University of Nottingham
UK | CHINA | MALAYSIA

Studies Towards the Total Synthesis of *Illicium* Derived Neolignans

Salvatore Giangone, BSc

Thesis submitted to The University of Nottingham for the degree of Master of Research.

September 2022

Supervisor: Prof. Ross M. Denton

Acknowledgements

I would like to thank the University of Nottingham for allowing me to carry out my research in their facilities. I would like to extend a special thank you to Professor Ross Denton for giving me the opportunity to carry out this challenging but exciting project and for his continuous assistance and support throughout my MRes degree. I am grateful to the Denton group members, past and present, for their knowledge and helpful inputs towards my research. I would like to thank the NMR spectroscopy staff and Dr Stephen Argent for their help and support.

Abstract

Illicium derived neolignans are a class of structurally diverse secondary metabolites which arise in nature from the chemical manipulation of chavicol units. There is a growing interest in Illicium derived neolignans as they have been shown to provide neuroprotective effects. Recent studies have shown that neolignans can facilitate the growth and protection of developing neurons.

This thesis presents a bioinspired approach towards the challenging synthesis of simonsol A: a sesqui-neolignan with a characteristic [3.3.1] ring system. The key Claisen rearrangement in the synthesis of simonsol A has been calculated to be high and at 45.7 kcal mol. Untested catalytic methods were attempted to overcome this barrier but were unsuccessful. A Lewis-acid catalysed approach to overcome this barrier was also unsuccessful as an outcompeting side-reaction led to the isolation of an unwanted species. This species was fully characterised by IR and NMR spectroscopy, and X-ray crystallography. The rotational barrier for this unwanted species was calculated and reasoning for its diastereotopicity is provided. The synthetic route towards simonsol A presented herein was proved to be defunct on the basis of a competitive allyl group migration.

Studies towards the synthesis of simonol B are presented. A model system containing a dihydroxyl-cyclohexylbenzofuran core has been synthesised, providing proof of concept work which shows that simonol B can be accessed *via* simonsol F. We have determined that the Mukaiyama hydration is not compatible with substrates containing free hydroxyl or aryl-allyl groups. An NOE interaction observed for the model system between the two alcoholic protons suggested that the relative stereochemistry between the adjacent hydroxyl groups was *syn*. This was confirmed by a comparison between experimental ^{13}C NMR spectroscopic values and computationally predicted values for the *anti* and *syn* diastereomers of the model system.

Abbreviations

Standard abbreviations and acronyms, as defined by The Journal of Organic Chemistry, are used throughout this thesis. All others are listed below.

6-APA	(+)-6-aminopenicillanic acid
AChE	acetylcholinesterase
BChE	butyrylcholinesterase
$BTMABr_3$	benzyltrimethylammonium tribromide
CSA	camphorsulfonic acid
DAHP	3-deoxy-*D*-arabino-heptulosone-7-phopshate
DHP	3-dehydroquinate F
DIPEA	*N*,*N*-diisopropylethylamine
dpm	dipivaloylmethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
ECD	electronic circular dichroism
EPSP	5-enolpyruvylshikimate-3-phosphate
KHMDS	potassium bis(trimethylsilyl)amide
LC-MS	liquid chromatography mass spectroscopy
$NADP^+$	nicotinamide adenine dinucleotide phosphate
QM	quantum mechanics
RMSE	root-mean-square deviation
S_EAr	electrophilic aromatic substitution
TAL	tyrosine ammonia lyase
TPPTS	3,3',3''-phosphanetriyltris(benzenesulfonic acid) trisodium

Contents

1.0 Introduction 1
1.1 Natural Products 1
1.2 Phenolics 2
1.3 Lignans 2
1.4 Chavicol and the Biosynthesis of Lignans and Neolignans *via* the Shikimate Pathway 3
1.5 Isolation and Neurotrophic Activity of Sesqui-Neolignans from the Genus *Illicium* 6
1.6 Previous Syntheses of Sesqui Neolignans from the Genus *Illicium* 10
1.6.1 Dunnianol 10
1.6.2 Simonsol F 12
1.7 Simonsol A 15
1.7.1 Isolation and Biological Activity of Simonsol A 15
1.7.2 Biosynthesis of Simonsol A Proposed by Kong *et al.* 16
1.7.3 Biosynthesis of Simonsol A Proposed by Denton *et al.* 17
2.0 Results and Discussion: Studies Towards the Total Synthesis of Simonsol A 18
2.1 A Brief Summary of Previous Work Towards the Total Synthesis of Simonsol A 18
2.2 Synthetic Route Development 18
2.3 Forward Synthesis 20
2.3.1 Bromination 20
2.3.2 Suzuki Cross-Coupling 21
2.3.3 Allylation 23
2.3.4 Claisen Rearrangement 23
3.0 Results and Discussion: Creation of a Dihydroxyl-Cyclohexylbenzofuran Core Containing Model System 28
3.1 Synthetic Route Development 28
3.2 Forward Synthesis 29
4.0 Conclusion and Future Work 38
5.0 Supporting Information 40
5.1 General Details 40
5.2 Experimental Procedures 42
5.3 Computational Data 60
5.4 Crystallographic Data 70
6.0 References 71

1.0 Introduction

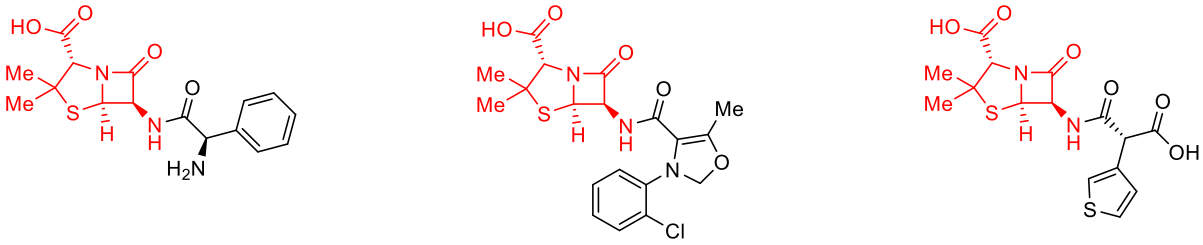
1.1 Natural Products

Natural products are defined as chemical compounds or substances synthesised by a biological source; they can be subdivided into two main categories: primary and secondary metabolites.[1] Primary metabolites constitute the molecular building blocks of life and are components of basic metabolic pathways which are essential for life. These include amino acids, fatty acids, carbohydrates, and nucleobases. Secondary metabolites are not directly involved in the essential functions of organisms. Instead, they play a role in the evolutionary behaviour of an organism within its ecological setting, promoting its competitive survivability and fecundity. Plant secondary metabolites can be classified within the subcategories of phenolics, alkaloids, terpenoids and sulfur-containing compounds.[2]

These secondary plant metabolites are one of the primary focuses of medicinal chemistry; their extractions and isolations provide a way of assessing the therapeutic potential of naturally derived drugs. One of the most commercially successful naturally derived drugs is morphine, an alkaloid which belongs to the family of opiates. First extracted by German pharmacist Friedrich Sertürner in 1804 from the opium poppy plant *Papaver somniferum*, morphine has been used as a pain medication and as a treatment for opioid addiction since its commercialisation in 1817.[3,4]

While natural products have been used widely in medicine for millennia, the past century has seen a decline in their implementation in drug discovery and development efforts in favour of semi-synthetic drug alternatives. [5] Antibiotic penicillins (derived from *Penicillium chrysogenum*) and paclitaxel (an anticancer drug derived from the Pacific yew tree, *Taxus brevifolia*) are examples of semi-synthetic drugs.[6,7] Ampicillin (**1**), cloxacillin (**2**) and ticarcillin (**3**) are examples of antibiotic penicillins which have been synthesised by adding various side-chains to the precursor (+)-6-aminopenicillanic acid (6-APA) which is itself synthesised from natural Penicillin G (Figure 1).[8]

Advancements in high throughput screening technologies and the facile synthesis of small molecular fragments have allowed for the generation of large combinatorial libraries and the rapid identification of synthetic lead compounds. In turn, the trend in the number of drug approvals has shown a gradual increase over the past two decades.[9] This had led to



Ampicillin (**1**) Cloxacillin (**2**) Ticarcillin (**3**)

Figure 1. Semi-synthetic medicines ampicillin (**1**), cloxacillin (**2**) and ticarcillin (**3**) are derived from the common precursor 6-APA (depicted in red).

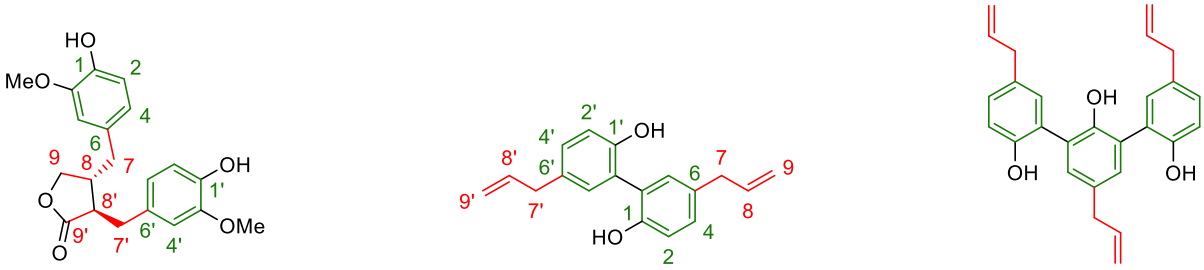
pharmaceutical companies terminating or substantially reducing their natural product research.[10] However, a resurgence in natural product-based drug discovery has recently been promoted thanks to advancements in bioinformatics, proteomics, genomics, and analytical technologies.[11] This thesis concentrates on the synthesis of natural products derived from the genus *Illicium*.

1.2 Phenolics

Phenolic compounds constitute the most abundant group of plant secondary metabolites. They are characterised by the presence of one or more phenol groups and range from simple structures containing one aromatic ring bearing one or more hydroxyl groups to more complex oligomeric substances. They are ubiquitous in plants where they contribute significantly to the colour, taste and flavour of many herbs, foods, and drinks.[12] Phenolics are of pharmacological interest as the phenolic hydroxyl group has a strong affinity for proteins and enzymes.[13] Phenolics have shown to exhibit antibacterial, anticancer and cardioprotective effects.[14] Additionally, many phenolics have proved to promote healthy immune system functions and have anti-inflammatory effects as well as antihepatotoxic properties.[12] Many phenolic molecules are also effective antioxidants and free radical scavengers.[14] Phenolics can be subdivided according to their structure into classes. These classes include but are not limited to simple phenolics, tannins, coumarins, flavonoids and lignans.[15]

1.3 Lignans

Lignans are a class of phenolic secondary metabolites which are distributed widely in the plant kingdom. Although many genera have been found to contain lignans, including the *Piper* genus, the *Magnolia* genus and the *Sassafras* genus, this thesis will concentrate on lignans derived from the genus *Illicium*. *Illicium* is a genus of flowering plants which are mostly



Matairesinol (**4**) Magnolol (**5**) Dunnianol (**6**)

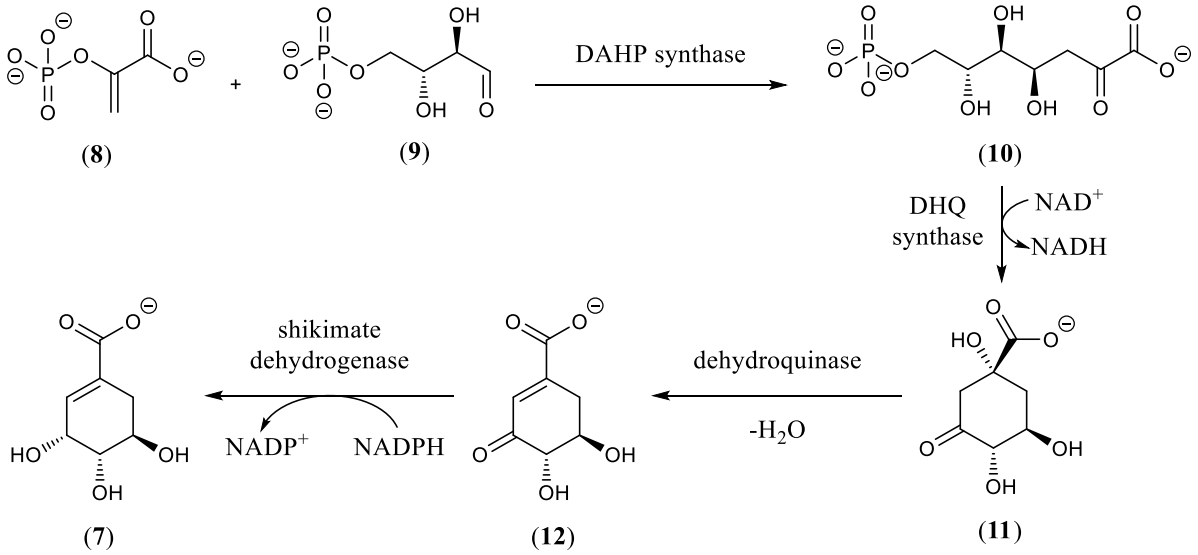
Figure 2. Structures of matairesinol (**4**) (a lignan), magnolol (**5**) (a neolignan) and dunnianol (**6**) (a sesqui-neolignan).

prevalent across the Asian continent, specifically in south-eastern China and northern Myanmar, but have also been found to grow in several parts of North America, including the south-eastern United States, Mexico, and the Caribbean.[16] There have been numerous accounts of plants from the genus *Illicium* being used in traditional medicines to treat vomiting, stomach aches, insomnia, skin inflammation and rheumatic pain.[17,18] The medicinal properties of these plants can be attributed to the presence of phenylpropanoid units (C_6C_3) known as lignans and neolignans. Structural differences in the position of the oligomerisation within the phenylpropanoid backbones serve to differentiate lignans and neolignans. Lignans are defined as two C_6C_3 units connected in an 8, 8’ fashion (Figure 2).[19] When two or more C_6C_3 units are connected in anything but an 8, 8’ fashion, the term neolignan is given. Sesqui-neolignans are a subclass of neolignans referring to triaryl lignans comprised of three C_6C_3 units.

1.4 Chavicol and the Biosynthesis of Lignans and Neolignans *via* the Shikimate Pathway

4-Allylphenol, commonly referred to as chavicol, is regarded as the starting material in the biosynthetic pathways of lignans and neolignans. It has been isolated from several plant sources from which lignans and neolignans are biosynthesised.[20,21] The broad library of structurally diverse neolignans arises from the oxidative phenolic coupling of chavicol units. Intermediates can undergo oxa-1,4-additions, oxidations, and dehydration reactions, further diversifying the library of neolignans. Chavicol is biosynthesised *via* the shikimate pathway.

Shikimic acid is a naturally occurring compound first isolated in Japan in 1885 from *Illicium religiosum*. It is a key intermediate in the biosynthesis of lignans as well as aromatic amino acids and alkaloids. [22, 23] The shikimate pathway is present in bacteria, plants, and fungi but not in mammals. This has led to the development of novel antimicrobial agents, anti-parasitic

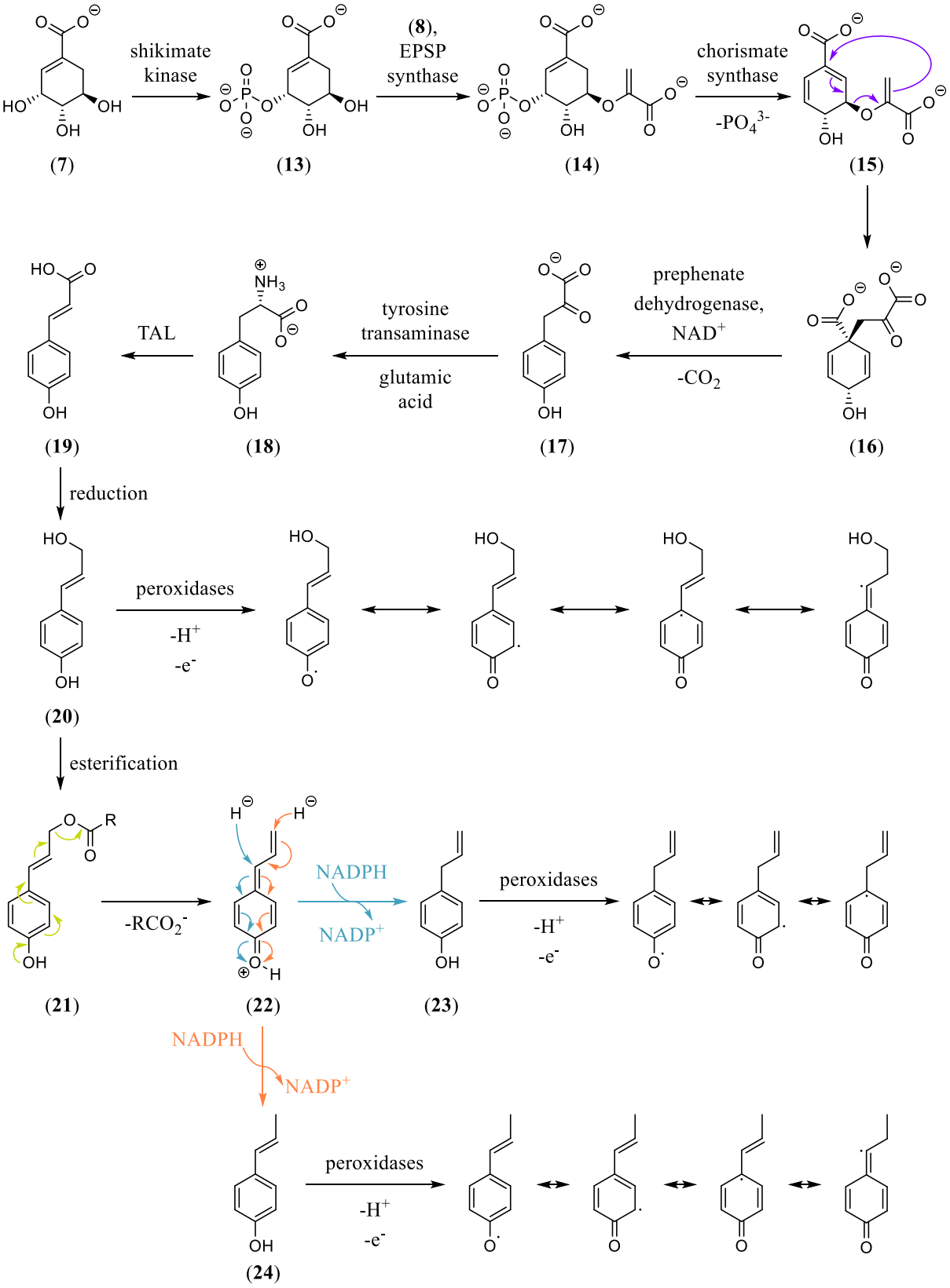


Scheme 1. Biosynthesis of shikimate.

agents, and herbicides which inhibit the shikimate pathway without directly affecting humans.[24] Shikimic acid is often used as a starting material for the industrial synthesis of the antiviral medication Oseltamivir phosphate (commercially sold as Tamiflu) as a treatment of influenza and can be prepared in 20% yield over nine synthesis steps.[25]

The biosynthesis of shikimate (**7**) (deprotonated shikimic acid) takes place over four steps (Scheme 1). Phosphoenolpyruvate (**8**) and D-*erythrose*-4-phosphate (**9**) condense in a reaction catalysed by the enzyme DAHP synthase to form 3-deoxy-D-arabino-heptulosone-7-phopshate (**10**) (DAHP). Subsequent cyclisation and dephosphorylation of DAHP, catalysed by DHP synthase, generates 3-dehydroquinate (**11**) (DHP), followed by dehydration, again catalysed by DHP synthase, to give 3-dehydroshikimate (**12**). Finally, reduction of the ketone by shikimate dehydrogenase produces shikimate (**7**).

The shikimate pathway is a seven-step metabolic route which converts shikimate into the amino acid *L*-tyrosine (Scheme 2). Shikimate undergoes a shikimate kinase-mediated phosphorylation into (**13**), which is coupled with phosphoenolpyruvate (**8**), in a reaction catalysed by 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase to give EPSP (**14**). A dephosphorylation reaction catalysed by chorismate synthase subsequently converts EPSP to chorismate (**15**). Chorismate undergoes an Claisen rearrangement catalysed by chorismate mutase to afford prephenate (**16**). Prephenate is oxidatively decarboxylated, with retention of the hydroxyl group, with prephenate dehydrogenase and NAD^+, to give *para*-hydroxyphenylpyruvate (**17**), which is transaminated using tyrosine transaminase and glutamic acid (as the nitrogen source) to give *L*-tyrosine (**18**).



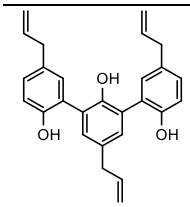
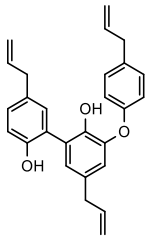
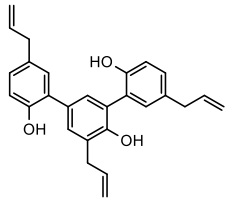
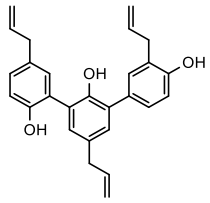
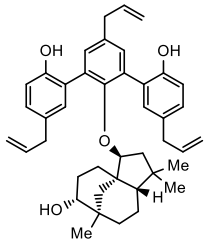
Scheme 2. Proposed biosynthesis of *para*-coumaryl alcohol (**20**), chavicol (**23**) and *para*-anol (**24**) *via* the shikimic acid pathway. Single electron oxidation of (**20**), (**23**) and (**24**) provide the oxidative coupling partners for the synthesis of lignans.

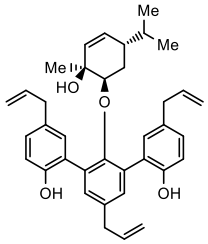
Deamination of L-tyrosine, catalysed by the enzyme tyrosine ammonia lyase (TAL), gives *para*-coumaric acid (**19**) and subsequent reduction affords *para*-coumaryl alcohol (**20**), which is suspected to be a key building block in the biosyntheses of lignans and neolignans.[26] *para*-Coumaryl alcohol can undergo esterification to form *para*-coumaryl ester (**21**). NAD(P)H catalysed decomposition of *para*-coumaryl ester *via* reduction at the trisubstituted alkene and at the terminal alkene yields chavicol (**23**) and *para*-anol (**24**), respectively. One electron oxidation and deprotonation of (**20**) or (**23**) or (**24**) produces a variety of oxidative phenolic coupling partners which in turn give rise to a range of structurally diverse lignans and neolignans (see Scheme 2).

1.5 Isolation and Neurotrophic Activity of Sesqui-Neolignans from the Genus *Illicium*

Recently, the growing potential of neolignan natural products to slow the progression of neurodegenerative diseases has been investigated.[27] Neolignans have been found to inhibit acetylcholinesterase (AChE) by the promotion of neurite outgrowth or by other pathways that result in neuroprotective effects. AChE is an enzyme that catalyses the breakdown of acetylcholine and other chloline esters which function as neurotransmitters. The primary function of AChE in the brain is to terminate neuronal transmissions and act as a signal between synapses, allowing activated cholinergic neurons to return to their resting state after activation.[28] Overly reactive AChE results in poor cholinergic signalling leading to neuron degradation. Whilst the irreversible inhibition of AChE can lead to respiratory failure, paralysis and death, reversible AChE inhibitors modulate the reactivity of AChE. By lowering the reactivity of AChE, in instances when it is overly reactive, cholinergic signalling can be increased, thus preventing further neuron degradation. Although not proven, it is believed that the degradation of neurons occurs *via* reactive oxygen species such as nitric oxide ($NO^{\bullet}$).[29] Such species have been identified in specific brain areas that have undergone neurodegeneration in patients with neurodegenerative disorders.

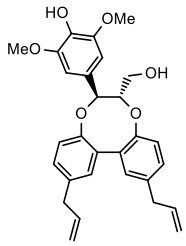
The sesqui-neolignans isolated from the genus *Illicium* that have been isolated to date are depicted in Table 1. Details regarding their isolation, neurotrophic activity and their most recent synthesis have also been provided.

 Dunnianol (**6**)	Isolation:	*Illicium dunnianum* in 1991.[30]
	Activity:	No anti-AChE activity <100 μM.[31]
	Synthesis:	Denton *et al*. 2010.[32]
 Isodunnianol (**25**)	Isolation:	*Illicium dunnianum* in 1991.[30]
	Activity:	Anti-AChE activity with an IC_{50} of 13.0 μM.[31] Promotion of neurite outgrowth of cultured rat cortical neurons between 0.1-10 μM.[27]
	Synthesis:	None reported.
 Macranthol (**26**)	Isolation:	*Illicium macranthum* in 1989.[33]
	Activity:	Neuroprotective activity of rat foetus cortical neurons between 5-10 μM.[34] No effect on the morphology of rat cortical neurons cultured in Neurobasal medium supplemented with B-27 at 10 μM.[34] No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1-10 μM.[27]
	Synthesis:	Denton *et al*. 2016.[35]
 Simonsinol (**27**)	Isolation:	*Illicium simonsii* in 1994.[36]
	Activity:	Anti-inflammatory response in LPS-stimulated RAW 264.7 cells.[37] 53% Increase of axon growth in primary mouse cortical neurons (versus DMSO control).[38]
	Synthesis:	None reported.
 Clovanedunnianol (**28**)	Isolation:	*Illicium simonsii* in 2013.[39]
	Activity:	Anti-AChE activity IC_{50} value of 4.58 μM.[39]
	Synthesis:	Denton *et al*. unpublished work.[40]



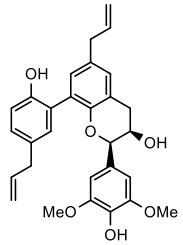
p-Menthadunnianol (**29**)

Isolation: *Illicium simonsii* in 2013.[39]
Activity: Anti-AChE activity IC50 value of 6.55 μM.[39]
Synthesis: None reported.



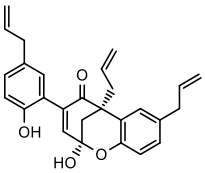
Difengpienol A (**30**)

Isolation: *Illicium difengpi* in 2018.[41]
Activity: NO• inhibition in RAW 264.7 cells with an IC_{50} of 16.9.[41]
Synthesis: None reported.



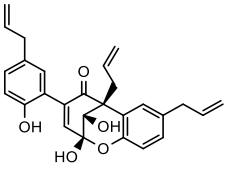
Difengpienol B (**31**)

Isolation: *Illicium difengpi* in 2018.[41]
Activity: NO• inhibition in RAW 264.7 cells with an IC_{50} of 23.8.[41]
Synthesis: None reported.



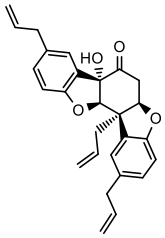
Simonsol A (**32**)
Simonol A (**32**)

Isolation: Isolated twice in 2013 from *Illicium simonsii* and given two different names.[39,42]
Stereochemistry depicted as (*R*,*R*) however this is of debate (see Section 1.7.1).
Activity: No anti-AChE activity <100 μM.[39]
Synthesis: None reported.



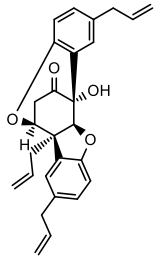
Simonsol B (**33**)

Isolation: *Illicium simonsii* in 2013.[39]
Activity: No anti-AChE activity <100 μM.[39]
Synthesis: None reported.



Fargenone A (**34**)

Isolation: *Illicium fargesii* in 2007.[27]
Activity: No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1-10 μM.[27]
Synthesis: Denton *et al.* unpublished work.[38]

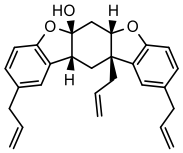


Fargenone B (**35**)

Isolation: *Illicium fargesii* in 2007.[27]

Activity: No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1-10 μM.[27]

Synthesis: None reported.

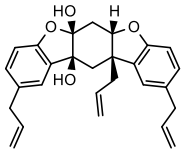


Simonsin A (**36**)

Isolation: *Illicium simonsii* in 2013.[39]

Activity: No anti-AChE activity <100 μM.[39]

Synthesis: None reported.

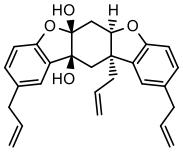


Simonsin B[a] (**37**)

Isolation: *Illicium simonsii* in 2013.[39]

Activity: No anti-AChE activity <100 μM.[39]

Synthesis: None reported.

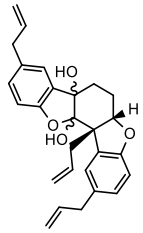


Simonol B[a] (**38**)

Isolation: *Illicium simonsii* in 2013.[42]

Activity: None reported.

Synthesis: None reported.



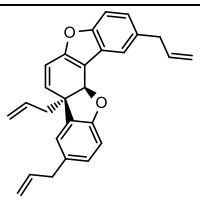
Simonin A[a] (**39**)

Isolation: *Illicium simonsii* in 2010.[43]

Stereochemistry not assigned (as displayed).

Activity: None reported.

Synthesis: None reported.

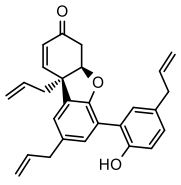


Fargenin (**40**)

Isolation: *Illicium fargesii* in 2007.[27]

Activity: No promotion of neurite outgrowth of cultured rat cortical neurons between 0.1-10 μM.[27]

Synthesis: Denton *et al.* unpublished work.[38]



Simonsol C (**41**)

Isolation: *Illicium simonsii* in 2013.[39]

Activity: No anti-AChE activity <100 μM.[39]

64% Increase of axon growth in primary mouse cortical neurons (versus DMSO control).[38]

Synthesis: Banwell *et al.* 2016.[44]

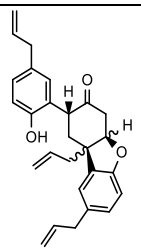
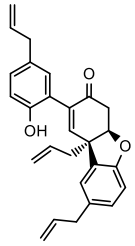
 Simonsol E (**42**)	Isolation:	*Illiicum simonsii* in 2013.[39] Stereochemistry has not been assigned (as displayed).
	Activity:	The enantiomeric mixture displayed an anti-AChE activity IC50 value of 10.34 μM.[39]
	Synthesis:	Denton *et al.* unpublished work.[38]
 Simonsol F (**43**)	Isolation:	*Illicium dunnianum* in 1996.[45]
	Activity:	35% Increase of axon growth in primary mouse cortical neurons (versus DMSO control).[38]
	Synthesis:	Denton *et al.* unpublished work.[38]

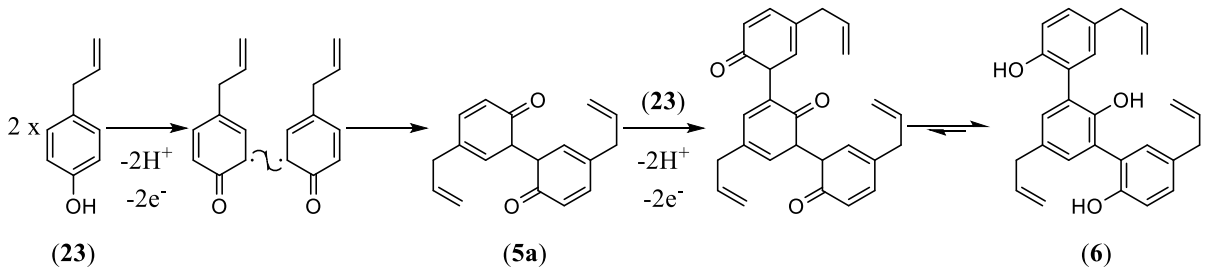
Table 1. Sesqui-neolignans isolated from the genus Illicium, to date, with details regarding their isolation, neurotrophic activity, and most recent synthesis. *a*: Based on computational studies, it is likely that the structures of simonin A, simonsin B and simonol B are united under a singular structural identity. Simonol B is believed to be the correct structure for all three compounds; this is yet to be confirmed by acquiring NMR data of synthetic simonol B.[46]

1.6 Previous Syntheses of Sesqui Neolignans from the Genus *Illicium*

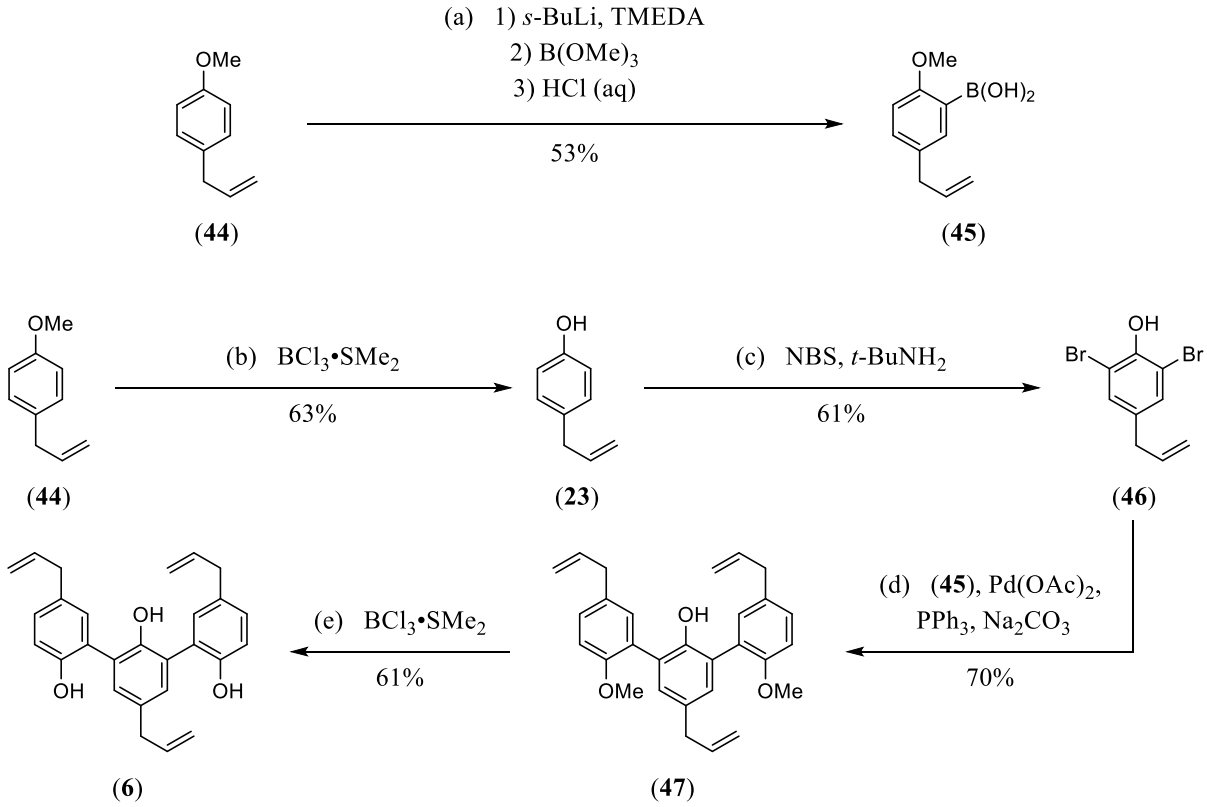
To date, many sesqui-neolignans have been synthesised (see Table 1). This thesis does not provide a comprehensive account of all the synthetic routes and chemical transformations used. Instead, we have selected to describe those which pertain the most relevance to the work detailed herein.

1.6.1 Dunnianol

Dunnianol is arguably the simplest sesqui-neolignan as it comprises of three *ortho*-linked chavicol units. Its biosynthesis is likely to arise from two sequential *ortho,ortho*-selective oxidative phenolic couplings of chavicol, *via* the dimer magnolol (**5**), in a process aided by an electron scavenger like Fe(III) (see Scheme 3).[47] Dunnianol is of medicinal interest as it has been demonstrated to possess moderate anti-inflammatory, antibacterial and anti-tumour properties.[48] The first reported synthesis of dunnianol was by Brown and Sy in 1998 *via* a biomimetic oxidative coupling of chavicol using potassium ferricyanide as the oxidant.[49] A similar approach was taken by Liu and Tzeng in 2004 using hydrogen peroxide and the catalyst



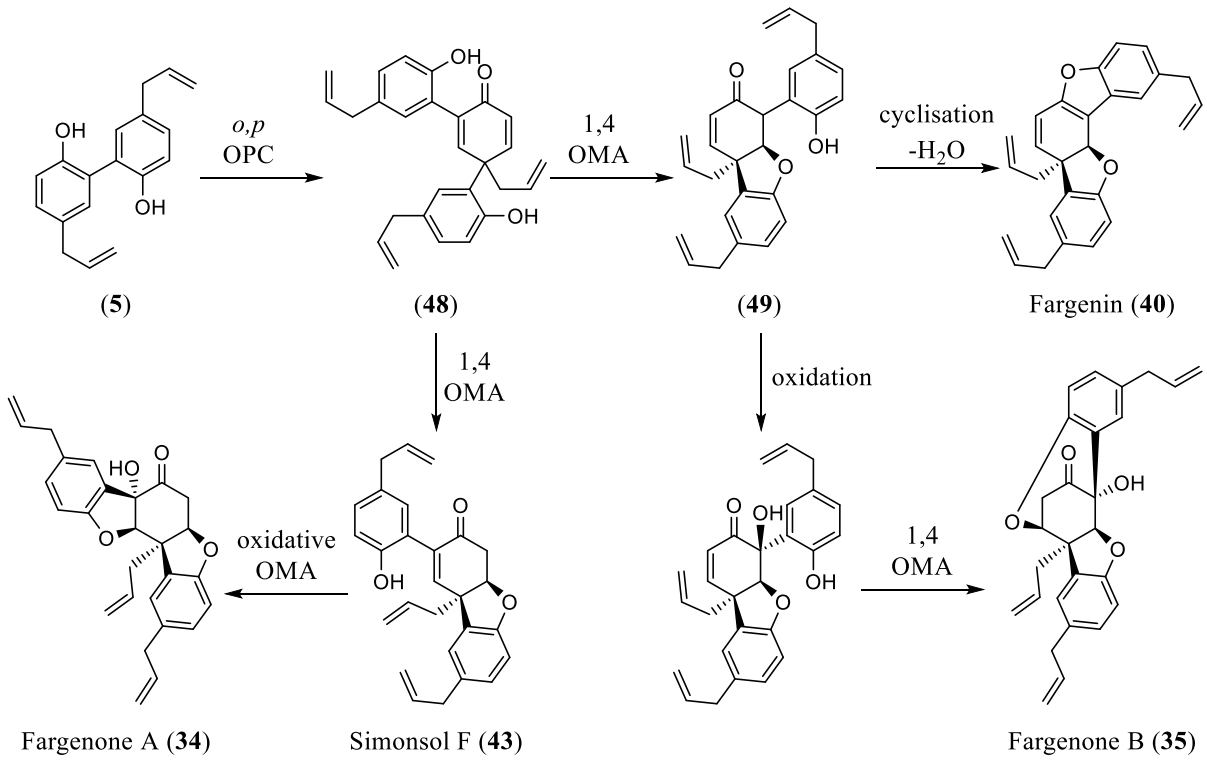
Scheme 3. Proposed biosynthesis of dunnianol (**6**).



Scheme 4. Synthesis of dunnianol by Denton *et al.* (bottom). Reagents and conditions: (a) *s*-BuLi, TMEDA, THF, -78 °C to 0 °C, 1 h, then $B(OMe)_3$, 0 °C to r.t, 24 h, then aqueous HCl ;(b) BCl_3•SMe_2, DCE, reflux, 18 h; (c) NBS, *t*-$BuNH_2$, CH_2Cl_2, 0 °C, 1 h; (d) $Pd(OAc)_2$, PPh_3, Na_2CO_3, *i*-PrOH/H_2O, reflux, 48 h; (e) BCl_3•SMe_2, DCE, reflux, 48 h. Equivalents of reagents unknown.

horseradish peroxidase.[50] In 2010, dunnianol was synthesised by Denton and Scragg; the success of this synthesis provided a basis by which more complicated sesqui-neolignans could be synthesised.[32]

The synthesis started with 4-allylanisole (**44**) (estragole), a far cheaper commercially available starting point compared to chavicol.[51] Estragole was regioselectively *ortho*-lithiated using *sec*-butyl lithium and treated with trimethyl borate providing one of the coupling partners for the key double Suzuki reaction: (**45**). Next, 4-allyl-2,6-dibromophenol (**46**), the other coupling partner, was prepared over two steps. Demethylation of estragole using boron trichloride



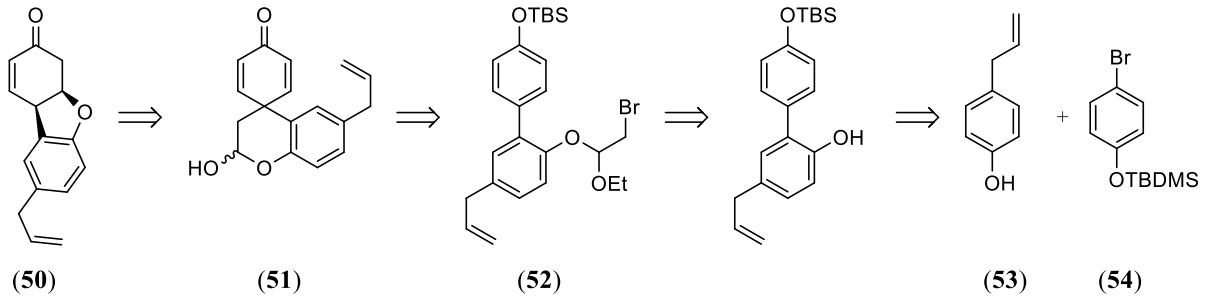
Scheme 5. Proposed biosynthesis of sesqui-neolignans containing a tetrahydrodibenzofuran motif. OMA = oxy-Michael addition. OPC = oxidative phenolic coupling.

followed by bromination using *n*-bromosuccinimide (NBS) and *tert*-butylamine provided (**46**). A Suzuki reaction between (**45**) and (**46**) provided (**47**) and subsequent demethylation of the remaining methyl ethers yielded dunnianol (**6**) in 17% yield over four steps (see Scheme 4).

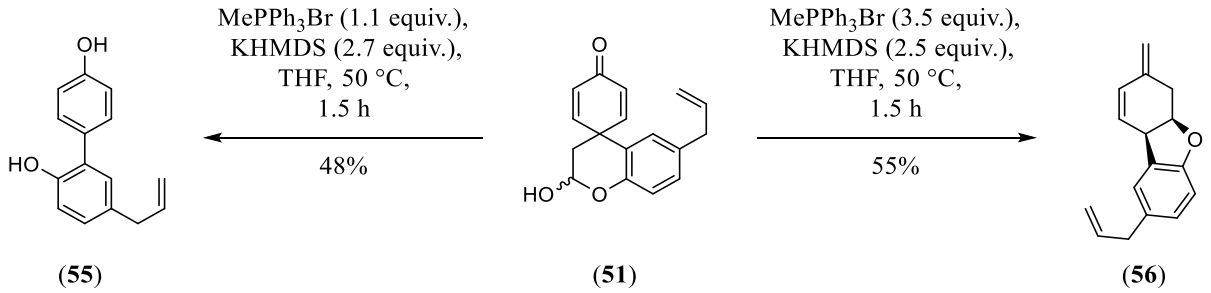
The successful synthesis of dunnianol elegantly demonstrated the ability of chavicol units to be synthetically linked *via* a different pathway to previously reported oxidative couplings. The usage of NBS, boron trichloride (a Lewis acid) and palladium highlighted the compatibility of these reagents with the sensitive aryl-allyl fragments, which, under basic conditions or with metals that can coordinate to the alkene, are prone to isomerisation to the thermodynamically favoured position. Additionally, the lack of isomerisation in the Suzuki step proved to be beneficial in preventing any Heck side reactions.

1.6.2 Simonsol F

Following the successful synthesis of dunnianol in 2010, in 2012, Denton and Scragg developed a strategy to access the fargenone/fargenin family of natural products.[20,32] Their plan



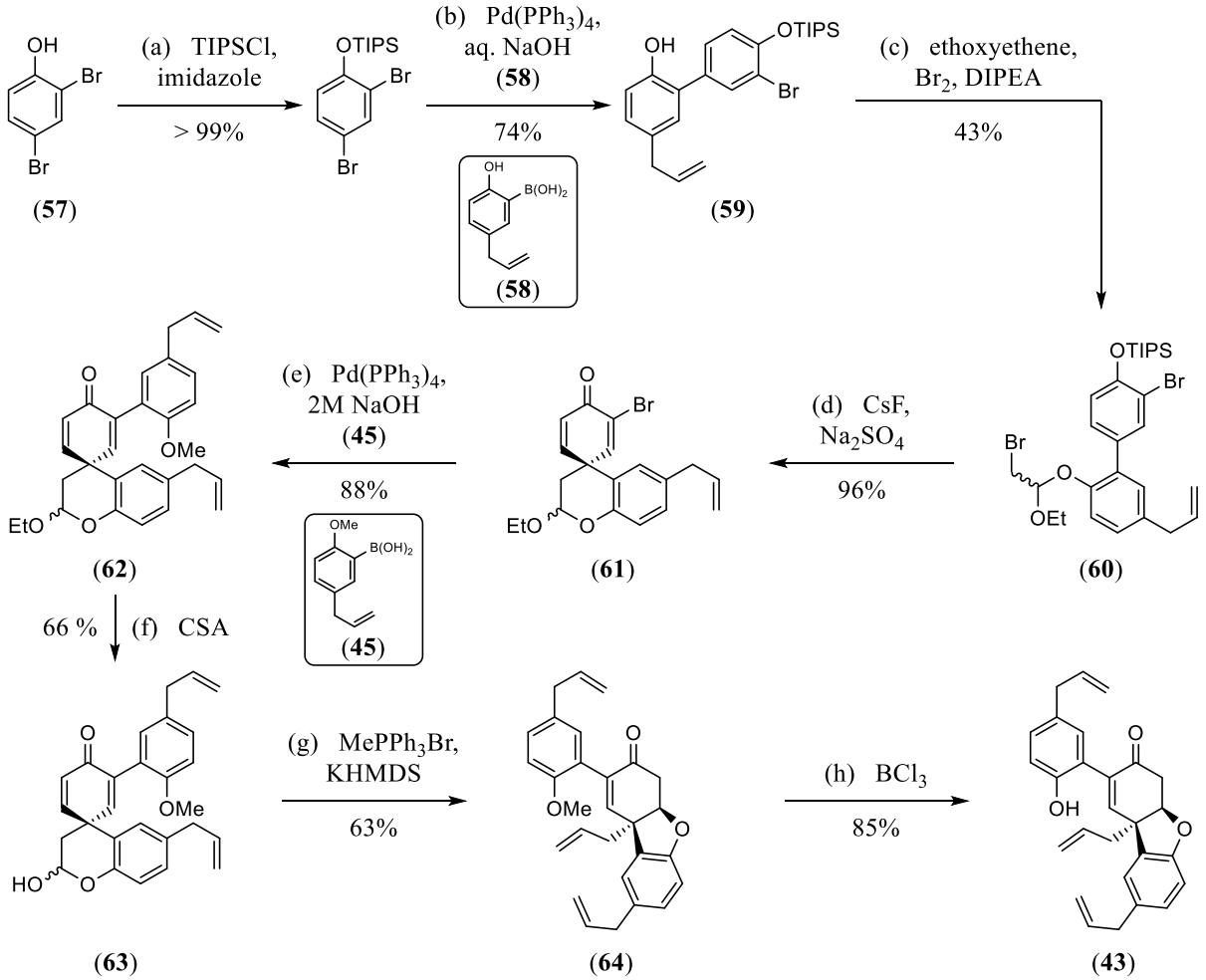
Scheme 6. First retrosynthetic analysis of simonsol G by Denton and Scragg in 2012.



Scheme 7. Unwanted products (**55**) and (**56**) resulted when (**51**) was treated under Wittig cascade conditions; Simonsol G (**50**) was not isolated cleanly.

for the construction of the characteristic tetrahydrodibenzofuran [4.3.0] ring system was inspired by the speculated biosyntheses of (**34**), (**35**) and (**40**) suggested by Fukuyama *et al.* (see Scheme 5), and is detailed as follows.[27] Two chavicol (**23**) units undergo an *ortho,ortho* oxidative phenolic coupling to form magnolol (**5**). This is followed by a second *ortho,para* oxidative phenolic coupling with another unit of chavicol to form (**48**). Subsequent oxy-Michael addition gives either simonsol F or intermediate (**49**), both of which can undergo further transformations to generate fargenone A (**34**), fargenone B (**35**) and fargenin (**40**) (see Scheme 5).

With this information, Denton and Scragg rationalised that they could form simonsol G (**50**), containing the tetrahydrodibenzofuran moiety *via* a Wittig cascade reaction of lactol (**51**). Lactol (**51**) could be generated *via* a desilylative intramolecular spirocyclisation reaction (developed by Magnus *et al.*) from bromo-acetal (**52**), which in turn could be prepared after protecting group manipulation from the Suzuki cross-coupling of (**53**) and (**54**) (see Scheme 6).[52] The initially attempted synthesis was moderately successful as the target model system was able to be formed. However, the key Wittig cascade reaction proved to be problematic, generating unwanted products (**55**) and (**56**) instead of the intended compound (**50**) (see Scheme 7). Additionally, hydrolysis of the intermediate acetal (after spirocyclisation of (**52**))



Scheme 8. Total synthesis of simonsol F. Reagents and conditions: (a) TIPSCl (1.1 equiv.), imidazole (2.5 equiv.), CH_2Cl_2, r.t, 3 h; (b) (**58**) (1.0 equiv.), NaOH (2.5 equiv.), $Pd(PPh_3)_4$ (20%), PhMe, 90 °C, 3.5 h; (c) ethoxyethene (2.5 equiv.), Br_2 (2.0 equiv.), DIPEA (4.0 equiv.), CH_2Cl_2, 0 °C to r.t, 2.25 h; (d) CsF (3.0 equiv.), Na_2SO_4 (10 equiv.), dry DMF, 130 °C, 1 h; (e) (**45**) (1.8 equiv.), Na_2CO_3 (6.4 equiv.), $Pd(PPh_3)_4$ (5%), PhMe/EtOH (7:3), 90 °C, 2 h; (f) CSA (60 equiv.), 1,4-dioxane/H_2O 57:43, 80 °C, 10.5 h; (g) $MePPh_3Br$ (3.0 equiv.), KHMDS (2.5 equiv.), dry THF, 2 h, (h) BCl_3 (2.1 equiv.), dry CH_2Cl_2, -18 °C, 72 h.

with aqueous HCl generated a mixture of unwanted products (of which lactol (**51**) was the major constituent) which were unable to be purified and thus had to be carried forwards without purification. The problems faced in this early synthesis of simonsol G were able to be mitigated in the later synthesis of simonsol F in 2020.[38]

The synthesis of simonsol F was planned *quasi* analogously to the initial route towards simonsol G and only contained minor modifications to account for the differences in the structures of the two compounds. The synthesis started with the silyl protection of 2-4-dibromophenol (**57**) followed by Suzuki cross-coupling with (**58**). Bromo-acetalisation of (**59**) gave acetal (**60**) and subsequent intramolecular desilylative spirocyclisation gave (**61**) as a diastereomeric mixture. Diastereomers (**61**) were cross-coupled with boronic acid (**45**)

providing acetal (**62**) which was treated with camphor-10-sulphonic acid (CSA) (as opposed to HCl used by Denton and Scragg in 2012) to afford lactol (**63**). Upon subjecting (**63**) to Wittig cascade conditions, methylated simonsol F (**64**) was formed. Finally, a boron trichloride mediated demethylation yielded simonsol F (**43**) in 10% over ten steps from estragole (see Scheme 8). A large-scale synthesis (50 mmol) of simonsol F starting from commercially available 2-bromo-4-chlorophenol was achieved in 17% yield over nine steps; however, it has not been detailed in this thesis.

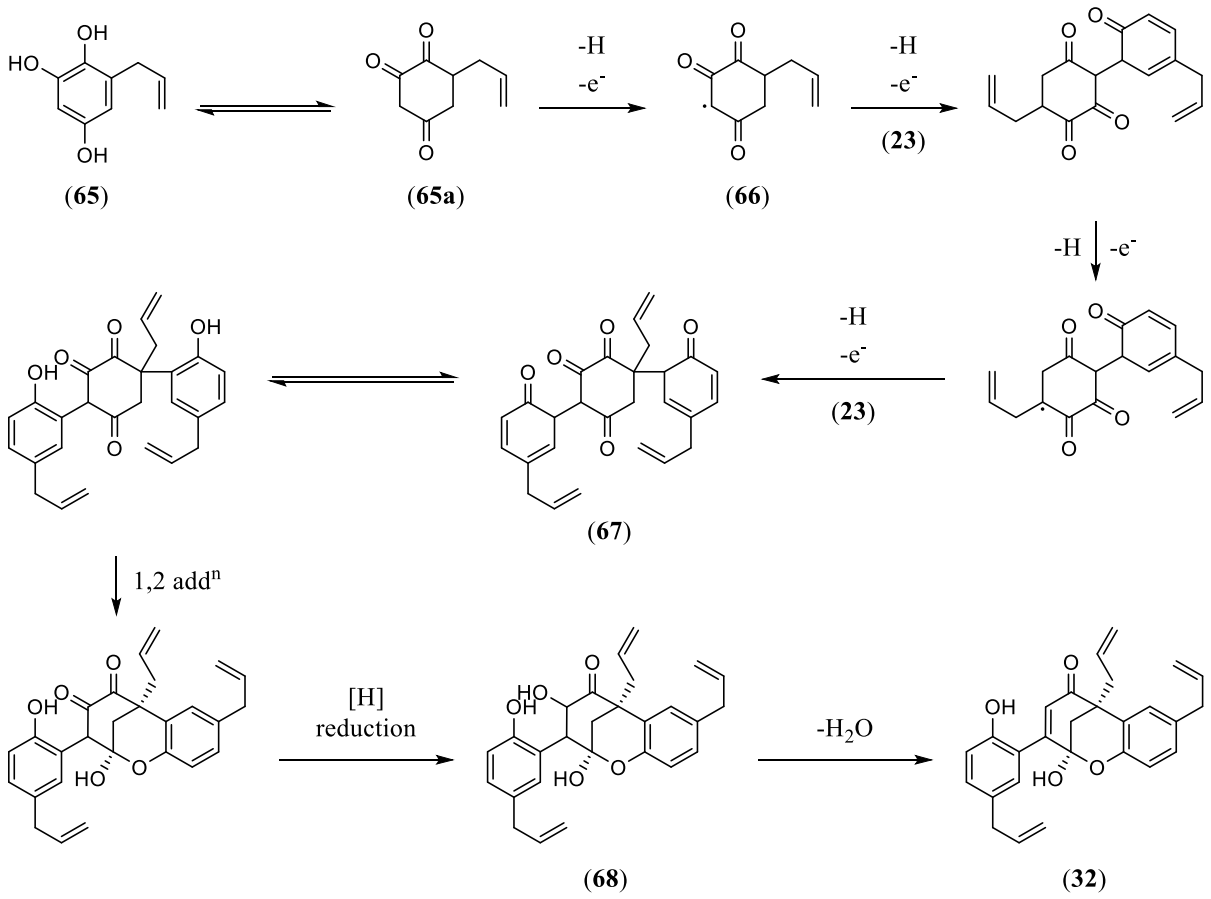
1.7 Simonsol A

Neolignans and sesqui-neolignans containing a tetrahydrodibenzofuran moiety have been studied extensively over the past decade. Many neolignans which do not contain the same motif remain to be synthesised. This thesis focuses on the total synthesis of simonsol A: a sesqui-neolignan with a characteristic [3.3.1] ring system.

1.7.1 Isolation and Biological Activity of Simonsol A

Simonsol A (also referred to as simonol A) was isolated in 2013 by two separate research groups, claiming their findings as novel.[39,42] The stereochemical assignments that were made by the two research groups are contradictory, with one group claiming that the molecule has an absolute configuration of (*S*,*S*) (Wang *et al.*) and the other group claiming the opposite enantiomer, with an absolute configuration of (*R*,*R*) (Kong *et al.*), as determined by the specific rotation, [α]. Kong *et al.* also obtained electronic circular dichroism (ECD) spectra and matched experimental values to those calculated using density functional theory, providing further credence to their claim.

Biological testing was carried out by Kong *et al.* to evaluate the cytotoxicity of simonsol A against four human cancer cell lines: NCI-H460, SMMC-7721, MCF-7 and BGC-823. In cell lines NCI-H460 and SMMC-7721, simonsol A had high inhibitory activities, comparable to those of the anticancer medication fluorouracil. The neurotrophic activities of simonsol A were investigated by Wang *et al.* It was found that simonsol did not inhibit AChE (<100 μM) or butyrylcholinesterase (BChE) (<50 μM).

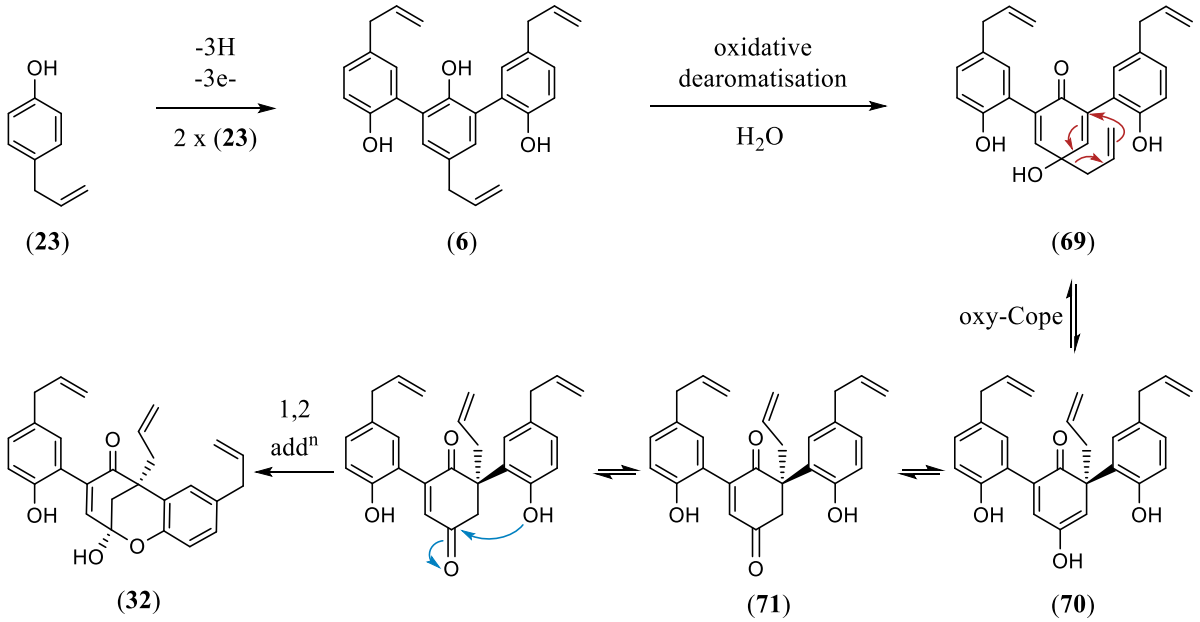


Scheme 9. Proposed biosynthesis of simonsol A (**32**) by Kong *et al.*

1.7.2 Biosynthesis of Simonsol A Proposed by Kong *et al.*

Kong *et al.* suggested that the biosynthesis of simonsol A starts with the tautomerisation of 6-allylbenzene-1,2,4-triol (**65**) which undergoes single electron oxidation to form radical (**66**), followed by two oxidative phenolic couplings with two chavicol (**23**) units to give (**67**). Subsequent tautomerisation, 1,2 addition and reduction generates (**68**) which undergoes a final dehydration to afford simonsol A (**32**) (see Scheme 9).

There are many reasons to doubt this biosynthesis. There is no evidence to suggest that triol (**65**) is present in *Illicium simonsii*; therefore, its appearance as a starting material is peculiar. Additionally, the tautomerisation of triol (**65**) is highly unlikely as it involves loss of aromatic stabilisation. The biosynthesis involves a selective reduction, which may be possible with a decarbonylase enzyme. However, it is unlikely that such enzymes could co-exist in the presence of oxidative enzymes, which are required for oxidative couplings.



Scheme 10. Proposed biosynthesis of simonsol A (**32**) by Denton *et al.*

1.7.3 Biosynthesis of Simonsol A Proposed by Denton *et al.*

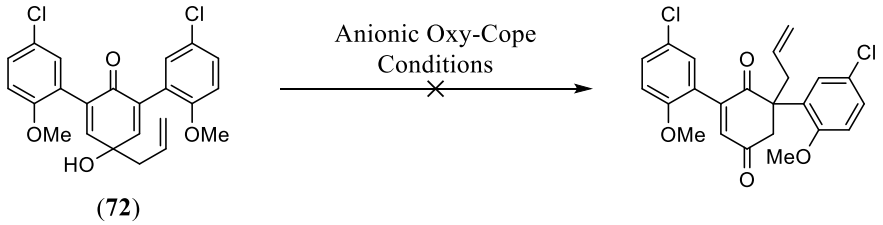
Denton *et al.* proposed an alternative biosynthesis of simonsol A, which relies solely on chavicol. Chavicol (**23**) undergoes two sequential *ortho,ortho* oxidative phenolic couplings to form dunnianol (**6**). Subsequent oxidative dearomatisation forms (**69**) which undergoes an oxy-Cope rearrangement to form (**70**). Tautomerisation of (**70**) followed by a 1,2 addition generates simonsol A (**32**) (see Scheme 10).

The energy barrier of the key oxy-Cope rearrangement has been calculated using the ωB97DX/6-31G* theoretical model (in a vacuum) to be 35.6 kcal•mol^{-1}. Although this value is high, studies have shown that such reactions can be enzyme catalysed.[53] Should the proposed oxy-Cope rearrangement be enzyme catalysed, the energy barrier would be much lower, increasing the likelihood of it occurring.

This thesis is split into two parts. The first part aims to explore a concise total synthesis of Simonsol A. The second part aims to build a dihydroxyl-cyclohexylbenzofuran core containing model system, providing evidence that simonol B can be accessed *via* simonsol F.

2.0 Results and Discussion: Studies Towards the Total Synthesis of Simonsol A

2.1 A Brief Summary of Previous Work Towards the Total Synthesis of Simonsol A

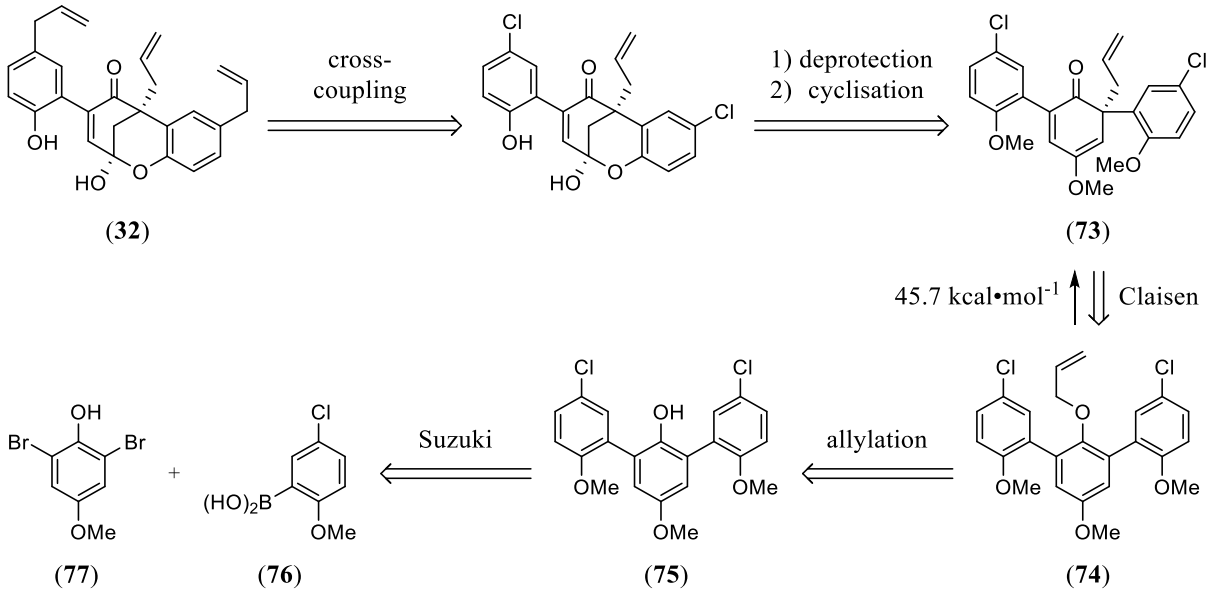


Equation 1. The previously trialled, unsuccessful oxy-Cope rearrangement of (**72**).

Retrosynthetic analyses of simonsol A (carried out by previous students) were guided by its proposed biosynthesis (see Scheme 10), aiming to synthesise a compound resembling (**71**, see Scheme 10) which could undergo further transformations to afford simonsol A.[54,55] Previous attempts at making ketone (**72**) were successful, but the key oxy-cope rearrangement was problematic (see Equation 1). QM calculations were carried out for the oxy-cope rearrangement of (**72**) and it was concluded that elevated temperatures >180 °C would be needed to promote a neutral oxy-cope rearrangement (ωB97DX/6-31G* energy barrier 35.6 kcal•mol^{-1} in a vacuum). Such elevated temperatures were deemed to be not practical as they would likely result in the thermal isomerisation of the allyl groups or even the decomposition of the substrate. A much lower barrier (8.1 kcal•mol^{-1}) was found when QM calculations were performed for the anionic oxy-cope rearrangement of (**72**). However, despite numerous attempts at promoting this anionic oxy-cope rearrangement, all the trialled conditions proved unsuccessful. This led to the abandonment of the originally proposed synthetic routes towards simonsol A.

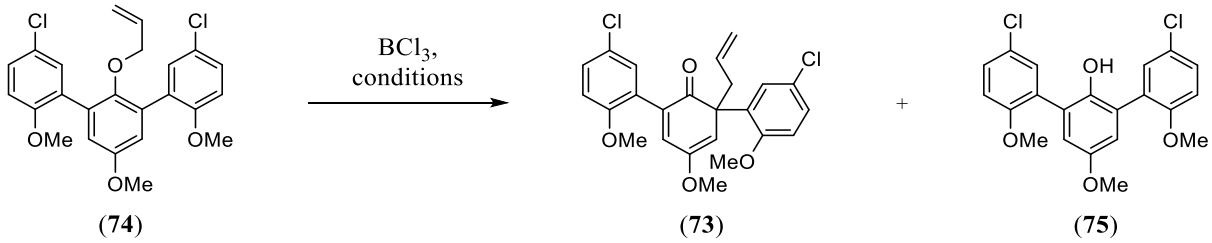
2.2 Synthetic Route Development

Our retrosynthetic analysis of simsonsol A (see Scheme 11) revisits the work carried out previously in the Denton group. As opposed to the oxy-cope rearrangement, this route focuses on a key Claisen rearrangement. The chemical transformations in our retrosynthetic analysis are based on previous experiences successfully synthesising other sesqui-neolignans within the Denton group. It was reasoned that simonsol A (**32**) could be obtained by deprotection and



Scheme 11. Retrosynthetic analysis of Simonsol A (**32**).

cyclisation of (**73**) which in turn could be formed *via* the key Claisen rearrangement of ether (**74**). Ether (**74**) could be generated *via* the allylation of triaryl (**75**) following a double Suzuki reaction of boronic acid (**76**) and dibromide (**77**) (see Scheme 11).



Entry	Solvent	Temp (°C)	Time (h)	Isolated Yield (%)	Diastereotopic Signals Observed[a] (ppm)
1	heptane	-18	unknown	0[b]	3.18, 3.30
2	CH_2Cl_2	-20	3	0[c]	3.06, 3.27

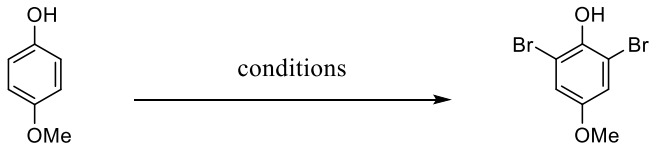
Table 2. Previous attempts at reaching (**73**). *a*: Diastereotopicity associated with the methylene group adjacent to the quaternary carbon centre in (**73**). *b*: Product not isolated due to low conversion. *c*: Inseparable mixture of (**73**) and (**75**) obtained.

The highlights of this synthesis plan include a double Suzuki reaction inspired by the synthesis of dunnianol (see Section 1.6.1). Additionally, late-stage allylation was incorporated into our plan to avoid the isomerisation of the sensitive aryl-allyl groups. QM calculations of the thermal Claisen rearrangement estimated the ωB97DX/6-31G* energy barrier in a vaccum to be 45.7 kcal•mol^{-1}; however it was reasoned that this could be dramatically reduced with the

aid of a Lewis-acid catalyst. Some evidence had been provided by previous work on this project that such a Lewis-acid catalysed rearrangement would be viable; diastereotopic signals had been observed by ^{1}HNMR spectroscopy when (**74**) was treated with boron trichloride (see Table 2).[54,55] Although we believed that these previously reported signals were higher than expected for the desired product (**73**), we sought to reach ether (**74**) and trial conditions which would trigger the key Claisen rearrangement, to characterise compound (**73**) and carry it forwards in the synthesis of simonsol A.

2.3 Forward Synthesis

2.3.1 Bromination



(**78**) (**77**)

Entry	Brominating agent	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$BTMABr_3$ (2.2 equiv.)	CH_2Cl_2/MeOH (7:3)	r.t	2	82
2	Br_2 (2.1 equiv.)	MeOH	0	3	0[a]
3	NBS (2.2 equiv.)	CH_2Cl_2/MeOH (7:3)	r.t	2	0[a]

Table 3. Bromination of anisole (**78**). *a*: TLC and ^{1}HNMR spectroscopy showed no presence of dibromide (**77**).

Our synthesis began with the bromination of 4-methoxyphenol (anisole) (**78**) (see Table 3). From a glance through the literature surrounding this bromination benzyltrimethylammonium tribromide ($BTMABr_3$) was deemed the primary bromination agent of choice.[56] Treatment of (**78**) with $BTMABr_3$ could be carried out at room temperature, in the presence of air and occurred in excellent 82% yield (see Table 3). During work-up, excess $BTMABr_3$ and other salt by-products were triturated using acetone, a poor solubiliser of salts. Although the material obtained after work-up only contained minor impurities, as observed by ^{1}HNMR spectroscopy, we chose to and were successful in purifying the material further by recrystallisation from MeOH/H_2O.

Due to slow shipments of $BTMABr_3$ we attempted to perform the same reaction (see Table 3) using different brominating agents. NBS was unsuccessful, as deemed by thin layer chromatography (TLC) and ^{1}HNMR spectroscopic analyses, generating unwanted species that could not be characterised from the crude reaction mixture following work-up. Despite

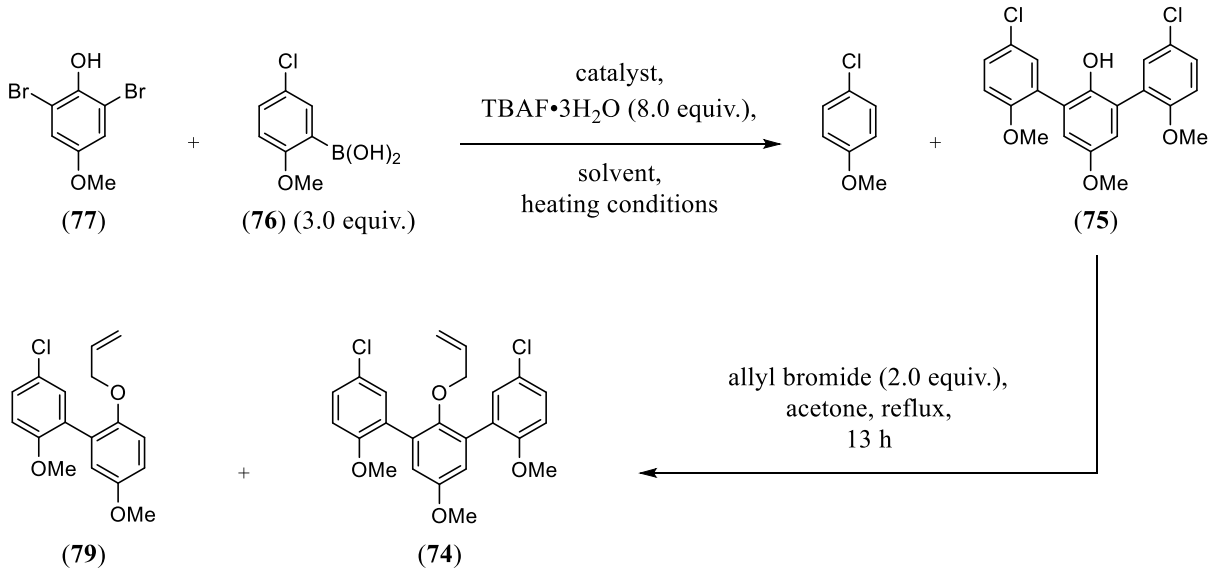
literature precedent showing that Br_2 could be used instead of $BTMABr_3$, our attempts were unsuccessful, and we were again unable to characterise any species after work-up.[57]

2.3.2 Suzuki Cross-Coupling

Following the bromination of (**78**), dibromo (**77**) and commercially available 5-chloro-2-methoxyphenylboronic acid (**76**) were reacted in a microwave-assisted double Suzuki cross-coupling reaction to obtain triaryl (**75**) (see Table 4). The reaction conditions were inspired by a previous student working on this project who had found success in obtaining (**75**) using these conditions after a trial of many Suzuki reaction conditions had proven unsuccessful.[55] Palladium on carbon (Pd/C), tetra-*n*-butylammonium fluoride trihydrate ($TBAF•3H_2O$), and H_2O were chosen as the catalyst, base, and solvent, respectively.

We opted for microwave-assisted heating, given its association with reduced reaction times, improved yields, and increased product purities compared to conventional heating methods.[58] Water was chosen as our reaction solvent of choice. Despite the inability of water to solubilise organic compounds efficiently at room temperature, it can solubilise organic compounds at high temperatures owing to its high dielectric constant.[59] TBAF was chosen as the base due to its ability to aid the solvation of organic substances in aqueous media. Additionally, it is believed that TBAF (alongside other quaternary ammonium salts) can enhance the reaction rate of the transmetallation step by activating the boronic acid by the formation of $[ArB(OH)_3^-][R_4N^+]$. Further credence can be given to this claim as reactions with CsF and KF *ceteris paribus* (previously trialled) were unsuccessful.[55] Finally, Pd/C was opted for as our heterogeneous catalyst as it is widely recognised for its efficiency in mediating cross-coupling reactions and its air-stable nature.[60]

We initially tried small-scale runs (0.25 mmol) of the Suzuki reaction (see Table 4, Entry 1) as it had been reported that scaling the reaction (beyond 0.50 mmol) led to low yields or no conversion completely.[55] At this scale, multiple reaction batches were run sequentially and combined to be worked up and purified together; typically, 10 reaction batches were combined. Unfortunately, we obtained low yields (20% average) that were contrary to the previously reported values (48% and 61%).[54,55] The low yields obtained were attributed to significant amounts of protodeboronated boronic acid (**76**) which was observed following purification by flash column chromatography. Additionally, we were often unable to isolate triaryl (**75**) cleanly, and we were later able to identify, after subsequent allylation, that our



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield of (**75**) (%)	Yield of (**74**) (%)	Yield of (**79**) (%)
1[a]	Pd/C	H_2O	150[c]	0.5	20	46	15
2[a]	Pd/C	dioxane/H_2O (1:1)	reflux	16	0[d]	N/A	N/A
3[a]	Pd(dppf)Cl_2	H_2O	150[c]	0.5	0[d]	N/A	N/A
4[a]	Pd(dppf)Cl_2	dioxane/H_2O (1:1)	reflux	16	0[d]	N/A	N/A
5[b]	Pd/C	H_2O	reflux	16	45	62	trace

Table 4. Trialled conditions for the optimisation of the Suzuki reaction to form (**75**). *a*: 0.25 mmol scaling. *b*: 4.76 mmol scaling. *c*: Microwave heating was used. *d*: Complex mixture by ^{1}H NMR spectroscopy.

substrate had undergone partial dehalogenation generating (**79**). In our experience, we found it essential to run the reactions in the microwave as our microwave vials could not withstand the internal pressure at 150 °C when using a conventional DrySyn heating block. These factors severely limited our throughput of material to the next stage and prompted a brief investigation to try and improve this.

In consulting Blakemore's review on the Suzuki reaction, we trialled novel conditions which we thought would result in higher yields and cleaner reaction mixtures.[61] Pd(dppf)Cl_2 was evaluated as a substitute for Pd/C as its wide bite angle and bidentate nature has proven effective in increasing the rate of reductive elimination in the Suzuki reaction's catalytic cycle.[62] The choice of TBAF was retained for the reasons discussed previously. We changed the reaction solvent to a mixture of dioxane/H_2O (1:1) to increase the solubility at a lower

temperature and lowered the reaction temperature to reflux, hoping that these changes would decrease the degree of protodeboronation and any other unwanted decomposition reactions. These two changes were implemented both separately and simultaneously and are summarised for clarity in Table 4 (Entries 2-4). Despite these changes, in each case, the crude reaction mixture after work-up was too complex and no significant improvement in reducing the number of unwanted side reactions was evident from the crude ^{1}H NMR spectra.

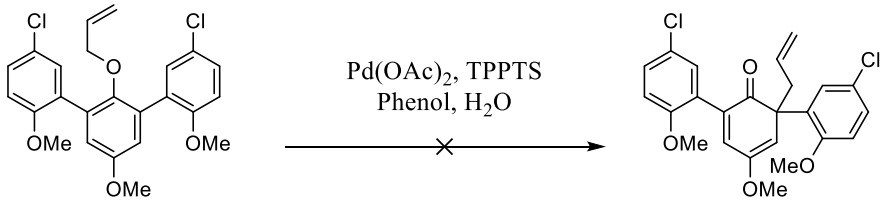
Despite being unsuccessful in reducing the number of unwanted side reactions (observed in the crude ^{1}H NMR spectra), we attempted a large, gram-scale reaction (4.76 mmol) of the Suzuki reaction using conditions which had previously been successful (see Table 4, Entry 5). At this scale, the contents of the reaction were too large to fit in the microwave vial, so we opted to reflux the reaction mixture for 16 hours in standard glassware instead. Surprisingly, we obtained a much higher yield (45%) than we had previously been able to, and we had now managed to throughput more material in less time. Furthermore, at this lower temperature, our reaction mixture was cleaner after column chromatography, and we observed little to no compound (**79**) at the following allylation stage.

2.3.3 Allylation

Following the Suzuki reaction, the next stage of the synthesis involved the allylation of the central phenolic hydroxyl group. Triaryl (**75**) was treated with allyl bromide in acetone and was refluxed for 16 hours to afford ether (**74**) in 62% yield (see Table 4, Entry 5). With ether (**74**) in hand, we were ready to trial conditions which would trigger the key Claisen rearrangement.

2.3.4 Claisen Rearrangement

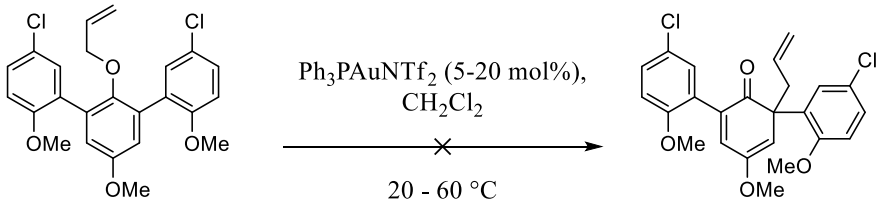
First discovered in 1912, the Claisen rearrangement is a [3,3] sigmatropic rearrangement which converts allyl vinyl ethers into γ,δ-unsaturated carbonyls.[63] Our initial efforts towards the Claisen rearrangement of ether (**74**) focussed on catalytic methods, which had previously not been attempted. Catalytic approaches were employed with a view to lowering the high calculated energy barrier for this reaction when uncatalysed. Reactions were analysed by ^{1}H NMR spectroscopy of the crude reaction mixture since we realised that product (**73**) would have diagnostic diastereotopic hydrogen environments for the methylene group adjacent to the newly formed quaternary centre (see Section 2.2). We started with a palladium sodium triphenylphosphine trisulfonate (Pd(0) TPPTS) mediated approach however, this mostly returned starting material alongside other unwanted by-products (see Equation 2).[64]



(**74**) (**73**)

Equation 2. Attempted Pd catalysed Claisen rearrangement of (**74**).

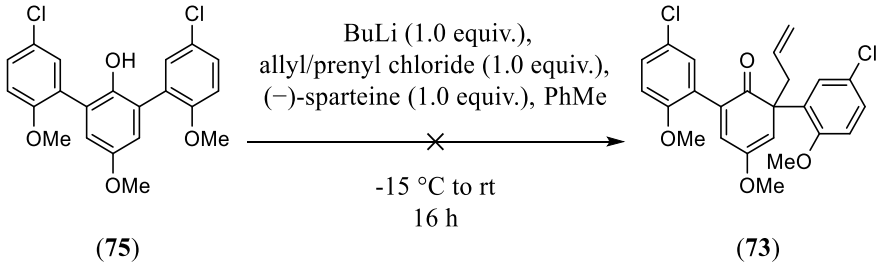
Following this, we explored the literature to find examples of dearomatising Claisen rearrangements. Although examples of such reactions were scarce, the use of [$Ph_3PAuNTf_2$] had been reported by Gagné *et al*. in 2017 for the controlled migration and transposition of a variety of oxygen-allyl-type fragments to substituted *ortho* positions, producing quaternary carbon stereocenters following the dearomatisation of napthyl and phenyl-based substrates.[65] Our synthesis of [$Ph_3PAuNTf_2$] occurred over two steps. Firstly, dimethyl sulfide gold(I) chloride [(Me_2S)AuCl], was reacted with triphenylphosphine to make triphenylphosphinegold(I) chloride, [(Ph_3P)AuCl].[66] Subsequent transmetallation between silver(I) triflimide [$AgNTf_2$] and [(Ph_3P)AuCl] generated [$Ph_3PAuNTf_2$] (confirmed by ^{31}P, ^{13}C and ^{1}H NMR spectroscopy) in 85% yield over two steps.[67] Unfortunately, the use of [$Ph_3PAuNTf_2$] proved unsuccessful in promoting the desired Claisen rearrangement on our substrate (see Equation 3). Despite heating the reaction mixture and increasing the catalyst loading, the reaction mixtures mainly contained starting material and other unwanted by-products.



(**74**) (**73**)

Equation 3. Attempted $Ph_3PAuNTf_2$ catalysed Claisen rearrangement of (**74**).

Following this, we briefly attempted a direct alkylation approach starting from triaryl (**75**) using a methodology developed by Fráter *et al.*[68] Triaryl (**75**) was reacted with (-)-sparteine, butyl lithium (BuLi) and allyl chloride as shown in Equation 4. From the crude reaction mixture, we were unable to observe the presence of any characteristic diastereotopic peaks. We attempted the same reaction again; however, we changed our use of allyl chloride

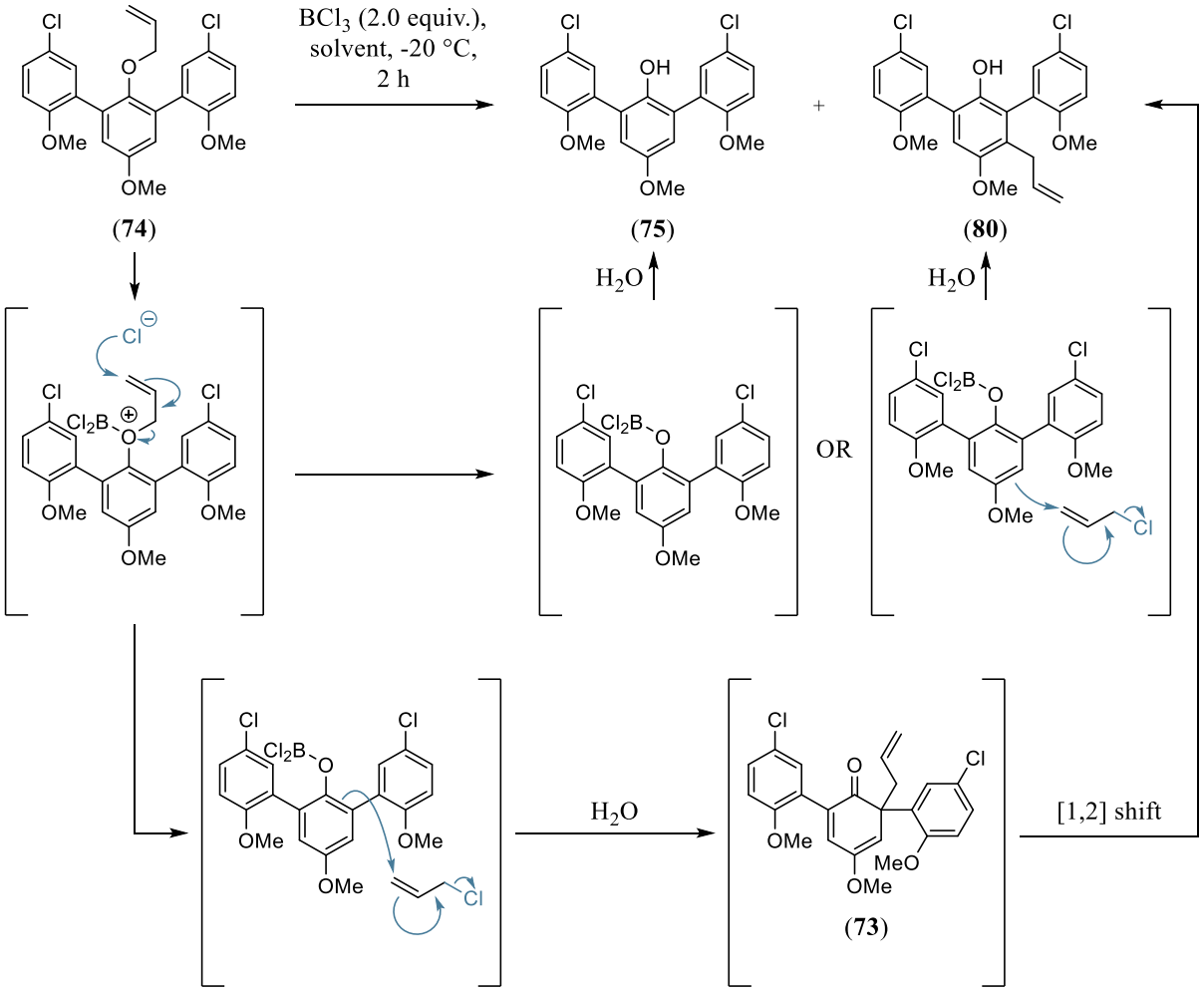


(**75**) (**73**)

Equation 4. Attempted C-directed allylation of (**75**).

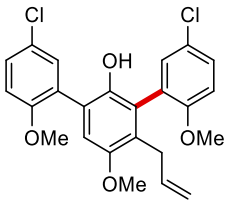
to prenyl chloride under analogous conditions described by Fráter *et al*. Once again, however, we did not observe any diastereotopic peaks associated with the rearranged product. From the initial catalytic methods described above, we reasoned that our substrate and the associated high energy barrier for its dearomatisation was the likely cause for the lack of reactivity observed and any promotion of unwanted side reactions.

At this juncture, we decided to revisit the Lewis-acid catalysed Claisen rearrangement of (**74**), which previously had been examined during earlier studies.[54,55] Ether (**74**) was screened using a variety of Lewis acids; reactions were performed using 2.0 equivalents of Lewis acid, in deuterated chloroform (dried over 3Å molecular sieves), and aliquots were taken at regular intervals to be examined by ^{1}H NMR spectroscopy. Gratifyingly, we were able to observe diastereotopic signals in the range between (3.0-3.5 ppm) however, in each case, we observed significant allyl cleavage returning us to triaryl (**75**). After work-up with $NaHCO_3$, the diastereotopic signals were more pronounced; the highest ratio of (**75**) to (**80**) (8:1, determined by ^{1}H NMR spectroscopy w/w, see Table 4) was obtained when using boron trichloride as the Lewis acid. In an attempt to increase the conversion of desired product, we changed our reaction solvent from chloroform to CH_2Cl_2, a more commonly used solvent when carrying out Claisen rearrangements.[69] In doing so, we were able to increase our conversion to *ca*. 40%, and we were able to isolate our product. Upon fully characterising this product, we determined that it was not the result of the desired Claisen rearrangement. Instead, we had formed triaryl (**80**) which was likely a result of either a [1,2] migratory shift from our product or from a S_EAr reaction following allyl cleavage (see Table 4). An *in situ* ^{1}HNMR spectroscopic analysis was attempted to determine whether triaryl (**73**) was formed during the course of the reaction. At -50 °C we observed no reactivity of starting material after *ca*. 1 hour; at -25 °C we slowly observed the formations of (**75**) and (**80**) over 2 hours (-25 to 0 °C); no other species were observed.



Entry	Solvent	Ratio of (**75**) to (**80**)[a]	Isolated Yield of (**80**)
1	$CDCl_3$	8:1	N/A[b]
2	CH_2Cl_2	3:2	18%[c]

Table 4. Possible mechanistic routes from (**74**) to (**80**). *a*: Ratio of (**75**) to (**80**) was deemed by ^{1}HNMR spectroscopy (w/w). *b*: Isolation of (**80**) not attempted. *c*: Low yield of (**80**) due to partial coelution of (**75**) and (**80**); successive column chromatography was not attempted on the mixture of (**75**) and (**80**).



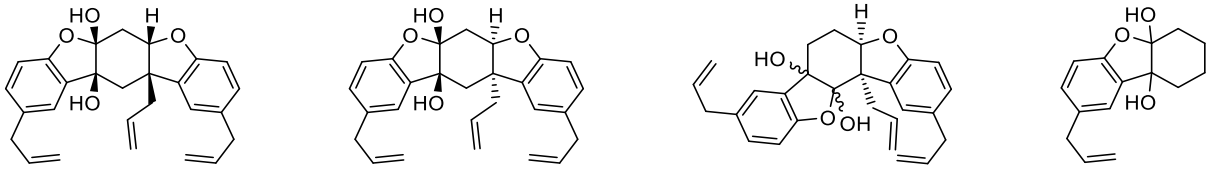
(**80**)

Figure 1. Diasterotopicity arising due to restricted rotation about the biaryl bond (highlighted).

The nature of the diasteretopic peaks in triaryl (**80**) was investigated; it was believed that the diastereotopicity was due to restricted rotation around the biaryl bond highlighted in Figure 1. In order to calculate the barrier to rotation about the stereogenic axis, a low energy conformer was obtained from an equilibrium conformer molecular mechanics calculation. This, along with all other calculations, was implemented in Spartan 2020 Macintosh version. Equilibrium and transition state geometries derived from the lowest energy conformer of the molecular mechanics search were then calculated using the ωB97XD/6-31G* theoretical model in a vacuum. A single imaginary frequency corresponding to the bond rotation was found for the transition state geometry. The ground state conformer had no imaginary frequency. A barrier of 28 kcal•mol^{-1} was calculated from the uncorrected electronic energies of the ground state and transition state.[70] The half-life of this rotational barrier was calculated to be 1 year and 81 days at 25 °C, explaining the diastereopicity observed by ^{1}H NMR spectroscopy.

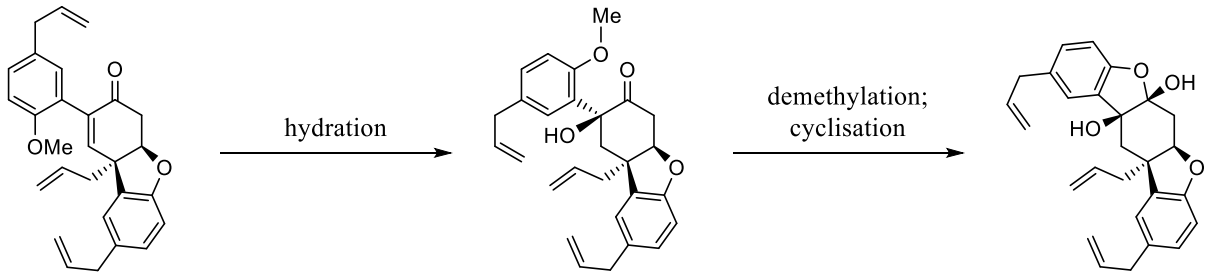
The investigations presented herein have demonstrated that the Claisen rearrangement could not be implemented without significant competition from the migration of the allyl group to restore the aromaticity of the central phenolic ring. At this point in the project, it was decided that work towards the synthesis of simonsol A be halted until an alternative synthetic plan could be devised. This prompted us to start working towards the synthesis of a sesqui-neolignan which we believed could be derived from simonsol F.

3.0 Results and Discussion: Creation of a Dihydroxyl-Cyclohexylbenzofuran Core Containing Model System



(**37**) (**38**) (**39**) (**81**)

Figure 2. Simonin A (**39**), simonol B (**38**), simonsin B (**37**) and model system (**81**).



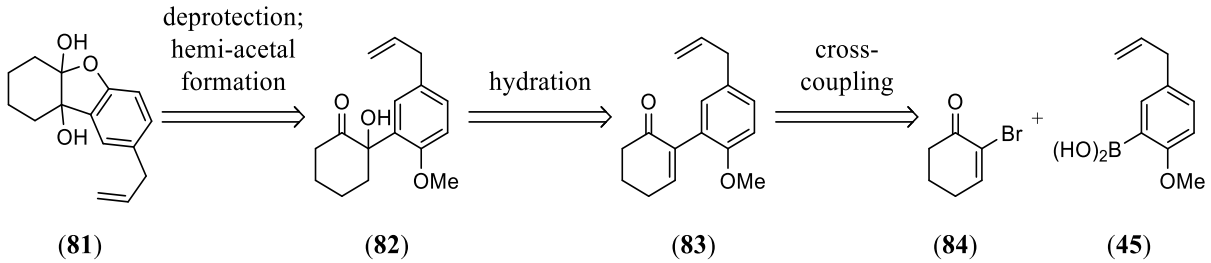
(**64**) (**38**)

Scheme 12. Steps proposed to transform methylated simonsol F (**64**) into simonol B (**38**).

Simonin A (**39**), simonol B (**38**), and simonsin B (**37**) have been previously assigned as three separate structures (see Figure 2).[39,42,43] Computational studies performed within the Denton group suggest that the structures of (**37**) and (**39**) have been misassigned and that the aforementioned separate structures all exist under the singular structural identity of (**38**).[46] It is of interest to synthesise (**38**) to compare its synthetic NMR spectra to the NMR data provided in its isolation paper. We believe that (**38**) can be accessed *via* hydration of methylated Simonsol F followed by a boron trichloride promoted cyclisation (see Scheme 12). Before attempting to prepare (**38**) we reasoned it would be sensible to create a model system (**81**) to prove that we could synthesise the key dihydroxyl-cyclohexylbenzofuran core.

3.1 Synthetic Route Development

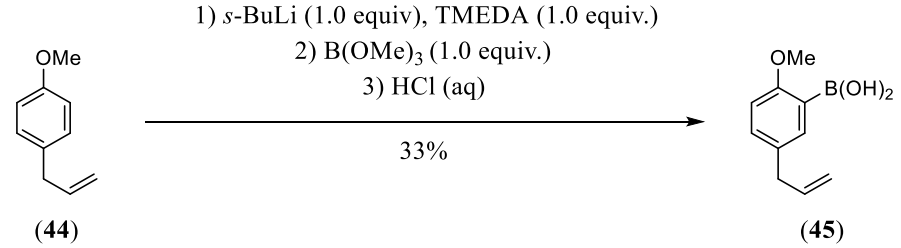
Our initial retrosynthetic analysis of model system (**81**) focused on a key Mukaiyama hydration followed by a cyclisation to form the [4.3.0] ring system (see Scheme 13). We envisioned that we could carry out a similar cyclisation to that carried out in the syntheses of the fargenone/fargenin family of natural products by deprotection of alcohol (**82**).[38] Alcohol (**82**) could be formed from model compound (**83**) by selective hydration α to the ketone. Model



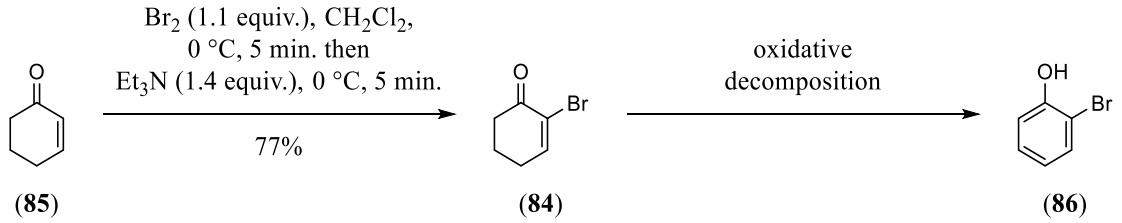
Scheme 13. Retrosynthetic analysis of model system (**81**).

compound (**83**) could be in turn generated *via* a cross-coupling reaction between bromo enone (**84**) and boronic acid (**45**).

3.2 Forward Synthesis

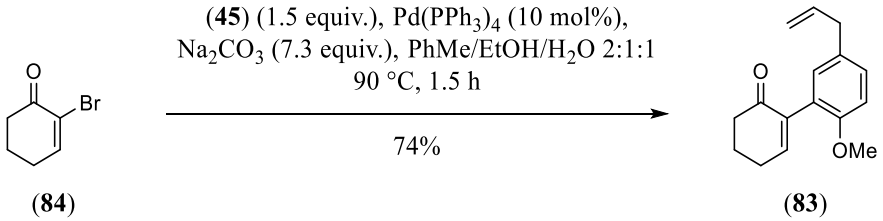


Equation 5. Preparation of in-house boronic acid (**45**).



Scheme 14. Formation of bromo enone (**84**) and its likely oxidative decomposition to form (**86**).

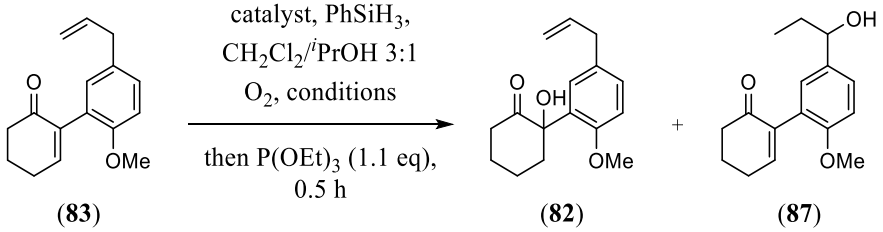
Our synthesis started with the preparation of the two coupling partners (**84**) and (**45**). Boronic acid (**45**) was prepared in 33% yield *via* the lithiation of commercially available estragole (**44**) followed by subsequent treatment with trimethyl borate and hydrolysis of the boronate ester (see Equation 5). Separately, commercially available cyclohexenone (**85**) was dibrominated with Br_2 and subsequently treated with triethylamine to afford bromo enone (**84**) in 77% yield (see Scheme 14). In our case, it was discovered that (**84**) was unstable when exposed to heat (when removing solvent) and/or air for prolonged periods of time. Such exposures would cause (**86**) to oxidise and aromatise likely leading to phenol (**86**) and related oligomers. Despite this, we were able to successfully cross-couple (**84**) with in-house boronic acid (**45**) in 74% yield



(**84**) (**83**)

Equation 6. Suzuki reaction between (**84**) and (**45**) to form model compound (**83**).

(see Equation 6). With model compound (**83**) in hand, we proceeded to trial conditions which would selectively hydrate the alkene within the enone whilst leaving the sensitive allyl group intact.

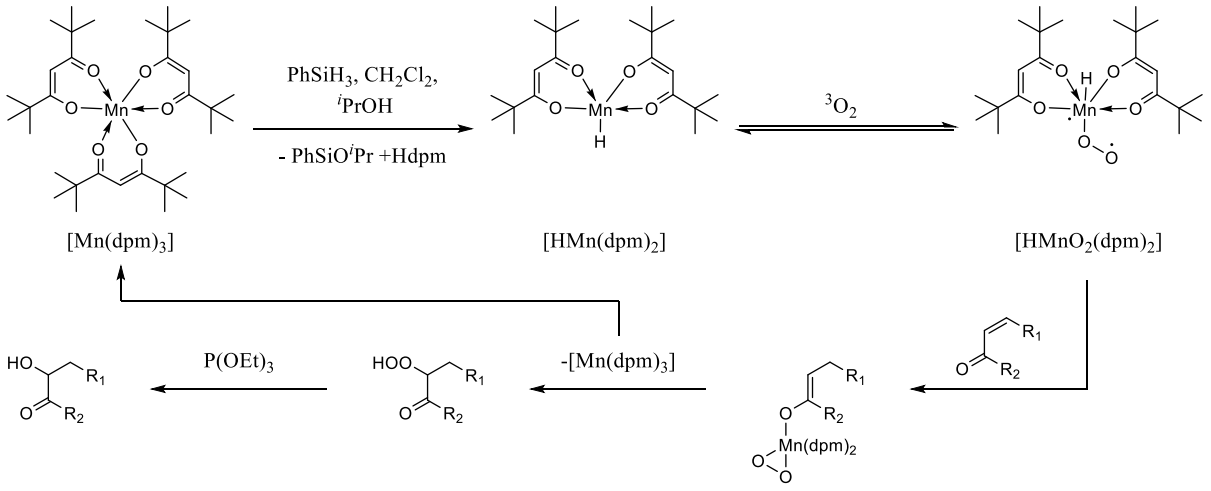


(**83**) (**82**) (**87**)

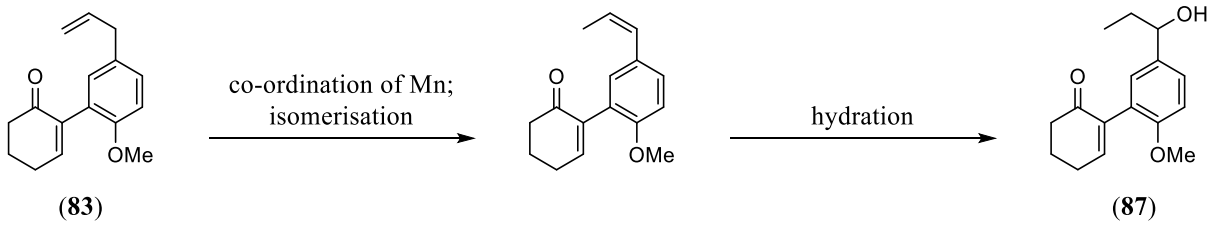
Entry	Catalyst	Loading (%)	$PhSiH_3$ Equivalents	Temp (°C)	Time (h)	Yield of (**82**) (%)	Yield of (**87**) (%)
1[a]	$Mn(dpm)_3$	5	1.3	0	2.5	0[c,d]	0[c,d]
2[a]	$Mn(dpm)_3$	5	1.3	0 to r.t	16	0[c,d]	0[c,d]
3[a]	$Mn(dpm)_3$	5	2.6	0 to r.t	16	0[c,d]	0[c,d]
4[a]	$Mn(dpm)_3$	20	1.3	0 to r.t	16	0[c,d]	0[c,d]
5[a]	$Co(acac)_2$	5	1.3	0 to r.t	16	0[c,d]	0[c,d]
6[a]	$Mn(acac)_3$	5	1.3	0 to r.t	16	0[c,d]	0[c,d]
7[b]	$Mn(dpm)_3$	5	1.3	0 to r.t	16	0[c]	13[e]

Table 5. Attempted Mukaiyama hydration of (**83**). *a*) 0.5 mmol scale. *b*) 10 mmol scale. *c*) Complex mixture as determined by LC-MS/HPLC and ^{1}H NMR spectroscopy. *d*) No species were able to be isolated by flash column chromatography. *e*) Multiple flash column chromatography runs were needed.

Our initial efforts on this challenging chemical transformation employed conditions developed by Mukaiyama *et al*., which have been proven by Magnus *et al*. to selectively convert α,β-unsaturated ketones/esters into α-hydroxy ketones/esters (see Scheme 15).[71, 72] Model compound (**83**) was treated with phenyl silane and manganese(III) tris dipivalolymethane under an atmosphere of oxygen (see Table 5). Unfortunately, this reaction did not proceed as anticipated; many species were observed by LC-MS/HPLC and TLC and it was unclear



Scheme 15. Mechanism of the Mukaiyama hydration using conditions developed by Magnus *et al*.

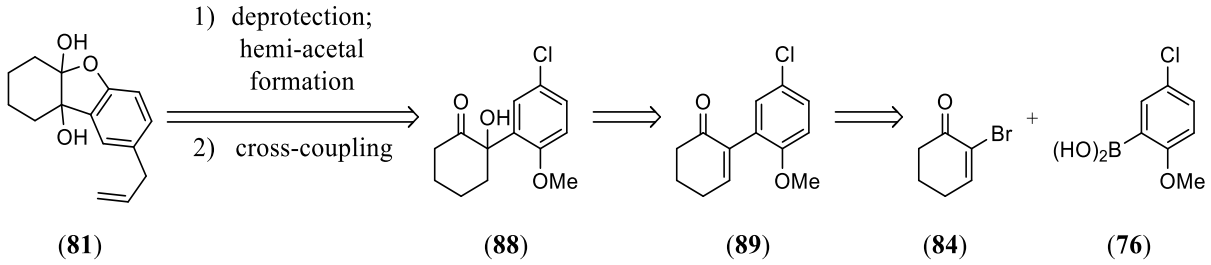


(**83**) (**87**)

Scheme 16. Likely formation of (**87**) *via* isomerisation of (**83**) followed by hydration to the conjugated aryl-olefin.

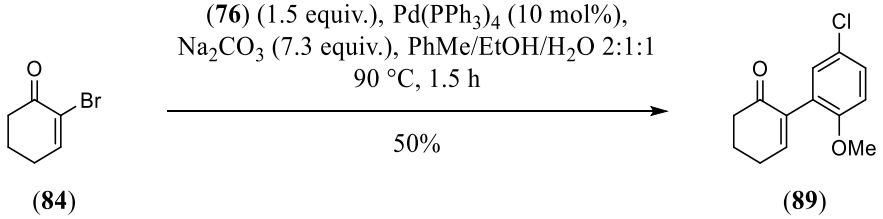
whether our desired product had been formed by ^{1}H NMR spectroscopy. Despite our best efforts to isolate a major species from the reaction mixture that we believed to be our product with a lower retention factor than our starting material, we were unable to obtain it cleanly. From the ^{1}H NMR spectrum obtained from this isolate, we were unable to distinguish any significant changes to the triplet at the β position to the ketone. From this, we determined that the α,β-unsaturated ketone had not been hydrolysed and an unwanted side-product had been formed instead. Attempts to optimise the reaction to favour the formation of our intended product by varying the temperature, changing catalyst loadings, and altering the amount of phenyl silane, were futile. We tried changing the catalyst to cobalt(II) acetylacetonate and manganese(III) acetylacetonate however, we did not observe any favourable improvements. Upon repeating our original conditions (see Table 5, Entry 7) at a much larger scale, we were able to successfully isolate (**87**) from the reaction mixture, which had likely been formed *via* the isomerisation of the sensitive aryl-allyl groups and subsequent hydration of the aryl-olefin (see Scheme 16). Following the isolation of (**87**), we were unable to characterise any other species within the reaction mixture; we realised that multiple products could arise from the

hydration of substrate (**83**). Indeed, complex mixtures and the formation of unwanted by-products have also been observed by Magnus *et al*. in substrates containing conjugated olefins.[72]



(**81**) (**88**) (**89**) (**84**) (**76**)

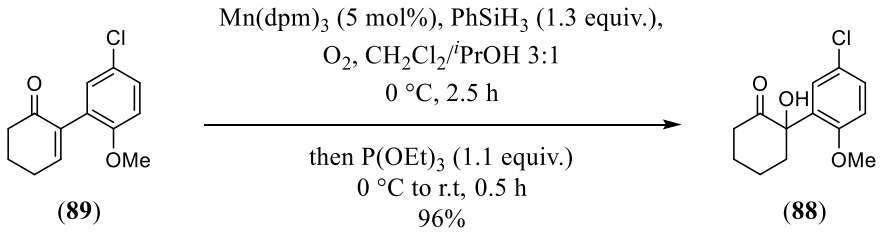
Scheme 17. Revised retrosynthetic analysis of model system (**81**).



(**84**) (**89**)

Equation 7. Suzuki reaction between (**84**) and (**76**) to form our second model compound (**89**).

With this in mind, we revised our synthetic route (see Scheme 17) to include a late-stage allylation to prevent the abovementioned issues. Our second model compound (**89**) was prepared in 50% yield from the cross-coupling of 5-chloro-2-methoxy phenylboronic acid (**76**) and bromo enone (**84**) (see Equation 7). Subsequently, we subjected (**89**) to the same conditions that had been initially trialled on our first model compound (**83**) (see Table 5, Entry 1, and Equation 8).

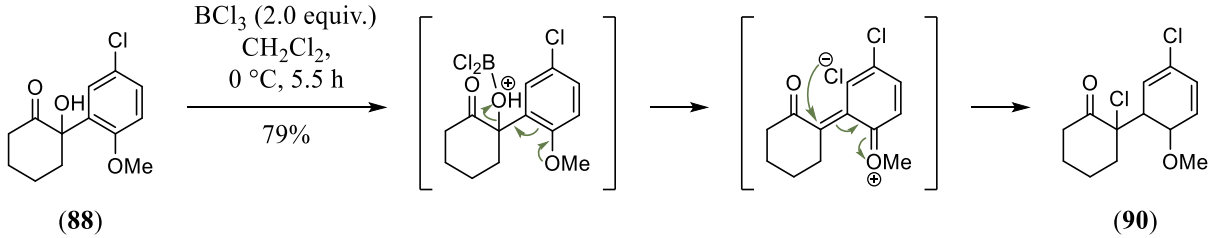


(**89**) (**88**)

Equation 8. Mukaiyama hydration of (**89**).

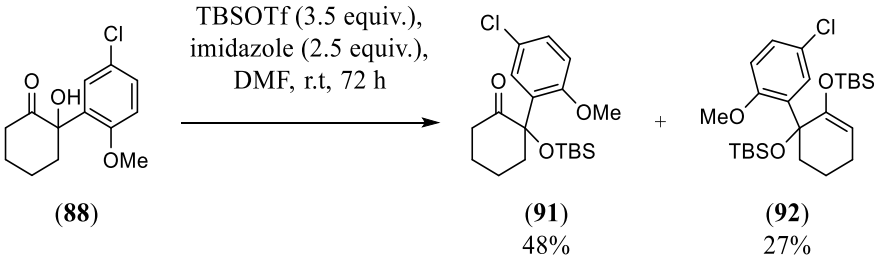
Gratifyingly, the reaction mixture was far cleaner than it had been before; an inseparable mixture of alcohol (**88**) and (**89**) was obtained in a 1.67:1 ratio as determined by ^{1}H NMR spectroscopy (w/w) which, after being reapplied to the reaction conditions yielded alcohol (**89**) in 96% yield. Alcohol (**88**) was treated with boron trichloride in an attempt to deprotect the methyl ether and promote the [1,2] cyclisation to form the [4.3.0] ring system.

However, as opposed to our intended product we obtained chloro (**90**) resulting from the expulsion of the benzylic alcohol and subsequent attack by Cl^- (see Scheme 18).

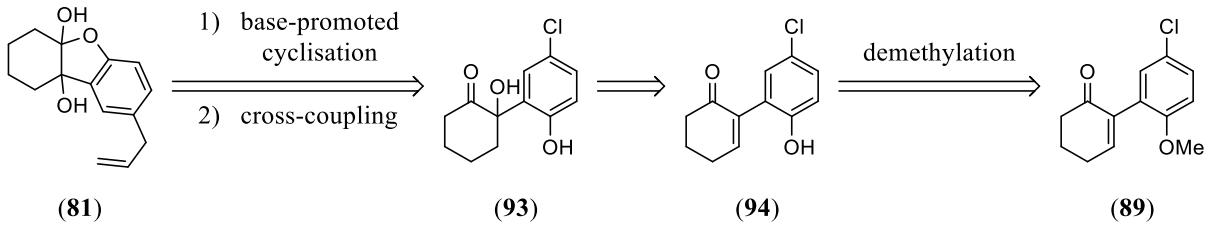


Scheme 18. Attempted deprotection of (**88**) leading to unwanted product (**90**).

We rationalised that we could protect alcohol (**88**) as a silyl ether. It was predicted that coordination of boron trichloride would not be possible to the non-Lewis-basic silyl ether, shutting down the pathway depicted in Scheme 18. Since we postulated that the protection of tertiary alcohol (**88**) would be slow, we opted for the use of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), imidazole and chose DMF as our solvent (see Equation 9), since it has been proven that DMF significantly increases the rate of such reactions.[73] Despite these forcing conditions, the reaction proceeded slowly and required the addition of a total of 3.5 equivalents of TBSOTf and 120 hours until TLC showed the complete consumption of starting material. Silyl ether (**91**) was obtained in 48% yield; however, the use of TBSOTf caused over-protection of alcohol (**88**), generating silyl enol ether (**92**) as a minor unwanted by-product. With silyl ether (**91**) in hand, we attempted the same boron trichloride demethylation as detailed previously for alcohol (**88**) (see Scheme 18). However, we obtained the same product (**90**) as we had done so before. Since this protection group strategy had not worked successfully, we changed the order of our synthetic route.

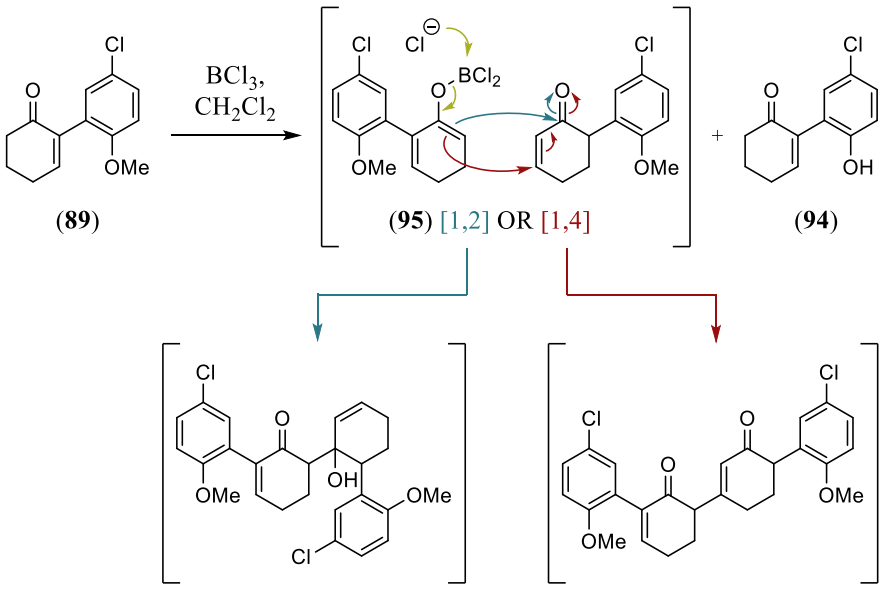


Equation 9. Protection of alcohol (**88**).



Scheme 19. Revised retrosynthetic analysis of model system (**81**).

Our revised synthetic route aimed to demethylate our second model compound (**89**) to create a third model compound (**94**) which would provide the basis for performing the subsequent Mukaiyama step forming alcohol (**93**) which could undergo a base-promoted cyclisation to form the [4.3.0] ring system (see Scheme 19). In practice, however, upon subjecting (**89**) to demethylation conditions (see Table 6) we were unable to form (**94**). Instead, an unsymmetrical dimer of (**89**) had formed, likely *via* a [1,2] or [1,4] attack of enolate (**95**) to (**89**). We tried the same reaction again at a lower temperature and changed our work-up

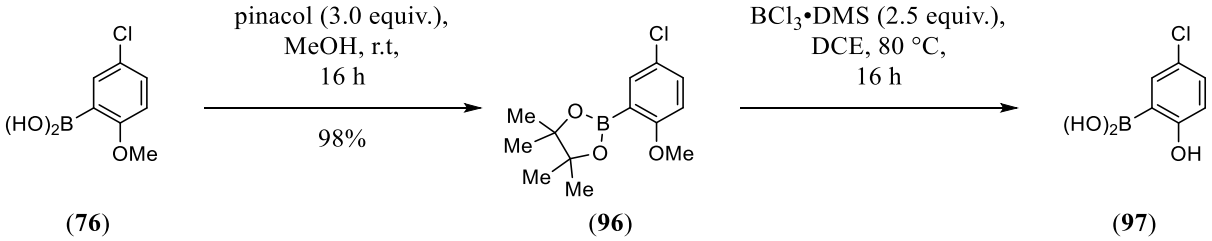


Entry	Equivalents of BCl_3	Temp (°C)	Time (h)	Work-up Conditions	Yield of (**94**) (%)
1	1.5	0	5.5	*a*	0[c]
2	1.8	-78 to -20	16	*b*	trace[c]

Table 6. Attempted demethylation of (**89**). *a*): The reaction mixture was added to a rapidly stirred solution of CH_3CN/H_2O (49:1) at 0 °C and washed with H_2O. *b*) The reaction was mixture added to a biphasic mixture of 2 M $NaOH/CH_2Cl_2$ (6:4) and washed with 3 M HCl. *c*): Remaining mass balance was an uncharacterised unsymmetrical dimer likely resulting from enolate (**95**).

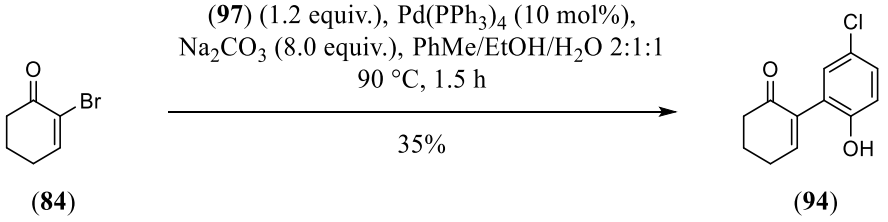
conditions; however, the same dimer was formed as before and only trace amounts of (**95**) were isolated. The dimer formed in these reactions was not investigated thoroughly.

Following this, we attempted to form our third model compound (**93**) *via* a different approach by the Suzuki cross-coupling of bromo enone (**84**) and 5-chloro-2-hydroxyl phenyl boronic acid (**97**). Boronic acid (**97**) was prepared over two steps from 5-chloro-2-methoxy phenyl boronic acid, *via* boronic acid pinacol ester (**96**) and is shown in Scheme 20. Since (**97**) was obtained as a mixture of monomer, dimer and (likely) higher order oligomers we were unable to acquire ^{1}H and ^{13}C spectroscopic information for this compound; given this, we are unable to provide a yield % for this reaction. In the subsequent Suzuki reaction between (**84**) and (**97**) (see Equation 10), we assumed that (**97**) was entirely in its monomeric form, which likely meant that a large over-estimation of (**97**) was used. From this reaction, obtained our



(**76**) (**96**) (**97**)

Scheme 20. Preparation of 5-chloro-2-hydroxy phenyl boronic acid (**97**).



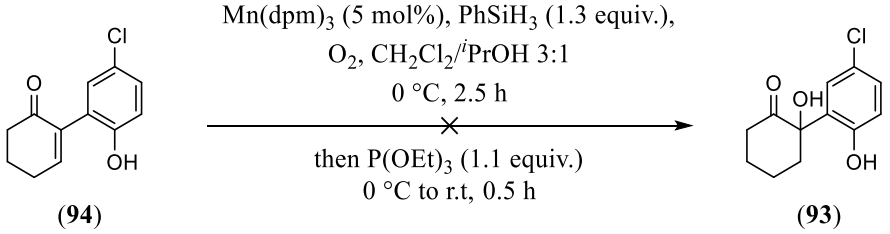
(**84**) (**94**)

Equation 10. Suzuki reaction between (**84**) and (**97**) to form our third model compound (**94**).

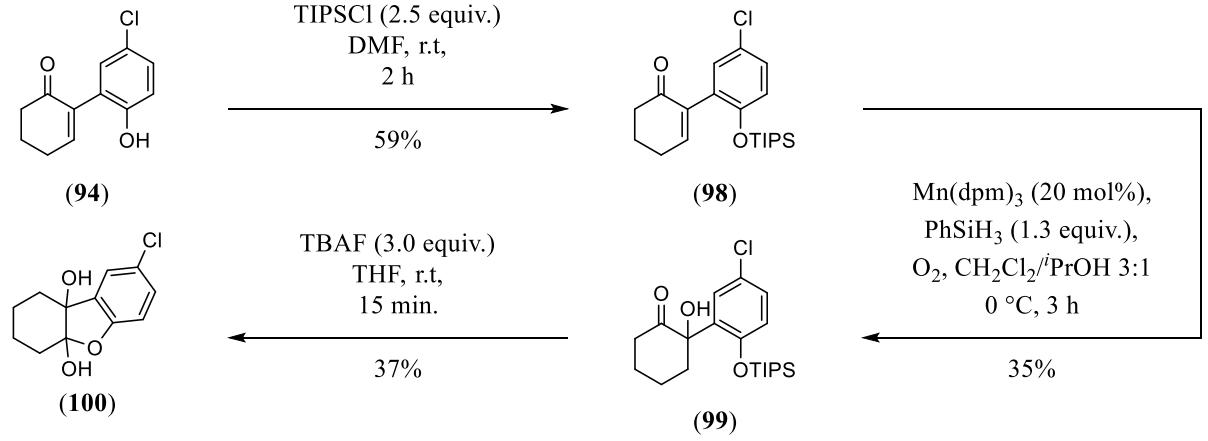
third model compound (**93**) in 35% yield. We noted that this reaction was more practical to carry out on a large scale (>10 mmol w.r.t (**94**)) as successive column chromatography runs were needed due to the partial coelution of impurities with our desired compound.

With our third model compound (**94**) in hand, it was subjected to the Mukaiyama hydration conditions which had been successful for our second model compound (**89**) (see Equations 8 and 11). Unfortunately, our attempts at this transformation were unsuccessful; many impurities were formed over the course of the reaction, and we were unable to isolate the desired alcohol (**93**). We believed that the free hydroxyl group on (**94**) was interfering with our

reaction as our reaction mixture would turn bright red, indicating the potential presence of phenoxide anion. In their original communication, Magnus *et al*. employed protecting group strategies on substrates containing free hydroxyl groups when carrying out analogous transformations; although unstated, these transformations are likely incompatible with free hydroxyl groups.[72]



Equation 11. Attempted Mukaiyama hydration of (**94**).



Scheme 21: Formation of lactol (**100**) from compound (**94**) *via* silyl ether (**98**) and alcohol (**99**).

With this in mind, we decided to protect the free hydroxyl group of (**94**) from which we could subsequently carry out the Mukaiyama hydration. We believed that a subsequent desilylative cyclisation could be carried out which would generate the desired [4.3.0] ring system. Our third model compound was reacted with triisopropylsilyl chloride (TIPSCl) and imidazole in DMF, generating silyl ether (**98**) in 59% yield (see Scheme 21). A subsequent Mukaiyama hydration generated alcohol (**99**) in 35% yield. Finally, a TBAF promoted desilylation, transformed alcohol (**99**) into lactol (**100**) in 37% yield. At this stage of the synthesis, we did not have enough of (**100**) to carry out the final cross-coupling to install the aryl-allyl group; repeating the synthesis of (**100**) seemed unnecessary since we had formed a model system whose core ring-system matched that of our initially intended compound, (**81**).

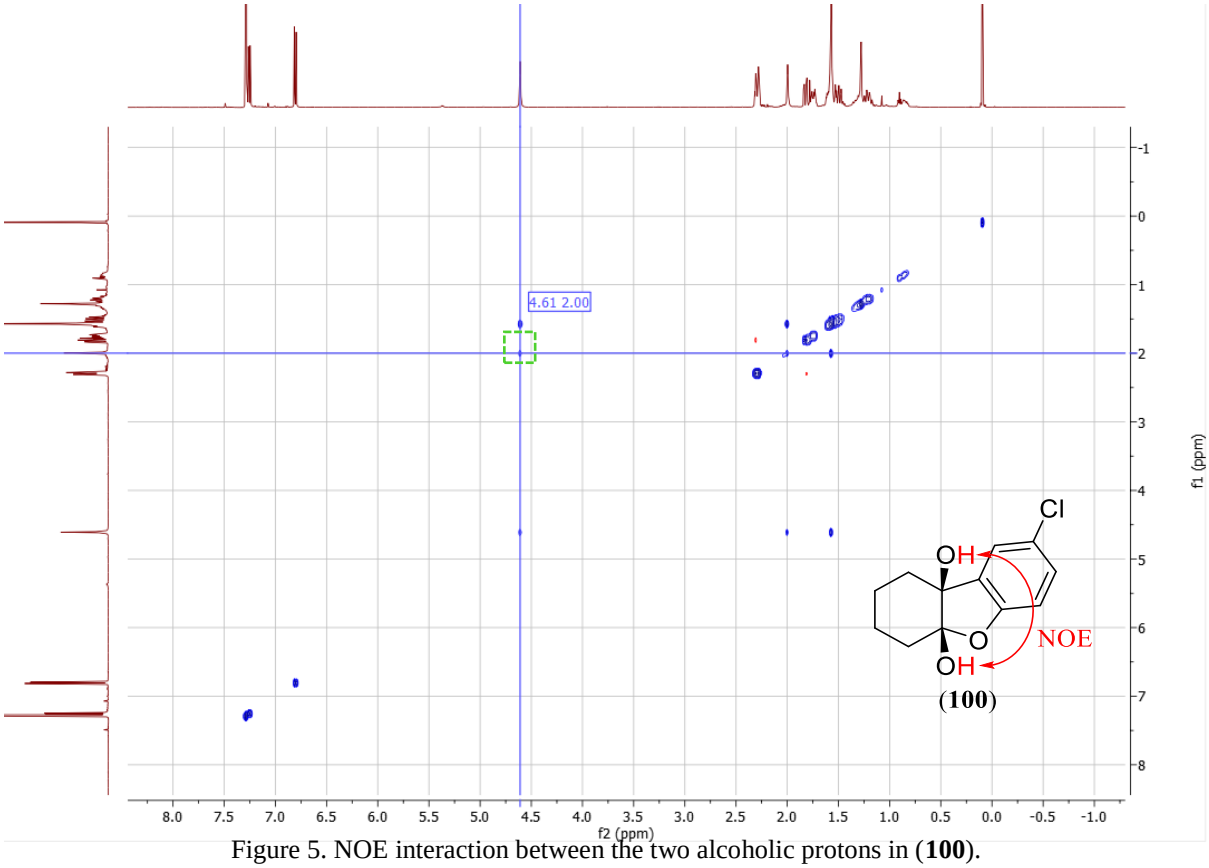


Figure 5. NOE interaction between the two alcoholic protons in (**100**).

C Atom Number	Type	*Syn* Isomer Computational (ppm)	*Anti* Isomer Computational (ppm)	Experimental (ppm)	*Syn* |σ exp - σ comp| (ppm)	*Anti* |σ exp - σ comp| (ppm)
1	Cq	79.7	80.8	77.3	2.4	3.5
2	CH_2	30.9	27.7	32.0	1.1	4.3
3	CH_2	22.3	19.8	21.8	0.5	2.0
4	CH_2	21.8	22.2	22.3	0.5	0.1
5	CH_2	34.3	29.1	34.3	0.0	5.2
6	Cq	114.0	113.9	111.0	3.0	2.9
7	Cq	157.8	157.7	156.3	1.5	1.4
8	Cq	123.9	125.5	126.0	2.1	0.5
9	CH	112.5	112.9	112.9	0.4	0.0
10	Cq	131.5	135.6	132.4	0.9	3.2
11	CH	125.2	125.6	123.7	1.5	1.9
12	CH	131.9	130.5	131.1	0.8	0.6
				RMSE	**1.5**	**2.7**

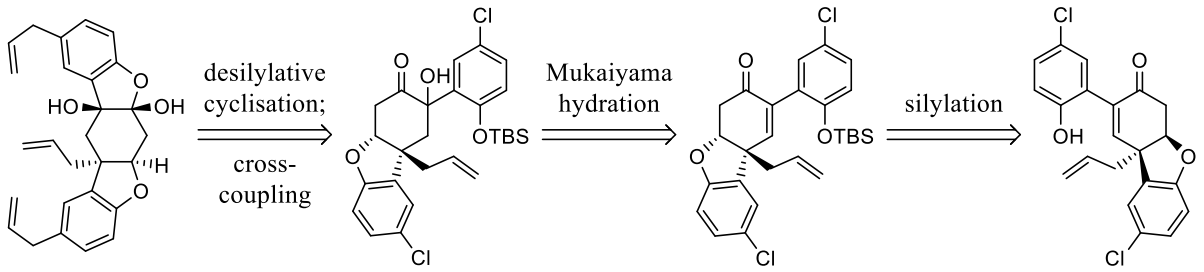
Table 7. ^{13}C NMR spectroscopic comparison of experimental and computationally obtained shifts of the *anti* and *syn* diastereomers of lactol (**100**). The RMSE for each comparison has been displayed below and is highlighted.

We determined that lactol (**100**) existed as its *syn* diastereomer from an NOE interaction of the two alcoholic protons (see Figure 5). The ^{13}C NMR spectrum of the *anti* and *syn* diastereomers of lactol (**100**) have been predicted computationally and the predicted ^{13}C peaks for the *anti* and *syn* diastereomer have been compared to our experimentally obtained data; from this the root mean squared error (RMSE) for each comparison has been calculated (see Table 7). We observed a lower RMSE for the *syn* |σ exp - σ comp| dataset (1.5 ppm) than for the *anti* |σ exp - σ comp| dataset (2.7 ppm). This is in accordance with the NOE interaction discussed previously, which confirms that lactol (**100**) was obtained as its *syn* diastereomer.

4.0 Conclusion and Future Work

In conclusion, we have explored a synthetic route towards simonsol A. The optimisation of a challenging double Suzuki cross-coupling was developed. The high throughput achieved in this reaction allowed for the trialling of several unsuccessful catalytic methods to try and synthesise triaryl (**73**). Studies towards the Lewis acid catalysed rearrangement of (**74**) proved that the Claisen rearrangement of (**74**) was not possible. A secondary reaction which outcompeted the Claisen rearrangement led to the formation of (**80**). The diastereotopicity observed in (**80**) was reasoned due to the restricted rotation about one of the biaryl bonds. The rotational barrier about the stereogenic axis and its half-life were calculated to be 28 kcal•mol^{-1} and 1 year and 81 days respectively. The structure of (**80**) was confirmed by X-ray crystal structure analysis.

Following this, a model system containing a dihydroxyl-cyclohexylbenzofuran core was synthesised. We faced difficulty attempting the Mukaiyama hydration on substrates containing aryl-allyl or free hydroxyl groups. In these reactions, unwanted species were isolated, and no desired products were formed. By removing any aryl-allyl groups and protecting any free hydroxyl groups, silyl ether (**98**) was converted into lactol (**100**) containing the desired core system. An NOE signal in the $^{1}HNMR$ spectrum of lactol (**100**) showed that the relative stereochemistry of the two hydroxyl groups was *syn*. This observation was consistent with computational investigations carried out for the *syn* and *anti* isomers of (**100**).



(**38**) (**103**) (**102**) (**101**)

Scheme 22: Proposed steps from (**101**) to simonol B (**38**).

In carrying on this project towards the original goal of synthesising simonol B (**38**) from simonsol F (**43**), an analogue of (**43**) should be synthesised which incorporates the lessons learned herein. Analogue (**101**) should be prepared using similar methodologies used in the total synthesis of simonsol F. Silylation of the free hydroxyl group in (**101**) will provide key intermediate (**102**) which can undergo the Mukaiyama hydration. We predict that the allyl group in (**102**) will not interfere with the Mukaiyama hydration since it is not conjugated. Following this, a desilylative cyclisation should deliver simonol B (see Scheme 22).

5.0 Supporting Information

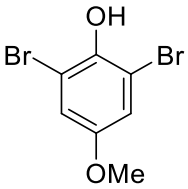
5.1 General Details

Unless otherwise stated, all reactions were carried out under an atmosphere of argon in conventional glassware. Degassing was achieved by purging solutions for *ca*. 5 minutes under a constant stream of nitrogen. Glassware used in the presence of moisture sensitive reagents or reactions that required anhydrous conditions was flame-dried under vacuum and cooled under a stream of nitrogen before use. Cooling to 0 °C was achieved using an ice-water bath. Cooling between -18 to -20 °C was achieved using an ice-salt bath (3:1 w/w respectively). For cooling at -20 °C for extended periods, samples were put in a freezer set to -20 °C. Temperatures below -20 °C was achieved using dry-ice-acetone mixtures. All water was deionised before use. Commercially available solvents and reagents were used as supplied. Solvents were dried using 3Å molecular sieves or fresh sodium wire. Room temperature varied between 15 °C and 25 °C. Analytical TLC was performed on Merck aluminium-backed silica gel 60 F_{254} plates. Developed TLC plates were visualised by irradiation with UV light (254 nm), staining with $KMnO_4$ solution when required. Column chromatography was carried out using Fluorochem silica gel 60 Å, 40-63 μ. Preparative TLC was performed on Analtech preparative TLC Plates. Melting points were measured using a Sigma Aldrich Stuart SMP3. Fourier transform infrared spectrometry (FT-IR) were obtained neat on a Bruker ALPHA FTIR spectrometer outfitted with an attenuated total reflection (ATR) attachment. High resolution mass spectrometry (HRMS) were acquired on a Bruker MicrOTOF II with electron spray ionisation and a time of flight detector (ESI-TOF). HRMS data were quoted to four decimal place (0.1 mDa). Nuclear magnetic resonance (NMR) spectra were obtained at 298 K on Bruker Avance III spectrometers operating at nominal ^{1}H frequencies of 400 and 500 MHz. Chemical shifts (δ) are given in ppm and are referenced to residual solvent signals: ($CDCl_3$ is referenced at δ 7.26 and 77.16 for ^{1}H and ^{13}C NMR respectively and C_6D_6 is referenced at δ 3.31 and 49.00 for ^{1}H and ^{13}C NMR respectively. ^{11}B NMR spectra were referenced through the solvent lock (2H) signal according to the IUPAC recommended secondary referencing method and according to Bruker protocols. Coupling constants (J) are given in Hz. $^{1}HNMR$ spectroscopic signals are designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, td = triplet of doublets, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublets of doublets, ddt = doublet of doublet of triplets, m=multiplet. Labelling of structures in the experimental sections is to highlight the position of H atoms for

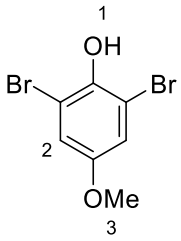
their assignment within their respective structures; 2D NMR spectroscopic techniques COSY, HSQC, HMBC and NOESY have been used to help assign H atoms within their structures. Crystal structure data was collected as follows. A single crystal was selected and mounted using Fomblin® (YR-1800 perfluoropolyether oil) on a polymer-tipped MiTeGen MicroMountTM and cooled rapidly to 120 K in a stream of cold N_2 using an Oxford Cryosystems open flow cryostat.[74] Single crystal X-ray diffraction data were collected on an Oxford Diffraction GV1000 (AtlasS2 CCD area detector, mirror-monochromated Cu-Kα radiation source; λ = 1.54184 Å, ω scans). Cell parameters were refined from the observed positions of all strong reflections and absorption corrections were applied using a Gaussian numerical method with beam profile correction (CrysAlisPro).[75] The structure was solved within Olex2 by dual space iterative methods (SHELXT) and all non-hydrogen atoms refined by full-matrix least-squares on all unique F2 values with anisotropic displacement parameters (SHELXL).[76,77] Hydrogen atoms were refined with constrained geometries and riding thermal parameters. Structures were checked with checkCIF.[78,79]

5.2 Experimental Procedures

2,6-Dibromo-4-methoxyphenol: (77)[80]

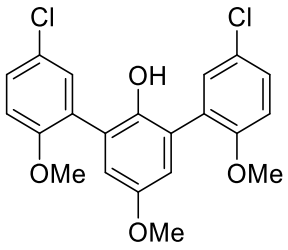


To a solution of 4-methoxyphenol (2.00 g, 16.1 mmol) in CH_2Cl_2 (14 mL) was added $BTMABr_3$ (13.8 g, 35.4 mmol, 2.20 equiv.) in CH_2Cl_2 (100 mL) and MeOH (40 mL) and the reaction mixture was stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The resulting mixture was triturated with acetone (50 mL) and filtered. The filtrate was concentrated *in vacuo* to give a brown oil. The oil was dissolved in MeOH (10 mL) and the organics were precipitated with H_2O (40 mL). The mixture was heated until boiling and the precipitate was recrystallised to give the title compound as clear colourless needles/grey crystals (3.72 g, 82%).

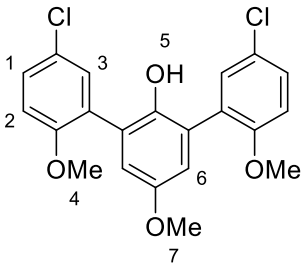


R_f (EtOAc/pentane, 1:4): 0.71. **IR** (cm^{-1}) ν_{max}: 3361, 3085, 3011, 2986, 2938, 2836, 1681, 1601, 1562, 1473, 1438, 1340, 1277, 1252. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.03 (s, 2H, H-2), 5.49 (s, 1H, H-1), 3.75 (s, 3H, H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 153.8 (Cq), 143.9 (Cq), 118.0, 109.8, 56.3 (CH_3). **HRMS** (ESI^+): $C_7H_6{}^{79}Br_2O_2$ $[M+Na]^+$ m/z calcd 302.8627; found 302.8634. **mp**: 81-82 °C (literature mp: 83-84 °C).[81]

5,5''-Dichloro-2,2'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-ol: (75)[54,55]

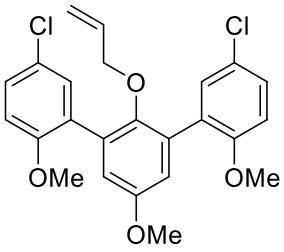


To a suspension of dibromophenol (**77**) (1.34 g, 4.76 mmol) and 5-chloro-2-methoxyphenylboronic acid (2.67 g, 14.3 mmol, 3.00 equiv.) in H_2O (47 mL) was added TBAF•$3H_2O$ (12.0 g, 38.1 mmol, 8.00 equiv.) and the mixture was sparged with argon for 5 minutes at room temperature. To the mixture was added Pd/C (50% wet, 25.3 mg, 239 μmol, 5 mol%) and the mixture was sparged for a further 5 minutes. The reaction mixture was heated at reflux for 13 hours and subsequently was cooled back to room temperature. The resulting suspension was acidified with HCl (50 mL of a 1.0 M solution), and the aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a viscous brown oil. Purification by graduated flash column chromatography (EtOAc/pentane 1:9 to 1:3) gave the title compound as an orange solid (877 mg, 45%).

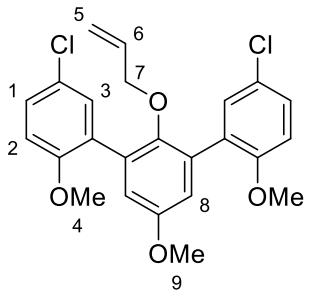


R_f (EtOAc/pentane, 1:4): 0.24. **IR** (cm^{-1}) ν_{max}: 3394, 3000, 2939, 2838, 1666, 1593, 1489, 1460, 1437, 1391, 1331, 1285, 1260, 1239. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 2.7 Hz, 2H, H-3), 7.32 (dd, *J* = 8.8, 2.7 Hz, 2H, H-1), 6.94 (d, *J* = 8.8 Hz, 2H, H-2), 6.84 (s, 2H, H-6), 5.94 (s, 1H, H-5), 3.84 (s, 6H, H-4), 3.81 (s, 3H, H-7). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 155.0 (2 x Cq), 153.5 (Cq), 145.2 (Cq), 131.9 (2 x CH), 129.5 (2 x Cq), 128.8 (2 x CH), 127.2 (2 x Cq), 126.3 (2 x Cq), 116.6 (2 x CH), 112.7 (2 x CH), 56.5 (2 x CH_3), 56.0 (CH_3). **HRMS** (ESI^+): $C_{21}H_{18}{}^{35}Cl_2O_4$ $[M+H]^+$ m/z calcd 405.0655; found 405.0655.

2'-(Allyloxy)-5,5''-dichloro-2,2'',5'-trimethoxy-1,1':3',1''-terphenyl: (74)[54,55]

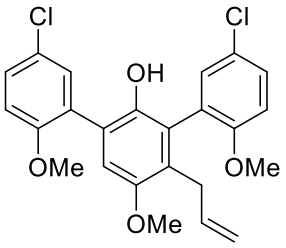


To a solution of triaryl (**75**) (877 mg, 2.16 mmol) in acetone (11 mL) was added allyl bromide (374 µL, 4.33 mmol, 2.00 equiv.) and K_2CO_3 (598 mg, 4.33 mmol, 2.00 equiv.) and the reaction mixture was heated at reflux for 13 hours. The reaction mixture was cooled to room temperature, then quenched with MeOH (20 mL) and extracted with EtOAc (20 mL x 3). The combined organics were washed with H_2O (60 mL), brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Purification by graduated flash chromatography (EtOAc/pentane 1:19 to 1:4) gave the title compound as a pale-yellow oil (610 mg, 62%).

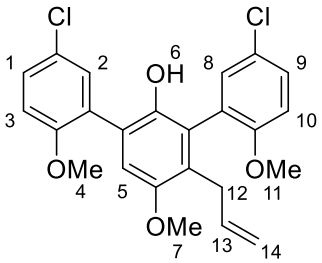


R_f (EtOAc/pentane, 1:4): 0.53. **IR** (cm^{-1}) ν_{max}: 3078, 2938, 2836, 1736, 1600, 1566, 1490, 1459, 1434, 1399, 1372, 1285, 1242, 1199. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 2.7 Hz, 2H, H-3), 7.28 (dd, *J* = 8.7, 2.7 Hz, 2H, H-1), 6.89 (d, *J* = 8.7 Hz, 2H, H-2) , 6.81 (s, 2H, H-8), 5.37 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H, H-6), 4.83 (ddd, *J* = 10.5, 1.7, 1.2 Hz, 1H, H-5), 4.78 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1H, H-5), 3.80 (s, 3H, H-9), 3.79 (s, 6H, H-4), 3.76 (dt, *J* = 5.6, 1.4 Hz, 2H, H-7). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 155.8 (2 x Cq), 154.7 (Cq), 148.7 (Cq), 134.0 (CH), 131.9 (2 x Cq), 131.4 (2 x CH), 129.5 (2 x Cq), 128.5 (2 x CH), 125.2 (2 x Cq), 116.5 (CH_2), 116.3 (2 x CH), 112.3 (2 x CH), 74.3 (CH_2), 56.1 (2 x CH_3), 55.7 (CH_3). **HRMS** (ESI^+): $C_{24}H_{22}{}^{35}Cl_2O_4$ $[M+H]^+$ m/z calcd 445.0968; found 445.0963.

4'-Allyl-5,5''-dichloro-2,2'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-ol: (80)



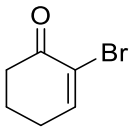
To a flame dried microwave vial was added a solution of triaryl (**74**) (44.5 mg, 0.10 mmol) in dry CH_2Cl_2 (1 mL). The solution was cooled to -20 °C and BCl_3 (200 µL, 0.20 mmol of a 1.00 M solution in hexanes, 2.00 equiv.) was added. The reaction mixture was stirred at -20 °C for 2 hours and then quenched with $NaHCO_3$ (1 mL of a saturated aqueous solution). The organics were extracted with EtOAc (5 mL x 3), and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale-yellow oil. Purification by graduated flash chromatography (EtOAc/pentane 1:19 to 1:4) gave the title compound as a colourless oil (8.02 mg, 18%).



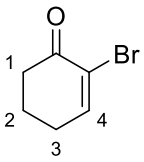
R_f (EtOAc/pentane, 1:4): 0.38. **IR** (cm^{-1}) ν_{max}: 3439, 3069, 2971, 2835, 2116, 1867, 1634, 1609, 1593, 1490, 1461, 1434, 1392, 1323. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 2.7 Hz, 1H, H-2), 7.34 (dd, *J* = 5.0, 2.7 Hz, 1H, H-1), 7.32 (dd, *J* = 5.0, 2.7 Hz, 1H, H-9), 7.21 (d, *J* = 2.7 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 1H, H-3, H-8), 6.93 (d, *J* = 8.9 Hz, 1H, H-10), 6.82 (s, 1H, H-5), 5.83 (dddd, *J* = 16.9, 10.1, 6.7, 6.0 Hz, 1H, H-13), 5.61 (s, 1H, H-6), 4.90 (ddd, *J* = 10.1, 1.5, 1.5 Hz, 1H, H-14), 4.77 (ddd, *J* = 17.1, 1.7 Hz, 1H, H-14), 3.87 (s, 3H, H-7), 3.86 (s, 3H, H-4), 3.75 (s, 3H, H-11), 3.30 (ddd, *J* = 14.4, 6.0, 1.7, Hz, 1H, H-12), 3.07 (ddd, *J* = 14.4, 6.7, 1.5, 1.5 Hz, 1H, H-12). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 156.0 (Cq), 154.5 (Cq), 151.8 (Cq), 144.9 (Cq), 136.5 (CH), 132.1 (CH), 131.7 (CH), 129.5 (Cq), 128.8 (CH), 128.7 (CH), 128.7 (Cq), 127.4 (Cq), 127.4 (Cq), 126.7 (Cq), 125.3 (Cq), 123.0 (Cq), 114.7 (CH_2), 112.8 (CH), 112.8 (CH), 112.3 (CH), 56.6 (CH_3), 56.2 (CH_3), 56.0 (CH_3), 32.4 (CH_2). **HRMS** (ESI^+): $C_{24}H_{22}{}^{35}Cl_2O_4$ $[M+H]^+$ m/z calcd 445.0968; found 445.0946.

A crystal of (**80**) was grown by slow evaporation from CH_2Cl_2/hexanes (19:1) (see Section 5.4).

2-Bromocyclohex-2-en-1-one: (84)[82]

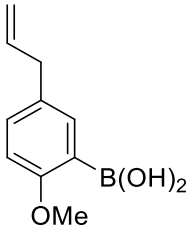


To a solution of cyclohex-2-en-1-one (4.00 mL, 41.3 mmol) in CH_2Cl_2 (82 mL) at 0 °C was added a solution of bromine (2.30 mL, 44.8 mmol, 1.08 equiv.) in CH_2Cl_2 (82 mL), dropwise, over 30 minutes. The reaction mixture was stirred for 5 minutes at 0 °C followed by the addition of Et_3N (8.00 mL, 57.4 mmol, 1.39 equiv.). The reaction mixture was stirred for a subsequent 5 minutes at 0 °C followed by the addition of HCl (60 mL of a 1.0 M solution). The organics were extracted with CH_2Cl_2 (2 x 200 mL) and the combined organics were washed with NaOH (2 x 100 mL of a 1.0 M aqueous solution), then $Na_2S_2O_3$ (2 x 60 mL of a saturated aqueous solution), then brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound as a light blue crystalline solid (5.60 g, 77%) which was carried through in subsequent steps without further purification.

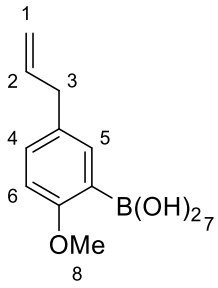


R_f (EtOAc/pentane, 1:4): 0.44. **IR** (cm^{-1}) ν_{max}: 3043, 2959, 2941, 2871, 2821, 1682, 1598, 1451, 1423, 1407, 1317, 1232, 1196, 1158. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.42 (t, *J* = 4.5 Hz, 1H, H-4), 2.66 - 2.61 (m, 2H, H-1), 2.47 - 2.44 (m, 2H, H-3), 2.11 - 2.03 (m, 2H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 191.4 (Cq), 151.3 (CH), 124.1 (Cq), 38.5 (CH_2), 28.5 (CH_2), 22.8 (CH_2). **HRMS** (ESI^+): $C_6H_7{}^{79}BrO$ $[M+Na]^+$ m/z calcd 196.9572; found 196.9576.

(5-Allyl-2-methoxyphenyl)boronic acid: (45)[32,38]

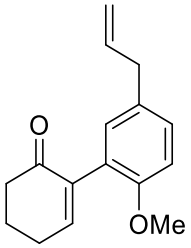


To a solution of 4-allylanisole (10.4 g, 70.0 mmol) in dry THF (220 mL) under argon at -78 °C was added TMEDA (10.5 mL, 70.0 mmol, 1.00 equiv.). To the mixture was added *s*-BuLi (50.0 mL, 70.0 mmol of a 1.40 M solution in hexanes, 1.00 equiv.), dropwise, over 30 minutes, and the mixture was stirred for 1 hour at -78 °C. The reaction mixture was warmed to room temperature, trimethyl borate (7.80 mL, 70.0 mmol, 1.00 equiv.) was added and the reaction mixture was stirred for 13 hours at room temperature. 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 (300 mL), washed with brine (3 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Purification by graduated flash column chromatography (EtOAc/pentane 1:9 to 1:3) gave the title compound as a yellow oil. Subsequent trituration with pentane gave the title compound as a colourless powder (4.48 g, 33%).

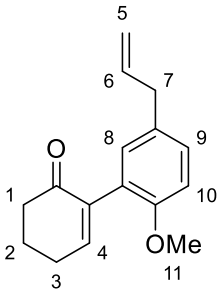


R_f (EtOAc/pentane, 1:4): 0.31. **IR** (cm^{-1}) ν_{max}: 3346, 3079, 3006, 2972, 2941, 2912, 2836, 1640, 1606, 1581, 1511, 1490, 1469, 1455. **^{1}H NMR** (500 MHz, C_6D_6) δ: 8.09 (d, *J* = 2.5 Hz, 1H, H-5), 7.06 (dd, *J* = 8.4, 2.5 Hz, 1H, H-4), 6.69 (s, 2H, H-7), 6.38 (d, *J* = 8.4 Hz, 1H, H-6), 5.87 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1H, H-2), 5.00 - 4.95 (m, 2H, H-1), 3.18 (dd, *J* = 6.6, 1.5 Hz, 2H, H-3), 3.01 (s, 3H, H-8). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 163.2 (Cq), 137.8 (CH), 137.0 (CH), 133.0 (CH), 132.7 (Cq), 115.8 (CH_2), 110.2 (CH), 55.7 (CH_3), 39.4 (CH_2). **^{11}B NMR** (128 MHz, $CDCl_3$) δ: 29.2. **HRMS** (ESI^+): $C_{10}H_{13}{}^{11}BO_3$ $[M+Na]^+$ m/z calcd 215.0850; found 215.0851. **mp**: 74-76 °C (literature mp: 77-79 °C).[32]

5'-Allyl-2'-methoxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one: (83)[38]

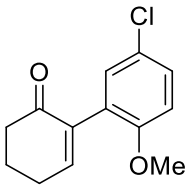


To a solution of bromo enone (**84**) (215 mg, 1.23 mmol) and boronic acid (**45**) (356 mg, 1.85 mmol, 1.50 equiv.) in PhMe (9.7 mL) and EtOH (4.5 mL) was added Na_2CO_3 (4.50 mL of 2.0 M solution, 9.00 mmol, 7.30 equiv.) and the mixture was sparged with argon for 5 minutes at room temperature. To the mixture was added $Pd(PPh_3)_4$ (143 mg, 1.23 μmol, 10 mol%) and the mixture was sparged for a further 5 minutes. The reaction mixture was heated to 90 °C for 1.5 hours and then was cooled back to room temperature. The organics were diluted with Et_2O (20 mL) and washed with HCl (2 x 10 mL of a 1.0 M solution), then brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a dark brown oil. Purification by graduated flash column chromatography (EtOAc/pentane 1:19 to 1:4) gave the title compound as a yellow oil (220 mg, 74%).

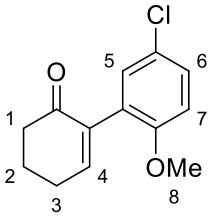


R_f (EtOAc/pentane, 1:4): 0.29. **IR** (cm^{-1}) ν_{max}: 3017, 2937, 2868, 2834, 1679, 1603, 1496, 1463, 1441, 1354, 1296, 1241, 1174, 1155. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.10 (dd, *J* = 8.4, 2.3 Hz, 1H, H-9), 6.89 (t, *J* = 4.2 Hz, 1H, H-4), 6.87 (d, *J* = 2.3 Hz, 1H, H-8), 6.82 (d, *J* = 8.4 Hz, 1H, H-10), 5.95 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, H-6), 5.10 - 5.02 (m, 2H, H-5), 3.32 (dd, *J* = 6.8, 1.5 Hz, 1H, H-7), 2.61 - 2.56 (m, 2H, H-1), 2.51 (td, *J* = 6.0, 4.1 Hz, 2H, H-3), 2.16 - 2.09 (m, 2H, H-2). **^{13}C NMR** (126 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), 23.2 (CH_2). **HRMS** (ESI^+): $C_{16}H_{18}O_2$ $[M+H]^+$ m/z calcd 243.1380; found 243.1376.

5'-Chloro-2'-methoxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one: (89)

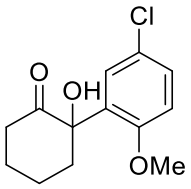


To a solution of bromo enone (**84**) (323 mg, 1.85 mmol) and boronic acid (**76**) (516 mg, 2.77 mmol, 1.50 equiv.) in PhMe (15 mL) and EtOH (7 mL) was added Na_2CO_3 (6.75 mL of 2.0 M solution, 13.5 mmol, 7.30 equiv.) and the mixture was sparged with argon for 5 minutes at room temperature. To the mixture was added $Pd(PPh_3)_4$ (215 mg, 1.85 µmol, 10 mol%) and the mixture was sparged for a further 5 minutes. The reaction mixture was heated to 90 °C for 1.5 hours and then was cooled back to room temperature. The organics were diluted with Et_2O (30 mL) and washed with HCl (2 x 15 mL of a 1.0 M solution), then brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a dark brown oil. Purification by graduated flash column chromatography (EtOAc/pentane 1:19 to 1:4) gave the title compound as a dark orange oil (220 mg, 50%).

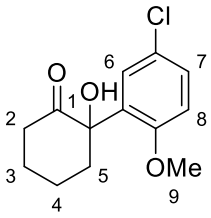


R_f (EtOAc/pentane, 1:4): 0.24. **IR** (cm^{-1}) ν_{max}: 3005, 2939, 2867, 2835, 1678, 1593, 1487, 1462, 1441, 1401, 1351, 1292, 1262, 1240. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.23 (dd, *J* = 8.8, 2.7 Hz, 1H, H-6), 7.03 (d, *J* = 2.7 Hz, 1H, H-5), 6.90 (t, *J* = 4.2 Hz, 1H, H-4), 6.80 (d, *J* = 8.8 Hz, 1H, H-7), 3.73 (s, 3H, H-8), 2.60 - 2.55 (m, 2H, H-1), 2.51 (td, *J* = 6.1, 4.1 Hz, 2H, H-3), 2.16 - 2.08 (m, 2H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 197.2 (Cq), 155.9 (Cq), 148.7 (CH), 138.2 (Cq), 130.5 (CH), 128.9 (CH), 128.4 Cq), 125.4 (Cq), 112.2 (CH), 56.1 (CH_3), 38.7 (CH_2), 26.5 (CH_2), 23.1 (CH_2). **HRMS** (ESI^+): $C_{13}H_{14}{}^{35}ClO_2$ $[M+H]^+$ m/z calcd 237.0677; found 237.0675.

2-(5-Chloro-2-methoxyphenyl)-2-hydroxycyclohexan-1-one: (88)

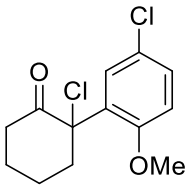


To a solution of compound (**89**) (569 mg, 2.40 mmol) in CH_2Cl_2 (9 mL) and $^{i}PrOH$ (3 mL) was added $Mn(dpm)_3$ (147 mg, 120 μmol, 5 mol%). The mixture was cooled to 0 °C, sparged with O_2 for 5 minutes, and then $PhSiH_3$ (385 μL, 3.13 mmol, 1.30 equiv.) was added. The mixture was stirred for 2.5 hours at 0 °C. To the mixture was added $P(OEt)_3$ (454 μL, 2.64 mmol, 1.10 equiv.) and the mixture was stirred for a subsequent 0.5 hours over which time the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with $Na_2S_2O_3$ (5 mL of a saturated aqueous solution). The organics were extracted with CH_2Cl_2 (5 mL x 3) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale yellow oil. Purification by graduated flash column chromatography (EtOAc/pentane 1:19 to 1:4) gave an inseparable mixture of the title compound and starting material (**90**) in a 1.67:1 ratio as determined by ^{1}H NMR spectroscopy. This mixture was resubjected to the reaction conditions - identical to those shown above - affording the title compound as a colourless oil (587 mg, 96%).

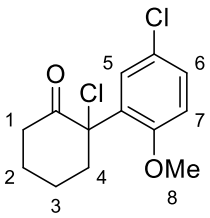


R_f (EtOAc/pentane, 1:4): 0.24. **IR** (cm^{-1}) ν_{max}: 3432, 2922, 2850, 1717, 1595, 1488, 1462, 1408, 1369, 1336, 1287, 1245, 1180, 1115. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 2.6 Hz, 1H, H-6), 7.28 (dd, *J* = 8.7, 2.6 Hz, 1H, H-7), 6.82 (d, *J* = 8.7 Hz, 1H, H-8), 4.54 (s, 1H, H-1), 3.69 (s, 3H, H-9), 2.86 - 2.80 (m, 1H, H-5), 2.55 - 2.49 (m, 1H, H-2), 2.38 - 2.28 (m, 1H, H-2), 2.04 - 1.94 (m, 1H, H-3), 1.82 - 1.57 (m, 4H, H-3, H-4 and H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 211.8 (Cq), 155.7 (Cq), 130.6 (Cq), 129.6 (CH), 127.8 (CH), 126.4 (Cq), 113.4 (CH), 78.3 (Cq), 55.9 (CH_3), 40.7 (CH_2), 38.3 (CH_2), 29.3 (CH_2), 22.8 (CH_2). **HRMS** (ESI^{+}): $C_{13}H_{15}{}^{35}ClO_3$ $[M+Na]^{+}$ m/z calcd 277.0602; found 277.0597.

2-Chloro-2-(5-chloro-2-methoxyphenyl)cyclohexan-1-one: (90)

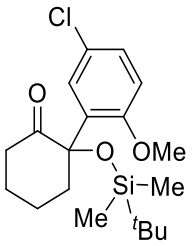


To a flame dried microwave vial was added alcohol (**88**) (40.9 mg, 161 μmol) as a solution in dry CH_2Cl_2 (0.80 mL). The solution was cooled to 0 °C, then BCl_3 (240 μL, 0.24 mmol, of a 1.00 M solution in hexanes, 1.50 equiv.) was added, and the resulting mixture was stirred at 0 °C for 5.5 hours. The reaction mixture was injected into a vigorously stirring solution of CH_3CN/H_2O (2.5 mL, 49:1 respectively) at 0 °C and the mixture was concentrated *in vacuo*. To the resulting residue was added H_2O (5 mL) and the organics were extracted with CH_2Cl_2 (5 mL x 3). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the title compound as an orange oil (34.8 mg, 79%).

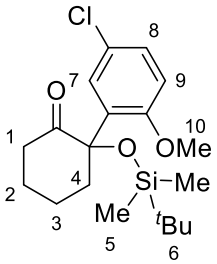


R_f (EtOAc/pentane, 1:4): 0.40. **IR** (cm^{-1}) ν_{max}: 2941, 2867, 1726, 1596, 1485, 1463, 1404, 1351, 1336, 1290, 1247, 1193, 1179, 1128. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 2.6 Hz, 1H, H-5), 7.29 (dd, *J* = 8.7, 2.6 Hz, 1H, H-6), 6.84 (d, *J* = 8.7 Hz, 1H, H-7), 3.75 (s, 3H, H-8), 2.83 - 2.73 (m, 2H, H-1 and H-4), 2.50 (dddd, *J* = 15.4, 6.0, 4.7, 1.2 Hz, 1H, H-1), 2.21 (dddd, *J* = 14.8, 5.7, 3.5, 1.9 Hz, 1H, H-4), 2.03 - 1.74 (m, 4H, H-2 and H-3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 201.8 (Cq), 154.2 (Cq), 131.1 (Cq), 129.6 (CH), 128.2 (CH), 126.4 (Cq), 113.3 (CH), 74.5 (Cq), 56.1 (CH_3), 41.9 (CH_2), 37.8 (CH_2), 26.0 (CH_2), 22.1 (CH_2). **HRMS** (ESI^+): $C_{13}H_{14}{}^{35}Cl_2O_3$ $[M+H]^+$ m/z calcd 273.0444; found 273.0446.

2-((Tert-butyldimethylsilyl)oxy)-2-(5-chloro-2-methoxyphenyl)cyclohexan-1-one: (91)

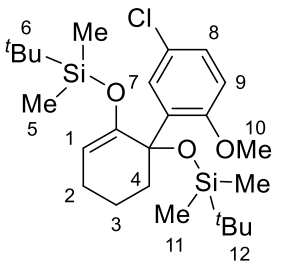


To a solution of alcohol (**88**) (153 mg, 0.60 mmol) in dry DMF (3 mL) was added imidazole (102 mg, 1.50 mmol, 2.50 equiv.) and the resulting mixture was sparged with argon for 5 minutes. Tert-butyldimethylsilyl trifluoromethanesulfonate (276 µL, 1.20 mmol, 2.00 equiv.) was added and the mixture was stirred at room temperature for 72 hours. Following this time, TLC analysis showed the presence of unreacted starting material. Thus, a further 1.5 equivalents of tert-butyldimethylsilyl trifluoromethanesulfonate were added in 3 separate instances over the course of 48 hours until TLC showed the complete consumption of the starting material. The reaction was quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution), and the organics were extracted with Et_2O (20 mL x 3). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by graduated flash chromatography (EtOAc/pentane 1:99 to 1:9) gave the title compound as a colourless oil (108 mg, 48%) and silyl enol ether (**92**) as a colourless oil (78.3 mg, 27%).



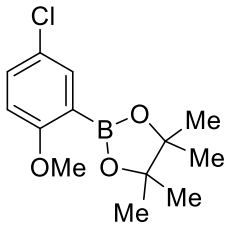
R_f (EtOAc/pentane, 1:5): 0.43. **IR** (cm^{-1}) ν_{max}: 2951, 2933, 2886, 2856, 1732, 1596, 1488, 1472, 1462, 1402, 1360, 1328, 1287, 1250. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 2.6 Hz, 1H, H-7), 7.25 (dd, *J* = 8.7, 2.6 Hz, 1H, H-8), 6.78 (d, *J* = 8.7 Hz, 1H, H-9), 3.69 (s, 3H, H-10), 2.58 - 2.43 (m, 1H, H-1 and H-4), 2.36 (ddd, *J* = 13.4, 9.6, 5.4 Hz, 1H, H-1), 1.94 - 1.72 (m, 4H, H-2, H-3 and H-4), 1.63 - 1.53 (m, 1H, H-3), 0.84 (s, 9H, H-6), -0.08 (s, 3H, H-5), -0.09 (s, 3H, H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 209.4 (Cq), 155.1 (Cq), 132.9 (Cq), 129.0 (CH), 127.7 (CH), 125.9 (Cq), 113.0 (CH), 80.9 (Cq), 55.5 (CH_3), 41.7 (CH_2), 39.5 (CH_2), 27.9 (CH_2), 26.0 (CH_3), 22.3 (CH_2), 18.7 (Cq), -3.0 (CH_3), -3.1 (CH_3). **HRMS** (ESI^+): $C_{19}H_{29}{}^{35}ClO_3Si$ $[M+Na]^+$ m/z calcd 391.1467; found 391.1464.

((5'-Chloro-2'-methoxy-5,6-dihydro-[1,1'-biphenyl]-1,2(4H)-diyl)bis(oxy))bis(tert-butyldimethylsilane): (92)

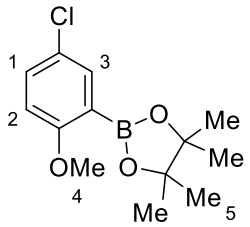


R_f (EtOAc/pentane, 1:5): 0.77. **IR** (cm^{-1}) ν_{max}: 2980, 2931, 2889, 2858, 1661, 1473, 1463, 1390, 1249, 1172, 1118, 1077, 1041, 1008. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 2.7 Hz, 1H, H-7), 7.11 (dd, *J* = 8.6, 2.8 Hz, 1H, H-8), 6.65 (d, *J* = 8.6 Hz, 1H, H-9), 4.80 (dd, *J* = 5.7, 2.6 Hz, 1H, H-1), 3.70 (s, 3H, H-10), 2.30 - 2.21 (m, 1H, H-4), 2.21 - 2.06 (m, 2H, H-2), 1.89 - 1.77 (m, 1H, H-3), 1.66 (ddd, *J* = 13.2, 3.3, 1.2 Hz, 1H, H-4), 1.62 - 1.54 (m, 1H, H-3), 0.99 (s, 9H, H-6 or H-12), 0.64 (s, 9H, H-6 or H-12), 0.16 (s, 3H, H-5 or H-11), 0.15 (s, 3H, H-5 or H-11), 0.09 (s, 3H, H-5 or H-11), -0.17 (s, 3H, H-5 or H-11). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 154.1 (Cq), 150.7 (Cq), 137.5 (Cq), 128.6 (CH), 126.9 (CH), 125.2 (Cq), 111.1 (CH), 105.4 (CH), 76.4 (Cq), 55.0 (CH_3), 38.1 (CH_2), 26.2 (CH_3), 25.8 (CH_3), 24.5 (CH_2), 19.2 (Cq), 18.9 (CH_2), 18.1 (Cq), -2.6 (CH_3), -3.3 (CH_3), -4.4 (CH_3), -5.4 (CH_3). **HRMS** (ESI^+): Expected mass not found upon both positive and negative ionisation.

2-(5-Chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: (96)[83]



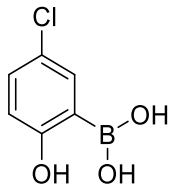
To a solution of 5-chloro-2-methoxy phenylboronic acid (**76**) (1.86 g, 10.0 mmol) in MeOH (30 mL) was added pinacol (3.55 g. 30.0 mmol, 3.00 equiv.) and the mixture was stirred at room temperature for 16 hours. Following this time, the reaction mixture was concentrated *in vacuo*. The organics were subsequently dissolved in Et_2O (20 mL) and were washed with H_2O (3 x 10 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a colourless oil. Purification by graduated flash column chromatography (pentane /EtOAc, 19:1 to 9:1) afforded the title compound a colourless oil (2.63 g, 98%).



R_f (EtOAc/pentane, 1:4): 0.63. **IR** (cm^{-1}) ν_{max}: 2980, 1594, 1571, 1485, 1463,1399, 1372, 1338, 1313, 1247, 1214, 1179. 1142. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 2.8 Hz, 1H, H-3), 7.29 (dd, *J* = 8.8, 2.8 Hz, 1H, H-1), 6.75 (d, *J* = 8.8 Hz, 1H, H-2), 3.77 (s, 3H H-4), 1.31 (s, 12H H-5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 162.7, 136.1, 132.0, 125.4, 112.0, 83.9, 75.1, 56.2, 24.9.* **^{11}B NMR** (128 MHz, $CDCl_3$) δ: 30.5. **HRMS** (ESI^+): $C_{13}H_{18}{}^{11}B^{35}ClO_3$ $[M+Na]^+$ m/z calcd 269.1110; found 269.1115.

*Ar(C)-B signal was not observed due to quadrupolar relaxation.

(5-Chloro-2-hydroxyphenyl)boronic acid: (97)



To a solution of boronic acid pinacol ester (**96**) (2.63 g, 9.79 mmol) in DCE (40 mL) was added BCl3•SMe2 (4.39 g, 24.5 mmol). The reaction mixture was heated at 80 °C for 16 hours and subsequently cooled to 0 °C. To the reaction mixture was added HCl (30 mL of a 1.0 M aqueous solution), the organics were extracted with EtOAc (3 x 25 mL) and the combined organics were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude grey solid. Subsequent trituration with pentane afforded the title compound as an off-white solid.

^{11}B NMR (128 MHz, DMSO-d_6) δ: 28.7.

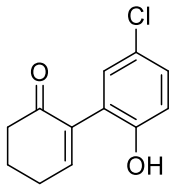
HRMS (ESI$^+$): $C_6H_6{}^{11}B^{35}ClO_3$ $[M+Na]^+$ m/z calcd 194.9991; found 194.9987.

Dimer:

HRMS (ESI$^+$): $C_{12}H_8{}^{11}B_2{}^{35}Cl_2O_4$ $[M-H]^-$ m/z calcd 306.9913; found 306.9916.

Since (**97**) was obtained as a mixture of monomer, dimer and (likely) higher order oligomers, further spectroscopic information was not able to be obtained. A yield % is also not provided.

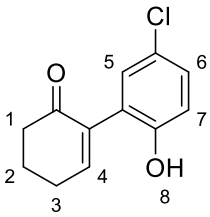
5'-Chloro-2'-hydroxy-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one: (94)



To a solution of bromo enone (**84**) (1.75 g, 10.0 mmol) and boronic acid (**97**)* (2.07 g, 12.0 mmol 1.20 equiv.) in PhMe (80 mL) and EtOH (40 mL) was added Na_2CO_3 (40.0 mL of 2.00 M solution, 80.0 mmol, 8.00 equiv.) and the mixture was sparged with argon for 5 minutes at room temperature. To the mixture was added $Pd(PPh_3)_4$ (1.16 g, 1.00 mmol, 10 mol%) and the mixture was sparged for a further 5 minutes. The reaction mixture was heated to 90 °C for 1.5 hours and then was cooled back to room temperature. The organics were diluted with Et_2O (150 mL) and washed with HCl (2 x 80 mL of a 1.0 M solution), then brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a dark brown oil. Purification by graduated flash column chromatography** (EtOAc/pentane 1:19 to 1:4) gave the title compound as a yellow oil (779 mg, 35%).

*Boronic acid (**97**) was assumed to be entirely in its monomeric form.

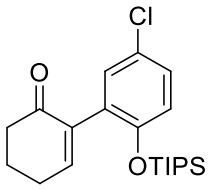
**Flash chromatography was carried out twice due to the partial coelution of the title compound and other impurities.



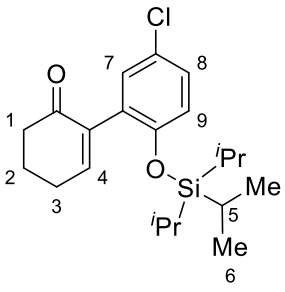
R_f (EtOAc/pentane, 1:4): 0.14. **IR** (cm^{-1}) ν_{max}: 3305, 2995, 2870, 1657, 1599, 1481, 1409, 1344, 1264, 1220, 1184, 1157, 1004, 996. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.81 (s, 1H, H-8), 7.21 - 7.19 (m, 2H, H-4 and H-6)***, 7.05 (d, *J* = 2.6 Hz, 1H, H-5), 6.90 (d, *J* = 8.6 Hz, 1H, H-7), 2.68 - 2.66 (m, 2H, H-1), 2.61 (td, *J* = 6.0, 4.3 Hz, 2H, H-3), 2.16 - 2.11 (m, 2H, H-2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 203.2 (Cq), 154.9 (CH), 152.8 (Cq), 139.0 (Cq), 130.0 (CH), 129.9 (CH), 127.0 (Cq), 125.7 (Cq), 120.2 (CH), 38.9 (CH_2), 27.1 (CH_2), 22.6 (CH_2). **HRMS** (ESI^+): $C_{12}H_{11}{}^{35}ClO_2$ $[M+H]^+$ m/z calcd 223.0520; found 223.0522.

***Overlapping triplet from H-4 (*J* = 4.3 Hz) and doublet of doublets from H-6 (*J* = 8.6, 2.6 Hz).

5'-Chloro-2'-((triisopropylsilyl)oxy)-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one: (98)

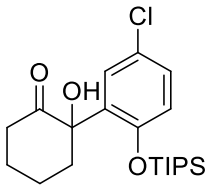


To a solution of compound (**94**) (42.4 mg, 191 µmol) in dry DMF (1 mL) was added imidazole (32.4 mg, 476 µmol, 2.50 equiv.) and the resulting mixture was sparged with argon for 5 minutes. Triisopropylsilyl chloride (61.1 µL, 286 µmol, 1.50 equiv.) was added and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with $NaHCO_3$ (3 mL of a saturated aqueous solution), and the organics were extracted with Et_2O (10 mL x 3). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative thin layer chromatography (EtOAc/pentane 1:9) gave the title compound as a colourless oil (42.6 mg, 59%).

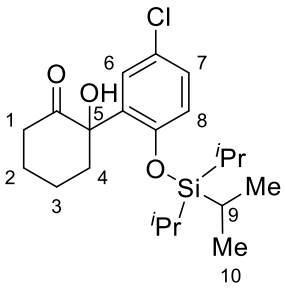


R_f (EtOAc/pentane, 1:5): 0.69. **IR** (cm^{-1}) ν_{max}: 2945, 2865, 2816, 2769, 1680, 1594, 1519, 1485, 1462, 1404, 1349, 1331, 1284, 1199. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.10 (dd, *J* = 8.7, 2.7 Hz, 1H, H-8), 7.02 (d, *J* = 2.7 Hz, 1H, H-7), 6.92 (t, *J* = 4.2 Hz, 1H, H-4), 6.72 (d, *J* = 8.7 Hz, 1H, H-7), 2.58 - 2.52 (m, 2H, H-1), 2.49 (td, *J* = 6.0, 4.1 Hz, 2H, H-3), 2.14 - 2.06 (m, 2H, H-2), 1.22 (hept, *J* = 7.4 Hz, 3H), 1.05 (d, *J* = 7.4 Hz, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 196.7 (Cq), 152.4 (Cq), 148.9 (CH), 138.5 (Cq), 130.9 (CH), 130.0 (Cq), 128.5 (CH), 125.2 (Cq), 119.2 (CH), 38.7 (CH_2), 26.4 (CH_2), 23.1 (CH_2), 18.1 (CH_3), 13.1 (CH). **HRMS** (ESI^+): $C_{21}H_{31}{}^{35}ClO_2Si$ $[M+H]^+$ m/z calcd 379.1855; found 379.1843.

2-(5-Chloro-2-((triisopropylsilyl)oxy)phenyl)-2-hydroxycyclohexan-1-one: (99)



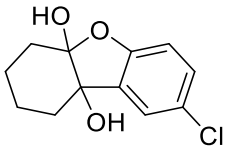
To a solution of compound (**98**) (42.8 mg, 113 µmol) in CH_2Cl_2 (0.80 mL) and ^{i}PrOH (0.20 mL) was added $Mn(dpm)_3$ (13.7 mg, 22.6 µmol, 20 mol%). The mixture was cooled to 0 °C, sparged with O_2 for 5 minutes, and then $PhSiH_3$ (20.9 µL, 169 µmol, 1.30 equiv.) was added. The mixture was stirred for 3 hours at 0 °C. The reaction mixture was quenched with $Na_2S_2O_3$ (5 mL of a saturated aqueous solution). The organics were extracted with CH_2Cl_2 (5 mL x 3) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale yellow oil. Purification by preparative thin layer chromatography (EtOAc/pentane 1:9) gave the title compound as a pale-yellow oil (15.9 mg, 35%).



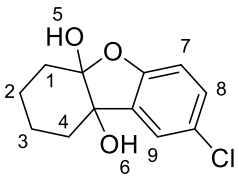
R_f (EtOAc/pentane, 1:5): 0.69. **IR** (cm^{-1}) ν_{max}: 3451, 2944, 2867, 1719, 1593, 1485, 1407, 1365, 1275, 1246, 1187, 1116, 1099, 1072. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 2.7 Hz, 1H, H-6), 7.16 (dd, *J* = 8.7, 2.6 Hz, 1H, H-7), 6.76 (d, *J* = 8.7 Hz, 1H, H-8), 4.62 (s, 1H, H-5), 2.87 - 2.80 (m, 1H, H-4), 2.62 - 2.54 (m, 1H, H-1), 2.45 - 2.38 (m, 1H, H-1), 2.06 - 1.97 (m, 1H, H-2), 1.84 - 1.60 (m, 4H, H-2, H-3 and H-4), 1.31 (hept, *J* = 7.6, 3H, H-9), 1.10 (d, *J* = 7.6 Hz, 3H, H-10)*, 1.07 (d, *J* = 7.5 Hz, 3H, H-10)*. **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 211.8 (Cq), 152.7 (Cq), 131.2 (Cq), 129.1 (CH), 128.2 (CH), 125.8 (Cq), 119.5 (CH), 78.5 (Cq), 41.3 (CH_2), 38.5 (CH_2), 29.7 (CH_2), 22.7 (CH_2), 17.9 (CH_3), 17.8 (CH_3), 13.2 (CH). **HRMS** (ESI^+): $C_{21}H_{33}{}^{35}ClO_3Si$ $[M+Na]^+$ m/z calcd 419.1780; found 419.1777.

*Two signals observed for H-10 due to diastereotopicity.

Syn-8-chloro-1,2,3,4-tetrahydrodibenzo[b,d]furan-4a,9b-diol: (100)



To a solution of compound (**99**) (15.9 mg, 40.0 μmol) in dry THF (0.50 mL) was added TBAF (120 μL, 120 μmol of a 1.00 M solution in THF, 3.00 equiv.) and the reaction was stirred at room temperature for 15 minutes. Following this time, an aliquot analysed by TLC and HRMS showed that the starting material had been completely consumed. The reaction mixture was allowed to stand at room temperature for 16 hours. Subsequently, the reaction mixture was washed with NH_4Cl (5 mL of a saturated aqueous solution) and the organics were extracted with EtOAc (5 mL x 3). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale-yellow oil. Purification by preparative thin layer chromatography (EtOAc/pentane 1:4) gave the title compound as a pale-yellow oil (3.56 mg, 37%)



R_f (EtOAc/pentane, 1:4): 0.29. **IR** (cm^{-1}) ν_{max}: 3655, 3414, 2980, 2931, 1712, 1609, 1463, 1382, 1354, 1290, 1255, 1189, 1143, 1096, 1070. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 2.4 Hz, 1H, H-9), 7.23 (dd, *J* = 8.5, 2.3 Hz, 1H, H-8), 6.78 (d, *J* = 8.5 Hz, 1H, H-7), 4.58 (s, 1H, H-5), 2.30 - 2.24 (m, 2H, H-1 and H-4)*, 1.97 (s, 1H, H-6), 1.83 - 1.68 (m, 2H, H-3 and H-4)*, 1.62 - 1.40 (m, 3H, H-1 and H-2)*, 1.24 - 1.10 (m, 1H, H-3)*. **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 156.6 (Cq), 132.7 (Cq), 131.4 (CH), 126.3 (Cq), 124.0 (CH), 113.2 (CH), 111.3 (Cq), 77.6 (Cq), 34.6 (CH_2), 32.3 (CH_2), 22.6 (CH_2), 22.1 (CH_2). **HRMS** (ESI^+): $C_{12}H_{13}{}^{35}ClO_3$ $[M+Na]^+$ m/z calcd 263.0445; found 263.0448.

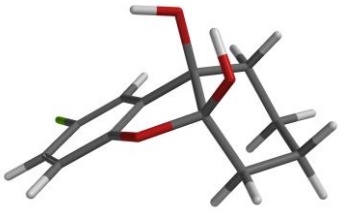
*Assignments made tentatively using 2D NMR data and aided by ^{13}C NMR predictions.

5.3 Computational Data[84]

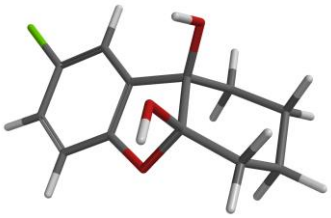
Part 1: Calculated ^{13}C NMR chemical shifts of model compound 100

Syn diastereoisomer

A molecular mechanics conformational search revealed two low energy conformers of the *syn* diastereoisomer (shown below), each of which adopts a different intramolecular hydrogen bonding arrangement.

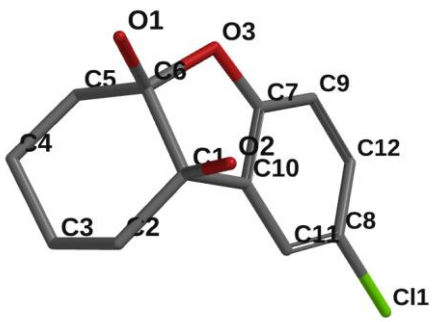


100a -722112.73 kcal/mol



100b -722110.83 kcal/mol

The equilibrium geometry of each conformer was then obtained using the ωB97X-D/6-31G* theoretical mode and ^{13}C NMR chemical shifts were obtained by Boltzmann weighting chemical shifts for both conformers that were calculated using ωB97X-V/6-311+G(2DF,2P)[6-311G*] single point calculations.



position	δ C	mult	δ H	(J in Hz)	HMBC(H→C)
1	79.7	C			...
2	30.9	CH_2	1.90	ddd (-18.4,12.3,3.4)	4, 6, 10
.			2.22	ddd (-18.4,4.3,3.4)	4, 6, 10
3	22.3	CH_2	1.67	m (-14.0,4.6,4.3,3.4)	1, 5
.			1.30	m (-14.0,12.3,12.0,3.4,2.8)	1, 5
4	21.8	CH_2	1.66	m (12.4,12.0,-3.7,3.5)	2, 6
.			1.48	m (4.6,4.2,-3.7,2.8)	2, 6
5	34.3	CH_2	2.35	ddd (-14.6,4.2,3.5)	1, 3
.			1.41	dd (-14.6,12.4)	1, 3
6	114.0	C			...
7	157.8	C			...
8	123.9	C			...
9	112.5	CH	6.70	d (7.0)	8, 10
10	131.5	C			...
11	125.2	CH	7.19	s	1, 7, 12
12	131.9	CH	7.17	d (7.0)	7, 11
Label	**δ**	**..**			
O1	268.6	xH	4.01	s	
O2	264.4	xH	0.60	s	
O3	173.3				...
Cl1	762.5				...

Anti diasteroisomer

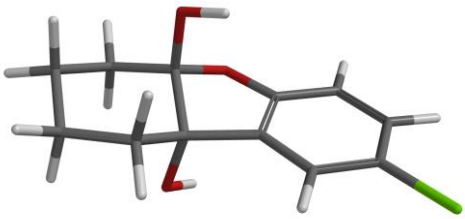
The same computational approach was used to obtain calculated ^{13}C chemical shifts for the *anti* diastereoisomer of **100**. In this case four low energy conformers shown below were found and the calculated chemical shifts were weighted based upon their relative energies.

100c -722103.64 kcal/mol

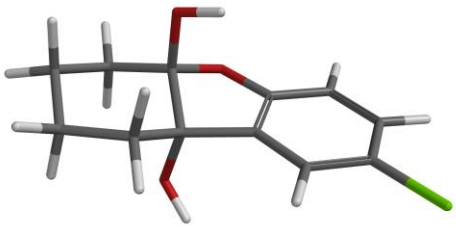
100d -722102.08 kcal/mol

100e -722102.17 kcal/mol

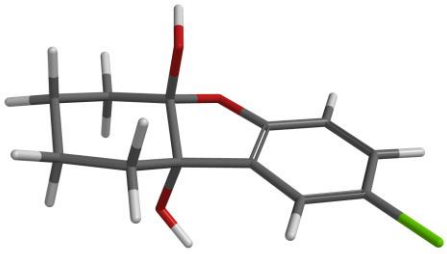
100f -722103.60 kcal/mol



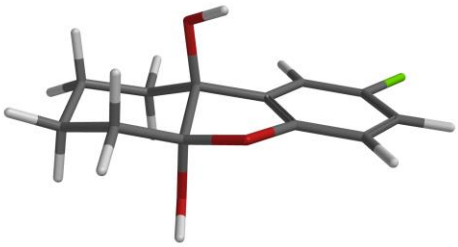
100c



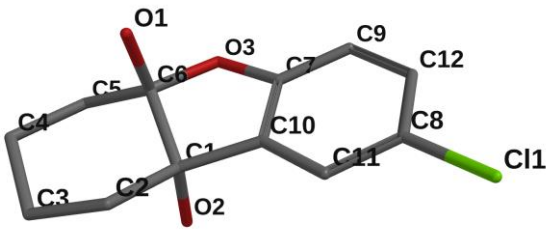
100d



100e



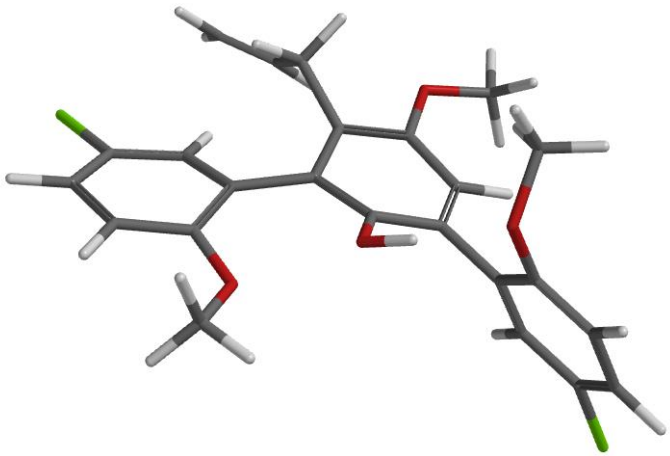
100f



position	δ_C	mult	δ_H	(J in Hz)	HMBC(H→C)
1	80.8	C			...
2	27.7	CH_2	2.14	dd (13.3,4.2)	4, 6, 10
.			2.14	dd (4.8,2.0)	4, 6, 10
3	19.8	CH_2	1.52	m (31.8,4.7,4.2,2.0,2.0)	1, 5
.			2.27	m (31.8,13.3,12.6,4.8,4.7)	1, 5
4	22.2	CH_2	2.03	m (13.5,12.6,11.8,4.9,4.7)	2, 6
.			1.65	m (11.8,4.7,4.1,2.0)	2, 6
5	29.1	CH_2	1.73	dd (9.7,4.9)	1, 3
.			2.48	ddd (13.5,9.7,4.1)	1, 3
6	113.9	C			...
7	157.7	C			...
8	125.5	C			...
9	112.9	CH	6.82	d (7.0)	8, 10
10	135.6	C			...
11	125.6	CH	7.21	s	1, 7, 12
12	130.5	CH	7.17	d (7.0)	7, 11
Label	**δ**	**..**			
O1	254.7	xH	1.33	s	
O3	181.3				...
Cl1	760.8				...
O2	252.2	xH	0.48	s	

Part 2 Rotational barrier of 80

Equilibrium and transition state geometries and energies were obtained using the ωB97X-D/6-31G* theoretical model in vacuum. Frequency calculations were then carried out using the same method. The starting geometry was obtained from a molecular mechanics equilibrium conformer calculation. The energies reported are uncorrected electronic energies.



80 transition structure

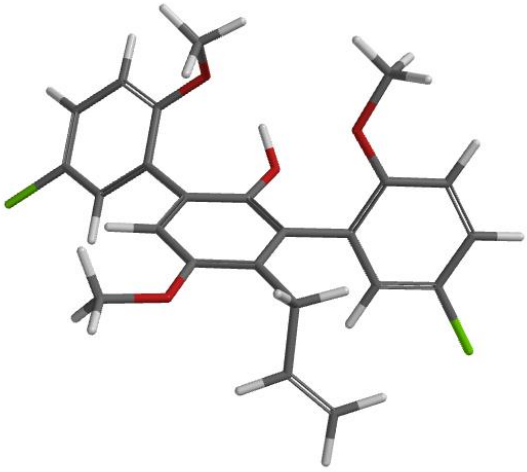
-1348245.85 kcal/mol

one imaginary frequency i54

C	-1.685158	4.833089	-0.865600
C	0.196672	3.199096	-2.035696
C	-1.330952	3.640702	-0.249070
C	-1.114062	5.220652	-2.072213
C	-0.165351	4.389702	-2.653496
C	-0.379941	2.791586	-0.826272
H	-1.807637	3.347621	0.680480
H	-1.407218	6.150231	-2.546857
H	0.304908	4.651653	-3.595505
C	-0.010866	1.543086	-0.097545
C	0.658416	-0.733699	1.379392
C	-0.128062	0.265199	-0.669906
C	0.447243	1.683038	1.213060
C	0.870168	0.559542	1.895386

C	-0.055366	-0.904856	0.156228
H	0.549242	2.678778	1.628735
C	-0.655454	-2.247410	-0.196446
C	-1.482474	-4.951641	-0.684567
C	-0.712633	-3.228964	0.812829
C	-1.306898	-2.634696	-1.407204
C	-1.608971	-3.978931	-1.661090
C	-1.095348	-4.539966	0.578091
H	-0.486297	-2.968023	1.833727
H	-2.011063	-4.260285	-2.626647
H	-1.742033	-5.984811	-0.886820
O	-0.263241	0.161483	-2.008015
H	0.198279	0.915594	-2.417228
O	1.540190	0.617831	3.087298
C	1.826927	1.883714	3.629192
H	2.440622	2.486893	2.946650
H	2.386218	1.696041	4.546979
H	0.911198	2.437742	3.874029
O	1.113992	2.391082	-2.683379
O	-1.718234	-1.683661	-2.256062
C	2.422486	2.388735	-2.110719
H	2.855749	3.393345	-2.165540
H	3.013649	1.696249	-2.711443
H	2.397737	2.049308	-1.070093
C	-2.107204	-2.005245	-3.567021
H	-3.058059	-2.553940	-3.587810
H	-1.336831	-2.589991	-4.085548
H	-2.234069	-1.047206	-4.073264
Cl	-2.885097	5.858449	-0.114470
Cl	-1.106193	-5.691259	1.900330
C	1.442726	-1.819936	2.118772
H	2.445065	-1.392913	2.258767
H	1.570982	-2.705077	1.491985
C	0.942482	-2.205927	3.490645

H	0.620105	-1.382006	4.121919
C	0.922605	-3.450331	3.959808
H	0.583716	-3.671564	4.967556
H	1.233693	-4.298101	3.353670



80 equilibrium geometry

-1348273.34 kcal/mol

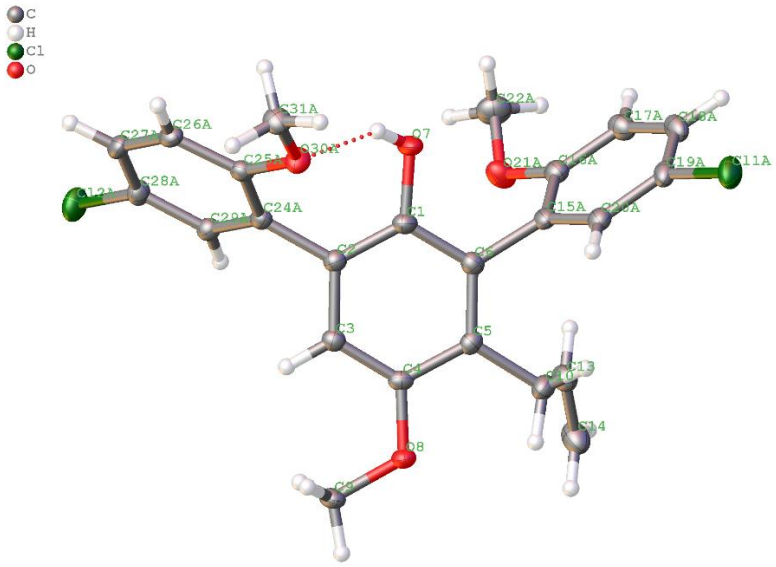
no imaginary frequencies

C	-1.811585	4.921967	-0.748870
C	-0.492522	2.930096	-2.096647
C	-1.413835	3.787653	-0.076182
C	-1.562984	5.072635	-2.097245
C	-0.901245	4.064067	-2.767778
C	-0.735010	2.771102	-0.739862
H	-1.644968	3.677559	0.962394
H	-1.886219	5.954015	-2.610020
H	-0.705160	4.141907	-3.816892
C	-0.297818	1.564744	0.012493
C	0.457124	-0.641871	1.552744
C	-0.575922	0.285113	-0.427233
C	0.375082	1.737493	1.223905

C	0.745896	0.657957	1.980071
C	-0.201287	-0.814597	0.352174
H	0.603911	2.731573	1.544875
C	-0.570348	-2.165839	-0.151983
C	-1.266799	-4.683226	-1.093073
C	-1.566871	-2.893000	0.463320
C	0.081371	-2.701390	-1.261623
C	-0.268888	-3.955514	-1.721106
C	-1.909579	-4.148692	-0.005014
H	-2.069204	-2.482921	1.313495
H	0.219965	-4.383357	-2.569896
H	-1.535051	-5.654236	-1.454433
O	-1.234452	0.037280	-1.602364
H	-0.825519	0.531944	-2.338222
O	1.415514	0.753284	3.182027
C	1.787894	2.031812	3.716668
H	2.454461	2.560267	3.046051
H	2.298356	1.821702	4.642197
H	0.917185	2.645195	3.913472
O	0.149131	1.921885	-2.814514
O	1.059817	-1.932038	-1.830840
C	1.610296	1.934541	-2.806550
H	1.969294	2.844176	-3.266673
H	1.912159	1.076881	-3.383140
H	1.977957	1.854117	-1.795113
C	1.813593	-2.416712	-2.953422
H	1.175984	-2.588215	-3.811428
H	2.343242	-3.329184	-2.709536
H	2.525169	-1.639755	-3.180299
Cl	-2.660037	6.181520	0.117960
Cl	-3.172208	-5.057174	0.799312
C	0.917055	-1.795158	2.429479

H	1.935863	-1.592241	2.737163
H	0.899990	-2.716998	1.868322
C	0.052392	-1.920101	3.667084
H	0.025503	-1.041528	4.282451
C	-0.613490	-3.002966	4.008244
H	-1.204164	-3.040489	4.904003
H	-0.599039	-3.895285	3.410052

5.4 Crystallographic Data



Crystal data and structure refinement for (**80**).

Empirical formula	$C_{24}H_{21}Cl_2O_4$
Formula weight	444.31
Temperature/K	120(2)
Crystal system	monoclinic
Space group	I2/a
a/Å	24.6054(5)
b/Å	6.96180(10)
c/Å	27.5720(5)
α/°	90
β/°	116.079(2)
γ/°	90
Volume/Å^3	4242.17(15)
Z	8
ρ_{calc}g/cm^3	1.391
μ/mm^{-1}	2.992
F(000)	1848.0
Crystal size/mm^3	0.088 × 0.08 × 0.022
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.138 to 147.546
Index ranges	-29 ≤ h ≤ 30, -8 ≤ k ≤ 8, -34 ≤ l ≤ 33
Reflections collected	36625
Independent reflections	4253 [R_{int} = 0.0290, R_{sigma} = 0.0141]
Data/restraints/parameters	4253/800/370
Goodness-of-fit on F^2	1.133
Final R indexes [I>=2σ (I)]	R_1 = 0.0393, wR_2 = 0.0991
Final R indexes [all data]	R_1 = 0.0416, wR_2 = 0.1002
Largest diff. peak/hole / e Å^{-3}	0.41/-0.32

6.0 References

[1] *Nat. Chem. Biol.*, 2007, **3**, 351-351.

[2] G. Guerriero, R. Berni, J. Muñoz-Sanchez, F. Apone, E. M. Abdel-Salam, A. A. Qahtan, A. A. Alatar, C. Cantini, G. Cai, J. F. Hausman, K. Siddiqui, S. M. Hernández-Sotomayor and M. Faisal, *Genes*, 2018, **9**, 309.

[3] A. N. Hayes and S. G. Gilbert, in *Molecular, Clinical and Environmental Toxicology*, ed. A. Luch, Birkhauser Verlag, Basel, 1st edn, vol. 1, ch. 1, pp. 1-35, 2009.

[4] R. P. Mattick, E. Digiusto, C. Doran, S. O'Brien, M. Shanahan, J. Kimber, N. Henderson, C. Breen, J. Shearer, J. Gates, A Shakeshaft and NEPOD Trial Investigators, *National Evaluation of Pharmacotherapies for Opioid Dependence: Report of Results and Recommendations*, National Drug and Alcohol Research Centre, Sydney, 2001.

[5] D. A. Dias, S. Urban and U. Roessner, *Metabolites*, 2012, **2**, 303-336.

[6] B. T. Oshiro, Prim Care Update Ob/Gyns, 1999, 6, 56-60.

[7] M. Lahlou, *Pharm. Pharmacol.*, 2013, **04**, 17-31.

[8] F. R. Batchelor, F. P. Doyle, J. H. C. Nayler and G. N. Rolinson, *Nature*, 1959, **183**, 257-258.

[9] B. S. Kalra, A. Batta and R. Khirasaria, *Fam. Med. Prim. Care*, 2020, **9**, 105.

[10] S. Mathur and C. Hoskins, *Biomedical Reports*, 2017, **6**, 612-614.

[11] F. Li, Y. Wang, D. Li, Y. Chen and Q. Dou, *Expert Opin. Drug Discovery*, 2019, **14**, 417-420.

[12] R. A. Hussein and A. A. El-Anssary, in *Herbal Medicine*, ed. P. F. Builders, IntechOpen, London, 1st edn, ch. 2, 2019.

[13] H. Wagner, in *Biochemistry of Plant Phenolics*, ed. T. Swain, J. B. Harbone, C. F. Van Sumere, Springer, Boston, 1st edn, vol. 12, ch. 18, pp. 589-616, 1979.

[14] D. Lin, M. Xiao, J. Zhao, Z. Li, B. Xing, X. Li, M. Kong, L. Li, Q. Zhang, Y. Liu, H. Chen, W. Qin, H. Wu and S. Chen, *Molecules*, 2016, **21**, 1374.

[15] C. S. Evans, *Phytochemical Analysis*, 1991, **2**, 48-48.

[16] I. C. Oh, T. Denk and E. M. Friis, *Plant Syst. Evol.*, 2003, **240**, 175-209.

[17] X. Tian, X. Guo, Z. Zhuo, R. Zeng, X. Fang, X. Xu, H. Li, Y. Shen and W. Zhang, *RSC Advances*, 2017, **7**, 10849-10854.

[18] Q. Lin, PhD thesis, Forestry College, South China Agricultural University, Guangzhou, 1997.

[19] G. P. Moss, *Pure Appl. Chem.*, 2000, **72**, 1493-1523.

[20] R. M. Denton and J. Scragg, *Org. Biomol. Chem.*, 2012, **10**, 5629.

[21] J. F. Eykman, *Ber. Dtsch. Chem. Ges.*, 1890, **22**, 2736. First isolation of chavicol; chavicol has since been isolated from several different plant sources.

[22] J. F. Eykman, *Rec. Trav. Chim.*, 1885, **4**, 32-54.

[23] D. V. Bochkov, S. V. Sysolyatin, A. I. Kalashnikov and I. A. Surmacheva, *J. Chem. Biol.*, 2011, **5**, 5-17.

[24] J. Liu, W. Cheng, H. Wang, Y. Chen and W. Wang, *Biochem. Biophys. Res. Commun.*, 2008, **373**, 1-7.

[25] M. Karpf and R. Trussardi, *Angew. Chem. Int. Ed.*, 2009, **48**, 5760-5762.

[26] O. R. Gottlieb, *Phytochemistry*, 1972, **11**, 1537-1570.

[27] M. Moriyama, J. M. Huang, C. S. Yang, H. Hioki, M. Kubo, K. Harada and Y. Fukuyama, *Tetrahedron*, 2007, **63**, 4243-4249.

[28] M. B. Colovic, D. Z. Krstic, T. D. Lazarevic-Pasti, A. M. Bondzic and V. M. Vasic, *Curr. Neuropharmacol.*, 2013, **11**, 315-335.

[29] J. K. Andersen, *Nat. Med.*, 2004, **10**, S18-S25.

[30] I. Kouno, T. Morisaki, Y. Hara and C. S. Yang, Chem. *Pharm. Bull.*, 1991, **39**, 2606-2608.

[31] Z. Y. Guan, C. F. Dong, L. Gao, J. P. Wang, S. D. Luo and Y. Wang, *Nat. prod. Bioprospect.*, 2013, **3**, 43-47.

[32] R. M. Denton and J. T. Scragg, *Synlett*, 2010, **4**, 633–635.

[33] I. Kouno, A. Hashimoto, N. Kawano and C. S. Yang, *Chem. Pharm. Bull.*, 1989, **37**, 1291–1292.

[34] M. Moriyama, J. M. Huang, C. S. Yang, M. Kubo, K. Harada, H.Hioki and Y. Fukuyama, *Chem. Pharm. Bull.*, 2008, **56**, 1201-1204.

[35] A. Fearnley, PhD Thesis, University of Nottingham, 2016.

[36] I. Kouno, C. Iwamoto, Y. Kameda, T. Tanaka and C. S. Yang, *Chem. Pharm. Bull.*, 1994, **42**, 112-114.

[37] L. C. Li, Z. H. Pan, D. S. Ning and Y. X. Fu, *Molecules*, 2020, **25**, 3573.

[38] R. E. Arnold, PhD Thesis, University of Nottingham, 2021.

[39] C. Dong, L. Liu, X. Li, Z. Guan, H. Luo and Y. Wang, *Planta Med.*, 2013, **79**, 338–347.

[40] B. Simpson, MRes Thesis, University of Nottingham, 2021.

[41] Z. H. Pan, L. Cheng, D. S. Ning, L. Y. Peng, Y. X. Fu and L. C. Li, *Phytochem. Lett.*, 2019, **30**, 210-214.

[42] P. J. Yin, J. S. Wang, D. D. Wei, Y. Zhang, P. R. Wang, X. B. Wang and L. Y. Kong, *Fitoterapia*, 2013, **88**, 31-37.

[43] J. F. Liu, Z. Y. Jiang, C. A. Geng, X. B. Zou, Y. Shi, Y. B. Ma, X. M. Zhang and J. J. Chen, *Planta Med.*, 2010, **76**, 1464-1467.

[44] J. Nugent, M. G. Banwell and B. D. Schwartz, *Org. Lett.*, 2016, **18**, 3798-3801.

[45] L. Sy and G. D. Brown, *Phytochemistry*, 1996, **43**, 1417-1419.

[46] R. Phillips and R. M. Denton, unpublished work.

[47] F. Toda, K. Tanaka and S. Iwata, *J. Org. Chem.*, 1989, **54**, 3007-3009.

[48] Y. Guo, C. Bao, F. Li, E. Hou, S. Qin, Q. Zhang and J. Liu, *ACS Infect. Dis.*, 2020, **6**, 2478-2489.

[49] L. Sy and G. D. Brown, *J. Chem. Res.*, 1998, 476-477.

[50] S. C. Tzeng and Y. C. Liu, *J. Mol. Catal. B Enzym.*, 2004, **32**, 7-13.

[51] Estragole: £0.65 per gram (Sigma Aldrich). Chavicol: £500 per gram (TCI Chemicals).

[52] P. Magnus, N. Sane, B. P. Fauber and V. Lynch, *J. Am. Chem. Soc.*, 2009, **131**, 16045–16047

[53] S. Li, A. Lowell, F. Yu, A. Raveh, S. Newmister, N. Bair, J. M. Schaub, R. M. Williams and D. H. Sherman, *J. Am. Chem. Soc.*, 2015, **137**, 15366-15369.

[54] J. Zaidi, MRes Thesis, University of Nottingham, 2021.

[55] G. Boden, MRes Thesis, University of Nottingham, 2021.

[56] Reaxys search for the bromination of anisole (see Table 3), 2022; 12 out of 13 entries use $BTMABr_3$ as the brominating agent of choice.

[57] *WO Pat.*, WO2009124968A1, 2009.

[58] A. de la Hoz, A. Díaz-Ortiz and P. Prieto, in *Alternative Energy Sources for Green Chemistry*, ed. G. Stefanidis and A. Stankiewicz. The Royal Society of Chemistry, London, 1st edn, 2016, vol. 1, ch. 1, pp. 1-33.

[59] N. E. Leadbeater and M. Marco, *J. Org. Chem.*, 2002, **68**, 888-892.

[60] F. Felpin, T. Ayad and S. Mitra, European Journal of Organic Chemistry, 2006, 2006, 2679–2690.

[61] D. Blakemore, in *Synthetic Methods in Drug Discovery*, ed. David C Blakemore, Paul M Doyle and Y. M. Fobian, The Royal Society of Chemistry, London 1st edition, 2016, vol. 1, ch. 1, pp. 1-69.

[62] P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741-2769.

[63] L. Claisen, *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 3157-3166.

[64] E. Kuntz, A. Amgoune, C. Lucas and G. Godard, *J. Mol. Catal. A Chem.*, 2006, **244**, 124-138.

[65] M T. Peruzzi, S. J. Lee, and M. R. Gagné, *Org. Lett*. 2017, **19**, 6256-6259.

[66] T. E. Müller, J. C. Green, M. P. Mingos, M. McPartlin, C. Whittingham, D. J. Williams and T. M. Woodroffe, *J. Organomet. Chem.*, 1998, **551**, 313-330.

[67] T. Iwai, H. Okochi, H. Ito and M. Sawamura, *Angew. Chem. Int. Ed.*, 2013, **52**, 4239-4242.

[68] M. A. Lovchik, A. Goeke and G. Fráter, *Tetrahedron: Asymmetry*, 2006, **17**, 1693-1699.

[69] R. P. Lutz, *Chem. Rev.*, 1984, **84**, 205-247.

[70] R. M. Denton, unpublished work.

[71] S. Inoki, K. Kato, S. Isayama and T. Mukaiyama, *Chem. Lett.*, 1990, **19**, 1869-1872.

[72] P. Magnus, A. H. Payne, M. J. Waring, D. A. Scott and V. Lynch, *Tetrahedron Lett.*, 2000, **41**, 9725-9730.

[73] P. Patschinski, C. Zhang and H. Zipse, *J. Org. Chem.*, 2014, **79**, 8348-8357.

[74] J. Cosier and A. M. Glazer, *J. Appl. Crystallogr.*, 1986, **19**, 105-107.

[75] Rigaku Oxford Diffraction, (2018), CrysAlisPro Software system, version 1.171.40.45a, Rigaku Corporation, Oxford, UK.

[76] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst*. 2009, **42**, 339-341.

[77] G. M. Sheldrick, *Acta Crystallogr. A* 2015, **71**, 3-8.

[78] "CheckCIF" can be found under http://checkcif.iucr.org

[79] Crystallography service and information provided by S. Argent at The University of Nottingham.

[80] *WO Pat.*, WO2004094401A1, 2004

[81] S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa and T. Okamoto, *Chem. Lett*., 1987, **16**, 627-630.

[82] K. Li and A. Alexakis, *Angew*. *Chem*. *Int*. *Ed*., 2006, **45**, 7600-7603.

[83] J. Liang, J. Han, J. Wu, P. Wu, J. Hu, F. Hu and F. Wu, *Org*. *Lett*., 2019, **21**, 6844-6849.

[84] All data in this section is referenced as following: R. M. Denton, unpublished work.