University of Nottingham
UK | CHINA | MALAYSIA

# Studies Towards a Biomimetic Synthesis of Simonol A

**Jaffer M. Zaidi, BSc**

**Thesis submitted to the University of Nottingham for**

**the degree of Master of Research**

**September 2021**

**Supervisor: Prof Ross M. Denton**

# Acknowledgements

I would like to thank the University of Nottingham for giving me the opportunity to carry out my research using their facilities. I am grateful to Prof Ross Denton for the faith he showed in choosing me to undertake this exciting project and for his continuous support throughout the duration of my time here. I would also like to thank all the members of the Denton Group for providing me with guidance and encouragement on a daily basis. Special mentions must go to my direct lab supervisors, PhD student Nick Atkinson and PDRA Dr Tom Barber, for their valuable contributions to my project. It has been a true privilege to be part of a team of such high-quality researchers and this has undoubtedly helped to make this a positive and memorable experience for me.

# Abstract

*Illicium*-derived neolignan natural products are of interest due to their often potent medicinal properties, particularly in the promotion of neurite outgrowth. Herein, we report our efforts towards the synthesis of simonol A, a recently discovered sesqui-neolignan. Three synthetic routes were designed, each based on our proposed biosynthesis of this compound and taking into account our experience with this general class of natural products. The routes were executed with varying degrees of success, the most effective being the third, in which a key intermediate in the synthesis of simonol A was isolated. Preparation of a dibrominated species, followed by a microwave-assisted double Suzuki-Miyaura cross coupling and finally allylation of a free phenol, gave us this intermediate in 35% yield over three steps. Investigations into a possible [3,3] sigmatropic rearrangement of this molecule were then carried out, supported by some computational studies. The thermal energy barrier for our proposed Claisen rearrangement was calculated to be 45.7 kcal/mol, indicating that a Lewis acid catalyst would most likely be required in order to carry out this reaction in practice. In comparison, the proposed neutral oxy-Cope rearrangement was found to have a calculated energy barrier of 35.6 kcal/mol, while the anionic equivalent had a much lower barrier of 8.1 kcal/mol. This suggested that if a neutral oxy-Cope rearrangement were to occur in the biosynthesis of simonol A as proposed, then this would need to be an enzyme-mediated process.

# Abbreviations

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

| | |
|---|---|
| 10-DAB | 10-deacetylbaccatin III |
| AChE | acetylcholinesterase |
| BChE | butyrylcholinesterase |
| $BTMABr_3$ | benzyltrimethylammonium tribromide |
| CAN | ceric ammonium nitrate |
| DAHP | 3-deoxy-*D*-arabino-heptulosone-7-phopshate |
| dba | dibenzylideneacetone |
| DHQ | 3-dehydroquinic acid |
| EDC | electronic circular dichroism |
| EPSP | 5-enolpyruvylshikimate-3-phosphate |
| [H] | reductant |
| [M] | metal |
| MSM | methylsulfonylmethane |
| [O] | oxidant |
| PIDA | phenyliodine(III) diacetate |
| QM | quantum mechanics |
| TAL | tyrosine ammonia lyase |

# Contents

Acknowledgements ..... 2

Abstract ..... 3

Abbreviations ..... 4

1. Introduction ..... 7

1.1. Natural Products ..... 7

1.2. Lignans and Neolignans ..... 10

1.3.1. Chavicol ..... 12

1.3.2. Shikimic Acid ..... 12

1.3.3. Shikimate Pathway ..... 14

1.3.4. Biosynthesis of Chavicol ..... 15

1.4.1. Previous Syntheses of Neolignans ..... 17

1.4.2. Dunnianol ..... 18

1.4.3. Honokiol ..... 21

1.5.1. Isolation of Simonol A ..... 23

1.5.2. Proposed Biosyntheses of Simonol A ..... 24

2. Results and Discussion ..... 30

2.1.1. Original Retrosynthetic Analysis of Simonol A ..... 30

2.1.2. Quinone Precursor Synthesis ..... 31

2.1.3. Suzuki-Miyaura Coupling ..... 33

2.2.1. Second-Generation Retrosynthetic Analysis ..... 39

2.2.2. Second Route Development ..... 40

2.2.3. Oxy-Cope Rearrangement ..... 46

2.3.1. Third-Generation Retrosynthetic Analysis ..... 53

2.3.2. Key Intermediate Synthesis ..... 54

2.3.3. Claisen Rearrangement ..... 57

3. Conclusions and Future Work ..... 63

4. Supporting Information ..... 65

4.1. General Details ..... 65

4.2. Experimental Procedures ..... 67

4.3. Computational Data ..... 82

5. References ..... 111

# 1. Introduction

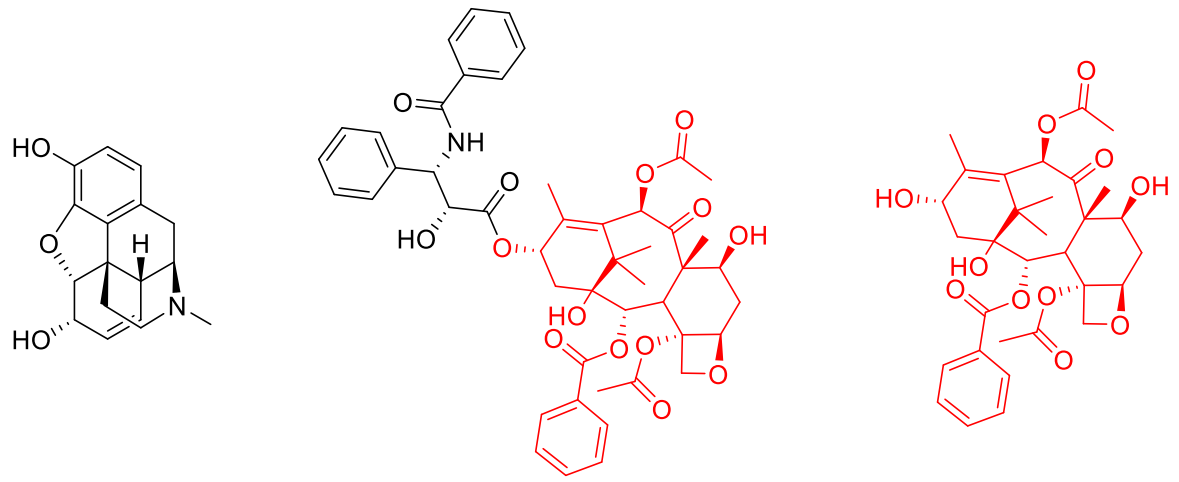
## 1.1. Natural Products

Natural products are generally defined as any organic compound synthesised by an organism.[1] Natural products can be subdivided into two main groups: primary and secondary metabolites. Primary metabolites are molecules that play a crucial role in the function of an organism, without which that organism would be unable to live. Examples include amino acids, sugars and fatty acids.[2] Secondary metabolites, on the other hand, have more of an extrinsic function that mainly affects other organisms. Some of these are derived forms of primary metabolites. Alkaloids and steroids are both types of secondary metabolite. Secondary metabolites are not essential for survival, however they do contribute towards the competitiveness of an organism within its environment. It is also this class of natural product that tends to be of interest for use in drug discovery due to their often potent pharmacological activities.[3]

Natural products have been a major source of medicines throughout history, in particular for the treatment of cancer and infectious diseases.[4] In the past, a lack of available purification methods meant that crude plant extracts were used as remedies, without any isolation of the active compound.[5] When compared to those drugs which have been chemically synthesised, natural products tend to have a greater number of $sp^3$ hybridised centres, fewer aromatic rings, lower nitrogen content and

increased oxygen content.[6] This results in molecules with highly complex three-dimensional structures that tend to have better binding affinity with biological targets than the more structurally planar compounds usually found in synthetic compound libraries.

An example of a pharmacologically potent natural product is morphine (**1**). This is a strong painkiller of the opiate family and can be isolated from the straw of the poppy plant, *Papaver somniferum*. Natural products can also be obtained *via* semisynthesis. Semi-synthetic drugs are therapeutic agents normally made by taking starting materials from natural sources and converting them into the final products using chemical transformations.[7] Paclitaxel (**2**), brand name Taxol, is a chemotherapy medication used to treat various types of cancer and is an example of a semi-synthetic drug. The commercial semisynthesis of paclitaxel (**2**) by Bristol Myers Squibb started from 10-deacetylbaccatin III (10-DAB) (**3**).[8] This is isolated from the English yew tree, *Taxus baccata*. The structures of these molecules are shown in Figure 1.




morphine (**1**) paclitaxel (**2**) 10-DAB (**3**)

**Figure 1.** Structures of morphine (**1**), paclitaxel (**2**) and 10-DAB (**3**) (10-DAB motif highlighted in red).

Despite the many advantages to their use, natural products had somewhat fallen out of favour with big pharmaceutical companies over the past two decades.[9] This was in part due to their perceived incompatibility with high-throughput screening, which is more suited to smaller molecules. Combinatorial synthesis, in which large numbers of related compounds are rapidly generated by linking molecular 'building blocks' together, has also emerged as an interesting alternative to using natural products as medicines.[10] However, the excellent coverage of biologically-relevant chemical space that is provided by natural products, coupled with the development of new technologies such as bioinformatics, proteomics and genomics, has arguably led to a resurgence in the use of natural products in drug discovery.[11] This thesis concentrates on the synthesis of a bioactive neolignan natural product.

## 1.2. Lignans and Neolignans

*Illicium simonsii* is a rare evergreen shrub mainly found in India, Myanmar and southwestern China. Traditionally, the various structural components of this species, along with others in the genus *Illicium*, have been used as herbal medicines for the treatment of pain, rheumatoid arthritis and skin inflammation.[12] The curative properties of this plant can be attributed to the presence of phenylpropanoid units known as lignans and neolignans.[13] These are normally located within the dark green leathery leaves and pale yellow flowers of *Illicium simonsii* (Figure 2).

**Figure 2.** *Illicium simonsii* (figure reproduced from Bluebell Nursery).[14]

Lignans and neolignans can be differentiated by the location of the C-C bond between the constituent phenylpropanoids. In a lignan, *e.g.*, secoisolariciresinol (**4**), this C-C bond connects the two propyl groups at the 8 and 8’ position.[15] If the linker is situated anywhere else in the molecule, for example between the two phenyl groups, then this is a

neolignan.[16] Dieugenol (**5**) is an example of a neolignan. Triaryl neolignans, *i.e.*, those made up of three phenylpropanoid units, are sometimes referred to as sesqui-neolignans.[17] Simonol A (**6**), the natural product which is the main focus of this project, is classed as a sesqui-neolignan (Figure 3). The advantageous biological activities of these phenolic compounds include, but are not limited to, anti-tumour, anti-neurodegenerative and anti-viral capabilities.[18]

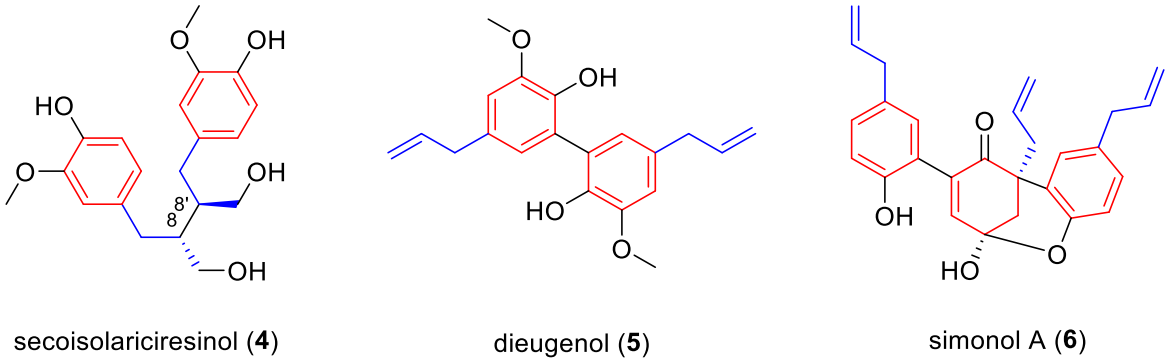
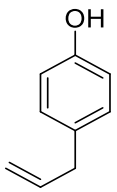



**Figure 3.** Structures of secoisolariciresinol (**4**), dieugenol (**5**) and simonol A (**6**) (phenyl groups in red, propyl groups in blue).

Many neolignans feature allylated phenyl groups. This implies a common biosynthetic origin, which is discussed in the next section.

### 1.3.1. Chavicol

4-Allylphenol, more commonly known as chavicol (**7**) (Figure 4), is considered to be the main starting material in the biosynthesis of many *Illicium*-derived neolignans.[19] Chavicol (**7**) can undergo various chemical transformations, for example oxidative phenolic coupling, resulting in the generation of a wealth of structurally diverse species. In terms of commercial applications, chavicol (**7**) is used as an odorant in some perfumes and essential oils.[20] Chavicol (**7**) originates from the shikimate pathway, which is detailed below.




chavicol (**7**)

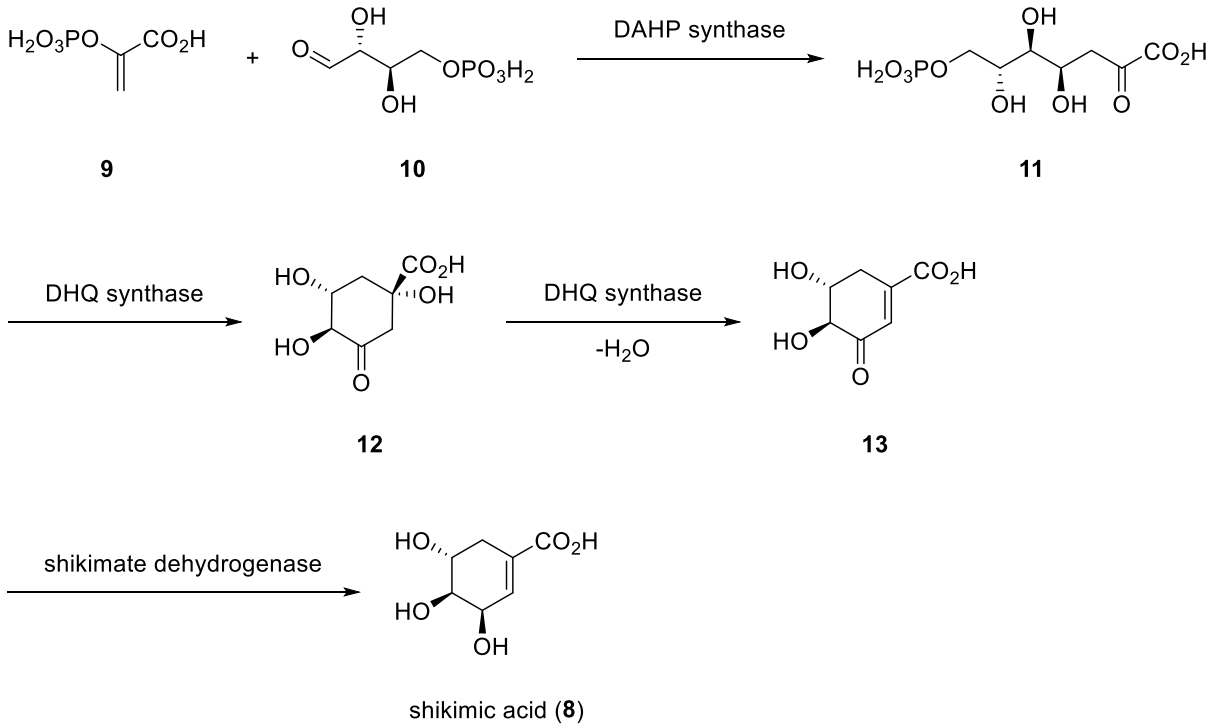
**Figure 4.** Structure of chavicol (**7**).

### 1.3.2. Shikimic Acid

Shikimic acid (**8**) is a naturally occurring organic compound and an important precursor in the biosynthesis of several crucial metabolites in plants and microorganisms.[21] It is also often the starting material in the industrial synthesis of the antiviral medication oseltamivir, trade name Tamiflu, commonly used to treat influenza. Shikimic acid (**8**) was first

isolated from the Japanese star anise, *Illicium anisatum*, in 1885. Its name comes from the Japanese word for this flower, 'shikimi'.

The biosynthesis of shikimic acid (**8**) starts from phosphoenolpyruvic acid (**9**) and takes place over four steps (Scheme 1). **9** reacts with *D*-erythrose-4-phosphate (**10**) to form 3-deoxy-*D*-arabino-heptulosone-7-phopshate (DAHP) (**11**). This step is catalysed by the enzyme DAHP synthase. **11** then undergoes a ring closure to give 3-dehydroquinic acid (DHQ) (**12**), followed by a dehydration to make 3-dehydroshikimic acid (**13**). DHQ synthase is the enzyme responsible for both steps. Finally, selective reduction of the ketone in **13** by shikimate dehydrogenase produces shikimic acid (**8**).

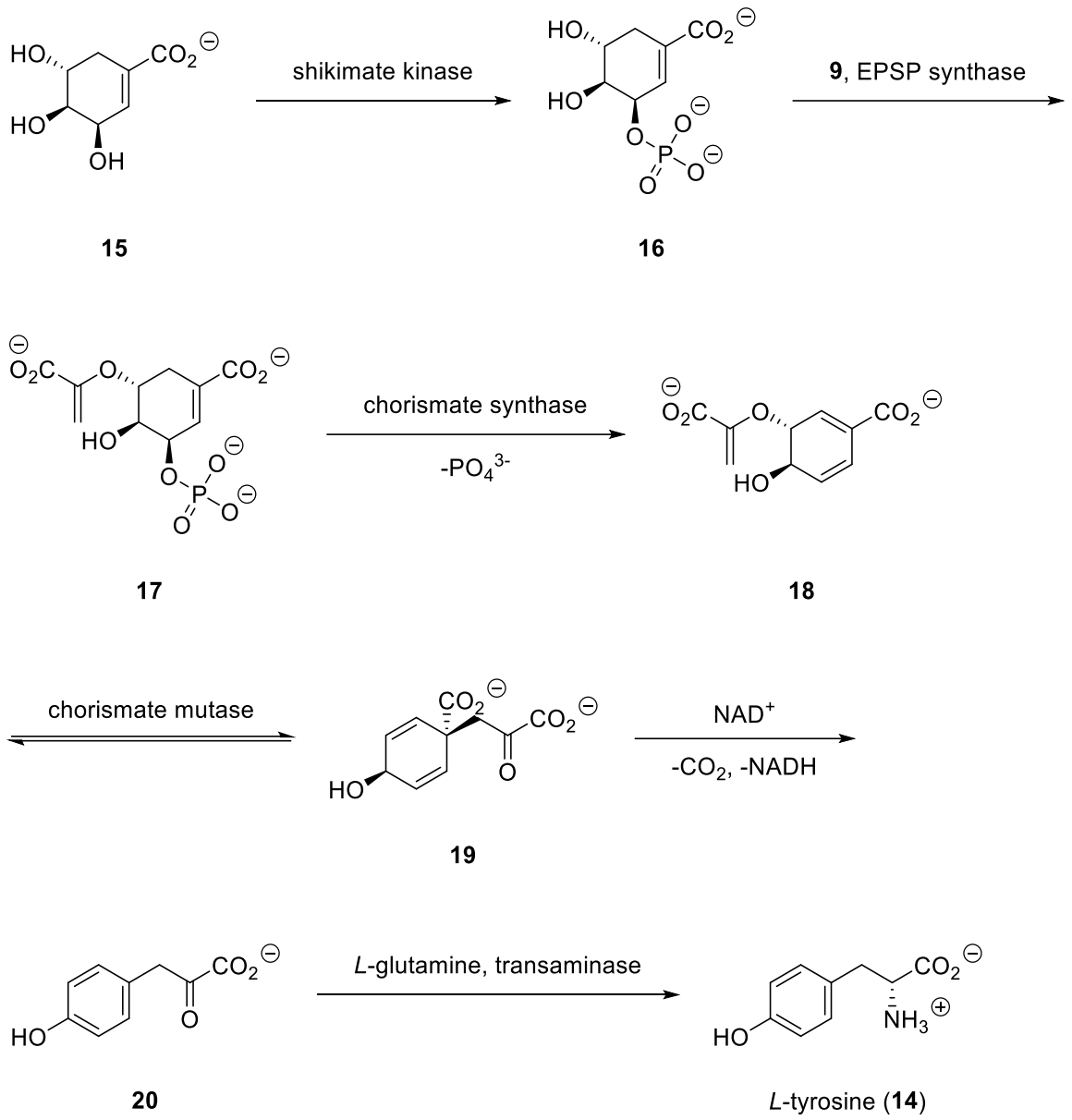



**Scheme 1.** Biosynthesis of shikimic acid (**8**)**.**

### 1.3.3. Shikimate Pathway

The shikimate pathway is utilised by plants and bacteria in the production of aromatic amino acids, as well as other metabolites.[22] This pathway provides the platform for obtaining many of the organic compounds that are essential for the survival of that organism. Interestingly, the shikimate pathway is not present in animals, who must instead obtain these metabolites from their diet.[23]

One example of the application of the shikimate pathway is in the biosynthesis of the amino acid *L*-tyrosine (**14**) (Scheme 2). This is used as a precursor in the preparation of a range of key biological building blocks, including chavicol (**7**). Deprotonated shikimic acid (**15**) undergoes a shikimate kinase-mediated phosphorylation to form intermediate (**16**). This reacts with phosphoenolpyruvic acid (**9**), catalysed by 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, to give 5-enolpyruvylshikimate-3-phosphate (**17**), which is subsequently transformed into chorismate (**18**) by chorismate synthase. **18** then undergoes a Claisen rearrangement by chorismate mutase to afford prephenate (**19**), followed by an oxidative decarboxylation with $NAD^+$ to yield 4-hydroxyphenylpyruvate (**20**). Finally, transamination occurs, using another amino acid (*L*-glutamine) as the nitrogen source and transaminase as the enzyme, to produce *L*-tyrosine (**14**).

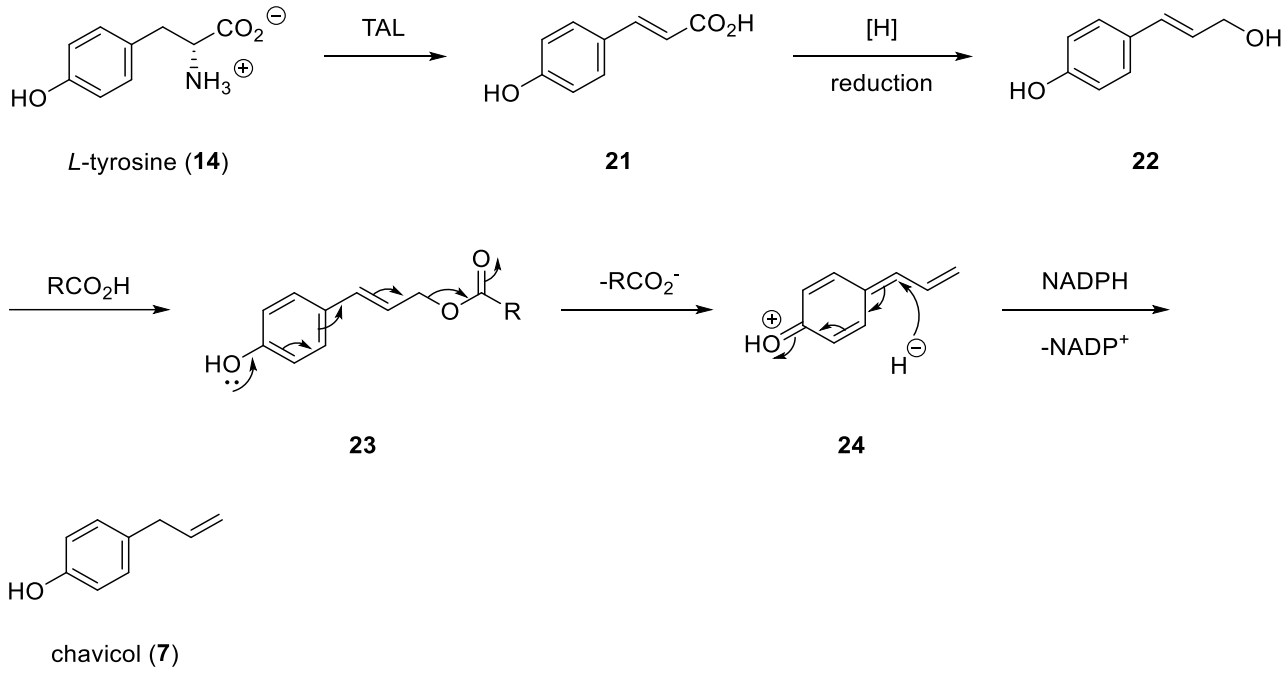



**Scheme 2.** Biosynthesis of *L*-tyrosine (**14**).

## 1.3.4. Biosynthesis of Chavicol

As mentioned previously, *L*-tyrosine (**14**) is thought to be the precursor in the biosynthesis of chavicol (**7**) (Scheme 3), which in turn is often used as the starting point in the biosynthesis of *Illicium*-derived neolignans. Deamination of *L*-tyrosine (**14**), catalysed by the enzyme tyrosine

ammonia lyase (TAL), yields 4-hydroxycinnamic acid (**21**), reduction of which gives 4-hydrocinnamyl alcohol (**22**). It has been suggested that **22** can then be further manipulated to give chavicol (**7**).[24] Esterification of this species to intermediate (**23**) is followed by decomposition to dienone (**24**). Reduction by NADPH reforms the phenol and produces a terminal alkene, giving chavicol (**7**).

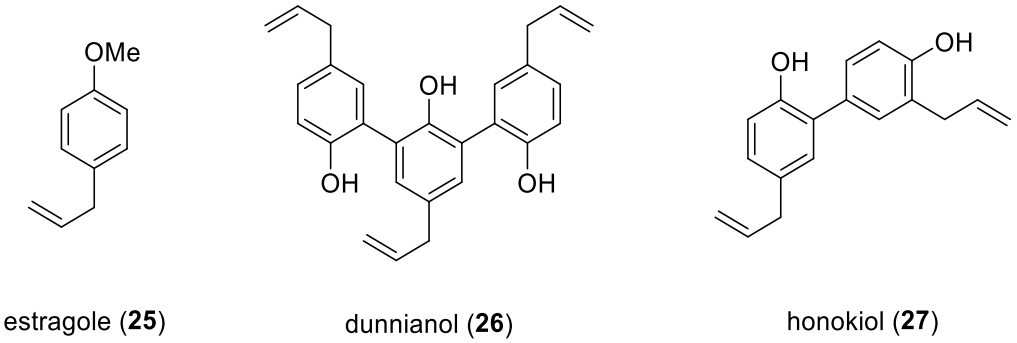



**Scheme 3.** Proposed biosynthesis of chavicol (**7**).

### 1.4.1. Previous Syntheses of Neolignans

From a medicinal point of view, neolignans are of interest primarily due to their neurological effects.[25] In particular, these natural products have displayed promising neurite outgrowth promoting and acetylcholinesterase (AChE) inhibiting activities. As a result, neolignans have the potential to slow the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's.

There have been several reported biomimetic syntheses of neolignans in recent years. A biomimetic synthesis is one which aims to make a target molecule using similar reactions, and therefore which passes through similar intermediates, to those that occur during the biosynthesis of that molecule in its natural source.[26] Chavicol (**7**) would be an ideal starting material for such endeavours, but it is prohibitively expensive at £234 for 1 g.[27] As a result, 4-allylanisole (estragole (**25**), which is much more affordable at £61.50 for 100 g) is often used instead.[28] This is the case in the biomimetic syntheses of the natural products dunnianol (**26**) and honokiol (**27**), the structures of which can be found in Figure 5. For the purposes of this thesis, only the syntheses of these particular neolignans that were carried out by Denton and co-workers are discussed in detail in the next two sections. The reason for this is that these specific examples inspired some of the synthetic strategies used in this work when designing potential routes to simonol A (**6**) and so they were considered useful to include here.




estragole (**25**) dunnianol (**26**) honokiol (**27**)

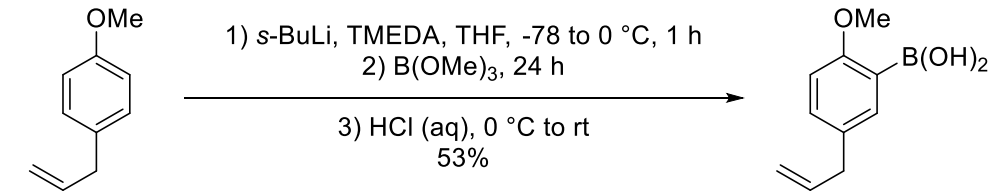
**Figure 5.** Structures of estragole (**25**), dunnianol (**26**) and honokiol (**27**).

## 1.4.2. Dunnianol

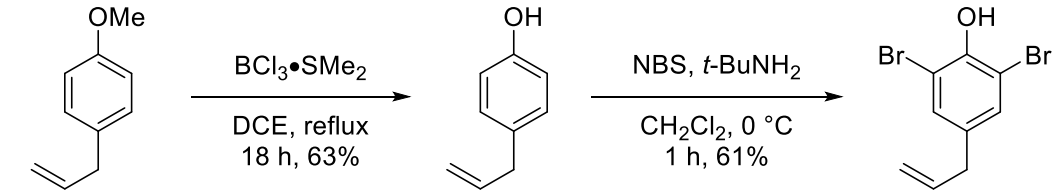
Dunnianol (**26**) was first isolated from the bark of *Illicium dunnianum* in 1991.[29] It is a triaryl neolignan made up of three units of chavicol (**7**) joined in an *ortho* fashion. Dunnianol (**26**) has been shown to possess anti-microbial, anti-tumour, anti-inflammatory and AChE inhibitory activities.[30] The first reported synthesis of this molecule was in 1998 by Brown and co-workers via oxidative phenolic coupling of chavicol (**7**) using $K_3[Fe(CN)_6]$.[31] An oxidative coupling was also used by Liu and co-workers in 2004, using $H_2O_2$, with the reaction being catalysed by the enzyme horseradish peroxidase.[32] In 2010, Denton and co-workers reported a concise synthesis of dunnianol (**26**), based upon a double Suzuki-Miyaura cross-coupling as the key step (Scheme 4).[33]

Directed *o*-lithiation of estragole (**25**) was followed by addition of trimethylborate and hydrolysis of the resulting boronate ester to give boronic acid (**28**). Preparation of the corresponding aryl halide was

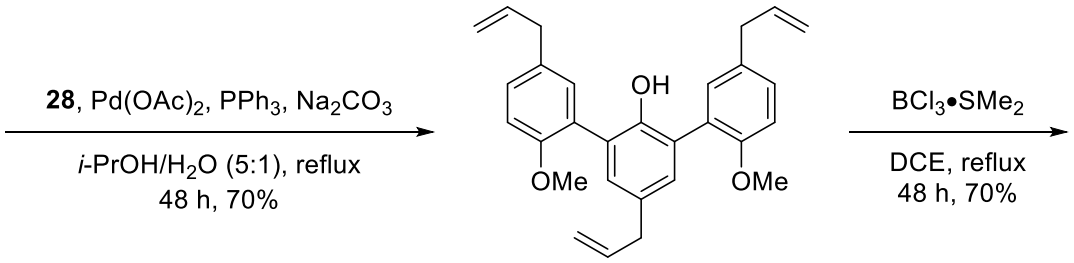
achieved in two steps. Demethylation of estragole (**25**) to chavicol (**7**) was carried out using $BCl_3$•$SMe_2$, with no detectable isomerisation of the allyl group, followed by bromination with NBS to give dibromide (**29**). The palladium-catalysed Suzuki coupling was then executed to afford bismethyldunnianol (**30**).[33] This was an impressive feat given the difficulty in performing such reactions on *o*-bromophenols, as well as the dual possibility of either a Heck side reaction occurring due to the presence of the allyl group or isomerisation of this sensitive alkene into conjugation with the benzene rings. Finally, demethylation of **30**, again using $BCl_3$•$SMe_2$, was accomplished to yield dunnianol (**26**). As with the first demethylation, no isomerisation was observed. In summary, dunnianol (**26**) had been prepared by Denton and co-workers in 17% overall yield over four steps, in the longest linear sequence, from commercially available estragole (**25**).[33]



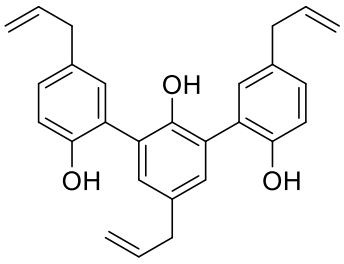

estragole (**25**) **28**




estragole (**25**) chavicol (**7**) **29**




**30**



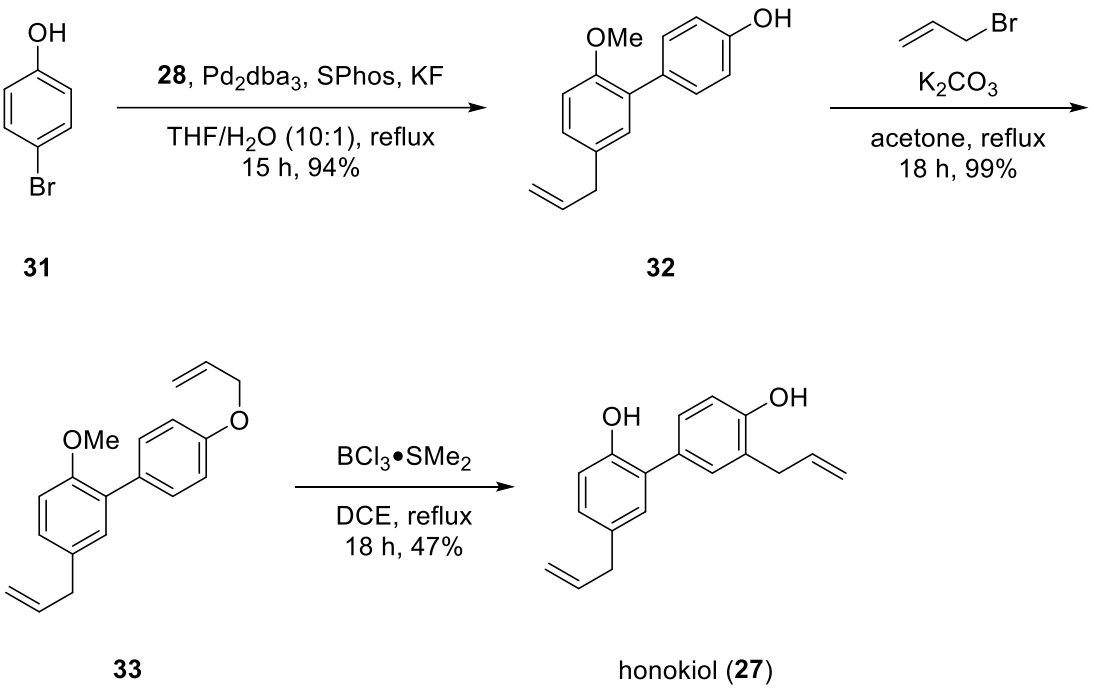

dunnianol (**26**)

**Scheme 4.** Synthesis of dunnianol (**26**) by Denton and co-workers.

### 1.4.3. Honokiol

Honokiol (**27**) was first isolated from the bark of *Magnolia obovata* in 1972.[34] It is a biaryl neolignan with demonstrable anti-arrhythmic, anti-thrombocytic, anti-angiogenic and anti-anxiety effects, among others.[35] There have been numerous published syntheses of honokiol (**27**), the first of which was reported by Tobinga and co-workers in 1986.[36] In 2010, following on from their successful synthesis of dunnianol (**26**), Denton and co-workers reported a concise synthesis of honokiol (**27**) (Scheme 5).[37]

This route combined some of the elements from previously reported syntheses, namely the use of a Suzuki coupling, with boronic acid (**28**) being used once again. This was prepared in the same way as before, *via* directed *o*-lithiation of estragole (**25**), before being reacted with 4-bromophenol (**31**) in a Suzuki coupling to give biaryl (**32**). A variety of conditions were attempted for this transformation, the most effective being the use of $Pd_2dba_3$, SPhos and KF, in which no isomerisation of the sensitive allyl group was observed. The free hydroxyl group in **32** was then allylated to give ether (**33**). Finally, treatment of this intermediate with $BCl_3{\bullet}SMe_2$ enabled a one-pot Claisen rearrangement/methoxy group cleavage to give honokiol (**27**). In summary, honokiol (**27**) had been prepared by Denton and co-workers in 34% overall yield over four steps from commercially available **31**.[37]




**Scheme 5.** Synthesis of honokiol (**27**) by Denton and co-workers.

Having now completed the syntheses of both dunnianol (**26**) and honokiol (**27**), Denton and co-workers had a solid foundation from which they could plan the more challenging synthesis of the sesqui-neolignan simonol A (**6**).

### 1.5.1. Isolation of Simonol A

Simonol A (**6**) was extracted from the fruits of *Illicium simonsii* in Yunnan, China by Kong and co-workers in 2013.[38] A full structural assignment of this natural product was made by means of spectroscopic methods (*i.e.*, NMR, IR and HRMS). The absolute stereochemistry was also established by comparing the experimental electronic circular dichroism (ECD) spectra with the predicted spectra calculated using DFT. From all this information it was determined that simonol A (**6**) contains a 5,5-dihydropyran ring and an allylated quaternary carbon centre, as well as the fact that the molecule has an absolute configuration of (*R,R*).

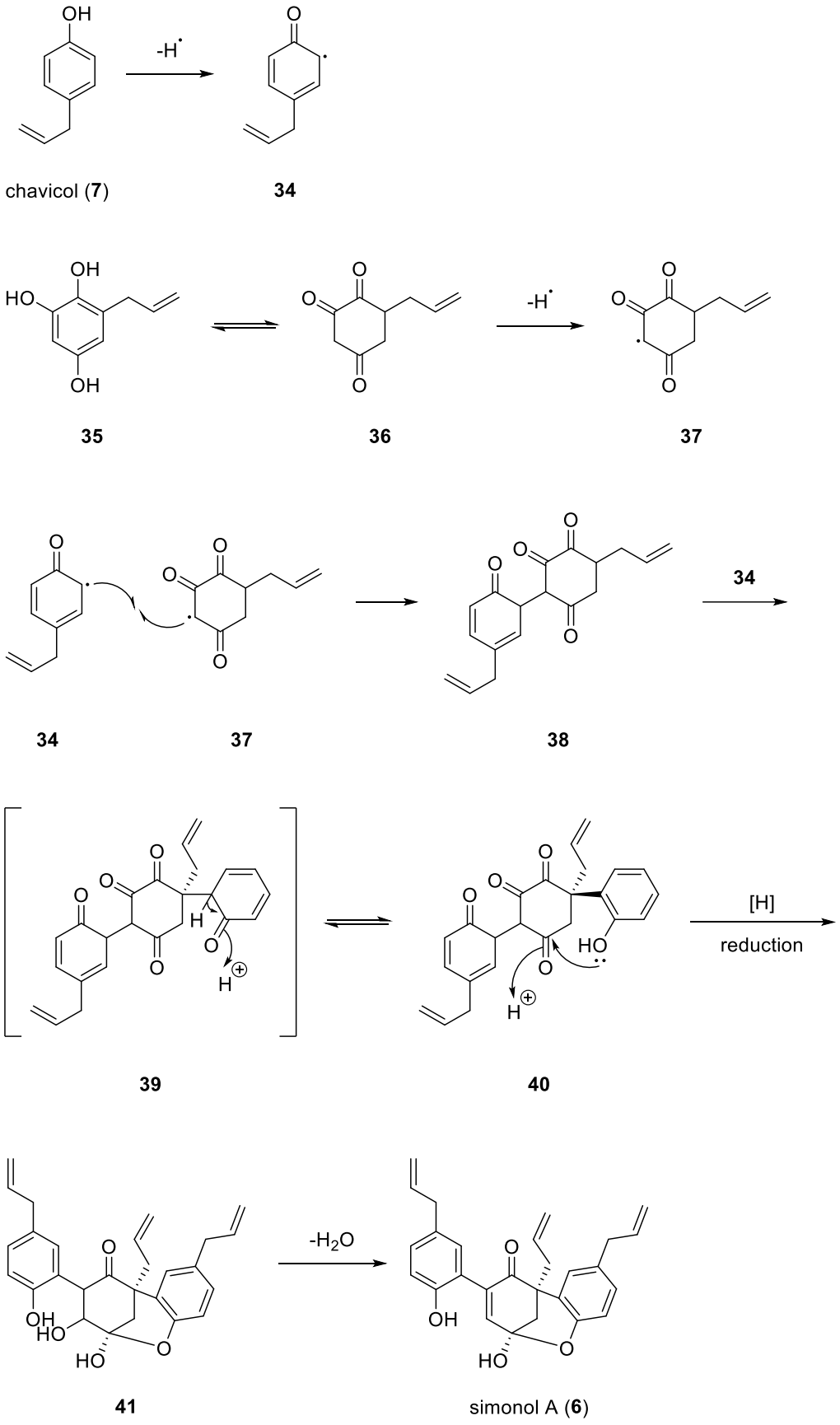
Biological testing carried out by Kong and co-workers discovered that simonol A (**6**) exhibited strong inhibitory activities against four lines of human cancer cells, NCI-H460, SMMC-7721, MCF-7 and BGC-823.[38] In fact the cytotoxicity data was comparable to that of the chemotherapy medication fluorouracil (brand name Adrucil). Given its structural similarity to other *Illicium*-derived neolignans, it would be reasonable to suggest that simonol A (**6**) may also have some neurological activity. However, analysis by Wang and co-workers, who also isolated this compound in 2013, found that it had no activity against AChE or butyrylcholinesterase (BChE).[39] There are currently no reported total syntheses of simonol A (**6**). However, given its anti-cancer activity, a feasible synthetic route to this natural product is highly desirable and would enable further biological investigations to take place.

### 1.5.2. Proposed Biosyntheses of Simonol A

Kong and co-workers hypothesised that the biosynthesis of simonol A (**6**) begins with the single electron oxidation of chavicol (**7**) to radical (**34**).[38] 6-allylbenzene-1,2,4-triol (**35**) tautomerises to triketone (**36**) and is also oxidised to afford radical (**37**). This prompts oxidative coupling of **34** and **37** to occur to form intermediate (**38**), which can then generate another radical and undergo a second oxidative coupling with **34** to give compound (**39**). Tautomerisation of this species affords phenol (**40**), followed by hemiacetal formation to molecule (**41**) and finally selective reduction of the ketone to yield simonol A (**6**). The full biosynthesis, reproduced in exactly the same form as it is in the paper, is depicted in Scheme 6.[38]

There are a number of issues with this suggested biosynthetic route. There is currently no evidence to indicate that **35** is present in *Illicium simonsii* and so it is strange that this would be chosen as one of the starting materials. It also seems doubtful that this compound would tautomerise to **36**, seeing as this would require an unfavourable loss of aromaticity. As well as this, the radical cross-couplings proposed would be difficult to carry out selectively as these reactions tend to give a complex mixture of products, even in homodimerisation events. Additionally, such processes are oxidative in nature, with the electron lost from the phenol expected to be transferred to a metalloenzyme. Given the selective reduction of **41** would also likely require an enzyme, it seems unfeasible that these reactions, which are redox incompatible, could occur in the same

environment. In summary, there are several implausible aspects in this proposed biosynthesis and therefore further investigation is warranted.

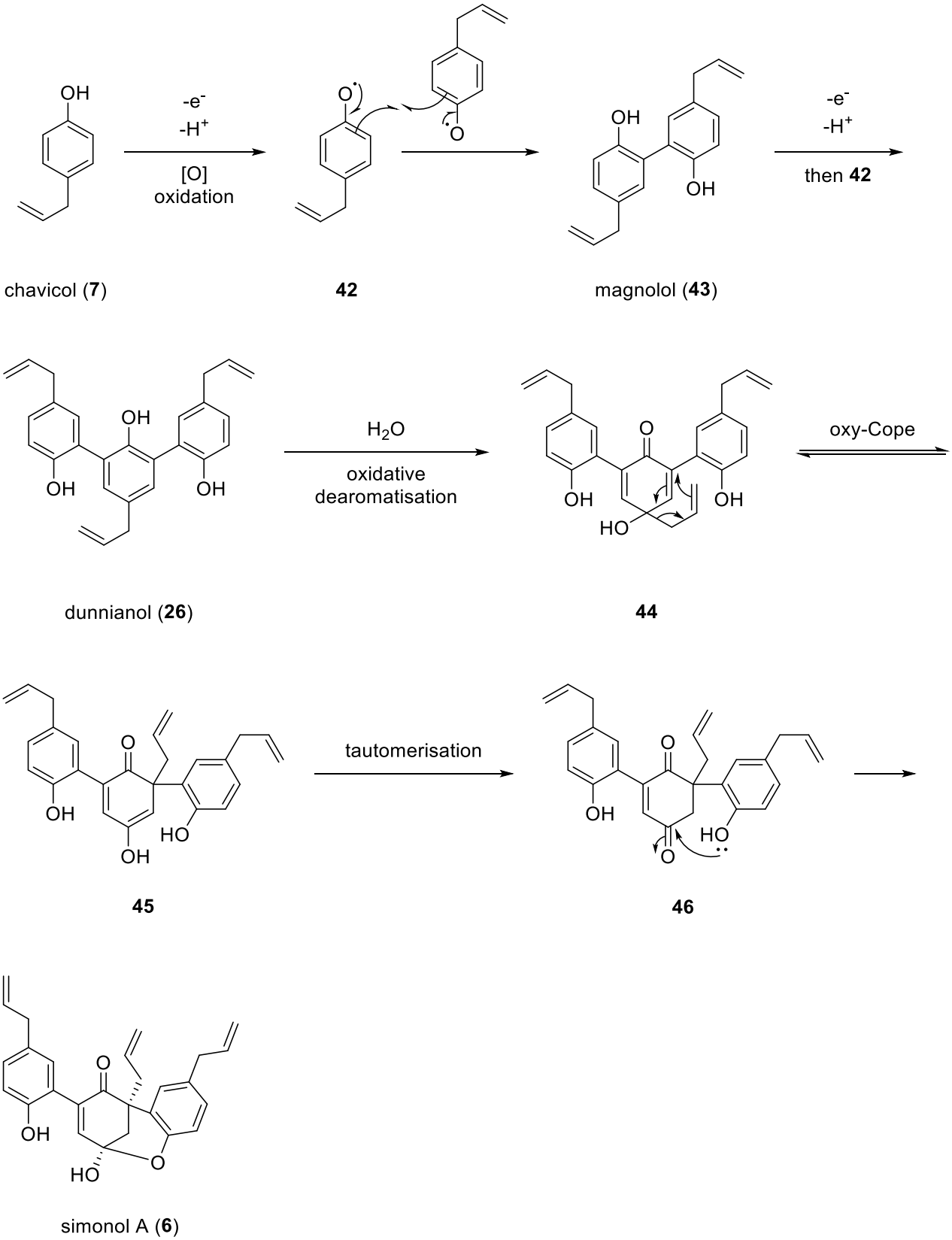



**Scheme 6.** Proposed biosynthesis of simonol A (**6**) by Kong and co-workers.[38]

An alternative biosynthesis of simonol A (**6**), proposed by Denton and co-workers, uses chavicol (**7**), a compound which is abundant in plants of the genus *Illicium*, as the sole precursor.[40] Chavicol (**7**) is converted to radical (**42**), followed by dimerisation to form magnolol (**43**), a known *Illicium*-derived neolignan which has been synthesised in this way previously.[41] Another oxidative coupling then occurs to yield dunnianol (**26**). The electrons lost in these oxidative dimerisation processes are very likely to be accepted by a metal centre like $Fe^{III}$, a component in haemoproteins.[42] After this there is a selective oxidative dearomatisation of the central ring to give dienone (**44**). At this point an oxy-Cope rearrangement could potentially occur to afford enol (**45**), which contains the allylated quaternary centre seen in the natural product. Keto-enol tautomerisation to diketone (**46**) now takes place and finally there is a ring-closing hemiacetal formation to produce simonol A (**6**). The complete biosynthetic route is illustrated in Scheme 7.

In comparison with the original biosynthesis proposed by Kong and co-workers, the revised route appears to be more feasible as it relies only on chavicol (**7**). This proposed route is further supported by the fact that magnolol (**43**) and dunnianol (**26**), two known neolignans, are intermediates in this route. The proposed oxy-Cope rearrangement, which is the key step in this biosynthesis, has been calculated to have an energy barrier of 35.6 kcal/mol using the wB97DX/6-31G* theoretical model.[43] Such a high value suggests that, for the reaction to be plausible in the

water-based environment of *Illicium simonsii*, an enzyme catalyst would be required to lower this barrier. There is literature precedent for such reactions and such enzymes, so this could well be a possibility.[44] Overall, this biosynthesis seems more feasible.



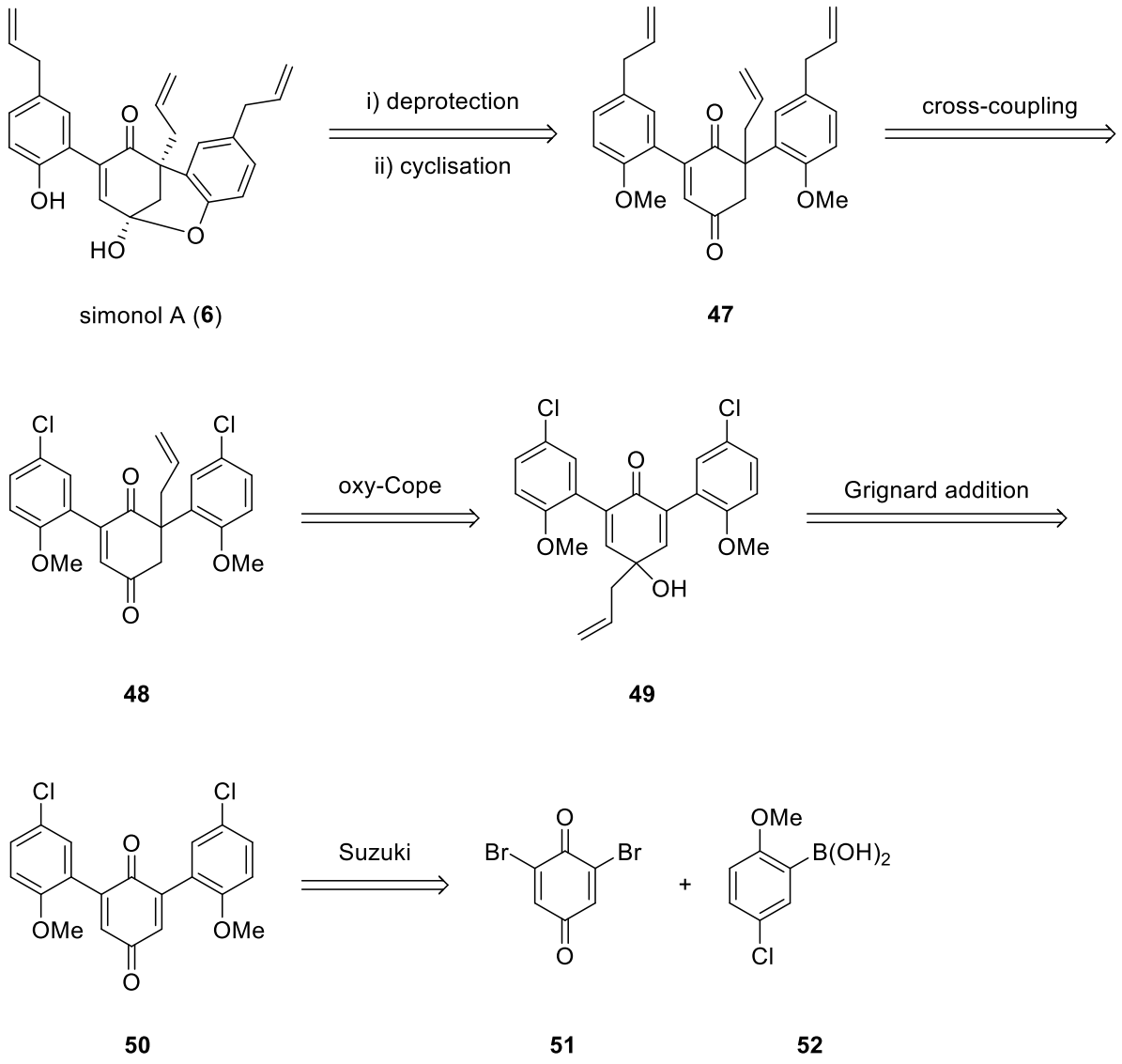

**Scheme 7.** Proposed biosynthesis of simonol A (**6**) by Denton and co-workers.

# 2. Results and Discussion

## 2.1.1. Original Retrosynthetic Analysis of Simonol A

Our first-generation retrosynthetic analysis is based upon our experience with this general class of natural products. Important points to note in this synthesis plan (Scheme 8) are the introduction of isomerisation-prone allyl groups at a late stage in the synthesis and the use of methyl ether protecting groups which can be selectively cleaved in the presence of these allyl groups.

It was reasoned that the hemiacetal of simonol A (**6**) could be obtained *via* a one-pot deprotection and cyclisation of intermediate (**47**) using $BCl_3 \bullet SMe_2$. The allyl groups in **47** could be installed as a result of a double cross-coupling (either Suzuki or Stille) of the corresponding aryl chlorides in diketone (**48**), which in turn could be accessed through an oxy-Cope rearrangement of dienone (**49**), the latter being the key step in this synthesis. **49** could be formed by means of a Grignard reaction of triaryl (**50**) with commercially available allyl magnesium bromide. The selectivity here is governed by sterics, with the bulky phenyl substituents in **50** blocking nucleophilic addition at the unwanted carbonyl group. Finally, **50** could be prepared from a double Suzuki coupling of quinone (**51**) with commercially available 5-chloro-2-methoxyphenylboronic acid (**52**). **51** is not commercial and so would need to be made in a separate synthesis, which is detailed in the next section.




**Scheme 8.** Original retrosynthetic analysis of simonol A (**6**).

## 2.1.2. Quinone Precursor Synthesis

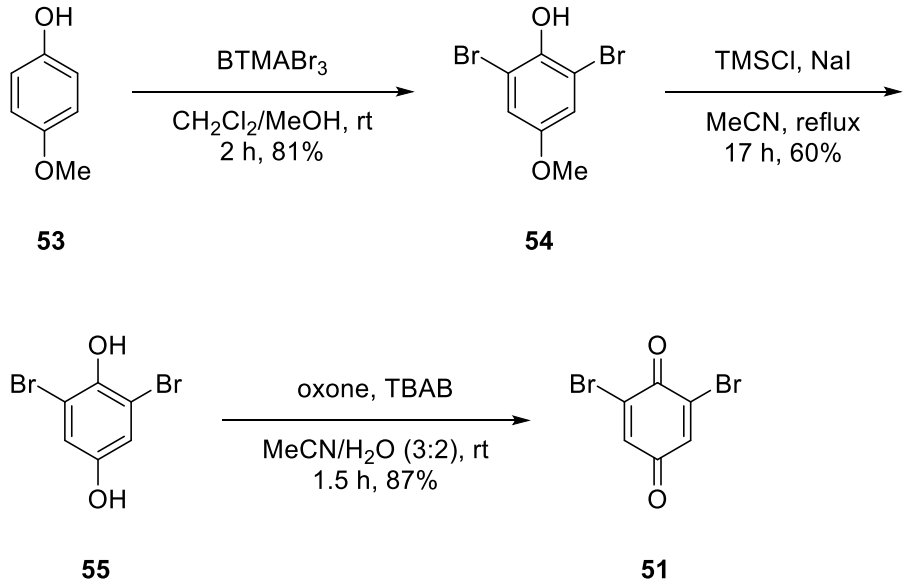
Our synthesis began with the preparation of quinone (**51**) (Scheme 9). This had already been accomplished by a previous student working on this project.[45] Broadly similar methodology was therefore used, with some modifications to the experimental procedures for optimisation.

Commercially available 4-methoxyphenol (**53**) was dibrominated with benzyltrimethylammonium tribromide ($BTMABr_3$) to give dibromo (**54**) in an excellent 81% yield. Acetone was chosen as the triturating agent in the workup as this is a poor solubiliser of salts and so the hope was that any residual $BTMABr_3$ would be removed in this way. Initial attempts to further purify the material using column chromatography proved problematic with co-elution of product fractions occurring. Instead, recrystallisation was found to be much more straightforward and successful in this instance.

**54** was then demethylated using TMSI, formed *in situ* from TMSCl and NaI, to afford hydroquinone (**55**). This method was determined to be more effective than using the TMSI reagent directly, which is prone to hydrolysis and so difficult to handle and store. **55** was isolated in a lower, but still acceptable, 60% yield.

Finally, **55** was oxidised to **51** using Oxone and TBAB. This compound was found to be light-sensitive and so it was imperative that the synthesis, workup and purification were all completed as quickly as possible and with minimal exposure to light. In this way, **51** was obtained in satisfactory purity and high yield (87%) and this could now be used in the main synthetic route. Given that the next step was a Suzuki cross-coupling, which almost always requires chromatographic purification to remove the Pd, it was reasoned that any remaining impurities in **51** would be eliminated

at this stage. In summary, **51** had been prepared from commercially available **53** in 42% yield over three steps.

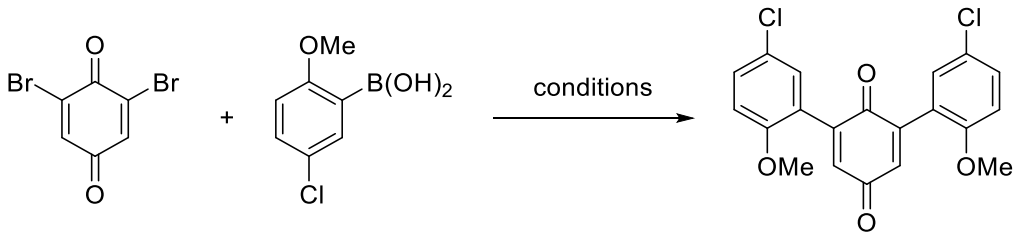



**Scheme 9.** Synthesis of **51**.

## 2.1.3. Suzuki-Miyaura Coupling

The Suzuki-Miyaura coupling is one of the most frequently used reactions in medicinal chemistry, with its initial discovery having taken place in the 1980s.[46] The popularity of the Suzuki coupling in drug synthesis arises from its ability to carry out a wide range of $sp^2$-$sp^2$ couplings with excellent functional group tolerance, thus enabling the generation of many complex biaryl motifs.[47] Given our track record in utilising this transformation in the synthesis of neolignan natural products, we were hopeful that these successes could be replicated to make triaryl (**50**) from quinone (**51**) and commercially available 5-chloro-2-methoxyphenylboronic acid (**52**).

As a starting point, we decided to try a set of conditions employed by a previous group member for a similar aryl halide and identical aryl boronic acid, catalysed by $Pd(PPh_3)_4$ (1 mol%).[48] In our case the reaction did work to some extent, with analysis of the $^1H$ NMR spectroscopic data confirming that **50** had indeed been isolated, albeit in a rather poor 25% yield. Taking into consideration that this was a first attempt at synthesising a novel compound, we were sufficiently encouraged by this initial result to begin optimising the reaction (Table 1). Increasing the catalyst loading, changing the Pd source, employing bulky phosphine ligands and using a different solvent/base all had little to no effect on the yield. In the majority of cases, the major product was protodeboronated starting material, as confirmed by the crude $^1H$ NMR spectrum, which matched that of 4-chloroanisole.[49]

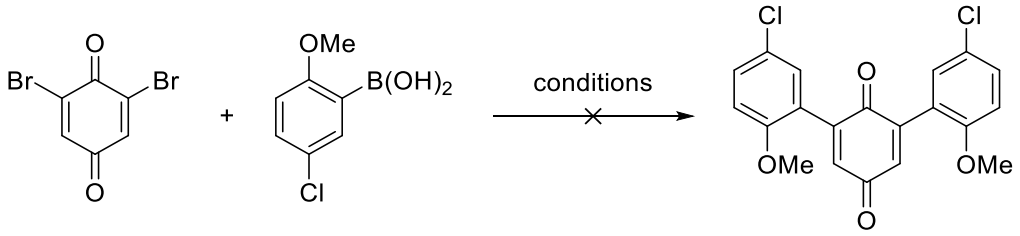



**51** **52** **50**

| Entry | Catalyst | Loading /mol% | Ligand | Base (aq) | Solvent | Temp/ °C | Time/h | Yield/ %[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | 1 | N/A | $Na_2CO_3$ | PhMe/EtOH | 90 | 17 | 25 |
| 2 | $Pd(PPh_3)_4$ | 5 | N/A | $K_2CO_3$ | THF | 70 | 18 | 16 |
| 3 | $Pd(OAc)_2$ | 1 | N/A | $Na_2CO_3$ | PhMe/EtOH | 90 | 15 | 0 |
| 4 | $Pd(PPh_3)_4$ | 5 | N/A | $Na_2CO_3$ | PhMe/EtOH | 90 | 23 | 9 |
| 5 | XPhos Pd G3 | 5 | N/A | $Na_2CO_3$ | PhMe/EtOH | 90 | 23 | 0 |
| 6 | $Pd(PPh_3)_4$ | 1 | P(*o*-tol)$_3$ | $Na_2CO_3$ | PhMe/EtOH | 90 | 18 | 0 |
| 7 | $Pd(PPh_3)_4$ | 5 | N/A | $K_2CO_3$ | THF | 70 | 16 | 0 |

**Table 1.** Suzuki coupling optimisation part 1 (a = isolated yield).

In an effort to conserve time, all further attempts consisted of reaction progress being judged by analysis of a $^1$H NMR spectrum of the crude reaction mixture, with methylsulfonylmethane (MSM) being used as an internal standard (Table 2). The chemical inertness and cheap cost of MSM, combined with the simplicity of its NMR spectrum, in which there are no overlapping peaks with **50**, meant it was the ideal reference material to use in this transformation.[50] Unfortunately, none of these experiments were successful and we were unable to find a set of conditions that improved upon our initial isolated yield of 25% for **50**.



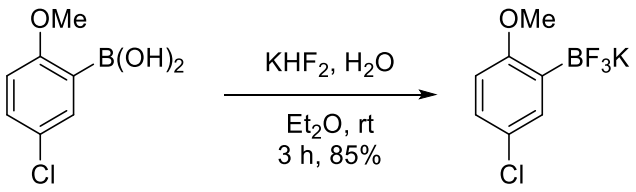

**51** **52** **50**

| Entry | Catalyst | Loading /mol% | Ligand | Base | Solvent | Temp/°C | Time/h |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | 1 | N/A | $Na_2CO_3$ (aq) | PhMe/EtOH | 90 | 18 |
| 2 | $Pd_2(dba)_3$ | 1 | $PCy_3$ | $Na_2CO_3$ (aq) | PhMe/EtOH | 90 | 18 |
| 3 | $Pd(PPh_3)_4$ | 3 | N/A | CsF | DME | 90 | 16 |
| 4 | XPhos Pd G3 | 2 | N/A | $K_3PO_4$ (aq) | THF | 25 | 0.5 |
| 5 | $Pd(OAc)_2$ | 1 | $PPh_3$ | $Na_2CO_3$ (aq) | PhMe/EtOH | 90 | 16 |
| 6 | $Pd(PPh_3)_4$ | 1 | P(*o*-tol)$_3$ | $Na_2CO_3$ (aq) | PhMe/EtOH | 90 | 16 |

**Table 2.** Suzuki coupling optimisation part 2.

A common solution to the protodeboronation problem in Suzuki couplings is to utilise an organotrifluoroborate salt as the nucleophilic cross-coupling partner, as opposed to a boronic acid.[51] The $BF_3K$ salt is slowly hydrolysed to the boronic acid under the basic conditions of the Suzuki, with the latter then able to effect the cross-coupling.[52] Significantly less protodeboronation is often seen this way and so we decided to attempt this ourselves by making a $BF_3K$ salt of **52**. The addition of $KHF_2$ to **52** afforded $BF_3K$ salt (**56**) in a superb 85% yield (Equation 1). However, subsequent attempts to use **56** in the Suzuki coupling to obtain **50** surprisingly failed,

suggesting that there were further issues with this reaction other than just protodeboronation.



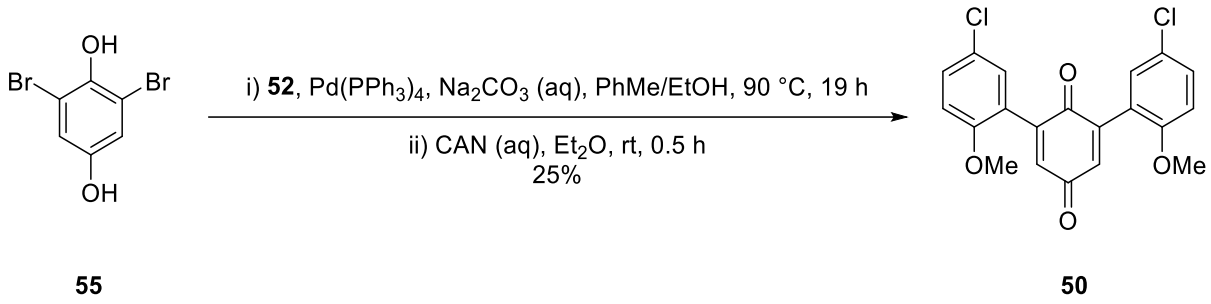

**52** **56**

**Equation 1.** Synthesis of **56**.

During this period of optimisation, it was also established that **50** was unstable with respect to silica gel chromatography. This was demonstrated by carrying out 2D TLC analysis for this compound. Another possible explanation for the low yields obtained was that **51** was inhibiting the Pd catalyst by oxidising it from $Pd^0$ to $Pd^{II}$. Indeed, there is literature precedent for quinones being used as oxidants.[53]

With there being no reported Suzuki couplings of **51** in the literature, compared to many examples of **52**, we considered it far more likely that, out of these two, our aryl halide was the problematic cross-coupling partner. An alternative sequence of steps was therefore explored whereby a Suzuki coupling was instead executed using hydroquinone (**55**). The crude product of this reaction was then oxidised to **51** using ceric ammonium nitrate (CAN), following the methodology of Anderson and co-workers.[54] This gave an overall yield of 25% over two steps (Scheme 10),

only an marginal improvement on the results obtained using our original strategy, which gave a cumulative yield of 22% for the same two steps with order reversed. Having spent a significant amount of time optimising this step, with various issues being encountered along the way, this route was eventually abandoned and an alternative synthesis plan for making simonol A (**6**) was devised.



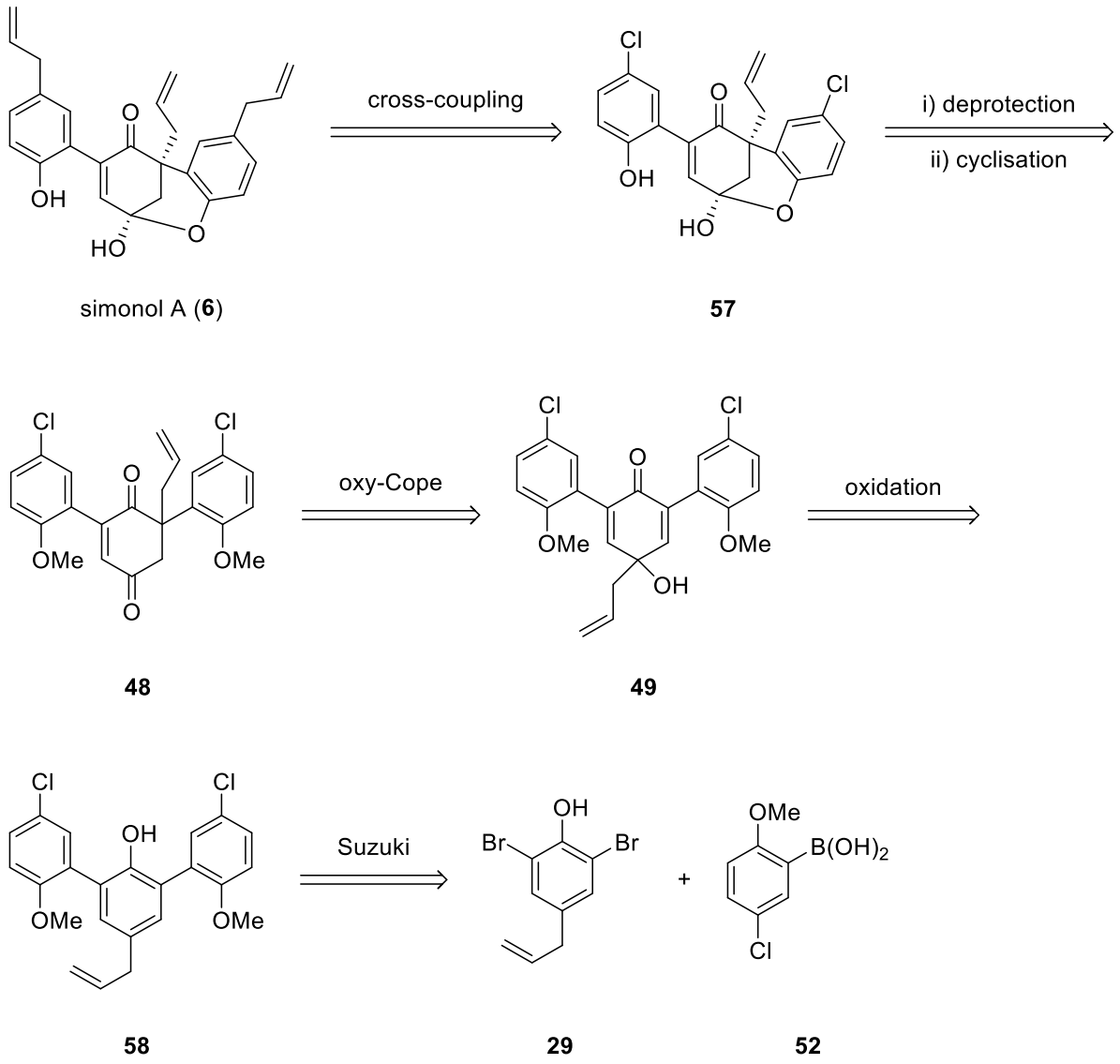

**55** **50**

**Scheme 10.** Alternative synthesis of **50**.

### 2.2.1. Second-Generation Retrosynthetic Analysis

Our second-generation retrosynthetic analysis of simonol A (**6**) closely resembles our proposed biosynthesis of this natural product, with chavicol (**7**) as the main precursor. This route also incorporates some of the steps from the previously reported synthesis of dunnianol (**26**).[33] The full retrosynthetic analysis is presented in Scheme 11.

At this stage it was decided that the final two steps of the previous route would still be carried out but in reverse order. Given the sensitivity of the allyl groups to isomerisation it seemed logical to incorporate those last to give simonol A (**6**) from intermediate (**57**). This in turn could be accessed from a one-pot deprotection and cyclisation of diketone (**48**) using $BCl_3$•$SMe_2$. **48** could be obtained *via* an oxy-Cope rearrangement of dienone (**49**), with this once again being the key step in the reaction sequence. It is at this point that the two routes begin to differ. Rather than a Grignard reaction, it was suggested that **49** could be made using an oxidative dearomatisation of triaryl (**58**), the latter being the product of a Suzuki coupling of dibromo (**29**) and 5-chloro-2-methoxyphenylboronic acid (**52**). **29** could then be prepared in two steps from estragole (**25**), as was the case in the synthesis of dunnianol (**26**).

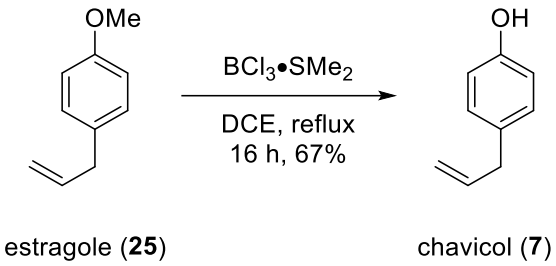



**Scheme 11.** Second retrosynthetic analysis of simonol A (**6**).

## 2.2.2. Second Route Development

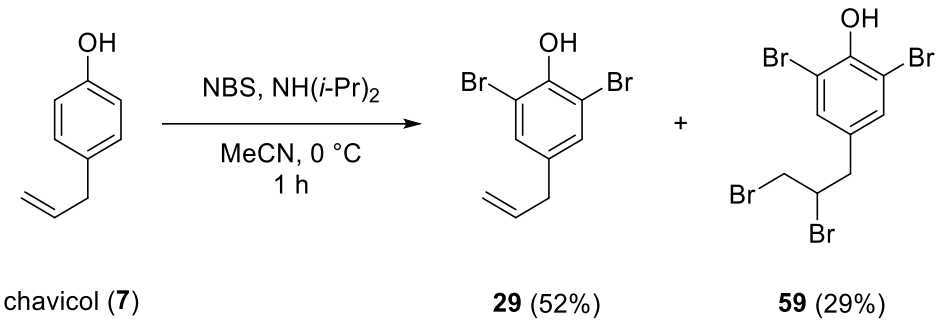
This route commenced with the demethylation of estragole (**25**) using $BCl_3 \bullet SMe_2$ to give chavicol (**7**) (Equation 2). This step was facile, with chavicol (**7**) being isolated in a reasonable 67% yield and with high purity, even when carrying out the reaction on a large scale. As well as this, no

isomerisation of the sensitive alkene group was observed, nor was there any addition of HCl (formed from $BCl_3$ hydrolysis) to the alkene.



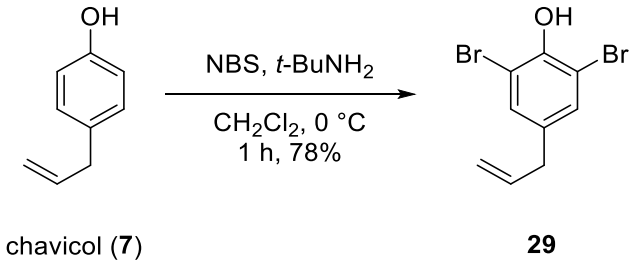

**Equation 2.** Synthesis of chavicol (**7**).

The dibromination of chavicol (**7**) to afford dibromo (**29**), on the other hand, was found to be more problematic. Initially, we were following an established procedure which made use of NBS as the brominating agent, $NH(i\text{-}Pr)_2$ as the base and MeCN as the solvent.[55] Under these conditions we obtained both our desired product and tetrabrominated species (**59**) in a roughly 9:5 ratio, as determined by the mass balance (Equation 3). The latter would have been made by bromination of both the phenol and alkene in chavicol (**7**) by NBS. This was in contrast to what was observed in the synthesis of dunnianol (**26**), in which the mass balance was the monobrominated product.[33] **59**, the structure of which was confirmed by both MS and $^1H$ NMR spectroscopy, was formed in significant quantities and the lack of regioselectivity in this step resulted in low yields of 30-40% on average. It was reasoned that shortening the reaction time from 1 h to 15 min may alter the product distribution, as this would give less time for **59** to form, however this proved to be false.




**Equation 3.** Original synthesis of **29**.

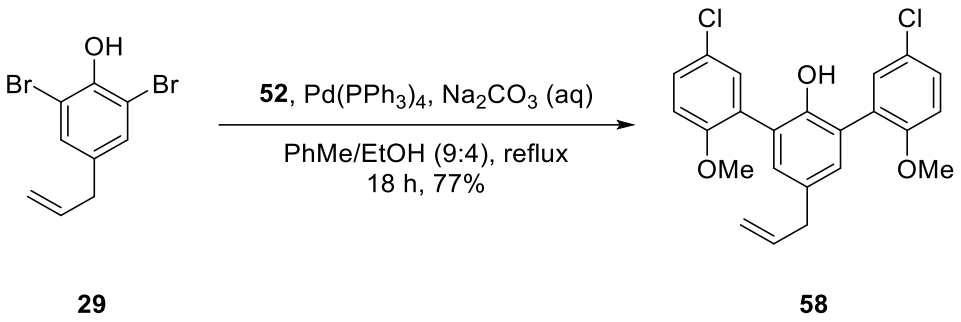
After some deliberation, it was decided that we should attempt the conditions from the dunnianol (**26**) publication instead, in which *t*-$BuNH_2$ was the base and $CH_2Cl_2$ was the solvent (Equation 4).[33] These were much more successful and a considerably higher isolated yield of 78% was obtained for **29**.




**Equation 4.** Improved synthesis of **29**.

Following the successful preparation of **29**, our next task was to use this compound in a Suzuki coupling with 5-chloro-2-methoxyphenylboronic acid (**52**) to yield triaryl (**58**) (Equation 5). For this we used similar conditions to our previously attempted Suzuki coupling with quinone (**51**),

but with markedly improved results. 1 mol% of $Pd(PPh_3)_4$ was used in the first instance but this prompted the formation of a mixture of the mono coupled product and unreacted starting material. Increasing the catalyst loading to 3 mol% led to **58** being produced as the major product in 77% yield. Far less protodeboronation was observed compared to in the previous Suzuki coupling and **58** was found to be more stable on silica, making purification easier. Once again, no isomerisation or undesired side reactions were observed.

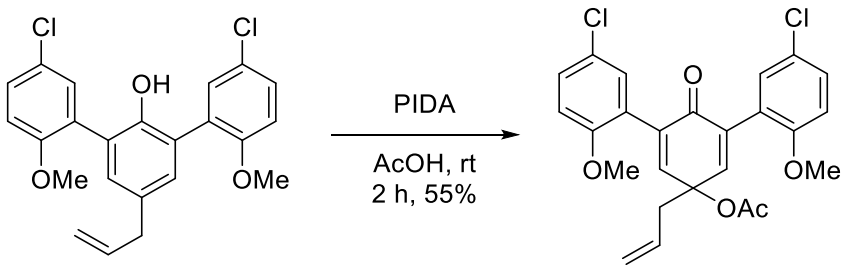



**29** **58**

**Equation 5.** Synthesis of **58**.

Now that we had finally executed the Suzuki coupling, we were in a position to attempt an oxidative dearomatisation on **58**, using phenyliodine(III) diacetate (PIDA) as the oxidising agent. We were confident that this would work, having previously employed this reagent for a similar transformation in our reported concise synthesis of 4'-*O*-methyl honokiol.[56] At the outset, the reaction was carried out in AcOH to afford intermediate (**60**) in a moderate 55% yield (Equation 6). The logic in using AcOH as the solvent was that the installation of an acetate group would give us a good

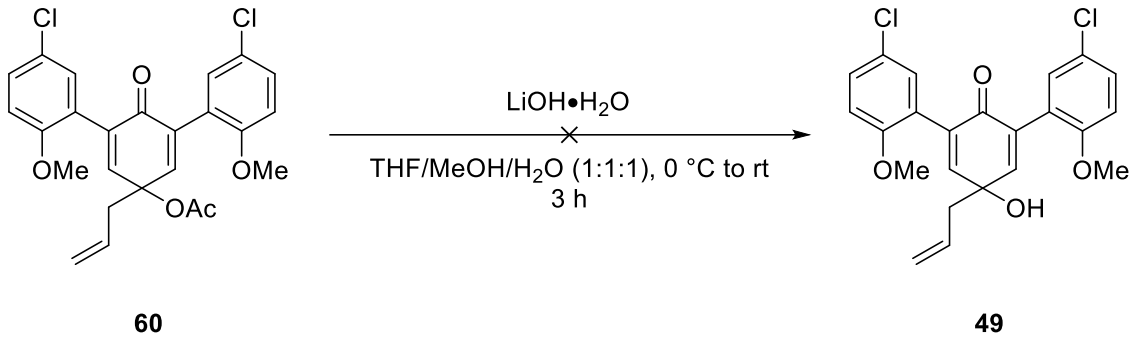
diagnostic signal to see if the reaction had worked by analysis of the crude $^1$H NMR spectrum. The $^1$H NMR data for **60** was as expected with the peak corresponding to the allylic protons notably further upfield now that it was no longer benzylic (chemical shift of 2.47 ppm, compared to 3.18 ppm in **58**).




**58** **60**

**Equation 6.** Synthesis of **60**.

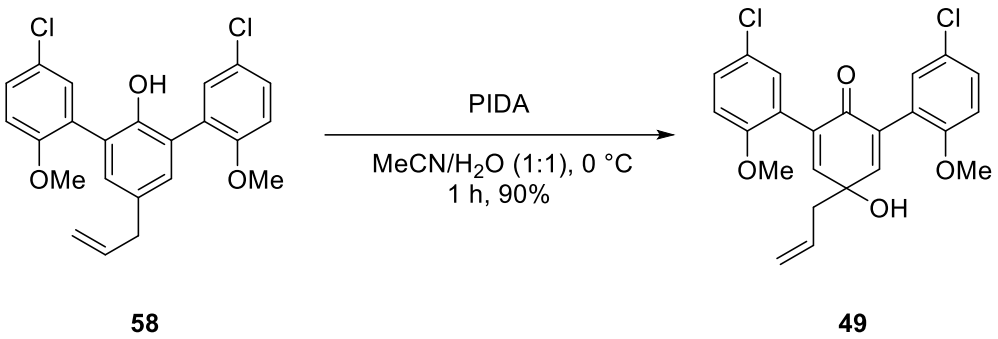
We next sought to hydrolyse the acetate group in **60** using LiOH•$H_2O$ to yield dienone (**49**) and potentially trigger the oxy-Cope rearrangement (Equation 7).[57] Unfortunately this step proved more difficult than expected, with the rather complicated crude $^1$H NMR spectrum indicating that something other than simple ester hydrolysis had occurred. As a result, this particular strategy of forming the acetate first and then hydrolysing it to the alcohol was abandoned.




**60** **49**

**Equation 7.** Unsuccessful synthesis of **49**.

Having established that an oxidative dearomatisation was possible for our substrate, it was proposed that **49** could be accessed directly from **58** by switching the solvent for this reaction from AcOH to wet MeCN. This indeed proved to be the case and **49** was successfully isolated through this method in an exceptional 90% yield (Equation 8). Once again, the distinctive shift of the peak for the allylic protons confirmed that the reaction had worked. Pleasingly, the $^{1}$H NMR spectrum was clean enough after the workup that the material could be carried through to the next step in the sequence without the need for further purification. We now had in our hands a viable candidate to test out the oxy-Cope rearrangement. In summary, **49** had successfully been prepared in 36% yield over four steps from estragole (**25**).



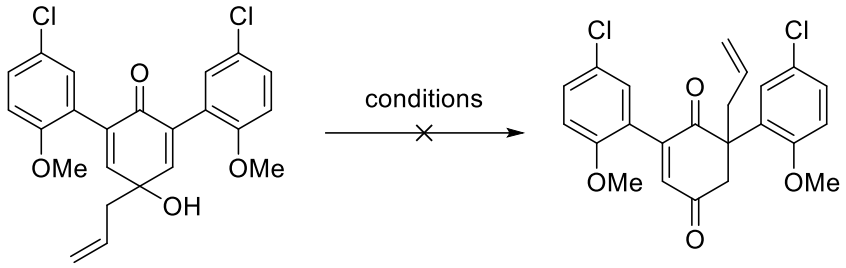

58 49

**Equation 8.** Successful synthesis of **49**.

## 2.2.3. Oxy-Cope Rearrangement

The oxy-Cope rearrangement is a [3,3] sigmatropic rearrangement of a 3-hydroxy-1,5-hexadiene to form an enol, which spontaneously then tautomerises to the more stable ketone.[58] The net result is the production of a δ,ε-unsaturated carbonyl. A vast range of substrates are suitable for this transformation, meaning it is an extremely useful synthetic tool.[59] There are two known ways of carrying out an oxy-Cope rearrangement. The method first discovered was a thermal process, for which very high temperatures are generally required (above 200 °C).[60] A more convenient approach is *via* anionic deprotonation of the alcohol to give an alkoxide.[61] This leads to an observed rate acceleration of $10^{10}$-$10^{17}$ and significantly lowers the activation barrier for the reaction, allowing it to be performed at room temperature. Typical reagents used for this are KH and 18-crown-6, with the latter sequestering the $K^+$ ion in the base to make it more reactive.

We began our investigations into using this rearrangement as part of our total synthesis of simonol A (**6**) by examining the anionic oxy-Cope rearrangement as a method of accessing diketone (**48**) from dienone (**49**). A variety of conditions were trialled for this reaction, unfortunately none of which were successful (Table 3). In the majority of cases there was simply unreacted starting material, with no sign of the diastereotopic $CH_2$ signals for the protons on the central ring and allyl group (expected between 2.40-3.40 ppm), which would have been present in the $^1$H NMR spectrum had the reaction been successful. Heat was applied to some of the reactions left overnight at room temperature to try and accelerate the process but this had no effect. One thermal oxy-Cope rearrangement was attempted (entry 6), yet this also failed. We decided following this that, given the large energy barrier for the thermal rearrangement, it would be difficult to reach a high enough temperature using standard laboratory equipment to enable the transformation to occur. We did see consumption of the starting material in entry 8, however after workup and purification we obtained a complex mixture of products and it was not possible to determine if **48** was present or not from the $^1$H NMR spectrum. Additionally, the fact that the starting material and product had identical masses meant that MS was not of much use here.




**49** **48**

| Entry | Base | Crown Ether | Additive | Solvent | Temp/°C | Time/h |
|---|---|---|---|---|---|---|
| 1 | NaH | N/A | N/A | $Et_2O$ | 25 | 22 |
| 2 | NaH | 15-crown-5 | N/A | $Et_2O$ | 25 | 20 |
| 3 | NaH | N/A | N/A | DME | 85 | 3 |
| 4 | KH | 18-crown-6 | N/A | THF | 25 | 21 |
| 5 | $CsOH•H_2O$ | N/A | Thiourea Cat | PhCl | 25 | 21 |
| 6 | N/A | N/A | N/A | DCB | 200 | 23 |
| 7 | KHMDS | N/A | N/A | DME | 50 | 16 |
| 8 | *t*-BuOK | 18-crown-6 | N/A | THF | 70 | 23 |

**Table 3.** Attempted oxy-Cope rearrangements.

In an effort to gain further insight into the oxy-Cope rearrangement, quantum mechanics (QM) calculations were carried out using the wB97DX/6-31G* theoretical model.[62] A summary of these calculations can be found in Figure 6, presented here for completeness alongside the experimental data that we collected. It should be noted that the relative energies given here are uncorrected electronic energies in kcal/mol at 298 K. From the data, we can see that the energy barrier for this reaction is quite large, a point further reinforced by the fact that the half-lives of dienone (**44**) in vacuum were estimated to be 50 y at 25 °C, compared to

28 s at 180 °C.[43] These values indicate that a very high temperature, *i.e.*, over 180 °C, would be required in order to carry out the reaction in a laboratory at a reasonable rate. This is undesirable as subjecting our substrate to such elevated temperatures could well result in isomerisation of the allyl groups.[63] In addition to this, if the oxy-Cope rearrangement were to occur in the biosynthesis then it is likely that some sort of enzyme catalyst would be required to lower the activation energy.[44] Moreover, the keto tautomer is clearly much more stable than the enol form and so this should render the oxy-Cope rearrangement irreversible, assuming that the high barrier can be overcome.

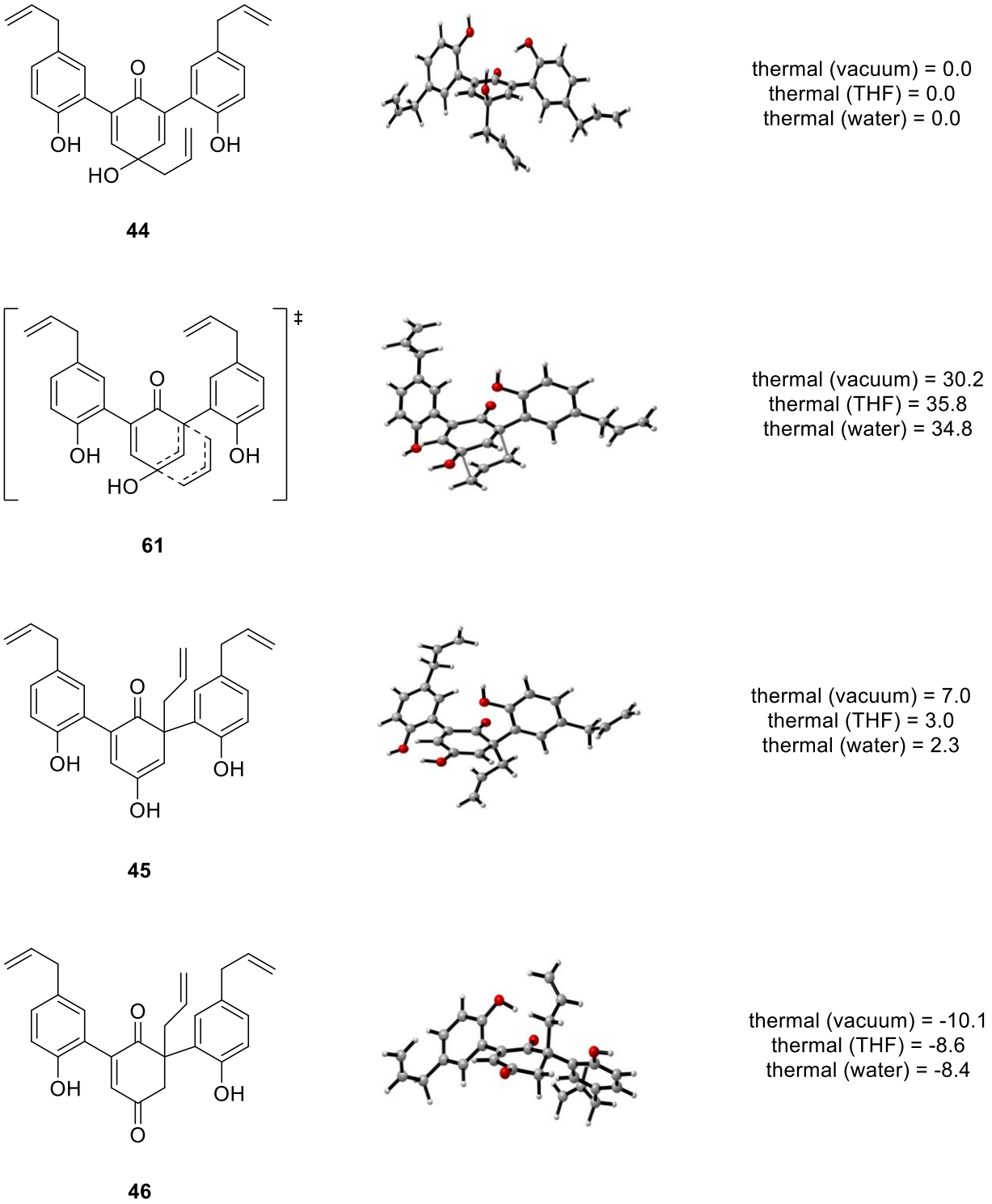
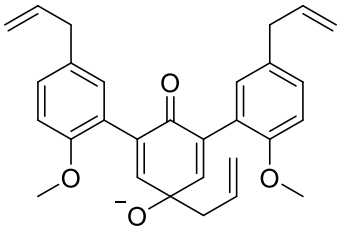


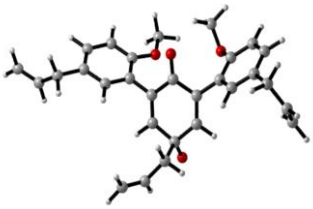

**Figure 6.** Calculated structures and relative energies (kcal/mol) for thermal oxy-Cope rearrangement.[62]

Another set of calculations was performed for the anionic oxy-Cope rearrangement and these results were compared against the thermal

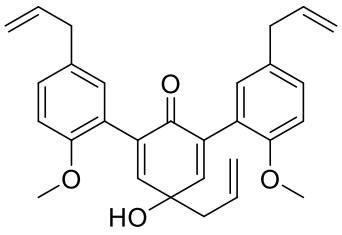
process, as shown in Figure 7. Methyl groups were added to the modelled structures to account for the fact that protecting groups would need to be in place for a total synthesis of simonol A (**6**). This would ensure selective deprotonation of the less acidic aliphatic hydroxyl group and avoid the formation of a trianonic species during the anionic oxy-Cope rearrangement. These calculations determined that the anionic oxy-Cope rearrangement has an energy barrier of 8.1 kcal/mol, much lower than its thermal equivalent of 35.6 kcal/mol. The half-life of alkoxide (**44a**) was calculated to be $9.75 \times 10^{-8}$ s. This means, in theory at least, that the anionic oxy-Cope rearrangement is more suitable for carrying out in a laboratory setting at room temperature. However, as a result of our difficulties in getting this reaction to work in practice, a third-generation retrosynthetic analysis was investigated.



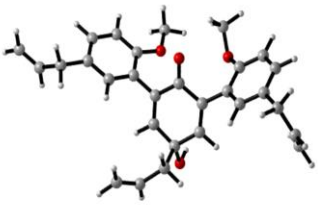
**44a**



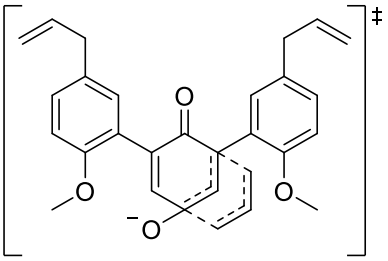
anionic = 0.0



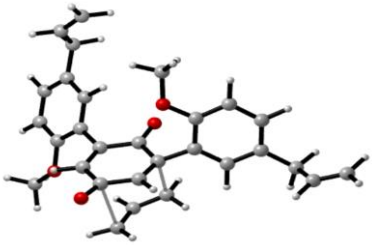
**44b**



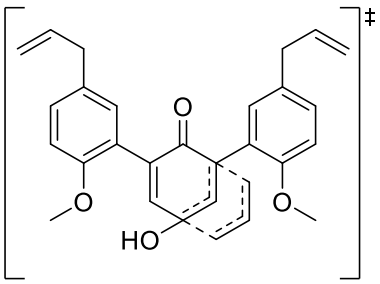
thermal = 0.0



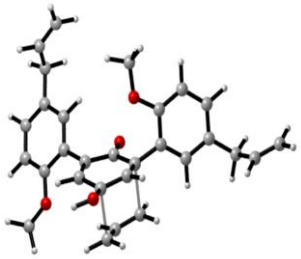
**61a**



anionic = 8.1



**61b**



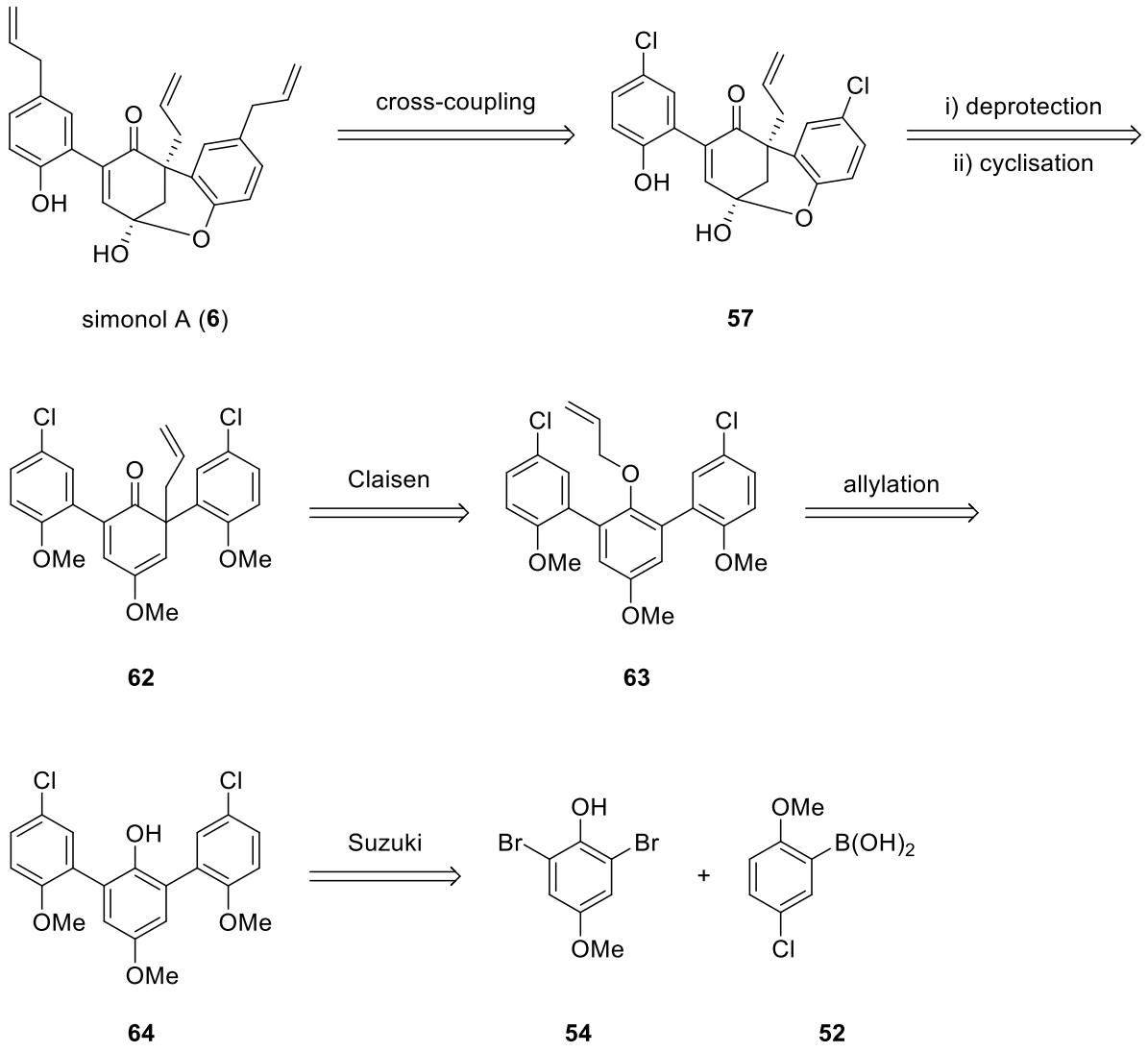
thermal = 35.6

**Figure 7.** Calculated structures and relative energies (kcal/mol) for anionic oxy-Cope rearrangement.[62]

### 2.3.1. Third-Generation Retrosynthetic Analysis

Our third-generation retrosynthetic analysis of simonol A (**6**) revisits some of the work being carried out by the former student on this project.[45] There are several similarities between this route and the earlier two, however the main difference is that the key step here is a Claisen rearrangement, as opposed to the oxy-Cope rearrangement that was discussed previously. The main precursor in this synthesis plan is dibromo (**54**), as was the case in the first route. The full retrosynthetic analysis is shown in Scheme 12.

As before, the final step would be a cross-coupling to afford simonol A (**6**) from intermediate (**57**). **57** could be made through a one-pot deprotection and cyclisation of enol ether (**62**), which in turn could be accessed *via* a Claisen rearrangement of ether (**63**). **63** could be prepared by allylation of triaryl (**64**), with the latter being the product of a Suzuki coupling of **54** and 5-chloro-2-methoxyphenylboronic acid (**52**). As before, **54** could be synthesised by bromination of commercially available 4-methoxyphenol (**53**). At a total of six steps, this synthetic route is the most concise of the three routes described in this thesis (eight steps in first route and seven in second route).

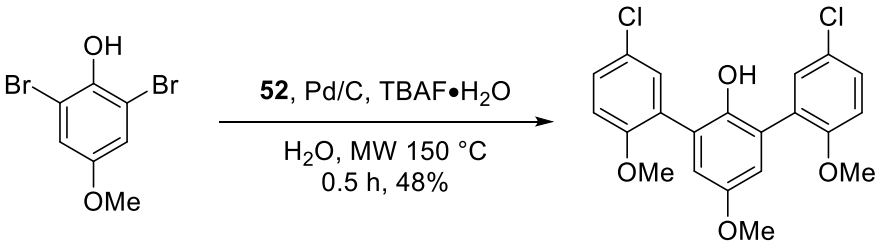



**Scheme 12.** Third retrosynthetic analysis of simonol A (**6**).

## 2.3.2. Key Intermediate Synthesis

As mentioned previously, the first step in our third synthetic route to simonol A (**6**) was a dibromination of 4-methoxyphenol (**53**) to give dibromo (**54**). This was carried out in the same way as before using $BTMABr_3$ and hence is not detailed again here.

After this, **54** and 5-chloro-2-methoxyphenylboronic acid (**52**) were reacted together in a double Suzuki coupling to afford triaryl (**64**) in an average 48% yield (Equation 9). We found that this reaction was more efficient on a milligram scale. On a gram scale the yields were considerably lower, between 19-21%. Another issue with scale up was a limit on how much solvent could be used in the microwave vial, however this could be solved by preparing multiple reaction batches and running them in the microwave sequentially. In our particular case we observed that the reaction seemed to work equally well whether carried out in a microwave or using a DrySyn heating block, although with the latter the reaction time was longer as expected.



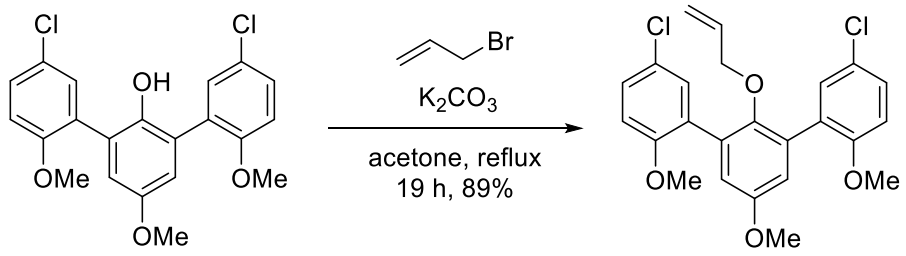

**54** **64**

**Equation 9.** Synthesis of **64**.

There are a few differences between this transformation and our previous Suzuki couplings. Firstly, it was accomplished by means of microwave irradiation. The main advantages of microwave experiments are shorter reaction times and, in some instances, higher yields when compared to those carried out using conventional heating methods.[64] Water was utilised

as our reaction medium here, a sharp contrast to the organic solvents employed previously. At first glance, water seems an odd choice of solvent given its ability to solubilise organic compounds is generally poor. However, its large dielectric constant means that, at high temperatures, water can be considered as a pseudo-organic solvent. Finally, the catalyst for this Suzuki coupling was Pd/C, as opposed to the $Pd(PPh_3)_4$ we used prior to this. Pd/C is a popular choice of catalyst in industry due to its high efficiency in mediating carbon-carbon bond formation, low cost and bench-stable nature.[65] Attempts to use the previously employed conditions for the Suzuki coupling were unsuccessful here.

After the Suzuki coupling, the next stage of the synthesis was allylation of **64** using allyl bromide to yield ether (**63**) (Equation 10). This reaction was carried out without too many issues and **63** was isolated in an excellent 89% yield. As well as this, the material was clean enough after the workup to carry through to the following step without further purification. When we initially designed this synthetic route, we thought about completing the allylation before the Suzuki coupling. However, the risk of either a Heck side reaction or insertion of the Pd into the π-bond occurring was too great and so we decided not to do this. Having gotten to the key intermediate in this route, obtained in 35% overall yield over three steps from **53**, we could now begin investigations into the Claisen rearrangement.




**64** **63**

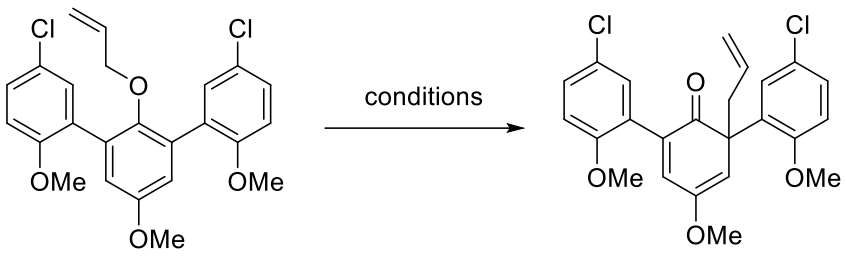
**Equation 10.** Synthesis of **63**.

## 2.3.3. Claisen Rearrangement

The Claisen rearrangement is the conversion of an allyl vinyl ether into a γ,δ-unsaturated carbonyl and, having been discovered in 1912, is the first recorded case of a [3,3] sigmatropic rearrangement.[66] Claisen rearrangements have traditionally been carried out under thermal conditions. However, like the oxy-Cope rearrangement, the thermal barrier for this reaction is rather high, to the extent that all reported examples of this rearrangement to date have involved temperatures of above 100 °C if uncatalysed.[67] Following its development into one of the most powerful tools for carbon-carbon bond formation in organic synthesis, in more recent times investigations have been carried out into Lewis acid-catalysed Claisen rearrangements.[68] These have been found to display a rapid rate acceleration and usually have a broad substrate scope. It is this methodology which we were hoping to apply in our own work.

As previously mentioned, our aim was to use the Claisen rearrangement as a means of accessing enol ether (**62**) from ether (**63**). Like with the oxy-

Cope rearrangement, different conditions were trialled for this transformation, as shown in Table 4. It should be noted that time was short at this stage of the project and so there is certainly scope for more work to be done on this reaction.



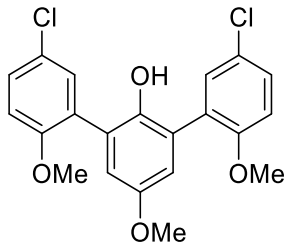

**63** **62**

| Entry | Additive | Solvent | Temp/°C | Time/h | Yield/%[a] |
|---|---|---|---|---|---|
| 1 | $BCl_3$•$SMe_2$ | DCE | 85 | 20 | 0 |
| 2 | N/A | DMF | 200 | 1 | 0 |
| 3 | $Bi(OTf)_3$ | MeCN | 85 | 19 | 0 |
| 4 | $BCl_3$ | $CH_2Cl_2$ | -15 | 3 | trace |

**Table 4.** Attempted Claisen rearrangements.

Despite our best efforts we were unable to isolate **62**, however we did see some promising signs and generally had an improved understanding of what was occurring in the test reactions compared to with the oxy-Cope rearrangement. We attempted first of all to carry out the rearrangement using $BCl_3$•$SMe_2$ (entry 1), in the hope that this could be combined with the one-pot deprotection and cyclisation step to give us intermediate (**57**) directly from **63**. We had accomplished a similar transformation in our

concise synthesis of honokiol (**27**) and so had some background in the area.[37] In this case, unfortunately, we observed significant cleavage of the allyl group, leading to the formation of triaryl (**64**) (Figure 8) as the major product, as confirmed by spectroscopic analysis ($^1$H NMR and MS).




**64**

**Figure 8.** Structure of **64**.

Attempts to perform the rearrangement under thermal conditions (entry 2), as well as by using $Bi(OTf)_3$ as the Lewis acid catalyst (entry 3), were both unsuccessful, with exclusively unreacted starting material in each case. Our most promising results came with $BCl_3$ (entry 4). Here we witnessed diastereotopic peaks in the $^1$H NMR spectrum of the isolated crude product at 3.06 ppm and 3.27 ppm. This was in line with what was the observed by the previous student working on this project who also attempted this transformation.[45] Upon purification of the crude material, these diastereotopic signals were still present, however the major product of this reaction appeared to be an inseparable mixture of **62**, our target compound, and **64**, an undesired side product formed as a result of the allyl group in **63** being removed. While this was obviously not ideal, we at

least now had a starting point to carry out further optimisation of this process.

As was the case with the oxy-Cope rearrangement, some computational studies were carried out in an attempt to gain further insight into the Claisen rearrangement. QM calculations using the wB97DX/6-31G* theoretical model were performed to obtain geometries and relative energies for all the key intermediates associated with this transformation.[62] This information, which can also be found in the thesis of the previous student working on this project, is outlined in Figure 9.[45] Once more, the computational work is presented alongside our synthetic work in the interest of completeness. It should be noted that the two allyl groups not involved in the Claisen rearrangement have been truncated in these structures in order to make the calculations faster. Again, the relative energies given here are uncorrected electronic energies in kcal/mol at 298 K. From this, we learnt that the thermal energy barrier for the Claisen rearrangement is 45.7 kcal/mol. The half-life of ether (**65**) was estimated to be 1.2 x $10^{13}$ y at 25 °C, compared to 26 y at 180 °C. While the energy barrier is quite large and may be overestimated by the theoretical model, these findings suggest that some sort of Lewis acid catalyst is almost certainly required in order to carry out the rearrangement, which is in agreement with our experimental data. Furthermore, similar to the oxy-Cope rearrangement, diketone (**68**) has a lower energy than enol (**67**), indicating that keto-enol tautomerisation is probable. In summary, the

smaller energy barriers associated with the oxy-Cope rearrangement (35.6 kcal/mol for neutral and 8.1 kcal/mol for anionic) suggest that this is a more likely rearrangement to take place in the biosynthesis of simonol A (**6**) than the Claisen rearrangement, for which the concerted energy barrier is very high.

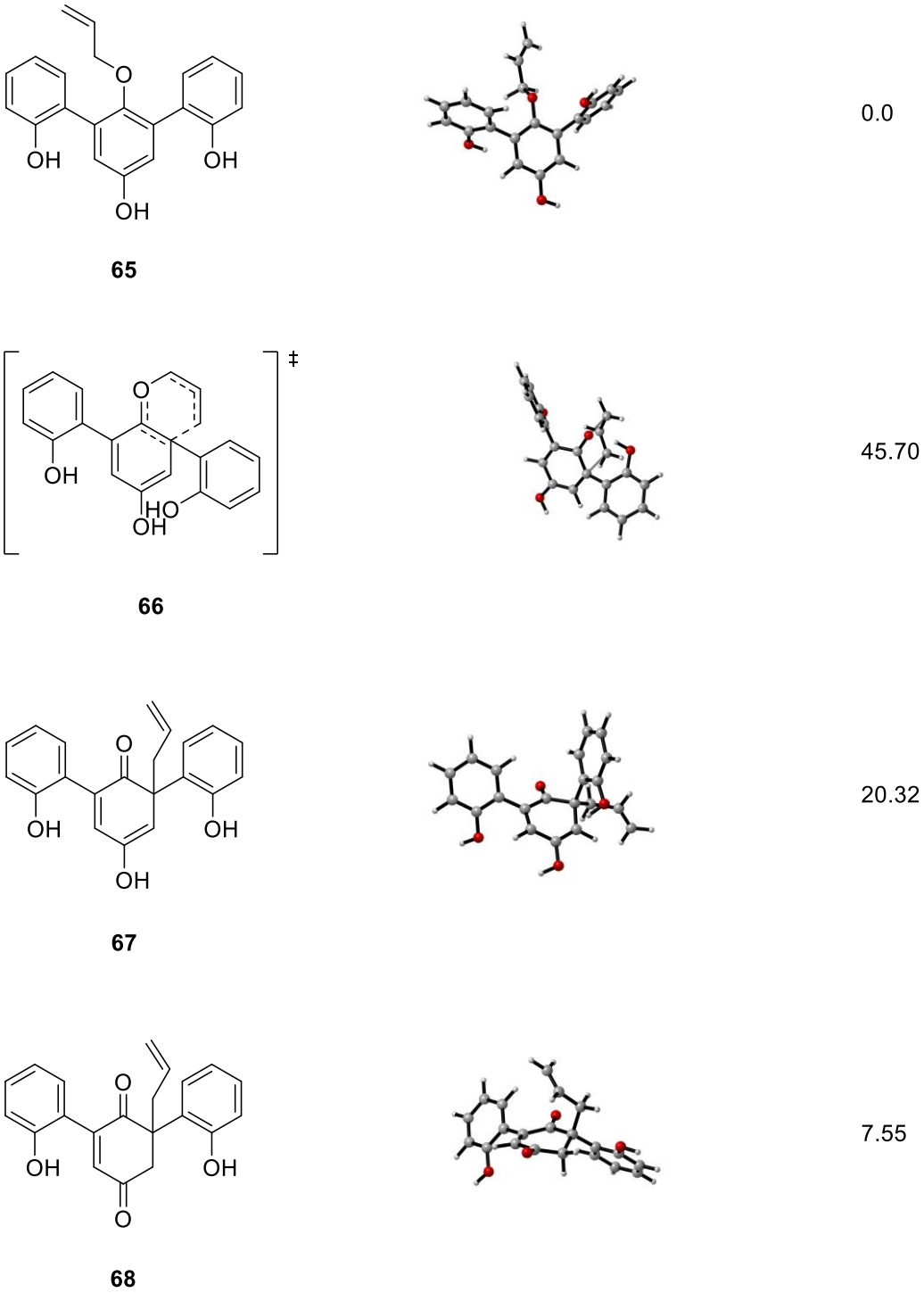


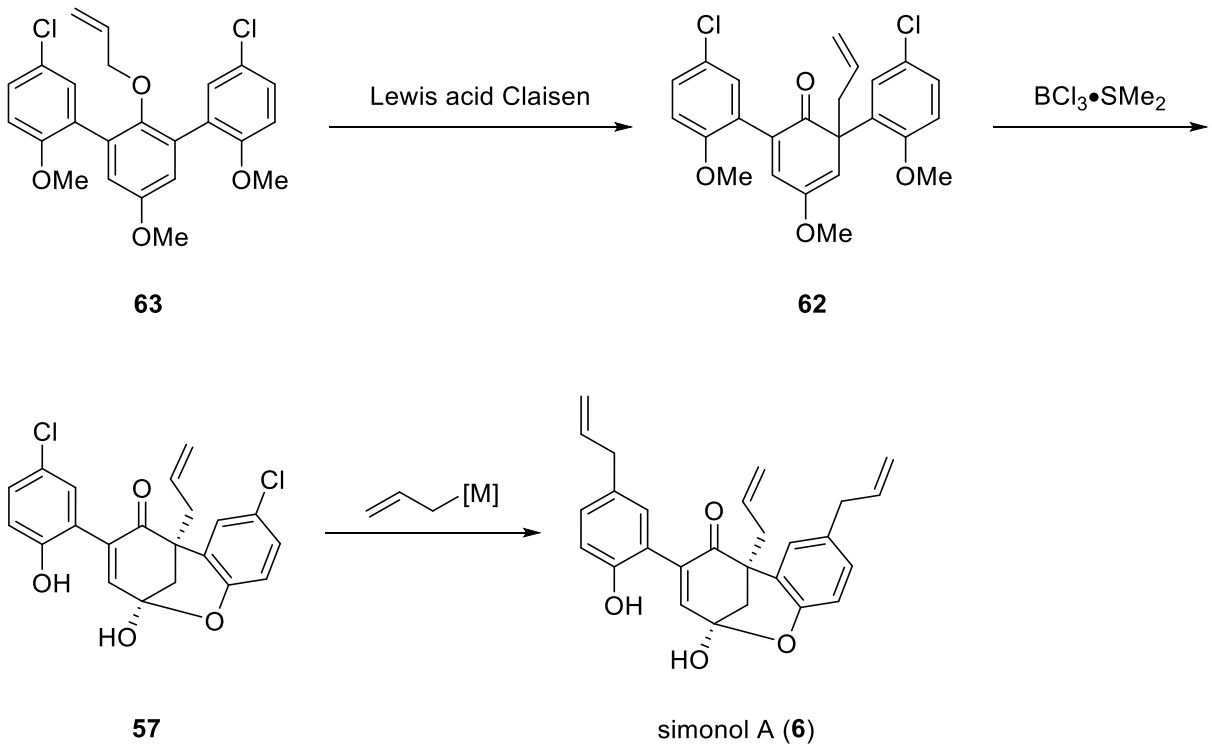

**Figure 9.** Calculated structures and relative energies (kcal/mol) for Claisen rearrangement.[45]

# 3. Conclusions and Future Work

In conclusion, three different synthetic routes to simonol A (**6**) have been explored in this project, each with varying degrees of success. Highlights include the efficient execution of a challenging double Suzuki coupling after trialling several different sets of conditions. Although attempts to carry out a [3,3] sigmatropic rearrangement were generally unsuccessful, there were some signs that a $BCl_3$-mediated Claisen rearrangement may be viable, if the issue of allyl group cleavage can be resolved. We believe that the third route, an extension of the work performed by the previous student on this project, remains our most promising avenue to simonol A (**6**).

Carrying on from the work in this thesis, it would be beneficial to further develop the third synthetic route towards simonol A (**6**) by optimising the Claisen rearrangement of ether (**63**) to enol ether (**62**). In the first instance, additional test reactions using $BCl_3$ should be carried out, however if this is unsuccessful then it would be worth trying some other Lewis acid catalysts for this transformation. The synthesis of **63**, the key intermediate in this route, has currently been achieved in 35% yield over three steps from 4-methoxyphenol (**53**). However, there is scope for improvement here, particularly in the case of the microwave Suzuki step, which is something that could be revisited once the rest of the route has been finished. After the rearrangement, there are two steps remaining in the synthesis (Scheme 13). The one-pot cyclisation and deprotection of **62** to

give intermediate (**57**) using $BCl_3 \bullet SMe_2$ should hopefully be straightforward. The double cross-coupling of **57** to afford simonol A (**6**) has the potential to be more difficult given that the substrate is an aryl chloride, however there are a number of possible ways of performing this transformation, *e.g.*, Suzuki, Stille, Grignard alkylation etc, so this should also not present too many challenges. Finally, once simonol A (**6**) has been successfully isolated, it would be of interest to carry out biological testing of this natural product, as well as synthesise some non-natural analogues, to enable us to begin constructing structure-activity relationships for this class of potential neuroprotective agents.




**Scheme 13.** Remaining steps in the synthesis of simonol A (**6**).

# 4. Supporting Information

## 4.1. General Details

Unless otherwise stated, all reactions were carried out under an atmosphere of argon in conventional glassware. Degassing was achieved by purging solutions with argon for 10-15 minutes. 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 effected using an ice-water bath. All water was deionised before use. Commercially available solvents and reagents were used as supplied, with the exception of dry MeCN, dry THF, dry DMF, dry $Et_2O$ and dry $CH_2Cl_2$, which were collected from solvent towers. Room temperature varied between 18 °C and 25 °C.

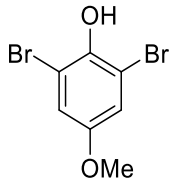
Analytical TLC was performed on Merck aluminium-backed silica gel 60 $F_{254}$ plates. Developed TLC plates were visualised by irradiation with UV light (254 nm), staining with $KMnO_4$ solution when required. Column chromatography was carried out using Fluorochem silica gel 60 Å, 40-63 µ. Melting points were measured using a Sigma Aldrich Stuart SMP3. IR spectra were obtained neat on a Bruker ALPHA FTIR spectrometer. HRMS spectra were acquired on a Bruker MicrOTOF II ESI-TOF instrument. NMR spectra were recorded at 298 K on Bruker Avance III spectrometers operating at nominal $^1H$ frequencies of 400 and 500 MHz. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks for $^1H$

and $^{13}C\{^{1}H\}$ respectively: $CDCl_3$ (7.26 ppm; 77.16 ppm), $C_6D_6$ (7.16 ppm; 128.06 ppm), DMSO-$d_6$ (2.50 ppm; 39.52 ppm). Coupling constants (J) are given in Hz. The multiplicity of a $^{1}H$ NMR signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet.

Calculations were performed using the wB97DX/6-31G* theoretical model implemented using Spartan 2018. Energies quoted refer to uncorrected electronic energies at 298 K. Starting geometries for equilibrium geometry calculations were obtained from molecular mechanics (equilibrium conformer) calculations performed in Spartan. To estimate energies in different solvents single point energy calculations were performed using the SM8 implicit solvent model and the appropriate solvent keywords. X, Y, Z coordinates from calculations are listed in the relevant section.

## 4.2. Experimental Procedures

2,6-Dibromo-4-methoxyphenol (**54**)[69]




**54**

To a suspension 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 eq) in $CH_2Cl_2$ (100 mL) and MeOH (40 mL) and the reaction mixture was stirred at rt for 2 h. The solvent was removed *in vacuo* and the resulting residue was triturated with acetone (50 mL) and filtered under suction. The filtrate was concentrated under reduced pressure. Recrystallisation from MeOH and $H_2O$ (1:4) yielded **54** as grey crystals (3.66 g, 81%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3393, 1601, 1562, 1475, 1438, 1402, 1342, 1252, 1203, 1160, 1037

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.04 (2H, s, Ar*H*), 5.48 (1H, s, ArO*H*), 3.75 (3H, s, OC$H_3$)

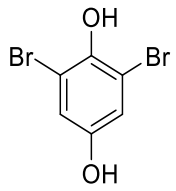
**$^{13}$C{$^1$H} NMR** (101 MHz, $CDCl_3$) δ: 153.8 (Cq), 143.9 (Cq), 118.0 (CH), 109.8 (CH), 56.3 ($CH_3$)

**HRMS** ($ESI^-$): $C_7H_6O_2Br_2$ $[M-H]^-$ m/z calcd 280.8641; found 280.8639

**mp**: 85-87 °C (**literature mp**: 83-84 °C)[70]

Spectroscopic data in accordance with literature.[71]

2,6-Dibromobenzene-1,4-diol (**55**)[69]




**55**

To a solution of **54** (1.96 g, 6.95 mmol) in MeCN (36 mL) was added TMSCl (4.42 mL, 34.8 mmol, 5.00 eq) and NaI (5.22 g, 34.8 mmol, 5.00 eq) and the reaction was heated at reflux for 17 h. Upon cooling to rt, the reaction mixture was poured over an ice/water slurry and the aqueous phase was extracted with EtOAc (3 x 100 mL). The organic layer was washed with $Na_2SO_3$ (100 mL), $H_2O$ (100 mL) and brine (100 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallisation from $CHCl_3$ and hexane (3:1) yielded **55** as off-white crystals (1.12 g, 60%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3278, 1605, 1574, 1468, 1353, 1205

**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ: 9.57 (1H, s, ArO*H*), 9.08 (1H, s, ArO*H*), 6.94 (2H, s, Ar*H*)

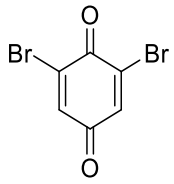
**$^{13}C\{^1H\}$ NMR** (126 MHz, DMSO-$d_6$) δ: 151.6 (Cq), 143.3 (Cq), 118.7 (CH), 112.8 (CH)

**HRMS** ($ESI^-$): $C_6H_4O_2Br_2$ $[M-H]^-$ m/z calcd 266.8485; found 264.8484

**mp**: 161-163 °C (**literature mp**: 161-162 °C)[72]

Spectroscopic data in accordance with literature.[69]

2,6-Dibromocyclohexa-2,5-diene-1,4-dione (**51**)[71]




**51**

To a solution of **55** (1.11 g, 4.14 mmol) in MeCN (9.0 mL) and $H_2O$ (6.0 mL) was added Oxone (1.39 g, 4.52 mmol, 1.09 eq) and TBAB (150 mg, 465 μmol, 0.112 eq) and the reaction was stirred at rt for 1.5 h. Solid was filtered out from the reaction mixture and brine (15 mL) was then added to the filtrate. The aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was passed through silica, using $Et_2O$ as the eluent, and concentrated *in vacuo* to yield **51** as a yellow solid (954 mg, 87%).

**IR** ($cm^{-1}$) $v_{max}$: 1692, 1651, 1579, 1263, 1003

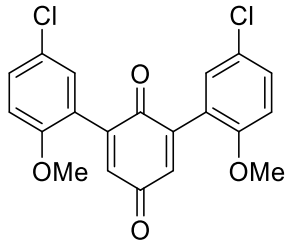
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.33 (2H, s, C*H*)

**$^{13}$C{$^1$H} NMR** (126 MHz, $CDCl_3$) δ: 182.5 (Cq), 172.6 (Cq), 138.4 (CH), 135.8 (Cq)

**mp**: 122-124 °C (**literature mp**: 128-129 °C)[73]

Spectroscopic data in accordance with literature.[71]

5,5''-Dichloro-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-2',5'-dione (**50**)[48]




**50**

To a microwave vial was added **51** (100 mg, 376 μmol), 5-chloro-2-methoxyphenylboronic acid (157 mg, 842 μmol, 2.20 eq) and $Pd(PPh_3)_4$ (4.37 mg, 3.76 μmol, 1 mol%). A mixture of PhMe (2.7 mL) and EtOH (1.2 mL) was degassed and added to the reaction vessel, followed by degassed $Na_2CO_3$ (1.2 mL of a 2.0 M aqueous solution). The reaction was heated at reflux for 17 h. The reaction mixture was allowed to cool to rt and the organics were diluted with EtOAc (10 mL), washed with $H_2O$ (2 x 20 mL) and then brine (20 mL). The organics were dried over $MgSO_4$,

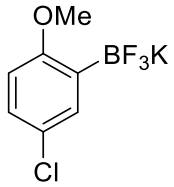
filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (80:20-70:30, pentane:EtOAc) to yield **50** as a red oil (36.9 mg, 25%).

**IR** ($cm^{-1}$) $v_{max}$: 1588, 1488, 1453, 1391, 1237, 1180, 1119, 1024

**$^1$H NMR** (400 MHz, $C_6D_6$) δ: 7.30 (2H, d, *J* = 2.7 Hz, Ar*H*), 7.07 (2H, dd, *J* = 8.8, 2.7 Hz, Ar*H*), 6.47 (2H, s, C*H*), 6.22 (2H, d, *J* = 8.8 Hz, Ar*H*), 3.02 (6H, s, OC*H*$_3$)

**$^{13}$C{$^1$H} NMR** (101 MHz, $CDCl_3$) δ: 183.5 (Cq), 180.2 (Cq), 155.4 (Cq), 145.7 (Cq), 132.2 (CH), 130.2 (CH), 128.6 (CH), 126.3 (Cq), 118.2 (Cq), 112.8 (CH), 55.6 ($CH_3$)

Potassium (5-chloro-2-methoxyphenyl)trifluoroborate (**56**)[74]




**56**

To a solution of 5-chloro-2-methoxyphenylboronic acid (932 mg, 5.00 mmol) in $Et_2O$ (10 mL) was added $KHF_2$ (1.09 g, 14.0 mmol, 2.80 eq). $H_2O$ (5.0 mL) was added over 0.5 h via syringe pump and the reaction was then stirred vigorously for 3 h at rt. The reaction mixture was concentrated

under reduced pressure and the resultant residue was dissolved in hot acetone. The solution was filtered and the filtrate concentrated *in vacuo*. The residue was again dissolved in hot acetone and $Et_2O$ was added to precipitate the product. Suction filtration yielded **56** as a white solid (1.06 g, 85%).

**IR** ($cm^{-1}$) $\nu_{max}$: 1471, 1446, 1387, 1219, 1178, 1136

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ: 7.19 (1H, d, *J* = 2.9 Hz, Ar*H*), 7.01 (1H, dd, *J* = 8.6, 2.9 Hz, Ar*H*), 6.67 (1H, d, J = 8.6 Hz, Ar*H*), 3.60 (3H, s, OC*H*$_3$)

**$^{13}$C{$^1$H} NMR** (101 MHz, DMSO-$d_6$) δ: 161.2 (Cq), 132.6 (CH), 125.8 (Cq), 123.3 (Cq), 111.4 (CH), 55.0 ($CH_3$)

**$^{19}$F{$^1$H} NMR** (376 MHz, DMSO-$d_6$) δ: -137.6

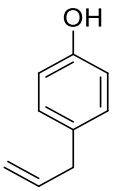
**$^{11}$B NMR** (128 MHz, DMSO-$d_6$) δ: 2.10

**HRMS** ($ESI^+$): $C_7H_6BClF_3KO$ $[M+Na]^+$ m/z calcd 270.9687; found 270.9691

**mp**: >270 °C (**literature mp**: >260 °C)[74]

Spectroscopic data in accordance with literature.[74]

4-Allylphenol (**7**)[55]




**7**

To a solution of 4-allylanisole (3.07 mL, 20.0 mmol) in DCE (90 mL) was added $BCl_3$•$SMe_2$ (15.0 mL, 30.0 mmol, 1.50 eq of a 2.00 M solution in $CH_2Cl_2$). The reaction was heated under reflux for 16 h. Upon cooling to rt, the reaction was quenched with $H_2O$ (90 mL) and then diluted with $CH_2Cl_2$ (60 mL). The organic layer was washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified using column chromatography (90:10, pentane:EtOAc) to yield **7** as a deep orange oil (1.80 g, 67%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3362, 1494, 1407, 1355, 1263, 1167, 1008

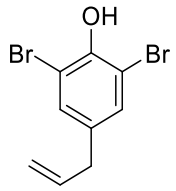
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.06 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.77 (2H, d, *J* = 8.4 Hz, Ar*H*), 5.95 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, C*H*$CH_2$), 5.08-5.03 (2H, m, CHC$H_2$), 4.64 (1H, s, ArO*H*), 3.32 (2H, d, *J* = 8.3 Hz, ArC$H_2$)

**$^{13}$C{$^1$H} NMR** (126 MHz, $CDCl_3$) δ: 153.9 (Cq), 138.0 (CH), 132.4 (Cq), 129.9 (CH), 115.6 ($CH_2$), 115.4 (CH), 39.5 ($CH_2$)

**HRMS** ($ESI^-$): $C_9H_{10}O$ $[M-H]^-$ m/z calcd 133.0659; found 133.0668

Spectroscopic data in accordance with literature.[75]

4-Allyl-2,6-dibromophenol (**29**)[33]




**29**

A solution of **7** (1.99 g, 14.8 mmol) in $CH_2Cl_2$ (150 mL) was cooled to 0 °C. *t*-$BuNH_2$ (156 µL, 1.48 mmol, 0.100 eq) was added and the reaction was stirred for 0.25 h. NBS (6.60 g, 37.1 mmol, 2.50 eq) was then added and the reaction was stirred for a further 1 h. The reaction mixture was warmed to rt and quenched using sat. aq. $Na_2S_2O_3$ (190 mL). The organic layer was washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified using column chromatography (95:5, pentane:EtOAc) to yield **29** as a pale yellow oil (3.38 g, 78%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3491, 1560, 1473, 1405, 1318, 1271, 1238, 1198, 1156

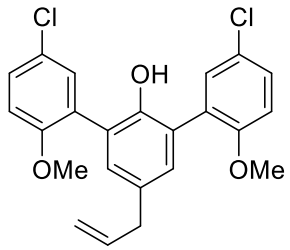
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.27 (2H, s, Ar*H*), 5.88 (1H, ddt, *J* = 16.8, 10.0, 6.7 Hz, C*H*$CH_2$), 5.75 (1H, s, ArO*H*), 5.13-5.06 (2H, m, CHC$H_2$), 3.28 (2H, d, *J* = 6.7 Hz, ArC$H_2$)

**$^{13}$C{$^1$H} NMR** (101 MHz, $CDCl_3$) δ: 147.8 (Cq), 136.3 (CH), 134.8 (Cq), 132.2 (CH), 117.0 ($CH_2$), 109.8 (Cq), 38.8 ($CH_2$)

**HRMS** ($ESI^-$): $C_9H_8O_2$ $[M-H]^-$ m/z calcd 290.8849; found 290.8861

Spectroscopic data in accordance with literature.[76]

5’-Allyl-5,5’’-dichloro-2,2’’-dimethoxy-[1,1’:3’,1’’-terphenyl]-2’-ol (**58**)[48]




**58**

To a solution of **29** (1.23 g, 4.21 mmol) in PhMe (30 mL) and EtOH (13 mL) was added $Na_2CO_3$ (13 mL of a 2.0 M aqueous solution) and the biphasic mixture was sparged with argon for 10 min. 5-chloro-2-methoxyphenylboronic acid (2.35 g, 12.6 mmol, 3.00 eq) and $Pd(PPh_3)_4$ (146 mg, 126 μmol, 3 mol%) were added and the reaction mixture was sparged with argon for a further 5 min. The reaction was heated at reflux for 16 h, before being cooled to rt and diluted with EtOAc (50 mL). The organic layer was washed with 1.0 M HCl (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified using column chromatography (80:20, pentane:EtOAc), to yield **58** as a pale yellow solid (1.34 g, 77%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3379, 1487, 1391, 1224, 1172, 1135, 1096, 1018

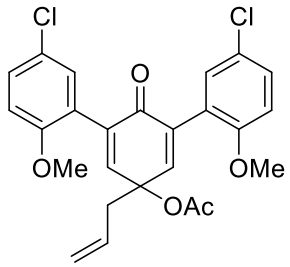
**$^1$H NMR** (500 MHz, $C_6D_6$) δ: 7.35 (2H, d, *J* = 2.7 Hz, Ar*H*), 7.09 (2H, dd, *J* = 8.8, 2.7 Hz, Ar*H*), 7.01 (2H, s, Ar*H*), 6.24 (2H, d, *J* = 8.8 Hz, Ar*H*), 6.12 (1H, s, ArO*H*), 5.86 (1H, ddt, *J* = 16.8, 10.0, 6.8 Hz, C*H*$CH_2$), 5.03-4.93 (2H, m, CHC*H*$_2$), 3.18 (2H, d, *J* = 6.8 Hz, ArC*H*$_2$), 3.04 (6H, s, OC*H*$_3$)

**$^{13}$C{$^1$H} NMR** (126 MHz, $CDCl_3$) δ: 155.5 (Cq), 150.5 (Cq), 138.0 (CH), 132.4 (CH), 132.3 (Cq), 131.7 (CH), 130.3 (CH), 128.6 (Cq), 126.8 (Cq), 126.4 (Cq), 115.7 (CH), 112.7 ($CH_2$), 55.6 ($CH_3$), 39.7 ($CH_2$)

**HRMS** ($ESI^-$): $C_{23}H_{20}Cl_2O_3$ $[M-H]^-$ m/z calcd 413.0716; found 413.0719

**mp**: 102-104 °C

5'-Allyl-5,5''-dichloro-2,2''-dimethoxy-2'-oxo-2',5'-dihydro-[1,1':3',1''-terphenyl]-5'-yl acetate (**60**)[55]



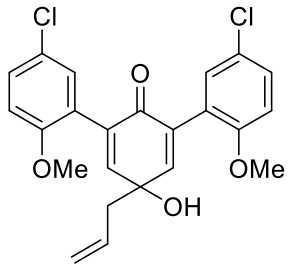

**60**

To a solution of **58** (224 mg, 539 μmol) in AcOH (9.0 mL) was added PIDA (348 mg, 1.08 mmol, 2.00 eq) and the reaction was stirred at rt for 2 h, before being neutralised to pH 7 using sat. aq. $NaHCO_3$. The aqueous layer was washed with EtOAc (200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was

purified by column chromatography (80:20, pentane:EtOAc) to yield **60** as a viscous orange oil (140 mg, 55%).

**$^1$H NMR** (500 MHz, $C_6D_6$) δ: 7.34 (2H, d, *J* = 2.7 Hz, Ar*H*), 7.09 (2H, dd, *J* = 8.7, 2.7 Hz, Ar*H*), 6.61 (2H, s, Ar*H*), 6.26 (2H, d, *J* = 8.7 Hz, 2H, C*H*), 5.67 (1H, ddt, *J* = 17.4, 10.2, 7.3 Hz, C*H*$CH_2$), 4.99 (1H, dd, *J* = 10.2, 1.9 Hz, CHC$H_{2cis}$), 4.93 (1H, dd, *J* = 17.0, 1.8 Hz, CHC$H_{2trans}$), 3.18 (6H, s, OC$H_3$), 2.47 (2H, d, *J* = 7.2 Hz, ArC$H_2$), 1.59 (3H, s, $CO_2CH_3$)
**HRMS** (ESI$^+$): $C_{25}H_{22}Cl_2O_5$ $[M+H]^+$ m/z calcd 473.0917; found 473.0916

5'-Allyl-5,5''-dichloro-5'-hydroxy-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-2'(5'H)-one (**49**)[77]




**49**

A solution of **58** (319 mg, 768 μmol) in MeCN (4.6 mL) and $H_2O$ (4.6 mL) was cooled to 0 °C. PIDA (272 mg, 845 μmol, 1.10 eq) was added and the reaction was stirred for 1 h, before being diluted with EtOAc (20 mL) and $H_2O$ (5.0 mL). The organic layer was collected and the aqueous layer re-extracted with EtOAc (2 x 20 mL). The combined organics were washed

with brine (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield **49** as an orange solid (297 mg, 90%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3465, 1644, 1487, 1462, 1391, 1261, 1227, 1177, 1135, 1115, 1096, 1075

**$^1$H NMR** (400 MHz, $C_6D_6$) δ: 7.25 (2H, d, *J* = 2.7 Hz, Ar*H*), 7.11 (2H, dd, *J* = 8.8, 2.7 Hz, Ar*H*), 6.43 (2H, s, Ar*H*), 6.28 (2H, d, *J* = 8.8 Hz, C*H*), 5.67 (1H, ddt, *J* = 17.4, 10.3, 7.4 Hz, C*H*$CH_2$), 4.95-4.84 (2H, m, CHC*H*$_2$), 3.21 (6H, s, OC*H*$_3$), 2.28 (2H, d, *J* = 7.4 Hz, ArC*H*$_2$)

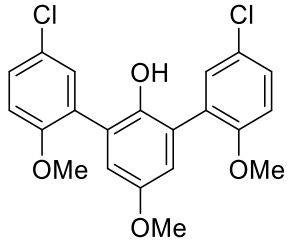
**$^{13}$C{$^1$H} NMR** (101 MHz, $C_6D_6$) δ: 180.6 (Cq), 156.7 (CH), 148.2 (Cq), 136.9 (CH), 132.0 (CH), 131.1 (CH), 129.3 (Cq) 125.6 (Cq), 119.6 ($CH_2$), 112.7 (CH), 69.4 (Cq), 55.7 ($CH_3$), 45.2 ($CH_2$)

**HRMS** ($ESI^+$): $C_{23}H_{20}Cl_2O_4$ $[M+H]^+$ m/z calcd 431.0812; found 431.0811

**mp**: 129-131 °C

OH proton not observed.

5,5''-Dichloro-2,2'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-ol (**64**)[78]




**64**

To a microwave vial was added **54** (100 mg, 355 μmol), 5-chloro-2-methoxyphenylboronic acid (198 mg, 1.06 mmol, 3.00 eq), TBAF•$3H_2O$ (896 mg, 2.84 mmol, 8.00 eq) and 10% Pd/C (50% wet, 1.89 mg, 17.8 μmol, 5 mol%). Degassed $H_2O$ (3.5 mL) was then added and the suspension was heated at 150 °C through microwave irradiation for 0.5 h. The reaction was cooled to rt and acidified to pH 6 with 1.0 M HCl. The aqueous phase was extracted with EtOAc (3 x 5.0 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified using column chromatography (70:30, pentane:EtOAc) to yield **64** as an orange solid (69.4 mg, 48%).

**IR** ($cm^{-1}$) $\nu_{max}$: 3402, 1593, 1489, 1459, 1435, 1390, 1331, 1284, 1239, 1199, 1173, 1117, 1023

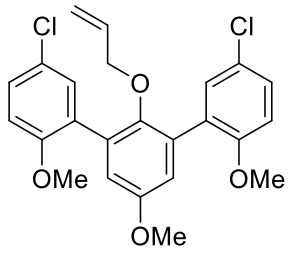
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.36 (2H, d, *J* = 2.6 Hz, Ar*H*), 7.32 (2H, dd, *J* = 8.7, 2.6 Hz, Ar*H*), 6.94 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.84 (2H, s, Ar*H*), 5.94 (1H, s, ArO*H*), 3.84 (6H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$)

**$^{13}$C{$^1$H} NMR** (101 MHz, $CDCl_3$) δ: 155.0 (Cq), 153.4 (Cq), 131.9 (CH), 128.9 (CH), 127.2 (Cq), 126.3 (Cq), 116.6 (CH), 112.7 (CH), 56.5 ($CH_3$), 56.0 ($CH_3$)

**HRMS** ($ESI^-$): $C_{21}H_{18}Cl_2O_4$ $[M-H]^-$ m/z calcd 403.0509; found 403.0510

**mp**: 61-63 °C

2'-(Allyloxy)-5,5''-dichloro-2,2'',5'-trimethoxy-1,1':3',1''-terphenyl (**63**)[37]




**63**

To a solution of **64** (458 mg, 1.13 mmol) in acetone (5.6 mL) was added allyl bromide (195 µL, 2.26 mmol, 2.00 eq) and $K_2CO_3$ (312 mg, 2.26 mmol, 2.00 eq) and the reaction was heated at reflux for 19 h. The reaction mixture was cooled to rt, quenched with MeOH (10 mL) and diluted with EtOAc (20 mL). The organic layer was washed with $H_2O$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield **63** as a viscous orange oil (448 mg, 89%).

**IR** ($cm^{-1}$) $v_{max}$: 1592, 1490, 1455, 1433, 1398, 1330, 1285, 1242, 1199, 1175, 1137, 1124, 1051, 1027

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ: 7.39 (2H, dd, *J* = 8.9, 2.7 Hz, Ar*H*), 7.27 (2H, d, *J* = 2.7 Hz, Ar*H*), 7.11 (2H, d, *J* = 8.9 Hz, Ar*H*), 6.78 (2H, s, Ar*H*), 5.30 (1H, ddd, *J* = 22.5, 10.5, 5.2 Hz, C*H*$CH_2$), 4.83-4.71 (2H, m, CHC*H*$_2$), 3.75 (6H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$)

**$^{13}C\{^{1}H\}$ NMR** (101 MHz, DMSO-$d_6$) δ: 155.5 (Cq), 154.2 (Cq), 148.0 (Cq), 133.8 (CH), 131.4 (CH), 130.4 (CH), 128.8 (Cq), 128.5 (Cq), 123.7 ($CH_2$), 116.0 (CH), 113.1 (CH), 73.3 ($CH_2$), 55.8 ($CH_3$), 55.4 ($CH_3$)

**HRMS** ($ESI^+$): $C_{24}H_{22}Cl_2O_4$ $[M+H]^+$ m/z calcd 445.0968; found 445.0963

## 4.3. Computational Data

Dienone (**44**):

| | | | |
|---|---|---|---|
| C | 0.627513 | 4.954766 | -1.471990 |
| C | 2.215732 | 3.243020 | 0.092215 |
| C | 0.124623 | 3.748101 | -0.981373 |
| C | 1.944436 | 5.283759 | -1.163703 |
| C | 2.735376 | 4.440553 | -0.388560 |
| C | 0.894981 | 2.882788 | -0.211194 |
| H | -0.898934 | 3.462596 | -1.213355 |
| H | 2.364877 | 6.217330 | -1.528623 |
| H | 3.759001 | 4.721394 | -0.150808 |
| C | 1.056544 | -2.249670 | 0.025927 |
| C | 1.958684 | -4.856100 | -0.477947 |
| C | 0.164006 | -3.309755 | -0.199865 |
| C | 2.435854 | -2.517225 | -0.061718 |
| C | 2.866125 | -3.826382 | -0.298335 |
| C | 0.583418 | -4.608623 | -0.451708 |
| H | -0.902508 | -3.094011 | -0.178646 |
| H | 3.935573 | -4.004994 | -0.339911 |
| H | 2.317528 | -5.867226 | -0.653506 |
| O | 2.923480 | 2.401818 | 0.891508 |
| O | 3.395784 | -1.581551 | 0.124796 |
| C | 0.967290 | 0.340648 | -0.147811 |

| | | | |
|---|---|---|---|
| O | 1.886033 | 0.369521 | -0.958706 |
| C | 0.326569 | 1.611209 | 0.295807 |
| C | 0.474841 | -0.940289 | 0.428400 |
| C | -0.733569 | 1.582581 | 1.111690 |
| H | -1.195582 | 2.507669 | 1.451384 |
| C | -0.562624 | -0.902842 | 1.281906 |
| H | -0.920873 | -1.820285 | 1.741155 |
| C | -1.362964 | 0.319466 | 1.619003 |
| O | -1.573400 | 0.410995 | 3.025202 |
| H | -0.704651 | 0.449705 | 3.446419 |
| C | -2.778159 | 0.185436 | 0.995539 |
| H | -2.678086 | 0.197704 | -0.095037 |
| H | -3.338721 | 1.080904 | 1.293928 |
| C | -3.511740 | -1.045973 | 1.444091 |
| H | -3.697173 | -1.124199 | 2.513202 |
| C | -3.920808 | -2.010674 | 0.624041 |
| H | -4.454556 | -2.882177 | 0.991456 |
| H | -3.745984 | -1.959452 | -0.448888 |
| H | 3.839305 | 2.700155 | 0.939927 |
| H | 3.072595 | -0.745546 | -0.262543 |
| C | -0.250430 | 5.878942 | -2.278598 |
| H | 0.373486 | 6.527409 | -2.908556 |
| H | -0.860990 | 5.293123 | -2.979643 |
| C | -0.412411 | -5.728277 | -0.684421 |

| | | | |
|---|---|---|---|
| H | -0.310902 | -6.119474 | -1.704883 |
| H | -1.429126 | -5.321986 | -0.602585 |
| C | -1.173071 | 6.751170 | -1.458653 |
| H | -1.825171 | 7.399394 | -2.044080 |
| C | -1.246607 | 6.788114 | -0.131493 |
| H | -1.942740 | 7.451311 | 0.373155 |
| H | -0.616426 | 6.162520 | 0.495032 |
| C | -0.241712 | -6.855245 | 0.298538 |
| H | -0.348544 | -6.584678 | 1.348817 |
| C | 0.049548 | -8.110824 | -0.030045 |
| H | 0.172964 | -8.884330 | 0.722337 |
| H | 0.172292 | -8.412312 | -1.068289 |

TS (**61**):

| | | | |
|---|---|---|---|
| C | -1.156687 | 1.479479 | 2.036574 |
| H | -1.305159 | 2.344702 | 2.680205 |
| C | -0.534120 | 1.630258 | 0.848307 |
| C | -0.338389 | 0.451444 | -0.033969 |
| O | 0.192946 | 0.538178 | -1.132039 |
| C | -0.816094 | -0.862593 | 0.502985 |
| C | -1.678327 | 0.201211 | 2.485247 |
| C | -1.287180 | -0.951165 | 1.805506 |
| H | -1.465771 | -1.919219 | 2.264009 |

| | | | |
|---|---|---|---|
| O | -2.070324 | 0.055884 | 3.789585 |
| H | -2.274772 | 0.925377 | 4.153185 |
| C | -0.001726 | 2.935191 | 0.397194 |
| C | 1.068260 | 5.374724 | -0.465118 |
| C | -0.787398 | 4.097503 | 0.400913 |
| C | 1.315334 | 3.033859 | -0.050590 |
| C | 1.870079 | 4.236775 | -0.483421 |
| C | -0.250503 | 5.308601 | -0.027404 |
| H | 1.922189 | 2.133932 | -0.060633 |
| H | -0.866827 | 6.205754 | -0.023024 |
| H | 1.470592 | 6.327905 | -0.799447 |
| C | -0.169766 | -2.054802 | -0.131416 |
| C | 1.227766 | -4.219345 | -1.232190 |
| C | -0.813659 | -3.011134 | -0.910152 |
| C | 1.209797 | -2.203809 | 0.085929 |
| C | 1.900545 | -3.280816 | -0.460318 |
| C | -0.137116 | -4.095065 | -1.473885 |
| H | -1.876414 | -2.909475 | -1.105070 |
| H | 2.968260 | -3.385998 | -0.278872 |
| H | 1.773885 | -5.061895 | -1.648633 |
| O | -2.085529 | 4.001288 | 0.825344 |
| O | 1.823836 | -1.266298 | 0.858746 |
| C | -2.848579 | -0.518105 | -0.546030 |
| H | -2.469148 | -0.432432 | -1.559536 |

| | | | |
|---|---|---|---|
| H | -3.161629 | -1.508283 | -0.230997 |
| C | -3.333863 | 0.581748 | 0.143862 |
| H | -3.161469 | 1.574819 | -0.262421 |
| C | -3.700034 | 0.469528 | 1.474653 |
| H | -4.025415 | 1.346806 | 2.027837 |
| H | -4.009419 | -0.484983 | 1.888615 |
| H | -2.515069 | 4.853561 | 0.686076 |
| H | 2.774349 | -1.427326 | 0.854830 |
| C | 3.320331 | 4.288188 | -0.920592 |
| H | 3.498316 | 5.220410 | -1.472713 |
| H | 3.533441 | 3.463272 | -1.610654 |
| C | -0.865638 | -5.135412 | -2.300975 |
| H | -0.277262 | -5.385182 | -3.192305 |
| H | -1.815349 | -4.714899 | -2.656789 |
| C | 4.260337 | 4.215963 | 0.254485 |
| H | 4.138688 | 5.000129 | 1.002073 |
| C | 5.179170 | 3.272254 | 0.438333 |
| H | 5.823524 | 3.266967 | 1.312877 |
| H | 5.322791 | 2.469939 | -0.282515 |
| C | -1.135852 | -6.390331 | -1.513053 |
| H | -1.741193 | -6.260317 | -0.615943 |
| C | -0.671944 | -7.597606 | -1.822569 |
| H | -0.889570 | -8.466838 | -1.208813 |
| H | -0.057244 | -7.762322 | -2.705286 |

Enol (**45**):

| | | | |
|---|---|---|---|
| C | -1.561577 | -1.046592 | 2.201571 |
| H | -2.393070 | -0.996174 | 2.902408 |
| C | -1.753218 | -0.610309 | 0.939586 |
| C | -0.628000 | -0.685755 | -0.028288 |
| O | -0.738777 | -0.325112 | -1.185784 |
| C | 0.692243 | -1.342290 | 0.423855 |
| C | -0.295954 | -1.564735 | 2.692091 |
| C | 0.765556 | -1.676845 | 1.886045 |
| H | 1.707541 | -2.057300 | 2.269430 |
| O | -0.201416 | -1.912110 | 4.009428 |
| H | -1.063834 | -1.814695 | 4.427726 |
| C | -3.037901 | -0.036607 | 0.480615 |
| C | -5.431849 | 1.102292 | -0.426636 |
| C | -4.269703 | -0.654302 | 0.754087 |
| C | -3.049389 | 1.154296 | -0.247212 |
| C | -4.226992 | 1.738598 | -0.709898 |
| C | -5.455438 | -0.083166 | 0.300296 |
| H | -2.102991 | 1.641199 | -0.455885 |
| H | -6.405101 | -0.568888 | 0.516570 |
| H | -6.368228 | 1.530175 | -0.776065 |
| C | 1.849104 | -0.403685 | 0.069490 |
| C | 3.950000 | 1.375361 | -0.479632 |

| | | | |
|---|---|---|---|
| C | 2.989731 | -0.813084 | -0.615440 |
| C | 1.786571 | 0.933761 | 0.485395 |
| C | 2.827214 | 1.815182 | 0.209614 |
| C | 4.045383 | 0.053328 | -0.905235 |
| H | 3.067463 | -1.841735 | -0.953224 |
| H | 2.760670 | 2.849502 | 0.540987 |
| H | 4.762786 | 2.067428 | -0.682973 |
| O | -4.268200 | -1.817763 | 1.468790 |
| O | 0.671986 | 1.323604 | 1.165936 |
| C | 0.758379 | -2.678017 | -0.390540 |
| H | 0.864214 | -2.406614 | -1.447208 |
| H | 1.649642 | -3.235555 | -0.082281 |
| C | -0.456997 | -3.543010 | -0.210296 |
| H | -1.362415 | -3.214177 | -0.718726 |
| C | -0.487603 | -4.646208 | 0.530841 |
| H | -1.393786 | -5.234875 | 0.638895 |
| H | 0.394073 | -4.999612 | 1.061174 |
| H | -5.168876 | -2.161689 | 1.496351 |
| H | 0.684920 | 2.280135 | 1.286445 |
| C | -4.170474 | 3.024291 | -1.512931 |
| H | -5.193704 | 3.343574 | -1.749544 |
| H | -3.666939 | 2.840728 | -2.470242 |
| C | 5.258865 | -0.422631 | -1.681816 |
| H | 5.260141 | 0.022628 | -2.684999 |

| | | | |
|---|---|---|---|
| H | 5.185837 | -1.508761 | -1.823491 |
| C | -3.455919 | 4.129169 | -0.782055 |
| H | -3.907960 | 4.444947 | 0.158145 |
| C | -2.326648 | 4.699684 | -1.193087 |
| H | -1.845167 | 5.489669 | -0.623566 |
| H | -1.844734 | 4.399351 | -2.120999 |
| C | 6.555619 | -0.095728 | -0.992079 |
| H | 6.678921 | -0.514870 | 0.006392 |
| C | 7.514889 | 0.667964 | -1.507923 |
| H | 8.432211 | 0.878073 | -0.965652 |
| H | 7.418902 | 1.107956 | -2.498457 |

Diketone (**46**):

| | | | |
|---|---|---|---|
| C | -0.988474 | 4.239199 | -1.224340 |
| C | 0.993091 | 2.831810 | 0.211294 |
| C | -1.234262 | 2.974574 | -0.704283 |
| C | 0.266585 | 4.804623 | -0.990812 |
| C | 1.241188 | 4.109861 | -0.292390 |
| C | -0.279480 | 2.253907 | 0.027020 |
| H | -2.208429 | 2.519324 | -0.868495 |
| H | 0.486642 | 5.798945 | -1.371373 |
| H | 2.223868 | 4.536598 | -0.122162 |
| O | 1.992232 | 2.248255 | 0.916623 |

| | | | |
|---|---|---|---|
| C | 0.141588 | -0.252107 | 0.521304 |
| O | 1.223750 | -0.170977 | -0.037715 |
| C | -0.717133 | 0.974661 | 0.641635 |
| C | -1.894436 | 0.915383 | 1.298082 |
| H | -2.482792 | 1.813726 | 1.464353 |
| C | -2.459826 | -0.333221 | 1.854961 |
| O | -3.430257 | -0.306487 | 2.586104 |
| C | -0.274072 | -1.525811 | 1.257235 |
| C | -1.807523 | -1.616173 | 1.403235 |
| H | -2.238120 | -1.860230 | 0.422368 |
| H | -2.080903 | -2.420032 | 2.089540 |
| C | 0.374621 | -1.296652 | 2.676185 |
| H | -0.034090 | -2.058337 | 3.342318 |
| H | 0.045922 | -0.322619 | 3.057248 |
| C | 1.871781 | -1.361154 | 2.685402 |
| H | 2.312195 | -2.318068 | 2.410618 |
| C | 2.661132 | -0.338246 | 3.003354 |
| H | 3.742681 | -0.435085 | 3.007424 |
| H | 2.257579 | 0.638340 | 3.262593 |
| C | 0.207000 | -2.811017 | 0.571909 |
| C | 0.951743 | -5.199855 | -0.728828 |
| C | 0.584880 | -2.837478 | -0.771721 |
| C | 0.166588 | -4.046710 | 1.242790 |
| C | 0.551207 | -5.220487 | 0.599724 |

| | | | |
|---|---|---|---|
| C | 0.959753 | -4.004310 | -1.438577 |
| H | 0.618348 | -1.912134 | -1.332536 |
| H | 0.531019 | -6.160768 | 1.147418 |
| H | 1.251443 | -6.126201 | -1.212072 |
| O | -0.268742 | -4.083669 | 2.538907 |
| H | 1.994321 | 1.296449 | 0.711897 |
| H | -0.254639 | -4.997122 | 2.848086 |
| C | -2.066314 | 4.994406 | -1.961139 |
| H | -1.611418 | 5.649313 | -2.716766 |
| H | -2.695110 | 4.291712 | -2.524846 |
| C | 1.349368 | -3.958374 | -2.904897 |
| H | 0.446615 | -3.917634 | -3.528583 |
| H | 1.861248 | -4.895205 | -3.161756 |
| C | -2.961224 | 5.833374 | -1.077560 |
| H | -3.739271 | 6.382685 | -1.607632 |
| C | -2.875173 | 5.945706 | 0.244535 |
| H | -3.564811 | 6.573996 | 0.800100 |
| H | -2.115283 | 5.419822 | 0.816405 |
| C | 2.237602 | -2.792220 | -3.243001 |
| H | 3.173283 | -2.733224 | -2.687834 |
| C | 1.939991 | -1.847408 | -4.130170 |
| H | 2.614562 | -1.020376 | -4.329852 |
| H | 1.007954 | -1.867278 | -4.691326 |

Alkoxide (**44a**):

| | | | |
|---|---|---|---|
| C | 4.877866 | -0.092889 | -1.621609 |
| C | 3.129106 | -1.727494 | -0.161456 |
| C | 3.695052 | 0.411378 | -1.080423 |
| C | 5.173027 | -1.439307 | -1.419778 |
| C | 4.306875 | -2.248693 | -0.693083 |
| C | 2.800810 | -0.376468 | -0.352410 |
| H | 3.441280 | 1.457895 | -1.234398 |
| H | 6.093524 | -1.857632 | -1.822184 |
| H | 4.553805 | -3.291034 | -0.511059 |
| C | -2.235266 | -0.504944 | 0.290904 |
| C | -4.717379 | -1.731014 | -0.141332 |
| C | -3.301444 | 0.189329 | -0.270956 |
| C | -2.439745 | -1.849159 | 0.654103 |
| C | -3.673541 | -2.457825 | 0.430205 |
| C | -4.549639 | -0.397831 | -0.495864 |
| H | -3.136398 | 1.229639 | -0.543064 |
| H | -3.839971 | -3.494508 | 0.702469 |
| H | -5.679090 | -2.214107 | -0.300793 |
| O | 2.326423 | -2.506584 | 0.627133 |
| O | -1.389518 | -2.466549 | 1.252712 |
| C | 0.258958 | -0.356833 | -0.164736 |
| O | 0.160410 | -1.220814 | -1.033292 |

| | | | |
|---|---|---|---|
| C | 1.568638 | 0.230920 | 0.210953 |
| C | -0.936881 | 0.174226 | 0.531580 |
| C | 1.613451 | 1.330691 | 0.985223 |
| H | 2.575599 | 1.762230 | 1.262774 |
| C | -0.843463 | 1.274976 | 1.298222 |
| H | -1.730407 | 1.666019 | 1.795193 |
| C | 0.430983 | 2.031465 | 1.626525 |
| O | 0.598664 | 2.144488 | 2.941415 |
| C | 0.315700 | 3.449655 | 0.895785 |
| H | 0.157503 | 3.367541 | -0.189849 |
| H | 1.287918 | 3.933461 | 1.071883 |
| C | -0.750750 | 4.260276 | 1.551621 |
| H | -0.718325 | 4.189856 | 2.638795 |
| C | -1.700101 | 4.965973 | 0.937057 |
| H | -2.461755 | 5.508457 | 1.493877 |
| H | -1.756454 | 5.026189 | -0.149451 |
| C | 5.826668 | 0.810378 | -2.370867 |
| H | 6.390328 | 0.226927 | -3.112995 |
| H | 5.256039 | 1.548812 | -2.951723 |
| C | -5.684955 | 0.389964 | -1.122479 |
| H | -5.916106 | 0.000940 | -2.123268 |
| H | -5.358794 | 1.429431 | -1.257716 |
| C | 6.814856 | 1.555952 | -1.503363 |
| H | 7.507161 | 2.200460 | -2.047391 |

| | | | |
|---|---|---|---|
| C | 6.896158 | 1.493150 | -0.177672 |
| H | 7.636303 | 2.072247 | 0.367570 |
| H | 6.222425 | 0.872109 | 0.406143 |
| C | -6.932891 | 0.369796 | -0.283427 |
| H | -6.821591 | 0.755615 | 0.729892 |
| C | -8.113465 | -0.098221 | -0.681254 |
| H | -8.980864 | -0.096431 | -0.026670 |
| H | -8.254738 | -0.502091 | -1.682109 |
| C | 1.718671 | -3.606203 | -0.024005 |
| H | 1.164799 | -4.146375 | 0.746523 |
| H | 2.465300 | -4.285230 | -0.460992 |
| H | 1.028811 | -3.252617 | -0.794916 |
| C | -1.571174 | -3.768049 | 1.735848 |
| H | -0.645864 | -4.028557 | 2.252611 |
| H | -1.745923 | -4.486070 | 0.921475 |
| H | -2.406620 | -3.826917 | 2.448094 |

Alcohol (**44b**):

| | | | |
|---|---|---|---|
| C | 4.843904 | -0.079491 | -1.708218 |
| C | 3.088693 | -1.733216 | -0.268124 |
| C | 3.690827 | 0.435940 | -1.116764 |
| C | 5.100477 | -1.441706 | -1.566057 |
| C | 4.235213 | -2.264363 | -0.852533 |

| | | | |
|---|---|---|---|
| C | 2.802285 | -0.368601 | -0.405092 |
| H | 3.461559 | 1.493487 | -1.227047 |
| H | 5.996151 | -1.868122 | -2.010980 |
| H | 4.464183 | -3.318233 | -0.731669 |
| C | -2.246406 | -0.498230 | 0.299383 |
| C | -4.715903 | -1.697581 | -0.167743 |
| C | -3.289549 | 0.212916 | -0.284244 |
| C | -2.457445 | -1.836362 | 0.666891 |
| C | -3.693527 | -2.433511 | 0.426039 |
| C | -4.535207 | -0.366331 | -0.530363 |
| H | -3.111394 | 1.249912 | -0.560556 |
| H | -3.876228 | -3.466163 | 0.700277 |
| H | -5.679036 | -2.171280 | -0.340193 |
| O | 2.252052 | -2.482612 | 0.508009 |
| O | -1.415595 | -2.449796 | 1.284391 |
| C | 0.255153 | -0.361171 | -0.179039 |
| O | 0.141749 | -1.180824 | -1.071058 |
| C | 1.582884 | 0.215457 | 0.200069 |
| C | -0.940660 | 0.155708 | 0.553314 |
| C | 1.640025 | 1.284133 | 1.004218 |
| H | 2.601274 | 1.717918 | 1.275462 |
| C | -0.835475 | 1.228121 | 1.345393 |
| H | -1.711559 | 1.622398 | 1.854753 |
| C | 0.441533 | 1.983742 | 1.580237 |

| | | | |
|---|---|---|---|
| O | 0.632764 | 2.196402 | 2.978445 |
| H | 0.680697 | 1.325679 | 3.394409 |
| C | 0.341095 | 3.397861 | 0.956453 |
| H | 0.260414 | 3.288786 | -0.130398 |
| H | 1.287389 | 3.909789 | 1.174968 |
| C | -0.807176 | 4.203702 | 1.492526 |
| H | -0.784335 | 4.410056 | 2.560456 |
| C | -1.817569 | 4.648510 | 0.750397 |
| H | -2.627221 | 5.231240 | 1.179907 |
| H | -1.868674 | 4.452733 | -0.318922 |
| C | 5.796509 | 0.827042 | -2.447419 |
| H | 6.354557 | 0.248427 | -3.196007 |
| H | 5.229284 | 1.573818 | -3.020017 |
| C | -5.655974 | 0.418951 | -1.184904 |
| H | -5.852077 | 0.025090 | -2.190342 |
| H | -5.331471 | 1.459580 | -1.314580 |
| C | 6.788395 | 1.554607 | -1.569341 |
| H | 7.461776 | 2.224966 | -2.103463 |
| C | 6.900443 | 1.442406 | -0.249209 |
| H | 7.649320 | 2.006061 | 0.299189 |
| H | 6.254215 | 0.786786 | 0.328222 |
| C | -6.927624 | 0.388260 | -0.381045 |
| H | -6.854763 | 0.784236 | 0.631720 |
| C | -8.087124 | -0.098995 | -0.813846 |

| | | | |
|---|---|---|---|
| H | -8.974643 | -0.102313 | -0.187774 |
| H | -8.192488 | -0.508960 | -1.816254 |
| C | 1.739686 | -3.657991 | -0.095865 |
| H | 1.037566 | -4.084174 | 0.621184 |
| H | 2.528541 | -4.393274 | -0.297645 |
| H | 1.209788 | -3.408409 | -1.019747 |
| C | -1.594905 | -3.773286 | 1.727690 |
| H | -0.671058 | -4.046685 | 2.239458 |
| H | -1.764084 | -4.460575 | 0.888584 |
| H | -2.431233 | -3.852463 | 2.434416 |

TS (**61a**):

| | | | |
|---|---|---|---|
| C | -1.184560 | 1.302547 | 2.108343 |
| H | -1.333389 | 2.169731 | 2.748438 |
| C | -0.613654 | 1.442484 | 0.890616 |
| C | -0.376478 | 0.257329 | 0.034586 |
| O | 0.247192 | 0.333935 | -1.030189 |
| C | -0.856750 | -1.033395 | 0.588237 |
| C | -1.540691 | 0.001478 | 2.729980 |
| C | -1.318464 | -1.140406 | 1.890220 |
| H | -1.493227 | -2.121293 | 2.325645 |
| O | -1.880241 | -0.042325 | 3.927709 |
| C | -0.082086 | 2.742994 | 0.412049 |

| | | | |
|---|---|---|---|
| C | 1.054448 | 5.161143 | -0.447472 |
| C | -0.861038 | 3.913806 | 0.340260 |
| C | 1.253239 | 2.828274 | 0.029566 |
| C | 1.842096 | 4.018626 | -0.399625 |
| C | -0.292025 | 5.114268 | -0.085205 |
| H | 1.847530 | 1.921388 | 0.065305 |
| H | -0.883730 | 6.021468 | -0.139595 |
| H | 1.482921 | 6.106004 | -0.776765 |
| C | -0.226835 | -2.222368 | -0.070394 |
| C | 1.135281 | -4.354846 | -1.293658 |
| C | -0.901451 | -3.197735 | -0.790980 |
| C | 1.174201 | -2.351479 | 0.047685 |
| C | 1.847872 | -3.403307 | -0.566712 |
| C | -0.244441 | -4.265154 | -1.414627 |
| H | -1.977633 | -3.113440 | -0.899302 |
| H | 2.925610 | -3.494203 | -0.480174 |
| H | 1.667550 | -5.178103 | -1.766243 |
| O | -2.171348 | 3.791313 | 0.696265 |
| O | 1.795370 | -1.408776 | 0.802571 |
| C | -2.791590 | -0.523577 | -0.674040 |
| H | -2.403448 | -0.333825 | -1.670087 |
| H | -3.109603 | -1.542579 | -0.473978 |
| C | -3.407423 | 0.493053 | 0.075898 |
| H | -3.252324 | 1.521857 | -0.246705 |

| | | | |
|---|---|---|---|
| C | -3.953612 | 0.291353 | 1.309409 |
| H | -4.276174 | 1.119763 | 1.933066 |
| H | -4.104370 | -0.707721 | 1.707841 |
| C | 3.310071 | 4.033181 | -0.780524 |
| H | 3.576535 | 5.030452 | -1.157026 |
| H | 3.493368 | 3.322957 | -1.596818 |
| C | -1.017652 | -5.312470 | -2.192194 |
| H | -0.518386 | -5.524826 | -3.146380 |
| H | -2.012423 | -4.916256 | -2.435341 |
| C | 4.196995 | 3.686650 | 0.385542 |
| H | 4.115967 | 4.347490 | 1.248919 |
| C | 5.014068 | 2.637768 | 0.439651 |
| H | 5.613305 | 2.425187 | 1.320941 |
| H | 5.102375 | 1.943992 | -0.393989 |
| C | -1.169313 | -6.592534 | -1.415412 |
| H | -1.656838 | -6.493113 | -0.445440 |
| C | -0.733483 | -7.785590 | -1.811895 |
| H | -0.857064 | -8.673249 | -1.197478 |
| H | -0.230036 | -7.916788 | -2.768137 |
| C | -3.013851 | 4.896879 | 0.520208 |
| H | -2.725512 | 5.740553 | 1.163955 |
| H | -4.013392 | 4.559692 | 0.799792 |
| H | -3.025458 | 5.237148 | -0.525143 |
| C | 3.179222 | -1.239590 | 0.657199 |

| | | | |
|---|---|---|---|
| H | 3.427556 | -0.316077 | 1.184527 |
| H | 3.462113 | -1.140025 | -0.399182 |
| H | 3.745113 | -2.069715 | 1.106287 |

TS (**61b**):

| | | | |
|---|---|---|---|
| C | -1.170265 | 1.303449 | 1.976062 |
| H | -1.293058 | 2.166480 | 2.628685 |
| C | -0.582687 | 1.454945 | 0.771970 |
| C | -0.427415 | 0.281703 | -0.124799 |
| O | 0.047340 | 0.379486 | -1.246749 |
| C | -0.870197 | -1.038450 | 0.430797 |
| C | -1.678158 | 0.020976 | 2.437901 |
| C | -1.286755 | -1.128370 | 1.751891 |
| H | -1.429908 | -2.096983 | 2.221434 |
| O | -2.017852 | -0.125966 | 3.758044 |
| H | -2.241458 | 0.739166 | 4.121197 |
| C | -0.019470 | 2.746619 | 0.318090 |
| C | 1.140787 | 5.140785 | -0.523496 |
| C | -0.791410 | 3.920300 | 0.255360 |
| C | 1.317096 | 2.806816 | -0.060641 |
| C | 1.920566 | 3.991482 | -0.481906 |
| C | -0.206246 | 5.113364 | -0.163986 |
| H | 1.903606 | 1.893393 | -0.025060 |

| | | | |
|---|---|---|---|
| H | -0.783898 | 6.028907 | -0.216851 |
| H | 1.579730 | 6.081392 | -0.847566 |
| C | -0.218083 | -2.216780 | -0.222252 |
| C | 1.193971 | -4.330540 | -1.381955 |
| C | -0.869051 | -3.196414 | -0.958989 |
| C | 1.179959 | -2.310001 | -0.072634 |
| C | 1.880153 | -3.364538 | -0.650011 |
| C | -0.182762 | -4.258813 | -1.554824 |
| H | -1.943137 | -3.130615 | -1.100620 |
| H | 2.955216 | -3.444757 | -0.535159 |
| H | 1.747825 | -5.154618 | -1.824908 |
| O | -2.103794 | 3.804252 | 0.612429 |
| O | 1.755345 | -1.325097 | 0.664879 |
| C | -2.921662 | -0.737851 | -0.537802 |
| H | -2.578836 | -0.655384 | -1.564610 |
| H | -3.219564 | -1.728556 | -0.209959 |
| C | -3.397539 | 0.362260 | 0.159443 |
| H | -3.241625 | 1.354113 | -0.256908 |
| C | -3.712670 | 0.253989 | 1.504408 |
| H | -4.033958 | 1.129487 | 2.063411 |
| H | -4.005093 | -0.700611 | 1.930683 |
| C | 3.389864 | 3.996003 | -0.854691 |
| H | 3.655166 | 4.977503 | -1.268547 |
| H | 3.577104 | 3.256072 | -1.642700 |

| | | | |
|---|---|---|---|
| C | -0.918887 | -5.320670 | -2.347025 |
| H | -0.357858 | -5.566537 | -3.256757 |
| H | -1.887941 | -4.919724 | -2.672796 |
| C | 4.268310 | 3.696766 | 0.331548 |
| H | 4.185300 | 4.394438 | 1.165042 |
| C | 5.089269 | 2.654331 | 0.429192 |
| H | 5.693368 | 2.486180 | 1.316339 |
| H | 5.193313 | 1.934596 | -0.380378 |
| C | -1.141802 | -6.574924 | -1.543470 |
| H | -1.702927 | -6.446436 | -0.617736 |
| C | -0.690464 | -7.780843 | -1.875785 |
| H | -0.874894 | -8.650858 | -1.252349 |
| H | -0.120206 | -7.943417 | -2.788258 |
| C | -2.942582 | 4.917217 | 0.407932 |
| H | -2.658208 | 5.763827 | 1.046510 |
| H | -3.948444 | 4.589829 | 0.674935 |
| H | -2.932992 | 5.239159 | -0.641205 |
| C | 3.158947 | -1.218602 | 0.671706 |
| H | 3.386575 | -0.294205 | 1.205408 |
| H | 3.558975 | -1.156193 | -0.348078 |
| H | 3.625972 | -2.062531 | 1.196164 |

Ether (**65**):

| | | | |
|---|---|---|---|
| H | 4.806519 | 2.197159 | -1.387733 |
| C | 3.759215 | 2.398293 | -1.254361 |
| C | 1.048593 | 2.901962 | -0.890646 |
| C | 3.024023 | 1.680543 | -0.322288 |
| C | 3.125285 | 3.371024 | -2.007100 |
| C | 1.775547 | 3.625705 | -1.824694 |
| C | 1.667214 | 1.908331 | -0.129480 |
| H | 3.507939 | 0.920225 | 0.264885 |
| H | 3.675380 | 3.939171 | -2.735815 |
| H | 1.282857 | 4.388971 | -2.402233 |
| C | 0.908877 | 1.129131 | 0.898382 |
| C | 0.523624 | 0.608681 | 3.220105 |
| C | -0.768581 | -0.502259 | 1.514383 |
| C | -0.463388 | -0.291972 | 2.854641 |
| C | -0.066882 | 0.205047 | 0.536318 |
| C | 1.199681 | 1.320236 | 2.245071 |
| H | -1.003702 | -0.815390 | 3.622522 |
| H | 1.950894 | 2.036031 | 2.529663 |
| C | -1.856997 | -1.464245 | 1.149198 |
| C | -3.933010 | -3.220451 | 0.517515 |
| C | -3.029230 | -1.007801 | 0.548251 |
| C | -1.743420 | -2.826607 | 1.420318 |

| | | | |
|---|---|---|---|
| C | -2.779284 | -3.699126 | 1.105335 |
| C | -4.064354 | -1.866888 | 0.232787 |
| H | -3.121316 | 0.041479 | 0.333707 |
| H | -2.658448 | -4.744001 | 1.326065 |
| H | -4.960320 | -1.489007 | -0.225130 |
| H | -4.728933 | -3.903391 | 0.279354 |
| O | -0.261233 | 3.146596 | -0.670855 |
| H | -0.578670 | 3.826615 | -1.253441 |
| O | 0.772592 | 0.764627 | 4.540657 |
| H | 1.450918 | 1.414336 | 4.683426 |
| O | -0.641445 | -3.376414 | 1.981238 |
| H | 0.029654 | -2.721819 | 2.135228 |
| O | -0.358720 | 0.011460 | -0.782641 |
| C | 0.352120 | -1.036597 | -1.425762 |
| H | 1.405462 | -0.788956 | -1.480069 |
| H | 0.244266 | -1.947567 | -0.846456 |
| C | -0.230351 | -1.216911 | -2.794439 |
| H | -1.291789 | -1.402097 | -2.826682 |
| C | 0.474993 | -1.180263 | -3.908020 |
| H | 0.018971 | -1.341461 | -4.868903 |
| H | 1.535448 | -0.992398 | -3.902299 |

TS (**66**):

| | | | |
|---|---|---|---|
| H | 1.510529 | 2.092372 | -4.733670 |
| C | 1.898589 | 2.017456 | -3.734080 |
| C | 2.903760 | 1.795716 | -1.159670 |
| C | 1.408170 | 1.060549 | -2.870155 |
| C | 2.892629 | 2.882961 | -3.296102 |
| C | 3.391634 | 2.776649 | -2.014871 |
| C | 1.899397 | 0.925706 | -1.572553 |
| H | 0.627299 | 0.397089 | -3.193707 |
| H | 3.280447 | 3.638501 | -3.956118 |
| H | 4.161640 | 3.434232 | -1.656125 |
| C | 1.354589 | -0.134186 | -0.668200 |
| C | 1.622834 | -2.186904 | 0.572878 |
| C | -0.573100 | -1.119943 | 0.514380 |
| C | 0.317452 | -2.162011 | 0.928967 |
| C | -0.044505 | -0.049834 | -0.272020 |
| C | 2.136586 | -1.170814 | -0.266397 |
| H | -0.067750 | -2.941885 | 1.561640 |
| H | 3.159057 | -1.250330 | -0.592130 |
| C | -2.046343 | -1.421378 | 0.628737 |
| C | -4.746104 | -2.204441 | 0.894222 |
| C | -2.452198 | -2.760861 | 0.533578 |
| C | -3.069249 | -0.477249 | 0.799522 |

| | | | |
|---|---|---|---|
| C | -4.393308 | -0.873859 | 0.947955 |
| C | -3.766379 | -3.158313 | 0.667459 |
| H | -1.716167 | -3.512452 | 0.323130 |
| H | -5.128543 | -0.103963 | 1.091597 |
| H | -4.022073 | -4.198954 | 0.582583 |
| H | -5.776345 | -2.492557 | 1.004052 |
| O | 3.444432 | 1.751117 | 0.085254 |
| H | 3.165026 | 0.961098 | 0.526915 |
| O | 2.505425 | -3.141477 | 0.965170 |
| H | 2.058582 | -3.839182 | 1.424073 |
| O | -2.829645 | 0.846520 | 0.855510 |
| H | -2.120956 | 1.038908 | 0.221219 |
| O | -0.697032 | 0.980368 | -0.592315 |
| C | -0.248277 | 2.548465 | 1.265702 |
| H | 0.245026 | 3.334040 | 0.727042 |
| H | -1.316126 | 2.566060 | 1.287268 |
| C | 0.466819 | 1.654384 | 2.014438 |
| H | 1.537232 | 1.725385 | 2.036132 |
| C | -0.154528 | 0.528414 | 2.517526 |
| H | 0.403554 | -0.229091 | 3.031176 |
| H | -1.222083 | 0.473693 | 2.569988 |

Enol (**67**):

| | | | |
|---|---|---|---|
| H | 2.332312 | 2.902321 | -3.564878 |
| C | 1.821988 | 3.206455 | -2.654236 |
| C | 0.498478 | 3.975625 | -0.327799 |
| C | 1.299934 | 2.237799 | -1.793442 |
| C | 1.683188 | 4.558603 | -2.349629 |
| C | 1.019894 | 4.946648 | -1.186152 |
| C | 0.633399 | 2.607710 | -0.614341 |
| H | 1.414809 | 1.187660 | -2.055825 |
| H | 2.088588 | 5.310187 | -3.022471 |
| H | 0.920551 | 6.004967 | -0.965124 |
| C | 0.095500 | 1.550079 | 0.262638 |
| C | -0.112896 | 0.479333 | 2.436526 |
| C | -0.902366 | -0.886200 | 0.472231 |
| C | -0.713250 | -0.613264 | 1.957807 |
| C | -0.841752 | 0.498154 | -0.264357 |
| C | 0.423845 | 1.484651 | 1.563820 |
| H | -1.080705 | -1.356873 | 2.662632 |
| H | 1.107446 | 2.216282 | 1.985719 |
| O | -1.488561 | 0.729971 | -1.290333 |
| C | 0.146514 | -1.839985 | -0.165645 |
| C | 1.891241 | -3.629633 | -1.534491 |
| C | 0.140238 | -1.973905 | -1.577616 |

| | | | |
|---|---|---|---|
| C | 1.068092 | -2.647136 | 0.524159 |
| C | 1.917768 | -3.533979 | -0.148260 |
| C | 1.001077 | -2.845388 | -2.251838 |
| H | -0.561448 | -1.403670 | -2.187092 |
| H | 2.606355 | -4.153779 | 0.421231 |
| H | 0.959784 | -2.917688 | -3.335778 |
| H | 2.555633 | -4.318729 | -2.047721 |
| C | -2.351742 | -1.444128 | 0.253006 |
| H | -2.560371 | -1.555171 | -0.819605 |
| H | -3.079512 | -0.701025 | 0.610868 |
| C | -2.644097 | -2.783917 | 0.891221 |
| H | -2.034601 | -3.627540 | 0.570315 |
| C | -3.605538 | -2.989992 | 1.800427 |
| H | -3.769819 | -3.979230 | 2.217121 |
| H | -4.246740 | -2.186359 | 2.148736 |
| O | -0.158359 | 4.370402 | 0.808246 |
| H | -0.329614 | 5.325021 | 0.748883 |
| O | 0.060134 | 0.650384 | 3.785096 |
| H | 0.311944 | 1.574384 | 3.956871 |
| O | 1.215251 | -2.672769 | 1.880796 |
| H | 1.267403 | -1.756278 | 2.198285 |

Diketone (**68**):

| | | | |
|---|---|---|---|
| H | 2.364559 | 2.685193 | -4.091302 |
| C | 1.959940 | 2.935620 | -3.116390 |
| C | 0.928984 | 3.562334 | -0.601153 |
| C | 1.696281 | 1.930568 | -2.193700 |
| C | 1.696301 | 4.259440 | -2.780764 |
| C | 1.181231 | 4.572801 | -1.529187 |
| C | 1.184079 | 2.220686 | -0.926545 |
| H | 1.892443 | 0.895636 | -2.448230 |
| H | 1.890865 | 5.055989 | -3.492530 |
| H | 0.974347 | 5.608193 | -1.266287 |
| C | 0.937491 | 1.145252 | 0.064313 |
| C | 1.298181 | 0.110952 | 2.286043 |
| C | -0.252549 | -1.142499 | 0.632995 |
| C | 0.077401 | -0.752148 | 2.094112 |
| C | 0.103949 | -0.026330 | -0.368151 |
| C | 1.509829 | 1.170594 | 1.279935 |
| H | -0.760556 | -0.161327 | 2.489030 |
| H | 2.193575 | 1.966237 | 1.560190 |
| H | 0.165315 | -1.638566 | 2.723161 |
| C | -1.746898 | -1.507354 | 0.564718 |
| C | -4.504198 | -2.154209 | 0.555449 |
| C | -2.677334 | -0.772384 | -0.175026 |

| | | | |
|---|---|---|---|
| C | -2.253561 | -2.579413 | 1.325162 |
| C | -3.609879 | -2.900330 | 1.310809 |
| C | -4.034580 | -1.080534 | -0.186824 |
| H | -2.339095 | 0.060012 | -0.777156 |
| H | -3.963915 | -3.741020 | 1.904668 |
| H | -4.714848 | -0.480094 | -0.781890 |
| H | -5.558212 | -2.414182 | 0.553917 |
| O | -0.211691 | -0.141244 | -1.536576 |
| O | 2.037493 | 0.000440 | 3.245961 |
| C | 0.614184 | -2.354363 | 0.145549 |
| H | 0.290859 | -2.585347 | -0.874079 |
| H | 0.378136 | -3.210650 | 0.780764 |
| C | 2.095208 | -2.097544 | 0.169936 |
| H | 2.563440 | -2.024044 | 1.151417 |
| C | 2.846451 | -1.953071 | -0.919105 |
| H | 3.914541 | -1.767527 | -0.854721 |
| H | 2.415874 | -2.020975 | -1.916092 |
| O | 0.423596 | 3.836739 | 0.633006 |
| H | 0.272084 | 4.786610 | 0.704350 |
| O | -1.391472 | -3.305372 | 2.100332 |
| H | -1.887851 | -3.992770 | 2.559888 |

# 5. References


1. H. Abozenadah, Bishop, A., Bittner, S. and Flatt, P.M., *Consumer Chemistry: How Organic Chemistry Impacts Our Lives*, Western Oregon University, Monmouth, 2017.
2. D. A. Dias, Urban, S. and Roessner, U., *Metabolites*, 2012, **2**, 303-336.
3. W. Rungsung, Ratha, K. K., Dutta, S., Dixit, A. K. and Hazra J., *World J. Pharm. Res.*, 2015, **4**, 604-613.
4. A. L. Harvey, *Drug Discovery Today*, 2008, **13**, 894-901.
5. N. E. Thomford, D. A. Senthebane, A. Rowe, D. Munro, P. Seele, A. Maroyi and K. Dzobo, *Int. J. Mol. Sci.*, 2018, **19**.
6. G. D. Wright, *Microb. Biotechnol.*, 2019, **12**, 55-57.
7. S. Mathur and C. Hoskins, *Biomed. Rep.*, 2017, **6**, 612-614.
8. R. N. Patel, *Annu. Rev. Microbiol.*, 1998, **52**, 361-395.
9. A. L. Harvey, R. Edrada-Ebel and R. J. Quinn, *Nat. Rev. Drug Discovery*, 2015, **14**, 111-129.
10. R. Liu, X. Li and K. S. Lam, *Curr. Opin. Chem. Biol.*, 2017, **38**, 117-126.
11. F. Li, Y. Wang, D. Li, Y. Chen and Q. P. Dou, *Expert Opin. Drug Discovery*, 2019, **14**, 417-420.
12. Y. N. Liu, X. H. Su, C. H. Huo, X. P. Zhang, Q. W. Shi and Y. C. Gu, *Chem. Biodiversity*, 2009, **6**, 963-989.

13. D.-Y. Zhang, X.-X. Wang, P.-Y. Zhuang, Y.-J. Feng and X.-Y. Jin, *Biochem. Syst. Ecol.*, 2019, **83**, 47-50.
14. Bluebell Nursery, https://www.bluebellnursery.com/Illicium/1863507-569-Illicium-simonsii.html, (accessed September 2021).
15. R. D. Haworth, *J. Chem. Soc.*, 1942, 448-456.
16. O. R. Gottlieb, in *Progress in the Chemistry of Organic Natural Products*, Springer, Vienna, 1978, vol. 35, pp. 1-72.
17. Queen Mary University of London, https://www.qmul.ac.uk/sbcs/iupac/lignan/LG6n7.html, (accessed August 2021).
18. F. Zalesak, D. J. D. Bon and J. Pospisil, *Pharmacol. Res.*, 2019, **146**, 104284.
19. R. M. Denton and J. T. Scragg, *Org. Biomol. Chem.*, 2012, **10**, 5629-5635.
20. The Good Scents Company, http://www.thegoodscentscompany.com/data/rw1015241.html, (accessed August 2021).
21. D. V. Bochkov, S. V. Sysolyatin, A. I. Kalashnikov and I. A. Surmacheva, *J. Chem. Biol.*, 2012, **5**, 5-17.
22. A. Escalante, S. B. Carmona, D. C. Diaz Quiroz and F. Bolivar, *Res. Rep. Med. Chem.*, 2014, **4**, 35-46.

23. L. Eagling, D. J. Leonard, M. Schwarz, I. Urruzuno, G. Boden, J. S. Wailes, J. W. Ward and J. Clayden, *Chem. Sci.*, 2021, DOI: 10.1039/d1sc03554a.
24. D. G. Vassao, D. R. Gang, T. Koeduka, B. Jackson, E. Pichersky, L. B. Davin and N. G. Lewis, *Org. Biomol. Chem.*, 2006, **4**, 2733-2744.
25. J. Nugent, M. G. Banwell and B. D. Schwartz, *Org. Lett.*, 2016, **18**, 3798-3801.
26. Nature, https://www.nature.com/subjects/biomimetic-synthesis, (accessed August 2021).
27. Fluorochem, http://www.fluorochem.co.uk/Products/Search?searchType=N&searchText=3-(4-Hydroxyphenyl)-1-propene, (accessed August 2021).
28. Sigma Aldrich, https://www.sigmaaldrich.com/GB/en/product/ALDRICH/A29208, (accessed August 2021).
29. I. Kouno, T. Morisaki, Y. Hara and C. S. Yang, *Chem. Pharm. Bull.*, 1991, **39**, 2606-2608.
30. Y. Guo, C. Bao, F. Li, E. Hou, S. Qin, Q. Zhang and J. Liu, *ACS Infect. Dis.*, 2020, **6**, 2478-2489.
31. L. K. Sy and G. D. Brown, *J. Chem. Res., Synop.*, 1998, 476-477.
32. S. C. Tzeng and Y. C. Liu, *J. Mol. Catal. B: Enzym.*, 2004, **32**, 7-13.
33. R. M. Denton and J. T. Scragg, *Synlett*, 2010, **2010**, 633-635.
34. M. Fujita, Itokawa H. and Sashida, Y., *Chem. Pharm. Bull.*, 1972, **20**, 212-213.

35. S. Arora, S. Singh, G. A. Piazza, C. M. Contreras, J. Panyam and A. P. Singh, *Curr. Mol. Med.*, 2012, **12**, 1244-1252.

36. T. Takeya, Okubo, T. and Tobinga, S., *Chem. Pharm. Bull.*, 1986, **34**, 2066-2070.

37. R. M. Denton, J. T. Scragg, A. M. Galofré, X. Gui and W. Lewis, *Tetrahedron*, 2010, **66**, 8029-8035.

38. 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.

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

40. R. M. Denton, G. Boden and I. Wood, unpublished work.

41. H. Erdtman and J. Runeberg, *Acta Chem. Scand.*, 1957, **11**, 1060-1061.

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

43. I. Wood, MSci Thesis, University of Nottingham, 2021.

44. E. C. Mundorff, M. A. Hanson, A. Varvak, H. Ulrich, P. G. Schultz and R. C. Stevens, *Biochemistry*, 2000, **39**, 627-632.

45. G. Boden, MRes Thesis, University of Nottingham, 2021.

46. D. G. Brown and J. Bostrom, *J. Med. Chem.*, 2016, **59**, 4443-4458.

47. D. Blakemore, in *Synthetic Methods in Drug Discovery: Volume 1*, The Royal Society of Chemistry, 2016, vol. 1, pp. 1-69.

48. R. E. Arnold, PhD Thesis, University of Nottingham, 2021.

49. D. A. Rogers, A. T. Bensalah, A. T. Espinosa, J. L. Hoerr, F. H. Refai, A. K. Pitzel, J. J. Alvarado and A. A. Lamar, *Org. Lett.*, 2019, **21**, 4229-4233.

50. R. Wells, J. Cheung and J. Hook, *Accredit. Qual. Assur.*, 2004, **9**, 450-456.

51. G. A. Molander, *J. Org. Chem.*, 2015, **80**, 7837-7848.

52. A. J. J. Lennox and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2012, **134**, 7431-7441.

53. K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 9651-9653.

54. J. C. Anderson, R. M. Denton, H. G. Hickin and C. Wilson, *Tetrahedron*, 2004, **60**, 2327-2335.

55. J. T. Scragg, PhD Thesis, University of Nottingham, 2013.

56. R. M. Denton, J. T. Scragg and J. Saska, *Tetrahedron Lett.*, 2011, **52**, 2554-2556.

57. F. Han, Y. Guo and T. Ye, *Org. Chem. Front.*, 2020, **7**, 1658-1662.

58. J. A. Berson and M. Jones, *J. Am. Chem. Soc.*, 1964, **86**, 5019-5020.

59. L. A. Paquette, *Tetrahedron*, 1997, **53**, 13971-14020.

60. K. E. B. Parkes and S. K. Richardson, in *Comprehensive Organic Functional Group Transformations*, eds. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Elsevier Science, Oxford, 1995, vol. 3, pp. 1-52.

61. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 1975, **97**, 4765-4766.

62. R. M. Denton, unpublished work.

63. J. J. Molloy, T. Morack and R. Gilmour, *Angew. Chem., Int. Ed.*, 2019, **58**, 13654-13664.

64. A. de la Hoz, A. Díaz-Ortiz and P. Prieto, in *Alternative Energy Sources for Green Chemistry*, The Royal Society of Chemistry, 2016, DOI: 10.1039/9781782623632-00001, pp. 1-33.

65. F.-X. Felpin, T. Ayad and S. Mitra, *Eur. J. Org. Chem.*, 2006, **2006**, 2679-2690.

66. L. Claisen, *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 3157-3166.

67. Organic Chemistry Portal, https://www.organic-chemistry.org/namedreactions/claisen-rearrangement.shtm, (accessed September 2021).

68. T. P. Yoon, V. M. Dong and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1999, **121**, 9726-9727.

69. *WO Pat.,* WO2004094401A1, 2004.

70. S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa and T. Okamoto, *Chem. Lett.*, 1987, 627-630.

71. Y. Kitagawara, T. Ohe, K. Tachibana, K. Takahashi, S. Nakamura and T. Mashino, *Drug Metab. Dispos.*, 2015, **43**, 1303-1306.

72. L. C. Dorman, *J. Org. Chem.*, 1966, **31**, 3666-3671.

73. J. M. Saa, J. Morey and C. Rubido, *J. Org. Chem.*, 1986, **51**, 4471-4473.

74. J. L. Shih, T. S. Nguyen and J. A. May, *Angew. Chem., Int. Ed. Engl.*, 2015, **54**, 9931-9935.

75. D. Phillips, G. Brodie, S. Memarzadeh, G. L. Tang and D. J. France, *RSC Adv.*, 2020, **10**, 30624-30630.

76. J. M. Lin, A. S. Prakasha Gowda, A. K. Sharma and S. Amin, *Bioorg. Med. Chem.*, 2012, **20**, 3202-3211.

77. A. Mckillop, L. Mclaren and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2047-2048.

78. B. Schmidt and M. Riemer, *J. Org. Chem.*, 2014, **79**, 4104-4118.