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**Studies Towards the Biomimetic
Synthesis of Members of the Kingianin
Family of Natural Products**

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ABSTRACT

This thesis details investigations into the biomimetic synthesis of kingianin A and other members of the kingianin family of natural products. As part of these studies the proposed biosynthetic transformation, the Diels-Alder dimerisation of bicyclo[4.2.0]octadienes was investigated.

Initially, a route is described to a pair of diastereomeric bicyclo[4.2.0]octadienes, which were used as a model system to probe this mode of reactivity. The synthesis of these compounds was achieved through a convergent route which utilised the Stille cross-coupling of two dienes. Following an $8\pi/6\pi$ electrocyclisation cascade, the resultant bicyclo[4.2.0]octadienes were shown not to undergo radical cation Diels-Alder dimerisation upon treatment with tris(4-bromophenyl)amminium hexachloroantimonate.

Secondly an alternative route is described, where the Suzuki-Miyaura cross-coupling reaction was used to generate a related pair of bicyclo[4.2.0]octadienes.

Finally, the electrochemically initiated radical cation Diels-Alder dimerisation of bicyclo[4.2.0]octadienes was investigated. Initially, the redox behaviour of these compounds was studied using cyclic voltammetry and then preparative electrochemical techniques were employed. This resulted in a formal synthesis of kingianin A, providing the first example of an electrochemically induced Diels-Alder dimerisation approach to a natural product synthesis.

ACKNOWLEDGEMENTS

I would like to thank Dr John Moses for welcoming me into his research group and giving me the opportunity to work on this project. Many thanks are also due to the friends that I have made throughout my time here at Nottingham. In particular, I would like to thank my past and present lab mates in the Moses group, for their helpful discussions and suggestions on a day-to-day basis.

DEDICATION

This thesis is dedicated to my daughter, Ilse Elin Rachel Mooring, who was born during the preparation of the manuscript.

*"When something goes wrong, I'm the first to admit it,
I'm the first to admit it, but the last one to know.
When something goes right, well it's likely to lose me,
It's apt to confuse me, it's such an unusual sight."* – Paul Simon

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ABBREVIATIONS

aq.	aqueous
b.p.	boiling point
cDNA	complementary DNA
con	conrotatory
CV	cyclic voltammetry
δ	chemical shift (ppm)
Δ	reflux or heat
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
dis	disrotatory
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
EDC-HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ESI	electrospray ionisation
ESI-MS-MS	electrospray ionisation mass spectrometry mass spectrometry
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
h ν	irradiation with light or photochemical
LAH	lithium aluminium hydride
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
MoOPH	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
m.p.	melting point
NBS	<i>N</i> -bromosuccinamide
RCDA	radical cation Diels-Alder
R _f	retention factor
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBATFB	tetrabutylammonium tetrafluoroborate
TBPA	<i>tris</i> (4-bromophenyl)amminium hexachloroantimonate
TBTH	tributyltin hydride
TBTf	tributylstannyl trifluoromethanesulfonate
TEACN	tetraethylammonium cyanide
Tf	triflyl/trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TLC	thin layer chromatograph

1. INTRODUCTION

1.1 KINGIANINS A-N (1-14)

The isolation and characterisation of kingianin A (**1**) was reported by Litaudon *et al.* in 2010 (Figure 1.1).¹ The natural product was isolated as a racemic mixture of enantiomers and was the first reported member of a new family of compounds² with a novel pentacyclic framework.

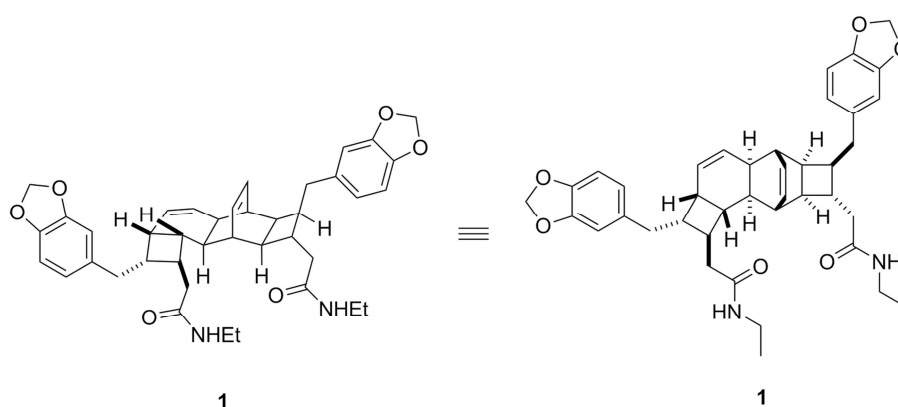


Figure 1.1: Kingianin A (**1**).

As part of Litaudon's investigations into the range of bioactive natural products available from Malaysian plants, successive ethyl acetate and methanol extractions were carried out on the air dried barks of *Endiandra kingiana* Gamble. This tree is one of a hundred species of the genus *Endiandra* whose members are distributed across East Asia, Australia and the West Pacific Ocean.³ Subsequent chromatography of the organic extracts yielded a number of biologically active fractions, one of which was further purified by silica gel column chromatography and preparative C-18 high pressure liquid chromatography (HPLC) to yield kingianin A (**1**) as a white powder.¹

In the following year the same group published a detailed report disclosing a further thirteen members of the kingianin family (Figure 1.2) along with lead results on a biological assay.²

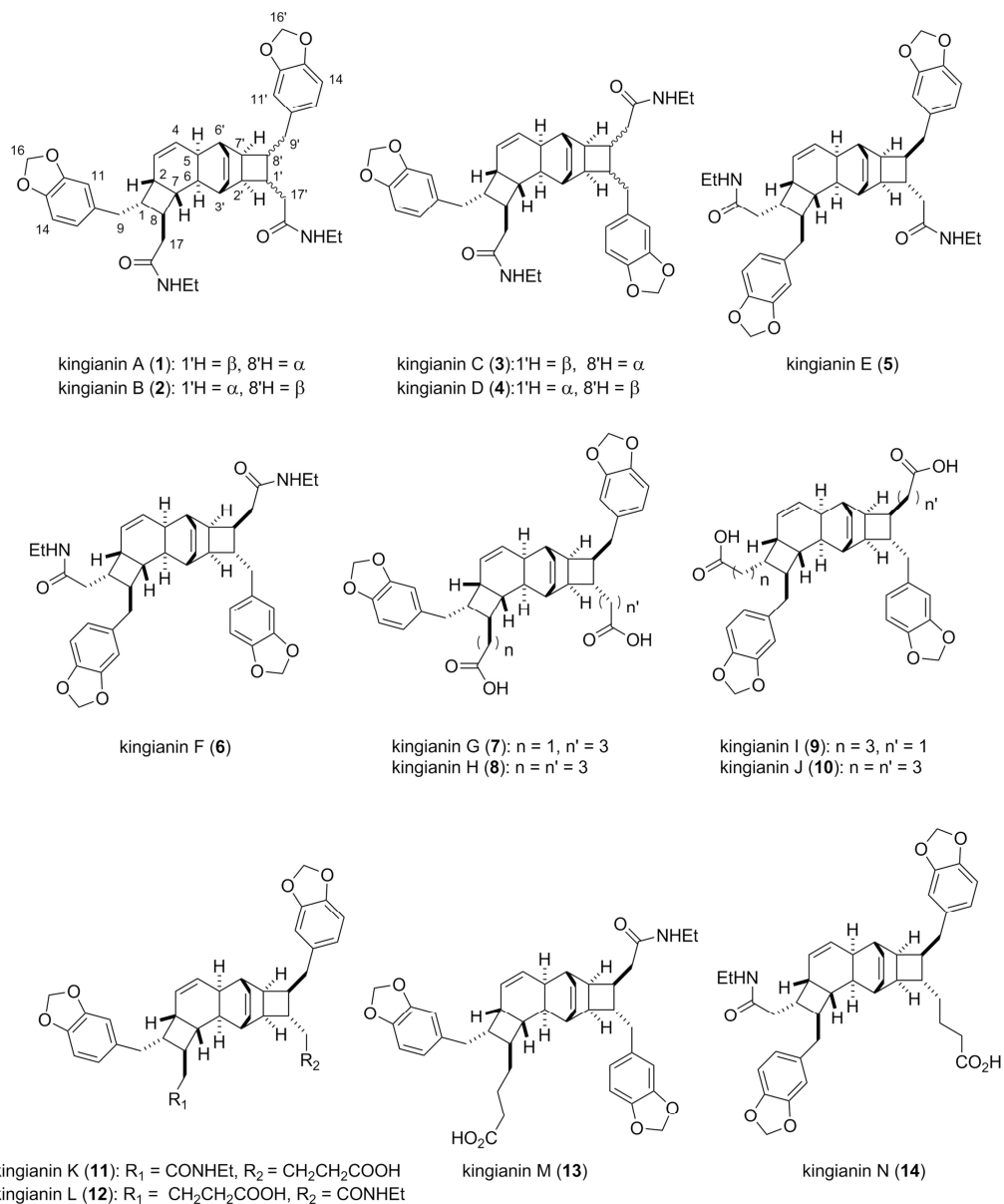


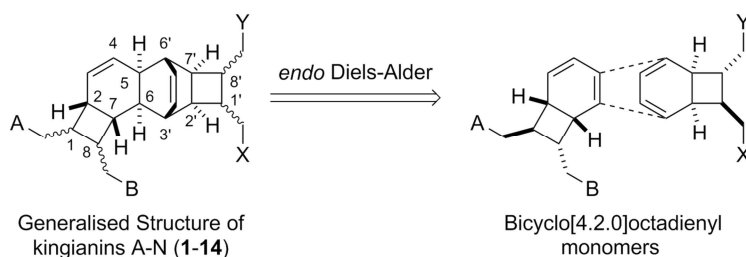
Figure 1.2: Kingianins A-N (1-14).

Kingianins A-N (1-14) possess the same pentacyclic core, with the relative stereochemical assignment of carbons 2, 5, 6, 7, 2', 3', 6' and 7' being identical in each case (Scheme 1.1).

The compounds differ with respect to the functionality of carbons 1, 8, 1' and 8' found on the cyclobutane rings. They also vary with respect to the stereochemical assignment of carbons 1' and 8' (which remain *trans*) whilst the assignment of carbons 1 and 8 is uniform throughout the family.

It can also be noted that two of these four positions; one on the 'western' side of the molecule (C1 or C8) and one on the 'eastern' side of the molecule (C1' or C8') is in each case substituted with a 5-methylbenzo[*d*][1,3]dioxole moiety. The remaining two positions are substituted with either an alkyl acid or an alkyl amide moiety.

These observations led to the biosynthetic hypothesis that the kingianin family of natural products could arise from the Diels-Alder cycloaddition reactions of various bicyclo[4.2.0]octadienyl monomers (Scheme 1.1).^{1,2}



Scheme 1.1: Proposed general biogenesis of the kingianin family of natural products.

1.2 BIOLOGICAL ACTION

Interest in the biological action of the kingianins stems from their ability to bind and inhibit the protein Bcl-xL, with K_i values in the μM range (1.0 ± 0.2 to $231 \pm 47 \mu\text{M}$). Bcl-xL is an anti-apoptotic protein from the Bcl-2 family, a class of proteins involved in the regulation of apoptosis (programmed cell death). Impairment of the healthy apoptotic process is a prerequisite for tumorigenesis⁴ and it has long been established that there is a significant up-regulation of anti-apoptotic proteins expressed in various

types of cancer.⁵ Members of the Bcl-2 family are considered some of the most promising apoptotic targets for cancer drug discovery. The Bcl-xL protein was first discovered in a cDNA library from avian lymphoid cells.⁶ It was identified as a homologue to Bcl-2 and it was indeed found that 44% of Bcl-xL's open reading frame (the section of a gene that codes for a protein) is identical to that of human and mouse Bcl-2. Bcl-xL is a potent inhibitor of apoptosis and like Bcl-2 it is localised in the outer mitochondrial membrane. It is presumed that Bcl-xL inhibits apoptosis in the same manner as Bcl-2, *via* its interaction with the pro-apoptotic peptide BAK (Figure 1.3).⁷



Figure 1.3: Bcl-xL/Bak peptide complex.

The inhibition of Bcl-xL is a highly appealing characteristic of the kingianins (**1-14**), and one which makes them desirable synthetic targets.

1.3 DIELS-ALDER SELECTIVITY IN THE FORMATION OF KINGIANINS A-N (1-14)

The regio- and stereoselectivity of the Diels-Alder reactions proposed to be responsible for the formation of kingianins A-N (**1-14**) is governed by three factors.

1. *Endo/exo* diastereoselectivity.
2. π -Diastereofacial selectivity.
3. Dienophile site regioselectivity.

1. *Endo/exo* diastereoselectivity

The Diels-Alder reaction has a well-documented *endo* selectivity.⁸ This is often referred to as the "Alder rule". Indeed, kingianins A-N (**1-14**) have each been formed through an *endo* rather than an *exo* transition state (Figure 1.4). The transition state selectivity of cyclic dienes has been studied in depth and is generally attributed to secondary orbital overlap.⁹

2. π -Diastereofacial selectivity

If we consider the three dimensional structure of the proposed bicyclo[4.2.0]octadienyl monomers, one face of the cyclohexadiene ring is sterically encumbered by the presence of the cyclobutane ring (Figure 1.4). The monomers therefore possess a sterically hindered 'concave' face and a less sterically hindered 'convex' face. If we consider the possibility of either face of the dienophile approaching either face of the diene, there are several possible *endo* transition states that can be envisaged. This steric feature appears to have a pronounced effect however, as in all cases both the diene and the dienophile have reacted through their convex faces.

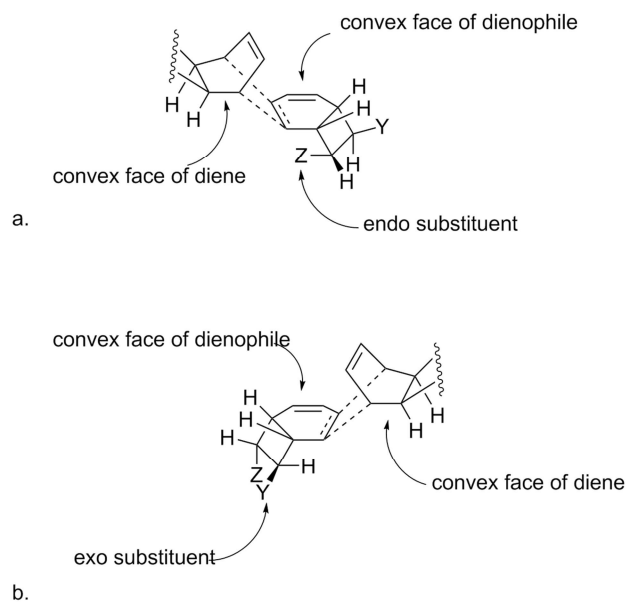


Figure 1.4: a) Disfavoured *endo* docking mode. The approach is from the convex face of the diene to the convex face of the dienophile. The dienophilic olefin is proximal to the *endo* substituent. b) Favoured *endo* docking mode. The approach is from the convex face of the diene to the convex face of the dienophile. The dienophilic olefin is proximal to the *exo* substituent.

3. Dienophilic olefin selectivity

A third factor of selectivity issue arises from the fact that the monomer acting as the dienophile could theoretically react through either of the two alkene moieties. In the case of the reported natural products however, the double bond which has reacted is always proximal to the *endo* substituent on the cyclobutane ring (Figure 1.4).

The *endo* preference of many Diels-Alder reactions is well established and can be explained using a transition state model. A steric argument for the facial selectivity (concave/convex) is also intuitive. The chemoselectivity between the dienophilic olefins however is more challenging to explain. Parker *et al.* have attributed this selectivity to "a second steric factor that

develops in the transition state where the dienophilic olefin is proximal to the *endo* substituent".¹⁰

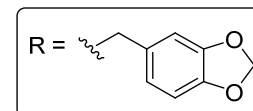
Under the proposed biosynthetic pathway, the formation of kingianins (A-N) (**1-14**) would require 12 distinct species; 6 bicyclo[4.2.0]octadienes and their corresponding enantiomers. These 6 compounds are comprised of 3 pairs of diastereomers. Despite adhering to the described rules of *endo/exo*, facial, and dienophilic olefin selectivity, 144 distinct products (72 pairs of enantiomers) could theoretically be formed from the combination of these 12 species. (Table 1.1).

DIENEOPHILES

	1	2	3	4	5	6	7	8	9	10	11	12
DIENES	1	A	E		D				L			
	2	C	F		B				M			
	3	B		F	C							M
	4	D		E	A							L
	5											
	6									I		
	7										I	
	8											
	9	K	N		G				H			
	10									J		
	11										J	
	12			N	K			G				H

Legend:

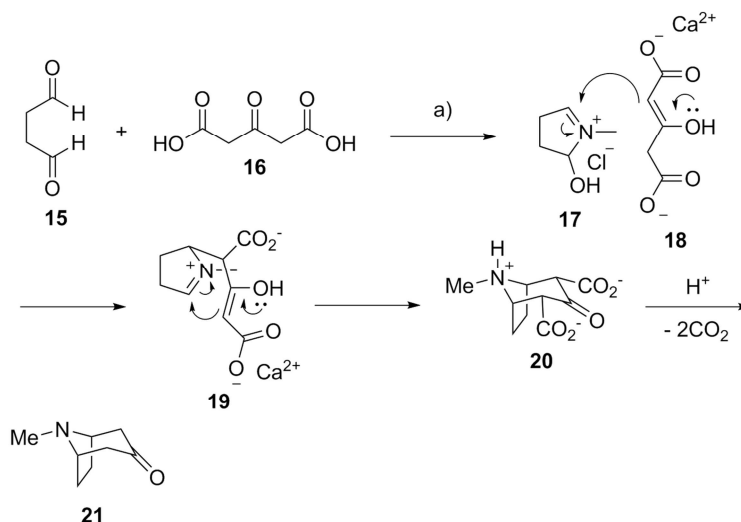
- = Dimers formed from two equivalents of the same enantiomer.
- = Dimers formed from two different enantiomers of the same diastereomer.
- = Dimers formed from two different diastereomers.

**Table 1.1:** Kingianins A-N (1-14) and their proposed bicyclo[4.2.0]octadienyl monomers.

As described, the proposed biosynthetic pathway to the kingianin family of natural products culminates in the Diels-Alder dimerisation of bicyclo[4.2.0]octadienes.^{1,2} Since the biogenesis of the latter class of compounds is well established and experimentally verified (*vide infra* - Section 1.4.1), the kingianins A-N (**1-14**) are ideal candidates for a biomimetic synthesis.

1.4 BIOMIMETIC SYNTHESIS

The term biomimetic synthesis can be used to describe any synthetic effort that is inspired by or is mimicking a proposed biosynthetic pathway. The term was first coined in 1917 by Sir Robert Robinson upon his landmark synthesis of tropinone (**21**) (Scheme 1.2).¹¹



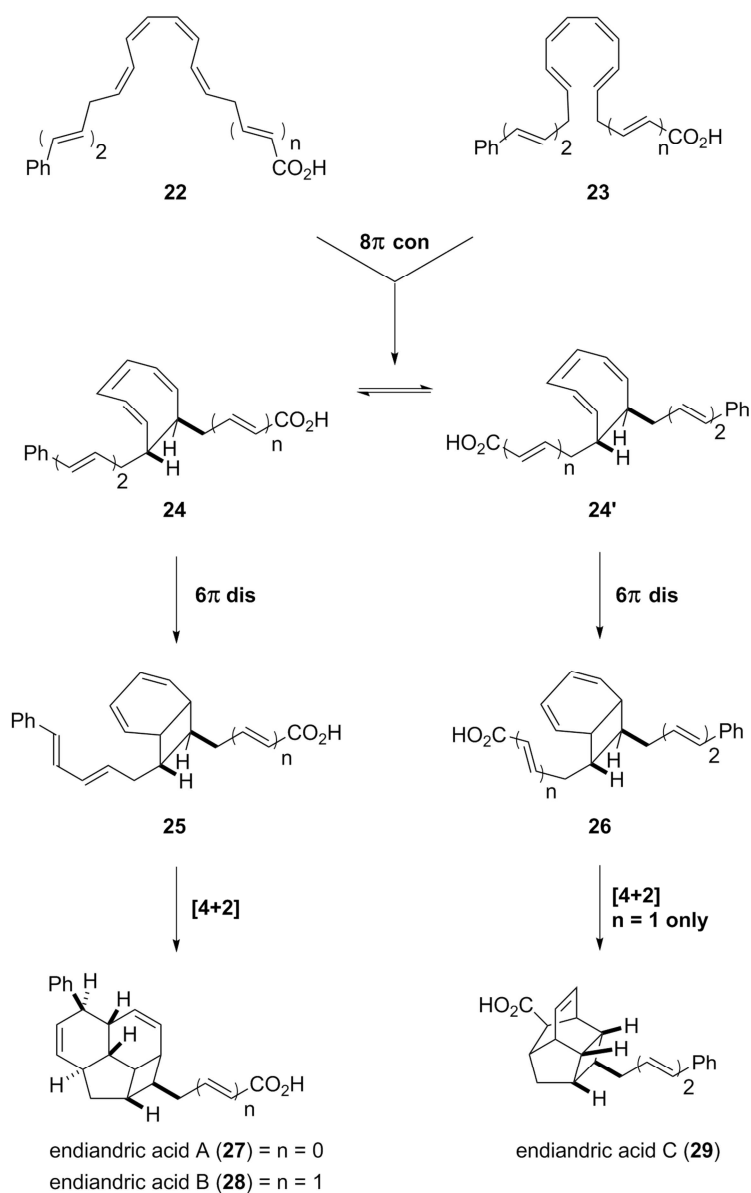
Scheme 1.2: Robinson's one step, biomimetic synthesis of tropinone (**21**). *Reagents and conditions:* a) MeNH₂·HCl, CaCO₃, H₂O, 50 h, 42%.

In a single synthetic step, succinaldehyde (**15**), methylamine hydrochloride and acetone dicarboxylic acid (**16**) were reacted at physiological pH to form four new bonds and two new rings, completing the synthesis of tropinone (**21**) in an impressive 42% yield.

The true elegance of this approach is best appreciated through comparison to the first synthesis of tropinone (**21**), which was achieved by Willstätter in 1901. The latter, 21 step procedure included a plethora of harsh reagents and forcing conditions and resulted in an overall yield of 0.75%.¹² In contrast, the materials employed in Robinson's synthesis could all be found in the sap of trees. Naturally the biosynthetic hypothesis,¹³ which was published contemporaneously by the same author, bears a striking similarity to the synthetic procedure. Robinson embraced the concept that the mechanisms of synthesis available to a chemist are not wholly different to those available in a biological system.¹² He realised that through identifying the inherent reactivity locked in to simple organic compounds, comparatively complex architectures can be accessed with relative ease. The key to achieving this is a fundamental understanding of organic reactivity combined with insightful biosynthetic speculation. Through this model of biomimetic synthesis, a huge number of complex targets have been achieved and our understanding of biogenesis advanced. For his contributions to synthesis, Robinson was awarded the Nobel Prize for Chemistry in 1945.

1.4.1 Bicyclo[4.2.0]octadienes

The biosynthetic pathway for the bicyclo[4.2.0]octadiene functionality was first postulated by Black *et al.* in 1980.¹⁴ The authors proposed that endiandric acids A–C (**27–29**) could be derived from the linear conjugated tetranes **22** and **23** *via* two related routes, each consisting of two electrocycloisatation reactions followed by a [4+2] cycloaddition (Scheme 1.3).



Scheme 1.3: Proposed biosynthetic pathway to the endiandric acids A-C (**27-29**), $n = 0$ or 1.

In accordance with Black's proposition (Scheme 1.3), spontaneous 8π electrocyclicalisation of the tetraenes **22** and **23** would result in the conformers **24** and **24'**. Subsequent 6π electrocyclicalisations would convert these cyclooctatrienes to the bicyclo[4.2.0]octadienes **25** and **26** respectively. The final step in this reaction cascade is in each case an intramolecular Diels-Alder reaction to form the endiandric acids A-C (**27-29**).

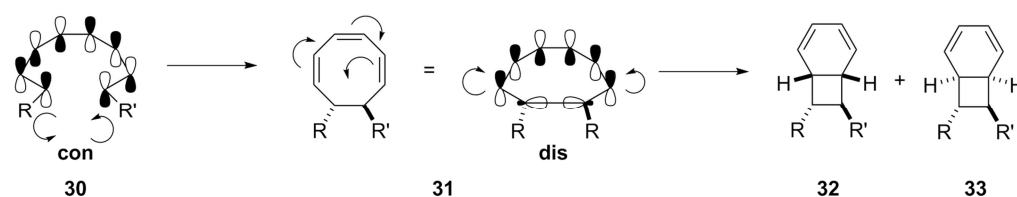
In 1982, Nicolaou *et al.* provided experimental evidence to support Black's hypothesis with a synthetic proof of principle; the total synthesis of the natural products **27-29**.¹⁵ This pivotal example of biomimetic synthesis would lay the framework for an emerging field of bio-inspired total synthesis of polyene derived natural products.¹⁶ Examples include members of the tridachiahdropyrone¹⁷ and SNF¹⁸ families.

In accordance with Black's hypothesis, Nicolaou *et al.* demonstrated that a linear and non-chiral (*E,Z,Z,E*)-tetraene will spontaneously convert into two diastereomeric bicyclo[4.2.0]octadienes. A particularly interesting feature of this reaction is its stereospecificity. The *cis-trans* configuration around the cyclobutane ring is introduced into the products as a result of the geometric configurations that must be adopted to provide the necessary molecular orbital alignment. The rationale underpinning this phenomenon has become known as the Woodward-Hoffman rules.¹⁹

1.4.2 The Stereochemistry of Electrocyclic Reactions

Based on the theory of the conservation of orbital symmetry, Woodward and Hoffman deduced a series of rules to determine the stereochemistry of the products of electrocyclisations.²⁰ Since their early rationalisation, electrocyclic reactions have developed from mechanistic curiosities into powerful synthetic tools for approaching challenging targets.¹⁶ This development has been grounded on a fundamental understanding of how the stereochemistry of the products will be determined predominantly by two factors; the number of conjugated π -bonds in the system and whether the reaction occurs under thermal or photochemical conditions. The significance of these factors derive from the fact that they determine the relative direction of rotation that must be undertaken by the terminal

substituents of a polyene as it undergoes an electrocyclic reaction.²⁰ As pioneered by Fukui *et al.*,²¹ analysis of the frontier molecular orbitals of a given compound can facilitate determination of the compound's reactivity. In application to a polyene system such as **30**, this allows the predictions of the Woodward-Hoffman rules to be visualised diagrammatically; simply by considering the highest occupied molecular orbital (HOMO) of the system (Scheme 1.4).



Scheme 1.4: Formation of the bicyclo[4.2.0]octadienes *via* the thermal electrocyclicisations of tetraenes.

As tetraenes **30** have 8π electrons ($4n$) the HOMO of these compounds have the depicted configuration in the groundstate (Scheme 1.4). Constructive overlap occurs by rotating the terminal substituents in the same direction. This process is described as 'conrotatory' and the resulting stereogenic centres are formed with a *trans* configuration. The resulting cyclooctatrienes **31** have 6π electrons ($4n+2$) and for constructive overlap to occur the process must be 'disrotatory'. As such, the newly formed stereocentres have a *cis* configuration and the stereochemistry of the bicyclo[4.2.0]octadienyl products **32** and **33** is installed. The favoured mode for any electrocyclic process can be predicted by following some simple guidelines (Table 1.2).

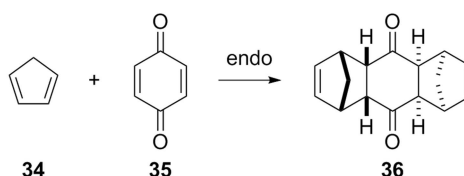
Number of π -electrons	Thermal	Photochemical
4n	Conrotatory	Disrotatory
4n+2	Disrotatory	Conrotatory

Table 1.2: Thermal and photochemical modes of electrocyclisations.²²

As described, formation of the proposed bicyclo[4.2.0]octadienyl kingianin monomers could be achieved *via* the double electrocyclisation of the corresponding tetraenes. Following this, the appropriate *endo* Diels-Alder dimerisation of these compounds would yield the natural products kingianins A-N (**1-14**).

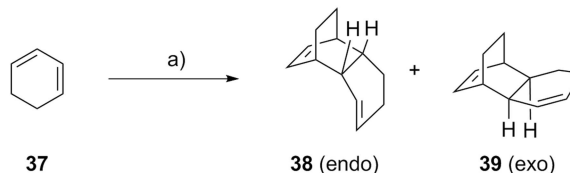
1.5 THE DIELS-ALDER REACTION

The [4+2] cycloaddition reaction was first described by Otto Diels and his student, Kurt Alder in 1928.²² For their work, which included study of the mechanistic underpinnings of this process, they were awarded the Nobel Prize in 1950. Since its conception, the Diels-Alder reaction has become one of the most useful transformations in organic chemistry, not least in its application to the synthesis of complex natural products.²³ The classical Diels-Alder reaction describes the [4+2] cycloaddition of an electron rich diene and an electron deficient dienophile. A key example is the reaction of cyclopentadiene (**34**) with quinone (**35**), which was described in the seminal publication by the namesakes of this reaction (Scheme 1.5).



Scheme 1.5: The [4+2] cycloaddition reaction, as described by Diels and Alder in 1928.

Another powerful variant of the process is the inverse electronic demand Diels-Alder reaction, where an electron poor diene reacts with an electron rich dienophile. In the case of many Diels-Alder dimerisations however, the dienophilic functionality is comprised of one olefin from the corresponding diene (e.g. the [4+2] dimerisation of butadiene). In these cases, the reaction is neither normally nor inversely accelerated as the reaction partners are electronically (and otherwise) identical. As such, these reactions can be challenging synthetic operations. The formation of kingianin A *via* Diels-Alder dimerisation is one example of this class of reaction. In general, the Diels-Alder reactions proposed to be responsible for the formation kingianins A-N (**1-14**) are analogous to the dimerisation of 1,3-cyclohexadiene (**37**). Under a conventional thermal process, the latter transformation requires extremely forcing conditions (Scheme 1.6a).²⁴



Scheme 1.6a: Thermal dimerisation of 1,3-cyclohexadiene (**37**). *Reagents and conditions:* a) 200 °C, 24 h, neat, 30% (**38:39** = 4:1).

After 20 hours at 200 °C, the Diels-Alder dimerisation of **37** is effected in only 30% yield.²⁴ One exception is the related compound cyclopentadiene (**34**), which is known to dimerise readily at room temperature.²⁵ Recently, the relative rates of reactivity of various cyclic dienes has been studied computationally.^{25,26} It was shown that in many cases a linear relationship exists between activation energy and the energy required to distort the diene into the transition-state geometry.²⁶ It has been shown that in 1,3-cyclohexadiene (**37**), a larger out-of-plane distortion energy is required than for 1,3-cyclopentadiene (**34**). This helps to explain the significantly

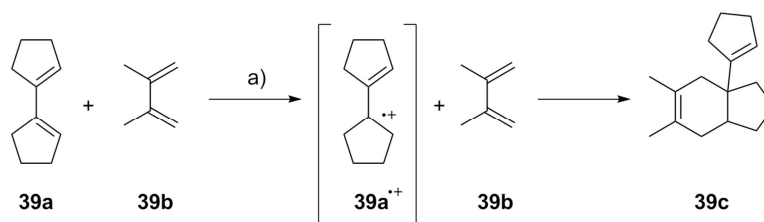
lower Diels-Alder reactivity of the former compound. It should be noted however that a correlation between the 1,4-distance and the rate of reactivity with dienophiles is also accepted to be a factor controlling the difference in reactivity of these species.²⁵

A wide variety of methods have been reported which can be used to bring about a Diels-Alder reaction. These include high pressure techniques,²⁷ microwave irradiation²⁸ and Lewis acid catalysis.²⁹ One of the most powerful ways however to bring about the Diels-Alder reaction of electronically mismatched partners is the use of a radical-cation mediated process.

1.5.1 The Radical Cation Diels-Alder Reaction

The Diels-Alder reaction between two electron rich components will typically require forcing conditions and extended reaction times. In many cases however, it has been shown that by performing single electron oxidation, a cationic radical species can be generated which is highly reactive. One way to achieve single electron oxidation is to use a stable radical cation reagent. The existence of these species was explicitly demonstrated for the first time in 1926 by Weitz *et al.*³⁰

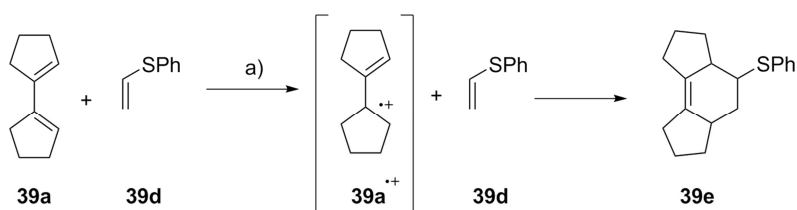
In the majority of reported examples, the reaction proceeds *via* oxidation of what is formally the dienophilic component. Using the Woodward-Hoffman nomenclature, where the number of participating π -electrons is used to define the reaction, this process can be considered a [4+1] cycloaddition. One example of this mode of reactivity is the reaction between the bicyclic diene **39a** and 2,3-dimethylbuta-1,3-diene (**39b**) (Scheme 1.6b).³¹



Scheme 1.6b: A [4+1] type RCDA reaction. *Reagents and conditions:* a) Tris(4-bromophenyl)amminium hexachloroantimonate (TBPA) (**40**), 45%.

Initially, an electron is removed from the species with the lowest oxidation potential; in this case it is the diene **39a**, the most electron rich of the two dienes. The resultant intermediate **39⁺⁺** goes on to react in the role of a dieneophile, thus defining the process as a [4+1] cycloaddition.

The RCDA reaction can in some cases proceed *via* a [3+2] pathway however. One example is the reaction of the same diene **39a** with phenyl vinylsulfide (**39d**) (Scheme 1.6c).³²



Scheme 1.6c: A [3+2] type RCDA reaction. *Reagents and conditions:* a) *p*-dicyanobenzene, MeCN, 31%.

In this case, the same intermediate **39⁺⁺** behaves in what is formally the role of a diene and as such, the reaction can be considered a [3+2] cycloaddition.

One of the most well studied reagents for the initiation of an RCDA reaction is tris(4-bromophenyl)amminium hexachloroantimonate (TBPA) (**40**) (Figure 1.5).

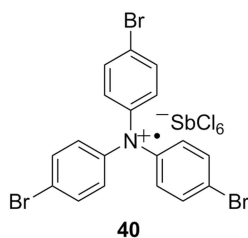
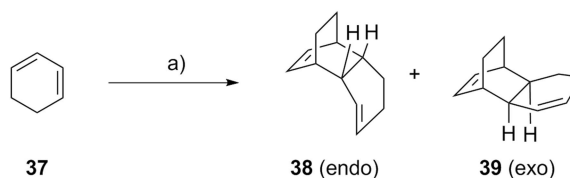


Figure 1.5: Tris(4-bromophenyl)amminium hexachloroantimonate (TBPA) (**40**).

This bench-stable radical cation reagent was first prepared by Ledwith and Sherrington *et al.* in 1969³³ and has been subject to extensive examination by Bauld *et al.* for its ability to initiate the dimerisation of 1,3-cyclohexadiene (**37**) (Scheme 1.7).^{34–38}

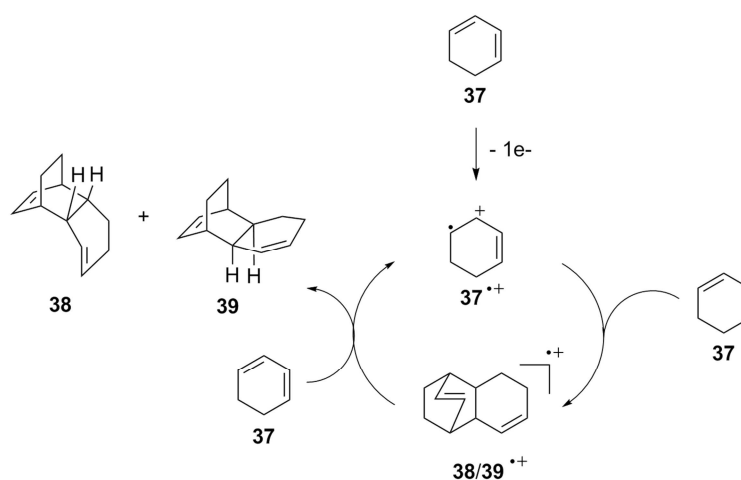


Scheme 1.7: Radical cation dimerisation of 1,3-cyclohexadiene (**37**). *Reagents and conditions:* a) TBPA, CH₂Cl₂, 0 °C, 15 min, 70% (**38:39**=5:1).

When compared to the previously reported thermal procedure (Scheme 1.6a) the TBPA (**40**) mediated process provides a greatly improved yield of 70% under milder conditions and in only 15 minutes reaction time.³⁴ The process was also shown to occur with higher *endo* selectivity (*endo:exo*=5:1) than the uncatalysed reaction (*endo:exo*=4:1).

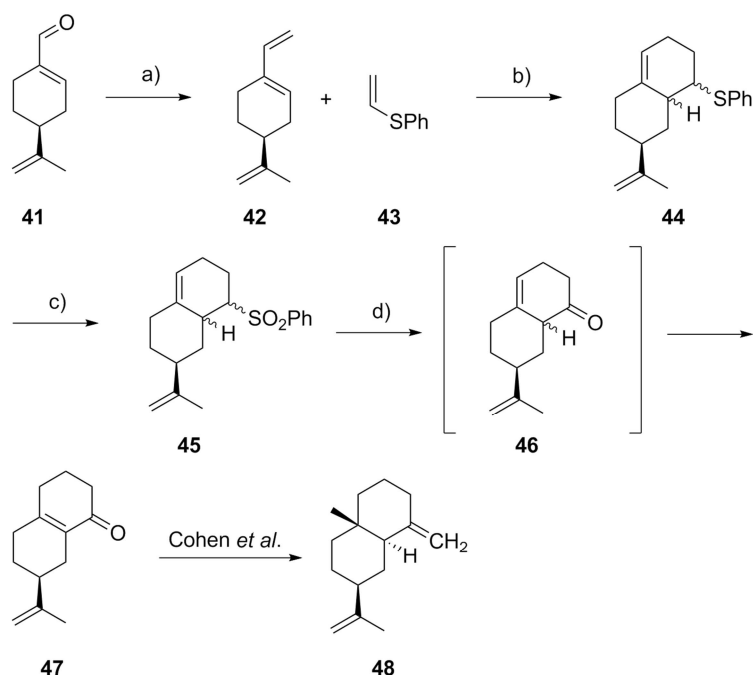
The mechanism of the RCDA dimerisation of 1,3-cyclohexadiene (**37**) has been studied extensively.^{36,37} One recent contribution utilised electron spray ionisation-mass spectrometry-mass spectrometry (ESI-MS-MS).³⁸ Coupling of a microreactor and an electron spray ionisation source allowed *in situ* analysis of the reaction mixture. The MS-MS spectra for ion peaks at *m/z*: 80 and 160 from the reaction mixture were then compared to atmospheric pressure-mass spectrometry-mass spectrometry (APCI-MS-

MS) spectra collected for authentic radical cations of 1,3-cyclohexadiene (**37**^{•+}) and the dimer **38/39**^{•+} and found to be almost identical. This gives unambiguous evidence for the existence of the transient species **37**^{•+} and **38/39**^{•+} and strongly supports the radical cation chain mechanism originally proposed by Bauld *et al.* (Scheme 1.8).³⁴



Scheme 1.8: Radical cation chain mechanism pathway.

The first use of the RCDA reaction in the total synthesis of a natural product was reported in 1988.³⁹ The "hole-catalysed" Diels-Alder addition of vinyl sulfide **43** to (*S*)-(-)-1-ethenyl-4-isopropenylcyclohexene **42** was utilised in formation of a key intermediate **44** for the total synthesis of the natural product (-)-(β)-selinene (**48**) (Scheme 1.9).

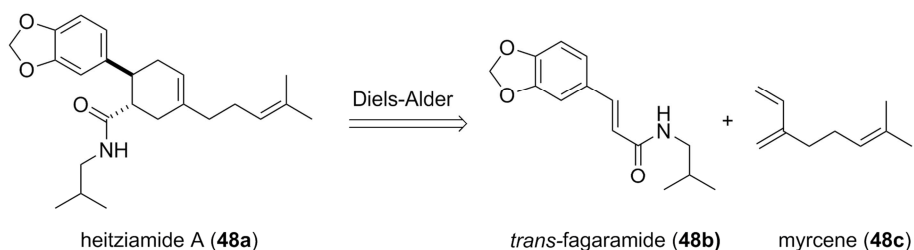


Scheme 1.9: Bauld's (-)-(β)-selinene (**48**) synthesis. *Reagents and conditions:* a) Ph_3PCH_2 , 85%; b) 1,4-dicyanobenzene, CH_3CN , $h\nu$, 48 h, 60%; c) *m*CPBA, -30°C , CH_2Cl_2 , 91%; d) LDA, -78°C , MoOPH, 45%.

The synthesis began with a Wittig reaction on the commercially available (-)-perillaldehyde (**41**) to yield the diene **42** for the key radical cation Diels-Alder step. The latter transformation was initiated by 1,4-dicyanobenzene and proceeded smoothly, giving Diels-Alder adducts in $\geq 90\%$ yield and with complete periselectivity over the possible [2+2] cycloaddition. Conversion of the Diels-Alder adduct **44** to the corresponding sulfone **45** was facile and subsequent oxidation led to a mixture of unconjugated enones which upon treatment with alumina converted to the single conjugated enone **47**. From this point the synthesis converged with that previously reported by Cohen *et al.*⁴⁰

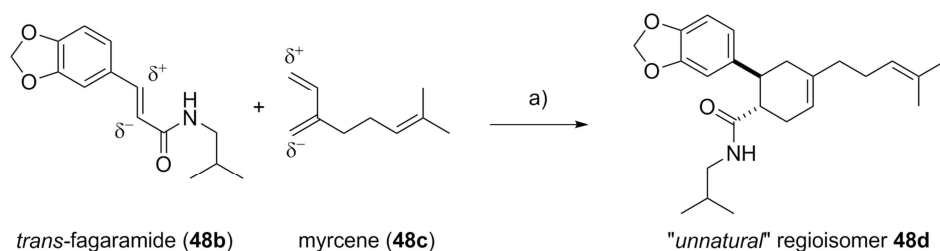
Arguably the first example of a biomimetic RCDA reaction was described by Yoon *et al.* in 2011.⁴¹ As part of their work describing the use of ruthenium(II) polypyridyl complexes for the photo-redox catalysed RCDA reaction, the synthesis of heitziamide A (**48a**) was undertaken. The

biosynthetic origins of this natural product are almost certainly the Diels-Alder reaction of *trans*-fagaramide (**48b**) and myrcene (**48c**) (Scheme 1.9a).



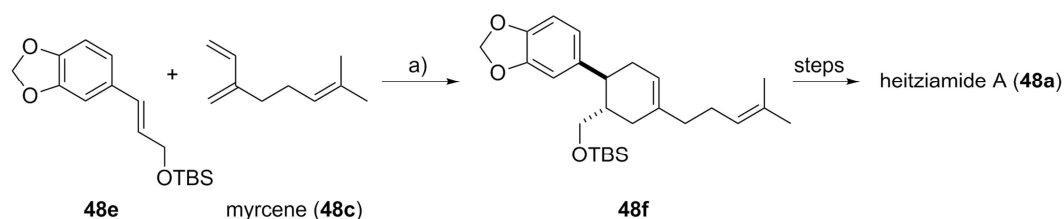
Scheme 1.9a: Likely biogenesis of heiziamide A (**48a**).

When these two compounds were treated to thermal Diels-Alder conditions however, only the “unnatural” regioisomer **48d** was observed, with no sign of the natural product heiziamide A (**48a**) being detected (Scheme 1.9b).



Scheme 1.9b: Thermally initiated Diels-Alder reaction. *Reagents and conditions:* a) Neat, 150 °C, 72 h, 60%.

The observed regio-selectivity can be rationalised by considering the polarisation of the π -bonds in the diene and dienophile (Scheme 1.9b). In the case of an RCDA reaction however, we would expect umpolung reactivity in comparison to the conventional thermal process (*vide infra* – Section 1.7.4). Indeed, when the styrene **48e** and myrcene (**48c**) were subjected to irradiation in the presence of 2 mol% $\text{Ru}(\text{bpz})_3(\text{PF}_6)_2$, the Diels-Alder adduct **48f** was formed in 80% yield.⁴¹ Under these conditions, no trace of the “unnatural” regioisomer was observed (Scheme 1.9c).



Scheme 1.9c: RCDA by visible light photocatalysis. *Reagents and conditions:*
 a) Ru(bpz)₃(PF₆)₂ (2 mol%), visible light, air, CH₂Cl₂, AcOH, 80%.

The regiochemistry of the cycloaddition was confirmed by completing a total synthesis of heitziamide A (**48a**) in a further four steps. The obtained product was spectrographically identical to the naturally obtained material.

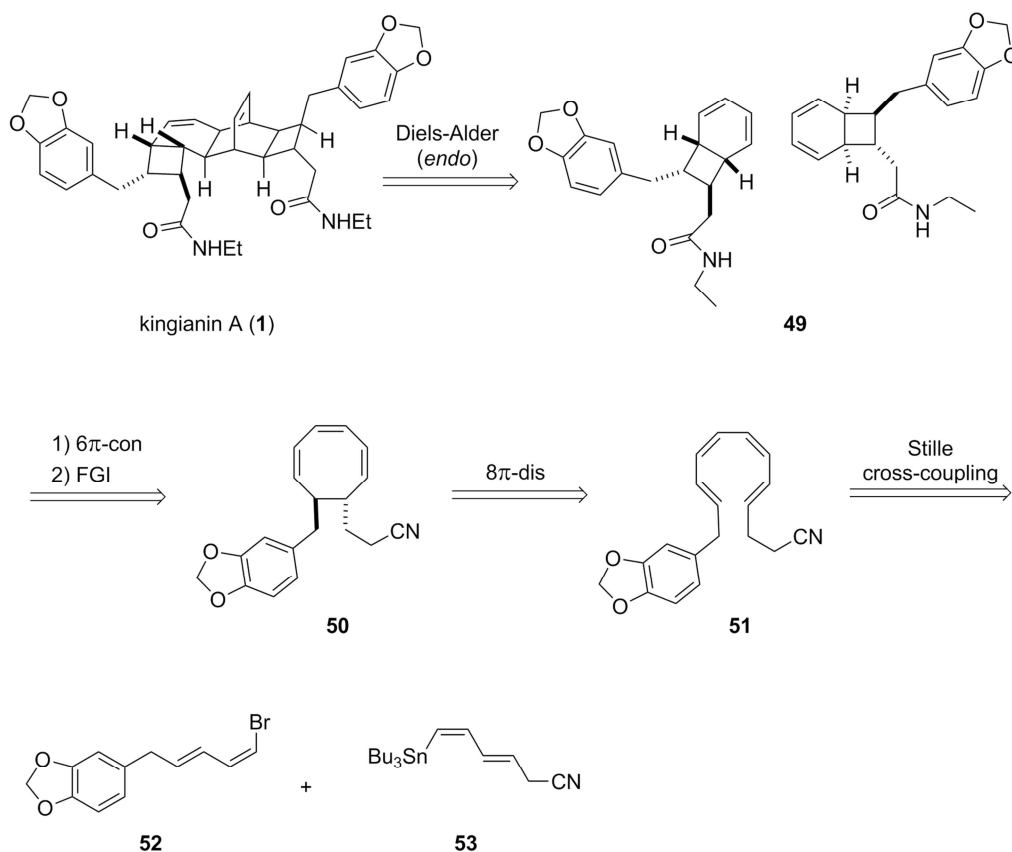
As described, the RCDA reaction has been studied in depth and several chemical techniques have been developed to bring about this transformation. One less well studied method of initiating an RCDA reaction is the use of an electrochemical cell (*vide infra* - Section 1.7).⁴²

1.6 PREVIOUS WORK

1.6.1 A Biomimetic Approach to Kingianin A (**1**)

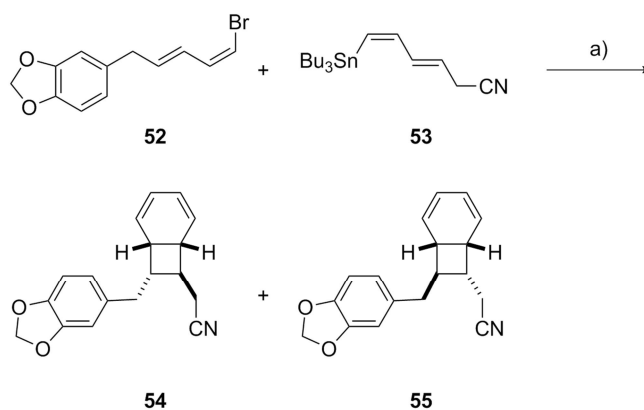
In 2011, shortly before Litaudon's publication detailing the extended kingianin family,² a synthetic approach to kingianin A (**1**) was published by Moses *et al.*⁴³ Specifically, the group were intrigued by an aspect of Litaudon's biosynthetic speculation; that the Diels-Alder dimerisation of the monomer dubbed prekingianin A (**49**) could occur spontaneously (Scheme 2.0). In the group's own experience with related bicyclo[4.2.0]octadienes, as well as in several literature examples such as the endiandric acids,⁴⁴ no dimeric species had been observed. This contrast motivated synthesis of the putative monomer **49** and investigations into its propensity to undergo dimerisation. In accordance with Litaudon's biosynthetic analysis,

formation of the bicyclo[4.2.0]octadienyl core was achieved *via* the concurrent electrocyclisation reactions of a tetraene. The tetraene **51** was synthesised by a convergent strategy; the cross-coupling of two dienes, **52** and **53** (Scheme 2.0).



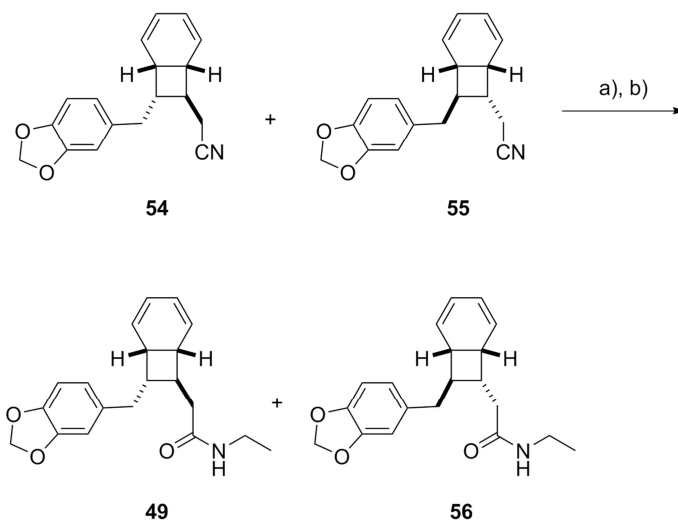
Scheme 2.0: Moses' kingianin A (**1**) retrosynthetic analysis.

Stille cross-coupling of the stannane **53** and the bromide **52** was performed using a catalytic system comprising of $\text{Pd}_2(\text{dba})_3$ and tri-2-furylphosphine (TFP) (Scheme 2.1).⁴⁵



Scheme 2.1: Moses' synthesis of the bicyclo[4.2.0]octadienes **54** and **55**. *Reagents and conditions:* a) $\text{Pd}_2(\text{dba})_3$, TFP, toluene, 100 °C, 10 h, 60% (**54**:**55**=1:1).

Following hydrolysis of the nitrile functionality with hydrogen peroxide and potassium hydroxide, the resulting primary amides were subjected to reductive *N*-alkylation with acetaldehyde to complete the synthesis of prekingianin A (**49**) and the diastereoisomer (**56**) (Scheme 2.2).⁴⁶



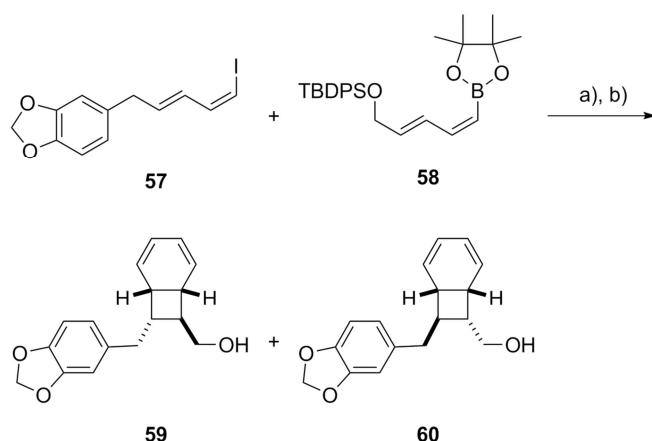
Scheme 2.2: Moses' synthesis of prekingianin A (**49**) and the diastereoisomer **56**. *Reagents and conditions:* a) KOH, H_2O_2 , EtOH, 5 h then b) CH_3CHO , toluene, Et_3SiH , TFA, 120 °C, 1 h, 62% (over two steps).

With the proposed monomers in hand, conditions to bring about the desired Diels-Alder dimerisation were investigated. The group observed that **49** and **56** were stable at room temperature over several weeks,

showing no sign of dimerisation.⁴³ This finding was in agreement with the group's supposition that dimerisation would not occur spontaneously. In order to further examine the favourability of this reaction, a range of conditions were tested to bring about the "reagent free" dimerisation of the monomers. The application of different solvent systems, microwave irradiation and sublimation was unsuccessful in bringing about the [4+2] reaction, the only change to the separated monomers **49** and **56** being isomerisation to a 1:1 mixture of the two. This isomerisation was presumed to occur *via* a thermal 6π ring opening to the corresponding cyclooctatrienes followed by subsequent 6π electrocyclic ring closure. The dimerisation was also attempted under Grieco's conditions⁴⁷ (5 M LiClO₄ solution) and again, only cycloisomerisation was observed.

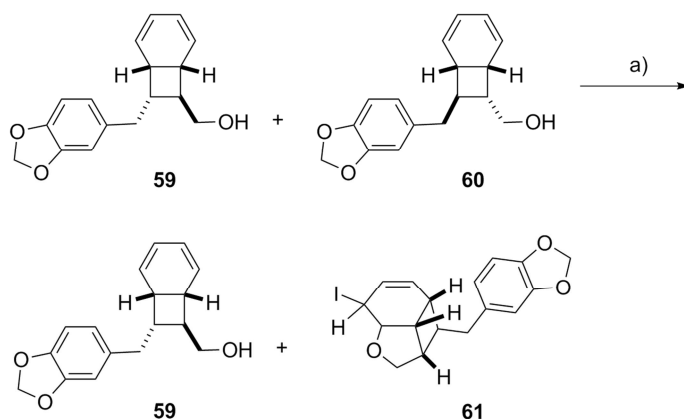
1.6.2 Total Synthesis of Kingianin A (**1**) – Parker *et al.*

In December 2012, Parker *et al.* reported the first total synthesis of kingianin A (**1**).¹⁰ In accordance with the biosynthetic proposal, the carbon framework of the natural product was formed *via* the Diels-Alder reaction of two bicyclo[4.2.0]octadienes. In keeping with the literature precedent,⁴³ this functionality was itself installed by the cross-coupling of two dienes. In this case however, a Suzuki-Miyaura rather than a Stille cross-coupling procedure was employed (Scheme 2.3).



Scheme 2.3: Parker's synthesis of the bicyclo[4.2.0]octadienes **59** and **60**. *Reagents and conditions:* a) $\text{Pd(PPh}_3)_4$, NaOH (1 M, 4 equiv.), THF, reflux, 12 h then b) TBAF, THF, r.t., 2 h, 80% (over two steps).

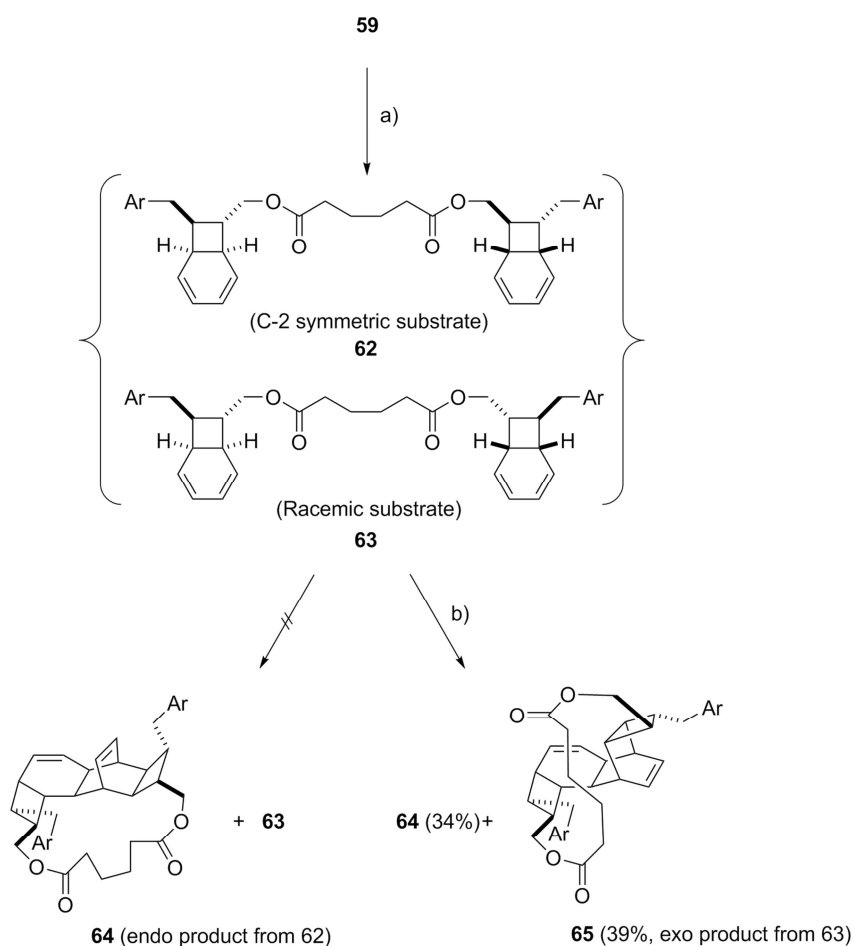
Following removal of the silyl protecting groups, the alcohols **59** and **60** were obtained as a mixture of diastereoisomers in 80% yield over two steps. The desired diastereoisomer **59** was then isolated by treating the mixture with iodine and potassium carbonate (Scheme 2.4).



Scheme 2.4: Diastereomeric separation of **59** and **60** via selective iodoetherification. *Reagents and conditions:* a) I_2 , K_2CO_3 , CH_2Cl_2 , $-30\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, 3 h, **59** (45%) and **61** (37%).

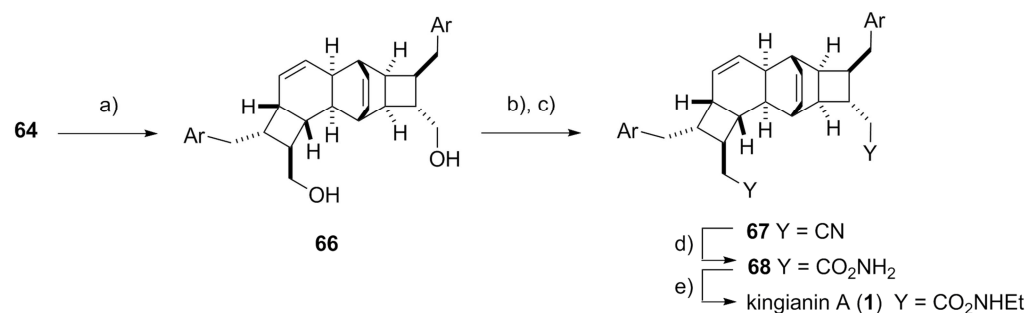
Only the undesired diastereoisomer **60** underwent iodoetherification and the unreacted alcohol **59** was isolated from the reaction mixture by column chromatography. With a single diastereoisomer in hand, the group employed a plan to further reduce the complexity of products expected

from a RCDA reaction. It was envisaged that by linking together two molecules of racemic **59**, it may be possible to find a pair of diastereoisomers where only the C-2 symmetric dimer could reach the transition state for *endo* cycloaddition. As such, several dimeric diesters were synthesised and subjected to RCDA conditions. It was in fact observed that in all cases both isomers underwent intramolecular cycloadditions. The tethered substrates **62** and **63** were formed from the reaction of the alcohol **59** with adiopyl dichloride. Upon treatment with TBPA (**40**) this mixture yielded compounds **64** and **65** (Scheme 2.5).



Scheme 2.5: Synthesis of the tethered substrates **62** and **63** - postulated RCDA product mixture and actual RCDA product mixture. *Reagents and conditions:* a) Adiopyl dichloride, DMAP, CH₂Cl₂, 0 °C to r.t., overnight, 75%; b) TBPA, CH₂Cl₂, 0 °C, 2 h.

The target macrocycle **64** (possessing the kingianin A (**1**) core) was formed from the *endo* RCDA reaction of the C-2 symmetric substrate **62**. Contrary to expectations, the racemic substrate **63** also underwent RCDA (in this case through the *exo* transition state) to yield compound **65**. These isomers were found to be separable and upon removal of the tether, compound **66** was elaborated to kingianin A (**1**) (Scheme 2.6).



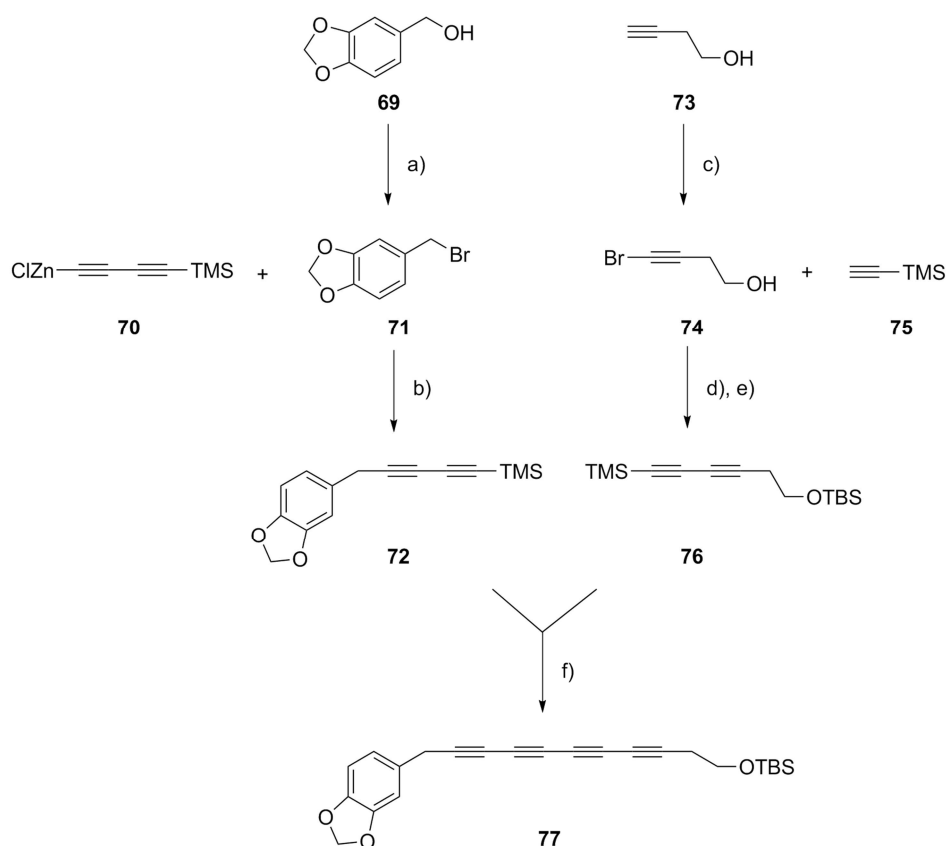
Scheme 2.6: Removal of the tether and double homologation; completion of the synthesis of kingianin A (**1**). *Reagents and conditions:* a) LiAlH_4 , THF, 0 °C, 30 min, 85%; b) MsCl , Et_3N , CH_2Cl_2 , 0 °C, 1 h then c) NaCN , NaI , DMF, 70 °C, 12 h, 85% (over two steps); d) H_2O_2 (35% in H_2O), EtOH-THF, reflux, 4 h then e) CH_3CHO , Et_3SiH , $\text{CF}_3\text{CO}_2\text{H}$, MeCN, r.t., 20 h, 36% (over two steps).

Initially, the ester functionalities of the tether were reduced with LiAlH_4 to release the diol **66**. This compound was then doubly homologated by mesylation and displacement with cyanide to form the dinitrile **67**. Following hydrolysis with hydrogen peroxide, the diamide **68** was subjected to *N*-alkylation according to the procedure of Dube *et al.*⁴⁶ to yield kingianin A (**1**).

1.6.3 Total Synthesis of Kingianins A (**1**), D (**4**), and F (**6**) - Sherburn and Lawrence *et al.*

In March 2013, Sherburn and Lawrence *et al.* published a total synthesis of kingianin A (**1**) alongside the first reported syntheses of kingianins D (**4**)

and **6**).⁴⁸ The group explored the potential of (Z,Z,Z,Z)-tetraenes as precursors to the bicyclo[4.2.0]octadiene functionality. They embarked upon the synthesis in an unprecedented manner; the stereoselective partial reduction of a conjugated tetrayne. As such, the two diynes **72** and **76** were synthesised and their cross-coupling investigated (Scheme 2.7).



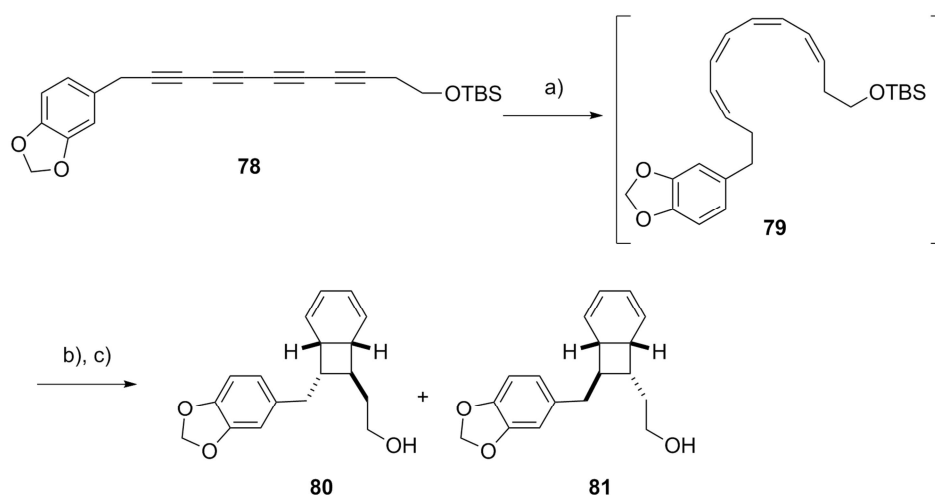
Scheme 2.7: Synthesis of the conjugated tetrayne **77**. *Reagents and conditions:* a) PBr₃, Et₂O, 0 °C, 45 min, 96%; b) PdCl₂(dppf), THF, Et₂O, 66 °C, 20 h, 84%; c) NBS, AgNO₃, acetone, r.t., 3.5 h, 87%; d) CuI, piperidine, 0 °C, 30 min, 89%; e) imidazole, TBSCl, THF, r.t., 2.5 h, 86%; f) CuCl, dry air, DMF, 60 °C, 5 h, 40%.

The diyne **76** was prepared *via* the Alami modified⁴⁹ Cadiot-Chodkiewicz cross-coupling of the known bromobutynol **74** with TMS-acetylene (**75**). Its cross-coupling partner, the diyne **72**, was prepared by the Negishi reaction of the benzyl bromide **71** and the organozinc reagent **70**. The two diynes **72** and **76** were then successfully cross-coupled with CuCl in dry air. This reaction represented the first reported crossed Mori-Hiyama

reaction and also the first gram-scale synthesis of an unsymmetrical tetrayne.

During the preparation of this thesis, an alternative synthesis of the tetrayne **78** was disclosed by Sherburn and Lawrence *et al.*⁵⁰ This approach involved the reaction of the corresponding terminal tetrayne with the benzyl bromide **71**. The use of two alternative alkyl halides was also shown to enable the synthesis of endiandric acid A (**27**) and the first reported synthesis of the related natural product kingianic acid E.

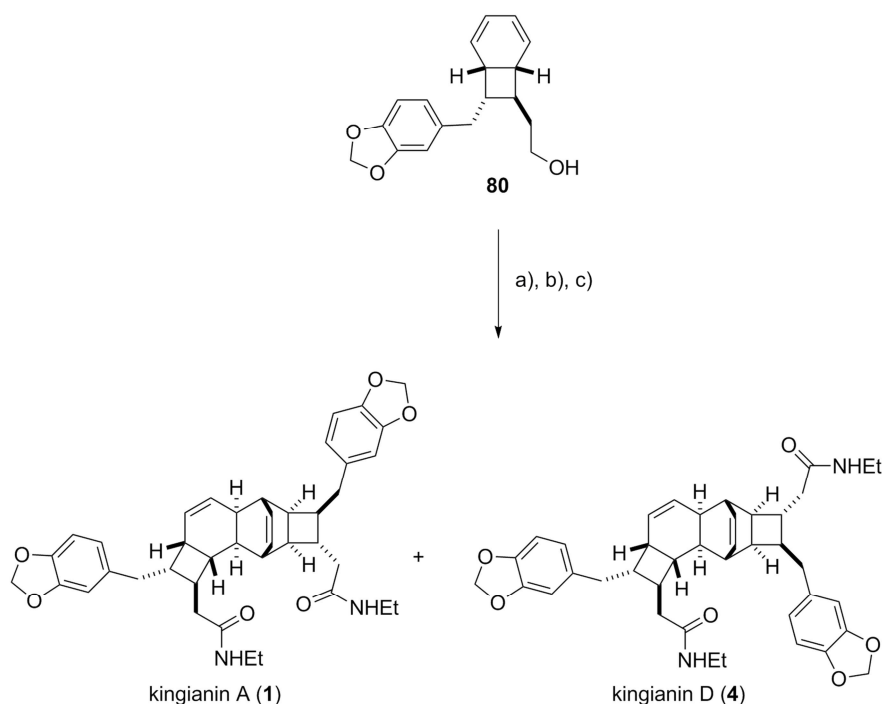
With the desired tetrayne **78** in hand, the team proceeded to the four-fold reduction.



Scheme 2.8: Four-fold selective reduction to form the all-Z-tetraene **79** and its double electrocyclisation to form the diastereomeric alcohols **80** and **81**. *Reagents and conditions:* a) Rieke Zn, EtOH, THF, 0 °C, 15 h then b) toluene, 100 °C, 16 h then c) TBAF, THF, r.t., 1.5 h, 21% (over three steps) (**80**:**81**=1:1).

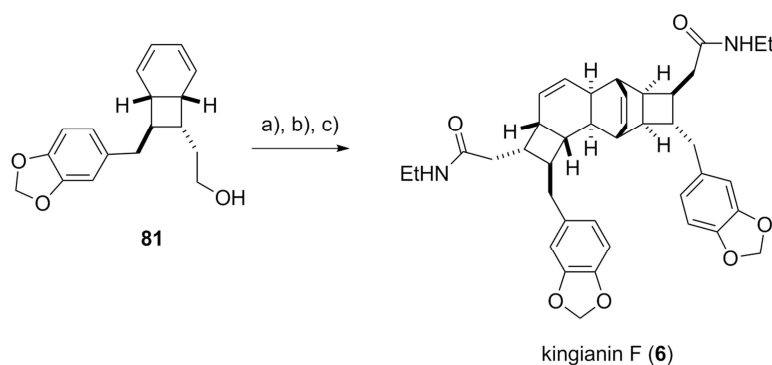
After significant experimentation, it was found that Rieke zinc in ethanol afforded the (Z,Z,Z,Z)-tetraene **79** in a completely chemoselective and highly diastereoselective manner. Following heating in toluene to bring about the double $8\pi/6\pi$ electrocyclisation, the silyl protecting group was removed to yield the diastereomeric alcohols **80** and **81**, which were

separated by preparative reverse phase HPLC. These compounds were found to undergo a rapid dimerisation upon treatment with TBPA (**40**). The experimental procedure was optimised to a sequence involving oxidation of the alcohol functionality in **80** to a carboxylic acid and then dimerisation with TBPA (**40**). Finally, amide coupling with EDC·HCl installed the ethyl amide to yield kingianins A (**1**) and D (**4**) alongside another unidentified product (Scheme 2.9).



Scheme 2.9: Functional group interconversion and dimerisation of alcohol **80** to yield kingianins A (**1**) and D (**4**). *Reagents and conditions:* a) TPAP, NMO, H₂O, MeCN, r.t., 10 min then b) 5 mol% TBPA, CH₂Cl₂, 0 °C, 30 min, then c) EtNH₂, HOBT, EDC·HCl, 40 °C, 20 h, 17% over three steps (kingianin A (**1**):kingianin D (**4**):other=10:3:2).

In the case of the other alcohol diastereoisomer **81**, a superior reaction sequence was found to be dimerisation, oxidation and then amidation (Scheme 3.0).



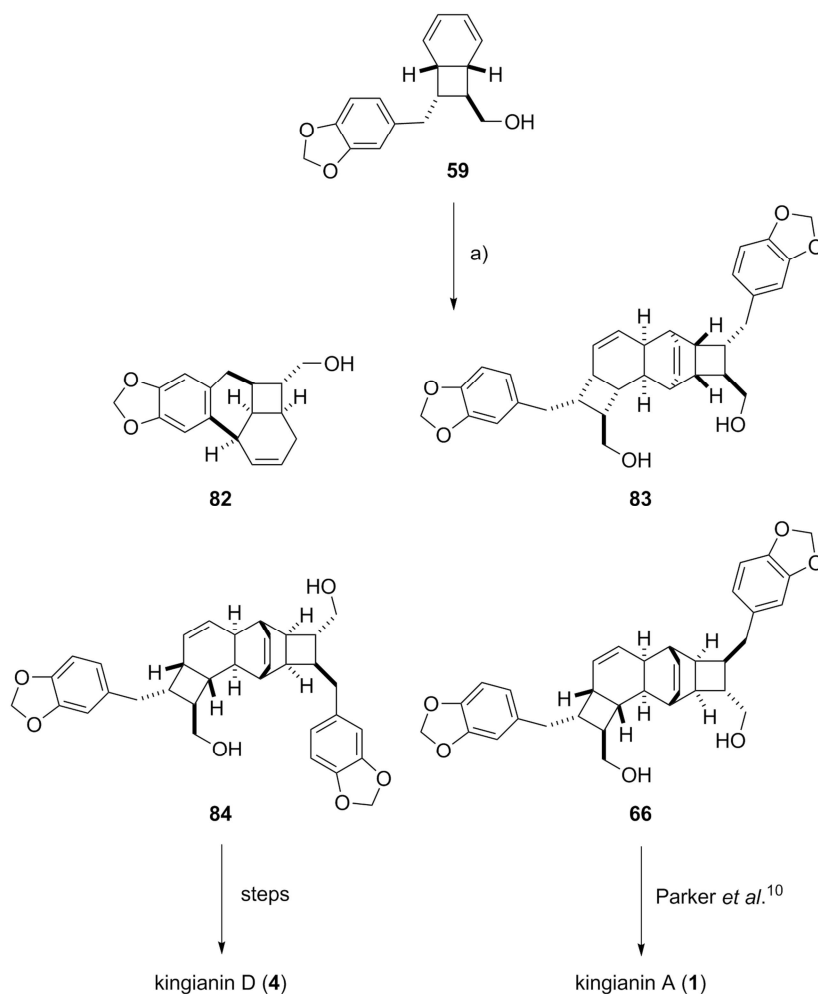
Scheme 3.0: Dimerisation and functional group interconversion of **81** to form kingianin F (**6**). *Reagents and conditions:* a) 30 mol% TBPA, CH₂Cl₂, 0 °C, 30 min, then b) TPAP, NMO, H₂O, MeCN, r.t., 20 min, then c) EtNH₂, HOBT, EDC·HCl, 40 °C, 17 h, 37% over three steps (kingianin F (**6**):others = 8:3:2:1).

In this case the only isolated natural product was kingianin F (**6**), which was recovered alongside three unidentified side products.

Interestingly, the group also reported that when prekingianin A (**49**), the putative monomer to kingianin A (**1**), was treated with TBPA (**40**), no dimeric species were observed. This result is in accordance with unreported observations of Moses *et al.*

1.6.4 Intermolecular RCDA Approach – Parker *et al.*

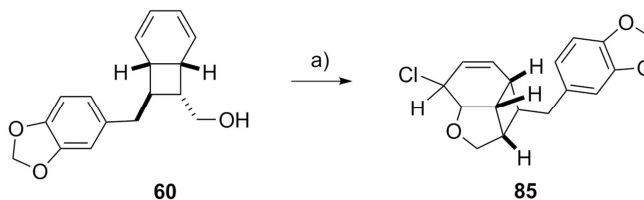
In 2014, Parker *et al.* published a second paper on the kingianin family of natural products, following a related intermolecular dimerisation strategy. They observed that when the bicyclo[4.2.0]octadiene **59** (which had been previously utilised in their tether based strategy) was subjected directly to RCDA conditions, four separable compounds were formed (Scheme 3.1).



Scheme 3.1: Parker's intermolecular RCDA approach to kingianin A (**1**) and D (**4**). *Reagents and conditions:* a) TBPA, CH_2Cl_2 , r.t., 1 h, **66** (37%), **83** (10%), **84** (18%), **82** (7%).

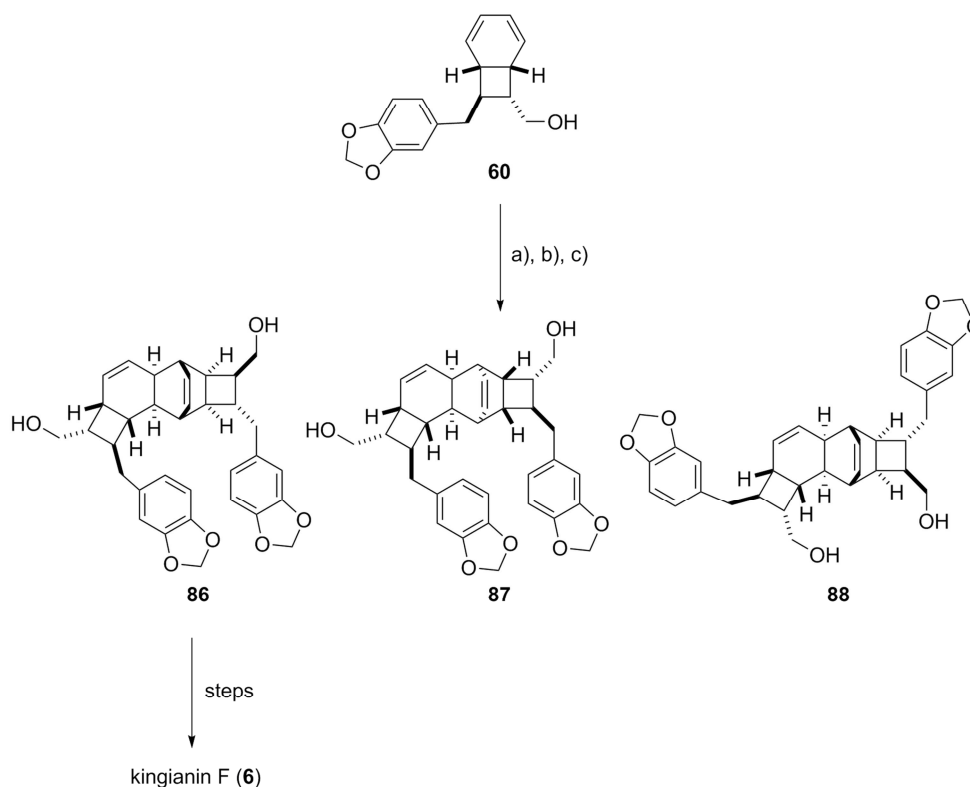
Formation of the diol **66** constituted a formal synthesis of kingianin A (**1**) through convergence with the route previously published by the same group.¹⁰ Using a corresponding chemical procedure, the diol **84** was converted to kingianin D (**4**). The diol **83** was formed through an *exo* Diels-Alder reaction and as such has a carbon skeleton not corresponding to any isolated member of the kingianin family. The non-Diels-Alder product **82** appears to have resulted from an electrophilic aromatic substitution reaction between the benzodioxole ring system and the activated diene.

The authors also targeted kingianin F (**6**) but observed that when the corresponding bicyclo[4.2.0]octadiene **60** was subjected to the RCDA conditions, no dimeric species were obtained (Scheme 3.2).



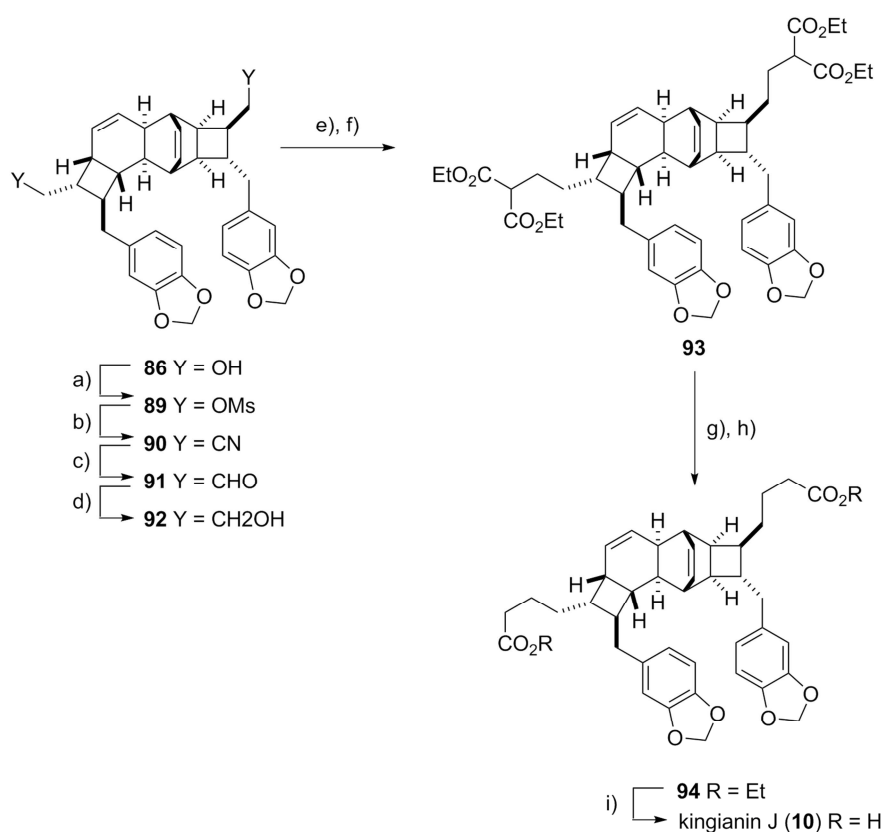
Scheme 3.2: Treatment of the alcohol **60** with TBPA (**40**). *Reagents and conditions:* a) TBPA, CH₂Cl₂, 0 °C, 1 h, 36%.

Instead, only the chloroether **85** was isolated. This issue was circumvented by protecting the alcohol functionality prior to treatment with TBPA (**40**) (Scheme 3.3).



Scheme 3.3: Parker's intermolecular RCDA approach to diols **87** and **88** and kingianin F (**6**). *Reagents and conditions:* a) Ac₂O, DMAP, CH₂Cl₂, r.t., 1 h, 89%; b) TBPA, CH₂Cl₂, 0 °C, 1 h then c) LiAlH₄, THF, 0 °C to r.t., **87** (12%), **86** (46%) and **88** (30%) (over two steps).

As such, the alcohol was first acetylated and then dimerisation was performed with TBPA (**40**). Following deprotection with lithium aluminium hydride, the dimeric diols **86**, **87**, and **88** were isolated. The diol **86** was then converted to kingianin F (**6**) using a procedure analogous to that described for the conversion of diol **66** to kingianin A (**1**). Using a different procedure, the diol **86** was also converted to kingianin J (**10**) (Scheme 3.4).

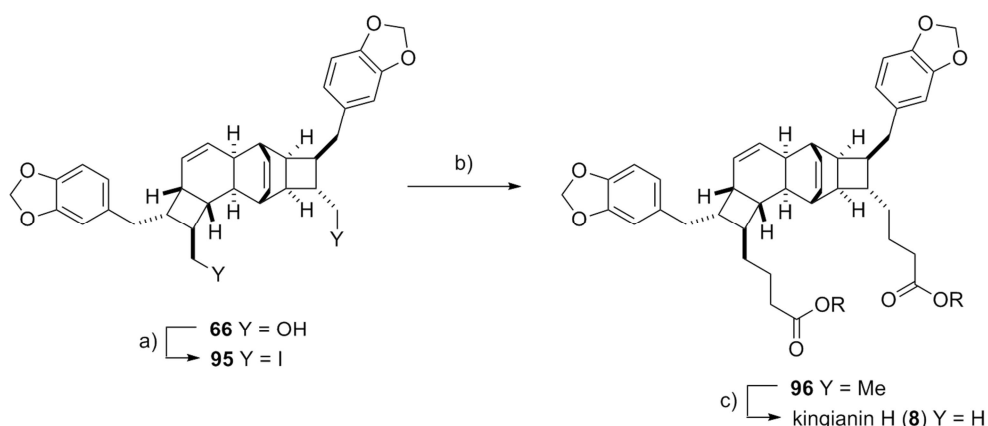


Scheme 3.4: Conversion of diol **86** to kingianin J (**10**). *Reagents and conditions:* a) MsCl, Et₃N, CH₂Cl₂, 0 °C, 30 min then b) NaI, NaCN, DMF, 70 °C, 16 h, 74% (over two steps); c) DIBAL-H, CH₂Cl₂, -78 °C then d) NaBH₄, MeOH, 0 °C, 30 min, 55% (over two steps); e) MsCl, Et₃N, CH₂Cl₂, 0 °C, 30 min then f) NaH, diethyl malonate, r.t. to Δ, 18 h, 51% (over two steps); g) LiCl, wet DMSO, 150 °C, 4 h, 36%; h) NaOH, EtOH-H₂O, r.t., 18 h, 84%.

The diol **86** was doubly homologated *via* mesylation and cyanation to form the dinitrile **90**. Following this, hydration and then reduction formed the diol **92**. This compound was then converted to the dimesylate and treated

with ethyl malonate to form the dimalonate **93**. Using Krapcho conditions,⁵¹ decarboxylation of the dimalonate yielded the diester **94**, which was hydrolysed to form kingianin J (**10**).

The group also pursued the synthesis of kingianin H (**8**), this compound has the same pentacyclic core as kingianin A (**1**) and hence the same dimeric diol **66** could be used as a starting point for the synthesis (Scheme 3.5).



Scheme 3.5: Conversion of diol **66** to kingianin H (**8**). *Reagents and conditions:* a) I_2 , PPh_3 , imidazole, CH_2Cl_2 , r.t., 1.5 h, 77%; b) methyl acrylate, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, Zn, pyridine, 60 °C to r.t., 4.5 h, 70%; c) NaOH, $\text{EtOH-H}_2\text{O}$, r.t., 18 h, 93%.

Using an Appel reaction, the diol **66** was converted to the corresponding diiodide **95**. The latter species was then subjected to Manchand's one pot three carbon homologation protocol,^{28,29} to form the diester **96**. This compound was then hydrolysed to form kingianin H (**8**).

Following the work of Parker *et al.*,^{10,54} and Sherburn and Lawrence *et al.*,⁴⁸ a change in strategy was deemed necessary to retain novelty in the project. The possibility of bringing about the RCDA dimerisation of bicyclo[4.2.0]octadienes *via* electrochemical means was intriguing. As mentioned previously, the electrochemically initiated RCDA reaction has been reported⁴² but in general the method has not been widely explored.

1.7 ELECTROSYNTHESIS

1.7.1 Introduction to Electrochemistry

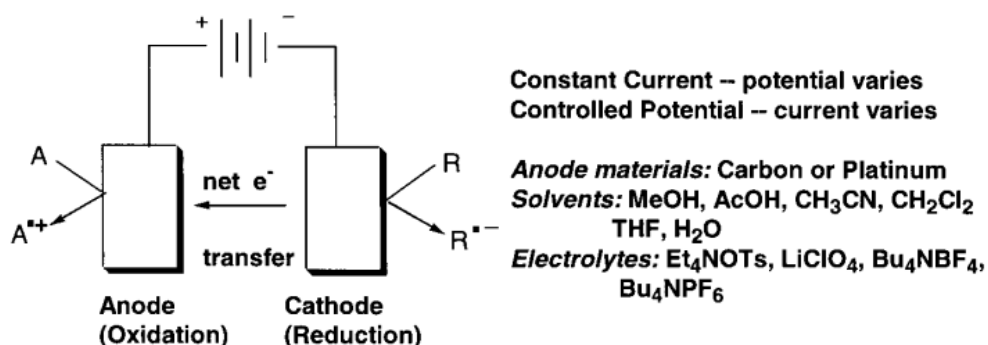


Figure 1.6: Generalised electrochemistry experiment. Figure reproduced from the literature.⁵⁵

In essence, all electrochemical experiments utilise an electrical circuit that has been broken.⁵⁵ On either side of the break electrodes are placed, which are then inserted into a solution that contains the substrate(s) of interest and an electrolyte. The electrolyte is an ionic material, which helps increase the conductivity of the solution and provides counterions for the electrogenerated species. At the anode, molecules are oxidised and the liberated electrons are transferred into the electrode. At the cathode the reverse process occurs; electrons are transferred from the electrode into the solution and molecules are reduced. These two processes result in completion of the electrical circuit, facilitating a flow of current. The descriptors "working electrode" and "counter/secondary electrode" are commonly used to describe the anode and cathode, depending on whether oxidation or reduction is the process of interest. Before performing preparative scale electrochemical experiments, it is common to study the redox behaviour of a substrate of interest. One of the most common methods for studying the electrochemical behaviour of a system is cyclic voltammetry.

1.7.2 Cyclic Voltammetry

In this experiment the voltage applied to the working electrode is ramped and cycled linearly between two chosen values with respect to time (Figure 1.7).

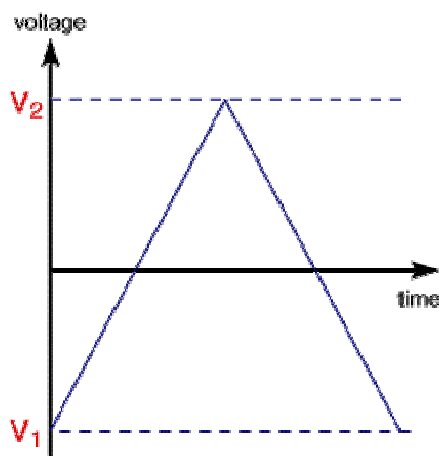


Figure 1.7: Voltage vs. time plot for a typical cyclic voltammetric measurement.⁵⁶

Simultaneously, the current is measured and plotted against voltage. If the system is electrochemically reversible, a characteristic curve is obtained (Figure 1.8).

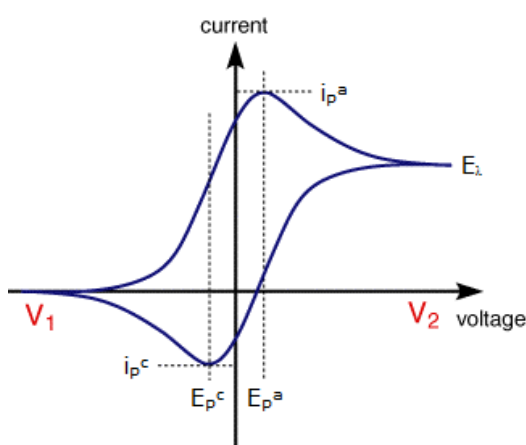


Figure 1.8: The classical cyclic voltammogram for an electrochemically reversible system (E_p^a = peak anodic potential; E_p^c = peak cathodic potential; i_p^a = peak anodic current; i_p^c = peak cathodic current).⁵⁶

Initially, the potential is swept in the forward direction. At the point where it becomes sufficient to oxidise some component of the system (the onset potential), the flow of electrons from this component into the electrode results in an increase in current (faradaic current). The current continues to rise until a point where the system is limited by the rate of diffusion of un-oxidised material onto the surface of the electrode. The potential at which this occurs is referred to as the peak anodic potential (E_p^a). At the switching potential (E_λ) the potential is reversed and swept in the opposite direction. The current then slowly increases (in the opposite direction to that observed in the forward scan) until the point where the corresponding reduction can occur. At this stage the neutral species is regenerated and there is a corresponding influx of current. Again, this is a diffusion limited process and the potential at which maximum current is observed is referred to as the peak cathodic potential (E_p^c).

Studying the redox behaviour of an analyte can help assist in the design of a preparative procedure. In general, preparative electrochemical reactions can be controlled in one of two ways; constant current and constant voltage experiments.

1.7.3 Preparative Electrochemistry

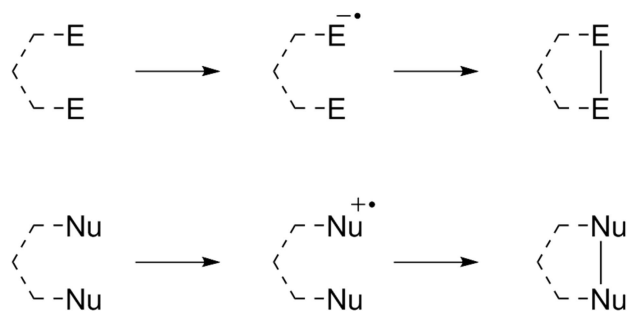
In a constant current experiment, the desired current is set and the voltage at the electrodes is allowed to vary as required to maintain this current. In this type of experiment the voltage at the anode will rise until the set current is met by the oxidation of the species in solution. This voltage will be determined by the substrate (or functional group within a substrate) with the lowest oxidation potential. The observed voltage will then plateau until the point that this substrate is consumed. At this point the voltage will again begin to rise until the set current can be maintained by the oxidation of the substrate with the second lowest oxidation

potential. This process will continue until either the solvent itself becomes oxidised or the current is switched off. The main benefit of a constant current experiment is that the set-up is very straightforward. The drawback is that as the first substrate starts to be consumed, the voltage begins to climb and the selectivity of the oxidation can decrease. For this reason, it is sometimes necessary to perform a constant voltage experiment.

In a constant voltage experiment, a reference electrode is introduced and the voltage at the working electrode is held constant relative to this reference. The benefit of this set-up is that only substrates with an oxidation potential lower or equal to the applied voltage can be oxidised and therefore a greater selectivity can be achieved. One negative feature of a constant voltage experiment is that as the substrate is consumed the current will drop off, causing a decreased rate of electrolysis. For this reason, longer time periods can be required to push a reaction to completion.

1.7.4 Electrosynthesis over Conventional Reagents

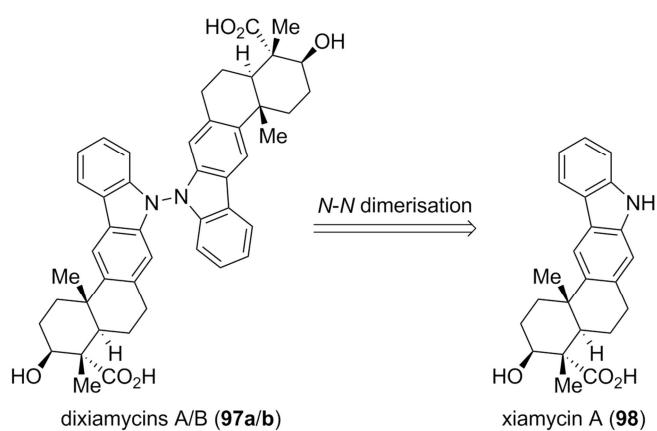
One of the most powerful features of electrosynthesis is that it allows umpolung reactivity of a wide range of substrates. If anodic oxidation is performed on a nucleophile for example, the resulting species will be a radical cation, and hence electrophilic. Conversely, if cathodic reduction is performed on an electrophile then a radical anion will be generated and the species becomes nucleophilic. Through these two complementary processes, a whole host of reactions can be achieved where either two nucleophiles or two electrophiles are coupled together in ways that would otherwise be extremely challenging (Scheme 3.6).⁵⁷



Scheme 3.6: Generalised umpolung reactivity accessible through electrocyclic reactions. Scheme reproduced from the literature.⁵⁷

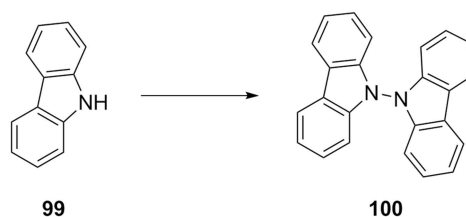
1.7.5 Electrosynthesis of Natural Products

One other advantage of electrocyclic reactions has recently been demonstrated in the field of natural product synthesis. In their work towards the atropisomeric indoloterpenoid natural products dixiamycins A /B (**97a/b**), Baran *et al.* pursued an *N-N* dimerisation strategy (Scheme 3.7).⁵⁸



Scheme 3.7: Baran's retrosynthetic analysis of dixiamycins A/B (**97a/b**).

Retrosynthetically, this is arguably the most appealing disconnection but in reality there are few known methods to bring about such a dimerisation. As a model system, the group decided to focus initially on bringing about the corresponding dimerisation of the parent substrate carbazole (**99**) (Scheme 3.8).



Scheme 3.8: The desired *N-N* dimerisation of carbazole (**99**).

An exhaustive screening of chemical oxidants failed to elucidate synthetically viable conditions; the best result being <20% yield, obtained through treatment with potassium permanganate in refluxing acetone. In light of these results, the group became interested in the idea of an electrochemical oxidation. Observation of the cyclic voltammogram of carbazole (**99**) revealed why chemical oxidation had failed (Figure 1.9).

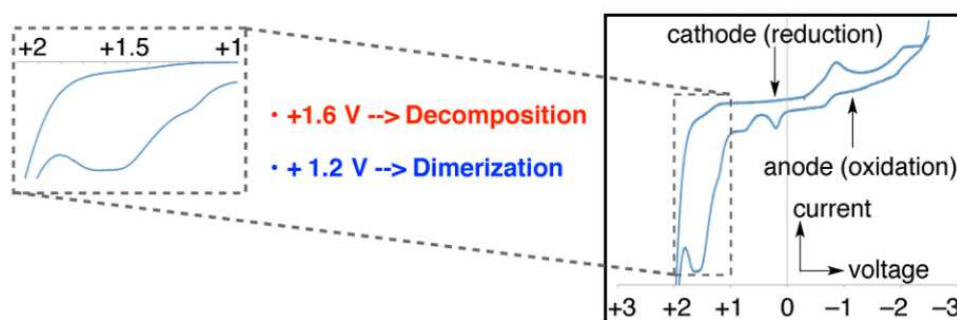


Figure 1.9: Cyclic voltammogram of carbazole (**99**). Et₄NBr used as electrolyte.⁵⁸

Experiments where a constant potential of >+1.6 V was applied resulted in substantial decomposition. On the other hand, when potentials of <+1.1 V were applied, only minimal conversion was observed. By tuning the voltage to +1.2 V an isolated yield of 60% of the carbazole dimer **100** was obtained. Whilst screening the reaction for substrate scope, the authors observed that in all cases where comparison was possible, electrochemical oxidation was superior to any previously reported means of effecting this transformation. Finally, the electrochemical dimerisation strategy was applied to the proposed natural product monomer xiamycin A (**98**). The

cyclic voltammogram of this compound indicated that a potential of +1.2 V would be appropriate. At this voltage, anodic oxidation afforded small amounts of dixiamycin B (**97b**) alongside substantial recovered starting material and several by-products. A slight decrease in applied potential however (to +1.15 V) improved the isolated yield to 28%, along with 13% recovery of the monomer **98**.

1.7.6 The Electrochemical Dimerisation of 1,3-Cyclohexadiene (**37**)

Intrigued by a series of reports implicating the intermediacy of 1,3-cyclohexadienyl radical cation in its Diels-Alder reactions, Nigenda and co-workers decided to study the generation and chemistry of this reactive species under electrochemical conditions.⁴² Initially, the cyclic voltammogram (CV) of 1,3-cyclohexadiene (**37**) was measured in CH_2Cl_2 with tetrabutylammonium tetrafluoroborate as supporting electrolyte (Figure 2.0).

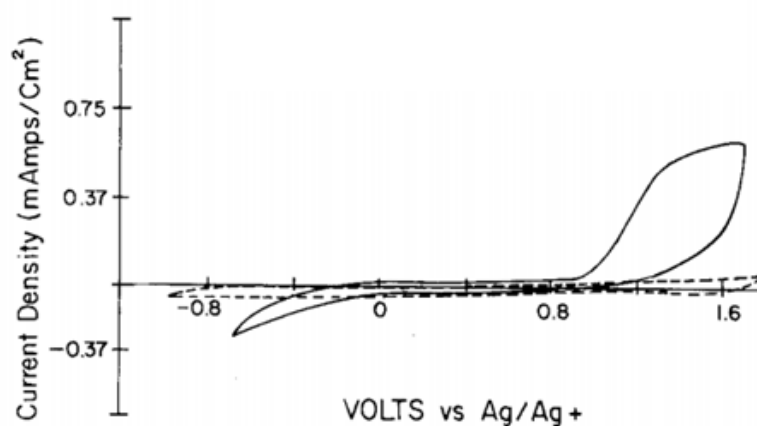
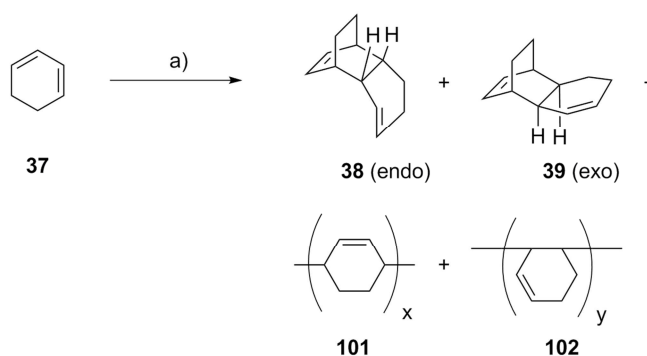


Figure 2.0: Cyclic voltammogram of 0.08 M tetrabutylammonium tetrafluoroborate in CH_2Cl_2 : (-----) without 1,3-cyclohexadiene (**37**); (—) with 0.1 M 1,3-cyclohexadiene (**37**). Sweep rate: 0.2 V s^{-1} .⁴²

The observed CV shows that the oxidation starts at a potential of 1.1 V (E_1 , vs. Ag/Ag^+ saturated in CH_2Cl_2 , reference electrode) and the peak at 1.7 V represents the peak anodic potential (E_p^a) for the oxidation (Figure 2.0). Key to this study was the fact that the oxidation was found to be irreversible, as indicated by the lack of a peak in the reverse sweep. The implication of this observation is that the 1,3-cyclohexadienyl radical cation $\mathbf{37}^{+\bullet}$ is not stable under the given electrochemical conditions; it undergoes a chemical reaction before the corresponding reduction to the neutral species can occur. Encouraged by their voltammetric studies, the group proceeded to a preparative scale experiment.

Upon bulk electrolysis, the single electron oxidation of 1,3-cyclohexadiene (**37**) was observed to bring about dimerisation alongside the major competing reaction of polymerisation (Scheme 3.9).⁴²



Scheme 3.9: Electrochemical dimerisation of 1,3-cyclohexadiene (**37**). *Reagents and conditions:* a) electrolysis ($-\text{e}^-$), 1.7 V, 9.6% Q'' passed, 0.08M tetrabutylammonium hexafluorophosphate, CH_2Cl_2 , r.t., 30% (**38**+**39**:polymer = 5:<1).

The effect of diene concentration, supporting electrolyte and applied potential were investigated with respect to Diels-Alder adduct yield. The best results were obtained when a potential of 1.7 V was applied to a dilute (0.04 M) solution of diene with tetrabutylammonium hexafluorophosphate electrolyte. The authors also report that the highest yield was achieved when only 10% Q'' was passed. Q'' represents the total charge required by

Faraday's law for complete electrolysis of a component of the system. It can be calculated according to the following equation (Figure 2.1).

$$Q'' = m \times n \times F$$

Figure 2.1: Calculation of Q'' where: m = mols of substrate; n = electrons required; F = Faraday's constant. (In the case of a RCDA, a single electron oxidation is required so $n=1$.)

Under these conditions, the Diels-Alder dimers **38** and **39** were isolated in a combined yield of 25% alongside <5% polymeric fractions. These polymeric fractions showed mainly 1,4-addition mode segments **101** with a smaller fraction of 1,2-addition mode segments **102** and were identical to cyclohexadiene polymer obtained by chemical means. Interestingly, the Diels-Alder polymer **103** (which is obtained in chemically initiated polymerisation) was not observed in any of the electrochemical experiments (Figure 2.2).

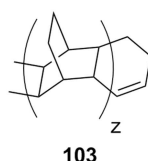


Figure 2.2: Diels-Alder polymer of 1,3-cyclohexadiene (**103**).

1.8 AIMS

The principal aim of this work was to pursue a biomimetic total synthesis of kingianin A (**1**) and other members of the kingianin family of natural products. As part of these studies, the proposed biosynthetic transformation: the Diels-Alder dimerisation of bicyclo[4.2.0]octadienes was also investigated.

Initially, a route was envisaged to a pair of diastereomeric bicyclo[4.2.0]octadienes that could act as a model system. The synthesis

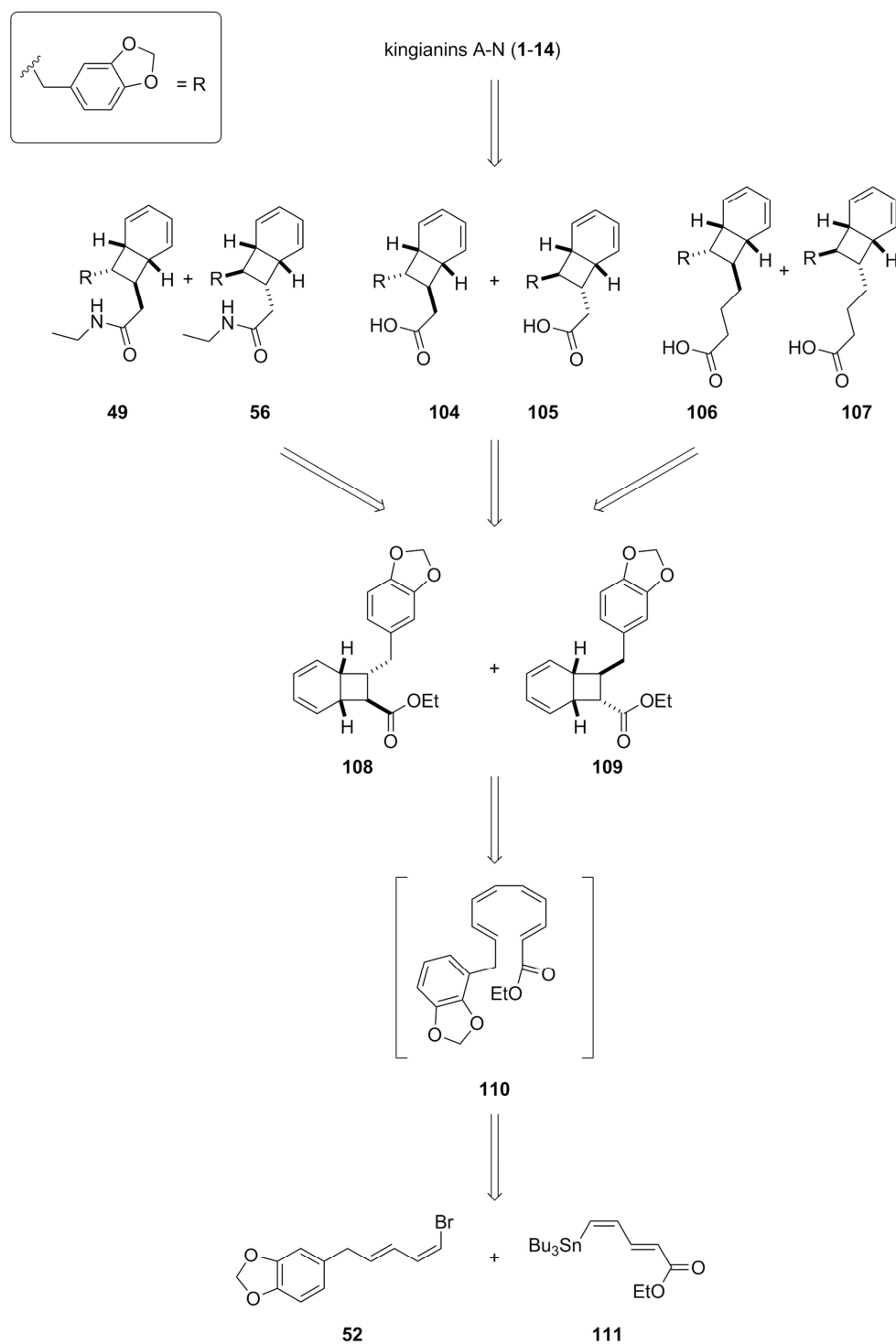
of these compounds was achieved through a convergent route which utilised the Stille coupling reaction. The resultant bicyclo[4.2.0]octadienes were subjected to chemically initiated RCDA conditions.

Following the work of Parker *et al.* and Lawrence and Sherburn *et al.* (*vide supra* – Section 1.6), there was a shift in focus towards investigating the possibility of an electrochemically initiated RCDA dimerisation of bicyclo[4.2.0]octadienes. Initially, the redox behaviour of these compounds was studied using cyclic voltammetry and then preparative electrochemical techniques were employed with the aim of achieving a formal synthesis of kingianin A (**1**).

2. RESULTS AND DISCUSSION

1st Generation Synthesis – Stille Cross-Coupling Route

At the time that this programme of research was initiated, no example of the Diels-Alder dimerisation of a bicyclo[4.2.0]octadiene had been reported. Furthermore, the only substrate to be studied in this capacity was prekingianin A (**49**) and this compound had been found to be resistant to both thermal and RCDA conditions. As such, a model substrate was sought after to further investigate this elusive mode of reactivity. It was envisaged that the diastereomeric bicyclo[4.2.0]octadienyl esters **108** and **109** could be prepared in fewer steps than were required for the synthesis prekingianin A (**49**). It was also conceivable that these compounds could be elaborated into any of the proposed kingianin monomers **49**, **56** and **104-107**. In light of literature precedent^{18,59,60} for using a Stille cross-coupling reaction to access the [4.2.0]-ring system, a retrosynthesis was devised (Scheme 4.0).

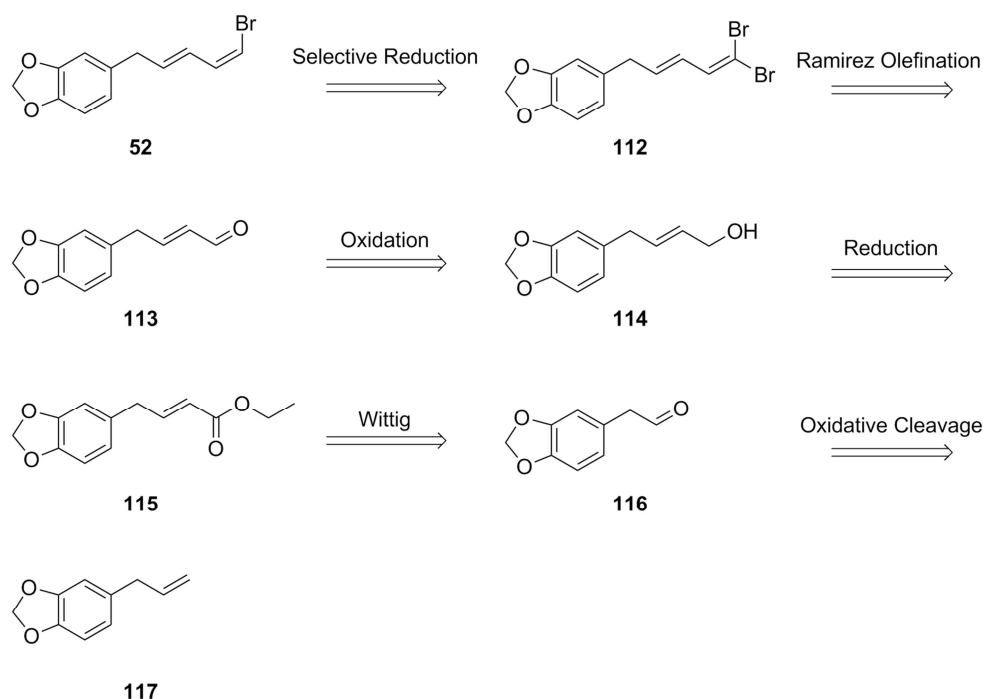


Scheme 4.0: Revised retrosynthetic analysis of kingianins A-N (**1-14**).

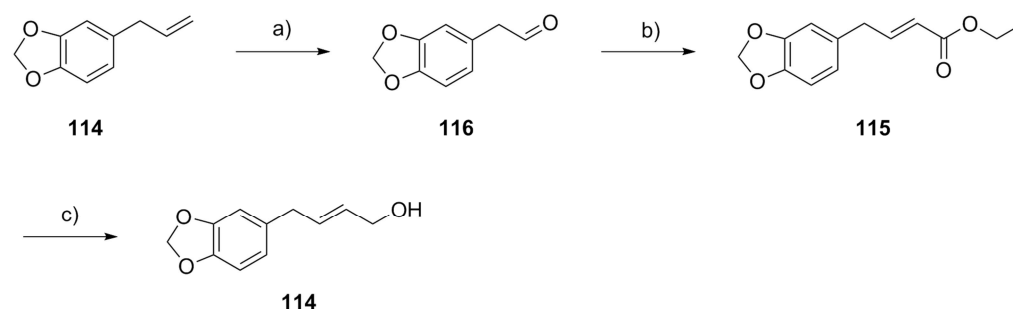
According to this proposal, the synthesis of the esters **108** and **109** would culminate in the Stille cross-coupling of the vinyl bromide **52** and the vinyl stannane **111**.

2.1 SYNTHESIS OF THE DIENYL BROMIDE CROSS-COUPLING PARTNER **52**

As previously reported by Moses *et al.*,⁴³ synthesis of the vinyl bromide cross-coupling partner **52** can be achieved in six steps from the commercially available compound safrole (**117**):



Scheme 4.1: Retrosynthetic analysis of the vinyl bromide **52**.

2.1.1 Synthesis of the Allyl Alcohol **114**

Scheme 4.2: Synthesis of the alcohol **114**. *Reagents and conditions:* a) OsO_4 (0.5 mol%), NaIO_4 , H_2O , MeOH , r.t., 16 h; b) ethyl 2-(triphenylphosphoranylidene)acetate, CH_2Cl_2 , Δ , 16 h, 80% (over two steps); c) DIBAL-H, CH_2Cl_2 , -78°C to r.t., 40 min, 71%.

The first three steps in the synthesis of the dienyl bromide cross-coupling partner **52** proceeded smoothly and in high yields. The synthesis began with the osmium tetroxide-catalysed oxidative cleavage of the terminal alkene in safrole (**117**) to give the aldehyde **116**. This reaction occurred with quantitative conversion, as determined by ^1H NMR analysis of the crude mixture. Upon filtration through Celite[®] and removal of the solvent, the crude aldehyde **116** was used directly for the next step.

Wittig olefination of aldehyde **116** proceeded smoothly to yield exclusively the target (*E*)-alkene **115**, with no observation of the other diastereoisomer. The α,β -unsaturated ester **115** was found to be stable at room temperature; no isomerisation of the double bond into conjugation with the aromatic ring was observed. Next, this compound was treated with DIBAL-H, to reduce the ester functionality. It was found in some instances that during the reaction, isomerisation to the conjugated species **118** was observed (Figure 2.3)

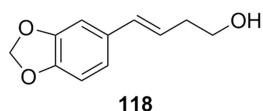
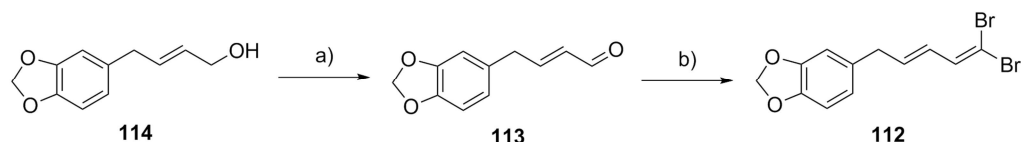


Figure 2.3: The isomeric side-product **118**.

This problem was circumvented by monitoring the reaction by thin layer chromatography (TLC) and quenching immediately after consumption of the starting material was observed. As such, a clean conversion of the ester **115** to the alcohol **114** was achieved and the product was isolated in 71% yield.

2.1.2 Synthesis of the Dienyl Dibromide **112**



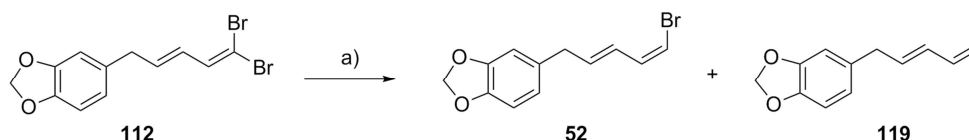
Scheme 4.3: Synthesis of the dibromide **112**. *Reagents and conditions:* a) DMP, CH₂Cl₂, 0 °C, 30 min, 92%; b) CBr₄, PPh₃, Et₃N, DCM, r.t., 15 min, 93%.

The oxidation of **114** was performed with Dess-Martin periodinane (DMP). The reaction resulted in formation of the α,β -unsaturated aldehyde **113**, which was isolated in 92% yield following column chromatography.

In application to the oxidation of an allylic alcohol, MnO₂ can often offer a simplified purification procedure in comparison to a DMP mediated process. As such, the use of this reagent was investigated for the oxidation of **114**. In this case however, the target aldehyde **113** was not observed. Instead, an unidentified product was formed, which was found to decompose in CDCl₃ overnight.

Treatment of the aldehyde **113** to the Ramirez olefination⁶¹ (carbon tetrabromide and triphenylphosphine) resulted in the formation of the dibromoalkene **112** in 93% yield.

2.1.3 Synthesis of the Dienyl Bromide **52**



Scheme 4.4: Reduction of dibromide **112**. *Reagents and conditions:* a) $\text{Pd}(\text{PPh}_3)_4$ (10 mol%), Bu_3SnH , toluene, r.t., 3 h, **52** (74%).

The final step in this linear sequence was selective mono-protodehalogenation of the dibromide **112**. Originally reported by Yonemitsu *et al.*⁶², the $\text{Pd}(\text{PPh}_3)_4$ -catalysed reduction of geminal dibromoalkenes with tributyltin hydride (TBTH) can form (*Z*)-vinylbromides with excellent selectivity.

In the case of the dibromide **112** however, the procedure was complicated by formation of the over reduced species **119**, which was observed to form in small amounts before complete consumption of the starting material had occurred. As such, minor amounts of both **112** and **119** were commonly present alongside the target bromide **52** in the crude reaction mixture. Separation of these species by column chromatography was found to be extremely challenging and the isolated yields of **52** were severely reduced as a result of co-elution.

It was therefore desirable to push the reaction as close to completion as possible whilst minimising the formation of **119**. The best way to achieve this was to use precisely 1 equivalent of TBTH. The presence of any impurity in either the starting material or the reducing agent therefore was

found to significantly affect the product distributions. Due to the thermal and photochemical instability of TBTH it was necessary to freshly distil this reagent before use and even so, it was invariably observed that either the starting material **52** or the over reduced species **119** (or both) were present in the reaction mixture.

After much experimentation, a procedure was adopted whereby a carefully measured, sub-stoichiometric quantity of TBTH was initially employed. Progress of the reaction was then monitored by ^1H NMR spectroscopy and when the TBTH had been consumed (and the reaction had stopped), the percentage conversion of the dibromide **112** to the target compound **52** was ascertained through integration of the characteristic peaks for the benzylic proton environment (observed at 3.37 and 3.42 ppm respectively in an unreferenced spectrum) (Figure 2.4).

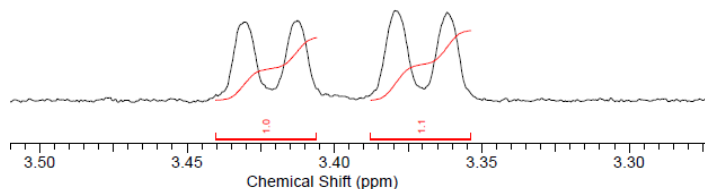
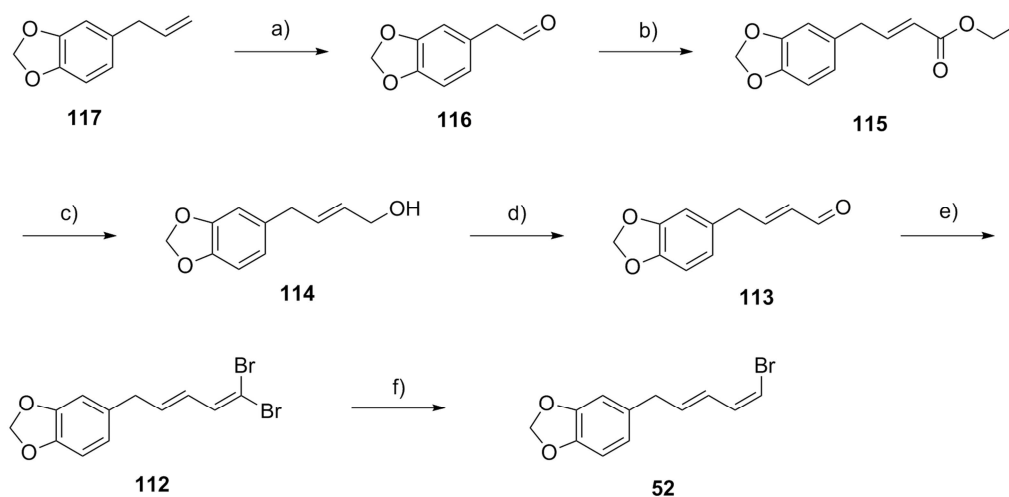


Figure 2.4: ^1H NMR spectroscopy expansion showing the characteristic peaks for benzylic proton environments of the dibromide **112** and the target bromide **52**.

By determining the percentage conversion achieved through the addition of a known volume of TBTH (of unknown purity), the volume required to push the reaction to completion could be calculated. Following this procedure, a greatly improved product distribution was achieved, although it was not possible to completely eliminate the presence of the over-reduced species **119**. Isolated yields were therefore still somewhat hampered by co-elution but it was possible to isolate the desired bromide **52** in up to 74% yield.

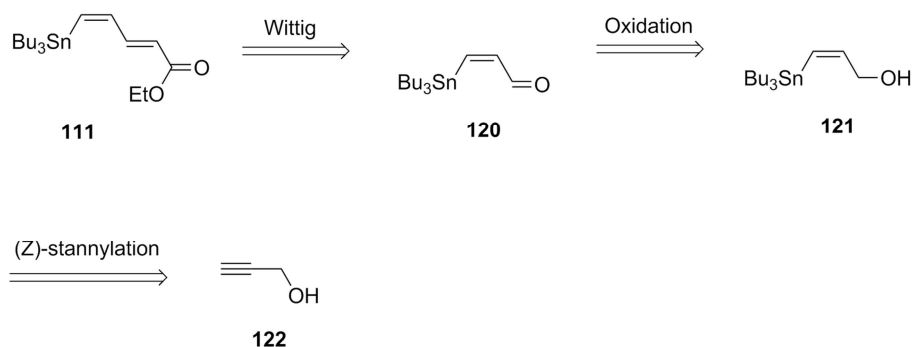
This completed the synthesis of the desired coupling partner **52** in an overall yield of 41% over six steps (Scheme 4.5). This is comparable to the 37% yield reported previously by Moses *et al.* for synthesis of the same compound.



Scheme 4.5: Synthesis of the vinyl bromide **52**. *Reagents and conditions:* a) OsO_4 (0.5 mol%), NaIO_4 , H_2O , MeOH , r.t., 16 h; b) ethyl 2-(triphenylphosphoranylidene)acetate, CH_2Cl_2 , Δ , 16 h, 80% (over two steps); c) DIBAL-H, CH_2Cl_2 , -78°C to r.t., 40 min, 81%; d) DMP, CH_2Cl_2 , 0°C , 30 min, 92%; e) CBr_4 , PPh_3 , Et_3N , CH_2Cl_2 , r.t., 15 min, 93%; f) HSnBu_3 , $\text{Pd}(\text{PPh}_3)_4$ (10 mol%), toluene, r.t., 1 h, 74%.

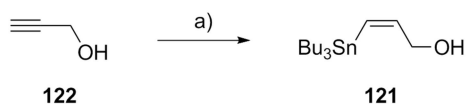
2.2 SYNTHESIS OF THE VINYL STANNANE **111**

The vinyl stannane **111** had previously been utilised by Moses *et al.* as an intermediate to the nitrile substituted cross-coupling partner **53**.⁴³ The Stille cross-coupling of **111** however, was not reported. Retrosynthetic analysis of the vinyl stannane **111** was inspired by syntheses of related compounds that had been reported in the literature (Scheme 4.6).^{63–65}



Scheme 4.6: Retrosynthetic analysis of the vinyl stannane **111**.

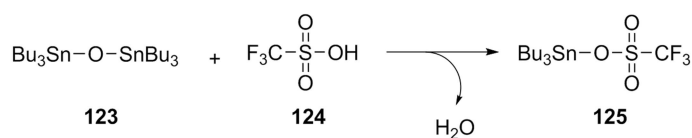
2.2.1 Synthesis of the Stannyl Alcohol **121**



Scheme 4.7: Synthesis of the alcohol **121**. *Reagents and conditions:* a) LAH, THF, 0 °C to r.t., 16 h then Bu₃SnOTf, 0 °C to r.t., 16 h, 23%.

A method for the synthesis of the allyl alcohol **121** from propargyl alcohol (**122**) has been reported in a patent.⁶⁶ Thus, reduction of **122** was carried out with lithium aluminium hydride and the intermediate aluminate was trapped with tributyltin chloride. Following laborious column chromatography, this procedure resulted in the isolation of the target product **121** in just 13% yield. Complete selectivity over formation of the (*E*)-alkene was however observed.

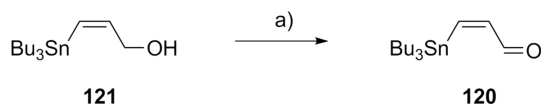
A modification to this procedure has been described by Corey.⁶⁷ An 80% yield of the target (*Z*)-alkene **121** was reported when using tributyltin triflate (**125**) as the electrophilic source of tin. As such, preparation of **125** was carried out *via* an azeotropic dehydration reaction of bis(tributyltin)oxide (**123**) and triflic acid (**124**) (Scheme 4.8).⁶⁸



Scheme 4.8: Synthesis of tributyltin triflate (**125**).

Purification of **125** *via* distillation was found to be challenging. Difficulties arose as a result of the relatively small temperature difference between the boiling point of the crude mixture and the decomposition temperature of the product. When the stannylation of propargyl alcohol (**122**) was attempted using this reagent, the reported yield could not be replicated. A small improvement was however observed and the isolated yield of **121** was improved from 13% to 23%. The poor yield may be attributed, in part, to difficulties in removing the large quantities of tributyltin and aluminium derived by-products that are generated in this reaction.

2.2.2 Synthesis of the Stannyl Aldehyde **120**



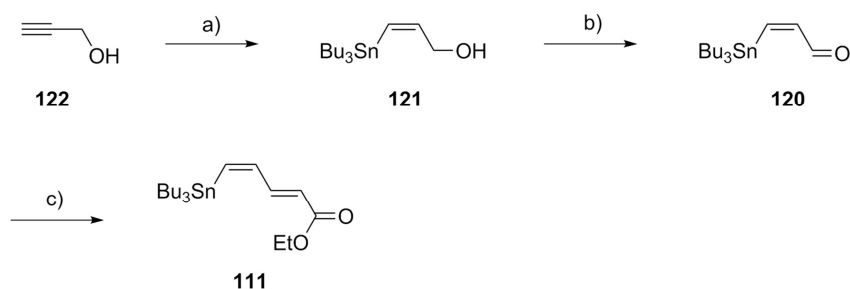
Scheme 4.9: Synthesis of the aldehyde **120**. *Reagents and conditions:* a) MnO_2 , CHCl_3 , 8 h, r.t., quantitative.

Oxidation of the alcohol **121** to the corresponding aldehyde **120** was carried out initially with DMP and was achieved in 65% yield. Whilst satisfactory, it was desirable to achieve the conversion in a higher yield. As such, the oxidation was also attempted with MnO_2 , under a procedure that involved heating to reflux in chloroform. After 5 hours, a substantial amount of the (*E*)-alkene was observed by ^1H NMR spectroscopy alongside the target (*Z*)-alkene **120**. When the same reaction was attempted at room temperature however, **120** was formed with quantitative conversion.

Following filtration through a short plug of celite, the product was used directly for the next step, without the need for further purification.

2.2.3 Synthesis of the Stannyl Ester **111**

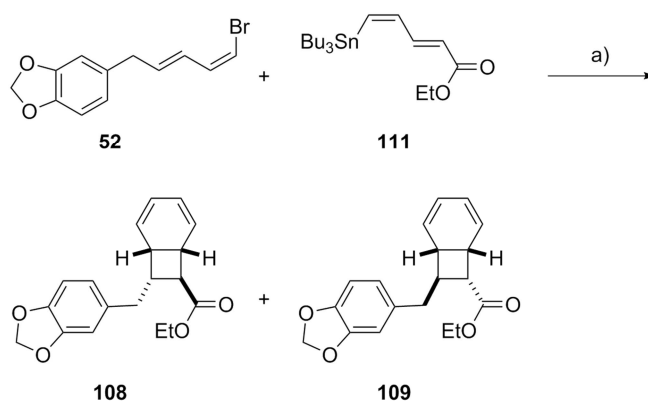
The final step in this sequence was the Wittig reaction of the aldehyde **120** with ethyl 2-(triphenylphosphoranylidene)acetate, which was prepared according to the literature procedure.⁶⁹ The olefination occurred readily at room temperature in 93% yield, thus completing the synthesis of the desired cross-coupling partner **111** in an overall yield of 21% over three steps (Scheme 5.0).



Scheme 5.0: Synthesis of the ester **111**. *Reagents and conditions:* a) LAH, THF, 0 °C to r.t., 16 h then Bu₃SnOTf, 0 °C to r.t., 16 h, 23%; b) MnO₂, CH₂Cl₂, 8 h, quantitative; c) ethyl 2-(triphenylphosphoranylidene)acetate, CH₂Cl₂, r.t., 16 h, 93%.

2.3 STILLE CROSS-COUPLING OF THE BROMIDE **52** AND THE STANNANE **111**

The final step in the synthesis of the bicyclo[4.2.0]octadienes **108** and **109** was the Stille cross-coupling of the vinyl bromide **52** and the vinyl stannane **111** (Table 1.3).



Entry	Catalytic System	Yield
1	$\text{Pd}_2(\text{dba})_3$ (5 mol%), tri(2-furyl)phosphine, 100 °C, 16 h	15%
2	$\text{Pd}_2(\text{dba})_3$ (5 mol%), AsPh_3 , 100 °C, 16 h	12%
3 ^a	$\text{Pd}(\text{OAc})_2$ (10 mol%), PPh_3 , r.t. to 50 °C, 16 h	Trace
4 ^a	$\text{Pd}(\text{OAc})_2$ (10 mol%), PPh_3 , 70 °C, 15 h	Trace
5	PdCl_2 (2 mol%), P^tBu_3 , CsF, CuI, DMF, 45 °C, 15 h	53%

Table 1.3: Stille cross-coupling of **52** and **111**. Reactions performed in toluene as solvent unless otherwise stated. Yield represents a combined yield, in all cases **108:109**=3:2, as determined by ^1H NMR spectroscopy analysis of the isolated material. ^aPolymer bound PPh_3

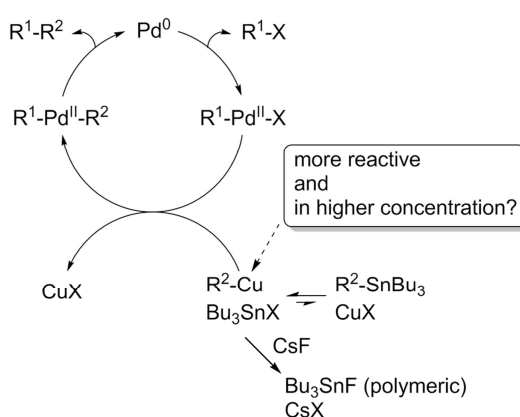
The first protocol investigated utilised a catalytic system comprising of $\text{Pd}_2(\text{dba})_3$ and tri(2-furyl)phosphine (Entry 1, Table 1.3). These conditions had been reported previously by Moses *et al.* for the analogous cross-coupling of the bromide **52** and nitrile **53** in application to the synthesis of prekingianin A (**49**).⁴³ Disappointingly however, these conditions were found not to be amenable to the current system. In application to the cross-coupling of **52** and **111**, the highest yield obtained was 15%.

Similarly to tri(2-furyl)phosphine, triphenylarsine has been shown to drastically improve rates of reaction when compared to the classical triphenylphosphine system.⁷⁰ As such, the reaction was attempted using triphenylarsine as a replacement for tri-2-furylphosphine (Entry 2, Table 1.3). This modification was found to have only minimal effect on the reaction outcome and yields obtained for the transformation continued to

be unsatisfactory. The highest isolated yield obtained under these conditions was 12%. The poor yields were attributed in part to difficulties encountered in purification. The dibenzylidene acetone ligand from the palladium catalyst was observed to co-elute with the product during column chromatography, necessitating repeated purification attempts on the same sample.

The cross-coupling was then attempted using polymer bound triphenylphosphine as a ligand. After stirring at room temperature for 16 h, only a trace amount of the products **108** and **109** was observed by ^1H NMR analysis. As such, the reaction mixture was heated to 50 °C for a further 6 h. After this period, no significant change was observed (Entry 3, Table 1.3). The reaction was then repeated at 70 °C. Again, only a trace of the products **108** and **109** was formed (Entry 4, Table 1.3).

A catalytic system that has been shown to significantly enhance the Stille reaction has been reported by Baldwin *et al.*⁷¹ The methodology utilises the synergistic benefits of copper iodide and caesium fluoride as additives (Scheme 5.1).

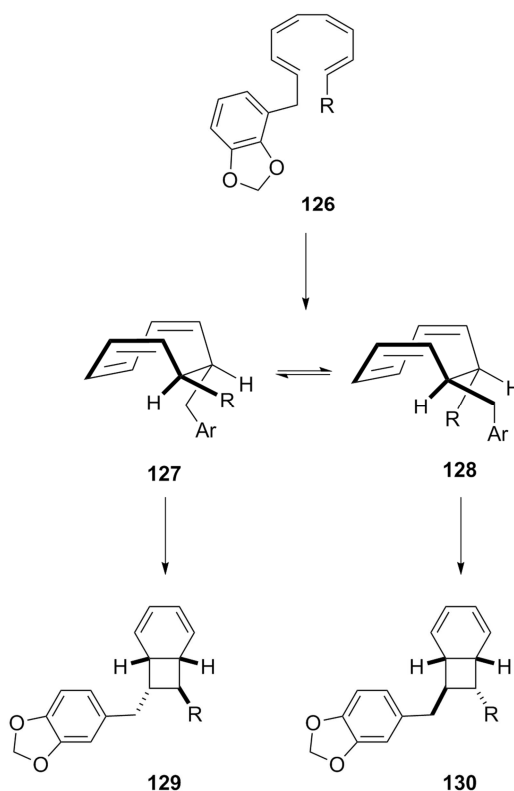


Scheme 5.1: Proposed mechanism for Baldwin's Stille cross-coupling protocol.

Copper iodide is assumed to undergo transmetalation with the vinyl stannane to form a highly reactive organocopper intermediate. The

caesium fluoride is proposed to perform a second transmetalation with the newly formed tin halide by-product. The resulting tributyltin fluoride is observed to precipitate out of solution as a grey polymeric solid, driving the reaction forward by Le Chatelier's principle. This protocol proved to offer an improvement to the cross-coupling of **52** and **111**; purification was simplified and the desired products **108** and **109** were isolated as an inseparable mixture of diastereoisomers in 53% yield (Entry 5, Table 1.3). It should be noted however that this reaction was found to be somewhat capricious and isolated yields ranged from 20-53%. In all cases, the observed ratio of **108:109**=3:2.

It has been proposed that the origin of diastereoselectivity in $8\pi/6\pi$ electrocyclisation cascades is the result of the two conformations which can be adopted by the intermediate cyclooctatrienes, prior to the second (6π) electrocyclisation (Table 1.4).⁷² The cyclooctatriene conformers **127** give the bicyclo[4.2.0]octadienes **129**, whereas the conformers **128** give the bicyclo[4.2.0]octadienes **130**. By considering the results reported both in the literature and herein, it is clear that the influence of the terminal substituent on the tetraenes **126** is significant (Table 1.4).



Entry	R =	129:130
1 ^a	CH ₂ CH ₂ CN	1:1
2 ^b	CH ₂ OTBDPS	3:2
3 ^c	CH ₂ CH ₂ OH	1:1
4	CO ₂ Et	3:2

Table 1.4: Effect of tetraene substitution on the ratio of resulting bicyclo[4.2.0]octadienes.

^aReported by this research group.⁴³ ^bOriginally reported by Parker *et al.*¹⁰ and confirmed in this work (*vide infra* - Section 2.7). ^cReported by Sherburn and Lawrence *et al.*⁴⁸

When the terminal substituent is CH₂CH₂CN or CH₂CH₂OH (Entries 1 and 3 respectively, Table 1.4) the bicyclo[4.2.0]octadienes **129** and **130** are isolated in a 1:1 ratio. When the terminal substituent is CH₂OTBDPS or CO₂Et however (Entries 2 and 4 respectively, Table 1.4) the bicyclo[4.2.0]octadienes **129** and **130** are isolated in a 3:2 ratio. One possible explanation for this diastereoselectivity is that cyclooctatriene conformers **128** are less favoured in the case of entries 2 and 4, as a

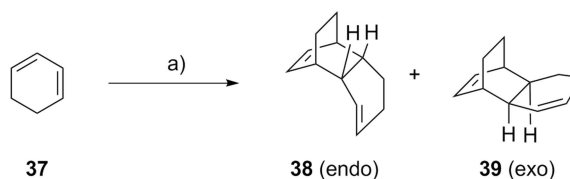
result of steric repulsion between the comparatively large functional groups and the triene.

With the bicyclo[4.2.0]octadienes **108** and **109** in hand, conditions to bring about the Diels-Alder dimerisation of these compounds was next investigated.

2.4 STUDIES INTO DIELS-ALDER DIMERISATION

2.4.1 Dimerisation of 1,3-Cyclohexadiene (**37**)

As part of our investigations into the dimerisation of the proposed kingianin monomers, the dimerisation of 1,3-cyclohexadiene (**37**) was studied (Table 1.5).



Entry	Conditions	Yield	<i>Endo:Exo</i>
1	neat, 200 °C, 24 h	30%	4:1
2	TBPA, CH ₂ Cl ₂ , 0 °C, 15 min	67%	5:1

Table 1.5: Dimerisation of 1,3-cyclohexadiene (**37**).

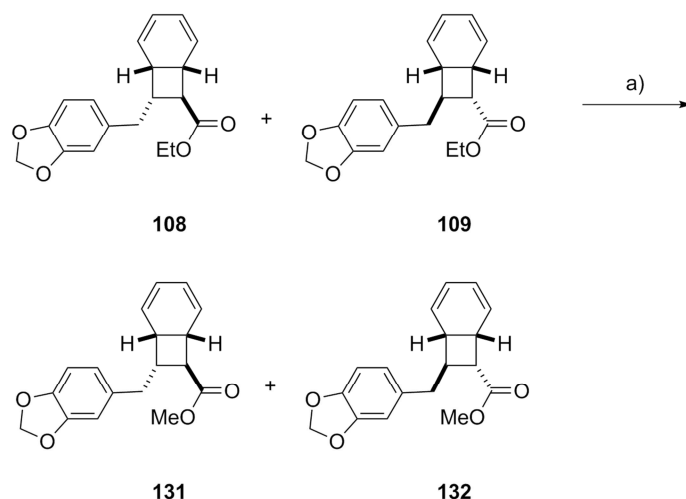
Initially the reaction was performed using a conventional thermal protocol (Entry 1, Table 1.5). As such, 1,3-cyclohexadiene (**37**) was heated at 200 °C in a sealed glass ampoule for 48 h. ¹H NMR analysis of the crude reaction mixture indicated that some starting material was still present after this period. Following its removal under reduced pressure, the dimeric products **38** and **39** were isolated in 30% yield (*endo:exo* = 4:1) (Entry 2,

Table 1.5). This is in accordance to the results reported by Hammond *et al.* (*cf.* 32%, *endo:exo* = 4:1).²⁴

The reaction was then repeated under radical cation conditions using TBPA (**40**). In accordance with the procedure reported by Bauld *et al.*, the reaction was carried out at 0 °C in CH₂Cl₂ for 15 min.³⁴ A mixture of Diels-Alder adducts were obtained in 67% yield (*endo:exo* = 5:1), which is in accordance with the published results (*cf.* 70%, *endo:exo* = 5:1). Having established that the literature reports for both thermally and TBPA (**40**)-catalysed dimerisation of 1,3-cyclohexadiene (**37**) could be reliably reproduced, an investigation into the corresponding dimerisation of the bicyclo[4.2.0]octadienyl esters **108** and **109** was undertaken.

2.4.2 Dimerisation Studies on the Bicyclo[4.2.0]octadienes **108** and **109**

With the bicyclo[4.2.0]octadienes **108** and **109** in hand (*vide supra* – Section 2.3), a procedure to bring about their Diels-Alder dimerisation was sought after. In light of the reported resistance of prekingianin A (**49**) to a range of thermal Diels-Alder conditions, our focus became the RCDA reaction. Perhaps the most promising reagent for this purpose was TBPA (**40**). In accordance with the procedure used to bring about the dimerisation of 1,3-cyclohexadiene (**37**), the esters **108** and **109** were added to a solution of TBPA (**40**) in CH₂Cl₂ at 0 °C (Scheme 5.2).



Scheme 5.2: Attempted RCDA dimerisation of the esters **108** and **109**. *Reagents and conditions:* a) TBPA, CH₂Cl₂, 0 °C, r.t., 30

In contrast to the reaction of 1,3-cyclohexadiene (**37**), after 15 minutes TLC analysis showed that the starting materials were still present. After 30 minutes, the reaction mixture was quenched with NaOMe/MeOH (25% w/w). Following purification by column chromatography, the transesterified compounds **131** and **132** were recovered from the reaction mixture in 63%. These compounds were presumably formed during quenching of the reaction mixture with methoxide.³⁴ The remaining material was recovered as a highly polar, inseparable mixture of products.

Logical modifications appeared to be an increase in reaction time and the exchange of NaOMe/MeOH for NaOEt/EtOH (25% w/v). After 1 hour reaction time under the same conditions, complete consumption of the starting material was observed by TLC. Disappointingly however, no dimeric product was detectable by ¹H NMR spectroscopy or HRMS. Again, a complex mixture of products was obtained. This result was consistent with the previously unreported observations of Moses *et al.* that prekingianin A (**49**) also failed to yield Diels-Alder dimers upon treatment with TBPA (**40**).

It was at this stage of our investigations that the first total synthesis of kingianin A was reported by Parker *et al.*¹⁰ (*vide supra* - Section 1.6.2). In the previously described route to the bicyclo[4.2.0]octadienyl esters **108** and **109**, the quantities of material that could be obtained was severely reduced by the poorly yielding (53%) and capricious, late stage Stille cross-coupling reaction (*vide supra* - Section 2.3). In contrast, the analogous Suzuki-Miyaura cross-coupling utilised by Parker *et al.* was reported to occur in 80% yield.¹⁰ It seemed probable therefore that this route could provide a more substantial amount of material to be used for electrochemical investigations. The Suzuki-Miyaura cross-coupling approach also offered the benefit of avoiding the use of highly toxic organostannanes.

2nd Generation Synthesis – Suzuki-Miyaura Cross-Coupling Route

In light of the comparably high yield reported by Parker *et al.* for the cross-coupling of the vinyl iodide **57** and the boronic ester **58** (Figure 2.5),¹⁰ these compounds became the targets of our synthetic efforts.

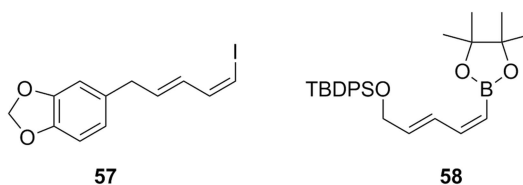
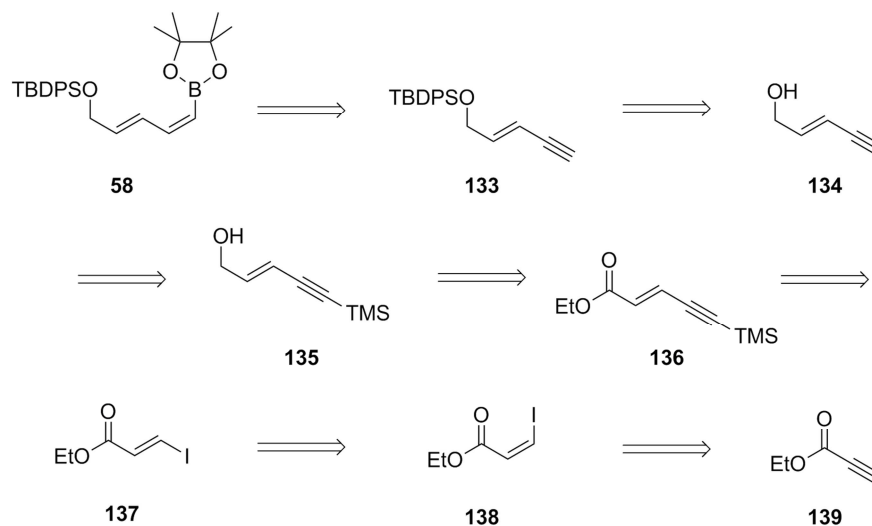


Figure 2.5: Synthetic targets for the Suzuki-Miyaura cross-coupling route.

2.5 SYNTHESIS OF THE BORONIC ESTER **58**

A route to the boronic ester **58** from the enynol **134** (Scheme 5.3) was originally reported by McDonald *et al.* as part of the group's synthesis of the natural product fostriecin.⁷³

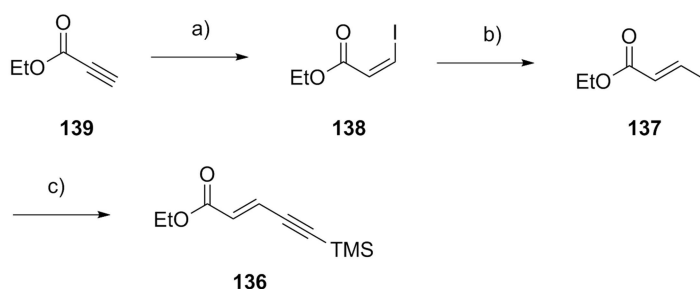


Scheme 5.3: Retrosynthetic analysis of the boronic ester **58**.

The enynol **134** can itself be formed *via* reduction and desilylation of ethyl ester **136**, itself available from ethyl propynoate (**139**) as reported by Trost *et al.*⁷⁴

2.5.1 Synthesis of the Enynyl Ester **136**

Following the reported procedure,⁷⁴ synthesis of the enynyl ester **136** began with the commercially available compound ethyl propynoate (**139**) (Scheme 5.4).

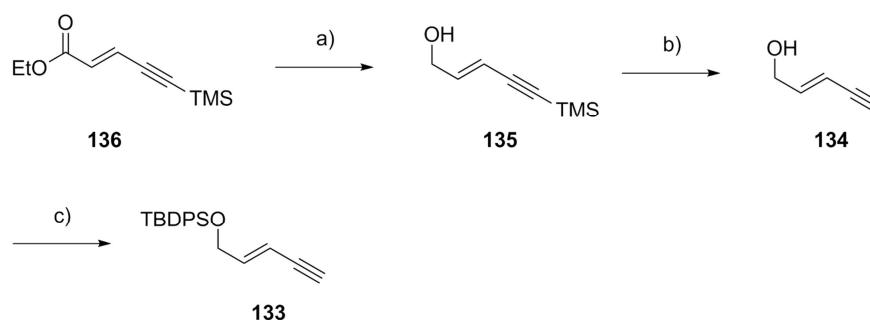


Scheme 5.4: Synthesis of the enynyl ester **136**. *Reagents and conditions:* a) NaI, AcOH, 70 °C, 6 h, 90%; b) HI, toluene, 80 °C, 8 h, 83%; c) PdCl₂(PPh₃)₂ (1 mol%), CuI (0.5 mol%), TMS-acetylene, Et₃N, 85 °C, 15 h, 88%.

The starting material **139** was treated with a solution of sodium iodide in acetic acid to form selectively the *Z*-vinyl iodide **138** in 90% yield, without the need for further purification. An acid-catalysed isomerisation was performed with hydroiodic acid to yield the *E*-vinyl iodide **137** in 83% yield. Finally, synthesis of the ethyl ester **136** was completed *via* the Sonogashira cross-coupling of **137** with trimethylsilyl acetylene. This reaction also proceeded smoothly to provide the ethyl ester **136** in 88% yield.

2.5.2 Synthesis of the Protected Enynyl Alcohol **133**

With the ethyl ester **136** in hand, synthesis of the protected enynol precursor **133** to the desired Suzuki-Miyaura cross-coupling partner **58** could be undertaken (Scheme 5.5).



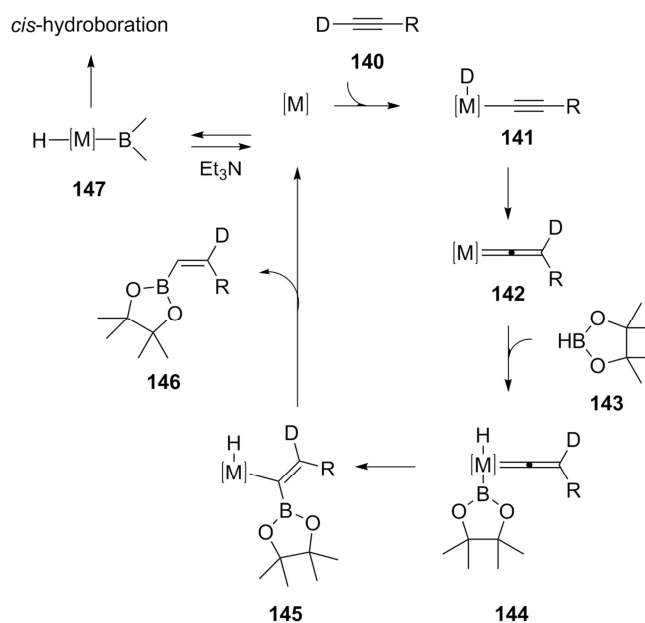
Scheme 5.5: Synthesis of protected enynol **133**. *Reagents and conditions:* a) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to r.t., 2 h, 61%; b) TBAF·3H₂O, THF, $0\text{ }^\circ\text{C}$ to r.t., 2 h then c) TBDPSCI, imidazole, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to r.t., 65% (over two steps).

The ethyl ester **136** was reduced with DIBAL-H to yield the corresponding alcohol **135** in 61% yield. Removal of the TMS protecting group was achieved with TBAF trihydrate. The resulting enynol **134** was found to be volatile and despite clean conversion (determined by TLC), low crude yields were obtained following rotary evaporation of the crude residue. As such, the best yields were obtained when the crude residue was only partially concentrated and then carried directly on to the next step. Accordingly, the residue of **134** was added dropwise to a $0\text{ }^\circ\text{C}$ solution of TBDPSCI and imidazole. This reaction proceeded smoothly to yield the silyl protected alcohol **133** in 65% yield over two steps.

2.5.3 Synthesis of the Boronic Ester **58** – Hydroboration

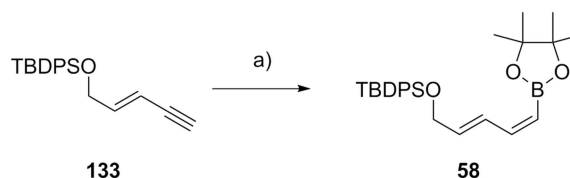
With the TBDPS protected enynol **133** in hand, only the hydroboration of this compounds alkyne functionality was required to form the Suzuki-Miyaura cross-coupling partner **58**. The procedure utilised by Parker *et al.*¹⁰ for the conversion of protected enynol **133** into the desired (*Z*)-dienylboronic ester **58** is a hydroboration methodology that was originally reported by Miyaura *et al.*⁷⁵

Due to *anti*-Markovnikov and *syn*-addition, direct hydroboration of an alkyne will result in (*E*)-1-alkenylboranes.⁷⁶ The synthesis of (*Z*)-1-alkenylboranes therefore had previously required a two-step process before the methodology of Miyaura *et al.* was reported. The authors found the best performing catalyst to be $[\text{Rh}(\text{cod})\text{Cl}]_2\text{-4P}^i\text{Pr}_3$. In the presence of an excess of Et_3N , this complex was proposed to carry out the formal *trans*-hydroboration *via* a mechanism proceeding through the vinylidene complex **142** (Scheme 5.6). This mechanistic proposal was supported by a deuterium labelling study.



Scheme 5.6: Proposed *trans*-hydroboration catalytic cycle.

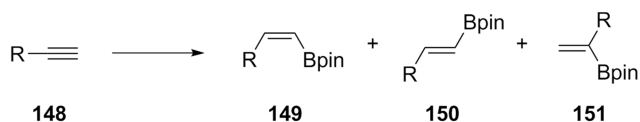
The methodology has previously been applied to the synthesis of the target boronic ester **58**⁷³ but the reported yield of 68% could not be replicated (Scheme 5.7).



Scheme 5.7: Synthesis of Suzuki-Miyaura cross-coupling partner **58** via hydroboration.

Reagents and conditions: $[\text{Rh}(\text{cod})\text{Cl}]_2$ (1.5 mol%), $i\text{Pr}_3\text{P}$ (6 mol%), Et_3N , pinacolborane, cyclohexane, r.t., 4.5 h, 44%.

It was found that handling of the triisopropylphosphine by plastic syringe resulted in a non-selective hydroboration. Here, three products were observed by ^1H NMR spectroscopy. These compounds correspond to the three isomers that were reported by Miyaura *et al.* when a non-selective catalytic system was employed (Scheme 5.8).



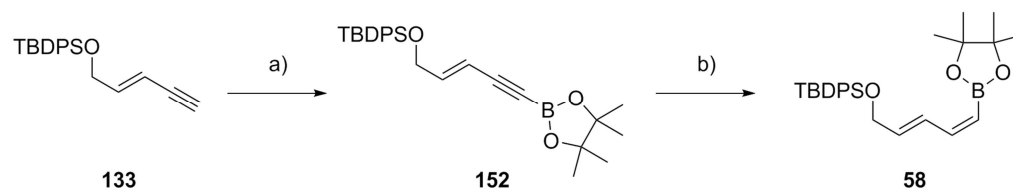
Scheme 5.8: Range of products obtained when non-selective hydroboration was observed.

This problem was overcome by using an argon flushed glass syringe to handle this sensitive reagent. Freshly distilled pinacol borane was also found to be essential, otherwise only starting material was recovered.

Despite adhering to these modifications, the maximum yield obtained following column chromatography was 44%, which can be attributed, in part, to the observed instability of this species. Despite efforts to minimise the compound's exposure to light and elevated temperature, a colour change of yellow to light brown was observed within a few hours of purification. Due to the moderate yield obtained for this reaction, an alternative method for the synthesis of the target boronic ester **58** was also investigated.

2.5.4 Synthesis of the Boronic Ester **58** - Alkynyl Dioxaborolane Reduction

An alternative route to the target boronic ester **58** has been reported by Lopez.⁷⁷ This two-step process involves formation of the alkynyl boronic ester **152** followed by its stereoselective reduction using Schwartz's reagent (Scheme 5.9).



Scheme 5.9: Reported synthesis of Suzuki-Miyaura cross-coupling partner **58** via reduction of the alkynyl boronic ester **152**. *Reagents and conditions:* a) ⁿBuLi, isopropoxypinacolborolane, Et₂O, -78 °C to r.t., 4 h, quantitative; b) Cp₂ZrHCl, THF, r.t., 4 h, 68%.

The functionalisation of the alkyne is performed through generation of the lithium acetylide by treatment with ⁿBuLi followed by trapping with the dioxaborolane **153** (Figure 2.6).

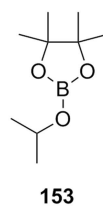
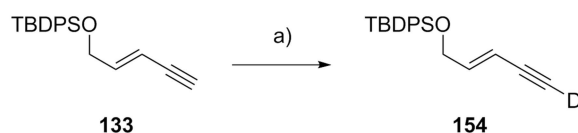


Figure 2.6: 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**153**).

Despite several attempts at reproducing the reported procedure, no evidence of the product was ever detected, either by HRMS or by ¹H NMR spectroscopy. Instead, complete recovery of starting material was observed in every case. In order to test whether the intermediate lithium acetylide was being formed, an experiment was performed where the starting material was treated with ⁿBuLi and then quenched with D₂O.



Scheme 6.0: Formation of deuterated alkyne **154**. *Reagents and conditions:* $n\text{BuLi}$, D_2O , Et_2O , $-78\text{ }^\circ\text{C}$ to r.t., 30 min.

It was observed in the crude ^1H NMR spectrum that the signal corresponding to the acetylenic proton had almost completely disappeared. This result suggested that failure to form the desired alkynyl borolane **152** was not due to failure in forming the intermediary acetylide. Another possibility was that the desired compound **152** was in fact being formed but then hydrolysed during the work-up procedure to reform the starting material. In accordance to the reported procedure, work-up involved quenching the reaction mixture with a solution of HCl in Et_2O . It was speculated that the accumulation of moisture in the ether could be responsible for the observed result. Despite changing to a fresh bottle of HCl in Et_2O however, only the starting material **133** could be recovered. The hypothesis that the product was being formed but then hydrolysed was further examined by taking a small sample from the reaction vessel (before quenching), concentrating it under reduced pressure and then running a ^1H NMR experiment. Again, no sign of the desired alkynyl borolate **152** could be observed. These results suggested that the inhibiting factor was likely to be the isopropoxyborolane **153**. This reagent had previously been purified by distillation however (which served to remove the trace impurity of isopropanol) and appeared to have a high level of purity (as determined by ^1H and ^{11}B NMR analysis).

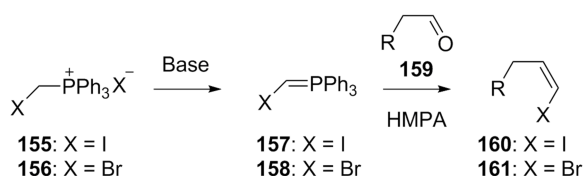
In light of the continued difficulties in bringing about this transformation, it was decided that the previously reported hydroboration route (*vide supra* – Section 2.5.3) would be used for the synthesis of the desired boronic ester

58. Subsequently, investigations into the Suzuki-Miyaura cross-coupling of this compound were undertaken (*vide infra* – Section 2.7).

2.6 SYNTHESIS OF THE DIENYL IODIDE CROSS-COUPLING PARTNER **57**

2.6.1 Stork-Zhao Olefination of the Aldehyde **113**

One method for the synthesis of (*Z*)-vinyl halides from the corresponding aldehydes is the Stork-Zhao olefination.⁷⁸ This variation of a Wittig reaction makes use of an unstabilised phosphonium ylide **157/158**. This species is generated *in situ* from its halide salt **155/156**, usually with NaHMDS or KHMDS. The reaction often makes use of a coordinating co-solvent such as hexamethylphosphoramide (HMPA) (Scheme 6.1).



Scheme 6.1: Generalised Stork-Zhao-Wittig reaction.

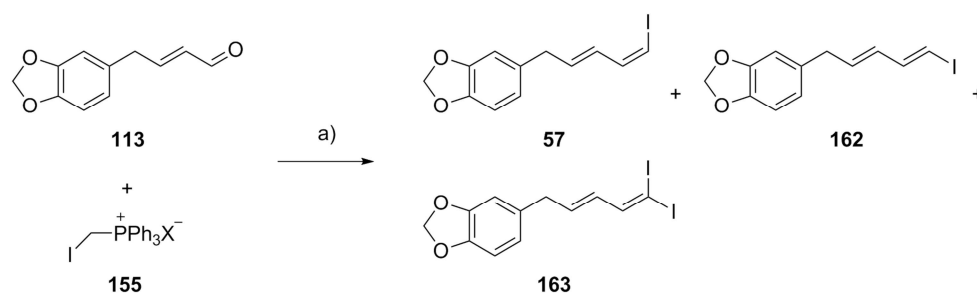
A range of different experimental procedures for the Stork-Zhao reaction were applied to the synthesis of (*E,Z*)-iododiene **57** and (*E,Z*)-bromodiene **52**. It was observed that the results obtained varied enormously depending on which procedure was used.

Initially, the syntheses of iododiene **57** and bromodiene **52** were investigated using a procedure where the salt **155/156** was added in one portion to a suspension of KO^tBu in THF at 0 °C.⁷⁹ After 10 min, the aldehyde **113** was added as a solution in THF. In the case of both the bromo and the iodo equivalents, no product could be observed and only

the starting material was recovered. It was speculated that the poor solubility of the base and/or the ylide precursor **155/156** could be responsible.

It has been reported that the addition of HMPA can improve the results of a Stork-Zhao olefination.⁷⁸ This additive is known to selectively solvate cations and in doing so increase the relative nucleophilicity of the corresponding anion. The above procedure was repeated with the addition of HMPA but again only starting material could be recovered.

Several alternative experimental procedures have been reported for carrying out the Stork-Zhao reaction using NaHMDS as the base. Three of these procedures were applied to the synthesis of iododiene **57** (Table 1.6).



Entry	Procedure	Equivs. of 155	Equivs. of Base	Yield	162:57:163
1 ^a	1	1.25	1.25	0-56%	6:1:0
2 ^b	2	2.1	2.1	69%	0:4:1
3 ^c	3	1.5	1.5	5%	0:21:1
4 ^c	3	1.5	1.7	Trace	N/A
5 ^c	3	1.7	1.7	24%	0:12:1
6 ^c	3	2.1	2.1	2%	0:0:1

Table 1.6: Stork-Zhao synthesis of (E,Z)-iododiene **57**. *Reagents and conditions:*

a) NaHMDS, HMPA, THF, $-30\text{ }^{\circ}\text{C}$ to r.t., 1 h. Yield represents isolated yields. Ratio of products determined by integration of characteristic peaks in ^1H NMR spectroscopy after column chromatography. ^aTHF:HMPA = 3:1. ^bNo HMPA was used in this experiment. ^cTHF:HMPA = 7:1.

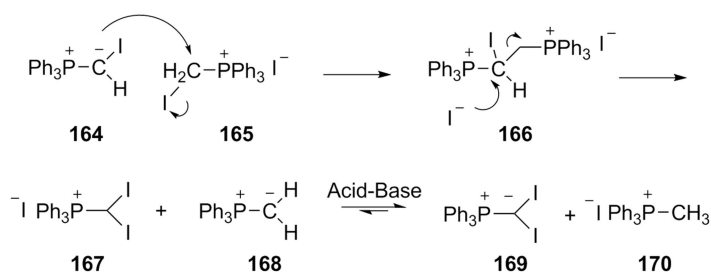
Procedure 1 (Classical Stork-Zhao⁷⁸): NaHMDS is added slowly to a room temperature suspension of the iodo salt **155** in THF. After 1 min, the reaction mixture was cooled to $-60\text{ }^{\circ}\text{C}$ and HMPA was added. The reaction mixture was then cooled further to $-78\text{ }^{\circ}\text{C}$ and the aldehyde **113** was added as a solution in THF. Following this procedure, the desired (E,Z)-iododiene **57** was formed as the minor product with the major product being the E,E-iododiene **162** (Entry 1, Table 1.6).

An alternative procedure was utilised by Menche in his work on the total synthesis of etnangien,⁸⁰ the reaction is carried out under “salt-free” conditions.

Procedure 2 ("Salt-free" conditions⁸¹): To a suspension of the iodo-salt **155** in THF at $-30\text{ }^{\circ}\text{C}$ was added NaHMDS. After stirring for 15 min, the supernatant "salt-free" ylide is removed and added to a solution of the aldehyde in THF at $-78\text{ }^{\circ}\text{C}$.

Under these conditions, the desired (*E,Z*)-iododiene **57** was formed selectively with respect to the (*E,E*)-iododiene **162** but in this case was recovered alongside the geminal diiododiene **163** (Entry 2, Table 1.6). In all repeat reactions, the ratio of these two products was consistent but the reaction was found to be highly irreproducible with respect to yield. Several attempts to repeat the reaction under these conditions returned only starting material and other attempts returned a yield of less than 10%. This was despite attempting to carry out the procedure in an identical manner each time.

Interestingly, in the same publication where Menche *et al.* utilise the "salt-free" conditions (Procedure 2) they also demonstrate the capricious nature of this reaction. When the same conditions were applied to a different substrate, they too observed the formation of a geminal diiodo product. Similar results had been reported in the literature⁸² and this lead the authors to propose a mechanism to explain the formation of this unwanted side-product (Scheme 6.2).



Scheme 6.2: Proposed mechanism to explain the formation of the geminal diiodo alkene species.

According to their proposal, the salt **165** could be attacked by the ylide **164**, displacing an iodide ion which could in turn perform an S_N2 reaction on the newly generated species **166**. This process would release an equivalent of the doubly protonated ylide **168** and one of the diiodo salt **167**. Acid base equilibrium between these species which would result in the formation of the salt **170** and the geminal diiodo ylide **169**. Upon reaction with an aldehyde, the diiodo ylide **169** would generate the geminal diiodo alkene species that was observed.

Based on this proposal, Menche *et al.* formulated an alternative experimental procedure which would minimise the amount of the iodo salt **165** present at the time that the ylide **164** was being formed.⁸⁰ This procedure would later be utilised by Parker *et al.* in their synthesis of kingianin A (**1**).¹⁰

Procedure 3 (HMPA salt suspension⁸⁰):

A suspension of the iodo salt **155** in HMPA was added dropwise to a solution of NaHMDS in THF at $-10\text{ }^{\circ}\text{C}$. After 1 min, the reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and the aldehyde was added dropwise. After 30 min, the reaction mixture was warmed to $-20\text{ }^{\circ}\text{C}$ and quenched by the addition of a saturated solution of $\text{NH}_4\text{Cl}_{(\text{aq})}$.

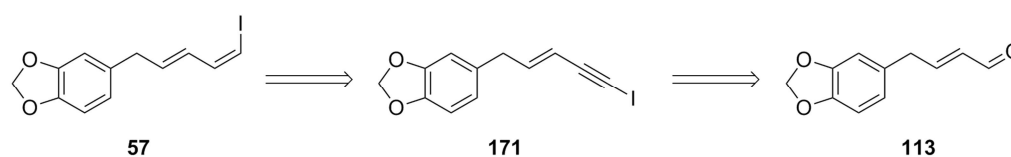
Under these conditions, the (*E,E*):(*E,Z*) selectivity was excellent with no sign of the undesired (*E,E*) compound **162** being observed by ^1H NMR spectroscopy. Although formation of the diiodo equilvant **163** was still not entirely inhibited, this compound was formed in a much lower equivalence (**57**:**163**=21:1) than when procedure 2 was applied. Despite the satisfactory selectivity, the overall yield of the reaction was now extremely poor (Entry 3, Table 1.6). It was speculated that this low yield could be

due to the ylide not being completely formed. As such, the reaction was repeated using an increased amount of base. As previously reported in the literature,⁷⁷ this proved to suppress the reaction all together and only starting material was recovered (Entry 4, Table 1.6). When the ratio of salt and base were kept at 1:1 but 1.7 equivalents of each were used, the best overall results were obtained. The target compound **57** was obtained in 24% yield as (**57**:**163**=12:1) (Entry 5, Table 1.6). When the number of equivalents of these reagents was increased further however, the reaction was almost completely suppressed and the only product detected was the diiododiene **163**.

Due to the difficulties experienced in bringing about this transformation, an alternative synthesis of the vinyl iodide **57** was investigated.

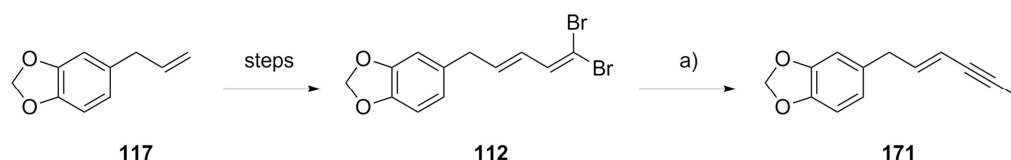
2.6.2 Synthesis of the Iodoalkyne **171**

A reported route to (*E,Z*)-iododienes involves the stereoselective reduction of the corresponding (*E*)-iodoenynes, themselves available from α,β -unsaturated aldehydes in two steps *via* a modified⁸³ Corey-Fuchs⁸⁴ procedure (Scheme 6.3).



Scheme 6.3: Revised retrosynthetic analysis of (*E,Z*)-iododiene **57**.

The iodoenynone **171** was synthesised from the dibromide **112**, itself available from safrole (**117**) in 4 steps (*vide supra* – Section 2.1).

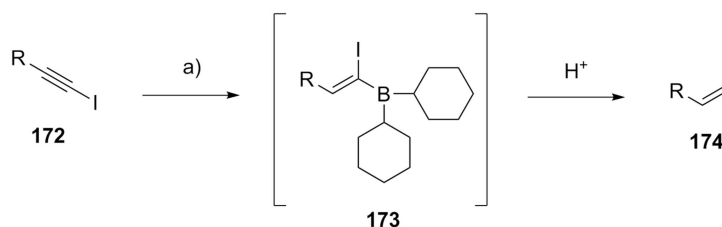


Scheme 6.4: Synthesis of iodoalkyne **171**. *Reagents and conditions:* a) $n\text{BuLi}$, I_2 , THF, $-78\text{ }^\circ\text{C}$ to r.t., 4 h, 59%.

Formation of the iodoalkyne functionality in **171** was achieved by treatment of **112** with $n\text{BuLi}$ and I_2 . In this reaction, one equivalent of base deprotonates the alkenyl proton to eliminate the first bromine, followed by lithium halogen exchange with a second equivalent of $n\text{BuLi}$. The intermediate lithium acetylide was then quenched with iodine to yield the iodoalkyne **171** in 93% yield.

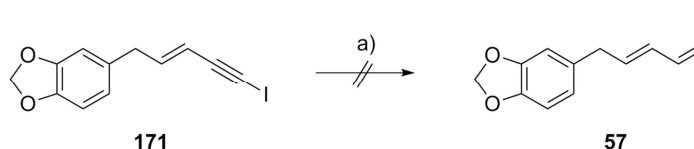
2.6.3 Stereoselective Reduction of the Iodoalkyne **171**

With the iodoalkyne **171** in hand, the stereoselective reduction of this compound was investigated. One method for the formation of (*Z*)-vinyl iodides **174** from the corresponding iodoalkynes **172** utilises bis(cyclohexyl)borane.⁸⁵ This reagent can be generated *in situ* from borane-DMS complex and cyclohexene. The reaction proceeds initially through hydroboration of the alkyne. The resulting boronic compound is then protodeborylated by reaction with glacial acetic acid (Scheme 6.5).⁸⁶



Scheme 6.5: Bis(cyclohexyl)borane reduction of iodoalkynes **172**.

When this procedure was applied to iodoalkyne **171** however, complete decomposition of the starting material was observed, with no indication that the product was being formed (Scheme 6.6).



Scheme 6.6: Attempted bis(cyclohexyl)borane reduction of the iodoalkyne **171**. *Reagents and conditions:* $\text{BH}_3\cdot\text{DMS}$, cyclohexene, Et_2O , $0\text{ }^\circ\text{C}$ to r.t., 30 min.

The reaction conditions were considered too harsh and as such a milder approach to bring about the transformation was sought after. Another class of reductants that have been used to bring about similar reactions utilise diimide. This species can either be employed directly or generated *in situ*. One such reagent that is known to bring about these reactions in a mild manner is *o*-nitrobenzene sulfonylhydrazine (NBSH) (**175**) (Figure 2.8).⁸⁷

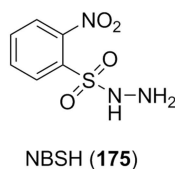
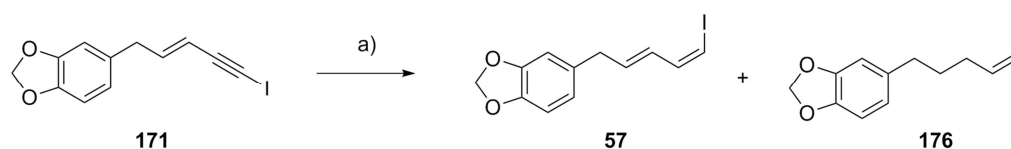


Figure 2.8: *o*-Nitrobenzene sulfonylhydrazine (NBSH) (**175**).

In polar solvents, NBSH (**175**) releases diimide *via* decomposition to *o*-nitrobenzenesulfinic acid. This process occurs at room temperature or below and at neutral pH, making it an attractive choice of reductant for sensitive substrates. However, when employing a standard protocol⁸⁷ to the reduction of iodoalkyne **171**, it was observed that alongside the target dienyl iodide **57**, the over-reduced species **176** was also being formed (Table 1.7).



Entry No.	Equivs. of 175	Reaction Time	Consumption of 171	Ratio of 57:176
1 ^a	2	18 h	100%	2.5:1
2 ^a	1	18 h	28%	18:1
3	1	30 h	0%	N/A
4	2	30 h	19%	1:0
5	2	48 h	39%	12.7:1
6	2	71 h	75%	6.7:1
7	2	115 h	90%	4.9:1
8	2	124 h	100%	3.5:1
9	5	29 h	27%	1:0
10	5	48 h	54%	8.6:1
11	5	124 h	100%	2.2:1

Table 1.7: NBSH (**175**) reduction of iodoalkyne **171**. *Reagents and conditions:* a) NBSH (**175**), Et₃N, IPA:THF = 1:1, 4 °C (Unless otherwise stated). ^aReaction performed at r.t. Ratio of products (**57:176**) and consumption of starting material **171** determined by integration of characteristic peaks in crude ¹H NMR spectrum.

It was also found this unwanted side product **176** was inseparable from the desired product **57** by silica gel column chromatography. In an attempt to suppress the formation of this over-reduced compound, the number of equivalents of NBSH (**175**), the reaction temperature and reaction time were varied (Table 1.7). This optimisation process was made more difficult by the fact that the desired product **57** and the over-reduced species **176** were indistinguishable by thin layer chromatography (TLC) and neither could be detected by ESI mass spectrometry, presumably due to their thermal instability.

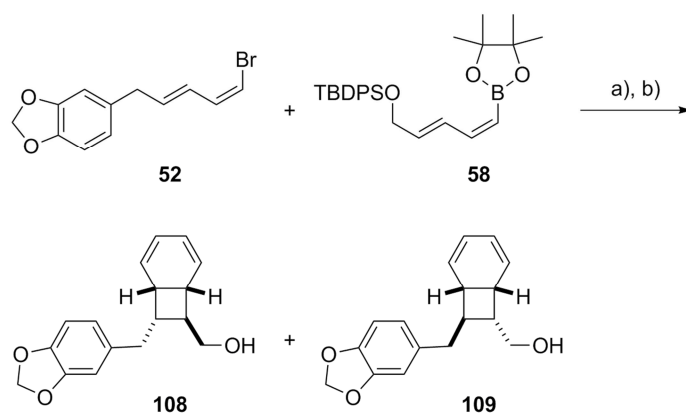
Despite the literature precedent for using at least two equivalents of NBSH (**175**), it seemed likely that over-reduction was being performed by the excess reagent, after the initial alkyne reduction can occurred. To test this, the reaction was performed using exactly one equivalent of NBSH (Entry 2, Table 1.7). It was found that whilst the reaction only went to 28% completion, the over-reduced species could still be observed. This result indicated that despite being a slower reaction, the undesired alkene to alkane reduction was occurring in the presence of unreacted iodoalkyne. It was speculated that by reducing the reaction temperature it may be possible to suppress the side reaction whilst allowing the desired transformation to reach completion. When the reaction was performed with 1 equivalent of NBSH (**175**) at 4 °C, no reaction was observed after 30 h (Entry 3, Table 1.7). With two equivalents however, the reaction had reached 19% completion in the same amount of time and at the same temperature. In this case, only the target product **57** was observed (Entry 4, Table 1.7). Disappointingly however, when the reaction time was increased from 30 h to 48 h, the unwanted side reaction started to occur (Entry 5, Table 1.7). Unsurprisingly, as the reaction time was increased, percentage consumption went up but the ratio of the target compound **57** to the over-reduced species **176** went down (Entries 5-8, Table 1.7). The same trend was observed when 5 equivalents of NBSH (**175**) was employed (Entries 9-11, Table 1.7). The best result was achieved using 5 equivalents of NBSH (**175**); after 29 h at 4 °C, 27% of the starting material had been consumed and none of the over-reduced species **176** was observed (Entry 9, Table 1.7).

Under these optimised conditions, the overall yield for conversion of the aldehyde **113** to the vinyl iodide **57** was 15% over three steps. The corresponding vinyl bromide **52** on the other hand could be synthesised

from the same aldehyde **113** in 69% yield over two steps (*vide supra* – Section 2.1). For this reason, the focus became the Suzuki-Miyaura cross-coupling of the vinyl bromide **52** and the boronic ester **58**.

2.7 SUZUKI-MIYAJURA CROSS-COUPPLING OF THE VINYL BROMIDE **52** AND THE BORONIC ESTER **58**

With the boronic ester **58** and the vinyl bromide **52** in hand, the cross-coupling of these compounds under Suzuki-Miyaura conditions was investigated. The analogous cross-coupling of the boronic ester **58** and the vinyl iodide **57** has been utilised by Parker *et al.*¹⁰ and the conditions provided the starting point for these experiments. It should be noted that in Parker's work, following an aqueous work-up, the crude cross-coupling product was passed through a short silica plug and then subjected to desilylation with TBAF·3H₂O (this was presumably to aid in separation; a number of compounds with similar R_f values were observed by TLC in the cross-coupling of **58** and **52**). In order to make a direct comparison to the work of Parker *et al.*, the same strategy was adopted here (Table 1.8). As such, the reported yields are those obtained over two steps.



Entry	58:52	Conditions	Yield
1	1.5:1	Pd(PPh ₃) ₄ , NaOH, 90 °C	14%
2	1.5:1	Pd(PPh ₃) ₄ , TIOEt, r.t., 15 h	Minimal Conversion ^a
3	3:1	Pd(PPh ₃) ₄ , TIOEt, r.t.	Minimal Conversion ^a
4	1.5:1	Pd(PPh ₃) ₄ , TIOEt, 90 °C, 18 h	57%
5	3:1	Pd(PPh ₃) ₄ , TIOEt, 90 °C, 18 h	83%

Table 1.8: The Suzuki-Miyaura cross-coupling of the vinyl bromide **52** and the boronic ester **58**. 10 mol% Pd(Ph₃)₄ in each case. Yield represents isolated yield over two steps. *Reagents and conditions:* a) see table; b) TBAF·3H₂O, THF, 0 °C to r.t., 4 h. ^aDetermined due to large amounts of unreacted **52**.

In contrast to the 80% yield obtained with the iodo equivalent **57**, the bromide **52** was found to undergo cross-coupling to **58** in only 14% yield (Entry 1, Table 1.8). This is perhaps not surprising; brominated substrates often perform less well in palladium-catalysed cross-coupling reactions in comparison to their iodinated equivalents.⁸⁸

The use of thallium ethoxide as a base in the Suzuki-Miyaura reaction has been shown to vastly improve yields, shorten reaction times and facilitate room temperature procedures.⁸⁹ As such, the use of this reagent was investigated. Initially, the standard protocol reported by Roush *et al.* was applied. As such, the cross-coupling partners were mixed in a solution of THF and H₂O (3:2) and then degassed. To this was added first Pd(PPh₃)₄

and then thallium ethoxide. The reaction mixture was allowed to stir at room temperature.

In each of the “successful” cases reported by Roush, the reaction had reached completion within 30 min. In the case of the substrates **52** and **58** however, a large amount of unreacted bromide **52** remained after 30 minutes (determined by TLC and ^1H NMR analysis of the crude reaction mixture). Furthermore, allowing a further 15 hours reaction time made no discernible change to the reaction mixture (Entry 2, Table 1.8).

Roush *et al.* did however observe that in certain cases, the thallium boronate intermediate was insoluble in a wide range of solvents. In these cases, the authors found it necessary to increase the number of equivalents of boronic ester relative to the halide. As such, the cross-coupling of the bromide **52** and the boronic ester **58** was repeated with 3 equivalents of **58**. This modification was found not to affect the reaction outcome however. Again, only minimal conversion was achieved (Entry 3, Table 1.8).

Since it was presumed that the failure of the reaction was due to the insolubility of the intermediate “ate” complex, the reaction was next attempted at 90 °C, with an aim to improving the solubility of this species. Thus, **58** and **52** (1.5:1) were subjected to the thallium ethoxide promoted conditions and heated at 90 °C. Gratifyingly, the bromide **52** was observed to be consumed under these conditions and following work-up, desilylation and purification, the products **108** and **109** (3:2) were obtained in 57% yield (Entry 4, Table 1.8).

In order to try and improve upon this result, the same conditions were applied to a 3:1 mixture of **58** and **52** (Entry 5, Table 1.8). Under these conditions, the products **108** and **109** (3:2) were obtained in 83% yield.

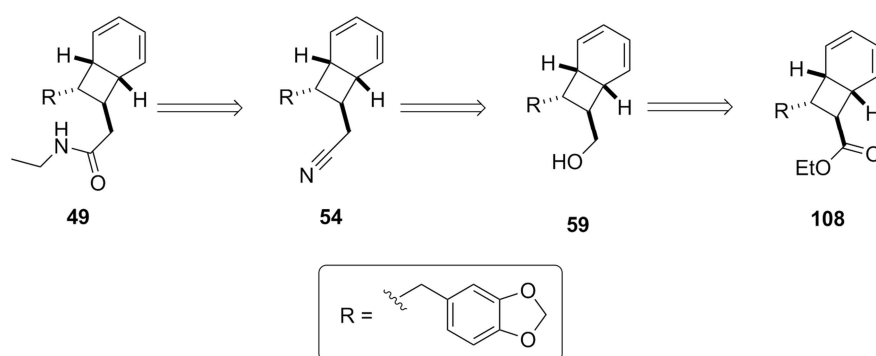
With these compounds in hand, conditions to bring about the target Diels-Alder dimerisation *via* electrolysis could be investigated (*vide infra* – Section 2.8).

2.8 TOWARDS THE SYNTHESIS OF PREKINGIANIN A (49)

It was desirable to study the redox behaviour of prekingianin A (**49**) and investigate the possibility of bringing about its dimerisation *via* electrolysis. It was envisaged that a tin free route to prekingianin A (**49**) could be developed that was divergent with respect to the successfully applied Suzuki-Miyaura cross-coupling route to the bicyclo[4.2.0]octadienyl alcohols **108** and **109**.

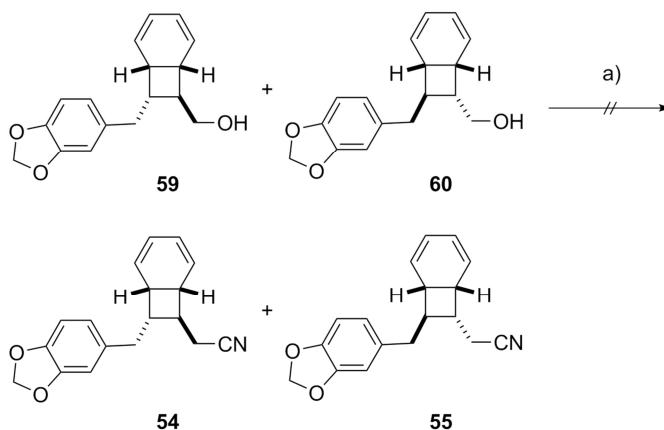
2.8.1 Functional Group Interconversion of Bicyclo[4.2.0]octadienes.

It has been previously reported by this research group that prekingianin A (**49**) can be formed from the nitrile **54** (Scheme 6.7).⁴³



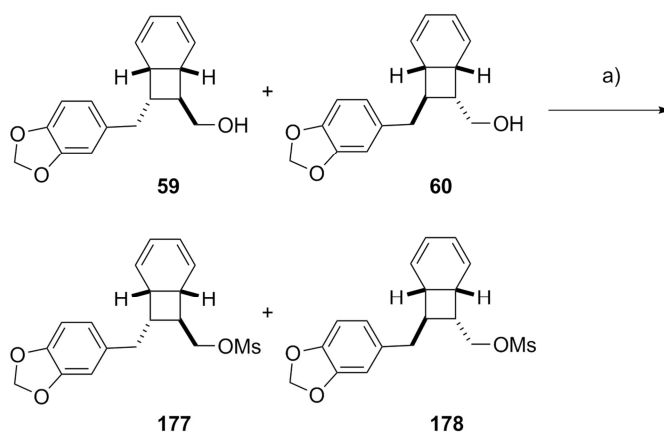
Scheme 6.7: Revised retrosynthetic analysis of prekingianin A (**49**).

It was anticipated that this compound might itself be available *via* a modified Mitsunobu reaction of the alcohol **59** with acetone cyanohydrin. As such, a mixture of the diastereomers **59** and **60** (3:2) were subjected to the procedure of Wilk *et al.* (Scheme 6.8).⁹⁰



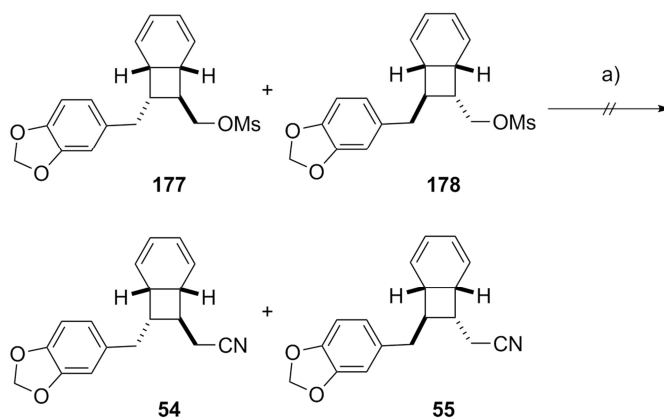
Scheme 6.8: Attempted Mitsunobu synthesis of the bicyclo[4.2.0]octadienyl nitriles **54** and **55**. *Reagents and conditions:* a) PPh_3 , acetone cyanohydrin, DEAD, THF, 0 °C, 1 h.

Under these conditions, the mass of the products was detected by HRMS alongside that of the starting materials. No product was detectable in the rather complex ^1H NMR spectrum however. The residue was separated into several fractions by column chromatography but none contained ^1H NMR signals corresponding to the product. An alternative two step route from the alcohols **59** and **60** to the desired nitriles **54** and **55** was investigated. Namely, mesylation of the alcohols followed by displacement with cyanide. Mesylation of the alcohols **59** and **60** proceeded smoothly and the products **177** and **178** were isolated in 78% yield (Scheme 6.9).



Scheme 6.9: Mesylation of bicyclo[4.2.0]octadienyl alcohols **59** and **60**. *Reagents and conditions:* a) MsCl, Et₃N, CH₂Cl₂, -10 °C, 1 h, 78%.

Due to the known instability of mesylates and the purity that was observed in the crude ¹H NMR spectrum, these compounds were used directly for the next step without further purification. Cyanation of this mixture of diastereoisomers was attempted with sodium cyanide at various temperatures (Scheme 7.0).



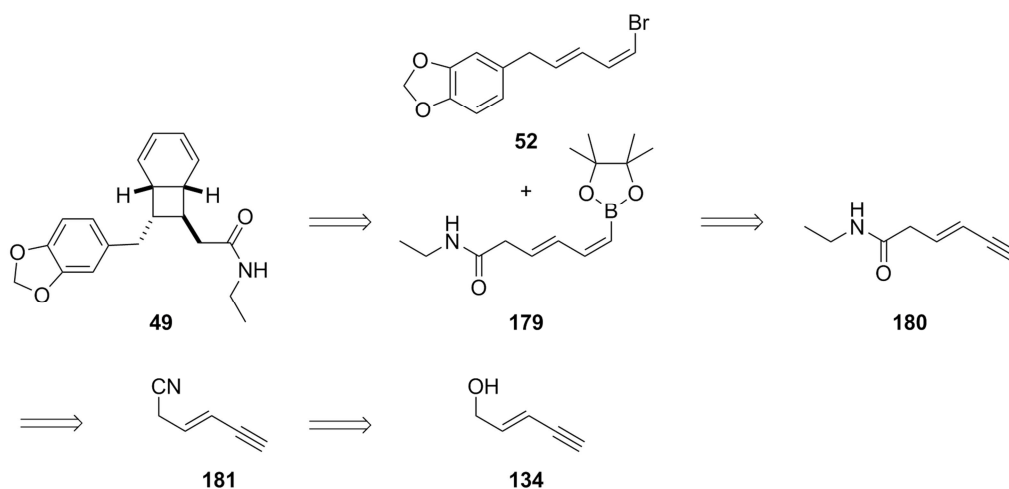
Scheme 7.0: Attempted cyanation of mesylates **177** and **178**. *Reagents and conditions:* a) NaCN, DMF, 50 °C to 70 °C or r.t., 18 h.

Multiple spots were observed in TLC monitoring of this reaction and although in one experiment the mass of the desired products was detected, the nitriles **54** and **55** could not be isolated.

A likely explanation for the resistance to S_N2 substitution in these systems is the steric bulk at the β -position. Due to the difficulties encountered with the interconversion of the existing bicyclo[4.2.0]octadienes, an alternative strategy was sought after for a tin-free synthesis of prekingianin A (**49**), whereby the amide functionality could be installed before the key cross-coupling reaction.

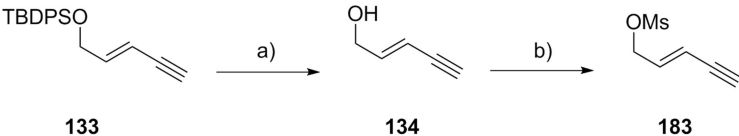
2.8.2 Studies Towards the Synthesis of the Amide Substituted Diene **179**

It was envisioned that conversion of the alcohol functionality in **134** to a leaving group followed by displacement with cyanide would form **181**. Hydrolysis/*N*-alkylation would lead to **180** and finally, hydroboration of this compound would provide the boronic ester **179** (Scheme 7.1).



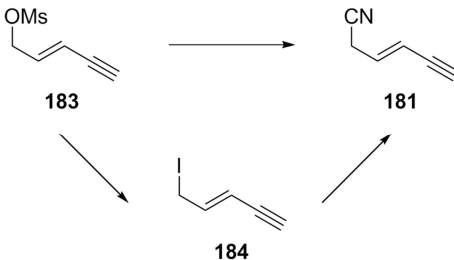
Scheme 7.1: Revised retrosynthetic analysis of prekingianin A (**49**).

Initially, the mesylate **183** was synthesised from the protected alcohol **133**, which had been previously utilised in the synthesis of the bicyclo[4.2.0]octadienyl alcohols **59** and **60** (Scheme 7.2).



Scheme 7.2: Synthesis of the mesylate **183**. *Reagents and conditions:* a) TBAF·3H₂O, THF, 0 °C to r.t., 1 h, 82%; b) MsCl, Et₃N, CH₂Cl₂, −10 °C to r.t., 1 h, quantitative conversion.

The TBDPS protected alcohol **133** was desilylated to yield the free alcohol **134** in 82% yield following column chromatography. This compound was then treated with MsCl and triethylamine. ¹H NMR analysis of the crude reaction mixture determined that quantitative conversion of the starting material had been achieved. The mesylate **183** was used directly for the cyanation investigations without further purification (Table 1.9).



Entry	Conditions	Outcome
1	NaCN, DMF, 0 °C to r.t, 45 min	No Reaction
2	NaCN, DMF, TBAI, 0 °C, 15 min	Decomposition
3	TBAI, r.t., 1.5 h	Iodide 184
4	TBAI, r.t., 1.5 h then TEACN	Decomposition
5	TEACN, 0 °C, 3 min	Decomposition

Table 1.9: Attempted synthesis of the nitrile **181**. All reactions performed in MeCN-d₃.

In order to better study this transformation, reactions were performed in deuterated solvent and ^1H NMR experiments were used to ascertain the progress of the reaction. Initially, mesylate **183** was dissolved in MeCN-d_3 , cooled to 0 °C and to it was added sodium cyanide. At this temperature the cyanide salt was found to be insoluble. The reaction mixture was warmed to room temperature and stirred for 30 min. After this period, the salt had

not dissolved and ^1H NMR analysis confirmed that no heterogeneous reaction had occurred. The mixture was therefore returned to 0 °C and dimethylformamide (DMF) was added dropwise until dissolution occurred. After 30 min at 0 °C, no reaction had occurred. Furthermore, following warming to room temperature and stirring for 30 min, no change could be observed (Entry 1, Table 1.9). It was also intriguing to test the possibility of generating the corresponding iodinated compound **184**. For this reason, an equivalent of tetrabutylammonium iodide (TBAI) was added to the same reaction mixture. Following 15 min at room temperature, ^1H NMR analysis showed total decomposition of the starting material into a complex mixture of degradation products (Entry 2, Table 1.9). At this stage however, it was unclear whether the iodo compound **184** had indeed been formed and then decomposed *via* reaction with sodium cyanide or if the reaction between the mesylate and TBAI had itself resulted in decomposition.

As such, the formation of iodide **184** was attempted in the absence of a cyanide source. The mesylate **183** was dissolved in MeCN-d_3 in an NMR tube and TBAI was added, sequential ^1H NMR experiments over 1.5 h showed complete conversion of the starting material to a spectroscopically similar compound, presumed to be the target iodide **184** (Entry 3, Table 1.9). This strongly suggests that the decomposition previously described (Entry 2, Table 1.9) was due to reaction of the iodide **184** with sodium cyanide. The reaction was also attempted with an alternative cyanide source, tetraethylammonium cyanide (TEACN). Under these conditions, an immediate colour change from colourless to brown was observed and ^1H NMR analysis indicated total decomposition (Entry 4, Table 1.9).

The direct reaction of the mesylate **183** with TEACN was also investigated. Whilst the mesylate had been shown to be stable to NaCN at room temperature, the weaker ionic attraction between the cyanide anion and

the tetraethylammonium cation makes TEACN a more nucleophilic source of cyanide. To a 0 °C solution of mesylate **183** in MeCN was added TEACN. After stirring for 3 min at this temperature, ^1H NMR analysis indicated that the starting material had decomposed to form a complex mixture of degradation products (Entry 5, Table 1.9).

At this stage of the investigations, it was concluded that the mesylate **183** was an unsuitable starting material for the synthesis of the target nitrile **181**.

2.9 ELECTROCHEMICAL STUDIES

With the bicyclo[4.2.0]octadienes **59** and **60** (3:2) and **108** and **109** (3:2) in hand, the possibility of bringing about their dimerisation *via* electrolysis was investigated (Figure 2.9).

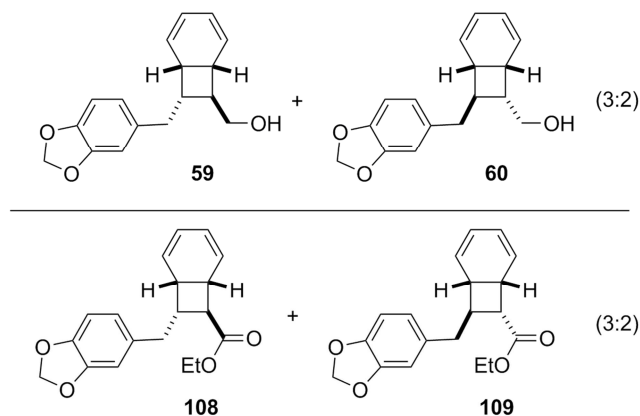


Figure 2.9: Substrates for electrochemical studies.

Initially, the redox activity of these species was studied by cyclic voltammetry. The results were then compared to the voltammogram of the analogous compound 1,3-cyclohexadiene (**37**), which has been shown to undergo dimerisation upon electrolysis.

2.9.1 Cyclic Voltammetry of 1,3-Cyclohexadiene (**37**)

The voltammetric studies of 1,3-cyclohexadiene (**37**) reported by Nigenda *et al.* demonstrate that a potential of 1.1 V (E_1 , vs. Ag/Ag^+) is required to instigate oxidation (Figure 3.0).⁴²

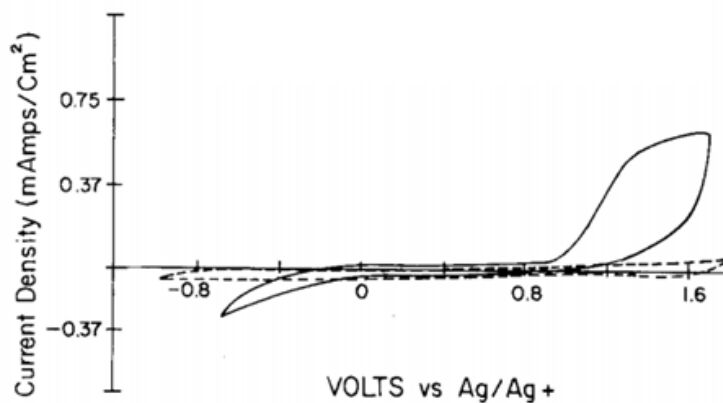


Figure 3.0: Previously reported cyclic voltammogram for 1,3-cyclohexadiene (0.1 M) (—) and background (-----) in CH_2Cl_2 containing $n\text{Bu}_4\text{NBF}_4$ (0.08 M) at ambient temperature and at a scan rate of 0.2 V s^{-1} . Figure reproduced from the literature.⁴²

In order to be confident in the results obtained from voltammetric studies on bicyclo[4.2.0]octadienes, the cyclic voltammetry of 1,3-cyclohexadiene (**37**) was initially replicated (Figure 3.1).

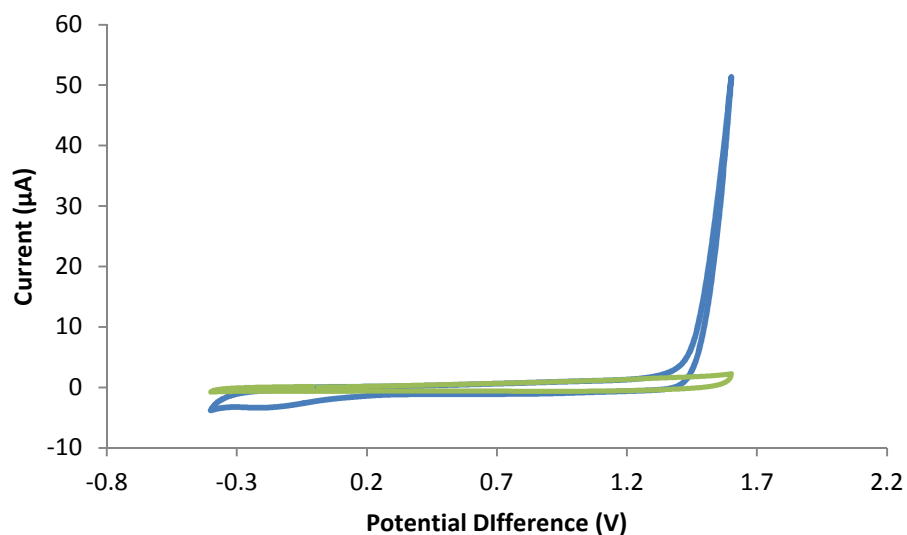


Figure 3.1: Cyclic voltammogram recorded on a glassy carbon disc electrode (3 mm) for 1,3-cyclohexadiene (**37**) (0.1 M) (blue line) and the background (green line) in CH_2Cl_2 containing $n\text{Bu}_4\text{NBF}_4$ (0.08 M) at ambient temperature and at a scan rate of 0.2 V s^{-1} .

In accordance with the results reported by Nigenda *et al.*⁴² the cyclic voltammogram showed an irreversible oxidation. The onset potential for this oxidation however was observed at 1.3 V (vs. Ag/Ag^+) as opposed to the 1.1 V that was originally reported. In order to further investigate this, the cyclic voltammogram was also recorded using an alternative electrolyte; tetrabutylammonium hexafluorophosphate (Figure 3.2).

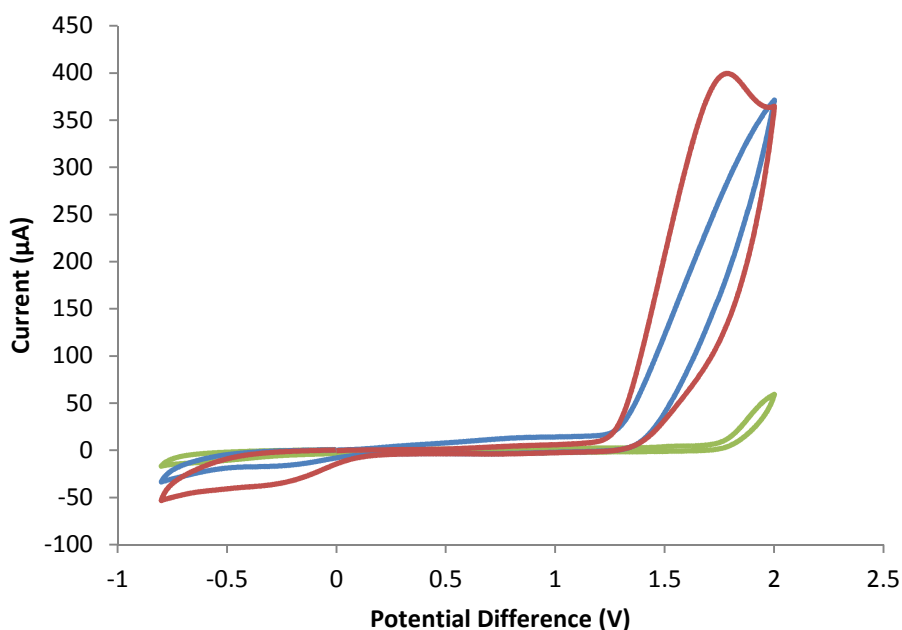


Figure 3.2: Cyclic voltammogram recorded on a glassy carbon disc electrode (3 mm) for 1,3-cyclohexadiene (**37**) (0.1 M) and $n\text{Bu}_4\text{NPF}_6$ (0.1 M) (blue line); 1,3-cyclohexadiene (0.1 M) and $n\text{Bu}_4\text{NPF}_6$ (0.2 M) (red line) and the background (green line) in CH_2Cl_2 at ambient temperature and at a scan rate of 0.2 V s^{-1} .

Under these conditions, the onset of the oxidation was again observed to occur at 1.3 V (vs. Ag/Ag^+). As expected, changing the concentration of electrolyte had no effect on the observed oxidation onset potential. In light of these results, it was concluded that the obtained results were reliable and that the discrepancy between the values recorded in these measurements and those reported by Nigenda *et al.* was due to an external variable.

2.9.2 Electrochemical Studies on the Alcohols **59** and **60**

Cyclic voltammetry of the bicyclo[4.2.0]octadienyl alcohols **59** and **60** was recorded on a glassy carbon electrode in a solution of tetrabutylammonium tetrafluoroborate in CH_2Cl_2 . Ferrocene was added to the analyte solution as an internal reference (Figure 3.3).

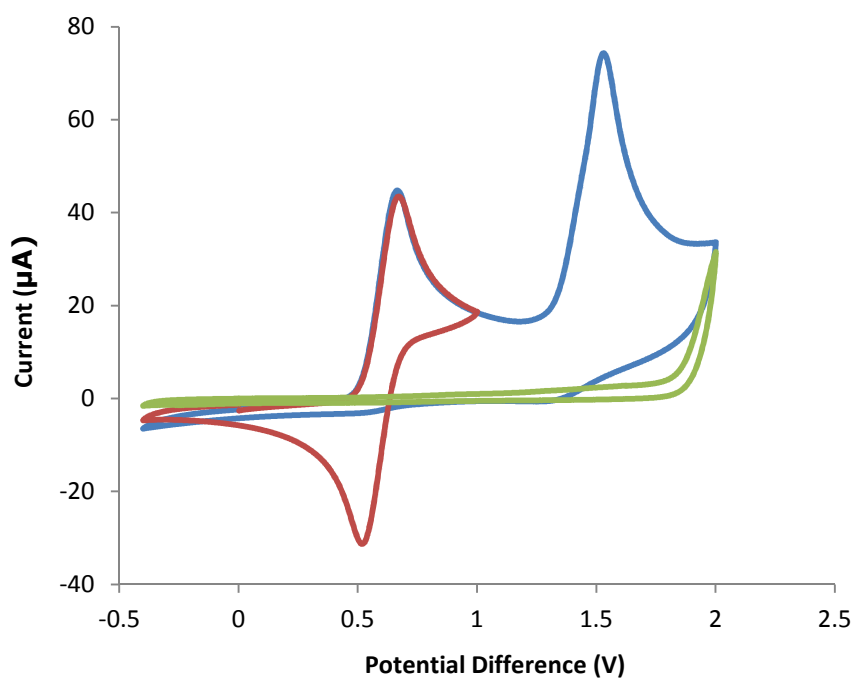


Figure 3.3: Cyclic voltammogram recorded on a glassy carbon disc electrode (3 mm) for **59** and **60** (1:1) (3 mM) (blue line) in the presence of ferrocene (red line) and the background (green line) in CH_2Cl_2 containing $n\text{Bu}_4\text{NBF}_4$ (0.4 M) at ambient temperature and at a scan rate of 0.1 V s^{-1} .

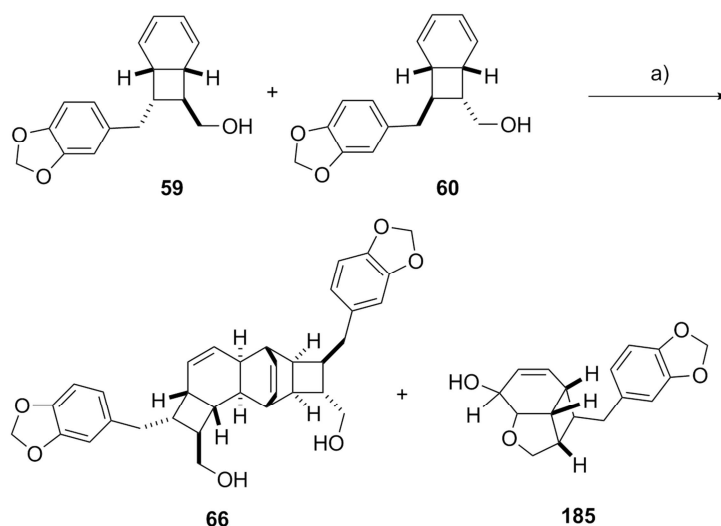
The cyclic voltammogram showed an oxidation wave with an onset potential of 1.25 V (vs. Ag/Ag^+), without evidence of a reduction in the return sweep. The oxidation current reached a diffusion-limited peak current of 74 μA at a peak potential of 1.53 V (vs. Ag/Ag^+).

In some instances, the absence of a reduction peak during the return sweep of a cyclic voltammogram can be attributed to chemical reactions that follow electron transfer into the electrode. Examples include the so-called EC and ECC reactions, where E represents the electron-transfer reaction and C a following chemical reaction.⁹¹ If, on the timescale of the experiment, an EC process had occurred and the product of the chemical reaction was itself electrochemically inactive in the range of potentials scanned, no return peak would be observed. The work by Nigenda *et al.*

indicated that in the case of 1,3-cyclohexadiene (**37**), an EC process had occurred. Following electron transfer from 1,3-cyclohexadiene (**37**) into the electrode (oxidation), RCDA dimerisation had ensued.⁴² With these results in mind, it seemed probable that the observed CV for the bicyclo[4.2.0]octadienyl alcohols **59** and **60** (Figure 3.0) was indicative that a corresponding process had occurred. If this was in fact the case, it would be likely that an electrochemical dimerisation strategy could be applied to synthesis of the kingianins (**1-14**). Since cyclic voltammetry is a purely analytical technique however, it was necessary to carry out preparative scale electrolysis in order to confirm this hypothesis.

As a starting point for preparative electrochemical experiments, work on the dimerisation of 1,3-cyclohexadiene (**37**) was used as a model. As described (*vide supra* - Section 1.7.6), in the case of **37**, the optimum yield of Diels-Alder adducts was obtained when the substrate was electrolysed until 10% Q'' was obtained.⁴² Accordingly, a solution of the bicyclo[4.2.0]octadienyl monomers **59** and **60** (3:2) in 0.4 M ⁿBu₄NBF₄ in CH₂Cl₂ was electrolysed at 1.5 V. A reticulated vitreous carbon working electrode (ca. 1x1x4 cm³) was employed. Current was passed until 10% of the theoretical Q'' was obtained. Following removal of the electrolyte by trituration, only starting material was observed by ¹H NMR analysis and the mass of the target dimer **66** could not be detected by HRMS.

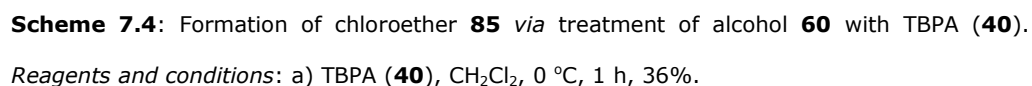
The experiment was then repeated and 100% Q'' was passed. Following which, ¹H NMR analysis showed that the starting material had been consumed and encouragingly, the mass of the dimer was detected by HRMS. Following purification by preparative thin layer chromatography (prep-TLC), the polycyclic compounds **66** (13%) and **185** (16%) were isolated as the major reaction products (Scheme 7.3).



Scheme 7.3: Electrochemical oxidation of the alcohols **59** and **60**. *Reagents and conditions:* a) anodic oxidation, 1.5 V, ${}^n\text{Bu}_4\text{NBF}_4$, CH_2Cl_2 , **66** (13%) and **185** (16%).

The occurrence of the diol **66** was significant and through convergence with the work of Parker,¹⁰ constituted a formal synthesis of kingianin A (**1**).⁹² It is noteworthy that of the various possible modes for Diels-Alder dimerisation, the only isolable dimer was **66**. This species was formed with the same regio and diastereoselectivity that is observed in the family of natural products. This phenomenon was further investigated by *in silico* modelling (*vide infra* – Section 2.9.3).

The formation of the hydroxyl ether **185** was also intriguing. This compound is the product of oxidation/intramolecular etherification from the diastereoisomer **60**, whereby the close proximity of the *endo*-alcohol functionality and the cyclohexadiene core is sufficient to allow nucleophilic attack on the activated diene. The same is not possible for the diastereoisomer **59**, in which case the Diels-Alder dimerisation to yield **66** is free to occur. The practical outcome of this phenomenon is that when the diastereoisomers **59** and **60** were subjected to electrochemical oxidation, no cross-dimerisation was observed. Whilst the ether **185** is a



99

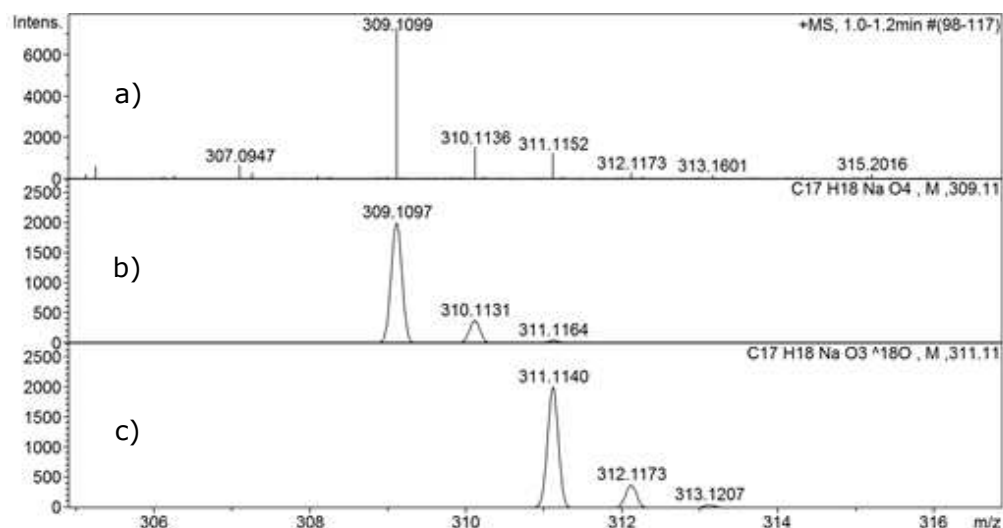


Figure 3.4: a) Obtained HRMS spectrum for O^{18} labelling study. b) Calculated HRMS spectrum of unlabelled **185**. c) Calculated HRMS spectrum of O^{18} labelled **185**.

The obtained HRMS trace for the crude reaction mixture clearly showed the mass of the unlabelled **185**: Calculated for $C_{17}H_{18}NaO_4$ $[M+Na]^+$ 309.1097 obtained 309.1099. The mass of the O^{18} labelled dimer was also detected: Calculated for $C_{17}H_{18}NaO_4$ $[M+Na]^+$ 311.1140 obtained 311.1152. This fit was calculated with an error of -3.9 [ppm]. In order to confirm that this signal was not due to a species with the mass of **185** plus two protons, a calculation was performed for the species $C_{17}H_{20}O_4$: Calculated for $C_{17}H_{20}NaO_4$ $[M+Na]^+$ 311.1254. This model was found to fit the obtained peak at 311.1152 with a much higher error of 32.8 [ppm]. These results confirm the presence of the O^{18} labelled species **185** and provide strong evidence to support the hypothesis that the mechanism for formation of ether **185** involves water as a reagent.

2.9.3 Molecular Modelling of the Diels-Alder Dimerisation of Prekingianin A (49)

As described previously, there are several selectivity features that are observed in the Diels-Alder reactions proposed to be responsible for the

formation of kingianins A-N (**1-14**) (*vide supra* – Section 1.3). It was particularly appealing to investigate the selectivity over which double bond acts as the dienophile. In order to probe this interesting feature of reactivity, *in silico* calculations were performed by a collaborator, Dr. David Robinson, University of Nottingham.

Initially, density functional theory (DFT) geometry optimisation was performed on the putative monomer prekingianin A (**49**) using the ω B97X-D functional with the 6-31G* basis set. The geometrically optimised structure was then used for transition state calculations. Initially, the energy barrier was calculated for the reaction where the double bond proximal to the *exo* substituent has acted as the dienophile (as observed in the natural product) (Figure 3.5).

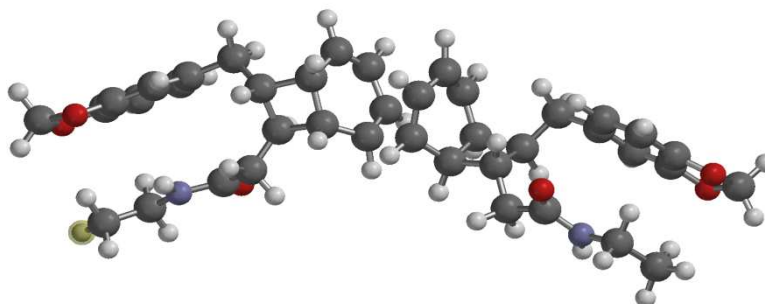


Figure 3.5: Transition state model for the dimerisation of prekingianin A (**49**) to form kingianin A (**1**). The double bond proximal to the *exo* substituent has acted as the dienophile.

This pathway was found to have an energy barrier of 23.6 kcal mol⁻¹.

Next, the transition state was calculated where the other double bond (that proximal to the *endo* substituent) has acted as the dienophile (Figure 3.6).

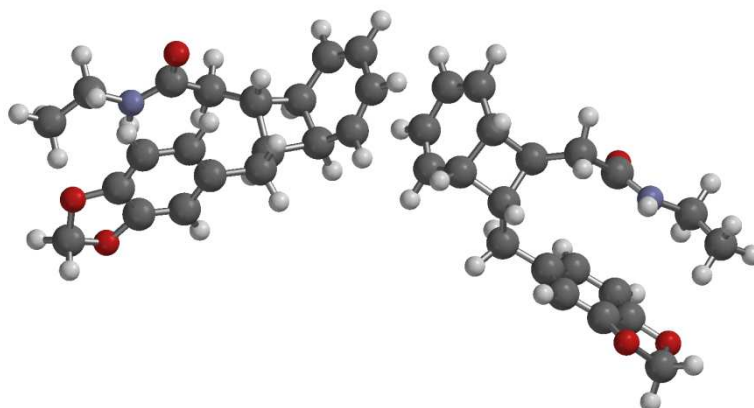


Figure 3.6: Alternative transition state model for the dimerisation of prekingianin A (**49**) where the double bond proximal to the *endo* substituent has acted as the dienophile.

This pathway was found to have an energy barrier of 27.6 kcal mol⁻¹. This equates to an energy difference of 4.0 kcal mol⁻¹ between the two pathways, suggesting that a steric factor could be responsible for the observed chemoselectivity in this putative reaction. One caveat that should be noted however is that these calculations were performed for a charge neutral, rather than a radical cation Diels-Alder reaction.

2.9.4 Electrochemical Studies on the Esters **108** and **109**

The redox behaviour of the bicyclo[4.2.0]octadienyl esters **108** and **109** was next investigated (Figure 3.7).

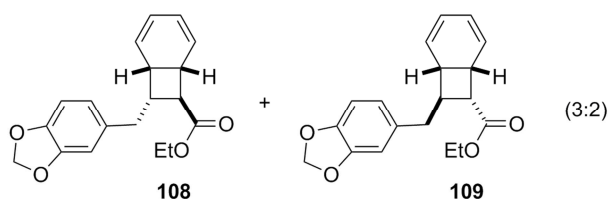


Figure 3.7: The bicyclo[4.2.0]octadienyl esters **108** and **109**.

These compounds had been synthesised as model substrates to investigate dimerisation protocols. Upon treatment with the single electron oxidant TBPA (**40**) however, no evidence for RCDA dimerisation could be observed

(*vide supra* – Section 2.4.2). Interestingly, under the same conditions the analogous alcohols **59** and **60** have been observed to dimerise readily.⁵⁴ It was intriguing to investigate whether the redox behaviour of these compounds, as studied by cyclic voltammetry, would in any way reflect this difference in reactivity.

Cyclic voltammetry of the bicyclo[4.2.0]octadienyl esters **108** and **109** was recorded using the same procedure that had been applied to the corresponding alcohols **59** and **60** (Figure 3.8). Again, ferrocene was added to the analyte solution as an internal reference.

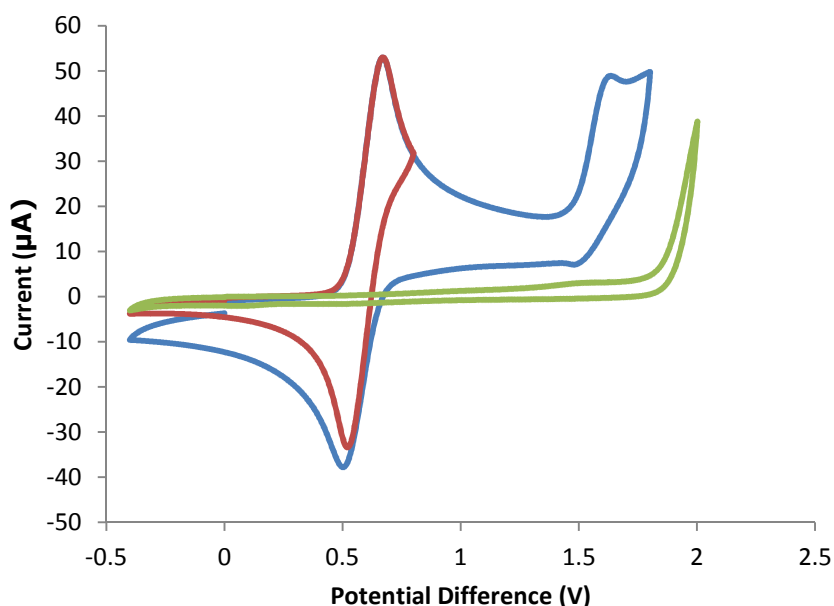


Figure 3.8: Cyclic voltammogram recorded on a glassy carbon disc electrode (3 mm) for **108** and **109** (3:2) (2 mM) (blue line) in the presence of ferrocene (red line) and the background (green line) in CH₂Cl₂ containing ⁿBu₄NBF₄ (0.4 M) at ambient temperature and at a scan rate of 0.2 V s⁻¹.

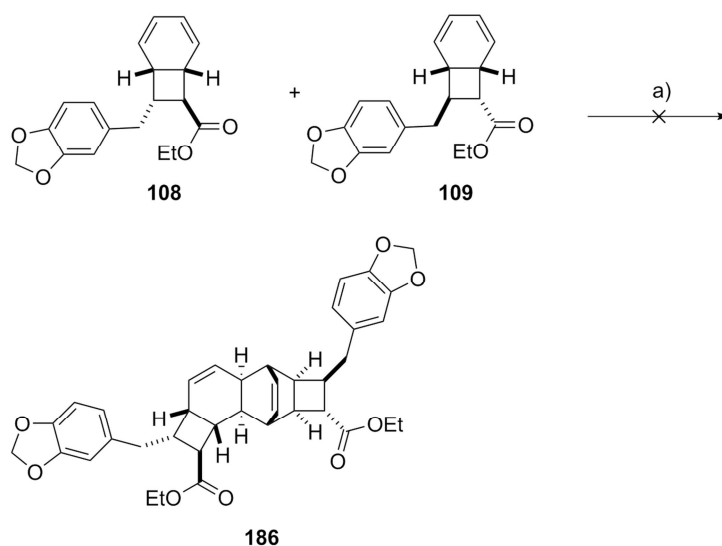
The cyclic voltammogram clearly showed an oxidation wave with an onset potential of 1.45 V (*vs.* Ag/Ag⁺), without evidence of a reduction in the return sweep. The oxidation reached a diffusion-limited peak current of 47 μA at a peak potential of 1.64 V (*vs.* Ag/Ag⁺).

In order to more reliably compare these results to those obtained for the alcohols **59** and **60**, the values were also recorded vs. $E_{1/2} \text{Fc/Fc}^+$ (Table 2.0).

Substrates	Oxidation Onset	E_p^a
	(vs. Fc^+/Fc)	(vs. Fc^+/Fc)
Alcohols 59 + 60 (1:1)	0.65 V	0.93 V
Esters 108 + 109 (3:2)	0.85 V	1.12 V

Table 2.0: Comparison of the redox activity of alcohols **59** and **60** and the esters **108** and **109**.

As shown, the E_p^a of the esters **108** and **109** is 0.19 V (vs. Fc/Fc^+) higher than that of the alcohols **59** and **60**. Furthermore, the oxidation onset is 0.20 V (vs. Fc/Fc^+) higher. As the oxidation of dichloromethane occurs at 1.7 V (vs. Ag/Ag^+) however, electrolysis of **108** and **109** was performed at 1.6 V (vs. Ag/Ag^+) (Scheme 7.5).



Scheme 7.5: Electrochemical oxidation of the esters **108** and **109**. *Reagents and conditions:*

a) anodic oxidation, 1.6 V, $n\text{Bu}_4\text{NBF}_4$, CH_2Cl_2 .

Upon removal of the electrolyte, ^1H NMR analysis of the crude reaction mixture revealed that complete consumption of the starting materials had occurred. In contrast to the experiments with the alcohols **59** and **60**

however, no evidence for dimeric species could be detected by HRMS. Several broad peaks were observed by ^1H NMR spectroscopy, in regions of the spectrum that correspond to peaks in the starting materials (Figure 3.9).

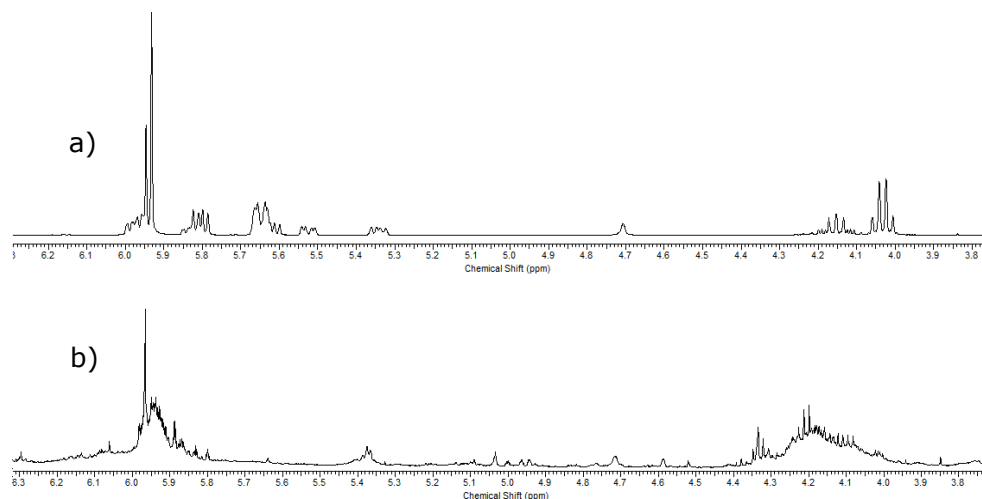


Figure 3.9: a) ^1H NMR spectrum of the starting materials **108** and **109** (3:2); b) Crude ^1H NMR spectrum obtained following electrolysis.

Qualitatively, these peaks are reminiscent of those obtained for polymeric material. The hypothesis that the esters **108** and **109** underwent polymerisation seems probable as in case of 1,3-cyclohexadiene (**37**) polymerisation is reported as a major side-reaction alongside RCDA dimerisation.⁴² This would also tie in with the fact that oxidation of **108** and **109** with TBPA (**40**) lead only to a complex mixture of highly polar materials.

2.10 Conclusions

In conclusion, two synthetic routes have been utilised for the synthesis of bicyclo[4.2.0]octadienes. The first route, which culminated in the Stille cross-coupling of two dienes, yielded the diastereomeric esters **108** and **109**. The related alcohols **59** and **60** were prepared *via* an analogous Suzuki-Miyaura cross-coupling route. The dimerisation of the esters **108** and **109** was shown not to occur with TBPA (**40**). This is in contrast to the alcohols **59** and **60**, which have been shown to dimerise readily upon treatment with this reagent.¹⁰

Cyclo-voltammetric analysis was performed on the aforementioned bicyclo[4.2.0]octadienes (**108/109** and **59/60**) and on the parent compound 1,3-cyclohexadiene (**37**). Preparative electrochemical techniques were then applied to the alcohols **59** and **60**. It was observed that one diastereoisomer underwent oxidation/intramolecular etherification whilst the other underwent radical cation Diels-Alder dimerisation, completing a formal synthesis of the natural product kingianin A (**1**).

In a related experiment, the electrolysis of the esters **108** and **109** was shown not to yield dimeric species. Further investigations would be required however to ascertain whether these compounds should be considered as unsuitable substrates for an electrochemical dimerisation strategy.

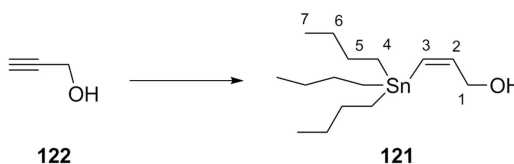
3. EXPERIMENTAL PROCEDURE

Reactions were performed in flame-dried glassware under an atmosphere of argon and stirred magnetically unless otherwise stated. CH_2Cl_2 and DMF were freshly distilled from CaH_2 ; THF was freshly distilled from sodium and benzophenone; Et_2O and toluene were degassed and dried over alumina under nitrogen. All other reagents were obtained commercially and used without further purification unless otherwise stated. Thin layer chromatography was carried out on aluminium-backed plates pre-coated with silica (0.2 mm, 60 F₂₅₄, Merck). The plates were developed using UV light and basic potassium permanganate solution. Flash chromatography was performed using Merck silica gel 60 as the stationary phase. Petrol refers to petroleum ether (b.p. 40-60 °C).

Compounds previously described in the literature were characterised to levels consistent with that reported. Infra-red spectra were recorded using a Bruker Tensor 27 FT-IR spectrophotometer and their peaks are quoted as ν_{max} in cm^{-1} . ^1H and ^{13}C NMR spectra were recorded in CDCl_3 , at ambient temperature using Bruker DPX400 (400 MHz), AV400 (400 MHz), AV3400 (400 MHz) and AV3500 (500 MHz) spectrometers. Data are expressed as chemical shifts in parts per million (ppm) relative to the residual solvent signal of CDCl_3 (^{13}C NMR 77.0) and CHCl_3 (^1H NMR 7.27) as the internal standard on the δ scale. The following abbreviations are used to designate the multiplicity of each signal; s, singlet; d, doublet; dd, doublet of doublets; dddd, doublet of doublet of doublet of doublets; t, triplet; dt, doublet of triplets; ddt, doublet of doublet of triplets; q, quartet; m, multiplet; apt, apparent; br, broad. Coupling constants J are given in hertz (Hz). High-resolution mass spectra were obtained using a Bruker

MicroTOF mass spectrometer operating in electrospray ionisation (ESI) mode or a Waters AutoSpec operating in electron ionisation (EI) mode.

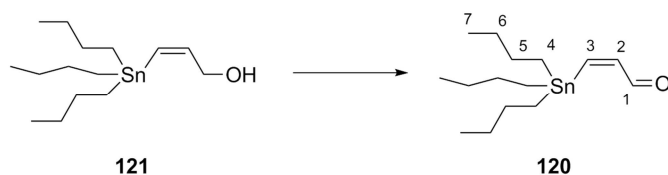
Electrochemical experiments were carried out on a Metrohm AutoLab PGSTAT100N potentiostat. Cyclic voltammograms were recorded using a Metrohm glassy carbon disk electrode (3mm), a Metrohm platinum sheet counter electrode (10 mm²) and a Metrohm saturated Ag/AgCl reference electrode. Bulk electrolysis experiments, at a controlled potential, were carried out using a two-compartment cell. Reticulated vitreous carbon (Bulk Density: 0.05 g/cm³; Porosity: 96.5%; Pores/cm: 40) was purchased from Goodfellow Cambridge Limited and used as the working electrode (ca. 1x1x3 cm³). This was connected to the potentiostat *via* a graphite rod (3x20 mm) and was separated from a wound Pt/Rh gauze secondary electrode by a glass frit. A saturated Ag/AgCl reference electrode was bridged to the test solution through a vycor frit that was orientated at the centre of the working electrode. The working electrode compartment was fitted with a magnetic stirrer bar and the test solution was stirred rapidly during electrolysis. Each solution contained ⁿBu₄NBF₄ (0.4 M) as the supporting electrolyte and was prepared using Schlenk line techniques.

(Z)-3-(Tributylstannyl)prop-2-en-1-ol (121)

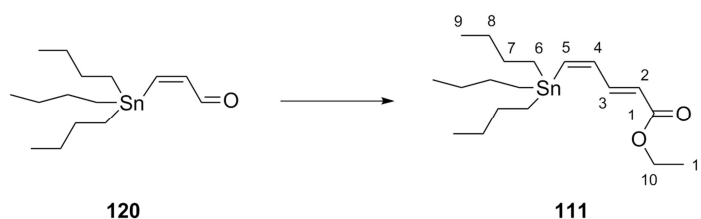
THF (10.0 mL) was cooled to 0 °C and lithium aluminium hydride (169 mg, 4.46 mmol) was added portionwise. To the resultant suspension was added dropwise propargyl alcohol (**122**) (0.51 mL, 8.93 mmol). The reaction mixture was allowed to warm to room temperature and stir for 16 hours. The mixture was cooled to –78 °C and tributyltin triflate (1.12 g, 2.55 mmol) was added. The solution was maintained at –78 °C and stirred for 5 hours before being allowed to warm to room temperature and stir for a further 16 hours. The solution was cooled to 0 °C and to it was carefully added sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (200 mL). The aqueous phase was separated and extracted with Et_2O (3 x 150 mL). The combined organic phases were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (2% EtOAc in petrol) to yield the title compound **121** (228 mg, 23%) as a colourless oil.

R_f = 0.60 (10% EtOAc in petrol); ν_{max} (cm^{-1}) (Thin film): 3339 (O-H), 2924 (C-H alkane), 2853 (C-H alkane), 1598 (C=C alkene), 1462; δ_{H} (CDCl_3 , 400 MHz): 6.71 (1H, dt, J = 12.8, 5.8 Hz, 2- H_1), 6.09 (1H, d, J = 12.8 Hz, 3- H_1), 4.16 - 4.09 (2H, m, 1- H_2) 1.55 - 1.45 (6H, m, 4- H_2), 1.36 - 1.23 (6H, m, 5- H_2), 0.95 - 0.86 (15H, m, 6- H_2 and 7- H_3); δ_{C} (CDCl_3 , 100 MHz): 146.2 (2-CH), 131.8 (3-CH), 66.1 (1- CH_2), 29.1 (4- CH_2), 27.3 (5- CH_2), 13.7 (6- CH_2), 10.66 (7- CH_3); **HRMS** (ESI): Calculated for $\text{C}_{15}\text{H}_{32}\text{NaOSn}$ $[\text{M}+\text{Na}]^+$ 371.1367, obtained 371.1374.

This data is consistent with that reported by Corey *et al.*⁶⁷

(Z)-3-(Tributylstannyl)-2-propenal (120)

To a 0 °C solution of the alcohol **121** (6.60 g, 18.96 mmol) in CHCl_3 (500 mL) was added MnO_2 (49.44 g, 568.72 mmol) portionwise. The reaction was stirred at room temperature for 16 hours. The mixture was then filtered through a pad of celite and eluted with CHCl_3 (300 mL). The solvent was removed under reduced pressure to yield the title compound **120** (6.80 g) which was carried on directly to the next step without further purification.

(2E,4Z)-Ethyl 5-(tributylstannyl)penta-2,4-dienoate (111)

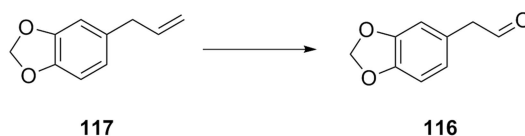
To a solution of the crude aldehyde **120** (6.80 g) in CH_2Cl_2 (20.0 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (9.890 g, 28.39 mmol). The mixture was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography (petrol) to yield the title compound **111** (7.124 g, 93%) as a colourless oil.

R_f = 0.40 (5% EtOAc in petrol); ν_{max} (cm^{-1}) (Thin film): 2958 (C-H alkane), 2928 (methylene), 2872 (alkane), 2854 (methylene), 1717 (C=O ester), 1627 (C=C alkene), 1463, 1265 (C-O ester), 1154 (C-O ester); δ_{H} (CDCl_3 ,

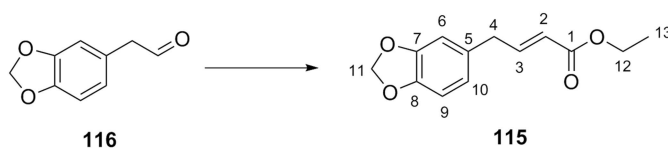
400 MHz): 7.25 - 7.11 (2H, m, 4-H₁ and 3-H₁), 6.81 - 6.62 (1H, d, J = 11.8 Hz, 5-H₁), 5.94 - 5.84 (1H, d, J = 14.3 Hz, 2-H₁), 4.26 - 4.18 (2H, q, J = 7.2 Hz, 10-H₂), 1.64 - 1.42 (6H, m, 7-H₂), 1.38 - 1.24 (9H, m, 8-H₂ and 11-H₃) 1.11 - 0.93 (6H, m, 6-H₂), 0.92 - 0.87 (9H, t, J = 7.4 Hz, 9-H₃); δ_c (CDCl₃, 100 MHz): 167.0 (1-C), 147.9 (5-CH), 146.6 (3-CH), 144.0 (4-CH), 122.6 (2-CH), 60.3 (10-CH₂), 29.1 (7-CH₂), 27.2 (11-CH₃), 14.3 (8-CH₂), 13.7 (9-CH₃), 10.7 (6-CH₂); **HRMS** (ESI): Calculated for C₁₉H₃₇O₂Sn [M+H]⁺ 417.1810 obtained 417.1817, calculated for C₁₉H₃₆NaO₂Sn [M+Na]⁺ 439.1629 obtained 439.1636.

This data is consistent with that previously reported by Moses *et al.*⁴³

2-(Benzo[*d*][1,3]dioxol-5-yl)acetaldehyde (**116**)



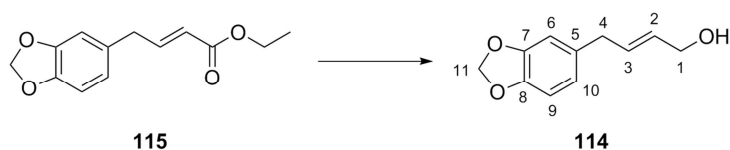
To a rapidly stirring suspension of safrole (**117**) (10.0 g, 61.7 mmol) in H₂O (200 mL) and methanol (300 mL) was added dropwise the minimum amount of THF (70 mL) to induce complete dissolution. To this solution was added OsO₄ (79.0 mg, 0.31 mmol, 1.98 mL, 4% w/v H₂O) followed by NaIO₄ (33.0 g, 154 mmol) and the solution was stirred vigorously at room temperature (16 h). The reaction mixture was filtered through celite and washed with EtOAc (200 mL). The volume of solvent was reduced (approximately 200 mL) under reduced pressure and then the crude residue was diluted with H₂O (200 mL) and extracted with EtOAc (3 x 400 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the title compound **116** (11.1 g) which was carried on directly to the next step without further purification.

(E)-Ethyl 4-(benzo[d][1,3]dioxol-5-yl)but-2-enoate (115)

The crude aldehyde **116** (11.1 g) and ethyl 2-(triphenylphosphoranylidene)acetate (36.2 g, 104 mmol) were dissolved in CH_2Cl_2 (200 mL), heated to reflux and stirred (24 h). Upon completion of the reaction the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography (5% EtOAc in petrol) to yield the title compound **115** as a pale yellow oil (10.3 g, 80% over two steps).

R_f = 0.51 (20% EtOAc in petrol); ν_{max} (cm^{-1}) (CHCl_3): 1718 (C=O ester), 1654 (C=C alkene), 1490 (C=C aromatic), 1444 (C=C aromatic), 1247 (C-O aromatic ether); δ_{H} (CDCl_3 , 400 MHz): 7.06 (1H, dt, J = 15.6, 6.8 Hz, 3- H_1), 6.76 (1H, d, J = 7.9 Hz, 9- H_1), 6.70 - 6.61 (2H, m, 10-H and 6-H), 5.95 (2H, s, 11- H_2), 5.79 (1H, dt, J = 15.6, 1.5 Hz, 2- H_1), 4.19 (2H, q, J = 7.2 Hz, 12- H_2), 3.44 (2H, dd, J = 6.8, 1.5 Hz, 4- H_2), 1.28 (3H, t, J = 7.2 Hz, 13- H_3); δ_{C} (CDCl_3 , 100 MHz): 166.5 (1-C), 147.8 (7-C), 147.4 (3-CH), 146.3 (8-C), 131.4 (5-C), 122.2 (2-CH), 121.8 (10-CH), 109.3 (6-CH), 108.4 (9-CH), 101.0 (11- CH_2), 60.3 (12- CH_2), 38.1 (4- CH_2), 14.3 (13- CH_3); **HRMS** (ESI): Calculated for $\text{C}_{13}\text{H}_{15}\text{O}_4$ $[\text{M}+\text{H}]^+$ 235.0965 obtained 235.0966, calculated for $\text{C}_{13}\text{H}_{14}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 257.0784 obtained 257.0779.

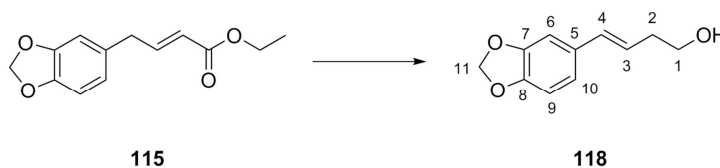
This data is consistent with that previously reported by Moses *et al.*⁴³

(E)-4-(Benzo[d][1,3]dioxo-5-yl)but-2-en-1-ol (114)

The ester **115** (515 mg, 2.13 mmol) was dissolved in CH₂Cl₂ (5.0 mL) and the solution was cooled to -78°C . DIBAL-H (4.70 mL, 4.70 mmol, 1 M in heptanes) was added dropwise over 10 min. The solution was warmed to room temperature and stirred for 30 min. The solution was cooled to 0°C and methanol (1.25 mL) was added carefully. A sat. aq. solution of potassium sodium tartrate (7.0 mL) was added and the mixture was allowed to warm to room temperature and stir until both layers became clear. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography (10% EtOAc in petrol) to yield the title compound **114** (371 mg, 81%) as a viscous pale yellow oil.

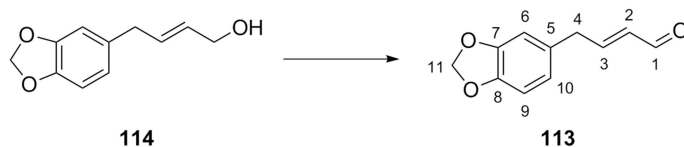
R_f = 0.32 (40% EtOAc in petrol); **v_{max}** (cm⁻¹) (CHCl₃): 3355 (O-H alcohol), 2895, 1503 (C=C aromatic), 1489 (C=C aromatic), 1443 (C=C aromatic), 1245 (C-O aromatic ether), 1040 (C-O alcohol); **δ_H** (CDCl₃, 400 MHz): 6.75 (1H, d, *J* = 7.9 Hz, 9-H₁), 6.69 - 6.67 (1H, m, 6-H₁), 6.66 - 6.62 (1H, m, 10-H₁), 5.93 (2H, s, 11-H₂), 5.87 - 5.78 (1H, m, 3-H₁), 5.74 - 5.65 (1H, m, 2-H₁) 4.13 (2H, d, *J* = 5.8 Hz, 4-H₂), 3.31 (2H, d, *J* = 6.5 Hz, 1-H₂); **δ_C** (CDCl₃, 100 MHz): 147.7 (8-C), 145.9 (7-C), 133.8 (5-C), 131.7 (3-CH), 130.2 (2-CH), 121.3 (10-CH₂), 109.1 (9-CH), 108.2 (6-CH), 100.8 (11-CH), 63.5 (1-CH₂), 38.3 (4-CH); **HRMS** (ESI): Calculated for C₁₁H₁₂NaO₃ [M+Na]⁺ 215.0679 obtained 215.0685.

This data is consistent with that previously reported by Moses *et al.*⁴³

(*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)but-3-en-1-ol (118**)**

The procedure for the synthesis of (*E*)-ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)but-2-enoate (**114**) was carried out as described but the reaction mixture was allowed to stir for 16 hours at room temperature before being cooled to 0 °C and quenched. In this case, the title compound **118** was the only observed product. A small sample was purified by recrystallisation (petrol/ EtOAc) to obtain analytically pure material as a white solid.

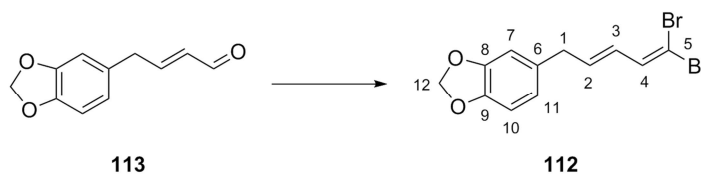
R_f = 0.35 (40% EtOAc in petrol); **v_{max}** (cm⁻¹) (CHCl₃): 3690, 3616 (O-H alcohol), 2886, 1604 (C=C alkene), 1490, 1251 (C-O aromatic ether), 1042; **δ_H** (CDCl₃, 270 MHz): 6.92 (1H, d, *J* = 1.4 Hz, 9-H₁), 6.82 – 6.73 (2H, m, 6-H₁, 10-H₁), 6.42 (1H, d, *J* = 15.8 Hz, 4-H₁), 6.04 (1H, dt, *J* = 15.8, 7.2 Hz, 3-H₁), 5.95 (2H, s, 11-H₂), 3.75 (2H, t, *J* = 6.3 Hz, 1-H₂), 2.47 (2H, apt. qd, *J* = 6.3, 1.2 Hz, 2-H₂); **δ_C** (CDCl₃, 68 MHz): 148.0 (7-C), 146.9 (8-C), 132.4 (4-CH), 131.7 (5-C), 124.5 (3-CH), 120.6 (10-CH), 108.2 (9-CH), 105.4 (6-CH), 101.0 (11-CH₂), 62.0 (1-CH₂), 36.3 (2-CH₂); **HRMS** (ESI): Calculated for C₁₁H₁₂NaO₃ [M+Na]⁺ 215.0679 obtained 215.0692.

(E)-4-(Benzo[d][1,3]dioxol-5-yl)but-2-enal (113)

To a solution of the alcohol **114** (307 mg, 1.60 mmol) in CH₂Cl₂ (4.0 mL) was added Dess-Martin periodinane (813 mg, 1.92 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min. After completion of the reaction (TLC), the mixture was cooled to 0 °C and sat. NaHCO_{3(aq)} (80.0 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (10% EtOAc in petrol) to yield the title compound **113** (280 mg, 92%) as a pale yellow oil.

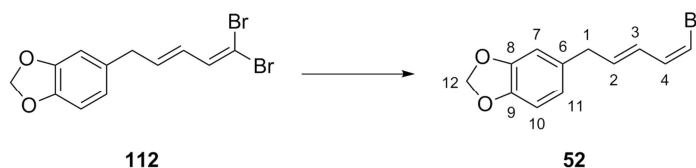
R_f = 0.48 (40% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 2896, 1686 (C=O aldehyde), 1634, 1488, 1443, 1246 (C-O aromatic ether); **δ_H** (CDCl₃, 400 MHz): 9.55 (1H, d, *J* = 7.9 Hz, 1-H₁), 6.93 (1H, dt, *J* = 15.6, 6.7 Hz, 3-H₁), 6.80 - 6.76 (1H, d, *J* = 7.8 Hz, 9-H₁), 6.67 - 6.62 (2H, m, 6-H₁ and 10-H₁), 6.15 - 6.06 (1H, dd, *J* = 15.6, 7.9 Hz, 2-H₁), 5.96 (2H, s, 11-H₂), 3.57 (2H, dd, *J* = 6.7 Hz, 4-H₂); **δ_C** (CDCl₃, 100 MHz): 193.8 (1-CH), 156.5 (3-CH), 148.0 (8-C), 146.6 (7-C), 133.4 (2-CH), 130.6 (5-C), 121.8 (10-CH), 109.2 (6-CH), 108.6 (9-CH), 101.1 (11-CH₂), 38.7 (4-CH₂); **HRMS** (ESI): Calculated for C₁₁H₁₀NaO₃ [M+Na]⁺ 213.0522 obtained 213.0532, calculated for C₁₁H₉O₃ [M-H]⁻ 189.0557 obtained 189.0550.

This data is consistent with that previously reported by Moses *et al.*⁴³

(E)-5-(5,5-Dibromopenta-2,4-dien-1-yl)benzo[d][1,3]dioxole**(112)**

To a solution of CBr_4 (879 mg, 2.68 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was added a solution of PPh_3 (1.41 g, 5.36 mmol) in CH_2Cl_2 (8.0 mL). The mixture was stirred for 10 min followed by addition of Et_3N (952 mg, 9.41 mmol). To this mixture was added the aldehyde **113** (179 mg, 0.94 mmol) in CH_2Cl_2 (2.5 mL) dropwise. The mixture was stirred at room temperature for 15 min. and then sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (15.0 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified using flash silica gel column chromatography (petrol) to yield the title compound **112** (273 mg, 93%) as viscous orange oil which solidified upon standing at lowered temperature.

R_f = 0.60 (5% EtOAc in petrol); ν_{max} (cm^{-1}) (CHCl_3): 3291, 2891 (C-H), 1488, 1442, 1247 (C-O aromatic ether), 1040; δ_{H} (CDCl_3 , 400 MHz): 6.95 - 6.90 (1H, d, J = 10.0 Hz, 4- H_1), 6.78 - 6.73 (1H, d, J = 7.9 Hz, 10- H_1), 6.68 - 6.65 (1H, m, 7- H_1), 6.65 - 6.61 (1H, m, 11- H_1), 6.20 - 6.11 (1H, ddt, J = 15.2, 10.0, 1.3 Hz, 3- H_1), 6.03 - 5.93 (3H, m, 2- H_1 and 12- H_2), 3.31 (2H, d, J = 7.1, 1- H_2); δ_{C} (CDCl_3 , 400 MHz): 171.2 (5-C), 147.8 (9-C), 146.1 (8-C), 137.4 (2-CH), 136.7 (4-CH), 132.7 (6-C), 128.0 (3-CH), 121.4 (11-CH), 109.0 (7-CH), 108.3 (10-CH), 100.9 (12- CH_2), 39.0 (1- CH_2); **HRMS** (EI): Calculated for $\text{C}_{12}\text{H}_{10}\text{O}_2\text{Br}_2$ $[\text{M}]^+$ 343.9048 obtained 343.9054.

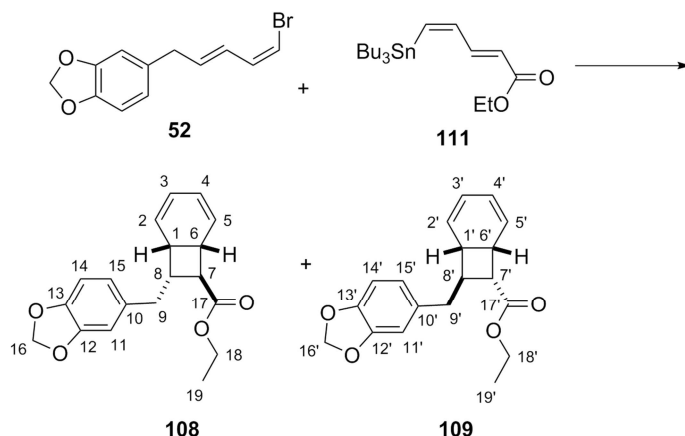
5-((2E,4Z)-5-Bromopenta-2,4-dien-1-yl)benzo[d][1,3]dioxole (52)

To a solution of the dibromide **112** (3.70 g, 11.8 mmol) in toluene (2.5 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (90.0 mg, 1.18 mmol). To this was added tributyltin hydride (239 μL , 8.88 mmol) dropwise. The mixture was stirred at room temperature for 90 min. The reaction mixture was filtered through a pad of silica gel, concentrated under reduced pressure and purified by flash silica gel column chromatography (petrol) to yield the title compound **52** (2.05 g, 74%) as a pale yellow oil which solidified upon standing at lowered temperature.

R_f = 0.58 (5% EtOAc in petrol); mp: 38-40 $^{\circ}\text{C}$; ν_{max} (cm^{-1}) (CHCl_3): 3009, 2896 (C-H), 1608, 1504, 1489, 1442, 1247 (C-O aromatic ether), 1041; δ_{H} (CDCl_3 , 400 MHz): 6.76 (1H, d, J = 7.9 Hz, 5- H_1), 6.70 - 6.68 (1H, m, 10- H_1), 6.70 - 6.59 (2H, m, 7- H_1 and 11- H_1), 6.50 - 6.41 (1H, m, 4- H_1), 6.10 (1H, apt. br d, J = 7.2 Hz, 3- H_1), 6.02 (1H, dt, J = 15.1, 7.2 Hz, 2- H_1), 5.94 (2H, s, 12- H_2), 3.40 (2H, br d, J = 7.2 Hz, 1- H_2); δ_{C} (CDCl_3 , 100 MHz): 147.7 (9-C), 146.0 (8-C), 137.5 (2-CH), 133.2 (6-C), 132.4 (7-CH), 127.0 (4-CH), 121.4 (11-CH), 109.1 (10-CH), 108.3 (5-CH), 106.7 (3-CH), 100.9 (12- CH_2), 39.0 (1- CH_2); **HRMS** (EI): Calculated for $\text{C}_{12}\text{H}_{11}\text{NaO}_2\text{Br}$ $[\text{M}+\text{Na}]^+$ 265.9942 obtained 265.9944.

This data is consistent with that previously reported by Moses *et al.*⁴³

Ethyl (1*R,6*R**,7*R**,8*S**)-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (**108**) and ethyl (1*R**,6*R**,7*S**,8*R**)-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (**109**)**

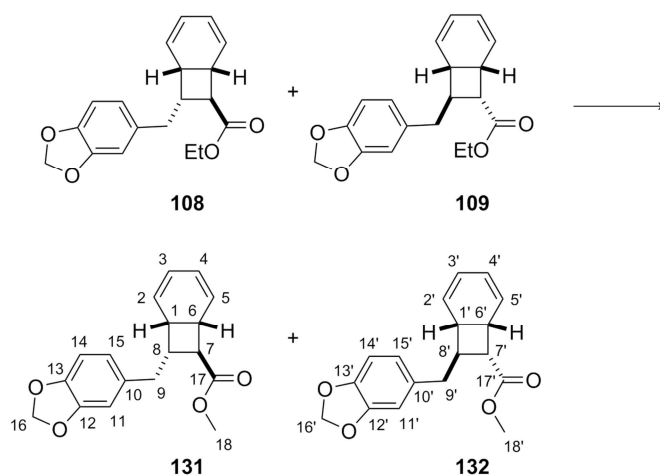


To a degassed solution of the vinyl bromide 5-((2*E*,4*Z*)-5-bromopenta-2,4-dien-1-yl)benzo[*d*][1,3]dioxole (**52**) (100 mg, 0.427 mmol) in DMF (1.0 mL) was added the vinyl stannane (2*E*,4*Z*)-ethyl 5-(tributylstannyl)penta-2,4-dienoate (**111**) (196 mg, 0.470 mmol) and caesium fluoride (130 mg, 0.855 mmol). In a separate flask, PdCl₂ (1.5 mg, 0.084 mmol), tri-*tert*-butylphosphine (3.5 mg, 0.017 mmol) and CuI (3.25 mg, 0.016 mmol) were combined in DMF (1.0 mL) and degassed. The catalyst mixture was added to the above reaction dropwise over 10 min and the mixture was heated at 100 °C for 10 hours. The mixture was filtered through a pad of silica and eluted with EtOAc (20 mL). Solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography (2% EtOAc in petrol) to yield the inseparable diastereoisomers **108** and **109** (**108**:**109**=3:2, 58 mg, 44%) as a pale yellow oil.

R_f = 0.20 (2% EtOAc in petrol); $\nu_{\max}$ (cm⁻¹) (Thin film): 3033, 2904, 1726 (C=O ester), 1503, 1489, 1444, 1250 (C-O aromatic ether), 1039; δ_H

(CDCl₃, 400 MHz): 6.81 - 6.62 (6H, m, 11-H₁, 11'-H₁, 14-H₁, 14'-H₁, 15-H₁, 15'-H₁), 6.02 - 5.32 (12H, m, 2-H₁, 2'-H₁, 3-H₁, 3'-H₁, 4-H₁, 4'-H₁, 5-H₁, 5'-H₁, 16-H₂, 16'-H₂), 4.25 - 3.98 (4H, m, 18-H₂, 18'-H₂), 3.49 - 2.57 (12H, m, 1-H₁, 1'-H₁, 6-H₁, 6'-H₁, 7-H₁, 7'-H₁, 8-H₁, 8'-H₁, 9-H₂, 9'-H₂), 1.37 - 1.15 (6H, m, 19-H₃, 19'-H₃); **HRMS** (ESI): Calculated for C₁₉H₂₁O₄ [M+H]⁺ 313.1434 obtained 313.1434, calculated for C₁₉H₂₀NaO₄ [M+Na]⁺ 335.1254 obtained 335.1245, calculated for C₁₉H₂₄NO₄ [M+NH₄]⁺ 330.1700 obtained 330.1698.

Methyl (1*R*^{*},6*R*^{*},7*R*^{*},8*S*^{*})-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (131**) and methyl (1*R*^{*},6*R*^{*},7*S*^{*},8*R*^{*})-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (**132**)**

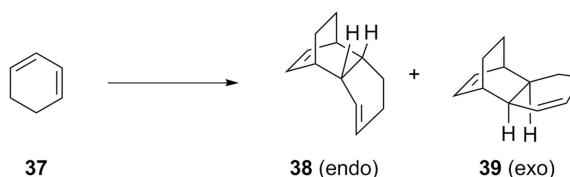


To 0 °C solution of tris(4-bromophenyl)amminium hexachloroantimonate (10 mg, 0.012 mmol) in CH₂Cl₂ (1.0 mL) was added a solution of the bicyclo[4.2.0]octadienes **108** and **109** (**108:109**=3:2, 37 mg, 0.118 mmol) in CH₂Cl₂ (0.5 mL) dropwise. The reaction mixture was stirred at 0 °C for 30 min before being quenched with NaOMe/MeOH solution (1 mL, 25% w/w). The aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL) and

the combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (2% EtOAc in petrol) to yield the inseparable diastereoisomers **131** and **132** (**131:132**=3:2, 22 mg, 63%) as a pale yellow oil.

R_f = 0.2 (2% EtOAc in petrol); ν_{max} (cm^{-1}) (Thin film): 3032, 2920, 1728 (C=O ester), 1489, 1442, 1248 (C-O aromatic ether), 1038; δ_{H} (CDCl_3 , 400 MHz): 6.80 - 6.62 (6H, m, 11- H_1 , 11'- H_1 , 14- H_1 , 14'- H_1 , 15- H_1 and 15'- H_1), 6.02 - 5.30 (12H, m, 2- H_1 , 2'- H_1 , 3- H_1 , 3'- H_1 , 4- H_1 , 4'- H_1 , 5- H_1 , 5'- H_1 , 16- H_2 and 16'- H_2), 3.71 - 3.58 (6H, m, 18- H_2 and 18'- H_2), 3.48 - 2.56 (8H, m, 1- H_1 , 1'- H_1 , 6- H_1 , 6'- H_1 , 7- H_1 , 7'- H_1 , 8- H_1 and 8'- H_1), 2.95 - 2.56 (4H, m, 9- H_2 , 9'- H_2); **HRMS** (ESI): Calculated for $\text{C}_{18}\text{H}_{18}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 321.1097 obtained 321.1083, calculated for $\text{C}_{18}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{NH}_4]^+$ 316.1543 obtained 316.1543.

(4a*S*,8a*R*)-1,4,4a,5,6,8a-Hexahydro-1,4-ethanonaphthalene (38)
and (4a*R*,8a*S*)-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene
(39)



Thermal Procedure

1,3-cyclohexadiene (**37**) (0.12 mL, 1.25 mmol) was taken neat and sealed inside a 1 mL glass ampoule. The ampoule was placed in a sand bath and heated to 200 °C for 24 hours. Remaining starting material was removed

under reduced pressure to yield the dimeric products **38** (*endo*) and **39** (*exo*) (**38:39**=4:1, 31 mg, 31%).

Radical Cation Procedure

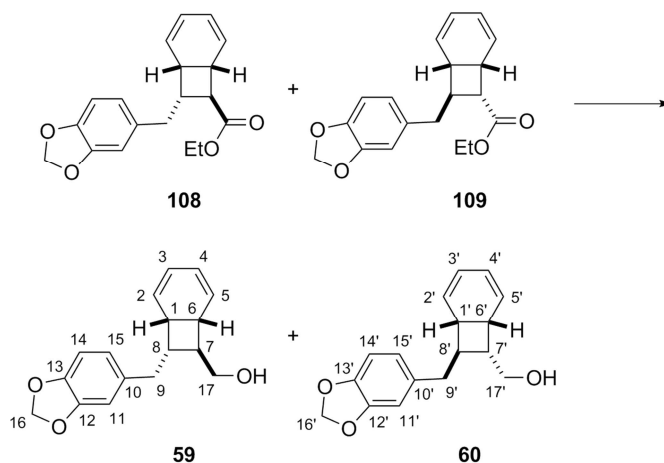
A solution of tris(4-bromophenyl)amminum hexachloroantimonate (**40**) (0.101 g, 0.125 mmol) in CH₂Cl₂ (3.0 mL) was cooled to 0 °C and to it was added dropwise 1,3-cyclohexadiene (**37**) (0.12 mL, 1.25 mmol). The reaction mixture was stirred at 0 °C for 15 min and then filtered through silica gel and eluted with CH₂Cl₂ (30 mL). The solvent and remaining starting material were removed under reduced pressure to yield the title compounds **38** (*endo*) and **39** (*exo*) (**38:39**=5:1, 66 mg, 66%).

δ_{H} (CDCl₃, 400 MHz): 6.41 - 6.31 (2H, m, *exo*), 6.22 - 6.12 (2H, m, *endo*), 6.02 - 5.50 (4H, m, *endo* + *exo*), 2.50 - 0.93 (24H, m, *endo+exo*); δ_{C} (CDCl₃, 100 MHz): 134.1, 132.8, 132.3, 128.2, 40.2, 39.1, 36.8, 36.6, 27.3, 26.4, 25.4, 23.5 (*endo+exo*).

This data is consistent with that reported by Bauld *et al.*³⁷

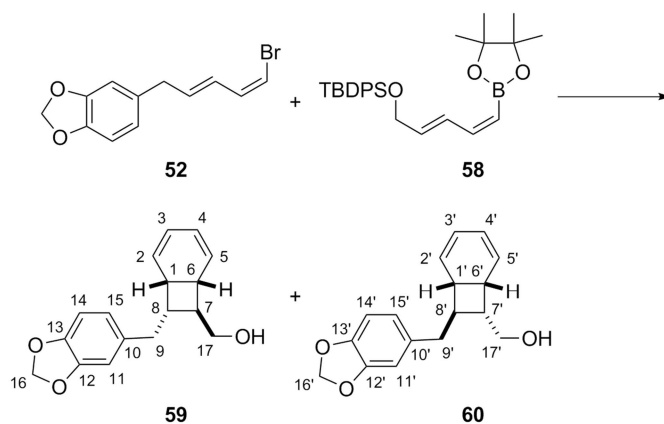
((1*R,6*R**,7*R**,8*S**)-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-dien-7-yl)methanol (**59**) and
((1*R**,6*R**,7*S**,8*R**)-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-dien-7-yl)methanol (**60**)**

Method 1 - Reduction of the esters **108** and **109**



A solution of the esters **108** and **109** (**108:109**=3:2, 37 mg, 0.118 mmol) in CH_2Cl_2 (1 mL) was cooled to $-78\text{ }^\circ\text{C}$. DIBAL-H (0.26 mL, 1 M in hexanes, 0.260 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 30 min before being allowed to warm to room temperature and stir for 4 hours. The reaction mixture was returned to $-78\text{ }^\circ\text{C}$ and MeOH (1 mL) was added carefully before the addition of a sat. aq. solution of potassium sodium tartrate (1 mL). The reaction mixture was then allowed to stir for 16 hours at which point both layers had become clear. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4 and then concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (5 - 14% EtOAc in petrol) to yield the inseparable title compounds **59** and **60** as a pale yellow oil (**59:60**=3:2, 34 mg, 64%).

Method 2 – Suzuki-Miyaura cross-coupling of the vinyl bromide **52** and the boronic ester **58**



To a solution of boronic ester **58** (100 mg, 0.22 mmol) and vinyl bromide **52** (17 mg, 0.07 mmol) in THF:H₂O (3:1, 1 mL) was added Pd(PPh₃)₄ (9 mg, 0.007 mmol) and the solution was stirred for 5 min. Thallium ethoxide (33 mg, 0.13 mmol, 9.4 μ L) was added by micropipette, upon which a yellow precipitate formed. The reaction mixture was heated to 90 $^{\circ}$ C and stirred for 23 h. After cooling to room temperature, Et₂O (2 mL) and sodium thiosulfate (10% w/v H₂O, 1 mL) were added and the solution was stirred for 5 min, filtered through a pad of celite and washed with Et₂O (3 x 5 mL). The organic layer was separated and the aqueous layer extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with brine (10 mL) and then H₂O (10 mL) and then dried over Na₂SO₄, filtered and volatile solvent removed under reduced pressure. The concentrate was passed through a short pad of silica gel with ethyl acetate and hexane (1:1) (300 mL). The yellow fractions were combined and the volatile solvents were removed under reduced pressure. The crude products were carried directly on to the next step without further purification.

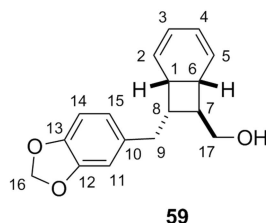
To the above was added THF (0.6 mL) and the reaction mixture was cooled to 0 °C. To this solution was added portion wise tetrabutylammonium fluoride trihydrate (70 mg, 0.22 mmol) and the reaction was allowed to warm to room temperature. After stirring for 4 h, the mixture was returned to 0 °C and sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (0.5 mL) was added. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (5 – 14% EtOAc in petrol) to furnish the inseparable title compounds **59** and **60** (**59:60**=3:2, 16.6 mg, 83% over two steps) as a pale yellow oil.

R_f = 0.37 (20% EtOAc in petrol); ν_{max} (cm^{-1}) (Thin film): 3355, 2918, 1502, 1442, 1247 (C-O-C), 1039; δ_{H} (CDCl_3 , 400 MHz): 6.75 - 6.60 (3H, m), 5.95 - 5.90 (2.6H, m), 5.89 - 5.83 (0.4H, m), 5.73 (0.6H, dd, J = 9.5, 5.4 Hz), 5.66 - 5.57 (2H, m), 5.45 (0.4H, dd, J = 9.7, 5.5 Hz), 3.72 (0.4H, dd, J = 10.8, 8.2 Hz), 3.58 (0.4H, dd, J = 10.8, 5.7 Hz), 3.46 - 3.33 (1.2H, m), 3.28 - 3.18 (1H, m), 2.91 - 2.54 (5H, m); δ_{C} (CDCl_3 , 100 MHz): 147.7, 147.6, 145.8, 145.7, 134.8, 134.3, 127.2, 126.7, 126.2, 125.3, 124.4, 124.3, 121.8, 121.5, 121.4, 121.2, 109.05, 108.95, 108.24, 108.17, 100.8 (x2), 65.3, 63.3, 53.6, 50.4, 51.7, 48.3, 41.6, 36.2, 36.1, 34.5, 32.9, 32.5; **HRMS** (ESI): Calculated for $\text{C}_{17}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$ 271.1329 obtained 271.1338, calculated for $\text{C}_{17}\text{H}_{18}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 293.1148, obtained 293.1140.

This data is consistent with that reported by Parker *et al.*¹⁰

The mixture of diastereoisomers was subjected to repeated purification by preparative thin layer chromatography (2-7% ethyl acetate in hexanes) to obtain an analytically pure sample of the alcohol **59**.

((1*R,6*R**,7*R**,8*S**)-8-(benzo[*d*][1,3]dioxol-5-ylmethyl)bicyclo[4.2.0]octa-2,4-dien-7-yl)methanol (59)**

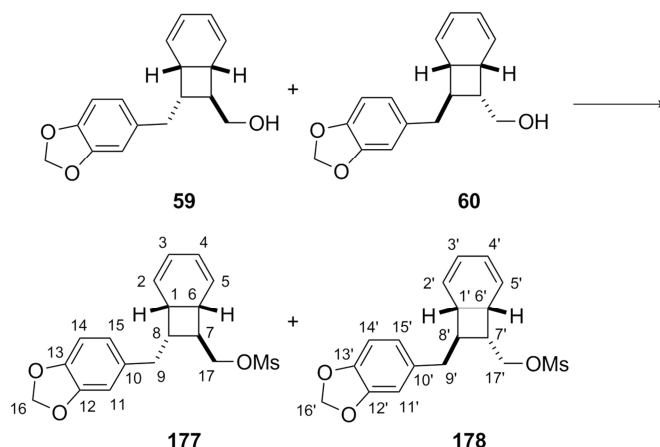


δ_{H} (CDCl₃, 400 MHz): 6.73 (1H, d, J = 7.9 Hz, 15-H), 6.69 (1H, apt d, J = 1.7 Hz, 11-H), 6.65 (1H, apt dd, J = 7.9, 1.7 Hz, 14-H), 5.93 (s, 2H, 16-H₂), 5.95 - 5.90 (m, 1H, 4-H), 5.73 (1H, dd, J = 9.5, 5.2 Hz, 3-H), 5.57 - 5.65 (2H, m, 2-H and 5-H), 3.43 - 3.32 (2H, m, 9-H₂), 3.25 - 3.18 (m, 1H, 6-H), 2.90 - 2.70 (m, 4H, 17-H₂, 7-H and 1-H), 2.62 - 2.55 (m, 1H, 8-H₁);

δ_{C} (CDCl₃, 125 MHz): 147.7 (13-C), 145.7 (12-C), 134.8 (10-C), 126.7 (2-CH), 126.2 (5-CH), 124.3 (4-CH), 121.8 (3-CH), 121.2 (14-C), 108.95 (11-CH), 108.17 (15-CH), 100.8 (16-CH₂), 65.3 (9-CH₂), 53.6 (8-CH), 48.3 (7-CH), 36.2 (17-CH₂), 34.5 (6-CH), 32.9 (1-CH).

This data is consistent with that reported by Parker *et al.*¹⁰

5-(((1*R,6*R**,7*S**,8*R**)-8-((mesityloxy)methyl)bicyclo[4.2.0]octa-2,4-dien-7-yl)methyl)benzo[*d*][1,3]dioxole (177) and 5-(((1*R**,6*R**,7*S**,8*R**)-8-((mesityloxy)methyl)bicyclo[4.2.0]octa-2,4-dien-7-yl)methyl)benzo[*d*][1,3]dioxole (178)**

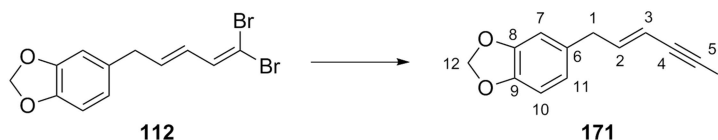


To a $-10\text{ }^{\circ}\text{C}$ solution of alcohols **59** and **60** (**59:60**=3:2, 30.0 mg, 0.111 mmol) and Et_3N (16.8 mg, 0.167 mmol) in CH_2Cl_2 (0.2 mL) was added methane sulfonylchloride (14 mg, 0.122 mmol). The reaction mixture was stirred for 1 hour at $-10\text{ }^{\circ}\text{C}$ and then transferred to a separating funnel which had been chilled with dry ice. The reaction mixture was washed with $10\text{ }^{\circ}\text{C}$ H_2O (10 mL), $0\text{ }^{\circ}\text{C}$ HCl (1 M, 10 mL), sat. $\text{NaHCO}_{3(\text{aq})}$ (3 x 10 mL) and then brine (10 mL). The combined organic fractions were dried over MgSO_4 , filtered and then concentrated under reduced pressure to yield the title compounds **177** and **178** (**177:178**=3:2, 30 mg, 78%) as a pale yellow oil.

$R_f = 0.43$ (20% EtOAc in petrol); ν_{max} (cm^{-1}) (Thin film): 3030, 2924 (C-H), 1503, 1489, 1443, 1353, 1248 (C-O-C); δ_{H} (CDCl_3 , 400 MHz): 6.75 - 6.58 (6H, 11- H_1 , 11'- H_1 , 14- H_1 , 14'- H_1 , 15- H_1 , 15'- H_1), 5.98 - 5.40 (12H, 2- H_1 , 2'- H_1 , 3- H_1 , 3'- H_1 , 4- H_1 , 4'- H_1 , 5- H_1 , 5'- H_1 , 16- H_2 , 16'- H_2), 4.32 - 3.80 (4H, 9- H_2 , 9'- H_2), 3.31 - 2.53 (18H, 1- H_1 , 1'- H_1 , 6- H_1 , 6'- H_1 , 7- H_1 , 7'- H_1 , 8- H_1 , 8'- H_1 , 16- H_2 , 16'- H_2 , $(\text{SO}_2\text{C}-\text{H}_3)_2$); **HRMS** (ESI): Calculated for

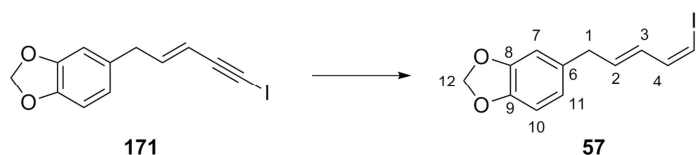
$C_{18}H_{20}NaO_5S$ $[M+Na]^+$ 371.0924 obtained 371.0924, calculated for $C_{18}H_{24}NO_5S$ $[M+NH_4]^+$ 366.1370 obtained 366.1373.

(*E*)-5-(5-iodopent-2-en-4-yn-1-yl)benzo[*d*][1,3]dioxole (171**)**



A solution of the 1,1-dibromodiene **112** (100 mg, 0.289 mmol) in THF (4 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. To this was added $n\text{BuLi}$ (0.261 mL, 2.43 M in hexane, 0.635 mmol) dropwise and the reaction was stirred for 1 hour at this temperature and then warmed to $0\text{ }^{\circ}\text{C}$. A solution of iodine (110 mg, 0.433 mmol) in THF (2 mL) was added and then the reaction mixture was warmed to room temperature and stirred for 3 hours. Sat. $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over MgSO_4 , filtered and then concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (0 – 1% EtOAc in petrol) to yield the title compound **171** (97 mg, 59%) as a yellow solid.

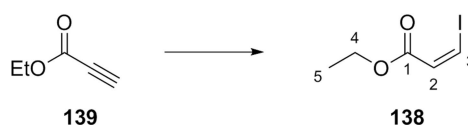
R_f = 0.15 (1% EtOAc in petrol); ν_{max} (cm^{-1}) (CHCl_3): 2895 (C-H), 1504, 1488, 1443, 1247 (C-O-C); δ_{H} (CDCl_3 , 400 MHz): 6.78 - 6.73 (1H, m, 10- H_1), 6.66 - 6.59 (2H, m, 11- H_1 , 7- H_1), 6.30 (1H, dt, J = 15.8, 6.9 Hz, 2- H_2), 5.94 (2H, s, 12- H_2), 5.61 (1H, dt, J = 15.8, 1.6 Hz, 3- H_1), 3.37 (2H, d, J = 6.9 Hz, 1- H_2); δ_{C} (CDCl_3 , 100 MHz): 147.8 (9-C), 146.2 (8-C), 145.4 (2-CH), 132.2 (6-C), 121.5 (11-CH), 111.1 (3-CH), 109.2 (7-CH), 108.3 (10-CH), 100.9 (12- H_2), 92.7 (4-C), 38.6 (1- CH_2), 4.7 (5-C); **HRMS** (ESI): Calculated for $\text{C}_{12}\text{H}_{10}\text{IO}_2$ $[M+H]^+$ 312.9720 obtained 312.9734.

5-((2E,4Z)-5-iodopenta-2,4-dien-1-yl)benzo[d][1,3]dioxole (57)

A solution of the 1-iodoalkyne **171** (22 mg, 0.064 mmol) in THF:IPA (1:1, 0.74 mL) was cooled to 4 °C. To this was added 2-nitrobenzenesulfonylhydrazine (70 mg, 0.320 mmol) and then Et₃N (0.05 mL, 0.320 mmol). The reaction mixture was stirred at 4 °C for 29 hours and then warmed to room temperature. Et₂O (2.5 mL) was added and the reaction mixture was washed with brine (2 x 2.5 mL) and then H₂O (2.5 mL). The organic fraction was dried over MgSO₄, filtered and then concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (0 - 1% EtOAc in petrol to yield the title compound **57** (4.4 mg, 22%) as a pale yellow oil.

R_f = 0.74 (1% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 2891 (C-H), 1502, 1640 (C=C), 1608 (C=C), 1488, 1442, 1247 (C-O-C), 1040; **δ_H** (CDCl₃, 400 MHz): 6.78 - 6.62 (4H, m, 4-H₁, 7-H₁, 10-H₁, 11-H₁), 6.30 (1H, ddd, *J* = 15.2, 9.8, 1.0 Hz, 3-H₁), 6.19 (1H, d, *J* = 7.7 Hz, 5-H₁), 6.12 - 6.03 (1H, m, 2-H₁), 5.94 (2H, s, 12-H₂), 3.40 (2H, d, *J* = 7.2, 1-H₂); **δ_C** (CDCl₃, 100 MHz): 147.8 (9-C), 146.0 (8-C), 138.2 (2-CH), 138.2 (4-C), 133.1 (6-C), 131.4 (3-CH), 121.4 (11-CH), 109.1 (7-CH), 108.3 (10-CH), 100.9 (12-CH₂), 80.8 (5-CH), 39.1 (1-CH₂); **HRMS** (EI): Calculated for C₁₂H₁₁IO₂ [M]⁺ 313.9804 obtained 312.9800.

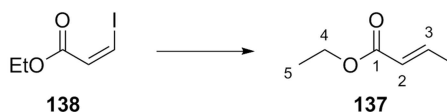
This data is consistent with that reported by Parker *et al.*¹⁰

Ethyl (2Z)-3-iodoacrylate (138)

A stirred suspension of sodium iodide (3.00 g, 20.0 mmol) and acetic acid (10 mL) was heated to 70 °C and stirred until all the solid material was dissolved. Ethylpropynoate (**139**) (1.94 g, 19.7 mmol) was added and the mixture was heated to 70 °C for 12 h. Upon cooling to room temperature, Et₂O (20 mL) and H₂O (20 mL) were added. The organic layer was separated and the aqueous phase was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with sodium hydroxide solution (10% in H₂O, 30 mL), Na₂S₂O₃ (10% in H₂O, 30 mL), and then brine (30 mL). The colourless solution was dried over MgSO₄, filtered and then concentrated under reduced pressure to afford the title compound **138** (4.00 g, 90%) as a pale yellow oil.

R_f = 0.51 (5% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 3064, 2982 (C-H), 1726 (C=O), 1600, 1323, 1198 (C-O), 1164; **δ_H** (CDCl₃, 400 MHz): 7.44 (1H, d, *J* = 8.9 Hz, 3-H₁), 8.90 (1H, d, *J* = 8.9 Hz, 2-H₁), 4.26 (2H, q, *J* = 7.2 Hz, 4-H₂), 1.33 (3H, t, *J* = 7.2 Hz, 5-H₃); **δ_C** (CDCl₃, 100 MHz): 164.6 (1-C), 130.0 (2-CH), 94.6 (3-CH), 60.8 (4-CH₂), 14.17 (5-CH₃); **HRMS** (ESI): Calculated for C₅H₈IO₂ [M+H]⁺ 226.9563 obtained 226.9567, calculated for C₅H₇INaO₂ [M+Na]⁺ 248.9383 obtained 248.9397.

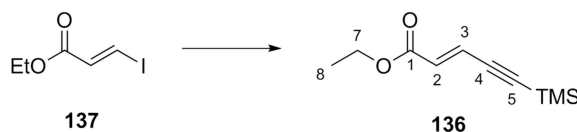
This data is consistent with that reported by Trost *et al.*⁷⁴

Ethyl (2*E*)-3-iodoacrylate (137**)**

To a solution of (*Z*)-vinyl iodide **138** (6.49 g, 28.7 mmol) in toluene (10 mL) was added a 47% aqueous solution of hydroiodic acid (0.45 mL). The resulting mixture was heated to 80 °C for 8 h, whereupon the dark brown solution was cooled to room temperature and diluted with Et₂O (120 mL). The organic layer was separated and washed with sat. NaHCO_{3(aq)} (30 mL), Na₂S₂O₃ (10% in H₂O, 30 mL) and brine (30 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to afford the title compound **137** (5.40 g, 83%) as a pale yellow oil.

R_f = 0.63 (5% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 3064, 2982 (C-H), 1726 (C=O), 1600, 1323, 1198 (C-O), 1164; **δ_H** (CDCl₃, 400 MHz): 7.88 (1H, d, *J* = 14.8 Hz, 3-H₁), 6.88 (1H, d, *J* = 14.8 Hz, 2-H₁), 4.21 (2H, q, *J* = 7.1 Hz, 4-H₂), 1.30 (3H, t, *J* = 7.1 Hz, 5-H₃); **δ_C** (CDCl₃, 100 MHz): 164.2 (1-C), 136.6 (2-CH), 99.3 (3-CH), 61.0 (4-CH₂), 14.2 (5-CH₃); **HRMS** (ESI): Calculated for C₅H₁₁INO₂ [M+NH₄]⁺ 243.9829 obtained 243.9833.

This data is consistent with that reported by Trost *et al.*⁷⁴

Ethyl (2*E*)-5-(trimethylsilyl)pent-2-en-4-ynoate (136)

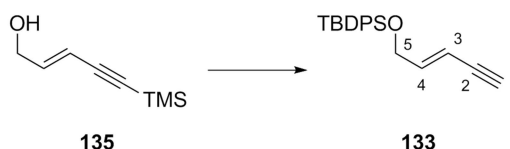
To a degassed solution of (*E*)-vinyl iodide **137** (2.85 g, 12.6 mmol) in anhydrous Et₃N (42 mL) was added dichlorobis(triphenylphosphine)palladium (88 mg, 0.126 mmol) and CuI (12 mg, 0.063 mmol). The pale yellow suspension was heated to 50 °C and stirred until the palladium complex was dissolved (ca. 10 min). Trimethylsilylacetylene (1.92 mL, 13.86 mmol) was added and the resulting yellow reaction mixture was stirred for 9 h at 50 °C, during which a precipitate was formed. The dark brown mixture was cooled to room temperature, the precipitate was removed by filtration and the filter cake was washed several times with Et₂O (40 mL). The reaction mixture was concentrated under reduced pressure and the brown residue was dissolved with Et₂O (150 mL), washed with sat. NH₄Cl_(aq) (2 × 20 mL) and brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (1 - 3% EtOAc in petrol) to afford the title compound **136** (1.71 g, 88%) as a colourless oil.

R_f = 0.50 (5% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 2962, 1720 (C=O), 1620, 1303, 1178 (C-O), 1072; **δ_H** (CDCl₃, 400 MHz): 6.75 (1H, d, *J* = 16.0 Hz, 3-H₁), 6.25 (1H, d, *J* = 16.0 Hz, 2-H₁), 4.22 (2H, q, *J* = 7.1 Hz, 7-H₂), 1.30 (3H, t, *J* = 7.1 Hz, 8-H₃); **δ_C** (CDCl₃, 100 MHz): 165.8 (1-C), 131.2 (2-CH), 124.9 (3-CH), 104.8 (5-C), 101.3 (4-C), 60.4 (7-CH₂), 14.2 (8-CH₃), -0.4 (Si-(CH₃)₃); **HRMS** (ESI): Calculated for C₁₀H₁₇O₂Si [M+H]⁺ 197.0992 obtained 197.0993, calculated for C₁₀H₁₆NaO₂Si [M+Na]⁺ 219.0812 obtained 219.0810.

R_f = 0.29 (20% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 3333 (O-H), 2960 (C-H), 2134 (C≡C), 1251 (C-O); **δ_H** (CDCl₃, 400 MHz): 6.32 (1H, dt, *J* = 16.0, 5.1 Hz, 2-H₁), 5.78 (1H, dt, *J* = 16.0, 1.9 Hz, 3-H₁), 4.26 - 4.16 (2H, m, 1-H₂), 1.50 (1H, br t, *J* = 5.1 Hz, O-H), 0.20 (9H, s, Si-CH₃); **δ_C** (CDCl₃, 100 MHz): 142.9 (2-CH), 110.4 (3-CH), 103.0 (4-C), 95.3 (5-C), 62.9 (1-CH₂), -0.1 (Si-CH₃); **HRMS** (ESI): Calculated for C₈H₁₄NaOSi [M+Na]⁺ 177.0706 obtained 177.0712.

This data is consistent with that reported by Trost *et al.*⁷⁴

(2E)-5-(*tert*-Butyldiphenylsilyloxy)-pent-3-en-1-yne (133)



A solution of the alcohol **135** (1.50 g, 9.72 mmol) in THF (50 mL) was cooled to 0 °C and tetrabutylammonium fluoride trihydrate (9.20 g, 29.14 mmol) was added portion-wise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was returned to 0 °C and sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (30 mL) was added slowly. The reaction mixture was extracted into Et_2O (3 x 50 mL), dried over MgSO_4 and then filtered. The remaining solution was partially concentrated under reduced pressure to give a residue of ~20 mL.

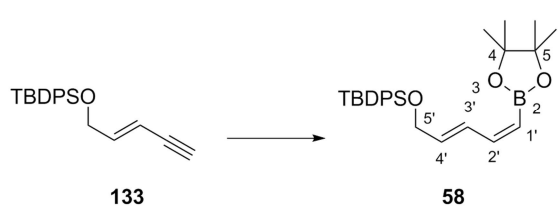
A solution of imidazole (992 mg, 14.57 mmol) in CH_2Cl_2 (60 mL) was cooled to 0 °C. To this solution was added first *tert*-butylchlorodiphenylsilane (3.79 mL, 14.57 mmol) dropwise and then the partially concentrated solution from above. The reaction mixture was allowed to warm to room temperature and stirred for 8 hours. Sat. $\text{NaHCO}_{3(\text{aq})}$ (30 mL) was added slowly and the reaction mixture was diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL). The organic phases were separated and the aqueous phase was washed with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (0 - 10% EtOAc in petrol) to yield the title compound **133** (3.11 g, 65% over two steps) as a colourless oil.

R_f = 0.52 (20% EtOAc in petrol); ν_{max} (cm^{-1}) (Thin film): 3294, 3071, 2959, 2893 (C-H), 2858, 1428, 1114; δ_{H} (400 MHz, CDCl_3): 7.69 - 7.65

(4H, m, Si-C₆H₅), 7.47 - 7.37 (6H, m, Si-C₆H₅), 6.31 (1H, dt, $J = 15.8$, 3.9 Hz, 4-H₁), 5.92 (1H, dq, $J = 15.8$, 2.3 Hz, 3-H₁), 4.28 - 4.25 (2H, m, 5-H₂), 2.92 - 2.89 (1H, m, 1-H₁), 1.08 (9H, s, SiC-CH₃); **δ_c** (CDCl₃, 100 MHz): 143.9 (4-CH), 135.4 (Si-C₆H₅), 133.2 (Si-C₆H₅), 129.8 (Si-C₆H₅), 127.8 (Si-C₆H₅), 107.6 (3-CH), 82.1 (2-C), 77.4 (1-CH), 63.4 (5-CH₂), 26.8 (SiC-CH₃), 19.2 (SiC-CH₃); **HRMS** (ESI): Calculated for C₂₁H₂₄NaOSi [M+Na]⁺ 343.1489 obtained 343.1480.

This data is consistent with that reported by McDonald *et al.*⁷³

2-[(1'*Z*,3'*E*)-5'-(*tert*-Butyldiphenylsilyloxy)penta-1',3'-dien-1'-yl]-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (58**)**

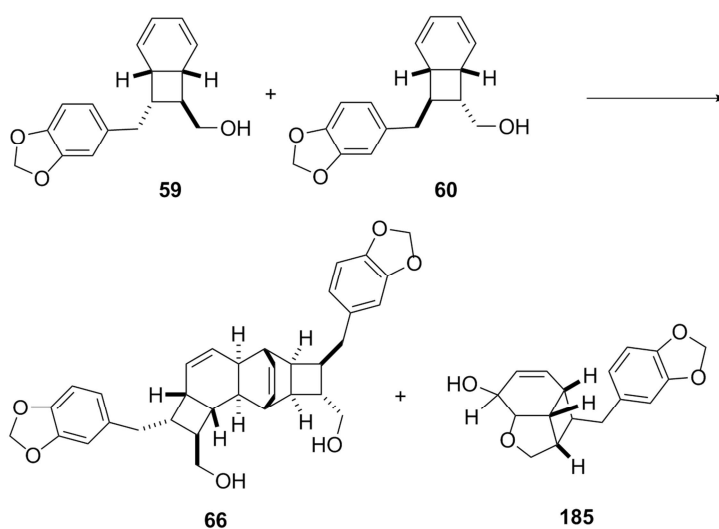


To a room temperature solution of [Rh(cod)Cl]₂ (2 mg, 0.004 mmol) in cyclohexane (0.5 mL) was added triisopropylphosphine (2.6 mg, 0.003 mL, 0.016 mmol) by glass syringe. To this was added anhydrous Et₃N (0.22 mL, 1.56 mmol) and then freshly distilled pinacolborane (33 mg, 0.259 mmol). The reaction mixture was stirred for 30 min before the dropwise addition of a solution of protected enynol **133** (100 mg, 0.312 mmol) in cyclohexane (0.1 mL). The reaction mixture was stirred at room temperature for 4 hours and then concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (pre-treated with 2.5% Et₃N in hexanes, 0 - 4% EtOAc in hexanes) to yield the title compound **58** (51 mg, 44%) as a viscous yellow oil.

R_f = 0.15 (2% EtOAc in petrol); $\nu_{\max}$ (cm^{-1}) (Thin film): 2928 (C-H), 2856, 1592, 1428, 1379, 1259 (C-O), 1112; δ_H (CDCl_3 , 400 MHz): 7.74 - 7.69 (4H, m, Si-C₆H₅), 7.47 - 7.36 (6H, m, Si-C₆H₅), 7.33 - 7.28 (1H, m, 3'-H), 6.90 (1H, t, J = 13.1 Hz, 2'-H), 5.90 (1H, dt, J = 15.2, 4.2 Hz, 4'-H), 5.37 (1H, d, J = 13.1, 1'-H), 4.33 - 4.29 (2H, m, 5'-H), 1.27 (12H, s, OC-CH₃), 1.11 (9H, s, SiC-CH₃); **HRMS** (ESI): Calculated for C₂₇H₃₇BNaO₃Si [M+Na]⁺ 471.2497 obtained 471.2484, calculated for C₂₇H₄₁BNO₃Si [M+NH₄]⁺ 466.2943 obtained 466.2928.

This data is consistent with that reported by Parker *et al.*¹⁰

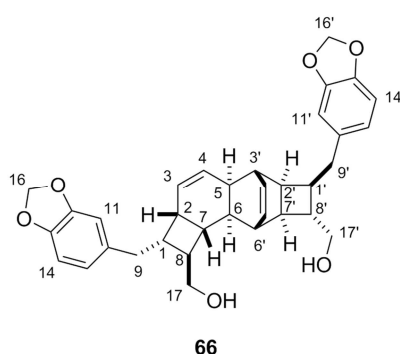
The Diol **66** and the Ether **185**



To a solution of tetrabutylammonium tetrafluoroborate (1.97 g, 5.97 mmol) in CH₂Cl₂ (15 mL) was added the mixture of alcohols **59** and **60** (**59:60**=3:2, 10.0 mg, 0.04 mmol). The reaction mixture was subjected to anodic oxidation at 1.5 V until 3.57 C of charge had been passed. The solution was concentrated under reduced pressure and the resulting solids were ground to a fine powder in a mortar and pestle and then triturated with Et₂O (5 x 10 mL). The organic washings were combined and dried over anhydrous MgSO₄, filtered and concentrated

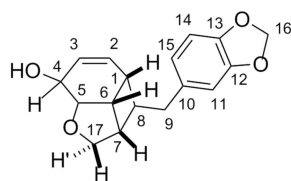
under reduced pressure. The above procedure was repeated for a second batch of alcohol (10.0 mg, 0.04 mmol) and the crude products were combined and purified by preparative thin layer chromatography (Et₂O:Hexanes:CH₂Cl₂:MeOH = 1:1:1:0.02) to yield the diol **66** (1.5 mg, 13%) and the ether **185** (1.3 mg, 16%).

The Diol **66**



R_f = 0.13 (67% EtOAc in petrol); **v_{max}** (cm⁻¹) (Thin film): 3429 (O-H), 1646 (C=C); **δ_H** (CDCl₃, 400 MHz): 6.74 - 6.56 (6H, m), 6.28 (1H, t, *J* = 7.0 Hz, 5'-H₁), 6.14 (1H, t, *J* = 7.0 Hz, 4'-H₁), 5.92^a (2H, s, 16-H₂), 5.91^a (2H, s, 16'-H₂), 5.72 (1H, br d, *J* = 10.3 Hz, 4-H₁), 5.64 (1H, br d, *J* = 10.3 Hz, 3-H₁), 3.41 - 3.31 (4H, m), 2.70 - 2.16 (12H, m), 2.03 - 1.93 (2H, m), 1.88 - 1.79 (1H, m), 1.73 (1H, d, *J* = 9.0 Hz, 6-H₁); **δ_C** (CDCl₃, 125 MHz): 147.7, 147.6, 145.60 (x2), 135.4, 135.1, 135.0, 132.1, 132.0, 125.3, 121.1, 121.0, 108.9, 108.8, 108.2 (x2), 100.7 (x2), 67.0, 65.2, 47.7, 44.1, 42.7, 41.2, 40.73, 40.67, 39.5, 38.8, 38.6, 38.3, 38.0, 36.3, 35.3, 32.8; **HRMS** (ESI): Calculated for C₃₄H₃₆NaO₆ [M+Na]⁺ 563.2404 obtained 563.2392.

This data is consistent with that reported by Parker *et al.*¹⁰ ^aValues interchangeable.

The Ether 185

$R_f = 0.27$ (67% EtOAc in petrol); $\nu_{\max}$ (cm^{-1}) (Thin film): 3425 (O-H), 1641 (C=C); δ_{H} (CDCl_3 , 400 MHz): 6.73 (1H, d, $J = 7.9$ Hz, 15- H_1), 6.65 (1H, apt d, $J = 1.5$ Hz, 11- H_1), 6.61 (1H, apt dd, $J = 7.9, 1.5$ Hz, 14- H_1), 5.93 (2H, s, 16- H_2), 5.90 - 5.84 (1H, m, 3- H_1), 5.67 (1H, dd, $J = 10.1, 4.3$ Hz, 2- H_1), 4.34 (1H, br s, 4- H_1), 3.91 (1H, br dd, $J = 6.2, 2.1$ Hz, 5- H_1), 3.66 (1H, d, $J = 9.3$ Hz, 17'- H_1), 3.48 (1H, dd, $J = 9.3, 4.5$ Hz, 17- H_1), 3.03 - 2.96 (1H, m, 6- H_1), 2.74 (2H, d, $J = 8.2$ Hz, 9- H_2), 2.66 - 2.61 (1H, m, 7- H_1), 2.47 (1H, dddd, $J = 8.6, 6.5, 4.5, 1.9$ Hz, 1- H_1), 1.95 - 1.86 (1H, m, 8- H_1); δ_{C} (CDCl_3 , 125 MHz): 147.6 (13-C), 145.8 (12-C), 133.6 (10-C), 132.1 (2-CH), 124.0 (3-CH), 121.4 (14-CH), 108.9 (11-CH), 108.1 (15-CH), 100.8 (16- CH_2), 78.8 (5-CH), 72.4 (17- CH_2), 62.9 (4-CH), 47.3 (8-CH), 41.8 (7-CH), 41.5 (9- CH_2), 33.3 (1-CH), 31.4 (6-CH); **HRMS** (ESI): Calculated for $\text{C}_{17}\text{H}_{18}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 309.1097 obtained 309.1088.

This data is consistent with that reported by Moses *et al.*⁹²

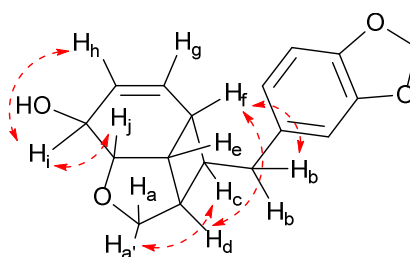


Figure 3.5: Key NOESY correlations for the ether **185**.

O¹⁸-Ether 185

The procedure described for the synthesis of the ether **185** was repeated but 0.2 mL of H₂O¹⁸ was added to the reaction mixture immediately prior to applying voltage to the electrodes.

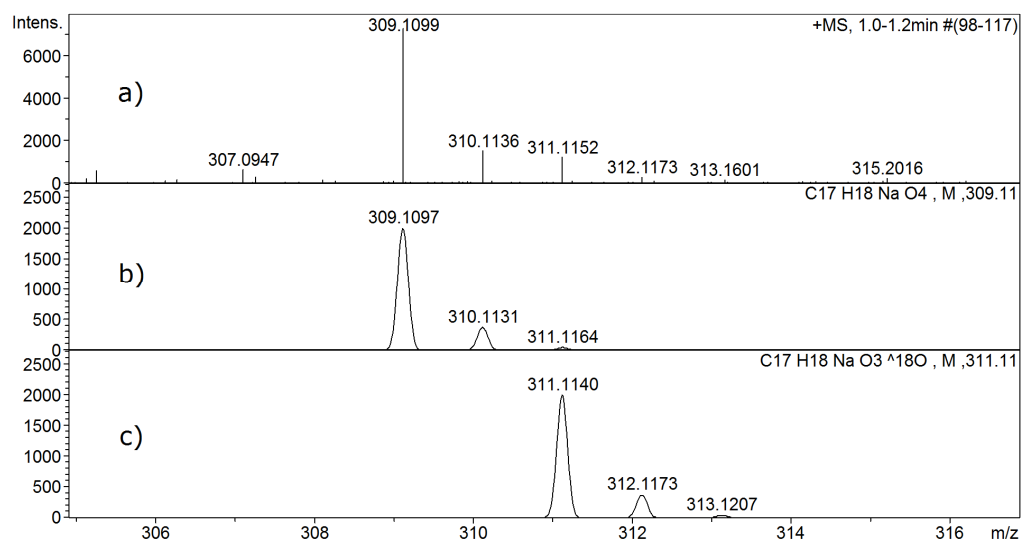


Figure 3.6: a) Obtained HRMS spectrum from O¹⁸ labelling study. b) Calculated HRMS spectrum of unlabelled **185**. c) Calculated HRMS spectrum of labelled **185**.

HRMS (ESI): Calculated for C₁₇H₁₈NaO₃O¹⁸ [M+Na]⁺ 311.1140 obtained 311.1152.

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