UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

School of Chemistry

Total Synthesis of (–)-Colombiasin A and (–)-Elisapterosin B and the Discovery of New Thermal Cyclobutenone Rearrangements

by

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ABSTRACT

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TOTAL SYNTHESIS OF (–)-COLOMBIASIN A AND (–)-ELISAPTEROSIN B AND THE DISCOVERY OF NEW THERMAL CYCLOBUTENONE REARRANGEMENTS

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This thesis concerns the total synthesis of the natural products (–)-colombiasin A and (–)-elisapterosin B, isolated from the Caribbean sea whip, *Pseudopterogorgia elisabethae*. These marine diterpenes have displayed interesting biological activity, with both being potent inhibitors of *Mycobacterium tuberculosis* H37Rv. Indeed, (–)-elisapterosin B has also shown strong antiplasmodial activity against *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria.

The fascinating molecular architecture of (–)-colombiasin A and (–)-elisapterosin B has made them attractive and challenging targets for the synthetic organic chemist. Previous synthetic approaches to both natural products are reviewed in Chapter 1.

Our own total synthesis of (–)-colombiasin A and (–)-elisapterosin B is described in Chapter 2. A key feature of our approach is the use of a Moore rearrangement to set up intramolecular [4 + 2] and [5 + 2] cycloadditions to assemble the tetracyclic carbon skeletons.

Studies towards 'second generation' syntheses of (–)-colombiasin A and (–)-elisapterosin B (Chapter 3), unearth a new thermal rearrangement of vinylcyclobutenones leading to spirocycles. Further investigation reveals four new rearrangements of cyclobutenones that can be used to access a variety of carbocyclic ring systems (Chapter 4). Work on the regioselectivity of carbanion addition to a cyclobutendione, and studies towards (+)-elisabethin A are also described (Chapter 5).

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Preface

The research described in this thesis was carried out under the supervision of Prof. D. C. Harrowven at the University of Southampton between October 2003 and October 2006. No part of this thesis has previously been submitted for a degree.

Acknowledgements

The long and seemingly never ending process of constructing this thesis would never have been completed without the fantastic support of my family and friends – a big, collective thank you to everyone who has helped me over the past 3 and a bit years!

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Massive thanks must go to Emily for giving me the most incredible support over the past few years. You have given me the confidence and drive to succeed, and always made me laugh when needed! Many thanks also to Annie and Mike for their brilliant hospitality.

Finally, a huge thanks to Mum and Dad. You have given me amazing support throughout my whole time at university. Your love, advice and inspiration have enabled me to always give my best.

Abbreviations

Ac	acetyl
acac	acetylacetonate
Ac_2O	acetic anhydride
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Ar	aryl
BINOL	1,1'-bi-2,2'-naphthol
Bu	butyl
^{t}Bu	*tert*-butyl
^{n}BuLi	*n*-butyllithium
^{t}BuLi	*tert*-butyllithium
c	concentration
CAN	cerium(IV) ammonium nitrate
cat.	catalytic
CHN	elemental analysis
CI	chemical ionisation
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
2,2-DMB	2,2-dimethylbutane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DOSP	(*N*-dodecylbenzenesulfonyl)prolinate
d.r.	diastereoisomeric ratio
DTBP	dimethyl-3,3'-dithiobispropionimidate
ee	enantiomeric excess
EI	electron impact ionisation
eq.	equivalents

ES	electrospray
Et	ethyl
ether	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FT	Fourier transform
g	grams
h	hours
HMBC	heteronuclear multiple bond connectivity
HMDS	hexamethyldisilylazide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
Ipc	isopinocamphyl
IR	infra-red
LDA	lithium diisopropylamide
L-selectride	lithium tri-*sec*-butylborohydride
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
lit.	literature
KO^{t}Bu	potassium *tert*-butoxide
LRMS	low resolution mass spectrometry
M	molar
m	*meta*
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MeOH	methanol
min	minutes
mL	millilitres
MP	melting point
MS	molecular sieves
NBS	*N*-bromosuccinimide
NEt_3	triethylamine

NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
petrol	petroleum ether 40/60
Ph	phenyl
PhLi	phenyllithium
PhMe	toluene
ppm	parts per million
^{i}Pr	isopropyl
p-TsOH	*para*-toluenesulfonic acid
py.	pyridine
RSM	recovered starting material
RT	room temperature
sat.	saturated (aqueous solution)
SiO_2	silica
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Trisyl	2,4,6-triisopropylbenzenesulfonyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
Δ	heat/reflux
μwave	microwave

Chapter 1 – Introduction to (–)-Colombiasin A and (–)-Elisapterosin B

1.1 Background

The Caribbean sea whip *Pseudopterogorgia elisabethae* has proved to be a rich source of structurally complex marine natural products, many possessing interesting biological activity.[1] It gained prominence in the late 1980's when Fenical *et al.* found that its chloroform extract displayed potent anti-inflammatory activity, leading to the discovery of a new family of natural products, which they named the pseudopterosins.[2] The most abundant of these, pseudopterosin C **1.3**, was soon utilised as the active ingredient in the topical skin cream *Resilience*®.[3]

In recent years the hexane extract of *Pseudopterogorgia elisabethae*, collected near San Andres Island, Colombia, has been found to be a potent inhibitor of *Mycobacterium tuberculosis* H37Rv.[4] Study of the gorgonian octocoral in greater detail followed, resulting in the isolation and identification of a number of structurally related diterpenes (Figure 1.1).[5-10]

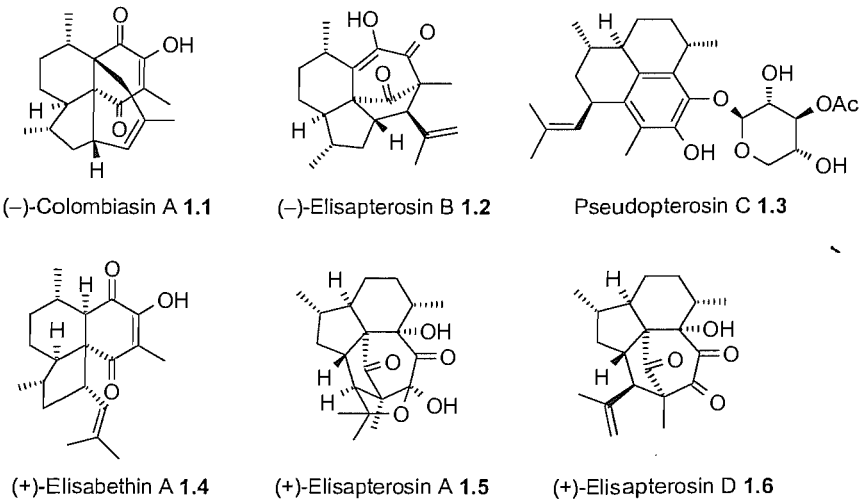


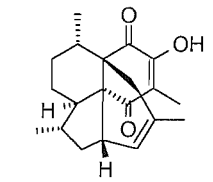
Figure 1.1. Natural products isolated from *Pseudopterogorgia elisabethae*.

(–)-Colombiasin A **1.1**, with its highly unusual tetracyclic structure, attracted the immediate interest of the synthetic chemistry community though (–)-elisapterosin B **1.2** was the most interesting from a biological perspective – it being the most potent of the congeners isolated. Indeed the latter, along with other family members such as (+)-elisapterosins A **1.5** and D **1.6**, showed strong antiplasmodial activity against

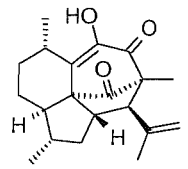
Plasmodium falciparum, the parasite responsible for the most severe forms of malaria.[10,11]

1.2 The Targets

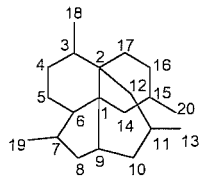
Our primary synthetic targets are (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. Both are structurally complex diterpenes recently isolated from the hexane extract of the Caribbean sea whip *Pseudopterogorgia elisabethae*.[6,7]



(–)-Colombiasin A **1.1**



(–)-Elisapterosin B **1.2**



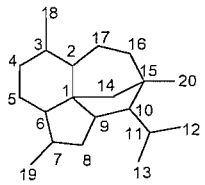
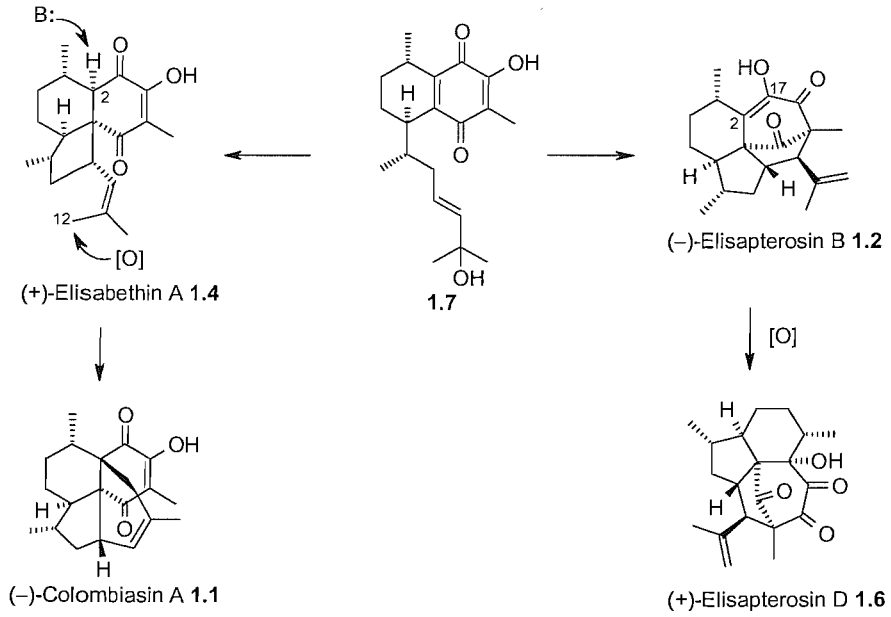


Figure 1.2. Colombiane and elisapterane numbering.[6,7]

As well as their significant promise as therapeutic agents, the fascinating molecular architecture of colombiasin A **1.1** and elisapterosin B **1.2** make them attractive and challenging targets for the synthetic organic chemist. Colombiasin A's tetracyclic skeleton is modest in size, but the presence of six stereogenic centres and carbon atoms of various oxidation levels make a total synthesis a difficult proposition. The C_{20} carbon framework contains three 6 membered rings which all share a common carbon to carbon bond (C1-C2). To this "propellane" is fused a further 5 membered ring in which four of the contiguous stereogenic centres are found (Figure 1.2). Elisapterosin B has a similar tetracyclic structure with 7 chiral centres. Its skeleton is comprised of two fused 6 membered rings conjoined to two 5 membered rings (Figure 1.2). Like colombiasin A it has an embedded 1,2,4-tricarbonyl where one of the carbonyls favours the enol tautomer.

1.3 Biosynthesis

Rodriguez and co-workers have proposed that many of the natural products isolated are derived from a common biogenetic precursor and are interrelated. Serrulatane diterpene **1.7**, also isolated from *Pseudopterogorgia elisabethae*, is postulated as the common precursor of **1.4** and **1.2** *via* two distinct biosynthetic cyclisation pathways (Scheme 1.1).[8] (+)-Elisabethin A **1.4** may then be hydroxylated at C12 and converted to a suitable leaving group. Base catalysed removal of the C2 proton then instigates intramolecular alkylation to give (–)-colombiasin A **1.1**.[6] (+)-Elisapterosin D **1.6** is likely to be derived from (–)-elisapterosin B **1.2** by oxidation of the C2-C17 alkene.



Scheme 1.1. Proposed biosynthesis of natural products from *Pseudopterogorgia elisabethae* by Rodriguez *et al.*[6,8]

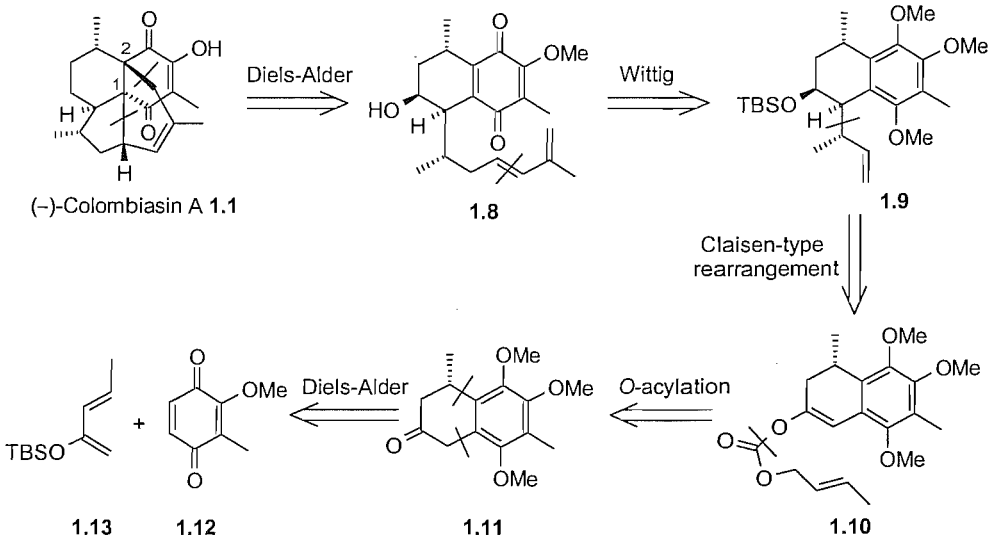
Over the past 5 years several syntheses of these marine natural products have been reported in the literature. Bio-mimetically inspired approaches have featured prominently in efforts to design practical routes to these complex molecules.

1.4 Previous Syntheses

1.4.1 The Nicolaou Synthesis

The first total synthesis of (–)-colombiasin A **1.1** was reported by K. C. Nicolaou *et al.* in 2001.[12,13] The strategy employed involved two Diels-Alder cycloadditions and a palladium-catalysed rearrangement as key steps (Scheme 1.2).

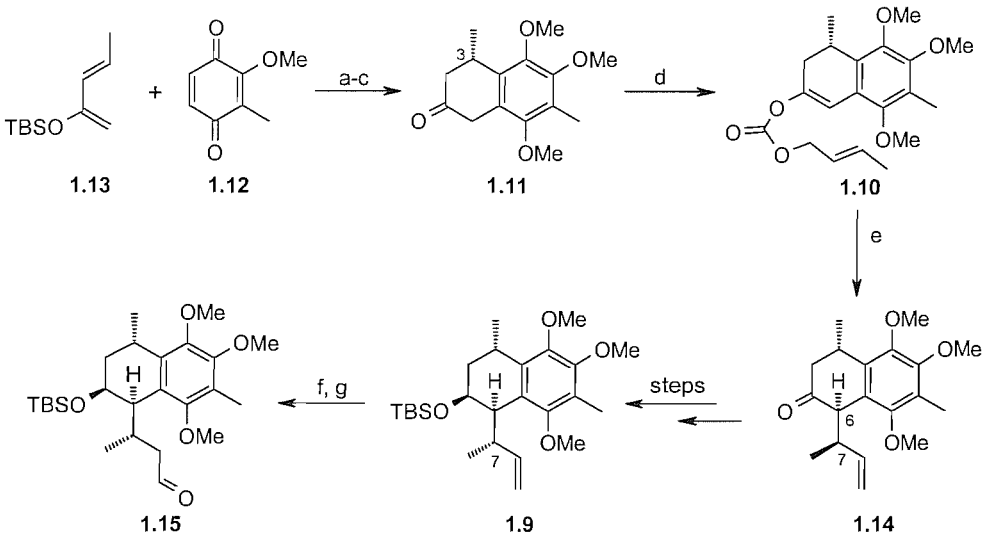
On closer inspection it is evident that the complex core of colombiasin A **1.1** can be accessed by an intramolecular Diels-Alder cycloaddition to form the two adjacent quaternary centres at C1 and C2. Thus, the precursor diene-quinone **1.8** was a key intermediate in the synthesis. This can be accessed by Wittig chemistry from **1.9**, which in turn can be made by Pd-catalysed rearrangement of **1.10**. Further disconnections lead back to quinone **1.12** and diene **1.13** as possible starting materials (Scheme 1.2).



Scheme 1.2. Retrosynthetic strategy employed by Nicolaou *et al.*[12,13]

Nicolaou's synthesis began with the union of **1.12** and **1.13** by a Diels-Alder cycloaddition (Scheme 1.3). A chiral Lewis acid was used to install the C3 stereogenic centre with the correct configuration. Aromatisation, methylation and desilylation gives ketone **1.11**. *O*-Acylation of the enolate derived from **1.11** with crotyl chloroformate next yields **1.10** which, on treatment with Pd(0) undergoes an intramolecular allylic alkylation to **1.14**. This Claisen-type rearrangement gave an undesired stereochemical outcome at C7, necessitating an untidy sequence of steps to epimerise that centre.

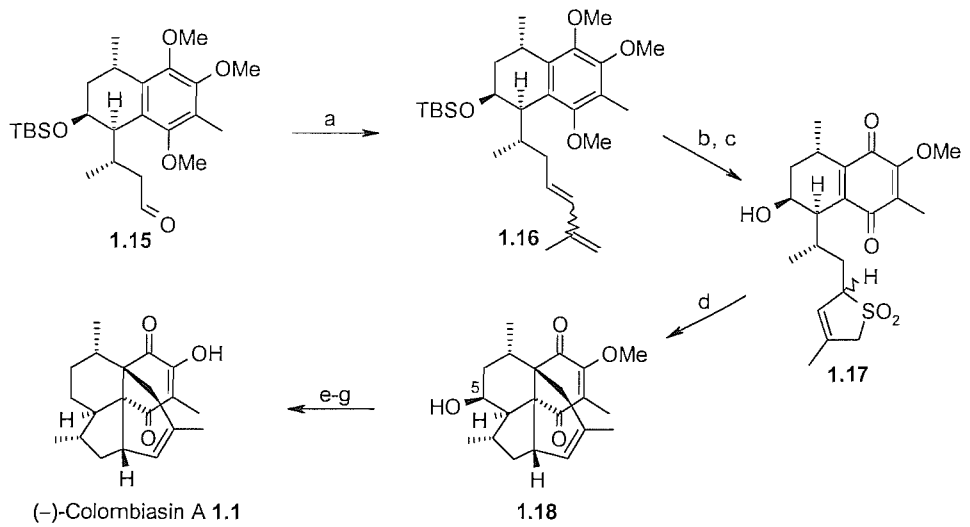
Alkene **1.9** was next converted to aldehyde **1.15** by a hydroboration-oxidation procedure (Scheme 1.3).



Scheme 1.3. Synthetic route to intermediate aldehyde **1.15**.[12,13]

Reagents and conditions: (a) 30 mol% [(*S*)-BINOL-$TiCl_2$], PhMe, −60 to −10 °C; (b) K_2CO_3, MeI, acetone, Δ; (c) 2% TFA in DCM, 70% over 3 steps; (d) (i) LiHMDS, THF, −78 °C (ii) crotyl chloroformate, RT, 94%; (e) $Pd(PPh_3)_4$, THF, 62%; (f) BH_3.THF, then $NaOH/H_2O_2$, 81%; (g) PCC, DCM, 97%.

With aldehyde **1.15** in hand and three of the six stereogenic centres installed, Nicoloau *et al.* could now complete the total synthesis. A Wittig reaction was used to introduce the diene unit of **1.16** (Scheme 1.4). Attempts to unveil the quinone by treatment of **1.16** with AgO/HNO_3 in the presence of the diene side chain failed, making it necessary to protect the diene as its SO_2 adduct. Removal of the TBS protecting group and oxidation of the arene to a quinone then gave **1.17**. On heating in the dark, **1.17** first extruded SO_2 to reveal the diene which spontaneously underwent a Diels-Alder cycloaddition to give **1.18** with the tetracyclic skeleton of (−)-colombiasin A **1.1**. Deoxygenation at the C5 position followed by a low yielding deprotection of the methyl ether then gave the natural product **1.1** (Scheme 1.4).



Scheme 1.4. Completion of the total synthesis of (–)-colombiasin A **1.1**.[12,13]

Reagents and conditions: (a) 2-methyl-2-propenyltriphenylphosphonium bromide, ^{n}BuLi, THF, 0 °C; then aldehyde **1.15**, 70 °C, 97% (*E*:*Z* = 3:1); (b) SO_2, sealed tube, RT, 91%; (c) 1,4-dioxane/6 M HNO_3 10:1, RT; then AgO, RT, 79%; (d) PhMe (sealed tube), 180 °C, 89%; (e) NaH, THF, CS_2, MeI, 50 °C, 95%, (f) AIBN, Bu_3SnH, PhMe, 110 °C, 77%; (g) BBr_3, *cis*-cyclooctene, DCM, –78 °C, 30%.

The Nicolaou approach incorporates two Diels-Alder cycloadditions to efficiently construct the complex tetracyclic skeleton of **1.1**. However, the synthesis is long (19 linear steps for a 20-carbon molecule) and the overall yield low (1.9%). The poor yield is due in part to the final deprotection step (30%) with the harsh acidic conditions giving several unwanted by-products.[12,13] The approach also suffers from an inability to control the C7 stereochemistry in the Claisen-type rearrangement of **1.10** to **1.14**. Despite these faults, completion of the first synthesis gave confirmation of the absolute stereochemistry of **1.1** and set the standard for future endeavours.

Shortly after this first synthesis, Harrowven and Tyte[14] disclosed their own approach to colombiasin A **1.1**. The same intramolecular Diels-Alder endgame was used. Unfortunately, the approach they devised led to the wrong configuration at C6, which in turn led to an unnatural diastereoisomer of **1.1** being formed.

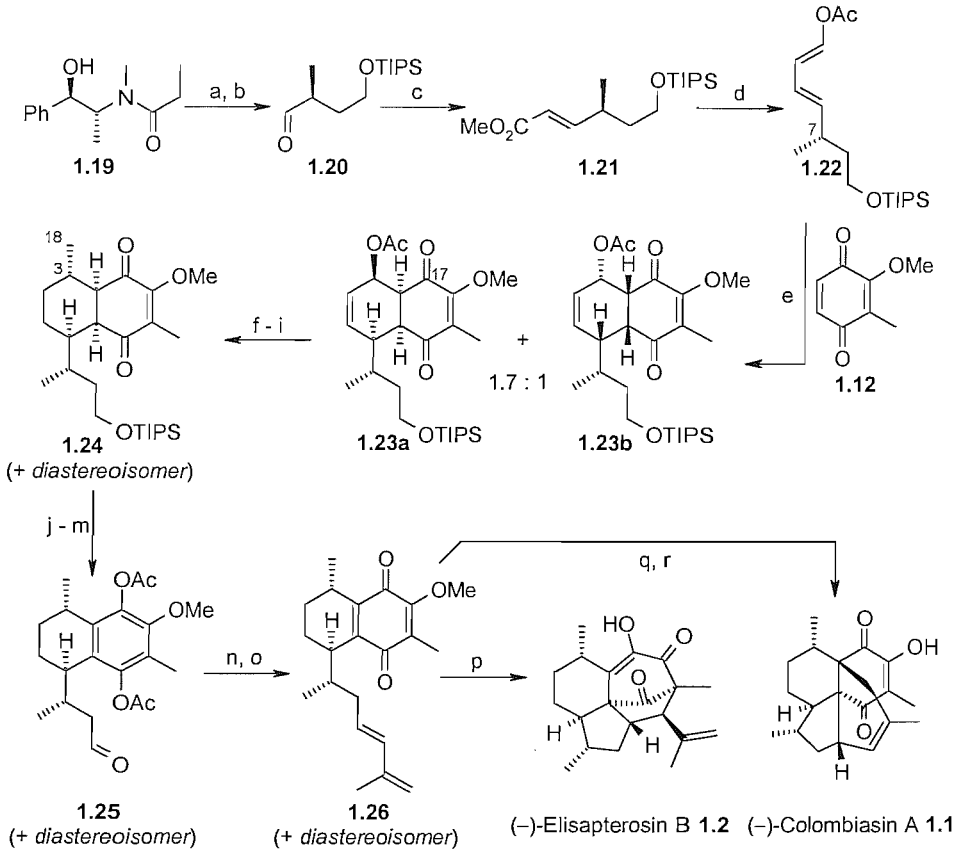
1.4.2 The Rychnovsky Synthesis

More recently Kim and Rychnovsky disclosed a synthetic route to both (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. It was the first published synthesis of (–)-elisapterosin B, and was noteworthy as both natural products were accessed from a common late-stage intermediate.[15]

Their synthesis began with an auxiliary-mediated stereoselective alkylation of amide **1.19** which, after reduction and hydrolysis gave enantiomerically pure aldehyde **1.20** (Scheme 1.5). Wittig olefination to ester **1.21** and homologation next gave acetoxy diene **1.22**, which underwent an intermolecular Diels-Alder reaction with quinone **1.12** to give decalins **1.23a** and **1.23b** in a 1.7:1 ratio. Although the complex structure of **1.23** was established in just 5 steps, diastereoselectivity was poor and the inseparable mixture had to be carried through the remainder of the sequence.[15]

Reduction of the ketone at C17 with $NaBH_4$ allowed introduction of the C18 methyl group by S_N2 displacement of the acetate group with lithium dimethylcuprate. Hydrogenation of the resulting alkene followed by Dess-Martin oxidation gave **1.24**. A lengthy sequence followed to transform silyl ether **1.24** into aldehyde **1.25**. Another Wittig reaction then installed the diene side chain prior to deprotection of the latent hydroquinone with K_2CO_3/MeOH and subsequent aerial oxidation to quinone **1.26**. This intermediate was now set up to undergo [4 + 2] and [5 + 2] cycloaddition reactions giving access to the natural product targets.

The [5 + 2] cycloaddition was discovered many years previously by Joseph-Nathan *et al.*[16,17] but has rarely been used in total synthesis. Treatment with a large excess of $BF_3.OEt_2$ effected simultaneous deprotection of the methyl ether of **1.26** and induced the required intramolecular [5 + 2] cycloaddition to give (–)-elisapterosin B **1.2** in modest yield. (–)-Colombiasin A **1.1** was accessed using the Diels-Alder strategy developed by Nicolaou *et al.*[12,13] wherein a toluene solution of **1.26** is heated to 180 °C to facilitate the intramolecular [4 + 2] cycloaddition. Deprotection using $AlCl_3$ buffered with *N,N*-dimethylaniline completed the total synthesis (Scheme 1.5).[15]



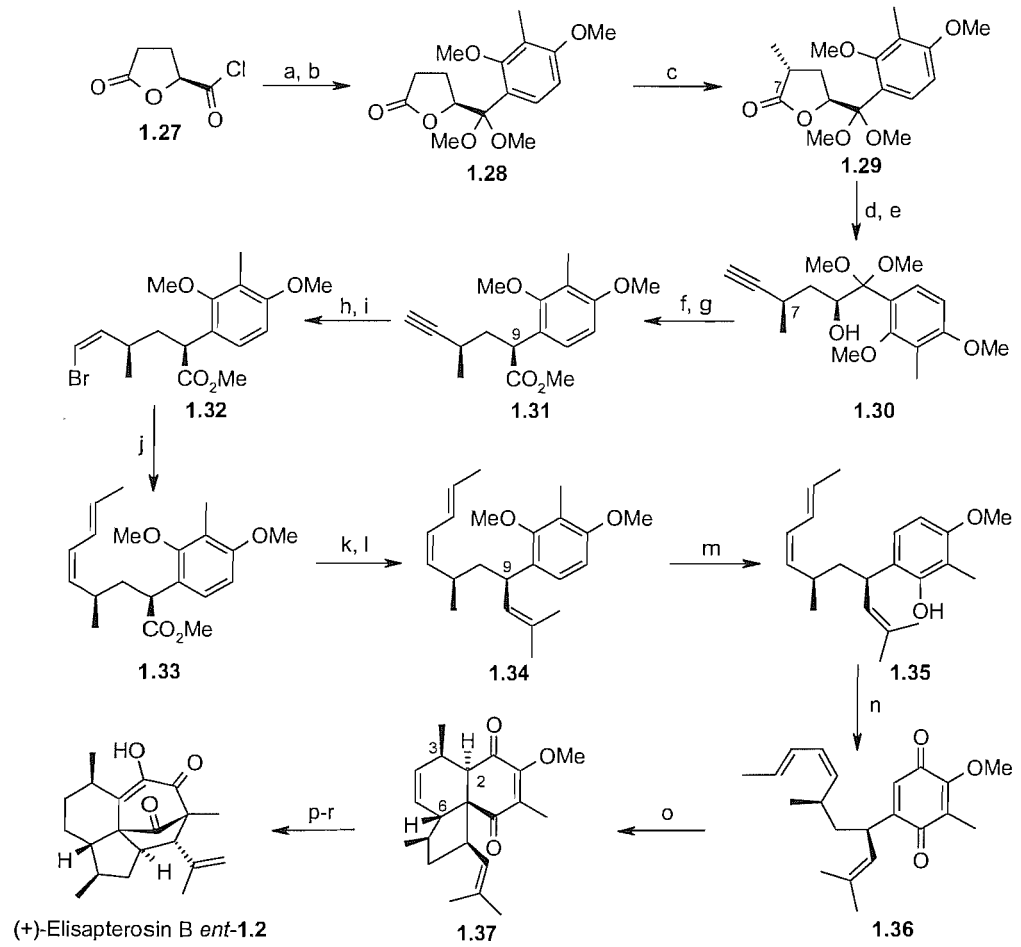
Scheme 1.5. Rychnovsky and Kim's synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**.[15]

Reagents and conditions: (a) LDA, LiCl, ICH_2CH_2OTIPS, 94%, >97% *de*; (b) $LiAlH(OEt)_3$, then H^+, 77%; (c) $Ph_3P{=}CHCO_2Me$, MeCN, Δ, 85%; (d) (i) $LiCH_2Br$, THF, –78 °C; (ii) ^{n}BuLi, –78 °C to RT; (iii) LiH, Δ; (iv) Ac_2O, 79%; (e) $LiClO_4$, Et_2O, 75%, 1.7:1 ratio of **1.23a**:**1.23b**; (f) $NaBH_4$, $CeCl_3$, MeOH, 93%; (g) $LiCuMe_2$, Et_2O, 0 °C to RT, 89%; (h) H_2, Pd/C, EtOH, 95%; (i) DMP, DCM, 92%; (j) DBU, DCM, air, 70%; (k) Zn, Ac_2O, NaOAc, then Ac_2O, py., 96%; (l) HF-py., THF, 94%; (m) DMP, DCM, 99%; (n) phosphonium ylide, THF, 78%, 3:1 *E*:*Z*; (o) K_2CO_3, MeOH, air, 79%; (p) 25 eq. $BF_3.OEt_2$, DCM, –78 °C, 41%; (q) 180 °C, PhMe, 83%; (r) $AlCl_3$, $PhNMe_2$, DCM, 0 °C, 73%.

The Rychnovsky synthesis used a regio- and diastereoselective intermolecular Diels-Alder cycloaddition to build quinone **1.26**. From this common intermediate, [5 + 2] and [4 + 2] intramolecular cycloadditions rapidly delivered both targets.[15] The approach does suffer from poor stereocontrol (*d.r.* 1.7:1) in the establishment of the C3 and C6 stereocentres, requiring a complex mixture to be carried through the bulk of the synthesis. The endgame is quick and well designed, but some untidy oxidation-reduction sequences mean the synthesis is long (16 and 17 steps for **1.2** and **1.1** respectively) and the overall yield modest (2.6% for **1.2**, 3.9% for **1.1**).

A model study towards (–)-colombiasin A **1.1** by Flynn *et al.*,[18] employing a similar double Diels-Alder approach, was also published at this time. However, this has yet to be translated into a completed total synthesis.

1.4.3 The Rawal Synthesis of (+)-Elisapterosin B



Scheme 1.6. Synthesis of (+)-elisapterosin B *ent*-**1.2** by Rawal and co-workers.[19]

Reagents and conditions: (a) ArMgBr, $ZnCl_2$, cat. $PdCl_2(PPh_3)_2$, THF, 75%; (b) cat. TsOH, $CH(OMe)_3$, MeOH; KO^{t}Bu, THF, 83%; (c) NaHMDS, MeI, THF, 86%, *d.r.* 8:1; (d) DIBAL-H, PhMe; (e) $(MeO)_2P(O)CHN_2$, KO^{t}Bu, THF, 70% over 2 steps; (f) MsCl, 2,6-lutidine, 50 °C; (g) $CaCO_3$, wet MeOH, 50 °C, 72% over 2 steps; (h) cat. $AgNO_3$, NBS, acetone; (i) 6 eq. $TsNHNH_2$, 7 eq. NaOAc, MeOH, Δ, 65% over 2 steps; (j) (i) (*E*)-1-bromopropene, ^{t}BuLi, –78 °C then $ZnCl_2$; (ii) $PdCl_2(dppf)$ (1 mol%), THF, 70%; (k) DIBAL-H, –95 °C; (l) Wittig, 62% over 2 steps; (m) 10 eq. NaSEt, DMF, 90 °C, 67%; (n) O_2, cat. salcomine, DMF, 49%; (o) PhMe, 80 °C, 67%; (p) H_2, Wilkinson's catalyst, quant.; (q) LiI, 2,6-lutidine, 80 °C, 99%; (r) CAN, MeCN, 0 °C; py., Et_3N, 50 °C, 84%.

In 2003 Rawal *et al.*[19] completed a synthesis of (+)-elisapterosin B *ent*-**1.2** by a vastly different approach to that of Kim and Rychnovsky. Starting with the commercially available chiral acid chloride **1.27**, they accessed lactone **1.28** *via* a Negishi coupling and subsequent ketal formation (Scheme 1.6). Reaction of the lithium enolate of **1.28** with MeI gave the *trans* product **1.29** preferentially, forming the future C7 stereocentre with 8:1 diastereoselectivity. Reduction to the lactol followed by treatment with the Seyferth reagent[20] afforded acetylene **1.30**. Forming the mesylate of **1.30** and heating in the presence of $CaCO_3$ allowed a pinacol-type ketal rearrangement to occur, forming methyl ester **1.31** in 72% yield. This transformation is of note as it establishes the C9 stereocentre in the target molecules.

Bromination and diimide reduction of the alkyne next gave (*Z*)-bromoalkene **1.32** which underwent a Negishi cross-coupling to yield (*E,Z*)-diene **1.33**. The ester in **1.33** was then converted to alkene **1.34** by DIBAL-H reduction and Wittig olefination of the intermediate aldehyde. The desired quinone **1.36** was next unmasked in demethylation and oxidation steps, setting up an intramolecular Diels-Alder cycloaddition with the diene side chain to form **1.37** as a single diastereoisomer (setting the desired C3 and C6 stereochemistry). Notably, the Diels-Alder product **1.37** has the carbon skeleton of elisabethin A **1.4** (Figure 1.1). However, attempts to epimerise the C2 stereochemistry (necessary for a total synthesis of *ent*-**1.4**) by deprotonation were met with failure. The synthesis of (+)-elisapterosin B *ent*-**1.2** from **1.37** could be realised with selective hydrogenation of the disubstituted alkene, deprotection of the methyl ether and oxidative cyclisation to effect the final ring closure (Scheme 1.6).

The Rawal synthesis of (+)-elisapterosin B *ent*-**1.2** is achieved in 18 steps from acid chloride **1.27**. Use of the more expensive enantiomer of **1.27** would deliver the naturally occurring (–)-elisapterosin B **1.2**. The chirality of **1.27** is used to good effect, with several highly diastereoselective transformations installing the key stereocentres. The key feature is an intramolecular Diels-Alder reaction to form the elisabethin skeleton of precursor **1.37**, followed by a biosynthetic oxidative cyclisation.[19] The approach benefits from its novel strategy and high stereoselectivity, but is longer than the synthesis of Kim and Rychnovsky[15] (18 steps vs 16) and lower yielding (1.4% overall vs 2.6%).

At the same time Mülzer and Heckrodt[21] published the first synthesis of (+)-Elisabethin A **1.4** (Figure 1.1) using a similar approach to Rawal *et al.*[19] However, Zanoni and Franzini[22] have recently queried Mülzer's work. Observations of large discrepancies in NMR chemical shifts between the naturally occurring and synthetic samples, along with the fact that an epimerisation of the C2 stereocentre was successful for Mulzer but not for Rawal, cast doubt on the claimed first total synthesis of (+)-elisabethin A **1.4**.

1.4.4 The Harrowven Synthesis

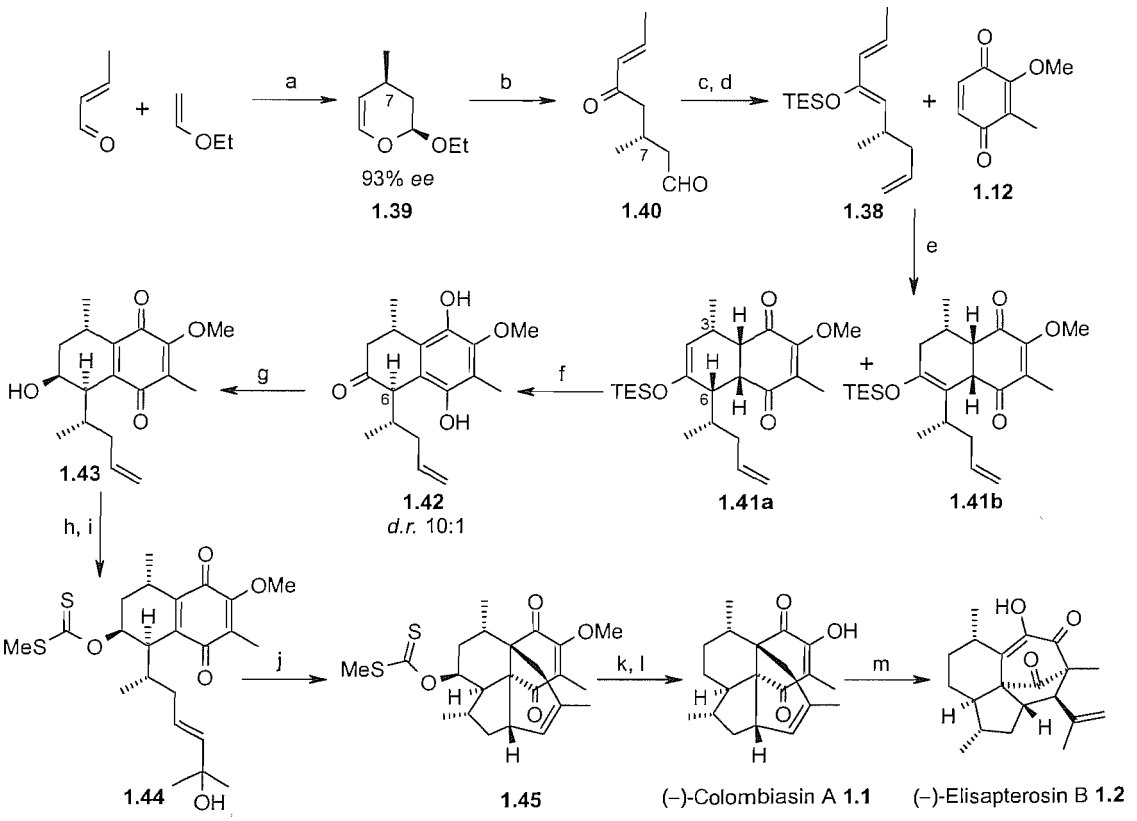
At this juncture our own syntheses of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2** were disclosed, details of which are reported in this thesis (see Chapter 2).

1.4.5 The Jacobsen Synthesis

In 2005 Jacobsen *et al.*[23] reported a new total synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. Again, a key feature of the synthesis was an intermolecular Diels-Alder reaction – this time between diene **1.38** and quinone **1.12** (Scheme 1.7). The synthesis began with a hetero-Diels-Alder cycloaddition between *trans*-crotonaldehyde and ethyl vinyl ether, with a chiral chromium catalyst[24] used to exert asymmetric induction. Cycloadduct **1.39** had the requisite C7 stereogenic centre set with high enantioselectivity (93% *ee*). Lithiation of **1.39** and transmetallation with $ZnCl_2$, allowed Palladium-catalysed Negishi coupling with 1-bromopropene to give ketoaldehyde **1.40** in 81% yield after hydrolysis. Assembly of triene **1.38** was completed by Wittig olefination and silyl enol ether formation.

A monomeric chromium complex developed by Jacobsen *et al.*[25] for diastereo- and regioselective quinone Diels-Alder reactions, was then used to catalyse the reaction of diene **1.38** and quinone **1.12**. The resulting silyl enol ethers **1.41a** and **1.41b** were formed with the correct configuration at C3 and with high diastereoselectivity (*d.r.* 17:1) – the C6 stereocentre in **1.41a** was however incorrect (Scheme 1.7). This was easily rectified as treatment of the mixture with acid led to deprotection of the silyl enol

ethers, tautomerisation of the cyclohexenedione to a hydroquinone and, crucially, epimerisation of the C6 stereochemistry giving ketone **1.42** (*d.r.* 10:1).



Scheme 1.7. Approach to **1.1** and **1.2** by Jacobsen *et al.*[23]

Reagents and conditions: (a) Catalyst (5 mol%), 4Å MS, 81%; (b) (i) ^{t}BuLi, THF, –78 to 0 °C; (ii) $ZnCl_2$, 0 °C to RT; (iii) $Pd(PPh_3)_4$ (2.5 mol%), 1-bromopropene (*E*:*Z* 1:1); (iv) aq. HCl, 81%; (c) (i) $MePPh_3Br$, KHMDS, PhMe, 0 °C; (ii) **1.40**, –78 to 0 °C, 82%; (d) KHMDS, THF, –78 °C then TESCl, 90%; (e) Catalyst (10 mol%), 5Å MS, PhMe, 0 °C, 86% - combined yield of **1.41a** and **1.41b**; (f) conc. HCl, MeOH, 0 °C to RT; (g) (i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, –78 °C; (ii) air, RT, 75% over 2 steps; (h) NaH, THF, 0 °C to RT then CS_2 followed by MeI, 84%; (i) 2-methyl-3-buten-2-ol, Grubbs (II) Ru catalyst (10 mol%), DCM, 87%; (j) $MgSO_4$, PhH, Δ, 77%; (k) AIBN, ^{n}Bu$_3$SnH, PhMe, Δ; (l) $AlCl_3$, $PhNMe_2$, DCM, 0 °C to RT, 67% over 2 steps; (m) excess $BF_3.OEt_2$, DCM, RT, 94%.

Reduction of the ketone to an alcohol and *in situ* aerobic oxidation of the hydroquinone gave **1.43**. Conversion to the xanthate ester followed by a cross-metathesis reaction with 2-methyl-3-buten-2-ol introduced the side chain of **1.44**. A tandem dehydration-intramolecular Diels-Alder reaction to **1.45** was realised by heating **1.44** at reflux in benzene in the presence of $MgSO_4$ – giving the tetracyclic colombiane framework. A de-oxygenation and demethylation sequence introduced by Nicolaou *et al.*[12,13] was then

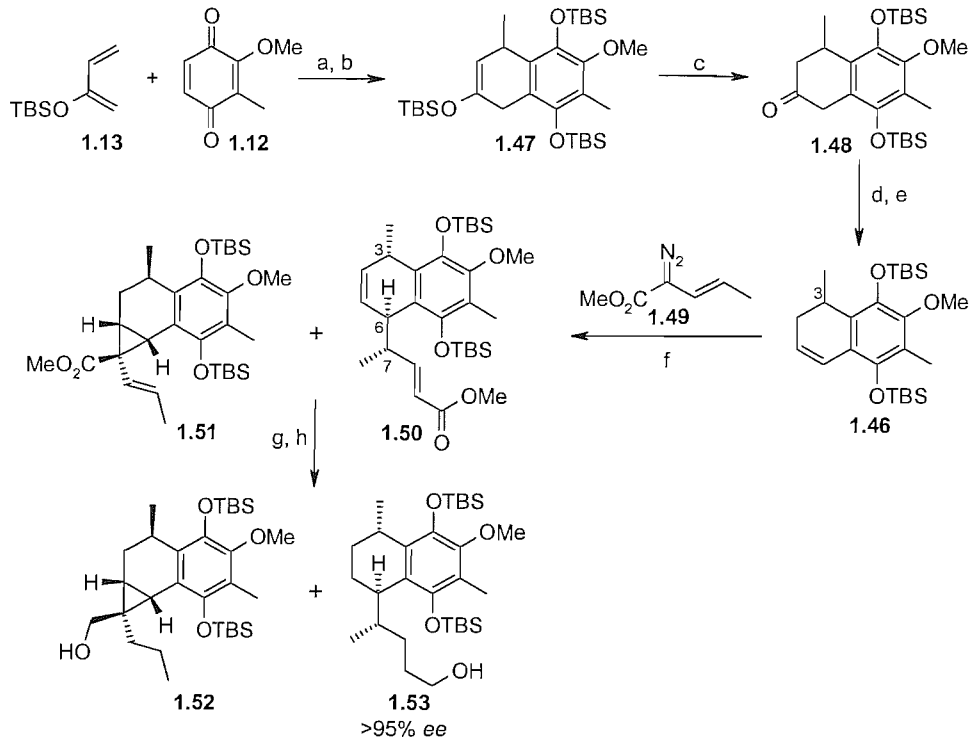
employed to complete the synthesis of (–)-colombiasin A **1.1**. Interestingly, exposure of **1.1** to superstoichiometric quantities of $BF_3.OEt_2$ resulted in conversion to (–)-elisapterosin B **1.2**. Presumably, rearrangement occurs by a retro [4 + 2] cycloaddition followed by a [5 + 2] cycloaddition.[23]

The Jacobsen synthesis is short (12 steps) and high yielding (11.5% overall) making it the most efficient synthesis of (–)-colombiasin A **1.1** to date. High stereocontrol of the C3/C7 stereocentres is achieved by asymmetric catalysis of the Diels-Alder cycloaddition reactions.[23] The synthesis employs a similar strategy to that of Rychnovsky and Kim[15] and of Nicolaou *et al.*;[12,13] and is a vast improvement on both.

1.4.6 The Davies Synthesis

The most recent approach to **1.1** and **1.2** was published in 2006 by Davies *et al.*[26] The strategy adopted differed from the previous syntheses quite markedly, with the key step being a combined C-H activation/Cope rearrangement of dihydronaphthalene **1.46** which sets three stereogenic centres (C3, C6 and C7) in one step.

Their synthesis began with a Diels-Alder reaction developed by Nicolaou *et al.*,[12,13] between quinone **1.12** and diene **1.13** (Scheme 1.8). The resulting dihydroquinone was then protected as the disilyl derivative **1.47**, and the TBS-enol ether unmasked by acidic hydrolysis to deliver β-tetralone **1.48**. Conversion to the corresponding enol triflate facilitated a palladium-catalysed reductive coupling to give racemic dihydronaphthalene **1.46** in high yield.



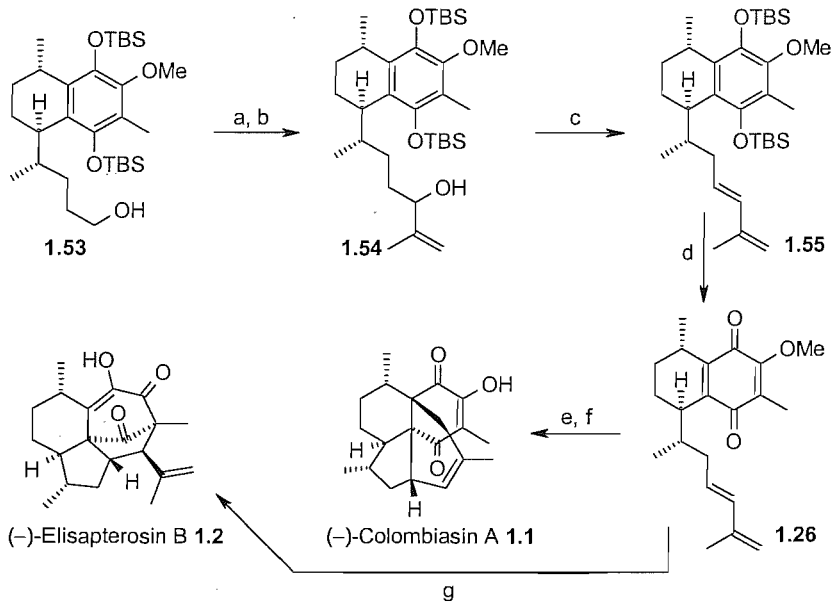
Scheme 1.8. Combined C-H activation/Cope rearrangement of dihydronapthalene **1.46** to ester **1.50** employed by Davies *et al.*[26]

Reagents and conditions: (a) EtOH, RT; (b) TBSCl, imidazole, 86% over 2 steps; (c) TFA, DCM, 84%; (d) NaHMDS, THF, –78 °C then Comins' reagent, 75%; (e) $Pd(PPh_3)_3$, LiBr, Et_3SiH, THF, Δ, 96%; (f) Rh_2(*R*-DOSP)$_4$ (2 mol%), 2,2-DMB, RT; (g) 10 mol% Pd-C, H_2, EtOH; (h) $LiAlH_4$, THF, °C to RT, 34% (68% in theory) over 3 steps.

The intermolecular C-H insertion chemistry of rhodium carbenoids was then exploited in an impressive enantiodivergent key step.[27] When dirhodium tetrakis ((*R*)-(*N*-dodecylbenzenesulfonyl)prolinate), Rh_2(*R*-DOSP)$_4$, was used to catalyse the reaction between vinyldiazoacetate **1.49** and dihydronaphthalene **1.46**, a 1:1 mixture of **1.50** and **1.51** was obtained. Remarkably, cyclopropanation occurs with the undesired enantiomer of **1.46**, while a C-H activation/Cope rearrangement proceeds with the desired enantiomer of **1.46** to yield unsaturated ester **1.50**. The mixture of **1.50** and **1.51** was hydrogenated and subsequently reduced to separable alcohols **1.52** and **1.53** – the desired C-H functionalisation product **1.53** being isolated in 34% yield over 3 steps as a single diastereoisomer in >95% *ee* (Scheme 1.8).[26]

With alcohol **1.53** in hand the synthesis could now be completed using some standard chemistry. Oxidation of **1.53** with PCC, followed by a Grignard addition to the resultant aldehyde afforded **1.54** (Scheme 1.9). Elimination of the triflate formed from **1.54** gave

diene **1.55**, which was then deprotected with TBAF and oxidised to quinone **1.26** on exposure to air. The chemistry of Kim and Rychnovsky[15] was then followed to complete the synthesis of both natural products **1.1** and **1.2**.



Scheme 1.9. Completion of the total synthesis.[26]

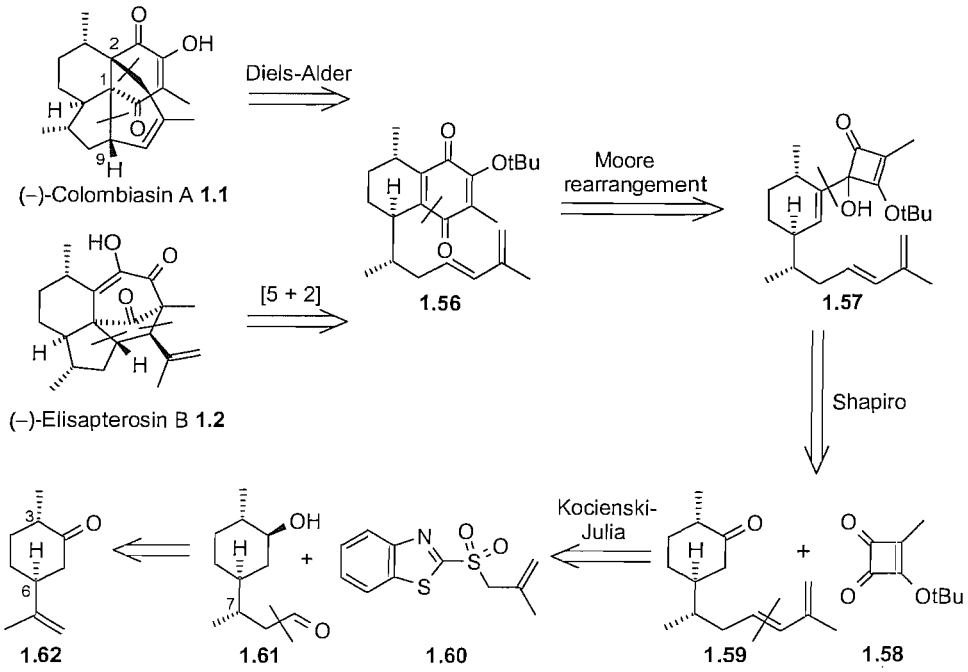
Reagents and conditions: (a) PCC, DCM, 87%; (b) 1-methylvinylmagnesium bromide, 85%; (c) Tf_2O, DTBP, 75%; (d) TBAF, THF, air, 89%; (e) 180 °C, PhMe, 88%; (f) $AlCl_3$, $PhNMe_2$, 70%; (g) $BF_3.OEt_2$, DCM, –78 °C, 51%.

The Davies synthesis of **1.1** and **1.2** is not the shortest route (14 and 13 steps respectively) but does provide the highest degree of stereocontrol over the C3, C6 and C7 stereocentres. The key step, an enantiodivergent C-H activation/Cope rearrangement, is impressive – installing 3 chiral centres in one step.[26] However, as half of the material is thrown away, the overall yield suffers (5.4% for **1.1** and 4.5% for **1.2**) meaning the approach is not as efficient as the Jacobsen synthesis.[23]

1.5 Our Approach

Our proposed synthesis of (–)-colombiasin A **1.1** includes an intramolecular Diels-Alder cycloaddition, **1.56** → **1.1**, to construct the propellane ring system. Previous approaches have found that this method provides an efficient way of accessing three (C1, C2 and C9) of the six stereogenic centres.[12,13,15] From quinone **1.56** it should be possible to access (–)-elisapterosin B **1.2** *via* a [5 + 2] cycloaddition used by Rychnovsky and Kim.[15] The use of a *tert*-butyl protective group should enable mild deprotection conditions to be used and thus prevent undesired side reactions.[12,13,28]

We propose to form quinone **1.56** from **1.57** *via* a vinylcyclobutenone rearrangement developed by Moore *et al.*[29,30] A Shapiro reaction[31-34] will allow fragments **1.58** and **1.59** to be coupled, with the diene side chain in **1.59** being introduced by means of a Kocienski-Julia olefination reaction[35-38] between sulfone **1.60** and aldehyde **1.61**. Further disconnection of **1.61** leads back to our proposed chiral starting material, (–)-dihydrocarvone **1.62**, with the C3 and C6 stereogenic centres already present (Scheme 1.10).



Scheme 1.10. Retrosynthesis of our proposed approach to (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**.

1.6 Aims and Objectives

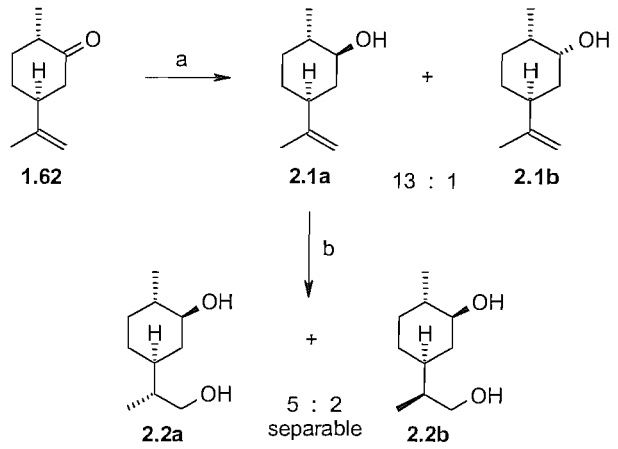
Our goal is to complete a short and efficient total synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. Key steps planned are the Moore rearrangement of **1.57** to **1.56**, and the Shapiro reaction of **1.59** to form **1.57**. Previous research at Southampton[39] has allowed some of the chemistry to be studied. This 'prior art' will be exploited in developing synthetic pathways to the intended targets.

Chapter 2 – Total Synthesis of (–)-Colombiasin A and (–)-Elisapterosin B

2.1 Installation of the C7 Stereogenic Centre

Our synthesis began with the commercially available terpene (–)-dihydrocarvone **1.62**. Using this compound from the 'chiral pool' meant that the desired C3 and C6 stereogenic centres were present from the outset. In the first phase of the synthesis, the task was to install the desired stereochemistry at C7. This had proved problematic for Nicolaou *et al.*[12,13] and gave similar difficulties in our hands.

(–)-Dihydrocarvone **1.62** was first reduced to the separable alcohols **2.1a/2.1b** using lithium aluminium hydride (Scheme 2.1). This reagent was superior to other reducing agents as it gave the highest diastereoselectivity (~13:1) and hence yield (88%) of alcohol **2.1a**. A diastereoselective hydroboration of the alkene in **2.1a** with diisopinocampheylborane,[40-43] followed by *in situ* oxidation with basic hydrogen peroxide, produced diols **2.2a/2.2b** in near quantitative yield.



Scheme 2.1. Conversion of (–)-dihydrocarvone **1.62** to diol **2.2a**.

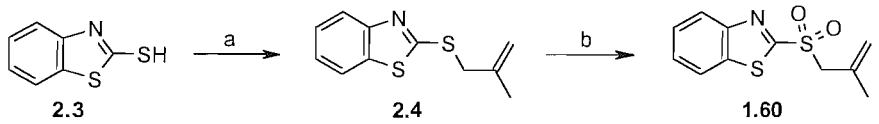
Reagents and conditions: (a) $LiAlH_4$, THF, –78 °C, 5 min, 88% of **2.1a** and 7% of **2.1b**; (b) (i) (–)-$(ipc)_2BH$, THF, 0 °C, 1 h; (ii) NaOH, H_2O_2, RT, 16 h, 98%, *d.r.* ~ 5:2 of **2.2a** : **2.2b**.

The method was originally developed by Brown *et al.* for the asymmetric hydroboration of *cis*-alkenes in high enantiomeric excess.[40] In most cases, terminal 1,1-disubstituted alkenes such as **2.1a** do not show high asymmetric induction, with 20% *ee* being typical for those transformations reported.[43] Our substrate performed a little better, with hydroboration of **2.1a** using (–)-$(ipc)_2BH$ giving a 5:2 mixture of diols **2.2a/2.2b**.

Separation of these diastereoisomers proved a major hurdle of the project as they are virtually co-polar. A solvent system of 3:1:1 ether:THF:petrol was eventually found to allow some separation by column chromatography on silica. Repeated chromatography along with fractional recrystallisation of the minor diastereoisomer **2.2b** gave the desired diol **2.2a** in an enriched form, with a 9:1 mixture of **2.2a/2.2b** being used in subsequent steps.

2.2 Synthesis of Sulfone 1.60 and Squarate 1.58

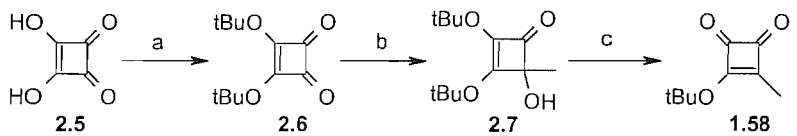
The sulfone **1.60**, for our planned Kocienski-Julia olefination reaction,[38] was prepared in two steps from 2-mercapto-benzothiazole **2.3**. A nucleophilic substitution reaction with methallyl chloride yielded benzothiazole **2.4**, which was then oxidized to the intermediate sulfone **1.60** with ammonium molybdate(VI) tetrahydrate and aqueous hydrogen peroxide (Scheme 2.2).[44]



Scheme 2.2. Synthesis of intermediate sulfone **1.60**.

Reagents and conditions: (a) (i) NaOMe, MeOH (ii) methallyl chloride, 4 h, 97%; (b) $(NH_4)_6Mo_7O_{24}.4H_2O$, aq. H_2O_2, EtOH, 0 °C, 2 h, 68%.

Cyclobutenedione **1.58** was prepared in 3 steps from commercially available squaric acid **2.5**. Firstly, **2.5** was converted to squarate ester **2.6** by refluxing in *tert*-butanol in the presence of trimethyl orthoformate.[45] Treatment of **2.6** with methyllithium next yielded **2.7** which, on exposure to acid, underwent dehydration with loss of *iso*-butene to give squarate **1.58** in good yield (Scheme 2.3).[30,46,47]

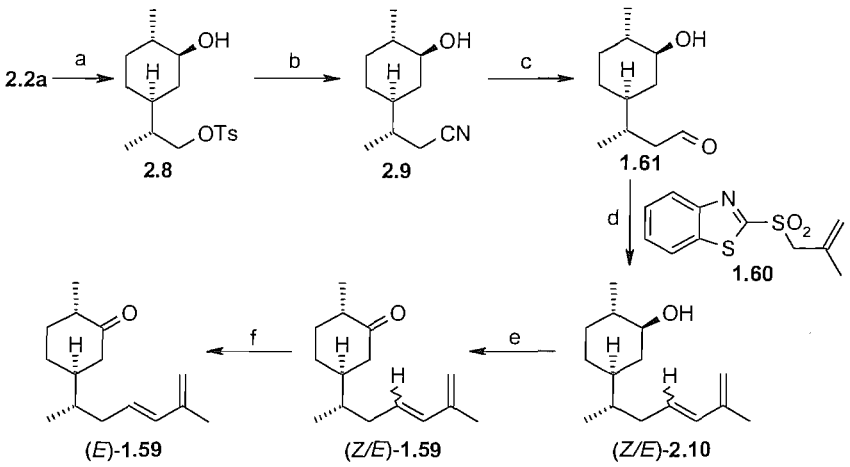


Scheme 2.3. Synthesis of intermediate squarate **1.58** from squaric acid **2.5**.

Reagents and conditions: (a) ^{t}BuOH, $(MeO)_3CH$, Δ, 1 h, 67%; (b) MeLi, THF, −78 °C, 15 min, 96%; (c) conc. HCl, DCM, 30 min, 84%.

2.3 Synthesis of Intermediate Dienone 1.59

With enriched diol **2.2a** in hand, our next task was to introduce the diene side chain and advance to **1.59**. Reaction of **2.2a** with 1 eq. of TsCl proved painfully slow (> 5 days for near completion) so a protocol was developed wherein diol **2.2a** was treated with 5 eq. of TsCl and the reaction stopped after 3 hours (Scheme 2.4). This gave tosylate **2.8** in 67% yield together with the recovered diol **2.2a** (30%) which could then be cycled through another tosylation reaction. Treatment of tosylate **2.8** with sodium cyanide in DMSO gave nitrile **2.9**, which was subsequently reduced to aldehyde **1.61** using DIBAL-H.[48]



Scheme 2.4. Synthetic pathway to key intermediate ketone (*E*)-**1.59**.

Reagents and conditions: (a) 5 eq. TsCl, Et_3N, DCM, 3 h, 67% of **2.8** and 30% **2.2a**; (b) NaCN, DMSO, 100 °C, 1 h, 93%; (c) DIBAL-H, PhMe, 0 °C, 1 h then H^+/H_2O, 76%; (d) **1.60** + **1.61**, DME, then 2 eq. NaHMDS, –60 °C → RT, 2 h, 79%, *Z*:*E* ~ 3:1; (e) $(COCl)_2$, DMSO, DCM, –78 °C, 30 min then Et_3N, 30 min, 93%; (f) I_2, DCM, 1 h, 99%.

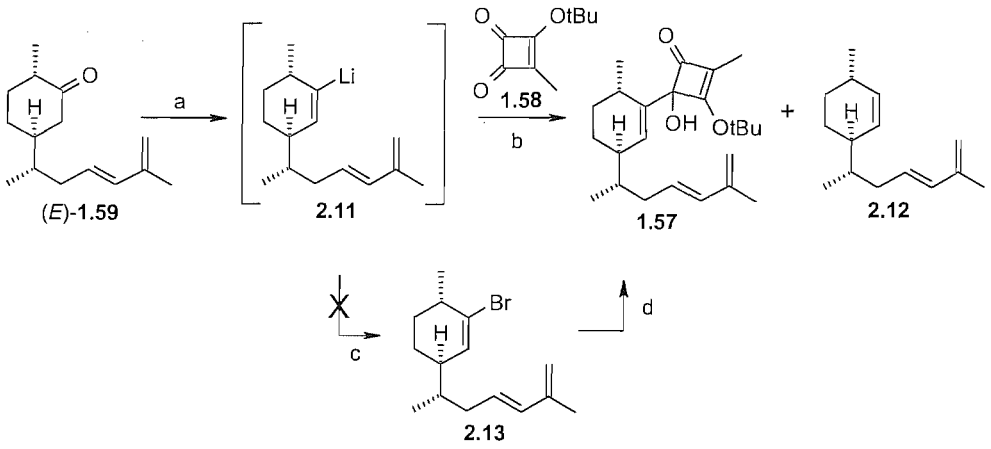
Aldehyde **1.61** was then used in a Julia olefination with sulfone **1.60**.[35] It was not necessary to protect the free hydroxyl group of **1.61** when the 'Barbier-type' conditions disclosed by Kocienski *et al.*[49] were employed, these giving an inseparable 3:1 mixture of dienes (*Z*)-**2.10** and (*E*)-**2.10** (Scheme 2.4). The high *cis* selectivity displayed in this reaction was quite unexpected as the reaction has good precedence for preferential formation of *trans* alkenes.[38]

Initially, the Dess-Martin periodinane reagent[50] was used to effect the oxidation of alcohols (*Z*)-**2.10** and (*E*)-**2.10**. Although these conditions are mild, the yield was often

compromised by the formation of by-products which appeared to form as a result of the acidic nature of the reagent. The Swern oxidation[51] proved an excellent alternative, giving access to dienones (*Z*)-**1.59** and (*E*)-**1.59** in high yield (Scheme 2.4). Treatment of the products (*Z*)-**1.59** and (*E*)-**1.59** with catalytic iodine gave the key intermediate dienone (*E*)-**1.59** with the required *trans* alkene geometry installed for the future Diels-Alder cycloaddition.

2.4 Towards (–)-Colombiasin A and (–)-Elisapterosin B - The Final Steps

Previous work[39] had found that cyclobutenone **1.57** could be formed from (*E*)-**1.59** using a Shapiro reaction.[31-34] Importantly, an inability to isolate the trisylhydrazone[52] derived from (*E*)-**1.59** led to the development of a 'one pot' procedure. Thus, dienone (*E*)-**1.59** was first treated with trisyl hydrazide[53] at RT for 2 h to form the corresponding hydrazone. The reaction was then cooled to –78 °C and 4 eq. of ^{t}BuLi added. Subsequent warming induced decomposition to vinyllithium **2.11**. Trapping this with squarate **1.58** then gave adduct **1.57** in 34% yield together with triene **2.12**. The highest yields were attained when a large excess of **1.58** was added. The resulting cyclobutenones **1.57** were formed as a 3:2 mixture of diastereoisomers (Scheme 2.5). The proton source responsible for quenching vinyllithium **2.11** to give the corresponding triene **2.12** is not known. It seems likely that the methyl group in squarate **1.58** is deprotonated by vinyllithium **2.11** as the temperature is raised to –20 °C. Attempts to improve the yield of **1.57** by trapping **2.11** with 1,2-dibromoethane[54] failed to give vinyl bromide **2.13** (Scheme 2.5).



Scheme 2.5. Shapiro reaction of dienone (*E*)-**1.59** to yield cyclobutenones **1.57**.

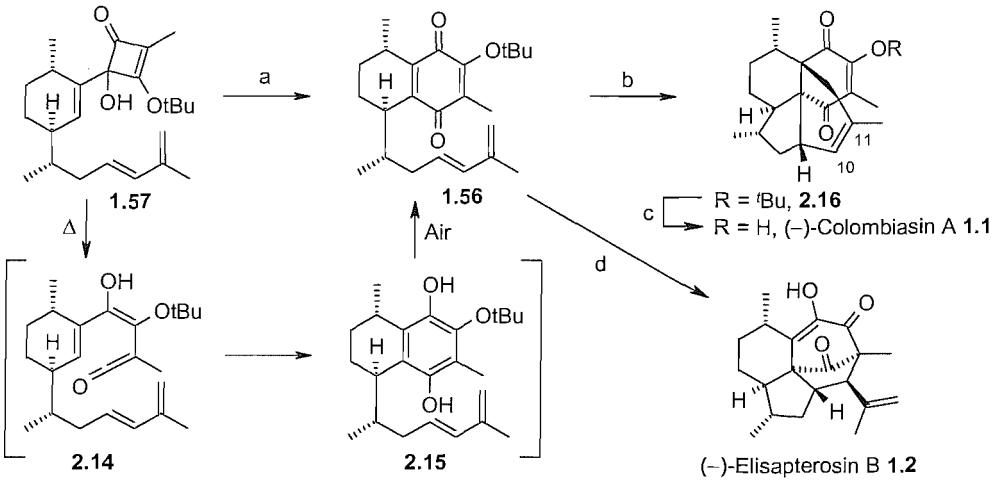
Reagents and conditions:- (a) (i) TrisylNHNH$_2$, THF, RT, 2 h; (ii) 4 eq. ^{t}BuLi, –78 °C, 2 h; (iii) warm to –20 °C, 5 min; (b) 6 eq. **1.58**, THF, –78 °C, 30 min, 34%, *d.r.* ~ 3:2; (c) BrCH$_2$CH$_2$Br, THF, –78 °C; (d) proposed: ^{t}BuLi, THF, –78 °C then **1.58**.

Despite the disappointing yield of the Shapiro reaction, our precursor now had all the carbons needed to complete a total synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. Thus, heating vinylcyclobutenones **1.57** at 110 °C in THF under microwave irradiation triggered the desired Moore rearrangement[29,30] to give hydroquinone **2.15** (*via* cycloreversion and then electrocyclisation of the resulting ketene **2.14**). After cooling to ambient temperature and stirring in air, quinone **1.56** was isolated in a satisfying 80% yield (Scheme 2.6).

Now with our key intermediate in hand we were confident of achieving the synthesis of both synthetic targets. Heating a toluene solution of quinone **1.56** in the microwave to 150 °C for 15 hours induced an intramolecular Diels-Alder cycloaddition[12,13] to form the tetracyclic colombiane skeleton of **2.16** in 61% yield (Scheme 2.6). The cascade sequence from vinylcyclobutenones **1.57** to (–)-colombiasin *tert*-butyl ether **2.16** is of particular note, as no reagents are required to enact this complex sequence of transformations.

After our success in forming **2.16**, we believed treatment with TiCl$_4$[28] would remove the *tert*-butyl protection and complete the synthesis of (–)-colombiasin A **1.1**. The reaction appeared successful, however simultaneous Markovnikov addition of HCl had occurred across the C10-11 alkene. Nicolaou *et al.*[12,13] also noted that this alkene was extremely sensitive to acidic conditions. This was a major setback. The small amount of remaining

material was exhausted and, as a result, the whole synthesis was repeated. With more (–)-colombiasin *tert*-butyl ether **2.16** now available, we treated it first with $BF_3.OEt_2$. Pleasingly, this effected removal of the *tert*-butyl protective group while leaving the sensitive C10-11 alkene intact, providing (–)-colombiasin A **1.1** in high yield (Scheme 2.6).



Scheme 2.6. The final steps – completion of the total synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**.

Reagents and conditions: (a) (i) THF, μwave, 110 °C, 30 min; (ii) air, dark, THF, RT, 16 h, 80%; (b) PhMe, μwave, dark, 150 °C, 15 h, 61%; (c) $BF_3.OEt_2$, DCM, 0 °C, 5 min, 78%; (d) 2 eq. $BF_3.OEt_2$, DCM, dark, –78 °C, 1 h, 71%.

Another pleasing result was attained when quinone **1.56** was exposed to 2 eq. of $BF_3.OEt_2$ as this induced simultaneous *tert*-butyl deprotection and the [5 + 2] cycloaddition to give (–)-elisapterosin B **1.2** in 71% yield (Scheme 2.6). Rychnovsky and Kim had required 25 eq. of $BF_3.OEt_2$ to induce the same sequence with the corresponding methyl ether **1.26**, for the reaction to occur in 41% yield (Scheme 1.5).[15] The greater lability of the *tert*-butyl ether, when compared to the methyl ether, allows use of milder conditions and an enhanced yield for the [5 + 2] cyclisation step.

2.5 Conclusions

Total syntheses of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2** were achieved in 12 and 11 steps respectively from (–)-dihydrocarvone **1.62**. A distinctive feature of our approach is the use of a Moore rearrangement to set up intramolecular [4 + 2] and [5 + 2] cycloadditions to assemble the tetracyclic carbon skeletons. The use of a *tert*-butyl ether protective group has great advantage over the methyl ether used previously by Nicolaou *et al.*,[12,13] and Rychnovsky and Kim;[15] allowing milder deprotection conditions to be used and enhanced yields of both natural products.

Our synthesis of (–)-elisapterosin B **1.2**, at 11 steps, is still the shortest to date. Jacobsen *et al.*[23] has recently equalled our effort of 12 steps for the most direct approach to (–)-colombiasin A **1.1**. The overall yield for the synthesis (2.9% for **1.1** and 4.3% for **1.2**) compares well with most routes developed thus far (Chapter 1). The efficiency suffers from modest stereoselectivity (5:2) in the hydroboration of **2.1a** to **2.2a** which sets the C7 stereogenic centre, and the low yielding Shapiro reaction. We decided to address both issues in 'second generation' syntheses of both targets.

Our approach to (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2** was recently published as a communication entitled "Total Synthesis of (–)-Colombiasin A and (–)-Elisapterosin B", Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. *Angew. Chem.*, **2005**, *117*, 1247-1248; *Angew. Chem. Int. Ed.*, **2005**, *44*, 1221-1222.

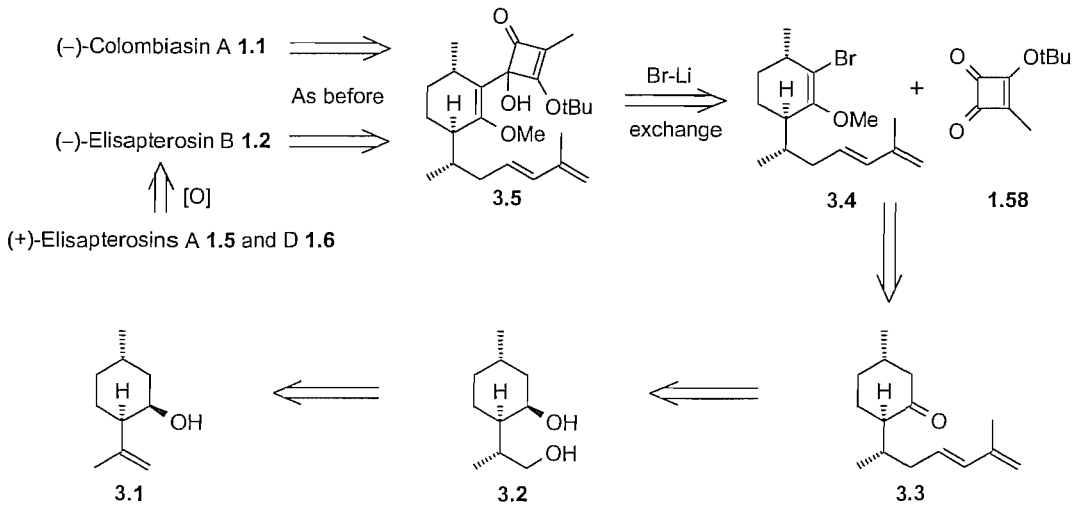
Chapter 3 – Towards 'Second Generation' Syntheses of (–)-Colombiasin A and (–)-Elisapterosin B

3.1 A New Approach

Building on our successful approach to (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2** (Chapter 2) we now considered ways of improving our synthesis. The main concerns were poor stereocontrol in setting the C7 stereogenic centre and the low yielding Shapiro reaction.

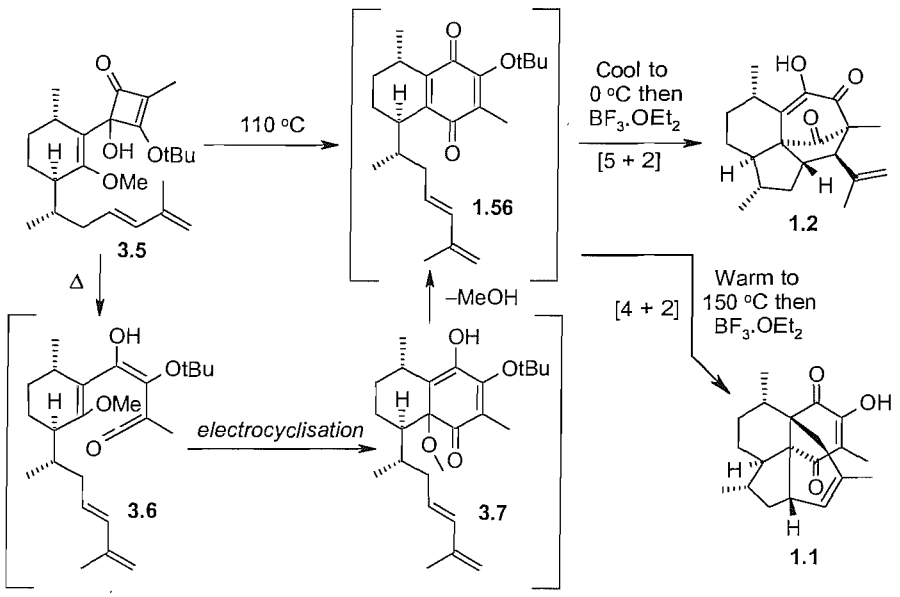
A more efficient synthetic route would allow us to make a greater quantity of (–)-elisapterosin B **1.2** which, in turn, we hoped to transform into (+)-elisapterosins A **1.5** and D **1.6** - two demanding targets yet to succumb to total synthesis.[7,10] Both are at a higher oxidation level and should be accessible by oxidation of **1.2**.

It seemed appropriate to retain the Moore rearrangement as a key step, and reasonable to examine the use of a halogen-lithium exchange reaction[33] in place of the low yielding Shapiro reaction. (–)-Neoisopulegol **3.1** was a good starting point. The molecule has the required C3 and C6 stereogenic centres in place and can be readily transformed in high yield to diol **3.2** – setting the troublesome C7 stereocentre (Scheme 3.1).[55]



Scheme 3.1. 'Second generation' retrosynthetic pathway to **1.1** and **1.2**.

The subtle inclusion of a methoxy substituent in cyclohexene **3.5** is of particular significance. Firstly, it provides us with a simple means of preparing the vinyl bromide precursor **3.4** *via* enolisation of an α-bromoketone. In addition, it should help to stabilise the troublesome vinyllithium intermediate through a Lewis acid-Lewis base interaction. Moreover, one can envision that the cascade sequence from cyclobutenone **3.5** to both natural products can be performed without interruption, cutting out two steps in our synthesis. Thus, heating **3.5** should first induce cycloreversion to the transient vinylketene **3.6** (Scheme 3.2). Spontaneous electrocyclisation to **3.7** ought then to be followed by ejection of methanol to give quinone **1.56** directly – bypassing the hydroquinone intermediate. Raising the temperature at this juncture will thus facilitate an intramolecular Diels-Alder cycloaddition giving (–)-colombiasin A **1.1** after deprotection with $BF_3.OEt_2$. Alternatively, the solution of **1.56** can be cooled before addition of $BF_3.OEt_2$ to promote simultaneous deprotection of the *tert*-butyl ether and an intramolecular [5 + 2] cycloaddition to (–)-elisapterosin B **1.2**. Such one-pot domino sequences triggered by a Moore rearrangement would complete an innovative and exciting route to both natural products.

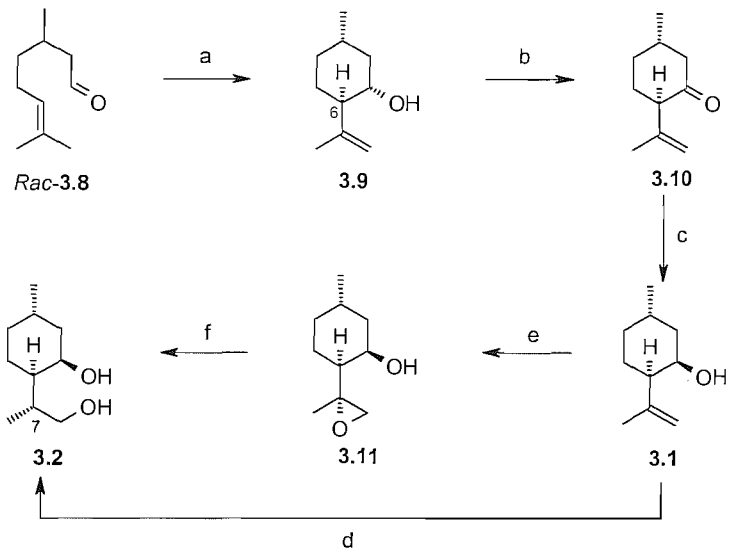


Scheme 3.2. Planned domino sequence to convert vinylcyclobutenone **3.5** to **1.1** and **1.2**.

3.2 Setting the Key C7 Stereochemistry

Our inability to control the C7 stereocentre was a major weakness of our previous approach towards (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. Schulte-Elte and Ohloff[55] reported high diastereoselectivity (*d.r.* 9:1) when hydroborating (–)-neoisopulegol **3.1**, and we planned to incorporate this into our synthesis. Although isopulegol **3.9** and neoisopulegol **3.1** can be obtained from suppliers we began our work with (±)-citronellal **3.8** – the racemate being cheap and widely available. The single enantiomer required for our synthesis is commercially available but expensive; therefore a racemic series was used while the synthesis was in development.

Treatment of (±)-citronellal **3.8** with zinc bromide provides isopulegol **3.9** *via* a carbonyl-ene reaction that shows high diastereoselectivity to install the relative C6 stereochemistry (Scheme 3.3).[56] A Jones oxidation[57] to **3.10** followed by a diastereoselective reduction with L-selectride then gave neoisopulegol **3.1**.[58] Hydroboration of **3.1** with $BH_3.SMe_2$ followed by oxidative work-up gave diol **3.2** in near quantitative yield but the diastereoselectivity displayed was poor (*d.r.* 2.5:1) and the diastereomers were completely inseparable. Similar diastereoselectivity was observed by Kocienski *et al.*[59] in a synthesis of pseudopterosin calling into question the accuracy of the report by Schulte-Elte and Ohloff.[55] Our attention thus turned to an approach to diol **3.2** by Kocienski *et al.*[59] *via* epoxide **3.11**.



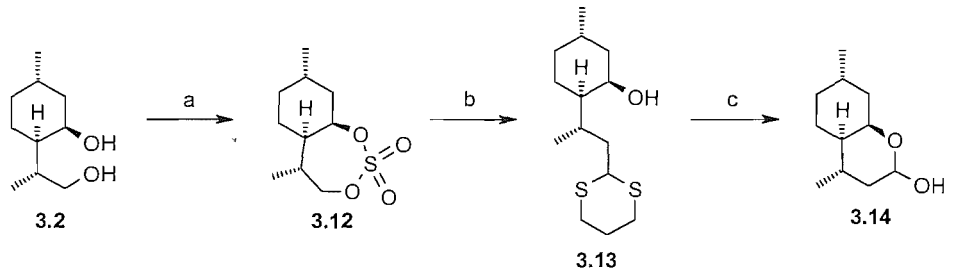
Scheme 3.3. Conversion of (±)-citronellal **3.8** to diol **3.2**.

Reagents and conditions: (a) $ZnBr_2$, PhMe, 0 °C, 90 min, 70%; (b) Jones reagent, acetone, 0 °C, 3 h, 83%; (c) L-selectride, THF, −78 °C, 30 min, 84%; (d) (i) $BH_3.SMe_2$, THF, 0 °C; (ii) H_2O_2, NaOH, RT, 1 h, 98%, *d.r.* 2.5:1; (e) $V(acac)_3$, ^tBuOOH, PhMe, RT, 3 h, 80%, *d.r.* 15:1; (f) $Na(CN)BH_3$, $BF_3.OEt_2$, THF, RT, 4 h, 84%.

Although adding an extra step to our synthesis, this method proved excellent at establishing the C7 stereocentre. The vanadium directed epoxidation of **3.1** is controlled by the neighbouring hydroxyl group, meaning the diastereoselectivity is high (15:1) in the formation of epoxy alcohol **3.11**.[58] The minor diastereoisomer was easily removed by chromatography so that **3.11** could be isolated in 80% yield. Regioselective ring opening of epoxide **3.11**, by treatment with sodium cyanoborohydride in the presence of $BF_3.OEt_2$,[60] occurs with complete inversion of configuration to give diol **3.2** as a single diastereoisomer with the desired C7 stereochemistry installed (Scheme 3.3).

3.3 Installation of the Diene Side Chain

Diol **3.2** was then converted to cyclic sulfate **3.12** by reaction with thionyl chloride followed by oxidation (Scheme 3.4).[61,62] Cyclic sulfates show similar reactivity towards nucleophiles as epoxides but have so far been little used in total synthesis.[63] Disappointingly, the one carbon homologation with cyanide that we had employed in our previous approach failed, with no reaction occurring under a variety of conditions. Reaction with lithiated 1,3-dithiane was successful in opening cyclic sulfate **3.12** by the course of lowest steric demand to give **3.13** in 77% yield after hydrolysis of the resulting sulfate ester.[64] With the chain now extended, dithiane **3.13** was unmasked using a classical mercury(II) mediated hydrolysis[65,66] to yield lactols **3.14**.

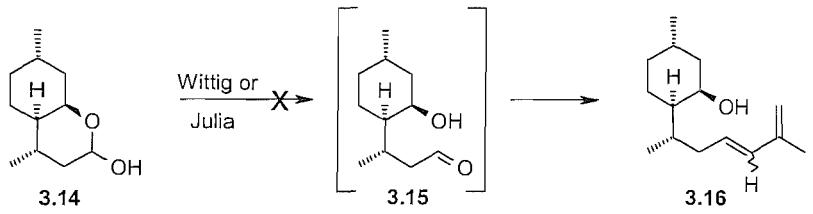


3.2 **3.12** **3.13** **3.14**

Scheme 3.4. Synthesis of lactols **3.14** *via* cyclic sulfate **3.12**.

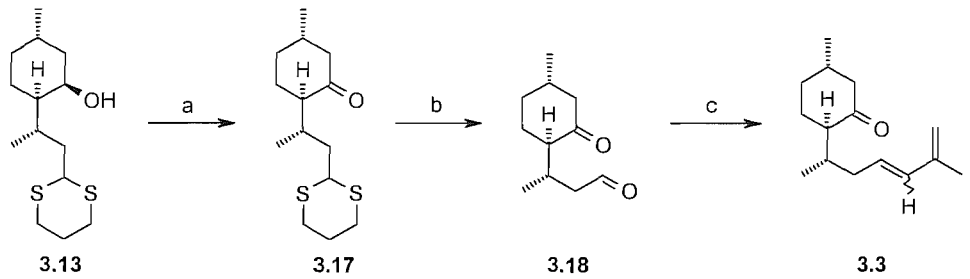
Reagents and conditions:- (a) (i) $SOCl_2$, Et_3N, DCM, 0 °C, 5 min (ii) $NaIO_4$, cat. $RuCl_3.H_2O$, MeCN, H_2O, 1 h, 89%; (b) (i) 1,3-dithiane, ^nBuLi, THF, −78 °C → RT, 1 h; (ii) **3.12**, THF, −78 °C → RT, 90 min; (iii) H_2SO_4, 1,4-dioxane, Δ, 1 h, 77%; (c) HgO, $HgCl_2$, MeCN, H_2O, Δ, 1 h, 80%, *d.r.* 11:3.

With lactol **3.14** in hand, we now attempted to install the diene side chain. Subjecting **3.14** to Wittig and Kocienski-Julia olefination reactions under a variety of conditions failed to give dienol **3.16**, returning only lactol **3.14** (Scheme 3.5). Even when a large excess of base was used, conditions that should promote ring opening to the hydroxy aldehyde **3.15**, only recovered lactol was obtained. It appeared that lactol **3.14** was too stable and would not open to reveal the aldehyde needed for the olefination chemistry to occur.



Scheme 3.5. Failure to convert lactols **3.14** to dienol **3.16**.

To overcome this problem, alcohol **3.13** was first oxidised to ketone **3.17** using the Dess-Martin periodinane reagent (Scheme 3.6).[50] Deprotection of the dithiane now gave dicarbonyl **3.18**, allowing us to exploit the higher reactivity of aldehydes relative to ketones in Wittig reactions. Although some of the desired dienone **3.3** was isolated, the reaction produced a myriad of other products and the low yield meant that this was not a viable synthetic route.

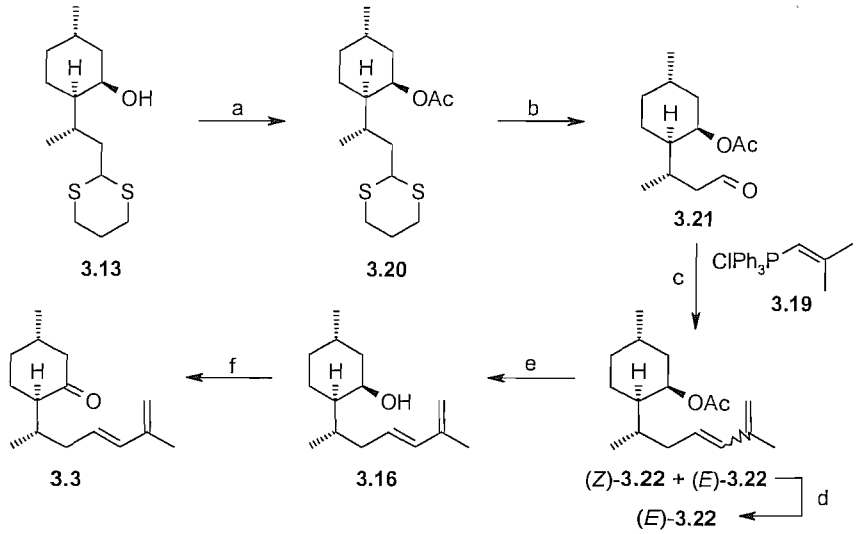


Scheme 3.6. Formation of dienone **3.3** *via* dicarbonyl **3.18**.

Reagents and conditions:- (a) DMP, DCM, 0 °C to RT, 4 h, 61%; (b) HgO, $HgCl_2$, MeCN, H_2O, Δ, 45 min; (c) 2-Methyl-1-propenylphosphonium chloride **3.19**, ^{n}BuLi, THF, 0 °C, 1 h then **3.18**, Δ, 5 h, 30% over 2 steps from **3.17**, *E*:*Z* ~ 2:1.

Although it would lengthen our route to dienone **3.3** by two steps, protection of alcohol **3.13** seemed the logical solution to our problems. This would allow the dithiane to be unmasked to an aldehyde free of other reactive functional groups, and then used to install the diene side chain more efficiently. To that end, we found that protection of **3.13** as the corresponding acetate **3.20** worked well (Scheme 3.7).[67] Deprotection of the dithiane gave aldehyde **3.21** and a high yielding Wittig reaction with the ylide derived from phosphonium salt **3.19** gave diene **3.22** (*E*:*Z* ~ 2:1). Of note from a practical perspective is that although aldehyde **3.21** was rapidly consumed in the Wittig reaction, diene **3.22** could only be isolated in high yield if the reaction was heated at reflux for 4

h. This suggests that a stable intermediate betaine is formed which requires sufficient energy in order for it to collapse to the reaction products.[12,13]



Scheme 3.7. A high yielding synthesis of dienone **3.3**.

Reagents and conditions:- (a) Ac_2O, py., 64 h, 99%; (b) MeI, $CaCO_3$, MeCN, H_2O, 16 h, 90%; (c) (i) **3.19**, KO^{t}Bu, THF, 0 °C, 1 h; (ii) aldehyde **3.21**, RT, 1 h then Δ, 4 h, 93%, *E*:*Z* ~ 2:1; (d), I_2, DCM, 3 h, quant.; (e) LiOH, MeOH, Δ, 16 h, 93%; (f) DMP, DCM, 0 °C, 2 h, 94%.

Dienes *(E)*-**3.22** and *(Z)*-**3.22** were then isomerised with catalytic iodine to give *(E)*-**3.22** exclusively (Scheme 3.7). The acetate protective group was removed by treatment with LiOH to give alcohol **3.16**, which was subsequently oxidized with the Dess-Martin periodinane reagent to yield key intermediate dienone **3.3**. Although a protection strategy was required, the overall yield for this sequence was very high – dithiane **3.13** being converted to dienone **3.3** in 6 steps and 72% overall yield.

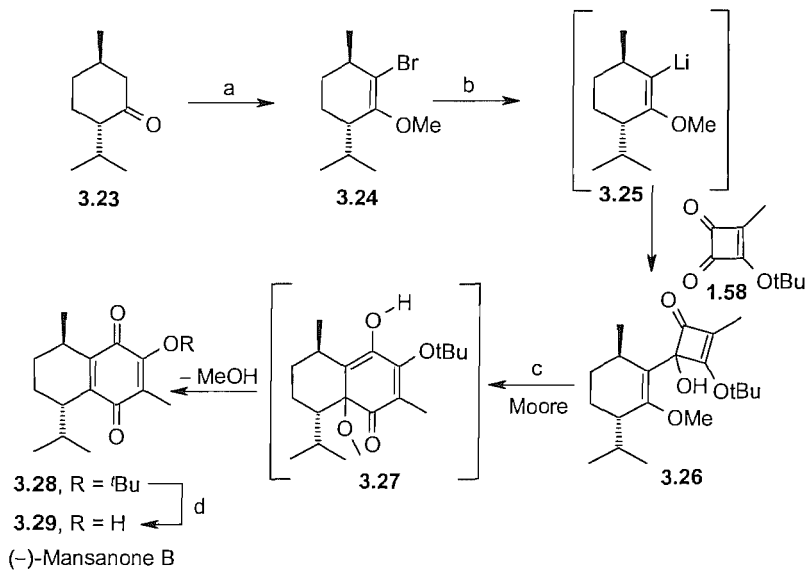
The synthesis of dienone **3.3** is significantly longer (11 steps from isopulegol **3.9** vs 8 steps) than our route to dienone **1.59** described in Chapter 2. Despite this, some significant improvements have been made. Stereocontrol at C7 has been increased from *d.r.* 5:2 to 15:1 by using a directed epoxidation to form **3.11**. The fact that the diastereoisomers are easily separable means time and money are saved as we can avoid repetitious chromatography. The reactions are also more robust and higher yielding meaning the synthesis has greater overall efficiency (28% overall yield vs 21%).

3.4 Model Study

3.4.1 Background

Alongside the development of a synthesis of dienone **3.3**, the planned final steps of the synthesis were modelled. An excellent model compound for dienone **3.3** is (–)-menthone **3.23**. It is available commercially and only differs in structure by an isopropyl group being in place of the diene side chain.

Our plan was to convert (–)-menthone **3.23** to the bromo-enol ether **3.24** from which the key carbon-carbon bond forming reactions could be attempted (Scheme 3.8). A halogen-lithium exchange reaction was to be used to form vinyllithium **3.25** for addition to squarate **1.58**. The resultant vinylcyclobutenone **3.26** would then be heated to induce a Moore rearrangement to **3.27** with concomitant elimination of methanol to yield quinone **3.28**. Removal of the *tert*-butyl group would complete a short synthesis of the sesquiterpene (–)-mansanone B **3.29**,[68] before transferring this chemistry to dienone **3.3** and the synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**.

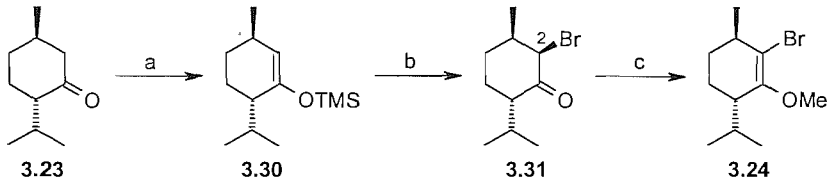


Scheme 3.8. Proposed synthesis of (–)-mansanone B **3.29**.

Proposed reagents and conditions: (a) (i) LiTMP, THF, –78 °C then NBS; (ii) LiTMP, THF, –78 °C then Me_3OBF_4; (b) ^tBuLi, THF, –78 °C; (c) THF, Δ; (d) $BF_3.OEt_2$, DCM, 0 °C.

3.4.2 Synthesis of Vinylcyclobutenone 3.26

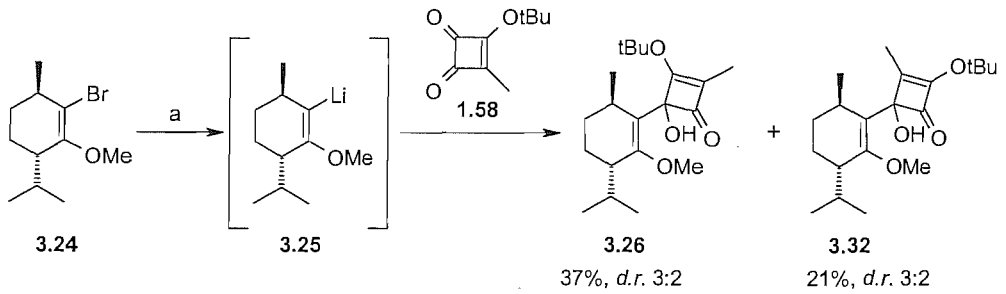
Attempts to convert (–)-menthone **3.23** to bromoketone **3.31** directly failed, so a method used by Corey *et al.* was employed.[69] Kinetic deprotonation of (–)-menthone **3.23** with LiTMP and protection of the resulting enolate with TMSCl gave silyl enol ether **3.30**,[70] which was brominated with NBS to give **3.31** in high yield as a single diastereoisomer (Scheme 3.9). A second deprotonation with LiTMP selectively removed the α-proton at C2 to allow *O*-alkylation of the enolate with Meerwein's salt[71] to give enol ether **3.24**.



Scheme 3.9. Synthesis of model enol ether **3.24**.

Reagents and conditions: (a) LiTMP, THF, –78 °C then TMSCl, 97%; (b) NBS, $NaHCO_3$, THF, –78 °C, 96%; (c) LiTMP, THF, –78 °C then Me_3OBF_4, 64%.

We were now in a position to examine our key halogen-lithium exchange reaction. Unexpectedly, this performed little better than the Shapiro reaction used previously. Vinyllithium **3.25** was formed readily on treatment of **3.24** with 2 eq. of ^{t}BuLi, but on addition of squarate **1.58** a complex product mixture was formed. The desired vinylcyclobutenone **3.26** was isolated in 37% yield (*d.r.* ~ 3:2) along with 21% of vinylcyclobutenone **3.32** - this product resulting from nucleophilic addition to the carbonyl of the vinylogous ester (Scheme 3.10)! This was a surprising result as addition to this carbonyl has never been observed previously by us or others. A significant amount of de-brominated starting material was also observed, believed to be from deprotonation of the methyl group of squarate **1.58** (small quantities of several squarate dimers were observed). Of concern was that vinyllithium **3.25**, with the methoxy group on the distal carbon, was now more sterically encumbered and was therefore behaving as a base rather than a nucleophile.



3.24 3.25 3.26 3.32

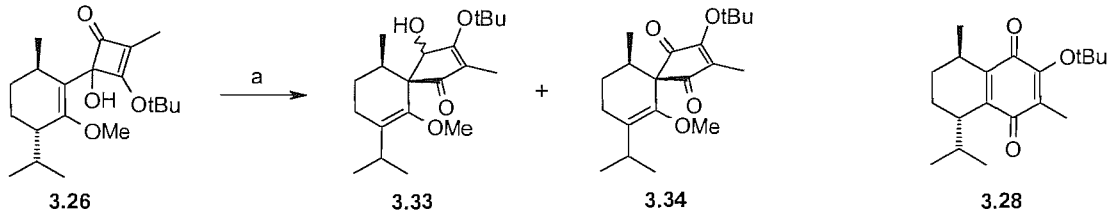
37%, *d.r.* 3:2 21%, *d.r.* 3:2

Scheme 3.10. Formation of vinyl lithium **3.25** and addition to squarate **1.58**.

Reagents and conditions: (a) 2 eq. ^{t}BuLi, THF, –78 °C, 15 min then **1.58**, THF, –78 °C, 30 min.

3.4.3 A New Rearrangement

Despite the low yield we did have key intermediate **3.26** in sufficient quantity to conduct our model study – the cascade sequence based on a Moore rearrangement. Unexpectedly, heating a THF solution of **3.26** at 120 °C for 30 min by microwave irradiation failed to yield the anticipated quinone **3.28**, giving instead a complex product mixture from which two diastereoisomers of spirocycle **3.33** and enedione **3.34** were isolated (Scheme 3.11).

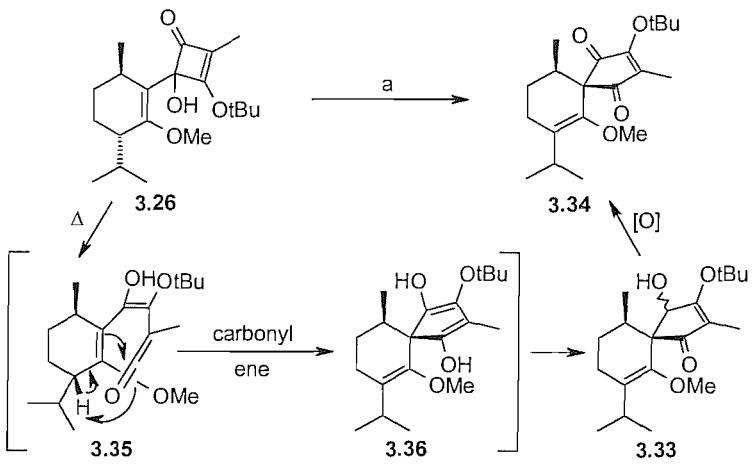


3.26 3.33 3.34 3.28

Scheme 3.11. Thermolysis of vinylcyclobutenone **3.26**.

Reagents and conditions: (a) THF, μwave, 120 °C, 30 min.

Further experimentation showed that enedione **3.34** was an artefact derived by aerial oxidation of **3.33**, and that it could be produced in 75% yield from **3.26** by oxidation of the crude product mixture with the Dess-Martin periodinane reagent.[50] Of note was that spirocycle **3.34** was formed as a single diastereoisomer, suggesting that rearrangement occurs by an initial cycloreversion to ketene **3.35**, which in turn induces a carbonyl-ene reaction to spirocycle **3.36** and tautomerism to **3.33** (Scheme 3.12).[72]

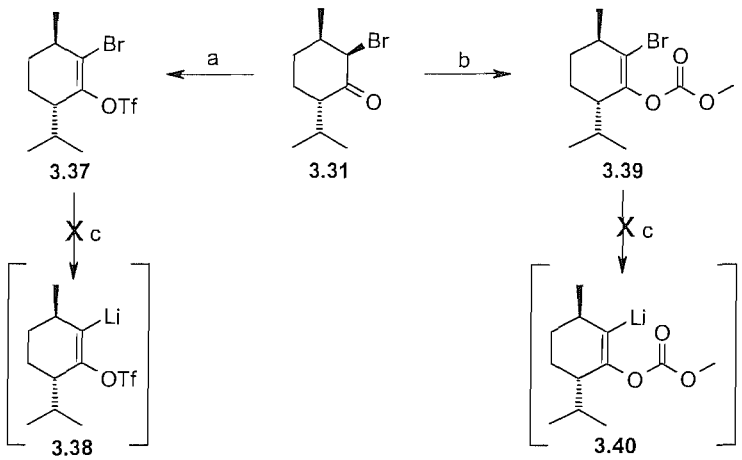


Scheme 3.12. Thermal rearrangement of cyclobutenone **3.26** to spirocycle **3.34** and proposed mechanistic course.

Reagents and conditions: (a) (i) THF, μwave, 120 °C, 30 min; (ii) DMP, DCM, 0 °C, 30 min, 75%.

The discovery that thermolysis of cyclobutenone **3.26** gave spirocycle **3.34** and not the desired quinone **3.28** was a huge blow in our efforts to develop the 'second generation' synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. The effect of replacing the hydrogen atom on the alkene (cf. vinylcyclobutenone **1.57**, Scheme 2.6) with a methoxy group, as in **3.26**, was to completely shut down the Moore rearrangement pathway in favour of the carbonyl-ene reaction. However, as rearrangements of this type have not been reported previously we felt that this novel reaction was worthy of further investigation (see Chapter 4).

Unclear as to the origin of the dichotomy, we decided to examine alternative enolate protecting groups. To that end bromoketone **3.31** was converted to enol triflate **3.37** by quenching the enolate with triflic anhydride (Scheme 3.13) - the idea being that the vinyltriflate would have different electronic characteristics compared to the methyl vinyl ether and thus may promote the Moore rearrangement over the carbonyl-ene pathway. However, when enol triflate **3.37** was treated with ^{t}BuLi the resultant vinyllithium **3.38** was incredibly unstable and decomposed rapidly to a myriad of products. Similarly, though we were able to prepare enol carbonate **3.39** in high yield, halogen-lithium exchange again led to rapid decomposition (Scheme 3.13). Other reactions to protect the enolate of **3.31** (thus altering the alkene electronics) all failed and this approach was abandoned.



Scheme 3.13. Failed attempts to form vinyllithiums **3.38** and **3.40**.

Reagents and conditions: (a) LiTMP, THF, –78 °C, 1 h then Tf_2O, 45 min, 49%; (b) LiTMP, THF, –78 °C, 1 h then $MeCO_2Cl$, warm to RT, 1 h, 71%; (c) ^{t}BuLi, THF, –78 °C.

3.5 Conclusions and Further Work

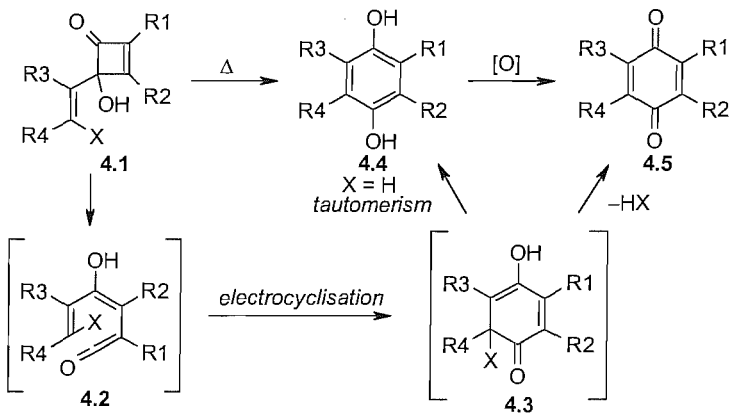
An efficient synthesis of dienone **3.3**, a key intermediate towards a 'second generation' synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**, has been completed. Model studies on the planned 'endgame' uncovered a new thermal rearrangement of vinylcyclobutenones **3.26**, leading to spirocycles. This result thwarted our new approach to (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. That said, it also provided us with an opportunity to develop a new rearrangement of vinylcyclobutenones leading to spirocyclic products.

Chapter 4 – Novel Cyclobutenone Rearrangements

4.1 Background

The thermal rearrangement of vinylcyclobutenones **4.1** has been well studied in the past two decades, most notably by the teams of Moore and Liebeskind.[29,30,73-76] In general, heating a vinylcyclobutenone **4.1** induces cycloreversion to ketene **4.2** followed by electrocyclisation to **4.3** (Scheme 4.1). In all cases reported to date, the vinyl appendage carries only one substituent on the distal carbon (X = H) so tautomerism swiftly gives hydroquinone **4.4**. Oxidation to quinones **4.5** by the action of air or CAN usually follows.

The method has seen application in total synthesis[29,77-79] and has been extended to various aryl- and heteroaryl-cyclobutenones.[80-84] Surprisingly, the effect of adding a second substituent X to the distal carbon of the vinyl appendage has never been investigated. As noted in Chapter 3, we thought that the inclusion of a leaving group (e.g. X = OMe) might promote elimination of HX from **4.3** to give quinone **4.5** directly. In the event a carbonyl-ene reaction was found to outpace the desired electrocyclisation pathway leading instead to a spirocycle.

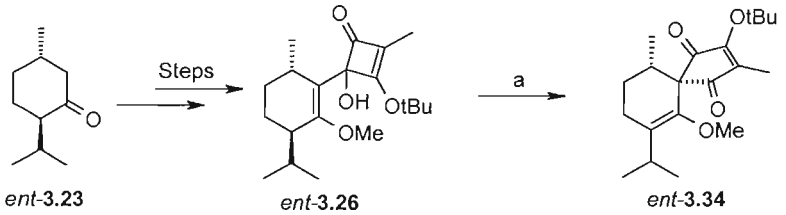


Scheme 4.1. The Moore rearrangement and our planned route to quinones.

Our discovery of a new vinylcyclobutenone rearrangement (Chapter 3, **3.26** → **3.34**) raised questions as to those factors responsible for promoting a carbonyl-ene pathway over the usual Moore rearrangement sequence. We also wanted to ascertain whether the reaction was general. To that end, our initial aim was to prepare a series of related enol ethers to **3.26** and examine their behaviour on thermolysis.

4.2 Thermal Rearrangement of (Alkoxyvinyl)cyclobutenones (X = OMe)

First, vinylcyclobutenone *ent*-**3.26** was prepared from (+)-menthone *ent*-**3.23** using the sequence described in Chapter 3 (Schemes 3.9 and 3.10). Following thermolysis of *ent*-**3.26** and oxidation, the enantiomeric spirocyclic dione *ent*-**3.34** was given in 72% yield.



Scheme 4.2. Thermal rearrangement of *ent*-**3.26** to *ent*-**3.34**.

Reagents and conditions: (a) (i) THF, μwave, 120 °C, 30 min; (ii) DMP, DCM, 0 °C, 30 min, 72%.

Spirocycle *ent*-**3.34** was highly crystalline, allowing us to prove its structure and stereochemistry by way of X-ray crystallographic analysis (Figure 4.1). Pleasingly, the stereochemistry observed was consistent with our proposed mechanism involving a carbonyl-ene reaction (Scheme 3.12). While a non-concerted addition of the nucleophilic enol ether to the ketene carbonyl is also plausible, it is hard to rationalise the stereochemical course of the reaction in that case.

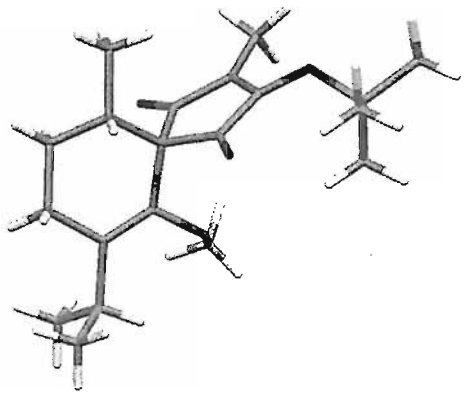
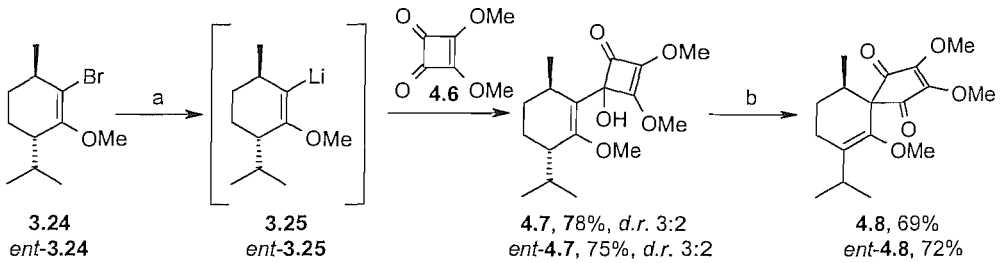


Figure 4.1. X-Ray crystal structure of *ent*-**3.34**.

Coupling the vinyllithium derived from **3.24** and *ent*-**3.24** with dimethyl squarate **4.6**[45] provided two further substrates for our study (Scheme 4.3). These reactions gave vinylcyclobutenones **4.7** and *ent*-**4.7**, which on heating and oxidation with DMP yielded spirocycles **4.8** and *ent*-**4.8** in comparable yields (69% and 72% respectively).

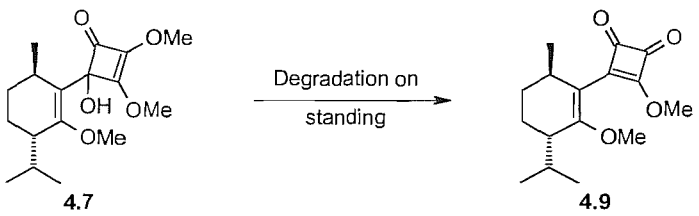


3.24 *ent*-3.24 | 3.25 *ent*-3.25 | **4.7**, 78%, *d.r.* 3:2 *ent*-**4.7**, 75%, *d.r.* 3:2 | **4.8**, 69% *ent*-**4.8**, 72%

Scheme 4.3. Thermolysis of vinylcyclobutenones **4.7** to spirocycle **4.8**.

Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C, 10 min then **4.6**, 1 h; (b) (i) THF, μwave, 120 °C, 30 min; (ii) DMP, DCM, 0 °C, 1 h.

The change of substituent on the cyclobutenone had no effect on the course of the reaction with the carbonyl-ene pathway again dominating. The switch to using dimethyl squarate **4.6** removed the complication associated with deprotonation and the regioselectivity of organolithium addition (Scheme 3.10, Chapter 3 and Chapter 5). Yields attained in the halogen-lithium exchange reaction were as a consequence, greatly improved. The only negative point was that cyclobutenones such as **4.7** proved more sensitive due to the higher electron-donating properties of the methoxy substituents. If left standing in air for short periods of time, these cyclobutenones (e.g. **4.7**) degraded to a cyclobutendione (e.g. **4.9**) with loss of methanol (Scheme 4.4). Consequently, it was generally beneficial to take these materials through to the thermolysis stage as crude product mixtures.

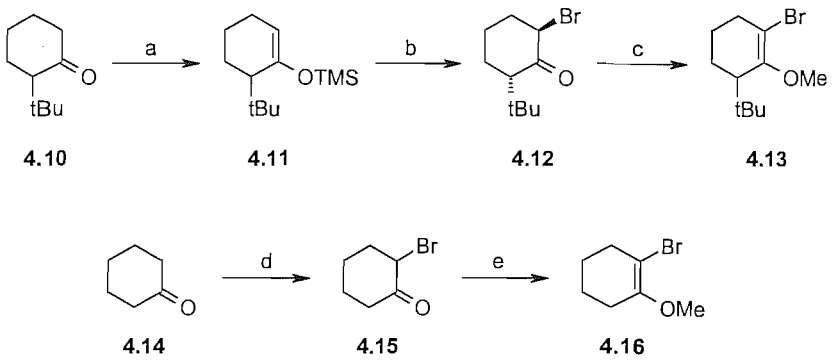


4.7 | **4.9**

Scheme 4.4. Degradation of cyclobutenone **4.7** to cyclobutendione **4.9**.

Access to precursors for our study was a major burden as tetra-substituted double bonds are notoriously difficult to make. In particular, the brominated-enol ethers we needed have seldom been reported in the literature. Enol ether **4.13** could be prepared from 2-*tert*-butylcyclohexanone **4.10** using the chemistry developed previously (Scheme 4.5). Regioselective enolate formation gives access to silyl enol ether **4.11**, which can then be brominated to give **4.12** in good yield. A second deprotonation followed by quenching with Meerwein's salt yields enol ether **4.13**. In a similar manner enol ether **4.16** was

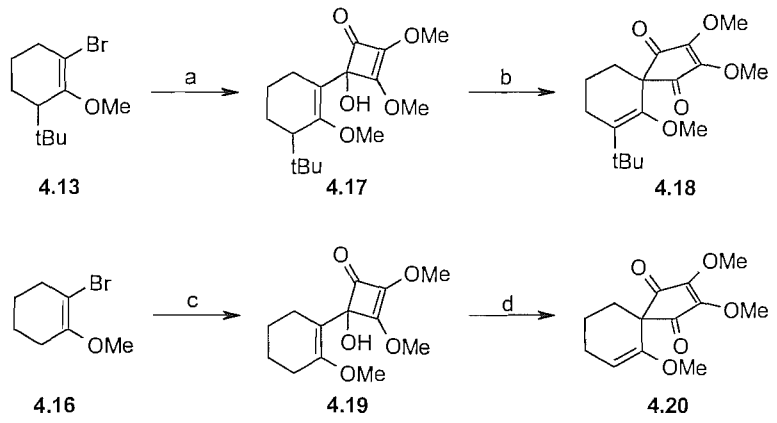
prepared from cyclohexanone **4.14** *via* bromoketone **4.15** (Scheme 4.5). In this case, however, the absence of a bulky α-substituent reduced regioselectivity in the second deprotonation with a consequent impact on the overall yield.



Scheme 4.5. Synthesis of enol ethers **4.13** and **4.16**.

Reagents and conditions: (a) LiTMP, THF, –78 °C then TMSCl, 87%; (b) NBS, $NaHCO_3$, THF, –78 °C, 92%; (c) LiTMP, THF, –78 °C then Me_3OBF_4, 42%; (d) NBS, NH_4OAc, Et_2O, 83%; (e) LiTMP, THF, –78 °C then Me_3OBF_4, 13%.

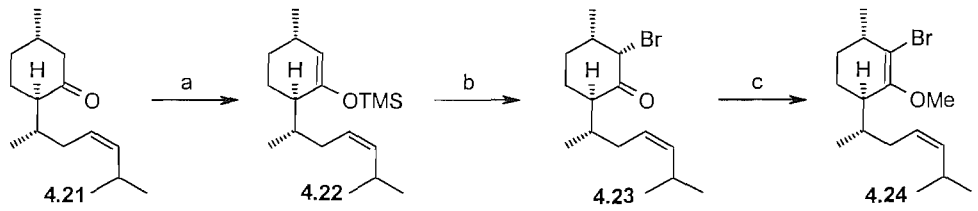
Both enol ethers were subjected to halogen-lithium exchange and reacted with dimethyl squarate **4.6**. On heating to 120 °C by microwave irradiation, the vinylcyclobutenones (**4.17** and **4.19**) were smoothly transformed into a spiro[4.5]deca-2,6-dien-1,4-dione (**4.18** and **4.20**) following oxidation with the Dess-Martin periodinane reagent (Scheme 4.6).[50]



Scheme 4.6. Thermal rearrangement of (alkoxyvinyl)cyclobutenones leading to spirocycles.

Reagents and conditions: (a) ^{t}BuLi, THF, −78 °C, 15 min then **4.6**, 1 h, 89%; (b) (i) THF, μwave, 120 °C, 30 min; (ii) DMP, DCM, 0 °C, 30 min, 61%; (c) ^{t}BuLi, THF, −78 °C, 15 min then **4.6**, 45 min, 42%; (b) (i) THF, μwave, 120 °C, 30 min; (ii) DMP, DCM, 0 °C, 30 min, 60%.

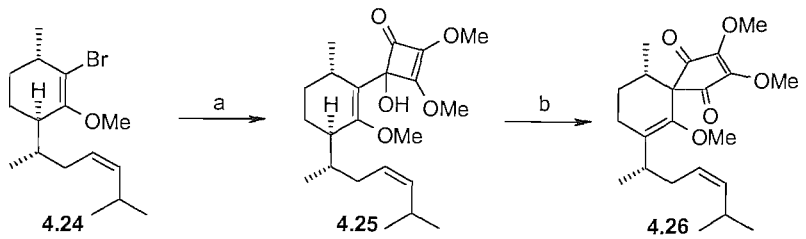
Ketone **4.21** (see Chapter 5 for its synthesis) was also a good precursor and was converted to enol ether **4.24** in good overall yield *via* the 3 step sequence used previously (Scheme 4.7).



Scheme 4.7. Conversion of ketone **4.21** to enol ether **4.24**.

Reagents and conditions: (a) LiTMP, THF, −78 °C, 1 h then TMSCl, RT, 30 min, 93%; (b) NBS, $NaHCO_3$, THF, −78 °C, 1 h, 96%; (c) LiTMP, THF, −78 °C, 1 h then Me_3OBF_4, RT, 16 h, 80%.

Treatment with ^{t}BuLi gave the intermediate vinyllithium which was reacted with dimethyl squarate **4.6** to yield vinylcyclobutenones **4.25** (Scheme 4.8). After thermolysis and oxidation with DMP, spirocycle **4.26** was isolated in 73% yield.



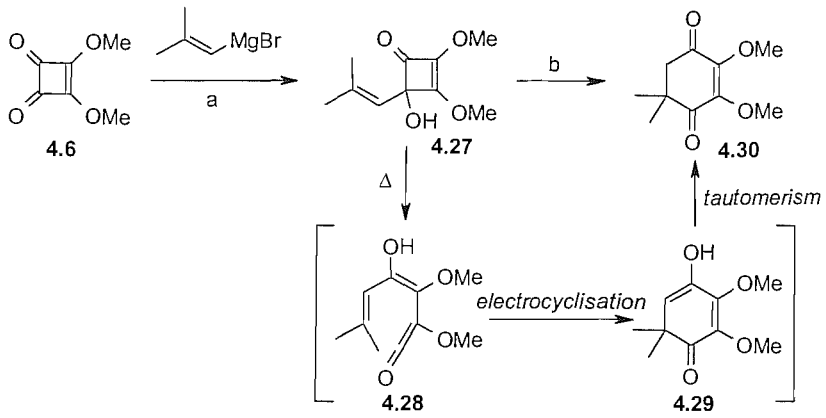
Scheme 4.8. Thermal rearrangement of vinylcyclobutenone **4.25** to spirocycle **4.26**.

Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C, 30 min then **4.6**, 30 min, 67%, *d.r.* ~ 3:2; (b) (i) THF, μwave, 120 °C, 30 min; (ii) DMP, DCM, 0 °C, 30 min, 73%.

The aforementioned examples provided clear evidence that the carbonyl-ene pathway predominates when the vinylcyclobutenone bears a methoxy substituent on the distal carbon of the vinyl appendage. Thus, our next aim was to prepare a series of vinylcyclobutenones that had two organyl substituents on the distal carbon of the vinyl group, allowing us to ascertain whether the course of a vinylcyclobutenone rearrangement was determined by electronic or steric factors.

4.3 Thermal Rearrangements of (Alkylvinyl)cyclobutenones (X = alkyl)

An obvious starting point was addition of 2-methyl-1-propenylmagnesium bromide to dimethyl squarate **4.6** giving a vinylcyclobutenone **4.27** with two alkyl substituents (methyl groups) on the distal carbon of the vinyl appendage. On heating the only product identified was cyclohex-2-en-1,4-dione **4.30**, implicating a mechanistic pathway akin to the Moore rearrangement. Thus, the initial cycloreversion of **4.27** to ketene **4.28** is followed by electrocyclisation to enol **4.29**. At this point, aromatisation is blocked by the presence of the *gem*-dimethyl group, so the system tautomerises to give enedione **4.30** (Scheme 4.9).

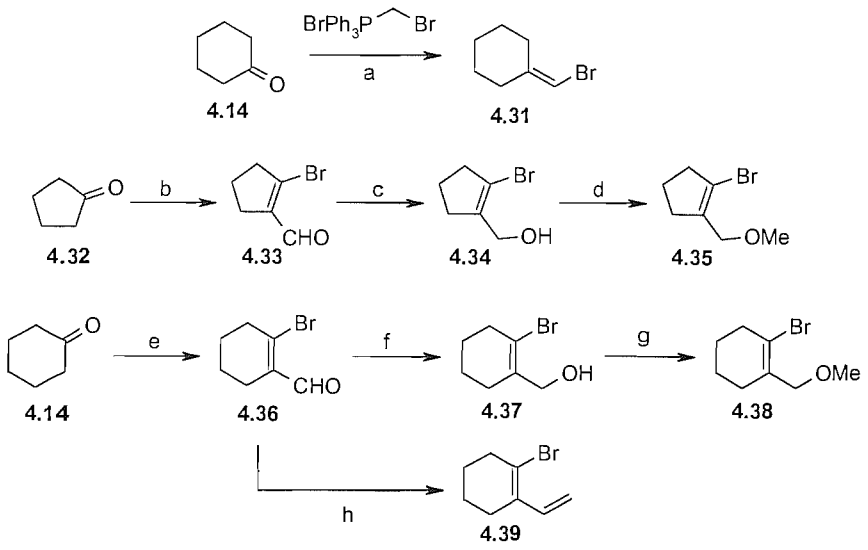


Scheme 4.9. Thermal rearrangement vinylcyclobutenone **4.27** to enedione **4.30**.

Reagents and conditions: (a) THF, –78 °C, 1 h, 42%; (b) THF, μwave, 120 °C, 30 min, 73%.

Although Moore and Liebeskind have studied rearrangements of vinylcyclobutenones for the past two decades, this very simple experiment had not been reported. In fact no vinylcyclobutenone rearrangements of this type have been published making it another novel reaction pathway. Importantly, the aforementioned experiment showed that the course of the rearrangement was determined by electronic factors rather than sterics.

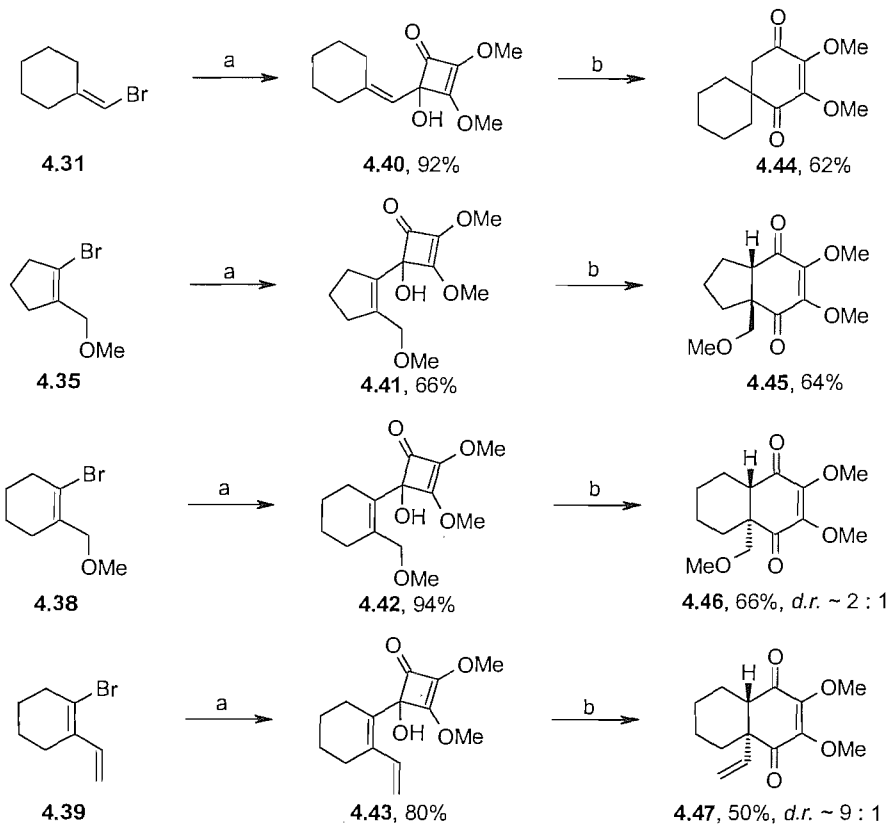
To further develop this new rearrangement we next prepared a series of vinyl bromides (Scheme 4.10). Tri-substituted alkene **4.31** was made by a Wittig reaction with cyclohexanone **4.14**.[85] Tetra-substituted alkene **4.35** was prepared from cyclopentanone **4.32** *via* a 3 step sequence involving a modified Vilsmeier reaction to give **4.33**, reduction to **4.34** and methyl protection to yield **4.35**.[86] The analogous cyclohexene **4.38** was accessed using the same sequence from cyclohexanone **4.14**. This route additionally gave access to vinyl bromide **4.39** by subjecting bromo-aldehyde **4.36** to a Wittig reaction with methyltriphenylphosphonium bromide.[87]



Scheme 4.10. Synthesis of four substituted vinyl bromides **4.31**, **4.35**, **4.38** and **4.39**.

Reagents and conditions: (a) KO^{t}Bu, THF, 16 h, 55%; (b) DMF, PBr_3, $CHCl_3$, 0 °C, 20 min then **4.32**, Δ, 2 h, 47%; (c) $NaBH_4$, MeOH, 1 h, 97%; (d) NaH, MeI, THF, 2 h, 84%; (e) DMF, PBr_3, $CHCl_3$, 0 °C, 30 min then **4.14**, Δ, 2 h, 62%; (f) $NaBH_4$, MeOH, 1 h, 96%; (g) NaH, MeI, THF, 2 h, 97%; (h) $MePPh_3Br$, KO^{t}Bu, THF, 30 min then **4.36**, Δ, 14 h, 75%.

All four vinyl bromides were treated with ^{t}BuLi to give the corresponding vinyllithium which was then reacted with dimethyl squarate **4.6**. In each case thermolysis of the vinylcyclobutendiones **4.40–4.43** produced a cyclohex-2-en-1,4-dione **4.44–4.47** (Scheme 4.11), demonstrating that the electrocyclisation pathway is dominant over the carbonyl-ene reaction in circumstances where the distal carbon of the vinyl group carries two organyl substituents.



Scheme 4.11. Rearrangements leading to cyclohex-2-en-1,4-diones **4.44–4.47**.

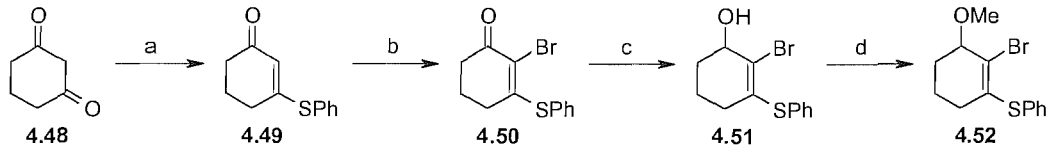
Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C then **4.6**; (b) THF, μwave, 120 °C, 30 min. *(Stereochemical assignment of **4.46** and **4.47** was based on a GOESY NMR experiment of **4.46**.)*

These reactions made it clear that electronic rather than steric factors dictated the course of thermal vinylcyclobutenone rearrangements. A powerful electron-donating group on the vinyl appendage (e.g. **4.1**, X = OMe) promotes the spirocyclisation pathway. In other cases (e.g. **4.1**, X = alkyl) the electrocyclisation pathway dominates leading to fused cyclohexendiones.

4.4 Thermally Induced Domino Reactions Leading to Quinones

For further proof of this hypothesis, we decided to attenuate the electron donating character of the substituent on the vinyl appendage. Again, an inability to prepare the necessary tetra-substituted alkenes proved a major limitation. We noted that Koreeda *et al.*[88] had developed a synthesis of vinyl sulfide **4.51** – an alkene containing the required bromide and a different heteroatom on the vinyl appendage. It was readily prepared in 3

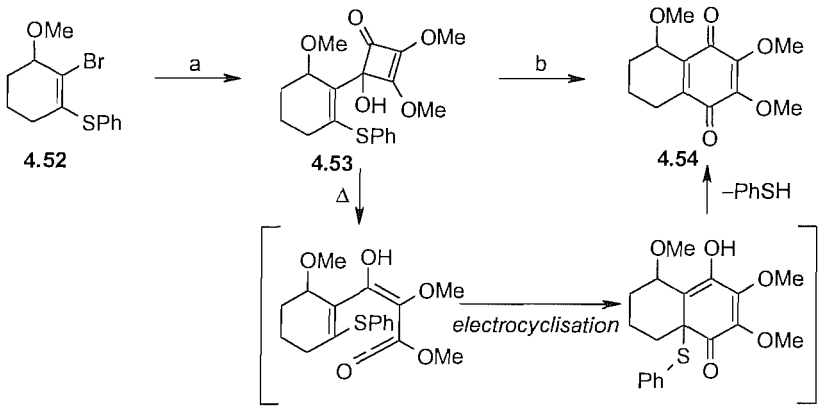
steps from 1,3-cyclohexanedione **4.48** by reaction with thiophenol to enone **4.49**,[89] bromination with NBS to **4.50** and Luche reduction to alcohol **4.51** (Scheme 4.12).[88] The hydroxyl was then protected as a methyl ether to give vinyl sulfide **4.52** – a system set-up for our key steps.



Scheme 4.12. Synthetic route to vinyl sulfide **4.52**.

Reagents and conditions: (a) PhSH, TsOH, PhMe, Δ, 16 h, 54%; (b) NBS, DCE, dark, 40 h, 74%; (c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 30 min, 99%; (d) NaH, MeI, THF, 2 h, 84%.

Halogen-lithium exchange and reaction with dimethyl squarate **4.6** then gave vinylcyclobutenones **4.53** which on thermolysis rearranged to give quinone **4.54** in 72% yield (Scheme 4.13).



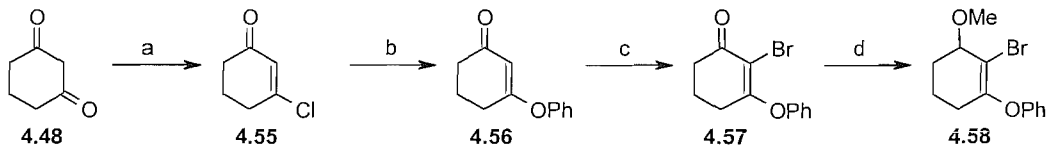
Scheme 4.13. Thermally induced domino reaction of vinylcyclobutenones **4.53**.

Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C then **4.6**, 30 min, 74%, *d.r.* 1:1; (b) THF, μwave, 120 °C, 30 min, 72%.

The formation of **4.54** as the major product was pleasing. We were unsure whether the thioether, being an electron donating substituent, would tip the scales in favour of the spirocyclisation pathway. Instead, the desired electrocyclisation-elimination pathway was promoted to give the quinone. This realisation of our original goal, a direct synthesis of quinones *via* an electrocyclisation-elimination domino sequence, is of

significance as it might provide a means of accessing (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**.

The analogous phenyl vinyl ether **4.58** was now prepared using a similar sequence (Scheme 4.14). First, **4.48** was converted to enone **4.55**[90] and the chloride displaced by phenoxide to yield **4.56**.[91] Bromination with NBS, followed by reduction of the carbonyl and subsequent methyl protection yielded the desired phenyl vinyl ether **4.58** in good overall yield. Unfortunately attempts to prepare related compounds with methoxy, SMe and NPhMe substituents proved intractable.

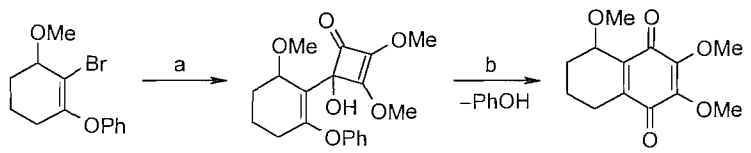


4.48 **4.55** **4.56** **4.57** **4.58**

Scheme 4.14. Synthetic pathway to phenyl vinyl ether **4.58**.

Reagents and conditions: (a) DMF, $(COCl)_2$, DCM, 0 °C, 10 min, 94%; (b) PhOH, K_2CO_3, acetone, Δ, 16 h, 81%; (c) NBS, DCE, dark, 40 h, 74%; (d) (i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 30 min; (ii) NaH, MeI, THF, 90 min, 84% over 2 steps.

Converting vinyl bromide **4.58** to the corresponding vinyllithium and addition to dimethyl squarate **4.6** gave **4.59** which on heating was converted to the same quinone **4.54** in 74% yield (Scheme 4.15). A slightly higher temperature (140 °C vs 120 °C for **4.53**) was required to force the reaction to completion.



4.58 **4.59** **4.54**

Scheme 4.15. Thermally induced domino reaction of vinylcyclobutenone **4.59**.

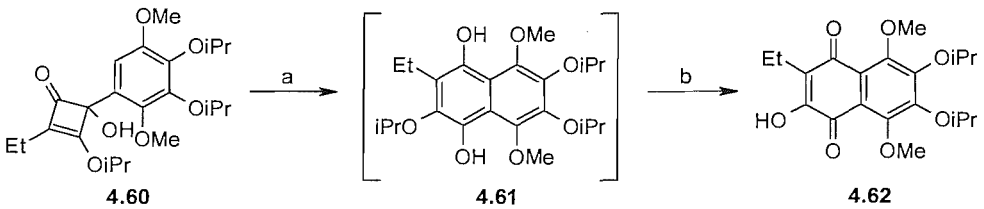
Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C then **4.6**, 30 min, 67%, *d.r.* 1:1; (b) THF, μwave, 140 °C, 30 min, 74%.

This observation provides further evidence that electronic rather than steric factors dictate the course of thermal vinylcyclobutenone rearrangements. In stark contrast to the analogous methyl vinyl ethers (e.g. **4.19**, Scheme 4.6), phenyl vinyl ether **4.59** followed the electrocyclisation-elimination pathway on thermolysis rather than giving the

carbonyl-ene reaction. As the oxygen lone pair is delocalised into the π-system of the arene, its π-electron donation to the alkene is significantly reduced when compared to the methyl ether. Thus, by the simple expedient of attenuating electron density in the vinyl ether it is possible to promote the electrocyclisation-elimination sequence at the expense of the spirocyclisation pathway.

4.5 Thermal Rearrangement of 4-(*o*-Styryl)cyclobutenones

At this juncture we decided to extend our study of the thermal rearrangement of cyclobutenones. Our attention was drawn to other systems where the electrocyclisation pathway might be outpaced by an alternative pericyclic process. Liebeskind[75,80] and Moore[81,82] have shown that arylcyclobutenones will undergo rearrangement on heating to give napthoquinones. A recent example of the reaction appears in a synthesis of echinochrome A reported by Liebeskind and Pena-Cabrera.[79] Thus, when arylcyclobutenone **4.60** is heated to 160 °C, rearrangement to hydroquinone **4.61** is observed (Scheme 4.16). Subsequent oxidation and hydrolysis gave napthoquinone **4.62** in high yield.



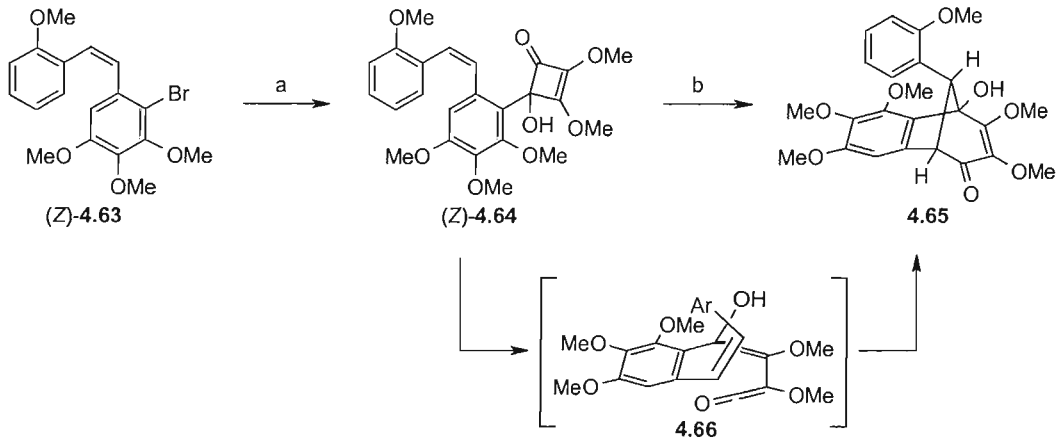
4.60 **4.61** **4.62**

Scheme 4.16. Thermal rearrangement of an arylcyclobutenone **4.60** to napthoquinone **4.62** by Liebeskind and Pena-Cabrera.[79]

Reagents and conditions: (a) neat, 160 °C, 15 min; (b) CAN, Et_2O, H_2O, 7 h, 91%.

We speculated that for 4-(*o*-styryl)cyclobutenones the electrocyclisation pathway might be outpaced by a [2 + 2] cycloaddition between the transient ketene intermediate and the proximal alkene. Harrowven *et al.*[92] had recently prepared *ortho*-bromostilbene (*Z*)-**4.63** allowing us to test this hypothesis. Generation of the corresponding aryllithium by halogen-lithium exchange facilitated its addition to dimethyl squarate **4.6**, yielding cyclobutenone (*Z*)-**4.64** in 76% yield (Scheme 4.17). A THF solution of (*Z*)-**4.64** was

then heated to 140 °C by microwave irradiation inducing rearrangement to benzobicyclo[3.2.1]octenone **4.65** in 75% yield. Elucidating the structure of **4.65** was no easy task – a deficiency of ^{1}H atoms making an NMR assignment difficult. Fortunately it could be crystallised from an EtOH solution enabling an X-ray crystal structure to be obtained (Figure 4.2).



Scheme 4.17. Thermal rearrangement of cyclobutenone (*Z*)-**4.64** to benzobicyclo-[3.2.1]octenone **4.65**.

Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C, 10 min then **4.6**, 1 h, 76%; (b) (i) THF, μwave, 140 °C, 1 h, 75% (+ 17% (*Z*)-**4.64**).

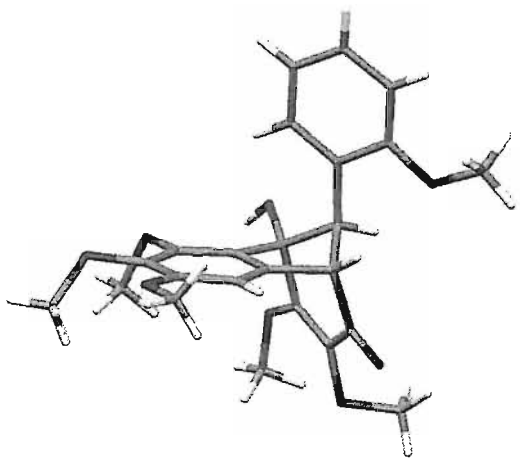
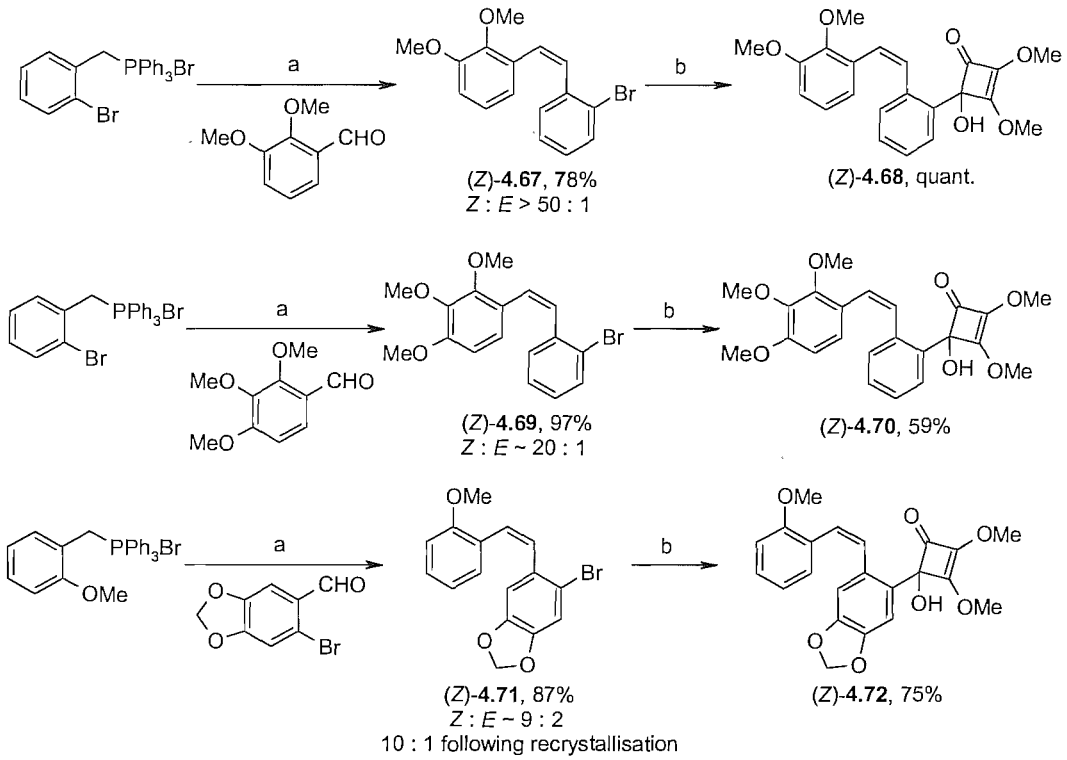


Figure 4.2. X-Ray crystal structure of benzobicyclo[3.2.1]octenone **4.65**.

The product was quite unexpected – being consistent with an intramolecular Diels-Alder cycloaddition between the transient vinylketene and the alkene within the stilbene moiety, *viz.* (*Z*)-**4.64** → [**4.66**] → **4.65** (Scheme 4.17). To test the generality of this new

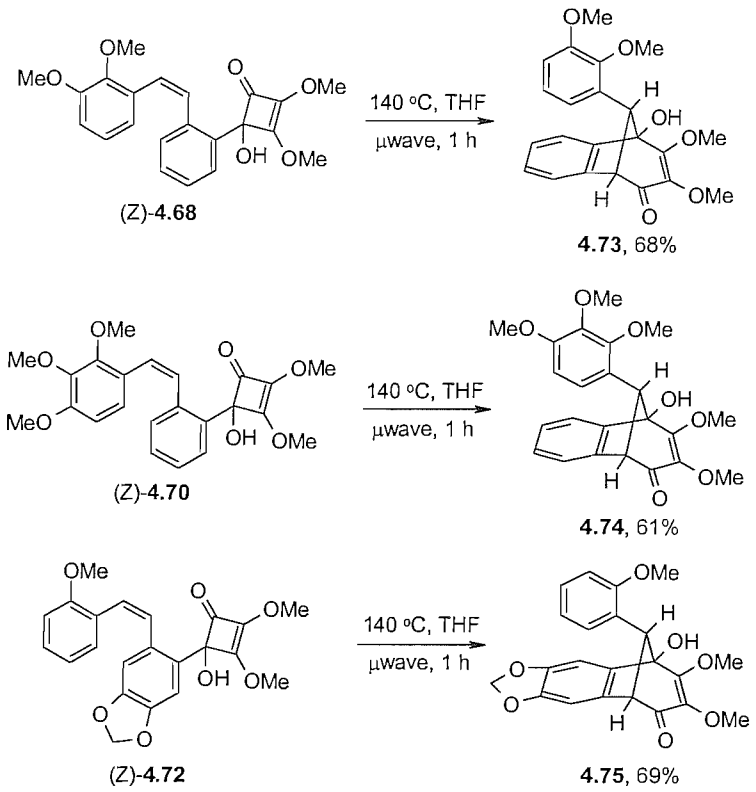
rearrangement three similar cyclobutenones were prepared. Stilbenes (*Z*)-**4.67**, (*Z*)-**4.69**, (*Z*)-**4.71** were synthesised using the *cis* selective Wittig chemistry developed by Harrowven *et al.* (Scheme 4.18).[92] Halogen-lithium exchange and addition of dimethyl squarate **4.6** then gave access to cyclobutenones (*Z*)-**4.68**, (*Z*)-**4.70**, (*Z*)-**4.72**.



Scheme 4.18. Synthesis of cyclobutenones (*Z*)-**4.68**, (*Z*)-**4.70** and (*Z*)-**4.72**.

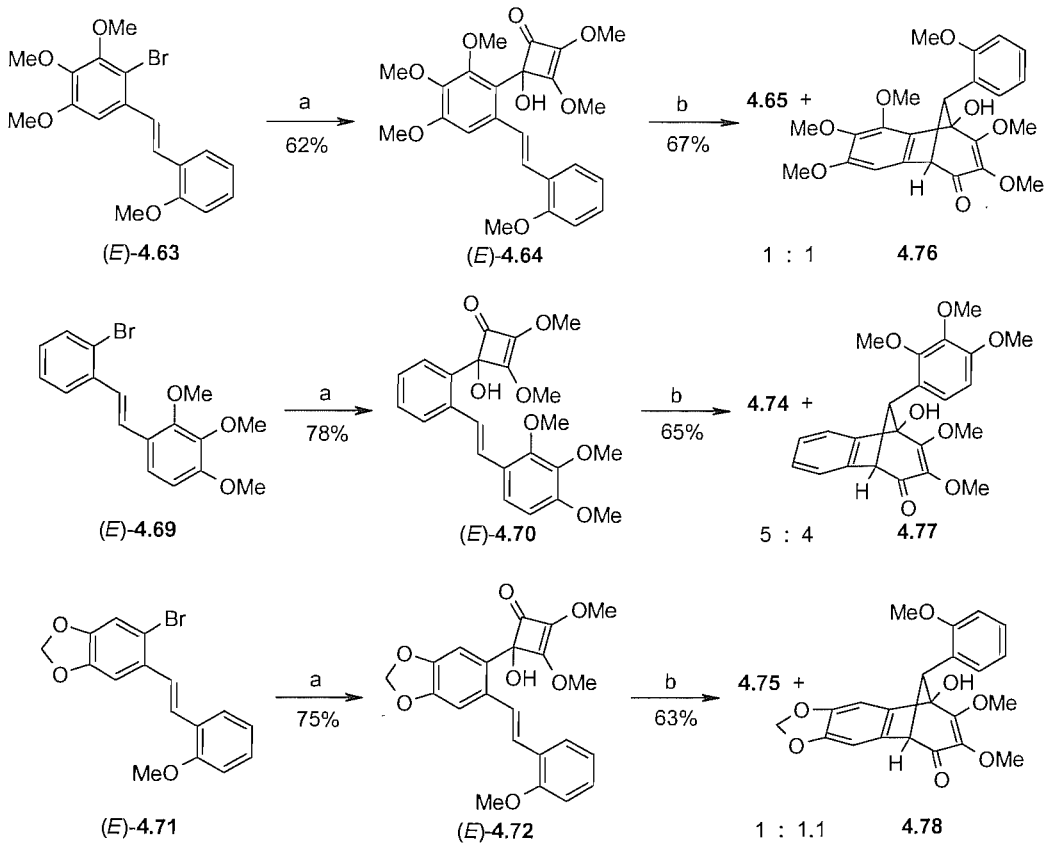
Reagents and conditions: (a) KO^{t}Bu, THF, 16 h; (b) ^{t}BuLi, THF, –78 °C, 30 min then **4.6**, 30 min.

Thermolysis of each of these cyclobutenones induced rearrangement to the corresponding benzobicyclo[3.2.1]octenones **4.73–4.75** in good yields, showing that the new reaction is indeed general for such systems (Scheme 4.19).



Scheme 4.19. Rearrangements of (*Z*)-4-(*o*-styryl)-cyclobutenones to benzobicyclo-[3.2.1]octenones.

For completeness we decided to examine the influence of the alkene geometry on the stereochemical course of rearrangement. Three *trans*-stilbenes, (*E*)-**4.63**, (*E*)-**4.69** and (*E*)-**4.71**, were thus prepared in near quantitative yield by isomerisation of the corresponding *cis* isomers, (*Z*)-**4.63**, (*Z*)-**4.69** and (*Z*)-**4.71** respectively, with catalytic iodine.[93] As before, halogen-lithium exchange and reaction of the resultant aryllithium with dimethyl squarate **4.6** led to cyclobutenones (*E*)-**4.64**, (*E*)-**4.70** and (*E*)-**4.72** (Scheme 4.20). Thermolysis then facilitated rearrangement of the cyclobutenones (*E*)-**4.64**, (*E*)-**4.70** and (*E*)-**4.72** to the respective benzobicyclo[3.2.1]octenones. In stark contrast to the (*Z*)-stilbene series, these were produced as diastereoisomeric mixtures: **4.65** and **4.76**, **4.74** and **4.77**, **4.75** and **4.78** respectively (Scheme 4.20).

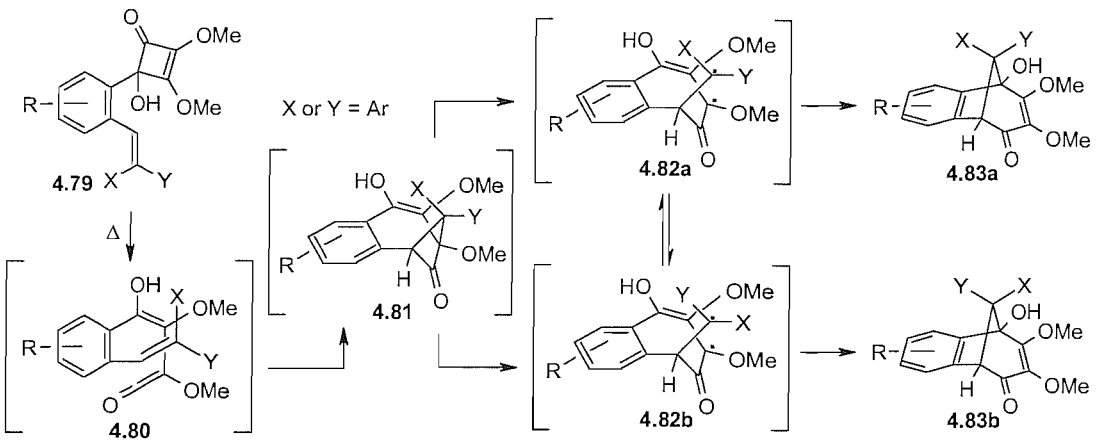


Scheme 4.20. Rearrangement of (*E*)-4-(*o*-styryl)-cyclobutenones to benzobicyclo-[3.2.1]octenones.

Reagents and conditions: (a) ^{t}BuLi, THF, –78 °C, 30 min then **4.6**, 30 min; (b) THF, μwave, 140 °C, 1 h.

This formation of diastereomeric mixtures from the *trans*-stilbene series militates against a mechanism involving an intramolecular Diels-Alder cycloaddition, *viz.* **4.79** → [**4.80**] → **4.83a** (Scheme 4.21). Moreover, the transition state for a [4 + 2] cycloaddition between the diene and alkene moieties in **4.80** is highly strained, while that for the more usual [2 + 2] cycloaddition to benzobicyclo[4.1.1]octenone **4.81** is readily adopted.

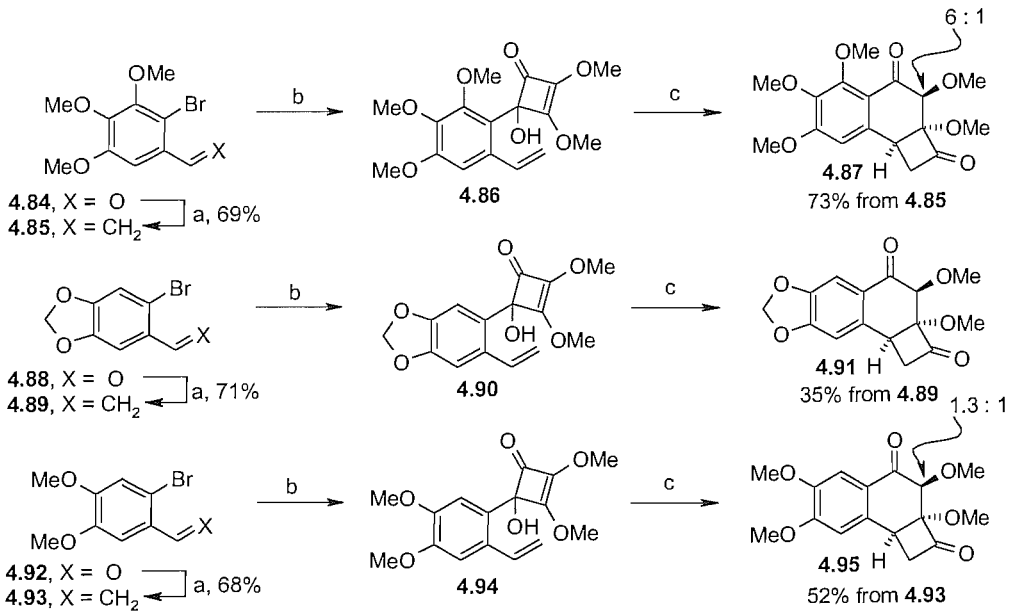
The results can be explained by invoking an initial electrocyclic opening of the cyclobutenone **4.79** to unsaturated ketene **4.80** which in turn undergoes a [2 + 2] cycloaddition to benzobicyclo[4.1.1]octenone **4.81**. A vinylcyclobutane rearrangement *via* "*a biradical that does not live long enough to achieve its equilibrium nuclear configuration*", as proposed by Carpenter *et al.*,[94] completes the sequence (Scheme 4.21).



Scheme 4.21. Proposed mechanism for the thermal rearrangement of 4-(*o*-styryl)-cyclobutenones **4.79** to benzobicyclo[3.2.1]octenones **4.83a** and **4.83b**.

For reactions in the *cis*-stilbene series, the biradical intermediate **4.82a** collapses instantaneously to the benzobicyclo[3.2.1]octenone **4.83a** giving no time for equilibration of the rotamers **4.82a** and **4.82b**. By contrast, reactions in the *trans*-stilbene series give a longer-lived biradical intermediate, allowing equilibration of the rotamers **4.82a** and **4.82b**. Consequently a diastereomeric mixture of benzobicyclo[3.2.1]octenones **4.83a** and **4.83b** is produced.

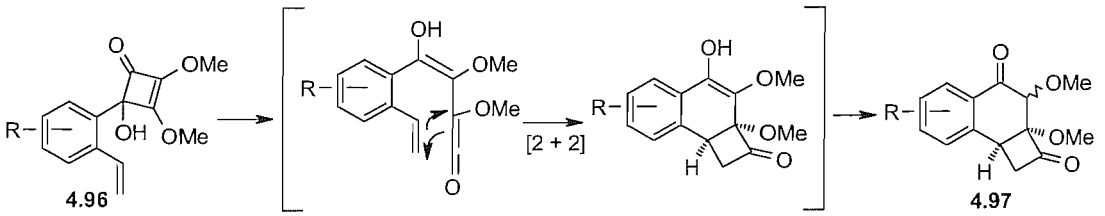
Further evidence in support of this mechanism was provided in a study of some simple styrylcyclobutenones (Scheme 4.22). When subjected to thermolysis, cyclobutenones **4.86**, **4.90** and **4.94** gave benzobicyclo[4.2.0]octenones **4.87**, **4.91** and **4.95** respectively – presumably resulting from a [2 + 2] cycloaddition between the ketene and the styrene alkene (Scheme 4.23). The efficiency of such rearrangements was variable. Thermolysis of **4.90**, for example, produced a complex product mixture from which diastereoisomer **4.91** could be isolated in low yield. By contrast, thermolysis of **4.86** gave benzobicyclo[4.2.0]octenone **4.87** in 73% yield. The inconsistency of the reaction may be due to the sensitivity of the products, which decompose to black tars on prolonged standing at ambient temperature.



Scheme 4.22. Rearrangement of 4-(*o*-styryl)-cyclobut-2-enones **4.86**, **4.90** and **4.94** to benzobicyclo[4.2.0]octenones **4.87**, **4.91** and **4.95**.

Reagents and conditions: (a) $MePPh_3Br$, KO^{t}Bu, THF, 30 min then aldehyde **4.84**, **4.88** or **4.92**, 16 h; (b) ^{t}BuLi, THF, –78 °C, 30 min then **4.6**, 30 min; (c) THF, μwave, 120 °C, 1 h.

*(Structure determination of **4.87**, **4.91** and **4.95** was aided by a long range ^1H-^{13}C COSY (HMBC) NMR experiment. Stereochemical assignment was based on a GOESY NMR experiment of **4.95**.)*



Scheme 4.23. Proposed mechanism for the formation of benzobicyclo-[4.2.0]octenones **4.97** from 4-(*o*-styryl)-cyclobut-2-enones **4.96**.

4.6 Conclusions and Further Work

In summary, four new cyclobutenone rearrangements and a domino reaction leading to quinones have been discovered, giving access to a diverse array of carbocyclic ring systems. Of particular note is our finding that the course of vinylcyclobutenone rearrangements is determined by the nature of substituents on the vinyl appendage. The high yields and absence of reagents add to the appeal of the transformations described. Further studies are ongoing in an attempt to apply some of the newly discovered methodologies in natural product synthesis.

The rearrangements described in Chapter 4 have recently been published in a preliminary communication entitled "Thermally Induced Cyclobutenone Rearrangements and Domino Reactions", Harrowven, D. C.; Pascoe, D. D.; Guy, I. G. *Angew. Chem.*, **2006**, *in press*; *Angew. Chem. Int. Ed.*, **2006**, *in press*.

Chapter 5 – Pot Pourri

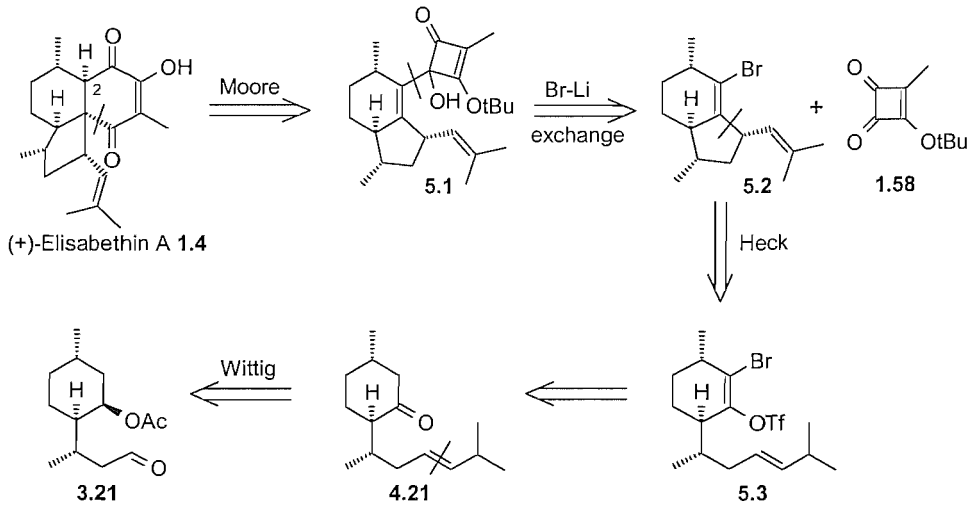
5.1 Introduction

The previous Chapters have been concerned with the total synthesis of (–)-colombiasin A and (–)-elisapterosin B, and our discovery of some new rearrangements involving cyclobutenones. During the course of these studies we have followed a number of avenues that could not appropriately be included in the preceding discussion, yet are worthy of comment. These are collectively presented in this final Chapter entitled 'Pot Pourri'.

5.2 Towards (+)-Elisabethin A

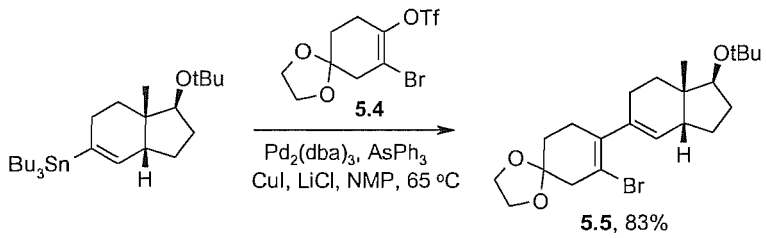
5.2.1 Background

The Moore rearrangement of alkylvinylcyclobutenones proved to be an excellent method for forming cyclohex-2-en-1,4-diones containing an sp^3 quaternary centre (Chapter 4). We believed it would be possible to exemplify this method in a total synthesis of (+)-elisabethin A **1.4** – a further diterpene isolated from *Psuedopterogorgia elisabethae*.[5] It was hoped that thermolysis of cyclobutenone **5.1** would give the elisabethin skeleton *via* Moore rearrangement and tautomerism to a cyclohexenedione (Scheme 5.1). Notably, the stereochemistry at C2 can be easily inverted should it be established incorrectly.[21] Cyclobutenone **5.1** would be obtained by halogen-lithium exchange of **5.2** and addition of squarate **1.58**, while an intramolecular Heck reaction of triflate **5.3** can be envisioned to close the 5 membered ring to form diene **5.2**. Aldehyde **3.21** (made previously – Chapter 2) would be an ideal starting point, with a Wittig reaction being used to install the side chain.



Scheme 5.1. Retrosynthetic approach towards (+)-elisabethin A **1.4**.

The key step in the planned sequence is the Pd(0) catalysed intramolecular Heck reaction of **5.3** to **5.2**. A number of potential pitfalls stand out, the first being the regioselectivity of Pd(0) oxidative insertion. De Meijere *et al.*[95] recently described a chemoselective Stille reaction, whereby insertion of Pd(0) into the C-OTf bond of **5.4** outpaces insertion into the C-Br bond to give vinyl bromide **5.5** in 83% yield (Scheme 5.2).



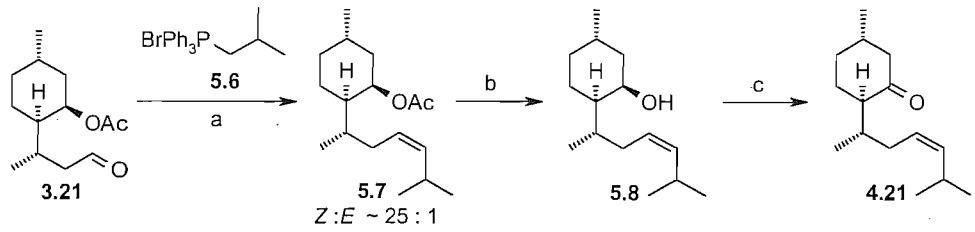
Scheme 5.2. Chemoselective Stille coupling of a 2-bromocyclohexenol triflate.[95]

The other main concern is the regiochemistry of dehydropalladation,[96] as we require this to form the skipped rather than the conjugated diene. Stereochemistry in the cyclisation is also an issue. The best way to resolve these matters is to perform the reaction in the laboratory!

5.2.2 Discussion

Assembly of the requisite ketone intermediate **4.21** proved straightforward. Wittig olefination between aldehyde **3.21** and the ylide derived from 2-methyl-propyl-

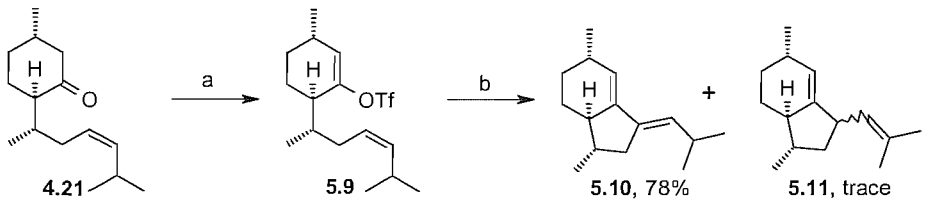
phosphonium bromide **5.6** afforded alkene **5.7**, predominantly as the *cis* isomer (*Z*:*E* ~ 25:1). Hydrolysis of the protective ester gave alcohol **5.8** which was then oxidised with Dess-Martin periodinane to yield **4.21** (Scheme 5.3).



Scheme 5.3. Synthesis of ketone **4.21** from aldehyde **3.21**.

Reagents and conditions: (a) **5.6**, KO^{t}Bu, THF, 0 °C, 1 h then **3.21**, Δ, 16 h, 81%; (b) LiOH, MeOH, Δ, 16 h, 89%; (c) DMP, DCM, 3 h, 98%.

In order to test the feasibility of the intramolecular Heck reaction, ketone **4.21** was converted to enol triflate **5.9** by forming the kinetic lithium enolate and trapping with *N*-phenyltriflimide (Scheme 5.4).[97] The Heck reaction of triflate **5.9** proved disappointing. Although 5-*exo*-*trig* cyclisation was facile using $Pd(OAc)_2$ and PPh_3, dehydropalladation gave the conjugated diene **5.10** in 78% yield rather than the desired skipped diene **5.11**. Trace impurities were assigned to the desired hydrocarbon **5.11**.



Scheme 5.4. Failed intramolecular Heck reaction of triflate **5.9** to diene **5.11**.

Reagents and conditions: (a) LiTMP, THF, –78 °C, 1 h then $PhNTf_2$, RT, 5 h, 63%; (b) 10 mol% $Pd(OAc)_2$, PPh_3, NEt_3, MeCN, Δ, 1 h, 78%.

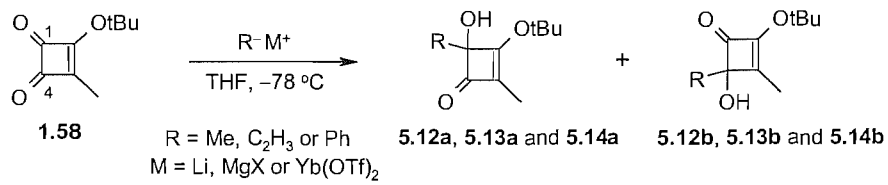
Other palladium sources ($PdCl_2$, Pd(dppf)) yielded the same product but in lower yield. Consequently, the approach to elisabethin A was abandoned at this juncture allowing us to focus our efforts on the novel rearrangements of cyclobutenones described in Chapter 4. Plans are in place to modify the substrate for the key palladium mediated cyclisation in order to facilitate formation of the skipped diene **5.2** so that we might apply our new rearrangement in a synthesis of (+)-elisabethin A **1.4**.

5.3 Controlling the Regioselectivity of Carbanion Addition to Squarate 1.58

5.3.1 Discussion

During our studies directed towards (–)-colombiasin A and (–)-elisapterosin B, we found that the addition of vinyllithium **3.25** to squarate **1.58** gave products derived from addition to both the ketone and the vinylogous ester carbonyl (Scheme 3.10). This unexpected behaviour prompted us to investigate the addition of other organometallic reagents to squarate **1.58**, with some surprising results.

The C1 ketone carbonyl should in theory be far more reactive towards nucleophiles than the C4 vinylogous ester. Our findings suggested that the nature of the carbanion could influence the regioselectivity of nucleophile addition.



1.58 R = Me, C_2H_3 or Ph; M = Li, MgX or $Yb(OTf)_2$ **5.12a, 5.13a** and **5.14a** **5.12b, 5.13b** and **5.14b**

Scheme 5.5. Regioselectivity of nucleophilic addition of carbanions to squarate **1.58**.

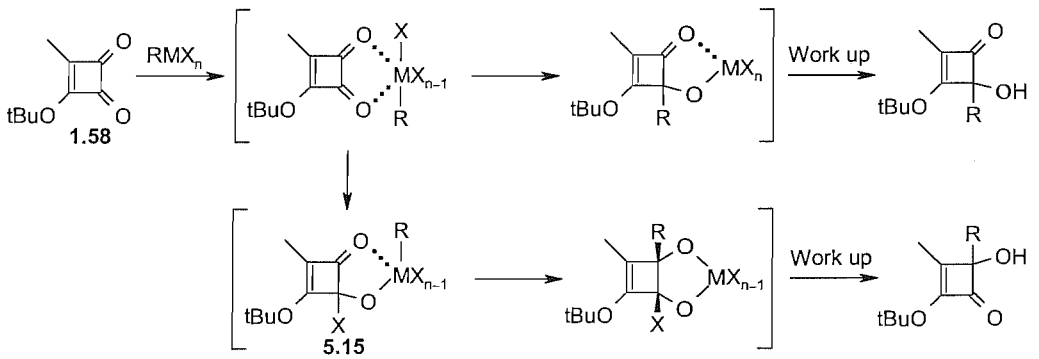
Three simple carbanions, $R^- = Me^-$, $C_2H_3^-$ (vinyl) and Ph^-, were added to squarate **1.58** in THF at –78 °C with the metal counterion being varied – $M^+ = Li^+$, MgX^+ or $Yb(OTf)_2^+$ (Scheme 5.5). The organolithium and Grignard reagents were used as supplied from commercial sources, while the organoytterbium reagents were prepared *in situ* by addition of the corresponding organolithium/Grignard reagent to anhydrous ytterbium(III) triflate ($Yb(OTf)_3$).[98] The C1/C4 addition products were easily separated by column chromatography. The isolated yields obtained for each reaction are summarised in Table 5.1. (*Note. Long range ^1H-^{13}C COSY (HMBC) NMR experiments allowed conclusive structural determination of each regioisomer.*)

	Li		MgX		$Yb(OTf)_2$	
	Yield **a**	Yield **b**	Yield **a**	Yield **b**	Yield **a**	Yield **b**
Me, 5.12	61	16	14	64	7	78
Vinyl, 5.13	31	43	11	57	6	73
Ph, 5.14	48	41	22	67	7	67

Table 5.1. Isolated percentage yields for addition of carbanions to squarate **1.58**. **a** = C1 addition product; **b** = C4 addition product (Scheme 5.5).

Our study showed that organolithium reagents display poor regioselectivity in their addition to squarate **1.58**. Although addition to the C1 ketone was favoured with MeLi, vinyl- and phenyllithium gave C1 and C4 addition products in comparable yields. Even more surprising was the observation that Grignard and organoytterbium reagents displayed a clear preference for addition to the vinylogous ester!

The tendency for organometallic reagents to favour addition to the vinylogous ester over the C1 ketone is hard to rationalise. One possibility is that the counterion first adds to the reactive ketone carbonyl leading to alkoxide **5.15**. This effectively protects the ketone, and promotes addition of the organyl residue to the less reactive vinylogous ester (Scheme 5.6).

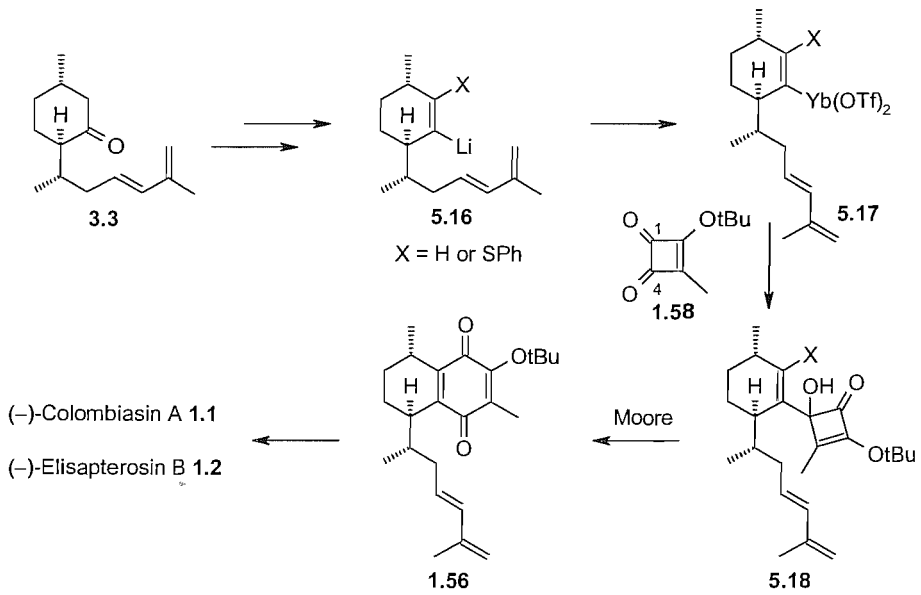


Scheme 5.6. A possible mechanism for the addition of organometallic reagents to squarate **1.58**.

5.3.2 Application to Future Research

This study was initiated to establish conditions to effect the selective addition of a carbon nucleophile to the C1 ketone, as is needed in our 'second generation' synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2**. The unexpected observation that Grignard and organoytterbium reagents show high regioselectivity for addition to the C4 carbonyl of squarate **1.58**, is one that could be advantageous in future work.

If a vinyllithium such as **5.16** could be obtained from dienone **3.3** (possibly *via* a Shapiro reaction), then transmetallation to the corresponding organoytterbium reagent **5.17** would be expected to give selective addition to the C4 carbonyl of squarate **1.58** (Scheme 5.7). A Moore rearrangement of the resultant vinylcyclobutenone **5.18** (X = H) would give quinone **1.56** to complete a formal total synthesis of (–)-colombiasin A **1.1** and (–)-elisapterosin B **1.2** following aerial oxidation of the intermediate hydroquinone. If the same thermolysis conditions were applied to vinyl sulfide **5.18** (X = SPh), there is the potential to exploit our newly discovered electrocyclisation-elimination domino reaction in a one-pot cascade sequence to the natural products **1.1** and **1.2** (Scheme 5.7).



Scheme 5.7. Proposed future work towards quinone **1.56**.

Chapter 6 – Experimental

6.1 General

All reactions were performed in oven-dried glassware and when required under an inert atmosphere of nitrogen or argon. Thermolysis reactions using microwave irradiation were carried out in a CEM Discover microwave reactor operating at a power of 150 W.

TLC was performed using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm. The plates were visualised under a UV lamp (254 nm) and by staining with either 20% phosphomolybdic acid in ethanol or 10% aqueous potassium permanganate. Column chromatography was achieved using Apollo silica gel (0.040-0.063 mm, 230-400 mesh), which was slurry packed and run under low pressure.

Infrared spectroscopy was performed using a Bio-Rad FT-IR goldengate spectrometer. Adsorption maxima (ν_{max}) are quoted as wavenumbers (cm^{-1}) and the following abbreviations used to describe their intensity: w - weak, m - medium, s - strong, b - broad, v - very.

Nuclear magnetic resonance spectroscopy was performed using a Bruker Avance 300 MHz spectrometer or a Bruker DPX 400 MHz spectrometer, run in a $CDCl_3$ solution. Chemical shifts are quoted as δ-values in ppm downfield of TMS (0 ppm) and referenced to the solvent peak – 7.27 ppm for ^1H spectra and 77.20 ppm for ^{13}C spectra. Coupling constants (*J*) are given in Hz and signals are described using the notation: s - singlet, d - doublet, t - triplet, q - quartet, quin. - quintet, m - multiplet, b - broad, app. - apparent and obsc. - obscured.

Mass spectrometry was performed using electron ionisation (EI) and chemical ionisation (CI) on a Thermoquest Trace GCMS spectrometer; and by electrospray positive (ES^+) ionisation on a Waters ZMD spectrometer. High resolution EIMS was performed on a VG Analytical 70-250-Se spectrometer and high resolution ESMS performed on a Bruker Apex III spectrometer. Optical rotations were measured on a PolAAr 2001 polarimeter at the d line of sodium (589 nm) and an external temperature of 25 °C. Melting points were determined using a Griffin melting point apparatus.

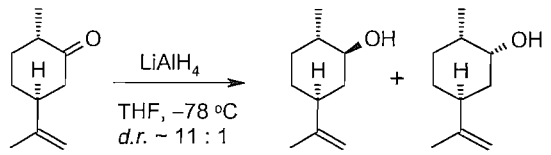
All solvents were distilled prior to use. Toluene, diethyl ether, THF and 1,2-dimethoxyethane were distilled from sodium with benzophenone as an indicator.

Chloroform and dichloromethane were distilled from calcium hydride. Anhydrous Ytterbium(III) triflate was obtained by drying the commercially supplied material *in vacuo* at 80 °C.[99] Other solvents and reagents were purified according to standard laboratory methods.[100]

6.2 Synthetic Procedures

6.2.1 Experimental for Chapter 2

(1*S*,2*S*,5*S*)-5-Isopropenyl-2-methylcyclohexan-1-ol, 2.1a and **(1*R*,2*S*,5*S*)-5-Isopropenyl-2-methylcyclohexan-1-ol, 2.1b**



1.62 $C_{10}H_{16}O$ (152.24)

2.1a **2.1b** $C_{10}H_{18}O$ (154.26)

To a stirred suspension of lithium aluminium hydride (2.28 g, 60.0 mmol) in THF (100 mL) at –78 °C was added a solution of (–)-dihydrocarvone **1.62** (18.1 g, 0.12 mol) in THF (50 mL) over 10 min. After a further 5 min the reaction was quenched with sat. NH_4Cl (75 mL) and allowed to warm to RT. The phases were separated and the aqueous phase extracted with ether (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (SiO_2, 10-30% ether/petrol) to yield firstly alcohol **2.1b** (1.3 g, 8.4 mmol, 7%) as a colourless oil, then alcohol **2.1a** as a colourless oil (16.3 g, 105.7 mmol, 88%). Spectroscopic data were in agreement with the literature.[101]

Data for **2.1a**:

FT-IR ν_{max} (neat, cm^{-1}) 3345 bw, 2924 m, 2857 w, 1645 w, 1452 m, 1373 w, 1049 m, 887 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.70 (2H, bs), 3.20 (1H, bt, *J* 9.2 Hz), 2.06-1.94 (2H, m), 1.81-1.65 (2H, m), 1.73 (3H, s), 1.50 (1H, bs), 1.32-1.07 (4H, m), 1.03 (3H, d, *J* 6.3 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 149.6 (*C*), 108.7 (CH_2), 76.5 (*C*H), 44.3 (*C*H), 40.7 (CH_2), 40.2 (*C*H), 33.4 (CH_2), 31.2 (CH_2), 21.0 (CH_3), 18.5 (CH_3).

LRMS $^m/_z$ (EI) 154 (M^+, 8%), 136 (100), 121 (98), 107 (100), 93 (95).

Data for **2.1b**:

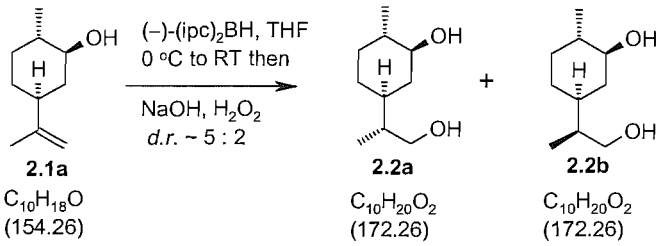
FT-IR ν_{max} (neat, cm^{-1}) 3405 bw, 2923 m, 2871 w, 2855 w, 1643 w, 1451 m, 1374 w, 884 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.70 (2H, bs), 3.90 (1H, bs), 2.28 (1H, tt, *J* 12.4, 3.2 Hz), 1.92 (1H, dq, *J* 13.6, 3.4 Hz), 1.77 (1H, m), 1.73 (3H, s), 1.56-1.37 (5H, m), 1.21 (1H, m), 0.98 (3H, d, *J* 6.4 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 150.3 (*C*), 108.4 (CH_2), 71.0 (*C*H), 38.7 (CH_2), 37.9 (*C*H), 36.2 (*C*H), 31.5 (CH_2), 28.2 (CH_2), 21.0 (CH_3), 18.4 (CH_3).

LRMS $^m/_z$ (EI) 154 (M^+, 4%), 136 (100), 121 (99), 107 (96), 93 (88).

(1*S*,2*S*,2'*R*,5*S*)-5-(1'-Hydroxyprop-2'-yl)-2-methylcyclohexanol, 2.2a and **(1*S*,2*S*,2'*S*,5*S*)-5-(1'-Hydroxyprop-2'-yl)-2-methylcyclohexanol 2.2b**



2.1a $C_{10}H_{18}O$ (154.26)

2.2a $C_{10}H_{20}O_2$ (172.26)

2.2b $C_{10}H_{20}O_2$ (172.26)

The title compounds were prepared using the method of Brown *et al.*[43] Borane-dimethyl sulfide complex (5.4 mL, 57.3 mmol) was added over 5 min to an ice-cooled solution of (–)-α-pinene (18.2 mL, 114 mmol) in THF (100 mL). After 1 h a solution of alkene **2.1a** (8.84 g, 57.3 mmol) in THF (50 mL) was added over 10 min and the reaction was allowed to warm to RT. After a further 3 h 10% aq. NaOH (22 mL) and 30% aq. H_2O_2 (19 mL) were added sequentially, followed after 16 h by water (50 mL) and chloroform (100 mL). The phases were separated and the aqueous phase extracted with chloroform (2 x 100 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (SiO_2, ether) to give a 5:2 mixture of diols **2.2a** and **2.2b** (9.63 g, 55.9 mmol, 98%) as a colourless oil. Partial separation of the diastereoisomers was achieved by column chromatography on silica using a 3:1:1 mixture of ether, THF and petrol as the eluting solvent. The enriched samples were then recrystallised from ether/petrol. After a single

recrystallisation **2.2a** was attained as a semi-solid contaminated with *ca.* 10% of **2.2b**, while **2.2b** was attained as colourless crystals. Spectroscopic data were in agreement with the literature.[102]

Data for **2.2b** (minor product):

MP 83-85 °C (ether/petrol).

FT-IR ν_{max} (neat, cm^{-1}) 3217 bm, 2920 m, 2872 m, 1446 w, 1370 w, 1029 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.62 (1H, dd, *J* 10.5, 5.9 Hz), 3.50 (1H, dd, *J* 10.5, 6.4 Hz), 3.15 (1H, td, *J* 10.2, 4.2 Hz), 1.92 (1H, d with fine splitting, *J* 12.0 Hz), 1.74 (1H, m), 1.65-1.43 (5H, m), 1.27 (1H, m), 1.16-0.98 (3H, m), 1.02 (3H, d, *J* 6.3 Hz), 0.91 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 76.8 (*C*H), 66.3 (*C*H_2), 40.4 (*C*H), 40.4 (*C*H), 38.3 (*C*H), 37.8 (*C*H_2), 33.4 (*C*H_2), 30.3 (*C*H_2), 18.5 (*C*H_3), 13.5 (*C*H_3).

LRMS $^m/_z$ (EI) 172 (M^+, 3%), 154 (10), 137 (24), 123 (38), 113 (100), 95 (90), 81 (69).

Data for **2.2a** (major product):

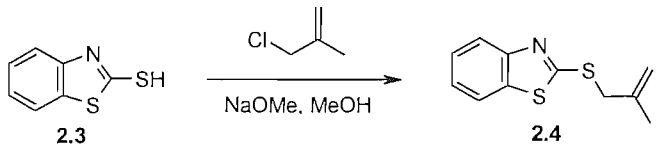
FT-IR ν_{max} (neat, cm^{-1}) 3337 bm, 2920 m, 2872 m, 1453 w, 1373 w, 1041 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.60 (1H, dd, *J* 10.7, 5.9 Hz), 3.48 (1H, dd, *J* 10.7, 6.4 Hz), 3.15 (1H, dt, *J* 10.2, 4.2 Hz), 1.90 (1H, m), 1.80-1.69 (3H, m), 1.63-1.41 (3H, m), 1.33-0.98 (4H, m), 1.11 (3H, d, *J* 6.4 Hz), 0.89 (3H, d, *J* 7.6 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 76.7 (*C*H), 66.3 (*C*H_2), 40.5 (*C*H), 40.3 (*C*H), 40.0 (*C*H_2), 38.3 (*C*H), 33.3 (*C*H_2), 27.9 (*C*H_2), 18.5 (*C*H_3), 13.6 (q, *C*H_3).

LRMS $^m/_z$ (EI) 172 (M^+, 2%), 154 (10), 136 (18), 113 (100), 95 (78), 81 (52).

2-(2'-Methyl-2'-propenylthio)-benzothiazole, 2.4



2.3
$C_7H_5NS_2$
(167.24)

2.4
$C_{11}H_{11}NS_2$
(221.34)

The title compound was prepared using the method of Whitham *et al.*[44] To a freshly prepared solution of sodium (962 mg, 41.8 gatom) in methanol (50 mL) was added 2-mercapto-benzothiazole (**2.3**) (7.0 g, 41.8 mmol), followed after 30 min by methallyl chloride (4.12 mL, 41.8 mmol). After 4 h the reaction mixture was partitioned between water (50 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (2 x 50 mL), then the combined organic phases were washed with 2 M NaOH (50 mL), 2 M HCl (50 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.4** as a yellow oil (8.99 g, 40.6 mmol, 97%). Spectroscopic data were in agreement with the literature.[44]

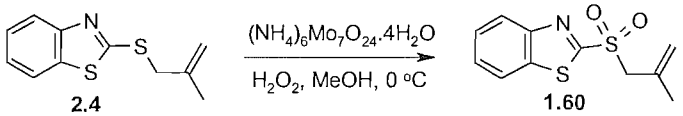
FT-IR ν_{max} (neat, cm^{-1}) 3074 w, 2973 w, 2914 w, 1650 w, 1456 m, 1425 s, 1237 m, 991 s, 899 m, 752 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.88 (1H, d, *J* 8.1 Hz), 7.77 (1H, d, *J* 8.1 Hz), 7.42 (1H, td, *J* 8.1, 1.1 Hz), 7.31 (1H, td, *J* 8.1, 1.1 Hz), 5.13 (1H, s), 4.96 (1H, t, *J* 1.3 Hz), 4.02 (2H, d, *J* 1.3 Hz), 1.91 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 166.9 (*C*), 153.3 (*C*), 139.9 (*C*), 135.4 (*C*), 126.2 (*C*H), 124.4 (*C*H), 121.7 (*C*H), 121.1 (*C*H), 115.6 (CH_2), 40.8 (CH_2), 21.5 (CH_3).

LRMS $^m/_z$ (EI) 221 (M^+, 22%), 206 ($[M - CH_3]^+$, 100), 188 (29), 173 (15), 166 (15), 149 (13), 135 (21), 122 (13), 108 (35).

2-(2'-Methyl-2'-propene-1-sulfonyl)-benzothiazole, 1.60



2.4
$C_{11}H_{11}NS_2$
(221.34)

1.60
$C_{11}H_{11}NO_2S_2$
(253.34)

The title compound was prepared using the method of Whitham *et al.*[44] To a solution of benzothiazole **2.4** (3.0 g, 13.6 mmol) in ethanol (50 mL) at 0 °C, was added a solution of ammonium molybdate tetrahydrate (0.67 g, 0.54 mmol) in 30% aq. H_2O_2 (5.4 mL, 47.9 mmol) over 5 min. After 2 h the reaction was warmed to RT and the solvent removed *in vacuo* to give a yellow solid. The residue was dissolved in DCM (30 mL), and washed with 2 M HCl (100 mL). The aqueous phase was re-extracted with DCM (2 x 50 mL), and the combined organic phases washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from DCM/EtOH to afford sulfone **1.60** as an off-white crystalline solid (2.34 g, 9.23 mmol, 68%). Physical and spectroscopic data were in agreement with the literature.[44]

MP 97-99 °C (DCM/EtOH). Lit.[44] 96-97 °C.

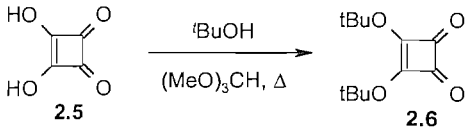
FT-IR ν_{max} (neat, cm^{-1}) 3085 w, 3064 w, 2974 w, 2908 w, 1646 w, 1554 w, 1468 s, 1311 s, 1247 m, 1161 s, 1126 s, 1083 m, 1025 m, 925 s, 757 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 8.24 (1H, dd, *J* 7.4, 1.8 Hz), 8.02 (1H, dd, *J* 7.4, 1.8 Hz), 7.66 (1H, td, *J* 7.4, 1.8 Hz), 7.60 (1H, td, *J* 7.4, 1.8 Hz), 5.12 (1H, s), 4.92 (1H, s), 4.22 (2H, s), 1.97 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 165.6 (*C*), 152.8 (*C*), 137.0 (*C*), 132.2 (*C*), 128.2 (*C*H), 127.8 (*C*H), 125.6 (*C*H), 122.5 (*C*H), 122.3 (CH_2), 62.7 (CH_2), 23.0 (CH_3).

LRMS $^m/_z$ (ES^+) 308 ($[M + Na + MeOH]^+$), 276 ($[M + Na]^+$).

3,4-Di-*tert*-butoxy-cyclobut-3-ene-1,2-dione, 2.6



The title compound was prepared using the method of Moore *et al.*[45] A suspension of squaric acid **2.5** (6.89 g, 60.4 mmol) and *tert*-butanol (240 mL) was heated at reflux for 1 h during which time trimethylorthoformate (66 mL, 0.6 mol) was added down the condenser. The resultant distillate was collected *via* short path distillation and any remaining solvent removed *in vacuo* to yield a crude white solid. Purification by column chromatography (SiO_2, 10-20% EtOAc/petrol) gave squarate **2.6** as a white crystalline solid (9.14 g, 40.4 mmol, 67%). Physical and spectroscopic data were in agreement with the literature.[45]

MP 102-103 °C (ether/petrol). Lit.[45] 103-104 °C.

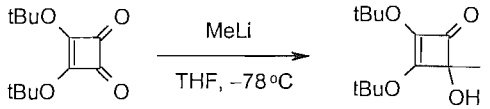
FT-IR ν_{max} (neat, cm^{-1}) 2978 w, 1803 s, 1723 s, 1573 s, 1476 m, 1371 s, 1276 s, 1138 s, 1068 s, 1006 s, 817 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.61 (18H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 188.8 (2 x *C*), 186.5 (2 x *C*), 87.2 (2 x *C*), 28.8 (6 x CH_3).

LRMS $^m/_z$ (ES^+) 475 ($[2M + Na]^+$), 281 ($[M + Na + MeOH]^+$), 249 ($[M + Na]^+$).

2,3-Di-*tert*-butoxy-4-hydroxy-4-methyl-cyclobut-2-enone, 2.7



2.6
$C_{12}H_{18}O_4$
(226.12)

2.7
$C_{13}H_{22}O_4$
(242.16)

To a solution of squarate **2.6** (8.62 g, 38.1 mmol) in THF (100 mL) at –78 °C, was added MeLi (1.6 M in ether, 26.0 mL, 41.9 mmol) over 10 min. After stirring for 15 min the reaction was quenched with water (100 mL) and warmed to RT. The reaction mixture was extracted with ether (2 x 100 mL), and the combined organic phases washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.7** as a white solid (8.86 g, 36.6 mmol, 96%).

MP 113-115 °C (ether/petrol).

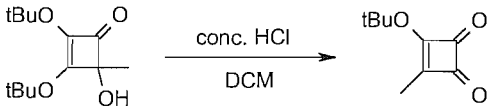
FT-IR ν_{max} (neat, cm^{-1}) 3290 bm, 2980 w, 2935 w, 1756 s, 1587 s, 1464 w, 1351 s, 1267 m, 1150 s, 1019 s, 917 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 2.32 (1H, bs), 1.53 (9H, s), 1.47 (9H, s), 1.45 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 187.3 (*C*), 168.3 (*C*), 129.0 (*C*), 83.7 (*C*), 82.2 (*C*), 80.4 (*C*), 29.0 (3 x CH_3), 28.5 (3 x CH_3), 19.1 (CH_3).

LRMS $^m/_z$ (ES^+) 507 ($[2M + Na]^+$), 297 ($[M + Na + MeOH]^+$), 265 ($[M + Na]^+$).

3-*tert*-Butoxy-4-methyl-cyclobut-3-ene-1,2-dione, 1.58



2.7
$C_{13}H_{22}O_4$
(242.16)

1.58
$C_9H_{12}O_3$
(168.19)

To a solution of **2.7** (8.46 g, 35.0 mmol) in DCM (100 mL) was added concentrated hydrochloric acid (2 mL) dropwise. The reaction was stirred for 30 min then water (30 mL) was added and the phases separated. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to a white solid. Recrystallisation from ether/petrol yielded squarate **1.58** as a white crystalline solid (4.92 g, 29.3 mmol, 84%). Physical and spectroscopic data were in agreement with the literature.[30]

MP 67-69 °C (ether/petrol). Lit.[30] 72-73 °C (EtOAc/hexane).

FT-IR ν_{max} (neat, cm^{-1}) 2993 w, 1795 s, 1741 s, 1573 s, 1389 m, 1370 s, 1342 s, 1151 s, 1058 s, 979 m, 939 m, 841 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 2.18 (3H, s), 1.61 (9H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 200.1 (*C*), 196.1 (*C*), 192.9 (*C*), 182.9 (*C*), 87.7 (*C*), 28.9 (3 x CH_3), 9.5 (CH_3).

LRMS $^m/_z$ (ES^+) 359 ($[2M + Na]^+$), 223 ($[M + Na + MeOH]^+$), 191 ($[M + Na]^+$), 135 ($[M - C_4H_8 + Na]^+$).

(1'*S*,2*R*,3'*S*,4'*S*)-2-(3'-Hydroxy-4'-methylcyclohexyl)propyl *p*-toluenesulfonate, 2.8

2.2a
$C_{10}H_{20}O_2$
(172.26)

2.8
$C_{17}H_{26}O_4S$
(326.45)

To a solution of diol **2.2a** (3.01 g, 17.5 mmol) in DCM (125 mL) was added triethylamine (7.3 mL, 52.5 mmol) followed by *p*-toluenesulfonyl chloride (10.0 g, 52.5 mmol). After 3 h at RT the solution was concentrated to *ca.* 75 mL and loaded directly onto a chromatography column with silica as the stationary phase. Elution firstly with DCM, then gradient elution with 25-75% ether/petrol mixtures, gave tosylate **2.8** (3.84 g, 11.8 mmol, 67%) as a colourless oil, followed by recovered diol **2.2a** (902 mg, 5.2 mmol, 30%) as a colourless oil. Spectroscopic data were in agreement with the literature.[39]

Data for tosylate **2.8**:

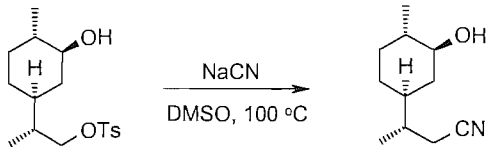
FT-IR ν_{max} (neat, cm^{-1}) 3402 bw, 2972 w, 2925 m, 2870 w, 1358 s, 1175 s, 1097 m, 962 s, 813 s, 667 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.2 Hz), 7.35 (2H, d, *J* 8.2 Hz), 3.95 (1H, dd, *J* 9.5, 6.0 Hz), 3.87 (1H, dd, *J* 9.5, 6.4 Hz), 3.08 (1H, td, *J* 10.2, 4.3 Hz), 2.45 (3H, s), 1.81-1.63 (2H, m), 1.52 (1H, bs), 1.51-1.38 (2H, m), 1.20 (1H, m), 1.02-0.83 (4H, m), 0.99 (3H, d, *J* 6.4 Hz), 0.87 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 144.9 (*C*), 133.3 (*C*), 130.0 (2 x *C*H), 128.1 (2 x *C*H), 76.3 (*C*H), 73.5 (CH_2), 40.2 (*C*H), 39.6 (CH_2), 38.0 (*C*H), 37.5 (*C*H), 33.0 (CH_2), 27.8 (CH_2), 21.8 (CH_3), 18.4 (CH_3), 13.4 (CH_3).

LRMS $^m/_z$ (ES^+) 675 ($[2M + Na]^+$), 349 ($[M + Na]^+$).

(1'*S*,3*S*,3'*S*,4'*S*)-3-(3'-Hydroxy-4'-methylcyclohexyl)butanenitrile, 2.9



2.8
$C_{17}H_{26}O_4S$
(326.45)

2.9
$C_{11}H_{19}NO$
(181.28)

A solution of tosylate **2.8** (3.66 g, 11.2 mmol) and sodium cyanide (604 mg, 12.3 mmol) in DMSO (40 mL) was heated to 100 °C for 1 h, then cooled to RT and water (100 mL) added. Following extraction of the aqueous phase with ether (4 x 100 mL), the combined organic phases were washed with water (4 x 200 mL) and brine (2 x 200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield nitrile **2.9** as a colourless oil (1.89 g, 10.4 mmol, 93%). Spectroscopic data were in agreement with the literature.[39]

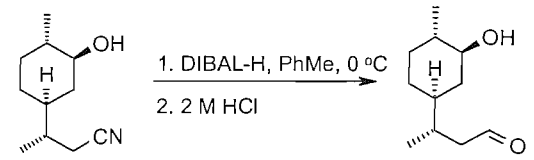
FT-IR ν_{max} (neat, cm^{-1}) 3407 bw, 2924 m, 2871 m, 2247 w, 1454 m, 1042 s, 1021 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.18 (1H, td, *J* 10.0, 4.2 Hz), 2.38 (1H, dd, *J* 16.8, 5.8 Hz), 2.29 (1H, dd, *J* 16.8, 7.4 Hz), 1.95 (1H, d with fine splitting, *J* 12.1 Hz), 1.83 (2H, m), 1.65 (1H, m), 1.60 (1H, bs), 1.47 (1H, m), 1.28 (1H, m), 1.11-0.91 (3H, m), 1.08 (3H, d, *J* 7.0 Hz), 1.02 (3H, d, *J* 6.4 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 119.2 (*C*), 76.2 (*C*H), 40.7 (*C*H), 40.2 (*C*H), 39.4 (CH_2), 35.3 (*C*H), 32.9 (CH_2), 28.2 (CH_2), 22.5 (CH_2), 18.4 (CH_3), 16.8 (CH_3).

LRMS $^m/_z$ (EI) 180 ($[M - H]^+$, 4%), 164 (8), 124 (8), 113 (31), 95 (74), 81 (22), 69 (28), 57 (58).

(1'*S*,3*S*,3'*S*,4'*S*)-3-(3'-Hydroxy-4'-methylcyclohexyl)butanal, 1.61



2.9
$C_{11}H_{19}NO$
(181.28)

1.61
$C_{11}H_{20}O_2$
(184.28)

To a solution of nitrile **2.9** (310 mg, 1.71 mmol) in toluene (20 mL) at 0 °C was added over 5 min DIBAL-H (1 M in hexanes, 5.1 mL, 5.13 mmol). After 1 h chloroform (5 mL) and 2 M HCl (12 mL) were added and the reaction stirred for a further 30 min. Following extraction with chloroform (3 x 30 mL), the combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give aldehyde **1.61** (241 mg, 1.31 mmol, 76%) as a pale yellow oil. Spectroscopic data were in agreement with the literature.[39]

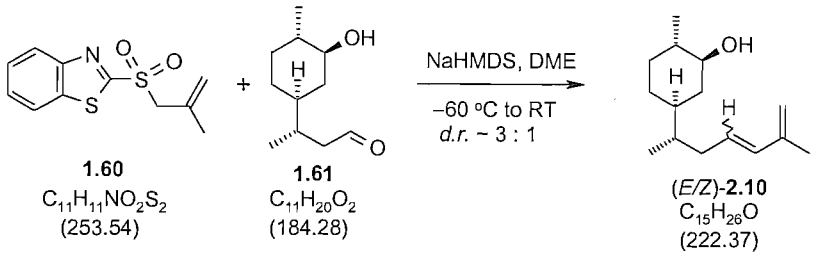
FT-IR ν_{max} (neat, cm^{-1}) 3402 bw, 2923 s, 2857 m, 2721 w, 1721 s, 1453 m, 1376 m, 1043 s, 1019 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.76 (1H, dd, *J* 2.7, 1.8 Hz), 3.14 (1H, td, *J* 10.4, 4.0 Hz), 2.47 (1H, ddd, *J* 16.1, 4.8, 1.8 Hz), 2.23 (1H, ddd, *J* 16.1, 8.8, 2.7 Hz), 2.03 (1H, m), 1.91 (1H, d with fine splitting, *J* 11.9 Hz), 1.75 (1H, m), 1.65-1.56 (2H, m), 1.36-1.18 (2H, m), 1.11-0.95 (3H, m), 1.01 (3H, d, *J* 6.4 Hz), 0.93 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 203.1 (*C*), 76.5 (*C*H), 48.6 (CH_2), 41.7 (*C*H), 40.4 (*C*H), 39.3 (CH_2), 33.2 (CH_2), 32.6 (*C*H), 28.4 (CH_2), 18.4 (CH_3), 17.1 (CH_3).

LRMS $^m/_z$ (CI) 202 ($[M + NH_4]^+$, 100%), 185 (MH^+, 32%), 167 (78), 149 (92), 122 (52), 95 (17).

(1*S*,2*S*,3'*E/Z*,5*S*,6'*S*)-5-(2'-Methylhepta-1',3'-dien-6-yl)-2-methylcyclohexanol, (*Z*)-**2.10** and (*E*)-**2.10**



1.60
$C_{11}H_{11}NO_2S_2$
(253.54)

1.61
$C_{11}H_{20}O_2$
(184.28)

(*E/Z*)-**2.10**
$C_{15}H_{26}O$
(222.37)

The title compound was prepared by adapting the method of Kocienski *et al.*[49] To a mixture of sulfone **1.60** (667 mg, 2.63 mmol) and aldehyde **1.61** (485 mg, 2.63 mmol) in DME (30 mL) at –60 °C was added NaHMDS (2 M in THF, 2.6 mL, 5.26 mmol). After 2 h the reaction mixture was allowed to warm to RT over 30 min, stirred for 1 h then partitioned between sat. NH_4Cl (10 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (2 x 30 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) gave a 3:1 mixture of dienes (*Z*)-**2.10** and (*E*)-**2.10** (464 mg, 2.09 mmol, 79%) as a pale yellow oil. Spectroscopic data were in agreement with the literature.[39] Data was recorded on the mixture.

FT-IR ν_{max} (neat, cm^{-1}) 3360 bw, 2920 s, 2868 m, 1453 m, 1373 m, 1044 s, 1020 m, 966 w, 888 s.

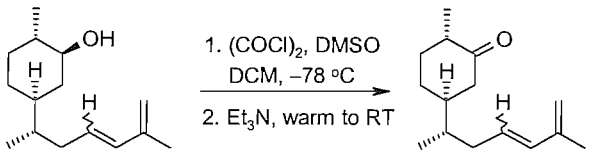
^{1}H NMR δ_H (300 MHz, $CDCl_3$) Major isomer (*Z*)-**2.10**: 5.88 (1H, d, *J* 11.8 Hz), 5.39 (1H, dt, *J* 11.8, 7.4 Hz), 4.95 (1H, s), 4.83 (1H, s), 3.14 (1H, td, *J* 10.4, 4.2 Hz), 2.33 (1H, m), 2.15 (1H, ddd, *J* 16.1, 8.1, 1.5 Hz), 1.91 (1H, m), 1.87 (3H, s), 1.73 (1H, m), 1.58-1.52 (2H, m), 1.46-1.21 (3H, m), 1.31 (1H, bs), 1.14-1.00 (2H, m), 1.01 (3H, d, *J* 6.2 Hz), 0.87 (3H, d, *J* 6.8 Hz). Additional signals attributed to the minor isomer (*E*)-**2.10** (~ $^1/_3$ the integral): 6.13 (1H, d, *J* 15.7 Hz), 5.62 (1H, dt, *J* 15.7, 7.4 Hz), 4.87 (2H, s), 1.83 (3H, s), 0.85 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) Major isomer (*Z*)-**2.10**: 142.0 (*C*), 131.7 (*C*H), 131.0 (*C*H) 115.2 (CH_2), 76.8 (*C*H), 41.4 (*C*H), 40.5 (*C*H), 39.9 (CH_2),

38.7 (*C*H), 33.4 (*C*H_2), 33.2 (*C*H_2), 28.0 (*C*H_2), 23.7 (*C*H_3), 18.5 (*C*H_3), 16.4 (*C*H_3). Additional signals attributed to the minor isomer (*E*)-**2.10**: 142.3 (*C*), 134.1 (*C*H), 129.9 (*C*H), 114.4 (*C*H_2), 38.2 (*C*H), 37.7 (*C*H_2), 18.9 (*C*H_3).

LRMS $^{m}/_{z}$ (EI) 222 (M^+, 10%), 189 (6), 161 (4), 122 (5), 109 (100), 93 (12), 82 (18), 67 (32), 55 (19).

(2*S*,3'*E/Z*,5*S*,6*S*)-5-(2'-Methyl-1',3'-heptadien-6'-yl)-2-methylcyclohexan-1-one, (*Z*)-1.59 and (*E*)-**1.59**

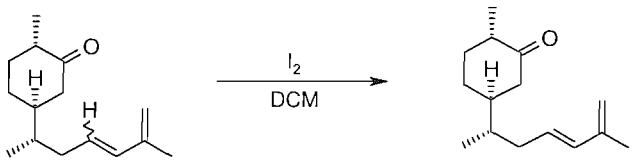


(*Z/E*)-**2.10**
$C_{15}H_{26}O$
(222.37)

(*Z/E*)-**1.59**
$C_{15}H_{24}O$
(220.35)

To a solution of oxalyl chloride (0.13 mL, 1.44 mmol) in DCM (15 mL) at –78 °C was added dimethyl sulfoxide (0.15 mL, 2.16 mmol) over 2 min. After 15 min a solution of alcohol (*Z/E*)-**2.10** (160 mg, 0.720 mmol) in DCM (5 mL) was added, followed after 30 min by triethylamine (0.60 mL, 4.32 mmol). After a further 10 min the reaction mixture was warmed to RT, washed with water (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) gave a 3:1 mixture of (*Z*)-**1.59** and (*E*)-**1.59** as a pale yellow oil (147 mg, 0.667 mmol, 93%). Data for (*E*)-**1.59** is given after the following experimental.

(2*S*,3'*E*,5*S*,6*S*)-5-(2'-Methyl-1',3'-heptadien-6'-yl)-2-methylcyclohexan-1-one, (*E*)-1.59



(*E/Z*)-**1.59**
$C_{15}H_{24}O$
(220.35)

(*E*)-**1.59**
$C_{15}H_{24}O$
(220.35)

To a solution of dienones (*Z*)-**1.59** and (*E*)-**1.59** (*d.r.* 3:1, 383 mg, 1.74 mmol) in DCM (10 mL) was added a solution of iodine (44 mg, 0.1 eq) in DCM (2 mL). After 2 h the reaction mixture was diluted with DCM (30 mL), washed with sat. $Na_2S_2O_3$ (2 x 20 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield dienone (*E*)-**1.59** (380 mg, 1.72 mmol, 99%) as a pale yellow oil.

FT-IR ν_{max} (neat, cm^{-1}) 2964 m, 2929 m, 2868 m, 1711 vs, 1608 w, 1453 m, 1377 m, 966 m, 822 m.

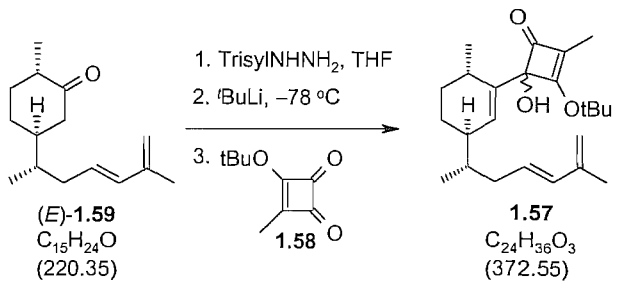
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.14 (1H, d, *J* 15.6 Hz), 5.59 (1H, dt, *J* 15.6, 7.2 Hz), 4.88 (2H, s), 2.41-2.27 (2H, m), 2.26-2.05 (3H, m), 1.96 (1H, app. dt, *J* 15.6, 6.3 Hz), 1.82 (1H, m), 1.83 (3H, s), 1.72 (1H, ddd, *J* 15.6, 8.1, 3.7 Hz), 1.59-1.38 (2H, m), 1.30 (1H, qd, *J* 12.9, 3.4 Hz), 1.02 (3H, d, *J* 6.6 Hz), 0.90 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 213.4 (*C*), 142.2 (*C*), 134.6 (*C*H), 129.1 (*C*H), 114.7 (CH_2), 46.4 (CH_2), 45.2 (*C*H), 44.7 (*C*H), 38.2 (*C*H), 37.5 (CH_2), 35.2 (CH_2), 27.7 (CH_2), 18.9 (CH_3), 16.0 (CH_3), 14.5 (CH_3).

LRMS $^m/_z$ (EI) 220 (M^+, 12%), 205 (3), 109 (100), 69 (42), 55 (50).

HRMS $^m/_z$ (EI) found 220.1835, M^+; $C_{15}H_{24}O$ requires 220.1827.

(3'*R*,3"*E*,4*RS*,6'*S*,6"*S*)-3-(*tert*-Butoxy)-4-hydroxy-2-methyl-4-(6'-methyl-3'-(2"-methyl-1",3"-heptadien-6-yl)-1-cyclohexenyl)-2-cyclobuten-1-one, 1.57



(*E*)-**1.59**
$C_{15}H_{24}O$
(220.35)

1.58

1.57
$C_{24}H_{36}O_3$
(372.55)

To a solution of TrisylNHNH$_2$[53](157 mg, 0.526 mmol) in THF (10 mL) under argon was added a solution of dienone (*E*)-**1.59** (116 mg, 0.526 mmol) in THF (5 mL). After 2 h at RT the reaction was cooled to –78 °C and ^{t}BuLi (1.3 M in pentane, 1.7 mL, 2.10 mmol) added. The resulting orange solution was maintained at –78 °C for 2 h then warmed to –20 °C over 20 min. Once N_2 evolution had ceased, the reaction was cooled to –78 °C and a solution of squarate **1.58** (531 mg, 3.20 mmol) in THF (5 mL) added over 5 min. After a further 20 min water (10 mL) was added and the reaction allowed to warm to RT. Following dilution with ether (20 mL), the aqueous phase was separated and extracted with ether (2 x 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (SiO_2, 5-50% ether/petrol) to give a ~ 3:2 mixture of cyclobutenones **1.57** (71 mg, 0.19 mmol, 36%) as a yellow oil. Data was recorded on the mixture.

FT-IR ν_{max} (neat, cm^{-1}) 3383 bw, 2951 m, 2926 m, 2869 w, 1750 m, 1597 vs, 1385 m, 1339 s, 1158 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) Integrals for the minor diastereoisomer are italicised and were ~ $^2/_3$ the value of the major diastereoisomer: 6.13 (1H + *1H*, d, *J* 15.5 Hz), 5.95 (*1H*, d, *J* 2.8 Hz), 5.69 (1H, bs), 5.63 (1H + *1H*, dt, *J* 15.5, 7.3 Hz), 4.86 (2H + *2H*, s), 2.17-1.90 (3H + *3H*, m), 1.84 (3H, s), 1.82-1.76 (2H + *2H*, m), 1.80 (*3H*, s), 1.73-1.45 (3H + *3H*, m), 1.57 (9H, s), 1.53 (*9H*, s), 1.44 (3H + *3H*, s), 1.29-1.23 (2H + *2H*, m), 1.17 (3H, d, *J* 7.0 Hz), 1.10 (*3H*, d, *J* 7.0), 0.87 (3H, d, *J* 6.8 Hz), 0.83 (*3H*, d, *J* 6.8 Hz).

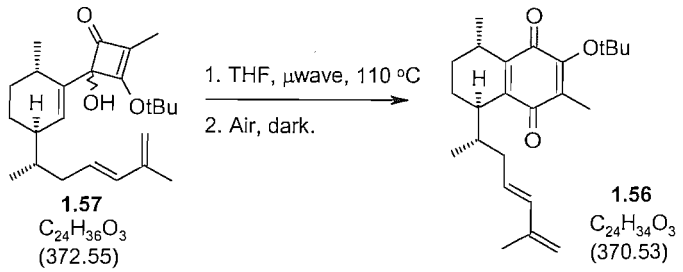
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 193.5 (*C*), 192.4 (*C*), 180.3 (*C*), 178.7 (*C*), 142.3 (2

x *C*), 139.7 (*C*), 139.2 (*C*), 134.2 (2 x *C*H), 130.2 (*C*H), 129.9 (2 x *C*H), 125.7 (*C*H), 122.4 (*C*), 121.8 (*C*), 114.4 (2 x CH_2), 94.9 (*C*), 94.2 (*C*), 83.7 (*C*), 83.3 (*C*), 39.4 (*C*H), 38.7 (*C*H), 38.5 (*C*H), 38.3 (*C*H), 37.9 (CH_2), 37.8 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 30.5 (*C*H), 30.0 (*C*H), 28.9 (3 x CH_3), 28.8 (3 x CH_3), 21.9 (CH_2), 21.0 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 18.9 (2 x CH_3), 16.6 (CH_3), 16.5 (CH_3), 9.7 (CH_3), 9.1 (CH_3).

LRMS $^{m}/_{z}$ (ES^{+}) 767 ($[2M + Na]^{+}$), 395 ($[M + Na]^{+}$).

HRMS $^{m}/_{z}$ (ES^{+}) found 395.2560, $(M + Na)^{+}$; $C_{24}H_{36}NaO_3$ requires 395.2557.

(3'*E*,6*R*,6'*S*,9*S*)-2-(*tert*-Butoxy)-3,9-dimethyl-6-(2'-methyl-1',3'-heptadien-6'-yl)-6,7,8,9-tetrahydro-1,4-napthalenedione, 1.56



1.57
$C_{24}H_{36}O_3$
(372.55)

1.56
$C_{24}H_{34}O_3$
(370.53)

A solution of cyclobutenones **1.57** (25 mg, 0.067 mmol) in THF (2 mL) was heated at 110 °C by microwave irradiation for 30 min. On cooling to RT, the reaction vessel was opened to the atmosphere and stirred in the dark for 24 h. Concentration *in vacuo* and purification by column chromatography (SiO_2, 1% ether/petrol) gave quinone **1.56** (20 mg, 0.054 mmol, 80%) as a bright yellow oil.

FT-IR ν_{max} (neat, cm^{-1}) 2960 s, 2930 s, 2871 m, 1659 vs, 1646 vs, 1607 s, 1369 s, 1144 vs, 1129 s.

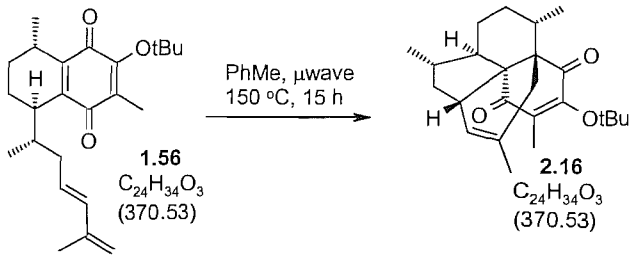
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.13 (1H, d, *J* 15.7 Hz), 5.65 (1H, dt, *J* 15.7, 7.0 Hz), 4.86 (2H, bs), 2.96 (1H, m), 2.85 (1H, m), 2.18-1.99 (2H, m), 1.97 (3H, s), 1.83 (1H, obsc. m), 1.84 (3H, s), 1.74 (1H, m), 1.64 (1H, m), 1.49 (1H, m), 1.40 (9H, s), 1.07 (3H, d, *J* 7.0 Hz), 0.87 (1H, m), 0.82 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 189.2 (*C*), 185.2 (*C*), 154.5 (*C*), 146.9 (*C*), 144.8 (*C*), 142.3 (*C*), 134.4 (*C*), 134.3 (*C*H), 130.1 (*C*H), 114.6 (CH_2), 84.0 (*C*), 39.3 (CH_2), 37.1 (*C*H), 35.3 (*C*H), 29.7 (3 x CH_3), 26.5 (*C*H), 26.3 (CH_2), 21.0 (CH_3), 18.9 (CH_3), 18.3 (CH_2), 17.7 (CH_3), 10.9 (CH_3).

LRMS $^m/_z$ (ES^+) 393 ($[M + Na]^+$).

HRMS $^m/_z$ (ES^+) found 393.2404, $(M + Na)^+$; $C_{24}H_{34}NaO_3$ requires 393.2400.

(–)-Colombiasin A *tert*-butyl ether, 2.16



1.56
$C_{24}H_{34}O_3$
(370.53)

2.16
$C_{24}H_{34}O_3$
(370.53)

A solution of quinone **1.56** (13 mg, 35.1 μmol) in toluene (3 mL) was heated at 150 °C by microwave irradiation for 15 h. After cooling to RT, the solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 1% ether/petrol) to give (–)-colombiasin A *tert*-butyl ether **2.16** (7.9 mg, 21.3 μmol, 61%) as a colourless oil.

FT-IR ν_{max} (neat, cm^{-1}) 2963 m, 2929 s, 1679 s, 1618 w, 1459 w, 1369 m, 1259 w, 1134 m, 1107 m.

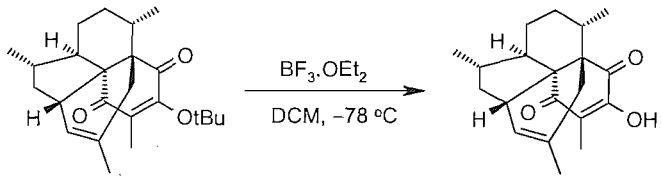
^{1}H NMR δ_H (400 MHz, ($CDCl_3$) 5.64 (1H, bs), 3.05 (1H, m), 2.39 (1H, bd, *J* 18.9 Hz), 2.11 (1H, m), 1.93 (3H, s), 1.91-1.74 (6H, obsc. m), 1.56 (3H, bs), 1.40 (9H, s), 1.38-1.28 (3H, m), 1.32 (3H, d, *J* 7.0 Hz), 0.80 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.5 (*C*), 200.2 (*C*), 153.4 (*C*), 137.4 (*C*), 129.4 (*C*), 123.3 (*C*H), 83.3 (*C*), 63.5 (*C*), 51.5 (*C*), 48.3 (*C*H), 39.6 (*C*H), 38.9 (*C*H), 36.4 (CH_2), 33.5 (CH_2), 33.5 (*C*H), 31.9 (CH_2), 31.3 (CH_2), 29.8 (3 x CH_3), 23.1 (CH_3), 22.5 (CH_3), 18.0 (CH_3), 12.4 (CH_3).

LRMS $^m/_z$ (ES^+) 763 ($[2M + Na]^+$), 425 ($[M + Na + MeOH]^+$), 393 ($[M + Na]^+$).

HRMS $^m/_z$ (ES^+) found 393.2401, $(M + Na)^+$; $C_{24}H_{34}NaO_3$ requires 393.2400.

(–)-Colombiasin A, 1.1



2.16
$C_{24}H_{34}O_3$
(370.53)

1.1
$C_{20}H_{26}O_3$
(314.42)

To a solution of (–)-colombiasin A *tert*-butyl ether **2.16** (3.5 mg, 9.4 μmol) in DCM (1 mL) at 0 °C was added $BF_3.OEt_2$ (1 M in DCM, 19 μL, 19 μmol). After 5 min the reaction mixture was loaded directly onto a chromatography column (silica) and eluted with DCM to give (–)-colombiasin A **1.1** (2.3 mg, 7.3 μmol, 78%) as a colourless film. Physical and spectral characteristics were consistent with those described in the literature.[6,13]

FT-IR ν_{max} (neat, cm^{-1}) 3381 bw, 2960 w, 2928 m, 2873 w, 1667 s, 1450 w, 1379 s, 1343 m, 1108 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.91 (1H, s), 5.69 (1H, bs), 3.06 (1H, bm), 2.42 (1H, bd, *J* 18.8 Hz), 2.13 (1H, dt, *J* 11.7, 9.0 Hz), 1.98-1.80 (6H, m), 1.92 (3H, s), 1.59 (1H, m), 1.57 (3H, bs), 1.38 (3H, d, *J* 7.0 Hz), 1.37-1.25 (2H, m), 0.82 (3H, d, *J* 7.3 Hz).

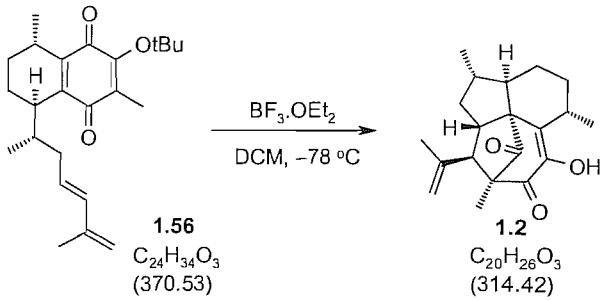
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 202.6 (*C*), 199.6 (*C*), 149.5 (*C*), 128.9 (*C*), 123.8 (*C*H), 120.4 (*C*), 64.0 (*C*), 51.6 (*C*), 48.2 (*C*H), 39.6 (*C*H), 38.7 (*C*H), 36.3 (CH_2), 33.6 (*C*H), 33.5 (CH_2), 31.8 (CH_2), 31.1 (CH_2), 22.9 (CH_3), 22.1 (CH_3), 17.7 (CH_3), 9.8 (CH_3).

LRMS $^m/_z$ (EI) 314 (M^+, 100%), 299 (28), 286 (33), 271 (19), 243 (18), 206 (27), 201 (24), 145 (26).

HRMS $^m/_z$ (EI) found 314.1881, M^+; $C_{20}H_{26}O_3$ requires 314.1882.

$[\alpha]_D$ –58.7° (c = 0.15, $CHCl_3$). Lit.[6] –55.3° (c = 0.9, $CHCl_3$). Lit.[13] –61.0° (c = 0.1, $CHCl_3$).

(–)-Elisapterosin B, 1.2



1.56
$C_{24}H_{34}O_3$
(370.53)

1.2
$C_{20}H_{26}O_3$
(314.42)

To a solution of quinone **1.56** (6.5 mg, 17.5 μmol) in DCM (1 mL) at –78 °C and in the dark was added $BF_3.OEt_2$ (1 M in DCM, 35 μL, 35.0 μmol). After 1 h sat. $NaHCO_3$ (1 mL) was added. The reaction was warmed to RT and partitioned between ether (5 mL) and brine (3 mL). The organic phase was separated, dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (SiO_2, 2-5% ether/petrol) to give (–)-elisapterosin B **1.2** (3.9 mg, 12.4 μmol, 71%) as a white solid. Physical and spectral characteristics were consistent with those described in the literature.[7,15]

MP 48 – 50 °C (ether). Lit.[7,15] not reported.

FT-IR ν_{max} (neat, cm^{-1}) 3426 bw, 2931 m, 1757 s, 1660 s, 1618 m, 1386 m, 1365 m, 1043 m, 1032 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.09 (1H, s), 4.88 (1H, quin., *J* 1.4 Hz), 4.68 (1H, bs), 3.22 (1H, bm), 2.44 (1H, ddd, *J* 11.9, 6.2, 5.6 Hz), 2.31 (1H, m), 2.29 (1H, d, *J* 5.6 Hz), 2.16 (1H, ddd, *J* 12.2, 6.2, 5.9 Hz), 2.02 (1H, app. ddqd, *J* 12.1, 10.3, 6.4, 5.9 Hz), 1.81-1.76 (2H, m), 1.65 (3H, dd, *J* 1.5, 0.7 Hz), 1.53 (1H, m), 1.48 (1H, m), 1.43 (3H, s), 1.15 (3H, d, *J* 7.1 Hz), 1.05 (3H, d, *J* 6.4 Hz), 0.85 (1H, q, *J* 12.1 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.8 (*C*), 193.0 (*C*), 146.1 (*C*), 142.6 (*C*), 141.5 (*C*), 114.8 (CH_2), 70.1 (*C*), 61.5 (*C*), 55.8 (*CH*), 55.0 (*CH*), 42.9 (CH_2), 41.6 (*CH*), 40.2 (*CH*), 28.5 (*CH*), 24.2 (CH_2), 22.8 (CH_3), 19.2 (CH_2), 18.2 (CH_3), 17.7 (CH_3), 13.3 (CH_3).

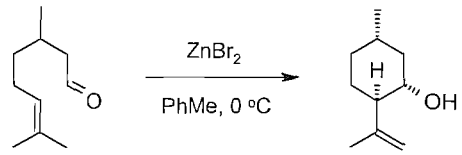
LRMS $^m/_z$ (CI) 315 ($[M + H]^+$, 100%), 287 (12), 271 (8), 243 (6), 206 (50), 109 (34), 93 (18).

HRMS $^m/_z$ (ES^+) found 337.1773, $(M + Na)^+$; $C_{20}H_{26}NaO_3$ requires 337.1774.

$[\alpha]_D$	–33.8° (c = 0.10, $CHCl_3$). Lit.[7] –3.0° (c = 4.4, $CHCl_3$). Lit.[15] –31.5° (c = 0.16, $CHCl_3$).

6.2.2 Experimental for Chapter 3

(±)-Isopulegol, 3.9



3.8
$C_{10}H_{18}O$
(154.25)

3.9
$C_{10}H_{18}O$
(154.25)

The title compound was prepared using the method of Nakatani and Kawashima.[56] To a solution of (±)-citronellal **3.8** (27.3 mL, 151 mmol) in toluene (200 mL) at 0 °C was added anhydrous zinc bromide (38.3 g, 170 mmol) portionwise over 5 min. After 90 min the precipitate was filtered and the solvent removed *in vacuo*. The residual oil was dissolved in ether (200 mL) and washed with water (2 x 150 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% ether/petrol) yielded (±)-isopulegol **3.9** as a colourless oil (16.3 g, 106 mmol, 70%). Spectroscopic data were in agreement with the literature.[56]

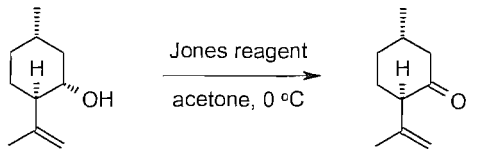
FT-IR ν_{max} (neat, cm^{-1}) 3394 bw, 3074 w, 2949 m, 2921 s, 2868 m, 1645 m, 1448 m, 1375 m, 1095 m, 1051 m, 1027 s, 999 m, 931 w, 885 s, 847 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.89 (1H, quin., *J* 1.5 Hz), 4.84 (1H, bs), 3.45 (1H, td, *J* 10.4, 4.2 Hz), 2.03 (1H, dtd, *J* 12.4, 3.8, 1.8 Hz), 1.92 (1H, bs), 1.87 (1H, ddd, *J* 12.7, 10.4, 3.2 Hz), 1.72-1.58 (2H, obsc. m), 1.70 (3H, dd, *J* 1.5, 0.6 Hz), 1.49 (1H, tqt, *J* 13.0, 6.6, 3.2 Hz), 1.32 (1H, qd, *J* 12.5, 3.5 Hz), 1.03-0.89 (2H, obsc. m), 0.94 (3H, d, *J* 6.6 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 146.8 (*C*), 112.9 (CH_2), 70.5 (*C*H), 54.3 (*C*H), 42.9 (CH_2), 34.5 (CH_2), 31.6 (*C*H), 29.8 (CH_2), 22.4 (CH_3), 19.4 (CH_3).

LRMS $^m/_z$ (EI) 154 (M^+, 4%), 136 ($[M - H_2O]^+$, 14), 121 (35), 93 (31), 81 (30), 67 (37), 55 (47), 41 (100).

(±)-Isopulegone, 3.10



3.9
$C_{10}H_{18}O$
(154.25)

3.10
$C_{10}H_{16}O$
(152.24)

The title compound was prepared using the method of Jones *et al.*[57] To a cooled (0 °C) solution of (±)-isopulegol **3.9** (1.15 g, 7.50 mmol) in acetone (10 mL) was added ice-cooled Jones reagent (1.7 M, 6 mL, 10 mmol) at a rate such that the internal reaction temperature was maintained below 20 °C. After complete addition (1 h) the reaction was warmed to RT, stirred for 2 h and powdered $NaHSO_3$ (~ 1.0 g) added. The aqueous phase was separated and extracted with petrol (4 x 25 mL) then the combined organic phases were washed with brine (75 mL), sat. $NaHCO_3$ (75 mL) and more brine (75 mL), then dried ($MgSO_4$). Concentration *in vacuo* gave (±)-isopulegone **3.10** as a pale yellow oil (951 mg, 6.25 mmol, 83%). Spectroscopic data were in agreement with the literature.[58]

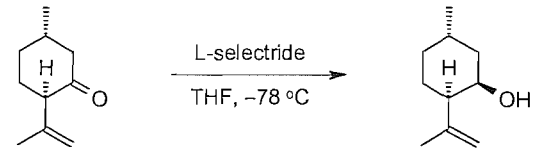
FT-IR ν_{max} (neat, cm^{-1}) 3075 w, 2953 m, 2927 m, 2870 w, 1709 vs, 1648 w, 1455 m, 1374 w, 1191 m, 1126 w, 889 s, 616 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.92 (1H, quin., *J* 1.6 Hz), 4.71 (1H, m), 2.95 (1H, dd, *J* 12.9, 5.3 Hz), 2.39 (1H, ddd, *J* 13.0, 3.8, 2.2 Hz), 2.08-1.71 (5H, m), 1.73 (3H, s), 1.42 (1H, qdd, *J* 12.5, 3.3, 1.5 Hz), 1.03 (3H, d, *J* 6.2 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 210.3 (*C*), 143.6 (*C*), 113.0 (CH_2), 57.9 (*C*H), 50.7 (CH_2), 35.5 (*C*H), 34.0 (CH_2), 31.4 (CH_2), 22.5 (CH_3), 21.5 (CH_3).

LRMS $^m/_z$ (EI) 152 (M^+, 83%), 137 ($[M - CH_3]^+$, 62), 123 (99), 109 (100), 93 (91), 81 (86), 67 (92), 53 (77).

(±)-Neoisopulegol, 3.1



3.10
$C_{10}H_{16}O$
(152.24)

3.1
$C_{10}H_{18}O$
(154.25)

The title compound was prepared using the method of Friedrich and Bohlmann.[58] To a solution of (±)-isopulegone **3.10** (1.59 g, 10.4 mmol) in THF (60 mL) at –78 °C was added L-selectride (1 M in THF, 11.5 mL, 11.5 mmol) over 5 min. After 30 min the reaction was warmed to RT and treated with 10% aq. NaOH (16 mL) followed by careful dropwise addition of 30% aq. H_2O_2 (12 mL). After 30 min the reaction mixture was extracted with ether (2 x 75 mL) and the combined organic phases washed with sat. $NaHSO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-10% ether/petrol) yielded (±)-neoisopulegol **3.1** as a pale yellow oil (1.36 g, 8.78 mmol, 84%). Spectroscopic data were in agreement with the literature.[58]

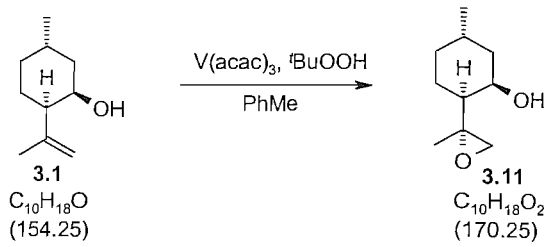
FT-IR ν_{max} (neat, cm^{-1}) 3394 bw, 3074 w, 2949 m, 2921 s, 2868 m, 1645 m, 1448 m, 1375 m, 1095 m, 1051 m, 1027 s, 999 m, 931 w, 885 s, 847 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.95 (1H, s), 4.79 (1H, s), 3.99 (1H, bs), 2.03-1.93 (2H, m), 1.87-1.65 (3H, obsc. m), 1.79 (3H, s), 1.54-1.43 (2H, m), 1.13 (1H, ddd, *J* 13.8, 12.0, 2.6), 0.92 (1H, qd, *J* 12.2, 3.4 Hz), 0.89 (3H, d, *J* 6.4 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 147.5 (*C*), 111.4 (CH_2), 66.5 (*C*H), 48.6 (*C*H), 41.1 (CH_2), 35.0 (CH_2), 26.0 (*C*H), 24.1 (CH_2), 22.9 (CH_3), 22.4 (CH_3).

LRMS $^m/_z$ (EI) 154 (M^+, 6%), 136 ($[M - H_2O]^+$, 11), 121 (33), 93 (35), 81 (27), 67 (37), 55 (100).

***rel*-(1*R*,1'*S*,2*S*,5*S*)-2-(1'-Methyl-1',2'-epoxyethyl)-5-methylcyclohexan-1-ol, 3.11**



3.1
$C_{10}H_{18}O$
(154.25)

3.11
$C_{10}H_{18}O_2$
(170.25)

The title compound was prepared using the method of Friedrich and Bohlmann.[58] To a solution of (±)-neoisopulegol **3.1** (6.03 g, 39.1 mmol) and vanadium(III) acetylacetenoate (150 mg) in toluene (60 mL) was added *tert*-butylhydroperoxide (70% aq., 7.0 g, 54.7 mmol). After 3 h the reaction mixture was partitioned between ether (100 mL) and water (75 mL). The aqueous phase was separated and extracted with ether (2 x 100 mL) then the combined organic phases were washed with sat. $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-30% ether/petrol) yielded epoxy alcohol **3.11** as a white crystalline solid (5.33 g, 31.3 mmol, 80%). Spectroscopic data were in agreement with the literature.[58]

MP 57-58 °C (ether/petrol). Lit.[58] 56-58 °C.

FT-IR ν_{max} (neat, cm^{-1}) 3470 bw, 2945 s, 2923 s, 2867 m, 2845 w, 1455 m, 1377 m, 1288 w, 1251 w, 1179 m, 1122 m, 1078 m, 1025 s, 945 s, 906 m, 855 m, 800 m.

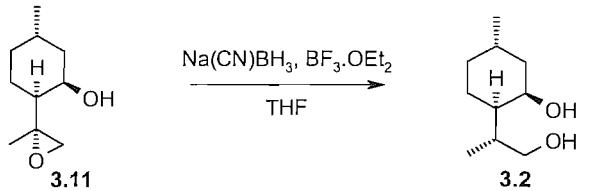
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.31 (1H, bs), 2.79 (1H, d, *J* 4.5 Hz), 2.59 (1H, bs), 2.48 (1H, d, *J* 4.5 Hz), 1.87 (1H, dq, *J* 13.6, 3.5 Hz), 1.83-1.70 (2H, m), 1.52-1.41 (3H, m), 1.39 (3H, s), 1.06 (1H, ddd, *J* 13.6, 11.8, 2.0 Hz), 0.91 (1H, qd, *J* 11.8, 3.8 Hz), 0.86 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 68.0 (*C*H), 60.4 (*C*), 51.5 (CH_2), 44.5 (*C*H), 42.1 (CH_2), 34.7 (CH_2), 25.7 (*C*H), 22.4 (CH_2), 22.3 (CH_3), 22.0 (CH_3).

LRMS $^m/_z$ (CI) 188 ($[M + NH_4]^+$, 6%), 171 ($[M + H]^+$, 8), 153 (100), 135 (37), 123 (34), 108 (63), 95 (37), 81 (36).

CHN Found C 70.56%, H 10.62%; $C_{10}H_{18}O$ requires C 70.55%, H 10.66%.

***rel*-(1*R*,1'*S*,2*R*,5*S*)-2-(2'-Hydroxy-1'-methylethyl)-5-methylcyclohexan-1-ol, 3.2**



3.11
$C_{10}H_{18}O_2$
(170.25)

3.2
$C_{10}H_{20}O_2$
(172.27)

The title compound was prepared using the method of Kocienski *et al.*[59] To a solution of epoxy alcohol **3.11** (6.55 g, 38.5 mmol) in THF (40 mL) was added bromocresol green (5 drops) followed by sodium cyanoborohydride (6.04 g, 96.2 mmol) causing the reaction mixture to turn light blue in colour. A solution of $BF_3.OEt_2$ in THF (0.8 M) was then added dropwise until a yellow colouration persisted. This colour was maintained over a 4 h period by further dropwise addition of the $BF_3.OEt_2$ solution (15 mL, 12 mmol added in total). Brine (40 mL) was then added and the mixture extracted with EtOAc (4 x 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40-50% EtOAc/petrol) afforded diol **3.2** as a colourless oil (5.57 g, 32.3 mmol, 84%). Spectroscopic data were in agreement with the literature.[55]

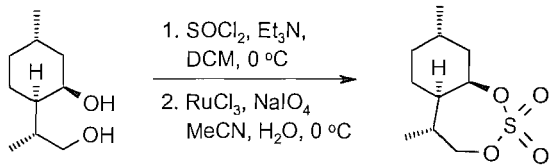
FT-IR ν_{max} (neat, cm^{-1}) 3281 bm, 2946 m, 2916 s, 2869 m, 1454 m, 1373 w, 1334 w, 1256 w, 1183 w, 1134 w, 1034 s, 917 m, 934 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.13 (1H, bs), 3.68 (1H, dd, *J* 10.8, 2.9 Hz), 3.55 (1H, dd, *J* 10.8, 5.9 Hz), 3.11 (2H, bs), 1.89-1.44 (6H, m), 1.27-1.08 (2H, m), 0.99 (3H, d, *J* 7.1 Hz), 0.91 (1H, obsc. m), 0.88 (3H, d, *J* 6.4 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 66.8 (*C*H), 65.3 (*C*H_2), 46.1 (*C*H), 42.5 (*C*H_2), 38.3 (*C*H), 35.6 (*C*H_2), 26.4 (*C*H), 25.6 (*C*H_2), 22.5 (*C*H_3), 16.1 (*C*H_3).

LRMS $^m/_z$ (EI) 172 (M^+, 2%), 154 ([M – H_2O)$^+$, 13), 137 (12), 123 (17), 112 (20), 95 (45), 81 (64), 55 (64), 41 (100).

***rel*-(5*R*,5a*R*,8*S*,9a*R*)-5,8-Dimethyl-octahydro-benzo[*d*][1,3,2]dioxathiepine-2,2-dioxide, 3.12**



3.2
$C_{10}H_{20}O_2$
(172.27)

3.12
$C_{10}H_{18}O_4S$
(234.32)

The title compound was prepared by adapting the method of Moon-Kim and Sharpless.[62] To a solution of diol **3.2** (2.36 g, 13.7 mmol) and triethylamine (4.8 mL, 34.3 mmol) in DCM (60 mL) at 0 °C was added thionyl chloride (1.1 mL, 15.1 mmol) dropwise. After 5 min sat. NH_4Cl (20 mL) was added, the reaction mixture warmed to RT and extracted with ether (3 x 75 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude orange oil (3.0 g). The crude material was dissolved in acetonitrile (50 mL), cooled to 0 °C and then treated with sodium metaperiodate (4.4 g, 20.6 mmol) followed by a solution of ruthenium trichloride hydrate (0.3 mg) in water (20 mL). After 1 h the reaction mixture was partitioned between ether (75 mL) and water (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) gave cyclic sulfate **3.12** as a white crystalline solid (2.85 g, 12.2 mmol, 89%).

MP 71-72 °C (ether/petrol).

FT-IR ν_{max} (neat, cm^{-1}) 2971 w, 2950 w, 2889 w, 1447 w, 1372 s, 1358 s, 1336 m, 1201 m, 1185 s, 938 s, 901 vs, 819 s, 692 s.

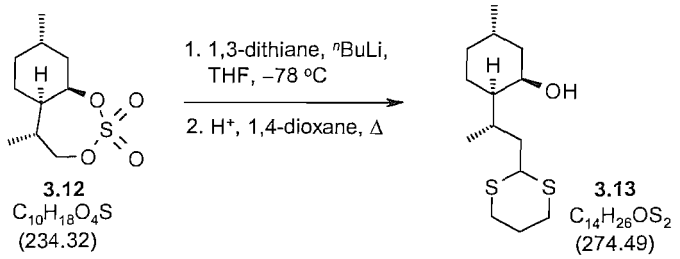
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.06 (1H, bs), 4.65 (1H, d, *J* 12.3 Hz), 4.04 (1H, dd, *J* 12.3, 2.8 Hz), 2.13 (1H, d with fine splitting, *J* 12.3 Hz), 1.94-1.73 (4H, m), 1.52-1.43 (2H, m), 1.23 (3H, d, *J* 7.3 Hz), 1.20 (1H, obsc. m), 1.04 (1H, qd, *J* 12.8, 3.8 Hz), 0.91 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 80.0 (*C*H), 72.6 (*C*H_2), 44.6 (*C*H), 39.6 (*C*H_2), 37.5 (*C*H), 34.4 (*C*H_2), 27.0 (*C*H_2), 26.3 (*C*H), 22.0 (*C*H_3), 17.1 (*C*H_3).

LRMS $^{m}/_{z}$ (ES^{+}) 491 ($[2M + Na]^{+}$), 289 ($[M + Na + MeOH]^{+}$), 257 ($[M + Na]^{+}$).

CHN Found C 51.16%, H 7.84%, S 14.14%; $C_{10}H_{18}O_4S$ requires C 51.26%, H 7.74%, S 13.68%.

***rel*-(1*R*,2*R*,2'*S*,5*S*)-2-(1'-(1",3"-Dithian-2"-yl)-prop-2'-yl)-5-methylcyclohexanol, 3.13**



3.12
$C_{10}H_{18}O_4S$
(234.32)

3.13
$C_{14}H_{26}OS_2$
(274.49)

To a solution of 1,3-dithiane (1.65 g, 13.7 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (1.72 M in hexanes, 8.0 mL, 13.7 mmol) dropwise. After 15 min the reaction was warmed to RT, stirred for 1 h, then re-cooled to –78 °C and a solution of cyclic sulfate **3.12** (2.68 g, 11.4 mmol) in THF (25 mL) added. After 30 min the reaction was allowed to warm to RT and stirred for a further 1 h. The solvent was removed *in vacuo* and the residual oil dissolved in 1,4-dioxane (40 mL). To this solution was added water (1 mL) followed by 2 M H_2SO_4 (0.2 mL) and the reaction heated at reflux for 1 h. On cooling to RT the mixture was partitioned between ether (75 mL) and water (50 mL). The aqueous phase was separated and extracted with ether (2 x 75 mL) then the combined organic phases were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) yielded dithiane **3.13** as a white crystalline solid (2.40 g, 8.75 mmol, 77%).

MP 73-74 °C (ether/petrol).

FT-IR ν_{max} (neat, cm^{-1}) 3460 bw, 2944 s, 2907 s, 2867 m, 2842 m, 1454 m, 1422 m, 1376 w, 1275 m, 1243 w, 1178 m, 1139 w, 1024 m, 961 m, 937 m, 908 m, 854 w, 772 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.08 (1H, bs), 4.06 (1H, dd, *J* 10.3, 4.6 Hz), 2.87 (1H, td, *J* 13.8, 2.6 Hz), 2.83-2.77 (3H, m), 2.12 (1H, d with fine splitting, *J* 13.3 Hz), 1.99 (1H, ddd, *J* 13.8, 10.3, 3.5 Hz), 1.92-1.69 (6H, m), 1.56 (1H, dq, *J* 13.3, 3.3 Hz), 1.48 (1H, ddd, *J* 13.8, 9.3, 4.6 Hz), 1.36 (1H, qd, *J* 13.1, 3.3 Hz), 1.13-0.99 (2H, m), 0.94 (3H, d, *J* 6.5 Hz), 0.85 (1H, obsc. m), 0.85 (3H, d, *J* 6.3 Hz).

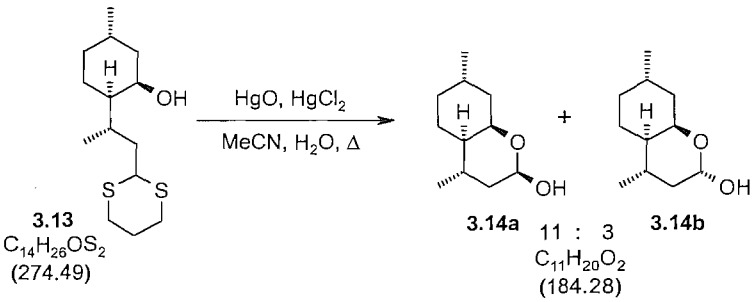
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 67.8 (*C*H), 46.4 (*C*H), 45.9 (*C*H), 42.8 (*C*H_2), 40.3 (*C*H_2), 35.2 (*C*H_2), 31.7 (*C*H), 30.6 (*C*H_2), 30.2 (*C*H_2), 26.2 (*C*H_2), 26.0 (*C*H), 23.8 (*C*H_2), 22.4 (*C*H_3), 17.8 (q, *C*H_3).

LRMS $^m/_z$ (EI) 274 (M^+, 28%), 256 ([M – H_2O]$^+$, 12), 181 (16), 167 (68), 149 (81), 132 (100), 119 (92), 106 (38), 95 (29), 81 (39), 67 (34), 55 (78).

HRMS $^m/_z$ (EI) found 274.1426, M^+; $C_{14}H_{26}OS_2$ requires 274.1425.

CHN Found C 60.96%, H 9.61%, S 23.50%; $C_{14}H_{26}OS_2$ requires C 61.26%, H 9.55%, S 23.36%.

***rel*-(2*R*,4*S*,4a*R*,7*S*,8a*R*)-2-Hydroxy-4,7-dimethylperhydrobenzo[b]pyran, 3.14a** and ***rel*-(2*S*,4*S*,4a*R*,7*S*,8a*R*)-2-Hydroxy-4,7-dimethylperhydrobenzo[b]pyran, 3.14b**



3.13 $C_{14}H_{26}OS_2$ (274.49)

3.14a 11 : 3 **3.14b** $C_{11}H_{20}O_2$ (184.28)

The title compounds were prepared by adapting the method of Harrowven.[66] To a solution of dithiane **3.13** (95 mg, 0.346 mmol) in 10% aq. acetonitrile (10 mL) was added mercury(II) oxide (82 mg, 0.381 mmol) followed by mercury(II) chloride (216 mg, 0.796 mmol). The reaction was heated at reflux for 1 h, cooled to RT then partitioned between sat. $NaHCO_3$ (30 mL) and chloroform (30 mL). The aqueous phase was separated and extracted with chloroform (30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered through a pad of celite and

concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) afforded an inseparable mixture of lactols **3.14a** and **3.14b** as a colourless oil (51 mg, 0.277 mmol, 80%, *d.r.* ~ 11:3 of **3.14a**:**3.14b**).

FT-IR ν_{max} (neat, cm^{-1}) 3391 bw, 2947 m, 2922 s, 2868 m, 1455 m, 1377 w, 1328 w, 1194 m, 1122 m, 1039 s, 1012 s, 994 s, 953 s, 878 w.

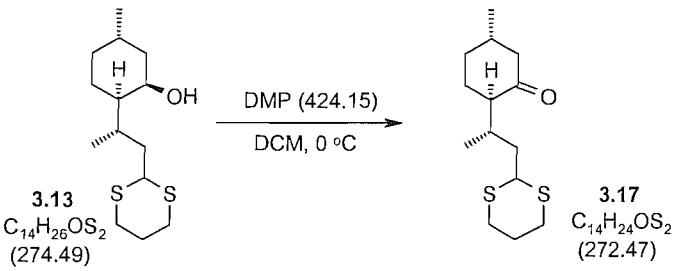
^{1}H NMR δ_H (400 MHz, $CDCl_3$) Major isomer: 4.94 (1H, dd, *J* 10.0, 2.2 Hz), 3.93 (1H, bs), 3.71 (1H, bs), 1.95-1.58 (7H, m), 1.49 (1H, app.dt, *J* 13.2, 2.2 Hz), 1.35 (1H, m), 1.10 (3H, d, *J* 7.3 Hz), 1.07 (1H, m), 0.92 (1H, m), 0.85 (3H, d, *J* 6.5 Hz). Additional signals attributed to the minor isomer (3/11 the integral): 5.28 (1H, bs), 4.33 (1H, bs), 3.03 (1H, bs), 1.22 (3H, d, *J* 7.3 Hz), 0.87 (3H, d, *J* 6.4 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) Major isomer: 93.8 (*C*H), 69.9 (*C*H), 40.2 (*C*H_2), 40.1 (*C*H), 35.0 (*C*H_2), 34.7 (*C*H_2), 32.5 (*C*H), 27.5 (*C*H_2), 26.7 (*C*H), 22.5 (*C*H_3), 19.7 (*C*H_3). Minor isomer: 93.3 (*C*H), 62.9 (*C*H), 40.8 (*C*H_2), 39.9 (*C*H), 34.8 (*C*H_2), 31.7 (*C*H_2), 30.6 (*C*H), 27.3 (*C*H_2), 26.8 (*C*H), 22.5 (*C*H_3), 21.7 (*C*H_3).

LRMS $^m/_z$ (EI) 184 (M^+, 11%), 166 ([M – H_2O]$^+$, 31), 151 (81), 127 (57), 109 (25), 95 (42), 81 (100), 67 (38).

HRMS $^m/_z$ (EI) found 184.1459 M^+; $C_{11}H_{20}O_2$ requires 184.1463.

***rel*-(2*R*,2'*S*,5*S*)-2-(1'-(1",3"-Dithian-2"-yl)-prop-2'-yl)-5-methylcyclohexanone, 3.17**



3.13
$C_{14}H_{26}OS_2$
(274.49)

3.17
$C_{14}H_{24}OS_2$
(272.47)

To a solution of alcohol **3.13** (963 mg, 3.51 mmol) in DCM (30 mL) at 0 °C was added DMP (2.08 g, 4.91 mmol). After 4 h, 1 M NaOH (20 mL) was added, the reaction mixture warmed to RT and extracted with ether (2 x 50 mL). The combined organic phases were washed with 1 M NaOH (25 mL), water (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% ether/petrol) yielded ketone **3.17** as a white crystalline solid (581 mg, 2.13 mmol, 61%).

MP 90-92 °C (ether/petrol).

FT-IR ν_{max} (neat, cm^{-1}) 2924 m, 2900 m, 2865 w, 2831 w, 1696 s, 1451 w, 1421 m, 1375 m, 1278 m, 1249 w, 1203 m, 1125 w, 906 m, 867 m, 772 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.02 (1H, dd, *J* 8.5, 6.3 Hz), 2.87 (1H, td, *J* 14.0, 2.8 Hz), 2.85-2.77 (3H, m), 2.48-2.39 (1H, m), 2.36 (1H, d with fine splitting, *J* 13.3 Hz), 2.20 (1H, dt, *J* 12.6, 4.3 Hz), 2.14-2.05 (1H, m), 2.02-1.78 (5H, m), 1.70 (1H, ddd, *J* 14.1, 8.5, 5.8 Hz), 1.63 (1H, ddd, *J* 14.1, 8.0, 6.3 Hz), 1.44 (1H, qd, *J* 12.8, 2.8 Hz), 1.35 (1H, qd, *J* 12.8, 2.8 Hz), 1.00 (3H, d, *J* 6.3 Hz), 0.89 (3H, d, *J* 6.8 Hz).

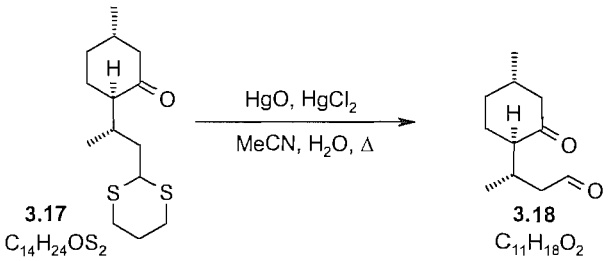
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 211.3 (*C*), 53.8 (*C*H), 50.9 (CH_2), 45.7 (*C*H), 40.4 (CH_2), 35.2 (*C*H), 34.0 (CH_2), 30.6 (CH_2), 30.3 (CH_2), 28.4 (*C*H), 27.1 (CH_2), 26.2 (CH_2), 22.5 (CH_3), 16.2 (CH_3).

LRMS $^m/_z$ (EI) 272 (M^+, 26%), 164 (32), 134 (37), 119 (100), 106 (17), 85 (41).

CHN Found C 61.50%, H 8.90%, S 23.41%; $C_{14}H_{24}OS_2$ requires C 61.72%,

H 8.88%, S 23.53%.

***rel*-(1'*R*,3*S*,4'*S*)-3-(2'-Oxy-4'-methylcyclohexyl)butanal, 3.18**



3.17
$C_{14}H_{24}OS_2$
(272.47)

3.18
$C_{11}H_{18}O_2$
(182.26)

To a solution of dithiane **3.17** (121 mg, 0.444 mmol) in 10% aq. acetonitrile (10 mL) was added mercury (II) oxide (105 mg, 0.488 mmol) followed by mercury (II) chloride (277 mg, 1.02 mmol). The reaction was heated at reflux for 45 min then cooled to RT and partitioned between chloroform (30 mL) and sat. $NaHCO_3$ (30 mL). The aqueous phase was separated and extracted with chloroform (30 mL), then the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), filtered through a pad of celite and concentrated *in vacuo* to yield dicarbonyl **3.18** as a colourless oil (73 mg, 0.401 mmol, 90%).

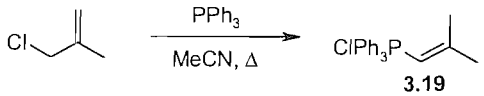
FT-IR ν_{max} (neat, cm^{-1}) 2951 s, 2926 s, 2869 m, 2719 w, 1706 vs, 1454 w, 1377 w, 1235 w, 1198 w, 1005 w, 962 w.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.73 (1H, app. t, *J* 2.2 Hz), 2.60 (1H, m), 2.44 (1H, ddd, *J* 16.3, 5.3, 1.8 Hz), 2.37 (1H, ddd, *J* 12.8, 3.8, 2.3 Hz), 2.32 (1H, ddd, *J* 16.3, 8.1, 2.6 Hz), 2.24-1.79 (4H, m), 1.44-1.26 (3H, m), 1.02 (3H, d, *J* 6.2 Hz), 0.93 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 211.6 (*C*), 202.6 (*C*H), 53.9 (*C*H), 51.0 (CH_2), 49.3 (CH_2), 35.6 (*C*H), 34.1 (CH_2), 28.6 (CH_2), 26.5 (*C*H), 22.5 (CH_3), 17.1 (CH_3).

LRMS $^m/_z$ (EI) 182 (M^+, 32%), 164 (22), 139 (96), 112 (100), 97 (70), 81 (54), 69 (86).

2-Methyl-1-propenylphosphonium chloride, 3.19



C_4H_7Cl
(90.55)

3.19
$C_{22}H_{22}ClP$
(352.84)

The title compound was prepared using the method of Baird *et al.*[103] A solution of triphenylphosphine (10.9 g, 41.4 mmol) and methallyl chloride (5.0 g, 55.2 mmol) in acetonitrile (40 mL) was heated at reflux for 24 h. After cooling to RT the precipitate was filtered, washed with petrol (100 mL) and dried *in vacuo* to yield phosphonium salt **3.19** as a white powder (12.3 g, 34.9 mmol, 84%). Spectroscopic data were in agreement with the literature.[104]

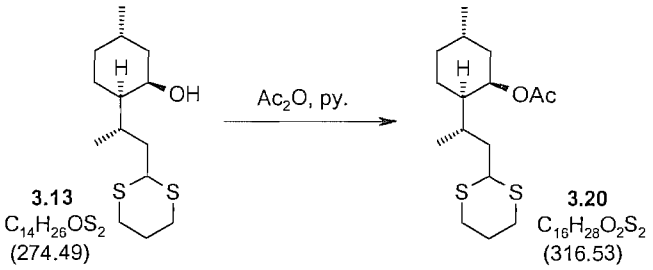
FT-IR ν_{max} (neat, cm^{-1}) 3048 w, 2978 w, 2854 m, 2768 m, 1638 w, 1585 w, 1482 m, 1432 s, 1167 m, 1108 s, 993 m, 915 m, 878 w.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.80-7.54 (15H, m), 6.48 (1H, d, *J* 22.9 Hz), 2.37 (3H, s), 1.70 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 172.3 (*C*), 135.1 (3 x *C*H), 133.4 (6 x *C*H ($J_{C\text{-}P}$ 11 Hz)), 130.8 (6 x *C*H ($J_{C\text{-}P}$ 12 Hz)), 119.5 (3 x *C* ($J_{C\text{-}P}$ 89 Hz)), 102.9 (*C*H ($J_{C\text{-}P}$ 88 Hz)), 30.1 (CH_3 ($J_{C\text{-}P}$ 19 Hz)), 24.9 (CH_3 ($J_{C\text{-}P}$ 8 Hz)).

LRMS $^m/_z$ (ES^+) 317 ($[M - Cl]^+$, 100%).

***rel*-(1*R*,2*R*,2'*S*,5*S*)-2-(1'-(1'',3''-Dithian-2''-yl)-prop-2'-yl)-5-methylcyclohexyl acetate, 3.20**



3.13
$C_{14}H_{26}OS_2$
(274.49)

3.20
$C_{16}H_{28}O_2S_2$
(316.53)

The title compound was prepared using the method of White *et al.*[67] To a solution of alcohol **3.13** (920 mg, 3.35 mmol) in pyridine (10 mL) at 0 °C was added acetic anhydride (16 mL, 168 mmol). The reaction mixture was warmed to RT and after 64 h poured onto a mixture of crushed ice (100 mL) and 2 M HCl (100 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic phases washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% ether/petrol) yielded acetate **3.20** as a white crystalline solid (1.05 g, 3.31 mmol, 99%).

MP 104-106 °C (ether/petrol).

FT-IR ν_{max} (neat, cm^{-1}) 2945 m, 2921 m, 2865 w, 2846 w, 1731 s, 1454 w, 1374 m, 1239 s, 1176 w, 1024 m, 963 w, 909 w.

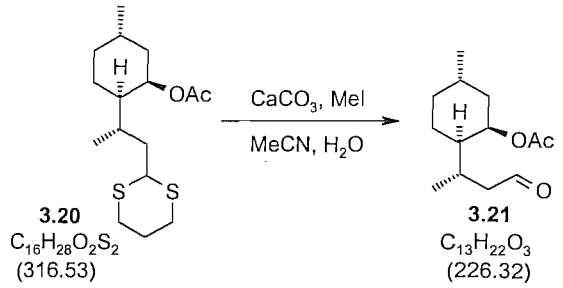
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.14 (1H, bs), 4.00 (1H, dd, *J* 10.0, 4.5 Hz), 2.86 (1H, td, *J* 14.1, 2.8 Hz), 2.83-2.75 (3H, m), 2.06 (1H, obsc. m), 2.03 (3H, s), 1.98-1.81 (3H, m), 1.78-1.70 (2H, m), 1.66-1.54 (2H, m), 1.49-1.34 (2H, m), 1.16 (1H, m), 1.00 (1H, qd, *J* 12.3, 3.5 Hz), 0.91 (3H, d, *J* 6.8 Hz), 0.90 (1H, obsc. m), 0.84 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 170.7 (*C*), 71.4 (*C*H), 45.6 (*C*H), 45.0 (*C*H), 40.2 (CH_2), 39.3 (CH_2), 34.9 (CH_2), 31.8 (*C*H), 30.5 (CH_2), 30.0 (CH_2), 26.8 (*C*H), 26.2 (CH_2), 24.6 (CH_2), 22.2 (CH_3), 21.6 (CH_3), 17.2 (CH_3).

LRMS $^m/_z$ (EI) 316 (M^+, 6%), 256 ([M – AcOH]$^+$, 15), 207 (5), 181 (23), 149 (22), 132 (100), 119 (72), 106 (28).

CHN Found C 60.80%, H 8.96%, S 20.28%; $C_{16}H_{28}O_2S_2$ requires C 60.72%, H 8.92%, S 20.26%.

***rel*-(1'*R*,2'*R*,3*S*,4'*S*)-3-(2'-Acetoxy-4'-methylcyclohexyl)butanal, 3.21**



3.20
$C_{16}H_{28}O_2S_2$
(316.53)

3.21
$C_{13}H_{22}O_3$
(226.32)

The title compound was prepared using the method of White *et al.*[67] To a solution of dithiane **3.20** (85 mg, 0.269 mmol) in 10% aq. acetonitrile (10 mL) was added calcium carbonate (483 mg, 4.83 mmol) followed by methyl iodide (0.84 mL, 13.5 mmol) and the reaction stirred at RT for 16 h. The mixture was diluted with EtOAc (50 mL) then filtered through a glass wool plug. The filtrate was washed with brine (2 x 25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) afforded aldehyde **3.21** as a pale yellow oil (55 mg, 0.243 mmol, 90%).

FT-IR ν_{max} (neat, cm^{-1}) 2947 m, 2923 m, 2868 w, 2844 w, 2716 w, 1730 vs, 1445 w, 1374 m, 1240 s, 1183 w, 1024 m, 964 w.

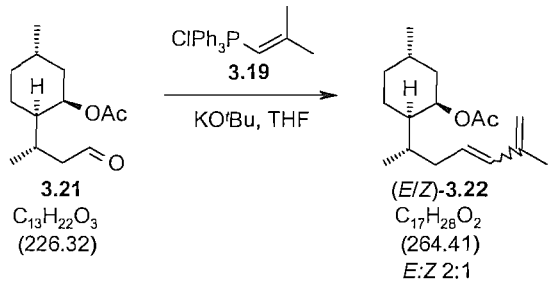
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 9.69 (1H, dd, *J* 2.8, 1.3 Hz), 5.16 (1H, bs), 2.56 (1H, dd, *J* 16.3, 3.5 Hz), 2.16 (1H, ddd, *J* 16.3, 9.1, 2.8 Hz), 2.05 (3H, s), 2.03-1.88 (2H, m), 1.77 (1H, d with fine splitting, *J* 13.1 Hz), 1.72-1.57 (2H, m), 1.41 (1H, qd, *J* 12.8, 3.5 Hz), 1.23 (1H, bm), 1.05 (1H, td, *J* 13.5, 2.3 Hz), 0.93 (1H, obsc. m), 0.95 (3H, d, *J* 6.5 Hz), 0.86 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 202.7 (*C*H), 170.7 (*C*), 70.9 (*C*H), 48.8 (CH_2), 44.8 (*C*H), 39.3 (CH_2), 34.8 (CH_2), 29.8 (*C*H), 26.7 (*C*H), 24.8 (CH_2), 22.2 (CH_3), 21.5 (CH_3), 18.3 (CH_3).

LRMS $^m/_z$ (CI) 244 ($[M + NH_4]^+$, 60%), 227 ($[M + H]^+$, 16), 167 (100), 149 (36), 122 (23), 95 (19).

HRMS $^{m}/_{z}$ (ES^{+}) found 249.1460, $(M + Na)^{+}$; $C_{13}H_{22}NaO_3$ requires 249.1461.

***rel*-(1*R*,3*S*,3'*E/Z*,6*R*,6'*S*)-6-(2'-Methylhepta-1',3'-dien-6'-yl)-3-methylcyclohexyl acetate,** (*E*)-**3.22** and (*Z*)-**3.22**



3.21
$C_{13}H_{22}O_3$
(226.32)

(*E/Z*)-**3.22**
$C_{17}H_{28}O_2$
(264.41)
E:*Z* 2:1

The title compound was prepared by adapting the method of Nicolaou *et al.*[13] To a suspension of phosphonium salt **3.19** (2.04 g, 5.79 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (650 mg, 5.79 mmol) causing the reaction mixture to turn red. After 1 h, a solution of aldehyde **3.21** (873 mg, 3.86 mmol) in THF (20 mL) was added over 2 min and the reaction warmed to RT. After 1 h, the reaction mixture was heated at reflux for 4 h, allowed to cool to RT and partitioned between water (50 mL) and ether (75 mL). The aqueous phase was separated and extracted with ether (2 x 75 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) gave dienes (*E/Z*)-**3.22** as a pale yellow oil (948 mg, 3.59 mmol, 93%) and an inseparable 2:1 mixture of *E*:*Z* isomers.

Data for the *E* isomer is provided after the following experimental.

***rel*-(1*R*,3*S*,3'*E*,6*R*,6'*S*)-6-(2'-Methylhepta-1',3'-dien-6'-yl)-3-methylcyclohexyl acetate, (*E*)-3.22**

(*E*/*Z*)-**3.22**
$C_{17}H_{28}O_2$
(264.41)
E:*Z* 2:1

(*E*)-**3.22**
$C_{17}H_{28}O_2$
(264.41)
100% *E*

To a solution of diene (*E*/*Z*)-**3.22** (114 mg, 0.431 mmol) in DCM (9 mL) was added a solution of iodine (6 mg, 0.026 mmol) in DCM (1 mL). After 3 h the solvent was removed *in vacuo* and the residue dissolved in ether (30 mL). The organic phase was washed with sat. $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield diene (*E*)-**3.22** as a colourless oil (114 mg, 0.431 mmol, 100%) and a single *E* isomer.

FT-IR ν_{max} (neat, cm^{-1}) 2946 m, 2920 s, 2849 m, 1735 s, 1608 w, 1455 w, 1374 m, 1240 s, 1177 w, 1023 w, 964 m, 882 w.

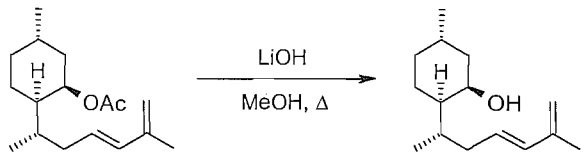
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.12 (1H, d, *J* 15.6 Hz), 5.58 (1H, dt, *J* 15.6, 7.4 Hz), 5.21 (1H, bs), 4.87 (2H, s), 2.24 (1H, ddd, *J* 12.5, 7.4, 5.3 Hz), 2.06 (3H, s), 1.98-1.86 (2H, m), 1.83 (3H, s), 1.76 (1H, d with fine splitting, *J* 12.8 Hz), 1.70-1.56 (2H, m), 1.49 (1H, m), 1.41 (1H, qd, *J* 12.9, 3.5 Hz), 1.21 (1H, m), 1.05 (1H, ddd, *J* 14.6, 12.6, 2.3 Hz), 0.93 (1H, obsc. qd, *J* 13.1, 3.8 Hz), 0.89 (3H, d, *J* 6.8 Hz), 0.86 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 170.9 (*C*), 142.3 (*C*), 134.6 (*C*H), 129.1 (*C*H), 114.5 (CH_2), 71.7 (*C*H), 44.4 (*C*H), 39.4 (CH_2), 37.8 (CH_2), 35.0 (CH_2), 34.8 (*C*H), 26.8 (*C*H), 24.6 (CH_2), 22.3 (CH_3), 21.6 (CH_3), 18.9 (CH_3), 17.4 (CH_3).

LRMS $^m/_z$ (CI) 265 (MH^+, 14%), 205 ($[M - OAc]^+$, 100), 149 (10), 123 (14), 107 (36).

HRMS $^m/_z$ (ES^+) found 287.1985, $(M + Na)^+$; $C_{17}H_{28}NaO_2$ requires 287.1981.

***rel*-(1*R*,3*S*,3'*E*,6*R*,6'*S*)-6-(2'-Methylhepta-1',3'-dien-6'-yl)-3-methylcyclohexanol, 3.16**



(*E*)-**3.22**
$C_{17}H_{28}O_2$
(264.41)

3.16
$C_{15}H_{26}O$
(222.37)

To a solution of acetate (*E*)-**3.22** (50 mg, 0.189 mmol) in methanol (2 mL) was added 2 M LiOH (0.30 mL, 0.567 mmol) and the reaction heated at reflux for 16 h. On cooling to RT the reaction mixture was partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), concentrated *in vacuo* then purified by column chromatography (SiO_2, 10% ether/petrol) to yield dienol **3.16** as a pale yellow oil (39 mg, 0.175 mmol, 93%).

FT-IR ν_{max} (neat, cm^{-1}) 3427 bw, 3078 w, 2946 m, 2916 m, 2867 w, 1607 w, 1454 w, 1376 w, 1026 w, 964 m, 881 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.15 (1H, d, *J* 15.6 Hz), 5.64 (1H, dt, *J* 15.6, 7.4 Hz), 4.87 (2H, s), 4.12 (1H, bs), 2.40-2.32 (1H, ddd, *J* 14.0, 7.4, 5.0 Hz), 1.99 (1H, ddd, *J* 14.0, 8.0, 7.4 Hz), 1.83 (1H, obsc. m), 1.84 (3H, s), 1.77-1.54 (5H, m), 1.34 (1H, qd, *J* 13.1, 3.3 Hz), 1.12 (1H, ddd, *J* 14.5, 12.1, 2.5 Hz), 1.07 (1H, obsc. m), 0.90 (1H, obsc. m), 0.92 (3H, d, *J* 6.8 Hz), 0.88 (3H, d, *J* 6.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 142.3 (*C*), 134.5 (*C*H), 129.5 (*C*H), 114.4 (CH_2), 68.1 (*C*H), 45.9 (*C*H), 42.9 (CH_2), 37.6 (CH_2), 35.3 (CH_2), 34.6 (*C*H), 26.1 (*C*H), 24.1 (CH_2), 22.5 (CH_3), 18.9 (CH_3), 17.8 (CH_3).

LRMS $^m/_z$ (EI) 222 (M^+, 49%), 207 ($[M - CH_3]^+$, 55), 189 (22), 152 (41), 139 (100), 123 (57), 107 (98), 93 (96), 81 (79), 67 (65).

HRMS $^m/_z$ (EI) found 222.1980, M^+; $C_{15}H_{26}O$ requires 222.1984.

***rel*-(3*S*,3'*E*,6*R*,6'*S*)-6-(2'-Methylhepta-1',3'-dien-6'-yl)-3-methylcyclohexanone, 3.3**

3.16
$C_{15}H_{26}O$
(222.37)

3.3
$C_{15}H_{24}O$
(220.35)

To a solution of dienol **3.16** (46 mg, 0.207 mmol) in DCM (5 mL) at 0 °C was added DMP (123 mg, 0.290 mmol). After 2 h, 2 M NaOH (2 mL) was added, the reaction warmed to RT and diluted with ether (40 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2-5% ether/petrol) yielded dienone **3.3** as a colourless oil (43 mg. 0.195 mmol, 94%).

FT-IR ν_{max} (neat, cm^{-1}) 3078 w, 2951 m, 2921 m, 2869 w, 1705 s, 1607 w, 1453 m, 1376 m, 1197 w, 1128 w, 1046 w, 965 s, 880 m.

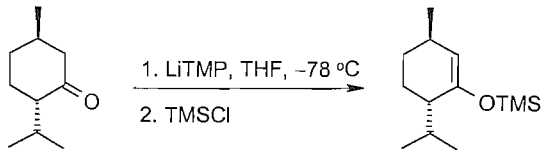
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.12 (1H, d, *J* 15.6 Hz), 5.59 (1H, dt, *J* 15.6, 7.5 Hz), 4.87 (2H, s), 2.37 (1H, d with fine splitting, *J* 12.6 Hz), 2.28-1.79 (7H, m), 1.83 (3H, s), 1.48-1.21 (3H, m), 1.02 (3H, d, *J* 6.0 Hz), 0.85 (3H, d, *J* 6.4 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 212.4 (*C*), 142.3 (*C*), 134.4 (*C*H), 129.5 (*C*H), 114.6 (CH_2), 53.2 (*C*H), 50.9 (CH_2), 38.4 (CH_2), 35.3 (*C*H), 34.1 (CH_2), 31.0 (*C*H), 27.0 (CH_2), 22.5 (CH_3), 18.9 (CH_3), 16.2 (CH_3).

LRMS $^m/_z$ (EI) 220 (M^+, 24%), 108 (100), 93 (62), 79 (39), 55 (47).

HRMS $^m/_z$ (EI) found: 220.1829, M^+; $C_{15}H_{24}O$ requires 220.1827.

(3*R*,6*S*)-3-Methyl-6-(prop-2-yl)-1-trimethylsilyloxy-cyclohexene, 3.30 and enantiomer.



3.23
$C_{10}H_{18}O$
(154.25)

3.30
$C_{13}H_{26}OSi$
(226.43)

The title compound was prepared using the method of Meinwald *et al.*[70] To a solution of 2,2,6,6-tetramethylpiperidine (2.85 mL, 16.9 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (1.92 M in hexanes, 8.8 mL, 16.9 mmol). After 30 min the reaction was cooled to –78 °C and a solution of L-menthone **3.23** (1.96 g, 12.7 mmol) in THF (20 mL) was added followed after 2 h by trimethylsilyl chloride (2.14 mL, 16.9 mmol). After a further 45 min the reaction warmed to RT and partitioned between sat. $NaHCO_3$ (40 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) yielded silyl enol ether **3.30** as a colourless oil (2.80 g, 12.4 mmol, 97%). Physical and spectroscopic data were in agreement with the literature.[70]

FT-IR ν_{max} (neat, cm^{-1}) 2955 m, 2925 w, 2868 w, 2849 w, 1655 m, 1454 w, 1367 w, 1312 w, 1251 s, 1216 m, 1179 s, 1000 w, 947 w, 905 s, 840 vs, 752 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.70 (1H, bs), 2.25-2.11 (2H, m), 2.05 (1H, m), 1.79-1.62 (2H, m), 1.32 (1H, m), 0.98 (1H, obsc. m), 0.93 (3H, d, *J* 6.8 Hz), 0.90 (3H, d, *J* 7.1 Hz), 0.77 (3H, d, *J* 6.8 Hz), 0.19 (9H, s).

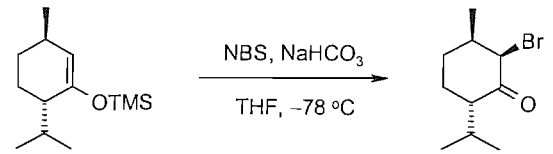
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 152.4 (*C*), 112.3 (*C*H), 44.6 (*C*H), 31.8 (*C*H_2), 30.3 (*C*H), 27.5 (*C*H), 23.1 (*C*H_3), 22.7 (*C*H_2), 20.4 (*C*H_3), 17.1 (*C*H_3), 0.5 (3 x *C*H_3).

LRMS $^{m}/_{z}$ (EI) 226 (M^+, 10%), 211 ($[M - CH_3]^+$, 53), 183 ($[M - C_3H_7]^+$, 25), 169 (14), 156 (40), 141 (7), 121 (6), 95 (11), 73 (100).

$[\alpha]_D$ –3.5° (c = 0.515, $CHCl_3$).

(The enantiomer was prepared analogously in 86% yield and exhibited $[\alpha]_D$ +3.9° (c = 0.625, $CHCl_3$).)

(2*R*,3*R*,6*S*)-2-Bromo-3-methyl-6-(prop-2-yl)-cyclohexanone, 3.31 and enantiomer



3.30
$C_{13}H_{26}OSi$
(226.43)

3.31
$C_{10}H_{17}BrO$
(233.15)

The title compound was prepared by adapting the method of Corey and Hu.[69] To a solution of silyl enol ether **3.30** (1.09 g, 4.81 mmol) in THF (35 mL) at –78 °C was added powdered $NaHCO_3$ (485 mg, 5.77 mmol) followed by *N*-bromosuccinimide (899 mg, 5.05 mmol). After 1 h, the reaction was warmed to RT and partitioned between sat. $NaHCO_3$ (20 mL) and ether (25 mL). The aqueous phase was separated and extracted with ether (2 x 25 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) yielded bromoketone **3.31** as a colourless oil (1.08 g, 4.62 mmol, 96%).

FT-IR ν_{max} (neat, cm^{-1}) 2960 m, 2932 m, 1710 vs, 1454 m, 1378 m, 1326 w, 1277 w, 1207 m, 1161 m, 1088 m, 982 w, 939 w, 778 m, 660 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.24 (1H, d, *J* 3.0 Hz), 3.00 (1H, dt, *J* 13.1, 5.7 Hz), 2.11 (1H, app. octet, *J* 6.9 Hz), 2.02 (1H, ddt, *J* 13.1, 5.7, 3.5 Hz), 1.86 (1H, m), 1.75 (1H, qd, *J* 13.1, 3.5 Hz), 1.63 (1H, m), 1.34 (1H, qd, *J* 13.1, 3.8 Hz), 1.09 (3H, d, *J* 6.3 Hz), 0.94 (3H, d, *J* 6.8 Hz), 0.87 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 206.3 (*C*), 62.3 (*C*H), 49.2 (*C*H), 38.8 (*C*H), 28.2 (CH_2), 27.9 (CH_2), 26.1 (*C*H), 21.1 (CH_3), 19.7 (CH_3), 18.8 (CH_3).

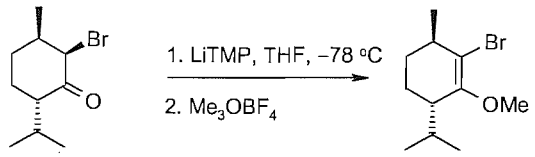
LRMS $^m/_z$ (EI) 234/232 (M^+, 12%), 219/217 ($[M - CH_3]^+$, 22), 192/190 ($[M - C_3H_6]^+$, 38), 153 ($[M - Br]^+$, 91), 111 (90), 97 (81), 83 (61), 69 (100), 55 (89).

HRMS $^{m}/_{z}$ (EI) found 232.0462, M^+; $C_{10}H_{17}{}^{79}BrO$ requires 232.0463.

$[\alpha]_D$ $-219.5°$ (c = 0.655, $CHCl_3$).

(The enantiomer was prepared analogously in 94% yield and exhibited $[\alpha]_D$ +210.3 ° (c = 0.510, $CHCl_3$).)

(3*S*,6*R*)-1-Bromo-2-methoxy-3-(prop-2-yl)-6-methylcyclohexene, 3.24 and enantiomer



3.31
$C_{10}H_{17}BrO$
(233.15)

3.24
$C_{11}H_{19}BrO$
(247.17)

To a solution of 2,2,6,6-tetramethylpiperidine (1.46 mL, 8.58 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.25 M in hexanes, 3.80 mL, 8.58 mmol). After 30 min the reaction was cooled to –78 °C and a solution of bromoketone **3.31** (1.00 g, 4.29 mmol) in THF (10 mL) added followed after 2 h by trimethyloxonium tetrafluoroborate (1.27 g, 8.58 mmol). The reaction was warmed to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (40 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0 - 2% ether/petrol) gave enol ether **3.24** as a colourless oil (682 mg, 2.76 mmol, 64%).

FT-IR ν_{max} (neat, cm^{-1}) 2957 s, 2932 s, 2870 w, 1640 w, 1452 m, 1385 w, 1368 w, 1307 w, 1221 m, 1135 w, 1021 s, 967 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.56 (3H, s), 2.51 (1H, m), 2.36 (1H, m), 2.12 (1H, m), 1.93 (1H, m), 1.71 (1H, m), 1.49 (1H, m), 1.31 (1H, m), 1.17 (3H, d, *J* 7.0 Hz), 0.95 (3H, d, *J* 7.0 Hz), 0.82 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 154.4 (*C*), 116.6 (*C*), 57.8 (CH_3), 42.4 (*C*H), 37.2 (*C*H), 31.4 (CH_2), 28.6 (*C*H), 22.0 (CH_3), 20.9 (CH_2), 20.7 (CH_3), 18.0 (CH_3).

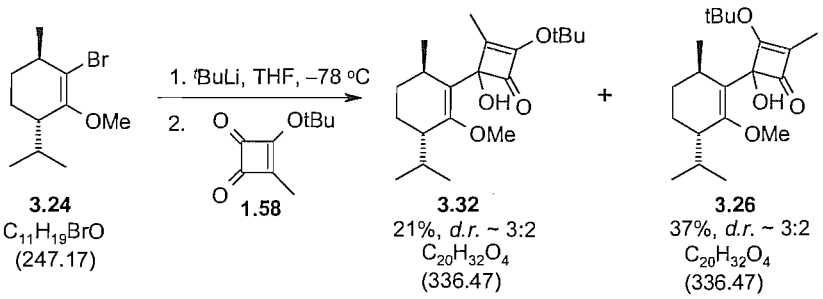
LRMS $^{m}/_{z}$ (EI) 248/246 (M^+, 23%), 233/231 ($[M - CH_3]^+$, 18), 203 (11), 167 ($[M - Br]^+$, 17), 123 (100), 109 (24), 91 (28), 77 (22).

HRMS $^{m}/_{z}$ (EI) found 246.0613, M^+; $C_{11}H_{19}{}^{79}BrO$ requires 246.0619.

$[\alpha]_D$ +75.6° (c = 0.665, $CHCl_3$).

(The enantiomer was prepared analogously in 55% yield and exhibited $[\alpha]_D$ −73.9 °(c = 0.450, $CHCl_3$).)

(3'*R*,4*RS*,6'*S*)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-2-methyl-3-(*tert*-butoxy)-cyclobut-2-enone, 3.32 and **(3'*R*,4*RS*,6'*S*)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-3-methyl-2-(*tert*-butoxy)-cyclobut-2-enone, 3.26**



3.24
$C_{11}H_{19}BrO$
(247.17)

1.58

3.32
21%, *d.r.* ~ 3:2
$C_{20}H_{32}O_4$
(336.47)

3.26
37%, *d.r.* ~ 3:2
$C_{20}H_{32}O_4$
(336.47)

To a solution of ^{t}BuLi (1.31 M in pentane, 0.37 mL, 0.482 mmol) in THF (2.5 mL) at −78 °C was added a solution of bromide **3.24** (60 mg, 0.241 mmol) in THF (2.5 mL) over 2 min. After 15 min a solution of squarate **1.58** (41 mg, 0.241 mmol) in THF (2 mL) was added over 2 min, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between ether (15 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (15 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-60% ether/petrol) yielded firstly vinylcyclobutenones **3.32** as a colourless oil (17 mg, 51 μmol, 21%, *d.r.* ~ 3:2), secondly the major diastereoisomer of vinylcyclobutenones **3.26** as a white solid (18 mg, 54 μmol, 22%) and finally the minor diastereoisomer of vinylcyclobutenones **3.26** as a colourless oil (12 mg, 36 μmol, 15%).

Data for **3.32**:

IR ν_{max} (neat, cm^{-1}) 3432 bw, 2954 m, 2937 m, 2868 w, 1762 s, 1630 w, 1570 w, 1458 w, 1370 m, 1320 w, 1158 m, 1028 m, 917 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) Major isomer: 5.63 (1H, s), 3.63 (3H, s), 2.18-2.04 (2H, m), 2.05 (3H, s), 1.74-1.59 (3H, m), 1.46 (9H, s), 1.31-1.21 (2H, m), 0.99 (3H, d, *J* 7.0 Hz), 0.95 (3H, d, *J* 6.8 Hz), 0.86 (3H, d, *J* 6.8 Hz). Additional signals attributed to the minor isomer (~ 2/3 the integral): 4.52 (1H, s), 3.48 (3H, s), 2.00 (3H, s), 0.98 (6H, d, *J* 6.5 Hz), 0.84 (3H, d, *J* 6.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) Major isomer: 188.6 (*C*), 156.4 (*C*), 155.7 (*C*), 154.4 (*C*), 125.0 (*C*), 90.4 (*C*), 79.9 (*C*), 58.5 (CH_3), 38.2 (*C*H), 30.1 (*C*H), 29.1 (*C*H), 28.9 (3 x CH_3), 28.7 (CH_2), 21.3 (CH_3), 21.3 (CH_3), 18.7 (CH_3), 18.6 (CH_2), 10.2 (CH_3). Minor isomer: 187.8 (*C*), 159.7 (*C*), 154.6 (*C*), 153.8 (*C*), 124.0 (*C*), 89.8 (*C*), 79.9 (*C*), 57.2 (CH_3), 38.1 (*C*H), 29.7 (*C*H), 29.1 (*C*H), 28.9 (3 x CH_3), 28.8 (CH_2), 21.6 (CH_3), 21.3 (CH_3), 18.7 (CH_3), 18.5 (CH_2), 9.6 (CH_3).

LRMS $^m/_z$ (ES^+) 695 ($[2M + Na]^+$), 359 ($[M + Na]^+$).

Data for the major diastereoisomer of **3.26**:

IR ν_{max} (neat, cm^{-1}) 3384 bw, 2951 m, 2930 m, 1757 m, 1602 s, 1379 s, 1324 s, 1225 w, 1153 s, 1117 s, 1009 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.16 (1H, s), 3.67 (3H, s), 2.37-2.27 (2H, m), 2.07 (1H, septet of d, *J* 6.9, 4.0 Hz), 1.77 (3H, s), 1.75-1.59 (3H, m), 1.53 (9H, s), 1.29 (1H, m), 0.98 (3H, d, *J* 7.0 Hz), 0.93 (3H, d, *J* 6.8 Hz), 0.84 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 193.7 (*C*), 178.8 (*C*), 155.7 (*C*), 124.8 (*C*), 124.1 (*C*), 95.7 (*C*), 83.6 (*C*), 59.1 (CH_3), 38.0 (*C*H), 29.8 (*C*H), 29.1 (*C*H), 28.8 (3 x CH_3), 28.5 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 18.7 (CH_3), 18.2 (CH_2), 8.5 (CH_3).

LRMS $^m/_z$ (ES^+) 695 ($[2M + Na]^+$), 359 ($[M + Na]^+$).

HRMS $^{m}/_{z}$ (ES^{+}) found 359.2193 $(M + Na)^{+}$; $C_{20}H_{32}NaO_4$ requires 359.2193.

*(Note: The minor diastereoisomer deteriorated more rapidly on standing and was best used immediately in the thermolysis reaction. In the enantiomeric series the analogous reaction yielded cyclobutenone ent-**3.26** in 33% yield, d.r. ~ 3:2.)*

(5*R*,10*S*)-2-(*tert*-Butoxy)-3,10-dimethyl-6-methoxy-7-(prop-2-yl)-spiro[4.5]deca-2,6-diene-1,4-dione, 3.34 and enantiomer

3.26
$C_{20}H_{32}O_4$
(336.47)

3.34
$C_{20}H_{30}O_4$
(334.45)

A solution of the major diastereoisomer of cyclobutenone **3.26** (16 mg, 48 μmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (31 mg, 72 μmol). After 30 min 1 M NaOH (1.5 mL) was added and the temperature raised to RT. Following dilution with ether (30 mL), the organic phase was separated, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) yielded spirocycle **3.34** as a pale yellow oil that crystallised on standing (12 mg, 36 μmol, 75%).

MP 89-91 °C ($EtOH/H_2O$).

FT-IR ν_{max} (neat, cm^{-1}) 2958 m, 2929 m, 2868 w, 2831 w, 1740 w, 1683 vs, 1622 m, 1458 w, 1377 m, 1319 m, 1152 s, 1037 w, 882 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s), 3.02 (1H, septet, *J* 6.8 Hz), 2.15-2.01 (3H, m), 1.93 (1H, obsc. m), 1.96 (3H, s), 1.54 (1H, obsc. m), 1.52 (9H, s), 1.03 (3H, d, *J* 6.8 Hz), 0.99 (3H, d, *J* 6.8 Hz), 0.71 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.4 (*C*), 201.9 (*C*), 169.3 (*C*), 145.9 (*C*), 144.7 (*C*), 133.6 (*C*), 85.3 (*C*), 61.9 (*C*H_3), 61.2 (*C*), 35.4 (*C*H), 29.7 (3 x *C*H_3), 27.0 (*C*H_2), 26.9 (*C*H), 21.9 (*C*H_2), 21.3 (*C*H_3), 20.8 (*C*H_3), 16.3 (*C*H_3), 7.9 (*C*H_3).

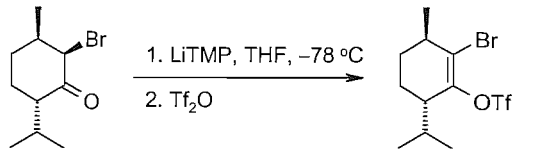
LRMS $^m/_z$ (ES^+) 691 ($[2M + Na]^+$), 357 ($[M + Na]^+$).

HRMS $^m/_z$ (ES^+) found 357.2039, $(M + Na)^+$; $C_{20}H_{30}NaO_4$ requires 357.2036.

$[\alpha]_D$ +61.3° (c = 0.550, $CHCl_3$).

(Note: Both diastereoisomers of ***3.26*** *gave* ***3.34*** *following thermolysis and oxidation. The enantiomer was prepared analogously in 72% yield and exhibited $[\alpha]_D$ –62.9° (c = 0.680, $CHCl_3$), MP 89-91 °C ($EtOH/H_2O$).)*

(3*S*,6*R*)-1-Bromo-6-methyl-3-(prop-2-yl)-2-trifluoromethanesulfonyloxy-cyclohexene, 3.37



3.31
$C_{10}H_{17}BrO$
(233.15)

3.37
$C_{11}H_{16}BrF_3O_3S$
(365.21)

To a solution of 2,2,6,6-tetramethylpiperidine (140 μL, 0.858 mmol) in THF (2 mL) at 0 °C was added ^{n}BuLi (1.72 M in hexanes, 0.50 mL, 0.858 mmol). After 30 min the solution was cooled to –78 °C and a solution of bromoketone **3.31** (100 mg, 0.429 mmol) in THF (2 mL) added followed after 1 h by trifluoromethanesulfonic anhydride (80 μL, 0.472 mmol). After 45 min sat. $NaHCO_3$ (2 mL) was added, the reaction mixture warmed to RT and partitioned between water (10 mL) and ether (30 mL). The organic phase was separated then washed with water (10 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) yielded triflate **3.37** as a colourless oil (76 mg, 0.208 mmol, 49%).

FT-IR ν_{max} (neat, cm^{-1}) 2963 m, 2935 w, 2874 w, 1647 w, 1420 s, 1246 m, 1202 vs, 1137 s, 1077 m, 979 m, 879 s, 809 s.

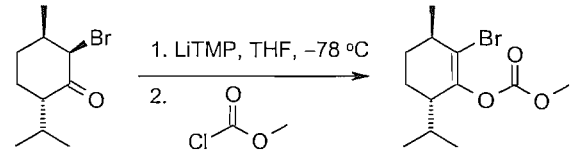
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.61 (1H, bm), 2.50 (1H, bm), 2.16 (1H, septet of d, *J* 7.0, 4.0 Hz), 1.98 (1H, m), 1.84 (1H, m), 1.55 (1H, m), 1.41 (1H, m), 1.26 (3H, d, *J* 6.8 Hz), 0.98 (3H, d, *J* 7.0 Hz), 0.84 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 148.5 (*C*), 125.3 (*C*), 118.6 (*C*F_3 ($J_{C\text{-}F}$ 319 Hz)), 45.1 (*C*H), 38.4 (*C*H), 30.3 (*C*H_2), 28.6 (*C*H), 21.7 (*C*H_3), 20.9 (*C*H_2), 20.4 (*C*H_3), 17.2 (*C*H_3).

LRMS $^m/_z$ (EI) 366/364 (M^+, 8%), 324/322 (25), 241 (100), 174/172 (26), 135 (79), 123 (52), 91 (99), 81 (62), 69 (89).

HRMS $^m/_z$ (EI) found 363.9950, M^+; $C_{11}H_{16}{}^{79}BrF_3O_3S$ requires 363.9956.

Methyl (3*R*,6*S*)-2-bromo-3-methyl-6-isopropylcyclohexenyl carbonate, 3.39



3.31
$C_{10}H_{17}BrO$
(233.15)

3.39
$C_{12}H_{19}BrO_3$
(291.19)

To a solution of 2,2,6,6-tetramethylpiperidine (140 μL, 0.858 mmol) in THF (2 mL) at 0 °C was added ^{n}BuLi (1.72 M in hexanes, 0.50 mL, 0.858 mmol). After 30 min the solution was cooled to –78 °C and a solution of bromoketone **3.31** (100 mg, 0.429 mmol) in THF (2 mL) added followed after 1 h by methyl chloroformate (70 μL, 0.858 mmol). The reaction was warmed to RT over 1 h and then quenched by addition of sat. $NaHCO_3$ (5 mL). The mixture was extracted with ether (2 x 15 mL) and the combined organic phases washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) gave enol carbonate **3.39** as a colourless oil (89 mg, 0.306 mmol, 71%).

FT-IR ν_{max} (neat, cm^{-1}) 2957 m, 2933 m, 2871 w, 1759 vs, 1658 w, 1439 m, 1388 w, 1370 w, 1249 vs, 1206 s, 1171 s, 1064 w, 979 w, 936 w, 779 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s), 2.57 (1H, bm), 2.48 (1H, bm), 2.07-1.92 (2H, obsc. m), 1.80 (1H, m), 1.58-1.38 (2H, m), 1.22 (3H, d, *J* 6.8 Hz), 0.94 (3H, d, *J* 6.8 Hz), 0.85 (3H, d, *J* 6.8 Hz).

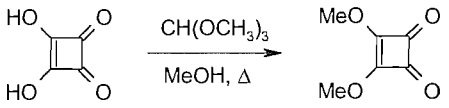
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 152.8 (*C*), 147.8 (*C*), 121.1 (*C*), 55.6 (CH_3), 44.1 (*C*H), 37.3 (*C*H), 31.0 (CH_2), 28.8 (*C*H), 21.6 (CH_3), 21.1 (CH_2), 20.6 (CH_3), 18.0 (CH_3).

LRMS $^m/_z$ (CI) 310/308 ($[M + NH_4]^+$, 78%), 293/291 ($[M + H]^+$, 15), 211 ($[M – Br]^+$, 100), 167 (18), 153 (28), 135 (63), 123 (46).

HRMS $^m/_z$ (ES^+) found 313.0407, $(M + Na)^+$; $C_{12}H_{19}{}^{79}BrNaO_3$ requires 313.0410.

6.2.3 Experimental for Chapter 4

3,4-Dimethoxy-3-cyclobutene-1,2-dione, 4.6



2.5
$C_4H_2O_4$
(114.04)

4.6
$C_6H_6O_4$
(142.11)

The title compound was prepared using the method of Moore *et al.*[45] Squaric acid **2.5** (2.0 g, 17.5 mmol) was suspended in methanol (20 mL) and trimethyl orthoformate (4.0 mL, 36.5 mmol) added. The reaction mixture was heated at reflux for 20 h, cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) afforded dimethyl squarate **4.6** as a white crystalline solid (2.27 g, 15.9 mmol, 91%). Physical and spectroscopic data were in agreement with the literature.[45]

MP 53-54 °C (ether/petrol). Lit.[45] 55-56 °C.

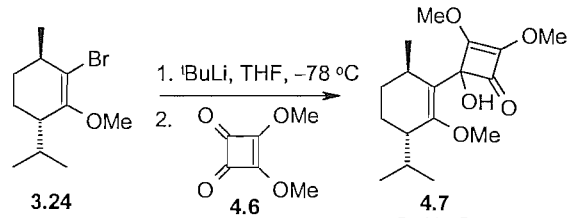
FT-IR ν_{max} (neat, cm^{-1}) 2963 w, 1809 m, 1720 s, 1579 vs, 1478 s, 1413 s, 1352 s, 1225 m, 1144 m, 1083 m, 1033 s, 922 s, 828 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.36 (6H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 189.3 (2 x *C*), 184.6 (2 x *C*), 61.1 (2 x CH_3).

LRMS $^m/_z$ (EI) 142 (M^+, 73%), 114 (35), 99 (21), 86 (57), 68 (28).

(3'*S*,4*RS*,6'*R*)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 4.7 and enantiomer



3.24
$C_{11}H_{19}OBr$
(247.17)

4.6

4.7
$C_{17}H_{26}O_5$
(310.39)

To a solution of ^{t}BuLi (1.31 M in pentane, 0.49 mL, 0.643 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **3.24** (159 mg, 0.643 mmol) in THF (2.5 mL) over 2 min. After 10 min a solution of dimethyl squarate **4.6** (87 mg, 0.611 mmol) in THF (2 mL) was added over 2 min, followed after 1 h by addition of sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and then partitioned between ether (20 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (2 x 20 mL) then the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil, crude **4.7** (188 mg).

Note: **4.7** could be purified at this juncture by column chromatography (SiO_2, 20-30% EtOAc/petrol, 78% yield, *d.r.* ~ 3:2). However, on standing the product steadily decomposed to (3'*S*,6'*R*)-4-(2'-methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-3-methoxy-cyclobuten-1,2-dione **4.9**. Consequently, higher overall yields were attained when the crude isolate was carried through the subsequent stages, as here.

Data for **4.7**:

FT-IR ν_{max} (neat, cm^{-1}) 3395 bw, 2952 m, 2868 w, 1773 m, 1632 s, 1464 m, 1330 s, 1212 w, 1107 w, 1032 m, 988 w, 849 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) Major isomer: 6.04 (1H, bs), 4.11 (3H, s), 3.98 (3H, s), 3.67 (3H, s), 2.34-2.26 (2H, m), 2.06 (1H, obsc. m), 1.76-1.59 (3H, m), 1.30 (1H, m), 1.07 (3H, d, *J* 6.8 Hz), 1.02 (3H, d, *J* 6.8 Hz), 0.83 (3H, d, *J* 6.8 Hz). Additional signals attributed to the minor isomer: 4.94 (1H, bs), 4.12 (3H, s), 3.99 (3H, s), 3.50 (3H, s), 2.53 (1H, m), 0.98 (6H, d, *J* 7.0 Hz), 0.84 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) Major isomer: 185.9 (*C*), 165.3 (*C*), 156.3 (*C*), 135.3 (*C*), 123.7 (*C*), 89.9 (*C*), 60.0 (CH_3), 59.2 (CH_3), 58.6 (CH_3), 38.1 (*C*H), 30.3 (*C*H), 29.2 (*C*H), 28.7 (CH_2), 21.4 (CH_3), 21.3 (CH_3), 18.8 (CH_3), 18.4 (CH_2). Minor isomer: 184.6 (*C*), 168.8 (*C*), 155.7 (*C*), 134.8 (*C*), 123.2 (*C*), 88.2 (*C*), 60.2 (CH_3), 58.6 (CH_3), 57.5 (CH_3), 38.3 (*C*H), 30.5 (*C*H), 29.5 (*C*H), 28.8 (CH_2), 21.3 (2 x CH_3) 18.7 (CH_3), 18.6 (CH_2).

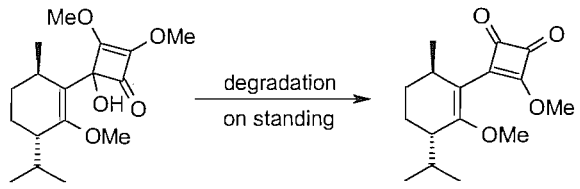
LRMS $^m/_z$ (ES^+) 643 ($[2M + Na]^+$), 333 ($[M + Na]^+$).

HRMS $^m/_z$ (ES^+) found 333.1673 $(M + Na)^+$; $C_{17}H_{26}NaO_5$ requires 333.1672.

(In the enantiomeric series the analogous reaction proceeded in 75% yield.)

Data for the degradation product:

(3'*S*,6'*R*)-4-(2'-Methoxy-6'-methyl-3'-(prop-2-yl)-cyclohexenyl)-3-methoxy-cyclobuten-1,2-dione, 4.9



4.7 (*d.r.* 3 : 2)
$C_{17}H_{26}O_5$
(310.39)

4.9
$C_{16}H_{22}O_4$
(278.35)

FT-IR ν_{max} (neat, cm^{-1}) 2957 m, 2929 m, 1783 s, 1746 s, 1575 s, 1449 s, 1373 s, 1341 m, 1326 m, 1130 m, 1036 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.47 (3H, s), 3.66 (3H, s), 2.95 (1H, m), 2.48 (1H, m), 2.10 (1H, octet, *J* 7.0 Hz), 1.85 (1H, m), 1.75 (1H, tdd, *J* 10.5, 7.3, 3.3 Hz), 1.64 (1H, m), 1.29 (1H, m), 1.02 (3H, d, *J* 7.0 Hz), 0.96 (3H, d, *J* 7.0 Hz), 0.85 (3H, d, *J* 7.0 Hz).

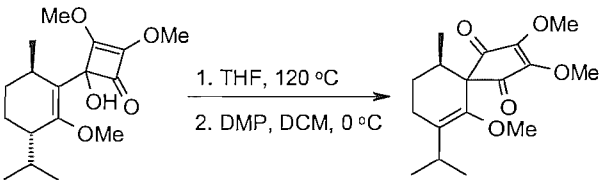
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.4 (*C*), 193.6 (*C*), 193.4 (*C*), 178.4 (*C*), 163.2 (*C*), 116.5 (*C*), 61.1 (CH_3), 57.8 (CH_3), 39.6 (*C*H), 29.3 (*C*H), 29.0 (*C*H), 28.1 (CH_2), 21.6 (CH_3), 21.1 (CH_3), 19.5 (CH_2), 18.7 (CH_3).

LRMS $^{m}/_{z}$ (ES^+) 611 ($[2M + Na + MeOH]^+$), 579 ($2M + Na]^+$), 333 ($[M + Na + MeOH]^+$), 301 ($[M + Na]^+$), 279 (MH^+).

HRMS $^{m}/_{z}$ (ES^+) found 279.1591, MH^+; $C_{16}H_{23}O_4$ requires 279.1591.

$[\alpha]_D$ +837.2° (c = 0.750, $CHCl_3$).

(*R*)-7-Isopropyl-2,3,6-trimethoxy-10-methyl-spiro[4.5]deca-2,6-diene-1,4-dione, 4.8 and enantiomer



4.7
$C_{17}H_{26}O_5$
(310.39)

4.8
$C_{17}H_{24}O_5$
(308.37)

A solution of the crude cyclobutenone **4.7** (188 mg) in THF (3 mL) was heated to 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL), cooled to 0 °C and treated with DMP (389 mg, 0.917 mmol). After 1 h, 1 M NaOH (3 mL) was added and the temperature raised to RT. Following dilution with ether (40 mL), the organic phase was separated then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-15 % EtOAc/petrol) gave spirocycle **4.8** as a yellow oil (101 mg, 0.328 mmol, 69%).

FT-IR ν_{max} (neat, cm^{-1}) 2958 w, 2929 w, 2868 w, 2840 w, 1683 s, 1622 s, 1458 m, 1315 s, 1209 m, 1136 m, 1107 m, 1042 m, 1009 m, 960 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.22 (3H, s), 4.21 (3H, s), 3.39 (3H, s), 3.01 (1H, septet, *J* 6.9 Hz), 2.13-1.99 (3H, m), 1.83 (1H, tdd, *J* 12.8, 10.5, 6.0 Hz), 1.55 (1H, dq, *J* 12.8, 2.5 Hz), 1.00 (3H, d, *J* 6.8 Hz), 0.97 (3H, d, *J* 7.0 Hz), 0.79 (3H, d, *J* 7.0 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 197.5 (*C*), 197.2 (*C*), 153.3 (*C*), 152.6 (*C*), 144.0 (*C*), 134.4 (*C*), 62.4 (CH_3), 60.7 (*C*), 59.9 (CH_3), 59.8 (CH_3), 35.0 (*C*H), 27.0 (CH_2), 26.9 (*C*H), 21.7 (CH_2), 21.1 (CH_3), 20.7 (CH_3),

16.4 (CH_3).

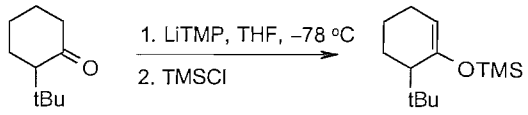
LRMS $^m/_z$ (EI) 308 (M^+, 100%), 293 ($[M - CH_3]^+$, 93), 277 (32), 265 (70), 233 (68), 219 (22), 183 (83), 119 (33), 91 (58).

HRMS $^m/_z$ (EI) found 308.1616, M^+; $C_{17}H_{24}O_5$ requires 308.1624.

$[\alpha]_D$ +92.9° (c = 0.660, $CHCl_3$).

(The enantiomer was prepared analogously in 72% yield and exhibited $[\alpha]_D$ –90.6° (c = 0.475, $CHCl_3$).)

6-(*tert*-Butyl)-1-trimethylsilyloxy-cyclohexene, 4.11



4.10
$C_{10}H_{18}O$
(154.25)

4.11
$C_{13}H_{26}OSi$
(226.43)

To a solution of 2,2,6,6-tetramethylpiperidine (1.42 mL, 8.43 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (1.91 M in hexanes, 4.4 mL, 8.4 mmol). After 1 h the reaction was cooled to –78 °C and a solution of 2-*tert*-butylcyclohexanone **4.10** (1.00 g, 6.48 mmol) in THF (10 mL) was added followed after 1 h by trimethylsilyl chloride (1.1 mL, 8.5 mmol). The reaction was allowed to warm to RT over 30 min then partitioned between sat. $NaHCO_3$ (30 mL) and ether (40 mL). The aqueous phase was separated and extracted with ether (2 x 40 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave silyl enol ether **4.11** as a colourless oil (1.28 g, 5.66 mmol, 87%).

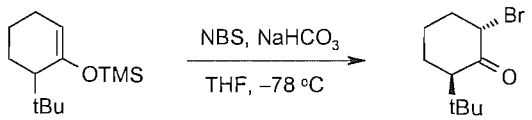
FT-IR ν_{max} (neat, cm^{-1}) 3040 w, 2950 m, 2925 m, 2860 w, 2840 w, 1650 w, 1446 w, 1360 m, 1246 s, 1217 m, 1164 s, 907 s, 833 s, 743 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.90 (1H, t, *J* 3.6 Hz), 1.99-1.92 (3H, m), 1.80-1.62 (2H, m), 1.50-1.28 (2H, m), 0.99 (9H, s), 0.20 (9H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 153.5 (*C*), 106.4 (*C*H), 48.4 (*C*H), 33.8 (*C*), 29.4 (3 x CH_3), 27.1 (CH_2), 24.6 (CH_2), 22.4 (CH_2), 0.6 (3 x CH_3).

LRMS $^{m}/_{z}$ (EI) 226 (M^+, 24%), 211 ($[M - CH_3]^+$, 22), 170 ($[M - C_4H_8]$, 100), 155 (51), 142 (28), 127 (22), 96 (12), 73 (64).

2-Bromo-6-(*tert*-butyl)-cyclohexanone, 4.12



4.11
$C_{13}H_{26}OSi$
(226.43)

4.12
$C_{10}H_{17}BrO$
(233.15)

To a solution of silyl enol ether **4.11** (1.14 g, 5.03 mmol) in THF (30 mL) at –78 °C was added powdered $NaHCO_3$ (507 mg, 6.03 mmol) followed by *N*-bromosuccinimide (941 mg, 5.29 mmol). After 1 h the reaction was warmed to RT and partitioned between sat. $NaHCO_3$ (30 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) yielded bromoketone **4.12** as a colourless oil (1.07 g, 4.61 mmol, 92%).

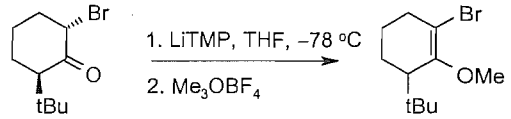
FT-IR ν_{max} (neat, cm^{-1}) 2954 m, 2864 w, 1712 vs, 1483 w, 1446 w, 1430 w, 1360 m, 1311 w, 1246 w, 1189 w, 1144 m, 1091 m, 988 w, 948 w, 858 m, 776 w.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.29 (1H, t, *J* 2.8 Hz), 3.10 (1H, dd, *J* 13.3, 4.7 Hz), 2.30-2.03 (4H, m), 1.79 (1H, m), 1.44 (1H, qd, *J* 12.8, 3.4 Hz), 1.01 (9H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 206.0 (*C*), 54.6 (*C*H), 53.8 (*C*H), 36.5 (CH_2), 31.8 (*C*), 29.6 (CH_2), 27.5 (3 x CH_3), 21.2 (CH_2).

LRMS $^m/_z$ (EI) 234/232 (M^+, 15%), 219/217 ($[M - CH_3]^+$, 80), 178/176 ($[M - C_4H_8]^+$, 30), 139 (21), 109 (33), 98 (83), 83 (91), 67 (83), 55 (100).

1-Bromo-3-(*tert*-butyl)-2-methoxy-cyclohexene, 4.13



4.12
$C_{10}H_{17}BrO$
(233.15)

4.13
$C_{11}H_{19}BrO$
(247.18)

To a solution of 2,2,6,6-tetramethylpiperidine (0.73 mL, 4.3 mmol) in THF (10 mL) at 0 °C was added ^{n}BuLi (1.91 M in hexanes, 2.25 mL, 4.3 mmol). After 1 h the reaction was cooled to –78 °C and a solution of bromoketone **4.12** (500 mg, 2.14 mmol) in THF (10 mL) added followed after 2 h by trimethyloxonium tetrafluoroborate (635 mg, 4.29 mmol). The reaction was warmed to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (10 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (30 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave enol ether **4.13** as a colourless oil (246 mg, 1.00 mmol, 42%).

FT-IR ν_{max} (neat, cm^{-1}) 2950 s, 2925 s, 2864 m, 2827 w, 1642 w, 1446 w, 1360 m, 1221 m, 1201 m, 1123 s, 1001 s, 984 m, 805 m.

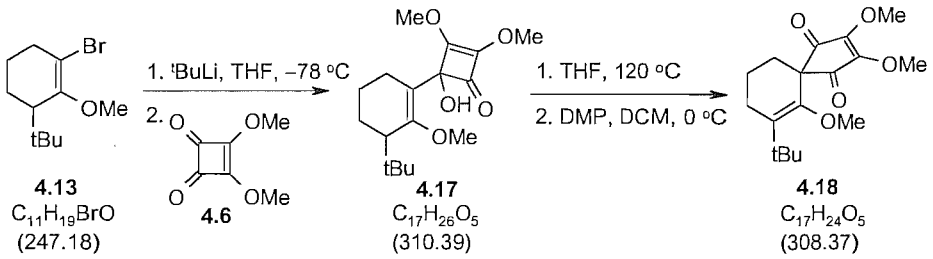
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.52 (3H, s), 2.55-2.39 (2H, m), 2.31 (1H, m), 1.82-1.71 (2H, m), 1.63-1.47 (2H, m), 0.99 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 155.5 (*C*), 111.6 (*C*), 57.2 (CH_3), 45.5 (*C*H), 35.3 (CH_2), 34.6 (*C*), 29.1 (3 x CH_3), 26.5 (CH_2), 23.4 (CH_2).

LRMS $^{m}/_{z}$ (EI) 248/246 (M^+, 7%), 192/190 ([M – C_4H_8]$^+$, 55), 111 (51), 95 (13), 79 (23), 57 (100).

HRMS $^{m}/_{z}$ (EI) found 246.0616, M^+; $C_{11}H_{19}{}^{79}BrO$ requires 246.0619.

7-*tert*-Butyl-2,3,6-trimethoxyspiro[4.5]deca-2,6-diene-1,4-dione, 4.18



4.13
$C_{11}H_{19}BrO$
(247.18)

4.6

4.17
$C_{17}H_{26}O_5$
(310.39)

4.18
$C_{17}H_{24}O_5$
(308.37)

To a solution of ^{t}BuLi (1.24 M in pentane, 0.71 mL, 0.87 mmol) in THF (2.5 mL) at −78 °C was added a solution of bromide **4.13** (108 mg, 0.437 mmol) in THF (2.5 mL) over 2 min. After 15 min a solution of dimethyl squarate **4.6** (124 mg, 0.874 mmol) in THF (2 mL) was added over 2 min, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between ether (20 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (2 x 10 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) gave an inseparable 1:1 mixture of vinylcyclobutenones **4.17** (121 mg, 0.390 mmol, 89%) as a yellow oil. These were used immediately in the following reaction due to instability.

Vinylcyclobutenones **4.17** (121 mg, 0.390 mmol) in THF (3 mL) were heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (199 mg, 0.468 mmol). After 30 min 2 M NaOH (2 mL) was added and the temperature raised to RT. Following dilution with ether (30 mL), the organic phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc/petrol) gave spirocycle **4.18** as a yellow oil (74 mg, 0.24 mmol, 61%).

FT-IR ν_{max} (neat, cm^{-1}) 2950 m, 2860 w, 2827 w, 1683 s, 1626 s, 1458 s, 1319 vs, 1193 s, 1140 s, 1107 s, 1025 s, 907 m, 723 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.23 (6H, s), 3.33 (3H, s), 2.15 (2H, t, *J* 6.0 Hz), 1.81-1.69 (4H, m), 1.16 (9H, s).

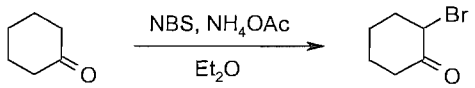
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 197.7 (2 x *C*), 150.6 (2 x *C*), 144.5 (*C*), 137.0

(*C*), 61.8 (*C*H_3), 59.8 (2 x *C*H_3), 57.3 (*C*), 35.8 (*C*), 31.6 (*C*H_2), 30.1 (3 x *C*H_3), 27.0 (*C*H_2), 19.5 (*C*H_2).

LRMS $^{m}/_{z}$ (EI) 308 (M^+, 39%), 293 ($[M - CH_3]^+$, 55), 243 (35), 205 (20), 169 (41), 105 (28), 91 (74), 79 (42), 43 (100).

HRMS $^{m}/_{z}$ (EI) found 308.1620, M^+; $C_{17}H_{24}O_5$ requires 308.1624.

2-Bromocyclohexanone, 4.15



4.14
$C_6H_{10}O$
(98.15)

4.15
C_6H_9BrO
(177.05)

The title compound was prepared using the method of Tanemura *et al.*[105] To a mixture of cyclohexanone **4.14** (1.00 g, 10.2 mmol) and *N*-bromosuccinimide (1.90 g, 10.7 mmol) in ether (10 mL) was added ammonium acetate (79 mg, 1.02 mmol). After 30 min the reaction mixture was filtered, diluted with ether (20 mL) and washed with water (15 mL). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (SiO_2, 5-10% ether/petrol) to afford 2-bromocyclohexanone **4.15** as a colourless oil (1.50 g, 8.47 mmol, 83%). Spectroscopic data were in agreement with the literature.[106]

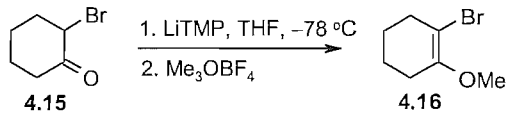
FT-IR ν_{max} (neat, cm^{-1}) 2938 m, 2864 w, 1708 vs, 1446 m, 1426 m, 1291 w, 1217 m, 1176 m, 1119 s, 1054 m, 960 w, 911 m, 813 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.44 (1H, t, *J* 5.4 Hz), 2.98 (1H, ddd, *J* 15.2, 10.0, 6.2 Hz), 2.38-2.17 (3H, m), 2.08-1.66 (4H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 203.6 (*C*), 53.6 (*C*H), 38.1 (*C*H_2), 36.9 (*C*H_2), 26.9 (*C*H_2), 22.3 (*C*H_2).

LRMS $^{m}/_{z}$ (EI) 178/176 (M^+, 58%), 148 (18), 134 (44), 132 (41), 97 ($[M - Br]^+$, 100), 79 (36), 69 (44).

1-Bromo-2-methoxy-cyclohexene, 4.16



4.15
C_6H_9BrO
(177.05)

4.16
$C_7H_{11}BrO$
(191.07)

To a solution of 2,2,6,6-tetramethylpiperidine (0.95 mL, 5.7 mmol) in THF (10 mL) at 0 °C was added ^{n}BuLi (1.92 M in hexanes, 2.90 mL, 5.65 mmol). After 30 min the reaction was cooled to –78 °C and a solution of 2-bromocyclohexanone **4.15** (500 mg, 2.82 mmol) in THF (10 mL) added followed after 90 min by trimethyloxonium tetrafluoroborate (635 mg, 4.29 mmol). The reaction was warmed to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (10 mL) and ether (40 mL). The aqueous phase was separated and extracted with ether (2 x 40 mL) then the combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1-3% ether/petrol) gave 1-bromo-2-methoxy-cyclohexene **4.16** as a colourless oil (69 mg, 0.36 mmol, 13%).

FT-IR ν_{max} (neat, cm^{-1}) 2929 s, 2860 w, 2835 w, 1663 s, 1446 m, 1328 m, 1262 m, 1221 s, 1152 s, 1066 m, 1009 s, 968 s, 805 m, 637 m.

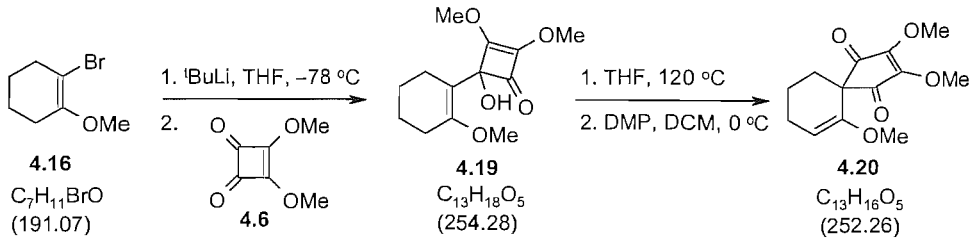
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.62 (3H, s), 2.47 (2H, tt, *J* 6.2, 2.2 Hz), 2.25 (2H, tt, *J* 6.1, 2.2 Hz), 1.79-1.62 (4H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 150.4 (*C*), 101.8 (*C*), 55.7 (CH_3), 34.5 (CH_2), 26.3 (CH_2), 24.5 (CH_2), 22.9 (CH_2).

LRMS $^{m}/_{z}$ (EI) 192/190 (M^+, 75%), 164 (62), 162 (61), 111 ($[M - Br]^+$, 100), 95 (26), 79 (57), 67 (51).

HRMS $^{m}/_{z}$ (EI) found 189.9986, M^+; $C_7H_{11}{}^{79}BrO$ requires 189.9993.

2,3,6-Trimethoxyspiro[4.5]deca-2,6-diene-1,4-dione, 4.20



To a solution of ^{t}BuLi (1.15 M in pentane, 0.85 mL, 0.97 mmol) in THF (2.5 mL) at –78 °C was added a solution of 1-bromo-2-methoxy-cyclohexene **4.16** (93 mg, 0.49 mmol) in THF (2.5 mL) over 2 min. After 30 min a solution of dimethyl squarate **4.6** (69 mg, 0.49 mmol) in THF (2 mL) was added over 2 min, followed after 45 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and the mixture extracted with ether (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-40% EtOAc/petrol) gave a yellow oil, vinylcyclobutenone **4.19** (52 mg, 0.210 mmol, 42%), that was used immediately in the following reaction due to instability.

A solution of vinylcyclobutenone **4.19** (52 mg, 0.210 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (207 mg, 0.487 mmol). After 30 min 1 M NaOH (3 mL) was added and the temperature raised to RT. The aqueous phase was separated and extracted with ether (2 x 20 mL) then the combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc/petrol) gave spirocycle **4.20** (31 mg, 0.125 mmol, 60%) as a yellow oil.

FT-IR ν_{max} (neat, cm^{-1}) 3003 w, 2942 m, 2844 w, 1683 s, 1618 s, 1458 s, 1315 s, 1242 m, 1209 s, 1144 s, 997 s, 882 m, 792 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.08 (1H, t, *J* 4.1 Hz), 4.22 (6H, s), 3.43 (3H, s), 2.21-2.16 (2H, m), 1.84-1.80 (4H, m).

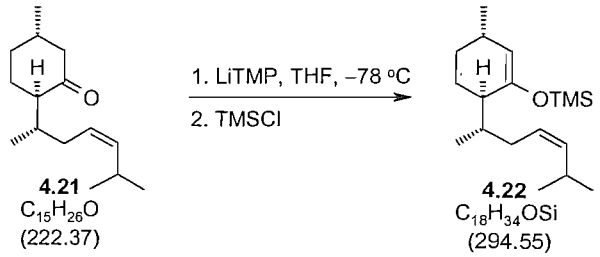
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 196.7 (2 x *C*), 151.2 (2 x *C*), 150.0 (*C*), 100.5 (*C*H), 59.8 (2 x CH_3), 54.9 (*C*), 54.8 (CH_3), 30.2 (CH_2), 23.2 (CH_2),

19.2 (CH_2).

LRMS $^{m}/_{z}$ (EI) 252 (M^+, 100%), 237 ($[M - CH_3]^+$, 40), 221 ($[M - OCH_3]^+$, 76), 209 (34), 169 (31), 149 (22), 135 (35), 121 (25), 79 (40).

HRMS $^{m}/_{z}$ (EI) found 252.0988, M^+; $C_{13}H_{16}O_5$ requires 252.0998.

***rel*-(2'*S*,3*S*,4'*Z*,6*R*)-3-Methyl-6-(6'-methyl-hept-4'-en-2'-yl)-1-trimethylsilyloxy-cyclohexene, 4.22**



4.21
$C_{15}H_{26}O$
(222.37)

4.22
$C_{18}H_{34}OSi$
(294.55)

To a solution of 2,2,6,6-tetramethylpiperidine (0.68 mL, 4.02 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.23 M in hexanes, 1.80 mL, 4.02 mmol). After 1 h the solution was cooled to –78 °C and a solution of ketone **4.21** (687 mg, 3.09 mmol) in THF (10 mL) added followed after 1 h by trimethylsilyl chloride (0.51 mL, 4.02 mmol). The reaction mixture was allowed to warm to RT over 30 min, then partitioned between sat. $NaHCO_3$ (30 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (2 x 30 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave silyl enol ether **4.22** as a colourless oil (843 mg, 2.86 mmol, 93%).

FT-IR ν_{max} (neat, cm^{-1}) 2954 m, 2925 m, 2867 w, 1655 m, 1456 w, 1376 w, 1251 s, 1204 m, 1176 s, 998 w, 971 w, 945 w, 908 s, 840 vs, 748 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.26-5.20 (2H, obsc. m), 4.72 (1H, d, *J* 0.8 Hz), 2.61 (1H, septet of d, *J* 6.5, 1.6 Hz), 2.22-2.18 (2H, bm), 2.07 (1H, dqd, *J* 13.3, 6.8, 3.3 Hz), 1.99-1.94 (2H, m), 1.75 (1H, dq, *J* 12.3, 4.0 Hz), 1.63 (1H, m), 1.34 (1H, dtd, *J* 13.3, 10.3, 2.9 Hz), 0.99 (1H, obsc. m), 0.95 (3H, d, *J* 6.5 Hz), 0.94 (3H, d, *J* 6.5 Hz), 0.93 (3H, d, *J* 6.5

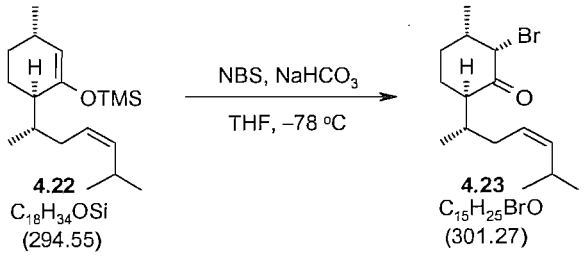
Hz), 0.76 (3H, d, *J* 6.8 Hz), 0.19 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 152.1 (*C*), 138.3 (*C*H), 126.8 (*C*H), 112.6 (*C*H), 42.5 (*C*H), 33.2 (*C*H), 32.4 (*C*H_2), 31.9 (*C*H_2), 30.4 (*C*H), 26.8 (*C*H), 23.4 (*C*H_3), 23.4 (*C*H_3), 23.1 (*C*H_3), 22.6 (*C*H_2), 14.7 (*C*H_3), 0.5 (3 x *C*H_3).

LRMS $^m/_z$ (EI) 294 (M^+, 5%), 279 ([M – CH_3]$^+$, 7), 209 (44), 184 (100), 169 (90), 156 (19), 73 (82).

HRMS $^m/_z$ (EI) found 294.2390, M^+; $C_{18}H_{34}OSi$ requires 294.2379.

***rel*-(2'*S*,2*S*,3*S*,4'*Z*,6*R*)-2-Bromo-3-methyl-6-(6'-methyl-hept-4'-en-2'-yl)-cyclohexanone, 4.23**



4.22
$C_{18}H_{34}OSi$
(294.55)

4.23
$C_{15}H_{25}BrO$
(301.27)

To a solution of silyl enol ether **4.22** (829 mg, 2.81 mmol) in THF (30 mL) at –78 °C was added powdered $NaHCO_3$ (283 mg, 3.37 mmol) followed by *N*-bromosuccinimide (526 mg, 2.96 mmol). After 1 h the reaction was warmed to RT and partitioned between sat. $NaHCO_3$ (30 mL) and ether (40 mL). The aqueous phase was separated and extracted with ether (2 x 40 mL) then the combined organic phases were washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) gave bromoketone **4.23** as a colourless oil (809 mg, 2.69 mmol, 96%).

FT-IR ν_{max} (neat, cm^{-1}) 2958 s, 2931 s, 2868 m, 1711 vs, 1455 s, 1378 m, 1361 w, 1319 w, 1283 w, 1201 w, 1160 m, 1086 w, 972 m, 778 m, 746 m, 662 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.25 (1H, d, *J* 10.8 Hz), 5.20 (1H, dt, *J* 10.8, 6.7 Hz), 4.25 (1H, dd, *J* 3.0, 1.5 Hz), 3.17 (1H, ddd, *J* 13.3, 5.8, 4.5 Hz),

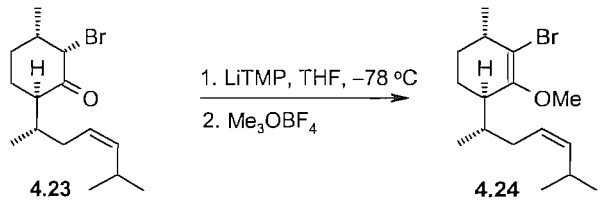
2.58 (1H, septet of d, *J* 6.8, 2.2 Hz), 2.13-1.82 (5H, m), 1.76 (1H, qd, *J* 12.8, 3.5 Hz), 1.65 (1H, m), 1.38 (1H, qd, *J* 13.0, 3.8 Hz), 1.10 (3H, d, *J* 6.3 Hz), 0.96 (3H, d, *J* 6.8 Hz), 0.95 (3H, d, *J* 6.8 Hz), 0.85 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 206.3 (*C*), 139.2 (*C*H), 125.5 (*C*H), 62.2 (*C*H), 46.6 (*C*H), 38.6 (*C*H), 32.6 (CH_2), 31.1 (*C*H), 28.1 (CH_2), 27.1 (CH_2), 26.8 (*C*H), 23.4 (CH_3), 23.3 (CH_3), 19.7 (CH_3), 16.1 (CH_3).

LRMS $^m/_z$ (ES^+) 325/323 ($[M + Na]^+$).

HRMS $^m/_z$ (ES^+) found 323.0985, $(M + Na)^+$; $C_{15}H_{25}{}^{79}BrNaO$ requires 323.0981.

rel-(2'_S_,3_R_,4'_Z_,6_S_)-1-Bromo-2-methoxy-6-methyl-3-(6'-methyl-hept-4'-en-2'-yl)-cyclohexene, 4.24



4.23
$C_{15}H_{25}BrO$
(301.27)

4.24
$C_{16}H_{27}BrO$
(315.30)

To a solution of 2,2,6,6-tetramethylpiperidine (0.36 mL, 2.11 mmol) in THF (10 mL) at 0 °C was added ^{n}BuLi (2.23 M in hexanes, 0.95 mL, 2.11 mmol). After 45 min the solution was cooled to –78 °C and a solution of bromoketone **4.23** (333 mg, 1.06 mmol) in THF (5 mL) added followed after 1 h by trimethyloxonium tetrafluoroborate (312 mg, 2.11 mmol). The reaction was allowed to warm to RT, stirred for 16 h then partitioned between sat. $NaHCO_3$ (15 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (2 x 20 mL) then the combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-2% ether/petrol) gave enol ether **4.24** as a colourless oil (267 mg, 0.847 mmol, 80%).

FT-IR ν_{max} (neat, cm^{-1}) 2956 s, 2929 s, 2868 m, 1638 w, 1456 s, 1377 m,

1210 s, 1153 m, 1101 m, 1022 s, 965 m, 858 w, 746 m, 697 m.

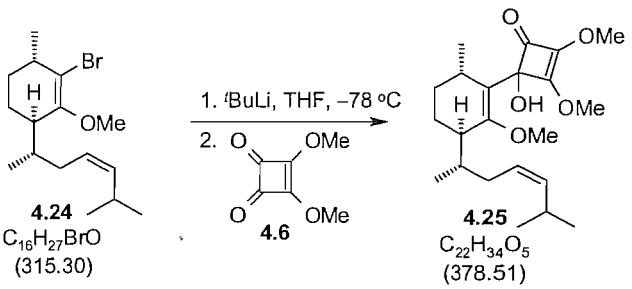
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.28-5.20 (2H, m), 3.54 (3H, s), 2.60 (1H, septet of d, *J* 6.5, 2.0 Hz), 2.52 (1H, bm), 2.06-1.89 (4H, m), 1.69 (1H, m), 1.48 (1H, m), 1.34-1.23 (2H, m), 1.17 (3H, d, *J* 6.8 Hz), 0.96 (3H, d, *J* 6.5 Hz), 0.95 (3H, d, *J* 6.5 Hz), 0.81 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 154.2 (*C*), 138.9 (*C*H), 126.0 (*C*H), 116.6 (*C*), 57.8 (CH_3), 39.9 (*C*H), 37.2 (*C*H), 34.0 (*C*H), 32.5 (CH_2), 31.7 (CH_2), 26.8 (*C*H), 23.4 (CH_3), 23.3 (CH_3), 22.1 (CH_3), 20.6 (CH_2), 15.6 (CH_3).

LRMS $^m/_z$ (ES^+) 339/337 ($[M + Na]^+$).

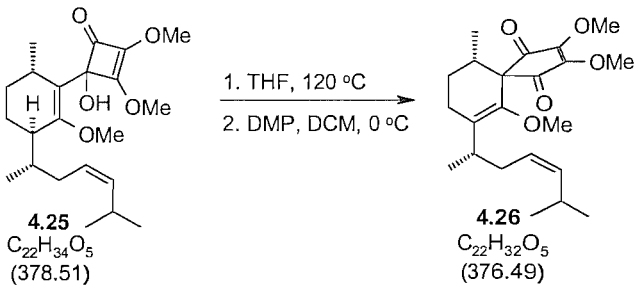
HRMS $^m/_z$ (ES^+) found 337.1139, $(M + Na)^+$; $C_{16}H_{27}{}^{79}BrNaO$ requires 337.1137.

rel-(2"_S_,3'_R_,4_RS_,4"_Z_,6'_S_)-4-Hydroxy-4-(2'-methoxy-6'-methyl-3'-(6"-methyl-hept-4"-en-2"-yl)-cyclohexenyl)-2,3-dimethoxy-cyclobut-2-enone, 4.25



To a solution of ^{t}BuLi (1.27 M in pentane, 0.67 mL, 0.856 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.24** (135 mg, 0.428 mmol) in THF (2.5 mL) over 2 min. After 30 min a solution of dimethyl squarate **4.6** (61 mg, 0.429 mmol) in THF (2 mL) was added over 2 min, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between water (5 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (30 mL) then the combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc/petrol) gave a yellow oil, vinylcyclobutenones **4.25** (*d.r.* ~ 3:2, 108 mg, 0.285 mmol, 67%), that was used immediately in the following reaction due to instability.

***rel*-(2'*S*,4'*Z*,10*R*)-7-(6-Methyl-hept-4'-en-2'-yl)-2,3,6-trimethoxy-10-methyl-spiro[4.5]deca-2,6-diene-1,4-dione, 4.26**



A solution of vinylcyclobutenones **4.25** (108 mg, 0.285 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL), cooled to 0 °C and Dess-Martin periodinane reagent added (181 mg, 0.428 mmol). After 30 min 1 M NaOH (3 mL) was added and the temperature raised to RT. The aqueous phase was separated and extracted with ether (2 x 20 mL) then the combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc/petrol) gave spirocycle **4.26** (78 mg, 0.207 mmol, 73%) as a yellow oil.

FT-IR ν_{max} (neat, cm^{-1}) 2957 m, 2868 w, 1685 s, 1626 s, 1459 s, 1320 s, 1208 m, 1133 m, 1111 m, 1039 m, 1012 m.

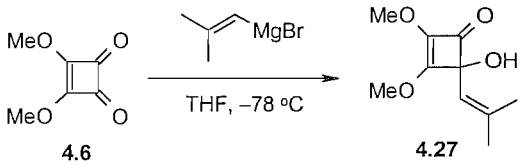
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.25-5.15 (2H, m), 4.23 (3H, s), 4.22 (3H, s), 3.40 (3H, s), 2.84 (1H, sextet, *J* 6.8 Hz), 2.57 (1H, septet of d, *J* 6.8, 1.8 Hz), 2.18-2.00 (5H, m), 1.92-1.83 (1H, m), 1.59-1.53 (1H, m), 1.01 (3H, d, *J* 6.8 Hz), 0.95 (3H, d, *J* 6.8 Hz), 0.94 (3H, d, *J* 6.8 Hz), 0.81 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 197.6 (*C*), 196.9 (*C*), 153.3 (*C*), 152.7 (*C*), 144.8 (*C*), 138.5 (*C*H), 133.2 (*C*), 125.6 (*C*H), 62.4 (CH_3), 60.8 (*C*), 59.9 (CH_3), 59.8 (CH_3), 35.1 (*C*H), 33.0 (*C*H), 32.8 (CH_2), 26.8 (CH_2), 26.8 (*C*H), 23.3 (2 x CH_3), 22.2 (CH_2), 18.5 (CH_3), 16.4 (CH_3).

LRMS $^m/_z$ (ES^+) 775 ($[2M + Na]^+$), 399 ($[M + Na]^+$).

HRMS $^m/_z$ (ES^+) found 399.2138, $(M + Na)^+$; $C_{22}H_{32}NaO_5$ requires 399.2142.

4-Hydroxy-4-(2-methylpropenyl)-2,3-dimethoxy-cyclobut-2-enone, 4.27



4.6
$C_6H_6O_4$
(142.11)

4.27
$C_{10}H_{14}O_4$
(198.22)

To a solution of dimethyl squarate **4.6** (200 mg, 1.41 mmol) in THF (5 mL) at –78 °C was added 2-methyl-1-propenyl-magnesium bromide (0.5 M in THF, 3.4 mL, 1.69 mmol) over 3 min. After 1 h sat. $NaHCO_3$ (3 mL) was added, the reaction mixture warmed to RT and extracted with ether (3 x 15 mL). The combined organic phases were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-30% EtOAc/petrol) yielded vinylcyclobutenone **4.27** as a pale yellow oil (118 mg, 0.595 mmol, 42%).

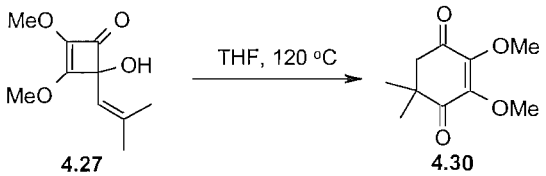
FT-IR ν_{max} (neat, cm^{-1}) 3391 bm, 2950 w, 2913 w, 2852 w, 1769 m, 1622 vs, 1467 s, 1332 vs, 1213 w, 1140 w, 1025 s, 988 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.41 (1H, septet, *J* 1.3 Hz), 4.12 (3H, s), 3.95 (3H, s), 2.58 (1H, bs), 1.89 (3H, d, *J* 1.1 Hz), 1.77 (3H, d, *J* 1.3 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 185.3 (*C*), 167.4 (*C*), 141.2 (*C*), 134.7 (*C*), 120.0 (*C*H), 85.3 (*C*), 60.2 (*C*H_3), 58.6 (*C*H_3), 26.7 (*C*H_3), 19.8 (*C*H_3).

LRMS $^m/_z$ (ES^+) 419 ($[2M + Na]^+$), 221 ($[M + Na]^+$).

2,3-Dimethoxy-5,5-dimethylcyclohex-2-ene-1,4-dione, 4.30



4.27
$C_{10}H_{14}O_4$
(198.22)

4.30
$C_{10}H_{14}O_4$
(198.22)

A solution of cyclobutenone **4.27** (94 mg, 0.474 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) gave cyclohexenedione **4.30** as a colourless oil (69 mg, 0.348 mmol, 73%).

FT-IR ν_{max} (neat, cm^{-1}) 2946 w, 2868 w, 2844 w, 1671 s, 1589 s, 1446 m, 1328 m, 1274 s, 1246 m, 1209 m, 1131 m, 1070 s, 993 m.

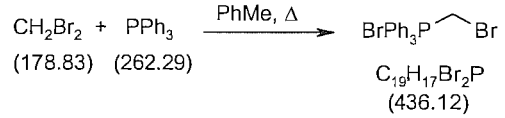
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.97 (3H, s), 3.95 (3H, s), 2.65 (2H, s), 1.24 (6H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 198.9 (*C*), 193.5 (*C*), 148.8 (*C*), 148.3 (*C*), 60.7 (2 x CH_3), 50.7 (CH_2), 44.4 (*C*), 26.3 (2 x CH_3).

LRMS $^m/_z$ (EI) 198 (M^+, 100%), 183 ($[M - CH_3]^+$, 94), 153 (55), 141 (28), 123 (54), 99 (55), 86 (83), 67 (49), 55 (71).

HRMS $^m/_z$ (EI) found 198.0894, M^+; $C_{10}H_{14}O_4$ requires 198.0892.

(Bromomethyl)triphenylphosphonium bromide



The title compound was prepared using the method of Rodriguez *et al.*[107] A solution of triphenylphosphine (5.00 g, 19.1 mmol) and dibromomethane (2.70 mL, 38.1 mmol) in toluene (40 mL) was heated at reflux for 64 h. On cooling to RT the resultant solid was collected by filtration and washed sequentially with toluene (50 mL) and petrol (50 mL) to afford (bromomethyl)triphenylphosphonium bromide as a white powder (5.36 g, 12.3 mmol, 64%). Spectroscopic data were in agreement with the literature.[107]

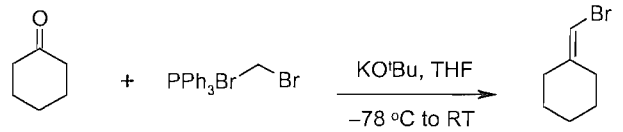
FT-IR ν_{max} (neat, cm^{-1}) 3048 w, 2987 w, 2905 w, 2848 m, 2762 w, 1581 w, 1479 w, 1430 s, 1176 w, 1111 s, 993 m, 817 m, 735 s, 719 s, 678 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.93 (6H, ddd, *J* 12.9, 7.9, 1.5 Hz), 7.83-7.74 (3H, m), 7.68 (6H, td, *J* 7.9, 3.6 Hz), 5.83 (2H, d, *J* 5.7 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 135.6 (3 x *C*H ($J_{C\text{-}P}$ 2.2 Hz)), 134.4 (6 x *C*H ($J_{C\text{-}P}$ 11.0 Hz)), 130.5 (6 x *C*H ($J_{C\text{-}P}$ 13.2 Hz)), 117.0 (3 x *C* ($J_{C\text{-}P}$ 87.9 Hz)), 18.6 (*C*H_2 ($J_{C\text{-}P}$ 53.9 Hz)).

LRMS $^m/_z$ (ES^+) 357/355 ($[M - Br]^+$).

(Bromomethylene)cyclohexane, 4.31



4.14
$C_6H_{10}O$
(98.15)

$C_{19}H_{17}Br_2P$
(436.12)

4.31
$C_7H_{11}Br$
(175.07)

The title compound was prepared using the method of Trost *et al.*[85] To a suspension of (bromomethyl)triphenyl-phosphonium bromide (3.00 g, 6.88 mmol) in THF (30 mL) at –78 °C was added potassium *tert*-butoxide (772 mg, 6.88 mmol). After warming to RT over 30 min, a solution of cyclohexanone **4.14** (519 mg, 5.29 mmol) in THF (10 mL) was added. After 16 h the reaction was partitioned between water (60 mL) and ether (60 mL). The aqueous phase was separated and extracted with ether (2 x 60 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave alkene **4.31** as a colourless oil (508 mg, 2.90 mmol, 55%). Spectroscopic data were in agreement with the literature.[85]

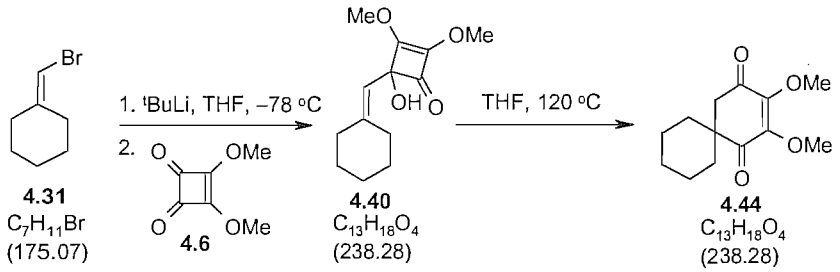
FT-IR ν_{max} (neat, cm^{-1}) 3064 w, 2929 s, 2856 m, 1630 w, 1446 s, 1332 m, 1279 s, 1225 m, 1168 w, 1124 w, 980 m, 854 m, 768 s, 695 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.85 (1H, t, *J* 1.0 Hz), 2.36-2.29 (2H, m), 2.22-2.15 (2H, m), 1.61-1.52 (6H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 145.3 (*C*), 97.7 (*C*H), 35.8 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 26.9 (CH_2), 26.4 (CH_2).

LRMS $^m/_z$ (EI) 176/174 (M^+, 45%), 134 (16), 132 (17), 95 ($[M - Br]^+$, 100), 67 (78), 53 (74).

2,3-Dimethoxyspiro[5.5]undec-2-ene-1,4-dione, 4.44



4.31
$C_7H_{11}Br$
(175.07)

4.6

4.40
$C_{13}H_{18}O_4$
(238.28)

4.44
$C_{13}H_{18}O_4$
(238.28)

To a solution of ^{t}BuLi (1.31 M in pentane, 1.10 mL, 1.44 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.31** (126 mg, 0.719 mmol) in THF (2.5 mL) over 2 min. The reaction was warmed to 0 °C over 30 min then re-cooled to –78 °C. Dimethyl squarate **4.6** (92 mg, 0.65 mmol) in THF (2 mL) was then added over 2 min, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between ether (15 mL) and brine (20 mL). The aqueous phase was separated and extracted with ether (2 x 15 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil, crude cyclobutenone **4.40** (142 mg, 0.596 mmol, 92%), was used directly in the next reaction due to its instability.

A solution of the crude cyclobutenone **4.40** (142 mg, 0.596 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% EtOAc/petrol) gave spirocycle **4.44** as a yellow oil (88 mg, 0.369 mmol, 62%).

FT-IR ν_{max} (neat, cm^{-1}) 2925 m, 2852 w, 1671 vs, 1591 s, 1450 m, 1307 m, 1266 s, 1189 m, 1095 s, 1058 s, 972 m, 915 m, 727 m.

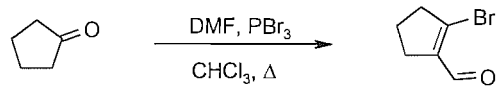
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s), 3.94 (3H, s), 2.73 (2H, s), 1.90-1.79 (2H, m), 1.68-1.59 (2H, m), 1.57-1.31 (6H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 199.4 (*C*), 193.6 (*C*), 148.7 (*C*), 148.0 (*C*), 60.7 (CH_3), 60.6 (CH_3), 48.0 (*C*), 46.5 (CH_2), 34.1 (2 x CH_2), 25.5 (CH_2), 21.6 (2 x CH_2).

LRMS $^m/_z$ (EI) 238 (M^+, 22%), 210 ($[M - CO]^+$, 72), 196 (43), 183 (100), 155 (73).

HRMS $^{m}/_{z}$ (EI) found 238.1206, M^{+}; $C_{13}H_{18}O_4$ requires 238.1205.

2-Bromocyclopentenecarboxaldehyde, 4.33



4.32
$C_5H_{10}O$
(84.12)

4.33
C_6H_7BrO
(175.02)

The title compound was prepared using the method of Rajamannar and Balasubramanian.[86] To a solution of *N,N*-dimethylformamide (2.8 mL, 35.7 mmol) in chloroform (20 mL) at 0 °C was added phosphorous tribromide (3.0 mL, 32.1 mmol). After 20 min the reaction was warmed to RT and a solution of cyclopentanone **4.32** (1.0 g, 11.9 mmol) in chloroform (10 mL) added. The reaction was heated at reflux for 2 h then cooled to RT and poured onto ice water (40 mL). Solid $NaHCO_3$ was added to neutralise the aqueous phase, which was then separated and extracted with ether (3 x 75 mL). The combined organic phases were washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% ether/petrol) yielded aldehyde **4.33** as a pale yellow oil (987 mg, 5.64 mmol, 47%). Spectroscopic data were in agreement with the literature.[86]

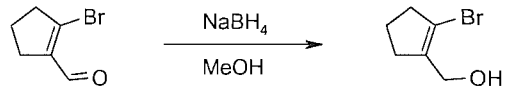
FT-IR ν_{max} (neat, cm^{-1}) 3330 w, 2946 w, 2831 w, 2721 w, 1667 vs, 1601 s, 1430 w, 1385 m, 1323 m, 1242 m, 1070 m, 919 m, 899 m, 719 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.91 (1H, s), 2.91 (2H, tt, *J* 7.9, 2.4 Hz), 2.54 (2H, tt, *J* 7.7, 2.4 Hz), 2.02 (2H, quin., *J* 7.8 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 189.3 (*C*H), 141.5 (*C*), 140.2 (*C*), 42.7 (*C*H_2), 29.4 (*C*H_2), 21.6 (*C*H_2).

LRMS $^{m}/_{z}$ (EI) 176/174 (M^{+}, 92%), 147/145 ($[M - CHO]^{+}$, 25), 95 ($[M - Br]^{+}$, 90), 67 (100).

2-Bromocyclopentenemethanol, 4.34



4.33
C_6H_7BrO
(175.02)

4.34
C_6H_9BrO
(177.04)

The title compound was prepared using the method of Rajamannar and Balasubramanian.[86] To a cooled (0 °C) solution of aldehyde **4.33** (941 mg, 5.38 mmol) in methanol (10 mL) was added sodium borohydride (214 mg, 5.65 mmol) portionwise over 10 min. The reaction was warmed to RT and after 1 h water (20 mL) and ether (50 mL) were added. The aqueous phase was separated and extracted with ether (2 x 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield alcohol **4.34** as a pale yellow oil (925 mg, 5.22 mmol, 97%). Spectroscopic data were in agreement with the literature.[108]

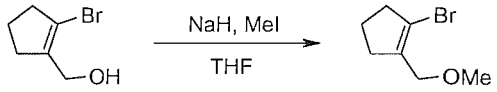
FT-IR ν_{max} (neat, cm^{-1}) 3297 bm, 2958 m, 2921 m, 2852 m, 1650 w, 1438 m, 1307 m, 1242 w, 1091 s, 1021 s, 997 s, 952 s, 903 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.27 (2H, d, *J* 5.3 Hz), 2.66 (2H, t with fine splitting, *J* 7.3 Hz), 2.48 (2H, t with fine splitting, *J* 7.5 Hz), 1.98 (2H, quin., *J* 7.4 Hz), 1.49 (1H, t, *J* 5.3 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 139.9 (*C*), 118.2 (*C*), 60.7 (CH_2), 40.5 (CH_2), 32.7 (CH_2), 21.9 (CH_2).

LRMS $^m/_z$ (EI) 178/176 (M^+, 15%), 97 ($[M - Br]^+$, 100), 79 (81), 67 (81).

1-Bromo-2-methoxymethyl-cyclopentene, 4.35



4.34
C_6H_9BrO
(177.04)

4.35
$C_7H_{11}BrO$
(191.07)

The title compound was prepared by adapting the method of Smith III *et al.*[109] To a solution of alcohol **4.34** (901 mg, 5.09 mmol) in THF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 611 mg, 15.3 mmol) portionwise over 5 min. After 5 min methyl iodide (1.6 mL, 25.5 mmol) was added. After a further 2 h the reaction was partitioned between ether (50 mL) and sat. NH_4Cl (40 mL). The organic phase was separated, washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% ether/petrol) gave methyl ether **4.35** as a pale yellow oil (818 mg, 4.28 mmol, 84%).

FT-IR ν_{max} (neat, cm^{-1}) 2925 m, 2852 m, 2823 m, 1654 w, 1446 w, 1373 w, 1319 w, 1283 w, 1185 m, 1111 s, 1082 s, 964 m, 890 m.

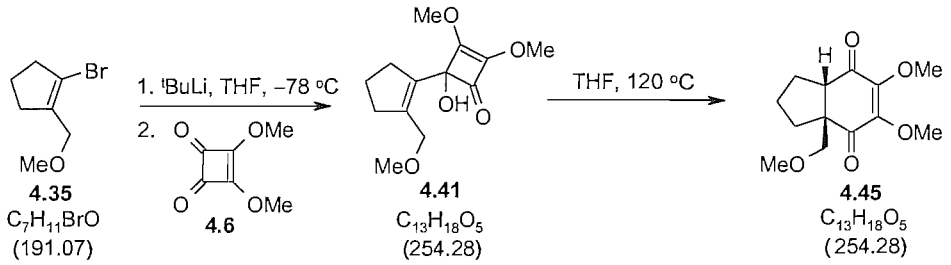
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.05 (2H, s), 3.32 (3H, s), 2.68 (2H, t with fine splitting, *J* 7.5 Hz), 2.42 (2H, t with fine splitting, *J* 7.5 Hz), 1.97 (2H, quin., *J* 7.5 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 137.9 (*C*), 119.6 (*C*), 69.7 (CH_2), 58.2 (CH_3), 40.5 (CH_2), 32.8 (CH_2), 21.9 (CH_2).

LRMS $^m/_z$ (EI) 192/190 (M^+, 6%), 111 ($[M - Br]^+$, 100), 79 (84), 65 (26).

HRMS $^m/_z$ (EI) found 189.9995, M^+; $C_7H_{11}{}^{79}BrO$ requires 189.9993.

***rel*-(3a*R*,7a*S*)-5,6-Dimethoxy-3a-methoxymethyl-2,3,3a,7a-tetrahydro-1*H*-indene-4,7-dione, 4.45**



To a solution of ^{t}BuLi (1.24 M in pentane, 0.90 mL, 1.12 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.35** (107 mg, 0.56 mmol) in THF (2.5 mL) over 2 min. After 10 min dimethyl squarate **4.6** (80 mg, 0.56 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT, partitioned between ether (25 mL) and water (5 mL) and the aqueous phase extracted with ether (2 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield crude cyclobutenone **4.41** as a pale yellow oil (94 mg, 0.37 mmol, 66%). The product was used directly in the next reaction due to instability.

A solution of the crude cyclobutenone **4.41** (94 mg, 0.37 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-25% EtOAc/petrol) gave a single diastereoisomer of dione **4.45** as a pale yellow oil (60 mg, 0.236 mmol, 64%).

FT-IR ν_{max} (neat, cm^{-1}) 2942 w, 2872 w, 1663 s, 1593 s, 1446 m, 1274 m, 1197 m, 1099 s, 931 m, 903 m.

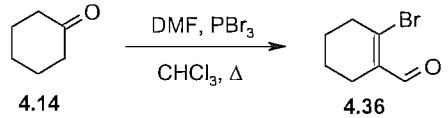
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.99 (3H, s), 3.93 (3H, s), 3.72 (1H, d, *J* 8.4 Hz), 3.24 (3H, s), 3.19 (1H, d, *J* 8.4 Hz), 3.00 (1H, t, *J* 8.4 Hz), 2.18-2.06 (2H, m), 1.88 (1H, m), 1.71-1.51 (3H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 197.7 (*C*), 195.7 (*C*), 149.6 (*C*), 149.3 (*C*), 78.9 (*C*H_2), 60.8 (*C*H_3), 60.7 (*C*H_3), 59.5 (*C*H_3), 59.2 (*C*), 54.3 (*C*H), 34.1 (*C*H_2), 31.4 (*C*H_2), 23.9 (*C*H_2).

LRMS $^{m}/_{z}$ (ES^+) 531 ($[2M + Na]^+$), 309 ($[M + Na + MeOH]^+$), 277 ($[M + Na]^+$).

HRMS $^{m}/_{z}$ (ES^+) found 255.1222, MH^+; $C_{13}H_{19}O_5$ requires 255.1227.

2-Bromocyclohexenecarboxaldehyde, 4.36



4.14
$C_6H_{10}O$
(98.15)

4.36
C_7H_9BrO
(189.05)

To a solution of *N,N*-dimethylformamide (2.40 mL, 30.6 mmol) in chloroform (20 mL) at 0 °C was added phosphorus tribromide (2.60 mL, 27.5 mmol). After 30 min the reaction was warmed to RT and a solution of cyclohexanone **4.14** (1.00 g, 10.2 mmol) in chloroform (10 mL) added. The reaction was heated at reflux for 3 h then cooled to RT and poured onto ice water (50 mL). Solid $NaHCO_3$ was added to neutralise the aqueous phase, which was then separated and extracted with ether (3 x 75 mL). The combined organic phases were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) yielded aldehyde **4.36** as a pale yellow oil (1.20 g, 6.35 mmol, 62%). Spectroscopic data were in agreement with the literature.[110]

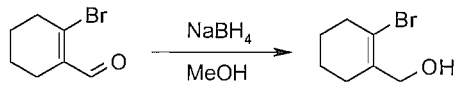
FT-IR ν_{max} (neat, cm^{-1}) 3334 w, 2933 m, 2860 w, 2733 w, 1671 s, 1610 s, 1417 w, 1340 m, 1262 m, 1201 s, 1058 w, 968 s, 796 m, 702 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 10.02 (1H, s), 2.77-2.73 (2H, m), 2.30-2.25 (2H, m), 1.80-1.64 (4H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 193.9 (*C*H), 143.7 (*C*), 135.5 (*C*), 39.0 (CH_2), 25.2 (CH_2), 24.4 (CH_2), 21.3 (CH_2).

LRMS $^{m}/_{z}$ (EI) 190/188 (M^+, 36%), 174/172 (34), 160/158 (36), 109 ($[M - Br]^+$, 52), 91 (27), 79 (100).

2-Bromocyclohexenemethanol, 4.37



4.36
C_7H_9BrO
(189.05)

4.37
$C_7H_{11}BrO$
(191.07)

To a cooled (0 °C) solution of aldehyde **4.36** (1.15 g, 6.08 mmol) in methanol (10 mL) was added sodium borohydride (242 mg, 6.39 mmol) portionwise over 10 min. The reaction was warmed to RT and after 1 h water (20 mL) and ether (50 mL) were added. The aqueous phase was separated and extracted with ether (2 x 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield alcohol **4.37** as a colourless oil (1.12 g, 5.86 mmol, 96%). Spectroscopic data were in agreement with the literature.[86]

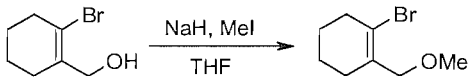
FT-IR ν_{max} (neat, cm^{-1}) 3297 bm, 2925 s, 2856 m, 2831 w, 1654 w, 1434 m, 1328 m, 1172 w, 1103 m, 1062 m, 1005 s, 972 s, 792 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.15 (2H, s), 2.53-2.45 (2H, m), 2.26-2.19 (2H, m), 1.75-1.59 (5H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 135.5 (*C*), 121.6 (*C*), 66.5 (*C*H_2), 36.8 (*C*H_2), 29.3 (*C*H_2), 24.8 (*C*H_2), 22.4 (*C*H_2).

LRMS $^m/_z$ (EI) 192/190 (M^+, 10%), 174/172 ($[M - H_2O]^+$, 4), 111 ($[M - Br]^+$, 67), 93 (82), 77 (53), 67 (100), 55 (56).

1-Bromo-2-methoxymethyl-cyclohexene, 4.38



4.37
$C_7H_{11}BrO$
(191.07)

4.38
$C_8H_{13}BrO$
(205.09)

To a solution of alcohol **4.37** (1.06 g, 5.57 mmol) in THF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 668 mg, 16.7 mmol) portionwise over 5 min. After 15 min methyl iodide (1.73 mL, 27.9 mmol) was added. After a further 2 h the reaction was partitioned between ether (50 mL) and sat. NH_4Cl (50 mL). The organic phase was separated, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% ether/petrol) gave methyl ether **4.38** as a colourless oil (1.11 g, 5.41 mmol, 97%).

FT-IR ν_{max} (neat, cm^{-1}) 2978 w, 2925 m, 2860 w, 2835 w, 2819 w, 1654 w, 1442 w, 1328 w, 1176 m, 1111 s, 1082 s, 968 s, 911 w, 796 m.

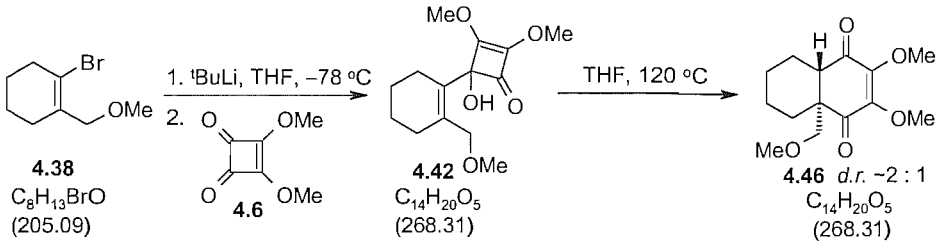
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.07 (2H, s), 3.32 (3H, s), 2.55-2.48 (2H, m), 2.24-2.16 (2H, m), 1.72-1.66 (4H, m).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 133.2 (*C*), 122.3 (*C*), 75.4 (CH_2), 58.0 (CH_3), 37.0 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 22.4 (CH_2).

LRMS $^m/_z$ (EI) 206/204 (M^+, 12%), 174/172 ([M – MeOH]$^+$, 31), 125 ([M – Br]$^+$, 99), 93 (100), 77 (52), 65 (37).

HRMS $^m/_z$ (EI) found 204.0151, M^+; $C_8H_{13}{}^{79}BrO$ requires 204.0150.

***rel*-(4a*S*,8a*S*)-2,3-Dimethoxy-4a-methoxymethyl-4a,5,6,7,8,8a-hexahydro[1,4]-naphthoquinone, 4.46**



4.38
$C_8H_{13}BrO$
(205.09)

4.42
$C_{14}H_{20}O_5$
(268.31)

4.46 *d.r.* ~2 : 1
$C_{14}H_{20}O_5$
(268.31)

To a solution of ^{t}BuLi (1.31 M in pentane, 0.85 mL, 1.12 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.38** (107 mg, 0.56 mmol) in THF (2.5 mL) over 2 min. After 10 min dimethyl squarate **4.6** (81 mg, 0.56 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between ether (15 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (10 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting pale yellow oil, crude cyclobutenone **4.42** (144 mg, 0.537 mmol, 94%), was used directly in the next reaction due to instability.

A solution of the crude cyclobutenone **4.42** (144 mg, 0.54 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-25% EtOAc/petrol) gave an inseparable 2:1 mixture of *trans*- and *cis*-hexahydro-naphthoquinones **4.46** as a pale yellow oil (95 mg, 0.36 mmol, 66%).

FT-IR ν_{max} (neat, cm^{-1}) 2933 m, 2860 w, 1671 s, 1589 s, 1450 m, 1279 m, 1205 m, 1189 m, 1107 s, 993 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) *Trans*-isomer: 3.98 (3H, s), 3.90 (3H, s), 3.55 (1H, d, *J* 9.4 Hz), 3.45 (1H, d, *J* 9.4 Hz), 3.21 (3H, s), 2.49 (1H, dd, *J* 12.0, 3.5 Hz), 2.08 (1H, m), 1.86 (1H, m), 1.69 (1H, m), 1.52-1.36 (3H, m), 1.29-1.13 (2H, m). Less intense signals attributed to the *cis*-isomer: 3.97 (3H, s), 3.93 (3H, s), 3.41 (1H, d, *J* 8.9 Hz), 3.28 (1H, d, *J* 8.9 Hz), 3.22 (3H, s), 2.70 (1H, dd, *J* 11.2, 4.4 Hz), 2.31 (1H, m).

nOe For the major diastereoisomer (*trans*): irradiation of the signal at δ_H 3.55 (1H, d, *J* 9.4 Hz, C*H*HOMe) caused nOe enhancement at δ_H 3.45

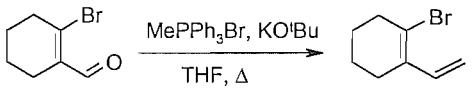
(1H, d, *J* 9.4 Hz, CH*H*OMe) and 3.21 (3H, s, OMe); irradiation of the signal at δ_H 3.45 (1H, d, *J* 9.4 Hz, CH*H*OMe) caused nOe enhancement at δ_H 3.55 (1H, d, *J* 9.4 Hz, C*H*HOMe) and 3.21 (3H, s, OMe); irradiation of the signal at δ_H 2.49 (1H, dd, *J* 12.0, 3.5 Hz, C*H*C=O) caused nOe enhancement at δ_H 2.08 (1H, m, CHC*H*H). For the minor diastereoisomer (*cis*): irradiation of the signal at δ_H 3.41 (1H, d, *J* 8.9 Hz, C*H*HOMe) caused nOe enhancement at δ_H 3.28 (1H, d, *J* 8.9 Hz, CH*H*OMe) and 3.22 (3H, s, OMe); irradiation of the signal at δ_H 3.28 (1H, d, *J* 8.9 Hz, CH*H*OMe), caused nOe enhancement at δ_H 3.41 (1H, d, *J* 8.9 Hz, C*H*HOMe), 3.22 (3H, s, OMe) and 2.70 (1H, dd, *J* 11.2, 4.4 Hz, C*H*C=O); irradiation of the signal at δ_H 2.70 (1H, dd, *J* 11.2, 4.4 Hz, C*H*C=O) caused nOe enhancement at δ_H 3.28 (1H, d, *J* 8.9 Hz, CH*H*OMe). *The aforementioned assignments were aided by a ^1H-^1H COSY experiment.*

^{13}C NMR δ_C (100 MHz, $CDCl_3$) *Trans*-isomer: 198.2 (*C*), 194.3 (*C*), 150.3 (*C*), 148.9 (*C*), 73.5 (CH_2), 60.7 (CH_3), 60.5 (CH_3), 59.6 (CH_3), 53.1 (*C*), 52.0 (*C*H), 29.4 (CH_2), 24.7 (CH_2), 21.1 (CH_2), 20.7 (CH_2). Less intense signals attributed to the *cis*-isomer: 197.2 (*C*), 196.8 (*C*), 149.1 (*C*), 149.0 (*C*), 80.1 (CH_2), 60.8 (CH_3), 60.5 (CH_3), 59.6 (CH_3), 53.0 (*C*), 52.5 (*C*H), 29.9 (CH_2), 29.7 (CH_2), 24.2 (CH_2), 22.0 (CH_2).

LRMS $^m/_z$ (EI) 268 (M^+, 30%), 223 ($[M - CH_2OMe]^+$, 46), 209 (64), 191 (12), 177 (19), 157 (15), 79 (22), 53 (17), 45 (100).

HRMS $^m/_z$ (EI) found 268.1311, M^+; $C_{14}H_{20}O_5$ requires 268.1311.

1-Bromo-2-vinylcyclohexene, 4.39



4.36
C_7H_9BrO
(189.05)

4.39
$C_8H_{11}Br$
(187.08)

The title compound was prepared using the method of Okamura *et al.*[87] To a suspension of methyltriphenylphosphonium bromide (1.92 g, 5.39 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (605 mg, 5.39 mmol). After warming to RT over 30 min, a solution of aldehyde **4.36** (679 mg, 3.59 mmol) in THF (10 mL) was added. The reaction was heated at reflux for 14 h then cooled to RT and partitioned between water (50 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) gave alkene **4.39** as a colourless oil (502 mg, 2.68 mmol, 75%). Spectroscopic data were in agreement with the literature.[87]

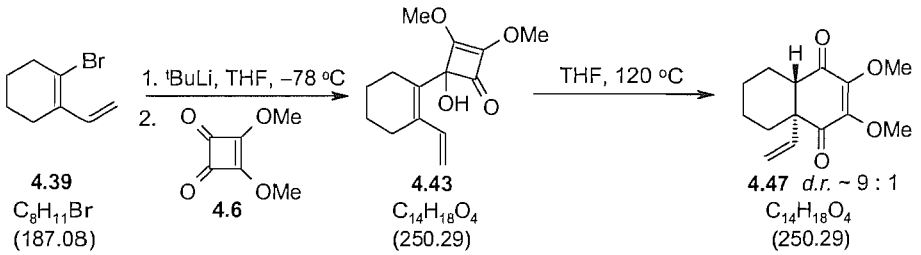
FT-IR ν_{max} (neat, cm^{-1}) 3085 w, 2929 s, 2856 m, 2835 m, 1626 s, 1446 m, 1430 m, 1409 m, 1336 m, 1021 s, 984 s, 964 s, 903 s, 792 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.92 (1H, dd, *J* 17.5, 10.9 Hz), 5.27 (1H, d, *J* 17.5 Hz), 5.14 (1H, d, *J* 10.9 Hz), 2.63 (2H, bs), 2.28 (2H, bs), 1.73 (4H, bs).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 137.3 (*C*H), 132.5 (*C*), 125.3 (*C*), 114.5 (CH_2), 37.7 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 22.3 (CH_2).

LRMS $^m/_z$ (EI) 188/186 (M^+, 18%), 107 ($[M - Br]^+$, 51), 91 (44), 79 (100), 65 (19), 51 (22).

***rel*-(4a*R*,8a*S*)-2,3-Dimethoxy-4a-vinyl-4a,5,6,7,8,8a-hexahydro[1,4]-naphthoquinone, 4.47**



4.39 $C_8H_{11}Br$ (187.08) | **4.6** | **4.43** $C_{14}H_{18}O_4$ (250.29) | **4.47** *d.r.* ~ 9 : 1 $C_{14}H_{18}O_4$ (250.29)

To a solution of ^{t}BuLi (1.31 M in pentane, 1.03 mL, 1.35 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.39** (126 mg, 0.674 mmol) in THF (2.5 mL) over 2 min. The reaction was warmed to RT over 20 min then re-cooled to –78 °C. Dimethyl squarate **4.6** (91 mg, 0.64 mmol) in THF (2 mL) was then added over 2 min, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between ether (20 mL) and brine (20 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield crude cyclobutenone **4.43** as a yellow oil (134 mg, 0.536 mmol, 80%), which was used directly in the next reaction due to its instability.

A solution of the crude cyclobutenone **4.43** (134 mg, 0.536 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc/petrol) gave an inseparable 9:1 mixture of *trans*- and *cis*-hexahydro-naphthoquinones **4.47** as a pale yellow oil (67 mg, 0.268 mmol, 50%).

FT-IR ν_{max} (neat, cm^{-1}) 2995 w, 2929 m, 2856 w, 1671 s, 1589 s, 1446 m, 1274 s, 1205 m, 1095 s, 1066 m, 1046 m, 980 m, 911 m, 821 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) *Trans*-isomer: 5.63 (1H, dd, *J* 17.3, 10.5 Hz), 5.32 (1H, d, *J* 10.5 Hz), 5.18 (1H, d, *J* 17.3 Hz), 3.95 (3H, s), 3.90 (3H, s), 2.62 (1H, dd, *J* 11.8, 3.3 Hz), 2.27 (1H, d with fine splitting, *J* 13.3 Hz), 2.08 (1H, m), 1.83 (1H, d with fine splitting, *J* 13.3 Hz), 1.64-1.54 (3H, m), 1.37 (1H, qt, *J* 13.3, 3.5 Hz), 1.19 (1H, qt, *J* 13.3, 3.8 Hz). Less intense signals attributed to the *cis*-isomer: 5.71 (1H, dd, *J* 17.6, 10.5 Hz), 5.11 (1H, d, *J* 10.5 Hz), 5.05 (1H, d, *J* 17.6 Hz), 2.78 (1H,

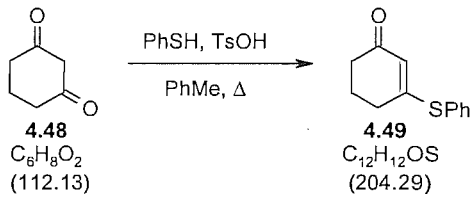
dd, *J* 12.3, 4.3 Hz), 2.46 (1H, d with fine splitting, *J* 13.3 Hz), 1.96 (1H, d with fine splitting, *J* 13.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) *Trans*-isomer: 195.3 (*C*), 195.2 (*C*), 149.2 (*C*), 149.0 (*C*), 135.9 (*C*H), 120.0 (CH_2), 60.7 (CH_3), 60.2 (CH_3), 54.8 (*C*), 53.2 (*C*H), 32.3 (CH_2), 24.8 (CH_2), 21.3 (CH_2), 21.0 (CH_2). Less intense signals attributed to the *cis*-isomer: 195.1 (*C*), 141.7 (*C*H), 116.4 (CH_2), 60.7 (CH_3), 60.6 (CH_3), 30.6 (CH_2), 24.3 (CH_2), 22.7 (CH_2).

LRMS $^m/_z$ (EI) 250 (M^+, 66%), 235 ($[M - CH_3]^+$, 14), 222 (83), 207 (59), 190 (23), 174 (34), 165 (53), 91 (81), 79 (100).

HRMS $^m/_z$ (EI) found 250.1205, M^+; $C_{14}H_{18}O_4$ requires 250.1205.

3-Phenylsulfanyl-cyclohex-2-enone, 4.49



4.48
$C_6H_8O_2$
(112.13)

4.49
$C_{12}H_{12}OS$
(204.29)

The title compound was prepared using the method of Danishefsky *et al.*[89] To a solution of 1,3-cyclohexandione **4.48** (4.49 g, 40.0 mmol) in toluene (50 mL) was added thiophenol (4.1 mL, 40.0 mmol) followed by *p*-toluenesulfonic acid monohydrate (76 mg, 0.40 mmol). The reaction mixture was heated at a vigorous reflux for 16 h, water being azeotropically removed from the reaction by use of Dean and Stark trap. After cooling to RT, the solvent was removed *in vacuo*, and the crude product purified by column chromatography (SiO_2, 50% ether/petrol) to yield enone **4.49** as a yellow oil (4.41 g, 21.6 mmol, 54%). Spectroscopic data were in agreement with the literature.[89]

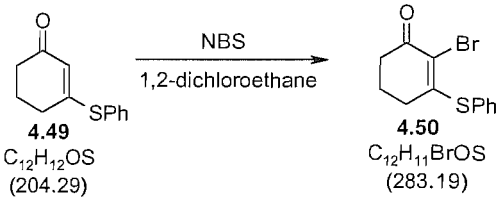
FT-IR ν_{max} (neat, cm^{-1}) 3052 w, 2942 w, 2860 w, 1645 vs, 1569 vs, 1475 m, 1438 m, 1336 m, 1319 m, 1287 s, 1238 s, 1185 s, 1131 m, 1054 m, 992 s, 870 m, 833 m, 813 m, 747 vs, 686 vs.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.50-7.39 (5H, m), 5.49 (1H, s), 2.53 (2H, t, *J* 6.5 Hz), 2.38 (2H, t, *J* 6.5 Hz), 2.05 (2H, quin., *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 196.2 (*C*), 166.9 (*C*), 135.6 (2 x *C*H), 130.3 (*C*H), 130.0 (2 x *C*H), 128.2 (*C*), 121.1 (*C*H), 37.4 (CH_2), 30.4 (CH_2), 23.1 (CH_2).

LRMS $^m/_z$ (EI) 204 (M^+, 56%), 187 (11), 176 (59), 147 (45), 127 (29), 110 (29), 77 (19), 67 (100).

2-Bromo-3-phenylsulfanyl-cyclohex-2-enone, 4.50



4.49
$C_{12}H_{12}OS$
(204.29)

4.50
$C_{12}H_{11}BrOS$
(283.19)

The title compound was prepared using the method of Koreeda *et al.*[88] To a solution of enone **4.49** (1.85 g, 9.07 mmol) in 1,2-dichloroethane (20 mL) was added *N*-bromosuccinimide (2.01 g, 11.3 mmol) and the reaction stirred in the dark at RT for 40 h. Sat. $NaHCO_3$ (25 mL) was added, the phases separated, and the aqueous phase extracted with DCM (50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a crude orange solid. Recrystallisation from EtOAc/hexane yielded bromide **4.50** as an off-white crystalline solid (1.91 g, 6.75 mmol, 74%). Physical and spectroscopic data were in agreement with the literature.[88]

MP 110-112 °C (EtOAc/hexane). Lit.[88] 112-113 °C.

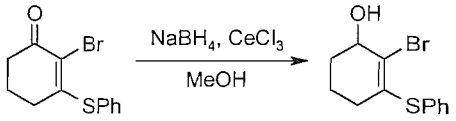
FT-IR ν_{max} (neat, cm^{-1}) 3052 m, 2942 w, 1654 vs, 1536 s, 1475 m, 1417 s, 1254 s, 1185 s, 1017 m, 976 s, 866 m, 829 m, 745 vs, 686 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.59-7.42 (5H, m), 2.56 (2H, t, *J* 6.3 Hz), 2.21 (2H, t, *J* 6.3 Hz), 1.95 (2H, quin., *J* 6.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 187.8 (*C*), 164.4 (*C*), 136.2 (2 x *C*H), 130.6 (*C*H), 129.8 (2 x *C*H), 129.3 (*C*), 117.0 (*C*), 37.3 (CH_2), 32.4 (CH_2), 22.7 (CH_2).

LRMS $^m/_z$ (EI) 284/282 (M^+, 37%), 203 ($[M - Br]^+$, 32), 175 (25), 147 (100), 109 (42), 77 (33), 65 (74).

2-Bromo-1-phenylsulfanyl-cyclohex-1-en-3-ol, 4.51



4.50
$C_{12}H_{11}BrOS$
(283.19)

4.51
$C_{12}H_{13}BrOS$
(285.21)

The title compound was prepared using the method of Koreeda *et al.*[88] To a suspension of enone **4.50** (861 mg, 3.04 mmol) in methanol (15 mL) was added cerium trichloride heptahydrate (1.25 g, 3.34 mmol) followed by sodium borohydride (126 mg, 3.34 mmol) in portions over 10 min. After 30 min water (20 mL) was added cautiously and the mixture extracted with EtOAc (2 x 40 mL). The combined organic phases were washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield allylic alcohol **4.51** as a colourless oil (866 mg, 3.03 mmol, 99%). Spectroscopic data were in agreement with the literature.[88]

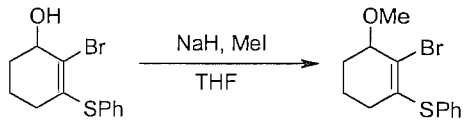
FT-IR ν_{max} (neat, cm^{-1}) 3395 bw, 3056 w, 2933 m, 2860 w, 1601 m, 1581 w, 1471 m, 1434 m, 1311 m, 1164 m, 1123 m, 1060 s, 993 s, 913 m, 743 vs, 685 vs.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.50-7.45 (2H, m), 7.37-7.33 (3H, m), 4.35 (1H, bs), 2.28 (1H, m), 2.05-1.56 (6H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 138.2 (*C*), 134.9 (2 x *C*H), 131.3 (*C*), 129.3 (2 x *C*H), 128.9 (*C*H), 121.9 (*C*), 71.5 (*C*H), 32.3 (CH_2), 31.8 (CH_2), 19.1 (CH_2).

LRMS $^m/_z$ (EI) 286/284 (M^+, 14%), 268/266 ($[M - H_2O]^+$, 24%), 205 ($[M - Br]^+$, 45), 109 (100), 77 (33), 65 (74).

2-Bromo-3-methoxy-1-phenylsulfanyl-cyclohexene, 4.52



4.51
$C_{12}H_{13}BrOS$
(285.21)

4.52
$C_{13}H_{15}BrOS$
(299.24)

To a solution of alcohol **4.51** (420 mg, 1.47 mmol) in THF (15 mL) was added sodium hydride (60% dispersion in mineral oil, 177 mg, 4.42 mmol). After 10 min methyl iodide (0.46 mL, 7.35 mmol) was added followed after 2 h by sat. NH_4Cl (25 mL). The aqueous phase was separated and extracted with ether (2 x 25 mL) then the combined organic phases were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-10% ether/petrol) gave methyl ether **4.52** as a colourless oil (372 mg, 1.24 mmol, 84%).

FT-IR ν_{max} (neat, cm^{-1}) 3052 w, 2933 m, 2814 w, 1605 m, 1581 w, 1471 m, 1435 m, 1344 m, 1189 m, 1081 vs, 1009 s, 968 s, 899 s, 829 m, 743 vs, 686 vs.

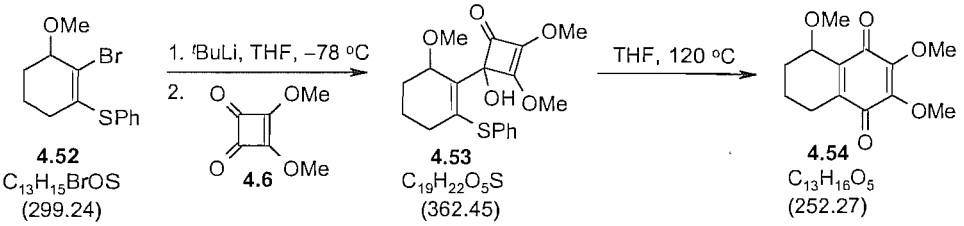
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.48-7.44 (2H, m), 7.36-7.32 (3H, m), 3.89 (1H, bs), 3.47 (3H, s), 2.02-1.54 (6H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 139.0 (*C*), 135.1 (2 x *C*H), 131.4 (*C*), 129.2 (2 x *C*H), 128.8 (*C*H), 118.8 (*C*), 80.4 (*C*H), 57.7 (CH_3), 32.2 (CH_2), 28.4 (CH_2), 18.7 (CH_2).

LRMS $^m/_z$ (EI) 300/298 (M^+, 21%), 268/266 ($[M - MeOH]^+$, 40), 219 ($[M - Br]^+$, 82), 187 (60), 154 (33), 109 (100), 77 (86), 65 (58).

HRMS $^m/_z$ (EI) found 298.0024, M^+; $C_{13}H_{15}{}^{79}BrOS$ requires 298.0027.

2,3,5-Trimethoxy-5,6,7,8-tetrahydro[1,4]naphthoquinone, 4.54



To a solution of ^{t}BuLi (1.15 M in pentane, 0.82 mL, 0.94 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.52** (141 mg, 0.47 mmol) in THF (2.5 mL) over 2 min. After 15 min dimethyl squarate **4.6** (67 mg, 0.47 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase extracted with ether (20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone **4.53** as a pale yellow oil (*d.r.* ~ 1:1, 126 mg, 0.348 mmol, 74%). The product was used directly in the next reaction due to instability.

Cyclobutenone **4.53** (56 mg, 0.155 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc/petrol) gave quinone **4.54** as an orange oil (28 mg, 0.111 mmol, 72%).

FT-IR ν_{max} (neat, cm^{-1}) 2938 m, 2819 w, 1648 s, 1605 s, 1450 m, 1291 s, 1230 s, 1197 s, 1140 s, 1082 s, 988 s, 903 m, 841 m, 739 w.

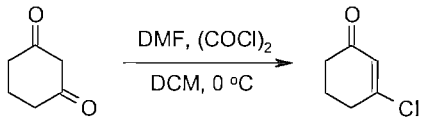
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.30 (1H, bs), 4.01 (3H, s), 3.96 (3H, s), 3.45 (3H, s), 2.64 (1H, dt, *J* 19.6, 3.5 Hz), 2.19-2.09 (2H, m), 1.79-1.71 (2H, m), 1.34 (1H, m).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 184.8 (*C*), 183.6 (*C*), 145.2 (*C*), 144.9 (*C*), 142.7 (*C*), 137.8 (*C*), 68.6 (*C*H), 61.3 (2 x *C*H_3), 58.0 (*C*H_3), 25.9 (*C*H_2), 22.7 (*C*H_2), 15.9 (*C*H_2).

LRMS $^m/_z$ (EI) 252 (M^+, 26%), 237 ([M – CH_3]$^+$, 13), 222 (100), 207 (74), 173 (63), 147 (43), 105 (75), 77 (88).

HRMS $^{m}/_{z}$ (EI) found 275.0889, $(M + Na)^+$; $C_{13}H_{16}NaO_5$ requires 275.0890.

3-Chlorocyclohex-2-enone, 4.55



4.48
$C_6H_8O_2$
(112.13)

4.55
C_6H_7ClO
(130.57)

The title compound was prepared using the method of Mewshaw.[90] To a solution of 1,3-cyclohexanedione **4.48** (1.01 g, 9.00 mmol) and DMF (0.91 mL, 11.7 mmol) in DCM (25 mL) at 0 °C was added oxalyl chloride (0.94 mL, 10.8 mmol) dropwise over 5 min. The reaction was warmed to RT and after 5 min partitioned between ether (100 mL) and water (40 mL). The organic phase was separated and washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 25% EtOAc/petrol) afforded 3-chlorocyclohex-2-enone **4.55** as a colourless oil (1.11 g, 8.50 mmol, 94%). Spectroscopic data were in agreement with the literature.[111]

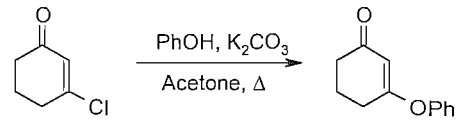
FT-IR ν_{max} (neat, cm^{-1}) 2954 w, 2889 w, 1671 vs, 1601 s, 1422 m, 1340 s, 1287 s, 1225 s, 1180 m, 1131 m, 1054 m, 984 s, 878 s, 833 m, 805 m, 739 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.22 (1H, t, *J* 1.5 Hz), 2.69 (2H, td, *J* 6.3, 1.5 Hz), 2.40 (2H, t, *J* 6.3 Hz), 2.08 (2H, quin., *J* 6.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 197.0 (*C*), 158.7 (*C*), 128.7 (*C*H), 36.5 (CH_2), 34.1 (CH_2), 22.4 (CH_2).

LRMS $^{m}/_{z}$ (EI) 132 (M^+ (^{37}Cl), 24%), 130 (M^+ (^{35}Cl), 71), 102 (100), 67 (88).

3-Phenoxy-cyclohex-2-enone, 4.56



4.55
C_6H_7ClO
(130.57)

4.56
$C_{12}H_{12}O_2$
(188.23)

The title compound was prepared using the method of McCoubrey.[91] To a solution of 3-chlorocyclohex-2-enone **4.55** (968 mg, 7.41 mmol) in acetone (30 mL) was added powdered potassium carbonate (1.23 g, 8.89 mmol) followed by phenol (698 mg, 7.41 mmol). The reaction was heated at reflux for 16 h, cooled to RT, filtered (rinsing with EtOAc (50 mL)) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded enone **4.56** as a colourless oil (1.13 g, 6.00 mmol, 81%).

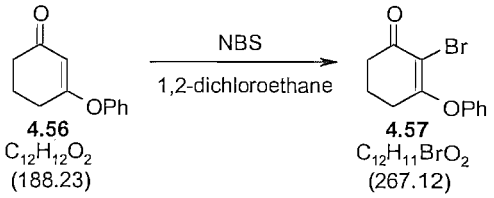
FT-IR ν_{max} (neat, cm^{-1}) 3064 w, 2946 w, 2872 w, 1659 s, 1614 s, 1581 s, 1483 m, 1368 s, 1201 s, 1160 s, 1131 s, 911 w, 862 w, 768 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.39 (2H, td, *J* 7.5, 1.0 Hz), 7.24 (1H, tt, *J* 7.5, 1.0 Hz), 7.03 (2H, dd, *J* 7.5, 1.0 Hz), 5.13 (1H, s), 2.66 (2H, t, *J* 6.3 Hz), 2.38 (2H, t, *J* 6.3 Hz), 2.09 (2H, quin., *J* 6.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 199.7 (*C*), 178.4 (*C*), 152.9 (*C*), 130.2 (2 x *C*H), 126.3 (*C*H), 121.5 (2 x *C*H), 106.3 (*C*H), 36.8 (*C*H_2), 28.7 (*C*H_2), 21.4 (*C*H_2).

LRMS $^m/_z$ (EI) 188 (M^+, 58%), 160 ($[M - CO]^+$, 94), 131 (15), 94 (100), 77 (49), 67 (83).

2-Bromo-3-phenoxy-cyclohex-2-enone, 4.57



4.56
$C_{12}H_{12}O_2$
(188.23)

4.57
$C_{12}H_{11}BrO_2$
(267.12)

To a solution of enone **4.56** (1.42 g, 7.54 mmol) in 1,2-dichloroethane (20 mL) at 0 °C in the dark was added *N*-bromosuccinimide (1.75 g, 9.81 mmol) portionwise over 20 min. The reaction was warmed to RT, stirred for 40 h then sat. $NaHCO_3$ (20 mL) was added. The aqueous phase was separated and extracted with DCM (2 x 40 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-30% EtOAc/petrol) gave bromide **4.57** as a white crystalline solid (1.50 g, 5.62 mmol, 74%).

MP 90-91 °C (EtOAc).

FT-IR ν_{max} (neat, cm^{-1}) 3052 w, 2938 w, 2880 w, 1663 s, 1601 s, 1573 s, 1479 s, 1356 s, 1336 s, 1279 m, 1225 s, 1172 s, 1136 s, 984 s, 907 s, 809 s, 768 s, 731 s, 698 s.

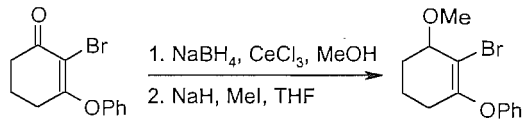
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.33 (2H, td, *J* 7.5, 1.3 Hz), 7.18 (1H, tt, *J* 7.5, 1.3 Hz), 6.98 (2H, dd, *J* 7.5, 1.3 Hz), 2.52 (2H, t, *J* 6.4 Hz), 2.37 (2H, t, *J* 6.4 Hz), 1.92 (2H, quin., *J* 6.4 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 191.7 (*C*), 171.3 (*C*), 153.3 (*C*), 130.2 (2 x *C*H), 126.1 (*C*H), 120.8 (2 x *C*H), 106.6 (*C*), 37.3 (CH_2), 29.1 (CH_2), 20.9 (CH_2).

LRMS $^m/_z$ (EI) 268/266 (M^+, 44%), 187 ($[M - Br]^+$, 57), 145 (35), 131 (45), 117 (44), 94 (100), 77 (78), 65 (77).

CHN Found C 53.61%, H 4.15%; $C_{12}H_{11}BrO_2$ requires C 53.96%, H 4.15%.

2-Bromo-3-methoxy-1-phenoxy-cyclohexene, 4.58



4.57
$C_{12}H_{11}BrO_2$
(267.12)

4.58
$C_{13}H_{15}BrO_2$
(283.16)

To a solution of enone **4.57** (750 mg, 2.81 mmol) in MeOH (15 mL) was added cerium trichloride heptahydrate (1.15 g, 3.09 mmol) followed by sodium borohydride (117 mg, 3.09 mmol) in portions over 8 min. After 30 min the reaction was partitioned between water (20 mL) and EtOAc (30 mL). The aqueous phase was separated and extracted with EtOAc (30 mL) then the combined organic phases were washed with sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield 2-bromo-3-phenoxy-cyclohex-2-enol as a colourless oil (764 mg).

The crude product was immediately dissolved in THF (20 mL) and sodium hydride (60% dispersion in mineral oil, 337 mg, 8.43 mmol) added. After 10 min methyl iodide (0.87 mL, 14.1 mmol) was added, followed after 90 min by sat. NH_4Cl (30 mL) and ether (30 mL). The aqueous phase was separated and extracted with ether (2 x 30 mL) then the combined organic phases were washed with water (60 mL) and brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% ether/petrol) gave 2-bromo-3-methoxy-1-phenoxy-cyclohexene **4.58** as a colourless oil (667 mg, 2.36 mmol, 84% over 2 steps).

FT-IR ν_{max} (neat, cm^{-1}) 2929 m, 2823 w, 1659 m, 1589 s, 1483 s, 1340 m, 1209 s, 1078 s, 984 m, 890 m, 845 m, 748 s, 687 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.31 (2H, dd, *J* 8.0, 7.5 Hz), 7.06 (1H, t, *J* 7.5 Hz), 6.95 (2H, d, *J* 8.0 Hz), 4.03 (1H, bs), 3.50 (3H, s), 2.24-2.03 (3H, m), 1.93 (1H, m), 1.79-1.68 (2H, m).

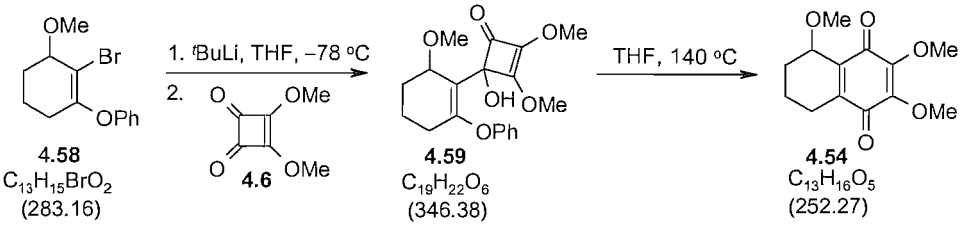
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 155.1 (*C*), 152.1 (*C*), 129.8 (2 x *C*H), 123.2 (*C*H), 117.6 (2 x *C*H), 109.3 (*C*), 80.0 (*C*H), 57.8 (CH_3), 28.4 (CH_2), 28.3 (CH_2), 18.1 (CH_2).

LRMS $^m/_z$ (EI) 284/282 (M^+, 12%), 252/250 ([M – MeOH]$^+$, 32), 203 ([M –

Br]$^+$, 16), 171 (48), 128 (32), 115 (26), 94 (47), 77 (100), 65 (50).

HRMS $^m/_z$ (EI) found 284.0238, M^+; $C_{13}H_{15}{}^{81}BrO_2$ requires 284.0235.

2,3,5-Trimethoxy-5,6,7,8-tetrahydro[1,4]naphthoquinone, 4.54

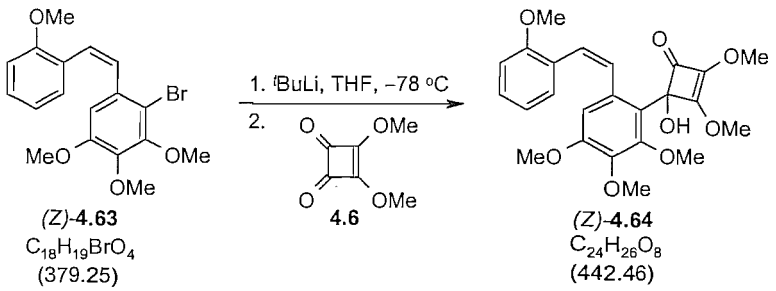


To a solution of ^{t}BuLi (1.15M in pentane, 0.87 mL, 0.996 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.58** (141 mg, 0.498 mmol) in THF (2.5 mL) over 2 min. After 15 min dimethyl squarate **4.6** (67 mg, 0.473 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between ether (20 mL) and water (5 mL). The aqueous phase was extracted with ether (20 mL) then the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone **4.59** as a pale yellow oil (*d.r.* ~ 1:1, 115 mg, 0.332 mmol, 67%). The product was used directly in the next reaction due to instability.

Cyclobutenone **4.59** (115 mg, 0.322 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 30 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% EtOAc/petrol) gave quinone **4.54** as an orange oil (62 mg, 0.246 mmol, 74%).

Spectroscopic data for quinone **4.54** as described previously.

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl] phenyl}cyclobut-2-enone, (*Z*)-4.64



(*Z*)-**4.63**
$C_{18}H_{19}BrO_4$
(379.25)

(*Z*)-**4.64**
$C_{24}H_{26}O_8$
(442.46)

To a solution of ^{t}BuLi (1.24 M in pentane, 0.57 mL, 0.704 mmol) in THF (2.5 mL) at −78 °C was added a solution of (*Z*)-1-bromo-2,3,4-trimethoxy-6-[2-(2-methoxy-phenyl)-vinyl]benzene (*Z*)-**4.63**[112] (133 mg, 0.352 mmol) in THF (2.5 mL) over 2 min. After 10 min dimethyl squarate **4.6** (100 mg, 0.704 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase re-extracted with ether (20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-40% EtOAc/petrol) yielded cyclobutenone (*Z*)-**4.64** as a pale yellow oil (119 mg, 0.269 mmol, 76%).

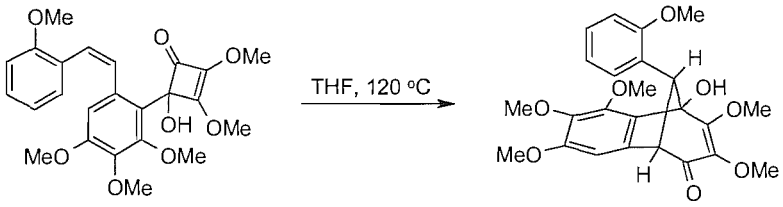
FT-IR ν_{max} (neat, cm^{-1}) 3281 bw, 3003 w, 2946 w, 2827 w, 1757 m, 1630 s, 1548 m, 1462 s, 1389 s, 1332 s, 1242 s, 1119 s, 1082 s, 1050 s, 1025 s, 971 s, 854 s, 837 s, 739 s, 715 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.14 (1H, td, *J* 7.8, 1.5 Hz), 7.04 (1H, d, *J* 12.1 Hz), 6.98 (1H, dd, *J* 7.8, 1.3 Hz), 6.80 (1H, d, *J* 12.1 Hz), 6.78 (1H, d, *J* 7.8 Hz), 6.74 (1H, t, *J* 7.8 Hz), 6.29 (1H, s), 5.36 (1H, s), 4.11 (3H, s), 3.99 (3H, s), 3.91 (3H, s), 3.82 (3H, s), 3.70 (3H, s), 3.46 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 183.6 (*C*), 165.7 (*C*), 156.7 (*C*), 152.7 (*C*), 152.1 (*C*), 141.4 (*C*), 134.5 (*C*), 133.0 (*C*), 131.2 (*C*H), 130.1 (*C*H), 128.7 (*C*H), 125.7 (*C*H), 125.4 (*C*), 121.2 (*C*), 120.5 (*C*H), 110.7 (*C*H), 110.2 (*C*H), 87.3 (*C*), 62.3 (CH_3), 60.9 (CH_3), 59.9 (CH_3), 58.5 (CH_3), 55.8 (CH_3), 55.3 (CH_3).

LRMS $^m/_z$ (ES^+) 907 ($[2M + Na]^+$), 465 ($[M + Na]^+$).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-1,2,3,7,8-pentamethoxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.65**



(Z)-**4.64**
$C_{24}H_{26}O_8$
(442.46)

4.65
$C_{24}H_{26}O_8$
(442.46)

Cyclobutenone (*Z*)-**4.64** (47 mg, 0.106 mmol) in THF (3 mL) was heated at 120 °C by microwave irradiation for 2 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded firstly recovered (*Z*)-**4.64** as a yellow oil (8 mg, 0.018 mmol, 17%), then benzobicyclo[3.2.1]octenone **4.65** as a cream solid (35 mg, 0.079 mmol, 75%).

MP 179-181 °C (EtOH).

FT-IR ν_{max} (neat, cm^{-1}) 3363 bw, 3003 w, 2983 w, 2950 w, 2929 w, 2831 w, 1659 m, 1593 m, 1458 m, 1328 m, 1266 s, 1225 m, 1160 m, 1103 s, 1042 s, 1013 m, 976 m, 756 s.

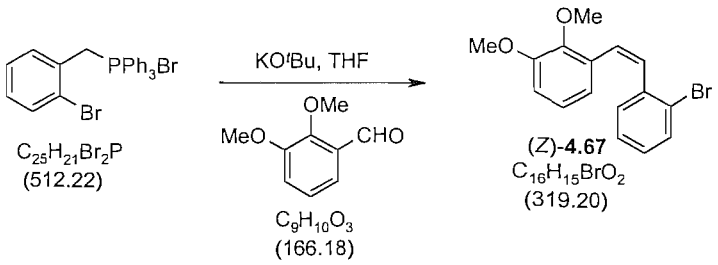
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.18 (1H, t, *J* 7.8 Hz), 6.92-6.85 (2H, m), 6.71 (1H, app. t, *J* 7.3 Hz), 6.71 (1H, s), 4.60 (1H, s), 4.22 (3H, s), 4.02 (1H, s), 3.94 (3H, s), 3.88 (1H, bs), 3.86 (3H, s), 3.85 (3H, s), 3.82 (3H, s), 3.66 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 195.1 (*C*), 169.5 (*C*), 158.1 (*C*), 154.0 (*C*), 150.1 (*C*), 141.4 (*C*), 135.4 (*C*), 129.3 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.4 (*C*), 125.9 (*C*), 120.2 (*C*H), 110.6 (*C*H), 105.8 (*C*H), 84.3 (*C*), 61.7 (*C*H), 61.7 (CH_3), 61.6 (CH_3), 61.3 (CH_3), 61.2 (CH_3), 60.4 (*C*H), 56.4 (CH_3), 55.8 (CH_3).

LRMS $^m/_z$ (ES^+) 907 ($[2M + Na]^+$), 465 ($[M + Na]^+$), 443 (MH^+).

HRMS $^m/_z$ (ES^+) found 443.1701, MH^+; $C_{24}H_{27}O_8$ requires 443.1697.

(*Z*)-1,2-Dimethoxy-3-[2-(2-bromophenyl)vinyl]benzene, (*Z*)-4.67



The title compound was prepared using the method of Guy.[112] To a suspension of (2-bromobenzyl)-triphenyl-phosphonium bromide (2.46 g, 4.80 mmol) in THF (30 mL) at 0 °C was added potassium *tert*-butoxide (628 mg, 5.60 mmol). After 30 min a solution of 2,3-dimethoxybenzaldehyde (665 mg, 4.00 mmol) in THF (10 mL) was added. The reaction was allowed to warm to RT, stirred for 16 h then partitioned between water (25 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-20% ether/petrol) yielded stilbene (*Z*)-**4.67** as a white crystalline solid (991 mg, 3.10 mmol, 78%). Physical and spectroscopic data were in agreement with the literature.[112]

MP 91-92 °C (hexane). Lit.[112] 88-92 °C.

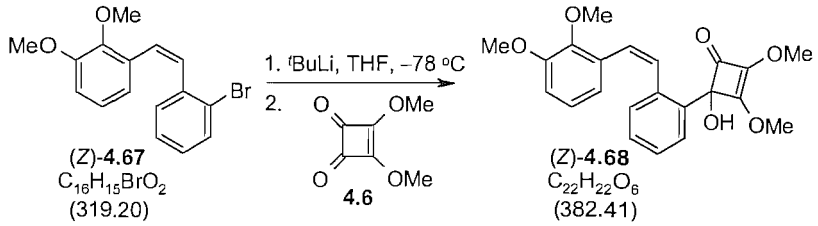
FT-IR ν_{max} (neat, cm^{-1}) 3064 w, 3007 w, 2962 w, 2929 w, 2831 w, 1573 m, 1475 s, 1458 s, 1426 s, 1254 s, 1213 s, 1172 s, 1070 s, 1005 s, 788 s, 756 vs, 731 s, 653 m.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.59 (1H, m), 7.17-7.04 (3H, m), 6.90 (1H, d, *J* 12.2 Hz), 6.80-6.75 (2H, m), 6.73 (1H, d, *J* 12.2 Hz), 6.57 (1H, m Hz), 3.89 (3H, s), 3.87 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 152.9 (*C*), 147.6 (*C*), 138.0 (*C*), 132.8 (*C*H), 131.1 (*C*H), 131.0 (*C*), 130.3 (*C*H), 128.7 (*C*H), 127.0 (*C*H), 126.9 (*C*H), 124.1 (*C*), 123.6 (*C*H), 122.2 (*C*H), 111.7 (*C*H), 61.0 (CH_3), 55.9 (CH_3).

LRMS $^m/_z$ (EI) 320/318 (M^+, 34%), 239 ($[M - Br]^+$, 33), 224 (89), 208 (62), 196 (38), 181 (61), 165 (54), 152 (100).

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{2-[2-(2,3-dimethoxyphenyl)vinyl]phenyl}-cyclobut-2-enone, (*Z*)-4.68



(*Z*)-**4.67**
$C_{16}H_{15}BrO_2$
(319.20)

(*Z*)-**4.68**
$C_{22}H_{22}O_6$
(382.41)

To a solution of ^{t}BuLi (1.22 M in pentane, 1.02 mL, 1.25 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide (*Z*)-**4.67** (200 mg, 0.627 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate **4.6** (89 mg, 0.627 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (3 mL). The reaction was warmed to RT and diluted with ether (20 mL). The aqueous phase was extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield cyclobutenone (*Z*)-**4.68** (240 mg, 0.627 mmol, 100%). The bulk was used without further purification due to product instability - an analytical sample being purified by recrystallisation from ether/petrol to yield a cream solid.

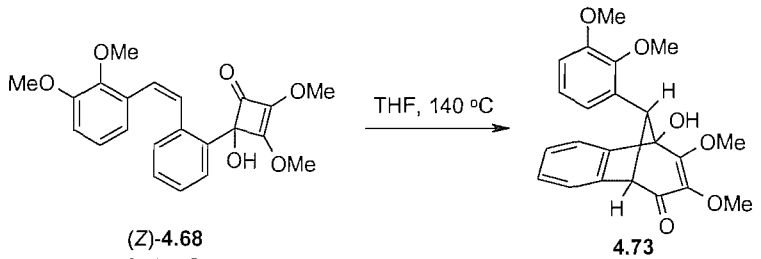
FT-IR ν_{max} (neat, cm^{-1}) 3399 bw, 2946 w, 2835 w, 1769 m, 1630 s, 1573 m, 1462 s, 1422 m, 1336 s, 1258 m, 1217 m, 1070 m, 1042 m, 988 m, 839 w, 747 w.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.48 (1H, d, *J* 7.5 Hz), 7.39 (1H, d, *J* 12.2 Hz), 7.18 (1H, td, *J* 7.5, 1.8 Hz), 7.06 (1H, td, *J* 7.5, 1.0 Hz), 7.05-7.02 (1H, m), 6.89 (1H, d, *J* 12.2 Hz), 6.79 (1H, t, *J* 7.9 Hz), 6.74 (1H, dd, *J* 7.9, 1.5 Hz), 6.60 (1H, dd, *J* 7.9, 1.5 Hz), 4.19 (3H, s), 4.01 (3H, s), 3.82 (3H, s), 3.78 (3H, s), 3.63 (1H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 184.5 (*C*), 166.0 (*C*), 152.8 (*C*), 147.2 (*C*), 136.7 (*C*), 136.2 (*C*), 135.1 (*C*), 131.8 (*C*H), 131.1 (*C*H), 131.0 (*C*), 128.4 (*C*H), 127.4 (*C*H), 126.9 (*C*H), 126.5 (*C*H), 123.6 (*C*H), 122.4 (*C*H), 111.7 (*C*H), 89.2 (*C*), 60.8 (CH_3), 60.6 (CH_3), 58.7 (CH_3), 55.9 (CH_3).

LRMS $^m/_z$ (ES^+) 787 ($[2M + Na]^+$), 405 ($[M + Na]^+$).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-7,8-dimethoxy-10-(2,3-dimethoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.73**



(*Z*)-**4.68**
$C_{22}H_{22}O_6$
(382.41)

4.73
$C_{22}H_{22}O_6$
(382.41)

Cyclobutenone (*Z*)-**4.68** (66 mg, 0.173 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 90 min then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded benzobicyclo[3.2.1]octenone **4.73** as a pale yellow oil (45 mg, 0.118 mmol, 68%).

FT-IR ν_{max} (neat, cm^{-1}) 3448 bw, 2999 w, 2954 m, 2831 w, 1663 s, 1581 s, 1471 s, 1454 s, 1426 m, 1254 vs, 1103 s, 1074 s, 1045 s, 999 s, 903 s, 723 vs.

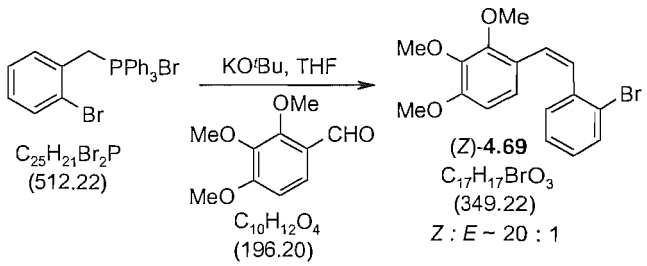
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.44-7.38 (1H, m), 7.32-7.18 (2H, m), 7.21 (1H, dd, *J* 5.3, 3.3 Hz), 6.80-6.74 (2H, m), 6.22 (1H, dd, *J* 6.8, 2.1 Hz), 4.54 (1H, s), 4.19 (3H, s), 4.08 (1H, s), 3.91 (3H, s), 3.88 (1H, bs), 3.83 (3H, s), 3.62 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.5 (*C*), 168.7 (*C*), 152.4 (*C*), 147.9 (*C*), 145.9 (*C*), 139.1 (*C*), 130.4 (*C*), 128.9 (*C*), 128.1 (*C*H), 127.9 (*C*H), 125.0 (*C*H), 124.0 (*C*H), 122.1 (*C*H), 119.7 (*C*H), 112.1 (*C*H), 84.2 (*C*), 62.5 (*C*H_3), 61.6 (*C*H_3), 61.1 (2 x *C*H_3), 60.8 (*C*H), 55.9 (*C*H).

LRMS $^m/_z$ (ES^+) 787 ($[2M + Na]^+$), 421 ($[M + K]^+$), 405 ($[M + Na]^+$), 383 (MH^+).

HRMS $^m/_z$ (ES^+) found 405.1303, $(M + Na)^+$; $C_{22}H_{22}NaO_6$ requires 405.1308.

(*Z*/*E*)-1,2,3-Trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene, (*Z*)-4.69



To a suspension of (2-bromobenzyl)triphenylphosphonium bromide (2.46 g, 4.80 mmol) in THF (30 mL) at 0 °C was added potassium *tert*-butoxide (628 mg, 5.60 mmol). After 30 min a solution of 2,3,4-trimethoxybenzaldehyde (785 mg, 4.00 mmol) in THF (10 mL) was added. The reaction was allowed to warm to RT, stirred for 16 h then partitioned between water (30 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) yielded a 20:1 mixture of (*Z*)- and (*E*)-stilbenes **4.69** as a colourless oil (1.35 g, 3.87 mmol, 97%). Data for the (*Z*)-isomer:

FT-IR ν_{max} (neat, cm^{-1}) 3048 w, 2995 w, 2929 w, 2827 w, 1601 m, 1487 s, 1450 s, 1405 s, 1274 s, 1230 m, 1193 m, 1091 vs, 1017 s, 936 m, 796 m, 756 s, 735 s, 653 m.

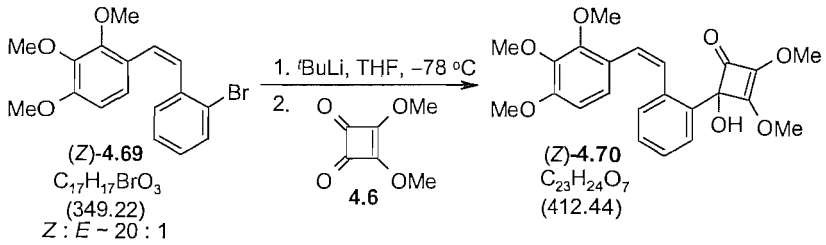
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.59 (1H, dd, *J* 7.3, 2.2 Hz), 7.19 (1H, dd, *J* 7.3, 2.2 Hz), 7.09 (1H, td, *J* 7.3, 2.2 Hz), 7.05 (1H, td, *J* 7.3, 2.2 Hz), 6.79 (1H, d, *J* 12.1 Hz), 6.67 (1H, d, *J* 8.8 Hz), 6.61 (1H, d, *J* 12.1 Hz), 6.40 (1H, d, *J* 8.8 Hz), 3.91 (3H, s), 3.88 (3H, s), 3.80 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 153.4 (*C*), 152.3 (*C*), 142.3 (*C*), 138.4 (*C*), 132.8 (*C*H), 130.9 (*C*H), 128.9 (*C*H), 128.6 (*C*H), 127.1 (*C*H), 126.4 (*C*H), 124.6 (*C*H), 124.1 (*C*), 123.4 (*C*), 107.2 (*C*H), 61.3 (*C*H_3), 61.1 (*C*H_3), 56.1 (*C*H_3).

LRMS $^m/_z$ (EI) 350/348 (M^+, 78%), 254 (26), 238 (100), 211 (36), 195 (33), 168 (58), 152 (46), 140 (79), 127 (40).

CHN Found C 58.88%, H 5.01%; $C_{17}H_{17}BrO_3$ requires C 58.47%, H 4.91%.

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{2-[2-(2,3,4-trimethoxyphenyl)vinyl]phenyl}-cyclobut-2-enone, (*Z*)-4.70



To a solution of ^{t}BuLi (1.22 M in pentane, 0.93 mL, 1.14 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide (*Z*)-**4.69** (*Z*:*E* ~ 20:1, 199 mg, 0.570 mmol) in THF (2.5 mL) over 2 min. After 30 min dimethyl squarate **4.6** (81 mg, 0.570 mmol) in THF (2 mL) was added, followed after a further 30 min by sat. $NaHCO_3$ (3 mL). The reaction was warmed to RT and diluted with ether (20 mL). The aqueous phase was extracted with ether (20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded cyclobutenone (*Z*)-**4.70** as a pale yellow oil (138 mg, 0.335 mmol, 59%).

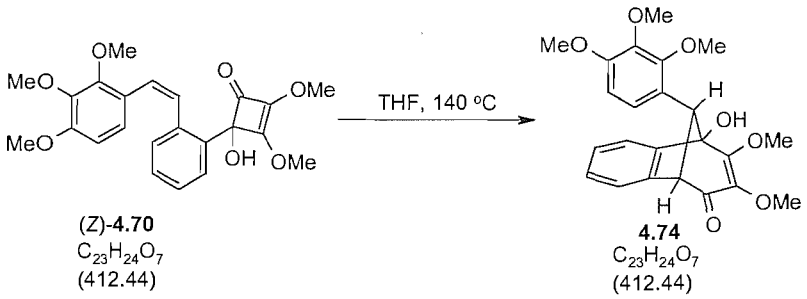
FT-IR ν_{max} (neat, cm^{-1}) 3399 bw, 2974 m, 2856 m, 1769 m, 1634 s, 1589 m, 1491 s, 1458 s, 1332 s, 1091 vs, 1037 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.49 (1H, d, *J* 8.0 Hz), 7.28 (1H, d, *J* 12.1 Hz), 7.24-7.04 (3H, m), 6.81 (1H, d, *J* 12.1 Hz), 6.68 (1H, d, *J* 8.8 Hz), 6.42 (1H, d, *J* 8.8 Hz), 4.19 (3H, s), 4.01 (3H, s), 3.90 (1H, bs), 3.80 (3H, s), 3.79 (3H, s), 3.78 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 184.5 (*C*), 165.8 (*C*), 153.3 (*C*), 151.9 (*C*), 142.3 (*C*), 137.1 (*C*), 136.1 (*C*), 135.1 (*C*), 130.9 (*C*H), 130.1 (*C*H), 128.5 (*C*H), 127.3 (*C*H), 126.9 (*C*H), 126.4 (*C*H), 124.8 (*C*H), 123.3 (*C*), 107.2 (*C*H), 89.2 (*C*), 61.1 (CH_3), 61.0 (CH_3), 60.5 (CH_3), 58.7 (CH_3), 56.1 (CH_3).

LRMS $^{m}/_{z}$ (ES^{+}) 847 ($[2M + Na]^{+}$), 435 ($[M + Na]^{+}$).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-7,8-dimethoxy-10-(2,3-dimethoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.74**



(Z)-**4.70**
$C_{23}H_{24}O_7$
(412.44)

4.74
$C_{23}H_{24}O_7$
(412.44)

Cyclobutenone (*Z*)-**4.70** (112 mg, 0.272 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) yielded a pale yellow solid which was recrystallised from EtOAc to give benzobicyclo[3.2.1]-octenone **4.74** as a white crystalline solid (68 mg, 0.165 mmol, 61%).

MP 222-224 °C (EtOAc).

FT-IR ν_{max} (neat, cm^{-1}) 3387 bw, 3056 w, 3032 w, 2974 w, 2933 w, 2827 w, 1652 m, 1587 s, 1491 m, 1446 s, 1405 m, 1254 s, 1234 s, 1093 vs, 1058 s, 1009 s, 952 m, 821 s, 747 s.

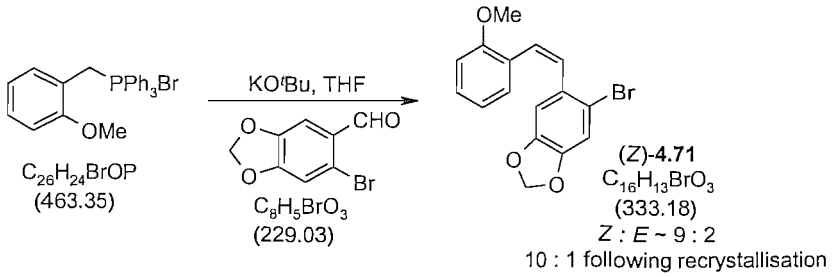
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.40 (1H, m), 7.28 (1H, b dd, *J* 8.2, 6.0 Hz), 7.24-7.18 (2H, m), 6.36 (1H, d, *J* 8.9 Hz), 6.28 (1H, d, *J* 8.9 Hz), 4.45 (1H, s), 4.19 (3H, s), 4.03 (1H, s), 3.96 (3H, s), 3.91 (1H, bs), 3.84 (3H, s), 3.73 (3H, s), 3.61 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.5 (*C*), 168.3 (*C*), 153.3 (*C*), 152.6 (*C*), 146.0 (*C*), 141.9 (*C*), 139.1 (*C*), 128.9 (*C*), 128.1 (*C*H), 127.8 (*C*H), 125.0 (*C*H), 122.6 (*C*), 122.1 (2 x *C*H), 107.2 (*C*H), 84.1 (*C*), 62.3 (*C*H), 61.5 (*C*H_3), 61.3 (*C*H_3), 61.2 (*C*H_3), 61.1 (*C*H_3), 60.8 (*C*H_3), 55.9 (*C*H).

LRMS $^m/_z$ (ES^+) 847 ($[2M + Na]^+$), 435 ($[M + Na]^+$), 413 (MH^+).

CHN Found C 66.58 %, H 5.79%; $C_{23}H_{24}O_7$ requires C 66.98%, H 5.87%.

(*Z*/*E*)-5-Bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole, (*Z*)-4.71



To a suspension of (2-methoxybenzyl)triphenylphosphonium bromide (2.20 g, 5.24 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (687 mg, 6.12 mmol). After 30 min a solution of 6-bromopiperonal (1.00 g, 4.37 mmol) in THF (10 mL) was added. The reaction was allowed to warm to RT, stirred for 16 h then partitioned between water (30 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) yielded a ~ 9:2 mixture of (*Z*)- and (*E*)-stilbenes **4.71** as a white solid (1.26 g, 3.78 mmol, 87%). Recrystallisation from hexane afforded a 10:1 mixture of the (*Z*)- and (*E*)-isomers as white needles. Data for the (*Z*)-isomer:

MP 116-118 °C (hexane).

FT-IR ν_{max} (neat, cm^{-1}) 3060 w, 3007 w, 2966 w, 2905 w, 2831 w, 1589 m, 1491 m, 1467 s, 1303 m, 1223 s, 1168 m, 1099 s, 1017 s, 968 m, 931 s, 858 s, 739 s.

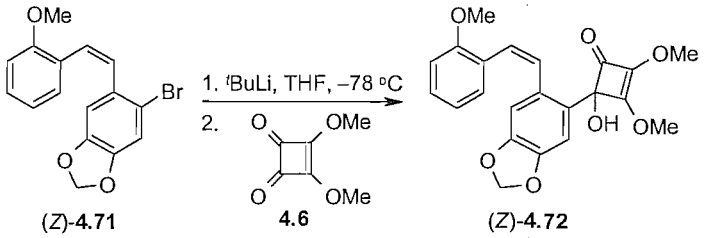
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.20 (1H, td, *J* 7.7, 1.6 Hz), 7.04 (1H, s), 7.03 (1H, m), 6.88 (1H, d, *J* 8.2 Hz), 6.77 (1H, d, *J* 12.2 Hz), 6.75 (1H, app. t, *J* 7.7 Hz), 6.61 (1H, d, *J* 12.2 Hz), 6.60 (1H, s), 5.90 (2H, s), 3.85 (3H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 157.4 (*C*), 147.7 (*C*), 147.0 (*C*), 131.3 (*C*), 130.3 (*C*H), 129.4 (*C*H), 128.9 (*C*H), 126.5 (*C*H), 125.5 (*C*), 120.5 (*C*H), 115.1 (*C*), 112.6 (*C*H), 110.8 (*C*H), 110.4 (*C*H), 101.7 (CH_2), 55.7 (CH_3).

LRMS $^{m}/_{z}$ (EI) 334/332 (M^+, 59%), 253 ([M – Br]$^+$, 10), 238 (42), 223 (33), 195 (31), 180 (27), 152 (100), 98 (40).

CHN Found C 57.99%, H 3.93%; $C_{16}H_{13}BrO_3$ requires C 57.68%, H 3.93%.

(*Z*)-4-Hydroxy-2,3-dimethoxy-4-{6-[2-(2-methoxyphenyl)vinyl]-benz[1,3]dioxol-5-yl}cyclobut-2-enone, (*Z*)-4.72



(*Z*)-**4.71**
$C_{16}H_{13}BrO_3$
(333.18)
Z : *E* ~ 10 : 1

4.6

(*Z*)-**4.72**
$C_{22}H_{20}O_7$
(396.40)

To a solution of ^{t}BuLi (1.22 M in pentane, 0.96 mL, 1.18 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide (*Z*)-**4.71** (*Z*:*E* ~ 10:1, 196 mg, 0.588 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate **4.6** (84 mg, 0.588 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (3 mL). The reaction was warmed to RT, partitioned between ether (20 mL) and water (5 mL) and the aqueous phase extracted with ether (20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ether/petrol yielded (*Z*)-**4.72** (174 mg, 0.439 mmol, 75%) as an off-white powder.

FT-IR ν_{max} (neat, cm^{-1}) 3297 bw, 2950 w, 2837 w, 1773 m, 1642 s, 1610 s, 1475 s, 1462 s, 1332 vs, 1234 vs, 1021 vs.

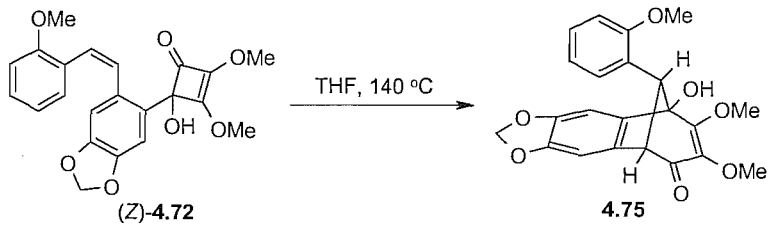
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* 11.8 Hz), 7.17 (1H, app. td, *J* 8.1, 1.5 Hz), 7.10 (1H, dd, *J* 7.5, 1.3 Hz), 6.98 (1H, s), 6.82 (1H, app. t, *J* 7.5 Hz), 6.78 (1H, d, *J* 8.1 Hz), 6.75 (1H, d, *J* 11.8 Hz), 6.43 (1H, s), 5.86 (2H, s), 4.20 (3H, s), 4.01 (3H, s), 3.89 (1H, s), 3.64 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 184.9 (*C*), 166.1 (*C*), 156.4 (*C*), 147.2 (*C*), 146.6 (*C*), 135.1 (*C*), 131.7 (*C*), 131.2 (*C*H), 130.5 (*C*H), 129.5 (*C*), 128.8 (*C*H), 126.9 (*C*H), 125.6 (*C*), 120.7 (*C*H), 111.1 (*C*H), 110.6 (*C*H), 107.2 (*C*H), 101.3 (CH_2), 88.9 (*C*), 60.6 (CH_3), 58.7 (CH_3), 55.3

(CH_3).

LRMS $^m/_z$ (ES^+) 815 ($[2M + Na]^+$), 419 ($[M + Na]^+$).

***rel*-(5*S*,9*S*,10*R*)-9-Hydroxy-7,8-dimethoxy-2,3-methylenedioxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.75**



(*Z*)-**4.72**
$C_{22}H_{20}O_7$
(396.40)

4.75
$C_{22}H_{20}O_7$
(396.40)

Cyclobutenone (*Z*)-**4.72** (109 mg, 0.275 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-50% EtOAc/petrol) gave benzobicyclo[3.2.1]-octenone **4.75** as a yellow oil (75 mg, 0.189 mmol, 69%).

FT-IR ν_{max} (neat, cm^{-1}) 3461 bw, 3003 w, 2954 w, 2925 w, 2835 w, 1659 m, 1589 m, 1487 m, 1467 s, 1283 s, 1234 s, 1160 m, 1091 s, 1033 s, 903 s, 813 m, 723 vs.

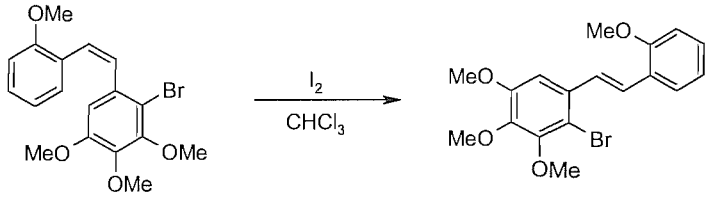
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.19 (1H, app. td, *J* 8.3, 1.7 Hz), 6.87 (1H, dd, *J* 8.3, 0.8 Hz), 6.86 (1H, s), 6.83 (1H, dd, *J* 7.7, 1.7 Hz), 6.81 (1H, s), 6.74 (1H, app. td, *J* 7.7, 0.8 Hz), 5.97 (1H, d, *J* 15.8 Hz), 5.93 (1H, d, *J* 15.8 Hz), 4.57 (1H, s), 4.19 (3H, s), 3.92 (1H, s), 3.87 (3H, s), 3.70 (1H, bs), 3.63 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.8 (*C*), 168.5 (*C*), 157.9 (*C*), 147.4 (*C*), 147.3 (*C*), 140.1 (*C*), 132.2 (*C*), 128.7 (*C*), 128.7 (*C*H), 128.4 (*C*H), 125.4 (*C*), 120.8 (*C*H), 110.6 (*C*H), 106.5 (*C*H), 103.7 (*C*H), 101.6 (CH_2), 83.7 (*C*), 62.3 (CH_3), 60.7 (*C*H), 60.3 (CH_3), 59.5 (CH_3), 54.9 (*C*H).

LRMS $^m/_z$ (ES^+) 815 ($[2M + Na]^+$), 419 ($[M + Na]^+$), 397 (MH^+).

HRMS $^m/_z$ (ES^+) found 419.1100, $(M + Na)^+$; $C_{22}H_{20}NaO_7$ requires 419.1101.

(*E*)-1-Bromo-2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]benzene, (*E*)-4.63



(*Z*)-**4.63**
$C_{18}H_{19}BrO_4$
(379.25)

(*E*)-**4.63**
$C_{18}H_{19}BrO_4$
(379.25)

The title compound was prepared by adapting the method of Hadfield *et al.*[93] To a solution of stilbene (*Z*)-**4.63** (200 mg, 0.527 mmol) in chloroform (10 mL) was added a solution of iodine (13 mg, 0.053 mmol) in chloroform (5 mL). After 16 h at RT the reaction was diluted with DCM (20 mL), washed with sat. $Na_2S_2O_3$ (20 mL) and water (20 mL) and dried ($MgSO_4$). Concentration *in vacuo* gave stilbene (*E*)-**4.63** (199 mg, 0.525 mmol, 99%) as a pale yellow oil.

FT-IR ν_{max} (neat, cm^{-1}) 3053 w, 2935 m, 1554 m, 1471 s, 1388 s, 1345 s, 1314 s, 1239 s, 1104 vs, 1006 s, 962 s, 749 s.

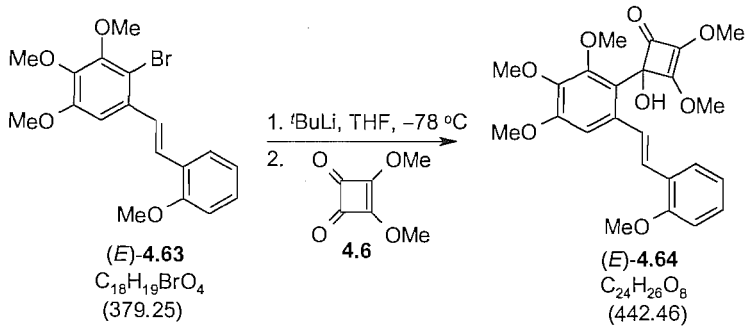
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.64 (1H, dd, *J* 7.5, 1.5 Hz), 7.49 (1H, d, *J* 16.3 Hz), 7.31 (1H, d, *J* 16.3 Hz), 7.29 (1H, td, *J* 7.9, 1.5 Hz), 7.06 (1H, s), 7.00 (1H, t, *J* 7.5 Hz), 6.93 (1H, d, *J* 7.9 Hz), 3.95 (3H, s), 3.93 (6H, s), 3.91 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 157.2 (*C*), 153.0 (*C*), 151.1 (*C*), 142.9 (*C*), 133.7 (*C*), 129.2 (*C*H), 128.3 (*C*H), 127.1 (*C*H), 126.3 (*C*), 125.7 (*C*H), 121.0 (*C*H), 111.3 (*C*), 111.1 (*C*H), 105.6 (*C*H), 61.4 (CH_3), 61.1 (CH_3), 56.4 (CH_3), 55.7 (CH_3).

LRMS $^m/_z$ (EI) 380/378 (M^+, 84%), 365/363 ($[M - CH_3]^+$, 22), 299 ($[M - Br]^+$, 16), 284 (43), 268 (100), 198 (32), 155 (50).

HRMS $^m/_z$ (EI) found 378.0469, M^+; $C_{18}H_{19}BrO_4$ requires 378.0466.

(*E*)-4-Hydroxy-2,3-dimethoxy-4-{2,3,4-trimethoxy-6-[2-(2-methoxyphenyl)vinyl]-phenyl}-cyclobut-2-enone, (*E*)-4.64

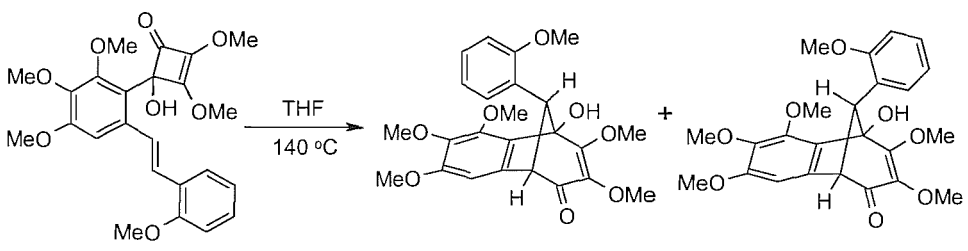


(*E*)-**4.63**
$C_{18}H_{19}BrO_4$
(379.25)

(*E*)-**4.64**
$C_{24}H_{26}O_8$
(442.46)

To a solution of ^{t}BuLi (1.24 M in pentane, 0.56 mL, 0.691 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide (*E*)-**4.63** (131 mg, 0.345 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate **4.6** (49 mg, 0.345 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone (*E*)-**4.64** (95 mg, 0.214 mmol, 62%) as a pale yellow oil, which was used immediately in the next reaction.

***rel*-(5*S*,9*S*,10*R*)- and *rel*-(5*S*,9*S*,10*S*)-9-Hydroxy-1,2,3,7,8-pentamethoxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.65 and 4.76**



(*E*)-**4.64**
$C_{24}H_{26}O_8$
(442.46)

4.65
$C_{24}H_{26}O_8$
(442.46)

~ 1 : 1

4.76
$C_{24}H_{26}O_8$
(442.46)

A solution of cyclobutenone (*E*)-**4.64** (95 mg, 0.214 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in*

vacuo, the product mixture was purified by column chromatography (SiO_2, 40-50% EtOAc/petrol) to afford firstly benzobicyclo[3.2.1]octenone **4.65** as a pale yellow oil (32 mg, 0.072 mmol, 34%) then diastereoisomer **4.76** as a cream solid (31 mg, 0.070 mmol, 33%).

Data for **4.65** as described previously. Data for **4.76**:

IR ν_{max} (neat, cm^{-1}) 3379 bw, 2933 m, 2852 w, 1668 s, 1593 s, 1467 s, 1323 s, 1254 s, 1111 s, 1050 m, 751 w.

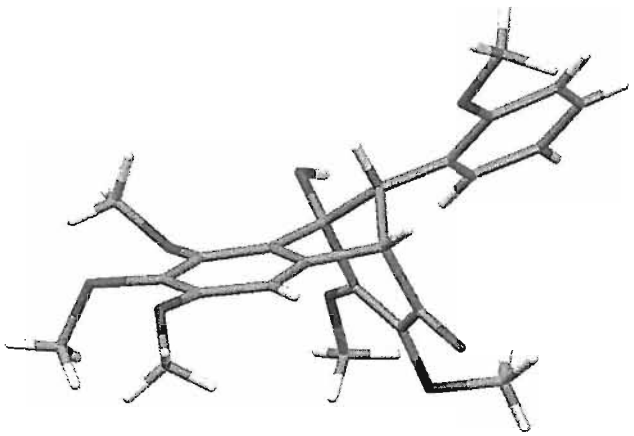
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.35 (1H, d, *J* 7.8 Hz), 7.21 (1H, t, 7.8 Hz), 6.91 (1H, t, *J* 7.8 Hz), 6.86 (1H, d, *J* 7.8 Hz), 6.81 (1H, s), 4.48 (1H, d, *J* 4.2 Hz), 4.45 (1H, bs), 4.37 (1H, d, *J* 4.2 Hz), 4.21 (3H, s), 4.00 (3H, s), 3.86 (3H, s), 3.85 (3H, s), 3.84 (3H, s), 3.31 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 193.9 (*C*), 164.4 (*C*), 158.8 (*C*), 153.6 (*C*), 149.1 (*C*), 140.9 (*C*), 136.3 (*C*), 131.7 (*C*), 130.3 (*C*H), 129.4 (*C*), 128.3 (*C*H), 124.0 (*C*), 120.1 (*C*H), 110.9 (*C*H), 105.6 (*C*H), 81.8 (*C*), 63.8 (*C*H), 61.8 (CH_3), 61.5 (CH_3), 61.2 (CH_3), 60.7 (CH_3), 58.8 (*C*H), 56.5 (CH_3), 55.4 (CH_3).

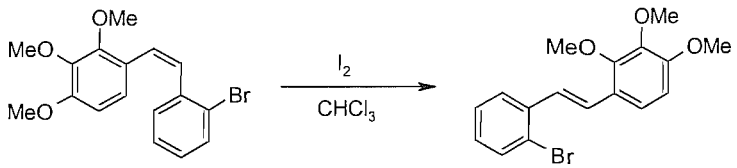
LRMS $^m/_z$ (ES^+) 923 ($[2M + K]^+$), 907 ($[2M + Na]^+$), 481 ($[M + K]^+$), 465 ($[M + Na]^+$), 443 (MH^+).

HRMS $^m/_z$ (ES^+) found 443.1699, MH^+; $C_{24}H_{27}O_8$ requires 443.1697.

X-Ray



(*E*)-1,2,3-Trimethoxy-4-[2-(2-bromophenyl)vinyl]benzene, (*E*)-4.69



(*Z*)-**4.69**
$C_{17}H_{17}BrO_3$
(349.22)

(*E*)-**4.69**
$C_{17}H_{17}BrO_3$
(349.22)

To a solution of stilbene (*Z*)-**4.69** (520 mg, 1.49 mmol) in chloroform (20 mL) was added a solution of iodine (38 mg, 0.149 mmol) in chloroform (5 mL). After 64 h at RT the reaction was diluted with DCM (30 mL), washed with sat. $Na_2S_2O_3$ (30 mL) and water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow solid (518 mg, 1.48 mmol, 99%). Recrystallisation from hexane gave stilbene (*E*)-**4.69** as an off-white crystalline solid.

MP 93-95 °C (hexane).

FT-IR ν_{max} (neat, cm^{-1}) 3032 w, 2964 w, 2930 w, 2840 w, 2819 w, 1593 m, 1492 s, 1464 s, 1412 s, 1297 m, 1277 m, 1247 m, 1226 m, 1091 s, 1014 s, 946 s, 907 m, 804 s, 750 s.

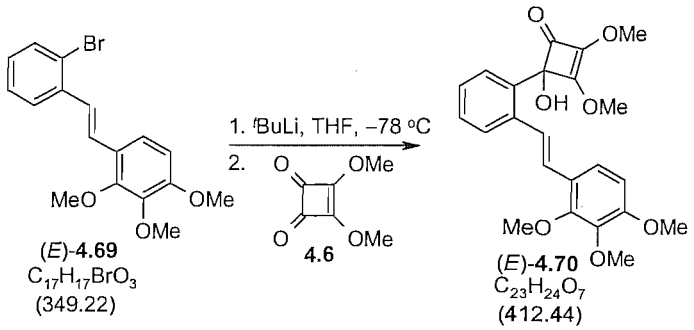
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.71 (1H, dd, *J* 8.0, 1.5 Hz), 7.59 (1H, dd, *J* 8.0, 1.0 Hz), 7.42 (1H, d, *J* 16.4 Hz), 7.38 (1H, d, *J* 8.8 Hz), 7.32 (1H, t, *J* 8.0 Hz), 7.27 (1H, d, *J* 16.4 Hz), 7.11 (1H, td, *J* 8.0, 1.5 Hz), 6.74 (1H, d, *J* 8.8 Hz), 3.94 (3H, s), 3.92 (3H, s), 3.91 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 153.9 (*C*), 152.2 (*C*), 142.7 (*C*), 137.9 (*C*), 133.2 (*C*H), 128.6 (*C*H), 127.7 (*C*H), 126.9 (*C*H), 126.9 (*C*H), 126.0 (*C*H), 124.4 (*C*), 124.2 (*C*), 121.5 (*C*H), 108.1 (*C*H), 61.6 (CH_3), 61.1 (CH_3), 56.3 (CH_3).

LRMS $^m/_z$ (EI) 350/348 (M^+, 93%), 254 (48), 238 (100), 211 (65), 195 (60), 168 (83), 152 (68), 140 (91), 127 (93).

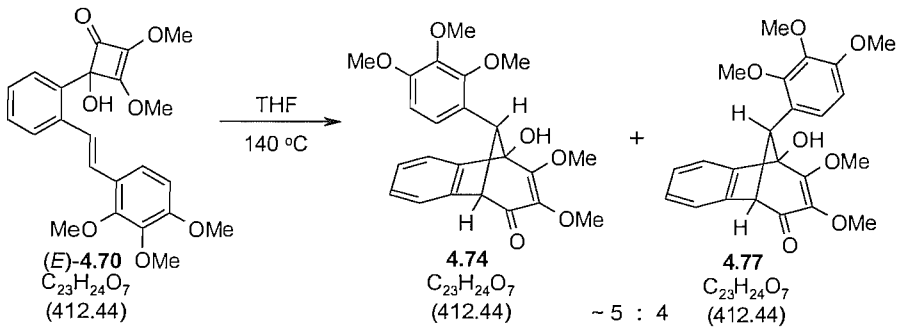
CHN Found C 58.12%, H 4.86%; $C_{17}H_{17}BrO_3$ requires C 58.47%, H 4.91%.

(*E*)-4-Hydroxy-2,3-dimethoxy-4-{2-[2-(2,3,4-trimethoxyphenyl)vinyl]phenyl}-cyclobut-2-enone, (*E*)-4.70



To a solution of ^{t}BuLi (1.15 M in pentane, 0.83 mL, 0.950 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide (*E*)-**4.69** (166 mg, 0.475 mmol) in THF (2.5 mL) over 2 min. After 30 min dimethyl squarate **4.6** (68 mg, 0.475 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone (*E*)-**4.70** (152 mg, 0.369 mmol, 78%) as a pale yellow oil, which was used immediately in the next reaction.

***rel*-(5*S*,9*S*,10*R*)- and *rel*-(5*S*,9*S*,10*S*)-9-Hydroxy-7,8-dimethoxy-10-(1,2,3-trimethoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.74 and 4.77**

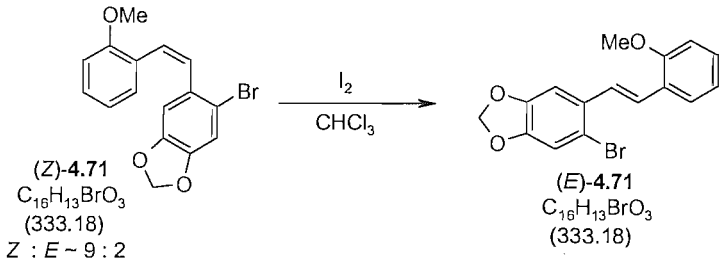


Cyclobutenone (*E*)-**4.70** (152 mg, 0.369 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 50% EtOAc/petrol) to afford a 5:4 mixture of benzobicyclo[3.2.1]octenones **4.74** and **4.77** (99 mg, 0.240 mmol, 65%) as a pale yellow oil. Data obtained on the mixture was identical to that described for **4.74** with the following additional NMR signals attributed to **4.77**:

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.45-7.38 (2H, m), 7.32-7.21 (2H, m), 6.98 (1H, d, *J* 8.8 Hz), 6.64 (1H, d, *J* 8.8 Hz), 4.97 (1H, s), 4.32 (1H, d, *J* 4.3 Hz), 4.28 (1H, d, *J* 4.3 Hz), 4.07 (3H, s), 3.94 (3H, s), 3.88 (3H, s), 3.85 (3H, s), 3.41 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.2 (*C*), 162.9 (*C*), 153.4 (*C*), 152.5 (*C*), 150.0 (*C*), 142.4 (*C*), 139.4 (*C*), 130.0 (*C*), 127.6 (*C*H), 127.5 (*C*H), 124.7 (*C*H), 124.4 (*C*H), 121.8 (*C*), 121.1 (*C*H), 107.4 (*C*H), 82.1 (*C*), 64.4 (*C*H), 61.4 (CH_3), 61.2 (CH_3), 61.0 (CH_3), 60.7 (CH_3), 59.1 (CH_3), 56.2 (*C*H).

(*E*)-5-Bromo-6-[2-(2-methoxyphenyl)-vinyl]-benzo[1,3]dioxole, (*E*)-4.71



To a solution of stilbene (*Z*)-**4.71** (*Z*:*E* ~ 9:2, 540 mg, 1.62 mmol) in chloroform (20 mL) was added a solution of iodine (41 mg, 0.16 mmol) in chloroform (5 mL). After 10 days at RT the reaction was diluted with DCM (40 mL), washed with sat. $Na_2S_2O_3$ (30 mL) and water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a white solid (538 mg, 1.61 mmol, 99%). Recrystallisation from hexane gave stilbene (*E*)-**4.71** as off-white needles.

MP 120-122 °C (hexane).

FT-IR ν_{max} (neat, cm^{-1}) 3064 w, 3007 w, 2905 w, 2835 w, 1593 m, 1463 s, 1307 m, 1232 s, 1036 m, 1022 s, 967 s, 932 m, 865 m, 741 s.

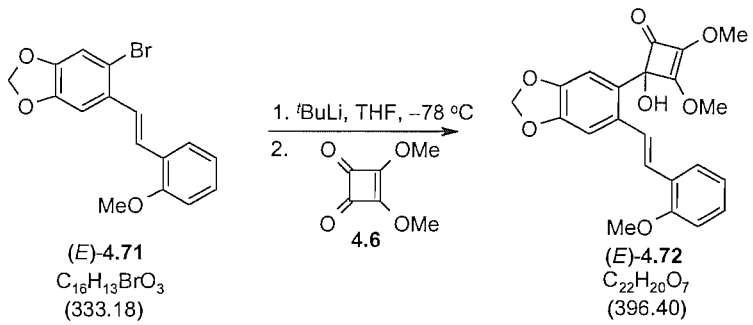
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.63 (1H, dd, *J* 7.5, 1.5 Hz), 7.43 (1H, d, *J* 16.3 Hz), 7.29 (1H, d, *J* 16.3 Hz), 7.28 (1H, ddd, *J* 8.3, 7.5, 1.5 Hz), 7.23 (1H, s), 7.05 (1H, s), 7.00 (1H, t, *J* 7.5 Hz), 6.93 (1H, d, *J* 8.3 Hz), 6.01 (2H, s), 3.92 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 157.1 (*C*), 147.9 (*C*), 147.9 (*C*), 131.5 (*C*), 129.1 (*C*H), 127.9 (*C*H), 126.9 (*C*H), 126.4 (*C*), 124.8 (*C*H), 121.0 (*C*H), 115.4 (*C*), 112.9 (*C*H), 111.2 (*C*H), 106.2 (*C*H), 101.9 (CH_2), 55.7 (CH_3).

LRMS $^m/_z$ (EI) 334/332 (M^+, 56%), 253 ($[M - Br]^+$, 8), 238 (38), 223 (31), 195 (36), 180 (25), 165 (34), 152 (100).

CHN Found C 57.27%, H 3.89%; $C_{16}H_{13}BrO_3$ requires C 57.68%, H 3.93%.

(*E*)-4-Hydroxy-2,3-dimethoxy-4-{6-[2-(2-methoxyphenyl)vinyl]-benz[1,3]dioxol-5-yl}cyclobut-2-enone, (*E*)-4.72

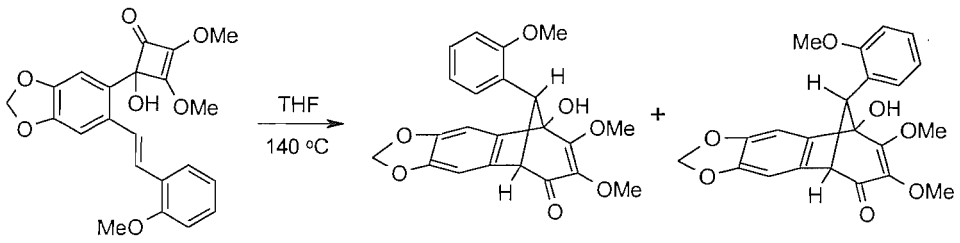


(*E*)-**4.71**
$C_{16}H_{13}BrO_3$
(333.18)

(*E*)-**4.72**
$C_{22}H_{20}O_7$
(396.40)

To a solution of ^{t}BuLi (1.15 M in pentane, 0.63 mL, 0.724 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide (*E*)-**4.71** (138 mg, 0.414 mmol) in THF (2.5 mL) over 2 min. After 45 min dimethyl squarate **4.6** (59 mg, 0.414 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc/petrol) yielded cyclobutenone (*E*)-**4.72** as a pale yellow oil (124 mg, 0.312 mmol, 75%), which was used immediately in the next reaction.

***rel*-(5*S*,9*S*,10*R*)-** and ***rel*-(5*S*,9*S*,10*S*)-9-Hydroxy-7,8-dimethoxy-2,3-methylenedioxy-10-(2-methoxyphenyl)-5,9-dihydro-5,9-methanobenzocyclohepten-6-one, 4.75** and **4.78**



(*E*)-**4.72**
$C_{22}H_{20}O_7$
(396.40)

4.75
$C_{22}H_{20}O_7$
(396.40)

~ 1 : 1.1

4.78
$C_{22}H_{20}O_7$
(396.40)

A solution of cyclobutenone (*E*)-**4.72** (124 mg, 0.312 mmol) in THF (3 mL) was heated at 140 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 30-45% EtOAc/petrol) to afford firstly benzobicyclo[3.2.1]octenone **4.78** as a pale yellow oil (41 mg, 0.103 mmol, 33%) then diastereoisomer **4.75** as a pale yellow oil (37 mg, 0.094 mmol, 30%).

Data for **4.75** as described previously. Data for **4.78**:

FT-IR ν_{max} (neat, cm^{-1}) 3236 bw, 2917 m, 2848 w, 1654 s, 1569 s, 1464 s, 1244 s, 1118 s, 1101 s, 1031 s, 937 s, 749 s.

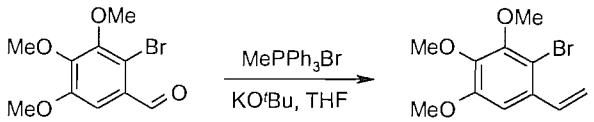
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.31-7.28 (2H, m), 6.99-6.94 (2H, m), 6.96 (1H, s), 6.92 (1H, s), 6.01 (1H, d, *J* 1.4 Hz), 5.97 (1H, d, *J* 1.4 Hz), 4.43 (1H, d, *J* 4.1 Hz), 4.41 (1H, s), 4.31 (1H, d, *J* 4.1 Hz), 4.15 (3H, s), 3.91 (3H, s), 3.40 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 194.3 (*C*), 162.8 (*C*), 158.1 (*C*), 147.0 (*C*), 146.9 (*C*), 144.0 (*C*), 132.9 (*C*), 130.1 (*C*H), 129.6 (*C*), 128.6 (*C*H), 124.5 (*C*), 120.9 (*C*H), 111.2 (*C*H), 106.3 (*C*H), 103.0 (*C*H), 101.4 (CH_2), 81.5 (*C*), 64.6 (*C*H), 61.5 (CH_3), 60.7 (CH_3), 58.3 (CH_3), 55.7 (*C*H).

LRMS $^m/_z$ (ES^+) 815 ($[2M + Na]^+$), 793 ($[2M + H]^+$), 419 ($[M + Na]^+$), 397 (MH^+).

HRMS $^m/_z$ (ES^+) found 397.1281, MH^+; $C_{22}H_{21}O_7$ requires 397.1282.

2-Bromo-3,4,5-trimethoxystyrene, 4.85



4.84
$C_{10}H_{11}BrO_4$
(275.10)

4.85
$C_{11}H_{13}BrO_3$
(273.13)

The title compound was prepared using the method of Van der Eycken *et al.*[113] To a suspension of methyltriphenyl-phosphonium bromide (974 mg, 2.73 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (286 mg, 2.55 mmol). The reaction mixture was warmed to RT and stirred for 30 min. After re-cooling to 0 °C a solution of 2-bromo-3,4,5-trimethoxybenzaldehyde **4.84** (500 mg, 1.82 mmol) in THF (10 mL) was added over 5 min. The reaction mixture was warmed to RT, then after 16 h was partitioned between water (20 mL) and ether (30 mL). The phases were separated and the aqueous phase extracted with ether (2 x 30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) gave styrene **4.85** as a colourless oil (343 mg, 1.26 mmol, 69%). Spectroscopic data were in agreement with the literature.[113]

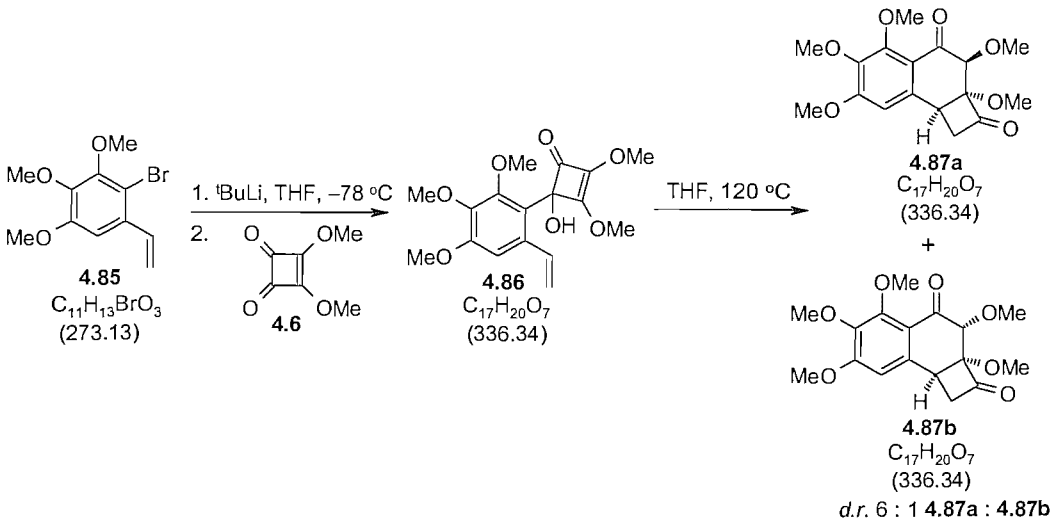
FT-IR ν_{max} (neat, cm^{-1}) 3085 w, 2929 w, 2844 w, 1552 m, 1479 s, 1381 s, 1319 s, 1197 s, 1160 m, 1099 s, 997 s, 911 s, 837 m, 796 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.04 (1H, dd, *J* 17.3, 10.9 Hz), 6.90 (1H, s), 5.60 (1H, d, *J* 17.3 Hz), 5.32 (1H, d, *J* 10.9 Hz), 3.89 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 152.9 (*C*), 151.0 (*C*), 143.2 (*C*), 136.0 (*C*H), 133.3 (*C*), 116.0 (CH_2), 110.7 (*C*), 105.4 (*C*H), 61.3 (CH_3), 61.0 (CH_3), 56.3 (CH_3).

LRMS $^m/_z$ (EI) 274/272 (M^+, 100%), 259/257 ($[M - CH_3]^+$, 52), 216/214 (44), 178 (21), 163 (46), 135 (66), 92 (82), 77 (96).

***rel*-(2a*R*,3*S*,8b*S*)-2a,3,5,6,7-Pentamethoxy-1,2a,3,8b-tetrahydrocyclobuta[*a*]-naphthalene-2,4-dione, 4.87a** and the ***rel*-(2a*R*,3*R*,8b*S*)-diastereoisomer, 4.87b**



To a solution of ^{t}BuLi (1.15 M in pentane, 0.63 mL, 0.724 mmol) in THF (2.5 mL) at –78 °C was added a solution of bromide **4.85** (99 mg, 0.362 mmol) in THF (2.5 mL) over 2 min. After 1 h dimethyl squarate **4.6** (52 mg, 0.362 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and diluted with ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil, crude cyclobutenone **4.86**, was dissolved in THF (3 mL) and heated at 120 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 30-50% EtOAc/petrol) to give firstly cyclobuta[*a*]naphthalene **4.87a** (76 mg, 0.226 mmol, 62% over 2 steps) then cyclobuta[*a*]naphthalene **4.87b** (14 mg, 0.0416 mmol, 11% over 2 steps) as pale yellow oils.

Data for **4.87a**:

FT-IR ν_{max} (neat, cm^{-1}) 3011 w, 2933 m, 2840 w, 1784 s, 1696 m, 1588 s, 1489 m, 1456 m, 1347 s, 1253 s, 1196 s, 1100 s, 1032 m, 747 vs.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.54 (1H, s), 4.36 (1H, s), 3.96 (3H, s), 3.92 (3H, s), 3.88 (3H, s), 3.72 (1H, app. t, *J* 10.1 Hz), 3.50 (3H, s), 3.41 (3H, s), 3.26 (1H, dd, *J* 17.4, 10.8 Hz), 2.90 (1H, dd, *J* 17.4, 9.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.1 (*C*), 194.1 (*C*), 158.0 (*C*), 153.9 (*C*), 142.2 (*C*), 138.8 (*C*), 119.3 (*C*), 107.1 (*C*H), 95.8 (*C*), 83.4 (*C*H), 62.5 (CH_3), 61.2 (CH_3), 59.0 (CH_3), 56.3 (CH_3), 53.6 (CH_3), 50.4 (CH_2), 33.1 (*C*H).

LRMS $^m/_z$ (ES^+) 695 ($[2M + Na]^+$), 391 ($[M + Na + MeOH]^+$), 359 ($[M + Na]^+$), 337 (MH^+).

HRMS $^m/_z$ (ES^+) found 359.1102, $(M + Na)^+$; $C_{17}H_{20}NaO_7$ requires 359.1101.

Data for **4.87b**:

FT-IR ν_{max} (neat, cm^{-1}) 2926 m, 2848 w, 1785 s, 1698 s, 1589 s, 1489 s, 1457 s, 1349 s, 1271 s, 1196 m, 1116 s, 1102 s, 1005 m.

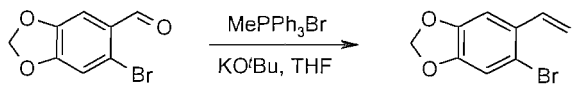
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.54 (1H, s), 3.98 (3H, s), 3.97 (1H, s), 3.94 (3H, s), 3.90 (3H, s), 3.73 (1H, app. t, *J* 10.1 Hz), 3.52 (3H, s), 3.43 (3H, s), 3.27 (1H, dd, *J* 17.6, 10.8 Hz), 2.94 (1H, dd, *J* 17.6, 9.3 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.2 (*C*), 194.1 (*C*), 158.0 (*C*), 154.0 (*C*), 142.2 (*C*), 138.8 (*C*), 119.4 (*C*), 107.1 (*C*H), 95.9 (*C*), 83.4 (*C*H), 62.5 (CH_3), 61.3 (CH_3), 59.1 (CH_3), 56.4 (CH_3), 53.7 (CH_3), 50.4 (CH_2), 33.2 (*C*H).

LRMS $^m/_z$ (ES^+) 695 ($[2M + Na]^+$), 391 ($[M + Na + MeOH]^+$), 359 ($[M + Na]^+$), 337 (MH^+).

HRMS $^m/_z$ (ES^+) found 359.1101, $(M + Na)^+$; $C_{17}H_{20}NaO_7$ requires 359.1101.

2-Bromo-4,5-methylenedioxystyrene, 4.89



4.88
$C_8H_5BrO_3$
(229.03)

4.89
$C_9H_7BrO_2$
(227.06)

To a suspension of methyltriphenylphosphonium bromide (1.87 g, 5.24 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (687 mg, 6.12 mmol). The reaction mixture was warmed to RT and stirred for 30 min. After re-cooling to 0 °C a solution of 6-bromopiperonal **4.88** (1.00 g, 4.37 mmol) in THF (10 mL) was added over 5 min. The reaction mixture was warmed to RT then after 16 h partitioned between water (30 mL) and ether (50 mL). The phases were separated and the aqueous phase extracted with ether (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% ether/petrol) gave styrene **4.89** as a colourless oil (704 mg, 3.10 mmol, 71%). Spectroscopic data were in agreement with the literature.[114]

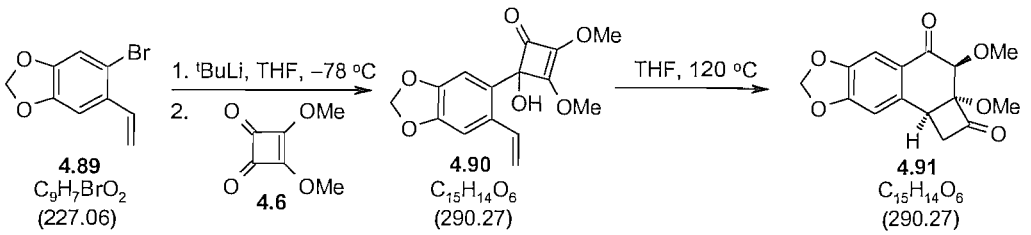
FT-IR ν_{max} (neat, cm^{-1}) 3085 w, 2974 w, 2897 w, 1622 w, 1467 vs, 1417 m, 1234 s, 1111 m, 1025 s, 931 s, 903 s, 858 s, 657 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.04 (1H, s), 7.01 (1H, s), 6.99 (1H, dd, *J* 17.3, 11.0 Hz), 5.98 (2H, s), 5.56 (1H, dd, *J* 17.3, 0.8 Hz), 5.27 (1H, dd, *J* 11.0, 0.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 148.3 (*C*), 147.9 (*C*), 135.7 (*C*H), 131.1 (*C*), 115.1 (CH_2), 114.9 (*C*), 112.8 (*C*H), 106.1 (*C*H), 101.9 (CH_2).

LRMS $^m/_z$ (EI) 228/226 (M^+, 100%), 147 ($[M - Br]^+$, 92), 114 (44), 89 (93).

***rel*-(2a*R*,3*S*,8b*S*)-2a,3-Dimethoxy-6,7-methylenedioxy-1,2a,3,8b-tetrahydro-cyclobuta[*a*]naphthalene-2,4-dione, 4.91**



4.89
$C_9H_7BrO_2$
(227.06)

4.6

4.90
$C_{15}H_{14}O_6$
(290.27)

4.91
$C_{15}H_{14}O_6$
(290.27)

To a solution of ^{t}BuLi (1.15 M in pentane, 1.24 mL, 1.43 mmol) in THF (2.5 mL) at −78 °C was added bromide **4.89** (162 mg, 0.713 mmol) in THF (2.5 mL) over 2 min. After 30 min a solution of dimethyl squarate **4.6** (101 mg, 0.713 mmol) in THF (2 mL) was added, followed after 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and diluted with ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil, crude cyclobutenone **4.90**, was dissolved in THF (3 mL) and heated at 120 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo,* the product mixture was purified by column chromatography (SiO_2, 10-20% EtOAc/petrol) to yield cyclobuta[a]naphthalene **4.91** as a yellow oil (72 mg, 0.248 mmol, 35% over 2 steps).

FT-IR ν_{max} (neat, cm^{-1}) 2917 w, 2831 w, 1785 s, 1680 s, 1615 m, 1503 m, 1479 vs, 1387 s, 1261 s, 1100 s, 1033 vs, 930 s, 878 m, 729 s.

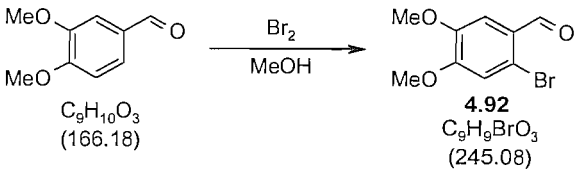
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.33 (1H, s), 6.64 (1H, s), 5.98 (1H, d, *J* 15.8 Hz), 5.97 (1H, d, *J* 15.8 Hz), 3.82 (1H, s), 3.70 (1H, app. t, *J* 10.3 Hz), 3.39 (3H, s), 3.26 (3H, s), 3.17 (1H, dd, *J* 17.1, 11.0 Hz), 2.95 (1H, dd, *J* 17.1, 9.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 203.8 (*C*), 193.2 (*C*), 153.3 (*C*), 147.9 (*C*), 138.1 (*C*), 125.2 (*C*), 108.2 (*C*H), 106.7 (*C*H), 102.2 (CH_2), 95.9 (*C*), 81.1 (*C*H), 58.9 (CH_3), 53.6 (CH_3), 49.9 (CH_2), 32.2 (*C*H).

LRMS $^m/_z$ (ES^+) 603 ($[2M + Na]^+$), 345 ($[M + Na + MeOH]^+$), 313 ($[M + Na]^+$), 291 (MH^+).

HRMS $^m/_z$ (ES^+) found 313.0685, $(M + Na)^+$; $C_{15}H_{14}NaO_6$ requires 313.0683.

2-Bromo-4,5-dimethoxy-benzaldehyde, 4.92



$C_9H_{10}O_3$
(166.18)

4.92
$C_9H_9BrO_3$
(245.08)

The title compound was prepared using the method of Van der Eycken *et al.*[113] To a solution of veratraldehyde (1.66 g, 10.0 mmol) in methanol (50 mL) was added bromine (0.54 mL, 11.0 mmol) dropwise. After 3 h the solvent was removed *in vacuo*, the residue dissolved in DCM (50 mL) and washed with sat. $Na_2S_2O_3$ (50 mL). The aqueous phase was extracted with DCM (50 mL) then the combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from EtOH afforded **4.92** as a white crystalline solid (1.88 g, 7.67 mmol, 77%). Physical and spectroscopic data were in agreement with the literature.[113,115]

MP 150-151 °C (EtOH). Lit.[115] 148-150 °C.

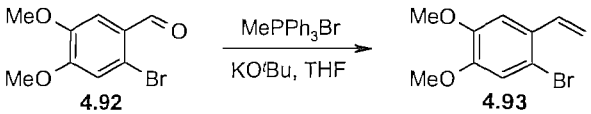
FT-IR ν_{max} (neat, cm^{-1}) 3309 w, 3077 w, 3003 w, 2864 w, 1666 s, 1583 s, 1504 s, 1442 s, 1384 s, 1340 m, 1268 s, 1216 s, 1153 s, 1040 s, 1014 s, 977 s, 864 s, 811 s, 736 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 10.19 (1H, s), 7.42 (1H, s), 7.06 (1H, s), 3.96 (3H, s), 3.92 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 190.9 (*C*H), 154.7 (*C*), 149.1 (*C*), 126.8 (*C*), 120.5 (*C*), 115.7 (*C*H), 110.7 (*C*H), 56.7 (CH_3), 56.4 (CH_3).

LRMS $^m/_z$ (EI) 246/244 (M^+, 100%), 231/229 ($[M - CH_3]^+$, 14), 94 (41).

2-Bromo-4,5-dimethoxystyrene, 4.93



4.92
$C_9H_9BrO_3$
(245.08)

4.93
$C_{10}H_{11}BrO_2$
(243.11)

To a suspension of methyltriphenylphosphonium bromide (2.14 g, 6.00 mmol) in THF (25 mL) at 0 °C was added potassium *tert*-butoxide (786 mg, 7.00 mmol). The reaction mixture was warmed to RT and stirred for 30 min. After re-cooling to 0 °C a solution of aldehyde **4.92** (1.23 g, 5.00 mmol) in THF (15 mL) was added over 5 min. The reaction mixture was warmed to RT and after 16 h partitioned between sat. NH_4Cl (40 mL) and DCM (40 mL). The phases were separated and the aqueous phase extracted with DCM (2 x 40 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% ether/petrol) gave styrene **4.93** as a pale yellow oil (831 mg, 3.42 mmol, 68%). Spectroscopic data were in agreement with the literature.[113]

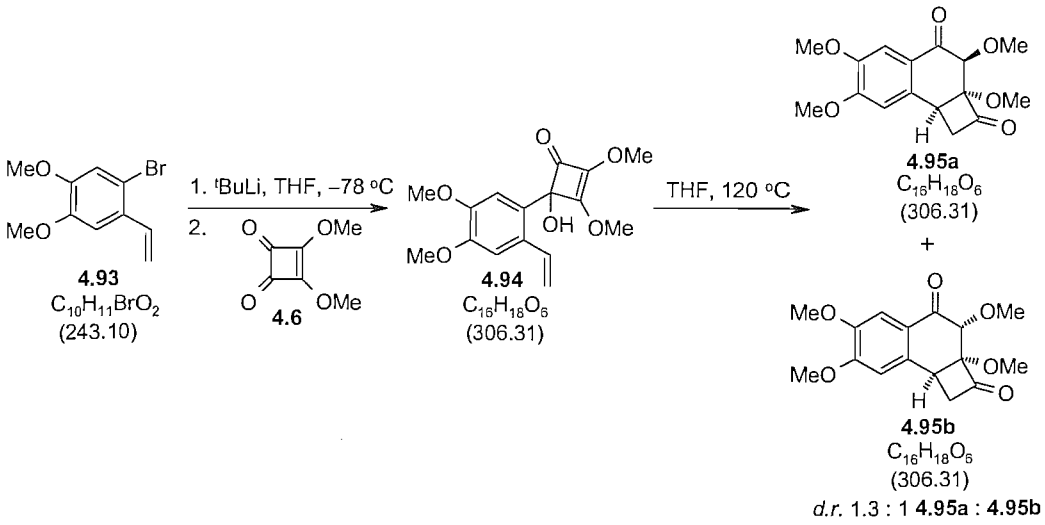
FT-IR ν_{max} (neat, cm^{-1}) 3085 w, 2999 w, 2933 w, 2909 w, 2835 w, 1600 m, 1497 s, 1417 m, 1383 m, 1255 s, 1207 s, 1160 s, 1024 s, 941 m, 895 m, 851 s, 793 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.05 (1H, s), 7.01 (1H, s), 6.99 (1H, dd, *J* 17.5, 11.0 Hz), 5.59 (1H, d, *J* 17.5 Hz), 5.28 (1H, d, *J* 11.0 Hz), 3.91 (3H, s), 3.88 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 149.7 (*C*), 148.8 (*C*), 135.6 (*C*H), 129.8 (*C*), 115.5 (*C*H), 114.7 (CH_2), 114.5 (*C*), 109.0 (*C*H), 56.4 (CH_3), 56.2 (CH_3).

LRMS $^m/_z$ (EI) 244/242 (M^+, 100%), 229/227 ([M – CH_3], 39), 120 (98), 105 (38), 89 (44), 77 (58).

***rel*-(2a*R*,3*S*,8b*S*)-2a,3,6,7-Tetramethoxy-1,2a,3,8b-tetrahydrocyclobuta[*a*]-naphthalene-2,4-dione, 4.95a** and the ***rel*-(2a*R*,3*R*,8b*S*)-diastereoisomer, 4.95b**



To a solution of ^{t}BuLi (1.15 M in pentane, 0.86 mL, 0.988 mmol) in THF (2.5 mL) at −78 °C was added bromide **4.93** (121 mg, 0.494 mmol) in THF (2.5 mL) over 2 min. After 45 min a solution of dimethyl squarate **4.6** (70 mg, 0.494 mmol) in THF (2 mL) was added, followed after 30 min by sat. $NaHCO_3$ (2 mL). The reaction mixture was warmed to RT and diluted with ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil, crude cyclobutenone **4.94**, was dissolved in THF (3 mL) and heated to 120 °C by microwave irradiation for 1 h. After cooling to RT and concentration *in vacuo*, the product mixture was purified by column chromatography (SiO_2, 50-75% EtOAc/petrol) to afford firstly cyclobuta[a]naphthalene **4.95a** (29 mg, 0.0947 mmol, 29%) followed by cyclobuta[a]naphthalene **4.95b** (23 mg, 0.0751 mmol, 23%) both as pale yellow oils.

Data for **4.95a**:

FT-IR ν_{max} (neat, cm^{-1}) 2925 m, 2835 w, 1786 s, 1681 s, 1598 s, 1509 s, 1463 s, 1364 s, 1268 s, 1219 s, 1159 s, 1103 s, 1054 s, 996 m, 876 m, 729 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.39 (1H, s), 6.71 (1H, s), 3.95 (3H, s), 3.93 (3H, s), 3.88 (1H, s), 3.79 (1H, app. t, *J* 10.1 Hz), 3.46 (3H, s), 3.34 (3H, s), 3.26 (1H, dd, *J* 17.1, 10.8 Hz), 3.05 (1H, dd, *J* 17.1, 9.4 Hz).

nOe Irradiation of the signal at δ_H 3.88 (1H, s, C*H*OCH$_3$) caused nOe enhancement at δ_H 3.46 (3H, s, OC*H*$_3$) and 3.34 (3H, s, OC*H*$_3$); irradiation of the signal at δ_H 3.79 (1H, app. t, *J* 10.1 Hz, C*H*CH$_2$) caused nOe enhancement at δ_H 3.46 (3H, s, OC*H*$_3$); irradiation of the signal at δ_H 3.46 (3H, s, OC*H*$_3$) caused nOe enhancement at δ_H 3.88 (1H, s, C*H*OCH$_3$) and 3.79 (1H, app. t, *J* 10.1 Hz, C*H*CH$_2$); irradiation of the signal at δ_H 3.34 (3H, s, OC*H*$_3$) caused nOe enhancement at δ_H 3.88 (1H, s, C*H*OCH$_3$). *The aforementioned assignments were aided by a ^{1}H-^{1}H COSY and a short and long-range ^{1}H-^{13}C COSY experiment (HMQC and HMBC respectively).*

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 204.0 (*C*), 193.4 (*C*), 154.8 (*C*), 149.0 (*C*), 136.2 (*C*), 123.6 (*C*), 110.4 (*C*H), 109.0 (*C*H), 96.3 (*C*), 81.0 (*C*H), 58.9 (*C*H$_3$), 56.4 (*C*H$_3$), 56.2 (*C*H$_3$), 53.6 (*C*H$_3$), 49.9 (*C*H$_2$), 31.7 (*C*H).

LRMS $^m/_z$ (ES$^+$) 635 ([2M + Na]$^+$), 361 ([M + Na + MeOH]$^+$), 329 ([M + Na]$^+$), 307 (MH$^+$).

HRMS $^m/_z$ (ES$^+$) found 307.1172, MH$^+$; $C_{16}H_{19}O_6$ requires 307.1176.

Data for **4.95b**:

FT-IR ν_{max} (neat, cm^{-1}) 2933 w, 2835 w, 1783 m, 1698 s, 1599 s, 1509 s, 1463 s, 1366 m, 1266 s, 1219 m, 1122 s, 910 s, 725 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.38 (1H, s), 6.69 (1H, s), 4.38 (1H, s), 3.96 (3H, s), 3.93 (3H, s), 3.92 (1H, obsc. m), 3.60 (3H, s), 3.45 (1H, obsc. dd, *J* 17.3, 10.6 Hz), 3.44 (3H, s), 3.18 (1H, dd, *J* 17.3, 9.0 Hz).

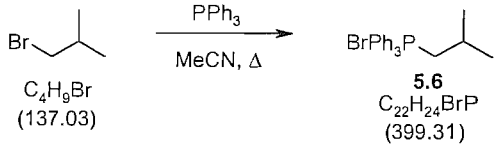
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 201.8 (*C*), 192.2 (*C*), 154.7 (*C*), 149.2 (*C*), 134.1 (*C*), 124.6 (*C*), 110.3 (*C*H), 108.8 (*C*H), 97.2 (*C*), 79.2 (*C*H), 59.7 (*C*H$_3$), 56.4 (*C*H$_3$), 56.3 (*C*H$_3$), 54.1 (*C*H$_3$), 47.0 (*C*H$_2$), 32.7 (*C*H).

LRMS $^m/_z$ (ES$^+$) 635 ([2M + Na]$^+$), 361 ([M + Na + MeOH]$^+$), 329 ([M + Na]$^+$).

HRMS $^m/_z$ (ES$^+$) found 307.1170, MH$^+$; $C_{16}H_{19}O_6$ requires 307.1176.

6.2.4 Experimental for Chapter 5

2-Methyl-propyl-phosphonium bromide, 5.6



The title compound was prepared using the method of Gannett *et al.*[116] A solution of triphenylphosphine (10.9 g, 41.4 mmol) and 1-bromo-2-methylpropane (7.56 g, 55.2 mmol) in acetonitrile (40 mL) was heated at reflux for 64 h then cooled to RT and concentrated *in vacuo*. The resulting solid was triturated with petrol (ice-cold, 50 mL), filtered and washed with more petrol (ice-cold, 75 mL) to yield phosphonium salt **5.6** as a white powder (9.21 g, 23.1 mmol, 56%). Spectroscopic data were in agreement with the literature.[116]

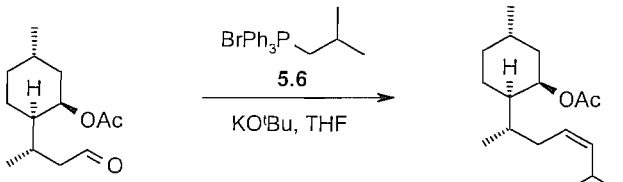
FT-IR ν_{max} (neat, cm^{-1}) 3052 w, 2974 w, 2954 w, 2844 w, 2782 w, 1585 w, 1483 m, 1430 s, 1160 w, 1099 s, 993 m, 821 m, 743 s, 715 s, 689 s.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.83-7.61 (15H, m), 3.60 (2H, dd, *J* 12.9, 6.4 Hz), 2.03 (1H, app. nonet, *J* 6.4 Hz), 1.00 (6H, dd, *J* 6.4, 0.8 Hz).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 135.1 (3 x *C*H ($J_{C\text{-}P}$ 3.3 Hz)), 133.6 (6 x *C*H ($J_{C\text{-}P}$ 9.9 Hz)), 130.5 (6 x *C*H ($J_{C\text{-}P}$ 13.2 Hz)), 118.7 (3 x *C* ($J_{C\text{-}P}$ 85.1 Hz)), 30.5 (*C*H_2 ($J_{C\text{-}P}$ 48.7 Hz)), 24.6 (*C*H ($J_{C\text{-}P}$ 4.4 Hz)), 24.4 (2 x *C*H_3 ($J_{C\text{-}P}$ 8.8 Hz)).

LRMS $^m/_z$ (ES^+) 319 ($[M - Br]^+$).

***rel*-(1*R*,2'*S*,3*S*,4'*Z*,6*R*)-3-Methyl-6-(6'-methyl-hept-4'-en-2'-yl)-cyclohexyl acetate, 5.7**



3.21
$C_{13}H_{22}O_3$
(226.32)

5.7
$C_{17}H_{30}O_2$
(266.42)
Z:*E* ~ 25:1

To a stirred suspension of phosphonium salt **5.6** (265 mg, 0.663 mmol) in THF (5 mL) at 0 °C was added potassium *tert*-butoxide (84 mg, 0.751 mmol). After 1 h a solution of aldehyde **3.21** (100 mg, 0.442 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to RT and then heated at reflux for 16 h. On cooling to RT, water (10 mL) was added and the mixture extracted with ether (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 2% ether/petrol) to yield alkene **5.7** as a colourless oil (95 mg, 0.357 mmol, 81%) and an inseparable 25:1 mixture of (*Z*) and (*E*)-isomers. Data of the (*Z*)-isomer:

FT-IR ν_{max} (neat, cm^{-1}) 2946 m, 2917 m, 2864 w, 2840 w, 1732 s, 1450 w, 1368 w, 1234 s, 1176 w, 1021 m, 960 w, 739 w.

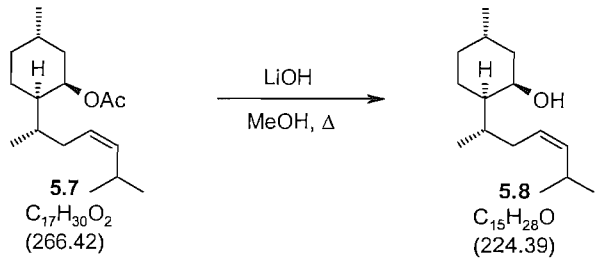
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.24-5.15 (3H, m), 2.55 (1H, septet of d, *J* 6.5, 2.0 Hz), 2.13 (1H, dt, *J* 14.3, 4.8 Hz), 2.04 (3H, s), 1.94 (1H, dq, *J* 14.1, 3.5 Hz), 1.83 (1H, dt, *J* 14.3, 7.3 Hz), 1.77 (1H, m), 1.69-1.62 (2H, m), 1.41 (1H, obsc. m), 1.41 (1H, qd, *J* 12.8, 3.5 Hz), 1.19 (1H, dtd, *J* 12.1, 3.5, 2.4 Hz), 1.04 (1H, ddd, *J* 14.5, 12.3, 2.3 Hz), 0.93 (1H, obsc. m), 0.93 (3H, d, *J* 6.5 Hz), 0.92 (3H, d, *J* 6.5 Hz), 0.88 (3H, d, *J* 6.8 Hz), 0.86 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 170.8 (*C*), 138.8 (*C*H), 125.5 (*C*H), 71.9 (*C*H), 44.4 (*C*H), 39.4 (CH_2), 35.1 (CH_2), 34.9 (*C*H), 32.0 (CH_2), 26.8 (*C*H), 26.7 (*C*H), 24.6 (CH_2), 23.4 (CH_3), 23.2 (CH_3), 22.4 (CH_3), 21.5 (CH_3), 17.3 (CH_3).

LRMS $^{m}/_{z}$ (ES^+) 555 ($[2M + Na]^+$), 289 ($[M + Na]^+$).

HRMS $^{m}/_{z}$ (ES^+) found 289.2136, $(M + Na)^+$; $C_{17}H_{30}O_2Na$ requires 289.2138.

***rel*-(1*R*,2'*S*,3*S*,4'*Z*,6*R*)-3-Methyl-6-(6'-methyl-hept-4'-en-2'-yl)-cyclohexanol, 5.8**



5.7
$C_{17}H_{30}O_2$
(266.42)

5.8
$C_{15}H_{28}O$
(224.39)

To a solution of acetate **5.7** (1.53 g, 5.74 mmol) in methanol (40 mL) was added 2 M LiOH (8.6 mL, 17.2 mmol). The reaction was heated at reflux for 16 h, cooled to RT and partitioned between water (50 mL) and ether (50 mL). The aqueous phase was further extracted with ether (2 x 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield alcohol **5.8** as a colourless oil (1.14 g, 5.08 mmol, 89%).

FT-IR ν_{max} (neat, cm^{-1}) 3412 bw, 2950 s, 2913 s, 2864 m, 1454 s, 1373 m, 1176 w, 1025 s, 956 s, 931 m, 841 w, 739 m.

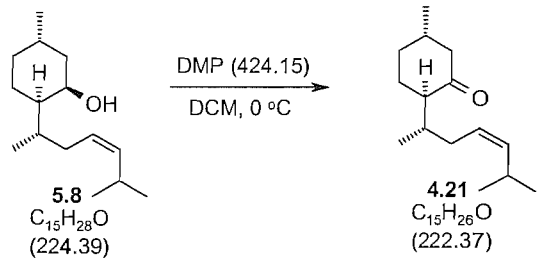
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.26-5.22 (2H, m), 4.10 (1H, bs), 2.60 (1H, septet of d, *J* 6.8, 1.8 Hz), 2.24 (1H, dt, *J* 14.3, 4.7 Hz), 1.97 (1H, ddd, *J* 14.3, 7.8, 6.5 Hz), 1.83 (1H, dq, *J* 13.7, 3.4 Hz), 1.79-1.69 (2H, m), 1.64-1.52 (2H, m), 1.33 (1H, qd, *J* 12.9, 3.3 Hz), 1.24 (1H, bs), 1.15-1.05 (2H, m), 0.96 (1H, obsc. m), 0.95 (6H, d, *J* 6.8 Hz), 0.92 (3H, d, *J* 6.8 Hz), 0.88 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 138.8 (*C*H), 125.8 (*C*H), 68.4 (*C*H), 45.8 (*C*H), 42.9 (CH_2), 35.3 (CH_2), 34.8 (*C*H), 32.0 (CH_2), 26.7 (*C*H), 26.2 (*C*H), 24.0 (CH_2), 23.3 (CH_3), 23.2 (CH_3), 22.5 (CH_3), 17.8 (CH_3).

LRMS $^{m}/_{z}$ (EI) 224 (M^+, 17%), 206 ($[M - H_2O]^+$, 14), 191 (8), 163 (49), 139 (99), 123 (78), 109 (70), 95 (100), 81 (96), 67 (90).

HRMS $^{m}/_{z}$ (EI) found 224.2138, M^+; $C_{15}H_{28}O$ requires 224.2140.

***rel*-(2'*S*,3*S*,4'*Z*,6*R*)-3-Methyl-6-(6'-methyl-hept-4'-en-2'-yl)-cyclohexanone, 4.21**



5.8
$C_{15}H_{28}O$
(224.39)

4.21
$C_{15}H_{26}O$
(222.37)

To a solution of alcohol **5.8** (58 mg, 0.258 mmol) in DCM (5 mL) at 0 °C was added Dess-Martin periodinane (164 mg, 0.388 mmol). The reaction mixture was allowed to warm to RT, stirred for 3 h and then 1 M NaOH (3 mL) added. The mixture was extracted with ether (2 x 20 mL), and the combined organic phases washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether/petrol) afforded ketone **4.21** as a colourless oil (56 mg, 0.252 mmol, 98%).

FT-IR ν_{max} (neat, cm^{-1}) 2999 w, 2950 s, 2925 s, 2868 m, 1704 vs, 1450 s, 1377 m, 1360 w, 1197 w, 1123 w, 1098 w, 1039 w, 968 w, 743 s.

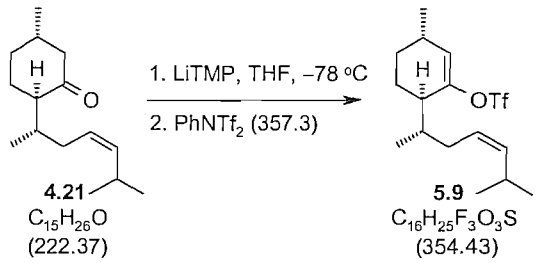
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.24 (1H, d, *J* 10.8 Hz), 5.18 (1H, dt, *J* 10.8, 7.1 Hz), 2.57 (1H, septet of d, *J* 6.7, 2.0 Hz), 2.36 (1H, dd, *J* 13.1, 2.3 Hz), 2.22-2.10 (2H, m), 2.05-1.83 (6H, m), 1.41 (1H, qd, *J* 12.7, 2.9 Hz), 1.33 (1H, m), 1.01 (3H, d, *J* 6.3 Hz), 0.94 (3H, d, *J* 6.8 Hz), 0.93 (3H, d, *J* 6.5 Hz), 0.84 (3H, d, *J* 6.8 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 212.3 (*C*), 138.9 (*C*H), 125.8 (*C*H), 53.1 (*C*H), 51.0 (CH_2), 35.4 (*C*H), 34.2 (CH_2), 32.7 (CH_2), 31.2 (*C*H), 27.0 (CH_2), 26.7 (*C*H), 23.4 (CH_3), 23.3 (CH_3), 22.5 (CH_3), 16.2 (CH_3).

LRMS $^m/_z$ (EI) 222 (M^+, 12%), 207 ($[M - CH_3]^+$, 4), 139 (15), 110 (100), 95 (98), 81 (34), 69 (82), 55 (93).

HRMS $^m/_z$ (EI) found 222.1980, M^+; $C_{15}H_{26}O$ requires 222.1984.

***rel*-(2'*S*,3*S*,4'*Z*,6*R*)-3-Methyl-6-(6'-methyl-hept-4'-en-2'-yl)-1-trifluoromethane-sulfonyloxy-cyclohexene, 5.9**



4.21
$C_{15}H_{26}O$
(222.37)

5.9
$C_{16}H_{25}F_3O_3S$
(354.43)

The title compound was prepared by adapting the method of Paquette *et al.*[97] To a solution of 2,2,6,6-tetramethyl-piperidine (91 μL, 0.540 mmol) in THF (4 mL) at 0 °C was added ^{n}BuLi (1.80 M in hexanes, 0.30 mL, 0.540 mmol). After 30 min, the solution was cooled to –78 °C and a solution of ketone **4.21** (100 mg, 0.450 mmol) in THF (2.5 mL) added over 2 min. After 1 h, a solution of *N*-phenyltriflimide[97] (192 mg, 0.540 mmol) in THF (2 mL) was added and the reaction warmed to RT over 5 h. Sat. $NaHCO_3$ (2 mL) was added and the mixture extracted with ether (2 x 30 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-1% ether/petrol) gave enol triflate **5.9** as a colourless oil (101 mg, 0.285 mmol, 63%).

FT-IR ν_{max} (neat, cm^{-1}) 2954 m, 2929 w, 2868 w, 1671 w, 1454 w, 1413 s, 1242 m, 1199 vs, 1140 vs, 1050 m, 968 s, 935 m, 890 s, 809 s.

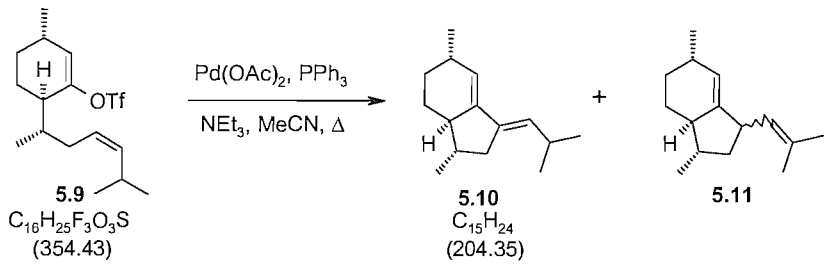
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.67 (1H, bs), 5.28 (1H, d, *J* 10.9 Hz), 5.22 (1H, dt, *J* 10.9, 6.4 Hz), 2.62 (1H, obsc. m), 2.58 (1H, septet of d, *J* 6.5, 2.2 Hz), 2.34 (1H, bm), 2.04-1.99 (3H, m), 1.87-1.74 (2H, m), 1.45 (1H, qt, *J* 13.1, 2.9 Hz), 1.14 (1H, qt, *J* 13.1, 2.9 Hz), 1.05 (3H, d, *J* 7.0 Hz), 0.96 (3H, d, *J* 6.5 Hz), 0.95 (3H, d, *J* 6.5 Hz), 0.83 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 151.8 (*C*), 139.2 (*C*H), 126.3 (*C*H), 125.3 (*C*H), 118.8 (*C*F_3 ($J_{C\text{-}F}$ 320 Hz)), 41.2 (*C*H), 33.0 (*C*H), 32.0 (*C*H_2), 30.9 (*C*H), 30.4 (*C*H_2), 26.8 (*C*H), 23.3 (*C*H_3), 23.2 (*C*H_3), 22.5 (*C*H_2), 21.5 (*C*H_3), 14.3 (*C*H_3).

LRMS $^m/_z$ (EI) 354 (M^+, 10%), 270 (90), 242 (18), 204 (24), 189 (28), 161 (31), 149 (49), 137 (81), 121 (53), 109 (69), 95 (88), 69 (100).

HRMS $^{m}/_{z}$ (EI) found 354.1484, M^+; $C_{16}H_{25}F_3O_3S$ requires 354.1477.

***rel*-(1*S*,3*E*,5*S*,7a*R*)-1,5-Dimethyl-3-(2-methylpropylidene)-2,3,5,6,7,7a-hexahydro-1*H*-indene, 5.10**



5.9
$C_{16}H_{25}F_3O_3S$
(354.43)

5.10
$C_{15}H_{24}$
(204.35)

5.11

Adapting the method of Overman *et al.*[117] To a solution of triflate **5.9** (84 mg, 0.237 mmol) in acetonitrile (5 mL) was added triphenylphosphine (25 mg, 95 μmol), palladium(II) acetate (5.3 mg, 24 μmol) and triethylamine (66 μL, 0.474 mmol). The reaction mixture was de-oxygenated (sonication and bubbling with Ar gas) then heated at reflux for 1 h. After cooling to RT, the reaction mixture was partitioned between sat. $NaHCO_3$ (5 mL) and ether (20 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petrol) afforded diene **5.10** as a colourless oil (38 mg, 0.186 mmol, 78%) contaminated with an inseparable trace impurity assigned to **5.11**. Data for **5.10**:

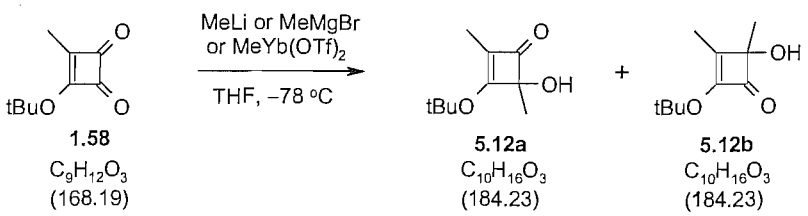
FT-IR ν_{max} (neat, cm^{-1}) 2949 s, 2917 s, 2864 s, 2847 m, 1650 w, 1450 s, 1372 m, 1098 w, 1008 w, 939 w, 861 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.72 (1H, bs), 5.21 (1H, d, *J* 2.5 Hz), 2.86 (1H, septet of d, *J* 6.5, 2.0 Hz), 2.42 (1H, dd, *J* 15.3, 7.3 Hz), 2.31 (1H, bm), 2.05-1.68 (6H, m), 1.41 (1H, m), 1.05 (3H, d, *J* 7.0 Hz), 1.04 (3H, d, *J* 6.8 Hz), 1.02 (3H, d, *J* 6.5 Hz), 0.99 (3H, d, *J* 6.5 Hz).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 141.9 (*C*), 136.0 (*C*), 131.7 (*C*H), 128.2 (*C*H), 50.2 (*C*H), 42.7 (CH_2), 39.9 (*C*H), 32.2 (*C*H), 32.0 (CH_2), 28.2 (CH_2), 28.0 (*C*H), 23.4 (CH_3), 23.2 (CH_3), 22.5 (CH_3), 18.1 (CH_3).

LRMS $^{m}/_{z}$ (EI) 204 (M^+, 93%), 189 ($[M - CH_3]^+$, 93), 175 (21), 161 ($[M - C_3H_7]^+$, 100), 147 (55), 133 (85), 119 (87), 105 (87), 91 (79).

3-*tert*-Butoxy-2,4-dimethyl-4-hydroxy-cyclobut-2-enone, 5.12a and **2-*tert*-Butoxy-3,4-dimethyl-4-hydroxy-cyclobut-2-enone, 5.12b**



1.58
$C_9H_{12}O_3$
(168.19)

5.12a
$C_{10}H_{16}O_3$
(184.23)

5.12b
$C_{10}H_{16}O_3$
(184.23)

To a solution of squarate **1.58** (198 mg, 1.18 mmol) in THF (5 mL) at –78 °C was added MeLi (1.6 M in ether, 0.77 mL, 1.24 mmol). After 1 h sat. $NaHCO_3$ (2 mL) was added, the reaction warmed to RT then partitioned between water (5 mL) and ether (15 mL). The aqueous phase was separated and extracted with ether (15 mL), then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-75% ether/petrol) yielded firstly cyclobutenone **5.12b** as a white amorphous solid (21 mg, 0.191 mmol, 16%) followed by cyclobutenone **5.12a** as a colourless oil (132 mg, 0.716 mmol, 61%) which crystallised on standing.

Alternatively:

To a solution of squarate **1.58** (202 mg, 1.20 mmol) in THF (5 mL) at –78 °C was added MeMgBr (3.0 M in ether, 0.42 mL, 1.26 mmol). After 30 min sat. $NaHCO_3$ (2 mL) was added, the reaction warmed to RT then partitioned between water (5 mL) and ether (15 mL). The aqueous phase was separated and extracted with ether (15 mL), then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-75% ether/petrol) yielded firstly cyclobutenone **5.12b** as a white amorphous solid (141 mg, 0.764 mmol, 64%), followed by cyclobutenone **5.12a** as a colourless oil (31 mg, 0.168 mmol, 14%), which crystallised on standing.

Alternatively:

Adapting the method of Proctor *et al.*[98] To a solution of ytterbium(III) triflate (155 mg, 0.250 mmol) in THF (3 mL) at –78 °C was added MeLi (1.6 M in ether, 0.22 mL, 0.350 mmol) dropwise. After 30 min a solution of squarate **1.58** (40 mg, 0.238 mmol) in THF (2 mL) was added followed after a further 30 min by sat. $NaHCO_3$ (2 mL). The reaction

was warmed to RT and partitioned between water (5 mL) and ether (15 mL). The aqueous phase was separated and extracted with ether (15 mL), then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30-75% ether/petrol) gave firstly cyclobutenone **5.12b** as a white amorphous solid (34 mg, 0.185 mmol, 78%), followed by cyclobutenone **5.12a** as a colourless oil (3 mg, 17 μmol, 7%).

Data for cyclobutenone **5.12a**:

MP 48-50 °C (petrol).

FT-IR ν_{max} (neat, cm^{-1}) 3277 bw, 2983 w, 2925 w, 2868 w, 1742 s, 1581 vs, 1450 m, 1387 s, 1371 s, 1338 s, 1256 m, 11 49 s, 1121 s, 1009 w, 897 s, 871 s, 823 m, 750 m, 732 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.89 (1H, bs), 1.74 (3H, s), 1.53 (9H, s), 1.48 (3H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 195.6 (*C*), 181.9 (*C*), 120.0 (*C*), 89.2 (*C*), 83.4 (*C*), 28.9 (3 x CH_3), 19.1 (CH_3), 9.0 (CH_3).

LRMS $^m/_z$ (ES^+) 391 ($[2M + Na]^+$), 207 ($[M + Na]^+$).

CHN Found C 64.79%, H 8.71%; $C_{10}H_{16}O_3$ requires C 65.19%, H 8.75%.

Data for cyclobutenone **5.12b**:

MP 91-93 °C.

FT-IR ν_{max} (neat, cm^{-1}) 3236 bw, 2974 w, 2927 w, 1751 s, 1628 s, 1371 s, 1323 s, 1242 w, 1172 m, 1119 s, 1089 m, 1052 m, 931 s, 921 s, 884 s.

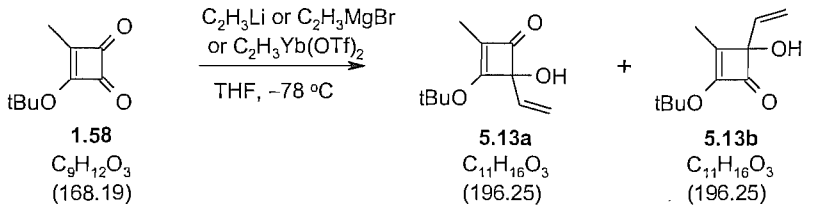
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.21 (1H, bs), 2.02 (3H, s), 1.45 (3H, s), 1.43 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 190.7 (*C*), 160.4 (*C*), 152.3 (*C*), 84.7 (*C*), 80.1 (*C*), 28.8 (3 x CH_3), 19.6 (CH_3), 8.5 (CH_3).

LRMS $^m/_z$ (ES^+) 391 ($[2M + Na]^+$), 239 ($[M + Na + MeOH]^+$), 207 ($[M + Na]^+$).

CHN Found C 64.86%, H 8.68%; $C_{10}H_{16}O_3$ requires C 65.19%, H 8.75%.

3-*tert*-Butoxy-4-hydroxy-2-methyl-4-vinyl-cyclobut-2-enone, 5.13a and **2-*tert*-Butoxy-4-hydroxy-3-methyl-4-vinyl-cyclobut-2-enone, 5.13b**



1.58 $C_9H_{12}O_3$ (168.19)

5.13a $C_{11}H_{16}O_3$ (196.25)

5.13b $C_{11}H_{16}O_3$ (196.25)

To a solution of ^{t}BuLi (1.27 M in pentane, 1.32 mL, 1.68 mmol) in THF (4 mL) at –78 °C was added vinyl bromide (1.0 M in THF, 0.84 mL, 0.840 mmol) dropwise. The reaction was warmed to 0 °C over 15 min, then re-cooled to –78 °C and treated with a solution of squarate **1.58** (135 mg, 0.800 mmol) in THF (2 mL). After 1 h sat. $NaHCO_3$ (2 mL) was added, the reaction warmed to RT and partitioned between water (5 mL) and ether (25 mL). The aqueous phase was separated and extracted with ether (25 mL), then the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-60% ether/petrol) afforded firstly cyclobutenone **5.13b** as a colourless oil (67 mg, 0.341 mmol, 43%) followed by cyclobutenone **5.13a** as a colourless oil (49 mg, 0.250 mmol, 31%).

Alternatively:

To a solution of squarate **1.58** (114 mg, 0.679 mmol) in THF (5 mL) at –78 °C was added vinylmagnesium bromide (1.0 M in THF, 0.71 mL, 0.712 mmol) dropwise. After 30 min sat. $NaHCO_3$ (2 mL) was added, the reaction warmed to RT and partitioned between water (5 mL) and ether (25 mL). The aqueous phase was separated and extracted with ether (25 mL), then the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-60% ether/petrol) afforded firstly cyclobutenone **5.13b** as a colourless oil (76 mg, 0.387 mmol, 57%) followed by cyclobutenone **5.13a** as a colourless oil (14 mg, 71 μmol, 11%).

Alternatively:

To a solution of ytterbium(III) triflate (155 mg, 0.250 mmol) in THF (3 mL) at –78 °C was added vinylmagnesium bromide (1.0 M in THF, 0.35 mL, 0.350 mmol) dropwise. After 45 min a solution of squarate **1.58** (40 mg, 0.238 mmol) in THF (2 mL) was added followed after a further 30 min by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL), then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-60% ether/petrol) gave firstly cyclobutenone **5.13b** as a colourless oil (34 mg, 0.173 mmol, 73%), followed by cyclobutenone **5.13a** as a colourless oil (3 mg, 17 μmol, 6%).

Data for cyclobutenone **5.13a**:

FT-IR ν_{max} (neat, cm^{-1}) 3350 bw, 2974 w, 2929 w, 1747 s, 1588 vs, 1387 s, 1338 s, 1259 m, 1150 vs, 1067 s 1005 m, 896 s, 730 w.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.92 (1H, dd, *J* 17.5, 10.8 Hz), 5.50 (1H, dd, *J* 17.5, 1.0 Hz), 5.31 (1H, dd, *J* 10.8, 1.0 Hz), 2.16 (1H, bs), 1.73 (3H, s), 1.51 (9H, s).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 192.8 (*C*), 181.5 (*C*), 135.0 (*C*H), 123.6 (*C*), 117.7 (*C*H_2), 92.5 (*C*), 84.6 (*C*), 29.0 (3 x *C*H_3), 8.1 (*C*H_3).

LRMS $^m/_z$ (ES^+) 415 ($[2M + Na]^+$), 251 ($[M + Na + MeOH]^+$), 219 ($[M + Na]^+$).

HRMS $^m/_z$ (EI) found 196.1103, M^+; $C_{11}H_{16}O_3$ requires 196.1099.

Data for cyclobutenone **5.13b**:

FT-IR ν_{max} (neat, cm^{-1}) 3395 bw, 2974 m, 2929 w, 1750 vs, 1626 s, 1469 w, 1370 s, 1322 s, 1258 m, 1161 s, 1064 s, 918 vs, 845 m.

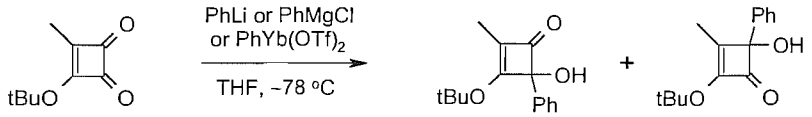
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.92 (1H, dd, *J* 17.5, 10.8 Hz), 5.42 (1H, dd, *J* 17.5, 0.8 Hz), 5.32 (1H, dd, *J* 10.8, 0.8 Hz), 2.35 (1H, bs), 2.01 (3H, s), 1.45 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 187.7 (*C*), 158.2 (*C*), 153.8 (*C*), 135.8 (*C*H), 117.6 (CH_2), 88.1 (*C*), 80.5 (*C*), 28.8 (3 x CH_3), 8.9 (CH_3).

LRMS $^m/_z$ (ES^+) 251 ($[M + Na + MeOH]^+$), 219 ($[M + Na]^+$).

HRMS $^m/_z$ (EI) found 196.1104, M^+; $C_{11}H_{16}O_3$ requires 196.1099.

3-*tert*-Butoxy-4-hydroxy-2-methyl-4-phenyl-cyclobut-2-enone, 5.14a and **2-*tert*-Butoxy-4-hydroxy-3-methyl-4-phenyl-cyclobut-2-enone, 5.14b**



1.58 $C_9H_{12}O_3$ (168.19)

5.14a $C_{15}H_{18}O_3$ (246.31)

5.14b $C_{15}H_{18}O_3$ (246.31)

To a solution of squarate **1.58** (121 mg, 0.719 mmol) in THF (5 mL) at –78 °C was added phenyllithium (1.8 M in di-*n*-butyl ether, 0.42 mL, 0.755 mmol) dropwise. After 30 min sat. $NaHCO_3$ (2 mL) was added, the reaction warmed to RT and partitioned between water (5 mL) and ether (25 mL). The aqueous phase was separated and extracted with ether (25 mL), then the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-75% ether/petrol) afforded firstly cyclobutenone **5.14b** as a colourless oil (72 mg, 0.292 mmol, 41%) followed by cyclobutenone **5.14a** as a colourless oil (85 mg, 0.345 mmol, 48%).

Alternatively:

To a solution of squarate **1.58** (134 mg, 0.797 mmol) in THF (5 mL) at –78 °C was added phenylmagnesium chloride (2.0 M in THF, 0.42 mL, 0.837 mmol) dropwise. After 1 h sat. $NaHCO_3$ (2 mL) was added, the reaction warmed to RT and partitioned between water (5 mL) and ether (25 mL). The aqueous phase was separated and extracted with ether (25 mL), then the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-75% ether/petrol) afforded firstly cyclobutenone **5.14b** as a colourless oil (132 mg, 0.536 mmol, 67%) followed by cyclobutenone **5.14a** as a colourless oil (43 mg, 0.175 mmol, 22%).

Alternatively:

To a solution of ytterbium(III) triflate (155 mg, 0.250 mmol) in THF (3 mL) at –78 °C was added phenyllithium (1.8 M in di-*n*-butylether, 0.19 mL, 0.350 mmol) dropwise. After 45 min a solution of squarate **1.58** (40 mg, 0.238 mmol) in THF (2 mL) was added followed after a further 1 h by sat. $NaHCO_3$ (2 mL). The reaction was warmed to RT and partitioned between water (5 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (20 mL), then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-75% ether/petrol) gave firstly cyclobutenone **5.14b** as a colourless oil (39 mg, 0.158 mmol, 67%), followed by cyclobutenone **5.14a** as a colourless oil (4 mg, 16 μmol, 7%).

Data for cyclobutenone **5.14a**:

FT-IR ν_{max} (neat, cm^{-1}) 3322 bm, 2978 w, 2917 w, 2852 w, 1743 s, 1605 s, 1587 vs, 1385 s, 1340 vs, 1209 w, 1144 vs, 1004 m, 872 m, 842 s, 761 m, 715 s, 661 m.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.49 (2H, dd, *J* 7.2, 1.5 Hz), 7.36 (2H, t, *J* 7.2 Hz), 7.30 (1H, tt, *J* 7.2, 1.5 Hz), 3.58 (1H, bs), 1.84 (3H, s), 1.47 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 192.0 (*C*), 179.7 (*C*), 137.7 (*C*), 128.6 (2 x *C*H), 128.2 (*C*H), 126.0 (2 x *C*H), 124.5 (*C*), 93.2 (*C*), 84.5 (*C*), 29.0 (3 x CH_3), 8.6 (CH_3).

LRMS $^m/_z$ (ES^+) 515 ($[2M + Na]^+$), 269 ($[M + Na]^+$).

HRMS $^m/_z$ (EI) found 246.1255, M^+; $C_{15}H_{18}O_3$ requires 246.1256.

Data for cyclobutenone **5.14b**:

FT-IR ν_{max} (neat, cm^{-1}) 3407 bw, 2978 w, 2929 w, 1752 vs, 1628 s, 1446 m, 1370 s, 1323 s, 1164 s, 1047 s, 974 m, 902 s, 837 m, 697 s.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.43 (2H, dd, *J* 7.2, 1.5 Hz), 7.38 (2H, t, *J* 7.2

Hz), 7.31 (1H, tt, *J* 7.2, 1.5 Hz), 2.47 (1H, bs), 2.03 (3H, s), 1.50 (9H, s).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 187.0 (*C*), 157.9 (*C*), 154.8 (*C*), 138.7 (*C*), 128.8 (2 x *C*H), 128.2 (*C*H), 125.9 (2 x *C*H), 89.1 (*C*), 80.6 (*C*), 28.9 (3 x *C*H_3), 9.0 (*C*H_3).

LRMS $^m/_z$ (ES^+) 515 ($[2M + Na]^+$), 301 ($[M + Na + MeOH]^+$), 269 ($[M + Na]^+$).

HRMS $^m/_z$ (EI) found 246.1257, M^+; $C_{15}H_{18}O_3$ requires 246.1256.

Chapter 7 – Appendices

7.1 X-Ray Crystal Data for *ent*-3.34

Table 1. Crystal data and structure refinement details.

Identification code	**2006sot0717**
Empirical formula	$C_{20}H_{30}O_4$
Formula weight	334.44
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 6.7285(3) Å
	b = 10.1110(4) Å β = 100.187(2)°
	c = 14.6062(4) Å
Volume	978.02(6) Å^3
Z	2
Density (calculated)	1.136 Mg / m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	364
Crystal	Block; Pale Yellow
Crystal size	0.35 × 0.3 × 0.3 mm^3
θ range for data collection	3.15 – 27.47°
Index ranges	$-8 \le h \le 8$, $-12 \le k \le 13$, $-18 \le l \le 18$
Reflections collected	12176
Independent reflections	2366 [R_{int} = 0.0340]
Completeness to θ = 27.47°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9771 and 0.9634
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2366 / 13 / 226
Goodness-of-fit on F^2	1.147
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0426, $wR2$ = 0.1091
R indices (all data)	$R1$ = 0.0481, $wR2$ = 0.1143
Absolute structure parameter	Not reliably determined
Extinction coefficient	0.122(13)
Largest diff. peak and hole	0.323 and –0.255 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	−2843(4)	3700(3)	7345(2)	41(1)	1
C2	−847(4)	4334(2)	7196(2)	28(1)	1
C3	163(4)	3456(3)	6566(2)	41(1)	1
C4	−1161(3)	5725(2)	6813(1)	24(1)	1
C5	−2702(3)	5914(2)	5935(2)	28(1)	1
C6	−2439(3)	7215(2)	5448(2)	29(1)	1
C7	−2282(3)	8369(2)	6128(1)	24(1)	1
C8	−404(3)	8179(2)	6902(1)	22(1)	1
C9	−126(3)	6755(2)	7213(1)	22(1)	1
C10	3240(4)	6228(4)	7932(2)	52(1)	1
C11	−2307(4)	9709(3)	5646(2)	32(1)	1
C12	1511(3)	8748(2)	6621(1)	24(1)	1
C13	2188(3)	9914(2)	7201(2)	28(1)	1
C14	1018(3)	10068(2)	7856(2)	28(1)	1
C15	−619(3)	9054(2)	7736(1)	25(1)	1
C16	3954(4)	10726(3)	7077(2)	34(1)	1
C17	1358(6)	11044(3)	9436(2)	55(1)	1
C18	2278(9)	9768(4)	9779(3)	98(2)	1
C20	2648(7)	12234(4)	9762(3)	71(1)	1
C29	−796(8)	11205(6)	9659(3)	94(2)	1
O1	1283(2)	6646(2)	8035(1)	31(1)	1
O2	−1971(2)	8966(2)	8182(1)	33(1)	1
O3	2347(2)	8314(2)	6008(1)	33(1)	1
O4	1169(3)	11121(2)	8418(1)	35(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.538(3)	C4–C2–C3	111.42(19)
C2–C4	1.515(3)	C4–C2–C1	111.8(2)
C2–C3	1.523(3)	C3–C2–C1	109.7(2)
C4–C9	1.330(3)	C9–C4–C5	120.07(19)
C4–C5	1.512(3)	C9–C4–C2	122.48(18)
C5–C6	1.520(3)	C5–C4–C2	117.45(19)
C6–C7	1.524(3)	C4–C5–C6	112.78(19)
C7–C11	1.526(3)	C5–C6–C7	110.97(17)
C7–C8	1.551(3)	C6–C7–C11	112.66(17)
C8–C9	1.511(3)	C6–C7–C8	109.49(17)
C8–C12	1.532(3)	C11–C7–C8	112.78(18)
C8–C15	1.534(3)	C9–C8–C12	111.89(17)
C9–O1	1.396(2)	C9–C8–C15	109.52(17)
C10–O1	1.416(3)	C12–C8–C15	101.43(17)
C12–O3	1.221(3)	C9–C8–C7	112.26(17)
C12–C13	1.476(3)	C12–C8–C7	111.98(16)
C13–C14	1.351(3)	C15–C8–C7	109.18(16)
C13–C16	1.481(3)	C4–C9–O1	122.61(18)
C14–O4	1.337(3)	C4–C9–C8	125.90(17)
C14–C15	1.492(3)	O1–C9–C8	111.33(18)
C15–O2	1.212(3)	O3–C12–C13	124.9(2)
C17–O4	1.473(3)	O3–C12–C8	125.5(2)
C17–C18	1.479(5)	C13–C12–C8	109.59(17)
C17–C20	1.511(5)	C14–C13–C12	109.8(2)
C17–C29	1.549(6)	C14–C13–C16	127.0(2)
		C12–C13–C16	123.1(2)
		O4–C14–C13	122.4(2)
		O4–C14–C15	126.4(2)
		C13–C14–C15	110.4(2)
		O2–C15–C14	126.6(2)
		O2–C15–C8	124.7(2)
		C14–C15–C8	108.53(17)
		O4–C17–C18	110.1(3)
		O4–C17–C20	102.6(3)
		C18–C17–C20	113.9(3)
		O4–C17–C29	106.9(3)
		C18–C17–C29	111.8(4)
		C20–C17–C29	110.9(3)
		C9–O1–C10	115.80(18)
		C14–O4–C17	124.2(2)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	41(1)	36(1)	49(1)	8(1)	13(1)	−6(1)
C2	31(1)	26(1)	28(1)	3(1)	8(1)	1(1)
C3	53(2)	29(1)	45(1)	5(1)	19(1)	11(1)
C4	24(1)	26(1)	24(1)	0(1)	6(1)	1(1)
C5	28(1)	30(1)	25(1)	−2(1)	−2(1)	−2(1)
C6	30(1)	30(1)	23(1)	1(1)	−2(1)	2(1)
C7	21(1)	27(1)	24(1)	2(1)	2(1)	4(1)
C8	21(1)	24(1)	20(1)	0(1)	4(1)	1(1)
C9	20(1)	27(1)	18(1)	2(1)	2(1)	3(1)
C10	26(1)	76(2)	48(1)	13(2)	−6(1)	9(1)
C11	37(1)	29(1)	30(1)	4(1)	1(1)	6(1)
C12	22(1)	27(1)	23(1)	1(1)	3(1)	0(1)
C13	26(1)	24(1)	31(1)	0(1)	4(1)	1(1)
C14	31(1)	28(1)	24(1)	−3(1)	3(1)	1(1)
C15	29(1)	26(1)	21(1)	1(1)	5(1)	2(1)
C16	29(1)	30(1)	45(1)	2(1)	8(1)	−2(1)
C17	99(3)	37(2)	25(1)	−7(1)	−2(1)	−2(2)
C18	170(5)	52(2)	47(2)	4(2)	−44(2)	4(3)
C20	101(3)	53(2)	51(2)	−24(2)	−11(2)	−5(2)
C29	130(4)	104(4)	63(2)	−41(3)	59(2)	−32(3)
O1	29(1)	35(1)	25(1)	2(1)	−4(1)	2(1)
O2	33(1)	39(1)	30(1)	−3(1)	14(1)	0(1)
O3	31(1)	40(1)	31(1)	−5(1)	13(1)	2(1)
O4	52(1)	27(1)	25(1)	−4(1)	5(1)	−2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	−3480	4262	7757	62	1
H1B	−2571	2825	7629	62	1
H1C	−3749	3609	6745	62	1
H2	67	4386	7814	34	1
H3A	−701	3395	5953	61	1
H3B	372	2571	6839	61	1
H3C	1469	3839	6500	61	1
H5A	−4073	5884	6093	34	1
H5B	−2589	5175	5503	34	1
H6A	−3605	7356	4940	34	1
H6B	−1202	7175	5169	34	1
H7	−3498	8333	6434	29	1
H10A	3130	5547	7448	78	1
H10B	3944	5862	8522	78	1
H10C	3999	6984	7754	78	1
H11A	−1193	9752	5296	49	1
H11B	−2152	10414	6113	49	1
H11C	−3593	9821	5218	49	1
H16A	3848	11602	7352	52	1
H16B	3985	10821	6412	52	1
H16C	5196	10292	7386	52	1
H18A	1382	9041	9526	146	1
H18B	2476	9750	10460	146	1
H18C	3584	9667	9579	146	1
H20A	4002	12110	9615	107	1
H20B	2746	12336	10436	107	1
H20C	2033	13028	9447	107	1
H29A	−1389	12032	9387	141	1
H29B	−725	11226	10335	141	1
H29C	−1637	10458	9396	141	1

7.2 X-Ray Crystal Data for 4.65

Table 1. Crystal data and structure refinement details.

Identification code	**2005sot1322**
Empirical formula	$C_{24}H_{26}O_8$
Formula weight	442.45
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 7.3275(2) Å
	b = 35.0308(14) Å β = 98.851(2)°
	c = 8.4647(3) Å
Volume	2146.91(13) Å^3
Z	4
Density (calculated)	1.369 Mg / m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	936
Crystal	Block; Colourless
Crystal size	0.35 × 0.25 × 0.05 mm^3
θ range for data collection	3.04 – 27.48°
Index ranges	$-9 \le h \le 8$, $-45 \le k \le 45$, $-10 \le l \le 10$
Reflections collected	16483
Independent reflections	4625 [R_{int} = 0.0637]
Completeness to θ = 27.48°	93.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9949 and 0.9647
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4625 / 0 / 296
Goodness-of-fit on F^2	1.058
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0633, *wR2* = 0.1568
R indices (all data)	*R1* = 0.1216, *wR2* = 0.1983
Largest diff. peak and hole	0.457 and –0.367 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	8264(3)	2152(1)	9178(3)	29(1)	1
O2	9991(2)	1210(1)	12210(2)	24(1)	1
O3	7723(2)	1071(1)	14427(2)	20(1)	1
O4	3764(2)	1171(1)	13150(2)	20(1)	1
O5	2711(2)	1532(1)	10514(2)	19(1)	1
O6	6372(2)	170(1)	6700(2)	19(1)	1
O7	2828(2)	176(1)	7367(2)	19(1)	1
O8	1688(2)	722(1)	9289(2)	17(1)	1
C1	9729(5)	2375(1)	8724(5)	50(1)	1
C2	6687(4)	2101(1)	8072(4)	23(1)	1
C3	6367(5)	2285(1)	6606(4)	33(1)	1
C4	4763(5)	2209(1)	5560(4)	37(1)	1
C5	3498(5)	1952(1)	5963(4)	36(1)	1
C6	3813(4)	1770(1)	7450(4)	24(1)	1
C7	5407(4)	1838(1)	8529(3)	17(1)	1
C8	5912(4)	1641(1)	10135(3)	14(1)	1
C9	7526(4)	1354(1)	10082(3)	16(1)	1
C10	8333(4)	1253(1)	11781(3)	17(1)	1
C11	7015(4)	1198(1)	12904(3)	15(1)	1
C12	5185(4)	1240(1)	12376(3)	15(1)	1
C13	4471(3)	1365(1)	10642(3)	15(1)	1
C14	8604(5)	1367(1)	15432(4)	34(1)	1
C15	3954(4)	973(1)	14664(3)	24(1)	1
C16	6497(3)	1015(1)	9258(3)	14(1)	1
C17	7139(4)	734(1)	8339(3)	15(1)	1
C18	5922(4)	449(1)	7690(3)	15(1)	1
C19	4101(3)	439(1)	8030(3)	15(1)	1
C20	3501(3)	729(1)	8982(3)	14(1)	1
C21	4687(4)	1018(1)	9569(3)	14(1)	1
C22	8229(4)	175(1)	6337(3)	21(1)	1
C23	3277(4)	−215(1)	7730(4)	24(1)	1
C24	1447(4)	462(1)	10551(3)	20(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C2	1.382(4)	C2–O1–C1	118.3(3)
O1–C1	1.427(4)	C11–O3–C14	112.9(2)
O2–C10	1.222(3)	C12–O4–C15	123.1(2)
O3–C11	1.387(3)	C18–O6–C22	116.7(2)
O3–C14	1.432(4)	C19–O7–C23	115.9(2)
O4–C12	1.335(3)	C20–O8–C24	112.4(2)
O4–C15	1.445(3)	O1–C2–C3	123.6(3)
O5–C13	1.405(3)	O1–C2–C7	114.9(3)
O6–C18	1.359(3)	C3–C2–C7	121.4(3)
O6–C22	1.440(3)	C4–C3–C2	119.6(3)
O7–C19	1.368(3)	C5–C4–C3	120.4(3)
O7–C23	1.433(4)	C4–C5–C6	119.9(3)
O8–C20	1.392(3)	C7–C6–C5	121.4(3)
O8–C24	1.434(3)	C6–C7–C2	117.3(3)
C2–C3	1.386(4)	C6–C7–C8	125.3(3)
C2–C7	1.411(4)	C2–C7–C8	117.4(3)
C3–C4	1.384(5)	C7–C8–C13	116.8(2)
C4–C5	1.371(5)	C7–C8–C9	110.4(2)
C5–C6	1.398(4)	C13–C8–C9	99.0(2)
C6–C7	1.388(4)	C10–C9–C16	110.4(2)
C7–C8	1.517(4)	C10–C9–C8	108.1(2)
C8–C13	1.543(4)	C16–C9–C8	101.1(2)
C8–C9	1.559(4)	O2–C10–C11	121.0(3)
C9–C10	1.510(4)	O2–C10–C9	122.5(2)
C9–C16	1.518(4)	C11–C10–C9	116.5(2)
C10–C11	1.468(4)	C12–C11–O3	123.5(2)
C11–C12	1.355(4)	C12–C11–C10	119.3(2)
C12–C13	1.543(4)	O3–C11–C10	117.0(2)
C13–C21	1.539(4)	O4–C12–C11	128.7(3)
C16–C17	1.382(4)	O4–C12–C13	110.0(2)
C16–C21	1.391(4)	C11–C12–C13	121.2(2)
C17–C18	1.395(4)	O5–C13–C21	117.4(2)
C18–C19	1.408(4)	O5–C13–C8	112.1(2)
C19–C20	1.409(4)	C21–C13–C8	101.2(2)
C20–C21	1.375(4)	O5–C13–C12	111.3(2)
		C21–C13–C12	106.7(2)
		C8–C13–C12	107.2(2)
		C17–C16–C21	122.0(3)
		C17–C16–C9	128.9(2)
		C21–C16–C9	109.1(2)
		C16–C17–C18	118.7(2)
		O6–C18–C17	123.8(2)
		O6–C18–C19	115.9(2)
		C17–C18–C19	120.3(3)
		O7–C19–C18	122.6(2)
		O7–C19–C20	117.9(2)
		C18–C19–C20	119.3(2)
		C21–C20–O8	121.0(2)
		C21–C20–C19	120.1(2)
		O8–C20–C19	118.9(2)
		C20–C21–C16	119.6(3)
		C20–C21–C13	132.6(2)
		C16–C21–C13	107.8(2)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	29(1)	27(1)	35(1)	−4(1)	17(1)	−12(1)
O2	13(1)	36(1)	23(1)	−1(1)	3(1)	1(1)
O3	18(1)	25(1)	16(1)	−2(1)	−2(1)	−3(1)
O4	14(1)	30(1)	16(1)	6(1)	5(1)	−1(1)
O5	15(1)	24(1)	21(1)	5(1)	7(1)	5(1)
O6	16(1)	26(1)	17(1)	−8(1)	3(1)	2(1)
O7	17(1)	19(1)	21(1)	−2(1)	−2(1)	−2(1)
O8	11(1)	21(1)	20(1)	3(1)	4(1)	0(1)
C1	47(2)	55(3)	55(3)	−6(2)	27(2)	−25(2)
C2	28(2)	13(2)	31(2)	0(1)	16(1)	1(1)
C3	44(2)	19(2)	42(2)	12(2)	26(2)	4(2)
C4	44(2)	33(2)	37(2)	20(2)	14(2)	11(2)
C5	34(2)	43(2)	31(2)	14(2)	6(2)	8(2)
C6	24(2)	19(2)	31(2)	9(1)	8(1)	6(1)
C7	21(2)	12(1)	20(2)	1(1)	11(1)	3(1)
C8	16(1)	13(1)	16(1)	−3(1)	7(1)	−1(1)
C9	14(1)	18(2)	16(1)	−1(1)	5(1)	0(1)
C10	13(1)	16(2)	21(2)	−4(1)	2(1)	3(1)
C11	16(1)	13(1)	16(1)	−2(1)	2(1)	−3(1)
C12	15(1)	17(2)	15(1)	−2(1)	8(1)	−2(1)
C13	11(1)	17(2)	17(1)	2(1)	4(1)	1(1)
C14	34(2)	44(2)	21(2)	−7(2)	−1(1)	−13(2)
C15	21(2)	38(2)	14(1)	3(1)	6(1)	0(1)
C16	13(1)	17(2)	13(1)	2(1)	0(1)	−1(1)
C17	12(1)	20(2)	13(1)	2(1)	2(1)	2(1)
C18	16(1)	18(2)	10(1)	1(1)	1(1)	2(1)
C19	13(1)	17(2)	13(1)	0(1)	−2(1)	0(1)
C20	11(1)	15(2)	15(1)	6(1)	1(1)	2(1)
C21	13(1)	16(2)	14(1)	1(1)	2(1)	1(1)
C22	19(2)	22(2)	23(2)	−3(1)	8(1)	3(1)
C23	24(2)	23(2)	23(2)	2(1)	2(1)	−3(1)
C24	19(2)	22(2)	20(2)	5(1)	7(1)	0(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H95	2069	1411	11087	29	1
H1A	10085	2271	7741	75	1
H1B	10794	2368	9580	75	1
H1C	9316	2640	8539	75	1
H3	7243	2462	6321	39	1
H4	4537	2335	4556	44	1
H5	2410	1898	5232	43	1
H6	2916	1597	7727	29	1
H8	6274	1836	10991	17	1
H9	8479	1456	9466	19	1
H14A	9441	1510	14853	50	1
H14B	9309	1254	16396	50	1
H14C	7665	1540	15736	50	1
H15A	4583	729	14575	36	1
H15B	2728	926	14951	36	1
H15C	4680	1129	15492	36	1
H17	8385	735	8153	18	1
H22A	8445	415	5803	31	1
H22B	8399	−40	5631	31	1
H22C	9107	152	7330	31	1
H23A	4286	−295	7166	35	1
H23B	2190	−375	7387	35	1
H23C	3663	−244	8885	35	1
H24A	1824	205	10276	30	1
H24B	145	459	10693	30	1
H24C	2207	546	11546	30	1

7.3 X-Ray Crystal Data for 4.76

Table 1. Crystal data and structure refinement details.

Identification code	**2005sot1615**
Empirical formula	$C_{24}H_{26}O_8$
Formula weight	442.45
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 16.5429(4) Å
	b = 8.2582(2) Å β = 100.4940(10)°
	c = 15.8707(3) Å
Volume	2131.90(8) Å^3
Z	4
Density (calculated)	1.378 Mg / m^3
Absorption coefficient	0.104 mm^{-1}
F(000)	936
Crystal	Fragment; Colourless
Crystal size	0.2 × 0.11 × 0.02 mm^3
θ range for data collection	2.96 – 27.48°
Index ranges	$-21 \le h \le 21$, $-10 \le k \le 10$, $-20 \le l \le 20$
Reflections collected	28538
Independent reflections	4883 [R_{int} = 0.0513]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9979 and 0.9696
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4883 / 210 / 297
Goodness-of-fit on F^2	0.870
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0796, $wR2$ = 0.2351
R indices (all data)	$R1$ = 0.1087, $wR2$ = 0.2681
Extinction coefficient	0.0486(7)
Largest diff. peak and hole	0.516 and –0.440 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	5174(1)	7712(1)	709(1)	57(1)	1
C2	4848(1)	5086(1)	1195(1)	41(1)	1
C3	5648(1)	4560(1)	1235(1)	53(1)	1
C4	5862(1)	3011(1)	1528(1)	55(1)	1
C5	5292(1)	2003(1)	1799(1)	52(1)	1
C6	4494(1)	2561(1)	1775(1)	46(1)	1
C7	4249(1)	4089(1)	1458(1)	39(1)	1
C8	3396(1)	4786(1)	1415(1)	37(1)	1
C9	2842(1)	4943(1)	515(1)	39(1)	1
C10	2705(1)	3276(1)	112(1)	41(1)	1
C11	2592(1)	1935(1)	683(1)	41(1)	1
C12	2614(1)	2215(1)	1525(1)	39(1)	1
C13	2785(1)	3925(1)	1890(1)	37(1)	1
C14	3120(1)	−380(1)	113(1)	80(1)	1
C15	2254(1)	−449(1)	1982(1)	80(1)	1
C16	2049(1)	5529(1)	767(1)	40(1)	1
C17	1431(1)	6511(1)	337(1)	53(1)	1
C18	778(1)	6896(1)	744(1)	60(1)	1
C19	732(1)	6285(1)	1548(1)	56(1)	1
C20	1353(1)	5259(1)	1970(1)	49(1)	1
C21	2015(1)	4938(1)	1578(1)	39(1)	1
C22	−277(1)	7806(1)	−334(1)	115(1)	1
C23	−590(1)	5771(1)	1853(1)	99(1)	1
C24	1253(1)	5464(1)	3427(1)	138(1)	1
O1	4577(1)	6601(1)	917(1)	49(1)	1
O2	2676(1)	3070(1)	−663(1)	55(1)	1
O3	2414(1)	429(1)	317(1)	53(1)	1
O4	2485(1)	1189(1)	2141(1)	52(1)	1
O5	3081(1)	3934(1)	2778(1)	46(1)	1
O6	184(1)	7976(1)	395(1)	114(1)	1
O7	100(1)	6765(1)	1951(1)	81(1)	1
O8	1316(1)	4536(1)	2732(1)	71(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.4290(6)	O1–C2–C3	123.51(4)
C2–O1	1.3743(5)	O1–C2–C7	114.97(3)
C2–C3	1.3844(6)	C3–C2–C7	121.50(4)
C2–C7	1.4083(5)	C2–C3–C4	119.18(4)
C3–C4	1.3853(7)	C5–C4–C3	120.94(4)
C4–C5	1.3831(7)	C4–C5–C6	119.22(4)
C5–C6	1.3924(6)	C7–C6–C5	121.56(4)
C6–C7	1.3907(6)	C6–C7–C2	117.53(3)
C7–C8	1.5139(5)	C6–C7–C8	124.70(3)
C8–C13	1.5407(5)	C2–C7–C8	117.70(3)
C8–C9	1.5554(5)	C7–C8–C13	119.46(3)
C9–C10	1.5176(5)	C7–C8–C9	117.47(3)
C9–C16	1.5182(6)	C13–C8–C9	99.13(3)
C10–O2	1.2333(5)	C10–C9–C16	109.28(3)
C10–C11	1.4647(6)	C10–C9–C8	109.22(3)
C11–C12	1.3503(5)	C16–C9–C8	100.21(3)
C11–O3	1.3808(5)	O2–C10–C11	121.71(4)
C12–O4	1.3405(5)	O2–C10–C9	121.44(4)
C12–C13	1.5325(5)	C11–C10–C9	116.84(3)
C13–O5	1.4054(4)	C12–C11–O3	122.41(4)
C13–C21	1.5288(5)	C12–C11–C10	119.92(3)
C14–O3	1.4327(7)	O3–C11–C10	117.55(3)
C15–O4	1.4165(6)	O4–C12–C11	129.40(4)
C16–C17	1.3850(6)	O4–C12–C13	110.42(3)
C16–C21	1.3873(5)	C11–C12–C13	120.17(3)
C17–C18	1.3925(7)	O5–C13–C21	116.10(3)
C18–O6	1.3671(6)	O5–C13–C12	113.02(3)
C18–C19	1.3877(7)	C21–C13–C12	107.26(3)
C19–O7	1.3795(6)	O5–C13–C8	110.34(3)
C19–C20	1.4037(6)	C21–C13–C8	99.84(3)
C20–O8	1.3597(6)	C12–C13–C8	109.39(3)
C20–C21	1.3807(6)	C17–C16–C21	120.84(4)
C22–O6	1.2718(8)	C17–C16–C9	130.76(4)
C23–O7	1.3902(8)	C21–C16–C9	108.39(3)
C24–O8	1.3620(9)	C16–C17–C18	118.05(4)
		O6–C18–C19	117.05(5)
		O6–C18–C17	121.41(5)
		C19–C18–C17	121.40(4)
		O7–C19–C18	119.63(4)
		O7–C19–C20	120.20(4)
		C18–C19–C20	120.06(4)
		O8–C20–C21	118.98(4)
		O8–C20–C19	122.81(4)
		C21–C20–C19	118.18(4)
		C20–C21–C16	121.37(3)
		C20–C21–C13	129.90(3)
		C16–C21–C13	108.71(3)
		C2–O1–C1	117.47(3)
		C11–O3–C14	113.25(3)
		C12–O4–C15	123.17(4)
		C22–O6–C18	124.38(5)
		C19–O7–C23	116.99(5)
		C20–O8–C24	119.67(5)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	47(1)	55(1)	69(1)	4(1)	11(1)	−15(1)
C2	35(1)	44(1)	43(1)	−3(1)	5(1)	−2(1)
C3	35(1)	65(1)	59(1)	−4(1)	9(1)	−3(1)
C4	37(1)	70(1)	59(1)	−8(1)	6(1)	10(1)
C5	45(1)	54(1)	51(1)	−1(1)	−3(1)	10(1)
C6	40(1)	48(1)	48(1)	6(1)	1(1)	1(1)
C7	33(1)	43(1)	38(1)	−3(1)	5(1)	−2(1)
C8	32(1)	34(1)	42(1)	−1(1)	3(1)	−1(1)
C9	38(1)	36(1)	40(1)	4(1)	4(1)	−1(1)
C10	33(1)	47(1)	42(1)	−3(1)	4(1)	3(1)
C11	37(1)	37(1)	47(1)	−2(1)	2(1)	1(1)
C12	33(1)	36(1)	48(1)	4(1)	4(1)	0(1)
C13	35(1)	38(1)	36(1)	1(1)	4(1)	0(1)
C14	81(1)	50(1)	115(1)	−20(1)	32(1)	7(1)
C15	113(1)	42(1)	86(1)	10(1)	20(1)	−20(1)
C16	39(1)	34(1)	45(1)	0(1)	0(1)	1(1)
C17	54(1)	45(1)	55(1)	1(1)	−6(1)	8(1)
C18	47(1)	51(1)	76(1)	−14(1)	−8(1)	17(1)
C19	36(1)	53(1)	79(1)	−16(1)	6(1)	3(1)
C20	40(1)	48(1)	60(1)	−7(1)	11(1)	−3(1)
C21	32(1)	36(1)	46(1)	−2(1)	3(1)	−2(1)
C22	114(1)	77(1)	124(1)	−5(1)	−58(1)	29(1)
C23	63(1)	110(1)	132(1)	−8(1)	44(1)	−7(1)
C24	180(1)	159(1)	67(1)	−27(1)	1(1)	73(1)
O1	39(1)	47(1)	63(1)	5(1)	13(1)	−6(1)
O2	63(1)	60(1)	43(1)	−5(1)	10(1)	1(1)
O3	54(1)	39(1)	67(1)	−11(1)	10(1)	−5(1)
O4	61(1)	42(1)	55(1)	10(1)	12(1)	−7(1)
O5	46(1)	50(1)	39(1)	2(1)	2(1)	2(1)
O6	102(1)	100(1)	118(1)	−28(1)	−37(1)	67(1)
O7	45(1)	83(1)	117(1)	−32(1)	19(1)	11(1)
O8	68(1)	83(1)	69(1)	4(1)	33(1)	2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	5614	7855	1207	85	1
H1B	4910	8758	548	85	1
H1C	5405	7285	228	85	1
H3	6047	5254	1063	63	1
H4	6407	2635	1543	67	1
H5	5444	942	1999	62	1
H6	4108	1883	1979	55	1
H8	3470	5906	1657	44	1
H9	3066	5732	139	46	1
H14A	3421	362	−200	121	1
H14B	2943	−1330	−243	121	1
H14C	3479	−725	643	121	1
H15A	1755	−500	1542	120	1
H15B	2147	−948	2511	120	1
H15C	2699	−1033	1782	120	1
H17	1451	6911	−221	64	1
H22A	−313	8837	−645	173	1
H22B	−827	7475	−257	173	1
H22C	−46	6977	−663	173	1
H23A	−836	5697	1244	148	1
H23B	−991	6229	2171	148	1
H23C	−428	4689	2074	148	1
H24A	1651	6354	3473	207	1
H24B	1368	4798	3946	207	1
H24C	696	5907	3361	207	1
H5A	3357	3091	2918	68	1

Chapter 8 - References

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