BIOINSPIRED SYNTHESIS OF *ILLICIUM*-DERIVED NEOLIGNANS AND THEIR NEUROLOGICAL ACTIVITY

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Thesis submitted to the University of Nottingham for

the degree of Doctor of Philosophy

JUNE 2020

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Acknowledgements

I would like to thank Prof. Ross Denton for all the continued help and support he has provided over the course of my PhD. It has been an excellent experience to be a part of such a supportive, innovative, and social group and I would also like to thank all members, past and present, for their helpful inputs and discussions towards my research.

I am grateful to have met Dr Raquel Ribeiro at a pint of science talk which sparked a collaboration between the Denton group and Dajas-Bailador group.

I would like to thank the NMR spectroscopy staff, mass-spectroscopy team, and the crystallographers for their assistance and support.

Special thanks belong to the EPSRC and the University of Nottingham for financial support of this project.

Finally, I would like to thank my fiancée, Lydia Page, for all her encouragement, understanding and for giving me daily boosts of positive mentality.

Abstract

Illicium-derived neolignans present a wealth of structurally diverse species that arise initially from the oxidative phenolic coupling of common unit chavicol whereby it is proposed that intermediates can also undergo *oxa*-1,4-additions, oxidations, and dehydrating transformations. More recently, *Illicium*-derived neolignans have been tested for their neurological benefits in the promotion of growth and protection of developing neurons.

This thesis presents a bioinspired approach for the total synthesis of simonsol C, simonsol F (previously unnamed) and simonsol G (previously unnamed), as well as their respective biomimetic transformations to simonsinol, macranthol and honokiol *via* plausible hydroxydienone intermediates. From simonsol F, the total synthesis of fargenin, simonsol E, simonsin A and two further possibly over-looked natural products *epi*-simonsol E and *epi*-simonsin A are described. Studies towards the synthesis of two possible diastereoisomers of fargenone A, "bowl" and "ladder" are presented. Efforts have begun towards an enantioselective synthesis of simonsol F. *Illicium*-derived neolignans, intermediates from synthesis and purposefully modified derivatives have been tested in an SAR study on the promotion of axon growth of primary cultured mouse cortical neurons.

Abbreviations

Å	angstrom
°C	degrees Celsius
1,2-DCE	1,2-dichloroethane
Ac	acetyl
Ac	acetate
acac	acetylacetone
AChE	acetylcholinesterase
Ad	adamantane
AD-mix	asymmetric dihydroxylation mix
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	unspecified aromatic chemical group
b.pt.	boiling point
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
BMIDA	*N*-methylimidodiacetic boronic acid ester
bmim	1-Butyl-3-methylimidazolium
Bn	benzyl
brsm	based on recovered starting material
BuChE	butyrylcholinesterase
Bz	benzoyl
calcd.	calculated
cat.	catalyst
Ch	choline
cod	1,5-cyclooctadiene
Cp	cyclopentadiene
CSA	camphor-10-sulfonic acid

CuTc	copper(I) thiophene-2-carboxylate
cy	cyclohexane
d	doublet (NMR spectroscopy)
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
DAHP	3-deoxy-*D*-arabino-heptulosonate-7-phosphate
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublets (NMR spectroscopy)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DES	deep eutectic solvents
DETA	diethylenetriamine
DHQ	3-dehydroquinate
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,3-bis(diphenylphosphino)propane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dq	doublet of quartets (NMR spectroscopy)
dt	doublet of triplets (NMR spectroscopy)
DTBPY	4,4'-di-*tert*-butyl-2,2'-dipyridyl

e.e.	enantiomeric excess
e.r.	enantiomeric ratio
epi	epimer
EPSP	5-enolpyruvylshikimate-3-phosphate
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
FGI	functional group interconversion
g	gram(s)
h	hour(s)
HBcat	catecholborane
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisiloxane
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high resonance mass spectroscopy
HSCCC	high-speed counter-current chromatography
HSQC	heteronuclear single quantum correlation
Hz	hertz
IC_{50}	half maximal inhibitory concentration
ICcE	intermittent counter-current extraction
IPNBSH	*N*-isopropylidene-*N'*-2-nitrobenzenesulfonyl hydrazine
IR	infrared
J	coupling constant (NMR spectroscopy)
KHMDS	potassium bis(trimethylsilyl)amide
L.H.S.	left hand side
LC-MS	liquid chromatography - mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide

lit.	literature
L_n	ligand
m	multiplet (NMR spectroscopy); milli
m	meta (position)
m.p.	melting point
m/z	mass-to-charge ratio
m-CPBA	3-chloroperbenzoic acid
Me	methyl
MM	molecular mechanics
mM	millimol
mmol	millimolar
MOM	methoxymethyl
MS	mass spectrometry
n	nano
NAD(P)+	nicotinamide adenine dinucleotide phosphate
NAD^+	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinamide
NBSH	2-nitrobenzenesulfonyl hydrazide
NHC	*N*-heterocyclic carbenes
nM	nanomol
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
NPhth	phthalimide
N-PSP	*N*-phenylselenophthalimide
o	ortho (position)
p	pentet (NMR spectroscopy)

p	para (position)
Pd	palladium
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
pin	pinacolato
ppm	part(s) per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
p-TSA	*p*-toluenesulfonic acid
pyr.	pyridine
pyr.PTS	pyridinium p-toluenesulfonate
q	quartet (NMR spectroscopy)
QM	quantum mechanics
quant.	quantitative
R	unspecified chemical group
R.H.S.	right hand side
r.t.	room temperature
ref.	reference
s	singlet (NMR spectroscopy)
S.I.	supporting information
SAR	structure activity relationship
SEM	2-(trimethylsilyl)ethoxymethyl acetal
SET	single electron transfer
SM	starting material
Sphos	2-Dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
t	triplet (NMR spectroscopy)
TAL	tyrosine ammonia lyase
TBAF	tetrabutylammonium fluoride

TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
tBuOOH	*tert*-butyl hydroperoxide
td	triplet of doublets (NMR spectroscopy)
TEOC	2-(trimethylsilyl)ethoxycarbonyloxy
Tf	triflate
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
w/w	weight per unit weight
Xphos	xantphos
Xphos Pd G3	Xphos-Generation 3-Palladacycle (Buchwald pre-cat.)
Xphos Pd G4	Xphos-Generation 4-Palladacycle (Buchwald pre-cat.)
δ	chemical shift
μ	micro
μM	micromol
ν_{max}	absorption maximum

Contents

1: Introduction

1.1: Lignans and Neolignans

Lignans are a class of secondary metabolites that are found throughout the plant kingdom and are abundant in the genus *Illicium*. Lignans can be extracted from the roots, bark, stems, seeds, rhizomes, leaves and the fruit of the plants. A commonly known member of the genus *Illicium* is the anise, which includes star, swamp and purple anise. The genus is formed from over 70 plants with the other names being of Chinese origin or unnamed. These flowering plants are commonly found throughout Asia but also North America, south-eastern United States, the Caribbean, and Mexico.

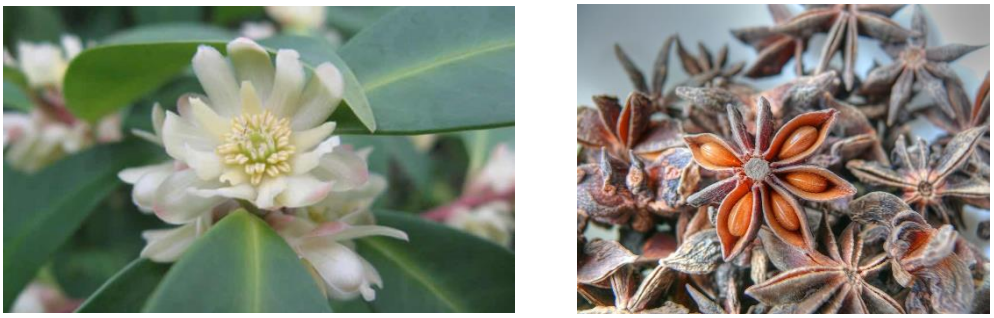


Figure 1. *Illicium simonsii*[1] *(L.H.S.) and Illicium verum (star anise) (R.H.S.).*[2]

All lignans are made up of phenylpropanoid subunits. Structural differences divide lignans into two main classes, classical lignans and neolignans, which differ by the position of oligomerisation in the C_6-C_3 unit (see Figure 2).[3,4] Classical lignans are linked in an 8-8’ fashion whereas neolignans are two or more phenylpropanoid units linked by any other position than 8-8’. Classical lignans are split further into 6

sub-classes and neolignans into 15 sub-classes due to their greater structural diversity. When naming compounds containing more than two C_6–C_3 units, additional nomenclature can be used, for example sesquineolignans contain three C_6–C_3 units.

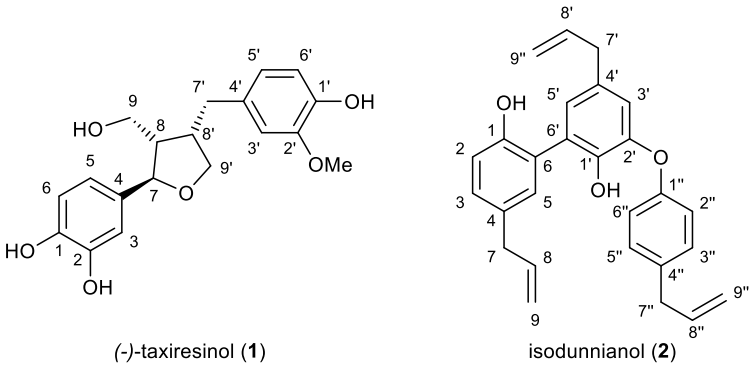


Figure 2. *Example of classical lignan ((-)-taxiresinol)*[5] *(**1**) joined by phenylpropanoid tail (8,8') and a sesqui-neolignan (isoduinnianol)*[6] *(**2**), an ortho,ortho-/ortho,O linked trimer.*

1.2: Biosynthesis of lignans and neolignans

Apart from uses in Chinese medicine, Shikimic acid (**3**) was isolated in 1885 by Eykman and co-workers who extracted this important species from the fruit of *Illicium religiosum*.[7,8] The first gram-scale extraction was reported in 1953 by Grewe and Lorenzen[9] using the ground seeds and carpels of *Illicium anisatum*. With the abundance of shikimic acid (**3**) and structurally diverse lignans found in the genus *Illicium*, it is reasonable to generalize the biosynthesis of classical lignans and neolignans from the shikimic acid pathway (see Schemes 1 to 3).[10] The shikimic acid pathway is absent in humans, which has consequently led to specific development of antimalarials,

antifungals, herbicides and antibacterial agents that act by inhibiting enzymatic activity along this pathway.[11,12]

Viral neuraminidase inhibitors prevent the reproduction by budding from the host cell. The most widely known success is the pro-drug oseltamivir phosphate (**4**) (marketed as Tamiflu) which is used to treat seasonal influenza and can be synthesized from shikimic acid in 20% yield over 9 synthesis steps.[13,14]

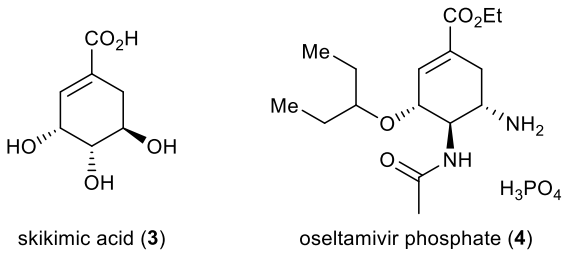
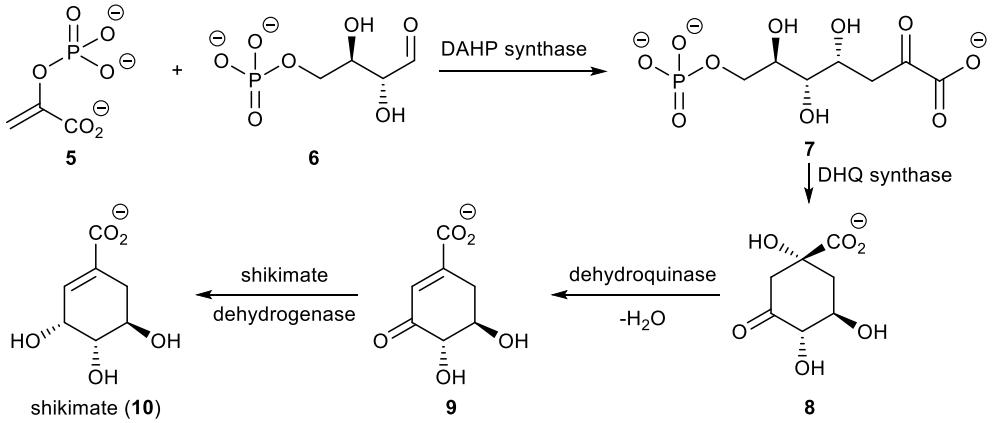


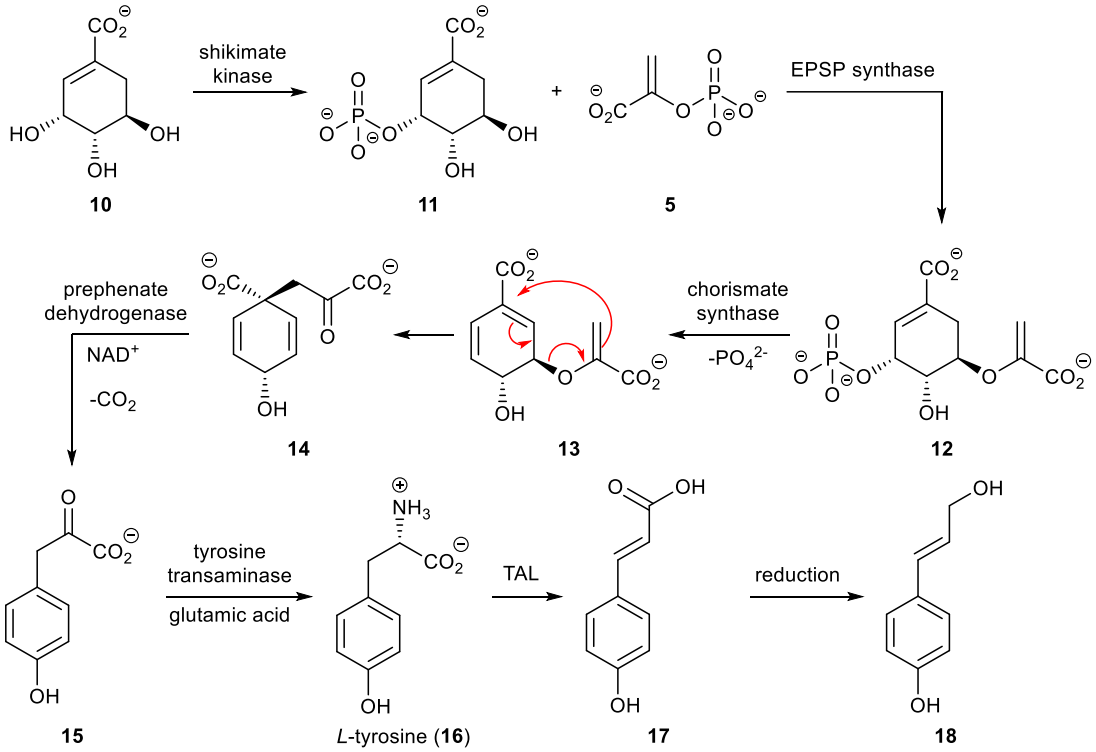
Figure 3. *Shikimic acid (**3**) and oseltamivir / Tamiflu (**4**).*

Enzymes DAHP synthase and DHQ synthase catalyse the production of 3-dehydroquinate (**8**) from precursors phosphoenolpyruvate (**5**) and D-*erythrose*-4-phosphate (**6**). DHQ dehydratase dehydrates **8** to form 3-dehydroshikimate (**9**) followed by a reduction by shikimate dehydrogenase forming shikimate (**10**).



Scheme 1. *Biosynthesis of shikimate (**10**)*

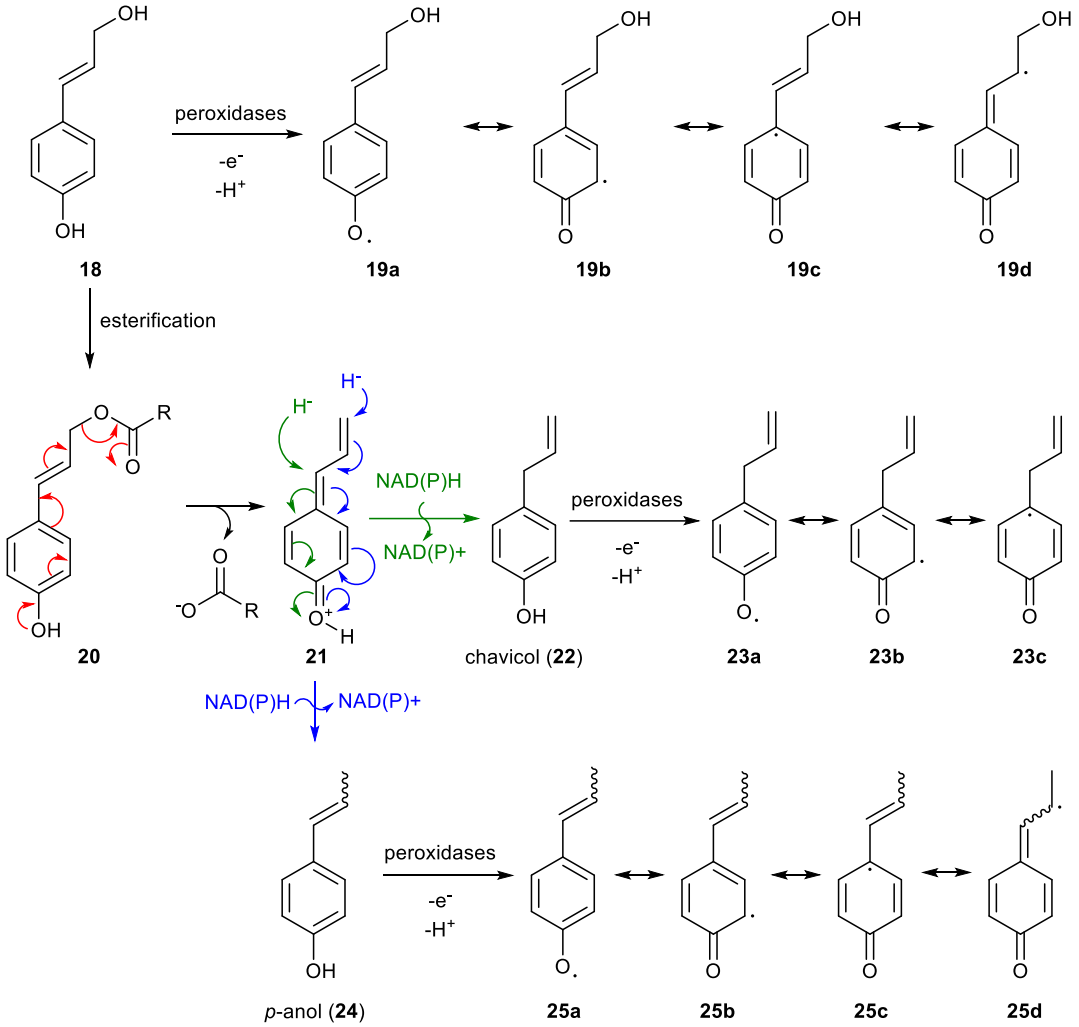
Shikimate (**10**) is transformed by shikimate kinase-mediated phosphorylation into **11**, which is subsequently coupled with phosphoenolpyruvate (**5**), catalysed by 5-enolpyruvylshikimate-3-phsophate (EPSP) synthase, to afford 5-enolpyruvylshikimate-3-phosphate (**12**). Chorismate synthase catalyses the transformation of **12** into chorismate (**13**) which then rearranges into prephenate (**14**). With retention of the hydroxyl group, **14** undergoes oxidative decarboxylation with prephenate dehydrogenase and NAD^+ affords *p*-hydroxyphenylpyruvate (**15**). Tyrosine transaminase and glutamic acid (as the nitrogen source) converts **15** into the amino-acid *L*-tyrosine (**16**) (see Scheme 2).



Scheme 2. *Biosynthesis of 4-hydroxycinnamyl alcohol (**18**) via shikimic acid pathway.*

L-tyrosine (**16**) is transformed into 4-coumaric acid (**17**) by cleavage of the amine group, catalysed by the enzyme tyrosine ammonia

lyase. Reduction of **17** affords 4-hydroxycinnamyl alcohol (**18**) which is believed to be a key building block in the biosynthesis of lignans and neolignans (see Schemes 2 and 3).[15,16]



Scheme 3. *Proposed biosynthesis and resonance structures of oxidative coupling partners for the synthesis of classical lignans or neolignans.* [15,16]

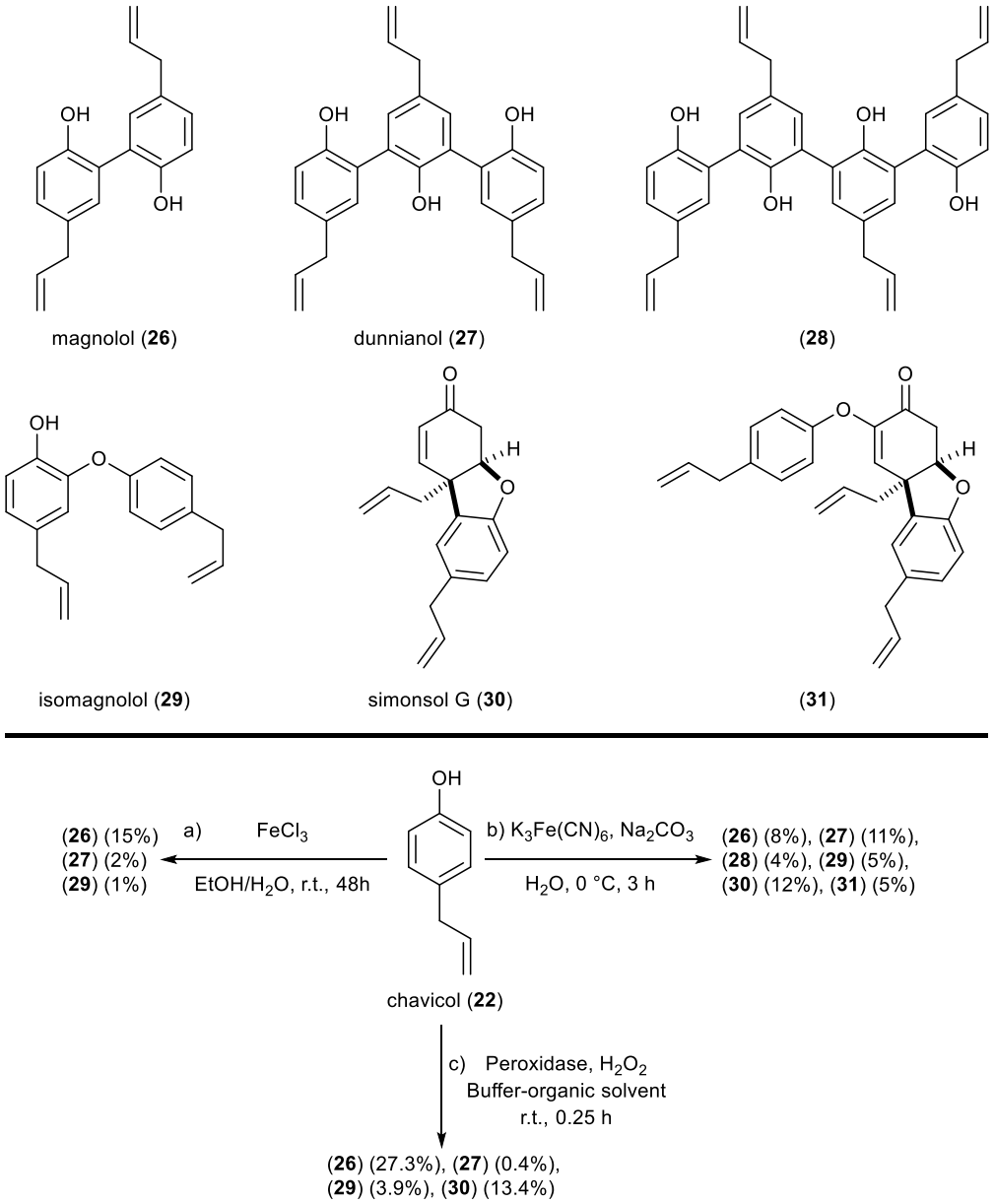
In 1972, Gottlieb proposed that **20**, **22** and **24** were the likely biological precursors to lignans.[15] In 2006, i*n vivo* studies conducted by Lewis *et al.*[16] indicated that 4-hydroxycinnamyl alcohol (**18**) can be esterified to *p*-coumaryl ester **20** which can subsequently decompose to dienone **21**. Reduction by NAD(P)H at the

trisubstituted alkene (coloured green Scheme 3) reforms the phenol and yields the terminal alkene giving chavicol (**22**). If reduction by NAD(P)H occurs at the terminal alkene (coloured blue Scheme 3), then *p*-anol (**24**) is formed with the allylic alkene in conjugation with the phenolic ring. One electron oxidation of **18** or **22** or **24** affords a range of free radical species that can give rise to the wealth of structurally diverse lignans and neolignans (see Scheme 3).

1.3: Biomimetic synthesis and extraction of structurally related bioactive neolignans

Oxidative phenolic coupling is a well-established process in the biosynthesis of secondary plant metabolites.[17,18] In 1972, Gottlieb hypothesized the biosynthetic pathway to an array of neolignans and classical lignans was *via* oxidative coupling reactions.[15] Previous to this proposal, in 1957, Erdtman and Runeberg treated chavicol (**22**) with $FeCl_3$ and isolated the oxidatively coupled species magnolol (**26**).[19] In 1985, Ho *et al.* also demonstrated that oxidative coupling of chavicol (**22**) was possible to yield the neolignan magnolol (**26**).[20] Inspired by these findings, Brown and co-workers[21] (in 1998) as well as Liu and co-workers[22] (in 2004) attempted to exploit the phenolic radical coupling of chavicol (**22**) in order to access neolignans of biological interest. Brown and co-workers treated chavicol with Fe^{III} reagents, a method previously employed by Erdtman and Runeberg,[19,23] whereas Liu *et al*. treated chavicol with peroxidase

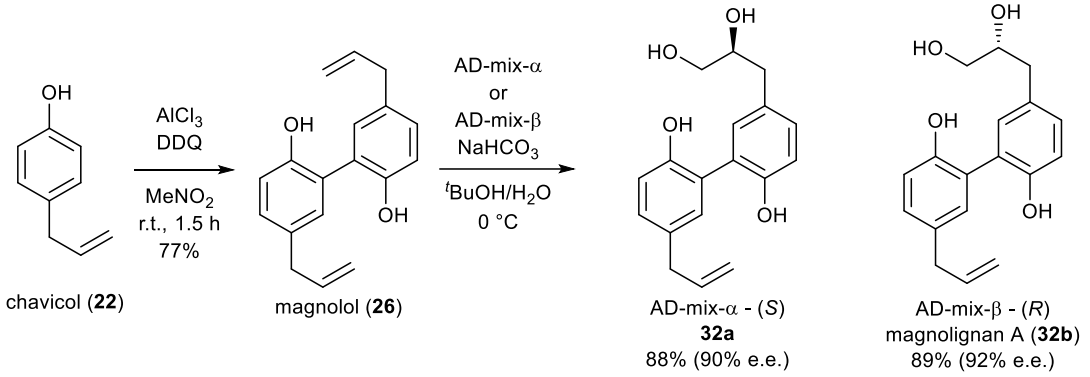
enzymes (from horseradish). Both conditions lead to the production of numerous natural products but, as expected, with little selectivity. The peroxidase enzyme was slightly more selective in providing magnolol (**26**) compared to the Fe^{III} systems (see Scheme 4).



Scheme 4. *Neolignans produced through oxidative coupling experiments by a,b) Brown and co-workers; c) Liu and co-workers.*

In 1998, Pan and co-workers determined the absolute stereochemistry of magnolignan A (**32b**) by the synthesis of both

enantiomers.[24,25] The synthesis featured a selective *ortho,ortho* oxidative phenolic coupling of chavicol (**22**) to form magnolol (**26**) in 77% yield (see Scheme 5). Subsequent Sharpless asymmetric dihydroxylation steps provided (*S*)- and (*R*)-enantiomers which were then compared against natural magnolignan A (**32b**).



Scheme 5. *Selective oxidative phenolic coupling of chavicol (**22**) to magnolol (**26**) in the synthesis and structural assignment of magnolignan A (**32b**).*[24]

Although magnolol (**26**) and honokiol (**33**) are the main constituents of the ethanolic extract of *Magnoliae officinalis* cortex,[26,27] they were once very expensive to purchase due to the difficulty associated with their separation. A range of assays were first developed to identify and quantify magnolol (**26**) and honokiol (**33**) in plant biomass extracts.[28–31] Table 1 contains a representative summary of the methods developed to separate magnolol (**26**) and honokiol (**33**) on a preparative scale, either from plant extract or from commercial sources.

In 2000, Bae and co-workers reported that successive column chromatography could be applied to the ethanolic extracts of *Magnolia obovata* (1.5 Kg dried stem bark gave 120 g extract) to

obtain magnolol (**26**) (1.6 g) and honokiol (**33**) (0.2 g).[32] In 2004, Zheng and co-workers used high-speed counter-current chromatography (HSCCC) on 150 mg of an approximate 90% purity mixture of magnolol (**26**) and honokiol (**33**) which separated them in >80% combined yield.[33] In 2007, Chen and co-workers progressed this method to high-capacity HSCCC.[34] They chromatographed 43.0 g of an approximate 80% purity mixture which separated magnolol (**26**) and honokiol (**33**) in >95% combined yield. In 2010, Chen and co-workers later used intermittent counter-current extraction (ICcE) which had a higher throughput than HSCCC methods. ICcE separated the constitutional isomers in excellent yield, however lower purities were obtained.[35] In 2011, Jin and co-workers reported the separation of magnolol (**26**) from an extract of *Magnoliae officinalis* cortex by selective clathration.[36] Magnolol (**26**) selectively formed a complex with DETA which crystallised out of solution. The DETA could be removed by acid hydrolysis to give magnolol (**26**). This method was not used for the isolation of honokiol (**33**).

Of particular note for its simplicity, in 2006 Schinazi *et al.* reported an acetal derivatisation strategy that selectively modified magnolol (**26**) to facilitate separation from honokiol (**33**) by conventional column chromatography (see Scheme 6).[37] This method was applied to a commercial mixture of magnolol (**26**), honokiol (**33**) and other unknown compounds (8.0 g, 33:58:9 respective mixture determined by HPLC analysis). After acetal formation, flash column

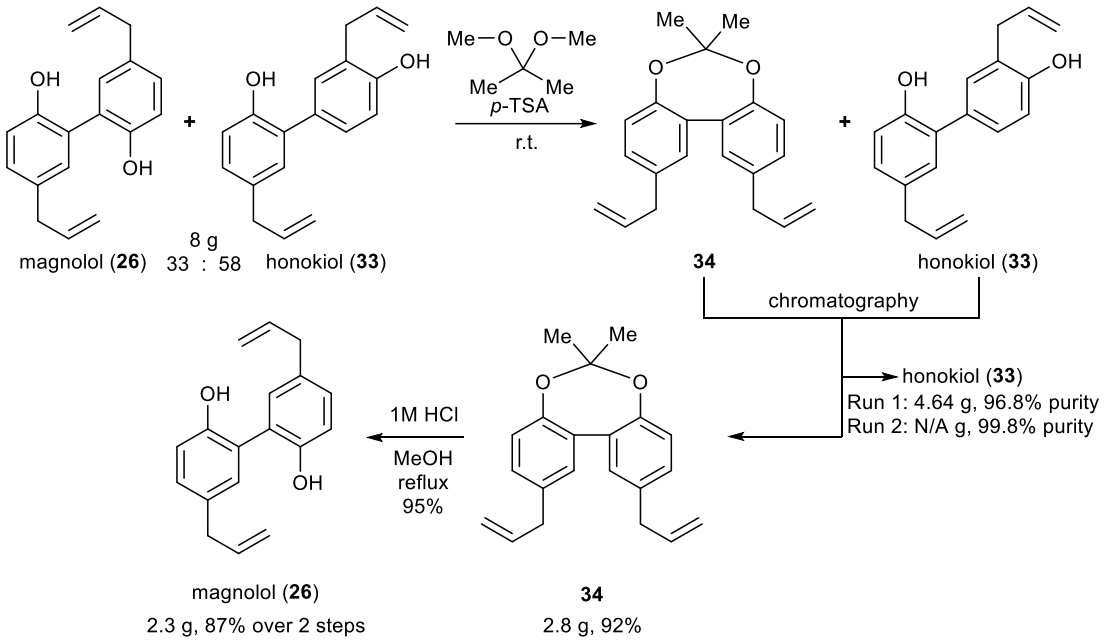
chromatography provided **34** (2.8 g, 92% yield based on HPLC ratio) and honokiol (**33**) (96.8% purity by HPLC, 4.64 g, 97% yield based on HPLC ratio). The 3.2% impurity associated with the isolation of honokiol (**33**) was magnolol (**26**). Therefore, honokiol (**33**) (96.8% purity by HPLC, 4.64 g) was re-subjected to the acetal formation conditions which after flash column chromatography gave honokiol (**33**) (99.8% purity by HPLC, no mass/yield given). Subsequent acid hydrolysis of **34** gave magnolol (**26**) (99.8% purity by HPLC, 2.3 g, 87% yield over 2 steps from starting mixture based on HPLC ratio).

Purification Method	Crude mixture[a]	Magnolol (26)			Honokiol (33)		
	(Magnolol:Honokiol)	Y (%)	Mass	P (%)[d]	Y (%)	Mass	P (%)[d]
column chromatography[32]	120 g (plant extract)[b]	N/A[b]	1.6 g	N/A[b]	N/A[b]	0.2 g	N/A[b]
HSCCC[33]	150 mg (~90% mixture)	>80	45 mg	98.2	>80	80 mg	99.2
high-capacity HSCCC[34]	43.0 g (~80% mixture)	>95	19.4 g	99.9	>95	16.9 g	98.4
ICcE[35]	30.0 g (55.2:44.5)	96[c]	16.1 g	98.6	90[c]	12.8 g	93.7
clathration[36]	10.0 g (45.7:49.1)	76[c]	3.54 g	98.1	N/A[b]	N/A[b]	N/A[b]
acetal derivatisation[37]	8.0 g (33:58)	87[c]	2.3 g	99.8	97[c]	4.64 g	96.8[e]

Table 1. *Summary of methods for the preparative scale separation of magnolol (**26**) from honokiol (**33**). HSCCC = high-speed counter-current chromatography. ICcE = intermittent counter-current extraction. P = purity. Y = yield. a) approximate % purity given from commercial source. Ratio given based on prior HPLC analysis. Unknown compounds present in all mixtures. b) Not given or not applicable. c)* $\frac{(Mass\ x\ (0.01\ x\ P)}{(Crude\ mixture\ mass\ x\ (0.01\ x\ HPLC\ ratio\ value))}$*. d) Determined by HPLC analysis. e) 99.8% purity obtained after re-subjection of material to purification method.*

Unfortunately, other neolignans of biological interest cannot be isolated in large quantities from plant matter, nor can they be as

successfully formed *via* oxidative couplings of chavicol (**22**) with high selectivity. These factors have provided a stimulus for synthetic chemistry groups, including the Denton group, to develop routes to natural and non-natural *Illicium*-derived neolignans.

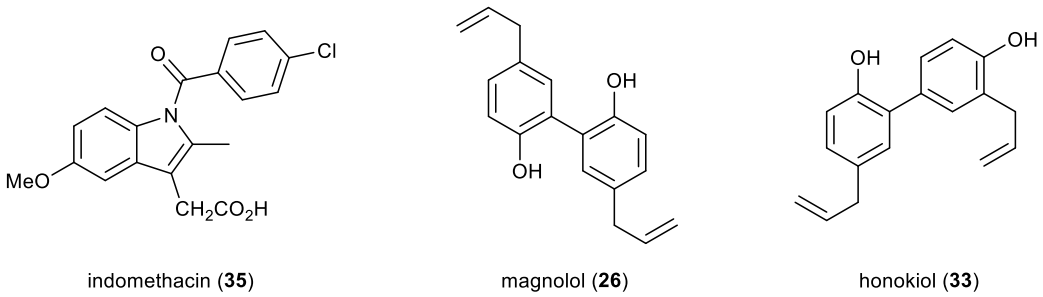


Scheme 6. *Derivatization and separation strategy of magnolol (**26**) and honokiol (**33**). Yields based on starting mixture ratio determined by HPLC analysis.*

1.4.1: General biological activity of *Illicium*-derived neolignans

Dating back to early Asian medicine, neolignans have been found to have medicinal benefits. With a wealth of structurally diverse species isolated from the genus *Illicium*, it is unsurprising that a lot of the species have been tested and have been found to be biologically active. Honokiol (**33**) and magnolol (**26**) are by far the most

investigated neolignans, due to their high natural abundance, early isolation, and simple structures. Both have exhibited anti-oxidative, anti-anxiety, anti-malarial, anti-cancer/tumour, anti-viral, anti-inflammatory and many more biologically desirable properties.[38–47,48] Magnolol (**26**) is reported to have similar *in vitro* potency to indomethacin (**35**),[40] an approved anti-inflammatory medication (see Figure 4). Multiple SAR studies on magnolol (**26**) and honokiol (**33**) have shown a requirement for at least one free hydroxyl group in order to observe biologically relevant activity in assays at low concentrations.[49–51]



indomethacin (**35**) magnolol (**26**) honokiol (**33**)

Figure 4. *Indomethacin (**35**), magnolol (**26**) and honokiol (**33**).*

1.4.2: Neurotrophic activity of neolignans from the genus *Illicium*

More recently, attention has been focused on the potential of neolignan natural products (and non-natural derivatives)[51] to slow the progression of neurodegenerative diseases. For example, by inhibition of acetylcholinesterase (AChE), by promotion of neurite outgrowth or by other pathways that result in neuroprotective effects.

A neurite is an immature or developing neuron. Growth of a neurite is measured as any projection from the cell body of a neuron, which can be the axon and dendrite (see Figure 5).

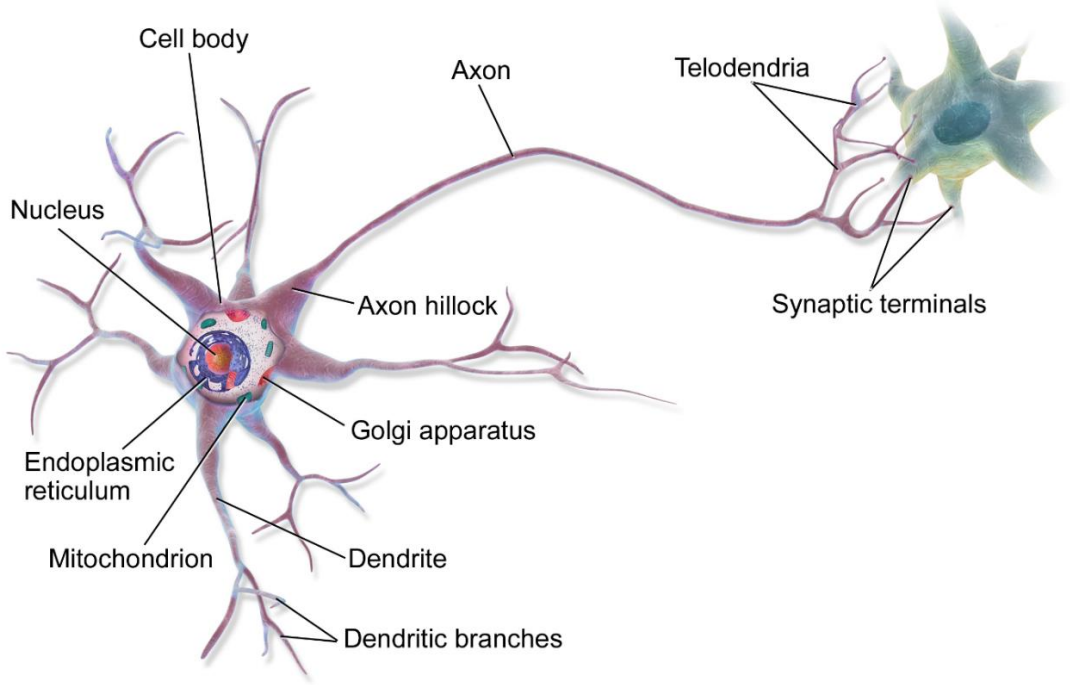


Figure 5. *A multipolar neuron – possess a single axon and many dendrites for high integration and information transfer from and to other neurons.*[52]

Nearly all (endogenous or exogenous) neurotrophic factors – compounds that are known to promote neurite outgrowth, and repair damaged neurons – are peptides or small proteins. Exogenous neurotrophic factors (based on peptides or small proteins) may be too large to pass through the blood-brain barrier and must instead be injected into the cerebrospinal fluid.[53] Therefore, neurotrophic small molecules present interesting alternatives as they are more likely to pass the blood-brain barrier.

In the brain, acetylcholine functions as a neurotransmitter and as a neuromodulator. AChE converts acetylcholine into choline and acetic acid, thus allowing activated cholinergic neurons to return to their resting state. If AChE is overactive, it can lead to a lack of synaptic transmission, the process by which our brain cells "communicate" *via* the axon terminal of a neuron and the receptors of the dendrites of another neuron a short distance away.[54] Therefore, reversible inhibitors of AChE (and butyrylcholinesterase (BuChE), a non-specific cholinesterase) are attractive targets to slow down the rate of degeneration in neurodegenerative diseases.

A neuroprotective compound is one that protects neurons from injury or degeneration. One of the most common mechanisms of neuroprotection is to alleviate oxidative stress. Reactive oxygen species (such as superoxide ($O_2^{\bullet-}$), nitric oxide ($NO^{\bullet}$), hydroxyl radical ($OH^{\bullet}$), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$)) are highly toxic to cells. They can be found post-mortem in brain tissue derived from sufferers of neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease.[54]

Several neolignans of structural interest have documented neurotrophic activity and what follows is a summary of their isolation, neurotrophic activity, and synthesis. For the purpose of clarity, the following compounds have been split into 5 categories based on structural similarity or relevance to this thesis (see Tables 2 to 6).

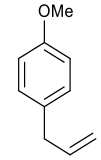
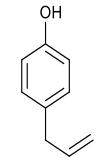
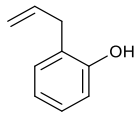
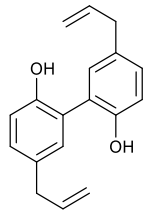
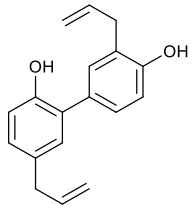
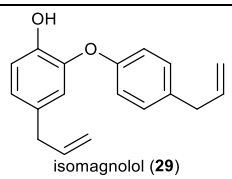
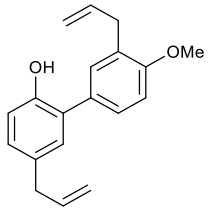
 estragole (**36**)	**Isolation:** *Ravensara anisate, Ocimum basilicum, Croton zehntneri*.[55] Further sources.[57] **Activity:** Blocks neuronal excitability by direct inhibition of Na^+ channels at 4 mM.[55] **Synthesis:** Extracted from essential oils.[55,56]
 chavicol (**22**)	**Isolation:** *Piper betle* in 1889.[57,58] **Activity:** Toxic to rat cortical neurons at 1 μM.[51] **Synthesis:** Synthesized from commercial sources.[59,60]
 2-allylphenol (**37**)	**Isolation:** marine bacterium in 2010.[61] **Activity:** Toxic to rat cortical neurons at 1 μM.[51] **Synthesis:** Synthesized from commercial sources.[62,63]
 magnolol (**26**)	**Isolation:** *Magnolia obovata* in 1930.[64,65] **Activity:** 48% growth increase of embryonic hippocampal neurons at 10 nM.[66,67] 56% growth increase of embryonic cortical neurons at 100 nM.[66,67] **Synthesis:** Runeberg and Erdtman 1957,[19] Runeberg 1958,[23] LeBel *et al.* 1995,[68] Pan *et al.* 1998,[24] Brown *et al*. 1998,[21] Liu *et al*. 2004,[22]Denton *et al.* 2012.[69]
 honokiol (**33**)	**Isolation:** *Magnolia obovata* in 1972.[46] **Activity:** Promotion of neurite outgrowth of fetal rat cortical neurons as well as aid to neuronal survival at 10 μM.[70] Promotion of neurite outgrowth of rat cortical neurons at 0.1 μM and 1.0 μM.[51] **Synthesis:** Tobinaga *et al*. 1986,[71] Fukuyama *et al.* 2004,[51] Liu *et al.* 2009,[72] Denton *et al.* 2010,[73] Chen *et al*. 2012,[74] Fukuyama *et al.* 2014,[75] Kumar *et al*. 2014,[76] Subba Reddy *et al*. 2014,[77] O'Neil and Wright 2016.[78]
 isomagnolol (**29**)	**Isolation:** S*assafras randaiense* in 1983.[79] **Activity:** None reported. **Synthesis:** Brown *et al*. 1998,[21] Liu *et al*. 2004.[22]
 4-*O*-methylhonokiol (**38**)	**Isolation:** *Magnolia grandiflora L.* in 1978.[80,81] **Activity:** Inhibits AChE activity *in vitro* with IC_{50} at 12 nM.[82,83] No effect on the promotion of neurite outgrowth on primary cultured rat cortical neurons at 0.1–1.0 μM.[51] **Synthesis:** Fukuyama *et* al. 2004,[51] Jung *et al.* 2011,[59] Denton *et al*. 2011,[84] Amin *et al*. 2012.[85]

Table 2. *Isolation, neurotrophic activity, and total synthesis of monoaryl species and biaryl neolignans.*

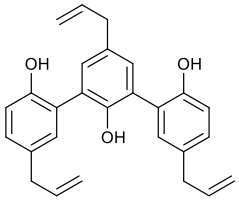
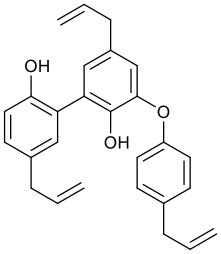
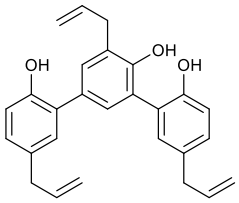
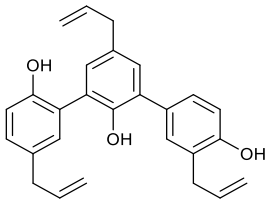
 dunnianol (**27**)	**Isolation:** *Illicium dunnianum* in 1991.[6] **Activity:** No anti-AChE activity <100 μM.[86] **Synthesis:** Brown *et al*. 1998,[21] Liu *et al*. 2004,[22] Denton *et al.* 2010.[87]
 isodunnianol (**2**)	**Isolation:** *Illicium dunnianum* in 1991.[6] **Activity:** Anti-AChE activity with an IC_{50} of 13.0 μM.[86] Promotion of neurite outgrowth of cultured rat cortical neurons between 0.1–10 μM.[88] **Synthesis:** None reported.
 macranthol (**39**)	**Isolation:** *Illicium macranthum* in 1989.[89] **Activity:** Neuroprotective activity of rat foetus cortical neurons between 5–10 μM.[90] No effect on the morphology of rat cortical neurons cultured in Neurobasal medium supplemented with B-27 at 10 μM.[90] No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1–10 μM.[88] **Synthesis:** Denton *et al*. 2016.[91]
 simonsinol (**40**)	**Isolation:** *Illicium simonsii* in 1994.[92] **Activity:** None reported. **Synthesis:** None reported.

Table 3. *Isolation, neurotrophic activity, and total synthesis of triaryl neolignans.*

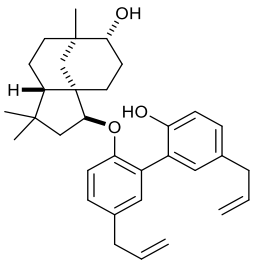
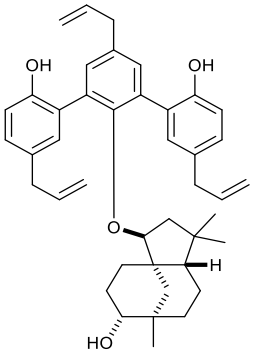
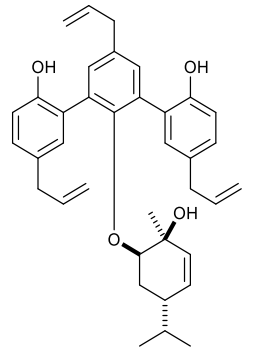
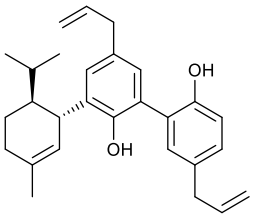
 clovanemagnolol (**41**)	**Isolation:** *Magnolia obvata* in 1990.[93,94] **Activity:** Accelerates neurite sprouting and increases choline acetyltransferase activity between 0.1-10 μM.[82] 63% growth increase of embryonic hippocampal neurons at 10 nM.[66,67] 44% growth increase of embryonic cortical neurons at 10 nM.[66,67] *In vivo* study on worms (*C. elegans*) displayed axonal branching in 35% of all worms treated.[95] **Synthesis:** Siegel *et al.* 2010.[96]
 clovanedunnianol (**42**)	**Isolation:** *Illicium simonsii* in 2013.[97] **Activity:** Anti-AChE activity IC_{50} value of 4.58 μM.[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.
 *p*-menthadunnianol (**43**)	**Isolation:** *Illicium simonsii* in 2013.[97] **Activity:** Anti-AChE activity IC_{50} value of 6.55 μM.[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.
 monoterpenylmagnolol (**44**) piperitylmagnolol (**44**)	Isolated twice in 1991 and given two different names: **Isolation:** Monoterpenylmagnolol (**44**) from *Magnolia officinalis* in 1991[98] **Isolation:** Piperitylmagnolol (**44**) from *Magnoliae cortex* in 1991.[25] **Activity:** None reported. **Synthesis:** LeBel *et* al. 1995,[68] Kobayashi *et al*. 2016.[99]

Table 4. *Isolation, neurotrophic activity, and total synthesis of terpene-neolignans. This thesis does not focus on the synthesis of these neolignans.*

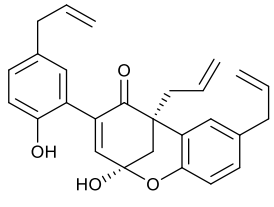
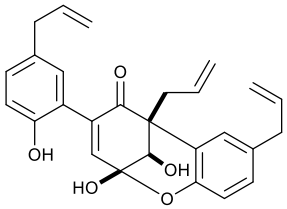
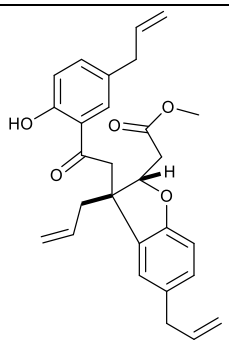
 simonsol A (**45**) simonol A (**45**)	**Isolation:** Simonsol A (**45**) from *Illicium simonsii* in 2013.[97] **Isolation:** Simonol A (**45**) from *Illicium simonsii* in 2013.[100] **Activity:** No anti-AChE activity (i.e. no inhibition <100 μM).[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.
 simonsol B (**46**)	**Isolation:** *Illicium simonsii* in 2013.[97] **Activity:** No anti-AChE activity (i.e. no inhibition <100 μM).[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.
 simonsol D (**47**)	**Isolation:** *Illicium simonsii* in 2013.[97] **Activity:** No anti-AChE activity (i.e. no inhibition <100 μM).[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.

Table 5. *Isolation, neurotrophic activity, and total synthesis of neolignans that were isolated from Illicium simonsii. This thesis does not focus on the synthesis of these neolignans.*

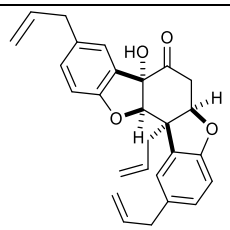
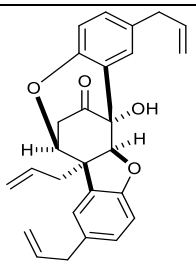
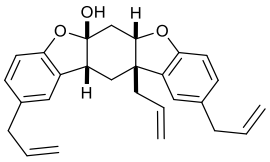
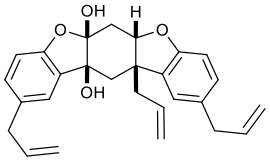
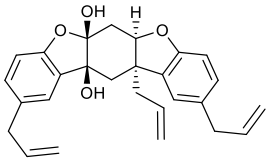
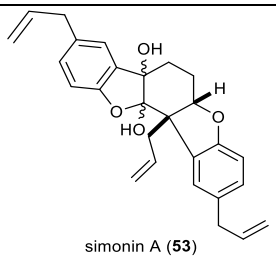
 fargenone A (**48**)	**Isolation:** *Illicium fargesii* in 2007.[88] **Activity** No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1–10 μM.[88] **Synthesis:** None reported.
 fargenone B (**49**)	**Isolation:** *Illicium fargesii* in 2007.[88] **Activity** No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1–10 μM.[88] **Synthesis:** None reported.
 simonsin A (**50**)	**Isolation:** *Illicium simonsii* in 2013.[97] **Activity:** No anti-AChE activity (i.e. no inhibition <100 μM).[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.
 simonsin B (**51**)	**Isolation:** *Ilicium simonsii* in 2013.[97] **Activity:** No anti-AChE activity (i.e. no inhibition <100 μM).[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.
 simonol B (**52**)	**Isolation:** *Illicium simonsii* in 2013.[100] **Activity:** None reported. **Synthesis:** None reported.
 simonin A (**53**)	**Isolation:** *Illicium simonsii* in 2010.[47] Stereochemistry of diol not assigned.[47] **Activity:** None reported. **Synthesis:** None reported.

Table 6. *Isolation, neurotrophic activity, and total synthesis of neolignans containing a hydrodibenzofuran core.*

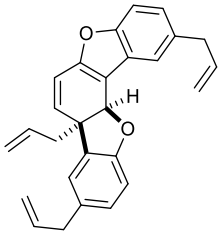
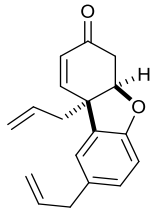
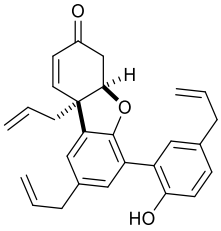
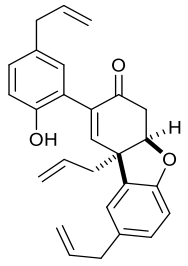
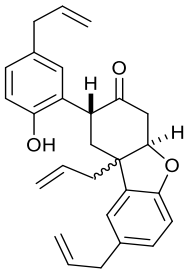
 fargenin (**54**)	**Isolation:** *Illicium fargesii* in 2007.[88] **Activity** No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1–10 μM.[88] **Synthesis:** None reported.
 simonsol G (**30**) (previously un-named)	**Isolation:** *Magnolia grandiflora* in 2017.[101] Previously unnamed but for the clarity of this thesis, it is simonsol G (**30**). **Activity:** None reported. **Synthesis:** Brown *et al*. 1998,[21] Liu *et al*. 2004,[22]Studies towards by Denton and Scragg, 2012.[102]
 simonsol C (**55**)	**Isolation:** *Illicium simonsii* in 2013.[97] **Activity:** No anti-AChE activity (i.e. no inhibition <100 μM).[97] No anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** Banwell *et al*. 2016.[103]
 simonsol F (**56**) (previously un-named)	**Isolation:** *Illicium dunnianum* in 1996.[104,105] Previously unnamed but for the clarity of this thesis, it is simonsol F (**56**). **Activity:** None reported. **Synthesis:** None reported.
 simonsol E (**57**)	**Isolation:** *Illiicum simonsii* in 2013.[97] Full stereochemistry at ring-junction not assigned.[97] **Activity:** The inseparable mixture displayed anti-AChE activity, IC_{50} value of 10.34 μM.[97] The inseparable mixture displayed no anti-BuChE activity (i.e. no inhibition <50 μM).[97] **Synthesis:** None reported.

Table 6. *Isolation, neurotrophic activity, and total synthesis of neolignans containing a hydrodibenzofuran core. The stereochemical assignment of simonsol E (**57**) is as depicted by the authors.*[97]

Of particular interest are several neolignans whose biological activity is yet to be explored but which have a close structural resemblance to existing neuroprotective compounds. Simonsol C (**55**), simonsol E (**57**) and simonsol F (**56**) contain a hydrodibenzofuran core moiety which can also be found in the clinically used Alzheimer's medication (-)-galanthamine (**58**) (see Figure 6).

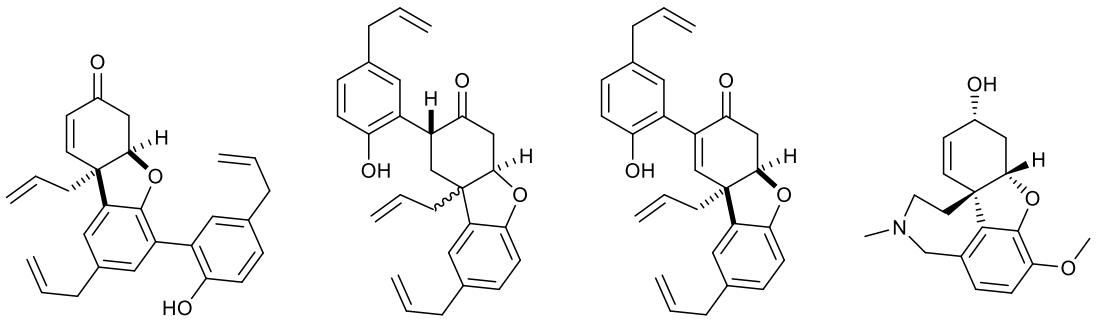


Figure 6. *Simonsol C (**55**), simonsol E (**57**), simonsol F (**56**) and (-)-galanthamine (**58**). The stereochemical assignment of simonsol E (**57**) is as depicted by the authors.*[97]

1.5: Biosynthetic speculation on neolignans containing a hydrodibenzofuran core

It is believed, due to its natural abundance, and biomimetic experiments,[19,21–24] that neolignans from the genus *Illicium* originate from a common repeating unit, chavicol (**22**). Through the combination of oxidative phenolic coupling, *oxa*-1,4-additions, oxidations and dehydrations, a wide range of simple dimers and trimers to more complex ring systems arise from chavicol (**22**). Tetrameric natural products have not been isolated (to date), but have been obtained from biomimetic synthesis experiments.[21]

Magnolol (**26**) is likely to arise from *ortho*,*ortho*-selective oxidative phenolic coupling of chavicol (**22**).[19,21–24] A third oxidative phenolic coupling in an *ortho para* fashion can yield one of two hydroxydienones, hydroxydienone A **59** or hydroxydienone B **60** (see Scheme 7). An alternative oxidative phenolic coupling of magnolol (**26**) in an *ortho*,*ortho* fashion would afford dunnianol (**27**).

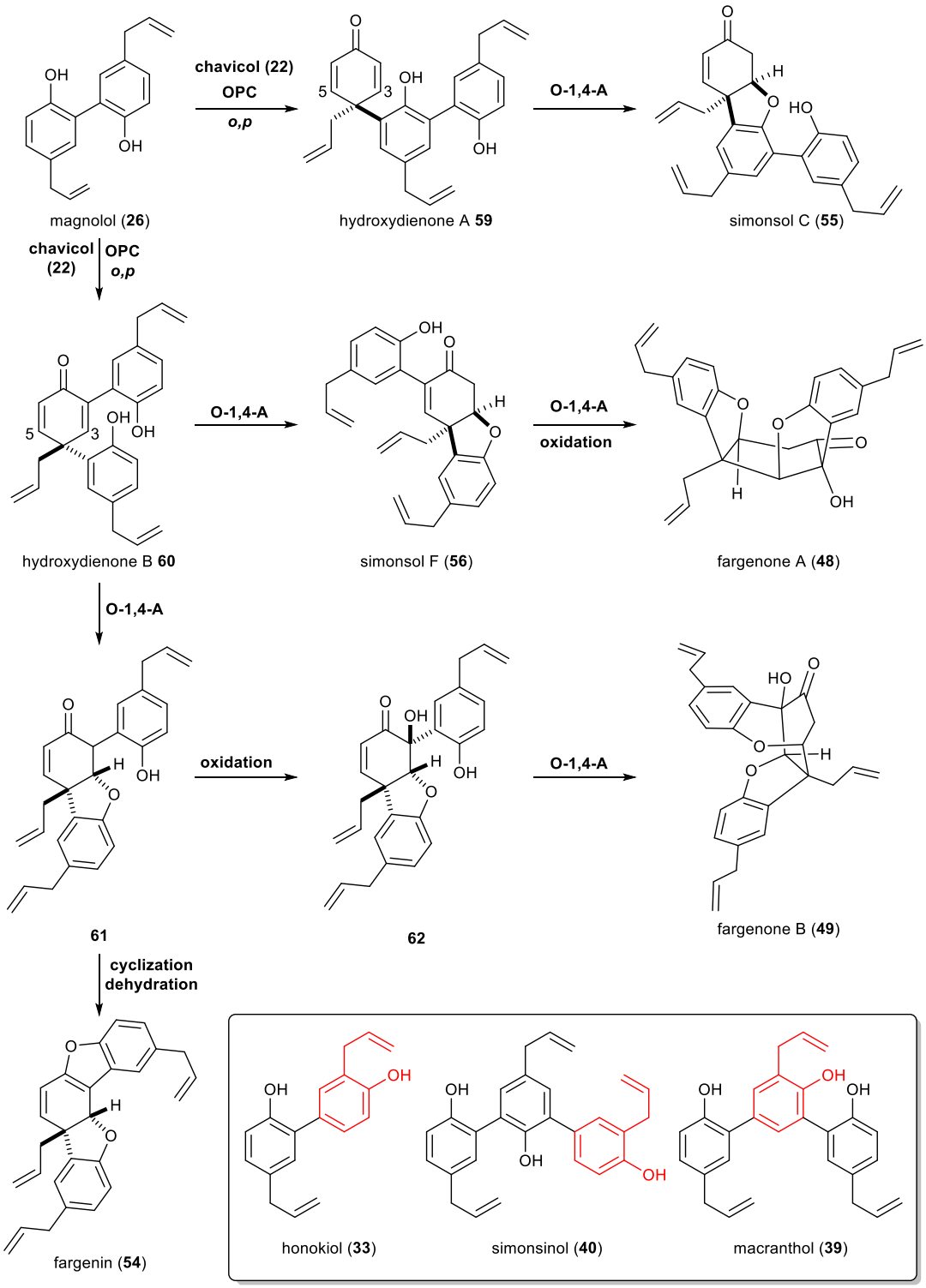
Fukuyama *et al*.[88] proposed biosynthesis pathways for fargenin (**54**), fargenone A (**48**) and fargenone B (**49**) from hydroxydienone B **60**, which can undergo two different *oxa*-1,4-addition reactions to establish the characteristic [4.3.0] ring system. O*xa*-1,4-addition of **60** at C3 gives species **61**, which can then undergo either a dehydrative cyclisation to generate fargenin (**54**), or an oxidation followed by a second *oxa*-1,4-addition to generate fargenone B (**49**) (see Scheme 7). Alternatively, *oxa*-1,4-addition of hydroxydienone B **60** at C5 gives simonsol F (**56**) which can undergo another *oxa*-1,4-addition and oxidation to afford fargenone A (**48**).

After analysis of NMR spectroscopy data, predominantly NOESY, Fukuyama *et al*. reported that fargenone A (**48**) has the stereochemical configuration designated as "bowl" fargenone A (**48a**).[88] The indicated NOE interactions (see Scheme 8, purple double-headed arrows) were key in supporting the stereochemical assignment. However, this assignment is incongruous with the proposed biosynthesis as the likely stereochemical outcome of the

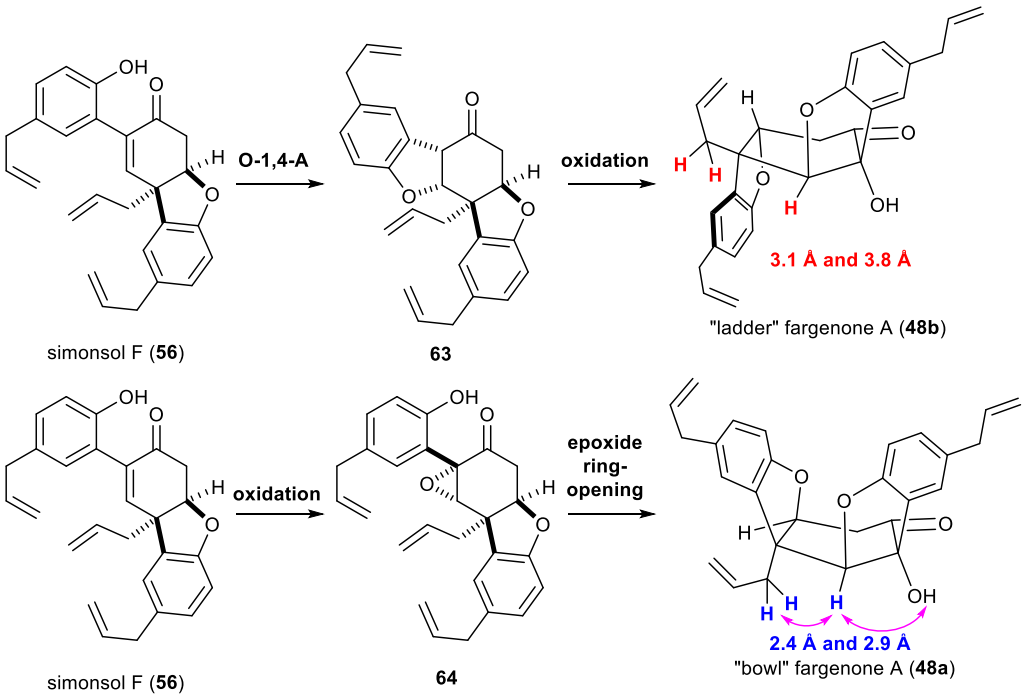
oxa-1,4-addition would occur on the convex face to provide intermediate **63**. Subsequent oxidation would result in the opposite stereochemistry and give fargenone A "ladder" (**48b**).

It is my belief that if the order is reversed and oxidation occurs first, for example an epoxidation to give **64**, then intramolecular ring-opening would lead to "bowl" fargenone A (**48a**) (see Scheme 8). Furthermore, based on simple molecular mechanics calculations, it is likely that a similar NOE interaction would also be possible between the protons highlighted red in "ladder" fargenone A (**48b**) (see Scheme 8). To resolve this stereochemical discrepancy, total synthesis of both "ladder" and "bowl" diastereoisomers is necessary.

Highlighted in scheme 7 (bottom-right) are the structures of honokiol (**33**) simonsinol (**40**) and macranthol (**39**). The three natural products appear to be derived from chavicol (**22**) and a second phenolic monomer, 2-allylphenol (**37**). In the plant, oxidative phenolic coupling is a likely process that occurs, however the presence of both 4-allylphenol (**22**) and 2-allylphenol (**37**) radicals coupling in a manner that would form only these three isolated neolignans is highly unlikely. Given the reactive nature of these species and that 2-allylphenol (**37**) has never been isolated (to date) from any extraction of plant material from the genus *Illicium*, their biosynthesis solely by oxidative phenolic coupling is doubtful and a plausible biosynthetic route is discussed later (see section 2.2.1).



Scheme 7. *Speculated biosynthetic pathway to neolignans and highlighting the anomalous structures of honokiol (**33**) simonsinol (**40**) and macranthol (**39**). OPC = oxidative phenolic coupling, O-1,4-A = oxa-1,4-addition o = ortho, p = para.*



Scheme 8. *Alternative biosynthetic proposals, dependent when oxidation occurred, to either "bowl" fargenone A (**48a**) or "ladder" fargenone A (**48b**). Distances shown between coloured protons have been calculated from molecular mechanics derived structures.*[106] *Double-headed purple arrow are the "key" NOE interactions observed by Fukuyama and co-workers.*[88]

1.6.1: Previous syntheses of neolignans in the fargenin/fargenone and simonsol family

This thesis has focused on the synthesis of neolignans containing a hydrodibenzofuran core, specifically a tetrahydrodibenzofuran core (see Tables **6a** and **6b**). This section will cover previous syntheses of *Illicium* derived neolignans with the characteristic [4.3.0] ring system, however the reported syntheses do not highlight the difficulties associated with maintaining the integral position of the allyl group olefin. The terminal olefin of aromatic allyl groups is very

prone to isomerisation to the conjugated thermodynamic position, especially in the presence of strong base and co-ordinating transition metals (used in cross-couplings). Sections 1.7.1 to 1.7.6 cover an overview of synthesis tactics applicable to neolignans from the genus *Illicium*, focusing on; the construction of biaryl bonds in the presence of aromatic allyl groups, allylation of arenes, olefin group protection strategies, contra-thermodynamic isomerisation of aromatic allyl groups, and selective functionalisation of isomerised allyl group impurities (obtaining separation on column chromatography from desired non-isomerised products).

The synthesis of neolignans and model systems containing a tetrahydrodibenzofuran ring system has been reported by the Denton[102] and Banwell[103] groups. Aside from these reports, neolignans from this class have otherwise been generated by non-selective oxidative phenolic coupling (see section 1.3).[21,22]

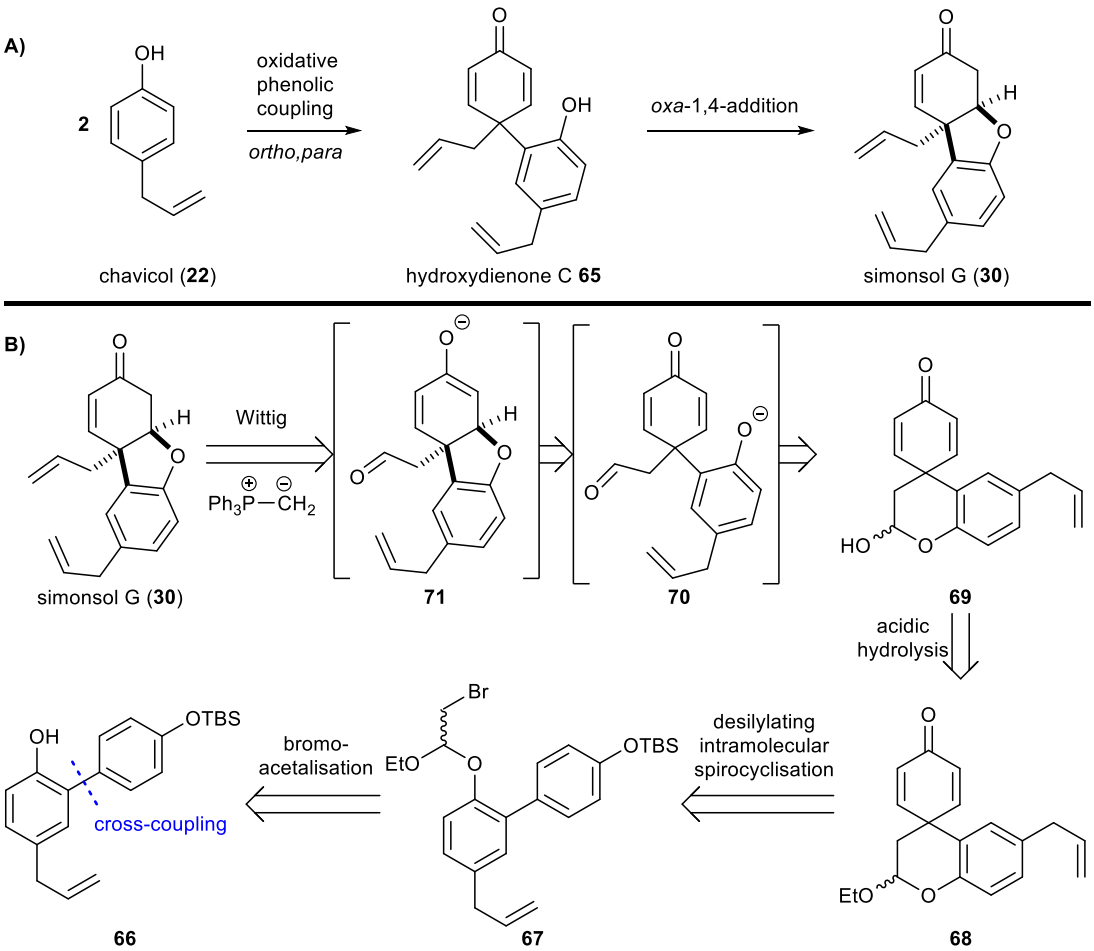
1.6.2: Denton and co-workers simonsol G strategy

Denton and Scragg developed a strategy based upon biosynthetic speculation which featured a synthetic equivalent of hydroxydienone C **65**, a transient intermediate that was invoked in the proposed biosynthesis (see Scheme 9).[102]

The strategy centred on the synthesis of lactol **69**, which is in equilibrium with the corresponding aldehyde and phenol. Treatment

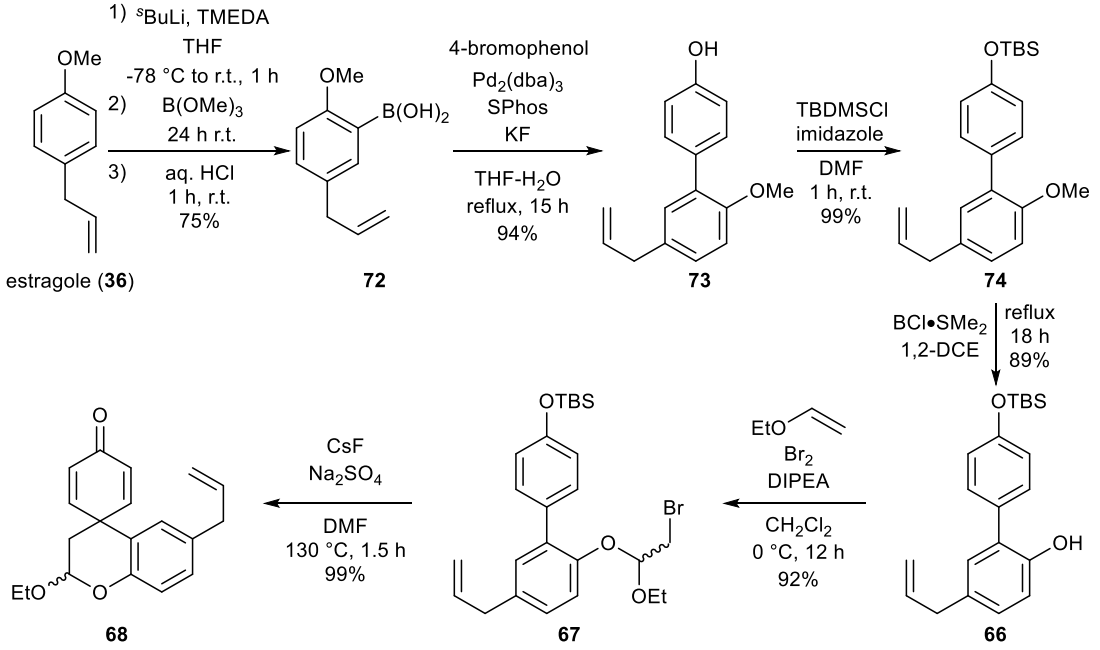
of lactol **69** with the indicated phosphonium ylide should result in ring opening, cyclisation and methylenation to give simonsol G (**30**).

Magnus *et al.* developed a desilylative intramolecular spirocyclisation reaction which formed similar cyclic-acetal spirocycles to **68** in their synthesis of (-)-galanthamine (**58**).[107] Therefore, acetal **68** could be formed from bromo-acetal **67** which in turn can be accessed from the bromo-acetalisation of biaryl **66**. Biaryl **66** could be formed from a cross-coupling reaction (see Scheme 9).



Scheme 9. A) *Proposed biosynthesis of simonsol G (**30**).* ***B)*** *Retrosynthetic analysis of simonsol G (**30**).*

The Denton group had previously demonstrated Suzuki-Miyaura coupling reactions in substrates containing potentially sensitive aromatic allyl groups.[73,87] Therefore, the synthesis towards simonsol G (**30**) began with estragole (**36**) which was *ortho* lithiated, then reacted with $B(OMe)_3$ and subsequently hydrolysed which gave boronic acid **72**. Suzuki-Miyaura cross-coupling of boronic acid **72** with 4-bromophenol gave biaryl **73** in excellent yield without isomerisation of the sensitive allyl group. The hydroxyl group within biaryl **73** was protected as TBS silyl ether **74** followed by selective demethylation with $BCl_3{\bullet}SMe_2$ to give **66** in excellent yield. Conversion of **66** to bromo-acetal **67** was achieved in excellent yield using ethyl vinyl ether and bromine. Using the conditions developed by Magnus *et al*.,[107] bromo-acetal was converted to acetal spirocycle **68** in near quantitative yield (see Scheme 10).

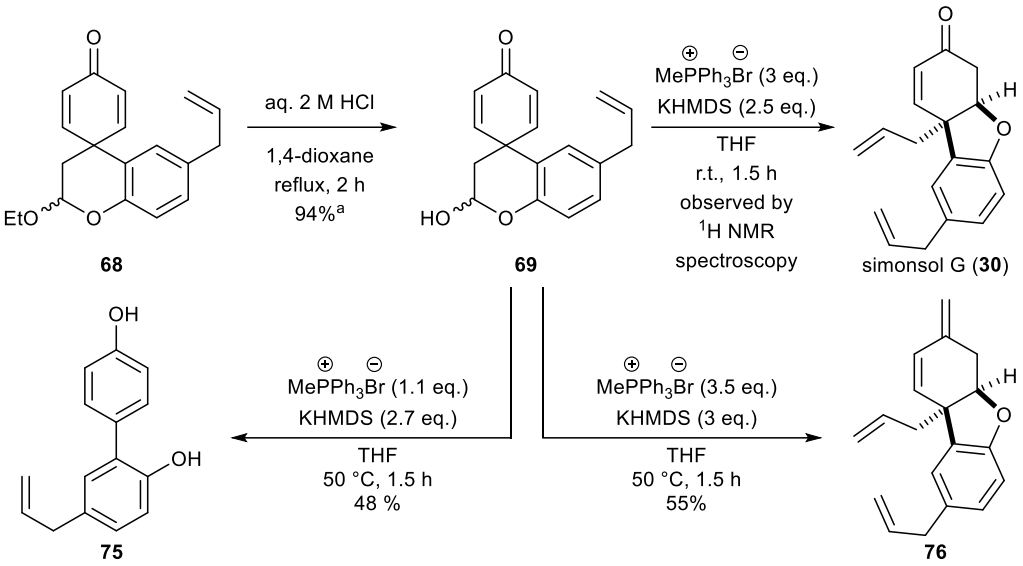


Scheme 10. *Synthesis of acetal spirocycle* ***68*** *from commercial estragole (****36****).*

Treatment of acetal spirocycle **68** with aqueous HCl resulted in a complex mixture of products. Separation of the mixture by normal phase column chromatography was problematic (however, this problem is resolved in this thesis, see section 2.1.7). Careful analysis of the crude material by ^{1}H and ^{13}C NMR spectroscopy indicated that lactol **69** was the major constituent of the crude mixture which was progressed directly into the Wittig cascade reaction.

Conducting the Wittig cascade reaction on the crude mixture at room temperature gave low conversion and formed a small amount of simonsol G (**30**) (observed by ^{1}H NMR spectroscopy)[21,22] (see Scheme 11). A substantial amount of lactol **69** was also present which led to several attempts at optimisation. In summary, when the temperature was increased to 50 °C, fewer products were generated. Although NMR spectroscopy analysis confirmed the formation of the characteristic [4.3.0] ring system found in simonsol G (**30**), an unwanted second Wittig methylenation had occurred which produced diene **76**. Alternatively, the ratio of phosphonium salt to base was adjusted which resulted in the undesired formation of biaryl **75** (see Scheme 11).

Although a high-yielding synthesis of simonsol G (**30**) was not realised in this initial study, a method for the construction of the characteristic [4.3.0] allylic ring system *via* a bioinspired synthesis was validated.



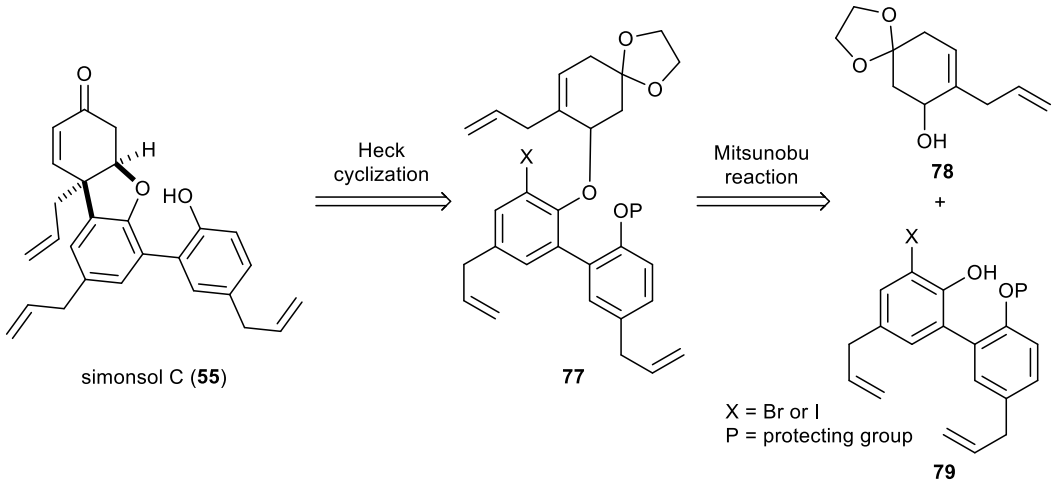
Scheme 11. *Studies towards the synthesis of simonsol G (**30**).*[102] ***a)*** *Yield was calculated by* $\frac{crude\ mass\ obtained}{possible\ crude\ mass}$ *and it was assumed that all crude mass was relevant.*

1.6.3: Banwell and co-workers simonsol C synthesis

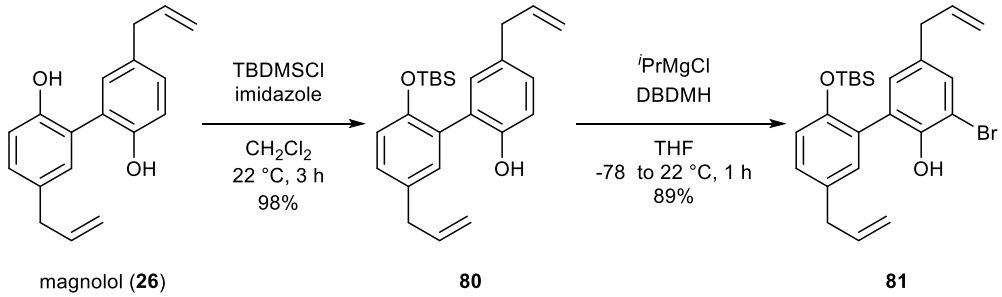
Banwell and co-workers retrosynthetic analysis of simonsol C (**55**) involved a Mitsunobu reaction[108–113] followed by an intramolecular Heck cyclisation to construct the tetrahydrodibenzofuran core. Banwell and co-workers first-generation retrosynthetic analysis (see Scheme 12) incorporated an allyl group present on the A-ring species **77**. The desired Heck cross-coupling in the presence of a nearby allyl group olefin was not possible and so a protected allyl group strategy was eventually sought.

The synthesis started with the preparation of the phenolic Mitsunobu coupling partner **81**. Magnolol (**26**) was mono-protected using *tert*-butyldimethylsilyl chloride followed by a chemo- and regioselective

bromination (over the allyl group olefin) which gave the desired phenol **81** in excellent yield (see Scheme 13).[114]



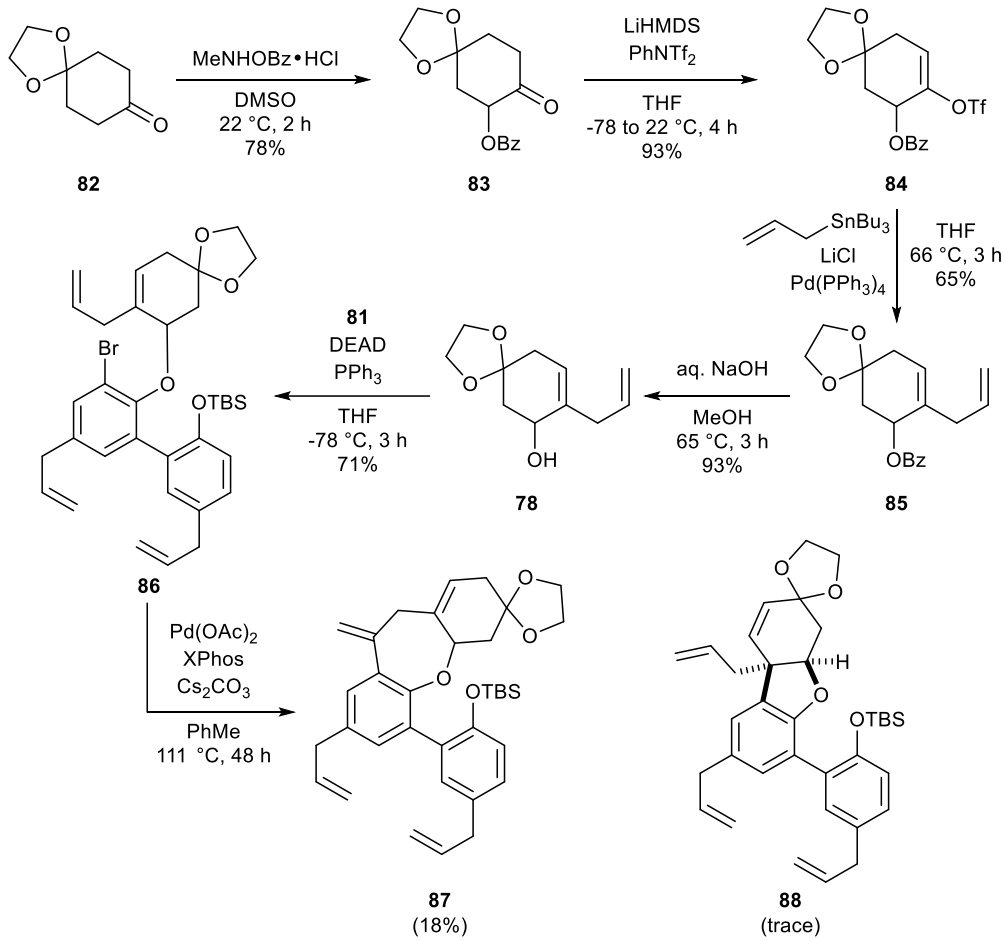
Scheme 12. *Banwell and co-workers retrosynthetic analysis of simonsol C (**55**).*



Scheme 13. *Synthesis of phenolic Mitsunobu coupling partner **81**.*

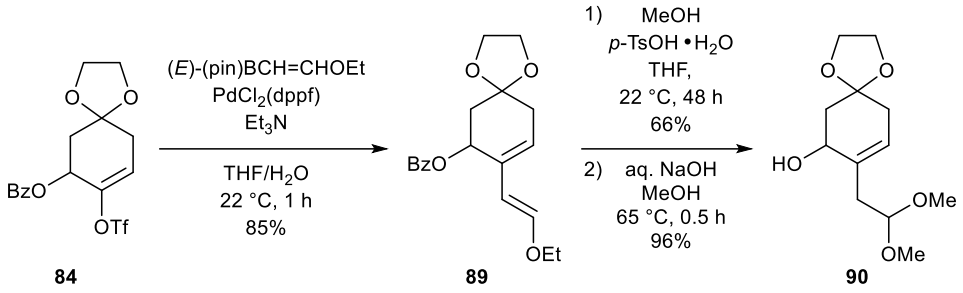
With phenol **81** in hand, the synthesis of the A-ring precursor **78** began by α-benzoyloxylation of commercially available ketal **82** to oxidation product **83**. This was converted to enol triflate **84** under conditions developed by McMurry and Scott.[115] Stille (or Migita-Kosugi-Stille)[116,117,126,118–125] cross-coupling installed the allyl group and subsequent cleavage of the benzoate moiety gave **78**. Mitsunobu coupling of alcohol **78** with phenol **81** gave ether **86** in good yield. However, the only isolable product from the intramolecular Heck

reaction[170] was oxepin derivative **87**, whilst only trace amounts of tetrahydrodibenzofuran **88** was observed by NMR spectroscopy (see Scheme 14).



Scheme 14. *Synthesis towards tetrahydrodibenzofuran core via Heck coupling.*

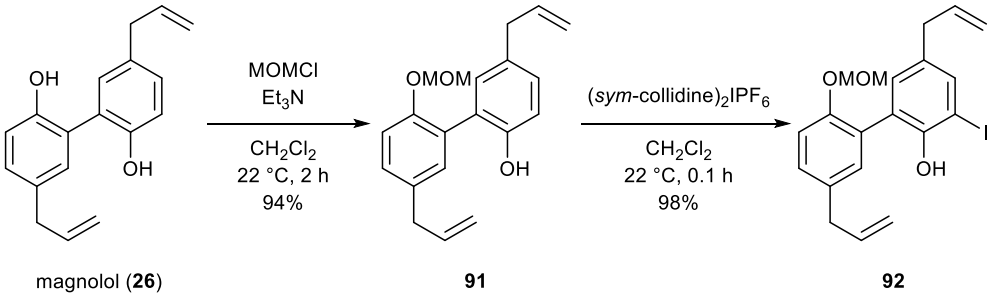
Based upon this observation, a second-generation approach was developed in which installation of the allyl group was delayed until after the intramolecular Heck cyclisation. Suzuki-Miyaura cross-coupling of triflate **84** with (*E*)-(pin)BCH=CHOEt gave enol ether **89**, which was protected as the acetal under standard conditions, followed by base-mediated hydrolysis of the benzoate ester which provided alcohol **90** (see Scheme 15).



Scheme 15. *Synthesis of A-ring precursor* ***90*** *for Mitsunobu coupling reaction.*

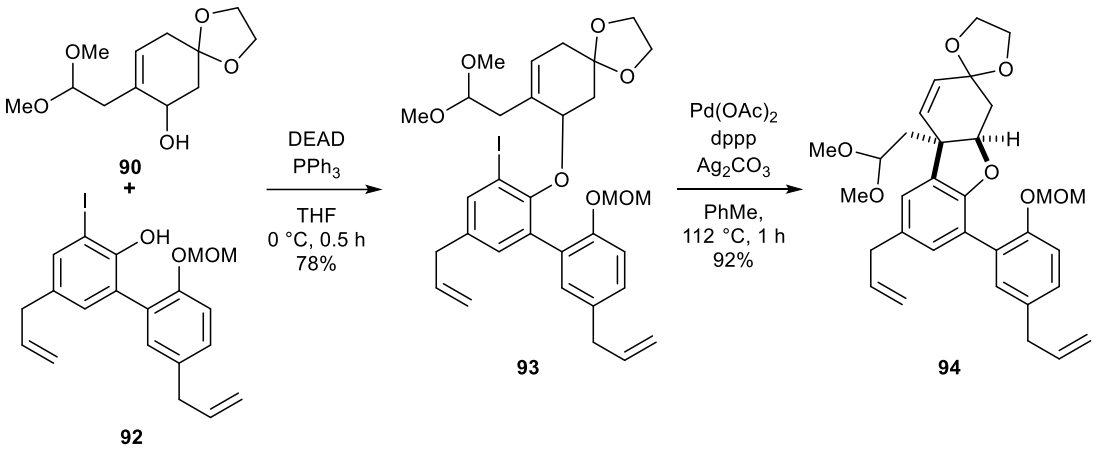
Due to complications arising from observed migration of the TBS group from one phenolic residue to the other within compound **81**, and since aryl iodides are more reactive than aryl bromides in Heck cross-couplings,[127] the magnolol derived Mitsunobu coupling partner was modified.

Magnolol (**26**) was treated with chloromethyl methyl ether[128] which gave mono MOM protected magnolol **91** that was regio- and chemoselectively iodinated with bis(*sym*-collidine)iodine(I) hexafluorophosphate[129,130] which generated **92** (see Scheme 16).



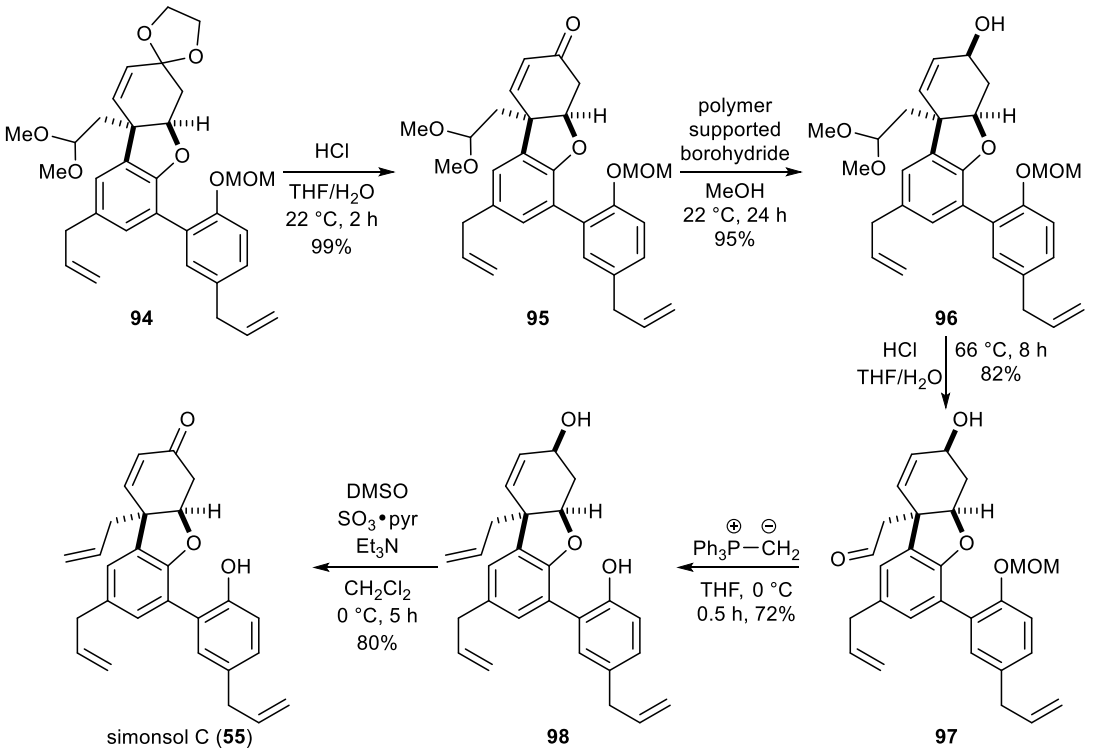
Scheme 16. *Synthesis of Mitsunobu coupling partner phenol* ***92****.*

Mitsunobu coupling reaction of **90** and **92** provided ether **93** that successfully gave tetrahydrodibenzofuran **94** in excellent yield from an intramolecular Heck cyclization (see Scheme 17).



Scheme 17. *Mitsunobu coupling reaction and intramolecular Heck cyclization to generate tetrahydrodibenzofuran-containing model system.*

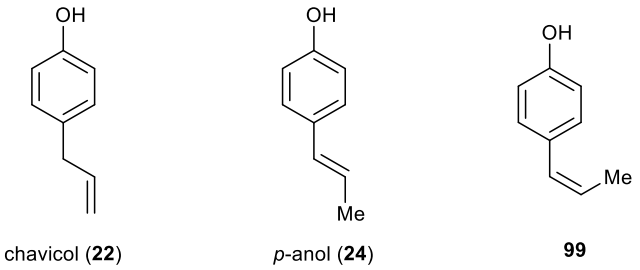
The ethylene ketal moiety of **94** was hydrolysed to enone **95**. A highly diastereoselective 1,2-reduction gave allylic alcohol **96**. Subsequent hydrolysis of the acetal followed by Wittig olefination provided **98** which after Parikh-Doering oxidation,[131] gave (±)-simonsol C (**55**) in 12.5% overall yield (12 steps from magnolol (**26**)) (see Scheme 18).



Scheme 18. *Completion of the synthesis of (±)-simonsol C (**55**).*

1.7.1: Construction and control of aryl allyl groups

This section provides an overview of the strategies employed in the synthesis of *Illicium*-derived neolignans that do not contain a hydrodibenzofuran core. A summary of methodology is also provided that may be of use for future syntheses of neolignans or other species containing aryl allyl groups. The aryl allyl group is difficult to work with as the alkene has a tendency to isomerize to the thermodynamic position in conjugation with the arene (see Figure 7). In our experience, isomerisation of the aryl allyl group occurs more readily under basic conditions or with metals that can co-ordinate to the alkene, especially in the presence of electron donating ligands.

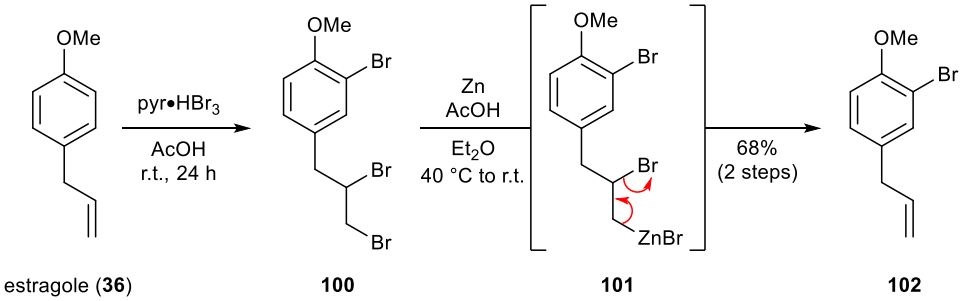


chavicol (**22**) *p*-anol (**24**) **99**

Figure 7. *Chavicol (**22**) and thermodynamically favoured isomers p-anol (**24**) and **99**.*

In addition to isomerisation, there are numerous reactions/reagents that are incompatible with allyl groups, such as electrophilic aromatic substitution reactions. These challenges have been overcome in the *ortho* bromination of estragole (**36**) (see Scheme 19).[72,79,132] Subsequent Zn mediated reduction of the vicinal dibromoalkane of **100**, which was generated by electrophilic aromatic bromination and 1,2-dibromination, afforded 4-allyl-2-bromoanisole (**102**) in good

yield. In our hands, we obtained a much lower yield of **102**, complicated further by the isolation of estragole (**36**) with **102** which were inseparable by normal-phase column chromatography.



Scheme 19. *Synthesis of 4-allyl-2-bromoanisole (**102**) from estragole (**36**).*[72]

Apart from magnolol (**26**), neolignans of interest have not been synthesized selectively in high yields biomimetically by the oxidative phenolic coupling of chavicol (**22**). This has led to a variety of strategies to selectively form carbon-carbon or carbon-oxygen bonds in the presence of aryl allyl groups.

Csp^2-Csp^2 bond coupling reactions have been studied for decades, with Akira Suzuki, Richard F. Heck and Ei-ichi Negishi winning the Nobel prize in chemistry in 2010 for their work on "palladium-catalysed cross-couplings in organic synthesis".[133] Named reactions have been shortened over time for ease of communication. The Suzuki cross-coupling may also be called the Suzuki-Miyaura cross-coupling for their work in 1979.[134] In 1972, Richard F. Heck improved the practicality and generality[135] of Mizoroki's seminal report from 1971.[136] Therefore, the Heck cross-coupling may also be referred to

as the Mizoroki-Heck cross-coupling.[137] The seminal report for the Negishi cross-coupling reaction was reported in 1977.[138]

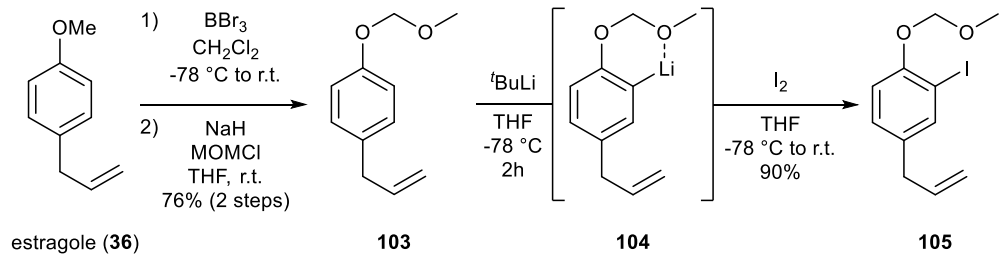
Cross-coupling reactions represent a chemistry tool that has allowed the expansion of medicinally relevant compounds to be made quickly, reliably, and efficiently. In general, substrate scopes provided for cross-coupling reactions do not provide examples of compounds with an aryl ally group and are unlikely to show a compound with a free phenol. Most examples of cross-couplings in literature that include an aryl allyl group as a cross-coupling partner, are found in total syntheses of natural products. However, the reported conditions are usually substrate specific and often lead to thermodynamic isomerization of an aryl allyl group when applied to similar substrates.[59,73,78,87]

1.7.2: Strategies to *ortho*-functionalise chavicol units

Illicium-derived neolignans have provided a wealth of structurally diverse species derived from a common repeating unit, chavicol (**22**). Chavicol (**22**) is expensive (accessed 19/03/2020; Fluorochem charges £234 for 1 g) but estragole (**36**), i.e. *O*-methylated chavicol, is affordable (accessed 19/03/2020; Tokyo Chemical Industry charges £43 for 100 g). Therefore, reported syntheses of *Illicium*-derived neolignans usually start from estragole (**36**), however the *ortho*-functionalisation of estragole (**36**) is challenging, especially by

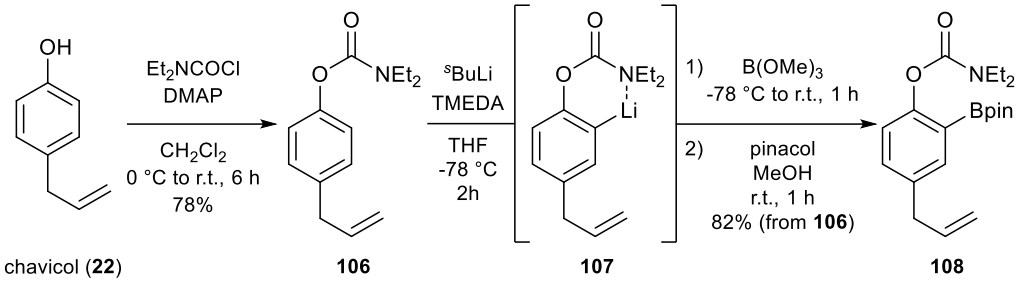
lithiation due to competing benzylic deprotonation. Installation of a better directing group requires two synthesis-steps which is unappealing but can dramatically increase the overall yield of the formal *ortho*-functionalization of chavicol (**22**).

To obtain a better directing group for *ortho*-lithiation, LeBel *et al*.[68] demethylated estragole (**36**) and subsequently formed MOM ether **103**.[139] Subsequent lithiation and iodine quench gave **105** in excellent yield (see Scheme 20).



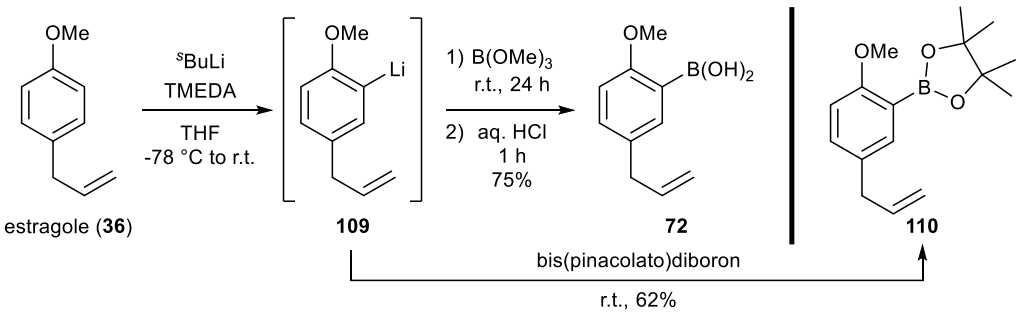
Scheme 20. *Synthesis of aryl iodide **105** via directed ortho-lithiation.*[68]

Siegel *et al*. formed carbamate **106** from chavicol (**22**) which directed lithiation to form organolithium **107** *in situ.*[96] Subsequent addition of $B(OMe)_3$ followed by transesterification provided boronic acid pinacol ester **108** in 64% yield from chavicol (**22**) (see Scheme 21). In our hands, estragole (**36**) can be demethylated to chavicol (**22**) in 90% yield. Therefore, this sequence can be considered to provide **108** in 58% yield from the more affordable estragole (**36**).



Scheme 21. *Ortho-lithiation mediated synthesis of boronic acid pinacol ester* ***108****.*[96]

Denton *et al.* developed a method to access boronic acid **72** directly from estragole (**36**) (see Scheme 22). This was applied in the concise synthesis of honokiol (**33**),[73] dunnianol (**27**),[87] macranthol (**39**),[91] and others.[69,102] Grée and co-workers applied this method in their synthesis of honokiol (**33**) derivatives.[140] Schuster *et al*. adapted the method to access boronic acid pinacol ester **110** directly from estragole (**36**) without further transesterification (see Scheme 22).



Scheme 22. *Ortho-lithiation and subsequent borylation of estragole (****36****).*[87,102,141]

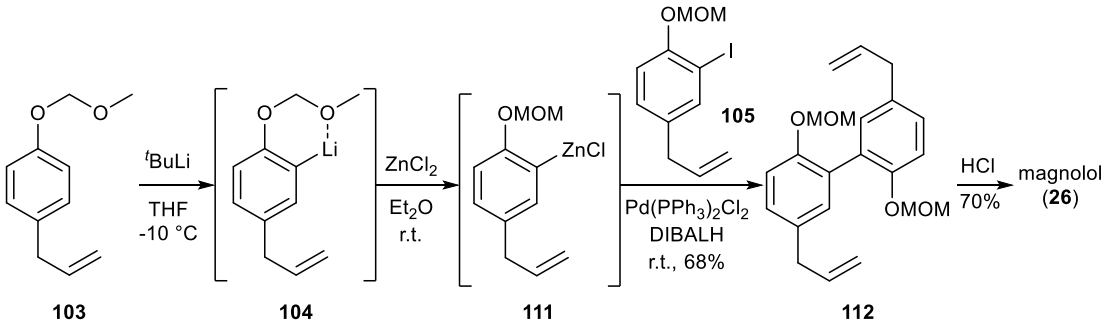
It should be noted that when organolithium **109** is quenched with other electrophiles such as iodine, NBS or Bu_3SnCl, a complex mixture of products is obtained. In these instances, the use of a better directing group, such as MOM ether, should be employed.

1.7.3: Methods to form biaryl bonds in the presence of aryl allyl groups

The Suzuki-Miyaura cross coupling reaction[142,143] has been used regularly for the formation of biaryl bonds in the presence of aryl allyl groups and free phenols.[59,66,139–141,144,69,72,73,78,87,91,102,132] The cross-coupling has a large set of studied variables, in particular the choice of catalyst and ligands[145–154] which in turn strongly affects the temperature at which the reaction can be performed. The choice of boron coupling partner (boronic acid, trifluoroborate salt etc.),[155] choice of base (important for boron species that are easily protodeboronated)[156] and solvent(s) are also important, ranging from water being omitted to being the primary solvent.[145,149] Finding the right set of conditions that does not lead to thermodynamic isomerisation of the olefin is not well understood and is regularly found by trial and error.[59,72,73] In our experience, the use of strong bases or electron rich ligands such as alkylphosphines and NHC's often leads to thermodynamic isomerisation of the olefin.

LeBel *et al.* reported Negishi cross-coupling reactions[138,157] in their synthesis of magnolol (**26**) and monoterpenylmagnolol (**44**).[68] Organozinc **111** was generated *in situ via* a directed *ortho*-lithiation of MOM ether **103** followed by transmetallation with $ZnCl_2$.[139] Negishi cross-coupling of **111** with aryl iodide **105** formed di-MOM-protected magnolol **112** and subsequent deprotection of the MOM groups under

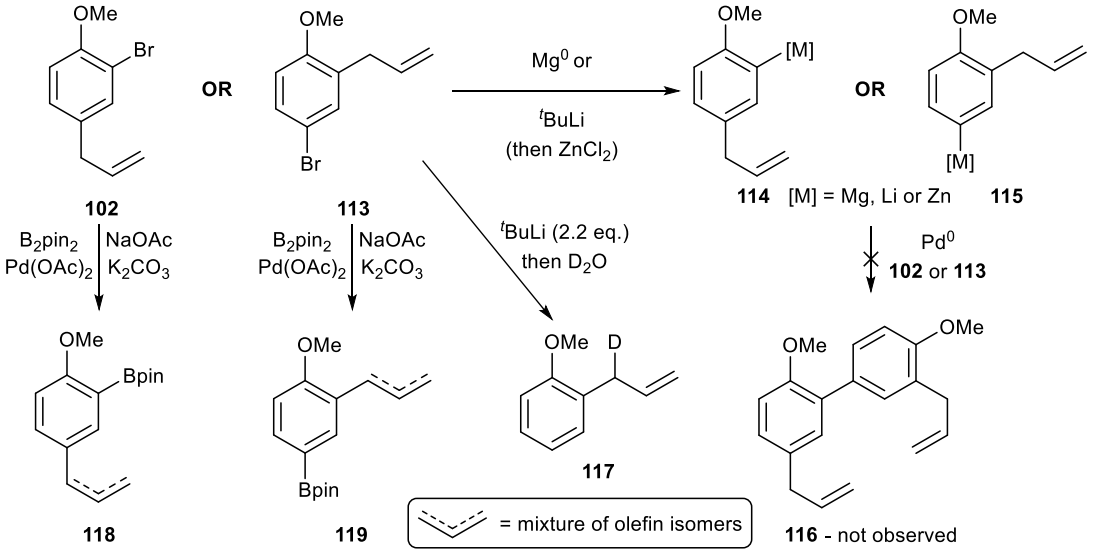
standard conditions afforded magnolol (**26**) (see Scheme 23). Switching from Pd^0 to Ni^0 catalysis at higher temperature resulted in substantial thermodynamic isomerisation of the aryl allyl groups. An organotin derivative was formed *in situ* by the addition of Bu_3SnCl to organolithium **104**, however the Stille cross-coupling with aryl iodide **105** also resulted in substantial thermodynamic isomerisation of one or both aryl allyl groups.



Scheme 23. *Negishi cross-coupling used in the synthesis of magnolol (**26**).*[68]

O'Neil and Wright reported several difficulties encountered in their synthesis of honokiol (**33**).[78] Initially, 2-bromo-4-allylanisole (**102**) and 4-bromo-2-allylanisole (**113**) were made with the ambition to derivatise either **102** or **113** to an organometallic species *in situ* followed by cross-coupling with the non-derivatised aryl bromide. However, dimethylated honokiol **116** was not observed under Kumada (Kumada-Tamao-Corriu),[158–162] organolithium[163–171] or Negishi cross-coupling. To gain insight into why **116** was not observed, **113** was treated with ^{t}BuLi and was then quenched with D_2O. The major product observed by ^{1}H NMR spectroscopy was **117**, formed by proto-dehalogenation and benzylic deprotonation (see

Scheme 24). Next, O'Neil and Wright attempted to make the requisite boronic acid pinacol esters from **102** or **113** by Miyaura boration.[172,173] Although the boronic acid pinacol esters were formed, the aryl allyl groups had substantially isomerised which gave **118** and **119**. It should be noted that using K_2CO_3 is incompatible with Miyaura borations as it facilitates the Suzuki-Miyaura cross-coupling between the starting material and product. Also, Miyaura borations of electron-rich aryl bromides are sluggish, whereas the equivalent electron-rich aryl iodide reacts faster.[174]



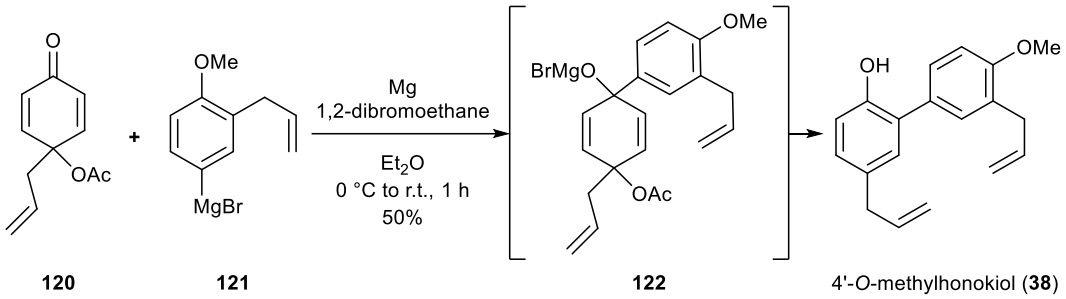
Scheme 24. *Observed problems cross-coupling in the presence of aryl allyl groups.*[78]

This isomerisation ultimately prevented O'Neil and Wright from pursuing this synthesis route. Therefore, they installed the aryl allyl groups after cross-coupling from benzaldehydes (see Scheme 31).[78]

In 2016, Banwell and co-workers reported the total synthesis of simonsol C (**55**) (see Section 1.6.3).[103] The reported intramolecular Heck cross-coupling in the presence of two allyl group olefins proceeded in 92% yield (see Scheme 17) but resulted in

approximately 5-10% thermodynamic isomerisation of the aryl allyl groups (not discussed but observed in the ^{1}H NMR spectra).

Inspired by Tobinaga and co-workers synthesis of honokiol (**33**),[71] Denton *et al*. reported the total synthesis of 4'-*O*-methylhonokiol (**38**).[84] PIDA mediated oxidation of chavicol (**22**) provided dienone **120** that was reacted with the *in situ* formed Grignard reagent **121** which gave intermediate **122**. Subsequent 1,2-shift with loss of acetate, followed by tautomerization which aromatized the phenol ring, gave 4'-*O*-methylhonokiol (**38**) (see Scheme 26).



Scheme 26. *Synthesis of 4'-O-methylhonokiol (**38**) from dienone **120**.*[84]

1.7.4: Methods used to install the allyl group

Aryl allyl groups may be installed at a late stage of a synthesis to avoid unwanted reactivity including thermodynamic isomerisation. Due to the commercial availability of various allyl or vinyl containing reagents, there is greater literature precedent for the installation of allyl groups onto aromatic rings than there is for the cross-coupling of arenes with aryl allyl groups. Scheme 27 provides a representative summary conditions used to install allyl groups onto arenes. Specific

conditions (Ⓕ to Ⓙ) are only provided when the methodology has not been adapted further than the seminal reports.

Generally, Suzuki-Miyaura (Ⓐ and Ⓓ above arrow), Kumada (Pd^0 and Ni^0) or Kumada-type (Cu^I) (Ⓑ and Ⓒ) and Stille (Ⓓ below arrow and Ⓔ) cross-coupling conditions are used to cross-couple aryl halides, triflates or benzyl bromides with allyl or vinyl containing reagents respectively (see Scheme 27). The rate of transmetallation in the Stille cross-coupling can be enhanced by Cu^I salts and F^- sources, whilst LiCl is used to prevent catalyst poisoning.[123,175,176]

ⒻUnder Hiyama-Hatanaka cross-coupling conditions,[177–182] DeShong and Mowery[183] generated 4-allyltoluene in 60% yield.

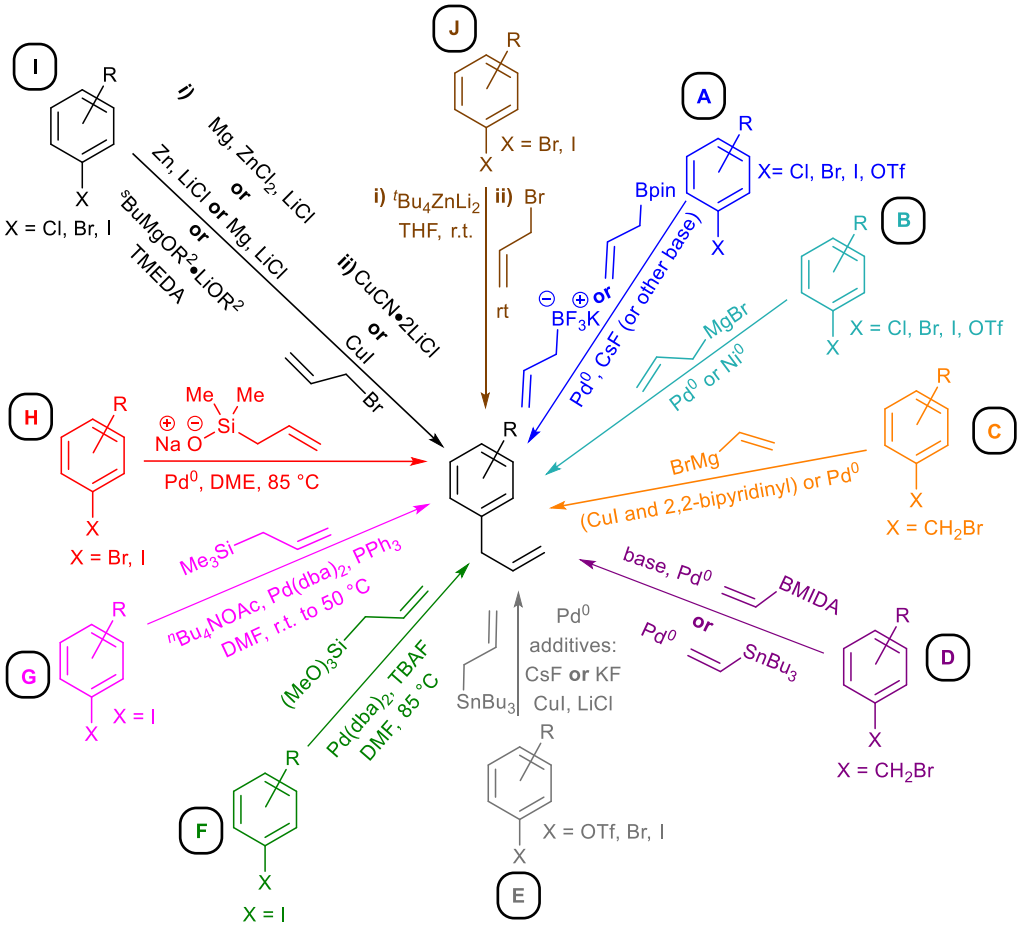
ⒼJeffery developed a Heck-type cross-coupling of allyltrimethylsilane with aryl iodides under Pd^0 catalysis.[184] $^nBu_4NOAc$ promoted trimethylsilyl elimination over β-hydride elimination. From 4-iodoanisole, estragole (**36**) was produced in 78% yield.

ⒽUnder Hiyama-Denmark cross-coupling conditions,[182,185–187] Denmark and Werner cross-coupled aryl bromides with allylic silanoate salts with an allylpalladium chloride dimer (Pd^0). From 4-bromoanisole, estragole (**36**) was provided in 82% yield.

ⒾKnochel *et al*. developed various conditions to insert magnesium or zinc into aryl iodides, bromides and chlorides,[188–190] which in the presence of a Cu^I catalyst, underwent allylation when reacted with

allyl bromides. From 4-iodoanisole, estragole (**36**) was produced in 94% yield.[188]

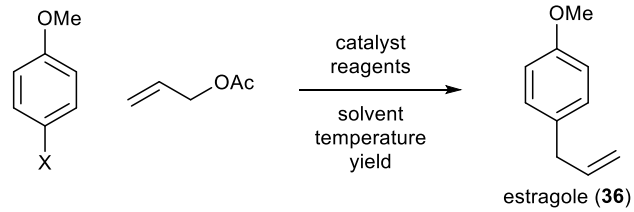
Ⓙ Uchiyama and co-workers treated aryl halides (including free phenols) with $^{t}Bu_4ZnLi_2$ which gave organozinc species *in situ* that were reacted with allyl bromide or other electrophiles.[60,191] From 4-iodophenol, chavicol (**22**) was provided in 79% yield.



Scheme 27. *Installation of allyl groups onto aromatic systems.*

Table 7 contains a representative summary of methods developed which provided estragole (**36**) from allyl acetate. Lee *et al.* reported a Pd-catalysed cross-coupling of aryl halides or triflates with postulated allylindium species formed *in situ* from allyl acetate (see Table 7, entry 1).[192–194] Gosmini *et al*. established two methods, both

catalytic in $CoBr_2$, for the electrochemical[195] or Negishi-type cross-coupling of aryl halides with allyl acetate (see Table 7, entry 2).[196] Von Wangelin *et al.* developed an Fe catalysed cross-coupling of aryl Grignard reagents with allyl acetate or other allyl electrophiles (see Table 7, entry 3).[197] Balme *et al.* developed mild Suzuki-Miyaura cross-coupling conditions of aryl boronic acids with allyl acetate (see Table 7, entry 4).[198] Other conditions reported that used allyl acetate to form aryl allyl groups were considered underdeveloped for the synthesis of *Illicium*-derived neolignans.[199–205]



#	X	catalyst	reagents	Solvent	T (°C)	Y (%)
1	Br	Pd_2dba_3	Xantphos, In, $InCl_3$, LiCl, $^nBuNMe_2$	DMF	100	67[193]
2	Br	$CoBr_2$	Zn, AcOH	MeCN	22	60[196]
3	Br	$Fe(acac)_3$	Mg, LiCl	THF	0–22	75[197]
4	$B(OH)_2$	$[PdCl_2(TFP)_2]$	KF	MeOH	22	65[198]

Table 7. *Conditions used to cross-couple allyl acetate with functionalised aryls.*

Aryl radicals, formed from aryldiazonium salts or aryl chlorides, can be generated to install aryl allyl groups. Frejd *et al*. developed an allylation of electron-poor arenes by the diazotization of anilines. The authors proposed a radical mechanism (as depicted in Scheme 28A), but without a reductant, it is more likely an aryl cation is formed.[206]

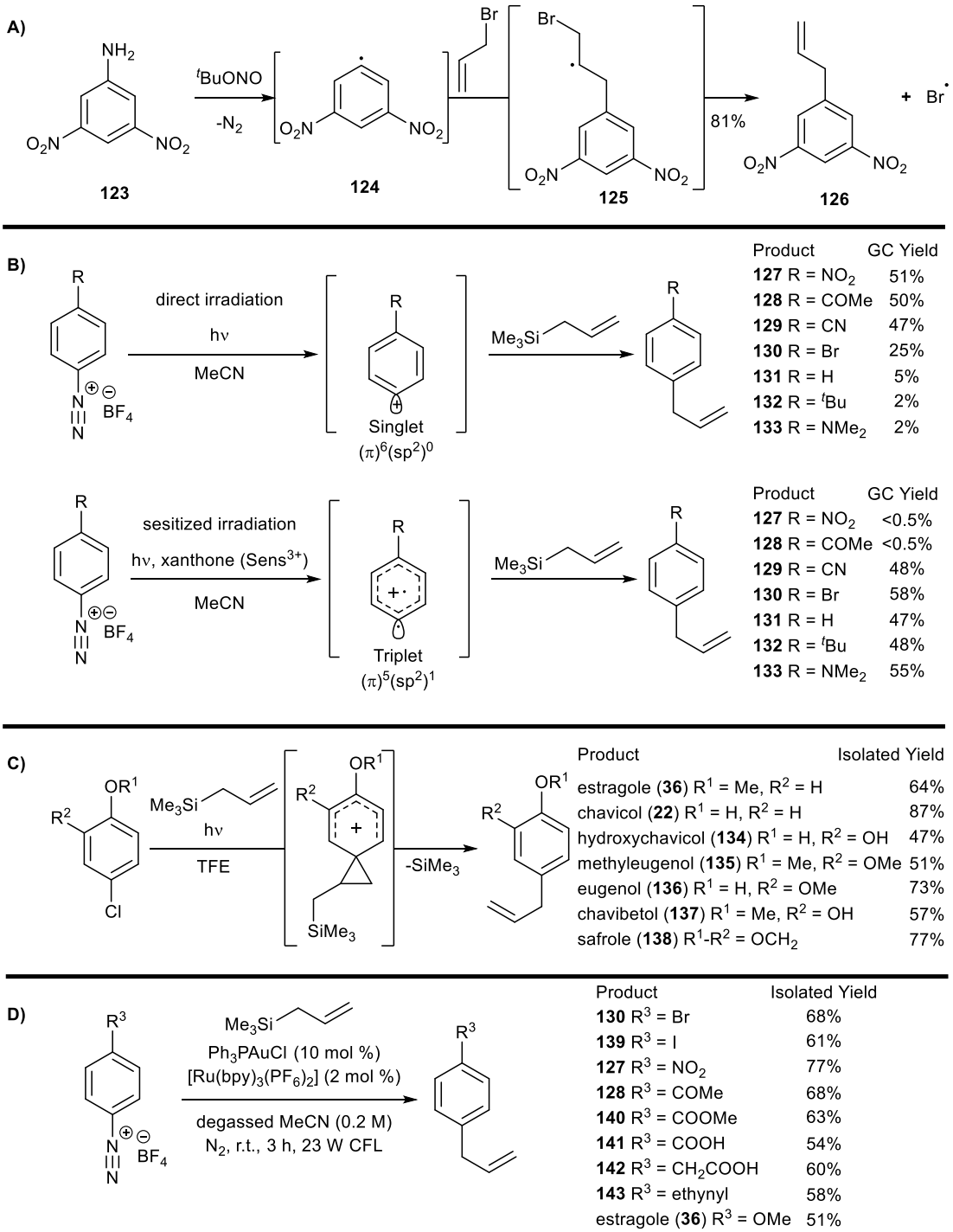
Allyltrimethylsilane is a unique commercial allylating reagent because of the β-silicon-effect which has led to the most varied set of reactions

to allylate an arene. The long Si-C bond stabilizes β-carbocations by pushing electron density into the empty p-orbital, which makes the alkene terminus of allyltrimethylsilane nucleophilic. The TMS group is a good electrofuge and can eliminate to form the desired allyl group.

Albini and co-workers reported a direct and sensitized photolysis of diazonium salts to form allylated aromatics *via* interception of singlet or triplet state carbocations with allyltrimethylsilane.[207] Direct irradiation of aryldiazonium species formed a singlet state carbocation intermediate which unless stabilized by electron-withdrawing groups, would react with the solvent (acetonitrile). The sensitized photolysis (xanthone absorbed 95% of the UV irradiation) of aryldiazonium salts formed triplet cations of aromatics, which favoured reactions of electron-rich aromatics with π-nucleophiles (such as allyltrimethylsilane) (see Scheme 28B).

Albini *et al*. developed a metal-free photoallylation of chlorophenols *via* a triplet state carbocation intermediate to form bioactive allylphenol constituents from the genus *Piper* (see Scheme 28C).[208] The triplet-state carbocation intermediate reacted with allyltrimethylsilane which then re-aromatised and expelled trimethylsilane to form the allyl group olefin.

Patil and co-workers reported the use of merged Au and visible light photoredox catalysis (using Ru) which cross coupled aryldiazonium salts with allylsilanes (see Scheme 28D).[209]

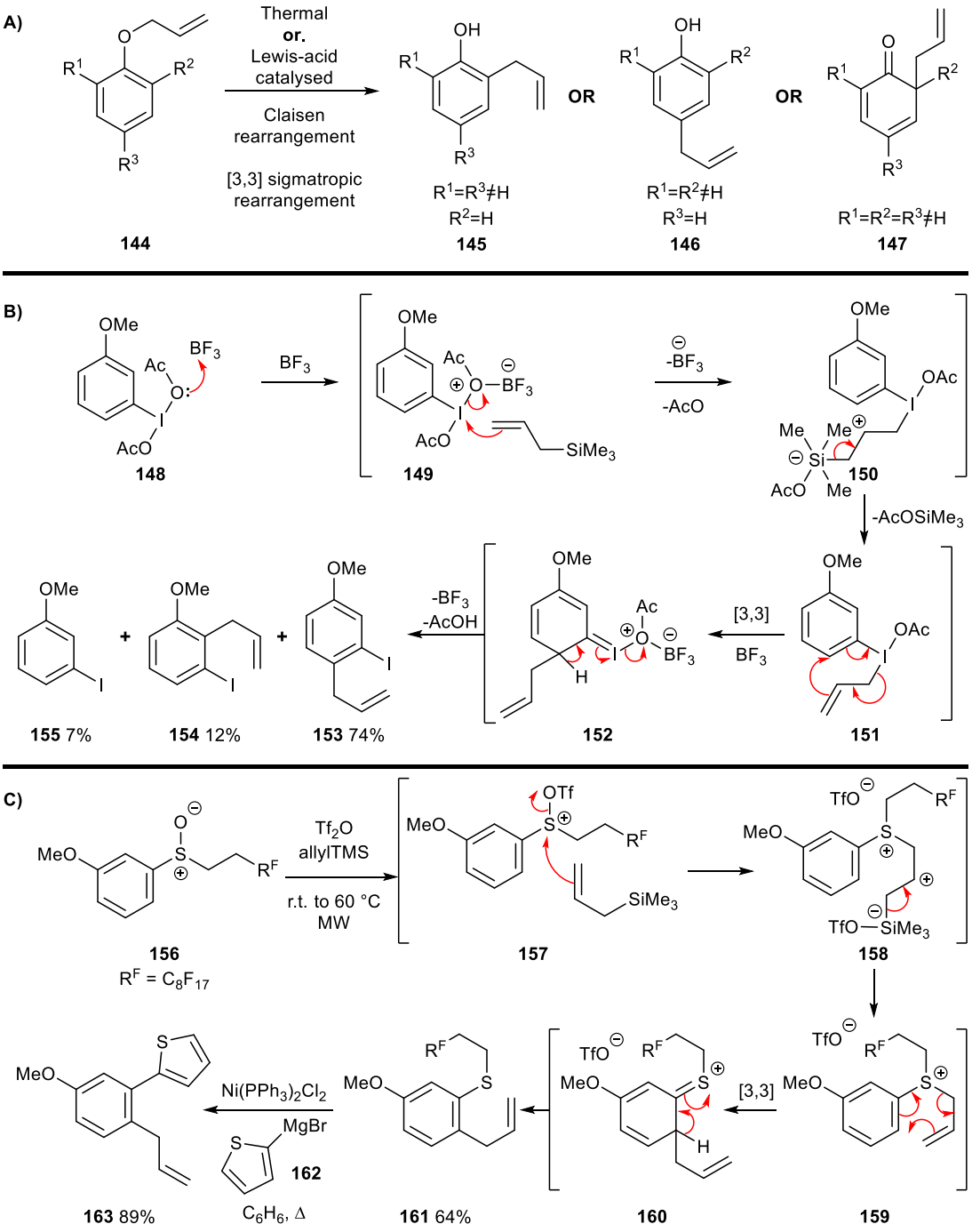


Scheme 28. A) *Allylation of electron-poor aromatics via diazotization.* ***B)*** *Direct and sensitized irradiation, photolysis of diazonium salts to generate aryl cations.* ***C)*** *Photoallylation of chlorophenols.* ***D)*** *Merged Au/visible light photoredox catalysis for the allylation of aryl diazonium salts.*

The thermal or Lewis-acid (usually BCl_3 or Et_2AlCl)[71–74,78,84,144,210] promoted Claisen rearrangement[62,63] of allyl phenyl ethers is regularly used to generate *ortho*-, *para*- or dearomatized allylated phenols, dependent on substituents around the arene ring (see Scheme 29A). Lewis-acids can promote the Claisen rearrangement to occur below 0 °C.

In 2012, Zhu and Khatri reported a reductive iodonio-Claisen rearrangement.[211] Aryl iodide^{III} **148** was treated with BF_3 and allyltrimethylsilane which formed transient intermediate **150**. Elimination of electrofugal trimethylsilyl acetate gave **151** that underwent the reductive iodonio-Claisen rearrangement and generated functionalized allylated anisoles **153** and **154** (see Scheme 29B). This methodology was applied in the synthesis of non-natural derivatives of magnolol (**36**) and honokiol (**33**).[212]

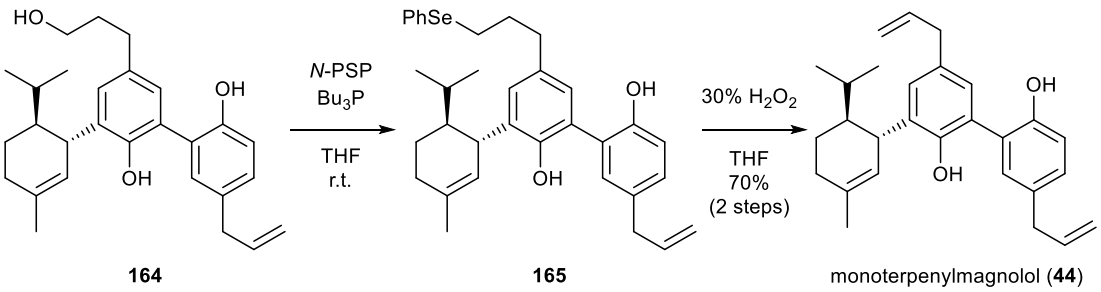
Inspired by the seminal thio-Claisen rearrangements reports by Yorimitsu *et al.*,[213,214] Procter and co-workers developed a cascade reaction (interrupted Pummerer reaction then thio-Claisen rearrangement) whereby aryl sulfoxides generated *ortho*-aryl-allylated aryl sulfides.[215] Generated sulfides like **161** were cross-coupled with aryl Grignard reagents under nickel-catalysis (see Scheme 29C). This methodology, alike to the iodonio-Claisen rearrangement, provides access to *meta*-derivatised chavicol-type species for the synthesis of non-natural *Illicium*-derived neolignans.



Scheme 29. A) *Claisen rearrangement products from allyl phenyl ethers dependent on "R=H or not H". **B)** Reductive iodonio-Claisen rearrangement. **C)** Interupted Pummerer reaction then thio-Claisen rearrangement of activated aryl sulfoxide and subsequent cross-coupling.*

Functional group interconversion (FGI) is an alternative strategy used for the installation of an allyl group at a late stage in a synthesis. Wittig methylenation[216–218] of aldehydes is commonly applied in total synthesis.[102,103] However, aldehydes are inherently unstable to a range of conditions, and can often oxidize in air to the respective acid. Therefore, aldehydes are formed as a penultimate step to methylenation, usually produced by; oxidation of alcohols, reduction of esters, hydrolysis of acetals[103] or deprotonation of a hemi-acetal.[102]

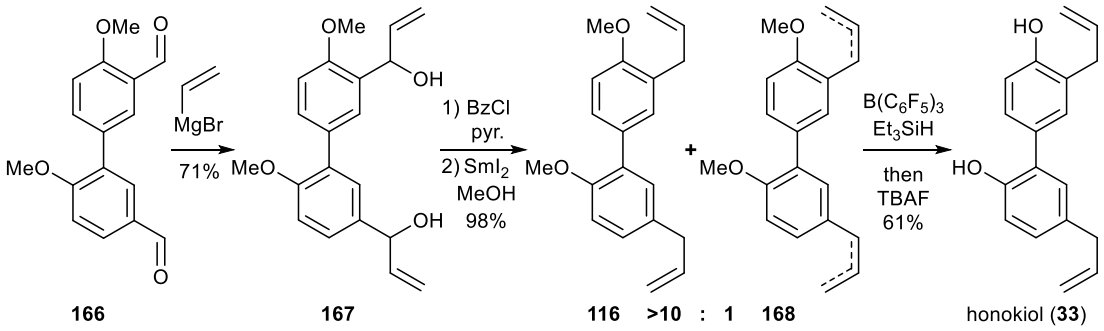
LeBel *et al.* installed the allyl group of monoterpenylmagnolol (**44**) by Grieco elimination[219,220] of primary alcohol **164** (see Scheme 30).[68]



Scheme 30. *FGI of alcohol to alkene.*[68]

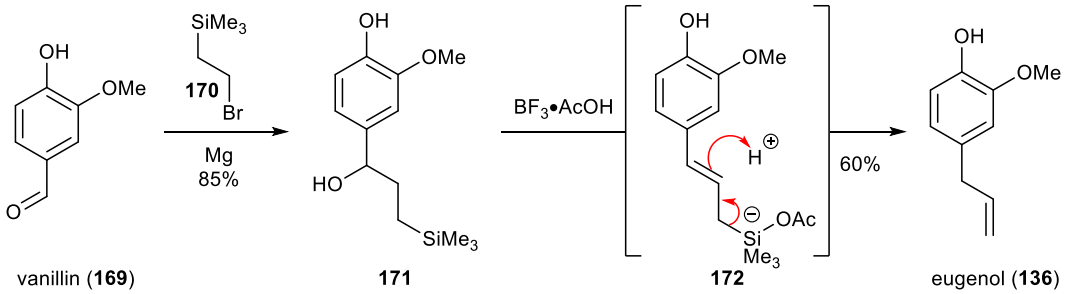
O'Neil and Wright were unable to develop conditions to form the biaryl bond of honokiol (**33**) by cross-coupling in the presence of aryl allyl groups (see Scheme 24).[78] Instead, biaryl **166** was formed with aldehydes in position for FGI. Grignard addition gave bis-allylic alcohol **167** which was transformed into the bis-benzoyl ester and then reductively cleaved with SmI_2. This sequence provided

dimethylated honokiol **116** with >10:1 selectivity for both non-conjugated allyl groups. Under conditions developed by Gevorgyan *et al.*,[221] demethylation provided honokiol (**33**) (see Scheme 31).



Scheme 31. *FGI of benzaldehydes to aryl allyl groups via allylic benzoyl esters.*[78]

Wilson and Shedrinsky developed a two-step sequence, tolerant of free phenols, for the 2-carbon homologation of various ketones and benzaldehydes into the corresponding vinyl or allyl groups.[222] The Grignard reagent formed from (2-bromoethyl)trimethylsilane (**170**) was reacted with vanillin (**169**) which generated alcohol **171**. Subsequent dehydration provided transient allylsilane **172** which after protonolysis, gave eugenol (**136**) (see Scheme 32).

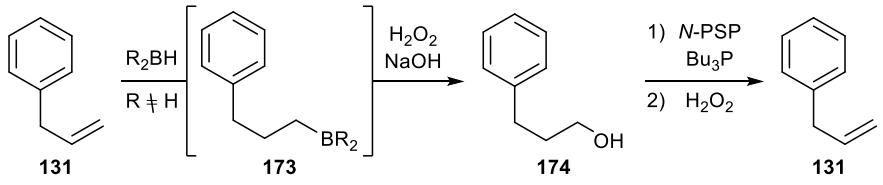


Scheme 32. *Reductive vinylation of vanillin (**169**) to eugenol (**136**).*[222]

1.7.5: Protection strategies for allyl group olefins

Although there is not a general protecting group strategy reported for masking alkenes, there are numerous reaction sequences to achieve protection in principle. In the following order, a summary is provided on the derivatisation of olefins to alcohols, alkyl halides, epoxides, thiiranes and diols and the respective conversions of the listed derivatives to the corresponding olefin.

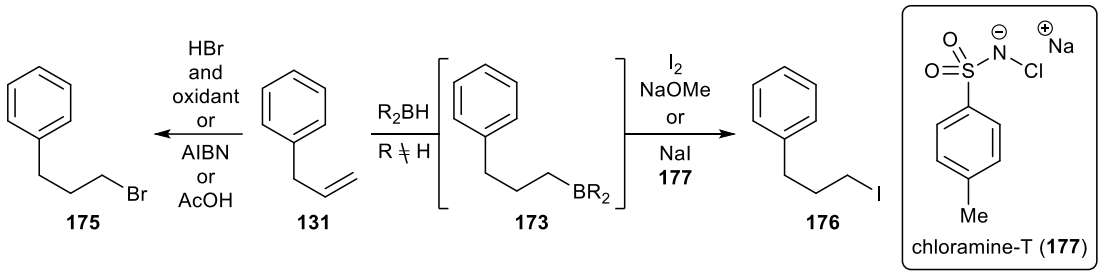
Hydroboration of olefins occurs in an anti-Markovnikov fashion.[223] The alkyl-borane formed can be oxidised with hydrogen peroxide under basic conditions to the corresponding alcohol. Alternatively, a radical initiated anti-Markovnikov hydrosilylation then Tamao oxidation[224,225] sequence has been developed which generated alcohols from olefins, although lower yields were generally obtained.[226] Using the conditions described earlier (see Scheme 30), primary alcohols can be converted to terminal alkenes by the Grieco elimination (see Scheme 33).[68,227]



Scheme 33. *Hydroboration-based alkene masking strategy.*

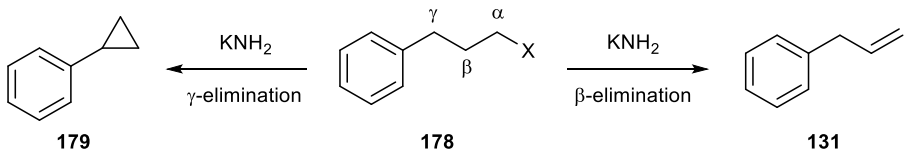
When allyl group olefins are reacted with hydrogen bromide in the presence of either an oxidant (*m*-CPBA or benzoyl peroxide),[228] a radical initiator (AIBN)[229] or AcOH,[229,230] primary alkyl bromides are

generated through anti-Markovnikov addition (see Scheme 34).[231] Alkyl iodides can be formed from olefins when hydroborated intermediates are reacted with iodine and sodium methoxide[232,233] or sodium iodide and chloramine-T (**177**)[234,235] (see Scheme 34).



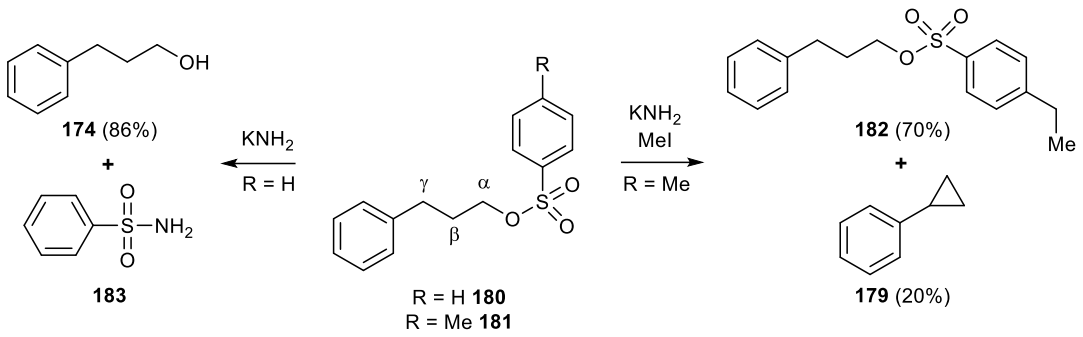
Scheme 34. *Synthesis of primary alkyl halides from allyl group olefins.*

Moving through the halogen series of 3-phenylpropyl derivatives of **178**, a gradual shift from base-mediated β-elimination (olefin **131**) to γ-elimination (cyclopropane **179**) was observed due to the halogen becoming less polarizable and more tightly bound to the α-carbon (see Table 8).[236] The tosylate group was shown to favour γ- over β-elimination, however the majority of deprotonation (using potassium amide) occurs on the methyl group of the tosyl group. Removal of the methyl group to a benzenesulfonyl derivative resulted in the cleavage of the sulfur oxygen bond (see Scheme 35).[236]



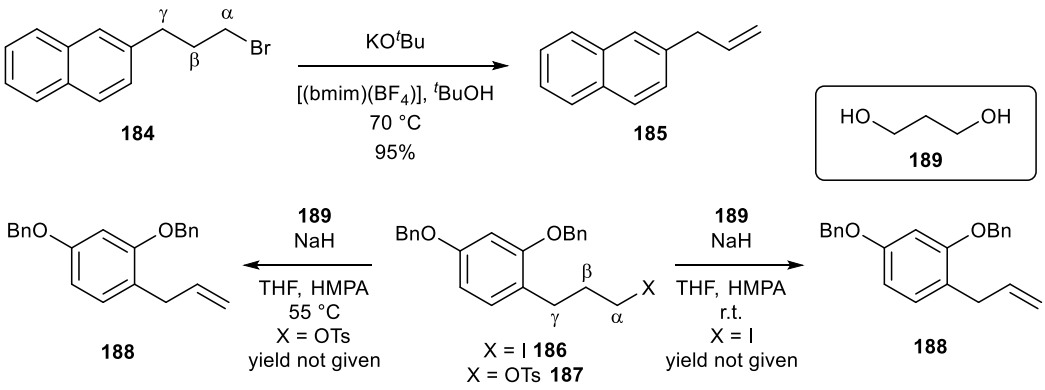
X	elimination	X	elimination
I	β	F	γ
Br	β	OTs	γ
Cl	β , γ		

Table 8. *Trends of β- versus γ-elimination of 3-phenylpropyl derivatives.*[236]



Scheme 35. *KNH_2 mediated deprotonation of Ts or benzenesulfonyl 3-phenylpropyl.*[236]

When Chi and co-workers heated naphthalene **184** with KO^{t}Bu in ionic liquid ([bmim][BF_4]), they observed an alkene in 95% yield.[237] Unfortunately, the group did not provide a structure for the alkene, but it was insinuated to be species **185** (see Scheme 36). Bergeron *et al.* reported their unsuccessful conditions to form an ether under Williamson ether synthesis conditions. Instead of constructing the ether, iodide **186** or tosylate **187** formed β-elimination product **188** (see Scheme 36).[238] The β-elimination of tosylate **187** is contrary to the observations reported by Bumgardner *et al*.,[236] which is likely attributed to the difference in electronics of arene **178** versus **187**.



Scheme 36. *Reported β-eliminations of 3-phenylpropyl derivatives.*[237,238]

Aryl allyl groups are usually epoxidized by treatment with peracids or dioxiranes. In 1920,[239] the deoxygenation of epoxides to olefins was

reported and has since received attention in the chemistry community to date.[240] Consequently, several methods have been developed and what follows is a representative summary.[241,242]

Classically, deoxygenation of epoxides to olefins occurs over multiple steps, either with or without stereocontrolled outcomes. HBr ring-opens epoxides to bromohydrins, which can then be reduced with Zn to give the olefin non-stereospecifically.[243] Cornforth *et al.* developed conditions for the stereospecific ring-opening of epoxide **190** to iodohydrin **192** which was deoxygenated to olefin **194** with retention of configuration (see Scheme 37A).[244] Single-step procedures were developed that mirror the reaction pathway shown.[242] These included; the use of Lewis-acidic reagents such as AlI_3[245] or a mixture of BF_3 and KI[246] or W^{VI} and LiI,[247] the use of electrophilic phosphonium species and iodide sources,[248–250] the use of HMDS and KOMe.[251]

The deoxygenation of oxiranes using dimethyl diazomalonate (**197**) and $Rh_2(OAc)_4$ provided alkenes with retention of configuration, however a mechanism was not provided (see Scheme 37B).[252]

Anionic Te or Se agents, such as $O{=}P(EtO)_2TeNa$[253,254] or KSeCN,[255] deoxygenated epoxides to olefins with retention of configuration. The reaction mechanism using KSeCN is similar to that depicted for Te in Scheme 37C, however as KSeCN must be used in excess,[255] which would produce substantial toxic and pungent waste, the conditions are favoured less than the described catalytic Te conditions.[253,254]

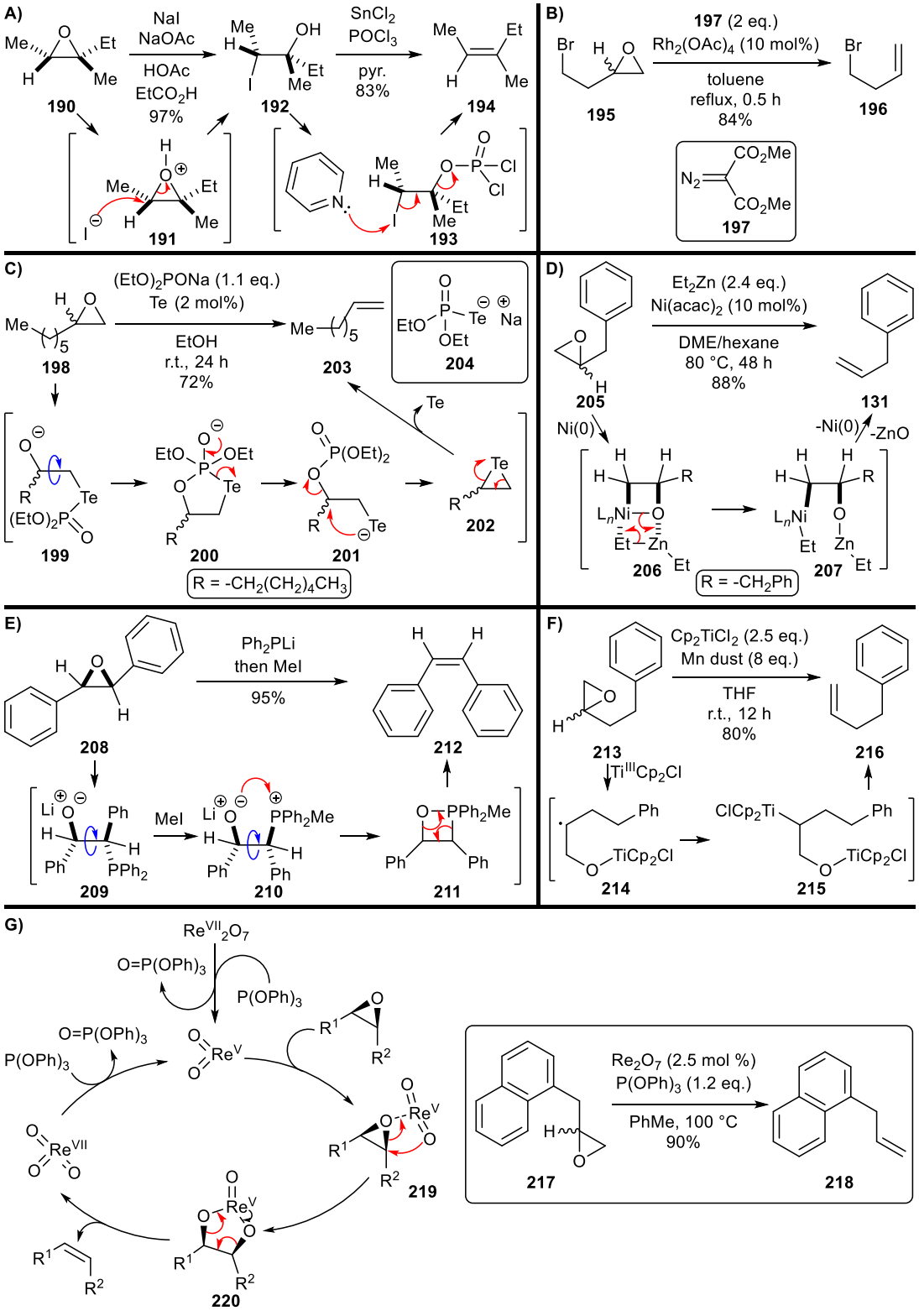
Formed *in situ*, **204** ring-opened epoxide **198** to alkoxide **199** which gave transient epitelluride[256] **202** *via* 5-membered ring intermediate **200**. Extrusion of Te afforded olefin **203** and regenerated **204**.[257]

2-Nickela(II)oxetanes are formed by oxidative addition of Ni(0) to the C-O bond of epoxides.[258,259] Mori and co-workers reported that $ZnEt_2$ coordinated to 2-nickela(II)oxetanes. Two ethyl transfers from Zn to Ni generated the olefin, ZnO and Et_2Ni^{II} that regenerated Ni^0 by reductive elimination of butane (see Scheme 37D).[240]

Vedejs and Fuchs treated epoxide **208** with Ph_2PLi which ring-opened the epoxide to **209**. Next, addition of MeI generated phosphorus betaine **210** which subsequently formed oxyphosphetane **211** that provided inverted olefin **212** *via* retro-[2+2] (see Scheme 37E).[260]

$Ti^{III}Cp_2Cl$ is a mild and selective reagent used to deoxygenate epoxides to olefins in a non-stereospecific manner by SET (see Scheme 37F).[261–265] Alternatively, the deoxygenation of **205** to **131** was achieved in 82% yield with SmI_2 by SET.[266] Cr^{II} species or Zn-Cu couple have been used to deoxygenate epoxides by SET however the yields are much lower and the reagent toxicity is greater.[267–269]

Takai *et al.* reported a stereoretentive deoxygenation of epoxides to alkenes under Re^V catalysis.[270] Re^VO_2 coordinated and ring-opened epoxides to a 5-membered rhena-2,5-dioxolane intermediate **220**. Extrusion of the olefin gave $Re^{VII}O_3$ that was reduced by $P(OPh)_3$ which regenerated the active catalyst Re^VO_2 (see Scheme 37G).



Scheme 37. *Deoxygenation of epoxides to olefins. Substrates shown were chosen from reported reaction scopes as closest examples of relevance to allyl group or terminal olefins.*

Thiiranes[271] are commonly synthesized from the corresponding oxirane using either thiourea,[272–277] potassium thiocyanate,[272,278] or phosphine sulfides,[279] but can also be accessed directly from alkenes (see Scheme 38A-C).[280]

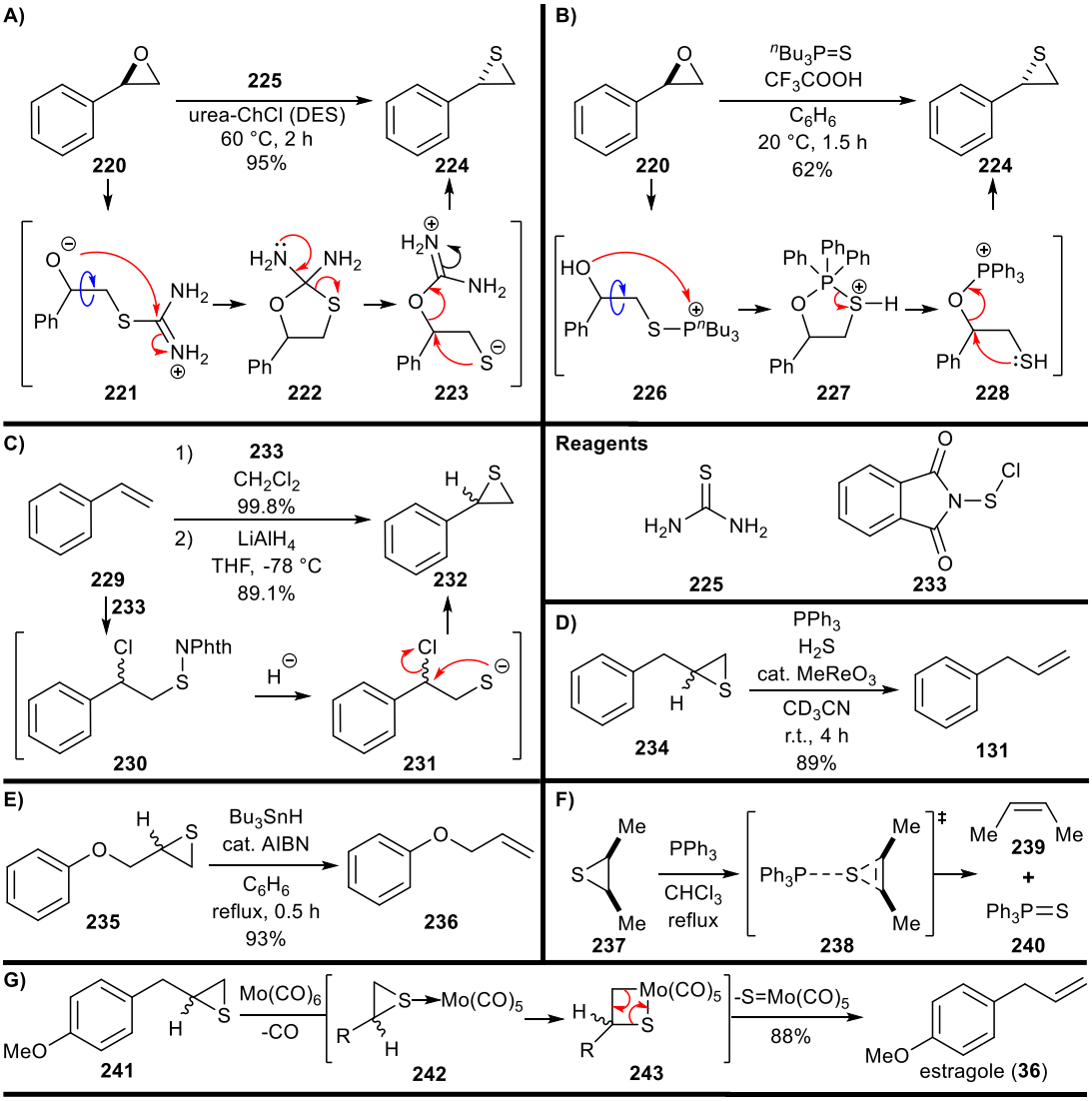
Espenson and Jacob reported the stereospecific Re^{V} catalysed desulfurisation of thiiranes to alkenes (see Scheme 38D).[281] The mechanism is similar to the rhenium catalysed deoxygenation of epoxides (see Scheme 37G).[270] An induction period for the reduction of Re^{VII} to Re^{V} was eliminated by first bubbling H_2S through a solution of $MeReO_3$ as sulfur transfers faster to phosphine than oxygen.

Thiiranes are ring-opened and eliminated to alkenes by tributyltin radical (see Scheme 38E).[282] An aminium radical protocol has also been described however the episulfides must be bonded to at least one phenyl group which is not applicable to allyl group olefins.[283]

Denney and Boskin[278] confirmed the stereoretentive observations made by Neureiter and Bordwell[284] on the desulfurisation of thiiranes to alkenes with PPh_3. Transition state **238** was proposed which gave the olefin after extrusion of $Ph_3P{=}S$ (see Scheme 38F). Terminal alkenes have also been formed under these conditions.[278,285,286]

Thiiranes desulfurized with stoichiometric $Mo(CO)_6$ provided stereoretentive olefins.[287] $Mo(CO)_5$ coordinated and oxidatively inserted into thiirane **241** which provided metallocyclobutane **243**. Subsequent retro-[2+2] gave estragole (**36**) (see Scheme 38G).

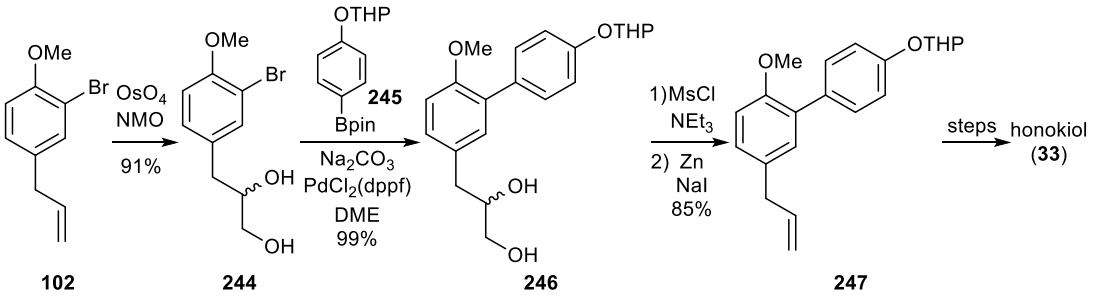
Other reagents that are reported to desulfurize thiiranes to alkenes are alkyllithiums,[274,288,289] Grignard reagents[288] and iron carbonyl reagents.[274] Generally, lower yields of olefins were obtained and these methods were less tolerant of other functional groups.



Scheme 38. (A-C) *Methods to form thiiranes.* ***(D-G)*** *Methods to desulfurize thiiranes to olefins.*

Diols are generally formed from olefins by the Upjohn dihydroxylation.[290,291] Chen *et al.* observed thermodynamic isomerisation of the aryl allyl group of **102** under various Suzuki-Miyaura cross-coupling conditions.[74] Therefore, the integral position

of the allyl group alkene was "protected" by transforming it into diol **244**. Biaryl **246** was formed in near quantitative yield and the allyl group was reinstalled *via* the elimination of an *in situ* generated iodohydrin using Zn metal which gave **247**. Further manipulations provided honokiol (**33**) (see Scheme 39).



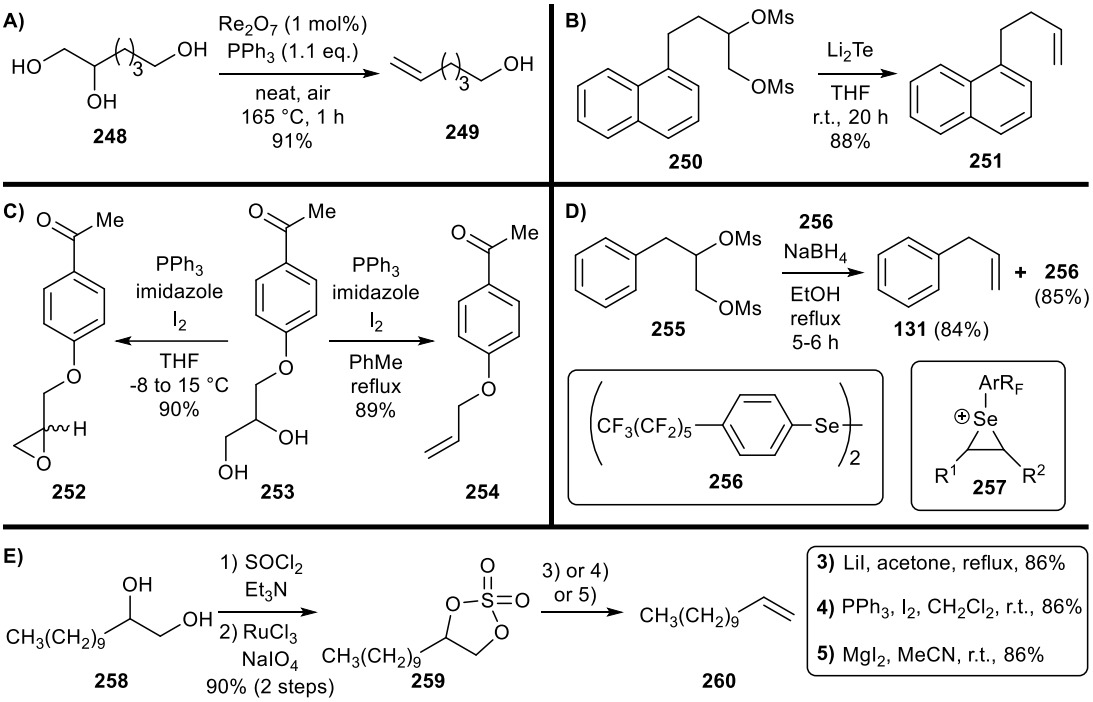
Scheme 39. *Protection of allyl group strategy by diol formation and deprotection.*

De Vries *et al.* reported the Re^{V} catalysed deoxydehydration of vicinal diols to olefins[292] (see Scheme 40A) which is mechanistically similar to the Re^{V} deoxygenation of epoxides to alkenes (see Scheme 37G).

Dimesylate **255** was treated with recoverable fluorus diselenide **256** and $NaBH_4$ which provided transient episelenide[257] **257** that extruded an aryl selenium species and provided olefin **131**.[293] Similarly, when dimesylates are reacted with telluride dianion, an epitelluride intermediate was formed that extruded tellurium and gave the alkene[294,295] (see Scheme 40D and 40B).

Mereyala and co-workers generated epoxides or olefins directly from vicinal-diols under Appel-like conditions, the outcome of which was controlled by the solvent and temperature (see Scheme 40C).[296]

Vicinal-diols can be transformed into cyclic sulfates.[297,298] The Jang group reported three conditions to convert cyclic sulfates such as **259** to the corresponding olefin **260** (see Scheme 40E).[299–301]



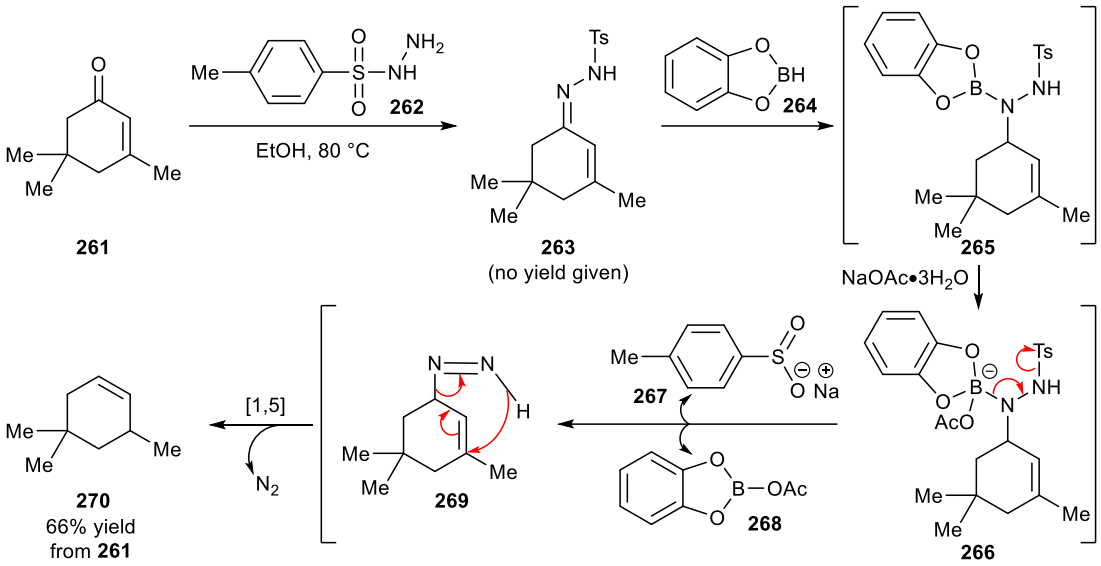
Scheme 40. *Transformation of vicinal diols or dimesylates to olefins.*

1.7.6: Transposition or removal of conjugated allyl group impurities

Aryl allyl group species cannot be separated by conventional column chromatography from their thermodynamically isomerized allyl group isomer. However, there are two strategies that in practice overcome this problem. If thermodynamic isomerisation has occurred in low proportions, then it is possible to selectively derivatise the di-substituted olefin over the mono-substituted olefin by Prilezhaev epoxidation[302] or Upjohn dihydroxylation. Once derivatised, separation from the desired non-conjugated allyl group can be

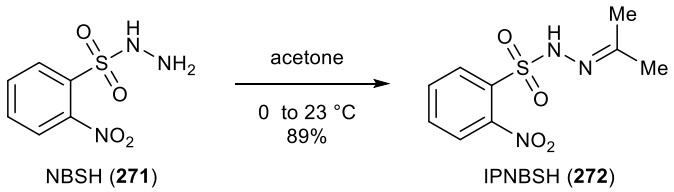
achieved by normal-phase column chromatography. In Banwell and co-workers synthesis of simonsol C (**56**), they carried through an impurity associated with thermodynamic isomerisation of the aryl allyl groups (observed in ^{1}H NMR spectra) from species **94** to **98** (see Scheme 18). Parikh-Doering oxidation of **98** formed simonsol C (**55**) free from isomeric impurities (by NMR spectroscopy). Therefore, it is assumed that the Parikh-Doering oxidation conditions selectively derivatised the di-substituted olefin which facilitated separation.

If the aryl allyl group has isomerized to a large extent at a late stage of a synthesis, discarding the material and starting again is undesirable. Contra-thermodynamic transposition of a double bond was first described in 1975 by Hutchins *et al.*[303] but refined to milder conditions in 1976 and 1981 by Kabalka and co-workers.[304,305] Condensation of enone **261** with **262** formed *N*-tosylhydrazone **263** which was reduced with catecholborane (**264**) and gave intermediate **265**. Addition of NaOAc•$3H_2O$ consequently formed diazene **269** that underwent a [1,5]-sigmatropic rearrangement which transposed the alkene with loss of N_2 and gave **261** (see Scheme 41).[297] The conditions also proved to be a mild alternative to the Wolff-Kishner-Huang(-Minlon) reduction,[306,307] the Mozingo reduction[308,309] or the Clemmensen reduction[310] for the reduction of α,β-saturated ketones or aldehydes to methylene or methyl groups respectively. To note, Myers and Furrow have also reported a mild alternative to the Wolff-Kishner reduction *via* TBS silylated diazene intermediates.[311]



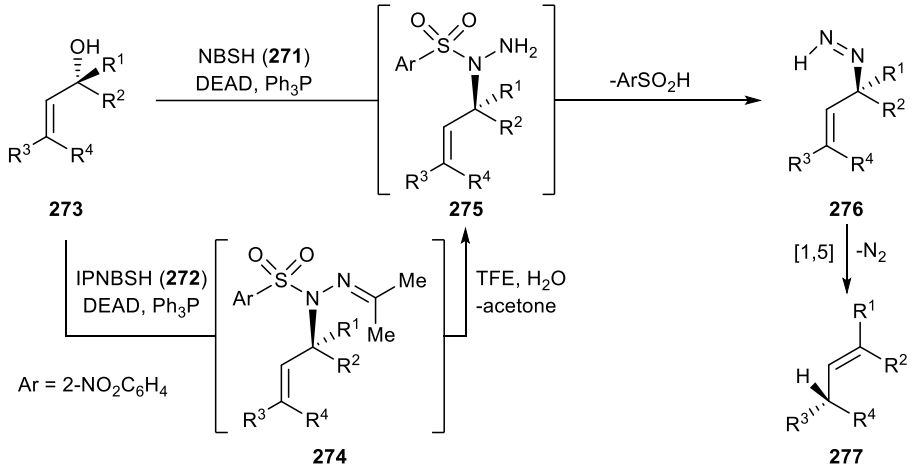
Scheme 41. *Reductive transposition of tosylhydrazone* ***263****.*

Myers *et al.* reported the reductive transposition of allylic alcohols with NBSH (**271**) under Mitsunobu conditions,[312,313] which also formed a diazene intermediate that underwent a [1,5]-shift (see Scheme 43). However, as the Mitsunobu gives products with inversion of stereochemistry, the hydride was delivered stereospecifically on the inverse face of the starting alcohol (see Scheme 43). The thermal instability of NBSH (**271**) required sub-ambient temperatures which resulted in the formation of undesired 2-nitrobenzenesulfinic acid derived Mitsunobu products. Movassaghi *et al*. developed IPNBSH (**272**) (see Scheme 42) which exhibited greater thermal stability than NBSH (**271**).[314]



Scheme 42. *Transformation of NBSH (****271****) to IPNBSH (****272****).*[314]

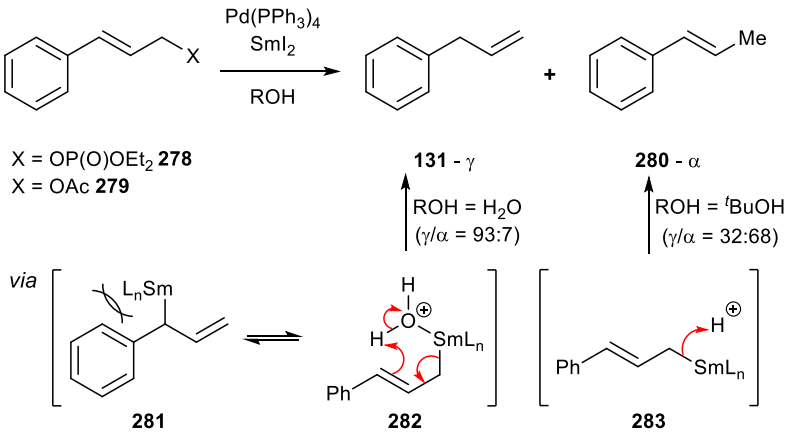
IPNBSH (**272**) also provided greater flexibility with respect to order of addition, reaction temperature, solvent choice and concentration of substrate and reagents.[314] Intermediate **274** formed from the Mitsunobu reaction of allylic alcohol **273** with IPNBSH (**272**) can be isolated or can be treated with 2,2,2-TFE/H_2O in a one-pot reaction upon completion of the initial Mitsunobu reaction to provide **275** (see Scheme 43). Subsequent loss of 2-nitrobenznesulfinic acid followed by a stereospecific [1,5]-shift provides **277**. IPNBSH (**272**) has also been used to reductively transpose allylic carbonates under Pd^0 catalysis *via* π-allyl metal complexed intermediates.[315,316]



Scheme 43. *Mitsunobu reaction with NBSH (**271**) or IPNBSH (**272**) to reductively transpose generic allylic alcohol **273** stereospecifically.*

In 1998 and in 2013, Mikami *et al.* and O'Neil *et al.* respectively reported on the samarium iodide mediated elimination/isomerization of allylic esters (see Scheme 44).[317,318] Mikami and co-workers proposed a radical reaction mechanism which formed a ligated samarium allyl complex intermediate. The samarium isomerized

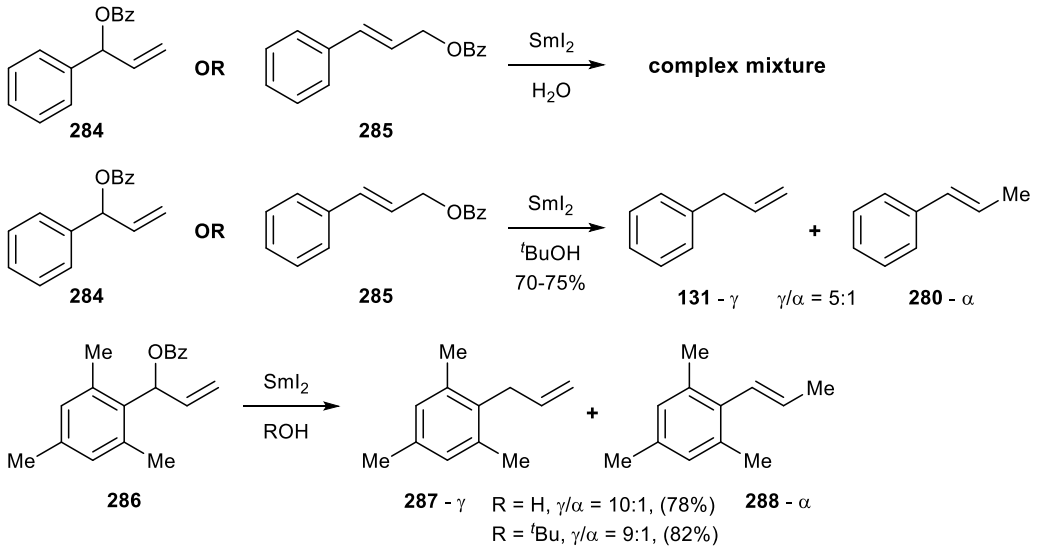
between α and γ positions until eliminated by a proton source. The ratio of internal to external allyl groups formed was proposed to be based on steric effects. Bulky proton sources with poor coordinating ability, such as ^{t}BuOH, reacted with allylsamarium through an S_E2 pathway which gave primarily the α-protonated isomer **280**. As H_2O coordinated strongly to samarium, the water molecule is proposed to be delivered in an intramolecular fashion through a 6-membered transition state **282** to give the γ-protonated isomer **131** (see Scheme 44). This was evidenced by the addition of HMPA which reversed the selectivity to α-protonation when quenched with H_2O.



Scheme 44. *SmI_2 mediated elimination/isomerization of allylic esters.*[317]

Although O'Neil and co-workers reported numerous results that were in keeping with the observations by Mikami *et al.*, alternative reactivity was detected when the steric influence on terminal allylic benzoate reductions was studied (see Scheme 45).[311] Either allylic benzoate **284** or **285** was treated with SmI_2 followed by H_2O which led to complex mixtures of products. However, when quenched with

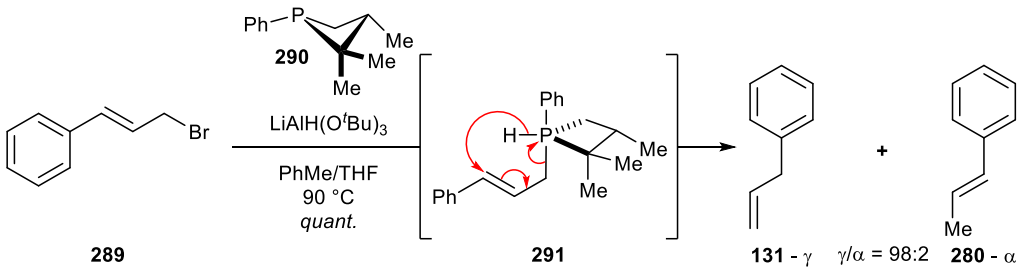
^{t}BuOH, a mixture of isomers formed that favoured γ-isomer **131**. Sterically bulky **286** was treated with SmI_2 followed by H_2O or ^{t}BuOH which surprisingly favoured the formation of γ-isomer **287** in both cases. This irregularity is not understood and is not in keeping with the sterically controlled pathway reported by Mikami and co-workers.



Scheme 45. *SmI_2 mediated elimination/isomerization of allylic benzoyl esters.*[318]

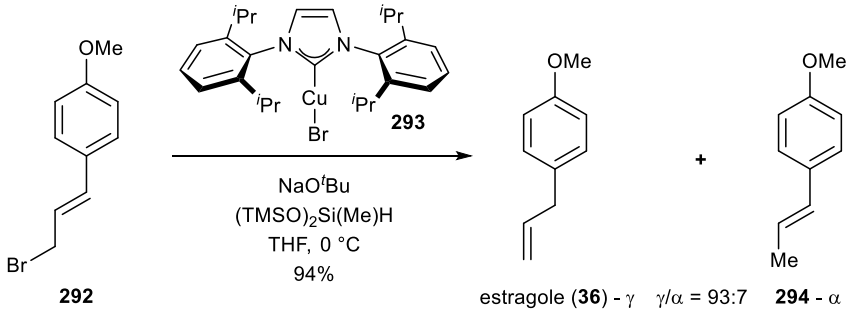
In 2015, Radosevich *et al*. reported the biphilic organophosphorus catalysed regioselective reductive transposition of allylic bromides *via* P^{III}/P^{V} redox cycling.[319] Allylic bromide **289** underwent S_N2 attack from (σ^3-P)(P^{III}) phosphetane **290** which formed an isolable (σ^4-P)(P^{V})$^{+}$ phosphetanium species. However, in the presence of $LiAlH(O^{t}Bu)_3$, the (σ^4-P)(P^{V})$^{+}$ phosphetanium was converted into (σ^5-P)(P^{V}) hydridophosphorane species **291**, which underwent a thermally promoted [1,5]-sigmatropic shift and regenerated (σ^3-P)(P^{III}) phosphetane **290** (see Scheme 46). Overall, the reaction proceeds with retention of configuration at phosphorus.

Computational and mechanistic studies have been performed which tentatively assigned the trigonal bipyramidal configuration of **291**.



Scheme 46. *Biphilic phosphetane catalysed regioselective reductive transposition of allylic bromides via P^{III}/P^{V} redox cycling.*[319]

In 2016, Teichert *et al.* reported copper(I) species **293** catalysed allylic substitutions with a hydride nucleophile derived from a hydrosilane, which led to the reductive transposition of allylic bromides (see Scheme 47).[320] The reaction is mild and was carried out between -78 to 35 °C dependent on the electronics of the arene substrate.



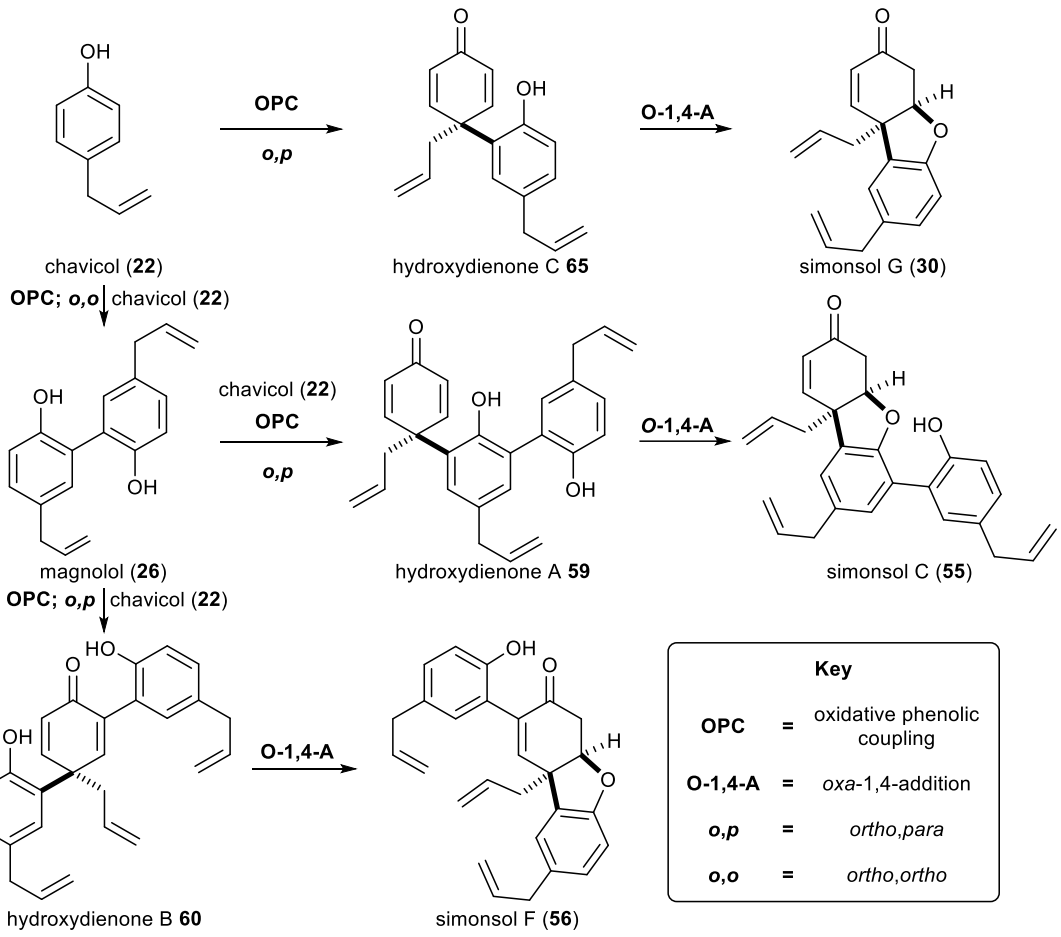
Scheme 47. *Copper catalysed reductive transposition of allylic bromides.*[320]

2: Results and Discussion

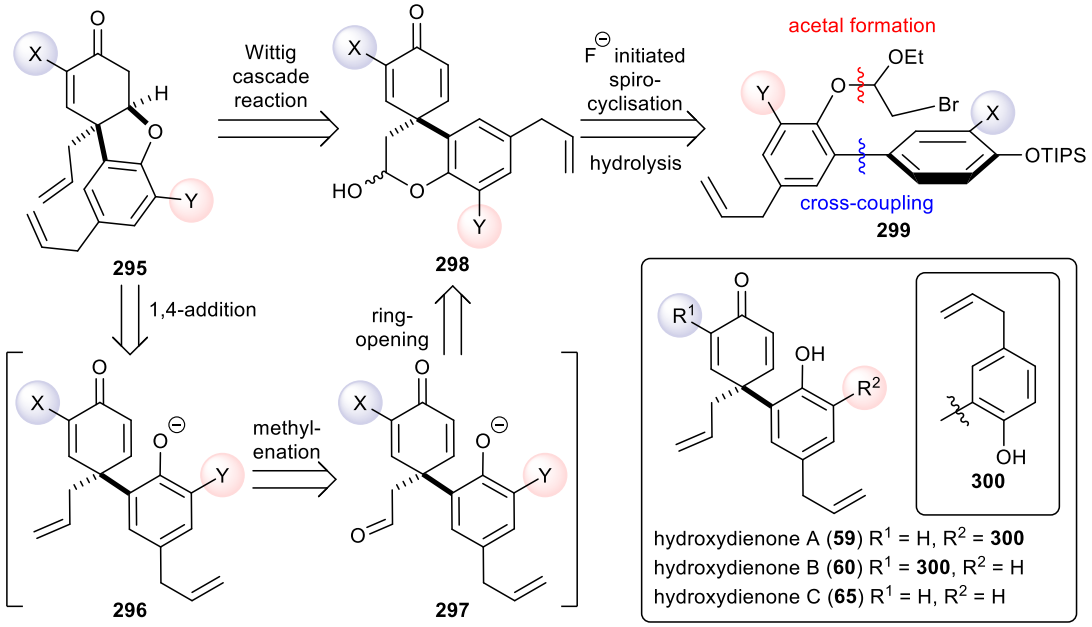
2.1.1: Biosynthesis and retrosynthetic analysis of simonsol C, simonsol F, and simonsol G

Our retrosynthetic analysis of simonsol C (**55**), simonsol F (**56**) and simonsol G (**30**) was guided by the proposed biosynthesis (see Scheme 48).[88,102] We reasoned that hemi-acetal **298** would act as a masked biosynthetic equivalent to the proposed hydroxydienone intermediates. Treatment of hemi-acetal **298** under Wittig methylenation conditions was proposed to ring-open the hemi-acetal to **297**, followed by methylenation and *oxa*-1,4-addition to give the functionalised hydrodibenzofuran core **295** (see Scheme 49). Dependent on the functionalisation at X or Y of **295**, cross-coupling with a derivatised unit of chavicol (**22**) should furnish simonsol C (**55**) or simonsol F (**56**), whereas if X = Y = H, simonsol G (**30**) is made.

We envisaged that the spirocyclic hemi-acetal **298** would be made from the corresponding acetal which we reasoned could be accessed from biaryl **299** using a fluoride-initiated desilylative intramolecular alkylation reaction[102] developed by Magnus *et al.* during their synthesis of (-)-galanthamine (**58**).[107] Owing to previous success within the Denton group,[73,87,102,132] it was reasoned that the biaryl bond could be made in the presence of the isomerisation prone allyl groups by Suzuki-Miyaura cross-coupling.



Scheme 48. *Biosynthesis of Illicium-derived neolignans from chavicol (**22**).*



Scheme 49. *Retrosynthetic analysis of simonsol C (**55**) (X = H, Y = Br), simonsol F (**56**) (X = Br, Y = H) and simonsol G (**30**) (X = Y = H) and their analogy to hydroxydienone intermediates proposed in the biosynthesis.*

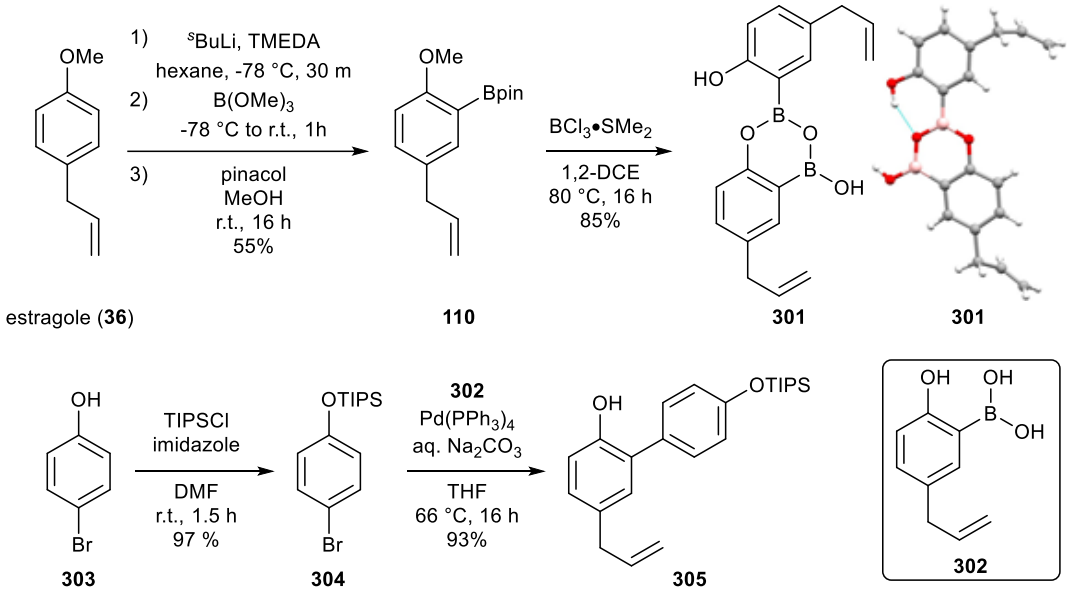
2.1.2: Simonsol C

In 2016, Banwell and co-workers completed the total synthesis of simonsol C (**55**).[103] The following unoptimised total synthesis of simonsol C (**55**) from estragole (**36**) was originally completed by Denton and Saska in 2016.[321] The optimisation of reaction conditions, isolation of previously unknown intermediates, and full characterisation of several species has since been completed.

2.1.3: Total synthesis of simonsol C

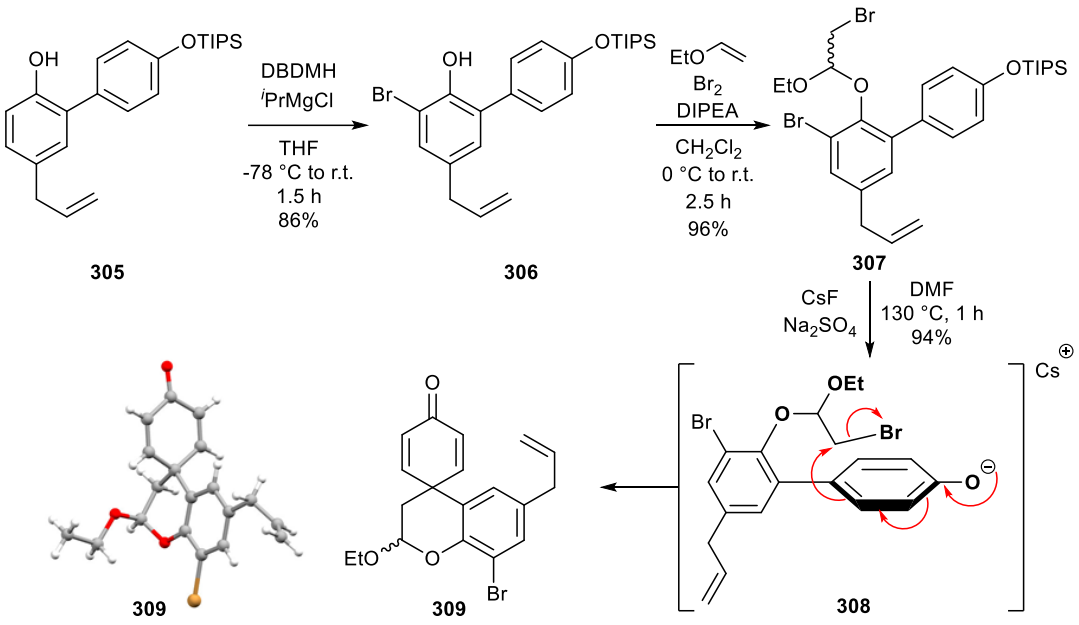
Estragole (**36**) was lithiated using ^{s}BuLi and TMEDA and the corresponding organolithium species was reacted with $B(OMe)_3$. After acidic work-up and subsequent transesterification with pinacol, boronic acid pinacol ester **110** was obtained (see Scheme 50). Transesterification was performed as the boronic acid pinacol ester **110** was both easier to isolate and was less prone to protodeboronation in the subsequent step compared to boronic acid **72**. Demethylation of **110** was achieved when BCl_3•SMe_2 was used at 80 °C which provided dimeric boronic acid **301** after 16 hours, or an approximate 1:1 mixture of monomeric boronic acid **302** and **301** after 1 hour. Gratifyingly, **301** acted as 2 eq. of **302** in subsequent Suzuki-Miyaura cross-couplings. For the purpose of this thesis, although mixtures of **301** and **302** were used, only the monomeric boronic acid **302** will be depicted for clarity. To prepare the halogen

coupling-partner, 4-bromophenol (**303**) was protected as a TIPS silyl ether **304** and was subsequently coupled with **302** under Suzuki-Miyaura cross-coupling conditions which afforded biaryl **305** (see Scheme 50).



Scheme 50. *Synthesis of novel boronic acid **301**/**302** and formation of biaryl **305**.*

A chemo- and regioselective bromination of biaryl **305** was achieved when reacted with ^{i}PrMgCl and DBDMH[59,103,114] which gave brominated biaryl **306**. A pre-mixed solution of ethyl vinyl ether and bromine generated a bromonium species *in situ* that was attacked by **306** in the presence of DIPEA which gave bromo-acetal **307**. Using conditions developed by Magnus and co-workers,[107] bromo-acetal **307** was desilylated which gave intermediate **308** that underwent a dearomatizing intramolecular alkylation reaction and afforded spirocyclic dienone **309** (see Scheme 51).

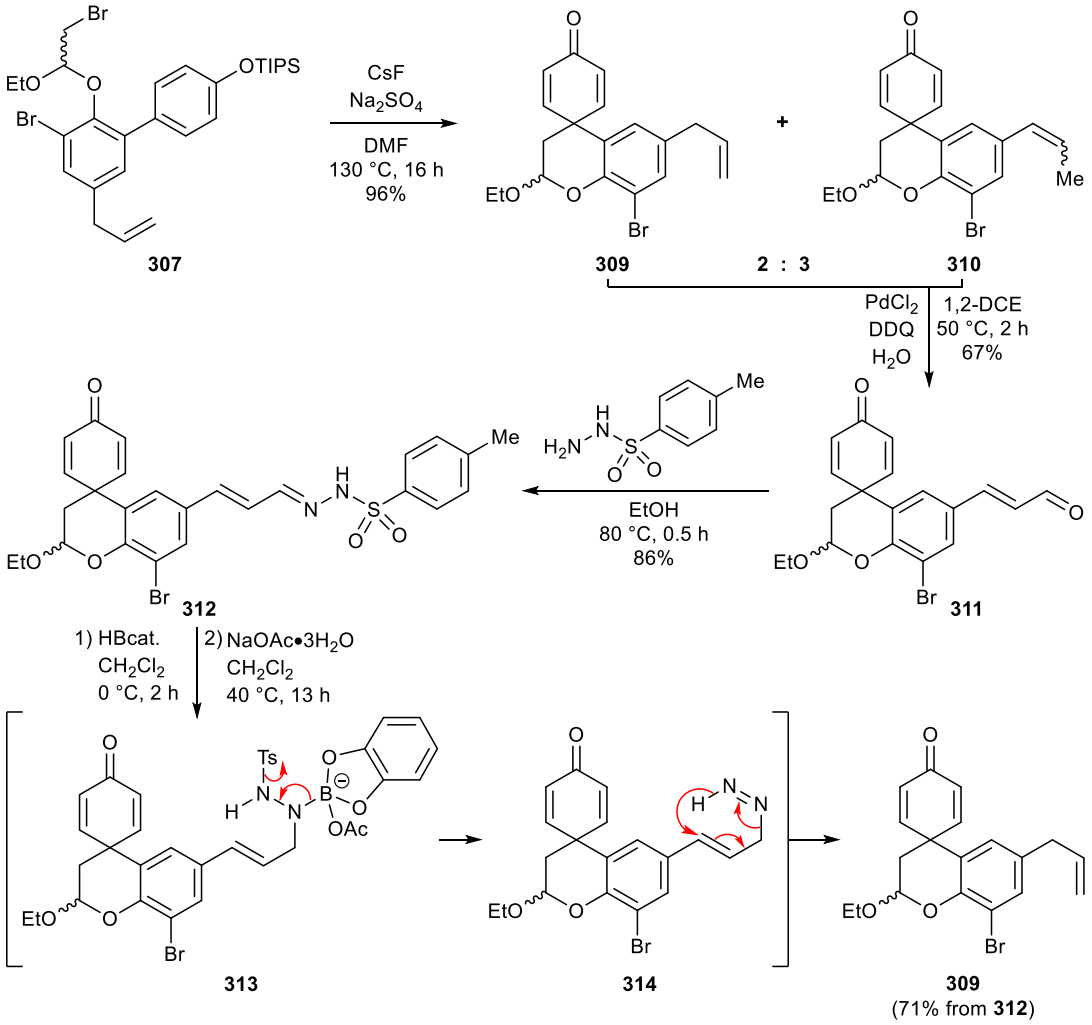


Scheme 51. *Synthesis towards dienone* ***309****.*

The conditions for the intramolecular spirocyclisation reaction to form **309** required high dilution (100 mL/mmol) in DMF, a toxic and environmentally damaging solvent. To overcome this problem on a 6.89 mmol scale, **309** was injected into the reaction mixture over 15 hours. Intermolecular alkylation was avoided, but unfortunately a substantial amount of the thermodynamically favoured alkene isomer **310** was produced. Due to the large scale, contra-thermodynamic transposition of the alkene was explored (see Scheme 52).

Oxidation[322] of alkenes **309** and **310** afforded enal **311** which underwent condensation with *p*-toluenesulfonyl hydrazide and provided tosylhydrazone **312**. Subsequent reduction by HBcat[304] followed by acetylation of boron with NaOAc•3H_2O gave intermediate **313**. The elimination of an acetate catecholborane derivative and

tosyl anion afforded transient diazene **314** which underwent a [1,5]-shift with expulsion of dinitrogen and gave **309** (see Scheme 52).

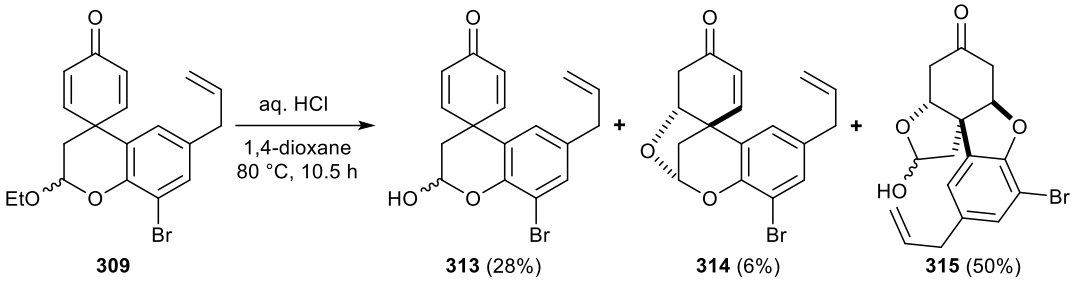


Scheme 52. *Contra-thermodynamic transposition sequence to obtain* ***309****.*

Acid-mediated hydrolysis of acetal **309** afforded hemi-acetal **313**, as well as inconsequential products of further *oxa*-conjugate addition products, enone **314** and inseparable[323] ketone diastereoisomers **315** (see Scheme 53).

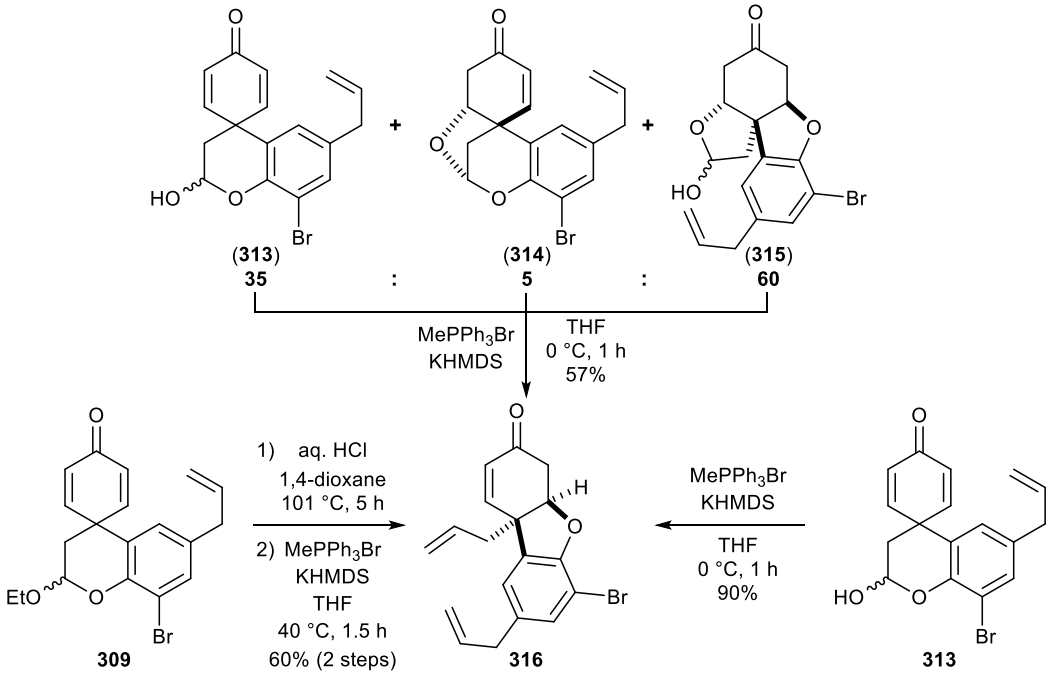
The Wittig cascade reaction was developed in the Denton group to construct the tetrahydrodibenzofuran core found in *Illicium*-derived neolignans.[102] Contrary to previous reports (see Scheme 11),[102] the

Wittig cascade reaction was efficient at 0 °C when applied in the total synthesis of simonsol C (**55**), simonsol F (**56**) and simonsol G (**30**).



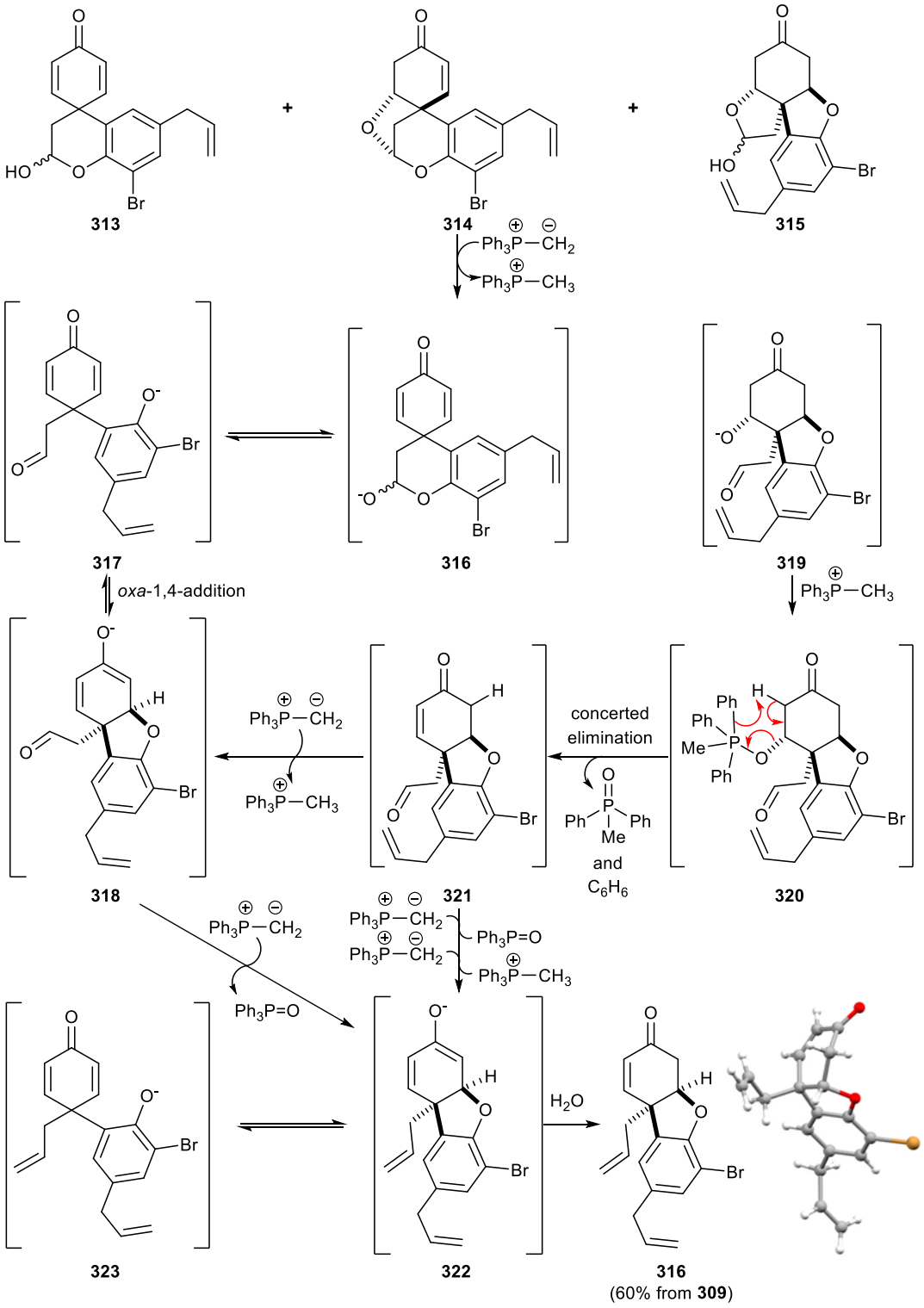
Scheme 53. *Acid-mediated hydrolysis of acetal* ***309****.*

Dienone **313**, enone **314**, and ketones **315** were reacted separately under the Wittig cascade conditions which all provided bromo tetrahydrodibenzofuran **316**. To avoid the challenging isolation of **313**–**315**, a two-step sequence from acetal **309** was also developed that gave bromo tetrahydrodibenzofuran **316** in 60% yield over the two-steps (see Scheme 54).



Scheme 54. *Synthesis of bromo tetrahydrodibenzofuran* ***316****.*

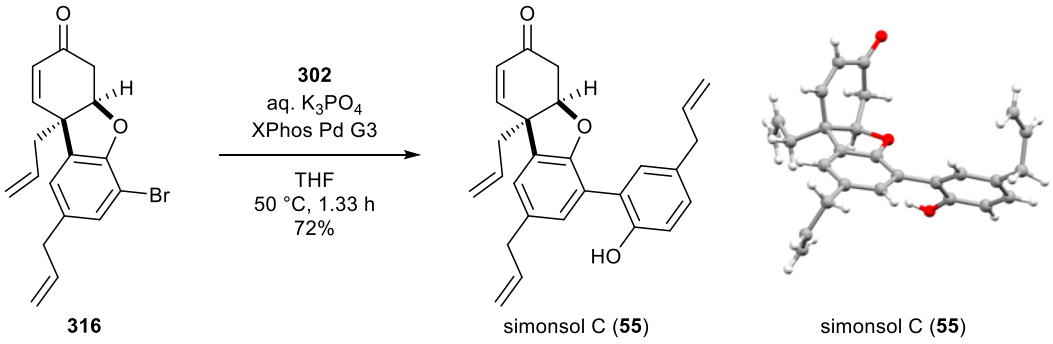
Under the reaction conditions, it is speculated that dienone **313** and enone **314** converged to ring-opened hemi-acetal **317**. Subsequent intramolecular *oxa*-1,4-addition provided aldehyde **318** which was irreversibly capped to the allyl group species **322** by Wittig methylenation. The addition of H_2O protonated the equilibrated mixture of **322** and phenolate **323** which gave the desired bromo tetrahydrodibenzofuran core **316** (see Scheme 55). The inseparable[323] ketone diastereoisomers **315** were deprotonated to alkoxide **319** that underwent an unusual elimination, possibly through the intermediary of oxyphosphorane **320**, in a concerted fashion (as depicted, see Scheme 55) or *via* an E1cB-elimination pathway which provided aldehyde **321**.[324] Experimentation carried out on the analogous reaction in the synthesis of simonsol G (**30**) (see Table 10) showed that ketone **345** gave dienone **69** under the Wittig cascade conditions. Therefore, either aldehyde **321** was deprotonated which gave **318** or dienone **321** underwent Wittig methylenation and was then deprotonated which gave **322**. Both pathways converged to a species previously described in the Wittig cascade reaction of **313** and **314** (see Scheme 55). The bromo substituent within **316** allowed late-stage functionalization to either provide simonsol C (**55**) or non-natural derivatives that may be of interest from assay-based SAR studies.



Scheme 55. *Proposed Wittig cascade reaction mechanism for the synthesis of tetrahydrodibenzofuran* ***316*** *from a mixture of* ***313***, ***314*** *and* ***315***.

To this end we examined the conversion of **316** into simonsol C (**55**) *via* a Suzuki-Miyaura cross-coupling with boronic acid **302** (see

Scheme 56). This final coupling was complicated by the free hydroxyl group present within the boronic acid, the sensitivity of the allyl groups towards thermodynamic isomerization, as well as an unexpected rearrangement to tri-aryl species simonsinol (**40**) which occurred readily at temperature ≥ 55 °C (see Section 2.2.1). After some preliminary experiments, a coupling reaction was developed using Buchwald's third generation palladacycle pre-catalyst (XPhos Pd G3) at 50 °C which provided simonsol C (**55**) in 72% yield (see Scheme 56).[325] The spectroscopic data obtained for synthetic simonsol C (**55**) were in excellent agreement with both natural[97] and synthetic samples.[103]



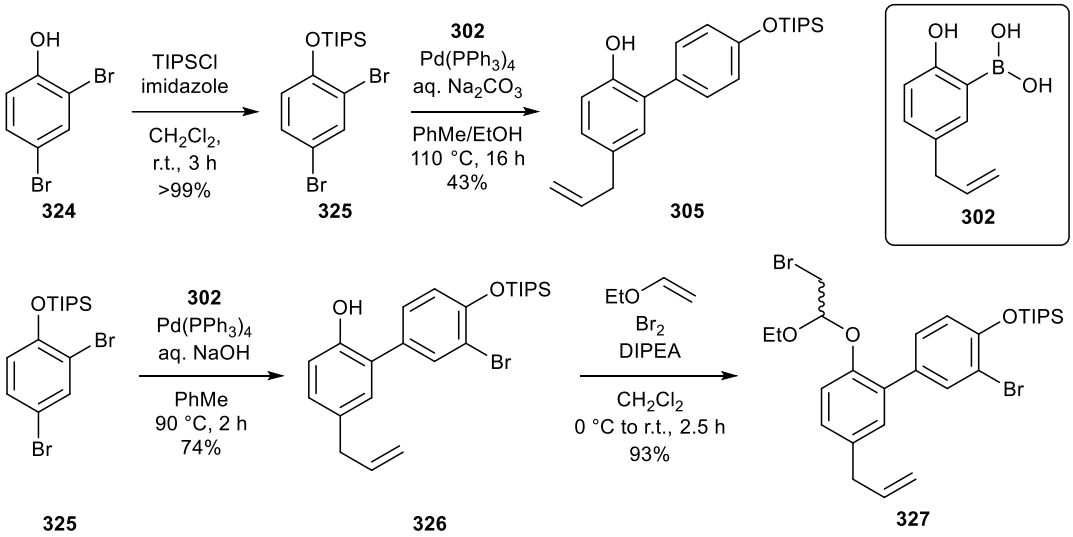
Scheme 56. *Completion of the synthesis of simonsol C (**55**) using a Suzuki-Miyaura cross-coupling reaction.*

2.1.4: Simonsol F

To date, there has been no previous reported synthesis of simonsol F (**56**). The following synthesis starts from estragole (**36**) and contains analogous steps to those described in our synthesis of simonsol C (**55**).

2.1.5: Total synthesis of simonsol F

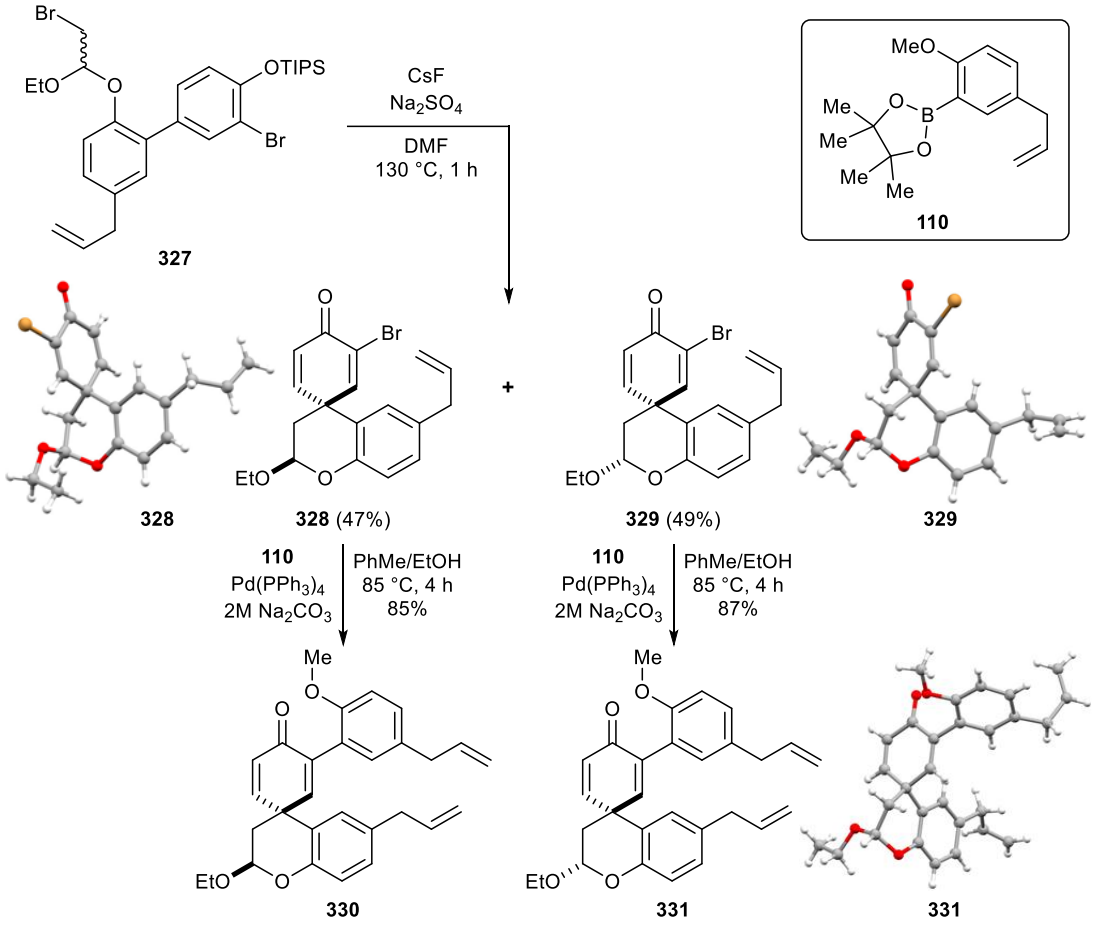
Silylation of 2-4-dibromophenol (**324**) under standard conditions gave **325** which underwent cross-coupling with **302** using conditions previously developed from the first study towards simonsol F (**56**) (see Section 2.3.1). Unfortunately, this provided des-bromo **305** but after some tweaking, a successful regioselective Suzuki-Miyaura cross-coupling was realised which gratifyingly gave **326**. Subsequent bromoacetalisation gave **327** in excellent yield (see Scheme 57).



Scheme 57. *Formation of bromo-acetal **327** from 2-4-dibromophenol (**324**).*

Bromo-acetal **327** was treated with CsF at 130 °C which provided dienone diastereoisomers **328** and **329** through a desilylating-intramolecular-alkylation reaction developed by Magnus and co-workers.[107] When bromo-dienone **328** and **329** were reacted under the acid-catalysed hydrolysis reaction then Wittig cascade reaction, no bromine containing species were visible by HRMS or LC-MS. Therefore, Suzuki-Miyaura cross-coupling conditions were applied to bromo-dienone diastereoisomers **328** and **329** both separately and

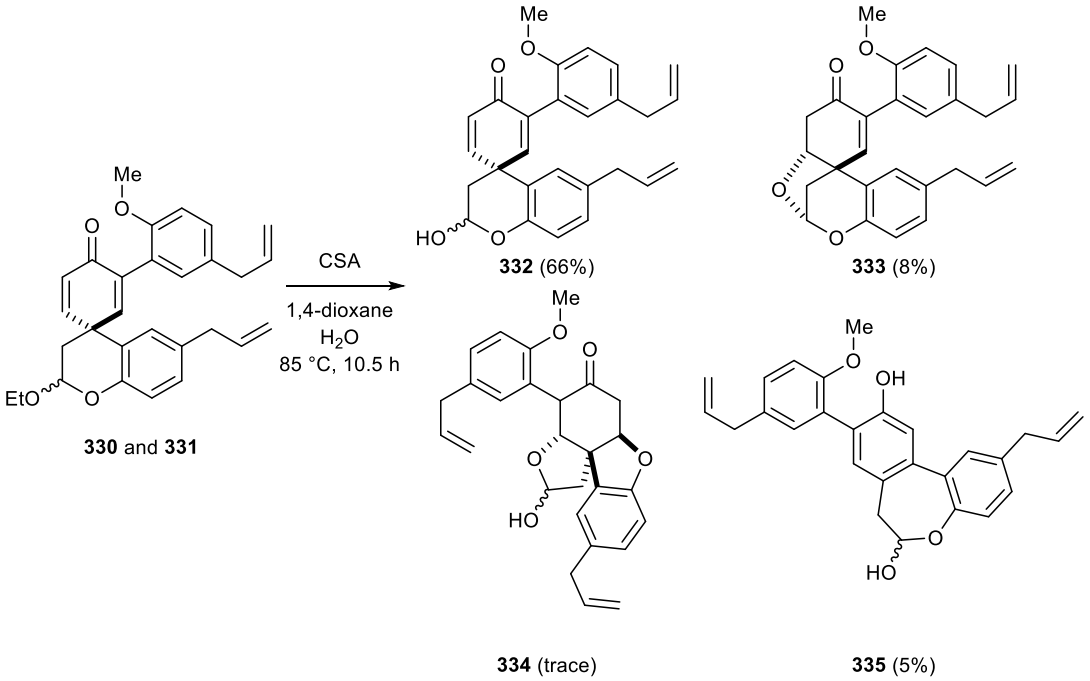
as a mixture with boronic acid pinacol ester **110** which gave acetal diastereoisomers **330** and **331** in excellent yield (see Scheme 58).



Scheme 58. *Spirocyclisation of bromo-acetal **327** and subsequent Suzuki-Miyaura cross-coupling which installed the third unit of chavicol (**22**).*

Acetal diastereoisomers **330** and **331** were heated with aq. HCl under the same conditions used in the synthesis of simonsol C (**55**) but this resulted in a complex mixture of products (not depicted). Gratifyingly, acidic hydrolysis using camphorsulfonic acid provided the inseparable[323] hemi-acetal diastereoisomers **332** in 66% yield, enone **333** in 8% yield and trace amounts of two further compounds, likely ketone diastereoisomers **334** (detected by ^{1}H NMR

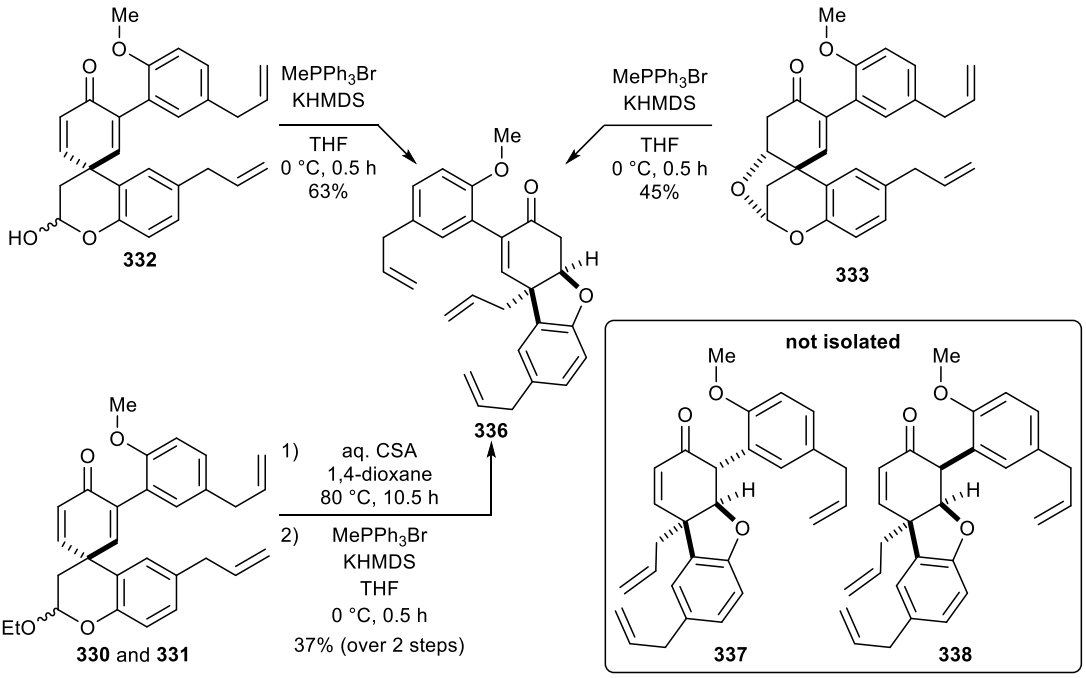
spectroscopy). Phenol **335** was also isolated in 5% yield as the product of a dienone phenol rearrangement (see Scheme 59).[326,327]



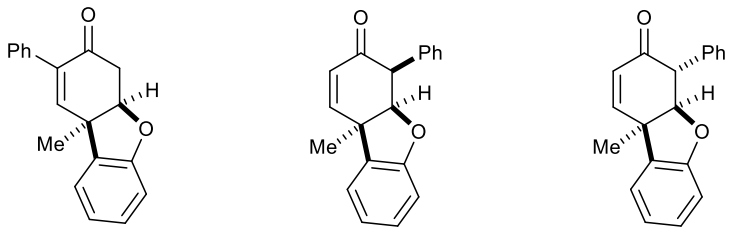
Scheme 59. *Products from the CSA-mediated acid hydrolysis of acetal* ***330*** *and* ***331****.*

Inseparable[323] hemi-acetal diastereoisomers **332** or enone **333** were reacted under the developed Wittig cascade conditions which gave methylated simonsol F **336**. Alternatively, the crude material obtained after acid hydrolysis of **330** and **331** was subjected to the Wittig cascade conditions which also provided methylated simonsol F **336**, although in lower yield (see Scheme 60). Due to the non-symmetrical nature of the dienone intermediate generated from ring-opening of the hemi-acetal in the Wittig cascade reaction, three hydrodibenzofurans **336**, **337** and **338** can theoretically form (see Scheme 60). However, as the reaction is under thermodynamic control, only **336** was provided. Quantum chemical calculations were undertaken on a model system that truncated the allyl groups to

methyl groups (see Table 9)[328] which confirmed **339**/**336** as the thermodynamically favoured tetrahydrodibenzofuran isomer.



Scheme 60. *Synthesis of methylated simonsol F* ***336****.*



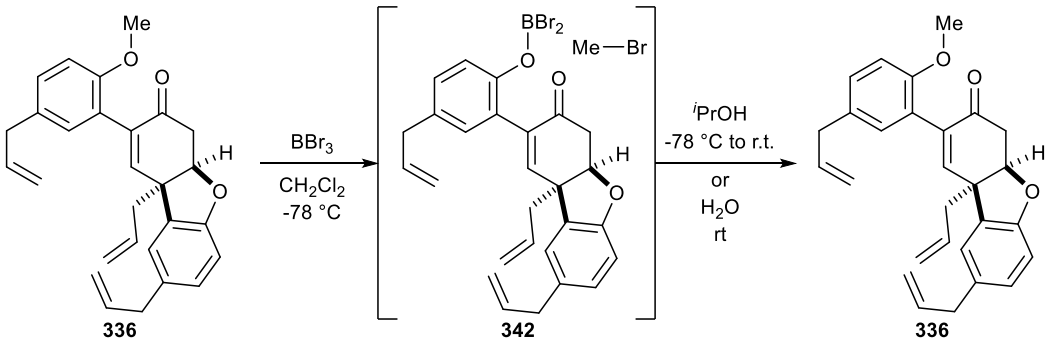
339 **340** **341**

Model system	E_{rel} (Kcal mol^{-1})
339	0
340	5.29
341	6.05

Table 9. *Uncorrected relative electronic energies at the B3LYP/B-31G* (in vacuo) level of theory for the products resulting from a model system of the Wittig cascade reaction.*[328]

The final step in the synthesis of simonsol F (**56**) was the demethylation of **336** which was remarkably challenging. Initially,

methylated simonsol F **336** was reacted with BBr_3 at -78 °C which was monitored by LC-MS. Aliquots were taken by quick withdrawal and injection of an aliquot of the reaction mixture into a solution of MeCN/H_2O (19:1) which showed by LC-MS analysis that the starting material was consumed, and a new peak associated with simonsol F (**56**) was present. However, when the reaction mixture was quenched at ambient temperature with H_2O or at -78 °C with ^{i}PrOH, methylated simonsol F **336** was the dominant species and simonsol F (**56**) was no longer detected by LC-MS analysis (see Scheme 61). When the reaction was performed at ambient temperature, above the boiling point of MeBr (b.pt. 4 °C), several products formed but none contained the characteristic [4.3.0] ring system as judged by ^{1}H or ^{13}C NMR spectroscopy.



Scheme 61. *Demethylation and re-methylation of methylated simonsol F* ***336****.*

Next, a BCl_3-mediated demethylation was investigated which generated MeCl (b.pt. -24 °C) as a by-product. No reaction was observed by LC-MS analysis when methylated simonsol F **336** was reacted with BCl_3 at -78 °C. The reaction mixture was warmed incrementally to -18 °C, 0 °C, and room temperature and aliquots of

the reaction mixture were analysed by LC-MS (see Figure 8). At -18 °C, demethylation of **336** was slow whereas at 0 °C, the reaction progressed substantially after 45 minutes. At room temperature, **336** was consumed and simonsol F (**56**) was the dominant species after 1 hour, however, after 3 hours a new peak formed which became the only major species present after 18 hours at room temperature. The peak at 2.59 minutes was later confirmed to be macranthol (**39**) and its formation is discussed in Section 2.2.1.

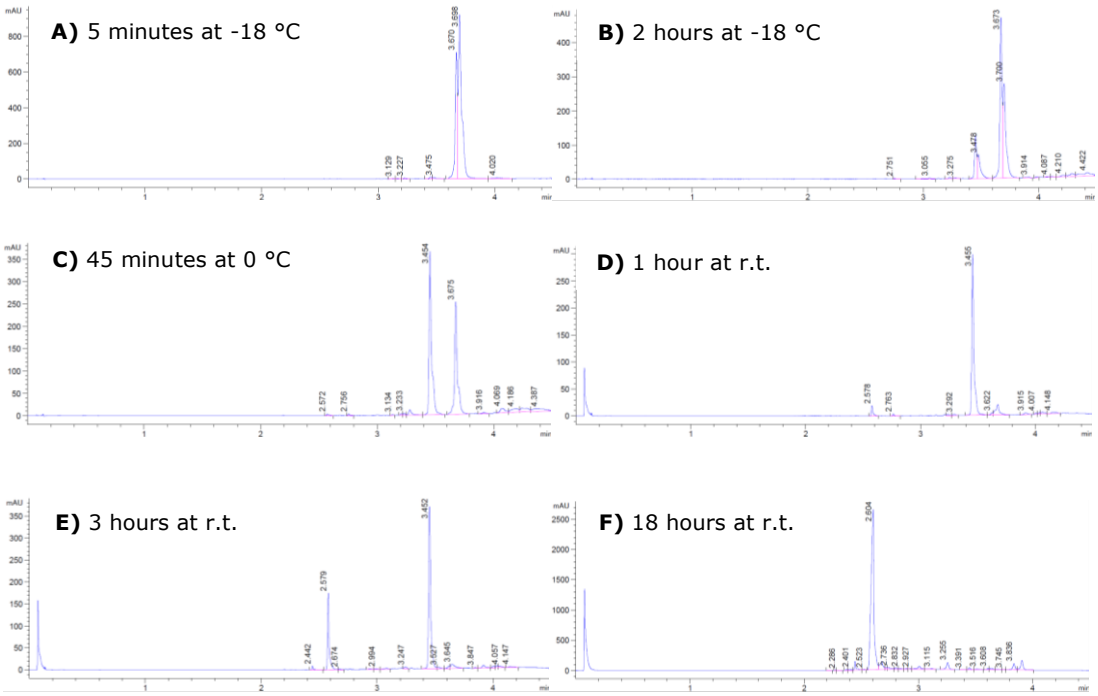
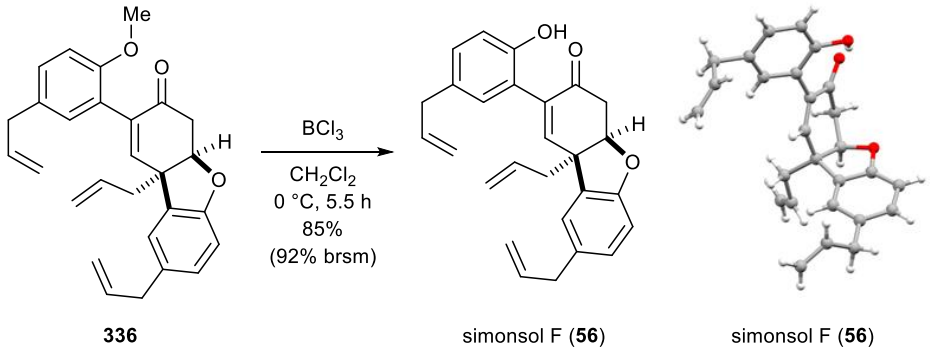


Figure 8. *LC-MS traces from aliquots taken from the same reaction mixture at different time and temperature of the BCl_3 mediated demethylation of* ***336****. The doubling of peaks in traces A and B is an instrument artifact. Average peak times (min); methylated simonsol F* ***336*** *= 3.68, simonsol F (****56****) = 3.45, macranthol (****39****) = 2.59.*

A mixture of methylated simonsol F **336** (92-96% w/w) and its thermodynamically favoured allyl group isomers (4-8% w/w) were reacted with BCl_3 at -18 °C for 72 hours which showed full

consumption of **336** by LC-MS analysis. The reaction mixture was injected into a large volume of MeCN/H_2O (19:1), which mimicked the quench conditions used to take aliquots of the reaction mixture for LC-MS analysis, and provided simonsol F (**56**) in 72% yield (88% brsm) as a single isomer. The conjugated di-substituted alkene of the isomerised aryl allyl group species was likely derivatised by addition of HCl across the alkene which gave a product that could be separated[329] from simonsol F (**56**).

The final conditions developed for the demethylation of **336** provided simonsol F (**56**) in 5.5 hours and in 85% yield (92% brsm) (see Scheme 62) if the reaction mixture was injected into MeCN/H_2O (19:1) at 0 °C. If instead, saturated aq. $NaHCO_3$ was added to the reaction mixture after 5.5 hours, simonsol F (**56**) was not obtained and the outcome of this deviation is discussed in Section 2.2.2.



Scheme 62. *BCl_3 mediated demethylation of **336** which completed the synthesis of simonsol F (**56**). Reaction was worked-up by the addition of the reaction mixture into MeCN/H_2O (19:1) at 0 °C.*

The spectroscopic data obtained for synthetic simonsol F (**56**) were in excellent agreement with the natural sample.[104,105]

2.1.6: Simonsol G

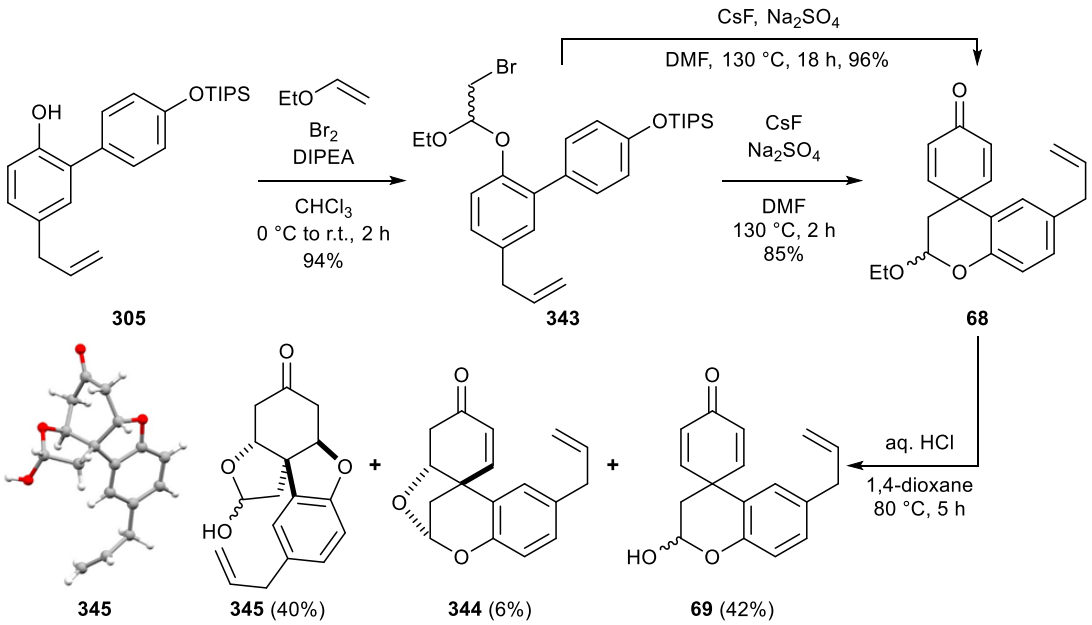
To date, the synthesis of simonsol G (**30**) has been achieved by the uncontrolled biomimetic oxidative phenolic coupling of chavicol (**22**)[21,22] and has been studied by Denton and Scragg.[102] The following synthesis starts from estragole (**36**) and contains analogous steps to those described in our synthesis of simonsol C (**55**) and F (**56**).

2.1.7: Total synthesis of simonsol G

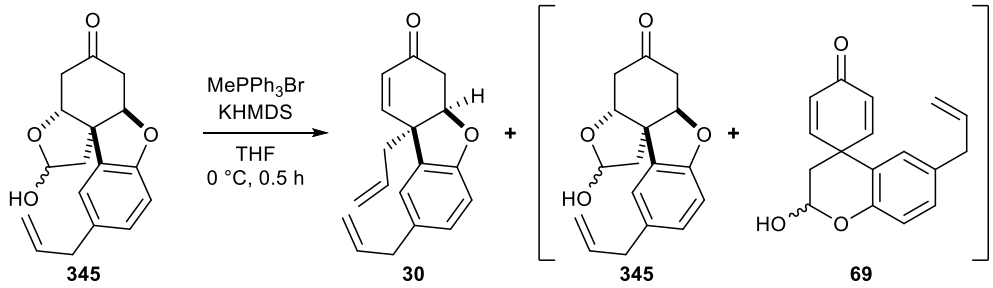
Common intermediate biaryl **305** (see Scheme 50) was transformed into bromo-acetal **343** which in turn formed spirocycle **68** after the desilylating-dearomatizing-intramolecular-alkylation. Contrary to the analogous attempt to reduce the amount of DMF used in the synthesis of simonsol C (**55**) (see Scheme 52), when bromo-acetal **343** was injected slowly into the reaction mixture, **68** was formed in excellent yield without isomerisation of the sensitive allyl group (see Scheme 63). Acetal **68** was heated with aqueous HCl which provided dienone **69**, enone **344**, and inseparable[323] ketone diastereoisomers **345** (see Scheme 63).

Ketone diastereoisomers **345** were reacted under the Wittig cascade conditions using different equivalents of reagents (see Table 10). To summarise, we observed the formation of dienone **69** which supported our proposed reaction mechanism (see Scheme 55).

Conversion of **345** to simonsol G (**30**) was increased when 5.1 eq. of ylide were used. As reported by Denton and Scragg,[102] an excess of KHMDS was detrimental to the construction of the hydrodibenzofuran core which provided only trace amounts of simonsol G (**30**).



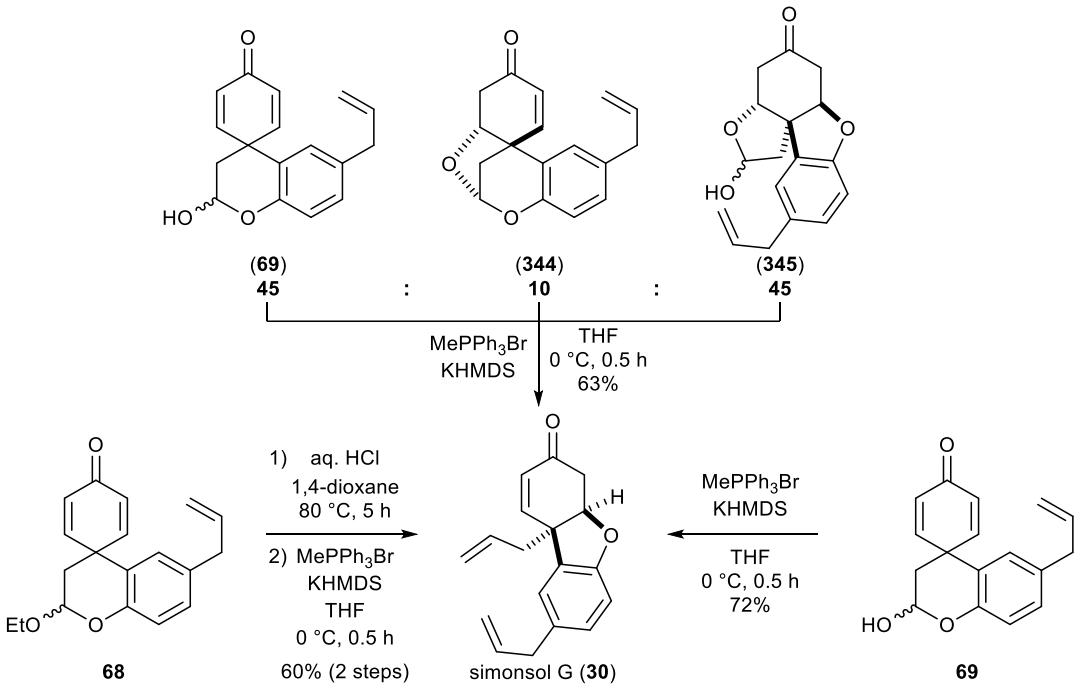
Scheme 63. *Steps towards the synthesis of simonsol G (**30**).*



Entry	Eq. KHMDS	Eq. $MePPh_3Br$	Simonsol G (**30**) yield[a]	**345** & **69** yield[a]
1	2.55	6.0	50%	25%
2	5.1	3.0	<10%	50%
3	5.1	6.0	65%	<10 %

Table 10. *Inseparable[323] ketone diastereoisomers **345** reacted under the Wittig cascade reaction using different equivalents of reagents.* ***a)*** *Isolated yield.*

A 45:10:45 respective mixture of purified dienone **69**, enone **344** and ketone **345** was treated under the Wittig cascade conditions which gave simonsol G (**30**) in good yield (see Scheme 64). Alternatively, the crude mixture after acid hydrolysis of acetal **68** was subjected to the Wittig cascade conditions which gave simonsol G (**30**) in 60% yield over the two-steps (see Scheme 64). Dienone **69** was reacted under the Wittig cascade conditions which gave simonsol G (**30**) in 72% yield (see Scheme 64).



Scheme 64. *Completion of the synthesis of simonsol G (**30**).*

The spectroscopic data obtained for synthetic simonsol G (**30**) were in excellent agreement with both natural[101] and synthetic samples.[21,22]

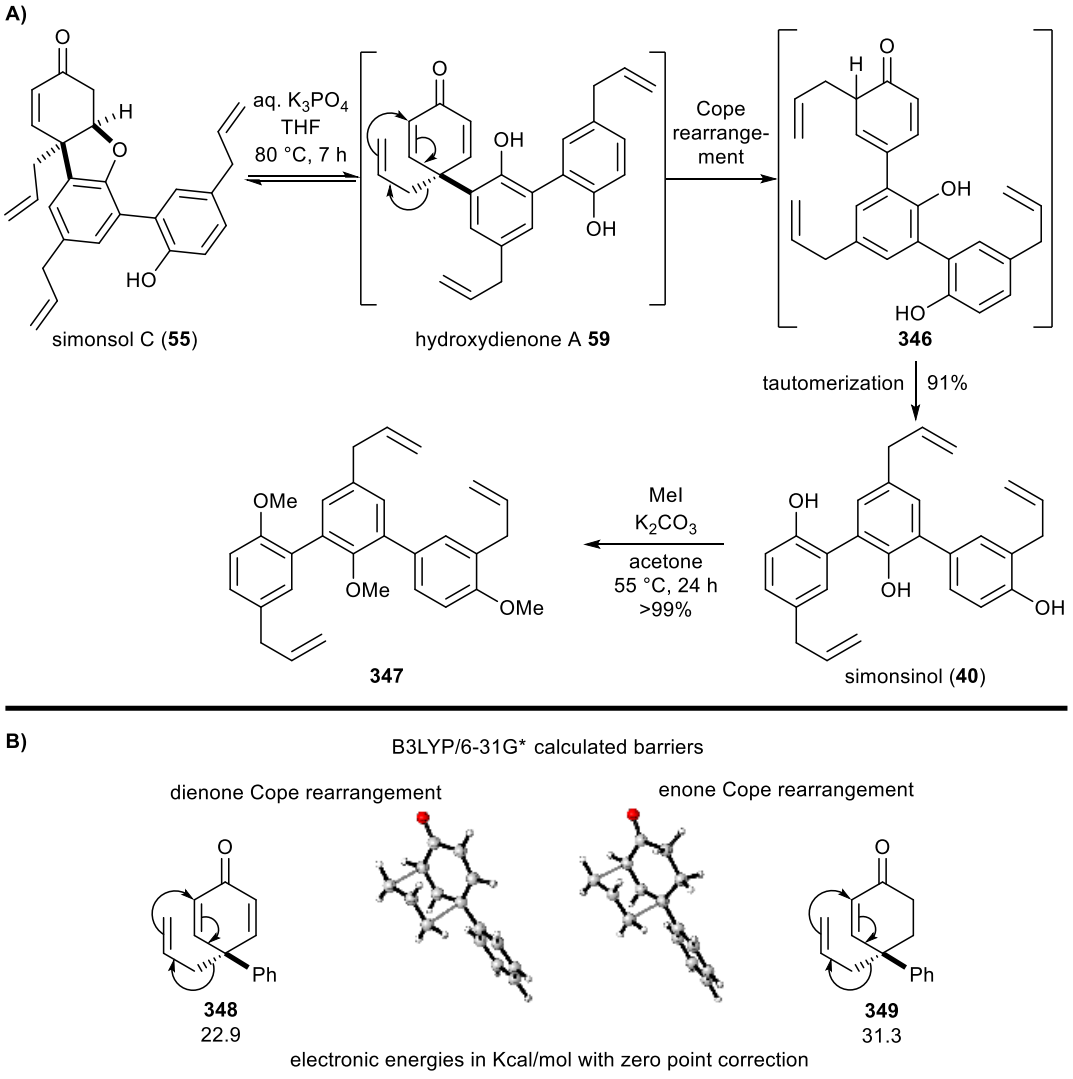
2.2.1: Biomimetic synthesis of simonsinol, macranthol, and honokiol

A new biosynthesis proposal for simonsinol (**40**), macranthol (**39**) and honokiol (**33**), all of which contain an unusual 2-allylphenol (**37**) moiety, is discussed in this section. The final-step in our synthesis of simonsol C (**55**) was a Suzuki-Miyaura cross-coupling (see Scheme 56). Coupling did not take place at ambient temperature, while at 60 °C we observed the formation of simonsol C (**55**) and simonsinol (**40**).[92]

After obtaining simonsol C (**55**), we sought a method to observe the transformation of simonsol C (**55**) into simonsinol (**40**) and to determine if its formation was dependent upon Pd-catalysis or if it could be obtained under thermal conditions. Heating alone had no effect, however, in the presence of base at 80 °C, simonsol C (**55**) converted to simonsinol (**40**) in 91% yield. We propose that under the thermal basic conditions, simonsol C (**55**) underwent a retro-*oxa*-1,4-addition to give hydroxydienone A **59**, followed by Cope rearrangement which provided **346** that subsequently tautomerized to simonsinol (**40**) (see Scheme 65A).

To corroborate the proposed order of retro-*oxa*-1,4-addition followed by Cope rearrangement versus Cope rearrangement then retro-*oxa*-1,4-addition, the energy barriers for Cope rearrangement were calculated for dienone **348** versus enone **349** (see Scheme 65B).[330]

The B3LYP/6-31G* calculated energy barriers for the Cope rearrangement gave an 8.4 kcal/mol difference in favour of the cross-conjugated dienone **348** for Cope rearrangement to occur which supports the intermediacy of hydroxydienone A (see Scheme 60B).



Scheme 65. A) *Transformation of simonsol C (**55**) to simonsinol (**40**) by Cope rearrangement of hydroxydienone A **59**. Subsequent permethylation of simonsinol (**40**) for ^{13}C NMR comparison.* ***B)*** *Calculated energy barriers for Cope rearrangement as dienone **348** versus enone **349**.*[330]

The spectroscopic data obtained for synthetic simonsinol (**40**) were in excellent agreement with the natural sample.[92] However, due to

overlap of several ^{13}C signals, Kouno and co-workers permethylated simonsinol (**40**) and observed a trimethyl phenol ether species **347** which provided distinct non-overlapped ^{13}C signals for all 30 environments. Therefore, the synthetic simonsinol (**40**) was permethylated which provided **347**. The spectroscopic data we obtained for **347** were in excellent agreement with that reported (see Scheme 65A).[92]

The facile conversion of simonsol C (**55**) into simonsinol (**40**) provides very strong experimental support for the intermediacy of hydroxydienone A **59** in the biosynthesis of both natural products.

To test this alternative biosynthesis proposal, reaction conditions were explored to transform simonsol F (**56**) and simonsol G (**30**) into macranthol (**39**) and honokiol (**33**) respectively. Simonsol F (**56**) was heated in DMSO-d_6 and ^1H NMR spectra were acquired at various time points and temperatures. When heated at 80 °C for 18 hours, a clean conversion to a new tri-arylated species was observed, identified as macranthol (**39**).[89] Other intermediates were not observed which means that the elimination to give the dienone is slow compared to the [3,3] rearrangement (see Figure 9 and Scheme 66). The transformation of simonsol G (**30**) into honokiol (**33**) required 40 hours of heating with base which converted >90% of simonsol G (**30**) and provided honokiol (**33**) in 70% yield.

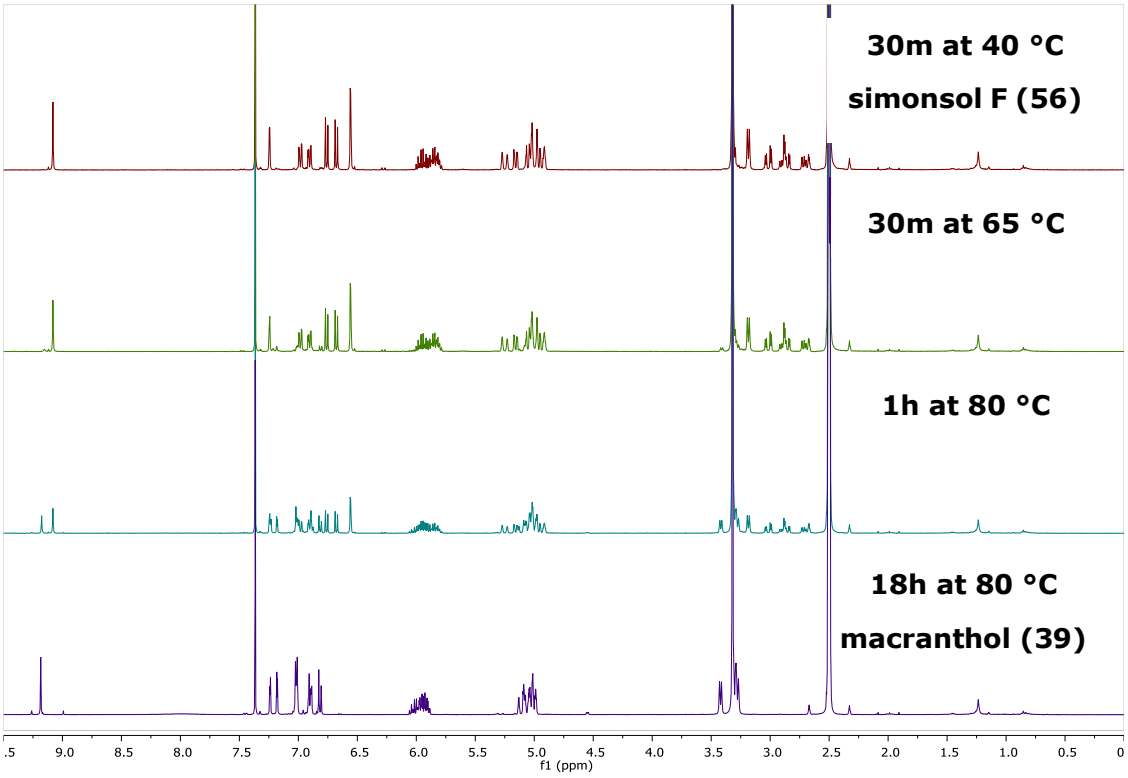
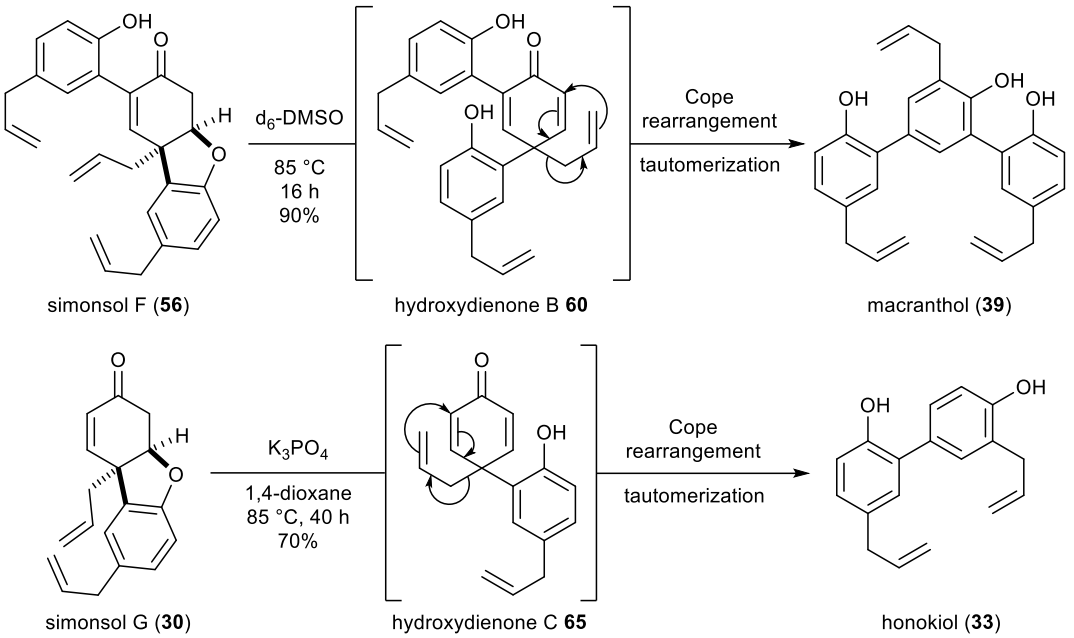


Figure 9. *^{1}H NMR spectra of the thermal rearrangement of simonsol F (**56**) to macranthol (**39**) in DMSO-d_6.*

Similarly to simonsol C (**55**), it is proposed that simonsol F (**56**) and simonsol G (**30**) underwent retro-*oxa*-1,4-addition to hydroxydienone B **60** and hydroxydienone C **65** respectively, followed by Cope rearrangement and tautomerisation which gave macranthol (**39**) and honokiol (**33**) respectively (see Scheme 66).

As a corollary, simonsinol (**40**), macranthol (**39**) and honokiol (**33**) can now be derived from chavicol (**22**) alone *via* hydroxydienone intermediates (**59**, **60**, and **65**) and it is no longer necessary to invoke the oxidative coupling of two constitutionally isomeric phenolic starting materials (**22** and **37**). This is arguably a more plausible biogenesis.

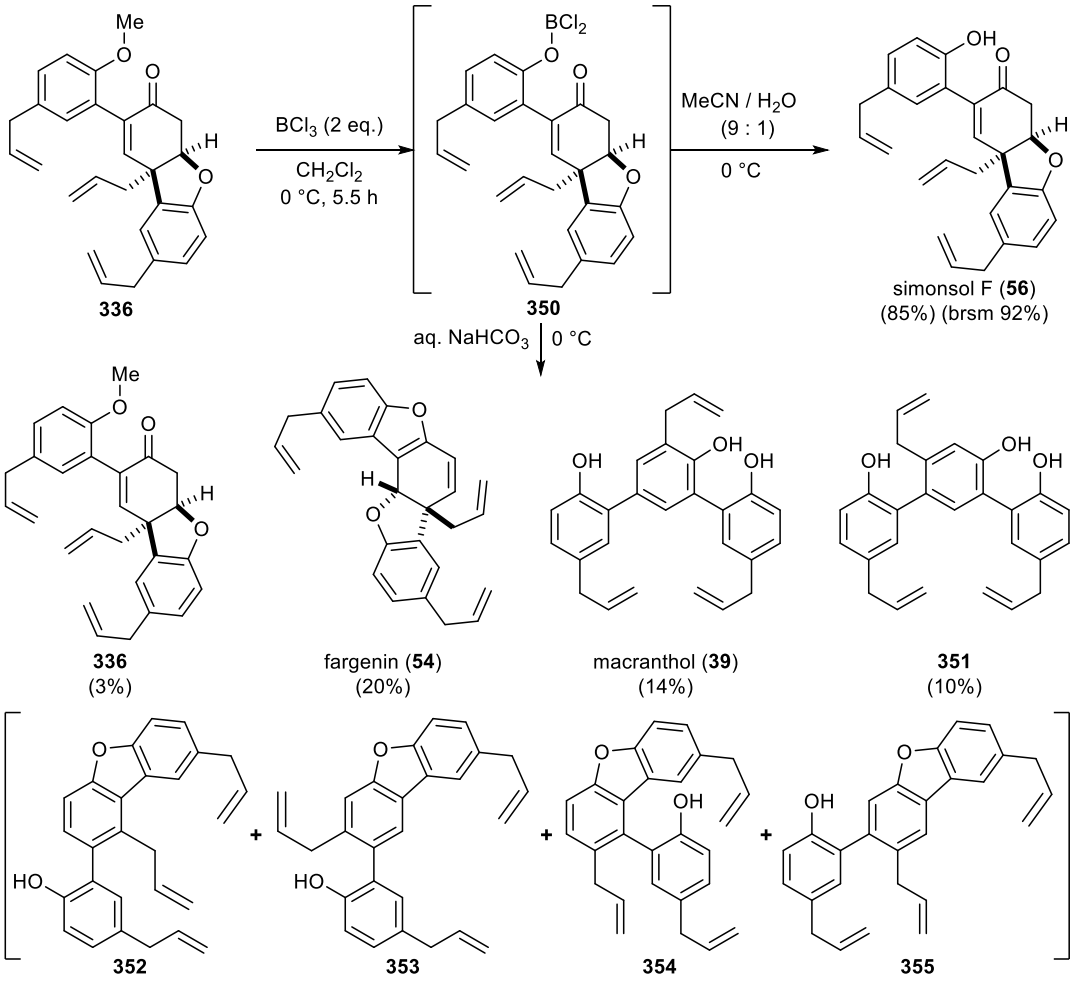


Scheme 66. *Rearrangement of simonsol F (**56**) and simonsol G (**30**) to macranthol (**39**) and honokiol (**33**) respectively via proposed hydroxydienone intermediates.*

2.2.2: Biomimetic synthesis of fargenin from simonsol F

The final step in the total synthesis of simonsol F (**56**) was a BCl_3-mediated demethylation of **336** which was investigated in detail. A series of experiments revealed that if the reaction mixture was quenched by injection of the reaction mixture into a large volume of MeCN/H_2O (19:1) at 0 °C, simonsol F (**56**) was obtained in excellent yield. However, if saturated aq. $NaHCO_3$ was added dropwise at 0 °C to the reaction mixture, simonsol F (**56**) was not obtained. Instead, fargenin (**54**) (20%),[88,331] macranthol (**39**) (14%), tri-phenol **351** (10%), methylated simonsol F **336** (3%) and an inseparable[323] mixture of four likely species **352**–**355** (35%) were isolated (see

Scheme 67). The proposed structures of **352**–**355** have been tentatively assigned by ^{1}H and ^{13}C NMR spectroscopy, HRMS, and LC-MS analysis.

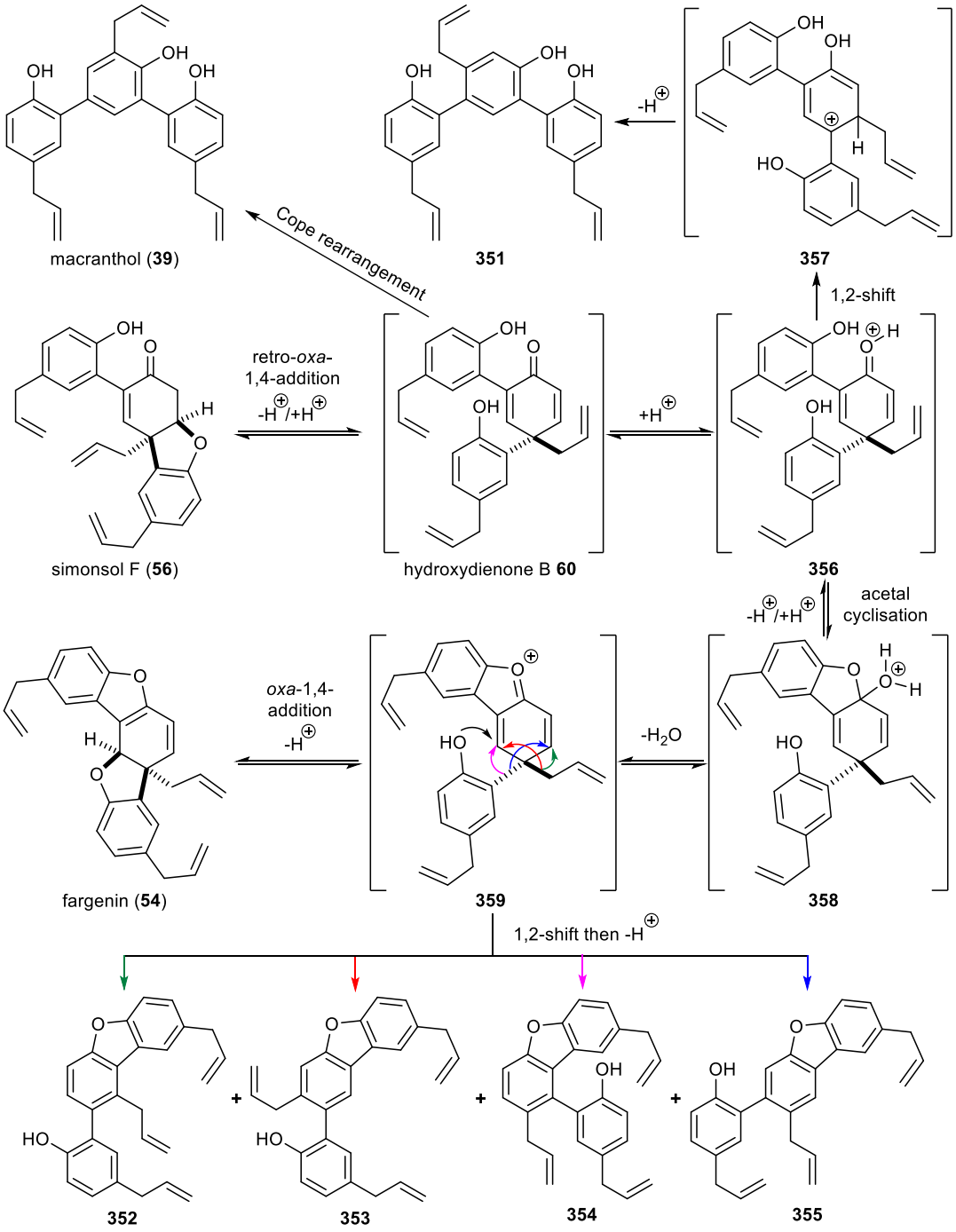


Scheme 67. *BCl_3-mediated demethylation of **336**. Different product mixtures obtained which depended on how the reaction mixture was quenched.*

The products formed from the dropwise addition of aqueous $NaHCO_3$ to the BCl_3 mediated demethylation of **336** are likely formed under acidic (or Lewis-acidic) conditions. For clarity of depiction, our proposed reaction mechanism does not account for any Lewis-acid adducts but Lewis-acidic adducts may also be involved (see Scheme 68). Retro-*oxa*-1,4-addition of simonsol F (**56**) generates

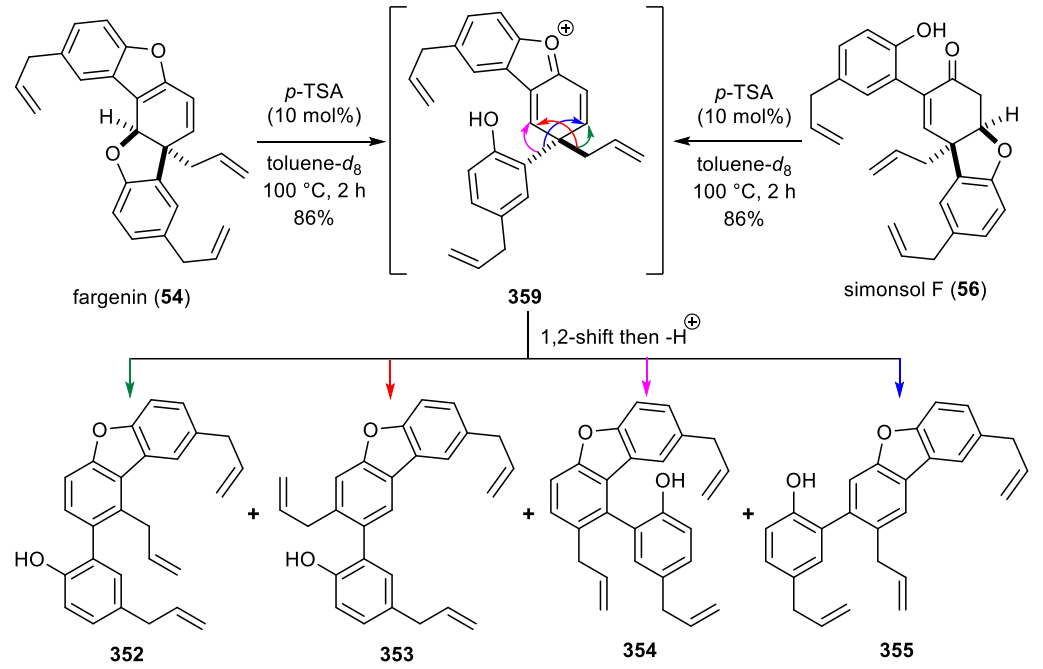
hydroxydienone B **60** which provides macranthol (**39**) *via* a Cope rearrangement (see Scheme 66). Alternatively, hydroxydienone B can undergo protonation to yield intermediate **356** that can either provide tri-phenol **351** by a dienone phenol rearrangement or **356** can undergo dehydrative cyclization to give **359**. Subsequent intramolecular *oxa*-1,4-addition of **359** provides fargenin (**54**) whereas dienone phenol rearrangement of **359** yields **352**–**355** dependent on alkyl shift (see Scheme 68). To provide experimental support towards this proposed mechanism, simonsol F (**56**) and fargenin (**54**) were heated independently with substoichiometric *para*-toluenesulfonic acid which provided identical product mixtures of the tentatively assigned species **352**–**355** (see Scheme 69).

The formation of fargenin (**54**) was investigated. Simonsol F (**56**) was heated in toluene-d_8 at 100 °C which initiated a slow but clean conversion to an unexpected product, benzofuran **360** (see Figure 9). Simonsol F (**56**) likely underwent intramolecular *oxa*-1,4-addition followed by triplet oxygen oxidation of the formed enol and subsequent dehydration (see Scheme 70). When the reaction was scaled up, benzofuran **360** (23%), fargenin (**54**) (29%), macranthol (**39**) (15%) and simonsol F (**56**) (30%) were isolated (see Scheme 71). It is likely that weakly-acidic residue on the glassware was present which promoted the rearrangements of simonsol F (**56**) as described in Scheme 68 but it was not acidic enough to promote dienone phenol rearrangements.



The structures of **352–353** have been tentatively assigned by ^{1}H and ^{13}C NMR spectroscopy, HRMS and LC-MS

Scheme 68. *Acid-mediated transformation of simonsol F (**56**) to macranthol (**39**), fargenin (**54**) and other related compounds via plausible intermediate hydroxydienone B **60**.*



The structures of **352–355** have been tentatively assigned by ^{1}H and ^{13}C NMR spectroscopy, HRMS and LC-MS

Scheme 69. *Treatment of simonsol F (**56**) or fargenin (**54**) with p-TSA at 100 °C.*

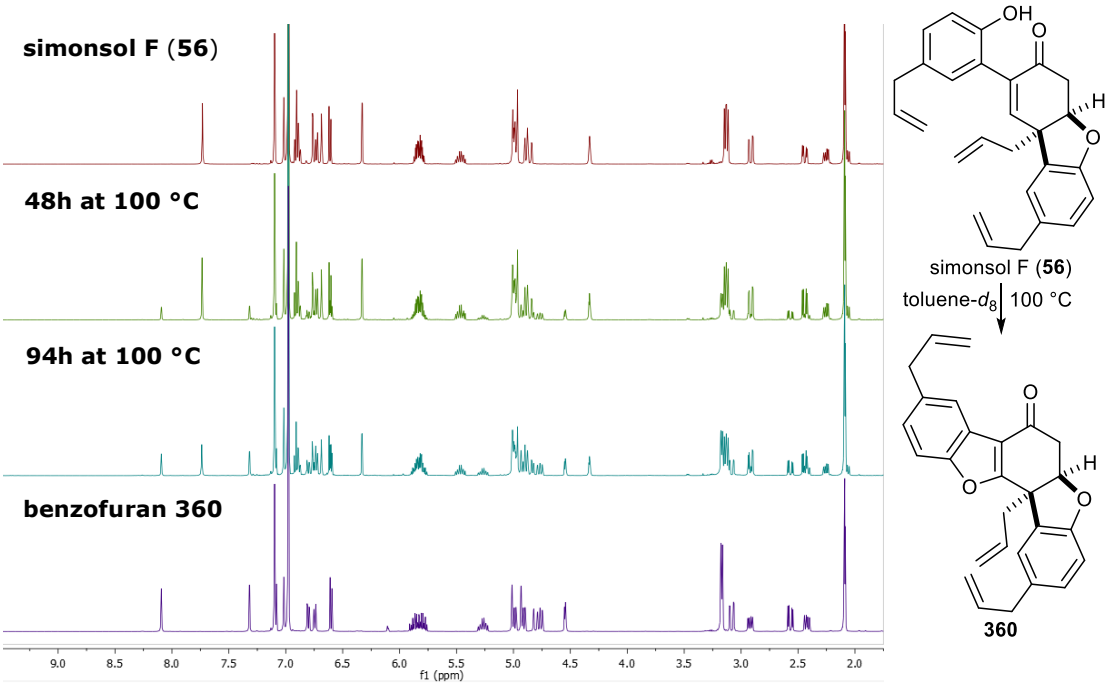
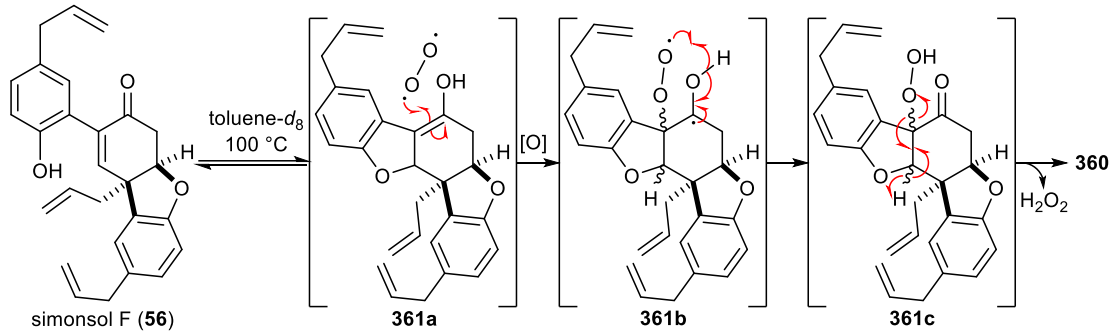
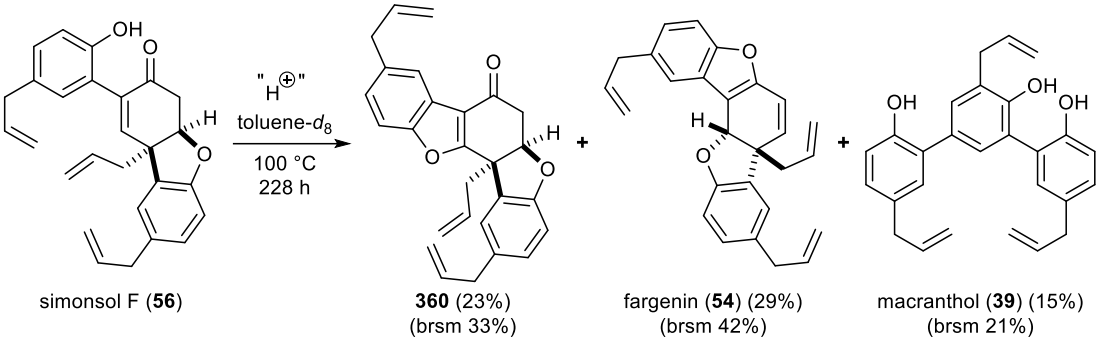


Figure 9. *^{1}H NMR spectra (toluene-d_8) of the thermal oxidative conversion of simonsol F (**56**) to benzofuran **360**.*



Scheme 70. *Proposed synthesis of benzofuran* ***360*** *from simonsol F (****56****).*



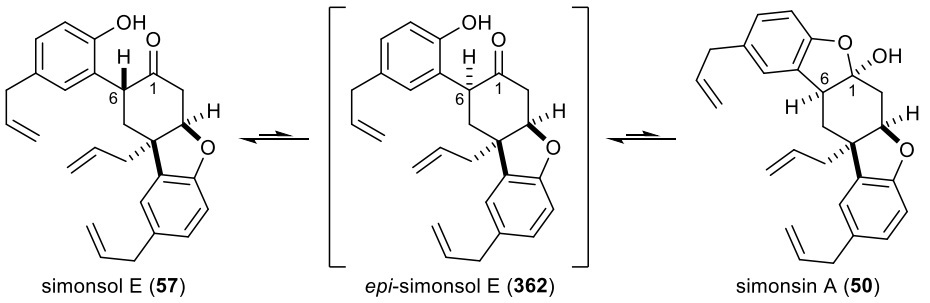
Scheme 71. *Rearrangement of simonsol F (****56****) to* ***360*** *and likely acid-mediated formation of fargenin (****54****) and macranthol (****39****). A source of* H^+ *was not added to the reaction mixture but there was likely acidic residue on glassware.*

The facile conversion of simonsol F (**56**) to both macranthol (**39**) and fargenin (**54**) provides very strong experimental support for the intermediacy of hydroxydienone B **60** in the biosynthesis of all three natural products.

2.2.3: 1,4-Reduction of simonsol F: Synthesis of simonsol E, simonsin A, and their respective epimers

Wang and co-workers isolated species from the aerial parts of *Illicium simonsii*. They reported the isolation of simonsol E (**57**) and simonsin A (**50**) as an inseparable 2:1 keto/hemi-acetal equilibrated mixture in >90% purity. It should be noted that epimerization at C-6 must

occur to give *epi*-simonsol E (**362**) for these two species to be in equilibrium, assuming that the authors have not just drawn the wrong stereocentre (see Scheme 72). Wang *et al*. also isolated simonsin A (**50**) with reported >90% purity. The reported conditions to isolate the inseparable mixture of "simonsol E (**57**) and simonsin A (**50**)" and "simonsin A (**50**)" were identical. These statements are contradictory, as it should not be possible to obtain pure simonsin A (**50**) if it exists with simonsol E (**57**) as an "inseparable equilibrated mixture".



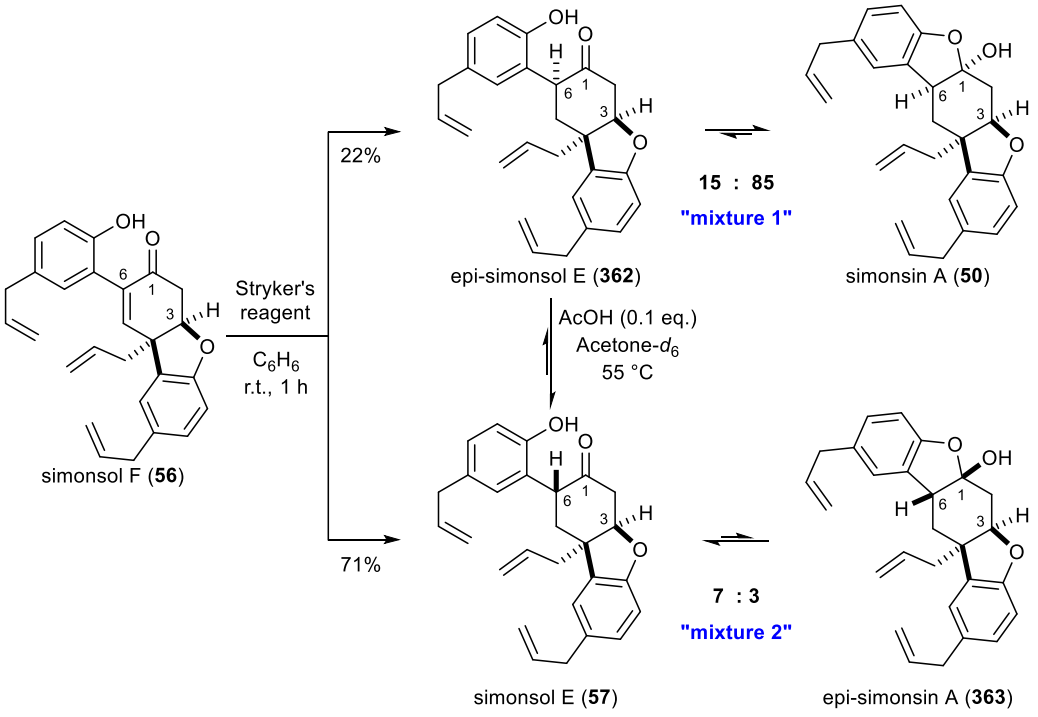
Scheme 72. *Reported equilibrium mixture of simonsol E (**57**) and simonsin A (**50**).*

We reduced simonsol F (**56**) with Stryker's reagent[332] which provided two separable mixtures, each of which contained two inseparable species. "Mixture 1" (22% yield) was an 85:15 respective mixture of simonsin A (**50**) and a species whose data did not match simonsol E (**57**) but resembled simonsol E (**57**). Due to the similarity, we assumed that this unknown species was *epi*-simonsol E (**362**). "Mixture 2" (71% yield) was a 7:3 respective mixture of simonsol E (**57**) and a species whose data did not match simonsin A (**50**) but resembled simonsin A (**50**). Due to the similarity, we assumed that

this unknown species was *epi*-simonsin A (**363**) (see Scheme 73). Our proposed inseparable mixtures (1 & 2) are ratiometrically similar to the mixtures reported by Wang *et al*. and are formed from compounds in a keto/hemi-acetal equilibrium which do not necessitate epimerization. Next, we explored conditions to epimerise simonsol E (**57**) and obtain *epi*-simonsol E (**362**) (*vice versa*) but observed zero to very little change to either mixture at room temperature or when heated to 55 °C in acetone-d_6, with or without SiO_2 (see table 11). However, when AcOH was added at room temperature, significant epimerisation occurred for the conversion of "mixture 1" into "mixture 2". The mixtures were heated at 55 °C which promoted further epimerisation whereby the equilibrium favoured "mixture 2" (see Scheme 73). As Wang and co-workers did not use acidic, basic, or thermal conditions for separation, it is unlikely that their reported epimerization at C-6 occurred at ambient temperature.

Characteristic ^{1}H and ^{13}C NMR data of natural and synthetic simonsol E (**57**) and simonsin A (**50**), as well as their proposed epimers, are shown in Table 12. Wang and co-workers provided the raw ^{1}H and ^{13}C NMR spectra for simonsin A (**50**) which matched "mixture 1" (see Figure 10). The ^{13}C NMR spectroscopy data collected for the natural sample is missing several peaks which are not distinguishable from baseline noise including the ^{13}C signal of C-1 of *epi*-simonsol E (**362**).

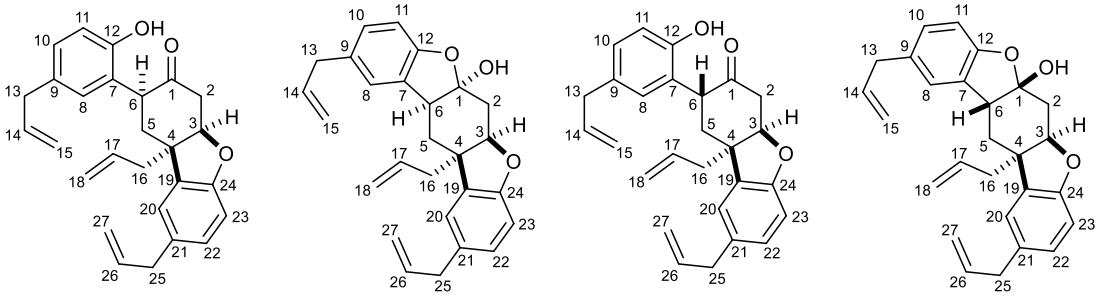
Wang and co-workers likely overlooked the isolation of *epi*-simonsol E (**362**) as a low-level impurity when they isolated simonsin A (**50**).



Scheme 73. *1,4-reduction of simonsol F (**56**) and epimerization of products.*

		"mixture 1"			"mixture 2"		
Entry	**Conditions in acetone-d_6**	**Mix. 1**	**:**	**Mix. 2**	**Mix. 1**	**:**	**Mix. 2**
1	isolated mixtures	93	:	7	<1	:	>99
2	r.t. – 96 h	93	:	7	<1	:	>99
3	55 °C – 2 h	90	:	10	4	:	96
4	55 °C with SiO_2 (30 eq.) – 6.5 h	88	:	12	5	:	95
5	r.t. with AcOH (0.1 eq.) – 0.25 h	65	:	35	7	:	93
6	55 °C with AcOH (0.1 eq.) – 3 h	56	:	44	10	:	90
7	55 °C with AcOH (0.1 eq.) – 18 h	44	:	56	14	:	86
8	55 °C with AcOH (0.1 eq.) – 114 h	32	:	68	19	:	81

Table 11. *Conditions used to convert "mixture 1" into "mixture 2" (vice versa). ^{1}H NMR spectra were acquired at time points as described. The ratio of "mixture 1":"mixture 2" was calculated by comparison of integrations for H-3 (see Scheme 73).*



^{1}H or ^{13}C environment	^{1}H or ^{13}C NMR spectroscopy data (ppm (coupling constant (Hz)))		
	Nat. simonsol E (57)	**Syn. simonsol E (57)**	***epi*-simonsol E (362)**
^{1}H-5[a]	1.97 (dd, 13.5, 11.6)	1.98 (dd, 13.7, 4.3)	2.30 (dd, 13.9, 4.5)
^{13}C-5	39.8	39.9	38.7
^{1}H-6	2.96 (dd, 11.6, 5.2)	2.98 (dd, 13.6, 4.2)	3.75 (dd, 13.3, 4.4)
^{13}C-6	49.3	49.4	48.8
^{1}H-3	5.03 (dd, 12.8, 5.5)	N/A[b]	4.88 (dd, 9.9, 5.4)
^{13}C-3	86.0	86.1	85.7
^{13}C-1	208.7	208.6	208.1
^{13}C-24	158.9	159.0	157.7
^{1}H-11	6.70 (d, 8.1)	6.71 (d, 8.1)	6.74 (d, 8.1)
^{1}H-23	6.67 (d, 8.0)	6.67 (d, 8.1)	6.70 (d, 8.1)

^{1}H or ^{13}C of numbered C	^{1}H or ^{13}C NMR spectroscopy data (ppm (coupling constant (Hz)))		
	Nat. simonsin A (50)	**Syn. simonsin A (50)**	***epi*-simonsin A (363)**
^{1}H-5[a]	1.67 (dd, 14.2, 12.3)	1.68 (dd, 13.9, 12.4)	1.69 (dd, 13.9, 11.9)
^{13}C-5	37.9	38.0	38.9
^{1}H-6	3.37 (dd, 12.3, 5.1)	3.38 (dd, 12.4, 5.4)	2.82 (m)[c]
^{13}C-6	46.7	46.8	47.1
^{1}H-3	4.71 (dd, 11.2, 5.2)	4.72 (dd, 11.1, 5.3)	4.82 (dd, 4.2, 3.6)
^{13}C-3	85.0	85.1	85.2
^{13}C-1	109.9	109.9	109.7
^{13}C-24	158.1	158.2	159.3
^{1}H-11	6.57 (d, 8.2)	6.56 (d, 8.1)	6.62 (d, 8.1)
^{1}H-23	6.59 (d, 8.1)	6.59 (d, 8.1)	6.63 (d, 8.1)

Table 12. *Selected (for full comparison, see SI) ^{1}H and ^{13}C NMR spectroscopy shifts of natural (Nat.) simonsol E (**57**) and simonsin A (**50**) versus constituents of synthetic (Syn.) mixture 1 and mixture 2.* ***a)*** *Reported as α-H.* ***b)*** *^{1}H NMR spectroscopy signal is overlapped by allyl group signals but matched natural sample by 2D NMR spectroscopy.* ***c)*** *multiplicity not assigned due to overlapped signals.*

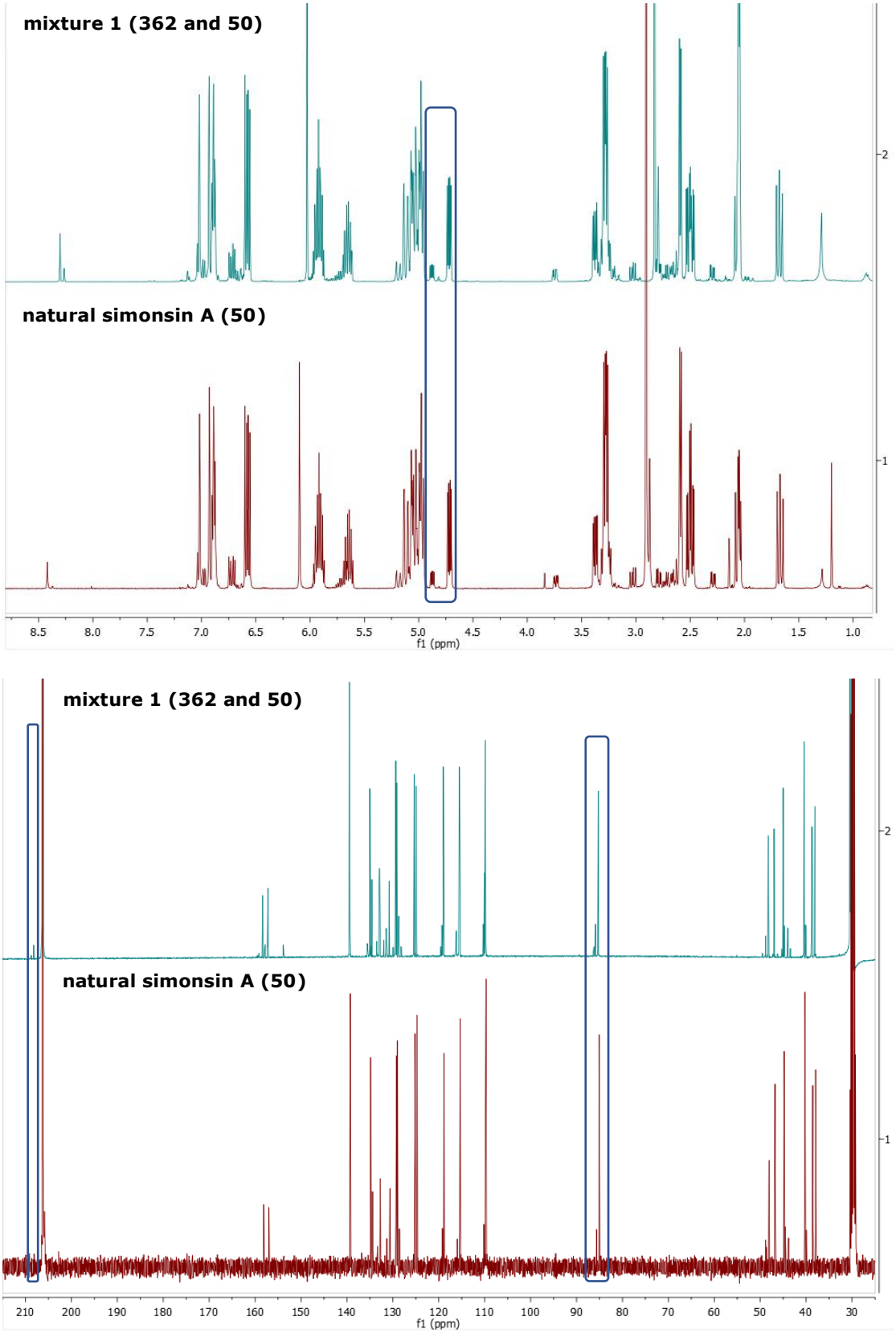
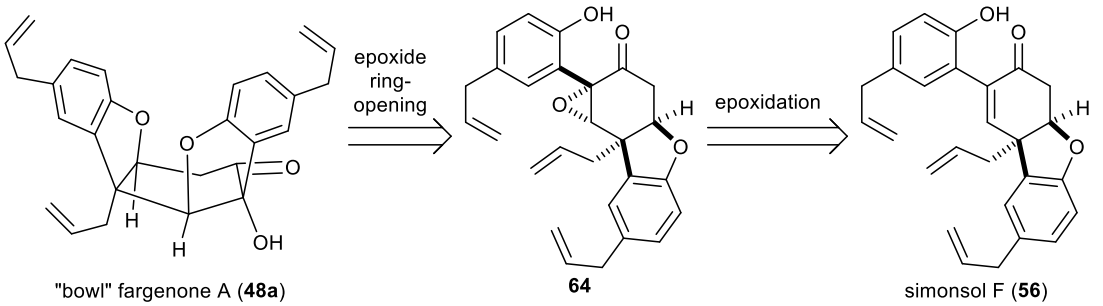


Figure 10. *Natural simonsin A (**50**) (maroon) versus synthetic mixture 1 of simonsin A (**50**) and epi-simonsol E (**362**) (blue). ^{1}H (top) and ^{13}C (bottom) NMR spectra in acetone-d_6.*

Wang and co-workers could not locate the raw data for the reported 2:1 mixture of simonsol E (**57**) and simonsin A (**50**) which made it difficult to challenge with absolute certainty the validity of their reported mixture versus our "mixture 2" and further investigation is required.

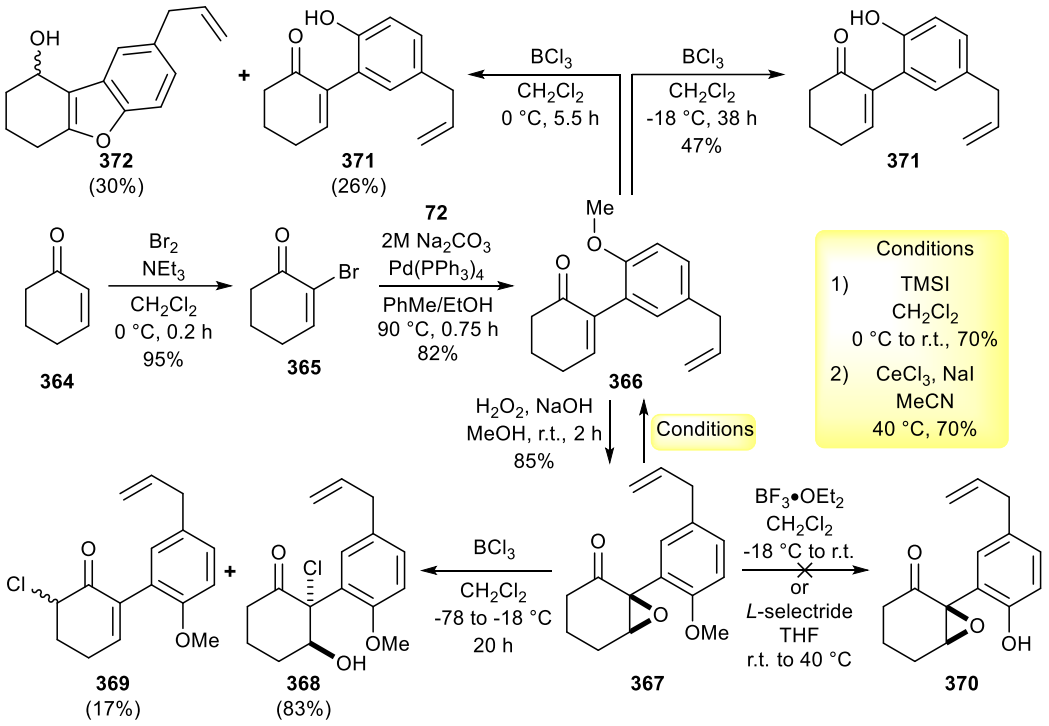
2.2.4: Studies towards the synthesis of fargenone A "bowl" and "ladder" from simonsol F

To resolve the stereochemical discrepancy associated with fargenone A (**48**) (see Section 1.5), total synthesis of both "bowl" (**48a**) and "ladder" (**48b**) diastereoisomers is necessary. We focused on the synthesis of "bowl" fargenone A (**48a**) as this was the reported structure of fargenone A (**48**) as established by NMR spectroscopy. Our first-generation retrosynthetic analysis of **48a** mirrored our new biosynthesis proposal (see Scheme 74) which involved epoxidation of the less-hindered convex face of Simonsol F (**56**) followed by subsequent intramolecular ring-opening of the epoxide by the phenol.

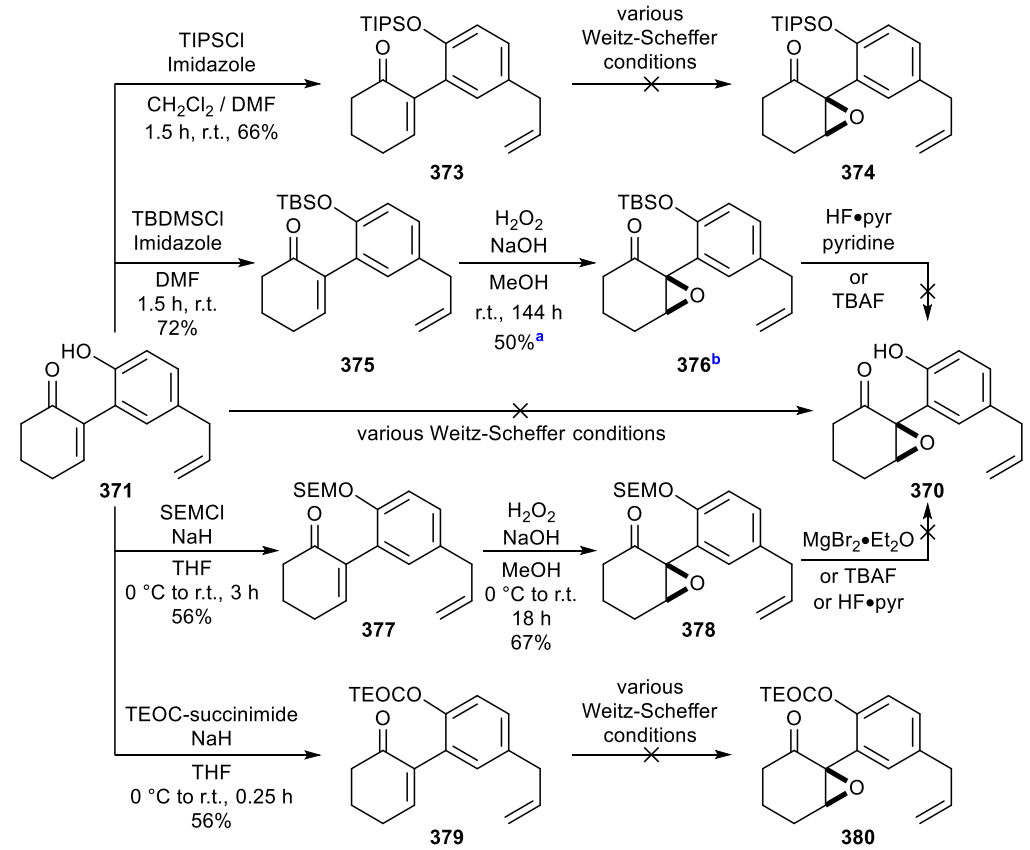


Scheme 74. *First-generation retrosynthetic analysis of "bowl" fargenone A (**48a**).*

As we only possessed a small amount of simonsol F (**56**) a model compound **366** was used to investigate suitable conditions for the epoxidation and subsequent epoxide ring-opening sequence. The model compound was prepared from 2-cyclohexen-1-one (**364**) which was di-brominated and then treated with Et_3N which gave **365**. Subsequent Suzuki-Miyaura cross-coupling with boronic acid **72** gave the model compound **366**. Under Weitz-Scheffer epoxidation conditions, **366** was transformed into **367**. Next, conditions to demethylate **367** in the presence of the epoxide were explored, however the epoxide was either deoxygenated *via in situ* formed iodohydrins, or was ring-opened to other products, whilst the methoxy ether moiety remained intact. A more labile protecting group was therefore investigated. Demethylation of **366** was challenging but phenol **371** was provided in moderate yield (see Scheme 75). Subsequent protection as either TIPS silyl ether **373** or TEOC[333] carbamate **379** was successful but following Weitz-Scheffer epoxidation conditions failed to produce the respective α,β-epoxy-ketone. Protection of phenol **371** to TBS silyl ether **375** or SEM ether **377** followed by epoxidation under Weitz-Scheffer conditions was successful but subsequent deprotection of either **376** or **378** did not provide **370** (see Scheme 76).

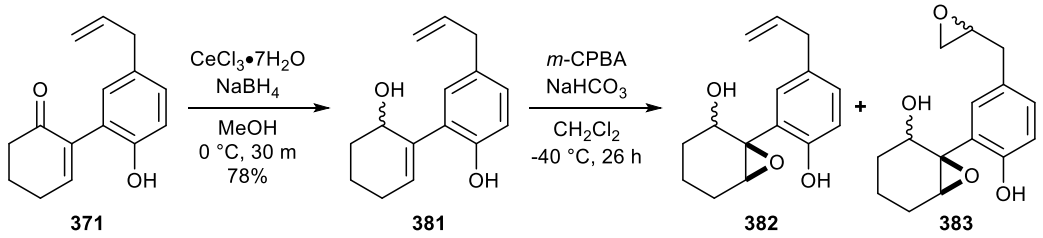


Scheme 75. *Synthesis of simonsol F (**56**) fragments towards the synthesis of **370**.*



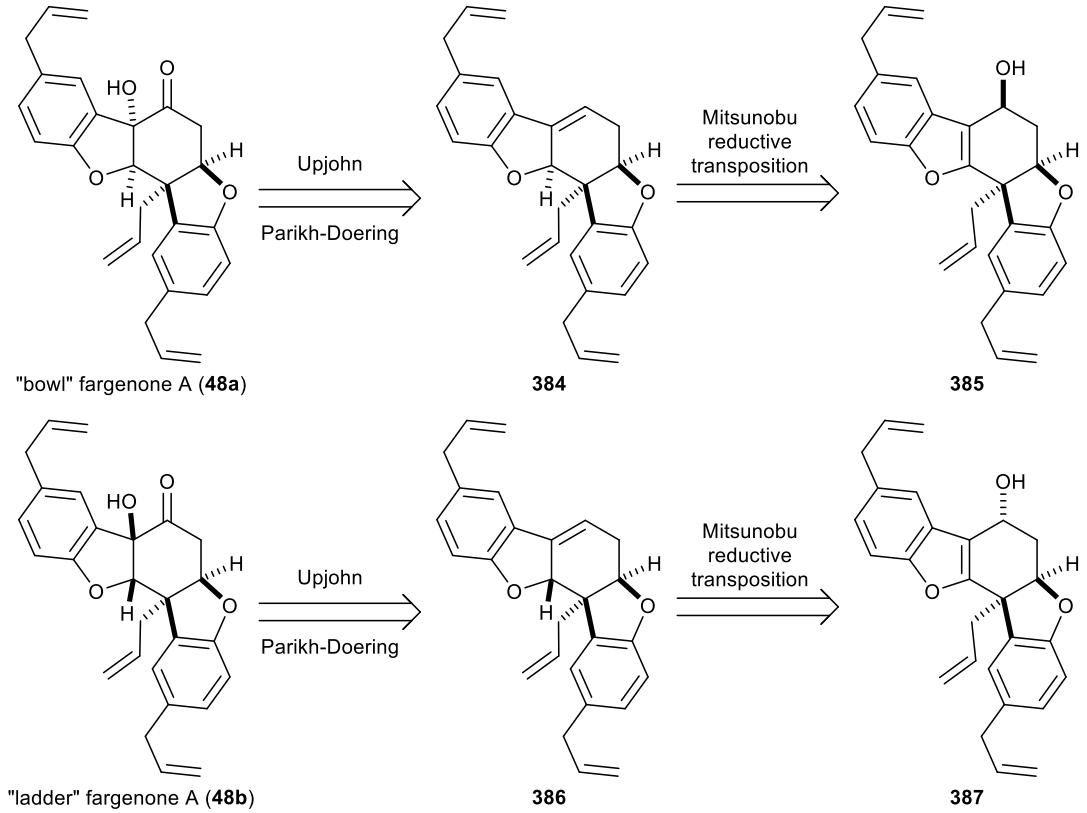
Scheme 76. *Protection, epoxidation and deprotection strategies surveyed to access **370**. **a)** Yield estimated based on ^{1}H NMR spectroscopy. **b)** Obtained in approximately 60% purity (determined by ^{1}H NMR spectroscopy). Taken forward onto next step.*

Based on previous experiments, a phenol deprotection strategy in the presence of the epoxide did not seem feasible. Therefore, we revised our plan and reduced **371** under Luche conditions which gave the corresponding diol **381**. Subsequent Prilezhaev epoxidation gave indication based on ^{1}H NMR analysis of the crude reaction mixture that **382** and **383** had formed, however the species that had formed were unstable to silica gel chromatography (see Scheme 77). Due to lack of material, we returned to the synthesis of simonsol F (**56**) with the ambition to use a Luche reduction, Prilezhaev epoxidation and Parikh-Doering oxidation sequence to access α,β-epoxy ketone **64**.



Scheme 77. *Luche reduction and Prilezhaev epoxidation sequence from* ***371****.*

During our study on the biomimetic transformation of simonsol F (**56**) to fargenin (**54**), we unexpectedly formed benzofuran **360** (see Scheme 71). This observation led to a new retrosynthetic analysis of fargenone A "bowl" (**48a**) and "ladder" (**48b**). We reasoned the hydrated benzofuran moiety could be formed from dihydroxylation and oxidation of the prerequisite alkene that in turn could be generated from the Mitsunobu reductive transposition of the diastereomeric allylic alcohols produced from the reduction of **360** (see Scheme 78).

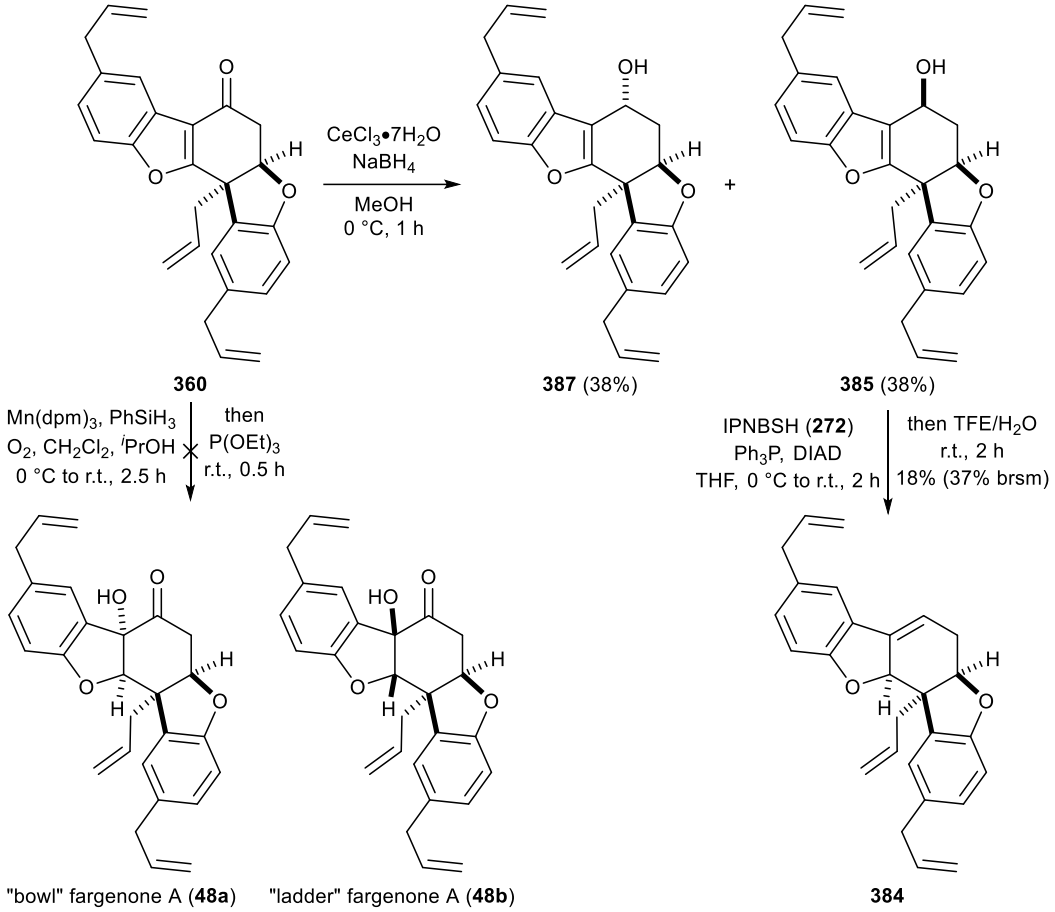


Scheme 78. *Retrosynthetic analysis of fargenone A "bowl" (**48a**) & "ladder" (**48b**).*

Benzofuran **360** was reduced under Luche conditions which gave separable allylic alcohols **385** and **387** (assigned by NOE interactions or lack thereof between hydroxyl and alkyl allyl group respectively). Allylic alcohol **385** was reacted with IPNBS H (**272**) under the Mitsunobu reductive transposition conditions developed by Movassaghi and Ahmad,[314] which gave **384**, albeit in low yield. Importantly, we detected by NMR spectroscopy that the alkene had transposed, which consequently dearomatized the benzofuran ring, and the [1,5]-shift of the diazene occurred exclusively on the opposite face with respect to the starting alcohol (see Scheme 79).

Prompted by the small amount of benzofuran **360** in-hand, we discussed procedures that may give "bowl" fargenone A (**48a**) and

"ladder" fargenone A (**48b**) in one-step. Benzofuran **360** was treated under Mukaiyama hydration conditions modified by Magnus *et al*.,[334] which unfortunately did not provide either diastereoisomer of fargenone A (**48a** or **48b**) (see Scheme 79). By ^{1}H NMR spectroscopy analysis, it was observed that the conditions preferentially hydrated or otherwise derivatised the allyl group olefins.

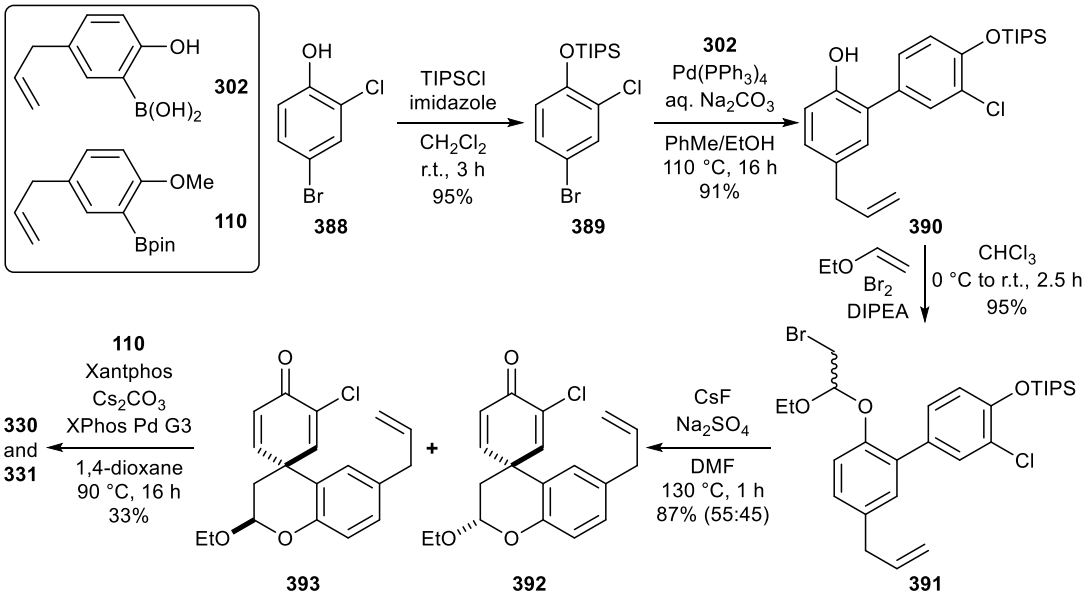


Scheme 79. *Studies towards the synthesis of fargenone A (**48**) from **360**.*

Further development of conditions and completion of the synthesis of fargenone A "bowl" (**48a**) and "ladder" (**48b**) based on this retrosynthetic analysis is required.

2.3.1: Studies towards the synthesis of simonsol F

In this section, alternative studies towards and a larger scale synthesis of simonsol F (**56**) are discussed. Our first study towards the synthesis of simonsol F (**56**) started with TIPS protection of 2-chloro-4-bromophenol (**388**) which gave **389**. Subsequent chemoselective Suzuki-Miyaura cross-coupling with boronic acid **302** generated **390**. Next, bromo-acetal **391** was formed and underwent a desilylative-intramolecular-alkylation reaction which generated diastereoisomers **392** and **393**. Unfortunately, satisfactory Suzuki-Miyaura conditions to cross-couple either **392** or **393** with **110** were not realised due to low yield and isomerisation of aryl allyl groups (see Scheme 80). Therefore, we reasoned a regioselective Suzuki-Miyaura cross-coupling of TIPS protected 2,4-dibromophenol (**324**) could be possible, which would provide analogous bromo dienones **328** and **329** (see Section 2.1.5).

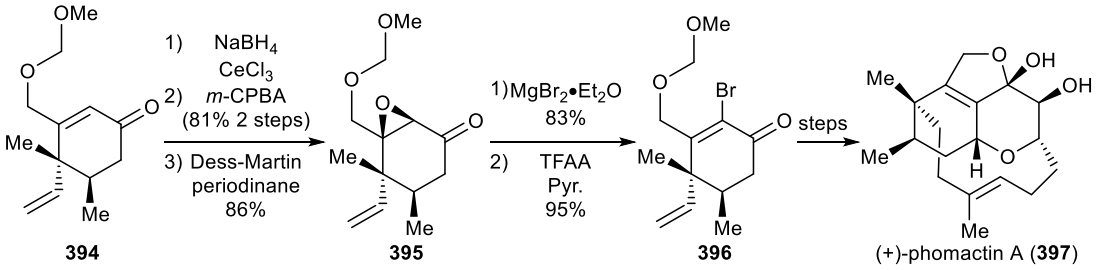


Scheme 80. *First study towards the synthesis of simonsol F (**56**).*

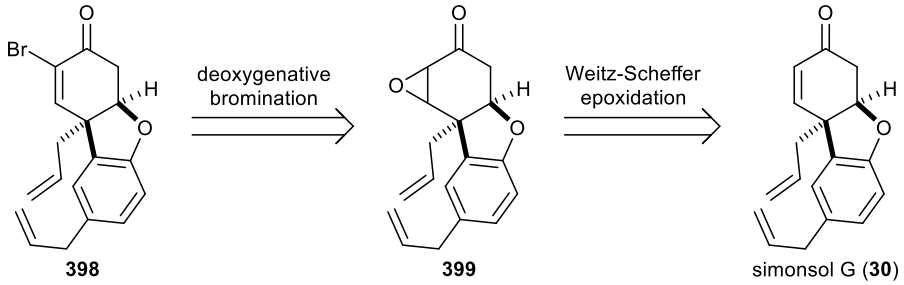
2.3.2: Studies towards the synthesis of simonsol F from simonsol G

Our first-generation retrosynthetic analysis of simonsol F (**56**) included a functionalised tetrahydrodibenzofuran core for late-stage derivatisation towards the efficient synthesis of both *Illicium*-derived neolignans and non-natural derivatives (see Scheme 49). Unfortunately, this was not possible due to the instability of α-halogenated dienones/enones under the Wittig cascade conditions. However, with simonsol G (**30**) in hand, we reasoned the enone could be chemoselectively halogenated at the α-position which would give the initially desired functionalised tetrahydrodibenzofuran core.

We were inspired by Halcomb and Mohr's total synthesis of (+)-phomactin A,[335] in which they successfully brominated the α-position of an enone in the presence of a vinyl group over a 5-step sequence (see Scheme 81). We envisioned that simonsol G (**30**) could be epoxidized chemoselectively under Weitz-Scheffer[336] conditions followed by deoxygenative bromination[337] to transform α,β-epoxy-ketone **399** to α-bromo enone **398** (see Scheme 82).

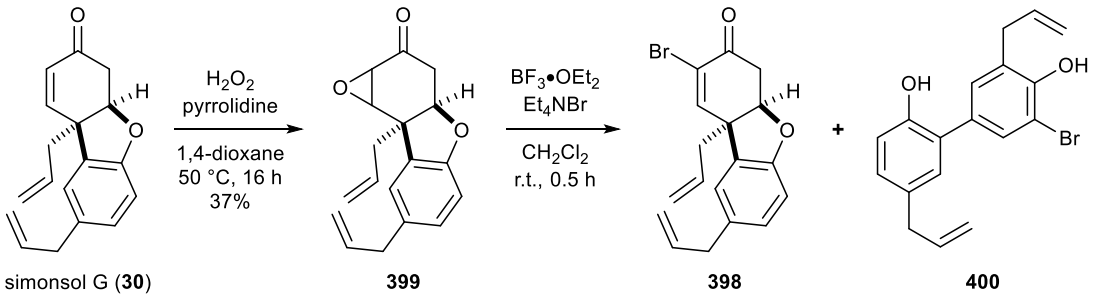


Scheme 81. *5-step sequence to brominate at the α-position of enone* ***394*** *in the total synthesis of (+)-phomactin A.*[335]



Scheme 82. *Retrosynthetic analysis of functionalized core* ***398*** *from simonsol G (****30****).*

Epoxy ketone **399** was not isolated under various standard (H_2O_2 or ^{t}BuOOH) or alternative (tetrabutylammonium peroxydisulfate)[338] Weitz-Scheffer conditions. Instead, simonsol G (**30**) was heated with excess pyrrolidine and H_2O_2 which gratifyingly gave **399**, albeit in low yield (see Scheme 83). Epoxy ketone **399** was treated with BF_3•OEt_2 and Et_4NBr which gave indication by ^{1}H and ^{13}C NMR spectroscopy, HRMS and LC-MS that both α-bromo enone **398** and biaryl **400** had formed. The data were compared to other attempts to make **398** (see Table 13) which supported the presence of both species in this product mixture.



Scheme 83. *Synthesis of bromo-functionalized tetrahydrodibenzofuran core* ***398****. No yield given for bromination due to small scale of reaction (9 µmol scale).*

Due to the low yielding Weitz-Scheffer epoxidation of simonsol G (**30**), a different strategy was sought and our focus turned to Morita-Baylis-Hillman type-conditions.[339–341] Nitrogenous bases were used in

excess to promote electrophilic halogenation of the enone versus the allyl group olefins. LC-MS was used to quickly screen reaction conditions and the results are summarised in Table 13. Although sources of Br^+ seemed promising, when the equivalents of Br^+ were increased to improve the conversion of simonsol G (**30**), over-halogenation was observed (see Table 13, entries 1–4). Sources of I^+ gave higher conversions and yields by % UV absorption by LC-MS analysis. Altering the equivalents of I_2, AgOTf[342,343] and DABCO used led to the realisation that AgOTf was not required and using >3 eq. of DABCO led to higher conversion but also a higher proportion of di-iodinated species (see Table 13, entries 6–16). Krafft and Cran reported DMAP was an effective catalyst for the α-iodination of α,β-unsaturated carbonyl compounds.[344] They also used K_2CO_3 to remove any HI generated *in situ* from the reaction between I_2 and H_2O. Aggarwal and Mereu have reported that DBU can stabilise the formed enolate through conjugation, thus increasing its equilibrium concentration and overall rate of reaction (see Figure 11).[345] The final conditions combined the use of I_2, DBU and K_2CO_3 which gave iodo-enone **403** consistently in 66% yield (see Table 13, entry 18).

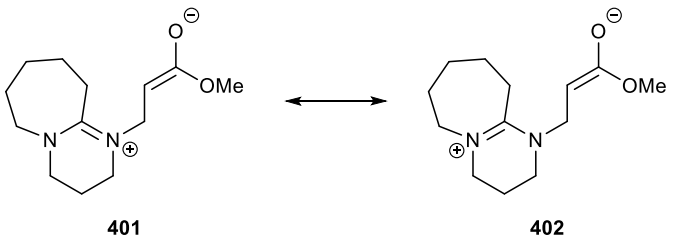
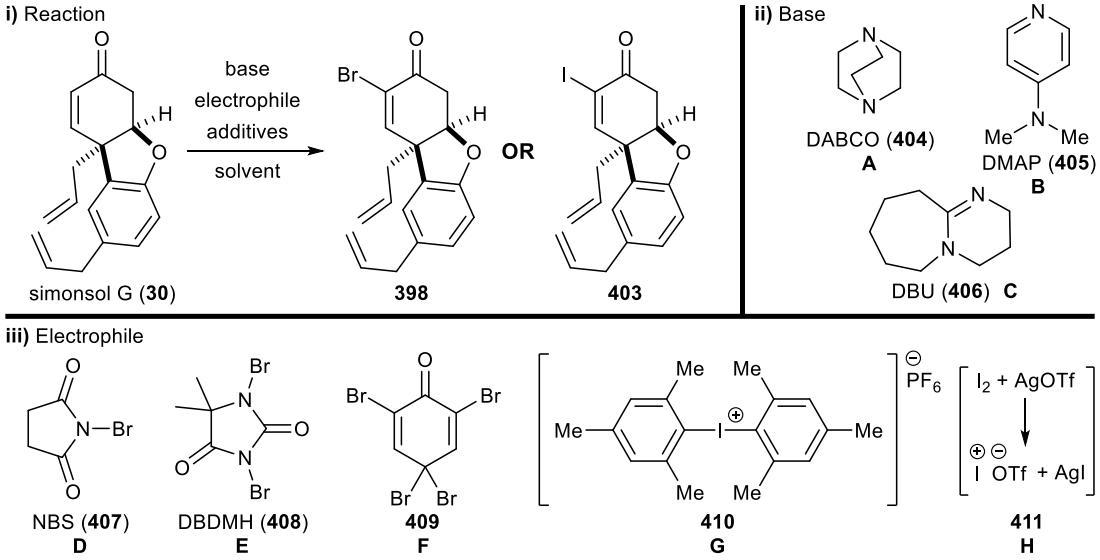


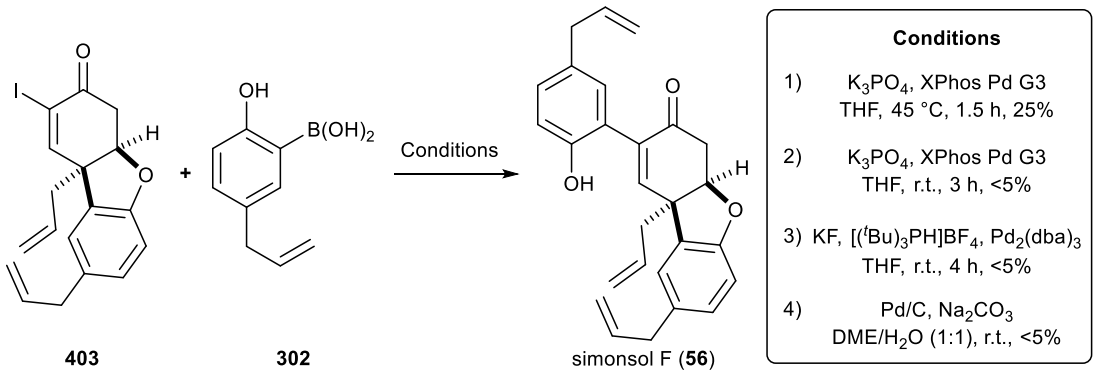
Figure 11. *DBU promoted β-ammonium enolate stabilised through conjugation.*[345]



					Species LC-MS UV % area[b] (λ = 254 nm) (%)			Isolated yield of species (%)	
No.	**Base**	**E⁺**	**Solvent**	**Time**	**30**	**398/403[c]**	**Ohal.**	**30**	**403**
1	**A** (1.0 eq.)	**D** (1.0 eq.)	THF	16 h	38	49	4	-	-
2	**A** (1.4 eq.)	**D** (1.4 eq.)	THF	16 h	17	38	36	-	-
3	**A** (1.4 eq.)	**E** (0.7 eq.)	THF	16 h	11	32	50	-	-
4	**A** (1.4 eq.)	**F** (1.4 eq.)	THF	16 h	36	<1	<1	-	-
5	**A** (1.4 eq.)	**G** (1.4 eq.)	THF	16 h	24	<1	<1	-	-
6	**A** (1.4 eq.)	**H** (1.3 eq.)	THF/CH_2Cl_2	16 h	24	50	13	25	36
7	**A** (1.7 eq.)	**H** (2.0 eq.)	CH_2Cl_2	3 h	25	50	11	-	-
8	**A** (1.7 eq.)	**H** (3.0 eq.)	CH_2Cl_2	16 h	22	59	7	-	-
9	**A** (5.7 eq.)	**H** (3.0 eq.)	CH_2Cl_2	3 h	7	40	35	-	-
10	-	**H** (1.5 eq.)	CH_2Cl_2	19 h	<1	<1	<1	-	-
11	**A** (2.5 eq.)	**H** (1.4 eq.)	CH_2Cl_2	19 h	20	53	17	-	-
12	**A** (6.0 eq.)	**H** (1.4 eq.)	CH_2Cl_2	19 h	3	50	33	-	-
13	-	I_2 (1.0 eq.)	CH_2Cl_2	19 h	39	<1	<1	-	-
14	**A** (3.0 eq.)	I_2 (1.0 eq.)	CH_2Cl_2	19 h	42	40	10	-	-
15	**A** (4.0 eq.)	I_2 (1.0 eq.)	CH_2Cl_2	1 h	44	36	13	-	-
16	**A** (4.0 eq.)	I_2 (1.0 eq.)	CH_2Cl_2	3 h	40	41	11	-	-
17[a]	**B** (2.0 eq.)	I_2 (1.5 eq.)	THF/H_2O	20 h	10	57	5	17	51
18[a]	**C** (2.0 eq.)	I_2 (1.5 eq.)	THF/H_2O	2 h	-	-	-	10	66

Table 13. *Morita-Baylis-Hillman type halogenation of simonsol G (**30**). E^+ = electrophile, Ohal. = products of over-halogenation detected by mass ion patterns in LC-MS analysis.* ***a)*** *K_2CO_3 (1.2 eq.) added.* ***b)*** *Crude reaction mixture analysis.* ***c)*** *Dependent on electrophile used, either **398** or **403** could be generated.*

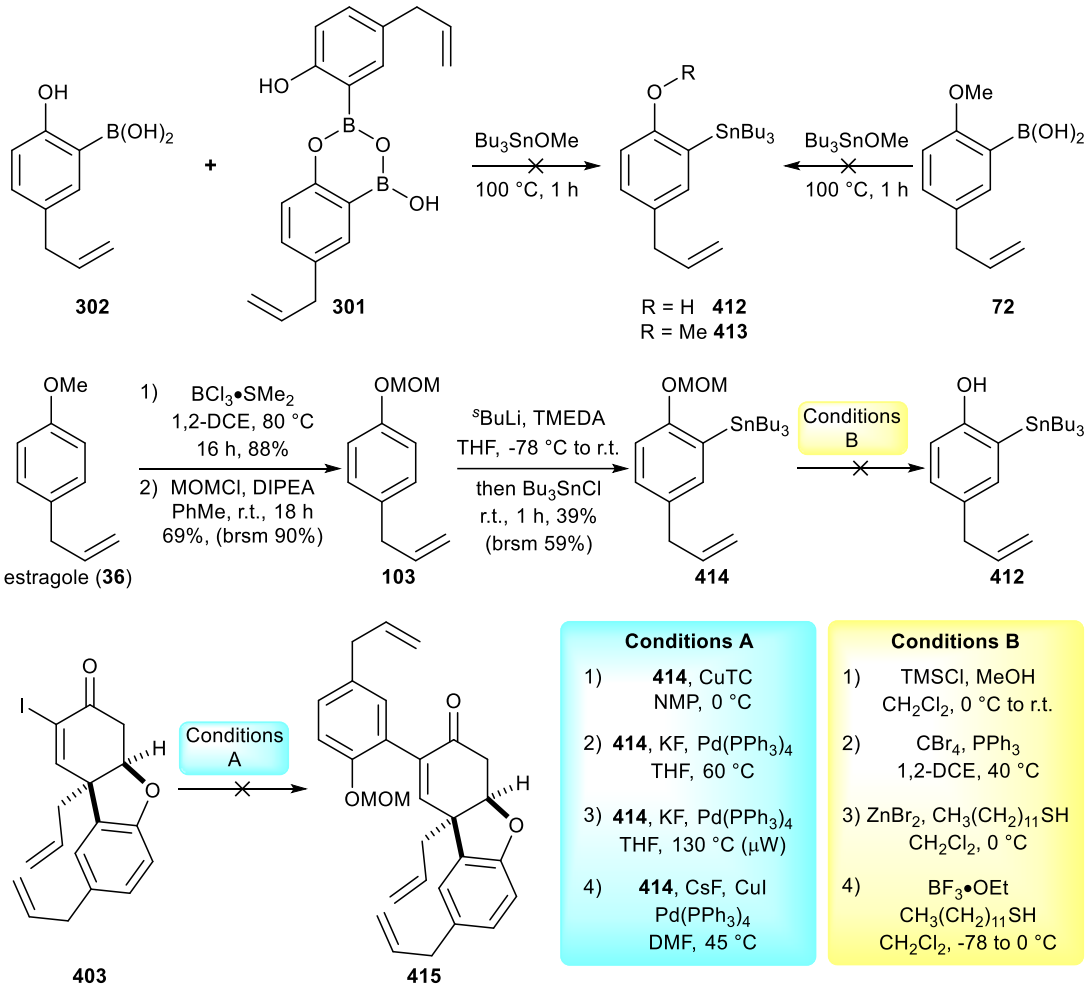
Initially, Suzuki-Miyaura cross-coupling conditions were applied to couple iodo enone **403** with in-house boronic acid **302** (see Scheme 84). Attempts to increase the yield obtained from condition 1 were unsuccessful. Conditions 2 to 4[346] either substantially isomerised the allyl group olefin, produced simonsol G (**30**) by protodehalogenation or gave biaryl species with a honokiol (**33**) type structure *via* likely hydroxydienone intermediates (see Section 2.2.1).



Scheme 84. *Suzuki-Miyaura conditions attempted to form simonsol F (**56**).*

Next, alternative milder cross-coupling conditions were explored which started with the synthesis of an organotin chavicol unit for Stille cross-coupling. Hoshi *et al.* reported the transmetallation of aryl boronic acids to aryltributylstannanes by reaction with tributyltin methoxide.[347] However, when these conditions were applied to in-hand boronic acids **72**, **301** or **302**, the respective organotin species **412** or **413** were not obtained. Therefore, MOM protected chavicol **103** was treated with ^{s}BuLi and the *in situ* generated organolithium was reacted with Bu_3SnCl which gave organotin **414** in low yield (see Scheme 85). Several Stille cross-coupling conditions were applied to

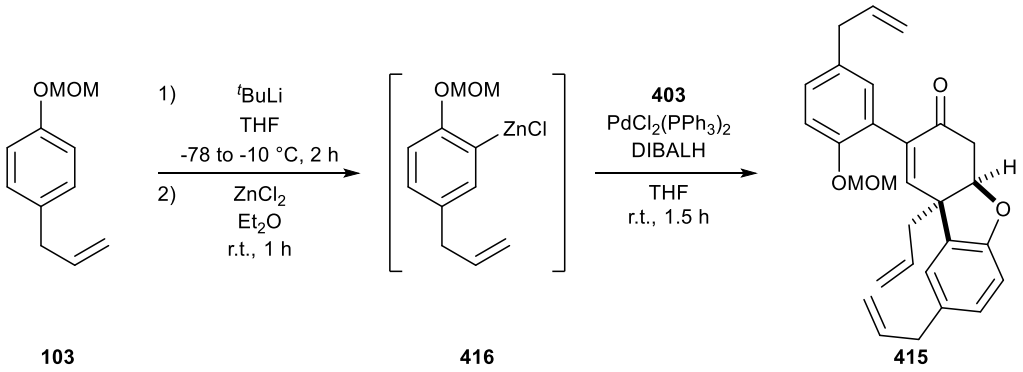
403 and **414** however **415** or simonsol F (**56**) was not observed. Instead, isomerised aryl allyl group products, protodestannylated products or protodehalogenated products were isolated. Various MOM group deprotection strategies were attempted to relieve steric hindrance around arylstannane **414** but all conditions caused protodestannylation before deprotection (see Scheme 85).



Scheme 85. *Stille cross-coupling attempts to generate MOM simonsol F* ***415****.*

LeBel and Agharahimi reported successful Negishi cross-coupling conditions in their synthesis of (-)-monoterpenylmagnolol (**44**).[68] Following the reported protocol, MOM protected chavicol **103** was treated with ^{t}BuLi then $ZnCl_2$ to form organozinc **416** *in situ* which

was reacted under Negishi cross-coupling conditions with iodo enone **403** (see Scheme 86). Unfortunately, the outcome of the reaction was insufficiently investigated but after re-analysis of ^{1}H NMR spectroscopy reports, it is likely that **415** was formed in approximately 10-20% yield. Approximately 80% of MOM chavicol **103** and 30% of iodo enone **403** was recovered. Importantly, the aryl allyl group olefins did not undergo thermodynamic isomerisation and products arising from Cope rearrangement of hydroxydienone intermediates were not observed (see Section 2.2.1).

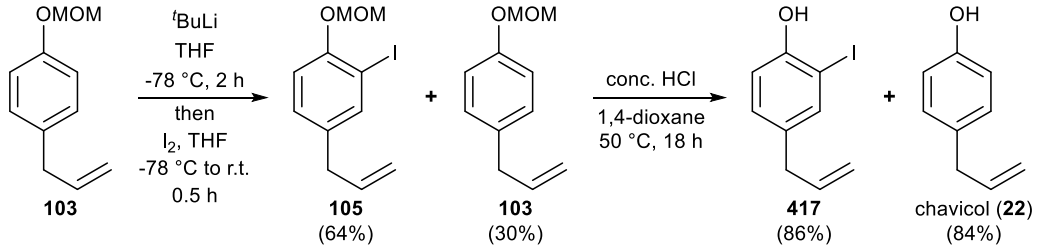


103 **416** **415**

Scheme 86. *Negishi cross-coupling attempt to produce MOM simonsol F **415**.*

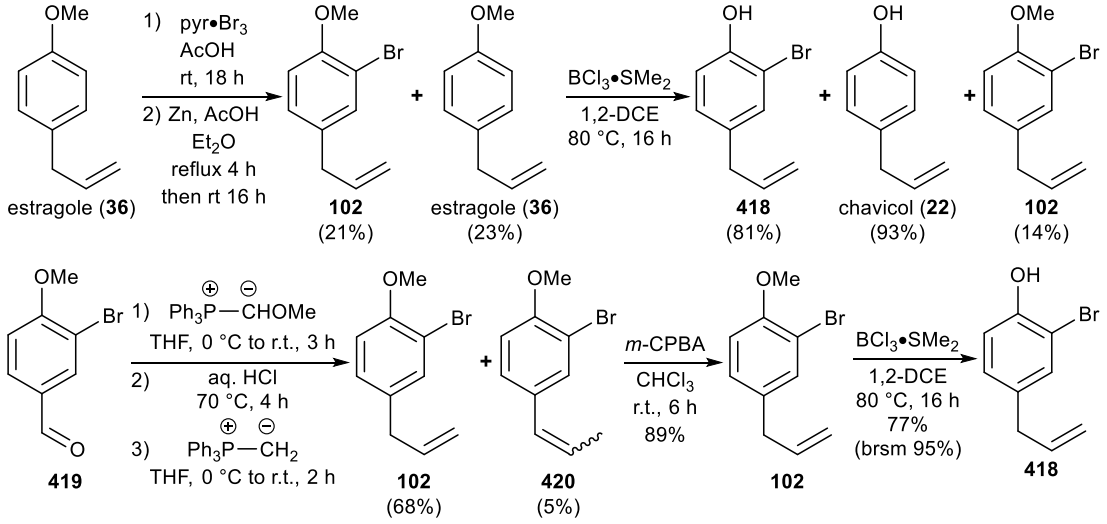
2-iodocyclohexenone (**422**) was used herein as a fragment of **403** to find suitable cross-coupling conditions. Due to the recovery of **103**, alternative methods to form *in situ* organozinc species like **416** were investigated starting from prerequisite aryl halides.[157,188,189,348]

Following LeBel and Agharahimi's protocol,[68] MOM aryl iodide **105** was isolated but as an inseparable[323] mixture with MOM chavicol **103**. Deprotection of the MOM group under standard conditions gave *ortho* iodinated chavicol **417** and chavicol (**22**) which were separated[329] (see Scheme 87).



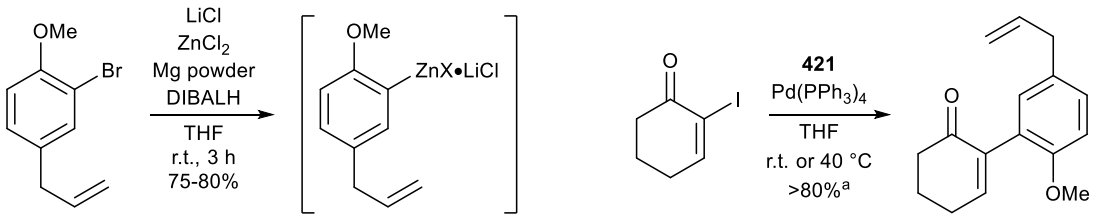
Scheme 87. *Synthesis of ortho iodinated chavicol **417**.*

When following Chen and Liu's method to obtain aryl bromide (**102**), it was generated as an inseparable[323] mixture with estragole (**36**) and in much lower yield than what was reported (see Scheme 19).[72] Subsequent demethylation gave separable[329] *ortho* brominated chavicol **418**, chavicol (**22**) and recovered **102** (see Scheme 88). We developed a more reliable synthesis of **102** whereby commercially available benzaldehyde **419** underwent a Wittig homologation and subsequent methylenation which gave **102** as well as its inseparable[323] thermodynamic allyl group isomer **420**. Prilezhaev epoxidation conditions selectively epoxidised the more reactive di-substituted olefin of **420** which facilitated separation[329] from **102**. Subsequent demethylation of **102** gave **418** (see Scheme 88).



Scheme 88. *Reported conditions tried (top) versus our developed conditions (bottom) used to obtain bromo estragole **102** and subsequently bromo chavicol **418**.*

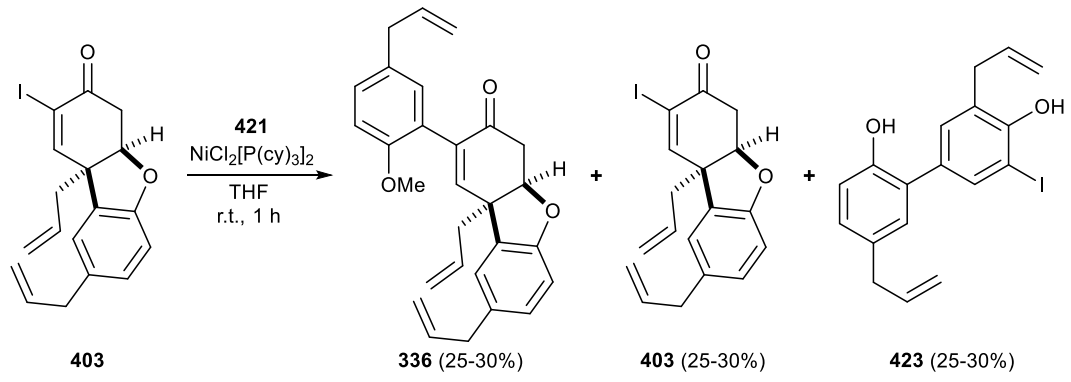
Although aryl iodides tend to undergo metal insertion reactions under milder conditions, the synthesis towards **105** was longer than our developed synthesis of **102**. Hence, the formation of organometallic species for cross-coupling reactions from **102** or **418** was explored. Knochel *et al*. generated organozinc species *in situ* from electron-rich aryl bromides under mild conditions by magnesium insertion, promoted by LiCl, and subsequent transmetallation with $ZnCl_2$.[189] The conditions were applied to **102** which consistently formed organozinc **421** *in situ* in 75-80% yield.[349] Subsequent Negishi cross-coupling with 2-iodocyclohexenone (**422**)[344] at either ambient temperature or 40 °C showed by ^{1}H NMR spectroscopy that **422** was fully consumed and that **366** was the only species present that contained a cyclohexanone moiety (see Scheme 89).



Scheme 89. *Generation of organozinc species **421** and application to a Negishi cross-coupling.* ***a)*** *Estimated yield base on crude ^{1}H NMR spectroscopy (see S.I.).*

Encouraged by these results, iodinated tetrahydrodibenzofuran core **403** was reacted with **421** under several Negishi cross-coupling conditions. The reactions were monitored by ^{1}H NMR spectroscopy and the results are summarised. Catalysts (Pd, Ni or Co) were all surveyed at temperatures ranging between -18 to 40 °C. The best results were obtained using $NiCl_2$(dppp) and $NiCl_2[P(cy)_3]_2$, whereas

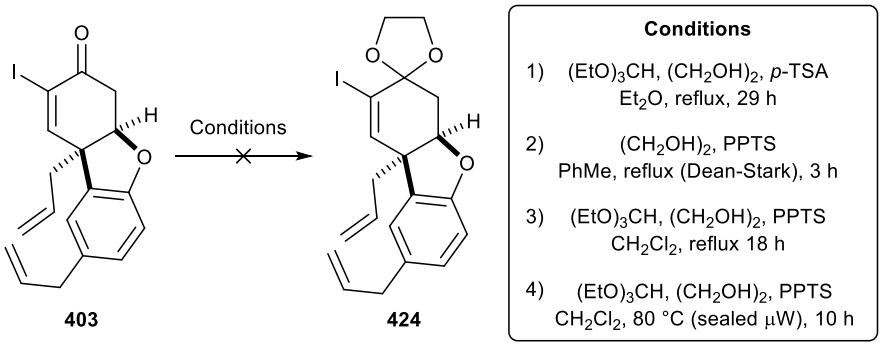
$CoCl_2$ did not provide any **336**. No reaction occurred at -18 °C, however when the temperature was raised to between 0 to 40 °C, coupled product **336**, iodo enone **403**, simonsol G (**30**) and products of Cope rearrangement of intermediary hydroxydienones (see Section 2.2.1) such as **423** were observed. After an extended period, 16 hours, no species containing a tetrahydrodibenzofuran core were observed, whereas reactions left for 0.5 to 4 hours tended to give an approximate 10-30% yield of **336**. The rate of the Negishi cross-coupling did not significantly outcompete the rate at which the tetrahydrodibenzofuran core underwent rearrangement to bi- or tri-aryl species and so it was realised that obtaining **336** in >30% yield was unlikely. Our optimised conditions (see Scheme 90) gave an approximate 1:1:1 mixture of **336**, **403** and **423**.



403 **336** (25-30%) **403** (25-30%) **423** (25-30%)

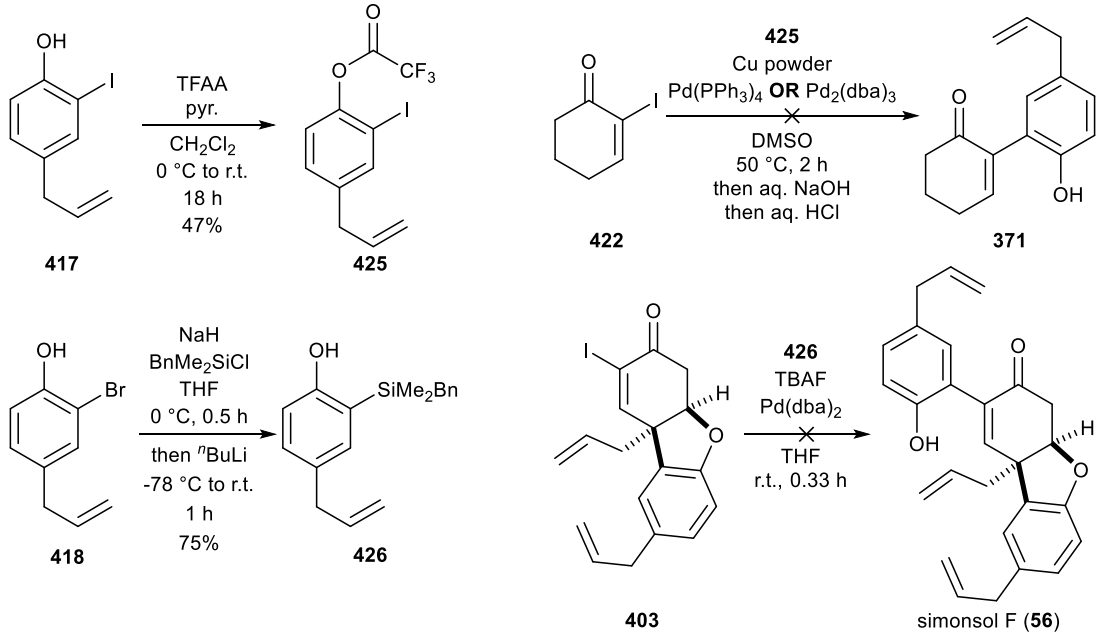
Scheme 90. *Optimised Negishi cross-coupling conditions of **403** and **421**. Yields are estimated based on crude ^{1}H NMR spectroscopy.*

In an attempt to overcome the tetrahydrodibenzofuran core ring-opening to a hydroxydienone intermediate followed by Cope rearrangement, conditions were surveyed to form cyclic acetal **424** but all attempts resulted in the recovery of **403** (see Scheme 91).



Scheme 91. *Attempted formation of acetal **424** from enone **403**.*

With **417** and **418** in-hand, alternative cross-couplings were explored. Banwell *et al*. reported a Pd^0-mediated Ullmann cross-coupling of electron-deficient arenes with **422**,[350] whilst Denmark and Tymonko reported a Hiyama-Denmark cross-coupling using alkene bound benzyldimethylsilanes.[351] Iodo-chavicol **417** was transformed into unstable TFA ester **425** however the subsequent Ullman coupling was unsuccessful. Retro-Brook rearrangement of bromo-chavicol **418** gave **426** which did not provide simonsol F (**56**) under the Hiyama-Denmark conditions (see Scheme 92).



Scheme 92. *Attempted Pd^0-mediated Ullman and Hiyama-Denmark cross-couplings.*

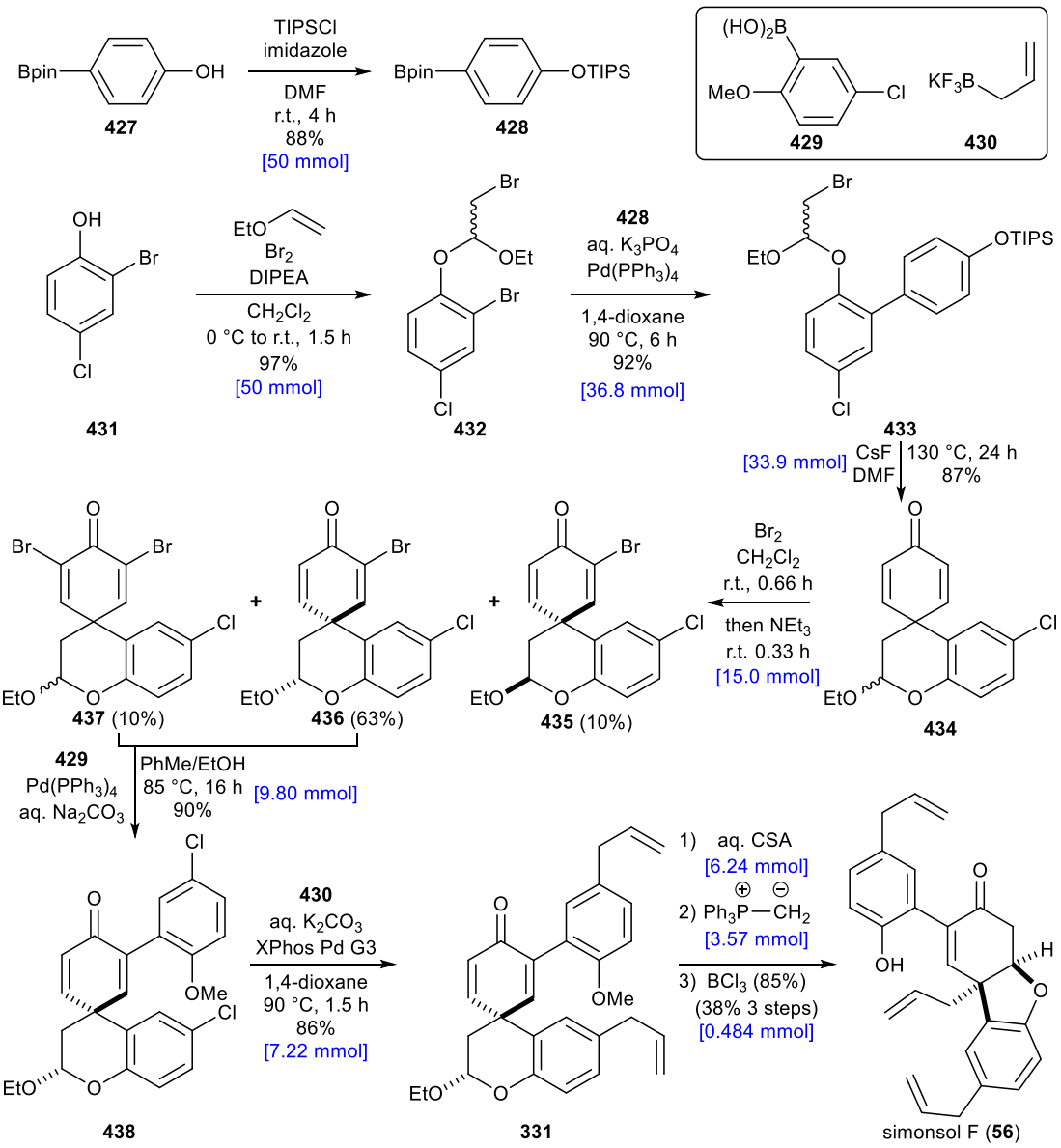
The cross-coupling of the iodinated tetrahydrodibenzofuran core **403** was not explored further for the purpose of this thesis but details on possible future work have been provided (see Section 5.1.1).

2.3.3: Total synthesis of simonsol F by late-stage allylation

The following large-scale synthesis of simonsol F (**56**) was envisaged as a possible enantioselective synthesis, whereby it was reasoned installation of the allyl group would be possible after α-arylation of an enolate (see Section 2.3.4). Consequently, the bottleneck in terms of material throughput was also addressed as the key desilylating-intramolecular-alkylation reaction could now be performed by slow addition without concern that isomerisation of the sensitive allyl groups would occur.

Commercially available 2-bromo-4-chlorophenol (**431**) was reacted under conditions previously described (see Scheme 51) which generated bromo-acetal **432** (see Scheme 93). Commercially available phenol **427** was protected as the corresponding TIPS silyl ether **428**. Subsequent chemoselective Suzuki-Miyaura cross-coupling of the two prepared partners gave biaryl **433**. Slow addition of **433** into the heated reaction mixture ensured intramolecular alkylation occurred which provided **434** in excellent yield (see Scheme 93). Next, 1,2-dibromination of the dienone followed by

elimination of the β-bromide diastereoselectively generated **435** and **436**. As the over-brominated species **437** could not be separated[323] from **436**, the mixture was reacted under Suzuki-Miyaura cross-coupling conditions with boronic acid **429** which provided **438**. A Suzuki-Miyaura allylation with trifluoroborate **430** provided intermediate **331** that in turn provided simonsol F (**56**) from previously discussed transformations (see Section 2.1.5).



Scheme 93. *Large scale total synthesis of simonsol F (**56**).*

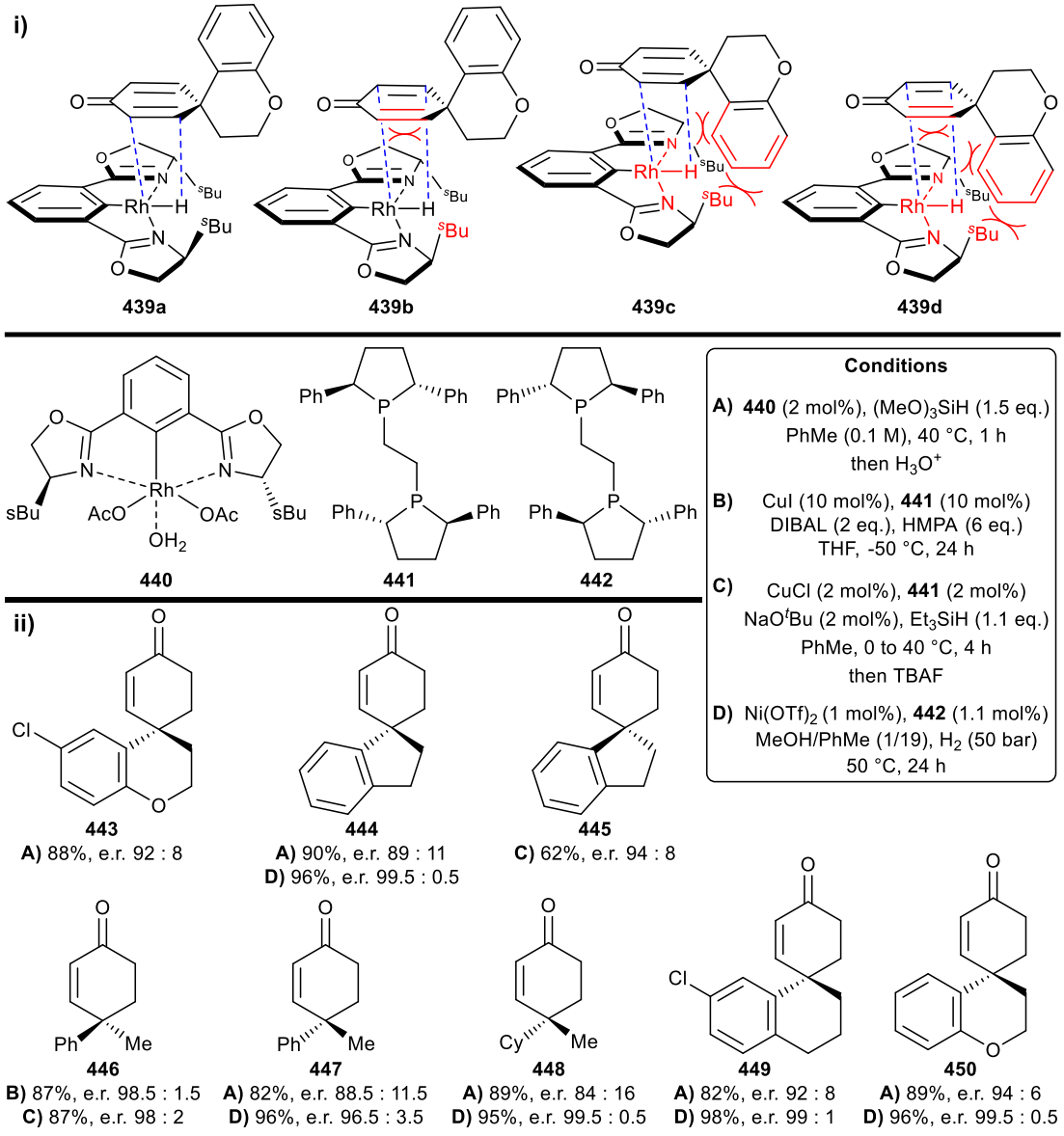
By this route, simonsol F (**56**) was provided in 17% yield from commercially available 2-bromo-4-chlorophenol (**431**). A revised plausible synthesis route is described in Section 5.1.2.

2.3.4: Studies towards an enantioselective synthesis of the tetrahydrodibenzofuran core

The field of asymmetric induction at remote quaternary centres of cyclohexadienones has attracted recent attention. For example, Nishiyama *et al*. developed a chiral Rh-catalyst for asymmetric desymmetrization of γ,γ-disubstituted cyclohexadienones by formal 1,4-hydride addition that generally gave better enantioselectivity for spirocarbocyclic versus acyclic γ,γ-disubstituted species (23–93% e.e. versus 37–81% e.e. respectively) (see Scheme 94ii).[352,353] The enantioselective coordination of a rhodium-hydride species to the cyclohexadienone was guided by steric repulsion, which favoured transition states such as **439a** (see Scheme 94i). The following asymmetric 1,4-hydride additions of γ,γ-disubstituted cyclohexadienones have applied the same principle of ligand-assisted steric repulsion which has guided the face and side selectivity of 1,4-hydride addition.

Corey and co-workers established a Cu-catalysed enantioselective desymmetrization of γ,γ-disubstituted cyclohexadienones (see Scheme 94ii).[354] Jeon *et al.* developed milder Cu-catalysed conditions

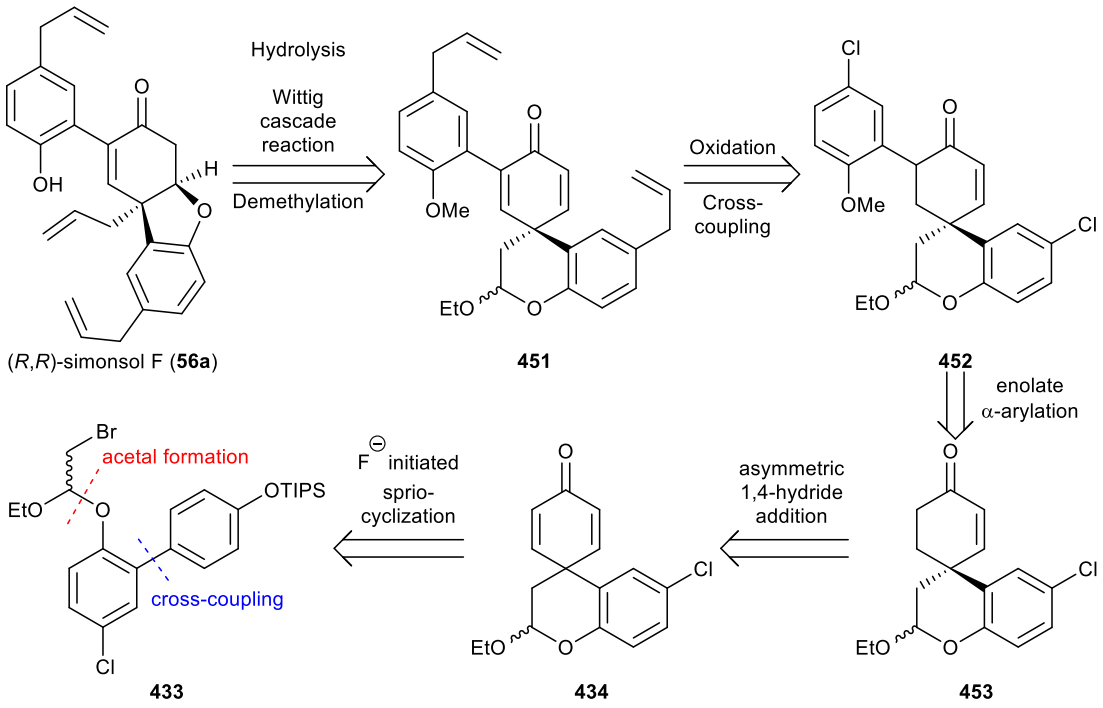
and applied them to a wider range of γ,γ-disubstituted cyclohexadienones which generally gave products with high e.e. (77-99% e.e.) (see Scheme 94ii).[355] Zhang *et al.* developed a chiral Ni-catalyst that asymmetrically desymmetrized both spirocarbocyclic



Scheme 94. i) *Proposed transition states for the Rh-catalysed asymmetric desymmetrization of cyclohexadienones by 1,4-hydride addition. Blue dashed lines indicate the side and face delivery of the hydride. Red indicates steric repulsion.* ***ii)*** *Products generated from the corresponding γ,γ-disubstituted cyclohexadienones. Letter underneath each structure denotes the conditions employed from box.*

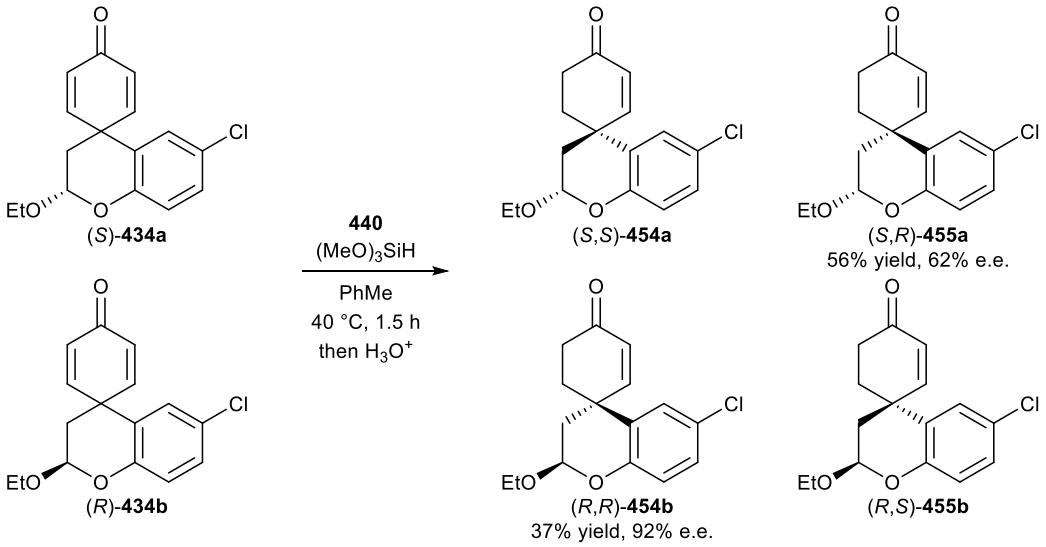
and acyclic γ,γ-disubstituted cyclohexadienones by 1,4-hydride addition in excellent yield and e.e. (94-98% yield, 96-99% e.e. and 92-98% yield, 92-99% e.e. respectively) (see Scheme 94ii).[356]

Our first-generation asymmetric retrosynthetic analysis of simonsol F (**56**) focused on generating the quaternary stereocentre of **453** which we reasoned could be accessed by the asymmetric 1,4-hydride addition of dienone **434**. Previously developed conditions for the α-arylation of enolates use electron rich ligands, which in our experience leads to substantial isomerisation of the allyl groups and therefore these should be installed after α-arylation. From previous experiments and computational analysis (see Scheme 60 and Table 9), the phenolate generated in the Wittig cascade reaction should only attack on one side of the dienone, and can only attack on one face due to the stereodefined quaternary centre (see Scheme 95).



Scheme 95. *First-generation retrosynthetic analysis of (R,R)-simonsol F (**56a**).*

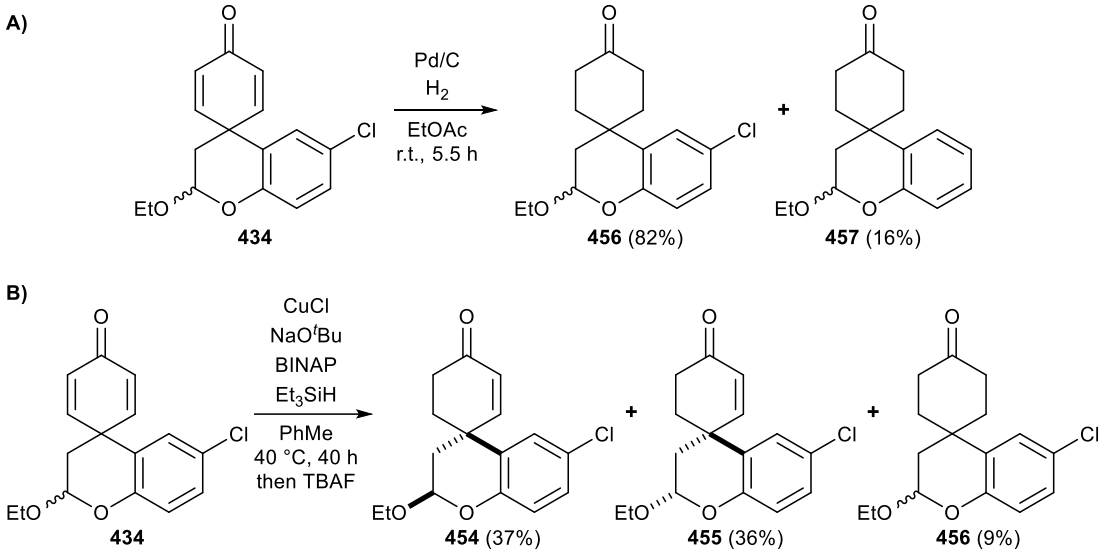
The required Rh-catalyst was made over three steps[352] and the conditions developed by Nishiyama and co-workers were applied to **434** which gave separable[329] diastereoisomers **454** and **455** (see Scheme 96). However, under kinetic control guided by steric interactions (see Scheme 94i), a possible matched/mismatched effect on the chiral Rh-catalyst might have ensued due to the presence of the ethoxy stereocentre. Based upon previous observations, the nature of the Rh-catalyst should favour the formation of (*R*)-stereochemistry at the quaternary centre. Therefore, from the observed e.e. values and an assumption that (*R*,*R*) and (*S*,*R*) are the preferentially formed enantiomers, the quaternary centre was produced with 77% enantiomeric excess.



Scheme 96. *Rh-catalysed asymmetric 1,4-hydride addition of racemic mixture of* ***434a*** *and* ***434b****. Yield and e.e. value given under the diastereoisomer that is likely the major constituent of each mixture.*

The e.e. values of the compounds in Scheme 96 were determined by chiral HPLC which required the synthesis of racemic enones **454** and

455. To this end, dienone **434** was hydrogenated which gave aryl chloride spirocyclic ketone **456** and dehalogenated spirocyclic ketone **457** in a 4:1 respective mixture. Separation of **456** from **457** was challenging however mixtures were obtained in 95:5 and 5:95 ratios respectively (determined by ^{1}H NMR spectroscopy) (see Scheme 97A). Success was found with a Cu-BINAP-mediated 1,4-hydride addition to dienone **434** which directly gave enones **454** and **455**, however ketone **456** was also formed in low amounts and was inseparable[323] from **455** (see Scheme 97B). Gratifyingly, these compounds proved separable by chiral HPLC so e.e. values could be calculated.



Scheme 97. *Synthesis of racemic **454** and **455**. **A)** Hydrogenation of dienone **434**. **B)** Cu-BINAP-mediated 1,4-hydride addition to dienone **434**.*

Further investigation into the synthesis towards an enantioselective synthesis of *Illicium*-derived neolignans is required, and a synthesis route that installs the acetal or hemi-acetal after the asymmetric 1,4-hydride reduction is discussed in Section 5.1.3.

3: Biology and SAR study

3.1: Promoting the axonal growth of primary mouse cortical neurons

Neurotrophic factors are compounds that are known to promote neurite outgrowth which is an attractive target to slow the progression of neurodegenerative diseases (see Section 1.4.2).

We collaborated with the research group of Dr. Federico Dajas-Bailador at the University of Nottingham (to date), who have a research interest in understanding key processes that control axon development, degeneration, and regeneration. Dr Raquel Ribeiro led the laboratory work and developed an assay to assess the promotion in axon growth of mouse primary cortical neurons (see Figure 12). The compounds were applied (as a solution in DMSO) to freshly isolated primary embryonic mouse cortical neurons, 24 hours after they were plated. Subsequently, the plate was incubated for 48 hours, followed by fixation and immunostaining (acetylated tubulin). The plate was imaged at 20 random points and the neurons imaged (~60-80 per image) were measured computationally. Magnolol (**26**) has been shown to promote neurite outgrowth,[66,67] but SAR studies on magnolol (**26**) and honokiol (**33**) have shown a requirement for at least one free hydroxyl group in order to observe biologically relevant activity in assays at low concentrations.[49–51] Therefore,

magnolol (**26**) and dimethylated magnolol (**468**) were initially tested to find suitable conditions to conduct the assay, and DMSO was used throughout as the control. The optimal concentration of compounds tested in the assay was found to be 1 μM (0.1 μM showed less effects whereas 10 μM was generally toxic to neuron development).

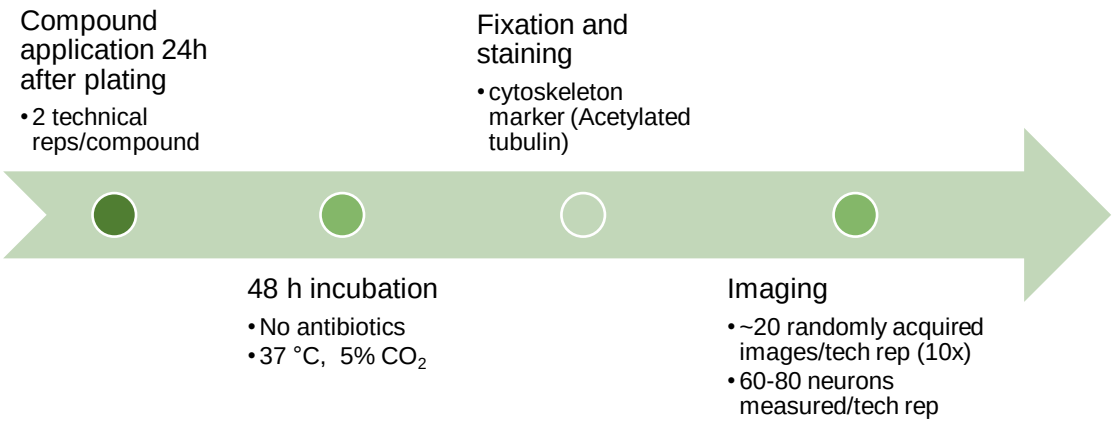


Figure 12. *Promotion in axon growth of mouse primary cortical neurons assay.*

First, *Illicium*-derived neolignans and intermediate compounds were screened which showed that magnolol (**26**), simonsol F (**56**), simonsinol (**40**) and simonsol C (**55**) increased the length of mouse primary cortical axons at 1 μM (see Figure 13). Simonsinol (**40**) has both a magnolol (**26**) and honokiol (**33**) moiety which have both individually been shown to promote neurite outgrowth.[51,66,67,70] Although simonsol C (**55**) has a magnolol (**26**) moiety, this does not explain the observed high promotion of axon growth. Consequently, simonsol F (**56**) and simonsol C (**55**) underwent modifications in an SAR study to probe possible biological interactions that may be occurring between the neuron and the tetrahydrodibenzofuran core.

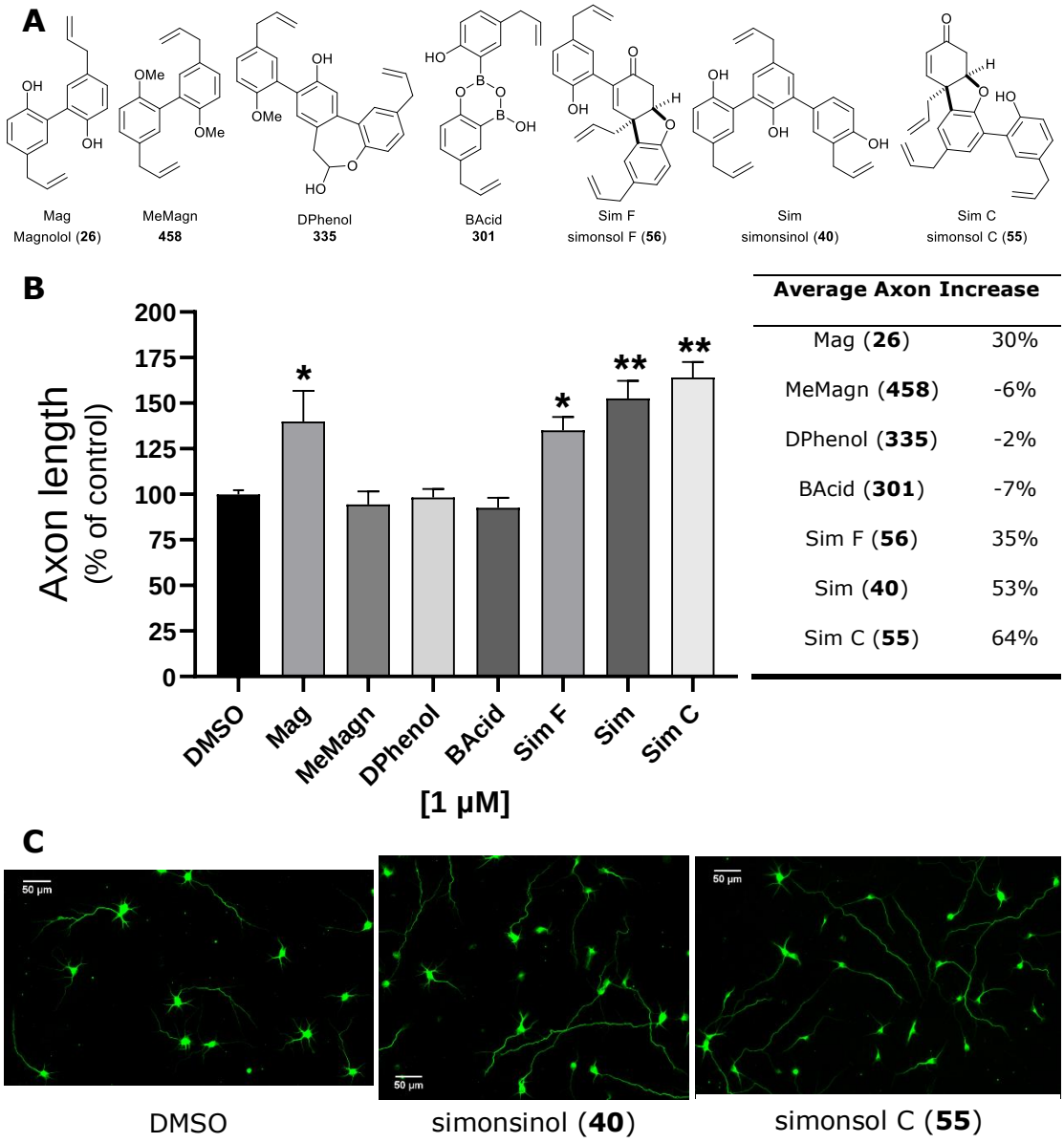
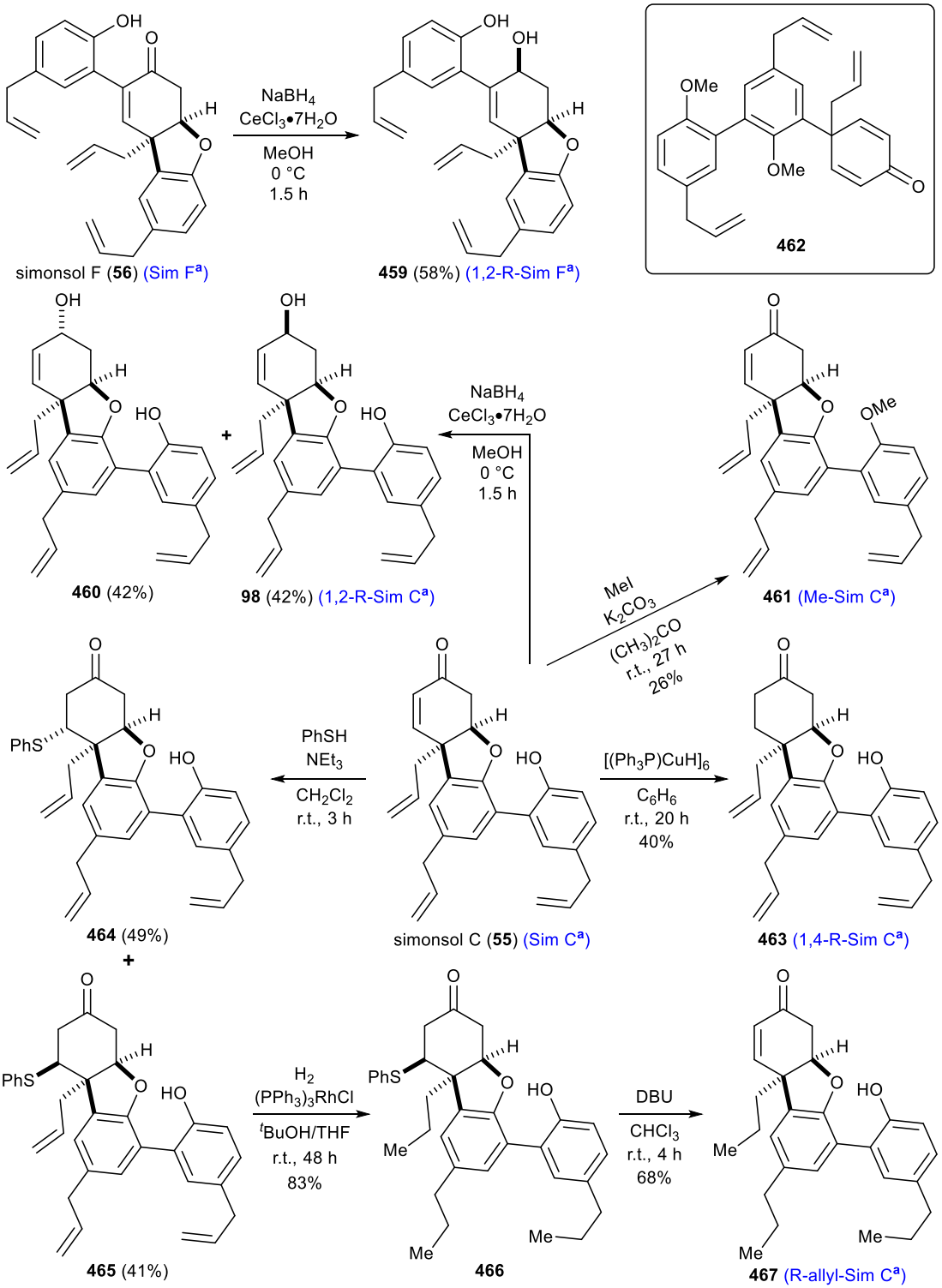


Figure 13. *Screen of Illicium-derived neolignans and intermediate compounds in axon growth of mouse primary cortical neurons.* ***A)*** *Compounds tested.* ***B)*** *Analysis of the effect of Illicium-derived neolignans and intermediate compounds in the growth of the axon of cortical neurons 48 hours after incubation in culture as compared to control DMSO. Data shows magnolol (**26**), simonsol F (**56**), simonsinol (**40**) and simonsol C (**55**) incubation at 1 µM leads to an increase in the length of cortical axons. Data obtained from 3–5 individual experiments; *p<0.05, **p<0.01, One-way ANOVA with posthoc Dunnet's multiple comparison test.* ***C)*** *Representative immunostaining images (acetylated tubulin; scale bar 50 µm).*

Luche reduction of simonsol F (**56**) gave 1,2-reduced simonsol F (1,2-R-Sim F) **459** (see Scheme 98) which showed no activity in the growth of axons when compared to control DMSO (see Figure 14A). We hypothesized that a nucleophilic residue, such as a thiol, on the axon may undergo conjugate addition at the enone moiety of the tetrahydrodibenzofuran core. Next, given that simonsol C (**55**) was more promising (see Figure 13), several analogues were made to hopefully promote the growth of axons. Luche reduction of simonsol C (**55**) gave 1,2-reduced simonsol C (1,2-R-Sim C) **98** and **460** (**460** was not biologically tested). Methylation of simonsol C (**55**) gave **461** in low-yield due to difficulty isolating **461** from tentatively assigned dienone **462**. Copper-hydride mediated conjugate reduction of the enone of Simonsol C (**55**) with Stryker's reagent[332] gave **463** in low yield. A better yield can likely be obtained if less Stryker's reagent is used in this unoptimized experiment. The allyl groups of simonsol C (**55**) were reduced over a three-step sequence which began by protection of the enone moiety as thiophenol ethers **464** and **465**. Due to co-elution of unreacted simonsol C (**56**) with **464**, only **465** was taken forward and was hydrogenated with Wilkinson's catalyst which gave **466**. Subsequent base-mediated E1cB elimination of thiophenol then generated **467**. Compounds **98**, **461** and **463** were tested against DMSO and simonsol C (**55**) at 1 μM which all showed statistically significant reduced axon growth compared to simonsol C (**55**) (see Figure 14B). However, R-allyl-Sim C **467** was toxic to

neuron development at 1 μM and was therefore tested at 0.1 μM which showed comparable promotion to axon growth when compared to simonsol C (**55**) at 0.1 μM (see Figure 14B).



Scheme 98. *Synthesis of modified Illicium-derived neolignans from simonsol F (**56**) and simonsol C (**55**).* ***a)*** *Compound was tested in the neurite outgrowth assay.*

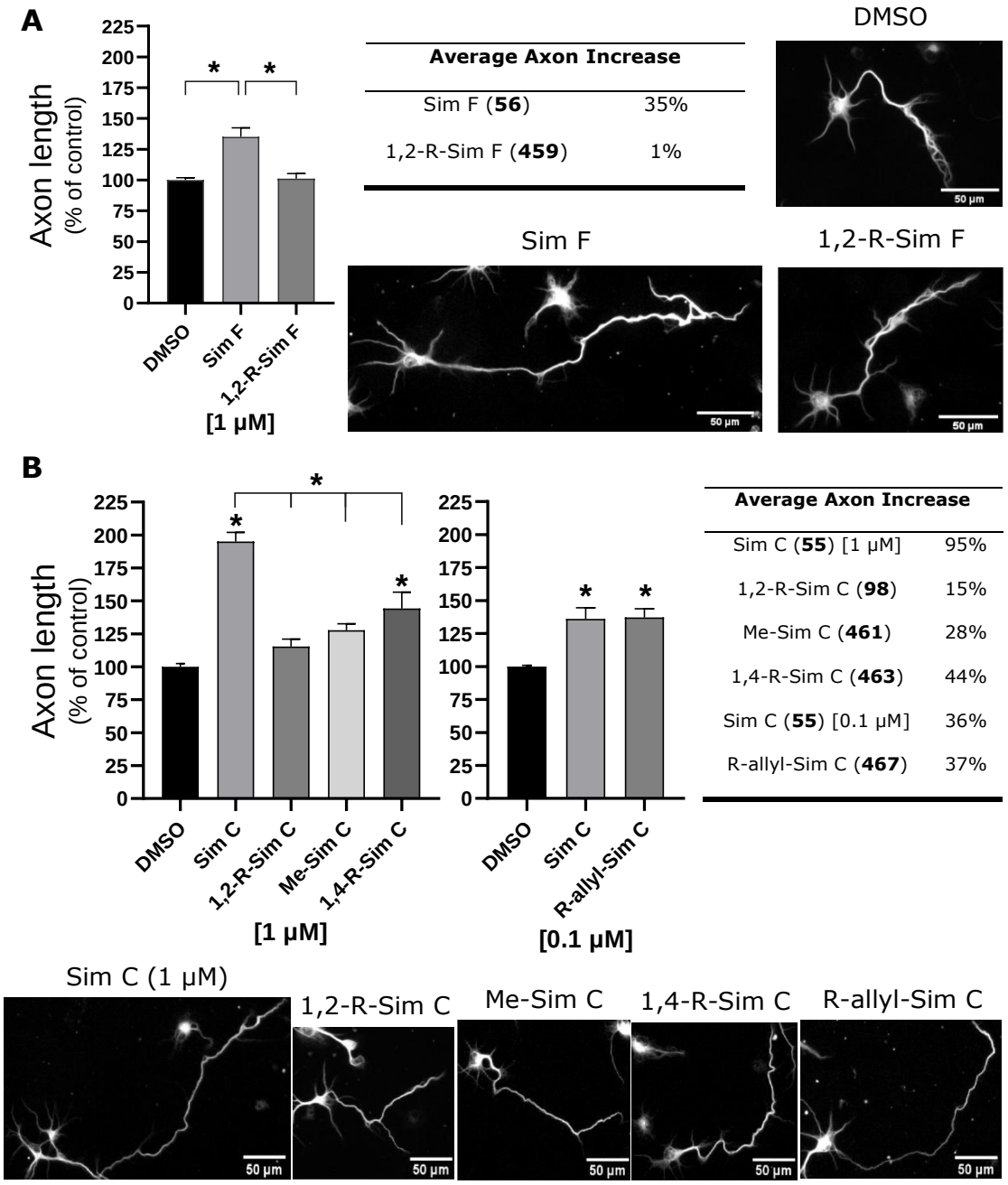


Figure 14. *Structure-activity consequences of modifications in Illicium-derived neolignans in the growth of axons from mouse primary cortical neurons and representative immunostaining images (acetylated tubulin; scale bar 50 µm).*[357] ***A)*** *Tested derivative of simonsol F (**56**).* ***B)*** *Tested derivatives of simonsol C (**55**).*

In the comparison of simonsol C (**55**) versus its derivatives (**98**, **461** and **463**), it was found that simonsol C (**55**) promoted axon growth by 95% at 1 µM compared to DMSO control. This leap from 64% (see

Figure 13) to 95% (see Figure 14B) can be attributed to testing healthier neuron cultures.

The observation that R-allyl-Sim C **467** has similar efficacy to simonsol C (**55**) in the promotion of axon growth warrants further investigation. Species that contain alkenes and benzylic protons are readily oxidised (by cytochrome P450 enzymes)[358] and then excreted by the body before passing into the blood circulatory system. Therefore, simonsol C (**55**) derivatives that lack any propyl chains, perhaps replaced by proton, fluoride, or other non-metabolized functional groups, should be explored.

4: Conclusions

4.1: Summary of results

In conclusion, a Wittig cascade reaction has been developed that has provided access to structurally complex *Illicium*-derived neolignans with a hydrodibenzofuran core. The synthesis of 9 reported *Illicium*-derived neolignans and two further likely species that were possibly over-looked in the isolation of simonsol E (**57**) and simonsin A (**50**) have been completed. New biosynthesis proposals for honokiol (**33**), simonsinol (**40**) and macranthol (**39**) *via* plausible hydroxydienone intermediates have been provided that do not require the addition phenolic starting material 2-allylphenol (**37**). Chavicol (**22**) can be considered as the single building block for the biosynthesis of all *Illicium*-derived neolignans that have been focused on in this thesis. Investigations towards the synthesis of both diastereoisomers of fargenone A (**48a** and **48b**), as well as an enantioselective synthesis of simonsol F (**56**) have been begun, and proof-of-concept established. Simonsol C (**55**) showed the highest average % increase in the promotion of axon growth in primary mouse cortical neurons out of all compounds tested when compared against DMSO control.

4.2: Simonsol C and simonsinol

The synthesis of simonsol C (**55**) was achieved in 10 steps (longest linear sequence) from estragole (**36**) in a total yield of 15% (see Schemes 49, 50, and 52, and Scheme 56). Subsequently, the synthesis of simonsinol (**40**) was achieved in 1 step from simonsol C (**55**) in 91% yield (see Scheme 65A) *via* a likely biomimetic hydroxydienone intermediate and Cope rearrangement. The synthesis of simonsol C (**55**) has the highest yield and lowest step-count reported to date,[103] whereas the synthesis of simonsinol (**40**) has not been previously reported.

4.3: Simonsol F and macranthol

The synthesis of simonsol F (**56**) was achieved in 10 steps (longest linear sequence) from estragole (**36**) in a total yield of 10% (see Schemes 57–62) or in 9 steps (longest linear sequence) from 2-bromo-4-chlorophenol (**431**) in a total yield of 17% (see Scheme 93). Subsequently, the synthesis of macranthol (**39**) was achieved in 1 step from simonsol F (**56**) in 90% yield (see Scheme 66) *via* a likely biomimetic hydroxydienone intermediate and Cope rearrangement. The synthesis of simonsol F (**56**) has not been previously reported to date. The synthesis of macranthol (**39**) has previously been completed within the Denton group whereby macranthol (**39**) was

formed in 7% overall yield from estragole (**36**) over 5-steps (unpublished results).[91]

4.4: Simonsol G and honokiol

The synthesis of simonsol G (**30**) was achieved in 8 steps (longest linear sequence) from estragole (**36**) in a total yield of 24% (see Schemes 49, 58 and 59). Subsequently, the synthesis of honokiol (**33**) was achieved in 1 step from simonsol G (**30**) in 70% yield (see Scheme 66) *via* a likely biomimetic hydroxydienone intermediate and Cope rearrangement. The synthesis of simonsol G (**30**) has provided the *Illicium*-derived neolignan in the highest yield to date compared to the biomimetic oxidative phenolic coupling studies of chavicol (**22**) which provided simonsol G (**30**) in lower yield (12–13%) but from a single step.[21,22] The synthesis route for honokiol (**33**) is convoluted and was not designed to directly access this simple biaryl species which is resonated by its high-step count and low yield when compared to other reported synthesis routes.[71–78]

4.5: Fargenin

The synthesis of fargenin (**54**) was achieved in 1 step from simonsol F (**56**) and in 29% yield (see Scheme 71). The data reported by Fukuyama and co-workers for the isolation and characterisation of fargenin (**54**) was reported with two typographical errors in the ^{13}C

NMR spectroscopy data.[88] However, the raw ^{1}H and ^{13}C NMR spectra provided by Fukuyama agreed excellently our observations.[359]

4.6: Simonsol E and simonsin A

The synthesis of an inseparable[323] 15:85 respective mixture ("mixture 1") of *epi*-simonsol E (**362**) and simonsin A (**50**) was achieved in 1 step from simonsol F (**56**) in a total yield of 22% (see Scheme 73). The synthesis of an inseparable[323] 7:3 respective mixture ("mixture 2") of simonsol E (**57**) and *epi*-simonsin A (**363**) was achieved in 1 step from simonsol F (**56**) in a total yield of 71% (see Scheme 73). We have observed that epimerisation of "mixture 1" to "mixture 2" (*vice versa*) does not occur at room temperature and does not occur readily when heated for extended periods. Epimerisation occurred readily in the presence of AcOH at ambient temperature and when heated in the presence of AcOH (see Scheme 73 and Table 11). Overall, epimerisation favoured the transformation of "mixture 1" into "mixture 2". Wang and co-workers[97] could not provide the raw NMR spectra for their reported 2:1 respective mixture of simonsol E (**57**) and simonsin A (**50**) which has made it difficult to challenge the validity of their results which are contrary to ours. A full comparison and discussion of ^{1}H and ^{13}C NMR spectroscopy data is shown in the SI (see Section 6.2.3).

4.7: Fargenone A

Simonsol F (**56**) underwent an unexpected transformation that generated benzoquinone species **360** (see Figure 9 and Scheme 71) which led to a new retrosynthetic analysis of both fargenone A "bowl" (**48a**) and "ladder" (**48b**) (see Scheme 78). A unified synthesis to access both diastereoisomers has been started and the steps carried out thus far have provided validity for the completion of the synthesis of both diastereoisomers.

4.8: Enantioselective synthesis of simonsol F

A study towards the enantioselective synthesis of (*R*,*R*)-simonsol F (**56a**) was started which has prompted a second-generation retrosynthetic analysis (see Scheme 103) to install a potentially sterically interfering ethoxy group after the asymmetric 1,4-hydride addition to avoid matched/mismatched effects between the substrate and the catalyst. However, it is assumed that an overall e.e. value of 77% was obtained with (*R*)-stereochemistry for the quaternary centre of generated diastereoisomers **454** and **455** (see Scheme 96).

4.9: Promotion of axon growth in developing neurons

The average length of axons were found to increase (versus DMSO control) when primary mouse cortical neurons were incubated with; magnolol (**26**) [1 μM] by 30%, simonsol F (**56**) [1 μM] by 35%, simonsinol (**40**) [1 μM] by 53% and simonsol C (**55**) [1 μM] by 64% (see Figure 13). The simonsol F allylic alcohol derivative **459** showed no statistically significant promotion of axon growth versus the DMSO control. Three derivatives of simonsol C (**55**) whereby the enone moiety was either reduced to an allylic alcohol which gave **98** or to a ketone which gave **463**, or whereby the free phenol of simonsol C (**55**) was methylated which gave **461**, led to a significant drop in observed axon growth compared to simonsol C (**55**). Dependent on the health of the cultured neurons, simonsol C (**55**) was found to promote axon growth by up to 95% (see Figure 14B). The simonsol C propyl group derivative **467** was toxic to developing neurons at 1 μM but gave 37% average axon growth promotion at 0.1 μM which matched simonsol C (**55**) (36% average axon growth promotion at 0.1 μM) versus DMSO control.

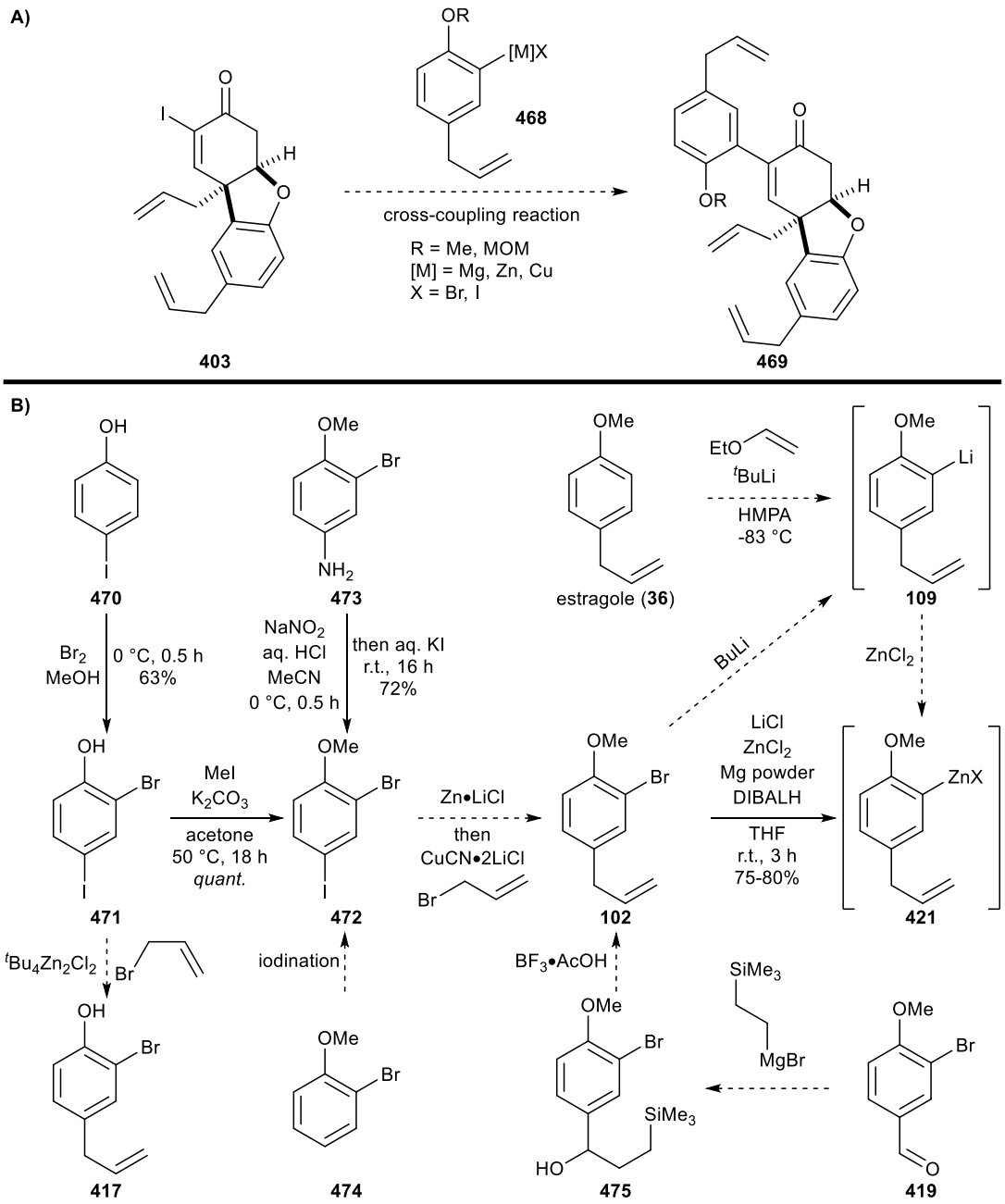
5: Future Work

5.1.1: Future work towards the synthesis of simonsol F from simonsol G

Negishi cross-coupling conditions to form simonsol F (**56**) or other species from iodinated simonsol G **403** should be developed. Work had begun to explore alternative routes to generate 2-bromo-4-allylanisole (**102**) *via* chemoselective metal-halogen insertion reactions followed by reaction with allyl bromide (see Scheme 99). Mono-bromination of 4-iodophenol (**470**) was achieved however the reaction was complicated as over-brominated species were generated. The halogen-metal exchange reaction developed by Uchiyama *et al*. was reported to be chemoselective (ArI > ArBr) and tolerated free phenols,[60] and so it is reasoned that phenol **417** can be accessed directly from 2-bromo-4-iodophenol (**471**). 2-bromo-4-iodoanisole (**472**) has been generated either by a Sandmeyer-type reaction of aniline **473** or by the methylation of phenol **471**. Subsequently, known chemoselective metal-halogen exchange of **472** (ArI > ArBr) should produce an organozinc species that can be reacted with allyl bromide and CuCN•2LiCl to give anisole **102**.[188]

Another possible route to access **102** is by 2-carbon homologation of benzaldehyde **419**.[222] Meyers and Shimano have reported an ethoxyvinyllithium-HMPA base-system that selectively metallated the

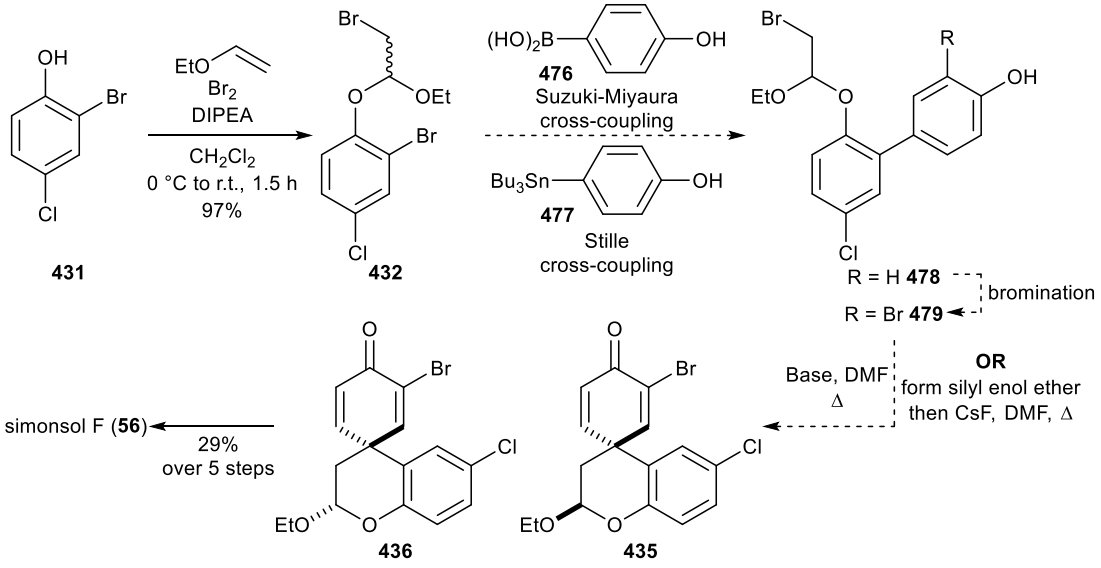
ortho-position of an aryl methoxy group versus oxazoline or dimethoxybenzamide directing groups.[360] It would be interesting to see if this base-system can overcome competing benzylic deprotonation as has been observed with better directing groups.[67,68]



Scheme 99. A) *Cross-coupling reaction to access simonsol F derivative* ***469****.* ***B)*** *Proposed routes to metallated chavicol units for cross-coupling reactions.*

5.1.2: Future work towards the synthesis of simonsol F, fargenone A, simonin A and fargenone B

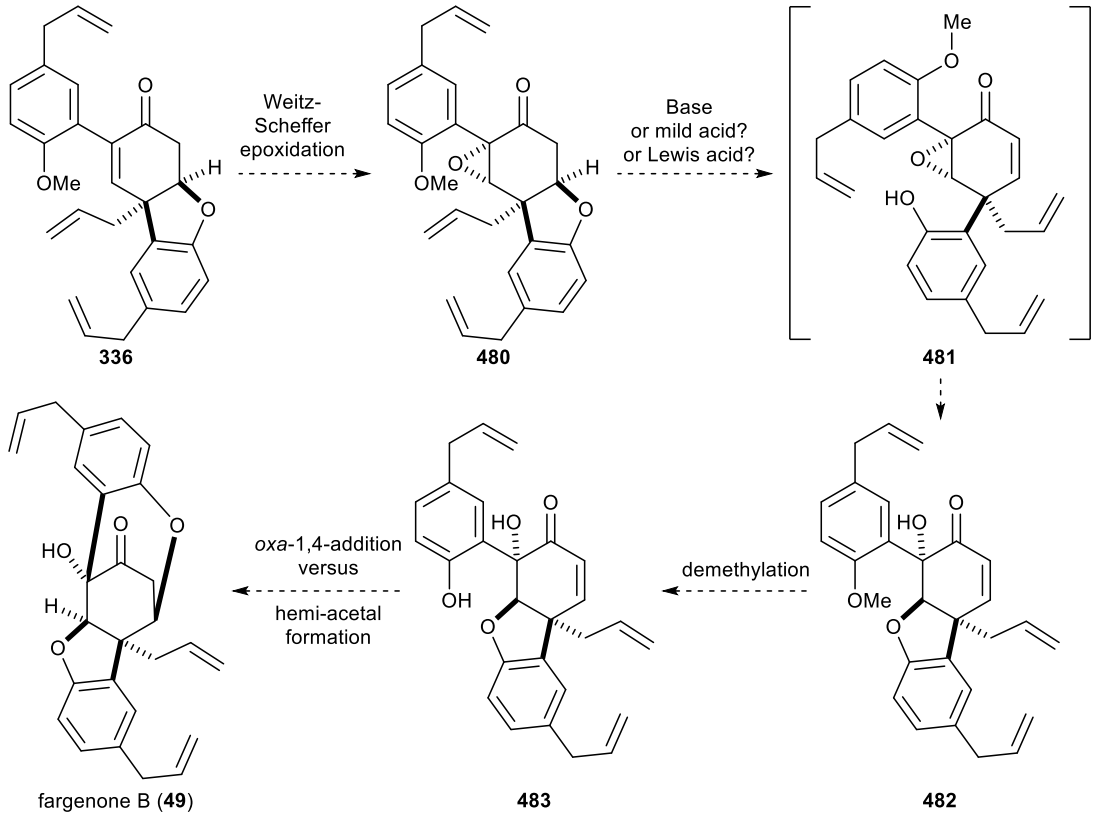
A large-scale synthesis of simonsol F (**56**) which avoids the previous problem associated with over-bromination and incomplete conversion of starting material should be developed (see Scheme 100). Previously made bromo-acetal **432** could undergo Suzuki-Miyaura cross-coupling with boronic acid/boroxine **476** if phenol alkylation can be prevented. Alternatively, Stille cross-coupling of **432** with organostannane **477** should provide biaryl **478** which could be mono-brominated to give **479**. Either a suitable base and solvent system should be found to directly provide spirocarbocycles **435** and **436** from phenol **479**, or the silyl enol ether can be formed followed by a desilylative-intramolecular-alkylation reaction to give **435** and **436** (see Scheme 100). Previously discussed conditions would provide simonsol F (**56**) (see Scheme 93).



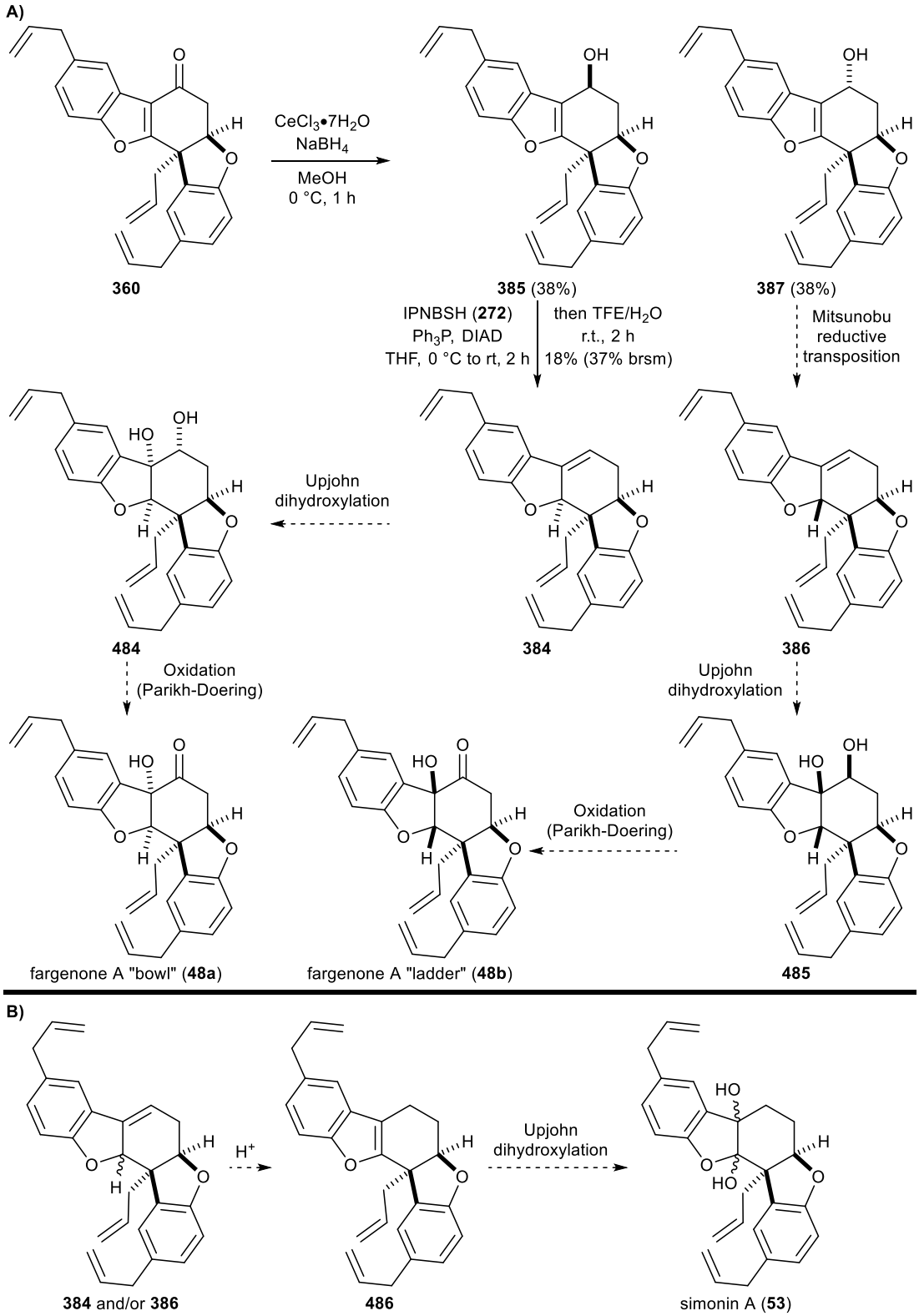
Scheme 100. *Proposed large-scale synthesis of simonsol F (**56**).*

From simonsol F (**56**), the synthesis of fargenone A "bowl" (**48a**) and "ladder" (**48b**) should be completed (see Scheme 102A). Intermediate **384** and/or **386** arising from the proposed synthesis of fargenone A (**48**) should also be used to generate and unambiguously assign the stereochemistry of simonin A (**53**) (see Scheme 102B).

Methylated simonsol F (**56**) could provide access to fargenone B (**49**) (see Scheme 101). Chemoselective Weitz-Scheffer epoxidation of **336** should provide **480** that could undergo base-, acid-, or Lewis-acid-mediated retro-*oxa*-1,4-addition followed by nucleophilic ring-opening of the epoxide to give **482**. Subsequent demethylation should provide phenol **483** and if *oxa*-1,4-addition is favoured over hemi-acetal formation of **483**, fargenone B (**49**) will be generated.



Scheme 101. *Proposed synthesis route to fargenone B (**49**).*

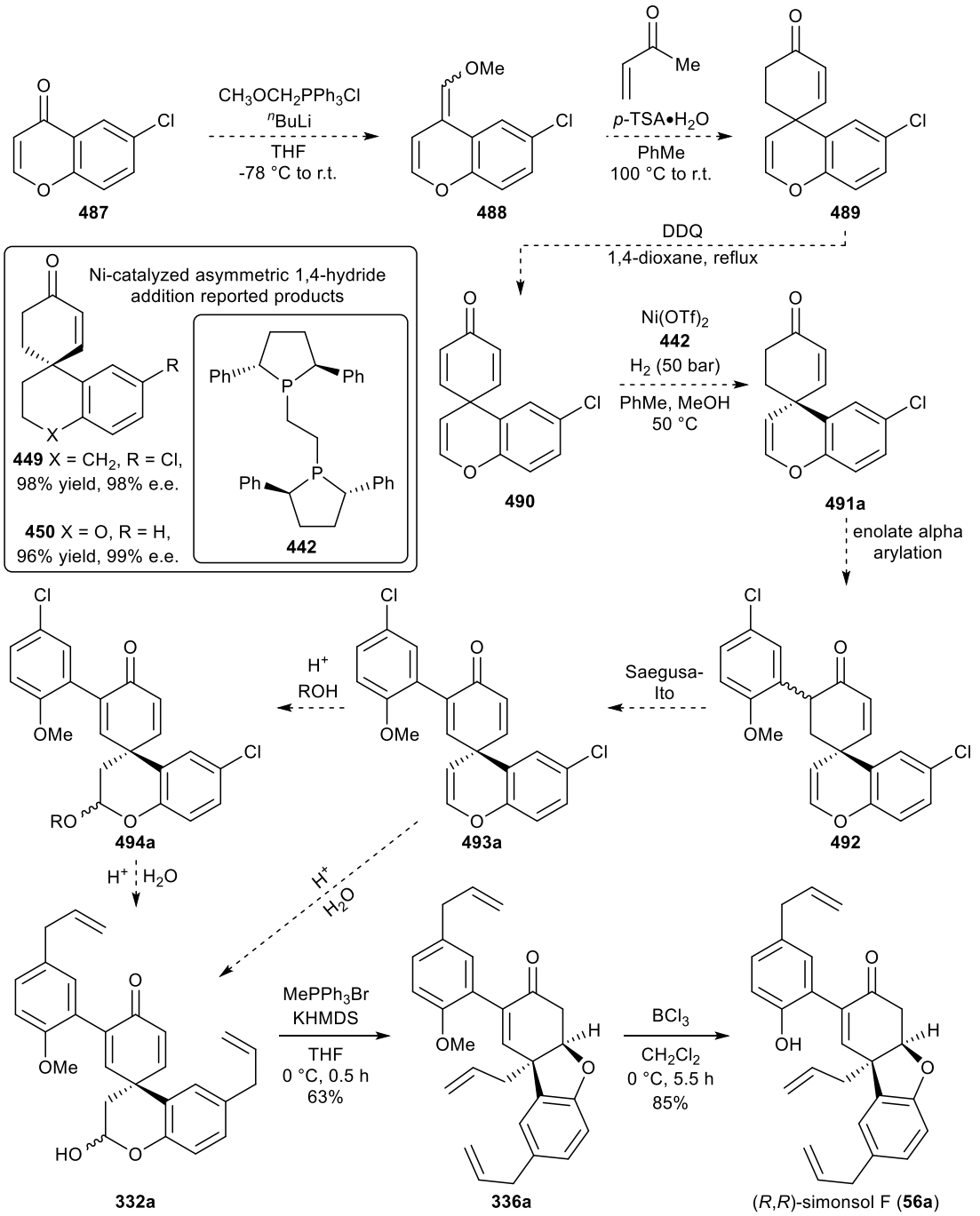


Scheme 102. A) *Incomplete and proposed synthesis route to fargenone A diastereoisomers* ***48a*** *and* ***48b****.* ***B)*** *Proposed synthesis route to generate both possible dihydroxylated diastereoisomers of simonin A (****53****), the stereochemistry of which is yet to be assigned.*

5.1.3: Future work towards the enantioselective synthesis of simonsol F

Work should be continued towards the enantioselective synthesis of simonsol F (**56**). It is proposed that commercially available 6-chlorochromane (**487**) can be transformed into racemic dienone **489** *via* the 3-step sequence shown (see Scheme 103) which was developed and used by Nishiyama and co-workers on similar substrates.[352] It is reasoned that the Ni-catalysed asymmetric 1,4-hydride addition to dienone **489** should provide enone **490** in high yield and with high e.e. when compared to similar substrates reported **449** and **450** (see Scheme 103 in box). Pd-catalysed α-arylation of the corresponding enolate of **491a** with 2-bromo-4-chloroanisole should provide **492** as a mixture of diastereoisomers. Subsequent Saegusa-Ito oxidation will remove the stereocentre at the α-position to the enone but will retain the quaternary stereocentre as the dienone is no longer symmetric which should provide **493a**. Either hemi-acetal **332a** can be accessed directly from acid-hydrolysis of enol ether **493a** or a two-step acid hydrolysis method could be used.[361,362] Subsequently, treatment of hemi-acetal **332a** under Wittig cascade reaction followed by demethylation reaction should provide (*R*,*R*)-simonsol F (**56a**) (see Scheme 103).

To generate (*S*,*S*)-simonsol F (**56b**) (not depicted), the opposite phosphine ligand enantiomer **441** should be used in the asymmetric 1,4-hydride addition of **490** and all other steps are as described in Scheme 103.



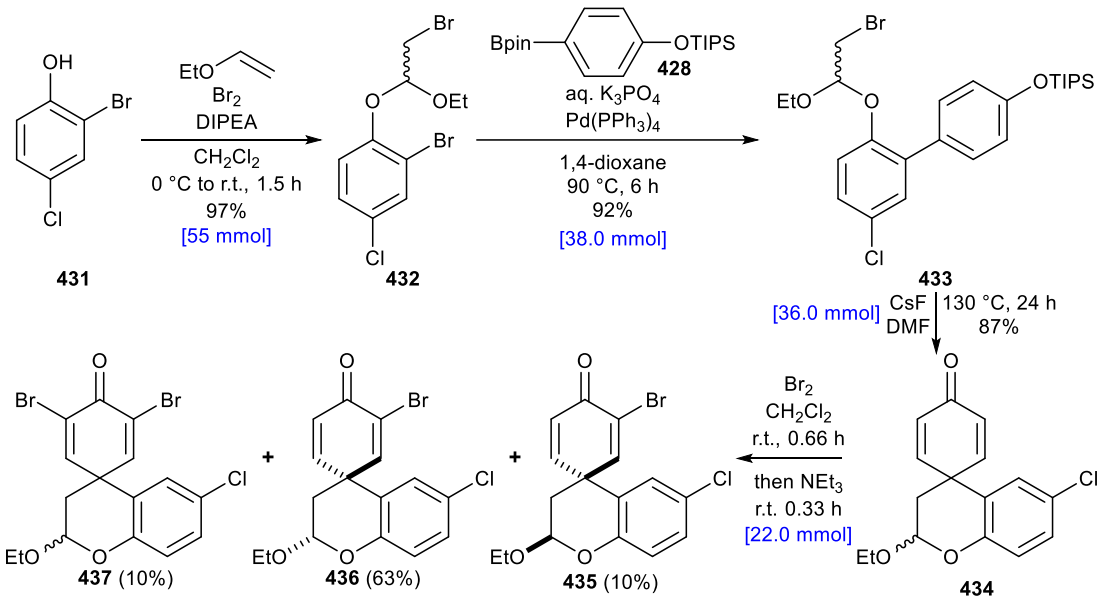
Scheme 103. *Proposed synthesis of (R,R)-simonsol F (**56a**).*

6: Appendix – Extra results

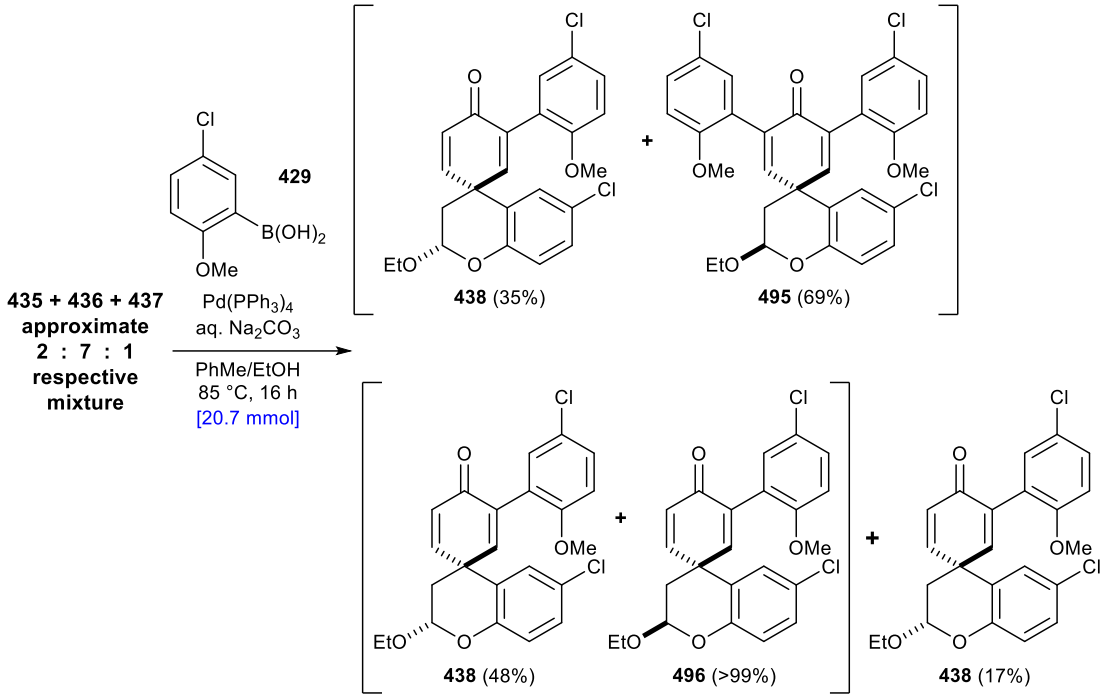
Beyond the submission of this thesis for examination, further studies were performed towards the synthesis of Fargenone A "bowl" (**48a**) and ladder (**48b**). This work was completed shortly after the Carbon Neutral Laboratories re-opened during the Covid-19 pandemic which meant that access to analytical equipment and time allowed in the lab per day was limited. Because of these limitations, an alternative synthesis of simonsol F (**56**) as outlined in Scheme 100 was not performed.

6.1: Synthesis of simonsol F

Following the synthesis outlined in Scheme 93, 2-bromo-4-chlorophenol was transformed over four steps into bromo-dienones **435**, **436**, and **437** (see Scheme 104). Efforts to avoid the formation of di-bromo **437** by cooling the reaction mixture to 0 °C and by slower addition of bromine were unsuccessful. The approximate 2:7:1 respective mixture of **435**, **436** and **437** was reacted under Suzuki-Miyaura cross-coupling conditions which afforded an "approximate 3:1 respective mixture of **438** and **495**", an "approximate 55:45 respective mixture of **438** and **496**" and clean **438** after conventional column chromatography (see Scheme 105).



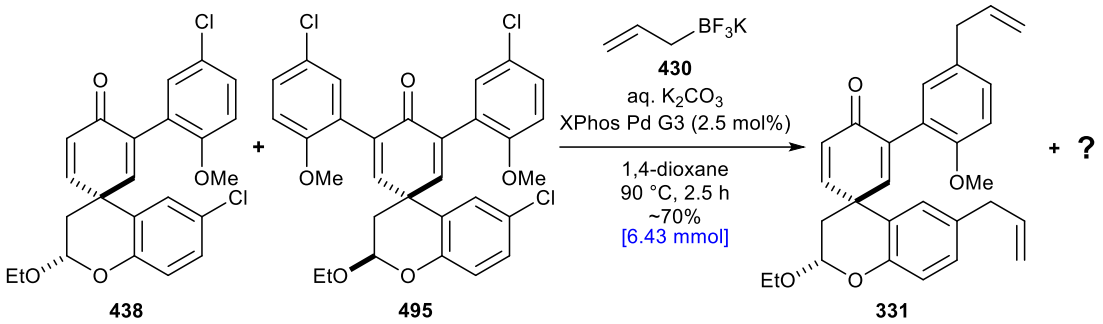
Scheme 104. *Synthesis of bromo-dienones* ***435****,* ***436*** *and* ***437*** *from phenol* ***431****.*



Scheme 105. *Suzuki-Miyaura cross-coupling of* ***435****,* ***436*** *and* ***437*** *with* ***429****. Yields have been calculated from the starting 2:7:1 mixture.*

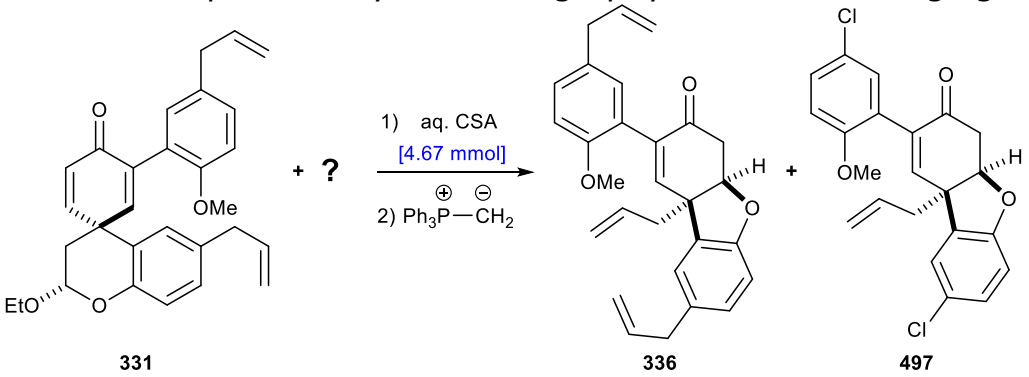
The mixture of "**438** and **495**" was reacted under Suzuki-Miyaura conditions to install the allyl group[363] which gave **331** as a mixture with an unconfirmed species (see Scheme 106). At the time, the

unconfirmed species was thought to be a derivative of **495** which was thought to be separable later in the synthesis.[364]



Scheme 106. *Pd-catalysed allylation of the mixture of **438** and **495**.*[363] *Yield is estimated based on isolated mass of products.*

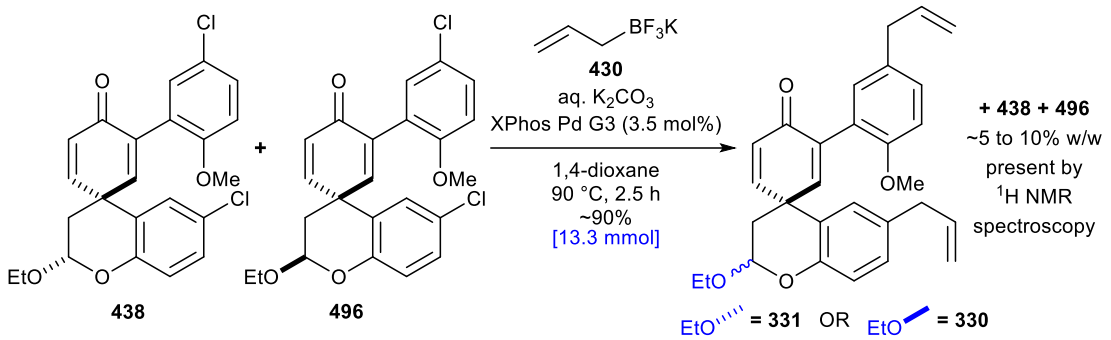
In the interest of time, the mixture of **331** and unknown species were reacted under acidic hydrolysis and then Wittig cascade conditions which gave **336** as a mixture with an impurity identified as **497** (see Scheme 107). Unfortunately, due to the sensitivity of the [4.3.0] ring system with respect to opening and Cope rearrangement (see Section 2.2.1), allylation of **336** was not investigated. Due to the greater quantity of **497** compared to **336** in the mixture, the material was discarded as separation by chromatography was too challenging.



Scheme 107. *Synthesis of methylated simonsol F **336** and impurity **497**.*

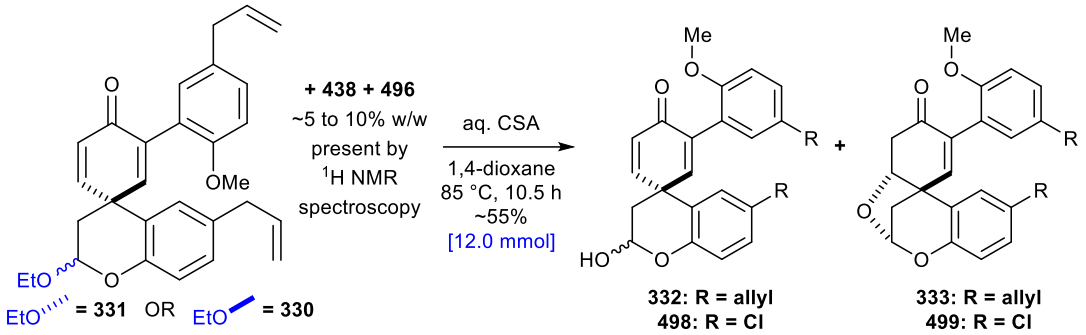
The mixture of "**438** and **496**" was reacted under palladium-catalysed allylation conditions. Due to slightly higher catalyst loading,

the allylation of "**438** and **496**" progressed further (compared to "**438** and **495**") but unfortunately did not reach completion before the reaction was worked-up (see Scheme 108). The product mixture of **330**, **331**, **438** and **496** could not undergo re-treatment as there was no more XPhos Pd G3 or other suitable catalyst to-hand.

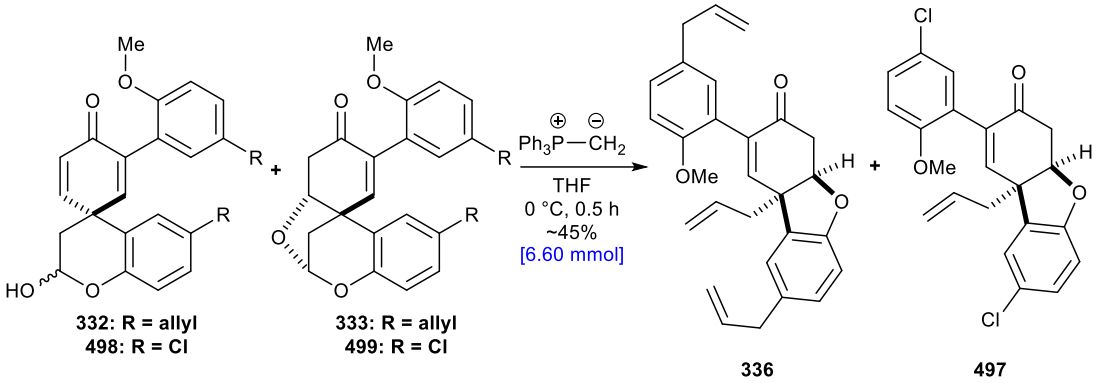


Scheme 108. *Pd-catalysed allylation of the mixture of **438** and **495**.*[363] *Yield is estimated based on isolated mass of products.*

The mixture of **330**, **331**, **438** and **496** were treated together under acidic hydrolysis conditions which gave dienone **332** and enone **333** (and dienone phenol rearranged species **335** not depicted) but unfortunately separation from the respective aryl chloride impurities **498** and **499** was not achieved at this stage (see Scheme 109). Therefore, all species were combined and were treated under Wittig cascade conditions which gave methylated simonsol F **336** and **497** (see Scheme 110). Optimised conditions were developed to separate **336** from **497** by normal-phase chromatography which were realised by using a mobile phase gradient of 10 to 25% Et_2O in pentane (respective R_f's of 0.35 and 0.32 in 40% Et_2O in pentane). This consistently provided clean fractions of **336** and mixed fractions of **336** with **497**.

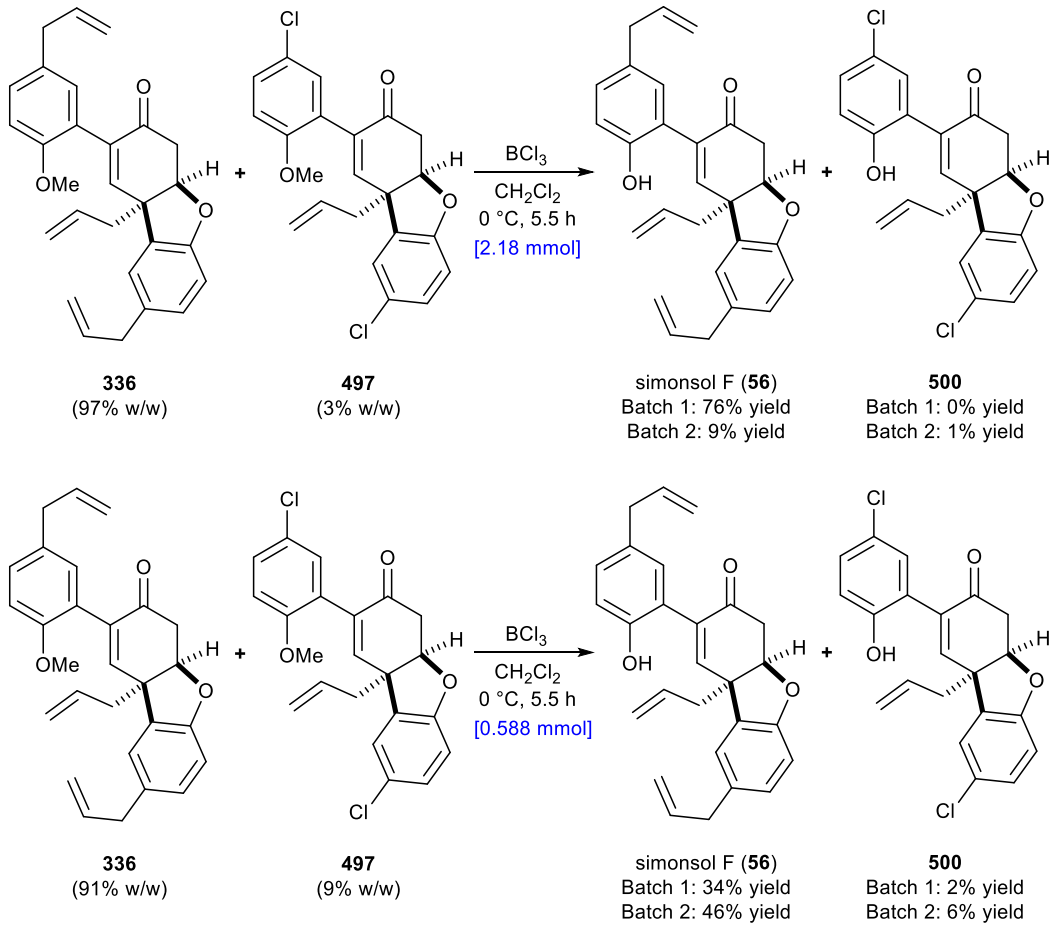


Scheme 109. *Products from the CSA-mediated acid hydrolysis of the mixture of* ***330***, ***331***, ***438*** *and* ***496****. Yield is estimated based on isolated mass of products.*



Scheme 110. *Products from the Wittig cascade reaction of the mixture of* ***332***, ***333***, ***498*** *and* ***499****. Yield is estimated based on isolated mass of products.*

Different batches of methylated simonsol F **336** were obtained with approximate 3% or 9% w/w (calculated by ^{1}H NMR spectroscopy) of aryl chloride **497** present. Subsequent treatment of these different w/w mixtures with BCl_3 gave a substantial amount of clean simonsol F (**56**) (if **497** was present at 3% w/w) or gave a mixture of simonsol F (**56**) with **500** (if **497** was present at 9% w/w) (see Scheme 111). Consequently, it is recommended to separate methylated simonsol F **336** from **497** before demethylation to obtain clean simonsol F (**56**).

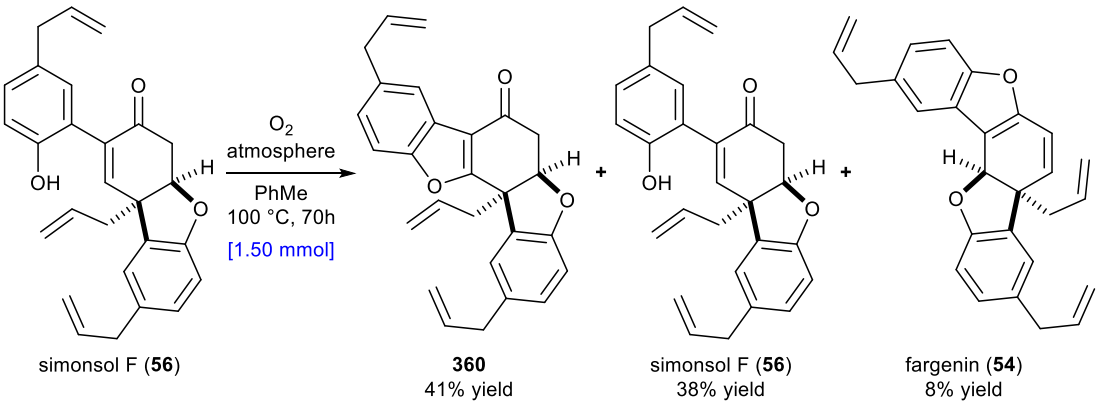


Scheme 111. *Outcome of the BCl_3-mediated demethylation of* ***336*** *to obtain simonsol F (****56****) with different amounts of aryl chloride* ***497*** *present. Different batches of simonsol F (****56****) and* ***500*** *were collected after column chromatography.*

6.2: Studies towards Fargenone A bowl and ladder

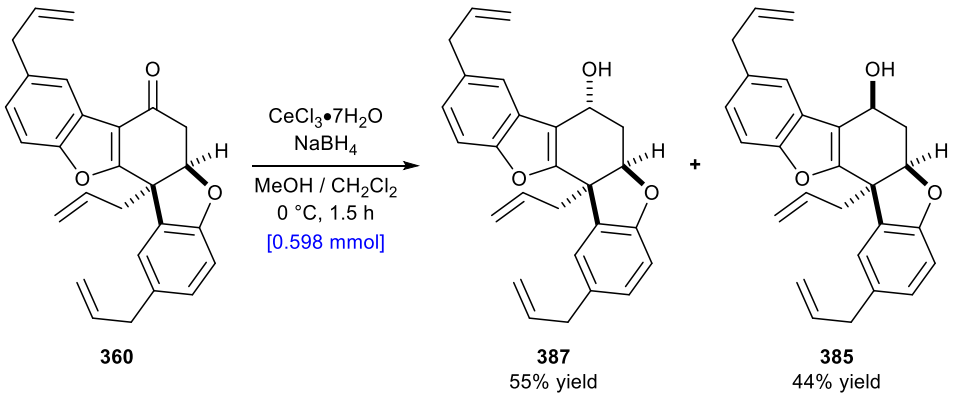
With simonsol F (**56**) in hand, studies towards the synthesis of fargenone A "bowl" (**48a**) and "ladder (**48b**) could continue. Following the synthesis shown in Scheme 102A, simonsol F (**56**) was heated under an atmosphere of oxygen in toluene that had been sparged with oxygen. It was observed under previous conditions (no sparging, reaction performed under air) that simonsol F (**56**)

converted to **360** at an approximate rate of 10% per 24 hours. Under these new oxygenated conditions, in 70 hours, benzofuran **360** was obtained in 41% yield with 38% recovered simonsol F (**56**) (see Scheme 112) which supports the involvement of oxygen in our proposed reaction mechanism (see Scheme 70).



Scheme 112. *Rearrangement of simonsol F (**56**) to **360** under oxygen enriched conditions. Macranthol (**39**) was also observed by TLC but was not isolated.*

Benzofuran **360** was reduced under Luche conditions which gave separable diastereoisomers **387** and **385** (see Scheme 113).



Scheme 113. *Luche reduction of **360** which gave alcohols **385** and **387**.*

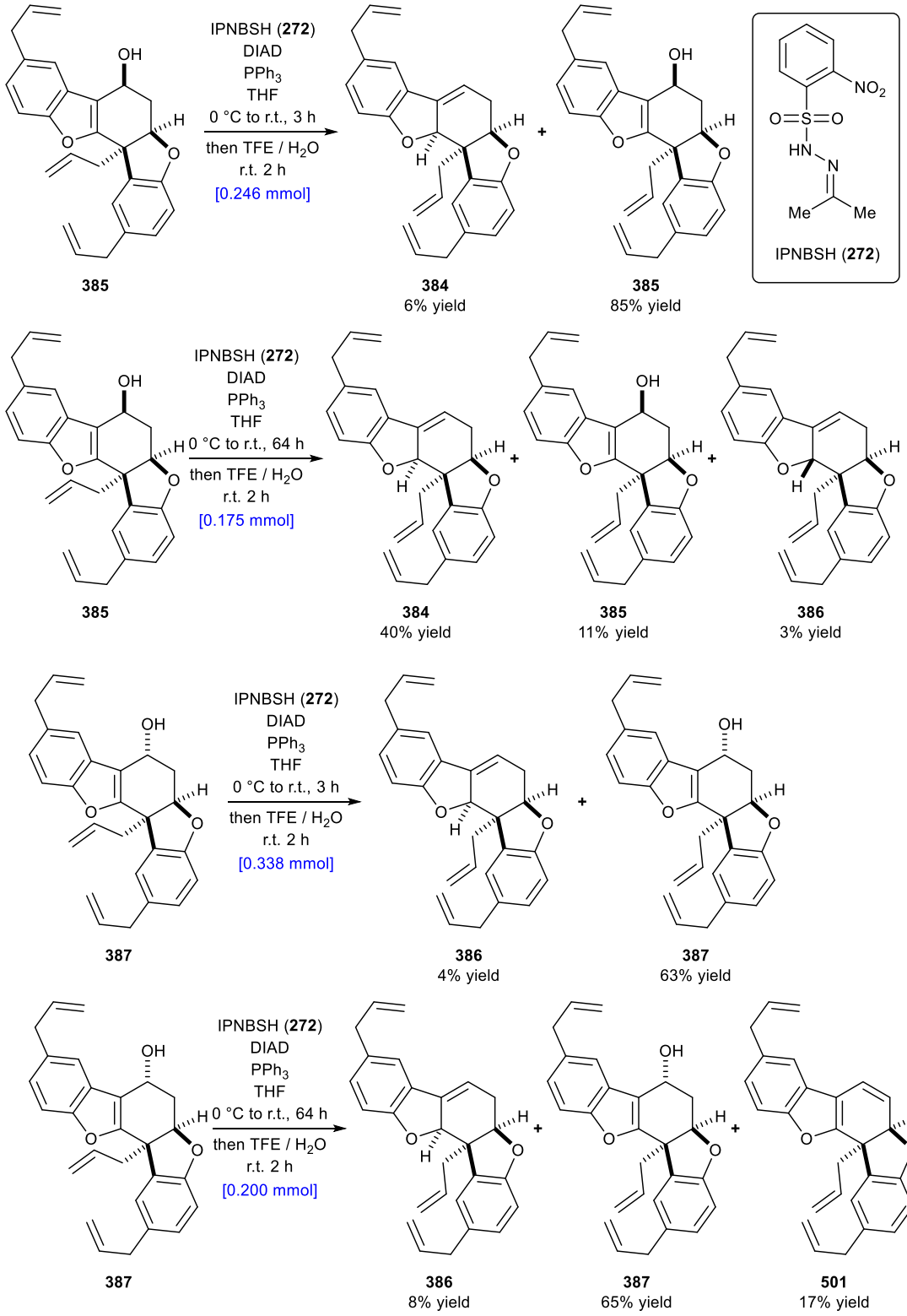
IPNBSH (**272**) was made fresh according to literature.[314,365] Allylic alcohols **385** and **387** were reacted with IPNBSH (**272**) under the Mitsunobu reductive transposition conditions developed by

Movassaghi and Ahmad,[314] which gave **384** and **386** respectively but in low yield with high recovery of starting material. The reaction was repeated allowing for an extended time for the Mitsunobu reaction to occur which gave greater conversion for **385** but a substantial amount of **387** was still recovered (see Scheme 114). This result is consistent with greater steric hinderance blocking the approach of the bulky nucleophile IPNBSH (**272**) with respect to allylic alcohol **387**. It was observed that **386** was formed in the reaction for **385** which indicates that a cation had likely formed by elimination of the phosphorus activated alcohol, perhaps influenced by the benzofuran lone pair in conjugation with the alkene.

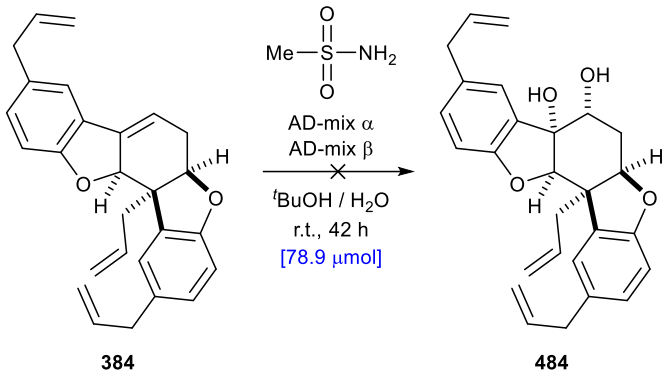
Nevertheless, **384** was obtained and was subjected to asymmetric Sharpless dihydroxylation conditions (see Scheme 115). No reaction was observed by TLC, even after substantial quantities of both AD-mix α and β were employed, as well as methyl-sulfonamide,[366,367] a catalyst used to help phase-transfer hydroxide ions for the osmate ester. Unfortunately, no starting material was recovered either.

A final attempt to synthesize fargenone A (**48**) was initiated from allylic alcohol **459** which was treated with *m*-CPBA. Analysis by TLC indicated that two new species had formed (see Scheme 116) which were not isolated due to time constraints. Instead, the reaction mixture underwent an aqueous work-up and then the organics were

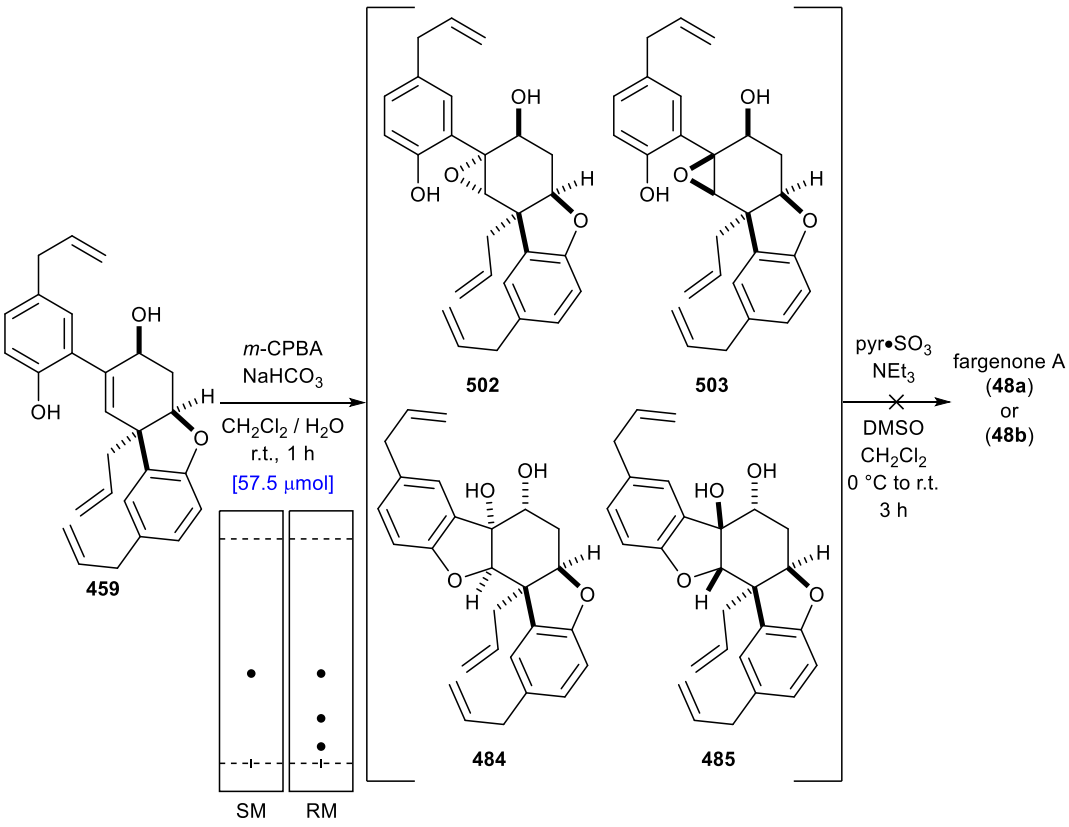
reacted under Parikh-Doering oxidation conditions but unfortunately the species isolated were not characterizable.



Scheme 114. *Outcome of the Mitsunobu reductive transposition chemistry applied to allylic alcohols* ***385*** *and* ***387****.*



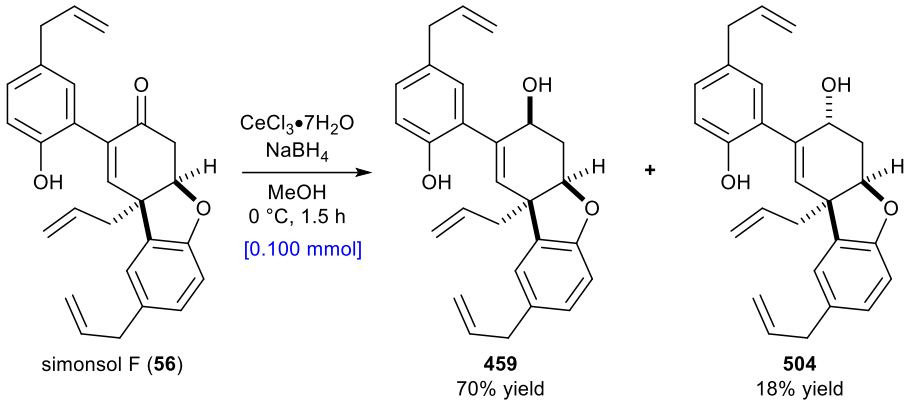
Scheme 115. *Studies towards the synthesis of fargenone A "bowl" (**48a**).*



Scheme 116. *Speculated products (**502**, **503**, **484** and **485**) from the Prilezhaev epoxidation of **459**. Subsequent Parikh-Doering oxidation conditions of the mixture did not provide fargenone A "bowl" (**48a**) or "ladder" (**48b**). Thin layer chromatography (to scale) is of the worked-up reaction mixture from Prilezhaev epoxidation run in 1 : 1 : 8 respective mixture of EtOAc : acetone : petroleum ether; SM = starting material, RM = reaction mixture.*

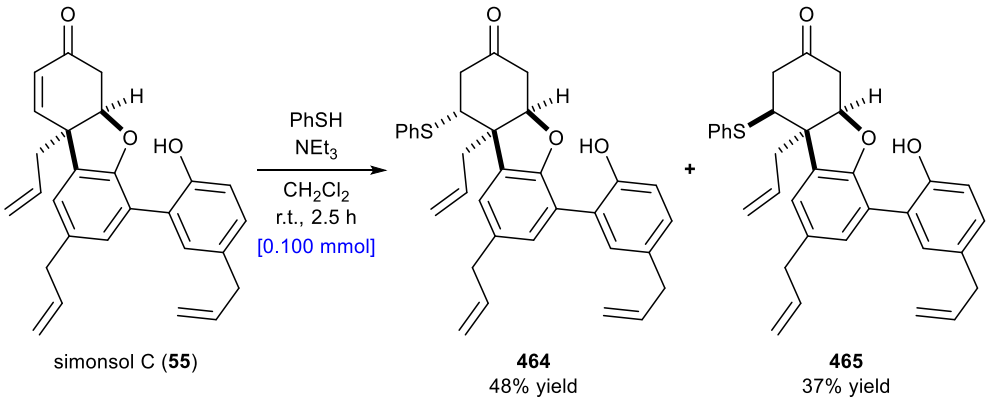
6.3: Repeated synthesis for better data

The Luche reduction of simonsol F (**56**) was repeated on a larger scale which provided both diastereoisomers **459** and **504** (see Scheme 117).



Scheme 117. *Luche reduction of simonsol F (**56**).*

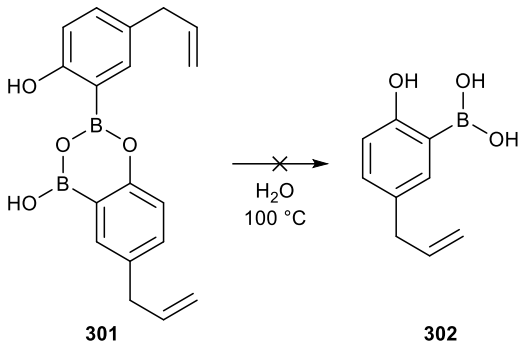
The 1,4-addition of thiophenol into simonsol C (**55**) was repeated on a batch of simonsol C (**55**) that had no trace of allyl alkene isomerisation by ^{1}H NMR spectroscopy. Previously, diastereoisomer **464** was isolated with simonsol C (**55**) but this time **464** was isolated clean (see Scheme 118).



Scheme 118. *Products from the 1,4-addition of thiophenol to simonsol C (**55**).*

Boronic acid monomer **302** and boronic acid dimer **301** were isolated as a 3:1 respective mixture, however only ^{1}H NMR spectroscopy data

was obtained for **302**. This material was re-analysed and was found to have become a 1:3 respective mixture of **302** and **301**. A successful method applied to crack boroxines into their respective monomeric boronic acids is to recrystalise the boroxine in water. This was tried on **301** but unfortunately **301** did not dissolve in boiling water and **302** was not obtained (see Scheme 119).



Scheme 119. *Attempted cracking of boronic acid dimer* ***301*** *to boronic acid monomer* ***302*** *by recrystallization in water.*

6.4: Future work

The synthesis of Fargenone A "bowl" (**48a**) and "ladder" (**48b**) is yet to be completed but it is with hope that these species can be selectively formed from the allylic alcohol diastereoisomers **459** and **504** which in turn are generated from the Luche reduction of simonsol F (**56**). With the knowledge that diastereoisomers **459** and **504** were distinguishable by NMR spectroscopy, subsequent Jacobson epoxidation of **459** and **504** could selectively provide the epoxides on the same face as the allylic alcohol. Alternatively, *m*-CPBA should be re-tried and the two new species with lower R_f's by TLC (see

Scheme 116) should be isolated. Ring closure from phenol **502** or **503** and a subsequent oxidation of the secondary alcohol should provide Fargenone A "bowl" (**48a**) and "ladder" (**48b**) dependant on allylic alcohol **459** or **504** used in this route.

Failing the above, the route depicted in Scheme 102A should be reconsidered but it does require further optimisation. With respect to the Mitsunobu reductive transposition step, perhaps using a less sterically hindered phosphine and nucleophile (NBSH (**271**) instead of IPNBSH (**272**)) would increase the yield and conversions of **385** to **384** and **387** to **386**. Suitable conditions to dihydroxylate the tri-substituted alkene of **384** and **386** will need to be investigated as well as the final oxidation conditions to afford fargenone A "bowl" (**48a**) and "ladder" (**48b**).

7: Supporting information and experimental procedures

Reagents and Solvents

All compounds were stored sealed in a freezer at -20 °C. Unless otherwise noted, all reactions were carried out under an atmosphere of argon in conventional glassware. Glassware used in the presence of moisture sensitive reagents or reactions that required anhydrous conditions was dried in the oven (125 °C) for >16 hours and/or was flame-dried under vacuum and cooled under a stream of argon. Cooling to 0 °C was effected using an ice-water bath. Cooling to -18 to -20 °C was effected using an ice-salt bath (3:1 w/w respectively). For cooling at -20 °C for extended periods (>5 hours), samples were put in a freezer set to -20 °C. Temperatures below -20 °C was effected using dry-ice-acetone mixtures. All water was deionised before use. The term petroleum ether refers to the fraction with boiling point between 40 and 60 °C. When noted, distilled pentane and distilled Et_2O were collected using non-dried glassware. As BHT was removed, the distilled Et_2O was used within 2 months before being re-distilled. Commercially available solvents and reagents were used as supplied with the following exceptions. Dry THF, dry CH_2Cl_2 and dry DMF were collected from a solvent tower, where a degassed solvent was passed through two columns of activated alumina and a

7 micron filter under a 4 bar pressure, and stored under an argon atmosphere over sodium wire (THF) or activated 4 Å molecular sieves (CH_2Cl_2 and DMF). Commercially available 4-allylanisole was purified by flash column chromatography (petroleum ether/EtOAc, 9:1). TMEDA was distilled over sodium wire and was stored under argon. All butyllithium solutions were titrated with *N*-benzylbenzamide when beyond a month of the previous recorded titration. Trimethyl borate was distilled over sodium wire and was stored under argon. 'Room temperature' can vary between 18 °C and 25 °C.

Analysis and Characterisation

Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica gel 60 F254 plates (product code: 105554.) Developed TLC plates were visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate.

Column chromatography was carried out according to Still's method,[368] using Fluorochem silica gel 60 Å, 40–63 mesh (product code = LC401).

Melting points were measured using a Stuart SMP3 (Sigma Aldrich product Z645729.)

Fourier Transform Infrared Spectrometry (FTIR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment; species were loaded as either solids or as thin-layer films and peaks are reported in terms of frequency of absorption (cm^{-1}).

High Resolution Mass Spectrometry (HRMS) were acquired using a Bruker microTOF II with Electron Spray Ionization (ESI-TOF). HRMS data were quoted to four decimal places (0.1 mDa). The spectrometer was programmed to find the masses of species using only the following isotopes: ^{11}B, ^{79}Br, ^{35}Cl and ^{120}Sn. Masses of the species with isotopes (that are >10% abundant) ^{10}B, ^{81}Br, ^{37}Cl, ^{116}Sn and ^{118}Sn were in all cases observed by HRMS but have not been reported.

Liquid chromatography-mass spectrometry (LC-MS) analyses were performed using an Agilent 1260 Infinity HPLC with a 6120 Quadrupole mass spectrometer. Chromatography conditions: Waters XBridge C18 3.5µm 2.1 x 30 mm column. Mobile phase A: 0.1% Ammonia in water, mobile phase B: acetonitrile. Flow rate 0.8 mL/min in a gradient of 5 – 95 % mobile phase B over 3.5 minutes at 40 °C with UV detection at 210 – 400 nm reported at 254nm.

Chiral HPLC analysis was performed on Agilent 1200 Infinity series instruments using 4.6 × 250 mm columns.

Preparative TLC was performed on Preparative TLC Plates, Analtech (VWR catalogue: 800086-350) (Supplier Miles Scientific Corp).

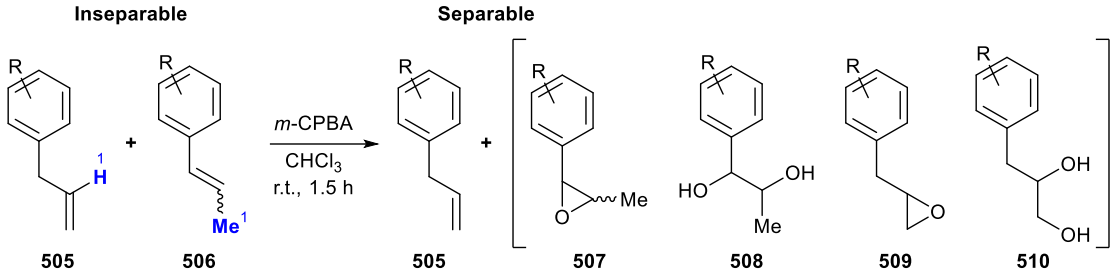
X–ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation.

All NMR spectra were recorded at 298 K on either a Bruker AV 400, Bruker AV 3400 or Bruker Ascent 500 and are internally referenced to residual solvent signals (CDCl3 is referenced at δ 7.26 and 77.16

for ^{1}H and ^{13}C NMR respectively, DMSO-d6 is referenced at δ 2.50 and 39.52 for ^{1}H and ^{13}C NMR respectively, C_6D_6 is referenced at δ 3.31 and 49.00 for ^{1}H and ^{13}C NMR respectively, acetone-d_6 is referenced at δ 2.05 and 29.84 for ^{1}H and ^{13}C NMR respectively, toluene-d_8 is referenced at δ 2.09 and 20.4 for ^{1}H and ^{13}C NMR respectively). ^{19}F NMR spectra and ^{11}B NMR spectra were referenced through the solvent lock (2H) signal according to IUPAC-recommended secondary referencing method according to Bruker protocols. All NMR chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons). The ^{13}C NMR coupling constants (*J*) are quoted to the nearest 0.1 Hz. ^{13}C NMR assignments were made using the DEPT sequence with secondary pulses at 90° and 135° and assignments were aided by 2D NMR spectroscopy techniques (COSY, HSQC, and HMBC (and by NOESY when required)). Numbering of atoms of compounds in the experimental is for the purpose of characterization and does not follow IUPAC numbering.

The following experimental methods have been ordered according to their appearance in the Results and Discussion (see Section 2). References to sections are given in headings to which the experimental methods are associated with from the results and discussion. Spectroscopic data is provided below the first described method of the compound with respect to the results and discussion.

General Method A: Separation of allyl group isomers by chemoselective derivatisation of di-substituted olefin



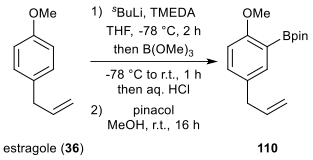
Prior to reaction, the ratio of **505** : **506** was calculated by ^{1}H NMR spectroscopy by comparison of proton integration for those highlighted and bolded in blue (H-1 on both structures).

To an inseparable[323] mixture of **505** and **506** ("a" mmol : "b" mmol respectively) was added $CHCl_3$ (25 mL per ("a" mmol + "b" mmol)) then *m*-CPBA (≤ 77% purity, 3 x "b" mmol) at room temperature. The reaction mixture was stirred open to air for 1.5 hours and then $Na_2S_2O_5$ (10 mL per ("a" mmol + "b" mmol) of a saturated aqueous solution) was added and the biphasic mixture was stirred for 2 minutes. Then $NaHCO_3$ (30 mL per ("a" mmol + "b" mmol) of a saturated aqueous solution) was added and the biphasic mixture was stirred for 5 minutes. The organics were diluted with Et_2O (300 mL per ("a" mmol + "b" mmol)) and were washed with $NaHCO_3$ (4 x 30 mL per ("a" mmol + "b" mmol) of a saturated aqueous solution), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography gave **505** with either undetectable levels of allyl group isomer **506** or up to 1% w/w of **506** detected by ^{1}H NMR spectroscopy. Compounds **507**–**510** were not isolated.

7.1: Total synthesis of simonsol C, simonsol F, simonsol G, simonsinol, macranthol and honokiol

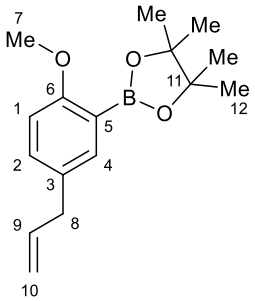
7.1.1: Synthesis of boron coupling partners 110, 301, 302 and 72

110: 2-(5-allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To dry THF (170 mL) under argon at −78 °C was added ^{s}BuLi (60.0 mL, 70.9 mmol of a 1.18 M solution in hexanes) and TMEDA (10.6 mL, 70.9 mmol). The yellow solution was stirred for 30 minutes and then a solution of 4-allylanisole (9.06 mL, 59.1 mmol) in dry THF (13.0 mL) was added over 15 minutes. After 4 hours at −78 °C, trimethyl borate (13.2 mL, 118 mmol) was added and the solution became colourless. The reaction mixture was allowed to warm to room temperature over 1 hour. To the reaction mixture was added HCl (250 mL of a 0.1 M aqueous solution) and the organics were extracted with Et_2O (3 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave a colourless crude oil which was dissolved in MeOH (183 mL) and pinacol (20.9 g, 177 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours and was then concentrated *in vacuo*. The organics were dissolved in Et_2O (100 mL) and were washed with H_2O (3 x 50 mL),

then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 37:3) afforded boronic acid pinacol ester **110** as a colourless oil (8.97 g, 55%).



110

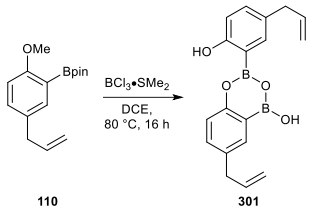
110: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 2.4 Hz, 1H, H-4), 7.21 (dd, *J* = 8.4, 2.4 Hz, 1H, H-2), 6.80 (d, *J* = 8.4 Hz, 1H, H-1), 5.95 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-9), 5.09 – 5.00 (m, 2H, H-10), 3.81 (s, 3H, H-7), 3.33 (d, *J* = 6.7 Hz, 2H, H-8), 1.35 (s, 12H, H-12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 162.9 (Cq), 138.1 (CH), 136.8 (CH), 132.6 (CH), 131.6 (Cq), 115.5 (Cq), 110.8 (Cq), 83.6 (2x Cq), 56.1 (CH_3), 39.4 (CH_2), 25.0 (4x CH_3); **^{11}B NMR** (128 MHz, $CDCl_3$) δ: 31.0; **HRMS** (ESI^+): $C_{16}H_{23}{}^{11}BO_3$ $[M+H]^+$ calcd. 275.1813, found 275.1813; **IR** ν_{max} cm^{-1}: 3076, 2977, 2933, 2904, 2833, 1639, 1605, 1582, 1493, 1346, 1143, 1030.

Spectroscopic data obtained for **110** were consistent with those previously reported.[141]

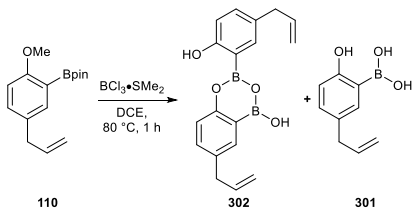
^{13}C NMR: C-5 signal was not observed due to quadrupolar relaxation.

301: 6-allyl-2-(5-allyl-2-hydroxyphenyl)-4H-benzo[e][1,3,2,4]dioxadiborinin-4-ol

302: (5-allyl-2-hydroxyphenyl)boronic acid



To a solution of boronic acid pinacol ester **110** (8.37 g, 30.5 mmol) in DCE (122 mL) was added $BCl_3•SMe_2$ (13.7 g, 76.3 mmol). The reaction mixture was heated at 80 °C for 16 hours. The reaction mixture was cooled to 0 °C and to the reaction mixture was added HCl (100 mL of a 1.0 M aqueous solution). The organics were extracted with EtOAc (3 x 70 mL) and the combined organics were washed with brine (70 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave a crude grey solid. Subsequent trituration with pentane gave boronic acid **301** as an off-white solid (4.14 g, 85%) **m.p.** 149–152 °C.

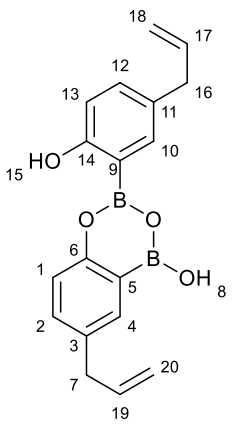


To a solution of boronic acid pinacol ester **110** (5.04 g, 18.4 mmol) in DCE (92.0 mL) was added $BCl_3•SMe_2$ (9.88 g, 55.2 mmol). The reaction mixture was heated at 80 °C for 1.2 hours. The reaction mixture was cooled to 0 °C and to the reaction mixture was added H_2O (70 mL). The organics were extracted with EtOAc (4 x 80 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave a crude grey solid. The solid was triturated with pentane and the solid was collected and dried under

suction filtration which gave a 3:1 respective mixture (calculated by ^{1}H NMR spectroscopy) of boronic acid dimer **301** and boronic acid monomer **302** (2.52 g, 84%).

From a different experiment using the same procedure described (heated for 1.2 hours at 80 °C), a solid was analysed and was found to be a 3:1 respective mixture of boronic acid monomer **302** and boronic acid dimer **301** of which ^{1}H NMR spectroscopy data for **302** was obtained.

A crystal of boronic acid dimer **301** was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).

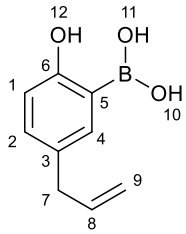


301

301: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (s, 1H, ArOH), 7.71 (d, *J* = 2.4 Hz, 1H, H-4 or H-10), 7.63 (d, *J* = 2.3 Hz, 1H, H-4 or H-10), 7.42 (dd, *J* = 8.4, 2.3 Hz, 1H, H-2 or H-12), 7.27 (dd, *J* = 8.4, 2.4 Hz, 1H, H-2 or H-12), 7.19 (d, *J* = 8.4 Hz, 1H, H-1 or H-13), 6.89 (d, *J* = 8.4 Hz, 1H, H-1 or H-13), 6.05 – 5.91 (m, 2H, H-17 and H-19), 5.21 (s, 1H, B-OH), 5.16 – 5.02 (m, 4H, H-18 and H-20), 3.43 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, H-7 or H-16), 3.37 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, H-7 or H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 162.8 (Cq), 158.4 (Cq), 138.1 (CH), 137.3 (CH), 136.0 (CH), 135.6 (Cq), 135.2 (CH), 135.1 (CH), 133.3 (CH), 131.2 (Cq), 117.9 (CH), 116.3 (CH_2), 116.3 (CH), 115.7 (CH_2), 39.6 (CH_2), 39.5 (CH_2); **^{11}B NMR** (128 MHz, $CDCl_3$) δ: 28.7; **HRMS**

(ESI$^-$): $C_{18}H_{18}{}^{11}B_2O_4$ $[M-H]^-$ calcd. 319.1318, found 319.1336; **IR** ν_{max} cm^{-1}: 3351, 3215, 3080, 3030, 3002, 2977, 2904, 1638, 1333, 1223.

^{13}C NMR: C-5 and C-9 signals were not observed due to quadrupolar relaxation.

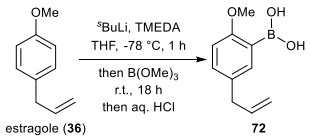


302

302: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 2.4 Hz, 1H, H-4), 7.33 (dd, *J* = 8.3, 2.4 Hz, 1H, H-2), 7.00 (d, *J* = 8.3 Hz, 1H, H-1), 6.01 – 5.92 (m, 1H, H-8), 5.12 – 5.03 (m, 2H, H-9), 4.69 (s, 1H, OH-10 or OH-11 or OH-12), 4.04 (s, 1H, OH-10 or OH-11 or OH-12), 3.38 (ddd, *J* = 7.3, 1.4, 1.4 Hz, 2H, H-7), 1.34 – 1.27 (m, 1H, OH-10 or OH-11 or OH-12).

The sample that was a 3:1 respective mixture of **302** and **301** had dehydrated over time to a 1:3 respective mixture of **302** and **301**. Therefore, further spectroscopic could not be obtained for **302** in time for the purpose of this thesis.

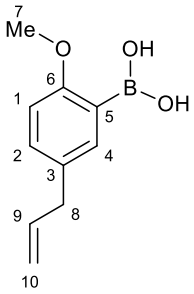
72: (5-allyl-2-methoxyphenyl)boronic acid



estragole (**36**) **72**

To a solution of 4-allylanisole (2.29 g, 14.7 mmol) in dry THF (46.0 mL) under argon at –78 °C was added TMEDA (2.20 mL, 14.7 mmol) followed by ^{s}BuLi (20.4 mL, 14.7 mmol of a 1.08 M solution in hexanes) that was added dropwise over 15 minutes. After addition was complete, the mixture

was stirred for 1 hour at -78 °C. The reaction mixture was allowed to warm to room temperature and then trimethyl borate (1.64 mL, 14.7 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. To the reaction mixture was acidified to pH 3 with HCl (1.0 M aqueous solution) and then the resulting solution was stirred for 1 hour. The organics were diluted with EtOAc (60 mL) and were washed with brine (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 3:1) gave boronic acid **72** as an off-white solid. Subsequent trituration with pentane provided boronic acid **72** as a colourless solid (1.15 g, 40%) **m.p.** 73–75 °C (lit. 77–79 °C).[87]



72

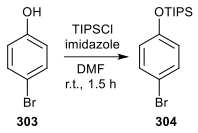
72: ^{1}H NMR (500 MHz, C_6D_6) δ: 8.06 (d, *J* = 2.4 Hz, 1H, H-4), 7.05 (dd, *J* = 8.4, 2.4 Hz, 1H, H-2), 6.37 (d, *J* = 8.4 Hz, 1H, H-1), 6.28 (s, 2H, 2x B-OH), 5.96 – 5.76 (m, 1H, H-9), 4.99 – 4.94 (m, 2H, H-10), 3.17 (ddd, *J* = 6.6, 1.6, 1.6 Hz, 2H, H-8), 2.99 (s, 3H, H-7); **^{13}C NMR** (126 MHz, C_6D_6) δ: 163.6 (Cq), 138.2 (CH), 137.9 (CH), 132.9 (CH), 132.8 (Cq), 115.5 (CH_2), 110.2 (CH), 54.9 (CH_3), 39.6 (CH_2); **^{11}B NMR** (128 MHz, $CDCl_3$) δ: 29.2; **HRMS** (ESI^+): $C_{10}H_{13}{}^{11}BO_3$ $[M+H]^+$ calcd. 193.1031, found 193.1031; **IR** ν_{max} cm^{-1}: 3373, 1606, 1492, 1420, 1339, 1234, 1047.

^{13}C NMR: C-5 signal was not observed due to quadrupolar relaxation.

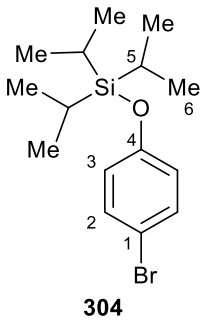
Spectroscopic data obtained for **72** were consistent with those previously reported when analysed in $CDCl_3$.[87]

7.1.2: Synthesis of simonsol C (Section 2.1.3)

304: (4-bromophenoxy)triisopropylsilane



To a solution of 4-bromophenol (**303**) (1.73 g, 10.0 mmol) and imidazole (13.7 g, 20.1 mmol) in DMF (2.50 mL) at room temperature was added triisopropylsilyl chloride (2.25 mL, 10.5 mmol). The reaction mixture was stirred at room temperature for 1.5 hours and then brine (40 mL) was added. The organics were extracted with Et_2O (2 x 30 mL) and then the combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 39:1) afforded silyl phenol ether **304** as a colourless oil (3.20 g, 97%).



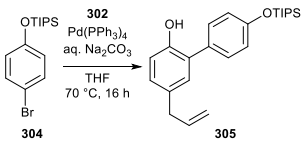
304

304: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 – 7.28 (m, 2H, H-2), 6.78 – 6.73 (m, 2H, H-3), 1.29 – 1.19 (m, 3H, H-5), 1.09 (d, *J* = 7.3 Hz, 18H, H-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.4 (Cq), 132.4 (2x CH), 121.8 (2x CH), 113.3 (Cq), 18.0 (6x CH_3), 12.8 (3x CH); **IR** ν_{max} cm^{-1}: 2946, 2893, 2868, 1586, 1487, 1273, 910, 883, 828, 732, 685.

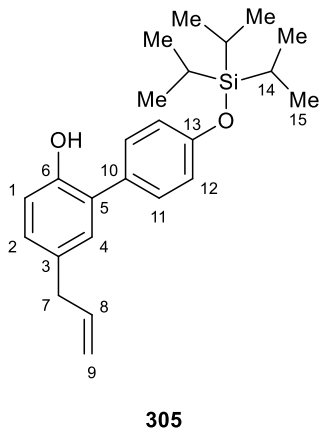
HRMS: Compound did not provide targeted mass upon ionisation.

Spectroscopic data obtained for **304** were consistent with those previously reported.[369]

305: 5-allyl-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-ol



To a solution of boronic acid **302** (316 mg, 0.988 mmol) and silyl phenol ether **304** (487 mg, 1.47 mmol) in THF (15.0 mL) was added $Pd(PPh_3)_4$ (85 mg, 0.074 mmol) and Na_2CO_3 (2.2 mL of a 2.0 M aqueous solution, 4.4 mmol). The reaction mixture was sparged for 5 minutes with argon and was then heated in an oil bath set at 70 °C for 16 h after which it was cooled to room temperature and diluted with EtOAc (20 mL). The organics were washed with HCl (3 x 20 mL of a 1.0 M aqueous solution) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 4:1) gave biaryl **305** as a colourless oil that solidified upon standing to a colourless solid (527 mg, 93%) **m.p.** 48–50 °C.

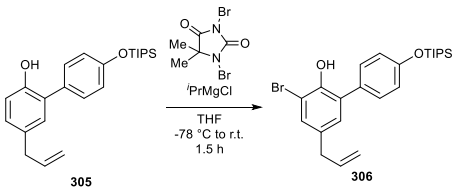


305

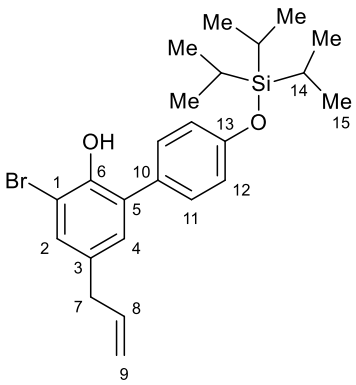
305: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 – 7.28 (m, 2H, H-11), 7.06 – 7.02 (m, 2H, H-2 and H-4), 7.00 – 6.96 (m, 2H, H-12), 6.90 (d, *J* = 8.1 Hz, 1H, H-1), 5.98 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-8), 5.12 – 5.03 (m, 3H, H-9 and ArOH), 3.35 (ddd, *J* = 6.6, 1.4, 1.4 Hz, 2H, H-7), 1.34 – 1.24 (m, 3H, H-14), 1.13 (d, *J* = 7.3 Hz, 18H, H-15); **^{13}C NMR**

(101 MHz, $CDCl_3$) δ: 156.1 (Cq), 150.9 (Cq), 138.0 (CH), 132.3 (Cq), 130.34 (CH), 130.27 (2x CH), 129.6 (Cq), 128.9 (CH), 127.9 (Cq), 120.8 (2x CH), 115.71 (CH), 115.68 (CH_2), 39.6 (CH_2), 18.1 (6x CH_3), 12.9 (3x CH); **HRMS** (ESI^+): $C_{24}H_{34}O_2Si$ $[M+Na]^+$ calcd. 405.2220, found 405.2215; **IR** ν_{max} cm^{-1}: 3552, 3041, 2947, 2868, 1605, 1512, 1490, 1275, 1186, 997, 915.

306: 5-allyl-3-bromo-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-ol



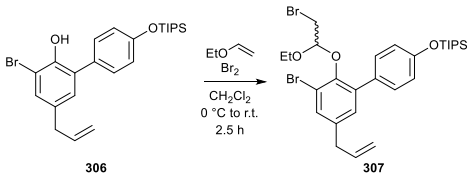
To a solution of biaryl **305** (475 mg, 1.24 mmol) in THF (6.1 mL) at -78 °C was added ^{i}PrMgCl (1.00 mL of a 1.5 M solution in Et_2O, 1.50 mmol) and the reaction mixture was stirred at -78 °C for 30 min after which 1,3-dibromo-5,5-dimethylhydantoin (284 mg, 0.992 mmol) was added and the reaction mixture was allowed to warm to room temperature and was then stirred for 1.5 hours. To the reaction mixture NH_4Cl (8 mL of a 1.0 M aqueous solution) was added and the organics were extracted with EtOAc (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2/acetone, 94:5:1) afforded biaryl **306** as a pale-yellow oil (491 mg, 86%).



306

306: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 – 7.34 (m, 2H, H-11), 7.26 (d, *J* = 2.1 Hz, 1H, H-2) 7.04 (d, *J* = 2.1 Hz, 1H, H-4), 6.98 – 6.92 (m, 2H, H-12), 5.94 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H-8), 5.55 (s, 1H, ArOH), 5.14 – 5.06 (m, 2H, H-9), 3.33 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, H-7), 1.35 – 1.24 (m, 3H, H-14), 1.13 (d, *J* = 7.3 Hz, 18H, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 156.0 (Cq), 147.6 (Cq), 137.2 (CH), 133.5 (Cq), 131.0 (CH), 130.33 (CH), 130.29 (CH), 129.8 (Cq), 129.3 (Cq), 120.1 (CH), 116.4 (CH_2), 110.8 (Cq), 39.2 (CH_2), 18.1 (6x CH_3), 12.9 (3x CH); **HRMS** (ESI^+) $C_{24}H_{33}{}^{79}BrO_2Si$ $[M+H]^+$ calcd. 461.1506, found 461.1502; **IR** ν_{max} cm^{-1}: 3513, 3052, 3040, 3011, 2947, 2868, 1605, 1511, 1468, 1270, 1229, 938.

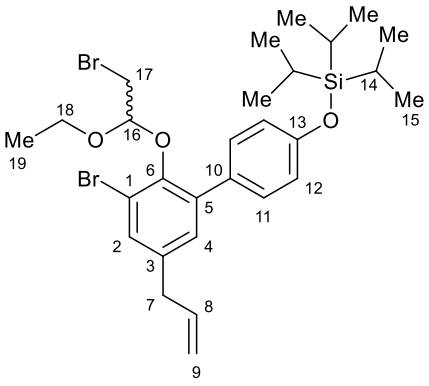
307: ((5'-allyl-3'-bromo-2'-(2-bromo-1-ethoxyethoxy)-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane



306 307

To a solution of ethyl vinyl ether (0.21 mL, 2.2 mmol) in CH_2Cl_2 (2.2 mL) at 0 °C was added bromine (87 µL, 1.7 mmol) over 1 minute and the reaction mixture was stirred at 0 °C for 15 min after which a solution of biaryl **306** (391 mg, 0.850 mmol) and DIPEA (0.59 mL, 3.4 mmol) in CH_2Cl_2 (2.2 mL) was added. The reaction mixture was warmed to room temperature, stirred for 2.5

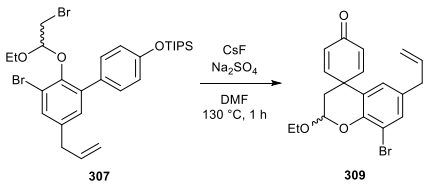
hours, then diluted with EtOAc (15 mL). The organics were washed with $NaHCO_3$ (2 x 5 mL of saturated aqueous solution), then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/CH_2Cl_2, 9:1 to 3:1) afforded acetal **307** as a colourless oil (502 mg, 96%).



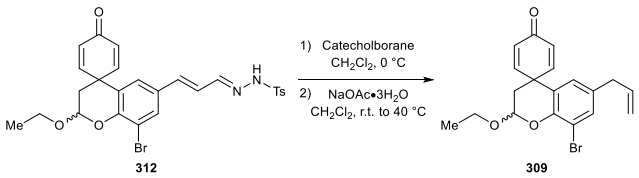
307

307: ^{1}H NMR (400 MHz, C_6D_6) δ: 7.35 – 7.31 (m, 2H, H-12), 7.29 (d, *J* = 2.1 Hz, 1H, H-2), 6.96 (d, *J* = 2.1 Hz, 1H, H-4), 6.94 – 6.90 (m, 2H, H-11), 5.71 (dddd, *J* = 16.9, 10.3, 6.8, 6.8 Hz, 1H, H-8), 5.16 – 5.12 (m, 1H, H-16), 4.97 – 4.89 (m, 2H, H-9), 3.55 – 3.45 (m, 1H, H-18), 3.37 – 3.20 (m, 3H, H-17 and H-18), 3.00 (d, *J* = 6.7 Hz, 2H, H-7), 1.23 – 1.13 (m, 3H, H-14), 1.11 (d, *J* = 6.4 Hz, 18H, H-15), 0.90 (dd, *J* = 7.0, 7.0 Hz, 2H, H-19); **^{13}C NMR** (101 MHz, C_6D_6) δ: 156.3 (Cq), 149.0 (Cq), 138.1 (Cq), 137.7 (Cq), 136.7 (CH), 132.6 (CH), 131.4 (Cq), 131.1 (CH), 130.9 (CH), 120.2(CH), 119.2 (Cq), 116.6 (CH_2), 104.6 (CH), 66.1 (CH_2), 39.3 (CH_2), 32.4 (CH_2), 18.2 (CH_3), 15.2 (CH_3), 13.1 (CH); **HRMS** (ESI$^+$) $C_{28}H_{40}{}^{79}Br_2O_3Si$ $[M+Na]^+$ calcd. 633.1006, found 633.1021; **IR** ν_{max} cm^{-1}: 3039, 3013, 2948, 2868, 1606, 1510, 1454, 1268, 1173, 918.

309: 6-allyl-8-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



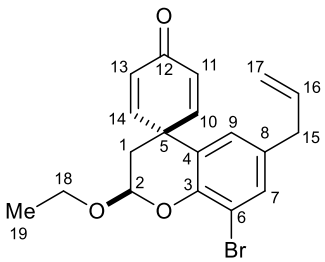
To a solution of acetal **307** (495 mg, 0.808 mmol) in DMF (81.0 mL) was added Na_2SO_4 (3.44 g, 24.2 mmol) and CsF (368 mg, 2.42 mmol). The reaction mixture was heated at 130 °C for 1 hour after which, the reaction mixture was cooled to room temperature and then the organics were concentrated *in vacuo*. The organics were dissolved in Et_2O (60 mL) and were washed with water (30 mL), then brine (2 x 15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/Et_2O, 9:1 to 3:2) afforded spirocycle **309** as a colourless solid (284 mg, 94%) **m.p.** 128–130 °C.



To a suspension of hydrazide **312** (1.05 g, 1.88 mmol) in CH_2Cl_2 (18.8 mL) at 0 °C was added catecholborane (0.60 mL, 5.64 mmol). The reaction mixture was stirred for 2 hours at 0 °C and then sodium acetate trihydrate (1.54 g, 11.3 mmol) was added and the reaction mixture was heated at 40 °C for 13 hours. The reaction mixture was cooled to room temperature and was diluted with CH_2Cl_2 (50 mL). The organics were washed with NaOH (30 mL of a 1M aqueous

solution), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 7:3) provided spirocycle **309** as a colourless solid (503 mg, 71%) **m.p.** 128–130 °C.

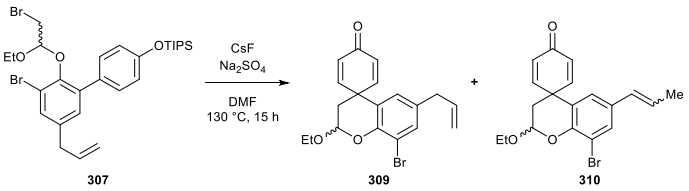
A crystal of spirocycle **309** was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).



309

309: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (dd, *J* = 10.2, 3.0 Hz, 1H, H-10), 7.29 (d, *J* = 2.1 Hz, 1H, H-7), 6.75 (dd, *J* = 10.0, 3.0 Hz, 1H, H-14), 6.65 (d, *J* = 2.1 Hz, 1H, H-9), 6.36 (dd, *J* = 10.0, 1.9 Hz, 1H, H-13), 6.22 (dd, *J* = 10.2, 1.9 Hz, 1H, H-11), 5.84 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H, H-16), 5.49 (dd, *J* = 3.0, 3.0 Hz, 1H, H-2), 5.08 – 5.00 (m, 2H, H-17), 3.94 (dq, *J* = 9.7, 7.1 Hz, 1H, H-18), 3.68 (dq, *J* = 9.7, 7.1 Hz, 1H, H-18), 3.22 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-15), 2.31 (dd, *J* = 14.2, 3.0 Hz, 1H, H-1), 2.14 (dd, *J* = 14.2, 3.0 Hz, 1H, H-1), 1.23 (dd, *J* = 7.1, 7.1 Hz, 3H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 185.9 (Cq), 154.3 (CH), 153.7 (CH), 146.1 (Cq), 136.6 (CH), 134.6 (Cq), 133.2 (CH), 128.7 (CH), 128.1 (CH), 126.4 (CH), 121.4 (Cq), 116.7 (CH_2), 112.7 (Cq), 96.3 (CH), 64.8 (CH_2), 40.9 (Cq), 39.0 (CH_2), 36.4 (CH_2), 15.2 (CH_3). **HRMS** (ESI$^+$) $C_{19}H_{19}{}^{79}BrO_3$ $[M+H]^+$ calcd. 375.0590, found 375.0582; **IR** ν_{max} cm^{-1}: 3038, 3026, 3011, 1666, 1467, 1208, 1126, 861.

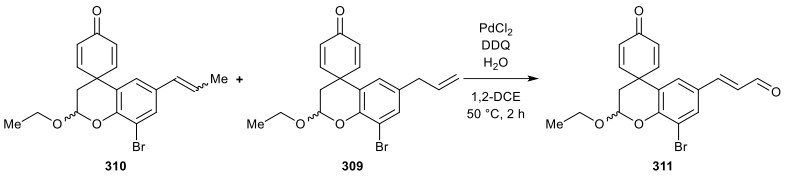
309 and 310 mixture: 6-allyl-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one **and** 2-ethoxy-6-(prop-1-en-1-yl)spiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



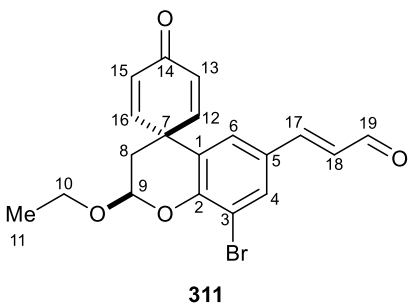
307 309 310

To a flame-dried flask was added CsF (4.19 g, 27.6 mmol) and Na_2SO_4 (49.0 g, 345 mmol). The flask was evacuated under vacuum and was then back-filled with dry DMF (350 mL) and argon. The suspension was heated to 130 °C. To this mixture was added a solution of bromo acetal **307** (4.22 g, 6.89 mmol) in dry DMF (16 mL) over 15 hours at 130 °C. After addition was complete, the reaction mixture was stirred for a further 2 hours at 130 °C and was then cooled to room temperature. The reaction mixture was filtered through cotton wool and the organics were concentrated *in vacuo*. The crude oil was dissolved in Et_2O (200 mL) and was washed successively with H_2O (80 mL) and brine (2 x 50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 9:1 to 3:2) afforded a 3:7 respective mixture of inseparable[323] isomers **309** and **310** (2.33 g, 90%). Spectral data for **310** was not obtained, and the mixture was taken through to the following step.

311: (*E*)-3-(8-bromo-2-ethoxy-4'-oxospiro[chromane-4,1'-cyclohexane]-2',5'-dien-6-yl)acrylaldehyde



To a solution of the inseparable[323] mixture of spirocycles **309** and **310** (1.77 g, 4.72 mmol) in 1,2-dichloroethane (23.6 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.57 g, 11.3 mmol), $PdCl_2$ (84 mg, 0.47 mmol) and H_2O (127 mg, 7.08 mmol). The reaction mixture was heated to 50 °C for 2 hours and was then allowed to cool to room temperature. A precipitate formed which was removed by suction filtration and the filter cake was washed with 1,2-dichloroethane (2 x 5 mL). The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 7:3) gave enal **311** as an orange solid (1.23 g, 67%). Further purification by trituration with Et_2O followed by suction filtration gave enal **311** as a colourless solid (1.04 g, 57%) **m.p.** 169-171 °C. The filtrate was concentrated *in vacuo* which gave enal **311** as an orange solid (190 mg, 10%).

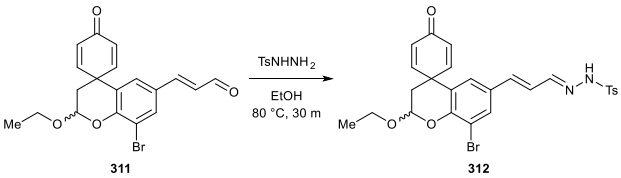


311

311: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.62 (d, *J* = 7.6 Hz, 1H, H-19), 7.73 (d, *J* = 2.1 Hz, 1H, H-4), 7.42 (dd, *J* = 10.1, 3.0 Hz, 1H, H-12), 7.25 (d, *J* = 15.9 Hz, 1H, H-17), 7.03 (d, *J* = 2.1 Hz, 1H, H-6), 6.74

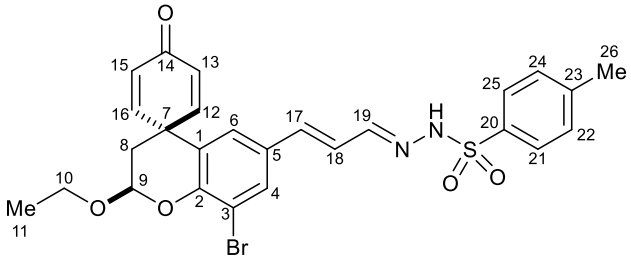
(dd, *J* = 10.0, 3.0 Hz, 1H, H-16), 6.53 (dd, *J* = 15.9, 7.6 Hz, 1H, H-18), 6.41 (dd, *J* = 10.0, 1.9 Hz, 1H, H-15), 6.27 (dd, *J* = 10.1, 1.9 Hz, 1H, H-13), 5.57 (dd, *J* = 2.9, 2.9 Hz, 1H, H-9), 3.96 (dq, *J* = 9.7, 7.1 Hz, 1H, H-10), 3.72 (dq, *J* = 9.7, 7.1 Hz, 1H, H-10), 2.35 (dd, *J* = 14.3, 2.9 Hz, 1H, H-8), 2.21 (dd, *J* = 14.3, 2.9 Hz, 1H, H-8), 1.24 (dd, *J* = 7.1, 7.1 Hz, 3H, H-11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 193.2 (CH), 185.3 (Cq), 153.3 (CH), 152.6 (CH), 150.3 (Cq), 150.0 (CH), 132.3 (CH), 129.33 (CH), 129.29 (CH), 128.9 (Cq), 128.4 (CH), 126.9 (CH), 122.5 (Cq), 114.0 (Cq), 96.9 (CH), 65.3 (CH_2), 40.6 (Cq), 36.2 (CH_2), 15.2 (CH_3); **HRMS** (ESI^+): $C_{19}H_{17}{}^{79}BrO_4$ $[M+H]^+$ calcd. 389.0383, found 389.0381; **IR** ν_{max} cm^{-1}: 3058, 2978, 1667, 1624, 1597, 1462, 1258, 1122, 1038, 983, 903, 860, 732.

312: *N*'-((1*E*,2*E*)-3-(8-bromo-2-ethoxy-4'-oxospiro[chromane-4,1'-cyclohexane]-2',5'-dien-6-yl)allylidene)-4-methylbenzenesulfonohydrazide



A suspension of enal **311** (1.02 g, 2.62 mmol) and tosylhydrazide (488 mg, 2.62 mmol) in EtOH (2.62 mL) was heated at 80 °C for 30 minutes. The reaction mixture was allowed to cool to room temperature and was diluted with EtOH (3.0 mL) which gave an oil suspended in the EtOH. The mixture was sonicated and a precipitate formed which was

collected by suction filtration and the filter cake was washed with EtOH (20 mL) which gave a 95:5 respective mixture of hydrazide **312** and enal **311** as a light yellow solid (1.32 g, 86% yield for hydrazide **312**) **m.p.** 186–188 °C.



312

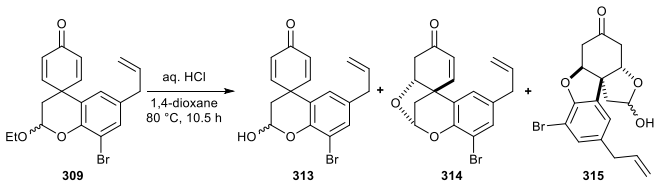
312: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (s, 1H, NH), 7.83 (d, *J* = 8.2 Hz, 2H, H-21 and H-25), 7.55 (d, *J* = 2.1 Hz, 1H, H-4), 7.49 (d, *J* = 8.8 Hz, 1H, H-19), 7.41 (dd, *J* = 10.2, 2.9 Hz, 1H, H-12), 7.32 (d, *J* = 8.2 Hz, 2H, H-22 and H-24), 6.86 (d, *J* = 2.1 Hz, 1H, H-6), 6.73 (dd, *J* = 10.0, 3.0 Hz, 1H, H-16), 6.64 (dd, *J* = 16.0, 8.8 Hz, 1H, H-18), 6.55 (d, *J* = 16.0 Hz, 1H, H-17), 6.38 (dd, *J* = 10.0, 1.9 Hz, 1H, H-15), 6.24 (dd, *J* = 10.2, 1.9 Hz, 1H, H-13), 5.52 (dd, *J* = 2.9, 2.9 Hz, 1H, H-9), 3.94 (dq, *J* = 9.7, 7.1 Hz, 1H, H-10), 3.69 (dq, *J* = 9.7, 7.1 Hz, 1H, H-10), 2.42 (s, 3H, H-26), 2.32 (dd, *J* = 14.2, 2.9 Hz, 1H, H-8), 2.16 (dd, *J* = 14.2, 2.9 Hz, 1H, H-8), 1.23 (dd, *J* = 7.1, 7.1 Hz, 3H, H-11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 185.6 (Cq), 153.8 (CH), 153.1 (CH), 149.0 (CH), 148.5 (Cq), 144.5 (Cq), 137.3 (CH), 135.4 (Cq), 131.2 (CH), 130.6 (Cq), 129.9 (2x CH), 129.1 (CH), 128.1 (2x CH), 127.3 (CH), 126.7 (CH), 124.5 (CH), 122.1 (Cq), 113.6 (Cq), 96.6 (CH), 65.1 (CH_2), 40.7 (Cq), 36.3 (CH_2), 21.8 (CH_3), 15.2 (CH_3); **HRMS** (ESI$^+$): $C_{26}H_{25}{}^{79}BrN_2O_5S$ $[M+H]^+$ calcd. 557.0740, found 557.0744; **IR** ν_{max} cm^{-1}: 3058, 2973, 2874, 2852, 2768, 1655, 1608,

1464, 1408, 1357, 1326, 1300, 1252, 1208, 1168, 1124, 1065, 1035, 978, 934, 921, 902, 893, 865, 819, 732, 691, 664, 586, 568, 544, 466.

313: 6-allyl-8-bromo-2-hydroxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

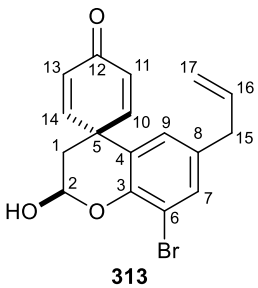
314: (±)-(6*S*,7a*R*,11a*R*)-2-allyl-4-bromo-7a,8-dihydro-9H-6,11a-methanodibenzo[d,f][1,3]dioxepin-9-one

315: (±)-ketone species



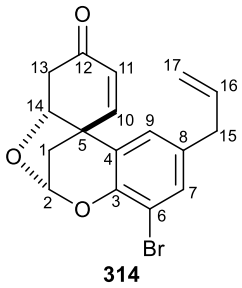
To a solution of spirocycle **309** (87 mg, 0.23 mmol) in 1,4-dioxane (4.6 mL) was added HCl (4.64 mL of a 3.0 M aqueous solution, 13.9 mmol) and the reaction mixture was heated at 80 °C for 10.5 hours. The reaction mixture was allowed to cool to room temperature and was diluted with H_2O (20 mL) and the organics were extracted with CH_2Cl_2 (4 x 15 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/EtOAc, 17:3 to 1:1) gave several products that have been summarised below:

- dienone **313** as a colourless solid (23 mg, 28%) **m.p.** 189–191 °C
- enone **314** that was purified further by flash column chromatography (petroleum ether/Et_2O, 7:3) and was then triturated with pentane which gave enone **314** as a colourless solid (5 mg, 6%) **m.p.** 133–135 °C
- inseparable[323] ketone diastereoisomers **315** (major/minor, 7:3) as an off-white solid (43 mg, 50%).



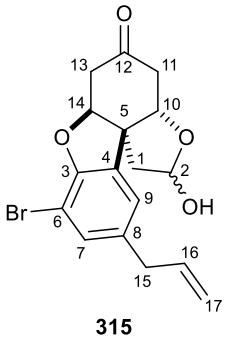
313

313: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (dd, *J* = 10.2, 3.0 Hz, 1H, H-10), 7.30 (d, *J* = 2.1 Hz, 1H, H-7), 6.79 (dd, *J* = 10.0, 3.0 Hz, 1H, H-14), 6.67 (d, *J* = 2.1 Hz, 1H, H-8), 6.37 (dd, *J* = 10.0, 1.9 Hz, 1H, H-13), 6.27 (dd, *J* = 10.2, 1.9 Hz, 1H, H-11), 5.89 (ddd, *J* = 3.9, 3.9, 2.9 Hz, 1H, H-2), 5.83 (dddd, *J* = 16.9, 10.2, 6.5, 6.5 Hz, 1H, H-16), 5.08 – 4.99 (m, 2H, H-17), 3.72 (dd, *J* = 3.9, 1.7 Hz, 1H, OH), 3.22 (ddd, *J* = 6.5, 1.5, 1.5 Hz, 2H, H-15), 2.29 (ddd, *J* = 14.1, 2.9, 1.7 Hz, 1H, H-1), 2.19 (dd, *J* = 14.1, 3.9 Hz, 1H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 185.7 (Cq), 153.8 (CH), 153.1 (CH), 146.1 (Cq), 136.4 (CH), 134.5 (Cq), 133.3(CH), 128.5 (CH), 127.9 (CH), 126.7 (CH), 120.9 (Cq), 116.6 (CH_2), 112.3 (Cq), 91.3 (CH), 40.8 (Cq), 38.8 (CH_2), 36.6 (CH_2); **HRMS** (ESI^+) $C_{17}H_{15}{}^{79}BrO_3$ $[M+H]^+$ calcd. 347.0277, found 347.0283; **IR** ν_{max} cm^{-1}: 3281, 3078, 2976, 2918, 2849, 1660, 1467, 862.



314

314: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 2.0 Hz, 1H, H-7), 7.09 (d, *J* = 10.2 Hz, 1H, H-10), 6.74 (d, *J* = 2.0 Hz, 1H, H-8), 6.30 (d, *J* = 10.2 Hz, 1H, H-11), 6.03 (dd, *J* = 1.8, 1.8 Hz, 1H, H-2), 5.89 (dddd, *J* = 16.9, 10.3, 6.7, 6.7 Hz, 1H, H-16), 5.11 – 5.04 (m, 2H, H-17), 4.78 (dd, *J* = 11.3, 6.6 Hz, 1H, H-14), 3.29 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-15), 2.87 (ddd, *J* = 16.1, 6.6, 0.9 Hz, 1H, H-13), 2.52 (dd, *J* = 16.1, 11.3 Hz 1H, H-13), 2.49 (d, *J* = 1.8 Hz, 2H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 196.3 (Cq), 146.8 (Cq), 146.1 (CH), 136.7 (CH), 134.3 (Cq), 133.2 (CH), 131.8 (Cq), 131.6 (CH), 123.8 (CH), 116.8 (CH_2), 110.9 (Cq), 100.7 (CH), 87.5 (CH), 44.3 (Cq), 43.5 (CH_2), 39.2 (CH_2), 36.4 (CH_2); **HRMS** (ESI^+) $C_{17}H_{15}{}^{79}BrO_3$ $[M+Na]^+$ calcd. 369.0097, found 369.0086; **IR** ν_{max} cm^{-1}: 3076, 3001, 2974, 2959, 2918, 2850, 1692, 1674, 1465, 1221, 893.

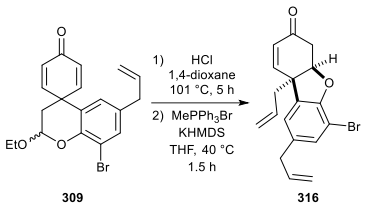


315

315: ^{1}H NMR (400 MHz, C_6D_6) δ: 7.12 (d, *J* = 1.7 Hz, 1H, H-major 7), 7.10 (d, *J* = 1.7 Hz, 1H, H-minor 7), 6.92 (d, *J* = 1.7 Hz, 1H, H-major 9), 6.42 (d, *J* = 1.7 Hz, 1H, H-minor 9), 5.83 – 5.64 (m, 2H, H-major 16 and H-minor 16), 5.06 – 4.87 (m, 6H, H-major 17, H-minor 17, H-major 2, H-minor 2), 4.49 (ddd, *J* = 3.6, 2.6, 1.1 Hz, 1H, H-minor 10), 4.07 (ddd, *J* = 3.1, 3.1, 1.1 Hz, 1H, H-major 10), 4.00 (ddd, *J* = 3.1, 3.1, 1.1 Hz, 1H, H-major 14), 3.59 (ddd, *J* = 3.6, 2.4, 1.1 Hz, 1H, H-minor 14), 3.37 (dd, *J* = 18.5, 3.7 Hz, 1H, H-minor 11), 3.03 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-minor 15), 2.97

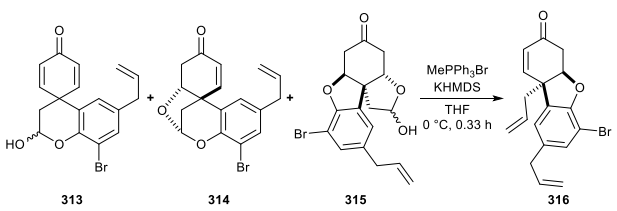
(ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-major 15), 2.89 (dd, *J* = 18.5, 2.6 Hz, 1H, H-minor 11), 2.75 (dd, *J* = 18.4, 2.9 Hz, 1H, H-major 13), 2.58 (s, 1H, minor OH), 2.47 (dd, *J* = 17.5, 3.6 Hz, 1H, H-minor 13), 2.46 (dd, *J* = 17.7, 3.3 Hz, 1H, H-major 11), 2.29 – 2.25 (m, 1H, major OH), 2.21 (dd, *J* = 14.6, 2.1 Hz, 1H, H-major 1), 2.19 (dd, *J* = 18.4, 3.2 Hz, 1H, H-major 13), 2.09 (dd, *J* = 14.0, 6.0 Hz, 1H, H-minor 1), 1.97 (dd, *J* = 17.7, 2.8 Hz, 1H, H-major 11), 1.91 (dd, *J* = 17.5, 2.5 Hz, 1H, H-minor 13), 1.58 (d, *J* = 14.0 Hz, 1H, H-minor 1), 1.52 – 1.44 (m, 1H, H-major 1); **^{13}C NMR** (101 MHz, C_6D_6) δ: 204.82 (Cq minor), 203.54 (Cq major), 155.88 (Cq minor), 155.70 (Cq major), 137.35 (CH minor), 137.28 (CH major), 135.65 (Cq major), 134.79 (Cq minor), 132.87 (CH minor), 132.71 (CH major), 132.33 (Cq major), 131.15 (Cq minor), 122.86 (CH major), 122.17 (CH minor), 116.25 (CH_2 minor), 116.16 (CH_2 major), 103.53 (Cq major), 103.51 (Cq minor), 98.08 (CH minor), 97.46 (CH major), 88.77 (CH minor), 88.40 (CH major), 84.62 (CH minor), 81.33 (CH major), 53.37 (Cq major), 52.54 (Cq minor), 46.26 (CH_2 major), 45.69 (CH_2 minor), 40.28 (CH_2 minor), 39.91 (CH_2 minor), 39.55 (CH_2 minor), 39.49 (CH_2 major), 39.15 (CH_2 major), 38.34 (CH_2 major); **HRMS** (ESI$^-$) $C_{17}H_{17}{}^{79}BrO_4$ $[M-H]^-$ calcd. 363.0237, found 363.0237; **IR** ν_{max} cm^{-1}: 3417, 2923, 2854, 1721, 1469, 1048.

316: (±)-(4a*R*,9b*R*)-8,9b-diallyl-6-bromo-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



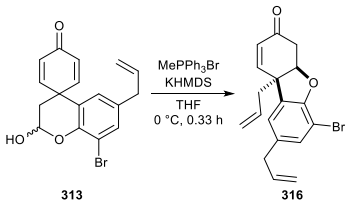
To a solution of dienone **309** (67 mg, 0.18 mmol) in 1,4-dioxane (1.8 mL) was added HCl (1.80 mL of a 3.0 M aqueous solution, 10.8 mmol). The reaction mixture was heated at 101 °C for 5 hours after which the organics were diluted with EtOAc (5 mL) and were washed with H_2O (2 x 5 mL), then brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

To a suspension of methyltriphenylphosphonium bromide (191 mg, 0.534 mmol) in dry THF (4.6 mL) at 0 °C was added KHMDS (0.46 mL of a 1.0 M solution in THF, 0.46 mmol) over 15 minutes. The reaction mixture was stirred at this temperature for 1 hour after which a solution of the previously prepared crude residue in dry THF (4.6 mL) was added. The reaction mixture was stirred at 40 °C for 1.5 hours after which the organics were diluted with Et_2O (10 mL), washed with H_2O (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (hexane/Et_2O, 3:2) gave bromo-tetrahydrodibenzofuran **316** as a colourless solid (37 mg, 60%) **m.p.** 73–75 °C.



To a suspension of methyltriphenylphosphonium bromide (1.79 g, 5.00 mmol)

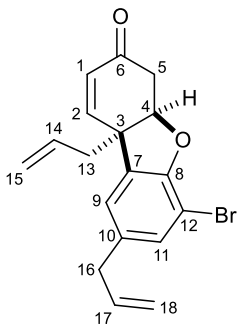
in dry THF (33.0 mL) at 0 °C was added KHMDS (3.75 mL of a 1.0 M solution in THF, 3.75 mmol) over 15 minutes. The reaction mixture was stirred at this temperature for 30 minutes after which a solution of dienone **313** (153 mg, 0.441 mmol), enone **314** (20 mg, 0.058 mmol) and inseparable[323] ketone diastereoisomers **315** (275 mg, 0.753 mmol) in dry THF (33.0 mL) was added over 30 minutes at 0 °C. The reaction mixture was stirred for 20 minutes post full injection and then to the reaction mixture was added H_2O (50 mL) and brine (20 mL). The organics were extracted with Et_2O (3 x 40 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 7:3) gave bromo-tetrahydrodibenzofuran **316** as a colourless solid (247 mg, 57%) **m.p.** 73–75 °C.



To a suspension of methyltriphenylphosphonium bromide (238 mg, 0.666 mmol) in dry THF (5.9 mL) at 0 °C was added KHMDS (0.56 mL of a 1.0 M solution in THF, 0.56 mmol) over 15 minutes. The reaction mixture was stirred at this temperature for 30 minutes after which a solution of dienone **313** (77 mg, 0.22 mmol) in dry THF (5.9 mL) was added over 30 minutes at 0 °C. The reaction mixture was stirred for 20 minutes post full injection and then to the reaction mixture was added H_2O (10 mL) and brine (2 mL). The organics were extracted with Et_2O (3 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated

in vacuo. Purification by flash column chromatography (petroleum ether/Et_2O, 7:3) gave bromo-tetrahydrodibenzofuran **316** as a colourless solid (70 mg, 90%) **m.p.** 73–75 °C.

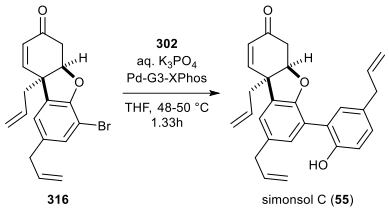
A crystal of **316** was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).



316

316: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 1.6 Hz, 1H, H-11), 6.94 (d, *J* = 1.6 Hz, 1H, H-9), 6.47 (dd, *J* = 10.2, 1.8 Hz, 1H, H-1), 6.03 (dd, *J* = 10.2, 0.8 Hz, 1H, H-2), 5.90 (dddd, *J* = 16.9, 10.4, 6.7, 6.7 Hz, 1H, H-17), 5.76 (dddd, *J* = 16.9, 10.2, 8.0, 6.8 Hz, 1H, H-14), 5.25 – 5.04 (m, 4H, H-15 and H-18), 4.91 (ddd, *J* = 4.5, 2.8, 1.8 Hz, 1H, H-4), 3.32 (d, *J* = 6.7 Hz, 2H, H-16), 3.09 (ddd, *J* = 17.7, 2.8, 0.8 Hz, 1H, H-5), 2.82 – 2.70 (m, 2H, H-5 + H-13), 2.64 (dd, *J* = 14.2, 8.0 Hz, 1H, H-13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 194.8 (Cq), 154.6 (Cq), 147.9 (CH), 137.0 (CH), 135.3 (Cq), 132.53 (CH), 132.45 (Cq), 131.8 (CH), 127.9 (CH), 122.2 (CH), 120.24 (CH_2), 116.6 (CH_2), 103.5 (Cq), 85.40 (CH), 49.5 (Cq), 40.9 (CH_2), 39.5 (CH_2), 38.6 (CH_2); **HRMS** (ESI^+) $C_{18}H_{17}{}^{79}BrO_2$ $[M+Na]^+$ calcd. 367.0304, found 367.0307; **IR** ν_{max} cm^{-1}: 3040, 3027, 3010, 1686, 1471, 1216, 1197, 994.

(±)-simonsol C (55): (±)-(4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one

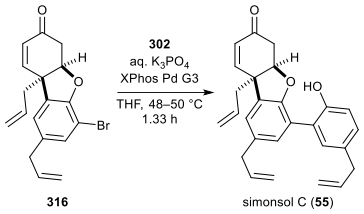


To a solution of aryl bromide **316** (205 mg, 0.594 mmol) in THF (8.30 mL) was added K_3PO_4 (3.56 mL of a 0.5 M aqueous solution, 1.78 mmol). The biphasic mixture was sparged with argon for 5 minutes and then boronic acid **302** (295 mg, 1.78 mmol) and XPhos Pd G3 (50 mg, 0.059 mmol) were added. The reaction mixture was heated at 48-50 °C for 1.33 hours. The reaction mixture was cooled to room temperature, diluted with H_2O (10 mL) and the organics were extracted with CH_2Cl_2 (3 x 10 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 4:1) gave simonsol C (**55**) as a yellow oil (180 mg) which was dissolved in Et_2O (1 mL) and diluted with pentane (6 mL) and then cooled to –20 °C for 16 hours. A precipitate formed which was collected by suction filtration and subsequently washed with pentane (2 x 5 mL) which gave simonsol C (**55**) as a colourless solid (3-6% isomerized, 132 mg, 56%).* The filtrate was concentrated which gave simonsol C (**55**) as a yellow oil (3-6% isomerized, ~70% purity as determined by ^{1}H NMR spectroscopy, 50 mg, 15%).

*simonsol C (**55**) (3-6% isomerized, 132 mg, 56%) was purified according to general method A. Purification by flash column

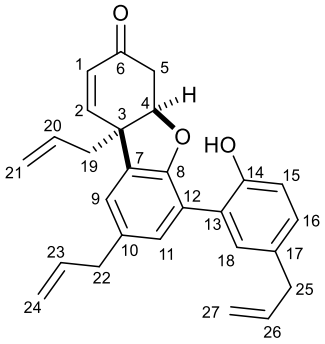
chromatography (petroleum ether/EtOAc, 4:1) gave simonsol C (**55**) as a colourless solid (113 mg, 92-95% yield dependant on 3-6% isomerized starting material) ****m.p.** 122–124 °C.

**No melting point given for either natural[97] or synthetic samples.[103]



A biphasic mixture of bromo-tetrahydrodibenzofuran **316** (28 mg, 0.081 mmol) in THF (1.1 mL) and K_3PO_4 (0.48 mL of a 0.5 M aqueous solution, 0.24 mmol) was sparged with argon for 10 minutes (or until THF volume had reduced by ~50-70%). To the biphasic mixture was added XPhos Pd G3 (6 mg, 0.007 mmol) and boronic acid **302** (43 mg, 0.24 mmol). The reaction mixture was heated in a sealed tube at 48-50 °C for 1.33 h after which to the reaction mixture was added H_2O (3 mL) and the organics were extracted with CH_2Cl_2 (3 x 2 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (hexane/EtOAc, 4:1) gave simonsol C (**55**) as a colourless solid (23 mg, 72%).

A crystal of simonsol C (**55**) was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).



simonsol C (**55**)

simonsol C (55): ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.65 (s, 1H, ArOH), 7.23 (d, *J* = 1.8 Hz, 1H, H-9), 7.13 (d, *J* = 1.8 Hz, 1H, H-11), 7.08 (d, *J* = 2.3 Hz, 1H, H-18), 7.01 (dd, *J* = 8.3, 2.3 Hz, 1H, H-16), 6.86 (d, *J* = 8.3 Hz, 1H, H-15), 6.71 (dd, *J* = 10.3, 1.9 Hz, 1H, H-2), 6.07 – 5.84 (m, 3H, H-20, H-23 and H-26), 5.93 (dd, *J* = 10.3, 0.6 Hz, 1H, H-1), 5.32 – 5.16 (m, 2H, H-19), 5.14 – 4.96 (m, 5H, H-4, H-24 and H-27), 3.40 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-22), 3.31 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-25), 2.97 (dddd, *J* = 14.1, 7.1, 1.3, 1.3 Hz, 1H, H-19), 2.92 – 2.83 (m, 2H, H-5), 2.80 – 2.74 (m, 1H, H-19); **^{13}C NMR** (101 MHz, acetone-d_6) δ: 195.1 (Cq), 155.3 (Cq), 153.6 (Cq), 149.5 (CH), 139.1 (CH), 139.0 (CH), 134.3 (Cq), 133.9 (CH), 132.8 (Cq), 132.0 (CH), 131.9 (Cq), 131.7 (CH), 129.7 (CH), 127.6 (CH), 125.0 (Cq), 123.3 (CH), 122.3 (Cq), 119.7 (CH_2), 117.3 (CH), 115.8 (CH_2), 115.5 (CH_2), 85.8 (CH), 49.6 (Cq), 40.8 (CH_2), 40.4 (CH_2), 39.9 (CH_2), 39.4 (CH_2); **HRMS** (ESI^-) $C_{27}H_{26}O_3$ $[M-H]^-$ calcd. 397.1809, found 397.1803; **IR** ν_{max} cm^{-1}: 3412, 3067, 3046, 3005, 1687, 1498, 1232, 1128, 994.

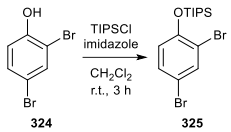
Nat. **55**[97]	Syn. **55**	Dif.	Nat. **55**[97]	Syn. **55**	Dif.
195.1	195.1	0	124.9	125.0	0.1
155.2	155.3	0.1	123.3	123.3	0
153.5	153.6	0.1	122.2	122.3	0.1
149.5	149.5	0	119.6	119.7	0.1
139	139.1	0.1	117.2	117.3	0.1
138.9	139.0	0.1	115.7	115.8	0.1
134.2	134.3	0.1	115.5	115.5	0
133.8	133.9	0.1	85.7	85.8	0.1
132.7	132.8	0.1	49.5	49.6	0.1
131.9	132.0	0.1	40.7	40.8	0.1
131.8	131.9	0.1	40.3	40.4	0.1
131.6	131.7	0.1	39.9	39.9	0
129.7	129.7	0	39.3	39.4	0.1
127.5	127.6	0.1			

Table 14. *Comparison (Dif. = difference (Syn. – Nat. ^{13}C δ value)) of natural (Nat.) versus synthetic (Syn.) simonsol C (**55**) ^{13}C NMR spectroscopy data in acetone-d_6.*[97]

Spectroscopic data obtained for synthetic simonsol C (**55**) were in excellent agreement with both natural[97] and synthetic samples.[103]

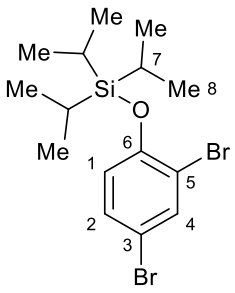
7.1.3: Synthesis of simonsol F (Section 2.1.5)

325: (2,4-dibromophenoxy)triisopropylsilane



324 **325**

To a solution of 2,4-dibromophenol (**324**) (300 mg, 1.19 mmol) and imidazole (203 mg, 2.98 mmol) in CH_2Cl_2 (7.2 mL) at room temperature was added triisopropylsilyl chloride (280 µL, 1.31 mmol). The reaction mixture was stirred at room temperature for 3 hours and then H_2O (20 mL) was added. The organics were extracted with CH_2Cl_2 (3 x 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 9:1) afforded silylated phenol **325** as a colourless oil (486 mg, >99%).

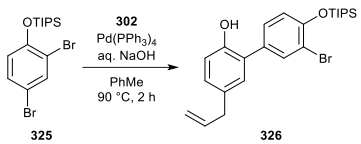


325

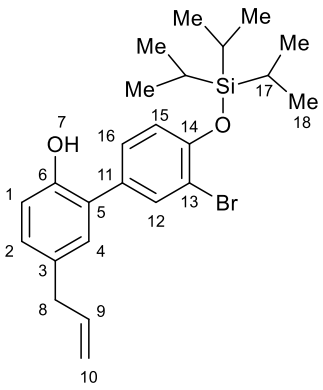
325: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 2.5 Hz, 1H, H-4), 7.25 (dd, *J* = 8.7, 2.5 Hz, 1H, H-2), 6.76 (d, *J* = 8.7 Hz, 1H, H-1), 1.35 – 1.25 (m, 3H, H-7), 1.12 (d, *J* = 7.4 Hz, 18H, H-8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 152.5 (Cq), 135.7 (CH), 131.2 (CH), 120.8 (CH), 116.1 (Cq), 113.0 (Cq), 18.1 (6x CH_3), 13.1 (3x CH); **IR** ν_{max} cm^{-1}: 2944, 2891, 2866, 1576, 1469, 1380, 1287, 997.

HRMS: Compound did not provide targeted mass upon ionisation.

326: 5-allyl-3'-bromo-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-ol



A biphasic mixture of silylated phenol **325** (449 mg, 1.10 mmol), boronic acid **302** (352 mg, 1.10 mmol), NaOH (5.6 mL of a 0.5 M aqueous solution, 2.8 mmol) and PhMe (11.0 mL) was sparged with argon for 5 minutes at room temperature. To the biphasic mixture was added $Pd(PPh_3)_4$ (254 mg, 0.220 mmol) and the reaction mixture was sparged with argon for a further 5 minutes and was then heated at 90 °C for 3.5 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (15 mL) and then HCl (10 mL of a 3.0 M aqueous solution) was added. The organics were extracted with EtOAc (2 x 10 mL) and the combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 97:3) afforded biaryl **326** as a colourless oil (374 mg, 74%).

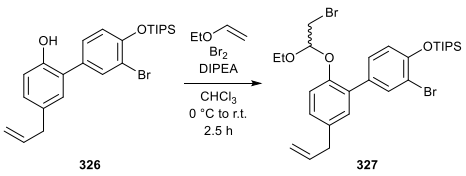


326

326: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 2.2 Hz, 1H, H-12), 7.26 (dd, *J* = 8.3, 2.2 Hz, 1H, H-16), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H, H-2), 7.02 (d, *J* = 2.2 Hz, 1H, H-4), 6.97 (d, *J* = 8.3 Hz, 1H, H-15), 6.89 (d, *J* = 8.2 Hz, 1H, H-1), 5.97 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-9), 5.12 – 5.03 (m, 2H, H-10), 4.96 (s, 1H, ArOH), 3.34 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-8), 1.42 – 1.30 (m, 3H, H-17), 1.16 (d, *J* = 7.3

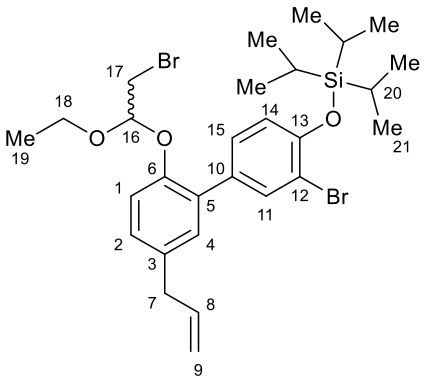
Hz, 18H, H-18); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 152.8 (Cq), 150.8 (Cq), 137.8 (CH), 134.1 (CH), 132.6 (Cq), 131.0 (Cq), 130.4 (CH), 129.3 (CH), 129.0 (CH), 126.7 (Cq), 112.0 (CH), 116.0 (CH), 115.9 (Cq), 115.8 (CH), 39.5 (CH_2), 18.2 (6x CH_3), 13.1 (3x CH); **HRMS** (ESI^-): $C_{24}H_{33}{}^{79}BrO_2Si$ $[M-H]^-$ calcd. 459.1360, found 459.1350; **IR** ν_{max} cm^{-1}: 3557, 3418, 2644, 2892, 2866, 1639, 1597, 1485, 1292, 916, 882.

327: ((5'-allyl-3-bromo-2'-(2-bromo-1-ethoxyethoxy)-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane



326 327

To a solution of ethyl vinyl ether (0.73 mL, 7.6 mmol) in CH_2Cl_2 (7.8 mL) was added bromine (0.31 mL, 6.1 mmol) over 1 minute at 0 °C. The solution was stirred for 15 minutes at 0 °C and then a solution of biaryl **326** (1.38 g, 3.03 mmol) and DIPEA (2.11 mL, 12.1 mmol) in CH_2Cl_2 (8.0 mL) was added. The reaction mixture was warmed to room temperature and was stirred for 2 hours. The reaction mixture was diluted with EtOAc (30 mL) and the organics were washed with $NaHCO_3$ (2 x 15 mL of a saturated aqueous solution) then brine (15 mL). The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 97:3) afforded bromo-acetal **327** as a colourless oil (1.71 g, 93%).

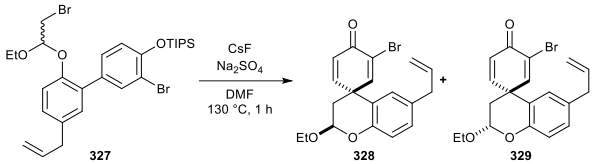


327

327: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 2.2 Hz, 1H, H-11), 7.34 (dd, *J* = 8.4, 2.2 Hz, 1H, H-15), 7.15 – 7.12 (m, 1H, H-2), 7.12 – 7.06 (m, 2H, H-1 and H-4), 6.91 (d, *J* = 8.4 Hz, 1H, H-14), 5.97 (dddd, *J* = 16.8, 10.1, 6.7, 6.7 Hz, 1H, H-8), 5.12 – 5.05 (m, 2H, H-9), 3.62 (dq, *J* = 9.3, 7.0 Hz, 1H, H-18), 3.47 (dq, *J* = 9.3, 7.0 Hz, 1H, H-18), 3.40 – 3.35 (m, 4H, H-7 and H-17), 1.40 – 1.31 (m, 3H, H-20), 1.16 (d, *J* = 7.5 Hz, 18H, H-21), 1.13 (dd, *J* = 7.0, 7.0 Hz, 3H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 152.2 (Cq), 151.8 (Cq), 137.5 (CH), 135.2 (Cq), 134.4 (CH), 132.2 (Cq), 131.6 (Cq), 131.1 (CH), 129.6 (CH), 128.8 (CH), 119.1 (CH), 118.5 (CH), 116.1 (CH_2), 114.7 (Cq), 102.4 (CH), 63.0 (CH_2), 39.6 (CH_2), 31.6 (CH_2), 18.2 (6x CH_3), 15.2 (CH_3), 13.2 (3x CH); **HRMS** (ESI$^+$): $C_{28}H_{40}{}^{79}Br_2O_3Si$ $[M+Na]^+$ calcd. 633.1006, found 633.1041; **IR** ν_{max} cm^{-1}: 2944, 2892, 2867, 1639, 1598, 1502, 1483, 1291, 918.

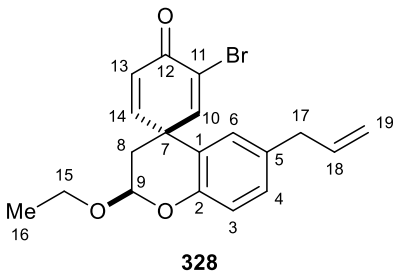
328: (±)-(2*R*,4*R*)-6-allyl-3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

329: (±)-(2*S*,4*R*)-6-allyl-3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



To a solution of bromo-acetal **327** (175 mg, 0.286 mmol) in dry DMF (29.0 mL) was added CsF (130 mg, 0.858 mmol) and Na_2SO_4 (406 mg, 2.86 mmol). The reaction mixture was heated at 130 °C for 1 hour and was then allowed to cool to room temperature at which point H_2O (300 mL) was added. The organics were extracted with Et_2O (2 x 50 mL) and the combined organics were washed with H_2O (25 mL) then brine (3 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 7:3) afforded spirocylce **328** as a colourless solid (50 mg, 47%) **m.p.** 113–116 °C and spirocycle **329** as a pale yellow solid (53 mg, 49%) **m.p.** 70–73 °C.

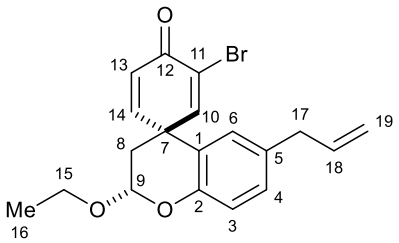
Crystals of **328** and **329** were grown by vapour diffusion method; distilled pentane/distilled Et_2O (see Section 6.9).



328

328: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 2.7 Hz, 1H, H-10), 7.05 (dd, *J* = 8.4, 2.2 Hz, 1H, H-4), 6.88 (d, *J* = 8.4 Hz, 1H, H-3), 6.80 (dd, *J* = 9.8, 2.7 Hz, 1H, H-

14), 6.68 (d, *J* = 2.2 Hz, 1H, H-6), 6.46 (d, *J* = 9.8 Hz, 1H, H-13), 5.93 – 5.82 (m, 1H, H-18), 5.38 (dd, *J* = 2.8, 2.8 Hz, 1H, H-9), 5.06 – 5.00 (m, 2H, H-19), 3.90 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.65 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.25 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-17), 2.29 (dd, *J* = 14.1, 2.9 Hz, 1H, H-8), 2.17 (dd, *J* = 14.1, 2.7 Hz, 1H, H-8), 1.23 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 178.9 (Cq), 155.0 (CH), 154.3 (CH), 149.2 (Cq), 137.2 (CH), 133.8 (Cq), 130.2 (CH), 128.5 (CH), 127.1 (CH), 122.3 (Cq), 118.9 (CH), 118.0 (Cq), 116.2 (CH_2), 95.3 (CH), 64.5 (CH_2), 43.8 (Cq), 39.4 (CH_2), 35.9 (CH_2), 15.2 (CH_3); **HRMS** (ESI$^+$): $C_{19}H_{19}{}^{79}BrO_3$ $[M+H]^+$ calcd. 375.0590, found 375.0583; **IR** ν_{max} cm^{-1}: 3076, 2977, 2916, 2849, 1667, 1494, 1220, 1116.

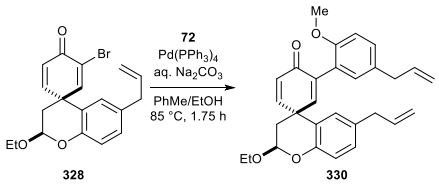


329

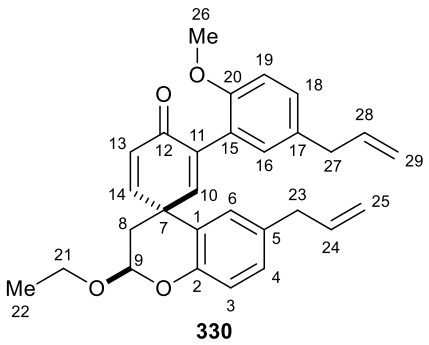
329: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (dd, *J* = 10.0, 2.7 Hz, 1H, H-14), 7.25 (d, *J* = 2.7 Hz, 1H, H-10), 7.05 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 6.88 (d, *J* = 8.3 Hz, 1H, H-3), 6.67 (d, *J* = 2.2 Hz, 1H, H-6), 6.30 (d, *J* = 10.0 Hz, 1H, H-13), 5.92 – 5.81 (m, 1H, H-18), 5.37 (dd, *J* = 3.1, 3.1 Hz, 1H, H-9), 5.06 – 5.00 (m, 2H, H-19), 3.91 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.64 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.25 (ddd, *J* = 6.8, 1.4, 1.4 Hz, 2H, H-17), 2.31 (dd, *J* = 14.0, 3.0 Hz, 1H, H-8), 2.16 (dd, *J* = 14.0, 3.2 Hz, 1H, H-8), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 179.0 (Cq), 154.9 (CH), 154.1 (CH), 149.3 (Cq), 137.2 (CH), 133.8 (Cq), 130.2 (CH), 128.5 (CH), 124.6 (CH), 124.5 (Cq),

118.9 (CH), 118.1 (Cq), 116.2 (CH_2), 95.5 (CH), 64.6 (CH_2), 44.1 (Cq), 39.4 (CH_2), 36.1 (CH_2), 15.3 (CH_3); **HRMS** (ESI^+): $C_{19}H_{19}{}^{79}BrO_3$ $[M+H]^+$ calcd. 375.0590, found 375.0598; **IR** ν_{max} cm^{-1}: 3076, 2976, 2928, 2908, 1666, 1494, 1225, 1116.

330: acetal dienone



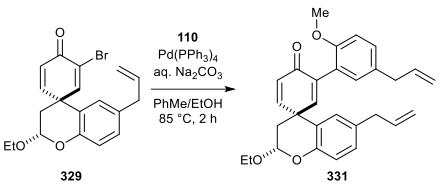
To spirocycle **328** (250 mg, 0.667 mmol) and boronic acid **72** (230 mg, 1.20 mmol) in PhMe (4.7 mL) and EtOH (2.1 mL) was added Na_2CO_3 (2.1 mL of a 2.0 M aqueous solution, 4.2 mmol). The biphasic mixture was sparged for 5 minutes under argon and then $Pd(PPh_3)_4$ (39 mg, 0.034 mmol) was added. The reaction mixture was sparged for a further 5 minutes and was then heated at 85 °C for 1.75 hours. The reaction mixture was allowed to cool to room temperature and was then diluted with EtOAc (20 mL). The organics were washed with HCl (2 x 10 mL of a 1.0 M aqueous solution) then brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 3:1) afforded acetal **330** as a colourless oil (255 mg, 85%).



330

330: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 3.0 Hz, 1H, H-10), 7.11 (dd, *J* = 8.4, 2.4 Hz, 1H, H-18), 7.02 (dd, *J* = 8.4, 2.2 Hz, 1H, H-6), 6.93 (d, *J* = 2.3 Hz, 1H, H-16), 6.89 – 6.81 (m, 4H, H-3, H-4, H-14 and H-19), 6.41 (d, *J* = 9.9 Hz, 1H, H-13), 6.00 – 5.82 (m, 2H, H-24 and H-28), 5.38 (dd, *J* = 4.2, 2.9 Hz, 1H, H-9), 5.08 – 4.98 (m, 4H, H-25 and H-29), 3.93 (dq, *J* = 9.7, 7.1 Hz, 1H, H-21), 3.75 (s, 3H, H-26), 3.64 (dq, *J* = 9.7, 7.1 Hz, 1H, H-21), 3.32 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-27), 3.27 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, H-23), 2.32 (dd, *J* = 14.0, 2.9 Hz, 1H, H-8), 2.24 (dd, *J* = 14.0, 4.2 Hz, 1H, H-8), 1.19 (dd, *J* = 7.1, 7.1 Hz, 3H, H-22); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 184.4 (Cq), 155.9 (Cq), 152.7 (CH), 152.6 (CH), 149.8 (Cq), 137.9 (CH), 137.5 (CH), 135.6 (Cq), 133.4 (Cq), 132.0 (Cq), 130.9 (CH), 129.6 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 125.9 (Cq), 120.1 (Cq), 118.5 (CH), 115.9 (CH_2), 115.6 (CH_2), 111.3 (CH), 96.0 (CH), 64.5 (CH_2), 56.0 (CH), 41.3 (Cq), 39.5 (CH_2), 39.5 (CH_2), 37.0 (CH_2), 15.2 (CH_3); **HRMS** (ESI^+) $C_{29}H_{30}O_4$ $[M+H]^+$ calcd. 443.2217, found 443.2209; **IR** ν_{max} cm^{-1}: 3075, 3001, 2975, 2930, 2834, 1666, 1637, 1496, 1267, 1241, 1117, 1035.

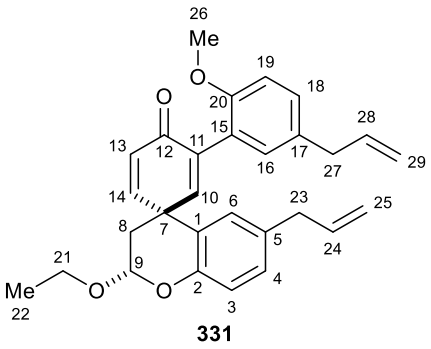
331: acetal dienone



To a solution of spirocycle **329** (425 mg, 1.13 mmol) and boronic acid pinacol ester **110** (559 mg, 2.04 mmol) in PhMe (8.0 mL) and EtOH (3.7 mL) was added Na_2CO_3 (3.7 mL of a 2.0 M aqueous solution, 7.4 mmol). The biphasic mixture was sparged for 5 minutes under argon and then $Pd(PPh_3)_4$ (65 mg, 0.057 mmol) was added. The reaction mixture was sparged for a further 5 minutes and was then heated at 85 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and was then diluted with EtOAc (20 mL). The organics were washed with HCl (2 x 10 mL of a 1.0 M aqueous solution) then brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 4:1) gave acetal **331** as a colourless solid (436 mg, 87%) **m.p.** 110–112 °C.

A crystal of acetal **331** was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).

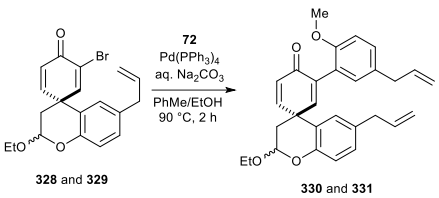
An alternative experimental method that successfully formed **331** is described in Section 6.5.1.



331

331: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (dd, *J* = 10.1, 2.9 Hz, 1H, H-14), 7.12 (dd, *J* = 8.4, 2.3 Hz, 1H, H-18), 7.03 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 6.94 (d, *J* = 2.3 Hz, 1H, H-16), 6.90 (d, *J* = 2.2 Hz, 1H, H-6), 6.87 (d, *J* = 8.3 Hz, 1H, H-19), 6.86 (d, *J* = 8.4 Hz, 1H, H-19), 6.73 (d, *J* = 2.9 Hz, 1H, H-10), 6.30 (d, *J* = 10.1 Hz, 1H, H-13), 6.00 – 5.84 (m, 2H, H-24 and H-28), 5.38 (dd, *J* = 3.1, 3.1 Hz, 1H, H-9), 5.10 – 5.00 (m, 4H, H-25 and H-29), 3.94 (dq, *J* = 9.6, 7.1 Hz, 1H, H-21), 3.75 (s, 3H, H-26), 3.65 (dq, *J* = 9.6, 7.1 Hz, 1H, H-21), 3.33 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-27), 3.27 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-23), 2.33 (dd, *J* = 14.1, 3.0 Hz, 1H, H-8), 2.23 (dd, *J* = 14.1, 3.2 Hz, 1H, H-8), 1.23 (dd, *J* = 7.1, 7.1 Hz, 3H, H-22); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 184.5 (Cq), 155.8 (Cq), 153.6 (CH), 152.3 (CH), 149.6 (Cq), 137.9 (CH), 137.5 (CH), 137.2 (Cq), 133.4 (Cq), 132.0 (Cq), 130.9 (CH), 129.6 (CH), 129.5 (CH), 129.1 (CH), 126.6 (CH), 125.5 (Cq), 119.9 (Cq), 118.5 (CH), 115.9 (CH_2), 115.7 (CH_2), 111.3 (CH), 95.9 (Cq), 64.5 (CH_2), 56.0 (CH_3), 41.0 (Cq), 39.51 (CH_2), 39.46 (CH_2), 36.4 (CH_2), 15.3 (CH_3); **HRMS** (ESI^+): $C_{29}H_{30}O_4$ $[M+H]^+$ calcd. 443.2217, found 443.2222; **IR** ν_{max} cm^{-1}: 3076, 3057, 2975, 2925, 2854, 2835, 1665, 1638, 1495, 1268, 1116, 1035, 913.

330 and 331: Suzuki-Miyaura cross-coupling that generated a mixture of acetals



To a solution of bromo-spirocycles **328** (49 mg, 0.13 mmol), **329** (46 mg, 0.12 mmol) and boronic acid **72** (87 mg, 0.45 mmol) in PhMe (1.8 mL) and EtOH (0.8 mL) was added Na_2CO_3 (0.80 mL of a 2.0 M aqueous solution, 1.6 mmol). The biphasic mixture was sparged for 5 minutes under argon and then $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) was added. The reaction mixture was sparged for a further 5 minutes and was then heated at 90 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and was then diluted with EtOAc (20 mL). The organics were washed with HCl (2 x 10 mL of a 1.0 M aqueous solution) then brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. (*) Purification by flash column chromatography (petroleum ether/acetone/CH_2Cl_2, 90:5:5) afforded an approximate 1:1 mixture of acetals **330** and **331** as a pale-yellow oil (145 mg, 88%).

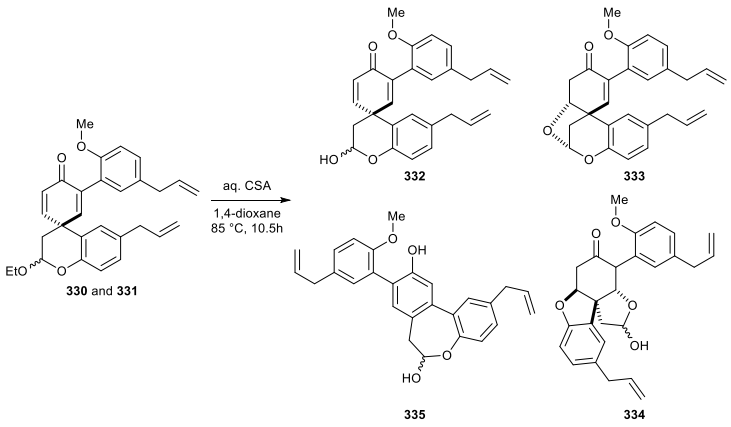
*Alternatively, acetals **330** and **331** were obtained separately by flash column chromatography (petroleum ether/Et_2O, 4:1) which separated **330** from **331**. Subsequent flash column chromatography (petroleum ether/acetone, 17:3) was applied to each acetal to remove minor impurities.

332: (±)-Dienone hemi-acetal inseparable[323] diastereoisomers

333: (±)-(6*S*,7a*S*,11a*R*)-2-allyl-10-(5-allyl-2-methoxyphenyl)-7a,8-dihydro-9H-6,11a-methanodibenzo[d,f][1,3]dioxepin-9-one

334: (±)-ketone

335: 2-allyl-9-(5-allyl-2-methoxyphenyl)-6,7-dihydrodibenzo[b,d]oxepine-6,10-diol

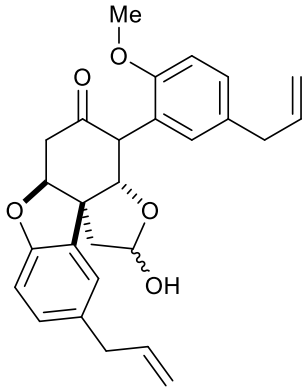


To a solution of acetals **330** and **331** (2.76 g, 6.24 mmol) in 1,4-dioxane (125 mL) and H_2O (94 mL) was added camphor-10-sulfonic acid (86.8 g, 374 mmol). The reaction mixture was heated at 80 °C for 10.5 hours and was then allowed to cool to room temperature. The reaction mixture was diluted with water (200 mL) and the organics were extracted with CH_2Cl_2 (4 x 125 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/EtOAc, 9:1 to 3:7) gave several products that have been summarised below:

- an inseparable[323] mixture of diastereomeric dienones **332** as a yellow gummy solid (1.95 g) that was purified further by graduated column chromatography (petroleum

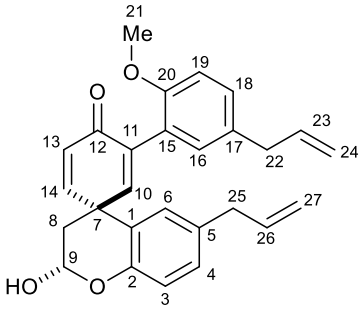
ether/Et_2O/acetone, 6:3:1 to 5:4:1) which gave an inseparable[323] mixture of diastereomeric dienones **332** (major/minor, 55:45) as an off-white solid (1.72 g, 66%)

- enone **333** as a yellow solid that was recrystallized from EtOH which gave **333** as a colourless solid (207 mg, 8%) **m.p.** 123–125 ˚C.
- ketone **334** (< 1 mg*****).
- phenol **335** as an orange oil that was triturated in pentane/CH_2Cl_2 (15:1 respectively) which gave **335** as a colourless solid (131 mg, 5%) **m.p.** 130–132 °C.

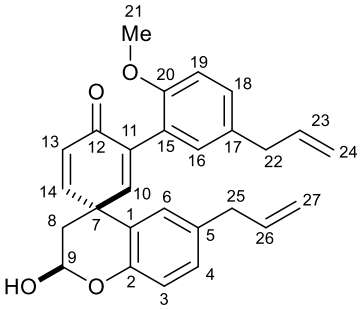


334

334: ***Species was not isolated; however, signals were observed in the ^{1}H NMR spectra that suggested **334 was formed when compared to similar substrates **315** and **345**.



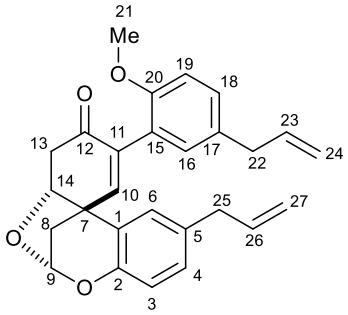
332 - major



332 - minor

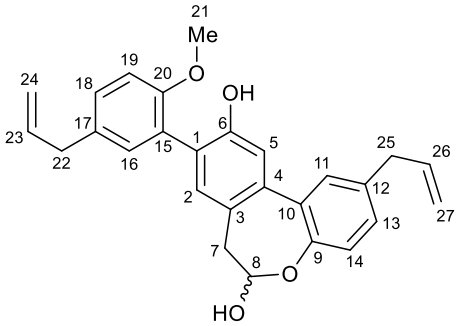
332: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (dd, *J* = 10.0, 3.0 Hz, 1H, H-major 14), 7.18 (d, *J* = 3.0 Hz, 1H, H-minor 10), 7.12 (dd, *J* = 8.3, 2.4 Hz, 1H, H-minor 18), 7.11 (dd, *J* = 8.3, 2.4 Hz, 1H, H-major 18), 7.05 (d, *J* = 2.2 Hz, 1H, H-minor 6),

7.02 (d, *J* = 2.3 Hz, 1H, H-major 6), 6.94 – 6.92 (m, 2H, H-major 1x ArH, minor 1x ArH), 6.91 – 6.90 (m, 1H, H-major 1x ArH), 6.90 – 6.87 (m, 2H, H-minor 2x ArH), 6.87 – 6.83 (m, 3H, H-major 2x ArH, minor 1x ArH), 6.78 (d, *J* = 3.0 Hz, 1H, H-major 10), 6.40 (d, *J* = 9.9 Hz, 1H, H-minor 13), 6.35 (d, *J* = 10.0 Hz, 1H, H-major 13), 6.00 – 5.83 (m, 4H, H-major 23 & 26, minor 23 & 26), 5.79 – 5.72 (m, 2H, H-major 9, minor 9), 5.10 – 4.98 (m, 8H, H-major 24 & 27, minor 24 & 27), 3.75 (s, 3H, H-major 21), 3.74 (s, 3H, H-minor 21), 3.35 – 3.30 (m, 4H, H-major 22 or 25, minor 22 or 25), 3.30 – 3.24 (m, 4H, H-major 22 or 25, minor 22 or 25), 3.19 (s, 2H, H-major OH, minor OH), 2.37 – 2.30 (m, 2H, H-major 8, minor 8), 2.29 – 2.22 (m, 2H, H-major 8, minor 8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 184.5 (Cq), 184.4 (Cq), 155.9 (Cq), 155.8 (Cq), 153.3 (CH), 152.3 (CH), 152.2 (CH), 151.8 (CH), 150.0 (Cq), 149.7 (Cq), 137.84 (CH), 137.81 (CH), 137.43 (CH), 137.42 (CH), 137.0 (Cq), 136.3 (Cq), 133.6 (Cq), 132.0 (Cq), 130.9 (CH), 130.8 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 127.2 (CH), 125.5 (Cq), 125.4 (Cq), 119.7 (Cq), 119.6 (Cq), 118.4 (CH), 116.0 (2 x CH_2), 115.73 (CH_2), 115.68 (CH_2), 111.3 (CH), 91.1 (CH), 91.0 (CH), 56.01 (CH_3), 55.99 (CH_3), 41.6 (Cq), 41.2 (Cq), 39.5 (2 x CH_2), 39.4 (2 x CH_2), 37.7 (CH_2), 37.1 (CH_2); **HRMS** (ESI^+): $C_{27}H_{26}O_4$ $[M+H]^+$ calcd. 415.1904, found 415.1922; **IR** ν_{max} cm^{-1}: 3369, 3002, 2975, 2928, 2906, 2834, 1658, 1627, 1494, 1268, 1240, 1218, 1140, 1127, 1115, 1033, 908, 729.



333

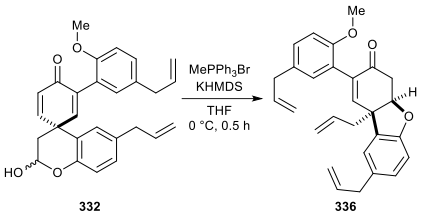
333: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (dd, *J* = 8.4, 2.3 Hz, 1H, H-18), 7.05 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 7.03 (s, 1H, H-10), 6.99 (d, *J* = 2.3 Hz, 1H, H-16), 6.98 (d, *J* = 2.2 Hz, 1H, H-6), 6.89 (d, *J* = 8.4 Hz, 1H, H-19), 6.84 (d, *J* = 8.3 Hz, 1H, H-3), 6.05 – 5.88 (m, 2H, H-23 & 26), 5.93 (d, *J* = 3.3 Hz, 1H, H-9), 5.15 – 5.04 (m, 4H, H-24 & 27), 4.85 (dd, *J* = 11.7, 6.3 Hz, 1H, H-14), 3.79 (s, 3H, H-21), 3.40 – 3.31 (m, 4H, H-22 & 25), 2.94 (dd, *J* = 14.7, 6.3 Hz, 1H, H-13), 2.78 (dd, *J* = 14.7, 11.7 Hz, 1H, H-13), 2.60 (dd, *J* = 11.7, 3.3 Hz, 1H, H-8), 2.47 (d, *J* = 11.7 Hz, 1H, H-8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 195.6 (Cq), 155.5 (Cq), 149.7 (Cq), 143.9 (CH), 140.0 (Cq), 137.7 (CH), 137.6 (CH), 132.9 (Cq), 132.2 (Cq), 131.3 (Cq), 131.0 (CH), 130.0 (CH), 129.5 (CH), 125.1 (Cq), 124.7 (CH), 116.9 (CH), 116.1 (CH_2), 115.9 (CH_2), 111.3 (CH), 100.6 (CH), 87.6 (CH), 55.9 (CH_3), 44.8 (Cq), 44.4 (CH_2), 39.7 (CH_2), 39.5 (CH_2), 36.4 (CH_2); **HRMS** (ESI^+): $C_{27}H_{26}O_4$ $[M+H]^+$ calcd. 415.1904, found 415.1925; **IR** ν_{max} cm^{-1}: 3076, 2999, 2975, 2909, 2835, 1683, 1493, 1244, 1214, 1117, 1037, 983, 910, 879, 816.



335

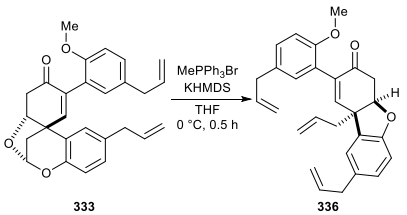
335: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 2.2 Hz, 1H, H-11), 7.23 (dd, *J* = 8.2, 2.3 Hz, 1H, H-18), 7.22 (d, *J* = 2.4 Hz, 1H, H-16), 7.19 (s, 1H, H-5), 7.17 (s, 1H, H-2), 7.16 (dd, *J* = 8.2, 2.2 Hz, 1H, H-13), 7.09 (d, *J* = 8.1 Hz, 1H, H-14), 7.01 (d, *J* = 8.2 Hz, 1H, H-19), 6.39 (s, 1H, H-ArOH), 6.06 – 5.92 (m, 2H, H-23 & 26), 5.82 (dd, *J* = 9.1, 4.1 Hz, 1H, H-8), 5.17 – 5.06 (m, 4H, H-24 & 27), 3.92 (s, 3H, H-21), 3.45 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-25), 3.41 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-22), 3.09 (s, 1H, H-OH), 2.99 (dd, *J* = 14.4, 4.1 Hz, 1H, H-7), 2.70 (dd, *J* = 14.3, 8.9 Hz, 1H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 154.0 (Cq), 153.4 (Cq), 149.3 (Cq), 139.5 (Cq), 137.5 (CH), 137.5 (CH), 136.8 (Cq), 134.1 (Cq), 133.7 (Cq), 132.7 (CH), 131.7 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 126.8 (Cq), 126.7 (Cq), 125.7 (Cq), 123.9 (CH), 117.1 (CH), 116.2 (CH_2), 116.1 (CH_2), 111.9 (CH), 103.6 (CH), 56.6 (CH), 39.9 (CH_2), 39.5 (CH_2), 39.0 (CH_2); **HRMS** (ESI^+): $C_{27}H_{26}O_4$ $[M+H]^+$ calcd. 415.1904, found 415.1899; **IR** ν_{max} cm^{-1}: 3377, 3076, 3004, 2924, 2852, 1492, 1237, 1204, 1024, 987.

336: (±)-(4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-methoxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



332 336

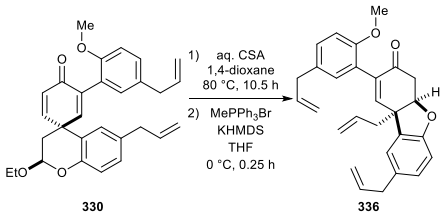
To a flame-dried flask containing methyltriphenylphosphonium bromide (3.82 g, 10.7 mmol) was added dry THF (95.0 mL). The suspension was cooled to 0 °C and KHMDS (9.10 mL of a 1.0 M solution in THF, 9.10 mmol) was added over 0.25 hours. The yellow solution was stirred for 0.66 hours at 0 °C and then a solution of **332** (1.48 g, 3.57 mmol) in dry THF (95.0 mL) was added over 30 minutes at 0 °C. Upon full addition of **332**, the reaction mixture was stirred for 0.5 hours at 0 °C and then H_2O (100 mL) and brine (50 mL) were added. The organics were extracted with Et_2O (3 x 100 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/acetone, 9:1) gave enone **336** as a yellow oil (930 mg, 63%).



333 336

To a flame-dried flask containing methyltriphenylphosphonium bromide (761 mg, 2.13 mmol) was added dry THF (19.0 mL). The suspension was cooled to 0 °C and KHMDS (1.81 mL of a 1.0 M solution in THF, 1.81 mmol) was added over 15 minutes. The yellow solution was stirred for 0.75 hours at 0 °C and then a solution of enone **333** (295 mg, 0.711 mmol) in dry THF (19.0 mL)

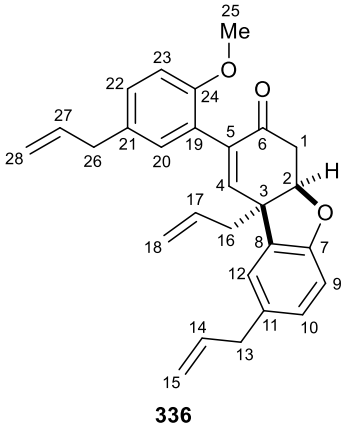
was added over 30 minutes at 0 °C. Upon full addition of **333**, the reaction mixture was stirred for 0.5 hours at 0 °C and then H_2O (20 mL) and brine (10 mL) were added. The organics were extracted with Et_2O (3 x 40 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/acetone, 9:1) gave enone **336** as a yellow oil (133 mg, 45%).



330 336

To a solution of dienone **330** (28 mg, 0.063 mmol) in 1,4-dioxane (1.3 mL) was added camphor-10-sulfonic acid (880 mg, 3.79 mmol) and H_2O (1.0 mL). The reaction mixture was heated at 80 °C for 10.5 hours and was then allowed to cool to room temperature. The organics were diluted with EtOAc (5 mL) and were washed with H_2O (2 x 5 mL) then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave a crude yellow oil. To a separate flame-dried flask was added methyltriphenylphosphonium bromide (68 mg, 0.19 mmol) followed by dry THF (1.6 mL) and the suspension was cooled to 0 °C and then KHMDS (0.16 mL of a 1.0 M solution in THF, 0.16 mmol) was added over 15 minutes. The ylide solution was stirred for 1 hour at 0 °C and then the crude yellow oil was added as a solution in dry THF (1.6 mL) over 30 minutes at 0 °C. After addition was complete, the reaction mixture was stirred for a further 0.25 hours at 0 °C and then H_2O (5 mL) was added. The organics were diluted with Et_2O (10 mL) and were washed with a

H_2O/brine solution (2 x 5 mL of a 4:1 respective mixture), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/acetone 9:1) provided enone **336** as a yellow oil (10 mg, 37%).

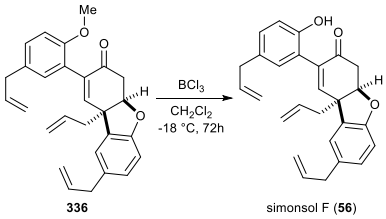


336

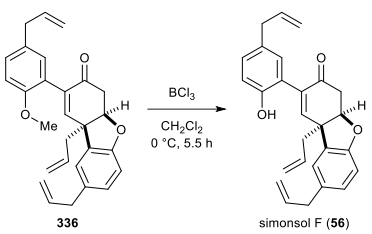
336: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09 (dd, *J* = 8.3, 2.3 Hz, 1H, H-22), 7.04 – 6.99 (m, 2H, H-10 and H-12), 6.80 (d, *J* = 8.3 Hz, 1H, H-23 or H-9), 6.78 (d, *J* = 2.3 Hz, 1H, H-20), 6.78 (d, *J* = 8.3 Hz, 1H, H-23 or H-9), 6.48 (d, *J* = 1.6 Hz, 1H, H-4), 6.03 – 5.82 (m, 3H, H-14, H-17 and H-27), 5.26 – 5.18 (m, 2H, H-18), 5.11 – 4.99 (m, 4H, H-15 and H-28), 4.90 (ddd, *J* = 4.1, 4.1, 1.6 Hz, 1H, H-2), 3.68 (s, 3H, H-25), 3.36 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-13), 3.28 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-26), 3.10 (dd, *J* = 16.5, 3.8 Hz, 1H, H-1), 2.96 (dd, *J* = 16.5, 4.3 Hz, 1H, H-1), 2.83 (dddd, *J* = 14.1, 6.5, 1.3, 1.3 Hz, 1H, H-16), 2.66 (dddd, *J* = 14.1, 8.2, 1.0, 1.0 Hz, 1H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 194.2 (Cq), 157.3 (Cq), 155.5 (Cq), 146.0 (CH), 137.9 (CH), 137.8 (CH), 136.6 (Cq), 133.2 (Cq), 132.7 (CH), 132.1 (Cq), 131.6 (Cq), 130.9 (CH), 129.5 (CH), 129.4 (CH), 125.6 (Cq), 123.2 (CH), 119.6 (CH_2), 115.8 (CH_2), 115.7 (CH_2), 111.3 (CH), 110.4 (CH), 85.1 (CH), 56.0 (CH_3), 49.2 (Cq), 42.0 (CH_2), 40.2 (CH_2), 39.9 (CH_2), 39.4 (CH_2); **HRMS** (ESI^+): $C_{28}H_{28}O_3$ $[M+H]^+$ calcd. 413.2111, found 413.2120; **IR** ν_{max} cm^{-1}:

3076, 3003, 2975, 2916, 2834, 1689, 1495, 1487, 1263, 1239, 1032, 993, 915.

(±)-simonsol F (56): (±)-(4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



To a flame-dried microwave vial was added a solution of enone **336** (26 mg, 0.063 mmol) in dry CH_2Cl_2 (1.5 mL). The solution was cooled to -18 °C and then BCl_3 (0.13 mL of a 1.0 M solution in hexanes, 0.13 mmol) was added dropwise. The vial was sealed and was placed in the freezer at -20 °C without stirring for 72 hours. The reaction mixture was removed from the freezer and was kept at -18 °C. To a vigorously stirring solution of CH_3CN/H_2O 95:5 (50 mL) at 0 °C was added the reaction mixture over 15 seconds. The solution was concentrated *in vacuo* at 35 °C. Purification by graduated column chromatography (petroleum ether/EtOAc, 9:1 to 7:3) gave simonsol F (**56**) as a colourless oil which solidified to give a colourless solid* (18 mg, 72%) ****m.p.** 97–99 °C, and enone **336** as a yellow oil (5 mg, 18%).



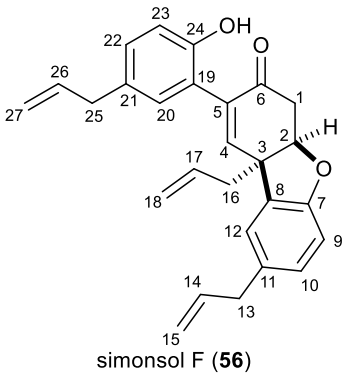
To a flame-dried microwave vial was added methyl simonsol F **336** (200 mg, 0.484 mmol) and dry CH_2Cl_2 (3.0 mL). The solution was cooled to 0 °C and then BCl_3 (0.90 mL of a 1.0 M solution in hexanes, 0.90 mmol) was added dropwise over

2 minutes. The resulting solution was stirred for 5.5 hours at 0 °C. In a separate flask open to air was added CH_3CN (4.5 mL) and H_2O (0.5 mL) which was cooled to 0 °C and was stirred rapidly. The reaction mixture was quickly withdrawn into a syringe and was injected into the rapidly stirring CH_3CN/H_2O mixture at 0 °C over 10-20 seconds. To the quenched reaction mixture in CH_3CN/H_2O was added H_2O (20 mL) and the organics were extracted with CH_2Cl_2 (5 x 10 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (distilled pentane/distilled Et_2O, 7:3 to 1:1) gave methyl simonsol F **336** as a yellow oil (15 mg, 8%) and simonsol F (**56**) as an off white solid* (164 mg, 85% (brsm 92%)) ****m.p.** 97–99 °C.

*Residual Et_2O must be removed for solid to form. This was accomplished by azeotroping with $CHCl_3$ followed by cooling to -20 °C for 18 hours.

**Previously reported as a gum.[104,105]

A crystal of simonsol F (**56**) was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).



simonsol F (**56**)

simonsol F (56): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 – 7.45 (m, 1H, ArOH), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H, H-10), 7.04 – 6.99 (m, 2H, H-20 and H-22), 6.86 (d, *J* = 8.2 Hz, 1H, H-9), 6.77 (d, *J* = 8.2 Hz, 1H, H-23), 6.77 (d, *J* = 2.3 Hz, 1H, H-12), 6.62 (d, *J* = 1.7 Hz, 1H, H-4), 6.01 – 5.80 (m, 3H, H-14, H-17 and H-26), 5.32 – 5.23 (m, 2H, H-18), 5.11 – 5.02 (m, 4H, H-15 and H-27), 4.88 (ddd, *J* = 4.1, 3.2, 1.7 Hz, 1H, H-2), 3.34 (ddd, *J* = 6.9, 1.6, 1.6 Hz, 2H, H-13), 3.30 (ddd, *J* = 6.9, 1.6, 1.6 Hz, 2H, H-25), 3.21 (dd, *J* = 16.8, 3.2 Hz, 1H, H-16), 2.99 (dd, *J* = 16.8, 4.2 Hz, 1H, H-16), 2.91 (dddd, *J* = 14.2, 7.0, 1.3, 1.3 Hz, 1H, H-1), 2.73 (dddd, *J* = 14.0, 7.9, 1.0, 1.0 Hz, 1H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 199.4 (Cq), 157.2 (Cq), 152.4 (Cq), 150.8 (CH), 137.72 (CH), 137.71 (CH), 137.6 (Cq), 133.7 (Cq), 132.3 (Cq), 132.2 (CH), 130.73 (CH), 130.69 (Cq), 130.3 (CH), 129.8 (CH), 124.3 (Cq), 123.2 (CH), 120.2 (CH_2), 118.8 (CH), 116.0 (CH_2), 115.8 (CH_2), 110.6 (CH), 84.4 (CH), 49.6 (Cq), 41.5 (CH_2), 40.4 (CH_2), 39.8 (CH_2), 39.4 (CH_2); **^{1}H NMR** (400 MHz, acetone-d_6) δ: 8.03 (s, 1H, OH), 7.27 (d, *J* = 1.8 Hz, 1H, H-12), 7.02 (dd, *J* = 8.2, 1.8 Hz, 1H, H-10), 6.96 (dd, *J* = 8.2, 2.3 Hz, 1H, H-22), 6.75 (d, *J* = 8.2 Hz, 1H, H-23), 6.74 (d, *J* = 8.2 Hz, 1H, H-9), 6.73 (d, *J* = 2.3 Hz, 1H, H-20), 6.67 (d, *J* = 1.8 Hz, 1H, H-4), 6.05 – 5.83 (m, 3H, H-14, H-17 and H-26), 5.35 – 5.15 (m, 2H, H-18), 5.09 – 4.92 (m, 5H, H-2, H-15 and H-27), 3.35 (d, *J* = 6.7 Hz, 2H, H-13),

3.23 (d, *J* = 6.7 Hz, 2H, H-25), 3.09 (dd, *J* = 16.5, 4.1 Hz, 1H, H-1), 3.04 – 2.94 (m, 2H, H-1 and H-16), 2.79 (dd, *J* = 14.2, 8.1 Hz, 1H, H-16); **^{13}C NMR** (101 MHz, acetone-d_6) δ: 195.5 (Cq), 158.2 (Cq), 153.7 (Cq), 148.1 (CH), 139.03 (CH), 139.02 (CH), 137.3 (Cq), 134.11 (CH), 134.05 (Cq), 132.8 (Cq), 131.6 (Cq), 131.5 (CH), 130.1 (CH), 129.9 (CH), 125.1 (Cq), 124.6 (CH), 119.6 (CH_2), 116.8 (CH), 115.6 (CH_2), 115.5 (CH_2), 110.6 (CH), 85.7 (CH), 50.1 (Cq), 41.6 (CH_2), 40.7 (CH_2), 40.3 (CH_2), 39.8 (CH_2); **HRMS** (ESI$^+$): $C_{27}H_{26}O_3$ $[M+H]^+$ calcd. 399.1955, found 399.1951; **IR** ν_{max} cm^{-1}: 3377, 3077, 3004, 2977, 2907, 1670, 1487, 1211, 993, 915, 821.

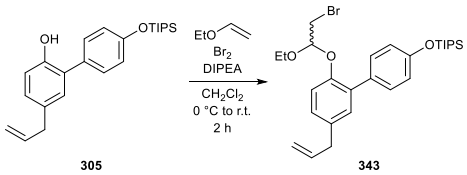
Nat. **56**[104]	Syn. **56**	Dif.	Nat. **56**[104]	Syn. **56**	Dif.
199.1	199.4	0.3	124.2	124.3	0.1
157.1	157.2	0.1	123.1	123.2	0.1
152.3	152.4	0.1	120.1	120.2	0.1
150.5	150.8	0.3	118.5	118.8	0.3
137.6	137.7	0.1	115.8	116	0.2
137.6	137.7	0.1	115.7	115.8	0.1
137.4	137.6	0.2	110.4	110.6	0.2
133.6	133.7	0.1	84.3	84.4	0.1
132.1	132.3	0.2	49.5	49.6	0.1
132.1	132.2	0.1	41.4	41.5	0.1
130.6	130.7	0.1	40.3	40.4	0.1
130.5	130.7	0.2	39.7	39.8	0.1
130.2	130.3	0.1	39.2	39.4	0.2
129.7	129.8	0.1			

Table 15. *Comparison (Dif. = difference (Syn. – Nat. ^{13}C δ value)) of natural (Nat.) versus synthetic (Syn.) simonsol F (**56**) ^{13}C NMR spectroscopy data in $CDCl_3$.*[104,105]

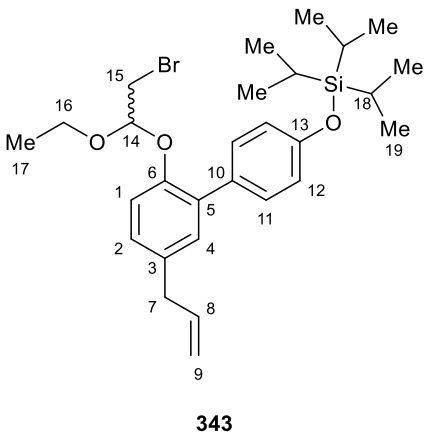
Spectroscopic data obtained for synthetic simonsol F (**56**) were in excellent agreement with the natural sample.[104,105]

7.1.4: Synthesis of simonsol G (Section 2.1.7)

343: ((5'-allyl-2'-(2-bromo-1-ethoxyethoxy)-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane



To a solution of ethyl vinyl ether (2.60 mL, 27.2 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C was added bromine (1.09 mL, 21.2 mmol) over 10 minutes. The solution was stirred for 20 minutes at 0 °C and then a solution of biaryl **305** (3.24 g, 8.45 mmol) and DIPEA (5.92 mL, 34.0 mmol) in CH_2Cl_2 (14.0 mL) was added over 15 minutes at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 1.5 hours. The organics were diluted with EtOAc (100 mL) and were washed with $NaHCO_3$ (2 x 50 mL of a saturated aqueous solution), then brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2, 7:3) afforded acetal **343** as a colourless oil (4.22 g, 94%).

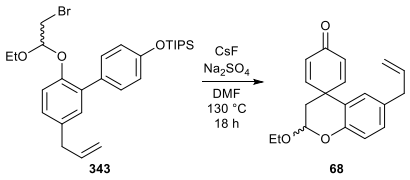


343

343: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 – 7.36 (m, 2H, H-11), 7.17 – 7.14 (m, 1H, H-4), 7.09 – 7.07 (m, 2H, H-1 and H-2), 6.93 – 6.89 (m, 2H, H-12), 5.98 (dddd, *J* = 16.8, 10.0, 6.7, 6.7 Hz, 1H, H-8), 5.15 – 5.04 (m, 3H, H-9 and H-14), 3.62 (dq, *J* = 9.3, 7.0 Hz, 1H, H-16), 3.45 (dq, *J* = 9.3, 7.0 Hz,

1H, H-16), 3.38 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-7), 3.35 – 3.28 (m, 2H, H-15), 1.36 – 1.21 (m, 3H, H-18), 1.15 – 1.10 (m, 21H, H-17 and H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.5 (Cq), 151.8 (Cq), 137.6 (CH), 135.2 (Cq), 133.2 (Cq), 131.2 (CH), 131.0 (Cq), 130.8 (CH), 128.2 (CH), 119.6 (CH), 119.0 (CH), 116.0 (CH_2), 102.7 (CH), 63.1 (CH_2), 39.7 (CH_2), 31.7 (CH_2), 18.1 (CH_3), 15.1 (CH_3), 12.9 (CH); **HRMS** (ESI^+): $C_{28}H_{41}{}^{79}BrO_3Si$ $[M+Na]^+$ calcd. 555.1901, found 555.1911; **IR** ν_{max} cm^{-1}: 2943, 2892, 2866, 1606, 1512, 1487, 1262, 909, 882, 838, 676.

68: 6-allyl-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

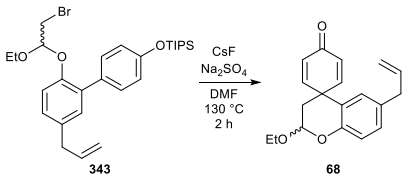


343 68

To an oven-dried flask was added Na_2SO_4 (68.6 g, 483 mmol) and CsF (7.34 g, 48.3 mmol) and the flask was cooled under argon, after which dry DMF (380 mL) was added and the suspension was heated to 130 °C. To the suspension was added a solution of acetal **343** (5.13 g, 9.65 mmol) in dry DMF (16.0 mL) over 15 hours. Upon full addition, the reaction mixture stirred for a further 3 hours at 130 °C. The reaction mixture was cooled to room temperature, filtered, and then concentrated *in vacuo*. The organics were dissolved in EtOAc (150 mL) and were washed with water (50 mL), then brine (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

Purification by graduated column chromatography (petroleum ether/Et_2O, 4:1 to 7:3) afforded spirocycle **68** as a yellow oil. To the oil was added Et_2O (~1.0-2.0 mL (until homogenous)) followed by pentane (20 mL) and the mixture was cooled to -20 °C for 16 hours. A precipitate formed which was collected by suction filtration and the filter cake was washed with pentane (3 x 5 mL) which gave **68** as a colourless solid (2.43 g, 85%) **m.p.** 44–46 °C. The filtrate was concentrated which gave **68** as a yellow oil* (90% purity by ^1H NMR spectroscopy, 339 mg, 11% yield).

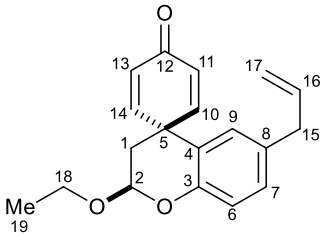
*The yellow 10% impurity was the desilylated non-cyclized derivative of acetal **343**. Separation is possible by first TIPS protecting the free-phenol impurity under standard conditions followed by graduated column chromatography (petroleum ether/Et_2O, 9:1 to 3:2).



343 68

Split evenly between two flame-dried flasks cooled under argon was added Na_2SO_4 (7.10 g, 50.0 mmol), dry DMF (500 mL) and CsF (2.28 g, 15.0 mmol mmol). The suspensions were heated to 130 °C and then a solution of acetal **343** (2.66 g, 5.00 mmol) in dry DMF (16.0 mL) was added over 5 minutes between the two flasks and the reaction mixtures were heated at 130 °C for 1.5 hours. The reaction mixtures were cooled to room temperature and the organics were combined, filtered through cotton wool, and concentrated *in vacuo*. The organics were dissolved in Et_2O (100 mL)

and were washed with brine (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 4:1) gave spirocycle **68** as an off-white solid (1.26 g, 85%).



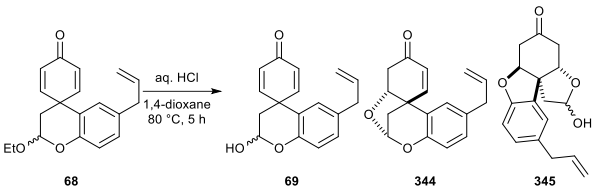
68

68: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, *J* = 10.1, 2.9 Hz, 1H, H-10), 7.02 (dd, *J* = 8.3, 2.2 Hz, 1H, H-7), 6.87 (d, *J* = 8.3 Hz, 1H, H-6), 6.80 (dd, *J* = 10.0, 2.9 Hz, 1H, H-14), 6.69 (d, *J* = 2.2 Hz, 1H, H-9), 6.35 (dd, *J* = 10.0, 1.9 Hz, 1H, H-13), 6.22 (dd, *J* = 10.1, 1.9 Hz, 1H, H-11), 5.87 (dddd, *J* = 17.6, 9.5, 6.7, 6.7 Hz, 1H, H-16), 5.37 (dd, *J* = 3.1, 3.1 Hz, 1H, H-2), 5.06 – 4.98 (m, 2H, H-17), 3.92 (dq, *J* = 9.6, 7.1 Hz, 1H, H-18), 3.64 (dq, *J* = 9.6, 7.1 Hz, 1H, H-18), 3.24 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-15), 2.26 (dd, *J* = 14.1, 2.9 Hz, 1H, H-1), 2.12 (dd, *J* = 14.1, 3.3 Hz, 1H, H-1), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 186.2 (Cq), 154.9 (CH), 154.2 (CH), 149.5 (Cq), 137.4 (CH), 133.5 (Cq), 129.8 (CH), 128.7 (CH), 128.5 (CH), 126.2 (CH), 119.4 (Cq), 118.6 (CH), 116.0 (CH_2), 95.7 (CH), 64.5 (CH_2), 40.8 (Cq), 39.4 (CH_2), 36.4 (CH_2), 15.3 (CH_3). **HRMS** (ESI^+): $C_{19}H_{20}O_3$ $[M+H]^+$ calcd. 297.1485, found 297.1476; **IR** ν_{max} cm^{-1}: 2975, 2930, 2895, 1663, 1625, 1494, 1397, 1254, 1175, 915, 853, 823, 684.

69: 6-allyl-2-hydroxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

344: (±)-(6*R*,7a*R*,11a*S*)-2-allyl-7a,8-dihydro-9H-6,11a-methanodibenzo[d,f][1,3]dioxepin-9-one

345: (±)-ketone species



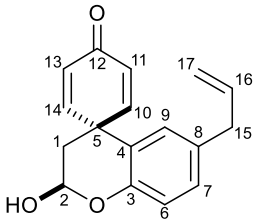
To spirocycle **68** (1.70 g, 5.74 mmol) in 1,4-dioxane (115 mL) was added HCl (115 mL of a 3.0 M aqueous solution, 345 mmol). The reaction mixture was heated at 80 °C open to air for 5 hours. The reaction mixture was cooled to room temperature, diluted with H_2O (200 mL) and the organics were extracted with CH_2Cl_2 (4 x 115 mL). The organics were combined and were washed with brine (115 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/EtOAc, 9:1 to 1:1) gave several products that have been summarised below:

- enone **344** as a light-yellow solid and subsequent trituration with 2-propanol gave enone **344** a colourless solid (95 mg, 6%) **m.p.** 115–117 °C.
- dienone **69** as an off-white solid which was dissolved in a minimum amount of Et_2O and then pentane was added until precipitation was observed. The mixture was cooled to -20 °C for 16 hours and then the precipitate was collected by suction

filtration. The filter cake was washed with pentane (3 x 3 mL) which gave dienone **69** as a colourless solid (326 mg, 21%) **m.p.** 143–145 °C.

- a mixture of dienone **69** and inseparable[323] ketone diastereoisomers **345** (major/minor, 13:7) as a yellow solid to which the filtrate from the trituration of **69** was added. The mixture was purified by graduated flash column chromatography (petroleum ether/Et_2O, 7:3 to 1:4) which gave:
    - dienone **69** as a colourless solid (330 mg, 21%).
    - an inseparable[323] mixture of diastereotopic ketones **345** (major/minor, 13:7) as a colourless solid (661 mg, 40%).

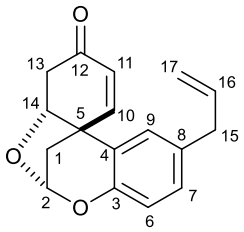
A crystal of the inseparable[323] mixture of diastereotopic ketones **345** was grown by vapour diffusion method from distilled pentane/distilled Et_2O (see Section 6.9).



69

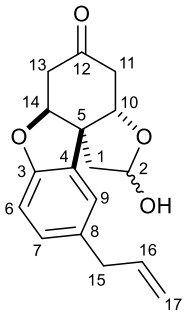
69: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, *J* = 10.1, 3.0 Hz, 1H, H-10), 7.04 (dd, *J* = 8.3, 2.2 Hz, 1H, H-7), 6.87 (d, *J* = 8.3 Hz, 1H, H-9), 6.85 (dd, *J* = 10.0, 3.0 Hz, 1H, H-14), 6.71 (d, *J* = 2.2 Hz, 1H, H-9), 6.35 (dd, *J* = 10.0, 1.9 Hz, 1H, H-13), 6.28 (dd, *J* = 10.1, 1.9 Hz, 1H, H-11), 5.86 (dddd, *J* = 18.2, 9.4, 6.7, 6.7 Hz, 1H, H-16), 5.77 (ddd, *J* = 4.2, 4.2, 2.8 Hz, 1H, H-2), 5.05 – 4.98 (m, 2H, H-17),

3.30 (dd, *J* = 4.1, 1.6 Hz, 1H, OH), 3.24 (ddd, *J* = 6.4, 1.4, 1.4 Hz, 2H, H-15), 2.26 (ddd, *J* = 14.0, 2.8, 1.6 Hz, 1H, H-1), 2.16 (dd, *J* = 14.0, 4.3 Hz, 1H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 186.1 (Cq), 154.5 (CH), 153.7 (CH), 149.6 (Cq), 137.3 (CH), 133.8 (Cq), 123.0 (CH), 128.6 (Cq), 128.3 (CH), 126.9 (CH), 119.1 (Cq), 118.6 (CH), 116.1 (CH_2), 90.9 (CH), 41.0 (Cq), 39.4 (CH_2), 37.0 (CH_2); **HRMS** (ESI^+): $C_{17}H_{16}O_3$ $[M+H]^+$ calcd. 269.1172, found 269.1180; **IR** ν_{max} cm^{-1}: 3339, 3076, 3057, 2976, 2928, 1657, 1614, 1493, 1129, 1029, 860.



344

344: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, *J* = 10.3 Hz, 1H, H-11), 7.04 (dd, *J* = 8.3, 2.1 Hz, 1H, H-9), 6.83 (d, *J* = 8.3 Hz, 1H, H-6), 6.79 (d, *J* = 2.1 Hz, 1H, H-7), 6.29 (dd, *J* = 10.3, 0.9 Hz, 1H, H-10), 5.97 – 5.86 (m, 2H, H-2 and H-16), 5.10 – 5.02 (m, 2H, H-17), 4.78 (dd, *J* = 11.3, 6.6 Hz, 1H, H-14), 3.31 (ddd, *J* = 6.8, 1.6, 1.6 Hz, 2H, H-15), 2.85 (ddd, *J* = 16.1, 6.6, 1.0 Hz, 1H, H-13), 2.52 (dd, *J* = 16.1, 11.4 Hz, 1H, H-13), 2.47 – 2.44 (m, 2H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 196.5 (Cq), 149.5 (Cq), 146.8 (CH), 137.4 (CH), 133.0 (Cq), 131.3 (CH), 130.4 (Cq), 129.5 (CH), 124.3 (CH), 116.9 (CH), 116.0 (CH_2), 100.2 (CH), 87.4 (CH), 44.1 (Cq), 43.5 (CH_2), 39.5 (CH_2), 36.3 (CH_2); **HRMS** (ESI^+): $C_{17}H_{16}O_3$ $[M+H]^+$ calcd. 269.1172, found 269.1176; **IR** ν_{max} cm^{-1}: 3076, 3000, 2920, 2837, 1685, 1492, 1210, 1140, 1050, 1039, 982, 890.



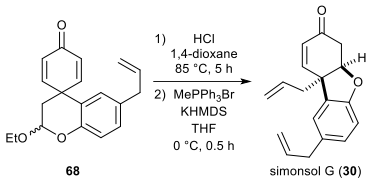
345

345: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 1.8 Hz, 1H, H-major 9), 7.08 – 7.01 (m, 2H, H-major 7 and H-minor 7), 6.98 (d, *J* = 1.8 Hz, 1H, H-minor 9), 6.75 (d, *J* = 8.1 Hz, 2H, H-major 7 and H-minor 7), 6.01 – 5.89 (m, 2H, H-major 16 and H-minor 16), 5.76 – 5.70 (m, 2H, H-major 2 and H-minor 2), 5.12 – 5.04 (m, 4H, H-major 17 and H-minor 17), 4.96 (ddd, *J* = 3.1, 3.1, 1.0 Hz, 1H, H-minor 14), 4.72 (ddd, *J* = 3.0, 3.0, 1.0 Hz, 1H, H-major 14), 4.42 (ddd, *J* = 3.0, 3.0, 1.0 Hz, 1H, H-major 10), 4.18 (ddd, *J* = 3.1, 3.1, 1.0 Hz, 1H, H-minor 10), 3.54 (dd, *J* = 18.4, 3.5 Hz, 1H, H-minor 13), 3.39 – 3.32 (m, 4H, H-major 15 and H-minor 15), 3.07 (s, 1H, minor OH), 2.98 – 2.89 (m, 2H, H-major 13 and H-minor 13), 2.81 (s, 1H, major OH), 2.77 – 2.63 (m, 5H, H-major 11, H-major 13, H-minor 11), 2.41 – 2.34 (m, 2H, H-major 1), 2.31 (dd, *J* = 17.8, 2.5 Hz, 1H, H-minor 1), 2.23 (d, *J* = 14.2 Hz, 1H, H-minor 1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 207.1 (Cq minor), 205.9 (Cq major), 158.0 (Cq minor), 157.8 (Cq major), 137.72 (CH major), 137.68 (CH minor), 133.9 (Cq major), 133.3 (Cq minor), 130.0 (CH minor), 129.8 (CH major), 128.9 (Cq minor), *, 123.7 (CH major), 123.0 (CH minor), 116.02 (CH_2 minor), 115.95 (CH_2 major), 110.12 (CH major), 110.11 (CH minor), 98.4 (CH minor), 97.7 (CH major), 87.9 (CH minor), 87.8 (CH major), 84.7 (CH minor), 81.3 (CH major), 52.8 (Cq major), 51.7 (Cq minor), 46.4 (CH_2 major), 45.8 (CH_2 minor), 40.3 (CH_2 minor), 40.2 (CH_2 minor), 39.89 (CH_2 major), 39.87 (CH_2 minor), 39.2 (CH_2 major),

39.0 (CH_2 major); **HRMS** (ESI^-): $C_{17}H_{18}O_4$ $[M-H]^-$ calcd. 285.1132, found 285.1138; **IR** ν_{max} cm^{-1}: 3410, 2903, 1714, 1486, 1246, 1212, 1041, 917.

*Quaternary carbon from major diastereoisomer was not observed.

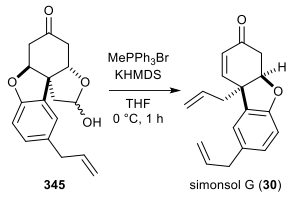
(±)-simonsol G (30): (±)-(4a*R*,9b*R*)-8,9b-diallyl-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



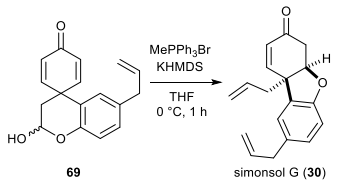
To a solution of dienone acetal **68** (1.01 g, 3.41 mmol) in 1,4-dioxane (68.0 mL) was added HCl (68.0 mL of a 3.0 M aqueous solution, 204 mmol). The reaction mixture was heated at 85 °C for 5 hours. The reaction mixture was cooled to room temperature and then H_2O (200 mL) was added. The organics were extracted with CH_2Cl_2 (4 x 100 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave a crude yellow oil.

In a separate flame-dried flask was added methyltriphenylphosphonium bromide (4.86 g, 13.6 mmol) and dry THF (90.0 mL). To the suspension at 0 °C was added KHMDS (11.9 mL of a 1.0 M solution in THF, 11.9 mmol) over 15 minutes. The ylide mixture was stirred at 0 °C for 0.5 hours after which a solution of the previously prepared crude yellow oil in dry THF (90.0 mL) was added over 30 minutes at 0 °C. After addition, the reaction mixture was

stirred for a further 0.5 hours at 0 °C and then H_2O (100 mL) and brine (50 mL) were added. The organics were extracted with Et_2O (3 x 80 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/acetone, 9:1 to 4:1) gave simonsol G (**30**) as a pale-yellow oil (543 mg, 60%).

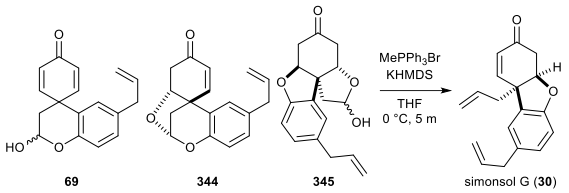


To a flame-dried flask was added methyltriphenylphosphonium bromide (135 mg, 0.378 mmol) and dry THF (1.60 mL). The suspension was cooled to 0 °C and KHMDS (0.32 mL of a 1.0 M solution in THF, 0.32 mmol) was added over 15 minutes. The yellow solution was stirred for 0.75 hours at 0 °C and then a solution of ketone **345** (18 mg, 0.063 mmol) in dry THF (1.60 mL) was added over 30 minutes at 0 °C. Upon full addition, the reaction mixture was stirred for 60 minutes at 0 °C and then H_2O (10 mL) and brine (3 mL) were added. The organics were extracted with Et_2O (2 x 20 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/Et_2O, 85:15 to 3:2) gave simonsol G (**30**) as a colourless oil (11 mg, 65%).



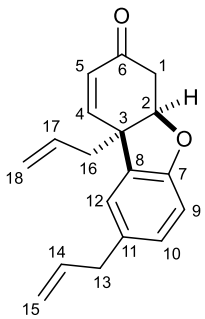
To a flame-dried flask was added methyltriphenylphosphonium bromide (100 mg, 0.280 mmol) and dry THF (2.50 mL). The

suspension was cooled to 0 °C and KHMDS (0.24 mL of a 1.0 M solution in THF, 0.24 mmol) was added over 15 minutes. The yellow solution was stirred for 0.75 hours at 0 °C and then a solution of hemi-acetal **69** (25 mg, 0.093 mmol) in dry THF (2.50 mL) was added over 30 minutes at 0 °C. Upon full addition, the reaction mixture was stirred for 60 minutes at 0 °C and then H_2O (10 mL) and brine (3 mL) were added. The organics were extracted with Et_2O (2 x 20 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/Et_2O, 85:15 to 3:2) gave simonsol G (**30**) as a colourless oil (18 mg, 72%).



To a flame-dried flask was added methyltriphenylphosphonium bromide (700 mg, 1.96 mmol) and dry THF (11.6 mL). The suspension was cooled to 0 °C and KHMDS (1.53 mL of a 1.0 M solution in THF, 1.53 mmol) was added over 15 minutes. The yellow solution was stirred for 0.75 hours at 0 °C and then a solution of **69**, **344** and **345** (95 mg, 45:10:45 mixture respectively, 0.344 mmol) in dry THF (11.6 mL) was added over 30 minutes at 0 °C. Upon full addition, the reaction mixture was stirred for 5 minutes at 0 °C and then H_2O (25 mL) and brine (10 mL) were added. The organics were extracted with Et_2O (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column

chromatography (petroleum ether/EtOAc, 9:1 to 3:2) afforded simonsol G (**30**) as a pale-yellow oil (58 mg, 63%).



simonsol G (**30**)

simonsol G (30): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 – 6.99 (m, 2H, H-10 and H-12), 6.76 – 6.72 (m, 1H, H-9), 6.50 (dd, *J* = 10.2, 1.9 Hz, 1H, H-5), 6.01 (dd, *J* = 10.2, 0.7 Hz, 1H, H-4), 6.00 – 5.87 (m, 1H, H-14), 5.79 (dddd, *J* = 16.9, 10.1, 8.1, 6.7 Hz, 1H, H-17), 5.24 – 5.16 (m, 2H, H-18), 5.11 – 5.04 (m, 2H, H-15), 4.82 (ddd, *J* = 4.6, 2.9, 1.9 Hz, 1H, H-2), 3.35 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-13), 3.00 (ddd, *J* = 17.6, 2.9, 0.8 Hz, 1H, H-1), 2.80 (dddd, *J* = 14.1, 6.7, 1.5, 1.5 Hz, 1H, H-16), 2.76 (dd, *J* = 17.6, 4.2 Hz, 1H, H-1), 2.64 (dddd, *J* = 14.1, 8.1, 1.0, 1.0 Hz, 1H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 195.5 (Cq), 157.2 (Cq), 148.6 (CH), 137.8 (CH), 133.5 (Cq), 132.3 (CH), 131.2 (Cq), 129.6 (CH), 127.4 (CH), 123.1 (CH), 119.8 (CH_2), 115.9 (CH_2), 110.4 (CH), 84.9 (CH), 48.6 (Cq), 40.8 (CH_2), 39.9 (CH_2), 38.9 (CH_2); **^{1}H NMR** (500 MHz, acetone-d_6) δ: 7.24 (d, *J* = 1.8 Hz, 1H, H-12), 7.02 (dd, *J* = 8.1, 1.8 Hz, 1H, H-10), 6.71 (d, *J* = 8.1 Hz, 1H, H-9), 6.66 (dd, *J* = 10.2, 1.9 Hz, 1H, H-4), 6.04 – 5.81 (m, 2H, H-14 and H-17), 5.91 (d, *J* = 10.2 Hz, 1H, H-5), 5.30 – 5.15 (m, 2H, H-18), 5.09 – 4.98 (m, 2H, H-15), 4.91 – 4.88 (m, 1H, H-2), 3.35 (ddd, *J* = 6.6, 1.5 Hz, 2H, H-13), 2.93 (dddd, *J* = 14.2, 7.2, 1.4, 1.4 Hz, 1H, H-16), 2.88 – 2.83 (m, 2H, H-1), 2.77 – 2.72 (m, 1H, H-16); **^{13}C NMR** (126 MHz, acetone-d_6) δ: 195.2 (Cq), 158.1 (Cq), 149.5 (CH), 139.0 (CH), 134.1 (Cq), 133.9 (CH), 132.6

(Cq), 130.0 (CH), 127.5 (CH), 124.5 (CH), 119.6 (CH_2), 115.7 (CH_2), 110.5 (CH), 85.7 (CH), 49.5 (Cq), 40.5 (CH_2), 40.3 (CH_2), 39.4 (CH_2); **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 7.23 (d, *J* = 1.9 Hz, 1H, H-12), 6.98 (dd, *J* = 8.1, 1.9 Hz, 1H, H-10), 6.73 (d, *J* = 8.1 Hz, 1H, H-9), 6.67 (dd, *J* = 10.2, 1.9 Hz, 1H, H-4), 5.94 (dddd, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-14), 5.92 (dd, *J* = 10.2, 0.9 Hz, 1H, H-5), 5.79 (dddd, *J* = 17.4, 10.1, 7.4 Hz, 1H, H-17), 5.27 – 5.11 (m, 2H, H-18), 5.09 – 5.01 (m, 2H, H-15), 4.88 – 4.84 (m, 1H, H-2), 3.31 (d, *J* = 6.7 Hz, 2H, H-13), 2.90 (dd, *J* = 17.5, 3.9 Hz, 1H, H-1), 2.85 (dddd, *J* = 14.0, 7.4, 1.2 Hz, 1H, H-16), 2.78 (ddd, *J* = 17.5, 2.7, 0.9 Hz, 1H, H-1), 2.70 (dddd, *J* = 14.0, 7.4, 1.1 Hz, 1H, H-16); **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 195.2 (Cq), 156.6 (Cq), 149.4 (CH), 138.0 (CH), 132.9 (CH), 132.8 (Cq), 131.3 (Cq), 128.9 (CH), 126.2 (CH), 123.9 (CH), 119.4 (CH_2), 115.6 (CH_2), 109.5 (CH), 84.2 (CH), 48.2(Cq), 39.0 (CH_2), 38.8 (CH_2), 38.5 (CH_2); **HRMS** (ESI^+): $C_{18}H_{18}O_2$ $[M+H]^+$ calcd. 267.1380, found 267.1380; **IR** ν_{max} cm^{-1}: 3054, 2923, 2854, 1685, 1486, 1265, 1250, 996, 733, 703.

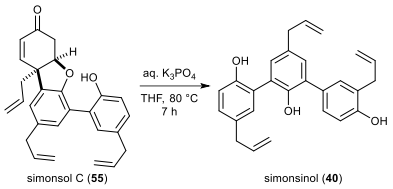
Rep. Syn. **30**[21]	Syn. **30**	Dif.	Rep. Syn. **30**[21]	Syn. **30**	Dif.
195.2	195.5	0.3	122.9	123.1	0.2
157	157.2	0.2	119.6	119.8	0.2
148.4	148.6	0.2	115.7	115.9	0.2
137.5	137.8	0.3	110.1	110.4	0.3
133.2	133.5	0.3	84.6	84.9	0.3
132.1	132.3	0.2	48.4	48.6	0.2
131	131.2	0.2	40.5	40.8	0.3
129.4	129.6	0.2	39.6	39.9	0.3
127.1	127.4	0.3	38.7	38.9	0.2

Table 16. *Comparison (Dif. = difference (Syn. – Rep. Syn. ^{13}C δ value)) of reported synthetic (Rep. Syn.) versus synthetic (Syn.) simonsol G (**30**) ^{13}C NMR spectroscopy data in $CDCl_3$.*[21] *Only ^{1}H NMR spectroscopy data in $CDCl_3$ was reported for natural simonsol G (**30**).*[101]

Spectroscopic data obtained for synthetic simonsol G (**30**) were in excellent agreement with both natural[101] and synthetic samples.[21,22]

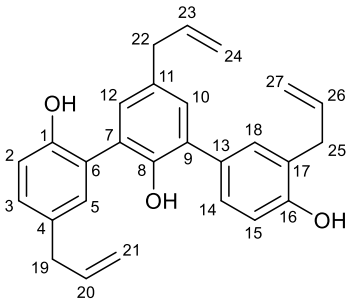
7.1.5: Synthesis of simonsinol, macranthol, and honokiol (Section 2.2.1)

simonsinol (40): 3'',5,5'-triallyl-[1,1':3',1''-terphenyl]-2,2',4''-triol



To a solution of simonsol C (**55**) (11 mg, 0.028 mmol) in THF (60 µL) was added K_3PO_4 (0.11 mL of a 0.5 M aqueous solution, 0.06 mmol) and the reaction mixture was heated in a sealed tube at 80 °C for 7 h. The organics were diluted with EtOAc (2 mL), washed with H_2O (2 x 2 mL), then brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane/EtOAc, 2:1) gave simonsinol (**40**) as a colourless solid (10 mg, 91%) ***m.p.** 69–71 °C.

*Previously reported as an oil.[92]


simonsinol (**40**)

simonsinol (40): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 – 7.27 (m, 2H, H-6 and H-14), 7.14 (dd, *J* = 8.0, 1.8 Hz, 1H, H-4), 7.13 – 7.11 (m, 2H, H-10 and H-12), 7.09 (d, *J* = 2.2 Hz, 1H, H-18), 6.98 (d, *J* = 8.1 Hz, 1H, H-3), 6.93 (d, *J* = 7.9 Hz, 1H, H-15), 6.08 – 5.94 (m, 3H, H-20, H-23 and H-26), 5.76 (s, 1H, ArOH), 5.59 (s, 1H, ArOH), 5.24 – 5.17 (m, 2H, H-27), 5.15 – 5.04 (m, 5H, H-21, H-24 and ArOH), 3.47 (ddd, *J* = 6.4, 1.6, 1.6 Hz, 2H, H-25), 3.40 (ddd, *J* = 7.4, 1.4, 1.4 Hz, 2H, H-19), 3.38 (ddd, *J* = 7.4, 1.4, 1.4 Hz, 2H, H-22); **^{13}C NMR** (126 MHz,

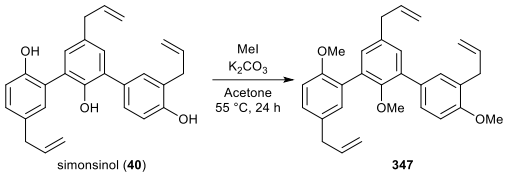
$CDCl_3$) δ: 154.2 (Cq), 151.9 (Cq), 147.4 (Cq), 137.8 (CH), 137.5 (CH), 136.1 (CH), 133.3 (Cq), 133.0 (Cq), 131.4 (CH), 131.3 (CH), 131.0 (CH), 130.6 (CH), 129.9 (CH), 129.5 (Cq), 128.9 (CH), 128.8 (Cq), 126.4 (Cq), 124.9 (Cq), 124.5 (Cq), 117.3 (CH), 117.2 (CH_2), 116.7 (CH), 116.1 (CH_2), 115.8 (CH_2), 39.6 (2x CH_2), 35.4 (CH_2); **HRMS** (ESI^-) $C_{27}H_{26}O_3$ $[M-H]^-$ calcd. 397.1809, found 397.1805; **IR** ν_{max} cm^{-1}: 3594, 3536, 3047, 3005, 1638, 1499, 1461, 1250, 1183, 931.

Nat. **40**[92]	Syn. **40**	Dif.		Nat. **40**[92]	Syn. **40**	Dif.
154.1	154.2	0.1		129.7	129.9	0.2
151.7	151.9	0.2		129.4	129.5	0.1
147.4	147.4	0		128.9	128.9	0
133.1	133.3	0.2		128.7	128.8	0.1
132.8	133	0.2		126.4	126.4	0
131.3	131.4	0.1		124.9	124.9	0
131.2	131.3	0.1		124.5	124.5	0
130.8	131	0.2		117.7	117.3	-0.4[a]
130.5	130.6	0.1		116.4	116.7	0.3

Table 17. *Comparison (Dif. = difference (Syn. – Nat. ^{13}C δ value)) of natural (Nat.) versus synthetic (Syn.) simonsinol (**40**) ^{13}C NMR spectroscopy data in $CDCl_3$.*[92] *The ^{13}C NMR spectral data for the allyl groups of natural simonsinol (**40**) was not provided by the authors due to overlapped signals.*[92] *For full comparison, see permethylated simonsinol **347**. **a)** Likely typographical error as no signal was observed between 117.3 ppm to 124.5 ppm for synthetic simonsinol (**40**).*

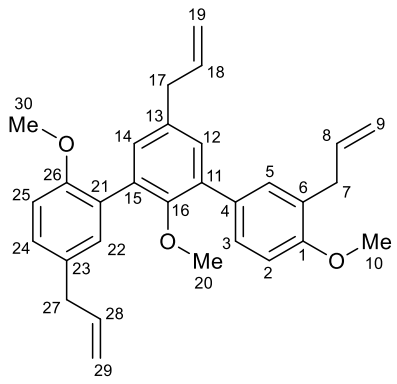
Spectroscopic data obtained for synthetic simonsinol (**56**) were in excellent agreement with the natural sample.[92] Due to the overlapped signals in the ^{13}C NMR spectral data, full comparison was made against permethylated simonsinol **347**.

347: 3'',5,5'-triallyl-2,2',4''-trimethoxy-1,1':3',1''-terphenyl



simonsinol (**40**) **347**

To a solution of simonsinol (**40**) (7 mg, 0.02 mmol) in acetone (2 mL) was added iodomethane (0.11 mL, 1.76 mmol) and K_2CO_3 (121 mg, 0.877 mmol). The reaction mixture was heated at 55 °C in a sealed tube for 24 hours. The reaction mixture was allowed to cool to room temperature and was then filtered through a short pad of celite. The organics were concentrated *in vacuo* which gave permethylated simonsinol **347** as a colourless oil (8 mg, >90% yield).



347

347: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.4, 2.3 Hz, 1H, H-24), 7.39 (d, *J* = 2.3 Hz, 1H, H-22), 7.15 (dd, *J* = 8.3, 2.2 Hz, 1H, H-3), 7.14 – 7.12 (m, 2H, H-5 and H-12 or H-14), 7.03 (d, *J* = 2.4 Hz, 1H, H-12 or H-14), 6.92 (d, *J* = 8.3 Hz, 1H, H-2), 6.90 (d, *J* = 8.4 Hz, 1H, H-25), 6.08 – 5.93 (m, 3H, H-8, H-18 and H-28), 5.17 – 5.00 (m, 6H, H-9, H-19 and H-29), 3.87 (s, 3H, H-30),

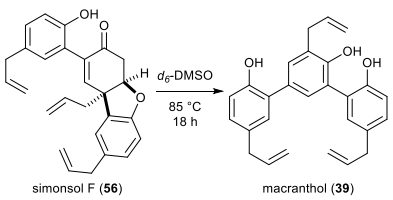
3.78 (s, 3H, H-20), 3.43 (ddd, *J* = 7.1, 1.6, 1.6 Hz, 1H, H-7), 3.41 (ddd, *J* = 7.1, 1.4, 1.4 Hz, 2H, H-17 or H-27), 3.37 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-17 or H-27), 3.20 (s, 3H, H-10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.6 (Cq), 155.4 (Cq), 153.9 (Cq), 138.0 (CH), 137.6 (CH), 137.2 (CH), 135.0 (Cq), 134.5 (Cq), 132.6 (Cq), 131.9 (Cq), 131.7 (CH), 131.4 (Cq), 130.9 (CH), 130.6 (CH), 130.5 (CH), 128.6 (CH), 128.3 (Cq), 128.2 (Cq), 128.1 (CH), 116.0 (CH_2), 115.6 (CH_2), 115.5 (CH_2), 111.1 (CH), 110.2 (CH), 60.6 (CH), 55.9 (CH), 55.6 (CH), 39.8 (CH_2), 39.5 (CH_2), 34.5 (CH_2); **HRMS** (ESI^+) $C_{30}H_{32}O_3$ $[M+H]^+$ calcd. 441.2424, found 441.2430.

Rep. Syn. **347**[92]	Syn. **347**	Dif.	Rep. Syn. **347**[92]	Syn. **347**	Dif.
156.4	156.6	0.2	128.3	128.6	0.3
155.2	155.4	0.2	128.1	128.3	0.2
153.7	153.9	0.2	128.0	128.2	0.2
137.8	138.0	0.2	127.9	128.1	0.2
137.4	137.6	0.2	115.7	116.0	0.3
137.0	137.2	0.2	115.3	115.6	0.3
134.7	135.0	0.3	115.2	115.5	0.3
134.3	134.5	0.2	110.9	111.1	0.2
132.4	132.6	0.2	110.0	110.2	0.2
131.7	131.9	0.2	60.2	60.6	0.4
131.5	131.7	0.2	55.7	55.9	0.2
131.2	131.4	0.2	55.3	55.6	0.3
130.7	130.9	0.2	39.5	39.8	0.3
130.4	130.6	0.2	39.2	39.5	0.3
130.2	130.5	0.3	34.2	34.5	0.3

Table 18. *Comparison (Dif. = difference (Syn. – Rep. Syn. ^{13}C δ value)) of reported synthetic (Rep. Syn.) versus synthetic (Syn.) permethylated simonsinol* ***347*** *^{13}C NMR spectroscopy data in $CDCl_3$.*[92]

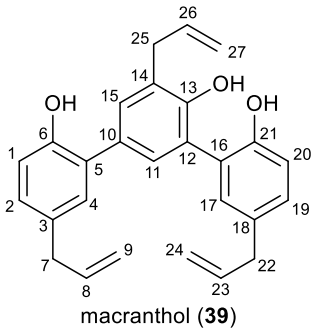
Spectroscopic data obtained for permethylated simonsinol **347** were in excellent agreement with the synthetic sample provided whereby natural simonsinol (**40**) was used as the precursor to **347**.[92]

macranthol (39): 5,5',5''-triallyl-[1,1':3',1''-terphenyl]-2,2'',4'-triol



Simonsol F (**56**) (10 mg, 0.025 mmol) was dissolved in d_6-DMSO (0.55 mL) and was heated in an NMR spectroscopy tube at 85 °C for 18 hours. Analysis by ^{1}H NMR showed complete conversion of simonsol F (**56**) to macranthol (**39**) (see Figure 9, Section 2.2.1). Previous NMR spectral data reported for macranthol (**39**) is analysed in $CDCl_3$. The organics were diluted with Et_2O (10 mL) and were washed with H_2O (3 x 5 mL) then brine (3 x 2 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave macranthol (**39**) as a colourless solid (9 mg, 90%) **m.p.** 136–138 °C (lit. 140–141 °C).[89]

Further experimental methods that have formed macranthol (**39**) are described in Sections 6.2.1 and 6.2.2.



macranthol (39): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.20 (s, 1H, ArOH), 7.25 (d, *J* = 2.3 Hz, 1H, H-15), 7.19 (d, *J* = 2.3 Hz, 1H, H-11), 7.05 – 7.01 (m, 3H, H-2 or H-19, H-4 and H-17), 6.93 – 6.89 (m, 2H, H-2 or H-19 and H-1 or H-20), 6.83 (d, *J* = 8.1 Hz, 1H, H-1 or H-20), 6.08 – 5.88 (m, 3H, H-8, H-23 and H-26), 5.16 – 4.98 (m, 6H, H-9, H-24 and H-27), 3.43 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-H-25), 3.31 (ddd, *J* = 6.5, 1.9, 1.9 Hz, 2H, H-7 or H-22), 3.29 (ddd, *J* = 6.2, 1.8, 1.8 Hz, 2H, H-7 or H-

22); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 152.4 (Cq), 152.0 (Cq), 150.5 (Cq), 138.4 (CH), 138.2 (CH), 137.3 (CH), 131.7 (CH), 130.7 (Cq), 130.3 (Cq), 130.1 (Cq), 130.1 (CH), 129.9 (CH), 129.4 (CH), 128.4 (CH), 127.60 (Cq), 127.58 (CH), 127.1 (Cq), 126.4 (Cq), 125.8 (Cq), 115.9 (CH), 115.7 (CH), 115.44 (CH_2), 115.40 (CH_2), 115.2 (CH_2), 38.8 (CH_2), 38.7 (CH_2), 34.4 (CH_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 2.2 Hz, 1H, H-15), 7.26 (d, *J* = 2.2 Hz, 1H, H-11), 7.15 (dd, *J* = 8.3, 2.3 Hz, 1H, H-2), 7.11 (d, *J* = 2.2 Hz, 1H, H-4), 7.06 (d, *J* = 2.2 Hz, 1H, H-17), 7.06 (dd, *J* = 8.9, 2.2 Hz, 1H, H-19), 6.97 (d, *J* = 8.2 Hz, 1H, H-1), 6.90 (d, *J* = 8.9 Hz, 1H, H-20), 6.07 (dddd, *J* = 16.8, 10.0, 6.7, 1.2 Hz, 1H, H-26), 5.98 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H, H-8), 5.93 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H, H-23), 5.75 – 5.70 (m, 1H, ArOH), 5.49 – 5.38 (m, 1H, ArOH), 5.24 – 5.13 (m, 2H, H-27), 5.13 – 5.11 (m, 1H, ArOH), 5.11 – 5.03 (m, 4H, H-9 and H-24), 3.53 (d, *J* = 6.6 Hz, 2H, H-25), 3.36 (d, *J* = 6.6 Hz, 2H, H-22), 3.35 (d, *J* = 6.6 Hz, 2H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 151.3 (Cq), 151.0 (Cq), 150.9 (Cq), 137.9 (CH), 137.5 (CH), 136.3 (CH), 133.6 (Cq), 132.5 (Cq), 131.4 (CH), 131.0 (CH), 130.40 (CH), 130.35 (CH), 130.2 (Cq), 130.1 (CH), 129.1 (CH), 128.4 (Cq), 127.6 (Cq), 124.9 (Cq), 123.4 (Cq), 116.9 (CH), 116.9 (CH_2), 116.1 (CH_2), 115.9 (CH), 115.8 (CH_2), 39.5 (CH_2), 39.5 (CH_2), 35.2 (CH_2); **HRMS** (ESI^-): $C_{27}H_{26}O_3$ $[M-H]^-$ calcd. 397.1809, found 397.1824; **IR** ν_{max} cm^{-1}: 3514, 3378, 3297, 3196, 3177, 3078, 3004, 2977, 2901, 2832,

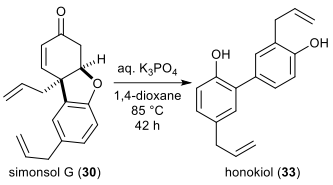
1639, 1610, 1587, 1498, 1468, 1432, 1415, 1360, 1329, 1287, 1270, 1230, 1178, 1127, 994, 910, 820, 788, 729.

Nat. **39**[89]	Syn. **39**	Dif.	Nat. **39**[89]	Syn. **39**	Dif.
151.2	151.3	0.1	129	129.1	0.1
150.9	151	0.2	128.3	128.4	0.1
150.8	150.9	0.1	127.5	127.6	0.1
137.7	137.9	0.2	124.7	124.9	0.2
137.4	137.5	0.1	123.3	123.4	0.1
136.2	136.3	0.1	116.8	116.9	0.1
133.4	133.6	0.2	116.7	116.9	0.2
132.4	132.5	0.1	116	116.1	0.1
131.3	131.4	0.1	115.8	115.9	0.1
130.9	131	0.1	115.6	115.8	0.2
130.3	130.4	0.1	39.4	39.5	0.1
130.3	130.4	0.1	39.3	39.5	0.2
130.2	130.2	0	35	35.2	0.2
130	130.1	0.1	123.3	123.4	0.1

Table 19. *Comparison (Dif. = difference (Syn. – Nat. ^{13}C δ value)) of natural (Nat.) versus synthetic (Syn.) macranthol (**39**) ^{13}C NMR spectroscopy data in $CDCl_3$.*[89]

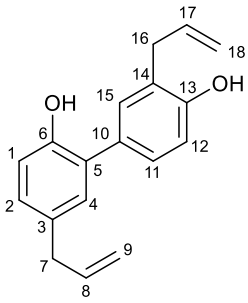
Spectroscopic data obtained for synthetic macranthol (**39**) were in excellent agreement with both natural[89] and synthetic samples.[91]

honokiol (33): 3',5-diallyl-[1,1'-biphenyl]-2,4'-diol



simonsol G (**30**) honokiol (**33**)

To simonsol G (**30**) (20 mg, 75 µmol) in 1,4-dioxane (0.60 mL) and H_2O (0.20 mL) at room temperature was added K_3PO_4 (95 mg, 0.45 mmol). The reaction mixture was heated in a sealed tube at 85 °C for 42 hours and was then cooled to room temperature. The organics were diluted with Et_2O (15 mL) and were then washed with HCl (2 x 5 mL of a 1.0 M aqueous solution), then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (distilled pentane/distilled Et_2O, 7:3) gave honokiol (**33**) as a colourless solid (14 mg, 70%) **m.p.** 89–91 °C (lit. 85–87 °C).[73]



honokiol (**33**)

honokiol (33): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 – 7.20 (m, 2H, H-11 and H-15), 7.05 (dd, J = 8.2, 2.2 Hz, 1H, H-2), 7.02 (d, J = 2.2 Hz, 1H, H-4), 6.92 (d, J = 8.2 Hz, 1H, H-12), 6.90 (d, J = 8.2 Hz, 1H, H-1), 6.11 – 5.90 (m, 2H, H-8 and H-17), 5.25 – 5.16 (m, 2H, H-18), 5.14 – 5.01 (m, 4H, H-9 and 2x OH), 3.46 (ddd, J = 6.4, 1.5, 1.5 Hz, 2H, H-16), 3.35 (ddd, J = 6.7, 1.5, 1.5 Hz, 2H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 154.1 (Cq), 150.9 (Cq), 137.9 (CH), 136.1 (CH), 132.4 (Cq), 131.3 (CH), 130.3 (Cq), 129.8 (CH), 129.0 (CH), 128.7 (CH), 127.8 (Cq), 126.5 (Cq), 117.1 (CH_2), 116.8

(CH), 115.7 (2x CH), 39.6 (CH_2), 35.4 (CH_2); **HRMS** (ESI^-): $C_{18}H_{18}O_2$ $[M-H]^-$ calcd. 265.1234, found 265.1236.

Rep. Syn. **33**[73]	Syn. **33**	Dif.		Rep. Syn. **33**[73]	Syn. **33**	Dif.
153.9	154.1	0.2		128.5	128.7	0.2
150.7	150.9	0.2		127.7	127.8	0.1
137.8	137.9	0.1		126.3	126.5	0.2
135.9	136.1	0.2		116.9	117.1	0.2
132.2	132.4	0.2		116.6	116.8	0.2
131.1	131.3	0.2		115.6	115.7	0.1
130.2	130.3	0.1		115.5	115.7	0.2
129.6	129.8	0.2		39.4	39.6	0.2
128.8	129.0	0.2		35.2	35.4	0.2

Table 20. *Comparison (Dif. = difference (Syn. – Rep. Syn. ^{13}C δ value)) of reported synthetic (Rep. Syn.) versus synthetic (Syn.) honokiol (**33**) ^{13}C NMR spectroscopy data in $CDCl_3$.*[73] *Only ^1H NMR spectroscopy data in $CDCl_3$ was reported for natural honokiol (**33**).*[370]

Spectroscopic data obtained for synthetic honokiol (**33**) were in excellent agreement with both the natural[370] and synthetic samples.[73]

7.2: Transformations of simonsol F

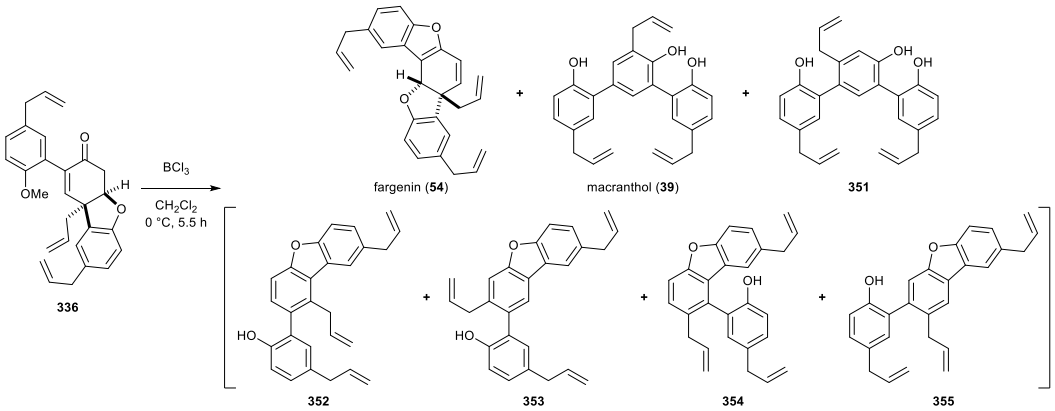
7.2.1: BCl_3-mediated demethylation of 336: $NaHCO_3$ work-up (Section 2.2.2)

(±)-fargenin (54)

macranthol (39): 5,5',5''-triallyl-[1,1':3',1''-terphenyl]-2,2'',4'-triol

351: 5,5'',6'-triallyl-[1,1':3',1''-terphenyl]-2,2'',4'-triol

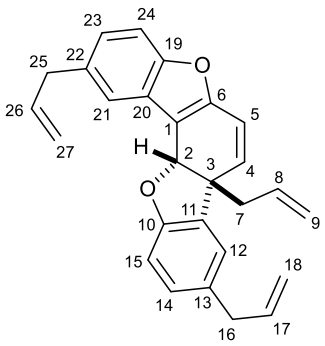
352–355: mixture of four tentatively assigned species



To a flame-dried vial was added methyl simonsol F **336** (645 mg, 1.56 mmol) and dry CH_2Cl_2 (9.4 mL) and the solution was cooled to 0 °C. At 0 °C, BCl_3 (3.1 mL of a 1.0 M solution in hexanes, 3.1 mmol) was added dropwise over 3 minutes. The reaction mixture was stirred for 5.5 hours at 0 °C. To the reaction mixture at 0 °C was added dropwise $NaHCO_3$ (1.0 mL of a saturated aqueous solution that had been pre-cooled to 0 °C) over 3 minutes followed by the addition of further $NaHCO_3$ (9 mL of a saturated aqueous solution that had been pre-cooled to 0 °C) over 2 minutes. The aqueous was diluted with H_2O (20 mL) and the organics were extracted with CH_2Cl_2 (3 x 20

mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (distilled pentane/distilled Et_2O, 9:1 to 3:7) gave several products that have been summarised below:

- fargenin (**54**) as a colourless oil (117 mg, 20%).
- tentatively assigned compounds **352–355** (200 mg, 34%).
- macranthol (**39**) as a yellow oil (80% purity, 115 mg, 15%) which was dissolved in Et_2O (~1 mL) and diluted with pentane (~20 mL). The solution was cooled to -20 °C for 48 hours and a precipitate formed which was collected by suction filtration and was washed with pentane (3 x 3 mL) which gave macranthol (**39**) as a colourless solid (60 mg, 10%). Spectral data were consistent with those previously reported in this thesis as well as with synthetic[91] and natural samples.[89]
- tri-phenol **351** as a yellow oil (80% purity, 82 mg, 11%) which was dissolved in Et_2O (~1 mL) and diluted with pentane (~20 mL). The solution was cooled to -20 °C for 48 hours and a precipitate formed which was collected by suction filtration and was washed with pentane (3 x 3 mL) which gave **351** as a colourless solid (45 mg, 7%) **m.p.** 140–142 °C.
- methyl simonsol F **336** as a yellow oil (21 mg, 3%).



fargenin (**54**)

fargenin (54): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 1.8 Hz, 1H, H-12), 7.37 (d, *J* = 8.4 Hz, 1H, H-15), 7.11 (dd, *J* = 8.4, 1.8 Hz, 1H, H-14), 7.03 (d, *J* = 1.9 Hz, 1H, H-21), 6.93 (dd, *J* = 8.2, 1.9 Hz, 1H, H-23), 6.77 (d, *J* = 8.2 Hz, 1H, H-24), 6.51 (d, *J* = 9.9 Hz, 1H, H-5), 6.10 – 5.90 (m, 2H, H-17 and H-26), 5.98 (d, *J* = 9.9 Hz, 1H, H-4), 5.98 (s, 1H, H-2), 5.61 (dddd, *J* = 17.2, 10.1, 7.3, 7.3 Hz, 1H, H-8), 5.17 – 5.00 (m, 6H, H-9, H-18 and H-27), 3.51 (ddd, *J* = 6.7, 1.6, 1.6 Hz, 2H, H-16), 3.35 (ddd, *J* = 6.4, 1.4, 1.4 Hz, 2H, H-25), 2.69 (dd, *J* = 14.3, 7.3 Hz, 1H, H-7), 2.64 (dd, *J* = 14.3, 7.3 Hz, 1H, H-7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 157.3 (Cq), 154.0 (Cq), 153.2 (Cq), 138.03 (CH), 138.02 (CH), 135.9 (CH), 135.6 (Cq), 132.7 (Cq), 132.2 (CH), 131.8 (Cq), 128.6 (CH), 127.3 (Cq), 125.3 (CH), 123.7 (CH), 119.4 (CH_2), 118.9 (CH), 115.9 (CH_2), 115.7 (CH_2), 115.2 (CH), 111.4 (CH), 109.9 (CH), 108.8 (Cq), 82.0 (CH), 51.3 (Cq), 44.9 (CH_2), 40.4 (CH_2), 39.9 (CH_2); **^{1}H NMR** (400 MHz, acetone-d_6) δ: 7.53 (d, *J* = 1.7 Hz, 1H, H-21), 7.43 (d, *J* = 8.4 Hz, 1H, H-24), 7.25 (d, *J* = 1.8 Hz, 1H, H-12), 7.17 (dd, *J* = 8.4, 1.7 Hz, 1H, H-23), 6.95 (dd, *J* = 8.1, 1.8 Hz, 1H, H-14), 6.71 (d, *J* = 8.1 Hz, 1H, H-15), 6.58 (d, *J* = 10.0 Hz, 1H, H-5), 6.21 (d, *J* = 10.0 Hz, 1H, H-4), 6.06 (s, 1H, H-2), 6.13 – 5.89 (m, 2H, H-17 and H-26), 5.65 (dddd, *J* = 17.3, 10.2, 7.2, 7.2 Hz, 1H, H-8), 5.21 – 4.96 (m, 6H, H-9, H-18 and H-27), 3.53 (d, *J* = 6.8 Hz, 2H, H-25), 3.35 (d, *J* = 6.7 Hz, 2H, H-16),

2.81 (dd, *J* = 14.0, 7.2 Hz, 1H, H-7), 2.68 (dd, *J* = 14.0, 7.2 Hz, 1H, H-7); **^{13}C NMR** (101 MHz, acetone-d_6) δ: 158.1 (Cq), 154.6 (Cq), 154.0 (Cq), 139.2 (CH), 139.0 (CH), 137.5 (CH), 136.5 (Cq), 133.44 (Cq), 133.37 (CH), 132.8 (Cq), 129.2 (CH), 128.1 (Cq), 126.1 (CH), 124.9 (CH), 119.7 (CH), 119.4 (CH_2), 115.9 (CH_2), 115.5 (CH_2), 115.3 (CH), 111.9 (CH), 110.2 (CH), 109.9 (Cq), 82.4 (CH), 52.2 (Cq), 45.4 (CH_2), 40.7 (CH_2), 40.3 (CH_2); **HRMS** (ESI$^+$): $C_{27}H_{24}O_2$ $[M+H]^+$ calcd. 381.1849, found 381.1849; **IR** ν_{max} cm^{-1}: 3076, 3006, 2977, 2900, 2850, 2835, 1637, 1611, 1486, 1455, 1434, 1415, 1331, 1273, 1240, 1192, 1124, 992, 911, 819, 801, 754, 666, 584.

Nat. **54**[88]	RNat. **54**[a]	Syn. **54**	Dif.	Nat. **54**[88]	RNat. **54**[a]	Syn. **54**	Dif.
157.2	157.1	157.3	0.2	119.2	119.3	119.4	0.1
153.9	153.8	154	0.2	119.2	118.8	118.9	0.1
152.3	153.0	153.2	0.2	115.7	115.8	115.9	0.1
137.9	137.9	138	0.1	115.6	115.6	115.7	0.1
137.9	137.9	138	0.1	115	115.1	115.2	0.1
135.5	135.8	135.9	0.1	111.2	111.3	111.4	0.1
135.4	135.4	135.6	0.2	109.8	109.8	109.9	0.1
132.5	132.6	132.7	0.1	108.7	108.8	108.8	0
132.1	132.1	132.2	0.1	81.9	82.0	82	0
131.7	131.6	131.8	0.2	51.2	51.4	51.3	-0.1
128.5	128.5	128.6	0.1	44.7	45.0	44.9	-0.1
127.1	127.1	127.3	0.2	40.2	40.5	40.4	-0.1
125.1	125.1	125.3	0.2	39.7	40.0	39.9	-0.1
123.6	123.6	123.7	0.1				

Table 21. *Comparison (Dif. = difference (Syn. – RNat. ^{13}C δ value)) of natural (Nat.)*[92] *versus raw data natural (RNat.)*[331] *versus synthetic (Syn.) fargenin (**54**) ^{13}C NMR spectroscopy data in $CDCl_3$. Reported data typographical errors highlighted in yellow.* ***a)*** *Raw ^{13}C NMR spectroscopy data that was provided by Prof. Fukuyama has been calibrated to $CHCl_3$ peak (77.16 ppm (+0.16 ppm to chemical shifts observed in ^{13}C NMR spectra (see Figure 15))).*[359]

Spectroscopic data obtained for synthetic fargenin (**54**) were in excellent agreement with the natural sample when compared against the raw ^{13}C NMR spectroscopy data supplied by Prof. Fukuyama.[359]

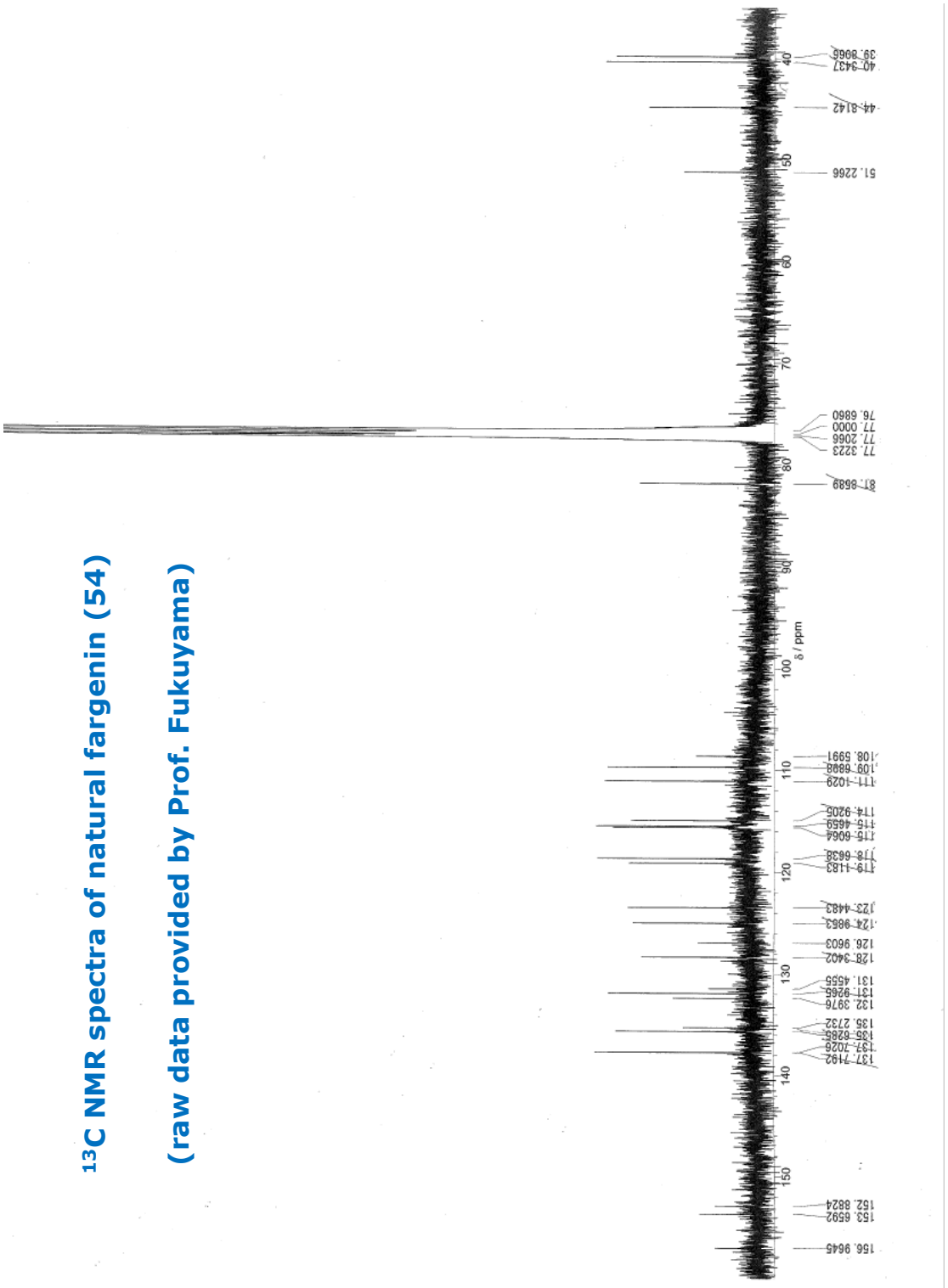
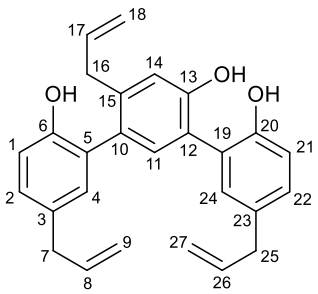


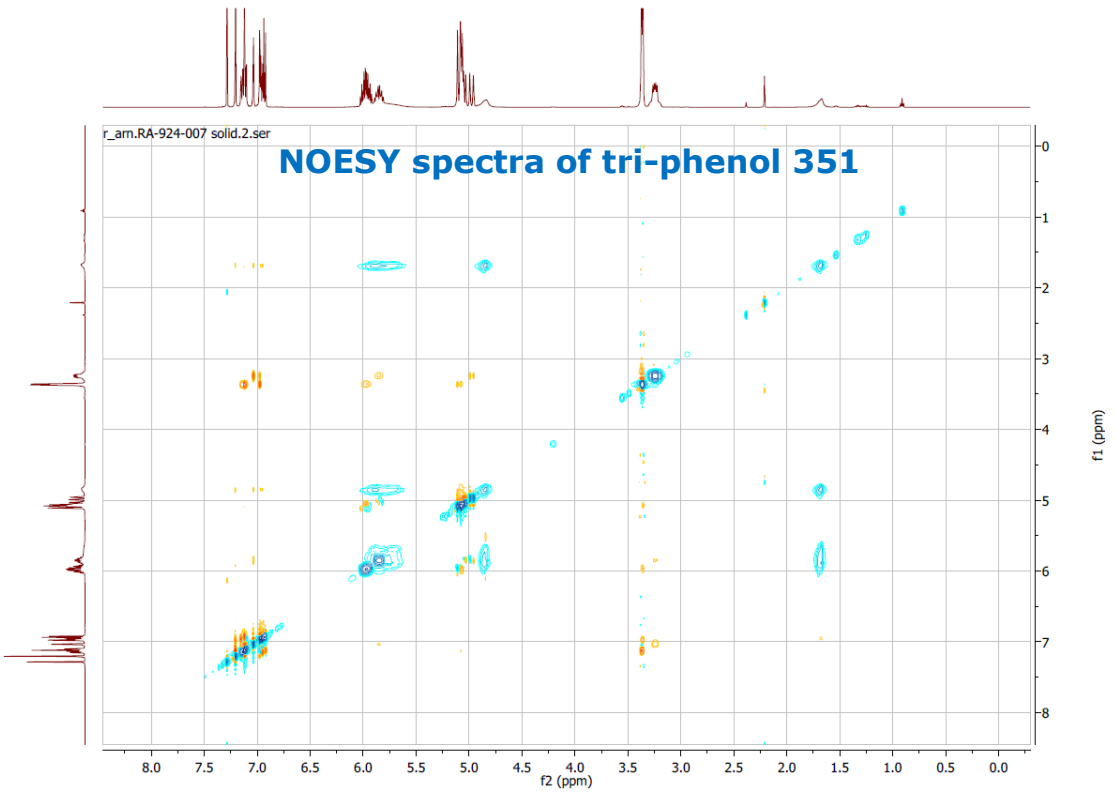
Figure 15. *Raw data: ^{13}C NMR spectra of natural fargenin (**54**).*[359]



351

351: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (s, 1H, H-11), 7.13 (dd, *J* = 8.2, 2.3 Hz, 1H, H-2 or H-22), 7.09 (d, *J* = 2.3 Hz, 1H, H-4 or H-24), 7.09 (dd, *J* = 8.2, 2.3 Hz, 1H, H-2 or H-22), 7.02 (s, 1H, H-14), 6.95 (d, *J* = 2.3 Hz, 1H, H-4 or H-24), 6.94 (d, *J* = 8.2 Hz, 1H, H-1 or H-21), 6.90 (d, *J* = 8.2 Hz, 1H, H-1 or H-21), 6.02 – 5.88 (m, 2H, H-8 and H-26), 5.89 – 5.76 (m, 1H, H-17), 5.82 (s, 1H, ArOH), 5.58 (s, 1H, ArOH), 5.11 – 4.92 (m, 6H, H-9, H-18 and H-27), 4.78 (s, 1H, ArOH), 3.37 – 3.31 (m, 4H, H-7 and H-25), 3.29 – 3.15 (m, 2H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 153.1 (Cq), 151.3 (Cq), 151.0 (Cq), 141.6 (Cq), 137.9 (CH), 137.5 (CH), 136.6 (CH), 133.67 (CH), 133.65 (Cq), 132.0 (Cq), 131.6 (CH), 131.0 (CH), 130.2 (CH), 129.5 (CH), 129.1 (Cq), 126.6 (Cq), 123.4 (Cq), 123.0 (Cq), 118.1 (CH), 116.9 (CH), 116.6 (CH_2), 116.1 (CH_2), 115.7 (CH_2), 115.4 (CH), 39.49 (CH_2), 39.45 (CH_2), 37.5 (CH_2); **HRMS** (ESI^-): $C_{27}H_{26}O_3$ $[M-H]^-$ calcd. 397.1809, found 397.1809; **IR** ν_{max} cm^{-1}: 3689, 3538, 3500, 3393, 3344, 3299, 3103, 3077, 3020, 3004, 2977, 2937, 2904, 2844, 2833, 1638, 1613, 1588, 1562, 1490, 1430, 1411, 1397, 1351, 1326, 1285, 1229, 1182, 1114, 993, 913, 867, 822, 790, 561.

Assigned structure of **351** supported by NOESY (see Figure 16).



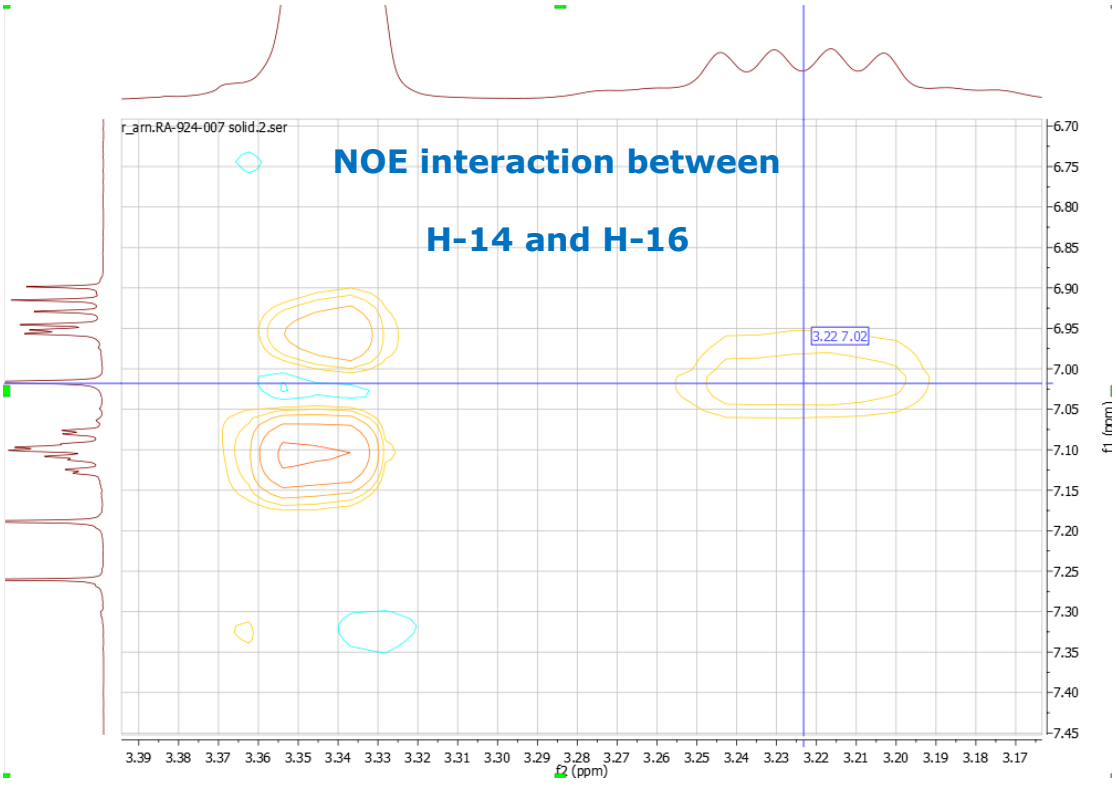
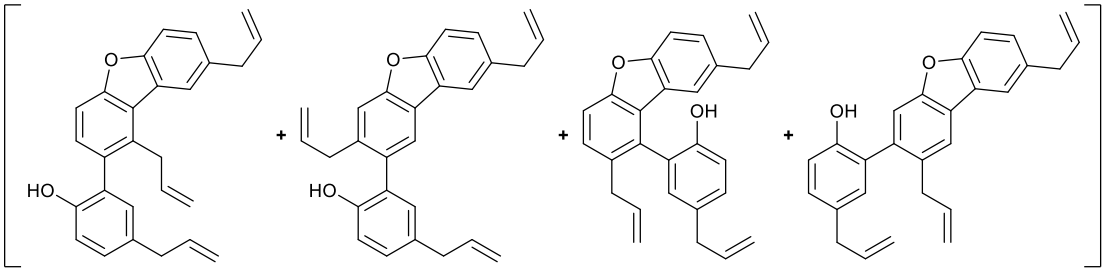


Figure 16. NOESY spectra of **351** that provides evidence for the structure drawn.

352, 353, 354, 355: tentatively assigned structures



352 353 354 355

The structures were tentatively assigned based on the following observations:

- HRMS (ESI$^-$): $C_{27}H_{24}O_2$ $[M-H]^-$ calcd. 379.1704, found 379.1705. This was the only peak observed in the trace.
- The LC-MS trace showed two separated peaks, each associated with a compound with the chemical formula $C_{27}H_{24}O_2$.
- ^{1}H NMR spectroscopy: singlets are present in the aromatic region which would correspond to 1,2,4,5-tetrasubstituted arene species (associated with **353** and **355**). The singlets were confirmed to be signals from C-H and not OH by HSQC.
- ^{1}H and ^{13}C NMR spectroscopy: no diastereotopic protons associated with a tetrahydrodibenzofuran core observed.
- ^{13}C NMR spectroscopy: No carbonyl peak observed.
- ^{13}C NMR spectroscopy: 9 signals (3 sets of 3) associated with phenolic quaternary carbons (157.0–151.0 ppm) observed which indicates that there are only 3 of the four tentatively assigned compounds present in the mixture.

^{1}H and ^{13}C NMR spectroscopy data is reported without assignment and the integration values of proton signals have been deleted. Chemical shift value inaccuracies are present in the data due to overlapping signals

352–**355**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 1.8 Hz), 7.81 (s), 7.79 (d, *J* = 1.7 Hz), 7.76 (d, *J* = 1.7 Hz), 7.69 (d, *J* = 1.7 Hz), 7.56 (d, *J* = 8.5 Hz), 7.54 (d, *J* = 1.5 Hz), 7.53 (d, *J* = 1.4 Hz), 7.49 (d, *J* = 8.4 Hz), 7.44 (d, *J* = 3.6 Hz), 7.43 (d, *J* = 3.6 Hz), 7.35 (d, *J* = 8.3 Hz), 7.32 (dd, *J* = 8.4, 1.8 Hz), 7.29 (dd, *J* = 8.5, 1.8 Hz), 7.25 (dd, *J* = 8.4, 2.1 Hz), 7.19 (dd, *J* = 8.4, 1.9 Hz), 7.14 (dd, *J* = 8.3, 2.0 Hz), 7.13 (d, *J* = 7.8 Hz), 7.11 (dd, *J* = 8.4, 2.1 Hz), 7.05 (d, *J* = 8.1 Hz), 7.04 (d, *J* = 2.4 Hz), 7.00 (d, *J* = 4.3 Hz), 7.00 (s), 6.96 (d, *J* = 3.2 Hz), 6.95 (d, *J* = 3.2 Hz), 6.60 (d, *J* = 1.8 Hz), 6.14 (ddt, *J* = 16.8, 10.1, 6.7 Hz), 6.09 – 5.93 (m), 5.93 – 5.78 (m), 5.24 – 4.80 (m), 4.66 (d, *J* = 5.6 Hz), 4.56 (s), 3.85 – 3.77 (m), 3.64 (ddt, *J* = 15.9, 5.9, 1.9 Hz), 3.58 – 3.51 (m), 3.42 – 3.30 (m), 3.28 (d, *J* = 6.8 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 157.0, 156.6, 155.44, 155.40, 155.3, 151.5, 151.3, 151.2, 151.0, 139.2, 138.0, 137.93, 137.89, 137.8, 137.7, 137.6, 136.9, 135.6, 135.0, 134.9, 134.8, 134.61, 134.56, 134.0, 132.6, 132.4, 132.0, 131.9, 131.8, 131.2, 131.0, 130.7, 130.43, 130.39, 130.38, 130.3, 129.8, 129.6, 129.5, 129.4, 129.2, 128.9, 128.4, 128.27, 128.25, 128.1, 127.93, 127.89, 127.3, 126.8, 124.2, 124.10, 124.08, 124.04, 123.99, 123.2, 122.90, 122.86, 121.71, 120.70, 120.5, 119.3, 116.9, 116.6, 116.4,

116.1, 116.04, 116.01, 115.9, 115.83, 115.77, 115.71, 115.69, 115.68, 115.6, 115.4, 112.9, 111.9, 111.7, 111.6, 111.5, 111.2, 110.4, 40.3, 40.22, 40.21, 40.1, 39.6, 39.5, 38.2, 37.0, 34.8, 34.1.

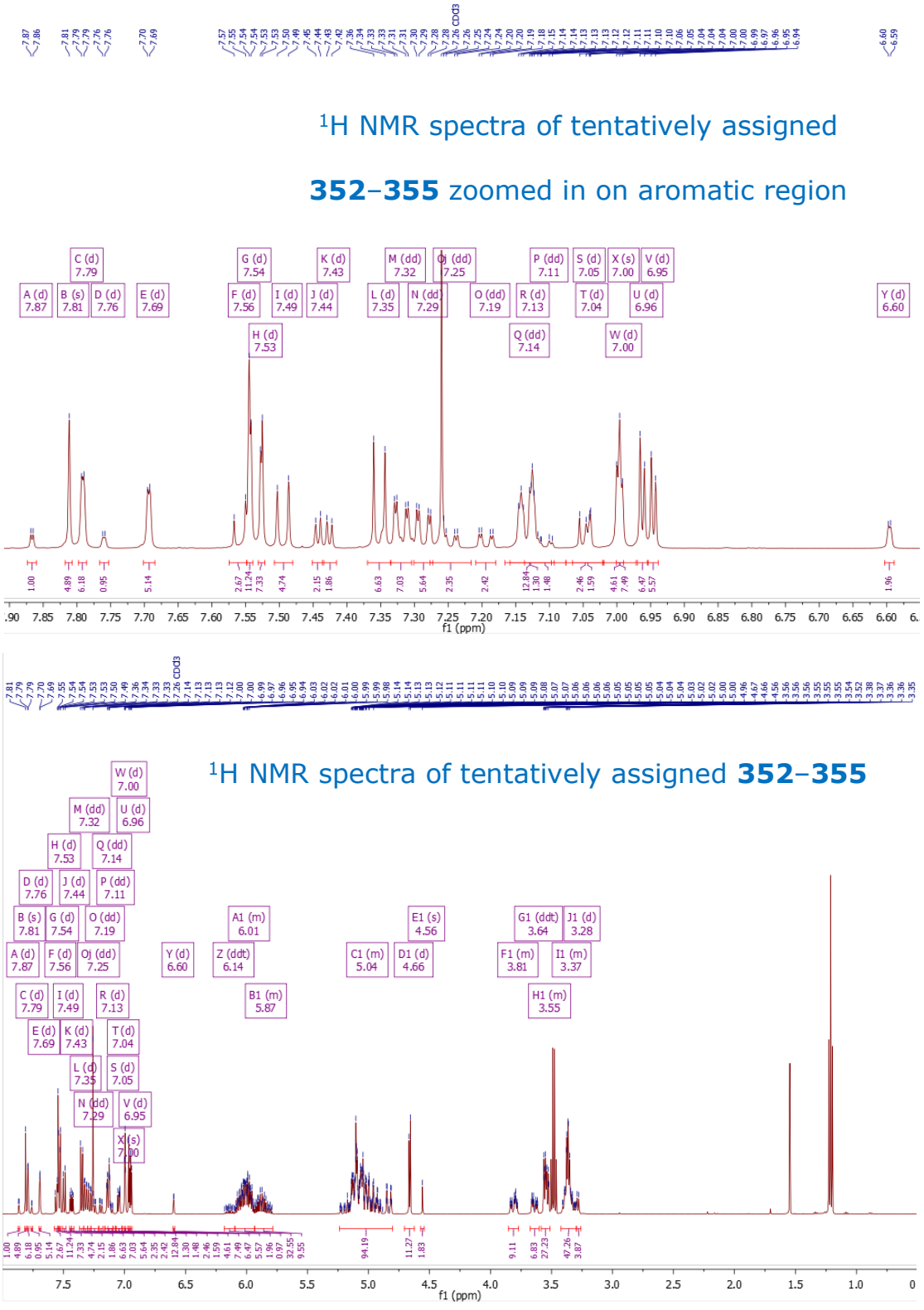


Figure 17. *^{1}H NMR spectra of the mixture of **352–355**.*

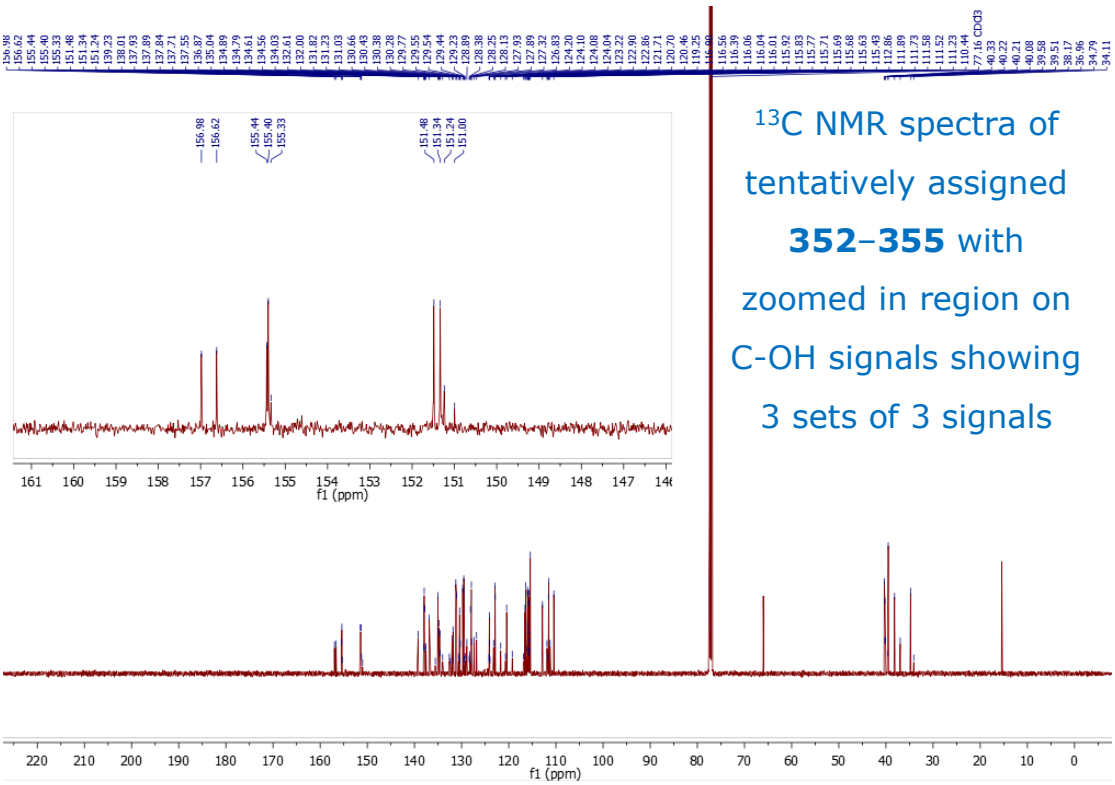
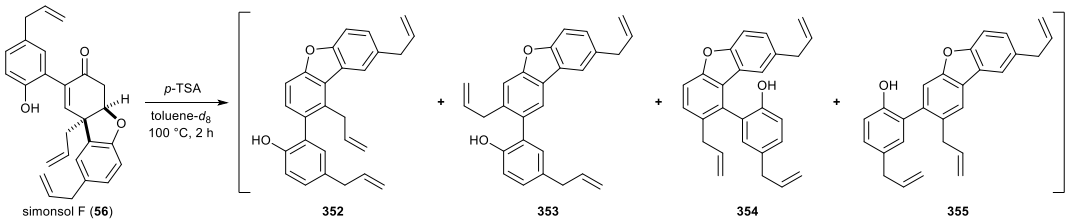
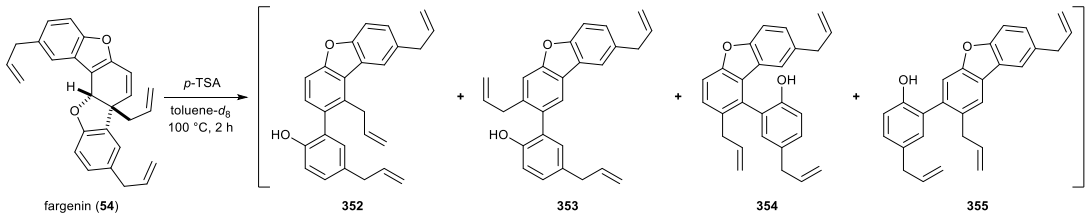


Figure 18. *^{13}C NMR spectra of the mixture of* ***352–355****.*

7.2.1.1: Transformation of simonsol F and fargenin to tentatively assigned 352–355



To a solution of simonsol F (**56**) (7 mg, 20 µmol) in toluene-d_8 (0.60 mL) was added *p*-TSA•H_2O (1 mg, 5 µmol) and the reaction mixture was heated to 100 °C for 2 hours. The reaction mixture was cooled to room temperature and was concentrated *in vacuo*. Purification by flash column chromatography (distilled pentane/distilled Et_2O, 9:1) afforded a mixture of tentatively assigned compounds **352–355** as a colourless oil (6 mg, 86%).

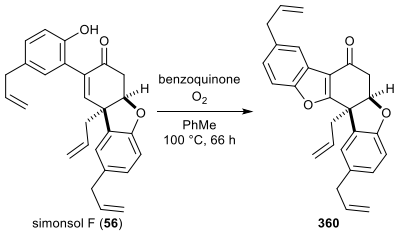


To a solution of fargenin (**54**) (7 mg, 20 μmol) in toluene-d_8 (0.60 mL) was added *p*-TSA•H_2O (1 mg, 5 μmol) and the reaction mixture was heated to 100 °C for 2 hours. The reaction mixture was cooled to room temperature and was concentrated *in vacuo*. Purification by flash column chromatography (distilled pentane/distilled Et_2O, 9:1) afforded a mixture of tentatively assigned compounds **352**–**355** as a colourless oil (6 mg, 86%).

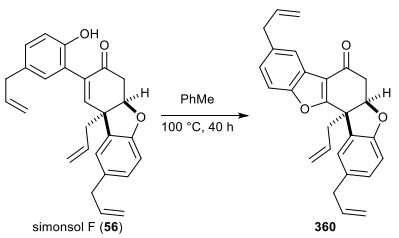
7.2.2: Transformation of simonsol F to benzofuran 360, fargenin, and macranthol (Section 2.2.2)

7.2.2.1: Studies towards a scaled-up synthesis of 360

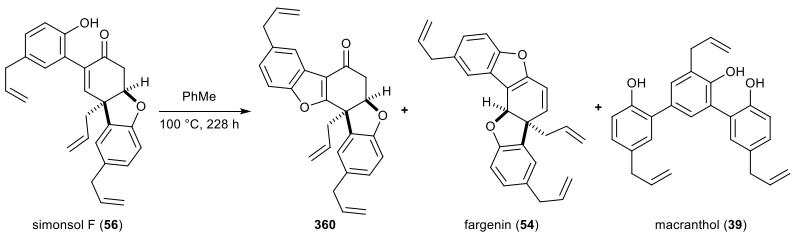
360: (±)-benzofuran simonsol F



A solution of simonsol F (**56**) (20 mg, 0.050 mmol) in PhMe (2.3 mL) was sparged with O_2 for 10 minutes and then benzoquinone (recrystallised from EtOH) (6 mg, 0.06 mmol) was added and the reaction mixture was heated at 100 °C for 66 hours in a sealed microwave vial. The reaction mixture was cooled to room temperature and the organics were concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 7:3 to 1:1) gave benzofuran simonsol F **360** as a yellow oil (5 mg, 25%) (50% yield brsm).



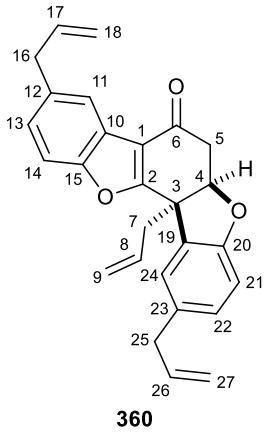
To a flame-dried microwave vial was added simonsol F (**56**) (113 mg, 0.284 mmol) and dry PhMe (10.0 mL). The vial was sealed, and the reaction mixture was heated at 100 °C for 40 hours and was then cooled to room temperature and the organics were concentrated *in vacuo*. Purification by flash column chromatography (pentane/acetone, 4:1) gave benzofuran **360** as a yellow oil (17 mg, 15%) (83% yield brsm).



To a flame-dried microwave vial was added simonsol F (**56**) (165 mg, 0.413 mmol) and dry PhMe (14.4 mL). The vial was sealed, and the reaction mixture was heated at 100 °C for 228 hours (the vial cap was replaced at 72 hours and 144 hours) and was then cooled to room temperature and the organics were concentrated *in vacuo*.* Purification by graduated flash column chromatography (pentane/acetone, 95:5 to 4:1) afforded fargenin (**54**) as a colourless oil (46 mg, 29%), benzofuran **360** as a yellow oil (38 mg, 23%), simonsol F (**56**) as a yellow oil (46 mg, 28%) and macranthol (**39**) as a pale-yellow oil (24 mg, 15%).

*Fargenin (**54**) and macranthol (**39**) were observed in the crude product mixture by ^{1}H NMR spectroscopy. These products likely arose from acid-catalysed pathways and the source of acid was likely from acidic residue on the glassware.

An updated experimental for the synthesis of **360** from simonsol F (**56**) has been provided in Section 7.10.



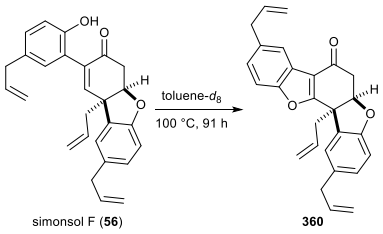
360

360: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 1.8 Hz, 1H, H-11), 7.41 (d, *J* = 8.5 Hz, 1H, H-14), 7.34 (d, *J* = 1.8 Hz, 1H, H-24), 7.15 (dd, *J* = 8.5, 1.8 Hz, 1H, H-13), 6.98 (dd, *J* = 8.2, 1.8 Hz, 1H, H-22), 6.70 (d, *J* = 8.2 Hz, 1H, H-21), 5.96 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 2H, H-17 and H-26), 5.64 (dddd, *J* = 16.6, 10.0, 8.2, 6.5, 6.5 Hz, 1H, H-8), 5.23 – 5.00 (m, 7H, H-4, H-9, H-18 and H-27), 3.46 (d, *J* = 6.7 Hz, 2H, H-16), 3.38 (d, *J* = 6.7 Hz, 2H, H-25), 3.32 (dd, *J* = 14.2, 6.5 Hz, 1H, H-7), 3.19 (dd, *J* = 17.7, 2.7 Hz, 1H, H-5), 2.96 (dd, *J* = 17.7, 4.4 Hz, 1H, H-5), 2.88 (dd, *J* = 14.2, 8.2 Hz, 1H, H-7); **^{13}C NMR*** (101 MHz, $CDCl_3$) δ: 190.8 (Cq), 167.3 (Cq), 157.0 (Cq), 154.0 (Cq), 137.8 (CH), 137.7 (CH), 137.0 (Cq), 133.6 (Cq), 131.9 (CH), 130.0 (CH), 129.2 (Cq), 126.3 (CH), 124.7 (CH), 123.5 (Cq), 122.0 (CH), 120.2 (CH_2), 116.0 (CH_2), 115.9 (CH_2), 111.3 (CH), 110.3 (CH), 86.2 (CH), 49.2 (Cq), 40.8 (CH_2), 40.4 (CH_2), 40.2 (CH_2), 39.8 (CH_2); **^{1}H NMR** (400 MHz, toluene-d_8) δ: 8.10 (d, *J* = 1.8 Hz, 1H, H-11), 7.32 (d, *J* = 1.8 Hz, 1H, H-24), 7.09 (d, *J* = 8.5 Hz, 1H, H-14), 6.80 (dd, *J* = 8.5, 1.8 Hz, 1H, H-13), 6.74 (dd, *J* = 8.2, 1.8 Hz, 1H, H-22), 6.60 (d, *J* = 8.2 Hz, 1H, H-21), 5.93 – 5.73 (m, 2H, H-17 and H-26), 5.27 (dddd, *J* = 16.8, 10.1, 8.1, 6.6 Hz, 1H, H-8), 5.04 – 4.95 (m, 2H, H-18 or H-27), 4.96 – 4.87 (m, 2H, H-18 or H-27), 4.86 – 4.70 (m, 2H, H-9), 4.55 (dd, *J* = 4.3, 2.8 Hz, 1H, H-4), 3.17 (d, *J* = 6.6 Hz, 4H, H-16 and H-25), 3.08 (dd, *J* = 17.5, 2.8 Hz, 1H, H-5), 2.92 (dd, *J* =

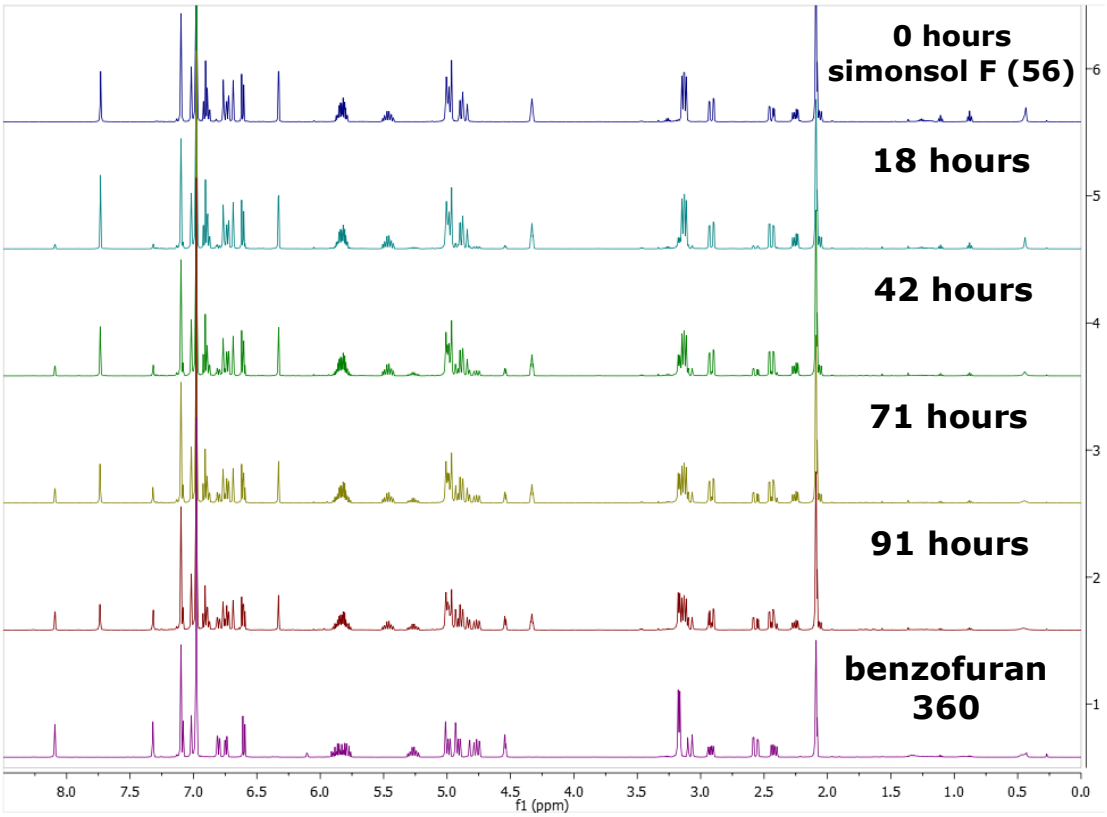
14.1, 6.6 Hz, 1H, H-7), 2.57 (dd, *J* = 17.5, 4.3 Hz, 1H, H-5), 2.42 (dd, *J* = 14.1, 8.1 Hz, 1H, H-7); **^{13}C NMR** (101 MHz, toluene-d_8) δ: 188.9 (Cq), 166.3 (Cq), 157.3 (Cq), 153.9 (Cq), 137.7 (CH), 137.6 (CH), 136.6 (Cq), 133.0 (Cq), 131.8 (CH), 129.7 (CH), 129.4 (Cq), 125.9 (CH), 124.3 (CH), 123.8 (Cq), 122.1 (CH), 119.0 (CH_2), 115.9 (Cq), 115.2 (2 x CH_2), 110.6 (CH), 110.2 (CH), 86.1 (CH), 48.8 (Cq), 40.4 (CH_2), 39.9 (CH_2), 39.8 (CH_2), 39.6 (CH_2); **HRMS** (ESI^+): $C_{27}H_{24}O_3$ $[M+H]^+$ calcd. 397.1798, found 397.1810; **IR** ν_{max} cm^{-1}: 3078, 3005, 2977, 2909, 1681, 1639, 1612, 1587, 1487, 1458, 1435, 1394, 1273, 1249, 1182, 1119, 1082, 1014, 992, 916, 879, 821, 807, 793, 693, 659, 70, 525, 435.

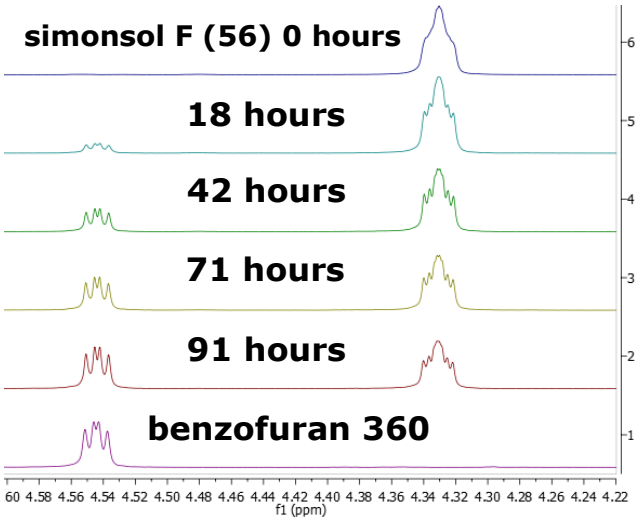
*One quaternary carbon was not observed in $CDCl_3$.

7.2.2.2: ^{1}H NMR spectroscopy study on the conversion of simonsol F to benzofuran 360 in toluene-d_8

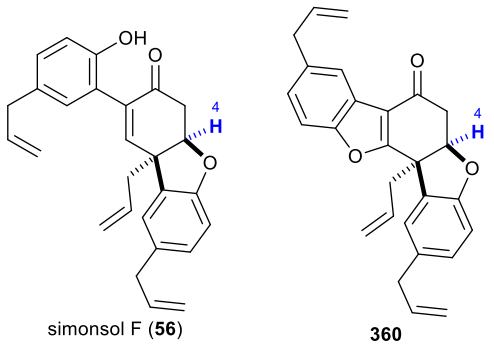


In an NMR tube, a solution of simonsol F (**56**) (7 mg, 0.050 mmol) in toluene-d_8 (0.55 mL) was heated at 100 °C and was analysed by ^{1}H NMR spectroscopy at 18, 42, 71 and 91 hours. A clean conversion of simonsol F (**56**) to benzofuran simonsol F **360** was observed whereby approximately 10–12% of simonsol F (**56**) was converted to benzofuran **360** every 24 hours.





Time (hours)	Ratio 56 : 360		
	56		**360**
0	100	:	0
18	88	:	12
42	76	:	24
71	66	:	34
91	58	:	42



Ratio of **56**:**360** (above) was calculated from the integration values of H-4 (bolded and coloured blue) of simonsol F (**56**) and benzofuran **360**.

Figure 19. *^{1}H NMR spectroscopy study on the thermally promoted conversion of simonsol F (**56**) to benzofuran **360** (toluene-d_8).*

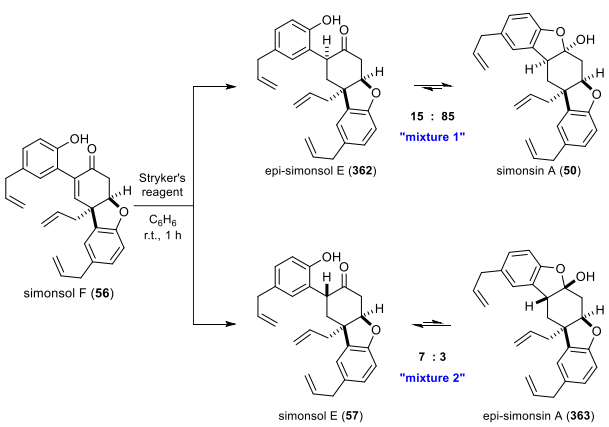
7.2.3: 1,4-Reduction of simonsol F: "mixture 1" and "mixture 2" (Section 2.2.3)

(±)-simonsol E (57): (±)-(2*R*,4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one

(±)-epi-simonsol E (362): (±)-(2*S*,4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one

(±)-simonsin A (50)

(±)-*epi*-simonsin A (363)



A solution of simonsol F (**56**) (50 mg, 0.126 mmol) in C_6H_6 (1.90 mL) was sparged with argon for 5 minutes and then H_2O (6.8 µL) and Stryker's reagent[332] (86 mg, 0.044 mmol) were added. The reaction mixture was sparged with argon for 2 minutes and was then stirred for 1 hour at room temperature. To the reaction mixture was added NH_4Cl (3 mL of a saturated aqueous solution) and the biphasic mixture was stirred for 1 hour at room temperature. The mixture was filtered through cotton wool and the residue was washed with EtOAc (3 x 5 mL). The organics were washed with H_2O (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* which gave a colourless solid. To the solid was

added Et_2O (10 mL) and then the resultant suspension was filtered under suction, and the filter cake was washed with Et_2O (2 x 3 mL). The filtrate was concentrated *in vacuo* which gave a colourless oil (65 mg). The colourless oil was dissolved in acetone (1.50 mL) and to the solution was added CuCl (15 mg). Precipitation did not occur and so the organics were concentrated *in vacuo* to a yellow oil (74 mg). Purification by graduated column chromatography (distilled pentane/distilled Et_2O, 4:1 to 7:3) gave:

- an inseparable[88] 15:85 respective mixture of *epi*-simonsol E (**362**) and simonsin A (**50**) ("mixture 1") as a colourless oil (11 mg, 22%). Further purification by graduated column chromatography (distilled pentane/CH_2Cl_2/distilled Et_2O, 3:7:0 to 25:70:5) gave an inseparable[88] 15:85 respective mixture of *epi*-simonsol E (**362**) and simonsin A (**50**) ("mixture 1") as a colourless oil (10 mg, 20%).
- an inseparable[88] 7:3 respective mixture of simonsol E (**57**) and *epi*-simonsin A (**363**) ("mixture 2") as a colourless oil (35 mg, 71%).

"mixture 1" **HRMS** (ESI^-): $C_{27}H_{28}O_3$ $[M-H]^-$ calcd. 399.1966, found 399.1967.

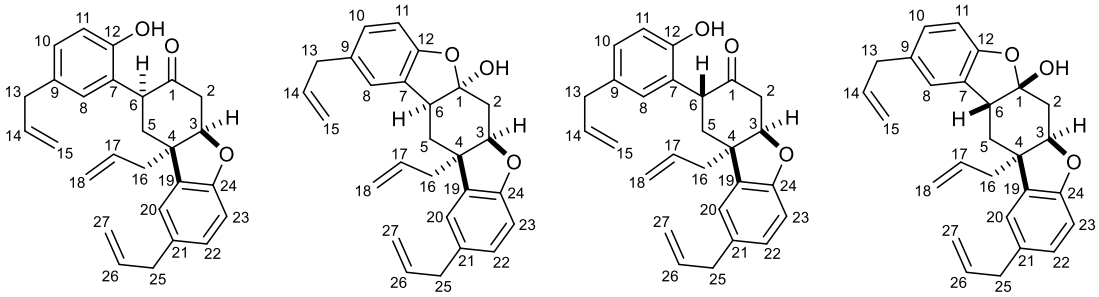
"mixture 2" **HRMS** (ESI^-): $C_{27}H_{28}O_3$ $[M-H]^-$ calcd. 399.1966, found 399.1963.

7.2.3.1: Natural simonsol E (57) v.s. synthetic simonsol E (57) v.s. *epi*-simonsol E (362) ^{1}H and ^{13}C NMR spectroscopy data

The reported natural ^{1}H and ^{13}C NMR spectroscopy data for natural simonsol E (**57**) have been coloured red where discrepancies are observed when compared to synthetic simonsol E (**57**) (see Table 22).

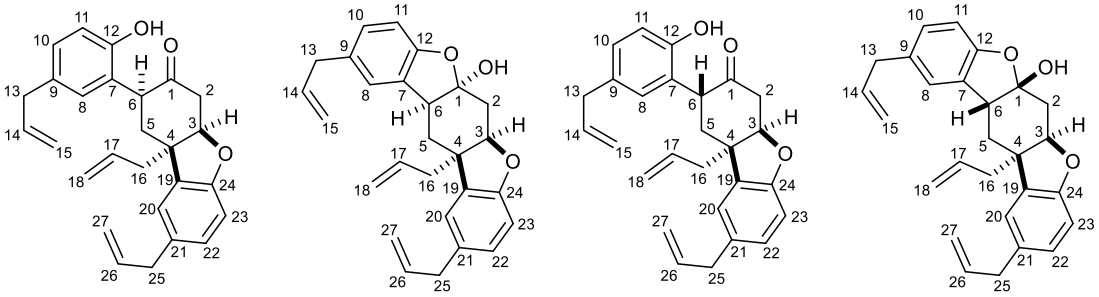
- The ^{1}H NMR spectroscopy assignments for the aryl allyl groups of natural simonsol E (**57**) (H-13 to H-15 and H-25 to H-27) are assigned to the wrong aryl group. Consequently, the corresponding ^{13}C chemical shifts have also been assigned incorrectly. This misassignment likely arose from the misassignment of aromatic protons H-8, H-10, H-20, and H-22 for which the allyl groups were likely assigned after by HMBC.
- The ^{1}H NMR chemical shifts reported for natural simonsol E (**57**) H-16, H-17 and H-18 do not exist in either "mixture 1" or "mixture 2". Also, H-16 has diastereotopic protons which we observed as two chemical shifts from our assignment of "mixture 2". Contrarily, the corresponding ^{13}C data for the alkyl allyl group (C-16 to C-18) matched our data.

What follows is comparison of spectral data, followed by zoomed in NMR spectra that provide evidence to support our reassignments of simonsol E (**57**) (see Figures 20 to 22). Full ^{1}H and ^{13}C NMR spectra are provided after the discussion (see Figures 23 and 24).



Proton No.	simonsol E (**57**) and *epi*-simonsol E (**362**) ^{1}H NMR spectroscopy data (ppm (chemical shift (Hz)))		
	Nat. simonsol E (**57**)	Syn. simonsol E (**57**)	Syn. *epi*-simonsol E (**362**)
1	-	-	-
2	2.82 (dd, 14.0, 12.8) 3.19 (dd, 14.0, 5.5)	2.77 (dd, 16.1, 3.0) 3.18 (dd, 16.1, 3.3)	2.79 (dd, 14.7, 5.4) 3.03 (dd, 14.7, 9.9)
3	5.03 (dd, 12.8, 5.5)	5.04 (m)[a,c]	4.88 (dd, 9.9, 5.4)
4	-	-	-
5	1.97 (dd, 13.5, 11.6) 2.78 (dd, 13.5, 5.2)	1.98 (dd, 13.7, 4.3) 2.80 (m)[a,c]	2.30 (dd, 13.9, 4.5) 2.64 (d, 13.9)
6	2.96 (dd, 11.6, 5.2)	2.98 (dd, 13.5, 4.2)	3.75 (dd, 13.3, 4.4)
7	-	-	-
8	7.13 (d, 2.0)	6.64 (d, 2.3)	6.90 (m)[a,c]
9	-	-	-
10	6.99 (dd, 8.1, 2.0)	6.85 (dd, 8.2, 2.2)	6.90 (m)[a,c]
11	6.70 (d, 8.1)	6.71 (d, 8.1)	6.74 (d, 8.1)
12	-	-	-
13	3.34, (d, 6.5, 2H)	3.20 (d, 6.6)	3.24 (d, 7.1)
14	5.82 (ddt, 16.0, 12.0, 6.5)	5.88 (dddd, 16.8, 10.0, 6.6, 6.6)	5.88 (m)[a,c]
15	4.93 (dd, 12.0, 3.5) 4.95 (dd, 16.0, 3.5)	4.98 (m)[a,c]	4.97 (m)[a,c]
16	2.66 (dt, 6.8, 1.6)	2.61 (13.8, 8.2) 2.68 (dddd, 13.8, 6.5, 1.4, 1.4)	2.67 (dd, 12.7, 8.3) 2.73 (dddd, 12.7, 6.8, 2.3, 2.3)
17	5.76 (ddt, 16.0, 12.0, 6.8)	5.80 (dddd, 16.8, 10.2, 8.2, 6.5)	5.74 (dddd, 16.8, 10.2, 8.3, 6.8)
18	5.11 (ddt, 12.0, 2.5, 1.6) 5.18 (ddt, 16.0, 2.5, 1.6)	5.22 – 5.09 (m)[a,c]	5.22 – 5.10 (m)[a,c]
19	-	-	-
20	6.63 (d, 2.3)	7.13 (d, 1.9)	7.04 (d, 1.9)
21	-	-	-
22	6.85 (dd, 8.0, 2.3)	7.00 (dd, 8.2, 1.9)	6.98 (dd, 8.1, 1.9)
23	6.67 (d, 8.0)	6.67 (d, 8.2)	6.70 (d, 8.1)
24	-	-	-
25	2.75 (dd, 13.6, 3.2) 3.17(dd, 13.6, 4.0)	3.35 (ddd, 6.6, 1.6, 1.6)	3.31 (ddd, 6.6, 1.5, 1.5)
26	5.89 (dddd, 17.0, 12.0, 4.0, 3.2)	5.98 (dddd, 16.8, 10.0, 6.6, 6.6)	5.95 (m)[a,c]
27	5.01 (dd, 12.0, 2.4) 5.04 (dd, 17.0, 2.4)	5.03 (m)[a,c]	5.04 (m)[a,c]
ArOH	8.37	8.26 (s)	8.30 (s)

Table 22 (1 of 2). *See next page for description.*



epi-simonsol E (**362**) | simonsin A (**50**) | simonsol E (**57**) | epi-simonsin A (**363**)

mixture 1 | mixture 2

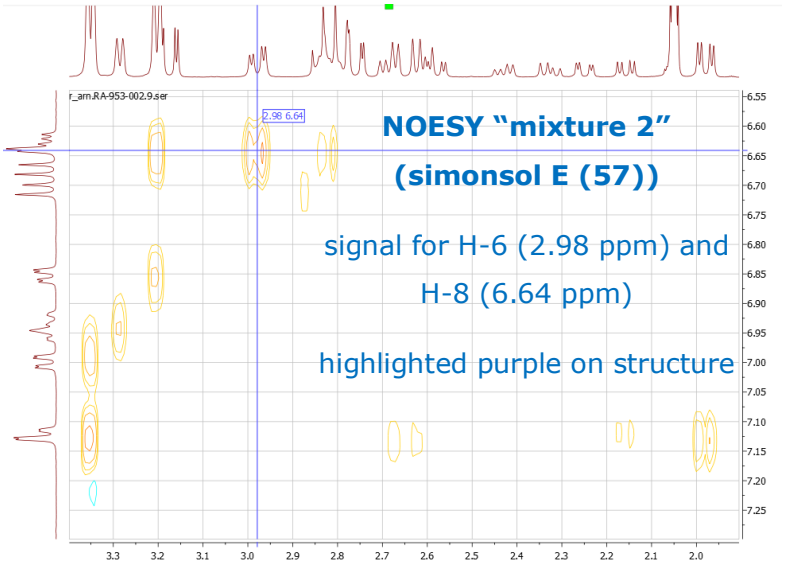
Carbon No.	simonsol E (**57**) and *epi*-simonsol E (**362**) ^{13}C NMR spectroscopy data (ppm)		
	Nat. simonsol E (**57**)	Syn. simonsol E (**57**)[e]	Syn. *epi*-simonsol E (**362**)
1	208.7	208.6 (-0.1)	208.1
2	39.8	43.3 (3.5)	44.6
3	86.0	86.1 (0.1)	85.7
4	48.7	48.8 (0.1)	48.7
5	39.8	39.9 (0.1)	38.7
6	49.3	49.4 (0.1)	48.8
7	128.5	128.5[b] (0)	128.1
8	124.8	131.3 (6.5)	131.3
9	131.6	131.8[b] (0.2)	131.8
10	129.8	128.6 (-1.2)	128.6
11	116.1	116.1 (0)	116.0
12	153.7	153.8 (0.1)	153.7
13	40.2	39.9 (-0.3)	39.9[d]
14	139.3	139.1 (-0.2)	139.17[d]
15	115.3	115.3[d] (0)	115.4[d]
16	45.1	45.2 (0.1)	43.9
17	134.5	134.6 (0.1)	134.8
18	119.4	119.4 (0)	119.2
19	133.4	133.5 (0.1)	135.4
20	131.2	124.9 (-6.3)	124.76
21	134.5	132.8[b] (-1.7)	133.4
22	128.6	129.8 (1.2)	129.4
23	109.6	109.6 (0)	110.2
24	158.9	159.0 (0.1)	157.7
25	43.2	40.2 (-3.0)	40.0[d]
26	139.1	139.3 (0.2)	139.21[d]
27	115.4	115.5[d] (0.1)	115.4[d]

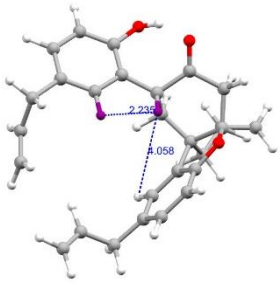
Table 22 (2 of 2). *^{1}H and ^{13}C NMR spectroscopy data of synthetic simonsol E (**57**) and epi-simonsol E (**362**) versus natural simonsol E (**57**). **a)** multiplicity not assigned due to overlapped signals. **b)** simonsol E (**57**) C-7, C-9 and C-21 are not assigned with absolute certainty. However, the signals at 128.5, 131.8, and 132.8 ppm are associated with simonsol E (**57**). **c)** central position (δ (ppm)) of proton signal was found by COSY and HSQC. **d)** ^{13}C NMR spectroscopy signals are interchangeable: simonsol E (**57**) "C-15 and C-27". epi-simonsol E (**362**) "C-15 and C-27", "C-14 and C-26", "C-13 and C-25". **e)** values in parenthesis are the difference in ^{13}C chemical shifts calculated by "Syn. simonsol E (**57**) – Nat. simonsol E (**57**)".*

Reassignment of H-8, H-10, H-13, H-14, H-15, H-20, H-22, H-25, H-26, H-27 and C-8, C-10, C-13, C-14, C-20, C-22, C-25 and C-26 of simonsol E (57): We assigned H-8 (J ~ 2.0 Hz) from the observation of a NOESY interaction between H-6 and H-8. Computational analysis supported our reassignment with calculated distances through space from H-6 to H-8 (2.235 Å) and from H-6 to H-20 (4.058 Å) (see Figure 20).[106] Subsequently, H-10 and H-11 were assigned by HMBC correlations associated with the phenolic signal at 153.7 ppm which was also linked with H-8 (see Figure 20). Also, a signal was seen for H-10 and H-11 by COSY (not provided). The aryl allyl groups were subsequently assigned by HMBC and NOESY correlations with the assigned aromatic protons.

Reassignment of H-2 and C-2 of simonsol E (57): H-3 (assigned by HSQC (distinctive ^{13}C NMR signal 86.1 ppm)) is at 5.04 ppm. By COSY, H-3 is adjacent to two signals which are H-2 at 2.77 ppm (dd, 16.1, 3.0) and 3.18 ppm (dd, 16.1, 3.3). The two protons for H-2 are associated with one ^{13}C signal by HSQC at 43.3 ppm (see Figure 21).

Reassignment of C-21 of simonsol E (57): ^{13}C NMR data for natural simonsol E (**57**) C-21 was assigned as 134.5 ppm however this carbon was not a quaternary carbon (observed by DEPT ^{13}C NMR spectroscopy) (see Figure 22). Therefore, the signal at 134.5 ppm should be solely associated with C-17. The signal at 134.6 ppm is associated with C-17 (CH) of *epi*-simonsin A (**363**).





simonsol E (**57**)

Bond distances calculated using MM derived structure (displayed on Mercury).[106]

(H-6 to H-8 = 2.235 Å)

(H-6 to H-20 = 4.058 Å)

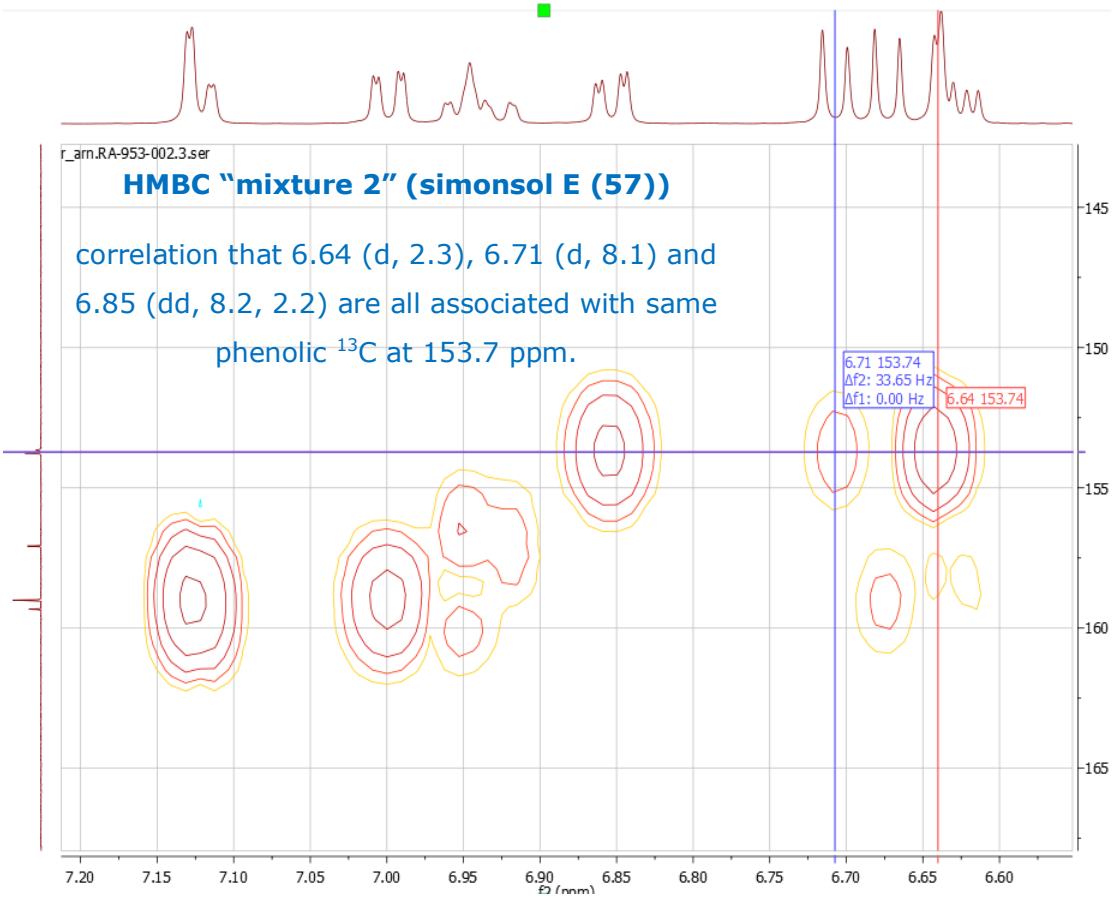


Figure 20. *Evidence by NOESY and HMBC to support the reassignment of H-8, H-10, H-20, and H-22 of simonsol E (**57**) which in turn led to the reassignment of the associated aryl allyl groups. Equilibrium geometry of simonsol E (**57**) was obtained using the wB97X-D/6-31G* level of theory (in vacuo) from MM derived structure.*[106] *Subsequently, distances from H-6 to H-8 and H-6 to H-20 were acquired from Mercury.*

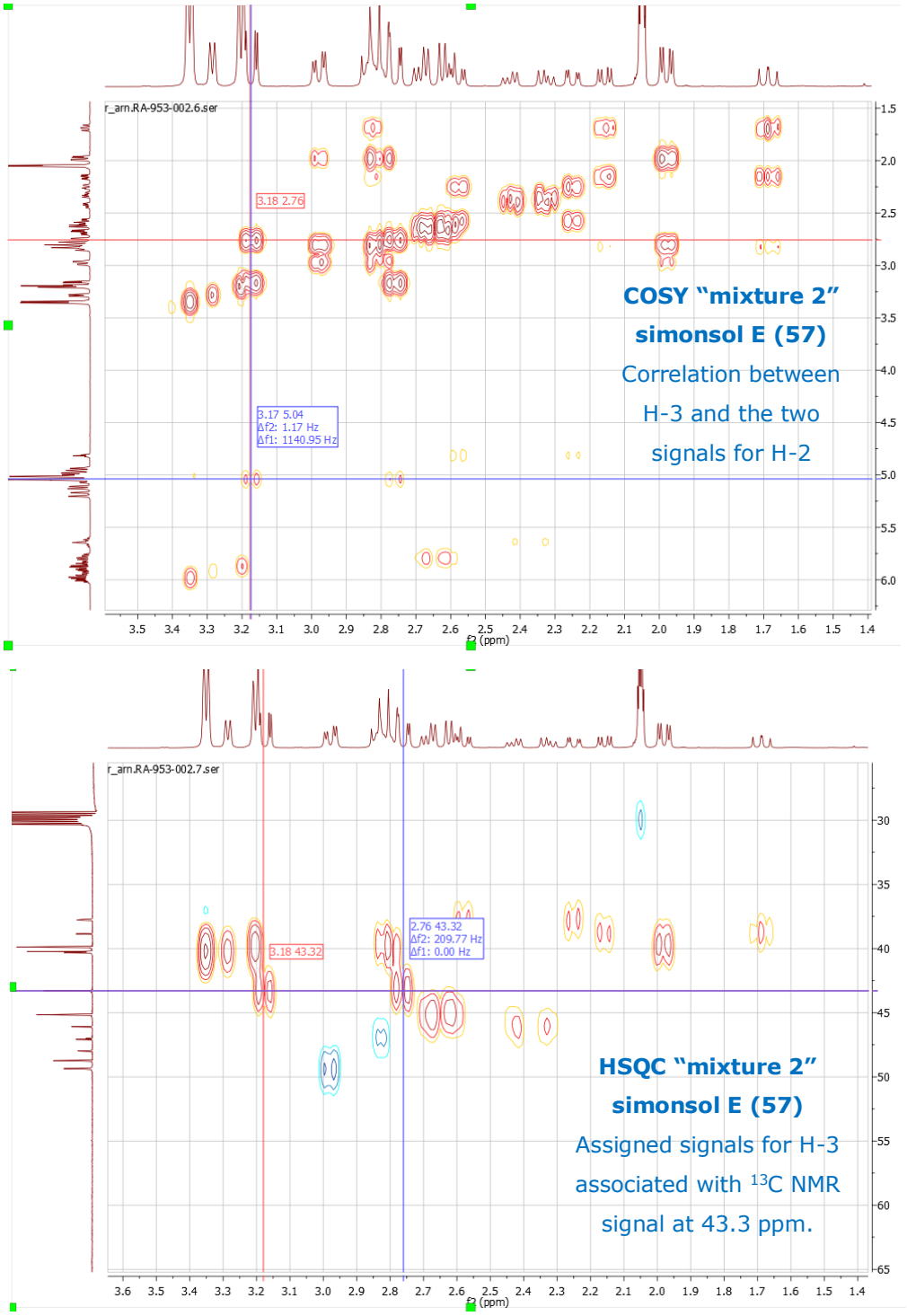


Figure 21. *Evidence by COSY (in relation to distinctive H-3) and HSQC to support the reassignment of C-2 and H-2 of simonsol E (**57**).*

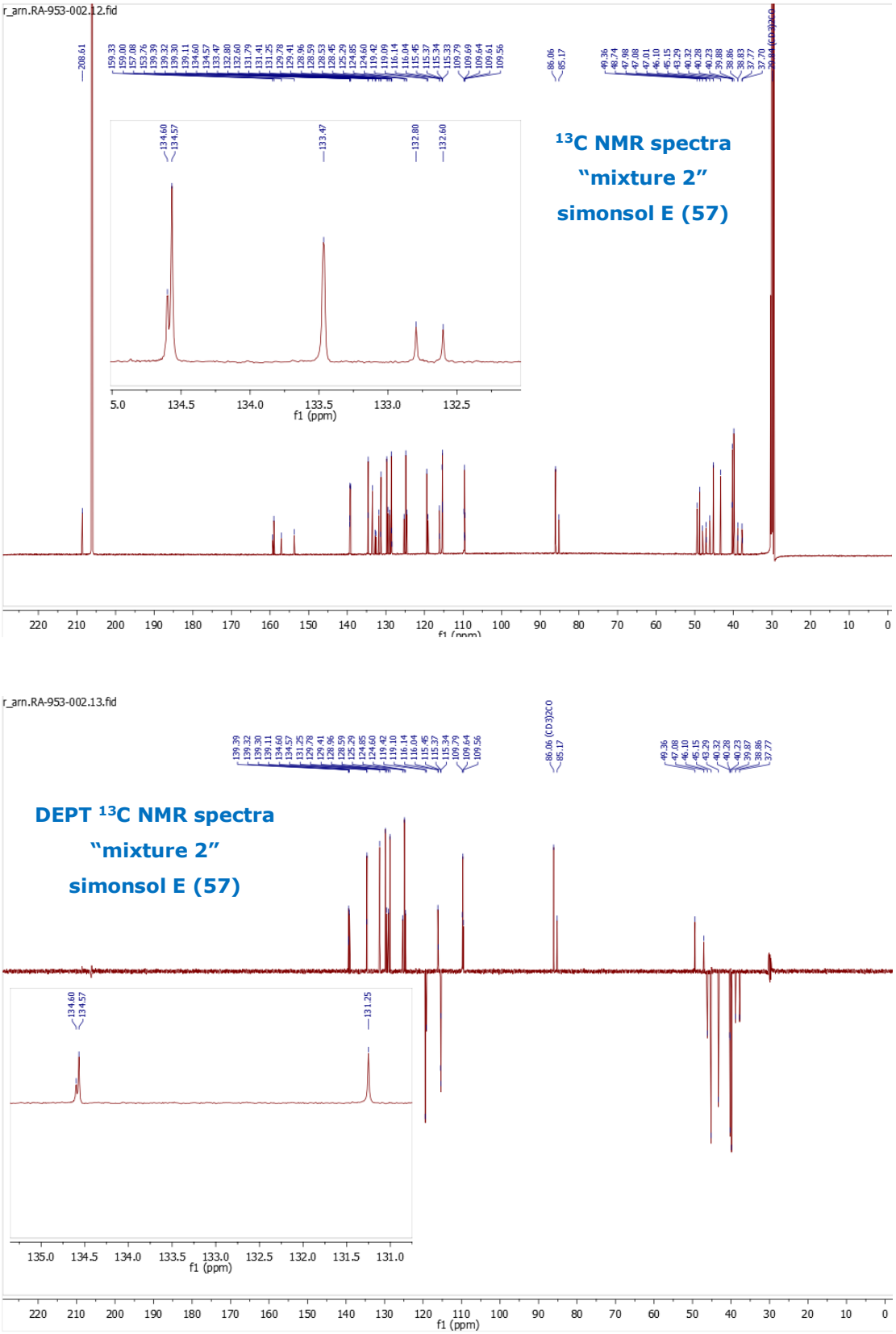
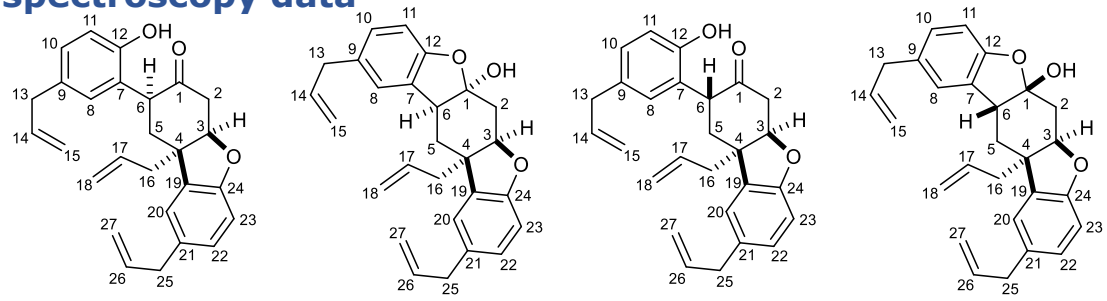


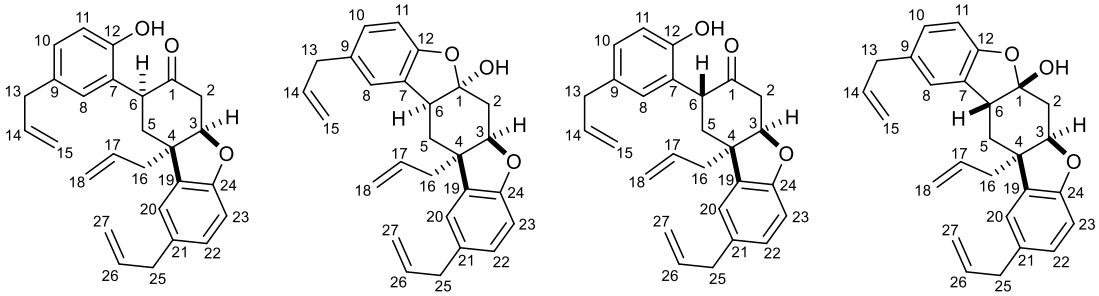
Figure 22. *Evidence by ^{13}C and DEPT ^{13}C NMR spectroscopy to support the reassignment of C-21 of simonsol E (**57**).*

7.2.3.2: Natural simonsin A (50) v.s. synthetic simonsin A (50) v.s. *epi*-simonsin A (363) ^{1}H and ^{13}C NMR spectroscopy data



Proton No.	simonsin A (**50**) and *epi*-simonsin A (**363**) ^{1}H NMR spectroscopy data (ppm (chemical shift (Hz)))		
	Nat. simonsin A (**50**)	Syn. simonsin A (**50**)	Syn. *epi*-simonsin A (**363**)
1	-	-	-
2	2.06 (dd, 12.9, 11.2) 2.48 (12.9, 5.2)	2.07 (dd, 13.9, 11.1) 2.48 (dd, 13.9, 5.3)	2.25 (dd, 14.8, 3.6) 2.58 (dd, 14.8, 4.2)
3	4.71 (dd, 11.2, 5.2)	4.71 (dd, 11.1, 5.3)	4.82 (dd, 4.2, 3.6)
4	-	-	-
5	1.67 (dd, 14.2, 12.3) 2.52 (dd, 14.2, 5.1)	1.68 (dd, 13.9, 12.4) 2.52 (dd, 13.9, 5.3)	1.69 (dd, 13.9, 11.9) 2.16 (13.9, 5.0)
6	3.37 (dd, 12.3, 5.1)	3.38 (dd, 12.4, 5.4)	2.82 (m)[a,c]
7	-	-	-
8	7.02 (d, 1.9)	7.02 (d, 1.9)	6.95 (d, 1.8)
9	-	-	-
10	6.90 (dd, 8.2, 1.9)	6.90 (dd, 8.1, 1.9)	6.93 (dd, 8.2, 1.8)[d]
11	6.57 (d, 8.2)	6.56 (d, 8.1)	6.62 (d, 8.2)[d]
12	-	-	-
13	3.29 (dt, 6.9, 1.9)	3.29 (d, 6.7)	3.35 (ddd, 6.5, 1.6, 1.6)
14	5.90 (ddt, 15.6, 10.2, 6.8)	5.92 (dddd, 16.8, 10.0, 6.6, 6.6)	5.98 (m)[a,c]
15	4.96 (ddt, 10.2, 3.2, 1.9) 4.99 (ddt, 15.6, 3.2, 1.9)	5.08 – 4.94 (m)[a,c]	5.03 (m)[a,c]
16	2.59 (d, 7.3)	2.59 (ddd, 7.2, 1.2, 1.2)	2.33 (dd, 13.8, 8.2) 2.43 (dddd, 13.8, 6.5, 1.4, 1.4)
17	5.64 (ddt, 17.3, 10.2, 7.3)	5.66 (dddd, 17.3, 10.1, 7.2, 7.2)	5.64 (m)[a,c]
18	5.06 (dd, 10.2, 2.1) 5.12 (dd, 17.3, 2.1)	5.15 – 5.03 (m)[a,c]	5.03 (m)[a,c]
19	-	-	-
20	6.94 (d, 2.0)	6.93 (d, 1.9)	7.11 (d, 1.9)
21	-	-	-
22	6.89 (dd, 8.1, 2.0)	6.88 (dd, 8.1, 1.9)	6.95 (dd, 8.2, 1.9)[d]
23	6.59 (d, 8.1)	6.59 (d, 8.1)	6.63 (d, 8.2)[d]
24	-	-	-
25	3.27 (dt, 6.4, 1.7)	3.27 (d, 7.0)	3.29 (ddd, 6.8, 1.6, 1.6)
26	5.93 (ddt, 15.0, 11.1, 6.4)	5.92 (dddd, 16.8, 10.0, 6.6, 6.6)	5.90 (m)[a,c]
27	5.02 (ddt, 11.1, 3.4, 1.7) 5.05 (ddt, 15.0, 3.4, 1.7)	5.08 – 4.94 (m)[a,c]	5.01 (m)[a,c]
OH	6.11	6.03 (s)	5.64 (s)

***Table 23 (1 of 2)**. See next page for description.*



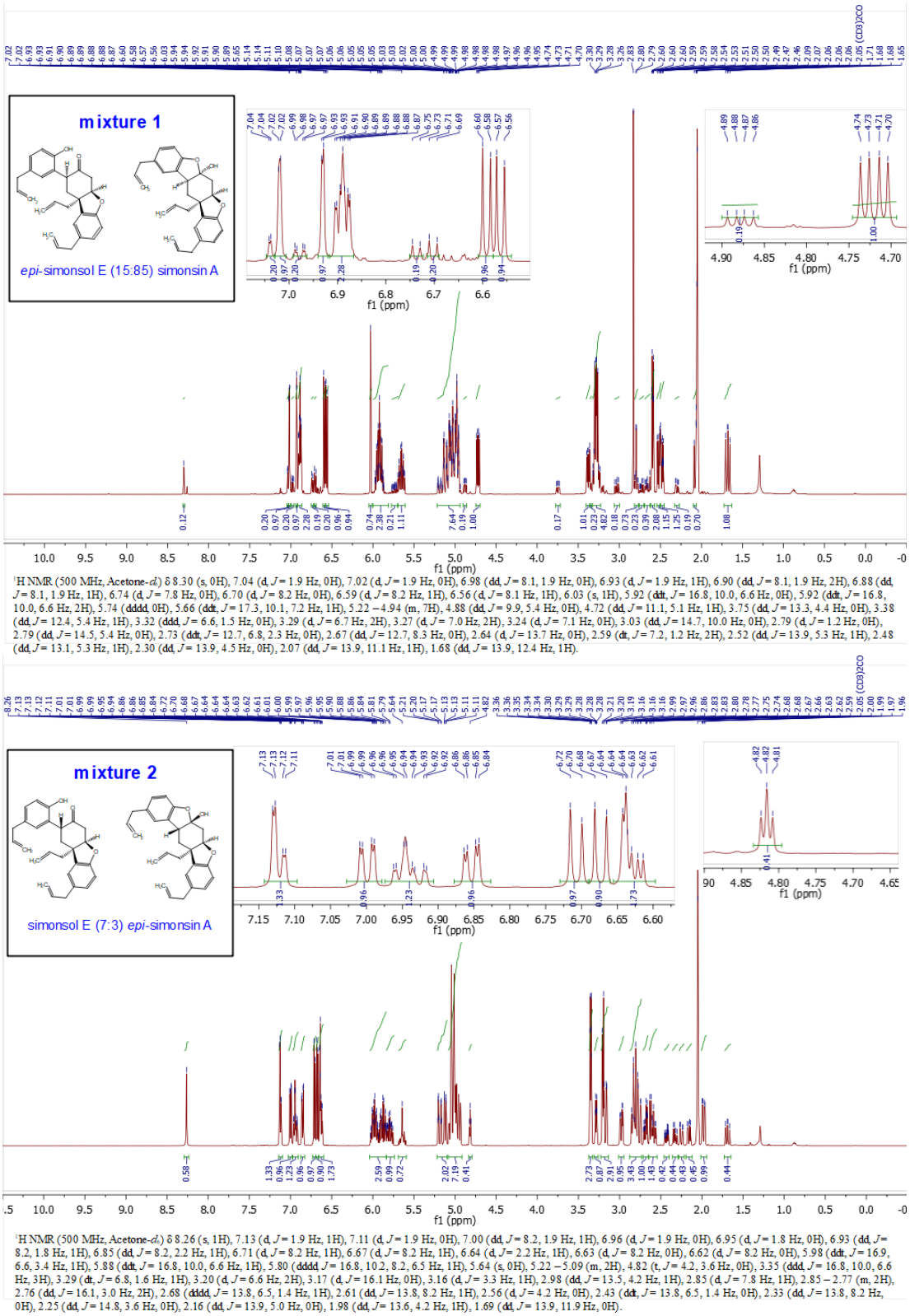
epi-simonsol E (**362**) simonsin A (**50**) simonsol E (**57**) epi-simonsin A (**363**)

mixture 1 mixture 2

Carbon No.	simonsin A (**50**) and *epi*-simonsin A (**363**) ^{13}C NMR spectroscopy data (ppm)		
	Nat. simonsin A (**50**)	Syn. simonsin A (**50**)[f]	Syn. *epi*-simonsin A (**363**)
1	109.9	109.9 (0)	109.7
2	38.5	38.6 (0.1)	37.8
3	85.0	85.1 (0.1)	85.2
4	48.1	48.1 (0)	48.0
5	37.9	38.0 (0.1)	38.9
6	46.7	46.8 (0.1)	47.1
7	130.6	130.7 (0.1)	128.45[b]
8	125.2	125.2 (0)	129.4
9	132.7	132.8[d] (0.1)	131.4[b]
10	129.0	129.0[d] (0)	129.0
11	109.7	109.74[d] (0)	109.6[d]
12	157.0	157.0 (0)	157.1
13	40.2	40.25[d] (0.1)	40.28[d]
14	139.2	139.3[e] (0.1)	139.4[d]
15	115.3	115.3[d] (0)	115.3[d]
16	44.8	44.9 (0.1)	46.1
17	134.8	134.9 (0.1)	134.6
18	118.8	118.9 (0.1)	119.1
19	134.4	134.5 (0.1)	-[b]
20	124.7	124.8 (0.1)	124.6
21	132.8	132.9[d] (0.1)	132.6[b]
22	129.2	129.2[d] (0)	125.3
23	109.7	109.72[d] (0)	109.8[d]
24	158.1	158.2 (0.1)	159.3
25	40.2	40.31[d] (0.1)	40.32[d]
26	139.2	139.3[e] (0.1)	139.3[d]
27	115.4	115.4[d] (0)	115.4[d]

Table 23 (2 of 2). *^{1}H and ^{13}C NMR spectroscopy data of synthetic simonsin A (**50**) and epi-simonsin A (**363**) versus natural simonsin A (**50**).* ***a)*** *multiplicity not assigned due to overlapped signals.* ***b)*** *quaternary carbons of epi-simonsin A (**363**) C-7, C-9, C-19, and C-21 are tentatively assigned. The ^{13}C signals at 128.45, 131.4, and 132.6 ppm are associated with epi-simonsin A (**363**), however a fourth quaternary carbon signal was not observed.* ***c)*** *central position (δ (ppm)) of proton signal was found by COSY and HSQC.* ***d)*** *^{1}H or ^{13}C NMR spectroscopy signals are interchangeable: simonsin A (**50**) "C-9 and C-21", "C-10 and C-22", "C-11 and C-23" "C-13 and C-25", "C-15 and C-27". epi-simonsin A (**363**) "H-10 and H-22", "H-11 and H-23", "C-11 and C-23", "C-13 and C-25", "C-14 and C-26", "C-15 and C-27".* ***e)*** *simonsin A (**50**) C-14 and C-26 (139.3 ppm) are overlapped.* ***f)*** *numbers in parenthesis are the difference in ^{13}C chemical shifts calculated by "Syn. simonsin A (**50**) – Nat. simonsin A (**50**)".*

Spectroscopic data obtained for synthetic simonsin A (**50**) were in excellent agreement with the natural sample.[97]



^{1}H NMR (500 MHz, Acetone-*d*$_6$) δ 8.30 (s, 0H), 7.04 (d, *J* = 1.9 Hz, 0H), 7.02 (d, *J* = 1.9 Hz, 0H), 6.98 (dd, *J* = 8.1, 1.9 Hz, 0H), 6.93 (d, *J* = 1.9 Hz, 1H), 6.90 (dd, *J* = 8.1, 1.9 Hz, 2H), 6.88 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 0H), 6.70 (d, *J* = 8.2 Hz, 0H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 1H), 5.92 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 0H), 5.92 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 2H), 5.74 (dddd, 0H), 5.66 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.22 – 4.94 (m, 7H), 4.88 (dd, *J* = 9.9, 5.4 Hz, 0H), 4.72 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.75 (dd, *J* = 13.3, 4.4 Hz, 0H), 3.38 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.32 (ddd, *J* = 6.6, 1.5 Hz, 0H), 3.29 (d, *J* = 6.7 Hz, 2H), 3.27 (d, *J* = 7.0 Hz, 2H), 3.24 (d, *J* = 7.1 Hz, 0H), 3.03 (dd, *J* = 14.7, 10.0 Hz, 0H), 2.79 (d, *J* = 1.2 Hz, 0H), 2.79 (dd, *J* = 14.5, 5.4 Hz, 0H), 2.73 (ddt, *J* = 12.7, 6.8, 2.3 Hz, 0H), 2.67 (dd, *J* = 12.7, 8.3 Hz, 0H), 2.64 (d, *J* = 13.7 Hz, 0H), 2.59 (dt, *J* = 7.2, 1.2 Hz, 2H), 2.52 (dd, *J* = 13.9, 5.3 Hz, 1H), 2.48 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.30 (dd, *J* = 13.9, 4.5 Hz, 0H), 2.07 (dd, *J* = 13.9, 11.1 Hz, 1H), 1.68 (dd, *J* = 13.9, 12.4 Hz, 1H).

^{1}H NMR (500 MHz, Acetone-*d*$_6$) δ 8.26 (s, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 0H), 7.00 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.96 (d, *J* = 1.9 Hz, 0H), 6.95 (d, *J* = 1.8 Hz, 0H), 6.93 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 0H), 6.62 (d, *J* = 8.2 Hz, 0H), 5.98 (ddt, *J* = 16.9, 6.6, 3.4 Hz, 1H), 5.88 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.80 (dddd, *J* = 16.8, 10.2, 8.2, 6.5 Hz, 1H), 5.64 (s, 0H), 5.22 – 5.09 (m, 2H), 4.82 (t, *J* = 4.2, 3.6 Hz, 0H), 3.35 (dddd, *J* = 16.8, 10.0, 6.6 Hz, 3H), 3.29 (dt, *J* = 6.8, 1.6 Hz, 1H), 3.20 (d, *J* = 6.6 Hz, 2H), 3.17 (d, *J* = 16.1 Hz, 0H), 3.16 (d, *J* = 3.3 Hz, 1H), 2.98 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.85 (d, *J* = 7.8 Hz, 1H), 2.85 – 2.77 (m, 2H), 2.76 (dd, *J* = 16.1, 3.0 Hz, 2H), 2.68 (dddd, *J* = 13.8, 6.5, 1.4 Hz, 1H), 2.61 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.56 (d, *J* = 4.2 Hz, 0H), 2.43 (ddt, *J* = 13.8, 6.5, 1.4 Hz, 0H), 2.33 (dd, *J* = 13.8, 8.2 Hz, 0H), 2.25 (dd, *J* = 14.8, 3.6 Hz, 0H), 2.16 (dd, *J* = 13.9, 5.0 Hz, 0H), 1.98 (dd, *J* = 13.6, 4.2 Hz, 1H), 1.69 (dd, *J* = 13.9, 11.9 Hz, 0H).

Figure 23. *^{1}H NMR spectra of "mixture 1" and "mixture 2" with zoomed in sections which highlight "H-11 and H-23" and "H-3".*

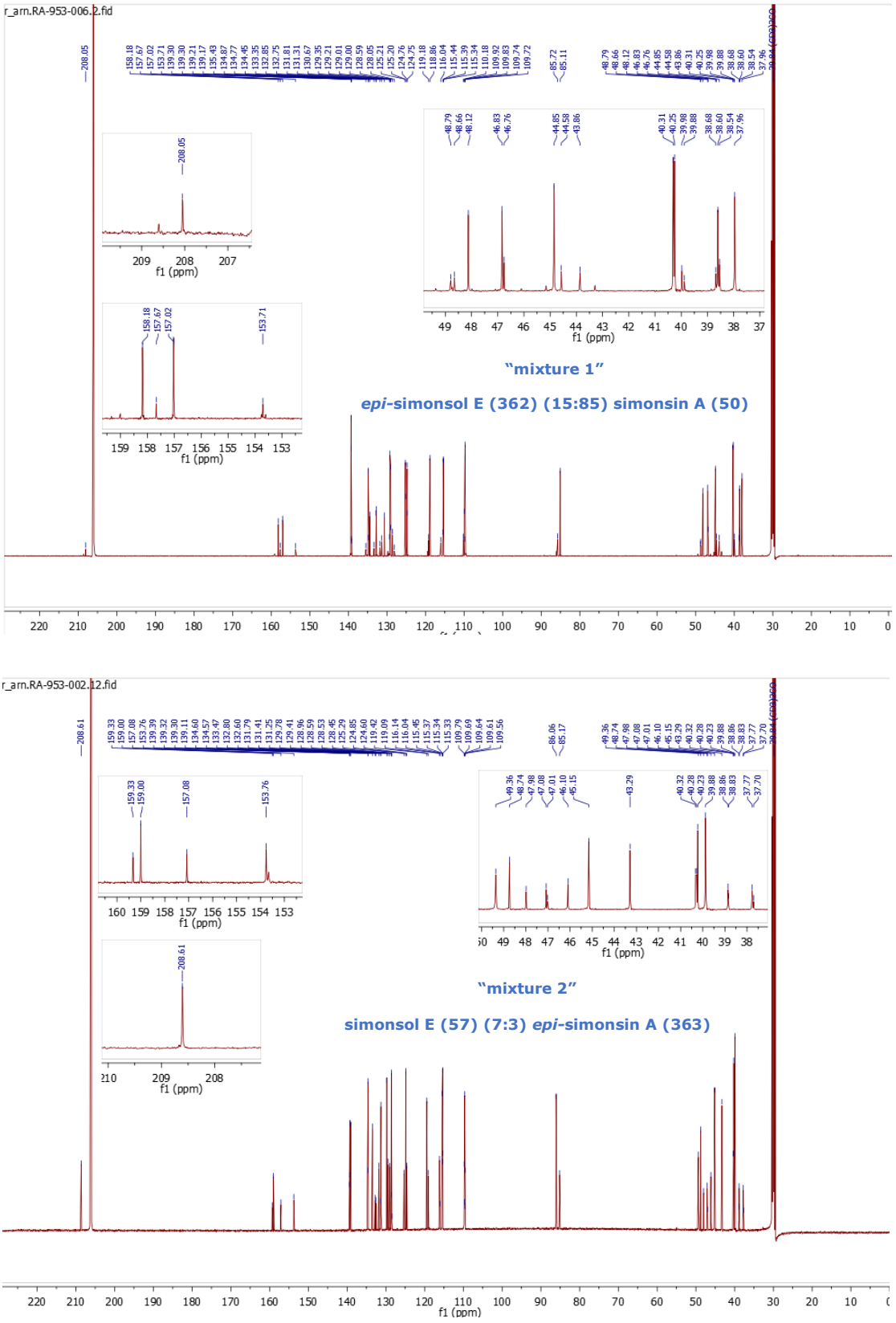
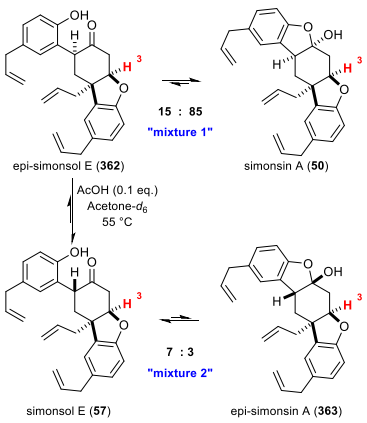


Figure 24. *^{13}C NMR spectra of "mixture 1" and "mixture 2" with zoomed in sections which highlight the differences in chemical shift of "C-1 of simonsol E (**57**) versus epi-simonsol E (**362**)", "C-12 and C-24" and "various CH_2 signals and C-4".*

7.2.3.3: Epimerisation study: "mixture 1" & "mixture 2"



In an NMR tube, "mixture 1" (9 mg) was dissolved in acetone-d_6 (0.60 mL) and conditions were applied as described in Table 24.

In an NMR tube, "mixture 2" (11 mg) was dissolved in acetone-d_6 (0.60 mL) and conditions were applied as described in Table 24.

		Mixture 1			Mixture 2		
Entry	**Conditions in acetone-d_6**	**Mix. 1**	**:**	**Mix. 2**	**Mix. 1**	**:**	**Mix. 2**
1	isolated mixtures	93	:	7	<1	:	>99
2	r.t. – 96 h	93	:	7	<1	:	>99
3	55 °C – 2 h	90	:	10	4	:	96
4	55 °C with SiO_2 (30 eq.) – 6.5 h	88	:	12	5	:	95
5	r.t. with AcOH (0.1 eq.) – 0.25 h	65	:	35	7	:	93
6	55 °C with AcOH (0.1 eq.) – 3 h	56	:	44	10	:	90
7	55 °C with AcOH (0.1 eq.) – 18 h	44	:	56	14	:	86
8	55 °C with AcOH (0.1 eq.) – 114 h	32	:	68	19	:	81

Table 24. *Conditions used to convert "mixture 1" into "mixture 2" (vice versa). ^{1}H NMR spectra were acquired at time points as described. The ratio of "mixture 1":"mixture 2" was calculated by comparison of integrations for H-3.*

The ^{1}H NMR spectra taken after the conditions described in Table 24 and zoomed in extracts of δ (ppm) regions "H-5 (simonsin A (**50**) and *epi*-simonsin A (**363**) only)", "H-3" and "H-11 and H-23" (see Tables 22 and 23) are provided (see Figures 25 to 32).

After prolonged periods of heating at 55 °C with AcOH (0.1 eq.), a new species formed which has not been identified.

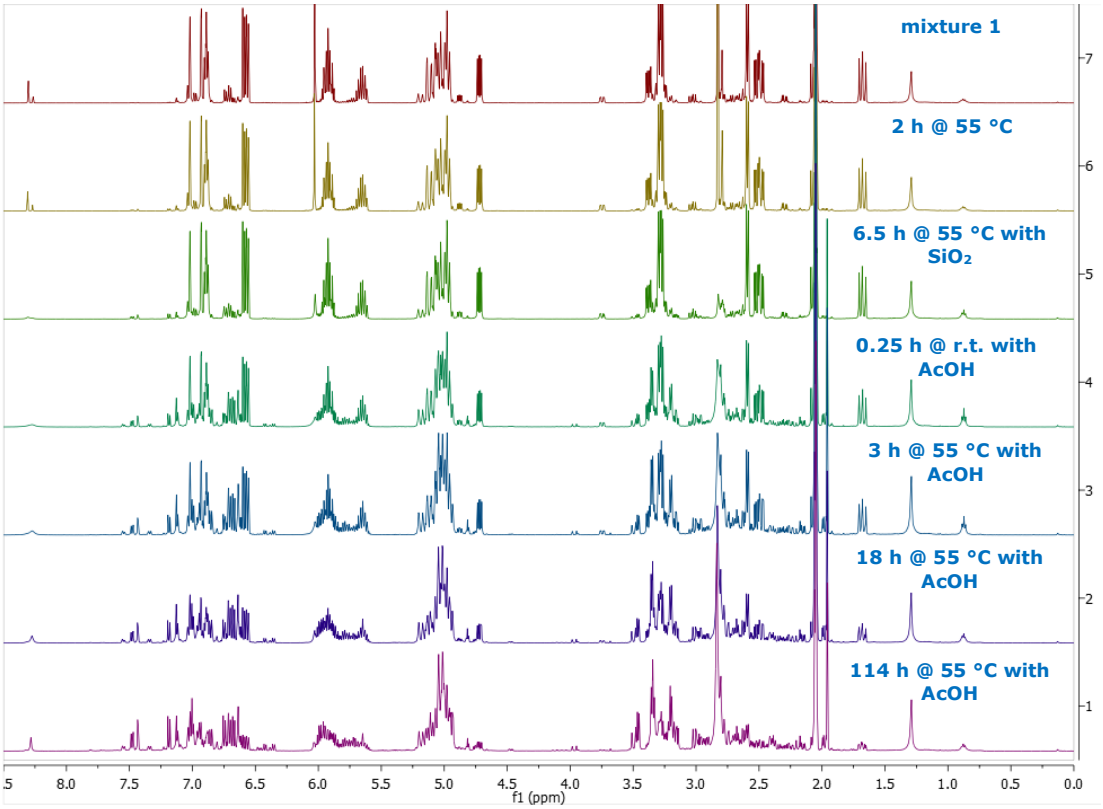


Figure 25. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 1".*

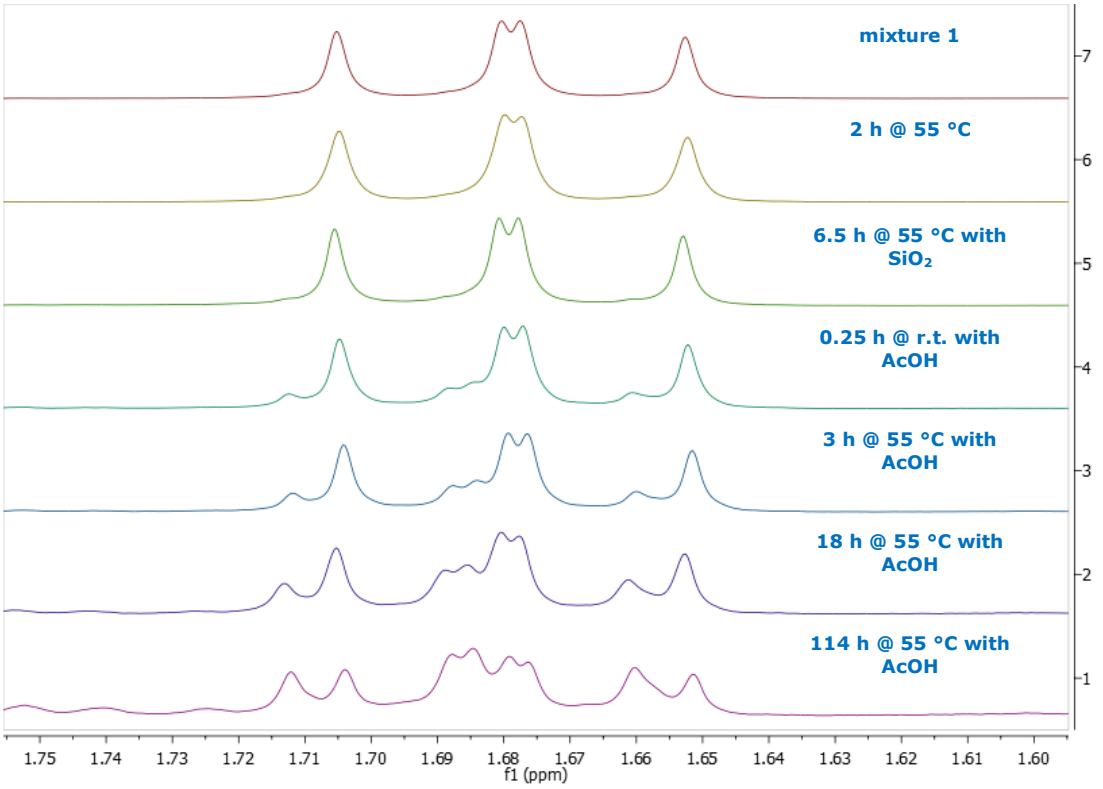


Figure 26. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 1" zoomed in on H-5 of simonsin A (**50**) versus epi-simonsin A (**363**).*

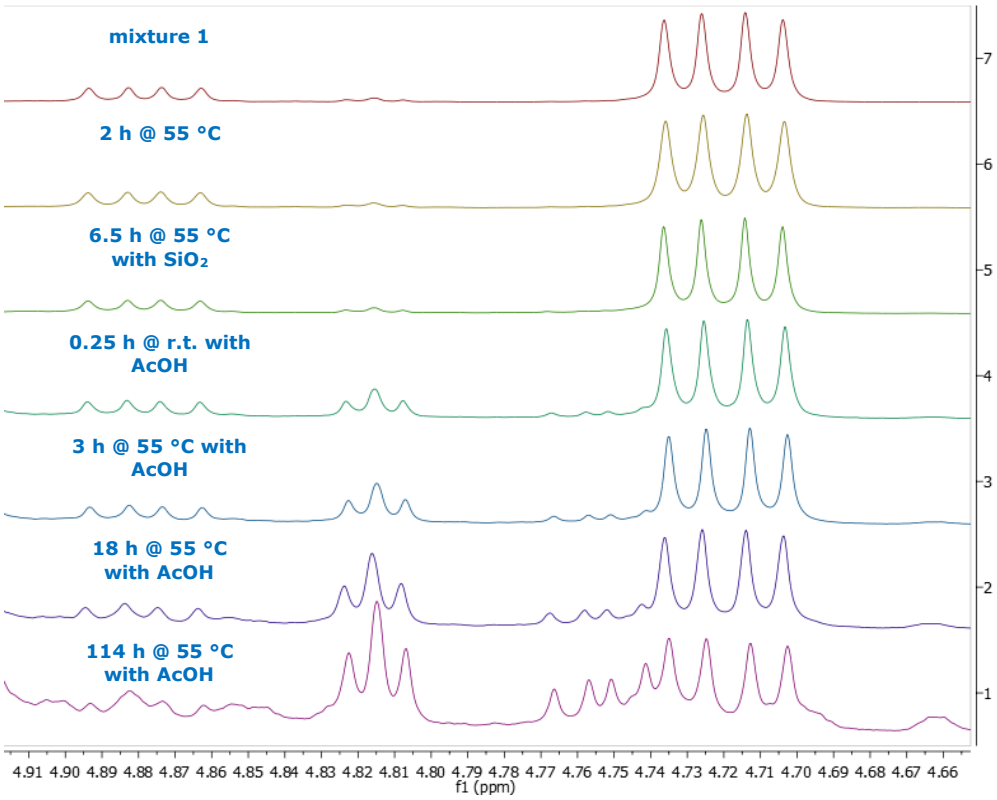


Figure 27. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 1" zoomed in on H-3.*

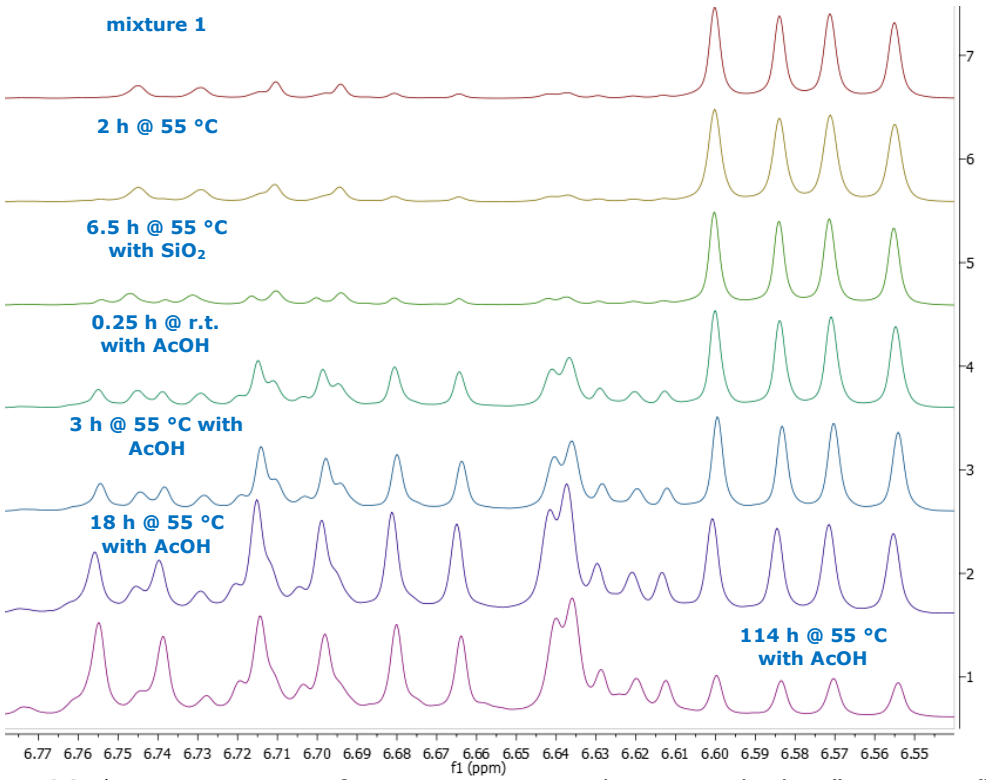


Figure 28. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 1" zoomed in on H-11 and H-23.*

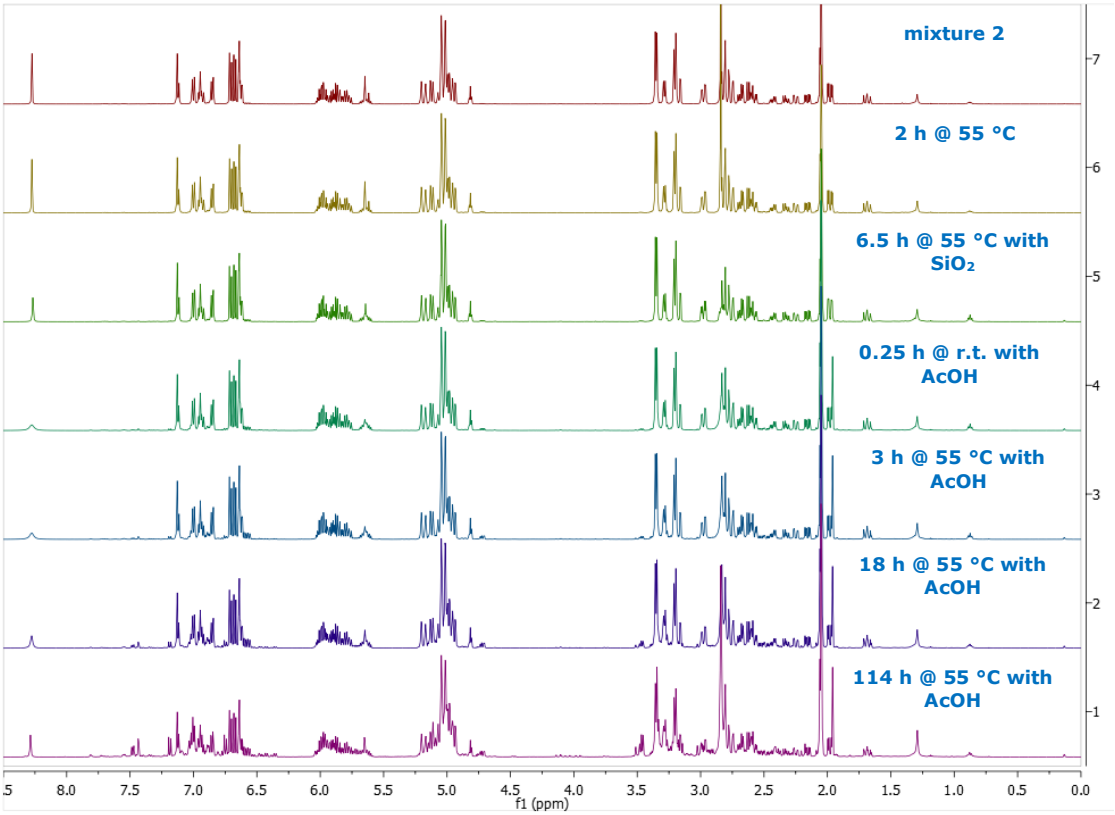


Figure 29. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 2".*

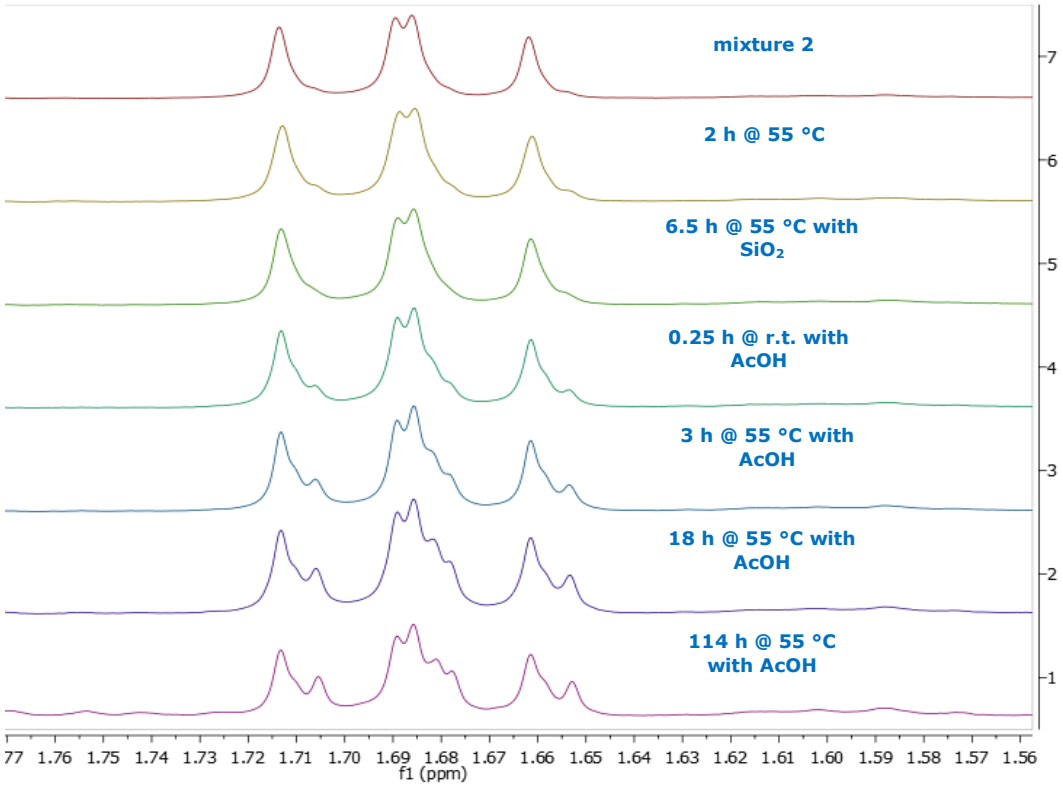


Figure 30. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 2" zoomed in on H-5 of epi-simonsin A (**363**) versus simonsin A (**50**).*

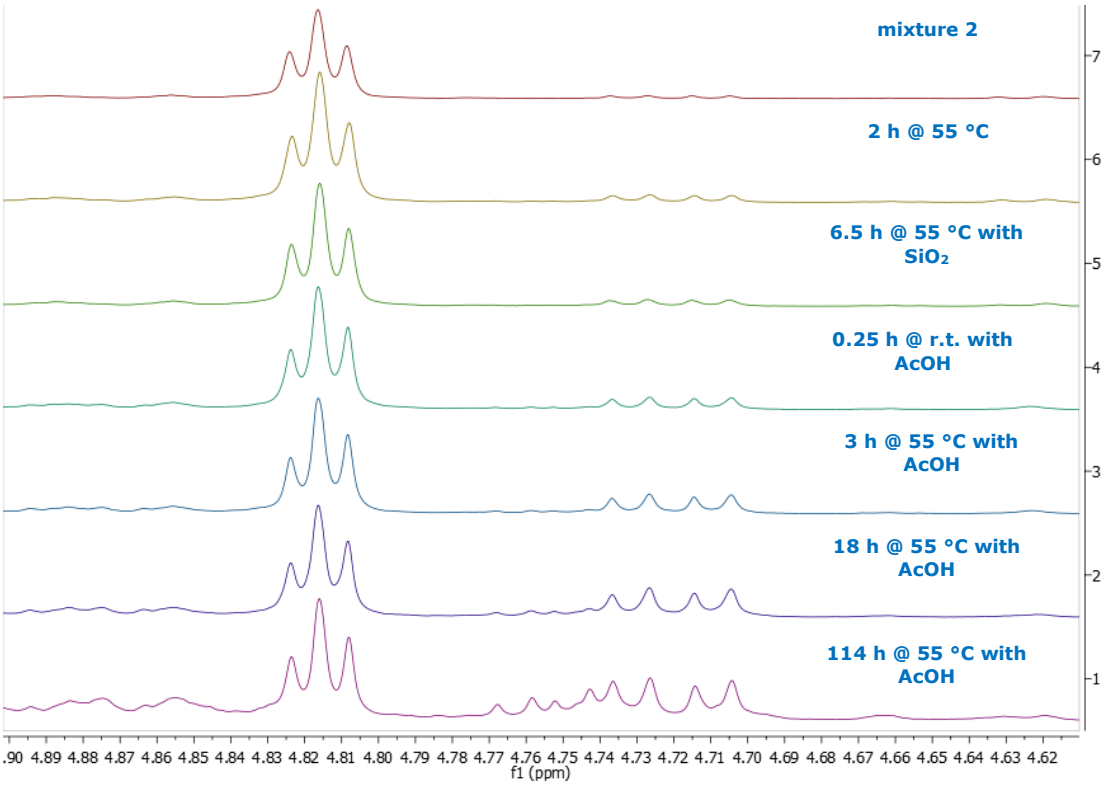


Figure 31. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 2" zoomed in on H-3.*

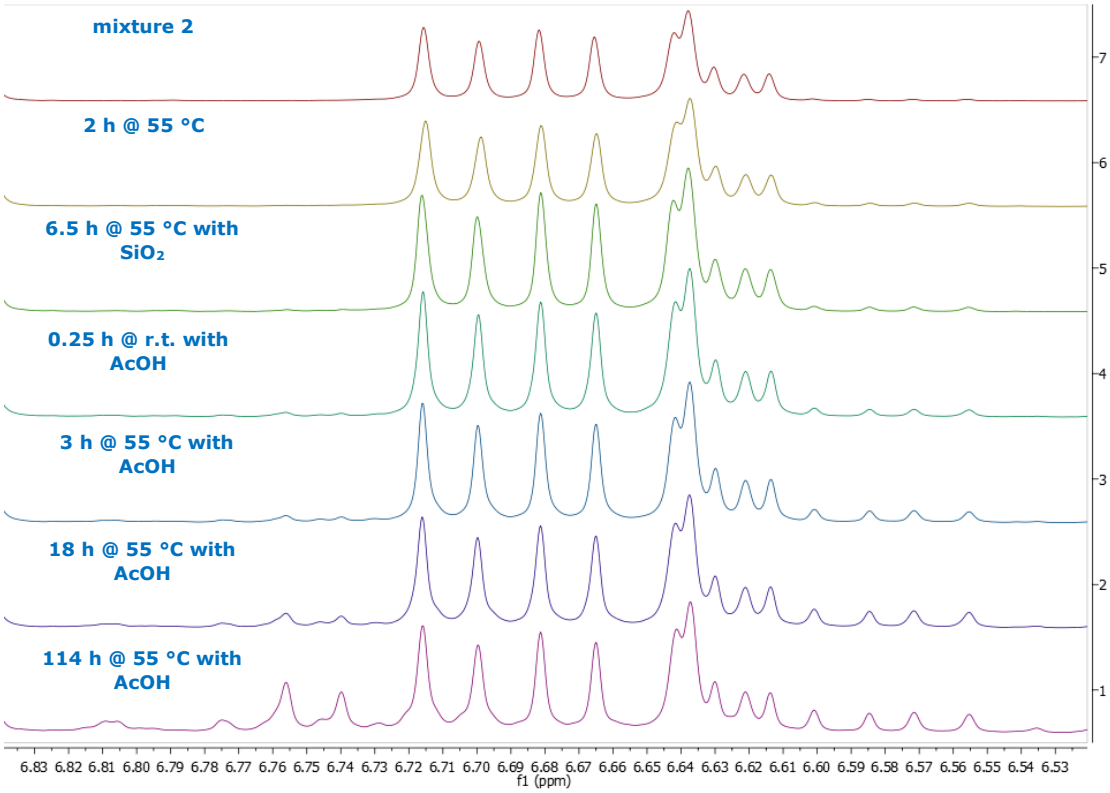
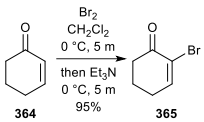


Figure 32. *^{1}H NMR spectra of epimerisation conditions applied to "mixture 2" zoomed in on H-11 and H-23.*

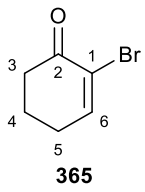
7.3: Studies towards the synthesis of fargenone A

7.3.1: Synthesis of simonsol F fragments (Section 2.2.4)

365: 2-bromocyclohex-2-en-1-one



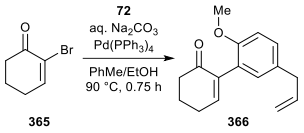
To a solution of 2-cyclohexene-1-one (**364**) (0.40 mL, 4.1 mmol) in CH_2Cl_2 (8.2 mL) at 0 °C was added a solution of bromine (230 µL, 4.56 mmol) in CH_2Cl_2 (8.20 mL) over 15 minutes. The reaction mixture was stirred for 5 minutes at 0 °C and then Et_3N (800 µL, 5.80 mmol) was added. The solution was stirred for a further 5 minutes at 0 °C and then HCl (6 mL of a 1.0 M aqueous solution) was added. The organics were extracted with EtOAc (2 x 20 mL) and the combined organics were washed with NaOH (2 x 10 mL of a 1.0 M aqueous solution), then $Na_2S_2O_3$ (2 x 6 mL of a saturated aqueous solution), then brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* which gave bromo enone **365** as a light blue solid (698 mg, 97%).



365: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (td, *J* = 4.5, 1.4 Hz, 1H, H-6), 2.65 – 2.60 (m, 2H, H-3), 2.47 – 2.41 (m, 2H, H-5), 2.12 – 2.04 (m, 2H, H-4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 191.4 (Cq), 151.3 (CH), 124.0 (Cq), 38.5 (CH_2), 28.5 (CH_2), 22.8 (CH_2). **HRMS** (ESI^+): $C_6H_7{}^{79}BrO$ $[M+H]^+$ calcd. 174.9753, found 174.9744.

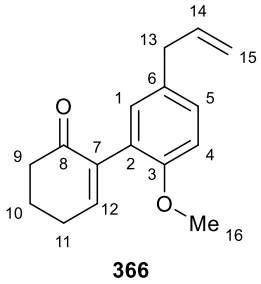
Spectroscopic data obtained for **365** were consistent with those previously reported.[371]

366: 5'-allyl-2'-methoxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one



In a microwave vial, to a solution of bromo enone **365** (215 mg, 1.23 mmol) and boronic acid **72** (356 mg, 1.86 mmol) in PhMe (9.7 mL) and EtOH (4.5 mL) at room temperature was added Na_2CO_3 (4.50 mL of a 2.0 M aqueous solution, 9.00 mmol) and the biphasic mixture was sparged with argon for 5 minutes. To the biphasic mixture was added $Pd(PPh_3)_4$ (128 mg, 0.111 mmol) and the reaction mixture was sparged with argon for a further 5 minutes and was then sealed and heated at 90 °C for 0.75 hours. The reaction mixture was cooled to room temperature and the organics were diluted with Et_2O (20 mL). The organics were washed with HCl (2 x 10 mL of a 1.0 M aqueous solution), then brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2/acetone 90:5:5) gave enone **366** as a pale-yellow oil (243 mg, 82 %).

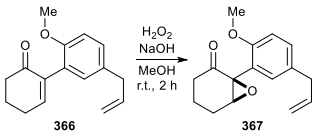
An alternative experimental procedure for the synthesis of **366** is described in Section 6.4.2.1.



366

366: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (dd, *J* = 8.4, 2.3 Hz, 1H, H-5), 6.89 (t, *J* = 4.2 Hz, 1H, H-12), 6.87 (d, *J* = 2.3 Hz, 1H, H-1), 6.82 (d, *J* = 8.4 Hz, 1H, H-4), 5.95 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-14), 5.10 – 5.01 (m, 2H, H-15), 3.73 (s, 3H, H-16), 3.32 (ddd, *J* = 6.8, 1.4, 1.4 Hz, 2H, H-13), 2.61 – 2.56 (m, 2H, H-9), 2.51 (td, *J* = 6.0, 4.2 Hz, 2H, H-11), 2.16 – 2.08 (m, 2H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 197.7 (Cq), 155.6 (Cq), 148.0 (CH), 139.3 (Cq), 137.9 (CH), 132.0 (Cq), 130.9 (CH), 129.2 (CH), 126.8 (Cq), 115.7 (CH_2), 111.1 (CH), 56.0 (CH_3), 39.5 (CH_2), 38.8 (CH_2), 26.5 (CH_2), 23.3 (CH_2); **HRMS** (ESI^+): $C_{16}H_{18}O_2$ $[M+H]^+$ calcd. 243.1380, found 243.1382; **IR** ν_{max} cm^{-1}: 3077, 3002, 2941, 2833, 1680, 1498, 1269, 1241, 1032, 910.

367: (±)-(1*S*,6*S*)-1-(5-allyl-2-methoxyphenyl)-7-oxabicyclo[4.1.0]heptan-2-one



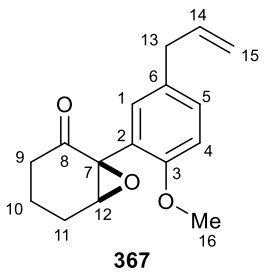
366 **367**

To a solution of enone **366** (242 mg, 1.00 mmol) in MeOH (10.0 mL) was sequentially added H_2O_2 (10.0 mL of a 30% aqueous solution, 98.0 mmol)* then NaOH (1.00 mL of a 1.0 M aqueous solution, 1.00 mmol). The reaction mixture was stirred for 2 hours at room temperature and was then diluted with H_2O (15 mL) and cooled to 0 °C. To the reaction mixture was cautiously** added $Na_2S_2O_3$ (20 mL of a saturated

aqueous solution). The organics were extracted with Et_2O (5 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc 9:1) afforded epoxide **367** as a colourless solid (211 mg, 85%) **m.p.** 48–50 °C.

*miscalculated the molarity of the aqueous solution and therefore a large excess was used. Reaction requires optimisation.

**exotherm produced upon addition of $Na_2S_2O_3$ due to large excess of H_2O_2 in reaction mixture.

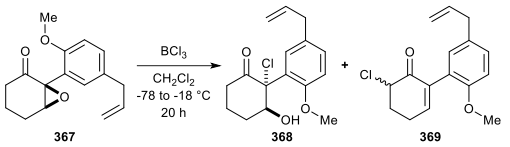


367

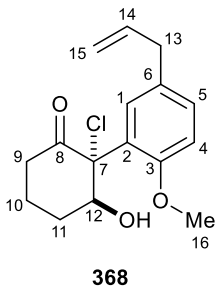
367: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, *J* = 2.3 Hz, 1H, H-1), 7.11 (dd, *J* = 8.3, 2.3 Hz, 1H, H-5), 6.79 (d, *J* = 8.3 Hz, 1H, H-4), 5.94 (dddd, *J* = 16.8, 10.0, 6.8, 6.8 Hz, 1H, H-14), 5.12 – 5.01 (m, 2H, H-15), 3.76 (s, 3H, H-16), 3.38 (dd, *J* = 2.0, 2.0 Hz, 1H, H-12), 3.33 (ddd, *J* = 6.7, 1.6, 1.6 Hz, 2H, H-13), 2.58 (dddd, *J* = 16.5, 4.3, 4.3, 1.0 Hz, 1H, H-9), 2.38 – 2.31 (m, 1H, H-11), 2.25 (ddd, *J* = 16.4, 12.1, 5.6 Hz, 1H, H-9), 2.16 – 2.06 (m, 1H, H-11), 1.99 – 1.87 (m, 1H, H-10), 1.83 – 1.75 (m, 1H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 203.5 (Cq), 171.4 (Cq), 155.8 (Cq), 137.7 (CH), 132.4 (Cq), 129.4 (CH), 127.4 (CH), 124.5 (Cq), 115.8 (CH_2), 110.3 (CH), 62.9 (CH), 60.8 (Cq), 55.8 (CH_3), 39.5 (CH_2), 37.5 (CH_2), 24.0 (CH_2), 17.3 (CH_2); **HRMS** (ESI^+): $C_{16}H_{18}O_3$ $[M+H]^+$ calcd. 259.1329, found 259.1321.

368: (±)-(2*R*,3*S*)-2-(5-allyl-2-methoxyphenyl)-2-chloro-3-hydroxycyclohexan-1-one

369: 5'-allyl-3-chloro-2'-methoxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one



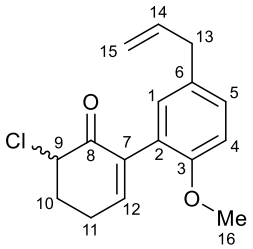
To a solution of epoxide **367** (21 mg, 81 µmol) in CH_2Cl_2 (2.0 mL) at -78 °C was added dropwise BCl_3 (0.11 mL of a 1.0 M solution in hexanes, 0.11 mmol). The reaction mixture was warmed to -18 °C for 20 hours without stirring. The reaction mixture was quickly injected (<5 seconds) into a vigorously stirring solution of CH_3CN/H_2O (5 mL, 49:1) at 0 °C. The organics were extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/EtOAc, 9:1 to 3:2) afforded ketone **130** as a colourless oil (20 mg, 83%) and enone **131** as a colourless oil (4 mg, 17%).



368

368: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 2.2 Hz, 1H, H-1), 7.17 (dd, *J* = 8.4, 2.2 Hz, 1H, H-5), 6.85 (d, *J* = 8.4 Hz, 1H, H-4), 5.96 (dddd, *J* = 16.9, 10.3, 6.8, 6.8 Hz, 1H, H-14), 5.13 – 5.04 (m, 2H, H-15), 4.67 (ddd, *J* = 9.3, 6.1, 3.3 Hz, 1H, H-12), 3.74 (s, 3H, H-16), 3.37 (ddd, *J* = 6.6, 1.7, 1.7 Hz, 2H, H-13), 2.75 (ddd, *J* = 15.2, 10.1, 5.2 Hz, 1H, H-9), 2.52 (dddd, *J* = 15.2, 5.6, 5.6, 1.5 Hz, 1H, H-9), 2.20 – 2.12 (m, 1H, OH), 2.11 – 1.91 (m, 3H, H-10 and H-11), 1.82

– 1.68 (m, 1H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 201.0 (Cq) 153.8 (Cq), 137.4 (CH), 132.9 (Cq), 130.2 (CH), 129.3 (CH), 126.5 (Cq), 116.1 (CH_2), 112.3 (CH), 81.6 (Cq), 74.9 (CH), 55.8 (CH_3), 39.6 (CH_2), 36.9 (CH_2), 29.2 (CH_2), 20.0 (CH_2); **HRMS** (ESI^+): $C_{16}H_{19}{}^{35}ClO_3$ $[M+H]^+$ calcd. 295.1095, found 295.1094; **IR** ν_{max} cm^{-1}: 3433, 3077, 2944, 2872, 2838, 1724, 1493, 1250, 1026, 914.

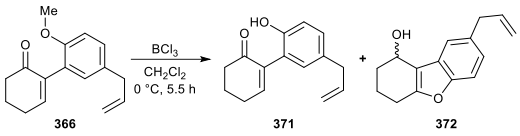


369

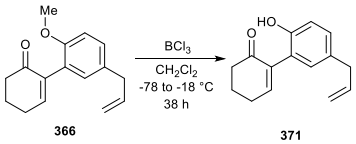
369: ^{1}H NMR (400 MHz, C_6D_6) δ: 7.01 (dd, *J* = 8.3, 2.3 Hz, 1H, H-5), 6.95 (d, *J* = 2.3 Hz, 1H, H-1), 6.56 (d, *J* = 8.3 Hz, 1H, H-4), 6.33 (dd, *J* = 4.1, 4.1 Hz, 1H, H-12), 5.92 (dddd, *J* = 16.8, 10.0, 6.6, 6.6 Hz, 1H, H-14), 5.09 – 4.98 (m, 2H, H-15), 4.27 – 4.20 (m, 1H, H-9), 3.35 (s, 3H, H-16), 3.23 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, H-13), 2.09 (dddd, *J* = 19.2, 6.2, 6.2, 3.7 Hz, 1H, H-11), 1.82 – 1.75 (m, 2H, H-10), 1.63 (dddd, *J* = 19.2, 5.1, 5.1, 4.5 Hz, 1H, H-11); **^{13}C NMR** (101 MHz, C_6D_6) δ: 188.9 (Cq), 156.4 (Cq), 146.3 (CH), 138.2 (CH), 137.5 (Cq), 132.0 (Cq), 131.2 (CH), 129.6 (CH), 126.9 (Cq), 115.6 (CH_2), 111.5 (CH), 60.2 (CH), 55.5 (CH_3), 39.7 (CH_2), 32.1 (CH_2), 23.6 (CH_2); **HRMS** (ESI^+): $C_{16}H_{17}{}^{35}ClO_2$ $[M+H]^+$ calcd. 277.0990, found 277.0995; **IR** ν_{max} cm^{-1}: 2925, 2851, 2835, 1690, 1497, 1267, 1245, 1030, 912, 814, 733, 643.

371: 5'-allyl-2'-hydroxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one

372: 8-allyl-1,2,3,4-tetrahydrodibenzo[b,d]furan-1-ol

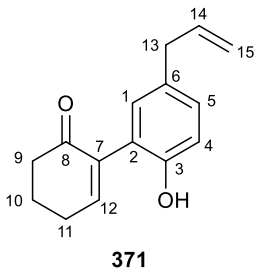


To a solution of enone **366** (171 mg, 0.707 mmol) in CH_2Cl_2 (3.6 mL) at 0 °C was added dropwise BCl_3 (1.06 mL of a 1.0 M solution in hexanes, 1.06 mmol). The reaction mixture was stirred at 0 °C for 5.5 hours and was then poured into a vigorously stirring solution of CH_3CN/H_2O (10 mL, 49:1 respectively) at 0 °C. The organics were concentrated *in vacuo* and then H_2O (20 mL) was added. The organics were extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc 85:15) afforded phenol **371** as a yellow solid (42 mg, 26%) **m.p.** 46–48 °C and benzofuran **372** as a yellow solid (46 mg, 28%) **m.p.** 77–79 °C.



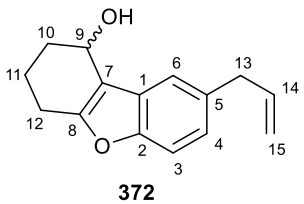
To a solution of enone **366** (609 mg, 2.52 mmol) in CH_2Cl_2 (12.6 mL) at -78 °C was added BCl_3 (4.53 mL of a 1.0 M solution in hexanes, 4.53 mmol) over 1 minute. The reaction mixture was warmed to -18 °C and was kept at temperature for 38 hours without stirring. The reaction mixture was added on top of a still biphasic mixture of NaOH (70 mL of a 2.0 M aqueous solution) and CH_2Cl_2 (45 mL). Once added, the biphasic mixture was stirred vigorously for 30 seconds and then HCl (70 mL

of a 3.0 M aqueous solution) was added. The organics were extracted with CH_2Cl_2 (2 x 15 mL) and the combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 4:1) afforded phenol **371** as a yellow solid (272 mg, 47%) **m.p.** 46–48 °C.



371

371: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (s, 1H, ArOH), 7.16 (t, *J* = 4.3 Hz, 1H, H-12), 7.08 (dd, *J* = 8.2, 2.2 Hz, 1H, H-5), 6.91 (d, *J* = 8.2 Hz, 1H, H-4), 6.87 (d, *J* = 2.2 Hz, 1H, H-1), 5.94 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, H-14), 5.10 – 5.02 (m, 2H, H-15), 3.32 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-13), 2.70 – 2.64 (m, 2H, H-9), 2.60 (td, *J* = 6.0, 4.3 Hz, 2H, H-11), 2.19 – 2.07 (m, 2H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 203.2 (Cq), 153.9 (CH), 152.4 (Cq), 140.1 (Cq), 137.9 (CH), 132.4 (Cq), 130.5 (CH), 130.4 (CH), 125.5 (Cq), 118.8 (CH), 115.7 (CH_2), 39.5 (CH_2), 39.0 (CH_2), 27.1 (CH_2), 22.8 (CH_2); **HRMS** (ESI$^+$): $C_{15}H_{16}O_3$ $[M+H]^+$ calcd. 229.1223, found 229.1218; **IR** ν_{max} cm^{-1}: 3381, 2930, 1661, 1655, 1507, 1495, 1428, 1360, 1230, 1173, 911, 824.

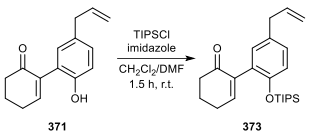


372

372: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 1.8 Hz, 1H, H-6), 7.33 (d, *J* = 8.4 Hz, 1H, H-3), 7.06 (dd, *J* = 8.4, 1.8 Hz, 1H, H-4), 6.01 (dddd, *J* = 16.8, 10.0, 6.7, 6.7 Hz, 1H, H-14), 5.12 – 5.01 (m, 3H, H-9 and

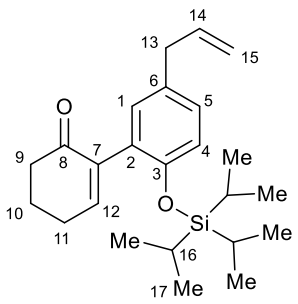
H-15), 3.48 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-13), 2.79 (ddd, *J* = 17.4, 5.1, 5.1 Hz, 1H, H-12), 2.68 (ddd, *J* = 16.8, 7.4, 4.7 Hz, 1H, H-12), 2.14 – 1.87 (m, 4H, H-10 and H-11), 1.66 (d, *J* = 6.9 Hz, 1H, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 156.5 (Cq), 153.5 (Cq), 138.2 (CH), 134.7 (Cq), 127.5 (Cq), 124.4 (CH), 118.9 (CH), 115.64 (CH_2), 115.60 (Cq), 110.9 (CH), 63.6 (CH), 40.4 (CH_2), 32.7 (CH_2), 23.6 (CH_2), 18.9 (CH_2); **HRMS** (ESI^+): $C_{15}H_{16}O_3$ $[M+Na]^+$ calcd. 251.1043, found 251.1032; **IR** ν_{max} cm^{-1}: 3272, 3076, 2974, 2939, 2864, 1634, 1461, 1435, 1190, 1064, 986, 937.

373: 5'-allyl-2'-((triisopropylsilyl)oxy)-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one



To a solution of phenol **371** (35 mg, 0.15 mmol) in CH_2Cl_2 (0.9 mL) at room temperature was added imidazole (26 mg, 0.39 mmol) and triisopropylsilyl chloride (36 µL, 0.17 mmol). The reaction mixture was stirred for 1.25 hours. Analysis by TLC (petroleum ether/EtOAc 4:1) showed incomplete consumption of phenol **371**. To the reaction mixture was added triisopropylsilyl chloride (36 µL, 0.17 mmol) and the reaction mixture was stirred for a further 2 hours at room temperature. TLC analysis showed incomplete consumption of phenol **371**. To the reaction mixture was added imidazole (20 mg, 0.30 mmol) and triisopropylsilyl chloride (50.0 µL, 0.24 mmol) and the reaction

mixture was stirred for a further 16 hours. TLC analysis showed incomplete consumption of phenol **371**. To the reaction mixture was added imidazole (73 mg, 1.1 mmol), triisopropylsilyl chloride (72.0 µL, 0.34 mmol) and DMF (0.1 mL) and the reaction mixture was stirred for a further 1.5 hours. By TLC analysis, there was a faint presence of phenol **371**. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was washed with HCl (10 mL of a 1.0 M aqueous solution). The organics were extracted with CH_2Cl_2 (2 x 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/EtOAc, 99:1 to 97:3) provided TIPS protected phenol **373**. Further purification by flash column chromatography (petroleum ether/acetone 49:1) was performed which gave **373** as a colourless solid (39 mg, 66%) **m.p.** 39–41 °C.

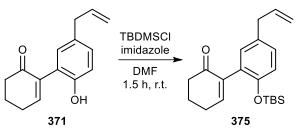


373

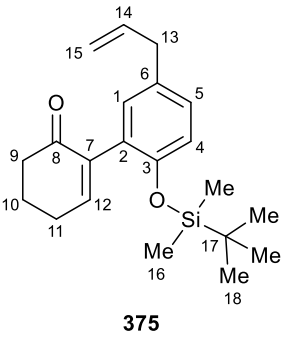
373: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 (dd, *J* = 8.3, 2.4 Hz, 1H, H-5), 6.91 (t, *J* = 4.2 Hz, 1H, H-12), 6.84 (d, *J* = 2.4 Hz, 1H, H-1), 6.73 (d, *J* = 8.3 Hz, 1H, H-4), 5.95 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H, H-14), 5.09 – 5.01 (m, 2H, H-15), 3.30 (ddd, *J* = 6.8, 1.4, 1.4 Hz, 2H, H-13), 2.59 – 2.52 (m, 2H, H-9), 2.48 (td, *J* = 6.0, 4.2 Hz, 2H, H-11), 2.14 – 2.06 (m, 2H, H-10), 1.27 – 1.16 (m, 3H, H-16), 1.05 (d, *J* = 7.3 Hz, 18H, H-17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 197.3 (Cq), 151.9 (Cq), 148.3 (CH), 139.4 (Cq), 138.0 (CH), 131.7 (Cq), 131.2 (CH), 128.8 (CH), 128.2 (Cq), 118.1

(CH), 115.6 (CH_2), 39.5 (CH_2), 38.9 (CH_2), 26.5 (CH_2), 23.2 (CH_2), 18.2 (CH_3), 13.2 (CH); **HRMS** (ESI^+): $C_{24}H_{36}O_2Si$ $[M+H]^+$ calcd. 385.2557, found 385.2557; **IR** ν_{max} cm^{-1}: 2943, 2892, 2866, 1683, 1494, 1279, 1244, 922, 882, 683.

375: 5'-allyl-2'-((tert-butyldimethylsilyl)oxy)-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one



To a solution of phenol **371** (60 mg, 0.26 mmol) in DMF (1.0 mL) at 0 °C was added imidazole (45 mg, 0.66 mmol) and TBSCl (44 mg, 0.29 mmol). The reaction mixture was warmed to room temperature and was stirred for 2.5 hours. The organics were diluted with EtOAc (20 mL) and were washed with HCl (5 mL of a 1.0 M aqueous solution), then brine (2 x 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 92:8) afforded silyl phenol ether **375** as a colourless solid (65 mg, 72%) **m.p.** 38–40 °C.

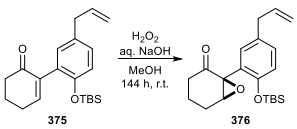


375

375: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (dd, *J* = 8.2, 2.4 Hz, 1H, H-5), 6.92 (t, *J* = 4.2 Hz, 1H, H-12), 6.86 (d, *J* = 2.4 Hz, 1H, H-1), 6.74 (d, *J* = 8.2 Hz, 1H, H-4), 5.95 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H, H-14), 5.11 – 5.00 (m, 2H, H-15), 3.31 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-13), 2.58 – 2.52 (m, 2H, H-9), 2.49

(td, *J* = 6.0, 4.2 Hz, 2H, H-11), 2.15 – 2.07 (m, 2H, H-10), 0.92 (s, 9H, H-18), 0.14 (s, 6H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 197.4 (Cq), 151.4 (Cq), 148.6 (CH), 139.2 (Cq), 137.9 (CH), 132.3 (Cq), 131.2 (CH), 128.9 (CH), 128.7 (Cq), 118.9 (CH), 115.6 (CH_2), 39.5 (CH_2), 38.9 (CH_2), 26.5 (CH_2), 25.9 (CH_3), 23.2 (CH_2), 18.2 (Cq), -4.16 (CH_3); **HRMS** (ESI^+): $C_{21}H_{30}O_2Si$ $[M+H]^+$ calcd. 343.2088, found 343.2098; **IR** ν_{max} cm^{-1}: 2953, 2929, 2895, 2857, 1680, 1493, 1244, 917, 838, 823, 806, 778, 734.

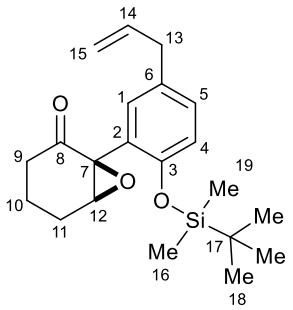
376: (±)-(1*S*,6*S*)-1-(5-allyl-2-((tert-butyldimethylsilyl)oxy)phenyl)-7-oxabicyclo[4.1.0]heptan-2-one



To a solution of TBS protected phenol **375** (60 mg, 0.18 mmol) in MeOH (1.8 mL) at room temperature was added sequentially H_2O_2 (2.90 mL of a 30% w/w aqueous solution, 28.4 mmol)* and NaOH (0.36 mL of a 2.0 M aqueous solution, 0.72 mmol). The reaction mixture was stirred for 144 hours at room temperature and ** then the organics were extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2/Et_2O, 36:1:3) gave epoxide **376** as a colourless oil (approximately 60% purity by ^{1}H NMR spectroscopy, 52 mg, 49%).

*miscalculated the molarity of the aqueous solution and therefore a large excess was used. Reaction requires optimisation.

a work-up using $Na_2S_2O_3$ to reduce any H_2O_2 should have been performed which likely led to the low purity obtained for **376.



375

376: ^{1}H NMR* (400 MHz, $CDCl_3$) δ: 7.13 (d, *J* = 2.4 Hz, 1H, H-1), 7.01 (dd, *J* = 8.3, 2.4 Hz, 1H, H-5), 6.73 (d, *J* = 8.3 Hz, 1H, H-4), 5.93 (dddd, *J* = 16.9, 10.0, 6.8, 6.8 Hz, 1H, H-14), 5.11 – 5.01 (m, 2H, H-15), 3.49 – 3.46 (m, 1H, H-12), 3.31 (d, *J* = 6.8 Hz, 2H, H-13), 2.68 – 2.57 (m, 1H, H-9), 2.40 – 2.30 (m, 1H, H-9 or H-11)*, 2.26 – 2.15 (m, 1H, H-9 or H-11)*, 2.14 – 1.95 (m, 2H, H-10 and H-11)*, 0.96 (s, 9H, H-18), 0.27 (s, 3H, H-16), 0.24 (s, 3H, H-19).; **^{13}C NMR**** (101 MHz, $CDCl_3$) δ: 203.4[a], 152.2[a], 137.7[a], 132.3[a], 131.1[a], 129.4, 128.7, 117.3[a], 115.8[a], 77.4, 62.9[a], 39.5, 37.3, 26.5, 26.1, 23.8, 17.6, -3.6, -3.7; **HRMS** (ESI^+): $C_{21}H_{30}O_3Si$ $[M+H]^+$ calcd. 359.2037, found 359.2028.

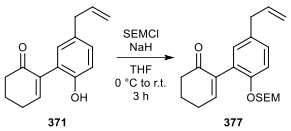
IR was not taken due to purity of sample.

*2D NMR spectroscopy was not taken. One ^{1}H chemical shift (likely H-10) was not observed. Unable to assign with confidence the chemical shifts associated with H-9, H-10 and H-11.

It was difficult to say with certainty which signals from the ^{13}C NMR spectra belong to **375 as 2D NMR spectra was not obtained. The signals that have been assigned with confidence due to their

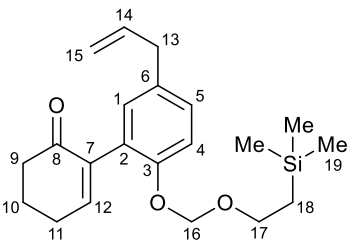
distinctive chemical shifts have been designated an "**a**". All other chemical shifts were estimated when compared against the ^{13}C chemical shifts of **375**. Likewise, assignments of Cq, CH, CH_2, and CH_3 were not made due to lack of data obtained.

377: 5'-allyl-2'-((2-(trimethylsilyl)ethoxy)methoxy)-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one



371 377

To phenol **371** (10 mg, 44 µmol) in dry THF (0.4 mL) at 0 °C was added sequentially SEMCl (20 µL, 110 µmol) then NaH (18 mg of a 60% w/w solid dispersion in mineral oil, 440 µmol). The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. To the reaction mixture was added $NaHCO_3$ (6 mL of a saturated aqueous solution), and the organics were extracted with CH_2Cl_2 (5 x 3 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 9:1) afforded SEM phenol ether **377** as a colourless oil (9 mg, 56%).

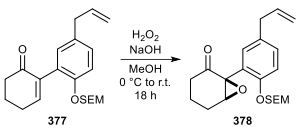


377

377: ^{1}H NMR (400 MHz, C_6D_6) δ: 7.27 (d, *J* = 8.3 Hz, 1H, H-4), 7.04 (dd, *J* = 8.3, 2.3 Hz, 1H, H-5), 6.97 (d, *J* = 2.3 Hz, 1H, H-1), 6.51 (t, *J* = 4.2 Hz, 1H, H-12), 5.90 (ddt, *J* = 16.7, 10.0, 6.7 Hz, 1H, H-14), 5.11 (s, 2H, H-16), 5.06 – 4.96 (m, 2H, H-

15), 3.79 – 3.70 (m, 2H, H-17), 3.22 (ddd, *J* = 6.5, 1.3, 1.3 Hz, 2H, H-13), 2.39 – 2.29 (m, 2H, H-9), 1.84 (td, *J* = 6.0, 4.2 Hz, 2H, H-11), 1.62 – 1.52 (m, 2H, H-10), 0.98 – 0.90 (m, 2H, H-18), -0.03 (s, 9H, H-19); **^{13}C NMR** (101 MHz, C_6D_6) δ: 195.3 (Cq), 154.5 (Cq), 146.6 (CH), 140.2 (Cq), 138.2 (CH), 133.0 (Cq), 131.3 (CH), 129.4 (CH), 128.5 (Cq), 115.6 (CH_2), 115.0 (CH), 93.7 (CH_2), 66.3 (CH_2), 39.8 (CH_2), 39.0 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 18.2 (CH_2), -1.29 (CH_3); **HRMS** (ESI$^+$): $C_{21}H_{30}O_3Si$ $[M+H]^+$ calcd. 359.2037, found 359.2038; **IR** ν_{max} cm^{-1}: 2951, 2925, 2895, 1682, 1495, 1248, 1228, 1083, 992, 857, 833.

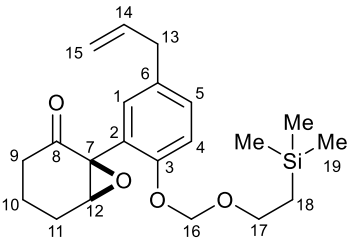
378: (±)-(1*S*,6*S*)-1-(5-allyl-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)-7-oxabicyclo[4.1.0]heptan-2-one



377 378

To SEM phenol ether **377** (9 mg, 0.030 mmol) in MeOH (0.3 mL) at room temperature was added sequentially H_2O_2 (0.25 mL of a 30% w/w aqueous solution, 2.5 mmol) and NaOH (60 µL of a 0.5 M aqueous solution, 30 µmol). The reaction mixture was stirred for 18 hours at room temperature and was then diluted with H_2O (5 mL) and cooled to 0 °C. To the reaction mixture was cautiously added $Na_2S_2O_3$ (2 mL of a saturated aqueous solution). The organics were extracted with CH_2Cl_2 (5 x 3 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash

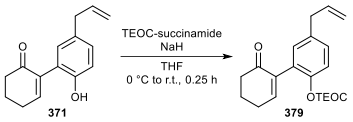
column chromatography (petroleum ether/EtOAc, 9:1) gave epoxide **378** as a colourless solid (6 mg, 66%) **m.p.** 40–42 °C.



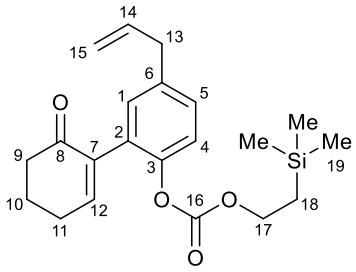
378

378: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 2.2 Hz, 1H, H-1), 7.09 (dd, *J* = 8.4, 2.2 Hz, 1H, H-5), 7.00 (d, *J* = 8.4 Hz, 1H, H-4), 5.94 (dddd, *J* = 16.9, 10.0, 6.8, 6.8 Hz, 1H, H-14), 5.17 – 5.12 (m, 2H, H-16), 5.10 – 5.01 (m, 2H, H-15), 3.72 – 3.62 (m, 2H, H-17), 3.39 (ddd, *J* = 2.4, 1.6, 0.6 Hz, 1H, H-12), 3.33 (ddd, *J* = 6.8, 1.4, 1.4 Hz, 2H, H-13), 2.59 (dddd, *J* = 16.4, 4.3, 4.3, 1.0 Hz, 1H, H-9), 2.40 – 2.32 (m, 1H, H-11), 2.23 (ddd, *J* = 16.4, 12.0, 5.6 Hz, 1H, H-9), 2.10 (dddd, *J* = 14.9, 11.1, 5.3, 1.6 Hz, 1H, H-11), 2.00 – 1.88 (m, 1H, H-10), 1.84 – 1.75 (m, 1H, H-10), 0.96 – 0.91 (m, 2H, H-18), 0.01 (s, 9H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 203.2 (Cq), 153.4 (Cq), 137.6 (CH), 133.3 (Cq), 129.5 (CH), 127.4 (CH), 125.0 (Cq), 115.9 (CH_2), 113.4 (CH), 92.9 (CH_2), 66.4 (CH_2), 62.9 (CH), 60.9 (Cq), 39.6 (CH_2), 37.6 (CH_2), 24.1 (CH_2), 18.1 (CH_2), 17.3 (CH_2), -1.26 (CH_3); **HRMS** (ESI^+): $C_{21}H_{30}O_4Si$ $[M+NH_4]^+$ calcd. 392.2252, found 392.2264; **IR** ν_{max} cm^{-1}: 2954, 2925, 2854, 1720, 1498, 1249, 1090, 995, 860, 836.

379: 5-allyl-2'-oxo-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl (2-(trimethylsilyl)ethyl) carbonate



To a solution of phenol **371** (11 mg, 48 µmol) in dry THF (0.45 mL) at 0 °C was added NaH (2 mg of a 60% w/w dispersion in mineral oil, 50 µmol). The mixture was stirred for 5 minutes at 0 °C and then TEOC-succinamide (18 mg, 68 µmol) was added. The reaction mixture was warmed to room temperature and was stirred for 10 minutes and then H_2O (2 mL) was added. The organics were diluted with Et_2O (5 mL) and were washed with H_2O (3 mL), then brine (3 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated flash column chromatography (petroleum ether/Et_2O, 9:1 to 7:3) afforded TEOC phenol ether **379** as a colourless oil (10 mg, 56%).

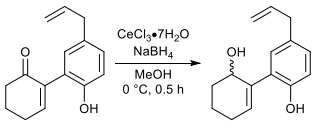


379

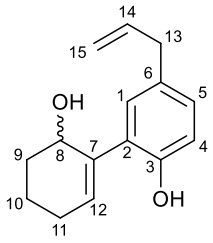
379: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (dd, *J* = 8.3, 2.2 Hz, 1H, H-5), 7.11 (d, *J* = 8.3 Hz, 1H, H-4), 6.97 (d, *J* = 2.2 Hz, 1H, H-1), 6.95 (t, *J* = 4.2 Hz, 1H, H-12), 5.95 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H, H-14), 5.18 – 4.98 (m, 2H, H-15), 4.34 – 4.21 (m, 2H, H-17), 3.37 (ddd, *J* = 6.8, 1.4, 1.4 Hz, 2H, H-13), 2.59 – 2.53 (m, 2H, H-9), 2.50 (td, *J* = 6.0, 4.1 Hz, 2H, H-11), 2.15 – 2.06 (m, 2H, H-10), 1.11 – 1.04 (m, 2H, H-18), 0.05 (s, 9H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 196.9 (Cq), 153.5 (Cq), 149.5 (CH), 147.1 (Cq), 137.8 (Cq), 137.6 (Cq), 137.1

(CH), 131.0 (CH), 129.7 (Cq), 129.2 (CH), 122.0 (CH), 116.3 (CH_2), 67.3 (CH_2), 39.7 (CH_2), 38.7 (CH_2), 26.5 (CH_2), 23.1 (CH_2), 17.6 (CH_2), -1.37 (CH_3); **HRMS** (ESI^+): $C_{21}H_{28}O_4Si$ $[M+Na]^+$ calcd. 395.1649, found 395.1659; **IR** ν_{max} cm^{-1}: 2954, 2924, 2854, 1760, 1684, 1248, 1227, 1202, 859, 839.

381: 5'-allyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2,2'-diol



To a suspension of phenol **371** (200 mg, 0.744 mmol) in MeOH (7.9 mL) at 0 °C was added sequentially $CeCl_3•7H_2O$ (351 mg, 0.942 mmol) then $NaBH_4$ (36 mg, 0.94 mmol). The reaction mixture was stirred for 0.5 hours at 0 °C and then H_2O (10 mL) was added. The organics were extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 85:15) afforded allylic alcohol **381** as a pale-yellow oil. To the pale-yellow oil was added pentane (20 mL) and the mixture was sonicated until the oil was dispersed and then the mixture was cooled to -20 °C for 7 days which gave a precipitate. The precipitate was collected by suction filtration and the filter cake was washed with pentane (3 x 3 mL) which gave allylic alcohol **381** as a colourless solid (142 mg, 78%) **m.p.** 50–53 °C.



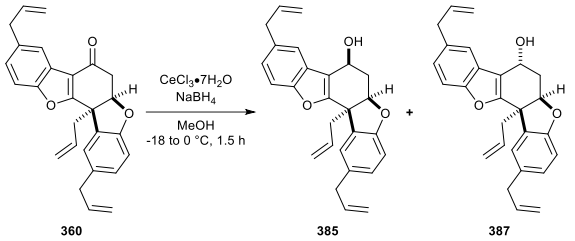
381

381: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (s, 1H, ArOH), 6.99 (dd, *J* = 8.2, 2.3 Hz, 1H, H-5), 6.85 (d, *J* = 2.3 Hz, 1H, H-1), 6.82 (d, *J* = 8.2 Hz, 1H, H-4), 6.01 (dd, *J* = 4.8, 3.0 Hz, 1H, H-12), 5.95 (dddd, *J* = 16.8, 10.0, 6.6, 6.6 Hz, 1H, H-14), 5.10 – 5.01 (m, 2H, H-15), 4.46 – 4.39 (m, 1H, H-8), 3.30 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-13), 2.41 (s, 1H, alkylOH), 2.38 – 2.28 (m, 1H, H-11), 2.24 – 2.10 (m, 1H, H-11), 1.99 – 1.91 (m, 1H, H-9), 1.89 – 1.79 (m, 2H, H-9 and H-10), 1.77 – 1.67 (m, 1H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 152.6 (Cq), 138.1 (CH), 136.8 (Cq), 133.3 (CH), 131.3 (Cq), 130.4 (CH), 129.19 (CH), 129.15 (Cq), 116.7 (CH), 115.5 (CH_2), 67.8 (CH), 39.5 (CH_2), 31.4 (CH_2), 26.1 (CH_2), 16.3 (CH_2); **HRMS** (ESI^-): $C_{15}H_{18}O_2$ $[M-H]^+$ calcd. 229.1234, found 229.1243; **IR** ν_{max} cm^{-1}: 3234, 3076, 3019, 2923, 2852, 1491, 1242, 914.

7.3.2: Studies towards fargenone A from benzofuran 360 (Section 2.2.4)

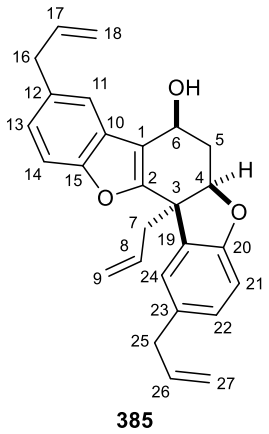
385: (±)-allylic alcohol benzofuran

387: (±)-allylic alcohol benzofuran



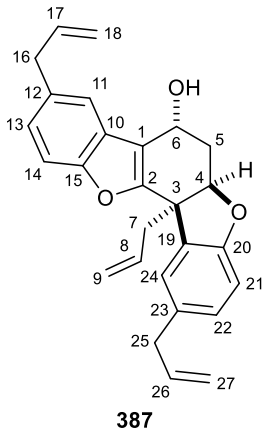
To a solution of benzofuran simonsol F **360** (35 mg, 0.088 mmol) in CH_2Cl_2 (0.30 mL) and MeOH (0.90 mL) at 0 °C was added $CeCl_3•7H_2O$ (41 mg, 0.11 mmol). The reaction mixture was stirred for 5 minutes at 0 °C and was then cooled to -18 °C. At temperature, to the reaction mixture was added $NaBH_4$ (4 mg, 0.1 mmol) and the reaction mixture was stirred for 1 hour at -18 °C and then 0.5 hours at 0 °C and then H_2O (10 mL) was added. The organics were extracted with EtOAc (3 x 15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (pentane/CH_2Cl_2/acetone, 90:5:5) gave allylic alcohol benzofuran **385** as a colourless oil (13 mg, 37%) and allylic alcohol benzofuran **387** as a colourless oil (13 mg, 37%).

The diastereoisomers were assigned by NOESY with an interaction through-space detected between "OH and H-4" and "OH and H-8" for **387**, whereas these interactions were not observed by NOESY for **385** (see Figure 33).



385

385: ^{1}H NMR (500 MHz, C_6D_6) δ: 7.56 (d, *J* = 1.8 Hz, 1H, H-11), 7.43 (d, *J* = 1.8 Hz, 1H, H-24), 7.29 (d, *J* = 8.4 Hz, 1H, H-14), 6.89 (dd, *J* = 8.4, 1.8 Hz, 1H, H-13), 6.82 (dd, *J* = 8.2, 1.8 Hz, 1H, H-22), 6.78 (d, *J* = 8.2 Hz, 1H, H-21), 5.93 (dddd, *J* = 16.8, 10.1, 6.6, 6.6 Hz, 1H, H-17), 5.84 (dddd, *J* = 17.0, 10.3, 6.6, 6.6 Hz, 1H, H-26), 5.48 (dddd, *J* = 16.7, 10.1, 8.2, 6.4 Hz, 1H, H-8), 5.04 – 4.94 (m, 5H, H-6, H-18 and H-27), 4.91 – 4.80 (m, 3H, H-4 and H-9), 3.29 (ddd, *J* = 6.6, 1.3, 1.3 Hz, 2H, H-16), 3.14 (ddd, *J* = 6.6, 1.3, 1.3 Hz, 2H, H-25), 3.05 (dddd, *J* = 14.1, 6.4, 1,4, 1.4 Hz, 1H, H-7), 2.60 (dd, *J* = 14.1, 8.2 Hz, 1H, H-7), 2.47 (ddd, *J* = 13.8, 5.0, 5.0 Hz, 1H, H-5), 1.79 (ddd, *J* = 13.8, 8.4, 3.4 Hz, 1H, H-5), 1.22 – 1.11 (m, 1H, OH); **^{13}C NMR** (126 MHz, C_6D_6) δ: 158.0 (Cq), 154.5 (Cq), 153.7 (Cq), 138.5 (CH), 138.3 (CH), 134.8 (Cq), 133.6 (CH), 133.0 (Cq), 131.5 (Cq), 129.6 (CH), 127.6 (Cq), 125.1 (CH), 124.9 (CH), 121.1 (CH), 118.7 (CH_2), 117.7 (Cq), 115.5 (CH_2), 115.4 (CH_2), 111.3 (CH), 110.4 (CH), 86.3 (CH), 62.6 (CH), 49.0 (Cq), 41.2 (CH_2), 40.5 (CH_2), 40.0 (CH_2), 36.5 (CH_2); **HRMS** (ESI$^+$): $C_{27}H_{26}O_3$ $[M+Na]^+$ calcd. 421.1774, found 421.1783; **IR** ν_{max} cm^{-1}: 3390, 3076, 3003, 2977, 2923, 2852, 1638, 1613, 1487, 1459, 1434, 1414, 1337, 1269, 1247, 1213, 1195, 1179, 1144, 1122, 1097, 1029, 995, 946, 915, 854, 820, 805, 794, 750, 736, 668, 587.



387

387: ^{1}H NMR (500 MHz, C_6D_6) δ: 7.53 (d, *J* = 1.8 Hz, 1H, H-11), 7.44 (d, *J* = 1.9 Hz, 1H, H-24), 7.25 (d, *J* = 8.4 Hz, 1H, H-14), 6.87 (dd, *J* = 8.4, 1.8 Hz, 1H, H-13), 6.78 (dd, *J* = 8.1, 1.9 Hz, 1H, H-22), 6.64 (d, *J* = 8.1 Hz, 1H, H-21), 5.96 – 5.82 (m, 2H, H-17 and H-26), 5.36 (dddd, *J* = 16.8, 10.1, 8.1, 6.6 Hz, 1H, H-8), 5.03 – 4.95 (m, 4H, H-18 and H-27), 4.89 (ddd, *J* = 11.2, 4.7, 3.0 Hz, 1H, H-6), 4.86 – 4.77 (m, 2H, H-9), 4.68 (dd, *J* = 4.4, 3.0 Hz, 1H, H-4), 3.27 (ddd, *J* = 6.3, 1.0, 1.0 Hz, 2H, H-16), 3.16 (ddd, *J* = 6.9, 1.5, 1.5 Hz, 1H, H-25), 2.95 (dddd, *J* = 14.1, 6.6, 1.4, 1.4 Hz, 1H, H-7), 2.56 – 2.47 (m, 2H, H-5 and H-7), 2.23 (ddd, *J* = 11.2, 2.7, 2.7 Hz, 1H, OH), 1.88 (ddd, *J* = 14.9, 4.7, 3.0 Hz, 1H, H-5); **^{13}C NMR** (101 MHz, C_6D_6) δ: 157.1 (Cq), 154.5 (Cq), 154.0 (Cq), 138.4 (CH), 138.2 (CH), 135.1 (Cq), 133.6 (Cq), 133.2 (CH), 131.7 (Cq), 129.6 (CH), 127.9 (Cq), 125.4 (CH), 125.0 (CH), 120.3 (CH), 118.7 (CH_2), 117.1 (Cq), 115.6 (CH_2), 115.5 (CH_2), 111.3 (CH), 110.7 (CH), 87.9 (CH), 62.0 (CH), 48.9 (Cq), 40.5 (CH_2), 40.4 (CH_2), 40.0 (CH_2), 34.2 (CH_2); **HRMS** (ESI^+): $C_{27}H_{26}O_3$ $[M+Na]^+$ calcd. 421.1774, found 421.1774; **IR** ν_{max} cm^{-1}: 3561, 3417, 3076, 3003, 2977, 2924, 2911, 2856, 2838, 1638, 1615, 1486, 1469, 1457, 1434, 1414, 1404, 1334, 1245, 1196, 1173, 1122, 1093, 1066, 1037, 995, 965, 954, 916, 882, 837, 818, 788, 669, 431.

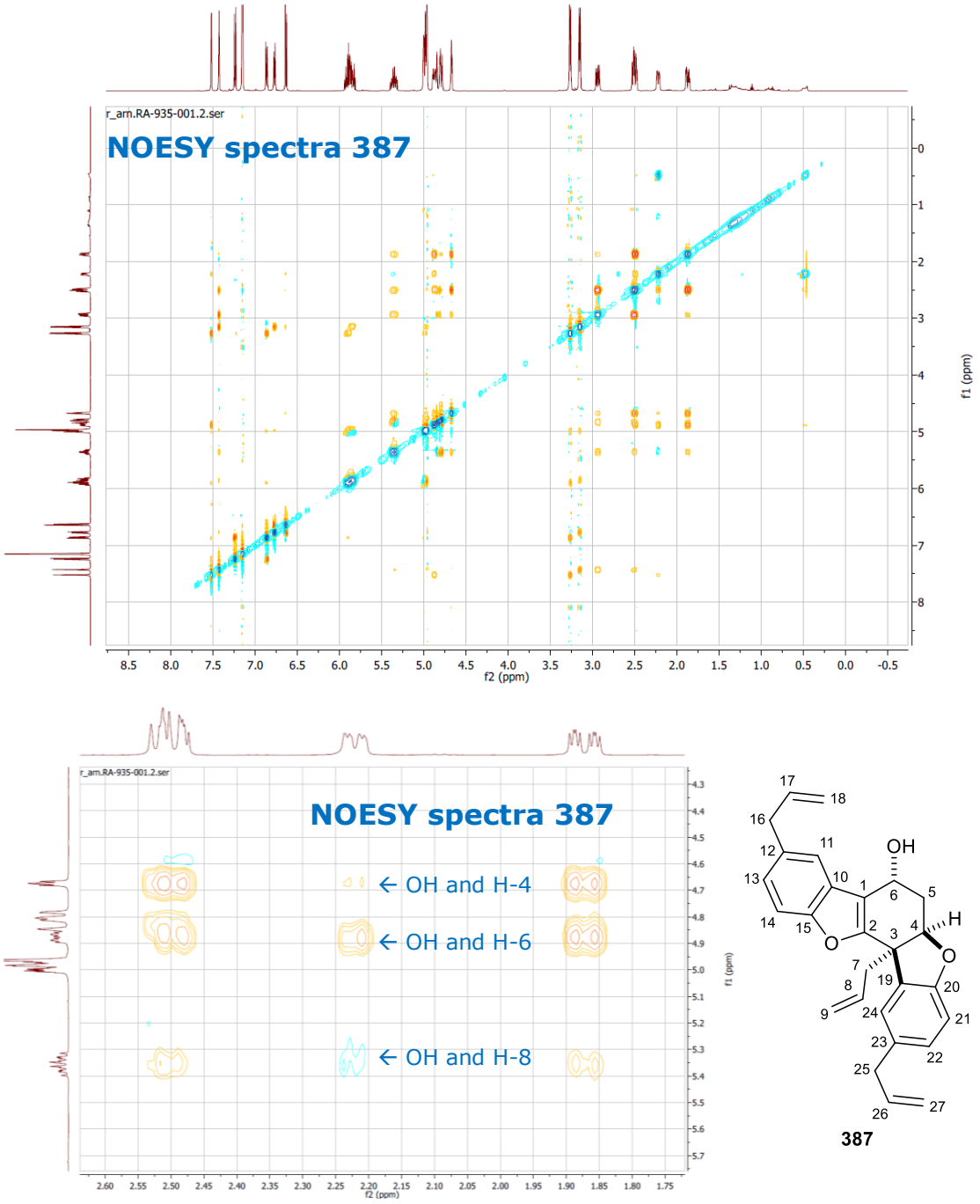
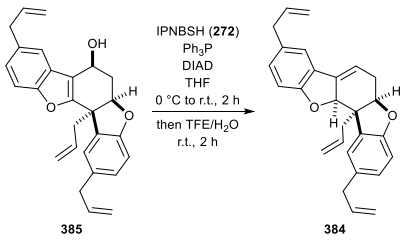


Figure 33. *Evidence by NOESY to support the assignment of stereochemistry of* ***387*** *and subsequently* ***385****. Interaction observed through space between "OH (C-6) and H-4" and "OH (C-6) and H-8".*

384: (±)-di(hydrodibenzofuran)

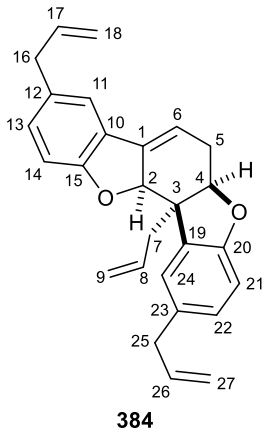


To a solution of allylic alcohol **385** (14 mg, 0.035 mmol), IPNBSH (**272**) (18 mg, 0.070 mmol) and PPh_3 (18 mg, 0.070 mmol) in dry THF (0.70 mL) at 0 °C was added DIAD (14 µL, 0.070 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was then stirred for 2 hours. To the reaction mixture was added a solution of 2,2,2-trifluoroethanol (0.18 mL) and H_2O (0.18 mL) and the reaction mixture was stirred for a further 2 hours at room temperature and then H_2O (0.7 mL) was added. The organics were extracted with Et_2O (3 x 0.7 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 95:5 to 7:3) afforded di(hydrodibenzofuran) **384** as a colourless oil (*approximate 80% purity by ^1H NMR spectroscopy, 3 mg, 18%) (37% brsm).

An interaction through space by NOESY was observed between H-2 and H-7 of **384** (see Figure 34).

*^1H and ^{13}C NMR spectroscopy showed high levels of BHT present (approximately 15% w/w determined by ^1H NMR spectroscopy) in sample.

An updated experimental for the synthesis of **384** from allylic alcohol **385** has been provided in Section 7.10.



384

384: ^{1}H NMR (500 MHz, C_6D_6) δ: 7.46 (d, *J* = 1.9 Hz, 1H, H-11), 7.12 (d, *J* = 1.9 Hz, 1H, H-24), 6.92 (d, *J* = 8.3 Hz, 1H, H-14), 6.91 (dd, *J* = 8.3, 1.9 Hz, 1H, H-13), 6.85 (dd, *J* = 8.1, 1.9 Hz, 1H, H-22), 6.83 (d, *J* = 8.1 Hz, 1H, H-21), 5.94 (ddd, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-17), 5.87 (ddd, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-26), 5.55 – 5.45 (m, 2H, H-6 and H-8), 5.06 – 4.98 (m, 5H, H-2, H-18 and H-27), 4.84 – 4.72 (m, 2H, H-9), 4.64 (dd, *J* = 8.5, 7.1 Hz, 1H, H-4), 3.25 (ddd, *J* = 6.6, 1.6 Hz, 2H, H-16), 3.18 (ddd, *J* = 6.6, 1.6 Hz, 2H, H-25), 2.93 (dddd, *J* = 14.2, 5.6, 1.7 Hz, 1H, H-7), 2.74 (ddd, *J* = 14.8, 7.1 Hz, 1H, H-5), 2.10 – 2.02 (m, 2H, H-5 and H-7); **^{13}C NMR** (126 MHz, C_6D_6) δ: 163.1 (Cq), 159.0 (Cq), 140.7 (Cq), 138.5 (CH), 138.1 (CH), 134.3 (CH), 133.0 (Cq), 132.9 (Cq), 132.2 (Cq), 131.0 (CH), 129.6 (CH), 124.81 (CH), 124.79 (Cq), 121.5 (CH), 118.6 (CH_2), 115.7 (CH_2), 115.4 (CH_2), 110.7 (CH), 109.9 (CH), 109.2 (CH), 88.9 (CH), 83.6 (CH), 54.8 (Cq), 40.1 (CH_2), 40.0 (CH_2), 37.9 (CH_2), 30.2 (CH_2); **HRMS** (ESI^+): $C_{27}H_{26}O_3$ $[M+H]^+$ calcd. 383.2006, found 383.2003.

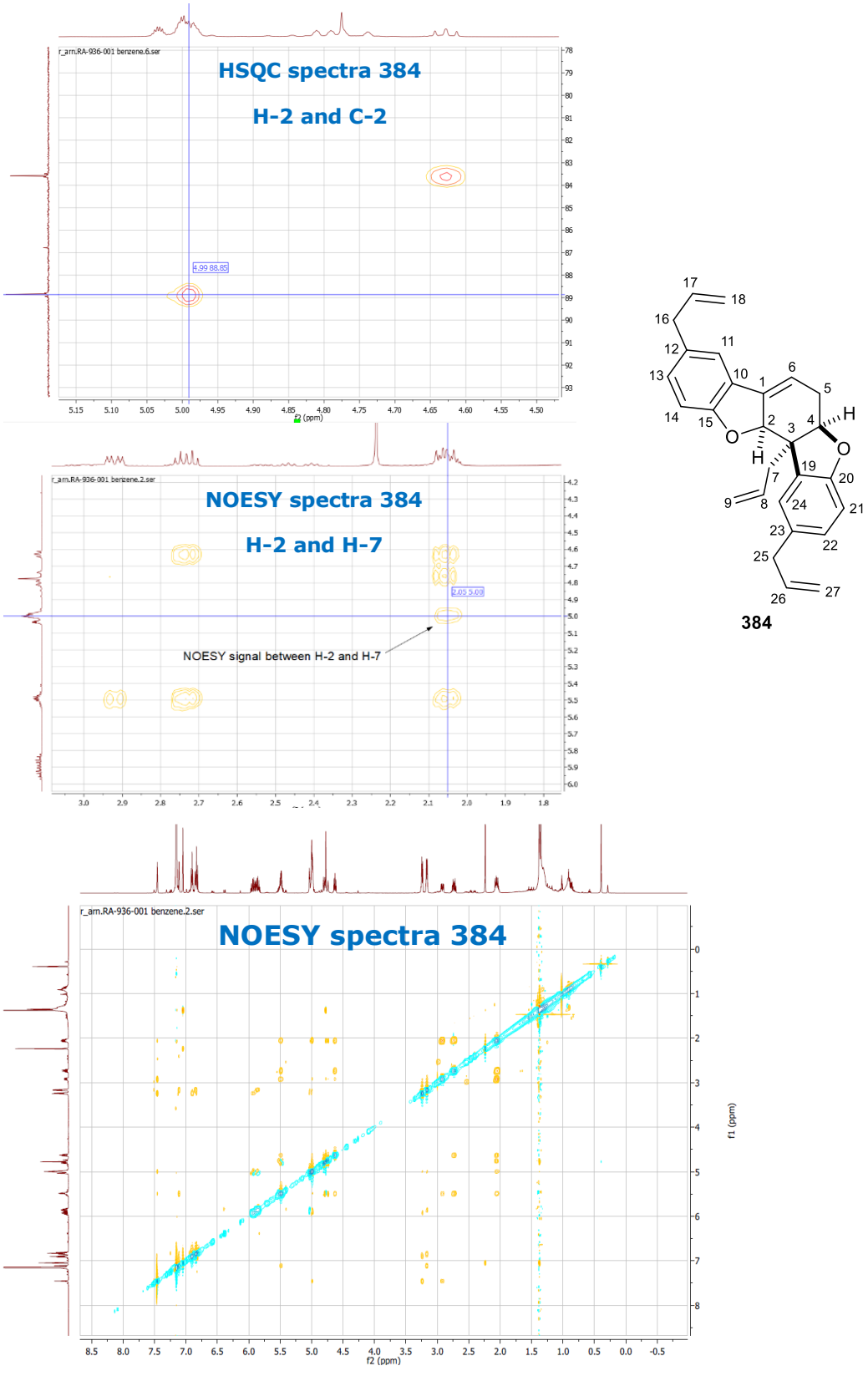
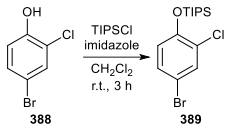


Figure 34. *Evidence by HSQC and NOESY to support the assignment of stereochemistry of* ***384****. H-2 was assigned by HSQC from the distinctive* ^{13}C *chemical shift of C-2. Interaction observed through space by NOESY between H-2 and H-7.*

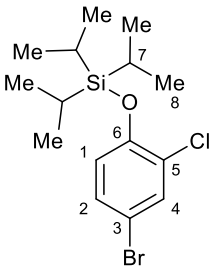
7.4: Studies towards the synthesis of simonsol F

7.4.1: First-generation study towards the synthesis of simonsol F (Section 2.3.1)

389: (4-bromo-2-chlorophenoxy)triisopropylsilane



To a solution of 4-bromo-2-chlorophenol (**388**) (1.00 g, 4.82 mmol) and imidazole (820 mg, 12.1 mmol) in CH_2Cl_2 (30.0 mL) at room temperature was added triisopropylsilyl chloride (1.23 mL, 5.74 mmol). The reaction mixture was stirred at room temperature for 3 hours and then H_2O (20 mL) was added. The organics were extracted with CH_2Cl_2 (3 x 5 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 97:3) gave silyl phenol ether **389** as a clear oil (1.67 g, 95%).



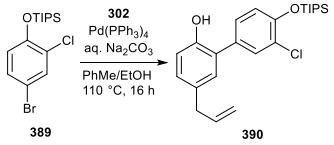
389

389: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 2.5 Hz, 1H, H-4), 7.20 (dd, *J* = 8.7, 2.5 Hz, 1H, H-2), 6.77 (d, *J* = 8.7 Hz, 1H, H-1), 1.35 – 1.24 (m, 3H, H-7), 1.11 (d, *J* = 7.3 Hz, 18H, H-8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 151.4 (Cq), 132.7 (CH), 130.4 (CH), 126.5 (Cq), 121.2 (CH), 112.7 (Cq), 17.9 (CH_3), 12.9 (CH); **IR** ν_{max} cm^{-1}: 2945, 2892, 2867, 1580, 1475, 1383, 1286, 1058.

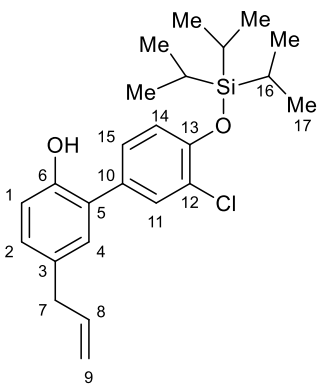
HRMS: Compound did not provide targeted mass upon ionisation.

Spectroscopic data obtained for **389** were consistent with those previously reported.[372]

390: 5-allyl-3'-chloro-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-ol



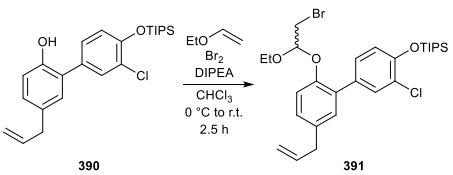
A biphasic mixture of silyl phenol ether **389** (1.04 g, 2.87 mmol), boronic acid **302** (920 mg, 5.16 mmol), Na_2CO_3 (9.20 mL of a 2.0 M aqueous solution, 18.4 mmol), PhMe (20.0 mL) and EtOH (9.2 mL) at room temperature was sparged with argon for 5 minutes. To the biphasic mixture $Pd(PPh_3)_4$ (132 mg, 0.114 mmol) was added and the reaction mixture was sparged with argon for a further 5 minutes. The reaction mixture was heated at 110 °C for 16 hours and was then cooled to room temperature. The organics were concentrated *in vacuo* and then the organics were diluted with EtOAc (25 mL) and were filtered through cotton wool. The organics were washed with HCl (2 x 30 mL of a 1.0 M aqueous solution), then brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 95:5) gave biaryl **390** as a pale-yellow oil (1.09 g, 91%).



390

390: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 2.3 Hz, 1H, H-11), 7.21 (dd, *J* = 8.3, 2.3 Hz, 1H, H-15), 7.06 (dd, *J* = 8.1, 2.2 Hz, 1H, H-2), 7.03 (d, *J* = 2.2 Hz, 1H, H-4), 6.99 (d, *J* = 8.3 Hz, 1H, H-14), 6.89 (d, *J* = 8.1 Hz, 1H, H-1), 5.97 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-8), 5.12 – 5.03 (m, 2H, H-9), 4.98 (s, 1H, ArOH), 3.35 (ddd, *J* = 6.8, 1.4, 1.4 Hz, 2H, H-7), 1.43 – 1.29 (m, 3H, H-16), 1.16 (d, *J* = 7.4 Hz, 18H, H-17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 151.7 (Cq), 150.7 (Cq), 137.7 (CH), 132.4 (Cq), 131.0 (CH), 130.6 (CH), 130.2 (CH), 129.2 (CH), 128.1 (CH), 126.6 (Cq), 126.0 (Cq), 120.3 (CH), 115.9 (CH), 115.7 (CH_2), 39.4 (CH_2), 18.0 (CH_3), 12.9 (CH); **HRMS** (ESI^-): $C_{24}H_{33}{}^{35}ClO_2Si$ $[M-H]^-$ calcd. 415.1866, found 415.1862; **IR** ν_{max} cm^{-1}: 3554, 3422, 2944, 2866, 1639, 1599, 1488, 1290.

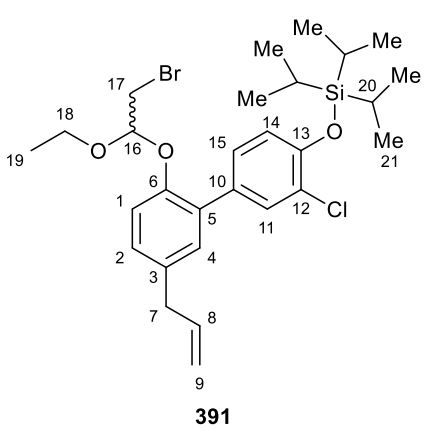
391: ((5'-allyl-2'-(2-bromo-1-ethoxyethoxy)-3-chloro-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane



390 391

To a solution of ethyl vinyl ether (420 µL, 4.38 mmol) in $CHCl_3$ (4.50 mL) at 0 °C was added dropwise bromine (180 µL, 3.50 mmol). The solution was stirred for 15 minutes at 0 °C and then a solution of biaryl **390** (730 mg, 1.75 mmol) and DIPEA (1.22 mL, 7.00 mmol) in $CHCl_3$ (4.50 mL) was added. The reaction mixture

was warmed to room temperature and was stirred for 2.5 hours. The organics were diluted with EtOAc (30 mL) and were washed with $NaHCO_3$ (2 x 25 mL of a saturated aqueous solution) then brine (25 mL). The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2, 4:1) afforded acetal **391** as a pale-yellow oil (950 mg, 95%).

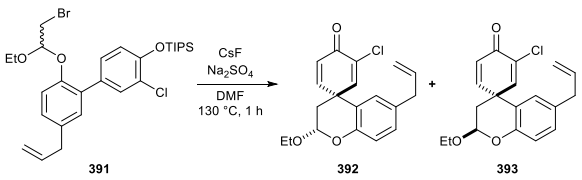


391

391: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 2.3 Hz, 1H, H-11), 7.29 (dd, *J* = 8.4, 2.3 Hz, 1H, H-15), 7.15 – 7.13 (m, 1H, H-Ar), 7.12 – 7.06 (m, 2H, H-Ar), 6.93 (d, *J* = 8.4 Hz, 1H, H-14), 5.97 (dddd, *J* = 16.8, 10.1, 6.7, 6.7 Hz, 1H, H-8), 5.16 – 5.06 (m, 3H, H-9 and H-16), 3.63 (dq, *J* = 9.2, 7.1 Hz, 1H, H-18), 3.48 (dq, *J* = 9.2, 7.1 Hz, 1H, H-18), 3.40 – 3.34 (m, 4H, H-7 and 17), 1.41 – 1.28 (m, 3H, H-20), 1.15 (d, *J* = 7.4 Hz, 18H, H-21), 1.15 – 1.09 (m, 3H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 151.6 (Cq), 151.1 (Cq), 137.3 (CH), 135.0 (Cq), 131.7 (Cq), 131.6 (Cq), 131.3 (CH), 130.9 (CH), 128.7 (CH), 128.6 (CH), 124.8 (Cq), 119.5 (CH), 118.3 (CH), 116.0 (CH_2), 102.3 (CH), 62.9 (CH_2), 39.5 (CH_2), 31.4 (CH_2), 18.0 (CH_3), 15.0 (CH_3), 12.9 (CH); **HRMS** (ESI^+): $C_{28}H_{40}{}^{79}Br^{35}ClO_3Si$ $[M+Na]^+$ calcd. 589.1511, found 589.1518; **IR** ν_{max} cm^{-1}: 2943, 2892, 2866, 1639, 1600, 1485, 1288, 1058.

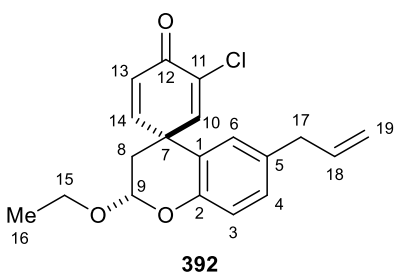
392: (±)-(2*R*,4*S*)-6-allyl-3'-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

393: (±)-(2*R*,4*R*)-6-allyl-3'-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



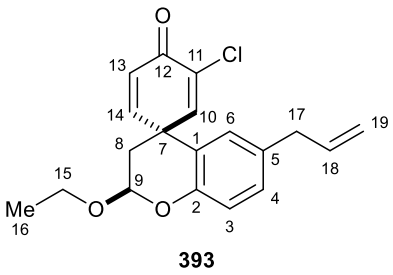
To a solution of acetal **391** (202 mg, 0.352 mmol) in DMF (35.0 mL) was added CsF (160 mg, 1.06 mmol) and Na_2SO_4 (500 mg, 3.52 mmol). The reaction mixture was heated at 130 °C for 1 hour and was then cooled to room temperature. To the reaction mixture was added H_2O (80 mL) and the organics were extracted with Et_2O (2 x 80 mL). The organics were combined and were washed with H_2O (60 mL) then brine (3 x 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O 4:1) afforded spirocycle **392** as a colourless solid (45 mg, 38%) **m.p.** 76–79 °C and spirocylce **393** as a colourless solid (57 mg, 49%) **m.p.** 81–83 °C.

Crystals of spirocycles **392** and **393** were grown by vapour diffusion method; distilled pentane/distilled Et_2O (see Section 6.9).



392: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 10.0, 2.7 Hz, 1H, H-14), 7.05 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 6.98 (d, *J* = 2.7 Hz, 1H, H-6), 6.88 (d, *J* = 8.3 Hz, 1H, H-

3), 6.67 (d, *J* = 2.2 Hz, 1H, H-6), 6.29 (d, *J* = 10.0 Hz, 1H, H-13), 5.87 (dddd, *J* = 17.5, 9.6, 6.7, 6.7 Hz, 1H, H-18), 5.37 (dd, *J* = 3.0, 3.0 Hz, 1H, H-9), 5.06 – 5.00 (m, 2H, H-19), 3.91 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 3.64 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 3.25 (d, *J* = 6.8, 1.5 Hz, 2H, H-17), 2.31 (dd, *J* = 14.0, 3.0 Hz, 1H, H-8), 2.16 (dd, *J* = 14.0, 3.1 Hz, 1H, H-8), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 179.0 (Cq), 154.8 (CH), 149.7 (CH), 149.2 (Cq), 137.1 (CH), 133.6 (Cq), 132.5 (Cq), 130.1 (CH), 128.3 (CH), 125.0 (CH), 118.7 (CH), 118.2 (Cq), 116.0 (CH_2), 95.4 (CH), 64.4 (CH_2), 43.0 (Cq), 39.2 (CH_2), 36.2 (CH_2), 15.10 (CH_3); **HRMS** (ESI^+): $C_{19}H_{19}{}^{35}ClO_3$ $[M+H]^+$ calcd. 331.1095, found 331.1093; **IR** ν_{max} cm^{-1}: 3081, 3049, 2974, 2928, 2913, 2886, 2854, 1667, 1494, 1228, 1120, 1068, 1036, 1007, 832.



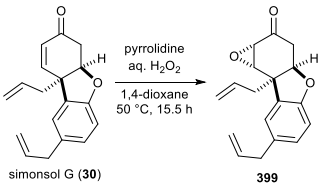
393

393: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 2.7 Hz, 1H, H-10), 7.05 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 6.88 (d, *J* = 8.3 Hz, 1H, H-3), 6.79 (dd, *J* = 9.8, 2.7 Hz, 1H, H-14), 6.67 (d, *J* = 2.2 Hz, 1H, H-6), 6.46 (d, *J* = 9.8 Hz, 1H, H-13), 5.87 (dddd, *J* = 17.5, 9.6, 6.7, 6.7 Hz, 1H, H-18), 5.39 (dd, *J* = 2.8, 2.8 Hz, 1H, H-9), 5.07 – 4.99 (m, 2H, H-19), 3.90 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.65 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.25 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-17), 2.30 (dd, *J* = 14.1, 2.9 Hz, 1H, H-8), 2.17 (dd, *J* = 14.1, 2.6 Hz, 1H, H-8), 1.22 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 179.0 (Cq), 154.2 (CH), 150.6

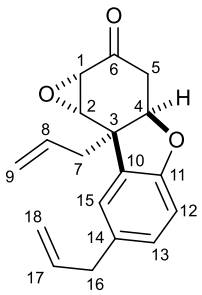
(CH), 149.1 (Cq), 137.1 (CH), 133.6 (Cq), 130.4 (Cq), 130.1 (CH), 128.4 (CH), 127.5 (CH), 118.7 (CH), 118.0 (CH), 116.0 (CH_2), 95.2 (CH), 64.4 (CH_2), 42.6 (Cq), 39.2 (CH_2), 35.9 (CH_2), 15.1 (CH_3); **HRMS** (ESI^+): $C_{19}H_{19}{}^{35}ClO_3$ $[M+H]^+$ calcd. 331.1095, found 331.1100; **IR** ν_{max} cm^{-1}: 3074, 2977, 2930, 1673, 1495, 1222, 1131, 1116, 1067, 1038, 1004, 829.

7.4.2: Studies towards the synthesis of simonsol F from simonsol G (Section 2.3.2)

399: (±)-(1a*S*,3a*R*,8b*R*,8c*S*)-7,8b-diallyl-3,3a,8b,8c-tetrahydrobenzo[b]oxireno[2,3-e]benzofuran-2(1aH)-one



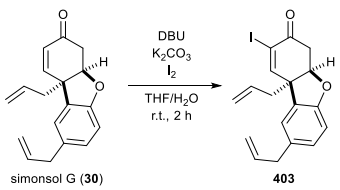
To a solution of simonsol G (**30**) (27 mg, 0.10 mmol) in 1,4-dioxane (0.55 mL) was added pyrrolidine (20 µL, 0.20 mmol) and H_2O_2 (0.90 mL of a 30% w/w aqueous solution, 8.8 mmol). The reaction mixture was heated in a sealed microwave vial at 50 °C for 15.5 hours and was then cooled to 0 °C. To the reaction mixture at 0 °C was added cautiously Na_2SO_3 (5 mL of a saturated aqueous solution) and then the organics were extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 7:3) gave epoxide **399** as a colourless oil (11 mg, 37%).



399

399: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05 (d, *J* = 1.9 Hz, 1H, H-15), 7.01 (dd, *J* = 8.2, 1.9 Hz, 1H, H-13), 6.71 (d, *J* = 8.2 Hz, 1H, H-12), 6.00 – 5.83 (m, 2H, H-8 and H-17), 5.28 – 5.18 (m, 2H, H-9), 5.10 – 5.03 (m, 2H, H-18), 4.79 – 4.71 (m, 1H, H-4), 3.45 (dd, *J* = 4.1, 2.1 Hz, 1H, H-2), 3.34 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-16), 3.25 (dd, *J* = 4.1, 1.0 Hz, 1H, H-1), 3.16 (dd, *J* = 14.6, 3.4 Hz, 1H, H-5), 2.89 (dddd, *J* = 14.2, 6.5, 1.4, 1.4 Hz, 1H, H-7), 2.80 (dddd, *J* = 14.2, 8.2, 1.0, 1.0 Hz, 1H, H-7), 2.62 (ddd, *J* = 14.6, 3.4, 1.1 Hz, 1H, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 204.1 (Cq), 157.8 (Cq), 137.7 (CH), 133.3 (Cq), 132.8 (CH), 130.0 (CH), 129.0 (Cq), 123.9 (CH), 119.9 (CH_2), 115.9 (CH_2), 110.2 (CH), 87.6 (CH), 64.2 (CH), 55.6 (CH), 46.7 (Cq), 39.81 (CH_2), 39.80 (CH_2), 37.4 (CH_2); **HRMS** (ESI^+): $C_{18}H_{18}O_3$ $[M+H]^+$ calcd. 283.1329, found 283.1317; **IR** ν_{max} cm^{-1}: 3078, 2977, 2954, 2922, 2852, 1729, 1639, 1612, 1489, 1439, 1403, 1244, 1215, 1005, 993, 916, 890, 819.

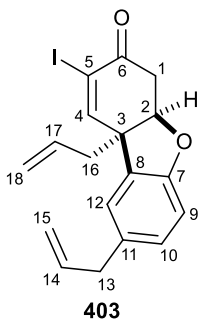
403: (±)-(4a*S*,9b*S*)-8,9b-diallyl-2-iodo-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



simonsol G (**30**) **403**

To a solution of simonsol G (**30**) (476 mg, 1.79 mmol) in THF (4.5 mL) and H_2O (4.5 mL) was added sequentially DBU (0.54 mL, 3.58 mmol), K_2CO_3 (297 mg, 2.15 mmol) and iodine (683 mg, 2.69 mmol).

The reaction mixture was stirred at room temperature for 2 hours and was then diluted with EtOAc (20 mL) and the organics were washed sequentially with $Na_2S_2O_3$ (30 mL of a saturated aqueous solution), HCl (30 mL of a 1M aqueous solution) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone, 19:1) afforded an approximate 9:1 respective mixture of iodinated enone **403** and simonsol G (**30**) as a yellow oil (547 mg). The yellow oil was dissolved in distilled Et_2O (3 mL) and was then diluted with distilled pentane (10 mL). The vial was sealed and cooled to -20 °C for 18 hours. A precipitate formed that was collected by suction filtration and the filter cake was washed with pentane (3 x 3 mL) which gave iodinated enone **403** as a colourless solid (372 mg, 53%) **m.p.** 88–90 °C. The filtrate was concentrated which gave a 2:1 respective mixture of iodinated enone **403** and simonsol G (**30**) as a yellow oil (138 mg, 13% yield iodinated enone **403**).

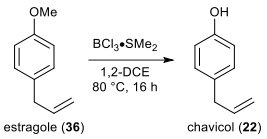


403

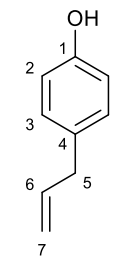
403: ^{1}H NMR (500 MHz, C_6D_6) δ: 6.90 (d, *J* = 1.7 Hz, 1H, H-4), 6.73 (dd, *J* = 8.2, 1.9 Hz, 1H, H-10), 6.65 (d, *J* = 1.9 Hz, 1H, H-12), 6.61 (d, *J* = 8.2 Hz, 1H, H-9), 5.89 – 5.80 (m, 1H, H-14), 5.26 (dddd, *J* = 16.9, 10.1, 8.0, 6.7 Hz, 1H, H-17), 5.05 – 4.99 (m, 2H, H-15), 4.80 – 4.69 (m, 2H, H-18), 4.27 (ddd, *J* = 4.0, 3.0, 1.7 Hz, 1H, H-2), 3.15 (ddd, *J* = 6.4, 1.4, 1.4 Hz, 2H, H-13), 3.04 (dd, *J* = 17.1, 3.0 Hz, 1H, H-1), 2.29 (dd, *J* = 17.1, 4.0 Hz, 1H, H-1), 2.08 (dd, *J* =

14.2, 6.7 Hz, 1H, H-16), 1.91 (dd, *J* = 14.2, 8.0 Hz, 1H, H-16); **^{13}C NMR** (126 MHz, C_6D_6) δ: 187.4 (Cq), 157.8 (Cq), 155.6 (CH), 138.0 (CH), 133.5 (Cq), 132.1 (CH), 130.5 (Cq), 130.1 (CH), 123.1 (CH), 119.5 (CH_2), 115.8 (CH_2), 110.8 (CH), 102.4 (Cq), 84.8 (CH), 52.9 (Cq), 40.00 (CH_2), 39.95 (CH_2), 37.9 (CH_2); **HRMS** (ESI^+): $C_{18}H_{17}IO_2$ $[M+H]^+$ calcd. 393.0346, found 393.0338; **IR** ν_{max} cm^{-1}: 3077, 3007, 2976, 2902, 1689, 1485, 1272, 996, 921.

chavicol (22): 4-allylphenol



To a solution of estragole (**36**) (1.69 mL, 11.0 mmol) in 1,2-dichloroethane (44 mL) at room temperature was added BCl_3•SMe_2 (2.95 g, 16.5 mmol). The reaction mixture was heated at 80 °C for 20 hours and was then cooled to 0 °C. To the reaction mixture was cautiously added $NaHCO_3$ (40 mL of a saturated aqueous solution) and the organics were extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/acetone, 9:1) gave chavicol (**22**) as a light-yellow oil (1.30 g, 88%).

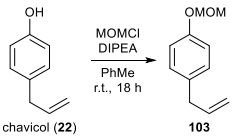


chavicol (**22**)

chavicol (22): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.09 – 7.04 (m, 2H, H-3), 6.79 – 6.74 (m, 2H, H-2), 5.95 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H-6), 5.10 – 5.01 (m, 2H, H-7), 4.74 – 4.67 (m, 1H, ArOH), 3.32 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 153.9 (Cq), 138.0 (CH), 132.4 (Cq), 129.8 (2x CH), 115.6 (CH_2), 115.4 (2x CH), 39.5 (CH_2); **HRMS** (ESI^-): $C_9H_{10}O$ $[M-H]^-$ calcd. 133.0659, found 133.0659; **IR** ν_{max} cm^{-1}: 3318, 3077, 2978, 2901, 1639, 1612, 1598, 1510, 1437, 1363, 1221, 1171, 1102, 993, 912, 846, 819, 776, 627, 520.

Spectroscopic data obtained for chavicol (**22**) were consistent with those previously reported.[84]

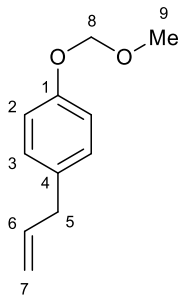
103: 1-allyl-4-(methoxymethoxy)benzene



chavicol (**22**) **103**

To a solution of MOMCl (2.17 mL (90% purity on bottle), 28.4 mmol) in PhMe (18.9 mL) at 0 °C was added sequentially chavicol (**22**) (2.53 g, 18.9 mmol) and DIPEA (4.11 mL, 23.6 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 18 hours. To the reaction mixture at room temperature was added EtOAc (25 mL) and NH_4Cl (25 mL of a saturated aqueous solution) and the biphasic mixture was stirred vigorously for 10 minutes. The organics were sequentially washed with $NaHCO_3$ (30 mL of a saturated

aqueous solution) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 95:5 to 3:1) gave MOM protected chavicol **103** as a colourless oil (2.31 g, 69%) (brsm 90%) and chavicol **22** as a light-yellow oil (613 mg, 24%).



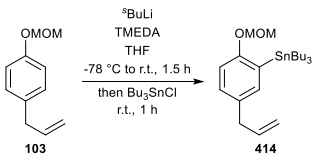
103

103: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13 – 7.09 (m, 2H, H-3), 7.00 – 6.95 (m, 2H, H-2), 5.95 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H, H-6), 5.16 (s, 2H, H-8), 5.10 – 5.03 (m, 2H, H-7), 3.48 (s, 3H, H-9), 3.34 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 155.7 (Cq), 137.9 (CH), 133.6 (Cq), 129.7 (CH), 116.4 (CH), 115.7 (CH_2), 94.7 (CH_2), 56.1 (CH_3), 39.6 (CH_2); **IR** ν_{max} cm^{-1}: 2954, 2897, 2826, 1639, 1611, 1585, 1508, 1465, 1436, 1406, 1311, 1231, 1198, 1174, 1150, 1107, 1077, 994, 918, 813, 759, 709, 654, 622, 526.

HRMS: Compound did not produce targeted mass upon ionisation in positive or negative mode.

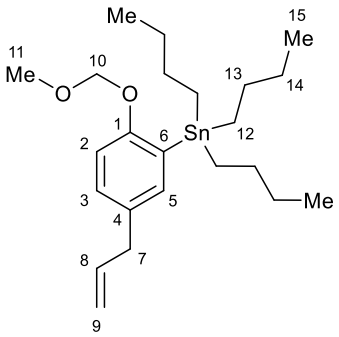
Spectroscopic data obtained for **103** were consistent with those previously reported.[68]

414: (5-allyl-2-(methoxymethoxy)phenyl)tributylstannane



To a flame-dried flask at -78 °C was sequentially added dry THF (10 mL), ^{s}BuLi (6.13 mL of a

1.14 M solution in hexanes, 5.38 mmol) and TMEDA (0.81 mL, 5.4 mmol). The solution was stirred for 0.25 hours at -78 °C and then a solution of MOM protected chavicol **103** (870 mg, 4.89 mmol) in dry THF (14.5 mL) was added over 5 minutes. The reaction mixture was stirred for 0.5 hours at -78 °C and was then allowed to warm to room temperature and was stirred for a further hour. To the reaction mixture was added Bu_3SnCl (1.46 mL, 5.38 mmol) and the reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture was added H_4NF (10 mL of a 1.0 M aqueous solution) and the biphasic mixture was stirred for 1 hour at room temperature. The organics were extracted with Et_2O (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/CH_2Cl_2, 85:15 to 3:2) gave stannane **414** as a colourless oil (888 mg, 39%) (brsm 59%) and MOM protected chavicol **103** (294 mg, 34%).

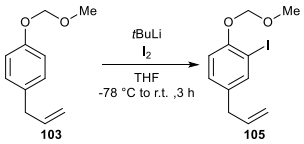


414

414: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 2.3 Hz, 1H, H-5), 7.08 (dd, *J* = 8.4, 2.3 Hz, 1H, H-3), 7.00 (d, *J* = 8.4 Hz, 1H, H-2), 5.97 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-8), 5.13 (s, 2H, H-10), 5.09 – 5.02 (m, 2H, H-9), 3.45 (s, 3H, H-11), 3.33 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-7), 1.60 – 1.45 (m, 6H, H-13), 1.37 – 1.28 (m, 6H, H-14), 1.12 – 0.97 (m, 6H, H-12), 0.88 (t, *J* = 7.3 Hz, 9H, H-15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 160.4 (Cq), 138.1 (CH), 137.3 (CH), 133.2 (Cq),

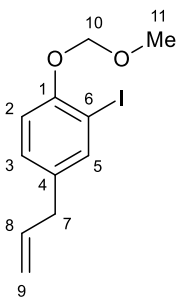
130.8 (CH), 129.9 (CH), 115.5 (CH_2), 112.1 (CH), 94.4 (CH_2), 55.9 (CH_3), 39.6 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 13.9 (CH_3), 10.0 (CH_2); **HRMS** (ESI^+): $C_{23}H_{40}O_2{}^{120}Sn$ $[M+H]^+$ calcd. 469.2123, found 469.2129; **IR** ν_{max} cm^{-1}: 3078, 2999, 2954, 2922, 2871, 2851, 1639, 1590, 1574, 1473, 1417, 1392, 1376, 1275, 1225, 1189, 1156, 1141, 1080, 1051, 1007, 923, 912, 815, 689, 666, 596.

105 and 103: 4-allyl-2-iodo-1-(methoxymethoxy)benzene[68] **and** 1-allyl-4-(methoxymethoxy)benzene



To a solution of MOM protected chavicol **103** (1.01 g, 5.67 mmol) in dry THF (5.0 mL) at -78 °C was added ^{t}BuLi (5.70 mL of a 1.5 M solution in hexanes, 8.51 mmol). The solution was stirred for 2 hours at -78 °C and then a solution of iodine (2.16 g, 8.51 mmol) in dry THF (7.5 mL) was added. The reaction mixture was stirred for a further 30 minutes at -78 °C and was then allowed to warm to room temperature. Once at temperature, the reaction mixture was poured onto Na_2SO_3 (5 mL of a 20% aqueous solution). The organics were extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (hexanes/EtOAc, 19:1) provided a yellow oil as an approximate 7:2:1

respective mixture of aryl iodide **105**, aryl **103** and residual solvent (1.57 g, 64% yield of **105** (brsm 93%), 31% yield of aryl **103**).



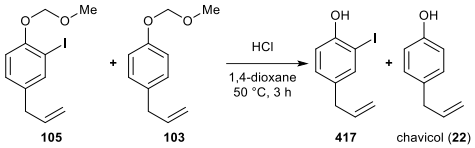
105

105: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 2.1 Hz, 1H, H-5), 7.10 (d, *J* = 8.4 Hz, 1H, H-2), 6.98 (dd, *J* = 8.4, 2.1 Hz, 1H, H-3), 6.00 – 5.86 (m, 1H, H-8), 5.21 (s, 2H, H-10), 5.11 – 5.05 (m, 2H, H-9), 3.51 (s, 3H, H-11), 3.30 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 154.6 (Cq), 139.5 (CH), 137.1 (CH), 135.7 (Cq), 129.7 (CH), 116.3 (CH_2), 115.1 (CH), 95.3 (CH_2), 87.4 (Cq), 56.5 (CH_3), 39.0 (CH_2); **HRMS** (ESI^+): $C_{11}H_{13}IO_2$ $[M+Na]^+$ calcd. 326.9852, found 326.9850.

Spectroscopic data obtained for **105** were consistent with those previously reported.[68]

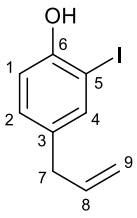
417: 4-allyl-2-iodophenol

chavicol (22): 4-allylphenol



To a solution of aryl iodide **105** (749 mg, 2.46 mmol) and **103** (260 mg, 1.46 mmol) in 1,4-dioxane (31 mL) at room temperature was added HCl (1.63 mL of a 12.0 M aqueous solution). The reaction mixture was heated at 50 °C for 3 hours and was then cooled to room temperature. To the reaction mixture was added H_2O (70 mL) and

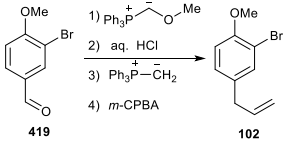
the organics were extracted with Et_2O (3 x 80 mL). The organics were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 37:3) gave 4-allyl-2-iodophenol (**417**) as a colourless oil (550 mg, 86%) and chavicol (**22**) as a colourless oil (165 mg, 84%).



417

417: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.1 Hz, 1H, H-4), 7.06 (dd, *J* = 8.3, 2.1 Hz, 1H, H-2), 6.92 (d, *J* = 8.3 Hz, 1H, H-1), 5.91 (ddt, *J* = 17.8, 9.1, 6.7 Hz, 1H, H-8), 5.14 (s, 1H, ArOH), 5.10 – 5.03 (m, 2H, H-9), 3.29 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.3 (Cq), 138.1 (CH), 137.2 (CH), 134.4 (Cq), 130.6 (CH), 116.3 (CH_2), 115.0 (CH), 85.8 (Cq), 38.9 (CH_2); **HRMS** (ESI$^-$) C_9H_9IO $[M-H]^-$ calcd. 258.9625, found 258.9628; **IR** ν_{max} cm^{-1}: 3495, 3075, 2948, 2932, 2868, 1638, 1598, 1573, 1485, 1430, 1408, 1326, 1288, 1248, 1199, 1173, 1033, 993, 914, 876, 856, 818, 782, 707, 667, 641, 632, 561, 484.

102: 4-allyl-2-bromo-1-methoxybenzene



419 **102**

To oven-dried glassware was added (methoxymethyl)triphenylphosphonium chloride (13.0 g, 38.0 mmol). The flask was sealed and allowed to cool to room temperature after which dry THF (20.0 mL) was added. To the

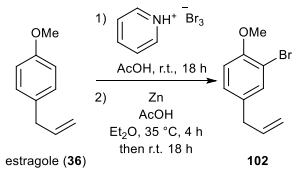
suspension at 0 °C was added KHMDS (33.0 mL of a 1.0 M solution in THF, 33.0 mmol) dropwise over 5 minutes. The dark red mixture was stirred for one hour at room temperature and was then cooled to 0 °C. To the ylide mixture was added a solution of 3-bromo-4-methoxybenzaldehyde (**419**) (4.30 g, 20.0 mmol) in dry THF (20.0 mL) over 5 minutes. The reaction mixture was then stirred at room temperature for 3 hours. An aliquot was taken which showed by ^{1}H NMR spectroscopy that benzaldehyde **419** was consumed.* The reaction mixture was sparged with argon for 10 minutes and then a sparged solution of HCl (50 mL of a 2.0 M aqueous solution that had been sparged with argon for 10 minutes, 100 mmol) was added. The reaction mixture was heated at 70 °C for 4 hours and it was confirmed by ^{1}H NMR spectroscopy that the intermediate methyl enol ether was consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc (150 mL) and the organics were washed with H_2O (2 x 50 mL), then brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* which provided a crude aldehyde intermediate as an orange oil.

*If **419** is not consumed in the first Wittig step, then **102** will be isolated with the corresponding styrene.

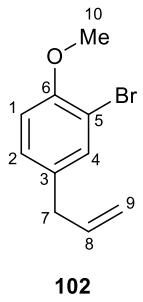
In a separate flame-dried flask was added methyltriphenylphosphonium bromide (12.9 g, 36.0 mmol) and then the flask was sealed and dry THF (20.0 mL) was added. The

suspension was cooled to 0 °C and then KHMDS (32.0 mL of a 1.0 M solution in THF, 32.0 mmol) was added dropwise over 5 minutes. The yellow ylide mixture was warmed to room temperature for 1 hour and was then cooled to 0 °C whereby the crude aldehyde was added dropwise as a solution in dry THF (20.0 mL) over 5 minutes at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 2 hours. To the reaction mixture was added H_2O (50 mL) and the organics were diluted with EtOAc (200 mL). The organics were washed with H_2O (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The organics were then dissolved in Et_2O (20 mL) and diluted with pentane (200 mL) which formed a precipitant. The precipitant was removed by suction filtration and the filter cake was washed with Et_2O/pentane (1:9) (3 x 50 mL). The filtrate was concentrated *in vacuo* and subsequent analysis by ^1H NMR spectroscopy found triphenylphosphine was present. Therefore, the crude oil was dissolved in acetone (15 mL) and CuCl (1 g) was added however no precipitation of the acetone insoluble CuCl•PPh_3 salt complex occurred and so the organics were concentrated *in vacuo*. The organics were diluted in petroleum ether/Et_2O (95:5) for column chromatography and a precipitant formed. The organics were loaded onto the silica column *via* passing through a cotton wool filter. Purification by flash column chromatography (petroleum ether/Et_2O, 95:5) provided 4-allyl-2-bromo-1-methoxybenzene **102** as a colourless oil (3.09 g, 68%)

along with its allyl group isomer **420** (227 mg, 5%). The inseparable[323] mixture was reacted according to general method A, purification by flash column chromatography (petroleum ether/Et_2O, 95:5) gave 4-allyl-2-bromo-1-methoxybenzene **102** as a colourless oil (2.75 g, 61% from 3-bromo-4-methoxybenzaldehyde (**419**)).



By Chen and Liu's modified method,[72] 4-allyl-2-bromo-1-methoxybenzene (**102**) was prepared from estragole (**36**). Starting from estragole (**36**) (3.65 g, 24.7 mmol), we obtained an inseparable[323] 3:2 respective mixture of 4-allyl-2-bromo-1-methoxybenzene (**102**) and estragole (**36**) (2.04 g, 21% yield of **102** (brsm 27%), 23% yield of **36**).

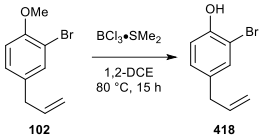


102

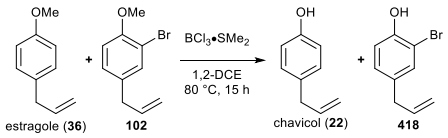
102: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (d, *J* = 2.0 Hz, 1H, H-4), 7.08 (dd, *J* = 8.4, 2.0 Hz, 1H, H-2), 6.83 (d, *J* = 8.4 Hz, 1H, H-1), 5.92 (ddt, *J* = 17.9, 9.1, 6.7 Hz, 1H, H-8), 5.15 – 5.00 (m, 2H, H-9), 3.87 (s, 3H, H-10), 3.31 (d, *J* = 6.7 Hz, 2H, H-7);**^{13}C NMR** (101 MHz, $CDCl_3$) δ: 154.4 (Cq), 137.2 (CH), 133.8 (Cq), 133.5 (CH), 128.6 (CH), 116.2 (CH), 112.1 (CH_2), 111.7 (Cq), 56.4 (CH_3), 39.1 (CH_2); **HRMS** (ESI^+): $C_{10}H_{11}{}^{79}BrO$ $[M+H]^+$ calcd. 225.9988, found 226.0018; **IR** ν_{max} cm^{-1}: 3078, 3005, 2956, 2924, 2851, 2838, 1639, 1603, 1494, 1461, 1439, 1403, 1277, 1253, 1181, 1152, 1054, 1022, 993, 913, 885, 807, 761, 711, 676, 636, 568, 550.

Spectroscopic data obtained for **102** were consistent with those previously reported.[79]

418: 4-allyl-2-bromophenol

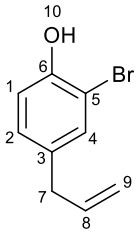


To 4-allyl-2-bromo-1-methoxybenzene (**102**) (1.30 g, 5.72 mmol) in 1,2-dichloroethane (23.0 mL) was added BCl_3•SMe_2 (2.56 g, 14.3 mmol). The solution was heated at 80 °C for 15 hours and was then cooled to 0 °C. At 0 °C, to the reaction mixture was cautiously added H_2O (20 mL). The aqueous was diluted with H_2O (40 mL) and the organics were extracted with EtOAc (3 x 50 mL). The organics were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 37:3 to 4:1) provided 4-allyl-2-bromo-1-methoxybenzene (**102**) as a light yellow oil (241 mg, 19%) and 4-allyl-2-bromophenol (**418**) as a yellow oil (934 mg, 77% (brsm 95%)).



To an inseparable[323] mixture of estragole (**36**) and 4-allyl-2-bromo-1-methoxybenzene (**102**) (2:3 respectively, 1670 mg, 8.91 mmol combined) in 1,2-dichloroethane (35 mL) was added BCl_3•SMe_2 (3.19 g, 17.8 mmol). The reaction mixture was heated at 80 °C for 24 hours and was then cooled to 0 °C. At 0 °C, to the reaction mixture was cautiously added H_2O (20 mL). The organics were extracted with

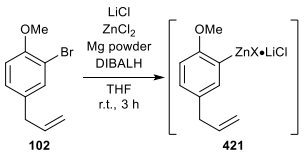
EtOAc (3 x 40 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 37:3 to 4:1) provided 4-allyl-2-bromo-1-methoxybenzene (**102**) as a colourless oil (148 mg, 19%), 4-allyl-2-bromophenol (**418**) as a colourless oil (728 mg, 78% (brsm 96%), and chavicol (**22**) as a colourless oil (559 mg, 93%).



418

418: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, *J* = 2.1 Hz, 1H, H-4), 7.04 (dd, *J* = 8.3, 2.1 Hz, 1H, H-2), 6.95 (d, *J* = 8.3 Hz, 1H, H-1), 5.91 (ddt, *J* = 16.4, 10.6, 6.7 Hz, 1H, H-8), 5.37 (s, 1H, OH-10), 5.11 – 5.04 (m, 2H, H-9), 3.30 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 150.7 (Cq), 137.2 (CH), 133.9 (Cq), 131.9 (CH), 129.5 (CH), 116.3 (CH_2), 116.0 (CH), 110.2 (Cq), 39.1 (CH_2); **HRMS** (ESI^-): $C_9H_9{}^{79}BrO$ $[M-H]^-$ calcd. 210.9764, found 210.9764; **IR** ν_{max} cm^{-1}: 3508, 3078, 3033, 3004, 2978, 2903, 2835, 1639, 1606, 1580, 1490, 1431, 1417, 1330, 1289, 1271, 1251, 1202, 1173, 1132, 1039, 993, 913, 883, 863, 819, 783, 708, 676, 637, 562.

421: Organozinc species



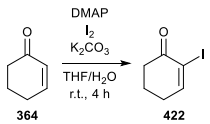
102 **421**

To a flame-dried Schlenck vial connected to a Schlenck line was added LiCl (127 mg, 3.00 mmol) which was dried under vacuum (~1.0–2.0 x 10^{-1} mbar) at 160 °C for 5 minutes. To the dried LiCl was added

$ZnCl_2$ (300 mg, 2.20 mmol) and the mixture was dried under vacuum (~1.0–2.0 x 10^{-1} mbar) at 160 °C for 5 minutes and was then cooled to room temperature. The Schlenk vial was put under an inert atmosphere (N_2) and then Mg powder (78 mg, 3.2 mmol) was added. The vial was evacuated and back-filled with N_2 three times. To the vial was added sequentially dry THF (5.0 mL), DIBALH (0.2 mL of a 0.1 M solution in PhMe/dry THF (1.0 M solution in PhMe was diluted with dry THF to a 0.1 M solution of DIBALH), 0.02 mmol) and aryl bromide **102** (454 mg, 2.00 mmol). The reaction mixture was stirred at room temperature for *3 hours.

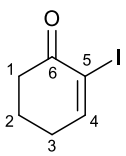
*Consistently from 3 repeats; at 2.5 hours, the concentration of organozinc species **421** was 0.27–0.28 M as a solution in THF. The molarity was calculated by iodometric titration and by the addition of aq. NH_4Cl to an aliquot of the reaction mixture followed by ^1H NMR spectroscopy and comparison of proton integrations for **102** versus estragole (**36**).

422: 2-iodocyclohex-2-en-1-one



To 2-cyclohexen-1-one (**364**) (0.97 mL mg, 10 mmol) in THF (25.0 mL) and H_2O (25.0 mL) at room temperature were added sequentially K_2CO_3 (1.66 g, 12.0 mmol), I_2 (5.08 g, 20 mmol) and DMAP (244 mg, 2.00 mmol). The reaction mixture was stirred for 4 hours at room temperature and was then

diluted with EtOAc (100 mL) and the organics were washed with $Na_2S_2O_3$ (200 mL of a saturated aqueous solution) and then HCl (200 mL of a 0.1 M aqueous solution). The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc, 4:1) gave 2-iodocyclohex-2-en-1-one (**422**) as a yellow oil (1.9 g) that solidified over 16 hours at -20 °C. The solid was triturated with pentane which was collected and dried by suction filtration which gave 2-iodocyclohex-2-en-1-one (**422**) as a colourless solid (1.58 g, 71%) **m.p.** 54–56 °C (lit. 47–50 °C).[373]



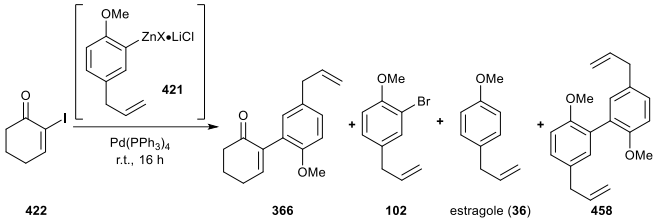
422

422: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (t, *J* = 4.4 Hz, 1H, H-4), 2.70 – 2.64 (m, 2H, H-1), 2.44 (td, *J* = 6.0, 4.4 Hz, 2H, H-3), 2.14 – 2.04 (m, 2H, H-2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.3 (Cq), 159.5 (CH), 104.0 (Cq), 37.4 (CH_2), 30.1 (CH_2), 23.0 (CH_2); **HRMS** (ESI$^+$) C_6H_7IO $[M+H]^+$ calcd. 222.9614, found 222.9616; **IR** ν_{max} cm^{-1}: 2948, 2932, 2880, 2868, 2820, 1682, 1585, 1454, 1423, 1330, 1315, 1229, 1154, 1120, 984, 965, 903, 800, 702, 636, 517, 487.

Spectroscopic data obtained for **102** were consistent with those previously reported.[373]

7.4.2.1: Negishi cross-coupling study of 421 with 422

366: 5'-allyl-2'-methoxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one



To a dry microwave vial were added 2-iodocyclohexen-1-one (**422**) (44 mg, 0.20 mmol), dry THF (0.70 mL) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol). The vial was sealed, and the solution was sparged with argon for 2 minutes. To the reaction mixture was added *via* syringe filter (45 µm) organozinc **421** (1.10 mL of 0.27 M solution, 0.30 mmol) at room temperature and the reaction mixture was stirred at room temperature for 15 h. To the reaction mixture was added NH_4Cl (3 mL of a saturated aqueous solution) and the organics were diluted with Et_2O (5 ml). The organics were transferred by pipette to a separatory funnel and to the aqueous was added Et_2O (10 mL). The organics were transferred by pipette to the separatory funnel and the combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. By ^{1}H and ^{13}C NMR spectroscopy, there was only one species seen that contained a cyclohexanone moiety which was **366** (see Table 25 and Figure 35). The other species present in the product mixture were **102**, **458** and estragole (**36**) which were confirmed by comparison to independent samples. By NMR spectroscopy analysis, it is likely that **366** was produced in >80% yield.

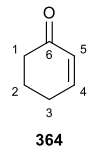
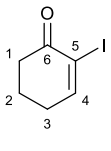
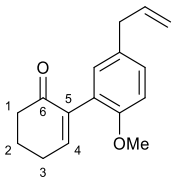
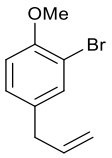
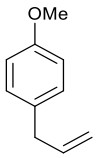
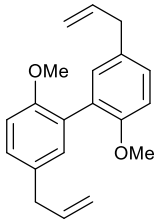
NMR environ. ($CDCl_3$)	 **364**	 **422**	 **366**	 **102**	 estragole (**36**)	 **458**
			Chemical shift (δ) (ppm) ($CDCl_3$)			
^{1}H: OMe	-	-	3.73	3.87	3.79	3.75
^{1}H: H-1	2.43–2.13	2.70–2.64	2.61–2.56	-	-	-
^{1}H: H-2	2.00–1.78	2.14–2.04	2.16–2.08	-	-	-
^{1}H: H-3	2.43–2.13	2.44	2.51	-	-	-
^{1}H: H-4	6.91	7.77	6.89	-	-	-
^{1}H: H-5	5.90	-	-	-	-	-
^{13}C: C-6	199.6	192.3	197.7	-	-	-

Table 25. *Summary of distinctive ^{1}H and ^{13}C chemical shifts of possible species formed in the product mixture from the Negishi cross-coupling of **421** and **422**.*

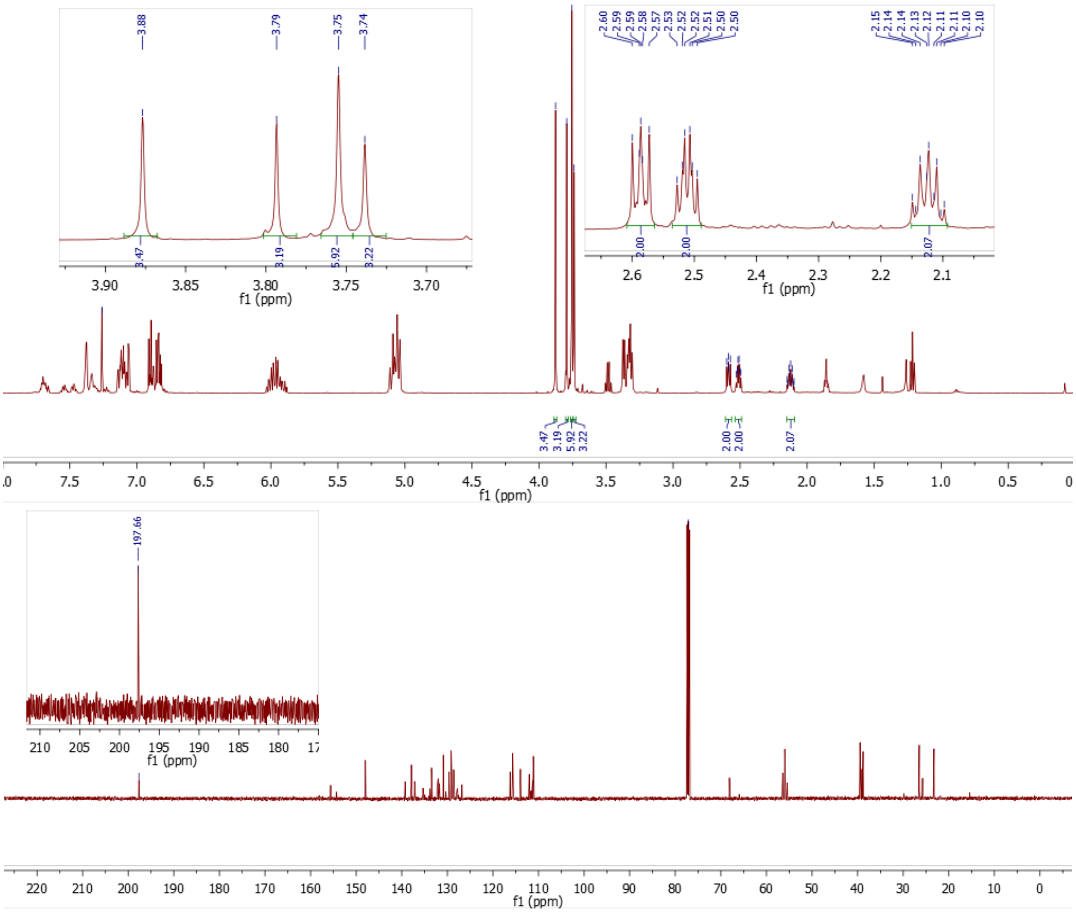
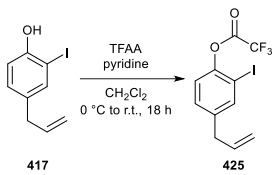


Figure 35. *^{1}H and ^{13}C NMR spectra (in $CDCl_3$) of the product mixture obtained from the Negishi cross-coupling of **421** and **422**.*

7.4.2.2: Chavicol derivatives for Ullman and Hiyama-Denmark cross-coupling

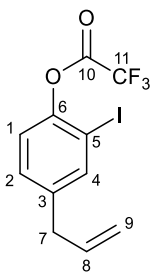
425: 4-allyl-2-iodophenyl 2,2,2-trifluoroacetate



To 4-allyl-2-iodophenol (**417**) (398 mg, 1.53 mmol) in dry CH_2Cl_2 (2.30 mL) at room temperature was added pyridine (0.19 mL, 2.4 mmol). The mixture was cooled to 0 °C and then trifluoroacetic anhydride (0.33 mL, 2.39 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 18 hours. To the reaction mixture was added H_2O (10 mL) and the organics were extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were washed with H_2O (2 x 5 mL), then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*.* Purification by column chromatography (petroleum ether/Et_2O, 19:1 to 17:3) afforded one clean fraction of 4-allyl-2-iodophenyl 2,2,2-trifluoroacetate (**425**) as a colourless oil (194 mg, 35 %). All other fractions were combined which gave a 3:1 respective mixture of **417** to **425** as a yellow oil (272 mg, 12% yield of **425** (brsm, 96%) and 51% yield of **417**).

*4-allyl-2-iodophenyl 2,2,2-trifluoroacetate (**425**) is not stable on silica gel and underwent rapid hydrolysis which gave 4-allyl-2-iodophenol (**417**). Over approximately 3 months stored at -20 °C,

approximately 10% of **425** converted into **417** (determined by ^{1}H NMR spectroscopy).

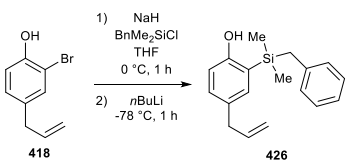


425

425: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.1 Hz, 1H, H-4), 7.24 (dd, *J* = 8.3, 2.1 Hz, 1H, H-2), 7.11 (d, *J* = 8.3 Hz, 1H, H-1), 5.92 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, H-8), 5.17 – 5.09 (m, 2H, H-9), 3.38 (ddd, *J* = 6.7, 1.4, 1.4 Hz, 2H, H-7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.4 (q, *J* = 44.1 Hz, C-10), 148.0 (Cq), 141.6 (Cq), 140.0 (CH), 136.0 (CH), 130.2 (CH), 121.8 (CH), 117.3 (CH_2), 114.8 (q, *J* = 285.9 Hz, C-11), 88.5 (Cq), 39.1 (CH_2); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -74.42; **IR** ν_{max} cm^{-1}: 3082, 2981, 2908, 1801, 1641, 1589, 1577, 1479, 1433, 1416, 1397, 1349, 1226, 1205, 1170, 1113, 1036, 993, 918, 880, 860, 813, 783, 762, 733, 698, 666, 641, 558, 524, 438.

HRMS: compound did not ionize in either (ESI^-) or (ESI^+).

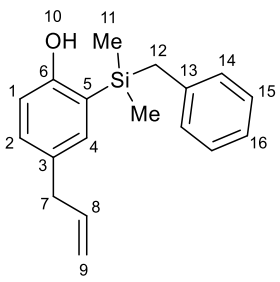
426: 4-allyl-2-(benzyldimethylsilyl)phenol



418 **426**

To a suspension of sodium hydride (22 mg, 60% dispersed in mineral oil, 0.55 mmol) in dry THF (0.40 mL) at 0 °C was added a solution of aryl bromide **418** (105 mg, 0.493 mmol) in dry THF (0.60 mL) over 5 minutes. The reaction mixture was stirred for 30 minutes at 0 °C and then benzylchlorodimethylsilane (0.10 mL, 0.55 mmol) was added dropwise over 5 minutes. The solution was stirred for 30

minutes at 0 °C and was then cooled to -78 °C. To the reaction mixture at -78 °C was added ^{n}BuLi (0.24 mL of a 2.1 M solution in hexanes, 0.50 mmol) dropwise over 5 minutes. The reaction mixture was stirred for 1 hour at -78 °C and was then allowed to warm to room temperature. To the reaction mixture was added NH_4Cl (5 mL of a saturated aqueous solution). The organics were diluted with Et_2O (10 mL) and were washed with H_2O (5 mL), then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 19:1 to 37:3) gave phenol **426** as a pale-yellow oil (106 mg, 75%).



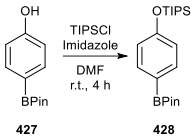
426

426: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H, H-15), 7.11 – 7.03 (m, 3H, H-2, H-4 H-16), 7.00 – 6.96 (m, 2H, H-14), 6.63 (d, *J* = 8.0 Hz, 1H, H-1), 5.93 (ddt, *J* = 17.6, 9.5, 6.7 Hz, 1H, H-8), 5.08 – 5.00 (m, 2H, H-9), 4.62 (s, 1H, H-10), 3.30 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-7), 2.42 (s, 2H, H-12), 0.26 (s, 6H, H-11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8 (Cq), 140.4 (Cq), 138.1 (CH), 135.8 (CH), 131.9 (Cq), 131.1 (CH), 128.5 (2x CH), 128.2 (2x CH), 124.1 (CH), 123.9 (Cq), 115.5 (CH_2), 114.7 (CH), 39.6 (CH_2), 25.8 (CH_2), -3.0 (2x CH_3); **HRMS** (ESI^-) $C_{18}H_{22}OSi$ [M-H]$^-$ calcd. 281.1367, found 281.1367; **IR** ν_{max} cm^{-1}: 3534, 3023, 2955, 2898, 1638, 1598, 1492, 1451, 1399, 1322, 1278, 1242, 1206, 1138, 1072, 994, 909, 880, 820, 795, 763, 699, 626, 558, 476, 450.

7.5: Large-scale synthesis of simonsol F

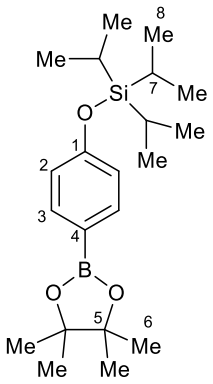
7.5.1: Total synthesis of simonsol F by late-stage allylation (Section 2.3.3)

428: triisopropyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)silane



To a solution of 4-hydroxybenzeneboronic acid pinacol ester (**427**) (11.0 g, 50.0 mmol) in DMF (20.0 mL) at room temperature was added imidazole (8.50 g, 125 mmol) and triisopropylsilyl chloride (12.9 mL, 60.0 mmol). The reaction mixture was stirred for 4 hours at room temperature. To the reaction mixture was added H_2O (500 mL) and brine (200 mL). The organics were extracted with Et_2O (2 x 200 mL) and the combined organics were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 95:5) gave aryl **428** as a colourless oil that became a colourless solid* after being cooled at -20 °C for 16 hours (18.4 g, 98%) **m.p.** 39–41 °C.

*Previously reported as an oil.[374]



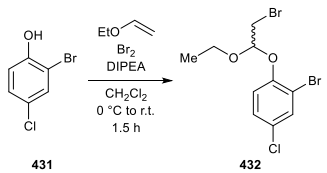
428

428: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 – 7.66 (m, 2H, H-3), 6.88 – 6.84 (m, 2H, H-2), 1.33 (s, 12H, H-6), 1.31 – 1.21 (m, 3H, H-7), 1.09 (d, *J* = 7.3 Hz, 18H, H-8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 159.1 (Cq), 136.6 (CH), 119.5 (CH), 83.7 (2x Cq), 25.0 (4x CH_3), 18.1 (6x CH_3), 12.9 (3x CH); **^{11}B NMR** (128 MHz, $CDCl_3$) δ: 31.2; **HRMS** (ESI^+): $C_{21}H_{37}{}^{11}BO_3Si$ $[M+H]^+$ calcd. 377.2678, found 377.2681; **IR** ν_{max} cm^{-1}: 2959, 2945, 2891, 2866, 1600, 1566, 1514, 1463, 1396, 1354, 1318, 1263, 1235, 1213, 1166, 1142, 1089, 1017, 994, 963, 911, 881, 859, 830, 739, 718, 690, 669, 650, 568, 517, 480, 448, 437.

^{13}C NMR: C-B (C-4) signal not observed due to quadrupolar relaxation.

Data is consistent to that previously reported.[374]

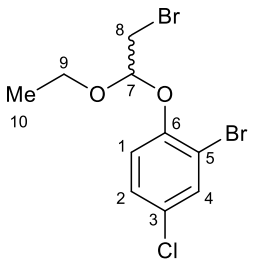
432: 2-bromo-1-(2-bromo-1-ethoxyethoxy)-4-chlorobenzene



431 **432**

To a solution of ethyl vinyl ether (19.1 mL, 200 mmol) in CH_2Cl_2 (230 mL) at 0 °C was added bromine (5.60 mL, 110 mmol) dropwise over 10 minutes. The solution was stirred for 20 minutes at 0 °C after which a solution of 4-chloro-2-bromophenol (**431**) (10.4 g, 50.0 mmol) and DIPEA (34.8 mL, 200 mmol) in CH_2Cl_2 (30.0 mL) was added over 15 minutes at 0 °C. The reaction mixture was allowed to warm to room

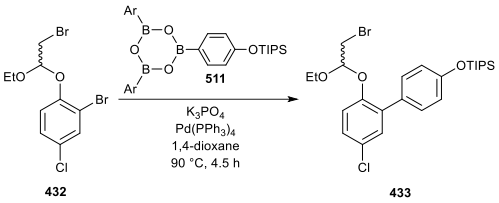
temperature and was stirred for a further 1.5 hours. The reaction mixture was diluted with EtOAc (500 mL) and the organics were washed with $NaHCO_3$ (2 x 200 mL of a saturated aqueous solution), then brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2, 7:3) gave bromo-acetal **432** as a colourless solid (17.4 g, 97%) **m.p.** 36–38 °C.



432

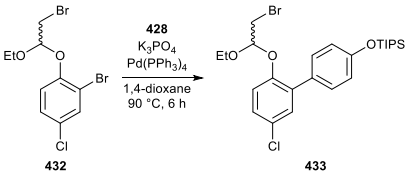
432: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 2.5 Hz, 1H, H-4), 7.23 (dd, *J* = 8.8, 2.5 Hz, 1H, H-2), 7.09 (d, *J* = 8.8 Hz, 1H, H-1), 5.35 (dd, *J* = 6.1, 4.8 Hz, 1H, H-7), 3.79 (dq, *J* = 9.3, 7.0 Hz, 1H, H-9), 3.68 – 3.54 (m, 3H, H-8 and H-9), 1.23 (dd, *J* = 7.0, 7.0 Hz, 3H, H-10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 152.2 (Cq), 133.3 (CH), 128.61 (CH), 128.60 (Cq), 119.3 (CH), 114.9 (Cq), 102.8 (CH), 63.1 (CH_2), 30.9 (CH_2), 15.1 (CH_3); **HRMS** (ESI^+): $C_{10}H_{11}{}^{79}Br_2{}^{35}ClO_2$ $[M+Na]^+$ calcd. 378.8707, found 378.8705; **IR** ν_{max} cm^{-1}: 2978, 2930, 2895, 1471, 1278, 1260, 1241, 1193, 1100, 1057, 1043, 966, 870, 806, 743.

433: ((2'-(2-bromo-1-ethoxyethoxy)-5'-chloro-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane



432 433

A biphasic mixture of aryl bromide **432** (1.23 g, 3.43 mmol) in 1,4-dioxane (13.7 mL) and K_3PO_4 (3.43 mL of a 3.0 M aqueous solution, 10.3 mmol) was sparged with argon for 5 minutes and then 2,4,6-tris-(4-triisopropylsilanyloxyphenyl)cyclotriboroxane (**511**) (1.99 g, 2.40 mmol) and $Pd(PPh_3)_4$ (79 mg, 0.069 mmol) were added. The reaction mixture was heated at 90 °C for 4.5 hours. The reaction mixture was cooled to room temperature and was diluted with EtOAc (70 mL). The organics were washed with HCl (20 mL of a 1.0 M aqueous solution), then brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/CH_2Cl_2, 9:1 to 85:15) gave biaryl **433** as a colourless oil (1.81 g, 98%).

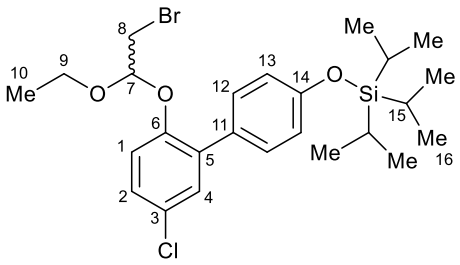


432 433

To a biphasic mixture of aryl bromide **432** (13.2 g, 36.8 mmol) in 1,4-dioxane (147 mL) and K_3PO_4 (36.8 mL of a 3.0 M aqueous solution, 110 mmol) was added boronic acid pinacol ester **428** (16.5 g, 44.0 mmol). The biphasic mixture was sparged with argon for 10 minutes and then $Pd(PPh_3)_4$ (850 mg, 0.736 mmol) was added. The reaction mixture was heated at 90 °C for 6 hours. The

reaction mixture was cooled to room temperature and was diluted with EtOAc (300 mL). The organics were washed with HCl (150 mL of a 1.0 M aqueous solution), then brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/CH_2Cl_2, 9:1 to 85:15) gave biaryl **433** as a light-yellow oil (85% purity*, 21.1 g, 92%).

*determined by ^1H NMR spectroscopy; approximately 10% w/w boronic acid pinacol ester **428** and 5% w/w other baseline aromatics.

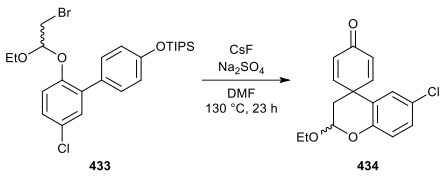


433

433 ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 – 7.35 (m, 2H, H-12), 7.32 (d, *J* = 2.7 Hz, 1H, H-4), 7.21 (dd, *J* = 8.7, 2.7 Hz, 1H, H-2), 7.10 (d, *J* = 8.7 Hz, 1H, H-1), 6.95 – 6.89 (m, 2H, H-13), 5.10 (dd, *J* = 6.1, 4.6 Hz, 1H, H-7), 3.58 (dq, *J* = 9.3, 7.1 Hz, 1H, H-9), 3.45 (dq, *J* = 9.3, 7.1 Hz, 1H, H-9), 3.38 – 3.30 (m, 2H, H-8), 1.32 – 1.24 (m, 3H, H-15), 1.12 (d, *J* = 7.4 Hz, 18H, H-16), 1.11 (dd, *J* = 7.1, 7.1 Hz, 3H, H-10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 156.0 (Cq), 152.1 (Cq), 134.8 (Cq), 130.8 (CH), 130.7 (CH), 129.7 (Cq), 128.5 (Cq), 127.9 (CH), 120.0 (CH), 119.8 (CH), 102.6 (CH), 63.0 (CH_2), 31.4 (CH_2), 18.1 (CH_3), 15.1 (CH_3), 12.8 (CH); **HRMS** (ESI^+): $C_{25}H_{36}{}^{79}Br^{35}ClO_3Si$ $[M+NH_4]^+$ calcd. 544.1644, found 544.1632; **IR** ν_{max} cm^{-1}: 2944, 2892, 2867, 1606, 1513, 1481, 1465, 1389, 1268,

1213, 1173, 1102, 1058, 1032, 995, 972, 913, 883, 840, 811, 714, 685, 582.

434: 6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

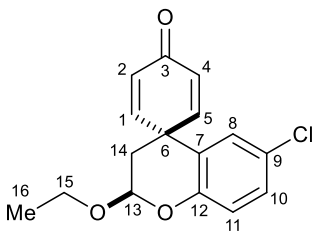


433 434

Across two oven-dried flasks was added sodium sulfate (160 g, 1.13 mol), CsF (15.5 g, 102 mmol) and dry DMF (660 mL). The mixtures were heated to 130 °C and then a solution of bromo acetal **433** (4.48 g, 8.48 mmol) in dry DMF (15 mL) was added dropwise over 8 hours at 130 °C to each flask. After addition was complete, another solution of bromo acetal **433** (4.48 g, 8.48 mmol) in dry DMF (15 mL) was added dropwise over 15 hours at 130 °C to each flask. The reaction mixtures were stirred for a further 1 hour at 130 °C and were then cooled to room temperature. The organics were filtered through cotton wool, combined, and concentrated *in vacuo*. The organics were dissolved in EtOAc (300 mL), washed with H_2O (100 mL), then brine (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 7:3) gave spirocycle **434** (after careful concentration*) as a yellow oil. The oil was suspended in ^{i}PrOH (~10-15 mL) and was cooled to -20 °C for 18 hours. A colourless precipitate formed that was collected by suction filtration and the filter cake was

washed with pentane (5 x 5 mL). The filtrate was concentrated *in vacuo* and was then re-subjected to the crystallisation method (^{i}PrOH) stated above until the combined yield of collected **434** was >85%. This method provided spirocycle **434** as a colourless solid (8.56 g, 87%) **m.p.** 112–114 °C.

* It is advised to keep the crude as a viscous oil before dissolving in ^{i}PrOH. If the organics are concentrated too much, an impure crystalline solid formed that required a large volume of solvent to dissolve (heat/sonication did not drastically promote solvation).



434

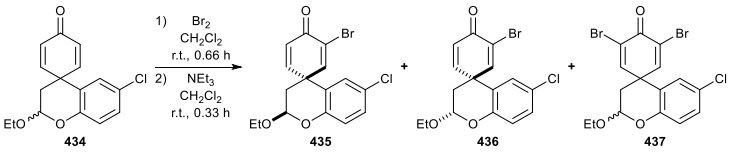
434: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (dd, *J* = 10.2, 3.0 Hz, 1H, H-5), 7.15 (dd, *J* = 8.7, 2.7 Hz, 1H, H-10), 6.87 (d, *J* = 8.7 Hz, 1H, H-11), 6.86 (d, *J* = 2.7 Hz, 1H, H-8), 6.75 (dd, *J* = 10.0, 3.0 Hz, 1H, H-1), 6.37 (dd, *J* = 10.0, 1.9 Hz, 1H, H-2), 6.23 (dd, *J* = 10.2, 1.9 Hz, 1H, H-4), 5.38 (dd, *J* = 3.0, 3.0 Hz, 1H, H-13), 3.90 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.64 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 2.26 (dd, *J* = 14.1, 3.0 Hz, 1H, H-14), 2.13 (dd, *J* = 14.1, 3.0 Hz, 1H, H-14), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 185.7 (Cq), 153.9 (CH), 153.2 (CH), 149.8 (Cq), 129.7 (CH), 129.0 (CH), 128.6 (CH), 126.7 (Cq), 126.6 (CH), 121.6 (Cq), 120.1 (CH), 95.8 (CH), 64.7 (CH_2), 40.5 (Cq), 36.1 (CH_2), 15.2 (CH_3); **HRMS** (ESI^+): $C_{16}H_{15}{}^{35}ClO_3$ $[M+H]^+$ calcd. 291.0782, found 291.0782; **IR** ν_{max} cm^{-1}: 2976, 2933, 2909, 2889, 1667, 1657, 1624,

1597, 1479, 1399, 1342, 1256, 1226, 1176, 1169, 1117, 1078, 1064, 1040, 1025, 983, 921, 909, 878, 858, 825, 692, 641, 601, 562, 454.

435: (±)-(2*R*,4*R*)-3'-bromo-6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

436: (±)-(2*S*,4*R*)-3'-bromo-6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one

437: 3',5'-dibromo-6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



To a solution of spirocycle dienone **434** (4.37 g, 15.0 mmol) in CH_2Cl_2 (30.0 mL) at room temperature was added a solution of bromine (0.77 mL, 15.0 mmol) in CH_2Cl_2 (30.0 mL) over 5 minutes. The reaction mixture was stirred for 40 minutes at room temperature and then triethylamine (3.13 mL, 22.5 mmol) was added. The reaction mixture was stirred for a further 20 minutes at room temperature. To the reaction mixture was added HCl (50 mL of a 1.0 M aqueous solution). The organics were extracted using EtOAc (3 x 80 mL) and the combined organics were washed sequentially with NaOH (3 x 50 mL of a 1.0 M aqueous solution), $Na_2S_2O_3$ (50 mL of a saturated aqueous solution) and brine (50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated *in*

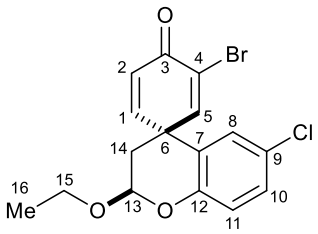
vacuo. Purification by graduated column chromatography (petroleum ether/Et_2O, 3:1 to 3:2) gave a 4:1 respective w/w mixture (determined by ^1H NMR spectroscopy) of bromo dienone **436** and dibromo **437** as a colourless solid (2.00 g) and a 15:20:60:5 respective w/w mixture (determined by ^1H NMR spectroscopy) of **434**:**435**:**436**:**437** as an off-white solid (3.20 g). The total yield for each compound was calculated (using w/w ratios of mixtures determined by ^1H NMR spectroscopy) as bromo dienone **436** (63%), bromo dienone **435** (10%), dibromo dienone **437** (10%) and dienone **434** (12%).

The 15:20:60:5 respective w/w mixture (determined by ^1H NMR spectroscopy) of **434**:**435**:**436**:**437** (3.20 g) was subjected to graduated column chromatography (petroleum ether/Et_2O, 7:3 to 3:2) gave several products that have been summarised below:

- a 9:1 respective w/w mixture (determined by ^1H NMR spectroscopy) of bromo dienone **436** and dibromo dienone **437** as a colourless solid (2.04 g).
- a 25:70:5 respective w/w mixture (determined by ^1H NMR spectroscopy) of **435**:**436**:**437** as a colourless solid (152 mg).
- a 25:65:10 respective w/w mixture (determined by ^1H NMR spectroscopy) of **434**:**435**:**436** (551 mg) that was dissolved in Et_2O (2 mL) and diluted with pentane (15 mL) and the

solution was cooled to -20 °C for 18 hours. A precipitate formed that was collected by suction filtration which gave a 6:92:2 respective w/w mixture (determined by ^{1}H NMR spectroscopy) of **434**:**435**:**436** as a colourless solid (331 mg). A portion of this mixture (50 mg) was subjected to column chromatography (petroleum ether/Et_2O/CH_2Cl_2, 7:2:1) to obtain a cleaner sample of **435** for NMR spectroscopy. The sample of **435** obtained was cleaner but still obtained trace amounts of **434** and **436**.

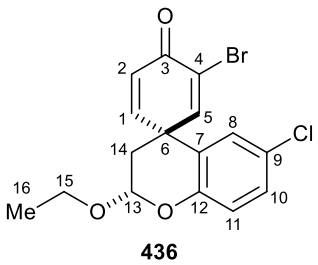
- a 9:1 respective w/w mixture (determined by ^{1}H NMR spectroscopy) of **434**:**435** as a colourless solid (289 mg).



435

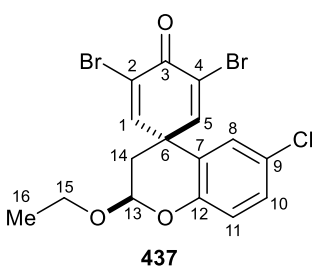
435: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 2.7 Hz, 1H, H-5), 7.18 (dd, *J* = 8.7, 2.5 Hz, 1H, H-10), 6.89 (d, *J* = 8.7 Hz, 1H, H-11), 6.86 (d, *J* = 2.5 Hz, 1H, H-8), 6.76 (dd, *J* = 9.8, 2.7 Hz, 1H, H-1), 6.48 (d, *J* = 9.8 Hz, 1H, H-2), 5.40 (dd, *J* = 2.9, 2.9 Hz, 1H, H-13), 3.89 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.66 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 2.28 (dd, *J* = 14.2, 2.9 Hz, 1H, H-14), 2.18 (dd, *J* = 14.2, 2.9 Hz, 1H, H-14), 1.23 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 178.5 (Cq), 154.0 (CH), 153.3 (CH), 149.6 (Cq), 130.1 (CH), 128.5 (CH), 127.5 (CH), 126.9 (Cq), 122.8 (Cq), 120.3 (CH), 120.1 (Cq), 95.5 (CH), 64.8 (CH_2), 43.5 (Cq), 35.7 (CH_2), 15.2 (CH_3); **HRMS** (ESI^+): $C_{16}H_{14}{}^{79}Br^{35}ClO_3$ $[M+H]^+$ calcd. 368.9888, found 368.9890; **IR** ν_{max} cm^{-1}: 3071, 3060, 2976, 2930,

2898, 2885, 1665, 1633, 1595, 1480, 1401, 1374, 1344, 1263, 1222, 1176, 1115, 1064, 1032, 993, 926, 892, 831, 732, 711, 624, 577, 481.



436

436: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (dd, *J* = 10.0, 2.7 Hz, 1H, H-1), 7.20 (d, *J* = 2.7 Hz, 1H, H-5), 7.18 (dd, *J* = 8.7, 2.5 Hz, 1H, H-10), 6.89 (d, *J* = 8.7 Hz, 1H, H-11), 6.86 (d, *J* = 2.5 Hz, 1H, H-8), 6.34 (d, *J* = 10.0 Hz, 1H, H-2), 5.39 (dd, *J* = 3.0, 3.0 Hz, 1H, H-13), 3.88 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.65 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 2.31 (dd, *J* = 14.2, 3.0 Hz, 1H, H-14), 2.17 (dd, *J* = 14.2, 3.0 Hz, 1H, H-14), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 178.5 (Cq), 154.0 (CH), 153.1 (CH), 149.7 (Cq), 130.1 (CH), 128.4 (CH), 126.9 (Cq), 125.0 (Cq), 124.9 (CH), 120.31 (CH), 120.27 (Cq), 95.6 (CH), 64.8 (CH_2), 43.8 (Cq), 35.8 (CH_2), 15.2 (CH_3); **HRMS** (ESI^+): $C_{16}H_{14}{}^{79}Br^{35}ClO_3$ $[M+H]^+$ calcd. 368.9888, found 368.9892; **IR** ν_{max} cm^{-1}: 3056, 2977, 2931, 2899, 1669, 1633, 1597, 1577, 1482, 1402, 1378, 1340, 1263, 1223, 1175, 1117, 1065, 1033, 998, 962, 925, 886, 830, 732, 705, 576.



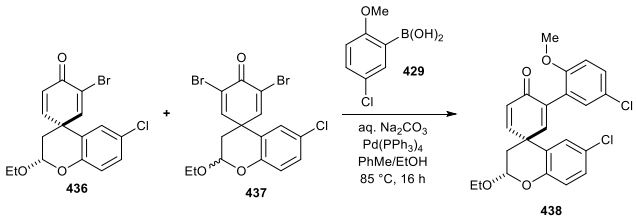
437

437: ^{1}H NMR (500 MHz, $CDCl_3$) δ:* 7.96 (d, *J* = 2.6 Hz, 1H, H-5), 7.21 (dd, ~*J* = 8.8, 2.5 Hz, 1H, H-10), 7.20 (d, ~*J* = 2.6 Hz, 1H, H-1), 6.90 (d, ~*J* = 8.8 Hz, 1H, H-11), 6.86 (d, ~*J* = 2.5

Hz, 1H, H-8), 5.40 (dd, ~*J* = 2.9, 2.9 Hz, 1H, H-13), 3.88 (dq, ~*J* = 9.7, 7.1 Hz, 1H, H-15), 3.66 (dq, ~*J* = 9.7, 7.1 Hz, 1H, H-15), 2.32 (dd, ~*J* = 14.2, 2.9 Hz, 1H, H-14), 2.22 (dd, ~*J* = 14.2, 2.9 Hz, 1H, H-14), 1.22 (dd, ~*J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 172.6 (Cq), 154.0 (CH), 153.2 (CH), 149.5 (Cq), 130.5 (CH), 128.3 (CH), 127.2 (Cq), 122.5 (Cq), 120.6 (CH), 120.1 (Cq), 119.0 (Cq), 95.3 (CH), 64.8 (CH_2), 45.7 (Cq), 35.5 (CH_2), 15.2 (CH_3); **HRMS** (ESI$^+$): $C_{16}H_{13}{}^{79}Br_2{}^{35}ClO_3$ $[M+H]^+$ calcd. 448.8972, found 448.8971; **IR**: not taken due to low purity of **437**.

*Approximate *J* values given (~*J*) due to overlapped peaks.

438: Arylated dienone

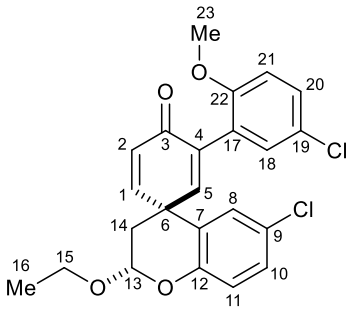


To a solution of an 87:13 respective w/w mixture (determined by ^{1}H NMR spectroscopy) of bromo dienone **436** and dibromo **437** (3.74 g, 9.80 mmol) in PhMe (70.6 mL) and EtOH (31.4 mL) was added Na_2CO_3 (31.4 mL of a 2.0 M aqueous solution) and the biphasic mixture was sparged with argon for 10 minutes. To the biphasic mixture was added 5-chloro-2-methoxyphenyl boronic acid (**429**) (2.46 g, 13.2 mmol) and $Pd(PPh_3)_4$ (113 mg, 0.0978 mmol) and the reaction mixture was sparged with argon for a further 5 minutes. The reaction mixture was heated at 85 °C (under reflux apparatus) for 16 hours

and was then allowed to cool to room temperature. The organics were diluted with EtOAc (200 mL) and were washed with H_2O (2 x 50 mL), then brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography* (petroleum ether/acetone/CH_2Cl_2, 85:10:5) gave dienone **438** as a colourless solid (3.31 g, 90%) **m.p.** 181–183 °C.

*Products precipitated on the silica column which led to elution of **438** over several fractions. The conditions of the mobile phase eluent are unoptimised and it should be considered to increase the polarity of the eluent. It is also recommended to dry-load the crude material.

An updated experimental for the synthesis of **438** and diastereoisomer **496** from bromo-dienones **436** and **435** respectively has been provided in Section 7.10.

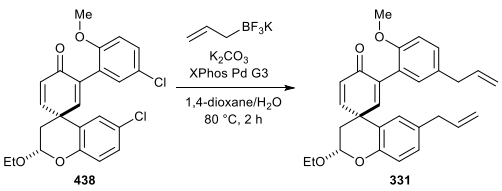


438

438: ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.53 (dd, *J* = 10.1, 3.0 Hz, 1H, H-1), 7.32 (dd, *J* = 8.8, 2.7 Hz, 1H, H-20), 7.25 (dd, *J* = 8.7, 2.6 Hz, 1H, H-10), 7.18 (d, *J* = 2.7 Hz, 1H, H-18), 7.14 (d, *J* = 2.6 Hz, 1H, H-8), 7.04 (d, *J* = 8.8 Hz, 1H, H-21), 6.98 (d, *J* = 8.7 Hz, 1H, H-11), 6.89 (d, *J* = 3.0 Hz, 1H, H-5), 6.23 (d, *J* = 10.1 Hz, 1H, H-2), 5.58 (dd, *J* = 3.0, 3.0 Hz, 1H, H-13), 3.93 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 3.80 (s, 3H, H-23), 3.72 (dq, *J* = 9.7, 7.1 Hz, 1H, H-15), 2.49 (dd, *J* = 14.2, 3.0 Hz, 1H, H-14), 2.27 (dd, *J* = 14.2, 3.0 Hz, 1H, H-14), 1.21 (dd, *J* = 7.1,

7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, acetone-d_6) δ: 182.5 (Cq), 156.3 (Cq), 152.7 (CH), 151.6 (CH), 150.3 (Cq), 135.8 (Cq), 130.2 (CH), 129.2 (CH), 128.69 (CH), 128.65 (CH), 127.4 (Cq), 126.2 (CH), 125.6 (Cq), 124.3 (Cq), 122.4 (Cq), 120.1 (CH), 112.6 (CH), 96.2 (CH), 64.2 (CH_2), 55.6 (CH_3), 40.6 (Cq), 35.4 (CH_2), 14.6 (CH_3); **HRMS** (ESI$^+$): $C_{23}H_{20}{}^{35}Cl_2O_4$ $[M+H]^+$ calcd. 431.0811, found 431.0810; **IR** ν_{max} cm^{-1}: 2974, 2932, 2886, 2851, 2842, 1667, 1638, 1604, 1578, 1483, 1442, 1401, 1345, 1291, 1262, 1240, 1226, 1199, 1175, 1118, 1067, 1031, 1005, 972, 927, 886, 842, 811, 752, 736, 716, 645, 594, 572, 563.

331: acetal dienone



To di-aryl chloride dienone **438** (3.11 g, 7.22 mmol) in 1,4-dioxane (52.0 mL) and H_2O (36.0 mL) was added K_2CO_3 (8.77 g, 63.5 mmol). The biphasic mixture was sparged with argon for 10 minutes and then XPhos Pd G3 (305 mg, 0.361 mmol) and potassium allyltrifluoroborate (4.27 g, 28.9 mmol) were added. The reaction mixture was heated at 90 °C for 2 hours (an aliquot taken at 1.5 hours was analysed by ^{1}H NMR spectroscopy which showed that **483** was consumed) and was then allowed to cool to room temperature. The organics were diluted with EtOAc (300 mL) and were washed with H_2O (100 mL), then brine (100 mL), dried over

$MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 4:1 to 7:3) gave acetal **331** as a colourless solid (2.76 g, 86%).

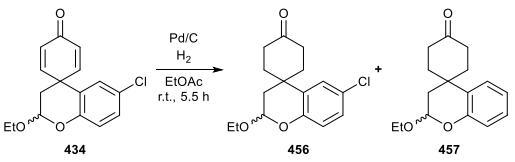
Data was consistent with previously synthesized acetal **331** (see Section 6.1.3).

7.6: Asymmetric 1,4-reduction of dienone 434

7.6.1: Studies towards an enantioselective synthesis of the tetrahydrodibenzofuran core (Section 2.3.4)

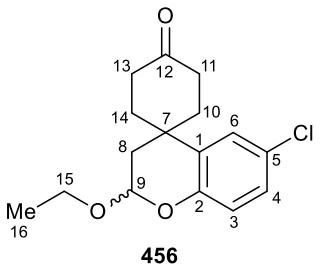
456: 6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexan]-4'-one

457: 2-ethoxyspiro[chromane-4,1'-cyclohexan]-4'-one



A flask containing a solution of dienone **434** (640 mg, 2.20 mmol) in EtOAc (44.0 mL) was evacuated and back-filled with argon three times and then Pd/C (440 mg of 10% Pd/C; 50% wet) was added. The flask was evacuated and back-filled with argon three times and was then evacuated and back-filled with hydrogen (from a balloon). The reaction mixture was stirred at room temperature for 5.5 hours and then the reaction flask was evacuated and back-filled with argon. The reaction mixture was filtered through

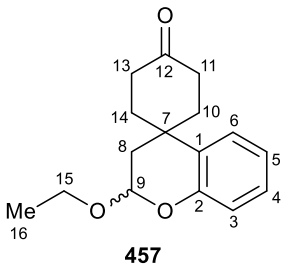
a plug of celite (EtOAc was used to wash the celite pad) and then the organics were concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/Et_2O, 4:1 to 3:2) gave aryl chloride ketone **456** as a colourless solid (351 mg, 54%) **m.p.** 105–107 °C, ketone **457** (31 mg, 6%) **m.p.** 68–70 °C, and a 7:3 respective mixture of **456** and **457** (180 mg, 28% yield of **456**, 10% yield of **457**).



456

456: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21 (d, *J* = 2.5 Hz, 1H, H-6), 7.10 (dd, *J* = 8.7, 2.5 Hz, 1H, H-4), 6.82 (d, *J* = 8.7 Hz, 1H, H-3), 5.27 (dd, *J* = 5.2, 3.0 Hz, 1H, H-9), 3.94 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 3.62 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 2.62 – 2.49 (m, 2H, H-11 and H-13), 2.45 – 2.34 (m, 3H, H-11, H-13 and H-10 or H-14), 2.32 (dd, *J* = 14.0, 5.2 Hz, 1H, H-8), 2.22 (ddd, *J* = 13.8, 13.8, 4.9 Hz, 1H, H-10 or H-14), 2.19 (dd, *J* = 14.0, 3.0 Hz, 1H, H-8), 2.11 (ddd, *J* = 13.8, 13.8, 4.6 Hz, 1H, H-10 or H-14), 1.94 (dddd, *J* = 13.8, 6.1, 3.0, 3.0 Hz, 1H, H-10 or H-14), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 210.4 (Cq), 150.3 (Cq), 131.3 (Cq), 128.0 (CH), 126.4 (Cq), 126.0 (CH), 119.2 (CH), 97.3 (CH), 64.5 (CH_2), 39.2 (CH_2), 37.9 (CH_2), 37.8 (CH_2), 37.7 (CH_2), 34.0 (CH_2), 33.8 (Cq), 15.3 (CH_3); **HRMS** (ESI^+): $C_{16}H_{19}{}^{35}ClO_3$ $[M+Na]^+$ calcd. 317.0915, found 317.0913; **IR** ν_{max} cm^{-1}: 2973, 2930, 2907, 2872, 1716, 1472, 1446, 1406, 1378, 1337, 1270,

1220, 1180, 1147, 1129, 1113, 1060, 1008, 985, 961, 909, 898, 874, 821.

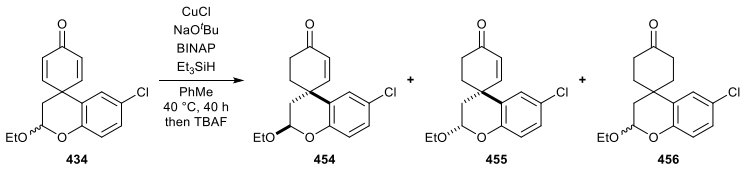


457

457: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (dd, *J* = 8.1, 1.7 Hz, 1H, H-6), 7.15 (ddd, *J* = 8.1, 7.2, 1.7 Hz, 1H, H-4), 6.95 (ddd, *J* = 8.1, 7.2, 1.4 Hz, 1H, H-5), 6.88 (dd, *J* = 8.1, 1.4 Hz, 1H, H-3), 5.27 (dd, *J* = 5.4, 3.1 Hz, 1H, H-9), 3.98 (dq, *J* = 9.5, 7.1 Hz, 1H, H-15), 3.63 (dq, *J* = 9.5, 7.1 Hz, 1H, H-15), 2.65 – 2.50 (m, 2H, H-11 and H-13), 2.45 – 2.37 (m, 2H, H-11 and H-13), 2.36 – 2.22 (m, 4H, H-8, H10 and H-14), 2.18 (ddd, *J* = 13.8, 13.8, 4.6 Hz, 1H, H-10 or H-14), 1.96 (dddd, *J* = 13.8, 6.1, 3.0, 3.0 Hz, 1H, H-10 or H-14), 1.23 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 211.1 (Cq), 151.7 (Cq), 129.5 (Cq), 128.0 (CH), 125.9 (CH), 121.5 (CH), 117.8 (CH), 97.2 (CH), 64.4 (CH_2), 39.2 (CH_2), 38.1 (CH_2), 37.9 (CH_2), 37.8 (CH_2), 34.5 (CH_2), 33.7 (Cq), 15.3 (CH_3); **HRMS** (ESI^+): $C_{16}H_{20}O_3$ $[M+H]^+$ calcd. 261.1485, found 261.1486; **IR** ν_{max} cm^{-1}: 2978, 2936, 2888, 1704, 1606, 1580, 1489, 1448, 1417, 1406, 1375, 1337, 1288, 1235, 1214, 1184, 1126, 1107, 1044, 1017, 955, 932, 909, 892, 792, 748, 693, 599, 575, 478, 438.

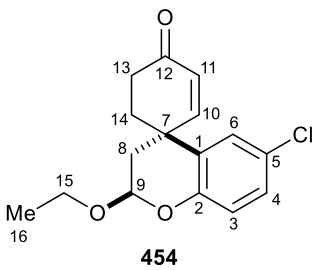
454: (±)-(2*R*,4*R*)-6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexan]-2'-en-4'-one

455: (±)-(2*S*,4*R*)-6-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexan]-2'-en-4'-one



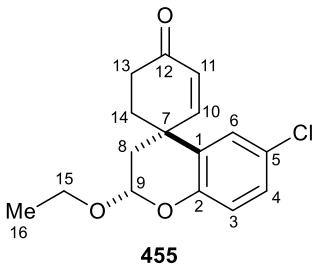
To a flame-dried flask was added CuCl (25 mg, 0.25 mmol), NaO^{t}Bu (24 mg, 0.25 mmol), BINAP (156 mg, 0.250 mmol) and PhMe (10.0 mL). The mixture was stirred for 10 minutes at room temperature and was then cooled to 0 °C. At temperature, Et_3SiH (2.23 mL, 14.0 mmol) was added and then a solution of dienone **434** (2.94 g, 10.0 mmol) in PhMe (10 mL) was added. The reaction mixture was heated at 40 °C for 40 hours (until **434** was consumed as determined by ^1H NMR spectroscopy (over-reduced ketone **456** was observed in the product mixture)). The reaction mixture was cooled to room temperature and then TBAF (14.5 mL of a 1.0 M solution in THF, 14.5 mmol) was added. The reaction mixture was stirred for 0.5 hours at room temperature and then brine (70 mL) was added. The organics were extracted with Et_2O (3 x 100 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (cyclohexane/Et_2O, 9:1 to 3:1) provided enone **454** as a colourless solid (1.08 g, 37%) **m.p.** 57–59 °C, and an

inseparable[323] 4:1 respective mixture of enone **455** and ketone **456** as an off white solid (1.31 g, 36% yield of **455**, 9% yield of **456**).



454

454: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13 (dd, *J* = 8.7, 2.5 Hz, 1H, H-4), 7.06 (d, *J* = 2.5 Hz, 1H, H-6), 6.83 (d, *J* = 8.7 Hz, 1H, H-3), 6.60 (dd, *J* = 10.1, 1.8 Hz, 1H, H-10), 6.09 (dd, *J* = 10.1, 0.8 Hz, 1H, H-11), 5.31 (dd, *J* = 3.4, 2.4 Hz, 1H, H-9), 3.86 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 3.59 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 2.80 (dddd, *J* = 13.7, 4.9, 4.8, 1.8 Hz, 1H, H-14), 2.56 (dddd, *J* = 17.5, 12.4, 4.9, 4.8 Hz, 1H, H-13), 2.48 (dddd, *J* = 17.5, 4.9, 4.8, 0.8 Hz, 1H, H-13), 2.30 (dd, *J* = 14.3, 2.4 Hz, 1H, H-8), 2.23 (ddddd, *J* = 13.7, 12.4, 4.9, 4.8, 1.1 Hz, 1H, H-14), 1.97 (ddd, *J* = 14.3, 3.4, 1.1 Hz, 1H, H-8), 1.18 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 199.2 (Cq), 155.8 (CH), 149.5 (Cq), 129.4 (CH), 129.2 (Cq), 128.8 (CH), 128.3 (CH), 126.4 (Cq), 119.3 (CH), 96.5 (CH), 64.5 (CH_2), 36.3 (Cq), 35.4 (CH_2), 33.8 (CH_2), 33.4 (CH_2), 15.3 (CH_3); **HRMS** (ESI^+): $C_{16}H_{17}{}^{35}ClO_3$ $[M+H]^+$ calcd. 293.0939, found 293.0938; **IR** ν_{max} cm^{-1}: 2976, 2927, 2875, 1675, 1614, 1576, 1481, 1402, 1375, 1344, 1293, 1263, 1223, 1210, 1192, 1168, 1115, 1096, 1080, 1049, 1026, 1006, 955, 901, 881, 812, 792, 755, 733, 686, 645, 581, 516, 468, 420.

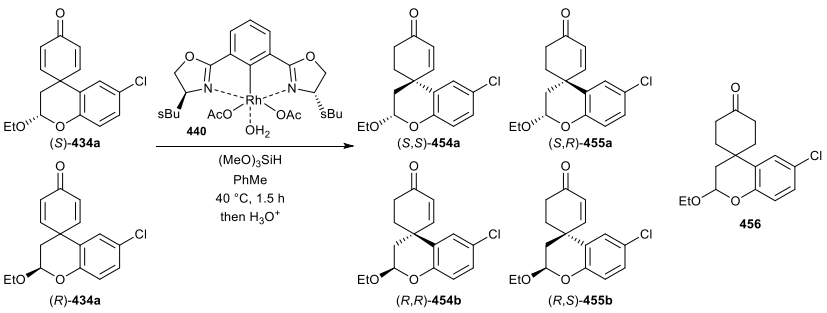


455

455: ^{1}H NMR (500 MHz, $CDCl_3$) δ: (dd, *J* = 8.7, 2.5 Hz, 1H, H-4), 7.07 (d, *J* = 2.5 Hz, 1H, H-6), 6.85 (d, *J* = 8.7 Hz, 1H, H-3), 6.78 (dd, *J* = 10.1, 1.4 Hz, 1H, H-10), 6.08 (d, *J* = 10.1 Hz, 1H, H-11), 5.28 (dd, *J* = 6.8, 2.9 Hz, 1H, H-9), 3.98 (dq, *J* = 9.5, 7.1 Hz, 1H, H-15), 3.65 (dq, *J* = 9.5, 7.1 Hz, 1H, H-15), 2.57 – 2.47 (*m, 2H, H-14), 2.41 – 2.34 (*m, 1H, H-13), 2.24 (dd, *J* = 13.8, 2.9 Hz, 1H, H-8), 2.17 – 2.09 (*m, 2H, H-8 and H-13), 1.24 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 198.3 (Cq), 155.7 (CH), 150.6 (Cq), 129.0 (CH), 128.7 (CH), 128.6 (Cq), 127.7 (CH), 126.3 (Cq), 119.4 (CH), 96.9 (CH), 64.7 (CH_2), 37.5 (CH_2), 37.3 (Cq), 36.8 (CH_2), 33.9 (CH_2), 15.3 (CH_3); **HRMS** (ESI^+): $C_{16}H_{17}{}^{35}ClO_3$ $[M+H]^+$ calcd. 293.0939, found 293.0937; **IR**: not taken due to purity of **456**.

*Multiplicity described as a multiplet due to overlapped signals produced by ketone **456**.

7.6.1.1: Asymmetric Rh-catalysed 1,4-hydride addition



To a flame-dried flask was added dienone **434** (87 mg, 0.30 mmol), Rh-catalyst **440** (4 mg, 7 μmol) and dry PhMe (3.0 mL). The reaction mixture was heated to 40 °C and then $(MeO)_3SiH$ (57 μL, 0.45 mmol)

was added dropwise and the reaction mixture was stirred at 40 °C for 1.5 hours (an aliquot was taken and analysed by ^{1}H NMR spectroscopy at 1 hour which showed full consumption of dienone **434**). The reaction mixture was cooled to 0 °C and then to the reaction mixture was added in quick succession THF (1.5 mL), MeOH (1.5 mL) and HCl (1.5 mL of a 1.0 M aqueous solution) and the reaction mixture was stirred for 1 hour at 0 °C. The organics were extracted with EtOAc (3 x 5 mL), and the combined organics were washed with $NaHCO_3$ (5 mL of a saturated aqueous solution), then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 7:3) gave several products which have been summarised below:

- a 97:3:0 respective w/w mixture of **454**:**455**:**456** (determined by ^{1}H NMR spectroscopy) as a colourless oil (22 mg, 24%:1%:0% yield respectively)
- a 24:72:4 respective w/w mixture of **454**:**455**:**456** (determined by ^{1}H NMR spectroscopy) as a colourless oil (44 mg, 12%:36%:2% yield respectively)
- a 5:83:12 respective w/w mixture of **454**:**455**:**456** (determined by ^{1}H NMR spectroscopy) as a colourless oil (20 mg, 1%:19%:3% yield respectively)

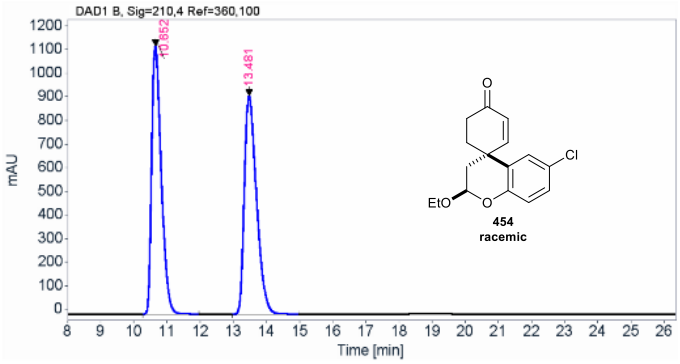
The compounds proved separable by chiral HPLC so e.e. values could be calculated. Therefore, the described 3 mixtures of **454**:**455**:**456**

were combined and were analysed as a single sample (see Figures 36 and 37).

Based upon previous observations, the nature of the Rh-catalyst should favour the formation of (*R*)-stereochemistry at the quaternary centre. Therefore, enantiomers (*R*,*R*) and (*S*,*R*) are assumed to be in excess.

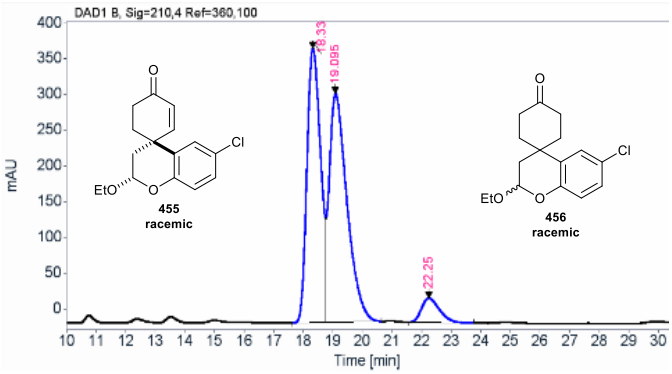
Diastereomeric excess of (*R*,*R*)-**454** was determined by HPLC with a Chiralpak OD-H column (98:2 isohexane:^{i}PrOH, 1.0 mL/min, 210 nm, 23 °C): tr (minor) = 10.7 min, tr (major) = 13.5 min, 92% e.e.

Diastereomeric excess of (*S*,*R*)-**455** was determined by HPLC with a Chiralpak IC column (90:10 isohexane:^{i}PrOH, 1.0 mL/min, 210 nm, 23 °C): tr (minor) = 18.5 min, tr (major) = 26.0 min, 62% e.e.



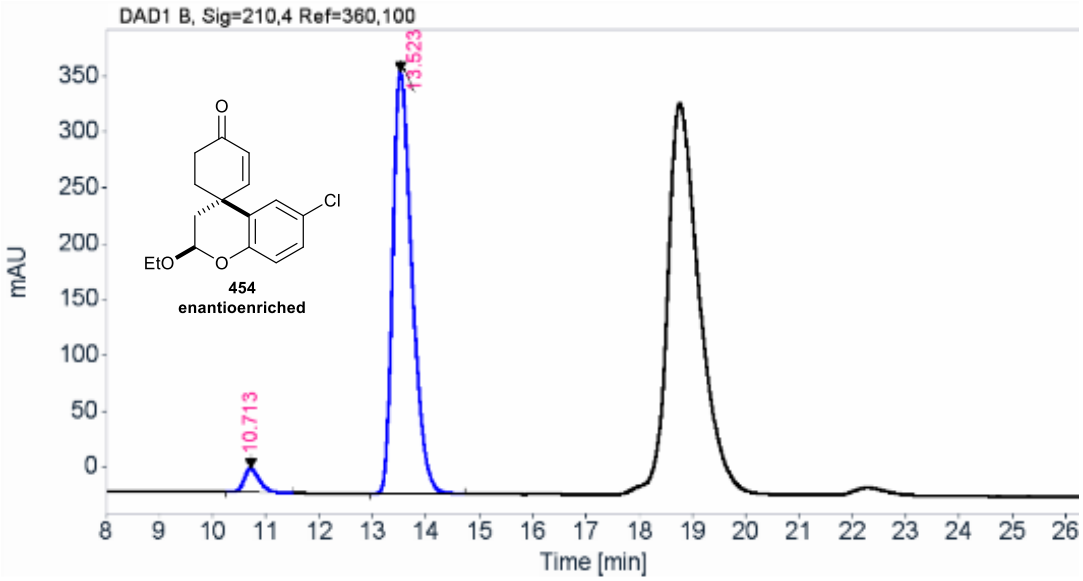
Signal: DAD1 B, Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
10.652	BB	0.3102	22788.732	1135.1411	49.10
13.481	BB	0.3943	23624.016	923.8783	50.90



Signal: DAD1 B, Sig=210,4 Ref=360,100

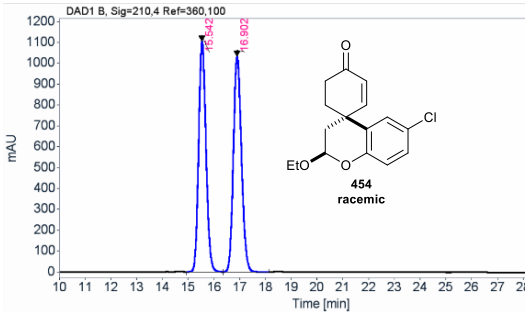
RT [min]	Type	Width [min]	Area	Height	Area%
18.330	BV	0.5012	12278.858	383.8001	45.20
19.095	VB	0.6304	13441.493	319.7993	49.48
22.250	BB	0.6410	1445.166	34.0582	5.32



Signal: DAD1 B, Sig=210,4 Ref=360,100

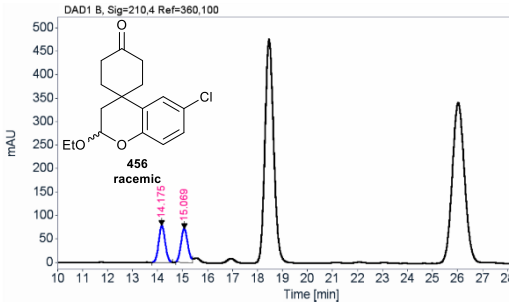
RT [min]	Type	Width [min]	Area	Height	Area%
10.713	BB	0.2987	427.056	21.4074	4.33
13.523	BB	0.3834	9426.728	377.3622	95.67

Figure 36. *HPLC traces (chiralpak OD-H column) used to calculate e.e. of* ***454****.*



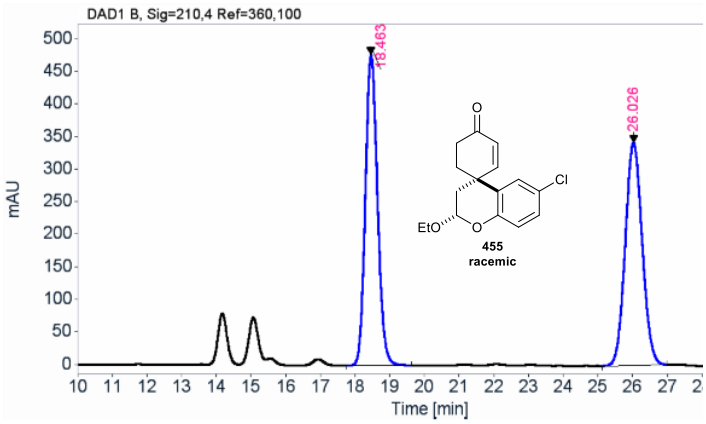
Signal: DAD1 B, Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
15.542	BB	0.3064	21834.268	1105.6732	49.25
16.902	BB	0.3376	22500.430	1034.9111	50.75



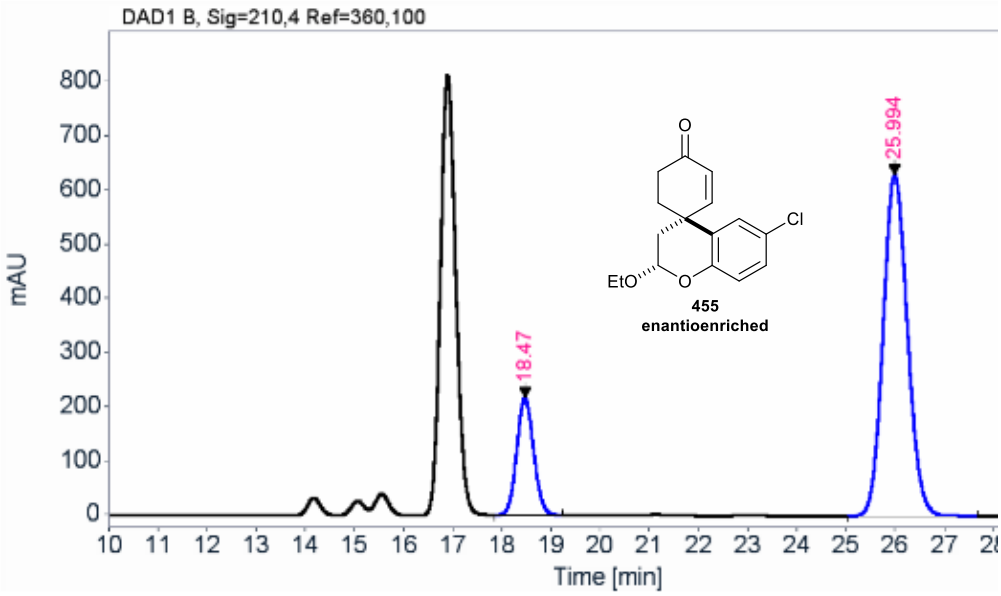
Signal: DAD1 B, Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
14.175	MM	0.3018	1418.899	78.3573	50.51
15.069	MM	0.3207	1390.429	72.2530	49.49



Signal: DAD1 B, Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
18.463	BB	0.3747	11566.213	477.3593	49.96
26.026	BB	0.5250	11583.311	342.0853	50.04



Signal: DAD1 B, Sig=210,4 Ref=360,100

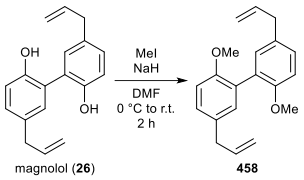
RT [min]	Type	Width [min]	Area	Height	Area%
18.470	MM	0.3990	5189.207	216.7384	19.39
25.994	MM	0.5702	21569.795	630.5103	80.61

Figure 37. *HPLC traces (chiralpak IC column) used to calculate e.e. of* ***455****.*

7.7: Biology SAR Compounds

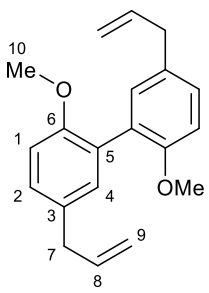
7.7.1: Derivatives of magnolol (Section 3.1)

458: 5,5'-diallyl-2,2'-dimethoxy-1,1'-biphenyl



To a solution of magnolol (**26**) (106 mg, 0.400 mmol) in dry DMF (1.20 mL) at 0 °C was added NaH (35 mg of a 60% w/w dispersion in mineral oil, 0.88 mmol). The reaction mixture was stirred for 2 minutes at 0 °C and then iodomethane (55 µL, 0.88 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours. To the reaction mixture was added NaOH (0.25 mL of a 2.0 M aqueous solution) and the biphasic mixture was stirred for 0.5 hours. To the biphasic mixture was added H_2O (10 mL) and the organics were extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (2 x 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (distilled pentane/distilled Et_2O, 9:1) gave dimethyl magnolol **458** as a colourless solid (97 mg, 82%) ***m.p.** 45–47 °C.

*Previously reported as an oil.[68]



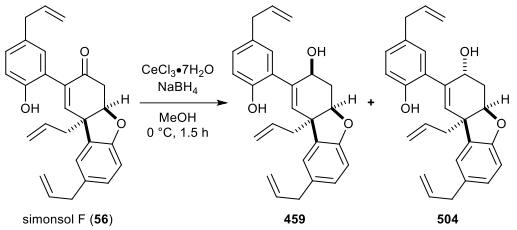
545

458: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (dd, *J* = 8.3, 2.3 Hz, 2H, H-2), 7.07 (d, *J* = 2.3 Hz, 2H, H-4), 6.91 (d, *J* = 8.3 Hz, 2H, H-1), 6.00 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 2H, H-8), 5.14 – 5.03 (m, 4H, H-9), 3.76 (s, 6H, H-10), 3.37 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 4H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.6 (Cq), 138.0 (CH), 131.9 (Cq), 131.7 (CH), 128.6 (CH), 128.0 (Cq), 115.6 (CH_2), 111.3 (CH), 56.0 (CH_3), 39.6 (CH_2); **HRMS** (ESI^+): $C_{20}H_{20}O_2$ $[M+H]^+$ calcd. 295.1693, found 295.1694; **IR** ν_{max} cm^{-1}: 3079, 3019, 3003, 2977, 2952, 2934, 2900, 2830, 1639, 1603, 1504, 1490, 1463, 1426, 1286, 1264, 1228, 1175, 1141, 1047, 1024, 995, 909, 811, 768, 718, 639, 596, 542, 497, 448.

Spectroscopic data obtained for **545** were consistent with those previously reported however the authors reported an extra ^{13}C chemical shift at 127.7 ppm which is assumed to be a typographical error.[68]

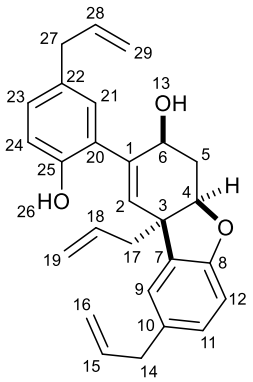
7.7.2: Derivatives of simonsol F (Section 3.1)

459: (±)-(3*S*,4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-3-ol



To a solution of simonsol F (**56**) (12 mg, 0.030 mmol) in MeOH (0.30 mL) at 0 °C was added sequentially $CeCl_3•7H_2O$ (30 mg, 0.080 mmol) and $NaBH_4$ (2 mg, 0.05 mmol). The reaction mixture was stirred for 1.5 hours at 0 °C. To the reaction mixture was added H_2O (0.5 mL) and the organics were extracted with EtOAc (3 x 0.5 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 3:2) gave allylic alcohol **459** as a colourless oil (~90% purity determined by ^1H NMR spectroscopy, 8 mg) and likely allylic alcohol **504** (~60% purity, 3 mg) which was discarded. Allylic alcohol **459** was purified further by flash column chromatography (petroleum ether/EtOAc/acetone, 8:1:1) which gave allylic alcohol **459** as a colourless oil (7 mg, 58%).

An updated experimental for the synthesis of **459** and **504** from simonsol F (**56**) has been provided in Section 7.10.



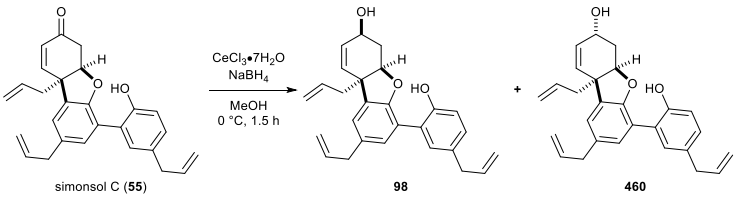
459

459: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.33 (s, 1H, OH-26), 7.02 (d, *J* = 1.8 Hz, 1H, H-9), 6.99 (dd, *J* = 8.2, 2.2 Hz, 1H, H-23), 6.98 (dd, *J* = 8.0, 1.8 Hz, 1H, H-11), 6.83 (d, *J* = 2.2 Hz, 1H, H-21), 6.79 (d, *J* = 8.2 Hz, 1H, H-24), 6.77 (d, *J* = 8.0 Hz, 1H, H-12), 6.01 – 5.87 (m, 2H, H-15 and H-28), 5.78 (s, 1H, H-2), 5.83 – 5.71 (m, 1H, H-18), 5.21 – 5.15 (m, 2H, H-19), 5.11 – 5.02 (m, 4H, H-16 and H-29), 4.83 – 4.78 (m, 1H, H-4), 4.42 – 4.35 (m, 1H, H-5), 4.07 (s, 1H, OH-13), 3.32 (d, *J* = 7.1 Hz, 2H, H-14), 3.30 (d, *J* = 7.1 Hz, 2H, H-27), 2.79 (ddd, *J* = 15.5, 3.2, 2.1 Hz, 1H, H-5), 2.76 (dd, *J* = 14.1, 7.1 Hz, 1H, H-17), 2.61 (dd, *J* = 14.1, 7.1 Hz, 1H, H-17), 2.09 (ddd, *J* = 15.5, 4.1, 2.5 Hz, 1H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 155.6 (Cq), 153.0 (Cq), 138.1 (CH), 137.7 (CH), 137.5 (Cq), 134.2 (Cq), 133.4 (Cq), 133.03 (CH), 132.97 (CH), 130.8 (Cq), 129.94 (CH), 129.89 (CH), 129.0 (CH), 127.9 (Cq), 123.7 (CH), 119.2 (CH_2), 117.3 (CH), 116.0 (CH_2), 115.5 (CH_2), 110.6 (CH), 85.1 (CH), 65.9 (CH), 48.4 (Cq), 41.7 (CH_2), 39.9 (CH_2), 39.4 (CH_2), 30.5 (CH_2); **HRMS** (ESI^-): $C_{27}H_{28}O_3$ $[M-H]^-$ calcd. 399.1966, found 399.1971; **IR** ν_{max} cm^{-1}: 3482, 3218, 3104, 3077, 3016, 3006, 2977, 2924, 2900, 2834, 1638, 1611, 1584, 1488, 1434, 1407, 1371, 1271, 1242, 1219, 1194, 1123, 1033, 993, 916, 824, 789.

7.8.3: Derivatives of simonsol C (Section 3.1)

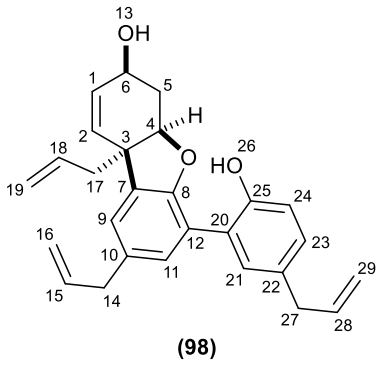
98: (±)-(3*S*,4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-3-ol

460: (±)-(3*R*,4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-3-ol



To a solution of simonsol C (**55**) (12 mg, 0.030 mmol) in MeOH (0.30 mL) at 0 °C was added sequentially $CeCl_3•7H_2O$ (34 mg, 0.090 mmol) and $NaBH_4$ (2 mg, 0.05 mmol). The solution was stirred for 1.5 hours at 0 °C and then H_2O (0.5 mL) was added. The organics were extracted with EtOAc (3 x 0.5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/Et_2O, 2:3) provided a mixture of allylic alcohols **98** and **460** as a light-yellow oil (15 mg). The mixture of allylic alcohols **98** and **460** were subjected to column chromatography (CH_2Cl_2/MeOH, 39:1) which provided a mixture of allylic alcohols **98** and **460** as a colourless oil (12 mg). The mixture of allylic alcohols **98** and **460** were separated by prep TLC (CH_2Cl_2/MeOH, 39:1 (3 runs)) which gave allylic alcohol **98** as a colourless oil (6 mg) and allylic alcohol **460** as a colourless oil (5 mg, 42%). Allylic alcohol **98** was freeze-dried which gave **98**

as a colourless solid (5 mg, 42%) **m.p.** 128–130 °C (lit. 110–112 °C).[103]



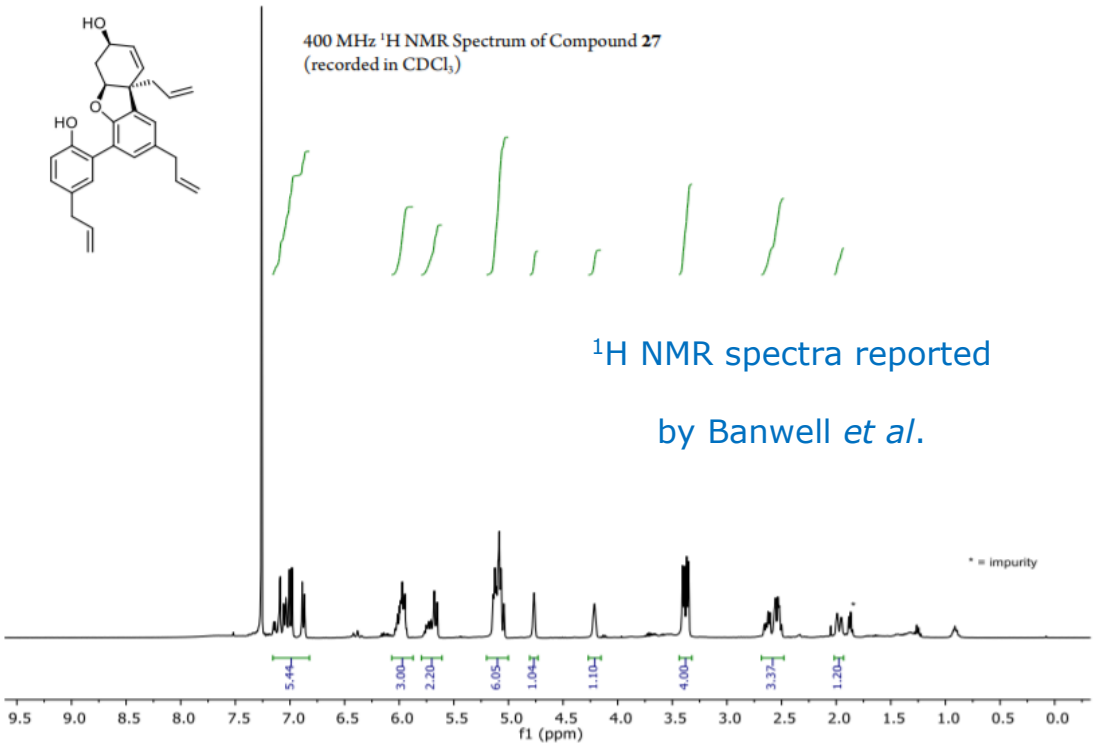
(98)

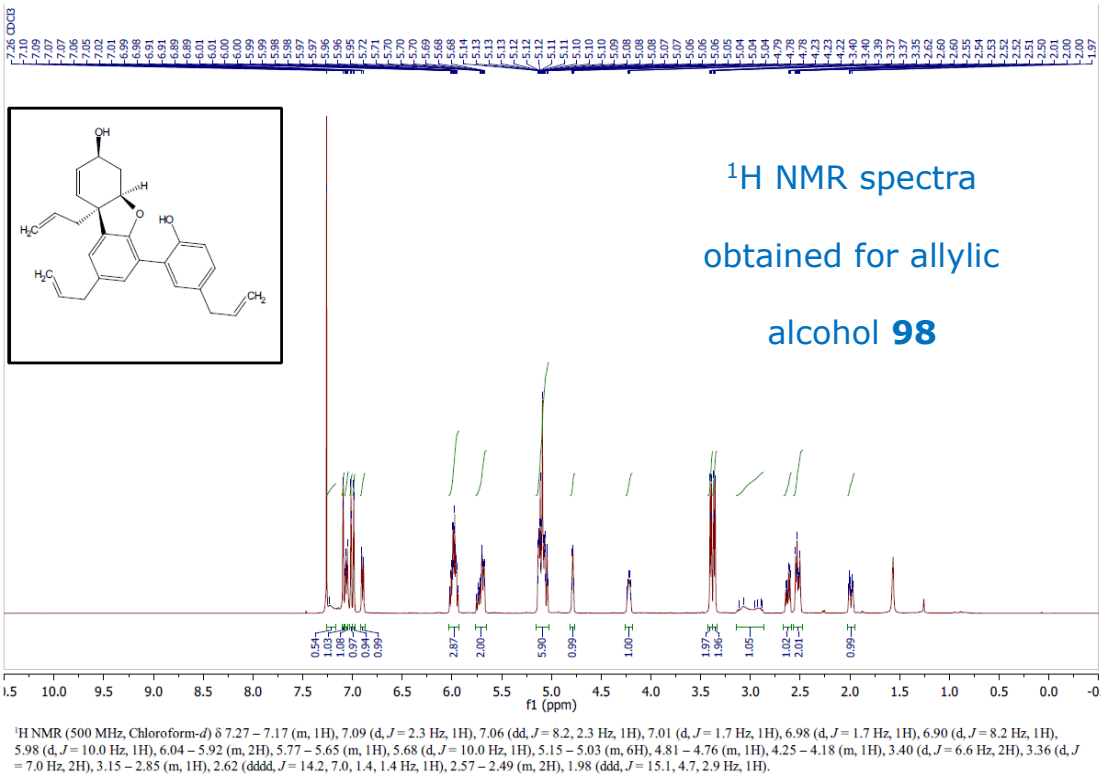
98: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 – 7.17 (m, 1H, ArOH-26), 7.09 (d, *J* = 2.3 Hz, 1H, H-21), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H, H-23), 7.01 (d, *J* = 1.7 Hz, 1H, H-11), 6.98 (d, *J* = 1.7 Hz, 1H, H-9), 6.90 (d, *J* = 8.2 Hz, 1H, H-24), 5.98 (d, *J* = 10.0 Hz, 1H, H-1), 6.04 – 5.92 (m, 2H, H-15 and H-28), 5.77 – 5.65 (m, 1H, H-18), 5.68 (d, *J* = 10.0 Hz, 1H, H-2), 5.15 – 5.03 (m, 6H, H-16, H-19 and H-29), 4.81 – 4.76 (m, 1H, H-4), 4.25 – 4.18 (m, 1H, H-6), 3.40 (d, *J* = 6.6 Hz, 2H, H-14), 3.36 (d, *J* = 6.6 Hz, 2H, H-27), 3.15 – 2.85 (m, 1H, OH-13), 2.62 (dddd, *J* = 14.2, 7.0, 1.4, 1.4 Hz, 1H, H-17), 2.57 – 2.49 (m, 2H, H-5 and H-17), 1.98 (ddd, *J* = 15.1, 4.7, 2.9 Hz, 1H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 153.1 (Cq), 152.3 (Cq), 138.0 (CH), 137.8 (CH), 134.0 (Cq), 133.32 (Cq), 133.25 (CH), 132.4 (CH), 132.3 (Cq), 130.8 (CH), 130.1 (CH), 129.4 (CH), 127.7 (CH), 124.8 (Cq), 122.5 (CH), 121.5 (Cq), 118.9 (CH_2), 117.3 (CH), 116.0 (CH_2), 115.7 (CH_2), 85.3 (CH), 61.8 (CH), 48.1 (Cq), 41.8 (CH_2), 40.0 (CH_2), 39.6 (CH_2), 31.5 (CH_2); **HRMS** (ESI^-): $C_{27}H_{28}O_3$ $[M-H]^-$ calcd. 399.1966, found 399.1968; **IR** ν_{max} cm^{-1}: 3436, 3178, 3076, 3019, 3005, 2976, 2918, 2898, 2829, 1639, 1607, 1510, 1474, 1417, 1369, 1287, 1255, 1220, 1045, 994, 987, 911, 826, 766, 746, 733, 661, 546.

Banwell and co-workers obtained crystal data for compound **98** which confirmed the stereochemistry of compound **98**.[103]

Our melting point for **98** is significantly higher than that reported,[103] however this is likely due to the presence of allyl group isomers in the reported sample (see Figure 38, highlighted as "* = impurity").

Our ^{13}C chemical shifts (δ values (ppm)) do not agree well with those reported by Banwell and co-workers.[103] Differences in chemical shift values range from -0.5 to 1.0 (see Table 26). This discrepancy could be due to sample concentration. The concentration of **98** in Banwell and co-workers NMR sample (see Figures 38 and 39),[103] was increased when the ^{13}C NMR spectral data was obtained compared to when the ^{1}H NMR spectral data was obtained.





¹H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.17 (m, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.01 (d, *J* = 1.7 Hz, 1H), 6.98 (d, *J* = 1.7 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.98 (d, *J* = 10.0 Hz, 1H), 6.04 – 5.92 (m, 2H), 5.77 – 5.65 (m, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.15 – 5.03 (m, 6H), 4.81 – 4.76 (m, 1H), 4.25 – 4.18 (m, 1H), 3.40 (d, *J* = 6.6 Hz, 2H), 3.36 (d, *J* = 7.0 Hz, 2H), 3.15 – 2.85 (m, 1H), 2.62 (dddd, *J* = 14.2, 7.0, 1.4, 1.4 Hz, 1H), 2.57 – 2.49 (m, 2H), 1.98 (ddd, *J* = 15.1, 4.7, 2.9 Hz, 1H).

Figure 38. *Banwell and co-workers*[103] *versus our reported* ¹*H NMR spectra of* ***98*** *in* $CDCl_3$.

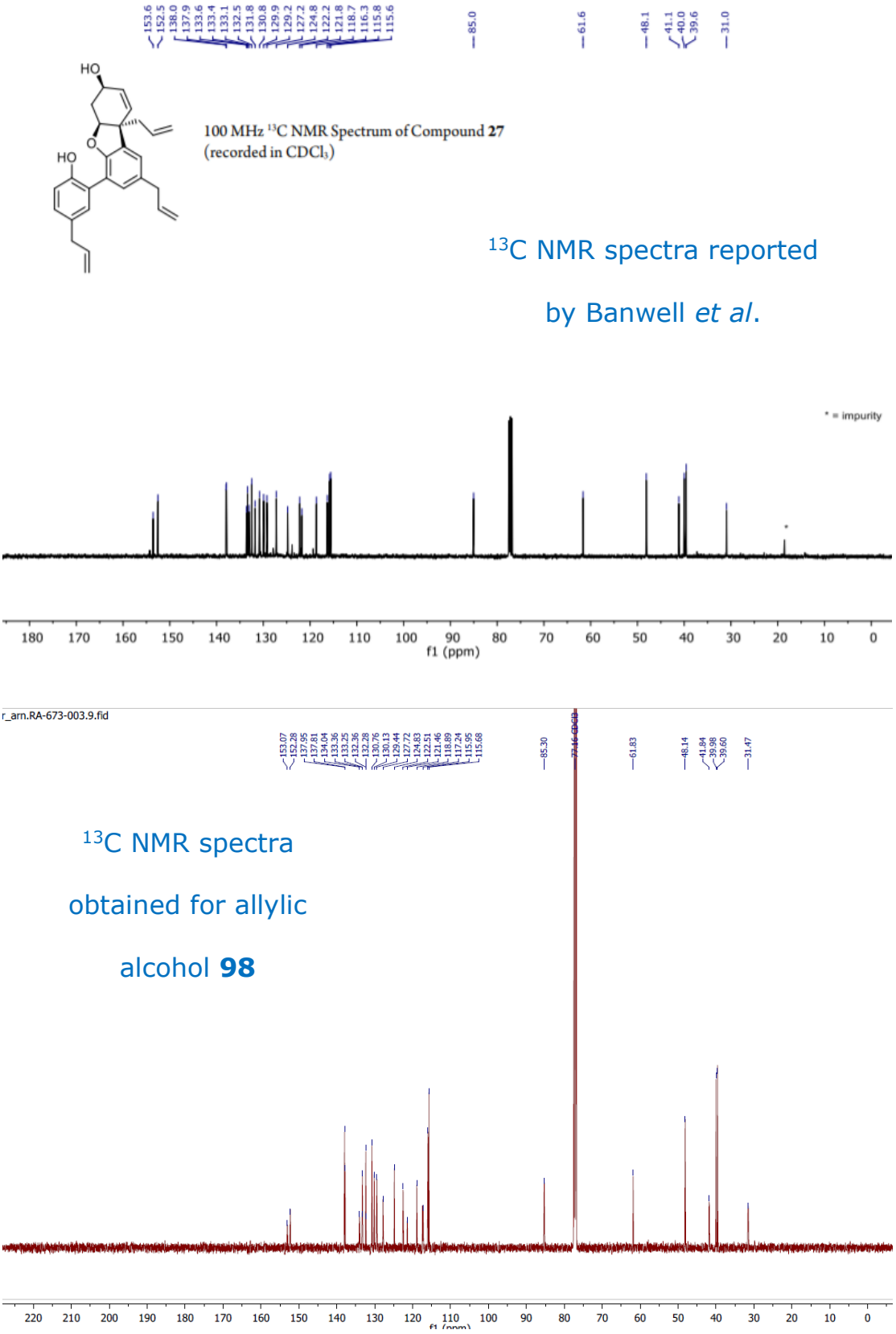
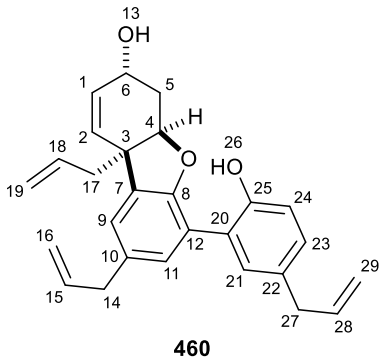


Figure 39. *Banwell and co-workers[103] versus our reported ^{13}C NMR spectra of* ***98*** *in $CDCl_3$.*

Rep. Syn. **98**[103]	Syn. **98**	Dif.	Rep. Syn. **98**[103]	Syn. **98**	Dif.
153.6	153.1	-0.5	122.2	122.5	0.3
152.5	152.3	-0.2	121.8	121.5	-0.3
138.0	138.0	0	118.7	118.9	0.2
137.9	137.8	-0.1	116.3	117.3	1.0
133.6	134.0	0.4	115.8	116.0	0.2
133.4	133.3	-0.1	115.6	115.7	0.1
133.1	133.3	0.2	85.0	85.3	0.3
132.5	132.4	-0.1	61.6	61.8	0.2
131.8	132.3	0.5	48.1	48.1	0
130.8	130.8	0	41.1	41.8	0.7
129.9	130.1	0.2	40.0	40.0	0
129.2	129.4	0.2	39.6	39.6	0
127.2	127.7	0.5	31.0	31.5	0.5
124.8	124.8	0			

Table 26. *Comparison (Dif. = difference (Syn. – Rep. Syn. ^{13}C δ value)) of reported synthetic (Rep. Syn.) versus synthetic (Syn.) allylic alcohol* ***98*** *^{13}C NMR spectroscopy data in $CDCl_3$.*[92]

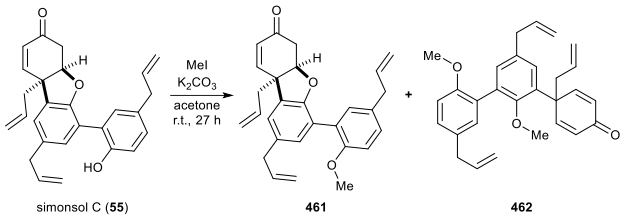
A tabulated comparison of the ^1H NMR spectroscopy data is not provided as Banwell and co-workers described the majority of their reported ^1H chemical shifts of **98** as a multiplet (which is likely due to the overlapped signals produced from the present allyl group isomer). However, the chemical shift δ values (ppm) agree excellently with one another.



460

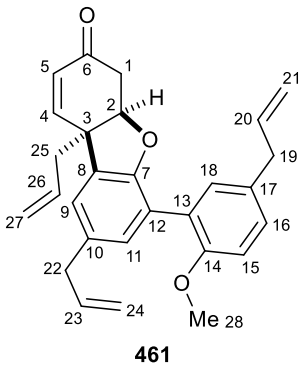
460: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13 (d, *J* = 2.2 Hz, 1H, H-21), 7.11 (dd, *J* = 8.2, 2.2 Hz, 1H, H-23), 7.05 (d, *J* = 1.6 Hz, 1H, H-11), 6.97 (d, *J* = 8.2 Hz, 2H, H-24), 6.96 (d, *J* = 1.6 Hz, 1H, H-9), 6.53 (s, 1H, ArOH-26), 5.97 (dddd, *J* = 16.8, 10.0, 6.8, 6.8 Hz, 2H, H-15 and H-28), 5.87 (ddd, *J* = 10.1, 2.2, 1.1 Hz, 1H, H-1), 5.80 – 5.70 (m, 1H, H-18), 5.65 (ddd, *J* = 10.1, 1.9, 1.1 Hz, 1H, H-2), 5.16 – 5.03 (m, 7H, H-16, H-19 and H-29), 4.88 (ddd, *J* = 4.4, 3.3, 0.9 Hz, 1H, H-4), 4.48 – 4.39 (m, 1H, H-6), 3.39 (d, *J* = 6.8 Hz, 2H, H-14), 3.38 (d, *J* = 6.8 Hz, 2H, H-27), 2.66 (dddd, *J* = 14.3, 6.7, 1.3, 1.3 Hz, 1H, H-17), 2.61 – 2.51 (m, 2H, H-5 and H-17), 1.80 (ddd, *J* = 13.9, 9.5, 3.2 Hz, 1H, H-5), 1.57 (d, *J* = 5.8 Hz, 1H, OH-13); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 152.6 (Cq), 152.1 (Cq), 137.9 (CH), 137.6 (CH), 134.6 (Cq), 133.6 (Cq), 133.3 (CH), 132.9 (Cq), 131.7 (CH), 131.6 (CH), 130.7 (CH), 130.4 (CH), 129.7 (CH), 125.0 (Cq), 122.9 (CH), 121.0 (Cq), 119.1 (CH_2), 118.5 (CH), 116.1 (CH_2), 115.7 (CH_2), 85.5 (CH), 62.6 (CH), 47.9 (Cq), 42.8 (CH_2), 39.9 (CH_2), 39.6 (CH_2), 33.6 (CH_2); **HRMS** (ESI^-): $C_{27}H_{28}O_3$ $[M-H]^-$ calcd. 399.1966, found 399.1964; **IR** ν_{max} cm^{-1}: 3354, 3075, 2924, 2855, 1733, 1639, 1497, 1472, 1433, 1416, 1279, 1245, 1219, 1034, 996, 915.

461: (±)-(4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-methoxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



simonsol C (**55**) **461** **462**

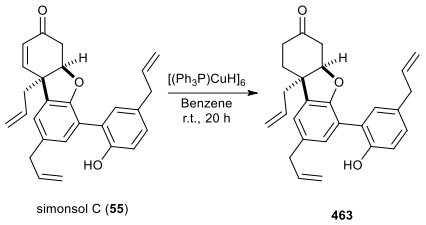
To a solution of simonsol C (**55**) (45 mg, 0.11 mmol) in acetone (2.85 mL) was added K_2CO_3 (236 mg, 1.71 mmol) and iodomethane (71 µL, 1.1 mmol). The reaction mixture was stirred for 27 hours at room temperature and then the organics were concentrated under a stream of nitrogen. Purification by graduated column chromatography (petroleum ether/EtOAc, 9:1 to 4:1) gave an inseparable[323] 4:1 respective mixture (determined by ^{1}H NMR spectroscopy) of methyl simonsol C **461** and tentatively assigned dienone **462** (38 mg). The mixture of **461** and **462** was dissolved in a minimal amount of distilled Et_2O (~0.2 mL) and the solution was diluted with distilled pentane (~2.0 mL), sealed and cooled to -20 °C for 18 hours. A colourless precipitate formed which was collected by suction filtration and the filter cake was washed with distilled pentane (3 x 1 mL) which gave methyl simonsol C **461** as a colourless solid (12 mg, 26%) **m.p.** 103–105 °C.



461

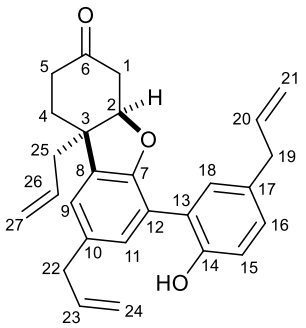
461: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13 (dd, *J* = 8.3, 2.3 Hz, 1H, H-16), 7.10 (d, *J* = 2.3 Hz, 1H, H-18), 7.07 (d, *J* = 1.7 Hz, 1H, H-11), 6.99 (d, *J* = 1.7 Hz, 1H, H-9), 6.89 (d, *J* = 8.3 Hz, 1H, H-15), 6.56 (dd, *J* = 10.2, 1.8 Hz, 1H, H-4), 6.04 (d, *J* = 10.2 Hz, 1H, H-5), 5.97 (dddd, *J* = 16.8, 9.9, 6.8, 6.8 Hz, 2H, H-20 and H-23), 5.82 (dddd, *J* = 16.8, 10.0, 8.1, 6.6 Hz, 1H, H-26), 5.23 – 5.16 (m, 2H, H-27), 5.15 – 5.03 (m, 4H, H-21 and H-24), 4.79 (ddd, *J* = 4.1, 3.0, 1.8 Hz, 1H, H-2), 3.72 (s, 3H, H-28), 3.39 (d, *J* = 6.8 Hz, 2H, H-22), 3.35 (d, *J* = 6.8 Hz, 2H, H-19), 2.97 (dd, *J* = 17.5, 3.0 Hz, 1H, H-1), 2.83 (dddd, *J* = 14.2, 6.6, 1.4, 1.4 Hz, 1H, H-25), 2.73 (dd, *J* = 17.5, 4.1 Hz, 1H, H-1), 2.66 (dd, *J* = 14.2, 8.1 Hz, 1H, H-25); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 195.8 (Cq), 155.5 (Cq), 155.0 (Cq), 148.8 (CH), 137.81 (CH), 137.78 (CH), 133.3 (Cq), 132.4 (CH), 132.1 (Cq), 131.3 (CH), 131.06 (Cq), 131.05 (CH), 129.1 (CH), 127.4 (CH), 125.9 (Cq), 121.9 (CH), 121.8 (Cq), 119.7 (CH_2), 116.0 (CH_2), 115.8 (CH_2), 111.6 (CH), 84.6 (CH), 55.9 (CH_3), 48.8 (Cq), 41.0 (CH_2), 40.0 (CH_2), 39.5 (CH_2), 39.0 (CH_2); **HRMS** (ESI^+): $C_{28}H_{28}O_3$ $[M+H]^+$ calcd. 413.2111, found 413.2100; **IR** ν_{max} cm^{-1}: 3076, 3001, 2956, 2904, 2848, 2834, 1686, 1639, 1616, 1503, 1466, 1437, 1415, 1404, 1276, 1245, 1217, 1182, 1132, 1082, 1027, 994, 916, 880, 815, 795, 765, 659, 592, 551.

463: (±)-(4a*R*,9b*S*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one



simonsol C (**55**) **463**

To a flame-dried microwave was added simonsol C (**55**) (25 mg, 0.063 mmol) and benzene (1.00 mL which had been sparged with argon for 5 minutes). The solution was then sparged with argon for a further 5 minutes and then Stryker's reagent[332] (247 mg, 0.126 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered through a plug of celite and the celite was washed with Et_2O. Purification by flash column chromatography (petroleum ether/Et_2O, 3:2) gave a mixture of ketone **463** and triphenylphosphine (as well as other baseline impurities). The mixture was purified by preparative TLC (petroleum ether/acetone, 33:7) which gave a mixture of ketone **463** and baseline impurities as a colourless solid (14 mg). The solid was dissolved in the minimum amount of distilled Et_2O (~0.2 mL) and the solution was diluted with distilled pentane (~2.0 mL). The solution was cooled to -20 °C for 20 hours. A colourless precipitate formed which was collected by suction filtration and the filter cake was washed with distilled pentane (3 x 0.5 mL) which gave ketone **463** as a colourless solid (10 mg, 40%) **m.p.** 91–93 °C.

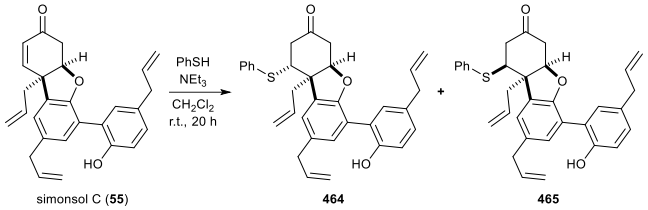


463

463: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.11 – 7.08 (m, 2H, H-15 and H-18), 7.08 (d, *J* = 1.8 Hz, 1H, H-11), 6.98 (d, *J* = 1.8 Hz, 1H, H-9), 6.98 – 6.92 (m, 1H, H-16), 6.14 (s, 1H, OH), 6.03 – 5.93 (m, 2H, H-20 and H-22), 5.74 (dddd, *J* = 16.8, 10.5, 8.2, 6.6 Hz, 1H, H-26), 5.22 – 5.16 (m, 2H, H-27), 5.13 – 5.04 (m, 5H, H-2, H-21 and H-24), 3.41 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 2H, H-22), 3.37 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 2H, H-19), 2.90 (dd, *J* = 17.1, 3.3 Hz, 1H, H-1), 2.67 (dd, *J* = 17.1, 3.7 Hz, 1H, H-1), 2.66 (dddd, *J* = 14.0, 6.6, 1.2, 1.2 Hz, 1H, H-25), 2.55 (dd, *J* = 14.0, 8.2 Hz, 1H, H-25), 2.35 – 2.29 (m, 1H, H-5), 2.22 – 2.13 (m, 1H, H-4), 2.08 – 1.97 (m, 2H, H-4 and H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 208.6 (Cq), 153.4 (Cq), 152.0 (Cq), 137.9 (CH), 137.6 (CH), 134.8 (Cq), 132.8 (Cq), 132.6 (CH), 132.5 (Cq), 131.0 (CH), 130.7 (CH), 129.8 (CH), 124.6 (Cq), 123.1 (CH), 120.6 (Cq), 120.3 (CH_2), 118.4 (CH), 116.2 (CH_2), 115.8 (CH_2), 85.7 (CH), 47.7 (Cq), 44.6 (CH_2), 42.1 (CH_2), 39.9 (CH_2), 39.6 (CH_2), 35.9 (CH_2), 32.4 (CH_2); **HRMS** (ESI^+): $C_{27}H_{28}O_3$ $[M+H]^+$ calcd. 401.2111, found 401.2116; **IR** ν_{max} cm^{-1}: 3390, 3076, 3003, 2976, 2902, 2838, 1719, 1638, 1609, 1497, 1472, 1433, 1416, 1365, 1349, 1327, 1287, 1271, 1242, 1213, 1148, 1122, 1047, 995, 914, 867, 825, 803, 792, 764, 692, 655, 564, 553, 544, 492.

464: (±)-(1*R*,4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-1-(phenylthio)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one

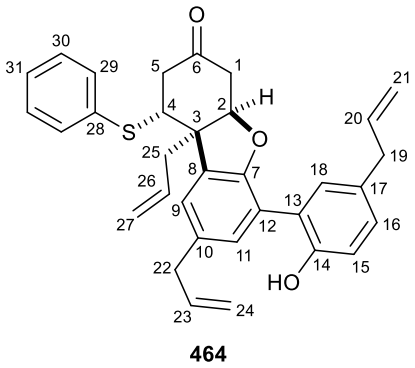
465: (±)-(1*S*,4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-1-(phenylthio)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one



To a solution of simonsol C (**55**)* (60 mg, 0.15 mmol) in CH_2Cl_2 (1.35 mL) at room temperature was added thiophenol (46 µL, 0.45 mmol) and triethylamine (12 µL, 0.086 mmol). The reaction mixture was stirred at room temperature for 3 hours and then the organics were concentrated under a stream of nitrogen. Purification by graduated column chromatography (distilled pentane/distilled Et_2O, 4:1 to 3:2) gave thioether **465** as a colourless oil (31 mg*, 41%), and a 9:1 respective mixture (determined by ^{1}H NMR spectroscopy) of thioether **464** and simonsol C (**55**) as a colourless solid (41 mg*, 49% yield of **464** and 7% yield of simonsol C (**55**)).

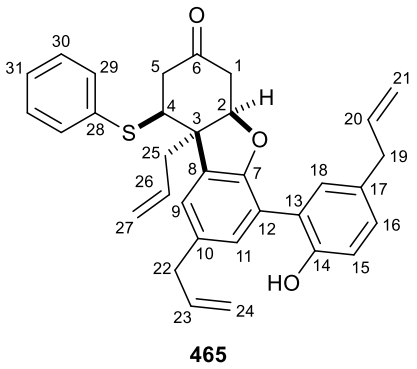
*8-16% of allyl group isomers present as determined by ^{1}H NMR spectroscopy.

An updated experimental for the synthesis of **464** and **465** from simonsol C (**55**) has been provided in Section 7.10.



464

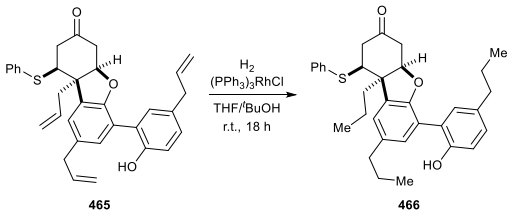
464: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 – 7.43 (m, 2H, H-29), 7.37 (d, *J* = 1.8 Hz, 1H, H-9), 7.35 – 7.30 (m, 3H, H-30 and H-31), 7.15 (d, *J* = 1.8 Hz, 1H, H-11), 7.13 – 7.08 (m, 2H, H-16 and H-18), 6.94 (d, *J* = 8.1 Hz, 1H, H-15), 6.09 – 5.92 (m, 3H, H-20, H-23 and OH), 5.77 (dddd, *J* = 16.7, 10.3, 8.5, 6.4 Hz, 1H, H-26), 5.30 – 5.23 (m, 2H, H-27), 5.18 – 5.04 (m, 5H, H-2, H-21 and H-24), 3.51 (dd, *J* = 13.8, 3.3 Hz, 1H, H-4), 3.47 (d, *J* = 6.8 Hz, 2H, H-19), 3.37 (d, *J* = 6.7 Hz, 2H, H-22), 3.14 (dd, *J* = 14.1, 8.5 Hz, 1H, H-25), 2.99 – 2.93 (m, 2H, H-1 and H-25), 2.66 – 2.55 (m, 2H, H-1 and H-5), 2.34 (dd, *J* = 18.1, 13.8 Hz, 1H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 206.5 (Cq), 153.7 (Cq), 151.8 (Cq), 137.8 (CH), 137.5 (CH), 134.4 (Cq), 133.9 (Cq), 133.6 (2x CH), 132.9 (Cq), 132.0 (CH), 131.6 (CH), 130.8 (CH), 129.8 (CH), 129.6 (2x CH), 128.9 (Cq), 128.4 (CH), 126.1 (CH), 124.5 (Cq), 120.9 (CH_2), 120.7 (Cq), 118.1 (CH), 116.2 (CH_2), 115.8 (CH_2), 85.7 (CH), 51.1 (Cq), 50.7 (CH), 44.0 (CH_2), 41.7 (CH_2), 41.5 (CH_2), 39.9 (CH_2), 39.6 (CH_2); **HRMS** (ESI^+): $C_{33}H_{32}O_3S$ $[M+H]^+$ calcd. 509.2145, found 509.2143.



465

465: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 – 7.40 (m, 2H, ArH), 7.37 – 7.31 (m, 3H, ArH), 7.12 – 7.07 (m, 4H, ArH), 6.96 – 6.92 (m, 1H, ArH), 6.05 (s, 1H, OH), 6.04 – 5.89 (m, 2H, H-20 and H-23), 5.66 (dddd, *J* = 17.1, 10.1, 8.8, 5.6 Hz, 1H, H-26), 5.26 – 5.16 (m, 2H, H-27), 5.13 – 5.03 (m, 5H, H-2, H-21 and H-24), 3.79 (dd, *J* = 4.6, 4.0 Hz, 1H, H-4), 3.40 (ddd, *J* = 6.7, 1.5 Hz, 2H, H-22), 3.37 (ddd, *J* = 6.7, 1.5 Hz, 2H, H-19), 3.24 (dd, *J* = 17.5, 4.9 Hz, 1H, H-1), 2.97 (dddd, *J* = 14.0, 5.6, 1.5, 1.5 Hz, 1H, H-25), 2.87 (dd, *J* = 17.5, 3.0 Hz, 1H, H-1), 2.80 (dd, *J* = 14.0, 8.8 Hz, 1H, H-25), 2.51 (dd, *J* = 18.1, 4.6 Hz, 1H, H-5), 2.39 (dd, *J* = 18.1, 4.0 Hz, 1H, H-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 206.0 (Cq), 153.3 (Cq), 151.9 (Cq), 137.8 (CH), 137.5 (CH), 134.7 (Cq), 133.6 (2 x CH), 133.3 (Cq), 132.9 (CH), 132.8 (Cq), 131.5 (CH), 131.4 (Cq), 130.7 (CH), 129.9 (CH), 129.6 (2 x CH), 128.5 (CH), 124.4 (Cq), 123.7 (CH), 120.9 (Cq), 120.5 (CH_2), 118.3 (CH), 116.2 (CH_2), 115.8 (CH_2), 85.4 (CH), 52.4 (CH), 51.7 (Cq), 42.5 (CH_2), 42.3 (CH_2), 41.8 (CH_2), 39.8 (CH_2), 39.6 (CH_2); **HRMS** (ESI^+): $C_{33}H_{32}O_3S$ $[M+H]^+$ calcd. 509.2145, found 509.2144.

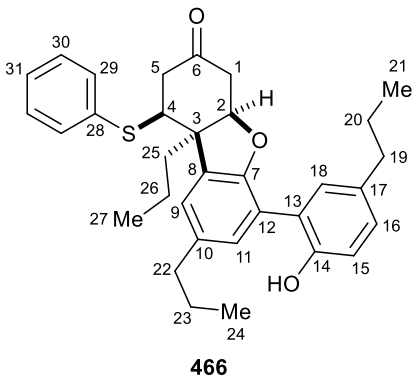
466: (±)-(1*S*,4a*R*,9b*R*)-6-(2-hydroxy-5-propylphenyl)-1-(phenylthio)-8,9b-dipropyl-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one



465 466

A solution of thioether **465*** (31 mg, 0.061 mmol) in THF (0.21 mL) and ^{t}BuOH (0.21 mL) was sparged with argon for 2 minutes. To the solution was added Wilkinson's catalyst (12 mg, 0.012 mmol) and then the flask was evacuated and was back-filled with argon three times. The flask was evacuated and was back-filled with hydrogen (from a balloon) and was stirred under an atmosphere of hydrogen at room temperature for 18 hours. The flask was evacuated and back-filled with argon and then the organics were concentrated *in vacuo*. Purification by flash column chromatography (distilled pentane/distilled Et_2O, 4:1) gave ketone **466** as a colourless solid (26 mg, 83%) **m.p.** 141–143 °C.

*8-16% of allyl group isomers present as determined by ^{1}H NMR spectroscopy.

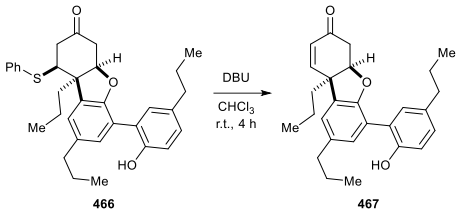


466

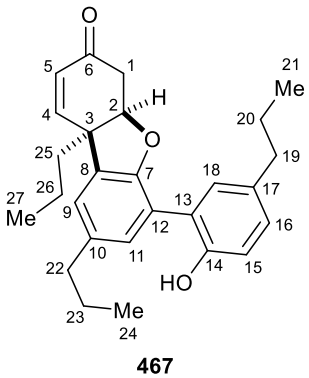
466: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 – 7.40 (m, 2H, H-29), 7.36 – 7.29 (m, 3H, H-30 and H-31), 7.11 – 7.08 (m, 2H, H-16 and H-18), 7.08 (d, *J* = 1.8 Hz, 1H, H-11), 7.03 (d, *J* = 1.8 Hz, 1H, H-9), 6.95 – 6.92 (m, 1H, H-15), 6.10 (s, 1H, OH),

5.05 (dd, *J* = 4.8, 3.0 Hz, 1H, H-2), 3.79 (dd, *J* = 4.5, 3.9 Hz, 1H, H-4), 3.26 (dd, *J* = 17.5, 4.8 Hz, 1H, H-1), 2.88 (dd, *J* = 17.5, 3.0 Hz, 1H, H-1), 2.63 – 2.53 (m, 4H, H-19 and H-22), 2.48 (dd, *J* = 18.2, 4.5 Hz, 1H, H-5), 2.35 (dd, *J* = 18.2, 3.9 Hz, 1H, H-5), 2.11 (ddd, *J* = 13.9, 12.1, 4.6 Hz, 1H, H-25), 2.02 (ddd, *J* = 13.9, 11.9, 4.6 Hz, 1H, H-25), 1.70 – 1.59 (m, 4H, H-20 and H-23), 1.48 – 1.34 (m, 1H, H-26), 1.34 – 1.20 (m, 1H, H-26), 0.97 (dd, *J* = 7.2, 7.2 Hz, 3H, H-27), 0.96 (dd, *J* = 7.3, 7.3 Hz, 3H, H-21 or H-24), 0.95 (dd, *J* = 7.3, 7.3 Hz, 3H, H-21 or H-24); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 206.3 (Cq), 152.9 (Cq), 151.5 (Cq), 137.3 (Cq), 135.5 (Cq), 133.6 (2x CH), 133.5 (Cq), 131.4 (Cq), 131.1 (CH), 130.5 (CH), 129.7 (CH), 129.6 (2x CH), 128.4 (CH), 124.4 (Cq), 123.4 (CH), 120.8 (Cq), 118.1 (CH), 86.0 (CH), 52.7 (CH), 52.0 (Cq), 42.8 (CH_2), 42.3 (CH_2), 39.9 (CH_2), 37.8 (CH_2), 37.4 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 18.0 (CH_2), 14.5 (CH_3), 14.1 (CH_3), 14.0 (CH_3); **HRMS** (ESI^+): $C_{33}H_{38}O_3S$ $[M+H]^+$ calcd. 515.2614, found 515.2613; **IR** ν_{max} cm^{-1}: 3400, 3058, 3020, 2958, 2929, 2870, 1721, 1583, 1497, 1471, 1439, 1416, 1340, 1268, 1243, 1210, 1181, 1151, 1123, 1086, 1068, 1041, 1025, 991, 900, 881, 823, 805, 785, 750, 704, 693, 666, 628, 619, 498, 489.

467: (±)-(4a*R*,9b*R*)-6-(2-hydroxy-5-propylphenyl)-8,9b-dipropyl-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



To a solution of ketone **466** (26 mg, 0.050 mmol) in $CHCl_3$ (0.60 mL) at room temperature was added DBU (9.3 µL, 0.062 mmol) and the reaction mixture was stirred for 4 hours at room temperature. To the reaction mixture was added HCl (5 mL of a 1.0 M aqueous solution) and the organics were extracted with $CHCl_3$ (3 x 5 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (distilled pentane/distilled Et_2O, 3:2) gave enone **467** as a colourless solid (92% purity determined by ^1H NMR spectroscopy, 15 mg, 68% yield). Enone **467** was subjected to preparative TLC (distilled pentane/acetone, 9:1) which gave enone **467** as a colourless solid (11 mg, 55%) **m.p.** 99–101 °C.



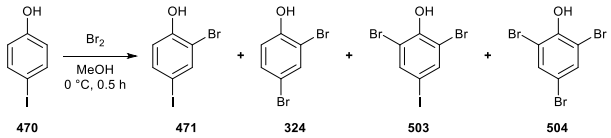
467: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.12 – 7.07 (m, 3H, H-11, H-16 and H-18), 7.02 (d, *J* = 1.8 Hz, 1H, H-9), 6.97 – 6.92 (m, 1H, H-15), 6.51 (dd, *J* = 10.2, 1.8 Hz, 1H, H-4), 6.14 (s, 1H, OH), 6.03 (d, *J* = 10.2 Hz, 1H, H-5), 4.99 (ddd, *J* = 4.2, 2.9, 1.8 Hz, 1H, H-2), 3.08 (dd, *J* = 17.8, 2.9 Hz, 1H, H-1), 2.80 (dd, *J* = 17.8, 4.2 Hz, 1H, H-1), 2.61 (dd, *J* = 8.2, 7.1 Hz, 2H, H-22), 2.56 (dd, *J* = 8.2, 7.1 Hz, 2H, H-19),

2.02 (ddd, *J* = 14.0, 11.4, 5.7 Hz, 1H, H-25), 1.94 (ddd, *J* = 14.0, 11.2, 6.2 Hz, 1H, H-25), 1.70 – 1.59 (m, 4H, H-20 and H-23), 1.51 – 1.38 (m, 2H, H-26), 1.03 (dd, *J* = 7.3, 7.3 Hz, 3H, H-27), 0.97 (dd, *J* = 7.4, 7.4 Hz, 3H, H-24), 0.95 (dd, *J* = 7.3, 7.3 Hz, 3H, H-21).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 194.6 (Cq), 152.5 (Cq), 151.5 (Cq), 149.3 (CH), 137.9 (Cq), 135.6 (Cq), 131.9 (Cq), 130.9 (CH), 130.5 (CH), 129.7 (CH), 127.4 (CH), 124.3 (Cq), 122.4 (CH), 121.3 (Cq), 118.2 (CH), 85.6 (CH), 49.2 (Cq), 39.0 (CH_2), 38.7 (CH_2), 37.8 (CH_2), 37.4 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 18.4 (CH_2), 14.8 (CH_3), 14.0 (2x CH_3); **HRMS** (ESI^+): $C_{27}H_{32}O_3$ $[M+H]^+$ calcd. 404.2424, found 404.2426; **IR** ν_{max} cm^{-1}: 3402, 3021, 2958, 2929, 2871, 1684, 1616, 1583, 1497, 1466, 1414, 1250, 1214, 1151, 1125, 1093, 1068, 1037, 1015, 980, 909, 877, 823, 800, 781, 760, 734, 649, 592, 565, 485.

7.8: Future Studies

7.8.1: Studies towards the synthesis of 2-bromo-4-allylanisole (Section 5.1.1)

471: 2-bromo-4-iodophenol[375]

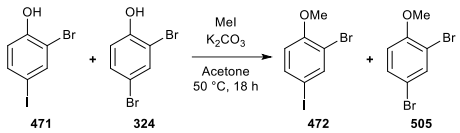


To a solution of 4-iodophenol (**470**) (7.20 g, 32.7 mmol) in MeOH (43.0 mL) at 0 °C was added bromine (1.84 mL, 35.9 mmol) dropwise over 5 minutes. The reaction mixture was stirred for 0.5 hours at 0 °C and then to the reaction mixture was added $Na_2S_2O_3$ (36 mL of a saturated aqueous solution). The organics were extracted with Et_2O (3 x 70 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/CH_2Cl_2, 4:1 to 3:2) gave several products several products that have been summarised below:

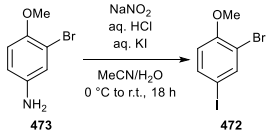
- an inseparable[323] 9:1 respective mixture (determined by ^1H NMR spectroscopy) of 2,6-dibromo-4-iodophenol (**503**) and 2,4,6-tribromophenol (**504**) as a colourless solid (1.30 g, 9% yield of **503**, 1% yield of **504**)
- an inseparable[323] 9:1 respective mixture (determined by ^1H NMR spectroscopy) of 2-bromo-4-iodophenol (**471**) and 2,4-dibromophenol (**324**) (6.60 g, 61% yield of **471** and 8% yield of **324**).

Spectroscopic data obtained for **324**, **471**, **503** and **504** were consistent with literature.[375–378]

472: 2-bromo-4-iodoanisole



To a solution of a 95:5 respective mixture of 2-bromo-4-iodophenol (**471**) and 2,4-dibromophenol (**324**) (100 mg, 0.33 mmol) in acetone (1.00 mL) at room temperature was added iodomethane (82 µL, 1.3 mmol) and K_2CO_3 (114 mg, 0.825 mmol). The reaction mixture was heated at 50 °C for 18 hours and was then allowed to cool to room temperature. The organics were concentrated *in vacuo* and then the organics were dissolved in CH_2Cl_2 (3 mL), filtered, and concentrated *in vacuo* which gave an inseparable[323] 95:5 respective mixture (determined by ^{1}H NMR spectroscopy) of 2-bromo-4-iodoanisole (**472**) and 2,4-dibromoanisole (**505**) (103 mg, >99%).



To a solution of 3-bromo-4-methoxyaniline (**473**) (202 mg, 1.00 mmol) in MeCN (2.75 mL) was added a solution of HCl (0.52 mL of a 12.0 M solution) and H_2O (1.72 mL). The reaction mixture was cooled to 0 °C and a solution of $NaNO_2$ (83 mg, 1.2 mmol) in H_2O (1.72 mL) was added dropwise over 5 minutes. The reaction mixture was stirred for 30 minutes at 0 °C and then a solution of KI (249 mg, 1.50 mmol) in H_2O (1.72 mL) was added* over two minutes. The reaction mixture was allowed to warm to room temperature and was stirred for 17 hours. The reaction mixture was poured onto H_2O (10 mL) and the organics were extracted with CH_2Cl_2 (3 x 10 mL). The organics were combined, dried

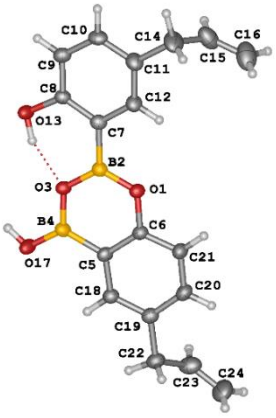
over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by graduated column chromatography (petroleum ether/EtOAc, 49:1 to 19:1) gave 2-bromo-4-iodoanisole (**472**) as a colourless solid (227 mg, 72%).

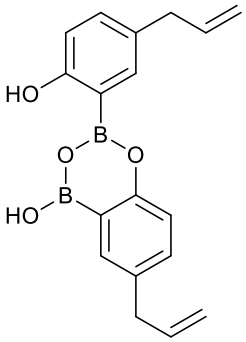
*An exit needle or bubbler should be attached as dinitrogen was evolved upon the addition of KI.

Spectroscopic data obtained for **472** and **505** were consistent with literature.[379,380]

7.9: Crystallographic data

301: 6-allyl-2-(5-allyl-2-hydroxyphenyl)-4H-benzo[e][1,3,2,4]dioxadiborinin-4-ol



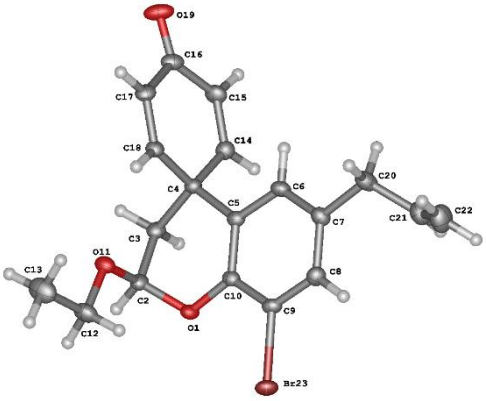


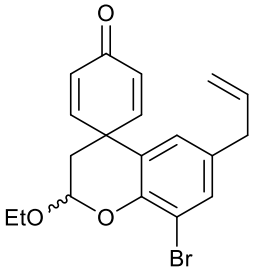
301

Crystal data and structure refinement for 301.

Empirical formula	$C_{18}H_{18}B_2O_4$
Formula weight	319.94
Temperature/K	120(2)
Crystal system	monoclinic
Space group	C2/c
a/Å	31.4184(9)
b/Å	4.96092(16)
c/Å	21.7474(7)
α/°	90
β/°	101.804(3)
γ/°	90
Volume/Å^3	3317.97(19)
Z	8
ρ_{calc}g/cm^3	1.281
μ/mm^{-1}	0.706
F(000)	1344.0
Crystal size/mm^3	0.347 × 0.06 × 0.019
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.308 to 147.492
Index ranges	-38 ≤ h ≤ 38, -6 ≤ k ≤ 6, -24 ≤ l ≤ 26
Reflections collected	19859
Independent reflections	3296 [R_{int} = 0.0353, R_{sigma} = 0.0179]
Data/restraints/parameters	3296/0/233
Goodness-of-fit on F^2	1.151
Final R indexes [I>=2σ (I)]	R_1 = 0.0835, wR_2 = 0.2607
Final R indexes [all data]	R_1 = 0.0875, wR_2 = 0.2630
Largest diff. peak/hole / e Å^{-3}	0.35/-0.38

309: 6-allyl-8-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



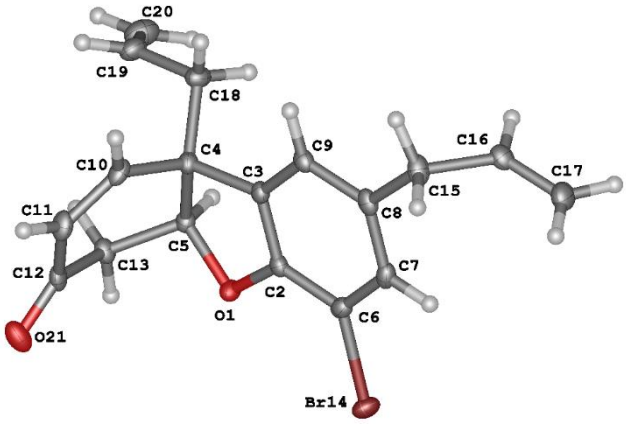


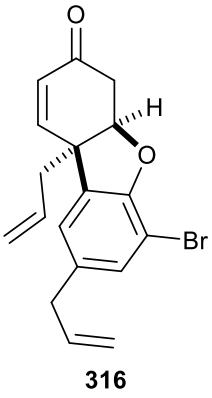
309

Crystal data and structure refinement for 309.

Empirical formula	$C_{19}H_{19}O_3Br$
Formula weight	375.25
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.0674(3)
b/Å	10.0413(5)
c/Å	11.4509(5)
α/°	90.265(4)
β/°	105.787(4)
γ/°	106.880(4)
Volume/Å^3	850.63(7)
Z	2
ρ_{calc}g/cm^3	1.465
μ/mm^{-1}	3.393
F(000)	384.0
Crystal size/mm^3	0.391 × 0.06 × 0.028
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.058 to 149.252
Index ranges	-9 ≤ h ≤ 10, -12 ≤ k ≤ 12, -14 ≤ l ≤ 13
Reflections collected	16326
Independent reflections	3423 [R_{int} = 0.0294, R_{sigma} = 0.0173]
Data/restraints/parameters	3423/0/209
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0234, wR_2 = 0.0612
Final R indexes [all data]	R_1 = 0.0242, wR_2 = 0.0617
Largest diff. peak/hole / e Å^{-3}	0.36/-0.32

316: (±)-(4a*R*,9b*R*)-8,9b-diallyl-6-bromo-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



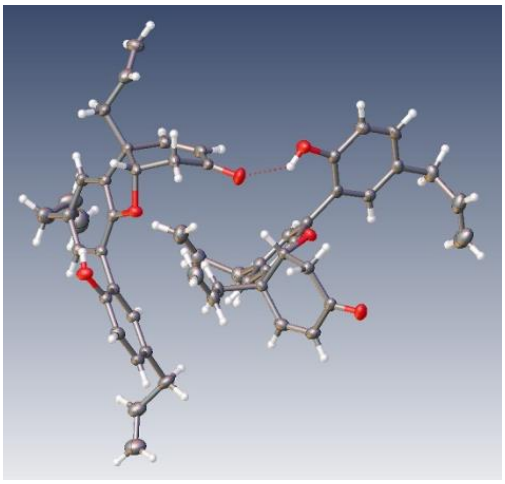


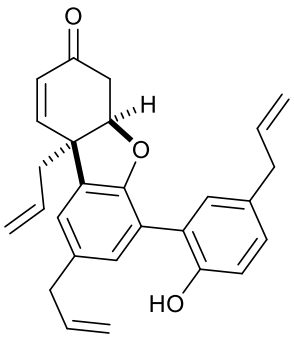
316

Crystal data and structure refinement for 316.

Empirical formula	$C_{18}H_{17}O_2Br$
Formula weight	345.23
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	17.6068(5)
b/Å	7.4294(2)
c/Å	12.3043(4)
α/°	90
β/°	108.692(3)
γ/°	90
Volume/Å^3	1524.62(8)
Z	4
ρ_{calc}g/cm^3	1.504
μ/mm^{-1}	3.683
F(000)	704.0
Crystal size/mm^3	0.601 × 0.543 × 0.233
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.608 to 149.108
Index ranges	-21 ≤ h ≤ 21, -8 ≤ k ≤ 9, -15 ≤ l ≤ 15
Reflections collected	25893
Independent reflections	3083 [R_{int} = 0.0310, R_{sigma} = 0.0122]
Data/restraints/parameters	3083/0/190
Goodness-of-fit on F^2	1.188
Final R indexes [I>=2σ (I)]	R_1 = 0.0291, wR_2 = 0.0750
Final R indexes [all data]	R_1 = 0.0292, wR_2 = 0.0751
Largest diff. peak/hole / e Å^{-3}	0.40/-0.70

simonsol C (55): (±)-(4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



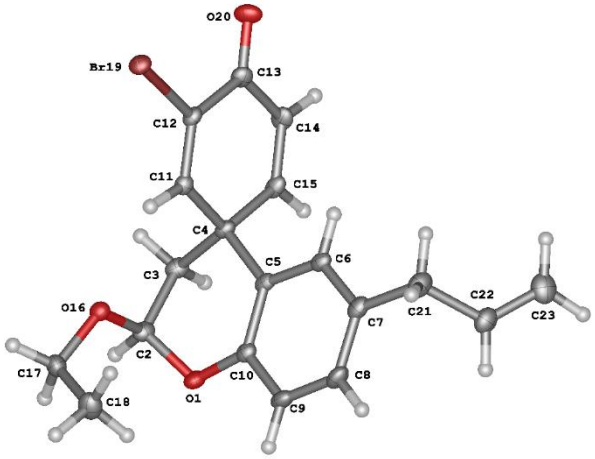


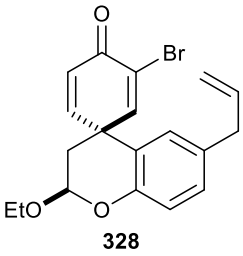
simonsol C (**55**)

Crystal data and structure refinement for simonsol C (55).

Empirical formula	$C_{27}H_{26}O_3$
Formula weight	398.48
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.5253(3)
b/Å	11.2640(3)
c/Å	33.0222(10)
α/°	90
β/°	92.545(2)
γ/°	90
Volume/Å^3	4282.7(2)
Z	8
ρ_{calc}g/cm^3	1.236
μ/mm^{-1}	0.627
F(000)	1696.0
Crystal size/mm^3	0.418 × 0.108 × 0.039
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.358 to 147.942
Index ranges	-13 ≤ h ≤ 14, -13 ≤ k ≤ 13, -39 ≤ l ≤ 40
Reflections collected	32607
Independent reflections	8478 [R_{int} = 0.0603, R_{sigma} = 0.0498]
Data/restraints/parameters	8478/0/543
Goodness-of-fit on F^2	1.085
Final R indexes [I>=2σ (I)]	R_1 = 0.0730, wR_2 = 0.1582
Final R indexes [all data]	R_1 = 0.0939, wR_2 = 0.1713
Largest diff. peak/hole / e Å^{-3}	0.57/-0.30

328: (±)-(2*R*,4*R*)-6-allyl-3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



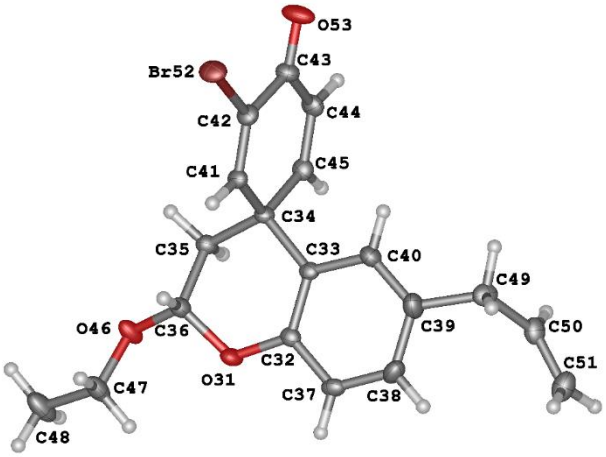


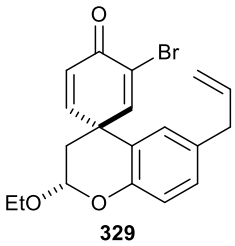
328

Crystal data and structure refinement for 328.

Empirical formula	$C_{19}H_{19}BrO_3$
Formula weight	375.25
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.0694(3)
b/Å	10.5320(3)
c/Å	17.2799(6)
α/°	90
β/°	100.156(3)
γ/°	90
Volume/Å^3	1624.70(9)
Z	4
ρ_{calc}g/cm^3	1.534
μ/mm^{-1}	3.553
F(000)	768.0
Crystal size/mm^3	0.719 × 0.486 × 0.412
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.878 to 148.898
Index ranges	-10 ≤ h ≤ 11, -13 ≤ k ≤ 11, -21 ≤ l ≤ 12
Reflections collected	6146
Independent reflections	3197 [R_{int} = 0.0244, R_{sigma} = 0.0245]
Data/restraints/parameters	3197/0/210
Goodness-of-fit on F^2	1.104
Final R indexes [I>=2σ (I)]	R_1 = 0.0294, wR_2 = 0.0777
Final R indexes [all data]	R_1 = 0.0307, wR_2 = 0.0785
Largest diff. peak/hole / e Å^{-3}	0.42/-0.37

329: (±)-(2*S*,4*R*)-6-allyl-3'-bromo-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



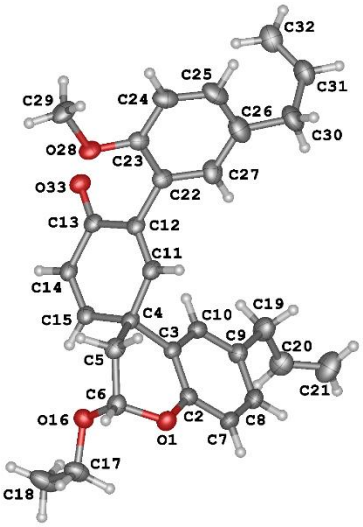


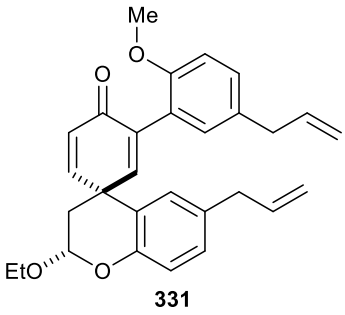
329

Crystal data and structure refinement for 329.

Empirical formula	$C_{19}H_{19}O_3Br$
Formula weight	375.25
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	11.1367(5)
b/Å	12.0896(6)
c/Å	14.1443(7)
α/°	66.361(5)
β/°	82.591(4)
γ/°	75.387(4)
Volume/Å^3	1687.30(16)
Z	4
ρ_{calc}g/cm^3	1.477
μ/mm^{-1}	3.421
F(000)	768.0
Crystal size/mm^3	0.345 × 0.254 × 0.105
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.826 to 147.354
Index ranges	-13 ≤ h ≤ 11, -14 ≤ k ≤ 15, -17 ≤ l ≤ 15
Reflections collected	12597
Independent reflections	6604 [R_{int} = 0.0214, R_{sigma} = 0.0249]
Data/restraints/parameters	6604/0/445
Goodness-of-fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0357, wR_2 = 0.1009
Final R indexes [all data]	R_1 = 0.0383, wR_2 = 0.1022
Largest diff. peak/hole / e Å^{-3}	0.60/-0.52

331: (±)-acetal dienone



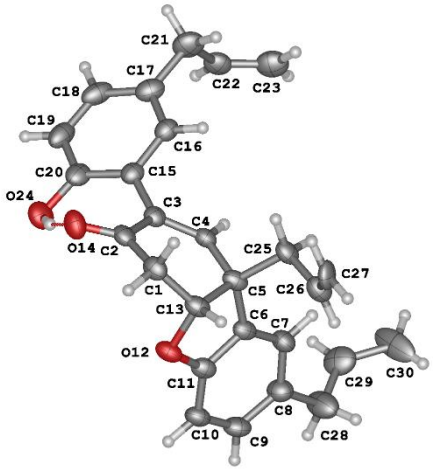


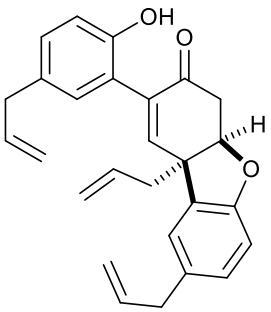
331

Crystal data and structure refinement for 331.

Empirical formula	$C_{29}H_{30}O_4$
Formula weight	442.53
Temperature/K	120(2)
Crystal system	monoclinic
Space group	I2/a
a/Å	19.1851(6)
b/Å	7.8229(2)
c/Å	31.2872(11)
α/°	90
β/°	90.510(3)
γ/°	90
Volume/Å^3	4695.5(3)
Z	8
ρ_{calc}g/cm^3	1.252
μ/mm^{-1}	0.655
F(000)	1888.0
Crystal size/mm^3	0.32 × 0.283 × 0.044
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.65 to 147.386
Index ranges	-21 ≤ h ≤ 23, -6 ≤ k ≤ 9, -37 ≤ l ≤ 38
Reflections collected	9181
Independent reflections	4611 [R_{int} = 0.0230, R_{sigma} = 0.0263]
Data/restraints/parameters	4611/273/387
Goodness-of-fit on F^2	1.040
Final R indexes [I>=2σ (I)]	R_1 = 0.0456, wR_2 = 0.1214
Final R indexes [all data]	R_1 = 0.0497, wR_2 = 0.1261
Largest diff. peak/hole / e Å^{-3}	0.49/-0.26

simonsol F (56): (±)-(4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



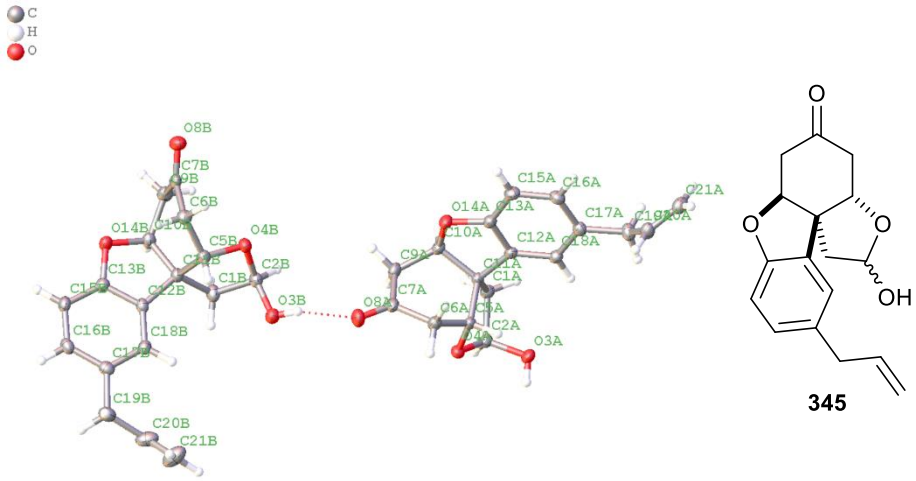


simonsol F (**56**)

Crystal data and structure refinement for simonsol F (56).

Empirical formula	$C_{27}H_{26}O_3$
Formula weight	398.48
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	18.6576(9)
b/Å	11.7041(5)
c/Å	10.0865(3)
α/°	90
β/°	102.695(4)
γ/°	90
Volume/Å^3	2148.74(16)
Z	4
ρ_{calc}g/cm^3	1.232
μ/mm^{-1}	0.625
F(000)	848.0
Crystal size/mm^3	0.402 × 0.05 × 0.026
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	4.854 to 147.642
Index ranges	-22 ≤ h ≤ 23, -14 ≤ k ≤ 14, -12 ≤ l ≤ 7
Reflections collected	8284
Independent reflections	4132 [R_{int} = 0.0423, R_{sigma} = 0.0505]
Data/restraints/parameters	4132/180/331
Goodness-of-fit on F^2	1.133
Final R indexes [I>=2σ (I)]	R_1 = 0.0584, wR_2 = 0.1526
Final R indexes [all data]	R_1 = 0.0934, wR_2 = 0.2029
Largest diff. peak/hole / e Å^{-3}	0.40/-0.35

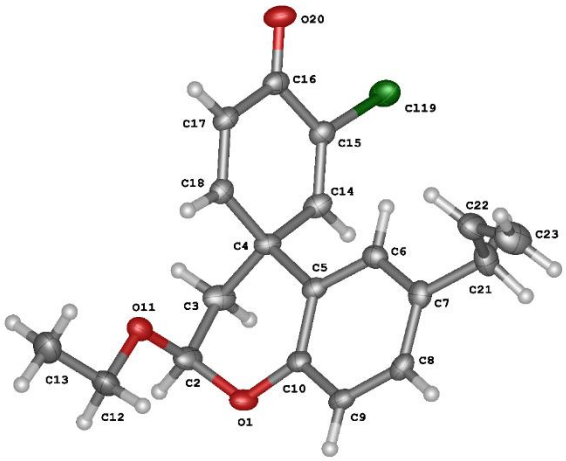
345: (±)-ketone species

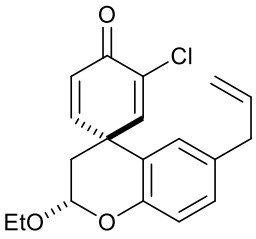


Crystal data and structure refinement for 345.

Empirical formula	$C_{17}H_{18}O_4$
Formula weight	286.31
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.6645(2)
b/Å	14.5472(3)
c/Å	10.2204(2)
α/°	90
β/°	99.289(2)
γ/°	90
Volume/Å^3	1418.06(5)
Z	4
ρ_{calc}g/cm^3	1.341
μ/mm^{-1}	0.777
F(000)	608.0
Crystal size/mm^3	0.546 × 0.153 × 0.019
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.766 to 147.366
Index ranges	-11 ≤ h ≤ 11, -17 ≤ k ≤ 17, -11 ≤ l ≤ 12
Reflections collected	12546
Independent reflections	5305 [R_{int} = 0.0300, R_{sigma} = 0.0296]
Data/restraints/parameters	5305/4/385
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0317, wR_2 = 0.0804
Final R indexes [all data]	R_1 = 0.0326, wR_2 = 0.0816
Largest diff. peak/hole / e Å^{-3}	0.21/-0.20

392: (±)-(2*R*,4*S*)-6-allyl-3'-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one



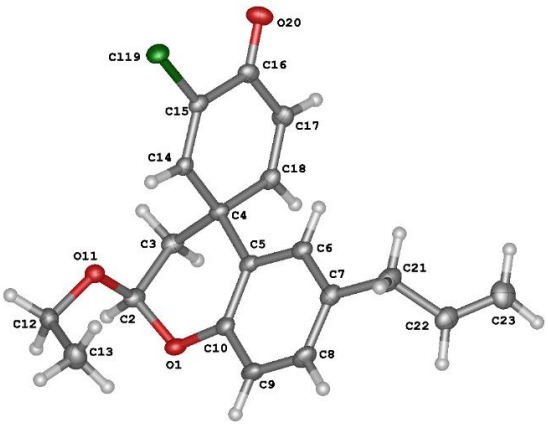


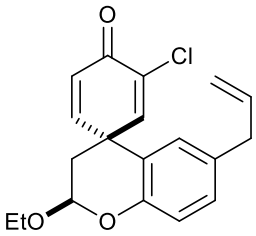
392

Crystal data and structure refinement for 392.

Empirical formula	$C_{19}H_{19}O_3Cl$
Formula weight	330.79
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	10.0625(13)
b/Å	10.1145(13)
c/Å	10.4319(13)
α/°	69.964(11)
β/°	67.073(12)
γ/°	60.707(13)
Volume/Å^3	837.4(2)
Z	2
ρ_{calc}g/cm^3	1.312
μ/mm^{-1}	2.119
F(000)	348.0
Crystal size/mm^3	0.608 × 0.396 × 0.273
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.374 to 149.034
Index ranges	-12 ≤ h ≤ 12, -12 ≤ k ≤ 11, -12 ≤ l ≤ 12
Reflections collected	9820
Independent reflections	3334 [R_{int} = 0.0269, R_{sigma} = 0.0209]
Data/restraints/parameters	3334/0/209
Goodness-of-fit on F^2	1.078
Final R indexes [I>=2σ (I)]	R_1 = 0.0373, wR_2 = 0.0999
Final R indexes [all data]	R_1 = 0.0383, wR_2 = 0.1010
Largest diff. peak/hole / e Å^{-3}	0.22/-0.39

393: (±)-(2*R*,4*R*)-6-allyl-3'-chloro-2-ethoxyspiro[chromane-4,1'-cyclohexane]-2',5'-dien-4'-one





393

Crystal data and structure refinement for 393.

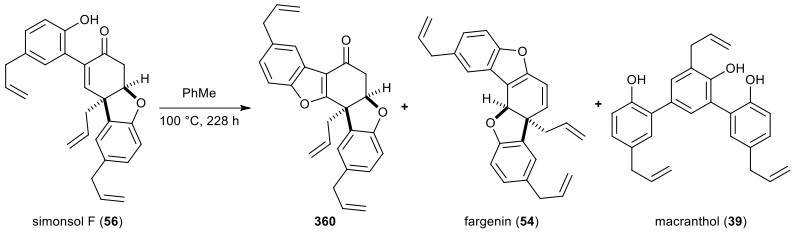
Empirical formula	$C_{19}H_{19}ClO_3$
Formula weight	330.79
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.9945(5)
b/Å	10.5564(4)
c/Å	17.1710(9)
α/°	90
β/°	99.996(5)
γ/°	90
Volume/Å^3	1605.62(13)
Z	4
ρ_{calc}g/cm^3	1.368
μ/mm^{-1}	2.210
F(000)	696.0
Crystal size/mm^3	0.34 × 0.164 × 0.108
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.878 to 147.53
Index ranges	-10 ≤ h ≤ 11, -12 ≤ k ≤ 13, -21 ≤ l ≤ 20
Reflections collected	12941
Independent reflections	3197 [R_{int} = 0.0300, R_{sigma} = 0.0236]
Data/restraints/parameters	3197/0/209
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0300, wR_2 = 0.0771
Final R indexes [all data]	R_1 = 0.0323, wR_2 = 0.0788
Largest diff. peak/hole / e Å^{-3}	0.21/-0.24

7.10: Appendix – New compounds and experimental

Compounds: 360, 384, 386, 501, 438, 496, 459, 504, 464, 465 and 497

360: (±)-benzofuran simonsol F[381]

Linked with Section 7.2.2



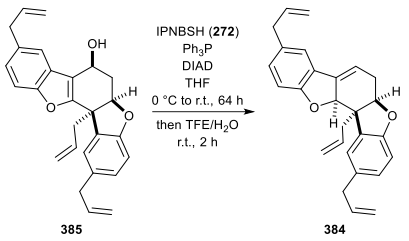
simonsol F (**56**) **360** fargenin (**54**) macranthol (**39**)

Prior to use, glassware was washed with Alconox® detergent (Sigma Aldrich MDL number MFCD00145747), followed by acetone and then dried under a stream of nitrogen.

To an oven-dried RBF containing simonsol F (**56**) (600 mg, 1.50 mmol) was added dry toluene (55.0 mL) *via* a short plug of $NaHCO_3$ under suction filtration. The reaction mixture was sparged with oxygen for 5 minutes and was then heated at 100 °C under an oxygen atmosphere (reflux apparatus was set-up with teflon tape around joints) for 70 hours. The reaction mixture was allowed to cool to room temperature and was then concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone, 4:1) gave fargenin (**54**) (43 mg, 8%) as a colourless oil, benzofuran **360** (247 mg, 41%) as a yellow oil and simonsol F (**56**) (230 mg, 38%) as a pale-yellow oil. Macranthol (**39**) was also detected by TLC but was not isolated in this experiment.

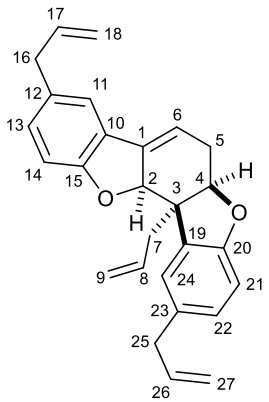
384: (±)-di(hydrodibenzofuran)[381]

Linked with Section 7.3.2



To a solution of allylic alcohol **385** (70 mg, 0.176 mmol), IPNBSH (**272**) (90 mg, 0.352 mmol) and PPh_3 (92 mg, 0.352 mmol) in dry THF (1.80 mL) at 0 °C was added DIAD (70 µL, 0.352 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was then stirred for 64 hours. To the reaction mixture was added a solution of 2,2,2-trifluoroethanol (0.44 mL) and H_2O (0.44 mL) and the reaction mixture was stirred for a further 2 hours at room temperature and then H_2O (7 mL) was added. The organics were extracted with Et_2O (3 x 7 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The organics were dissolved in acetone (5 mL) and to the organics was added Cu(I)Cl (70 mg, 0.701 mmol)[382] and the organics were stirred for 2 minutes and were then concentrated *in vacuo*. To the organics was added Et_2O (5 mL) and then the organics were concentrated *in vacuo*. To the organics was added Et_2O (5 mL) and petroleum ether (5 mL) and then the organics were filtered under gravity through cotton wool. The solids and flask were washed with Et_2O (3 x 5 mL) and the combined filtrates were concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 96:4 (to obtain **384** and **386**) then 7:3 (to recover **385**))

afforded di(hydrodibenzofuran) **384** as a colourless oil (*approximate 90% purity by ^{1}H NMR spectroscopy, 30 mg, 40%), **386** as a colourless oil (2 mg, 3%) and **385** as a colourless oil (8 mg, 11%).



384

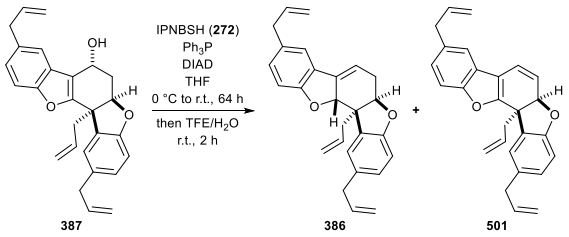
384: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 1.8 Hz, 1H, H-24), 7.23 (d, *J* = 1.9 Hz, 1H, H-11), 7.06 (dd, *J* = 8.2, 1.9 Hz, 1H, H-13), 7.00 (dd, *J* = 8.2, 1.8 Hz, 1H, H-22), 6.92 (d, *J* = 8.2 Hz, 1H, H-14), 6.72 (d, *J* = 8.2 Hz, 1H, H-21), 6.08 – 5.90 (m, 3H, H-6, H-17 and H-26), 5.45 – 5.31 (m, 1H, H-8), 5.14 – 5.03 (m, 5H, H-2, H-18 and H-27), 4.96 – 4.87 (m, 2H, H-9), 4.63 (dd, *J* = 7.7, 7.7 Hz, 1H, H-4), 3.39 (d, *J* = 6.6 Hz, 2H, H-25), 3.36 (d, *J* = 6.8 Hz, 2H, H-16), 3.14 – 3.01 (m, 1H, H-5), 2.82 – 2.73 (m, 1H, H-7), 2.31 – 2.19 (m, 1H, H-5), 2.02 – 1.91 (m, 1H, H-7); **^{13}C NMR*** (101 MHz, $CDCl_3$) δ: 162.6 (Cq), 158.1 (Cq), 140.5 (Cq), 138.3 (CH), 137.9 (CH), 134.0 (CH), 132.8 (Cq), 131.7 (Cq), 130.6 (CH), 129.1 (CH), 124.6 (CH), 124.4 (Cq), 121.2 (CH), 118.7 (CH_2), 115.9 (CH_2), 115.6 (CH_2), 110.5 (CH), 109.4 (CH), 109.0 (CH), 88.5 (CH), 83.5 (CH), 54.5 (Cq), 39.9 (CH_2), 39.8 (CH_2), 37.4 (CH_2), 30.0 (CH_2); **HRMS** (ESI^+): $C_{27}H_{26}O_3$ $[M+H]^+$ calcd. 383.2006, found 383.2003.

*Did not observe one quaternary carbon in $CDCl_3$ due to the purity of the sample.

An interaction through space by NOESY was observed between H-2 and H-7 of **384** (see Figure 34).

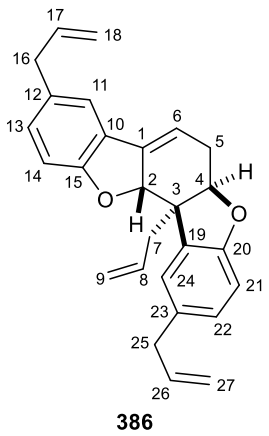
386: (±)-di(hydrodibenzofuran)

501: (±)-benzofuran species



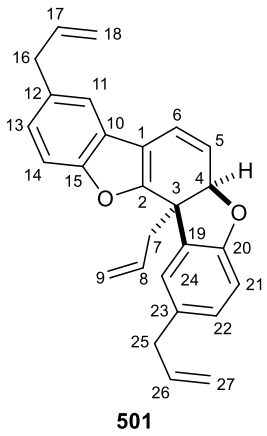
To a solution of allylic alcohol **387** (80 mg, 0.201 mmol), IPNBSH (**272**) (103 mg, 0.402 mmol) and PPh_3 (105 mg, 0.402 mmol) in dry THF (2.0 mL) at 0 °C was added DIAD (80 µL, 0.402 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was then stirred for 64 hours. To the reaction mixture was added a solution of 2,2,2-trifluoroethanol (0.5 mL) and H_2O (0.5 mL) and the reaction mixture was stirred for a further 2 hours at room temperature and then H_2O (8 mL) was added. The organics were extracted with Et_2O (3 x 8 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The organics were dissolved in acetone (5 mL) and to the organics was added Cu(I)Cl (80 mg, 0.808 mmol)[382] and the organics were stirred for 2 minutes and were then concentrated *in vacuo*. To the organics was added Et_2O (5 mL) and then the organics were concentrated *in vacuo*. To the organics was added Et_2O (5 mL) and petroleum ether (5 mL) and then the organics were filtered under gravity through cotton wool. The solids and flask

were washed with Et_2O (3 x 5 mL) and the combined filtrates were concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O, 96:4 (to obtain **386** and **501**) then 7:3 (to recover **387**)) afforded di(hydrodibenzofuran) **386** as a colourless oil (*approximate 90% purity by ^{1}H NMR spectroscopy, 7 mg, 8%), **501** as a colourless oil (13 mg, 17%) and **387** as a colourless oil (52 mg, 65%).



386

386: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 – 6.97 (m, 2H, H-24 and H-11), 6.96 – 6.90 (m, 1H, H-13), 6.85 – 6.77 (m, 1H, H-14), 6.75 – 6.69 (m, 1H, H-22), 6.47 (d, *J* = 8.0 Hz, 1H, H-21), 5.96 – 5.81 (m, 2H, H-6 and H-17), 5.79 – 5.60 (m, 2H, H-8 and H-26), 5.26 – 5.12 (m, 2H, H-9), 5.05 – 4.88 (m, 4H, H-2, H-4 and H-27), 4.86 – 4.65 (m, 2H, H-18), 3.24 (d, *J* = 6.4 Hz, 2H, H-25), 3.19 – 3.03 (m, 2H, H-16), 2.99 – 2.89 (m, 2H, H-5 and H-7), 2.73 (dd, *J* = 14.0, 8.5 Hz, 1H, H-5), 2.16 – 2.08 (m, 1H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 162.0 (Cq), 159.4 (Cq), 140.2 (Cq), 138.3 (CH), 137.9 (CH), 133.4 (CH), 132.3 (Cq), 131.3 (Cq), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.3 (Cq), 126.8 (CH), 124.5 (Cq), 121.2 (CH), 119.5 (CH_2), 115.6 (CH_2), 115.1 (CH_2), 110.0 (CH), 107.7 (CH), 85.9 (CH), 83.5 (CH), 54.8 (Cq), 43.3 (CH_2), 39.7 (CH_2), 39.6 (CH_2), 30.9 (CH_2); **HRMS** (ESI$^+$): $C_{27}H_{26}O_3$ $[M+H]^+$ calcd. 383.2006, found 383.2002.



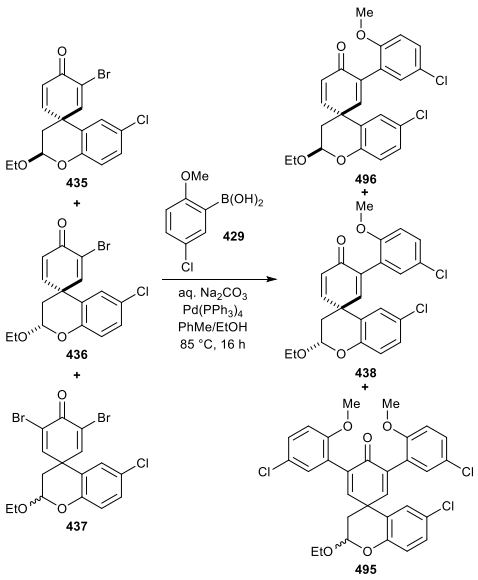
501

501: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 8.4 Hz, 1H, H-14), 7.36 (d, *J* = 1.8 Hz, 1H, H-23), 7.33 (d, *J* = 1.8 Hz, 1H, H-11), 7.07 (dd, *J* = 8.4, 1.8 Hz, 1H, H-13), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1H, H-22), 6.75 (d, *J* = 8.0 Hz, 1H, H-21), 6.74 (d, *J* = 9.6 Hz, 1H, H-6), 5.97 (d, *J* = 9.6 Hz, 1H, H-5), 6.06 – 5.89 (m, 2H, H-17 and H-26), 5.60 – 5.49 (m, 1H, H-8), 5.46 (d, *J* = 4.5 Hz, 1H, H-4), 5.14 – 4.99 (m, 6H, H-9, H-18 and H-27), 3.46 (d, *J* = 6.6 Hz, 2H, H-16), 3.36 (d, *J* = 6.7 Hz, 2H, H-25), 3.08 (dd, *J* = 14.1, 7.0 Hz, 1H, H-7), 2.73 (dd, *J* = 14.1, 7.4 Hz, 1H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 157.0 (Cq), 155.5 (Cq), 154.3 (Cq), 138.1 (2x CH), 135.0 (Cq), 132.8 (Cq), 132.4 (CH), 129.9 (Cq), 128.8 (CH), 125.5 (Cq), 125.1 (CH), 124.7 (CH), 121.9 (CH), 119.5 (CH), 119.4 (CH_2), 118.6 (CH), 115.8 (CH_2), 115.6 (CH_2), 111.4 (CH), 111.2 (Cq), 109.4 (CH), 86.5 (CH), 49.6 (Cq), 43.9 (CH_2), 40.3 (CH_2), 39.8 (CH_2); **HRMS** (ESI^+): $C_{27}H_{24}O_3$ $[M+NH_4]^+$ calcd. 398.2115, found 398.2097; **IR** ν_{max} cm^{-1}: 3076, 3049, 3006, 2976, 2957, 2926, 2907, 2872, 2859, 1639, 1611, 1596, 1487, 1461, 1434, 1269, 1245, 1205, 1186, 1121, 994, 916, 822, 808, 796, 769, 662.

438: Arylated dienone[381]

496: Arylated dienone[381]

Linked with Section 7.5.1

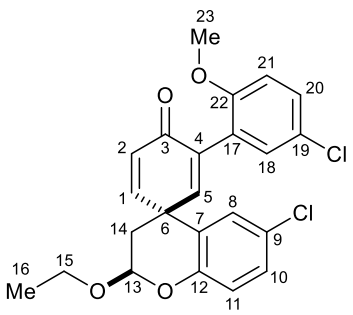


To a solution of an 2:7:1 respective w/w mixture (determined by ^{1}H NMR spectroscopy) of bromo dienones **435**, **436** and **437** (7.79 g, 20.7 mmol) in PhMe (150 mL) and EtOH (67.0 mL) was added Na_2CO_3 (67.0 mL of a 2.0 M aqueous solution) and the biphasic mixture was sparged with argon for 10 minutes. To the biphasic mixture was added 5-chloro-2-methoxyphenyl boronic acid (**429**) (5.19 g, 27.9 mmol) and $Pd(PPh_3)_4$ (478 mg, 0.414 mmol) and the reaction mixture was sparged with argon for a further 5 minutes. The reaction mixture was heated at 85 °C (under reflux apparatus) for 16 hours and was then allowed to cool to room temperature. The organics were diluted with EtOAc (200 mL) and were washed with H_2O (100 mL), then NaOH (150 mL of a 1.0 M aqueous solution), then brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (dry-loaded onto silica) (petroleum ether/Et_2O/CH_2Cl_2, 6:3:1) gave the following product mixtures (as determined by ^{1}H NMR spectroscopy):

- a 73:27 respective mixture of **438** and **495** as a yellow solid (3.00 g, 35% yield* of **438**, 69% yield* of **495**).
- a 58:35:7 respective mixture of **438**, **496** and unknown impurities as an off-white solid (5.14 g, 48% yield* of **438**, >99% yield* of **496**).
- **438** as an off-white solid (1.07 g, 17%*) **m.p.** 181–183 °C.

The following purification was performed to obtain a clean sample of **496**. The 58:35:7 respective mixture of **438**, **496** and unknown impurities (100 mg) was purified by column chromatography (petroleum ether/Et_2O/CH_2Cl_2, 6:3:1) which gave **496** as a colourless solid (23 mg) **m.p.** 81–83 °C.

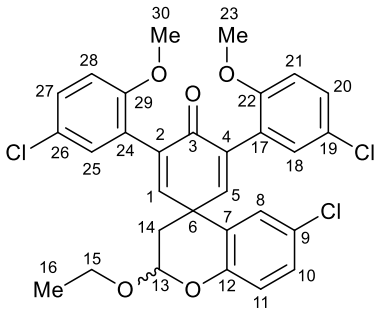
*The percentage yields of **438**, **495** and **496** have taken into consideration the theoretical yields that could be obtained from the respective 2:7:1 ratio mixture (determined by ^{1}H NMR spectroscopy) of **435**, **436** and **437** on a 20.7 mmol scale. Overall, the theoretical yield of **438** was 6.26 g, the theoretical yield of **495** was 1.18 g and the theoretical yield of **496** was 1.79 g.



496

496: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, *J* = 3.0 Hz, 1H, H-5), 7.26 (dd, *J* = 8.7, 2.7 Hz, 1H, H-20), 7.16 (dd, *J* = 8.7, 2.5 Hz, 1H, H-10), 7.12 (d, *J* = 2.7 Hz, 1H, H-18), 7.03 (d, *J* = 2.5 Hz, 1H, H-8), 6.88 (d, *J* = 8.7 Hz, 1H, H-11), 6.83 (d, *J* = 8.7 Hz, 1H, H-21), 6.81 (dd, *J* = 9.9, 3.0 Hz, 1H,

H-1), 6.44 (d, *J* = 9.9 Hz, 1H, H-2), 5.40 (dd, *J* = 3.7, 2.9 Hz, 1H, H-13), 3.90 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 3.77 (s, 3H, H-23), 3.65 (dq, *J* = 9.6, 7.1 Hz, 1H, H-15), 2.32 (dd, *J* = 14.1, 2.9 Hz, 1H, H-14), 2.23 (dd, *J* = 14.1, 3.7 Hz, 1H, H-14), 1.19 (dd, *J* = 7.1, 7.1 Hz, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 183.5 (Cq), 156.2 (Cq), 152.2 (CH), 152.0 (CH), 150.1 (Cq), 134.7 (Cq), 130.5 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 127.2 (Cq), 126.7 (Cq), 125.4 (Cq), 121.9 (Cq), 120.0 (CH), 112.3 (CH), 96.0 (CH), 64.7 (CH_2), 56.2 (CH_3), 41.0 (Cq), 36.6 (CH_2), 15.2 (CH_3); **HRMS** (ESI^+): $C_{23}H_{20}Cl_2O_4$ $[M+Na]^+$ calcd. 453.0631, found 453.0628; **IR** ν_{max} cm^{-1}: 2975, 2934, 2903, 2837, 1665, 1636, 1480, 1441, 1401, 1352, 1291, 1261, 1239, 1223, 1198, 1176, 1116, 1064, 1028, 997, 931, 899, 883, 841, 809, 714, 683, 644.



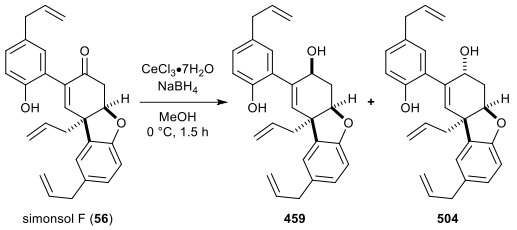
495

495: Analysis of **495** was not performed as the species was not isolated in high purity. From previous experiments, it was found that **495** and its derivatives could be separated from the desired products in the subsequent step. Therefore, no effort was made to obtain a clean sample of **495** for the purpose of this thesis.

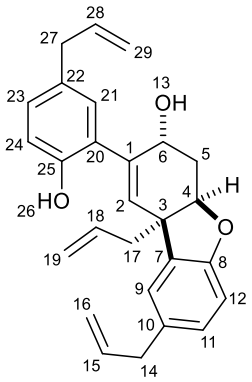
459: (±)-(3*S*,4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-3-ol[381]

504: (±)-(3*R*,4a*R*,9b*R*)-8,9b-diallyl-2-(5-allyl-2-hydroxyphenyl)-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-3-ol[381]

Linked with Section 7.7.2



To a solution of simonsol F (**56**) (40 mg, 0.100 mmol) in MeOH (1.00 mL) at 0 °C was added sequentially $CeCl_3•7H_2O$ (100 mg, 0.267 mmol) and $NaBH_4$ (6 mg, 0.158 mmol). The reaction mixture was stirred for 1.5 hours at 0 °C. To the reaction mixture was added H_2O (2.0 mL) and the organics were extracted with EtOAc (3 x 2.0 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/EtOAc/acetone, 8:1:1) gave allylic alcohol **459** as a colourless oil (28 mg, 70%) and allylic alcohol **504** as a colourless solid (7 mg, 18%) **m.p.** 119–121 °C.



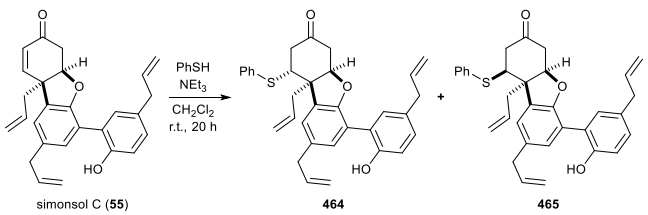
504: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (s, 1H, OH-26), 7.02 (dd, *J* = 8.3, 2.4 Hz, 1H, H-23), 6.99 (dd, *J* = 8.3, 2.2 Hz, 1H, H-11), 6.98 (d, *J* = 2.2 Hz, 1H, H-9), 6.83 (d, *J* = 8.3 Hz, 1H, H-24), 6.82 (d, *J* = 2.4 Hz, 1H, H-21), 6.75 (d, *J* = 8.3 Hz, 1H, H-12), 6.04 – 5.85 (m, 2H, H-15 and H-28), 5.93 (s, 1H, H-2), 5.78 (dddd, *J* = 17.3, 10.1, 7.3 Hz, 1H, H-18), 5.21 – 5.00 (m,

6H, H-16, H-19 and H-29), 4.96 (dd, *J* = 8.1, 5.1 Hz, 1H, H-4), 4.60 (dd, *J* = 4.8 Hz, 1H, H-6), 3.36 (d, *J* = 6.7 Hz, 2H, H-14), 3.29 (d, *J* = 6.7 Hz, 2H, H-27), 2.59 – 2.45 (m, 3H, OH-13 and H-17), 2.28 – 2.14 (m, 2H, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 156.7 (Cq), 152.2 (Cq), 138.1 (Cq), 138.0 (CH), 137.8 (CH), 133.8 (CH), 133.0 (CH), 132.8 (Cq), 132.7 (Cq), 131.9 (Cq), 129.8 (CH), 129.7 (CH), 128.9 (CH), 127.2 (Cq), 123.4 (CH), 119.3 (CH_2), 116.7 (CH), 115.73 (CH_2), 115.71 (CH_2), 110.3 (CH), 82.5 (CH), 66.7 (CH), 49.7 (Cq), 45.0 (CH_2), 39.9 (CH_2), 39.4 (CH_2), 34.6 (CH_2); **HRMS** (ESI^-): $C_{27}H_{28}O_3$ $[M-H]^-$ calcd. 399.1966, found 399.1971; **IR** ν_{max} cm^{-1}: 3346, 3076, 3006, 2975, 2923, 2853, 1740, 1712, 1638, 1609, 1486, 1433, 1277, 1238, 1196, 1174, 1127, 1062, 1029, 993, 913, 819, 792.

464: (1*R*,4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-1-(phenylthio)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one[381]

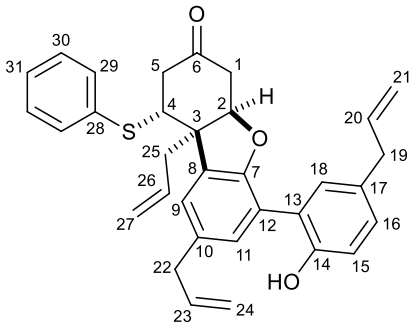
465: (1*S*,4a*R*,9b*R*)-8,9b-diallyl-6-(5-allyl-2-hydroxyphenyl)-1-(phenylthio)-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-3(2H)-one[381]

Linked with Section 7.8.3



To a solution of simonsol C (**55**) (40 mg, 0.10 mmol) in CH_2Cl_2 (0.3 mL) at room temperature was added thiophenol (52 µL, 0.50 mmol) and

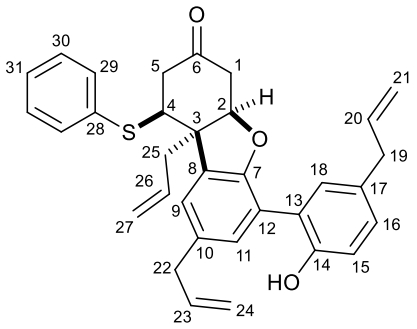
triethylamine (14 µL, 0.10 mmol). The reaction mixture was stirred at room temperature for 2.5 hours and then the organics were concentrated under a stream of nitrogen. Purification by graduated column chromatography (distilled pentane/distilled Et_2O, 4:1 to 3:2) gave thioether **465** as a colourless solid (20 mg, 39%) **m.p.** 110–112 °C and thioether **464** as a colourless solid (26 mg, 51% yield) **m.p.** 105–107 °C.



464

464: ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 – 7.43 (m, 2H, H-29), 7.37 (d, *J* = 1.7 Hz, 1H, H-9), 7.36 – 7.30 (m, 3H, H-30 and H-31), 7.14 (d, *J* = 1.7 Hz, 1H, H-11), 7.12 – 7.07 (m, 2H, H-16 and H-18), 6.97 – 6.90 (m, 1H, H-15), 6.11 – 5.90 (m, 2H, H-20 and H-23), 5.95 (s, 1H, OH), 5.76 (dddd, *J* = 16.5, 10.0, 8.4, 6.3 Hz, 1H, H-26), 5.31 – 5.22 (m, 2H, H-27), 5.19 – 5.04 (m, 5H, H-2, H-21 and H-24), 3.50 (dd, *J* = 13.9, 3.3 Hz, 1H, H-4), 3.47 (d, *J* = 7.0 Hz, 2H, H-19), 3.37 (d, *J* = 6.7 Hz, 2H, H-22), 3.14 (dd, *J* = 14.2, 8.4 Hz, 1H, H-25), 2.99 – 2.91 (m, 2H, H-1 and H-25), 2.64 – 2.58 (m, 2H, H-1 and H-5), 2.34 (dd, *J* = 18.1, 13.9 Hz, 1H, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 206.5 (Cq), 153.7 (Cq), 151.8 (Cq), 137.8 (CH), 137.5 (CH), 134.4 (Cq), 133.9 (Cq), 133.6 (2x CH), 132.9 (Cq), 132.0 (CH), 131.6 (CH), 130.8 (CH), 129.8 (CH), 129.6 (2x CH), 128.9 (Cq), 128.4 (CH), 126.1 (CH), 124.5 (Cq), 121.0 (CH_2), 120.7 (Cq), 118.1 (CH), 116.2 (CH_2), 115.8 (CH_2), 85.7 (CH),

51.1 (Cq), 50.7 (CH), 44.0 (CH_2), 41.7 (CH_2), 41.5 (CH_2), 39.9 (CH_2), 39.6 (CH_2); **HRMS** (ESI^+): $C_{33}H_{32}O_3S$ $[M+H]^+$ calcd. 509.2145, found 509.2143; **IR** ν_{max} cm^{-1}: 3422, 3075, 3060, 3003, 2975, 2956, 2922, 2853, 1721, 1638, 1582, 1498, 1471, 1438, 1416, 1341, 1287, 1215, 1180, 1024, 995, 972, 915, 824, 810, 747, 692.

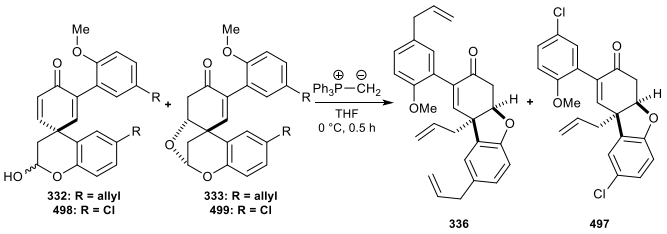


465

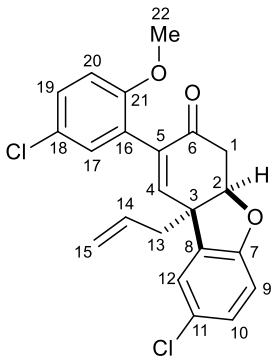
465: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.46 – 7.37 (m, 2H, ArH, H-29), 7.38 – 7.28 (m, 3H, H-30 and H-31), 7.13 – 7.04 (m, 4H, H-9, H-11, H-16 and H-18), 6.96 – 6.92 (m, 1H, H-15), 6.04 (s, 1H, OH), 6.03 – 5.89 (m, 2H, H-20 and H-23), 5.65 (dddd, *J* = 16.9, 10.1, 8.8, 5.5 Hz, 1H, H-26), 5.26 – 5.16 (m, 2H, H-27), 5.14 – 5.02 (m, 5H, H-2, H-21 and H-24), 3.78 (dd, *J* = 4.6, 4.0 Hz, 1H, H-4), 3.40 (d, *J* = 6.7 Hz, 2H, H-22), 3.37 (d, *J* = 6.8 Hz, 2H, H-19), 3.24 (dd, *J* = 17.5, 4.9 Hz, 1H, H-1), 2.97 (dd, *J* = 14.1, 5.6 Hz, 1H, H-25), 2.87 (dd, *J* = 17.5, 3.0 Hz, 1H, H-1), 2.79 (dd, *J* = 14.1, 8.8 Hz, 1H, H-25), 2.51 (dd, *J* = 18.1, 4.6 Hz, 1H, H-5), 2.39 (dd, *J* = 18.1, 4.0 Hz, 1H, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 206.0 (Cq), 153.3 (Cq), 151.9 (Cq), 137.8 (CH), 137.5 (CH), 134.7 (Cq), 133.7 (2 x CH), 133.3 (Cq), 132.89 (CH), 132.86 (Cq), 131.5 (CH), 131.4 (Cq), 130.7 (CH), 129.9 (CH), 129.6 (2 x CH), 128.6 (CH), 124.4 (Cq), 123.7 (CH), 120.9 (Cq), 120.5 (CH_2), 118.3 (CH), 116.2 (CH_2), 115.8 (CH_2), 85.4 (CH), 52.4 (CH), 51.7 (Cq), 42.5 (CH_2), 42.3 (CH_2), 41.8 (CH_2), 39.8 (CH_2), 39.6 (CH_2); **HRMS** (ESI^+): $C_{33}H_{32}O_3S$ $[M+H]^+$

calcd. 509.2145, found 509.2144; **IR** ν_{max} cm^{-1}: 3408, 3075, 3061, 3003, 2975, 2954, 2923, 2853, 1719, 1638, 1609, 1582, 1497, 1472, 1437, 1417, 1362, 1340, 1245, 1215, 1177, 992, 914, 823, 791, 748, 737, 692.

497: (±)-(4a*R*,9b*R*)-9b-allyl-8-chloro-2-(5-chloro-2-methoxyphenyl)-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one



For a general experimental, see the experimental described for **336** in section 7.1.3. Separation of **336** and **497** required exhaustive column chromatography as the R_f values (petroleum ether/Et_2O, 3:2) were 0.35 and 0.32 respectively. The optimised conditions (petroleum ether/Et_2O, 9:1 to 72:28) gave **336**, a mixture of "**336** and **497**" and **497**.



497

497: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (dd, *J* = 8.7, 2.7 Hz, 1H, H-10 or H-19), 7.18 – 7.14 (m, 2H, H-12 or H-17 and H-10 or H-19), 6.92 (d, *J* = 2.7 Hz, 1H, H-12 or H-17), 6.78 (d, *J* = 8.7 Hz, 1H, H-9 or H-20), 6.78 (d, *J* = 9.1 Hz, 1H, H-9 or H-20), 6.43 (d, *J* = 1.7 Hz, 1H, H-4), 5.85 (dddd, *J* = 17.0, 10.4, 8.0, 6.7 Hz, 1H, H-14), 5.29 – 5.21 (m, 2H, H-15),

4.93 (ddd, *J* = 4.2, 3.5, 1.7 Hz, 1H, H-2), 3.69 (s, 3H, H-22), 3.10 (dd, *J* = 16.6, 3.5 Hz, 1H, H-1), 2.95 (dd, *J* = 16.6, 4.2 Hz, 1H, H-1), 2.81 (dddd, *J* = 14.2, 6.7, 1.3, 1.3 Hz, 1H, H-13), 2.67 (dd, *J* = 14.2, 8.0 Hz, 1H, H-13).

No other data of **497** was acquired for the purpose of this thesis.

8: References

1 *https://www.theguardian.com/lifeandstyle/gardening-blog/2015/mar/18/illiciums-flowers-from-dinosaur-times (accessed 10/01/2021). No changes were made to the original image authored by Robbie Blackhall-Miles. This work was granted permission for use by the author (email correspondence 11/01/2021).*

2 *https://commons.wikimedia.org/wiki/File:Blausen_0657_MultipolarNeuron.png (accessed 01/07/2019). No changes were made to the original image authored by BruceBlaus. This work is free and may be used by anyone for any purpose (This file is licensed under the Creative Commons Attribution 3.0 Unported license).*

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382 *Cu(I)Cl and triphenylphosphine readily react to form a highly insoluble complex that can be removed by filtration and furthermore will not pass through a silica column when diethyl ether and petroleum ether are used as the eluent.*