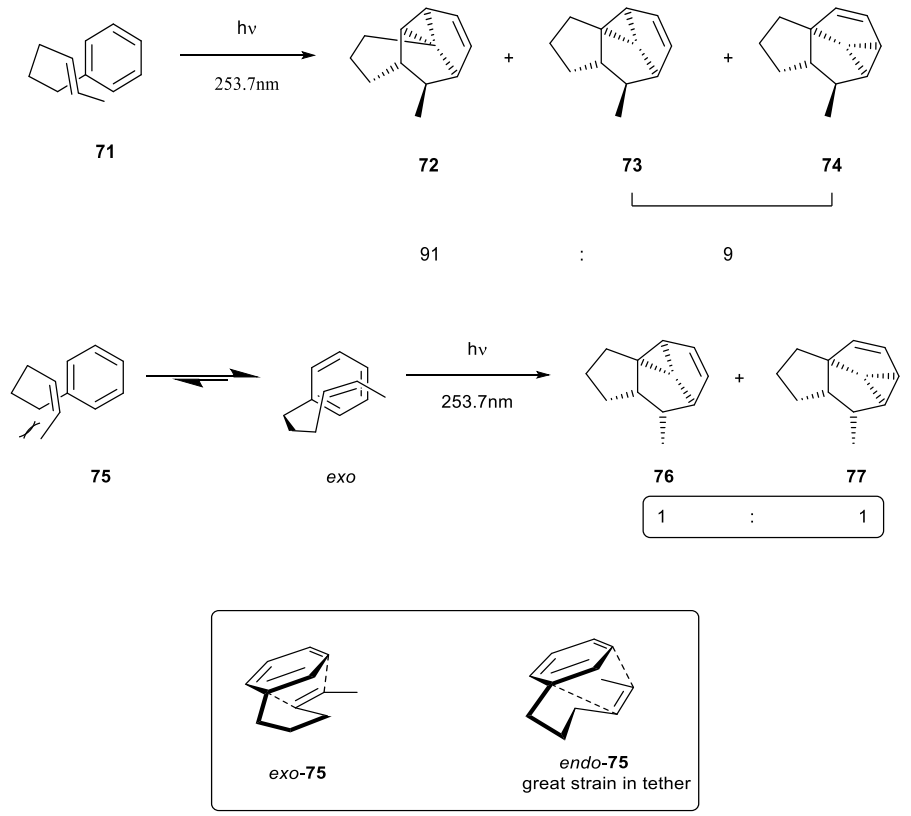


Scheme 23: π-facial selectivity in attack on the arene component by an alkene.

1.5.3 Intramolecular reactions

The regio-/stereochemical issues become entwined in intramolecular reactions. However, substrates with a three-atom tether connecting the arene-alkene moieties were reported in most studies. From the above-mentioned discussion, it might be likely that if the tether were the only substituent on the benzene ring, then cycloaddition would occur across the tether. However, for the terminal and *E*-distributed double bonds, this regiochemistry of addition is often found to furnish the major products such as **71** to **72** (Scheme 24).[39] Wender's approach toward

desdimethylquadrone has provided a good example of application of terminal and *E*-disubstituted double bonds.[40] The presence of a *Z*-double bond leads to a strong preference for 1,3-addition *e.g.* **75** to **76**/**77** (Scheme 24).



Scheme 24: Regio- and stereochemical preferences in intramolecular *meta*-photocycloaddition reactions.

This has been attributed to steric interactions of the vinyl methyl group with hydrogens in the linking tether.[41] The need to minimize strain in the tether while maximizing orbital overlap of the relevant alkene and arene orbital found in nearly all cases, has dictated the great preference for the *exo*-isomer (Scheme 24).[30] The corollary of these results is that, during *meta*-photocycloaddition reactions, alkene geometry is retained. Asymmetric induction from stereogenic centres on the tether has been proven effective in many reports.[30] In the context of intramolecular reactions with a three-carbon tether, the relationship of the two regioisomeric

cyclopropane products with respect to linear and angular triquinanes has being described as depicted in Figure 5.

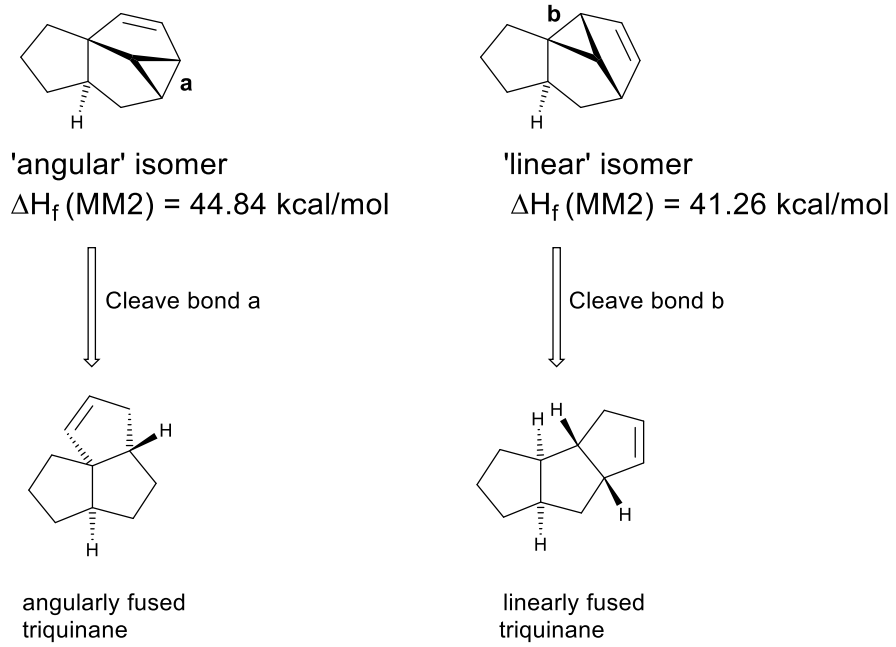


Figure 5: Calculated relative energies of 'angular' and 'linear' isomers.

Wender and Howbert performed MM2 calculations on this prototypical scenario and observed that the 'linear' isomer was 3.6 kcal/mol lower in energy than the 'angular' isomer.[42] The difference between the position of equilibrium between these isomers, under photochemical and thermal conditions must be attributed to this energetic difference. These MM2 calculations of product stability have proven helpful in rationalizing the outcome of the *meta*-photocycloaddition by Wender's laurenene synthesis.[43] Of course, these cycloadducts may be converted into compounds that are useful in natural product synthesis. In the case of any reaction that significantly increases molecular complexity, such as the *meta*-photocycloaddition, it is a key issue to notice whether that complexity is relevant to the target molecule. The adducts from *meta*-photocycloaddition reactions are usually overly complex because the cyclopropanes, so formed, are frequently not required in the target molecule. This suggests that any method that couples the fragmentation of the cyclopropane to a

transformation that further advances the synthesis is of significant interest, as noted in Wender and Howbert's synthesis of α-pipitzol and reported in Wender and Dreyer's synthesis of isocomene[44]. Some potential ring systems that might be prepared from a *meta*-photocycloadduct are displayed in Figure 6.

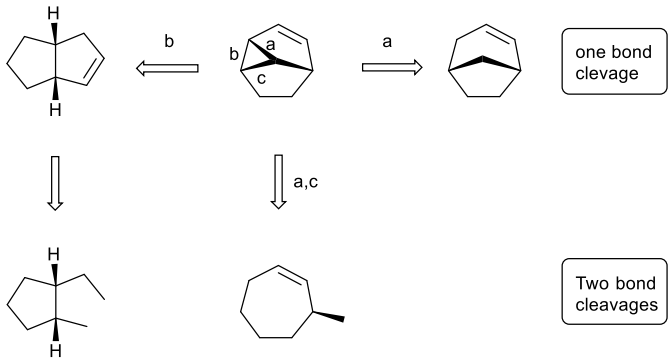
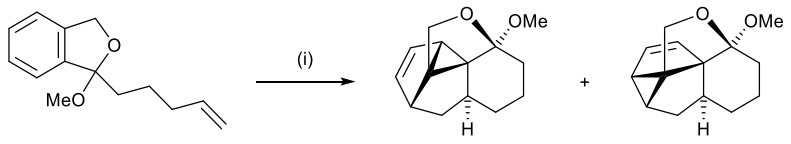


Figure 6: Ring systems accessible from a *meta*-photocycloadduct.

1.6 The significance of tether length

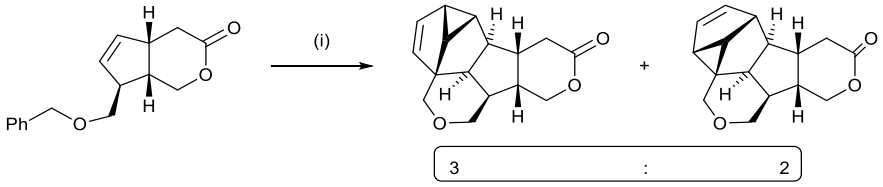
A significant difference in quantum yields was observed on intramolecular *meta*-photocycloaddition reactions, dependent on the length of tether linking the alkene and arene moieties. For instance, the quantum yield in 6-phenylhex-1-ene, $\phi < 0.005$;[45] whereas, for the isomer *Z*-6-phenylhex-2-ene, it is $\phi=0.26$.[29] This appears to have discouraged the use of longer linking tethers in natural product synthesis. It was reported that, if the conformational freedom of the tether can be restricted or at least if an appropriate conformation for cycloaddition is favoured, then greater than a three-atom tether may be feasible. The photolysis of **78**, which contains a four-atom tether in which a cyclic acetal provides some conformational restriction, gave a reasonable 68% yield of products **79** and **80** at 60% conversion (Scheme 25).[28]



78 79 80

Scheme 25: Studies of the photolysis of a substrate with a four-carbon atom tether. *Reagents conditions*: (i) h*v* (Vycor filter) (68% yield at 60% conversion).

During a study of tandem Norrish Type I - intramolecular alkene-arene *meta*-photocycloaddition reactions, De Keukeleire and He described that photolysis of **81** gives a 3:2 mixture of **82** and **83** in a significant 42% yield (Scheme 26).[46] However, the usual *exo*-selectivity was found with 1,3-addition to the benzene ring being driven by the *Z*-double bond.[46]

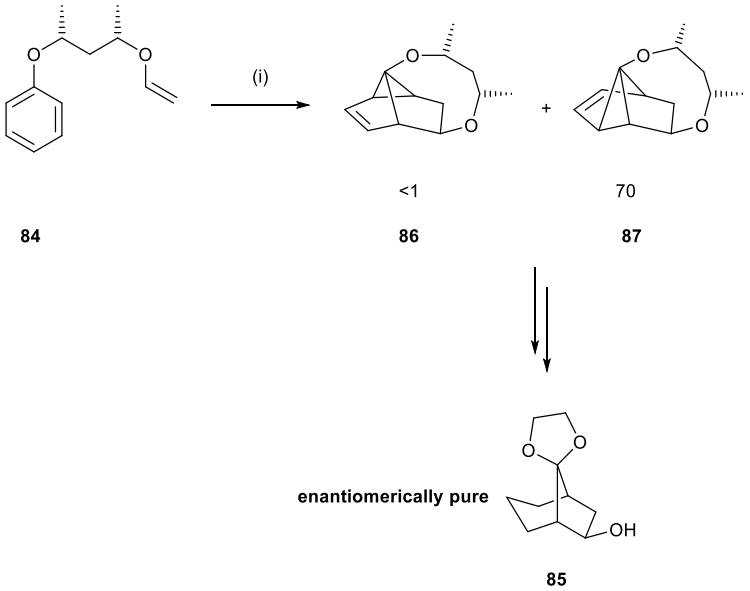


81 82 83

Scheme 26: De Keukeleire's study on four atom tethers. *Reagent and conditions*; (i) h*v* (254nm), Rayonet reactor (42%).

It is apparent that longer tethers are rare, but literature searches have shown that Sugimura has reported an example of compound with a five-atom tether **84**. In this case, the cleavable tether served as an effective chiral auxiliary to deliver enantiomerically pure **80** via **81** and **82** (Scheme 27).[47]The high yield was reduced in more substituted derivatives, *e.g*. tolyl analogues. This is not unexpected in very challenging substrates with regard to the problems with chemical yields, in intramolecular photocycloaddition of enol ethers/acetates reported in some synthetic studies (Schemes 44 and 47). It is interesting to note that the tether contains two oxygen atoms; De Keukeleire has reported the inconsistent influence of incorporating an oxygen atom in

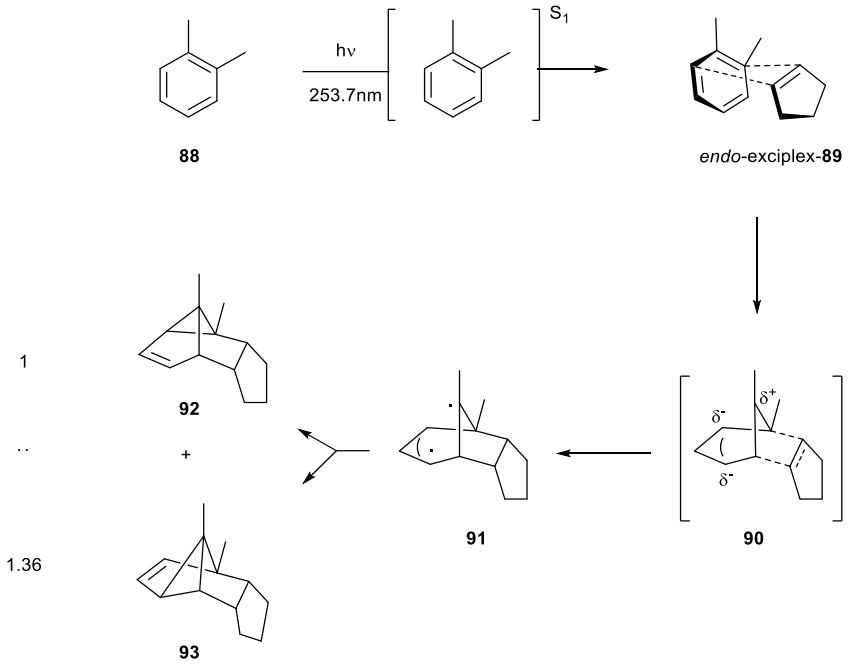
substrates featuring a tether of greater than three atoms and this shows the complex relationship as a balance between conformational and electronic effects (Scheme 27).[48]



Scheme 27: Sugimura's study of a diastereoselective *meta*-photocycloaddition with a five-atom tether. *Reagents and conditions*: (i) *hv* (low pressure mercury vapour lamp), vycor filter, pentane (**87**:70).

1.7 Mechanistic rationalisation

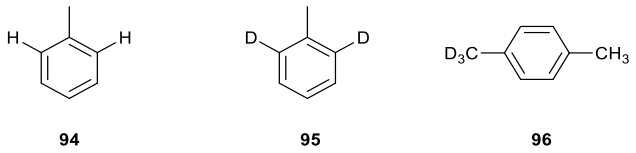
Many mechanistic and theoretical studies have been conducted on *meta*-photocycloaddition reactions and the following detailed pathway outlined in Scheme 28 appears to be in accord with the facts as suggested by P. de vaal *et al*.[49] This gives room for debate, and the theoretical studies by Robb have suggested that analysis of conical intersections between energy surfaces reveals a different picture.[50]



Scheme 28: A possible mechanism for *meta*-photocycloaddition illustrated for the case of *ortho*-xylene and cyclopentene.

Light of 253.7nm is required for the excitation of the benzene ring to its first singlet excited state to produce an *endo*-exciplex **89** with an alkene reaction partner.[30,51] In certain instances exciplexes were detected as reaction intermediaries that precede the product but are not formed in competition; however, only a limited number of such cases exist that are informative and favourable.[52] Considerable circumstantial support for exciplex formation, prior to generation of the product, comes from the ability to predict the stereo- and regio-chemical outcome of the *meta*-photocycloadditionon this basis. An inverse α-secondary deuterium isotope effect (k_H/k_D=0.93) in intermolecular competition experiments between substrates such as **93**/**94** and cyclopentene, suggest that the exciplex is followed by a rate-limiting addition step, and two C-C bonds are formed between alkene and arene as shown in Figure 7.[53] As the addition proceeds, a polarized species **90**, is implicated with a small positive charge on the one carbon bridge and a negative charge, allylically distributed, on the three-carbon bridge. Related studies on the addition of cyclopentene to, *inter alia*, photo-excited α,α,α-trideutero-*para*-xylene **95** lead to

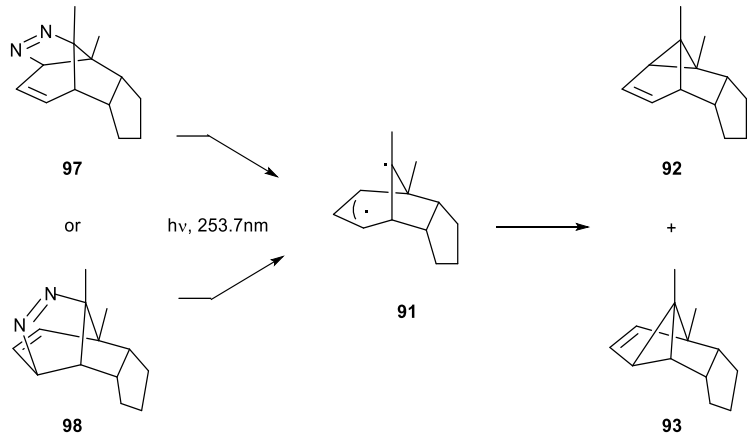
the observation of preferential addition across the CH_3 group. The positive β-secondary deuterium isotope (k_H/k_D=1.06) measured is in accordance with the preference of alkenes to add 2,6 across the donor group.[50]



94 **95** **96**

Figure 7: Substrates used in deuterium isotope effect studies.

A species that immediately precedes the products has been proposed to be biradical intermediate **91**. Sheridan and Reedich reported that irradiation of diazo compounds **97** and **98** with 253.7nm light, causes each to extrude nitrogen and yield the same compounds **92** and **93**, in roughly the same ratio (**97** gives **92**:**93 (**1:1), **98** gives **92**:93 (1:1.34)) as shown in Scheme 29. This is presented to be the same as obtained by direct photolysis of *ortho*-xylene and cyclopentene (Scheme 28).[54] It is not clear whether such a compound is a true intermediate or a species with a short-lived existence on a descending energy curve. However, all attempts to trap the species **90** and **91** mentioned above have proven abortive.[31]



Scheme 29: Sheridan's photolysis of diazo compounds **97** and **98**.

1.8 Syntheses of natural products *via* the *meta*-photocycloaddition routes

The whole synthetic strategy of *meta*-photocycloaddition reactions has depended on three conditions all being efficient, which comprise:

(i) access to the photocycloaddition substrate.

(ii) the photocycloaddition itself.

(iii) the conversion of the photocycloadduct into the target compound.

The key steps to consider in the *meta*-photocycloaddition reaction have generated a range of issues that need to be addressed in the application of this reaction in synthesis of natural products. For the purposes of this research, only the *meta*-mode of addition will be of concern. However, four key issues of selectivity will be considered during these syntheses which are as follows;

(i) the ratio of regioisomeric cyclopropanes and whether both isomers are viable intermediates to continue the synthesis.

(ii) the number of atoms in the tether for intramolecular reactions.

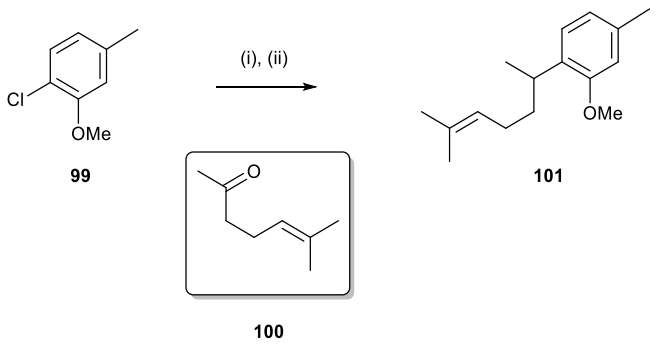
(iii) the regiochemistry of cycloaddition.

(iv) the stereochemistry, which include asymmetric induction from pre-existing stereogenic centres, *exo*/*endo*-selectivity in the cycloaddition step and conversion of alkene geometry.

In addition, the yields associated with these reactions and subsequently the increase in complexity that accompanies the transformation will be evaluated.[26]

1.8.1 Synthesis of α-cedrene

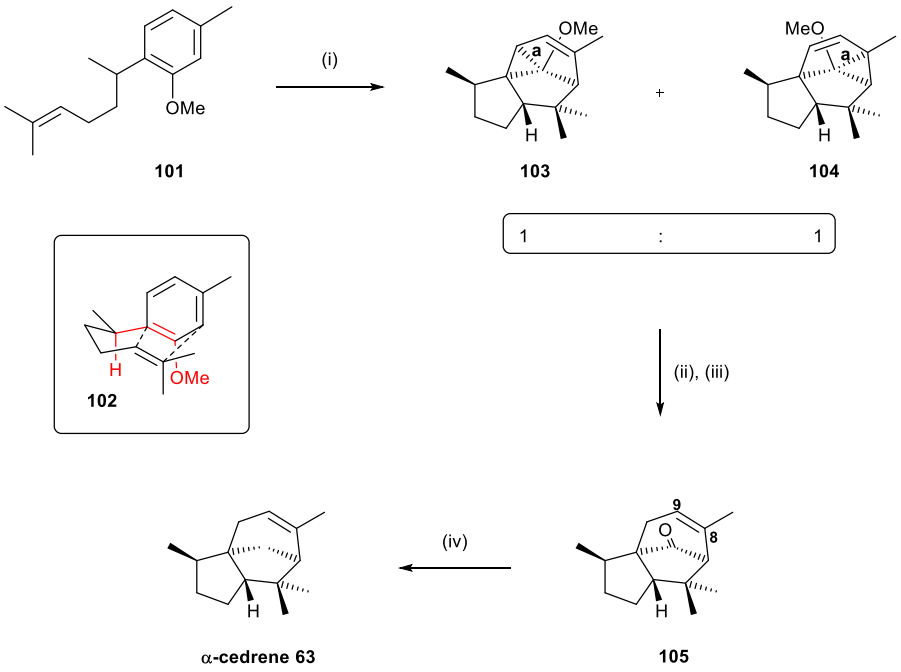
The bichromophore starting material used for the synthesis of α-cedrene, is simple to prepare and takes the benefit of a one-pot, two-step, reductive coupling developed by Hall and McEnroe, [55] in this case utilized chlorocresol **99** and ketone **100** (Scheme 30).



Scheme 30: Synthesis of α-cedrene; preparation of the photocycloaddition precursor. *Reagents and conditions*: (i) Li, Et_2O then **100**; (ii) Li, NH_3 then NH_4Cl (74%).

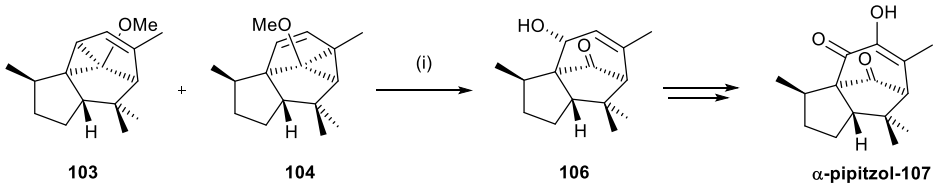
In general, photochemical transformations involve high energy intermediates and hence, selectivity can be a problem, commonly observed in terms of multiple reaction types, *e.g.* Norrish type I and type II reactions from a single carbonyl precursor. However, further issues such as stereoselectivity are crucial. Close examination of the structure of **101** reveals that many control features needed for the target, have been incorporated into its structural design to deal with some of the regio- and stereochemical features required. The alkene and arene moieties in most of synthetic studies involving *meta*-photocycloaddition reaction, are separated by a tether of three atoms in length, and a new five-membered ring is formed upon cycloaddition. This typically takes advantage of the high quantum yields to attend by this length of tether (Section 1.6). The preference for addition across the strongest π-donor group explains, in part, the presence of the methoxy group for the regiocontrol of *meta*-photocycloadditions that are permitted by this length of tether. This directing effect is augmented by the influence

of the *Z*-double bond that is probably of secondary importance and may be judged from the outcome of the cycloaddition step in the synthesis of many compounds, *e.g.* hirsutene, subergorgic acid and ceratopicanol, plus studies toward cerapicol by De Keukeleire and He[48]. The π-facial selectivity was controlled by stereogenic centre adjacent to the benzene ring. A formal allylic strain motif in **101** (red in **102**, Scheme 30) favours the local conformation shown which eventually leads to the most stable *exo*-exciplex **102**, with the tether adopting a distorted *syn*-pentane conformation with a pseudo-equatorial methyl group. Thus, Photolysis of **101** with light from a Vycor-filtered medium pressure mercury lamp[56] delivers two cycloadducts **103** and **104**, distinguished by regioisomeric cyclopropanes in a 1:1 ratio at photochemical equilibrium (65% yield). At thermal equilibrium **103**, the 'linear isomer', is formed exclusively. Regioselective cleavage of the internal cyclopropane bonds **a** in **103** and **104**, renders these two isomers synthetically equivalent. However, the means by which this is achieved is critical and by no means general. In the present case, regiocontrol is exerted by a push-pull effect in which electrophilic activation of the alkene is coupled with electron donation from an oxygen lone pair. There is some ambiguity as to whether the electrophile reacts at the double bond or the cyclopropane and different consequences have been reported. Thus, treatment of **103** and **104** with 4 N HCl affords the desired tricyclic skeleton but as a regioisomeric mixture of Δ8 and Δ9 alkenes. A two-step cleavage, with electrophilic activation by bromine preceding radical debromination with tri-*n*-butyltin hydride, gave **104** as a single alkene in 59% yield. It is interesting to contrast these outcomes with cyclopropane cleavage in De Keukeleire's[46] and Penkett's[85] work toward the synthesis of cerapicol and gelsemine respectively. The final step of the synthesis is a straightforward Wolff-Kishner reduction to deliver α-cedrene in 58% yield. Thus, a full assessment of this synthesis makes manifest the erudition in its design.



Scheme 30: Synthesis of α-cedrene **57**. *Reagents and conditions*: (i) *hv* (Vycor filter), pentane (65%); (ii) Br_2, CH_2Cl_2; (iii) Bu_3SnH (neat) (59%, 2 steps); (iv) NH_2NH_2, KOH, $(HOCH_2CH_2)_2O$, 200 ˚C (58%).

However, Wender and Howbert carried out a synthesis of pipitzol **107** as outlined in Scheme 31 by exploiting alternative post-cycloaddition functional group manipulations.[42,57]



Scheme 31: Synthesis of pipitzol. *Reagents and conditions*: (i) I_2, THF, H_2O.

It very clear that the synthesis of α-cedrene opened the door and advanced our understanding of the key structural factors controlling the outcome of these interesting and powerful *meta*-photocycloaddition reactions and to their application towards a considerable number of natural product syntheses.

1.8.2 Intramolecular meta-photocycloaddition reactions with a three-atom tether Rudmollin, isocomene and silphinene

The *ortho*-disubstituted aromatic substrates with similarities in structural arrangements have been grouped and studied in relation to the synthesis of rudmollin **108**, isocomene **109** and silphinene **110** (Figure 8). Isocomene and silphinene are converted into their respective target compounds despite the subtle differences in their precursors which provides an interesting challenge in the way they are related to their photocycloadducts. However, rudmollin, which appears distinctly different from the other natural products, follows the same route as for α-cedrene synthesis.

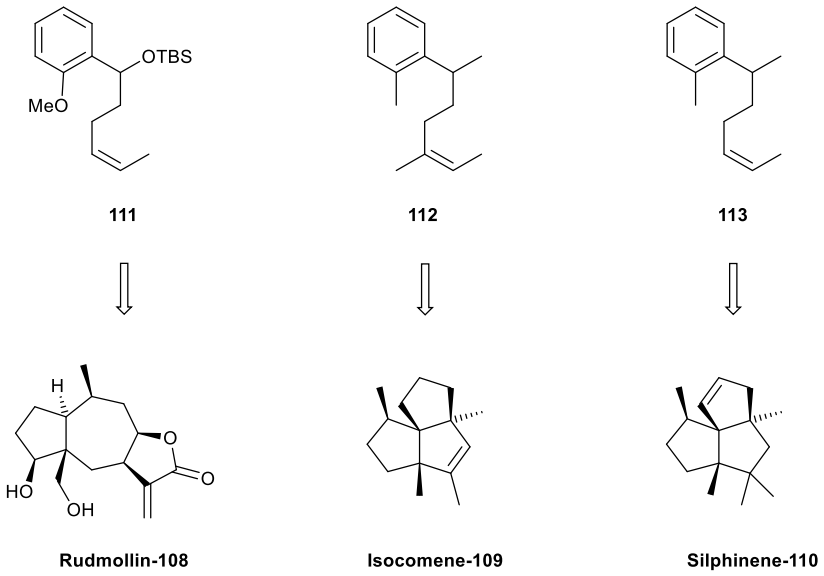
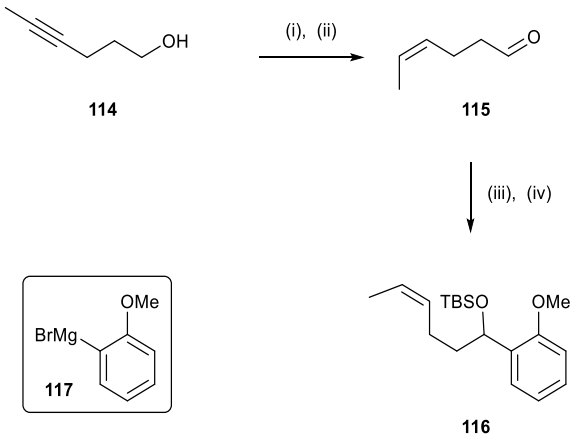


Figure 8: *Ortho*-disubstituted aromatic substrates for the synthesis of isocomene, rudmollin and silphinene.

1.8.2.1 Synthesis of rudmollin

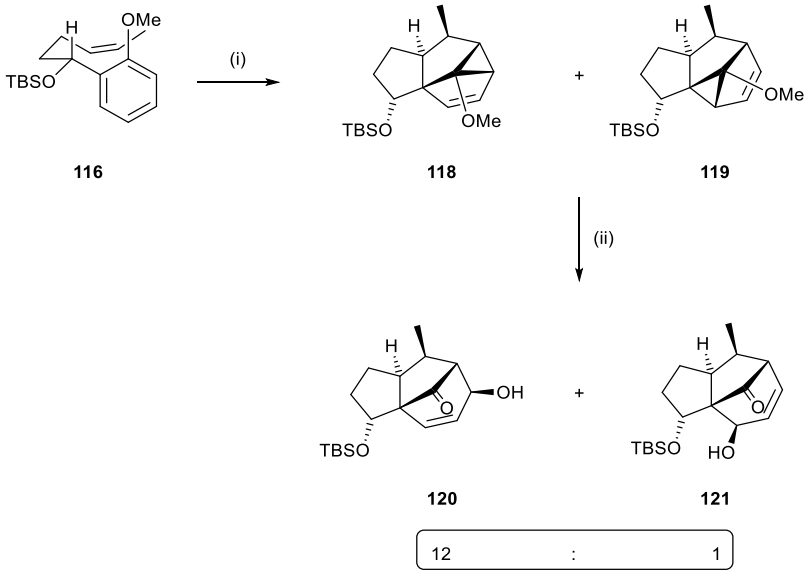
An essential procedure for the synthesis of rudmollin requires the cleavage of the two bonds present in the photocycloadduct which formed a complex seven-membered ring via a *meta*-photocycloaddition. However, all the carbons are used in the final compound and most of the stereochemical information is retained in the product. The photocycloaddition precursor is

easily produced via a Lindlar reduction with control over the double bond geometry (Scheme 32). [58]



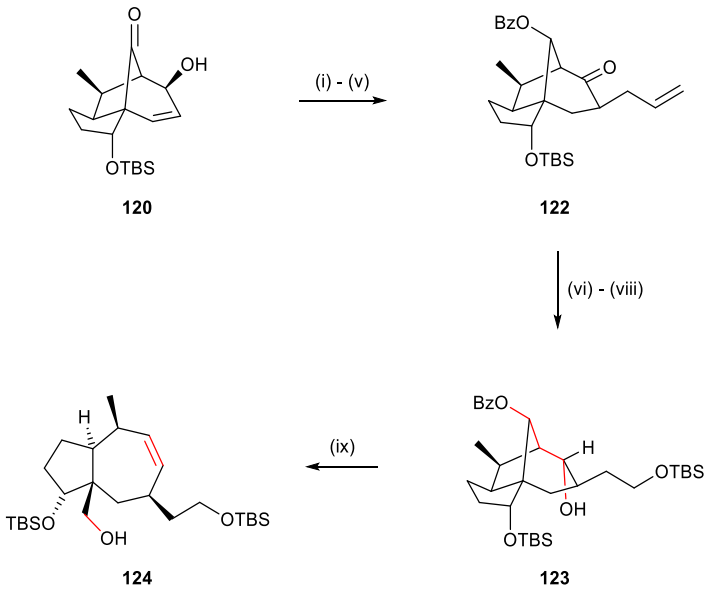
Scheme 32: Synthesis of rudmollin; photocycloaddition substrate preparation. *Reagents and conditions*: (i) H_2 (10-40 psi), $Pd/CaCO_3$ (Lindlar), quinoline, pentane (94%); (ii) PCC, CH_2Cl_2, 0-25 °C (54%); (iii) **117**, THF, 0 °C (98%); (iv) TBSCl, DMAP, NEt_3, DMF (97%).

However, the photocycloaddition of **116** appears closely related to that observed in the α-cedrene synthesis with good asymmetric induction from the stereogenic centre adjacent to the aromatic ring, the expected *exo*-selectivity, retention of alkene stereochemistry in the product and regioisomeric cyclopropanes **118** and **119** (2.3: 1 ratio) favouring the 'angular' isomer. In the α-cedrene synthesis, it was clearly shown that accessing a bicyclo [3.2.1] octane ring system renders both isomers synthetically equivalent in the first fragmentation of the photoadduct. In this case, the equivalence is being accomplished by treatment of isomer **119** with mercuric acetate and affording a 71% yield of allylic alcohol **120** accompanied by 6% of the allylic isomer **121**. When isomer **118** was subjected to with the same reaction conditions, two products were obtained **120** in 58% yield and less than 7% of **121** (ratio of 12: 1) (Scheme 33).



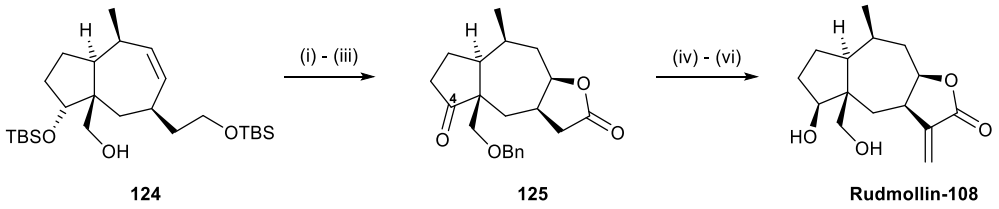
Scheme 33: Synthesis of rudmollin; photocycloaddition of **116**. *Reagents and conditions*: (i) hν (Vycor filter), pentane (63%); (ii) $Hg(OAc)_2$, THF, H_2O (71% + 6% allylic isomer from **119**).

The Grob-type ring-fragmentation method was carried out as a second phase of the ring-fragmentation process which produce the desired *trans*-fused bicyclo [5.7.0] decane ring system as shown in (Scheme 31). Thus, two of the remaining three carbons were introduced by a stereoselective enolate allylation to afford **122** *via* a series of functional group interconversions**.** The correct geometry for the Grob-type fragmentation (red in **123**) has been established by stereoselective reduction of the ketone followed by functional group manipulation of the double bond, then triggered by sequential mesylation of the alcohol and followed by $LiAlH_4$ cleavage of the benzoate ester, the resulting aldehyde being reduced *in situ* to yield **124.**



Scheme 34: Synthesis of rudmollin; Grob-type fragmentation to reveal seven-membered ring. *Reagents and conditions*: (i) $NaBH_4$, MeOH (94%); (ii) MnO_2, CH_2Cl_2(93%); (iii) H_2, 5% Pd/C, Et_2O (99%); (iv) $(PhCO)_2O$, DMAP, NEt_3, DMF, 46-50 °C (95%); (v) $KN(TMS)_2$, DME, 0 °C then BEt_3, THF, allyl iodide (75% at 75% conversion); (vi) $NaBH_4$, $CeCl_3$, MeOH (72%, 3 : 1 α : β); (vii) O_3, MeOH, CH_2Cl_2, -78 °C then $NaBH_4$, -78-25 °C (98%); (viii) TBSCl, imidazole, DMF (97%); (ix) MsCl, pyridine then $LiAlH_4$, DME, 0-25 °C (84%).

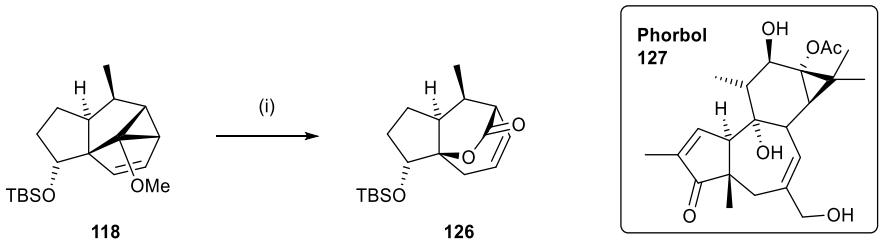
Synthesis of the final ring of rudmollin (Scheme 35), was achieved by cleavage of the silicon protecting groups from **119**, followed by a double oxidation with Jones' reagent which accessed the corresponding keto-acid to set-up an iodolactonisation. Reductive removal of the iodine under radical conditions gave **125**. Desmethylene rudmollin was delivered by stereoselective reduction of the ketone at C4 followed by hydrogenolysis of the benzyl protecting group. Introduction of the final methylene group using a method developed by Wasserman and Ives, and Ziegler and Fang completed the total synthesis rudmollin.[59]



124 125 Rudmollin-108

Scheme 35: Synthesis of rudmollin. *Reagents and conditions*: (i) KH, THF, BnBr (96%); (ii) HF-H_2O, CH_3CN, THF then Jones' reagent, acetone, 0-25 °C (82%); (iii) I_2, 2,4,6-collidine, CH_3CN then Bu_3SnH, AlBN, PhH, 80 °C (53%); (iv) $NaBH_4$, MeOH, -78-25 °C (92%); (v) H_2 (40 psi), 10% Pd/C, 70% $HClO_4$ (cat.), MeOH (82%); (vi) $(Me_2N)_3CH$, 90 °C then DIBAL, THF, 0 °C (54%).

Looking back to the selective fragmentation of the photocycloadducts, in Scheme 33, an alternative double fragmentation of **118** was examined. This in turn correlates compound **118** with the 5,7-bicyclic ring substructure in phorbol (**127**). An acid-catalysed cleavage takes the place of the bromine induced reaction used during the synthesis of α-cedrene; this delivered a bicyclo[3.2.1]octane that, after reprotection, allowed a regioselective Baeyer-Villiger reaction to complete the sequence. This sequence neatly expressed the issues of processing of the cycloadducts by demonstrating the diversity of structures that might be accessed. Yet, in this latter case, it is very important to have the correct regioisomer of cyclopropane (unless photoequilibration is effective).

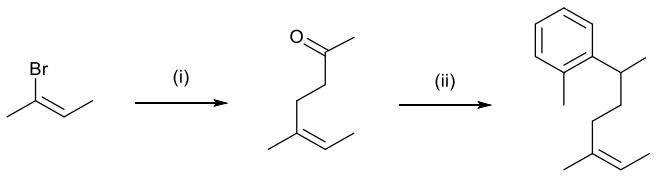


118 126

Scheme 36: Synthetic intermediate toward phorbol. *Reagents and conditions*: (i) H_2SO_4, H_2O, acetone, reflux then TBSCl, NEt_3, DMAP, DMF then TMSTf, $(TMSO)_2$, CH_2Cl_2, -30 °C.

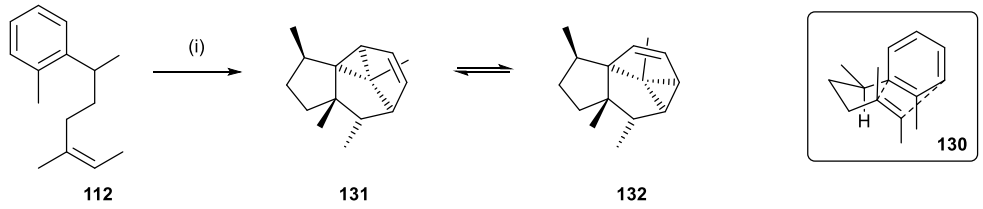
1.8.2.2 Synthesis of isocomene

Wender and Dreyer's synthesis of isocomene further develops some of the themes introduced in the α-cedrene work but emphasises the importance of the methodology of cleaving the cyclopropane ring. Contrasting the results with those obtained in the silphinene synthesis below is instructive, particularly the position of its *gem*-dimethyl group (Scheme 40).[60] The key bond construction in the synthesis of the photocycloaddition substrate **107** is again carried out according to the Hall protocol[55] with the additional consideration of alkene geometry addressed by use of *Z*-2-bromobut-2-ene as a starting material (Scheme 37).



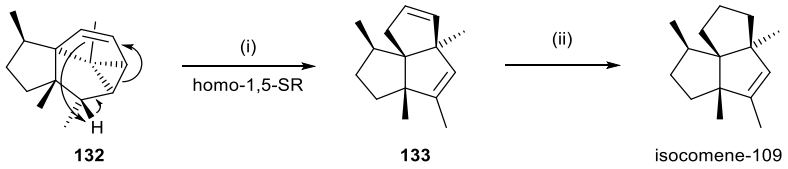
Scheme 37: Synthesis of isocomene; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) Li, Et_2O then CuI, -65 °C then methyl vinyl ketone (56%); (ii) *ortho*-bromotoluene, Li, Et_2O, room temperature, then **129** then NH_3, -78 °C (78%).

Irradiation of **112** with Vycor-filtered light from a medium pressure mercury lamp yielded, presumably *via* exciplex **130**, the two regioisomeric cyclopropanes **131** and **132** in 72% yield (Scheme 38). The tether adopts the now familiar distorted *syn*-pentane conformation bearing a pseudo-equatorial methyl group, and π-facial selectivity is controlled in the same way as for α-cedrene. An overriding preference for *exo*-selectivity is again observed and the stereochemistry of the alkene is retained during the cycloaddition process.



Scheme 38: Synthesis of isocomene; photocycloaddition of **112**. *Reagents and conditions*: (i) *hν* (Vycor filter), cyclohexane (72%).

The ratio of **131** and **132** is interesting, being 4.5:1 after 10 minutes but 1:1 after 4 hours of irradiation. Separation and re-subjection to photolysis demonstrated that these photoisomers could indeed be equilibrated, albeit with some decomposition. Given that, in this instance, both isomers were not equally suitable for conversion to isocomene (Scheme 39) *via* a homo-1,5-sigmatropic rearrangement, the ability to separate and photoequilibrate the isomers was potentially of synthetic value.

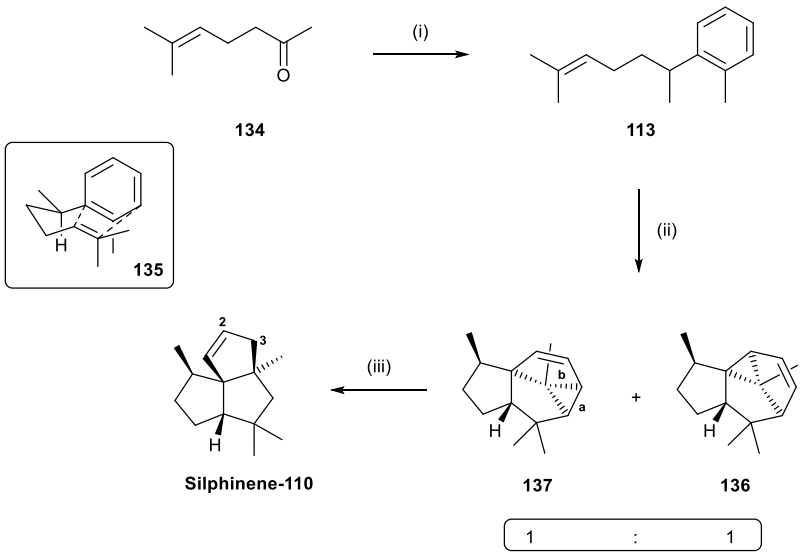


Scheme 39: Synthesis of isocomene; *Reagents and conditions*: (i) 235-240 °C (69%); (ii) H_2, 5% Pd/C, hexane (98%).

However, the separation of **131** and **132** has proved to be difficult in a large scale synthesis thus, it proved to be more efficient to thermolyse the mixture of the regioisomeric cyclopropanes to afford dehydroisocomene in 57% yield, with thermal rearrangement of **131** to **132** preceding the homo-1,5-rearrangement.[61] It may be noted that fragmentation to give an angular isomer results in the six carbons of the original benzene ring being converted into a linear chain forming part of the bicyclo[3.3.0]octane unit that arises from the alkene and arene moieties of the substrate.

1.8.2.3 Synthesis of silphinene

The *meta*-photocycloaddition reaction which led to the synthesis of silphinene is one of the most remarkable examples of this group (Scheme 40). This angularly fused triquinane that features three quaternary carbons and four stereogenic centres has been synthesized in three synthetic operations in multigram quantities.[62]



Scheme 40: Synthesis of silphinene. *Reagents and conditions*: (i) *o*-bromotoluene, Li (1% Na), Et_2O then NH_3, -78 °C to -33 ºC, NH_4Cl (87%); (ii) *hv* (Vycor filter), pentane (70%); (iii) Li, $MeNH_2$, -78 °C (74%; 9:1 alkene isomers).

A commercially available ketone **134** was treated with lithiated *ortho*-bromotoluene to afford substrate **113** in 87% yield by application of Hall and McEnroe's alkylation/reduction procedure.[55] Irradiation of **113** with Vycor-filtered light from a medium pressure mercury lamp gave a 1 : 1 mixture of regioisomeric cyclopropanes from an exciplex **135** whose conformation is dictated by previously discussed considerations. Only the 'angular' isomer **137** is suitable for conversion to silphinene and its treatment with lithium in methylamine results in selective cleavage of bond **a** over **b**, on the basis of better orbital overlap with the intermediate alkene-derived radical anion, to afford silphinene **110** in a 9:1 ratio with the Δ2,3 isomer (74% yield).

Consistent with this observation, the major isomer was calculated (MM2) to be the more stable alkene by 2.6 kcal mol^{-1}. The remarkable brevity of this route suggests that the *meta*-photocycloaddition is indeed a valuable strategic-level reaction. More recently, an additional example of this class of substrates has been reported by Gaich and Mulzer with the asymmetric synthesis of (-)-penifulvin A.[63]

1.8.3 Synthesis of desdimethylquadrone

Quadrone is a tetracyclic sesquiterpene natural product with interesting anticancer bioactivity. (Figure 9). Two synthetic studies on simplified versions of this structure have been carried out utilising the *meta*-photocycloaddition. [64,65]

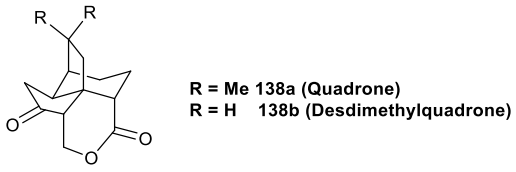
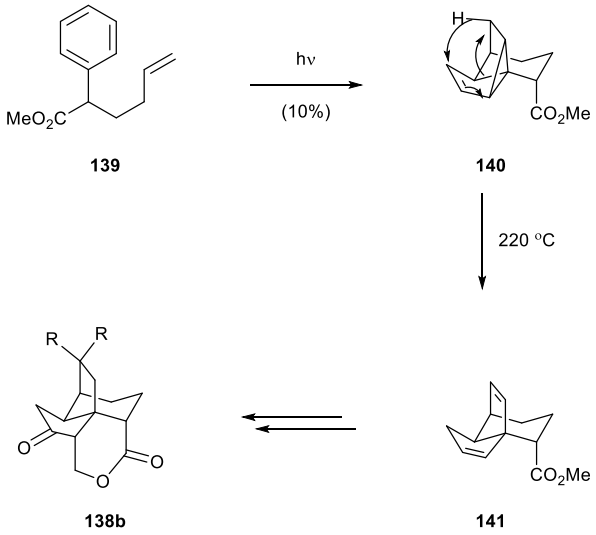


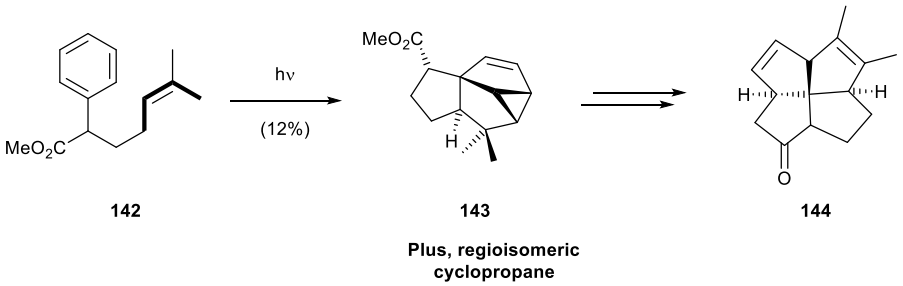
Figure 9: Structure of quadrone.

The synthetic studies carried out by Mehta[44] on descarboxyquadrone are based on an intermolecular *meta*-photocycloaddition whereas a synthetic study that employs an intramolecular *meta*-photocycloaddition directed toward desdimethylquadrone **138b**, was carried out by Wender and Wolanin (Scheme 41).[64]



Scheme 41: Synthetic study toward desdimethylquadrone.

Photolysis of **139**, although low yielding, afforded, as the main product, a single regioisomer of cyclopropane resulting from addition across the tether. That one cyclopropane is formed is understood in terms of the much higher energy of the alternative, regioisomeric compound. Having obtained **140,** the same homo1,5-sigmatropic rearrangement deployed during the isocomene synthesis successfully afforded **141:** this compound has three of the four rings of desdimethylquadrone **138b**. Addition across the tether (**139** to **140**) fits the pattern of adding across the strongest donor group unless sterics dictate otherwise, *e.g.* the presence of a *Z*-double bond. This latter point is illustrated by a parallel example (**142** to **143**) reported by Keese *et al.* during their work on the theoretically interesting fenestranes such as **144** (Scheme 42).[66]



Scheme 42: Keese and coworkers' approach to fenestranes.

1.8.4 Hirsutene, coriolin and laurenene

This group of natural products utilises *meta*-photocycloaddition-based syntheses which involved the 1,2,3-trisubstituted aromatics **145**, **146**/**147** and **148** with the tether positioned centrally (Figure 10). Photocycloadditions of such substrates represent an increase in the complexity of the starting material but will deliver more hindered photoadducts, thereby testing the ability of the excited state of these molecules to overcome this increased barrier to reaction. The close structural relationship of hirsutene **149** and coriolin **150** suggested that a common strategy should be possible. The more complex fenestrane, laurenene **151**, also proved to be accessible from a substrate of this class.

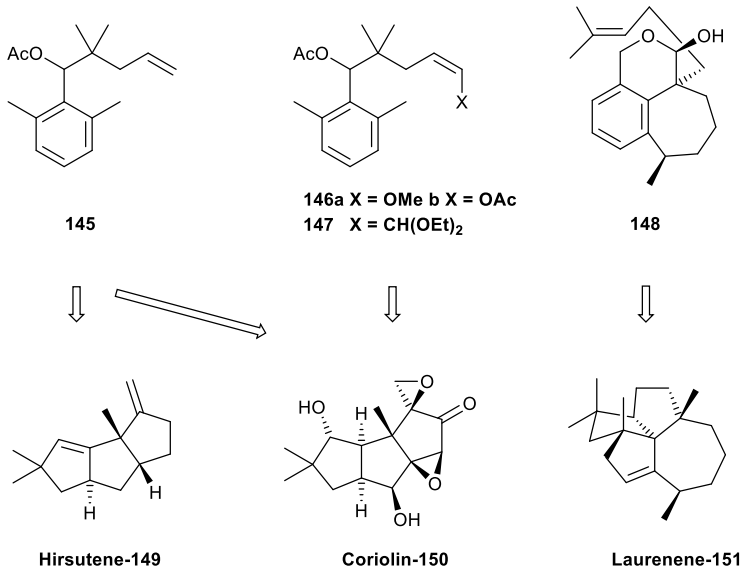
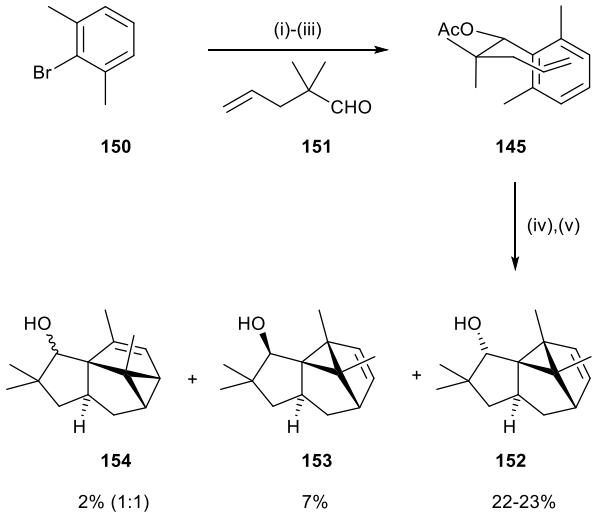


Figure 10: 1,2,3-Trisubstituted substrates leading to hirsutene, coriolin and laurenene.

1.8.4.1 Synthesis of hirsutene

The substrate **145** was prepared in a basic approach by reaction of the Grignard reagent derived from **150** to aldehyde **151** as reported by Wender and Howbert. The yield of this challenging cycloaddition was improved by acetylation before photolysis, even though this does not control stereoselectivity. A mixture of four adducts **152**, **153** and two diastereoisomers of **154**, with

152 predominating, was delivered on photolysis under the previously described conditions (Scheme 43).[67,]

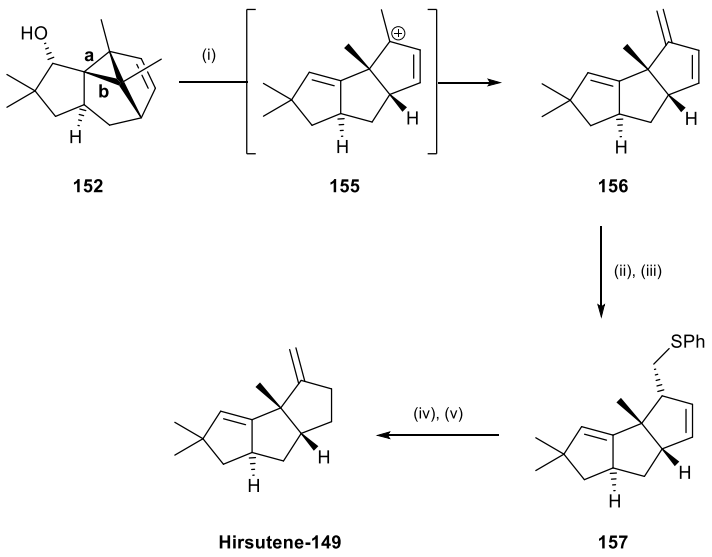


Scheme 43: Synthesis of hirsutene; photocycloaddition of **145**. *Reagents and conditions*: (i) Mg, Et_2O; (ii) **151**; (iii) Ac_2O, DMAP (79% overall); (iv) *hv* (Vycor filter), cyclohexane; (v) $LiAlH_4$, Et_2O.

It is remarkable that the reaction proceeds despite the steric hindrance each of the carbons in the cyclopropanes of **152** and **153** are quaternary), even though the yields are obviously lower than in many of the previous reactions described above. In addition, the cycloaddition has occurred across one of the electron-donating methyl groups and is thus sitting at a site that has a positive polarisation in the transition state, as reported by Cornelisse (Scheme 27).[31] The C–O bond is less effective at controlling asymmetric induction than the C–C bonds in the α-cedrene and isocomene examples. Certainly, the high levels of induction observed in the synthesis of rudmollin suggest that the influence of steric interactions between the adjacent *gem*-dimethyl group in **145** and the pseudo-equatorial C–O bond makes the corresponding pseudo-axial conformer less unfavourable. Since 2,6-addition involves a very hindered transition state, 1,3-addition across the *ortho*-donor group is preferred to 2,6-addition even though a *Z*-double bond is absent. Again, the usual *exo*-selectivity has been observed.

Treatment of compound **152** with camphorsulfonic acid initiates the ring-opening of the cyclopropane (Scheme 44). The two bonds labelled **a** and **b** offer approximately equal overlap with the recognized cation that develops on acid treatment. However, cleavage of **a** proceeds via a transition state that leads to formation of a tertiary allylic cation **150** that can be neutralised by *E*1 elimination to yield **155**.

To afford **156**, selective hydrogenation of the disubstituted double bond, was carried out by first masking the terminal double bond utilising a radical addition of thiophenol to that double bond in **155**. Use of Crabtree's catalyst and hydrogen then selectively reduced the disubstituted double bond before restoration of the terminal double bond, by pyrolysis of the sulfoxide corresponding to **156,** produced hirsutene **149** in approximately 60% yield.



152 **155** **156**

Hirsutene-149 **157**

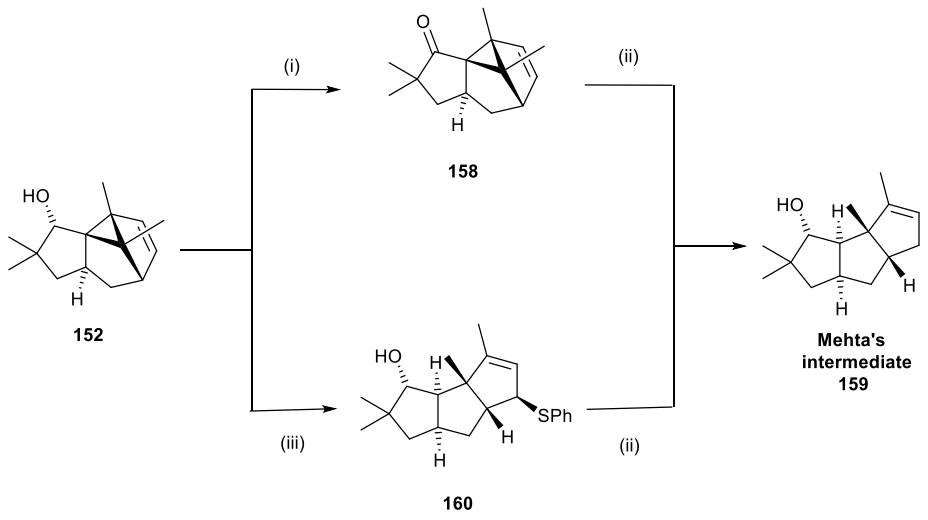
Scheme 44: Synthesis of hirsutene. *Reagents and conditions*: (i) 10-camphorsulfonic acid, C_6H_6 (71%); (ii) PhSH, 100 ^oC (78%); (iii) H_2, CH_2Cl_2, $[Ir(cod)PyPCy_3]PF_6$; (iv) $NaIO_4$, MeOH (86%); (v) 170 ^oC, $P(OMe)_3$ (60%).

1.8.4.2 Synthesis of coriolin

Two approaches for the synthesis of coriolin were described upon successful preparation of hirsutene. The first was developed from the photoadduct **152** prepared in the hirsutene

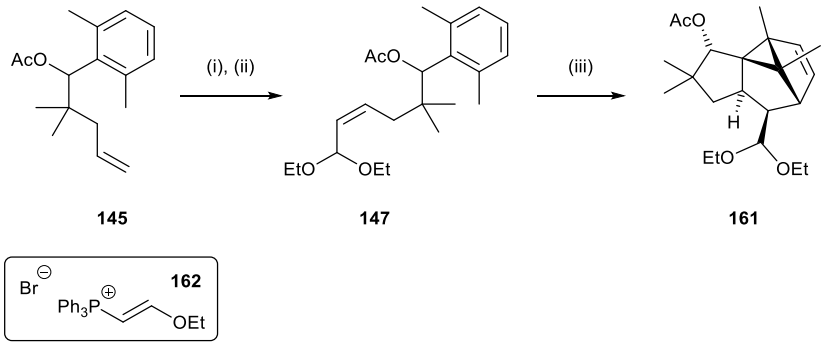
synthesis (again underlining the vital aspect of how the cyclopropane of the cycloadduct is cleaved) while the second begins from a more highly substituted precursor for the photocycloaddition.[68]

The oxidation of alcohol **152** to give ketone **158** affords a means to introduce electrons into the molecule and the ketyl that results from treatment with lithium in liquid ammonia creates a radical adjacent to the cyclopropane with ring-opening controlled by the ability to access a tertiary allylic radical. Further reduction *in situ* affords Mehta and coworkers' intermediate toward coriolin **159**. Alternatively, the aforementioned radical addition of thiophenol was employed to give **160** with the regiochemistry of ring-opening presumably being dictated by consideration of effective orbital overlap. Reductive cleavage of the C-S bond with lithium in liquid ammonia followed by protonation to give the more substituted double bond again delivers Mehta's intermediate **159** (Scheme 45).[69]



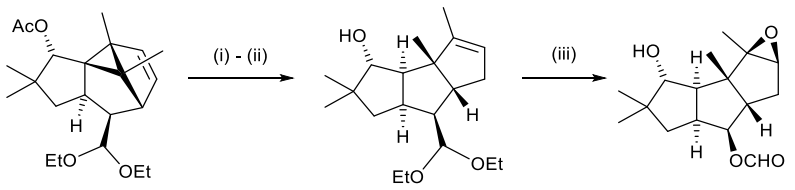
Scheme 45: First formal synthesis of coriolin. *Reagents and conditions*: (i) PDC (74%); (ii) Li, NH_3, Et_2O, EtOH (92%); (iii) PhSH (1equiv.) (quant.).

Irradiation of substrates bearing various *Z*-disubstituted double bonds was examined in an attempt to provide a more direct route to coriolin. Interestingly **146a**/**b** proved very poor substrates, a situation that parallels the relatively inefficient intermolecular cycloaddition of vinylacetates to aromatic compounds *en route* to isoiridomyrmecin, modhephene and descarboxyquadrone. By contrast, Photolysis of **147** was relatively successful and the modest 15% yield of **161** obtained must be judged against the extreme steric hindrance that develops in the transition state of the photocycloaddition reaction and the significant increase in useful complexity that is introduced into the product (Scheme 46).



Scheme 46: Second formal synthesis of coriolin; a new photolysis substrate. *Reagents and conditions*: (i) O_3, MeOH, -78 °C (61%); (ii) **162**, NaOEt, CH_2Cl_2 (55%); (iii) *hv* (Vycor filter), cyclohexane (~15%).

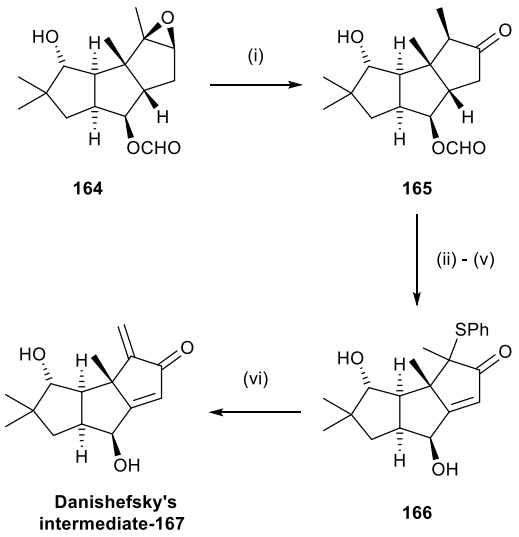
However, application of the thiophenol ring-opening tactic followed by a dissolving metal reduction establishes the required linear triquinane ring system (**163**) then treatment with *m*-CPBA in moist dichloromethane epoxidises the double bond and allows acid catalysed hydrolysis of the diethylacetal with concomitant Baeyer–Villiger reaction to afford formate **164** (Scheme 47). The ease of the latter reactions partially compensates for the disappointing yield from photolysis of **147**.



161 **163** **164**

Scheme 47: Second formal synthesis of coriolin; establishing the linear triquinanes framework. *Reagents and conditions*: (i) PhSH (1 equiv.), 100 °C (72%); (ii) Li, NH_3, Et_2O (80%); (iii) *m*-CPBA, CH_2Cl_2, H_2O (67%).

Lewis acid-catalysed rearrangement of the epoxide gave ketone **165** from compound **164**, which, in turn, following unsaturation using Saegusa *et al.*'s methodology,[15] required only introduction of a thiophenoxide α to the carbonyl group (**166**) to complete a formal total synthesis. Further elimination of the corresponding sulfoxide to afford diene **167** permitted correlation with Danishefsky's late-stage intermediate to coriolin (Scheme 48). The succinctness of this sequence emphasises the utility of the photocycloadduct in the preparation of these terpenoid compounds.[70]

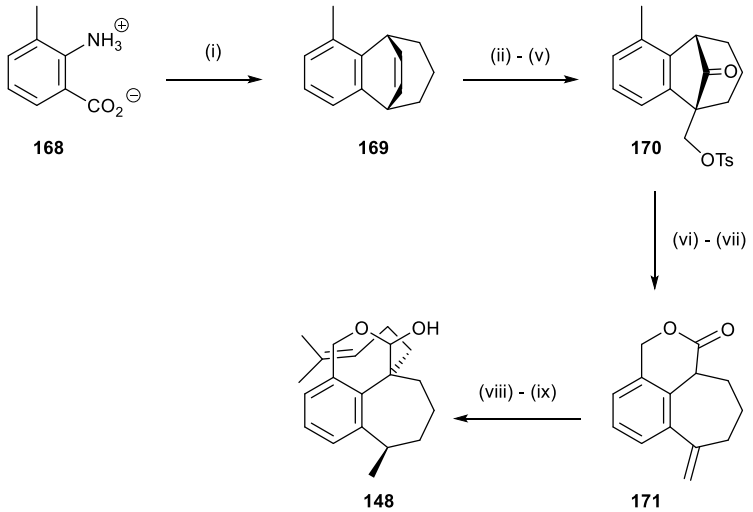


164 **165** **166**

Scheme 48: Second formal synthesis of coriolin. *Reagents and conditions*: (i) BF_3, C_6H_6; (ii) LDA, Me_3SiCl; (iii) $Pd(OAc)_2$, CH_3CN; (iv) LDA, $PhSSO_2Ph$ (42% over 4 steps); (v) HOAc, H_2O, THF (3 :1 :1) (100%); (vi) *m*-CPBA, EtOAc, heat.

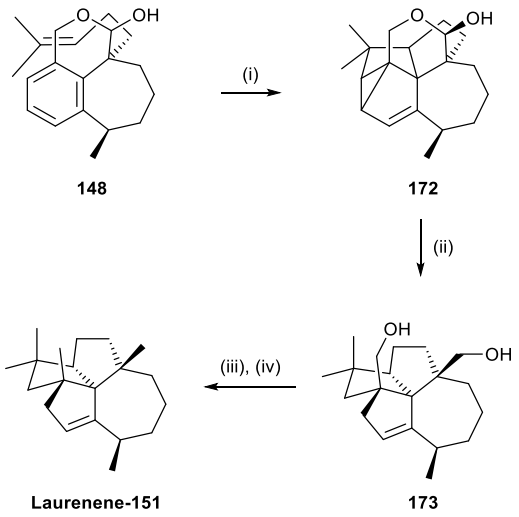
1.8.4.3 Synthesis of laurenene

Laurenene, a naturally occurring diterpene, a fenestrane-like compound, represents one of the most complex molecules prepared using the alkene–arene *meta*-photocycloaddition reaction. The substrate **148** was synthesised by an elegant route that employed a Diels-Alder reaction of a benzyne to cycloheptadiene to fuse on the seven-membered ring in **169** (Scheme 49). After cleavage of the alkene by ozonolysis, a regioselective aldol reaction, with enolisation controlled by the aromatic methyl group, a Grob-type fragmentation of the derived keto-tosylate **170** was set up. Prior to hydroxide treatment the methyl group was brominated with *N*-bromosuccinimide (NBS) to deliver lactone **171** concomitant with fragmentation. Hydrogenation of the alkene prepared the compound for stereoselective homoprenylation of the lactone enolate with good (8:1) 1,4-asymmetric induction. Finally, reduction to lactol **148** completed the synthesis of the photocycloaddition substrate. [70]



Scheme 49: Synthesis of laurenene; preparation of photocycloaddition substrate. *Reagents and conditions*: (i) isopentyl nitrite, Cl_3CCO_2H, cyclohepta-1,3-diene, CH_2Cl_2 (84% based on recovered starting material); (ii) O_3, Me_2S, NEt_3 (68%); (iii) $Zn(BH_4)_2$, Et_2O (98%); (iv) TsCl (72%); (v) PCC (98%); (vi) NBS, AIBN then KOH (72%); (vii) H_2, Pt (96%); (viii) LDA, DMPU, homoprenyliodide (48%); (ix) $LiAlH_4$, THF (95%).

Photocycloaddition of **148** proceeded to a single 'angular' regioisomer of cyclopropane **172** in 51% yield with the expected *exo*-selectivity (Scheme 50). This relatively unusual occurrence (*cf.* studies on aphidicolin and stemodin) was rationalised by Macromodel calculations that suggest that the alternative 'linear' regioisomer is significantly less stable. Contrasting this outcome with the prototypical case, discussed in the introduction (Figure 4), highlights the importance of calculating each case individually to take account of the effect of substituents and fused rings. Of particular note was the improved yield obtained in this challenging substrate when the incident light was filtered through $BiCl_3$ solution (the product was found to be 21% higher than when a Vycor filter was used), the problem being traced, in part, to product absorbance and subsequent degradation. According to the authors, when a cycloaddition is slow other processes often compete. In contrast to the studies on hirsutene and coriolin the aromatic moiety is not symmetrical; that addition does not occur across the tether is unsurprising but addition across just one of the two *ortho* substituents is worthy of comment, particularly as this is probably the worst donor of the two. Presumably, this selectivity is based on steric grounds. Orbital overlap controlled reductive cleavage of the cyclopropane with concomitant reduction of the lactol to a diol **173** leaves only reductive removal of the hydroxyls *via* their phosphordiamidates to complete an elegant solution to this complex problem (Scheme 50). [71]



Scheme 50: Synthesis of laurenene; preparation of photocycloaddition substrate. *Reagents and conditions*: (i) *hv* ($BiCl_3$ filter) (51%); (ii) Li, $MeNH_2$, -6 °C (96%); (iii) KHMDS, HMPA, $CIPO(NMe_2)_2$ (55%); (iv) Li, $EtNH_2$ (65%).

1.8.5 Silphiperfolenes, retigeranic acid and subergorgic acid

The potential of a second pattern of trisubstituted benzenes of general structure **174** has been explored by both Wender, Singh and deLong (Figure 11). They served to examine an alternative allylic strain element to control π-facial selectivity and introduced an interesting group of radical-based methods for opening of the cyclopropanes with concomitant formation of a C–C bond.

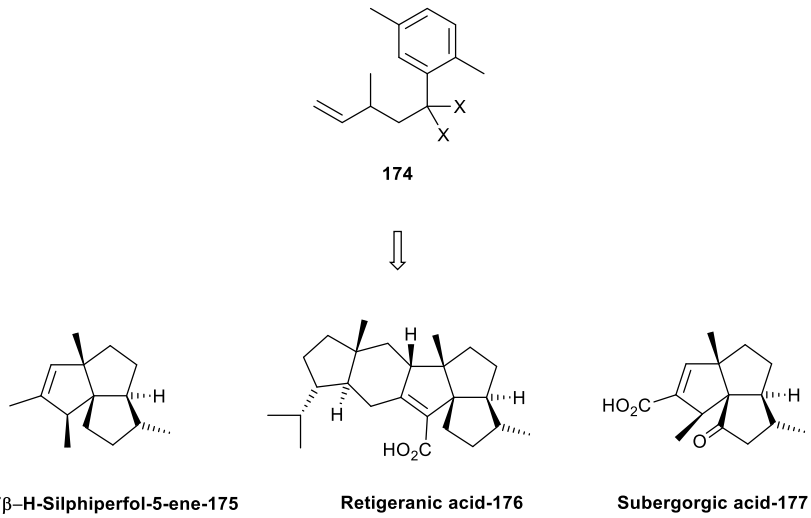
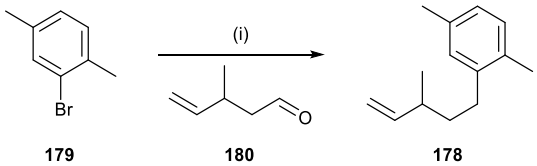


Figure 11: A common substrate motif for the synthesis of the silphiperfolenes, retigeranic acid and subergorgic acid.

1.8.5.1 Synthesis of the silphiperfolenes

A straightforward procedure by Hall and McEnroe was adopted to prepare the substrate **178** in 92% yield (Scheme 51).[55,72]

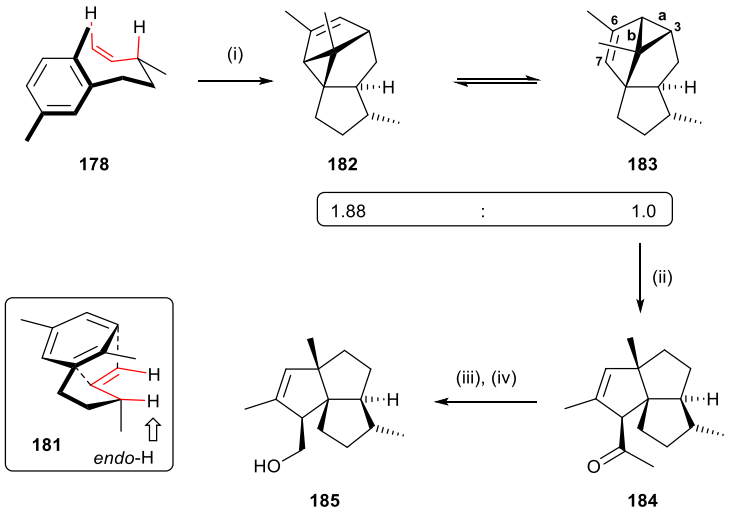


Scheme 51: Synthesis of the silphiperfolenes; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) Li, Et_2O, **180** then NH_3 (92%).

The photocycloaddition of **178** is typical in proceeding from the conformer shown (Scheme 52) with *exo*-selectivity. However, in this instance, π-facial selectivity is controlled by the allylic strain element that develops into a situation where the exciplex **181**, that precedes cycloaddition, has the hydrogen and not the methyl in an *endo*-position. Again, it may be noted that, despite the terminal alkene, addition takes place across the donor methyl group not across the tether. Two photocycloadducts **182** and **183** are obtained in a 1.88:1 ratio favouring the

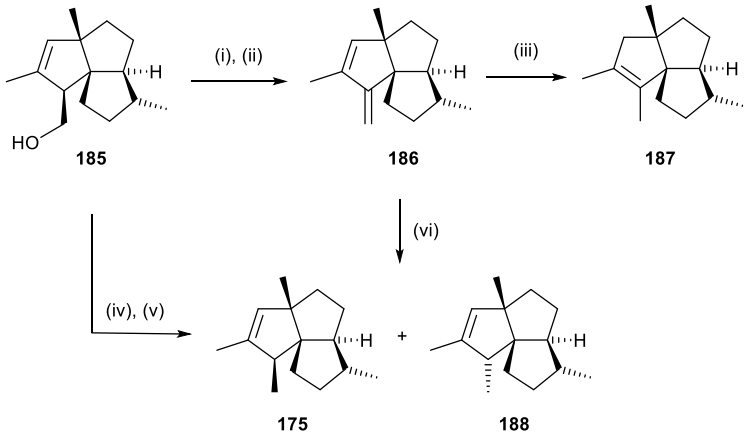
'linear' isomer in 72% yield, clearly superior to the more sterically congested 1,2,3-trisubstituted aromatics discussed previously. Given that it is the minor regioisomer that is required to complete the synthesis, the ability to photoequilibrate **182** and **183** is significant. However, as is often the case, some degree of degradation accompanies this procedure (*cf.* isocomene, subergorgic acid and crinipellin B).

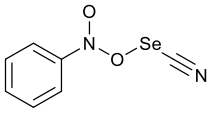
Having obtained the angular isomer **183** the cyclopropane is then regioselectively cleaved with concomitant formation of the required C–C bond at C7. This second photochemical step, in which acetaldehyde is added to **183**, is noteworthy for its highly stereoselective addition to the convex face and regioselective cleavage of the cyclopropane *via* a secondary rather than the apparently available tertiary radical. This is presumably explained by a more favourable alignment of the intermediate radical formed at C6 with bond **a** than bond **b** and the reaction being under kinetic control. The method is based upon a report by Kharasch *et al.* in which, following n-π* photoexcitation of the acetaldehyde, Norrish type I fragmentation can give an acyl radical (note the use of a Pyrex filter to cut off shorter wavelength radiation that can lead to direct extrusion of CO without radical generation).[67] This species begins a radical chain process by adding to the alkene in **183**. Following fragmentation of the cyclopropane with concomitant generation of a secondary radical at C3, hydrogen abstraction from acetaldehyde completes the chain. The two carbon atoms so added were reduced to the required single carbon atom in **185** by bromoform reaction and then treatment with $LiAlH_4$ (Scheme 52).



Scheme 52: Synthesis of the silphiperfolenes; preparation of a common intermediate. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (72%); (ii) *hv* (Pyrex filter), CH_3CHO, 0 °C (60%); (iii) Br_2, NaOH, H_2O, dioxane, reflux (95%); $LiAlH_4$, reflux (91%).

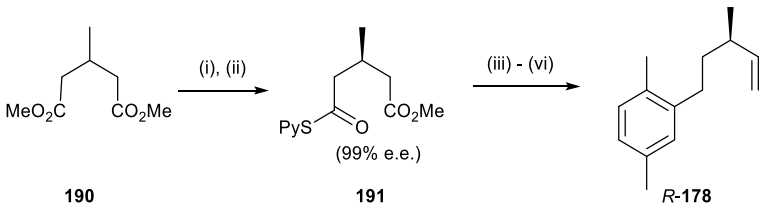
Elimination of the alcohol to give diene **186** from the common intermediate **185**, followed by reduction of the diene with lithium in liquid ammonia gave silphiperfol-6-ene **187** (Scheme 50). By contrast, selective reduction of the terminal alkene with Wilkinson's catalyst provided a 2.8:1 mixture of 7αH-silphiperfol-5-ene **188** to 7βH-silphiperfol-5-ene **175**. A highly stereoselective route to 7βH -silphiperfol-5-ene **175** was afforded by conversion of the alcohol of **185** into a diethyl phosphate followed by reduction with lithium in ethylamine (Scheme 53).



Scheme 53: Synthesis of silphiperfol-6-ene, 7αH-silphiperfol-5-ene and 7βH-silphiperfol-5-ene. *Reagents and conditions*: (i)  , n-Bu_3P, THF (99%); (ii) H_2O_2, THF (78%); (iii) Li, NH_3, Et_2O, -33 °C (91%); (iv) *n*-BuLi, $(EtO)_2POCl$, THF-TMEDA (4:1) (76%); (v) Li, *t*-BuOH, $EtNH_2$, THF, 0 °C (55%; **175** : **188**, 1 : 0); (vi) $(Ph_3P)_3RhCl/H_2$, C_6H_6-EtOH (3 : 1) (89%; **175** : **188**, 1 : 2.8).

1.8.5.2 Synthesis of retigeranic acid

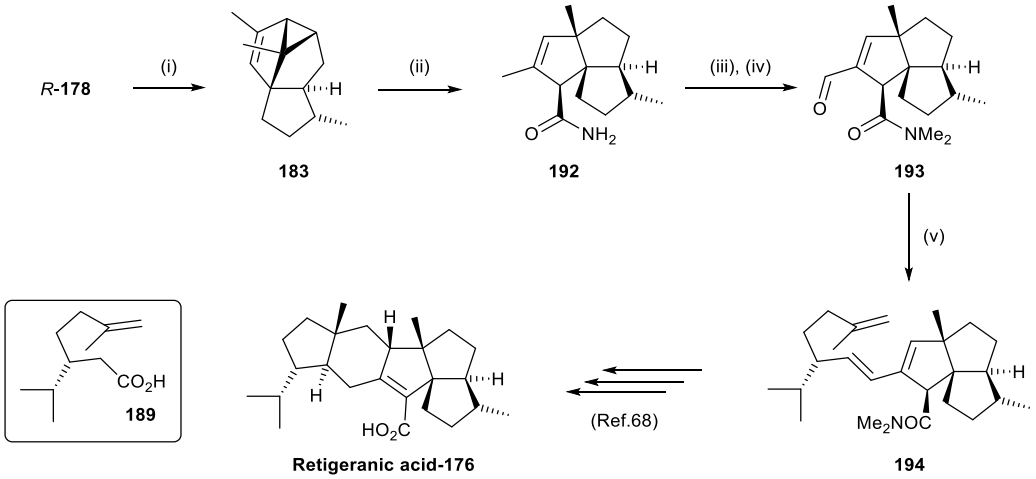
The work developed on the silphiperfolenes to approach the significantly more complex compound retigeranic acid **176** mandated a convergent approach in which the angularly fused triquinane portion would be combined, at a late stage of the synthesis, with chiral fragment **189** (Scheme 55). To remove the inevitable problems with separation of diastereoisomers, **178** would be required in homochiral form. Thus, the straightforward Hall procedure is replaced by a route based on enzymatic desymmetrisation (Scheme 54). [74]



Scheme 54: Synthesis of retigeranic acid; preparation of optically active **178**. *Reagents and conditions*: (i) pig liver esterase; (ii) dipyridyl disulfide, Ph_3P, CH_2Cl_2 (96%); (iii) 4-methylbenzyl bromide, Li, Et_2O, CuI, -78 °C to 0 °C then **186**, -78 °C (90%); (iv) $LiAlH_4$, Et_2O; (v) H_2, 10% Pd/C, EtOH-$HClO_4$ (100: 1) (93%, 2 steps); (vi) *n*-Bu_3P, *o*-nitrophenylSeCN then 30% H_2O_2 (84%).

R-**183** was produced by photocyclised as shown in Scheme 52, but on this occasion cyclopropane ring-opening was initiated using a one carbon radical generated by photolysis of formamide in the presence of **183** (Scheme 55). Following dimethylation of the nitrogen of **192** the allylic methyl group was oxidised with SeO_2 to set up an enolate-mediated coupling with

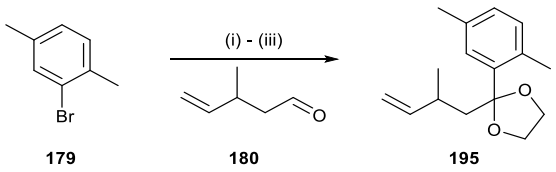
189. The final steps of the synthesis were based around a key intramolecular Diels–Alder reaction of **194**.[74]



Scheme 55: Synthesis of retigeranic acid. *Reagents and conditions*: *hv* (Vycor filter), cyclohexane (72%); (ii) *hv* (Pyrex filter), $HCONH_2$, acetone, *t*-BuOH; (iii) KOH, DMSO, MeI (80%); (iv) SeO_2, *t*-BuOOH, (CH_2Cl_2), reflux (53%); (v) **189**, LDA, THF, 50 °C to 0 °C then add to **193** (-78 °C), warm to 25 °C; AcOH then *N*,*N*-dimethylformamide dimethyl acetal, reflux (65%).

1.8.5.3 Synthesis of subergorgic acid

The synthesis of subergorgic acid as the final example of this group, explores the influence of more significant steric hindrance adjacent to the aromatic ring, specifically from a cyclic ketal. The synthesis of the precursor to the photocycloaddition requires only a slight modification from that described for **178** (Scheme 56). [75]

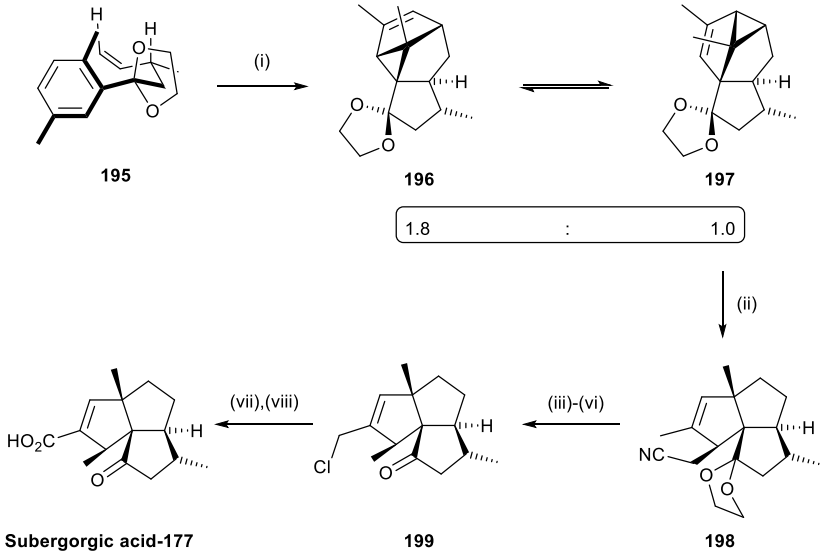


179 180 195

Scheme 56: Synthesis of subergorgic acid; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) Li, Et_2O, then **180**; (ii) PCC, CH_2Cl_2; (iii) $(CH_2OH)_2$, 10-camphorsulfonic acid, C_6H_6, reflux.

Irradiation of **195**, resulting in the formation of two regiosomeric cyclopropanes, each with three contiguous quaternary centres, represents a demanding reaction (*cf.* studies on the synthesis of grayanotoxin-II). The reaction was found to require stringent exclusion of the corresponding ketone to avoid complex mixtures and even with this precaution the reaction was only run to *ca.* 66% completion to give a 42% yield (61% based on recovered starting material) as a result of photolability of the product. Interestingly, despite the influence of the ketal on the photolysis conditions, the ratio of cyclopropane isomers was largely unaffected compared to those formed from **178** (Scheme 57).

The 'angular' isomer **197** was ring-opened using the same radical-based tactic discussed previously but this time initiated by thermal fragmentation of dibenzoyl peroxide. Reductive cleavage of the cyano group in **198** by the method by Oishi *et al.*[76] was followed by a three-step activation of the allylic methyl group with the ketal being lost during the thionyl chloride treatment to afford **199**. The final oxidation was effected in two stages with a silver mediated Kornblum oxidation followed by treatment with sodium chlorite (Scheme 57).



Scheme 57: Synthesis of Subergorgic acid. *Reagents and conditions*: (i) *hv* (Vycor filter), cyclohexane (42%); (ii) dibenzoyl peroxide, CH_3CN, reflux (67%); (iii) K, 18-crown-6, toluene (90%); (vi) *m*-CPBA (80%); (v) *N*-cyclohexyl, *N*-isopropylamine, MeMgBr (70%); (vi) $SOCl_2$, pyridine (85%); (vii) DMSO, $AgBF_4$ then NEt_3 (85%) (viii) $NaClO_2$.

1.8.6 Ceratopicanol, crinipellin B and grayanotoxin-II

The group of three trisubstituted aromatic compounds **200**, **201** and **202** that have been used in natural product synthesis display the difficult 1,2,3-trisubstituted pattern of substitution discussed earlier but with the tether positioned terminally, not centrally (Figure 12). Thus, if photocycloaddition was to occur in the normal way, across the donor group, it would necessarily deliver adducts with at least three contiguous quaternary centres.

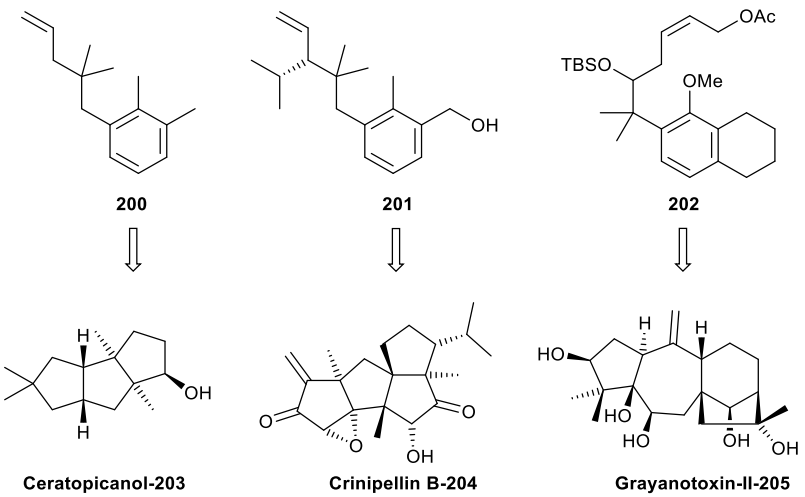
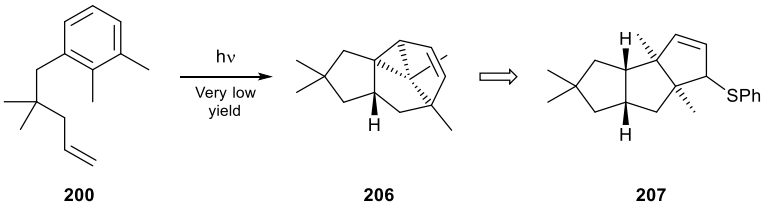


Figure 12: The 1,2,3-trisubstituted aromatic subunits studied for the synthesis of ceratopicanol, crinipellin B, and grayanotoxin-II (tetrasubstituted aromatic).

1.8.6.1 Synthesis of ceratopicanol

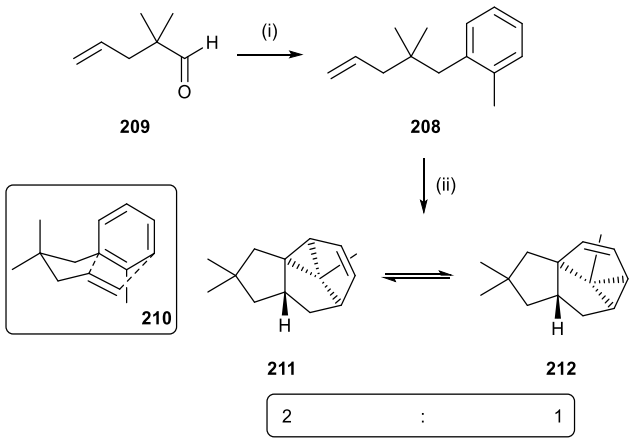
A short and efficient synthesis of ceratopicanol has described by Chanon *et al.* based around an intramolecular arene *meta*-photocycloaddition as part of their interest in holosynthons.[41] However, only very low yields for the transformation of **200** into **206**, has been achieved despite the kinetic advantage that often attends the presence of a *gem*-dimethyl group in the tether of a ring-closing process, indicating the great difficulty that these substrates present (Scheme 58).



Scheme 58: Synthesis of ceratopicanol; attempted photocycloaddition of **200**.

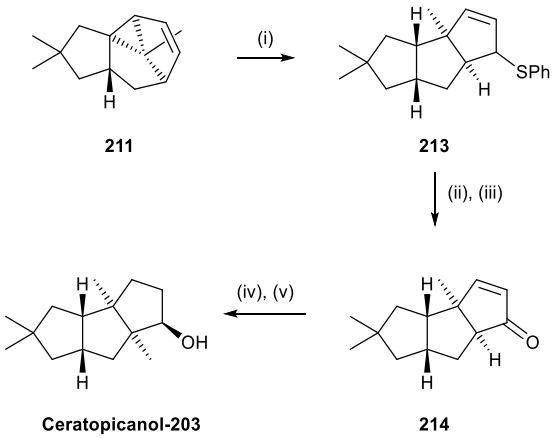
The synthetic plan was adapted based on the previous result which led to beginning with a less substituted aromatic **208** that was readily prepared in 98% yield from **209** by using the Hall procedure (Scheme 59).[55] The photolysis proceeded according to plan, through an *exo*-oriented exciplex **210**, with addition across the donor methyl group, in a much improved 72% yield

(again we note that in the absence of a *Z*-substituted double bond the preference is to avoid addition across the tether). The 'linear' isomer **211** was found to be the major isomer whilst the 'angular' isomer **212** was recycled by photoequilibration.



Scheme 59: Synthesis of ceratopicanol; photocycloaddition of **209**. *Reagents and conditions*: (i) Li, *o*-bromotoluene the Li, NH_3, NH_4Cl (98%); (ii) hν (254 nm), cyclohexane (72%).

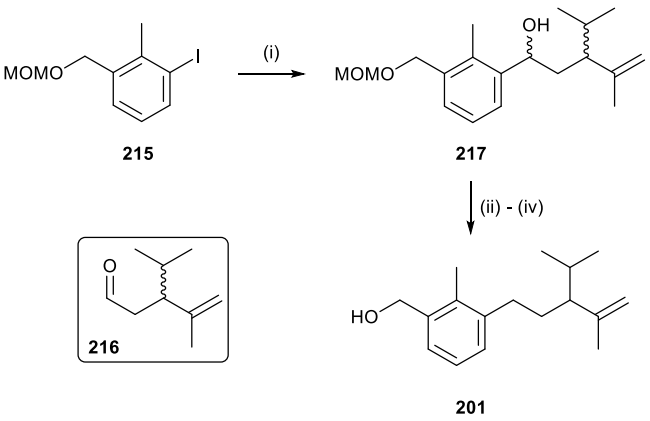
According to Wender and Howbert's method,[68] radical addition of thiophenol to **211** (though with the additional use of ultrasound) afforded the nor-ceratopicanol skeleton **213** (Scheme 60). The reductive cleavage of the C–S bond followed by oxidation to the corresponding ketone gave **214**. The ketone allowed introduction of the troublesome extra methyl group stereoselectively and in excellent (97%) yield. The synthesis was completed by a tandem conjugate reduction-1,2-reduction of the enone moiety by $NaBH_4$ to deliver the correct diastereoisomer of ceratopicanol **203**.



Scheme 60: Synthesis of ceratopicanol. *Reagents and conditions*: (i) PhSH, 100 °C, ultrasound (97%); (ii) Li, NH_3, -78 °C (80%); (iii) CrO_3-3,5-dimethylpyrazole (60%); (iv) LDA, -78 °C, MeI (97%); (v) $NaBH_4$, EtOH (60%).

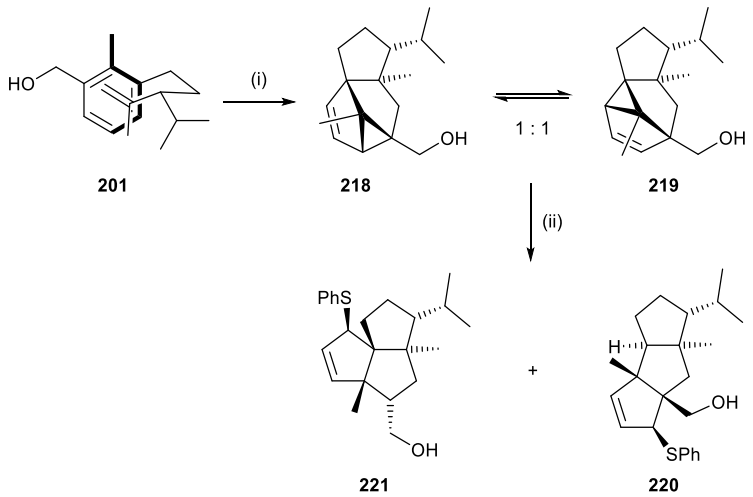
1.8.6.2 Synthesis of crinipellin B

Synthesis of crinipellin B **204** required access to a relatively complex photocycloaddition substrate **201** as reported by Wender and Dore. The starting material 3-nitro-2-methyl benzoic acid was used to prepare the aromatic portion **215** in three pots then, after halogen-lithium exchange, coupled to aldehyde **216**, itself available in three steps from isobutyraldehyde, to give **217** (Scheme 61). Oxidation to the ketone allowed deoxygenation *via* a Wolff-Kishner reduction and cleavage of the MOM group afforded the substrate **201**.[77]



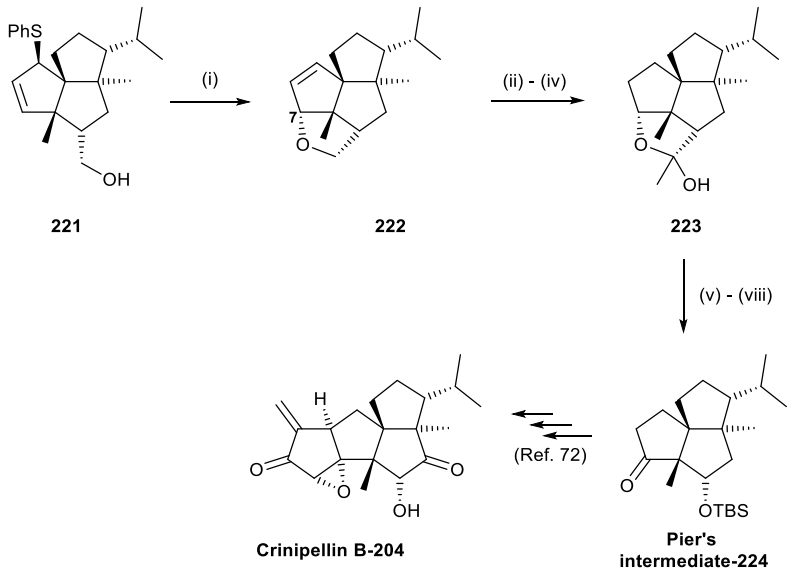
Scheme 61: Synthesis of crinipellin B; preparation of the photocycloaddition substrate. *Reagents and conditions*: (i) *t*-BuLi, THF, -78 °C then **216**; (ii) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 0 to 22 °C (78%; 2 steps); (iii) H_2NNH_2, KOH, diethylene glycol, 118 to 122 °C then 230 to 232 °C (92%); (iv) 3M HCl, THF, reflux (93%).

The percentage yield of 33% of the two regioisomeric cyclopropanes **218** and **219** was achieved despite the significant steric hindrance of this substrate and the four contiguous quaternary asymmetric centres formed in each of the products. However, it was observed that short irradiation times gave a mixture with a preponderance of the linear isomer **219** with regards to the isocomene synthesis, whereas more prolonged irradiations delivered an equal mixture. As observed in other cases, *e.g.* subergorgic acid, the adducts proved photolytically labile. In practice, the crude produced was treated with thiophenol under radical conditions[61] to afford an easily separable mixture of linear and angular triquinanes **220** and **221** (Scheme 62).



Scheme 62: Synthesis of crinipellin B; photocycloaddition and fragmentation of **201**. *Reagents and conditions*: (i) hν (Vycor filter), cyclohexane (33 %); (ii) PhSH, 95 - 105 ^{o}C (68 %).

The value of the thiophenol mediated cyclopropane ring-opening is evident as it facilitates the required oxygenation at C7. Thus, the sulfonium ion formed by methylation of **221** with Meerwein's salt induces an S_N2' tetrahydrofuran ring closure to give **222** (Scheme 63). The process of fragmenting the cyclopropane has thereby significantly advanced the synthesis. The double bond, having served its purpose was then removed by hydrogenation rendering the methylene group adjacent to the oxygen the most readily oxidisable, the latter being realised by treatment with ruthenium tetraoxide. Addition of methyllithium leads to hemi-acetal **223** from which the equilibrium keto-alcohol form was oxidised under Baeyer-Villiger conditions. The corresponding differentially protected diol allows selective oxidation to afford Piers' intermediate **224** and hence complete a formal total synthesis of crinipellin B.[78]



221 222 223

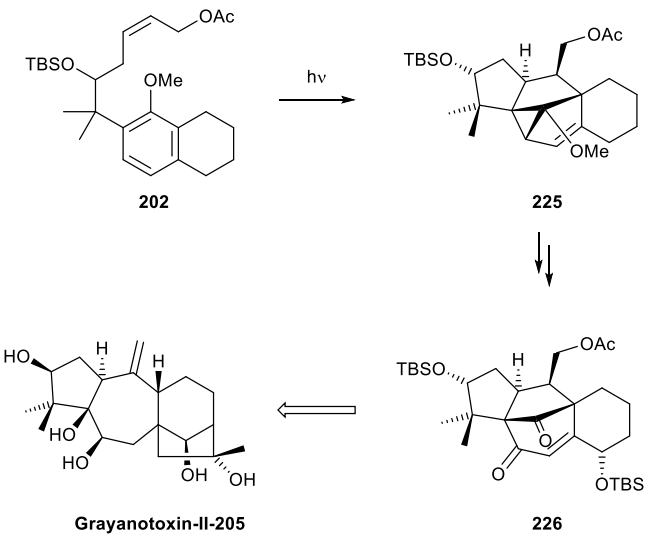
Crinipellin B-204 Pier's intermediate-224

Scheme 63: Synthesis of Piers' intermediate for crinipellin B. *Reagents and conditions*: (i) Me_3OBF_4, CH_2Cl_2, reflux (74%); (ii) H_2 (49 psi), 10% Pd/C, EtOAc (97%); (iii) $RuCl_3$, $NaIO_4$, 2 : 2 : 3 CCl_4-CH_3CN-H_2O (72%); (iv) MeLi, THF, -78 °C (95%); (v) *m*-CPBA, $CHCl_3$ (55%); (vi) Dess–Martin periodinane, CH_2Cl_2 (87%); (vii) $Ba(OH)_2$, MeOH, 0 °C (80%); (viii) TBSOTf, Et_3N, CH_2Cl_2, -78 °C (86%).

1.8.6.3 Synthetic studies toward grayanotoxin-II

Wender and Olivero reported a final example of this type of substrate arising from studies toward grayanotoxin-II **205** in which, in addition to the difficult 1,2,3-substitution pattern, is present a fourth substituent in **202**. Despite these apparent steric issues, the reaction was successful and at least one compound examined in this series gave a yield as high as 50% (Scheme 64).[39,79]

Overall, these substrates are on the limit of what is possible with this reaction, but impressive syntheses are still achievable.

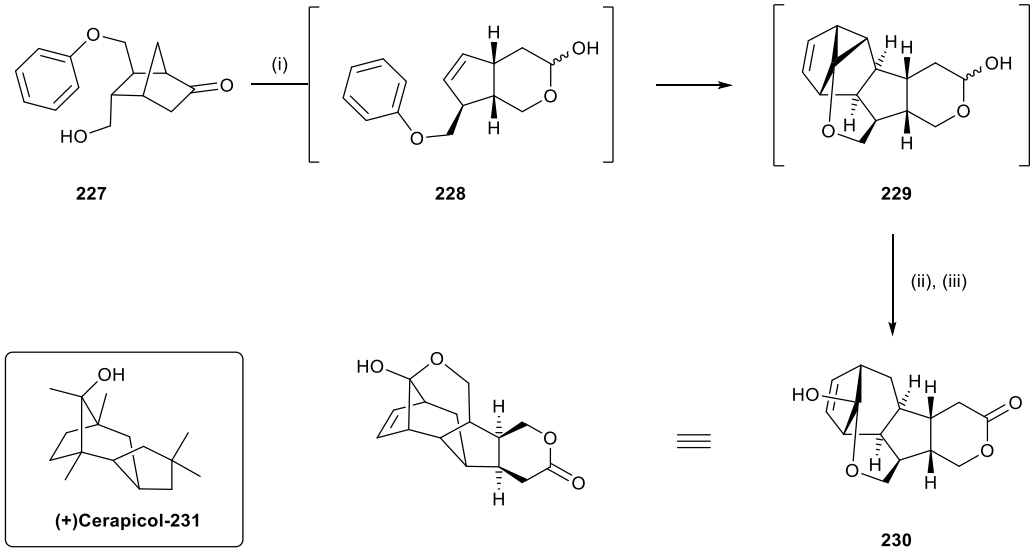


Scheme 64: Synthetic studies toward grayanotoxin-II.

1.8.7 Synthetic studies on cerapicol

De Keukeleire obtained **229**, upon irradiation of **227**, *via* lactols **228** as part of a study on tandem Norrish type-I *meta*-photocycloaddition reactions (Scheme 65). It is interesting that the photocycloaddition takes place across the donor group in **228** despite the presence of a *Z*-double bond to afford **229**. Alkene π-facial selectivity was imposed by the tether and the usual *exo*-stereoselectivity was found. As with the previously discussed studies on desdimethylquadrone (Scheme 41) only a single regioisomer of product was obtained. The cleavage of the cyclopropane in the δ-lactone corresponding to **229** is interesting and contrasts with the fragmentation of both the α-cedrene and rudmollin intermediates, **103**/**104** and **118**/**119** respectively, in not cleaving the bond adjacent to the alkene (*cf.* gelsemine, Scheme 66 and 67) but rather, it undergoes protonation to afford hemi-acetal **230**. The authors note that the observed mode of cleavage leads to the more stable product as judged by calculation using a combined SCA-MacroModel approach. The lone pairs on the ether oxygen may also align favourably to assist cleavage of this C-C bond. The clear relationship of **230** to compounds with a bullerane skeleton, *e.g.* cerapicol **231**, suggests a possible application of this type of *meta*-photocycloaddition. Srinivasin and Hoye and others noted that intermolecular

photocycloadditions to 2-methylanisole were slow and low yielding, though Hoye was able to isolate an 11% yield of photoadducts, after acid hydrolysis, following a 7 days of irradiation.[46]



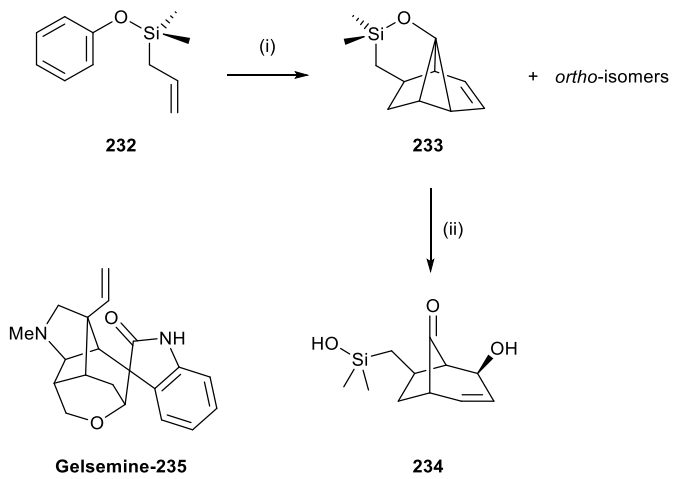
Scheme 65: Synthetic studies toward cerapicol. *Reagents and conditions*: (i) hν, cyclohexane-EtOAc (5:1); (ii) PDC, CH_2Cl_2 (34% overall); (iii) dil. HCl (quant.).

This in turn suggests a possible worth of this cleavable tether when the more hindered substrate required to prepare cerapicol is used, a point noted by Wender and Howbert in the context of the α-cedrene synthesis.[25,80]

1.8.8 Synthetic studies toward gelsemine

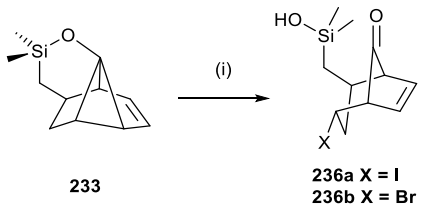
A study of the utility of a silicon-linked tether was carried out by Penkett *et al.*, following earlier work by Fleming *et al.*[81] The photocycloaddition of **232** led to addition across the tether, as seen in the studies on desdimethylquadrone and cerapicol, and gave rise to the same, single, regioisomer of *meta*-photocycloaddition product **233** in 38% yield (accompanied by 16% of products arising from initial *ortho*-addition). The potential value of the tether, as opposed to an equivalent intermolecular reaction, resides in the formation of this single regioisomeric cyclopropane (and with *exo*- rather than *endo*-stereoselectivity). Thus, treatment of **233** with

m-CPBA gives epoxidation with concomitant fragmentation to afford a single regioisomer of allylic alcohol **234** containing the bicyclo[3.2.1]octane skeleton found in gelsemine **235** (Scheme 66).[82]



Scheme 66: Synthetic studies toward gelsemine. *Reagents and conditions*: (i) hν, hexane (38%); (ii) *m*-CPBA (56%).

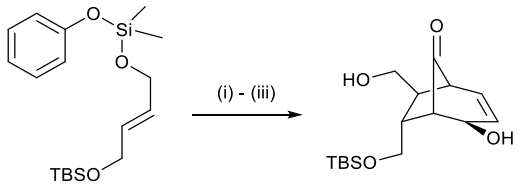
The fragmentation of cycloadduct **233** under alternative conditions flags up the subtlety in the preferred mode of reactivity. Thus, in the same manner as observed with protonation of the lactone corresponding to **229** (Scheme 65), treatment of **233** with either *N*-iodosuccinimide (NIS) or NBS leads to reaction at the cyclopropyl bond distal to, rather than proximal to, the alkene to afford **233a**/**b** (Scheme 67).



Scheme 67: Fragmentation of *meta*-photocycloaddition product **233**. *Reagents and conditions*: (i) NIS, X = I (57%) or NBS, X = Br (51%).

Studies on Heck reaction-induced fragmentation of such vinylcyclopropanes have led to further developments in the application of *meta*-photocycloadducts toward a synthesis of gelsemine.[82c,d]

Additional functionality was introduced into the core of the molecule by photolysis of substrate **237**. Following fragmentation of the initial photocycloadduct a single regioisomer of allylic alcohol **238** was obtained and it may be inferred from this result that a single regioisomer of photocycloadduct was generated (Scheme 68). Of particular interest is the presence of a four - atom tether in **238**. A relatively modest yield of **239** was obtained indicating that, in this instance, the presence of oxygen atoms in the tether was not as effective in improving yields as, say, in the examples in Schemes 25 and 26.



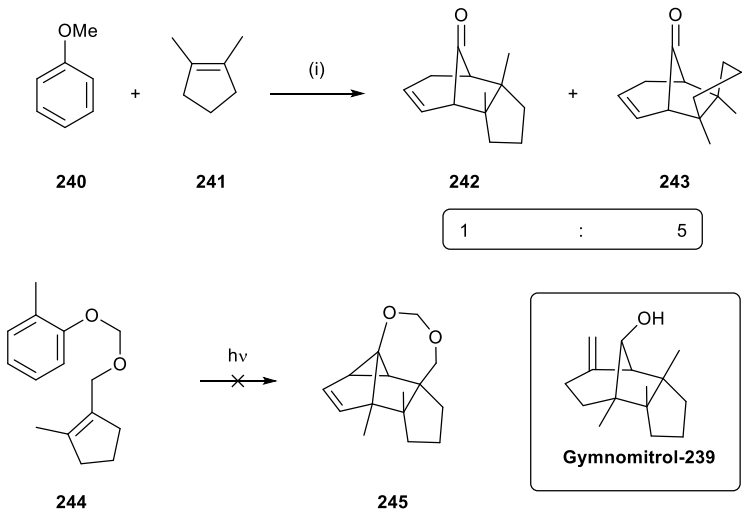
237 **238**

Scheme 68: Synthetic studies toward gelsemine. *Reagents and conditions*: (i) hν (low pressure Hg lamp), cyclohexane, 4 h; (ii) *m*-CPBA, CH_2Cl_2; (iii) MeOH, pyridinium *para*-toluene sulfonate, 4 days (11% overall).

This may imply that other features, *e.g.* rings that limit the conformational freedom of a tether, are more significant in raising yields in substrates with four-atom tethers in accordance with the paradoxical nature of including oxygen in the tether, *vide supra.* In addition to the above studies Penkett *et al.*, have also examined an approach toward gymnomitrol **239** (Scheme 68).[82b]

1.8.9 Four-atom tethers-gymnomitrol

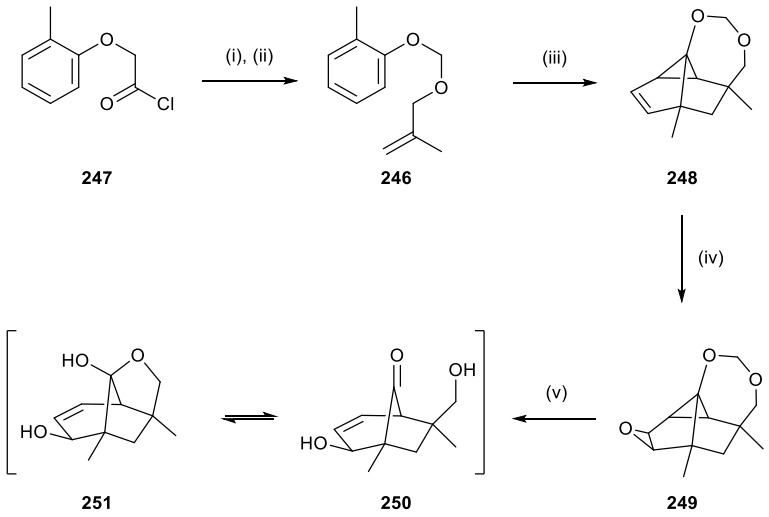
Studies on substrates in which there is a four-atom tether are sparse. The critical feature to achieve higher yields appears to be some bias of the conformational freedom of the tether towards the reactive conformation. To date, only three studies directed towards a natural product have been reported, each of which raises interesting points, with Penkett's studies on gelsemine having been discussed above (Scheme 68). Building on their previous work, Penkett's group utilised a four-atom cleavable tether in an approach to gymnomitrol **239**. An earlier attempt by Hoye to employ an intermolecular *meta*-photocycloaddition approach to **239**, had proved unsuccessful, presumably due to the significant steric hindrance associated with adding 1,2-dimethylcyclopentene to 2,5-dimethyl anisole. Indeed, the addition of **240** to **241** furnished only a 0.1% yield of a 1:5 mixture of **242** to **243** (Scheme 69). Seeking to take advantage of an intramolecular reaction, a series of substrates were prepared and photolysed. Unfortunately, the steric encumbrance of **244** still proved too much to allow the photocycloaddition to **245** to take place (Scheme 69).[80a,82b]



Scheme 69: Attempted photocycloaddition approaches to gymnomitrol. *Reagents and conditions*: (i) hν (253.7 nm), cyclohexane then H_3O^+ (0.1%).

However, the less hindered substrates examined, *e.g.* **246** (prepared in two steps from **247**) did undergo the desired reaction to give 17% of isomerically clean **248**, illustrating the use of this

type of acetal tether in a *meta*-photocycloaddition reaction. Facile fragmentation of the derived epoxide, **249**, to deliver **250**/**251**, regio- and stereoisomerically clean, suggests the potential of the method (Scheme 70).



Scheme 70: Studies toward the synthesis of gymnomitrol. *Reagents and conditions*: (i) $(Ph_3P)_3RhCl$, 170 °C; (ii) methallyl alcohol, 50% NaOH, benzene, Bu_4NCl (86%); (iii) h*v* (253.7 nm), cyclohexane (17%); (iv) dimethyldioxirane, CH_2Cl_2–acetone (1:1), 0 °C (100%); (v) HCl (aq.), acetone, 0 °C -room temperature (55%).

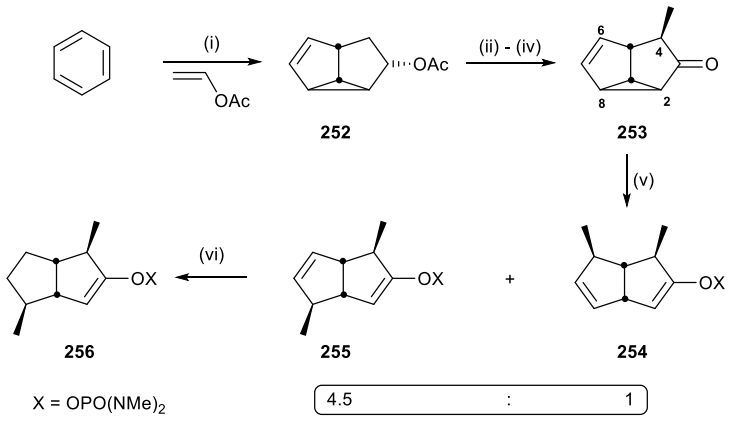
1.9 Intermolecular photocycloadditions

Most of the articles reported in the use of the *meta*-photocycloaddition in natural product synthesis have utilised the intramolecular reaction. However, there has been some very interesting work reported to originate from intermolecular photocycloadditions.

1.9.1 Synthesis of isoiridomyrmecin

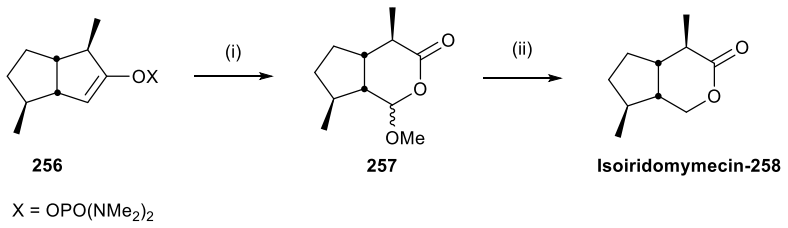
A low yield of compound **252** was produced upon irradiation of vinyl acetate in benzene.[77] This is consistent with the difficulties encountered with this type of alkene (*cf.* **146a** and **146b**) in Wender's studies on coriolin synthesis.[57] However, the cheapness of the starting materials and ease of the reaction compensates for this. In contrast to the intramolecular cases, and in keeping with fundamental studies on this reaction, *endo*-selectivity is observed (Scheme 71). The shape

of the ring system is then utilised to control first the regioselective enolate formation (using the difficulty of forming anti-Bredt alkenes, as discussed in relation to Scheme 5) then a subsequent *exo*-face alkylation to give **253**. Fragmentation of the cyclopropane is coupled with addition of a methyl group *via* a Gilman cuprate to afford **254** and **255**. The regioselectivity of this addition is controlled by unfavourable interactions with the methyl group at C-4 (*cf.* Scheme 75) and the stereochemistry by approach from the least hindered face with inversion of configuration at C-8. The enolate resulting from this addition was trapped as a phosphordiamidate. Selective hydrogenation of the least hindered double bond in **255** was carried out over Adam's catalyst to give **256**.



Scheme 71: Synthesis of isoiridomyrmecin; photocycloaddition and cyclopropane cleavage. *Reagents and conditions*: (i) hν (Vycor filter); (ii) $LiAlH_4$ (89%); (iii) MnO_2 (95%); (iv) LDA, -78 °C, MeI (75%); (v) Me_2CuLi, THF, -78 °C then $Cl_2PO(NMe_2)$ then Me_2NH (100%); (vi) H_2, PtO_2 (90%).

Having obtained **256**, ozonolysis in MeOH coupled with a reductive work-up gave the diastereoisomeric psuedolactones **257**. The synthesis was subsequently completed by reduction with sodium cyanoborohydride to give isoiridomyrmecin **258** in 68% yield (Scheme 72).



Scheme 72: Synthesis of isoiridomyrmecin. *Reagents and conditions*: (i) O_3, MeOH, CH_2Cl_2, -78 °C then $NaBH_4$ (92%; 1:1 epimers); (ii) $NaBH_3CN$, H_2O, THF, H_2SO_4 (68%).

Wender and Dreyer described a related photocycloadduct, **259**, arising from addition of vinyl acetate to indane, that has formed the key starting material for two syntheses: modhephene **260** and descarboxyquadrone **261** (Figure 13).[84]

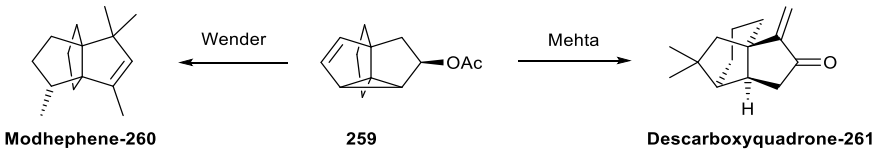
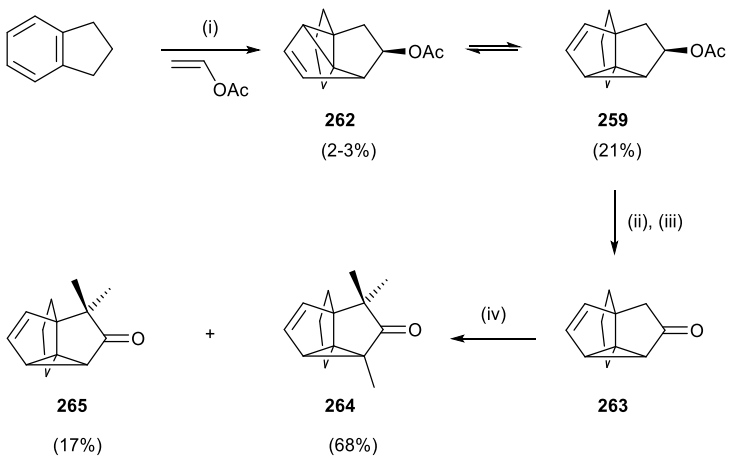


Figure 13: A common intermediate for modhephene and descarboxyquadrone.

1.9.2 Synthesis of modhephene

The synthesis of [3.3.3]propellane **260**, whilst not the most complex molecule made with a *meta*-photocycloaddition reaction is one that best exploits its various assets and represents a truly remarkable achievement in synthesis.

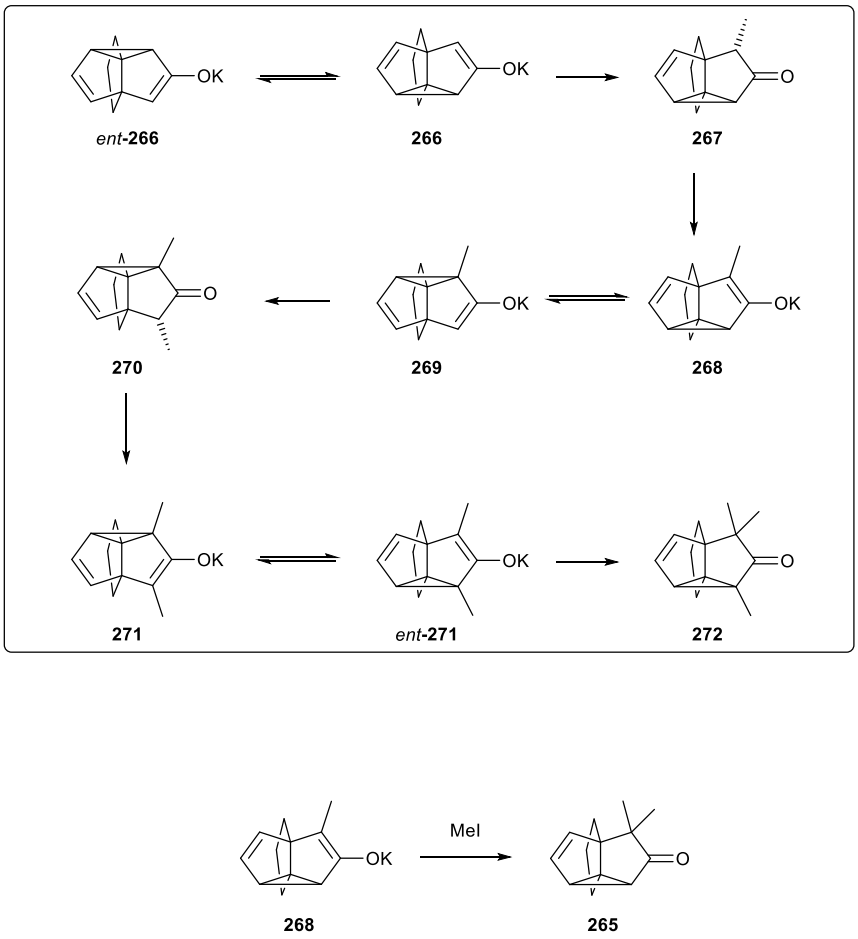
The photoadduct **259**, as with **252**, is formed in a modest 21% yield but again proceeds from readily available starting materials to allow multigram quantities to be prepared (Scheme 73). As expected, the reaction is *endo*-selective with addition taking place across a donor substituent. The two isomers **259** and **262** are formed in *ca.* 10:1 ratio and are photoequilibrated under the reaction conditions.



Scheme 73: Synthesis of modhephene; photocycloaddition and alkylation. *Reagents and conditions*: (i) hν (Vycor filter), cyclohexane (21%); (ii) KOH, MeOH (86%); (iii) $Ba(MnO_4)_2$ (95%); (iv) *t*-BuOK (15 eq.), MeI (10 eq.), THF (68% of **259**).

Hydrolysis of **259** was followed by oxidation to the corresponding ketone **263**. With the ring system in place there is a need to selectively introduce four methyl groups. Remarkably, treatment of **263** with methyl iodide in the presence of potassium *tert*-butoxide results in the formation of two compounds **264** and **265** the major one being trimethylated.

This apparently surprising reaction is readily rationalised when it is recognised that the enolate derived from **263** is a semibullvalene and hence susceptible to facile Cope rearrangement. The consequences of this rearrangement are set out in (Scheme 74).

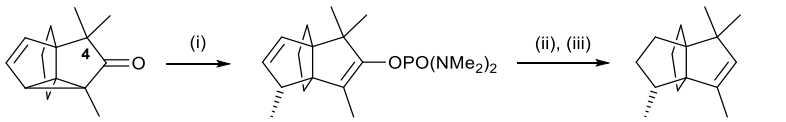


Scheme 74: Synthesis of modhephene; details of the enolate alkylation.

Two subtleties arise at this point: firstly, the rate of alkylation of **268** needs to be slower than rearrangement to **269** then alkylation, otherwise the 'cul-de-sac'compound **265** will predominate. Indeed, studies on an enol phosphate derived from **266** indicated facile Cope rearrangement at temperatures as low as -100 °C.[79] Secondly, Cope rearrangement of either **266** or **271** generates enantiomeric compounds and hence, if any attempt were made to turn this into an enantioselective synthesis, it must either happen post trimethylation or the alkylation itself could be conducted in the presence of, say, a chiral counterion.

Finally, fragmentation of the cyclopropane is tied to introduction of the fourth methyl group by a highly stereo and regioselective cuprate-mediated addition reaction akin to that discussed in the isoiridomyrmecin synthesis (Scheme 71). However, in this case, the greater steric hindrance

presented by the *gem*-dimethyl group at C4 of **264** prevents the side product arising from 1,7-addition that was seen in the previous case. The resultant enolate is trapped as its phosphordiamidate **273**. Thus, the cyclopropane, often the unnecessary element of the complexity introduced in the *meta*-photocycloaddition reaction, is used to remarkable effect. To complete the synthesis all that was required was a dissolving metal reduction of the phosphordiamidate in **273** followed by a selective hydrogenation of the least hindered double bond (Scheme 75).

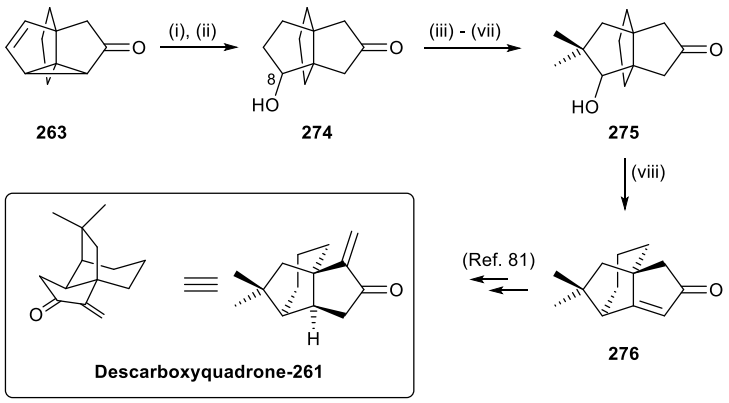


264 **273** **Modhephene-260**

Scheme 75: Synthesis of modhephene. *Reagents and conditions*: (i) Me_2CuLi (5 equiv.), THF, −78 °C, $Cl_2PO(NMe_2)$ then Me_2NH (76%); (ii) Li, $EtNH_2$, THF, *t*-BuOH, 0 °C (93%); (iii) H_2, PtO_2 (100%).

1.9.3 Synthesis of descarboxyquadrone

Mehta's preparation of descarboxyquadrone is the final synthesis examined. One approach to a quadrone derivative was set out above (Scheme 41) but this is a distinctively different strategy. This approach explores the strategy of rearrangement of the skeleton, post cyclopropane cleavage, and thus suggests a wider range of targets that could be approached using the *meta*-photocycloaddition reaction. Beginning from **263**, careful hydrogenation of the double bond in the presence of the strained cyclopropane allows a key oxygenation at C-8, concomitant with its cleavage, in a second step to give **274**. Following protection of the ketone, oxidation of the hydroxy group facilitates first, the introduction of the *gem*-dimethyl group then, after re-conversion to the alcohol and deprotection of the ketone, the critical Lewis acid mediated Wagner–Meerwein rearrangement of **275** to afford **276**.[86] This rearrangement, although not high yielding, is the first such rearrangement of this ring system and completes a formal synthesis of descarboxyquadrone (Scheme 76). [44,87]



Scheme 76: Synthesis of descarboxyquadrone. *Reagents and conditions*: (i) Cat. reduction; (ii) HCO_2H, heat then KOH, MeOH (95%); (iii) $HOCH_2CH_2OH$, PPTS, C_6H_6, 80 °C (95%); (iv) PCC, CH_2Cl_2 (82%); (v) *t*-BuOK, MeI, THF (71%); (vi) $LiAlH_4$, Et_2O (95%); (vii) acetone, PPTS, H_2O, 60 °C (95%); (viii) $BF_3{\cdot}OEt_2$, C_6H_6, 80 °C (20–25%).

1.10 Approach towards the polycyclic ring system of stemodinone and Aphidicolin utilizing the *meta*-photocycloaddition reaction

Consideration of the extensive theoretical and experimental studies of the *meta*-photocycloaddition reaction, some of which is described above, suggested that such a reaction might give a rapid entry into the aphidicolin/stemodin ring system and hence facilitate the synthesis of analogue structures.[25] However, to apply a *meta*-photocycloaddition reaction to the synthesis of stemodinone **1**/aphidicolin **3** and their analogues, several selectivity issues must be assessed. These include; the mode of cycloaddition (*ortho/meta*), the regio- and stereoselectivity and the effect of tether length. The latter point is of particular significance as, at the time of publication of the study reported below, four-atom tethers were very rarely found effective in these reactions. Subsequent work toward lancifodilactone F, by Chen, has confirmed their efficacy, with good substrate design.[88] With regards to the skeleton of aphidicolin structure (Figure 14), even though a *meta*-cycloaddition is expected to be the favoured mode, and while an electron-donating methoxy group can be employed to control the

regiochemistry of the addition,[33] the preference for product formation through an *exo*- rather than an *endo*-exciplex has been documented.[27,28] However, the biologically potent aphidicolin system might be difficult to access as suggested based on *exo*-exciplex preference.

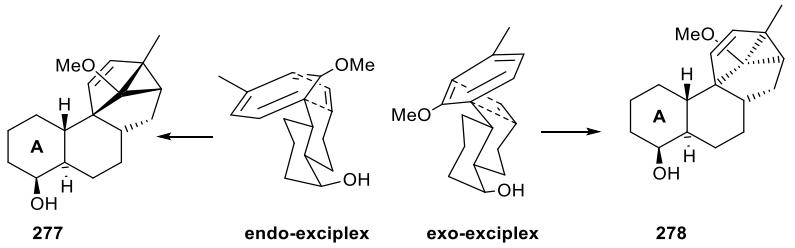
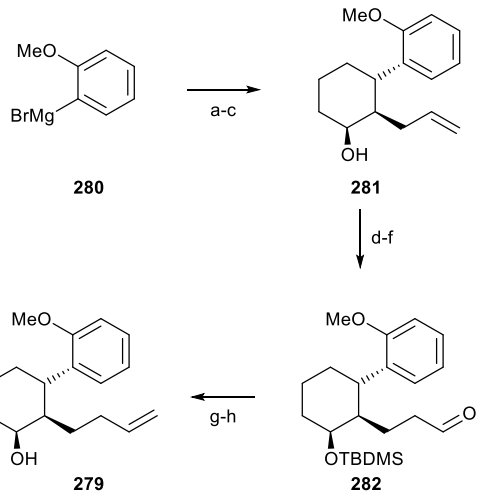


Figure 14: Possible exciplexes preceding the photocycloaddition to the ring systems of stemodinone and aphidicolin.

As described above, during a study of tandem Norrish Type I intramolecular alkene–arene photocycloaddition reactions, De Keukeleire and He described a highly *exo*-selective reaction that proceeded in 42% yield (Scheme 25); whereas, DeLong and Wender noted a highly *exo*-selective cycloaddition with 68% yield of product at 60% conversion for four-atom tethers (Scheme 24).[36] What appears to distinguish these two examples, which together represent the most efficient cycloadditions of this type, is some restriction of the conformational freedom of the tether. Given that the four-unit tether illustrated in Figure 13 allows the system to adopt a geometry that is suitable for the formation of an *endo*-exciplex (favoured for most intermolecular cases),[27, 28] without undue strain, the presence of the necessary fused six-membered ring should reduce the conformational freedom of the tether. The compound **279** was synthesized and photolyzed as illustrated in Scheme 77. First, using the chlorotrimethylsilane-accelerated, copper-catalyzed addition of **282** to cyclohexenone,[37] afforded the expected silyl enol ether in 68% yield. Second, generation of the corresponding lithium enolate, by treatment with methyl lithium, was followed by alkylation with allyl iodide. Then, to avoid any complications from Norrish-type reactions, the ketone was stereoselectively

reduced with L-selectride (lithium tri-sec-butylborohydride) to give the axial alcohol **281** as a crystalline solid in an overall yield of 77% (Scheme 77).[38]



Scheme 77: Synthesis of substrate **274**. Reagents and conditions: (a) CuCN (4%), TMSCl, DMPU, THF, cyclohex-2-enone, 68%; (b) MeLi, THF, allyliodide, -78 °C, 79%; (c) L-selectride, THF, -78 °C, 97%; (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; (e) 9-BBN then 3N NaOH, 30% H_2O_2, THF, 94%; (f) Dess-Martin periodinane, CH_2Cl_2, 99%; (g) H_3CPPh_3Br, MeLi, THF, 0 °C, 86%; (h) TBAF, THF, 50 °C, 94%.

The preparation of **279** by alkylation with homoallyl iodide was reported to be compromised by its low reactivity. Thus, homologation of **281** was used as shown in Scheme 77. The axial alcohol was protected by treatment of **281** with *tert*-butyldimethylsilyl (TBDMS) triflate, then hydroboration of the double bond with 9-BBN followed by a two-step oxidation reaction produced aldehyde **282** in 91% overall yield. A Wittig reaction (86%) and subsequent fluoride-mediated cleavage of the silyl ether (94%) completed the sequence of the reactions.

The fluorescence quenching of **279** was compared with that of its saturated analogue **283** (formed by quantitative hydrogenation of **279** over 10% Pd/C) and revealed a fairly strong interaction between the excited-singlet state S_1 of the arene and the alkene (Figure 15).

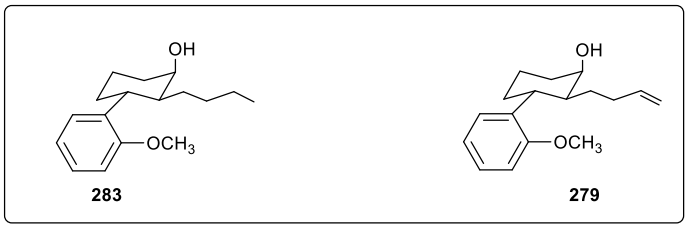
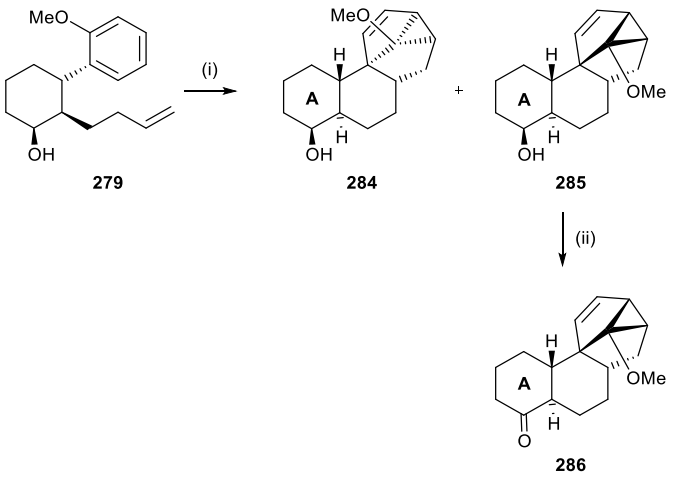


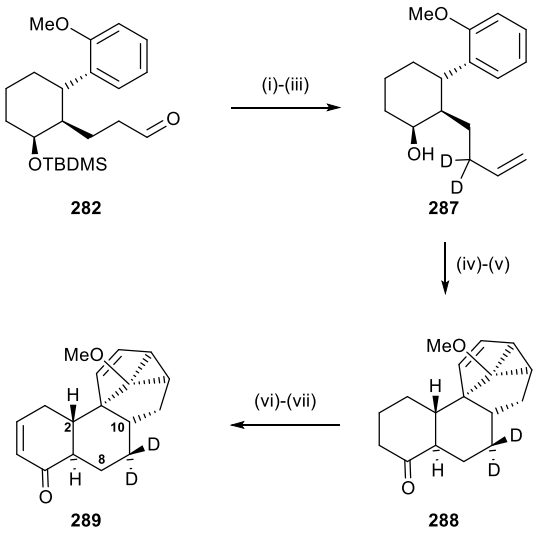
Figure 15: Conformational structures of **279** and **283** in cyclohexane (4mM) upon irradiation at *hv* = 267nm

Therefore, a solution of **279** in cyclohexane (0.45 m*m*) was photolyzed in a falling-film photoreactor[39] at 253.7 nm for 1.5 h. Such photolysis afforded a 1.0:1.2 mixture of two main photoadducts **284** and **285** in a remarkable 90% yield (Scheme 78).[89] The structure of the major product **285** was solved by a single-crystal X-ray structure of the ketone derivative **286** and was shown to arise from photocycloaddition of an *endo*-conformation, as illustrated in Figure 13.[40] The product **285** also exhibits the correct relative stereochemistry for aphidicolin.



Scheme 78: *endo*-selective intramolecular photochemical cycloaddition of **279**. *Reagents and conditions* (i) hv (λ=253.7nm), cyclohexane, 90% (**284**:**285,** 1.0:1.2); (ii) Dess-Martin periodinane, CH_2Cl_2, 81%.

Owing to the poor separation of resonances, it was difficult to assign the structure and stereochemistry of **284** by NMR spectroscopic techniques. Taking advantage of the homologation sequence developed to prepare **279** (Scheme 77), the aldehyde **282** was dideuterated by using sodium deuteromethoxide in deuterated methanol and then converted into **287** as shown in Scheme 79.



Scheme 79: Structural assignment of **284**. *Reagents and conditions*:(i) sodium [D_3] methoxide, [D_4]MeOH; (ii) H_3CPPh_3Br, MeLi, THF, 0 °C, 77%; (iii) TBAF, THF, 50 °C, 96%; (iv) hν (λ=253.7 nm), cyclohexane, 73% (then separate); (v) PCC, CH_2Cl_2, 73%; (vi) LDA, THF, PhSeCl, 78 °C, 61%; (vii) H_2O_2 (27.5%), THF, 0 °C, 94%.

Photolysis of **287** followed by oxidation of the product with pyridinium chlorochromate[90] afforded ketone **288** which, on desaturation to **289** by the Sharpless–Reich protocol,[91] allowed the relative stereochemistry at C-10 to be established by NOE measurements with irradiation of H-2 and H-8(axial) that showed a significant enhancement at H-10 (Scheme 79). Thus, **279** has exhibited a rare high regioselectivity of cyclopropane formation[31,35] to give two diastereoisomeric products of which **285** formed from a conformation that is analogous to the *exo*-arrangement shown in Figure 13 and proceeded via an *exo*-exciplex to give a relative stereochemistry that is appropriate for the stemodinone ring system (Scheme 78 and 79). It is

worthwhile to note that an intramolecular alkene–arene *meta* photocycloaddition has been carried out on **279** in a high yielding reaction despite the presence of a four-carbon-atom tether.[82] Furthermore, this is a unique example of such a reaction proceeding with a preference for an *endo* exciplex in an intramolecular case.[89] Taking into consideration both De Keukeleire's and Wender's results it is apparent that, with careful design of the tether, the restriction of three-linking-unit tethers in this type of reaction is no longer valid.[89] The products of these reactions hold promise of a rapid entry into the aphidicolin/stemodinone ring systems and to yield biologically active analogues.[89]

1.11 Heteroatom directed photoarylation: A method used for the introduction of angular Carbon-Carbon Bonds

The value of generating highly hindered quaternary carbons by the combination of sp^2 carbons via their π-faces has been clearly set out in the discussion above. Regarding the approach to the synthesis of stemodinone, adopted within the group, wherein a key quaternary centre is set with an intramolecular *meta*-photocycloaddition (Scheme 12), the substrate for this reaction requires another such centre to be prepared. It was envisaged that this could be achieved by a second photochemical reaction, the heteroatom directed photoarylation described by Schultz. Therefore, a review of this area is set-out below.

In 1974, Schultz and co-workers reported the first example of the heteroatom directed photoarylation reaction, a term which has been employed to describe an aromatic ring substitution process which is initiated photochemically and proceeds via electrocyclic reactions originating from the rearrangement of an available electron pair on the heteroatom and the electrons from at least one aromatic π-bond.[92] The photo-initiated reaction of six-electron heterocyclization of the compound **290** to afford **292**, through the ylide-alkene intermediate **291**, demonstrated the pathway of heteroatom directed photoarylation as shown in Figure 16.

The primary synthetic value of this electrocyclization reaction is the formation of a carbon-carbon bond to an aromatic ring. The heteroatom X such as an amine group (NR), sulfur group (S) or oxygen group (O) functions in the cyclization reaction as a connecting link, which allows the bonding centres to approach each other with the proper trajectory.[93] Heteroatom directed-photoarylation was described as the modern way of carbon-carbon bond formation utilising an unconventional energy source at the range of 254-300 nm.[94] Kellogg and co-workers reported that photocyclization of phenyl vinyl sulfides in the presence of iodine or oxygen to afforded benzothiophenes in low yield. However, the mechanistic details as well as the synthetic application of this stilbene-like photocyclization have not been investigated.[101]

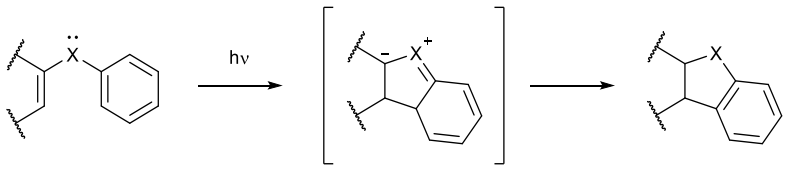


Figure 16: Schultz photo-initiated arylation reaction via a six-electron heterocyclization.

1.11.1 Photoarylation and the enone chromophore

The photoarylation reaction has been reported to achieve good synthetic results by utilizing the α,β-unsaturated carbonyl group which has also proved to be an excellent choice as a chromophore distinct from the aromatic ring.[93] The compound **293** with a carbonyl group cross-conjugated to the heteroatom may result in stabilization of the intermediate ylide **294** as shown in Figure 17. However, hydrogen migration can be coupled with epimerization α to the carbonyl group to extend stereochemical control to afford both compound **295** and its epimer α to the carbonyl, as depicted in Figure 17.[95a,95b,95c,95d] The photo-electrocyclisation/1,4-sigmatropic shift reaction *via* ylide intermediate has opened the way for the synthesis and screening of numerous bioactive secondary metabolites such as morphine alkaloids **368**, Codeine **369**, the galanthamine-type alkaloid lycoramine **370** and Hasubanan alkaloids-

cepharamine **371** as shown in Figure 26. Schultz reported that the reaction proceeds with high chemical yield and photochemical efficiency, whilst also being compatible with wide variety of functional groups within a molecular system.

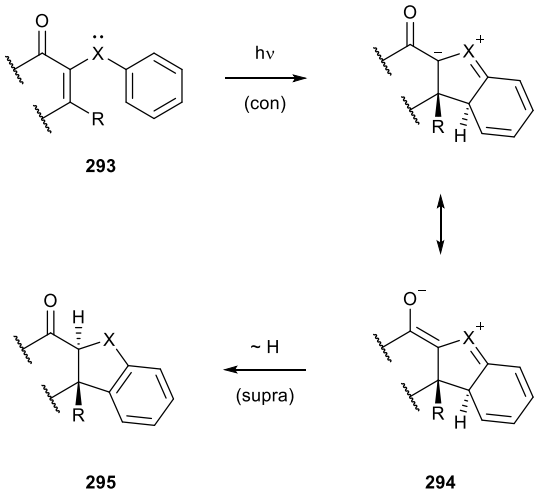
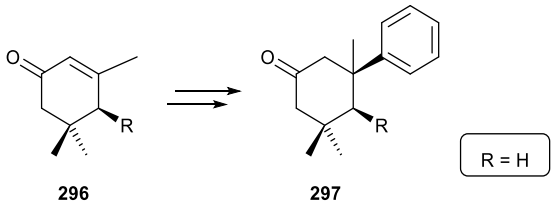


Figure 17: The conrotatory photo-electrocyclisation/1,4-sigmatropic shift reaction *via* ylide intermediate utilizing enone chromophore cross-conjugated to the heteroatom.

In 1972, Posner reported that an aryl substituent can be introduced at a carbon atom β to a carbonyl group by conjugate addition of organocopper reagents to α,β-unsaturated carbonyl substrates **296** to afford the product **297** (Figure 18).[96] Unfortunately, competing 1,2-addition may occur; however, for satisfactory conjugate addition, usually a twofold or threefold excess of organocopper reagent is required.[92] However, Schultz reported a simple route to the aryl annelated nucleus with potential for the synthesis of a variety of natural product of high medicinal values which have proved to be effective.[93] An attractive feature of heteroatom directed photoarylation is the regiospecificity of aromatic substitution *ortho* to the heteroatom, and the heteroatom sulfur can serve as a temporary directing group for carbon-carbon bond formation which could be removed in a subsequent step. The heteroatom sulfur is chosen to be suitable due to availability of a different variety of desulfurization techniques.

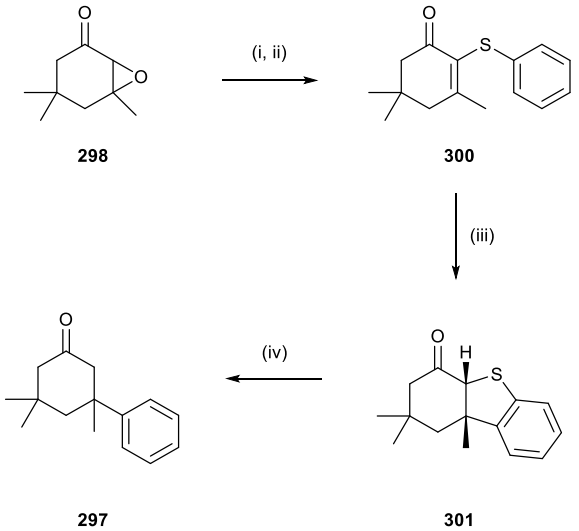


296 297

Figure 18: Posner's introduction of an aryl substituent at a carbon atom β to a carbonyl group.

1.12 Synthetic potential of the heteroatom sulfur in heteroatom directed photoarylation

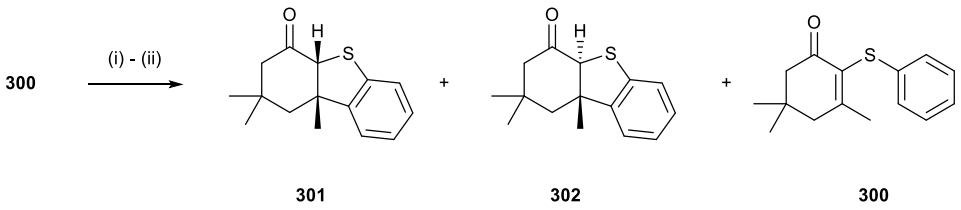
The key pathway to introduce an aromatic nucleus β to a carbonyl could be achieved by heteroatom directed photoarylation with aryl vinyl sulfides. Schultz has reported this method to be an efficient and experimentally simple synthetic route. This process involves the preparation of 2-thioaryloxyenones **300** by reaction of thiophenol **299** with isophorone epoxide **298** in the presence of base. Photocyclization-rearrangement of 2-thioaryloxyenone **300** to afforded dihydrothiophene compound **301**. However, desulfurization of **301** with Raney nickel gave 3-arylcyclohexanone **297** (Scheme 80).[94] Compounds of type **297** are the equivalent of those formed by cuprate additions, as illustrated in Figure 17. However, the key bond formation is achieved intramolecularly. Additionally, as discussed above in the context of synthetic routes toward stemodinone **1** and aphidicolin **3**, hindered quaternary centres are often formed effectively by the joining of the π-faces of sp^2 hybridised carbons.



298 300 297 301

Scheme 80: Synthesis of 3-arycyclohexanones via photoarylation. *Reagents and conditions*: (i) EtOH, NaOH, 15% KOH, 0 ºC, N_2-atm; (ii) **299** in THF, ~ 30 min. then 0 ºC for 8 h. 90%; (iii) PhH-MeOH, *hv* (450-W high-pressure mercury arc lamp), Ar-atm. 30 min prior and during irradiation, 20 h; (iv) Raney Ni-EtOH, heat to reflux, ~30 min.

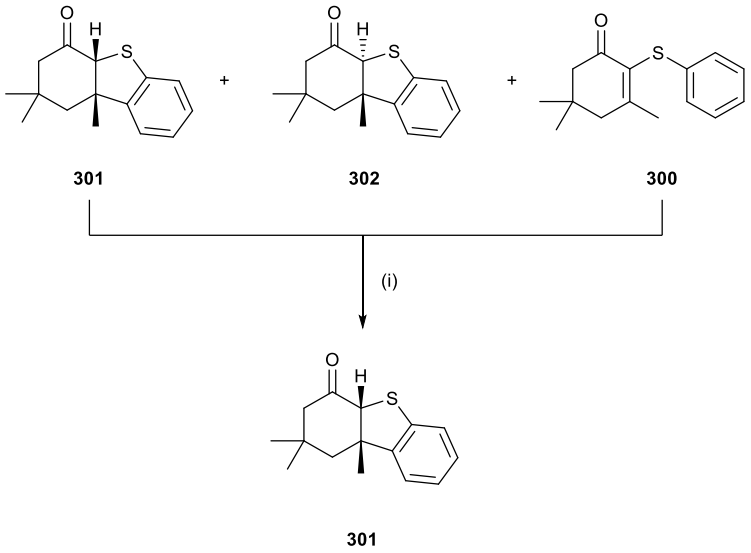
Schultz reported that photocyclization-rearrangement of 2-thioaryloxyenone **300** to afford dihydrothiophene compound **301** was solvent dependent. Pyrex-filtered photolysis of **300** in benzene-methanol solution (3:1) in a conventional preparative photoreactor for < 20 hours with a 450-W high-pressure mercury arc lamp generally gave the *cis*-fused dihydrothiophene **301** in excellent yield (Scheme 80). However, photolysis of **300** in degassed benzene solution (0.05 M) for 2 hours afforded mixture of isomeric products, *cis*-dihydrothiophene **301** (27%), *trans*-dihydrothiophenes **302** (27%) and 2-thioaryloxyenone **300** (6%) (Scheme 81).[94]



Scheme 81: Isomeric dihydrothiophenes formed by irradiation in benzene. *Reagents and conditions*: (i) PhH; (ii) h*v* (450-W high-pressure mercury arc lamp), Ar-atm. 30min prior and during irradiation, 2 h; 60% (**301**:**302:300,** 1:1: 0.2).

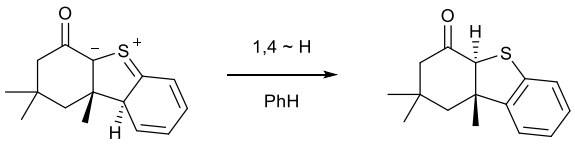
The proton NMR spectrum of **302** is characterised by sharp singlet at δ 4.71 (1H) for the methine proton. The photoadduct mixture was epimerized by treatment with sodium carbonate in benzene-methanol (1:1) solution at room temperature, followed by evaporation of solvent. Upon proton NMR analysis of the crude reaction mixture, it was shown that **302** had

completely disappeared along with formation of additional **301** characterised by a broadened singlet at δ 3.83 (1H) for the methine proton, in 53% yield (Scheme 82).[94]



Scheme 82: Epimerization to the more stable *cis*-dihydrothiophenes. *Reagents and conditions*: (i) Na_2CO_3, PhH-MeOH (1:1), rt.; 80% **301**.

According to Schultz, **300** in benzene solution experiences conrotatory photocyclization to an intermediate thiocarbonyl ylide **303**, from which suprafacial 1,4-hydrogen migration gives the strained *trans*-fused dihydrothiophene **302** (Figure 18). However, hydrogen migration within **302** may be stereospecific to give only *trans*-fused dihydrothiophene **302** from which the more stable **301** is generated by epimerization.[92] The *cis*-dihydrothiophene **301** represents the stable configuration of a fused five/six-membered ring system capable of epimerization.[96] In a related studies with aryloxyenones, Shultz and co-workers demonstrated photocyclization-rearrangement to be stereospecific to affording only *trans*-dihyrofurans as shown in Figure 19.[97]



303 302

Figure 19: Conversion of thiocarbonyl ylide **303** to *trans*-dihydrothiophene **302** via a suprafacial 1,4-sigmatropic rearrangement.

1.12.1 Regioselectivity issues with sulfur directed photoarylation

One of the features that makes heteroatom directed photoarylation attractive is the regiospecificity of aromatic substitution *ortho* to the heteroatom.[97] The regiospecificity of particular interest was the discovery that with aryl vinyl sulfides derived from 2-naphthalenethiol, only the dihydro[2,1-b]thiophenes were produced with no trace of the dihydro[2,3-b] isomers.[98] However, photocyclization of aryl vinyl sulfides has been reported to occur with varying regioselectivity if the benzene ring bears substituents. For *ortho*-tolyl **304**, and both *para*-tolyl **305** and *para*-hydroxy **306** substituted thiophenoxyenones, only one isomer of dihydrothiophenes **308**, **309** and **310** is possible. However, with *meta*-substituted thiophenoxyenone **312**, photocyclization afforded a 70:30 mixture of isomeric products **311** and **312**; interestingly, carbon-carbon formation *ortho* to the methyl substituent predominates to give the more hindered product, **311** (Figure 20).[96] With prospects for regioselective control in mind, Schultz investigated the use of the heteroatom as a temporary directing group for the carbon-carbon bond formation which could be removed in a subsequent step. The availability of a variety of desulfurization techniques makes the sulfur atom a suitable choice.

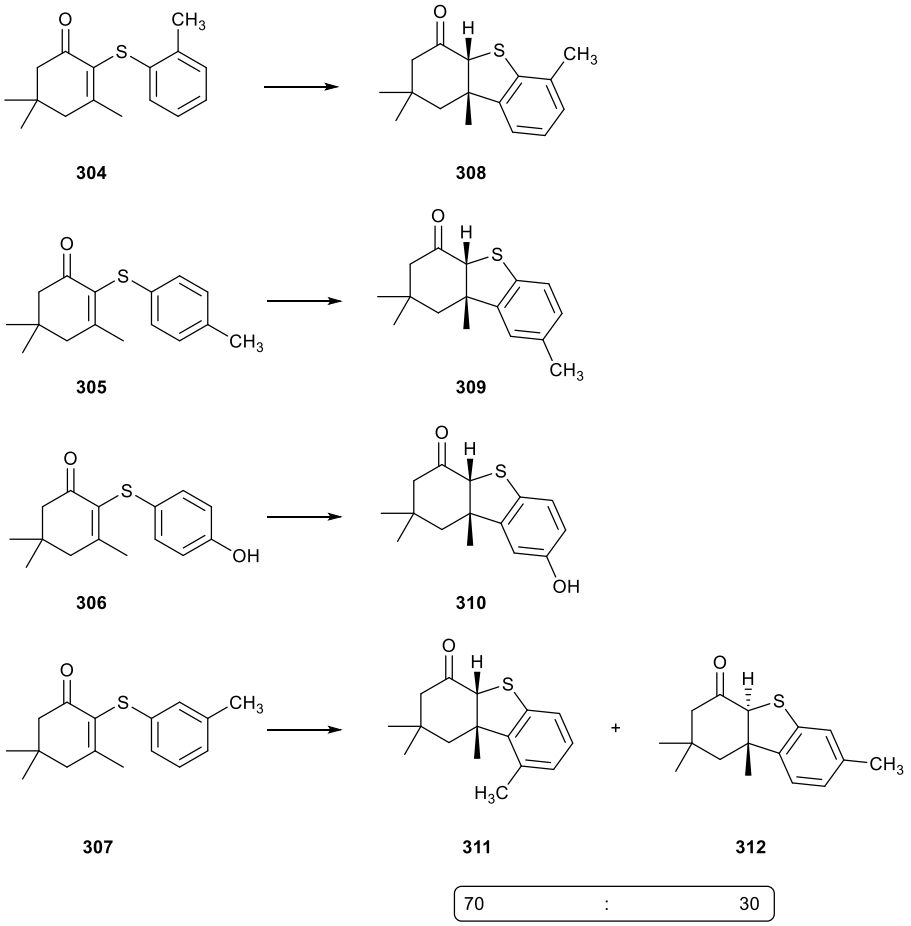


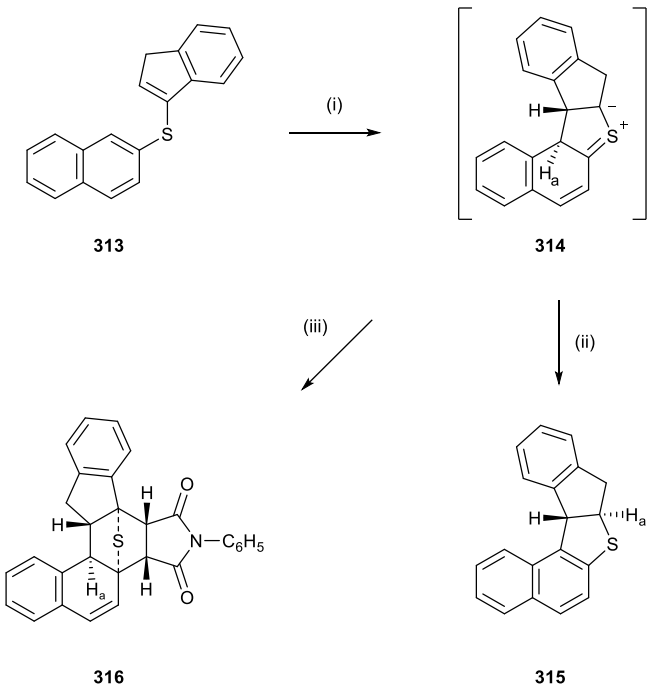
Figure 20: Regioselectivity issues with sulfur directed photoarylation.

1.12.2 Stereoselectivity issues of heteroatom Sulfur utilizing heteroatom directed photoarylation

The stereochemistry of photocyclization of 2-naphthyl vinyl sulfides has been studied by Schultz and co-workers (Scheme 83). Photolysis of a degassed benzene solution of 2-naphthyl vinyl sulfide **313** afforded *trans*-dihydrothiophene **315** in 78% isolated yield. However, photolysis of **313** in the presence of the dipolarophile *N*-phenylmaleimide (NPMI, 2 equiv) resulted in isolation of a single cycloadduct **316** in 90% yield and the structure of **316** was unambiguously determined by X-ray analysis. Furthermore, putting into consideration the stereochemistry in **315** and **316** reveals that cyclization of **313** is conrotatory to give the hypothetical thiocarbonyl ylide intermediate **314**, and that the hydrogen migration in **314** is

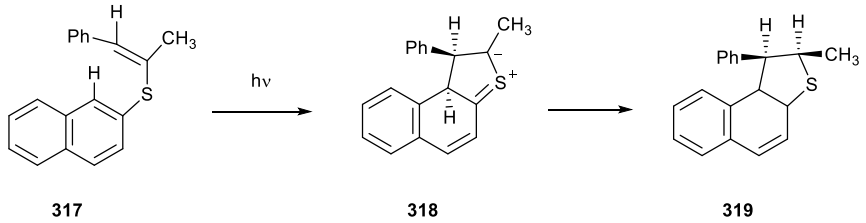
suprafacial (and probably [1,4], involving H_a to give the *trans*-dihydrothiophene **315.**[92] The unique ring annelation method involved the formation of three carbon-carbon bonds and six chiral centres are generated in single experimental operation which could prove to be generally useful in the construction of complex natural product ring systems.[93,100]

The proposed photoproduction of thiocarbonyl ylides has been studied by a flash photolysis technique to characterise them and probe the reactivities of excited state intermediates. Both chemical and spectroscopic evidence have been recorded to support the intermediacy of the ylide system.[95d] Moreover, some intramolecular addition reactions of ylide systems demonstrate that product distribution is influenced by reaction temperature, substrate structure, and wavelength of irradiation.[95d] With a series of five 2-naphthyl vinyl sulfides, transient species with absorption maxima near 630 nm were observed.[93] The rates of the disappearance of these transients are reported to be in the order of tens of milliseconds in degassed benzene, but are shortened to the microseconds in air-saturated solution. While the kinetic analysis for the disappearance of transients is complex, Schultz noted that the species absorbing at 630 nm are thiocarbonyl ylide intermediates corresponding to **314**. However, these reactive intermediates would be expected to undergo reactions with dissolved oxygen. The formation of thiocarbonyl ylides **314** can be sensitized by triplet state sensitizers with triplet energies near or greater than that of vinyl sulfides **313** (E_T = 60.9 Kcal/mol).[93] It should be noted that on direct photolysis of **313**, some quenching is observed with isoprene, *cis*-piperylene, and 2,5-dimethyl-2,4-hexadiene. However, the Stern-Volmer plots created from quenching data all show substantial curvature. Such observations are in accordance with both singlet and triplet reactivity for the photoexcited **313**. The Stern-Volmer plots gives a straight-line graph by trial-and-error reconstruction, when 50% of the photoreaction of **313** is assumed to occur through the singlet manifold and the remainder through the triplet state.



Scheme 83: Stereochemistry of photocyclization of 2-naphthyl vinyl sulfides. *Reagents and conditions* (i) PhH, h*v*; (ii) [1,4 ~ H]; (iii) NPMI.

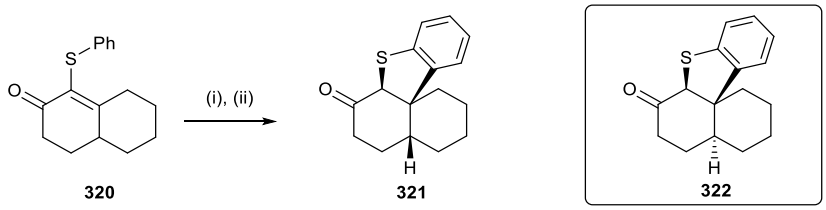
Brief Pyrex-filtered photolysis of 0.01 M degassed benzene solution of geometric isomer **317** leads to photoisomerization about the double bond. However, it was reported that naphthyl vinyl sulfide **317** under nonoxidative conditions undergoes regiospecific photocyclization to thiocarbonyl **318**. This potentially useful reactive intermediate experiences stereospecific hydrogen migration leading to naphthol[2,1-*b*]dihydrothiophene **319** as shown in Figure 21. The stereochemistry assignment in dihydrothiophene **319** was based primarily on the dihydrothiophene ring vicinal proton coupling constants (*J*ab) for *cis*- substituted (7.0 Hz). Thus, the structure of **319** exhibits nonaromatic resonance at δ 0.98 (CH_3, d, J = 7.0 Hz), 4.01 (CH, adjacent to sulfur, m, J = 7.0 Hz) and 5.58 (CH, d, J = 7.0 Hz). Furthermore, the stereochemistry of the final product **314** will be fixed if the intramolecular hydrogen migration occurs in the intermediate thiocarbonyl ylide.[100]



317 318 319

Figure 21: Thiocarbonyl ylide photogeneration, rearrangement and cycloaddition reaction.

Schultz reported that a Pyrex-filtered photolysis of **320** in benzene-methanol solution gave a single dihydrothiophene **321** as an oil in >95% yield. However, the stereochemical control possible with heteroatom directed photoarylation was exceptionally high as demonstrated by conversion of 2-thiophenoxyoctalone **320** to afford dihydrothiophene **321**.[99] Exclusive formation of *cis*-decalone **321** may be as a result of preferential cyclization from the least hindered face of the enone system (Scheme 84).[99]



320 321 322

Scheme 84: Control of relative stereochemistry with heteroatom directed photoarylation. *Reagents and conditions* (i) PhH-MeOH; (ii) h*v*, 95% yield.

Furthermore, the decalone ring system in **321** was shown to have a *cis*-fusion and the dihydrothiophene with *trans*-decalone **322** ring system could not be detected as reported by Shultz.[92] Thus, the remarkable stereoselectivity in the photocyclization of **320** to **321** could be a result of relative ring strain in thiocarbonyl ylides **323** and **324** (Figure 22), which were reported to be hypothetical intermediates resulting from the two possible conrotatory cyclization modes available to photoexcited **323**.[92] An argument based on orbital symmetry suggested that cyclization of aryl vinyl sulfides to thiocarbonyl ylides in the photoexcited state will be conrotatory, whereas cyclization from a vibrationally excited ground state will be disrotatory.[102]

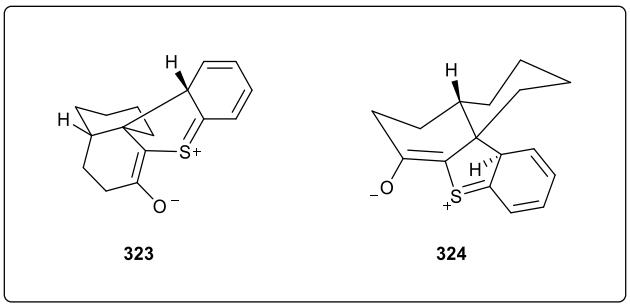


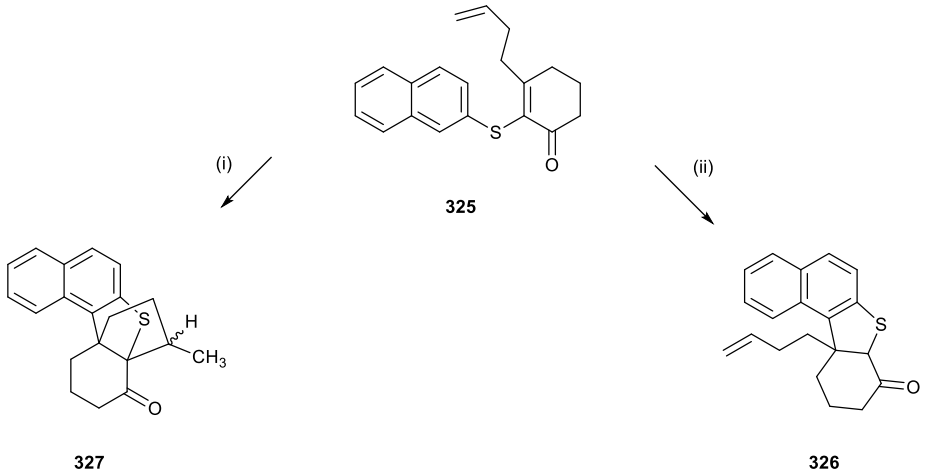
Figure 22: Intermediates resulting from the two possible conrotatory cyclization modes available for photoexcitation of **320**.

1.13 Tandem heteroatom-directed photoarylation intramolecular addition reaction

In 1989, Dittami and co-workers reported the intramolecular addition reactions of phototransient species generated by heteroatom directed photoarylation. Effects of temperature were noted for both photocyclization and intramolecular addition reactions. However, the addition products were observed to differ greatly from the [3 + 2] cycloadducts which were obtained upon intermolecular addition to the phototransient species.[100] The six-electron heteroatom directed photoarylation reaction proceeds *via* dipolar intermediates. Upon photolysis of aryl vinyl sulphides, aryl vinyl ethers and aryl vinyl amines the corresponding thiocarbonyl ylides, carbonyl ylides and azomethine ylides were obtained, respectively.[93,104] The studies on intramolecular addition reactions focused only on aryl vinyl sulphides and the products were reported to be [3 + 2] cycloadducts which arise from dipolar cycloaddition via a thiocarbonyl ylide intermediated. Moreover, the intramolecular addition reactions studied by Dittami and co-workers focus only on aryl vinyl sulfides and aryl vinyl ethers yield ene-like products.[95f]

Photolysis of a solution of **325** in 0.002 M benzene for 10 hours at 25 °C provided the photocyclized product **326** in 81% isolated yield. Interestingly, low temperature irradiation of

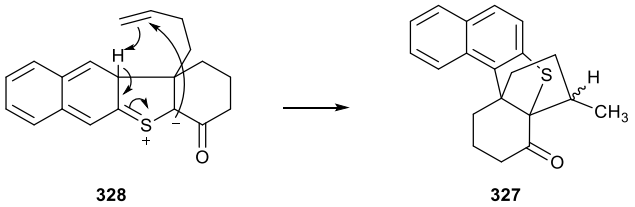
a solution **325** in 0.003 M toluene at -78 °C provided **326** in quantitative yield after only 25 minutes. In contrast to these experiments, high temperature photolysis of a solution of **325** in toluene 0.003 M at 110 °C for 3.5 hours resulted in formation of the addition product **327,** which was obtained as a mixture of diastereoisomers in 79% isolated yield. Control experiments demonstrated that both light and heat were required to effect the formation of **327**. Thus, heating a solution of **325** in toluene at reflux for 6 hours in the dark results in recovery of starting material. Likewise, **326** was shown to be stable in both refluxing toluene and under the heat and light reaction conditions used for the formation of **327**. These data suggest that a transient species generated from **325** *via* a photochemical process undergoes a thermally induced addition reaction to afford **327** as shown in Scheme 85.



Scheme 85: intramolecular addition reaction of naphthalene vinyl sulphide during heteroatom directed photoarylation. *Reagents and conditions* (i) h*v*, 110 °C, 79% yield **327**; (ii) h*v*, rt, or -80 °C, 81-100% yield of **326**.

Separation of the mixture of diastereoisomers **327** was achieved by HPLC (SiO_2, 16:1 hexane: ethyl acetate). Confirmation of the structure was obtained by analysis of the 2D ^{1}H-NMR of **327**, and ring closure in the naphthyl vinyl sulphide **325** occurred only toward the 1-position of the naphthalene system.

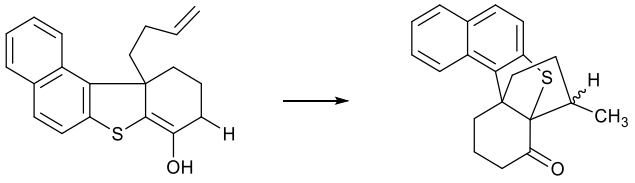
However, two possible mechanisms for formation of **327** were suggested; first, a radical addition pathway occurring from the thiocarbonyl ylide **328** with hydrogen abstraction either intramolecularly or from the solvent to provide the 5-membered ring product. Conversely, an ene-like process in **328** (Figure 23) may be operative.



328 **327**

Figure 23 A possible mechanism for formation of **327** through an ene-like pathway.

This pathway, however, requires a *cis* orientation of the hydrogen and butenyl side chain. Since the product which is expected from a photochemically allowed conrotatory cyclization places these substituents in a *trans* orientation, the latter process is less likely. However, an alternative ene reaction occurring from an enol tautomer of **326** (Figure 24), was also possible but was ruled out based on the control experiments described above. Thus, a radical pathway was proposed.

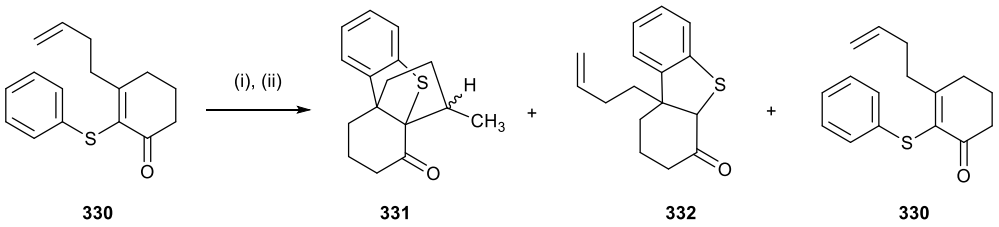


329 **327**

Figure 24: An ene reaction occurring from enol tautomer of **321**.

Furthermore, phenyl vinyl sulfide **330** provided similar results to **325**; however, higher reaction temperatures were required to produce the photocyclized adduct. Thus, photolysis of a solution of **330** in 0.004 M mesitylene at reflux temperature for 3 hours resulted in the formation of ketone **331** in 41% isolated yield. The product, which was obtained and characterized as a mixture of diastereoisomers, was accompanied by 31% of the photocyclized material **332** and

11% recovered starting material **330**. Both heat and light were required to effect the transformation of **330** to **331**.



Scheme 86: Intramolecular addition reaction of phenyl vinyl sulfide during heteroatom directed photoarylation. *Reagents and conditions* (i) h*v*; (ii) 160 °C, 41% yield.

Clearly, the ability to effect a photoarylation in the presence of an alkene side chain, by working at lower temperature, is of significance for generating starting materials of a suitable type for a *meta*-photocycloaddition *e.g.*, those shown in Scheme 12. Bach has shown different behaviour with oxygen directed photoarylation.[95f, 95g]

1.14 Flash photolysis studies on the sulfur directed heteroatom

In 1978, Wolff reported the reaction mechanism of the photochemical ring closure of S-aryl vinyl sulphides to form dihydrothiophenes, determined by flash photolysis. The reaction proceeds *via* the triplet excited state of the sulfides to the coloured dihydrothiophenes intermediates, from which by hydrogen shifts or by abstractions the final products are obtained.[103] Investigation using flash photolytic techniques were carried out by Wolff on 1-phenylthio-3,4-dihydronaphthalene **333**, 1-phenylthio-1-phenylpropene-1 **334**, and 1-(naphthyl-2-thio)-1-phenylpropene-1 **335**. After flash photolysis of 50 µM of a degassed solution of **333, 334,** and **335**, at room temperature, intermediates were observed which disappeared following first-order kinetics with time constants in the millisecond range. By monitoring the decay curves using monochromatic light at 10 nm intervals and extrapolating to zero-time, absorption spectra of these intermediates were obtained. They exhibited

absorption maxima at >620, 590 and 610 nm respectively, and the intermediates were assigned the zwitterionic dihydrothiophenes structures **336**, **337**, and **338**, respectively. To probe the nature of the zwitterion dihydrothiophenes and how they arose, evidence were obtained from experiments in which solutions of compounds **333**, **334**, and **335** containing triplet quenchers were subjected to flash photolysis. However, the presence of oxygen or benzil had no influence on the lifetime of **336**, **337** and **338** (Figure 25), as would be expected for ground state intermediates. The quantum yield of **336** is reduced to a value of 61% in air and 13% in oxygen-saturated solution. Upon addition of 0.003 M benzil to a degassed solution of **333**, reduced the quantum yield of **336**. This effect was reported to have been difficult to quantify due to the necessary corrections for the loss of excitation light as a result of benzil absorption and for the contribution to the transient absorption by a signal originating from the excitation of benzil.[103]

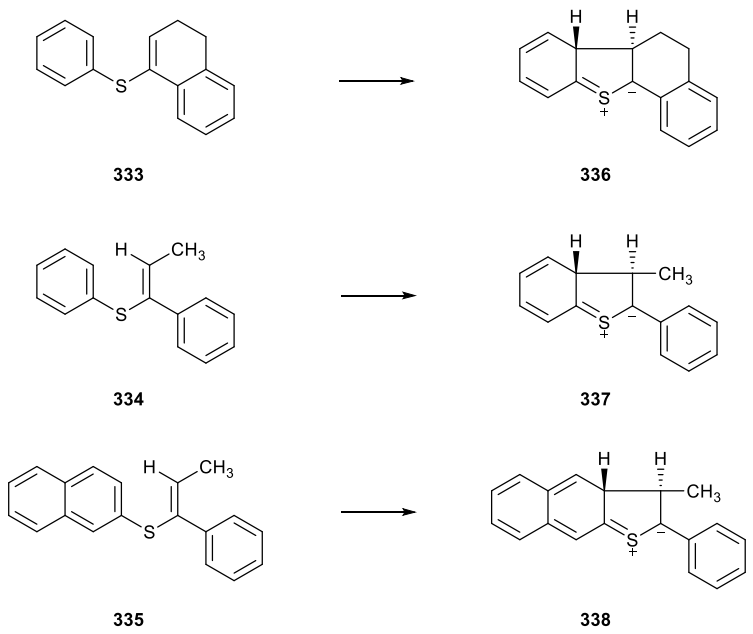


Figure 25: The zwitterionic intermediates leading to dihydrothiophenes detected by flash photolytic techniques.

Moreover, all these observations suggest a triplet precursor **336** which is quenched by oxygen or benzil. The sensitizing experiments have been reported to be a convincing proof for the involvement of this triplet state in the reaction sequence. After flash photolysis of a degassed

solution containing 0.02 M propiophenone and 0.03 M **334**, under conditions where only the propiophenone was excited, the transient absorption of **337** was observed. Furthermore, when a degassed solution of **333**, was cooled down, the quantum yield of **336**, remained constant until 190 K and then sank rapidly on further lowering of the temperature while the probe began to phosphoresce. This indicates that the chemical reaction of the triplet state leading to **336**, has been restricted, probably by activation energy, and that the triplet is now deactivated largely by emission.

Interestingly, the quenching of the formation of **337** and **338**, was reported to have been significantly less efficient when compared with **336**. In an oxygen saturated solution of **334**, the quantum yield of **337** was only reduced to 80%. In contrast to **333**, ‘‘*cis-trans*’’ photoisomerization about the olefinic double bond has been reported to be possible for **334** and **335**. [100]

For the intermediate appearance of a species that must be considered a precursor of zwitterion **336**, direct evidence has been obtained from laser flash photolysis studies which were carried out in the less than microsecond range. The experiment was carried out on **333** and subjected to the 337 nm emission of a nitrogen laser. Oscilloscope traces of transient absorptions of **333** after laser excitation in degassed and in air-saturated methylcyclohexane solution at room temperature were reported at flash intensities varying within 10%. At both wavelengths monitored, a transient was demonstrated to be formed immediately. The decay of this transient was observed at 430 nm. It also follows first-order kinetics and has been reported to have a lifetime of about 0.5 μs at room temperature. The signal does not reach the baseline, because the zwitterion **336** was formed, which absorb at this wavelength with a low extinction coefficient. The zwitterion **336** was reported to absorb more strongly at 610 nm than the short-lived transient. The increase of optical density at 610 nm proceeds with the same rate as the decrease at 430 nm within experimental error. Therefore, the decaying transient must be the

precursor of the one increasing. These are the observations expected for an excited triplet state of **333** that give rise to zwitterion **336**. Such interpretations strongly supported the fact that the decay at 430 nm was much more rapid in aerated than in deaerated solutions which obviously indicates efficiency in quenching by oxygen. Therefore, less zwitterion was formed under these conditions. In the initial stage, the triplet contributes even more to the optical density instead of an increase of optical density with time.

In 1984, Schultz and Herkstroeter reported photochemical evidence for the intermediacy of thiocarbonyl ylides and noted that flash photolysis could be designed to detect and characterize reaction intermediates.[101] The mechanism for the photocyclization of 2-naphthyl vinyl sulfide with structural variations were investigated using flash photolysis techniques and each sulfide tested was reported to form phototransient species with absorption maxima near 650 nm. The disappearance of these transient species required the presence of two species decaying independently at different rates, as has been analysed by kinetics. These transients were interpreted as reaction intermediates having zwitterionic thiocarbonyl ylide structures. However, all the sulfides were reported to show singlet-state reactivity and the triplet-state reactivity was shown only by those starting materials whose vinyl substituents were restricted from free rotation in the excited state.

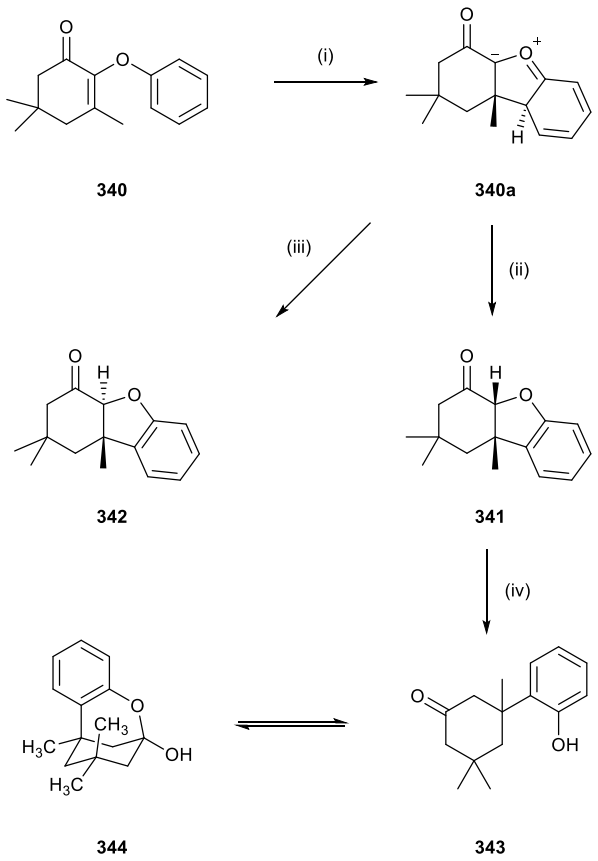
1.15 Synthetic potential of the oxygen directed photoarylation

In 1978, Shultz and co-workers reported an extension of the method used to demonstrate the synthetic potential of the heteroatom directed photoarylation with aryl vinyl sulfides to include the heteroatom oxygen as a useful tool for the construction of a variety of dihydrofurans and the method was found to be attractive for its potential to serve as a route for the synthesis of a variety of medicinally important secondary metabolites.[95a] A review of aryl ether photochemistry has documented the photochemical reactions of aryl vinyl ethers consistent

with the mechanism of bond cleavage of ethers followed by hydrogen abstraction from solvent to afford phenols and photorearrangement to give *ortho*- and *para*-substituted hydroxybiphenyls.[107,108] Schultz carried out the photochemistry of 2-aryloxyenones by considering a report documented on aryl vinyl sulfide photochemistry which had been proven to form dihydrothiophenes from 2-thioaryloxyenones with good efficiency.[92] Thioaryloxyenones were prepared in a quantitative yield by base catalysed reactions of an aryl mercaptan with 1 equivalent of an epoxyketone in protic solvents at or below room temperature. Due to the decreased nucleophilicity of phenoxide when compared to thiophenoxide, more vigorous conditions were required to effect epoxide ring opening with phenols. To accomplish that, catalytic amount of potassium hydride (0.1 equiv.) assisted the reaction of epoxide **298** with phenol **339** (1.1 equiv.) in refluxing THF solution containing hexamethylphosphoramide HMPA (0.75 equiv.) to afford analytically pure aryloxyenone **340** in 92% isolated yield.

Pyrex-filtered photolysis of **340** has been performed on a 20 g scale in degassed benzene-methanol-acetic acid solution (1:1:1) and *cis*-dihydrofuran **341** was formed in 95% yield. However, photolysis of **340** in pure benzene solution leads to a more complicated product distribution, but the major product is reported to be *trans*-dihydrofuran **342**. Upon treatment of the photoreaction mixture with sodium carbonate in benzene-methanol solution, epimerization of **342** to the *cis*-dihydrofuran **341** results. A probable mechanism for photocyclization of **339** in toluene solution involves conversion of **340** to carbonyl ylide **340a**, from which suprafacial 1,4-hydrogen migration gives the *trans*-fused dihydrofuran **342**. Schultz and co-workers documented that in protic solvents, *cis*-dihydrofuran **341** was formed by protonation of the carbonyl ylide followed by rearomatization *via* deprotonation. Alternatively, **340a** may rearrange to **342** and **342** may epimerize to the more stable **341**.[95a] Keto dihydrofuran **341** undergoes quantitative reductive cleavage of the C(2)-oxygen bond with zinc dust in refluxing

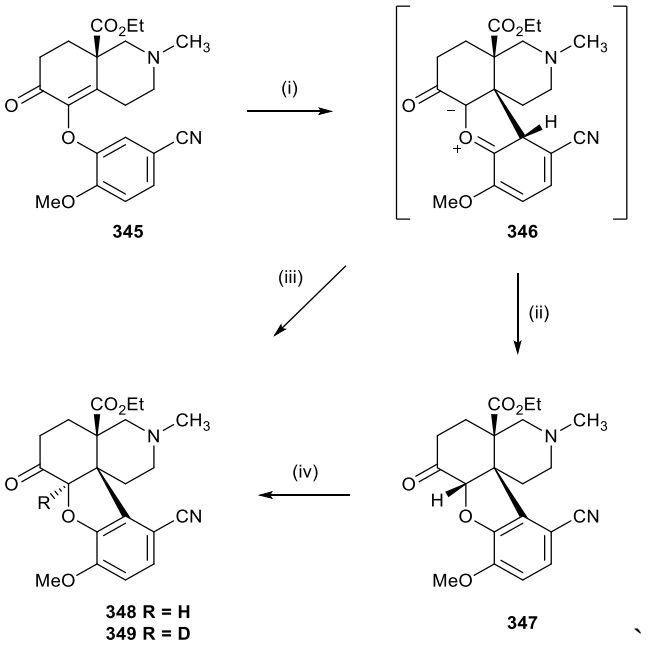
acetic acid solution to give the *ortho*-substituted phenol **343**, isolated as hemiketal **344** as shown in Scheme 87.



Scheme 87: Synthesis of aryl annelated dihydrofurans. *Reagents and conditions*: (i) hν; (ii) Tol:MeOH, Na_2CO_3, 95% yield; (iii) Toluene, [1,4]-sigmatropic shift (H); (iv) Zn, HOAc.

Photocyclization of certain fused ring aryloxyenones in aprotic solvents, leads to exclusive formation of *trans*-dihydrofurans. Pyrex-filtered photolysis of **345** in benzene solution (Scheme 88) afforded the tetracyclic morphine structural analogue **347** in a very good yield (>90%). On the other hand, photolysis of **345** in benzene-methanol solution (1:1), can afford the *trans*-dihydrofuran **347** and *cis*-fused dihydrofuran **348** in a ratio of 1.3:1. The two photoproducts obtained were epimers and established as such by quantitative conversion of **347** into **348** in MeOH solution saturated with Na_2CO_3. However, photolysis of **345** in benzene-methanol saturated with Na_2CO_3 afforded only **348** in 88% isolated yield. Furthermore,

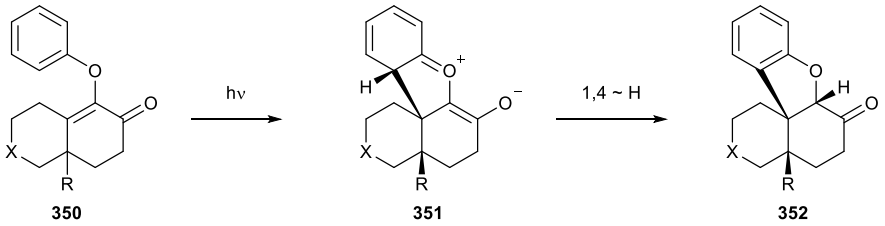
photolysis of **345** in methanol-d_1 gave **347** without the incorporation of deuterium and also a trace of **348** was obtained with complete deuteration at C(1). Control experiments revealed that while **347** was completely stable to the photolysis conditions, the compound **348** undergoes proton exchange with methanol-d_1 to afford **349**. However, both compounds **347** and **348** are formed by conrotatory photocyclization of **345** to carbonyl ylide intermediate **346**. With the assumption that cyclization of **345** to give only **346** occurs in both protic and aprotic solvents, then suprafacial 1,4-hydrogen migration in carbonyl ylide **349** gives the strained *trans*-fused dihydrofuran **347**, while competitive protonation-deprotonation of the ylide in protic solvents produced the more stable epimer **348**.[93,114]



Scheme 88: A mechanism for photocyclization of fused ring aryloxyenones. *Reagents and conditions*: (i) hv; (ii) PhH, [1,4]-sigmatropic shift (H); (iii) PhH:MeOH (1:1); (iv) MeOH solution saturated with Na_2CO_3.

In 1982, Schultz and co-workers reported the photocyclization of 2-aryloxy- and 2-thioaryloxyenones to afford an intermediate ylide via conrotatory electrocyclization which undergoes suprafacial 1,4-hydrogen migration to produce a *trans*-fused dihydrofuran while

ylide-solvent proton transfer gives a *cis*-fused dihydrofuran.[95a] Synthesis of heterocyclic systems such as those displayed in (Scheme 89) were reported to be possible and can occur *via* either of two diastereoisomeric conrotatory cyclizations, but only one has been observed. The photocyclization of **350** appears to be governed by product development control to give the relatively strain free delocalized ylide **351** with a *cis*-decalone-like ring fusion; this undergoes [1,4]-sigmatropic shift to give **352**. The corresponding ylide with a *trans*-decalone ring fusion was probably too strained to form.



350 **351** **352**

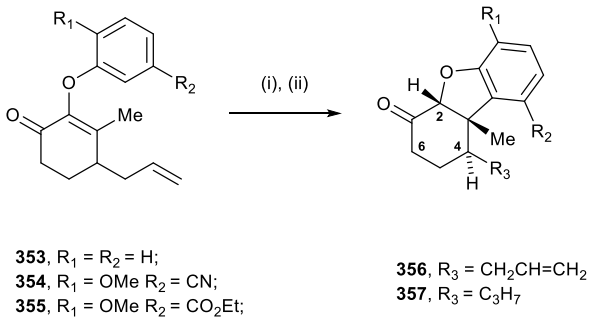
Scheme 89: Product development control in the photocyclization of **350** to **352**.

Noting the formation of adjacent quaternary stereocentres in this work, it was apparent that there was potential for this methodology to be applied to the synthesis of intermediates suitable for the preparation of stemodinone. Below is considered work by Schultz that is directly relevant to this proposal.

1.16 Stereoselectivity issues in heteroatom directed photoarylation relevant to stemodinone synthesis

Schultz also investigated whether product development control would operate for other systems in which the overriding constraint of ring strain is not present.[109] Thus, in 1982, Schutz and Napier reported the stereoselective photocyclization of 4-allyl-3-methyl-2-aryloxy-2-cyclohexen-1-one.[109] Pyrex-filtered photolysis of **353** in benzene-methanol solution (1:1, 0.06 M) for 2.5 hours afford a mixture of dihydrobenzofurans, diastereoisomeric at C(4), with **356** as a major isomer in 88% yield (Scheme 90). An attempted VPC analysis of **356** was made but the products decomposed, indicating thermal lability. However, catalytic hydrogenation of **356**

gave **357** in a very good yield (96%) and VPC analysis of **357** revealed the presence of two components in the mixture in a ratio of 8.4: 1.0, respectively. The two isomers were not separated and the dominant product of the photocyclization of **353** (~90%) was proposed to be the diastereoisomer of **357** shown in Scheme 90.



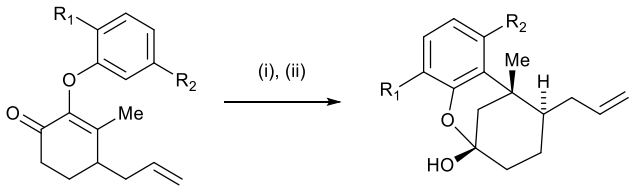
353, $R_1 = R_2 = H$;
354, R_1 = OMe R_2 = CN;
355, R_1 = OMe $R_2 = CO_2Et$;

356, $R_3 = CH_2CH{=}CH_2$
357, $R_3 = C_3H_7$

Scheme 90: Photolysis of 4-allyl-3-methyl-2-aryloxy-2-cyclohexen-1-one. *Reagents and conditions*: (i) hv; (ii) PhH:MeOH (1:1 0.06 M), 2.5 h, **356** in 88% yield, then, H_2, Pd/Cs **357** in 96% yield.

To examine the synthetic potential of this reaction, a series of transformations were studied. These are considered below as some may be of relevance to the proposed work and also serve to prove the stereochemistry of **356**.

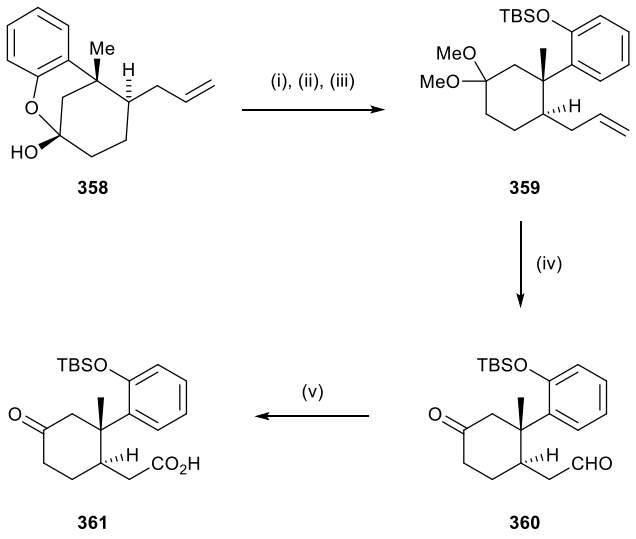
Dissolving metal reduction of the reaction mixture from photolysis of **353** with excess Al(Hg) in THF:H_2O (10:1, 0.1 M) for 90 minutes at room temperature gave hemiketal **358** in 95% yield (Scheme 91). Cleavage of the C-O adjacent to the carbonyl group is required in an application of this methodology to stemodinone **1**. However, the stability of the ketal is of significance and this has been investigated by Schultz as part of structure determination and general study of the molecule's synthetic potential.



353 **358**

Scheme 91: Preparation of hemiketal **358**. *Reagents and conditions*: (i) *hv*; (ii) Al(Hg) in THF:H_2O, r.t., 90 minute, 95 %.

Reaction of **358** with lithium tetramethylpiperidide (2 equiv.) in THF-HMPA solution at -78 °C followed by addition of *tert*-butyldimethylsilyl chloride and warming to room temperature gave a phenolic silyl ether enol silyl ether. This transformation cleverly exploits the lower pK_a of a phenolic OH over that of a hemiacetal OH to shift the equilibrium towards the ring-opened form. Ketalization (methanol, trimethylorthoformate, *p*-toluenesulfonic acid) followed by filtration chromatography on alumina gave **359** in 80% yield (Scheme 92). Ozonolysis in CH_2Cl_2 followed reduction of the ozonide with zinc and acetic gives aldehyde **360** (95%). Access to such aldehydes may prove valuable to facilitate varying the nature of the alkene when studying the proposed *meta*-photocycloaddition. On treatment with Jones reagent, this aldehyde gave keto acid **361** (86%).

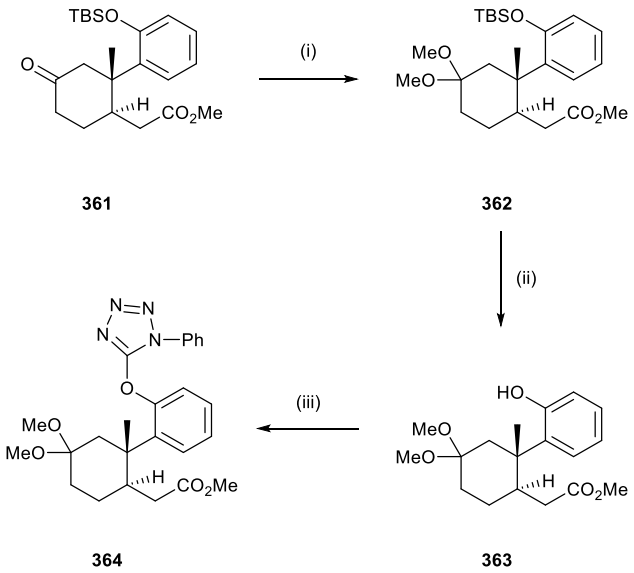


358 **359** **360** **361**

Scheme 92: preparation of methyl ester **356**. *Reagents and conditions*: (i) LTMP (2 equiv.), THF-HMPA, -78 ºC; (ii) TBDMSCl, r.t.; (iii) MeOH, TMOF, *p*TsOH (80%); (iv) CH_2Cl_2, Zn/AcOH (95%); (v) CrO_3/H_2SO_4.

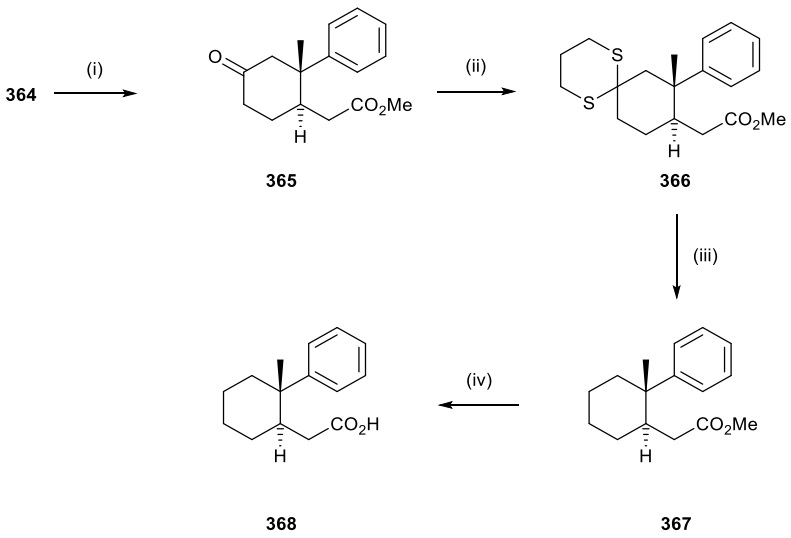
To establish the relative stereochemistry of the two centres a series of transformations were carried out. Thus, conversion of **360** to methyl ester **361** with diazomethane in ether was

followed by ketalization to give **362**. Deprotonation of phenolic oxygen atom was accomplished by either cleavage of the silyl ether in **362** with tetra-n-butylammonium fluoride in THF to afford **363** (61%) or reaction of **363** with excess K_2CO_3 and 5-chloro-1-phenyl-1H-tetrazole (2 equiv.) in DMF at room temperature gave **364** (70%) as shown in Scheme 93.



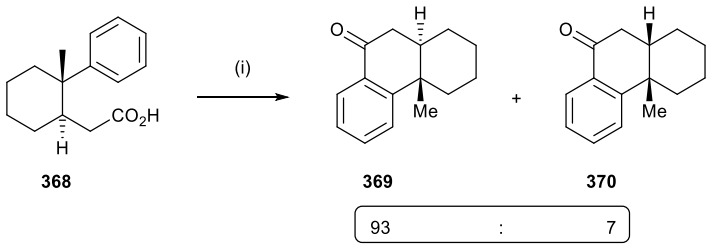
Scheme 93: Preparation of tetrazole **359**. *Reagents and conditions*: (i) CH_2N_2/Et_2O; (ii); TBAF/THF, 61% (iii) K_2CO_3, 5-chloro-1phenyl-1H-tetrazole (2 equiv.)/DMF, r.t., 70%.

Moreover, hydrogenolysis of tetrazole **364** (H_2, Pd/C in EtOAc) and filtration of the partially deketalized product through neutral alumina gives keto ester **365** in 86% yield. The keto group in **365** is reductively removed with a Mozingo reaction by conversion to thioketal **366** (3 equiv. propane-1,3-dithiol and 0.3 equiv BF_3-Et_2O in methylene chloride solution) and desulfurization of **366** (excess Raney nickel in refluxing EtOH: THF solution) to give **367** in 83% overall yield; saponification of **362** (KOH in methanol) gives carboxylic acid **368** (88%) as shown in Scheme 94.



Scheme 94: preparation of carboxylic acid; *Reagents and conditions*: (i) H_2, Pd/C, EtOAc; (ii) $HSCH_2CH_2CH_2SH$ (3 equiv.), BF_3-Et_2O (0.3 equiv.)/ CH_2Cl_2; (iii) excess Raney Ni in refluxing EtOH: THF, 83%; (iv) KOH/MeOH, 88%.

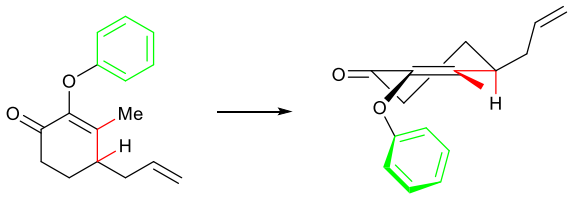
Cyclodehydration of **368** with polyphosphoric acid at 80 ºC for 2 hours and subsequent silica gel chromatography gave a mixture of two tricyclic ketone in 76% isolation yield. The *trans*-fused 9-keto octahydrophenanthrene **369** (93%) is the major product, while the minor product is the corresponding *cis*-isomer **370** (7%), thus confirming the relative stereochemistry of **356** (Scheme 95).[110]



Scheme 95: Synthesis of a mixture of two tricyclic ketone. *Reagents and conditions*: (i) $HO[PO_2OH]_nH$, 80 ºC, 2 h.

Furthermore, the factors governing the stereoselectivity of heteroatom directed photoarylation include the character of the transition state involved in the process of the electrocyclization.

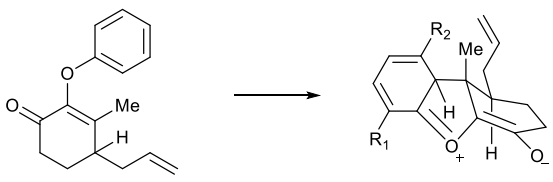
The transition state for the electrocyclization that resembles the geometry of the aryloxyenone **353** would probably be subject to steric approach control. Thus, if **371** is assumed to be a representation of the excited state of **353**, with the allyl group being pseudo-equatorial, then for the transition state, the phenyl group would approach C(3) from the least sterically hindered face of the C(2)-C(3) double bond, *trans* to the allyl group (Figure 26).



353 **371**

Figure 26: A model of the transition state for the electrocyclization of the excited state of **353**.

This transition state for the ylide formation leads to the conclusion that the predominant dihydrofuran resulting from ylide rearrangement ought to be that observed for **353**, with the allyl group *trans* to the phenyl group. Considering $A^{(1,2)}$ strain between the methyl and allyl group of **353** a pseudoaxial C(4) allyl group is probable and this would make an even more convincing argument for the approach of the aryl group to the C(2)- C(3) double bond, *trans* to the allyl group. Consideration of a late stage transition state for the electrocyclization of **353**, wherein the intermediate ylide closely resembles its structure (Hammond postulate) *e.g.* **372**, the potential for serious steric interaction between the C(4) allyl substituent and a group R_2 on the aromatic ring is apparent. This model (**372**) (Figure 27)for the transition state geometry has been reported to be less attractive than steric approach control.[93]

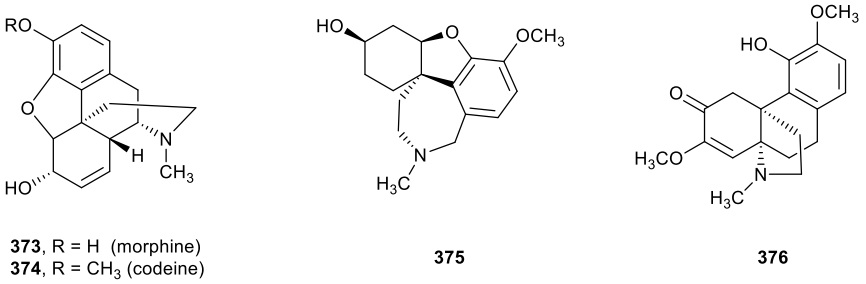


353 **372**

Figure 27: A model of a late-stage transition state for the electrocyclization of the excited state of the ylide represented by the carbonyl delocalized structure **372**.

1.17 Natural Product Synthesis Utilising heteroatom directed photoarylation

The total synthesis of natural products is frequently aimed at a deeper understanding of the synthesis of particular secondary metabolite frameworks, and the development of fundamentally new synthetic methods.[112] The synthetic potential of heteroatom directed photoarylation with aryl vinyl sulfides provides an efficient and experimentally accessible route for the formation of aryl annelated dihydrothiophenes. Schultz and co-workers extended this method to incorporate the heteroatom oxygen which has the potential for synthesis of a variety of medicinally important natural product compounds.[95a] Certainly, both the stereochemical and regiochemical control are good features of these photoarylation reactions. When not required in the final product, there is also the prospect of reductive removal of sulfur with Raney Ni.[99] Heteroatom directed photoarylation with aryl vinyl ethers provides a conceptually unique pathway to the synthesis of the alkaloids morphine **373**, codeine **374**, the galanthamine-type alkaloids such as lycoramine **375**, and hasubanan-type alkaloids such as cepharamine **376**, as shown in Figure 28.



373, R = H (morphine)
374, R = CH_3 (codeine)

375

376

Figure 28 Synthetic targets (**373-376**) for heteroatom directed photoarylation methodology.

1.17.1 Natural Product Syntheses

1.17.1.1 Synthesis of a tetracyclic precursor of morphine structural analogues by photocyclization-rearrangement

Detailed studies have been reported on the pharmacology and chemistry of the naturally occurring compounds morphine and related opium alkaloids, though very little is known about the photochemistry of this important class of secondary metabolites.[113] Gates and Tschudi 1955, reported the first total synthesis of morphine **373** and its structural analogue codeine **374**.[114] This landmark in organic chemistry was facilitated by the confirmation of the structure of morphine **373** by Robinson.[95c] Several approaches towards the total synthesis of these opium-derived compounds have been employed, but a common precursor in all of these has been the dihydrothebaine **381**, as shown in Figure 29.

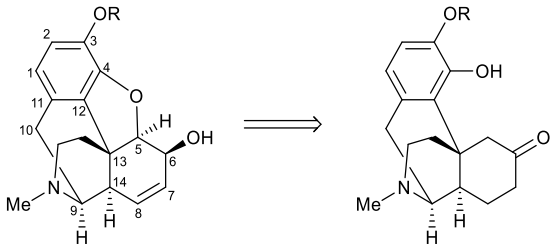
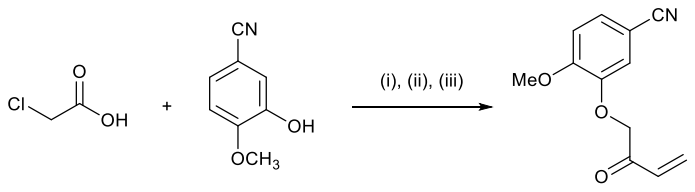


Figure 29: A common precursor dihydrothebaine **381** for the total synthesis of opium-derived compounds.

The key step in this approach involves the photolysis of the precursor **345** to afford a tetracyclic intermediate **347** with functionality necessary for formation of the remaining carbon-carbon bond in the morphine alkaloids. The successful approach toward the synthesis of morphine ring system evolved from the highly convergent route to aryloxyenone **345**. Starting from the reaction of chloroacetic acid **377** with 3-hydroxy-4-methoxybenzonitrile **378** (Scheme 96) in aqueous NaOH solution gave, after acidification, an aryloxyacetic acid. Remarkably, following lithium salt formation (Li_2CO_3 (1 equiv.) in H_2O) and drying, treatment with vinylmagnesium

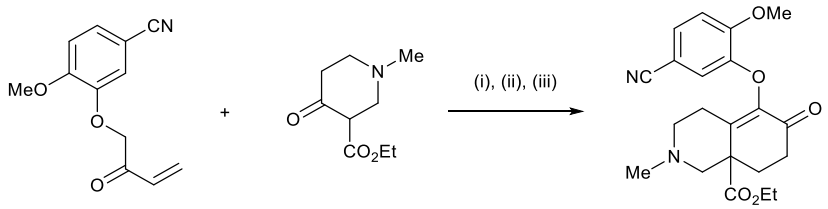
bromide (1.5 equiv.) in dimethoxyethane-tetrahydrofuran solution at room temperature gave the annelation reagent **379**. Usually, Grignard reagents react sluggishly with carboxylate salts; however, in this case an 80% yield was obtained. Presumably, the stability of the tetrahedral intermediate prevents formation and thence over-reaction of the product ketone before the acidic quench is added to the reaction.



377 **378** **379**

Scheme 96: preparation of aryloxy methyl vinyl ketone **374**. *Reagents and conditions*: (i) $NaOH_{(aq)}$; (ii) Li_2CO_3/H_2O; (iii) $CH_2CHMgBr$, DME-THF, r.t.

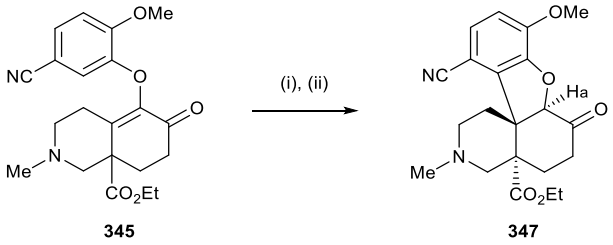
Furthermore, addition of annelation reagent **379** to a solution of the piperidone **380** (1 equiv.), followed by KOH in methanol-benzene gave the expected conjugate addition/aldol reaction. The Robinson annelation was completed by treatment of the aldol with pyrrolidine in refluxing benzene solution followed by warming with aqueous sodium acetate in acetic acid to give morphine precursor aryloxenone **345** in 40% isolated yield as shown in Scheme 97.



379 **380** **345**

Scheme 97: Synthesis of morphine precursor aryloxyenone **345**. *Reagents and conditions*: (i) KOH/MeOH-PhH; (ii) $(CH_2)_4NH$/PhH; (iii) $NaCO_2CH_3$/AcOH.

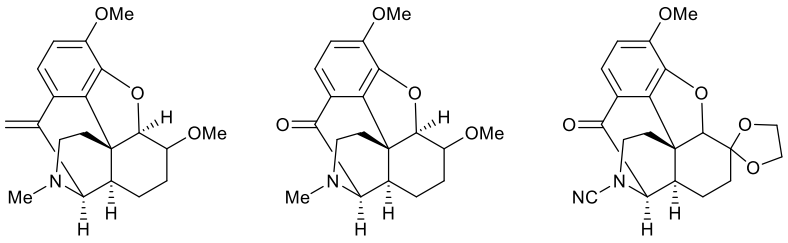
Ring-fused aryloxy enones such as **345** provide an interesting test of stereoselectivity in the photochemical bond forming step as shown in Scheme 88. Thus, Pyrex-filtered photolysis of **345** in 0.05 M degassed benzene solution gave the *trans*-fused dihydrofuran **347** in >90% yield (Scheme 98).



345 **347**

Scheme 98: Synthesis of tetracyclic morphine precursor **347**. *Reagents and conditions*: (i) hν; (ii) PhH, 90% yield.

In 1978, Schultz and Lucci reported a different approach towards the synthesis of morphine-like structures, whilst retaining key photo-electrocyclisations analogous to **345** to **347**.[115,116] Ultimately, these studies resulted in preparation of the *trans*-morphine ring systems **381**, **382** and **383** respectively as shown in Figure 30.



381 **382** **383**

Figure 30: *Trans*-morphine ring systems **381**, **382** and **383**.

Schultz and co-workers began the preparation of photocyclization precursors by reaction of the appropriate substituted phenol with epoxy ketones or by annelation of 4-oxopiperidines with aryloxy methyl vinyl ketones.

1.17.1.2 Schultz approach towards the synthesis of morphine structure using the octahydroisoquinoline photoannelation route

Following their preliminary study involving the photocyclization reaction of **345** to afford **347** (Scheme 88) in 90% isolated yield, Schultz and co-workers developed their approach to the morphine ring system through further study of the photoannelation route but aiming towards octahydroisoquinonoline substrates. From the point of view of the present thesis, it is the contrast in methods for establishing the substrates for, and the key photochemical reaction itself that is of greatest interest.

At outset of these studies, Schultz envisioned two conceptually different strategies for the construction of the remaining morphine skeleton ring. In one approach, conversion of **347** or a related substance to a stabilized anion **384** might result in an intramolecular 1,6-Michael addition reaction. Alternatively, a stabilized carbocation **385** might undergo an intramolecular aromatic ring alkylation or acylation reaction. Schultz noted that with regards to the development of precursor **384**, the weakly basic nitrogen atom in **347** was incompatible with the desired reactions of other functional groups as shown in Figure 31.

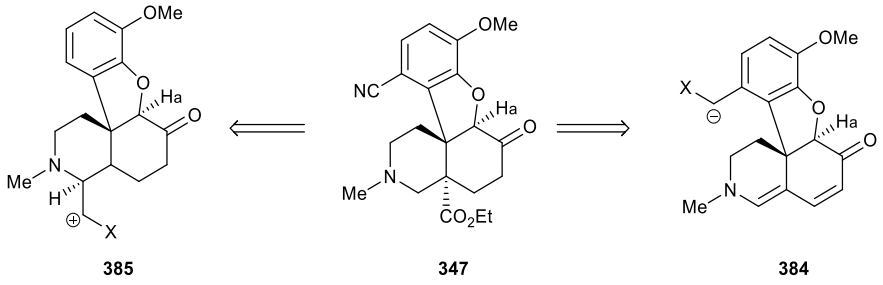
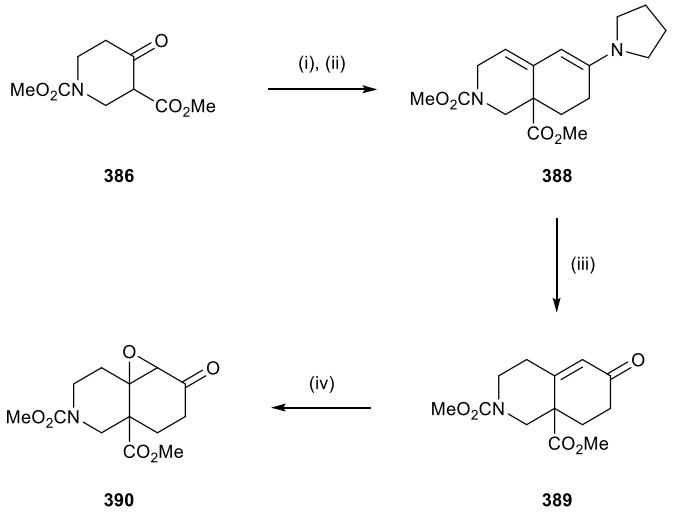


Figure 31: Construction of the remaining morphine skeleton ring by conversion of **347** to a stabilized anion **384** or a stabilized carbocation **385**.

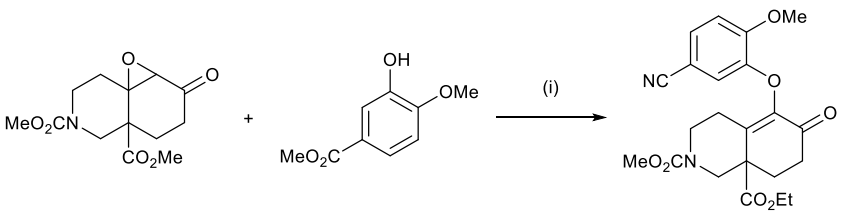
However, addition of 1,3-dicarbomethoxy-4-oxopiperidine **386** to methyl vinyl ketone **387** in benzene solution containing a catalytic amount of NaH, then followed by cyclization-dehydration of the intermediate diketone with pyrrolidine in refluxing benzene, afforded

dienamine **388**. Subsequent hydrolysis of **388** gave the enone **389** in 75% overall yield from **386**. Epoxidation of **389** with basic hydrogen peroxide in methanol afforded crystalline epoxyketone **390** in 70% yield, as shown in Scheme 99.



Scheme 99: Synthesis of epoxyketone **390**. *Reagents and conditions*: (i) **387**, then PhH, cat. NaH; (ii) pyrrolidine, reflux/PhH; (iii) hydrolysis; (iv) H_2O_2/NaOH, MeOH, 75% yield.

Reaction of epoxy ketone **390** (Scheme 100) with 2-methoxy-5-carbomethoxyphenol **391** in THF solution containing KH (~0.15 equiv.) and 18-crown-6 (~0.15 equiv.) gave the photo-precursor, aryloxyenone **391**, in 90% yield (47% overall from **353**). This experiment demonstrates the high efficiency and substituent compatibility of the epoxyketone route to the aryloxyenones.



390 391 392

Scheme 100: Synthesis of photoadduct precursor aryloxyenone **392**. *Reagents and conditions*: (i) THF, cat.KH, cat. 18-crown-6, 90% yield (45% overall yield from **386**).

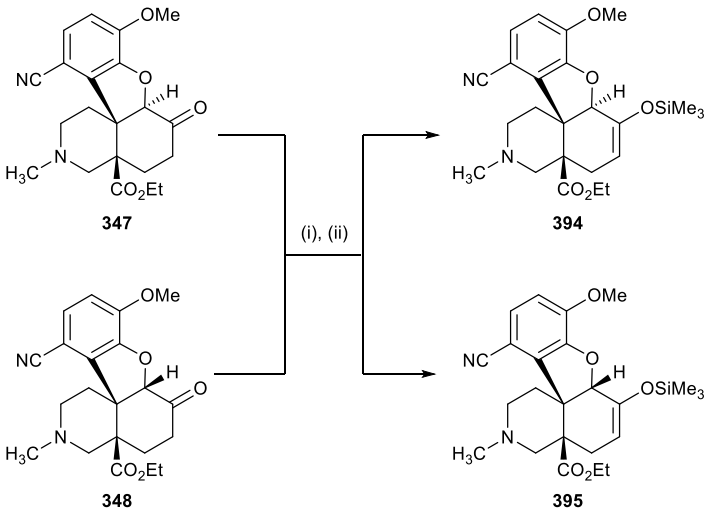
Photolysis of **392** in the aprotic solvent benzene results in isolation of the highly strained *trans*-fused dihydrofuran **393** in >90% yield as shown in Scheme 101. Schultz reported that aryloxyenone photocyclizations were performed on a 100g scale using a 2000 mL Pyrex photoreaction flask. When the photosubstrates are reasonably pure, photolysis with a 450 W mercury arc lamp requires 24 hours for complete conversion of starting material to product. The photoadducts may possess significant photoreactivity, so it is important to monitor the photoreactions with great care.[117]

392 393

Scheme 101: synthesis of tetracyclic precursor of morphine **393**. *Reagents and conditions*: (i) hν (a 450 W mercury arc lamp); (ii) PhH, 24 h, >90% yield of **393**.

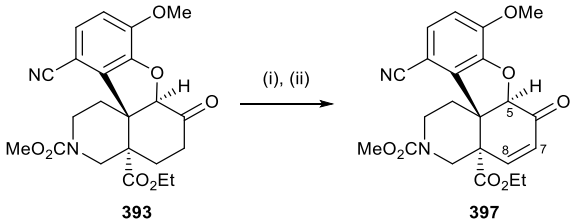
Furthermore, introduction of unsaturation necessary for the construction of the remaining ring in the morphine ring skeleton began by treatment of *cis*-ketone **347** with lithium diisopropylamide[118] in THF at -78 °C followed by addition of chlorotrimethylsilane to give

silyl enol ether **394** in 64% yield. Similarly, the strained *trans*-dihydrofuran **348** gives silyl enol ether **395** in 93% yield (Scheme 102).[119]



Scheme 102: preparation of silyl enol ethers **394** and **395**. *Reagents and conditions*: (i) LDA, THF, -78 °C (ii) TMSCl, 64% yield of **394** and 93% yield of **395** respectively.

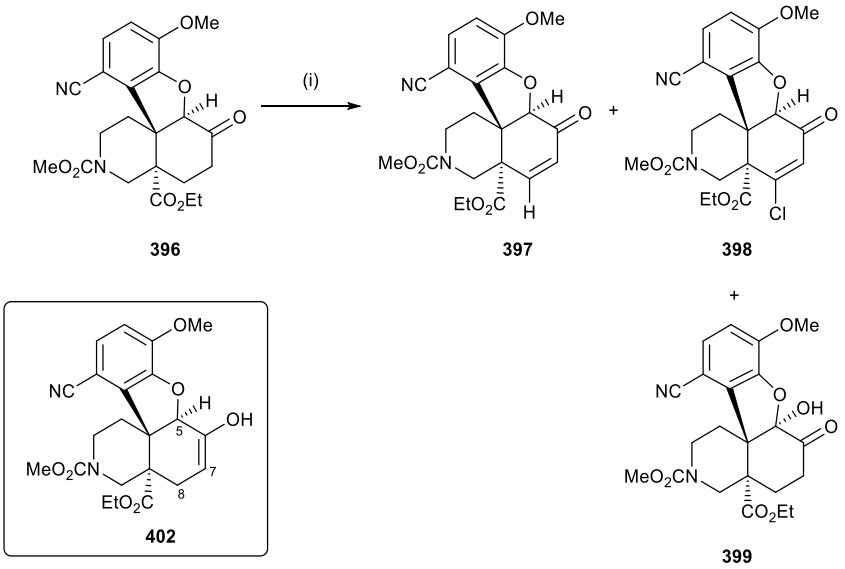
However, reaction of **394** and **395** with phenylselenenyl chloride and concentrated HCl in ethyl acetate or bromine in acetic acid resulted in apparent introduction of the heteroatom at C(5). There was not any reported case of Ketone **347** reacting with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing dioxane. Upon treatment of **393** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing dioxane enone **397** is formed in ~60% yield (Scheme 103).[120,121]



Scheme 103: Preparation of β-keto ester **397**. *Reagents and conditions*: (i) DDQ; (ii) then reflux in dioxane, 60% yield of **397**.

In 1967, Walker and Hiebert reported that acid catalyzed DDQ could be used as an oxidant for the dehydrogenation of alcohols, phenols and steroidal ketones.[121] Therefore, treatment of **396**

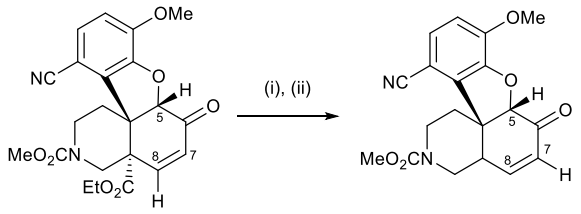
with DDQ in dioxane saturated with dry HCl, afforded enone **397** (50%), chloroenone **398** (27%) and diketone hemiketal **399** (23%) yield respectively (Scheme 104).[121]



Scheme 104: Walker and Hiebert dehydrogenation of **390**. *Reagents and conditions*: (i) DDQ, 1,4-dioxane/dry HCl.

Formation of the products **397**, **398** and **399** were best explained by hydride abstraction from enol **402** at either C-5 or C-8, generating an allylic cation or the protonated enone of **397**, respectively.[121] Conjugate addition of chloride ion to the later, followed by a further hydride extraction at C-8 would give β-chloroketone **398**. In the former case, quenching of the allylic cation at C-5 with water directly, or via a chloride adduct would give **399**. Enone **397** also might be generated by abstraction of a C-8 proton from the allylic carbocation. The optimum yield of enone **397** (70-75%) was obtained by using a saturated solution of dry HCl in dioxane as reaction solvent.

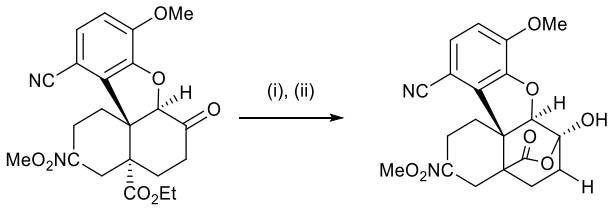
Decarboxylation of the vinylogous β-keto ester **397** to afford enone **400** was achieved by treatment of **396** with basic alumina in refluxing aqueous dioxane in 26% yield (Scheme 105). The low, variable yield encountered necessitated the development of an alternative way of preparation of **400**.[122,123]



397 400

Scheme 105: Preparation of enone **400**. *Reagents and conditions*: (i) basic Al_2O_3, 1,4-dioxane; (ii) then reflux, 26% yield of **400**.

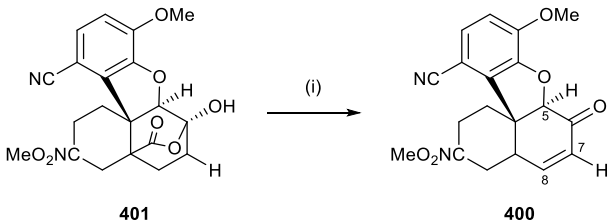
Thus, treatment of **393** with 1 M NaOMe or KOH at room temperature results in quantitative conversion to pseudo acid **401** in less than 30 minutes (Scheme 106). The hydrolysis is believed to occur by participation of the neighbouring C(6) carbonyl group.[124] Saponification of the hindered angular ester group in **393** is accomplished with remarkable facility.



392 401

Scheme 106: Preparation of enone **394**. *Reagents and conditions*: (i) 1 M NaOMe; (ii) r.t., 30min.

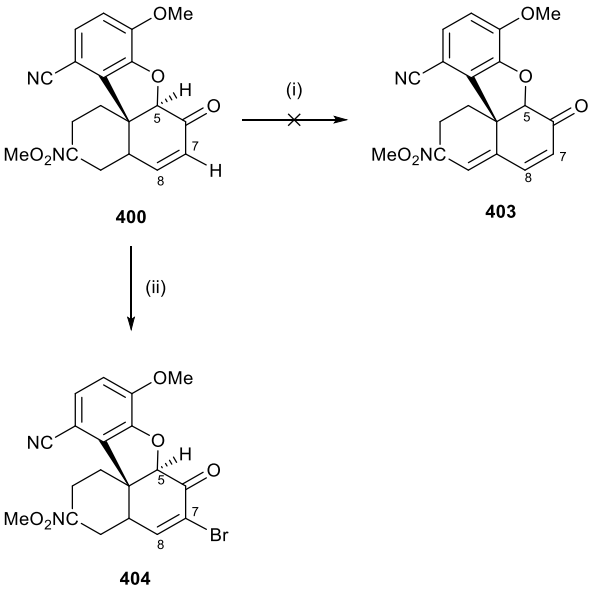
Treatment of **401** with DDQ in dry dioxane solution, saturated with HCl, provides enone **400** in 60% overall yield from photoadduct **393** (Scheme 107).[125]



401 400

Scheme 107: Preparation of enone **400**. *Reagents and conditions*: (i) $(CH_2)_4O_2$/dry HCl, 60% yield.

Upon bromination of **400**, which was hoped would afford a 7-bromo-β,γ-unsaturated ketone from which dienone **403** might be obtained by 1,4-elimination of HBr, 7-bromoenone **404** was obtained in 94% isolated yield.[95c]



Scheme 108: Preparation of 7-bromoenone **404**. *Reagents and conditions*: (i) Br_2, no conversion of **400** to **403** (ii) Br_2, 94% yield **404**.

1.17.1.3 Schultz photochemical approach towards the synthesis of the B/C trans-fused morphine structure

Schultz envisioned that the remaining part of morphine ring can be constructed from **405** by addition of cyanide ion to an immonium ion to afford **406** followed by intramolecular aromatic ring acylation in **406** (Figure 29). Alternatively, the synthesis of morphine might be achieved by conversion of the nitrile group in **407** into a suitable one carbon nucleophilic attachment at C-11 and then cyclization of *pro*-morphine C-10 with a C-9 immonium ion. The enamine function in **405** was to be established by reduction of a lactam precursor as shown in Figure 32.[95c]

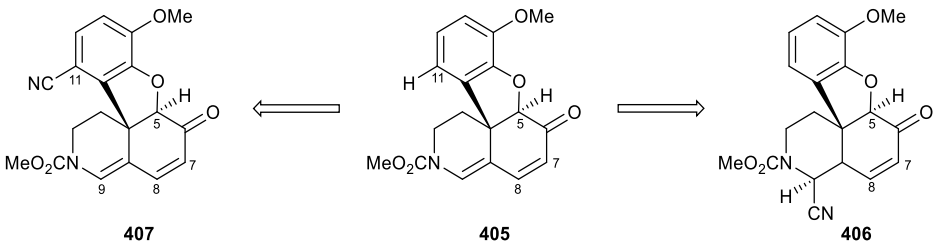
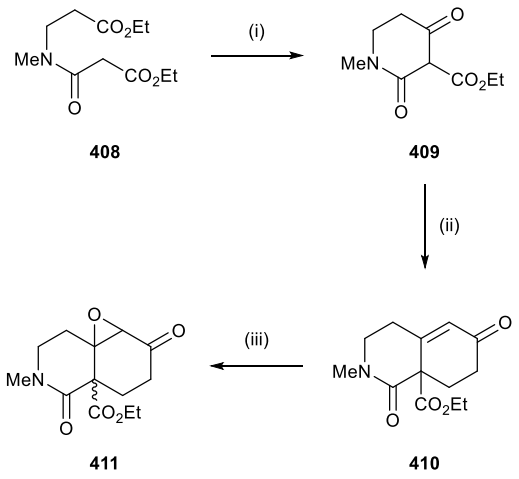


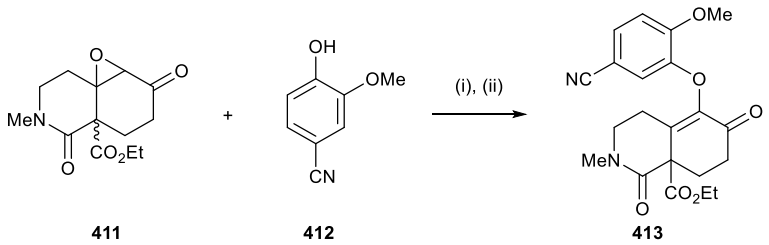
Figure 32: Construction of the remaining morphine skeleton ring by conversion of **405** to afford **406** or **407**.

Again, the required lactam precursor was prepared using the epoxyketone route, in this case **411** is the key reaction partner (Scheme 109). Thus, Dieckmann condensation of **408** with sodium hydride in benzene-ethanol gives β-ketoester[126] **409** in 80% yield, followed by annelation of crude **409** with methyl vinyl ketone (MVK) to afford enone **410** in 48% yield. Epoxidation of **410** using basic hydrogen peroxide gives epoxy ketone **411** as a mixture of diastereoisomers in 68-78% yield.[115]



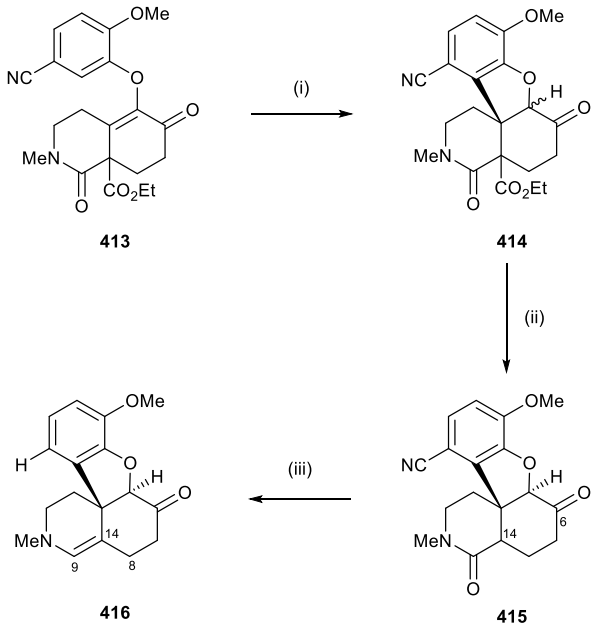
Scheme 109: Preparation of key intermediate epoxy ketone **411**. *Reagents and conditions*: (i) NaH/PhH-EtOH; (ii) MVK; (iii) H_2O_2/NaOH, MeOH, 68-78% yield.

Reaction of epoxy ketone **411** and 5-cyano-2-methoxyphenol **412** gives the key substrate for irradiation **413** (Scheme 110).[115]



Scheme 110: Synthesis of key substrate for irradiation aryloxyenone **413**. *Reagents and conditions*: (i) Reflux/THF; (ii) KH (~0.15 equiv.), 18-crown-6 (~0.15 equiv.).

Photolysis of aryloxyenone **413** in dichloromethane-dimethylsulfoxide solution affords a mixture of epimeric benzodihydrofurans **414**, which upon epimerization gives a crystalline compound **415** in 80% isolated yield (Scheme 111). Then, conversion of photoadduct **415** to enamine **416** requires decarbomethoxylation at C-14 and reductive elimination to produce the enamine alkene between C-9 and C-14.[92]

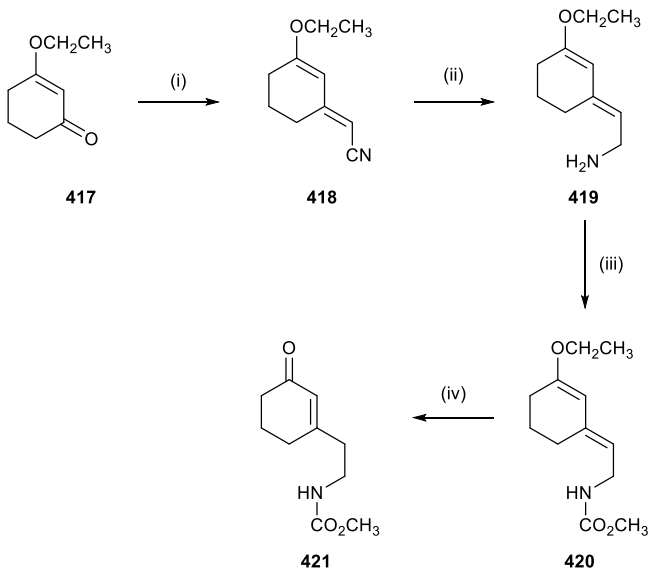


Scheme 111: Photolysis of aryloxyenone **413**. *Reagents and conditions*: (i) hν, DMSO-DCM, (ii) 1M NaOMe, rt, 30min., then excess KOH, reflux in MeOH, 48 hours; (iii) H_2 Pd/C.

1.17.2 Synthesis of the galanthamine-type alkaloid lycoramine

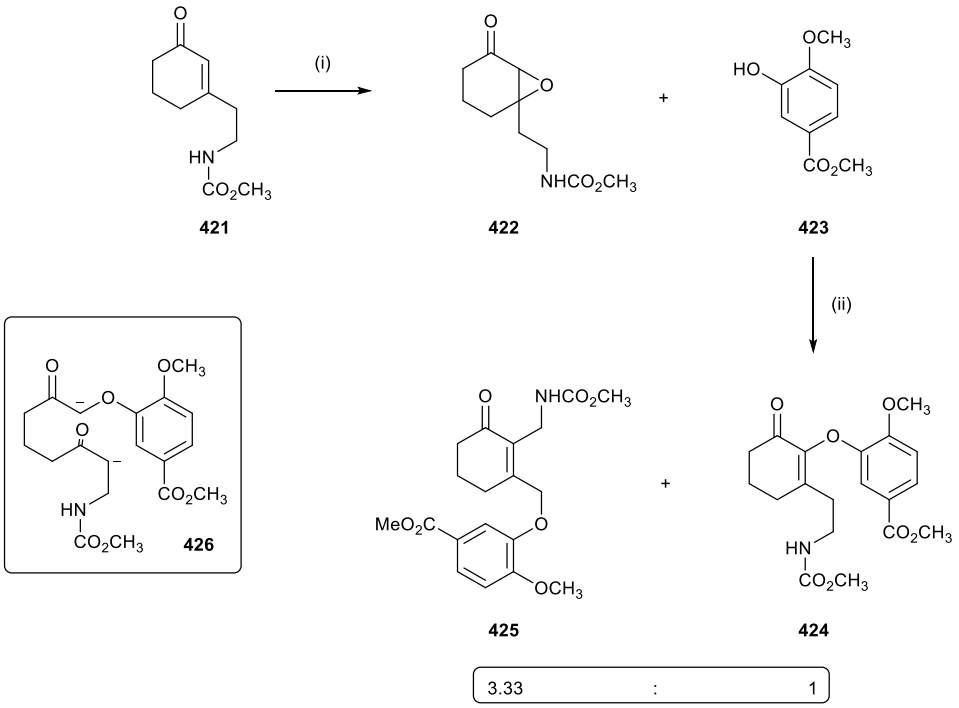
In 1977, Schultz and co-workers reported total synthesis of the galanthamine-type *Amaryllidaceae* alkaloids lycoramine **370** which represented their first remarkable achievement towards application of heteroatom directed photoarylation to natural product synthesis.[86] It presents another example of the success of the epoxyketone coupling approach to preparing the photoarylation substrates. The methodology developed by Schultz and co-workers for 1,2-carbonyl transposition significantly enhances the flexibility of using heteroatom directed photoarylation for the construction of 4-oxo and 3-oxo-hexahydrobenzofurans related to **431** and **436** respectively.[95b]

The key pathway for the synthesis of lycoramine **370** involved conversion of epoxyketone **422** to aryloxyenone precursor **424**. Under Horner conditions, reaction of the enol ethyl ether **417** with the sodium salt of diethyl cyanomethylphosphonate in refluxing THF solution affords the vinyl nitrile **418** as a mixture of two double bond isomers (60:40) in 98% yield (Scheme 112).[127] Without separation of isomers, **418** was converted to enone **421** by successive reduction with lithium aluminium hydride in ether to afford **419**, then reaction with methyl chloroformate in benzene-aqueous sodium bicarbonate to give urethane **420**, which upon hydrolysis with 10% H_2SO_4 in MeOH-THF solution at room temperature affords **421** in 76% overall yield from **417** as shown in Scheme 112.



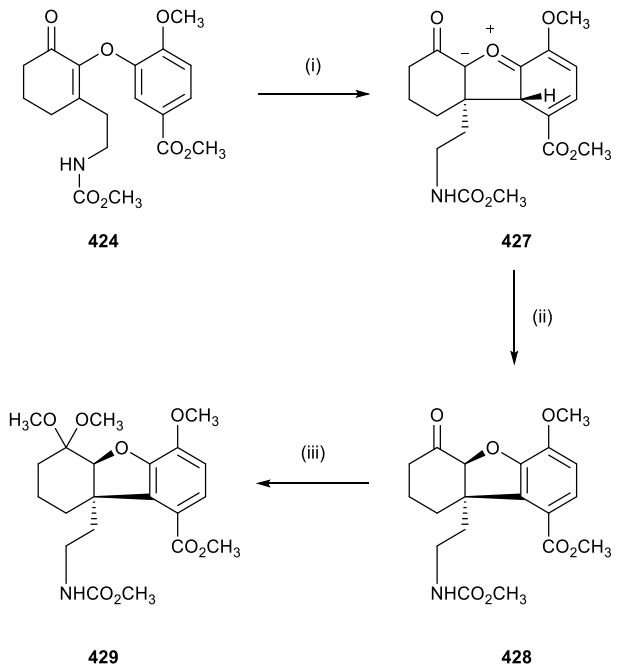
Scheme 112: Preparation enone **421**. *Reagents and conditions*: (i) sodium salt of diethyl cyanomethylphosphonate, reflux-THF; (ii) $LiAlH_4/Et_2O$; (iii) methyl chloroformate/PhH - aq. $NaHCO_3$; (iv) 10% H_2SO_4/MeOH-THF, 76% yield.

The next step involved epoxidation of **421** with alkaline hydrogen peroxide in aqueous methanol solution at room temperature to give epoxyketone **422** in 70% yield (Scheme 113). After reaction of 5-carbomethoxy-2-methoxyphenol[128] with one equivalent potassium hydride in 18-crown-6 (one equivalent)-THF solution, one equivalent epoxyketone **422** was added and heating to reflux for 8 hours gave aryloxyenone **424** in 50% isolated yield and isomeric enone **425** in 15% yield. Formation of the two products **424** and **425** can best be explained by consideration of an intermediate diketone enolate **426** in which cyclization-dehydration may occur to afforded either **424** or **425** as shown in Scheme 113. This indicates a potential weakness in this approach to the photoarylation precursors.



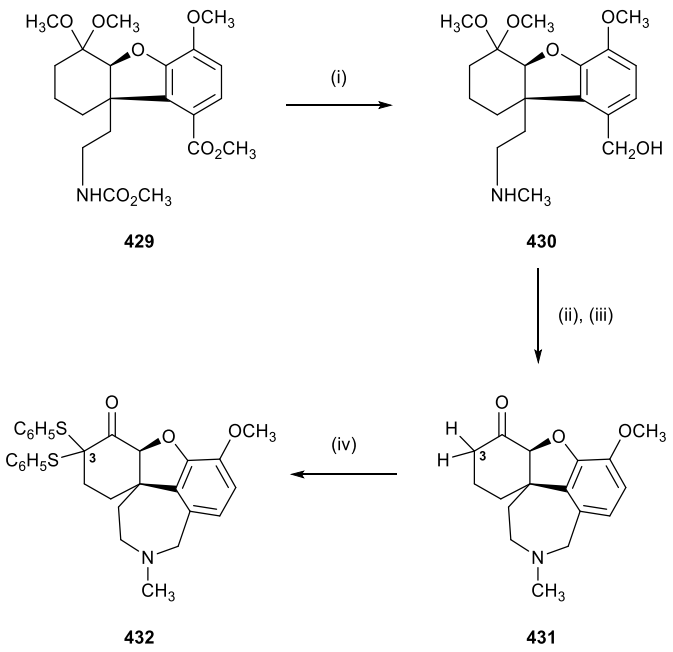
Scheme 113: Synthesis of aryloxy enone **424**. *Reagents and conditions*: (i) H_2O_2/NaOH, MeOH, r.t. 70% yield; (ii) KH (1.0 equiv.), $(C_2H_4O)_6$ (1.0 equiv.), Reflux, 8 h, **424** in 50% isolated yield and isomeric enone **425** in 15% yield.

Furthermore, the key photocyclization of **424** to give **428** establishes the crucial carbon-carbon bond joining an aromatic ring to a quaternary carbon atom located at a ring junction. Thus, Pyrex-filtered photolysis of 0.05 M aryloxyenone **424** (Scheme 114) in benzene-methanol (1:1) under an argon atmosphere for 1.5 hours affords the *cis*-fused dihydrofuran **445**. Conversion of **424** to **428** occurred by conrotatory cyclization of **424** to give an intermediate carbonyl ylide **427**, from which protonation-deprotonation in methanol gives the *cis*-fused dihydrofuran **428**. Ketalization of **428** with methanol-trimethyl orthoformate-sulfuric acid gave a crystalline compound **429** in 86% overall yield from **424** as shown in Scheme 114.



Scheme 114: Synthesis of ketal **429**. *Reagents and conditions*: (i) hν, PhH-MeOH (1:1), Ar-atm., 1.5 h; (ii) $+H^+/-H^+$ in MeOH; (iii) MeOH-$CH_3C(OCH_3)_3$, H_2SO_4.

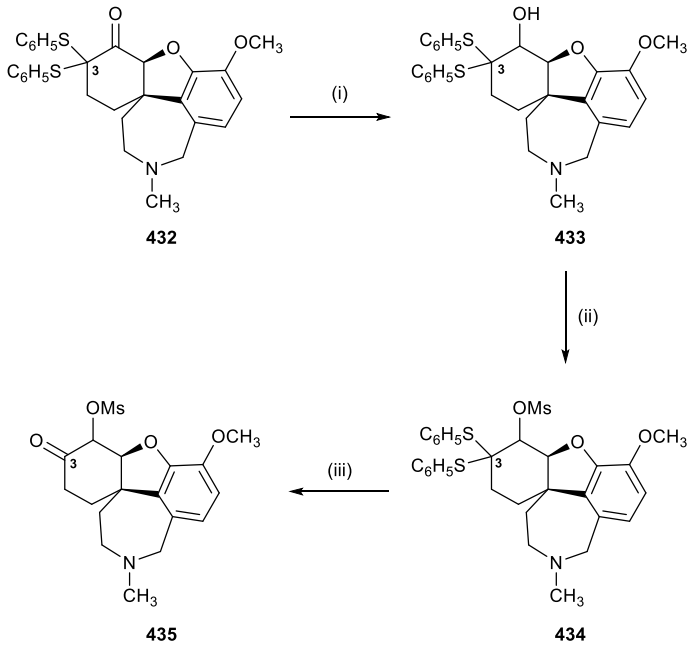
The azacycloheptane ring in lycoramine could be established upon reduction of ester **429** with lithium aluminium hydride to give amino alcohol **430** in 99% yield. Cyclization of **430** with two equivalents of thionyl chloride-triethylamine in chloroform solution at -20 °C and deketalization with 1 M sulfuric acid at room temperature gave aminoketone **431** (Scheme 115) in 76% yield. However, the 1,2-carbonyl transposition in **431** to afford lycoraminone **435** involved transformation of C-3 to the oxidation state of a ketone.[95b] Thus, generation of the lithium enolate of **431** with 2.1 equivalents of lithium tetramethylpiperidide in THF-hexamethylphosphoramide at -78 °C, followed by addition of 2.5 equivalent phenyl benzenethiosulfonate[129] in THF at 0 °C and subsequently warming to room temperature affords thioketal ketone **432**.



429 **430** **431** **432**

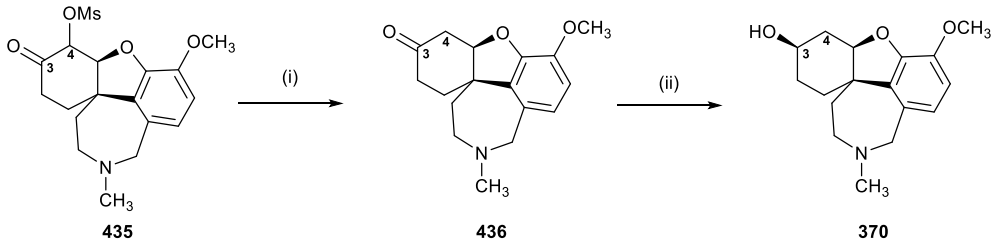
Scheme 115: Synthesis of thioketal ketone **432**. *Reagents and conditions*: (i) $LiAlH_4$; (ii) $SOCl_2/Et_3N$, $CHCl_3$, -20 °C; (iii) 1 M H_2SO_4, r.t., **431** in 76% yield; (iv) LTMP/THF-HMPA, -78 °C, $PhSSO_2Ph$/THF, 0 °C, then r.t.

Furthermore, reduction of **432** with lithium aluminium hydride in ether, at room temperature, affords alcohol **433**, which was further treated with methanesulfonyl chloride to be converted to mesylate **434** in 70% overall yield from **432**.[130] Thioketal hydrolysis in **434** was achieved with 2 equivalents of mercuric chloride-mercuric oxide in aqueous acetonitrile at 50 °C [131] to afforded keto mesylate **435** as shown in Scheme 116.



Scheme 116: Preparation of keto mesylate **435**. *Reagents and conditions*: (i) $LiAlH_4/Et_2O$, r.t.; (ii) MsCl, NEt_3, 70% yield; (iii) $HgCl_2$-HgO, aq-CH_3CN, 50 °C.

Completion of the synthesis involved treatment of **435** with chromium(II)chloride[132] in aqueous acetone to afford *dl*-lycoraminone **436** in 85% yield from **435.** The stereoselective reduction of **436** with lithium aluminium hydride in refluxing THF[133] affords *dl*-lycoramine **370**. TLC, ^{1}H-NMR, and mass spectra were reported to be identical with those of natural product lycoramine (Scheme 117).[134]



Scheme 117: Synthesis of *dl*-lycoramine **370**. *Reagents and conditions*: (i) $CrCl_2$, aq-$(CH_3)_2CO$, 85% yield; (ii) $LiAlH_4$, reflux-THF.

Overall, the synthetic studies discussed above establish that this class of photoarylation reaction can produce valuable and complex intermediates, in quantities sufficient to sustain a substantial synthetic undertaking. Two methods for the synthesis of the precursors to the key photoarylation were discussed and their merits considered.

1.18 Photochemistry

1.18.1 Photochemical transformations

Photochemistry has been employed as a powerful tool for the formation of complex compounds from simple starting materials in a single step. The feature of all light-promoted transformations involves electronically excited states which have been generated by absorption of photons. The reactivity of chemical compounds is altered significantly by the transient reactive intermediates formed.[135b] However, organic chemists are interested in the photochemical preparation of molecules. The most significant of all are the photochemical processes that capture the radiant energy of the sun; in particular, photosynthesis. Photochemistry involves the investigation of physical processes and chemical reactions which can occur in a molecule upon irradiation with UV light. Light waves are electromagnetic waves that are created by the oscillations of electrons within atoms. The electric and magnetic fields of such an electromagnetic wave contain energy. Experimental evidence (photoelectric effect, blackbody radiation) establishes that a light beam has particle properties, consisting of a stream of photons. Light of any wavelength is associated with an energy value given by equation 1.

$$E = h\nu \quad \ldots\ldots\ldots\ldots\ldots (1)$$

(where $\nu = c/\lambda$; E = energy of a photon; h = Planck constant (6.626×10^{-34} Js); ν = frequency (Hz); c = speed of light (2.998×10^{8} ms^{-1}); λ = wavelength (m).)

Equation 1: energy of a photon.

1.18.2 Electronic spectra and photophysical properties of benzene

The photochemistry of benzene has proven to be much more varied than its thermal chemistry. Whereas most of the thermal (electronic ground state) reactions produce aromatics products by substitution processes, the photoreactions generally afford non-aromatic products by either isomerization or photoaddition. An electron can be promoted from the ground-state energy level of a molecule (S_o) to an unoccupied orbital of higher energy if sufficient energy is supplied. Such an electronic transition can be illustrated for benzene (Figure 33). [37]

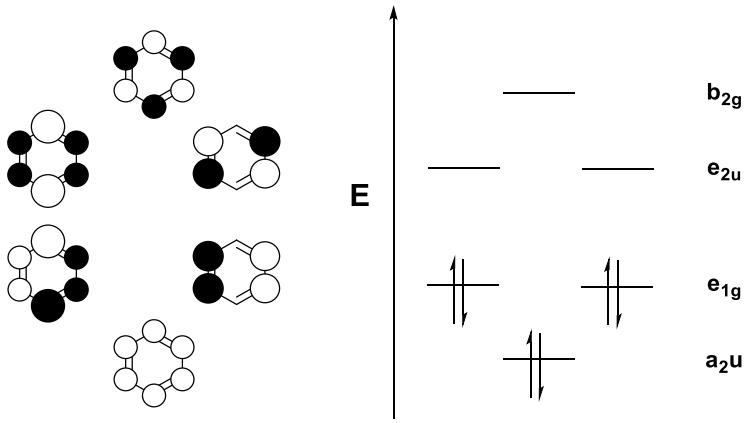


Figure 33: frontier molecular orbital diagram for benzene and their molecular symmetry.

However, the electronic configuration of the ground state and excited state benzene can be determined:

Ground state benzene: $a_{2u}^2e_{1g}^4$

Excited state benzene: $a_{2u}^2e_{1g}^3e_{2u}^1$

In this case, an electron has absorbed sufficient energy to be promoted into an antibonding π-orbital resulting in excited-state benzene. Other one electron excited-state configurations ($a_{2u}^2e_{1g}^3b_{2g}^1$ and $a_{2u}^2e_{1g}^4e_{2u}^1$) do not have proper symmetry and so are not allowed. Of the four possible states of excited-state benzene ($a_{2u}^2e_{1g}^3e_{2u}^1$), those being $^1B_{1u}$,$^1B_{2u}$ and $^1E_{1u}$ ($^1E_{1u}$ has two configurations), $^1B_{2u}$ is the lowest energy state.[27,31a]

The physical and chemical properties of atoms and molecules depend on the quantum behaviour of their electrons. These electrons pervade most of the atom and their arrangement in different orbitals determines the size of the atom, the ionisation energy and, perhaps most importantly, the chemical bonds the atom forms with other atoms. Excitations are rapid and, according to the Franck-Condon principle, the nuclear framework of the molecule remains constant so the transition may be thought of as a 'vertical transition' Figure 34.[135c]

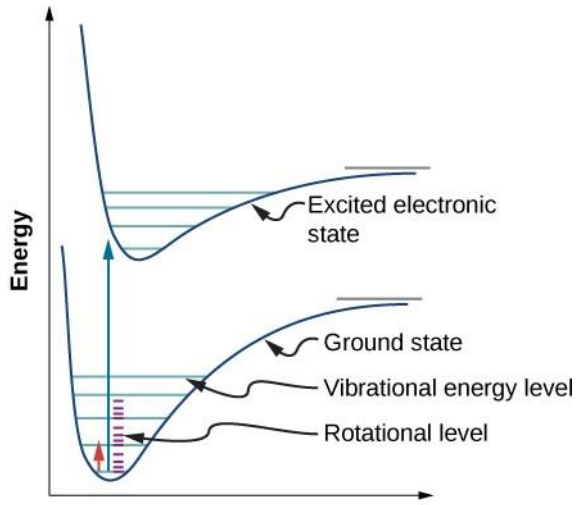


Figure 34: a diagram to illustrate vibronic transitions.

These transitions are governed by quantum mechanical selection rules in which a change in spin state is forbidden thus only allowing promotions from the molecule's ground-state (S_o) to S_1, S_2, …., depending on the amount of energy absorbed from each quanta. Due to the nuclei being so much more massive than the electrons an electronic transition takes place much faster than the nuclei can respond. As a result, the altered electron density exerts a new force on the molecule and causes it to vibrate. In solution, collisions with solvent molecules cause rapid vibrational energy loss (10^{-13} to 10^{-11}s) resulting in the relaxation of the internuclear geometry. According to the Franck-Condon principle, the most intense vibronic transition is from the ground vibrational state to the vibrational state lying vertically above it.[135c]

A molecule, photochemically promoted to an excited state, does not stay there for long. Excitations to S_2 and higher singlet states take place but in liquids and solids subsequent relaxation to the S_2 state in an 'energy cascade' occurs. Similarly, molecules at different vibrational levels S_1 cascade down to the lowest vibrational level of the S_o state and it is this state that can undergo various physical processes as explained by Kasha's rule. It must be noted that some chemical reactions occur from higher levels. A molecule in the S_1 state can cascade down to the ground-state through the vibrational levels of the S_o state via 'internal conversion'. They can undergo intersystem crossing to a T_1 (triplet) state without loss of energy and cascade down to its lowest vibrational level. Once in the T_1 state, a molecule can return to the S_1 state *via* thermally activated reverse intersystem crossing or by the release of light in the form of phosphorescence. A molecule in the S_1 state can also drop to some low vibrational level of the S_o state directly by releasing the energy all at once (10^{-9}s) in the form of fluorescence. Finally, a molecule in an excited state (S_1 or T_1) may transfer all its excess energy at once to another molecule in the environment in a process called 'photosensitization'. The excited molecule thus drops to S_o while the other molecule becomes excited. These transitions can be summarised in a modified Jablonski diagram as shown in Figure 35.[135d]

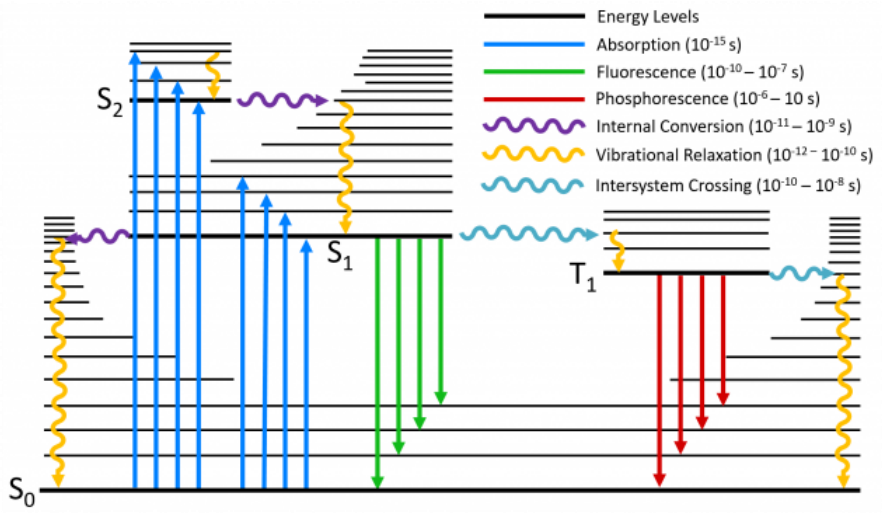


Figure 35: modified Jablonski diagram illustrating the excitation and emission processes.

1.18.3 Photochemistry of 6π-electron Heterocyclization reaction

The term photocyclization refers to light-induced unimolecular pericyclic ring-closure reactions. Conrotatory [6π] cyclization, which involves a change of π- and σ-bond positions within a conjugated system in a cyclic transition state, is an example of such a reaction. According to the Woodward-Hoffmann orbital symmetry rules,[135e] the 4n+2 π-electron system, in the excited state, reacts through a conrotatory pathway. Such a stereospecific process is, however, known to be in the opposite sense to that observed for reactions initiated thermally (disrotatory). These six-electron photocyclization reactions were judged to occur mostly on the singlet hypersurface and deliver stereochemically defined photo-adducts.[135f] The substrates employed for six-electron photocyclization determine the type of products to be produced and the majority of the reactions involve 1,3,5-trienes to produce carbocycles or enamides to generate heterocyclic photo-adducts. In cases such as **424** to **428**, an intermediate zwitterion **427** is formed as a result of conrotatory [6π] ring closure, which undergoes a suprafacial 1,4-H shift to afford the photo-adducts (Scheme 114).[135f] Flash photolysis studies of aryl vinyl thioethers and aryl vinyl ethers revealed that the ylide intermediates were formed following laser photolysis at λ=308 nm and the ylides possess a long-lived absorption bands in the region of 600-800 nm in benzene with a second weaker band at ~460 nm. However, in a solvent (methanol) which is known as a quencher of zwitterionic species, the lifetimes are significantly reduced. The decay kinetics measured within the long wavelength absorption envelope vary with wavelength, indicating the presence of more than one ylide species.[95d] The photocyclization of aryl vinyl ethers has been suggested to run in oxygen-free solutions since oxygen reacts with the intermediate zwitterions to yield by-products and it reduces the quantum yield by quenching the triplet states of the ethers and these reactions occur mostly from the singlet hypersurface.[95e] Visible light photo-redox catalysis or triplet energy transfer from an appropriate activated sensitizer has been found to afford efficient high yielding

photocyclization across a panoply of substrates. Quantum calculations strongly supported the view that these reactions proceed via conrotatory ring closure from the triplet excited state. Subsequent suprafacial 1,4-hydrogen shift and epimerization leads to the observed *cis*-fused products. The calculated energy required to promote cyclic 2-aryloxyketones and their substituted derivatives from singlet (S_o) to π-π* triplet (T_1) state is E_T = ~ 58 kcal/mol^{-1}. This matches with the emissive energy of the *fac*-Ir(dF-ppy)$_3$ catalyst E_T = ~ 60 kcal/mol^{-1} under irradiation with blue LEDs and in the presence of a base (KOAc) to afford a *cis*-fused dihydrobenzofuran in generally excellent yield and with near perfect diastereoselectivity as shown in Figure 36.[135g]

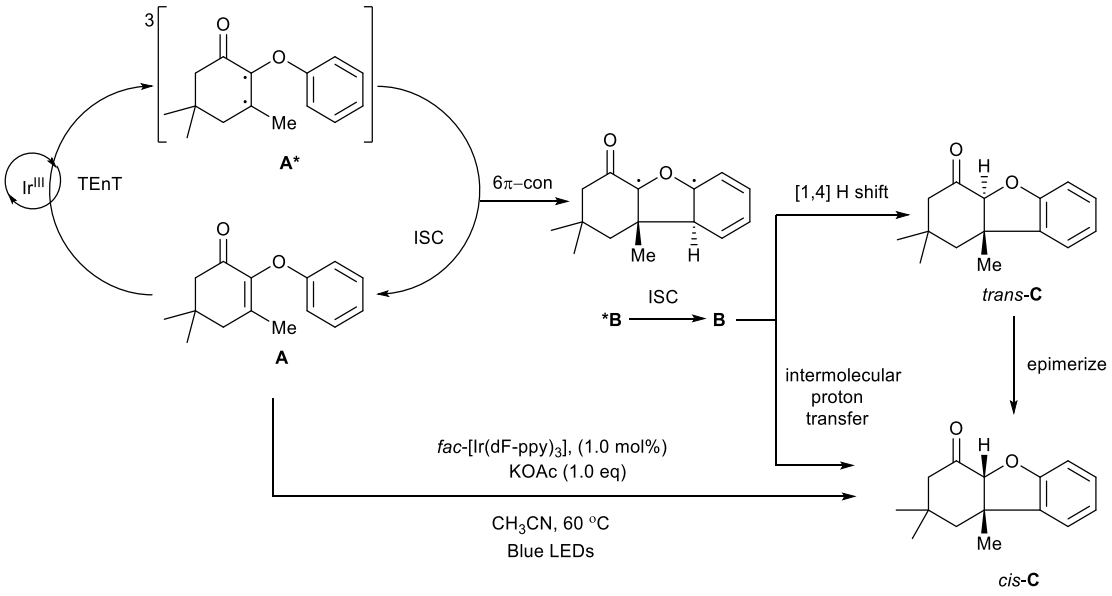


Figure 36: Application of Energy Transfer catalysis in a 6π electron heterocyclization.

Computational studies suggest that the reactions are initiated via Triplet Energy Transfer (TEnT) with the formation of triplet intermediates **A***, which, following conrotatory heterocyclization and intersystem crossing (ISC), afford open-shell singlet intermediates **B**. The singlet intermediates B then undergo a facile [1,4]-suprafacial H-shift to afford the *trans*-

cyclization products **C**, which rapidly epimerize to the more stable *cis*-isomers by reaction with KOAc as shown in Figure 33.[135h]

1.18.4 Frontier Orbital interaction of photoarylation reaction

The photoarylation of the aryl vinyl ether systems involves formation of a new σ-bond from two π-bonds, one from the aromatic ring system and the other one from enone the moiety. The six-electron photocyclization operates with the conservation of orbital symmetry. Thus, the sensitization and quenching experiments demonstrated that the photoarylation reaction may proceed *via* either a triplet or singlet excited sate. However, both theoretical arguments and experimental results suggested a general conrotatory cyclization mechanism (Figure 33). Flash photolysis studies support a possible triplet excited state of the aryl-vinyl system, leading to 6π electrocyclization, whereas the singlet excited state mechanism could not be totally ruled out (Figure 37).[95f]

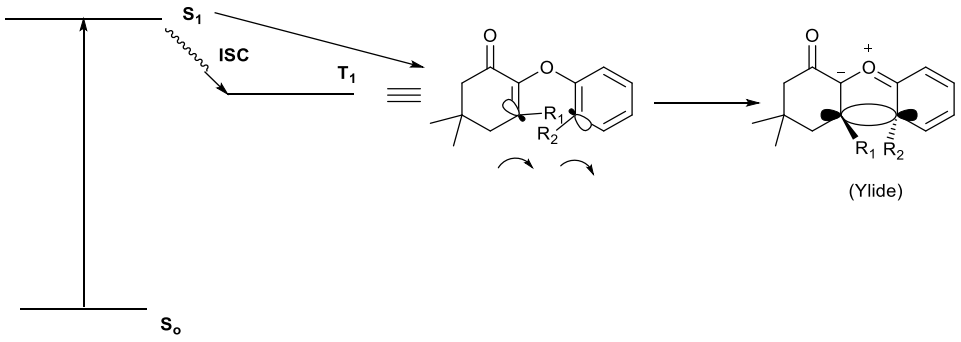


Figure 37: molecular orbital interactions for aryl vinyl ether systems.

Overall, photoarylation of heteroatom-linked aryl vinyl systems proceed via a photoexcited state which leads, by conrotatory ring closure, to ylide formation then re-aromatisation by [1,4]-sigmatropic shift or protonation and rearrangement. Provided there is no strong ground state interaction among the chromophores, it is likely that the energy absorbed by the aromatic system will stay localized in the ring.[95f, 95g]

1.19 Conclusions and prospects

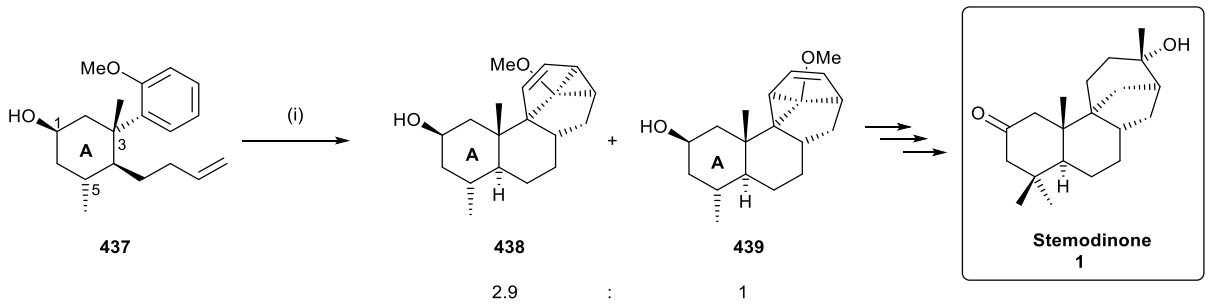
In conclusion, it has been seen how the total synthesis of α-cedrene set in train a series of studies which demonstrated the power of this strategic level *meta*-photocycloaddition reactions. Many examples of sophisticated and frequently brief synthetic routes to a range of diterpenoid secondary metabolites have been described. In particular, the capacity of these reactions to generate quaternary carbon centres was a noble feature. Much understanding of the factors governing the regio- and stereoselectivity issues associated with these reactions was determined on the course of fundamental mechanistic and theoretical studies. The synthetic work has capitalised and further advanced this knowledge. The general value of generating highly hindered quaternary carbons by the combination of sp^2 carbons via their π-faces was also noted in the context of the Schultz cyclization. In addition, the discipline of the target molecule synthesis has greatly enhanced our understanding of how to manipulate the Schultz cyclization with both Sulfur and Oxygen linking atoms. The potential value of flow photochemistry methods as compared to batch photolysis is an opportunity not fully exploited. It is hoped that the work contained herein will contribute significantly to the advancement of the use of the Schultz photo-electrocyclization towards the Synthesis of the Stemodinone and its analogous compounds.

Chapter 2. Results and Discussion

For the total synthesis of a complex molecule to be accomplished, there are often several different routes that can be taken in order to achieve the same outcome. Synthetic decisions can be made based upon the considerations of yield, ease of synthesis, reagents required and economic reasons to name but a few.[134b] The relative attributes of each synthetic route are subjective. It is often a delicate equilibrium between factors that defines a plausible synthetic route towards a target molecule. In this way, synthetic methodology can be just as important as syntheses of novel organic compounds. This kind of optimization is essential for larger-scale production of a drug in industry. Frequently, it can be the pure challenge of utilizing a novel reaction step within a synthesis that acts as motivation for the synthetic organic chemist.[134b]

2.0 Insertion of the A-ring *gem*-dimethyl group

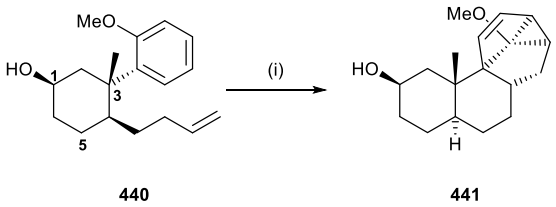
Past work in our group by Boyd established the stereochemical evidence which strongly suggested that the initial target structure of stemodinone **1** could be achieved by an intramolecular alkene-arene *meta*-photocycloaddition of 4-carbon tether substrate **437** to afford **438** & **439** (Scheme 118).[134a]



Scheme 118: *meta*-photocycloaddition of 4-carbon tether substrate **437** and the similarity between cycloadducts **438** and **493** and stemodinone **1**. *Reagent and conditions*: (i) hν (254 nm), cyclohexane, 1.25h (51%).[134a]

The steric bulk of the C5 methyl group on the A-ring of the photocycloaddition precursor **437** has been hypothesized to dictate the conformation of the adjacent homoallyl chain. Hence,

increasing the proximity of the terminal alkene to the arene ring promotes an efficient photoreaction and provides a dramatically increased yield compared to the analogous reaction with the desmethyl compound **440** as shown in Scheme 119.[134a]



Scheme 119: desmethyl compound **440** gives a less efficient *meta*-photocycloaddition than **437**. *Reagent and conditions*: (i) hv, cyclohexane, 1.25h (25%).

From these results, it may be inferred that the additional steric bulk of the *gem*-dimethyl group, requisite to the structure of the stemodinone, could further increase the efficiency of the photoreaction of the precursor **442**. This is purely conjecture unless the *gem*-dimethyl group can be incorporated into the structure of the photocycloaddition precursor as shown in Figure 38.[134a]

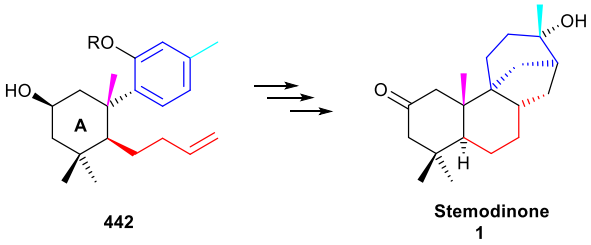
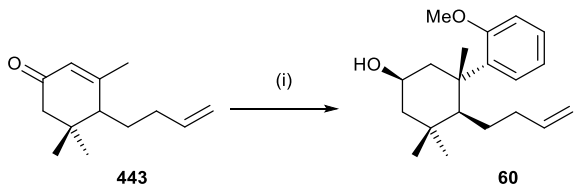


Figure 38: mapping of functionality from 'ideal' photocycloaddition precursor **442**.

A synthetic route that forms the basis for the preparation of the photocycloaddition precursor **437** has been established by Boyd and Chappell.[134a,b] Whilst this route has proved effective for the preparation of **437**, the addition of the second of the geminal methyl groups to afford **443** renders the subsequent aryl cuprate addition to give **60** ineffective delivering, at best, a 15% yield, as shown in Scheme 120.[134a]



Scheme 120: synthesis of **60** utilizing a cuprate addition. *Reagent and conditions*: (i) (2-MeOphenyl)$_2$CuMgBr, THF, -35 °C, (15%).

Numerous attempts to introduce the *gem*-dimethyl group using standard intermolecular methods were reported to be unsuccessful by Boyd and Chappell.[134a] The origin of the low yield may be traced to the conformational preference of **443**, wherein a steric interaction between the homoallyl side chain and the enone methyl group (highlighted in red) forces the homoallyl group into a pseudo axial position **443**-ax, effectively blocking one π-face of the enone to attack by the cuprate (Figure 39). The other π-face is blocked by one of the *gem*-dimethyl groups.

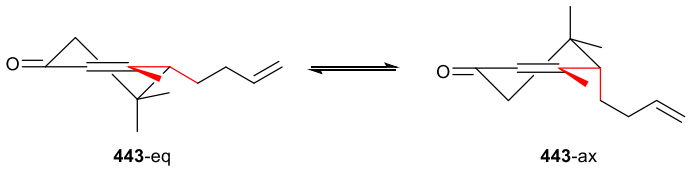


Figure 39: conformation of enone **443** with a preference for **443**-ax.

Given the success of photocycloaddition of the monomethylated precursor **437** (Scheme 118) it was decided that post-cycloaddition intra/intermolecular installation of the requisite additional C5 methyl group should be attempted but thus far, that has also been unsuccessful. Taken together, these studies suggested that further attempts at intermolecular reactions were likely to prove futile and so potential intramolecular variants were considered.[134b] This approach could allow inclusion of the *gem*-dimethyl group pre-photocycloaddition and facilitate the elegance and brevity of a synthesis downstream.

2.1 Retrosynthetic analysis to determine the functionality required around the aromatic moiety of stemodinone

As outlined earlier, the synthesis of stemodinone **1** and its analogues has been approached from several angles by different research groups utilizing a wide range of methodologies and, therefore, starting materials. However, a novel route to these compounds has adopted the little-known *meta*-photocycloaddition reaction; thus, allowing the use of economically viable starting materials and the utilization of a reaction not commonly employed in total synthesis. Based on this pattern, we proposed the retrosynthetic analysis shown in the Figure 40. This analysis identified the use of the little-used Schultz photoarylation reaction to prepare the precursor to the *meta*-photocycloaddition reaction.

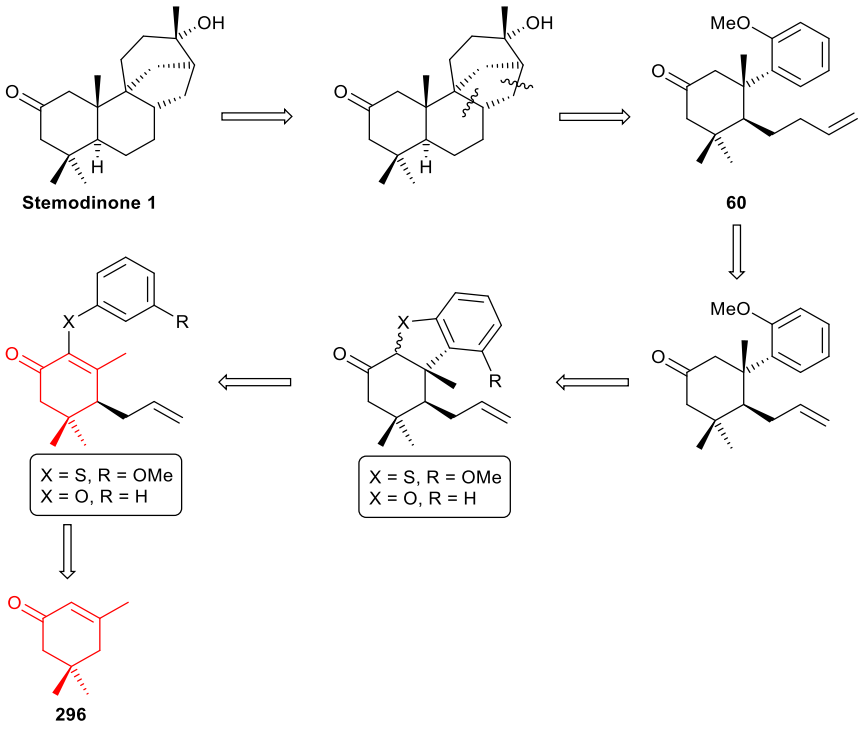


Figure 40: proposed retrosynthetic analysis of stemodinone **1** incorporating the Schultz photoarylation reaction.

2.1.1. General synthesis of the Shultz cyclization precursor and Schultz cyclization products.

To investigate the potential of the Schultz cyclisation in the context of a synthesis of stemodinone **1**, a model system that begins from the commercially available compound isophorone **296** was examined (Figure 41). Isophorone **296** can be obtained at approximately £17/L from Sigma Aldrich (Aug 2020) and possesses the required *gem*-dimethyl functionality at the δ-position, in addition to the vinyl methyl at the β-position. It only lacks the homoallyl group at the γ-position that would be required for the preparation of **1**. An added benefit is that Schultz has used isophorone in some of his investigations utilizing cyclisation reactions and that would assist us to develop these photochemical reactions within our laboratories.[93]

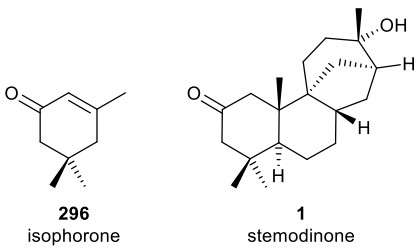
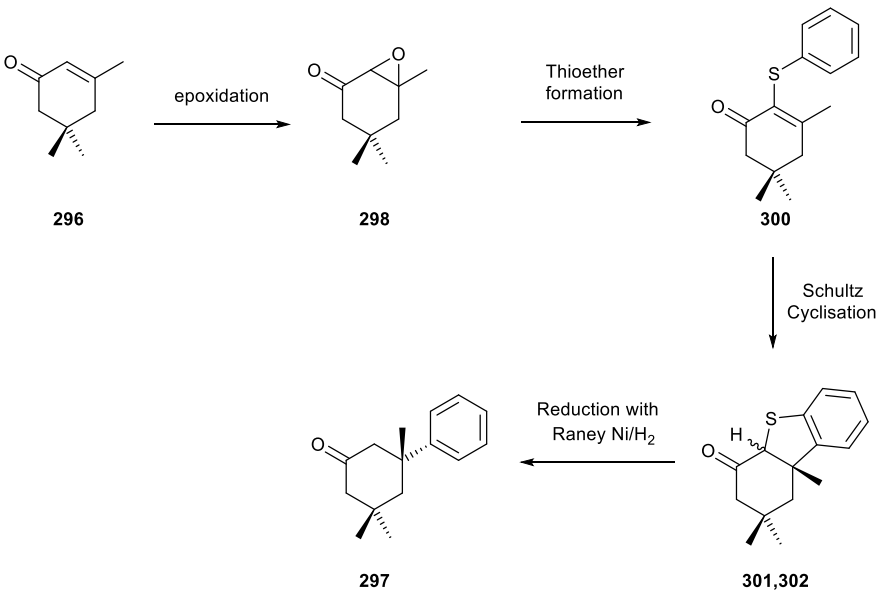


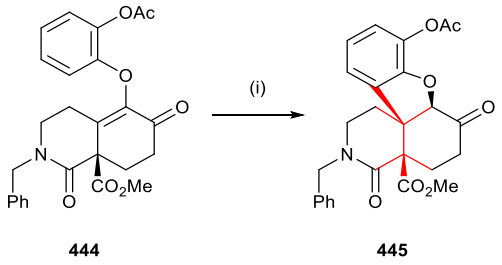
Figure 41: Comparison of isophorone **296** with stemodinone **1**.

The general route for the synthesis of precursor **300** required for the Schultz cyclisation features an epoxidation followed by thioether formation (Scheme121). This approach is flexible with respect to the atom linking the alkene and aromatic moieties, with both sulfur and oxygen analogues proceeding with high yields: albeit under different reaction conditions.[92,95a] Variation in this atom offers considerable opportunities for the subsequent manipulation of the products from the photocyclisation. As an example, treatment of the two diastereoisomers **301**/**302** with Raney nickel could be used to excise the sulfur atom used in the intramolecular delivery of the aryl group. This would deliver the same compound as would arise from an aryl cuprate addition to **296**.



Scheme 121: a generic example of the Schultz cyclisation reaction.

From Schultz's work, it is evident that this photo-electrocyclization is capable of delivering bond formation at highly hindered centres and in a diastereoselective manner. A particularly striking example, the conversion of **444** into benzodihydrofuran **445**, proceeded in an excellent yield as shown in Scheme 122.[95c]

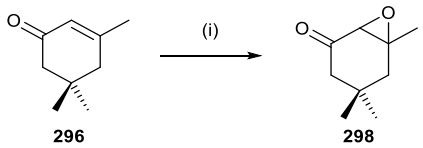


Scheme 122: Schultz cyclisation to give benzodihydrofuran **445**; a compound with adjacent quaternary centres (red). *Reagent and conditions*: (i) PhH-MeOH-AcOH (1:1:1), Ar-atm (degassed for 30 min. prior to reaction), hν (450 W mercury arc lamp, pyrex flask) 6 h, 95% yield of **445**.[95c]

Herein, we report the details of an examination of this reaction, with the intent of establishing its suitability in terms of yield and diastereoselectivity, for the synthesis of the compound **300**.

2.1.2 Preparation of 2,3-epoxyisophorone

The epoxidation of isophorone **269** in MeOH proceeded uneventfully and was successfully achieved by using 3.1 mole equivalents of hydrogen peroxide; following the cooling of the reaction down to 15 °C, 5.1 mole equivalent of sodium hydroxide solution was added in a dropwise manner and stirred over a period of 1 hour. The temperature of the reaction mixture was maintained at 20-25 °C for further 3 hours and subsequent TLC analysis revealed that no more starting was being consumed. Following the slow removal of solvent, the resulting epoxyisophorone **298** was obtained in 72% yield as a yellow oil shown in Scheme 123.[146a,146b]



Scheme 123: synthesis of epoxyisophorone **298**: *Reagent and conditions*: (i) 3.1 equiv. H_2O_2, 5.1 equiv. NaOH, MeOH, 20-25 °C, 3h, 72% yield.

All analytical data correlated with those reported in the literature[146a,146b] but perhaps the most demonstrative evidence was that a singlet observed in the ^{1}H NMR spectrum of the isophorone **296**, that corresponded to the isophorone olefinic proton at δ 5.86 had been lost and a new singlet was observed at δ 3.06 as a result of the proton adjacent to the epoxide. In addition, the HSQC (Figure 42) has indicated the presence of two different sets of diastereotopic protons, consistent with the presence of stereogenic centres. The carbonyl stretches in the IR region demonstrated a shift from 1665 cm^{-1} to 1721 cm^{-1}, showing the change from enone to ketone.

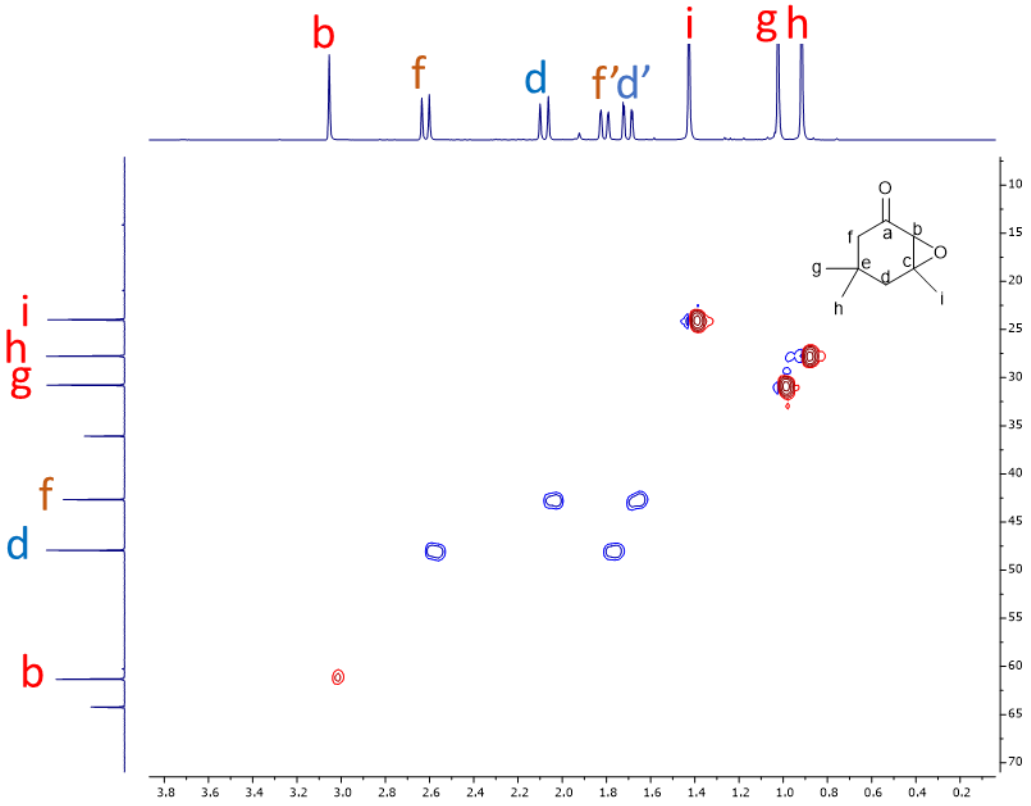


Figure 42: HSQC spectrum of the epoxy isophorone **298**.

The geometric requirements of an epoxide attached to six-membered ring requires a *cis*-ring junction and this was further highlighted when one considers the mechanism of nucleophilic epoxidation, known as the Weitz-Scheffer reaction.[136] In this reaction (Figure 43), HOO^- will attack the β-position of the enone **296**, the resulting enolate will then attack back onto the hydroperoxide forming the epoxide **298** and releasing hydroxide as a leaving group.

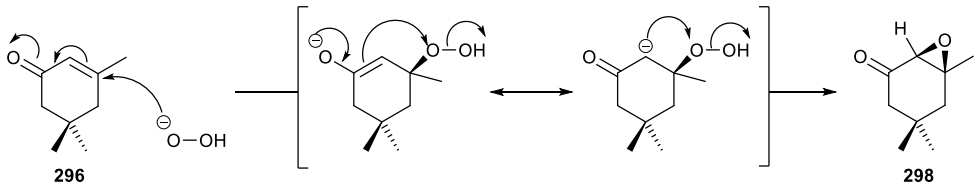
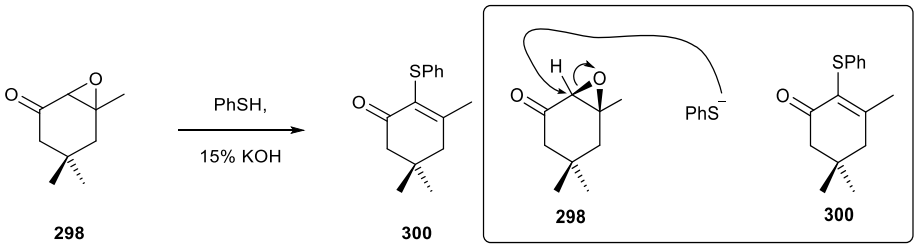


Figure 43: Wietz-Scheffer mechanism for the nucleophilic epoxidation of epoxyisophorone **298**

The reaction was scalable up to 20 g of starting material **296** and affords 52-90% yield of epoxyketone **298** which was sufficient to serve as a convenient precursor to the cyclic 2-thioaryloxyenones or cyclic 2-aryloxyenones.

2.1.3 Synthesis of (2*R*, 3*S*)-3-hydroxy-3,5,5-trimethyl-2-(phenylthiol)-cyclohexen-1-one and (2*S*, 3*S*)-3-hydroxy-3,5,5-trimethyl-2-(phenylthiol)-cyclohexen-1-one

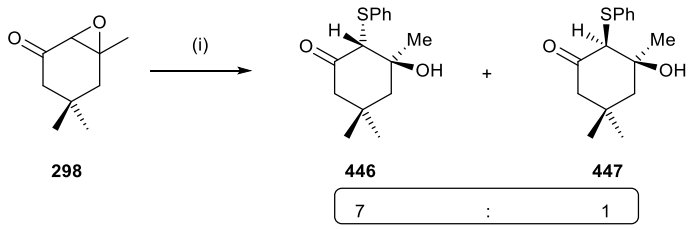
The ring strain present in epoxides (*ca*. 22 kcal/mol^{-1})[135] makes the epoxides highly susceptible to nucleophilic attack and that makes epoxides a versatile starting material for the synthesis of various compounds.[137] The next step in the synthesis was the reaction of epoxyketone **298** with thiophenol **299**. We anticipated that the presence of excess hydroxide ions (H_2O, pKa 15.7) in the reaction would first deprotonate the thiophenol (pKa 7) providing the anion PhS^-; the thiophenolate is expected to be a much better nucleophile and suitable for the S_N2 ring opening step of the epoxide as shown in Scheme 124. Thus, the reaction proceeds in an addition-elimination (S_N2 then $E1_{cb}$) manner to affords the vinyl thioether **300** (Scheme 124) as Schultz cyclisation precursor.[95a] We noticed that ring-opening of the epoxide **298**, with concomitant E1cb elimination to deliver the desired substrate has been reported in the literature.[144]



Scheme 124: Schultz cyclization precursor vinyl thioether **300.**

In addition, a second report on epoxide ring-opening with thiophenoxides described that the formation of the desired vinyl thioether **300** was not directly achieved upon utilizing the conditions outlined by Schultz (Scheme 125)[95a] for the reaction between epoxyisophorone **298**

and thiophenol **299**, but the reaction stalled with the formation of a mixture of diastereoisomers **446** and **447** (7:1 ratio) in 90% yield.



Scheme 125: Mixture of two diastereoisomers **446** and **447**: *Reagent and conditions*: (i) PhSH, EtOH, 15% KOH, 0 °C, 1h, 90% yield.

2.1.4 Epoxyketone ring opening 298

Assuming, that a straightforward S_N2 reaction mechanism has been followed, there are two possibilities for the nucleophilic attack: (a) at the α-carbon to the ketone as shown in red (Figure 41) or (b) at the β-carbon atom. Due to the principle of microscopic reversibility, the reaction must undergo *trans*-diaxial ring opening, known as the Fürst-Plattner rule[138] (Figure 44), then the thioether and hydroxyl groups should be *anti* to one another. Given the conformation of **298** shown, the *trans*-diaxial product forms preferentially from attack at the end of the epoxide that affords the diaxially substituted chair conformation. However, ring opening at the other end would yield a diaxially substituted twist-boat conformation, but this is higher in energy.[139] From the conformation shown, this also occurs at the least substituted end of the epoxide and avoids reaction at a tertiary carbon. Additionally, it is frequently observed that electrophiles α to a carbonyl are more reactive toward nucleophiles as a result of simultaneous overlap of the nucleophile HOMO with both σ* of the primary electrophile and π* of the carbonyl, thus lowering the activation energy. However, the loss of the epoxide resonance in the ^{1}H-NMR spectrum of **298** coincided with the generation of two new singlet resonances at δ 3.52 and δ3.88 for the methine protons of **446** and **447**, respectively; assuming a simple S_N2 reaction, only one (that associated with **446**) should be observed. Epoxide protons are typically observed

around δ 3.06 because of ring-strain from the epoxide increasing the s-character of the C-H bond. The analysis of the mass spectrum supported the formation of the diastereoisomers, in which the positive-ion mode, the [M+Na]+ ions of **446** are much more abundance than the corresponding [M+H]+ ions for the minor diastereoisomer **447** were barely detectable. Given that the subsequent E1cb elimination reported by Schultz, proceeds via an enolate, it may be proposed that protonation of this enolate proceeds more rapidly than the elimination and this results in epimerization α to the carbonyl to afford **447**. Given that an axial protonation is generally favoured in 6-membered ring **447** could arise by kinetic or thermodynamic means (equatorial SPh).

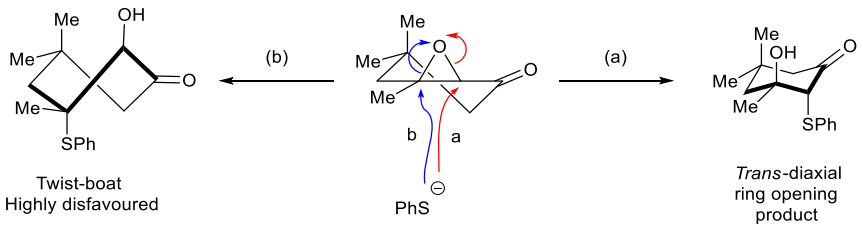


Figure 44: The Fürst-Plattner rule for *trans*-diaxial ring opening of epoxyketone **298**

Upon trituration with hexane, the crude was purified to afford a colourless solid which was further crystallized from hexane/diethyl ether to afford the major isomer **446** as an analytically pure colourless crystal (m.p. 102-103 ºC) in 75% yield. The successful assignment of the relative stereochemistry of both **446** and **447** was initially based upon the observation of 'W' couplings in the ^{1}H NMR spectrum (Figure 45), then confirmed by single crystal x-ray diffraction analysis (Figure 43). However, out of the two ring-flip conformers of **446**, the unfavourable 1,3-diaxial interactions between the methyl groups on C-3 and C-5 favoured the conformer with the alcohol and thioether groups in an axial position. On that basis, the proton at C-2 should be equatorial and subject to a 'W' coupling with the equatorial protons on C-4 and C-6. Interestingly, following the line sharpening by Gaussian multiplication, of the ^{1}H-NMR spectra of compound **446**, the equatorial protons at C-2 (δ 3.53) changed from a broad

singlet to a fine triplet with *J* 1.6 Hz. In addition, the two methylene hydrogens on C4 and C6 are diastereotopic. The equatorial hydrogen at C-4 resonate at δ 1.71 as an apparent doublet of triplets with *J* 14.6, 1.6 Hz; whereas, the equatorial hydrogen at C-6, resonates at δ 2.05 as a doublet of triplets with *J* 13.4, 1.6 Hz. Thus, the small coupling constants with *J* value between 1.6 and 2.0 Hz have been proven to be fully consistent with 'W' coupling as shown in Figure 42.[140]

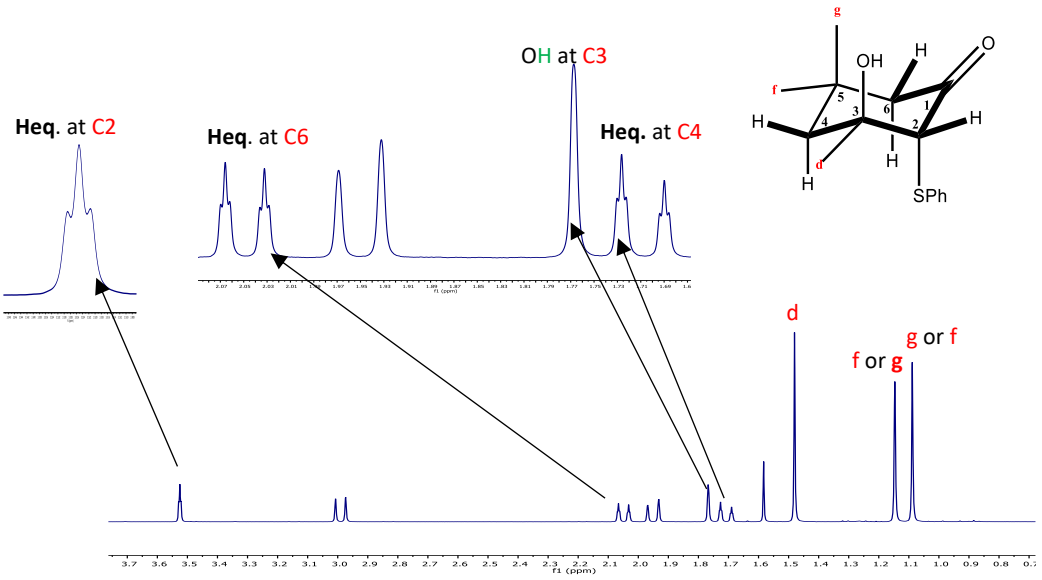
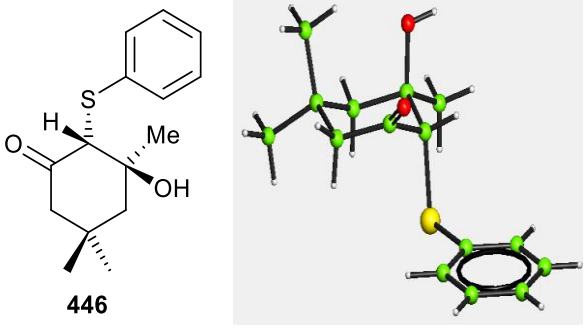


Figure 45: ^{1}H NMR (400MHz, $CDCl_3$) spectra of major distereoisomer (±)-(2*S*,3*R*) -3-hydroxy-3,5,5-trimethyl-2-(phenylthio)-cyclohexen-1-one, and the conformation of **446**.

Having proposed the stereochemistry of pure crystalline β-hydroxysulfide **446** by analysis of its ^{1}H NMR spectrum, an X-ray crystal structure confirmed both the regiochemistry of ring opening and its relative stereochemistry as shown in Figure 46.



446

Figure 46: Single X-ray crystal structure of (±)-(2*S*,3*R*) -3-hydroxy-3,5,5-trimethyl-2-(phenylthio)-cyclohexen-1-one **446**.

In addition, some of the problems faced in analyzing the crystalline structure of a compound may be attributed to building an unambiguous hierarchy of interactions. However, creating such a system is difficult when analyzing only a relative contact area on a Hirshfeld surface or a value of d_{norm}. On one side, despite the significant energy contribution of non-directional dispersion forces, they are more pliable in terms of geometry and often cannot be considered as determining factor when forming a crystal. Moreover, changes in directional, both strong and weak, bonds may lead to critical changes in energy and geometry of the system. [142] The evidence for hydrogen bonds interaction O-H….O in crystal structure of **446** (Figure 47) has been determined and it provides important information on the geometry of species constituting crystals structure and on the symmetry relations between them which justify the claim by Fürst-Plattner rule (Figure 44) that ring opening was *trans*-diaxial, the thioether and hydroxyl groups are *anti* to one another. However, the analysis of crystal structures is so conclusive that it allows us to understand the nature of various interactions.[143a]

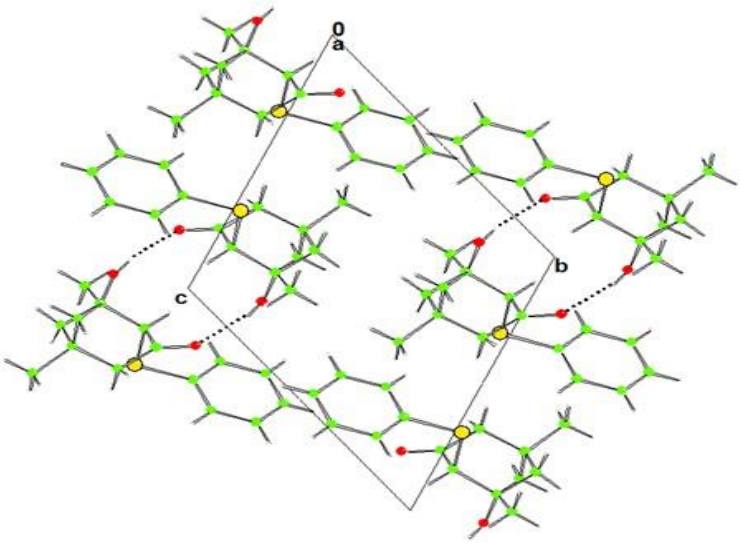


Figure 47: Fragment of the crystal packing for **446** along the axis 0c and 0b. The structures are depicted using a ball-and-stick model, intermolecular hydrogen bonding represented by dashed lines.

By comparison, the relative stereochemistry of the minor diastereoisomer, **447**, could be slated to have the hydroxyl and thioether groups *syn* to one another (Figure 48). In principle, out of the two ring-flip conformers **447a[1]** and **447b[1]** (Figure 48), the unfavourable 1,3-diaxial interactions between the methyl groups on C-3 and C-5 should not favour that with the thioether groups in an axial position. However, the prepared minor isomer should be conformer **447b[1]**; on that basis, the proton at C-2 should be axial and show no 'W' coupling with the equatorial protons on C-4 and C-6.

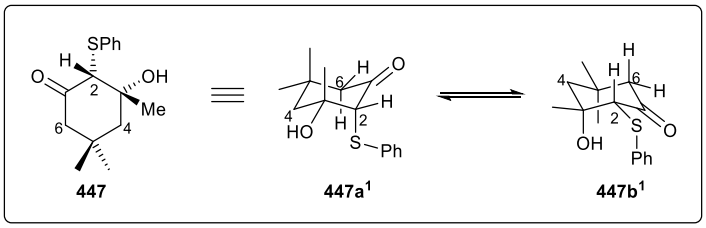


Figure 48: Minor distereoisomer (±)-(2*R*,3*R*) -3-hydroxy-3,5,5-trimethyl-2-(phenylthio)-cyclohexen-1-one **447** and ring-flip **447a[1]** and **447b[1]** conformers.

A comparison could be made of the major and minor diastereoisomers using a sample that contained both diastereomers, at C-2 protons in the ^{1}HNMR spectrum. The major diastereoisomer **446** resonates at δ 3.53 and displays the triplet structure (*J* 1.6 Hz) discussed above; whereas **447** resonates at δ 3.88 ppm as a broad singlet consistent with its axial position (Figure 49).

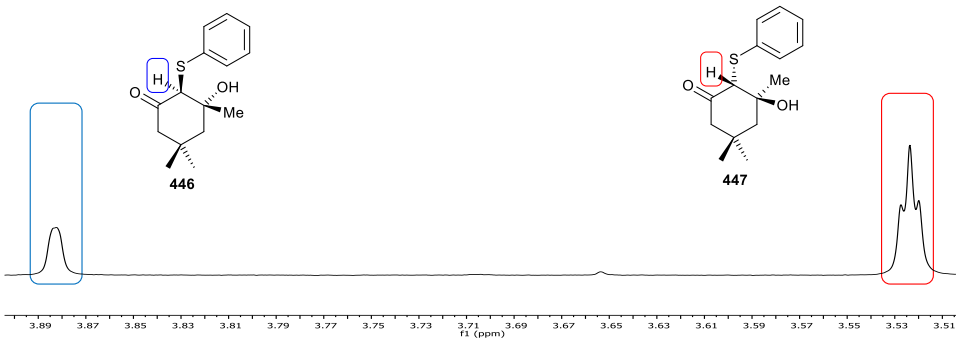


Figure 49: Proton NMR evidence of the presence of two diastereoisomers in the crude sample, both major isomer **446** and minor isomer **447**.

In addition, a study was then conducted with a range of different thiophenol nucleophiles with epoxyketone **298**. The aim was to prepare derivatives suitable to underpin a later study of the yield and regio/stereoselectivity of a subsequent Schultz cyclisation. The substituted thiophenol derivatives tended to follow the same pattern of reactivity as thiophenol (Figure 50). The stereo/regiochemical assignment of these adducts could be inferred from the previously described X-ray crystal structure with the stereochemistry of the major diastereoisomer being confirmed by 'W' coupling analysis.

Before beginning this study, alternative published conditions for these reactions were considered. A study on utilizing heterogeneous catalysts reported that inactivated Woelm-200 chromatographic column alumina catalyzes regioselective and stereospecific ring opening of a wide variety of epoxides by thiols to give various β-hydroxysulfides in favour of the *trans*-isomer in a very good yield. However, besides the catalytic ability to promote the ring opening of epoxides with sulfur nucleophiles at room temperature, the promoter was reported to be capable of effecting ring opening of epoxide with alcohols, selenols and amines to afford the

corresponding β-hydroxy analogues.[143b] Comparative studies were conducted on the catalytic activity of Lewis and Bronsted acids and bases for the thiolysis of epoxides using *p*-TsOH, $InCl_3$, K_2CO_3 and *n*-Bu_3P.[143b] Even though, all of them were reported to effect the thiolysis of alkyl and aryl epoxides under solvent- free conditions with 5 mol% of catalyst loading, the activity was highly dependent of the nature of the acid or base catalyst used. The Lewis acid $InCl_3$ and Brønsted base K_2CO_3 provided superior yields and reaction rates in comparison to the Brønsted acid *p*-TsOH and Lewis base *n*-Bu_3P.[143b] When the reactions were caried out under the same conditions but in aqueous and organic media, the solvent-free conditions were found to provide the β-hydroxysulfides in reasonable yields over short periods of time and at low catalyst loading. In addition, under the catalytic conditions, the reaction provided 94% yield of β-hydroxysulfide after two weeks of stirring while same product was obtained in 72% yield after only 12 hours which suggested the importance of solvent in this reaction. The regioselectivity of the reaction was strongly dependent on the acidity or basicity of the reaction conditions. Under acid conditions, nucleophilic attack of the thiol at the more-substituted α-carbon was favoured while under basic conditions attack at the less-substituted β-carbon was favoured.[143b] However, these conditions were more involved than those recommended by Schultz and did not seem to offer a significant advantage, particularly with respect to scale-up.

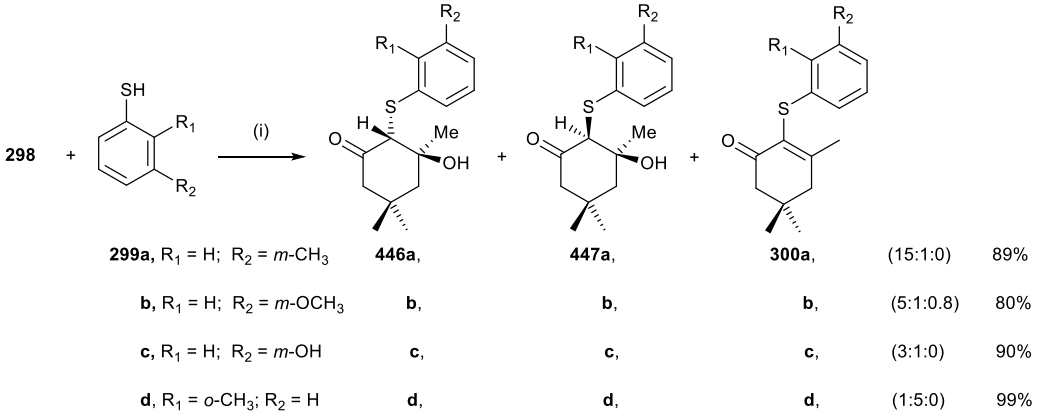


Figure 50: Epoxide ring opening by substituted thiophenol derivatives: *Reagent and conditions*: (i) EtOH, 15% KOH, 0 °C, 1h, 80-99% yield.

Consequently, upon treatment of epoxyketone **298** with *m*-thiocresol **299a** in the presence of a catalytic amount of base afforded a yellow solid as a mixture of diastereoisomers **446a** and **447a** (15:1) in 89% yield (Figure 47). Crystallization of the crude product from ether/hexane afforded colourless crystals of **446a** (m.p. 121-122 °C) as a single diastereoisomer in 47% yield. However, after removal of the solvent from the mother liquor a yellow solid residue was obtained as a mixture of **446a**, **447a** and **300a** (13:1:3 ratio) m.p. 114-115 ^{o}C in 42% yield. As the intent was to convert this mixture into the alkene **300a**, all of this material could be used. The ring opening of the epoxyketone with *meta*-thiocresol occurred with *anti*-selectivity to form the major product with *trans* relative configuration. Thus, the ^{1}H-NMR spectra of compound **446a** indicated the equatorial protons at C-2 (δ 3.51) changed from a broad singlet to a fine triplet with *J* 1.6 Hz upon Gaussian multiplication. In addition, the two methylene hydrogens on C4 and C6 are diastereotopic. The equatorial hydrogen at C-4 resonates at δ 1.70 as an apparent doublet of triplets with *J* 14.6, 1.6 Hz while the axial hydrogen resonates at 1.94 as doublet with *J* 14.6 Hz; whereas, the equatorial hydrogen at C-6 resonates at δ 2.04 as an apparent doublet of triplets with *J* 13.2, 1.6 Hz upon Gaussian multiplication, while the axial hydrogen resonates at 2.99 as doublet with *J* 13.2 Hz. A sharp singlet signal at δ 2.31 corresponds to the *meta*-methyl protons. All the protonated carbon signals were assigned *via* HSQC; this spectrum also indicated that the two set of diastereotopic protons at C-4 and C-6 were correlated to the same carbons from the cross peaks at δ 46.85 and δ 49.12, respectively. The assignment of the *m*-methyl carbon and the carbonyl carbon signals were confirmed to be at δ 21.26 and δ 208.41 from their HMBC cross peaks. The HRMS (+ESI) m/z [$(M+H)^{+}$] was consistent with the molecular formula of $C_{16}H_{22}O_2S$. ^{1}H-NMR spectra of the minor diastereoisomer **447a** showed the C-2 resonance at δ 3.87 as an axial proton. The two diastereotopic methylene hydrogens on C4 resonates at δ 1.81 and δ 1.94. That at δ 1.81 corresponded to the axial proton and this resonated as a doublet with *J* 14.6 Hz while the

equatorial proton resonates at 1.94 with *J* 14.6, 1.6 Hz upon Gaussian multiplication whereas, the other two set of diastereotopic hydrogens at C6 resonates at δ 2.57 as an apparent doublet of triplets with *J* 13.2, 1.6 Hz for the equatorial hydrogen. A sharp singlet signal at δ 2.32 corresponded to the *meta*-methyl protons. All the protonated carbon signals were assigned *via* HSQC. Other evidence from the ^{13}C NMR spectrum of minor diastereoisomer **446a** indicated the value of the two sets of diastereotopic geminal pair of protons at C-4 and C-6 were confirmed to be both correlated to the same carbons from the HSQC cross peaks at δ 45.29 and δ 50.74, respectively. The carbon shifts at δ 77.28 are consistent with those being adjacent to a tertiary oxygen atom. Assignment of the *m*-methyl carbon and the carbonyl carbon signals were confirmed to be at δ 21.42 and δ 200.19 from their respective HMBC cross peaks.

Following the treatment of isophorone oxide **298** with 3-methoxythiophenol **299b** (degassed by passage of nitrogen) at 0 ºC for 1 hour, in the presence of KOH, TLC analysis revealed that the reaction was completed, and a crude yellow oil was isolated. Purification of the crude product by flash column chromatography gave a yellow oil containing a mixture of diastereoisomers **446b** and **447b**, together with alkene **300b** in a ratio of 4.3:1.0:0.8 in 80% yield. Alternatively, a single major diastereoisomer could be isolated from the crude residue by trituration with warm acetonitrile, followed by addition of hexane. The compound was obtained as a colourless solid which was further crystallized to give **446b** as an analytically pure colourless crystalline solid (m.p. 108-109 ºC) in 59% yield. The ring opening of the epoxyketone **298** with a *meta*-methoxythiophenol **299b** occurred *anti*-selectivity to form the major product with *trans*-configuration. Thus, the ^{1}H-NMR spectrum for the major compound *meta*-methoxy hydroxy sulfide **446b** was characterized by considering the prominent equatorial proton at C-2 as a broad singlet at δ 3.56 which upon Gaussian enhancement changed to a fine apparent triplet with *J* 1.6 Hz. The two sets of methylene protons on C-4 and C-6 gave clearly defined diastereotopic pairs of doublets. The equatorial proton on C-4 resonate at δ 1.70

as an apparent doublet of triplets with *J* 14.7, 1.8 Hz upon Gaussian multiplication while the axial proton resonates at 1.93 as doublet with *J* 14.7 Hz; whereas, the equatorial hydrogen at C-6, resonates at δ 2.04 as an apparent doublet of triplet with *J* 13.4, 1.8 Hz. A sharp singlet corresponding to the *meta*-methoxy protons at the aromatic ring were observed at δ 3.75. The β-hydroxyl appears as a single, broad resonance at δ 2.86 (Figure 51). All the protonated carbon signals were assigned *via* DEPT and HSQC; in particular, the two sets of diastereotopic protons at C-4 and C-6 each correlate to the same carbons at δ 46.94 and δ 49.14, respectively. The assignment of the *m*-methoxy carbon and the carbonyl carbon signals were confirmed to be at δ 55.32 and δ 208.29 from their HMBC cross peaks. The HRMS (+ESI) m/z [$(MH)^+$] was consistent with the molecular formula of $C_{16}H_{22}O_3S$. Thus, ^{1}H-NMR spectra for the minor diastereoisomer **447b** showed the C-2 resonance appears at δ 3.93 as an axial proton. The equatorial proton on C4 resonates at δ 1.80 as an apparent doublet of triplets with *J* 14.6, 1.6 Hz upon Gaussian enhancement while the axial proton resonates at 1.92 as doublet with *J* 14.6 Hz; whereas, the other equatorial proton signal at C6 resonates at δ 2.30 as an apparent doublet of triplets with *J* 12.7, 1.6 Hz while the axial proton resonates at 2.52 as doublet with *J* 12.7 Hz. A sharp singlet resonance corresponding to the *meta*-methoxy protons at the aromatic ring was observed at δ 3.71. The β-hydroxyl proton appears as a single, broad resonance at δ 2.60. All the protonated carbon signals were assigned *via* DEPT and HSQC with the two sets of diastereotopic geminal protons at C-4 and C-6 both correlating to the same carbons at δ 50.34 and δ 52.99, respectively. The carbon shifts at δ 77.40 are consistent with a tertiary carbon adjacent to an oxygen atom. As before, assignment of the *meta*-methoxy carbon and the carbonyl carbon signals were confirmed to be at δ 55.17 and δ 205.53 from their HMBC cross peaks.

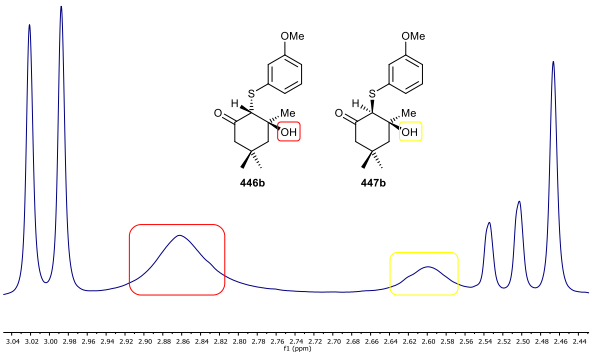


Figure 51: ^{1}H-NMR (400 MHz, $CDCl_3$) of the β-hydroxyl proton signal for the two diastereoisomers **446b** and **447b**.

For the reaction of epoxyketone **298** with a solution of 3-hydroxythiophenol **299c**, the issue of pK_a had to be considered. In general, thiophenols (pK_a ~ 8.0) are more acidic than phenols (pK_a ~ 10); thus, selective deprotonation of the desired nucleophile was to be expected. After stirring the two compounds in the presence of KOH at 0 ºC for 1hour, the reaction was judged to be completed by TLC and a crude yellow oil was isolated; upon trituration with acetonitrile, a white solid resulted and was found to be a mixture of diastereoisomers **446c** and **447c** (3:1) in 90% yield. Upon further purification by crystallization from hexane/acetonitrile, analytically pure colourless crystals **446c** (m.p. 171-172 ºC) were recovered containing a single major diastereoisomer in 68% yield. The ring opening of the epoxyketone **298** with a *meta*-hydroxythiophenol **299c** occurred with *anti*-selectivity to form the major product with *trans* configuration. Thus, the ^{1}H-NMR spectrum for the major diastereoisomer *meta*-hydroxyl hydroxy sulfide **446c** was assigned by considering the equatorial proton at C-2. As before, a broad singlet at δ 3.48, upon Gaussian enhancement, changed to a fine triplet with a small coupling constant *J* 1.6 Hz. The two sets of methylene protons on C4 and C6 gave clearly defined diastereotopic pairs of doublets. The equatorial proton on C-4 resonate at δ 1.59 as an

apparent doublet of triplets with *J* 14.4, 2.0 Hz upon Gaussian multiplication while the axial proton resonates at δ 1.72 as doublet with *J* 14.4 Hz; whereas, the equatorial hydrogen at C-6 resonates at δ 1.86 as an apparent doublet of triplets with *J* 13.4, 2.0 Hz upon Gaussian multiplication and the axial proton resonates at δ 2.99 as doublet with *J* 13.4 Hz. A broad singlet resonance at δ 9.64 corresponded to the *meta*-hydroxy proton at the aromatic ring, whilst, the β-hydroxyl proton appeared as a single, broad resonance at δ 5.06. All the protonated carbon resonances were assigned *via* HSQC with the two sets of diastereotopic protons at C-4 and C-6 each correlating to one carbon at δ 46.05 and δ 48.19, respectively. Assignment of the carbon attached to *meta*-hydroxyl and the carbonyl carbon signals were confirmed to be at δ 134.74 and δ 204.53 from HMBC cross peaks. The HRMS (+ESI) m/z $[(MH)^+]$ was consistent with the molecular formula of $C_{15}H_{20}O_3S$. Thus, ^{1}H-NMR spectra for the minor diastereoisomer **447c** indicated that the signal on C-2 appears at δ 4.23 as an axial proton. The two diastereotopic methylene hydrogens on C4 resonates at δ 1.75 and δ 1.99. That at δ 1.75 corresponded to the axial proton and resonated as a doublet with *J* 14.2 Hz while the equatorial proton resonates at 1.99 as an apparent doublet of triplet with coupling constants *J* 14.2, 1.6 Hz upon Gaussian multiplication; whereas, the other two sets of diastereotopic hydrogens at C6 resonates at δ 2.19 as an apparent doublet of triplets with *J* 12.4, 1.6 Hz corresponding to the equatorial proton and the axial proton resonates at 2.59 as doublet with *J* 12.4 Hz. The β-hydroxyl proton signal appears as a broad singlet at δ 4.73, while broad singlet signal at δ 9.43 corresponding to the *meta*-hydroxy proton at the aromatic ring. All the protonated carbon signals were assigned *via* HSQC; in particular, the two sets of diastereotopic protons at C-4 and C-6 each correlated with the same carbons at δ 50.40 and δ 53.58, respectively. The carbon shift at δ 76.77 is consistent with quaternary carbon being adjacent to an oxygen atom. Assignment of the carbon attached to *meta*-hydroxy and the carbonyl carbon signals were confirmed to be at δ 133.19 and δ 204.53 from HMBC cross peaks. To confirm the assignment

of the OH resonances, a mixture of diastereoisomers **446c** and **447c** in DMSO-*d6* solution was shaken with a drop of D_2O and the OH hydrogens were exchanged rapidly with the deuterons, and the signal of the OH disappeared from the spectrum at δ 9.64 for **446c** and δ 9.43 for **447c** corresponding to the *meta*-hydroxy proton at the aromatic ring as shown in the Figure 52.

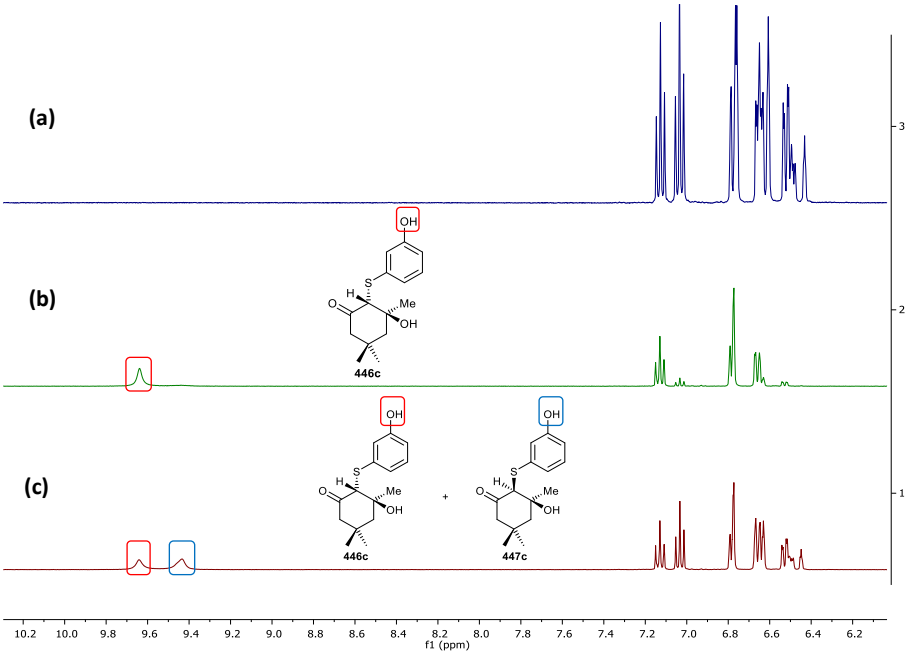


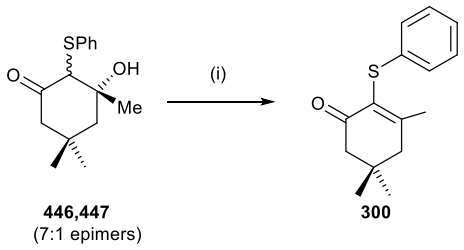
Figure 52: comparison of the ^{1}H-NMR spectrum (400 MHz, DMSO-*d6*) of (a) a mixture of diastereoisomer **446c** and **447c** with *meta*-hydroxyl-group exchanged due to D_2O shake; (b) sample enriched in diastereoisomer **446c** with *m*-hydroxyl group (in red); (c) a mixture of diastereoisomer **446c** with *meta*-hydroxyl-group (in red) and **447c** *meta*-hydroxyl-group (in blue).

Final, upon treatment of epoxide **298** with a degassed solution of 2-methylbenzenethiol **299d** in the presence of KOH, for 1 hour at 0 °C, under a nitrogen atmosphere completed the reaction. The crude product was triturated with hexane to afford a white solid compound **446d** and a yellow oily residue in a combined yield of 99%. The white solid was further purified by crystallization from hexane/ether (4:1) to give analytically pure colourless crystals (m.p. 129-130 °C) of **446d** with a 76% recovery and as a single diastereoisomer. However, the yellow oily residue was found to be a mixture of diastereoisomers (1:5) as a major **446d** and minor

447d mixture in 23% yield. ^{1}H-NMR analysis showed the hydrogen at C2 of the major compound **446d** resonated as a triplet at δ 3.43 with a small *J* coupling at 1.6 Hz; whereas, the minor compound **447d** exhibited a singlet at δ 3.82. In addition, a singlet for the *ortho*-methyl-group was observed at δ 2.42 and δ2.46 respectively. This assignment was expected considering the stereochemical model we already proposed from the major diastereoisomer **446**.

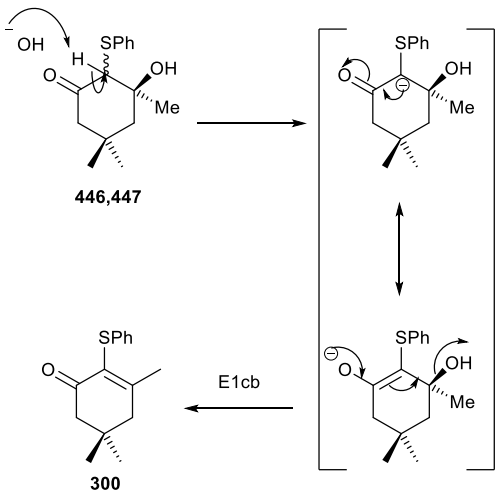
2.1.4 Preparation of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one

Given the stereospecific nature of the S_N2 reaction, this implies a subsequent base mediated epimerization to generate **447**, involving the same intermediate enolate required for elimination to give **300**. Interestingly, once purified, when **446/447** was re-subjected to the reaction conditions, a facile elimination to give **300** was observed as shown in Scheme 126.



Scheme 126: preparation of electrocyclization precursor **300**. *Reagent and conditions*: (i) KOH (cat.), ~15 min., 74% yield, **300**.

The mechanism for the conversion of **446/447** to the Schultz cyclization precursor **300** is highly likely to be E1cb in character. This took place in two steps, first by a base abstraction of the relatively acidic proton at C2 which resulted in the formation of an enolate, two resonance forms of which are shown in Scheme 125. Secondly, the enolate eliminated hydroxide to afford enone **300**, (Scheme 127). Thus, Schultz and co-workers reported that epoxyketone **298** reacted with aryl mercaptans **299** in ethanol and catalytic amount of potassium hydroxide under nitrogen atmosphere gave 2-thioaryloxyenone **300** in a very good yield.



Scheme 127: synthesis of Schultz cyclisation precursor **300** *via* E1cb elimination reaction.

The most obvious evidence for the formation of enone system **300** has been clearly provided by the proton-NMR spectrum by the disappearance of methine proton for C-2 at δ 3.53. Additionally, the absence of stereogenic centres in **300** causes the AB pattern observed for the protons at C4 and C6 in **446** to collapse to two new singlet peaks at δ 2.41 and 2.48 (Figure 53) indicating their characteristic homotopic nature.

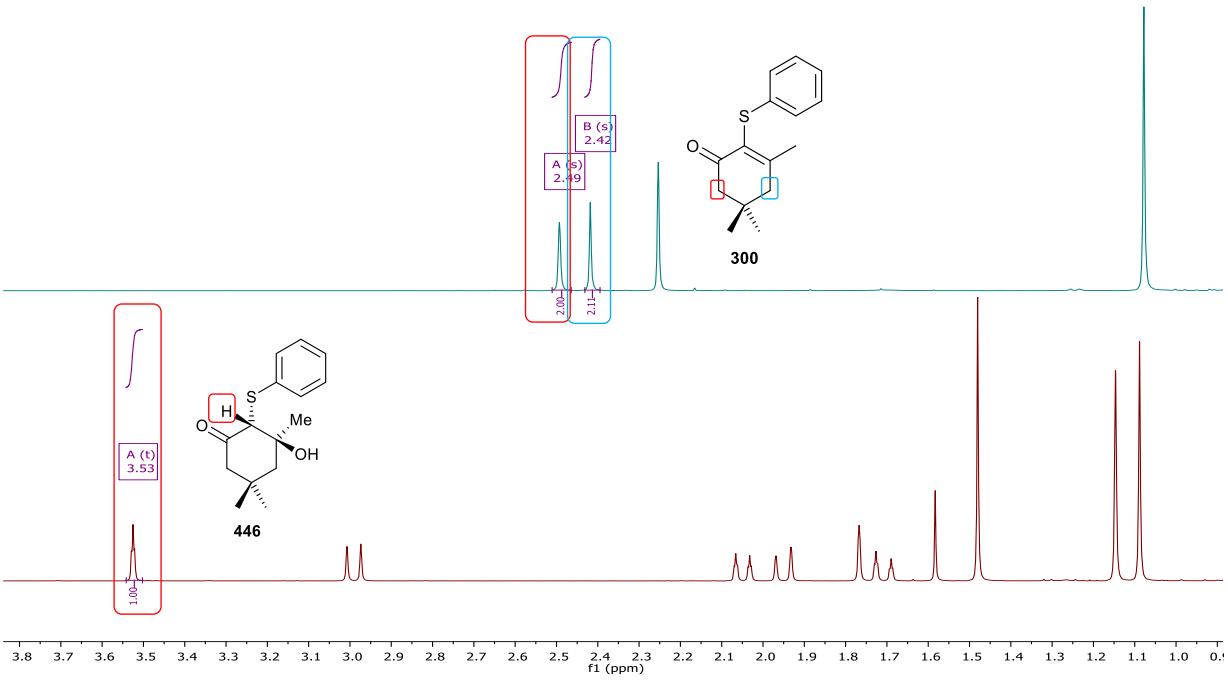


Figure 53: ^{1}H NMR (400 MHz, $CDCl_3$) spectra of precursor **300** and the major isomer **446**.

The UV-Vis spectrum of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** shows a significant band λ_{max} (EtOH) =313 nm, (red) and within the broad emission band of λ_{max} 310-350 nm of the commercially available Exo Terra UVB 200 Bulb 25W (blue) (Figure 54). The use of such a 25 W Bulb was chosen for its many safety, cost, and practical advantages over the medium pressure Hg lamps.

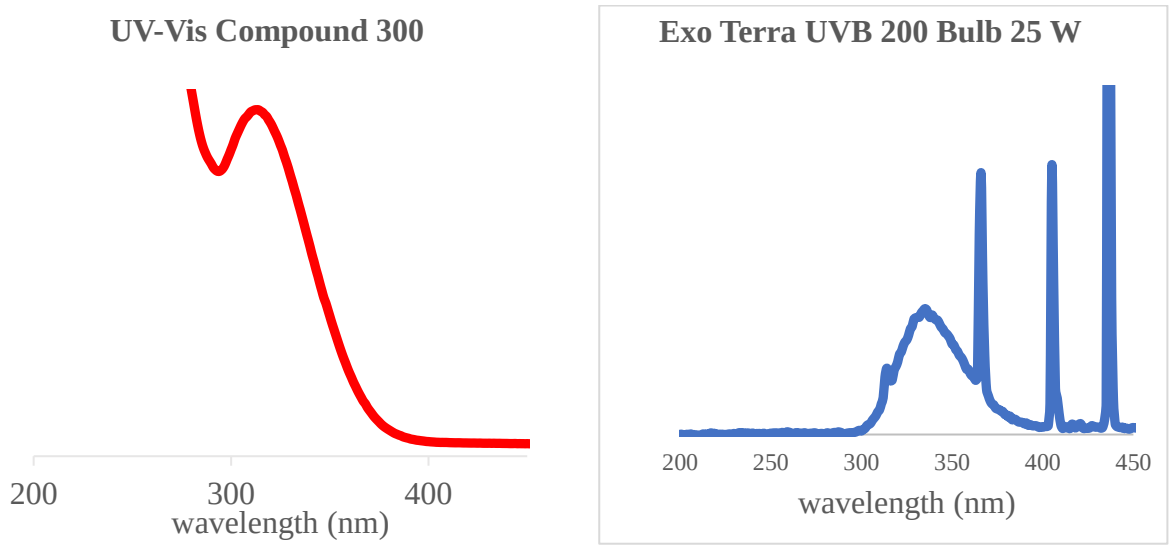
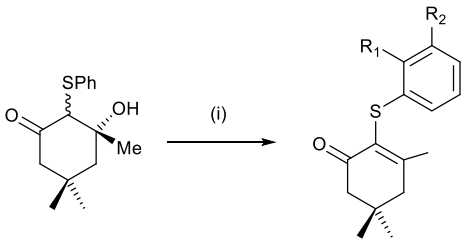


Figure 54: UV-Vis spectra of precursor **300** (red) and the output of the Exo Terra UVB 200 Bulb

In addition, the substituted thiophenol derivatives followed the same pattern of reactivity as the thiophenol derivate **446**/**447** (Scheme 128).



446a/447a, R_1 = H, R_2 = *m*-CH_3	**300a**	**83%**
b, R_1 = H, R_2 = *m*-OCH_3	**b**	**80%**
c, R_1 = H, R_2 = *m*-OH	**c**	**58%**
d, R_1 = *o*-CH_3, R_2 = H	**d**	**74%**

Scheme 128: synthesis of photoelectrocyclisation precursors **300a,b,c and d**. *Reagent and conditions*: (i) KOH (cat.), ~15 min. 83, 80, 58, and 74% yield, respectively.

Thus, preparation of the photoelectrocyclisation precursor **300a** was achieved by the reaction of the diastereoisomer **446a**/**447a** in ethanol with a catalytic amount of 15% KOH at room temperature. The resulting solution was stirred for approximately 15 minutes when TLC analysis indicated that all the starting material had been consumed to afford a yellow solid (m.p. 80-81 °C), **300a** in 83% yield. ^{1}H-NMR analysis revealed the presence of *meta*-methyl hydrogen signals as a 3H singlet resonating at δ 2.27, while the two methylene protons exhibited singlets at δ 2.42 and δ 2.49 respectively. Formation of both **300b** and **300c** was achieved in the same manner in 80% and 58% respectively as shown in Scheme 128.

Based upon this work, an improved method has been developed and the first group of photoelectrocyclisation precursors prepared.

2.1.5 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one and its derivatives to give their corresponding *cis* and *trans*-dihydrothiophenes

During these studies four different photo-reactors were employed; specifically, a Photochemical Reactors Ltd. 3010/PX0686 125-W medium pressure mercury lamp contained within a water-cooled quartz immersion well (lamp 1), a Vapourtec flow reactor (E-series) flowing the reaction mixture around a Reptile 25W Exo Terra UVB 200 bulb (lamp2), (this is

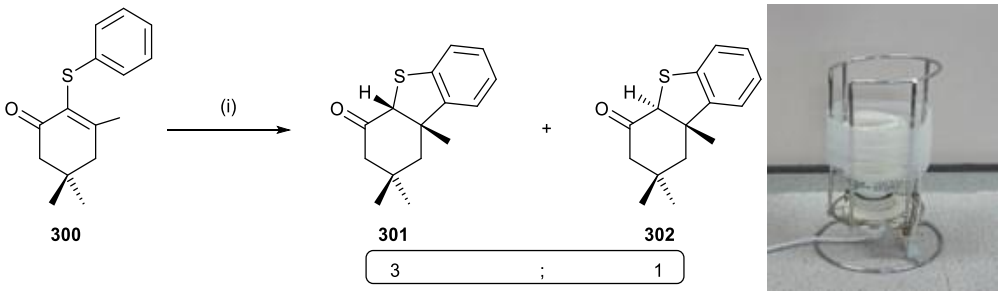
a microflow reactor as defined by Booker-Milburn),[154] a Photochemical reactors Ltd falling film photo reactor equipped with a 3020 10W low pressure Hg lamp (lamp 3) and a Southern New England Ultraviolet Company Rayonet© model RPR200 using 16 RPR-3000A low pressure Hg lamps operating at 40 °C (lamp 4) (Figure 55).

Figure 55: The series of four different sets of photochemical reactors used; a Photochemical Reactors Ltd. 3010/PX0686 125-W medium pressure mercury lamp (lamp-1), a Vapourtec flow reactor (E-series) (lamp-2), a Photochemical Reactors Ltd falling film photo reactor (lamp-3) and Rayonet© model RPR200 photoreactor (lamp-4).

To gain a preliminary assessment of these reactions, a study was conducted in both batch and flow modes. In addition, a time course study was carried out to monitor the progression of the reaction upon variation of solvents, and the overall product yield: these studies are set-out below.

From the Schultz's reports on the key cyclisation, an interesting observation was made with regards to its solvent dependency. Specifically, whilst Pyrex-filtered irradiation (cutoff around 280 nm) of a benzene solution of enone **300** afforded a diastereoisomeric mixture of **301** and **302**, irradiation in a MeOH:benzene mixture was reported to give exclusively **301**. These results were obtained using a batch reactor and irradiation with 400 W medium pressure lamp; as part of the present study, it was decided to evaluate the value of flow reactor methods against the batch method. Repeating the reaction of **300** in a MeOH: toluene (1:3) solution (with

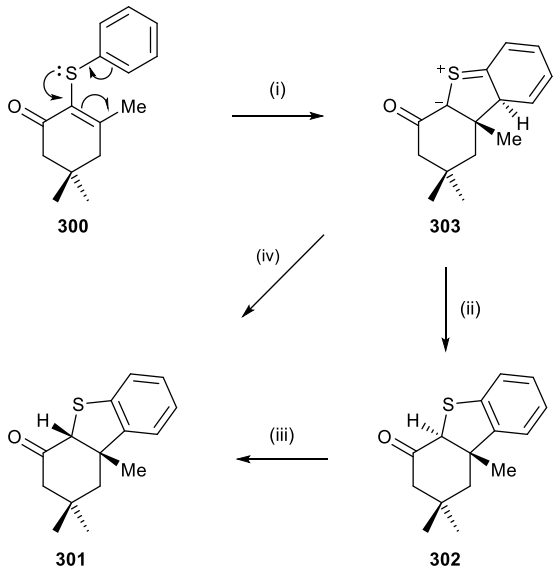
toluene substituted for benzene for safety reasons) but using flow reactor (lamp 2) with irradiation using a band with λ_{max} 320 nm for 3 hours [4.5 min (residence time)] gave a mixture of two diastereoisomers of *cis*- and *trans*-dihydrothiophenes **301** and **302** in 60-98% isolated yield range across several runs (Scheme 129). The variability was attributed to poor control of deoxygenation in the early attempts that led to some decomposition. The crude was further purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford two fractions; first, a mixture of diastereoisomers of *cis*- and *trans*-dihydrothiophene **301** and **302** (3:1) in 15% yield and, second, a single diastereoisomer of *cis*-dihydrothiophene **301** was isolated in 83% isolated yield. By contrast, irradiation of **300** in MeOH solution with flow reactor (lamp 2) for 3 hours (4.5 min (residence time)) delivered only *cis*-dihydrothiophene **301** in 97% isolated yield. The stereochemistries of **301** and **302** were assigned, as reported by Schultz, by noting that the ^{1}H NMR spectrum resonance of the methine proton at C2 in the *cis*-dihydrothiophene **301** appears at ~ δ 3.8, while that in *trans*-dihydrothiophene **302** shows a resonance at ~ δ 4.71.



Scheme 129: Schultz cyclisation of **300** to give diastereoisomers **301** and **302** using the flow reactor (lamp-2) shown. *Reagent and conditions*: (i) hν (320 nm), MeOH: toluene (1:3), 98% yield.

These observations have been rationalized via an intermediate thiocarbonyl ylide with more than one fate. Thus, photolysis of **300** in benzene:MeOH solution undergoes conrotatory photoelectrocyclization to provide an intermediate *trans*-fused thiocarbonyl ylide **303** (Scheme 130). In the absence of other effects, the ylide decays by a process involving a symmetry

allowed suprafacial intramolecular [1,4]-hydrogen shift to give the corresponding *trans*-fused dihydrothiophene **302** from which, by epimerization with Na_2CO_3 in MeOH, the more stable *cis*-isomer **301** can be obtained, whereas, photolysis of **300** in methanol solution gives *cis*-isomer **301**; this is considered to be formed by protonation of the carbonyl ylide, then, followed by rearomatization via deprotonation as shown in Scheme 130.[92] The presence of a protic solvent is therefore considered to be the key.



Scheme 130: Proposed mechanism for 6π electrocyclization of enone system **300** to give diastereoisomers **301** and **302**. *Reagent and conditions*: (i) hν (320 nm), MeOH: toluene (1:3); (ii) [1,4 H-shift]; (iii) Na_2CO_3/MeOH; (iv) hν, MeOH, +H, -H.

A comparison was then made to a batch version of the same reaction, with different lamps, to ascertain if there was a difference between batch and flow modes. The procedure of Schultz was followed[99] for the batch reaction, with a little modification by using a 1 mM solution of **300** in toluene and methanol (3:1), degassing with a slow stream of N_2 for 30min prior to the reaction and then photolyzed for 2 hours with a 125 W medium pressure mercury lamp (lamp 1), contained within a water-cooled quartz immersion well. The crude product was concentrated *in vacuo* to give a pale yellow oil in 96% yield which was further purified by flash

column chromatography (SiO_2 9:1 pet.ether/EtOAc) to deliver two fractions; first, a mixture of diastereoisomers of *cis*- and *trans*-dihydrothiophene **301** and **302** (4:1 ratio) in 24% yield and, second, a single diastereoisomer of *cis*-dihydrothiophene **301** was isolated in 72% yield. By contrast, irradiation of **300** for 2 hours with a 125 W medium pressure mercury lamp (lamp 1) in pure methanol, again degassed with a slow stream of N_2 for 30 min. prior to the reaction, delivered a cream solid (mp. 81-82 ^oC) as single diastereoisomer of *cis*-dihydrothiophene **301** in 86% yield. Thus, it can be said that either method is effective, but the flow system provides a small but measurable advantage in terms of irradiation time, so long as adequate exclusion of oxygen can be maintained (otherwise the chemical yield is reduced). This raised the question as to whether this was to do with flow *versus* batch or low-pressure lamp versus a medium-pressure lamp. Book-Miburn has discussed, at some length, the effect of different reactors and lamps; difference in yield of the scale being observed here have been seen in a number of cases.[154] The relatively short residence time noted under the flow conditions may reflect the superior light penetration in such systems, with most of the light in a typical photolysis frequently being absorbed within the outer 1 mm. Below is reported a batch-style irradiation using two different low-pressure lamps in two solvent systems.

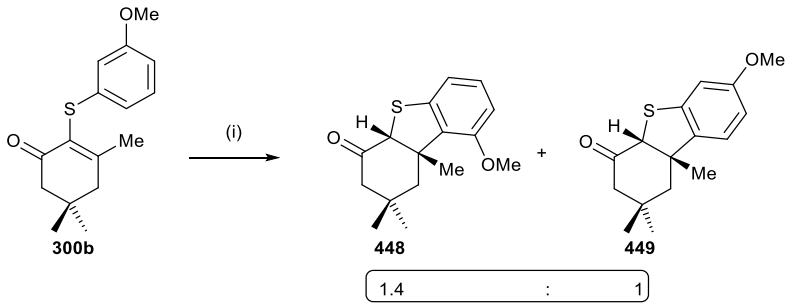
Thus, a solution of **300** in methanol was placed in a Pyrex test tube and degassed with a slow stream of N_2 for 30min prior to the reaction. The reaction mixture was then placed in the Rayonet photoreactor (lamp 4) and irradiated for 30 min with a broad band around 311nm (Rayonet RPR-200, equipped with 16 x RPR-3000Å lamp, 16 x 8 W (low pressure)). The crude product was concentrated *in vacuo* and an orange oil was obtained in 99% yield. The crude product was then triturated with hexane to afford a pale off-white solid which was further purified by crystallization from hexane/diethyl ether to give an analytically pure *cis*-dihydrothiophene **301** as colourless crystals (mp. 81-82 ^oC) in 90% isolated yield.

Upon irradiation of degassed solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** in methanol (1 mmol) with 311 nm Philips 9W low pressure mercury lamp, the crude was concentrated *in vacuo* to give a colourless solid (m.p. 81-82 °C) as single stereoisomer of *cis*-dihydrothiophene **301** in 88% isolated yield. Overall, it appears that there may be a marginal advantage to isolated chemical yields for flow methods over batch, but either method could reasonably be used. The true advantage of flow methods is more likely to be felt for highly absorbing solutions (with concomitant light penetration problems) or for those reactions for which secondary photoreactions of the product are a significant issue.

In respect of irradiation in the toluene/methanol (3:1) solvent mixture, 1mM a solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** in toluene/methanol (3:1) 1 mmol was placed in a Pyrex Schlenk tube and degassed with a slow stream of N_2 for 30 min. prior to the reaction. The degassed solution was irradiated for 1 hour, with a 311 nm Philips 9 W low pressure mercury lamp. The crude product was concentrated *in vacuo* to give pale yellow oil in 95% yield. The crude product was then purified by flash column chromatography to afford a mixture of diastereoisomers of *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **301** and *trans*-dihydrothiophene (±)-(4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*] thiophen-4(1*H*)-one **302** (3:1) in 25% isolated yield and a single diastereoisomer of *cis*-dihydrothiophene **301** in 70% isolated yield.

It should be noted that the product yields of the most stable *cis*-isomer from the photocyclization of **300** in protic solvents were significantly higher than those in a toluene-MeOH mixture. Consequently, all subsequent photoreactions of enones were performed in MeOH and the *cis*-dihydrothiophenes were isolated from column chromatography.

An interesting aspect of this photocyclization reaction was achieved by irradiation of solution of *meta*-methoxy-substituted enone **300b** using 125-W medium pressure mercury (lamp-1) in methanol and degassed with a slow stream of N_2 for 30min prior to the reaction. Irradiation for 2 hours afforded a yellow oily compound in 99% yield as a mixture of isomers. The crude product was purified by flash column chromatography to deliver two fraction: one pure single regio-isomer **448** in 68% isolated yield and two a mixture of the second regio-isomers **448** and **449** (1.4:1 ratio) in 29% yield (Scheme 131).



Scheme 131: Schultz cyclisation of **300b** to give **448** in 63% yield and a mixture of two regio-isomers **448** and **449** (1.4:1) ratio in 27% yield using batch reactor (lamp 2). *Reagent and conditions*: (i) hν (320 nm), MeOH.

However, the cyclisation of **300b** gave a **448** with carbon-carbon bond formation *ortho*- to the *meta*-methoxy substituent as the most predominant product. Evidence for the formation of a mixture of two regio-isomers **448** and **449** was provided by the pattern of the aromatic protons in the COSY spectrum (Figure 53). Analysis of COSY spectrum reveals the presence of three protons of regio-isomer **448** resonated at δ 6.59 as a doublet with *J* 8.0 Hz, δ 6.76 as a doublet with *J* 8.0 Hz, and δ 7.12 as triple *J* 8.0, 2.0 Hz, corresponding to the aromatic protons at C-8, C-6, C-7, respectively. In comparison, three protons of regio-isomer **449** resonated at δ 6.62 as a doublet with *J* 8.0 Hz, δ 6.74 as a singlet, and δ 6.93 as doublet *J* 8.0Hz, corresponding to the aromatic protons at C-8, C-6, C-7, respectively (Figure 56).

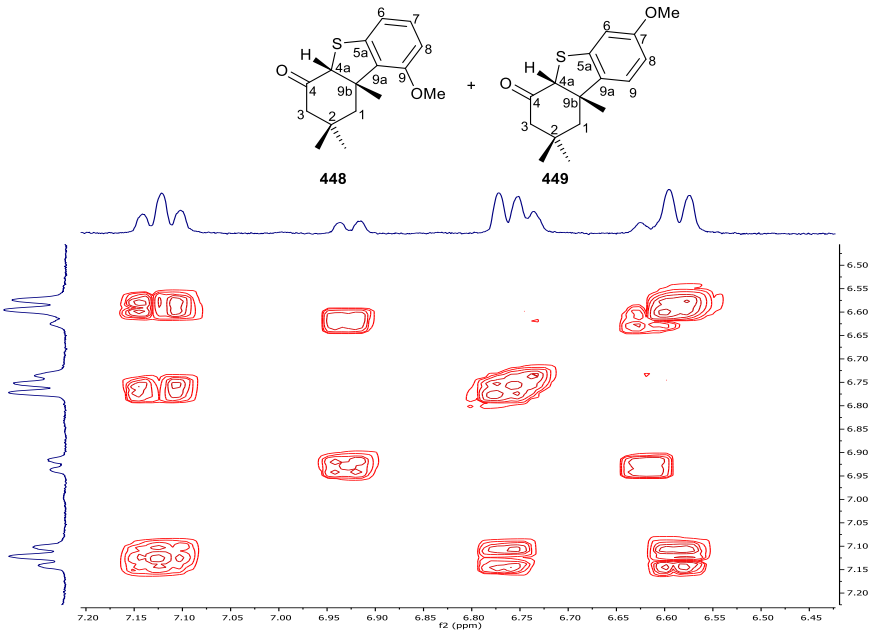
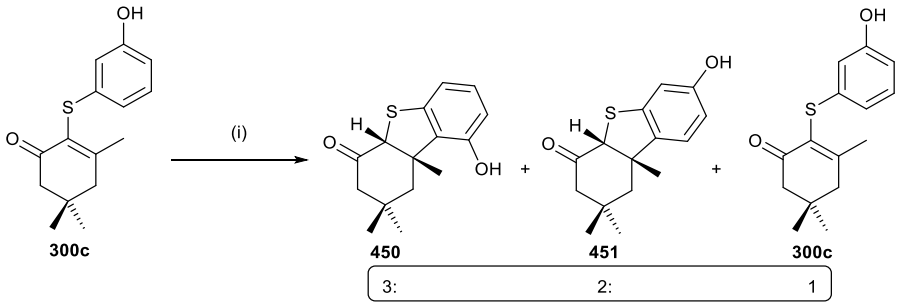


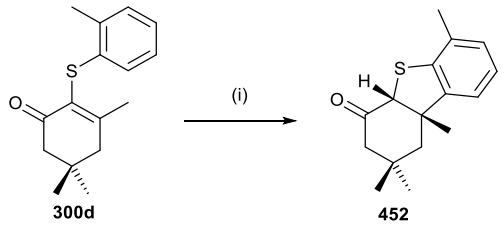
Figure 56: an expansion of the COSY spectrum of aromatic protons of regio-isomers **448** and **449.**

Furthermore, upon exposure of solution of **300c** in methanol to a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well for 2 hours with a slow stream of N_2 for 30min prior to the reaction, afforded yellow oily compounds as a mixture of **450** and **451** and starting material **300c** (3:2:1) in 84% yield as an inseparable mixture (Scheme 132).



Scheme 132: Schultz cyclisation of **300c** to give a mixture of two regio-isomers **450** and **451** (3:2:1) ratio in 84% yield using batch reactor (lamp 2). *Reagent and conditions*: (i) hν (320 nm). MeOH.

Thus, a solution of 2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone **300d** in methanol 1 mM was degassed with a slow stream of N_2 for 30min prior to the reaction and then irradiated for 2 hours, with a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well. The photolysis solution was concentrated *in vacuo* to give a yellow oil in 81% yield of a single regio-isomer (**452**) as shown in scheme (132).



Scheme 133: Schultz cyclisation of **300d** to give a single diastereoisomers **452** in 81% yield using batch reactor (lamp 2). *Reagent and conditions*: (i) hν (320 nm); (ii) MeOH.

As desulfurization of **448** or **450** could yield an *ortho*-alkoxy (hydroxy) aryl unit, suitable for incorporation into a synthesis of stemodinone, it was noted that the methoxy compound **448** is easier to work with and is afforded regioselectively of **449**. Presumably, the C2 aryl carbon has a larger orbital coefficient than that at C6, thus directing bond formation to C2.

2.1.6 Configurational analysis of *cis*-dihydrothiophene 301

The ^{1}H-NMR spectrum provided some convincing evidence for the gross structure of **301**. However, the stereochemistry within the compound was determined using the most prominent regions in the NOESY spectrum (Figure 57) which established a more direct interrogation of the spatial relationships between protons in the *cis*-dihydrothiophene **301**.

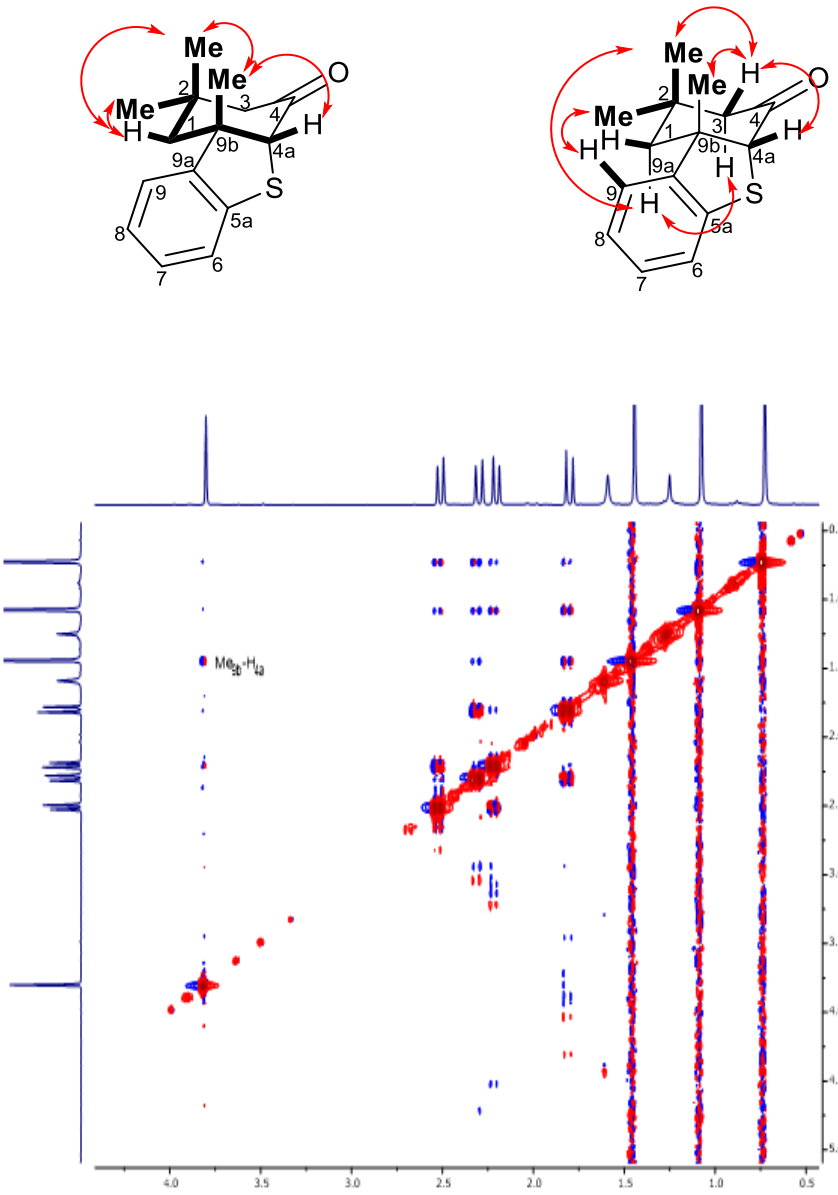


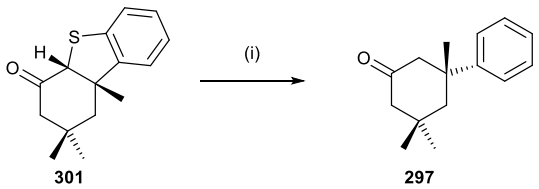
Figure 57: the NOESY spectrum of the *cis*-dihydrothiophene **301**.

Thus, support for the *cis*-stereochemistry of **301** was most clearly obtained from NOEs to the methyl groups. The methyl group on 9b was seen to correlate strongly with Me^{2}, H^{4a}, H^{1}, H^{9} suggesting these sit on the same, *exo*-face of the structure. The lack of a significant correlation to $H^{1'}$ suggested that this exists on the opposite, *endo*-face to Me^{9b}. Further strong NOEs are observed to Me^{2} which show strong correlation to Me^{9b}, H^{3}, H^{1}, H^{9}. However, $H^{1'}$ itself, correlates strongly with $Me^{2'}$ and $H^{3'}$, presenting a consistent picture of these occupying the

endo-face of the *cis*-dihydrothiophene **301**. The protons H^3, $H^{3'}$, and H^1, H^1 both give an NOE to $Me^{2'}$ identifying it as equatorial on the ring, sitting approximately midway between H^3, $H^{3'}$ and H^1, H^1 and therefore proved the other Me^2 group as being axial. Finally, the strong NOE between the methyl group at C-9b and the hydrogen at the C-4a established them as being on the *exo*-side of the compound, fully consistent with the *cis*-structure for **301**.

2.1.7 Synthesis of 3-phenyl-3,5,5-trimethylcyclohexanone

As noted above, introduction of an aromatic nucleus β to a carbonyl could be achieved by heteroatom directed photoarylation with aryl vinyl sulfides. However, the dihydrothiophene ring is superfluous to requirements for a synthesis of stemodinone. Hence, desulfurization is a necessary additional step. Thus, to a stirred suspension of Raney nickel in ethanol was added *cis*-dihydrothiophene **301**. The mixture was heated to reflux, and TLC analysis indicated that all starting material was consumed in ~30 min. While warm, the reaction mixture was filtered under vacuum and the filter cake was thoroughly washed with warm ethanol, then was reacted with dilute 2M HCl. The crude filtrate was concentrated *in vacuo* and gave a mixture of compounds which were separated by flash column chromatography to afford, as a colourless solid (m.p. 109-110 °C) **297** in 74% yield. Thus, conversion of **301** to 3-phenyl-3,5,5-trimethylcyclohexanone **297** was accomplished by desulfurization with freshly prepared Raney nickel in refluxing EtOH solution.[99]



Scheme 134: Schultz desulfurization of **301** to give **297**. *Reagent and conditions*: (i) Raney Ni, EtOH, reflux, ~30 min., 2M HCl, 74% yield.

The ^{1}H-NMR spectrum of **297** consists of three sharp singlet peaks which correspond to the methyl protons resonances on C-3 at δ1.37 and C-5 at δ 0.38 and 1.03 for both axial and equatorial groups. In a COSY spectrum of **297**, the cross-peaks labelled 2_{ax}-2_{eq}, identify the geminal coupling between the axial proton on C-2 at δ 1.91 and the equatorial proton on C-2 at δ 2.26. Likewise, the cross-peaks labelled 6_{eq}-6_{ax}, are the geminal coupling between the equatorial proton on C-6 at δ 2.10 and the axial proton on C-6 at δ 2.22. However, the cross-peaks labelled 4_{ax}-4_{eq}, identify the geminal coupling between the axial proton on C-2 at δ 2.38 and the equatorial proton on C-2 at δ3.06 respectively as shown in the Figure 58.

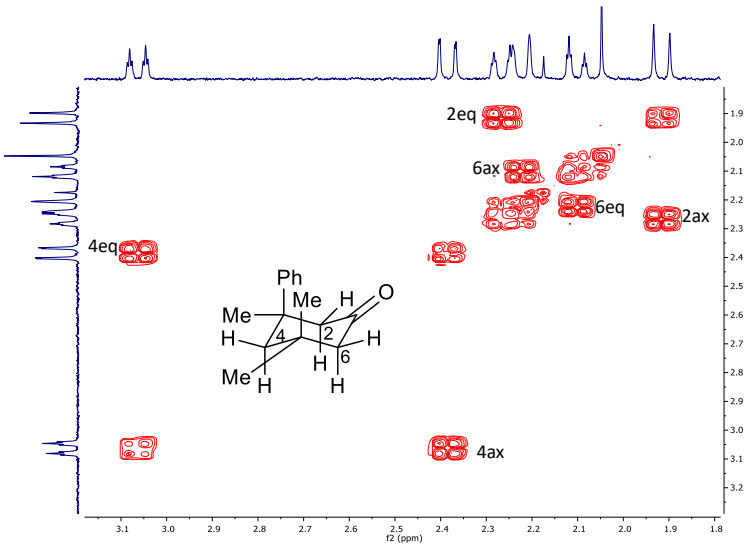


Figure 58: an expansion of the ^{1}H-^{1}H COSY spectrum of **297**.

In 1972, Posner reported that an aryl substituent may be introduced at a carbon atom β to a carbonyl group by conjugate addition of organocopper reagents to α,β-unsaturated carbonyl substrates, include adding a phenyl group to **296** to afford the product **297** (Figure 17).[96] Thus, a Schultz cyclisation followed by desulfurization with Raney nickel is the equivalent to aryl cuprate additions to cyclohexenones, in the present case to afford 3-phenylcyclohexanone **297** (Scheme 134).[92] This is the transformation that proved very low yielding in substrate **443** to give **60** (Scheme 120).

The conformational analysis of **297** has reported it to exist in chair-like conformations with the most favoured conformer having an axial aryl group which can simply ring-flip to place the phenyl group equatorial and severe steric intention between the axial methyl substituent at C-3 and C-5 is inevitable .[92b] The most interesting and informative aspect of the proton-NMR spectrum of **297** is the occurrence of a very high-field resonance for one of the methyl groups at C-5. These high-field shifts are considered to arise from the C-5 methyl group which sits *cis* to an axial aryl substituent, since in this conformation the methyl protons spend a considerable portion of time in the shielding region of the aromatic ring. The equatorial C-5 methyl shift is quite normal, while the C-3 methyl protons are deshielded because they lie near the edge of the aromatic substituent.[92b]

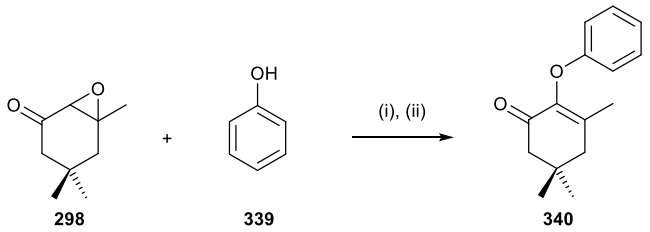
An attractive feature of heteroatom directed photoarylation is the regiospecificity of aromatic substitution *ortho* to the heteroatom, and the heteroatom sulfur can serve as a temporary directing group for carbon-carbon bond formation which can be removed in a subsequent step. The heteroatom sulfur is chosen to be suitable due to availability of a variety of desulfurization techniques.[92]

As we required an *ortho*-methoxy group in compound **60**, this would require desulfurization of a compound of the type **448**. As an alternative, if the directing heteroatom in the Schultz cyclisation was changed from sulfur to oxygen then, after electrocyclization, reductive cleavage of the C-O bond adjacent to the carbonyl would furnish a similar compound. It was decided that this version of the Schultz cyclisation should be compared to the thio-version before synthesis of the desired precursor to stemodinone was undertaken.

2.1.8 Synthesis of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one (340)[95a]

The synthesis of the oxygen analogues followed the same approach as that for compounds such as **300**, though without detection of the intermediate hydroxy compounds seen during the

synthesis of **300** and its analogues. Thus, to accomplish the synthesis of **340**, a solution of phenol **339** in freshly distilled THF was added to a stirred suspension of sodium hydride in THF under a nitrogen atmosphere. After consumption of the NaH, DMPU and isophorone epoxide **298** were added. The resulting solution was heated to reflux for 2 hours, after which TLC analysis showed the reaction to be complete. The crude product was purified by flash column chromatography to give 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1one **340** as a crystalline solid, (m.p. 103-104 ºC) in 95% isolated yield.



Scheme 135: synthesis of Schultz cyclization precursor aryloxyenone **340**. *Reagent and conditions*: (i) NaH, THF; (ii) DMPU, **298**, 2h, 95% yield.

Thus, due to the decreased nucleophilicity of phenoxide (χ_O 3.44) compared to thiophenoxide (χ_O 2.58) more vigorous condition were required to successfully effect the epoxide ring opening with phenol **339**.[95a] Schultz recommended use of KH in HMPA (hexamethylphosphoramide), however, the extremely pyrophoric nature of KH and the carcinogenic properties of HMPA suggested that alternative conditions might be better. Sodium hydride is also a strong base (pK_{aH} ~ 35) that will irreversibly deprotonate the phenol (pK_a ~10) providing the sodium phenoxide anion rather than potassium phenoxide. However, this was judged to be of little consequence if the metal ion was highly solvated. HMPA is a dipolar aprotic solvent with a high dielectric constant (ε = 30.54) and dipole moment (μ = 5.39 D)[155] and so needs to be replaced with a similar, but less dangerous solvent: Seebach has shown that DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) (ε = 36.1, μ = 4.23) is a suitable surrogate.[156] Related conclusions were reached by Bach, Jadhav and Smith.[157]

Furthermore, evidence for the formation of enone system **340** was provided by the ^{1}H-NMR spectrum, with the diastereotopic protons at C4 and C6 in **298** having collapsed to two new singlet peaks at δ 2.42 and δ 2.43, indicating their characteristic homotopic nature. The five protons of the aromatic ring appeared as three sets of resonance: one doublet at δ 6.83 for the two *ortho*- protons, one triplet at δ 6.97 for the *para*-proton and one doublet of doublets for the two *meta*-protons at δ 7.25. The DEPT/HSQC spectra were used to assign all the protonated carbon signals (Figure 56). Other evidence from the HSQC spectrum of **340** indicated that the two geminal pairs of protons at C-4 and C-6 correlated to resonances at δ 45.66 and δ 51.74, respectively. Assignment of the C2 carbon and the carbonyl carbon signals were confirmed to be at δ 129.63 and δ 192.83 from ^{13}C NMR spectra. The HRMS (+ESI) m/z [$(MH)^{+}$] was consistent with the molecular formula of $C_{15}H_{19}O_2$.

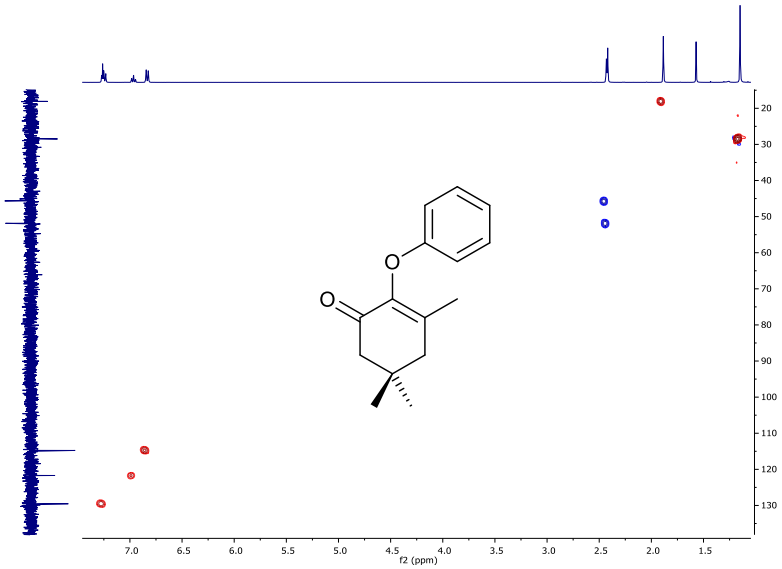
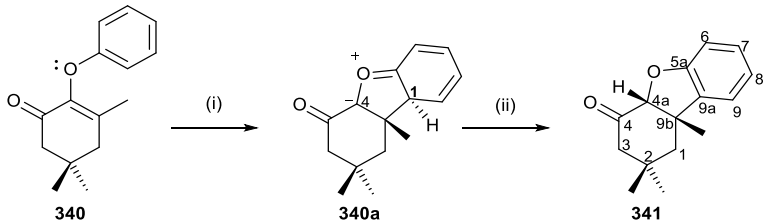


Figure 59: HSQC spectrum of Schultz cyclization precursor aryloxyenone **340**.

2.1.9 Synthesis of (±)-(4aR,9bS)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[b,d]furan-4(1H)-one (341) and (±)-(4aS,9bS)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[b,d]furan-4(1H)-one (342) [95]

Consideration of the reported aryl ether photochemistry and efficiency of the formation dihydrothiophene from 2-thioaryloxyenones suggested that the studies could begin with the photolysis of 2-aryloxyenone **340** for *cis*-dihydrofuran **341** to be formed. Pyrex-filtered photolysis of a deoxygenated methanol solution (nitrogen saturated) of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one **340** (23 mg) was performed in a Schlenk tube. The degassed solution was irradiated for 3 hours, with a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well, and this gave a white solid (19.6 mg, 85%) as mixture of *cis*-dihydrofuran **341** and starting material **340** (3:1 ratio). The crude product was purified by flash column chromatography to afford a colourless solid (m.p 86-87 °C, lit. m.p 85-87 °C) (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one **341** as a single isomer (14.8 mg, 64%) (86% based upon recovered starting material). As with **300a-d**, in methanol solvent **340** undergoes cyclization-rearrangement to form *cis*-dihydrofuran **341**.[95] This reaction presumably proceeds through the carbonyl ylide intermediate **340a** intermediate followed by rearomatization via protonation/deprotonation, as shown in Scheme136.

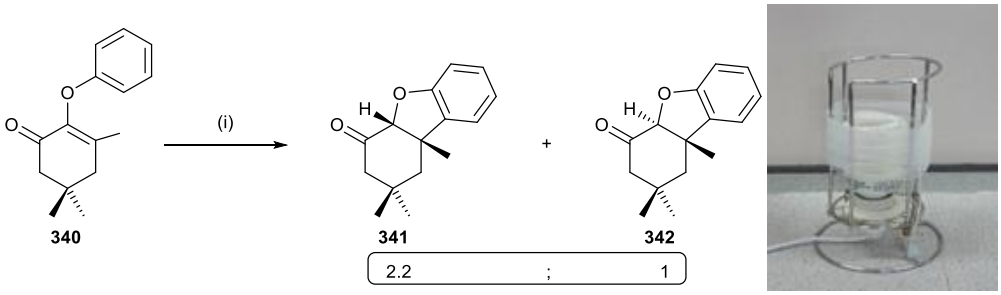


Scheme 136: Schultz mechanism for 6π electrocyclization of enone system **340** to give a single diastereoisomer **341** in 64% yield using batch reactor (lamp 1). *Reagent and conditions*: (i) hν (320 nm), MeOH; (ii) spontaneous +H, -H.

The stereochemistry of **341** was assigned, by noting that the resonance of the methine proton at C4a in the *cis*-dihydrofuran **341** appears at ~ δ 4.53, as reported by Schultz. Other evidence for the formation of **341**, provided by the ^{1}H-NMR included the two proton singlets at C4 and C6 in **340** having been changed to two new diastereotopic pairs of resonances. First, a doublet on C1 at δ 1.95 with *J* value 14.6 Hz for the axial proton and doublet of doublet at δ 2.27 with *J* 14.6, and small coupling at 1.6 Hz indicating the equatorial proton at C1. Second, a doublet of doublets at δ 2.22 with J_{gem} value of 13.0 Hz and a small W-coupling of 2.4 Hz is for the C3 equatorial protons and a doublet at δ 2.42 with *J* value at 13.0 Hz indicating the axial proton at C3. The four protons on the aromatic ring appeared as four resonances: one apparent triplet at δ 6.90 for a proton at C7Ar, one doublet at δ 6.96 for a proton at C6Ar, one doublet at δ 7.04 for a proton at C9Ar, and one apparent triplet at δ 7.14 for a proton at C8Ar respectively. The *cis*-dihydrofuran is considered to be the stable configuration for a fused five-six-membered ring system capable of epimerization, and on treatment with methanolic sodium hydroxide at room temperature, **341** was recovered unchanged.[150]

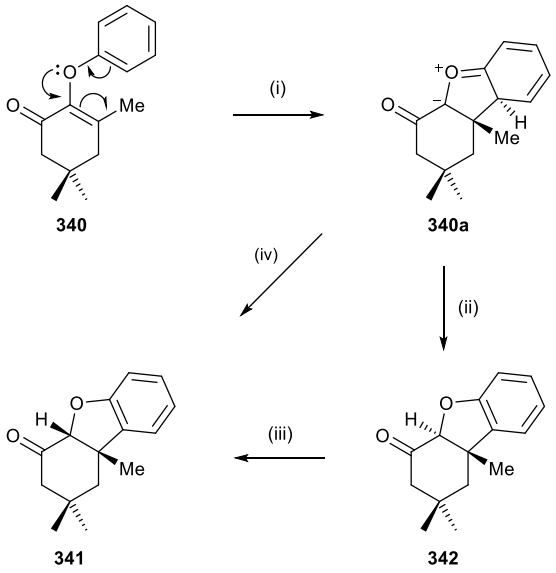
Photolysis (cutoff around 280 nm) of a toluene/methanol (3:1) solution of 2-aryloxyenone **340** in flow reactor (lamp 2) using a band with λ_{max} 320 nm for 16 min (residence time) gave a crude product as the expected mixture of two diastereoisomers in 97% yield. The crude product was further purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford two fractions; first a mixture of diastereoisomers of *cis*- and *trans*-dihydrothiophene **341** and second, a pure sample of **342** in 67% and **342** 30% yields (Scheme 137). The stereochemistries of **341** and **342** were assigned, as above, with the methine proton at C2 in the *cis*-dihydrofuran **341** appearing at ~ δ 4.53, while that in *trans*-dihydrofuran **342** resonated at ~ δ 4.90. It is interesting that when compared to the batch photo-reactor, that the flow photo-reactor gives a slightly higher yield. When compared to the equivalent reaction of thio-species **300**, the

stereoselectivity is slightly lower (2.2:1 compared to 3:1) suggesting more efficient intermolecular protonation of **340a** by MeOH; whereas the reaction time was a little slower.



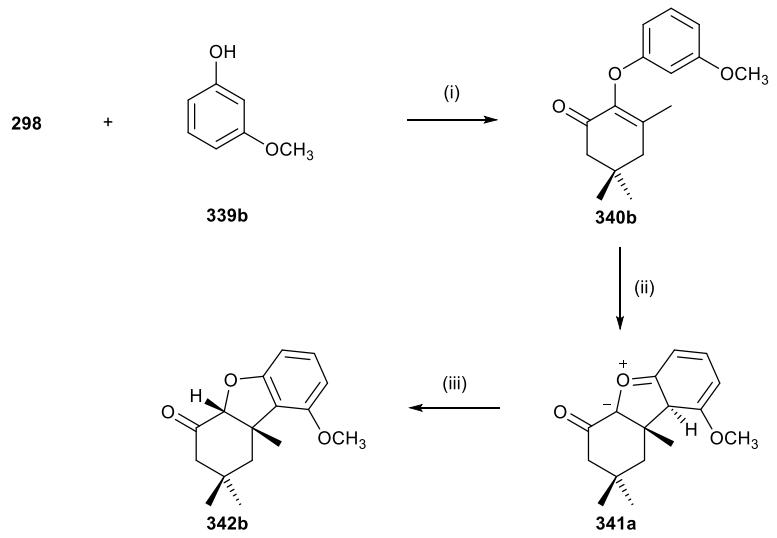
Scheme 137: Schultz cyclisation of **340** to give diastereoisomers **341** and **342** using the flow reactor (lamp 2) shown. *Reagent and conditions*: (i) hν (320 nm), MeOH: toluene (2.2:1), 97% yield.

These observations on the change of stereoselectivity upon variation of the solvent can be rationalized in the same manner as for the thio-analogues *i.e.*, via an intermediate carbonyl ylide with more than one fate. Thus, photolysis of **340** in benzene solution undergoes conrotatory photoelectrocyclization to provide an intermediate *trans*-fused carbonyl ylide **340a** (Scheme 138). In the absence of other effects, the ylide decays by a process involving a symmetry allowed suprafacial intramolecular [1,4]-hydrogen shift to give the corresponding *trans*-fused dihydrothiophene **342** from which, by epimerization with Na_2CO_3 in MeOH, the more stable *cis*-isomer **341** can be obtained as in the sulfur examples. Photolysis of **340** in methanol solution gives *cis*-isomer **341**; this is formed by protonation of the carbonyl ylide **340a** followed by rearomatization via deprotonation as shown in Scheme 138.[92]



Scheme 138: Proposed mechanism for 6π electrocyclization of enone system **340** to give diastereoisomers **341** and **342**. *Reagent and conditions*: (i) hν (320 nm), MeOH: toluene (1:3); (ii) [1,4 H-shift]; (iii) Na_2CO_3/MeOH; (iv) hν, MeOH, +H, -H.

The dihydrothiophenes prepared by heteroatom directed photoarylation have been reported to undergo a variety of high yielding, synthetically interesting transformations, whereas benzoannelated dihydrofurans have been used for natural product synthesis.[92] The reaction is flexible with phenols having bulky substituents at the *ortho*-position such as 2-*tert*-butyl-5-methyl phenol being successful. Furthermore, phenols with an electron-withdrawing substituent *e.g*. *m*-methoxyphenol **339a** work although their lower pK_a might have been expected to reduce phenoxide nucleophilicity, they are sufficiently reactive to afford aryloxyenones in a very high yields. Interestingly, Schultz noted that the photocyclization of 2-aryloxyenone **340** substituted in the *meta*-position with methoxy-group resulted in cyclization with the possibility of two regioisomeric products, with the major product exclusively with the methoxy group in a position *ortho* to furan ring (Scheme 139).

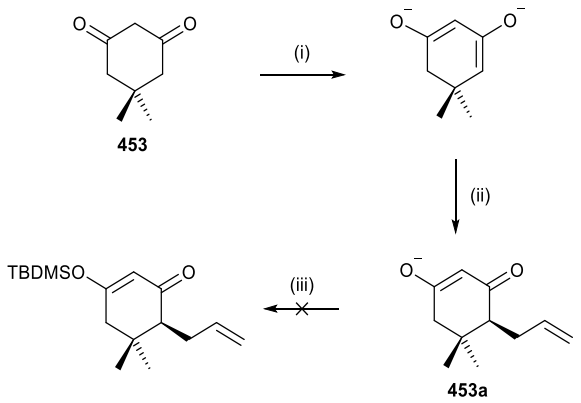


Scheme 139: Schultz photolysis of **340b** to give regioisomer **342b** . *Reagent and conditions*: (i) KH (0.1 equiv), **339b** (1.1 equiv.) THF, DMPU (0.75 equiv.), 90% yield; (ii) hν (320 nm); (iii) MeOH: benzene: AcOH (1:1:1), 8h, 92% yield.

This methodology offers a unique route to a wide variety of natural products with medicinal value. The formation of a carbon-carbon bond from the aryl group to a quaternary carbon atom by heteroatom directed photoarylation has been instrumental in total synthesis of the galanthamine-type alkaloid, lycoramine as well as the synthesis of structural analogues of morphine and codeine compounds. More recently, Smith has used a version of this reaction, based on a 2-aryloxy-α,β-unsaturated γ-lactone, to make morphine itself.[158] The ease of carrying out the photolysis and good chemical yields confirmed the worth of examining the heteroatom directed photoarylation method for the synthesis of stemodinone **1**. The key challenge remaining is the likely difficult task of carrying out the photoreaction with a 4-substituent on the enone, a problematical substrate type as discussed above, in respect of the cuprate addition to **443**.

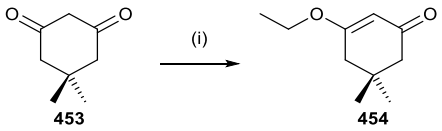
2.1.10 Synthesis of the gem-dimethylated starting material (454) [32]

From the reviewed literature, the direct alkylation of dimedone **453** using two equivalents of LDA[1470] and one equivalent of allyl iodide, with subsequent TBDMS trapping of the resultant enolate **453a** has proven ineffective (Scheme 140).[32]



Scheme 140: Proposed direct alkylation of dimedone **453.** *Reagents and conditions*: (i) LDA (2equiv.), THF, -78 °C; (ii) allyl iodide (1equiv.), -78 °C; (iii) TBDMSOTf, -78 °C.

This result suggests that an alternative two step alkylation procedure must be employed, with the first step consisting of preparation of the familiar 3-ethoxy-α,β-unsaturated ketone **454** which has literature precedent (Scheme 141).[147,148]



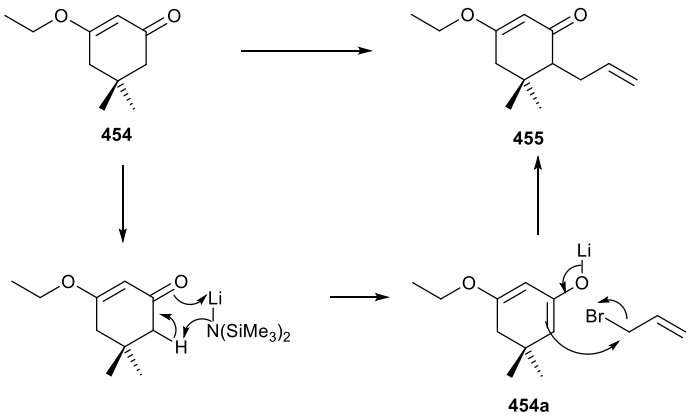
Scheme 141: Preparation of the *gem*-dimethylated starting material **454**. *Reagents and conditions*: (i) EtOH, benzene, cat. *p*-TsOH, reflux, 30min (76%).

Thus, a solution of dimedone **453** in benzene and ethanol was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate, before being heated at reflux for 30 minutes. Following the slow removal of the benzene/ethanol/water azeotrope via distillation a pale- yellow oil was

obtained that crystallized from hexane at -18 °C, yielding 3-ethoxy-5,5-dimethylcyclohex-2-enone **454** as a colourless crystalline solid, which was to be the foundation of the proposed synthesis (Scheme 141). All analytical data correlated with these reported in the literature,[147,148] and the presence of a triplet at δ 1.36 and quartet at δ 3.89 in the ^{1}H-NMR spectrum indicated the desired incorporation of the ethoxy-group. HRMS (+ESI) confirmed the molecular ion mass of 169.1223, consistent with the formula $C_{10}H_{17}O_2$ (Calc. 169.1229 [$(M+H)^+$]).

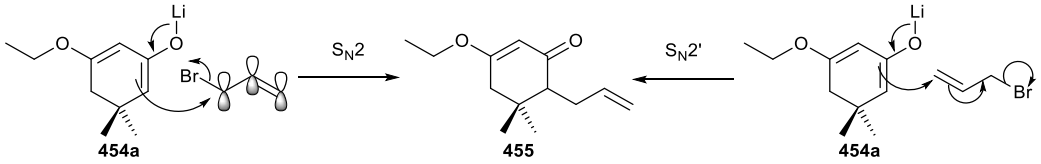
2.1.11 Addition of the carbon tether

In respect of the planned *meta*-photocycloaddition, it has been established that, unless the conformational freedom of tether linking the aromatic ring and the alkene is restricted, substrates with four-carbon tethers are inefficient as part of an intramolecular photocycloaddition reaction[80,82]. In this study, the four-carbon tether is to be restricted via incorporation into a rigid ring system. That is to say, two of the four required carbon atoms are already in place in the ring of α,β-unsaturated ketone **454** and only extension of the tether is necessary via alkylation (Scheme 142). In the present study, a three-carbon tether will be introduced first to suppress potential competitive intramolecular [2+2]-cycloaddition during the Schultz cyclisation, before subsequent one carbon homologation. Thus, allylation of **454** was carried out.



Scheme 142: Alkylation of the lithium enolate **454a**. *Reagents and conditions*: (i) LHMDS, DMPU, allyl bromide, THF, -78 °C, 15h, in 77% yield.

The lithium enolate **454a** was formed through deprotonation adjacent to the carbonyl and underwent S_N2 reaction with the required allyl substrate. It is important to note that allyl bromide (commercially obtained) was used during this study, and allylation is known to occur via both the S_N2 and S_N2' pathway (Scheme 142).



Scheme 142: degenerate S_N2 *vs* S_N2' pathways for allylation

Lithium diisopropylamide (LDA) is frequently the base of choice in such deprotonations (pK_a 35.7)[159] but upon consideration of the pK_a value of the proton α to the carbonyl (~20 in H_2O) it was determined that lithium hexamethyldisilazane (LHMDS) is basic enough (pK_a 29.5)[159] to effect deprotonation and it is both commercially available and significantly more stable towards storage. The generation of three new groups resonances in the low field region (δ 5.85, 502, and 494 in MeOH-*d*$_4$) of the ^{1}H NMR spectrum that are characteristic of a terminal alkene and that integrate to three protons indicate that the reaction was successful. The COSY -NMR spectrum provides further evidence by revealing coupling between protons on the alkyl chain and adjacent ring proton. However, the nature of NMR solvents can also have a significant influence on the appearance of the spectrum and as such substantial changes can sometime be observed on changing the solvents. A useful switch of NMR solvent is from a non-aromatic solvent such as $CDCl_3$ into an aromatic solvent C_6D_6, making use of magnetic anisotropy exhibited by the deuterated benzene.[151] When $CDCl_3$ and MeOD-*d*$_4$ were used to run the ^{1}H-NMR spectrum of **455** (Figure 56 (a) and (b)) overlapping protons multiplets were observed for the two sets of the geminal protons at the C4 and C11. Thus, C_6H_6-d_6 were employed and

those geminal protons were resolved into two pairs (Figure 56 (a)). Those at C4 on the cyclohexanone ring were found to resonate at δ 2.00 as a doublet with *J* value of 4.7 Hz (highlighted in black); whereas, the geminal protons on the allyl chain at C-12 (highlighted in yellow) appear as diastereotopic protons at δ 2.15 (apparent doublet of quartets J_{gem} = 14 Hz) and at 2.56 (doublet of doublet of doublets J_{gem} = 14 Hz). The proton on C6 resonates independently in the three deuterated solvents used, as highlighted in red in Figure 60.

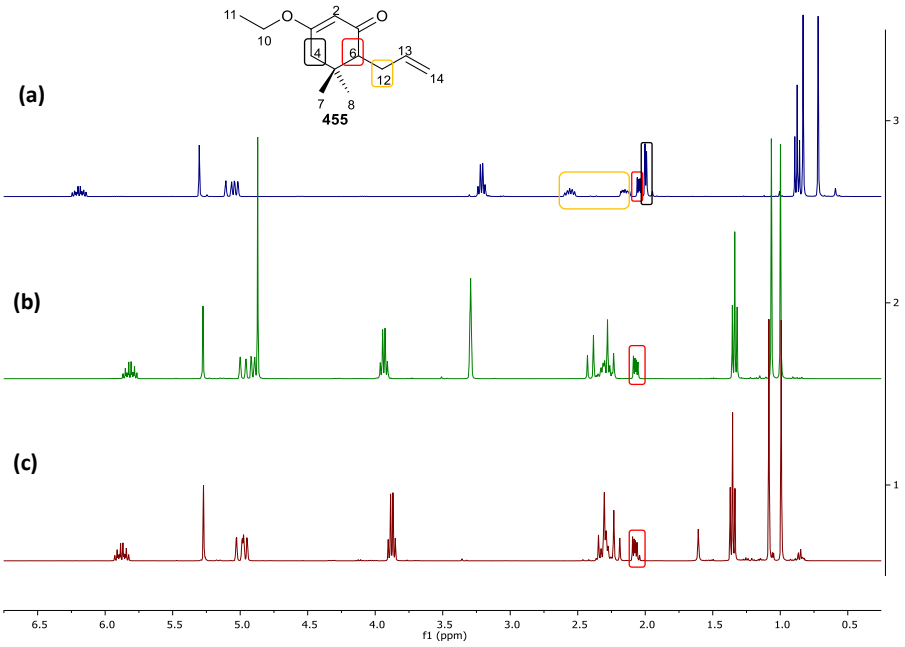


Figure 60: comparison of the ^{1}H-NMR spectrum of **455** in different solvents (a) **455** in benzene-d_6; (b) **455** in methanol-d_4; (c) **455** in $CDCl_3$.

2.1.12 Stork-Danheiser 1,3-carbonyl transpositions[160]

Inspection of the structure of stemodinone **1**, clearly reveals that installation of a methyl substituent would be required at the C3 position of the photocycloaddition precursor which will translate to that at the junction between the A and B rings of the stemodinone framework (Figure 61).

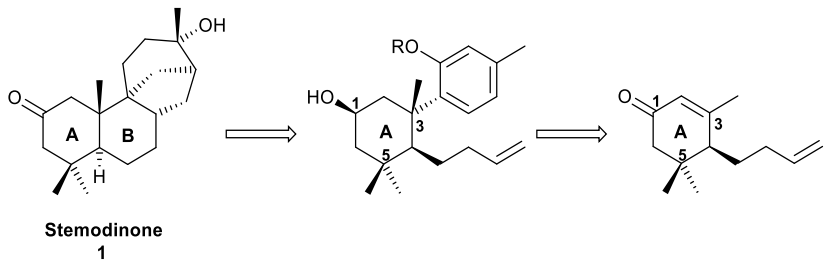
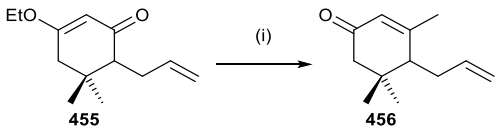


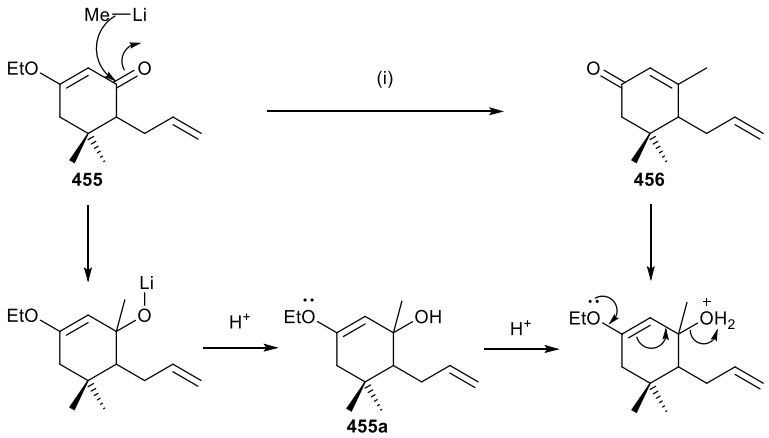
Figure 61: mapping of the C3 methyl group from stemodinone **1**.

The alkylated α,β-unsaturated ketone **455** were treated with methyllithium in diethyl ether and stirred for 3 hours prior to the addition of hydrochloric acid (Scheme 143).



Scheme 143 methylation and rearrangement of α,β-unsaturated ketone **455**. *Reagents and conditions*: (i) MeLi, Et_2O, r.t, 3h then HCl, r.t, 2h, 70% yield.

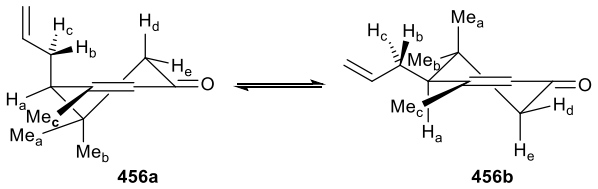
Because of the electropositive lithium atom, the Li-C bond has its electron density polarized towards carbon. This makes methyllithium a very powerful nucleophile which attacks the empty π* orbital of the carbonyl group. Thus, upon addition of acid, any excess methyllithium is protonated, and it facilitates the formation of the alcohol **455a**. The excess of acid initiates the 1,3-carbonyl transposition that affords the corresponding trimethylated ketone **456** (Scheme 144).



Scheme 144: mechanism of methylation and 1,3-carbonyl transposition.

2.1.13 Conformational analysis of trimethylated enone 456

Boyd reported that the controlling factor in the copper-catalyzed conjugate addition is the steric constraint imposed on the β-carbon of the enone **456** by the methyl group at C3, allyl group at C4 and *gem*-dimethyl at C5. Boyd further suggested that if substituents are only present on two of the three carbons then reaction proceeds swiftly and in high yield. Thus, conformational analysis of the trimethylated enone **456** reveals that a combination of the three substituents severely inhibits the aryl cuprate intermediate approach, hence the decision to employ the Schultz approach. It is reasonable to propose a half-chair conformation for the ring system (Figure 62), even though, the ring system may be slightly flatter.



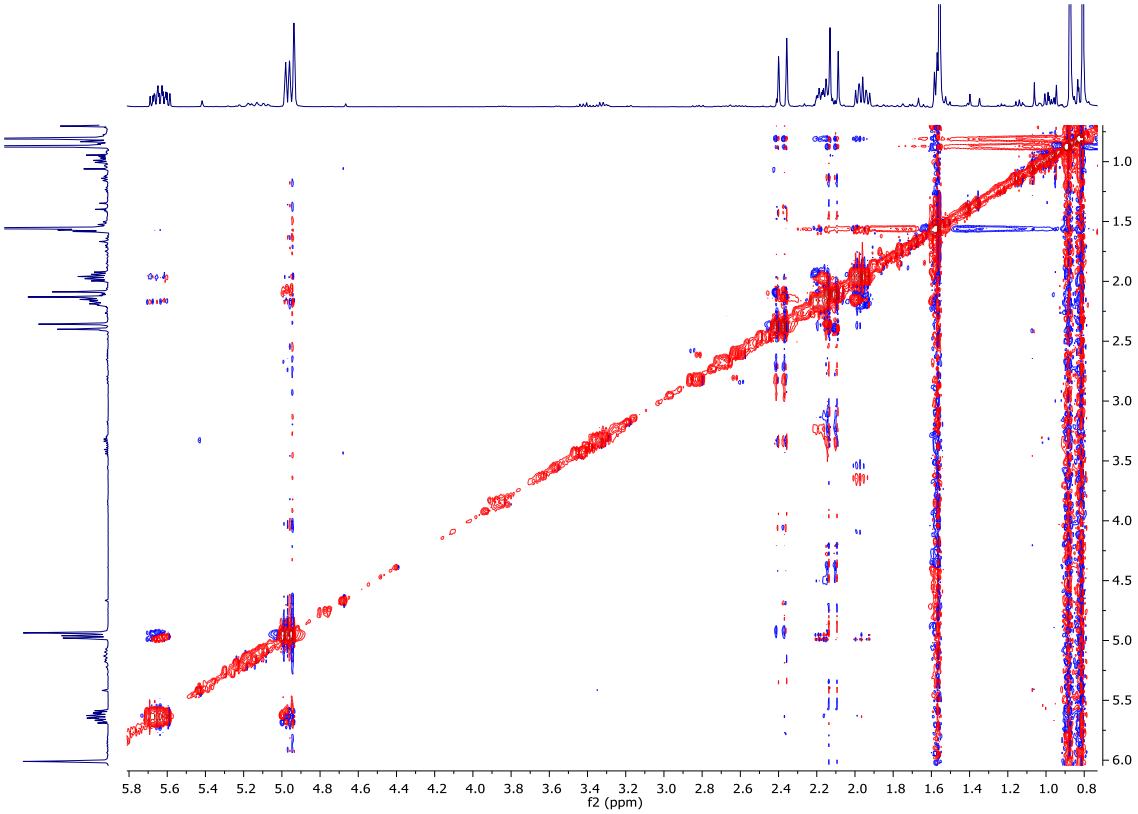


Figure 62: NOESY spectrum and the conformations of trimethylated enone **456a** and **456b**.

It has been reported that analysis of NOESY spectrum allows the determination of the preponderant conformation of the enone **456** in solution. Thus, enhancements of the spectrum at δ 1.46 indicate that H_a is equidistant from both Me_a and Me_b and this can only occur in conformation **456a** in which H_a is equatorial; whereas, in conformation **456b** H_a would have a greater proximity to Me_b than Me_a thereby effecting a significant difference in the intensity of the signals which is not evident. The lack of any interaction between H_a and H_e also implies that conformation **456b** is not the preponderant conformation since both protons would be related through a 1,3-diaxial interaction. In addition, in conformation **456b** it would be more likely that H_b and H_c would correlate to both Me_a and Me_b equally since the allyl chain is equatorial and bisects the *gem*-dimethyl group. Furthermore, the significant difference in intensity shown in both enhancements at δ 1.85 and δ 2.06 indicates that both H_b and H_c have a

greater proximity to Me_a than Me_b thereby suggesting that conformation **456a** is the predominant conformation.

Indeed, if the equilibrium does strongly favour conformation **456a**, then this explains why conjugate addition to trimethylated enone **456** is so difficult. The allyl chain is forced into an axial position due to $A_{1,2}$-strain with Me_c. This blocks approach of the cuprate species from the β-face and the axial methyl group Me_b subsequently restricts access from the α-face.[134b] However, without the allyl group chain, isophorone **296** only has an axial methyl group at C3 to restrict access to a single face in the same way that the allyl enone **456** has only an axial allyl group to block a single face. The dimethylated enone has no methyl group on the β-carbon of the enone and as such, $A_{1,2}$-strain is eliminated thereby allowing the allyl chain to adopt an equatorial orientation, leaving one face open to approach of the cuprate species (Figure 59).

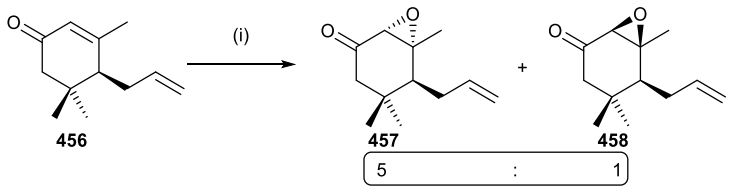
To account for the small amount of product that is formed by conjugate addition to **456**, either inefficient addition takes place to **456a** or reaction takes place through a minor amount of conformation **456b**.[134b]

The trimethylated ketone **456** was perfectly set up to investigate the next step in the preparation of the photocycloaddition precursor, **442**.

2.1.14 Epoxidation of trimethylated ketone

For the same reason that cuprate addition to **456** was found to be difficult, epoxidation was also likely to be problematical. However, peroxide is sufficiently stable for a slow reaction to be successful and peroxide is sterically much smaller than diaryl cuprate, particularly in view of the initial attack coming from the copper atom afford a Cu(III) intermediate. The epoxidation of trimethylated enone **456** in MeOH proceeded uneventfully using 3.1 mole equivalent of basic hydrogen peroxide at 15 °C. 5.1 mole equivalent of sodium hydroxide solution was added in a dropwise manner and stirred over a period of 1 hour. The temperature of the reaction

mixture was maintained at 20-25 °C for a further 3 hours and subsequent TLC analysis revealed that no more starting material was being consumed. Following workup, the resulting to afford an inseparable mixture of (±)-(1*R*,5*S*,6*R*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **457** and (±)-(1*S*,5*S*,6*S*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **458** (5:1) as a pale-yellow oil in 41% isolated yield (Scheme 145).[146a,146b] Considering the high level of steric hinderance in **456**, this was judged to be an acceptable yield; however, if the Schultz cyclisation proved successful, a new method for constructing **457**/**458**, or indeed **459** may prove necessary.



Scheme 145: epoxidation of trimethylated enone **456**: *Reagent and conditions*: (i) H_2O_2 (3.1 equiv.), NaOH (5.1 equiv.), MeOH, 20-25 °C, 3h, (5:1 ratio of **457** and **458**) (41%).

Mechanistically, by virtue of the electronegativity difference of the carbon and oxygen atoms, the trimethylated enone **456** is electrophilic at both the carbonyl carbon and the β-carbon atoms. The sodium hydroxide (pK_a = 15.7) and hydrogen peroxide (pK_a = 11.6) set up an equilibrium favouring the hydroperoxide anion, which is highly nucleophilic. This usually of high nucleophilicity, as compared to hydroxide, and this was originally considered as an example of the so-called α-effect, an increase in the energy of the ion's HOMO by interaction between its adjacent lone pairs. However, detailed study has traced this effect to the lower energy of solvation of hydroperoxide compared to hydroxide.[161] The nucleophile is preferentially added to the β-position of the trimethylated enone **456,** (Figure 63), giving an enolate anion, which is

itself a good nucleophile. Since the hydroperoxide carries a reasonable leaving group (-OH), and a low enthalpy O-O bond (146 kJ/mol^{-1}), internal attack occurs to give an epoxide.

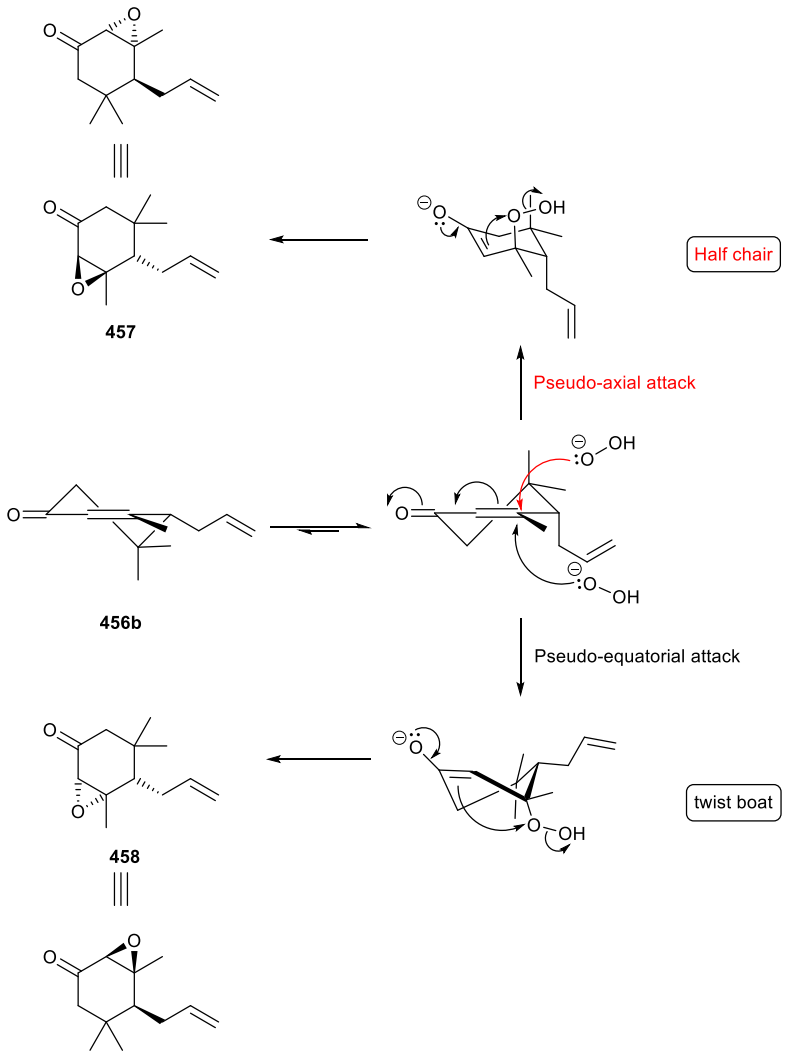
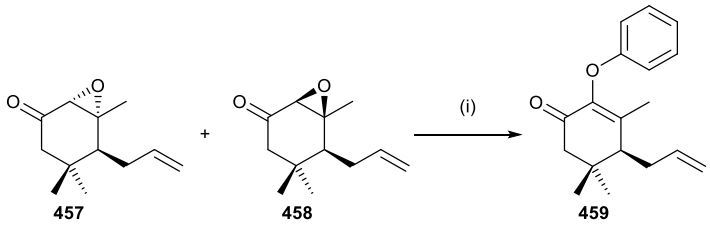


Figure 63: mechanism for the nucleophilic epoxidation of trimethylated enone **456**

The mechanism of the epoxidation of **456** is shown in Figure 60. In agreement with the earlier discussions, the hydroperoxide anion is seen to add in a conjugate fashion to conformer **456a**, with preferential attack *anti* to the allyl group, from the pseudo-axial direction, to deliver an enolate intermediate in a half-chair conformation that ring closes to give **457**.[152] By contrast, attack from the pseudo-equatorial direction (*syn* to the allyl group) leads to a higher energy twist-boat enolate intermediate that reacts further to give the minor diastereoisomer **458**. From the combined yield of 41%, the amount of **457** in the mixture was estimated as 34%.

2.1.15 Synthesis of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone (459)

A solution of phenol **339** in freshly distilled THF was added to a stirred suspension of sodium hydride in THF under a nitrogen atmosphere. After consumption of the NaH, DMPU and a mixture of (±)-(1*R*,5*S*,6*R*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **457** and (±)-(1*S*,5*S*,6*S*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **458** were added. The resulting solution was heated to reflux for 2 hours, and the reaction was judged to be completed by TLC analysis. Following isolation and chromatography, (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459** was obtained but with traces of phenol **339** still present. Taking advantage of phenol's relatively low pK_a (~10) it was removed by washing with aqueous 1 M NaOH. In this manner, **459** was obtained as yellow oil in a good 68% yield (Scheme 146).



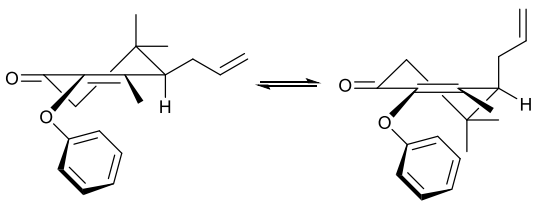
Scheme 146: synthesis of Schultz cyclization precursor (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459.** . *Reagents and conditions*: (i) PhOH, NaH(cat.) then **457**/**458**, THF, DMPU, 2h, 68% yield.

Evidence for the formation of enone **459** was provided by its ^{1}H-NMR spectrum; the diastereoisomeric epoxides **457**/**458** have been replaced a single compound with the methine proton at C1 in epoxides **457/458** having disappeared. The presence of a stereogenic centre is reflected in the appearance of the three methyl groups and diastereotopic protons at both at C6 and the allyl moiety. The five protons of the aromatic ring appeared as three sets of signals: a triplet for δ 6.97 for one *para*-proton, a multiplet at δ 7.10-7.18 for two *ortho*- protons, and a multiplet at δ 7.21-7.31 for *meta*-protons. The DEPT/HSQC spectra were used to assign all the protonated carbon signals. The ^{13}C NMR spectrum of **459** indicated that of the geminal pair of

protons at C-6 were found to be both correlated to the same carbon from the HSQC cross peak at δ 34.92.

2.1.16 Conformational analysis of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone (459)

Analysis of NOESY spectrum allows the determination of the preponderant conformation of the enone **459** in solution. By analogy with **456**, the $A_{1,2}$ interaction between the allyl group and the vinyl methyl group should favour a pseudo-axial allyl unit (**459b** in Figure 61). Each of the protons of the allyl CH_2 correlate to the same one of the two geminal methyl groups, and not the other. Allowing for free rotation of the allyl group, this is more consistent with **459b** than **459a**. The enhancements seen between the *ortho* and *meta*-phenoxy protons and one of the two geminal methyl groups is also more consistent with **459b**; interestingly, the observed enhancement is to the other geminal methyl to that enhanced by interaction with the geminal protons on the allyl group, again consistent with **459b**. That these enhancements with the phenoxy group are observed suggests that the ring is predominantly sitting on the opposite face of the molecule to the allyl group, as required for the synthesis of stemodinone. The lone proton at C4 shows the expected enhancements to both two geminal methyl groups.



459a **459b**

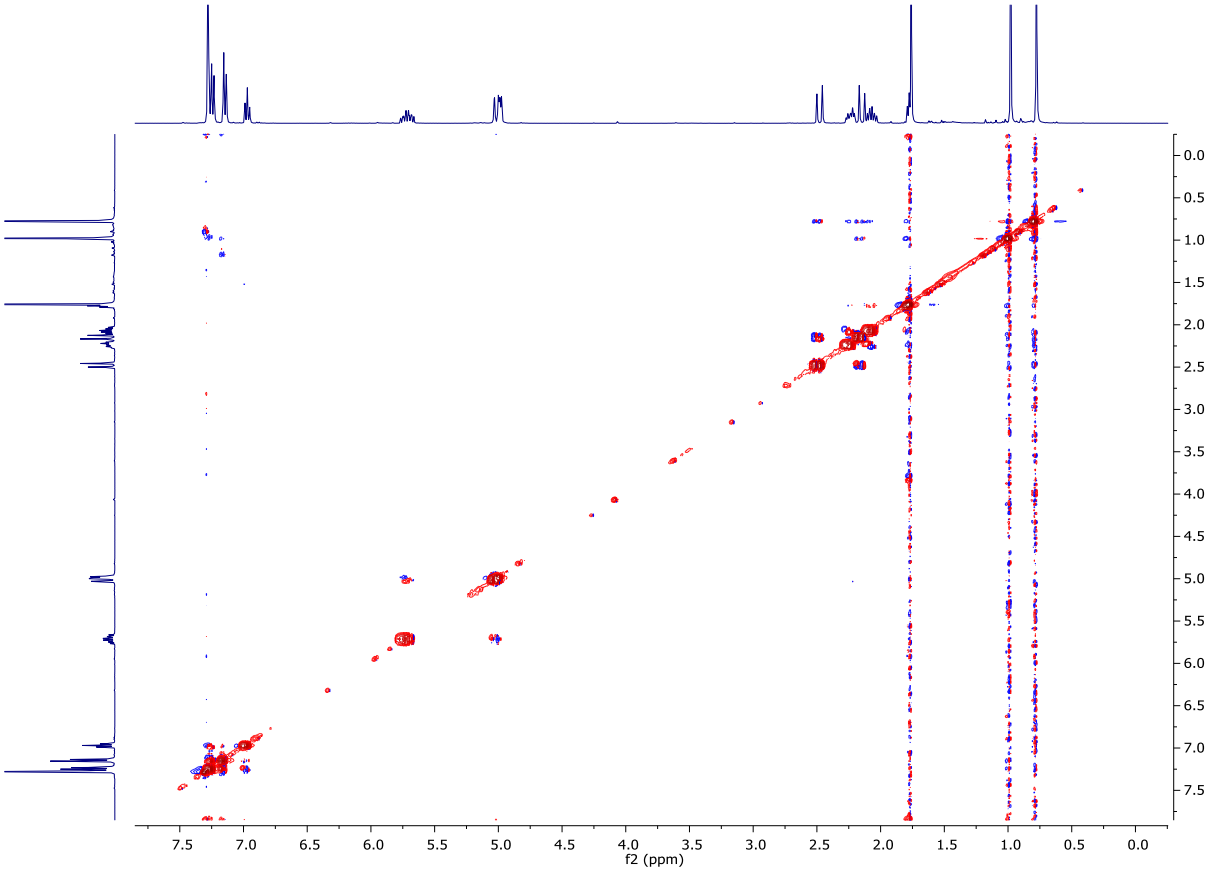


Figure 64: NOESY spectrum and conformations of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459a** and **456b**.

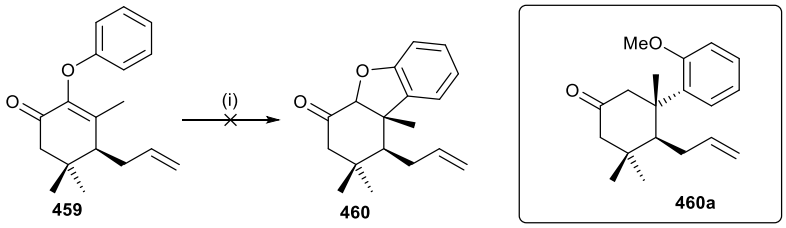
Indeed, if the equilibrium does strongly favour conformation **459a**, then this explains why conjugate addition to trimethylated enone **459** is so difficult. The allyl chain is forced into an axial position due to $A_{1,2}$-strain with Me_c. This blocks approach of the cuprate species from the β-face and the axial methyl group Me_b subsequently restricts access from the α-face.[134b] However, without the allyl group chain, isophorone **296** only has an axial methyl group at C3 to restrict access to a single face in the same way that the allyl enone **459b** has only an axial allyl group to block a single face. Schultz assumed that **459a** represented the conformation of **459**, which showed that the phenyl group should approach C-3 from the least sterically hindered face of the C2-C3 double bond, *trans* to allyl group.[153]

2..1.17 Attempted synthesis of (±)-(1S,4a*R*,9b*S*)-1-allyl-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b,d*]furan-4(1*H*)-one (460) [95]

Pyrex-filtered photolysis of a solution of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459** was performed on 0.0271 g of substrate in methanol solution in a Schlenk tube and degassed with a slow stream of N_2 for 30min prior to the reaction. The degassed solution was irradiated for 2 hours, with a 125 W medium pressure mercury lamp (lamp 1) contained within a water-cooled quartz immersion well and was demonstrated to be unsuccessful (Scheme147). The reaction was monitored for 3, 4, 5, 6, and 9 hours, by TLC which revealed the formation of 6 spots. The crude product was concentrated *in vacuo* and further purified by flash column chromatography (SiO_2 7:3 pet.ether/EtOAc) to give a yellow oil (Scheme 147). Upon irradiation of degassed solution of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459** in methanol (1 mmol) with 311 nm Philips 9 W low pressure mercury lamp, the crude product was concentrated *in vacuo* to give a pale yellow oil. Thus, a solution of **459** in methanol was placed in a Pyrex test tube and degassed with a slow stream of N_2 for 30 min prior to the reaction. The reaction mixture was then placed in the Rayonet photoreactor (lamp 4) and irradiated for 30 min, then 3 hours with a broad band around 311nm (Rayonet RPR-200, equipped with 16 x RPR-3000Å lamps, 16 x 8 W (low pressure)). The crude product was concentrated *in vacuo* and an orange oil was obtained. (Scheme 147).

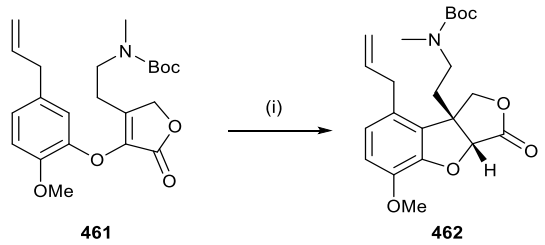
Repeating the reaction of **459** in a MeOH solution using flow reactor (lamp 2) with irradiation using a band with λ_{max} 320 nm for 3 hours [4.5 min (residence time)] and an orange oil was obtained. (Scheme 147).

Examination of the ^{1}H NMR spectra showed that all the starting material **459** had been consumed with no clearly identifiable resonances for **460**. It appears likely the same problem that beset the cuprate addition also slowed the Schultz cyclisation to the point where other processes began to complete.



Scheme 147: photolysis of a solution of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459**: *Reagent and conditions*: (i) hν (320 nm), MeOH.

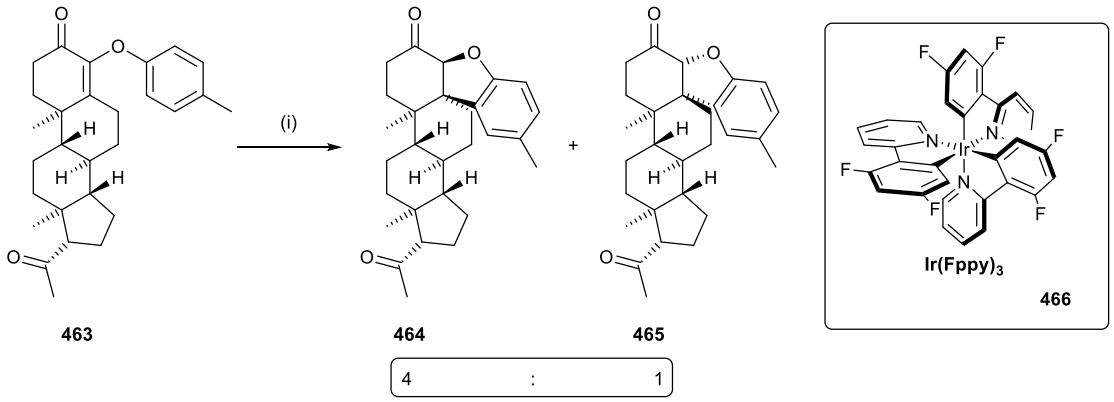
It is interesting to note that low yields accompanied a key 6π photoelectrocyclization (**461**-**462**) during Smith's synthesis of morphine (Scheme 148)[158]



Scheme 148: key photoelectrocyclisation during Smith's synthesis of morphine. *Reagents and conditions*: (i) high-pressure mercury vapour lamp irradiation with Pyrex filter, DCE/HFIP, 20 ˚C.

In response to this difficulty, the Smith group published a visible light photocatalysis method for carrying out the Schultz cyclization that showed very good yields. An example of C-C bond formation in a hindered steroid substrate (**463**), using this methodology, is illustrated in Scheme 149.[162]

Note that in this case both faces of the alkene onto which cyclisation takes place are sterically hindered. Unfortunately, time restrictions did not permit this to be attempted.



Scheme 149: visible light photocatalysis of the Schultz cyclisation. *Reagents and conditions*: (i) **463** (0.3 mmol), KOAc, (100 mol%), $Ir(Fppy)_3$ (1 mol%), 12 W blue LED, MeCN ([**463**] = 0.05 mol dm^{-3}), 60 ˚C, 36 h. (84%).

As part of the assessment of the direct photolysis method, whilst less desirable, it was clear that the overall strategy for the synthesis of stemodinone **1** could be altered to allow incorporation of the *gem*-dimethyl group later in the synthesis. Thus, we chose to remove to remove *gem*-dimethyl from the enone, but retain the allyl group in the γ-position and the methyl group at the β-position of the cyclohexenone; this would lead to the target molecule being **468**. Herein now describe the conversion of cyclohexenone **467** to **472** (Figure 65).

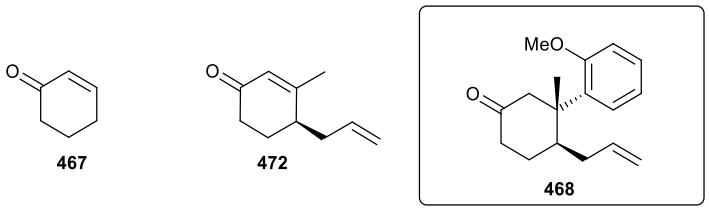
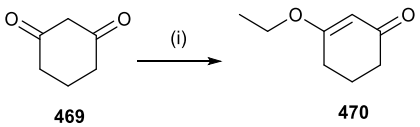


Figure 65: Comparison of cyclohexanone **467** with 4-allyl-monomethylated ketone **472**.

With the intention to utilize the method of desulfurization with Raney Ni as the final step, we first used thiophenol as nucleophile to establish whether this step would cause reduction of the terminal alkene.

2.1.18 Synthesis of 3-ethoxycyclohex-2-enone (470)

In parallel to the synthesis of **456**, preparation of **472** began from cyclohexane-1,3-dione **469**. A solution of cyclohexane-1,3-dione **469** in toluene and ethanol was treated with *p*-toluene sulfonic acid monohydrate before being heated at reflux for 30 minutes. Following the slow removal of the toluene/ethanol/water azeotrope via distillation, the cold solution was washed with a 10% aq. NaOH solution to remove the acid. After workup and drying, 3-ethoxycyclohex-2-enone **470** was obtained as a colourless oil in 62% yield (Scheme 150).



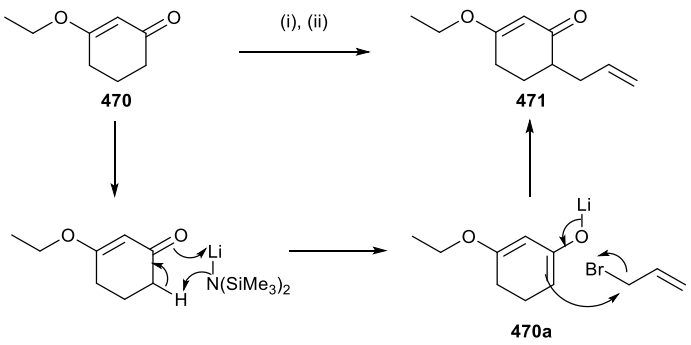
469 **470**

Scheme 150: preparation of 3-ethoxycyclohex-2-enone **470**. *Reagents and conditions*: (i) EtOH, toluene, cat. *p*-TsOH, reflux, 30 min. (62%).

All analytical data correlated with these reported in the literature,[147,148] and the presence of a triplet at δ 1.25 and quartet at δ 3.79 with coupling constant *J* 7.0 Hz in the ^{1}H-NMR spectrum indicated the desired incorporation of the ethoxy group at the β-position of the enone. HRMS (+ESI) confirmed the molecular ion mass of 163.0742

2.1.19 Synthesis of (±)-6-allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone (471)

A solution of 3-ethoxycyclohex-2-enone **470** in dry THF under nitrogen, at -78 ^{o}C, was enolized by treatment with NaHMDS over 2 hours. Following the addition of the dipolar aprotic solvent DMPU, the light amber solution was stirred for 30 minutes after which time allyl bromide was added as a solution in THF in a drop-wise manner. The resulting solution was stirred for a further 2 hours whilst being allowed to warm to room temperature and subsequent TLC analysis revealed that no more starting material was being consumed. Following workup and chromatography, (±)-6-allyl-3-ethoxy-2-cyclohexene-1-one **471** was afforded as a yellow oil in 70% yield.

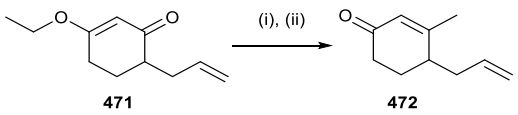


Scheme 151: Alkylation of the sodium enolate **470a**. *Reagents and conditions*: (i) NaHMDS, DMPU, (ii) allyl bromide, THF, -78 °C, 15h, in 70% yield.

Analysis of the ^{1}H NMR spectrum revealed two new resonances in the low field region; specifically, a 2H multiplet at δ 5.00-5.11 and a 1H multiplet at δ 5.71-5.86 characteristic of a terminal alkene. In support of this, the terminal carbon of the alkene resonates δ 116.56 ppm in the ^{13}C NMR spectrum whereas, the internal carbon is found at δ 136.36.

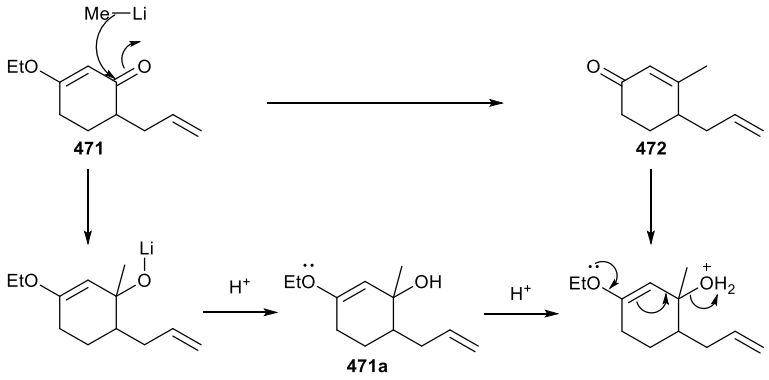
2.1.20 Synthesis of 4-allyl-3-methylcyclohex-2-enone (472)

To effect the Stork-Danheiser 1,3-carbonyl transposition, methyllithium was added in a dropwise manner to a stirring solution of 6-allyl-3-ethoxy-2-cyclohex-1-enone **471** in diethyl ether under a nitrogen atmosphere, before continuing to stir for a further 3 hours whereupon TLC indicated that no more starting material remained. Following acidification, the reaction mixture was stirred for 2 hours to complete the transposition. After workup and purification of the crude product (flash column chromatography) (±)-4-allyl-3- methylcyclohex-2-enone **472** was obtained as a yellow oil in 88% isolated yield (Scheme 152).



Scheme 152: methylation and rearrangement of α,β-unsaturated ketone **465**. *Reagents and conditions*: (i) MeLi, Et_2O, r.t, 3h; (ii) then HCl, r.t, 2h, 88% yield.

In respect of the mechanism, this will parallel that for **456**. Thus, the methyllithium attacks the empty π* orbital of the carbonyl group and following acidification, the intermediate tertiary, allylic alcohol **471a** undergoes ionization and hydrolysis to effect the 1,3-carbonyl transposition that affords the ketone **472** (Scheme 153).

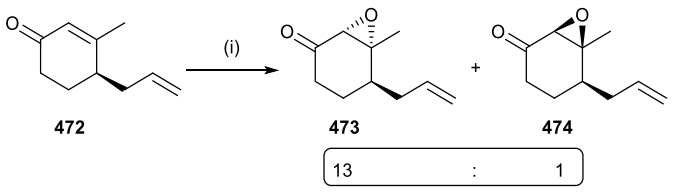


Scheme 153: mechanism of methylation and 1,3-carbonyl transposition of **471**.

2.1.21 Synthesis of (±)-(1*R*,5*R*,6*R*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (473) and (±)-(1*S*,5*R*,6*S*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (474)

The nucleophilic epoxidation of **472** was carried out by treatment with 30% aqueous hydrogen peroxide in MeOH at 15 °C followed by addition of 1 M NaOH over a period of 1 hour. The resulting solution was stirred for a further 5 hours while the temperature was maintained at 20-25 °C and subsequent TLC analysis revealed that no more starting material was being consumed. The reaction was quenched and concentrated *in vacuo* yielding the crude product as a yellow oil and as a mixture of two isomers (13:1 ratio) **473** and **474**. The crude product was purified by flash column chromatography to afford a pale-yellow oil (±)-(1*R*,5*R*,6*R*)-5-

allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one **473** as a major stereoisomer in 49% isolated yield (Scheme 154).



Scheme 154: epoxidation of enone **472**: *Reagent and conditions*: (i) 3.2 equiv. H_2O_2, 5.1 equiv. NaOH, MeOH, 20-25 °C, 3h, (13:1 ratio of **473** and **474**) in 49% isolated yield

Epoxidation of monomethylated ketone **472** afford a mixture (13:1) of **473** and **474** which were successfully separated to afford only the most abundant epoxide **473**. The ratio of diastereoisomers was greater than was the case following nucleophilic epoxidation of **456** (5:1). Considering the likely preferred conformation discussed in Figure 58, and comparing them in respect of nucleophilic attack of the hydroperoxide anion, it is clear that attack at the *re*-face is easier for **472a** than for **456a** (Figure 66).

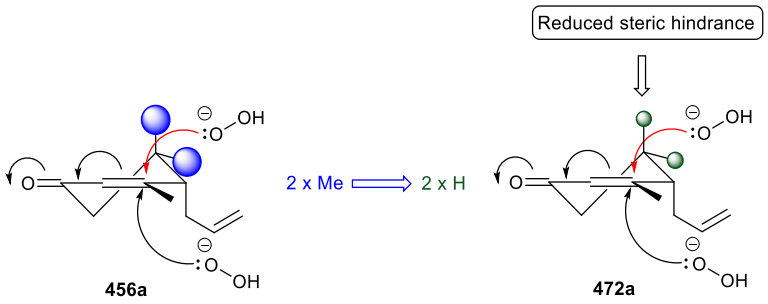


Figure 66: comparison of π-face accessibility in **456a** and **466a**.

Analysis of the ^{1}H-NMR spectrum of the crude epoxide reveals the two diastereomeric forms of the epoxide. The ratio of 13:1 **473**:**474** was determined by integration of the proton resonances at δ 3.11 and δ 3.12. The most demonstrative evidence of product formation was that a doublet (J = 1.6 Hz) observed in the ^{1}H NMR spectrum of **472**, that corresponded to the olefinic proton α to the carbonyl (δ 5.89 ppm), had been lost and a new singlet was observed

at δ 3.11 ppm for the proton at C1 fused to the epoxide of **473**. In addition, the HSQC cross-peaks (Figure 67) indicated the presence of two different sets of diastereotopic protons on the cyclohexanone ring skeleton and one on the allyl chain, consistent with the presence of stereogenic centres. These resonances occurred for C3, C4, and C8 at δ 31.55, 19.26, and δ 33.98, respectively. All the protonated carbon signals were assigned *via* HSQC. The assignments of the two allyl olefin carbons and the carbonyl carbon signals were confirmed to be at δ 117.20, δ 135.73 and δ 207.29 from HSQC cross-peaks or HMBC, respectively. The HRMS (+ESI) *m/z* $[(M+H)^+]$ was consistent with the molecular formula of $C_{10}H_{14}O_2$.

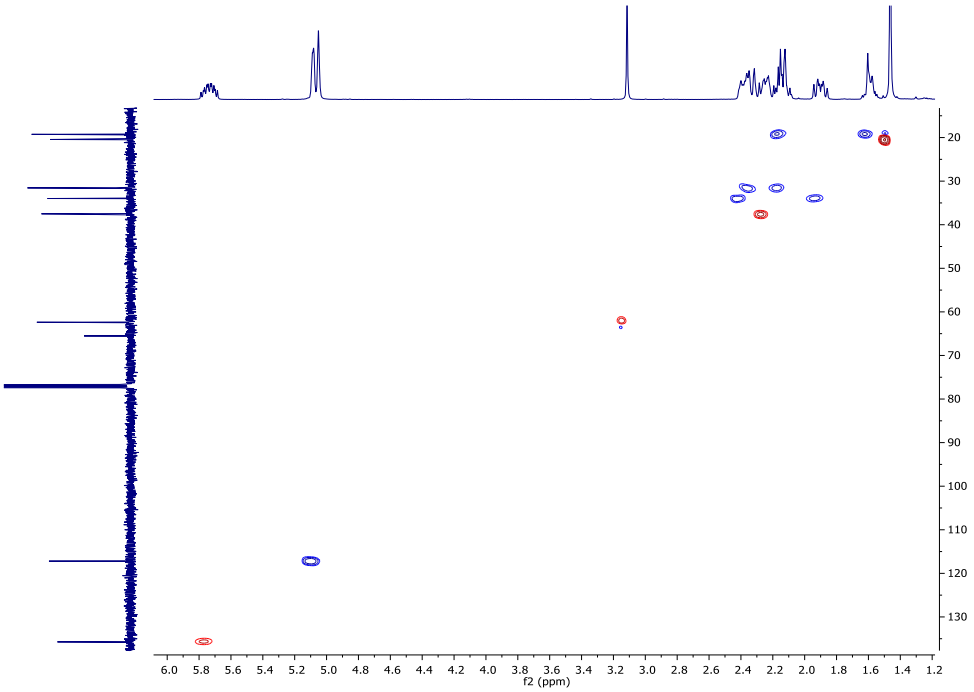
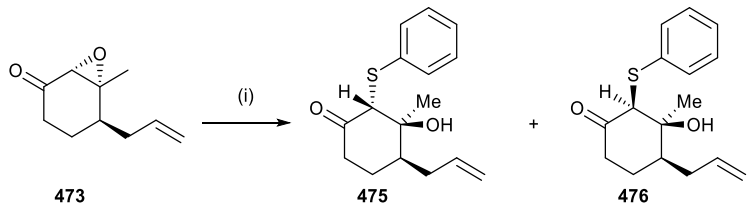


Figure 67: HSQC spectrum of (±)-(1*R*,5*R*,6*R*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**473**); CH_2 cross peaks are in blue.

2.1.22 Synthesis of (2*R*,3*S*,4*R*) -4-allyl-3-hydroxy-3-methyl-2-(phenylthio)cyclohexan-1-one (475) and (2*S*,3*S*,4*R*)-4-allyl-3-hydroxy-3-methyl-2-(phenylthiol)cyclohexan-1-one (476)

Treatment of the of epoxyketone **473** with thiophenol **339** and sodium hydroxide in ethanol solution at 0 ˚C produced epimers **475** and **476** (10:1 ratio) in 66% isolated yield (Scheme 155). The ring opening of epoxyketone **473** with thiophenol **339** occurred with *anti*-selectivity to form the major product **475** with *trans*-configuration. As before, the ring strain present in epoxides (*ca*. 22 kcal/mol^{-1})[135] makes the epoxides highly susceptible to nucleophilic attack.[137] We noticed that ring-opening of the epoxide **473**, with concomitant E1cb elimination to deliver the desired substrate has been reported in the literature.[144]



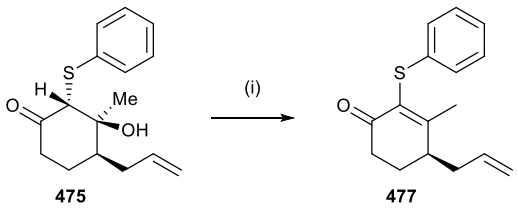
Scheme 155: epoxide ring opening: *Reagent and conditions*: (i) PhSH **339**, EtOH, 15% KOH, 0 °C, 1h, a mixture of two diastereoisomers **475** and **476** in 66% yield.

The ^{1}H-NMR spectrum for β-hydroxysulfide **475** is characterized by considering the absence of the prominent methine proton singlet on C-1 at δ 3.11 ppm in the epoxide **473**; that is replaced by a new resonance for C2 at δ 3.53 as a doublet with small *J* value 1.6 Hz, for the equatorial proton of the major diastereoisomer. The equivalent proton on the minor diastereoisomer, β-hydroxysulfide **476**, resonates as a singlet at δ 3.98 ppm, consistent with an axial position on the ring. All the protonated carbon signals were assigned *via* HSQC. For compound **475** the three sets of diastereotopic protons at C5, C6, and C8 were confirmed by HSQC cross peaks to correlate to carbons at δ 34.21, 33.29, and δ 36.04 ppm, respectively. The assignment of the two allyl olefin carbons and the carbonyl carbon resonances were confirmed

to be at δ 116.75, δ 137.04, and δ 207.03 ppm from HSQC or HMBC cross-peaks. The HRMS (+ESI) *m*/*z* [(MH)$^+$] was consistent with the molecular formula of $C_{16}H_{20}O_2S$. The corresponding diastereotopic protons at C5, C6, and C8 of **476** were determined from the HSQC cross peaks to correlate to carbons at δ 25.18, 24.88, and δ 33.90, respectively; whereas, the two allyl olefin carbons were confirmed to be at δ 117.85 and δ 135.07. 1D ^{13}C NMR showed the carbonyl carbon resonance to be at δ 194.11. The HRMS (+ESI) m/z [(MH)$^+$] was consistent with the molecular formula of $C_{16}H_{20}O_2S$.

2.1.23 Synthesis of (*R*)-4-allyl-3-methyl-2-(phenylthio)-2-cyclohexenone (477)

A solution of (2*R*,3*S*,4*R*)-4-allyl-3-hydroxy-3-methyl-2-(phenylthiol)cyclohexen-1-one **475** in ethanol was treated with catalytic amount of 15% KOH at room temperature. The resulting solution was stirred for approximately 15 minutes when TLC analysis indicated the completion of the reaction. The reaction was quenched and concentrated *in vacuo* to give a crude yellow solid which was further purified by crystallization from hexane/diethyl ether (4:1) to afford (*R*)-4-allyl-3-methyl-2-(phenylthio)cyclohex-2-enone **477** as an analytically pure colourless crystalline solid (m.p. 101-102 ºC) in 69% yield (Scheme 156).



475 477

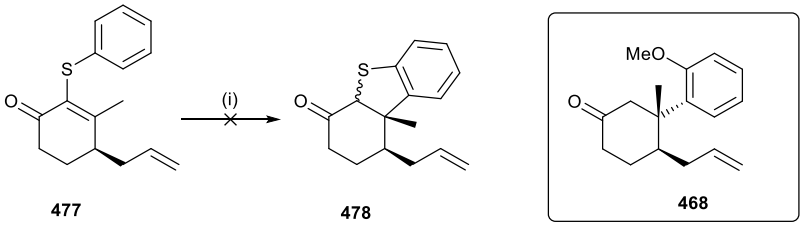
Scheme 156: synthesis of electrocyclization precursor **477**. *Reagent and conditions*: (i) KOH (cat.), ~15 min., EtOH, 69% yield, **477**.

The most obvious evidence for the formation of enone system **477** has been clearly provided by the proton-NMR spectrum by the disappearance of methine proton for C-2 at δ 3.53. Additionally, allylic proton at C4 resonates at δ 1.81 with *J* value 8.0 and a small coupling of 2.0 Hz. The olefinic proton at C9 resonates at δ 5.81 and the five protons of the aromatic ring

appeared as three sets of signals: a triplet for δ 7.25 for one *para*-proton, a multiplet at δ 7.27-7.30 for two *ortho*- protons, and a multiplet at δ 7.49-7.52 for *meta*-protons. All the protonated carbon signals were assigned *via* HSQC. For compound **477** the three sets of diastereotopic protons at C5, C6, and C8 were confirmed by HSQC cross peaks to correlate to carbons at δ 28.64, 33.72, and δ 39.95 ppm, respectively. The assignment of the two allyl olefin carbons and the carbonyl carbon resonances were confirmed to be at δ 127.88, δ 131.55, and δ 200.46 ppm from HSQC or HMBC cross-peaks, respectively.

2..1.24 Attempted synthesis of (±)-(1*R*,9b*S*)-1-allyl-9b-methyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (478) [95]

Photolysis of a solution of (*R*)-4-allyl-3-methyl-2-(phenylthio)-2-cyclohexenone **477** was performed on a 0.0142 g in methanol solution and degassed with a slow stream of N_2 for 30min prior to the reaction. The degassed solution was then placed in the Rayonet photoreactor (lamp 4) and irradiated with a broad band around 311nm (Rayonet RPR-200, equipped with 16 x RPR-3000Å lamp, 16 x 8 W (low pressure)), for 15 minutes. The reaction was monitored for 30 min., 45 min., 1 hour, and 1 hours 15 min, by TLC. The crude product was concentrated *in vacuo* and further purified by flash column chromatography (SiO_2 7:3 pet.ether/EtOAc) to give **478** as a pale-yellow oil in 52% yield (Scheme 157).



477 478 468

Scheme 157: photolysis of a solution of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459**: *Reagent and conditions*: (i) hν (320 nm), MeOH.

Examination of this photolysis by ^{1}H NMR, over time, revealed slow conversion of the starting material **477** with potential product **478** being formed up to 45 min. However, a significant and

growing amount of material was observed in the alkyl region between 0.75 and 1.75 ppm, strongly suggesting that a significant amount of **478** was not going to be obtained (Figure 68).

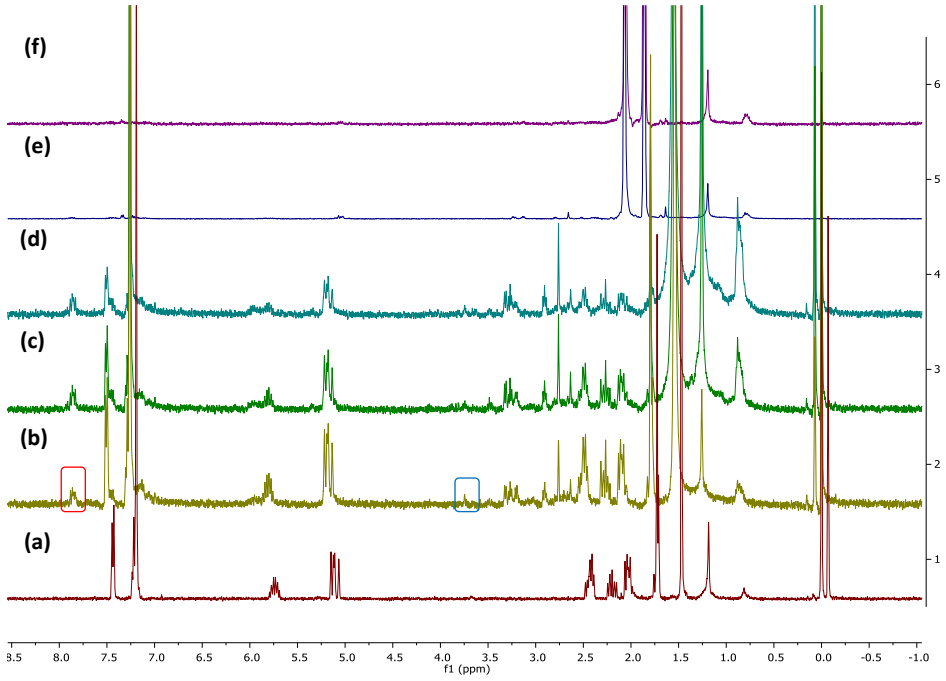


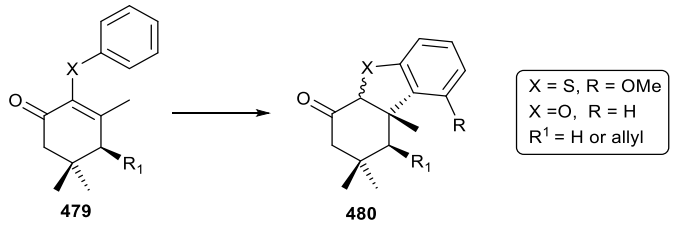
Figure 68: The 400-MHz ^{1}H NMR spectrum of photolysis of **477** in $CDCl_3$. (a) starting material **476**; (b) photolysis of **477** for 15 min., with two notable new resonances; one in the aromatic region (highlighted in red) and one in the region expected for C2 (highlighted in blue); (c) after 30 min., the resonance in the aromatic region intensified with a slow reduction of intensity for the proton expected to be at C2; (d) after 45 min., the intensities remain similar to (c). (e) photolysis of **477** for 1 hour indicated that the notable resonances disappeared; (f) photolysis of **477** for 1 hour 15 minutes confirmed the disappearance of the notable resonances.

Indeed, a proton NMR spectrum of photolysis of **477** appeared to give some prominent resonances after irradiation for 15 min. (Figure 68) with two notable new resonances (b); one in the aromatic (highlighted in red) and one in the region expected to for C2 (highlighted in blue), however, after 30 min. (c), the resonance in the aromatic region intensified with a slow reduction of intensity for the proton expected to be at C2. Upon irradiation for 45 min. (d), the intensities remain like those in (c). Irradiation of **477** for 1 hour (e) indicated that the notable

resonances disappeared. Further irradiation of **447** for 1 hour and 15 minutes (f) confirmed the disappearance of the notable resonances and led to a total decay of the proposed product **448**. It was clearly shown that the reaction was unsuccessful. Due to time constraints and lack material, no further progress was possible.

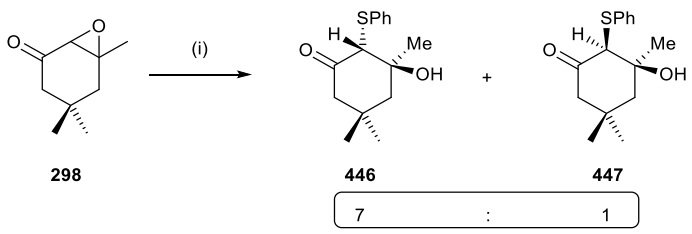
Chapter 3. Conclusions

To set up an examination of the Schultz cyclisation, under both flow and batch photolysis conditions, access to the substrates **479** had first to be secured.



Scheme 158: proposed investigation of the Schultz cyclisation of compounds **479** to **480**.

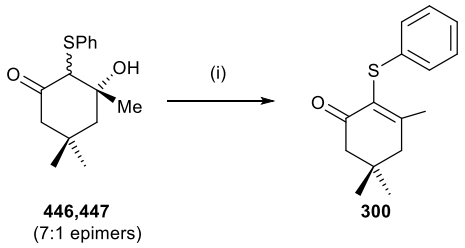
The chemistry to generate the sulfur linked substrates (**479** X = S) proved technically straightforward to carry out. However, it was observed that the originally reported reaction conditions for conversion of an appropriate epoxide to its corresponding vinyl thioether afforded a mixture of compounds, typically dominated by addition products *e.g*. Scheme 159.



Scheme 159: addition of thiophenoxide to isophorone oxide. *Reagent and conditions*: (i) PhSH, EtOH, 15% KOH, 0 °C, 1h, 90% yield.

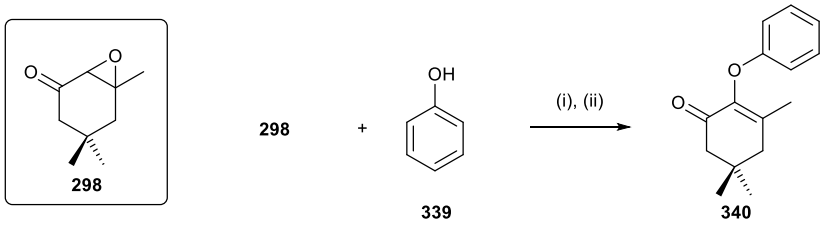
It was found that whilst some elimination occurred, to afford compounds of general structure **480**, a second treatment with base was required (Scheme 160). Though more vigorous

conditions could have been employed to effect a one-pot reaction, it was concluded that two rapid and very mild, high yielding reactions was a good approach.



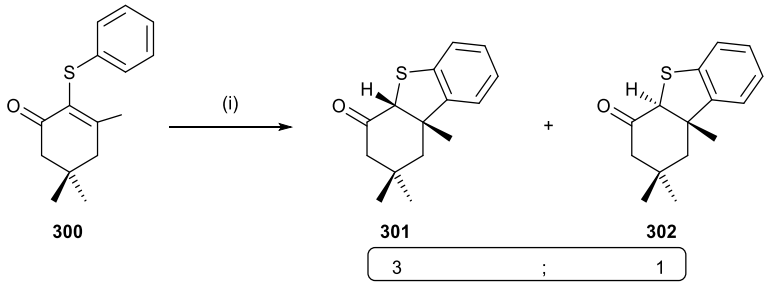
Scheme 160: elimination reaction to afford vinyl thioether **300**. *Reagent and conditions*: (i) KOH (cat.), ~15 min. 74% yield.

By contrast, using the modified reaction conditions devised for synthesis of the vinyl ether analogues, no intermediate structures were seen, presumably reflecting the increased basicity of the α-hydrogen.



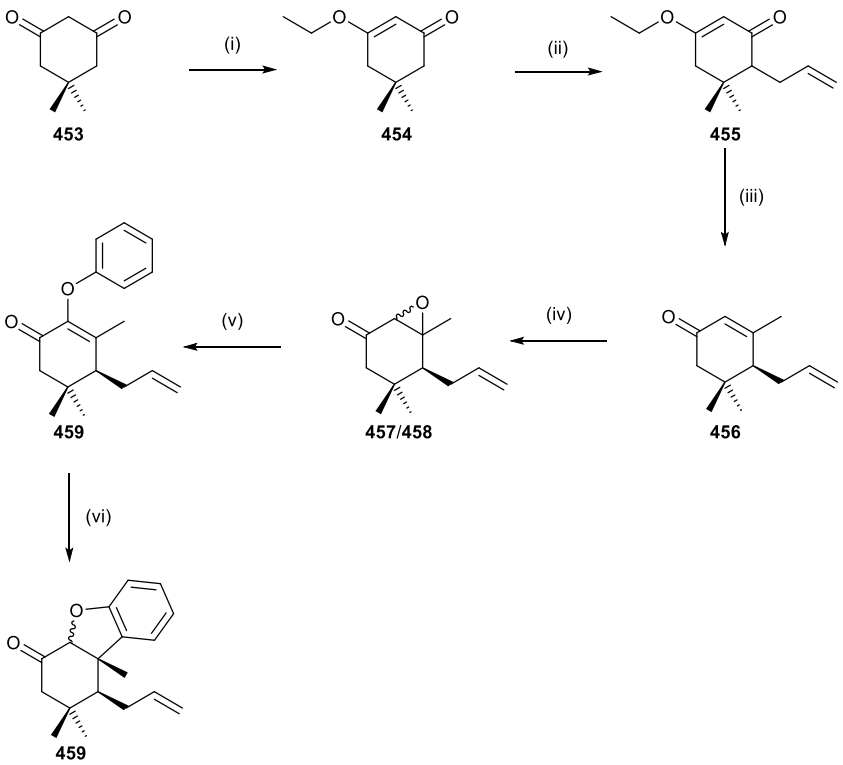
Scheme 161: synthesis of vinyl ether **340**. *Reagents and conditions*: (i) NaH, THF; (ii) DMPU, **298**, 2h, 95% yield.

Studies of the photolysis conditions showed similar outcomes under batch and flow conditions. This may reflect the photostability of the products, negating the advantages that can accrue to the short residence times identified for photolysis under flow conditions. However, the capacity of the flow system to run over many hours could have advantages in respect of scale up. Whether a mixture of diastereoisomers or a single, *cis*-diastereoisomer is obtained is controlled by choice of solvent with pure methanol affording the latter.



Scheme 162: Schultz cyclisation of **300** to give diastereoisomers **301** and **302** using the flow reactor (lamp 2). *Reagent and conditions*: (i) hν (320 nm), MeOH: toluene (1:3), 98% yield.

Applying these lessons in the context of stemodinone was successful apart from the final photolysis; this step failed to give the desired compound and will necessitate further study (Scheme 163). Clearly, forming the aryl bearing quaternary centre, by any means, will be very tricky. It likely reflects the considerable steric hindrance to both π-faces of the double bond of the vinyl ether.

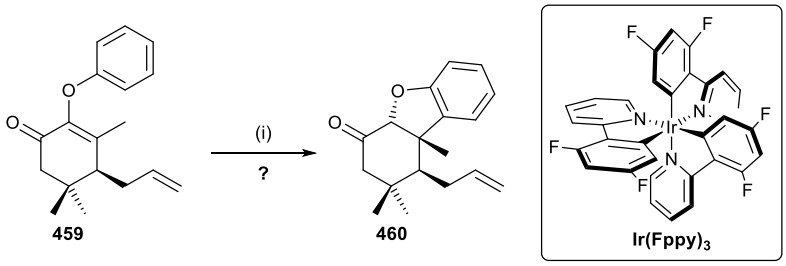


Scheme 163 synthetic route used to prepare study Schultz cyclization precursor **459**. *Reagents and conditions*: (i) EtOH, toluene, cat. *p*-TsOH, reflux, 30 min. (76%); (ii) NaHMDS, DMPU, allyl bromide, THF, -78 °C, 15h, in 77% yield; (iii) MeLi, Et_2O, r.t, 3h then HCl, r.t, 2h, 70% yield; (iv) H_2O_2 (3.1 equiv.), NaOH (5.1 equiv.), MeOH, 20-25 °C, 3h, (5:1 ratio of **457** and **458**) (41%); (v) PhOH, NaH(cat.) then **457**/**458**, THF, DMPU, 2h, 68% yield; (vi) hν (320 nm), MeOH.

If alternative photolysis conditions fail to deliver the desired compound, then we must conclude that the *gem*-dimethyl group will have to be introduced at a late stage in the synthesis, when the full ring system has been formed. Some hope in this respect is given in the work of Pearson and Tanaka.

Chapter 4. Future work

The discovery that direct UV photolysis of **459** failed to give the desired conversion to **460** is clearly the highest priority matter to address. The first approach to the problem should be to apply the visible light photocatalytic method described by Smith, as this has shown effectiveness in a demanding steric environment (Scheme 158).



Scheme 158: 459 (0.3 mmol), KOAc, (100 mol%), $Ir(Fppy)_3$ (1 mol%), 12 W blue LED, MeCN ([**459**] = 0.05 mol dm^{-3}), 60 °C.

Should this prove to be unsuccessful or have limited success, it is likely that the problem is the substantial steric hindrance on both π-faces of the double bond undergoing addition. During synthesis of **473**/**474** it was noted that conversion of the *gem*-dimethyl group in **456** to two protons in **472** increased the diastereoselectivity of its nucleophilic epoxidation. This indicates that the *re*-face became more accessible (Figure 66).

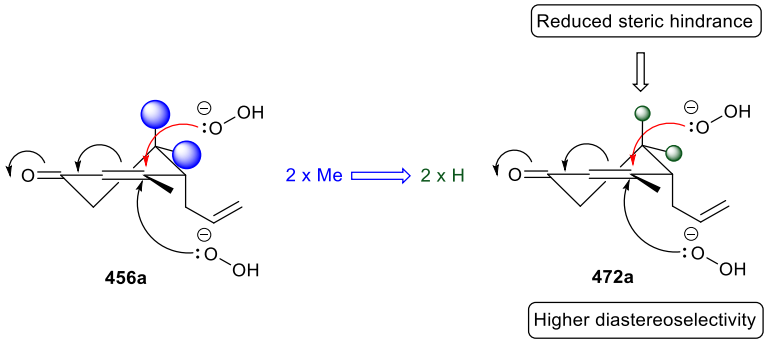


Figure 66: the effect of steric hindrance on the diastereoselectivity of epoxidation of **472**.

To build on this observation, the steric bulk of the *gem*-dimethyl group could be reduced by its substitution with a cyclopropane (Figure 67).

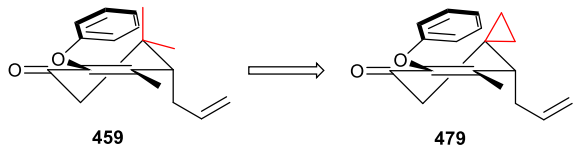
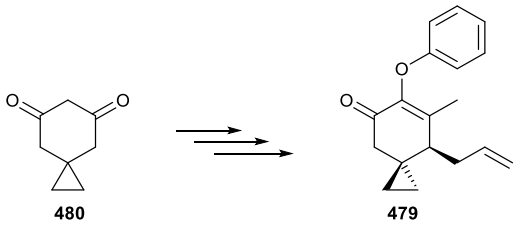


Figure 67: potential substitution of the *gem*-dimethyl group of **459** by a cyclopropane in **479**.

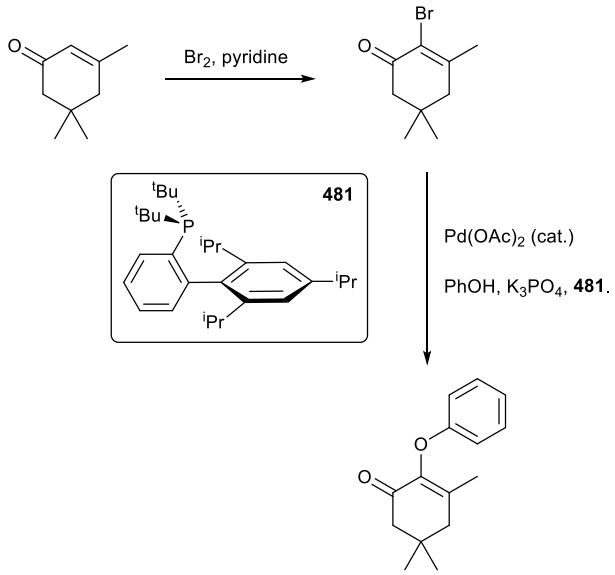
As compound **480** is a known compound, it should be possible to convert it, by the same means reported in the Results and Discussion to **479** (Scheme 159). At a later stage in the synthesis, it should prove possible to hydrogenolyse the cyclopropane to afford the desired *gem*-dimethyl group. It is hoped that **479** will facilitate access to the transition state for photocyclization.



Scheme 159: proposed starting material **480** for the synthesis of **479**.

Should the photocyclization still fail, introduction of the *gem*-dimethyl group will need to be delayed until a late stage in the synthesis.

To facilitate entry into the substrates required for the Schultz cyclisation reactions, an alternative method for their synthesis should be investigated. This will be based upon organopalladium methodology and utilize the Buchwald biphenylphosphine ligands *e.g.* **481** which have proven effective in C-O bond formations (Scheme 160).



Scheme 160: proposed methodology for a palladium mediated synthesis of Schultz cyclisation precursors.

Finally, once a suitable substrate for the *meta*-photocycloaddition reaction is prepared, attention will turn to completion of a synthesis of stemodinone **1**.

Chapter 5. Experimental

5.1 General Experimental Methods

5.1.1 Material Used

All reagent grade chemicals were either supplied by the Sigma-Aldrich chemical company, Fluka, Acros or Fisher. Anhydrous dichloromethane, toluene, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*) pyrimidinone (DMPU), allyl bromide and pyridine were obtained by distillation from CaH_2; whereas, tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl. Dimethyl sulfoxide was distilled from magnesium sulfate, and methanol was dried using freshly prepared magnesium methoxide.[145a]

All moisture/air sensitive reagents, such as methyllithium, lithium-tri-sec-butylborohydride, *n*-butyllithium and methyl magnesium bromide were purchased in sureseal® bottles and stored under an inert atmosphere in the refrigerator. However, bistrimethylsilylamides were usually stored at room temperature, and hydrogen peroxide stored in the refrigerator. Finally, sodium hydride was purchased as a 60% dispersion in mineral oil.

5.1.2 Separation technique

5.1.2.1 Thin Layer Chromatography (TLC)

All analytical thin layer chromatography (TLC) was performed on Merck aluminium sheets (6 x 2.5cm) coated in silica gel 60 F_{254}. Spots were visualized with UV light (254nm), iodine on silica and then stained by solutions of vanillin, potassium permanganate or phosphomolybdic acid. Retention factors (R_f) are quoted to the nearest 0.01.

5.1.2.2 Flash column chromatography

Silica gel (particle size 40-63 μm) was used for the majority of flash column chromatography. Florisil® (30-60 Mesh) was used when separating acid-sensitive materials. For chromatography, ether refers to diethyl ether.

5.1.2.3 Rotary evaporator

A Büchi Rotavapor-135 at 40 °C was used for evaporation of solvent, which is also referred to as concentrated *in vacuo*.

5.1.3 Analytical technique

5.1.3.1 Infrared Spectroscopy

A Perkin Elmer 1720-X IR-Fourier Transform spectrometer was used to record all IR spectra of samples either as a thin-film or as a nujol mull.

5.1.3.2 Nuclear Magnetic Resonance Spectroscopy

All ^{1}H-NMR spectra were recorded on a Bruker Nanobay (400 MHz) or Bruker DPX-400 (400MHz) spectrometers using tetramethylsilane ($SiMe_4$, δ_H = 0.00 ppm), $CDCl_3$, ($CDCl_3$, δ_H = 7.26ppm) as internal reference. ^{13}C-NMR spectra were recorded on Bruker Nanobay (100 MHz) or Bruker DPX-400 (100MHz) spectrometers using the central resonance of $CDCl_3$ (δ_C = 77.00 ppm) as internal reference. Methanol (MeOH-*d*$_4$), benzene (C_6D_6), dimethylsulfoxide (DMSO-*d*$_6$) and acetone-*d*$_6$ were also used as solvents.[145b]

Assignments were made using a range of NMR experiments (DEPT-135, COSY, NOESY, HMQC and HMBC). All the chemical shifts (δ_H) are quoted in parts per million (ppm) downfield from TMS, measured from the centre of the resonance except in the case of unassigned multiplets of more than one proton that are quoted as a range. Coupling constants (*J*) are quoted in Hertz to the nearest 0.2Hz. Splitting patterns are abbreviated as follows; singlets (s), doublet (d), triplet (t), quartet (q), quintet (quin.), sextet (sex.), multiplet (m), app. (apparent), broad (b) and in combinations where applicable.

5.1.3.3 Mass Spectrometry

All accurate mass data were recorded on a ThermoFisher Orbitrap Scientific Orbitrap XL mass spectrometer operating in electrospray ionisation mode.

5.1.3.4 UV-Vis Spectrum

UV-Vis spectra were recorded using a Varian Cary 300 spectrophotometer with heating compartment, using a 1 cm^3 quartz cuvette, in the wavelength range 200-800 nm.

5.1.3.5 X-ray crystallography

X-ray crystallography was performed using a Gemini S-Ultra single crystal diffractometer using either a Cu or Mo source.

5.1.3.6 Melting point

All melting points were recorded on a Stuart SMP10 melting point apparatus.

5.1.4 Photochemical apparatus

5.1.4.1 Batch photochemistry

5.1.4.1.1 Preparative Photoreactor

Preparative photochemical reactions were usually carried out using a Photochemical Reactors Ltd. Water cooled 3210/3230 immersion-well containing a 3010/PX0686 125 W medium pressure Hg lamp with the sample contained in a Pyrex Schlenk tube (cut off ~280 nm). Oxygen was removed from the solvent by bubbling nitrogen or argon through the solution. Medium pressure lamps emit their radiation over a wide range (mainly at ~ 365nm with other bands at both shorter and longer wavelength). The Pyrex Schlenk tube served as the spectral filter (cut-off ~280 nm).

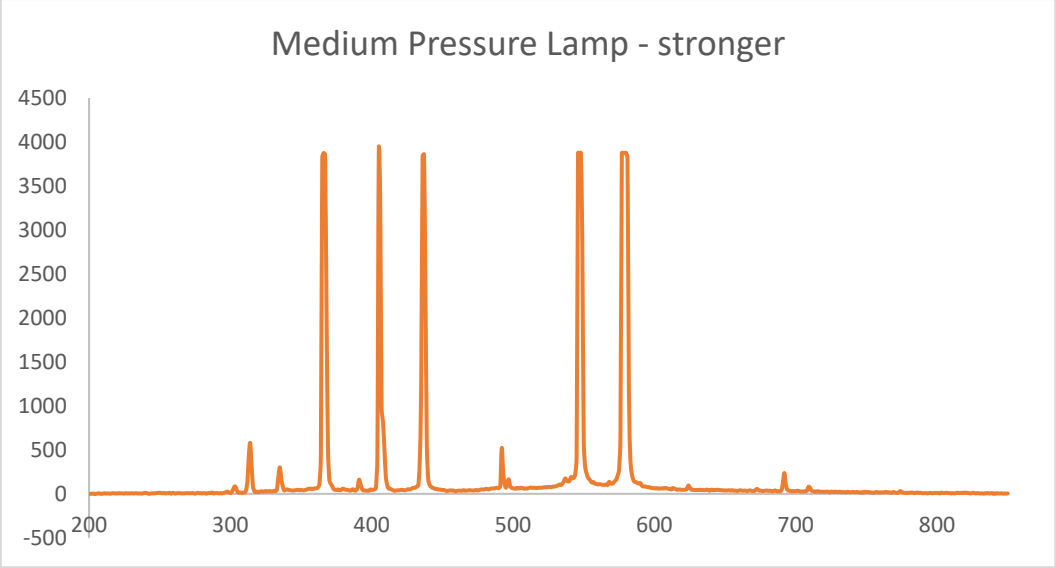


Figure 68: UV/Vis spectrum of the Photoreactors Ltd. 125 W (3010) medium pressure Hg Lamp.

Some small-scale reactions were carried out with a Philips PL-S 9 W low pressure Hg lamp that emits most of its UV radiation at *ca*. 311 nm; again, the sample was contained in a Pyrex Schlenk tube.

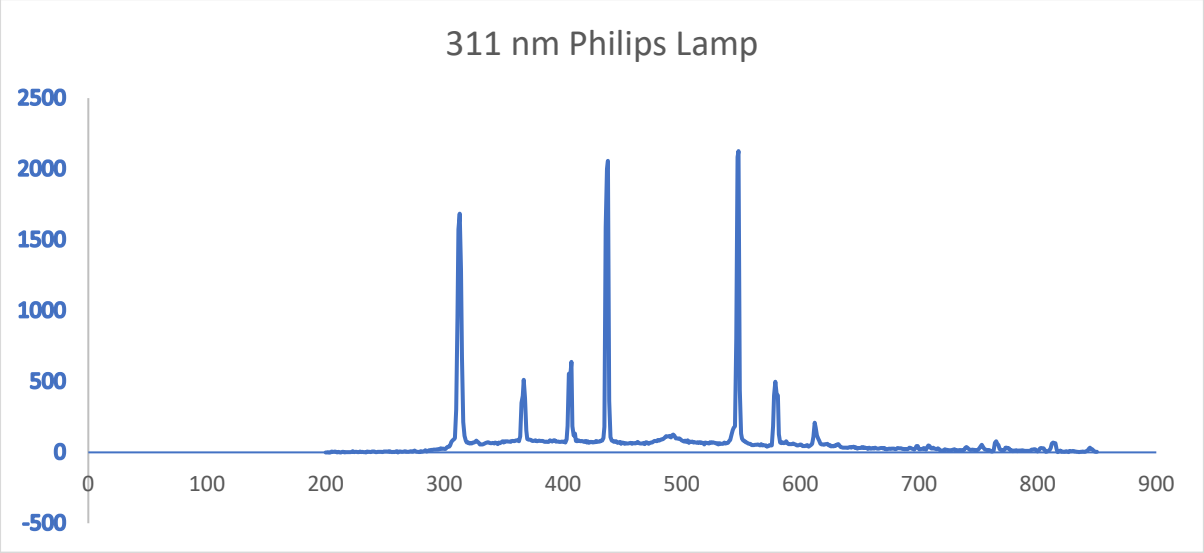


Figure 69: UV/Vis spectrum of the Philips PL-S 9W low pressure Hg Lamp.

Reactions were usually run at very low concentration (up to ~ 1.0 mM) and high purity solvents were chosen. However, great care should also be taken to make sure that the solvent must not decompose under ultraviolent irradiation and should not absorb at the wavelength being used

for the reaction. Work up often involves no more than evaporation of the solvent by purification.

5.1.4.1.2 Thin-Film photochemical reactor

A Photochemical Reactors Ltd. Thin-Film Photochemical Reactor was used with a low-pressure mercury arc lamp. The low-pressure mercury arc lamp emits >90% of its Ultraviolet light at a wavelength of 253.7 nm, which is enough to excite benzenoid arenes to their first excited state without producing many reaction by-products that can form because of emissions at lower wavelengths.

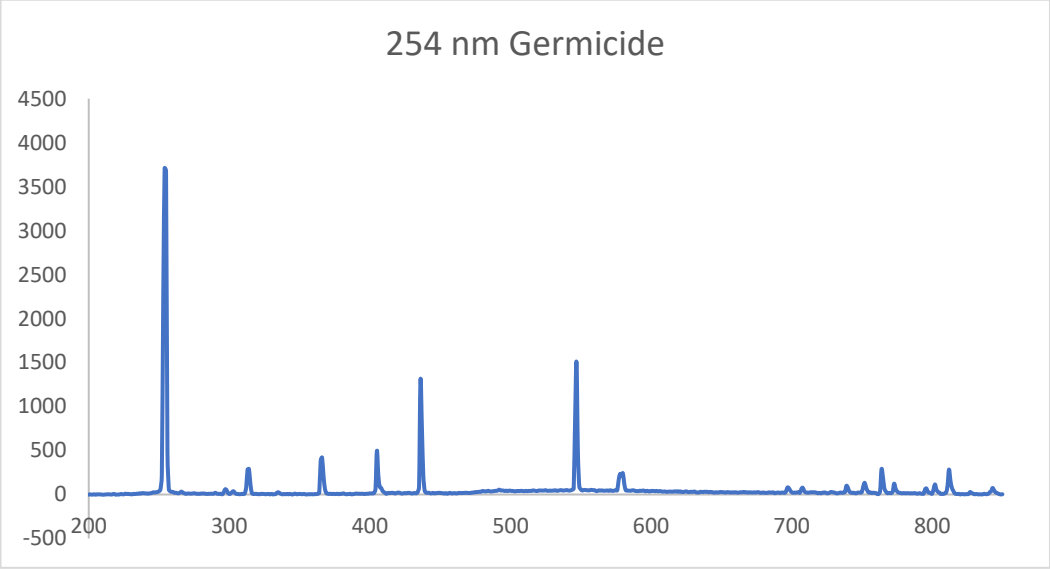


Figure 70: UV/Vis spectrum of the Photoreactors Ltd. 125W (3010) low pressure Hg Lamp.

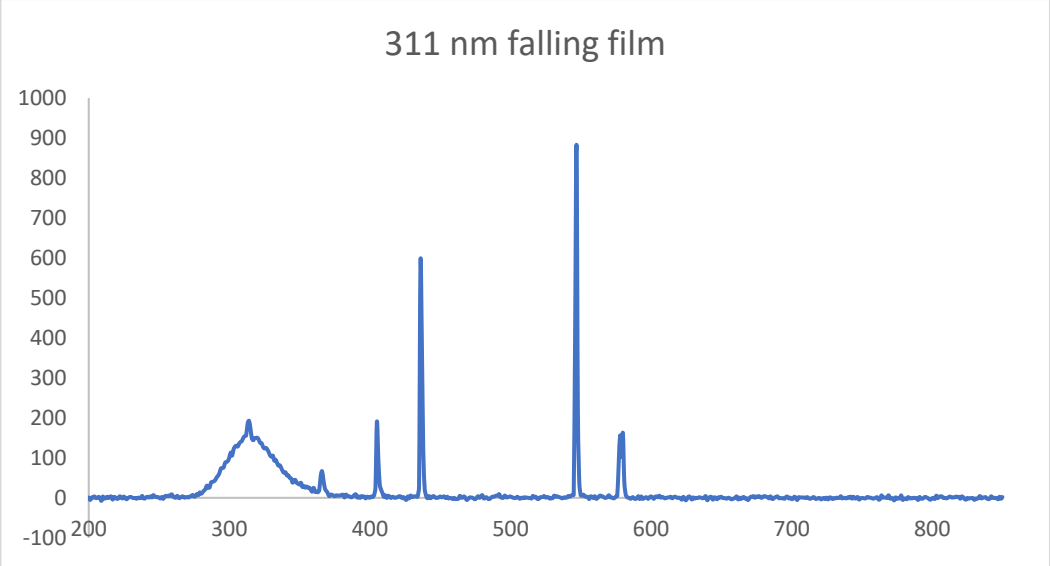


Figure 71: UV/Vis spectrum of the Photoreactors Ltd. 125W (3110) low pressure Hg Lamp.

5.1.4.1.3 Rayonet reactor

A Southern New England Ultraviolet Company Rayonet Reactor© model RPR200 was used when an intense light source was required. The reactor container consists of an enamelled housing that contains the reaction chamber, together with the ancillary equipment for supplying power to the lamps, the fan, and the carousel. All the electrical controls were on an external console to permit control of operation without the necessity for access to the interior. The internal walls of the reaction chamber were silvered, and the lamps were aligned vertically around the outside walls. The sample tubes were held in a rotating holder (the carousel), and the combination of sample rotation together with the internal silvering permits even illumination of a series of sample tubes in the same reactor. The reactor was used with 16 RPR-3000A low pressure Hg lamps operating at 40 ˚C that emit, *inter alia*, a broad band around 300 nm.

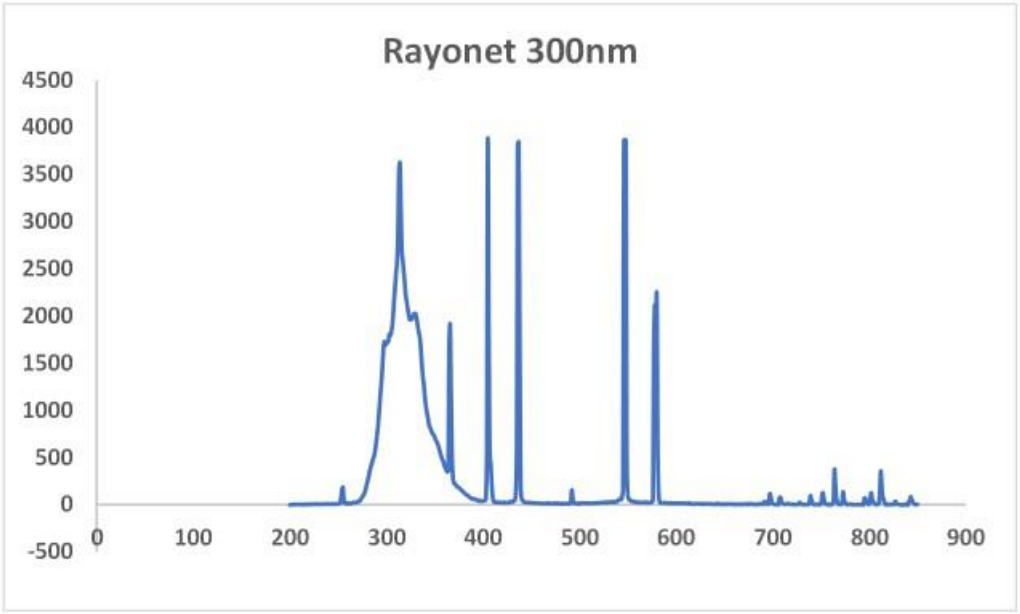


Figure 72: UV/Vis spectrum of the Rayonet reactor with 16 RPR-3000A low pressure Hg Lamps.

5.1.4.2 Flow photochemistry

5.1.4.2.1 Vapourtec E-Series

The Vapourtec e-series flow reactor system required the reaction to be carried out in a sequence of steps. The reactor was first plumbed into the lines where the reagents were introduced. A back-pressure device was fitted, after the reactor, which determines the pressure inside the flow reactor. Before the reagents were passed through the reactor, the correct reaction conditions were established, as follows: the reaction solvent was pumped through the reactor (slowly, to minimize solvent use, but at a sufficient rate to ensure that the reactor was pressurised), then the reactor was heated (or cooled) to the desired reaction temperature. Once the reactor was at the correct temperature, the flow rate was changed to the target value and the liquid stream was changed from solvent to the reaction mixture. The reaction mixture then began flowing into the reactor, while at the outflow the solvent was still passing out through the back-pressure regulator and was collected in the waste container. When the product starts to come out of the

reactor, it was redirected from waste container to a collection container. Once all the reaction mixture had passed through the reactor, the liquid stream was changed back to purely solvent, whilst maintaining the target flow rate and reactor temperature until the reactor was washed clean. Finally, the exit stream was diverted back to waste container. The heating (or cooling) was then stopped, and the pumps then turned off.

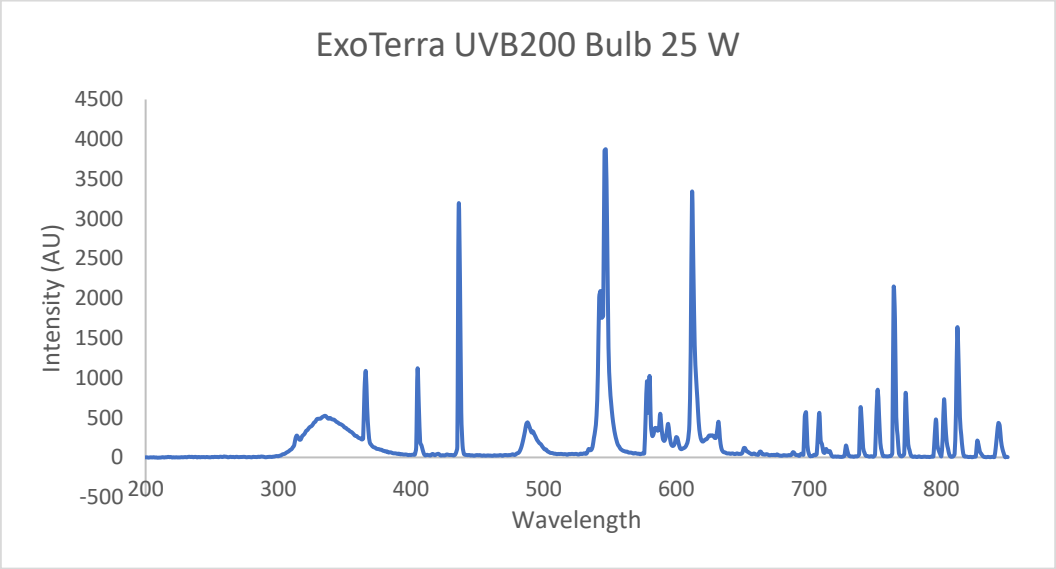
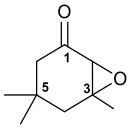


Figure 73 UV/Vis spectrum of the Reptile 25 W Exo Terra UVB200 bulb.

5.2 Experimental Procedure

5.2.1 Synthesis of 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (298) [146a,146b]



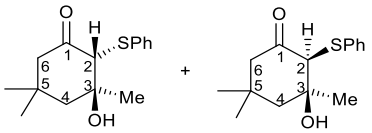
298

A solution of isophorone (**296**) (20 mL, 144.7 mmol) and 30 % aqueous hydrogen peroxide (40 mL, 1.62 mol) in MeOH (133 mL) was stirred and cooled down to 15 °C by means of a water/ice bath. 6 M NaOH (aq.) (11.58 mL, 0.29 mol) was added in a dropwise manner with stirring, over a period of 1 hour. The temperature of the reaction mixture was maintained below 15- 20 °C during the addition. The resulting solution was stirred for a further 2 hours while the

temperature was maintained at 20-25 °C and subsequent TLC analysis (9:1 pet. ether/EtOAc) revealed that no more starting material was being consumed. The reaction was diluted with water (167 mL) and extracted with diethyl ether (2 x 30 mL). The combined organic fractions were washed with water (10 mL), dried over $MgSO_4$, filtered by suction, and concentrated *in vacuo* to yield 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **298** as a yellow oil (14.95 g, 96.92 mmol, 67%).

R_f 0.38 (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1720 (C=O stretch), 2957.37 (C-H stretch). δ_H (400 MHz, $CDCl_3$) 0.92 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.02 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.43 (3H, s, -$C\underline{H}_3$ at C3), 1.70 (1H, dd, *J* 15.0, 2.3 Hz, equatorial -$C\underline{H}_2$ at C4), 1.81 (1H, ddd, *J* 13.2, 2.3,1.1 Hz, equatorial -$C\underline{H}_2$ at C6), 2.08 (1H, d, *J* 15.0 Hz, axial -$C\underline{H}_2$ at C4), 2.62 (1H, d, *J* 13.2 Hz, axial -$C\underline{H}_2$ at C6), 3.06 (1H, s, C$\underline{H}$ at C2); δ_C (100 MHz, $CDCl_3$) 24.03 (CH_3, -$\underline{C}H_3$ at C3), 27.83 (CH_3, one of the -C($\underline{C}H_3$)$_2$ at C5), 30.82 (CH_3, one of the -C($\underline{C}H_3$)$_2$ at C5), 36.15 (C, -$\underline{C}CH_3$ at C5), 42.73 (CH_2, -$\underline{C}H_2$ at C4), 47.98 (CH_2, -$\underline{C}H_2$ at C6), 61.41 (CH, -$\underline{C}$H at C2), 64.29 (C, -$\underline{C}(CH_3)_2$ at C3), 207.98 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_9H_{14}NaO_2$ requires 177.0884, found 177.0885.

5.2.2 Synthesis of (±)-(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(phenylthio)cyclohexen-1-one (446) and (±)-(2*S*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(phenylthiol)cyclohexen-1-one (447)[92]



446 **447**

Isophorone epoxide (**298**) (2.013 g, 12.96 mmol) in ethanol (5 mL) and 15% aq. KOH (0.2 mL, 0.53 mmol) solution was stirred at 0 °C under a nitrogen atmosphere. A solution of thiophenol (**299**) (1.424 g, 12.92 mmol) in THF (0.5 mL) was degassed with a stream of nitrogen for (30 min) then added dropwise over 20 min. After stirring at 0 °C for 1 hour, the reaction was judged

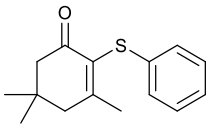
to be completed by TLC analysis (9:1 pet. ether/EtOAc). Water (10 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 10 mL). The combined organic fractions were washed with a saturated brine solution (2 x 2 mL). The organic fraction was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to produce a crude yellow solid as a mixture of two diastereoisomers **446**/**447** (7:1) (±) -(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(phenylthiol)cyclohexen-1-one and (±)-(2*S*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-phenylthiolcyclohexen-1-one (3.115 g, 11.78 mmol, 90%). The crude product was triturated with hexane (3 x 5 mL) to afford a colourless solid which was further purified by crystallisation (hexane/diethyl ether (5:1) 10 mL) to give analytically pure colourless crystalline solid (**446**) (2.590 g, 9.83 mmol, 75%) (m.p. 102-103 ºC) as the major isomer.

major diastereoisomer R_f 0.23 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3392.23 (O-H stretch), 1603.59 (C=O stretch). δ_H (400 MHz, $CDCl_3$) 1.09 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.15 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.48 (3H, s, -C$\underline{H}_3$ at C3), 1.71 (1H, app.dt. *J* 14.6, 1.6 Hz, equatorial -C$\underline{H}_2$, at C4), 1.76 (1H, bs, O$\underline{H}$ at C3). 1.97 (1H, d, *J* 14.6 Hz, axial -C$\underline{H}_2$, at C4), 2.05 (1H, app. dt. *J* 13.4, 1.6 Hz, equatorial -CH_2, at C6), 2.99 (1H, d, *J* 13.4 Hz, axial -C$\underline{H}_2$, at C6), 3.53 (1H, s, app.t. *J* 1.6 Hz, equatorial -C$\underline{H}$ at C2), 7.39-7.24 (5H, m, -C$\underline{H}$Ar); δ_C (100 MHz, $CDCl_3$) 29.32 (CH_3 one of -C($\underline{C}H_3$)$_2$ at C5), 29.44 (CH_3 one of -C($\underline{C}H_3$)$_2$ at C5), 33.00 (CH_3, -$\underline{C}H_3$ at C3), 34.89 (C, -$\underline{C}$(CH_3)$_2$ at C5), 46.98 (CH_2, -$\underline{C}H_2$ at C4), 49.17 (CH_2, -$\underline{C}H_2$ at C6), 65.45 (CH, -$\underline{C}$H(SAr) at C2), 125.63 (C, -$\underline{C}$(OH)CH_3 at C3), 127.66 (CH, two, *o*-$\underline{C}$Ar), 129.24 (CH, *p*-$\underline{C}$Ar), 131.48 (CH, two, *m*-$\underline{C}$Ar), 133.82 (C, S$\underline{C}$1Ar), 209.90 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_{15}H_{20}O_2NaS$ requires 287.1076 found 287.1078 with [M+2] 289.1090.

minor diastereoisomer R_f 0.7 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3392.23 (O-H stretch), 1603.59 (C=O stretch). δ_H (400 MHz, $CDCl_3$) 1.06 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.13 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.37 (3H, s, C$\underline{H}_3$ at C3), 1.81 (1H, d, *J* 14.6 Hz, axial, C$\underline{H}_2$, at C4), 1.93 (1H, app. dd, *J* 14.6, 1.6 Hz, equatorial C$\underline{H}_2$, at C4), 2.31 (1H, d, *J* 13.6 Hz,

axial C<u>H</u>$_2$, at C6), 2.38 (1H, bs, O<u>H</u> at C3), 2.57 (1H, app. dd. *J* 13.6, 1.6 Hz, equatorial -C<u>H</u>$_2$, at C6), 3.88 (1H, s, C<u>H</u> at C2), 7.38-7.44 (5H, m, -C<u>H</u>Ar); δ_C (100 MHz, $CDCl_3$) 29.32 (CH_3, one of the -C(<u>C</u>H$_3$)$_2$ at C5), 30.68 (CH_3, one of the -C(<u>C</u>H$_3$)$_2$ at C5), 31.94 (CH_3, -C<u>C</u>H$_3$ at C3), 34.82 (C, - <u>C</u>CH$_3$ at C5), 50.35 (CH_2, -<u>C</u>H$_2$ at C4), 52.90 (CH_2, -<u>C</u>H$_2$ at C6), 69.98 (CH, -<u>C</u>H(SAr) at C2), 125.32 (C, -<u>C</u>(OH)CH$_3$ at C3), 127.38 (CH, two, *o*-<u>C</u>Ar), 129.21 (CH, *p*-<u>C</u>Ar), 131.61 (CH, two, *m*-<u>C</u>Ar), 135.20 (C, S<u>C</u>1Ar), 205.47 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{15}H_{21}O_2S$ requires 265.1257, found 265.1258, [^{34}S give M+2 at 267.1220].

5.2.3 Synthesis of 3,5,5-trimethyl-2-(phenylthio)cyclohexen-1-one (300)[92]

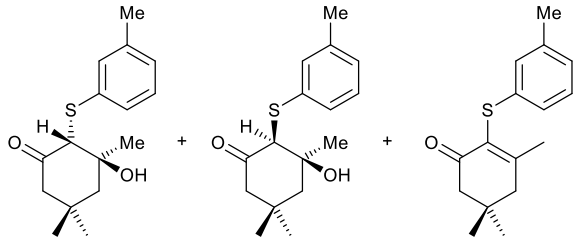


300

A solution of (±)-(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(phenylthiol)cyclohexen-1-one **446** (1.50 g, 5.67 mmol) in ethanol (1.5 mL) was treated with a catalytic amount of 15% KOH (0.31 mL, 0.56 mmol, 10 mol%) at room temperature. The resulting solution was stirred for approximately 15 minutes until TLC analysis (9:1 pet. ether/EtOAc) indicated that all the starting material had reacted. The solution was diluted with water (13 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to yield an orange solid 2-phenylthiol-3,5,5-trimethyl-2-cyclohexen-1-one **300** (1.03 g, 74%) (m.p. 56-57 °C; lit m.p 55-56 °C); R_f 0.28 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1749.70 (C=O stretch) 1616.14 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, two - C(C<u>H</u>$_3$)$_2$ at C5), 2.25 (3H, s, -C<u>H</u>$_3$ at C3), 2.42 (2H, s, -C<u>H</u>$_2$ at C4), 2.49 (2H, s, -C<u>H</u>$_2$ at C5), 7.07-7.24 (5H, m, -C<u>H</u>Ar); δ_C (400 MHz, $CDCl_3$) 24.53 (CH_3, -C<u>C</u>H$_3$ at C3), 28.26 (CH_3, two - C(<u>C</u>H$_3$)$_2$ at C5), 32.71 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 48.24 (CH_2, -<u>C</u>H$_2$ at C6), 51.66 (CH_2, -<u>C</u>H$_2$ at C4), 125.47 (CH, *p*-<u>C</u>Ar), 127.50 (CH, two, *o*-<u>C</u>Ar),128.71 (C, -<u>C</u>SAr) at C2), 128.85 (CH, two, *m*-<u>C</u>Ar), 136.75 (C, -S<u>C</u>1Ar), 166.87 (C, -<u>C</u>CH$_3$ at C3), 194.77 (C, -<u>C</u>=O); HRMS

(+ESI) m/z (MH^+) $C_{15}H_{19}OS$ requires 247.1150, found 247.1151,[^{34}S give M+2 at 249.1115]; [λ_{max} 310nm (ε = 17861 M^{-1} cm^{-1})].

5.2.4 Synthesis of (±)-(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(3-methylbenzenethiol) cyclohexen-1-one (446a), (±)-(2*S*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(3-methylbenzenethiol) cyclohexen-1-one (447a) and 2-(m-tolylthio)-3,5,5-trimethylcyclohex-2-enone (300a) [92]



446a **447a** **300a**

Isophorone epoxide **298** (2.001 g, 12.97 mmol) in ethanol (5 mL) and 15% aq. KOH (0.2 mL, 0.53 mmol) solution was stirred at 0 °C under a nitrogen atmosphere. A solution of *m*-thiocresol **299a** (1.610 g, 12.97 mmol) in THF (5 mL) was degassed with a stream of nitrogen for 30 min then added dropwise over 20 min. After stirring at 0 °C for 1hour, the reaction was judged to be completed by TLC. Water (10 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 10 mL). The combined organic fractions were washed with a saturated sodium chloride solution (2 x 2mL). The organic fraction was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to produce a crude yellow solid as a mixture of two diastereoisomers (15:1) (±)-(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(3-methylbenzenethiol)cyclohexan-1-one **446a** and (±)-(2*R*,3*R*)-3-hydroxy-3,5,5-trimethyl-2-(3-methylbenzenethiol)cyclohexan-1-one **447a** (2.244g, 8.060mmol, 62%). The crude product (2.0363g, 7.31mmol) was crystallised from ethanol/hexane to afford a colourless crystalline solid (0.9485 g, 3.41 mmol, 42%) (m.p. 121-122 °C) as a single major diastereoisomer (±)-(2*S*,3*R*)-3-hydroxy-3,5,5-trimethyl-2-(3-methylbenzenethiol)cyclohexan-1-one **446a**. After removal of the solvent from the mother liquor a yellow solid residue was found to be a mixture

of major diastereoisomer **446a**, minor diastereoisomer **447a** and 2-(m-tolylthio)-3,5,5-trimethylcyclohex-2-enone **300a**, ratio (13:1:3) (0.9513 g, 42%, m.p. 114-115 ^{o}C).

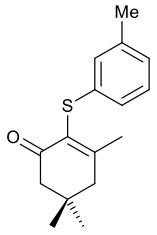
Major diastereoisomer R_f 0.22 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3392.23 (O-H stretch), 1603.59 (C=O stretch). δ_H (400MHz, $CDCl_3$) 1.08 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.14 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5, 1.47 (3H, s, -C$\underline{H}_3$ at C3), 1.70 (1H, app. dt, *J* 14.6, 1.6 Hz, equatorial -C$\underline{H}_2$ at C4), 1.94 (1H, d, *J* 14.6 Hz, axial -C$\underline{H}_2$ at C4), 2.04 (1H, app. dt, *J* 13.2, 1.6 Hz, equatorial -C$\underline{H}_2$ at C6), 2.19 (1H, bs, -(O$\underline{H}$ at C3), 2.31 (3H, s, -*m*-C$\underline{H}_3$Ar), 2.99 (1H, d, *J* 13.2 Hz, axial -C$\underline{H}_2$ at C6), 3.51 (1H, app. st, *J* 1.6 Hz, C$\underline{H}$ at C2), 7.13-7.19 (4H, m, -C$\underline{H}$Ar); δ_C (100 MHz, $CDCl_3$) 21.26 (CH_3, -*m*-$\underline{C}H_3$Ar) , 29.29 (CH_3, one of -C($\underline{C}H_3$)$_2$ one of C5), 29.41 (CH_3, one of -C($\underline{C}H_3$)$_2$ one of C5), 33.11 (CH_3, -$\underline{C}H_3$ at C3), 34.97 (C, -$\underline{C}$(CH$_3$)$_2$ at C5), 46.85 (CH_2, -$\underline{C}H_2$ at C4), 49.12 (CH_2, -$\underline{C}H_2$ at C6), 65.26 (CH, -$\underline{C}$H(SAr) at C2), 77.40 (C, -C(OH)CH3 at C3), 128.46 (CH, -S$\underline{C}$4Ar), 128.53 (CH, -S$\underline{C}$6Ar), 129.04 (CH, -S$\underline{C}$2Ar), 132.03 (CH, -S$\underline{C}$5Ar), 133.47 (C, -S$\underline{C}$3Ar), 139.07 (C, -S$\underline{C}$1Ar), 208.41 (C, -$\underline{C}$=O); HRMS (+ESI) m/z [(M+Na)$^+$] $C_{16}H_{22}NaO_2S$ requires 301.1234 found 301.1233, [^{34}S give M+2 at 303.1192].

Minor diastereoisomer R_f 0.47 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3392.23 (O-H stretch), 1603.59 (C=O stretch); δ_H (400MHz, $CDCl_3$) 1.05 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.12 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C5), 1.36 (3H, s, C$\underline{H}_3$ at C3), 1.81 (1H, d, *J* 14.6 Hz, axial, C$\underline{H}_2$, at C4), 1.94 (1H, app. dd, *J* 14.6, 1.6 Hz, equatorial C$\underline{H}_2$, at C4), 2.31 (CH_3, s, -*m*-C$\underline{H}_3$Ar), 2.37 (1H, d, *J* 13.6 Hz, axial C$\underline{H}_2$, at C6), 2.33 (1H, bs, O$\underline{H}$ at C3), 2.57 (1H, app. dd. *J* 13.6, 1.6 Hz, equatorial -C$\underline{H}_2$, at C6), 3.87 (1H, s, C$\underline{H}$ at C2), 6.98-7.08 (4H, m, -C$\underline{H}$Ar); δ_C (100 MHz, $CDCl_3$) 21.42 (CH_3, -*m*-$\underline{C}H_3$Ar), 28.32 (CH_3, one of -C($\underline{C}H_3$)$_2$ one of C5), 29.18 (CH_3, one of -C($\underline{C}H_3$)$_2$ one of C5), 33.19 (CH_3, -$\underline{C}H_3$ at C3), 34.76 (C, -$\underline{C}$(CH$_3$)$_2$ at C5), 45.29 (CH_2, -$\underline{C}H_2$ at C4), 50.74 (CH_2, -$\underline{C}H_2$ at C6), 69.97 (CH, -$\underline{C}$H(SAr) at C2), 77.28 (C, -

C(OH)CH3 at C3), 124.55 (CH, -SC4Ar), 128.00 (CH, -SC6Ar), 128.02 (CH, -SC2Ar), 128.91 (CH, -SC5Ar), 133.49 (C, -SC3Ar), 138.93 (C, -SC1Ar), 200.19 (C, -C=O); HRMS (+ESI) m/z [$(M+Na)^+$] $C_{16}H_{22}NaO_2S$ requires 301.1234 found 301.1233, [^{34}S give M+2 at 303.1192].

Alkene R_f 0.34 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1749.70 (C=O stretch) 1616.14 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, two - $C(CH_3)_2$ at C5), 2.26 (3H, s, -CH_3 at C3), 2.27 (3H, s, -*m*-CH_3Ar), 2.42 (2H, s, -CH_2 at C4), 2.49 (2H, s, -CH_2 at C6), 6.91 (2H, dt, *J* 7.7, 1.4 Hz, CH4Ar), 6.98 (1H, s, CH2Ar), 7.09 (1H, t, *J* 7.7 Hz, CH5Ar); δ_C (100 MHz, $CDCl_3$) 21.41 (CH_3, -CCH_3 at C3), 24.55 (CH_3, -*m*-CH_3Ar), 28.25 (CH_3, two -$C(CH_3)_2$ at C5), 32.71 (C, -$C(CH_3)_2$ at C3), 48.26 (CH_2, -CH_2 at C4), 51.70 (CH_2, -CH_2 at C6), 124.44 (CH, SC4Ar), 126.39 (CH, SC6Ar), 128.16 (CH, SC2Ar), 128.68 (CH, SC5Ar), 128.80 (CH, C(SAr) at C2), 136.45 (C, SC3Ar), 138.59 (C, SC1Ar), 166.87 (C, -CCH_3 at C3), 194.78 (C, -C=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{16}H_{21}OS$ requires 261.1308, found 261.1309,[^{34}S give (M+2) at 263.1266]; [λ_{max} 311nm (ε = 18879 M^{-1} cm^{-1})].

5.2.5 Synthesis of 2-(3-methylbenzenethiol)-3,5,5-trimethylcyclohex-2-enone (300a) [92]

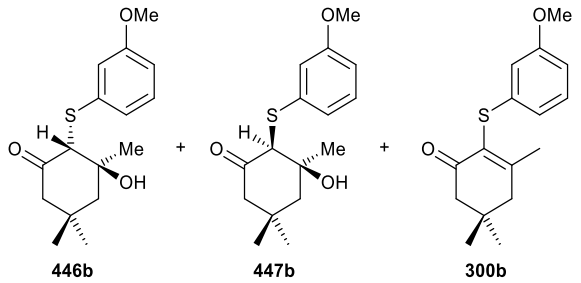


300a

A solution of (±)-(2*S*,3*R*)-3-hydroxy-3,5,5-trimethyl-2-(3-methylbenzenethiol)cyclohexan-1-one **446a** (0.1772 g, 0.636 mmol) in ethanol (1.5 mL) was treated with catalytic amount of 15% KOH (0.31 mL, 0.83 mmol, 10 mol%) at room temperature. The resulting solution was stirred for approximately 15 minutes until TLC analysis (9:1 pet. ether/EtOAc) indicated that all the starting material had reacted. The solution was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered by suction and

concentrated *in vacuo* to yield a yellow solid 2-(3-methylbenzenethiol)-3,5,5-trimethylcyclohex-2-enone **300a** (0.1368 g, 83%), (m.p. 80-81 °C), R_f 0.34 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1749.70 (C=O stretch) 1616.14 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, two - C(CH_3)$_2$ at C5), 2.26 (3H, s, -CH_3 at C3), 2.27 (3H, s, -*m*-CH_3Ar), 2.42 (2H, s, -CH_2 at C4), 2.49 (2H, s, -CH_2 at C6), 6.91 (2H, dt, *J* 7.7, 1.4 Hz, CH4Ar and CH6Ar), 6.98 (1H, s, CH2Ar), 7.09 (1H, t, *J* 7.7 Hz, CH5Ar). δ_C (100 MHz, $CDCl_3$) 21.41 (CH_3, -CCH_3 at C3), 24.55 (CH_3, -*m*-CH_3Ar), 28.25 (CH_3, two -C(CH_3)$_2$ at C5), 32.71 (C, -C(CH_3)$_2$ at C3), 48.26 (CH_2, -CH_2 at C4), 51.70 (CH_2, -CH_2 at C6), 124.44 (CH, SC4Ar), 126.39 (CH, SC6Ar), 128.16 (CH, SC2Ar), 128.68 (CH, SC5Ar), 128.80 (CH, C(SAr) at C2), 136.45 (C, SC3Ar), 138.59 (C, SC1Ar), 166.87 (C, -CCH_3 at C3), 194.78 (C, -C=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{16}H_{21}OS$ requires 261.1308, found 261.1309,[^{34}S give (M+2) at 263.1266]; [λ_{max} 311nm (ε = 18879 M^{-1} cm^{-1})].

5.2.6 Synthesis of (±)-(2*R*,3*S*)-3-hydroxy-2-(3-methoxyphenylthiol)-3,5,5-trimethylcyclohexanone (446b), (±)-(2*S*,3*S*)-3-hydroxy-2-(3-methoxyphenylthiol)-3,5,5-trimethylcyclohexanone (447b) and 2-(3-methoxyphenylthiol)-3,5,5-trimethylcyclohex-2-enone (300b)[92]



446b **447b** **300b**

Isophorone epoxide **298** (2.001 g, 12.97 mmol) in ethanol (5 mL) and 15% aq. KOH (0.2 mL) solution was stirred at 0 °C under a nitrogen atmosphere. A solution of 3-methoxythiophenol **299b** (1.82 g, 17.51 mmol) in THF (5 mL) was degassed with a stream of nitrogen for 30 min. then added dropwise over 20 min. After stirring at 0 °C for 1hour, the reaction was judged to

be completed by TLC (8:2 pet. ether/EtOAc). Water (10 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 10 mL). The combined organic fractions were washed with a saturated sodium chloride solution (2 x 2mL). The organic fraction was dried over $MgSO_4$, filtered by suction, and concentrated *in vacuo* to produce a crude yellow oil (3.0383 g, 10.32 mmol, 80%). Purification of a portion of the crude product (2.9445 g, 7.31mmol) by flash column gave a yellow oil alkene (0.8206 g, 2.97 mmol, 30%) as a mixture of major diastereoisomer **446b** and minor diastereoisomer **447b** and 2-(3-methoxyphenylthiol)-3,5,5-trimethylcyclohex-2-enone **300b**, ratio (4.3:1.5:1) (1.7677 g, 60%). The crude residue (1.1142 g, 3.78 mmol) was triturated with a mixture of hexane/acetonitrile (4:1) 8 mL) then, a little bit warmed up to afford a colourless solid by decantation which was further purified by crystallisation (hexane/acetonitrile (4:1) 10 mL) to give analytically pure white crystals of **446b** (0.6602 g, 2.24 mmol, 59%) (m.p. 108-109 ^oC) as the major diastereoisomer.

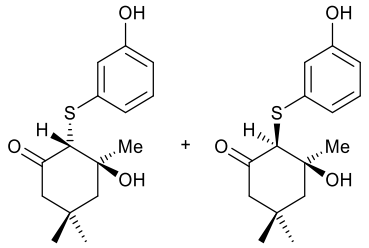
Major diastereoisomer R_f 0.70 (SiO_2, 8:2 pe t. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3498.03 (O-H stretch), 1698.43 (C=O stretch); δ_H (400MHz, $CDCl_3$) 1.08 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.14 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.48 (3H, s, -$C\underline{H}_3$ at C3), 1.70 (1H, d, app. dt, *J* 14.7, 1.8 Hz, equatorial -$C\underline{H}_2$ at C4), 1.93 (1H, d, *J* 14.7 Hz, axial -$C\underline{H}_2$ at C4), 2.04 (1H, d, app. dt, *J* 13.4, 1.8 Hz, equatorial -$C\underline{H}_2$ at C6), 2.86 (1H, bs, -(O$\underline{H}$) at C3), 2.99 (1H, d, *J* 13.4 Hz, axial -$C\underline{H}_2$ at C6), 3.56 (1H, app. st, *J* 1.6 Hz, -C$\underline{H}$ at C2), 3.75 (3H, s, -*m*-O$C\underline{H}_3$Ar), 6.76 (1H, d, app. dd, *J* 8.2, 2.5 Hz, -C$\underline{H}$4Ar), 6.94 (1H, d, *J* 8.3 Hz, -C$\underline{H}$6Ar), 6.96 (1H, s, -C$\underline{H}$2Ar), 7.18 (1H, t, *J* 8.0, 1.7 Hz, -C$\underline{H}$5Ar); δ_C (100 MHz, $CDCl_3$) 29.27 (CH_3, one of -C($\underline{C}H_3$)$_2$ at C5), 29.40 (CH_3, one of -C($\underline{C}H_3$)$_2$ at C5), 33.03 (CH_3, -$\underline{C}H_3$ at C3), 34.98 (C, -$\underline{C}$(OH)(CH_3) at C3, 46.94 (CH_2, -$\underline{C}H_2$ at C4), 49.14 (CH_2, -$\underline{C}H_2$ at C6), 55.32 (CH_3, -O$\underline{C}H_3$), 64.34 (CH, -$\underline{C}$H(SAr) at C2), 77.40 (C, -$\underline{C}CH_3$ at C5), 113.77 (CH, -S$\underline{C}$4Ar), 116.16 (CH, -S$\underline{C}$6Ar), 123.19 (CH, -S$\underline{C}$2Ar), 130.00 (CH, -S$\underline{C}$5Ar), 135.04 (C, -S$\underline{C}$3Ar), 159.85 (C, -S$\underline{C}$1Ar), 208.29 (C, -$\underline{C}$=O);

HRMS (+ESI) m/z [$(M+H)^+$] $C_{16}H_{22}O_3NaS$ requires 317.1182 found 317.1216, [^{34}S give M+2 at 296.13].

Minor diastereoisomer R_f 0.53 (SiO_2, 8:2 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3494.93 (O-H stretch), 1587.71 (C=O stretch); δ_H (400MHz, $CDCl_3$) 1.04 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.10 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.36 (3H, s, -$C\underline{H}_3$ at C3), 1.80 (1H, d, app. dd, *J* 14.6, 1.6 Hz, equatorial -$C\underline{H}_2$ at C4), 1.92 (1H, d, *J* 14.6 Hz, axial -$C\underline{H}_2$ at C4), 2.30 (1H, d, app. dd, *J* 12.7, 1.7 Hz, equatorial -$C\underline{H}_2$ at C6), 2.52 (1H, d, *J* 12.7 Hz, axial -$C\underline{H}_2$ at C6), 2.60 (1H, bs, -O$\underline{H}$) at C3), 3.71 (3H, s, -*m*-O$C\underline{H}_3$Ar), 3.93 (1H, s, C$\underline{H}$) at C2), 6.62-7.10 (4H, m, -C$\underline{H}$Ar); δ_C (100 MHz, $CDCl_3$) 24.52 (CH_3, one of -C($\underline{C}H_3$)$_2$ at C5), 28.20 (CH_3, one of -C($\underline{C}H_3$)$_2$ at C5), 28.92 (CH_3, -$\underline{C}H_3$ at C3), 34.92 (C, - $\underline{C}$(CH_3)$_2$ at C5), 50.34 (CH_2, -$\underline{C}H_2$ at C4), 52.99 (CH_2, -$\underline{C}H_2$ at C6), 55.17 (CH_3, -*m*-O$\underline{C}H_3$Ar), 69.50 (CH, -$\underline{C}$H(SAr) at C2), 77.40 (C, -$\underline{C}CH_3$ at C5), 111.19 (C, -$\underline{C}$(OH)CH_3 at C3), 119.63 (CH, -S$\underline{C}$4Ar), 129.66 (CH, -S$\underline{C}$6Ar), 123.37 (CH, -S$\underline{C}$2Ar), 136.60 (CH, -S$\underline{C}$5Ar), 138.06 (C, -S$\underline{C}$3Ar), 167.41 (C, -S$\underline{C}$1Ar), 205.53 (C, -$\underline{C}$=O); HRMS (+ESI) m/z [$(M+Na)^+$] $C_{16}H_{22}O_3NaS$ requires 317.1182 found 317.1216, [^{34}S give M+2 at 296.13].

Alkene R_f 0.30 (SiO_2, 8:2 pe t. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1749.70 (C=O stretch) 1616.14 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, two - C($C\underline{H}_3$)$_2$ at C5), 2.25 (3H, s, -$C\underline{H}_3$ at C3), 2.42 (2H, s, -$C\underline{H}_2$ at C4), 2.49 (2H, s, -$C\underline{H}_2$ at C6), 3.74 (3H, s, -$C\underline{H}_3$ at -*m*-(O$C\underline{H}_3$)Ar), 6.64 (1H, d, app. dd, *J* 8.2, 2.0 Hz, -C$\underline{H}$4Ar), 6.69 (1H, d, *J* 8.2, Hz, -C$\underline{H}$6Ar), 6.71 (1H, s, -C$\underline{H}$2Ar), 7.11 (1H, t, *J* 8.0, 2.0 Hz, -C$\underline{H}$5Ar). δ_C (100 MHz, $CDCl_3$) 24.52 (CH_3, -$\underline{C}CH_3$ at C3), 28.24 (CH_3, two -C($\underline{C}H_3$)$_2$ at C5), 32.68 (C, -$\underline{C}$(CH_3)$_2$ at C5), 48.25 (CH_2, -$\underline{C}H_2$ at C4), 51.67 (CH_2, -$\underline{C}H_2$ at C6), 55.19 (CH_3, -$\underline{C}H_3$ at -*m*-OCH_3Ar), 111.17 (CH, -S$\underline{C}$4Ar), 112.85 (CH, -S$\underline{C}$6Ar), 119.61 (CH, -S$\underline{C}$2Ar), 128.48 (CH, -$\underline{C}$SAr at C2), 129.64 (C, -S$\underline{C}$5Ar), 138.08 (C, -S$\underline{C}$3Ar), 159.86 (C, -S$\underline{C}$1Ar), 167.11 (C, -$\underline{C}CH_3$ at C3), 194.69 (C, -$\underline{C}$=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{16}H_{21}O_2NaS$ requires 277.1257 found 277.1253 [λ_{max} 311nm (ε =17219 M^{-1} cm^{-1})].

5.2.7 Synthesis of (±)-(2*R*,3*S*)-3-hydroxy-2-(3-hydroxyphenylthiol)-3,5,5-trimethylcyclohexan-1-one (446c) and (±)-(2*S*,3*S*)-3-hydroxy-2-(3-hydroxyphenylthiol)-3,5,5-trimethylcyclohexan-1-one (447c)[92]



446c **447c**

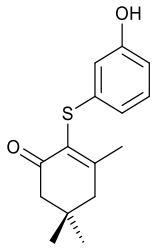
Isophorone epoxide **298** (2.3200 g, 15.04 mmol) in ethanol (5 mL) and 15% aq. KOH (0.2 mL, 0.53 mmol) solution was stirred at 0 °C under a nitrogen atmosphere. A solution of 3-hydroxythiophenol **299c** (1.90 g, 15.04 mmol) in THF (5 mL) was degassed with a stream of nitrogen for 30 min. then added dropwise over 20 min. After stirring at 0 ºC for 1hour, the reaction was judged to be completed by TLC (8:2 pet. ether/EtOAc). Water (10 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 10 mL). The combined organic fractions were washed with a saturated sodium chloride solution (2 x 2mL). The organic fraction was dried over $MgSO_4$, filtered by suction, and concentrated *in vacuo* to produce a mixture of diastereoisomers (3:1) (±)-(2*R*,3*S*)-3-hydroxy-2-(3-hydroxyphenylthiol)-3,5,5-trimethylcyclohexan-1-one **446c** (major isomer) and (±)-(2*S*,3*S*)-3-hydroxy-2-(3-hydroxyphenylthiol)-3,5,5-trimethylcyclohexan-1-one **447c** (minor isomer) as a yellow oil (2.6403 g, 9.42 mmol, 63%). The crude product was triturated with acetonitrile (5 mL) to afford a white solid as a single major diastereoisomer **446c**. The white solid was further purified by crystallisation (hexane/acetonitrile (4:1) 10 mL) to give analytically pure colourless crystal **446c** (2.3831 g, 8.50 mmol, 56%) (m.p. 171-172 ºC).

Major diastereoisomer R_f 0.42 (SiO_2, 8:2 pe t. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3270.11 (O-H stretch), 1684.7 9 (C=O stretch); δ_H (400MHz, DMSO-d_6) 1.01 (3H, s, one of -C($C\underline{H}_3$)$_2$ at

C5), 1.07 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.34 (3H, s, -C<u>H</u>$_3$ at C3), 1.59 (1H, d, app. dt, *J* 14.4, 2.0 Hz, equatorial -C<u>H</u>$_2$ at C4), 1.72 (1H, d, *J* 14.4 Hz, axial -C<u>H</u>$_2$ at C4), 1.86 (1H, d, app. dt, *J* 13.4, 1.8 Hz, equatorial -C<u>H</u>$_2$ at C6), 2.99 (1H, d, *J* 13.4 Hz, axial -C<u>H</u>$_2$ at C6), 3.48 (1H, app. st, *J* 1.6 Hz C<u>H</u> at C2), 5.06 (1H, bs, -O<u>H</u> at C3), 6.77 (1H, d, app. dt, *J* 8.2, 2.0 Hz, -C<u>H</u>4Ar), 6.78 (1H, d, *J* 8.2 Hz, -C<u>H</u>6Ar), 6.79 (1H, s, -C<u>H</u>2Ar), 7.13 (1H, d, *J* 8.2, 2.0 Hz, -C<u>H</u>5Ar), 9.64 (1H, bs, -*m*-(O<u>H</u>)Ar); δ_C (100 MHz, DMSO-d_6) 28.61 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C5), 28.75 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C5), 33.22 (CH_3, -<u>C</u>H$_3$ at C3), 34.77 (C, -<u>C</u>(OH)(CH_3) at C5), 46.05 (CH_2, -<u>C</u>H$_2$ at C4), 48.19 (CH_2, -<u>C</u>H$_2$ at C6), 62.85 (CH, -<u>C</u>H(SAr) at C2), 75.44 (C, -<u>C</u>(OH)CH$_3$ at C3), 114.35 (CH, -S<u>C</u>4Ar), 116.89 (CH, -S<u>C</u>6Ar), 120.76 (CH, -S<u>C</u>2Ar) 129.79 (CH, -S<u>C</u>5Ar), 134.74 (C, -S<u>C</u>3Ar), 157.72 (C, -S<u>C</u>1Ar), 207.22 (C, -<u>C</u>=O); HRMS (+ESI) m/z [(M+Na)$^+$] $C_{15}H_{20}O_3NaS$ requires 303.1025 found 303.1027, [^{34}S give M+2 at 305.0984].

Minor diastereoisomer R_f 0.30 (SiO_2, 8:2 pe t. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3217.75 (O-H stretch), 1599.23 (C=O stretch); δ_H (400MHz, DMSO-d_6) 1.00 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.03 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.38 (3H, s, -C<u>H</u>$_3$ at C3), 1.75 (1H, d, app. dd, *J* 14.2, 1.6 Hz, axial -C<u>H</u>$_2$ at C4), 1.99 (1H, d, *J* 14.2 Hz, equatorial -C<u>H</u>$_2$ at C4), 2.19 (1H, d, app. dd, *J* 12.4, 1.6 Hz axial -C<u>H</u>$_2$ at C6), 2.59 (1H, d, *J* 12.4 Hz, equatorial -C<u>H</u>$_2$ at C6), 4.23 (1H, s, C<u>H</u>) at C2), 4.73 (1H, bs, -O<u>H</u> at C23, 6.53 (1H, d, app. dt, *J* 8.1, 2.3 Hz, -C<u>H</u>4Ar), 6.63 (1H, d, *J* 8.2, Hz, -C<u>H</u>6Ar), 6.79 (1H, s, -C<u>H</u>2Ar), 7.03 (1H, t, *J* 8.0, 2.0 Hz, -C<u>H</u>5Ar), 9.43 (1H, bs, -*m*-(O<u>H</u>)-Ar); δ_C (100 MHz, DMSO-d_6) 28.62 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C5), 30.38 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C5), 33.35 (CH_3, -<u>C</u>H$_3$ at C3), 34.77 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 50.40 (CH_2, -<u>C</u>H$_2$ at C4), 53.58 (CH_2, -<u>C</u>H$_2$ at C6), 66.45 (CH, -<u>C</u>H(SAr) at C2), 76.77 (C, -<u>C</u>(OH)CH$_3$ at C3), 112.43 (CH, -S<u>C</u>4Ar), 115.23 (CH, -S<u>C</u>6Ar) 119.00 (CH, -S<u>C</u>2Ar), 129.53 (CH, -S<u>C</u>5Ar), 133.39 (C, -S<u>C</u>3Ar), 157.42 (C, -S<u>C</u>1Ar), 204.53 (C, -<u>C</u>=O); HRMS (+ESI) m/z [(MH)$^+$] $C_{15}H_{20}O_3S$ requires 280.1060 found 280.1067.

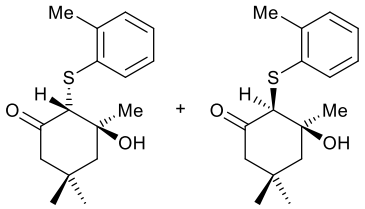
5.2.8 Synthesis of 2-(3-hydroxyphenylthiol)-3,5,5-trimethylcyclohex-2-enone (300c) [92]



300c

A solution of (±) -(2*S*,3*R*)-3-hydroxy-2-(3-hydroxyphenylthiol)-3,5,5-trimethylcyclohexan-1-one **446c** (0.0572 g, 204.01 µmol) in ethanol (1.5 mL) was treated with catalytic amount of 15% KOH (0.013 mL, 0.56 mmol, 10 mol%) at room temperature. The resulting solution was stirred for approximately 15 minutes until TLC analysis (9:1 pet. ether/EtOAc) indicated that all the starting material had reacted. The solution was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered by suction, and concentrated *in vacuo* to yield yellow gummy 2-(3-hydroxyphenylthio)-3,5,5-trimethylcyclohex-2-enone **300c** (0.0308 g, 58%). R_f 0.25 (9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3270.11 (O-H stretch), 1684.7 9 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, two - C(C<u>H</u>$_3$)$_2$ at C5), 2.26 (3H, s, -C<u>H</u>$_3$ at C3), 2.43 (2H, s, -C<u>H</u>$_2$ at C4), 2.50 (2H, s, -C<u>H</u>$_2$ at C6), 5.22 (1H, bs, -*m*-(O<u>H</u>)Ar) 6.56 (1H, d, app. dd, *J* 8.0, 2.0, Hz, -C<u>H</u>4Ar), 6.62 (1H, d, app. dd, *J* 8.0, 2.0, Hz, -C<u>H</u>6Ar), 6.68 (1H, s, -C<u>H</u>2Ar), 7.06 (1H, t, *J* 8.0, 2.0 Hz, -C<u>H</u>5Ar). δ_C (100 MHz, $CDCl_3$) 24.49 (CH_3, -C<u>C</u>H$_3$ at C3), 28.18 (CH_3, two -C(<u>C</u>H$_3$)$_2$ at C5), 34.98 (C, -<u>C</u>(CH$_3$)$_2$ at C3), 48.22 (CH_2, -<u>C</u>H$_2$ at C4), 51.59 (CH_2, -<u>C</u>H$_2$ at C6), 112.83 (CH, -S<u>C</u>4Ar), 114.21 (CH, -S<u>C</u>2Ar), 119.65 (CH, -S<u>C</u>6Ar), 129.80 (CH, -S<u>C</u>5Ar), 131.69 (C, -<u>C</u>(SAr) at C2), 156.01 (C, -S<u>C</u>3Ar), 159.85 (C, -S<u>C</u>1Ar), 167.47 (C, -<u>C</u>CH$_3$ at C3), 194.58 (C, -<u>C</u>=O); HRMS (+ESI) m/z [$(M+Na)^+$] $C_{15}H_{18}NaO_2S$ requires 285.0920, found 285.0922, [^{34}S give M+2 at 287. 0927]; [λ_{max} 311nm, (ε =16345 M^{-1} cm^{-1})].

5.2.9 Synthesis of (±)-(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(*o*-tolylthiol)cyclohexan-1-one (446d) and (±)-(2*S*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(*o*-tolylthiol)cyclohexan-1-one (447d) [92]



446d **447d**

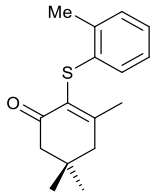
Isophorone epoxide **298** (2.0826 g, 13.51 mmol) in ethanol (5 mL) and 15% aq. KOH (0.2 mL, 0.53 mmol) solution was stirred at 0 °C under a nitrogen atmosphere. A solution of 2-methylbenzenethiol **299d** (1.6801 g, 12.94 mmol) in THF (5 mL) was degassed with a stream of nitrogen for 30 min then added dropwise over 20 min. After stirring at 0 °C for 1 hour, the reaction was judged to be completed by TLC. Water (10 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 10 mL). The combined organic fractions were washed with a saturated sodium chloride solution (2 x 5mL). The organic fraction was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to produce a crude yellow oil (2.6703 g, 9.59 mmol, 71%). A portion of the crude product (1.2455 g, 4.47 mmol) was triturated with hexane (5 mL) to afford a white solid (0.9113 g, 3.27 mmol, 73% recovery) and yellow oil residue, upon evaporation of the hexane. A portion of the white solid (0.5054 g, 1.82 mmol) was further purified by crystallisation (hexane/ether (4:1) (10 mL) to give analytically pure colourless crystals of **446d** (0.4816 g, 1.73 mmol, 95%) (m.p. 129-130 ^{o}C) as a single major diastereoisomer (±)-(2*S*,3*R*)-3-hydroxy-3,5,5-trimethyl-2-(*o*-methylbenzenethiol)cyclohexan-1-one. The yellow oil residue was found to be a (1:5) mixture of major **446d** and minor **447d** diastereoisomers.

Major diastereoisomer R_f 0.8 (SiO_2, 9:1 pe t. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3389.47 (O-H stretch), 1686.538 (C=O stretch). δ_H (400MHz, $CDCl_3$) 1.10 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5),

1.15 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.50 (3H, s, -C(OH)C<u>H</u>$_3$ at C3), 1.71 (1H, d, app. dt, *J* 14.6, 1.7 Hz, equatorial -C<u>H</u>$_2$ at C4), 1.76 (1H, bs, -(O<u>H</u>) at C3), 1.99 (1H, d, *J* 14.6 Hz, axial -C<u>H</u>$_2$ at C4), 2.04 (1H, d, app. dt, *J* 13.4, 1.7 Hz, equatorial -C<u>H</u>$_2$ at C6), 2.42 (3H, s, -*o*-C<u>H</u>$_3$Ar), 3.03 (1H, d, *J* 13.4 Hz, axial -C<u>H</u>$_2$ at C6), 3.43 (1H, s, app. st, *J* 1.6 Hz, C<u>H</u> at C2), 7.51-7.03 (4H, m, C<u>H</u>Ar); δ_C (100 MHz, $CDCl_3$) 20.68 (CH_3, -*o*-<u>C</u>H$_3$Ar), 29.99 (CH_3, two of -C(<u>C</u>H$_3$)$_2$), 33.11 (CH_3, -C(OH)<u>C</u>H$_3$ at C3), 34.89 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 46.95 (CH_2, -<u>C</u>H$_2$ at C4), 49.15 (CH_2, -<u>C</u>H$_2$ at C6), 64.60 (CH, -<u>C</u>H(SAr) at C2), 77.49 (C, -<u>C</u>CH$_3$ at C3), 126.80 (CH, -S<u>C</u>4Ar), 127.91 (CH, -S<u>C</u>6Ar), 130.56 (CH, -S<u>C</u>2Ar) 132.30 (CH, -S<u>C</u>5Ar), 132.84 (C, -S<u>C</u>3Ar), 139.60 (C, -S<u>C</u>1Ar), 207.69 (C, -<u>C</u>=O); HRMS (+ESI) m/z [(M+Na)$^+$] $C_{16}H_{22}NaO_2S$ requires 301.1234 found 301.1233.

Minor diastereoisomer R_f 0.2 (SiO_2, 9:1 pe t. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 3386.98 (O-H stretch), 1684.57 (C=O stretch). δ_H (400MHz, $CDCl_3$) 1.06 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.14 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.37 (3H, s, -C<u>H</u>$_3$ at C3), 1.81 (1H, d, app. dt, *J* 14.6, 1.6 Hz, axial -C<u>H</u>$_2$ at C4), 1.95 (1H, dd, *J* 14.6, 1.6 Hz, equatorial -C<u>H</u>$_2$ C4), 2.22 (1H, bs, -(O<u>H</u>) at C3), 2.30 (1H, dd *J* 12.7, 1.2 Hz, axial -C<u>H</u>$_2$ at C6), 2.46 (3H, s, -*o*-C<u>H</u>$_3$Ar), 2.61 (1H, dd, *J* 12.7, 1.6 Hz, equatorial -C<u>H</u>$_2$ at C6), 3.82 (1H, s, app. d, *J* 1.2 Hz, -C<u>H</u> at C2), 6.79-7.52 (4H, m, C<u>H</u>Ar); δ_C (100 MHz, $CDCl_3$) 19.91 (CH_3, -*o*-<u>C</u>H$_3$Ar), 29.26 (CH_3, two of -C(<u>C</u>H$_3$)$_2$), 30.51 (CH_3, -<u>C</u>H$_3$ at C3), 31.74 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 50.52 (CH_2, -<u>C</u>H$_2$ at C4), 52.53 (CH_2, -<u>C</u>H$_2$ at C6), 69.35 (CH, -<u>C</u>H(SAr) at C2), 76.93 (C, -<u>C</u>CH$_3$ at C3), 126.66 (CH, -S<u>C</u>4Ar), 127.32 (CH, -S<u>C</u>6Ar), 128.65 (CH, -S<u>C</u>2Ar) 130.27 (CH, -S<u>C</u>5Ar), 131.65 (C, -S<u>C</u>3Ar), 137.12 (C, -S<u>C</u>1 Ar), 205.35 (C, -<u>C</u>=O); HRMS (+ESI) m/z [(M+Na)$^+$] $C_{16}H_{22}NaO_2S$ requires 301.1234 found 301.1233.

5.2.10 Synthesis of 2-(*o*-tolylthiol)-3,5,5-trimethylcyclohex-2-enone (300a) [92]

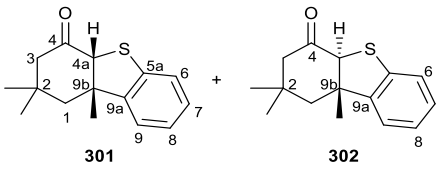


300d

A solution of (±)-(2*R*,3*S*)-3-hydroxy-3,5,5-trimethyl-2-(*o*-tolylthiol)cyclohexan-1-one **446d** (0.5085 g, 1.83 mmol) in ethanol (2 mL) was treated with a catalytic amount of 15% KOH (0.31 mL, 0.83 mmol, 10 mol%) at room temperature. The resulting solution was stirred for approximately 15 minutes until TLC analysis (9:1 pet. ether/EtOAc) indicated that all the starting material had reacted. The solution was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to yield a yellow oil 2-(*o*-tolylthiol)-3,5,5-trimethylcyclohex-2-enone **300d** (0.3514 g, 1.35 mmol) in 74% yield.

R_f 0.8 (SiO_2, 9:1 pet. Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1749.70 (C=O stretch) 1616.14 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 1.07 (6H, s, two - C($C\underline{H}_3$)$_2$ at C5), 2.25 (3H, s, -$C\underline{H}_3$ at C3), 2.23 (3H, s, -*o*-$C\underline{H}_3$Ar), 2.42 (2H, s, -$C\underline{H}_2$ at C4), 2.49 (2H, s, -$C\underline{H}_2$ at C6), 6.91 (2H, dt, *J* 7.7, 1.4 Hz, C<u>H</u>3Ar and C<u>H</u>5Ar), 6.98 (1H, d, C<u>H</u>6Ar), 7.09 (1H, t, *J* 7.7 Hz, C<u>H</u>4Ar). δ_C (100 MHz, $CDCl_3$) 21.40 (CH_3, -C<u>C</u>H_3 at C3), 24.54 (CH_3, -*o*-<u>C</u>H_3Ar), 28.24 (CH_3, two -C(<u>C</u>H_3)$_2$ at C5), 32.69 (C, -<u>C</u>(CH_3)$_2$ at C3), 48.26 (CH_2, -<u>C</u>H_2 at C4), 51.72 (CH_2, -<u>C</u>H_2 at C6), 124.44 (CH, S<u>C</u>4Ar), 126.39 (CH, S<u>C</u>6Ar), 128.15 (CH, S<u>C</u>3Ar), 128.68 (CH, S<u>C</u>5Ar), 128.80 (CH, <u>C</u>(SAr) at C2), 136.44 (C, S<u>C</u>2Ar), 138.59 (C, S<u>C</u>1Ar), 166.87 (C, -<u>C</u>CH_3 at C3), 194.76 (C, -<u>C</u>=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{16}H_{21}OS$ requires 261.1208, found 261.1209,[^{34}S give (M+2) at 263.1206]; [λ_{max} 311nm ε = 17861 M^{-1} cm^{-1}].

5.2.11 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one in Flow photoreactor to form the *cis*-dihydrothiophene (4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (301) and the *trans*-dihydrothiophene (4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (302)[92]



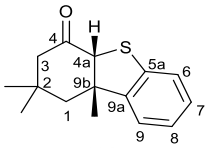
A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (20 mg, 81.18µmol) in toluene (30 mL) and methanol (10 mL) was placed in the flow photoreactor and the solution was degassed with nitrogen for 30 minutes prior to and during irradiation. The reaction mixture was re-circulated using a peristaltic pump at flow rate of 5ml/min through the reactor with irradiation at 320 nm using Reptile UV B 200 Exo terra lamp. The reaction time progression was monitored every 15 min, up to 2 hours, then at the following time points 3 hr, 4 hr, 5 hr, 6 hr, 7hr, 18hr and 24hr using TLC and ^{1}H NMR analysis and a yellow oil was obtained as the crude product. The reaction was completed after approximately 3 hours (4.5 min. residence time) after which a steady degradation of products was noted. The crude reaction product was concentrated *in vacuo* and this yielded a yellow solution (19.6 mg, 79.56 µmol, 98%). The crude product was purified by flash column chromatography (SiO_2 9:1 pet. ether/EtOAc) to afford a mixture of two diastereoisomers of *cis*-dihydrothiophene (4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **301** and *trans*-dihydrothiophene (4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **302** [(3:1) 0.0030 g, 12.18 µmol, 15%] and a single diastereoisomer of *cis*-dihydrothiophene **301** (0.0162 g, 65.76 µmol, 83%).

Major diastereoisomer A R_f 0.40 (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.08 (3H, s, one of

-C(C$\underline{H}_3$)$_2$ at C2), 1.45 (3H, s, -C$\underline{H}_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -C$\underline{H}_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -CH$_2$, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -C$\underline{H}_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -C$\underline{H}_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C$\underline{H}$ at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -C$\underline{H}$6Ar), 7.08 (1H, td, *J* 7.4, 6.9, 1.2 Hz, -C$\underline{H}$7Ar), 7.14 (1H, td, *J* 7.4, 1.6 Hz, -C$\underline{H}$8Ar), 7.19 (1H, d, *J* 8.0 Hz, -C$\underline{H}$9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH$_3$ - one of -C(C$\underline{H}_3$)$_2$ at C2), 30.90 (CH$_3$ - one of -C(C$\underline{H}_3$)$_2$ at C2), 31.35 (CH$_3$, -C$\underline{H}_3$ at C9b), 34.85 (C, -C$\underline{C}$H$_3$)$_2$ at C2), 46.84 (CH$_2$, -C$\underline{H}_2$ at C1), 51.27 (CH$_2$, -C$\underline{H}_2$ at C3), 54.15 (C, -(C$\underline{C}$H$_3$)$_2$ at C9b), 64.51 (CH, -C$\underline{H}$(SAr) at C4a), 122.37 (CH, -SC$\underline{H}$6Ar), 123.24 (CH, -SC$\underline{H}$7Ar), 124.69 (CH, -SC$\underline{H}$8Ar), 127.83 (CH, -SC$\underline{H}$9Ar), 138.56 (C, -SC9bAr), 145.84 (C, -SC5aAr), 207.65 (C, -C$\underline{C}$=O); HRMS (+ESI) *m/z* [(M+Na)$^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

Minor diastereoisomer R_f 0.44 (SiO_2, 9:1 pet. ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.07 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.53 (3H, s, C$\underline{H}_3$ at C9b), 1.65 (1H, app. dd, *J* 14.7, 2.5 Hz, equatorial C$\underline{H}_2$, at C1), 1.91 (1H, d, *J* 14.7 Hz, axial, C$\underline{H}_2$, at C1), 2.34 (1H, app. dd. *J* 13.5, 2.5 Hz, equatorial -C$\underline{H}_2$, at C3), 3.13 (1H, d, *J* 13.5 Hz, axial C$\underline{H}_2$, at C3), 4.85 (1H, s, C$\underline{H}$ at C4b), 7.25-7.08 (4H, m, Ar); HRMS (+ESI) *m/z* [(M+H)$^+$] $C_{15}H_{19}OS$ requires 247.1151 found 247.1152, [^{34}S give M+2 at 249.1111].

5.2.12 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one in Flow photoreactor to form the *cis*-dihydrothiophene (4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (301) in methanol [92]



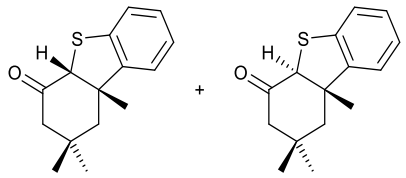
301

A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (0.4626 g, 1.88 mmol) in methanol (40 mL) was placed in the flow photoreactor and the solution was degassed with nitrogen for 30 minutes prior to and during irradiation. The reaction mixture was re-circulated using a peristaltic pump at flow rate of 5ml/min through the reactor with irradiation at 320 nm using Reptile UV B 200 Exo terra lamp. The reaction was judged to be completed after approximately 3 hours (4.5 min. residence time) upon using TLC and ^{1}H NMR analysis and a yellow solution was obtained as the crude product. The crude reaction mixture was concentrated *in vacuo* and this yielded a yellow oil. The crude product was purified by flash column chromatography (SiO_2 9:1 pet. ether/EtOAc) to afford a single diastereoisomers of *cis*-dihydrothiophenes **301** (0.4495 g, 1.82 mmol, 97%) as a pale-yellow oil.

Major diastereoisomer A R_f 0.40 (SiO_2, 9:1 pet. ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.08 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.45 (3H, s, -C$\underline{H}_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -C$\underline{H}_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -CH_2, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -C$\underline{H}_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -C$\underline{H}_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C$\underline{H}$ at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -C$\underline{H}$6Ar), 7.08 (1H, td, *J* 7.4, 6.9, 1.2 Hz, -C$\underline{H}$7Ar), 7.14 (1H, td, *J* 7.4, 1.6 Hz, -C$\underline{H}$8Ar), 7.19 (1H, d, *J* 8.0 Hz, -C$\underline{H}$9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH_3 - one of -C($\underline{C}H_3$)$_2$ at C2), 30.90 (CH_3 - one of -C($\underline{C}H_3$)$_2$ at C2), 31.35 (CH_3, -$\underline{C}H_3$ at C9b), 34.85 (C, -$\underline{C}CH_3$)$_2$ at C2), 46.84 (CH_2, -$\underline{C}H_2$ at C1), 51.27 (CH_2, -$\underline{C}H_2$ at C3), 54.15 (C, -

($\underline{C}CH_3)_2$ at C9b), 64.51 (CH, -$\underline{C}$H(SAr) at C4a), 122.37 (CH, -S$\underline{C}$6Ar), 123.24 (CH, -S$\underline{C}$7Ar), 124.69 (CH, -S$\underline{C}$8Ar), 127.83 (CH, -S$\underline{C}$9Ar), 138.56 (C, -S$\underline{C}$9bAr), 145.84 (C, -S$\underline{C}$5aAr), 207.65 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

5.2.13 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one under Batch Conditions to give the *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b,d*]thiophen-4(1*H*)-one (301) and the *trans*-dihydrothiophene (±)-(4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b,d*]thiophen-4(1*H*)-one (302) in toluene/methanol (medium pressure lamp)[92]



301 302

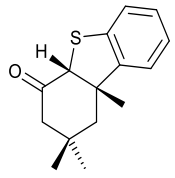
A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (0.0246 g, 99.9 µmol) in toluene (7.5 mL) and methanol (2.5 mL) 1 mM was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30min prior to the reaction. The degassed solution was irradiated for 2 hours, with a 125 W medium pressure mercury lamp, contained within a wate-cooled quartz immersion well. The crude reaction product was concentrated *in vacuo* to give a pale yellow oil (0.0244 g, 99.04 µmol, 99%). The crude product was purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford a mixture of diastereoisomers of dihydrothiophene **301** and **302** (4:1) (0.0058 g, 23.54 µmol, 24%) and a single stereoisomer of *cis*-dihydrothiophene **301** (0.0175 g, 71.03 µmol, 72%).

Major diastereoisomer R_f 0.40 (SiO_2, 9:1 pe t. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C($C\underline{H}_3)_2$ at C2), 1.08 (3H, s, one of

-C(C<u>H</u>$_3$)$_2$ at C2), 1.45 (3H, s, -C<u>H</u>$_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -C<u>H</u>$_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -CH$_2$, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -C<u>H</u>$_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -C<u>H</u>$_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C<u>H</u> at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -C<u>H</u>6Ar), 7.08 (1H, td, *J* 7.4, 6.9, 1.2 Hz, -C<u>H</u>7Ar), 7.14 (1H, td, *J* 7.4, 1.6 Hz, -C<u>H</u>8Ar), 7.19 (1H, d, *J* 8.0 Hz, -C<u>H</u>9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH$_3$ - one of -C(<u>C</u>H$_3$)$_2$ at C2), 30.90 (CH$_3$ - one of -C(<u>C</u>H$_3$)$_2$ at C2), 31.35 (CH$_3$, -<u>C</u>H$_3$ at C9b), 34.85 (C, -<u>C</u>CH$_3$)$_2$ at C2), 46.84 (CH$_2$, -<u>C</u>H$_2$ at C1), 51.27 (CH$_2$, -<u>C</u>H$_2$ at C3), 54.15 (C, -(<u>C</u>CH$_3$)$_2$ at C9b), 64.51 (CH, -<u>C</u>H(SAr) at C4a), 122.37 (CH, -S<u>C</u>6Ar), 123.24 (CH, -S<u>C</u>7Ar), 124.69 (CH, -S<u>C</u>8Ar), 127.83 (CH, -S<u>C</u>9Ar), 138.56 (C, -S<u>C</u>9bAr), 145.84 (C, -S<u>C</u>5aAr), 207.65 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [(M+H)$^+$] $C_{15}H_{18}OS$ requires 246.37 found 246.1154. HRMS (+ESI) *m/z* [(M+Na)$^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

Minor diastereoisomer R_f 0.44 (SiO_2, 9:1 pet. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.07 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.53 (3H, s, C<u>H</u>$_3$ at C9b), 1.65 (1H, app. dd, *J* 14.7, 2.5 Hz, equatorial C<u>H</u>$_2$, at C1), 1.91 (1H, d, *J* 14.7 Hz, axial, C<u>H</u>$_2$, at C1), 2.34 (1H, app. dd. *J* 13.5, 2.5 Hz, equatorial -C<u>H</u>$_2$, at C3), 3.13 (1H, d, *J* 13.5 Hz, axial C<u>H</u>$_2$, at C3), 4.85 (1H, s, C<u>H</u> at C4b), 7.25-7.08 (4H, m, Ar); HRMS (+ESI) *m/z* [(M+H)$^+$] $C_{15}H_{19}OS$ requires 247.1151 found 247.1152, [^{34}S give M+2 at 249.1111].

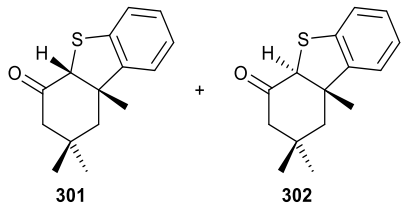
5.2.14 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one under Batch Conditions in methanol (medium pressure lamp) to give the *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (301)[92]



301

A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (0.0615 g, 249.63 µmol) in methanol (10 mL, 1 mM) was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30min prior to the reaction. The degassed solution was irradiated for 2 hours, with a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well. The crude was concentrated *in vacuo* to give a cream solid as single stereoisomer of *cis*-dihydrothiophene **301** (0.0531 g, 215.53 µmol, 86%) (mp. 81-82 ^oC). R_f 0.4 (SiO_2, 9:1 pe t. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.08 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.45 (3H, s, -$C\underline{H}_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -$C\underline{H}_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -CH_2, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -$C\underline{H}_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -$C\underline{H}_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C<u>H</u> at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -C<u>H</u>6Ar), 7.08 (1H, td, *J* 8.0, 6.9, 1.2 Hz, -C<u>H</u>7Ar), 7.14 (1H, td, *J* 8.0, 1.6 Hz, -C<u>H</u>8Ar), 7.19 (1H, d, *J* 8.0 Hz, -C<u>H</u>9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH_3 - one of -C($\underline{C}H_3$)$_2$ at C2), 30.90 (CH_3 - one of -C($\underline{C}H_3$)$_2$ at C2), 31.35 (CH_3, -$\underline{C}H_3$ at C9b), 34.85 (C, -$\underline{C}CH_3$)$_2$ at C2), 46.84 (CH_2, -$\underline{C}H_2$ at C1), 51.27 (CH_2, -$\underline{C}H_2$ at C3), 54.15 (C, -($\underline{C}CH_3$)$_2$ at C9b), 64.51 (CH, -<u>C</u>H(SAr) at C4a), 122.37 (CH, -S<u>C</u>6Ar), 123.24 (CH, -S<u>C</u>7Ar), 124.69 (CH, -S<u>C</u>8Ar), 127.83 (CH, -S<u>C</u>9Ar), 138.56 (C, -S<u>C</u>9bAr), 145.84 (C, -S<u>C</u>5aAr), 207.65 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

5.2.15 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one under Batch Conditions to give the *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (301) and the *trans*-dihydrothiophene (±)-(4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (302) in toluene/methanol (311 nm Philips low pressure Hg lamp)[92]



301 302

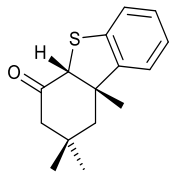
A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (0.0246 g, 99.9 µmol) in toluene (7.5 mL) and methanol (2.5 mL) 1 mM was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30min prior to the reaction. The degassed solution was irradiated for 1 hour, with a 311 nm low pressure mercury lamp, against the sample which was contained in a Pyrex Schlenk tube. The crude reaction product was concentrated *in vacuo* to give pale yellow oil (0.0234 g, 94.98 µmol, 95%). The crude product was purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford a mixture of diastereoisomers of *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **301** and *trans*-dihydrothiophene (±)- (4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*] thiophen-4(1*H*)-one 302 (3:1) (0.0058 g, 23.54 µmol, 25%) and a single diastereoisomer of *cis*-dihydrothiophene **301** (0.0163 g, 66.16 µmol, 70%).

Major diastereoisomer R_f 0.40 (SiO_2, 9:1 pe t. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.08 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.45 (3H, s, -$C\underline{H}_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -$C\underline{H}_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -CH_2, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -$C\underline{H}_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -$C\underline{H}_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C<u>H</u>

at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -CH6Ar), 7.08 (1H, td, *J* 7.4, 6.9, 1.2 Hz, -CH7Ar), 7.14 (1H, td, *J* 7.4, 1.6 Hz, -CH8Ar), 7.19 (1H, d, *J* 8.0 Hz, -CH9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH_3 - one of -C(CH_3)$_2$ at C2), 30.90 (CH_3 - one of -C(CH_3)$_2$ at C2), 31.35 (CH_3, -CH_3 at C9b), 34.85 (C, -CCH_3)$_2$ at C2), 46.84 (CH_2, -CH_2 at C1), 51.27 (CH_2, -CH_2 at C3), 54.15 (C, -(CCH_3)$_2$ at C9b), 64.51 (CH, -CH(SAr) at C4a), 122.37 (CH, -SC6Ar), 123.24 (CH, -SC7Ar), 124.69 (CH, -SC8Ar), 127.83 (CH, -SC9Ar), 138.56 (C, -SC9bAr), 145.84 (C, -SC5aAr), 207.65 (C, -C=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{15}H_{18}OS$ requires 246.37 found 246.1154. HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

Minor diastereoisomer R_f 0.44 (SiO_2, 9:1 pet. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, one of -C(CH_3)$_2$ at C2), 1.07 (3H, s, one of -C(CH_3)$_2$ at C2), 1.53 (3H, s, CH_3 at C9b), 1.65 (1H, app. dd, *J* 14.7, 2.5 Hz, equatorial CH_2, at C1), 1.91 (1H, d, *J* 14.7 Hz, axial, CH_2, at C1), 2.34 (1H, app. dd. *J* 13.5, 2.5 Hz, equatorial -CH_2, at C3), 3.13 (1H, d, *J* 13.5 Hz, axial CH_2, at C3), 4.85 (1H, s, CH at C4b), 7.25-7.08 (4H, m, Ar); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{15}H_{19}OS$ requires 247.1151 found 247.1152, [^{34}S give M+2 at 249.1111].

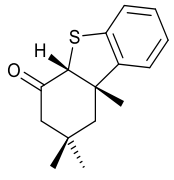
5.2.16 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one under Batch Conditions in methanol (Philips low pressure Hg lamp) to give the *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (301) in methanol.[92]



301

A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (0.0246 g, 99.9 µmol) in methanol (2.5 mL) 1 mM was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30 min prior to the reaction. The degassed solution was irradiated for 1 hour, with a 311 nm low pressure mercury lamp, against the sample which was contained in a Pyrex Schlenk tube. The crude reaction product was concentrated *in vacuo* to give a colourless solid as single stereoisomer of *cis*-dihydrothiophene **301** (0.0216 g, 87.67 µmol, 88%) (mp. 81-82 ^oC). R_f 0.4 (SiO_2, 9:1 pe t. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.08 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.45 (3H, s, -$C\underline{H}_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -$C\underline{H}_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -CH_2, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -$C\underline{H}_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -$C\underline{H}_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C$\underline{H}$ at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -C$\underline{H}$6Ar), 7.08 (1H, td, *J* 8.0, 6.9, 1.2 Hz, -C$\underline{H}$7Ar), 7.14 (1H, td, *J* 8.0, 1.6 Hz, -C$\underline{H}$8Ar), 7.19 (1H, d, *J* 8.0 Hz, -C$\underline{H}$9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH_3 - one of -C($\underline{C}H_3$)$_2$ at C2), 30.90 (CH_3 - one of -C($\underline{C}H_3$)$_2$ at C2), 31.35 (CH_3, -$\underline{C}H_3$ at C9b), 34.85 (C, -$\underline{C}CH_3$)$_2$ at C2), 46.84 (CH_2, -$\underline{C}H_2$ at C1), 51.27 (CH_2, -$\underline{C}H_2$ at C3), 54.15 (C, -($\underline{C}CH_3$)$_2$ at C9b), 64.51 (CH, -$\underline{C}$H(SAr) at C4a), 122.37 (CH, -S$\underline{C}$6Ar), 123.24 (CH, -S$\underline{C}$7Ar), 124.69 (CH, -S$\underline{C}$8Ar), 127.83 (CH, -S$\underline{C}$9Ar), 138.56 (C, -S$\underline{C}$9bAr), 145.84 (C, -S$\underline{C}$5aAr), 207.65 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

5.2.17 Photolysis of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-l-one under batch conditions in methanol (Rayonet reactor) to give the *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b,d*]thiophen-4(1*H*)-one(301) in methanol - large scale [92]

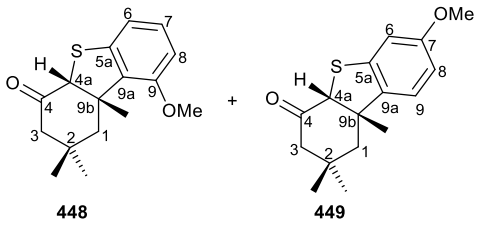


301

A solution of 2-phenylthio-3,5,5-trimethyl-2-cyclohexen-1-one **300** (0.6425g, 2.61 mmol) in methanol (320 mL) was placed in a Pyrex test tube and degassed with a slow stream of N_2 for 30min prior to the reaction. The reaction mixture was then placed in the Rayonet photoreactor and irradiated for 30 min. with a broad band around 311nm (Rayonet RPR-200, equipped with 16 x RPR-3000Å lamp, 16 x 8 W). The crude reaction product was concentrated *in vacuo* and obtained an orange oil (0.6335 g, 2.57 mmol, 99%). The crude product was triturated with hexane (3 x 2 mL) to afford a pale off-white solid which was further purified by crystallisation (hexane/diethyl ether (5:1) 5 mL to afford analytically pure *cis*-dihydrothiophene **301** as colourless crystals (0.5721 g, 2.32 mmol, 90%) (mp. 81-82 ^{o}C).

R_f 0.40 (SiO_2, 9:1 pe t. Ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.73 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.08 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.45 (3H, s, -C<u>H</u>$_3$ at C9b), 1.80 (1H, dt, *J* 14.7, 1.6, Hz, equatorial -C<u>H</u>$_2$, at C1), 2.20 (1H, dd, *J* 13.2, 1.6 Hz, equatorial -C<u>H</u>$_2$, at C3), 2.30 (1H, d, *J* 14.7 Hz, axial -C<u>H</u>$_2$, at C1), 2.52 (1H, d, *J* 13.2, Hz, axial -C<u>H</u>$_2$, at C3), 3.80 (1H, app. d, *J* 1.6 Hz, equatorial -C<u>H</u> at C4a), 7.05 (1H, dd, *J* 8.0, 2.0 Hz, -C<u>H</u>6Ar), 7.08 (1H, td, *J* 8.0, 6.9, 1.2 Hz, -C<u>H</u>7Ar), 7.14 (1H, td, *J* 8.0, 1.6 Hz, -C<u>H</u>8Ar), 7.19 (1H, d, *J* 8.0 Hz, -C<u>H</u>9Ar); δ_C (100 MHz, $CDCl_3$) 29.70 (CH_3 - one of -C(<u>C</u>H$_3$)$_2$ at C2), 30.90 (CH_3 - one of -C(<u>C</u>H$_3$)$_2$ at C2), 31.35 (CH_3, -<u>C</u>H$_3$ at C9b), 34.85 (C, -<u>C</u>CH$_3$)$_2$ at C2), 46.84 (CH_2, -<u>C</u>H$_2$ at C1), 51.27 (CH_2, -<u>C</u>H$_2$ at C3), 54.15 (C, -(<u>C</u>CH$_3$)$_2$ at C9b), 64.51 (CH, -<u>C</u>H(SAr) at C4a), 122.37 (CH, -S<u>C</u>6Ar), 123.24 (CH, -S<u>C</u>7Ar), 124.69 (CH, -S<u>C</u>8Ar), 127.83 (CH, -S<u>C</u>9Ar), 138.56 (C, -S<u>C</u>9bAr), 145.84 (C, -S<u>C</u>5aAr), 207.65 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [(M+Na)$^+$] $C_{15}H_{18}ONaS$ requires 269.0971, found 269.0972, [^{34}S give M+2 at 271. 0930].

5.2.18 Photolysis of 2-(*m*-methoxythiol)-3,5,5-trimethylcyclohex-2-enone under Batch Conditions (Medium pressure Lamp) to give the (±)-(4a*R*,9b*S*)-9-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (448) and (±)-(4a*R*,9b*S*)-7-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (449) [92]



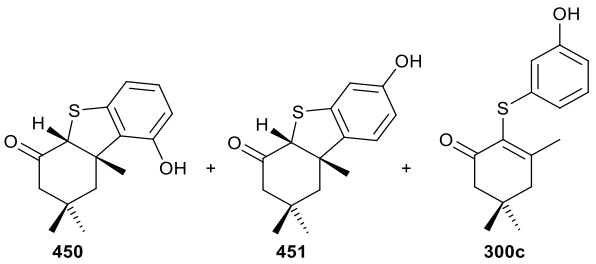
A solution of 2-(*m*-methoxythiol)-3,5,5-trimethylcyclohex-2-enone **300a** (0.0104 g, 37.63 µmol) in methanol (40 mL) 1 mM was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30 min prior to the reaction. The degassed solution was irradiated for 2 hours, with a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well. The photolysis solution was concentrated *in vacuo* to give a pale yellow oil (0.0103 g, 37.27 µmol, 99% isolated yield) as a mixture of isomers. The crude product was purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford (±)-(4a*R*,9b*S*)-9-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **448** (0.0065 g, 23.52 µmol, 63%) and a mixture of two regio-isomers (±)-(4a*R*,9b*S*)-9-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **448** and (±)-(4a*R*,9b*S*)-7-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **449** (1.4:1) ratio 0.0028 g, 10.13 µmol, 27% yield.

(±)-(4a*R*,9b*S*)-9-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (448) R_f 0.7 (SiO_2, 9:1 pe t. ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1729.80 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.02 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.47 (3H, s, -C$\underline{H}_3$ at C9b), 1.58 (1H, d, *J* 14.5, 1.6, Hz, equatorial -C$\underline{H}_2$, at C1),

2.05 (1H, dd, *J* 12.9, 1.6 Hz, equatorial -CH_2, at C3), 2.54 (1H, d, *J* 12.9 Hz, axial -C$\underline{H}_2$, at C3), 2.81 (1H, d, *J* 14.5 Hz, axial -C$\underline{H}_2$, at C1), 3.61 (1H, d, *J* 1.6 Hz, equatorial -C$\underline{H}$ at C4a), 3.83 (3H, s, -C$\underline{H}_3$ at C9Ar), 6.59 (1H, d, *J* 8.0 Hz, -C$\underline{H}$8Ar), 6.76 (1H, d, *J* 8.0 Hz, -C$\underline{H}$6Ar), 7.12 (1H, t, *J* 8.0 Hz, -C$\underline{H}$7Ar); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{15}H_{18}OS$ requires 277.1201 found 277.1204.

(±)-(4a*R*,9b*S*)-7-methoxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (449) R_f 0.5 (SiO_2, 9:1 pet. Ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.74 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.07 (3H, s, one of -C(C$\underline{H}_3$)$_2$ at C2), 1.42 (3H, s, -C$\underline{H}_3$ at C9b), 1.78 (1H, d, *J* 14.7, 1.6 Hz, equatorial -C$\underline{H}_2$, at C1), 2.19 (1H, d, *J* 13.2, 1.6 Hz, equatorial -CH_2, at C3), 2.25 (1H, d, *J* 14.7 Hz, axial -C$\underline{H}_2$, at C1), 2.50 (1H, d, *J* 13.2 Hz, axial -C$\underline{H}_2$, at C3), 3.76 (3H, s, -C$\underline{H}_3$ at -C$\underline{H}$7Ar), 3.79 (1H, s, -C$\underline{H}$ at C4a), 6.62 (1H, s, -C$\underline{H}$6Ar), 6.74 (1H, d, *J* 8.0 Hz, -C$\underline{H}$8Ar), 6.93 (1H, d, *J* 8.0, Hz, -C$\underline{H}$9Ar); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{15}H_{18}OS$ requires 277.1201 found 277.1204.

5.2.19 Photolysis of 2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone (300c) under Batch Conditions (Medium Pressure Lamp) to give (±)-(4a*R*,9b*S*)-9-hydroxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (450) and (±)-(4a*R*,9b*S*)-7-hydroxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (451)[92]



450 451 300c

A solution of 2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone **300c** (0.0542 g, 206.58 µmol) in methanol (20 mL) 1 mM was placed in a Schlenk tube and degassed with a slow

stream of N_2 for 30 min prior to the reaction. The degassed solution was irradiated for 2 hours, with a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well. The photolysis solution was concentrated *in vacuo* to give a yellow oil (0.0453 g, 172.66 µmol, 84%) as a mixture of two regio-isomers (±)-(4a*R*,9b*S*)-9-hydroxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **450** and (±)-(4a*R*,9b*S*)-7-hydroxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one **451** and 2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone **300c** (3:2:1).

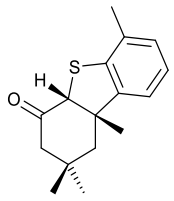
(±)-(4a*R*,9b*S*)-9-hydroxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (**450)** R_f 0.7 (SiO_2, 9:1 pe t. Ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.04 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.52 (3H, s, -C<u>H</u>$_3$ at C9b), 1.65 (1H, d, *J* 14.8, 1.6 Hz, equatorial -C<u>H</u>$_2$, at C1), 2.12 (1H, d, *J* 13.0, 1.6 Hz, equatorial -CH$_2$, at C3), 2.55 (1H, d, *J* 13.0, Hz, axial -C<u>H</u>$_2$, at C3), 2.85 (1H, d, *J* 14.8 Hz, axial -C<u>H</u>$_2$, at C1), 3.65 (1H, app. t, *J* 1.6 Hz, equatorial -C<u>H</u> at C4a), 5.30 (3H, bs, -O<u>H</u> at -C<u>H</u>9Ar), 6.39 (1H, d, *J* 8.0 Hz, -C<u>H</u>8Ar), 6.75 (1H, d, *J* 8.0 Hz, -C<u>H</u>6Ar), 7.01 (1H, t, *J* 8.0 Hz, -C<u>H</u>7Ar);

(±)-(4a*R*,9b*S*)-7-hydroxy-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (**451)** R_f 0.5 (SiO_2, 9:1 pet. Ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.74 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.07 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.41 (3H, s, -C<u>H</u>$_3$ at C3), 1.78 (1H, d, *J* 14.5, Hz, equatorial -C<u>H</u>$_2$, at C4), 2.20 (1H, d, *J* 14.7, Hz, equatorial -CH$_2$, at C6), 2.26 (1H, d, *J* 14.7, Hz, axial -C<u>H</u>$_2$, at C6), 2.49 (1H, d, *J* 14.5, Hz, axial -C<u>H</u>$_2$, at C4), 3.49 (1H, s, -C<u>H</u> at C2), 3.79 (3H, s, -O<u>H</u> at *o*-Ar to ring), 6.57 (1H, s, *o*-Ar<u>H</u>), 6.70 (1H, d, *J* 8.0, Hz, *p*-Ar<u>H</u>), 6.88 (1H, d, *J* 8.0, Hz, *m*-Ar<u>H</u>);

2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone 300c R_f 0.25. δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, two - C(C<u>H</u>$_3$)$_2$ at C5), 2.26 (3H, s, -C<u>H</u>$_3$ at C3), 2.43 (2H, s, -C<u>H</u>$_2$ at C4), 2.50 (2H, s, -C<u>H</u>$_2$ at C6), 5.22 (1H, bs, -*m*-(O<u>H</u>)Ar) 6.56 (1H, d, app. dd, *J* 8.0, 2.0, Hz, -C<u>H</u>4Ar), 6.62

(1H, d, app. dd, *J* 8.0, 2.0, Hz, -CH6Ar), 6.68 (1H, s, -CH2Ar), 7.06 (1H, t, *J* 8.0, 2.0 Hz, -CH5Ar). δ_C (100 MHz, $CDCl_3$) 24.49 (CH_3, -CCH_3 at C3), 28.18 (CH_3, two -C(CH_3)$_2$ at C5), 34.98 (C, -C(CH_3)$_2$ at C3), 48.22 (CH_2, -CH_2 at C4), 51.59 (CH_2, -CH_2 at C6), 112.83 (CH, -SC4Ar), 114.21 (CH, -SC2Ar), 119.65 (CH, -SC6Ar), 129.80 (CH, -SC5Ar), 131.69 (C, -C(SAr) at C2), 156.01 (C, -SC3Ar), 159.85 (C, -SC1Ar), 167.47 (C, -CCH_3 at C3), 194.58 (C, -C=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{15}H_{18}NaO_2S$ requires 285.3616, found 285.2309;

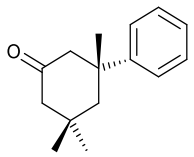
5.2.20 Photolysis of 2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone under Batch Conditions (Medium Pressure Lamp) to give (±)-(4a*R*,9b*S*)-2,2,4a,9b-tetramethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (452) [92]



452

A solution of 2-(3-hydroxythiol)-3,5,5-trimethylcyclohex-2-enone **300d** (0.0261 g, 9.98 µmol) in methanol (10 mL, 1 mM) was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30 min prior to the reaction. The degassed solution was irradiated for 2 hours, with a 125-W medium pressure mercury lamp contained within a water-cooled quartz immersion well. The photolysis solution was concentrated *in vacuo* to give a yellow oil (0.0211 g, 81.03 µmol, 81%) of (±)-(4a*R*,9b*S*)-2,2,4a,9b-tetramethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]thiophen-4(1*H*)-one (**452**). R_f 0.5 (SiO_2, 8:2 pet. ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, s, one of -C(CH_3)$_2$ at C2), 1.07 (3H, s, one of -C(CH_3)$_2$ at C2), 1.44 (3H, s, -CH_3 at C9b), 1.74 (1H, d, *J* 14.5, 1.6 Hz, equatorial -CH_2, at C1), 2.20 (1H, d, *J* 14.5, Hz, axial -CH_2, at C1), 2.26 (3H, s, - at -CH6Ar), 2.53 (1H, d, *J* 13.3, Hz, equatorial -CH_2, at C3), 3.14 (1H, d, *J* 13.3, Hz, axial -CH_2, at C3), 3.79 (1H, app. d, *J* 1.6 Hz -CH at C4a), 6.90 (1H, d, *J* 7.3 Hz, -CH7Ar); 6.97 (1H, d, *J* 8.0 Hz, -CH9Ar) 7.02 (1H, t, *J* 8.0 Hz, -CH8Ar).

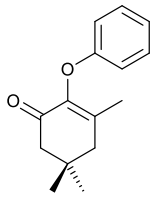
5.2.21 Synthesis of 3-phenyl-3,5,5-trimethylcyclohexanone (297) [92]



297

To a stirred suspension of Raney Nickel in ethanol (5 mL) was added *cis*-dihydrothiophene **301** (0.0465 g, 188.74 µmol). The mixture was heated to reflux, and TLC analysis indicated that all starting material was consumed in ~30 min. While warm, the reaction mixture was filtered under vacuum and the filter cake was thoroughly washed with warm ethanol (15 mL). Care was taken to ensure that the nickel residue remained wet to prevent ignition, then the reaction mixture was reacted with 2M HCl. Water (10 mL) and ether (15 mL) were added to the ethanol solution, and the organic layer was separated and washed with a 3:1 mixture of 1 N sodium bicarbonate and saturated sodium chloride (1 x 5 mL), dried over anhydrous magnesium sulfate and filtered. The crude reaction product was concentrated *in vacuo* gave a mixture of compounds which was separated by flash column chromatography (SiO_2, 8:2 pet. Ether/EtOAc) to afford colourless solid, 3-phenyl-3,5,5-trimethylcyclohexanone **297** (0.0301 g, 139.14 µmol, 74%, m.p. 109-110 °C); R_f 0.5 (SiO_2, 9:1 pet. Ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.38 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.03 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.37 (3H, s, -$C\underline{H}_3$ at C3), 1.91 (1H, d, *J* 14.1 Hz, axial at C2), 2.10 (1H, app. dt *J* 14.1, 1.6 Hz, equatorial at C6), 2.22 (1H, d, *J* 14.1 Hz, axial at C6), 2.26 (1H, dd, *J* 14.1, 1.6 Hz, equatorial at C2), 2.38 (1H, dd, *J* 14.0 Hz, axial at C4), 3.06 (1H, dt, *J* 14.0, 1.6 Hz equatorial at C4), 7.33-7.40 (5H, m, -C$\underline{H}$Ar); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_{15}H_{20}ONa$ requires 239.1400, found 239.1397.

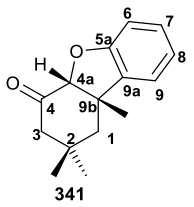
5.2.22 Synthesis of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one (340) [95a]



340

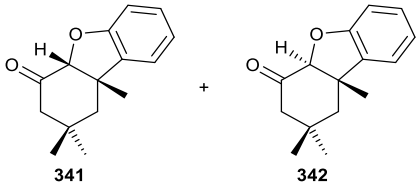
A solution of phenol **339** (0.6 g, 5.91 mmol) in freshly distilled THF was added to a stirred suspension of sodium hydride (0.1330 g, 5.58 mmol, 60% NaH in oil) in THF (0.3 mL) under a nitrogen atmosphere. After consumption of the NaH, DMPU (0.97 mL, 7.59 mmol) and isophorone epoxide **298** (1.0 g, 6.48 mmol) were added. The resulting solution was heated to reflux for 2 hours, TLC analysis showed the reaction was completed after 2 hours. Water (5 mL) was then added to the reaction mixture which was extracted with ether-toluene (1:1, 3 x 5 mL). The combined organic fractions were washed with water (3 x 2 mL), dried over anhydrous $MgSO_4$, then filtered by suction and concentrated *in vacuo* to produce a crude yellow liquid. The crude product was purified by flash column chromatography (SiO_2 9:1 pet. ether/EtOAc) to give 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1one **340** as a colourless solid, 1.4201 g, 6.17 mmol, 95%. (m.p. 103-104 ºC, lit. m.p. 104-105 ºC)[95a]. R_f 0.26. (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1676.95 (C=O stretch), 1589.35 (C=C stretch), 1222.43 (C-O stretch); δ_H (400 MHz, $CDCl_3$) 1.15 (6H, s, two - C($C\underline{H}_3$)$_2$ at C5), 1.89 (3H, s, -$C\underline{H}_3$ at C3), 2.42 (2H, s, -$C\underline{H}_2$ at C4), 2.43 (2H, s, -$C\underline{H}_2$ at C6), 6.83 (2H, d, 8.0 Hz, *o*-C<u>H</u>Ar), 6.97 (1H, t, *J* 8.0 Hz, *p*-C<u>H</u>Ar), 7.25 (2H, dd, *J* 8.0, 1.2 Hz, *m*-Ar<u>H</u>); δ_C (400 MHz, $CDCl_3$) 18.04 (CH_3, -C<u>C</u>H_3 at C3), 28.72 (CH_3, two - C(<u>C</u>H_3)$_2$ at C5), 33.24 (C, -<u>C</u>(CH_3)$_2$ at C5), 45.66 (CH_2, -<u>C</u>H_2 at C4), 51.74 (CH_2, -<u>C</u>H_2 at C6), 114.75 (CH, -*o*-<u>C</u>HAr), 121.70 (CH, -*p*-<u>C</u>HAr), 129.54 (CH, -*m*-<u>C</u>HAr), 129.63 (C, -<u>C</u>(OAr) at C2), 145.88 (C, -<u>OC</u>1Ar), 157.64 (C, -<u>C</u>CH_3 at C3), 192.83 (C, -<u>C</u>=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{15}H_{19}O_2$ requires 231.1380, found 231.1385; [λ_{max} 310nm (ε = 16697 M^{-1} cm^{-1})].

5.2.23 Photolysis of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-l-one under Batch Conditions in methanol (Medium Pressure Lamp) to give the *cis*-dihydrothiophene (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one (341)[95a]



A solution of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one **340** (0.0231 g, 100.30 µmol) in methanol (10 mL, 1 mM) was placed in a Schlenk tube and degassed with a slow stream of N_2 for 30 min prior to the reaction. The degassed solution was irradiated for 3 hours, with a 125 W medium pressure mercury lamp contained within a water-cooled quartz immersion well. The crude reaction product was concentrated *in vacuo* to give a colourless liquid (0.0196 g, 85.10 µmol, 85%) as a single stereoisomer of *cis*-dihydrofuran **341** and starting material **340** (3:1 ratio). The crude product was purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford a crystalline solid (m.p 86-87 °C) (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one **341** (major isomer) (0.0148 g, 64.26 µmol, 64%). R_f 0.23 (SiO_2, 9:1 pe t. ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.58 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.11 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.40 (3H, s, -C<u>H</u>$_3$ at C9b), 1.95 (1H, d, *J* 14.6 Hz, axial -C<u>H</u>$_2$, at C1), 2.22 (1H, dd, *J* 13.0, 2.5 Hz, equatorial -C<u>H</u>$_2$, at C3), 2.27 (1H, dd, *J* 14.6, 1.6 Hz, equatorial -CH$_2$, at C1), 2.42 (1H, d, *J* 13.0 Hz, axial -C<u>H</u>$_2$, at C3), 4.53 (1H, app t, equatorial -C<u>H</u> at C4a), 6.90 (1H, t, *J* 8.0 Hz, -C<u>H</u>7Ar), 6.96 (1H, d, *J* 8.0 Hz, -C<u>H</u>6Ar), 7.04 (1H, d, *J* 8.0, Hz, -C<u>H</u>8Ar), 7.14 (1H, t, *J* 8.0 Hz, -C<u>H</u>9Ar). HRMS (+ESI) m/z [$(M+H)^+$] $C_{15}H_{19}O_2$ requires 231.1378, found 231.1379.

5.2.24 Photolysis of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-l-on in flow to give (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one (341) and (±)-(4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one (342) in toluene/methanol[95a]



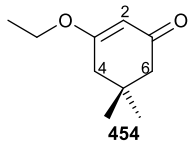
341 342

A solution of 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one **340** (0.0235 g, 102.05 µmol) in toluene/methanol (3:1) (50 mL) 1 mM was pumped into the flow photoreactor and the solution was degassed with nitrogen for 30 min. prior to and during irradiation. The reaction mixture was re-circulated using a peristaltic pump at flow rate 5ml/min through the reactor with irradiation at 320 nm using Reptile UV B 200 Exo terra lamp. The reaction was completed after approximately 16 min. (residence time). The crude reaction product was concentrated *in vacuo* and this yielded (0.0229 g, 99.43 µmol, 97%) of a colourless liquid. The crude product was purified by flash column chromatography (SiO_2 9:1 pet.ether/EtOAc) to afford (±)-(4a*R*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one **341** (major isomer) (0.0154 g, 66.87 µmol, 67%) and (±)-(4a*S*,9b*S*)-2,2,9b-trimethyl-2,3,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4(1*H*)-one **342** (minor isomer) (0.0069g, 29.83 µmol, 30%).

major diastereoisomer A R_f 0.23 (SiO_2, 9:1 pe t. Ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.58 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.11 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C2), 1.40 (3H, s, -$C\underline{H}_3$ at C9b), 1.95 (1H, d, *J* 14.6 Hz, axial -$C\underline{H}_2$, at C1), 2.22 (1H, dd, *J* 13.0, 2.5 Hz, equatorial -$C\underline{H}_2$, at C3), 2.27 (1H, dd, *J* 14.6, 1.6 Hz, equatorial -CH_2, at C1), 2.42 (1H, d, *J* 13.0 Hz, axial -$C\underline{H}_2$, at C3), 4.53 (1H, app t, equatorial -C$\underline{H}$ at C4a), 6.90 (1H, t, *J* 8.0 Hz, -C$\underline{H}$7Ar), 6.96 (1H, d, *J* 8.0 Hz, -C$\underline{H}$6Ar), 7.04 (1H, d, *J* 8.0, Hz, -C$\underline{H}$8Ar), 7.14 (1H, t, *J* 8.0 Hz, -C$\underline{H}$9Ar); HRMS (+ESI) m/z [$(M+H)^+$] $C_{15}H_{19}O_2$ requires 231.1378, found 231.1379.

minor diastereoisomer B R_f 0.60 (SiO_2, 9:1 pet. Ether/EtOAc); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.02 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C2), 1.47 (3H, s, C<u>H</u>$_3$ at C9b), 1.75 (1H, d, *J* 14.6 Hz, axial C<u>H</u>$_2$, at C1), 1.80 (1H, dd, *J* 14.6, 2.0 Hz, equatorial, C<u>H</u>$_2$, at C1), 2.35 (1H, dd. *J* 13.6, 2.0 Hz, equatorial -C<u>H</u>$_2$, at C3), 2.71 (1H, d, *J* 13.6 Hz, axial C<u>H</u>$_2$, at C3), 5.06 (1H, s, C<u>H</u> at C4a), 6.88 (1H, d, *J* 8.0 Hz, -C<u>H</u>6Ar), 6.99 (1H, t, *J* 8.0 Hz, -C<u>H</u>7Ar), 7.12 (1H, d, *J* 8.0 Hz, -C<u>H</u>8Ar), 7.19 (1H, t, *J* 8.0 Hz, -C<u>H</u>9Ar); HRMS (+ESI) m/z [$(M+H)^+$] $C_{15}H_{19}O_2$ requires 231.1378, found 231.1379.

5.2.25 Synthesis of 3-ethoxy-5,5-dimethylcyclohex-2-enone (454) [147, 148, 149]

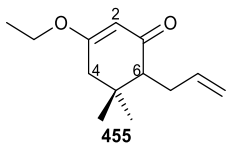


454

A solution of dimedone **453** (2.0 g 14.27 mmol) in benzene (28 mL) and ethanol (7.5 mL) was treated with *p*-toluenesulfonic acid monohydrate (0.07 g, 0.37 mmol, 2.5 mol %) before being heated at reflux for 30 minutes. Following the slow removal of the benzene/ethanol/water azeotrope via distillation, the cold solution was washed with a 10% aq.NaOH solution (15 mL) then with saturated NaCl (3 x 15mL) and water (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to yield a pale-yellow solid. The crude product that was allowed to stand overnight and it was then purified by crystallisation from hexane at -18 ºC (refrigerator) to furnish 3-ethoxy-5,5-dimethylcyclohex-2-enone **454** as a crystalline solid (1.8145 g, 10.79 mmol, 76%); m.p. 56.5-57 ºC (lit. m.p. 57-58 ºC) [147]; R_f 0.23 (SiO_2, 8:2 pet. ether /EtOAc); ν_{max} (ATR)/cm^{-1}, 1653.53 (α,β-unsaturated C=O stretch), 1603.53 (C=C stretch); δ_H(400MHz, $CDCl_3$) 1.06 (6H, s, two -C(C<u>H</u>$_3$)$_2$ at C5), 1.36 (3H, t, *J* 7.0 Hz, -OCH$_2$C<u>H</u>$_3$), 2.20 (2H, s, -C<u>H</u>$_2$ at C4), 2.26 (2H, s, -C<u>H</u>$_2$ at C6), 3.89 (2H, q, *J* 7.0 Hz, -OC<u>H</u>$_2$CH$_3$), 5.34 (1H, s, -C<u>H</u> at C2); δ_C (400MHz, $CDCl_3$) 14.15 (CH_3, -OCH$_2$<u>C</u>H$_3$), 28.30 (CH_3, two -C(<u>C</u>H$_3$)$_2$ at C5), 32.49 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 42.95 (CH_2, -<u>C</u>H$_2$ at C6), 50.76 (CH_2,

-$\underline{C}H_2$ at C4), 64.24 (CH_2, -O$\underline{C}H_2CH_3$), 101.52 (CH, -$\underline{C}$H at C2), 176.21 (C, -$\underline{C}$OEt), 199.68 (C, -$\underline{C}$=O); HRMS (+ESI) m/z [$(M+H)^+$] $C_{10}H_{17}O_2$ (MH^+) requires 169.1223 found, 169.1255.

5.2.26 Synthesis of (±)-6-allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone (455)

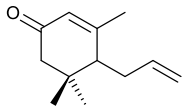


455

A solution of 3-ethoxy-5,5-dimethylcyclohex-2-enone **454** (0.4001 g, 2.38 mmol) in dry THF (10 ml) under nitrogen at -78 ºC was treated with LHMDS (1 M in THF, 2.68 ml, 2.68 mmol) before being stirred for 2 hours. Following the addition of DMPU (1.5 ml, ~15%w/v) the light amber solution was stirred for 30 minutes after which time allyl bromide (0.34 ml, 2.83 mmol) was added as a solution in THF (2.5 ml) in a drop-wise manner. The resulting solution was stirred for a further 15 hours whilst being allowed to warm to room temperature and subsequent TLC analysis revealed that no more starting material was being consumed. The solution was diluted with water (30 ml) and separated with diethyl ether (4 x 30 ml) before the combined organic fractions were washed with a saturated solution of NH_4Cl (20 ml) then water (20 ml). The organic fraction was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to produce a crude yellow oil. The crude product was purified via flash column chromatography (SiO_2, 8:2 pet ether/ EtOAc) yielding (±)-6-allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone **455** as a yellow liquid (0.3811g, 1.83 mmol, 77%). R_f 0.38 (SiO_2, 7:3 pet ether/ EtOAc); ν_{max} (ATR)/cm^{-1}, 1652.53 (α,β-unsaturated C=O stretch); δ_H (400MHz, MeOD-d_4) 1.04 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.10 (3H, s, one of -C($C\underline{H}_3$)$_2$ at C5), 1.37 (3H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$), 2.11 (1H, dd, *J* 8.7, 4.5 Hz, -$C\underline{H}(C_3H_5)$ at C6), 2.29 (1H, d, *J* 18.0 Hz, one of -$C\underline{H}_2$ at C4), 2.28-2.40 (2H, m, -$C\underline{H}_2CH{=}CH_2$ at C12), 2.44 (1H, d, *J* 18.0 Hz, one of -$C\underline{H}_2$ at C4), 3.94 (2H, q, *J* 7.0 Hz, -$OC\underline{H}_2CH_3$ at C10), 4.94 (1H, ddt, *J* 10.1, 2.0, 1.2 Hz, one of -CH=C$\underline{H}_2$ at C14), 5.02

(1H, dt, *J* 17.1, 2.0 Hz, one of -CH=C<u>H</u>$_2$ at C14), 5.31 (1H, s, -C<u>H</u>C=O at C2), 5.85 (1H, ddt, *J* 17.1, 10.1, 7.0 Hz, -C<u>H</u>=CH$_2$ at C13); δ_C (100 MHz, MeOD-d_4) 14.44 (CH_3, -OCH$_2$<u>C</u>H$_3$ at C11), 24.73 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C5), 28.93 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C5), 32.29 (CH_2, -<u>C</u>H$_2$CH=CH$_2$ at C12), 36.16 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 42.63(CH_2, -<u>C</u>H$_2$ at C4), 58.39 (CH, -<u>C</u>H(C_3H_5) at C6), 65.75 (CH_2, -O<u>C</u>H$_2$CH$_3$ at C10), 101.14 (CH, -<u>C</u>HC=O at C2), 115.82 (CH_2, -CH$_2$CH=<u>C</u>H$_2$ at C14), 138.83 (CH, -CH$_2$<u>C</u>H=CH$_2$ at C13), 177.81 (C, -<u>C</u>OEt at C3), 204.76 (C, -<u>C</u>=O); HRMS (+ESI) m/z [(M+H)$^+$] $C_{13}H_{21}O_2$ (MH^+) requires 209.1542 found 209.1538.

5.2.27 Synthesis of (±)-4-allyl-3,5,5-trimethylcyclohex-2-enone (456)

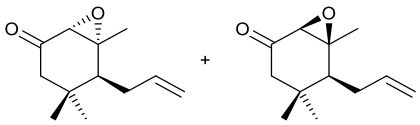


456

Methyllithium (1.6M in ether, 7.41 ml, 11.856 mmol) was added in a dropwise manner to a stirring solution of (±)-6-allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone **455** (1.9283 g, 9.26 mmol) in diethyl ether (64 ml) under nitrogen at room temperature before continuing to stir for a further 3 hours whereupon TLC indicated that no more starting material remained. Following the addition of 2M HCl (8.5 ml) the mixture was stirred for 2 hours to ensure complete rearrangement. Once TLC had confirmed that the reaction was complete the layers were separated, and the aqueous fraction extracted with diethyl ether (3 x 30 ml). The combined organic fractions were washed with a saturated solution of sodium bicarbonate (30 ml) and water (30 ml) prior to drying over $MgSO_4$, filtration by suction and concentration *in vacuo* to give a crude product. Purification of the crude product by flash column chromatography (SiO_2, 8:2 pet. ether/EtOAc) to afford (±)-4-allyl-3,5,5-trimethylcyclohex-2-enone **456** as a yellow liquid (1.1541 g, 6.47 mmol, 70 %); R_f 0.6 (9:1 pet. ether/EtOAc);); ν_{max} (ATR)/cm^{-1}, 1667.53 (α,β-unsaturated C=O stretch); δ_H (400MHz, C_6D_6) 0.69 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 0.76 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.44 (3H, d, *J* 1.3 Hz, -CH=CC<u>H</u>$_3$ at C3), 1.46 (1H, d, *J* 6.0 Hz,

-C<u>H</u>(C_3H_5) at C4), 1.86 (1H, dddt, *J* 15.0, 8.0, 6.0 Hz, one of -C<u>H_2</u>CH=CH_2 at C10), `1.99 (1H, dt, *J* 17.0, 1.0 Hz, one of -C<u>H_2</u>C=O at C6), 2.06 (1H, dddd, *J* 15.0, 8.0, 4.0, 2.0 Hz, one of -C<u>H_2</u>CH=CH_2 at C10), 2.36 (1H, d, *J* 17.0 Hz, one of -C<u>H_2</u> C=O at C6), 4.82 (1H, ddt, *J* 10.0, 2.0, 1.4 Hz, one of -CH_2CH=C<u>H_2</u> at C12), 4.85 (1H, dt, *J* 17.0, 2.0 Hz, one of -CH_2CH=C<u>H_2</u> at C12), 5.52 (1H, dddd, *J* 17.0, 10.0, 8.0, 6.0 Hz, -CH_2C<u>H</u>=CH_2 at C11), 5.89 (1H, app d, *J* 1.6 -C<u>H</u> C=O at C2); δ_C (400MHz, C_6D_6) 24.10 (CH_3, -CH=C<u>C</u>H_3 at C3), 27.00 (CH_3, one of -C(<u>C</u>H_3)$_2$ at C5), 28.77 (CH_3, one of -C(<u>C</u>H_3)$_2$ at C5), 34.46 (CH_2, -<u>C</u>H_2CH=CH_2 at C10), 36.02 (C, -<u>C</u>(CH_3)$_2$ at C5), 47.54 (CH_2, -<u>C</u>H_2 at C6), 50.92 (CH, -<u>C</u>H(C_3H_5) at C4), 116.18 (CH_2, -CH_2CH=<u>C</u>H_2 at C12), 126.38 (CH, <u>C</u>HC=O at C2), 137.22 (CH, -CH_2<u>C</u>H=CH_2 at C11), 161.87 (C, -<u>C</u>CH_3 at C3), 197.01 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{12}H_{18}O$ requires 178.1358, found 178.1354.

5.2.28 Synthesis of (±)-(1*R*,5*S*,6*R*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (457) and (±)-(1*S*,5*S*,6*S*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (458) [146a,146b]



457 458

A solution of (±)-4-allyl-3,5,5-trimethylcyclohex-2-enone **456** (2.0 mL, 11.89 mmol) and 30% aqueous hydrogen peroxide (1.55 mL, 45.72mmol) in MeOH (5 mL) was stirred and cooled down to 15 °C by means of a water/ice bath. 1 M NaOH (aq.) (0.7 mL, 16.83mmol) was added in a dropwise manner with stirring, over a period of 1 hour. The temperature of reaction mixture was maintained below 15-20 °C during the addition. The resulting solution was stirred for a further 5 hours while the temperature was maintained at 20-25 °C and subsequent TLC analysis (9:1 pet. ether/EtOAc) revealed that no more starting material was being consumed. The reaction was diluted with water (167 mL) and extracted with diethyl ether (2 x 30 mL). The

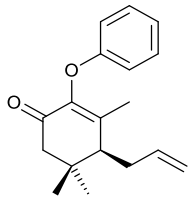
combined organic fractions were washed with water (10 mL), dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to yield a yellow oil. The crude product was purified by flash column chromatography to afford an inseparable mixture of (±)-(1*R*,5*S*,6*R*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **457** and (±)-(1*S*,5*S*,6*S*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **458** (5:1) as a pale-yellow oil (0.9385g, 4.83 mmol, 41%).

Major isomer R_f 0.5 (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1} 1709.81, 1639.30, 2960.54; δ_H (400 MHz, $CDCl_3$) 0.84 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C4), 1.09 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C4), 1.46 (3H, -CC<u>H</u>$_3$ at C6), 1.87 (1H, dd, *J* 16.0, 1.1 Hz, one of -C<u>H</u>$_2$C=O at C3), 2.12 (1H, dd, *J* 9.0, 2.0 Hz, -C<u>H</u>(C_3H_5) at C5), 2.16-2.26 (1H, m, one of -C<u>H</u>$_2$CH=CH$_2$ at C10), 2.39-2.28 (1H, m, one of -C<u>H</u>$_2$CH=CH$_2$ at C10), 2.65 (1H, d, *J* 16.0 Hz, one of -C<u>H</u>$_2$C=O at C3), 3.00 (1H, s, C<u>H</u> at C1), 5.10 (1H, d, *J* 10.0, 2.0 Hz, *cis*-H -CH$_2$CH=C<u>H</u>$_2$ at C12), 5.13 (1H, d, *J* 17.0, 2.0 Hz, *trans*-H -CH$_2$CH=C<u>H</u>$_2$ at C12), 5.81 (1H, dddd, *J* 17.0, 10.0, 7.1, 6.0 Hz, -CH$_2$C<u>H</u>=CH$_2$ at C11); δ_C (100MHz, $CDCl_3$) 22.46 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C4), 22.85 (CH_3, one of -C(<u>C</u>H$_3$)$_2$ at C4), 30.24 (CH_3, - <u>C</u>H$_3$ at C6), 31.86 (CH_2, -<u>C</u>H$_2$CH=CH$_2$ at C10), 39.95 (C, -<u>C</u>(CH$_3$)$_2$ at C4), 48.59 (CH, -<u>C</u>H(C_3H_5) at C5), 50.42 (CH_2, -<u>C</u>H$_2$ at C3), 62.83 (CH, <u>C</u>HC=O at C1), 66.91 (C, -<u>C</u>CH$_3$ at C6), 116.06 (CH_2, -CH$_2$CH=<u>C</u>H$_2$ at C12), 138.67 (CH, -CH$_2$<u>C</u>H=CH$_2$ at C11), 207.74 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{12}H_{19}O_2$ requires 195.1380 found, 195.1379.

Minor isomer; R_f 0.5 (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1} 1709.81, 2960.54; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C4), 0.96 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C4), 1.44 (3H, -CC<u>H</u>$_3$ at C6), 145 (1H, d, *J* 6.7 Hz, -C<u>H</u>(C_3H_5) at C5), 1.66 (1H, d, *J* 14.1 Hz, one of -C<u>H</u>$_2$C=O at C3), 2.17 (1H, t, *J* 8.3 Hz one of -C<u>H</u>$_2$CH=CH$_2$ at C10), 2.39 (1H, d, *J* 8.3 Hz, one of -C<u>H</u>$_2$CH=CH$_2$ at C10), 2.61 (1H, d, *J* 14.1 Hz, one of -C<u>H</u>$_2$C=O at C3), 3.01 (1H, d, *J* 1.2

Hz, C<u>H</u> at C1), 5.16-5.17 (1H, m, one of -$CH_2CH=C\underline{H}_2$ at C12), 5.21 (1H, dd, *J* 17.0, 2.0 Hz, one of -$CH_2CH=C\underline{H}_2$ at C12), 5.91 (1H, ddd, *J* 17.0, 10.1, 7.3 Hz, -$CH_2C\underline{H}=CH_2$ at C11);

5.2.29 Synthesis of (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone (459)

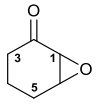


459

A solution of phenol **339** (101.40 mg, 1.08 mmol) in freshly distilled THF was added to a stirred suspension of sodium hydride (17.76 mg, 739.93 µmol, 60% NaH in oil) in THF (50.71 mg) under a nitrogen atmosphere. After consumption of the NaH, DMPU (177.54 mg, 1.39 mmol) and a mixture of (±)-(1*R*,5*S*,6*R*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **457** and (±)-(1*S*,5*S*,6*S*)-5-allyl-4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **458** (0.230 g, 1.18 mmol) was added. The resulting solution was heated to reflux for 2 hours, after which TLC analysis (9:1 pet. ether/EtOAc) showed the reaction to be completed. Water (5 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 5 mL). The combined organic fractions were washed with water (3 x 2 mL), dried over anhydrous $MgSO_4$, then filtered by suction and concentrated *in vacuo* to produce a crude dark brown oil (0.4310 g). The crude product was purified by flash column chromatography (7:3 hexane/EtOAc) to give (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459** with the traces of phenol **339**. The phenol was removed from the product by dissolving the whole in ether (0.5 ml), then washing with aqueous 1M NaOH (0.5 mL); upon separation, then drying over $MgSO_4$, filtration and concentration *in vacuo*, this afforded pure (±)-(*S*)-4-allyl-3,5,5-trimethyl-2-phenoxycyclohex-2-enone **459** as a yellow oil (0.1985 g, 734.17 µmol, 68%). R_f 0.30. (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1676.95 (C=O stretch), 1589.35 (C=C stretch); δ_H

(400 MHz, C_6D_6) 0.78 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 0.98 (3H, s, one of -C(C<u>H</u>$_3$)$_2$ at C5), 1.76 (3H, -CC<u>H</u>$_3$ at C3), 1.78 (1H, dd, *J* 6.0, 2.0 Hz, -C<u>H</u>(C_3H_5) at C4), 2.07 (1H, dt, *J* 15.0, 6.0 Hz, pseudo-axial, -C<u>H</u>$_2$C=O at C6), 2.15 (1H, dd, *J* 17.0, 1.2 Hz, one of -C<u>H</u>$_2$CH=CH$_2$ at C10), 2.24 (1H, ddd, *J* 15.0, 6.0, 2.0 Hz, pseudo-equatorial -C<u>H</u>$_2$C=O at C6), 2.48 (1H, d, *J* 17.0 Hz, one of -C<u>H</u>$_2$CH=CH$_2$ at C10), 4.98 (1H, dd, *J* 10.0, 2.0 Hz, *cis*-H, -CH$_2$CH=C<u>H</u>$_2$ at C12), 5.03 (1H, dd, *J* 17.0, 2.0 Hz, *trans*-H, -CH$_2$CH=C<u>H</u>$_2$ at C12), 5.71 (1H, ddd, *J* 17.0, 10.0, 6.0 Hz, -CH$_2$C<u>H</u>=CH$_2$ at C11), 6.97 (1H, t, *J* 8.0 Hz, *p*-C<u>H</u>Ar) 7.10-7.18 (2H, m, *m*-C<u>H</u>Ar), 7.21-7.31 (2H, m, *o*-C<u>H</u>Ar); δ_C (100MHz, C_6D_6) 17.94 (CH$_3$, -C<u>C</u>H$_3$ at C3), 27.03 (CH$_3$, one of -C(<u>C</u>H$_3$)$_2$ at C5), 29.01 (CH$_3$, one of -C(<u>C</u>H$_3$)$_2$ at C5), 34.92 (CH$_2$, -<u>C</u>H$_2$C=O at C6), 35.58 (C, -<u>C</u>(CH$_3$)$_2$ at C5), 48.53 (CH$_2$, -<u>C</u>H$_2$CH=CH$_2$ at C10), 51.81 (CH, -<u>C</u>H(C_3H_5) at C4), 115.61 (CH, -<u>C</u>H *p*-Ar), 116.73 (CH$_2$, -CH$_2$CH=<u>C</u>H$_2$ at C12), 121.87 (CH, - -<u>C</u>H *m*-Ar) 129.74 (CH, -<u>C</u>H *o*-Ar), 136.87 (CH, -CH$_2$<u>C</u>H=CH$_2$ at C11), 144.45 (C, -O<u>C</u>13Ar) 148.09 (C, -<u>C</u>(OAr) at C2) 158.54 (C, -<u>C</u>H$_3$ at C3), 190.46 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{18}H_{23}O_2$ requires 271.1693 found 271.1686.

5.2.30 Preparation of 7-oxabicyclo[4.1.0]heptan-2-one (461) [146a,146b]

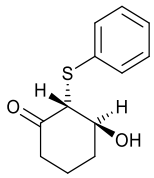


461

A solution of cyclohexenone **467** (2.0001, 20.81 mmol) and 30 % aqueous hydrogen peroxide (42 mL, 1.62 mol) in MeOH (133 mL) was stirred and cooled down to 15 °C by means of a water/ice bath. 6 M NaOH (aq.) (11.58 mL, 0.29 mol) was added in a dropwise manner with stirring, over a period of 1 hour. The temperature of the reaction mixture was maintained below 15- 20 °C during the addition. The resulting solution was stirred for a further 2 hours while the temperature was maintained at 20-25 °C and subsequent TLC analysis (9:1 pet. ether/EtOAc) revealed that no more starting material was being consumed. The reaction was quenched with

water (167 mL) and extracted with diethyl ether (2 x 30 mL). The combined organic fractions were washed with water (10 mL), dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* yielding 7-oxabicyclo[4.1.0]heptan-2-one **461** as a pale-yellow liquid (1.4832 g, 13.23 mmol, 64%). R_f 0.2 (SiO_2, 9:1 pet. ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1715.95 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 1.63-1.74 (1H, m, one of C<u>H</u>$_2$ at C4), 1.87-2.02 (1H, m, one of C<u>H</u>$_2$ at C5), 1.91-2.05 (1H, m, one of C<u>H</u>$_2$ at C4), 2.03-2.14 (1H, m, one of C<u>H</u>$_2$ at C6), 2.22-2.31 (1H, m, one of C<u>H</u>$_2$ at C5), 2.50-2.60 (1H, m, one of C<u>H</u>$_2$ at C6), 3.23 (1H, d, *J* 3.9 Hz, C<u>H</u> at C3), 3.57-3.62 (1H, m, C<u>H</u> at C2); δ_C (100 MHz, $CDCl_3$) 17.03 (CH_2, -<u>C</u>H_2 at C4), 22.87 (CH_2, -<u>C</u>H_2 at C5), 36.38 (CH_2, -<u>C</u>H_2 at C6), 55.15 (CH, -<u>C</u>H at C3), 55.96 (CH, -<u>C</u>H at C2), 206.03 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_6H_8NaO_2$ requires 135.0480, found 135.0484.

5.2.31 Synthesis of (2*R*,3*S*) -3-hydroxy-2-(phenylthio)cyclohexan-1-one (462)

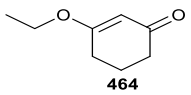


462

A solution of 7-oxabicyclo[4.1.0]heptan-2-one **461** (2.080 g, 18.59 mmol) in ethanol (5 mL) and 15% aq. KOH (0.2 mL, 3.72 mmol) was stirred at 0 °C under a nitrogen atmosphere. A solution of thiophenol (2.050 g, 18.59 mmol) in THF (2 mL) was degassed with a stream of nitrogen for 30 min. and then added dropwise over 20 min. After stirring at 0 °C for 1 hour, the reaction was judged to be completed by TLC analysis (9:1 pet. ether/EtOAc). Water (10 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 10 mL). The combined organic fractions were washed with a saturated brine solution (2 x 2 mL). The organic fraction was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to produce a crude colourless liquid as a single isomer of (±) -(2*S*,3*R*)-3-hydroxy-2-(phenylthiol)cyclohexan-1-one **462** (3.2500 g, 14.60 mmol, 79%). R_f 0.23 (SiO_2, 9:1 pet.

Ether/EtOAc); ν_{max} (ATR)/cm^{-1}, 1676.95 (C=O stretch); δ_H (400 MHz, $CDCl_3$) 1.72 (1H, (dddd, *J* 13.3, 11.4, 6.3, 3.7 Hz, one of C<u>H</u>$_2$ at C4), 1.82 (1H, dtd, *J* 13.4, 6.9, 3.4 Hz, one of C<u>H</u>$_2$ at C5), 2.01-2.13 (1H, m, one of C<u>H</u>$_2$ at C4), 2.14-2.24 (1H, m, one of C<u>H</u>$_2$ at C5), 2.25-2.34 (1H, m, one of C<u>H</u>$_2$ at C6), 2.80 (1H, ddd, *J* 13.8, 8.5, 5.3 Hz, one of C<u>H</u>$_2$ at C6), 2.99 (1H, bs, OH at C3), 3.66 (1H, dt, *J* 6.3, 1.0 Hz, one of C<u>H</u>$_2$ at C2), 4.09 (1H, td, *J* 6.5, 3.2 Hz, C<u>H</u> at C3), 7.23- 7.27 (2H, m, *o*-Ar<u>H</u>), 7.27-7.31 (1H, m, *p*-Ar<u>H</u>), 7.40-7.45 (2H, m, *m*-Ar<u>H</u>); δ_C (100 MHz, $CDCl_3$) 20.41 (CH_2, -<u>C</u>H_2 at C5), 29.66 (CH_2, -<u>C</u>H_2 at C4), 38.66 (CH_2, -<u>C</u>H_2 at C6), 63.72 (CH, -<u>C</u>H(OH) at C3), 72.88 (CH, -<u>C</u>H(SAr) at C2), 127.83 (CH, *o*-<u>C</u>HAr), 129.20 (CH, *p*-<u>C</u>HAr), 132.05 (CH, *m*-<u>C</u>HAr), 133.32 (C, S<u>C1</u>Ar), 206.28 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{12}H_{15}O_2S$ requires 223.0710 found 223.0716.

5.2.32 Preparation of 3-ethoxycyclohex-2-enone (464)

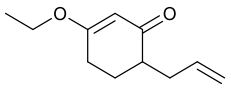


464

A solution of cyclohexane-1,3-dione **463** (2.0 g 17.84 mmol) in toluene (41.28 mL) and ethanol (9.38 mL) was treated with *p*-toluenesulfonic acid monohydrate (0.8753 g, 5.08 mmol) before being heated at reflux for 30 minutes. Following the slow removal of the toluene/ethanol/water azeotrope via distillation, the cold solution was washed with a 10% aq.NaOH solution (15 mL) then with saturated NaCl (3 x 15mL) and water (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* yielding 3-ethoxycyclohex-2-enone **464** as a colourless oil (1.5452 g, 11.02, 62%). R_f 0.30 (9:1 hexane/EtOAc); ν_{max} (ATR)/cm^{-1}, 1725.53 (α,β-unsaturated C=O stretch), 1591.29 (C=C stretch); δ_H (400MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.0 Hz, -OCH$_2$C<u>H</u>$_3$ at C9), 1.82-1.93 (2H, m, -C<u>H</u>$_2$ at C5), 2.22 (2H, dd, *J* 7.0, 6.0 Hz, C<u>H</u>$_2$ at C4), 2.30 (2H, t, *J* 6.0 Hz, C<u>H</u>$_2$ at C6), 3.79 (2H, q, *J* 7.0 Hz, -OC<u>H</u>$_2$CH$_3$ at C8), 5.23 (1H, s, -C<u>H</u>C=O at C2); δ_C (100 MHz, $CDCl_3$) 14.05 (CH_3, -OCH$_2$<u>C</u>H$_3$), 21.18 (CH_2, -<u>C</u>H_2 at C4),

29.01 (CH_2, -$\underline{C}H_2$ at C5), 36.69 (CH_2, -$\underline{C}H_2$ at C6), 64.09 (CH_2, -O$\underline{C}H_2CH_3$), 102.59 (CH, -$\underline{C}$H=COEt at C2), 177.86 (C, -CH=$\underline{C}$OEt at C3), 199.69 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* [$(M+Na)^+$] $C_8H_{12}NaO_2$ requires 163.0730, found 163.0730.

5.2.33 (±)-6-allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone (465)

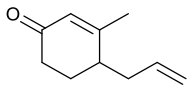


465

A solution of 3-ethoxycyclohex-2-enone **464** (2.0 g, 14.27 mmol) in dry THF (30 mL) under nitrogen at -78 ºC was treated with NaHMDS (1.0 M in THF, 17.27 mL, 94.16 mmol) before being stirred for 2 hours. Following the addition of DMPU (8.98 mL, ~15%w/v) the light amber solution was stirred for 30 minutes after which time allyl bromide (2.07 mL, 17.12 mmol, 1.20 equiv.) was added as a solution in THF (15 mL) in a dropwise manner. The resulting solution was stirred for a further 2 hours whilst being allowed to warm to room temperature and subsequent TLC analysis revealed that no more starting material was being consumed. The solution was diluted with water (30 mL) and separated with diethyl ether (4 x 30 mL) before the combined organic fractions were washed with a saturated solution of NH_4Cl (20 mL) then water (20 mL). The organic fraction was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to produce a crude yellow oil. The crude product was purified via flash column chromatography (SiO_2, 7:3 Hex/EtOAc) yielded (±)-6-allyl-3-ethoxy-2-cyclohexene-1-one **465** as a yellow liquid (1.8104 g, 10.04 mmol, 70%). R_f 0.5 (8:2 Hex/EtOAc); ν_{max} (ATR)/cm^{-1}, 1651.82 (α,β-unsaturated C=O stretch), 1602.59 (C=C stretch); δ_H (400MHz, $CDCl_3$) 1.36 (3H, t, *J* 7.1 Hz, -$OCH_2C\underline{H}_3$ at C9), 1.71 (1H, dddd, *J* 14.0, 11.0, 8.9, 6.0 Hz, one of -$C\underline{H}_2$ at C4), 2.02-210 (1H, m, one of -$C\underline{H}_2$ at C4), 2.14 (1H, dd, *J* 14.0, 8.0 Hz, one of -$C\underline{H}_2$ at C5), 2.25 (1H, ddt, *J* 10.5, 8.9, 4.4 Hz, -$C\underline{H}(C_3H_5)$ at C6), 2.37-2.51 (2H, m, -$C\underline{H}_2CH=CH_2$ at C10), 2.64 (1H, ddd, *J* 14.0, 6.0, 4.4 Hz, one of -$C\underline{H}_2$ at C5), 3.90 (2H, qd, *J* 7.0, 2.0 Hz, -

$OC\underline{H}_2CH_3$ at C8), 5.00-5.11 (2H, m, -CH=C$\underline{H}_2$ at C12), 5.33 (1H, s, -C$\underline{H}$C=O at C2), 5.71-5.86 (1H, m, -C$\underline{H}$=CH_2 at C11); δ_C (100 MHz, $CDCl_3$) 14.10 (CH_3, -$OCH_2\underline{C}H_3$ at C9), 25.77 (CH_2, -$\underline{C}H_2$ at C4), 28.11 (CH_2, -$\underline{C}H_2CH$=CH_2 at C10), 34.00 (CH_2, -$\underline{C}H_2$ at C5), 44.63 (CH, -$\underline{C}H(C_3H_5)$ at C6), 64.15 (CH_2, -$O\underline{C}H_2CH_3$ at C8), 102.17 (CH, -$\underline{C}$HC=O at C2), 116.56 (CH_2, -CH_2CH=$\underline{C}H_2$ at C12), 136.36 (CH, -$CH_2\underline{C}H$=CH_2 at C11), 176.95 (C, -$\underline{C}$OEt at C3), 200.39 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{11}H_{17}O_2$ requires 181.1220 found 181.1224.

5.2.34 Synthesis of 4-allyl-3-methylcyclohex-2-enone (472)

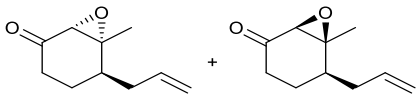


472

Methyllithium (1.6M in ether, 13.39 ml, 609.5 mmol) was added in a dropwise manner to a stirring solution of 6-allyl-3-ethoxy-2-cyclohex-1-enone **465** (3.010g, 16.70 mmol) in diethyl ether (115 ml) under a nitrogen atmosphere before continuing to stir for a further 3 hours whereupon TLC indicated that no more starting material remained. Following the addition of 2M HCl 5.22 ml the mixture was stirred for 2 hours to ensure complete rearrangement. Once TLC had confirmed that the reaction was complete the layers were separated, and the aqueous fraction extracted with diethyl ether (3 x 30 ml). The combined organic fractions were washed with a saturated solution of sodium bicarbonate (30 ml) and water (30 ml) prior to drying over $MgSO_4$, filtration by suction and concentration in vacuo. Purification of the crude product was effected by flashed column chromatography (8:2 Hex/EtOAc) to afford (±)-4-allyl-3-methylcyclohex-2-enone **466** as a yellow liquid (2.7502 g, 14.73 mmol, 88%); R_f 0.27 (8:2 Hex/EtOAc); ν_{max} (ATR)/cm^{-1}, 1664.01 (α,β-unsaturated C=O stretch); δ_H (400MHz, $CDCl_3$) 1.93 (1H, ddd, *J* 13.0, 8.0, 4.2 Hz, one of C$\underline{H}_2$ at C5), 1.99 (3H, s, C$\underline{H}_3$ at C3), 2.04 (1H, m, one of C$\underline{H}_2$ at C5), 2.22 (1H, dd, *J* 14.0, 8.8 -C$\underline{H}(C_3H_5)$ at C4), 2.26-2.38 (2H, m, one of -C$\underline{H}_2$CH=CH_2 at C8 and one of -C$\underline{H}_2$C=O at C6), 2.39-2.49 (2H, m, one of -C$\underline{H}_2$CH=CH_2 at C8

and one of -C<u>H</u>$_2$C=O at C6), 5.07-5.11 (1H, m, one of -CH$_2$CH=C<u>H</u>$_2$ at C10), 5.73-5.84 (1H, m, one of -CH$_2$C<u>H</u>=CH$_2$ at C9), 5.86 (1H, s, -C=C<u>H</u>C=O at C2); δ_C (100MHz, $CDCl_3$) 23.05 (CH_3, -C<u>C</u>H$_3$ at C3), 26.33 (CH_2, -C<u>H</u>$_2$ at C5), 33.81 (CH_2, -C<u>H</u>$_2$C=O at C6), 35.67 (CH_2, -<u>C</u>H$_2$CH=CH$_2$ at C8), 39.12 (CH, -<u>C</u>H(C_3H_5) at C4), 117.36 (CH_2, -CH$_2$CH=<u>C</u>H$_2$ at C10), 126.95 (CH, -C=<u>C</u>HC=O at C2), 136.03 (CH, -CH$_2$<u>C</u>H=CH$_2$ at C9), 165.04 (C, -<u>C</u>CH$_3$ at C3), 119.815 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{10}H_{15}O$ requires 151.1116 found 151.1117.

5.2.35 Synthesis of (±)-(1*R*,5*R*,6*R*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (467) and (±)-(1*S*,5*R*,6*S*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (468)

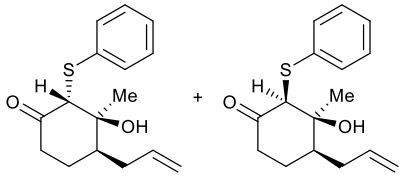


467 468

A solution of (±)-4-allyl-3-methylcyclohex-2-enone **472** (1.8955 mL, 12.62 mmol) and 30% aqueous hydrogen peroxide (7.00 mL, 205.67 mmol) in MeOH (15 mL) was stirred and cooled down to 15 °C by means of a water/ice bath. 1 M NaOH (3.03 mL, 75.71 mmol) was added in a dropwise manner with stirring, over a period of 1 hour. The temperature of the reaction mixture was maintained below 15-20 °C during the addition. The resulting solution was stirred for a further 5 hours while the temperature was maintained at 20-25 °C and subsequent TLC analysis (8:2 Hex/EtOAc) revealed that no more starting material was being consumed. The reaction was diluted with water (25 mL) and extracted with diethyl ether (2 x 25 mL). The combined organic fractions were washed with water (25 mL), dried over MgSO4, filtered by suction and concentrated *in vacuo* yielding a yellow liquid product as a mixture of two diastereoisomers (13:1 ratio) **467** and **468**. The crude product was purified by flash column chromatography (8:2 Hex /EtOAc) to afford pale-yellow liquid (±)-(1*R*,5*R*,6*R*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one **467** as a major stereoisomer (1.0128 g, 6.12 mmol, 49%). R_f 0.37 (SiO_2, 8:2 Hex /EtOAc); ν_{max} (ATR)/cm^{-1},1702.63 (C=O stretch), 1640.56 (C=C

stretch); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, -CC<u>H</u>$_3$ at C6), 1.54-1.65 (1H, m, one of -C<u>H</u>$_2$ at C4), 1.90 (1H, m, one of -C<u>H</u>$_2$CH=CH$_2$ at C8), 2.07-2.10 (2H, m, one of -C<u>H</u>$_2$ at C4 and one of -C<u>H</u>$_2$C=O at C3), 2.25 (1H, m, -C<u>H</u>(C_3H_5) at C5), 2.30-2.43 (2H, m, one of -C<u>H</u>$_2$C=O at C3 and one of -C<u>H</u>$_2$CH=CH$_2$ at C8), 3.11 (1H, s, C<u>H</u> at C1), 4.97-5.16 (2H, m, -CH$_2$CH=C<u>H</u>$_2$ at C10), 5.74 (1H, dtd, *J* 18.0, 9.0, 6.0 Hz, -CH$_2$C<u>H</u>=CH$_2$ at C9); δ_C (100MHz, $CDCl_3$) 19.26 (CH$_2$, <u>C</u>H$_2$ at C4), 20.44 (CH$_3$, -CC<u>H</u>$_3$ at C6), 31.55 (CH$_2$, -<u>C</u>H$_2$C=O at C3), 33.98 (CH$_2$,-<u>C</u>H$_2$CH=CH$_2$ at C8), 37.50 (CH, -<u>C</u>H(C_3H_5) at C5), 62.38 (CH, <u>C</u>HC=O at C1), 65.52 (C, -<u>C</u>CH$_3$ at C6), 117.20 (CH$_2$, -CH$_2$CH=<u>C</u>H$_2$ at C10), 135.73 (CH, -CH$_2$<u>C</u>H=CH$_2$ at C9), 207.29 (C, -<u>C</u>=O at C2); HRMS (+ESI) *m/z* [$(M+H)^+$] $C_{10}H_{15}O_2$ requires 167.1027 found 167.1024.

5.2.36 Synthesis of (2*R*,3*S*,4*R*) -4-allyl-3-hydroxy-3-methyl-2-(phenylthio)cyclohexan-1-one (469) and (2*S*,3*S*,4*R*)-4-allyl-3-hydroxy-3-methyl-2-(phenylthiol)cyclohexan-1-one (470)



469 470

A solution of (±)-(1*R*,5*R*,6*R*)-5-allyl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one **467** (74 mg, 445.19 µmol) in ethanol (135 mL) and 15% aq. KOH (7 mL, 0.2 equiv.) solution was stirred at 0 ºC under a nitrogen atmosphere. A solution of thiophenol (53.95 mg, 489.71 µmol) in THF (135 mL) was degassed with a stream of nitrogen for (30 min) then added dropwise over 20 min. After stirring at 0 °C for 1 hour, the reaction was judged to be completed by TLC analysis (8:2 Hex/EtOAc). Water (5 mL) was then added to the reaction mixture and extracted with ether-toluene (1:1, 3 x 5 mL). The combined organic fractions were washed with a saturated brine solution (2 x 2 mL). The organic fraction was dried over $MgSO_4$, filtered by suction, and concentrated *in vacuo* to produce a crude yellow oil. The crude product was purified by flash

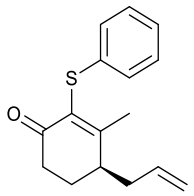
column chromatography (8:2 Hex/EtOAc) to afford yellow liquid as a mixture of two diastereoisomers (10:1) (±)-(2*R*,3*S*,4*R*)-4-allyl-3-hydroxy-3-methyl-2-(phenylthio)cyclohexan-1-one **469** and (±)-(2*S*,3*S*,4*R*)-4-allyl-3-hydroxy-3-methyl-2-(phenylthiol)cyclohexan-1-one **470** (0.0815 g, 294.87 µmol, 66%).

major diastereoisomer R_f 0.42 (SiO_2, 8:2 Hex/EtOAc); ν_{max} (ATR)/cm^{-1},3350.64 (O-H stretch), 1702.63 (C=O stretch), δ_H (400 MHz, $CDCl_3$) 1.16 (3H, s, -C$\underline{H}_3$ at C3), 1.73-1.81 (1H, m, one of -C$\underline{H}_2$C=O at C6), 2.31-2.38 (1H, m, one of -C$\underline{H}_2$CH=CH_2 at C8), 2.50 (1H, dt, *J* 17.0, 5.0 Hz, one of -C$\underline{H}_2$ at C5), 2.56-2.67 (2H, m, one of -C$\underline{H}_2$ at C5 and -C$\underline{H}$(C_3H_5) at C4), 2.74 (1H, ddd, *J* 11.0, 6.0, 4.0 Hz, axial, -C$\underline{H}_2$C=O at C6), 2.93 (1H, bs, O$\underline{H}$ at C3), 3.01 (1H, ddd, *J* 15.0, 14.0, 7.0 Hz, one of -C$\underline{H}_2$CH=CH_2 at C8), 3.53 (1H, d, *J* 1.6 Hz, equatorial -C$\underline{H}$ at C2), 4.98-5.24 (2H, m, two -CH_2CH=C$\underline{H}_2$ at C10), 5.81 (1H, dddd, *J* 17.0,10.0, 8.0, 6.0 Hz, -CH_2C$\underline{H}$=CH_2 at C9), 6.99-7.53 (5H, m, -C$\underline{H}$Ar); δ_C (100MHz, $CDCl_3$) 20.30 (CH_3, -C$\underline{C}H_3$ at C3), 33.29 (CH_2, -$\underline{C}H_2$C=O at C6), 34.21 (CH_2, -$\underline{C}H_2$ at C5), 36.04 (CH_2, -$\underline{C}H_2$CH=CH_2 at C8), 42.29 (CH, -$\underline{C}$H(C_3H_5) at C4), 71.02 (CH, -$\underline{C}$HC=O at C2), 116.75 (CH_2, -CH_2CH=$\underline{C}H_2$ at C10), 128.84 (CH, -*p*-$\underline{C}$HAr), 129.37 (CH, -*o*-$\underline{C}$HAr), 131.97 (CH, -*m*-$\underline{C}$HAr), 136.91 (C, -$\underline{C}$$CH_3$ at C3), 137.04 (CH, -$CH_2\underline{C}$H=CH_2 at C9), 171.84 (C, -S$\underline{C}$1Ar), 207.03 (C, -$\underline{C}$=O at C1); HRMS (+ESI) *m/z* [$(MH)^+$] $C_{16}H_{20}O_2S$ requires 276.1201 found 276.1206.

minor diastereoisomer R_f 0.36 (SiO_2, 8:2 Hex/EtOAc); ν_{max} (ATR)/cm^{-1},3350.64 (O-H stretch), 1702.63 (C=O stretch), δ_H (400 MHz, $CDCl_3$) 1.05 (3H, s, C$\underline{H}_3$ at C3), 1.18-1.26 (1H, m, one of -C$\underline{H}_2$ at C5), 1.30 (1H, dd, *J* 11.0, 6.0 Hz, one of -C$\underline{H}_2$C=O at C6), 1.73-1.81 (1H, m, -C$\underline{H}$(C_3H_5) at C4), 2.02-2.05 (1H, m, one of -C$\underline{H}_2$ at C5), 2.13 (1H, ddd, *J* 10.0, 5.0, 2.0 Hz, one of -C$\underline{H}_2$C=O at C6), 2.34-2.44 (1H, m, one of -C$\underline{H}_2$CH=CH_2 at C8), 2.48-2.54 (1H, m, one of -C$\underline{H}_2$CH=CH_2 at C8), 2.91 (1H, bs, O$\underline{H}$ at C3), 3.98 (1H, s, -C$\underline{H}$ at C2) 5.02-5.22 (1H, m, -CH_2CH=C$\underline{H}_2$ at C10), 5.89-5.72 (2H, m, two -CH_2C$\underline{H}$=CH_2 at C9), 7.03-7.51 (5H, m, -C$\underline{H}$Ar); δ_C (100MHz, $CDCl_3$) 18.28 (CH_3, -C$\underline{C}H_3$ at C3), 24.88 (CH_2, -$\underline{C}H_2$C=O at C6), 25.18 (CH_2, -

$\underline{C}H_2$ at C5), 33.90 (CH_2, -$\underline{C}H_2CH=CH_2$ at C8), 43.28 (CH, -$\underline{C}H(C_3H_5)$ at C4), 74.72 (CH, -$\underline{C}HC=O$ at C2), 117.85 (CH_2, -$CH_2CH=\underline{C}H_2$ at C10), 125.27 (CH, - *p*-$\underline{C}HAr$), 127.15 (CH, - *o*-$\underline{C}HAr$), 128.12 (CH, - *m*-$\underline{C}HAr$), 133.91 (C, -$\underline{C}CH_3$ at C3), 135.07 (CH, -$CH_2\underline{C}H=CH_2$ at C9), 136.55 (C, -S$\underline{C}$1Ar), 194.11 (C, -$\underline{C}$=O); HRMS (+ESI) *m/z* $[(MH)^+]$ $C_{16}H_{20}O_2S$ require 276.1201 found 276.1206.

5.2.37 Synthesis of (*R*)-4-allyl-3-methyl-2-(phenylthio)-2-cyclohexenone (471)



471

A solution of (2*R*,3*S*,4*R*)-4-allyl-3-hydroxy-3-methyl-2-(phenylthiol)cyclohexen-1-one **469** (0.0230 g, 83.21 µmol) in ethanol (0.5 mL) was treated with catalytic amount of 15% KOH (0.5 mL, 8.3 µmol) at room temperature. The resulting solution was stirred for approximately 15 minutes until TLC analysis (9:1 pet. ether/EtOAc) indicated that all the starting material had reacted. The solution was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered by suction and concentrated *in vacuo* to give a crude yellow solid. The crude solid was further purified by crystallisation (hexane/diethyl ether (4:1) 5 mL) to afford (*R*)-4-allyl-3-methyl-2-(phenylthio)cyclohex-2-enone **471** as an analytically pure colourless crystal (0.0148 g, 57.28 µmol, 69%) (m.p. 101-102 ^oC) as a major distereoisomer. R_f 0.25 (SiO_2, 8:2 Hex/EtOAc); ν_{max} (ATR)/cm^{-1}, 1683.63 (α,β-unsaturated C=O stretch), 1223.33 (C-C stretch); δ_H (400MHz, $CDCl_3$) 1.79 (1H, app d, *J* 1.0 Hz, one of -$C\underline{H}_2C=O$ at C6), 1.80 (3H, s, $C\underline{H}_3$ at C3), 1.81 (1H, dd, *J* 8.0, 2.0 Hz, -$C\underline{H}(C_3H_5)$ at C4), 2.09 (1H, dd, *J* 8.0, 1.0, Hz, one of -$C\underline{H}_2$ at C5), 2.11 (1H, dd, *J* 8.0, 2.0 Hz, one of -$C\underline{H}_2CH=CH_2$ at C8), 2.27 (1H, ddd, *J* 19.0, 11.0, 8.0 Hz, one of $C\underline{H}_2$ at C5), 2.46-2.54 (2H, m, one of -$C\underline{H}_2C=O$ at C6, and one of -$C\underline{H}_2CH=CH_2$ at C8), 5.16 (1H, dq, *J* 17.0, 2.0 Hz, *trans*-H -

$CH_2CH=C\underline{H}_2$ at C10), 5.21 (1H, ddt, *J* 10.0, 2.0, 1.0 Hz, *cis*-H $-CH_2CH=C\underline{H}_2$ at C10), 5.81 (1H, dddd, *J* 17.0, 10.0, 8.0, 6.0 Hz, $-CH_2C\underline{H}=CH_2$ at C9), 7.25 (1H, d, *J* 8.0 Hz, *p*-C<u>H</u>Ar) 7.27-7.30 (2H, m, *o*-C<u>H</u>Ar), 7.49-7.52 (2H, m, *m*-C<u>H</u>Ar); δ_C (100MHz, $CDCl_3$) 14.35 (CH_3, $-CH=C\underline{C}H_3$ at C3), 28.64 (CH_2, $-C\underline{H}_2$ at C5), 33.72 (CH_2, $-C\underline{H}_2C=O$ at C6), 39.95 (CH_2, $\underline{C}H_2CH=CH_2$ at C8), 73.88 (CH, $-\underline{C}H(C_3H_5)$ at C4), 120.27 (CH, -*p*-<u>C</u>HAr), 127.88 (CH_2, $CH_2CH=\underline{C}H_2$ at C10), 129.09 (CH, -*o*-<u>C</u>HAr), 131.55 (CH, $-CH_2\underline{C}H=CH_2$ at C9), 132.42 (CH, -*m*-<u>C</u>HAr), 136.30 (C, $-\underline{C}CH_3$ at C3) 143.90 (C, -<u>C</u>SAr at C2) 150.41 (C, -S<u>C</u>1Ar), 200.46 (C, -<u>C</u>=O); HRMS (+ESI) *m/z* $[(M+H)^+]$ $C_{16}H_{18}OS$ requires 258.1134 found 258.1140.

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