School of Chemistry

MRes Research Project

Title: Studies towards the total synthesis of simonsol A

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1. Acknowledgements

I'd like to thank The University of Nottingham for giving me the opportunity to conduct research in their facilities. To Prof. Ross Denton for providing me with a challenging but enjoyable project, and for supporting me throughout my time at the university. To Robert Arnold and the rest of the Denton group for their advice and constant words of encouragement, making every moment in the lab a pleasure.

2. Abbreviations

AChE: Acetylcholinesterase

Ar: Aryl

Bn: Benzyl

Bpin: (pinacolato)boron

BuChE: Butyrylcholinesterase

Bz: Benzoyl

Calcd.: Calculated

Cy: Cyclohexyl

dba: dibenzylideneacetone

DBE: 1,2-Dibromoethane

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE: 1,2-Dichlorethane

DEPT: Distortionless enhancement by polarization transfer

DHQ: Dihydroquinone

DIPEA: *N,N*-Diisopropylethylamine

DMF: Dimethylformamide

dppp: 1,3-Bis(diphenylphosphino)propane

EPSP: 5-Enolpyruvylshikimate-3-phosphate

Eq.: Equivalents

[H]: Reductant

HR-ESI-MS: High resolution electrospray ionisation mass spectroscopy

HTS: High throughput screening

IPA: *i*-Propanol

L-Glu: *L*-Glutamine

Ln: Ligand(s)

[M]: Metal catalyst

MIBK: 4-Methyl-2-pentanone

MOM: Methoxymethyl

NAD(P)H: Nicotinamide adenine dinucleotide phosphate

NAD^+: Nicotinamide adenine dinucleotide

NBS: *N*-Bromosuccinimide

NMR: Nuclear magnetic resonance

o: ortho (position)

[O]: Oxidant

p: para (position)

[Pd]: Palladium source

Pd G3 XPhos: (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

Piv: Pivaloyl

Pyr: Pyridine

R: Unspecified chemical group

Rf: Retention factor

r.t.: Room temperature

SPhos: 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TBAB: Tetrabutyl(n)ammomium bromide

TBAF: Tetrabutyl-n-ammonium fluoride

TBAI: Tetrabutyl(n)ammonium iodide

TBDPSCl: *tert*-Butyldiphenylsilylchloride

TEA: Triethylamine

TFA: Trifluoroacetic acid

TFAA: Trifluoroacetic anhydride

THF: Tetrahydrofuran

TLC: Thin layer chromatography

TMEDA: Tetramethylethylenediamine

XPhos: Xantphos

3. Table of Contents:

4. Abstract

Neolignans are secondary metabolites found in plants from the genus *Illicium* and investigations into their bioactivity have shown them to possess medicinal properties. Dunnianol, a sesquineolignan, has shown neurotrophic activity in the promotion of neurite outgrowth. We hypothesised that the biosynthesis of simonsol A is derived from dunnianol and this report focusses on the comparison between the two compounds and describes the synthesis towards simonsol A. An intermediate towards the synthesis of simonsol A was prepared through a microwave-assisted Suzuki-Miyaura cross-coupling reaction, followed by allylation of the phenolic core in 50% yield over 4 steps. Computational studies of the relative energies for the interconversion provide strong evidence towards the newly proposed biosynthesis of simonsol A. The energy barrier of the Claisen rearrangement was found to be 45.6 kcal/mol and for the Cope rearrangement, 32.5 Kcal/mol.

5. Introduction

5.1. Neolignans

Plants have been used medicinally for thousands of years with reported use on cuneiform dating back to 2600 BC.[1] Due to limited technologies, plant extracts were used as crude concentrates, not as the isolated compound.[2]

The therapeutic applications of natural remedies is attributed to specific groups of chemicals which are in abundance in a wide range plants. Although the pharmacological activities of such plants can often be explained by the bioactivity of one component, it is not uncommon that multiple constituents act together in a uniformed manner to amplify the effects of each.[3] This is referred to as a synergistic drug interaction, where the combined effects of two drugs have a greater than additive effect. This effect has been demonstrated with the antimalarial artemisinin in combination with casticin, where the drug interaction changes from antagonistic to synergistic on increasing the ratio of the two from 1:3 to 1:10-1000.[4] Evidently these compounds possess certain structural features which enable them to exhibit substantial bioactivities making them an interesting focal point for modern-day drug discovery.

Although the benefits of using plant extracts for therapeutic applications has been recognised for millennia, many pharmaceutical companies favour directing drug discovery through the development of synthetic compounds.[5] The development of advanced screening technologies, such as high throughput screening (HTS), directed drug discovery towards using small molecular fragments and combinatorial synthesis.[6] Natural product libraries consist of samples varying in purity, alongside plant extracts and concentrates[7] which aren't compatible with traditional HTS technologies.[8] Following the development of new cutting-edge technologies, there has been a resurgence in the use of natural products in modern-day drug discovery.[9] By synthesising natural products we can understand, structurally, what makes them active and apply this to potential new drug candidates in the hope to make them less complex.

5.1.1. Definitions

Classical lignans and neolignans are a class of naturally occurring compounds prevalent within the plant kingdom. The term lignan was first defined by Haworth in 1936 as two propenylphenyl units (**1**) linked by their central C-8 carbon.[10] An example of a lignan is dibenzylbutane (**2**). The term neolignan was introduced by Gottlieb as propenylphenyl units linked in ways other than through their C-8 carbons[11] and many other smaller sub-classes of similar compounds, such as norlignans[12] and flavonolignans,[13] exist with varying coupling modes. An example of an *ortho*-*ortho* coupled neolignan is dunnianol (**3**) and an example of an *ortho*-O coupled neolignan is isodunnianol (**4**) (see Figure 1).

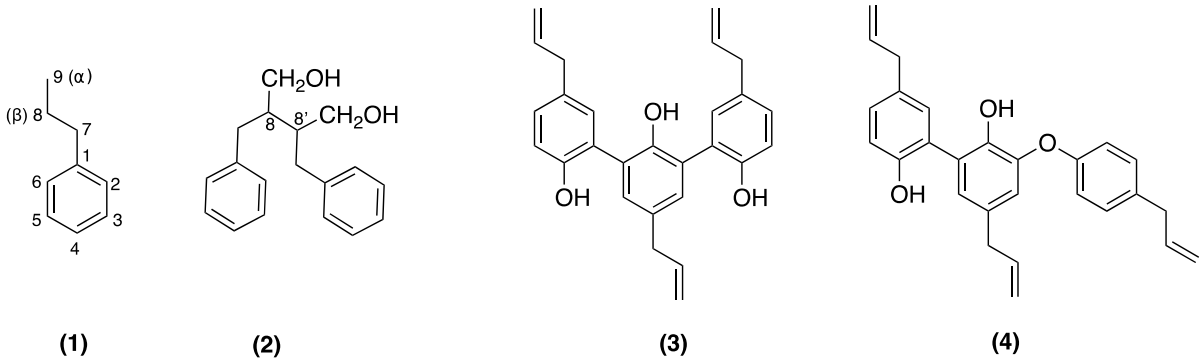
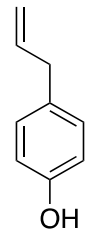


Figure 1: *The classical propenylphenyl unit **(1)**; dibenzylbutane, a classical lignan **(2);** dunnianol, a neolignan with ortho-ortho coupling **(3)**; isodunnianol, a neolignan with ortho-O coupling (**4**).*

Many neolignans are thought to be derived from repeating units of chavicol (**5**) which undergo various transformations, such as oxidative phenolic couplings at various positions, giving rise to the extensive structural diversity seen in the genus *Illicium (*see Figure 2).

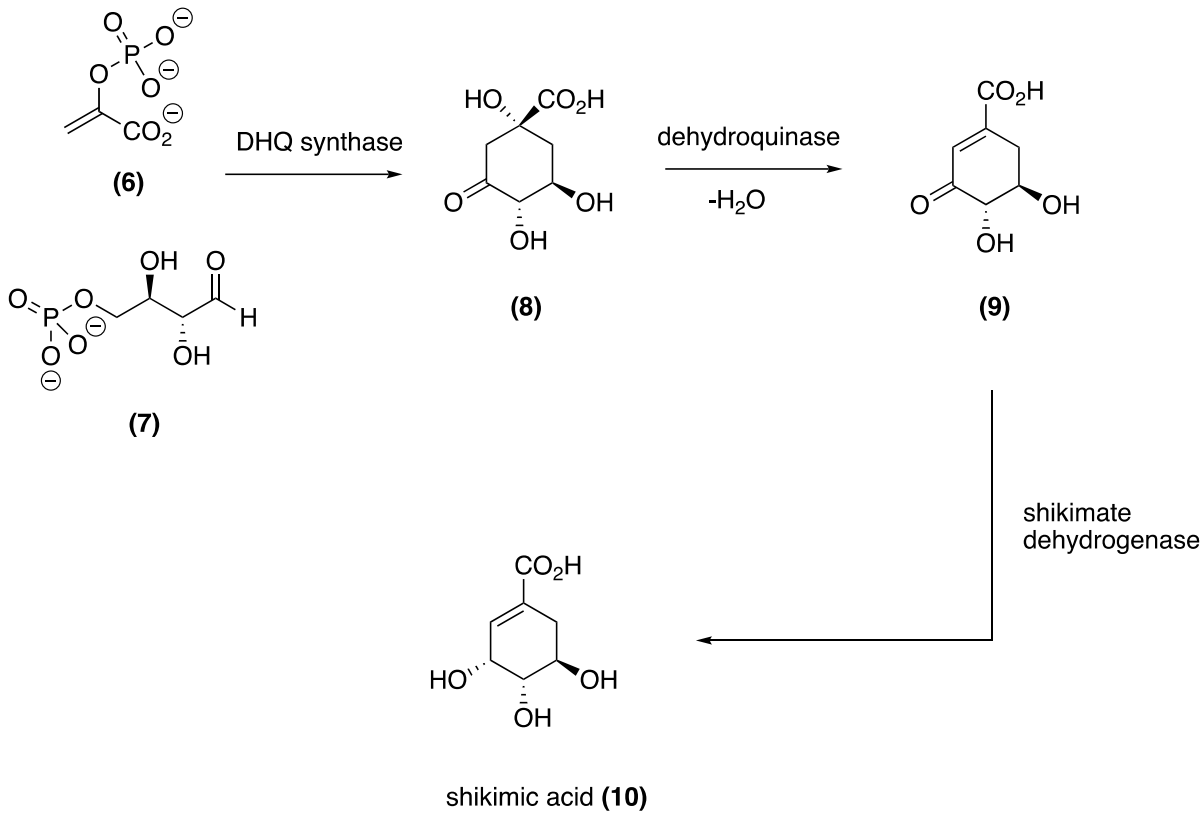


chavicol **(5)**

Figure 2: *Structure of chavicol (**5**).*

5.1.2. Biosynthesis of precursors

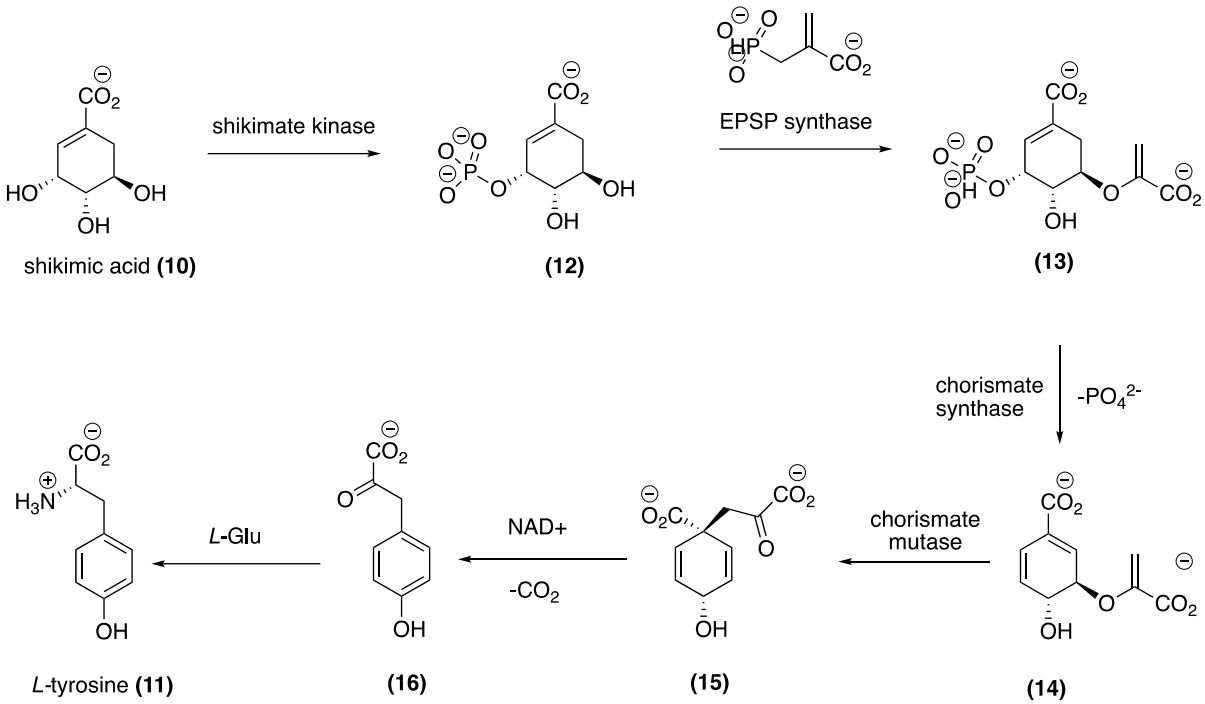
The shikimate pathway is a seven step biosynthesis[14] towards essential organic compounds, such as amino acids, that plants have developed to obtain all the chemical components it needs to survive. Found only in microorganisms and plants,[15] the shikimate pathway can be used to generate precursors to a vast range of monomeric sub-units which are then available to be used in biological processes. The biosynthesis starts with reaction of phosphoenolpyruvate (**6**) with (*D*)-ethyrose-4-phosphate (**7**) catalysed by the enzyme DHQ synthase forms intermediate **8.** Loss of water from **9** followed by selective reduction of the ketone, by shikimate dehydrogenase, leads to the formation of shikimic acid (**10**) (see Scheme 1).



Scheme 1: *Biosynthesis towards shikimic acid (**10**).*

Shikimic acid (**10**) is an intermediate in the biosynthesis of *L*-tyrosine (**11**), an amino acid which is a precursor in the biosynthesis of a wide range of other monomeric units.

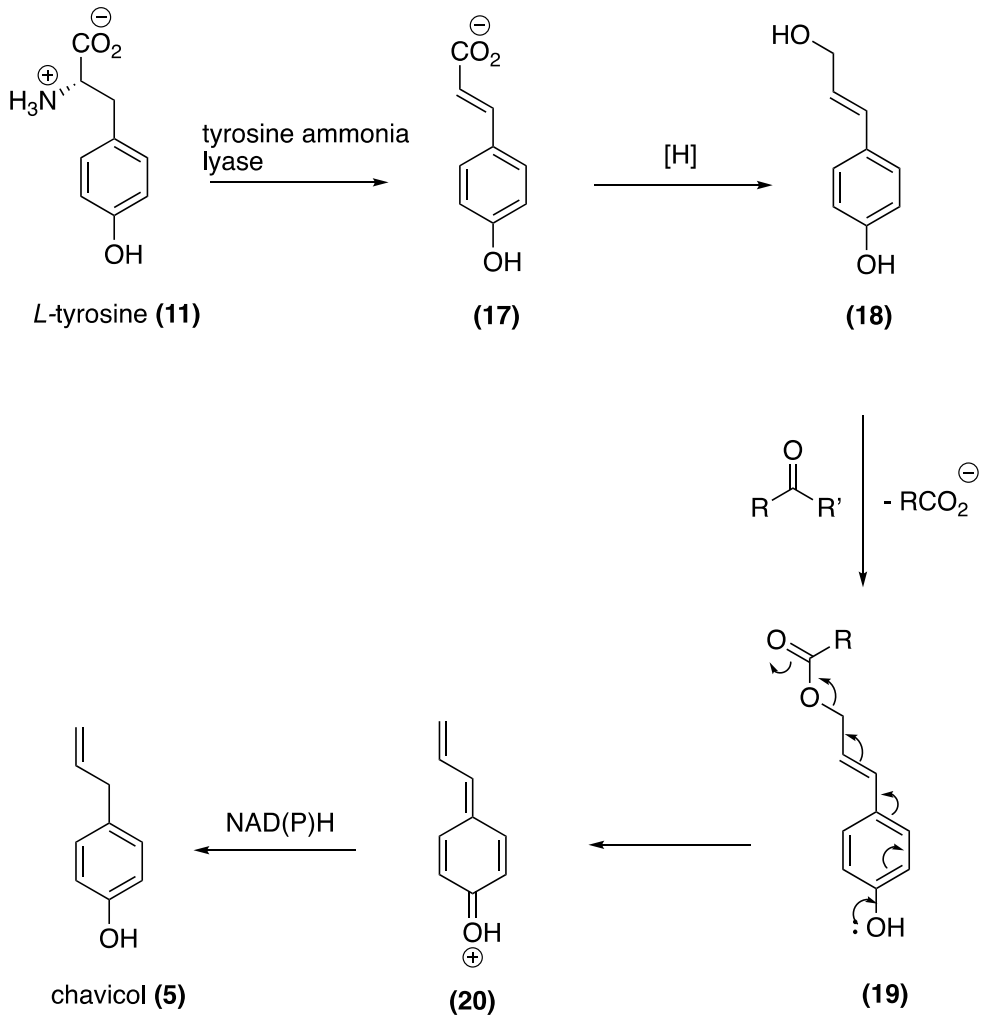
Catalysed by shikimate kinase, shikimic acid (**10**) is phosphorylated to intermediate **12.** Selective alkylation with phosphoenolpyruvate with 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase affords intermediate **13**, then successive loss of the 3-phosphate, catalysed by chorismite synthase, to **14** followed by rearrangement to **15**, and then a oxidative decarboxylation provides species **16** which is then finally converted to *L*-tyrosine (**11**) via a transamination reaction with the amino acid *L*-glutamine (see Scheme 2).



Scheme 2: *Biosynthesis of L-tyrosine (**11**) from shikimic acid (**10**).*

L-tyrosine (**11**) is a precursor to 4-hydrocinnamyl alcohol (**18**) and through further manipulation can be converted to chavicol, a common monomeric unit in the biosynthesis of simonsol A and other neolignans (see Scheme 3).

Deamination of *L*-tyrosine (**11**) by the enzyme tyrosine ammonia lyase followed by a reduction leads to *p*-coumaric acid (**17**). Subsequent reduction provides 4-hydrocinnamyl alcohol (**18**), a precursor to chavicol (**5**). It has been proposed that upon activation of the terminal alcohol via esterification followed by subsequent decomposition of **19** and reduction of resulting species **20** with NAD(P)H, chavicol (**5**) can be obtained.



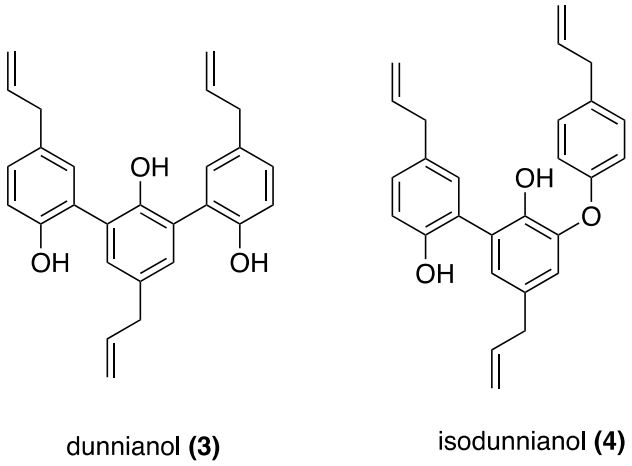
Scheme 3: *A proposed biosynthesis of chavicol (**5**) from L-tyrosine (**11**).*

5.2. Triaryl neolignans

Various sesquineolignans, which have previously been extracted from *Illicium simonsii,* have displayed promising bioactivities. Biological assays have demonstrated their anti-AChE and anti-BuChE, antioxidant,[16] anti-inflammatory[17] and antiviral capabilities with certain examples also having neurological benefits in promoting neurite outgrowth.[18] For the purpose of this dissertation, dunnianol, isodunnianol and simonsol A will be discussed only.

5.2.1. Dunnianol and isodunnianol

Dunnianol (**3**) was first isolated from *Illicium dunnianum i*n 1991.[19] It is composed of three units of chavicol (**5**) coupled at the ortho position. Dunnianol (**3**) has shown to be effective as an anti-inflammatory[20] and antimicrobial agent,[21] whilst its structural isomer, isodunnianol (**4**), displayed promising results for regulating autophagy and apoptosis for treating chemotherapy induced cardiotoxicity,[22] as well as anti-AChE activity.[23] There are currently no known syntheses of isodunnianol (**4**).



dunnianol **(3)** isodunnianol **(4)**

Figure 3: *Structures of dunnianol (**3**) and isodunnianol **(4)**.*

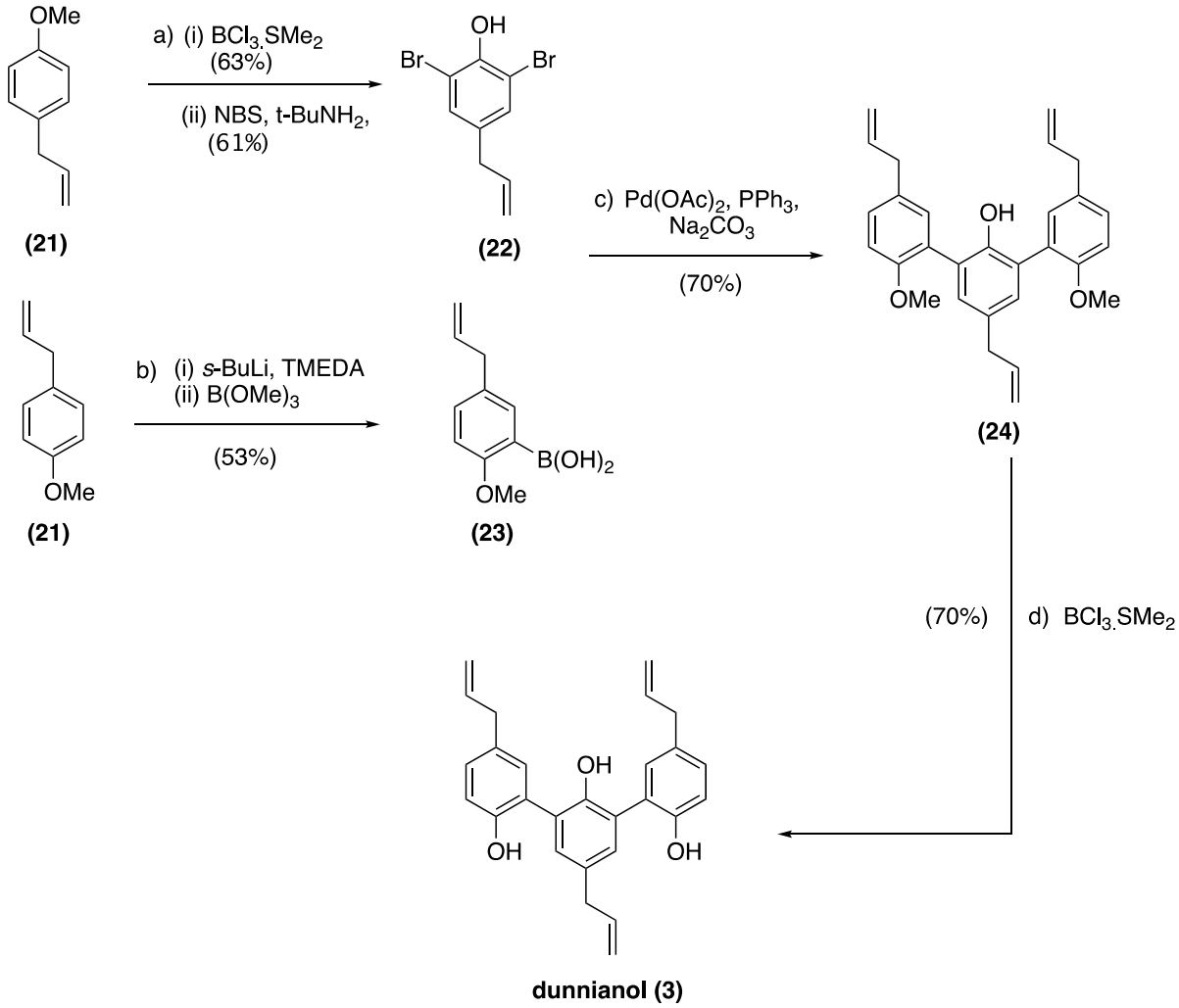
5.2.2. Synthesis of dunnianol

Dunnianol (**3**) was first synthesised in 1998 by Brown and co-workers through the non-selective oxidative phenolic coupling of chavicol (**5**) using $K_3Fe(CN)_6$,[24] and again by Liu and co-workers in 2004 using peroxidase and hydrogen peroxide.[25] In 2010, Denton and co-workers reported a concise synthesis of dunnianol (**3**).[26]

Demethylation of commercially available 4-allylanisole (**21**) to chavicol (**5**) and subsequent regio- and chemo-selective di-bromination gave species **22**.

Directed *ortho*-lithiation of 4-allylanisole (**21**) followed by reaction of the resulting organolithium species with trimethylborate provided boronic acid **23**. Suzuki-Miyaura cross-

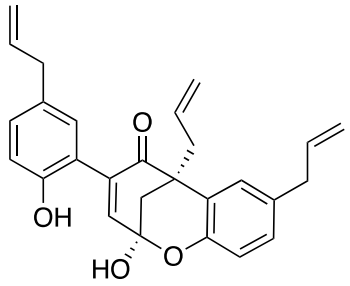
coupling reaction of **22** and **23** gave triaryl **24** which, after demethylation, provided dunnianol (**3**) in 17% yield over four steps (see Scheme 4).



Scheme 4: *Synthesis of dunnianol (**3**) as reported by Denton and co-workers.*

5.3. Simonsol A

Extracted from the fruits of *Illicium simonsii,* simonsol A (**25**) is an example of a sesquineolignan containing a dihydropyran core and an allylated quaternary carbon centre (see Figure 4). There are currently no reported syntheses of simonsol A (**25**).



simonsol A **(25)**

Figure 4: *Structure of simonsol A (**25**).*

5.3.1. Assignment of Simonsol A

Simonsol A (**25**) was isolated by Wang and co-workers[27] who were able to make a full stereochemical assignment by comparing experimental and calculated ECD spectra for the four possible isomers. The calculated ECD spectrum for **25b** matched closest to the experimental ECD spectrum allowing them to fully assign simonsol A (**25**) as (*R,R*) (see Figure 5).

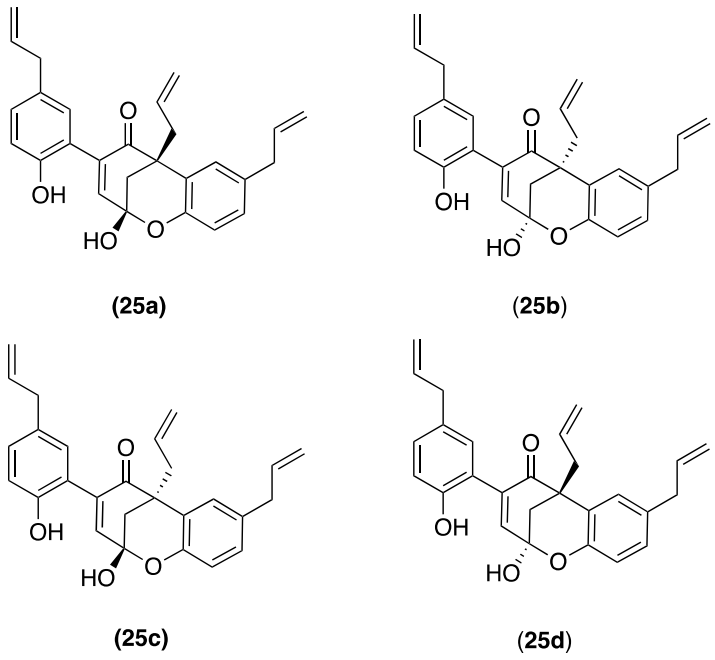
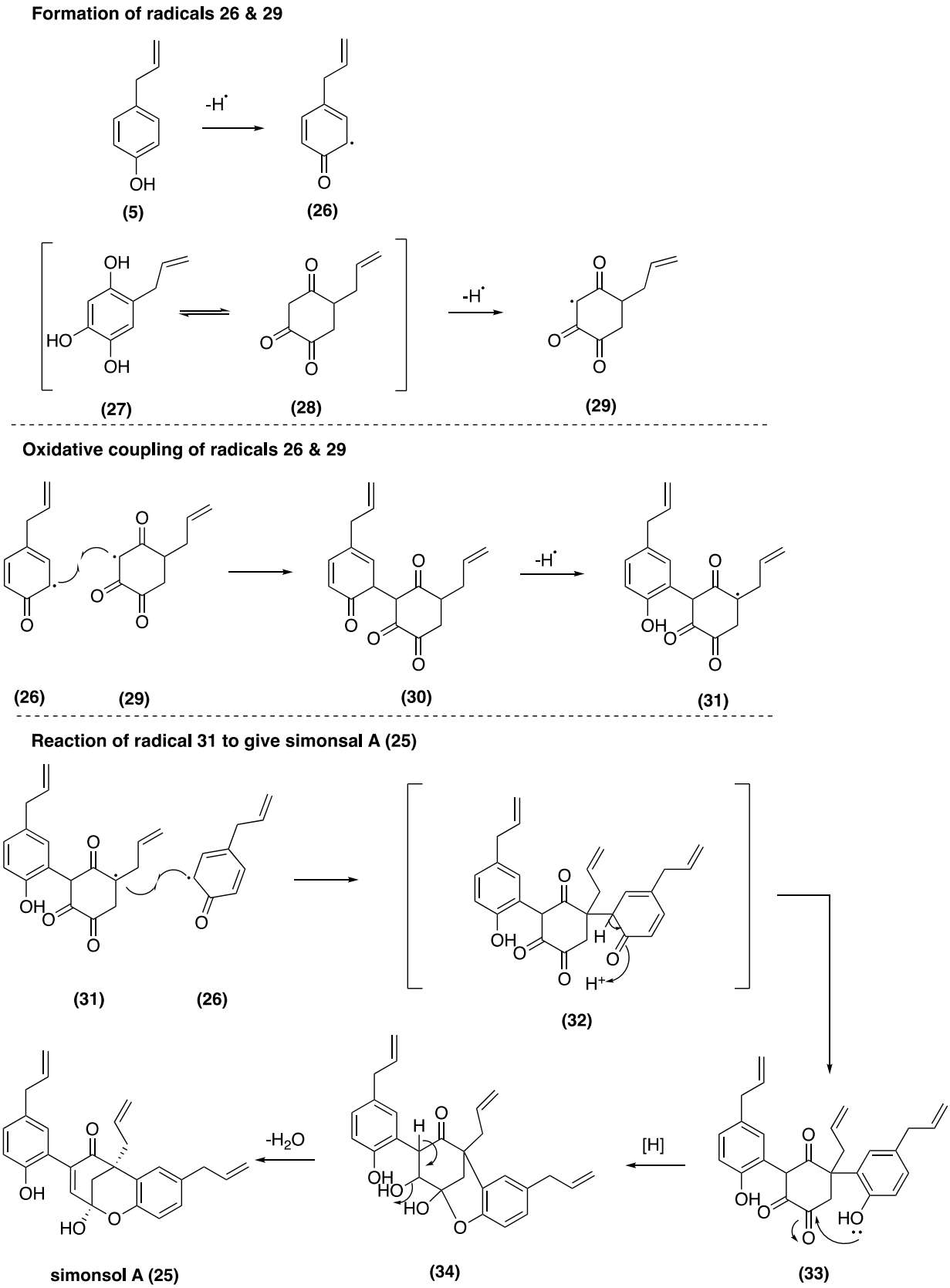


Figure 5: *The four possible stereoisomers of simonsol A (**25**).*

5.3.2. Proposed biosyntheses towards simonsol A

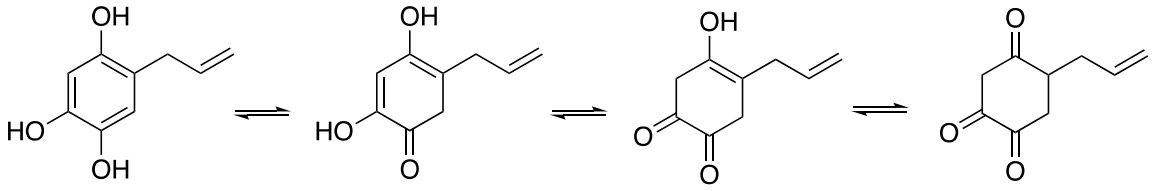
Wang et al proposed that the biosynthesis of simonsol A (**25**) starts with single electron reductions of chavicol (**5**) and triketone **28**, forming radicals **26** and **29** respectively. Oxidative coupling of **26** and **29** gives biaryl **30**. A single electron reduction of **30** to **31** provides the precursor to triaryl **32**. Subsequent tautomerisation to **33** followed by hemi-acetal formation and a selective ketone reduction gives **34** which undergoes loss of H_2O to give simonsol A (**25**) (see Scheme 5).



Scheme 5: *A proposed biosynthesis of simonsol A (**25**) by Wang et al.*[61]

From an organic chemistry perspective, this biosynthesis isn't plausible. The probability of the species **27** existing as the triketone tautomer **28** is very low as it involves loss of aromatic stabilisation (see Equation 1).

The synthesis also includes a selective reduction of the carbonyl at position 5 on the central ring of trimer **33**. This may be possible in the presence of an enzyme however as this is occurring alongside a series of oxidative additions, this seems unlikely. Therefore this proposed biosynthesis, which involves mutually incompatible redox steps, is chemically implausible.



(27) **(28)**

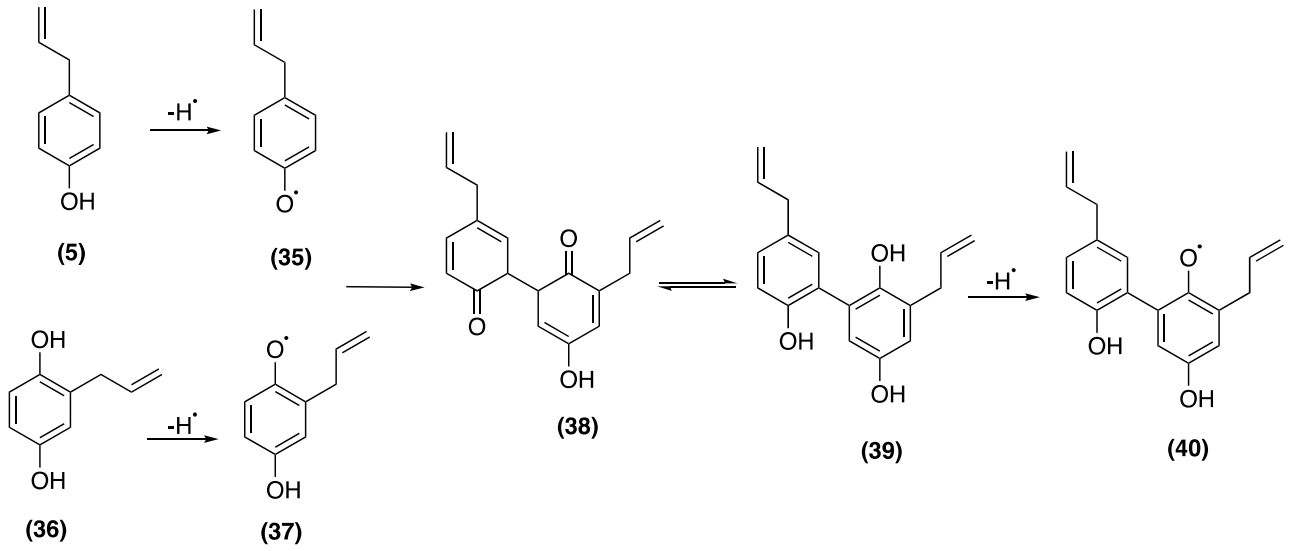
Aromatic **Not aromatic**

Equation 1: *Enol-keto tautomerization of **27** to triketone **28*** illustrating the loss of aromaticity.

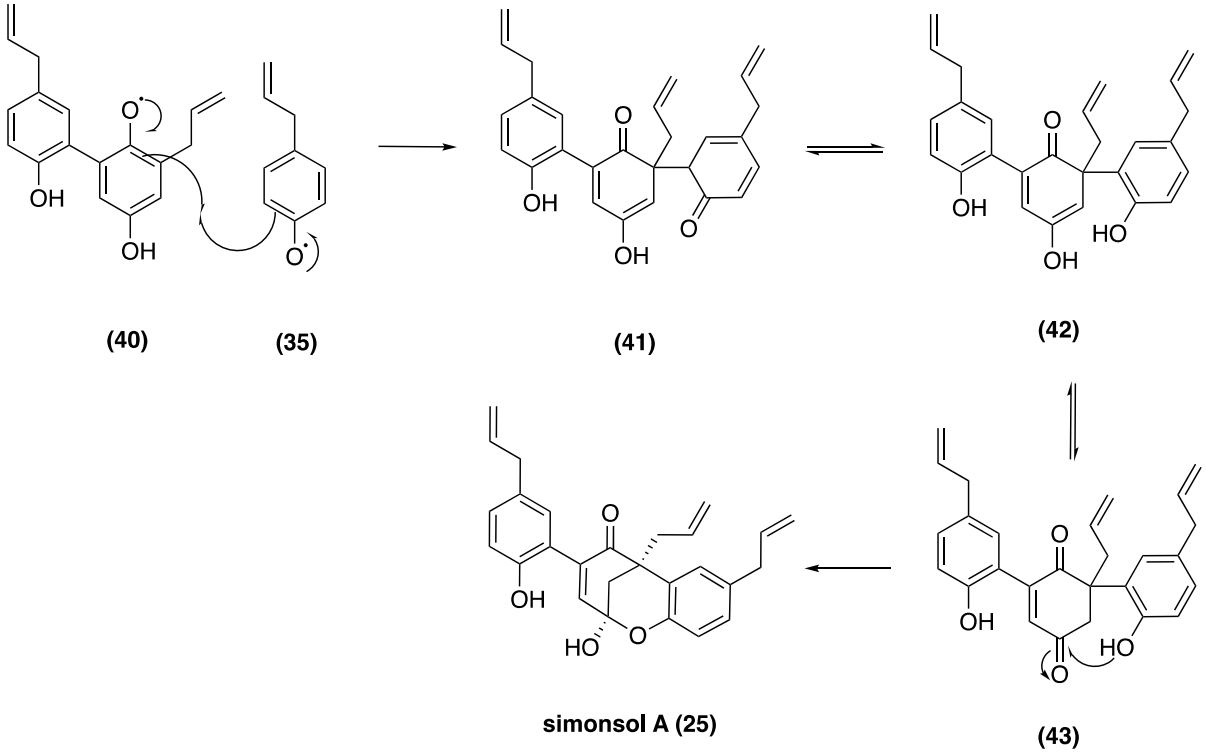
An alternative biosynthesis of simonsol A (**25**) proposed by members of the Denton group begins with oxidative phenolic coupling of radicals **35** and **37** in the *ortho* positions giving **38**. Subsequent tautomerisation gives biaryl **39**. A further oxidative coupling, at the *ortho* position, provides triaryl **41**, whilst also installing the allylic quaternary carbon centre. After a series of tautomerisations, triaryl **41** is converted to intermediate **43** and simonsol A (**25**) is then obtained through a ring-closing hemi-acetal formation (see Scheme 6).

This biosynthesis is more reasonable than the one preceding it, however it still relies on two different monomer units.

Formation and coupling of radicals 35 and 37

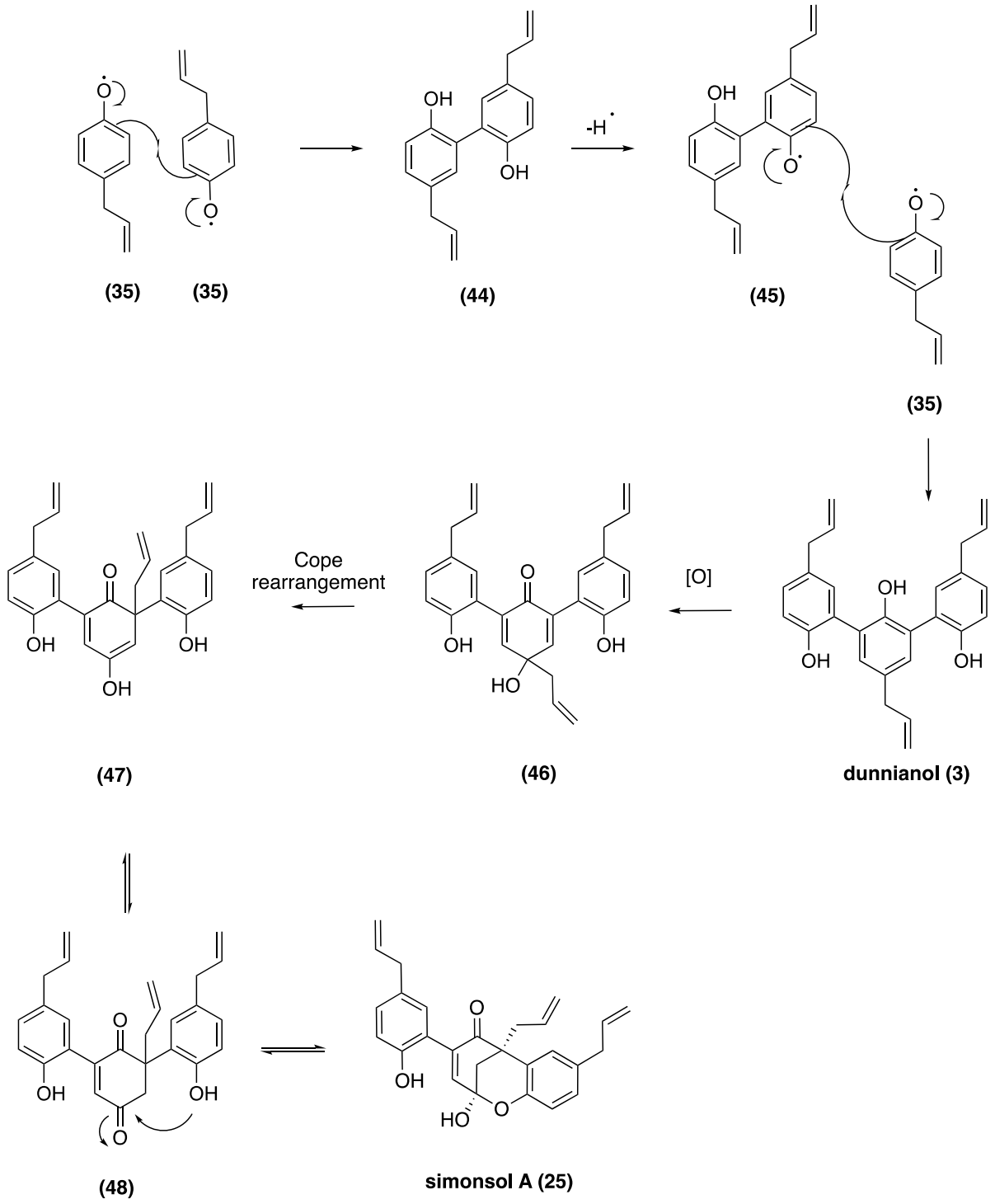


Coupling of radicals 40 and 35 to give simonsol A (25)



Scheme 6: *A proposed biosynthesis of simonsol A (**25**) from two units of chavicol (**5**) and one of 2-allylbenzene-1,4-diol (**36**).*

The final biosynthesis proposed in this report relies purely on chavicol (**5**) (see Scheme 7). Two consecutive oxidative additions of the chavicol radical **35** at the *ortho* position provides dunnianol (**3**), *via* biaryl **44**. Selective oxidation of the central ring forms triaryl **46**. A Cope rearrangement installs the quaternary carbon centre in trimer **47**. Tautomerisation to trimer **48** followed by a ring-closing hemi-acetal formation provides simonsol A (**25**).



Scheme 7: *An alternative biosynthesis of simonsol A from chavicol.*

Of the three biosyntheses presented in this report, the latter is most feasible due to it relying exclusively on chavicol, a compound present in abundance in the genus *Illicium*, and two other known natural products, namely magnolol and dunnianol. The intervention of a Cope rearrangement is something that may have previously been considered unlikely but has gained scientific proof from work that is currently unpublished from the Denton group.[28]

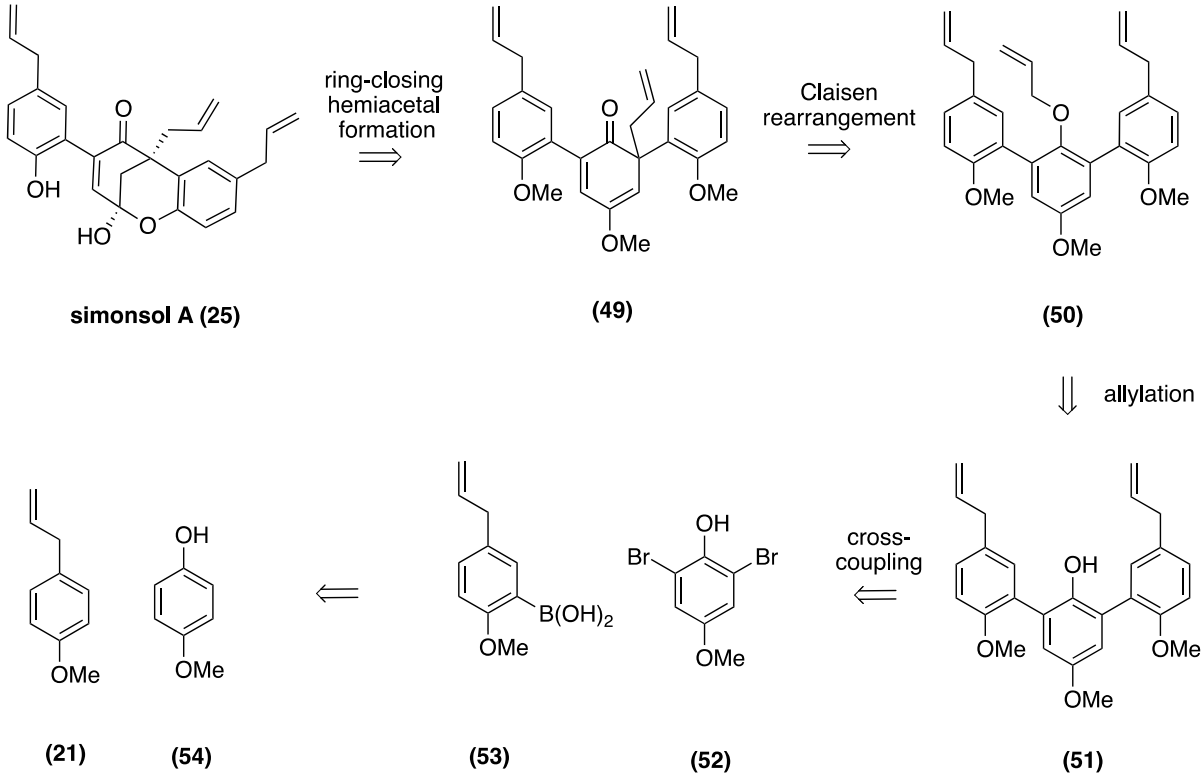
6. Project Outline

Following increased interest in sesquineolignans with respect to their bioactivities, the primary aim of this project is to develop a concise synthesis of simonsol A. Computational studies on the energies and corresponding transition states of key intermediates in the proposed chemical synthesis will also be carried out to provide insight into the different possible biosyntheses of simonsol A and to highlight possibly unknown natural products from this family.

7. Results and Discussion

7.1. Synthetic Route Development

Our first-generation retrosynthetic analysis incorporates a cross-coupling of monomer units **21** and **54**, and a Claisen rearrangement to access simonsol A (**25**).
It was reasoned that the hemi-acetal of simonsol A (**25**) could be obtained by global deprotection of tri-anisole **49**. This in turn could be accessed from a Claisen rearrangement of **50** which could be formed from phenol **51**. The triaryl unit could be formed by various different cross-coupling methods, depicted as Suzuki-Miyaura cross-coupling partners **52** and **53** for convenience (see Scheme 8).

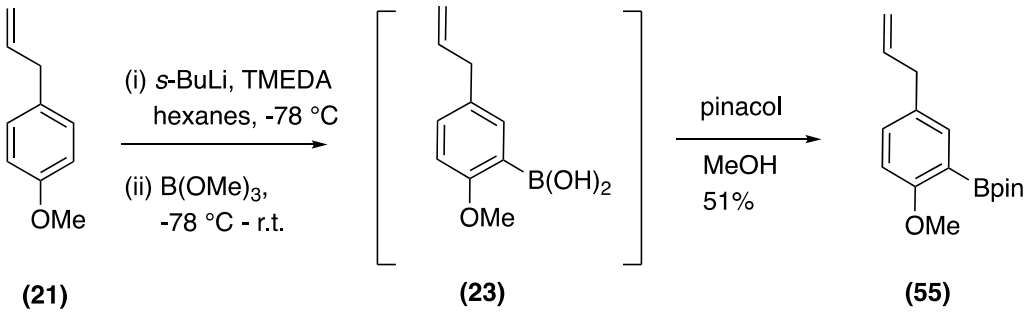


Scheme 8: *Retrosynthetic analysis for the formation of simonsol A (**25**).*

7.2. Cross-coupling reactions

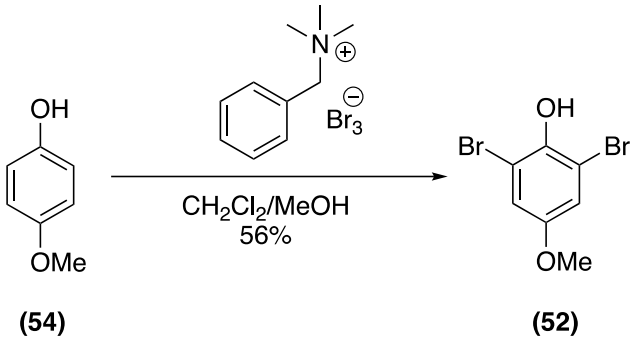
7.2.1. Suzuki-Miyaura cross-coupling reactions

Preparation of the monomer units for Suzuki-Miyaura cross-coupling reactions began with *ortho*-lithiation of 4-allylanisole (**21**) followed by subsequent reaction with trimethylborate to give boronic acid **23**. For ease of purification, **23** was treated with pinacol which gave boronic acid pinacol ester **55** in 51% yield over two steps (see scheme 9). Despite attempts to improve the yield by varying solvent choice and temperature during addition of trimethyl borate, no improvement on 51% was obtained.



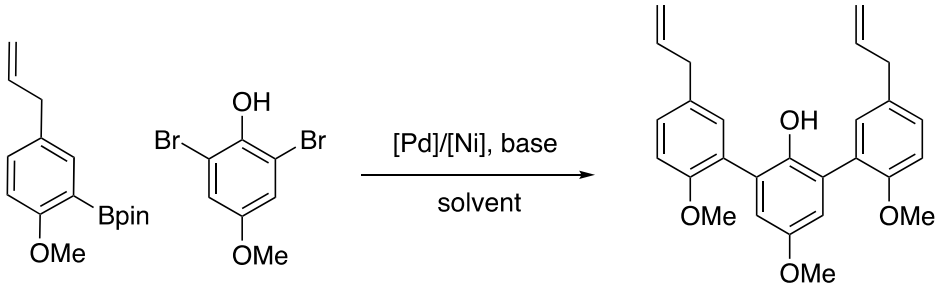
Scheme 9: *Synthesis of **49** from 4-allylanisole (**21**).*

Dibromination of 4-methoxyphenol (**54**) was achieved by using the brominating agent benzyl trimethylammonium tribromide and gave 2,6-dibromo-4-methoxyphenol (**52**) in moderate yield (see Equation 2). Initial attempts gave a light brown solid in >95% isolated yield with no chromatography, however after chromatography 56% of a colourless solid was obtained. This could be attributed to residual bromine or water in the solid.



Equation 2: *Synthesis of 2,6-dibromo-4-methoxyphenol (**52**) from 4-methoxyphenol (**54**).*

Next, the key Suzuki-Miyaura reaction towards the synthesis of triaryl **51** was investigated. Initial attempts were made with a variety of conditions. Generally, these reactions were unsuccessful with the best results obtained with Pd G3 XPhos and K_3PO_4 in H_2O/THF (Table 1, entry 5). The major products observed for the failed reactions were protodeboronated and dehalogenated starting material.

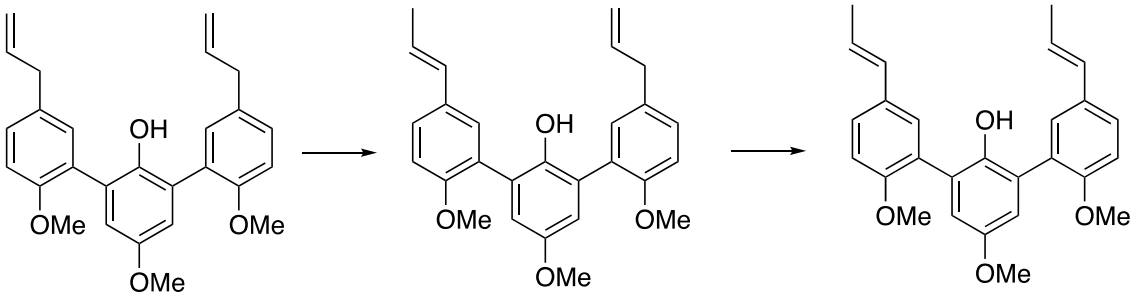


(55) **(52)** **(51)**

Entry	Catalyst (5 mol%)/ligand	Solvent	Base	Temp (°C)	Time (h)	Isolated yield (%)	Isomerisation (%)
1	$Pd(PPh_3)_4$	dioxane/H_2O	K_2CO_3	110	18	55	9-17
2	$Pd(PPh_3)_4$	THF/H_2O	NaOH	65	24	0	-
3	$Pd(PPh_3)_4$	THF/H_2O	Na_2CO_3	65	24	0	-
4	$Pd_2(dba)_3$/SPhos	THF/H_2O	KF	90	24	0	-
5	Pd G3 XPhos	THF/H_2O	K_3PO_4	r.t.	20	86	8-15
6	$Pd(PPh_3)_4$	DMF/H_2O	Cs_2CO_3	80	18	0	-
7	$Pd(PPh_3)_4$	DMF/H_2O	$NaHCO_3$	80	18	0	-
8	$Pd(PPh_3)_4$	THF	TEA	80	18	0	-
9	$Pd_2(dba)_3$	DMF/H_2O	$NaHCO_3$	80	18	0	
10	$Pd_2(dba)_3$	THF/H_2O	NaOH	80	18	0	-
11	$NiCl_2(PCy)_2/PPh_3$	toluene/H_2O	K_3PO_4	80	18	0	-
12	$NiCl_2(PCy)_2/PPh_3$	toluene/H_2O	NaOH	80	18	0	-
13	$NiCl_2$ glyme/PPh_3	toluene/H_2O	K_3PO_4	80	18	0	-
14	$NiCl_2$ glyme/PPh_3	toluene/H_2O	NaOH	80	18	0	-

Table 1: *Suzuki-Miyaura cross-coupling reaction conditions of phenol **52** and pinacol ester **55**.*

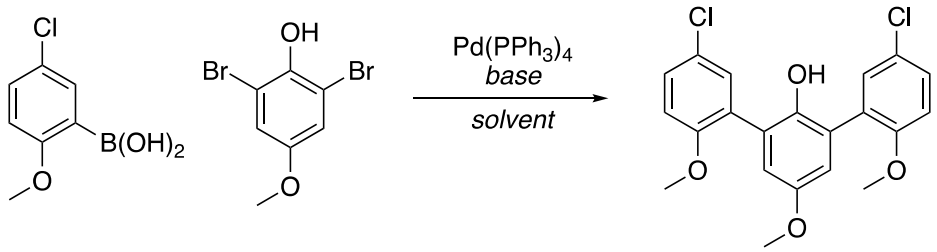
Isomerisation of the allyl groups occurred in many of these initial attempts. This process can occur through base or metal catalysis. This results in isomerisation to the more stable internal E-alkene[29], identified through *J* coupling analysis. Due to the presence of two allyl groups, mono- (to **51a**) or bis- (to **51b**) isomerisation can occur (see Scheme 10).



(**51**) (**51a**) (**51b**)

Scheme 10: *Isomerisation of **51** to **51a** and **51b**.*

To eliminate this, similar coupling reactions were performed with chlorine in place of the allyl groups allowing further functionalisation to be performed later on in the synthesis (see Table 2).



(56) **(52)** **(57)**

Entry	Catalyst (5 mol%)	Solvent	Base (Eq.)	Temp. (°C)	Time (h)
1	$Pd(PPh_3)_4$	dioxane/H_2O	K_2CO_3 (6)	85	16
2	$Pd(PPh_3)_4$	toluene/EtOH	Na_2CO_3 (6.4)	85	16

Table 2: *Investigations into the Suzuki-Miyaura cross-coupling of boronic acid **56** and phenol **52**.*

Several new observations were made during these reactions. The first was an obvious colour change of reaction mixture from colourless to deep red following addition of the base. The presence of the acidic phenolic proton suggests that the phenol coupling partner was present in solution as the phenolate, as these are typically highly coloured solutions. The second observation was that a distinctive set of peaks in the ^{1}H-NMR spectrum emerged as a major impurity which was not isolated during purification by chromatography. Depending on the number of equivalents of base used in the reaction, the ratios of the two peaks were either strictly 1:1 or 2:1. With the chemical shifts matching those of the deborylated and dehalogenated starting material, it suggests that this impurity is related to the starting materials. Its apparent instability on silica has led us to propose that it could be a boron complex, formed as a result of a phenolate attacking the boronic acid species (see Figure 7).

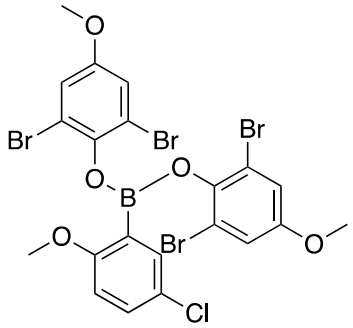
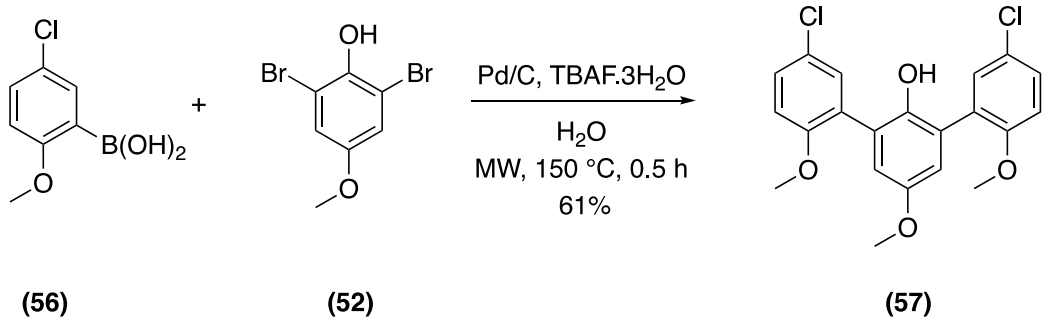


Figure 7: *Proposed structure of impurity.*

7.2.1.1. Microwave-assisted Suzuki-Miyaura cross-coupling reactions

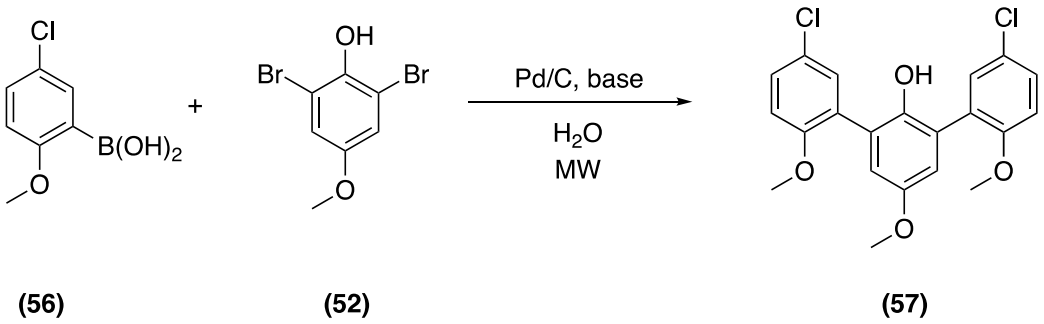
There are various reports of microwave-assisted Suzuki-Miyaura cross-couplings, the first being reported in 1996 by Larhed and Hallberg.[30] Microwave reactions are associated with shorter reaction times, more efficient heating and often higher yields than those that use conventional heating methods.[31] Due to it's high dielectric constant, water is considered a good choice of solvent for microwave-heated reactions, not to mention it's low cost, high availability and it's non-toxic properties. The primary issue with using water as a solvent is poor solubility of substrates, with reactions often needing a phase transfer agent or heterogeneous catalyst to overcome these barriers.[32] The coupling of halophenols with boronic acids with microwave irradiation is reported by Schmidt *et al*.[33] Catalysed by Pd/C (10%, 50% wet) in the presence of TBAF.$3H_2O$ in water, the reaction between boronic acid **56** and phenol **52** had reached completion after 30 minutes at 150 °C, through microwave irradiation (see Equation 3).



(56) **(52)** **(57)**

Equation 3: A *microwave-assisted Suzuki-Miyaura cross-coupling reaction of boronic acid **50** and phenol **46**.*

A variety of conditions were trialled. Use of KOH was unsuccessful with 0% conversion to the expected product. Use of TBAF.$3H_2O$ on a 0.25 mmol scale, with respect to **52**, at 150°C for 30 minutes gave a 61% yield, however following an increase in scale to 0.5 mmol, the reaction failed. Using TBAF (1.00 M solution in THF) gave a 28% yield. Reactions with CsF and KF were unsuccessful (see Table 3).



(56) **(52)** **(57)**

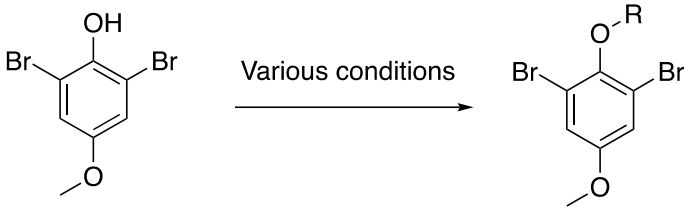
Entry (scale/mmol)	Catalyst (5 mol%)	Base (6 eq.)	Temp (°C)	T (min)	Isolated yield (%)
1 (0.25)	Pd/C	KOH	150	30	0
2 (0.25)	Pd/C	TBAF.$3H_2O$	150	30	61
3 (0.50)	Pd/C	TBAF.xH_2O	150	40	0
4 (0.50)	Pd/C	TBAF (1M THF)	80	40	28
5 (0.20)	Pd/C	CsF	180	30	0
6 (0.20)	Pd/C	KF	180	30	0

Table 3: *Conditions for microwave-assisted Suzuki-Miyaura cross-coupling reactions.*

7.2.1.2. Preparation and use of protected phenol coupling partner

Following numerous failed reactions it was speculated that the free phenol component of the central unit was preventing the coupling from occurring. In an attempt to prevent any participation from the phenol, use of a suitable protecting group to mask the OH through the coupling reaction was considered a viable solution.

Protection of the 2,6-dibromo-4-methoxyphenol (**52**) with a variety of protecting groups were trialled, to no avail (see Table 3).



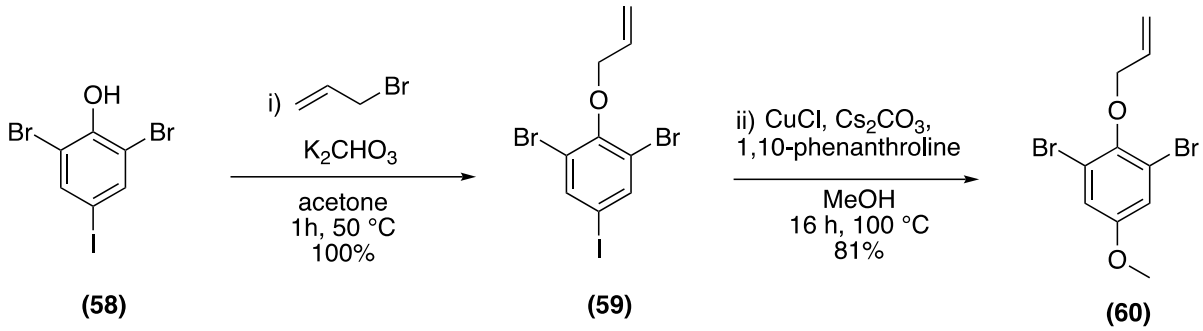
(52)

Entry	Protecting group/additive	Base	Solvent	Temp. (°C)	Conversion (%)
1	acetic anhydride	pyridine	pyridine	r.t.	0
2	allyl bromide	K_2CO_3	acetone	55	0
3	acetyl chloride	NaH	pyridine	0 - r.t.	0
4	allyl bromide	Cs_2CO_3	DMF	r.t.	0
5	allyl bromide	DBU	acetone	r.t.	0
6	allyl bromide/TBAI	K_2CO_3	DMF	r.t. - 120	0
7	allyl bromide	KOH	MIBK	r.t.	0
8	MOMCl	DIPEA	CH_2Cl_2	r.t.	0
9	BnBr/TBAI	NaH	THF	0 - r.t.	0
10	TBDPSCl	imidazole	CH_2Cl_2	0	0
11	Me_2SO_4	KOH	acetone	r.t.	0
12	BzCl	pyridine	CH_2Cl_2	r.t.	0
13	PivCl	K_2CO_3	THF	r.t.	0

Table 3: *Conditions for the protection of phenol **52**.*

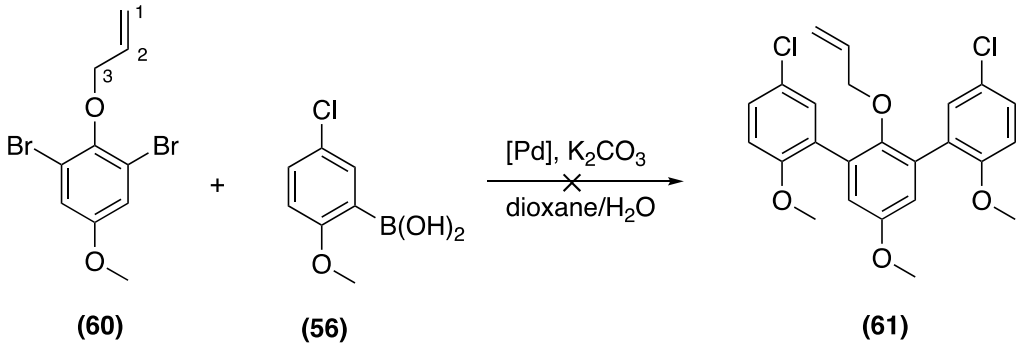
An analogous reaction with 2,6-dibromo-4-iodophenol (**58**) with allyl bromide and K_2CO_3 in acetone at reflux for one hour gave the protected phenol **59** in quantitative yields. This process was scalable and no further purification of the product was required. Following the successful preparation of **59**, a selective Ullmann cross-coupling with methanol using

catalytic Cu(I) chloride, 1,10-phenanthroline and Cs_2CO_3 gave the desired coupling partner **60** in good yields (see Scheme 10).



Scheme 10: i) *Allylation of phenol **58** to **59**; ii) Ullmann cross-coupling of **59** with methanol with to **60**.*

After obtaining the protected coupling partner **60**, Suzuki-Miyaura cross-couplings with boronic acid **56** using $Pd(PPh_3)_4$ and Pd G3 XPhos were carried out. Both reactions were unsuccessful (see Equation 4). The introduction of an allyl ether functionality creates an additional site in which palladium can insert which can in turn lead to alternative coupling reactions occurring instead, such as a Heck reaction or pi-allyl formation.

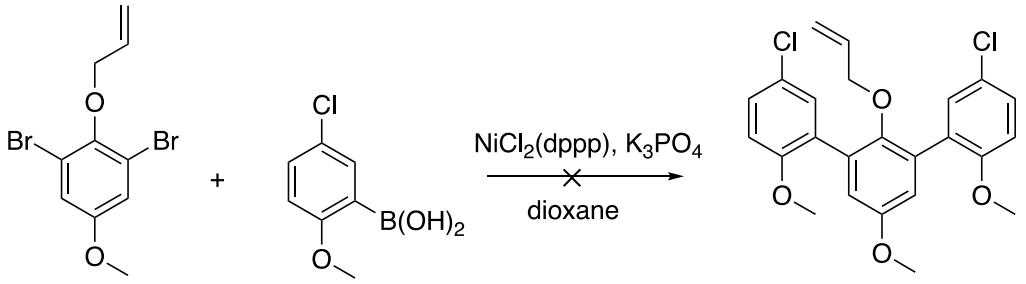


Equation 4: *Suzuki-Miyaura cross-coupling reaction with protected phenol **60** and boronic acid **56**.*

A shift in the characteristic allyl peak, proton 2 on the dibromo substrate **60**, from 6.15 Hz in the starting material to 5.94 Hz in the crude reaction mixtures indicates a marked change in its chemical environment. A slight change of shift for that allyl proton would be expected going from the monomeric coupling partner to the desired product, however, due to change in shift being so large, this suggested direct participation of the allyl group.

7.2.1.3. Nickel and Copper Catalysed Suzuki-Miyaura Reaction

There are reports in the literature of nickel and copper catalysed Suzuki-Miyaura cross-coupling reactions.[34–36] The reaction of protected phenol **60** and boronic acid **56** under nickel catalysis proved unsuccessful with the major product being protodeboronated starting material (see Equation 5).

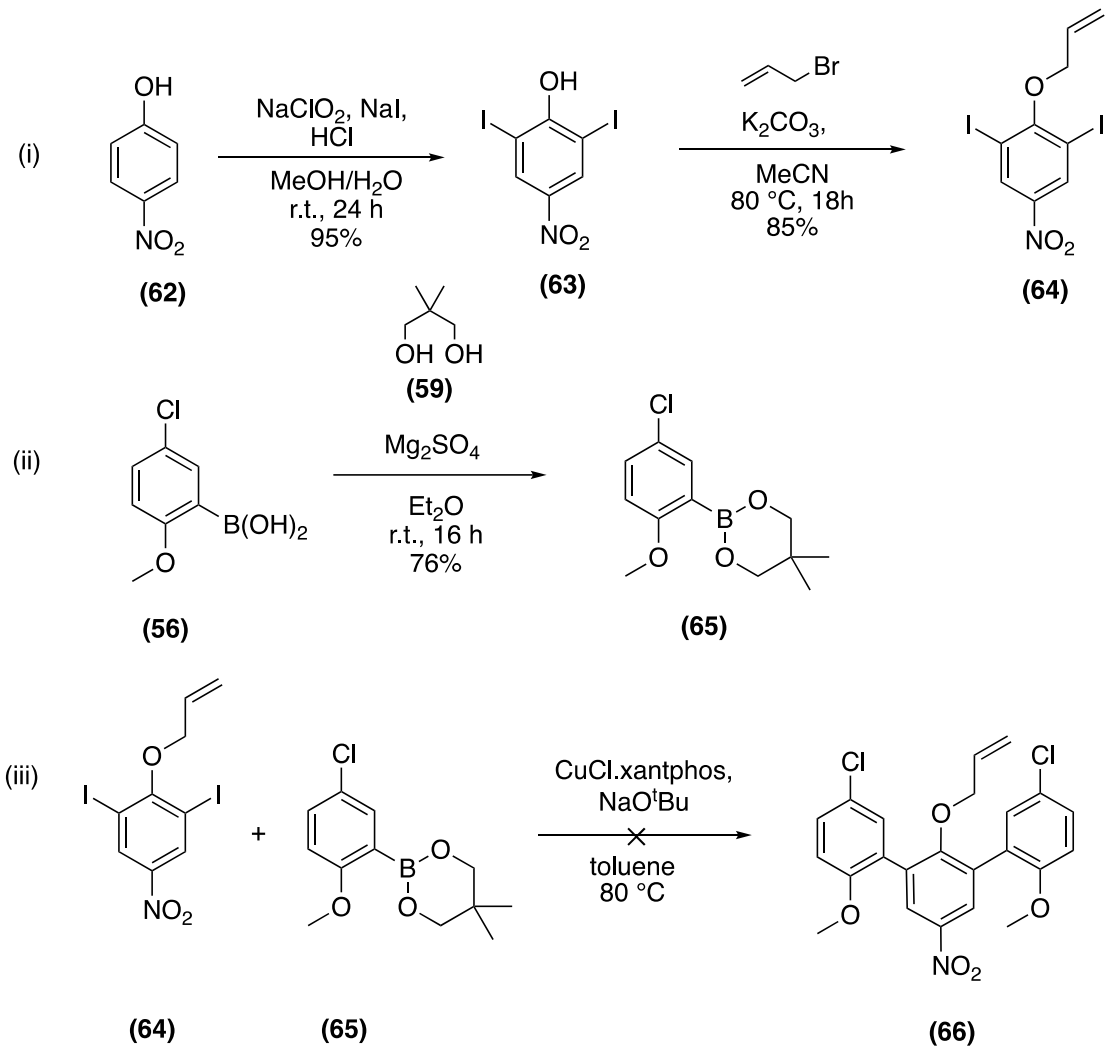


Equation 5: *Nickel catalysed Suzuki-Miyaura cross-coupling of dibromo **60** and boronic acid **56**.*

A literature review of copper-catalysed Suzuki-Miyaura cross-coupling reactions reported the successful coupling of similar substrates.[36] Diiodo species **63** was prepared from 4-nitrophenol (**62**), sodium chlorite, sodium iodide and HCl in a MeOH/H_2O solvent system in excellent yields. The allylation of **63** with allyl bromide, K_2CO_3 in MeCN at reflux afforded coupling partner **64** in 81% yield over two steps.

The formation of the boronic ester coupling partner **65** was a one-step process reacting boronic acid **56** with 2,2-dimethyl-1,3-propanediol in toluene with the drying agent $MgSO_4$, again, in good yields.

The coupling of **64** and **65** was attempted using catalytic CuCl.xantphos with NaO^tBu in toluene at 80°C, however this was not successful with a range of non-desired products forming (see Scheme 11).

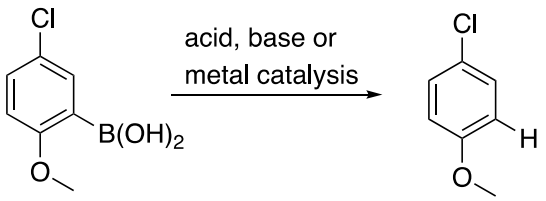


Scheme 11: i) *Preparation of diiodo **64**; ii) Preparation of boronic ester **65**; (iii) Conditions for copper-catalysed Suzuki-Miyaura reaction of **64** and **65**.*

Following from this, no further Suzuki-Miyaura reactions with substrates containing allyl groups were attempted.

7.2.1.4. Protodeboronation and alternative coupling partners

A number of side reactions are frequently observed with Suzuki-Miyaura cross-couplings, namely protodeboronation, oxidation and palladium catalysed homocoupling[37]. These processes can be acid[38], base[39] or metal salt catalysed (see Equation 6).[40]

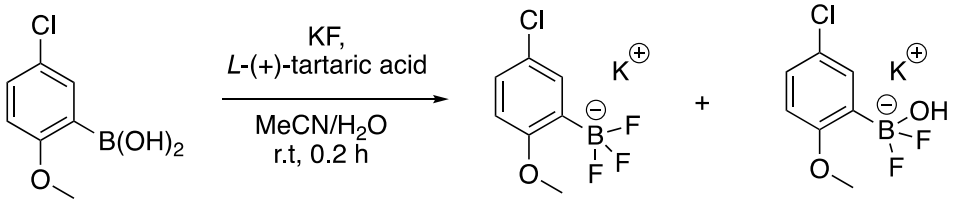


(56) **(67)**

Equation 6: *Protodeboronation can occur through acid, base or metal catalysis.*

One of the most effective strategies in minimising protodeboronation is to use the "slow release" method,[41] generating the boronic acid in situ. *N*-coordinated boronates[42] are less susceptible to protodeboronation than their boronic acid equivalents. Alternatively, potassium organotrifluoroborate reagents can be used.[43] In all cases, accumulation of the boronic acid is avoided reducing the number of side reactions from occurring.

Preparation of the potassium organotrifluoroborate is as reported by Lloyd-Jones and co-workers.[44] Subjecting boronic acid **56** to KF in the presence of *L*-(+)-tartaric acid, which acts as an alkali-metal sponge, gave the potassium organofluoroborate salts **68** and **69** in the ratio 2:1 respectively (see Equation 7).



(56) **(68)** **(69)**

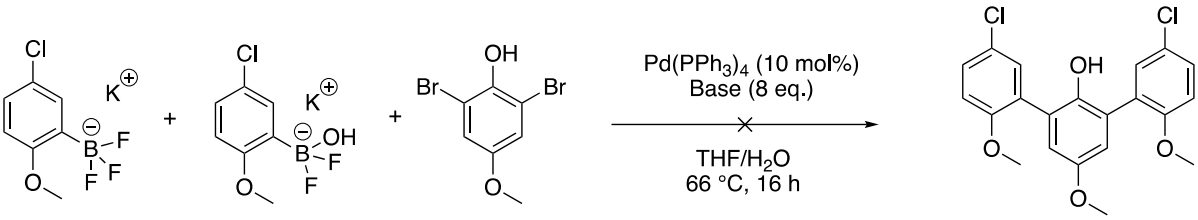
2 : **1**

Equation 7: *Preparation of potassium organofluoroborate salts **68** and **69**.*

During the reaction flocculation appeared to prevent full conversion to the trifluoroborate salt. Increased conversion was observed when the reaction mixture was sonicated

extensively, however there was still a substantial amount of the difluoroborate salt present and the two could not be separated.

Following the preparation of the organofluoroborate salts **68** and **69**, a Suzuki-Miyaura cross-coupling reaction was carried out with phenol **52** (see Equation 8). All reactions failed with a range of side-products forming.

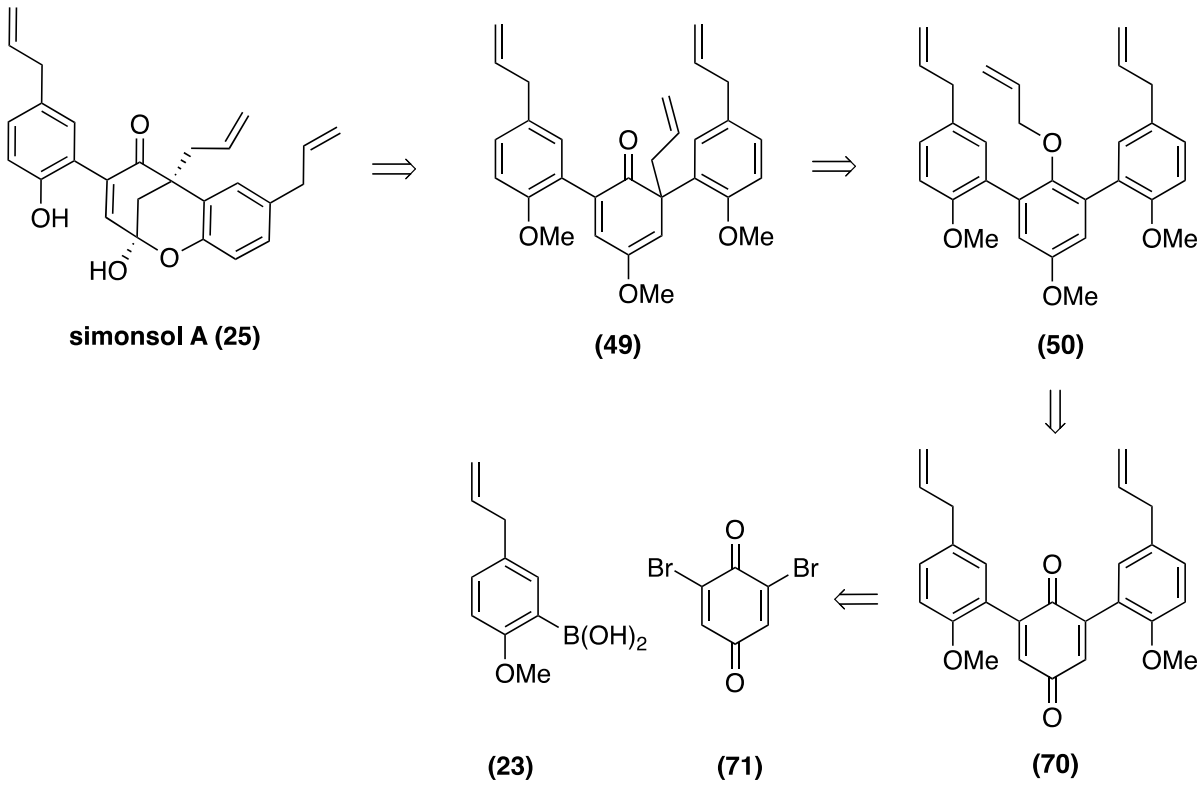


(68) **(69)** **(52)** **(57)**

Equation 8: *Suzuki-Miyaura cross-coupling reaction between organotrifluoroborates **68** and* **69**, and *phenol **50**. Bases trialled: K_2CO_3, TBAF, KF, Na_2CO_3.*

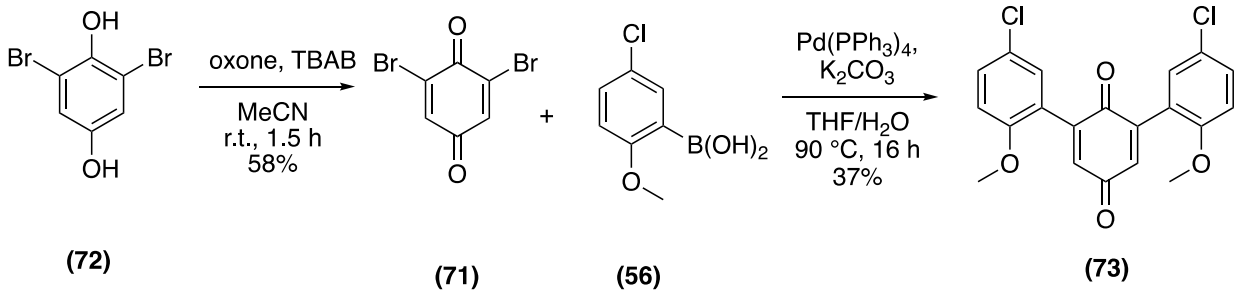
7.2.1.5. Suzuki-Miyaura coupling of quinone substrate

An alternative retrosynthetic analysis of simonsol A shows that quinone **70** can be obtained through the cross-coupling of boronic acid **23** and dibromoquinone **71**, depicted as Suzuki-Miyaura coupling partners for simplicity (see Scheme 12).



Scheme 12: *Second generation retrosynthetic analysis of simonsol A (**25**).*

Dibromoquinone **71** was prepared from the oxidation of 2,6-dibromohydroquinone (**72**) with oxone and TBAB in average yields. The coupling of **71** and boronic acid **56** with $Pd(PPh_3)_4$ provided trimer **73** in 37% yield (see Scheme 13). The same reaction with Pd G3 XPhos gave protodeboronated starting material as the major product.

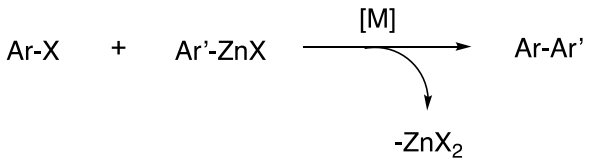


Scheme 13: *Preparation triaryl **73** with quinone **71** and boronic acid **56**.*

With alternative cross-coupling reactions yielding much higher, this route was abandoned.

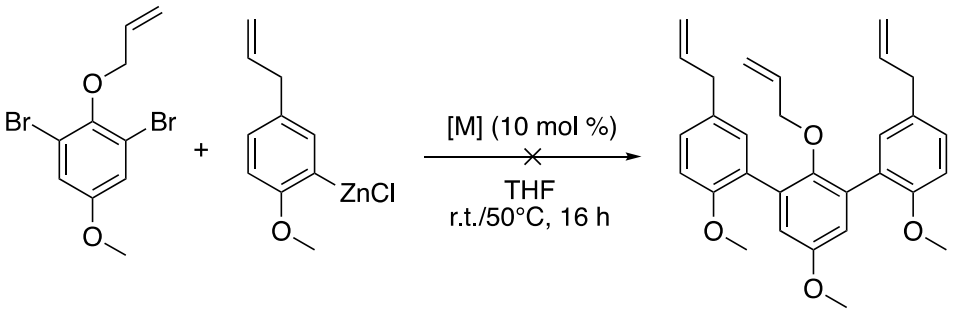
7.2.2. Negishi cross-coupling reactions

Negishi cross-couplings are an alternative coupling reaction of a zinc organometallic reagent and an unsaturated halide (see Equation 12). Due to the quick transmetallation of organozinc reagents to palladium, such reactions can take place under very mild conditions making them an attractive alternative to the Suzuki-Miyaura coupling.[45]



Equation 12: *A Negishi cross-coupling with an aryl halide (Ar-X) and organozinc reagent (Ar'-ZnX).*

Palladium is often the catalyst of choice, however there are reports of nickel[46] and, less commonly, cobalt[47] catalysed Negishi reactions. Coupling of dibromo **60** and organozinc species **74** under various conditions were carried out (see Table 4). Three different catalysts were chosen and the reactions performed at both room temperature and at 50 °C. All six reactions failed with the major products being dehalogenated and de-metallated starting material.



(60) **(74)** **(50)**

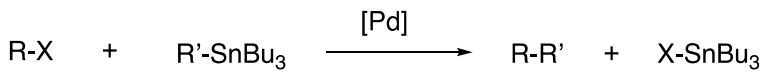
Entry	Catalyst [M]	Temperature (°C)	Conversion (%)
1	$Pd(PPh_3)_4$	r.t.	0
2	$Pd(PPh_3)_4$	50	0
3	$CoCl_2$	r.t.	0
4	$CoCl_2$	50	0
5	$Ni(dppp)Cl_2$	r.t.	0
6	$Ni(dppp)Cl_2$	50	0

Table 4: *Conditions for Negishi cross-coupling of dibromo **60** and organozinc **74**.*

Following the low success of these reactions, it was decided that no further Negishi reactions were to be carried out.

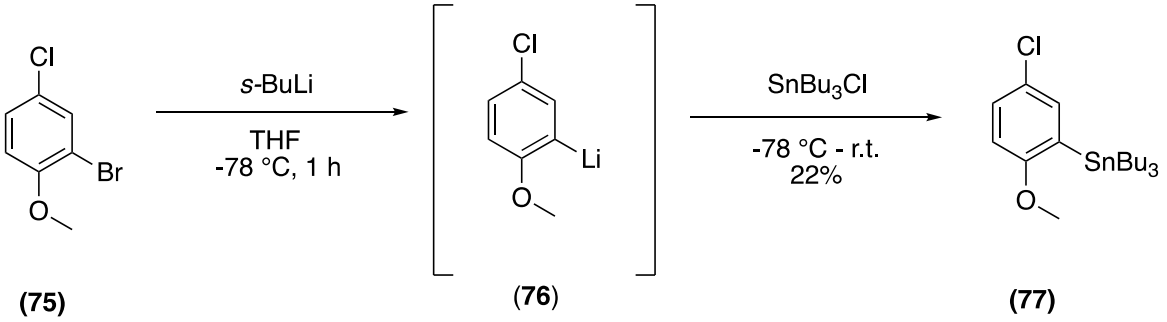
7.2.3. Stille cross-coupling reactions

Stille reactions (see Equation 13) employ an organotin reagent and an unsaturated halide to form C-C bonds.[48] Examples of palladium catalysed cross-couplings of stannanes and carbon electrophiles were first reported in 1977 by Kosugi and co-workers.[49] Use of the Stille reaction, particularly in the manufacturing of pharmaceuticals, is often frowned upon due to the high toxicities of organotin reagents. Despite this, they are often an efficient and versatile way of forming carbon-carbon bonds and are still widely used in research.



Equation 13: *A Stille cross-coupling reaction with an aryl halide (Ar-X) and an organostannane (R-$SnBu_3$).*

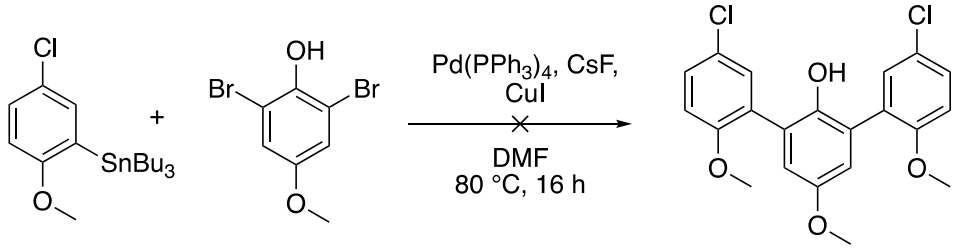
Preparation of organotin reagent **77** started with a selective lithium-halogen exchange on **75** providing the organolithium reagent **76**. Subsequent addition of tributyltin chloride, **77** was isolated in 22% yield (see Scheme 14).



(75) **(76)** **(77)**

Scheme 14: *Preparation of organostanne **72**.*

Coupling of organostannane **77** and 2,6-dibromo-4-methoxyphenol (**52**) was unsuccessful. (see Equation 15). Analysis of the reaction mixture showed de-stannylated material with no desired product. After evaluating the practicalities of this reaction it was decided that no further investigations into this line of work would take place. The low yielding preparation of the organostannane alongside the high toxicity associated with these reactions make them inappropriate in this scheme of work.

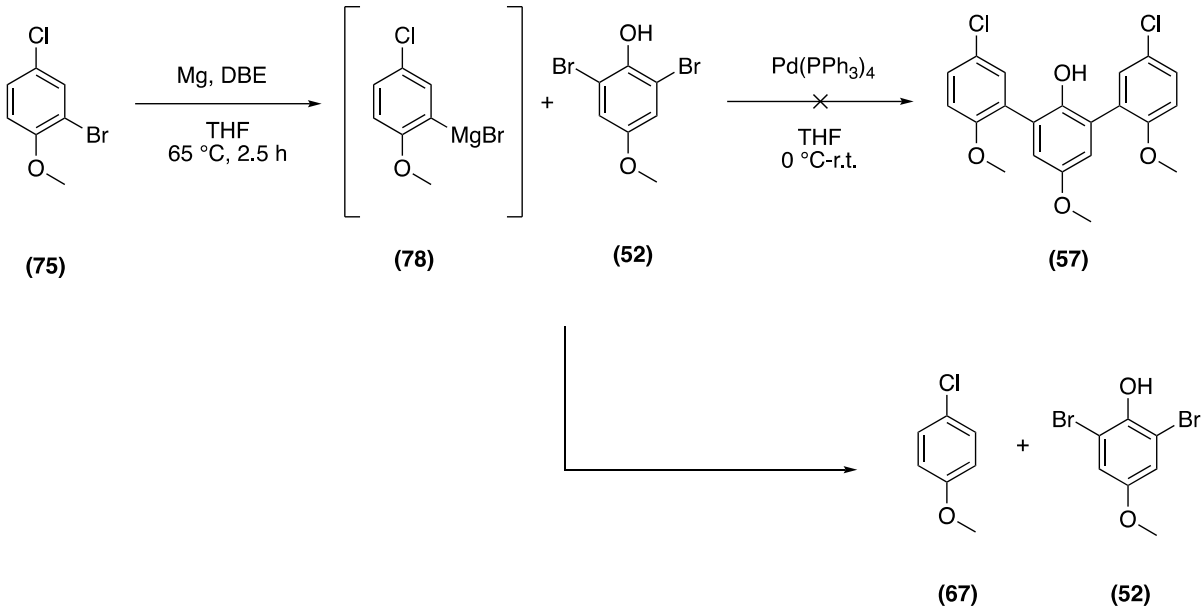


(77) **(52)** **(57)**

Equation 15: *Stille cross-coupling reaction with organostannane **77** and phenol **52**.*

7.2.4. Kumada-Corriu cross-coupling reactions

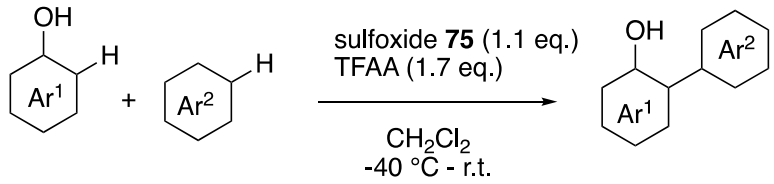
Kumada-Corriu cross-coupling reactions employ a Grignard reagent and an unsaturated halide. They are usually catalysed by either palladium or nickel[50] and occur readily at lower temperatures[51] making them an attractive alternative for carbon-carbon bond formations. Preparation of the aryl Grignard reagent **78** was achieved by reacting 2-bromo-4-chloromethoxybenzene (**75**) with magnesium turnings and 1,2-DBE in THF at 65 °C and was used directly in the next step. Following the addition of 2,6-dibromo-4-methoxyphenol (**52**) and $Pd(PPh_3)_4$ the major products that formed were 4-chloromethoxybenzene (**67**) and the starting phenol **52**. This suggested that the Grignard reagent had been quenched by the phenolic proton on **52** (see Scheme 15).



Scheme 15: *Preparation of Grignard reagent **78** and unsuccessful cross-coupling reaction with phenol **52**.*

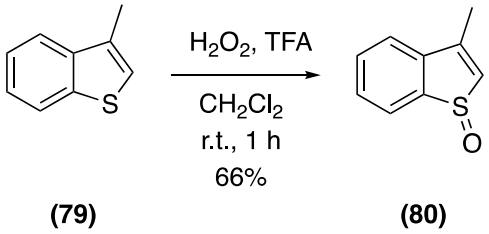
7.2.5. Oxidative-addition cross-coupling reactions

Oxidative addition cross-couplings occur in many of the biosynthetic pathways of secondary plant metabolites, [52] particularly those with phenolic cores. In early 2020, Proctor and co-workers developed a sulfoxide-mediated oxidative cross-coupling of phenols (see Equation 16).[53]



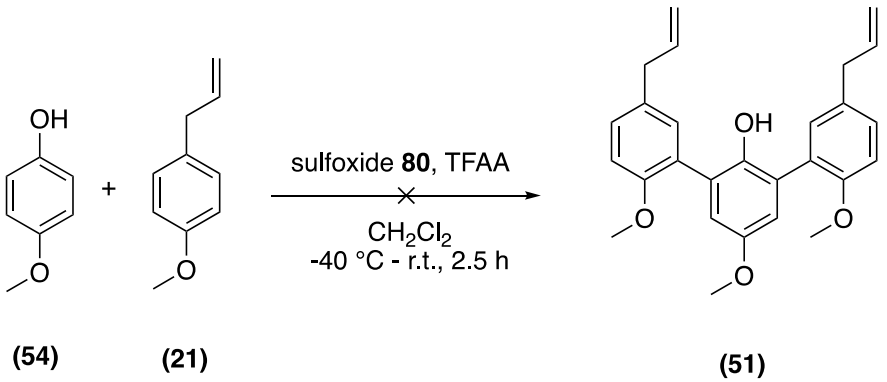
Equation 16: *Oxidative addition cross-coupling for the coupling of phenols with phenols, phenol derivatives and arenes.*

Oxidation of commercially available 3-methylbenzo[*b*]thiophene-1-oxide (**79**) with hydrogen peroxide and TFA provided **80** in 66% yield (see Equation 17).



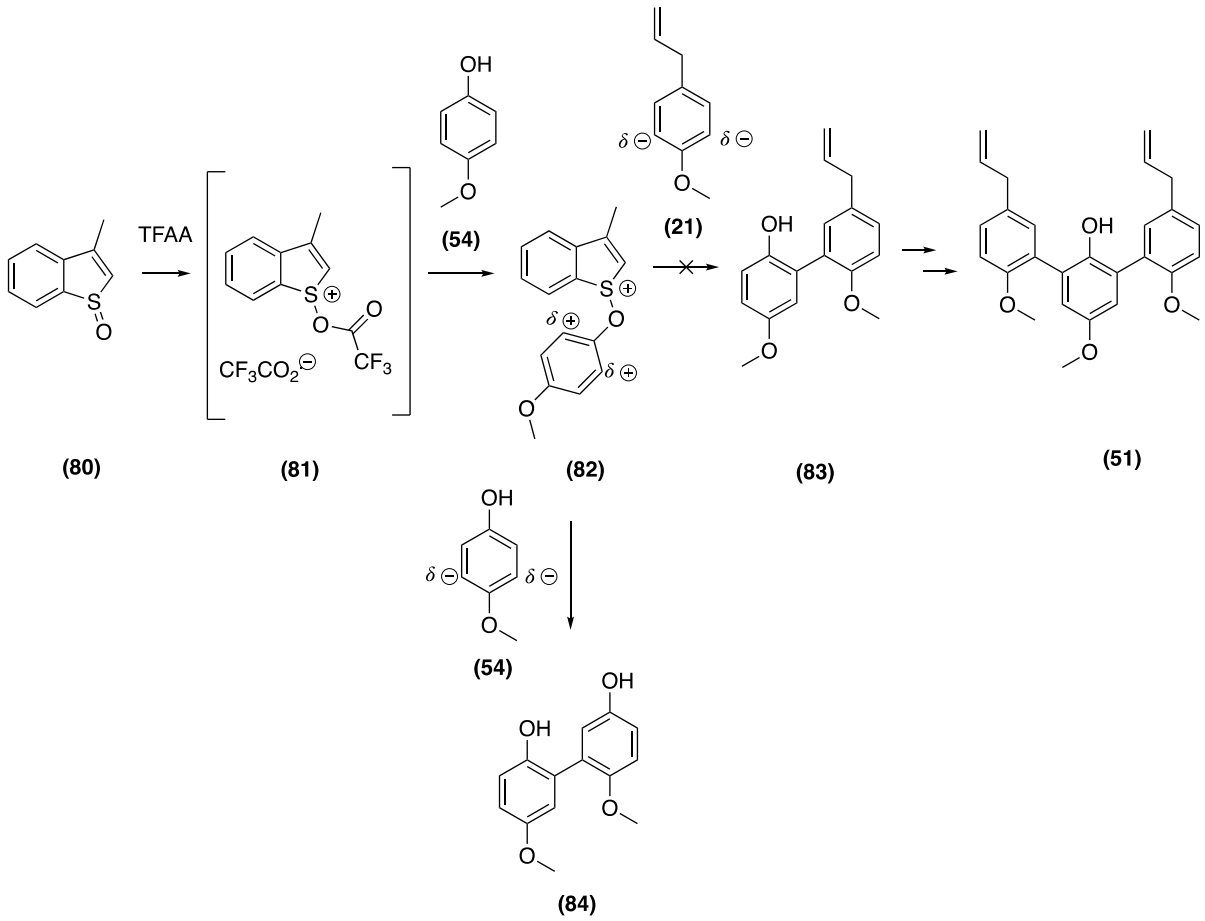
Equation 17: *Oxidation of benzothiophene **79** to sulfoxide **80**.*

Coupling of 4-methoxyphenol (**54**) and 4-allylanisole (**21**) were unsuccessful with the major product being homocoupling of phenol (**54**) (see Equation 18).



Equation 18: *Sulfoxide-mediated oxidative cross-coupling* of 4-methoxyphenol (**54**) and 4-allylanisole (**21**).

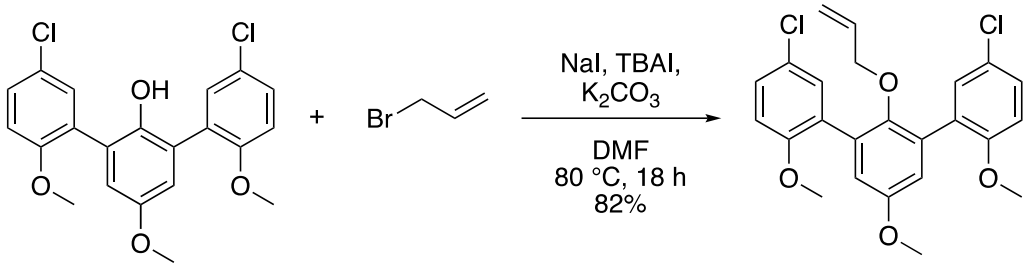
It has been proposed that the reaction proceeds following activation of sulfoxide **80** with TFAA to intermediate **81**. An interrupted Pummerer reaction with 4-methoxyphenol (**54**) provides sulfonium **82**, with partial positive charges *ortho* to the phenol oxygen. Nucleophilic attack from 4-allylanisole (**21**), with partial negative charges *ortho* to the methoxy group should have provided biaryl **83** which would then react further to form triaryl **51**. However, the major product observed was biaryl **84**, obtained through homo-coupling of 4-methoxyphenol (**54**) (see Scheme 16).



Scheme 16: *Proposed mechanism for the sulfoxide-mediated oxidative cross-coupling of chavicol (**21**) a*nd 4-methoxyphenol (**54**).

7.3. Investigations into Claisen rearrangements

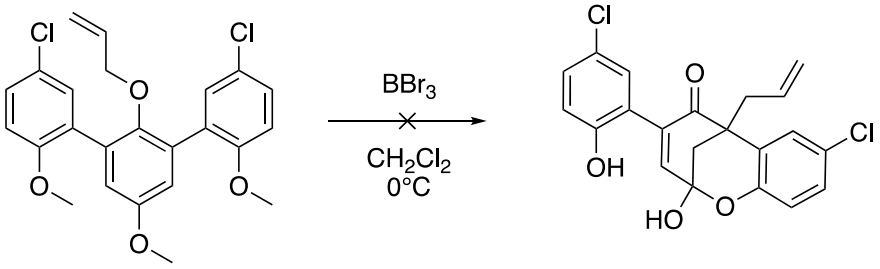
Following the successful synthesis of triaryl **57**, allylation of the central phenolic core with allyl bromide gave triaryl **61** in an 82% yield (see Equation 19).



(57) **(61)**

Equation 19: *Allylation of triaryl **57** with allyl bromide.*

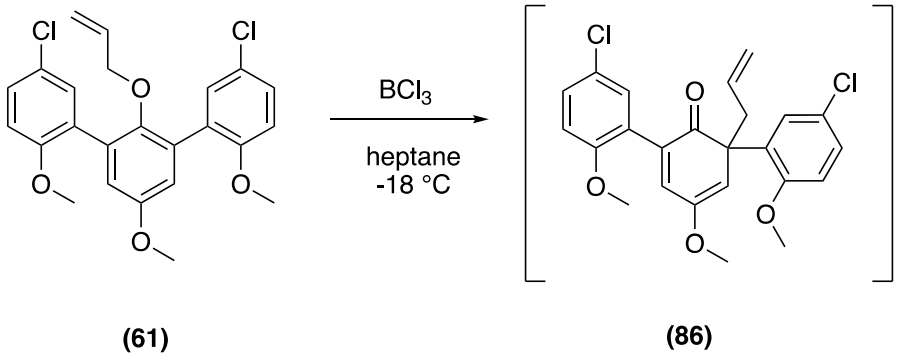
After obtaining key intermediate **61**, investigations into the Lewis acid-catalysed Claisen rearrangement were carried out. Initial attempts with BBr_3 were unsuccessful (see Equation 20). ^1H NMR spectra identified that all three methoxy groups had successfully been deprotected, however loss of the characteristic allyl peak suggested that HBr had added across the double bond.



(61) **(85)**

Equation 20: *Unsuccessful Lewis acid-catalysed Claisen rearrangement of **61** using BBr_3.*

Following this, an analogous experiment with BCl_3, a milder Lewis acid, was carried out with thermal control throughout in the hope that this would prevent addition of HCl across the allyl bond (see Equation 21). When BCl_3 was used to catalyse the Claisen rearrangement at -18 °C, it was observed that all three methoxy groups remained intact with a characteristic shift of allyl peak. Additionally, two dd peaks at 3.18 ppm and 3.30 ppm provided evidence that the two diastereotopic protons in **86** were present and that the rearrangement had been triggered. Due to ending the reaction early, full conversion of **61** to **86** was not observed, and **86** was never isolated.



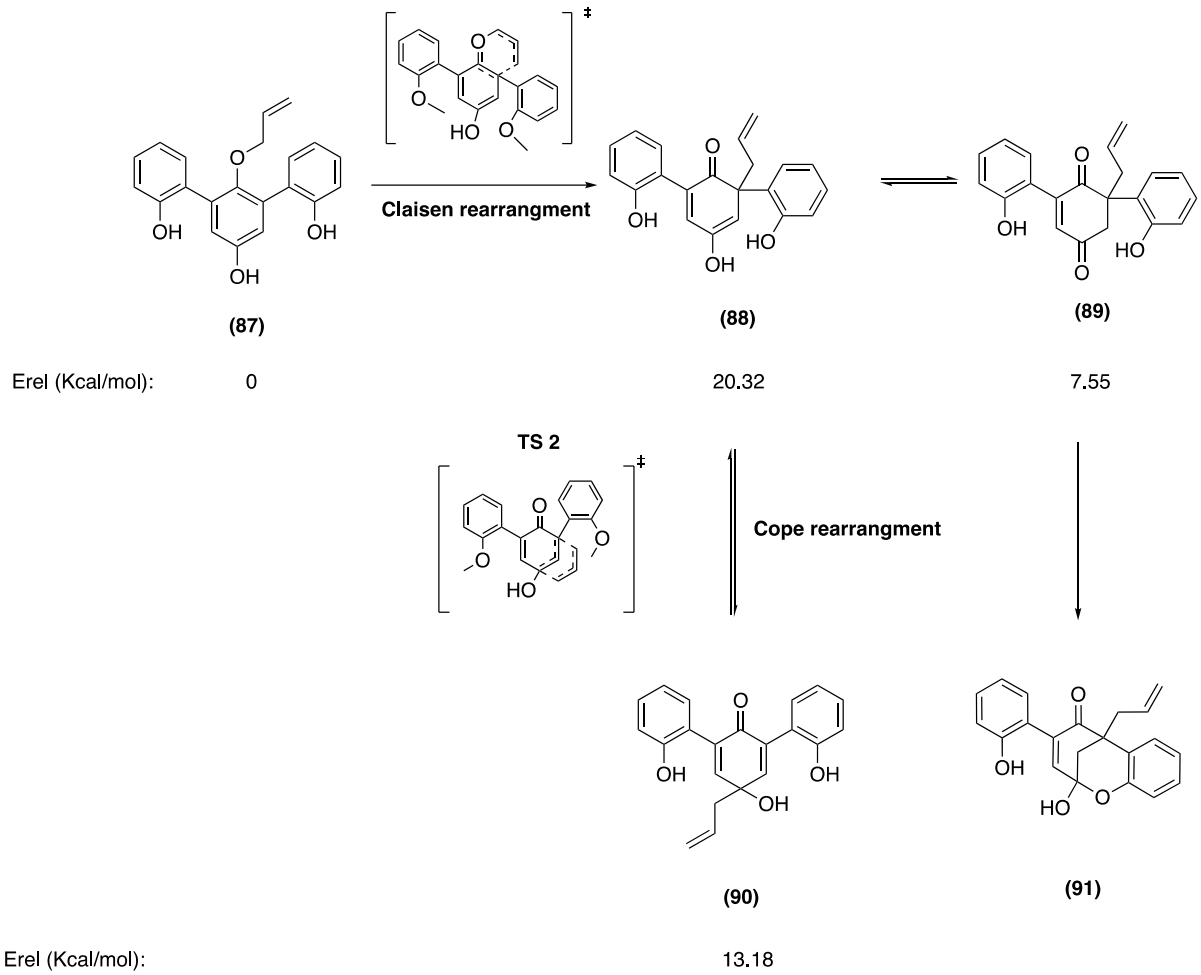
(61) **(86)**

Equation 21: *Lewis acid-catalysed Claisen rearrangement of **61** with BCl_3.*

8. Computational studies

To gain further insight into the proposed biosynthesis of simonsol A, quantum chemical calculations were carried out using the Spartan 2018 suite of software. The results are shown in Scheme x. The ωB97X-D/6-31g* theoretical model was chosen as appropriate as it has been used widely for the modelling of organic reactions. Calculations were carried out in the gas phase and molecular mechanics (equilibrium conformer) calculations were used on the starting materials to identify suitable conformations for the QM calculations. Transition structures were characterised by frequency calculations which had a single imaginary frequency corresponding to the breaking/forming bond(s) in the transition structure. calculated energies of the relevant structures has determined the energy barrier for the Claisen rearrangement to be 45.7 Kcal/mol and, for the Cope rearrangement, 33.6 Kcal/mol.

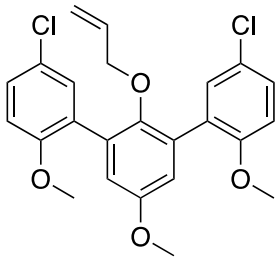
These barriers are very large and may be overestimated by this theoretical model. The Claisen rearrangement is yet to be carried out under simple thermal conditions. This suggests that a Lewis acid-mediated ionic "Claisen" rearrangement is likely to be required in the synthesis. This is in agreement with the experimental result obtained which suggested that boron trichloride had promoted the rearrangement. These calculations are also supportive of the newly proposed biosynthesis that relies on dunnianol (see Scheme 7, section 5.3.2.). **87** represents a truncated version of intermediate **47** in the dunnianol-based biosynthesis. The energy barrier associated with the Cope rearrangement of **88** to **90** is a much more reasonable 32.5 kcal/mol. This would give **90** a half-life of approximately 8 hours at 130 °C. Furthermore, the key tautomerisation of **88** to **90** is also shown to be viable with the ketone tautomer **89**, the precursor to natural product **91**, being favoured over **88**. In summary the calculations have shown that there is a very high barrier for a concerted Claisen rearrangement.



Scheme 17: *Interconversions of **87** to calculate energy barriers for Claisen and Cope rearrangements*

9. Conclusions

A range of cross-coupling reactions have been investigated towards the synthesis of simonsol A (**25**). Although these were generally unsuccessful, synthesis of key intermediate **61** (see Figure 6) was achieved in 50% yield over two steps.



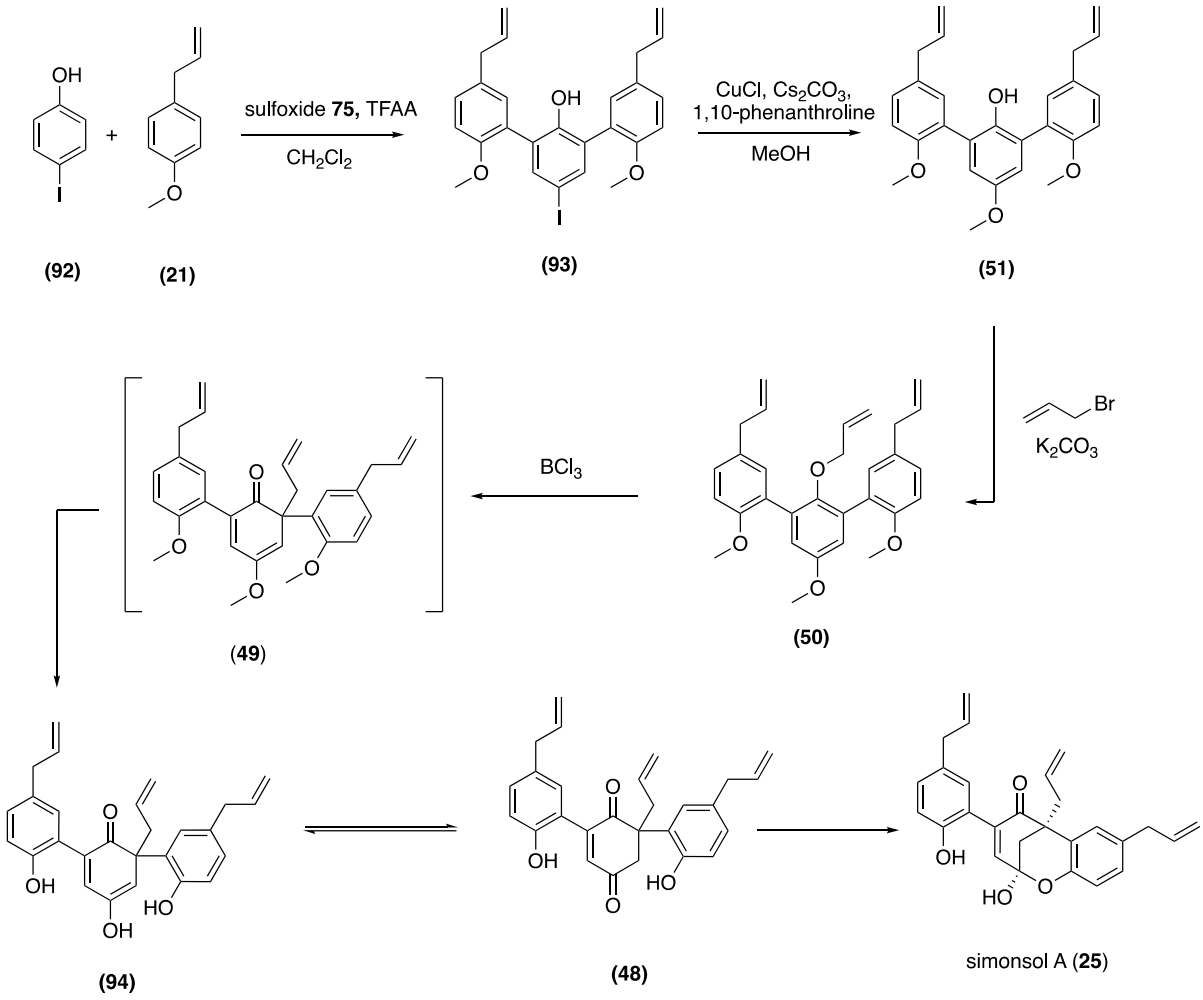
(61)

Figure 6: *Structure of key intermediate **61.***

Additionally, quantum calculations determined the energy barriers for the Claisen and Cope rearrangements as 45.7 Kcal/mol and 32.5 Kcal/mol respectively. This provides strong evidence for our proposed biosynthesis of simonsol A.

10. Future work

Carrying on from the work in this report, it would be of interest to further develop the synthetic route towards simonsol A by exploring the oxidative cross-coupling of 4-allylanisole (**21**) with a modified phenolic coupling partner, such as 4-iodophenol (**92**) (see Scheme 18). If successful, triaryl **93** could be further manipulated to form intermediate **51.** Allylation of **51** to triaryl **50**, followed by a Lewis acid-mediated Claisen rearrangement to **49** and deprotection to **94** could, following tautomerisation to **39**, undergo a ring-closing hemiacetal formation to simonsol A (**25**).



Scheme 18: *Future work - oxidative cross-coupling reaction with 4-iodophenol (**92**) and 4-allylanisole (**21**).*

11. Experimental

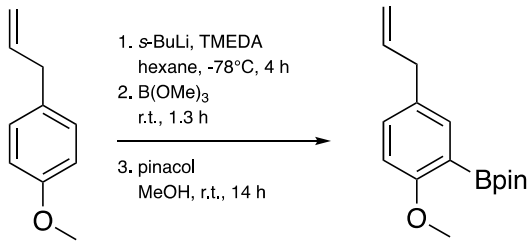
11.1. General details:

Unless stated, all reactions were carried out under an atmosphere of nitrogen in standard glassware. De-gassing was achieved by purging solutions with nitrogen for 10-15 minutes. For moisture sensitive reagents and reactions, glassware was dried in the oven (125 °C) overnight. 0 °C was achieved using an ice-water bath. -18 °C to -20 °C was achieved using an ice-salt bath (3:1 w/w). -78 °C was achieved using a dry ice-acetone bath. Petroleum ether refers to the fraction with bp 40-60 °C. Commercially available reagents were used as supplied, with the exception of dry THF, dry CH_2Cl_2, dry DMF which were dried on an alumina column before use. TMEDA and trimethyl borate were also distilled over sodium

wire and stored under argon before use. Butyllithium reagents were titrated with *N*-benzylbenzamide. Room temperature varied between 18 °C and 25 °C. Macherey-NagalTM Standard SIL G Silica sheets were visualised with ultra-violet light (254 nm), staining with $KMnO_4$ solution when required. Flash column chromatography was performed using Fluorochem silica gel 60, 35-70 microns. Infrared spectra were obtained neat on a Bruker ALPHA-IR Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ascend400 instrument as dilute solutions in a deuterated solvent. Chemical shifts (δ) are recorded in parts per million (ppm) relative to residual solvent peaks. All coupling partners (*J*) are reported in Hz. ^1H-NMR signals are described by the following abbreviations: s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets. Mass spectra were obtained on a Bruker MicroToF II instrument.

11.2. Synthesis of compounds

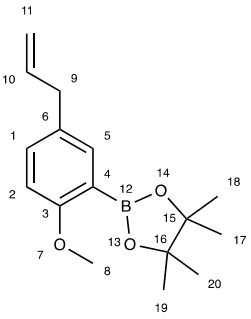
2-(5-allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (55):



(21) **(55)**

To a solution of hexane (21.0 mL) and TMEDA (1.90 mL, 12.7 mmol) at -78 °C was added *s*-BuLi (12 mL of a 1.10 M solution in hexanes, 13.2 mmol) over 15 minutes. After 1 hour, 4-allylanisole (1.10 mL, 7.17 mmol) was added over 25 minutes and the mixture was stirred at -78 °C for 4 hours. Trimethylborate (1.30 mL) was added at -78 °C and the reaction mixture was warmed to room temperature and was stirred for a further 80 minutes.
The reaction mixture was acidified to pH 2 with HCl (1.00 M aqueous solution) and then the aqueous phase was extracted with Et_2O (3 x 30.0 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To the crude oil at room temperature was added MeOH (21.0 mL) and pinacol (2.40 g, 20.3 mmol) and then the reaction mixture was stirred at room temperature for 14 hours. The organics were concentrated *in vacuo*.

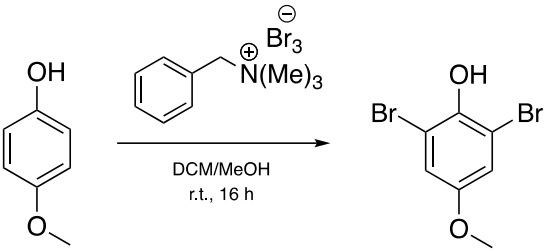
Purification by flash column chromatography (petroleum ether/EtOAc, 4:1) gave boronic acid pinacol ester **55** as a colourless oil (0.930 g, 51%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.4 Hz, 1H, H-5), 7.20 (dd, *J* = 8.4, 2.4 Hz, 1H, H-1), 6.80 (d, *J* = 8.4 Hz, 1H, H-2), 5.95 (ddt, *J* = 16.8, 10.0, 6.9 Hz, 1H, H-10), 5.04 (m, *J* = 13.4, 9.0 Hz, 2H, H-11''), 3.81 (s, 3H, H-8), 3.33 (d, *J* = 6.9 Hz, 2H, H-9), 1.35 (s, 12H, H-17, H-18, H-19, H-20); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (Cq), 138.1 (CH), 136.9 (Ar CH), 132.6 (Ar CH), 131.6 (Cq), 115.5 (CH_2), 110.8 (Ar CH), 83.6 (2 x Cq), 56.2 (CH_3), 39.4 (CH_2), 25.0 (4 x CH_3); **HRMS** (ESI$^+$): $C_{16}H_{23}BO_3$ $[M + H]^+$ calcd. 274.1670, found 275.1809; **IR**: V_{max} cm^{-1} 2977, 1605, 1415, 1370, 1283, 1143, 1071, 966.

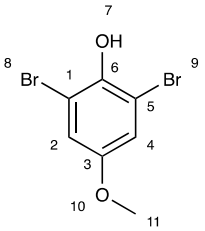
^{13}C NMR: C-B signal not observed due to quadrupolar relaxation.

2,6-dibromo-4-methoxyphenol (52):



(54) **(52)**

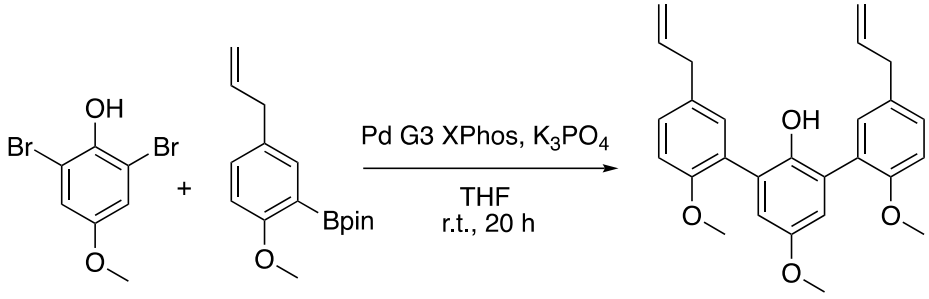
To 4-methoxyphenol (**54**) (25 mg, 0.202 mmol) in CH_2Cl_2 (0.180 mL) was added a solution of benzyltrimethylammonium tribromide (0.180 g, 0.462 mmol) in CH_2Cl_2 (1.27 mL) and MeOH (0.550 mL). The reaction mixture was stirred at r.t. for 16 hours. Following completion of the reaction, the organics were concentrated *in vacuo* and the brown residue was triturated with Et_2O/CH_2Cl_2 (1:1), filtered and dried through suction filtration to give 2,6-dibromo-4-methoxyphenol as a light brown solid (**52**) (48 mg, 85%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H, H-2, H-4), 3.7 (s, 3H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8 (Cq), 143.9 (Cq), 118.0 (2 x CH), 109.8 (2 x C-Br), 56.3 (CH_3); **HRMS** (ESI^-): $C_7H_6Br_2O_2$ [M - H]$^-$ calcd. 281.9310 found 280.8645.

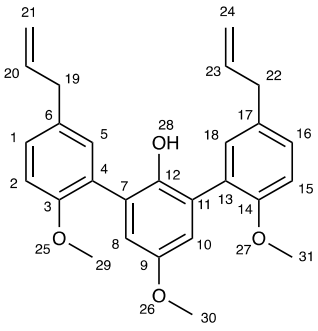
OH proton not observed. Spectroscopic data consistent with the literature.[54]

5,5''-diallyl-2,2'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-ol (51):



(52) **(55)** **(51)**

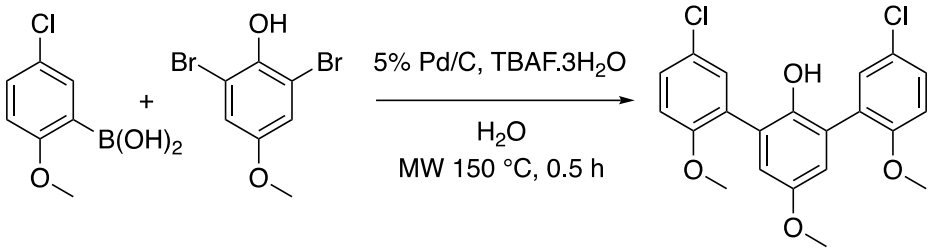
2,6-dibromo-4-methoxyphenol (**52**) (20 mg, 0.0714 mmol), 2-(5-allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**55**) (58 mg, 0.212 mmol), K_3PO_4 (0.5 M, 0.840 mL, 0.420 mmol) in THF (1.00 mL) were sparged with argon for 10 minutes and Pd G3 XPhos (3 mg, 0.00355 mmol) was added and the reaction was stirred at r.t. for 18 hours.
The organics were concentrated *in vacuo* and purified by flash column chromatography (cyclohexane:EtOAc, 9:1) to give triaryl **51** as a yellow oil (29 mg, 86%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.2 Hz, 2H, H-5, H-18), 7.20 (d, *J* = 8.3 Hz, 2H, H-1, H-16), 6.97 (d, *J* = 8.3 Hz, 2H, H-2, H-15), 6.88 (d, *J* = 2.2 Hz, 2H, H-8, H-10), 6.01 (ddt, *J* = 16.8, 9.7, 6.8 Hz, 2H, H-20, H-23), 5.20 – 5.05 (m, 4H, H-21, H-24), 3.85 (s, 6H, H-29, H-31), 3.4 (s, 3H, H-30), 3.42 (d, *J* = 6.8 Hz, 4H, H-19, H-22); **HRMS** (ESI^-): $C_{27}H_{28}O_4$ [M - H]$^-$ calcd. 416.1988 found 415.1915; **IR**: V_{max} cm^{-1} 3048, 2929, 1638, 1500, 1460, 1244, 1041, 964, 788.

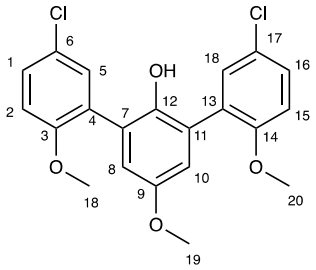
OH proton not observed by ^{1}H NMR. Missing ^{13}C NMR data.

5,5''-dichloro-2,2'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-ol (57):



(56) **(52)** **(57)**

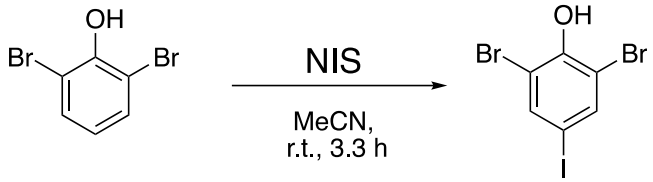
To a suspension of 2,6-dibromo-4-methoxyphenol (**52**) (71 mg, 0.252 mmol) and 3-chloro-5-methoxyphenylboronic acid (**56**) (120 mg, 0.645 mmol) in H_2O (2.50 mL), was added TBAF.3H_2O (630 mg, 2.00 mmol). The reaction mixture was sparged for 10 minutes and 10% Pd/C (50% wet, 27 mg, 0.0130 mmol) added. The suspension was heated at 150 °C through microwave irradiation for 30 minutes. The reaction was diluted with Et_2O (2.00 mL) and acidified to pH 6 with HCl (1.00 M aqueous solution). The aqueous phase was extracted with Et_2O (3 x 5.00 mL) and combined organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude material was purified by flash column chromatography (cyclohexane:EtOAc, 9:1 to 4:1) to give triaryl **57** as a an orange residue (62 mg, 61%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.6 Hz, 2H, H-5, H-18), 7.32 (dd, *J* = 8.7, 2.6 Hz, 2H, H-1, H-16), 6.94 (d, *J* = 8.7 Hz, 2H, H-2, H-15), 6.84 (s, 2H, H-8, H-10), 3.84 (s, 6H, H-18, H-20), 3.81 (s, 3H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0 (2 x Cq), 153.5 (Cq), 145.2 (Cq), 131.9 (2 x CH), 129.5 (2 x CH) 128.8 (2 x Cq), 127.2 (2 x Cq), 126.3 (2 x C-Cl), 116.6 (2 x CH), 112.7 (2x CH), 56.5 (2 x CH_3), 56.0 (1 x CH_3); **HRMS** (ESI^-): $C_{21}H_{18}Cl_2O_4$ $[M-H]^-$ calcd. 404.0582, found 403.0513.

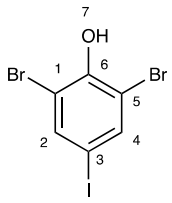
OH proton not observed by ^{1}H NMR. Missing IR data.

2,6-dibromo-4-iodophenol (58):



(58)

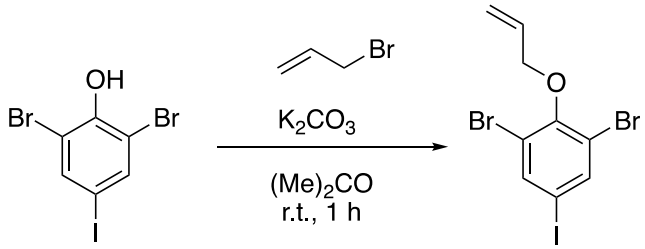
To a solution of 2,6-dibromophenol (2.00 g, 7.94 mmol) in MeCN (50 mL) was added NIS (2.20 g, 9.70 mmol) over 20 minutes. The orange solution was stirred at room temperature for 3 hours. The reaction mixture was diluted with Et_2O (30.0 mL) and quenched with a saturated solution of sodium thiosulfate (30.0 mL). The aqueous phase was extracted with Et_2O (3 x 50.0 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude material was purified by flash column chromatography (hexane:EtOAc, 95:5) to give 2,6-dibromo-4-iodophenol (**58**) as an off-white solid (2.46 g, 79%).



^{1}H NMR (400 MHz, CDCl3) δ 7.74 (s, 2H, H-2, H-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8 (Cq), 139.9 (2 x Ar CH), 111.0 (2 x C-Br), 82.0 (C-I); **R_f** (EtOAc/hexane, 1:1): 0.58.

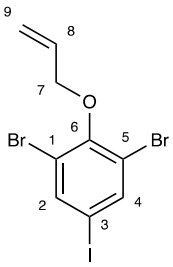
OH proton not observed by ^{1}H NMR. Correct M/Z was not found. Spectroscopic data consistent with the literature.[55]

2-(allyloxy)-1,3-dibromo-5-iodobenzene (59):



(58) **(59)**

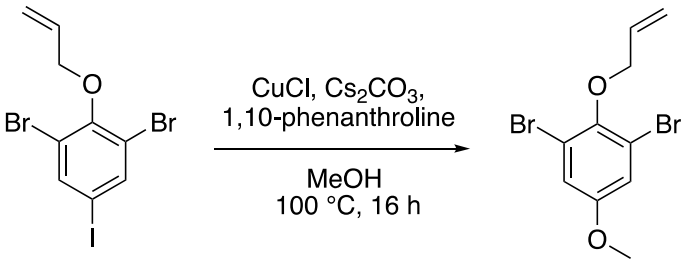
To a solution of 2,6-dibromo-4-iodophenol (**58**) (50 mg, 0.132 mmol) in acetone (0.400 mL) was added K_2CO_3 (36 mg, 0.261 mmol) and allyl bromide (23 µL, 0.266 mmol). The suspension was stirred at room temperature for 1 hour. The suspension was acidified to pH 1 with HCl (1.00 M aqueous solution) and the aqueous phase extracted with EtOAc (3 x 15.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and the organics were concentrated in *vacuo* to give **59** as on off-white powder (50 mg, 93%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 2H, H-2, H-4), 6.15 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 1H, H-8), 5.45 (dd, *J* = 17.2, 1.3 Hz, 1H, H-9'), 5.31 (dd, *J* = 10.3, 1.3 Hz, 1H, H-9''), 4.53 (dt, *J* = 5.9, 1.3 Hz, 2H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5 (Cq), 140.8 (2 x Ar CH), 132.8 (CH), 119.7 (CH_2), 119.2 (2 x C-Br), 87.7 (Cq), 74.4 (CH_2); **IR**: V_{max} cm^{-1} 2363,1436, 1411, 1236; **R_f** (CH_2Cl_2/petrol, 1:1): 0.69.

Spectroscopic data consistent with the literature.[55]

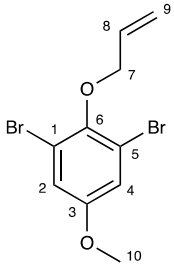
2-(allyloxy)-1,3-dibromo-5-methoxybenzene (60):



(59) **(60)**

A suspension of 2-(allyloxy)-1,3-dibromo-5-iodobenzene (**59**) (1.00 g, 2.39 mmol), Cs_2CO_3 (1.6 g, 4.92 mmol) and 1,10-phenanthroline (86 mg, 0.470 mmol) in MeOH (2.00 mL) was sparged for 10 minutes and CuCl (32 mg, 0.320 mmol) was added. The reaction mixture was heated at 60 °C for 16 hours. The reaction mixture was diluted with EtOAc (50.0 mL) and washed with HCl (1.00 M aqueous solution, 2 x 30.0 mL). The aqueous phase was extracted

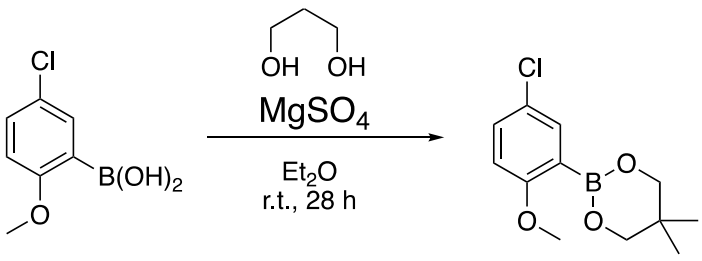
with EtOAc (3 x 30.0 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude material was purified by flash column chromatography (cyclohexane:CH_2Cl_2, 7:3) yielding 2-(allyloxy)-1,3-dibromo-5-methoxybenzene (**60**) as a colourless oil (0.670 g, 81%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H, H-2, H-4), 6.17 (m, 1H, H-8), 5.45 (dd, *J* = 17.2, 1.6 Hz, 1H, H-9'), 5.33– 5.25 (m, 1H, H-9''), 4.49 (d, *J* = 5.9 Hz, 2H, H-7), 3.76 (s, 3H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.4 (Cq), 147.0 (Cq), 132.7 (CH), 118.6 (2 x Ar CH), 118.3 (CH_2), 118.1 (Cq), 74.24 (CH_2), 56.0 (CH_3); **IR**: V_{max} cm^{-1} 3080, 3058, 3015, 2978, 2831, 1593, 1532, 1415, 1042, 966, 927.

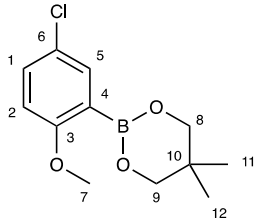
Correct M/Z was not found.

2-(5-chloro-2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (65):



(56) **(65)**

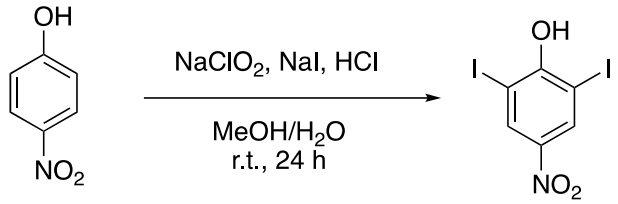
To a solution of (5-chloro-2-methoxyphenyl)boronic acid (**56**) (502 mg, 2.70 mmol) in Et_2O (3.50 mL) was added 2,2-dimethyl-1,3-diol (188 mg, 1.81 mmol) and $MgSO_4$ (257 mg, 2.14 mmol). The reaction mixture was stirred at r.t. for 28 hours. Additional 2,2-dimethyl-1,3-diol (93 mg, 0.894 mmol) was added and the reaction mixture stirred at r.t. for a further 16 hours. The reaction mixture was filtered through a pad of celite, rinsing with Et_2O to give boronic ester **65** as a light yellow oil (0.520 g, 76%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.8 Hz, 1H, H-5), 7.29 (dd, *J* = 8.8, 2.8 Hz, 1H, H-1), 6.78 (d, *J* = 8.8 Hz, 1H, H-2), 3.81 (s, 3H, H-7), 3.78 (s, 4H, H-8, H-9), 1.04 (s, 6H, H-11, H-12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.3 (Cq), 135.5 (Ar CH), 131.3 (Ar CH), 125.6 (C-Cl), 112.0 (Ar CH), 72.7 (2 x CH_2) 56.2 (OMe), 31.9 (Cq), 22.0 (2 x CH_3); **IR**: V_{max} cm^{-1} 2961, 1439, 1306, 1147, 1049.

B-C signal not observed due to quadripolar relaxation. The correct M/Z was not found. Spectroscopic data is consistent with the literature.[56]

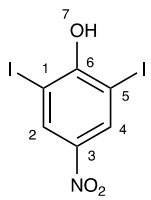
2,6-diiodo-4-nitrophenol (63):



(62) **(63)**

To a solution of $NaClO_2$ (360 mg, 4.00 mmol) and NaI (1.2 g, 8.00 mmol) in H_2O (100 mL) was added 4-nitrophenol (**62**) (309 mg, 2.22 mmol) in MeOH (100 mL). HCl (37%, 0.50 mL) was added the reaction stirred at r.t. for 24 hours.

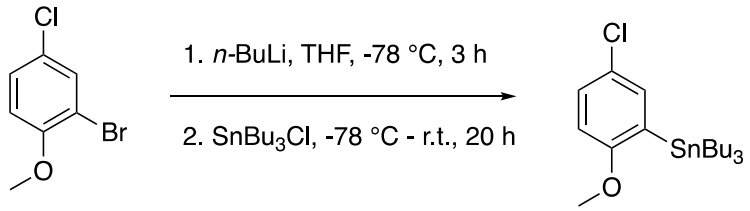
On completion of the reaction, the reaction mixture was diluted with EtOAc (150 mL) and the aqueous phase extracted with EtOAc (3 x 200 mL). Organic phases were combined and washed with brine (100 mL), dried over $MgSO_4$ and filtered. Concentration of the organics in *vacuo* gave 2,6-diido-4-nitrophenol (**63**) as a bright orange powder (0.950 g, 95%).



^{1}H NMR (400 MHz, DMSO) δ 8.4 (s, 2H, H-2, H-4). **HRMS** (ESI^-): $C_6H_3I_2NO_3$ [M - H]$^-$ m/z calcd. 390.8202, found 389.8142.

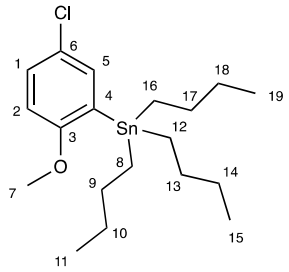
OH not observed. Missing ^{13}C NMR data. Spectroscopic data consistent with literature.[57]

tributyl(5-chloro-2-methoxyphenyl)stannane (77):



(75) **(77)**

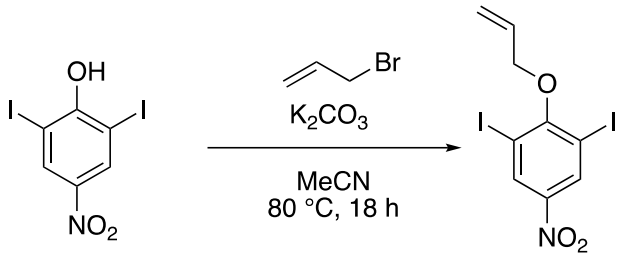
A solution of 2-bromo-4-chloroanisole (**75**) (550 mg) in THF (3.75 mL) was cooled to -78 °C and *n*-BuLi (1.20 mL) was added over 30 minutes. The reaction mixture was stirred for 2.5 hours. $SnBu_3Cl$ (0.540 mL) was added dropwise over 1 minute and the reaction mixture stirred at -78 °C for 3 hours. The reaction mixture was then warmed to room temperature where it was stirred for 17 hours. The reaction mixture was quenched with MeOH (1.00 mL) and organics concentrated in *vacuo.* The crude reaction material was purified by flash column chromatography (silica:K_2CO_3, 9:1, 100% pentane) to give organostannane **77** as a colourless oil (241 mg, 22%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.6 Hz, 1H, H-2), 7.24 (dd, *J* = 8.5, 2.6 Hz, 1H, H-1), 6.73 (d, *J* = 8.5 Hz, 1H, H-5), 3.76 (s, 3H, H-7), 1.52-0.9 (m, 27H, Bu_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2 (Cq), 136.2 (Ar CH), 133.1 (Ar CH), 129.1 (Cq), 126.1 (C-Cl), 110.0 (Ar CH), 55.4 (OMe), 29.2 (3 x CH_2), 27.3 (3 x CH_2), 13.7 (3 x CH_2), 9.9 (3 x CH_3).

Due to safety reasons, IR data could not be obtained.

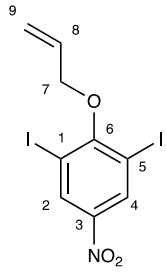
2-(allyloxy)-1,3-diiodo-5-nitrobenzene (64):



(63) **(64)**

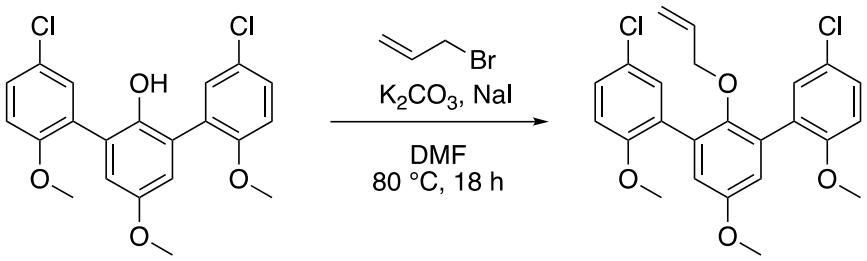
To a solution of 2,6-diido-4-nitrophenol (**63**) (250 mg, 0.639 mmol) in MeCN (2.00 mL) was added K_2CO_3 (178 mg, 1.29 mmol) and allyl bromide (0.120 mL, 1.39 mmol). The reaction mixture was heated at 80 °C for 18 hours. The organics were concentrated in *vacuo* and EtOAc (30.0 mL) added. The organic phase was washed with water (1 x 30.0 mL). The aqueous phase was extracted with EtOAc (3 x 30.0 mL) and combined organic phases dried over $MgSO_4$, filtered and concentrated in *vacuo.*

The crude material was purified by flash column chromatography (cyclohexane:EtOAc, 95:5) to give 2-(allyloxy)-1,3-diiodo-5-nitrobenzene (**64**) as a pale yellow solid (218 mg, 76%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 2H, H-2, H-4), 6.20 (ddt, *J* = 17.1, 10.4, 5.8 Hz, H-1H), 5.53 (dq, *J* = 17.1, 1.5 Hz, 1H, H-12'), 5.37 (dq, *J* = 10.4, 1.2 Hz, 1H, H-12''), 4.60 (dt, *J* = 5.8, 1.2 Hz, 2H, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (Cq), 144.8 (Cq), 135.2 (2 x Ar CH), 132.0 (CH), 119.9 (CH_2), 90.5 (2 x C-I), 74.5 (CH_2); **HRMS** (ESI^+): $C_6H_3I_2NO_3$ $[M + H]^+$ m/z calcd. 430.9679, found 431.8598; **IR**: V_{max} cm^{-1} 2976, 1504, 1432, 1050.

2'-(allyloxy)-5,5''-dichloro-2,2'',5'-trimethoxy-1,1':3',1''-terphenyl (61):

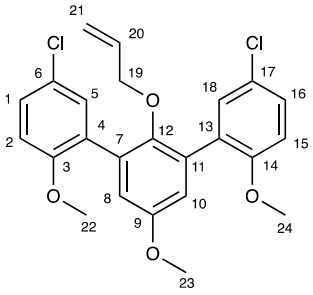


(57) **(61)**

To a solution of triaryl **57** (101 mg, 0.249 mmol), NaI (150 mg, 1.00 mmol) and K_2CO_3 (88 mg, 0.638 mmol) in DMF (0.800 mL) was added allyl bromide (87.0 µL, 1.00 mmol). The reaction mixture was heated at 80 °C for 18 hours.

The reaction mixtures were diluted with EtOAc (10.0 mL) and the organic phase washed with water (1 x 20.0 mL). The aqueous phase was extracted with EtOAc (3 x 30.0 mL) and the organics combined. The organic phases were washed with brine (3 x 30.0 mL) and then dried over $MgSO_4$, filtered and the solvent removed in *vacuo.*

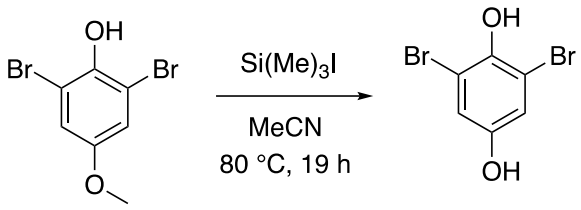
The crude material was purified by flash column chromatography (cyclohexane:EtOAc, 4:1) giving triaryl **61** (94 mg, 85%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.7 Hz, 2H, H-5, H-18), 7.28 – 7.24 (m, 2H, H-1, 16), 6.87 (d, *J* = 8.7 Hz, 2H, H-2, H-15), 6.79 (s, 2H, H-8, H-10), 5.35 (m, 1H, H-20), 4.81 (dt, *J* = 10.4, 1.7 Hz, 1H, H-21'), 4.76 (dq, *J* = 17.1, 1.7 Hz, 1H, H-21''), 3.78 (s, 3H, H-23), 3.77 (s, 6H, H-22, H-23), 3.74 (dt, *J* = 5.6, 1.7 Hz, 2H, H-19); **IR**: V_{max} cm^{-1} 2934, 1493, 1459, 1246, 1202, 1032, 810, 643.

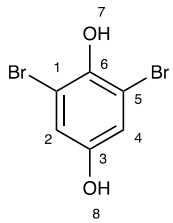
^{13}C NMR data missing.

2,6-dibromobenzene-1,4-diol (67):



(52) **(72)**

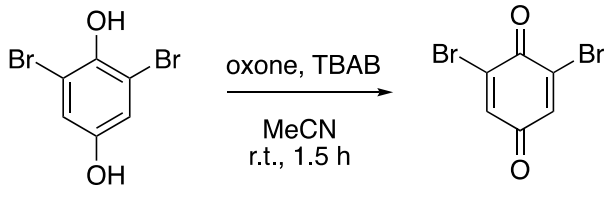
To a solution of 2,6-dibromo-4-methoxyphenol (**52**) (500 mg, 1.77 mmol) in MeCN (8.25 mL) was added TMSI (1.50 mL, 10.5 mmol). The reaction was refluxed for 3 hours. Additional TMSI (1.65 mL, 11.6 mmol) was added and the reaction refluxed for a further 16 hours. The reaction mixture was poured over ice/water and the aqueous phase extracted with EtOAc (3 x 30.0 mL). The organic phase was washed with Na_2SO_4 (1 x 30.0 mL), water (1 x 30.0 mL) and brine (1 x 30.0 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated in *vacuo* to afford 2,6-dibromobenzene-1,4-diol (**72**) as a light brown powder (443 mg, 93%).



^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H, H-7), 9.08 (s, 1H, H-8), 6.94 (s, 2H, H-2, H-4); **^{13}C NMR** (101 MHz, DMSO) δ 151.6 (Cq), 143.2 (Cq), 118.7 (2 x Ar CH) 112.8 (2 x C-Br); **HRMS** (ESI^-): $C_6H_4Br_2O_2$ $[M - H]^-$ m/z calcd. for 267.9040, found 266.8491.

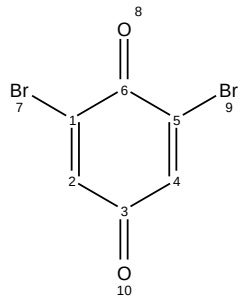
Spectroscopic data consistent with literature.[59]

2,6-dibromocyclohexa-2,5-diene-1,4-dione (71):



(72) **(71)**

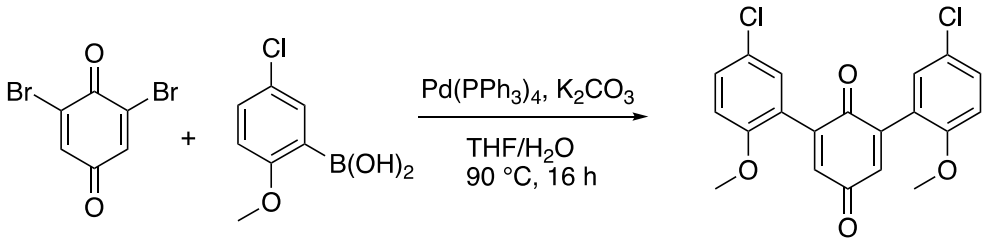
To a solution of 2,6-dibromobenzene-1,4-diol (**72**) (490 mg, 1.83 mmol) in MeCN (3.50 mL) and H_2O (2.50mL) was added oxone (610 mg, 4 mmol) and TBAB (181 mg, 0.562 mmol) and the reaction mixture stirred at r.t. for 1.5 hours. Brine (10.0 mL) was added and the aqueous phase extracted with EtOAc (3 x 10.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude material was purified by flash column chromatography (cyclohexane:EtOAc, 9:1) yielding 2,6-dibromocyclohexa-2,5-diene-1,4-dione (**71**) as a yellow powder (338 mg, 80%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2H, H-2, H-4); **HRMS** (ESI^-): $C_6H_2Br_2O_2$ $[M - H]^-$ m/z calcd. for 265.8880, found 264.8504; **IR**: V_{max} cm^{-1} 1692, 1577, 1263, 1003, 902

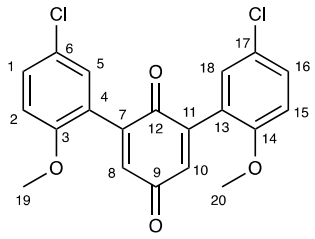
^{13}C NMR data missing. Spectroscopic data consistent with literature.[60]

5,5''-dichloro-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-2',5'-dione (68):



(71) **(56)** **(70)**

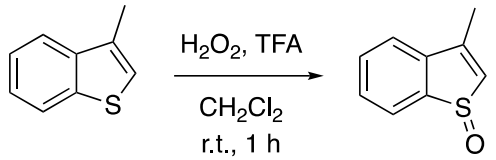
A solution of quinone **71** (30 mg, 0.113 mmol), boronic acid **56** (54 mg, 0.290 mmol) and K_2CO_3 (0.400 mL of a 2.00 M aqueous solution, 0.800 mmol) in THF (1.10 mL) was degassed for 10 minutes. $Pd(PPh_3)_4$ (6 mg, 0.00519 mmol) was added and the reaction heated at 90 °C for 16 hours. EtOAc (5.00 mL) was added and the organic phase was washed with HCl (5.00 mL of a 1.00 M aqueous solution). The aqueous phase was extracted with EtOAc (3 x 5.00 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude material was purified by flash column chromatography (cyclohexane:EtOAc, 4:1 to 3:1) yielding triaryl **70** as an orange residue (16 mg, 37%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H, H-1, H-16), 7.30 (d, *J* = 2.7 Hz, 2H, H-5, H-18), 6.93 (d, *J* = 8.6 Hz, 2H, H-2, H-15), 6.78 (s, 2H, H-8, H-10), 3.83 (s, 6H, H-19, H-20); **IR**: V_{max} cm^{-1} 2938, 1491, 1461, 1438, 1241, 1026, 805, 647.

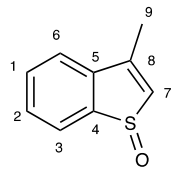
^{13}C NMR data missing. Correct M/Z not found

3-methylbenzo[*b*]thiophene 1-oxide (75):



(79) **(80)**

To a solution of CH_2Cl_2 (15.0 mL) and TFA (15.0 mL) was added 3-methylbenzo[*b*]thiophene (**79**) (0.9 mL, 6.73 mmol) and H_2O_2 (0.850 mL of a 30% aqueous solution). The purple solution was stirred at r.t. for 1 hour and reaction progress was monitored by TLC. The reaction was quenched with $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 (3 x 30.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude reaction material was purified by flash column chromatography (CH_2Cl_2:EtOAc, 4:1) to give sulfoxide **80** (729 mg, 66%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 1H, H-6), 7.60 – 7.39 (m, 3H, H-1, H-2, H-3), 6.78 (s, 1H, H-7), 2.29 (d, *J* = 1.4 Hz, 3H, H-9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.0 (Cq), 145.4 (Cq), 138.7 (Ar CH), 132.3 (Ar CH), 132.0 (Ar CH), 129.0 (Cq), 126.2 (Ar CH), 122.7 (Ar CH), 14.4 (CH_3); **HRMS** (ESI^+): C_9H_8OS $[M + H]^+$ m/z calcd. for 164.2220, found 165.0375. **Rf**=0.16 in CH_2Cl_2:EtOAc, 4:1.

Spectroscopic data consistent with literature.[61]

Coordinates for computational studies:

82:

C	0.632527	2.157291	1.028277
C	-0.122758	4.843516	1.345540
C	-0.702985	2.494619	1.330836
C	1.555591	3.198482	0.862143
C	1.193827	4.529256	1.015009
C	-1.061414	3.833839	1.494961
H	2.580776	2.946126	0.603477
H	1.931680	5.313366	0.879109
H	-2.095926	4.052854	1.737443
H	-0.422708	5.879168	1.474988
C	0.084578	-2.632577	-0.421117
C	-1.401760	-4.625646	-1.699564
C	0.642420	-3.391391	-1.452771
C	-1.236352	-2.900790	-0.022868
C	-1.973034	-3.893578	-0.667949
C	-0.088420	-4.382469	-2.096633
H	1.666188	-3.183920	-1.753005
H	-2.988308	-4.080297	-0.334246
H	0.360526	-4.957855	-2.899619
H	-1.986075	-5.397774	-2.191265
O	-1.673182	1.567467	1.534047
O	-1.847760	-2.245358	0.994229
C	0.439485	-0.251789	0.270351
C	2.760283	-0.911836	1.624926
C	0.876238	-1.583300	0.273182
C	1.112027	0.750415	0.976470
C	2.281966	0.395527	1.655070
C	2.049156	-1.903802	0.951937
H	2.805334	1.153966	2.232792

H	2.405745	-2.927983	0.979438
O	-0.696922	0.077452	-0.445476
O	3.897905	-1.287827	2.264453
H	4.283755	-0.522300	2.706933
C	-0.427934	0.506876	-1.779607
H	0.447828	1.170857	-1.770996
H	-0.173832	-0.376257	-2.383626
C	-1.598324	1.227808	-2.368959
H	-1.419447	1.591586	-3.380215
C	-2.769069	1.448644	-1.782062
H	-3.551023	1.997088	-2.297631
H	-2.992374	1.109696	-0.776426
H	-1.567882	0.877851	0.852223
H	-1.210345	-1.667003	1.436199

83:

C	-0.300243	0.942406	1.754686
H	-0.276529	1.774669	2.456133
C	0.063054	1.166431	0.474809
C	0.031122	0.037700	-0.490994
O	0.359568	0.167752	-1.655829
C	-0.541084	-1.315562	-0.022309
C	-0.712973	-0.354963	2.261672
C	-0.801540	-1.416929	1.453301
H	-1.108194	-2.381674	1.845924
O	-0.991682	-0.475971	3.592929
H	-0.917643	0.387219	4.014362
C	0.511962	2.494566	-0.001648
C	1.403148	4.995446	-0.921251
C	-0.201667	3.666476	0.299181
C	1.672580	2.613943	-0.772857

C	2.124047	3.846679	-1.227843
C	0.244159	4.905486	-0.159974
H	2.222698	1.713019	-1.017503
H	3.029280	3.907050	-1.822993
H	-0.322189	5.803050	0.081454
H	1.738435	5.966661	-1.272740
C	0.428332	-2.427537	-0.430754
C	2.282213	-4.447540	-1.064610
C	0.042272	-3.574946	-1.117293
C	1.777543	-2.316855	-0.058064
C	2.696131	-3.312288	-0.374680
C	0.952165	-4.581816	-1.436090
H	-0.991216	-3.694912	-1.422730
H	3.737134	-3.199182	-0.078691
H	0.617594	-5.461220	-1.976621
H	3.004454	-5.220792	-1.307850
O	-1.338653	3.558438	1.046712
O	2.141166	-1.193192	0.620884
C	-1.911069	-1.437294	-0.772395
H	-1.687677	-1.522345	-1.842057
H	-2.408339	-2.356699	-0.444870
C	-2.821567	-0.265014	-0.537040
H	-2.571653	0.653508	-1.066563
C	-3.872030	-0.284351	0.277415
H	-4.494154	0.593312	0.425617
H	-4.145392	-1.179897	0.831321
H	3.094504	-1.198415	0.764668
H	-1.758063	4.425584	1.095182

84:

H	-1.819266	5.197699	-2.630283
C	-1.136985	4.673760	-1.969229

C	0.607625	3.319306	-0.267563
C	-1.520161	3.472969	-1.378932
C	0.130540	5.185627	-1.714521
C	1.000638	4.516840	-0.858992
C	-0.653587	2.774383	-0.539736
H	-2.497145	3.047377	-1.590284
H	0.446098	6.117698	-2.173292
H	1.980584	4.931782	-0.636003
O	1.380393	2.656667	0.633421
C	-0.179243	0.282465	-0.315202
O	0.700078	0.424930	-1.136965
C	-1.042941	1.472094	0.046387
C	-2.125756	1.352911	0.832457
H	-2.712279	2.223556	1.114529
C	-2.558880	0.059029	1.400550
O	-3.438357	0.003900	2.238196
C	-0.397500	-1.016199	0.474631
C	-1.894452	-1.174901	0.836993
H	-2.446158	-1.432384	-0.077994
H	-2.031191	-1.998887	1.539872
C	0.445084	-0.773929	1.777558
H	0.125558	-1.512779	2.515964
H	0.199179	0.214957	2.180350
C	1.928551	-0.879823	1.579677
H	2.287348	-1.801535	1.124508
C	2.803363	0.050996	1.948796
H	3.872248	-0.091283	1.817111
H	2.478555	0.984828	2.401429
C	0.017552	-2.288335	-0.280085
C	0.615999	-4.689370	-1.663947
C	0.228290	-2.315577	-1.661802
C	0.084310	-3.526497	0.386879

C	0.391920	-4.703720	-0.294416
C	0.524802	-3.488217	-2.351239
H	0.181785	-1.391519	-2.219714
H	0.445252	-5.639568	0.259072
H	0.687440	-3.451900	-3.423521
H	0.853803	-5.612821	-2.182739
O	-0.170216	-3.566560	1.729863
H	2.309961	2.871087	0.493391
H	-0.102839	-4.479056	2.034820

85:

H	-0.427159	5.600063	-2.151598
C	0.225840	4.914609	-1.621776
C	1.895628	3.138661	-0.262348
C	-0.268730	3.703397	-1.145403
C	1.564966	5.227747	-1.421321
C	2.398907	4.345865	-0.740554
C	0.550062	2.800689	-0.470738
H	-1.308404	3.435347	-1.312262
H	1.969546	6.164910	-1.791363
H	3.443292	4.599555	-0.572418
C	0.878258	-2.312848	-0.243073
C	1.942621	-4.862400	-0.759462
C	0.049998	-3.431925	-0.414857
C	2.269697	-2.491525	-0.385621
C	2.783624	-3.768007	-0.627088
C	0.562869	-4.695779	-0.667632
H	-1.026232	-3.292530	-0.348901
H	3.860367	-3.867948	-0.714715
H	-0.107432	-5.539672	-0.795240
H	2.364706	-5.844236	-0.952930
O	2.652625	2.263073	0.450041

O	3.170395	-1.489429	-0.246334
C	0.641833	0.258788	-0.463068
O	1.476672	0.303397	-1.358838
C	0.016766	1.515394	0.039517
C	0.242124	-1.030774	0.163525
C	-0.995439	1.456869	0.912501
H	-1.451346	2.368079	1.295166
C	-0.754035	-1.025026	1.064718
H	-1.054694	-1.949702	1.550406
C	-1.573728	0.175485	1.436881
O	-1.722758	0.257421	2.851744
H	-0.837236	0.316592	3.233652
C	-3.011141	0.008779	0.877119
H	-2.959258	0.018734	-0.216790
H	-3.577965	0.892731	1.197192
C	-3.695337	-1.237097	1.362502
H	-3.832878	-1.313970	2.438826
C	-4.116092	-2.215569	0.565266
H	-4.611909	-3.097523	0.959901
H	-3.988828	-2.166852	-0.514408
H	3.572419	2.552881	0.444683
H	2.787387	-0.686255	-0.644903

TS1:

C	-1.161141	0.432458	2.184324
H	-1.334250	1.043421	3.068024
C	-0.671649	1.018128	1.049852
C	-0.458141	0.224956	-0.153678
O	-0.030566	0.772946	-1.210011
C	-0.560656	-1.219155	-0.018580
C	-1.428651	-0.959996	2.240303
C	-1.154756	-1.758600	1.168675

H	-1.357762	-2.819565	1.236701
C	1.604749	-1.183939	0.499315
H	1.605923	-2.242334	0.729882
H	1.519539	-0.515255	1.352358
C	2.174291	-0.722238	-0.692725
H	2.380236	-1.442421	-1.480322
C	2.139335	0.612598	-1.005245
H	2.437435	0.971369	-1.984253
H	2.026480	1.367442	-0.234283
O	-1.963571	-1.524111	3.361454
H	-2.134335	-0.831818	4.010168
C	-0.335433	2.461945	1.018037
C	0.334176	5.190919	0.940197
C	0.529227	3.018961	1.974993
C	-0.834164	3.303479	0.019988
C	-0.515493	4.655945	-0.022232
C	0.857712	4.374020	1.935235
H	-1.480347	2.874510	-0.736940
H	-0.924069	5.285810	-0.805752
H	1.530106	4.787503	2.684862
H	0.596839	6.244419	0.919694
C	-0.560283	-2.081725	-1.243501
C	-0.651650	-3.700386	-3.558358
C	-1.011536	-1.585727	-2.471348
C	-0.158192	-3.429758	-1.209872
C	-0.199087	-4.224389	-2.354131
C	-1.061852	-2.374637	-3.615349
H	-1.311008	-0.547710	-2.524238
H	0.124851	-5.262082	-2.296164
H	-1.420997	-1.949454	-4.547036
H	-0.679393	-4.329797	-4.442738
O	1.052224	2.191915	2.928371

O	0.292136	-3.950202	-0.026975
H	1.665135	2.698293	3.475268
H	0.528587	-4.875739	-0.163973

TS2:

C	-0.651195	0.991519	1.683698
H	-0.856712	1.848115	2.322631
C	-0.031036	1.173980	0.498288
C	0.237894	0.001493	-0.375148
O	0.751980	0.112803	-1.478790
C	-0.147505	-1.338245	0.176088
C	-1.098798	-0.314500	2.136967
C	-0.615343	-1.444435	1.478338
H	-0.727790	-2.416937	1.948084
O	-1.490061	-0.472912	3.441013
H	-1.798465	0.375759	3.779536
C	0.431233	2.504542	0.043350
C	1.371989	5.012137	-0.807387
C	-0.398271	3.635053	0.087187
C	1.730536	2.664976	-0.448176
C	2.206670	3.901446	-0.865605
C	0.072346	4.878785	-0.333072
H	2.368420	1.790372	-0.503074
H	3.221417	3.994345	-1.238931
H	-0.584346	5.745821	-0.290146
H	1.726674	5.985778	-1.132231
C	0.576002	-2.492013	-0.446659
C	2.117744	-4.577131	-1.529650
C	-0.014510	-3.528249	-1.162328
C	1.971542	-2.525448	-0.273673
C	2.734157	-3.557641	-0.810734
C	0.740940	-4.567528	-1.704277

H	-1.087223	-3.527570	-1.317824
H	3.812190	-3.564447	-0.662493
H	0.251389	-5.357597	-2.264479
H	2.721214	-5.376982	-1.948036
O	-1.678826	3.481886	0.545621
O	2.530009	-1.521357	0.455635
C	-2.174847	-1.151457	-0.881848
H	-1.792898	-1.057804	-1.893929
H	-2.428601	-2.154673	-0.555043
C	-2.742620	-0.077486	-0.214563
H	-2.630268	0.919956	-0.631560
C	-3.108734	-0.198467	1.116031
H	-3.497520	0.661365	1.655555
H	-3.364105	-1.166112	1.536586
H	-2.144271	4.319118	0.432665
H	3.489597	-1.610259	0.432383

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