INTER- AND INTRAMOLECULAR CYCLOADDITION REACTIONS OF 2*H*-CHROMENES

by

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ABSTRACT

The research described in this thesis concerns a study of a series of inter- and intramolecular cycloaddition reactions of the carbon-carbon double bond of 2*H*-chromenes. Firstly, a series of *mono*-2*H*-chromenes were prepared and it was shown that numerous intermolecular cycloaddition reactions could be performed. These findings were then applied to a C_3-symmetric *tris*-2*H*-chromene in order to prepare complex polycyclic compounds in a highly efficient manner. For example, a cycloaddition reaction product was prepared in two steps from readily-available starting materials that contained seven fused rings and six stereogenic centres. Moreover, the regiochemistry and stereoselectivities of these cycloaddition processes were determined.

A series of intramolecular cycloaddition reactions were then attempted on *mono*- and *tris*-2*H*-chromenes. It was found that intramolecular [2+2] cycloadditions proceeded adequately, however, intramolecular [2+4] cycloadditions were unsuccessful. Thus, preliminary investigations were then undertaken towards the synthesis of functionalized 2*H*-chromenes that would contain a more reactive carbon-carbon double bond.

Keywords: 2*H*-Chromene; Intermolecular; Intramolecular; Cycloaddition

To my parents, Patrick and Shelley.

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δ	chemical shift (NMR spectroscopy)
2D	two dimensional
Ac	acetyl
AcOH	acetic acid
amu	atomic mass unit (mass spectroscopy)
Anal.	elemental analysis
aq	aqueous
Ar	aromatic group
atm	atmospheres
Å	Ångstrom (0.1 nm)
B.p.	boiling point
br	broad (spectroscopy)
brsm	based on recovered starting material
Calcd.	calculated (elemental analysis)
cat.	catalytic (amount)
CI	chemical ionization (mass spectroscopy)
cm^{-1}	wavenumbers (IR spectroscopy)
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
COSY	^{1}H-^{1}H correlation spectroscopy
d	doublet (NMR spectroscopy)
dd	doublet of doublets (NMR spectroscopy)
dr	diastereoisomeric ratio
dt	doublet of triplets (NMR spectroscopy)

DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
dec.	decomposition
DIBAL-H	diisobutylaluminium hydride
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulphoxide
EC_{50}	median effective concentration
ef	evaporated film (IR spectroscopy)
equiv.	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
h	hour(s)
HMBC	heteronuclear multiple bond coherence spectroscopy
HMQC	heteronuclear multiple quantum coherence spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz (cycles per second)
IC_{50}	median inhibition concentration
IR	infrared spectroscopy
J	coupling constant (NMR spectroscopy)
KBr	potassium bromide disc (IR spectroscopy)
LDA	lithium *N*,*N*-diisopropylamide
lit.	literature value for a physical or spectroscopic property

m	multiplet (NMR spectroscopy)
M	molarity of a solution
M	molecular ion (mass spectroscopy)
M + H	molecular ion plus proton (mass spectroscopy)
M – OH	molecular ion minus hydroxide (mass spectroscopy)
M – OMe	molecular ion minus methoxide (mass spectroscopy)
MALDI-TOF	matrix assisted laser desorption ionization-time of flight (mass spectroscopy)
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol (methyl alcohol)
mg	milligram
MHz	megahertz (NMR spectroscopy)
min	minute(s)
mL	millilitres
mm Hg	millimetres of mercury
mmol	millimole(s)
M.p.	melting point
mol	mole(s)
MS	mass spectroscopy
m/z	mass to charge ratio
N/A	not applicable
n-BuLi	*n*-butyl lithium
NBS	*N*-bromosuccinimide

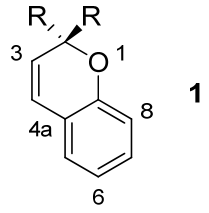
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetate
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million (NMR spectroscopy)
py	pyridine
q	quartet (NMR spectroscopy)
rel.	relative
R_f	retention factor (thin-layer chromatography)
s	singlet (NMR spectroscopy)
t	triplet (NMR spectroscopy)
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin-layer chromatography
W	Watt
v/v	volume by volume
w/v	weight by volume
w/w	weight by weight

1 INTRODUCTION

*Inter- and Intramolecular Cycloaddition Reactions of 2*H-*Chromenes*

1.1 Thesis Introduction

This thesis concerns a study of a series of inter- and intramolecular [2+1], [2+2] and [2+4] cycloaddition reactions of the carbon-carbon double bond of various 2*H*-chromenes **1** (Figure 1.1.1). 2*H*-chromenes, also referred to as 2*H*-1-benzopyrans, are a class of oxygen heterocycles that are common structural motifs in a number of natural products.[1] The objective of this study was to expand on the knowledge of cycloaddition reactions that can be performed on 2*H*-chromenes in order to access complex, stereochemically-rich polycyclic compounds in a concise and direct manner.



1

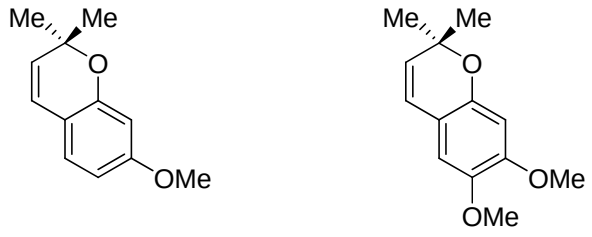
Figure 1.1.1 The parent 2*H*-chromene ring system (1).

1.2 2*H*-Chromenes: General Review of Biological Significance and Preparation

1.2.1 Biological Significance

The 2*H*-chromene moiety is found in a number of natural products such as tannins and polyphenols which are commonly found in a variety of fruits, vegetables, teas and red wines.[2] The interest in these compounds is increasing because of their reported benefit to health.[2] Additionally, the 2*H*-chromene moiety is present in a variety of naturally occurring compounds that have anti-tumour[3] and anti-bacterial activity.[4]

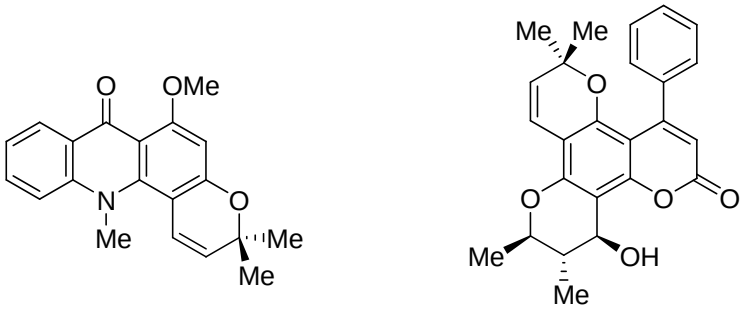
Though 2*H*-chromenes were first prepared in 1939,[5] these interesting heterocycles did not receive significant attention until 1976 when Bowers and co-workers isolated precocene I (**2**) and precocene II (**3**) from *Ageratum houstonianum* (Figure 1.2.1).[6]



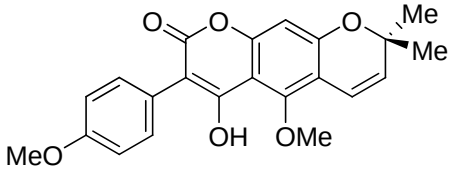
2 **3**

Figure 1.2.1 Molecular structures of precocene I (2) and II (3).

These two simple 2*H*-chromenes were shown to induce precocious metamorphosis in a variety of insects.[6] As such, these 2*H*-chromene moieties were identified as lead compounds for the development of environmentally friendly insecticides. A large number of 2*H*-chromene containing natural products have subsequently been isolated and characterized. For example, acronycine (**4**) is an antitumor drug with an IC_{50} value of 2.0 μg/mL.[7] Inophyllum B_{36} (**5**) is an HIV-1 reverse transcriptase inhibitor with an IC_{50} value of 1.6 μM.[8] Finally, robustic acid (**6**) is a *c*AMP inhibitor with an IC_{50} value of 10.0 μM (Figure 1.2.2).[9]



4 **5**



6

Figure 1.2.2 Molecular structures of acronycine (4), inophyllum B_{36} (5) and robustic acid (6).

1.2.2 Preparation of 2*H*-Chromenes

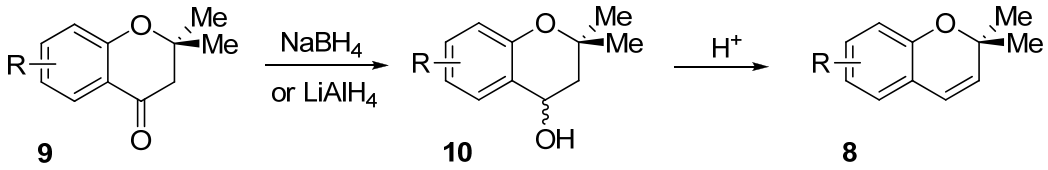
A variety of routes have been used to prepare 2,2-dialkyl-2*H*-chromenes. Initially, coumarins **7** and an appropriate organometallic reagent were used to afford the requisite 2,2-dialkyl-2*H*-chromene **8** (Scheme 1.2.1).[5] This reaction was first conducted by Shriner and co-workers nearly 70 years ago.[5] Unfortunately, this method is limited to the reactions of coumarins which do not contain functional groups that could react with the organometallic reagent, such as a hydroxyl functional group.

Scheme 1.2.1 Synthesis of 2*H*-Chromenes (8) from Coumarins (7) *via* Addition of Grignard Reagents

7 **8**

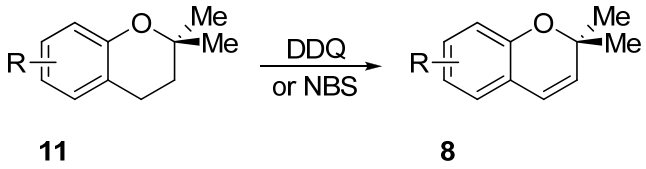
The dehydration reaction of chromanols **10** is another popular option for the preparation of 2*H*-chromenes.[3] Initially, an appropriately substituted chromanone **9** is reduced with either lithium aluminium hydride or sodium borohydride to afford the corresponding chromanol **10**. This chromanol **10** is then readily dehydrated upon treatment with acid to afford the desired 2*H*-chromene **8** (Scheme 1.2.2).

Scheme 1.2.2 Preparation of 2*H*-Chromenes (8) from Chromanones (10)



Additionally, chromanes **11** can be directly oxidized to the 2*H*-chromene **8** using either DDQ or NBS. This method was utilized by Solladie and co-workers to prepare 6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (precocene II, **3**) from the corresponding chromane (Scheme 1.2.3).[10]

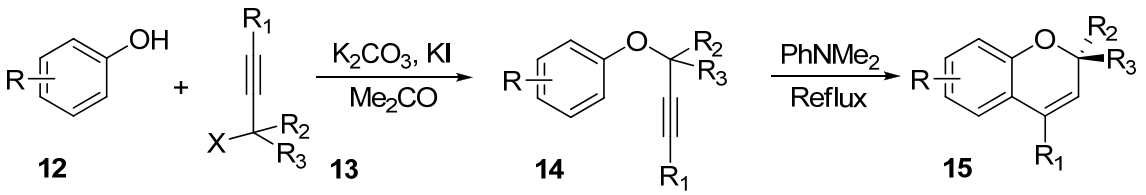
Scheme 1.2.3 Oxidation Reaction of Chromanes (11) to 2*H*-Chromenes (8)



The thermal rearrangement of aryl propargyl ethers is another general and convenient method for the preparation of 2*H*-chromenes. The aryl propargyl ether **14** can be readily prepared by the alkylation reaction of an appropriate phenol derivative **12** and a C3-halogenated alkyne **13**. The reaction is thought to proceed *via* a Claisen-like [3,3] sigmatropic rearrangement followed by a [1,5] sigmatropic shift. Finally, an

electrocyclization reaction completes the synthesis of the 2*H*-chromene **15** (Scheme 1.2.4).[11]

Scheme 1.2.4 Preparation of 2*H*-Chromenes (15) *via* Rearrangement of Propargyl Ethers (14)

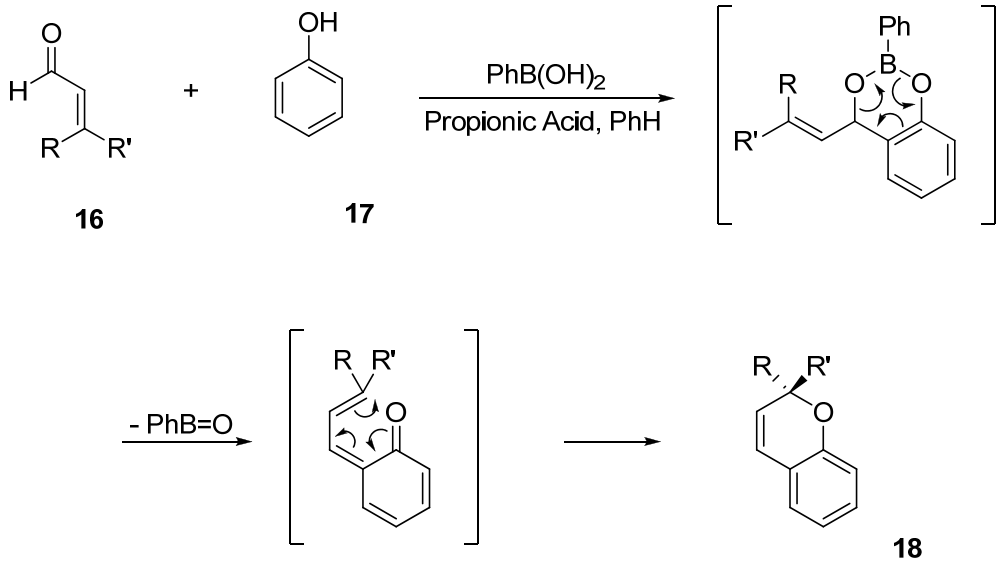


1.2.3 Synthesis of 2*H*-Chromenes from Phenols and α,β-Unsaturated Aldehydes

A variety of methods are available for the preparation of 2*H*-chromenes from a phenol and an appropriately substituted α,β-unsaturated aldehyde. For example, 2*H*-chromenes can be prepared either through base-promoted cyclization or by the phenylboronic acid-mediated condensation reaction of a phenol with an α,β-unsaturated aldehyde.[12,13] Throughout this thesis, the phenylboronic acid-mediated condensation reaction was selected for the preparation of various 2*H*-chromenes.

The phenylboronic acid-mediated condensation reaction involves the use of an α,β-unsaturated aldehyde, a phenol, phenylboronic acid and propionic acid, acting as a catalyst, that are heated at reflux in benzene with the azeotropic removal of water. It has been proposed that this reaction proceeds through an *ortho*-quinone methide intermediate, which would undergo a 6π electrocyclic rearrangement to afford the corresponding 2*H*-chromene moiety (Scheme 1.2.5).[13]

Scheme 1.2.5 Proposed Phenylboronic Acid-Mediated Condensation Reaction of Phenol (17) and an α,β-Unsaturated Aldehyde (16)



1.3 2*H*-Chromenes in Natural Product Chemistry: Daurichromenic Acid and the Xyloketal Family of Natural Products

The Wilson research group has prepared a variety of natural products containing a 2*H*-chromene moiety. For example, daurichromenic acid (**19**) is a natural product that contains a 2*H*-chromene core. In addition, the 2*H*-chromene moiety could serve as a precursor in the formation, through hydrogenation, of chromane containing compounds, such as xyloketal A (**20**) (Figure 1.3.1).

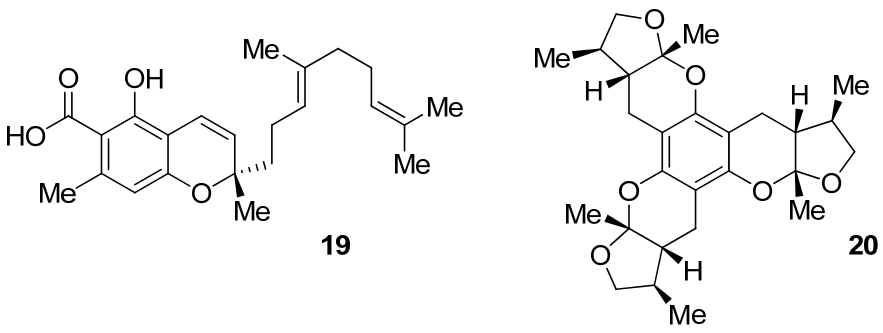


Figure 1.3.1 Molecular structures of daurichromenic acid (19) and xyloketal A (20).

1.3.1 Daurichromenic Acid (19)

Daurichromenic acid (**19**), along with rhododaurichromanic acid A and B (**21** and **22**), was isolated from the leaves and twigs of *Rhododendron dauricum*, by Kashiwada *et al*. in 2001.[14] Daurichromenic acid (**19**) was found to be biologically active, with potent anti-HIV activity against acutely infected H9 cells (EC_{50} = 0.00567 μg/mL).[14] In addition to being a natural product itself, daurichromenic acid (**19**) is thought to be the biosynthetic precursor of the chromane containing natural products, rhododaurichromanic acid A and B (**21** and **22**) (Figure 1.3.2). It has been proposed and demonstrated that the conversion of daurichromenic acid (**19**) into either rhododaurichromanic acid molecule proceeds *via* a [2+2] cycloaddition reaction.[15]

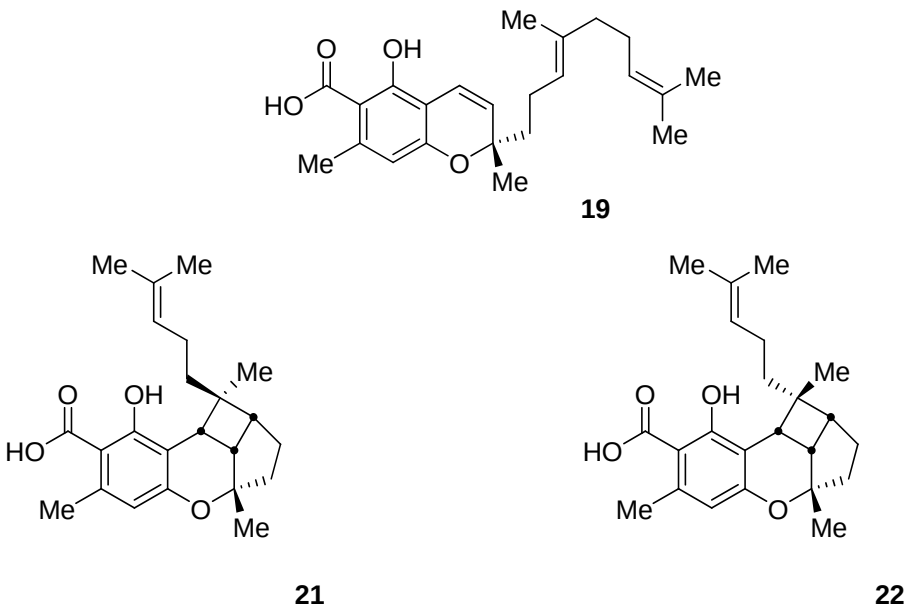
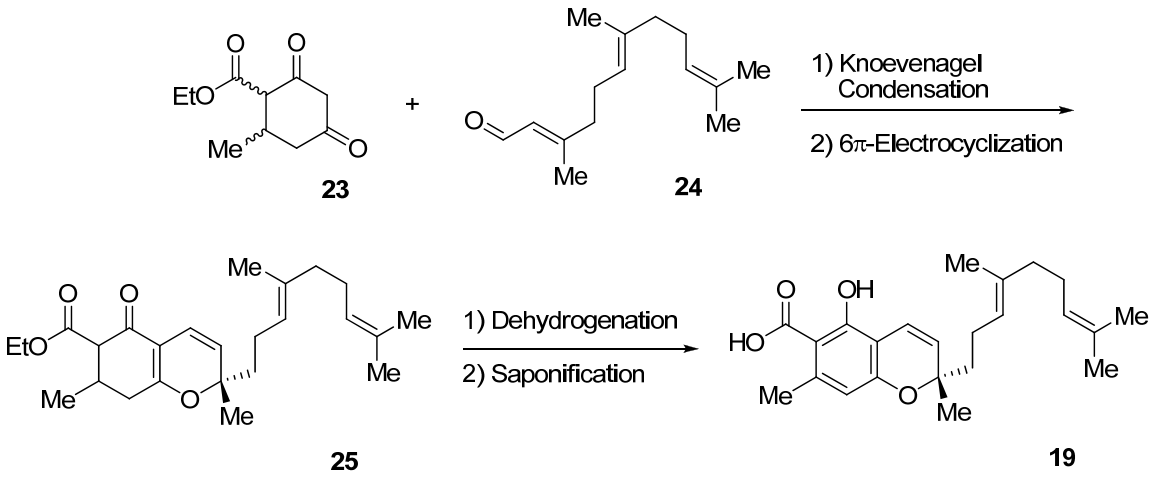


Figure 1.3.2 Molecular structures of daurichromenic acid (19), rhododaurichromanic acid A (21) and rhododaurichromanic acid B (22).

The total synthesis of daurichromenic acid (**19**) was recently completed by Hu *et al.*[16] The key step in this synthesis, the preparation of the 2*H*-pyran **25**, was accomplished in a highly convergent manner by utilizing a Knoevenagel condensation reaction followed by a tandem 6π-electrocyclization reaction of the 1,3-cyclohexanedione **23** with *trans*,*trans*-farnesal (**24**) (Scheme 1.3.1).

Scheme 1.3.1 Knoevenagel Condensation and Electrocyclization Reaction of 1,3-Cyclohexanedione (23) with *trans,trans*-Farnesal (24)



A subsequent dehydrogenation reaction afforded the corresponding 2*H*-chromene moiety, which was then hydrolyzed to the corresponding carboxylic acid, thus completing a concise total synthesis of daurichromenic acid (**19**).

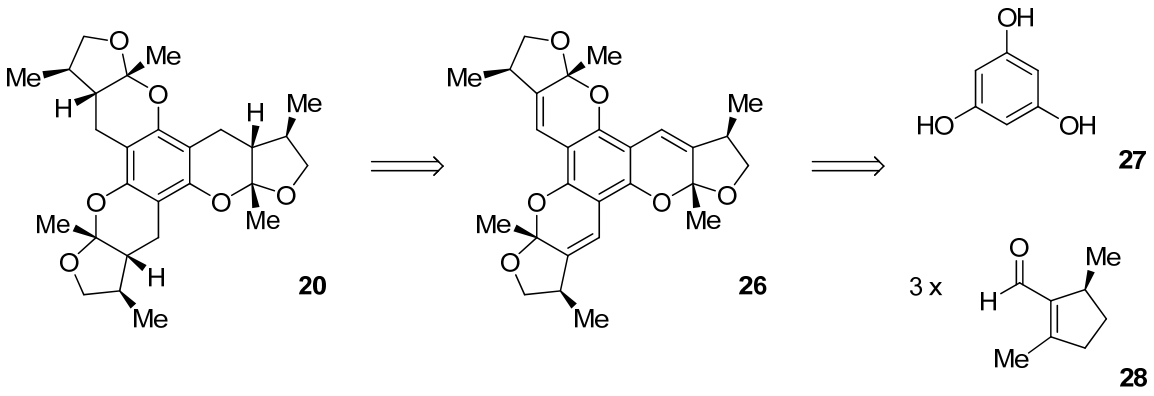
1.3.2 The Xyloketal Family of Natural Products

As previously stated, the 2*H*-chromene moiety could serve as a precursor, through hydrogenation, to afford a variety of chromanes. One such example is the natural product, xyloketal A (**20**). This natural product was isolated from a mangrove fungus of the *Xyleria species* and has been shown to possess notable biological activity.[17] Xyloketal A (**20**) is particularly interesting because it has a unique and aesthetically pleasing C_3-symmetric structure (Figure 1.3.1).

Xyloketal A (**20**) is a C_3-symmetric *tris*-chromane which could, in principle, be prepared upon hydrogenation of the C_3-symmetric *tris*-2*H*-chromene **26**. This *tris*-2*H*-chromene could be prepared from the corresponding α,β-unsaturated aldehyde **28** and

phloroglucinol (1,3,5-trihydroxybenzene) (**27**) *via* a phenylboronic acid-mediated condensation reaction (Scheme 1.3.2).

Scheme 1.3.2 Retrosynthetic Analysis of Xyloketal A (20): Phenylboronic Acid-Mediated Condensation Reaction

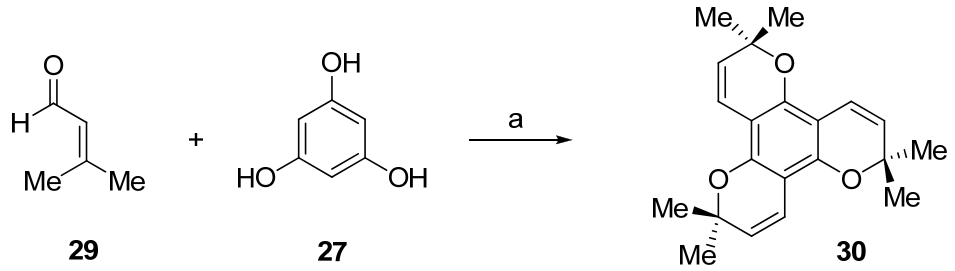


Unfortunately, when the requisite aldehyde **28** was employed in this reaction the compound proved to be unstable towards the reaction conditions. As such, this route could not be applied to complete the total synthesis of xyloketal A (**20**). However, a series of *tris*-2*H*-chromene analogues of this natural product were readily prepared *via* this route. The total synthesis of xyloketal A (**20**) was subsequently accomplished using a boron trifluoride diethyl etherate-promoted triple electrophilic aromatic substitution reaction using a hydroxymethyl dihydrofuran.[18]

In order to assess the feasibility of performing this phenylboronic acid-mediated condensation reaction with various α,β-unsaturated aldehydes, a model study was conducted to determine the optimal reaction conditions to prepare an unprecedented C_3-symmetric *tris*-2*H*-chromene. Pettigrew *et al*. were able to develop a concise method for the construction of C_3-symmetric *tris*-2*H*-chromenes using a simple model α,β-unsaturated aldehyde (senecialdehyde, **29**) (4 equiv) and phloroglucinol (**27**) (1 equiv)

using phenylboronic acid (3 equiv) as a Lewis acid and propionic acid as a catalyst.[19] This reaction was performed in benzene at reflux, with the azeotropic removal of water, to afford the *tris*-2*H*-chromene (**30**) in excellent yield (Scheme 1.3.3).

Scheme 1.3.3 Phenylboronic Acid-Mediated Reaction of Phloroglucinol (27) with Senecialdehyde (29)

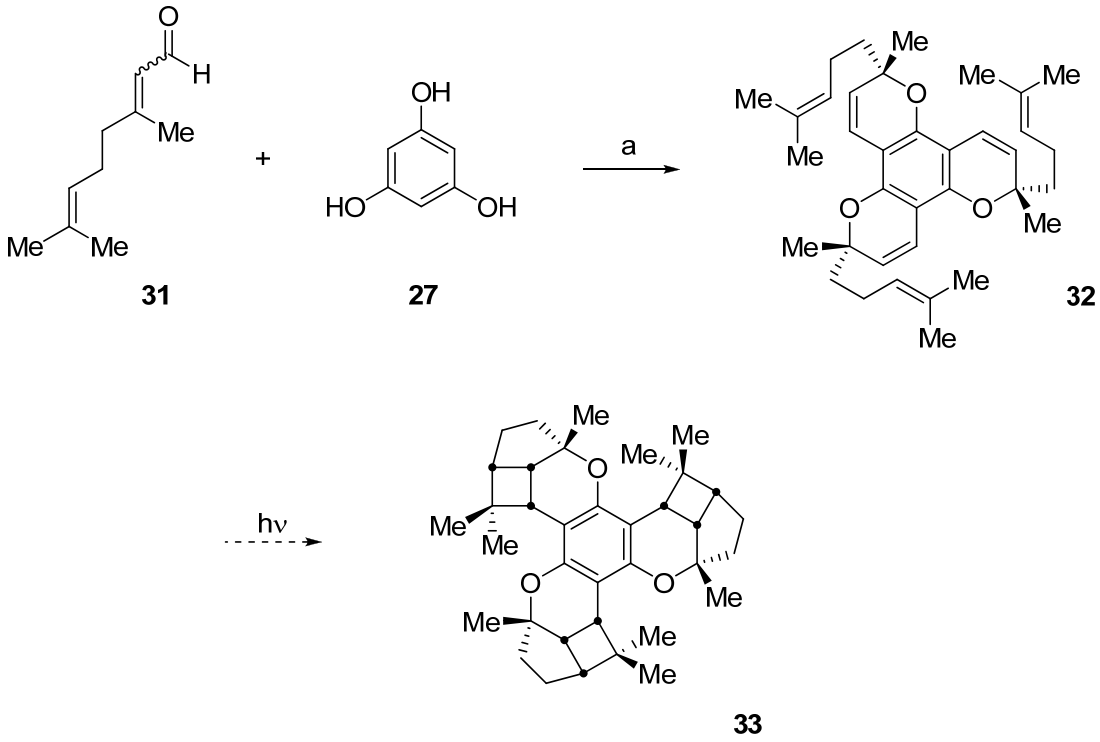


29 **27** **30**

Reagents and conditions: (a) Senecialdehyde (**29**) (4 equiv), $PhB(OH)_2$, propionic acid (cat.), benzene, reflux, 22 h, 92%.

Using this methodology, a variety of *tris*-2*H*-chromenes were prepared. Specifically, the *tris*-2*H*-chromene **32** was prepared from citral (**31**, *E*:*Z* = ~2.1) (4 equiv), phloroglucinol (**27**) (1 equiv), phenylboronic acid (3 equiv) and propionic acid (cat.) in benzene on heating at reflux with the azeotropic removal of water (Scheme 1.3.4). Interestingly, the chromene **32** has three pendant double bonds that are in a favourable position with the chromene carbon-carbon double bonds to potentially undergo a triple intramolecular [2+2] cycloaddition reaction to afford the remarkable product **33**. This cycloadduct would contain ten fused rings and twelve stereogenic centres which would be generated in a single step from the *tris*-2*H*-chromene **32**.

Scheme 1.3.4 Proposed Triple Intramolecular [2+2] Cycloaddition Reaction of the *tris*-2*H*-Chromene (32)



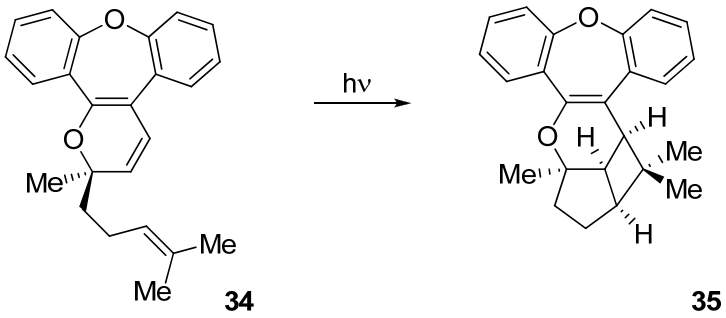
Reagents and conditions: (a) Citral (**31**, 4 equiv, *E*:*Z* = ~2:1), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 4 h, 61%.

The inspiration for performing a triple intramolecular [2+2] cycloaddition reaction on the *tris*-2*H*-chromene **32** and the research project described in this thesis came from other intramolecular cycloaddition reactions that have been completed in the Wilson research group.[20]

1.4 Proposed Studies: Inter- and Intramolecular Cycloaddition Reactions of *mono*- and *tris*-2*H*-Chromenes

A number of compounds have been successfully prepared by means of intramolecular cycloaddition processes. Specifically, the synthesis of an artocarpol A analogue **35** was completed by Paduraru *et al*. by means of an intramolecular [2+2] cycloaddition reaction of the 2*H*-pyran **34** in moderate yield (45%) (Scheme 1.4.1).[20]

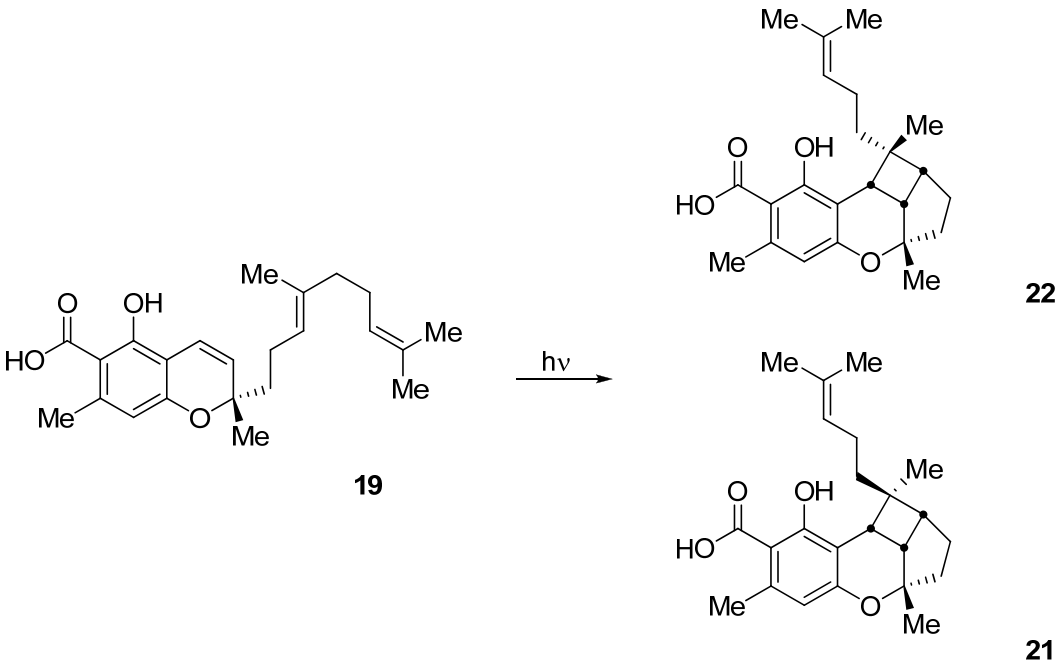
Scheme 1.4.1 Intramolecular [2+2] Cycloaddition Reaction of the 2*H*-Pyran (34)



34 **35**

In addition, although not pursued in the Wilson research group, Jin *et al*. successfully converted daurichromenic acid (**19**) to rhododaurichromanic acid A and B (**21** and **22**) *via* an intramolecular [2+2] cycloaddition process.[15] This photochemical process was performed in hexanes and afforded a mixture of rhododaurichromanic acid A and B (**21** and **22**) in 40% and 20% yields, respectively (Scheme 1.4.2). It was assumed that the *trans C*-11 – *C*-12 double bond of daurichromenic acid (**19**) was isomerized to the *cis*-isomer under the reaction conditions to afford rhododaurichromanic acid B (**22**).

Scheme 1.4.2 Intramolecular [2+2] Cycloaddition Reaction of Daurichromenic Acid (19)



19 **22** **21**

The successful execution of various intramolecular [2+2] cycloaddition reactions of various 2*H*-chromenes led to the idea that a variety of inter- and intramolecular cycloaddition reactions could be performed on *tris*-2*H*-chromene analogues of phloroglucinol (**27**).

Thus, it was envisioned that a series of cycloaddition reactions, both inter- and intramolecular, could be investigated to determine the reactivity of the 2*H*-chromene carbon-carbon double bond. Specifically, these cycloaddition reactions could be performed on simple *mono*-2*H*-chromenes, which would aid in the characterization of the products from multiple cycloaddition reactions of the corresponding *tris*-2*H*-chromenes. The regio- and stereoselectivity of these single and multiple cycloaddition reactions would also be studied. Moreover, these reactions can be used to build complex polycyclic compounds that contain multiple stereogenic centres in a rapid and concise

manner. As such, these reactions could provide a means to prepare C_3-symmetric compounds that could serve as structural analogues of the biologically active natural product xyloketal A (**20**).

1.5 Thesis Overview

The goal of this research project was to perform multiple cycloaddition reactions on the C_3-symmetric *tris*-2*H*-chromene **30** to evaluate the reactivity of the 2*H*-chromene carbon-carbon double bond. Specifically, the regioselectivity and stereoselectivity of a series of cycloaddition reactions would be determined and used to prepare complex polycyclic ring systems in a direct manner. Towards these ends, simple *mono*-2*H*-chromenes were also investigated as model systems.

In Chapter 2 of this thesis, the synthesis of a series of *mono*-2*H*-chromenes is described. These *mono*-2*H*-chromenes were subjected to a series of [2+1], [2+2] and [2+4] intermolecular cycloaddition reactions.

In Chapter 3, the synthesis of a C_3-symmetric *tris*-2*H*-chromene is described. Subsequently, a series of [2+1], [2+2] and [2+4] intermolecular cycloaddition reactions were performed.

In Chapter 4, the synthesis of two functionalized *mono*-2*H*-chromenes is described. These chromenes were used as model systems for both intramolecular [2+2] and [2+4] cycloaddition reactions.

In Chapter 5, the synthesis of two functionalized C_3-symmetric *tris*-2*H*-chromenes is described. These chromenes were used to evaluate the feasibility of performing triple intermolecular [2+2] and [2+4] cycloaddition reactions.

In Chapter 6, a means to install a more reactive 2*H*-chromene double bond is described and in Chapter 7, an outline of future research is presented together with an overall conclusion section on the research described in this thesis.

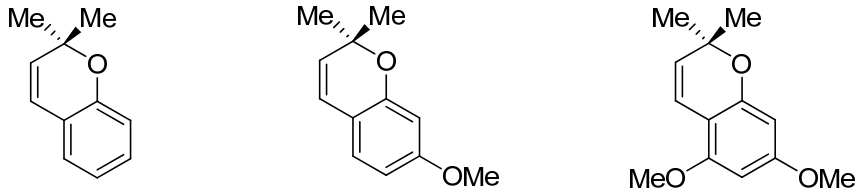
In the final chapter of this thesis, Chapter 8, the experimental procedures and full characterization data concerning all of the compounds discussed in this thesis are provided.

2 RESULTS AND DISCUSSION

Synthesis and Evaluation of mono-*2*H-*Chromenes as Substrates for Intermolecular Cycloaddition Reactions*

2.1 Introduction

In this chapter, the synthesis of a series of 2*H*-chromenes **36**, **2** and **37** is described (Figure 2.1.1). We envisioned that these *mono*-2*H*-chromenes would serve as model substrates to evaluate a series of [2+1], [2+2] and [2+4] intermolecular cycloaddition reactions. This would allow us to determine the reactivity of the 2*H*-chromene carbon-carbon double bond as well as the regioselectivity of these cycloaddition processes. Additionally, the structural analysis of these cycloaddition reactions would assist in the determination of the molecular structures of the products formed from multiple cycloaddition reactions of *tris*-2*H*-chromenes.



36 **2** **37**

Figure 2.1.1 Molecular structures of *mono*-2*H*-chromenes (36, 2 and 37).

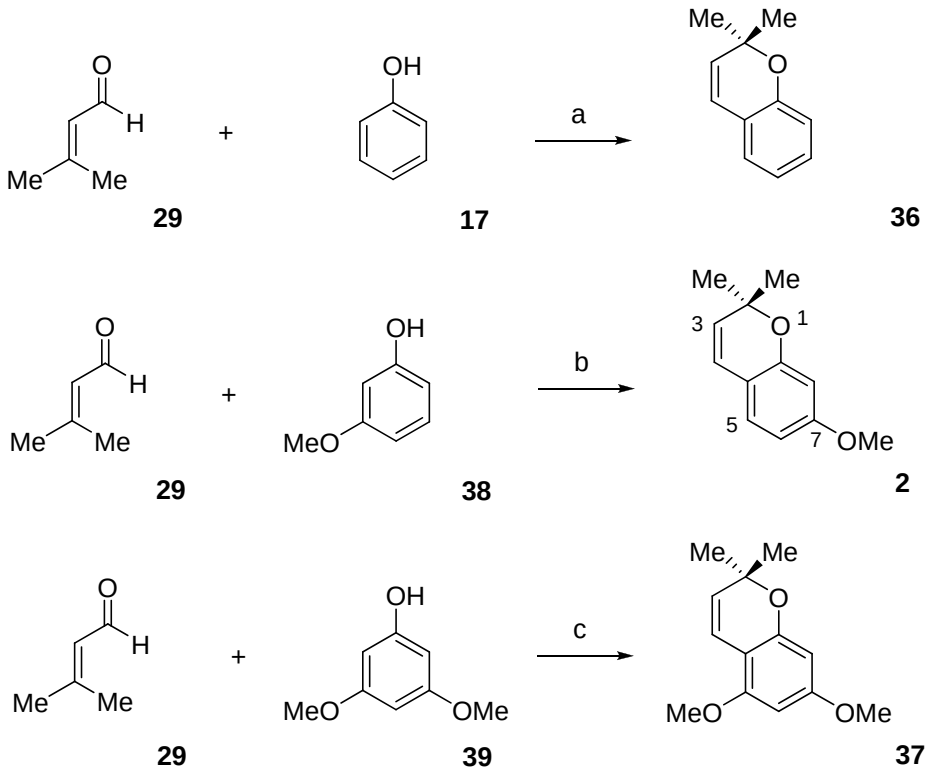
The *mono*-2*H*-chromenes **2** and **37** were prepared because the electron donating effects of the methoxy groups closely resemble the electronic nature of the C_3-symmetric *tris*-2*H*-chromene **30**. Additionally, the *mono*-2*H*-chromene **36** was prepared to represent the simplest 2*H*-chromene of this series of reaction substrates.

2.2 Preparation of *mono*-2*H*-Chromenes

A series of *tris*-2*H*-chromenes have been prepared by Pettigrew *et al*. using a phenylboronic acid-mediated condensation reaction from phloroglucinol (**27**) and an α,β-unsaturated aldehyde.[19] Using these reaction conditions, the three *mono*-2*H*-chromenes **36**, **2** and **37** were readily prepared from the corresponding phenols. In these cases, 3-methyl-but-2-enal (senecialdehyde **29**) was used as the α,β-unsaturated aldehyde precursor as this would lead to the simplest 2,2-disubstituted 2*H*-chromenes that would be expected to be stable.[21] Senecialdehyde (**29**) was prepared from the corresponding alcohol, 3-methyl-2-buten-1-ol, in a single step by oxidation with manganese dioxide following known literature procedures in good yield.[21]

The model chromenes were prepared using senecialdehyde (**29**) (1.3 – 1.5 equiv), the corresponding phenol (1 equiv), phenylboronic acid (1 equiv) and propionic acid (cat.) in benzene on heating at reflux with azeotropic removal of water from the reaction mixture (Scheme 2.2.1). The reaction of phenol (**17**) with senecialdehyde (**29**) afforded the *mono*-2*H*-chromene **36** in low yield, whereas the reactions of the two methoxy-substituted phenols **38** and **39** afforded the corresponding *mono*-2*H*-chromenes **2** and **37** in good yield, respectively. The additional methoxy groups around the benzene ring function to make this electrophilic aromatic substitution process more facile, resulting in a higher yield of the desired 2*H*-chromene products **2** and **37**.[22]

Scheme 2.2.1 Synthesis of the *mono*-2*H*-Chromenes (36, 2 and 37) from Senecialdehyde (29)



Reagents and conditions: (a) Senecialdehyde (**29**) (1.5 equiv), $PhB(OH)_2$ (1 equiv), propionic acid (cat.), PhH, reflux, 21 h, 28%; (b) senecialdehyde (**29**) (1.3 equiv), $PhB(OH)_2$ (1 equiv), propionic acid (cat.), PhH, reflux, 4 h, 75%; (c) senecialdehyde (**29**) (1.5 equiv), $PhB(OH)_2$ (1 equiv), propionic acid (cat.), PhH, reflux, 3 h, 81%.

The known *mono*-2*H*-chromenes **36,**[23] **2**[22] and **37**[24] were all readily purified by flash chromatography. Interestingly, the 2*H*-chromene **2** was prepared as a single regioisomer, as determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. The formation of this single product is likely due to decreased steric interactions at the *C*-6 position of the phenol **38** during the phenylboronic acid-mediated condensation reaction. The regiochemistry of this process was confirmed by examining the splitting pattern in the ^{1}H NMR spectrum of the *mono*-2*H*-chromene **2**. In particular, the aromatic proton, *H*-5, of chromene **2** corresponded to a doublet at δ = 6.9 ppm (J = 8.2 Hz) while the proton *H*-6, corresponded to a doublet of doublets located at δ = 6.41

ppm (J = 8.2, 2.3 Hz). In addition, the aromatic proton *H*-8 corresponds to a doublet located at δ = 6.38 (J = 2.3 Hz). This coupling pattern indicates that protons *H*-5 and *H*-6 are on adjacent carbon atoms.

During the preparation of the above mentioned chromenes, both of the methoxy substituted chromenes **2** and **37** were isolated as colourless oils in good yields where as the non-substituted chromene **36** was prepared as a yellow, gummy oil in low yield. Due to both the ease of preparation and handling of the two methoxy substituted chromenes **2** and **37**, they were used as the substrates for the majority of the subsequent reactions.

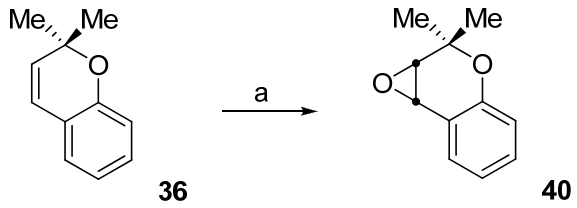
2.3 Intermolecular [2+1] Cycloaddition Reactions

With a series of *mono*-2*H*-chromenes in hand, a series of intermolecular cycloaddition reactions could be investigated. The first set of cycloaddition reactions selected for study focused on a [2+1] cycloaddition process. Specifically, a series of epoxidation and cyclopropanation reactions were attempted that are described in the following section.

2.3.1 Epoxidation Reactions of *mono*-2*H*-Chromenes

The known epoxide **40** was prepared upon reaction of the *mono*-2*H*-chromene **36** with *m*-CPBA (**41**) according to literature procedures (Scheme 2.3.1).[25]

Scheme 2.3.1 Epoxidation Reaction of the *mono*-2*H*-chromene (36)



36 **40**

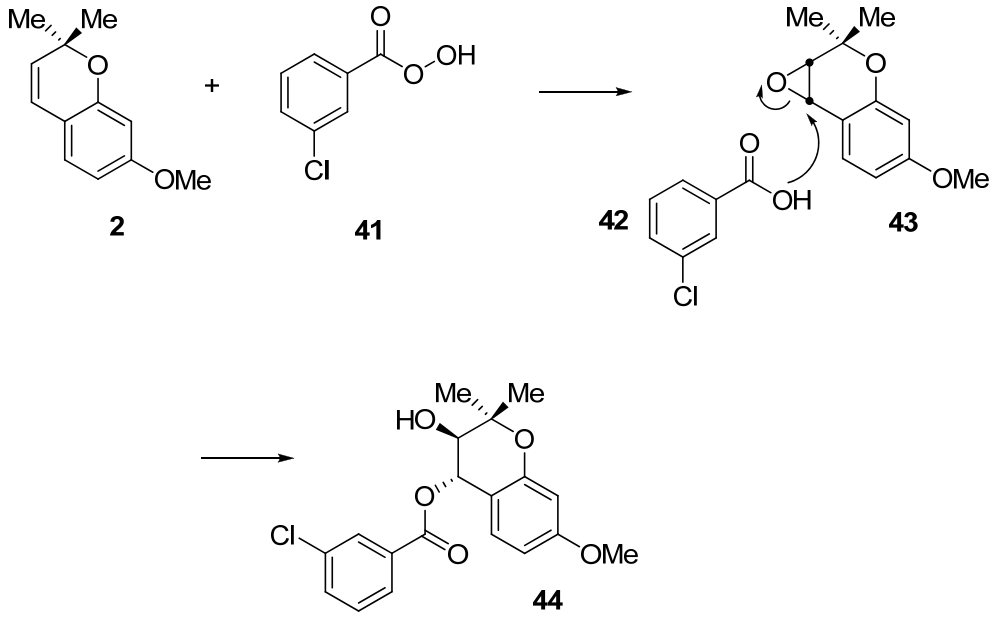
Reagents and conditions: (a) *m*-CPBA (**41**) (1 equiv), $NaHCO_3$ (0.5 M), CH_2Cl_2, 0 °C to room temperature, 48 h, 20%.

The epoxide **40** was found to readily decompose on flash chromatography. Neutralizing the silica gel with triethylamine or using neutral alumina did not aid in the purification of the epoxide **40** by chromatographic methods. Therefore, isolation of the epoxide was accomplished by precipitation of by-products and impurities from a mixture of chloroform-hexanes. The precipitate was then removed by filtration and the resultant filtrate was concentrated *in vacuo* to afford the epoxide **40** as a pale yellow oil.

The ^{1}H and ^{13}C NMR data was consistent with the data available for the known epoxide **40**.[26] Also, the mass spectrum (CI) had the expected M + H peak at 177 amu's.

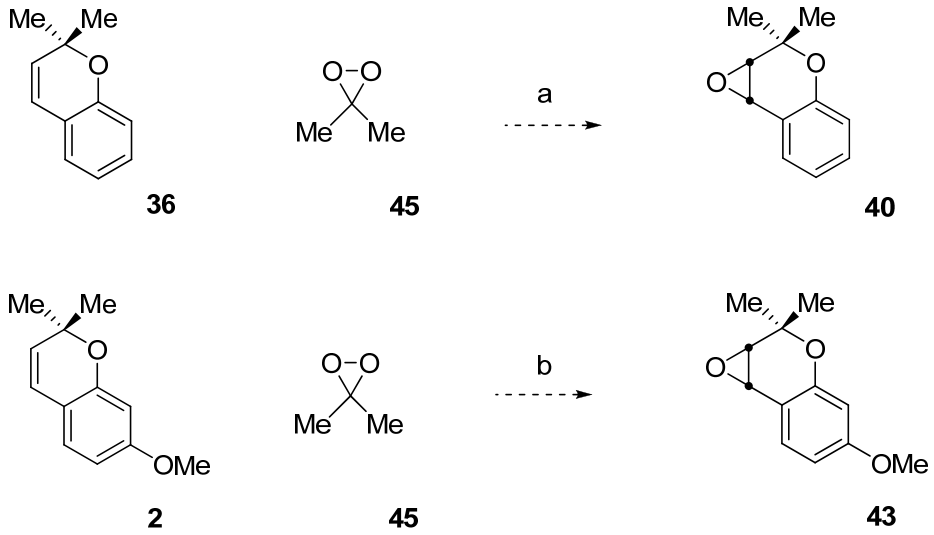
It has been stated by Bujons *et al*. that the electron donating nature of the chromene oxygen atom renders the epoxide ring susceptible to ring opening processes.[27] Specifically, when performing the epoxidation cycloaddition reaction with *m*-CPBA (**41**) as the oxidant, the resultant *m*-chlorobenzoic acid (**42**) or *m*-CPBA (**41**) could then attack the corresponding epoxide ring, opening it to afford the substituted alcohol **44** (Scheme 2.3.2).

Scheme 2.3.2 Proposed Reaction of *m*-Chlorobenzoic Acid (42) or *m*-CPBA (41) with the Epoxide (43)



Due to the high reactivity of the epoxide towards nucleophiles, different epoxidation methods were investigated. A mild route towards epoxidation involving the *in situ* generation of the oxidant dimethyldioxirane (**45**) has been discussed in a review by Murray.[28] The advantage of this system is that an unreactive by-product of the oxidation procedure is acetone and therefore this represents a very mild means to affect an epoxidation reaction. Dimethyldioxirane (**45**) was generated *in situ* from Oxone® (3 equiv) and acetone (3 equiv) in a basic solution as previously described by Shi (Scheme 2.3.3).[26]

Scheme 2.3.3 Attempted Epoxidation Reaction of the *mono*-2*H*-Chromenes (36 and 2) with Dimethyldioxirane (45)



Reagents and conditions: (a) Oxone® (3 equiv.), $NaHCO_3$ (12 equiv.), acetone, $(n\text{-}Bu)_4NHSO_4$ (cat.), CH_3CN/EDTA, 0°C to room temperature, 2.5 h; (b) Oxone® (3 equiv.), $NaHCO_3$ (12 equiv.), acetone, $(n\text{-}Bu)_4NHSO_4$ (cat.), CH_3CN/EDTA, 0°C to room temperature, 2.5 h.

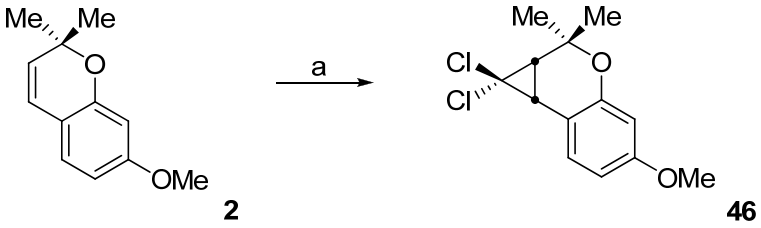
Unfortunately, ^1H NMR analysis of the crude reaction mixtures did not display any signals characteristic of either epoxide. Since epoxidation of the chromenes **36** and **2** was unsuccessful, the use of 5,7-dimethoxy-2,2-dimethyl-2*H*-chromene **37** was not attempted because of the expected higher propensity for ring opening.

2.3.2 Cyclopropanation Reactions of *mono*-2*H*-Chromenes

To further investigate [2+1] cycloaddition reactions, a series of cyclopropanation reactions were conducted. In the first instance, cyclopropanation reactions of the *mono*-2*H*-chromenes were performed by generating a dihalocarbene *via* an alpha-elimination reaction of either chloroform or bromoform on treatment with an aqueous solution of sodium hydroxide.

The known cyclopropane **46** was prepared, in moderate yield, upon treatment of the *mono*-2*H*-chromene **2** with chloroform, *n*-tetrabutylammonium bromide (cat.) and an aqueous solution of sodium hydroxide (8 M) (Scheme 2.3.4).[29]

Scheme 2.3.4 Dichlorocyclopropanation Reaction of the *mono*-2*H*-Chromene (2)

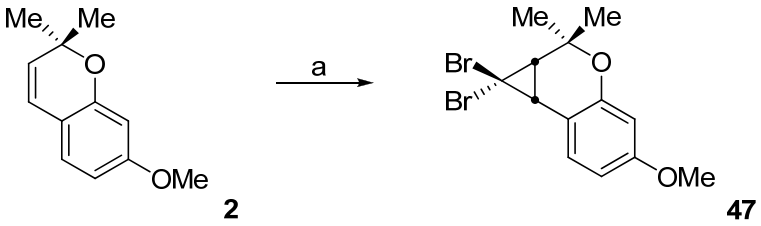


Reagents and conditions: (a) $CHCl_3$, NaOH (8 M), (*n*-Bu)$_4$NBr (0.2 equiv), room temperature, 12 h, 52%.

The known cyclopropane **46** was purified by flash chromatography to afford a white powder. The melting point as well as the ^{1}H and ^{13}C NMR data were all in agreement with that previously reported.[29] Moreover, the mass spectrum (CI) of the dichlorocyclopropane **46** displayed the expected molecular ion peaks for [M(2 x ^{35}Cl) + H], [M(^{35}Cl + ^{37}Cl) + H] and [M(2 x ^{37}Cl) + H] at 273, 275 and 277 amu's, respectively. These signals occurred in a 9:6:2 ratio, which is in close agreement with calculated values.[30]

In addition, the 2*H*-chromene **2** was reacted with dibromocarbene (prepared from bromoform) to afford the dibromocylopropane **47** (Scheme 2.3.5).

Scheme 2.3.5 Dibromocyclopropanation Reaction of the *mono*-2*H*-Chromene (2)

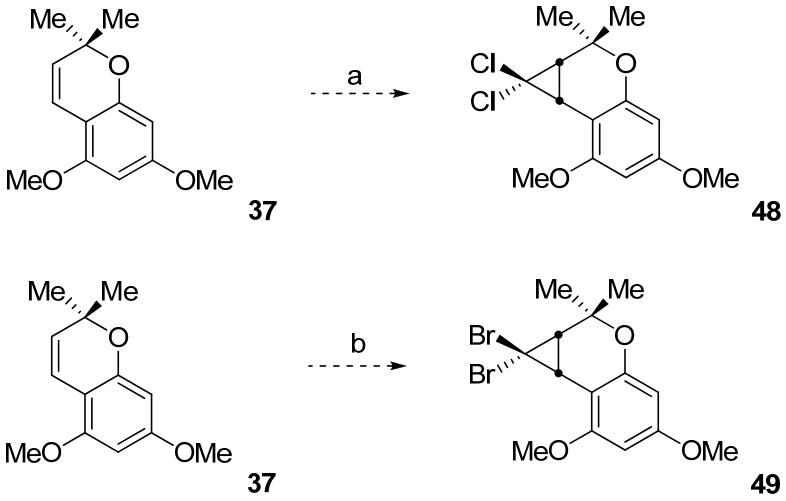


Reagents and conditions: (a) $CHBr_3$, NaOH (8 M), (*n*-Bu)$_4$NBr (0.2 equiv), room temperature, 19 h, 34%.

The dibromocyclopropane **47** was readily purified by flash chromatography to afford a colourless solid. The ^{1}H NMR spectrum of the dibromocyclopropane **47** was very similar to the dichlorocyclopropane **46**. The doublets corresponding to the protons of the cyclopropane ring were located at δ = 2.2 and 2.9 ppm (J = 10.7 Hz) with two sharp singlets corresponding to the two inequivalent methyl groups at δ = 1.2 and 1.7 ppm. Additionally, the ^{13}C NMR spectrum of the dibromocyclopropane **47** contained the thirteen carbon signals expected for this compound. The mass spectrum (CI) of the dibromocyclopropane **47** displayed the expected molecular ion peaks for [M(2 x ^{79}Br) + H], [M(^{79}Br + ^{81}Br) + H] and [M(2 x ^{81}Br) + H] at 361, 363 and 365 amu's, respectively. These signals occurred in a 1:2:1 ratio which is in agreement with those expected for a compound that contains two bromine atoms.[30] Finally, elemental analysis was used to confirm both the purity and elemental composition of the dibromocyclopropane **47**.

Interestingly, when the electron-rich dimethoxy-substituted *mono*-2*H*-chromene **37** was subjected to the above reaction conditions no corresponding dihalo-cyclopropanation products were isolated (Scheme 2.3.6). The reason for this remains unclear, however, it is likely that the additional methoxy groups decrease the electrophilic nature of the 2*H*-chromene double bond.

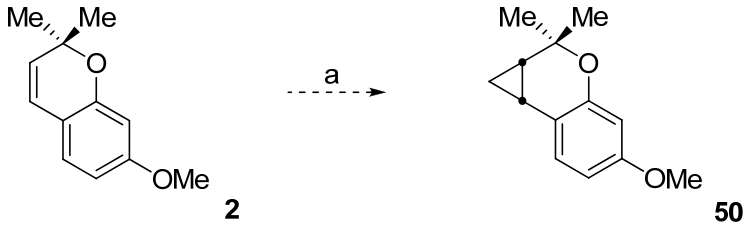
Scheme 2.3.6 Attempted Preparation of Dichlorocyclopropane (48) and Dibromocyclopropane (49) from the *mono*-2*H*-Chromene (37)



Reagents and conditions: (a) $CHCl_3$, NaOH (8 M), (*n*-Bu)$_4$NBr (0.2 equiv), room temperature, 22 h; (b) $CHBr_3$, NaOH (8 M), (*n*-Bu)$_4$NBr (0.2 equiv), room temperature, 22 h.

Additional cyclopropanation reactions were also investigated. Specifically, the synthesis of the cyclopropane **50** was attempted under a variety of reaction conditions as specified below (Scheme 2.3.7). Of note, only the single methoxy-substituted 2*H*-chromene **2** was used as this was the only chromene that had been shown to undergo an intermolecular [2+1] cyclopropanation reaction.

Scheme 2.3.7 Attempted Cyclopropanation of the *mono*-2*H*-Chromene (2)



Reagents and conditions: (a) See below: Table 2.3.1.

Table 2.3.1 Reagents and Conditions Corresponding to Scheme 2.3.7

Entry	Reagents and Conditions	Result
1	CH_2N_2 (2 equiv), $PdCl_2$ (5 mol %), Et_2O, 0 °C to room temperature, 24 h	No reaction
2	CH_2N_2 (20 equiv) (dropwise addition), $Pd(OAc)_2$ (10 mol%), Et_2O, 0 °C to room temperature, 60 h	No reaction
3	CH_2N_2 (20 equiv) (rapid addition), $Pd(OAc)_2$ (10 mol%), Et_2O, 0 °C to room temperature, 60 h	No reaction

In these reactions, diazomethane was generated *in situ* from *N*-methyl-*N*-nitroso urea and an aqueous solution of potassium hydroxide *via* a known procedure.[31] Unfortunately, it was found that none of the reaction conditions stated above afforded the cyclopropane **50** (Table 2.3.1).[32]

In addition, a copper(I)-catalyzed cyclopropanation reaction involving both the *mono*-2*H*-chromenes **2** and **37** with ethyl diazoacetate was performed. Unfortunately, no reaction products were observed and starting material was recovered. Interestingly, this reaction proceeded quite well on a *tris*-2*H*-chromene derivative (See: Section 3.3.2).

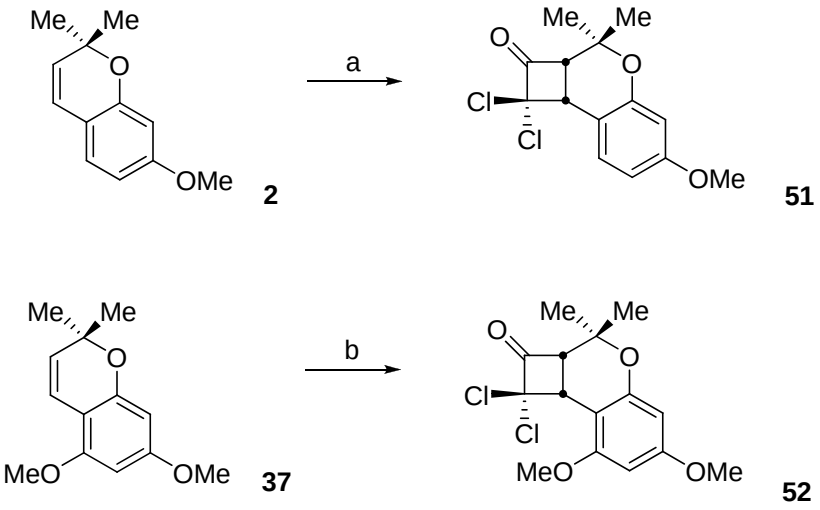
2.4 Intermolecular [2+2] Cycloaddition Reactions

A series of intermolecular [2+2] cycloaddition reactions of the *mono*-2*H*-chromenes **2** and **37** are described in the following sections.

2.4.1 Ketene Cycloaddition Reactions of *mono*-2*H*-Chromenes

An efficient way to prepare [2+2] cycloadducts of alkenes is *via* ketene cycloaddition reactions. The cycloadducts **51** and **52** were prepared from the *mono*-2*H*-chromenes **2** and **37** on reaction of dichloroketene, which was generated *in situ* from trichloroacetyl chloride (3 equiv) and zinc (4.5 equiv) in tetrahydrofuran according to known procedures (Scheme 2.4.1).[33]

Scheme 2.4.1 Synthesis of the Cycloadducts (51 and 52) from the *mono*-2*H*-Chromenes (2 and 37)



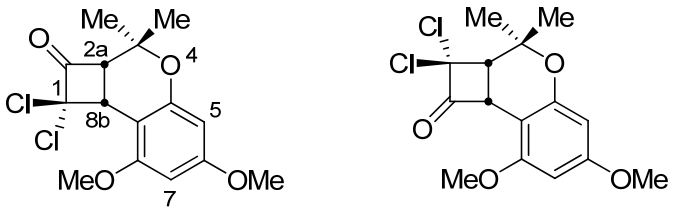
Reagents and conditions: (a) Cl_3CCOCl (3 equiv), Zn (4.5 equiv), THF, 0 °C to room temperature, 26 h, 26% (38% brsm); (b) Cl_3CCOCl (3 equiv), Zn (4.5 equiv), THF, 0 °C to room temperature, 2 h, 47%.

Both of the cycloadducts **51** and **52** were readily purified by flash chromatography to afford the corresponding products as white solids in moderate yields.

The structure of the cycloadducts **51** and **52** were both confirmed on analysis of the ^{1}H and ^{13}C NMR spectra and full characterization data. The cycloadduct **52** had no doublets associated with the chromene protons of the starting material and a new set of doublets at δ = 4.0 and 4.3 ppm (J = 10.8 Hz) indicate the formation of the cyclobutane ring. Furthermore, the ^{13}C NMR spectrum contains the fifteen expected carbon signals and notably the signal at δ = 192 ppm is characteristic of a cyclobutanone carbonyl group.[34] In addition, the mass spectrum (CI) of both cycloadducts **51** and **52** gave the expected masses in the expected isotopic ratios consistent for compounds that contain two chlorine atoms.

The addition of dichloroketene to the 2*H*-chromene double bond can occur in two different ways to afford the two possible regioisomeric products **52** and **52a** (Figure

2.4.1). However, it was expected that the ketene cycloaddition would afford the cycloadduct **52**.[34]



52 **52a**

Figure 2.4.1 The two regiochemical isomers of the [2+2] ketene cycloaddition reactions of the *mono*-2*H*-chromene (37).

The expected regiochemistry of the ketene addition to the 2*H*-chromene **37** was confirmed by extensive analysis of 2D NMR spectra. Based on the spectral data from the HMBC spectrum, the ketene addition occurred as shown below (Figure 2.4.2).

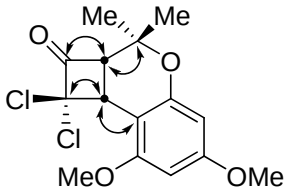


Figure 2.4.2 Diagnostic correlations observed in the HMBC spectrum of the cyclobutane (52).

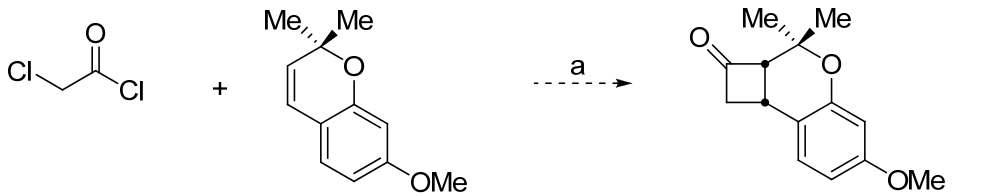
The key HMBC correlations that proved the regiochemistry of this cycloaddition process focussed on the assignment of protons *H*-2a and *H*-8b. *H*-8b has strong correlations to multiple aromatic ring carbons as well as a strong correlation to *C*-1. *H*-2a has a strong correlation to the quaternary carbon, *C*-3, as well as to both of the methyl groups (Figure 2.4.2).

Similarly, the structure of the cycloadduct **51** was confirmed by both ^{1}H and ^{13}C NMR analysis. Of note, the ^{1}H NMR spectrum displayed a two hydrogen multiplet at δ = 4.1 ppm. This multiplet is due to the overlap of the cyclobutane protons and as such the

regiochemistry of this cycloaddition reaction could not be confirmed. However, it is likely that the ketene cycloaddition regiochemistry would be that shown in the cycloadduct **52**.

After successfully generating the cyclobutanes **51** and **52**, an additional cycloaddition reaction involving the ketene (dihydroketene) was attempted. Initially, 2-chloroacetic acid was converted to the corresponding acid chloride on reaction with oxalyl chloride and *N*,*N*-dimethylformamide (cat.) in dichloromethane. The resultant 2-chloroacetyl chloride (**53**, 5 equiv) was then added to a suspension of the 2*H*-chromene **2** (1 equiv) and zinc powder (7.5 equiv) in tetrahydrofuran (Scheme 2.4.2). Unfortunately, no reaction products were observed and starting material was observed on analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

Scheme 2.4.2 Attempted [2+2] Cycloaddition Reaction of the *mono*-2*H*-Chromene (2)



53 **2** **54**

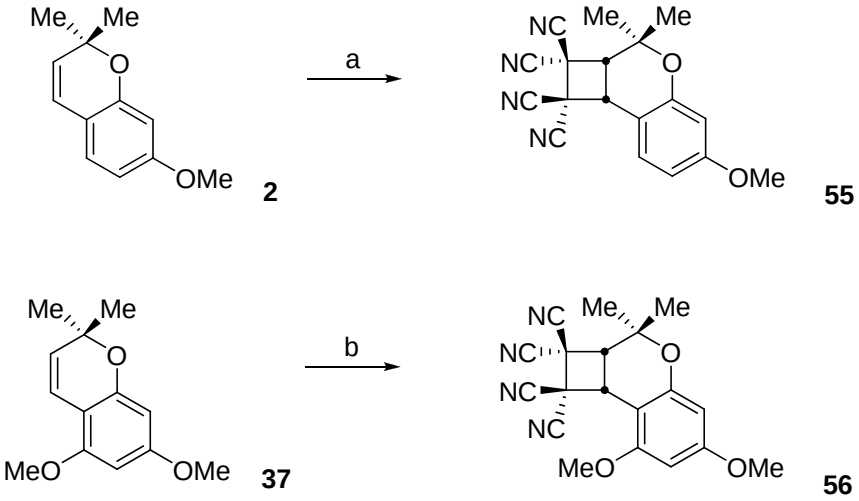
Reagents and conditions: (a) Chloroacetyl chloride **53** (5 equiv), Zn (7.5 equiv), THF, 0 °C to room temperature, 48 h.

2.4.2 Tetracyanoethylene Cycloaddition Reactions of *mono*-2*H*-Chromenes

Further [2+2] cycloaddition processes that were attempted involved the use of tetracyanoethylene as a reaction substrate. Tetracyanoethylene is an electrophilic olefin that readily undergoes [2+2] cycloadditions with nucleophilic alkenes, such as the 2*H*-chromene carbon-carbon double bond.[35] The synthesis of the tetracyanocyclobutanes **55** and **56** involved the addition of tetracyanoethylene (1.5 equiv) to a solution of either

mono-2*H*-chromene **2** or **37** in acetonitrile. On heating at reflux, the cyclobutanes **55** and **56** were isolated (Scheme 2.4.3). During the course of these reactions it was observed that the addition of tetracyanoethylene to the acetonitrile solution of the 2*H*-chromene resulted in a deep blue colour. Upon heating, the reaction mixture changed from a deep blue colour to a brown colour, indicating that the reaction was complete. This is presumably due to the formation of a charge-transfer complex prior to cycloaddition.[35] TLC analysis indicated that both 2*H*-chromenes **2** or **37** were completely consumed when this colour change occurred.

Scheme 2.4.3 Synthesis of Tetracyanocyclobutanes (55 and 56) from the *mono*-2*H*-Chromenes (2 and 37)



Reagents and conditions: (a) Tetracyanoethylene (1.5 equiv), CH_3CN, reflux, 20 h, 29%; (b) tetracyanoethylene (1.5 equiv), CH_3CN, reflux, 30 min, 33%.

Both of the tetracyanocyclobutanes **55** and **56** were purified by flash chromatography. However, it was noted that some decomposition occurs on silica gel.

The ^{1}H NMR spectrum of the cyclobutane **55** contained a pair of doublets located at δ = 4.1 and 4.5 ppm (J = 9.6 Hz) that indicated the formation of the cyclobutane ring. In addition, the ^{13}C NMR spectrum contains the eighteen carbon signals expected for this

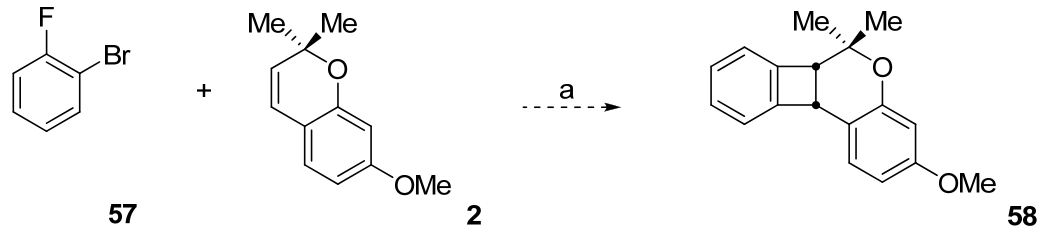
compound. The ^{1}H NMR spectrum of the cyclobutane **56** has a pair of doublets located at δ = 3.6 and 4.3 ppm (J = 9.4 Hz). Moreover, the ^{13}C NMR spectrum contains the nineteen carbon signals expected for this compound. The IR spectrum of both compounds displayed characteristic nitrile stretching frequencies at 2248 cm^{-1}. Finally, both the purity and elemental composition of the cyclobutanes **55** and **56** were verified by elemental analysis.

Having successfully completed two classes of [2+2] cycloaddition reactions, a third type of cycloaddition reaction was attempted involving the highly reactive species, benzyne.

2.4.3 Benzyne Cycloaddition Reactions of *mono*-2*H*-Chromenes

Benzyne is a highly reactive species which has been shown to readily undergo [2+2] cycloaddition reactions. Attempts at benzyne formation focussed on a known procedure involving oxidative addition of magnesium and subsequent elimination to form the benzyne intermediate.[36] Thus, a solution of *o*-fluorobromobenzene (**57**) in tetrahydrofuran was added *via* syringe pump over the course of 3 hours to a suspension of *mono*-2*H*-chromene **2** and magnesium turnings (1.1 equiv) in tetrahydrofuran at room temperature (Scheme 2.4.4). Upon completion of the addition process the mixture was brought to reflux for 2 hours, however, no reaction products were observed.

Scheme 2.4.4 Attempted Synthesis of Benzocyclobutane (58) from the *mono*-2*H*-Chromene (2) and 2-Fluorobromobenzene (57)



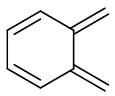
57 **2** **58**

Reagents and conditions: (a) Mg (1.1 equiv), THF, 60 °C to reflux, 2 h.

As no reaction products were observed efforts were then focussed on performing an intermolecular [2+4] cycloaddition reaction. As such, the highly reactive species, *o*-quinonedimethane (**59**) was evaluated as a possible route towards an intermolecular [2+4] cycloaddition reaction.

2.5 Intermolecular [2+4] Cycloaddition Reactions of *mono*-2*H*-Chromenes

Attempts to perform an intermolecular [2+4] cycloaddition have focussed on the generation and reaction of *o*-quinonedimethane (**59**) (Figure 2.5.1). Less reactive dienes, such as cyclopentadiene, were also later used in cycloaddition reactions of the *tris*-2*H*-chromene **30** (See: Section 3.5).

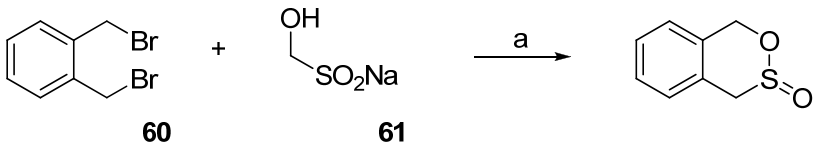


59

Figure 2.5.1 Molecular structure of *o*-quinonedimethane (59).

Towards these ends, Durst and co-workers have shown that the known sultine **62** affords *o*-quinonedimethane upon heating in benzene.[37] The sultine **62** was prepared on reaction of α,α'-dibromo-*o*-xylene (**60**) with Rongalite® (**61**) in *N*,*N*-dimethylformamide in moderate yield (Scheme 2.5.1).[38]

Scheme 2.5.1 Synthesis of the Sultine (62) from α,α'-Dibromo-*o*-xylene (60)

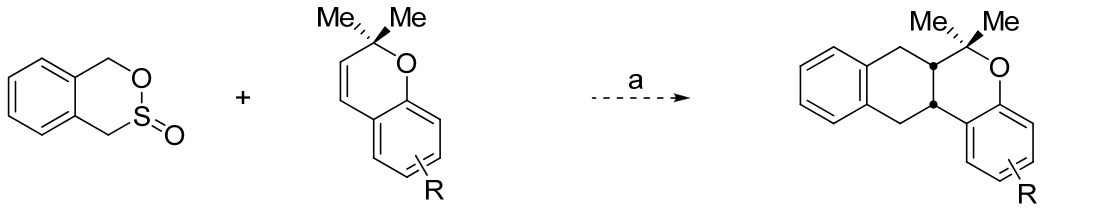


60 **61** **62**

Reagents and conditions: (a) Rongalite (**61**) (2 equiv), (*n*-Bu)$_4$NBr (0.2 equiv), DMF, 0 °C to room temperature, 20 h, 54%.

The spectral data for the sultine **62** was in agreement with the previously reported data.[38] With the requisite sultine **62** in hand, the Diels-Alder cycloaddition was attempted. In each case, the sultine **62** (1 equiv) was reacted with a *mono*-2*H*-chromene in benzene and heated at reflux (Scheme 2.5.2). All three *mono*-2*H*-chromenes were used as substrates in this reaction.

Scheme 2.5.2 Attempted Synthesis of Benzocyclohexanes (63, 64 and 65) from the *mono*-2*H*-Chromenes (36, 2 and 37)



62 **36, 2, 37** **63, 64, 65**

Reagents and conditions: (a) PhH, reflux, 24 h.

Unfortunately, no products were isolated from these reactions. Observations made by TLC analysis indicate that the sultine **62** was consumed on heating at reflux for 24 hours. This suggests that the *o*-quinonedimethane was generated but it did not undergo an intermolecular Diels-Alder cycloaddition reaction with the 2*H*-chromene carbon-carbon double bond.

2.6 Conclusions

Using methodology developed in the Wilson research group, three *mono*-2*H*-chromenes **36**, **2** and **37** were efficiently prepared to study a series of intermolecular cycloaddition reactions. Of these intermolecular cycloaddition reactions, an epoxidation reaction was shown to proceed on the unsubstituted 2*H*-chromene **36**, whereas the methoxy-substituted 2*H*-chromene **2** did not afford a stable epoxide that could be isolated or characterized. Dichloro- and dibromocarbene were shown to readily react with the *mono*-2*H*-chromene **2** to afford the corresponding cyclopropane adducts. Dichloroketene and tetracyanoethylene [2+2] cycloaddition reactions were shown to proceed with both *mono*-2*H*-chromenes **2** and **37**. However, the [2+2] cycloadducts from the reaction with benzyne were unsuccessful. Efforts to affect a [2+4] cycloaddition with *o*-quinonedimethane (**59**) were also unsuccessful. The results from this preliminary study provided a basis to the multiple intermolecular cycloadduct processes to a *tris*-2*H*-chromene which are described in the following chapter.

3 RESULTS AND DISCUSSION

Intermolecular Cycloaddition Reactions of tris-*2*H-*Chromenes*

3.1 Introduction

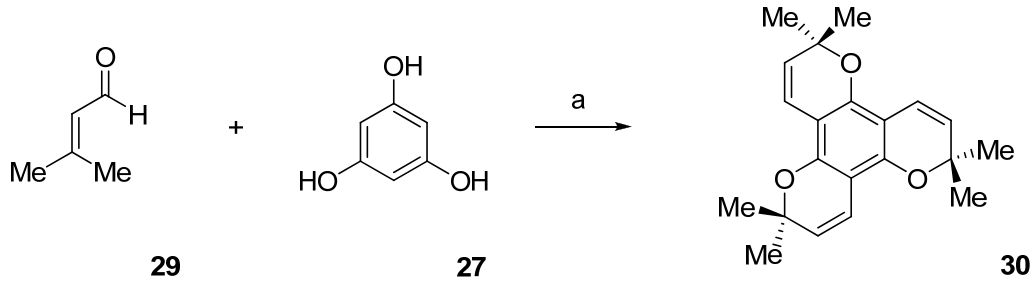
In this chapter, preparation of the known *tris*-2*H*-chromene **30** is described using the phenylboronic acid-mediated condensation reaction of senecialdehyde (**29**) with phloroglucinol (**27**). This will afford a C_3-symmetric substrate in order to study various multiple cycloaddition reactions. It was envisioned that a series of [2+1], [2+2] and [2+4] cycloaddition reactions could be performed. This would allow for the regio- and stereoselectivity of these multiple cycloaddition reactions to be determined and provide a rapid, modular and concise synthesis of complex polycyclic ring systems. Moreover, the adducts from these triple cycloaddition reactions could represent C_3-symmetric structural analogues of xyloketal A (**20**) whose biological activities could be subsequently determined. Of note, the C_3-symmetry of the *tris*-2*H*-chromene **30** greatly simplifies the stereochemical outcome of subsequent multiple cycloaddition reactions. In terms of the facial selectivity of these transformations only two possible diastereoisomeric products can arise. Specifically, three cycloaddition reactions can occur from the same face of the molecule or two cycloaddition reactions can occur on the same face, while the other cycloaddition reaction occurs from the opposite face.

3.2 Synthesis of the *tris*-2*H*-Chromene (30)

To investigate both the regioselectivity and stereoselectivity of multiple intermolecular cycloaddition reactions, the *tris*-2*H*-chromene **30** was prepared upon mixing senecialdehyde (**29**) (4 equiv), phloroglucinol (**27**) (1 equiv), phenylboronic acid

(3 equiv) and propionic acid (cat.) and heating in benzene at reflux with azeotropic removal of water (Scheme 3.2.1). The spectral data for this compound was identical to the data previously reported.[5]

Scheme 3.2.1 Synthesis of the *tris*-2*H*-Chromene (30) from Senecialdehyde (29) and Phloroglucinol (27)



29 **27** **30**

Reagents and conditions: (a) Senecialdehyde (**29**) (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 2 h, 61%.

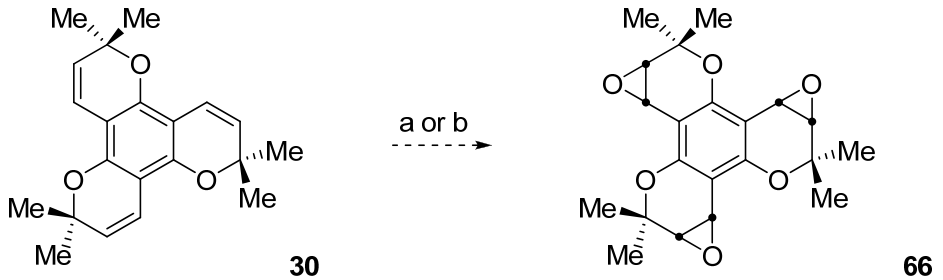
3.3 Intermolecular [2+1] Cycloaddition Reactions

With the requisite *tris*-2*H*-chromene **30** in hand, a series of [2+1] cycloaddition reactions were performed and are discussed in the following sections.

3.3.1 Epoxidation Reactions of the *tris*-2*H*-Chromene (30)

The epoxidation reaction of the *mono*-2*H*-chromene **36** was shown to be successful (See: Section 2.3.1). Thus, an identical approach was taken to prepare the desired *tris*-epoxide **66** from the *tris*-2*H*-chromene **30**. The reaction was conducted in two different ways. The first reaction involved using *m*-CPBA (**41**) (4 equiv) without a buffer and the second reaction involved the use of *m*-CPBA (**41**) (4 equiv) with sodium bicarbonate acting as the buffer (Scheme 3.3.1). In either case, no epoxidation products were observed on analysis of the ^{1}H NMR spectrum of the crude reaction mixtures.

Scheme 3.3.1 Attempted Synthesis of the *tris*-Epoxide (66) from the *tris*-2*H*-Chromene (30)



30 **66**

Reagents and conditions: (a) *m*-CPBA (**41**) (4 equiv), CH_2Cl_2, 0 °C to room temperature, 24 h; (b) *m*-CPBA (**41**) (4 equiv), $NaHCO_3$ (0.5 M), CH_2Cl_2, 0 °C to room temperature, 24 h.

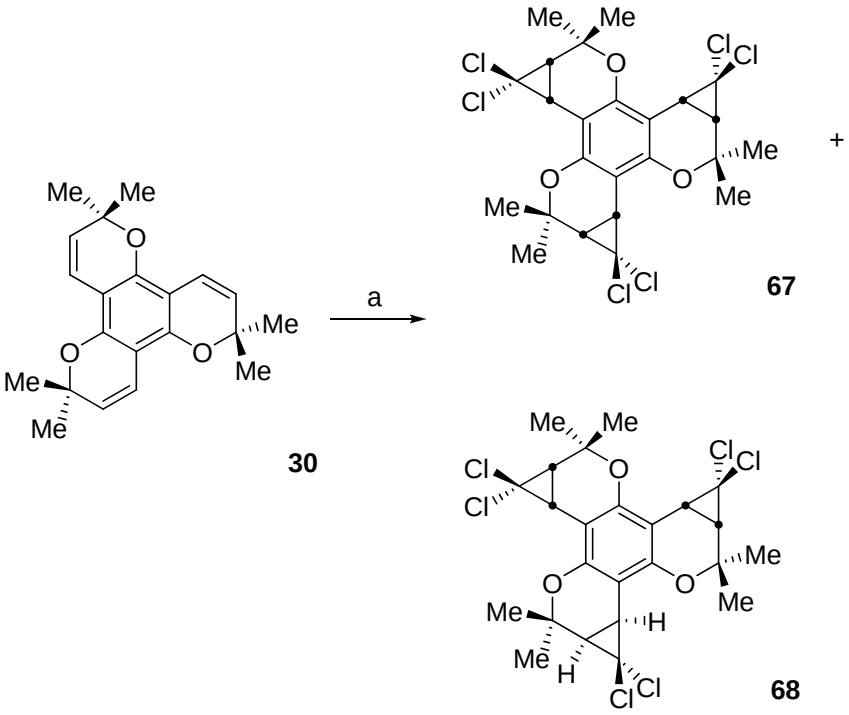
As mentioned earlier, Bujons *et al.* has established that when electron donating groups are present on the chromene the resultant epoxide is unstable.[27] Therefore, a more mild procedure was attempted to prepare the desired *tris*-epoxide **66**. Dimethyldioxirane (**45**) was described in *Chapter 2* as an alternative method to *m*-CPBA (**41**) for generating epoxides. Dimethyldioxirane (**45**) was generated *in situ* on reaction of Oxone® with acetone in an acetonitrile / potassium carbonate solution. Initial attempts indicated that the reaction was likely forming a *mono*-epoxide, based on analysis of the ^{1}H NMR spectrum of the crude reaction product and the mass spectral data. However, the compound proved to be unstable to flash chromatography, despite buffering the silica gel with triethylamine or with the use of neutral alumina as the chromatographic medium. Due to the unstable nature of these epoxides, the full characterization of the compound could not be performed. Thus, attention was turned to the study of other [2+1] cycloaddition reactions.

3.3.2 Cyclopropanation Reactions of the *tris*-2*H*-Chromene (30)

Several cyclopropanation reactions have been shown to readily occur on the *mono*-2*H*-chromenes, therefore these reactions were attempted on the *tris*-2*H*-chromene

30. The *tris*-dichlorocyclopropanes **67** and **68** were prepared, in good yield, upon addition of chloroform to a mixture of the *tris*-2*H*-chromene **30**, *n*-tetrabutylammonium bromide (cat.) and an aqueous solution of sodium hydroxide (8 M) at room temperature (Scheme 3.3.2).

Scheme 3.3.2 Synthesis of the *tris*-Dichlorocyclopropanes (67 and 68)



Reagents and conditions: (a) $CHCl_3$, NaOH (8 M), $(n\text{-Bu})_4NBr$ (0.3 equiv), room temperature, 21 h, 11% (**67**) and 55% (**68**).

The reaction proceeded well at room temperature, affording a mixture of both the C_3-symmetric and unsymmetrical cyclopropanes **67** and **68**, respectively. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that the diastereoselectivity of the reaction was ~3:2, in favour of the unsymmetric stereoisomer **68** based on integration of the methyl signals. The two diastereoisomers **67** and **68** were separated by flash chromatography.

The structures of these cyclopropanes were confirmed by spectroscopic analysis. The ^{1}H NMR spectrum clearly indicated the C_3-symmetry of cyclopropane **67**. Specifically, a single pair of doublets located at δ = 2.0 and 3.0 ppm (J = 11.0 Hz) correspond to the sets of protons at positions *H*-1a and *H*-9c, respectively, on the cyclopropane ring. In addition, two sharp singlets, located at δ = 1.3 and 1.7 ppm, represented the two sets inequivalent methyl groups (Figure 3.3.1).

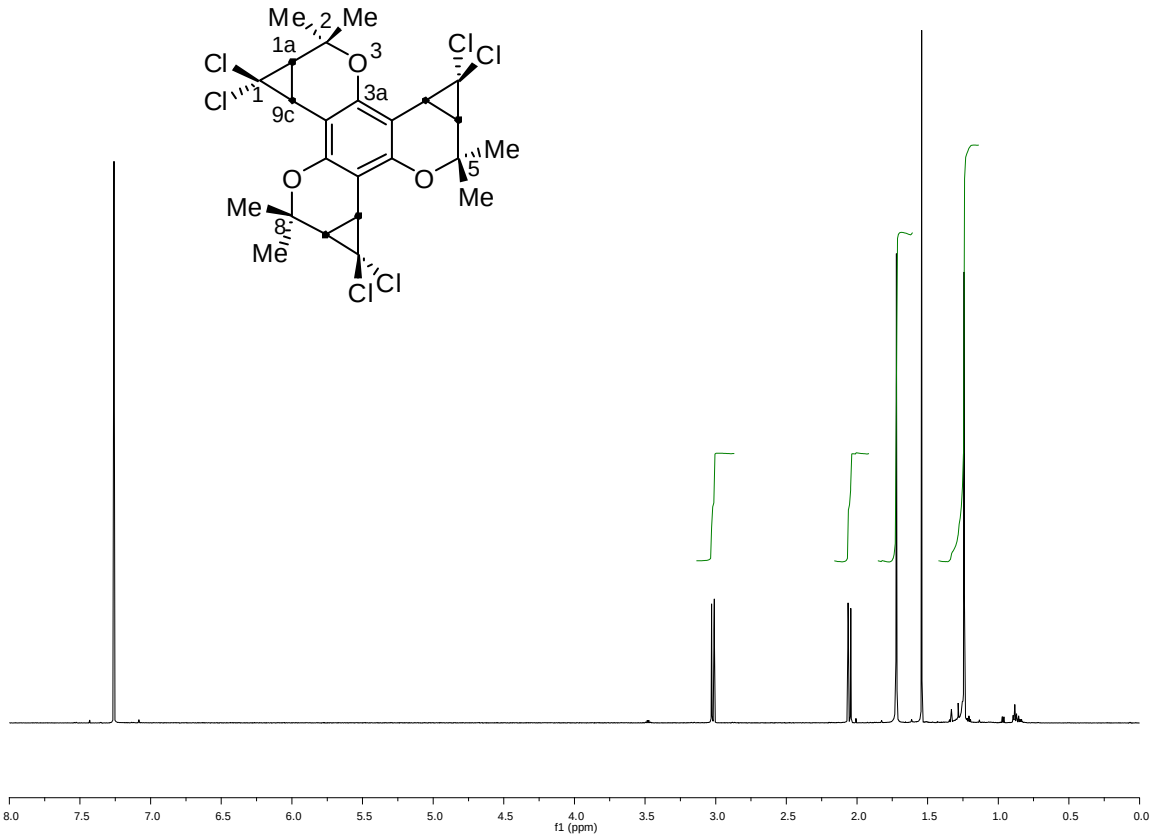


Figure 3.3.1 ^{1}H NMR (600 MHz, $CDCl_3$) of the *tris*-dichlorocyclopropane (67).

The two inequivalent hydrogen atoms of the three cyclopropane rings were assigned by analysis of the HMBC spectrum (Figure 3.3.2).

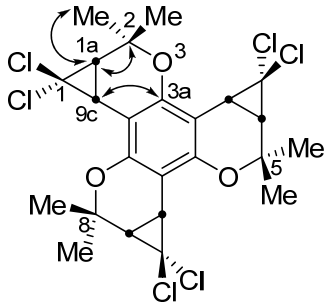


Figure 3.3.2 Diagnostic correlations observed in the HMBC spectrum of the *tris*-dichlorocyclopropane (67).

The proton *H*-1a was assigned based on HMBC correlations to the methyl groups, as well as to the quaternary carbon, *C*-2. As such, the proton *H*-9c was assigned based on HMBC correlations to the aromatic carbon, *C*-3a.

The cyclopropane **67** contains twenty-four individual carbon atoms, however, only eight carbon signals were observed in the ^{13}C NMR spectrum, further confirming the C_3-symmetry of this compound (Figure 3.3.3).

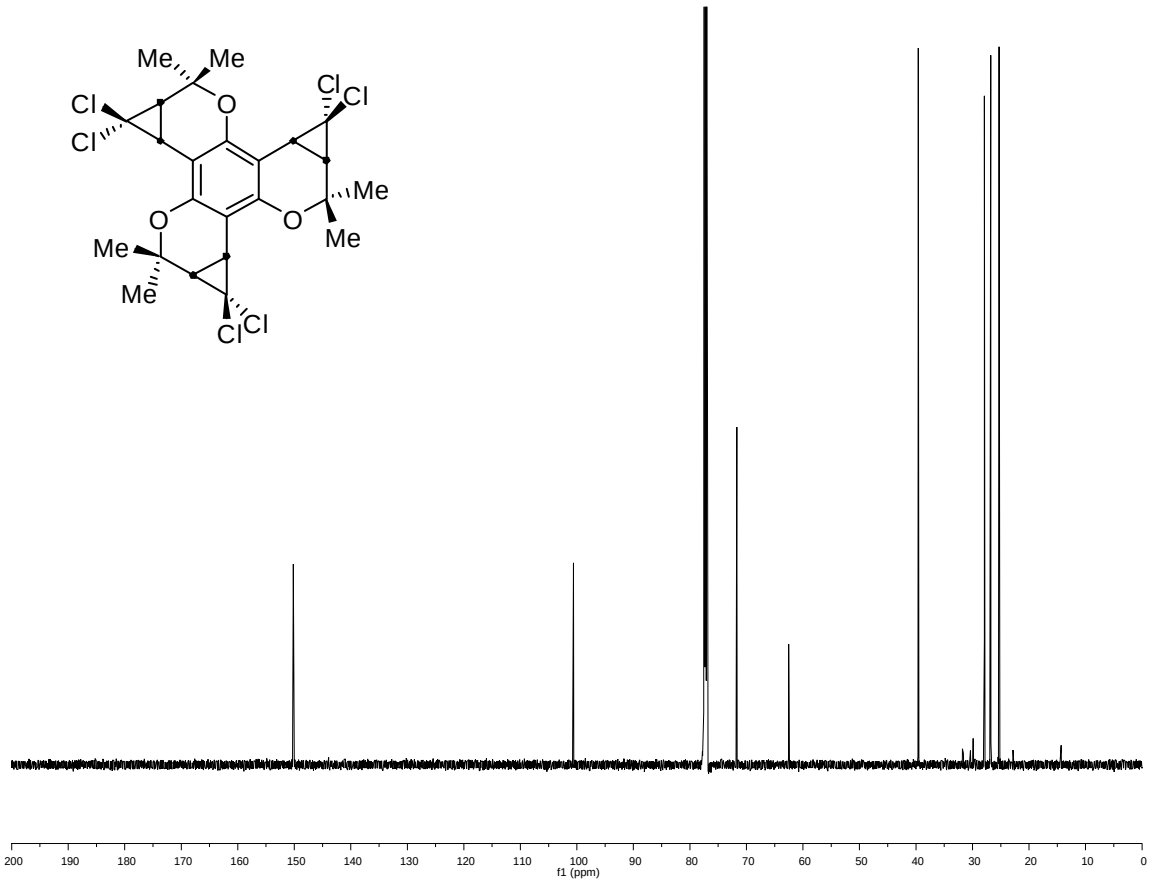


Figure 3.3.3 ^{13}C NMR (151 MHz, $CDCl_3$) of the *tris*-dichlorocyclopropane (67).

The ^{1}H NMR spectrum of the unsymmetrical diastereoisomer **68** contains six doublets ranging between δ = 2.1 – 3.1 ppm that correspond to the six unique protons of the cyclopropane rings. Additionally, there are four peaks, between δ = 1.25 – 1.72 ppm, that integrate for a total of eighteen hydrogen atoms, which confirm that there are six inequivalent methyl groups in the molecule (Figure 3.3.4). Of note, the apparent singlet located at δ = 1.25 ppm integrates for nine hydrogen atoms and can be attributed to three methyl groups that cannot be distinguished by ^{1}H NMR at 600 MHz.

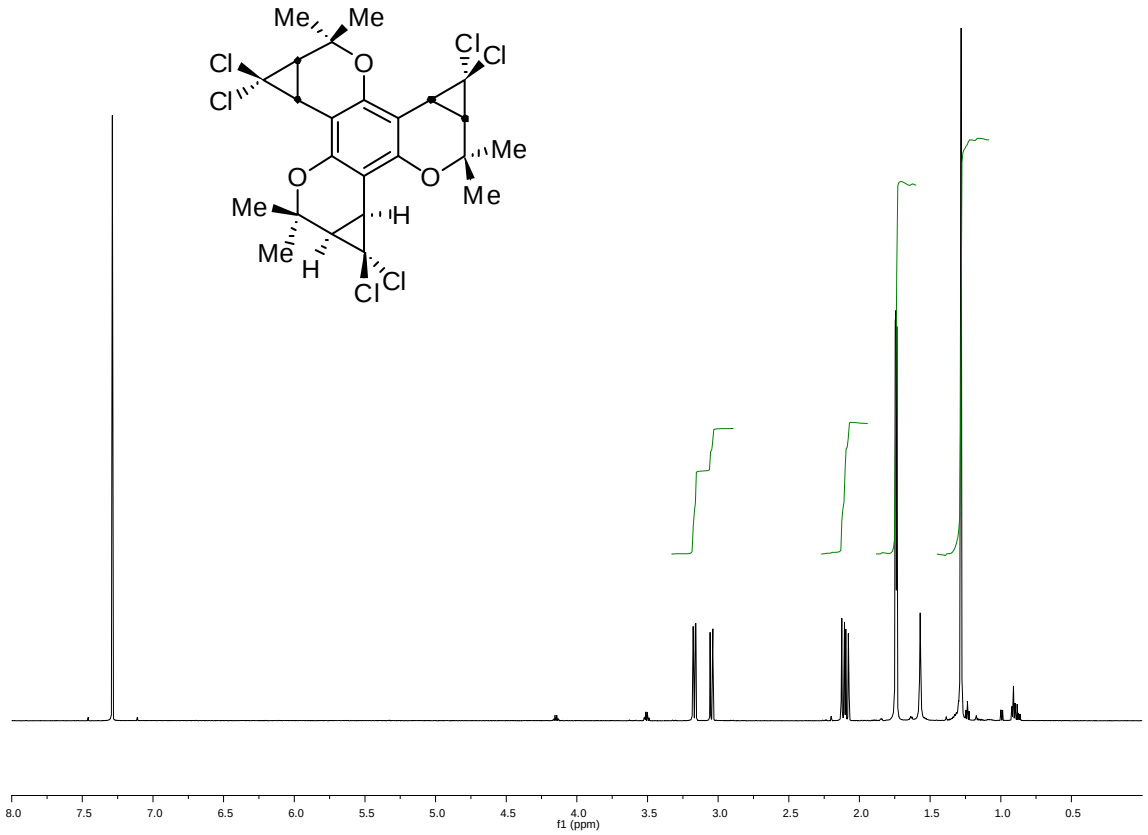


Figure 3.3.4 ^{1}H NMR (600 MHz, $CDCl_3$) of the *tris*-dichlorocyclopropane (68).

The ^{13}C NMR spectrum of the cycloadduct **68** displayed twenty-two of the expected twenty-four signals providing further indication that this is the unsymmetric isomer.

Since these compounds contain six chlorine atoms, a characteristic mass spectrum would be expected based on the isotopic abundance of chlorine. In the following table the expected isotopic ratio and the experimentally determined isotopic ratio for the unsymmetrical diastereoisomer **68** are displayed (Table 3.3.1). Similar data was also collected for the symmetrical diastereoisomer **67**.

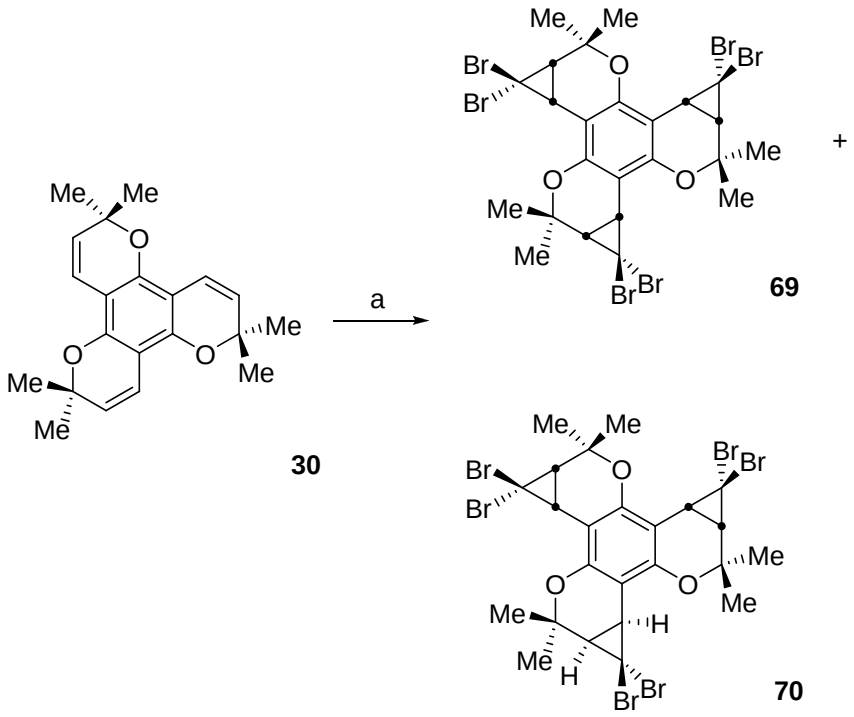
Table 3.3.1 Expected and Experimental Isotopic Ratios of the *tris*-Dichlorocyclopropane (68)

Isotope	Expected (%)	Found (%)
571 [M (6 x ^{35}Cl) + H]	48	45
573 [M (5 x ^{35}Cl + ^{37}Cl) + H]	100	100
575 [M (4 x ^{35}Cl + 2 x ^{37}Cl) + H]	88	86
577 [M (3 x ^{35}Cl + 3 x ^{37}Cl) + H]	42	38
579 [M (2 x ^{35}Cl + 4 x ^{37}Cl) + H]	11	9

The experimental values listed above were in very good agreement with the expected values for a compound with the molecular formula $C_{24}H_{24}Cl_6O_3$.[30] Finally, elemental analysis was used to confirm both the purity and elemental composition of both *tris*-dichlorocyclopropane diastereoisomers **67** and **68**.

Having successfully made the *tris*-dichlorocyclopropanes **67** and **68** the corresponding dibromocyclopropanes **69** and **70** were prepared. This involved the addition of bromoform to a mixture of the *tris*-2*H*-chromene **30**, *n*-tetrabutylammonium bromide (cat.) and an aqueous solution of sodium hydroxide (8 M) at room temperature. The requisite dibromocyclopropanes **69** and **70** were separated by flash chromatography and isolated in moderate yield. (Scheme 3.3.3).

Scheme 3.3.3 Synthesis of the *tris*-Dibromocyclopropanes (69 and 70)



Reagents and conditions: (a) $CHBr_3$, NaOH (8 M), $(n\text{-Bu})_4NBr$ (0.3 equiv), room temperature, 19 h, 19% (**69**) and 12% (**70**).

Analysis of the ^1H NMR spectrum of the crude reaction mixture indicated that the diastereoselectivity of the reaction was ~3:2, in favour of the unsymmetric stereoisomer **70** based on integration of the methyl signals.

The ^1H and ^{13}C NMR spectra of the dibromocyclopropanes **69** and **70** were quite similar to those recorded for the dichlorocyclopropanes **67** and **68**. Additionally, the *tris*-dibromocyclopropanes **69** and **70** displayed the expected isotopic patterns in the high resolution mass spectrum for a *hexa*-substituted bromine compound with a molecular formula $C_{24}H_{24}Br_6O_3$ (Table 3.3.2).[30]

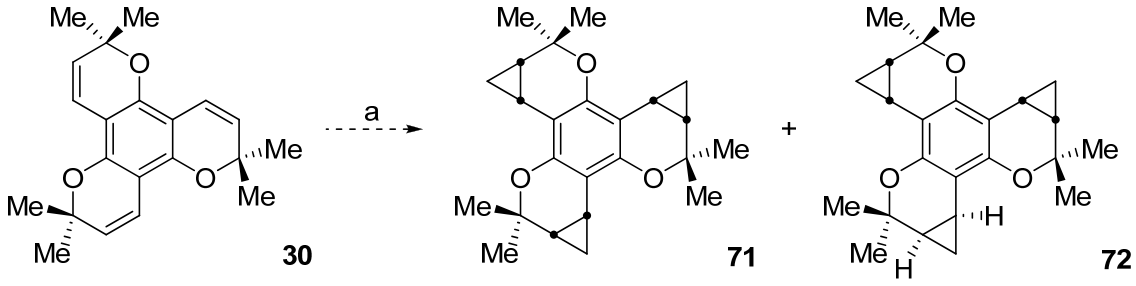
Table 3.3.2 Expected and Experimental Isotopic Ratios of the *tris*-Cyclopropane (70)

Isotope	Expected (%)	Found (%)
834 [M (6 x ^{79}Br) + H]	5	6
836 [M (5 x ^{79}Br + ^{81}Br) + H]	31	32
838 [M (4 x ^{79}Br + 2 x ^{81}Br) + H]	76	69
840 [M (3 x ^{79}Br + 3 x ^{81}Br) + H]	100	100
842 [M (2 x ^{79}Br + 4 x ^{81}Br) + H]	75	80
844 [M (^{79}Br + 5 x ^{81}Br) + H]	30	31
846 [M (6 x ^{81}Br) + H]	6	6

Of note, the three *individual* cyclopropanation reactions using dichlorocarbene and dibromocarbene on this *tris*-2*H*-chromene proceeded in good yield. The overall yield of the triple cycloaddition of dichlorocarbene was 66%, which corresponds to an average yield of 87% per individual cyclopropanation reaction. The dibromocyclopropane was isolated in an overall yield of 31%. This corresponds to an average yield of 68% per cyclopropanation reaction. Of additional and important note, the products of these reactions contain seven fused rings and six stereogenic centres and were prepared in two steps from simple and inexpensive commercially available starting materials.

Cyclopropanation reactions of the *tris*-2*H*-chromene **30** using the simplest carbene, dihydrocarbene, were also attempted. Although a variety of methods were attempted to affect this transformation, none were successful (Scheme 3.3.4).

Scheme 3.3.4 Attempted Cyclopropanation Reactions of the *tris*-2*H*-Chromene (30)



Reagents and conditions: See below: Table 3.3.3.

Table 3.3.3 Reagents and Conditions Corresponding to Scheme 3.3.4

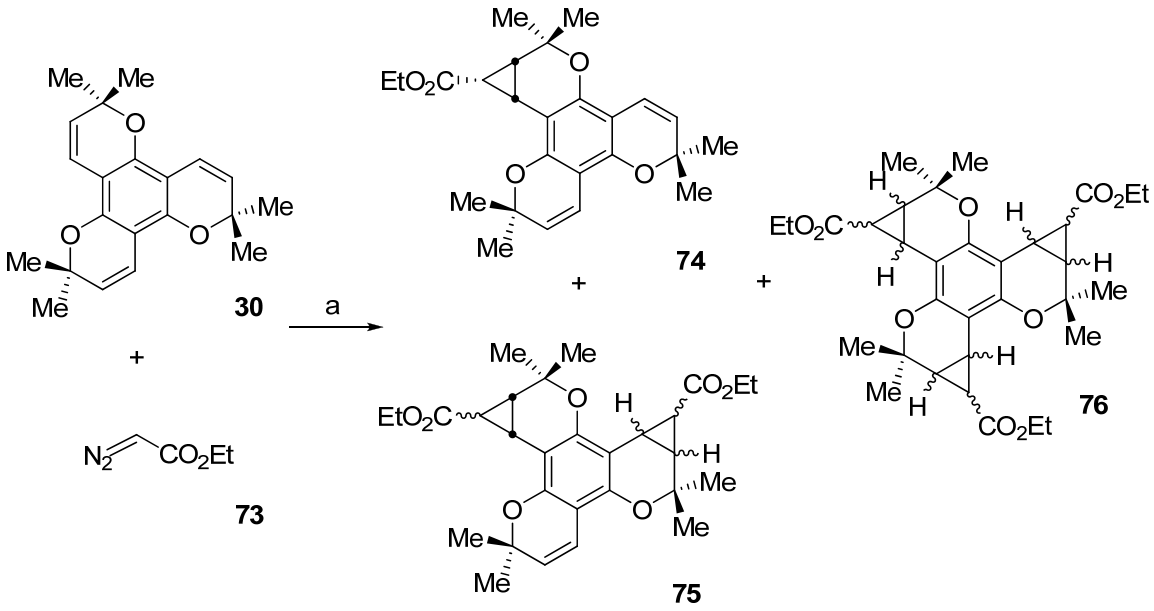
Entry	Reagents and Conditions	Result
1	CH_2N_2 (10 equiv), $Pd(OAc)_2$ (8 mol %), Et_2O, 0 °C to room temperature, 23 h	No reaction
2	CH_2N_2 (18 equiv), $Pd(OAc)_2$ (10 mol%), Et_2O, 0 °C to room temperature, 20 h	No reaction
3	Zn/Cu, I_2, CH_2I_2, Et_2O, reflux, 48 h	No reaction

In the first two instances, diazomethane was generated *in situ* from *N*-methyl-*N*-nitroso urea and reacted with palladium acetate in diethyl ether in the presence of the *tris*-2*H*-chromene **30** (entries 1 & 2). Unfortunately, no reaction products were observed and the starting material was recovered. A Simmons-Smith reaction was also performed using standard procedures (entry 3),[39] however, no reaction products were observed. Thus, attention was turned to other carbenes to prepare other cyclopropane adducts.

According to a procedure described by Lyle *et al*., carbenes can be generated *in situ* by reaction of a diazo compound with a copper(I) salt in the presence of a bipyridyl ligand to form a cyclopropane product.[40]

Initial studies involved the use of ethyl diazoacetate (**73**) as a diazo source and copper(I) triflate which was generated *in situ* from copper(II) triflate on reduction with phenylhydrazine (Scheme 3.3.5).[40]

Scheme 3.3.5 Synthesis of the *mono*-, *bis*- and *tris*-Cyclopropanes (74, 75 and 76) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) See below: Table 3.3.4.

Table 3.3.4 Reagents and Conditions Corresponding to Scheme 3.3.5

Entry	Equiv (73)	Addition Time (h)	Yield (%) 74	Yield (%) 75	Yield (%) 76
1	3	20	-	-	-
2	6	18	22 (53 brsm)	-	-
3	9	12	4 (37 brsm)	-	-
4	15	9	16	40	-
5	15	24	6	26	22

(*) General reaction conditions: $Cu(OTf)_2$ (1.25 mol%), 2,2'-bipyridyl (1.5 mol%), $PhNHNH_2$ (1.5 mol%), CH_2Cl_2, room temperature.

All of the cyclopropanation reactions were carried out in dichloromethane at room temperature. The equivalents of ethyl diazoacetate (**73**), along with the addition

times, were varied in order to optimize the yields of the *mono*-, *bis*- and *tris*-cycloadducts. Initially, the reaction was performed using ethyl diazoacetate (**73**) (3 equiv) which was added over a 20 hour period. However, no products were isolated from this reaction (entry 1). Thus, ethyl diazoacetate (**73**) (6 equiv) was used which was added over an eighteen hour period and this resulted in the isolation of the *mono*-cyclopropane **74** as a single diastereoisomer in 22% yield (53% brsm, entry 2). It was thought that further increasing the number of equivalents of ethyl diazoacetate (**73**) would afford the *bis*- and *tris*-cycloadducts. Therefore, ethyl diazoacetate (**73**) (9 equiv) was added over the course of 12 hours, however, the bis- and tris-cycloadducts were not isolated and only the mono-cycloadduct **74** was isolated in a 4% (37% brsm) yield (entry 3). Ethyl diazoacetate (**73**) (15 equiv) was subsequently added over 9 hours and this afforded both the *mono*- **74** as well as the *bis*-cyclopropane **75** cycloadducts in 16 and 40% yields, respectively (entry 4). Finally, ethyl diazoacetate (**73**) (15 equiv) was added over the course of 24 hours to afford the *mono*- , *bis*- and *tris*-cyclopropane adducts **74**, **75** and **76** with 6, 26 and 22% yields, respectively (entry 5).

The three cyclopropanation products **74**, **75** and **76** were separated by flash chromatography. The ^{1}H NMR spectrum of the *mono*-cyclopropane **74** had two sets of doublets at δ = ~5.5 and 6.6 ppm corresponding to the four remaining chromene protons. In addition, a doublet of doublets, which was located at δ = 2.8 ppm (J = 9.3, 3.8 Hz), corresponded to the proton *H*-11a. In addition, a multiplet located at δ = 2.0-2.2 ppm corresponded to the protons *H*-10a and *H*-11. The assignment of these protons was based on extensive analysis of the HMQC and HMBC spectra. The ^{13}C NMR spectrum also contained the expected twenty-five carbon signals for this compound. Additionally, the

mass spectrum (CI) showed the expected M + H peak at 411 amu's. Finally, elemental analysis was used to confirm both the purity and elemental composition of the *mono*-cyclopropane **74**.

As mentioned before, the *mono*-cycloadduct **74** was formed as a single diastereoisomer. 1D-nOe analysis of the *mono*-cyclopropane **74** indicated that the three cyclopropane protons were all on the same face of the molecule. The key nOe contacts are shown below (Figure 3.3.5). Of note, the ester functionality is projected over the centre of the chromene-core, which is also indicated from nOe contacts of the methylene (CH_2) group to the methyl groups of the three chromenes.

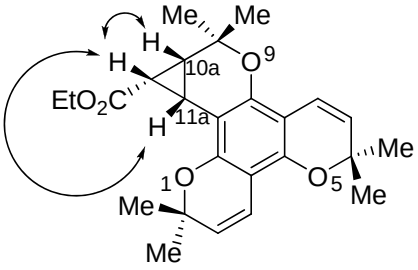


Figure 3.3.5 Diagnostic nOe contacts of the *mono*-cyclopropane (74).

The structure of the *bis*-cycloadduct **75** was confirmed by a variety of spectroscopic methods. The ^{1}H NMR spectrum of this compound displayed a pair of doublets, which were located at δ = 5.4 and 6.5 ppm (J = 9.9 Hz), which corresponded to the two remaining chromene protons. Moreover, two multiplets were located at δ = ~2.7 and ~2.8 ppm corresponded to either protons *H*-6a or *H*-10a. Additionally, a large multiplet located between δ = 2.0-2.1 ppm represented the remaining four protons around the cyclopropane rings. The *bis*-cyclopropane **75** is formed as a mixture of two diastereoisomers (dr = 4:3), as measured by integration of the multiplets at δ = 2.7 and 2.8 ppm in the ^{1}H NMR spectrum of the crude reaction mixture. Furthermore, the ^{13}C

NMR spectrum contained fifty six carbon signals, indicating that it was a mixture of two compounds. The elemental composition of these compounds were confirmed by high resolution mass spectrometry. A mass of 497.2534 amu's was calculated and a mass of 497.2538 amu's was experimentally found.

The structure of the *tris*-cyclopropane **76** was confirmed by analysis of the ^{1}H NMR spectrum. Notably, no proton signals were observed in the low field region, indicating that all of the chromene double bonds had reacted. In addition, a series of multiplets were located at the expected locations, notably δ = ~2.0 and ~2.7 ppm, corresponding to the protons around the cyclopropane rings. High resolution mass spectrometry further confirmed the elemental composition of this compound. A mass of 583.2902 amu's was calculated and a mass of 583.2897 amu's was recorded.

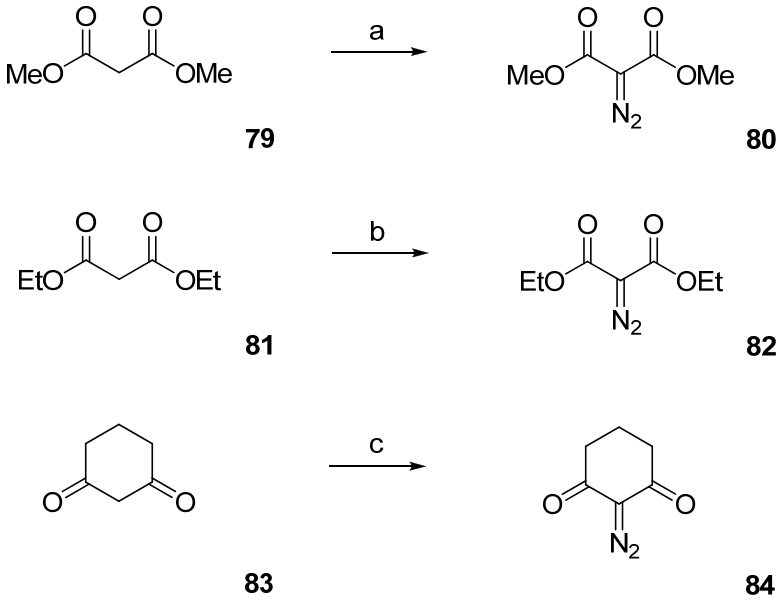
Unfortunately, the ^{1}H NMR spectrum of the crude reaction mixture was too complex to accurately define the peaks corresponding to the *mono*-, *bis*- and *tris*-cyclopropanes (Table 3.3.4, entry 5). However, on isolation of the *bis*-cyclopropane **75** by flash chromatography, the two diastereoisomers could be distinguished as there are two sets of peaks located at δ = ~2.7 ppm, as well as 12 singlets located between δ = 1.1-1.6 ppm. Integration of these signals indicates that a 5:3 ratio of diastereoisomeric bis-cyclopropanes were formed in this latter reaction. However, the stereochemistry of these cycloadducts could not be determined. Similarly, the *tris*-cyclopropane **76** was formed as a complex mixture of stereoisomers as indicated by ^{1}H NMR spectroscopy, which were inseparable by flash chromatography.

3.3.2.1 Synthesis and Evaluation of Additional Carbene Precursors

The successful use of a copper(I)-catalyzed cyclopropanation reaction led us to prepare a series of additional diazocompounds to further evaluate this reaction. These carbene precursors were chosen as they are symmetrical molecules and as such, the number of stereoisomers formed in the multiple cycloaddition processes would be reduced.

Initially, *p*-toluenesulphonyl azide (**77**) was prepared from *p*-toluenesulphonyl chloride (**78**) on reaction with sodium azide (1 equiv) in a mixture of acetone and water, which afforded the known azide **77** in excellent yield.[41] With the azide source in hand, preparation of the diazo compounds was performed using standard procedures.[42] This involved the slow addition of triethylamine (1.1 equiv) to a mixture of *p*-toluenesulphonyl azide (**77**) (1 equiv) with the requisite diester or dione (1 equiv) in acetonitrile. Diethyl diazomalonate (**82**) was isolated in low yield (28%) whereas dimethyl diazomalonate (**80**) and diazo-1,3-cyclohexadione (**84**) were isolated in good yield (Scheme 3.3.6). The spectral data was in agreement to that previously reported.[42-44]

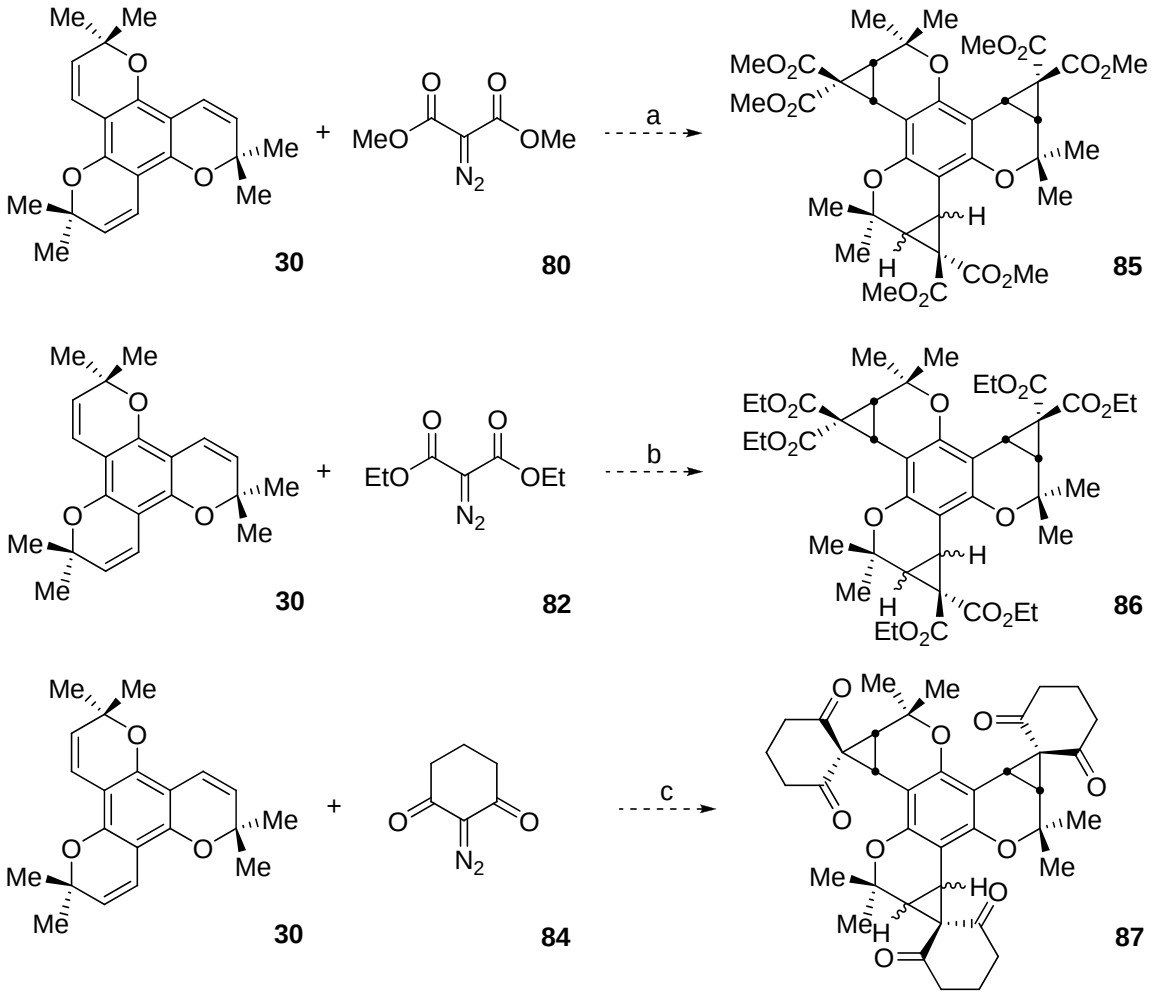
Scheme 3.3.6 Synthesis of the Stabilized Diazo Compounds (80, 82 and 84)



Reagents and conditions: (a) TsN_3 (**77**) (1 equiv), triethylamine (1.1 equiv), CH_3CN, room temperature, 17 h, 77%; (b) TsN_3 (**77**) (1 equiv), triethylamine (1.1 equiv), CH_3CN, room temperature, 17 h, 28%; (c) TsN_3 (**77**) (1 equiv), triethylamine (1.1 equiv), CH_3CN, room temperature, 14 h, 77%.

With the diazo compounds in hand, the copper(I)-catalyzed cyclopropanation reactions were performed using similar procedures to those described previously (Scheme 3.3.7). Unfortunately, no cycloaddition reaction products were isolated from these reactions.

Scheme 3.3.7 Attempted Synthesis of the *tris*-Cyclopropanes (85, 86 and 87) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) Diazo compound (**80**) (6 equiv), $Cu(OTf)_2$ (1.25 mol%), 2,2'-bipyridine (1.5 mol%), $PhNHNH_2$ (1.5 mol%), CH_2Cl_2, room temperature, 36 h; (b) Diazo compound (**82**) (6 equiv), $Cu(OTf)_2$ (1.25 mol%), 2,2'-bipyridine (1.5 mol%), $PhNHNH_2$ (1.5 mol%), CH_2Cl_2, room temperature, 36 h; (c) Diazo compound (**84**) (9 equiv), $Cu(OTf)_2$ (1.25 mol%), 2,2'-bipyridine (1.5 mol%), $PhNHNH_2$ (1.5 mol%), CH_2Cl_2, room temperature, 27 h.

Having established that a series of [2+1] cycloaddition reactions of the *tris*-2*H*-chromene **30** with various carbenes were possible, attention was turned to the study of a series of multiple [2+2] cycloadditions of the *tris*-2*H*-chromene **30**.

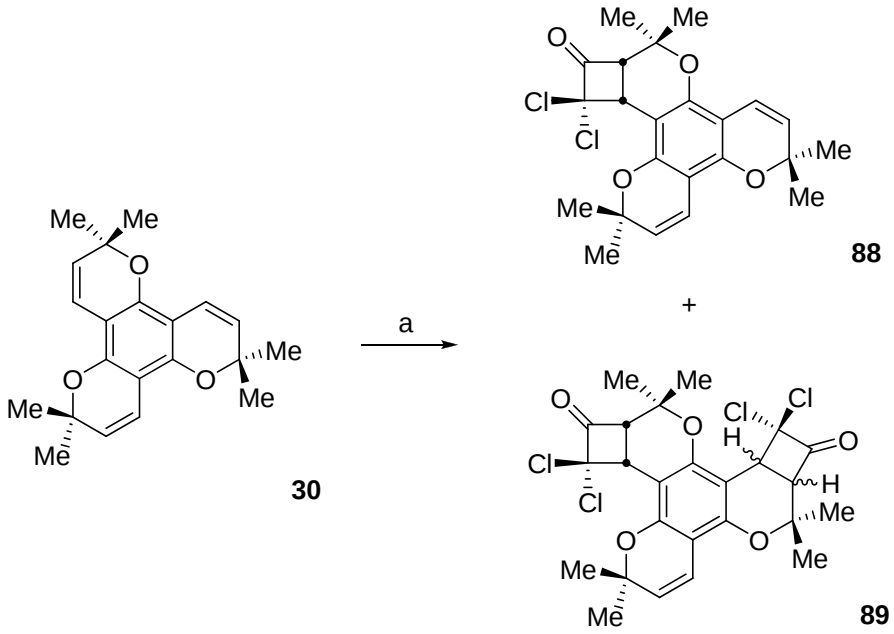
3.4 Intermolecular [2+2] Cycloaddition Reactions

Having established that intermolecular [2+2] cycloaddition reactions of *mono*-2*H*-chromenes are possible (See: Section 2.4), these reactions were applied to the *tris*-2*H*-chromene **30** and are discussed in the following section.

3.4.1 Ketene Cycloaddition Reactions of the *tris*-2*H*-Chromene (30)

Using the procedures described earlier for the generation of dichloroketene (See: Section 2.4.1), both the *mono*-cycloadduct **88** and *bis*-cycloadduct **89** were prepared from the corresponding *tris*-2*H*-chromene **30** under a variety of conditions. We have shown that by varying both the equivalents of trichloroacetyl chloride and the reaction temperature that either the *mono*-cycloadduct **88** or *bis*-cycloadduct **89** can be formed preferentially (Scheme 3.4.1). General reaction conditions are outlined below with the addition times of the trichloroacetyl chloride being ~1-2 minutes (Table 3.4.1).

Scheme 3.4.1 Synthesis of the *mono*- and *bis*-Cycloadducts (88 and 89) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) See below: Table 3.4.1.

Table 3.4.1 Reagents and Conditions Corresponding to Scheme 3.4.1

Entry	Reagents and Conditions	Yield (%) 88	Yield (%) 89
1	Cl_3CCOCl (9 equiv), Zn (13.5 equiv), THF, -78 °C to room temperature, 23 h	27 (38 brsm)	5 (8 brsm)
2	Cl_3CCOCl (9 equiv), Zn (13.5 equiv), THF, 0 °C to room temperature, 18 h	14	-
3	Cl_3CCOCl (9 equiv), Zn (13.5 equiv), THF, room temperature, 15 h	15	4
4	Cl_3CCOCl (15 equiv), Zn (22.5 equiv), THF, 0 °C to room temperature, 1 h	29	21
5	Cl_3CCOCl (15 equiv), Zn (22.5 equiv), THF, room temperature, 21 h	5	29

The initial reactions involved the use of trichloroacetyl chloride (9 equiv) and zinc powder (13.5 equiv) with addition temperatures ranging from -78 °C to room temperature (entries 1-3). The *mono*-cycloadduct **88** was the primary product formed using 9 equivalents of trichloroacetyl chloride, which indicated that more equivalents of trichloroacetyl chloride would be required for further addition processes to occur. The

number of equivalents of trichloroacetyl chloride and zinc powder were increased to 15 and 22.5, respectively. When the reaction was conducted at 0 °C, both the *mono*-cycloadduct **88** and the *bis*-cycloadduct **89** were prepared in nearly equivalent yields (entry 4). However, when the reaction was repeated at room temperature the *bis*-cycloadduct **89** was formed as the major product (entry 5).

Both the *mono*-cycloadduct **88** and the *bis*-cycloadduct **89** were readily separated by flash chromatography. The ^{1}H NMR spectrum of the *mono*-cycloadduct **88** displayed two pairs of doublets at δ = ~5.4 and ~6.5 ppm (J = ~9.9 Hz) which corresponded to the two remaining chromene double bonds. A pair of doublets representing the cyclobutane protons were located at δ = 3.9 and 4.3 ppm (J = 11.0 Hz). In addition, the ^{13}C NMR spectrum displayed the twenty-three individual carbon signals expected for this compound. Furthermore, the mass spectrum (CI) displayed the expected molecular ion peaks of [M(2 x ^{37}Cl) + H] and [M(2 x ^{35}Cl) + H] at 440 and 436 amu's, respectively. Of note, both the ^{1}H and ^{13}C NMR spectra indicated that this product was formed as a single regioisomer. The regiochemistry of this cycloaddition process was confirmed on analysis of the HMQC and HMBC spectra. Proton *H*-10a has a strong correlation to the quaternary carbon (*C*-10) as well as to the carbonyl carbon (*C*-11). Additionally, the proton *H*-12a has a strong correlation to the dichloro carbon (*C*-12) as well as strong correlations to carbons on the aromatic core (Figure 3.4.1).

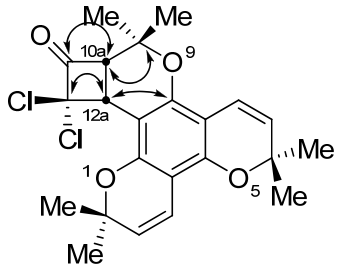
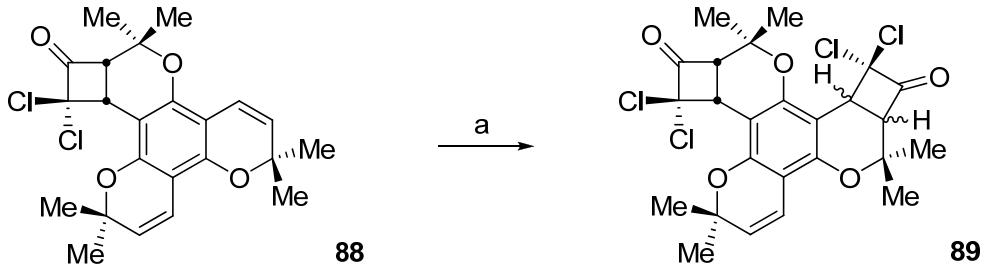


Figure 3.4.1 The key HMBC correlations of the cycloadduct (88).

The ^{1}H NMR spectrum of the *bis*-cycloadduct **89** has a single pair of doublets at δ = 5.4 and 6.5 ppm (J = 10.0 Hz) which correspond to the two remaining chromene protons. Additionally, two pairs of doublets, located at δ = ~4.0 and ~4.3 ppm (J = ~11 Hz), corresponded to the pairs of protons on the two cyclobutane rings. The ^{13}C NMR spectrum further confirmed that this product is a *bis*-addition as the twenty-five carbon signals expected were present. Furthermore, the mass spectrum (CI) has the expected molecular ion peak [M(4 x ^{37}Cl) + H] at 553 amu's. In addition, this cycloadduct was formed as a single regioisomer as shown by the ^{1}H and ^{13}C NMR spectra, although the relative stereochemistry could not be determined.

Conversion of the *mono*-cycloadduct **88** to the *tris*-cycloadduct **90** was attempted by resubjecting the *mono*-cycloadduct **88** to the reaction conditions. In this case, only the *bis*-cycloadduct **89** was afforded. The conversion of the *mono*-cycloadduct **88** to the *bis*-cycloadduct **89** was accomplished in moderate yield on using trichloroacetyl chloride (10 equiv) and zinc powder (15 equiv) in tetrahydrofuran from 0 °C to room temperature (Scheme 3.4.2).

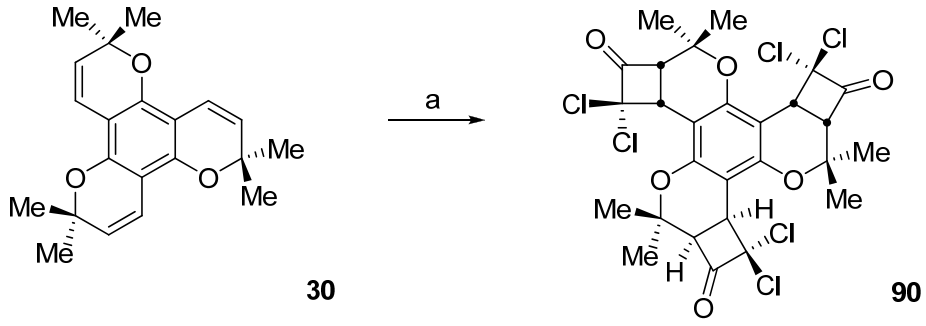
Scheme 3.4.2 Synthesis of the *bis*-Cycloadduct (89) from the *mono*-Cycloadduct (88)



Reagents and conditions: (a) Cl_3CCOCl (10 equiv), Zn (15 equiv), THF, 0°C to room temperature, 15 min, 40%.

During the preparation of both the *mono*- and *bis*-cycloadducts, the ketene was generated quickly. It was subsequently found that by generating the ketene slowly, a *tris*-cycloadduct **90** could be readily prepared. This involved the addition of a solution of trichloroacetyl chloride (9 equiv) in tetrahydrofuran *via* syringe pump over the course of twelve hours to a suspension containing zinc powder (13.5 equiv) and the *tris*-2*H*-chromene **30** in tetrahydrofuran at room temperature. This afforded the *tris*-cycloadduct **90** in good yield (Scheme 3.4.3). Of note, the three individual cycloaddition reactions proceeded in excellent yield. The overall yield of the cycloaddition process was 60% which corresponds to an average yield of 85% per individual cycloaddition reaction.

Scheme 3.4.3 Synthesis of the *tris*-Cycloadduct (90) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) Cl_3CCOCl (9 equiv), Zn (13.5 equiv), THF, 0 °C to room temperature, 12 h dropwise addition, 60%.

The synthesis of the *tris*-cycloadduct **90** was confirmed by a variety of spectroscopic methods. Analysis of the ^{1}H NMR spectrum revealed that no chromene protons were present, however, three pairs of doublets, located between δ = 3-4 ppm, indicated that the chromene double bonds had reacted to form the three cyclobutane rings (Figure 3.4.2). In addition, the presence of six methyl signals indicates that this is the unsymmetrical isomer **90**.

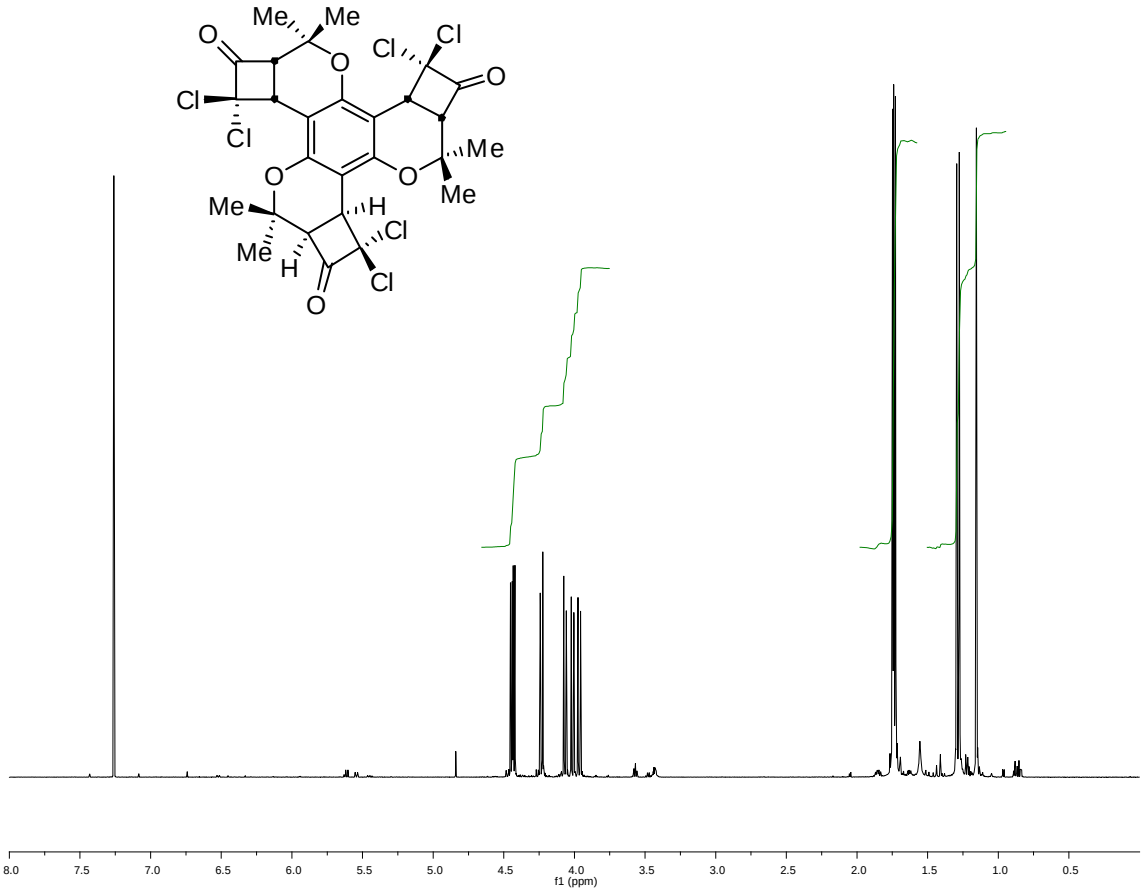


Figure 3.4.2 ^{1}H NMR (600 MHz, $CDCl_3$) of the *tris*-cycloadduct (90).

Interestingly, the stereochemical outcome for the *tris*-cycloadduct **90** was aided by the C_3-symmetry of the starting material. The ^{1}H NMR spectrum of the *tris*-cycloadduct **90** would be exceedingly simple if all six cyclobutane protons were on the same face of the molecule. However, the ^{1}H NMR spectrum shows six distinct doublets

indicating that the cycloaddition reactions occurred with two cycloadditions on the same face while the third cycloaddition occurred from the opposite face. This is the only non-symmetrical arrangement possible for this particular triple cycloaddition process.

The ^{13}C NMR spectrum displayed twenty-five carbon signals, which is two signals less than the twenty-seven expected and it can be concluded that certain peaks overlap. In addition, the presence of three distinct carbonyl peaks ranging from δ = 192-194 ppm further confirms that the unsymmetrical isomer **90** was prepared.

The MALDI-TOF displayed the following isotopic pattern for the molecular ion (Table 3.4.2).

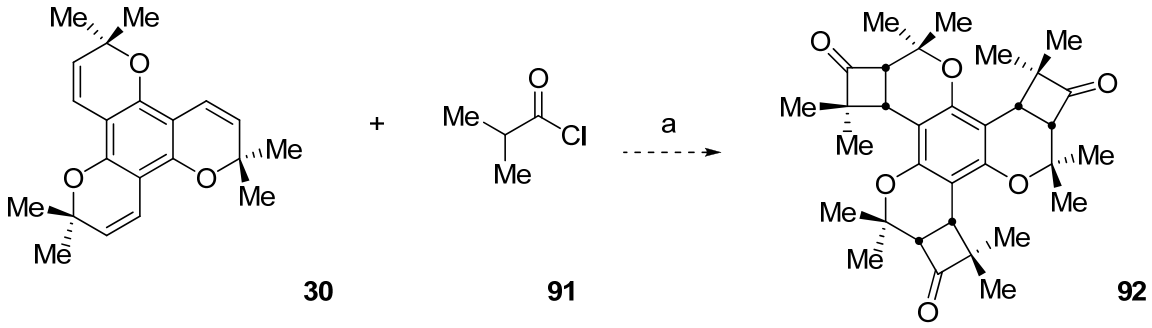
Table 3.4.2 Expected and Experimental Isotope Ratios of the *tris*-Cycloadduct (90)

Isotope	Expected (%)	Found (%)
654 [M (6 x ^{35}Cl)]	48	50
656 [M (5 x ^{35}Cl + ^{37}Cl)]	100	100
658 [M (4 x ^{35}Cl + 2 x ^{37}Cl)]	88	85

Finally, elemental analysis was used to confirm both the purity and elemental composition of the *tris*-cycloadduct **90**.

Having successfully prepared the *mono*-, *bis*- and *tris*-cycloadducts using dichloroketene, investigations were then turned to additional ketene substrates in order to prepare further [2+2] cycloadducts. A variety of attempts were made to generate other ketenes. Initial attempts focussed on the generation of dimethyl ketene by the reaction of 2-methylpropionyl chloride (**91**) under a variety of conditions (Scheme 3.4.4).

Scheme 3.4.4 Attempted Synthesis of the *tris*-Cycloadduct (92) from the *tris*-2*H*-Chromene (30)



30 91 92

Reagents and conditions: (a) See below: Table 3.4.3.

Table 3.4.3 Reagents and Conditions Corresponding to Scheme 3.4.4

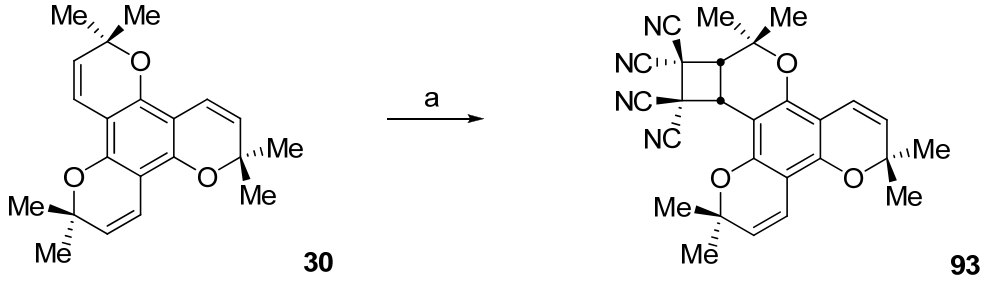
Entry	Reagents and Conditions	Result
1	Acyl chloride **91** (9 equiv), Et_3N (9 equiv), THF, 0 °C to room temperature, 22 h	No reaction
2	Acyl chloride **91** (9 equiv), Et_3N (13.5 equiv), Et_2O, room temperature, sonication, 30 min	No reaction
3	Acyl chloride **91** (9 equiv), LDA (10 equiv), Et_2O, -78 °C to room temperature, 21 h	No reaction
4	Acyl chloride **91** (4.5 equiv), NaH (4.8 equiv), THF, -78 °C to room temperature, 20 h	No reaction
5	Acyl chloride **91** (10 equiv), NaH (15 equiv), Et_2O, 0 °C to room temperature, 36 h	No reaction
6	Acyl chloride **91** (10 equiv), *n*-BuLi (11 equiv), Et_2O, -78 °C to room temperature, 36 h	No reaction

Initially, the acid chloride **91** was reacted with triethylamine to remove the alpha proton and generate dimethyl ketene, but with no success (entry 1). Under similar conditions, the number of equivalents of triethylamine were increased from 1 to 1.5 but again no cycloadducts were isolated (entry 2). Other bases were also employed in this reaction. Specifically, lithium diisopropylamide (entry 3), sodium hydride (entries 4 & 5) and *n*-butyllithium (entry 6) were used, however, no cycloadducts were isolated. Thus, a different [2+2] cycloaddition process was explored to further determine the reactivity of the *tris*-2*H*-chromene substrate.

3.4.2 Tetracyanoethylene Cycloaddition Reactions of the *tris*-2*H*-Chromene (30)

Intermolecular [2+2] cycloaddition reactions involving tetracyanoethylene were shown to proceed well on *mono*-2*H*-chromenes (See: Section 2.4.2). Using the same methodology, tetracyanoethylene (4 equiv) was added to a solution of the *tris*-2*H*-chromene **30** in acetonitrile and the reaction was heated at reflux for five minutes. This afforded the *mono*-tetracyanoethylene cycloadduct **93** (Scheme 3.4.5).

Scheme 3.4.5 Synthesis of the *mono*-Tetracyanoethylene Cycloadduct (93) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) Tetracyanoethylene (4 equiv), MeCN, reflux, 5 min, 29%.

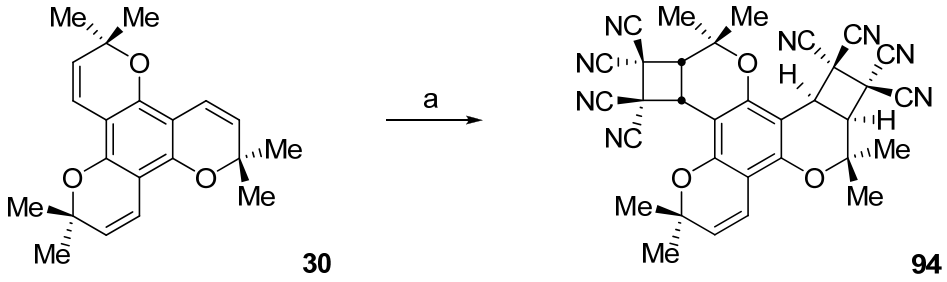
Of note, on addition of tetracyanoethylene to a solution of the *tris*-2*H*-chromene **30** in acetonitrile, the reaction mixture developed a deep blue colour. After five minutes of being heated at reflux, the reaction mixture then turned a deep brown colour. TLC analysis indicated that when this colour change occurred that the *tris*-2*H*-chromene **30** had been consumed.

The molecular structure of the *mono*-cycloadduct **93** was confirmed by a variety of spectroscopic methods. Analysis of the ^{1}H NMR spectrum displayed two pairs of doublets corresponding to the four remaining chromene protons as well as a pair of doublets, located at δ = 3.6 and 4.3 ppm (J = 9.7 Hz), which corresponded to the cyclobutane protons. Moreover, the ^{13}C NMR spectrum displayed the twenty-seven

signals that were expected for this compound. Additionally, the IR spectrum has a weak absorption peak at 2250 cm^{-1}, which is characteristic of cyano groups.

The *bis*-cycloadduct **94** was prepared, in moderate yield, *via* similar methodology. In this instance, the *tris*-2*H*-chromene **30** was reacted with tetracyanoethylene (9 equiv) in acetonitrile heated at reflux for 24 hours (Scheme 3.4.6).

Scheme 3.4.6 Synthesis of the *bis*-Tetracyanoethylene Cycloadduct (94) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) Tetracyanoethylene (4 equiv), MeCN, reflux, 24 h, 42%.

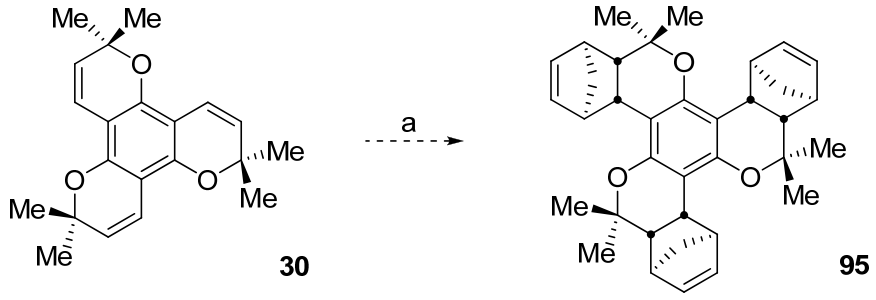
The ^{1}H NMR spectrum of the *bis*-cycloadduct **94** contained a single pair of doublets representing the two remaining chromene protons as well as two pairs of doublets which correspond to the protons of the two cyclobutane rings located at δ = ~4.1 and ~4.5 ppm. In addition, the *bis*-cycloadduct **94** was formed as a single diastereoisomer. Although the stereochemistry of the *bis*-cycloadduct **94** could not be determined, it is likely formed as shown above (Scheme 3.4.6). This assumption is based on the steric argument that the initial cycloaddition would prevent further cycloaddition reactions from occurring on the same face of the molecule, therefore the second cycloaddition would occur from the opposite face. In addition, the ^{13}C NMR spectrum displayed thirty-two carbon signals, which is one less signal than the thirty-three expected. The reason for this is attributed to the overlap of two similar carbon signals. Moreover, high resolution mass spectrometry was used to confirm the mass and the

elemental composition of this cycloadduct. Unfortunately, no triple cycloaddition products were isolated from these reactions. Having successfully performed a series of intermolecular [2+2] cycloaddition reactions, our attention was turned towards performing an intermolecular [2+4] cycloaddition reaction.

3.5 Intermolecular [2+4] Cycloaddition Reactions of the *tris*-2*H*-Chromene (30)

Initial attempts to affect a [2+4] cycloaddition involved mixing the *tris*-2*H*-chromene **30** with freshly distilled cyclopentadiene, which would serve as the diene component. This involved heating freshly distilled cyclopentadiene (10 equiv) at reflux with the *tris*-2*H*-chromene **30** in toluene for 6 days (Scheme 3.5.1). Unfortunately, no reaction products were observed from this reaction.

Scheme 3.5.1 Attempted Diels-Alder Cycloaddition Reaction of Cyclopentadiene with the *tris*-2*H*-Chromene (30)

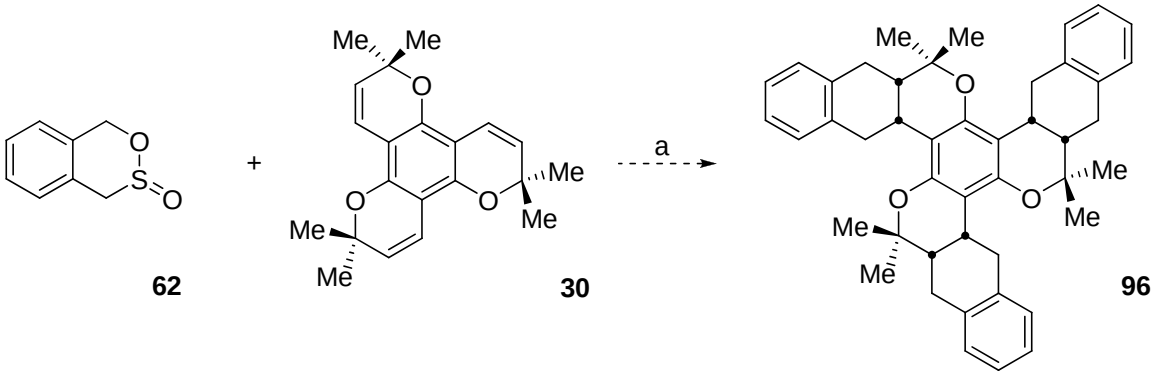


Reagents and conditions: (a) Cyclopentadiene (10 equiv), PhMe, reflux, 6 days.

In order to perform an intermolecular [2+4] cycloaddition reaction, it was concluded that a more reactive diene was required. As mentioned earlier (See: Section 2.4.1), the sultine **62** is a compound that can be readily prepared and that can serve as a precursor to the highly reactive diene, *o*-quinonedimethane (**59**).

Thus, the sultine **62** (3 equiv) was heated with the *tris*-2*H*-chromene **30** in benzene at reflux for 48 hours. Unfortunately, this did not result in the formation of the desired cycloadduct **96** (Scheme 3.5.2).

Scheme 3.5.2 Attempted Synthesis of *tris*-Cyclohexabenzene (96) from the *tris*-2*H*-Chromene (30)



Reagents and conditions: (a) Sultine **62** (3 equiv), PhH, reflux, 48 h.

This lack of reactivity likely indicates that the 2*H*-chromene double bond will need to be activated in order to engage in a Diels-Alder cycloaddition reaction.

3.6 Conclusions

It has been shown that the *tris*-2*H*-chromene **30** can undergo a variety of intermolecular cycloaddition reactions. Multiple intermolecular [2+1] cycloaddition reactions of both dichloro- and dibromocarbenes afforded both C_3-symmetric and unsymmetric cyclopropane adducts. Additionally, cyclopropanation reactions of ester-stabilized carbenes, generated *in situ via* a copper(I)-catalyst, were shown to afford *mono*-, *bis*- and *tris*-cycloadducts. Multiple [2+2] cycloaddition reactions also proved to be quite successful. Ketene cycloaddition reactions of the *tris*-2*H*-chromene **30** afforded the corresponding *mono*-, *bis*- and *tris*-cycloadducts. Additionally, [2+2] cycloadditions

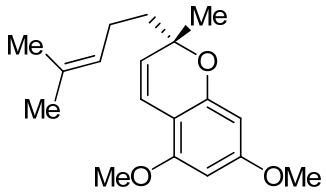
involving tetracyanoethylene were shown to afford both a *mono*- and *bis*-cycloadduct. Finally, [2+4] cycloaddition reactions were attempted. However, even when the highly reactive diene, *o*-quinonedimethane, was employed no reactions occurred. Therefore, in order to facilitate a [2+4] cycloaddition reaction, the 2*H*-chromene carbon-carbon double bond needs to be activated with an electron withdrawing group. Of note, these multiple cycloaddition processes afforded complex polycyclic compounds containing upwards of 7 fused rings and 9 stereogenic centres generated from readily available starting materials in two synthetic operations.

4 RESULTS AND DISCUSSION

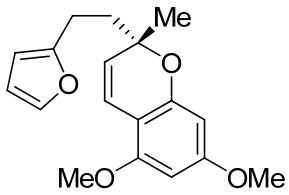
Intramolecular Cycloaddition Reactions of mono-*2*H-*Chromenes*

4.1 Introduction

In this chapter, the synthesis of two functionalized *mono*-2*H*-chromenes are described. These compounds were prepared to investigate the feasibility of intramolecular [2+2] and [2+4] cycloaddition reactions of the 2*H*-chromene carbon-carbon double bond (Figure 4.1.1). It was envisioned that the two model 2*H*-chromenes **97** and **98** could be prepared, using the phenylboronic acid-mediated condensation reaction, from the corresponding phenol and α,β-unsaturated aldehydes.



97



98

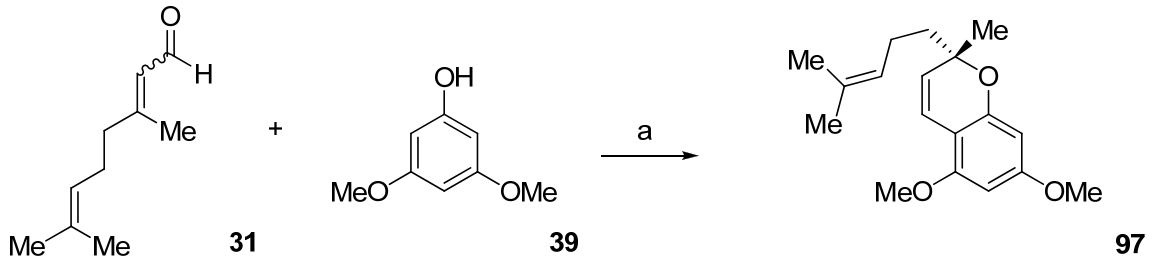
Figure 4.1.1 Molecular structures of the *mono*-2*H*-chromenes (97 and 98).

4.2 Intramolecular [2+2] Cycloaddition Reactions of the *mono*-2*H*-Chromene (97)

4.2.1 Synthesis of the *mono*-2*H*-Chromene (97)

In order to investigate an intramolecular [2+2] cycloaddition reaction, the requisite 2*H*-chromene **97** was prepared in excellent yield *via* the phenylboronic acid-mediated condensation reaction of commercially available citral (**31**) (*E*:*Z* = ~2:1) (1.3 equiv) and 3,5-dimethoxy phenol (**39**) (1 equiv) (Scheme 4.2.1).

Scheme 4.2.1 Synthesis of the *mono*-2*H*-Chromene (97) from Citral (31) and 3,5-Dimethoxyphenol (39)



31 **39** **97**

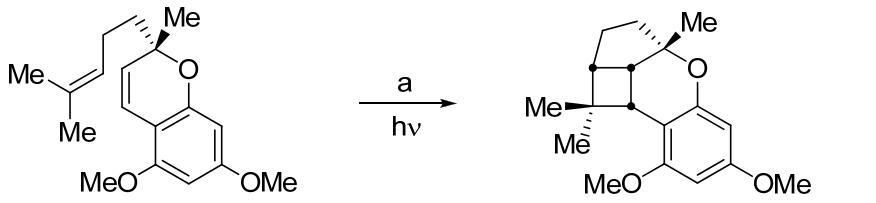
Reagents and conditions: (a) Citral (**31**, 1.3 equiv, *E*:*Z* = ~2:1), $PhB(OH)_2$ (1 equiv), propionic acid (cat.), PhH, reflux, 2.5 h, 94%.

The structure of the 2*H*-chromene **97** was determined by a variety of spectroscopic methods. The ^{1}H NMR spectrum contained characteristic signals for the chromene protons located at δ = 5.4 and 6.6 ppm (J = 9.8 Hz). The ^{13}C NMR spectrum displayed the expected eighteen signals for this compound. Moreover, the mass spectrum (CI) displayed the expected M + H signal at 289 amu's. Satisfactory elemental analysis results could not be obtained for this compound, however, high-resolution mass spectrometry was used to confirm the elemental composition of this compound.

4.2.2 Intramolecular [2+2] Cycloaddition Reaction of the *mono*-2*H*-Chromene (97)

With the functionalized 2*H*-chromene **97** in hand, the [2+2] cycloaddition reaction of the 2*H*-chromene was carried out under a variety of reaction conditions (Scheme 4.2.2).[45]

Scheme 4.2.2 Synthesis of the Cyclobutane (99) from the *mono*-2*H*-Chromene (97)



97 **99**

Reagents and conditions: (a) See below: Table 4.2.1.

Table 4.2.1 Reagents and Conditions Corresponding to Scheme 4.2.2

Entry	Reagents and Conditions	Yield (%)
1	$Ph_2(CO)$, PhH, 2 h	57
2	Acetone, 24 h	26
3	PhH, 12 h	No reaction
4	Hexanes, 12 h	No reaction
5	Acetone, *t*-BuOH (1:1), 2.5 h	No reaction

For all experiments, the irradiation source used was a Hanovia 450 Watt medium pressure mercury vapour lamp. In addition, all reactions were degassed by bubbling dry nitrogen gas through the reaction mixture over the course of ~25 minutes. A benzene solution containing the 2*H*-chromene **97** and a sensitizer [benzophenone (1 equiv)], was irradiated in a quartz reaction vessel to afford the cyclobutane **99** in good yield (entry 1). In addition, a solution of the 2*H*-chromene **97** in acetone was irradiated in a quartz reaction vessel to afford the cyclobutane **99** in moderate yield (entry 2). When either benzene or hexanes were used (entries 3 & 4), without a sensitizer, no reaction products were observed. Thus, a photosensitizer is required to elicit the desired cycloaddition

reaction. Finally, the use of an acetone:*t*-butanol mixture also resulted in no reaction products being observed (entry 5).[46]

The known cyclobutane **99** was readily purified by flash chromatography to afford a white solid. The melting point of the cyclobutane **99** (104-106 °C) is in close agreement with the previously reported literature value for this compound.[46]

The structure of cyclobutane **99** was verified by extensive 1D and 2D NMR spectral analysis. The ^{1}H NMR spectrum of the crude reaction mixture indicated that the reaction had gone to completion because the two doublets from the chromene protons at δ = 5.4 and 6.6 ppm were absent and a new set of peaks corresponding to the cyclobutane protons of compound **99** were present (Figure 4.2.1).

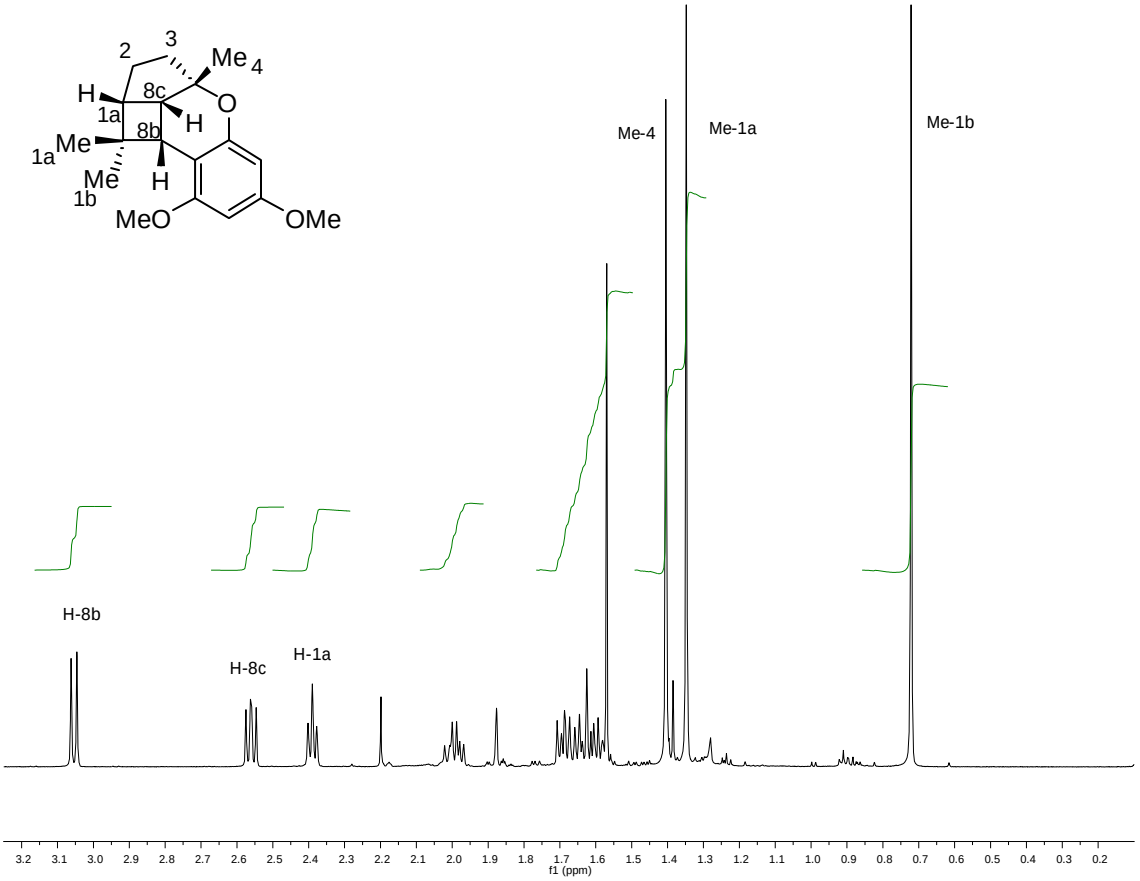


Figure 4.2.1 ^{1}H NMR (600 MHz, $CDCl_3$) of the cyclobutane (99).

Characterization of the cyclobutane **99** began with the highest upfield signal, the singlet at δ = 0.7 ppm, which corresponded to one of the methyl groups. Additionally, the two other methyl substituents gave sharp singlets at δ = 1.3 and 1.4 ppm. The singlets at 1.3 and 1.4 ppm were assigned to Me-1a and Me-4, respectively, based on nOe contacts of cyclobutane **99**, using *H*-8b as a characteristic signal (Figure 4.2.2). *H*-8b was assigned to the doublet at δ = 3.0 ppm based on observed ^{1}H-^{1}H COSY correlations and chemical shift (Figure 4.2.3). The observed nOe contacts of *Me*-1a were to *H*-1a and *H*-8b. The observed nOe contacts of *H*-8c were to *H*-1a, *H*-8b and *Me*-4. Additionally, *Me*-1b had nOe contacts to *Me*-1a and *H*-3$_{\beta}$. These stereochemical assignments indicate

that all three protons around the cyclobutane ring are on the same face of this molecule. These stereochemical assignments are consistent for 4,5,6 fused rings of this nature.

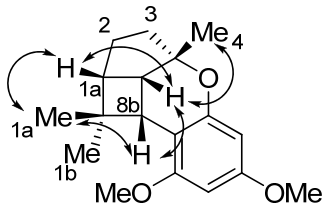


Figure 4.2.2 Selected nOe contacts for the cyclobutane (99).

Further analysis of the ^{1}H-^{1}H COSY spectrum reveals couplings between the protons of the four and five membered rings (Figure 4.2.3).

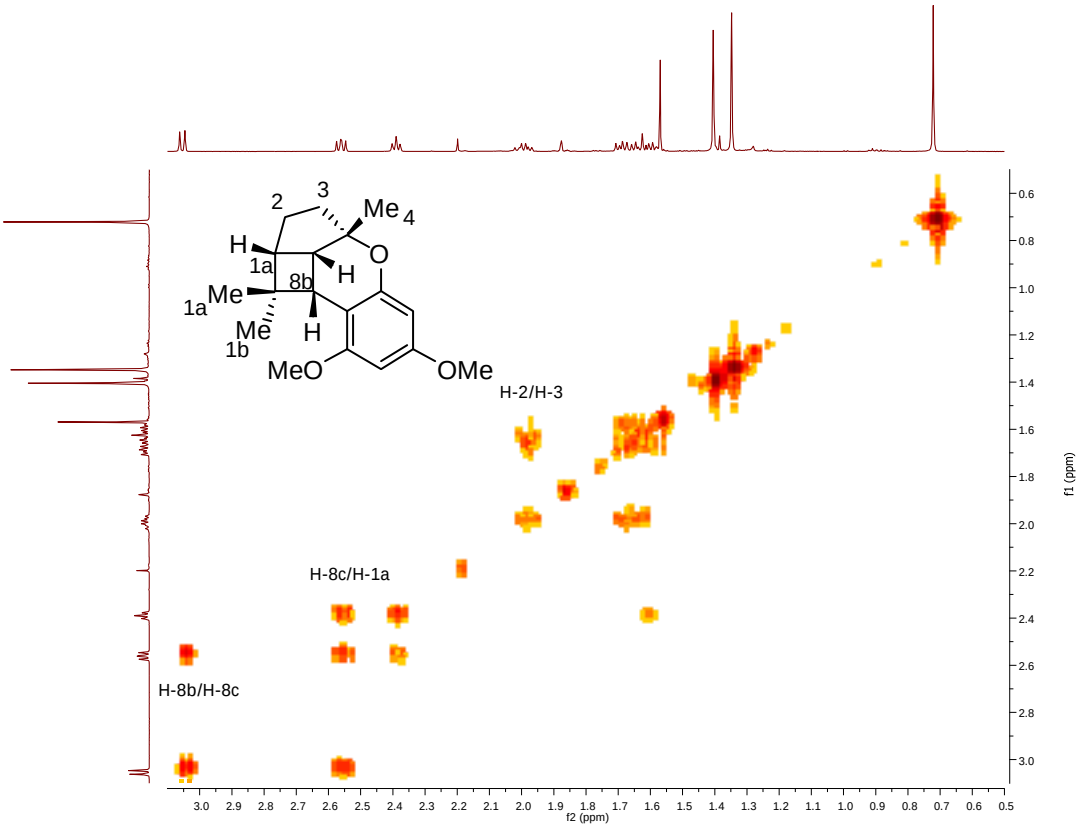


Figure 4.2.3 **^{1}H-^{1}H COSY (600 MHz, $CDCl_3$) of the cyclobutane (99).**

A coupling between protons *H*-8b and *H*-8c (J = 9.6 Hz) was observed. Additionally, coupling between protons *H*-8c and proton *H*-1a was observed (J = 7.4 Hz). Moreover, coupling between proton *H*-1a and proton *H*-2$_\alpha$ was observed. Thus, all protons around the cyclobutane ring have been assigned. On analysis of the HSQC spectrum of cyclobutane **99** it was possible to assign the protons on carbons *C*-2 and *C*-3. The protons *H*-2$_\alpha$ and *H*-2$_\beta$ were found to belong to the multiplet located at δ = 1.56-1.69 ppm. The HSQC spectrum displayed both proton signals located at δ = 1.58 and 1.68 ppm as belonging to *C*-2. Additionally, the HSQC spectrum displayed the proton signals located at δ = 1.64 and 1.97 ppm were found to belong to *C*-3.

Having established that an intramolecular [2+2] cycloaddition reaction is possible, studies were undertaken to prepare and evaluate a functionalized *mono*-2*H*-chromene for an intramolecular [2+4] cycloaddition reaction.

4.3 Intramolecular [2+4] Cycloaddition Reactions of the *mono*-2*H*-Chromene (98)

In order to evaluate the plausibility of an intramolecular [2+4] cycloaddition reaction, a furan moiety was selected as the diene component due to its synthetic ease.

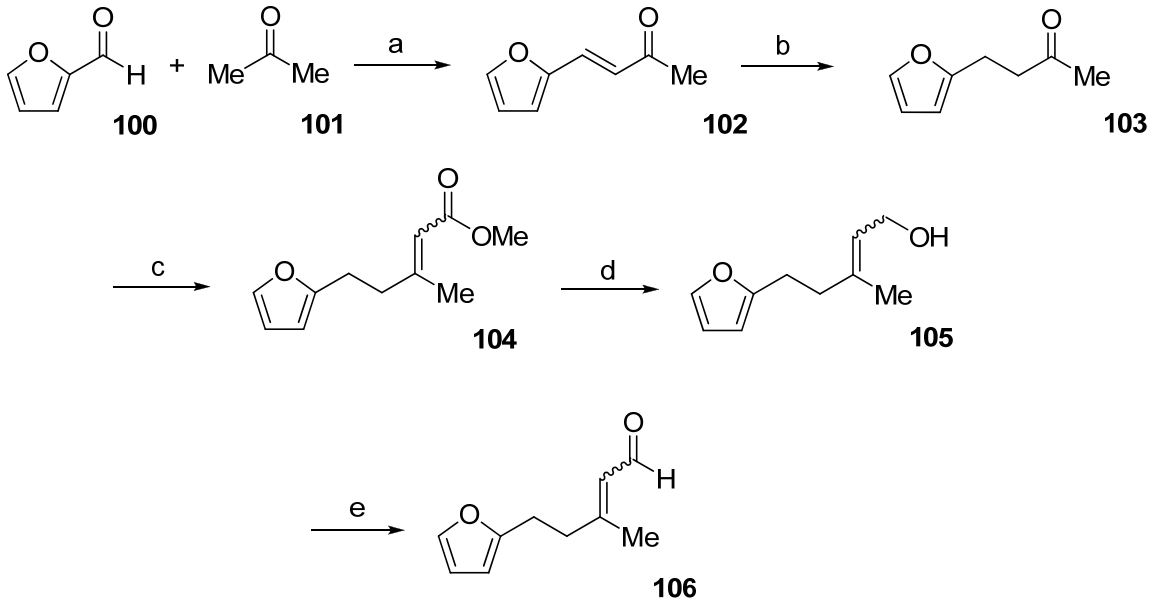
4.3.1 Synthesis of the *mono*-2*H*-Chromene (98)

The α,β-unsaturated aldehyde **106** is needed to prepare the novel *mono*-2*H*-chromene **98**. The aldehyde **106** was easily prepared *via* standard methodology from inexpensive starting materials.

Preparation of the aldehyde **106** began with the addition of furfural (**100**) to a mixture of acetone (**101**) (1 equiv) and water at room temperature and to this reaction mixture was added an aqueous solution of sodium hydroxide (8 M). The resultant mixture was allowed to stir for twenty-three hours, which afforded the known α,β-unsaturated ketone **102** in moderate yield.[47] This compound was then subjected to standard hydrogenation reaction conditions to afford the ketone **103** in good yield.[48] A Horner-Wadsworth-Emmons reaction of ketone **103** and trimethyl phosphonoacetate (1.3 equiv) afforded the α,β-unsaturated ester **104** in excellent yield. This ester was then reduced with lithium aluminium hydride (1.1 equiv) to afford the allylic alcohol **105** in excellent yield. This alcohol was subsequently oxidized with manganese dioxide to

afford the α,β-unsaturated aldehyde **106** in good yield (Scheme 4.3.1).[21] This aldehyde **106** was prepared in five steps with an overall yield of 18%.

Scheme 4.3.1 Synthesis of the α,β-Unsaturated Aldehyde (106) from Furfural (100) and Acetone (101)



Reagents and conditions: (a) NaOH, H_2O, 23 h, 57 %; (b) H_2, Pd/C, EtOAc, room temperature, 17 h, 69 %; (c) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then ketone **103**, reflux, 24 h, 84 % (*E*:*Z* = ~3:1); (d) $LiAlH_4$, Et_2O, 0°C to room temperature, 90 min, 85 % (*E*:*Z* = ~3:1); (e) MnO_2, CH_2Cl_2, room temperature, 14.5 h, 65 % (*E*:*Z* = ~3:1).

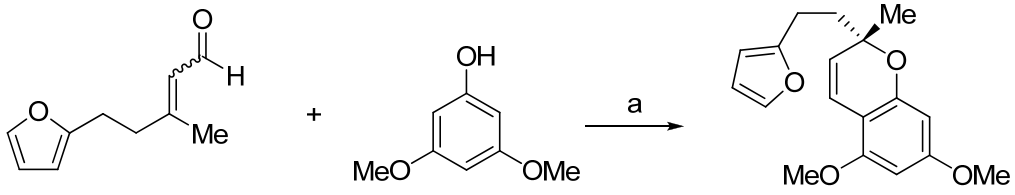
The ester **104**, the alcohol **105** and the aldehyde **106** were all formed as a mixture of isomers (*E*:*Z* ratio = ~3:1) that were not readily separated. The *E*:*Z* ratio of the isomers was measured using the area of integration of the methyl signals for each compound. Both the ester **104** and the alcohol **105** were new compounds and were fully characterized by spectroscopic methods as well as by elemental analysis.

The structure of the aldehyde **106** was confirmed by a variety of spectroscopic methods. Analysis of the ^{1}H NMR spectrum showed that the aldehyde proton was split by the vinylic proton *H*-2, affording two doublets at δ = 10.0 and 5.9 ppm (*J* = 8.0 Hz), respectively. The expected number of carbon signals for the aldehyde **106** was ten but

analysis of the ^{13}C NMR spectrum displayed twenty carbon signals, indicating a mixture of two isomers. In addition, the mass spectrum (CI) of the aldehyde **106** displayed the expected M + H signal at 165 amu's. Finally, elemental analysis was used to confirm both the elemental composition and the purity of this compound.

With the α,β-unsaturated aldehyde **106** in hand, the phenylboronic acid-mediated condensation reaction was performed. The *mono*-2*H*-chromene **98** was prepared, in moderate yield, upon reaction of the aldehyde **106** (1.3 equiv) with 3,5-dimethoxyphenol (**39**) (1 equiv), phenylboronic acid (1 equiv) and propionic acid (cat.) in benzene heated at reflux with the azeotropic removal of water (Scheme 4.3.2).

Scheme 4.3.2 Synthesis of the *mono*-2*H*-Chromene (98) from the Aldehyde (106) and 3,5-Dimethoxyphenol (39)



106 **39** **98**

Reagents and conditions: (a) Aldehyde **106** (1.3 equiv), $PhB(OH)_2$ (1 equiv), propionic acid (cat.), PhH, reflux, 4 h, 41%.

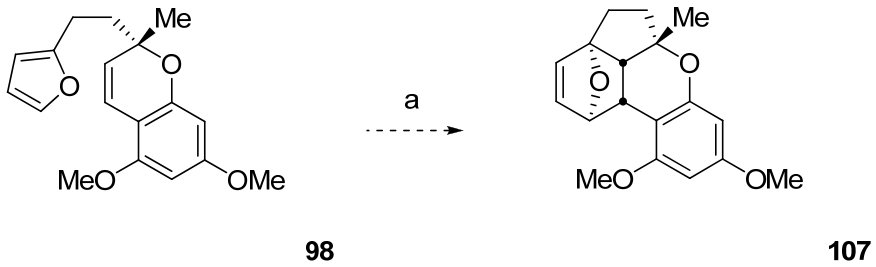
The *mono*-2*H*-chromene **98** was readily purified by flash chromatography and isolated as a colourless oil. Analysis of the ^{1}H NMR spectrum showed the presence of the pair of characteristic 2*H*-chromene double bond protons located at δ = 5.4 and 6.6 ppm (J = 10 Hz). Additionally, the ^{13}C NMR spectrum displayed the expected eighteen carbon signals for this compound. Moreover, the mass spectrum (CI) contained the expected M + H peak located at 301 amu's, which further confirmed the molecular

structure. Finally, elemental analysis of the 2*H*-chromene **98** confirmed both the elemental composition and the purity of the compound.

4.3.2 Intramolecular [2+4] Cycloaddition Reaction of the *mono*-2*H*-Chromene (98)

With the Diels-Alder precursor in hand, the intramolecular [2+4] cycloaddition reaction of this compound was explored. Using standard literature procedures, the 2*H*-chromene **98** was heated in toluene at different temperatures, in a sealed tube, to affect a [2+4] cycloaddition reaction (Scheme 4.3.3).[49]

Scheme 4.3.3 Attempted Synthesis of the Diels-Alder Cycloadduct (107) from the *mono*-2*H*-Chromene (98)



98 **107**

Reagents and conditions: (a) See below: Table 4.3.1.

Table 4.3.1 Reagents and Conditions Corresponding to Scheme 4.3.3

Entry	Reagents and Conditions	Result
1	PhMe, 135 °C, 20 h	No reaction
2	PhMe, 220 °C, 43 h	No reaction

Unfortunately, no reaction products were isolated, even at elevated temperatures.

4.4 Conclusions

The *mono*-2*H*-chromene **97**, derived from citral (**31**) and 3,5-dimethoxy phenol (**39**), was prepared to evaluate an intramolecular [2+2] cycloaddition reaction. This

chromene was shown to readily cyclize under two sets of photochemical conditions to afford the cyclobutane **99**. Thus, it has been established that an intramolecular [2+2] cycloaddition is possible on a 2*H*-chromene carbon-carbon double bond. Therefore, the possibility exists for this type of cycloaddition reaction on a C_3-symmetric *tris*-2*H*-chromene. In addition, as a means to study the intramolecular [2+4] cycloaddition reaction, the *mono*-2*H*-chromene **98** was required. In order to prepare the desired chromene **98**, the α,β-unsaturated aldehyde **106** first needed to be prepared. Using readily available starting materials the aldehyde **106** was prepared in five steps in an overall yield of 18%. Having prepared the requisite aldehyde, the *mono*-2*H*-chromene **98** was readily prepared, however, it was found that this particular system does not undergo the required cycloaddition reaction. In order to affect this type of intramolecular process it will be necessary to activate the 2*H*-chromene carbon-carbon double bond or a more reactive diene may be required.

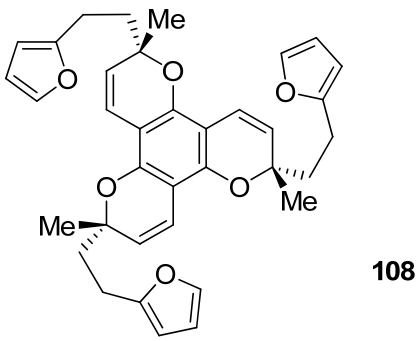
5 RESULTS AND DISCUSSION

Intramolecular Cycloaddition Reactions of tris-*2*H-*Chromenes*

5.1 Introduction

In this chapter, the synthesis of two functionalized C_3-symmetric *tris*-2*H*-chromenes is described in which an alkene and a diene moiety are tethered to the chromene core for subsequent triple intramolecular [2+2] and [2+4] cycloaddition reactions. If successful, these reactions would generate large, polycyclic ring systems that contain up to thirteen fused rings and fifteen stereogenic centres.

It was envisioned that the known *tris*-2*H*-chromene **32**, prepared from citral (**31**) and phloroglucinol (**27**), could undergo an intramolecular [2+2] cycloaddition reaction. Intramolecular [2+2] cycloaddition reactions performed on the *mono*-2*H*-chromene **97** were previously demonstrated (See: Section 4.2.2). Therefore, application of this methodology towards the C_3-symmetric *tris*-2*H*-chromene was planned. Additionally, a new C_3-symmetric *tris*-2*H*-chromene **108**, prepared from the α,β-unsaturated aldehyde **106**, was made to investigate a triple intramolecular [2+4] cycloaddition reaction (Figure 5.1.1).



108

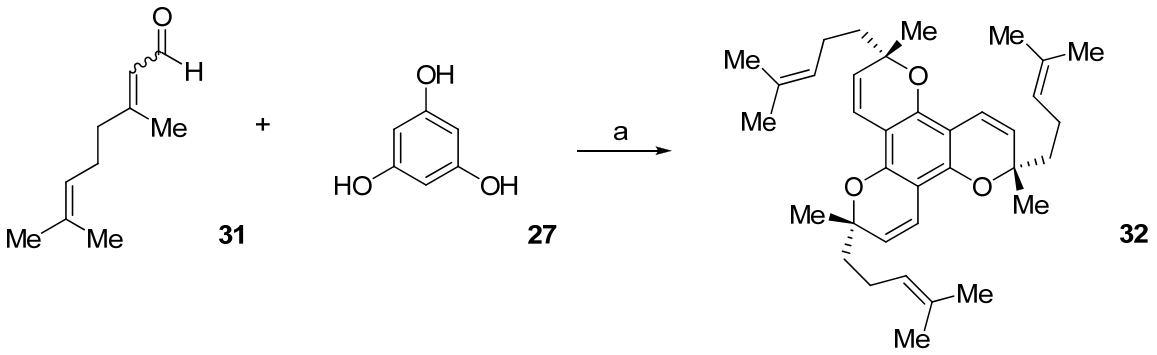
Figure 5.1.1 Molecular structure of the *tris*-2*H*-chromene (108).

5.2 Triple Intramolecular [2+2] Cycloaddition Reaction of the *tris*-2*H*-Chromene (32)

5.2.1 Synthesis of the *tris*-2*H*-Chromene (32)

The known *tris*-2*H*-chromene **32** was prepared according to the procedure previously described by Pettigrew *et al*.[19] Thus, commercially available citral (**31**, *E*:*Z* = ~2:1) (4 equiv) and phloroglucinol (**27**) (1 equiv) were mixed with phenylboronic acid (3 equiv) and propionic acid (cat.) in benzene and heated at reflux to afford the known *tris*-2*H*-chromene **32** in good yield (Scheme 5.2.1). Interestingly, only the symmetric diastereoisomer (all *cis*) of the *tris*-2*H*-chromene **32** was formed in this reaction. The spectroscopic data for this *tris*-2*H*-chromene **32** was identical to that previously reported.[19]

Scheme 5.2.1 Synthesis of the *tris*-2*H*-Chromene (32) from Citral (31) and Phloroglucinol (27)

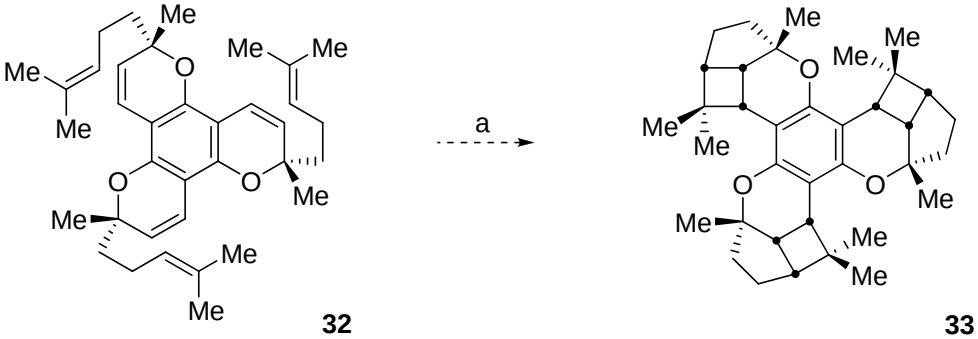


Reagents and conditions: (a) Citral (**31**, 4 equiv, *E*:*Z* = ~2:1), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 4 h, 57%.

5.2.2 Attempted Triple Intramolecular [2+2] Cycloaddition Reaction of the *tris*-2*H*-Chromene (32)

Earlier, it was shown that the intramolecular [2+2] cycloaddition readily occurred on a functionalized *mono*-2*H*-chromene (See: Section 4.2.2). The cycloaddition reaction proceeded in benzene with benzophenone as the sensitizer or in acetone. Using these conditions, the triple intramolecular [2+2] cycloaddition reaction of the *tris*-2*H*-chromene **32** was attempted (Scheme 5.2.2).

Scheme 5.2.2 Attempted [2+2] Cycloaddition Reaction of *tris*-2*H*-Chromene (32)



Reagents and conditions: (a) See below: Table 5.2.1.

Table 5.2.1 Reagents and Conditions Corresponding to Scheme 5.2.2

Entry	Reagents and Conditions	Result
1	$Ph_2(CO)$, PhH, 22 h	Decomposition
2	Acetone, 24 h	Complex Mixture

For all reactions, the irradiation source used was a Hanovia 450 Watt medium pressure mercury vapour lamp. All reaction mixtures were purged of oxygen by bubbling dry nitrogen gas through them for ~25 minutes. Unfortunately under these conditions, decomposition or a complex mixture of products formed from which it was not possible to isolate cycloadducts (entries 1 & 2).

However, based on results obtained from the *mono*-2*H*-chromene intramolecular [2+2] cycloaddition, the ^{1}H NMR spectrum of the crude reaction mixture revealed evidence of cyclobutane formation. The highest upfield signal is a singlet that corresponded to a methyl group at δ = ~0.7 ppm as well as a series of multiplets which were located at δ = ~2.25, ~2.45 and ~3.0 ppm. These multiplets are in very good agreement with the multiplets observed for the cyclobutane **99**, which corresponded to the protons around the cyclobutane ring.[20]

Purification of this compound proved exceedingly difficult. Repeated flash chromatography did not separate the starting material from the multiple products formed during the course of the reaction. Moreover, the ^{1}H NMR spectrum of the crude reaction mixture indicated that the chromene protons were still present and that the starting material had not fully reacted in the latter reaction (entry 2). It is also possible that the substrate could have undergone a number of intermolecular [2+2] cycloaddition reactions to form oligomers. Having been unsuccessful in attempts to prepare C_3-symmetirc [2+2]

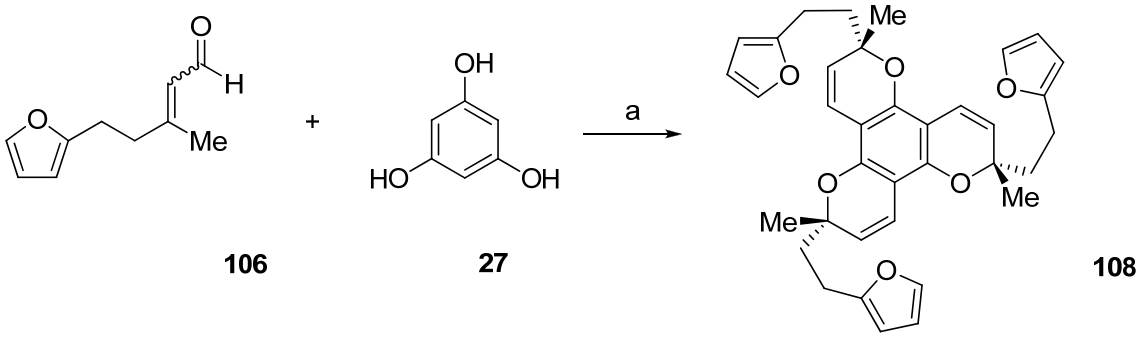
cycloadducts, efforts were focussed on performing a triple intramolecular [2+4] cycloaddition reaction.

5.3 Triple Intramolecular [2+4] Cycloaddition Reaction of the *tris*-2*H*-Chromene (108)

The study of intramolecular [2+4] cycloaddition reactions is of particular interest because of the potential to prepare compounds with multiple fused rings and stereogenic centres. As stated earlier, the functionalized *tris*-2*H*-chromene **108** would serve as an excellent substrate to evaluate triple intramolecular [2+4] cycloaddition reactions. This novel chromene could be prepared upon reaction of the α,β-unsaturated aldehyde **106** and phloroglucinol (**27**).

The synthesis of the required α,β-unsaturated aldehyde **106** was described earlier (See: Section 4.3.1). As such, the phenylboronic acid-mediated condensation reaction was performed on reacting the α,β-unsaturated aldehyde **106** (4 equiv) with phloroglucinol (**27**) (1 equiv), phenylboronic acid (3 equiv) and propionic acid (cat.) in benzene heated at reflux to afford the *tris*-2*H*-chromene **108** in good yield (Scheme 5.3.1). The resultant product was readily purified by flash chromatography to afford a light yellow oil. Of note, only the C_3-symmetric (all *cis*) diastereoisomer of the *tris*-2*H*-chromene **108** was isolated from this reaction and there is no evidence for the unsymmetrical isomer in the ^{1}H NMR spectrum of the crude reaction mixture.

Scheme 5.3.1 Synthesis of the *tris*-2*H*-Chromene (108) from the α,β-Unsaturated Aldehyde (106) and Phloroglucinol (27)



106 **27** **108**

Reagents and conditions: (a) Aldehyde **106** (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 4 h, 63 %.

The inherent simplicity of both the ^1H and ^{13}C NMR spectra confirmed that the 2*H*-chromene **108** was formed as a single, C_3-symmetric product. The ^1H NMR spectrum contained a sharp singlet at $\delta = 1.4$ ppm, indicating that only one type of methyl group is present. Moreover, the presence of a single pair of doublets, located at $\delta = 5.4$ and 6.6 ppm ($J = 10.0$ Hz) which corresponds to the protons of the three equivalent 2*H*-chromene double bonds, further confirms the C3-symmetry of this product (Figure 5.3.1).

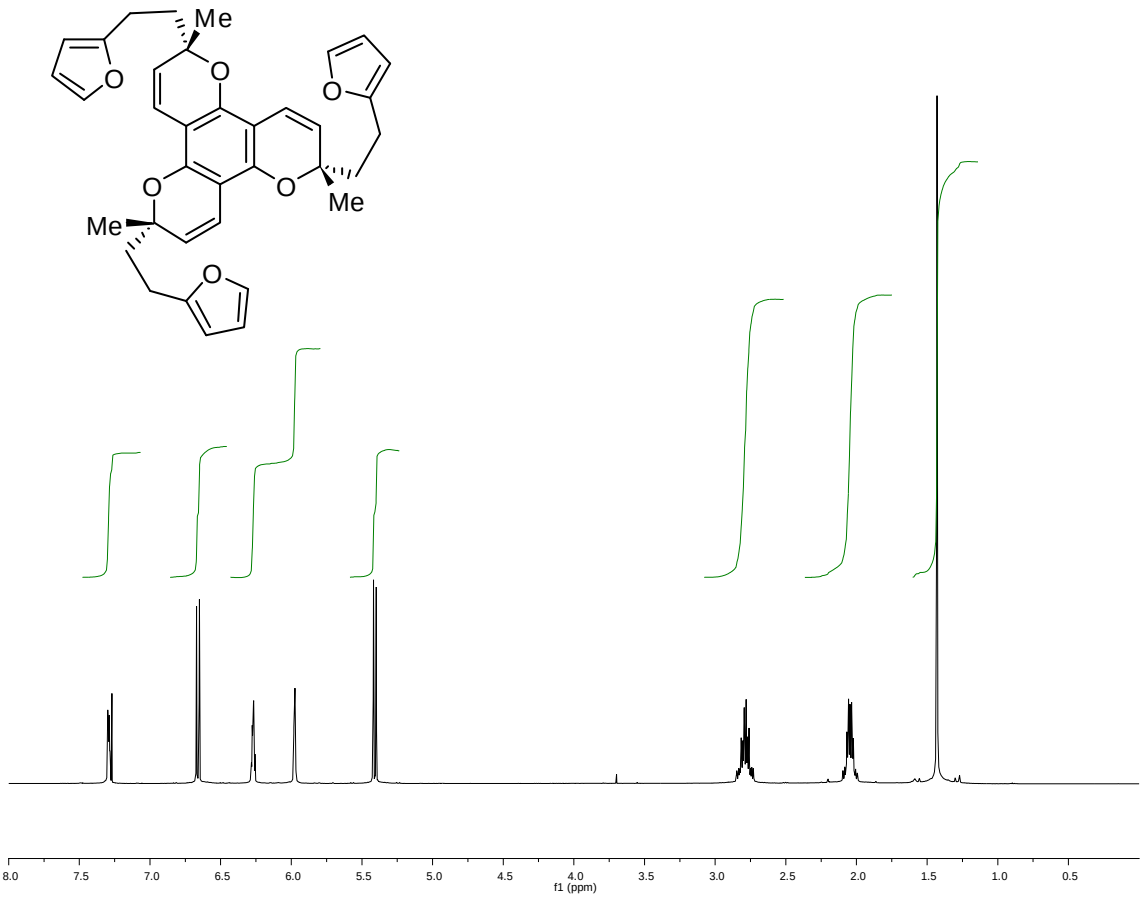


Figure 5.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of the *tris*-2*H*-chromene (108).

The ^{13}C NMR spectrum clearly indicated the C_3-symmetric nature of this compound (Figure 5.3.2). This compound has a molecular formula of $C_{36}H_{36}O_6$ and only twelve signals are observed in the ^{13}C NMR spectrum.

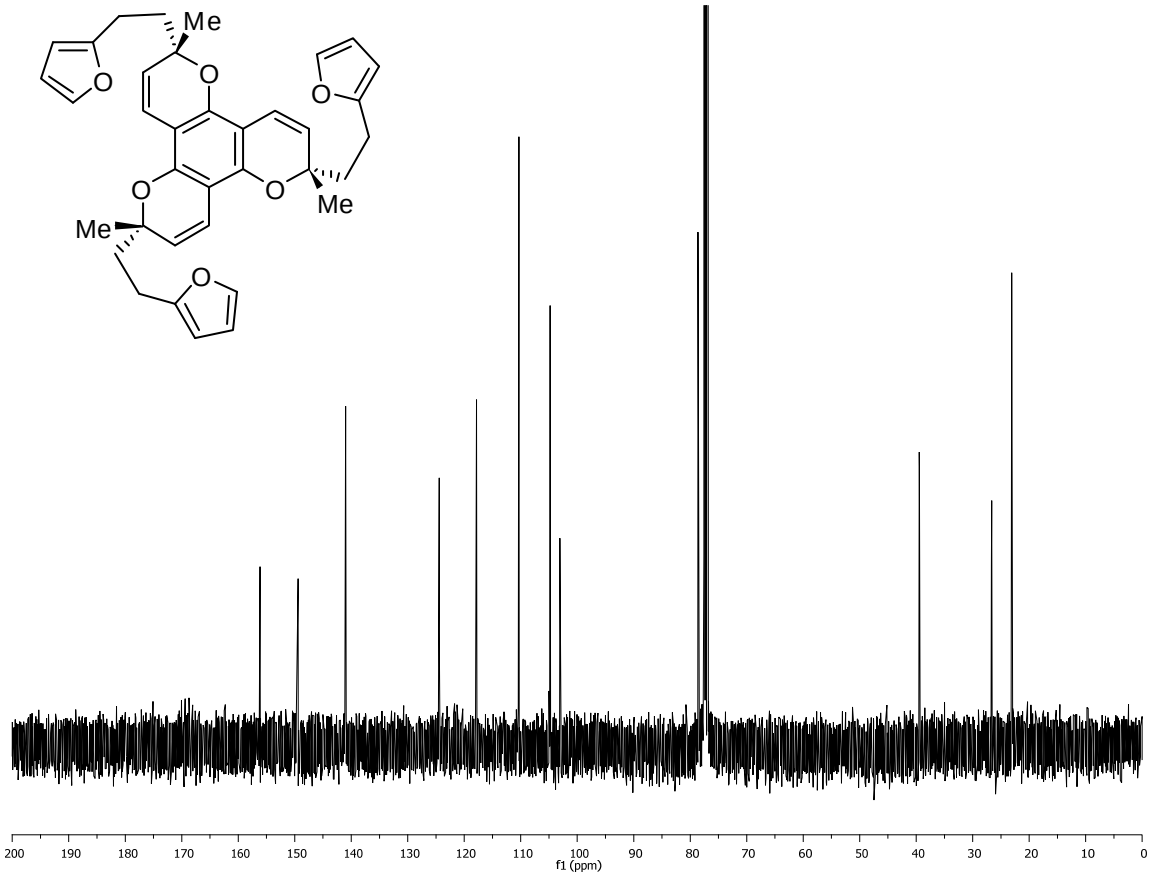
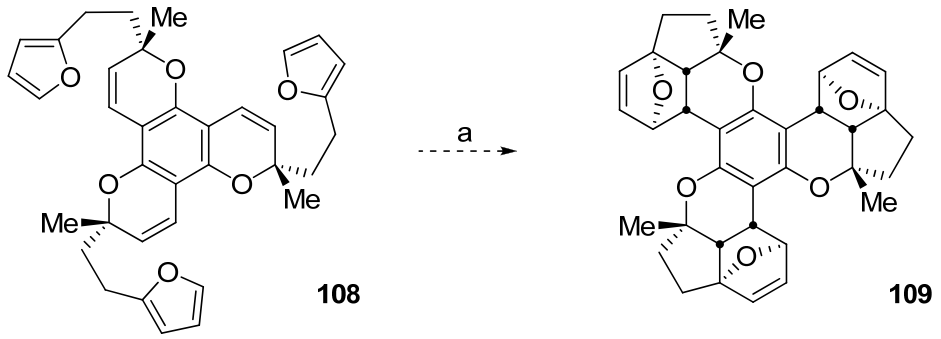


Figure 5.3.2 ^{13}C NMR (101 MHz, $CDCl_3$) of the *tris*-2*H*-chromene (108).

Furthermore, the synthesis of the *tris*-2*H*-chromene **108** was confirmed by the mass spectrum (CI) displaying the expected M + H peak located at 543 amu's. Finally, elemental analysis was used to confirm both the purity and elemental composition of this compound.

With the requisite *tris*-2*H*-chromene **108** in hand, the intramolecular Diels-Alder cycloaddition reaction was then attempted (Scheme 5.3.2).

Scheme 5.3.2 Attempted Diels-Alder Cycloaddition Reaction of the *tris*-2*H*-Chromene (108)



Reagents and conditions: (a) See below: Table 5.3.1.

Table 5.3.1 Reagents and Conditions Corresponding to Scheme 5.3.2

Entry	Reagents and Conditions	Result
1	PhMe, 210 °C, 22 h	Decomposition
2	Me_2AlCl (1.5 equiv), -78 °C, CH_2Cl_2, 23 h	No reaction
3	$MeAlCl_2$ (0.3 equiv), -78 °C, CH_2Cl_2, 22 h	No reaction
4	$MeAlCl_2$ (3 equiv), -78 °C, CH_2Cl_2, 24 h	No reaction

Initially, the *tris*-2*H*-chromene **108** was subjected to standard furan Diels-Alder cycloaddition reaction conditions which involved heating in a sealed tube at 210 °C for 22 hours (entry 1).[49] As this thermal process caused extensive decomposition of the starting material, two Lewis acids of varying reactivities were employed to promote these cycloaddition reactions (entries 2-4).[50] Unfortunately, no reaction products were observed.

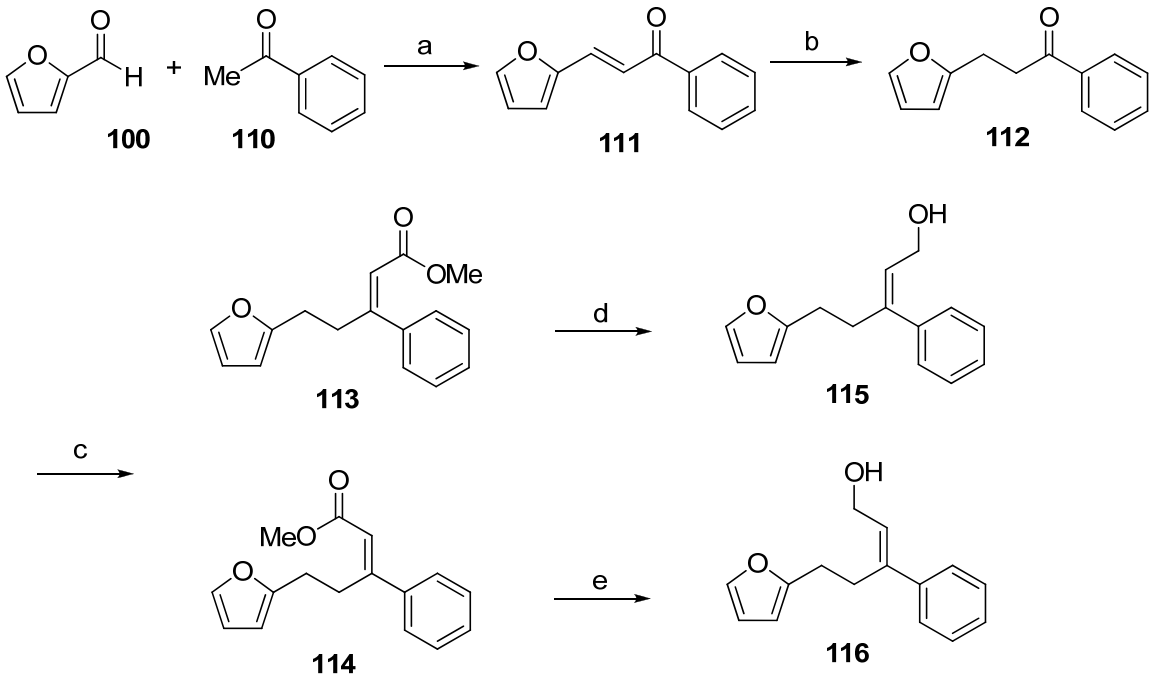
5.3.1 Synthesis of an Additional Functionalized Aldehyde for Subsequent [2+4] Cycloaddition Reactions

Having successfully prepared the *tris*-2*H*-chromene **108**, application of the methodology was extended to include an alternate substituent at the *C*-3 position of the

α,β-unsaturated aldehyde **106**. The phenyl group was chosen as this is a readily accessible substrate that can be easily prepared upon an aldol condensation of furfural (**100**) and acetophenone (**110**).

Initially, the aldol reaction with furfural (**100**) was attempted with both acetophenone (**110**) and *t*-butylacetone, however, only acetophenone (**110**) would react to afford the corresponding known α,β-unsaturated ketone **111**.[51] The α,β-unsaturated ketone **111** was then hydrogenated using standard hydrogenation procedures to afford the known ketone **112** in good yield.[52] Following the same methodology used earlier (See: Section 5.2.1), the α,β-unsaturated esters **113** and **114** were prepared in excellent yield over two steps from the α,β-unsaturated ketone **112**. Interestingly, the R_f value of the *E* isomer **113** matches the R_f value of the starting ketone **112** and so the reaction was stirred for twenty-four hours to ensure the reaction was complete. The esters **113** and **114** were then reduced with lithium aluminium hydride to afford the corresponding allylic alcohols **115** and **116** (Scheme 5.3.3).

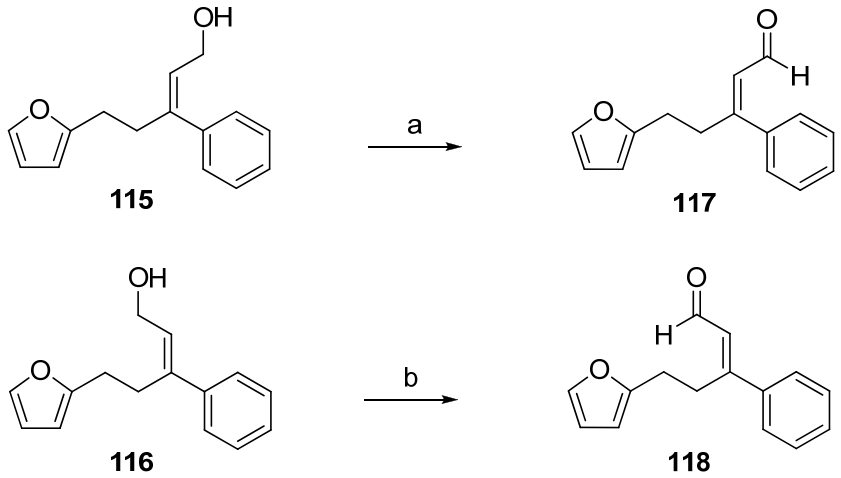
Scheme 5.3.3 Synthesis of the *Z*- and *E*-Alcohols (115) and (116) from Furfural (100) and Acetophenone (110)



Reagents and conditions: (a) NaOH, H_2O, 150 min, 63 %; (b) H_2, Pd/C, EtOAc, room temperature, 4.5 h, 72 %; (c) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then ketone **112**, reflux, 24 h, 43 % (**113**), 50 % (**114**); (d) $LiAlH_4$, Et_2O, 0°C to room temperature, 40 min, 74 %; (e) $LiAlH_4$, Et_2O, 0°C to room temperature, 30 min, 74 %.

The alcohols **115** and **116** were then oxidized with either Dess-Martin periodinane or with manganese dioxide to afford to corresponding α,β-unsaturated aldehydes **117** and **118** (Scheme 5.3.4).

Scheme 5.3.4 Synthesis of the *Z*-Aldehyde (117) and the *E*-Aldehyde (118) from the *Z*-Alcohol (115) and the *E*-Alcohol (116)



Reagents and conditions: (a) See below: Table 5.3.2; (b) see below: Table 5.3.3.

Table 5.3.2 Reagents and Conditions Corresponding to Scheme 5.3.4

Entry	Reagents and Conditions	Yield (%)
1	DMP, CH_2Cl_2, room temperature, 3 h	12
2	MnO_2, CH_2Cl_2, 16 h	79

Initially, a solution of the *Z*-alcohol **115** in dichloromethane was added to a suspension of Dess-Martin periodinane in dichloromethane at room temperature which afforded the corresponding aldehyde **117** in low yield (entry 1). Due to the isolated poor yield, manganese dioxide was used as the oxidant and this afforded the corresponding α,β-unsaturated aldehyde **117** in good yield (entry 2). Similar results were obtained during the oxidation of the *E*-alcohol **116** (Table 5.3.3).

Table 5.3.3 Reagents and Conditions Corresponding to Scheme 5.3.4

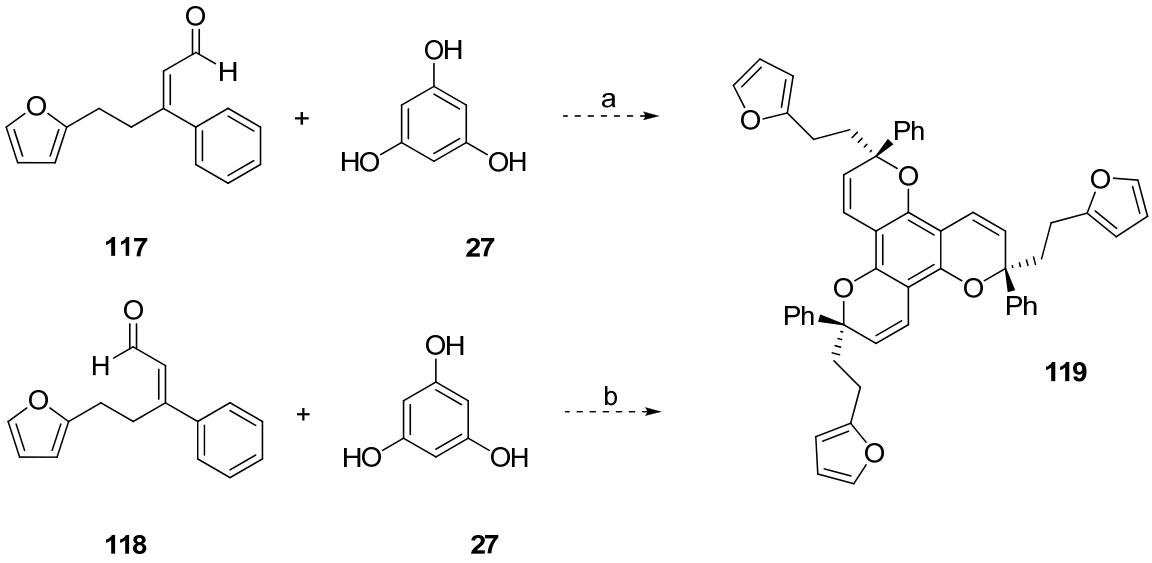
Entry	Reagents and Conditions	Yield (%)
1	DMP, CH_2Cl_2, room temperature, 3 h	38
2	MnO_2, CH_2Cl_2, 17 h	79

The structures of the aldehydes **117** and **118** were confirmed by analysis of the ^{1}H NMR spectra. Notably, the aldehyde proton was split by the vinylic proton *H*-2 leading to two doublets at δ = 10 and 5.4 ppm (J = 7 Hz). Moreover, the ^{13}C NMR spectrum of each aldehyde displayed the expected twelve carbon signals. Additionally, IR spectroscopy confirmed the presence of the aldehyde functional group as strong absorption at ~1675 cm^{-1} was noted. Finally, both the elemental composition and the purity of these new aldehydes were confirmed by elemental analysis.

The stereochemistry of the double bond isomers was confirmed by 1D-nOe experiments. The α,β-unsaturated aldehyde *Z*-isomer **117** was identified by nOe coupling between the vinylic proton, *H*-2, and both of the CH_2 protons. Additionally, the *E*-isomer **118** was identified by the nOe contact between the aldehyde proton and the CH_2 protons.

With the α,β-unsaturated aldehydes in hand, the phenylboronic acid-mediated condensation reaction was performed. The reaction was carried out using either aldehyde **117** or aldehyde **118** (4 equiv), phloroglucinol (**27**) (1 equiv), phenylboronic acid (3 equiv) and propionic acid (cat.) in benzene at reflux with azeotropic removal of water (Scheme 5.3.5).

Scheme 5.3.5 Attempted Synthesis of the *tris*-2*H*-Chromene (119) from the *Z*-α,β-Unsaturated Aldehyde (117) and the *E*-α,β-Unsaturated Aldehyde (118) and Phloroglucinol (27)



Reagents and conditions: (a) Aldehyde **117** (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 3 h; (b) Aldehyde **118** (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 3 h.

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that the 2*H*-chromene double bonds had formed based on the presence of multiplets located at δ = 5.3 and 6.5 ppm. Moreover, TLC analysis indicated the formation of a new compound. However, repeated attempts at purification by flash chromatography to isolate a pure compound were unsuccessful.

5.4 Conclusions

Using standard methodology, an appropriate C_3-symmetric *tris*-2*H*-chromene **32** was prepared to investigate a triple intramolecular [2+2] cycloaddition reaction. Although promising observations were made on analysis of the ^{1}H NMR spectrum of the crude reaction mixture, purification of the resultant products were unsuccessful. Using the α,β-unsaturated aldehyde **106**, the *tris*-2*H*-chromene **108** was readily prepared using the phenyl boronic acid-mediated condensation reaction. This chromene was subjected to

a variety of conditions to induce an intramolecular [2+4] cycloaddition reaction, however, no cycloaddition products were observed. Finally, two α,β-unsaturated aldehydes **117** and **118** were prepared to further evaluate the applicability of the phenylboronic acid-mediated condensation reaction and afford an additional *tris*-2*H*-chromene. Subjecting each of these aldehydes to the phenylboronic acid-mediated condensation reaction afforded a complex mixture containing the expected 2*H*-chromene **119**, but this mixture could not be purified.

6 RESULTS AND DISCUSSION

*Studies Towards the Synthesis of an Activated 2*H*-Chromene Carbon-Carbon Double Bond*

6.1 Introduction

In this chapter, the synthesis of precursors to prepare functionalized C_3-symmetric *tris*-2*H*-chromenes as activated substrates for [2+4] cycloaddition reactions is described. It was envisioned that the installation of an electron withdrawing group at *C*-3 of a 2*H*-chromene would increase the reactivity of the 2*H*-chromene carbon-carbon double bond (Figure 6.1.1).

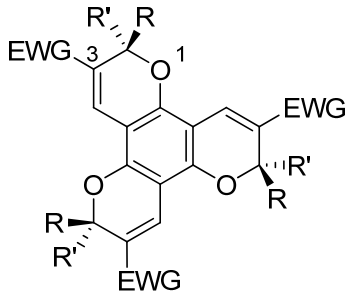
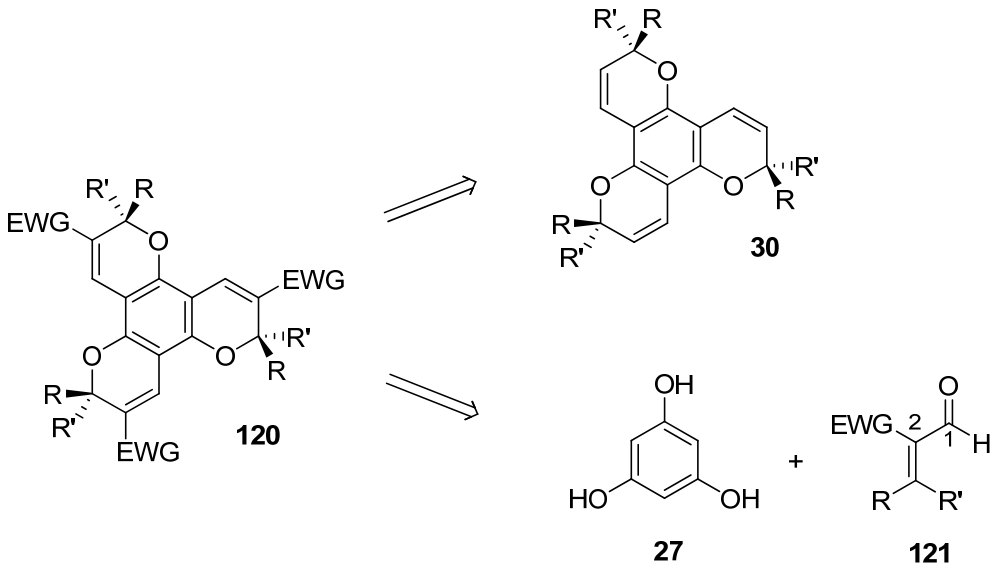


Figure 6.1.1 A *tris*-2*H*-chromene activated with an electron-withdrawing group.

Two routes were pursued to activate the chromene double bond. The first route involved the attempted direct installation of an electron withdrawing group onto *C*-3 of the 2*H*-chromene **30**. The second route involved the synthesis of a functionalized aldehyde **121** which could potentially be prepared by two synthetic routes. The first method would involve the reduction of the Meldrum's acid analogue **126** to afford an α,β-unsaturated dialdehyde. The second method would involve chemistry previously used (See: Section 4.3.1) to access various α,β-unsaturated dialdehydes. These aldehydes would contain an additional electron withdrawing group at the 2-position.

Thus, when the phenylboronic acid-mediated condensation reaction is performed the electron withdrawing group will be in conjugation with the 2*H*-chromene double bond (Scheme 6.1.1). Other electron withdrawing groups, such as cyano or nitro groups, could also be installed at this position.

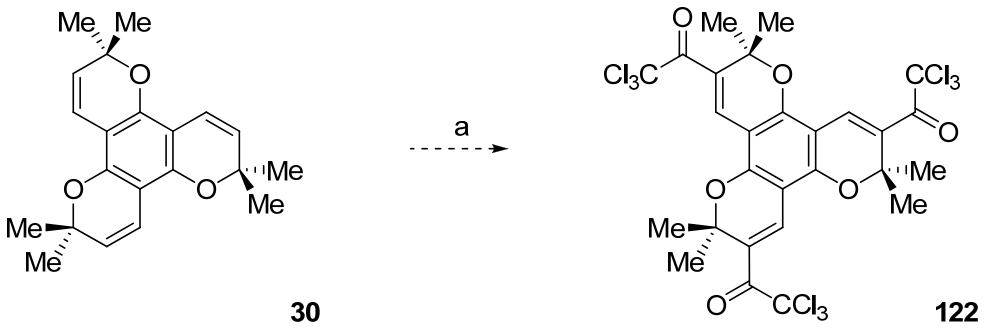
Scheme 6.1.1 Retrosynthetic Analysis of an Activated *tris*-2*H*-Chromene (120)



6.2 Attempted Activation of the Carbon-Carbon Double Bond of the *tris*-2*H*-Chromene (30)

Initial attempts towards activating the 2*H*-chromene carbon-carbon double bond involved the installation of a trichloroketone moiety at the 3-position of the *tris*-2*H*-chromene **30** using a synthetic method described by Hojo *et al.*[53] Thus, the chromene **30** was reacted with trichloroacetyl chloride and pyridine in dichloromethane at -20 °C (Scheme 6.2.1). However, no reaction products were observed on allowing this reaction to warm to room temperature.

Scheme 6.2.1 Attempted Synthesis of the Activated *tris*-2*H*-Chromene (122) *via* Trichloroacetyl chloride and the *tris*-2*H*-Chromene (30)

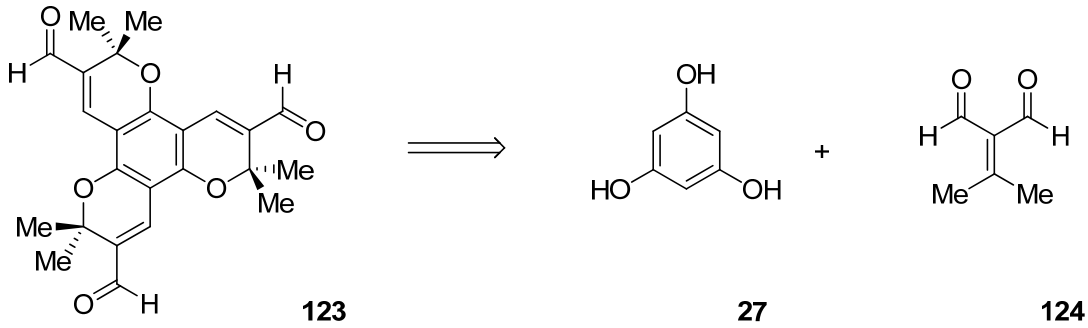


Reagents and conditions: (a) Cl_3CCOCl (4.5 equiv), py (4.5 equiv), CH_2Cl_2, -20 °C to room temperature, 20 h.

6.2.1 Attempted Synthesis of Functionalized Aldehydes

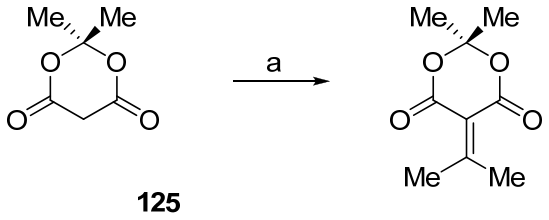
As it was found that the 2*H*-chromene carbon-carbon double bond was unreactive towards electrophilic substitution with trichloroacetyl chloride, the synthesis of the dialdehyde **124** was pursued in order to prepare the activated 2*H*-chromene **123** (Scheme 6.2.2).

Scheme 6.2.2 Retrosynthetic Analysis of the Activated *tris*-2*H*-Chromene (123) to the Dialdehyde (124)



Initially, a direct approach was taken to prepare the activated dialdehyde precursor. A Knoevenagel condensation between Meldrum's Acid (**125**) and acetone (**101**) with ammonium acetate (0.05 equiv), acetic acid (0.25 equiv) and 4Å molecular sieves in toluene afforded the known compound **126** in moderate yield (Scheme 6.2.3).[54]

Scheme 6.2.3 Synthesis of 2,2-Dimethyl-5-(propan-2'-ylidene)-1,3-dioxane-4,6-dione (126) from Meldrum's Acid (125)



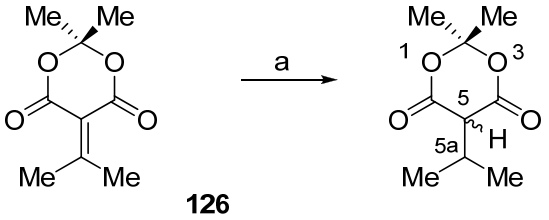
125 **126**

Reagents and conditions: (a) Acetone (1.5 equiv), NH_4OAc (0.05 equiv), AcOH (0.25 equiv), 4Å molecular sieves, PhMe, room temperature, 48 h, 34%.

Analysis of the ^1H NMR spectrum of compound **126** contained two sharp singlets, indicating that two types of methyl groups were present. Additionally, the compound was a colourless solid that had a melting point of 73-75 °C, which is in good agreement with the literature value.[54]

This compound **126** could then, in theory, be reduced by a hydride source to afford the dialdehyde **124**. Thus, the compound **126** was treated with diisobutylaluminium hydride (2.2 equiv) in dichloromethane at -78 °C which afforded the known compound **127** (Scheme 6.2.4). There, the hydride attacked the 4 position rather than the expected 2 position of the α,β-unsaturated carbonyl compound **126**.

Scheme 6.2.4 Synthesis of 5-Isopropyl-2,2-dimethyl-1,3-dioxane-4,6-dione (127) from 2,2-Dimethyl-5-(propan-2'-ylidene)-1,3-dioxane-4,6-dione (126)



126 **127**

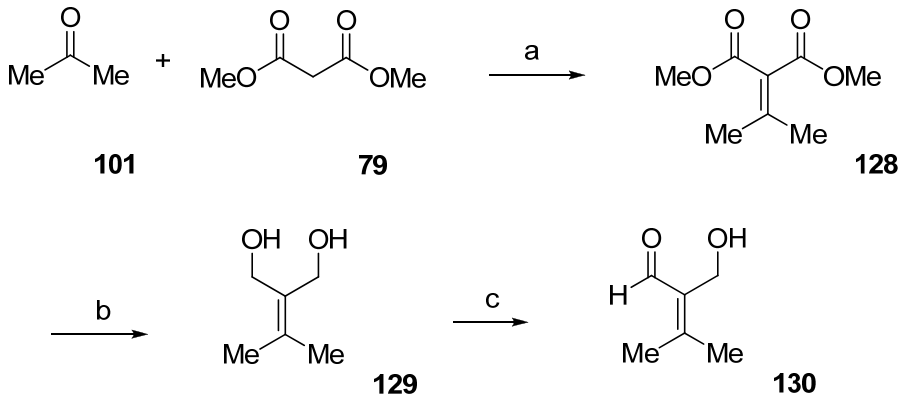
Reagents and conditions: (a) DIBAL-H (2.2 equiv), CH_2Cl_2, -78 °C, 3 h, 37%.

The 1,4 addition of the hydride was confirmed by ^1H NMR spectroscopy. The ^1H NMR spectrum of compound **127** contained a doublet at δ = 1.1 ppm (J = 7.2 Hz) and a

doublet of septets, corresponding to *H*-5a, located at δ = 2.7 ppm (J = 7.0, 3.0 Hz). In addition, a doublet corresponding to *H*-5 was located at δ = 3.6 ppm (J = 3.2 Hz). Moreover, the melting point of the product was 99-102 °C, which is in close agreement with the reported literature value of 102-104 °C.[55]

Unfortunately, the initial route to prepare the dialdehyde **124** was unsuccessful. Therefore, a different method was explored in which the dialdehyde could be prepared in a similar fashion as used to prepare the α,β-unsaturated aldehydes in the previous chapter (See: Section 4.3.1). Using acetone (**101**) (1 equiv) and dimethyl malonate (**79**) (1 equiv) under standard Knoevenagel conditions,[56] the diester **128** was prepared in good yield. This diester **128** was added to a suspension of lithium aluminium hydride in benzene and heated at reflux over 3 hours to afford the desired diol **129** in moderate yield. This diol was then treated with manganese dioxide in dichloromethane to afford the *mono*-aldehyde **130** in good yield (Scheme 6.2.5). Overall, the aldehyde **130** was prepared in 19% yield over three steps.

Scheme 6.2.5 Synthesis of 2-(Hydroxymethyl)-3-methylbut-2-enal (130) from Dimethyl Malonate (79) and Acetone (101)

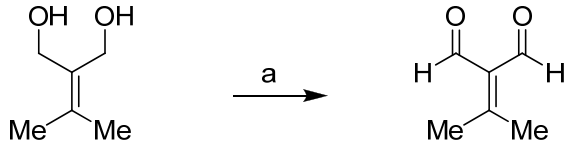


Reagents and conditions: (a) $TiCl_4$ (2 equiv), THF, 30 min, py (4 equiv), THF, room temperature, 16 h, 77 %; (b) $LiAlH_4$, PhH, reflux, 195 min, 38 %; (c) MnO_2, CH_2Cl_2, room temperature, 3.5 h, 64%.

Interestingly, manganese dioxide only afforded oxidization of one of the alcohols. The reaction was performed using 15 mass equivalents of manganese dioxide as well as 20 mass equivalents, however, only the *mono*-aldehyde **130** was formed. The *mono*-aldehyde **130** has a simple ^{1}H NMR spectrum with a singlet located at δ = 10.1 ppm, corresponding to the aldehyde proton and a 2H-singlet, located at δ = 4.4 ppm, which corresponded to the two methylene protons. Moreover, the ^{13}C NMR spectrum displayed the expected six signals for this compound, which further confirmed the structure of the *mono*-aldehyde **130**. Furthermore, the elemental composition was confirmed by high-resolution mass spectrometry. The calculated mass of the compound is 115.0759 amu's and a mass of 115.0762 amu's was found.

Since manganese dioxide was unable to oxidize the diol **129** to the corresponding dialdehyde a more powerful oxidant was needed. For this reason, the Swern oxidation reaction was chosen. Using standard Swern oxidation conditions,[57] the diol **129** was successfully converted to the dialdehyde **124** (Scheme 6.2.6).

Scheme 6.2.6 Synthesis of the Dialdehyde (124) from the Diol (129)



129 **124**

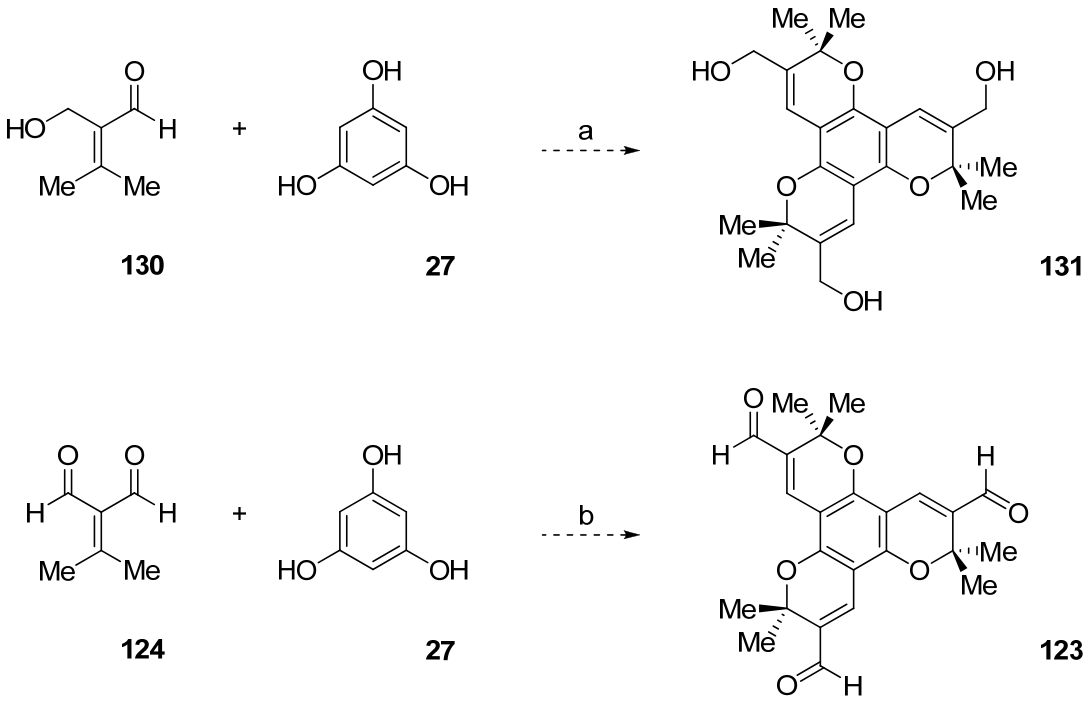
Reagents and conditions: (a) $(COCl)_2$ (3 equiv), DMSO (8 equiv) then Et_3N (10 equiv), CH_2Cl_2, -78 °C to room temperature, 1 h.

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture displayed two peaks located at δ = ~10 and ~2 ppm, which indicated the presence of the aldehyde protons as well as the methyl protons. Moreover, no methylene protons were observed in

the ^{1}H NMR spectra, indicating that the reaction had gone to completion. However, attempted purification of this compound was unsuccessful as the compound readily decomposed upon flash chromatography. Moreover, the compound is highly unstable and readily decomposed within a few hours of preparation.

Having prepared a *mono*-aldehyde **130** and the dialdehyde **124**, the phenyl boronic acid-mediated condensation reaction was then employed. The appropriate aldehyde (4 equiv) was reacted with phloroglucinol (1 equiv), phenyl boronic acid (3 equiv) and propionic acid (cat.) in benzene and heated at reflux (Scheme 6.2.7).

Scheme 6.2.7 Attempted Synthesis of the Functionalized 2*H*-Chromenes (131 and 123)



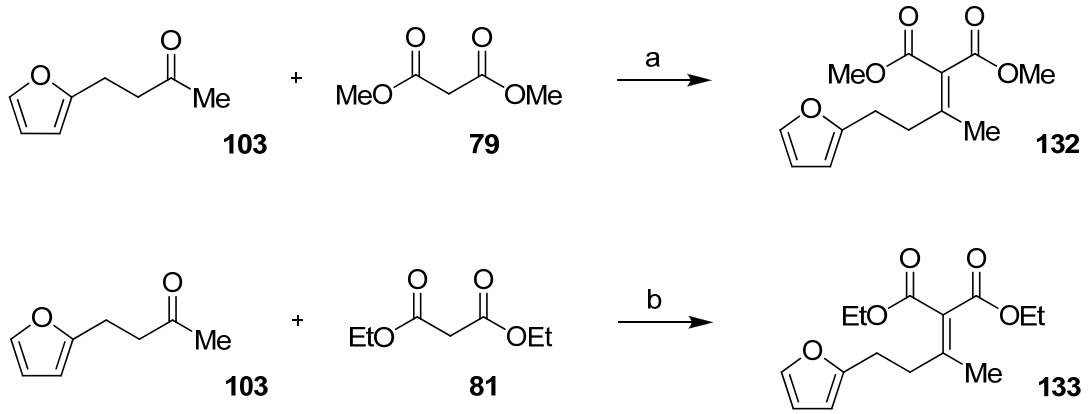
Reagents and conditions: (a) Aldehyde **130** (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 4 h; (b) Aldehyde **124** (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 3 h.

Unfortunately, the desired *tris*-2*H*-chromenes were not observed upon analysis of the ^{1}H NMR spectrum of the crude reaction mixtures. Despite these findings, the synthesis of the dialdehyde on the requisite furan system was evaluated.

6.3 Attempted Synthesis of the Dialdehyde (136)

A Knoevenagel condensation between the furan-ketone **103** and two diesters was performed. Both the dimethyl ester **132** and diethyl ester **133** were prepared in good yield from the corresponding dimethyl malonate (**79**) and diethyl malonate (**81**), respectively (Scheme 6.3.1).

Scheme 6.3.1 Synthesis of the α,β-Unsaturated Diesters (132 and 133) from 4-(Furan-2'-yl)butan-2-one (103)



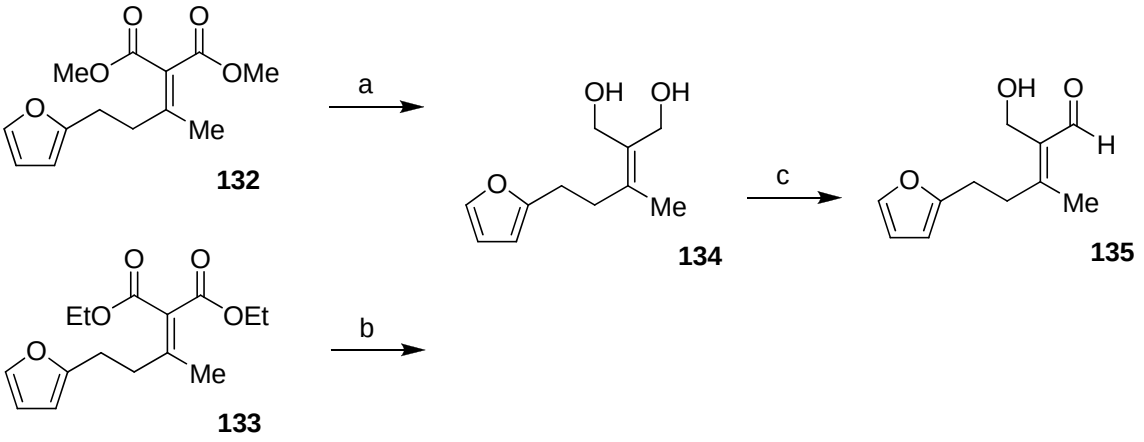
Reagents and conditions: (a) $TiCl_4$ (2 equiv), THF, 30 min, py (4 equiv), THF, room temperature, 16 h, 65 %; (b) $TiCl_4$ (2 equiv), THF, 30 min, py (4 equiv), THF, room temperature, 16 h, 62 %.

Both of the esters were readily purified by flash chromatography to afford analytically pure products. The dimethyl ester **132** has two sharp singlets at δ = 3.77 and 3.79 ppm in the ^{1}H NMR spectrum, indicating that the two methoxy groups are inequivalent. Also, the ^{13}C NMR spectrum displayed the expected thirteen peaks for this compound. As well, the mass spectrum (CI) displayed the expected M + H peak at 253 amu's.

The diethyl ester **133** was characterized by a variety of spectroscopic methods. The ^{1}H NMR spectrum displayed a multiplet at δ = 1.3 ppm which integrated for six hydrogens and another multiplet at δ = 4.2 ppm which integrated for four hydrogens that can be assigned to both methyl and methylene groups on the two inequivalent esters, respectively. In addition, the ^{13}C NMR spectrum displayed the expected fifteen peaks for this compound. Moreover, the mass spectrum (CI) displayed the expected M + H peak at 281 amu's. Finally, both the elemental composition and purity of the diesters **132** and **133** were validated by elemental analysis.

Both of the diesters **132** and **133** were then reduced using lithium aluminium hydride to afford the desired diol **134** in low yield. The novel diol **134** was then oxidized under various conditions to afford the *mono*-aldehyde **135** (Scheme 6.3.2).

Scheme 6.3.2 Synthesis of (2*E*)-5-(Furan-2'-yl)-2-hydroxymethyl-3-methylpent-2-enal (135) from the α,β-Unsaturated Diesters (132 or 133)



Reagents and conditions: (a) $LiAlH_4$, PhH, reflux, 18 h, 17 %; (b) $LiAlH_4$, PhH, reflux, 16 h, 12 %; (c) see below: Table 6.3.1.

Table 6.3.1 Reagents and Conditions Corresponding to Scheme 6.3.2

Entry	Reagents and Conditions	Yield (%)	*E*:*Z*
1	MnO_2, CH_2Cl_2, room temperature, 4 h	9	1:1
2	DMP, CH_2Cl_2, room temperature, 4.5 h	9	1:2

Initially, the diol **134** was oxidized by manganese dioxide in dichloromethane to afford the *mono*-aldehyde **135** as a mixture of *E*:*Z* isomers in low yield (entry 1). Changing the oxidant to Dess-Martin periodinane in dichloromethane afforded the *mono*-aldehyde **135** as a mixture of *E*:*Z* isomers also in low yield (entry 2). On flash chromatography of these two isomers, only the *E* isomer was isolated.

The *mono*-aldehyde **135** was characterized by analysis of the ^{1}H NMR spectrum. A singlet located at δ = 10 ppm was indicative of the aldehyde proton while a doublet at δ = 4.3 ppm (J = 6.6 Hz) corresponded to the methylene protons that are adjacent to the alcohol functional group. Additionally, the ^{13}C NMR spectrum displayed the expected eleven peaks for this compound. Moreover, high resolution mass spectrometry confirmed the elemental composition of this compound. The calculated mass of this compound is 195.1021 amu's and a mass of 195.1019 amu's was found. The geometry of the *E*-isomer was confirmed by 1D-nOe spectroscopy, specifically a nOe contact between the aldehyde proton and the methyl group was identified. Additionally, a nOe contact between the methylene protons was observed (Figure 6.3.1).

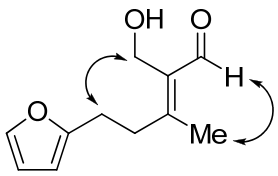
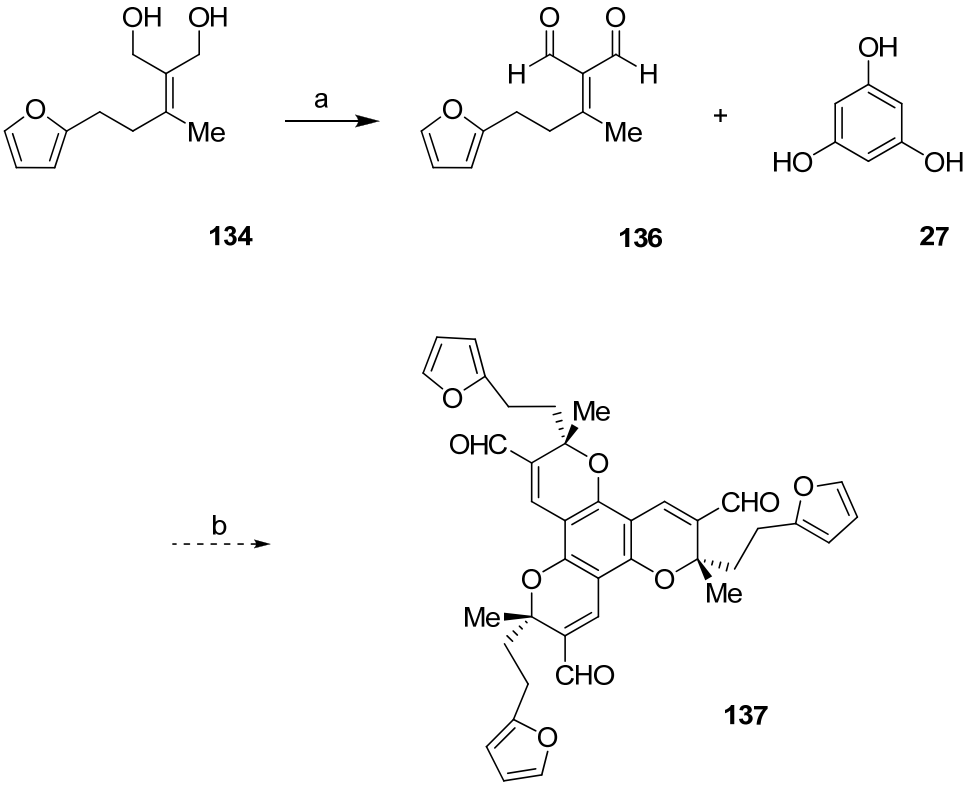


Figure 6.3.1 nOe Contacts of the *E*-isomer of the *mono*-aldehyde (135).

Having shown earlier that the dialdehyde can be prepared by Swern oxidation, this procedure was applied to the diol **134**, which afforded the dialdehyde **136**. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed two singlets at δ = ~10 ppm, which corresponded to the two inequivalent aldehyde protons of the dialdehyde **136**. Additionally, the ^{1}H NMR spectrum displayed the absence of the methylene protons of the starting material, indicating that the reaction had gone to completion.

Using the standard reaction conditions to prepare 2*H*-chromenes, the dialdehyde **136** (4 equiv) was mixed with phloroglucinol (**27**) (1 equiv), phenylboronic acid (3 equiv) and propionic acid (cat.) in benzene and heated at reflux with azeotropic removal of water (Scheme 6.3.3). Unfortunately, ^{1}H NMR analysis of the crude reaction mixture showed the complete decomposition of the starting materials.

Scheme 6.3.3 Attempted Synthesis of the Functionalized *tris*-2*H*-Chromene (137) from the Dialdehyde (136) and Phloroglucinol (27)



Reagents and conditions: (a) $(COCl)_2$ (3 equiv), DMSO (8 equiv) then Et_3N (10 equiv), CH_2Cl_2, -78 °C to room temperature, 1 h; (b) Aldehyde **136** (4 equiv), phloroglucinol (**27**) (1 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (cat.), PhH, reflux, 5 h.

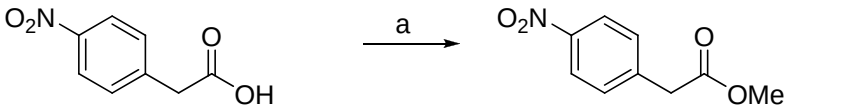
The dialdehyde **136** is, in principle, an appropriate precursor to increase the reactivity of the corresponding 2*H*-chromene double bond. However, the difficulty in preparation and instability of the compound makes this route problematic. Therefore, a different route was pursued to prepare an aldehyde with an alternative electron withdrawing group.

6.4 Attempted Synthesis of a Functionalized Aldehyde Towards the Preparation of an Activated 2*H*-Chromene Carbon-Carbon Double Bond

Using a Knoevenagel condensation, along with the furan-ketone **103**, an α,β-unsaturated ester with an electron withdrawing group could, in principle, be readily prepared.

p-Nitrophenylacetic acid (**138**) was reacted in methanol in the presence of sulphuric acid (cat.) and heated at 65 °C to afford methyl-(*p*-nitrophenyl)acetate (**139**) in excellent yield (Scheme 6.4.1).[58]

Scheme 6.4.1 Synthesis of Methyl-(*p*-nitrophenyl)acetate (139) from *p*-Nitrophenylacetic Acid (138)



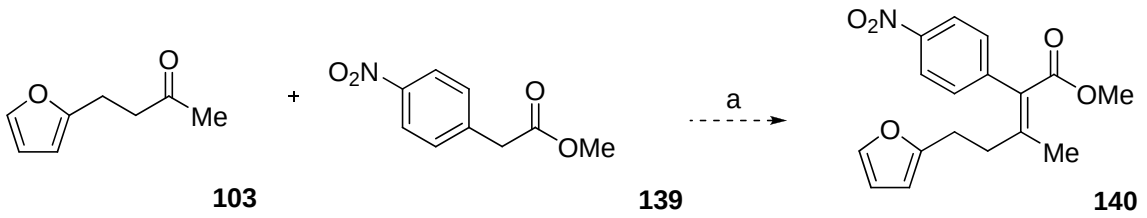
138 **139**

Reagents and conditions: (a) H_2SO_4 (cat.), MeOH, 65 °C, 2 h, 90%.

The methyl-(*p*-nitrophenyl)acetate (**139**) precipitated on cooling the reaction mixture to room temperature. After refrigeration at 0 °C overnight, fine pale yellow crystals were then collected. These crystals were found to have an identical melting point to the literature values.[59] Additionally, the ^{1}H and ^{13}C NMR spectra were identical to that reported for this known compound.[58]

The Knoevenagel condensation reaction of methyl-(*p*-nitrophenyl)acetate (**139**) with the furan-ketone **103** was performed under a variety of conditions (Scheme 6.4.2)

Scheme 6.4.2 Attempted Synthesis of (*E*)-Methyl 5-(furan-2'-yl)-3-methyl-2-(4-nitrophenyl)pent-2-enoate (140) from Methyl-(*p*-nitrophenyl)acetate (139) and 4-(Furan-2'-yl)butan-2-one (103)



103 **139** **140**

Reagents and conditions: (a) See below: Table 6.4.1.

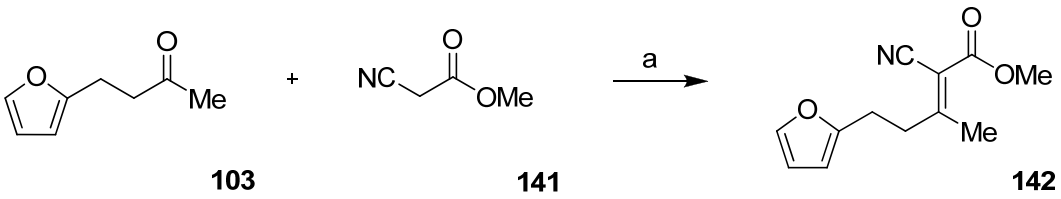
Table 6.4.1 Reagents and Conditions Corresponding to Scheme 6.4.2

Entry	Reagents and Conditions	Result
1	Ester **139** (1.5 equiv), NaOMe (2.5 equiv), MeOH, reflux, 5 days	No reaction
2	Ester **139** (2 equiv), NaH (2 equiv), PhH, 60 °C, 5 days	No reaction
3	Ester **139** (1.1 equiv), LDA (1.2 equiv), Et_2O, -78 °C to room temperature, 48 h	No reaction
4	NH_4OAc (0.05 equiv), AcOH (0.25 equiv), PhMe, 4Å molecular sieves, 24 h	No reaction
5	NH_4OAc (0.05 equiv), AcOH (0.25 equiv), PhH, reflux, 24 h	No reaction

In the first instance, the ketone **103** was added to a solution of the ester **139** (1 equiv), sodium methoxide in methanol and the mixture was heated at reflux for 5 days. (entry 1). The ester **139** was then reacted with sodium hydride in benzene at 60 °C followed by the addition of the ketone **103** (entry 2). The ester was then reacted with a solution of *N*,*N*-diisopropylamide in ether at -78 °C followed by the addition of the ketone **103** (1 equiv) (entry 3). In all of these cases, a deep purple colour was formed upon addition of the ester to the reaction mixtures. However, upon addition of the ketone **103** no reaction was observed by both TLC or by ^{1}H NMR analysis of the crude reaction mixture. Other standard Knoevenagel conditions were also attempted (entries 4 & 5).[49] Unfortunately, no desired reaction products were isolated from these reactions.

Repeated attempts to condense methyl-(*p*-nitrophenyl)acetate (**139**) with the ketone **103** were unsuccessful, therefore methyl-2-cyanoacetate (**141**) was selected as a subsequent reactant based on a literature precedent.[60] The α,β-unsaturated ester **142** was prepared on reaction of the ketone **103** and methyl-2-cyanoacetate (**141**) (1 equiv) with ammonium acetate (0.2 equiv) and acetic acid (0.8 equiv) on heating in benzene with azeotropic removal of water (Scheme 6.4.3).

Scheme 6.4.3 Synthesis of Methyl 2-cyano-5-(furan-2'-yl)-3-methylpent-2-enoate (142) from 4-(Furan-2'-yl)butan-2-one (103)



103 **141** **142**

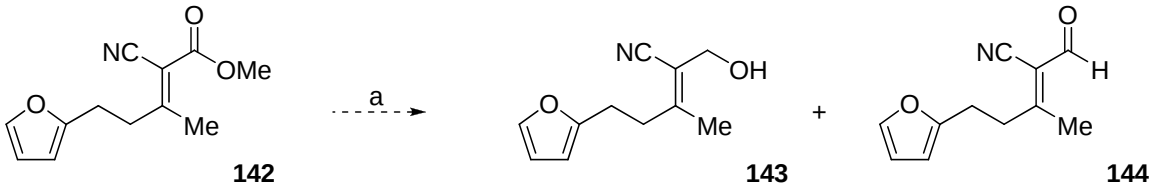
Reagents and conditions: (a) NH_4OAc (0.2 equiv), AcOH (0.8 equiv), PhH, reflux, 24 h, 11%.

This novel α,β-unsaturated ester was formed as a mixture of isomers (*E*:*Z* = ~1:1) that were not readily separated by flash chromatography. The ester **142** was fully characterized by a variety of spectroscopic methods. The ^{1}H NMR spectrum had two singlets at δ = 2.4 and 3.8 ppm, which corresponded to the methyl group and the methoxy group, respectively. In addition, the ^{13}C NMR spectrum displayed the expected twelve signals for this compound. Moreover, the mass spectrum (CI) displayed the expected M + H signal at 220 amu's. Finally, elemental analysis confirmed both the elemental composition and the purity of the compound.

Attempts were then made to reduce the ester **142** to either the alcohol **143** or the aldehyde **144**. The ester **142** was reacted with diisobutylaluminium hydride with the

intention of isolating the desired aldehyde **144** or the alcohol **143** (Scheme 6.4.4). Although the ^{1}H NMR spectrum of the crude reaction mixture displayed a small peak in the aldehyde region (δ = 9.9 ppm) this reaction afforded a complex mixture of products.

Scheme 6.4.4 Attempted Reduction of the Ester (142) using DIBAL-H

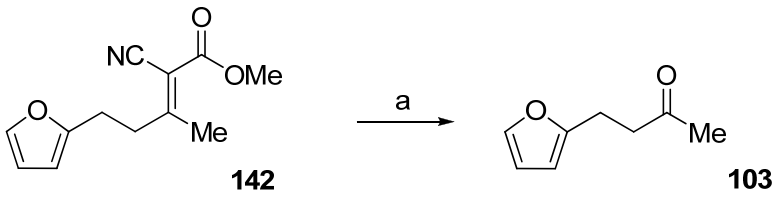


Reagents and conditions: DIBAL-H (2 equiv), CH_2Cl_2, -78 °C to room temperature, 1 h.

In addition, reduction of the ester **142** was attempted with lithium aluminium hydride in tetrahydrofuran,[61] however, a complex mixture of products was also formed.

Since the two reduction methods afforded a complex mixture of products, a different approach was taken to preparing the aldehyde **144**. It was initially thought that by hydrolyzing the ester **142** to the corresponding carboxylic acid, that a mild reduction could be performed to prepare the desired alcohol **143**, which could then be oxidized to the corresponding aldehyde **144**. As such, hydrolysis of the ester **142**, using a known procedure involving lithium hydroxide in a tetrahydrofuran/water mixture was attempted.[62] Surprisingly, it was found that the addition of lithium hydroxide to a solution of the α,β-unsaturated ester **142** afforded the ketone **103**, *via* a retro-Knoevenagel condensation reaction (Scheme 6.4.5).

Scheme 6.4.5 Retro-Knoevenagel Condensation of (2*E*)-Methyl 2-cyano-5-(furan-2'-yl)-3-methylpent-2-enoate (142)



142 **103**

Reagents and conditions: (a) LiOH, THF:H_2O (1:1), 22 h, room temperature, 34%.

Thus, it remains to devise alternative methods to prepare activated aldehydes for these proposed studies.

6.5 Conclusions

A variety of attempts were undertaken to prepare an activated aldehyde precursor, capable of undergoing the phenylboronic acid-mediated condensation reaction to afford an activated *tris*-2*H*-chromene. A Meldrum's acid analogue **126** was successfully prepared, however, reduction with diisobutylaluminium hydride afforded the undesired 1,4 addition product **127**. Attempts were then made to prepare a dialdehyde from diol precursors using manganese dioxide as the oxidant. However, only a *mono*-aldehyde was prepared *via* this method. However, a Swern oxidation successfully prepared the simple dialdehyde **124**. Both the *mono*-aldehyde **130** and the dialdehyde **124** were subjected to the phenyl boronic acid-mediated condensation reaction, however, the desired functionalized *tris*-2*H*-chromenes were not isolated. Subsequently, a Swern oxidation of the alcohol **134** allowed for the preparation of the dialdehyde **136**. However, when subjected to the phenylboronic acid-mediated condensation reaction conditions, the aldehyde **136** was found to decompose. Thus, the synthesis of a different activated aldehyde precursor was attempted using a Knoevenagel condensation of 2-cyano acetic

acid methyl ester (**141**) with the furan-ketone **103** to successfully prepare the α,β-unsaturated ester **142**. Surprisingly, it was found that the subsequent saponification of this ester caused a retro-Knoevenagel condensation, which afforded the starting ketone **103**. Thus, alternative routes towards these compounds will need to be devised.

7 GENERAL CONCLUSIONS AND FUTURE WORK

The research work described in this thesis has concerned studies on inter- and intramolecular cycloaddition reactions of various 2*H*-chromene carbon-carbon double bonds. A series of *mono*-2*H*-chromenes **36**, **2** and **37** were prepared to evaluate a series of intermolecular cycloaddition reactions of the 2*H*-chromene double bond. It was found that the cyclopropanation reactions of the *mono*-2*H*-chromene **2** using either dichloro- or dibromocarbene afforded the desired cycloadducts. Additionally, intermolecular [2+2] cycloaddition reactions utilizing dichloroketene and tetracyanoethylene were found to proceed quite well and afforded the corresponding cyclobutanes.

Having successfully demonstrated that these cycloaddition reactions can occur on the 2*H*-chromene double bond, these processes were then applied to the C_3-symmetric *tris*-2*H*-chromene **30**. It was subsequently found that the intermolecular [2+1] cyclopropanation reactions afforded the desired C_3-symmetric cyclopropane product as well as the unsymmetrical isomer. Also, it was found that by using the cyclopropanation procedure described by Lyle and co-workers,[40] that the corresponding *mono*-, *bis*- and *tris*-cycloadducts could be prepared and isolated. The intermolecular [2+2] cycloaddition reaction using dichloroketene was found to afford either the *mono*- or *bis*-cycloadducts depending on the reaction conditions. It was subsequently found that dropwise addition of dichloroketene to a reaction mixture containing the *tris*-2*H*-chromene **30** afforded the *tris*-cycloadduct **90**. Moreover, the intermolecular [2+2] cycloaddition involving tetracyanoethylene afforded the corresponding *mono*- and *bis*-cycloadducts. A [2+4] cycloaddition reaction was also attempted. This involved the generation of the highly reactive diene, *o*-quinonedimethane, as described by Durst *et al.*[37] Unfortunately, the

subsequent [2+4] cycloaddition reaction product was not isolated. As such, it was determined that a more reactive 2*H*-chromene carbon-carbon double bond would be required.

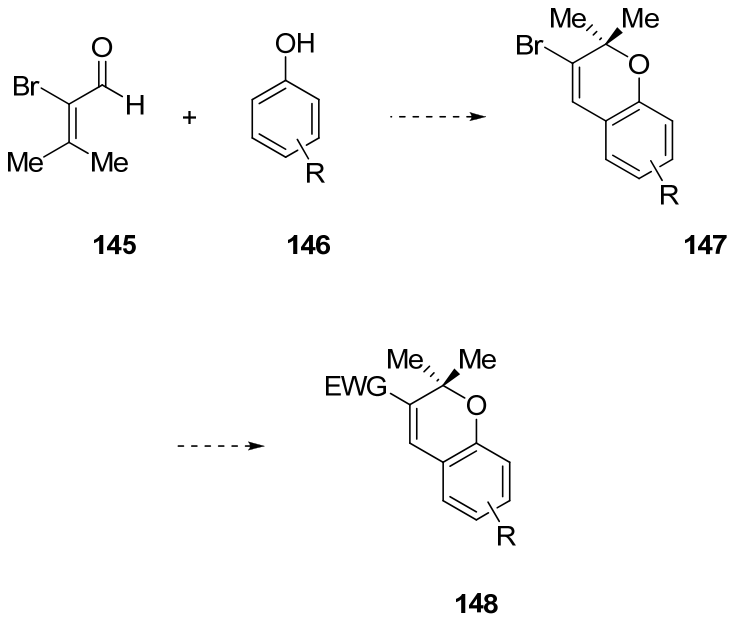
Having established that a series of intermolecular cycloaddition reactions are possible, efforts were then focussed on intramolecular cycloaddition reactions. A *mono*-2*H*-chromene **97**, which was readily prepared from citral (**31**) and 3,5-dimethoxyphenol (**39**), was prepared to evaluate an intramolecular [2+2] cycloaddition reaction. By subjecting this 2*H*-chromene to a variety of conditions it was found that the corresponding cyclobutane adduct **99** could be readily prepared and isolated. As such, studies were then undertaken towards executing a triple intramolecular [2+2] cycloaddition reaction of the C_3-symmetric *tris*-2*H*-chromene **32**. Unfortunately, the C_3-symmetric *tris*-2*H*-chromene **32**, though readily prepared as a single diastereoisomer, did not afford the desired cycloadduct, but instead resulted in a complex mixture of reaction products which could not be purified.

A novel α,β-unsaturated aldehyde **106** containing a furan group, which would function as the diene in an intramolecular [2+4] cycloaddition, was then prepared and reacted with phloroglucinol (**27**) to afford the desired C_3-symmetric *tris*-2*H*-chromene **108**. Although a variety of conditions were subsequently attempted to affect a triple cycloaddition process, the desired product was not isolated.

A study was then performed on preparing a more reactive 2*H*-chromene carbon-carbon double bond. Though initial efforts focussed on creating the highly reactive dialdehyde species **124**, it was subsequently determined a different electron withdrawing group would be much more appropriate. As such, the α,β-unsaturated cyanide ester **142**

was prepared. However, reduction of this ester to the corresponding alcohol was unsuccessful. Therefore, a different substrate and synthetic route is needed to prepare an activated aldehyde. Thus, the preparation of 2-bromo-senecialdehyde **145**, which could be used to prepare the corresponding 2*H*-chromene (**147**), could be subsequently used to install a variety of electron withdrawing groups. The installation of the electron withdrawing groups could occur before the phenylboronic acid-mediated condensation reaction or once the requisite 2*H*-chromene has already been formed (Scheme 7.1.1).

Scheme 7.1.1 Proposed Reaction of 2-Bromo-senecialdehyde (145) with Phenol (146) to Form the Functionalized 2*H*-Chromene (147)



145 **146** **147** **148**

8 EXPERIMENTAL

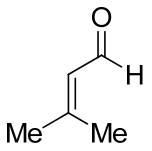
8.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, pyridine, toluene and triethylamine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. Methanol was dried over magnesium methoxide and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied.[63] Silica gel column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh).[64] Brine refers to a saturated aqueous solution of sodium chloride. Melting points (**M.p.**) were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. All proton and carbon nuclear magnetic resonance spectra (**^{1}H NMR**, **^{13}C NMR**, respectively) were recorded on 400 MHz (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz), 500 MHz (operating frequencies: ^{1}H, 499.77 MHz; ^{13}C, 125.68 MHz) and 600 MHz (operating frequencies: ^{1}H, 600.33 MHz; ^{13}C, 150.95) FT spectrometers at ambient temperature. The chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were δ 7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively. The reference values used for deuterated benzene (C_6D_6) were δ 7.15 and 128.02 ppm for ^{1}H and ^{13}C NMR

spectra, respectively. The reference values used for deuterated acetonitrile (CD_3CN) were δ 1.94 and 1.24 ppm for ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (**IR**) were recorded as either KBr pellets (KBr), evaporated films (ef) or as neat films (neat) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (**MS**) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was chemical ionization (CI) with methanol as the ionization gas. Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF) were recorded using 2,4-dihydroxybenzoic acid as the matrix. High-resolution mass spectra (**HRMS**) were recorded on an Agilent Technologies 6210 time-of-flight-LC/MS mass spectrometer. Microanalyses (**Anal.**) were performed on a Carlo Erba Model 1106 CHN analyzer.

8.2 Experimental Procedures and Characterization Data Concerning Chapter Two

8.2.1 3-Methyl-but-2-enal [Senecialdehyde] (29)[21]

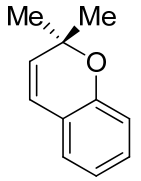


29

To a suspension of manganese dioxide (80.0 g, 919 mmol) in dichloromethane (325 mL) at room temperature was added 3-methyl-but-2-en-1-ol (9.29 mL, 92.9 mmol). After 39 h, the reaction was filtered through a pad of celite and the filter-cake was washed with dichloromethane (4 x 50 mL) and then the combined filtrates were concentrated *in vacuo*. Purification of the crude product by distillation at reduced pressure afforded the *title compound* **12** (5.17 g, 66%) as a colourless oil. $\mathbf{R}_f$ = 0.41, hexanes:ether (1:1); **B.p.** ~56 °C, ~35mm Hg (lit.[21] 133-135 °C, 760 mm Hg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.97 (s, 3H, *Me*), 2.16 (s, 3H, *Me*), 5.87 (d, *J* = 8.1 Hz, 1H, C*H*),

9.94 (d, *J* = 8.1 Hz, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.9, 27.2, 128.1, 160.6, 191.0; **IR** (neat) 2985, 2917, 2854, 2763, 1684, 1630, 1616, 1448, 1378, 1198, 1131, 1048 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 85 (M + H, 100).

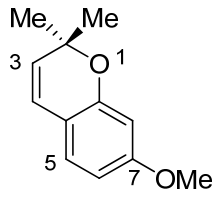
8.2.2 2,2-Dimethyl-2*H*-chromene (36)[23]



36

A mixture of senecialdehyde (**29**) (1.49 g, 17.7 mmol), phenol (**17**) (1.11 g, 11.8 mmol), phenylboronic acid (1.44 g, 11.8 mmol), propionic acid (40 drops) and benzene (30 mL) was heated at reflux in a Dean-Stark apparatus for 21 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (15:1) as the eluant afforded the *title compound* **36** (540 mg, 28%) as a light yellow oil. $\mathbf{R}_f$ = 0.55, hexanes:ether (15:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.43 (s, 6H, *Me*), 5.61 (d, *J* = 9.8 Hz, 1H, ArCHC*H*), 6.32 (d, *J* = 9.8 Hz, 1H, ArC*H*CH), 6.77 (apparent d, *J* = 8.0 Hz, 1H, Ar*H*), 6.84 (apparent t, *J* = 7.4 Hz, 1H, Ar*H*), 6.97 (dd, *J* = 7.4, 1.5 Hz, 1H, Ar*H*), 7.10 (dt, *J* = 7.8, 1.6 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.9, 76.1, 116.3, 120.7, 121.2, 122.3, 126.3, 129.0, 130.7, 152.9; **IR** (ef) 3043, 2973, 2924, 1604, 1486, 1456, 1376, 1360, 1260, 1164, 1120 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 161 (M + H, 100).

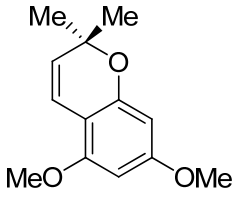
8.2.3 7-Methoxy-2,2-dimethyl-2*H*-chromene (2)[22]



2

A mixture of senecialdehyde (**29**) (1.60 g, 19.0 mmol), 3-methoxyphenol (**38**) (1.82 g, 14.6 mmol), phenylboronic acid (1.78 g, 14.6 mmol), propionic acid (50 drops) and benzene (35 mL) was heated at reflux in a Dean-Stark apparatus for 4 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (200 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **2** (2.07 g, 75%) as a colourless oil. $\mathbf{R}_f$ = 0.53, hexanes:ether (8:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.43 (s, 6H, *Me*), 3.77 (s, 3H, O*Me*), 5.47 (d, *J* = 9.8 Hz, 1H, ArCHC*H*), 6.28 (d, *J* = 9.8 Hz, 1H, ArC*H*CH), 6.38 (d, *J* = 2.3 Hz, 1H, *H*-8), 6.41 (dd, *J* = 8.2, 2.2 Hz, 1H, *H*-6), 6.88 (d, *J* = 8.2 Hz, 1H, *H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 28.0, 55.3, 76.3, 101.9, 106.6, 114.6, 121.9, 126.9, 127.8, 154.1, 160.6; **IR** (neat) 3043, 2976, 2928, 2836, 1615, 1568, 1502, 1315, 1280, 1195, 1158, 1129, 1033 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 191 (M + H, 100).

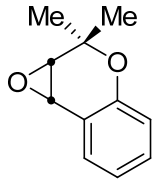
8.2.4 5,7-Dimethoxy-2,2-dimethyl-2*H*-chromene (37)[24]



37

A mixture of senecialdehyde (**29**) (1.50 g, 17.8 mmol), 3,5-dimethoxyphenol (**39**) (1.83 g, 11.9 mmol), phenylboronic acid (1.45 g, 11.9 mmol), propionic acid (50 drops) and benzene (50 mL) was heated at reflux in a Dean-Stark apparatus for 3 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **37** (2.21 g, 84%) as a colourless oil. $\mathbf{R}_f$ = 0.39, hexanes:ether (9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.43 (s, 6H, *Me*), 3.77 (s, 3H, O*Me*), 3.78 (s, 3H, O*Me*), 5.42 (d, *J* = 9.9 Hz, 1H, ArCHC*H*), 6.01 (d, *J* = 2.3 Hz, 1H, Ar*H*), 6.04 (d, *J* = 2.2 Hz, 1H, Ar*H*), 6.59 (d, *J* = 9.9 Hz, 1H, ArC*H*CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.7, 55.2, 55.4, 76.1, 91.3, 93.9, 104.1, 116.6, 125.8, 154.6, 156.0, 160.9; **IR** (neat) 2973, 2938, 2838, 1636, 1613, 1578, 1496, 1464, 1390, 1375, 1360, 1247, 1202, 1148, 1123, 1102, 1050 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 220 (M + H, 100).

8.2.5 (1a*SR*,7b*SR*)-2,2-Dimethyl-1a,7b-dihydro-2*H*-oxireno[c]chromene (40)[26]

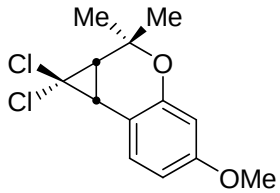


40

To a mixture of the chromene **36** (54 mg, 0.33 mmol), an aqueous solution of sodium bicarbonate (0.5 M, 3 mL) and dichloromethane (5 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (**41**) (77%, 82 mg, 0.33 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 48 h. Dichloromethane (10 mL) was then added and the resultant mixture was washed with a saturated aqueous solution of sodium bicarbonate (2 x 20 mL), water (20 mL), dried over anhydrous sodium

sulphate and then concentrated *in vacuo*. Purification of the resultant oil was accomplished by precipitation of impurities from a mixture of chloroform (1 mL) and hexanes (0.5 mL). Filtration and concentration of the filtrate *in vacuo* afforded the *title compound* **40** (12 mg, 20%) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.26 (s, 3H, *Me*), 1.58 (s, 3H, *Me*), 3.50 (d, *J* = 4.4 Hz, 1H, ArCHC*H*), 3.91 (d, *J* = 4.4 Hz, 1H, ArC*H*CH), 6.81 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.92 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.23 (dt, *J* = 7.7, 1.6 Hz, 1H, Ar*H*), 7.33 (dd, *J* = 7.4, 1.6 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.5, 25.6, 51.0, 62.8, 72.9, 117.9, 119.9, 121.0, 129.6, 130.3, 152.5; **IR** (ef) 2977, 2927, 1613, 1585, 1558, 1540, 1488, 1381, 1237, 1207, 1164 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 177 (M + H, 100).

8.2.6 (1a*SR*,7b*RS*)-1,1-Dichloro-5-methoxy-2,2-dimethyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene (46)[29]

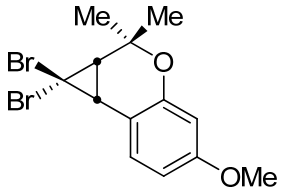


46

To a mixture of the chromene **2** (150 mg, 0.788 mmol), tetra-*n*-butylammonium bromide (50 mg, 0.16 mmol) and an aqueous solution of sodium hydroxide (8 M, 5 mL) was added chloroform (5.0 mL, 62 mmol) dropwise at room temperature. The reaction mixture was allowed to stir at room temperature for 12 h and then dichloromethane (5 mL) was added. The resultant mixture was separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant,

with dichloromethane to load, afforded the *title compound* **46** (110 mg, 52%) as a white powder. $\mathbf{R_f}$ = 0.33, hexanes:ether (9:1); **M.p.** 96-98 °C, hexanes:ether (lit.[29] 90-92 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.24 (s, 3H, *Me*), 1.69 (s, 3H, *Me*), 2.15 (d, *J* = 10.9 Hz, 1H, ArCHC*H*), 2.82 (d, *J* = 10.9 Hz, 1H, ArC*H*CH), 3.76 (s, 3H, O*Me*), 6.39 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.54 (dd, *J* = 8.3, 2.5 Hz, 1H, Ar*H*), 7.19 (d, *J* = 8.4 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 26.6, 27.2, 30.5, 40.4, 55.2, 62.2, 71.3, 103.1, 107.9, 110.2, 130.5, 152.4, 160.3; **IR** (ef) 2976, 2934, 2842, 1626, 1583, 1511, 1468, 1444, 1371, 1340, 1279, 1194, 1164, 1134 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 277 [M (2 x ^{37}Cl) + H, 15], 276 (15), 275 [M (^{35}Cl + ^{37}Cl) + H, 44], 274 (70), 273 [M (2 x ^{35}Cl) + H, 63], 272 (100), 237 (M – Cl, 77).

8.2.7 (1a*SR*,7b*RS*)-1,1-Dibromo-5-methoxy-2,2-dimethyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene (47)

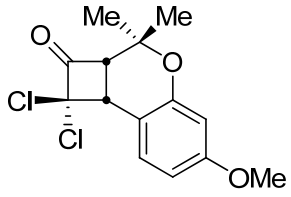


47

To a mixture of the chromene **2** (150 mg, 0.788 mmol), tetra-*n*-butylammonium bromide (50 mg, 0.16 mmol) and an aqueous solution of sodium hydroxide (8 M, 5 mL) was added bromoform (5.0 mL, 57 mmol) dropwise at room temperature. The reaction mixture was allowed to stir at room temperature for 19 h and then dichloromethane (5 mL) was added. The resultant mixture was separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL), brine (10 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether

(9:1) as the eluant, with dichloromethane to load, afforded the *title compound* **47** (100 mg, 34%) as a white powder. $\mathbf{R_f}$ = 0.28, hexanes:ether (9:1); **M.p.** 126-130 °C, hexanes:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.22 (s, 3H, *Me*), 1.70 (s, 3H, *Me*), 2.24 (d, *J* = 10.7 Hz, 1H, ArCHC*H*), 2.90 (d, *J* = 10.7 Hz, 1H, ArC*H*CH), 3.76 (s, 3H, O*Me*), 6.37 (d, *J* = 2.6 Hz, 1H, Ar*H*), 6.54 (dd, *J* = 8.4, 2.6 Hz, 1H, Ar*H*), 7.20 (d, *J* = 8.4 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.9, 27.6, 30.8, 31.2, 41.5, 55.2, 72.2, 103.1, 108.0, 111.9, 130.5, 152.3, 160.3; **IR** (ef) 2978, 2934, 2832, 1619, 1584, 1506, 1460, 1435, 1364, 1328, 1289, 1272, 1189, 1152, 1131 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 365 [M (2 x ^{81}Br) + H, 3], 363 [M (^{79}Br + ^{81}Br) + H, 7], 361 [M (2 x ^{79}Br) + H, 4], 283 (M – Br, 73), 281 (M – Br, 72), 202 (M – 2 x ^{81}Br, 100); **Anal.** Calcd. for $C_{13}H_{14}Br_2O_2$: C, 43.13; H, 3.90. Found: C, 42.99; H, 4.01.

8.2.8 (2a*SR*,8b*RS*)-1,1-Dichloro-6-methoxy-3,3-dimethyl-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[c]chromen-2-one (51)

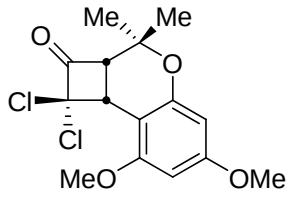


51

To a suspension of zinc powder (320 mesh, 191 mg, 2.92 mmol) and chromene **2** (124 mg, 0.638 mmol) in tetrahydrofuran (15 mL) at 0 °C was added trichloroacetyl chloride (0.22 mL, 1.9 mmol) dropwise over ~1 min. The resultant suspension was stirred at 0 °C for 15 min and then was allowed to warm to room temperature and stirred for an additional 26 h. A saturated aqueous solution of sodium bicarbonate (1 mL) was then added and the reaction mixture was allowed to stir for 10 min. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (3 x

10 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 25 mL), water (2 x 25 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **51** [52 mg, 26% (38% brsm)] as a white solid and the starting material (**2**) (39 mg, 20%). $\mathbf{R_f}$ = 0.25, hexanes:ether (5:1); **M.p.** 116-117 °C, hexanes:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.19 (s, 3H, *Me*), 1.69 (s, 3H, *Me*), 3.77 (s, 3H, O*Me*), 4.09 (m, 2H, ArC*H*C*H*), 6.41 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.60 (dd, *J* = 8.6, 2.6 Hz, 1H, Ar*H*), 7.14 (d, *J* = 8.4 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.3, 26.0, 46.6, 55.3, 63.3, 74.6, 87.3, 103.4, 108.9, 110.8, 132.4, 154.2, 160.9, 193.4; **IR** (KBr) 3015, 2979, 2964, 2938, 2835, 1795, 1618, 1586, 1504, 1464, 1441, 1368, 1273, 1197, 1133, 1106, 1030 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 305 [M (2 x ^{37}Cl) + H, 12], 303 [M (^{35}Cl + ^{37}Cl) + H, 75], 301 [M (2 x ^{35}Cl) + H, 100], 265 (M – Cl, 88); **Anal.** Calcd. for $C_{14}H_{14}Cl_2O_3$: C, 55.83; H, 4.69. Found: C, 55.87; H, 4.56.

8.2.9 (2a*SR*,8b*RS*)-1,1-Dichloro-6,8-dimethoxy-3,3-dimethyl-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[c]chromen-2-one (52)

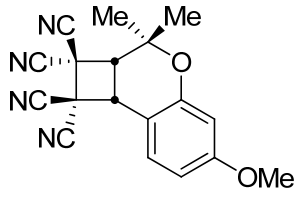


52

To a suspension of zinc powder (320 mesh, 134 mg, 2.05 mmol) and chromene **37** (100 mg, 0.454 mmol) in tetrahydrofuran (8 mL) at 0 °C was added trichloroacetyl chloride (0.15 mL, 1.4 mmol) dropwise over ~1 min. The resultant suspension was stirred at 0 °C for 10 min and then was allowed to warm to room temperature and stirred

for an additional 2 h. A saturated aqueous solution of sodium bicarbonate (1 mL) was then added and the reaction mixture was allowed to stir for 30 min. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 10 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (25 mL), water (40 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **52** (71 mg, 47%) as a white solid. $\mathbf{R}_f$ = 0.25, hexanes:ether (9:1); **M.p.** 158-160 °C, hexanes:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.19 (s, 3H, *Me*), 1.68 (s, 3H, *Me*), 3.76 (s, 3H, O*Me*), 3.85 (s, 3H, O*Me*), 4.01 (d, *J* = 10.8 Hz, 1H, ArCHC*H*), 4.29 (d, *J* = 10.8 Hz, 1H, ArC*H*CH), 6.04 (d, *J* = 2.3 Hz, 1H, Ar*H*), 6.14 (d, *J* = 2.3 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.2, 26.0, 42.3, 55.3, 55.7, 61.9, 74.6, 87.1, 92.5, 94.9, 100.8, 154.5, 159.9, 161.4, 194.1; **IR** (KBr) 2976, 2940, 2843, 1806, 1617, 1591, 1495, 1464, 1426, 1370, 1309, 1220, 1201, 1149, 1102, 1050 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 335 [M (2 x ^{37}Cl) + H, 11], 333 [M (^{35}Cl + ^{37}Cl) + H, 64], 331 [M (2 x ^{35}Cl) + H, 100]; **Anal.** Calcd. for $C_{15}H_{16}Cl_2O_4$: C, 54.40; H, 4.87. Found: C, 54.72; H, 4.89; **HRMS** Calcd. for $C_{15}H_{17}Cl_2O_4$: 331.0498. Found: 331.0489.

8.2.10 (2a*RS*,8b*SR*)-6-Methoxy-3,3-dimethyl-2a,8b-dihydro-cyclobuta[c]chromene-1,1,2,2-tetracarbonitrile (55)

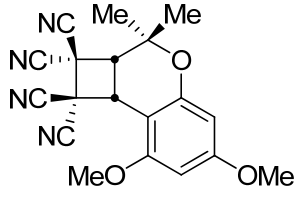


55

A solution of chromene **2** (138 mg, 0.711 mmol) and tetracyanoethylene (139 mg, 1.08 mmol) in acetonitrile (15 mL) was heated at reflux for 20 h. The reaction mixture

was then allowed to cool to room temperature and was concentrated *in vacuo*. The resultant solid was then partitioned between acetonitrile (10 mL) and a saturated aqueous solution of ammonium chloride (15 mL). The aqueous phase was separated and extracted with ether (2 x 10 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* **55** (66 mg, 29%) as a white solid. $\mathbf{R_f}$ = 0.30, hexanes:ethyl acetate (2:1); **M.p.** 205-206 °C, hexanes:ethyl acetate; **^{1}H NMR** (500 MHz, CD_3CN) δ 1.16 (s, 3H, *Me*), 1.61 (s, 3H, *Me*), 3.79 (s, 3H, O*Me*), 4.05 (d, *J* = 9.6 Hz, 1H, ArCHC*H*), 4.46 (d, *J* = 9.6 Hz, 1H, ArC*H*CH), 6.48 (d, *J* = 2.6 Hz, 1H, Ar*H*), 6.72 (dd, *J* = 8.7, 2.7 Hz, 1H, Ar*H*), 7.39 (d, *J* = 8.7 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, CD_3CN) δ 23.4, 24.0, 37.7, 40.8, 42.3, 49.4, 56.1, 73.9, 103.9, 106.2, 110.2, 110.7, 111.0, 112.5, 112.6, 133.4, 155.6, 163.0; **IR** (KBr) 2984, 2938, 2840, 2248, 1618, 1578, 1504, 1442, 1373, 1319, 1286, 1198, 1158, 1124, 1109 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 319 (M + H, 5), 191 (M – C_6N_4, 100); **Anal.** Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.82; H, 4.19; N, 17.23.

8.2.11 (2a*RS*,8b*SR*)-6,8-Dimethoxy-3,3-dimethyl-2a,8b-dihydro-cyclobuta[c]chromene-1,1,2,2-tetracarbonitrile (56)

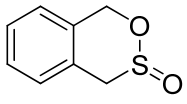


56

A solution of chromene **37** (100 mg, 0.454 mmol) and tetracyanoethylene (87 mg, 0.68 mmol) in acetonitrile (8 mL) was heated at reflux for 30 min. The reaction mixture

was then allowed to cool to room temperature and was concentrated *in vacuo*. The resultant solid was then partitioned between acetonitrile (10 mL) and a saturated aqueous solution of ammonium chloride (15 mL). The aqueous phase was separated and extracted with ether (2 x 10 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* **56** (52 mg, 33%) as a white solid. $\mathbf{R_f}$ = 0.41, hexanes:ethyl acetate (2:1); **M.p.** 188-191 °C, hexanes:ethyl acetate; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.25 (s, 3H, *Me*), 1.67 (s, 3H, *Me*), 3.59 (d, *J* = 9.4 Hz, 1H, ArCHC*H*) 3.80 (s, 3H, O*Me*), 3.87 (s, 3H, O*Me*), 4.33 (d, *J* = 9.4 Hz, 1H, ArC*H*CH), 6.16 (d, *J* = 2.2 Hz, 1H, Ar*H*), 6.19 (d, *J* = 2.2 Hz, 1H, Ar*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.8, 24.0, 36.7, 38.8, 39.8, 48.4, 55.5, 55.7, 72.6, 93.2, 93.6, 95.0, 108.4, 108.7, 110.9, 111.3, 154.7, 159.1, 163.5; **IR** (KBr) 3010, 2976, 2943, 2248, 1624, 1591, 1496, 1458, 1427, 1372, 1357, 1202, 1145, 1111 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 349 (M + H, 1), 221 (M – C_6N_4, 100); **Anal.** Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.37; H, 4.95; N, 16.24.

8.2.12 1,4-Dihydro-2,3-benzoxathiin-3-oxide (62)[38]



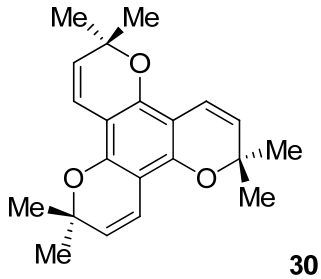
62

A mixture of α,α'-dibromo-*o*-xylene (**60**) (2.00 g, 7.58 mmol), Rongalite® (**61**) (2.35 g, 15.2 mmol), tetra-*n*-butylammonium bromide (489 mg, 1.52 mmol) and *N*,*N*-dimethylformamide (30 mL) was stirred at 0 °C for 3 h and then at room temperature for

17 h. Water (100 mL) was then added and the reaction mixture stirred an additional 30 min. The resultant aqueous mixture was extracted with ether (3 x 300 mL), dried over magnesium sulphate and concentrated *in vacuo*. The resultant oil was dissolved in ether (30 mL) and washed with water (3 x 150 mL), brine (2 x 150 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the *title compound* **62** (686 mg, 54%) as a pale yellow oil. $\mathbf{R_f}$ = 0.50, hexanes:ethyl acetate (1:2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.55 (d, *J* = 15.4 Hz, 1H, C*H*), 4.42 (d, *J* = 15.4 Hz, 1H, C*H*), 4.96 (d, *J* = 13.7 Hz, 1H, C*H*), 5.30 (d, *J* = 13.7 Hz, 1H, C*H*), 7.21 – 7.26 (m, 2H, Ar*H*), 7.33 – 7.38 (m, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 56.9, 62.9, 125.7, 126.2, 127.8, 128.6, 129.6, 133.7; **IR** (neat) 3029, 2968, 2921, 2874, 2245, 2109, 1784, 1719, 1695, 1495, 1459, 1404, 1207, 1142, 1119, 1094 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 169 (M + H, 100), 104 (M – SO_2, 3).

8.3 Experimental Procedures and Characterization Data Concerning Chapter Three

8.3.1 2,2,6,6,10,10-Hexamethyl-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (30)[19]

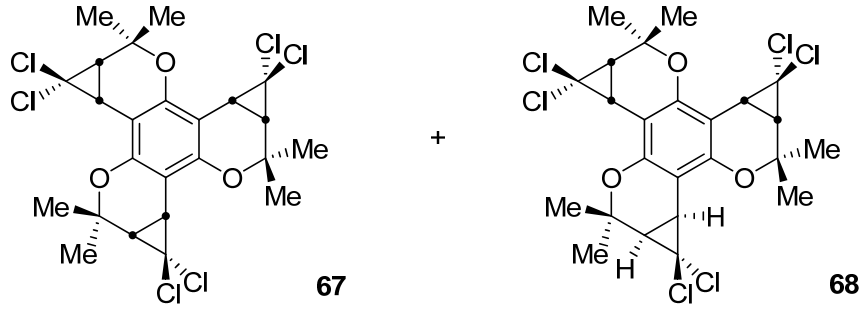


30

A mixture of senecialdehyde (**29**) (1.83 g, 21.7 mmol), phloroglucinol (**27**) (680 mg, 5.43 mmol), phenylboronic acid (1.99 g, 16.3 mmol), propionic acid (60 drops) and benzene (50 mL) was heated at reflux in a Dean-Stark apparatus for 2 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with

ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (15:1) as the eluant afforded the *title compound* **30** (1.08 g, 61%) as a white powder. $\mathbf{R_f}$ = 0.51, hexanes:ether (15:1); **M.p.** 110-113 °C, hexanes:ether (lit.[19] 110-113 °C, hexanes:ether); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.40 (s, 18H, *Me*), 5.41 (d, *J* = 9.8 Hz, 3H, ArCHC*H*), 6.58 (d, *J* = 9.8 Hz, 3H, ArC*H*CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.9, 76.4, 103.4, 116.8, 125.8, 149.1; **IR** (ef) 2974, 2913, 2863, 1639, 1592, 1459, 1434, 1378, 1365, 1243, 1218, 1138 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 325 (M + H, 100).

8.3.2 (1a*SR*,3c*RS*,4a*SR*,6c*RS*,7a*SR*,9c*RS*)-1,1,4,4,7,7-Hexachloro-2,2,5,5,8,8-hexamethyl-1,1a,2,3c,4,4a,5,6c,7,7a,8,9c-dodecahydrocyclopropa[*c*]*bis*-cyclopropa[3,4]pyrano[6,5-*f*,6',5'-*h*]chromene (67) and (1a*SR*,3c*RS*,4a*SR*,6c*SR*,7a*RS*,9c*RS*)-1,1,4,4,7,7-hexachloro-2,2,5,5,8,8-hexamethyl-1,1a,2,3c,4,4a,5,6c,7,7a,8,9c-dodecahydrocyclopropa[*c*]*bis*-cyclopropa[3,4]pyrano[6,5-*f*,6',5'-*h*]chromene (68)



To a mixture of the chromene **30** (93 mg, 0.29 mmol), tetra-*n*-butylammonium bromide (28 mg, 0.09 mmol) and an aqueous solution of sodium hydroxide (8 M, 6 mL) was added chloroform (10 mL, 120 mmol) dropwise at room temperature. The resultant mixture was allowed to stir at room temperature for 21 h and then ether (10 mL) was added. The resultant mixture was separated and the organic phase was washed with water (2 x 25 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. The resultant yellow solid was dissolved in a minimum amount of chloroform and to this

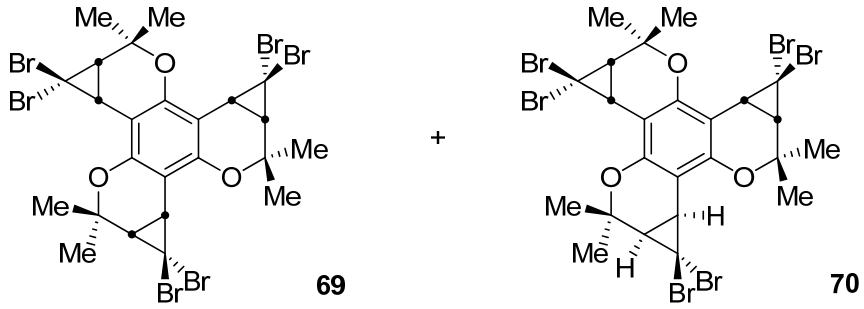
solution was added hexanes until a precipitate formed. The *title compound* **67** was collected by vacuum filtration (19 mg, 11%) as a white powder. The filtrate was concentrated *in vacuo* and triturated with hexanes (20 mL). Drying of the solid *in vacuo* afforded the *title compound* **68** (90 mg, 55%) as a white powder.

Title compound **67**: $\mathbf{R_f}$ = 0.21, hexanes:ether (15:1); **M.p.** 256-259 °C, chloroform; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (s, 9H, *Me*), 1.72 (s, 9H, *Me*), 2.05 (d, *J* = 11.0 Hz, 3H, ArCHC*H*), 3.02 (d, *J* = 11.0 Hz, 3H, ArC*H*CH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.1, 26.6, 27.7, 39.4, 62.3, 71.5, 100.4, 149.9; **IR** (KBr) 3041, 2974, 2929, 2850, 1612, 1469, 1454, 1384, 1368, 1308, 1156, 1142, 1079, 1034 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 577 [M (3 x ^{35}Cl + 3 x ^{37}Cl) + H, 29], 576 (12), 575 [M (4 x ^{35}Cl + 2 x ^{37}Cl) + H, 74], 574 (14), 573 [M (5 x ^{35}Cl + ^{37}Cl) + H, 100], 572 (7), 571 [M (6 x ^{35}Cl) + H, 38], 537 (M – Cl, 19), 501 (M – 2 x Cl, 12); **Anal.** Calcd. for $C_{24}H_{24}Cl_6O_3$: C, 50.29; H, 4.22. Found: C, 50.58; H, 4.19.

Title compound **68**: $\mathbf{R_f}$ = 0.37, hexanes:ether (15:1); **M.p.** 239-240 °C, hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.25 (apparent s, 9H, *Me*), 1.708 (s, 3H, *Me*), 1.714 (s, 3H, *Me*), 1.719 (s, 3H, *Me*), 2.06 (d, *J* = 11.0 Hz, 1H, ArC*H*), 2.088 (d, *J* = 11.1 Hz, 1H, ArC*H*), 2.090 (d, *J* = 11.1 Hz, 1H, ArC*H*), 3.02 (d, *J* = 11.0 Hz, 1H, ArC*H*), 3.140 (d, *J* = 11.1 Hz, 1H, ArC*H*), 3.143 (d, *J* = 11.1 Hz, 1H, ArC*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 24.9, 25.1, 25.3, 26.5, 26.57, 26.63, 27.33, 27.35, 27.7, 39.3, 39.46, 39.49, 62.3, 62.7, 71.6, 71.8, 100.4, 100.6, 100.8, 150.0, 150.1, 150.2; **IR** (KBr) 3063, 2990, 2977, 2934, 2870, 1615, 1471, 1366, 1308, 1156, 1140, 1080 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 579 [M (2 x ^{35}Cl + 4 x ^{37}Cl) + H, 9], 578 (9), 577 [M (3 x ^{35}Cl + 3 x ^{37}Cl) + H, 38], 576 (20), 575 [M (4 x ^{35}Cl + 2 x ^{37}Cl) + H, 86], 574 (25), 573 [M (5 x ^{35}Cl + ^{37}Cl) + H, 100], 572

(13), 571 [M (6 x ^{35}Cl) + H, 45], 539 (M – Cl, 21), 538 (6), 537 (M – Cl, 28), 503 [M – (2 x Cl), 23], 501 [M – (2 x Cl), 26]; **Anal.** Calcd. for $C_{24}H_{24}Cl_6O_3$: C, 50.29; H, 4.22. Found: C, 50.42; H, 4.22.

8.3.3 (1a*SR*,3c*RS*,4a*SR*,6c*RS*,7a*SR*,9c*RS*)-1,1,4,4,7,7-Hexabromo-2,2,5,5,8,8-hexamethyl-1,1a,2,3c,4,4a,5,6c,7,7a,8,9c-dodecahydrocyclopropa[*c*]*bis*-cyclopropa[3,4]pyrano[6,5-*f*,6',5'-*h*]chromene (69) and (1a*SR*,3c*RS*,4a*SR*,6c*SR*,7a*RS*,9c*RS*)-1,1,4,4,7,7-hexabromo-2,2,5,5,8,8-hexamethyl-1,1a,2,3c,4,4a,5,6c,7,7a,8,9c-dodecahydrocyclopropa[*c*]*bis*-cyclopropa[3,4]pyrano[6,5-*f*,6',5'-*h*]chromene (70)



To a mixture of the chromene **30** (100 mg, 0.308 mmol), tetra-*n*-butylammonium bromide (30 mg, 0.09 mmol) and an aqueous solution of sodium hydroxide (8 M, 8 mL) was added bromoform (10 mL, 110 mmol) dropwise at room temperature. The reaction mixture was allowed to stir at room temperature for 19 h and then water (20 mL) was added. The resultant mixture was then separated and the aqueous phase was extracted with chloroform (2 x 20 mL). The combined organic extracts where washed with water (50 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (15:1) as the eluant afforded the *title compound* **69** (44 mg, 19%) as a white powder and the *title compound* **70** (32 mg, 12%) as a white powder.

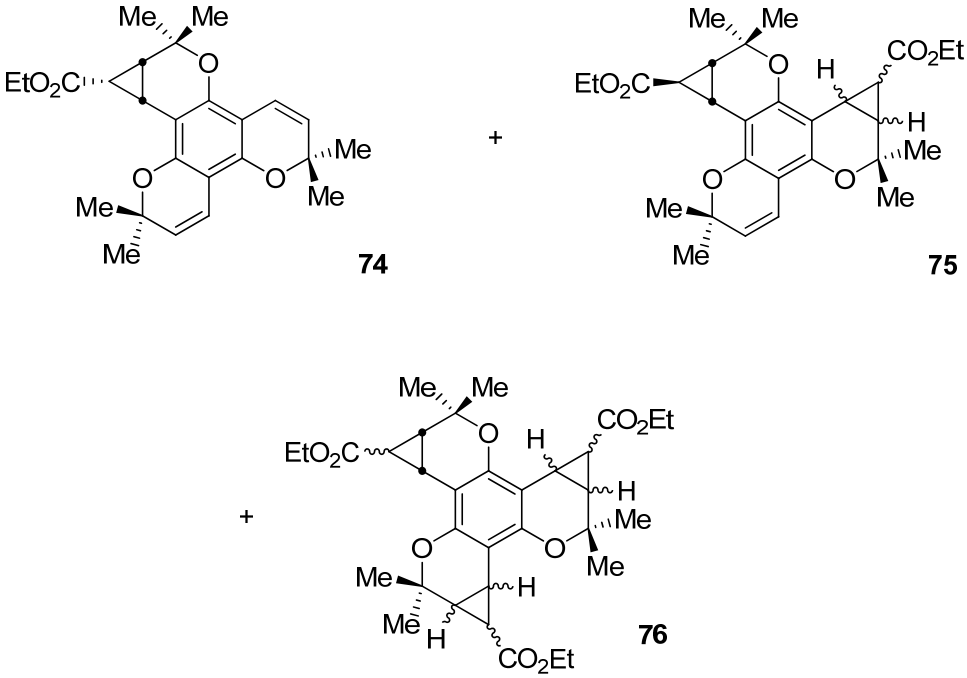
Title compound **69**: $\mathbf{R_f}$ = 0.28, hexanes:ether (15:1); **M.p.** 229-231 °C, hexanes:ether; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.26 (s, 9H, *Me*), 1.74 (s, 9H, *Me*), 2.16 (d,

J = 10.9 Hz, 3H, ArCHC*H*), 3.08 (d, *J* = 10.9 Hz, 3H, ArC*H*CH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.7, 26.0, 28.2, 31.0, 40.4, 72.4, 101.8, 150.0; **IR** (KBr) 2974, 2933, 1613, 1467, 1383, 1364, 1304, 1242, 1154, 1140, 1077, 1031, 727 cm^{-1}; **MS** (HRMS) *m/z* (rel. intensity) 846 [M (6 x ^{81}Br) + H, 6], 844 [M (5 x ^{81}Br + ^{79}Br) + H, 31], 842 [M (4 x ^{81}Br + 2 x ^{79}Br) + H, 80], 840 [M (3 x ^{81}Br + 3 x ^{79}Br) + H, 100], 838 [M (2 x ^{81}Br + 4 x ^{79}Br) + H, 69], 836 [M (^{81}Br + 5 x ^{79}Br) + H, 32], 834 [M (6 x ^{79}Br) + H, 6]; **HRMS** Calcd. for $C_{24}H_{25}Br_6O_3$: 842.6826. Found: 842.6839.

Title compound **70**: : $\mathbf{R_f}$ = 0.38, hexanes:ether (15:1); **M.p.** 199-201 °C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.25 (apparent s, 6H, *Me*), 1.27 (s, 3H, *Me*), 1.737 (apparent s, 6H, *Me*), 1.743 (s, 3H, *Me*), 2.17 (d, *J* = 10.9 Hz, 1H, ArC*H*), 2.18 (d, *J* = 11.0 Hz, 1H, ArC*H*), 2.19 (d, *J* = 11.0 Hz, 1H, ArC*H*), 3.09 (d, *J* = 10.9 Hz, 1H, ArC*H*), 3.22 (d, *J* = 11.0 Hz, 1H, ArC*H*), 3.23 (d, *J* = 11.0 Hz, 1H, ArC*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.6, 25.86, 25.91, 25.93, 26.00, 26.02, 27.7, 27.8, 28.2, 30.9, 31.43, 31.46, 40.3, 40.5, 72.4, 72.74, 72.76, 102.2, 102.3, 102.4, 149.9, 150.0, 150.2; **IR** (KBr) 2977, 2932, 1616, 1471, 1384, 1366, 1308, 1156, 1140, 1080, 1035, 813 cm^{-1}; **MS** (HRMS) *m/z* (rel. intensity) 846 [M (6 x ^{81}Br) + H, 5], 844 [M (5 x ^{81}Br + ^{79}Br) + H, 27], 842 [M (4 x ^{81}Br + 2 x ^{79}Br) + H, 73], 840 [M (3 x ^{81}Br + 3 x ^{79}Br) + H, 100], 838 [M (2 x ^{81}Br + 4 x ^{79}Br) + H, 67], 836 [M (^{81}Br + 5 x ^{79}Br) + H, 28], 834 [M (6 x ^{79}Br) + H, 5]; **HRMS** Calcd. for $C_{24}H_{25}Br_6O_3$: 840.6845. Found: 840.6839.

8.3.4 Ethyl-(10a*RS*,11*SR*,11a*SR*)-2,2,6,6,10,10-hexamethyl-10,10a,11,11a-tetrahydro-2*H*,6*H*-cyclopropa[*c*]-dipyrano[6,5-*f*,6',5'-*h*]chromene-11-carboxylate (74) and Diethyl-(6a*RS*,7*RS*,7a*RS*,9a*RS*,10*RS*,10a*RS*)-2,2,6,6,9,9-hexamethyl-6,6a,7,7a,9,9a,10,10a-octahydro-2*H*-cyclopropa[*c*]-cyclopropa[3,4]pyrano[6,5-*f*]pyrano[6,5-*h*]chromene-7,10-dicarboxylate (75) and Triethyl-(1*RS*,1a*RS*,3c*RS*,4*RS*,4a*RS*,6c*RS*,7*RS*,7a*RS*,9c*RS*)-3,3,6,6,9,9-

hexamethyl-1,1a,2,3c,4,4a,5,6c,7,7a,8,9c-dodecahydrocyclopropa[*c*]*bis*-cyclopropa[3,4]pyrano[6,5-*f*,6',5'-*h*]chromene-1,4,7-tricarboxylate (76)



Method A: To a solution of copper(II) triflate (17 mg, 46 μmol) in dichloromethane (15 mL) was added 2,2'-bipyridine (9 mg, 56 μmol) and the resultant solution was stirred at room temperature for 30 min. Phenylhydrazine (10 μL, 102 μmol) and chromene **30** (200 mg, 0.617 mmol) were then added. A solution of ethyl diazoacetate (**73**) (0.39 mL, 3.7 mmol) in dichloromethane (3 ml) was then added over the course of ~18 h *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 4 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **74** [57 mg, 22% (53% brsm)] as a colourless oil and the starting material (**30**) (117 mg, 58%).

Method B: To a stirred solution of copper(II) triflate (11 mg, 35 μmol) in dichloromethane (5 mL) was added 2,2'-bipyridine (7 mg, 42 μmol) and the resultant

solution was stirred at room temperature for 30 min. Phenylhydrazine (10 μL, 102 μmol) and chromene **30** (100 mg, 0.308 mmol) were then added. A solution of ethyl diazoacetate (**73**) (0.29 mL, 2.7 mmol) in dichloromethane (3 ml) was then added over the course of ~12 h *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 24 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. Purification by flash chromatography using hexanes:ether (5:1) as the eluant, using chloroform to load the column, afforded the *title compound* **74** (5 mg, 4%, [37% brsm]) as a colourless oil and the starting material (**30**) (90 mg, 90%).

Method C: To a stirred solution of copper(II) triflate (31 mg, 87 μmol) in anhydrous dichloromethane (12 mL) was added 2,2'-bipyridine (16 mg, 0.10 mmol) and the resultant solution was stirred at room temperature for 30 min. Phenylhydrazine (10 μL, 102 μmol) and chromene **30** (150 mg, 0.462 mmol) were then added. A solution of ethyl diazoacetate (**73**) (0.73 mL, 6.9 mmol) in dichloromethane (3 ml) was then added over the course of ~9 h *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 24 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **74** (30 mg, 16%) as a colourless oil and the *title compound* **75** (78 mg, 40%) as a pale yellow oil.

Method D: To a stirred solution of copper(II) triflate (21 mg, 58 μmol) in anhydrous dichloromethane (7 mL) was added 2,2'-bipyridine (11 mg, 69 μmol) and the resultant solution was stirred at room temperature for 30 min. Phenylhydrazine (10 μL, 102 μmol) and chromene **30** (100 mg, 0.31 mmol) were then added. A solution of ethyl diazoacetate (**73**) (0.49 mL, 4.6 mmol) in dichloromethane (3 ml) was then added over

the course of ~24 h *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 13 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. Purification by flash chromatography using hexanes:ether (9:1) followed by hexanes:ether (2:1) as the eluant, using chloroform to load, afforded the *title compound* **74** (6 mg, 6%) as a colourless oil, the *title compound* **75** (37 mg, 26%) as a pale yellow oil and the *title compound* **76** (28 mg, 22%) as a colourless oil.

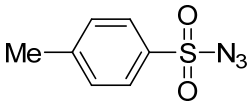
Title compound **74**: $\mathbf{R_f}$ = 0.34, hexanes:ether (5:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.22 (s, 3H, *Me*), 1.26 (t, *J* = 7.2 Hz, 3H, CH_2*Me*), 1.33 (s, 3H, *Me*), 1.38 (s, 3H, *Me*), 1.43 (s, 3H, *Me*), 1.44 (s, 3H, *Me*), 1.50 (s, 3H, *Me*), 2.01-2.06 (m, 2H, *H*-10a & *H*-11), 2.84 (dd, *J* = 9.3, 3.6 Hz, 1H, *H*-11a), 4.11-4.19 (m, 2H, C*H*$_2$Me), 5.41 (d, *J* = 9.9 Hz, 1H, ArCH-), 5.45 (d, *J* = 9.8 Hz, 1H, ArCH-), 6.49 (d, *J* = 9.8 Hz, 1H, ArCH-), 6.60 (d, *J* = 9.8 Hz, 1H, ArCH); **Observed nOe contacts** *H*-10a to *H*-11a, *H*-11 to *H*-10a, *H*-11 to *H*-11a; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 14.2, 18.3, 24.5, 25.5, 27.1, 27.4, 28.0, 28.2, 34.4, 60.5, 72.2, 76.1, 76.4, 103.8, 104.3, 104.8, 116.6, 116.7, 126.3, 126.5, 133.6, 147.3, 147.4, 151.1, 172.9; **IR** (ef) 2974, 2923, 1721, 1635, 1600, 1454, 1364, 1302, 1177, 1132 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 411 (M + H, 20); **Anal.** Calcd. for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.19; H, 7.53; **HRMS** Calcd. for $C_{25}H_{31}O_5$: 411.2166. Found: 411.2164.

Title compound **75**: $\mathbf{R_f}$ = 0.29, hexanes:ether (2:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.157 (s, 3H, *Me*), 1.209 (s, 3H, *Me*), 1.25–1.28 (m, 6H, CH_2*Me*), 1.35 (s, 3H, *Me*), 1.42 (s, 3H, *Me*), 1.486 (s, 3H, *Me*), 1.51 (s, 3H, *Me*), 1.98-2.09 (m, 4H, *H*-6a; *H*-7; *H*-9a, *H*-10), 2.72-2.74 (m, 1H, *H*), 2.86-2.88 (m, 1H, *H*), 4.12-4.19 (m, 4H, C*H*$_2$Me), 5.43 (d, *J* = 9.9 Hz, 1H, ArC*H*-3), 6.49 (d, *J* = 9.9 Hz, 1H, ArC*H*-4); **^{13}C NMR** (151 MHz, $CDCl_3$)

δ 14.20, 14.21, 18.28, 18.31, 24.4, 24.5, 25.38, 25.39, 27.4, 28.0, 28.1, 28.12, 34.6, 34.7, 60.5, 60.6, 71.9, 72.2, 76.1, 105.0, 105.5, 105.7, 116.6, 127.0, 145.5, 149.3, 149.4, 172.9, 173.0; **IR** (ef) 2977, 2934, 2912, 1723, 1638, 1610, 1467, 1365, 1321, 1300, 1263, 1179, 1151, 1130 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 498 (24), 497 (M + H, 100), 451 (M – C_2H_5O, 16); **HRMS** Calcd. for $C_{29}H_{37}O_7$: 497.2534. Found: 497.2538.

Title compound **76**: $\mathbf{R_f}$ = 0.21, hexanes:ether (2:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.15 (s, 3H, *Me*), 1.16 (s, 3H, *Me*), 1.19 (s, 3H, *Me*), 1.24-1.29 (m, 9H, CH_2*Me*), 1.476 (s, 3H, *Me*), 1.482 (s, 3H, *Me*), 1.492 (s, 3H, *Me*), 1.98-2.06 (m, 6H, C*H*), 2.74 (dd, *J* = 8.7, 4.2 Hz, 1H, C*H*), 2.79 (apparent dd, *J* = 9.3, 3.6 Hz, 3H, C*H*), 4.11-4.20 (m, 6H, C*H*$_2$Me); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 14.2, 18.3, 24.5, 25.5, 27.1, 27.4, 28.0, 28.2, 34.4, 60.5, 72.2, 76.1, 76.4, 103.8, 104.3, 104.8, 116.6, 116.7, 126.3, 126.5, 133.6, 147.3, 147.4, 151.1, 172.9; **IR** (ef) 2977, 2933, 1721, 1613, 1468, 1422, 1366, 1298, 1178, 1152, 1126 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 584 (31), 583 (M + H, 100), 537 (M – C_2H_5O, 34); **HRMS** Calcd. for $C_{33}H_{43}O_9$: 583.2902. Found: 583.2897.

8.3.5 *p*-Toluenesulphonyl azide (77)[41]

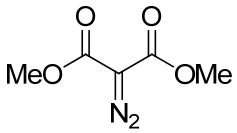


77

To a mixture of *p*-toluenesulphonyl chloride (**78**) (3.00 g, 15.7 mmol), acetone (50 mL) and water (50 mL) was added sodium azide (1.02 g, 15.7 mmol) at 0 °C. The resultant mixture was allowed to warm to room temperature over 2 h. The excess acetone was then removed *in vacuo* and the resultant aqueous solution was extracted with ether (2 x 100 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford the

title compound **77** (2.75 g, 89%) as a colourless oil. $\mathbf{R_f}$ = 0.43, hexanes:ether (3:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.48 (s, 3H, *Me*), 7.41 (apparent d, *J* = 8.2 Hz, 2H, Ar*H*), 7.84 (dd, *J* = 8.3, 1.8 Hz, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 21.8, 127.5, 130.2, 135.4, 146.2; **IR** (neat) 3067, 2926, 2871, 2349, 2126, 1595, 1494, 1451, 1399, 1371, 1297, 1169, 1086 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 155 (M – N_3, 100).

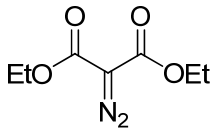
8.3.6 1,3-Dimethyl-2-diazopropanedioate (80)[42]



80

To a solution of *p*-toluenesulphonyl azide (**77**) (2.24 g, 11.4 mmol) and dimethyl malonate (**79**) (1.50 g, 11.4 mmol) in acetonitrile (30 mL) was added triethylamine (1.75 mL, 12.5 mmol) dropwise at room temperature. The resultant solution was allowed to stir for 17 h and then the solvent was removed *in vacuo*. The resultant solid was partitioned between dichloromethane (40 mL) and water (40 mL) and stirred at room temperature for 1 h. The two phases were then separated and the organic phase was washed with water (2 x 50 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (1:1) as the eluant afforded the *title compound* **80** (1.39 g, 77%) as a light yellow oil. $\mathbf{R_f}$ = 0.34, hexanes:ethyl acetate (1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.80 (s, 6H, O*Me*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 52.4, 161.3; **IR** (ef) 3006, 2958, 2849, 2139, 1762, 1741, 1694, 1439, 1355, 1334, 1276, 1191, 1098 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 159 (M + H, 100), 132 (M – N_2, 41).

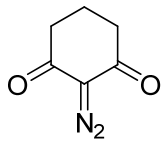
8.3.7 1,3-Diethyl-2-diazopropanedioate (82)[44]



82

To a solution of *p*-toluenesulphonyl azide (**77**) (1.85 g, 9.38 mmol) and diethyl malonate (**81**) (1.50 g, 9.37 mmol) in acetonitrile (35 mL) was added triethylamine (1.45 mL, 10.3 mmol) dropwise at room temperature. The resultant solution was allowed to stir for 17 h and then the solvent was removed *in vacuo*. The resultant solid was partitioned between dichloromethane (40 mL) and water (40 mL) and stirred at room temperature for 1 h. The two phases were then separated and the organic phase was washed with water (2 x 50 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* **82** (0.48 g, 28%) as a light yellow oil. $\mathbf{R_f}$ = 0.43, hexanes:ethyl acetate (2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 6H, *Me*), 4.28 (q, J = 7.6 Hz, 4H, OCH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 14.3, 61.5, 161.0; **IR** (ef) 2984, 2939, 2907, 2139, 1760, 1736, 1691, 1466, 1447, 1395, 1372, 1321, 1269, 1198, 1170, 1093 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 187 (M + H, 100), 159 (M – N_2, 35).

8.3.8 2-Diazocyclohexane-1,3-dione (84)[43]

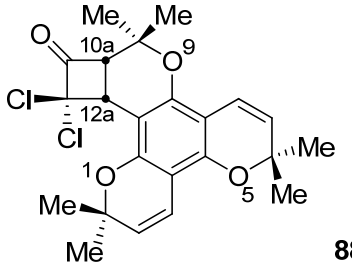


84

To a solution of *p*-toluenesulphonyl azide (**77**) (1.68 g, 8.55 mmol) and cyclohexa-1,3-dione (**83**) (959 mg, 8.55 mmol) in acetonitrile (30 mL) was added triethylamine (1.30 mL, 9.41 mmol) dropwise at room temperature. The resultant

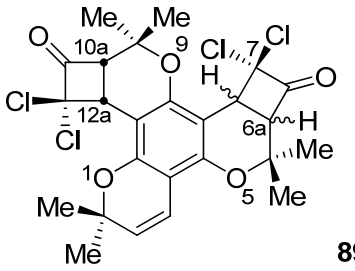
solution was allowed to stir for 14 h after which the solvent was removed *in vacuo*. The resultant oil was partitioned in dichloromethane (30 mL) and water (30 mL) and stirred at room temperature for 1 h. The two phases were then separated and the organic phase was washed with water (2 x 50 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (1:4) as the eluant afforded the *title compound* **84** (1.39 g, 77%) as a viscous yellow oil. $\mathbf{R}_f$ = 0.31, hexanes:ethyl acetate (1:4); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.03 (quintet, J = 6.4 Hz, 2H, CH_2), 2.55 (t, J = 6.6 Hz, 4H, C(O)CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 18.6, 36.8, 190.4; **IR** (ef) 2958, 2902, 2195, 2133, 1645, 1460, 1418, 1350, 1316, 1287 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 111 (M – N_2, 27), 85 (100).

8.3.9 (10a*SR*,12c*RS*)-12,12-Dichloro-2,2,6,6,10,10-hexamethyl-10,10a,12,12a-tetrahydro-2*H*,6*H*,11*H*-cyclobuta[*c*]dipyrano[6,5-*f*,6',5'-*h*]chromen-11-one (88) and (6a*SR*,8a*RS*,10a*SR*,12c*RS*)-8,8,12,12-tetrachloro-2,2,6,6,10,10-hexamethyl-6,6a,8,8a,10,10a,12,12a-octahydro-2*H*,7*H*,11*H*-cyclobuta[*c*]-cyclobuta[3,4]pyrano[6,5-*f*]pyrano[6,5-*h*]chromene-7,11-dione (89)



88

+



89

Method A: To a suspension of zinc powder (320 mesh, 204 mg, 3.12 mmol) and chromene **30** (75 mg, 0.23 mmol) in tetrahydrofuran (7 mL) at –78 °C was added trichloroacetyl chloride (0.23 mL, 2.1 mmol) dropwise over ~2 min. The resultant suspension was stirred at -78 °C for 15 min then was allowed to warm to room temperature and stirred for an additional 23 h. A saturated aqueous solution of sodium bicarbonate (1 mL) was then added and the reaction mixture was stirred for 1 h. The

resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 20 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 20 mL), water (2 x 15 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:dichloromethane (3:2) as the eluant afforded the *title compound* **88** [27 mg, 27% (38% brsm)] as a white solid and *title compound* **89** [4 mg, 5% (8% brsm)] as a white solid and the starting material (**30**) (5 mg, 2%).

Method B: To a suspension of zinc powder (320 mesh, 109 mg, 1.67 mmol) and chromene **30** (40 mg, 0.12 mmol) in tetrahydrofuran (5 mL) at 0 °C was added trichloroacetyl chloride (0.12 mL, 1.1 mmol) dropwise over ~1 min. The resultant suspension was stirred at 0 °C for 2 h and then was allowed to warm to room temperature and stirred for an additional 16 h. A saturated aqueous solution of sodium bicarbonate (1 mL) was then added and the reaction mixture was stirred for 30 min. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 10 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 15 mL), water (2 x 15 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:dichloromethane (3:2) as the eluant afforded the *title compound* **88** (7 mg, 14%) as a white solid.

Method C: To a suspension of zinc powder (320 mesh, 109 mg, 1.67 mmol) and chromene **30** (40 mg, 0.12 mmol) in tetrahydrofuran (5 mL) at room temperature was added trichloroacetyl chloride (0.12 mL, 1.1 mmol) dropwise over ~2 min. The resultant suspension was stirred for an additional 15 h. A saturated aqueous solution of sodium

bicarbonate (1 mL) was then added and the reaction mixture was stirred for 1 h. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 15 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 20 mL), water (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:dichloromethane (3:2) as the eluant afforded the *title compound* **88** (8 mg, 15%) as a white solid and the *title compound* **89** (3 mg, 4%) as a white solid.

Method D: To a suspension of zinc powder (320 mesh, 272 mg, 4.16 mmol) and chromene **30** (60 mg, 0.19 mmol) in tetrahydrofuran (8 mL) at 0 °C was added trichloroacetyl chloride (0.31 mL, 2.8 mmol) dropwise over ~2 min. The resultant suspension was stirred at 0 °C for 15 min and then was allowed to warm to room temperature and stirred for an additional 21 h. A saturated aqueous solution of sodium bicarbonate (1 mL) was then added and the reaction mixture was stirred for 1 h. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 25 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 25 mL), water (2 x 25 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **88** (23 mg, 29%) as a white solid and the *title compound* **89** (15 mg, 21%) as a white solid.

Method E: To a suspension of zinc powder (320 mesh, 272 mg, 4.16 mmol) and chromene **30** (60 mg, 0.19 mmol) in tetrahydrofuran (8 mL) at room temperature was added trichloroacetyl chloride (0.31 mL, 2.8 mmol) dropwise over ~2 min. The resultant suspension was stirred for an additional 21 h. A saturated aqueous solution of sodium

bicarbonate (1 mL) was then added and then reaction mixture was stirred for 1 h. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 25 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 25 mL), water (2 x 25 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant, using chloroform to load the column, afforded the *title compound* **88** (4 mg, 5%) as a white solid and the *title compound* **89** (28 mg, 29%) as a white solid.

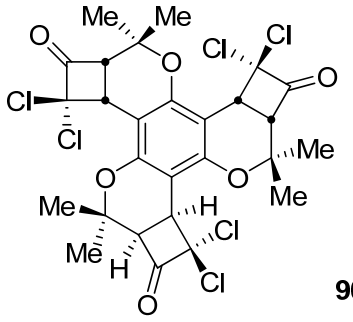
Method F: To a suspension of zinc powder (320 mesh, 70 mg, 1.1 mmol) and the *mono*-cycloadduct **88** (31 mg, 0.071 μmol) in tetrahydrofuran (8 mL) at 0 °C was added a solution of trichloroacetyl chloride (0.08 mL, 0.7 μmol) in tetrahydrofuran (1 mL) dropwise over ~2 min. The resultant suspension was then allowed to warm to room temperature and stirred for an additional 2 h. The resultant suspension was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 10 mL). The combined filtrates were washed with water (2 x 10 mL), a saturated aqueous solution of sodium bicarbonate (15 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **89** (16 mg, 40%) as a white solid

Title compound **88**: $\mathbf{R_f}$ = 0.38, hexanes:ether (9:1); **M.p.** 178-180 °C, hexanes:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.16 (s, 3H, *Me*), 1.39 (s, 3H, *Me*), 1.42 (s, 3H, *Me*), 1.46 (s, 3H, *Me*), 1.47 (s, 3H, *Me*), 1.68 (s, 3H, *Me*), 3.95 (d, *J* = 11.0 Hz, 1H, *H*-10a), 4.33 (d, *J* = 11.1 Hz, 1H, *H*-12a), 5.41 (d, *J* = 9.9 Hz, 1H, ArCHC*H*), 5.46 (d, *J* = 10.0 Hz, 1H, ArCHC*H*), 6.50 (d, *J* = 9.9 Hz, 1H, ArC*H*CH), 6.61 (d, *J* = 9.9 Hz, 1H,

ArC*H*CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.7, 25.9, 27.6, 28.2, 28.6, 28.8, 42.3, 62.0, 75.2, 76.6, 77.3, 87.5, 100.3, 103.8, 104.6, 116.2, 116.6, 125.9, 126.0, 149.0, 149.4, 152.6, 194.8; **IR** (ef) 2974, 2929, 2865, 1803, 1635, 1600, 1551, 1448, 1365, 1306, 1133, 1090, 1037, 999 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 440 [M (2 x ^{37}Cl) + H, 2], 439 (11), 438 [M (^{35}Cl + ^{37}Cl) + H, 11], 437 (64), 436 [M (2 x ^{35}Cl) + H, 100]; **Anal.** Calcd. for $C_{23}H_{24}Cl_2O_4$: C, 63.46; H, 5.56. Found: C, 63.74; H, 5.83.

Title compound **89**: $\mathbf{R_f}$ = 0.23, hexanes:ether (9:1); **M.p.** 190-192 °C, hexanes:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.11 (s, 3H, *Me*), 1.30 (s, 3H, *Me*), 1.46 (s, 3H, *Me*), 1.49 (s, 3H, *Me*), 1.67 (s, 3H, *Me*), 1.73 (s, 3H, *Me*), 3.91 (d, *J* = 11.3 Hz, 1H, C*H*), 4.03 (d, *J* = 11.0 Hz, 1H, C*H*), 4.36 (d, *J* = 11.0 Hz, 1H, C*H*), 4.39 (d, *J* = 11.3 Hz, 1H, C*H*), 5.44 (d, *J* = 10.0 Hz, 1H, ArCHC*H*), 6.52 (d, *J* = 10.1 Hz, 1H, ArC*H*CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.6, 25.9, 26.0, 26.2, 28.6, 29.1, 42.0, 42.2, 61.8, 62.8, 75.6, 75.7, 77.7, 87.4, 87.9, 100.8, 102.2, 105.1, 115.8, 126.2, 149.9, 152.1, 153.2, 194.4, 195.1; **IR** (ef) 2977, 2929, 2858, 1803, 1628, 1607, 1558, 1454, 1384, 1364, 1301, 1210, 1132, 1090 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 553 [M (4 x ^{37}Cl) + H, 4], 552 (4), 551 [M (^{35}Cl + 3 x ^{37}Cl) + H, 17], 550 (16), 549 [2 x ^{35}Cl + 2 x ^{37}Cl) + H, 64], 548 (100), 547 [M (3 x ^{35}Cl + ^{37}Cl) + H, 51]; **Anal.** Calcd. for $C_{25}H_{24}Cl_4O_5$: C, 54.97; H, 4.43. Found: C, 54.84; H, 4.47.

8.3.10 (2a*SR*,4c*RS*,6a*SR*,8c*SR*,10a*RS*,12c*RS*)-1,1,5,5,9,9-Hexachloro-3,3,7,7,11,11-hexamethyl-1,2a,3,4c,5,6a,7,8c,9,10a,11,12c-dodecahydro-2*H*,6*H*,10*H*-cyclobuta[*c*]*bis*-cyclobuta[3,4]pyrano[6,5-*f*,6',5'-*h*]chromene-2,6,10-trione (90)

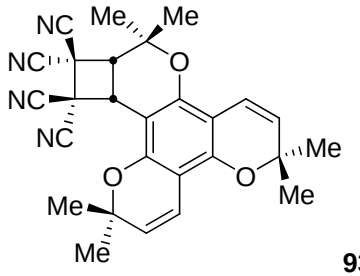


90

To a suspension of zinc powder (320 mesh, 218 mg, 3.33 mmol) and chromene **30** (80 mg, 0.25 mmol) in tetrahydrofuran (8 mL) at room temperature was added a solution of trichloroacetyl chloride (0.25 mL, 2.2 mmol) in tetrahydrofuran (3 mL) dropwise *via* syringe pump over 12 h. A saturated aqueous solution of sodium bicarbonate (1 mL) was then added and the reaction mixture was stirred for 30 min. The resultant mixture was filtered through a small pad of celite and the filter-cake was washed with ether (2 x 10 mL). The combined filtrates were washed with a saturated aqueous solution of sodium bicarbonate (2 x 20 mL), water (20 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) the eluant, with chloroform to load, afforded the *title compound* **90** (98 mg, 60%) as a white solid. $\mathbf{R}_f$ = 0.25, hexanes:ether (2:1); **M.p.** 245 °C (dec.), hexanes:ether; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.16 (s, 3H, *Me*), 1.28 (s, 3H, *Me*), 1.29 (s, 3H, *Me*), 1.73 (s, 3H, *Me*), 1.74 (s, 3H, *Me*), 1.75 (s, 3H, *Me*), 3.97 (d, *J* = 11.3 Hz, 1H, C*H*), 4.01 (d, *J* = 11.3 Hz, 1H, C*H*), 4.07 (d, *J* = 10.7 Hz, 1H, C*H*), 4.23 (d, *J* = 10.7 Hz, 1H, C*H*), 4.43 (d, *J* = 11.3 Hz, 1H, C*H*), 4.44 (d, *J* = 11.3 Hz, 1H, C*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.88, 25.9, 26.0, 26.2, 26.4, 41.9, 42.0, 61.3, 62.5, 62.8, 75.6, 76.15, 76.16, 87.0, 87.7, 87.8,

102.1, 102.6, 103.9, 152.5, 153.2, 153.9, 193.4, 194.4, 194.6; **IR** (ef) 2981, 2938, 1804, 1611, 1454, 1389, 1372, 1301, 1243, 1209, 1130, 1077, 1040 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 660 (3), 659 [M (4 x ^{35}Cl + 2 x ^{37}Cl) + H, 7], 658 (4), 657 [M (5 x ^{35}Cl + ^{37}Cl) + H, 8], 655 [M (6 x ^{35}Cl) + H, 4], 624 [M – Cl, 15], 622 [M – Cl, 20], 620 [M – Cl, 10], 588 (21), 586 (16), 552 (11); **Anal.** Calcd. for $C_{27}H_{24}Cl_6O_6$: C, 49.34; H, 3.68. Found: C, 49.45; H, 3.94.

8.3.11 (10a*SR*,12a*RS*)-2,2,6,6,10,10-Hexamethyl-10a,12a-dihydro-2*H*,6*H*-cyclobuta[*c*]dipyrano[6,5-*f*,6',5'-*h*]chromene-11,11,12,12-tetracarbonitrile (93)

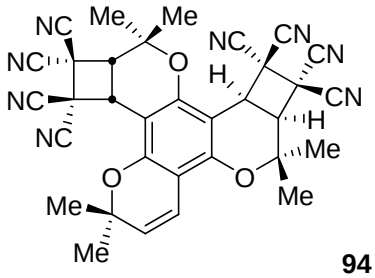


93

A solution of chromene **30** (250 mg, 0.771 mmol) and tetracyanoethylene (395 mg, 3.08 mmol) in acetonitrile (15 mL) was heated at reflux for 5 min and then allowed to cool to room temperature. A saturated aqueous solution of ammonium chloride (15 mL) was then added to the reaction mixture. The aqueous phase was then separated and extracted with ether (2 x 10 mL). The organic extracts were combined and washed with water (2 x 15 mL), brine (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **93** (66 mg, 29%) as a white solid. $\mathbf{R_f}$ = 0.36, hexanes:ether (1:1); **M.p.** 215-217 °C, hexanes:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.23 (s, 3H, *Me*), 1.42 (s, 3H, *Me*), 1.43 (s, 3H, *Me*), 1.44 (s, 3H, *Me*), 1.55 (s, 3H, *Me*), 1.68 (s, 3H, *Me*), 3.58 (d, *J* = 9.7 Hz, 1H, C*H*), 4.34 (d, *J* = 9.7 Hz, 1H, C*H*), 5.45

(apparent t, *J* = 10.0 Hz, 2H, ArCHC*H*), 6.55 (d, *J* = 10.0 Hz, 1H, ArC*H*CH), 6.57 (d, *J* = 10.1 Hz, 1H, ArCHC*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 23.9, 24.1, 27.9, 28.4, 29.2, 29.3, 36.5, 38.8, 39.4, 48.2, 73.0, 77.3, 79.1, 92.3, 103.9, 104.5, 108.4, 108.7, 111.1, 111.3, 115.3, 115.9, 125.9, 126.6, 148.3, 151.2, 152.2; **IR** (ef) 2973, 2924, 2851, 1646, 1635, 1597, 1465, 1460, 1364, 1352, 1246, 1172, 1133, 1005 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 325 (M – C_6N_4, 100); **Anal.** Calcd. for $C_{27}H_{24}N_4O_3$: C, 71.67; H, 5.35; N, 12.38. Found: C, 71.84; H, 5.34; N, 12.48.

8.3.12 (6a*SR*,8a*RS*,10a*SR*,12a*RS*)-2,2,6,6,10,10-Hexamethyl-6a,8a,10a,12a-tetrahydro-2*H*-cyclobuta[c]-cyclobuta[3,4]pyrano[6,5-*f*]pyrano[6',5'-*h*]chromene-7,7,8,8,11,11,12,12-octacarbonitrile (94)



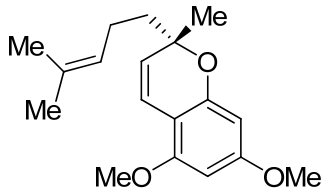
94

A solution of chromene **30** (77 mg, 0.24 mmol) and tetracyanoethylene (275 mg, 2.14 mmol) in acetonitrile (15 mL) was heated at reflux for 24 hours and then allowed to cool to room temperature and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the *title compound* **94** (58 mg, 42%) as a white solid. $\mathbf{R_f}$ = 0.32, hexanes:ethyl acetate (3:1); **M.p.** 240-242 °C, hexanes:ethyl acetate; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.08 (s, 3H, *Me*), 1.34 (s, 3H, *Me*), 1.43 (s, 3H, *Me*), 1.57 (s, 3H, *Me*), 1.68 (s, 3H, *Me*), 1.69 (s, 3H, *Me*), 4.06 (d, *J* = 10.3 Hz, 1H, C*H*), 4.15 (d, *J* = 9.7 Hz, 1H, C*H*), 4.51 (d, *J* = 10.3 Hz, 1H, C*H*), 4.56 (d, *J* = 9.7 Hz, 1H, C*H*), 5.63 (d, *J* = 10.2 Hz, 1H, ArCHC*H*), 6.58 (d, *J* = 10.2 Hz,

1H, ArC*H*CH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.3, 23.4, 24.1, 24.2, 28.8, 29.3, 37.3, 37.5, 38.7, 39.4, 39.6, 39.8, 47.9, 48.3, 75.6, 76.4, 80.4, 96.1, 96.9, 106.1, 110.0, 110.6, 110.8, 110.9, 112.08, 112.10, 112.5, 114.9, 128.1, 151.9, 153.0, 155.2; **IR** (KBr) 2983, 2933, 2248, 1642, 1605, 1469, 1395, 1377, 1171, 1133 cm^{-1}; **MS** (ESI) *m/z* (rel. intensity) 581 (M + H, 100); **HRMS** Calcd. for $C_{33}H_{25}N_8O_3$: 581.2049. Found: 581.2027.

8.4 Experimental Procedures and Characterization Data Concerning Chapter Four

8.4.1 (2*SR*)-5,7-Dimethoxy-2-methyl-2-(4'-methylpent-3'-enyl)-2*H*-chromene (97)

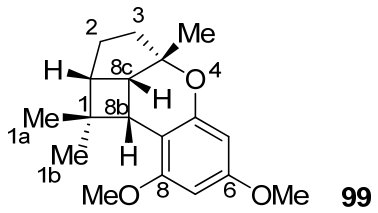


97

A mixture of citral (**31**) (*E*:*Z* = ~2:1, 1.1 mL, 6.3 mmol), 3,5-dimethoxyphenol (**39**) (750 mg, 4.86 mmol), phenylboronic acid (590 mg, 4.86 mmol), propionic acid (30 drops) and benzene (30 mL) was heated at reflux in a Dean-Stark apparatus for 2.5 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **97** (1.32 g, 94%) as a colourless oil. $\mathbf{R_f}$ = 0.33, hexanes:ether (8:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.38 (s, 3H, *Me*), 1.59 (s, 3H, *Me*), 1.64 (m, 1H, CH_2), 1.67 (s, 3H, *Me*), 1.73 (m, 1H, C$H_{2\text{-}\alpha}$), 2.11 (m, 2H, C$H_{2\text{-}\beta}$), 3.76 (s, 3H, O*Me*), 3.79 (s, 3H, O*Me*), 5.10 (m, 1H, C*H*), 5.38 (d, *J* = 9.8 Hz, 1H, ArCHC*H*), 5.99 (m, 1H, Ar*H*), 6.03 (m, 1H, Ar*H*), 6.61 (d,

J = 9.8 Hz, 1H, ArC*H*CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.6, 22.7, 25.7, 26.3, 41.0, 55.3, 55.5, 78.5, 91.2, 93.8, 103.9, 117.1, 124.2, 124.7, 131.5, 154.8, 156.0, 160.9; **IR** (ef) 2970, 2940, 2842, 1613, 1578, 1495, 1456, 1381, 1202, 1148, 1115 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 289 (M + H, 100); **HRMS** Calcd. for $C_{18}H_{25}O_3$: 289.1798. Found: 289.1789.

8.4.2 (1a*RS*,8b*SR*,8c*SR*)-6,8-Dimethoxy-1,1,3a-trimethyl-1a,2,3,3a,8b,8c-hexahydro-1*H*-bicyclo[3.2.0]hept-5-eno[4,5,6-bc]chromene (99)



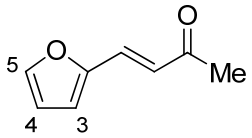
99

Method A: A solution of the chromene **97** (25 mg, 0.08 mmol) and benzophenone (16 mg, 0.08 mmol) in benzene (6 mL) was deoxygenated by purging with dry nitrogen for 20 minutes at room temperature. The quartz flask was then sealed and irradiated using a Hanovia 450 W high-pressure mercury lamp for 2 h. The reaction mixture was then concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **99** (14 mg, 57%) as a white solid.

Method B: A solution of the chromene **97** (35 mg, 0.12 mmol) in acetone (7 mL) was deoxygenated by purging with dry nitrogen for 25 minutes at room temperature. The quartz flask was then sealed and irradiated using a Hanovia 450 W high-pressure mercury lamp for 24 h. The reaction mixture was then concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **99** (9 mg, 26%) as a white solid. $\mathbf{R}_f$ = 0.29, hexanes:ether (8:1); **M.p.** 104-106 °C,

hexanes:ether (lit.[46] 107-108 °C, hexanes); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.70 (s, 3H, *Me*-1b), 1.32 (s, 3H, *Me*-1a), 1.38 (s, 3H, *Me*-3a), 1.56 – 1.68 (m, 3H, C*H*$_2$-C*H*-2a), 1.97 (m, 1H, C*H*-2b), 2.36 (apparent t, *J* = 7.4 Hz, 1H, C*H*-1a), 2.54 (dd, *J* = 9.6, 7.4 Hz, 1H, C*H*-8c), 3.03 (d, *J* = 9.6 Hz, 1H, C*H*-8b), 3.73 (s, 3H, O*Me*), 3.76 (s, 3H, O*Me*), 6.04 (d, *J* = 2.3 Hz, 1H, Ar*H*), 6.07 (d, *J* = 2.3 Hz, 1H, Ar*H*); **Observed nOe contacts** *H*-8b to *H*-8c, *H*-8b to *Me*-1a, *H*-8c to *H*-1a, *H*-8c to *Me*-3a, *H*-1a to *Me*-1a, *H*-1a to *H*-2a, *H*-1a to *H*-8b, *Me*-1b to C*H*-2b, *Me*-1b to C*H*$_2$-3, *Me*-1b to *Me*-1a; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 17.7, 25.7, 27.8, 33.7, 36.1, 37.7, 37.8, 38.9, 46.3, 55.0, 55.3, 83.5, 91.4, 94.4, 105.4, 154.3, 159.0, 159.4; **IR** (ef) 2943, 2865, 2839, 1615, 1589, 1558, 1494, 1457, 1419, 1371, 1216, 1202, 1146, 1111 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 289 (M + H, 100); **Anal.** Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.13; H, 8.18.

8.4.3 (3*E*)-4-(Furan-2'-yl)but-3-en-2-one (102)[47]

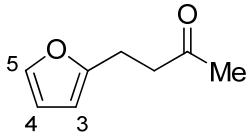


102

An ice cold aqueous solution of sodium hydroxide (12 M, 6.0 mL) was slowly added to a mixture of freshly distilled furfural (**100**) (44.1 g, 459 mmol), acetone (**101**) (67.5 mL, 918 mmol) and water (200 mL) at room temperature. The resultant mixture was stirred at room temperature for 23 h and then sulphuric acid (10% v/v, 50 mL) was added dropwise. The organic layer was then separated and direct purification of the crude product by distillation at reduced pressure afforded the *title compound* **102** (35.5 g, 57%) as a light yellow oil which solidified on standing. $\mathbf{R_f}$ = 0.31, hexanes:ethyl acetate (2:1); **M.p.** 32-34 °C, (lit. 37-39 °C); **B.p.** ~173 °C, ~35 mm Hg (lit. ~116 °C, ~10 mm

Hg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.32 (s, 3H, *Me*), 6.47 (dd, *J* = 3.4, 1.9 Hz, 1H, Ar*H*-4), 6.61 (d, *J* = 15.9 Hz, 1H, C*H*), 6.66 (apparent d, *J* = 3.4 Hz, 1H, Ar*H*-3), 7.27 (d, *J* = 15.9 Hz, 1H, C*H*), 7.49 (apparent d, *J* = 1.3 Hz, 1H, Ar*H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.9, 112.5, 115.6, 124.3, 129.4, 144.9, 150.9, 197.8; **IR** (ef) 3000, 2950, 2920, 1687, 1664, 1611, 1553, 1475, 1388, 1358, 1302, 1270, 1252, 1206, 1170 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 137 (M + H, 100).

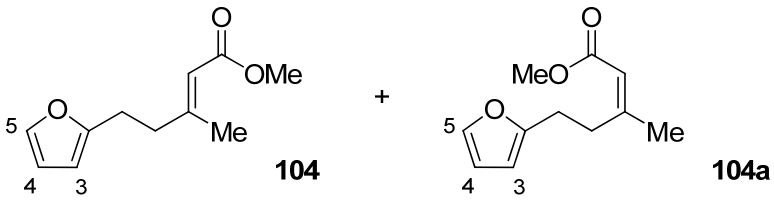
8.4.4 4-(Furan-2'-yl)butan-2-one (103)[48]



103

A mixture of the ketone **102** (29.9 g, 220 mmol), palladium on charcoal (1.69 g, 10% w/w) in ethyl acetate (200 mL) under an atmosphere of hydrogen (balloon pressure) was stirred at room temperature for 17 h. The resultant mixture was filtered through a pad of celite and the filter-cake was washed with ethanol (4 x 40 mL). The combined filtrates were then concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* **103** (20.9 g, 69%) as a pale yellow oil. $\mathbf{R_f}$ = 0.35, hexanes:ethyl acetate (2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.15 (s, 3H, *Me*), 2.77 (t, *J* = 7.7 Hz, 2H, CH_2), 2.90 (t, *J* = 7.7 Hz, 2H, CH_2), 5.98 (m, 1H, Ar*H*-3), 6.25 (m, 1H, Ar*H*-4), 7.28 (m, 1H, Ar*H*-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.2, 29.9, 41.7, 105.2, 110.2, 141.0, 154.5, 207.2; **IR** (neat) 3118, 3001, 2910, 2850, 1717, 1667, 1597, 1507, 1362, 1232, 1164, 1079, 1007 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 139 (M + H, 100), 43 (15).

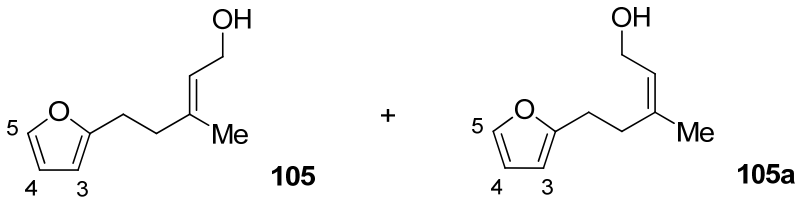
8.4.5 Methyl-(2*E*)-5-(furan-2'-yl)-3-methylpent-2-enoate (104) and Methyl-(2*Z*)-5-(furan-2'-yl)-3-methylpent-2-enoate (104a)



To a suspension of sodium hydride (60% w/w in mineral oil, 5.45 g, 136 mmol) in tetrahydrofuran (40 mL) at room temperature was added a solution of trimethyl phosphonoacetate (19.6 mL, 136 mmol) followed by an additional portion of tetrahydrofuran (40 mL). The resultant mixture was stirred for 30 min and then a solution of the ketone **103** (15.0 g, 109 mmol) in tetrahydrofuran (10 mL) was added. The reaction mixture was then heated at reflux for 24 h and then cooled to room temperature. A saturated aqueous solution of ammonium chloride (20 mL) and water (25 mL) were then added. The aqueous layer was separated and extracted with ether (3 x 30 mL). The organic extracts were combined and washed with brine (50 mL), water (50 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (7:1) as the eluant afforded the *title compounds* **104** and **104a** as a mixture of isomers (*E*:*Z* = ~3:1, 17.7 g, 84%) as a pale yellow oil. $\mathbf{R_f}$ = 0.31, hexanes:ether (7:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.84 (s, 3H, *Z*-*Me*), 2.19 (s, 3H, *E*-*Me*), 2.49 (t, *J* = 8.7 Hz, 2H, *E*-CH_2), 2.80 (m, 4H, *E*&*Z*-CH_2), 2.95 (m, 2H, *Z*-CH_2), 3.68 (s, 3H, O*Me*), 5.69 (s, 1H, *Z*-C*H*), 5.71 (s, 1H, *E*-C*H*), 6.01 (apparent d, *J* = 2.0 Hz, 1H, *E*-Ar*H*-3), 6.02 (d, J = 3.1 Hz, 1H, *Z*-Ar*H*-3), 6.26 (m, 2H, *E*&*Z*-Ar*H*-4), 7.30 (m, 1H, *E*&*Z*-Ar*H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 18.7, 25.2, 26.1, 26.6, 31.6, 32.0, 39.0, 50.8, 50.9, 105.2, 105.3, 110.1, 115.7, 116.5, 140.9, 141.0,

154.5, 155.1, 158.6, 159.3, 166.5, 167.1; **IR** (neat) 3116, 2993, 2943, 2843, 1718, 1648, 1595, 1507, 1360, 1340, 1282, 1225, 1149, 1078 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 195 (M + H, 83), 163 (100); **Anal.** Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.69; H, 7.39.

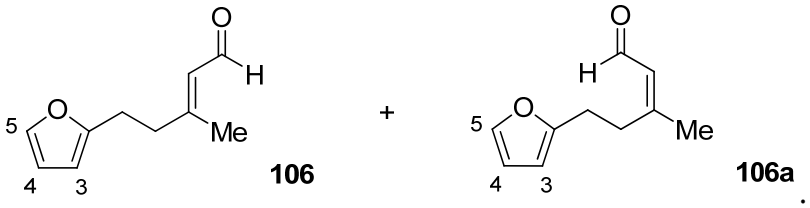
8.4.6 (2*E*)-5-(Furan-2'-yl)-3-methylpent-2-en-1-ol (105) and (2*Z*)-5-(Furan-2'-yl)-3-methylpent-2-en-1-ol (105a)



To a suspension of lithium aluminium hydride (2.93 g, 77.2 mmol) in ether (40 mL) at 0 °C was added a solution of the esters **104** and **104a** (12.0 g, 61.8 mmol) in ether (10 mL) and the reaction mixture was stirred at 0 °C for 90 min. Water (2.9 mL), an aqueous solution of sodium hydroxide (2 M, 2.9 mL) and water (8.7 mL) were then added sequentially, followed by addition of anhydrous magnesium sulphate. The resultant mixture was filtered through a pad of celite and the filter-cake was washed with ether (4 x 25 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:3) as the eluant afforded the *title compounds* **105** and **105a** as a mixture of isomers (*E*:*Z* = ~3:1, 8.76 g, 85%) as a colourless oil. $\mathbf{R_f}$ = 0.33, hexanes:ether (1:3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.39 (s, 1H, O*H*), 1.70 (s, 3H, *E-Me*), 1.76 (s, 3H, *Z-Me*), 2.36 (m, 2H, *E*-CH_2), 2.41 (m, 2H, *Z*-CH_2), 2.76 (m, 4H, *E*&*Z*-CH_2), 3.98 (d, J = 7.2 Hz, 2H, *Z*-CH_2OH), 4.14 (d, *J* = 6.9 Hz, 2H, *E*-CH_2OH) 5.43 (m, 2H, *E*&*Z*-C*H*) 5.98 (m, 2H, *E*&*Z*-Ar*H*-3), 6.27 (m, 2H, *E*&*Z*-Ar*H*-4), 7.29 (m, 2H, *E*&*Z*-Ar*H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.0, 23.0, 26.4, 26.4, 30.4,

37.6, 58.6, 58.9, 104.7, 105.2, 110.0, 110.0, 124.0, 125.3, 137.9, 138.1, 138.1, 140.7, 140.9, 155.1, 155.5; **IR** (neat) 3360, 2912, 2855, 1716, 1668, 1596, 1506, 1446, 1382, 1230, 1150, 1076 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 167 (M + H, 14), 149 (100); **Anal.** Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.38.

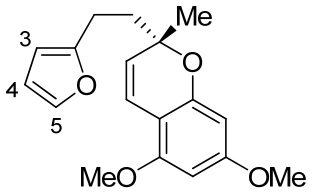
8.4.7 (2*E*)-5-(Furan-2'-yl)-3-methylpent-2-enal (106) and (2*Z*)-5-(Furan-2'-yl)-3-methylpent-2-enal (106a)



To a suspension of manganese dioxide (60.1 g, 690 mmol) in dichloromethane (180 mL) at room temperature was added a solution of the alcohols **105** and **105a** (8.14 g, 48.9 mmol) in dichloromethane (10 mL). After 14.5 h, the reaction mixture was filtered through a pad of celite and the filter-cake was washed with dichloromethane (4 x 50 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compounds* **106** and **106a** as a mixture of isomers (*E*:*Z* = ~3:1, 5.23 g, 65%) as a colourless oil. $\mathbf{R_f}$ = 0.27, hexanes:ether (2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.97 (s, 3H, *Z-Me*), 2.18 (s, 3H, *E-Me*), 2.56 (t, *J* = 7.9 Hz, 2H, *E*-CH_2), 2.86 (t, *J* = 7.3 Hz, 2H, *E*-CH_2), 2.89 (m, 4H, Z-CH_2CH_2), 5.89 (d, *J* = 8.0 Hz, 1H, C*H*) 6.01 (m, 2H, *E*&*Z*- Ar*H*-3), 6.27 (m, 2H, *E*&*Z*-Ar*H*-4), 7.31 (m, 2H, *E*&*Z*-Ar*H*-5), 9.75 (d, *J* = 8.1 Hz, 1H, *Z*-C*H*O), 9.99 (d, *J* = 8.1 Hz, 1H, *E*-C*H*O); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.4, 24.7, 25.7, 26.9, 31.2, 38.6, 105.5, 106.1, 110.1, 110.2, 127.6, 129.1, 141.1, 141.4, 153.4, 153.9, 161.9, 162.1, 190.4, 191.1;

IR (neat) 3117, 2918, 2854, 2770, 1672, 1634, 1507, 1439, 1381, 1195, 1153, 1121, 1076, 1009 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 165 (M + H, 100); **Anal.** Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.07; H, 7.20.

8.4.8 (2*SR*)-[2'-(Furan-2''-yl)ethyl]-5,7-dimethoxy-2-methyl-2*H*-chromene (98)

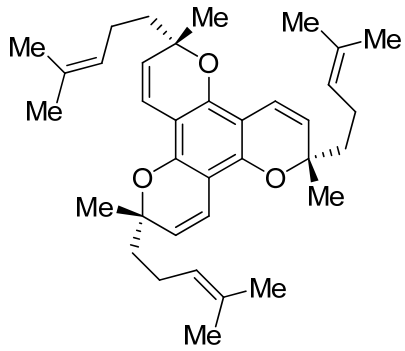


98

A mixture of the aldehydes **106** and **106a** (66 mg, 0.40 mmol), 3,5-dimethoxyphenol (**39**) (48 mg, 0.31 mmol), phenylboronic acid (38 mg, 0.31 mmol), propionic acid (10 drops) and benzene (12 mL) was heated at reflux in a Dean-Stark apparatus for 4 h. The resultant solution was cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **98** (38 mg, 41%) as a colourless oil. $\mathbf{R_f}$ = 0.34, hexanes:ether (8:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.41 (s, 3H, *Me*), 1.96-2.09 (m, 2H, C*H*$_2$), 2.67-2.89 (m, 2H, C*H*$_2$), 3.77 (s, 3H, O*Me*), 3.79 (s, 3H, O*Me*), 5.38 (d, *J* = 10.0 Hz, 1H, ArCHC*H*), 5.95-5.98 (m, 1H, Ar*H*-3), 6.00 (d, *J* = 2.3 Hz, 1H, Ar*H*), 6.03 (d, *J* = 2.3 Hz, 1H, Ar*H*), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H, Ar*H*-4), 6.65 (d, *J* = 10.0 Hz, 1H, ArC*H*CH), 7.28 (dd, *J* = 1.8, 0.8 Hz, 1H, Ar*H*-5); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 22.9, 26.4, 39.3, 55.3, 55.5, 78.1, 91.4, 93.8, 103.8, 104.6, 110.1, 117.6, 124.0, 140.7, 154.8, 156.0, 156.1, 161.1; **IR** (ef) 3000, 2959, 2938, 2835, 1613, 1578, 1496, 1465, 1454, 1202, 1148, 1114 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 301 (M + H, 100), 81 (2); **Anal.** Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.63; H, 6.76.

8.5 Experimental Procedures and Characterization Data Concerning Chapter Five

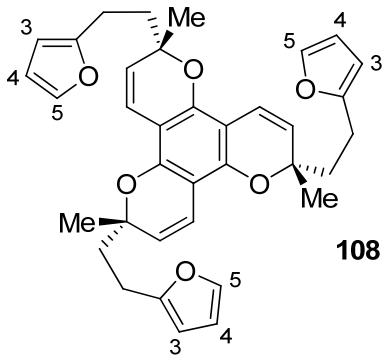
8.5.1 (2*SR*,6*SR*,10*SR*)-2,6,10-Trimethyl-2,6,10-tri-(4'-methylpent-3'-enyl)-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (32)[19]



32

A mixture of citral (**31**) (*E*:*Z* = ~2:1, 1.0 mL, 6.0 mmol), phloroglucinol (**27**) (190 mg, 1.51 mmol), phenylboronic acid (540 mg, 4.43 mmol), propionic acid (10 drops) and benzene (50 mL) was heated at reflux in a Dean-Stark apparatus for 4 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the *title compound* **32** (450 mg, 57%) as a light yellow oil. $\mathbf{R_f}$ = 0.37, hexanes:ether (99:1); **^{1}H NMR** (500 MHz, C_6D_6) δ 1.29 (apparent dd, *J* = 4.9, 1.8 Hz, 9H, *Me*), 1.51 (s, 9H, *Me*), 1.63 (s, 9H, *Me*), 1.69 (m, 6H, C*H*$_2$), 2.21 (m, 6H, C*H*$_2$), 5.12 (apparent d, *J* = 6.8 Hz, 3H, C*H*CMe$_2$), 5.21 (d, *J* = 10.0 Hz, 3H, ArCHC*H*), 6.92 (d, *J* = 10.1 Hz, 3H, ArC*H*CH); **^{13}C NMR** (126 MHz, C_6D_6) δ17.6, 23.2, 25.8, 26.5, 41.5, 79.1, 103.5, 117.8, 124.8, 124.9, 131.3, 150.1; **IR** (ef) 2969, 2924, 2851, 1639, 1593, 1451, 1375, 1214, 1152, 1129, 1076, 1000 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 529 (M + H, 58), 279 (100).

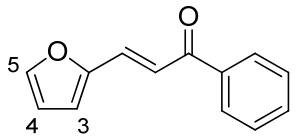
8.5.2 (2*SR*,6*SR*,10*SR*)-2,6,10-*Tris*-[2'-(furan-2''-yl)ethyl]-2,6,10-trimethyl-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (108)



108

A mixture of the aldehydes **106** and **106a** (5.23 g, 31.9 mmol), phloroglucinol (**27**) (1.00 g, 7.93 mmol), phenylboronic acid (3.39 g, 27.9 mmol), propionic acid (40 drops) and benzene (50 mL) was heated at reflux in a Dean-Stark apparatus for 4 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (250 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (6:1) as the eluant afforded the *title compound* **108** (2.14 g, 63%) as a light yellow oil. $\mathbf{R}_f$ = 0.42, hexanes:ether (6:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.42 (s, 9H, *Me*), 2.04 (m, 6H, C*H*$_2$), 2.78 (m, 6H, C*H*$_2$), 5.40 (d, *J* = 9.9 Hz, 3H, ArCHC*H*) 5.97 (m, 3H, Ar*H*-3), 6.26 (m, 3H, Ar*H*-4), 6.65 (d, *J* = 9.9 Hz, 3H, ArC*H*CH), 7.29 (m, 3H, Ar*H*-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.9, 26.4, 39.2, 78.4, 102.8, 104.6, 110.1, 117.6, 124.2, 140.7, 149.2, 155.9; **IR** (neat) 3055, 2972, 2925, 2856, 1639, 1593, 1507, 1449, 1366, 1148 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 565 (M + H, 100); **Anal.** Calcd. for $C_{36}H_{36}O_6$: C, 76.57; H, 6.43. Found: C, 76.24; H, 6.31.

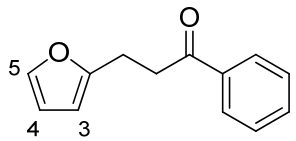
8.5.3 (2*E*)-3-(Furan-2'-yl)-1-phenylprop-2-en-1-one (111)[51]



111

An ice cold aqueous solution of sodium hydroxide (12 M, 20 mL) was slowly added to a mixture of freshly distilled furfural (**100**) (15.0 g, 156 mmol), acetophenone (**110**) (18.2 mL, 156 mmol) and ethanol (95%, 175 mL) at room temperature. The resultant mixture was stirred at room temperature for 2.5 h and then sulphuric acid (10% v/v, 50 mL) was added dropwise. The organic layer was then separated and direct purification of the crude extract by distillation at reduced pressure afforded the *title compound* **111** (19.7 g, 63%) as a light yellow oil. $\mathbf{R_f}$ = 0.28, hexanes:ether (3:1); **B.p.** 184-185 °C, ~25 mm Hg (lit. 177-178 °C, 7 mm Hg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 3.4, 1.7 Hz, 1H, Ar*H*-4), 6.72 (apparent d, *J* = 3.4 Hz, 1H, Ar*H*-3), 7.35 (apparent d, *J* = 1.7 Hz, 1H, Ar*H*-5), 7.46 (d, *J* = 15 Hz, 1H, C*H*), 7.51 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.57 (m, 2H, Ar*H*), 7.60 (d, *J* = 15 Hz, 1H, C*H*), 8.03 (d, *J* = 7.3 Hz, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 112.7, 116.2, 119.2, 128.4, 128.6, 130.6, 132.7, 138.1, 144.9, 151.6, 189.8; **IR** (ef) 3128, 3060, 1659, 1601, 1547, 1476, 1447, 1389, 1328, 1223, 1177 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 199 (M + H, 100).

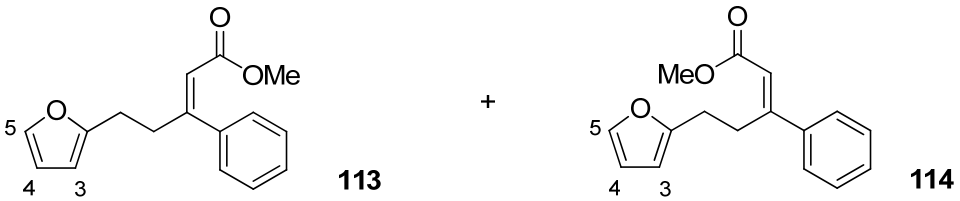
8.5.4 3-(Furan-2'-yl)-1-phenylpropan-1-one (112)[52]



112

A mixture of the ketone **111** (10.0 g, 50.4 mmol), palladium on charcoal (250 mg, 10% w/w) in ethyl acetate (175 mL) under an atmosphere of hydrogen (balloon pressure) was stirred at room temperature for 4.5 h. The resultant mixture was filtered through a pad of celite and the filter-cake was washed with ethyl acetate (4 x 50 mL). The combined filtrates were then concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **112** (7.32 g, 72%) as a colourless solid. $\mathbf{R_f}$ = 0.44, hexanes:ether (5:1); **M.p.** 35-36 °C, hexanes:ether (lit.[65] 36 °C, petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.09 (t, *J* = 7.7 Hz, 2H, C*H*$_2$), 3.31 (t, 8.0 Hz, 2H, C*H*$_2$), 6.06 (dd, *J* = 3.2, 0.7 Hz, 1H, Ar*H*-3), 6.29 (dd, *J* = 3.0, 2.0 Hz, 1H, Ar*H*-4), 7.31 (apparent d, *J* = 1.7 Hz, 1H, Ar*H*-5), 7.44 (td, *J* = 7.5, 1.5 Hz, 2H, Ph*H*), 7.54 (td, *J* = 7.4, 1.3 Hz, 1H, Ph*H*), 7.96 (d, *J* = 8.2 Hz, 2H, Ph*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 22.2, 36.6, 105.1, 110.0, 127.8, 128.4, 132.9, 136.5, 140.9, 154.5, 198.2; **IR** (ef) 3148, 3116, 3061, 2913, 2851, 1686, 1597, 1580, 1507, 1449, 1411, 1363, 1296, 1208, 1179 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 201 (M + H, 100).

8.5.5 Methyl-(2*Z*)-5-(furan-2'-yl)-3-phenylpent-2-enoate (113) and Methyl-(2*E*)-5-(furan-2'-yl)-3-phenylpent-2-enoate (114)



To a suspension of sodium hydride (60% w/w in mineral oil, 1.53 g, 38.2 mmol) in tetrahydrofuran (100 mL) at room temperature was added a solution of trimethyl phosphonoacetate (5.3 mL, 37 mmol) followed by an additional portion of tetrahydrofuran (120 mL). The resultant mixture was stirred for 30 min and then a

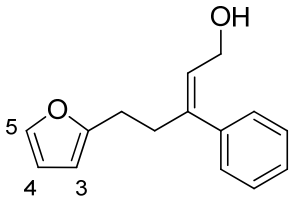
solution of the ketone **112** (5.88 g, 29.4 mmol) in tetrahydrofuran (10 mL) was added. The reaction mixture was then heated at reflux for 38 h and then cooled to room temperature. A saturated aqueous solution of ammonium chloride (35 mL) and water (35 mL) were then added. The aqueous layer was separated and extracted with ether (3 x 30 mL). The organic extracts were then combined and washed with brine (50 mL), water (50 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **113** (3.23 g, 43%) as a colourless oil and *title compound* **114** (3.74 g, 50%) as a pale yellow oil.

Title compound **113**: $\mathbf{R_f}$ = 0.27, hexanes:ether (5:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.75 (t, *J* = 8.2 Hz, 2H, C*H*$_2$), 2.84 (t, 8.2 Hz, 2H, C*H*$_2$), 3.57 (s, 3H, O*Me*), 5.94 (s, 1H, C*H*), 6.01 (m, 1H, Ar*H*-3), 6.29 (m, 1H, Ar*H*-4), 7.22 (m, 2H, Ar*H*), 7.32 (m, 1H, Ar*H*-5), 7.34 – 7.41 (m, 3H, Ar*H*); **Observed nOe contacts** *H*-2 to O*Me*, *H*-2 to C*H*$_2$-4; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.9, 38.5, 50.9, 105.3, 110.0, 117.3, 127.0, 127.7, 127.9, 139.2, 140.9, 154.2, 158.3, 166.0; **IR** (ef) 3119, 3080, 3060, 3026, 2949, 2851, 1730, 1636, 1599, 1575, 1558, 1540, 1507, 1491, 1434, 1378, 1339, 1228 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 257 (M + H, 100), 225 (M – OMe, 98); **Anal.** Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.68; H, 6.44.

Title compound **114**: $\mathbf{R_f}$ = 0.44, hexanes:ether (5:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.78 (t, *J* = 7.8 Hz, 2H, C*H*$_2$), 3.44 (t, 8.1 Hz, 2H, C*H*$_2$), 3.76 (s, 3H, O*Me*), 6.00 (m, 1H, Ar*H*-3), 6.09 (s, 1H, C*H*), 6.25 (m, 1H, Ar*H*-4), 7.28 (m, 1H, Ar*H*-5), 7.37 (m, 3H, Ar*H*), 7.43 (m, 2H, Ar*H*); **Observed nOe contacts** *H*-2 to O*Me*, *H*-2 to Ar*H*; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.3, 29.8, 51.2, 105.2, 110.0, 117.7, 126.7, 128.6, 129.0, 140.7,

140.9, 154.9, 159.1, 166.6; **IR** (ef) 3119, 3080, 3060, 3026, 2949, 2851, 1730, 1636, 1599, 1575, 1558, 1540, 1507, 1491, 1434, 1378, 1339, 1228 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 257 (M + H, 73), 225 (M – OMe, 100); **Anal.** Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.08; H, 6.42.

8.5.6 (2*Z*)-5-(Furan-2'-yl)-3-phenylpent-2-en-1-ol (115)

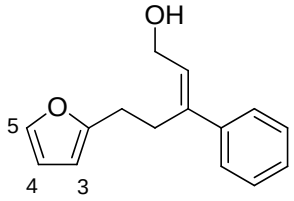


115

To a suspension of lithium aluminium hydride (289 mg, 7.62 mmol) in ether (60 mL) at room temperature was added a solution of the ester **113** (1.50 g, 5.85 mmol) in ether (10 mL) and the reaction mixture was stirred at room temperature for 40 min. Water (0.3 mL), an aqueous solution of sodium hydroxide (2 M, 0.3 mL) and water (1.0 mL) were then added sequentially, followed by addition of anhydrous sodium sulphate. The resultant mixture was filtered through a plug of cotton wool and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:3) as the eluant afforded the *title compound* **115** (997 mg, 74%) as a pale yellow oil. $\mathbf{R_f}$ = 0.38, hexanes:ether (1:3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.37 (s, 1H, O*H*), 2.68 (t, *J* = 7.2 Hz, 2H, CH_2), 2.75 (t, *J* = 6.9 Hz, 2H, CH_2), 4.03 (d, 2H, CH_2OH), 5.71 (t, *J* = 6.8 Hz, 1H, C*H*), 5.97 (m, 1H, Ar*H*-3), 6.27 (m, 1H, Ar*H*-4), 7.15 (d, 2H, Ar*H*), 7.29 (m, 2H, Ar*H* and Ar*H*-5), 7.35 (m, 2H, Ar*H*); **Observed nOe contacts** CH_2-1 to *H*-2, CH_2-1 to Ph*H*; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 26.6, 37.0, 59.9, 104.9, 109.9, 126.4, 127.1, 127.6, 128.1, 128.4, 139.2, 140.7, 155.2; **IR** (neat) 3384, 3055, 3023, 2926, 2857, 1718, 1657, 1598,

1507, 1493, 1442, 1145, 1077, 1003 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 211 (M – OH, 100), 81 (74); **Anal.** Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.55; H, 6.81.

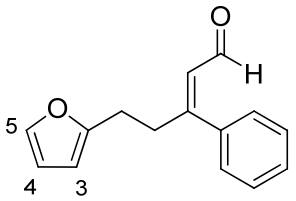
8.5.7 (2*E*)-5-(Furan-2'-yl)-3-phenylpent-2-en-1-ol (116)



116

To a suspension of lithium aluminium hydride (289 mg, 7.62 mmol) in ether (60 mL) at room temperature was added a solution of the ester **114** (1.50 g, 5.85 mmol) in ether (10 mL) and the reaction mixture was stirred at room temperature for 30 min. Water (0.3 mL), an aqueous solution of sodium hydroxide (2 M, 0.3 mL) and water (1.0 mL) were then added in succession, followed by addition of anhydrous sodium sulphate. The resultant mixture was filtered through a plug of cotton wool and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:3) as the eluant afforded the *title compound* **116** (985 mg, 74%) as a pale yellow oil. $\mathbf{R_f}$ = 0.39, hexanes:ether (1:3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.68 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 2.88 (t, *J* = 7.4 Hz, 2H, C*H*$_2$), 4.19 (d, *J* = 7.0 Hz, 2H, C*H*$_2$OH), 5.89 (t, *J* = 6.9 Hz, 1H, C*H*), 5.95 (m, 1H, Ar*H*-3), 6.28 (m, 1H, Ar*H*-4), 7.29 – 7.40 (m, 6H, Ar*H* & Ar*H*-5); **Observed nOe contacts** C*H*$_2$-1 to *H*-2, C*H*$_2$-1 to C*H*$_2$-4, *H*-2 to Ph*H*; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 26.9, 28.5, 59.2, 105.5, 110.1, 126.5, 127.3, 128.1, 128.3, 141.0, 141.2, 141.4, 154.9; **IR** (ef) 3449, 3051, 3026, 2932, 1719, 1681, 1594, 1493, 1447, 1351, 1001, 911 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 211 (M – OH, 100), 81 (52); **Anal.** Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.68; H, 7.14.

8.5.8 (2*Z*)-5-(Furan-2'-yl)-3-phenylpent-2-enal (117)



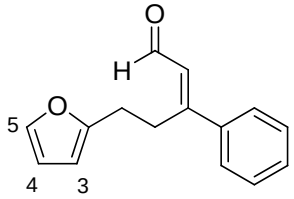
117

Method A: To a mixture of Dess-Martin periodinane (602 mg, 1.42 mmol) in dichloromethane (40 mL) at room temperature was added a solution of the alcohol **115** (295 mg, 1.29 mmol) in dichloromethane (3 mL). The resultant mixture was allowed to stir at room temperature for 3 h and then ether (10 mL) and an aqueous solution of sodium hydroxide (2 M, 10 mL) were added. The organic phase was separated and washed with water (30 mL), an aqueous solution of sodium hydroxide (2 M, 10 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **117** (36 mg, 12%) as a pale yellow oil.

Method B: To a suspension of manganese dioxide (10.0 g, 115 mmol) in dichloromethane (75 mL) at room temperature was added a solution of the alcohol **115** (1.00 g, 4.38 mmol) in dichloromethane (10 mL). After 16 h, the reaction was filtered through a pad of celite and the filter-cake was washed with dichloromethane (3 x 30 mL) and then the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **117** (779 mg, 79%) as a pale yellow oil. $\mathbf{R_f}$ = 0.34, hexanes:ether (2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.79 (t, *J* = 7.1 Hz, 2H, C*H*$_2$), 2.96 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 5.99 (d, *J* = 3.3 Hz, 1H, Ar*H*-3), 6.12 (d, *J* = 8.1 Hz, 1H, C*H*), 6.28 (apparent t, *J* = 3.0 Hz, 1H, Ar*H*-4), 7.28-7.31 (m, 3H, Ar*H*-5 and Ar*H*), 7.43-7.45 (m, 3H, Ar*H*), 9.46 (d, *J* = 8.2 Hz, 1H, C*H*O);

Observed nOe contacts *H*-2 to CH_2-4, *H*-2 to CH_2-5, *H*-2 to C*H*O; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 26.0, 37.8, 105.6, 110.1, 128.4, 128.6, 128.8, 129.1, 137.0, 141.2, 153.8, 164.5, 193.4; **IR** (ef) 3116, 3058, 3019, 2924, 2844, 2775, 2723, 1672, 1615, 1598, 1572, 1507, 1492, 1442, 1395, 1348, 1197, 1125, 1077, 1015 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 227 (M + H, 100), 143 (37), 81 (22); **Anal.** Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.98; H, 6.31.

8.5.9 (2*E*)-5-(Furan-2'-yl)-3-phenylpent-2-enal (118)



118

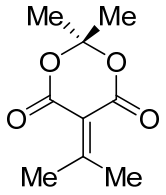
Method A: To a mixture of Dess-Martin periodinane (576 mg, 1.36 mmol) in dichloromethane (40 mL) at room temperature was added a solution of the alcohol **116** (282 mg, 1.24 mmol) in dichloromethane (3 mL). The resultant mixture was allowed to stir at room temperature for 3 h and then ether (10 mL) and an aqueous solution of sodium hydroxide (2 M, 10 mL) were added. The organic phase was separated and washed with water (30 mL), an aqueous solution of sodium hydroxide (2 M, 10 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **118** (108 mg, 38%) as a pale yellow oil.

Method B: To a suspension of manganese dioxide (10.0 g, 115 mmol) in dichloromethane (75 mL) at room temperature was added a solution of the alcohol **116** (985 mg, 4.31 mmol) in dichloromethane (10 mL). After 17 h, the reaction was filtered through a pad of celite and the filter-cake was washed with dichloromethane (3 x 30 mL)

and then the combined filtrates were concentrated *in vacuo* to afford the *title compound* **118** (771 mg, 79%) as a pale yellow oil. $\mathbf{R_f}$ = 0.34, hexanes:ether (2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.81 (t, *J* = 7.4 Hz, 2H, C*H*$_2$), 3.36 (t, *J* = 7.3 Hz, 2H, C*H*$_2$), 5.95 (d, *J* = 3.1 Hz, 1H, Ar*H*-3), 6.25 (dd, *J* = 3.1, 1.9 Hz, 1H, Ar*H*-4), 6.27 (d, *J* = 7.9 Hz, 1H, C*H*), 7.30 (d, *J* = 1.7 Hz, 1H, Ar*H*-5), 7.41 – 7.43 (m, 3H, Ar*H*), 7.48 – 7.50 (m, 2H, Ar*H*), 9.90 (d, *J* = 7.9 Hz, 1H, C*H*O); **Observed nOe contacts** C*H*O to *H*-2, C*H*O to C*H*$_2$-4; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.6, 28.5, 106.3, 110.1, 126.5, 128.5, 128.7, 129.8, 139.1, 141.4, 153.2, 160.4, 190.5; **IR** (neat) 3115, 3058, 2978, 2916, 2832, 2759, 1675, 1607, 1572, 1506, 1493, 1445, 1397, 1347, 1325, 1254, 1142, 1076, 1034, 1003 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 227 (M + H, 100), 143 (39), 81 (29); **Anal.** Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.95; H, 6.14.

8.6 Experimental Procedures and Characterization Data Concerning Chapter Six

8.6.1 2,2-Dimethyl-5-(propan-2'-ylidene)-1,3-dioxane-4,6-dione (126)[54]

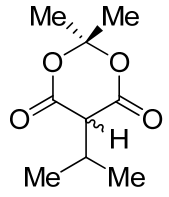


126

Acetone (**101**) (5.6 mL, 100 mmol) was added to a mixture of acetic acid (1.0 mL, 17 mmol), ammonium acetate (267 mg, 3.46 mmol), Meldrum's acid (**125**) (10.0 g, 69.4 mmol), 4Å molecular sieves (1.5 g) and toluene (80 mL) at room temperature. The resultant mixture was allowed to stir for 48 h and it was then filtered and concentrated *in vacuo* to half its original volume. To the resultant slurry was added toluene (40 mL) and a saturated aqueous solution of sodium bicarbonate (40 mL). The organic layer was

separated and washed with a saturated aqueous solution of sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Purification of the resultant solid was accomplished by trituration with hexanes, filtration and drying *in vacuo* to afford the *title compound* **126** (4.39 g, 34 %) as colourless crystals. $\mathbf{R_f}$ = 0.35, hexanes:ether (1:9); **M.p.** 73-75 °C, hexanes (lit.[42] 75-78.5 °C, methanol:water); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.72 (s, 6H, *Me*), 2.51 (s, 6H, *Me*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 26.8, 27.1, 103.5, 115.9, 161.1, 177.3; **IR** (KBr) 2997, 2948, 1750, 1719, 1605, 1426, 1396, 1386, 1360, 1285, 1245, 1202, 1118, 1096, 1021 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 127 (M – C_3H_6O, 100), 84 (47).

8.6.2 5-Isopropyl-2,2-dimethyl-1,3-dioxane-4,6-dione (127)[55]

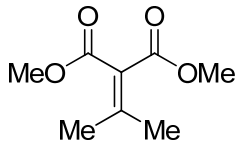


127

To a mixture of diisobutylaluminium hydride (1.0 M in hexanes, 2.4 mL, 2.4 mmol) in dichloromethane (15 mL) at -78°C was added a solution of compound **126** (200 mg, 1.09 mmol) in dichloromethane (5 mL). The resultant mixture was allowed to stir at -78°C for 3 h and then a saturated aqueous solution of ammonium chloride (3 mL) was added. The resultant mixture was allowed to warm to room temperature and then a saturated aqueous solution of ammonium chloride (7 mL) was added. The aqueous phase was separated and extracted with dichloromethane (2 x 15 mL). The combined organic extracts were then washed with water (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford the *title compound* **127** (76 mg, 37%) as a colourless

solid. $\mathbf{R_f}$ = 0.30, hexanes:ether (1:1); **M.p.** 99-102 °C, hexanes:ether (lit.[55] 102-104 °C, hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.12 (d, J = 7.2 Hz, 6H, CH*Me*$_2$), 1.69 (s, 3H, *Me*), 1.72 (s, 3H, *Me*), 2.71 (doublet of septets, J = 7.0, 3.0 Hz, 1H, C*H*Me$_2$), 3.39 (d, J = 3.1 Hz, 1H, C*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 19.0, 27.2, 28.1, 28.8, 51.39, 51.42, 104.5, 164.9; **IR** (KBr) 3003, 2977, 2964, 2946, 2869, 1775, 1736, 1460, 1386, 1371, 1308, 1252, 1211, 1066 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 186 (M + H, 1), 129 (M – C_3H_6O, 6), 103 (3), 85 (29), 59 (100).

8.6.3 Dimethyl 2-(propan-2'-ylidene)malonate (128)[66]

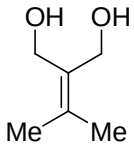


128

To a mixture of acetone (**101**) (2.63 g, 45.5 mmol) and dimethyl malonate (**79**) (6.00 g, 45.4 mmol) was added titanium tetrachloride (12.7 mL, 91.1 mmol) at 0 °C. A solution of pyridine (14.7 mL, 190 mmol) in tetrahydrofuran (30 mL) was then added to the resultant mixture over the course of 30 min. The reaction mixture was then allowed to warm to room temperature and stir for an additional 16 h. Ice cold water (100 mL) was then added to the reaction mixture which was then extracted with ether (3 x 75 mL). The organic extracts were then combined, dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **128** (5.99 g, 77%) as a colourless oil. $\mathbf{R_f}$ = 0.25, hexanes:ether (3:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.06 (s, 6H, *Me*), 3.76 (s, 6H, O*Me*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 22.2, 52.0, 124.0, 156.0, 166.1; **IR** (neat) 2954, 1726,

1641, 1435, 1375, 1245 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 173 (M + H, 70), 141 (M – OMe, 100).

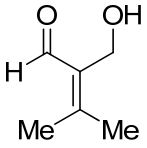
8.6.4 2-(Propan-2'-ylidene)propane-1,3-diol (129)[67]



129

To a suspension of lithium aluminium hydride (1.24 g, 32.7 mmol) in benzene (40 mL) at room temperature was added a solution of the ester **128** (2.50 g, 14.5 mmol) in benzene (10 mL). The reaction mixture was then heated at reflux for 3 h and then cooled to room temperature. Water (1.2 mL), an aqueous solution of sodium hydroxide (2 M, 1.2 mL) and water (3.6 mL) were then added sequentially. The resultant mixture was then filtered through a cotton plug with ether (3 x 5 mL). The combined filtrates were dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using acetone:chloroform (7:13) as the eluant afforded the *title compound* **129** (640 mg, 38%) as a colourless oil. $\mathbf{R_f}$ = 0.22, acetone:chloroform (7:13); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.78 (s, 6H, *Me*), 2.24 (s, 2H, O*H*), 4.31 (s, 4H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 20.3, 62.1, 130.7, 133.7; **IR** (neat) 3342, 1644 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 99 (M – OH, 46).

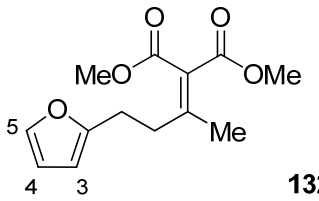
8.6.5 2-(Hydroxymethyl)-3-methylbut-2-enal (130)



130

To a suspension of manganese dioxide (400 mg, 4.60 mmol) in dichloromethane (5 mL) at room temperature was added a solution of the alcohol **129** (40 mg, 0.35 mmol) in dichloromethane (2 mL). After 3.5 h the reaction was filtered through a pad of celite and the filter-cake was washed with dichloromethane (2 x 10 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:9) as the eluant afforded the *title compound* **130** (26 mg, 64%) as a colourless oil. $\mathbf{R_f}$ = 0.26, hexanes:ether (1:9); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.08 (s, 3H, *Me*), 2.24 (s, 3H, *Me*), 4.36 (s, 2H, CH_2), 10.13 (s, 1H, C*H*O); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 19.7, 23.1, 56.9, 135.7, 158.9, 191.9; **IR** (ef) 3412, 2912, 2886, 1659, 1630, 1439, 1374, 1300, 1161, 1013 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 115 (M + H, 81), 97 (M – OH, 100); **HRMS** Calcd. for $C_6H_{11}O_2$: 115.0759. Found: 115.0762.

8.6.6 Dimethyl-[4'-(furan-2''-yl)butan-2'-ylidene]malonate (132)

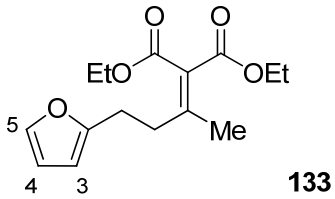


132

To a solution of the ketone **103** (1.88 g, 13.6 mmol) and dimethyl malonate (**79**) (2.25 g, 17.0 mmol) in carbon tetrachloride (20 mL) at 0 °C was added titanium tetrachloride (3.8 mL, 27 mmol) over the course of 25 min. After a further 15 min, a solution of pyridine (4.4 mL, 54 mmol) in tetrahydrofuran (50 mL) was added over the course of 10 min. The resultant mixture was allowed to warm to room temperature and was stirred for an additional 16 h. Ice cold water (75 mL) was then added and the aqueous layer was separated and extracted with ether (3 x 50 mL). The organic extracts were combined, dried over anhydrous sodium sulphate and concentrated *in vacuo*.

Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **132** (2.24 g, 65%) as a colourless oil. $\mathbf{R_f}$ = 0.25, hexanes:ether (3:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.03 (s, 3H, *Me*), 2.70 (t, *J* = 8.1 Hz, 2H, C*H*$_2$), 2.84 (t, *J* = 8.3 Hz, 2H, C*H*$_2$), 3.76 (s, 3H, O*Me*), 3.77 (s, 3H, O*Me*), 6.02 (m, 1H, Ar*H*-3), 6.27 (m, 1H, Ar*H*-4), 7.30 (m, 1H, Ar*H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 21.0, 26.3, 35.2, 52.0, 52.0, 105.4, 110.1, 124.6, 141.1, 154.2, 157.8, 165.5, 165.9; **IR** (neat) 3117, 3023, 2953, 2843, 1734, 1634, 1596, 1506, 1435, 1377, 1290, 1255, 1145, 1109, 1083 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 253 (M + H, 28), 221 (M – OMe, 100); **Anal.** Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.10; H, 6.37.

8.6.7 Diethyl-[4'-(furan-2''-yl)butan-2'-ylidene]malonate (133)

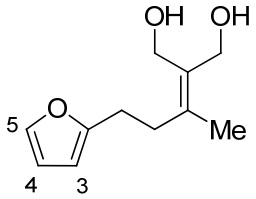


133

To a solution of the ketone **103** (4.00 g, 28.9 mmol) and diethyl malonate (**81**) (5.10 g, 31.9 mmol) in carbon tetrachloride (20 mL) at 0 °C was added titanium tetrachloride (8.1 mL, 58 mmol) over the course of 10 min. After a further 15 min, a solution of pyridine (9.4 mL, 120 mmol) in tetrahydrofuran (50 mL) was added over the course of 15 min. The resultant mixture was allowed to warm to room temperature and was stirred for an additional 16 h. Ice cold water (50 mL) was then added and the aqueous layer was separated and extracted with ether (3 x 25 mL). The organic extracts were combined, dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (7:2) as the eluant to afford the *title compound* **133** (5.01g, 62%) as a colourless oil. $\mathbf{R_f}$ = 0.36, hexanes:ether (7:2); **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 1.29 (m, 6H, OCH_2Me), 2.03 (s, 3H, *Me*), 2.70 (t, *J* = 7.6 Hz, 2H, CH_2), 2.84 (t, *J* = 7.4 Hz, 2H, CH_2), 4.23 (m, 4H, OCH_2Me), 6.02 (m, 1H, Ar*H*-3), 6.27 (m, 1H, Ar*H*-4), 7.29 (m, 1H, Ar*H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 13.9, 13.9, 20.9, 26.3, 35.1, 60.8, 60.9, 105.3, 110.1, 125.3, 141.0, 154.4, 156.8, 165.2, 165.5; **IR** (neat) 3117, 2981, 1736, 1635, 1596, 1507, 1444, 1367, 1300, 1158, 1057 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 281 (M + H, 39), 235 (M – OEt, 100); **Anal.** Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.97; H, 7.31.

8.6.8 2-[4'-(Furan-2''-yl)butan-2'-ylidene]propane-1,3-diol (134)



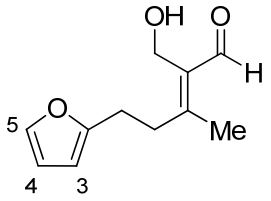
134

Method A: To a suspension of lithium aluminium hydride (254 mg, 6.68 mmol) in benzene (40 mL) at room temperature was added a solution of the ester **132** (750 mg, 2.97 mmol) in benzene (10 mL). The reaction mixture was then heated at reflux for 18 h and then cooled to room temperature. Water (0.25 mL), an aqueous solution of sodium hydroxide (2 M, 0.25 mL) and water (0.75 mL) were then added sequentially and the resultant mixture was then filtered through a pad of celite. The filter-cake was washed with ether (3 x 10 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using acetone:chloroform (7:13) as the eluant afforded the *title compound* **134** (101 mg, 17%) as a light yellow oil.

Method B: To a suspension of lithium aluminium hydride (993 mg, 26.2 mmol) in benzene (75 mL) at room temperature was added a solution of the ester **133** (2.95g, 10.5 mmol) in benzene (10 mL). The reaction mixture was then heated at reflux for 16 h

and then cooled to room temperature. Water (1.0 mL), an aqueous solution of sodium hydroxide (2 M, 1.0 mL) and water (3.0 mL) were then added sequentially and the resultant mixture was allowed to cool to room temperature and the solution was filtered through a pad of celite. The filter-cake was washed with ether (4 x 25 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using acetone:chloroform (7:13) as the eluant afforded the *title compound* **134** (252 mg, 12%) as a light yellow oil. $\mathbf{R_f}$ = 0.24, acetone:chloroform (7:13); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.79 (s, 3H, *Me*), 1.88 (s, 2H, O*H*), 2.46 (t, *J* = 7.4 Hz, 2H, CH_2), 2.75 (t, *J* = 7.4 Hz, 2H, CH_2), 4.18 (s, 2H, CH_2OH), 4.29 (s, 2H, CH_2OH), 5.99 (m, 1H, Ar*H*-3), 6.28 (m, 1H, Ar*H*-4), 7.31 (m, 1H, Ar*H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.9, 26.7, 32.8, 60.9, 61.5, 105.1, 110.1, 132.3, 135.6, 140.9, 155.1; **IR** (neat) 3481, 3116, 2928, 2879, 1717, 1660, 1595, 1507, 1438, 1371, 1213, 1147, 921 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 179 (M – OH, 10), 161 (M – 2 x OH, 100); **Anal.** Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.16; H, 8.43.

8.6.9 (2*E*)-5-(Furan-2'-yl)-2-hydroxymethyl-3-methylpent-2-enal (135)



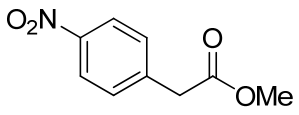
135

Method A: To a solution of the alcohol **134** (90 mg, 0.46 mmol) in dichloromethane (40 mL) at room temperature was added Dess-Martin periodinane (428 mg, 1.00 mmol). The resultant mixture was allowed to stir for 4.5 h and ether (15 mL) and an aqueous solution of sodium hydroxide (1.3 M, 15 mL) were added. The organic layer was then washed with water (25 mL), an aqueous solution of sodium hydroxide (2

M, 30 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (2:1) as the eluant afforded the *title compound* **135** as a mixture of isomers (*E*:*Z* = ~1:2, 8 mg, 9%) as a colourless oil.

Method B: To a suspension of manganese dioxide (600 mg, 6.90 mmol) in dichloromethane (5 mL) at room temperature was added a solution of the alcohol **134** (33 mg, 0.17 mmol) in dichloromethane (2 mL). After 4 h, the reaction mixture was filtered through a pad of celite and the filter-cake was washed with dichloromethane (2 x 10 mL). The combined filtrates were then concentrated *in vacuo*. Purification by flash chromatography using hexanes:ethyl acetate (2:3) as the eluant afforded the *title compound* **135** (3 mg, 9%) as a colourless oil. $\mathbf{R_f}$ = 0.26, hexanes:ethyl acetate (2:3); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.22 (s, 3H, *Me*), 2.71 (t, *J* = 7.8 Hz, 2H, C*H*$_2$), 2.86 (t, *J* = 7.6 Hz, 2H, C*H*$_2$), 4.25 (d, *J* = 6.6 Hz, 2H, C*H*$_2$OH), 6.01 (m, 1H, Ar*H*-3), 6.27 (m, 1H, Ar*H*-4), 7.31 (m, 1H, Ar*H*-5), 10.13 (s, 1H, C*H*O); **Observed nOe contacts**, C*H*O to *Me*, C*H*$_2$-OH to C*H*$_2$-5; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 17.7, 26.5, 35.3, 56.7, 105.9, 110.3, 136.4, 141.4, 153.7, 160.1, 192.4; **IR** (ef) 3428, 3118, 2917, 1663, 1624, 1506, 1305, 1140, 1011 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 177 (M – OH, 81), 81 (100); **HRMS** Calcd. for $C_{11}H_{15}O_3$: 195.1021. Found: 195.1019.

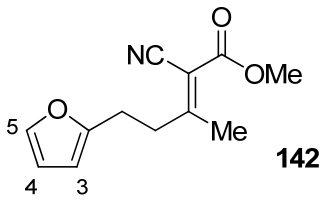
8.6.10 Methyl-(*p*-nitrophenyl)acetate (139)[58]



139

To a solution of *p*-nitrophenylacetic acid (**138**) (20.0 g, 110 mmol) in methanol (20 mL) was added concentrated sulphuric acid (15 drops) and the resultant mixture was heated at 65 °C for 2 h. The reaction mixture was then allowed to cool to room temperature. The resultant crystalline suspension was placed in a refrigerator overnight, after which it was filtered and then washed with ice cold methanol to afford the *title compound* **139** (19.3 g, 90%) as a pale yellow solid. $\mathbf{R_f}$ = 0.28, hexanes:ethyl acetate (2:1); **M.p.** 50-52 °C, methanol (lit.[59] 53-54 °C, methanol); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.74 (s, 3H, *Me*), 3.76 (s, 2H, C*H*$_2$), 7.47 (d, *J* = 8.6 Hz, 2H, Ar*H*-2' and Ar*H*-6'), 8.21 (d, *J* = 8.7 Hz, 2H, Ar*H*-3' and Ar*H*-5'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 40.8, 52.4, 123.7, 130.3, 141.2, 147.2, 170.6; **IR** (ef) 3116, 3090, 3006, 2961, 2852, 1733, 1607, 1518, 1436, 1354, 1228, 1112 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 196 (M + H, 100).

8.6.11 (2*E*)-Methyl 2-cyano-5-(furan-2'-yl)-3-methylpent-2-enoate (142)



142

To a mixture of acetic acid (1.0 mL, 17 mmol), ammonium acetate (334 mg, 4.33 mmol) and methyl-2-cyanoacetate (**141**) (2.15 g, 21.7 mmol) in benzene (100 mL) at room temperature was added the ketone **103** (2.99 g, 21.7 mmol). The reaction mixture then was heated at reflux in a Dean-Stark apparatus for 20 h. The resultant mixture was allowed to cool to room temperature and was then concentrated *in vacuo.* The residual oil was then dissolved in ethyl acetate (30 mL), washed with water (2 x 30 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **142**

(510 mg, 11%) as a pale yellow oil. $\mathbf{R_f}$ = 0.27, hexanes:ether (3:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.35 (s, 3H, *Me*), 2.92 (m, 4H, ArCH_2CH_2), 3.82 (s, 3H, O*Me*), 6.06 (dd, *J* = 3.1, 0.4 Hz, 1H, Ar*H*-3), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H, Ar*H*-4), 7.33 (dd, *J* = 1.8, 0.8 Hz, 1H, Ar*H*-5); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 20.9, 25.9, 39.1, 52.5, 105.2, 106.2, 110.3, 115.2, 141.6, 152.7, 162.2, 176.1; **IR** (neat) 2955, 2226, 1732, 1607, 1507, 1435, 1286, 1233, 1146, 1081 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 220 (M + H, 100), 188 (M – OMe, 47); **Anal.** Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.80; H, 5.96; N, 6.31.

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