

**Multiple Electrophilic Aromatic Substitution Reactions  
of Phloroglucinol and Studies Towards the Total  
Synthesis of Hopeanol**

**by**  
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Bachelor of Science, Simon Fraser University, 2006

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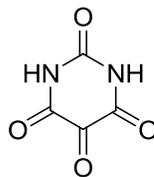
## Abstract

An investigation of the triple electrophilic aromatic substitution (EAS) reactions of phloroglucinol (1,3,5-trihydroxybenzene) has led to the preparation of both symmetrical triple Mannich bases and structurally-complex polycyclic adducts. This research was based on two synthetic approaches that were developed separately for the total synthesis of the polycyclic and  $C_3$ -symmetric natural product xyloketal A. The first systematic study led to the synthesis of a series of functionalized  $C_3$ -symmetric dendrimer cores. In the second study, polycyclic analogues of xyloketal A were prepared *via* the triple EAS reactions of phloroglucinol with various carbon-based electrophiles. In addition, a novel  $C_2$ -symmetric polycyclic quinone was isolated from the reaction of phloroglucinol with (+)-*p*-mentha-2-ene-1,8-diol.

In a separate study, the total synthesis of the natural product hopeanol was undertaken. This involved the preparation of a 1,2-diketone precursor which was tested with an array of acid promoters in an attempt to complete this synthesis in a single synthetic operation.

*“It makes you think of something solid, stable, well-linked. In fact it happens also in chemistry as in architecture that ‘beautiful’ edifices, that is symmetrical and simple, are also the most sturdy: in short the same thing happens with molecules as with the cupolas of cathedrals or the arches of bridges. And it is also possible that the explanation is neither remote nor metaphysical... ever since man has built he has wanted to build at the smallest expense and in the most durable fashion, and the aesthetic enjoyment he experiences when contemplating his work comes afterward.”*

Primo Levi,  
on the structure of alloxan in *The Periodic Table*. Pg. 179



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## List of Abbreviations

$[\alpha]_D$	specific rotation
$\alpha$	bottom face (steroid nomenclature)
$\beta$	top face (steroid nomenclature)
$\delta$	chemical shift (NMR spectroscopy)
(+)-	dextrorotatory
(-)-	laevorotatory
(±)-	racemic
2D	two dimensional
Ac	acetyl
AcOH	acetic acid
Ac <sub>2</sub> O	acetic anhydride
amu	atomic mass units (mass spectroscopy)
aq	aqueous
Ar	aromatic group
atm	atmospheres
Bn	benzyl (phenylmethyl)
B.p.	boiling point
br	broad (spectroscopy)
brsm	based on recovered starting material
<i>c</i>	concentration
Calcd.	calculated (mass spectrometry)
cat.	catalytic (amount)
CD	circular dichroism
CI	chemical ionization (mass spectroscopy)
cm <sup>-1</sup>	wavenumbers (IR spectroscopy)
<sup>13</sup> C NMR	carbon nuclear magnetic resonance spectroscopy
CoA	coenzyme A

conc.	concentrated
COSY	$^1\text{H}$ - $^1\text{H}$ correlation spectroscopy
CV	cyclic voltammetry
<i>D</i>	sodium <i>D</i> -line (589 nm)
d	doublet (NMR spectroscopy)
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
dd	doublet of doublets (NMR spectroscopy)
ddd	doublet of doublet of doublets (NMR spectroscopy)
DFT	density functional theory
dr	diastereoisomeric ratio
dt	doublet of triplets (NMR spectroscopy)
DIBAL-H	diisobutylaluminum hydride
DMAP	<i>N,N</i> -dimethyl-4-aminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMS	dimethyl sulfide
EAS	electrophilic aromatic substitution
ef	evaporated film (IR spectroscopy)
EI	electron impact ionization (mass spectroscopy)
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et <sub>2</sub> O	diethyl ether (ether)
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
$^1\text{H}$ NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	hertz (cycles per second)

IBX	2-iodoxybenzoic acid
IC <sub>50</sub>	median inhibition concentration
IR	infrared spectroscopy
<i>J</i>	coupling constant (NMR spectroscopy)
KBr	potassium bromide disc (IR spectroscopy)
LDA	lithium <i>N,N</i> -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 a proton (mass spectroscopy)
M + Na	molecular ion plus sodium (mass spectroscopy)
MALDI-TOF	matrix assisted laser desorption ionization-time of flight (mass spectroscopy)
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
Me <sub>2</sub> CO	acetone
MeI	methyl iodide (iodomethane)
MeOH	methanol (methyl alcohol)
Me <sub>2</sub> SO <sub>4</sub>	dimethyl sulfate
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
<i>m/z</i>	mass to charge ratio
μL	microlitre(s)
N	normal

N/A	not applicable
<i>n</i> -BuLi	<i>n</i> -butyl lithium
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
OAc	acetate
o/n	over night
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million (NMR spectroscopy)
PPTS	pyridinium <i>p</i> -toluenesulfonate
PSI	pounds per square inch
PTSA	<i>p</i> -toluenesulfonic acid monohydrate
py	pyridine
q	quartet (NMR spectroscopy)
quant.	quantitative
rel.	relative
$R_f$	retention factor (thin-layer chromatography)
s	singlet (NMR spectroscopy)
SAR	structure activity relationship
t	triplet (NMR spectroscopy)
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TBSCl	<i>t</i> -butyldimethylsilyl chloride
<i>t</i> -BuLi	<i>t</i> -butyl lithium
td	triplet of doublets (NMR spectroscopy)
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TOCSY	total correlation spectroscopy
tq	triplet of quartets (NMR spectroscopy)

trz	triazole
UV	ultra violet
v/v	volume by volume
wt. %	weight percent
w/v	weight by volume
w/w	weight by weight

## Chapter 1:

### *Introduction to Multiple Electrophilic Aromatic Substitution Reactions of Phloroglucinol and Studies Towards the Total Synthesis of Hopeanol*

#### 1.1 Thesis Introduction

This thesis concerns a discussion of two studies in the field of synthetic organic chemistry. The first study comprises an exploration of the multiple electrophilic aromatic substitution (EAS) reactions of phloroglucinol (1,3,5-trihydroxybenzene) with a series of carbon-based electrophiles. The impetus for this research was derived from the development of several approaches that were investigated *en route* towards the first total synthesis of the  $C_3$ -symmetric natural product, xyloketal A. The first of these methods involved the use of a phloroglucinol-derived triple Mannich base which was employed as a precursor for the construction of the polycyclic ring system of xyloketal A. This Mannich base was prepared using a triple electrophilic aromatic substitution reaction of phloroglucinol with iminium ions that were prepared from secondary amines and formaldehyde. Accordingly, the topic of *Chapter 2* concerns an expansion of this chemistry in order to prepare a series of functionalized,  $C_3$ -symmetric triple Mannich bases. The second method, which led to the first total synthesis of the  $C_3$ -symmetric and biologically-active natural product, xyloketal A, also involved multiple electrophilic aromatic substitution reactions of phloroglucinol. In this case however, the complex ring system was constructed using an electrophilic species, which was generated from an

allylic alcohol on treatment with a Lewis or protic acid, affording the desired complex polycyclic natural product in one synthetic operation and in a stereoselective manner. Thus, the second topic, which is discussed in *Chapter 3*, concerns multiple electrophilic aromatic substitution reactions of phloroglucinol with novel carbon-based electrophilic species, some of which have enjoyed alternative use as key precursors in other natural product total syntheses. As a result, the compounds thus prepared, constitute a series of chimeric xyloketal A analogues, as they contain structural features sourced from more than one natural product.

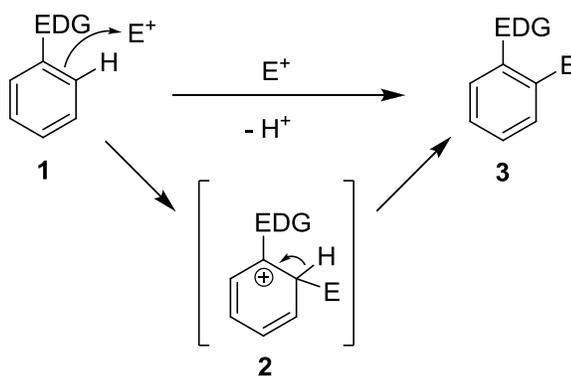
The second study, which is discussed in *Chapter 4*, concerns the progress made towards the total synthesis of the natural product, hopeanol. Here, a biosynthetically inspired dimerization reaction of a surrogate, resveratrol-based precursor, would potentially result in a racemic total synthesis of this natural product *via* a series of cascade reactions, which notably, also feature multiple electrophilic aromatic substitution reactions.

## **1.2 Overview of the Electrophilic Aromatic Substitution Reaction**

The electrophilic aromatic substitution reaction is an important and general process in organic chemistry that finds use in a variety of synthetic settings. Indeed, the ubiquity of aromatic systems in molecules of all types is perhaps due to the ease with which these systems can be employed as building blocks, which in turn can be assembled *via* the EAS reaction. As was alluded to above, the electrophilic aromatic substitution reaction figures prominently throughout this thesis, and as such, a brief introduction to this important synthetic process is provided here.

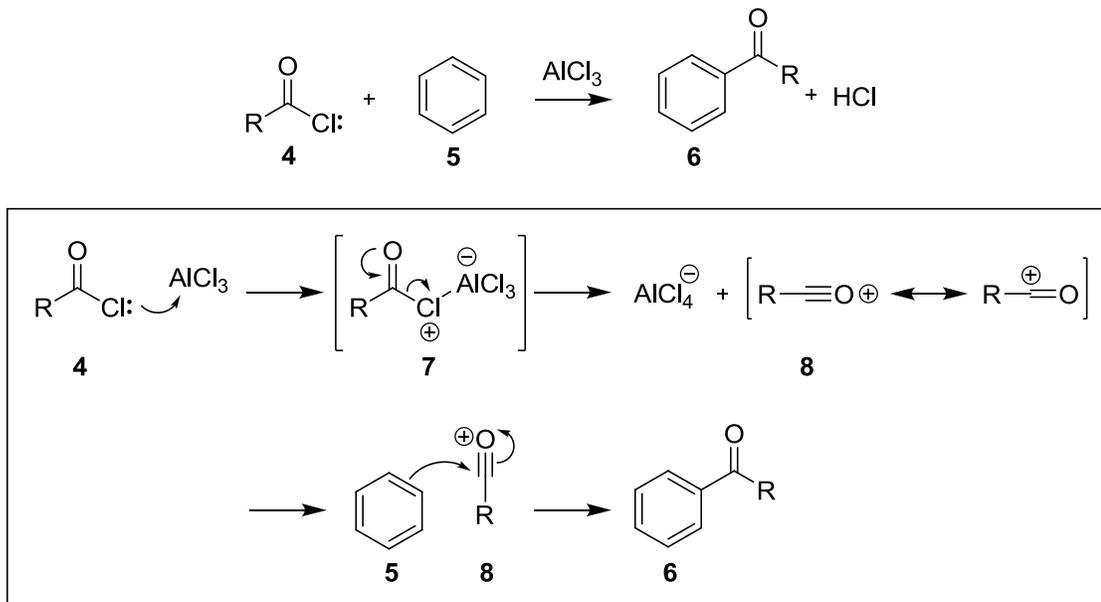
An electrophilic aromatic substitution is a general name for any reaction which serves to replace an aromatic hydrogen atom with another group *via* the mechanism outlined below (**Scheme 1.2.1**).

**Scheme 1.2.1 Mechanism of the Electrophilic Aromatic Substitution Reaction of an Electron-Rich Aromatic System [(1); EDG = Electron Donating Group]**



The first step of this process involves the nucleophilic attack of an aromatic system on an electrophilic species (generalized here as  $E^+$ ), which results in a temporary loss of aromaticity and the formation of a new bond between the aromatic ring and the electrophilic species. This is followed by the elimination of a proton from the intermediate **2**, which results in the substituted aromatic product (**3**). In principle, any suitably reactive electrophilic species could be employed; however, the most powerful aspect of this process is the proficiency with which it leads to the formation of carbon-carbon bonds. Indeed, arguably the most well-known versions of this method are the Friedel-Crafts acylation and alkylation reactions. These reactions were first reported by Charles Friedel and James M. Crafts in 1877 in the journal *Comptes Rendus*.<sup>1</sup> A generalized example of the Friedel-Crafts acylation reaction of benzene (**5**) is outlined below (**Scheme 1.2.2**).<sup>2</sup>

**Scheme 1.2.2 Mechanism of the Friedel-Crafts Acylation Reaction of Benzene (5)<sup>2</sup>**

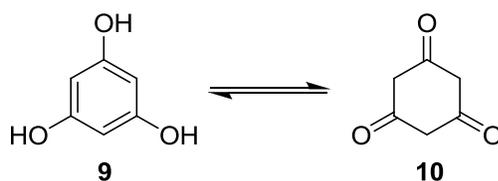


The first step of this sequence involves formation of the active electrophilic species, in this case the acylium ion **8**. This occurs through complexation of the acyl chloride **4** to an appropriate Lewis acid, here aluminum (III) chloride (**7**). Subsequent loss of tetrachloroaluminate ( $\text{AlCl}_4^-$ ) leads to formation of the requisite electrophilic acylium ion (**8**). Finally, the electrophilic aromatic substitution proceeds in a manner analogous to the generalized mechanism outlined above (**Scheme 1.2.1**).

### **1.3. Introduction to the Chemistry of Phloroglucinol [1,3,5-Trihydroxybenzene (**9**)]**

Whereas the electrophilic aromatic substitution reaction was the principle synthetic tool employed in the research reported in this thesis, phloroglucinol (**9**) served in large part as the substrate to which this general reaction was applied. Thus, a brief review of this noteworthy compound and its chemistry is presented in the following two sections of this chapter.

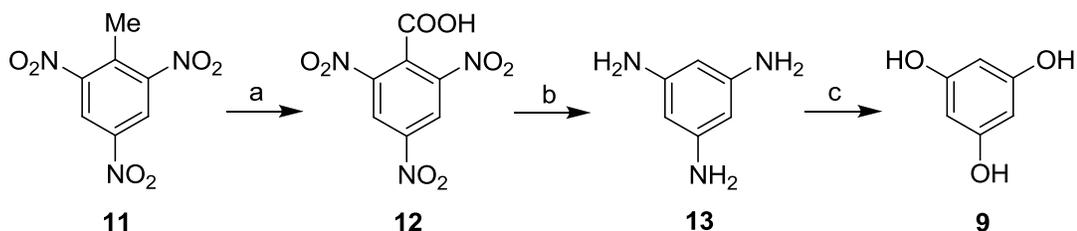
Phloroglucinol (**9**) was first isolated by Hlasiwetz in 1855 as the hydrolysis product of phloretin, a natural product extracted from the bark of fruit trees.<sup>3</sup> Indeed, the name phloroglucinol (**9**) is taken from the greek words; Γλυκό φλοιός, which means “sweet bark”. This molecule can be formally represented as two tautomeric forms; the phenolic form [1,3,5-trihydroxybenzene (**9**)] and the ketonic form [1,3,5-cyclohexanetrione (**10**)], which in turn is called phloroglucin [(**10**), **Figure 1.3.1**].<sup>3</sup>



**Figure 1.3.1** Molecular structure of phloroglucinol [1,3,5-trihydroxybenzene (**9**)].

The biosynthesis of phloroglucinol (**9**) is thought to involve the condensation reaction of three molecules of malonyl CoA, followed by a series of decarboxylation processes.<sup>4</sup> Phloroglucinol (**9**) has been prepared industrially *via* a number of different routes. A representative example of one such industrial process is shown below (**Scheme 1.3.1**).<sup>5</sup>

**Scheme 1.3.1** Industrial Synthesis of Phloroglucinol (**9**)<sup>5</sup>



Reagents and conditions: (a)  $\text{Na}_2\text{Cr}_2\text{O}_7$ ,  $\text{H}_2\text{SO}_4$ ; (b)  $\text{Fe-HCl}$ ; (c)  $\text{H}_2\text{O}/\text{H}^+$ .

This synthetic route begins with an oxidation reaction of trinitrotoluene [TNT, (11)], affording trinitrobenzoic acid (12). This is followed by reduction and decarboxylation reactions, which result in 1,3,5-triaminobenzene (13). Subsequent hydrolysis of the amino groups leads to production of phloroglucinol (9). This route however, has been questioned for its environmental impact, as the acidic waste products that are produced contain chromium, and are thus difficult to dispose of safely.

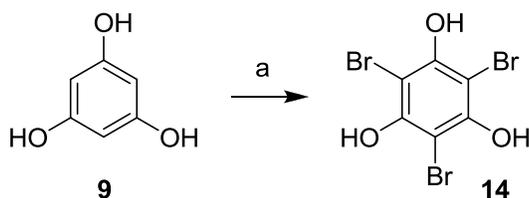
Phloroglucinol (9) itself constitutes a highly symmetrical and electron rich aromatic system that contains three chemically equivalent sites that are suitable for electrophilic aromatic substitution reactions, as well as three phenol moieties which could potentially be employed in further reactions. As a result, this molecule is highly reactive to both EAS reactions, as well as to reactions that would involve the phenolic functionality directly, such as acetal formation (*cf.* Section 1.4.5). The products of these potential multiple tandem reactions, in principle, could be highly complex, while still conserving the inherent  $C_3$ -symmetry of the phloroglucinol (9) template.

## 1.4 Overview of the Chemical Reactions of Phloroglucinol (9)

### 1.4.1 The Triple Electrophilic Aromatic Substitution Reaction of Phloroglucinol (9) with Bromine

A seminal example of the reactivity of phloroglucinol (9) towards electrophiles is Herzig's triple bromination reaction, which dates back to 1885 (Scheme 1.4.1).<sup>6</sup>

#### Scheme 1.4.1.1 Herzig's Triple Bromination of Phloroglucinol (9)<sup>6</sup>



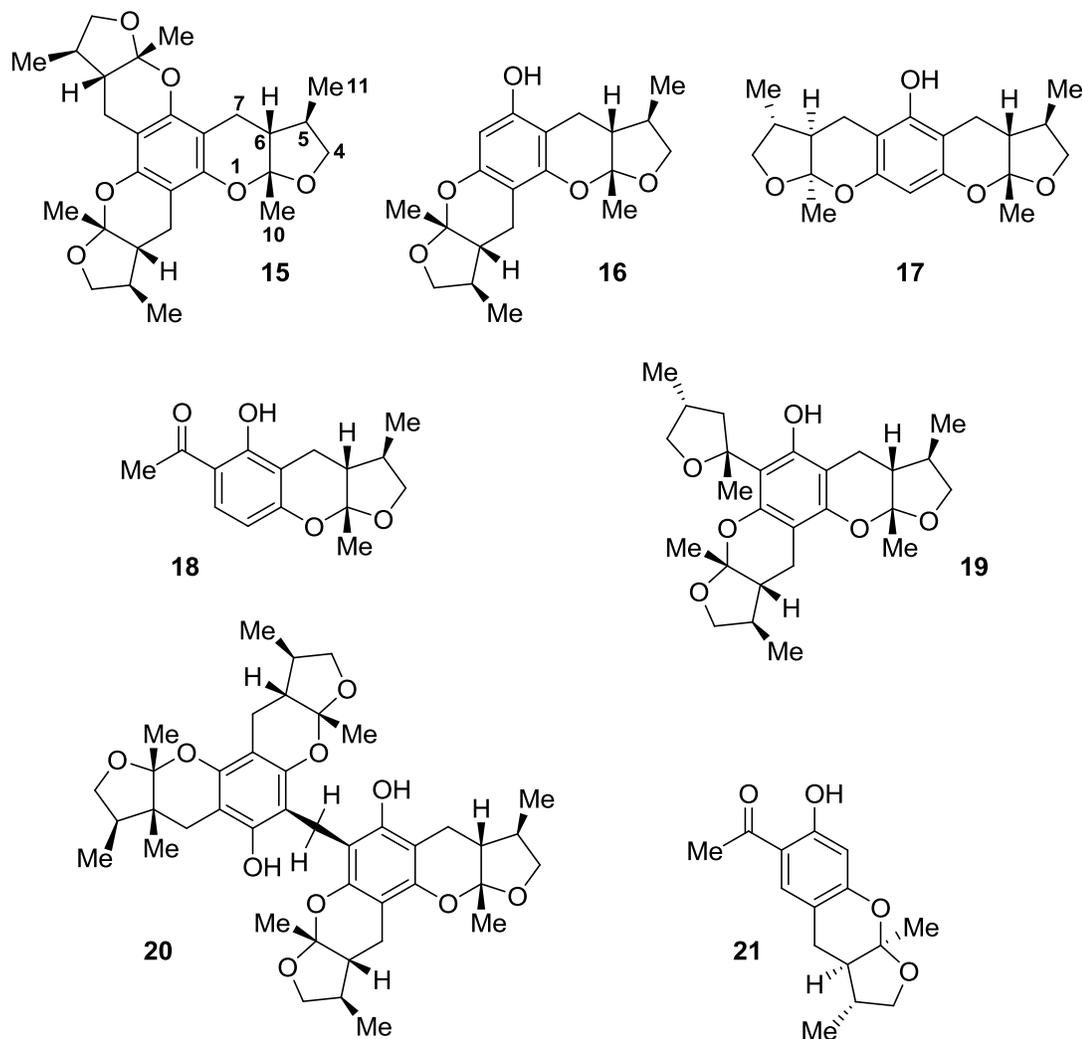
Reagents and conditions: (a) Br<sub>2</sub>, CH<sub>3</sub>CO<sub>2</sub>H.

The mild conditions under which this reaction proceeds, is indicative of phloroglucinol's (9) latent ability to undergo triple electrophilic aromatic substitution reactions in an efficient manner with many classes of both carbon- and non-carbon-based electrophiles (*vide infra*).

### 1.4.2 Overview of the Xyloketal Family of Natural Products

As was previously mentioned, the total synthesis of xyloketal A (15) and the methods devised to complete this synthesis, provided the inspiration for the majority of the research reported in this thesis. As such, a brief synopsis of this work, which was recently completed by Pettigrew *et al.*, as well as an overview of the family of natural products associated with xyloketal A (15), is included to provide background for the first two topics of this thesis. In addition, the syntheses described here will also serve as key examples highlighting the remarkable reactivity of phloroglucinol (9).

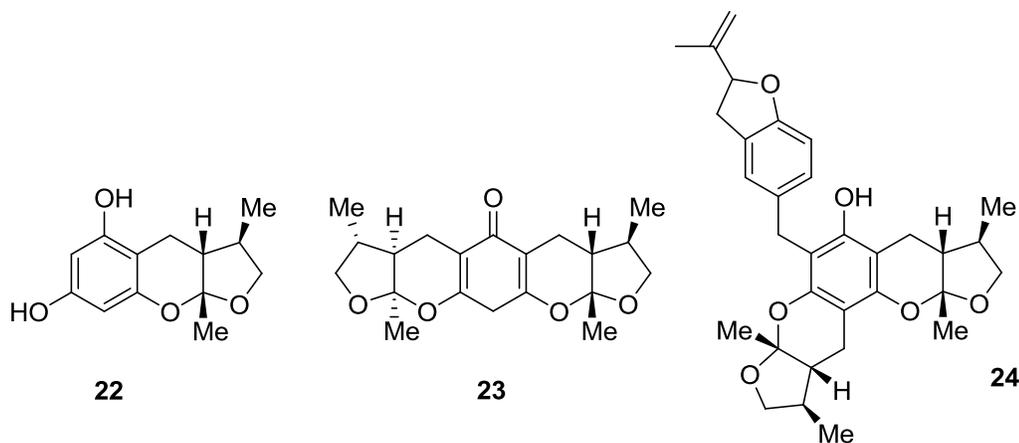
The xyloketals comprise a family of ten structurally-unique natural products (Figures 1.4.2.1 and 1.4.2.2).



**Figure 1.4.2.1** Molecular structures of xyloketal A (15), B (16), C (17), D (18), E (19), F (20) and G (21).<sup>7</sup>

Xyloketal A (15), B (16), C (17), D (18) and E (19) were isolated by Lin *et al.* in 2001 from a mangrove fungus of the *Xylaria* species.<sup>7</sup> Subsequently, xyloketal F (20) and G (21) were isolated by the same group in 2005.<sup>8</sup> More recently, Lin isolated three additional xyloketals through fermentation of the *Xylaria* fungus. The first two of these

compounds, isolated by Lin *et al.* in 2006 and 2008, respectively, were both assigned the same letter [xyloketal H (**22**) and H (**23**)].<sup>9,10</sup> Of note, the latter compound (**23**) is simply the keto-tautomer of xyloketal C (**17**). The third natural product, xyloketal J (**24**), was isolated in 2008 and is related to xyloketal B (**16**) (**Figure 1.4.2.2**).<sup>11</sup>



**Figure 1.4.2.2** Molecular structures of xyloketal H (**22**), H (**23**) and J (**24**).<sup>9,10,11</sup>

The molecular structures of xyloketal A (**15**), D (**18**), F (**20**) and G (**21**) were determined by extensive spectroscopic studies and by X-ray crystallography, and the absolute stereochemistry of these natural products was assigned through interpretation of their CD spectra. The stereochemistry and structure of the remaining members was assigned by analogy.<sup>7-11</sup> The common features of the xyloketals include 5,6-bicyclic acetal moieties fused to a central aromatic core. In addition, the *cis*-ring junctions are *syn* to the stereogenic methyl substituent at C-5 of the five-membered ring in all cases [see molecular structure of xyloketal A (**15**); **Figure 1.4.2.1**].

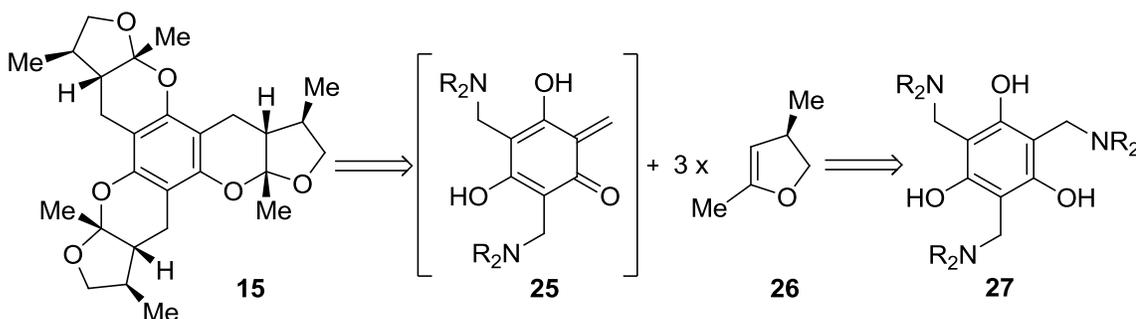
Xyloketal A (**15**), arguably the most interesting member of this family of secondary metabolites due to its bowl-shape and  $C_3$ -symmetry, exhibits notable

biological activity; namely acetylcholine esterase inhibition and L-calcium channel blocking activity.<sup>7</sup> Thus, xyloketal A (**15**) represents a potential lead compound for the treatment of Alzheimer's disease (AD), as a decrease in production of the neurotransmitter acetylcholine has been implicated in the onset of this degenerative condition.<sup>12</sup> The latter, L-calcium channel blocking activity, is a key characteristic of antiarrhythmic and antihypertensive agents, such as Verapamil and Diltiazem, both of which are Class IV antiarrhythmic drugs.<sup>13,14</sup> These biological activities, as well as the novel molecular structures of xyloketal A (**15**) and its related family members, made them attractive targets for total synthesis.

### 1.4.3 Brief Review of the Total Synthesis of Xyloketal A (**15**) and D (**18**)

Retrosynthetic analysis suggested that the 5,6-bicyclic acetal ring system of xyloketal A (**15**) and D (**18**) could be prepared by a [4 + 2] cycloaddition reaction of the *ortho*-quinone methide (**25**) and the dihydrofuran (**26**) (Schemes 1.4.3.1 and 1.4.3.2).<sup>15</sup>

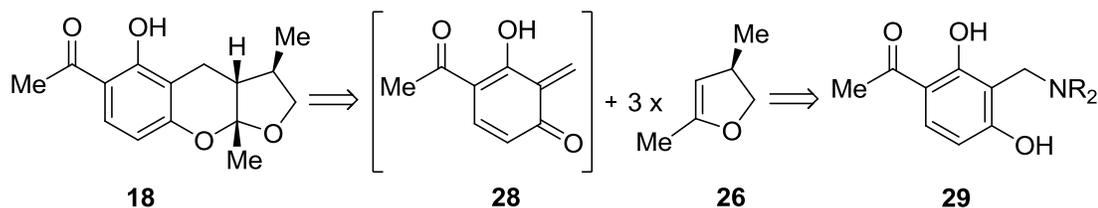
#### Scheme 1.4.3.1 A Retrosynthetic Analysis of Xyloketal A (**15**)<sup>15</sup>



This proposed process represents an example of an inverse electron demand heteroatomic Diels-Alder reaction, which in principle, could afford the target, xyloketal A (**15**) in a regio- and stereoselective manner. In this proposed synthetic route, a C<sub>3</sub>-

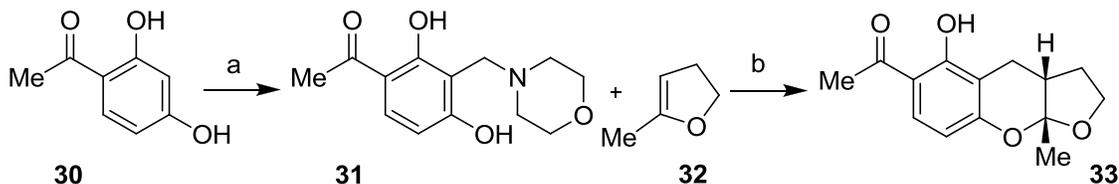
symmetric Mannich base (**27**) would serve as a precursor to the *ortho*-quinone methide (**25**), which in turn would undergo a series of consecutive cycloaddition reactions as described above. By analogy, xyloketal D (**18**) could also be constructed *via* this proposed synthetic route (Scheme 1.4.3.2).<sup>15</sup>

### Scheme 1.4.3.2 A Retrosynthetic Analysis of Xyloketal D (**18**)<sup>15</sup>



As a means to test the viability of the proposed [4 + 2] cycloaddition reaction, the commercially-available, 4,5-dihydro-2-methylfuran (**32**), was chosen as a model compound. The required Mannich base (**31**) was prepared from 2,4-dihydroxyacetophenone (**30**), morpholine, and formaldehyde, whereby the latter two condensed to form an iminium ion, which subsequently underwent an electrophilic aromatic substitution reaction. This led to the synthesis of ( $\pm$ )-norxyloketal D (**33**) (Scheme 1.4.3.3).<sup>15</sup>

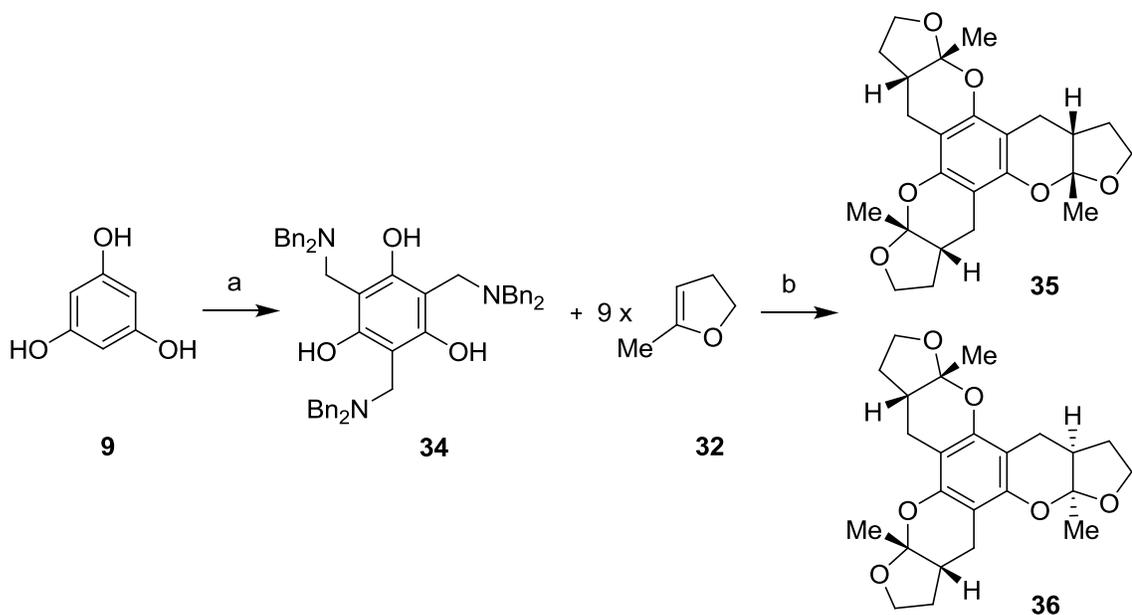
### Scheme 1.4.3.3 Synthesis of ( $\pm$ )-Norxyloketal D (**33**)<sup>15</sup>



Reagents and conditions: (a) Morpholine, CH<sub>2</sub>O, H<sub>2</sub>O, MeOH, reflux, 3 h (82%); (b) MeI (1.1 equiv.), benzene, reflux, 5 days (43%).

This model reaction was also successfully applied to the synthesis of the *tris*-demethyl xyloketal A analogue (**35**), using an adapted literature procedure for the preparation of the triple Mannich base (**34**) from phloroglucinol (**9**), dibenzylamine and formaldehyde *via* a triple electrophilic aromatic substitution reaction (**Scheme 1.4.3.4**).<sup>16</sup> Subsequent treatment of this triple Mannich base (**34**) with methyl iodide (3.1 equiv.) and 4,5-dihydro-2-methylfuran (**32**, 9 equiv.), yielded an inseparable mixture (1:4) of the desired  $C_3$ -symmetric xyloketal A analogue [(±)-**35**] and the diastereoisomer [(±)-**36**] in 19% yield. This was indeed an auspicious result when one considers that this process involves a total of nine reactions; three alkylation reactions, three elimination reactions and finally, three [4 + 2] cycloaddition reactions.

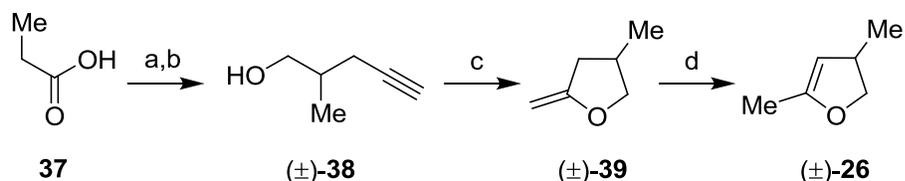
**Scheme 1.4.3.4 Synthesis of Xyloketal A Analogues (35 and 36)**<sup>15</sup>



Reagents and conditions: (a) Dibenzylamine,  $\text{CH}_2\text{O}$ ,  $\text{H}_2\text{O}$ , EtOH, rt, 24 h (93%); (b) MeI (3.1 equiv.), benzene, reflux, 24 h (19%).

In order to complete the synthesis of ( $\pm$ )-xyloketal D [( $\pm$ )-**18**], the racemic dihydrofuran ( $\pm$ )-**26** was prepared using modified literature procedures from propionic acid (**37**, **Scheme 1.4.3.5**).<sup>15</sup>

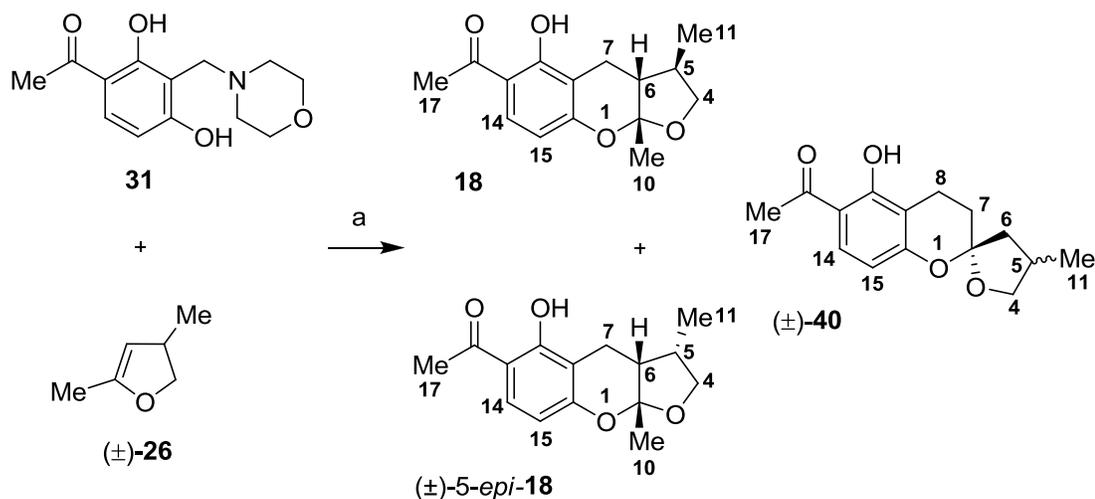
**Scheme 1.4.3.5 Synthesis of Racemic Dihydrofuran [( $\pm$ )-**26**]<sup>15</sup>**



Reagents and conditions: (a) LDA, HMPA, THF, 0 °C to rt, 1 h then propargyl bromide, 0 °C to rt, 3 h (63%); (b) LiAlH<sub>4</sub>, THF, 0 °C to rt, 16 h (74%); (c) NaNH<sub>2</sub>, reflux, 2 h (66%); (d) reflux, 16 h (87%).

First, the dianion of propionic acid (**37**) was reacted with propargyl bromide and the resultant product was reduced with lithium aluminum hydride to afford the alcohol ( $\pm$ )-**38**. Subsequent treatment of this compound with sodium amide facilitated the formation of the exocyclic enol ether ( $\pm$ )-**39**, which was thermally-isomerized to the dihydrofuran ( $\pm$ )-**26**. This compound was then subjected to the conditions which were employed in the synthesis of ( $\pm$ )-norxyloketal D [( $\pm$ )-**33**] discussed above (**Scheme 1.4.3.3**). Thus, reaction of the dihydrofuran ( $\pm$ )-**26** (3 equiv.) with the Mannich base **31** and methyl iodide (1.1 equiv.), led to a mixture of ( $\pm$ )-xyloketal D [( $\pm$ )-**18**], ( $\pm$ )-5-*epi*-xyloketal D [( $\pm$ )-5-*epi*-**18**] and a pair of diastereoisomeric ( $\pm$ )-spiroacetals ( $\pm$ )-**40** in 54% yield (11:1:3:3).<sup>15</sup> The spiroacetal byproducts of this reaction were proposed to arise from isomerisation and subsequent reaction of the exocyclic *regio*-isomer **39** of the dihydrofuran ( $\pm$ )-**26**, under these conditions. Of note, these spiroacetal byproducts were not observed in the model system involving 4,5-dihydro-2-methylfuran (**32**). It was concluded therefore, that the additional methyl substituent decreased the reactivity of the endocyclic double bond towards the cycloaddition reaction (**Scheme 1.4.3.6**).<sup>15,17</sup>

**Scheme 1.4.3.6 Synthesis of (±)-Xyloketal D [(±)-18]**<sup>15,17</sup>

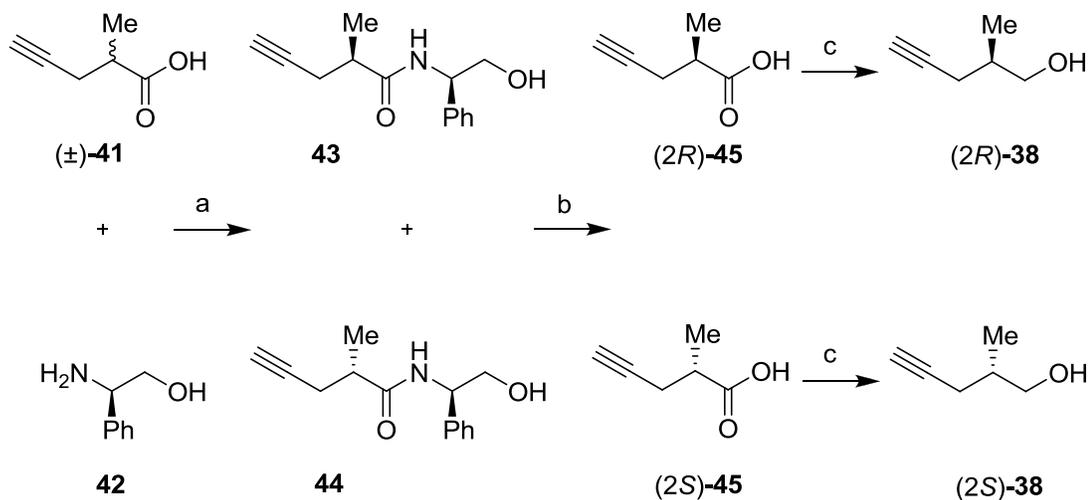


Reagents and conditions: (a) MeI (1.1 equiv.), benzene, reflux, 5 days [54% {**18**, (±)-5-*epi*-**18**, **40** and **40** (11:1:3:3)}].

Whereas (±)-xyloketal D [(±)-**18**] was successfully prepared using this method, it was not possible to isolate (±)-xyloketal A [(±)-**15**] from the complex mixtures that resulted when attempts were made to couple the dihydrofuran (±)-**26** with the triple Mannich base **34**. It was assumed that the observed array of inseparable reaction products was due to formation of numerous diastereoisomeric and spirocyclic isomers.<sup>15,17</sup>

Building on the successful synthesis of racemic (±)-xyloketal D [(±)-**18**], an asymmetric total synthesis of (–)-xyloketal D [(–)-**18**] and its enantiomer was undertaken. This would involve the preparation of both enantiomers of (±)-dihydrofuran (±)-**26**.<sup>17</sup> After a thorough investigation of possible resolution protocols, the diastereoisomeric amides **43** and **44** were prepared from the racemic carboxylic acid (±)-**41** and (*R*)-phenylglycinol (**42**), in reasonable yield and were found to be isolable and separable *via* flash chromatography (Scheme 1.4.3.7).<sup>17</sup>

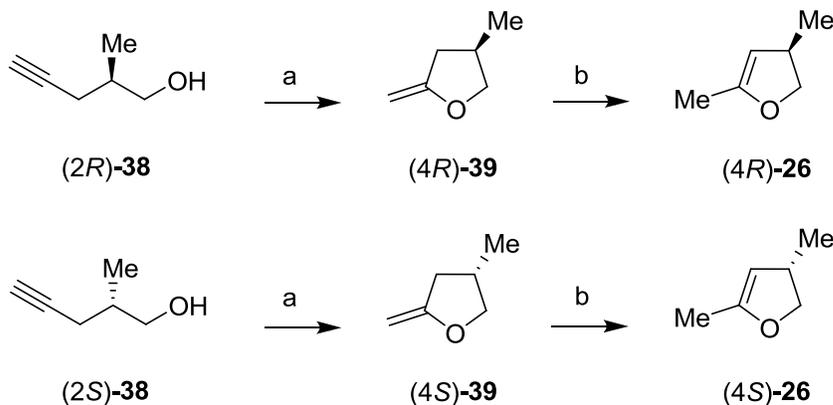
**Scheme 1.4.3.7 Resolution of ( $\pm$ )-Methylpent-4-ynoic Acid [( $\pm$ )-**41**] and Synthesis of (*2R*)-2-Methylpent-4-yn-1-ol [(*2R*)-**38**] and (*2S*)-2-Methylpent-4-yn-1-ol [(*2S*)-**38**]<sup>17</sup>**



Reagents and conditions: (a) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, DMF (cat.), 0 °C to rt, 2 h; (*R*)-phenylglycinol (**42**), NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 16 h [36% (**43**), 34% (**44**)]; (b) 3M H<sub>2</sub>SO<sub>4</sub>, *p*-dioxane, reflux, 7 h; (c) LiAlH<sub>4</sub>, THF, 0 °C to rt, 16 h [89% {(*2R*)-**38**}, 85% {(*2S*)-**38**}].

These amides were subsequently converted to their corresponding chiral nonracemic carboxylic acids (*2R*)-**45** and (*2S*)-**45** by hydrolysis under acidic conditions. These carboxylic acids were then reduced to the chiral nonracemic alcohols (*2R*)-**38** and (*2S*)-**38** using lithium aluminum hydride. A small sample of each of these was in turn converted to their corresponding benzyl ethers. The optical rotation of the benzyl ether of alcohol (*2R*)-**38** had been previously reported and as such the absolute stereochemistry of both enantiomers of the benzyl ether's progenitors could be confirmed.<sup>17</sup> Finally, using the method described above for the preparation of the racemic dihydrofuran [( $\pm$ )-**26**, Scheme 1.4.3.5], the chiral nonracemic dihydrofurans (*4R*)-**26** and (*4S*)-**26** were also prepared (Scheme 1.4.3.8).<sup>17</sup>

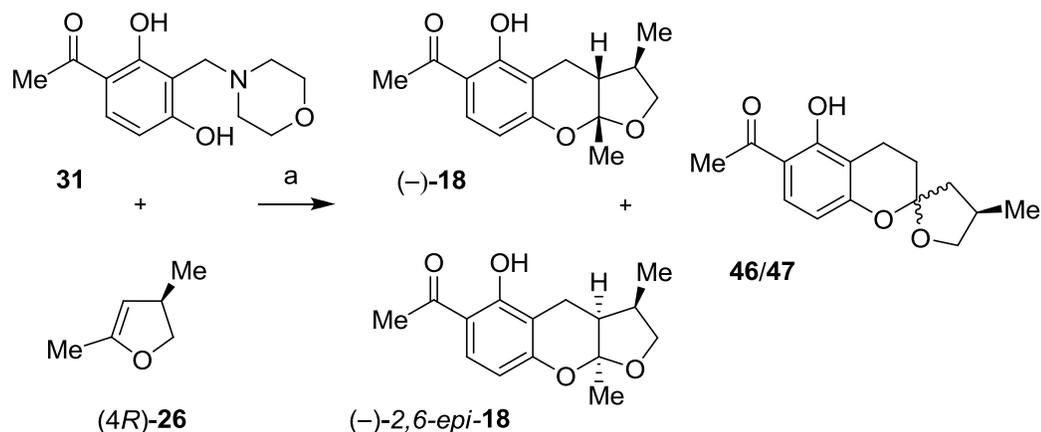
**Scheme 1.4.3.8** Synthesis of **(4R)-4,5-Dihydro-2,4-dimethylfuran [(4R)-26]** and **(4S)-4,5-Dihydro-2,4-dimethylfuran [(4S)-26]**<sup>17</sup>



Reagents and conditions: (a)  $\text{NaNH}_2$ , reflux, 2 h; (b) reflux, 2 h [44% {(4R)-26}, over two steps, 36% {(4S)-26}, over two steps].

In turn, these chiral nonracemic dihydrofurans **(4R)-26** and **(4S)-26** were subjected to the conditions that had been used previously for the synthesis of ( $\pm$ )-xyloketal D (**18**, **Scheme 1.4.3.6**). This led to the successful asymmetric syntheses of both ( $-$ )-xyloketal D [ $(-)$ -**18**, **Scheme 1.4.3.9**] and its enantiomer [*ent*-**18**, not shown].<sup>17</sup>

**Scheme 1.4.3.9 Asymmetric Total Synthesis of (-)-Xyloketal D [(-)-18]<sup>17</sup>**



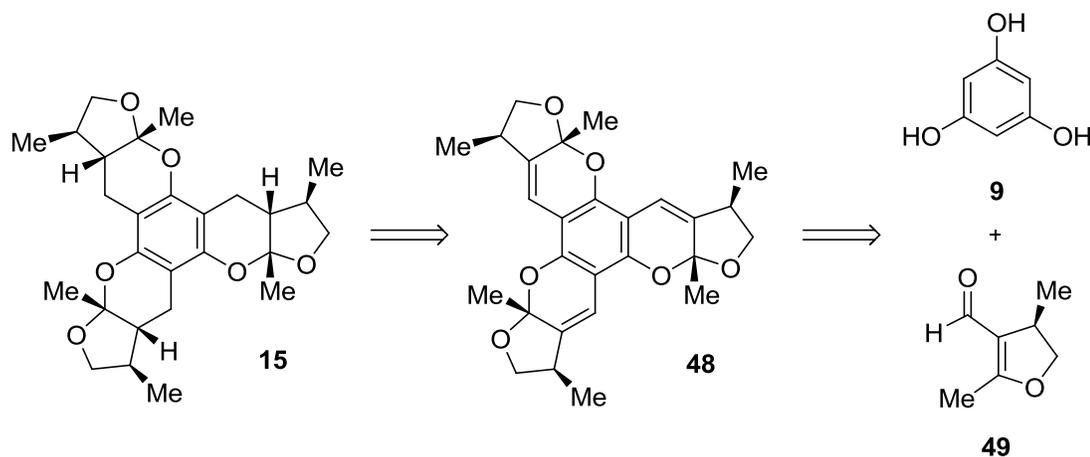
Reagents and conditions: (a) Dihydrofuran (*4R*)-**26** (3 equiv.), MeI (1 equiv.), benzene, reflux, 8 days [40% {**18**, (-)-2,6-*epi*-**18**, **46** and **47** (8:1:2:2)}] or dihydrofuran (*4R*)-**26** (3 equiv.), Me<sub>2</sub>SO<sub>4</sub> (1 equiv.), benzene, reflux, 3 days [37% {**18**, (-)-2,6-*epi*-**18**, **46** and **47** (16:1:4:4)}].

With respect to the asymmetric total synthesis of xyloketal A (**15**), attempts were also made to couple these chiral nonracemic dihydrofurans (*4R*)-**26** and (*4S*)-**26** to phloroglucinol (**9**) using the reagents and conditions that were employed to construct the demethyl xyloketal A analogues **35** and **36** (Scheme 1.4.3.4). The target molecule, (-)-xyloketal A [(-)-**15**] could not, however, be isolated from the complex mixture of reaction products that formed in this case. This result was analogous to the complex mixtures that were obtained from attempts to synthesize (±)-xyloketal A [(±)-**15**] using the racemic dihydrofuran (±)-**26**.

#### 1.4.4 Brief Review of Phenylboronic Acid-Mediated Triple Condensation Reaction of Phloroglucinol (**9**)

Concurrent with the investigations described in the previous section, an alternate route towards the total synthesis of xyloketal A (**15**) was also explored. This involved the potential use of a phenylboronic acid-mediated triple condensation reaction of phloroglucinol (**9**) (Scheme 1.4.4.1).<sup>18</sup>

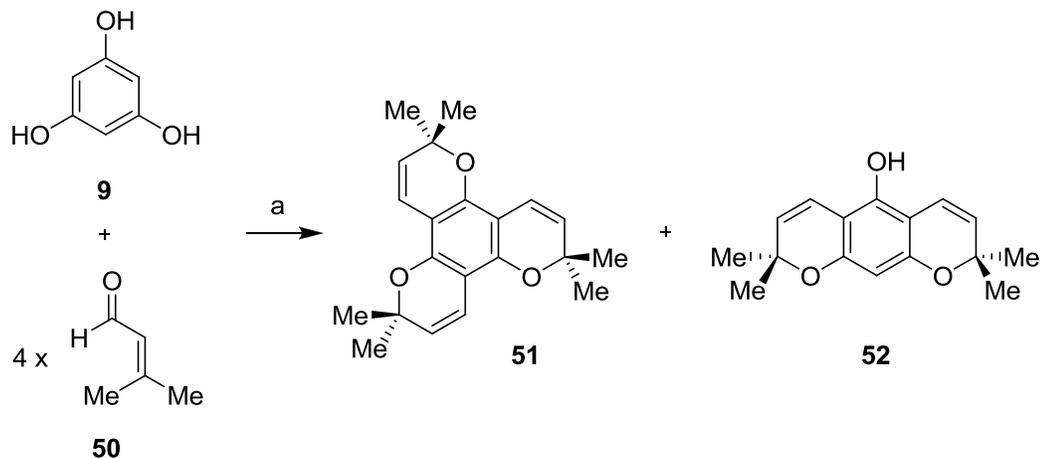
##### Scheme 1.4.4.1 Alternative Retrosynthetic Analysis of Xyloketal A (**15**)<sup>18</sup>



In this route, xyloketal A (**15**) could be formed by a stereoselective hydrogenation reaction of the C<sub>3</sub>-symmetric 2H-chromene derivative **48**. The penultimate step in this route, would involve the aforementioned phenylboronic acid-mediated triple condensation reaction of phloroglucinol (**9**) with three equivalents of the  $\alpha,\beta$ -unsaturated aldehyde **49**. Notably, this process features three electrophilic aromatic substitution reactions followed by three dehydrative-cyclization reactions. The conditions for this remarkable tandem reaction were optimized through an extensive methodological study involving phloroglucinol (**9**), senecialdehyde (**50**), phenyl boronic acid and various Lewis

and Brønsted acid promoters. The best set of reaction conditions for this transformation is indicated below (**Scheme 1.4.4.2**).<sup>18</sup>

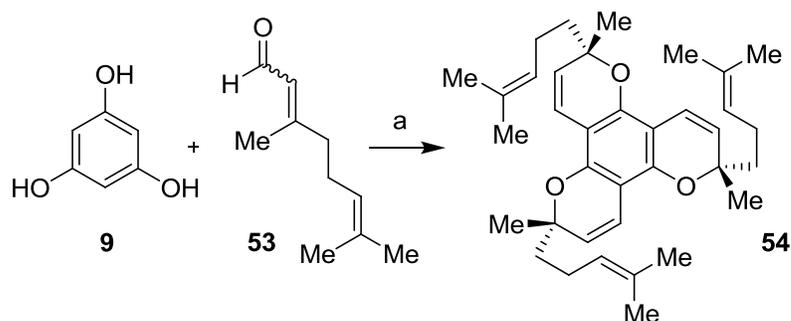
**Scheme 1.4.4.2** Synthesis of *C*<sub>3</sub>-Symmetric *2H*-Chromene Derivative (**51**)<sup>18</sup>



Reagents and conditions: (a)  $\text{PhB(OH)}_2$  (3 equiv.), propionic acid, benzene, reflux, Dean-Stark trap, 22 h [92% (**51**), 6% (**52**)].

The optimization study, that was carried out with senecialdehyde (**50**) serving as the model aldehyde, was part of a wider investigation in which a variety of  $\alpha,\beta$ -unsaturated aldehydes were tested in the phenylboronic acid-mediated triple condensation reaction. An example of one such member in the series of substituted *tris-2H*-chromene derivatives that were prepared using the prescribed method is shown below (**Scheme 1.4.4.3**).<sup>18</sup>

### Scheme 1.4.4.3 Synthesis of $C_3$ -Symmetric *tris*-2*H*-Chromene Derivative (**54**)<sup>18</sup>

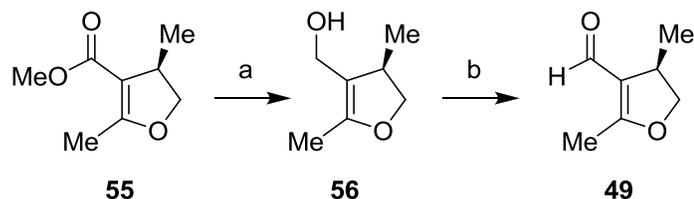


Reagents and conditions: (a)  $\text{PhB(OH)}_2$  (3 equiv.), propionic acid, benzene, reflux, Dean-Stark trap, 4 h (31%).

In this case, citral (**53**,  $E:Z = \sim 2:1$ ) was employed as the  $\alpha,\beta$ -unsaturated aldehyde substrate. The triple adduct **54** was prepared in good yield and was formed and isolated as a single  $C_3$ -symmetric diastereoisomer. Additionally, attempts were made, unsuccessfully, to affect a triple [2+2] cycloaddition reaction between the pendant trisubstituted double bonds and the 2*H*-chromene moieties. This reaction was proposed as part of a subsequent investigation, the goal of which was to probe the reactivity of the double bonds of these *tris*-2*H*-chromenes.<sup>18</sup>

In regard to the proposed synthetic route towards xyloketal A (**15**) outlined above (Scheme 1.4.4.1), the aldehyde precursor **49** that would be required, was prepared *via* a two-step reduction and oxidation reaction sequence from the chiral nonracemic methyl ester **55** (Scheme 1.4.4.4).<sup>19</sup> The synthesis of this methyl ester **55** *en route* to the alcohol **56** will be discussed in the following section.

#### Scheme 1.4.4.4 Synthesis of the $\alpha,\beta$ -Unsaturated Aldehyde (**49**)<sup>19</sup>



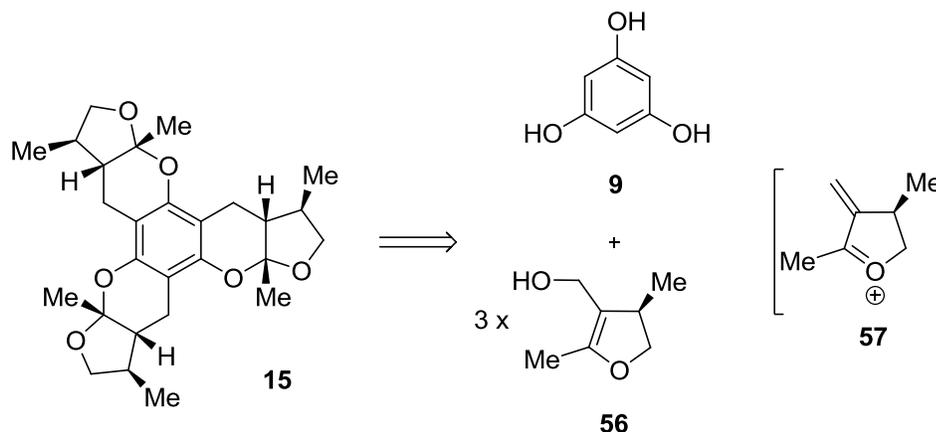
Reagents and conditions: (a)  $\text{LiAlH}_4$ , ether,  $0\text{ }^\circ\text{C}\rightarrow\text{rt}$ , 20 min; (b)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 46 h (34%, over two steps, ~70% pure)

Unfortunately, this  $\alpha,\beta$ -unsaturated aldehyde **49** proved to be unstable towards the conditions for the proposed triple electrophilic aromatic substitution and condensation reactions of phloroglucinol (**9**, Scheme 1.4.4.1).<sup>19</sup>

#### 1.4.5 Brief Review of the Total Synthesis of Xyloketal A (**15**) via a Triple Electrophilic Aromatic Substitution Reaction of Phloroglucinol (**9**)

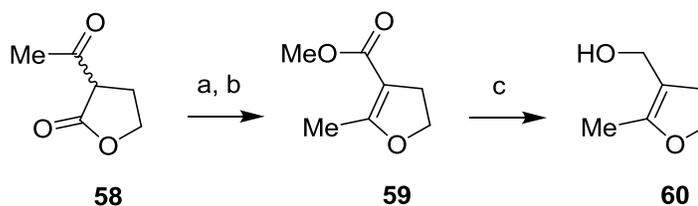
A third route that was considered for the total synthesis of xyloketal A (**15**), involved a proposed triple electrophilic aromatic substitution reaction of phloroglucinol (**9**) with the  $\alpha,\beta$ -unsaturated alcohol **56** upon treatment with an appropriate Lewis or protic acid. This would involve elimination of the alcohol functional group to form the carbon-based electrophilic species **57** which, in principle, would then undergo the aforementioned triple EAS reaction. Subsequently, the phenol moieties of phloroglucinol (**9**) could undergo acetal formation reactions, resulting in xyloketal A (**15**, Scheme 1.4.5.1).<sup>20</sup>

**Scheme 1.4.5.1 Second Alternative Retrosynthetic Analysis of Xyloketal A (15)<sup>20</sup>**



In order to test this hypothesis, a model system, using 3-hydroxymethyl-2-methyl-4,5-dihydrofuran (**60**) as a reaction substrate, was employed. This compound was prepared from the commercially-available lactone **58** *via* a two-step process. The known ester **59** was generated in the first step on heating the lactone **58** in methanol in the presence of hydrogen chloride and subsequent redistillation from a catalytic amount of sulfuric acid. In the second step, reduction of this ester **59** with lithium aluminum hydride afforded the required  $\alpha,\beta$ -unsaturated alcohol **60**. This model compound was found to be unstable however, and was thus carried forward to the next step without purification (**Scheme 1.4.5.2**).<sup>20</sup>

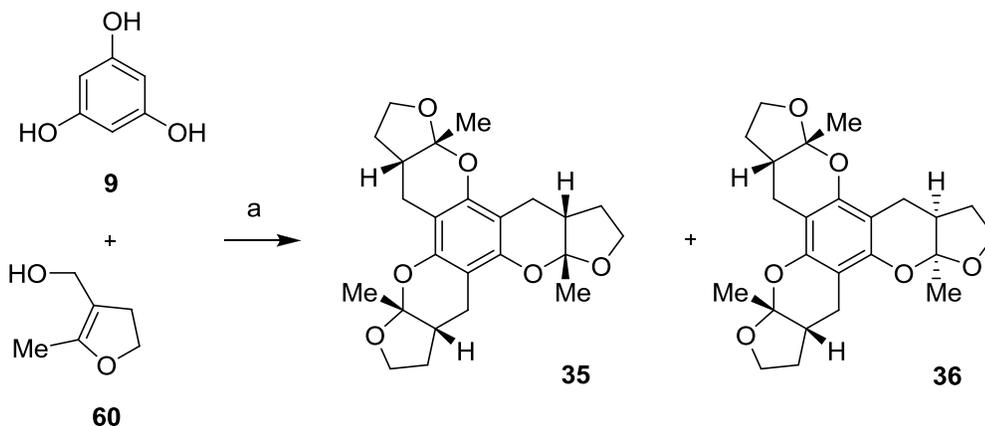
**Scheme 1.4.5.2 Synthesis of 3-Hydroxymethyl-2-methyl-4,5-dihydrofuran (60)<sup>20</sup>**



Reagents and conditions: (a) HCl (g), MeOH, reflux, 4 days followed by distillation; (b) H<sub>2</sub>SO<sub>4</sub> (cat.), distillation (19%, over two steps); (c) LiAlH<sub>4</sub>, ether, 0 °C to rt, 20 min (96%).

With a method to prepare the desired substrate in place, an extensive optimization study was undertaken to determine the conditions required to form the ring system of xyloketal A (**15**). The initial conditions that were used for this transformation were derived from those reported by Razdan *et al.* in their synthesis of  $\Delta^1$ -tetrahydrocannabinol (THC) (see Section 3.1).<sup>21</sup> Thus, for each phenolic reactive site on phloroglucinol (**9**), two equivalents of the alcohol **60** were used. These two starting materials were dissolved in ether at 0 °C and to this mixture was added anhydrous magnesium sulfate and boron trifluoride diethyl etherate (2.7 equivalents). Under these conditions, the known xyloketal A analogues **35** and **36** were isolated in 36% yield, as an inseparable mixture of diastereoisomers (~2:7, **35:36**).<sup>20</sup> The yield of this reaction, while only moderate, is indeed remarkable when the number of individual reactions that take place in this process (three electrophilic aromatic substitutions and three separate acetal formation reactions) and the complexity of the system being generated (seven rings and six stereogenic centres) is taken into account (*cf.* **Scheme 1.4.3.4**). Variation of parameters such as temperature and equivalents of acid, led to an optimized set of reaction conditions (**Scheme 1.4.5.3**).<sup>20</sup>

### Scheme 1.4.5.3 Synthesis of Xyloketal A Analogues (35 and 36)<sup>20</sup>



Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv.),  $\text{MgSO}_4$ , ether, 0 °C, ~15 min [93%, ~2:7 (35:36)].

Additionally, this model study was successfully adapted for the synthesis of the demethylated analogues of xyloketal B (61), D (33) and G (62).<sup>20</sup>

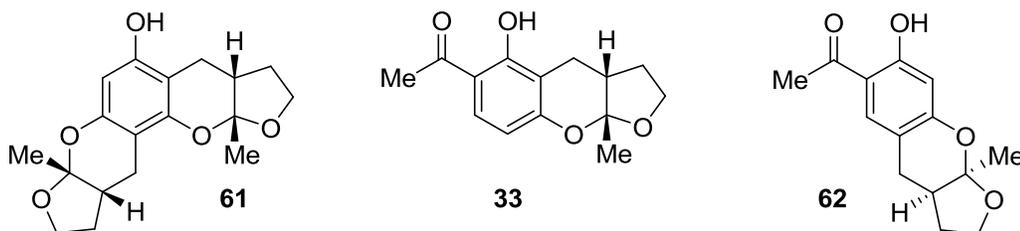
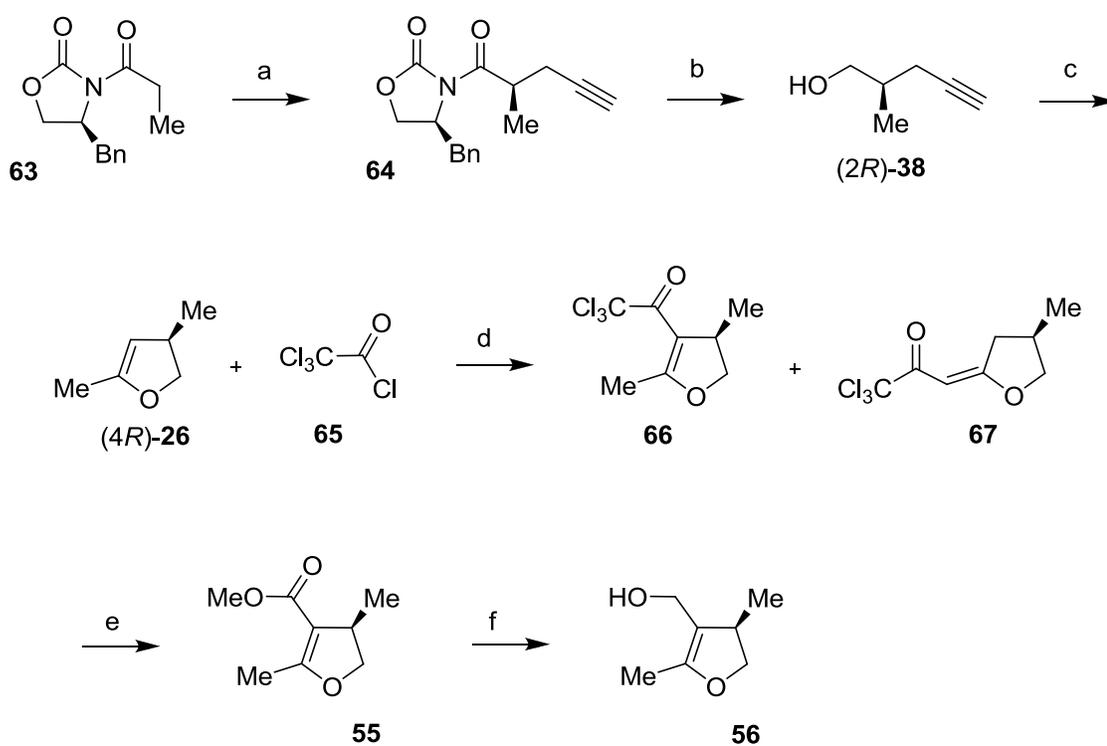


Figure 1.4.5.1 Analogues of xyloketal B (61), D (33) and G (62).<sup>20</sup>

Finally, in order to complete an asymmetric total synthesis of xyloketal A (15), a concise asymmetric method for the preparation of the chiral nonracemic alcohol 56 was developed (Scheme 1.4.5.4).<sup>22</sup> The known oxazolidinone chiral auxiliary (63) was deprotonated with lithium diisopropylamide (LDA, 1.5 equiv.) in a mixture of tetrahydrofuran and hexamethylphosphoramide (HMPA, ~ 10%), and then alkylated with propargyl bromide (4 equiv.), to yield the oxazolidinone 64 in 77% yield and as a single diastereoisomer. Subsequent reduction with lithium aluminum hydride resulted in the

formation of the chiral nonracemic alcohol (2*R*)-**38**, which upon heating with a substoichiometric amount of sodium amide followed by thermal isomerisation of the corresponding *exo*-cyclic dihydrofuran, led to the *endo*-cyclic dihydrofuran (4*R*)-**26**. This compound was then converted to the methyl ester **55** via methanolysis of the trichloroketone **66** using known literature procedures.<sup>22</sup>

#### Scheme 1.4.5.4 Asymmetric Synthesis of $\alpha,\beta$ -Unsaturated Alcohol (**56**)<sup>22</sup>

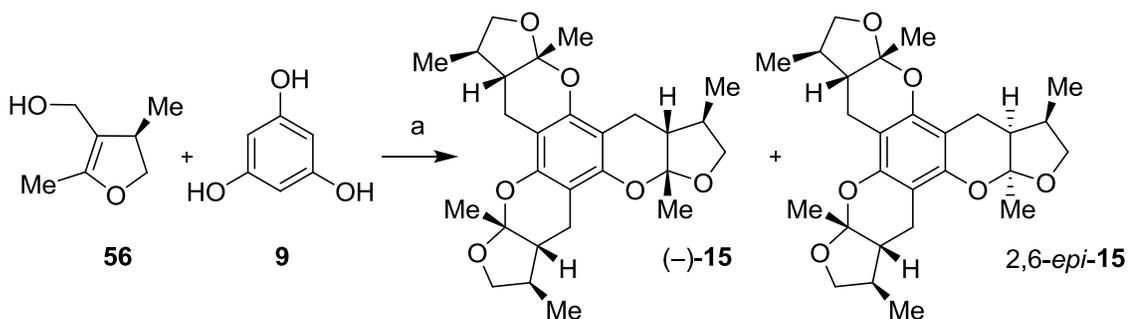


Reagents and conditions: (a) LDA, HMPA, -78 °C, 30 min; propargyl bromide, -78 °C, 20 h (77%); (b) LiAlH<sub>4</sub>, THF, 0 °C, 45 min (73%); (c) NaNH<sub>2</sub>, reflux, 4 h, distillation; reflux, 18 h (74%); (d) pyridine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min [45% (**66**), 46% (**67**)] or pyridine, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to rt, 21 h [93% (**66**)]; (e) NaHCO<sub>3</sub>, MeOH, reflux, 1 h (98%); (f) LiAlH<sub>4</sub>, Et<sub>2</sub>O, 0 °C to rt, 20 min.

Finally, treatment of the methyl ester **55** with lithium aluminum hydride led to formation of the desired  $\alpha,\beta$ -unsaturated alcohol **56** (Scheme 1.4.5.4). As this compound proved to be relatively unstable to isolation and purification, it was used directly in subsequent reactions. Thus, as per the method established for the model compound **35**

(*cf.* **Scheme 1.4.5.3**), six equivalents of the  $\alpha,\beta$ -unsaturated alcohol **56** were added to a suspension of phloroglucinol (**9**) and anhydrous magnesium sulfate in ether. To this mixture, boron trifluoride diethyl etherate was then added at 0 °C. The ensuing reaction was deemed complete by TLC after only 20 min, and resulted in the formation of an inseparable mixture of xyloketal A (**15**) and 2,6-*epi*-xyloketal A (2,6-*epi*-**15**) in 85% yield (dr = 5:2, **Scheme 1.4.5.5**).<sup>22</sup>

**Scheme 1.4.5.5 First Total Synthesis of Xyloketal A (**15**) and 2,6-*epi*-Xyloketal A (**15**)<sup>22</sup>**



Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv.),  $\text{MgSO}_4$ , ether, 0 °C, 20 min [85%, over two steps, dr = 5:2 (**15**:2,6-*epi*-**15**)].

Initially, the diastereoselectivity of the individual ring formation reactions was satisfactory, with dr = 9:1. However, when the above reaction was repeated at -78 °C, the diastereoselectivities of both the overall process and the individual ring formation reactions were greatly improved, increasing to 4:1 and ~19:1, respectively. Finally, the  $C_3$ -symmetric natural product, (-)-xyloketal A [(-)-**15**], was isolated in analytically pure form upon crystallization from petroleum ether. This result by Pettigrew and co-workers constituted the first asymmetric total synthesis of (-)-xyloketal A [(-)-**15**], and moreover, serves as an outstanding example of the remarkable reactivity of phloroglucinol (**9**). In

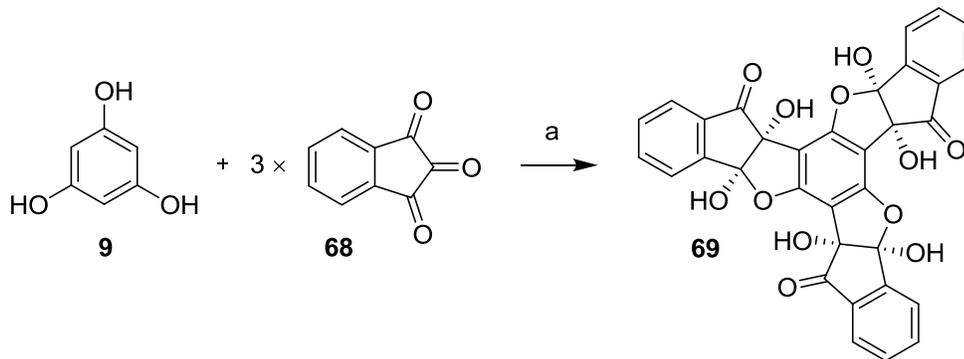
addition, this synthetic strategy, while not discussed here, was also applied to the asymmetric total syntheses of xyloketal B (**16**), D (**18**) and G (**21**).<sup>19,22</sup>

As an aside, Lin and co-workers, the group that was also responsible for the isolation and characterization of all of the constituent members of the xyloketal family of natural products, recently carried out a structure-activity relationship (SAR) study on a series of racemic xyloketal B (**16**) derivatives.<sup>23</sup> These analogues were assessed for their vasorelaxing activity in the thoracic aorta of rats, and their angiogenic activity in a Zebrafish angiogenesis screen. Several of the derivatives exhibited improved vasorelaxation activity over the lead compound, xyloketal B (**16**).

#### **1.4.6 Selected Literature Examples Highlighting the Chemistry of Phloroglucinol (9)**

Recently, Kim and co-workers reported the serendipitous one-pot synthesis of the structurally-complex molecule **69** in high yield and purity, from the reaction of phloroglucinol (**9**) and ninhydrin (**68**), in the presence of acetic acid. Furthermore, this bowl-shaped adduct **69** was prepared *via* a triple electrophilic aromatic substitution reaction, followed by three tandem hemiacetal formation reactions (**Scheme 1.4.6.1**).<sup>24</sup>

**Scheme 1.4.6.1 Kim's Synthesis of the  $C_3$ -Symmetric Bowl-Shaped Adduct (69) of Phloroglucinol (9) and Ninhydrin (68)<sup>24</sup>**

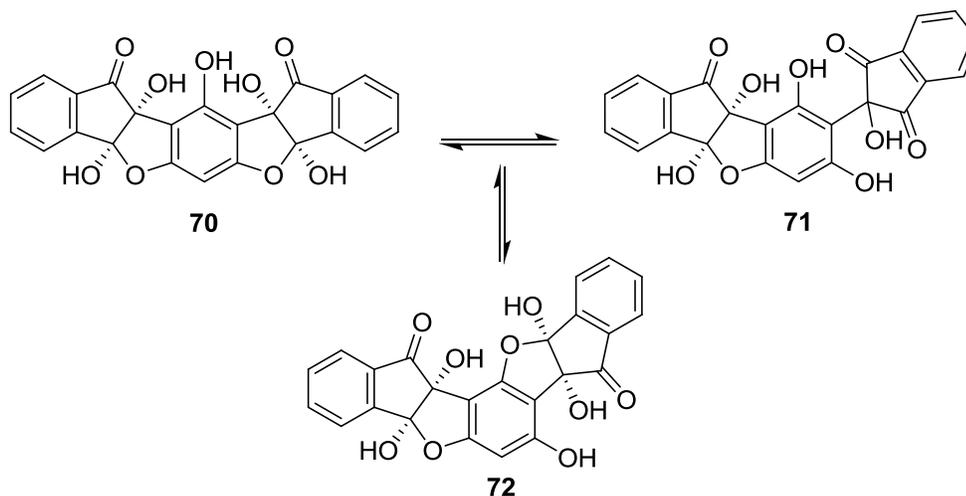


Reagents and conditions: (a) Acetic acid, 80-90 °C, 12 h (95%).

Interestingly, this study has led to the preparation of a molecule with so-called bipolarfacial properties. In other words, the opposing sides of this molecule are hydrophobic and hydrophilic.

In a subsequent study, Cohen and co-workers determined that the formation of Kim's  $C_3$ -symmetric *tris*-adduct and the related *mono*- and *bis*-adducts, involved dynamic interconversions between the fully-formed cyclic adducts (70 and 72) and the ring-open hemiketals (71, Scheme 1.4.6.2).<sup>25</sup>

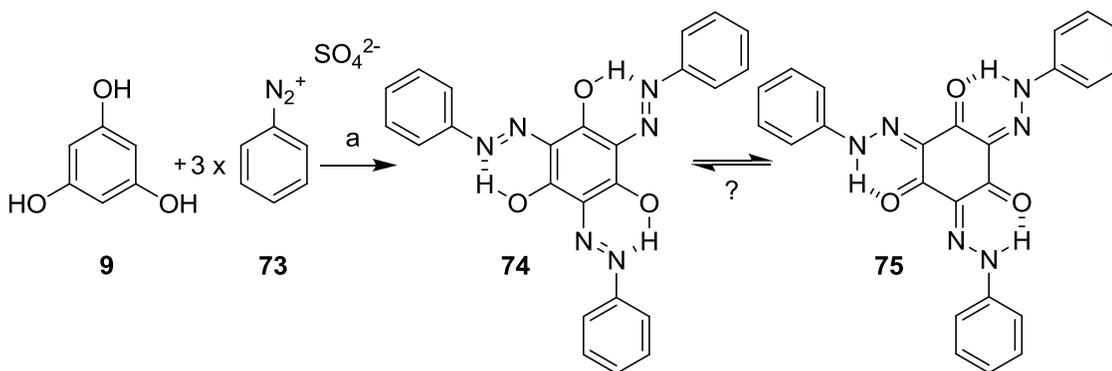
**Scheme 1.4.6.2** Cohen and Co-worker's Dynamic Equilibrium of *bis*-Adducts (**70**) and (**72**)<sup>25</sup>



The authors found that in the presence of less than three equivalents of ninhydrin (**68**), the C<sub>2</sub>-symmetric *bis*-adduct **70** was formed predominantly along with minor amounts of several other isomeric products. However, when a third equivalent of ninhydrin (**68**) was added to the reaction mixture, all of the *bis*-adducts were eventually converted to the C<sub>3</sub>-symmetric adduct **69**.

One of the earliest examples of a triple EAS reaction of phloroglucinol (**9**) was described by Perkin in 1897.<sup>26</sup> This involved a so-called triple azo coupling reaction, in the presence of aqueous sodium carbonate, with phloroglucinol (**9**), to form what at that time was reported as the *tris*(azo-enol) tautomer **74**. Subsequent studies have attempted to show that the tautomer **74** exists in equilibrium with the *tris*(keto-hydrazone) tautomer **75**. To date however, no study has succeeded in unambiguously assigning the predominant product of this reaction, or established the proposed equilibrium (**Scheme 1.4.6.3**).<sup>27</sup>

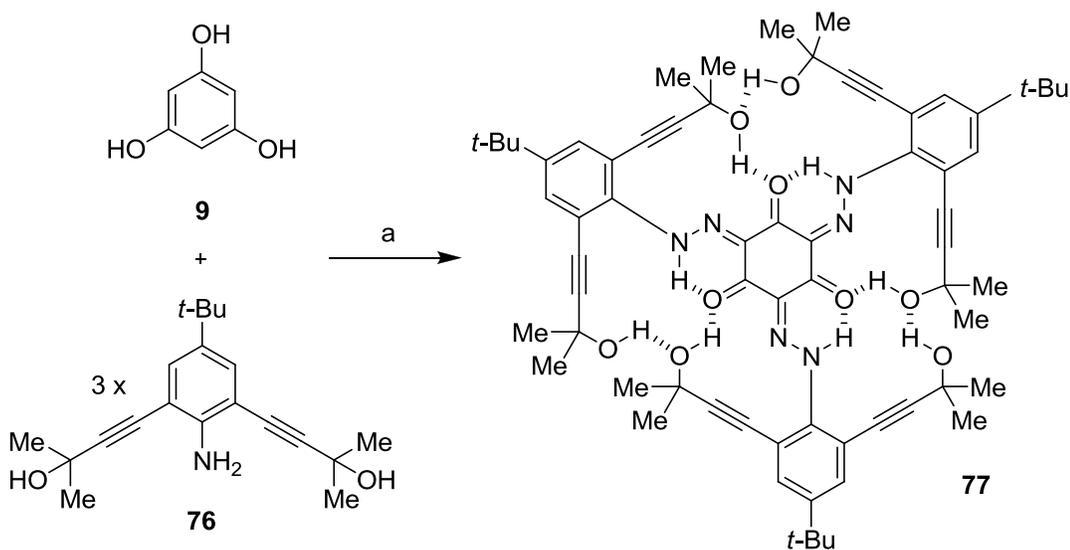
**Scheme 1.4.6.3 Perkin's Synthesis of the  $C_3$ -Symmetric Chromophore (74)<sup>26</sup>**



Reagents and conditions: (a)  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ .

In a recent study by Lee and co-workers, a series of molecules based on this triple azo coupling reaction with phloroglucinol (**9**) have been reported, one of which is shown below (Scheme 1.4.6.4).<sup>27</sup>

**Scheme 1.4.6.4 Lee's Synthesis of the Conjugated,  $C_3$ -Symmetric *tris*(hydrazone) Framework (77)<sup>27</sup>**



Reagents and conditions: (a) **76**, HCl (2M in  $\text{H}_2\text{O}/\text{MeOH}$ ), 0 °C, then  $\text{NaNO}_2$ ,  $\text{H}_2\text{O}$ , 0 °C, 20 min, then **9**, NaOH (2M in  $\text{H}_2\text{O}/\text{MeOH}$ ), 0 °C, 50 min (81%).

This study had two central aims, the first of which was to illuminate the nature of the azo-hydrazone tautomerism that has been proposed for molecules of this type, whilst the second entailed an exploration of the potential optoelectronic properties of the conjugated framework depicted in the *tris*(hydrazone) product **77**. The authors proposed that these properties could be modified through conformational switching, *via* disruption of the network of hydrogen bonds.

In regard to the first goal of the investigation, Lee and co-workers demonstrated that the keto-hydrazone tautomer predominated over the azo-enol tautomer for the series of molecules they prepared, through extensive NMR spectroscopy experiments and density functional theory calculations. As for the second goal, through interaction with so-called exogenous agents (*i.e.* additives such as small secondary amines), the authors established methods to disrupt the hydrogen bond network of compound **77** (and related compounds), thereby affecting reversible conformational changes in the conjugated framework, which in turn led to reversible colour-switching behaviours.

The above examples demonstrate that phloroglucinol (**9**) can be employed as a highly reactive core around which complex molecular architectures can be constructed. Moreover, the properties of the resultant molecules can be remarkable and interesting. Thus, there is potential to further augment these studies, and to explore the rapid assembly of complex  $C_3$ -symmetric polycyclic molecules from phloroglucinol (**9**) *via* triple electrophilic aromatic substitution reactions.

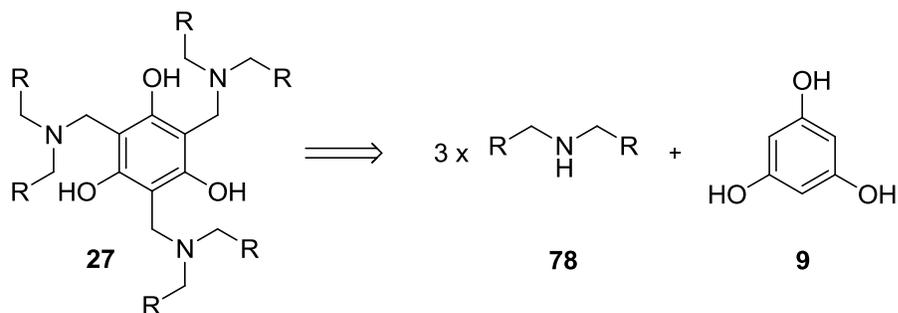
## 1.5 General Thesis Overview

As mentioned earlier (Section 1.1), this thesis comprises two investigations which are related thematically through the study of electrophilic aromatic substitution reactions. *Chapter 2* of this thesis concerns a discussion of the synthesis of a series of triple Mannich Bases from phloroglucinol (**9**) using electrophilic aromatic substitution reactions. *Chapter 3* similarly concerns the electrophilic aromatic substitution of phloroglucinol (**9**). Here, these studies are targeted towards the synthesis of a series of chimeric xyloketal A analogues. In *Chapter 4*, the progress made towards the total synthesis of the natural product hopeanol is discussed. Finally, *Chapter 5* contains detailed experimental procedures and full characterization data for all of the compounds reported throughout this thesis. Further details are provided below in order to outline the specific objectives and goals of these three research topics.

### 1.5.1 Overview of Chapter 2

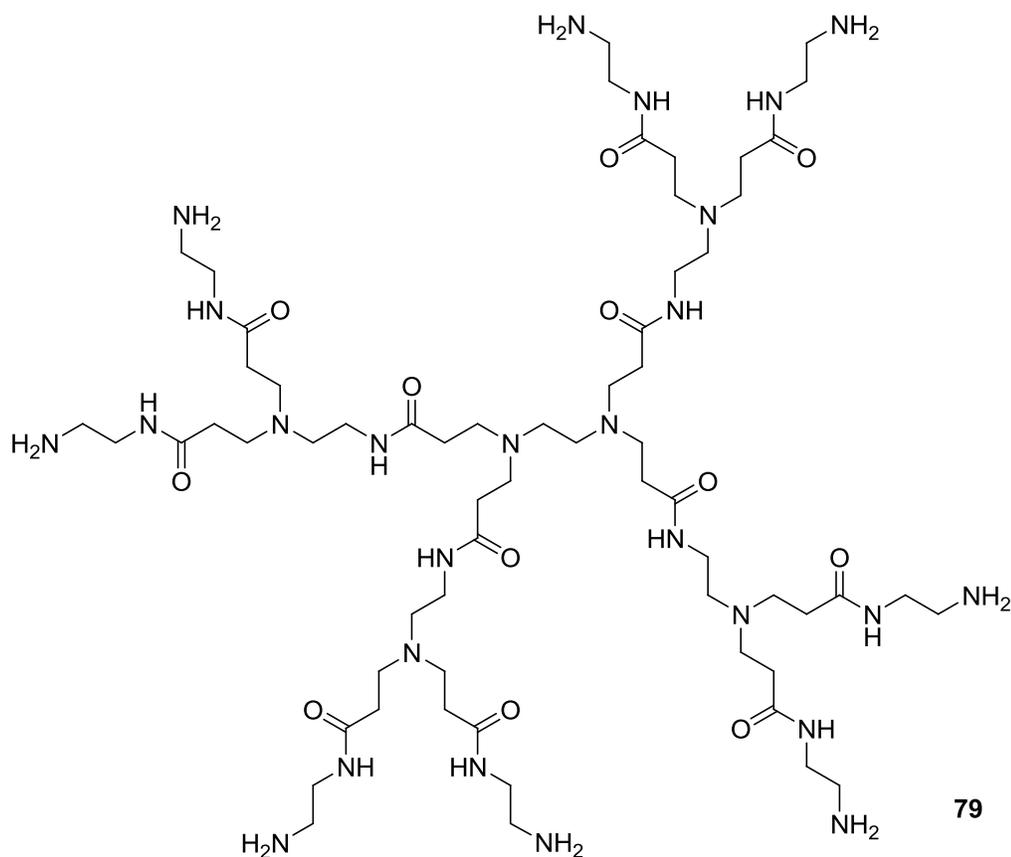
The inspiration for the research discussed in this chapter was taken from the first of the three routes that were explored as a means to complete the first total synthesis of xyloketal A (**15**) (*cf.* Section 1.4.5). The focus of this study was to prepare a broad series of triple Mannich bases of phloroglucinol (**9**), as well as to study the properties and potential uses of these adducts rather than to use them simply as precursors to the *ortho*-quinone methides (**25**) discussed above. Towards these ends, it was envisioned that a series of secondary amines (**78**), where the substituents (R-groups) could be varied, would in turn lead to a series of corresponding  $C_3$ -symmetric triple Mannich bases (**Scheme 1.5.1.1**).

### Scheme 1.5.1.1 Retrosynthesis of Generalized Triple Mannich Base (27)



A key feature of a triple Mannich base (**27**) of the type outlined here, is the inherent dendritic nature of the tertiary amine substituents. This observation led to the hypothesis that the triple EAS reaction of phloroglucinol (**9**) could serve as a platform to construct functionalized dendrimer cores in a facile manner. Moreover, these cores could feasibly be extended through the use of further coupling reactions such as the so-called “click reaction” (*i.e.* the Huisgen 1,3-dipolar cycloaddition reaction of azides and acetylenes).

The term dendrimer refers to any molecule that is highly symmetrical and is made of repeating branched units<sup>28</sup>. The first dendrimers were prepared by Vögtle in 1978.<sup>29</sup> Among the most well-known dendritic molecules are the poly(amidoamine) or PAMAM dendrimers (**79**). These are typically constructed by adding units of methyl acrylate around an ethylenediamine core (**Figure 1.5.1.1**).<sup>28</sup>



**Figure 1.5.1.1 Molecular structure of the poly(amidoamine) (PAMAM, 79) dendrimer ( $n = 2$ )<sup>28</sup>**

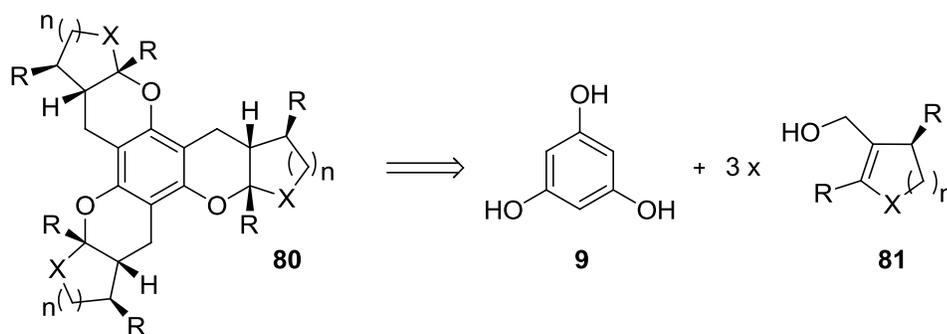
Dendrimers have found numerous applications in medicinal chemistry as drug delivery systems and in various material science applications, such as radioligands and imaging agents. The range of potential uses for dendritic molecules is derived in part from their multivalent nature. Thus, a guest molecule can interact with any number of possible sites, which enhances the latent properties of an individual unit.<sup>28</sup>

### 1.5.2 Overview of Chapter 3

As with the topic of *Chapter 2*, the investigation that will be discussed here, arose from a series of questions regarding extensions of certain aspects of the chemistry that

was developed *en route* to completing the total synthesis of xyloketal A (**15**). This chapter concerns one of these questions; principally, how can the chemistry of phloroglucinol (**9**) and the electrophilic aromatic substitution reaction be exploited in order to construct highly complex polycyclic adducts. Ergo, this chapter describes the synthesis of a series of structural analogues of the natural product xyloketal A (**15**) using novel carbon-based electrophiles (**Scheme 1.5.2.1**).

**Scheme 1.5.2.1 Retrosynthesis of Hypothetical Xyloketal A Analogues (80)**



In a general sense, a series of  $\alpha,\beta$ -unsaturated alcohols **81** could be prepared, where the ring size, heteroatom (X), and substituents (R) could all be varied. This would lead to an array of xyloketal A analogues **80**, which could be exploited in subsequent SAR studies. These analogues **80** could in principle be prepared from a triple electrophilic aromatic substitution reaction of phloroglucinol (**9**) with the aforementioned  $\alpha,\beta$ -unsaturated alcohols **81** using the previously described method for the synthesis of xyloketal A (**15**) (see above; **Scheme 1.4.5.5**). The effectiveness of such a strategy however, hinges on the ability to prepare the series  $\alpha,\beta$ -unsaturated alcohols **81**, and in turn, the corresponding reactive electrophilic species, in a facile and modular manner. The limitations of this approach are evinced by the relatively lengthy and complex synthesis of the chiral nonracemic alcohol **56**, that was necessary in order to complete the

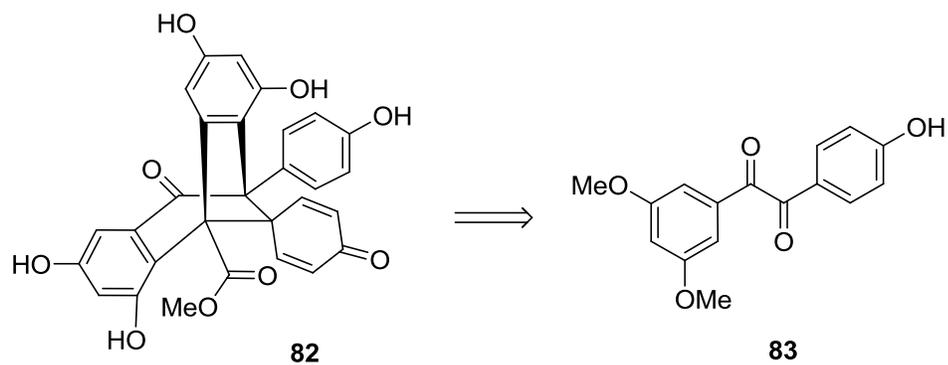
total synthesis of (-)-xyloketal A (**15**, see above; **Scheme 1.4.5.4**). Thus, instead of adopting a strategy of this type, it was considered prudent to mine the literature for suitable derivatives of, but not limited to, compounds related to the  $\alpha,\beta$ -unsaturated alcohol **81**. In this manner, the necessity to develop lengthy syntheses of each respective electrophilic precursor could be minimized, whilst the number of potential structural analogues of xyloketal A (**15**) in the series could be maximized. Each of the suitable precursors identified using this strategy, and the attempts to prepare the corresponding structural analogue of xyloketal A (**15**) derived from these precursors, will be discussed in turn. In two of these cases, the small molecules that were prepared have been employed as key synthetic precursors in the syntheses of other natural products. As such, the resultant polycyclic adducts contain features of two alternate natural products, whilst still constituting, to a certain degree, structural analogues of xyloketal A (**15**). The net result, in a sense, is a set of chimeric xyloketal A analogues which possess features derived from two different natural products.

### 1.5.3 Overview of Chapter 4

In this chapter, the progress made towards the total synthesis of the natural product hopeanol (**82**) is discussed. As part of this discussion, the isolation, biological activity and proposed biosynthesis, as well as the only reported total synthesis of this natural product, is briefly reviewed (Section **4.1**). Following this, the development of the synthetic strategy that was pursued with regard to the total synthesis of hopeanol (**82**) will be delineated.

A retrosynthetic analysis of this natural product led to the hypothesis that it could be prepared *via* a dimerization reaction of the 1,2-diketone **83** (**Scheme 1.5.3.1**).

### Scheme 1.5.3.1 Retrosynthetic Analysis of Hopeanol (82)



This biosynthetically inspired process would involve a series of tandem electrophilic aromatic substitution reactions upon treatment of the diketone **83** with an appropriate acid.

## Chapter 2:

### *Results and Discussion: Synthesis of Triple Mannich Bases of Phloroglucinol*

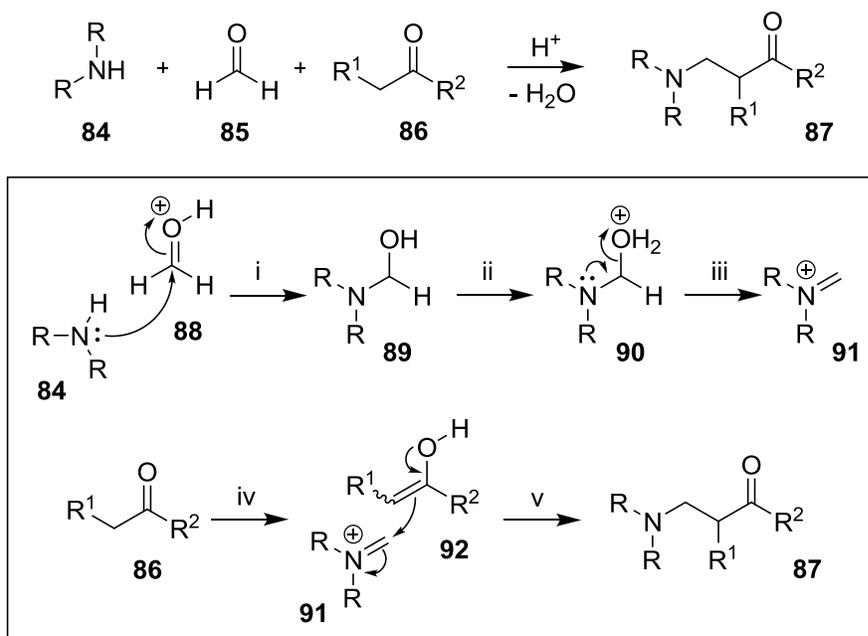
#### 2.1 Introduction

This chapter describes an investigation of the Mannich reaction and its application to the synthesis of  $C_3$ -symmetric triple Mannich bases of phloroglucinol (**9**). As such, in the following subsection (2.1.1), a brief review of the mechanism of the Mannich reaction and a synthetically relevant example of its use is provided. The subsequent sections of this chapter concern a discussion of the execution of this plan and the results thereof.

##### 2.1.1 The Mannich Reaction

The Mannich reaction is a three-component aminomethylation process which was first reported by German chemist Carl Mannich in 1912.<sup>30</sup> This reaction generally involves the condensation of an amine **84**, formaldehyde (**85**) and a third molecule with an acidic methylene moiety, such as a carbonyl compound or a phenol, the result of which is a so-called Mannich base **87** (Scheme 2.1.1.1).<sup>2</sup>

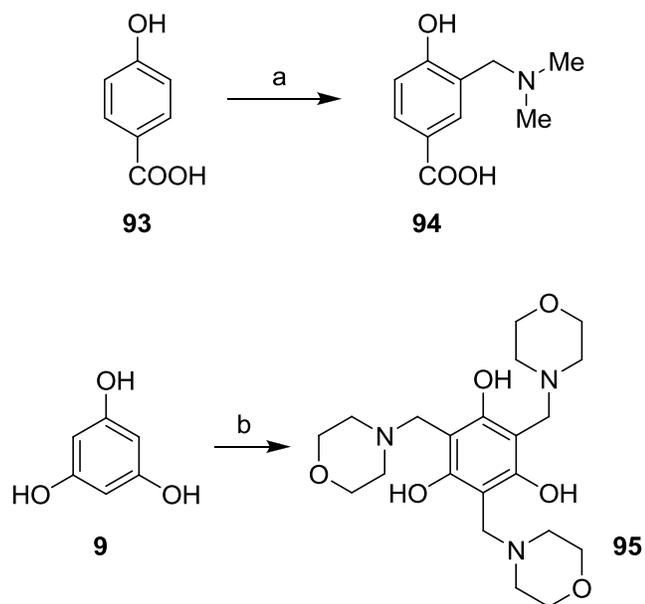
### Scheme 2.1.1.1 Mechanism of the Mannich Reaction<sup>2</sup>



The first step in this reaction sequence involves the condensation of an amine **84** with formaldehyde (**85**) which leads to the electrophilic iminium ion **91** via the hemiaminal **89**. Enolization of a ketone **86** under acidic conditions (note, this can also be performed under basic conditions), followed by reaction with the iminium ion **91**, leads to the Mannich base product **87**.

*En route* to the preparation of the demethylated analogue **35** containing the core ring system of xyloketal A (**15**) via the aforementioned inverse demand Diels-Alder reactions of the *ortho*-quinone methides **25**, the novel triple Mannich base **34** was synthesized from dibenzylamine and the phenolic compound, phloroglucinol (**9**), in the presence of formaldehyde (*cf.* **Scheme 1.4.3.4**). The procedure used to generate these triple Mannich bases was adapted from the method of Blicke *et al.*, which was originally used to couple various substituted phenols with dimethylamine and morpholine (**Scheme 2.1.1.2**).<sup>16</sup>

**Scheme 2.1.1.2 Blicke's Synthesis of Mannich Bases (94) and (95)<sup>16</sup>**



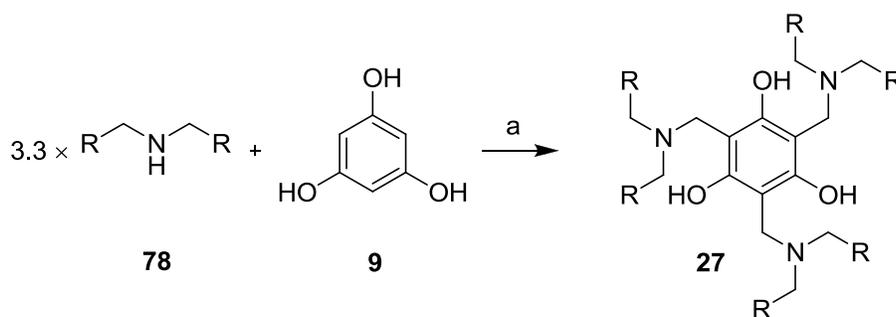
Reagents and conditions: (a)  $\text{CH}_2\text{O}$  (0.3 equiv.),  $(\text{CH}_3)_2\text{NH}$  (0.3 equiv.), ethanol, rt, 3 h (100%); (b)  $\text{CH}_2\text{O}$  (4 equiv.), morpholine (4 equiv.), ethanol, steam-bath temp., 3 h (98%).

## 2.2 Synthesis of Triple Mannich Bases

### 2.2.1 Triple Mannich Bases Prepared from Commercially-Available Secondary Amines

As only two examples of 2,4,6-trisubstituted phloroglucinol-derived triple Mannich bases have been reported (*i.e.* the triple Mannich bases **34** and **95**, derived from dibenzylamine (**96**) and morpholine (**99**), respectively; see **Schemes 1.4.3.4** and **2.1.1.2**), an investigation was undertaken to assess the types of secondary amines that would be amenable to this triple Mannich base forming reaction (**Scheme 2.2.1.1**).

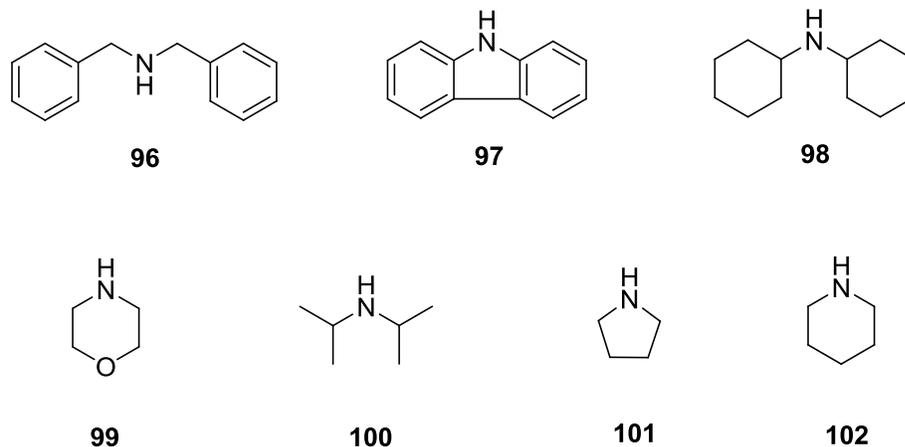
#### Scheme 2.2.1.1 Synthesis of $C_3$ -Symmetric Triple Mannich Base (**27**) of Phloroglucinol (**9**)



Reagents and conditions: (a)  $\text{CH}_2\text{O}$  (3.6 equiv.), ethanol, rt, 24 h.

Moreover, the obvious dendritic nature of the compounds **27**, where the R-groups could be varied, coupled with their high-symmetry and the potential straightforwardness of their preparation, led to the hypothesis that triple Mannich bases could serve as effective building blocks for the construction of dendrimers. As a means to rapidly probe the breadth and variety of simple secondary amines that could engage in this triple Mannich base forming process, and to potentially obtain crystallographic data for these adducts, a series of commercially-available secondary amines were employed as

substrates in this reaction. The yields of the corresponding triple adducts that resulted from these experiments are indicated in the figure below (**Figure 2.2.1.1**).



**Figure 2.2.1.1** Molecular structures of dibenzylamine (**96**), carbazole (**97**), dicyclohexylamine (**98**), morpholine (**99**), *N,N'*-diisopropylamine (**100**), pyrrolidine (**101**), piperidine (**102**).

In all cases, a solution of the secondary amine (**96-102**, 3.3 equiv.), phloroglucinol (**9**) and formaldehyde (37% *v/v* in water, 3.6 equiv.) in ethanol was stirred at room temperature until a precipitate was observed and all of the phloroglucinol (**9**) had been consumed. The triple Mannich bases of dibenzylamine (**96**) and morpholine (**99**) had previously been isolated in both high yield and purity, efficiently precipitating from the reaction mixture. In order to gain an understanding of idiosyncrasies of this method, these reactions were successfully repeated, and the  $C_3$ -symmetric triple Mannich bases derived from these two secondary amines were once again isolated in pure form and in good yield. Unlike the adducts formed from dibenzylamine (**96**) and morpholine (**99**) however, the products formed from dicyclohexylamine (**98**), *N,N'*-diisopropylamine (**100**), pyrrolidine (**101**) and piperidine (**102**), while also being precipitates, proved to be

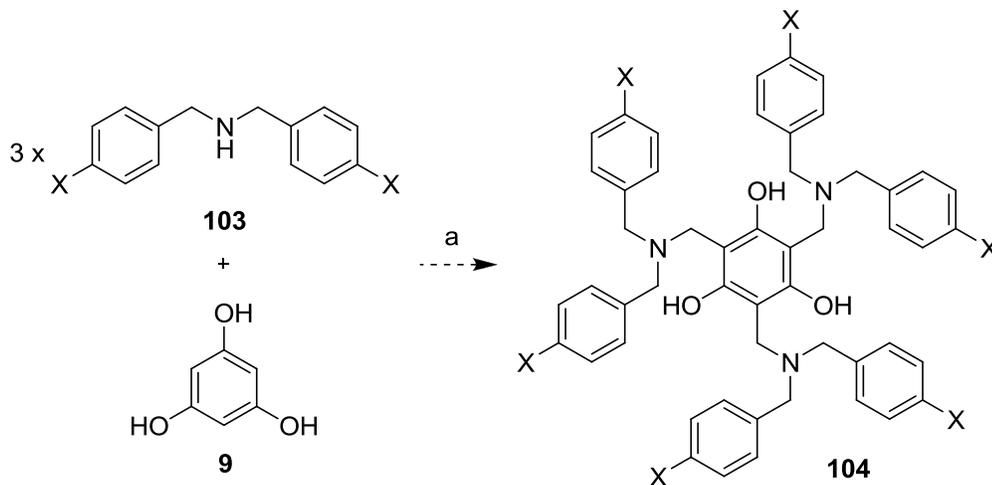
virtually intractable, and were found to be insoluble in all readily-available solvents. Moreover, attempts to form the hydrochloride salts of these adducts were also unsuccessful. Finally, no reaction products were obtained for carbazole (**97**) under the prescribed conditions. Of note, carbazole (**97**) constitutes the only amine employed here where the nitrogen lone pair is in conjugation with an aromatic ring.

In order to perhaps control the formation of the desired triple Mannich bases derived from dicyclohexylamine (**98**), *N,N'*-diisopropylamine (**100**), pyrrolidine (**101**) and piperidine (**102**), a solution of each amine and formaldehyde (37% *v/v* in water) was stirred in ethanol for 0.5 hours and then added dropwise *via* cannula to a solution of phloroglucinol (**9**) in ethanol at 0 °C. The reaction mixtures were then stirred over night at 0 °C. This approach however, did not have any effect on the physical or chemical properties of the resultant adducts that formed during this process.

### **2.2.2 Synthesis of Functionalized Dendrimer Cores**

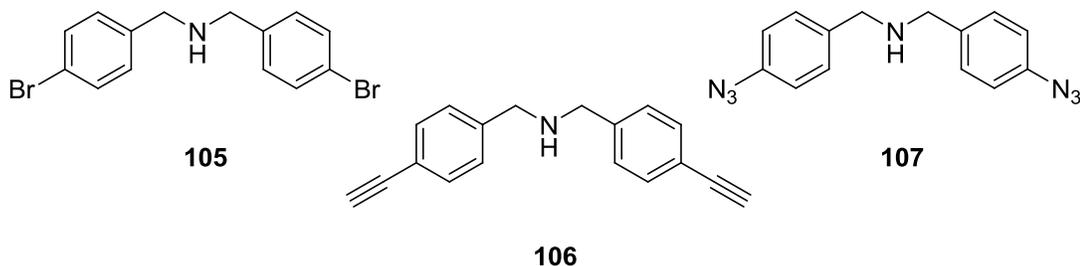
Of the two triple Mannich bases, derived from dibenzylamine (**98**) and morpholine (**101**), respectively, that proved amenable to isolation and purification, the former amine and its derivatives (*vide infra*), were identified for further study due to the potential for subsequent functionalization. Indeed, due to the ease and efficiency with which a new set of  $C_3$ -symmetric triple Mannich bases, derived from functionalized dibenzylamine derivatives, could potentially be constructed, it was thought that this would constitute a novel method for the construction of dendrimer cores (**Scheme 2.2.2.1**).

**Scheme 2.2.2.1 Proposed Synthesis of General Functionalized Dendrimer Core (104)**



Reagents and conditions: (a) CH<sub>2</sub>O (37% v/v in water), ethanol.

Through selection of appropriate functional groups, these cores could in turn be extended in a highly efficient and symmetrical manner. Thus, a series of three functionalized dibenzylamines (**105-107**) were chosen to test this hypothesis (**Figure 2.2.2.1**).

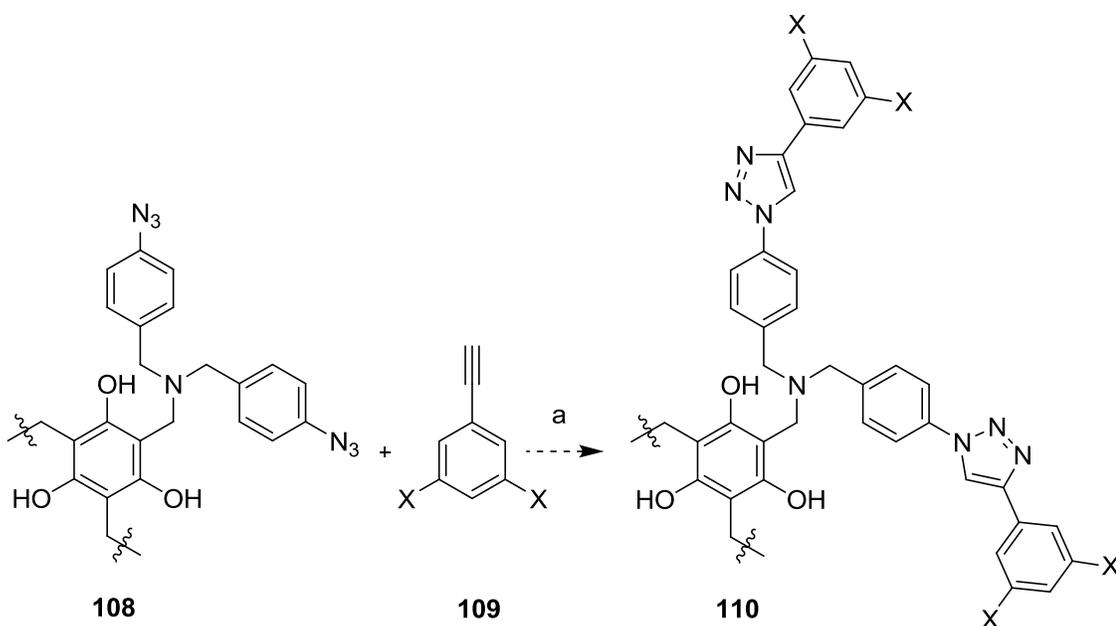


**Figure 2.2.2.1 Molecular structures of proposed functionalized dibenzylamines (105), (106) and (107).**

Each of the proposed functional groups would allow for straight-forward extension through coupling reactions with other appropriately functionalized aryl species.

For example, the triple Mannich base derived from the *bis*(azidodibenzyl)amine **107**, could in principle be extended through a Huisgen 1,3-dipolar cycloaddition (“click”) reaction with phenyl acetylene.<sup>31-33</sup> Appropriately substituted aryl units could facilitate one-unit chain extensions up to a desired length and degree of branching (**Scheme 2.2.2.2**).

**Scheme 2.2.2.2 Example of Potential One-Unit Chain Extension of the Dendrimer Core (108)**



Reagents and Conditions: (a) CuSO<sub>4</sub>, sodium ascorbate, THF, rt.

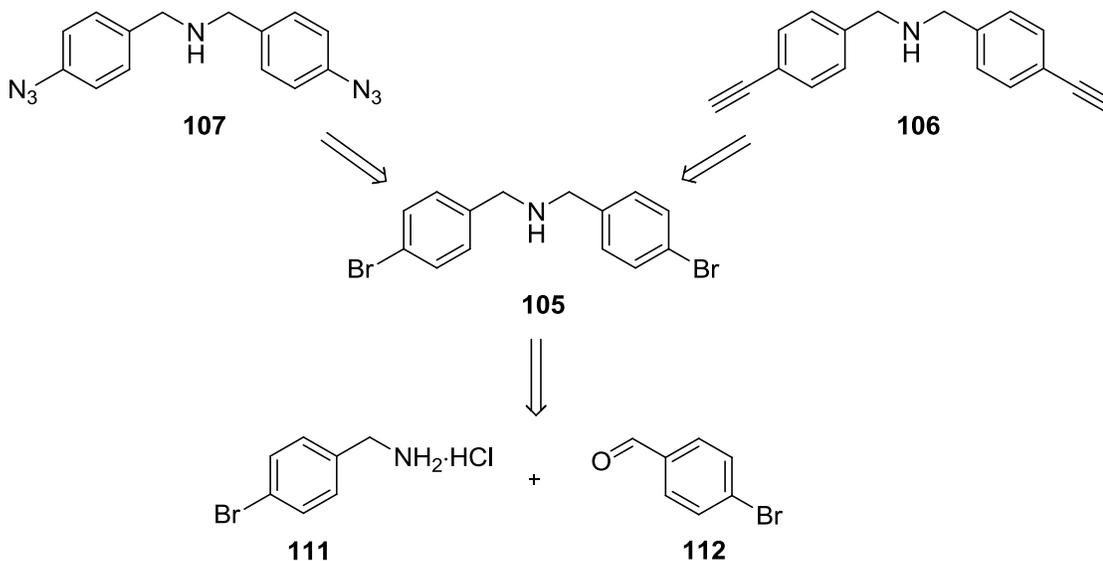
In an analogous fashion, the other two proposed dendrimer cores, based on dibenzylamines **105** and **106**, could also be extended.

### 2.2.3 Synthesis of Dibenzylamine Precursors (**105**), (**106**) and (**107**)

A divergent strategy was devised for the synthesis of all three dibenzylamine derivatives, with the 4,4'-dibromodibenzylamine **105** serving as precursor to the other

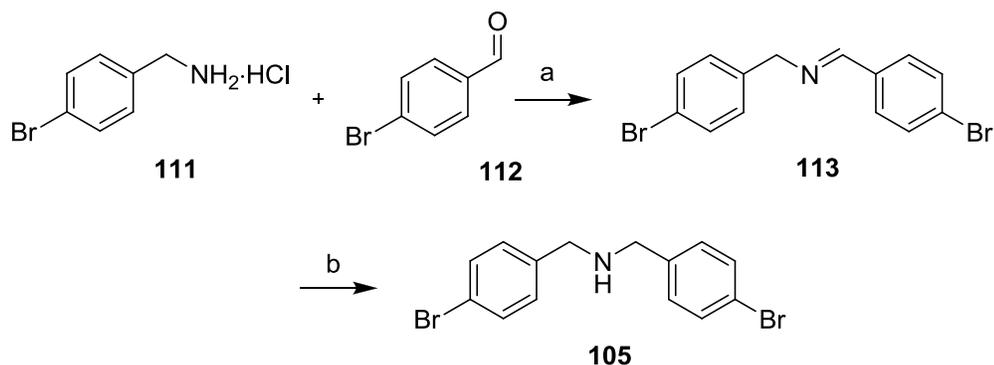
two. This brominated dibenzylamine derivative could in turn be prepared by known literature procedures from 4-bromobenzylamine hydrochloride (**111**) and 4-bromobenzaldehyde (**112**, **Scheme 2.2.3.1**).<sup>34</sup>

**Scheme 2.2.3.1 Retrosynthetic Analysis of the Dibenzylamine Derivatives (105), (106) and (107)**



The synthesis of dibromodibenzylamine **105** was undertaken according to the method outlined by Stoddart and co-workers.<sup>34</sup> This was completed in two steps and involved a condensation reaction of 4-bromobenzylamine hydrochloride (**111**) with 4-bromobenzaldehyde (**112**), to afford the imine **113**, followed by reduction with two equivalents of sodium borohydride in a mixture of tetrahydrofuran and methanol (**Scheme 2.2.3.2**).

### Scheme 2.2.3.2 Synthesis of 4,4'-Dibromodibenzylamine (**105**)<sup>34</sup>

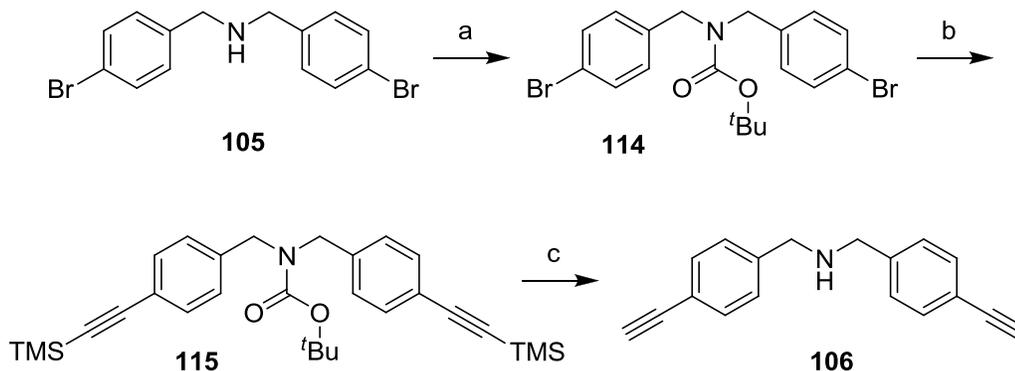


Reagents and conditions: (a) PhMe, Dean-Stark apparatus, reflux, 24 h; (b) NaBH<sub>4</sub>, THF/MeOH (1:1), rt, 48 h (88%, over two steps).

The product **105** was obtained as a low-melting solid that displayed peaks in its chemical ionization mass spectrum corresponding to protonated molecular ions at  $m/z$  354 [ $M(2 \times {}^{79}\text{Br}) + \text{H}$ ], 356 [ $M({}^{79}\text{Br} + {}^{81}\text{Br}) + \text{H}$ ] and 358 [ $M(2 \times {}^{81}\text{Br}) + \text{H}$ ] amu, in a ratio of 1:1.8:0.8, which was consistent with a compound containing two bromine atoms and having a molecular formula of C<sub>14</sub>H<sub>13</sub>Br<sub>2</sub>N. The molecular structure was assigned using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The single amine proton was evident as a broad singlet at  $\delta$  1.65 ppm in the <sup>1</sup>H NMR spectrum. The four methylene protons were assigned to the singlet at  $\delta$  3.74 ppm and the aromatic protons appeared as two doublets at  $\delta$  7.21 and 7.45 ppm, respectively. Of note, the <sup>13</sup>C NMR spectrum exhibited only five peaks. The benzylic carbons were assigned to the signal at  $\delta$  52.2 ppm, and the remaining peaks had chemical shifts that were consistent with aromatic carbons.

A literature search led to a recent paper by Hsu and co-workers that described the conversion of dibromodibenzylamine **105** to a hexafluorophosphate (PF<sub>6</sub><sup>-</sup>) salt of diethynyldibenzylamine **106**.<sup>35</sup> This procedure was adapted for the preparation of the diethynyldibenzylamine **106** as a free amine (Scheme 2.2.3.3).

### Scheme 2.2.3.3 Synthesis of Diethynyldibenzylamine (106)



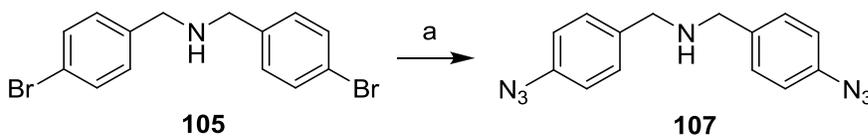
Reagents and conditions: (a)  $\text{Boc}_2\text{O}$ ,  $\text{NEt}_3$ ,  $\text{MeOH}$ , rt, 24 h (92%); (b) TMS-acetylene,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{CuI}$ ,  $\text{NEt}_3$ ,  $60\text{ }^\circ\text{C}$ , 4 days (96%); (c) (i)  $\text{K}_2\text{CO}_3$ ,  $\text{MeOH}$ , rt, 0.5 h; (ii)  $\text{TFA}$ ,  $\text{MeOH}$ , rt, 0.25 h (72%).

This first step of this synthesis involved the protection of the amine functionality of dibromodibenzylamine (**105**), which led to formation of the *N*-*tert*-butoxycarbonyl derivative **114** in good yield. This was followed by a double Sonogashira coupling reaction with TMS-acetylene (4.4 equiv.) under standard conditions to afford the diethynylated carbamate **115**. Of note, this reaction required four days at  $60\text{ }^\circ\text{C}$  for both bromine substituents to undergo the Sonogashira reaction. Deprotection of the trimethylsilyl group of compound **115** under basic conditions, followed by removal of the *t*-BOC group, led to the desired diethynyldibenzylamine **106** in good overall yield. The high-resolution mass spectrum of this free amine (**106**) displayed a prominent peak at  $m/z$  246.1269 amu, which corresponded to the protonated molecular ion for the expected molecular formula of this product ( $\text{C}_{18}\text{H}_{15}\text{N}$ ). The molecular structure was assigned using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. The single amine proton was evident as a broad singlet at  $\delta$  1.63 ppm in the  $^1\text{H}$  NMR spectrum. The terminal acetylene signals were assigned to a singlet at  $\delta$  3.07 ppm that integrated to two protons, and the methylene protons were assigned to a four-proton singlet at  $\delta$  3.79 ppm. The aromatic protons appeared as two doublets at  $\delta$  7.30 and 7.47 ppm, respectively. The  $^{13}\text{C}$  NMR spectrum

contained seven peaks, as predicted. The benzylic carbons were assigned to a signal at  $\delta$  52.9 ppm, and the terminal acetylene carbons were assigned to the signals at  $\delta$  77.1 and 83.7 ppm, respectively. The remaining signals appeared at chemical shifts consistent with aromatic carbons. In addition, the IR spectrum of this product displayed a strong absorption at  $3289\text{ cm}^{-1}$ , which provided further evidence that this compound contained terminal acetylene functional groups.

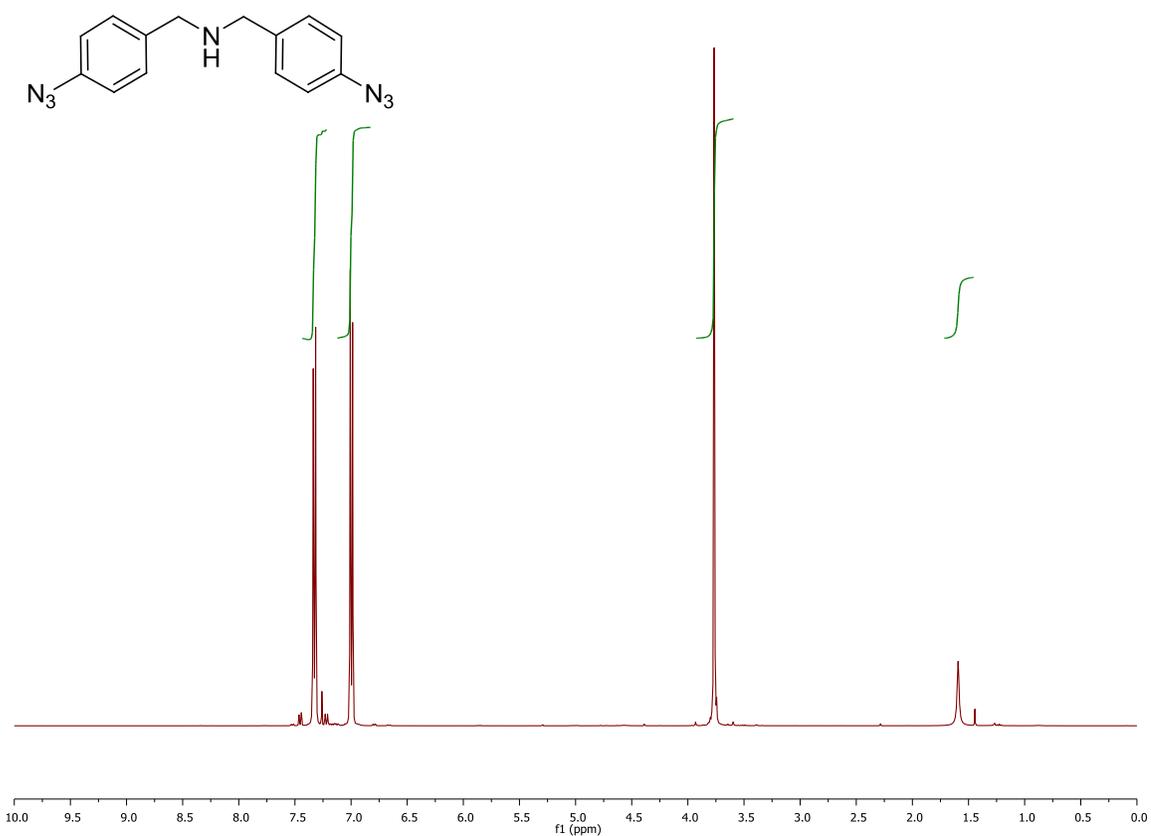
Preliminary attempts to convert the dibromodibenzylamine (**105**) to the corresponding diazido derivative **107** were unsuccessful. These attempts employed the method of Ma *et al.*, which involved the use of a catalytic amount of copper iodide, L-proline, sodium hydroxide and a stoichiometric amount of sodium azide in an ethanol:water mixture (7:3).<sup>36</sup> A subsequent literature search resulted in an alternate set of conditions developed by Liang *et al.*<sup>37</sup> This study involved the use a series of secondary amine ligands, including L-proline, as a means to increase the efficacy of this Ullman-type coupling reaction.<sup>38</sup> The optimized set of conditions in this case, for converting an aryl bromide to an aryl azide, employed *N,N'*-dimethylethylenediamine instead of L-proline, with sodium ascorbate added as a mild reducing agent to maintain the oxidation state of the copper (I) catalyst. Using these modifications, the desired diazido benzylamine (**107**) was produced in excellent yield (**Scheme 2.2.3.4**).

#### Scheme 2.2.3.4 Synthesis of Diazidodibenzylamine (**107**)



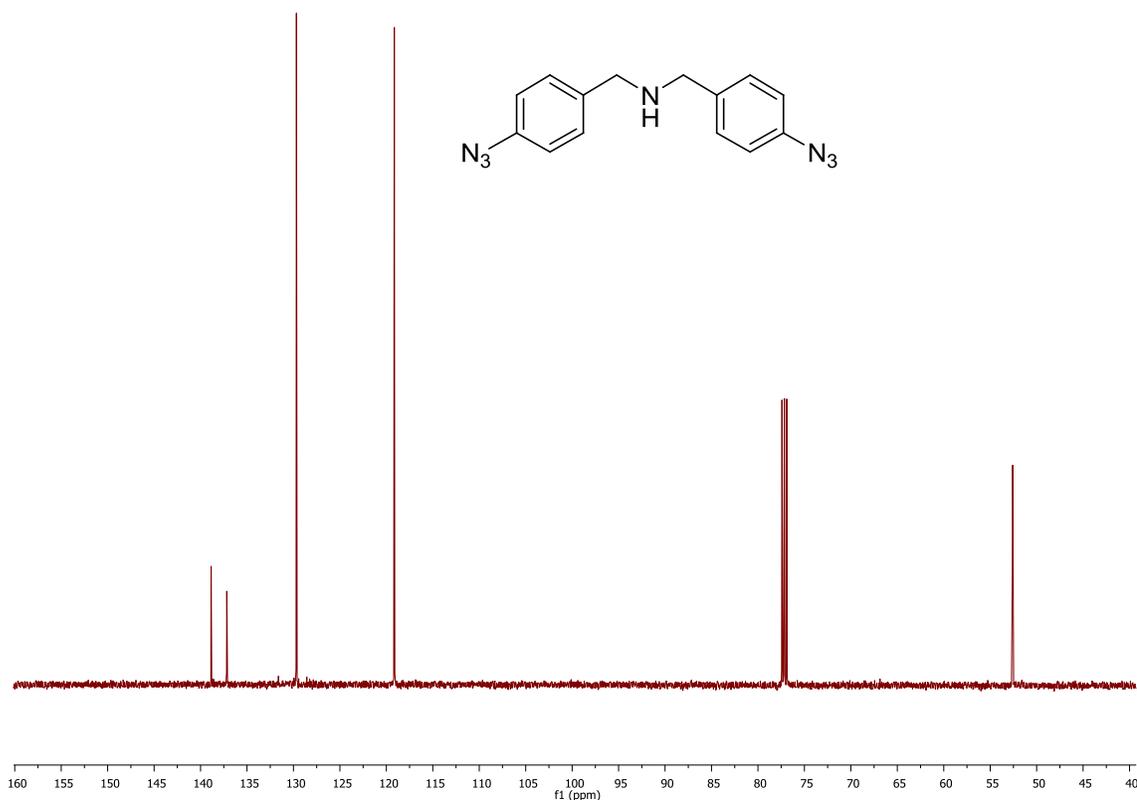
Reagents and conditions: (a)  $\text{NaN}_3$ ,  $\text{CuI}$ , sodium ascorbate, *N,N'*-dimethylethylenediamine,  $\text{EtOH:H}_2\text{O}$  (7:3), reflux, 12 h (93%).

The compound **107** was obtained as a yellow solid, the high resolution mass spectrum of which displayed a base peak at  $m/z$  280.1311 amu, which was consistent with the protonated molecular ion for the predicted molecular formula of  $C_{14}H_{13}N_7$ . The molecular structure was assigned using  $^1H$  and  $^{13}C$  NMR spectroscopy. The single amine proton was assigned to a broad singlet at  $\delta$  1.59 ppm in the  $^1H$  NMR spectrum. In an analogous fashion to dibromodibenzylamine **105**, the four methylene protons were assigned to the singlet at  $\delta$  3.77 ppm, and the aromatic protons appeared as the two doublets at  $\delta$  7.00 and 7.32 ppm, respectively. As a representative example of this series of dibenzylamines (**105-107**), the  $^1H$  NMR spectrum of the diazidobenzylamine **107**, is included below (**Figure 2.2.3.1**).



**Figure 2.2.3.1** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of diazidodibenzylamine (**107**).

Moreover, the <sup>13</sup>C NMR spectrum of this product **107** displayed 5 signals, all of which were consistent with previously reported data. Of note, the signal at  $\delta$  138.9 ppm, is consistent with the azide-substituted carbon of other azidobenzenes (**Figure 2.2.3.2**).<sup>37</sup>



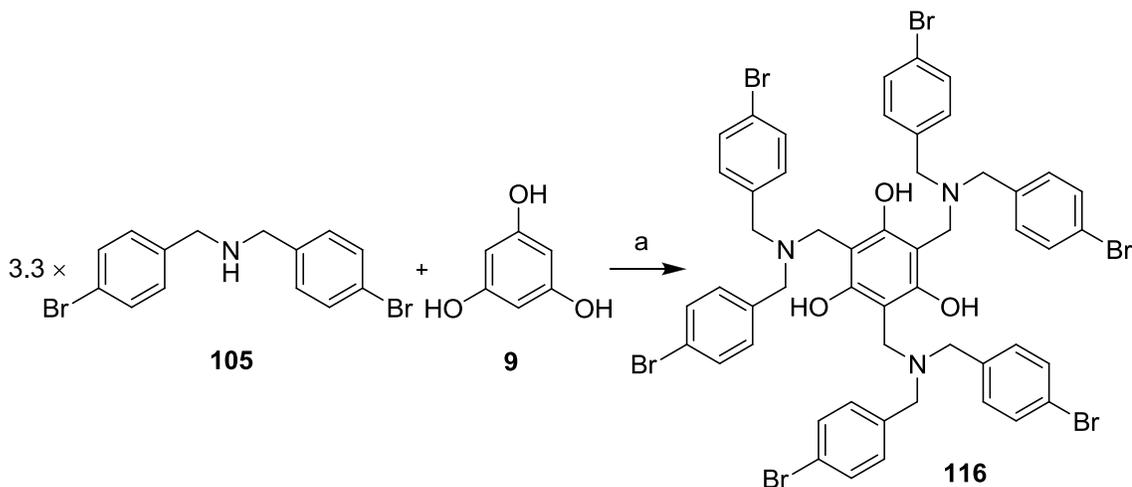
**Figure 2.2.3.2** <sup>13</sup>C NMR spectrum (125 MHz, CDCl<sub>3</sub>) of diazidodibenzylamine (**107**).

#### 2.2.4 Synthesis of C<sub>3</sub>-Symmetric Functionalized Dendrimer Cores

With all three of the desired dibenzylamine derivatives (**105**, **106** and **107**) in hand, the syntheses of the proposed functionalized dendrimer cores were undertaken. The first of these to be successfully prepared was the hexabrominated triple Mannich base **116**, using the method employed for the synthesis of the triple Mannich base derived from dibenzylamine (**96**).<sup>15</sup> In this case, the dibromodibenzylamine **105** (3.3 equiv.) was coupled to phloroglucinol (**9**) in the presence of a slight excess, with respect to the dibromodibenzylamine (**105**), of a 37% aqueous solution of formaldehyde (3.5 equiv.) in ethanol. The reaction was stirred for two days, whereupon all of the phloroglucinol (**9**)

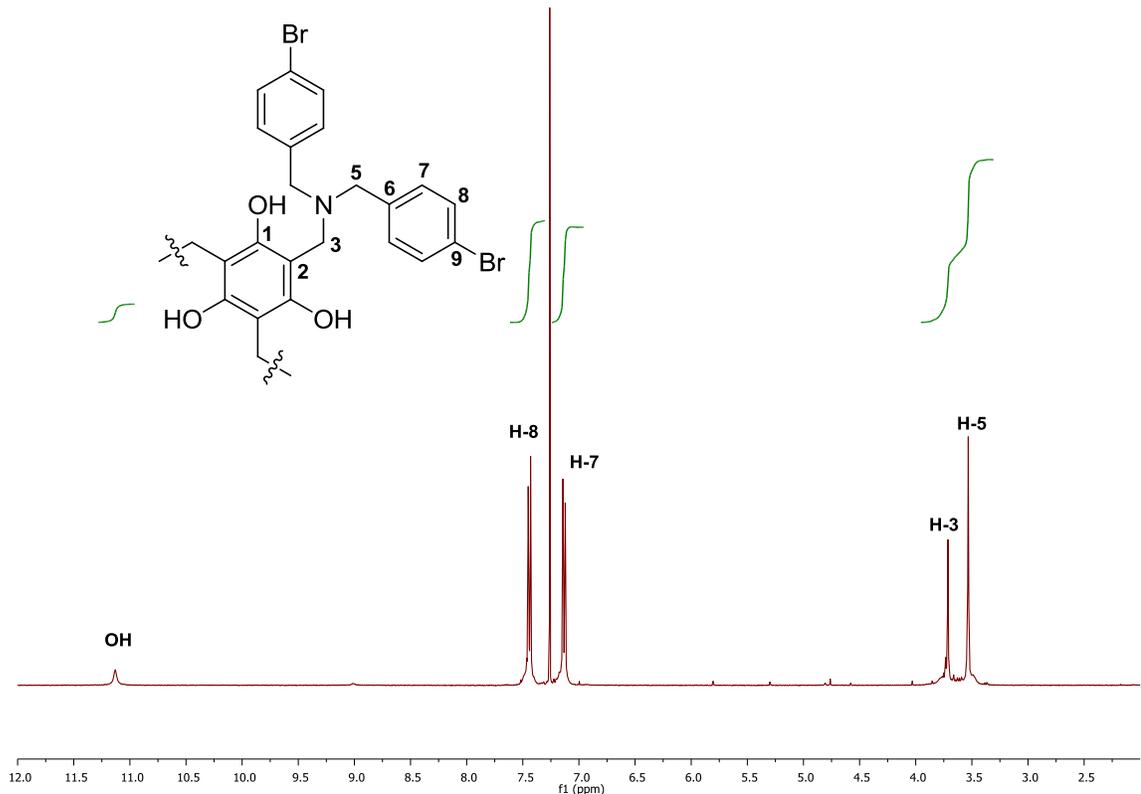
had been consumed, as indicated by TLC, and a creamy coloured precipitate had been deposited on the walls of the flask (**Scheme 2.2.4.1**).

**Scheme 2.2.4.1 Synthesis of the Hexabrominated Triple Mannich Base (116)**



Reagents and conditions: (a) CH<sub>2</sub>O (37% v/v in water, 3.6 equiv.), ethanol, rt, 48 h (64%).

The high resolution mass spectrum of this product exhibited the characteristic pattern of protonated molecular ion peaks for a molecule containing six bromine atoms, and were recorded at  $m/z$  1221.9 [M(6 x <sup>79</sup>Br) + H], 1223.9 [M(5 x <sup>79</sup>Br + <sup>81</sup>Br) + H], 1225.5 [M(4 x <sup>79</sup>Br + 2 x <sup>81</sup>Br) + H], 1227.9 [M(3 x <sup>79</sup>Br + 3 x <sup>81</sup>Br) + H], 1229.9 [M(2 x <sup>79</sup>Br + 4 x <sup>81</sup>Br) + H] and 1231.9 [M(1 x <sup>79</sup>Br + 5 x <sup>81</sup>Br) + H] amu, respectively. The peak at  $m/z$  1227.8558 amu was used to confirm the molecular formula of this adduct (C<sub>51</sub>H<sub>45</sub>Br<sub>6</sub>N<sub>3</sub>O<sub>3</sub>). The molecular structure of the hexabrominated triple Mannich base **116** was confirmed using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. Moreover, the simplicity of both the <sup>1</sup>H and <sup>13</sup>C NMR spectra, served as confirmation of its C<sub>3</sub>-symmetry. As such, only a single branch is numbered in the diagrams below (**Figure 2.2.4.1** and **2.2.4.2**).

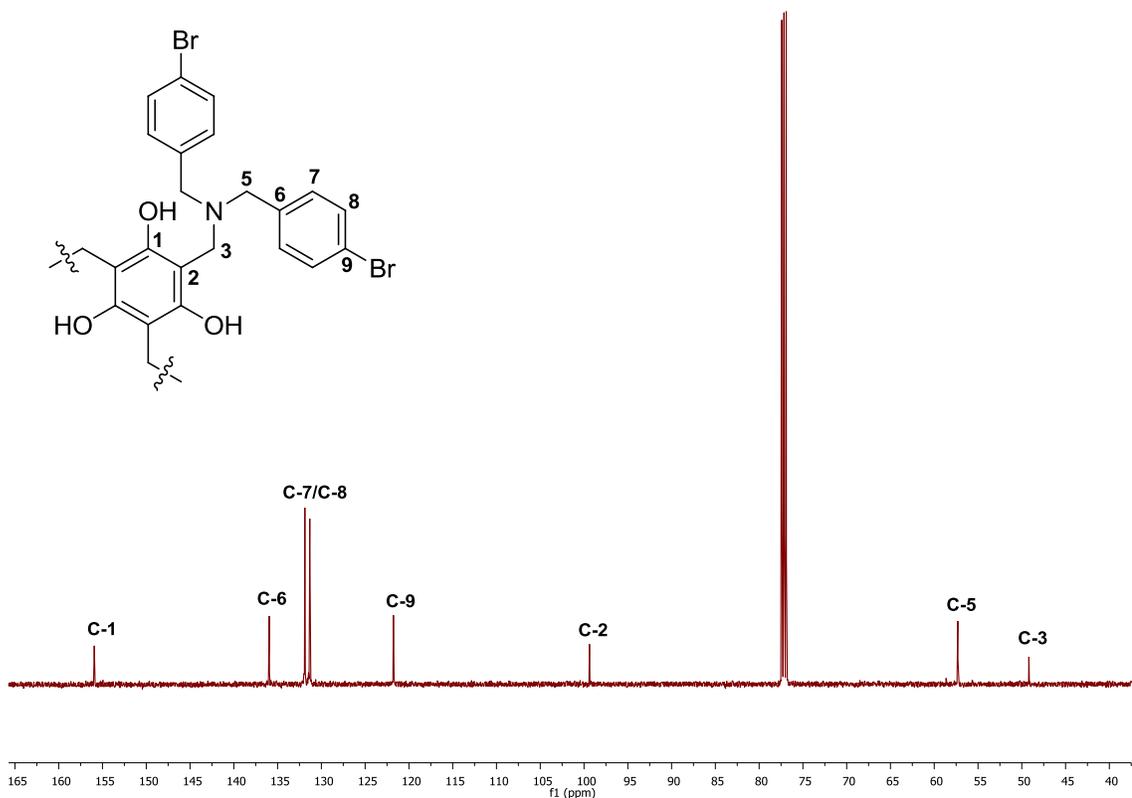


**Figure 2.2.4.1**  $^1\text{H}$  NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of the hexabrominated triple Mannich base (116).

The protons that are associated with the positions labelled *H-3* and *H-5* were assigned to the signals at  $\delta$  3.71 and 3.53 ppm, respectively. These peaks correspond to the benzylic methylene protons and were differentiated based on their integrals, since there are twelve protons associated with *H-5* and only six protons with *H-3*. The aromatic protons, labelled *H-7* and *H-8*, were assigned to the doublets at  $\delta$  7.13 and 7.44 ppm, respectively. The peak associated with *H-8* was attributed to the more downfield signal due to its proximity to the bromine atom at position 9. In addition, a coupling constant of  $J = 8.4$  Hz, is consistent with the magnitude of interaction for protons on a 1,4-disubstituted aromatic ring. The remaining signal at  $\delta$  11.13 ppm was assigned to the

free phenol moieties at positions 1. The fact that this peak is observable suggests that these phenols are perhaps hydrogen bonded to the pendant tertiary amine moieties.

The  $^{13}\text{C}$  NMR spectrum exhibited eight signals, a number consistent with the predicted  $C_3$ -symmetry of this dendrimer core **116** (Figure 2.2.4.2).



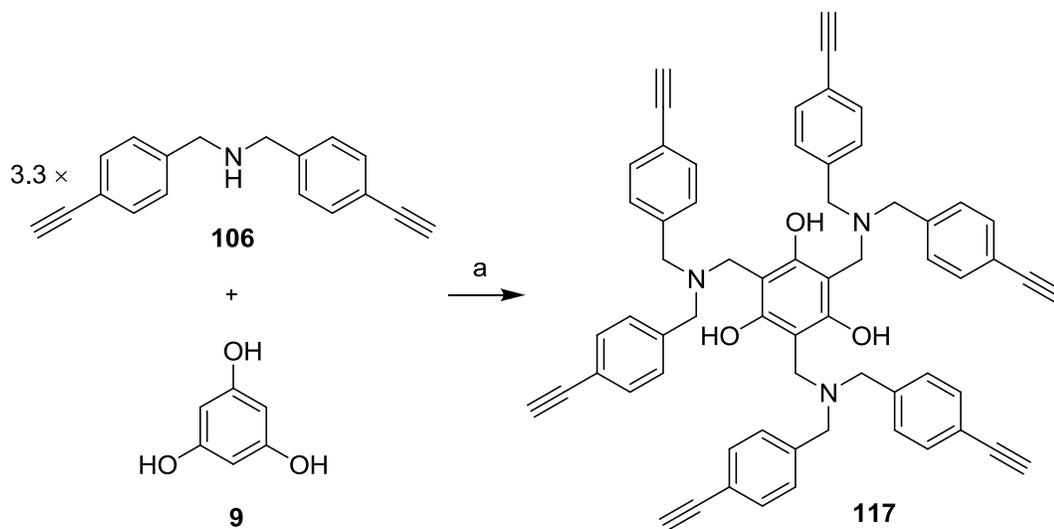
**Figure 2.2.4.2**  $^{13}\text{C}$  NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of the hexabrominated triple Mannich base (**116**).

The benzylic carbons labelled  $C-3$  and  $C-5$  were assigned to the signals at  $\delta$  49.2 and 57.3 ppm, respectively. The peak at  $\delta$  99.4 ppm was attributed to the carbon labelled  $C-2$ , which is consistent with an aromatic carbon situated at positions 2, 4 and 6 of a 1,3,5-trihydroxybenzene system. In addition, the peak at  $\delta$  156.0 ppm was consistent

with a phenolic carbon, and was thus assigned to the carbon labelled C-1. Subsequently, the signal at  $\delta$  136.0 ppm was attributed to the carbon labelled C-6. The aromatic carbon that was directly attached to the bromine substituent labelled C-9 was in turn assigned to the peak at  $\delta$  121.8 ppm, a chemical shift which is in accordance with other bromobenzene systems.<sup>39</sup> Finally, the remaining signals at  $\delta$  131.3 and 131.9 ppm were attributed to the carbons at positions C-7 and C-8, respectively.

Using similar conditions, the triple Mannich base **117**, containing six terminal acetylenes, was also successfully prepared (**Scheme 2.2.4.2**). The reaction proceeded in the prescribed manner, and afforded the desired product as a beige precipitate in moderate yield.

**Scheme 2.2.4.2 Synthesis of the Hexaethynyl Triple Mannich Base (117)**



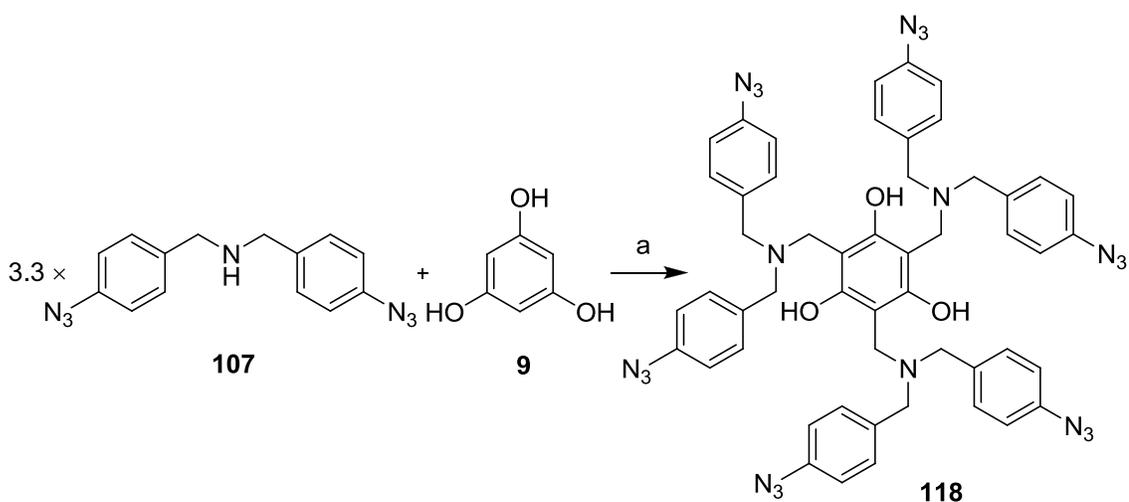
Reagents and conditions: (a) CH<sub>2</sub>O (37% v/v in water, 3.6 equiv.), ethanol, rt, 48 h (48%).

A high resolution mass spectrum of the product **117** displayed a peak at  $m/z$  898.3989 amu, which corresponded to the protonated molecular ion for the predicted molecular formula of this compound (C<sub>63</sub>H<sub>51</sub>N<sub>3</sub>O<sub>3</sub>). As with the previous example, the

$C_3$ -symmetry of the molecular structure was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. Moreover, only small changes in chemical shifts were observed between the signals for the triple Mannich base **117**, and those which were previously reported for the diethynyldibenzylamine precursor **106**. In the  $^1\text{H}$  NMR spectrum, two new signals were observed, a singlet at  $\delta$  3.73 ppm and a broad singlet at  $\delta$  11.12 ppm, which corresponded to the six newly formed benzylic methylene protons and to the three phenolic protons, respectively. The  $^{13}\text{C}$  NMR spectrum exhibited ten peaks that were analogous to the hexabrominated triple Mannich base **116** discussed above, and consistent with the data obtained for the diethynyldibenzylamine precursor **106**.

The final member of this series of functionalized dendrimer cores, namely the triple Mannich base **118**, which was derived from the diazidodibenzylamine **107**, was successfully prepared according to the prescribed method, and was isolated as a yellow solid in good yield (**Scheme 2.2.4.3**).

#### Scheme 2.2.4.3 Synthesis of the Hexaazido Triple Mannich Base (**118**)



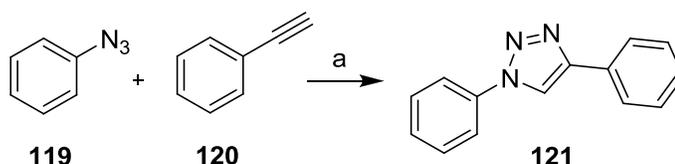
Reagents and conditions: (a)  $\text{CH}_2\text{O}$  (37% v/v in water, 3.6 equiv.), ethanol, rt, 48 h (80%).

A high resolution mass spectrum of the product obtained from this reaction, displayed a peak at  $m/z$  1000.4067 amu, which was consistent with the protonated molecular ion for the predicted molecular formula of compound **118** ( $C_{51}H_{45}N_{21}O_3$ ). The molecular structure of this adduct was confirmed using  $^1H$  and  $^{13}C$  NMR spectroscopy in a manner analogous to the previous two examples.

### 2.2.5 Attempted Chain Extension of Dendrimer Cores

In order to show proof of principle, attempts were made to extend these dendrimer cores (**116-118**) by one unit. It was anticipated that the two triple Mannich bases **117** and **118**, which featured the azide and acetylene functionalities, could be extended through the use of the Huisgen 1,3 dipolar cycloaddition (“click”) reaction. As a control, freshly prepared azidobenzene (**119**, from bromobenzene) and phenylacetylene (**120**) were successfully coupled together under standard conditions to afford the known triazole **121** (Scheme 2.2.5.1).<sup>31</sup>

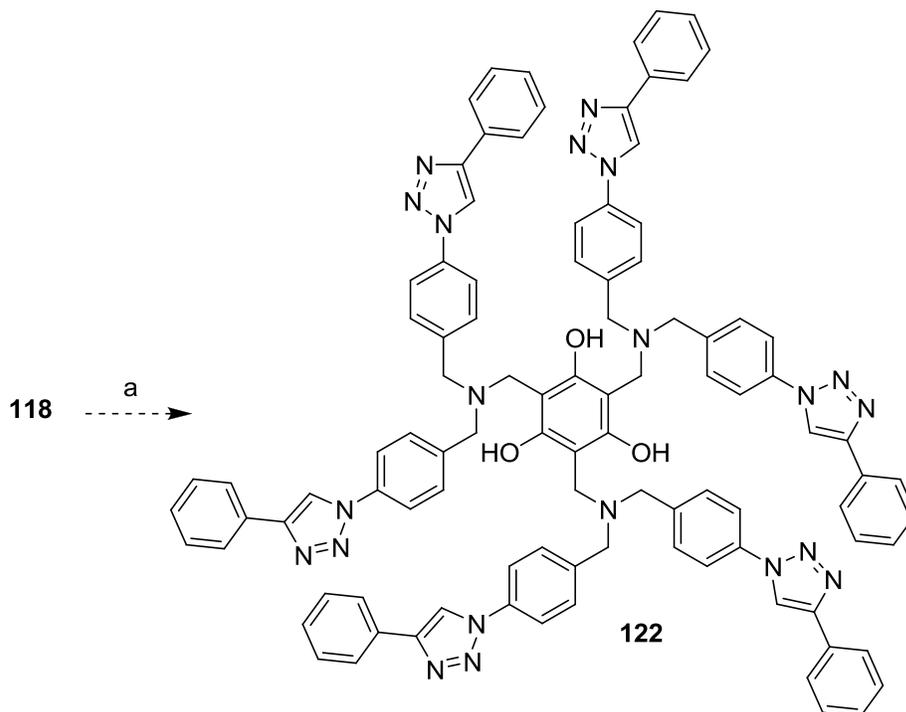
#### Scheme 2.2.5.1 Synthesis of Triazole (**121**)<sup>31</sup>



Reagents and conditions: (a) CuI (20 mol %), sodium ascorbate, THF, rt, 16 h (quant.).

However, no products were isolated from the crude reaction mixtures upon repeated attempts to affect the Huisgen 1,3-dipolar cycloaddition reaction on the azide-containing dendrimer core **118**. Of note, each attempt was made using a known literature procedure, in the presence of either copper (I) iodide or copper (II) sulfate (Scheme 2.2.5.2).<sup>31-33</sup>

**Scheme 2.2.5.2 Attempted Chain Extension of the Triple Mannich Base (118) via the Click Reaction<sup>31-33</sup>**



Reagents and conditions: (a) See below: Table 2.2.5.1

**Table 2.2.5.1 Reagents and Conditions Corresponding to Scheme 2.2.5.2**

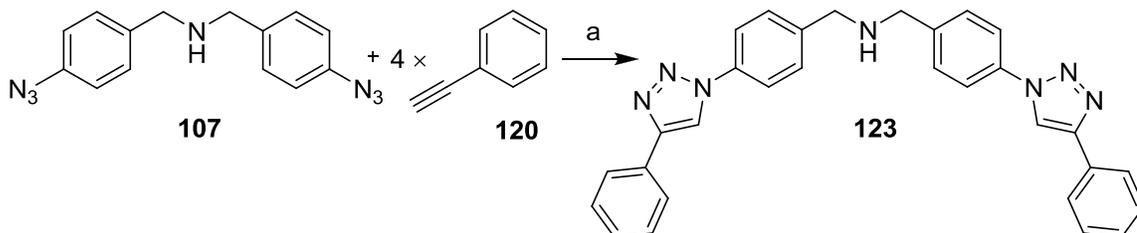
entry	catalyst (20 mol %)	solvent	time	temp.	result
1*	CuI	THF	rt	24 h	no reaction
2*	CuI	<i>t</i> -BuOH/H <sub>2</sub> O (3:1)	rt	24 h	no reaction
3*	CuSO <sub>4</sub>	THF	rt	24 h	no reaction
4*	CuSO <sub>4</sub>	<i>t</i> -BuOH/H <sub>2</sub> O (3:1)	rt	24 h	no reaction

\*In the presence of 0.1 equiv. sodium ascorbate and 12 equiv. of phenyl acetylene.

In a final effort to prepare this chain extended triple Mannich base **122**, attempts were made to prepare the ditriazole **123** (Scheme 2.2.5.3). Consequently, a solution of phenylacetylene (**120**, 4.4 equiv.) in tetrahydrofuran was added dropwise to a solution of diazidobenzylamine **107** in tetrahydrofuran, in the presence of sodium ascorbate and

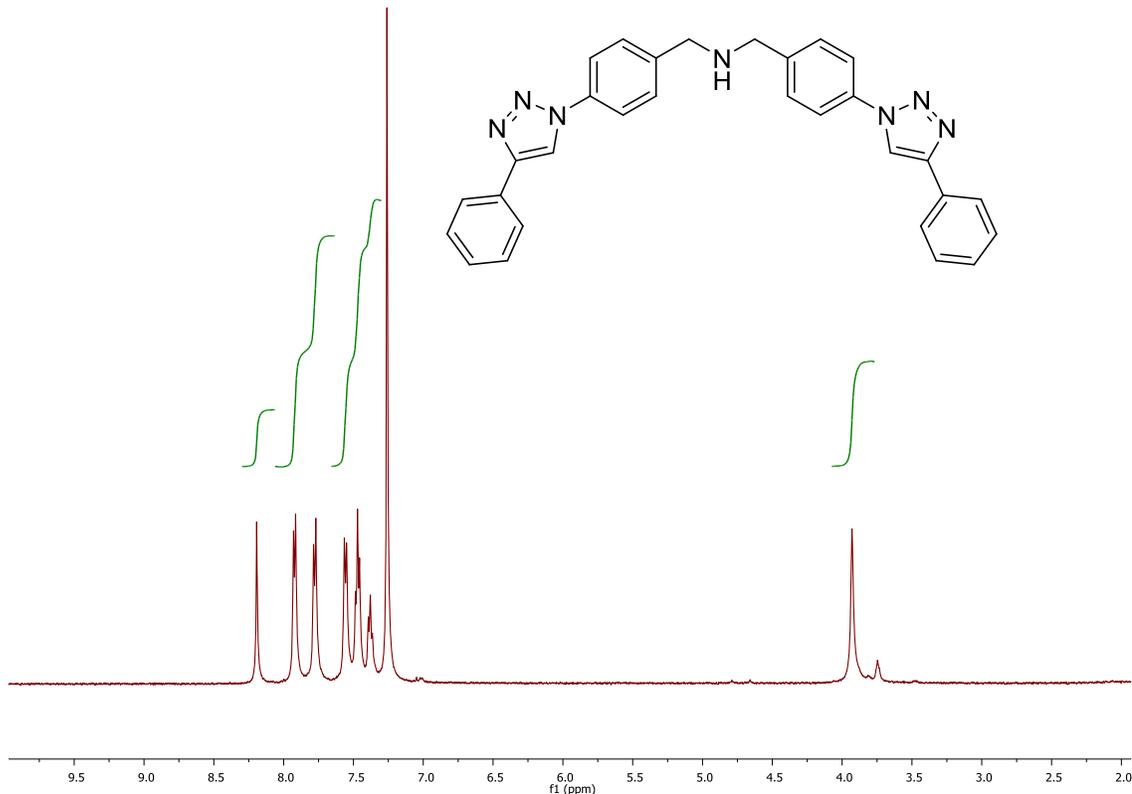
copper iodide. The resultant creamy coloured precipitate was filtered, leaving unreacted phenylacetylene (**120**) in the filtrate.

### Scheme 2.2.5.3 Synthesis of the Ditrizole (**123**)



Reagents and conditions: (a) CuI (20 mol %), sodium ascorbate, THF, rt, 24 h (88% crude).

The product **123** was highly insoluble in all readily-available solvents. In spite of this however, enough of this adduct dissolved in deuterated chloroform such that a crude  $^1\text{H}$  NMR spectrum could be obtained (**Figure 2.2.5.1**). The signal at  $\delta$  8.19 ppm was assigned to the two triazole protons and the four methylene protons were assigned to the singlet at  $\delta$  3.93 ppm. In addition, the splitting patterns and integrals of the remaining aromatic signals were consistent with the proposed structure of this product. The mass spectrum (ESI) of this compound displayed a prominent peak at  $m/z$  484.2274 amu, which was consistent with its protonated molecular ion (molecular formula:  $\text{C}_{30}\text{H}_{25}\text{N}_7$ ).



**Figure 2.2.5.1** Crude  $^1\text{H}$  NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of the ditriazole (**123**).

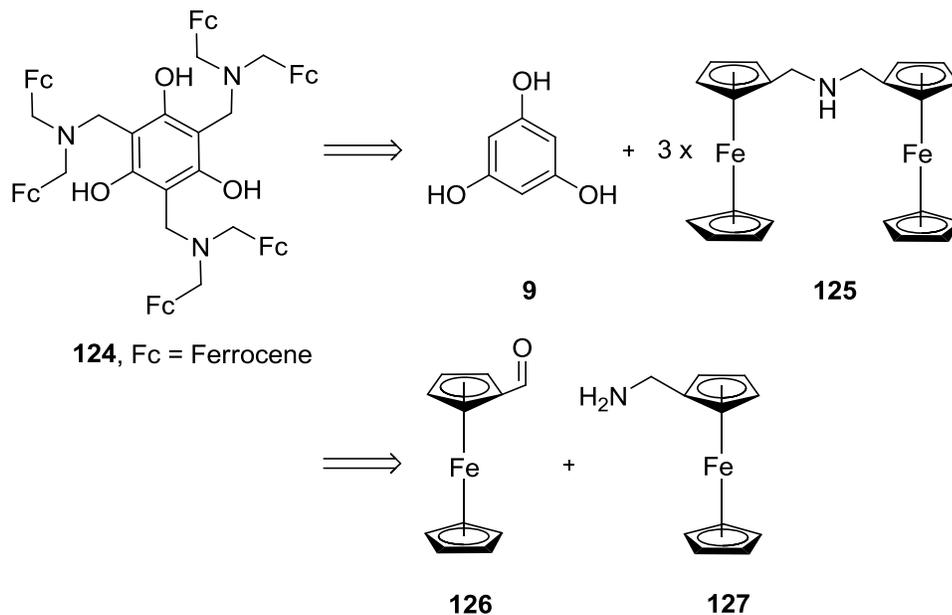
This material was then taken forward without purification and subjected to the standard triple Mannich base formation conditions (*cf.* section **2.2.1**). Even though it did not appear as if any of the ditriazole starting material **123** had gone into solution, it was hoped that enough material had dissolved such that the extended triple Mannich Base **122** could be prepared and then isolated. After heating the reaction mixture at reflux for three days however, no apparent change was observed. Moreover, neither ESI mass spectrometry nor a  $^1\text{H}$  NMR spectrum of the crude reaction mixture indicated that any of the desired product had formed.

Attempts were also made to extend the branches of the hexaethynylated triple Mannich base **117**, with freshly prepared phenyl azide (**119**), *via* the Huisgen 1,3-dipolar cycloaddition reaction, under standard conditions. However, as with the previous example, no evidence for the formation of the desired product was obtained. The elaboration of these three cores and related derivatives remains a topic of continued study.

### **2.2.6 Synthesis of the Hexaferrocenyl Triple Mannich Base**

As another example of a triple Mannich base containing an aromatic system, the synthesis of the hexaferrocenyl triple Mannich base **124** was proposed. This molecule would contain six ferrocene units wrapped around a single phloroglucinol (**9**) core (**Scheme 2.2.6.1**). Compounds containing multiple redox-active centres in this way have recently garnered interest for their potential applications in materials such as light emitting diodes.<sup>40</sup>

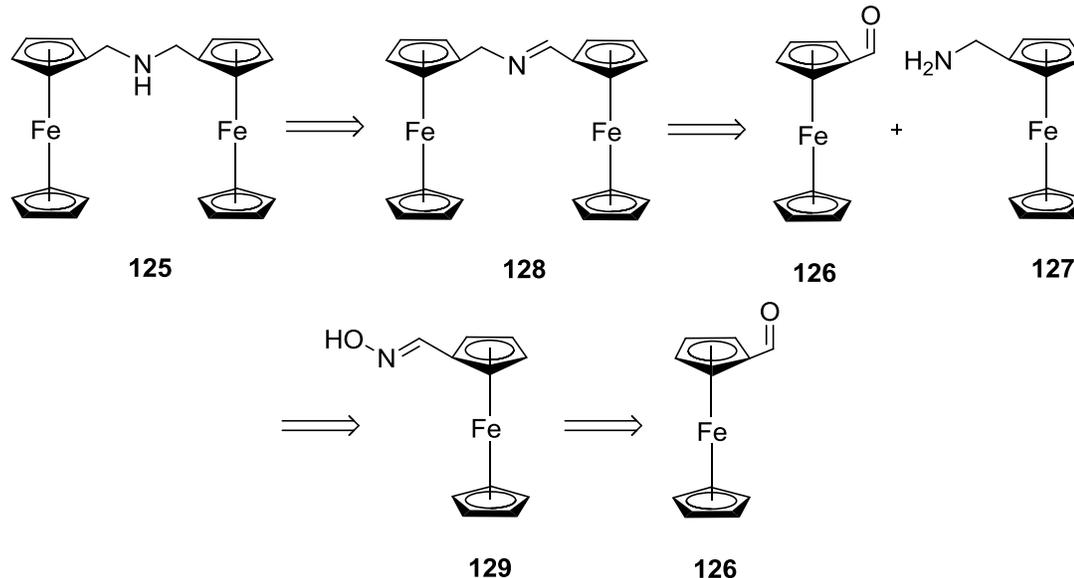
### Scheme 2.2.6.1 Retrosynthetic Analysis of the Hexaferrocenyl Triple Mannich Base (124)



As with the other triple Mannich bases reported above, this final example could be formed from a triple electrophilic aromatic substitution reaction of phloroglucinol (**9**) and the diferrocenyl secondary amine **125**. This species could in turn be formed from a condensation reaction of commercially available ferrocene carboxaldehyde (**126**) and the primary amine **127** on subsequent reduction of the corresponding imine intermediate. (*cf.* **Scheme 2.2.3.2**).

Several strategies were proposed for the preparation of the latter primary amine **127** from ferrocene carboxaldehyde (**126**). The most circuitous would involve conversion of ferrocene carboxaldehyde (**126**) to the oxime **129** with hydroxylamine hydrochloride, followed by reduction to yield the primary amine **127**. This would be followed by the aforementioned condensation and subsequent reduction reaction, resulting in the formation of the desired secondary amine (**125**, **Scheme 2.2.6.2**).

### Scheme 2.2.6.2 Retrosynthetic Analysis of the Secondary Amine (125)

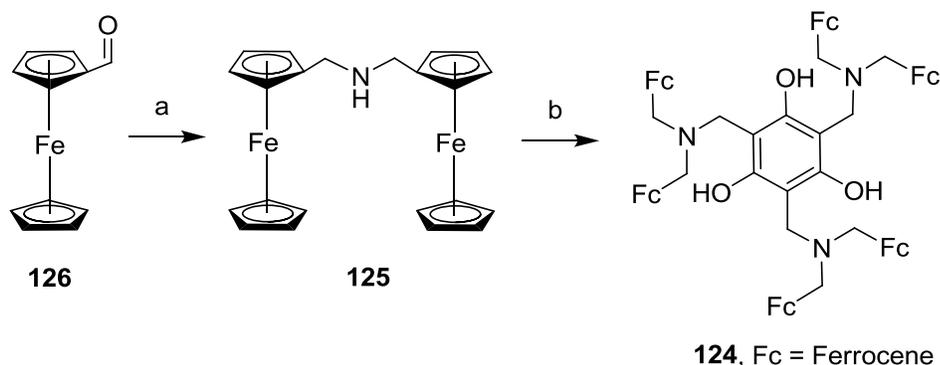


A more efficient process however, would involve a reductive amination reaction of ferrocene carboxaldehyde (**126**) directly to either the primary amine **127** or ideally to the desired secondary amine **125** in one step, upon treatment with an appropriate nitrogen source and in the presence of a reducing agent. Indeed, a literature search yielded a procedure for converting aromatic aldehydes to their corresponding primary amines in one step.<sup>41</sup> However, when this procedure was adapted, with ferrocene carboxaldehyde (**126**) as substrate, the desired secondary amine **125** was obtained in moderate yield (**Scheme 2.2.6.3**). This straight-forward procedure involved adding ammonium acetate (10 equiv.) and sodium cyanoborohydride (2.8 equiv.) to a methanolic solution of ferrocene carboxaldehyde (**126**).

The mass spectrum (CI) of this product displayed a peak at  $m/z$  414 amu, which was consistent with the protonated molecular ion peak of the secondary amine **125**. Moreover, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, while not unambiguously ruling out the primary amine **127**, were consistent with the proposed secondary amine product **125**. The four

benzylic methylene protons were assigned to a singlet at  $\delta$  3.73 ppm, a chemical shift which was congruent with previous examples (*cf.*  $^1\text{H}$  NMR spectral data of dibenzylamines **105-107**). The ten protons on the non-substituted cyclopentadienyl ring were in turn assigned to the singlet at  $\delta$  4.16 ppm. Finally, the remaining eight protons on the substituted cyclopentadienyl ring were assigned to the two apparent triplets at  $\delta$  4.21 and 4.30 ppm. Additionally, five peaks were observed in the  $^{13}\text{C}$  NMR spectrum, with furthest upfield at  $\delta$  48.4 ppm corresponding to the benzylic carbon, and the furthest downfield, at  $\delta$  82.5 ppm, corresponding to the substituted position of the cyclopentadiene ring. The remaining three signals corresponded to the unsubstituted carbons of the cyclopentadienyl rings and were observed at  $\delta$  69.7, 69.8 and 70.6 ppm, respectively. At this point, the final step towards the synthesis of the triple Mannich Base **124** was undertaken.

### Scheme 2.2.6.3 Synthesis of the Hexaferrocenyl Triple Mannich Base (**124**)



Reagents and conditions: (a)  $\text{NH}_4\text{OAc}$ ,  $\text{NaCNBH}_3$ , MeOH, rt, 2 days (40%); (b) **125** (4 equiv.), phloroglucinol (**9**),  $\text{CH}_2\text{O}$  (37% v/v), MeOH, rt, 2 days (85%).

The secondary amine **125** was subjected to the conditions which had been employed previously in the synthesis of the triple Mannich bases **116-118**. As with previous experiments, a brown precipitate had formed over a two day period which was

insoluble in all readily-available solvents with the exception of dimethylsulfoxide. Several additional attempts to solubilise this product in aqueous hydrochloric acid also proved ineffective.

A mass spectrum (ESI) of this adduct displayed a prominent peak at  $m/z$  1402.17 amu, which was consistent with the expected protonated molecular ion of the hexaferrocenyl triple Mannich base **124**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra in deuterated dimethylsulfoxide were somewhat convoluted, and as such further confirmation of the molecular structure of this adduct was not possible. Indeed, due to the intractable nature of the solid product formed in this process, further experiments were not pursued.

### 2.3 Conclusions

A series triple Mannich bases derived from the commercially-available secondary amines, dibenzylamine (**96**), carbazole (**97**), dicyclohexylamine (**98**), morpholine (**99**), *N,N'*-diisopropylamine (**100**), pyrrolidine (**101**) and piperidine (**102**), were prepared as intractable solids. In addition, three functionalized triple Mannich bases (**116-118**) were prepared from the dibenzylamines (**105-107**). It was envisioned that the triple Mannich bases (**116-118**) could serve as functionalized dendrimer cores. Attempts to extend the branches of the Mannich bases **117** and **118** were unsuccessful. A future study would involve the extension of the hexabrominated triple Mannich base **116** *via* a Negishi coupling reaction. Finally, the hexaferrocenyl triple Mannich base **124**, was prepared from the secondary amine **125**, however, in a similar manner to the first series of triple Mannich bases, this product was virtually intractable.

## Chapter 3:

### *Results and Discussion: Synthesis of Chimeric Xyloketal A Analogues*

#### 3.1 Introduction

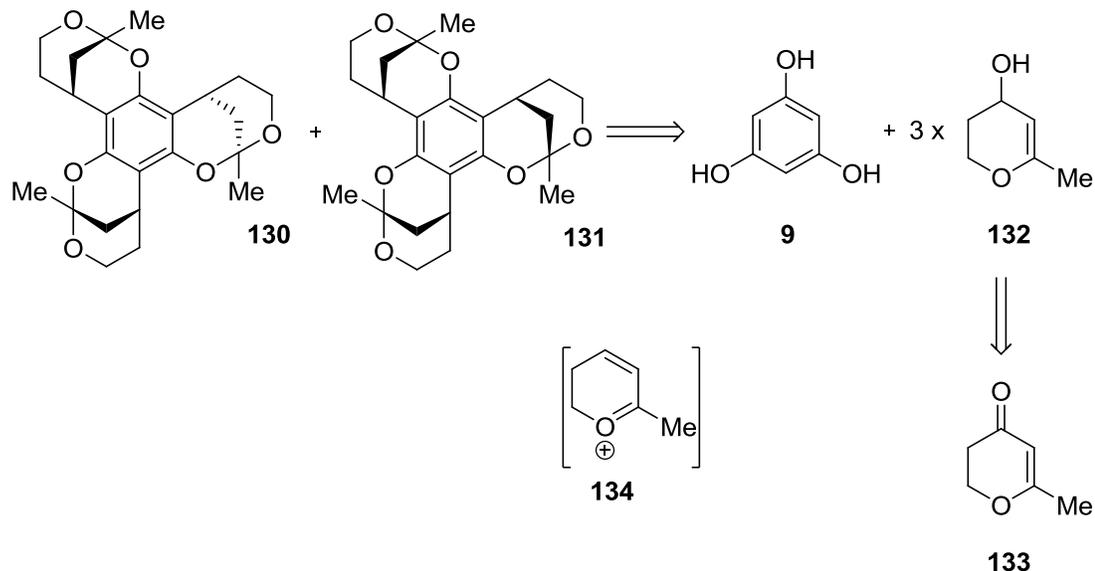
In this chapter the preparation of a series of chimeric xyloketal A analogues is described. In each case a small carbon-based electrophilic species was prepared using known literature procedures, and was then coupled to phloroglucinol (**9**) *via* a triple EAS reaction. This approach led to the isolation of the xyloketal A analogues ( $\pm$ )-**130** and ( $\pm$ )-**148**. In addition, the investigation of a third analogue **182**, derived from a precursor to  $\Delta^8$ -tetrahydrocannabinol (**188**), led to the isolation of the novel quinone **208**.

#### 3.2 Synthesis of a ( $\pm$ )-Xyloketal A Analogue

##### 3.2.1 Preparation of the $\alpha,\beta$ -Unsaturated Alcohol Precursor (**132**)

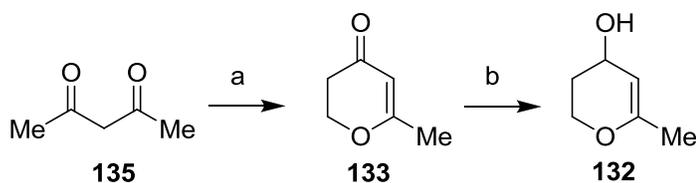
The first potential precursor with suitable features that was identified in this manner, was 2-methyl-5,6-dihydro-4*H*-pyran-4-one (**133**, Scheme 3.2.1.1).<sup>42</sup> It was hypothesised that this molecule could be reduced to the  $\alpha,\beta$ -unsaturated alcohol **132** and then converted to the active electrophilic species **134**, upon treatment with an appropriate acid, and then coupled to phloroglucinol (**9**). In principle, only two possible diastereoisomers (**130** and **131**), and their corresponding enantiomers, can be formed as a result of this process.

**Scheme 3.2.1.1 Retrosynthetic Analysis of ( $\pm$ )-Xyloketal A Analogues [( $\pm$ )-130 and ( $\pm$ )-131]**



The requisite  $\alpha,\beta$ -unsaturated alcohol **132** was prepared according to known literature procedures from acetylacetone (**135**, Scheme 3.2.1.2).<sup>42</sup>

**Scheme 3.2.1.2 Synthesis of  $\alpha,\beta$ -Unsaturated Alcohol (**132**)<sup>42</sup>**



Reagents and conditions: (a) (i) NaH, HMPA, THF, 2 h, 0 °C; (ii) 2.5 M *n*-BuLi, hexanes, 30 min, rt; (iii) (HCHO)<sub>n</sub>, 2 h, rt; (iv) 3 M HCl, 2.5 h, rt (51%); (b) LiAlH<sub>4</sub>, Et<sub>2</sub>O, 20 min, 0 °C (unstable to isolation).

The first step of this process involved the addition of a solution of acetylacetone (**135**) to a suspension of sodium hydride and hexamethylphosphoramide in tetrahydrofuran at 0 °C. Subsequently, a 2.5 M solution of *n*-butyl lithium in hexanes was added. These two bases were used in succession in order to prepare a solution containing the dianion of acetylacetone (**135**), to which dry paraformaldehyde powder

was added. Finally, a 3 M aqueous solution of hydrochloric acid was added, which facilitated a tandem cyclization and elimination reaction, to afford 2-methyl-5,6-dihydro-4*H*-pyran-4-one (**133**) in this multi-operation, one-pot procedure. Preliminary attempts to reduce this compound to the corresponding alcohol with lithium aluminum hydride proved fruitful. The reaction proceeded cleanly, as indicated by TLC, and was complete after stirring for 20 minutes at room temperature. A <sup>1</sup>H NMR spectrum of the crude reaction mixture confirmed the presence of the reduced alcohol product (**132**). However, this compound proved to be unstable to purification by flash chromatography. Thus, it was decided to use the crude product in subsequent reactions.

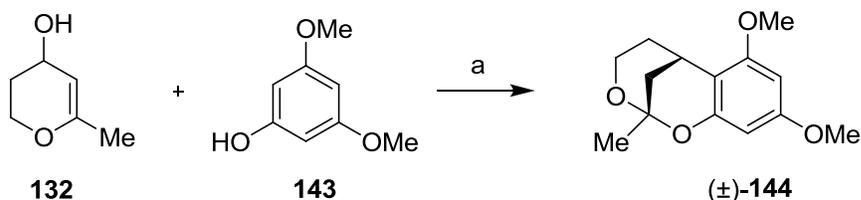
Of note, the precursor of this alcohol, 2-methyl-5,6-dihydro-4*H*-pyran-4-one (**133**) is itself a natural product and has been isolated from a liquid culture of the basidiomycete fungus *Physisporinus sanguinolentus*, as part of a study exploring the prevention of root rot in boreal forests.<sup>43</sup> This substance has also been employed by Haddad and co-workers as a key precursor in the enantioselective preparation of chiral 1,3-dioxin-4-ones.<sup>42</sup> The synthetic strategy that they developed in order to prepare these compounds was based on two previously reported synthetic methodologies. The first step of this strategy was devised by Weiler and co-workers at the University of British Columbia in 1973. This study concerned the alkylation of dianions of  $\beta$ -keto esters (**Scheme 3.2.1.3**).<sup>44</sup>



### 3.2.2 Synthesis of the Model Compound [(±)-144] of the Proposed (±)-Xyloketal A Analogues [(±)-130 and (±)-131]

Due to the potentially complicated nature of the structures of the two possible *tris*-adducts **130** and **131** that were considered for synthesis, a model study was designed. Here, a substrate was chosen that would lead to an adduct containing only one [6,6]-acetal unit (**Scheme 3.2.2.1**). This was done in order to obtain spectroscopic data for this ring system so that the structures of the more complicated *tris*-adducts of phloroglucinol could be clearly ascertained. Thus, 3,5-dimethoxyphenol (**143**) was chosen as a surrogate for phloroglucinol (**9**). It was hoped that this compound would have similar reactivity to phloroglucinol (**9**) and still engage in the desired ring-forming reaction.

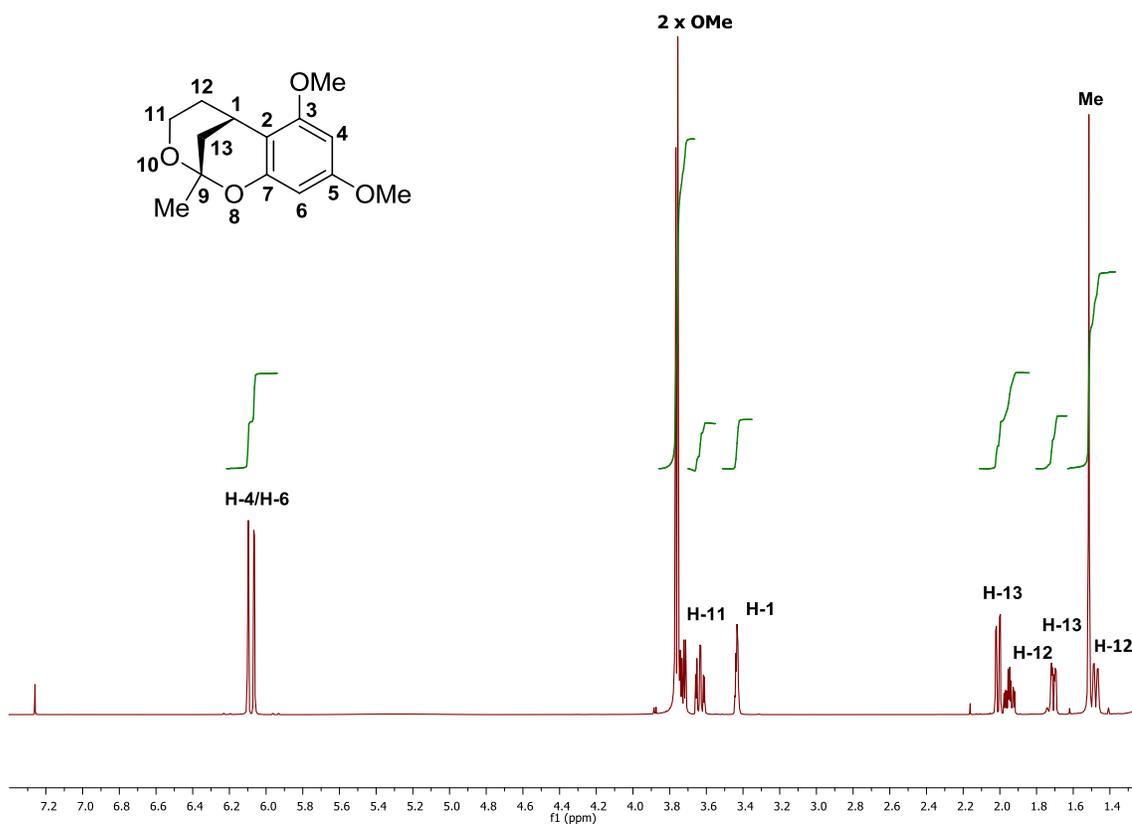
#### Scheme 3.2.2.1 Synthesis of (±)-[6,6]-Acetal Derivative [(±)-144]



Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{MgSO}_4$ , THF, 0 °C, 5 h (13%).

The xyloketal A analogue model compound **144** was prepared according to the conditions outlined for the synthesis of xyloketal A (**15**, **Scheme 1.4.5.5**). Whereas the yield of this adduct was modest, the goal, which was to obtain detailed spectroscopic data on the ring system, was achieved. A high-resolution mass spectrum of this material displayed a peak at  $m/z$  251.1274 amu, which corresponded to the protonated molecular ion for a compound that has a molecular formula of  $\text{C}_{14}\text{H}_{18}\text{O}_4$ . This was consistent with the predicted molecular formula of the model compound **144**. Extensive analysis of 2D-

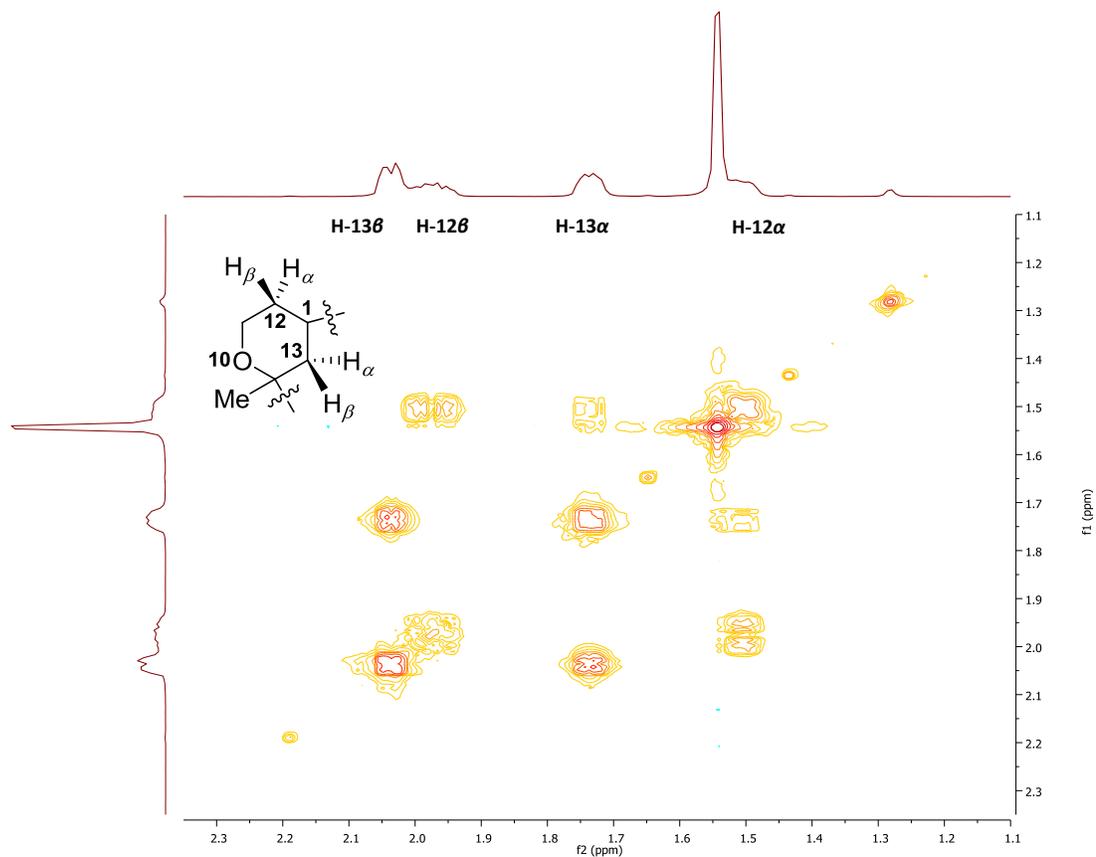
NMR spectra led to the assignment of all the signals in the [6,6]-acetal ring system. Examination of the HSQC NMR spectrum, led to the assignment of each of the three diastereoisotopic pairs of methylene signals and their corresponding carbons. This left the multiplet at  $\delta$  3.43 ppm as the signal corresponding to *H*-1, as it was the only correlation of a carbon with a single proton that could not be assigned to one of the two aromatic hydrogens. These, in turn, could be assigned to the doublets at  $\delta$  6.07 and 6.10 ppm, respectively (**Figure 3.2.2.1**).



**Figure 3.2.2.1**  $^1\text{H}$  NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of ( $\pm$ )-analogue [( $\pm$ )-144].

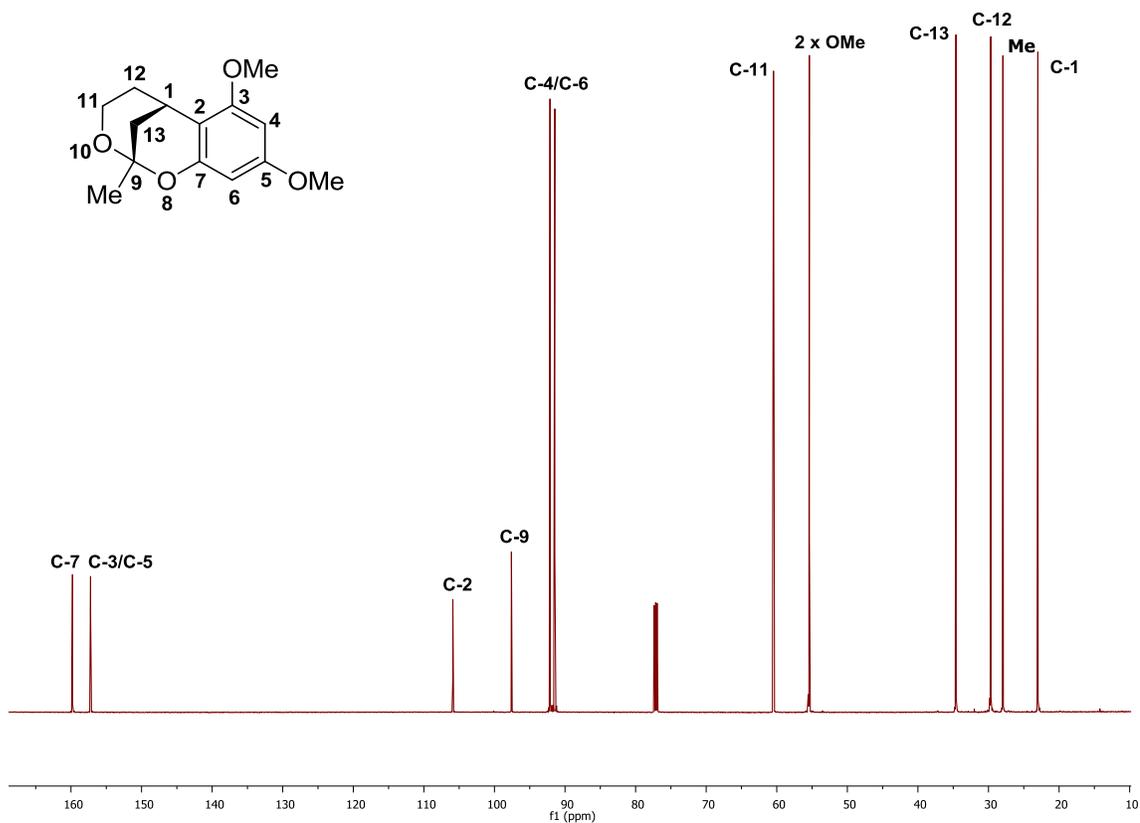
Due to their proximity to the oxygen, the protons at position 11 (*H*-11) were assigned to the apparent triplet of doublets at  $\delta$  3.63 ppm and the apparent doublet of

doublets at  $\delta$  3.73 ppm. With these two sets of signals firmly established, a detailed examination of the COSY and HMBC NMR spectra in tandem facilitated the assignment of the remaining aliphatic signals at positions 12 and 13. The signals, corresponding to the methyl and methoxy groups, as well as the aromatic signals at positions 2-7, were assigned in a similar fashion. Additionally, a correlation was observed between the multiplet at  $\delta$  1.48 ppm and the doublet of doublet of doublets at  $\delta$  1.71 ppm in the COSY NMR spectrum (**Figure 3.2.2.2**). This four-bond, long-range coupling suggests that these two hydrogen atoms, labelled H<sub>a</sub> at positions 12 and 13, are in a W-conformation and that the dihedral angle between them is close to zero – a hypothesis which is supported by inspection of molecular models. As such, the individual signals in these pairs of diastereoisotopic methylene protons could be tentatively assigned. Moreover, this assignment was consistent with the observed splitting patterns for both sets of signals.



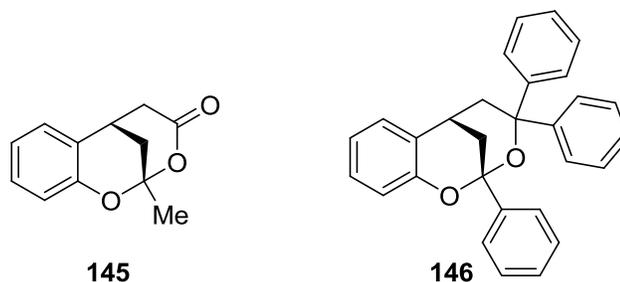
**Figure 3.2.2.2** COSY NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of ( $\pm$ )-analogue [( $\pm$ )-144].

In the  $^{13}\text{C}$  NMR spectrum, the carbon at the position labelled C-11 was assigned to the peak at  $\delta$  60.5 ppm for the reasons mentioned above (**Figure 3.2.2.3**). With this resonance established, the remaining signals were assigned in a manner similar to that used for the assignment of the  $^1\text{H}$  NMR spectrum.



**Figure 3.2.2.4**  $^{13}\text{C}$  NMR spectrum (150 MHz,  $\text{CDCl}_3$ ) of  $(\pm)$ -analogue [(±)-144].

While several examples of a [6,6]-acetal ring system of this type have been reported, this system has hitherto always been embedded in more complicated structures. The two closest related examples, in terms of this ring system, are shown below (**Figure 3.2.2.5**).<sup>46-49</sup>

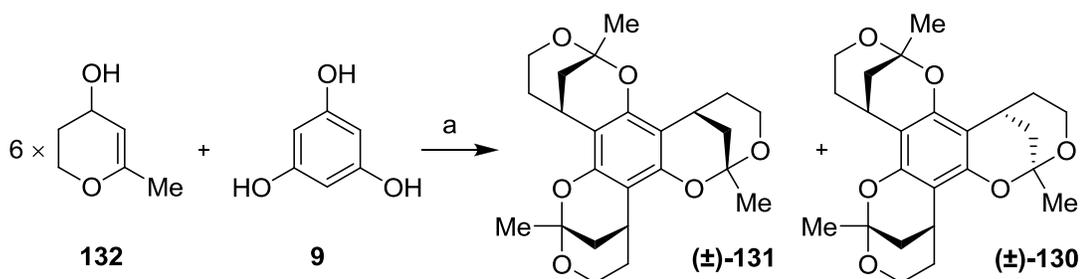


**Figure 3.2.2.5** Molecular structures of benzannulated [6,6]-acetal derivatives (**145**) and (**146**).<sup>46-49</sup>

### 3.2.3 Reaction of Phloroglucinol (**9**) with the $\alpha,\beta$ -Unsaturated Alcohol (**132**)

With the assignment of the observed signals for the [6,6]-acetal ring system firmly established, the synthesis of the triple  $C_3$ -symmetric derivative **131** was attempted (Scheme 3.2.3.1).

#### Scheme 3.2.3.1 Synthesis of ( $\pm$ )-Xyloketal A Analogues [( $\pm$ )-**130** and ( $\pm$ )-**131**]



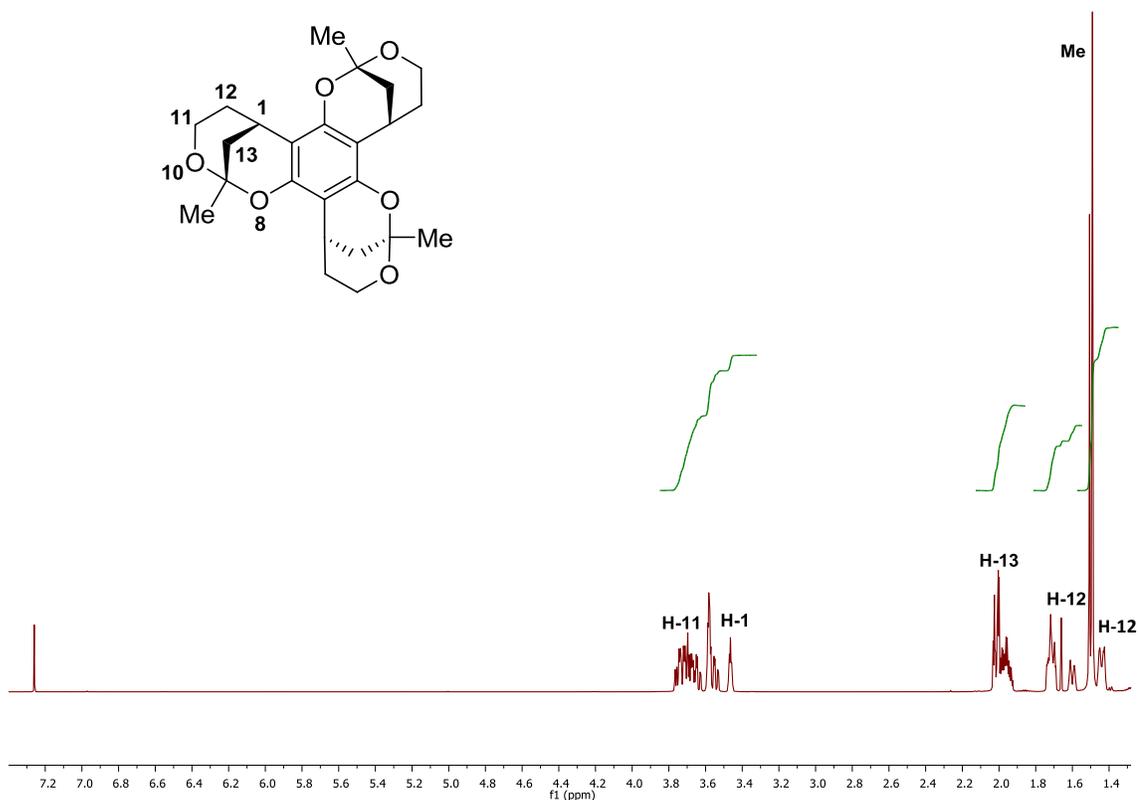
Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{MgSO}_4$ , THF, 0 °C, 18 h [0% (**131**), 71% (**130**)].

The prescribed reaction conditions for the synthesis of xyloketal A (**15**), when applied here, resulted exclusively, on work-up and purification, in the isolation of the unsymmetrical analogue ( $\pm$ )-**130** in excellent yield. The lack of any observed formation of the  $C_3$ -symmetric derivative ( $\pm$ )-**131** could be attributed to steric interactions between one fully-formed ring system and another that is still undergoing formation during the reaction. Since only one electrophilic aromatic substitution reaction can take place at a

time (*cf.* EAS mechanism, **Scheme 1.2.2**), if the rate of acetal formation is faster than a subsequent electrophilic aromatic substitution reaction, one could expect each ring system to be fully-formed before the second and third ring systems are installed. This could lead to a preferential arrangement of the latter ring systems which would minimize any steric interaction, perhaps resulting in the observed product. Moreover, formation of this unsymmetrical adduct [(±)-**130**] is more statistically probable than formation of its  $C_3$ -symmetric counterpart, a factor which led to the production of the former as the major product.

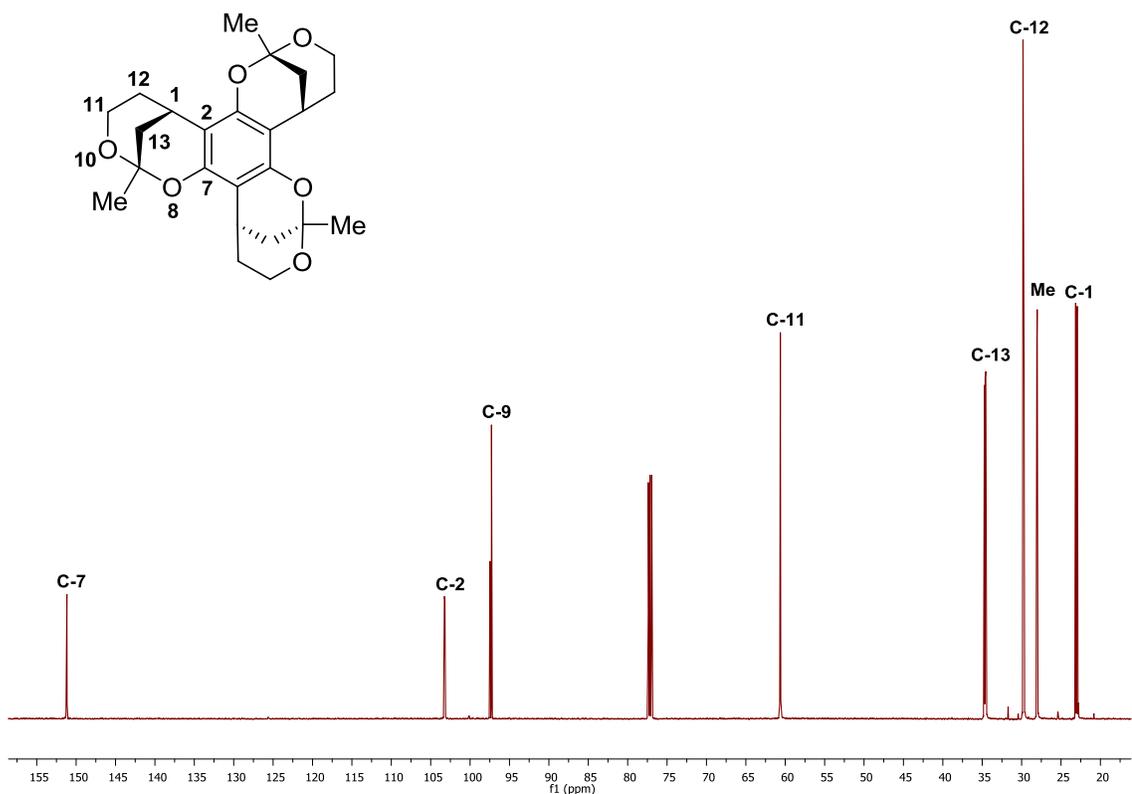
The high resolution mass spectrum of the adduct (±)-**130** exhibited a peak at  $m/z$  415.2109 amu, which was consistent with the protonated molecular ion for a compound with a molecular formula of  $C_{24}H_{30}O_6$ , which in turn corresponded to either of the desired products (±)-**130** or (±)-**131**. The molecular structure of this product was assigned using  $^1H$ ,  $^{13}C$ , COSY, HSQC and HMBC NMR spectroscopy techniques, along with the data obtained for the *mono*-adduct **144** as reference. The data obtained here, was similar to that obtained for the *mono*-adduct **144**, but with several key differences. Had the  $C_3$ -symmetric adduct been formed, one would expect its NMR data to approximate the data obtained for the *mono*-adduct **144** fairly closely, or at least be apparent as a single ring-system. The two sets of methyl signals (Me) at  $\delta$  1.49 and 1.51 ppm, which integrated to 6 and 3 protons respectively, were taken as partial evidence that the major product obtained from this reaction was the unsymmetrical diastereoisomer (and its enantiomer). Furthermore, the signals assigned as *H*-12, which in the *mono*-adduct **144** had corresponded to two multiplets, were evident here as the three multiplets at  $\delta$  1.44, 1.60, and 1.72 ppm, and which integrated to 2, 1 and 3 protons, respectively (**Figure 3.2.3.1**).

Of additional interest, the three pairs of diastereoisotopic protons corresponding to *H*-13, in this triple adduct, coalesced into a single multiplet at  $\delta$  1.88 ppm, whereas in *mono*-adduct **144**, these signals were resolved and separated by 0.30 ppm.



**Figure 3.2.3.1**  $^1\text{H}$  NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of  $(\pm)$ -analogue **[( $\pm$ )-130]**.

The  $^{13}\text{C}$  NMR spectrum provided further evidence of the subtle asymmetry of the *tris*-adduct **[( $\pm$ )-130]** (**Figure 3.2.3.2**). Indeed, the 22 signals in this spectrum are grouped, such that each grouping of three individual signals corresponds to the eight carbon signals associated with a single ring system. If the  $C_3$ -symmetric diastereoisomer had been isolated, it should have exhibited a reduced version of the  $^{13}\text{C}$  NMR spectrum presented here, containing only eight peaks.



**Figure 3.2.3.2**  $^{13}\text{C}$ -NMR spectrum (150 MHz,  $\text{CDCl}_3$ ) of  $(\pm)$ -analogue **[( $\pm$ )-130]**.

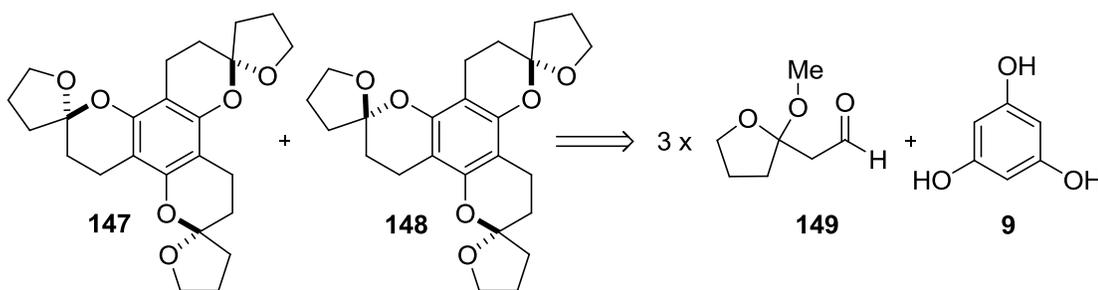
In summary, the synthesis of the unsymmetrical xyloketal A analogue **[( $\pm$ )-130]** was completed through the use of a triple electrophilic aromatic substitution and subsequent acetal formation reaction of phloroglucinol (**9**) with the novel carbon-based electrophile (**134**), derived from the hitherto unknown  $\alpha,\beta$ -saturated alcohol **132**. Moreover, this reaction resulted in the diastereoselective formation of seven fused rings and six stereogenic centres, in a single synthetic operation.

### 3.3 Synthesis of Chimeric Xyloketal A Analogue Containing a [5,6]-Spiroacetal Ring System Derived from Berkelic Acid

#### 3.3.1 Retrosynthetic Analysis of *tris*-[5,6]-Spiroacetals [(±)-147 and (±)-148]

In pursuit of another structurally-interesting, xyloketal A analogue, the aldehyde **149** was identified as a suitable electrophilic species that could lead to the  $C_3$ -symmetric triple [5,6]-spiroacetal **147** or the unsymmetrical adduct **148**, shown below (**Scheme 3.3.1.1**). As with previous examples, the proposed triple electrophilic aromatic substitution reaction would lead to the formation of seven rings and multiple stereogenic centres in a single transformation. In addition, commensurate with the xyloketal A analogues (±)-**130** and (±)-**131** described above, only two possible diastereoisomers [(±)-**147** and (±)-**148**] can be generated under the proposed scheme. The term chimeric is used here to imply that the indicated analogues contain salient features of two different natural products, namely xyloketal A (**15**) and berkelic acid (**153**).

#### Scheme 3.3.1.1 Retrosynthetic Analysis of Chimeric Xyloketal A Analogues [(±)-147] and [(±)-148]



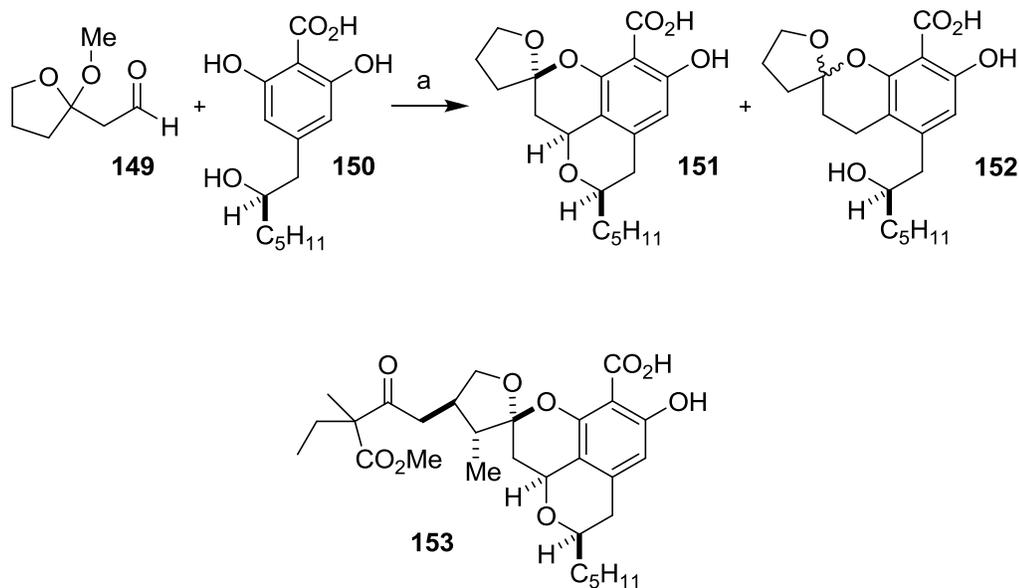
#### 3.3.2 Brief Review of Berkelic Acid (**153**) and its Total Synthesis by Snider *et al.*

Berkelic acid (**153**) was isolated by Stierle *et al.* in 2006 from a *Penicillium* species located in the surface waters of Berkeley Pit Lake in Montana.<sup>50</sup> This mile wide,

1500 foot deep lake is actually an abandoned open-pit copper mine, and is part of an extensive mine waste system. As a result, the water in the lake is extremely acidic, with a pH = 2.5, and contains high concentrations of metal sulfates. Thus, the seemingly toxic environment in the water has proven to be ideal for a variety of so-called extremophiles; bacteria, fungi, protists, algae and protozoans that thrive in these otherwise harsh conditions and produce an array of novel secondary metabolites, of which berkelic acid (**153**) is a preeminent example.

Berkelic acid (**153**) exhibits matrix metalloproteinase-3 (MMP-3) and caspase-1 inhibition activity in the micromolar and millimolar range, respectively. While both are signal transduction enzymes, the former has been implicated in the metastasis of ovarian cancer, and the latter is linked to inflammatory processes and to the retardation of the onset of Huntington's disease. To date, there have been four reported syntheses of berkelic acid (**153**).<sup>51-54</sup>

**Scheme 3.3.2.1 Snider and Co-worker's Synthesis of the Tetracyclic Core (151) of Berkelic Acid (153)<sup>55</sup>**

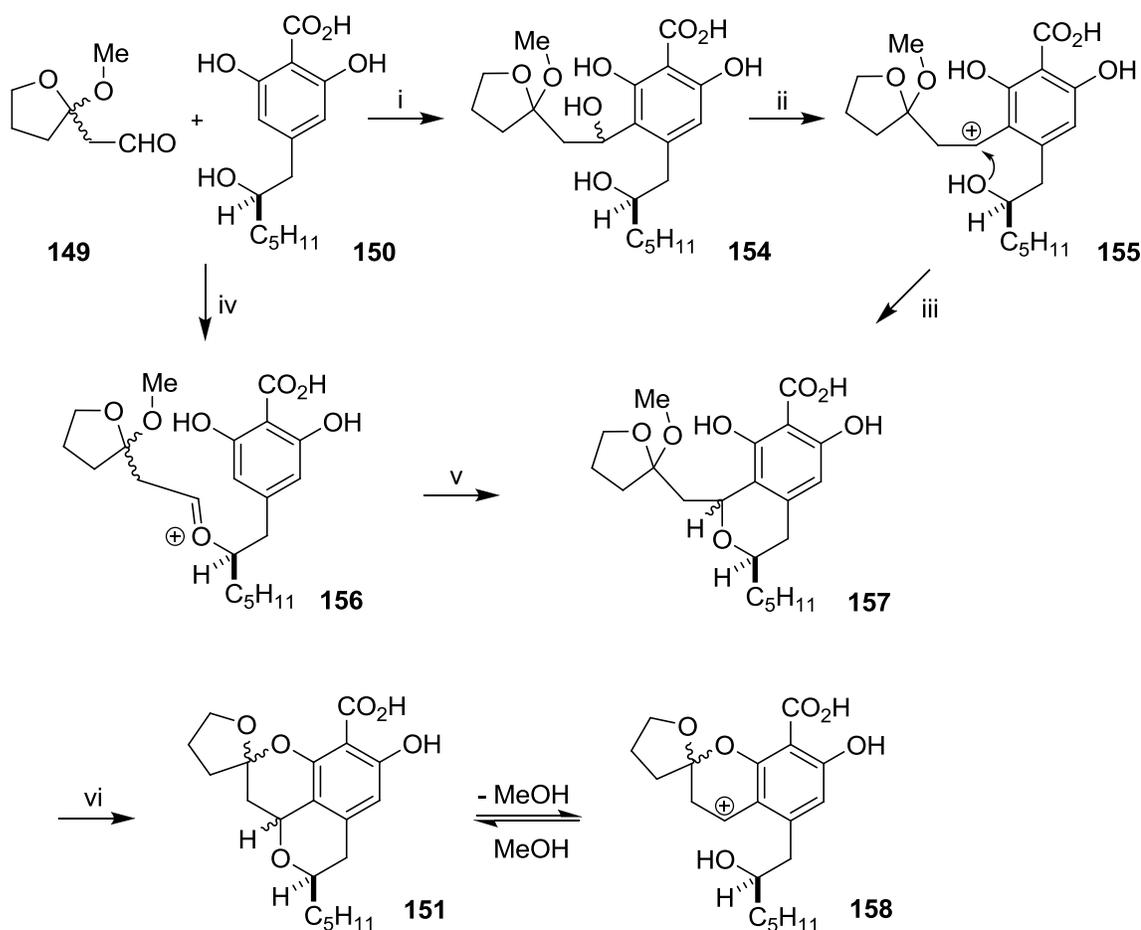


Reagents and conditions: (a) Dowex 50WX8-400H<sup>+</sup>, MeOH, 25 °C, 12 h; CH<sub>2</sub>N<sub>2</sub>, ether; TFA (0.2% in CDCl<sub>3</sub>), 25 °C, 12 h (50% of desired diastereoisomer **151** after TFA equilibration; 30% of **152** as a mix of diastereoisomers).

Snider and co-worker's synthetic route for the synthesis of the tetracyclic core of berkelic acid (**153**) involved the condensation of the aldehyde **149** with the 2,6-dihydroxybenzoic acid **150** (Scheme 3.3.2.1).<sup>55</sup> Thus, the desired tetracyclic acid was prepared as a mixture of four isomers. The yield of the desired isomer however, was increased to 50% *via* a TFA equilibration reaction. This reaction sequence was initially proposed to proceed *via* an oxa-Pictet-Spengler cyclization reaction which would lead to the formation of isochroman **157** (Scheme 3.3.2.2). The prescribed route for this reaction involves the formation of the oxocarbenium ion **156** (step iv) and a subsequent intramolecular Friedel-Crafts reaction resulting in the required isochroman **157** (step v). Alternatively, an intermolecular Friedel-Crafts reaction, resulting in the benzylic alcohol **154** (step i), followed by protonation and loss of water to give the benzylic cation **155** (step ii), was also proposed as a route leading to the advanced intermediate isochroman

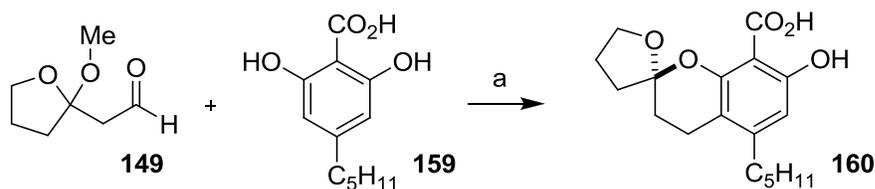
**157.** The final step in this sequence would involve a transacetalization reaction resulting in the tetracyclic core of berkelic acid (**151**) (step vi).<sup>55</sup>

**Scheme 3.3.2.2 Snider's Proposed Oxa-Pictet-Spengler Cyclization Leading to Formation of Berkelic Acid (**153**)**<sup>55</sup>



Whereas the proposed reaction sequence proved successful for the formation of the desired tetracyclic adduct **151**, it also led to the unexpected formation of the [5,6]-spiroacetal side product **152** as a mixture of diastereoisomers. As a means to aid in the elucidation of the molecular structure of this side product (**152**), Snider *et al.* prepared the [5,6]-spiroacetal derivative **160**, which notably, was lacking the pendant alcohol of the side product **152** (Scheme 3.3.2.3).

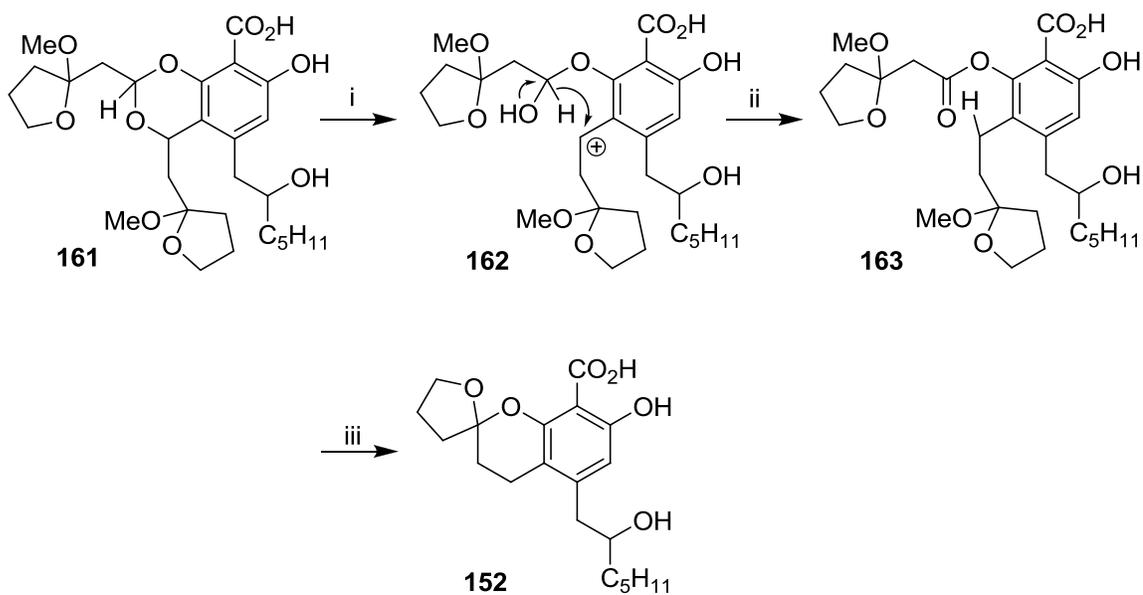
### Scheme 3.3.2.3 Synthesis of [5,6]-Spiroacetal (**160**)<sup>55</sup>



Reagents and conditions: (a) (i) Dowex 50WX8-400H<sup>+</sup>, MeOH, 18 h, 0 °C; (ii) CH<sub>2</sub>N<sub>2</sub>, ether (27%, 90% pure).

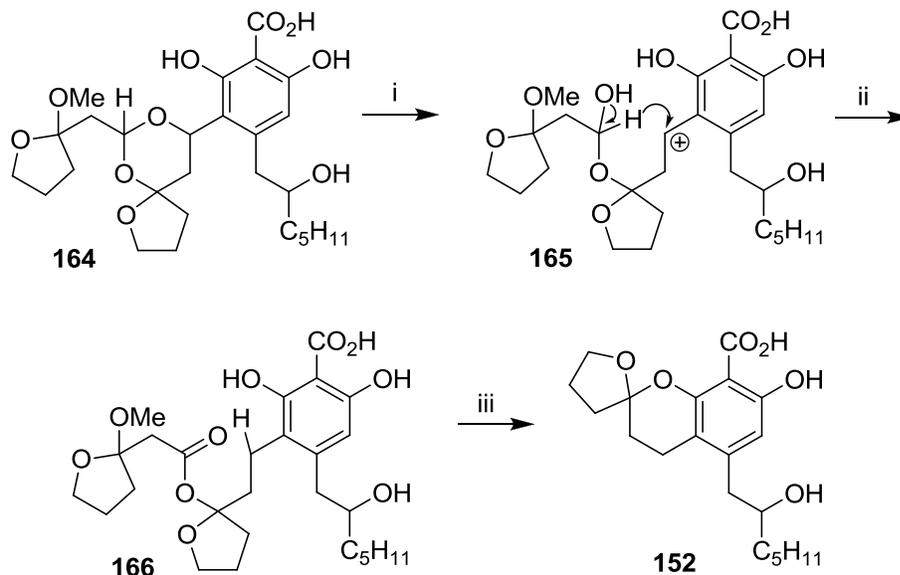
The mechanistic rationale for the formation these [5,6]-spiroacetal side products **152** and **160** employs a second equivalent of aldehyde **149** as a putative hydride donor. The authors purported that this aldehyde could react with a benzylic alcohol analogous to compound **154**, resulting in the 1,3-dioxane **161**. Subsequent protonation of this species, followed by a 1,5-hydride shift, would lead to the ester **163** (step ii). Finally, hydrolysis of this ester **163**, and a spiroketalization reaction would result in the [5,6]-spiroacetal **152** or **160** (Scheme 3.3.2.4).<sup>55</sup>

**Scheme 3.3.2.4 Snider's Proposed Mechanistic Rationale for Formation of the [5,6]-Spiroacetals (152) and (160)<sup>55</sup>**



An alternative reaction scheme was also proposed, which proceeds instead from the 1,3-dioxane **164** in an analogous fashion to that previously described (**Scheme 3.3.2.5**).<sup>55</sup>

**Scheme 3.3.2.5 Snider's Alternative Mechanistic Rationale for Formation of the [5,6]-Spiroacetals (152) and (160)<sup>55</sup>**



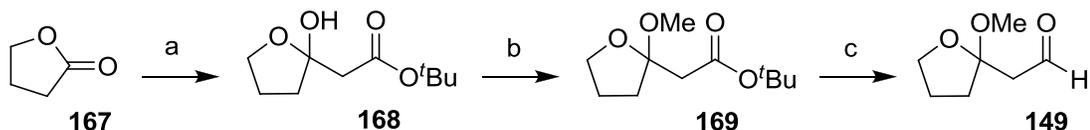
Moreover, Snider *et al.* stressed that very little of these [5,6]-spiroacetal products were obtained when the reaction was performed at room temperature. This observation was held to be in accordance with the proposed mechanism, due to the fact that the highly ordered transition state for a 1,5-hydride shift would have a large negative entropy and would thus be favoured at lower temperatures. These results led the authors to support, at least in part, the alternative mechanistic route for the oxa-Pictet-Spengler, which proceeds *via* the benzylic alcohol **154** and not the oxocarbenium ion **156**. Moreover, a reduction *via* a 1,5-hydride shift of the latter, leading to formation of the [5,6]-spiroacetal **152** would be unlikely, and impossible for the formation of the [5,6]-spiroacetal **160**, since the olivetol derivative starting material **159** lacks the pendant alcohol.

### 3.3.3 Synthesis of Aldehyde Precursor (149)

The aldehyde **149** was prepared according to Snider and co-worker's method.<sup>55</sup> The enolate of *tert*-butyl acetate was added to  $\gamma$ -butyrolactone (**167**), to afford the

hemiketal **168**. Using Dowex 50WX8-400-H<sup>+</sup> ion exchange resin in methanol, the ketal **169** was prepared in good yield over two steps (**Scheme 3.3.3.1**).

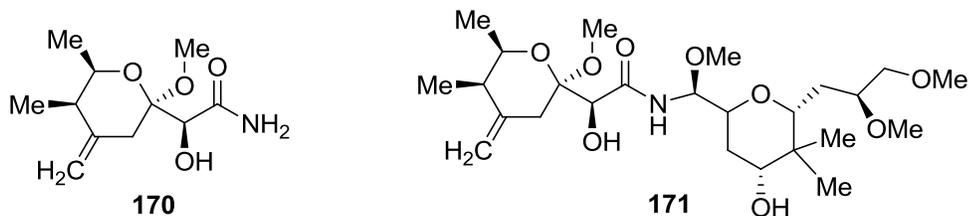
**Scheme 3.3.3.1 Synthesis of Aldehyde (149)**<sup>55</sup>



Reagents and conditions: (a) LDA, *t*-BuOAc, THF, 2 h, -78 to -30 °C; (b) Dowex 50WX8-400-H<sup>+</sup>, MeOH, 12 h, 25 °C (67%, over two steps); (c) DIBAL-H, ether, 1.5 h, -78 °C (unstable to isolation).

Subsequent reduction of the *tert*-butyl ester **169** with diisobutylaluminum hydride was then attempted on scales ranging up to a gram with no success. When the amount of ester **169** was reduced to 100 milligrams however, the amount used by Snider *et al.*, the reduction was successful. The reduced aldehyde product **149** was found to decompose over a period of several hours, and could not withstand any form of purification. As this compound has found limited use in the literature, a brief summary of its development and application is included below.

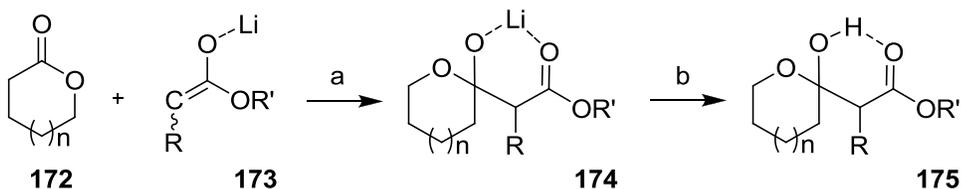
In 1978, Duggan *et al.* developed a method for the preparation of cyclic ketals bearing lactone moieties analogous to the molecular structure of the aldehyde **149**.<sup>56</sup> The impetus for this development was derived from attempts to prepare pederamide (**170**), a degradation product of pederin (**171**), a natural product that was isolated from the blister beetle (*sp.* *Paederus fuscipes*) in 1953. Pederin (**171**) inhibits protein biosynthesis and mitosis, and as such was explored as a potential anti-cancer agent (**Figure 3.3.3.1**).<sup>57</sup>



**Figure 3.3.3.1** Molecular structures of pederamide (170) and pederin (171).

The original experiments involved the addition of a variety of lithium ester enolates **173** to  $\delta$ -valerolactone (**172**,  $n = 1$ ) and  $\gamma$ -butyrolactone (**167**,  $n = 0$ ) (Scheme 3.3.3.2).<sup>56</sup>

**Scheme 3.3.3.2** Duggan's Synthesis of Cyclic Hemiketals (**175**) from  $\delta$ -Valerolactone ( $n = 1$ ) and  $\gamma$ -Butyrolactone ( $n = 0$ )<sup>56</sup>

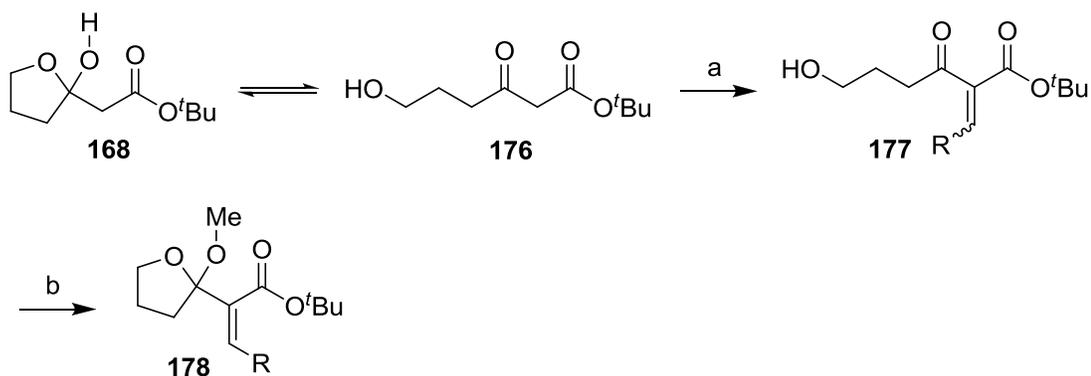


Reagents and conditions: (a) THF,  $-78\text{ }^{\circ}\text{C}$ ; (b)  $\text{H}_2\text{O}$  (50-97%).

The authors reported only minor amounts of the ring-open keto-form of the condensation product. They postulated that the cyclic hemiketal adduct was preferred over the ring-open ketol due to stabilization *via* lithium chelation in the reaction intermediate (**174**), and hydrogen-bonding in the final isolated product. Of the various alkyl substituents on the ester moiety, *tert*-butyl groups led to the highest corresponding yields in the final addition products of the  $\delta$ -valerolactone and  $\gamma$ -butyrolactone derivatives. The tautomeric ratio of ring-opened hydroxy keto ester to hemiketal was later determined by Kobayashi *et al.* in an unrelated study using NMR spectroscopy, to be approximately 35:65.<sup>58</sup> In 2000, both the  $\delta$ -valerolactone and  $\gamma$ -butyrolactone derived

$\beta$ -hemiacetals were employed by Kurth *et al.* in a model study to determine whether  $\beta$ -hemiacetals could undergo a Knoevenagel condensation reaction to form  $\omega$ -hydroxyl- $\beta$ -keto esters *en route* to developing a method for an attempted total synthesis of the natural product eleutherobin (**Scheme 3.3.3.3**).<sup>59</sup>

**Scheme 3.3.3.3 Kurth's Synthesis of the Knoevenagel Condensation Product (178)**<sup>59</sup>



Reagents and conditions: (a) RCHO, piperidine, EtOH, rt, 4-12 h; (b) MeOH, PPTS, rt, 1 h (51-91%).

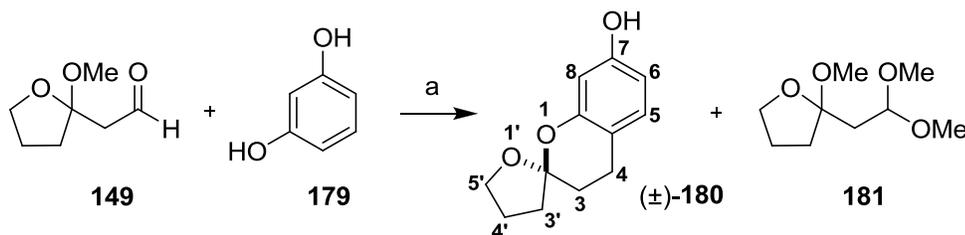
Subsequent to this work, in 2007, Snider *et al.* employed Kurth's synthesis of hemiacetal **168**, *en route* to preparing aldehyde **149** in his biomimetic synthesis of the tetracyclic core of berkelic acid (**151**), and its subsequent total synthesis.<sup>53</sup> Indeed, whereas the aldehyde **149** has found limited but important use in a variety of applications, it is in the context of Snider's total synthesis of berkelic acid (**153**) that this compound was identified as a suitable electrophilic precursor to prepare a structural analogue of xyloketal A (**15**).

### 3.3.4 Synthesis of the [5,6]-Spiroacetal Model Compound [(±)-180]

In accordance with the strategy used to prepare the xyloketal A analogue (±)-**130** discussed above (*cf.* Section **3.2.2**), a monobenzannelated model compound [(±)-**180**], in

this case containing the proposed [5,6]-spiroacetal ring system, was prepared (**Scheme 3.3.4.1**). This synthesis was undertaken as a means to gain an understanding of this somewhat complicated process and to obtain comprehensible structural data of the [5,6]-spiroacetal ring system. In theory, this data could be used to confirm whether or not the  $C_3$ -symmetric triple [5,6]-spiroacetal derivative ( $\pm$ )-**147** had formed, as it would exhibit signals in both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra corresponding to a single ring system as a result of the adduct's symmetry. In this case, resorcinol (**179**) was chosen as a surrogate for phloroglucinol (**9**) instead of 3,5-dimethoxyphenol (**143**), the model compound that was employed in the previous study [*cf.* xyloketal A analogue ( $\pm$ )-**130**]. This change was made for the simple reason that 3,5-dimethoxyphenol (**143**) had failed to work in another system, which had necessitated the use of resorcinol (**179**) instead (*vide infra*).

**Scheme 3.3.4.1** Synthesis of ( $\pm$ )-3,4-Dihydrospiro[1-benzopyran-2,2'-oxolane]-7-ol [( $\pm$ )-**180**]

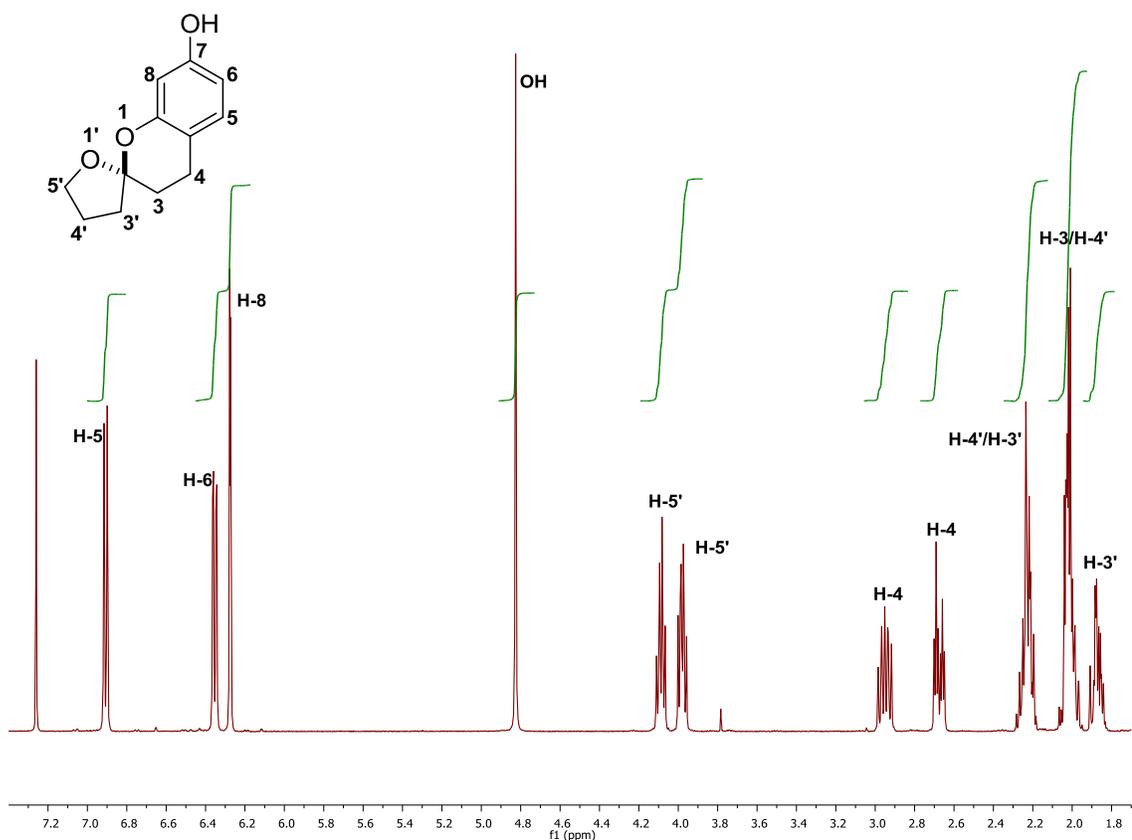


Reagents and conditions: (a) Dowex 50WX8-400- $\text{H}^+$ , MeOH, 16 h, 0 °C [29% (**180**), 15% (**181**)].

One equivalent of the aldehyde **149** was successfully coupled to a slight excess of resorcinol (**179**) in the prescribed manner to afford the *mono*-[5,6]-spiroacetal ( $\pm$ )-**180** (*cf.* **Scheme 3.3.2.3**). The temperature of the reaction was kept constant at 0 °C, and its progress was closely monitored by TLC. The yield of the desired [5,6]-spiroacetal [( $\pm$ )-

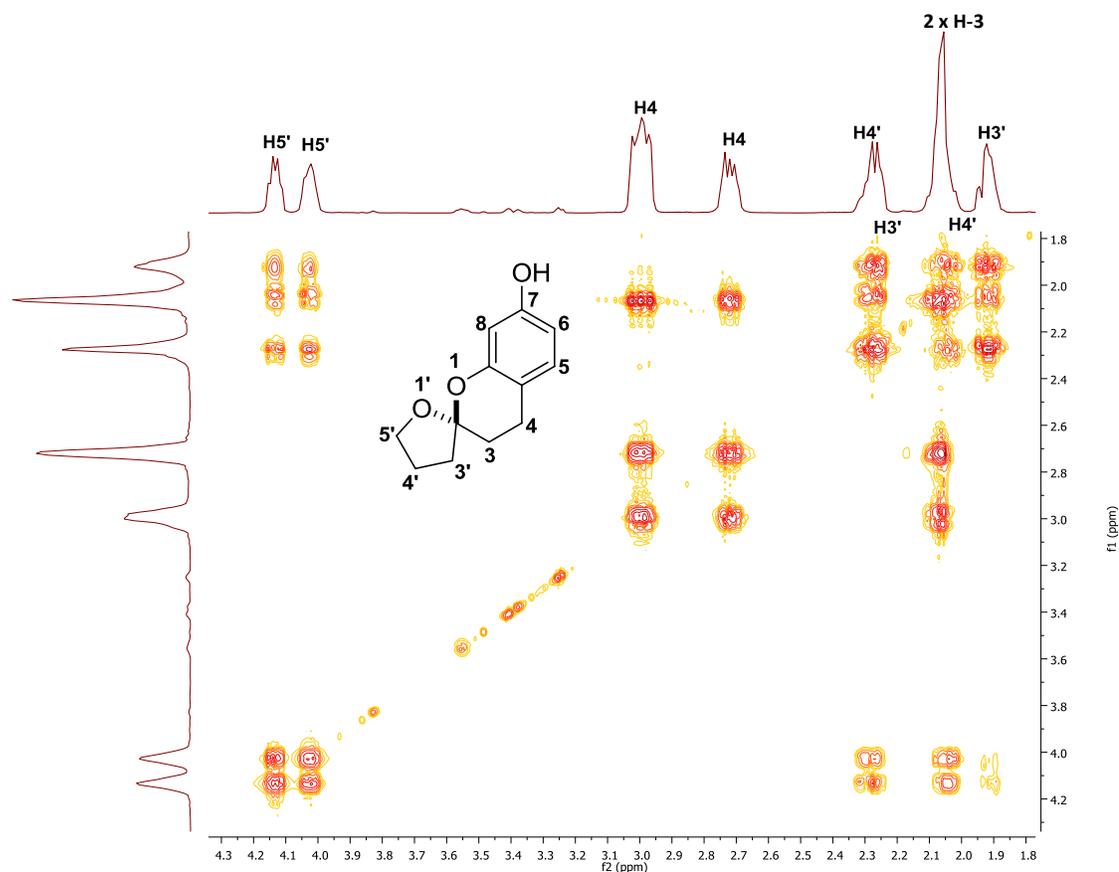
**180**] product however, was moderate, and a significant amount of the aldehyde precursor **149** was converted to the acetal byproduct **181** (Scheme 3.3.4.1).

A high resolution mass spectrum of compound ( $\pm$ )-**180** displayed a peak at  $m/z$  229.0838 amu, which was consistent with a molecular ion plus sodium for a compound containing the expected molecular formula ( $C_{12}H_{14}O_3$ ) of this product. The molecular structure of compound ( $\pm$ )-**180** was determined using  $^1H$  and  $^{13}C$ , COSY, HSQC and HMBC NMR spectroscopy techniques, and through comparison to literature data.<sup>55,60,61</sup> The protons at the position labelled *H*-5' were assigned to the multiplets centred at  $\delta$  4.08 and 3.98 ppm (Figure 3.3.4.1). This initial assignment was made based on the assumption that these signals, of all of those which corresponded to methylene protons, would appear the furthest downfield due to their proximity to the oxygen heteroatom. The diastereoisotopic methylene protons at position *H*-4 were assigned to the doublet of triplets at  $\delta$  2.67 ppm and to the multiplet centred at  $\delta$  2.96 ppm, an assignment which is consistent with the predicted chemical shifts ( $\delta$ ) of benzylic protons. In addition, the observed doublet of triplets splitting pattern for one of the protons labelled *H*-4, is consistent with a geminal coupling to the other proton at *H*-4 with additional coupling to the two adjacent protons labelled *H*-3.



**Figure 3.3.4.1** <sup>1</sup>H NMR spectrum (500 MHz, CDCl<sub>3</sub>) of (±)-analogue [(±)-180].

Once these assignments were tentatively established, interpretation of the COSY NMR spectrum led to the assignment of the remaining aliphatic signals (**Figure 3.3.4.2**). The only observed signal that correlated to the protons labelled *H-4*, namely the multiplet centred at  $\delta$  2.01 ppm was assigned in part to the diastereoisotopic protons at position 3 (labelled *H-3*). As this multiplet integrated to three hydrogens, the additional resonance was assigned to one of the protons labelled *H-4'*, since a correlation was also observed between this multiplet and the protons labelled *H-5'*.

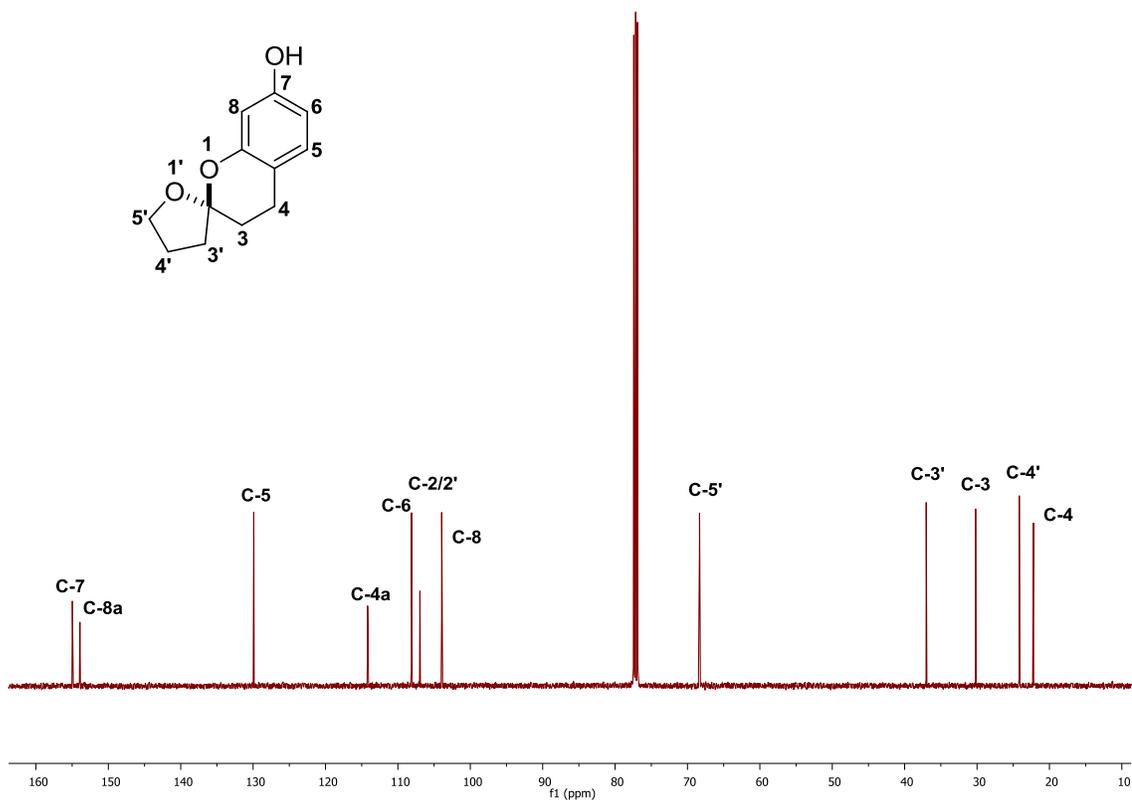


**Figure 3.3.4.2** COSY NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of ( $\pm$ )-analogue [( $\pm$ )-180].

The multiplet centred at  $\delta$  2.25 ppm, which integrated to two hydrogens was assigned to the other proton labelled  $H-4'$ . The remaining signals at  $\delta$  1.86 and 2.25 ppm were assigned to the pair of diastereoisotopic protons, labelled  $H-3'$ .

Regarding the aromatic signals, the doublet at  $\delta$  6.91 ppm was assigned to  $H-5$  as its chemical shift was consistent with protons at the *meta*-position of a phenol. The doublet of doublets at  $\delta$  6.35 ppm was in turn assigned to the proton labelled  $H-6$  and the remaining signal, the doublet at  $\delta$  6.27 ppm, was assigned to the proton labelled  $H-8$ .

The  $^{13}\text{C}$  NMR spectrum of the monobenzannulated [5,6]-spiroacetal ( $\pm$ )-**180** with all of the carbons assigned is shown below (**Figure 3.3.4.3**). The assignment of all carbon signals was confirmed through interpretation of the HSQC and HMBC 2D NMR spectra.

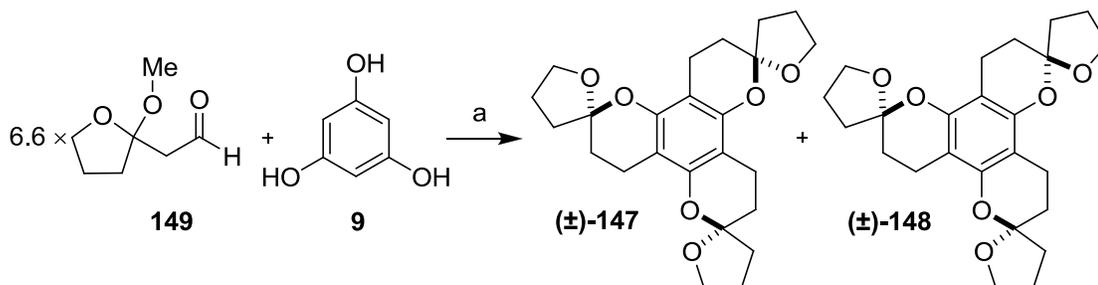


**Figure 3.3.4.3**  $^{13}\text{C}$  NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of ( $\pm$ )-analogue [( $\pm$ )-**180**].

### 3.3.5 Triple EAS Reaction of Phloroglucinol (**9**) and the Aldehyde (**149**)

With all of the signals associated with the [5,6]-spiroacetal ring system assigned in a model compound, the synthesis of the *tris*-[5,6]-spiroacetals ( $\pm$ )-**147** and ( $\pm$ )-**148** was undertaken (**Scheme 3.3.5.1**).

### Scheme 3.3.5.1 Synthesis of *tris*-[5,6]-Spiroacetals [(±)-**147**] and [(±)-**148**]

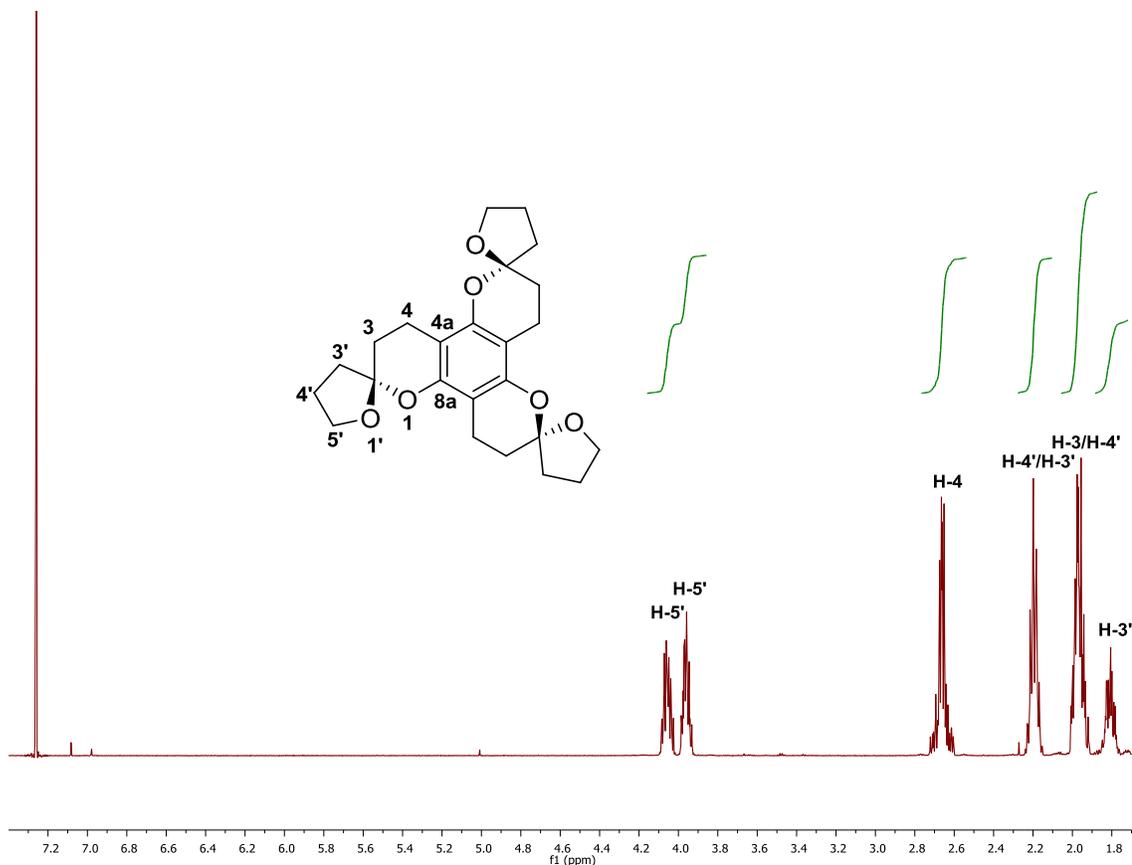


Reagents and conditions: (a) Dowex 50WX8-400-H<sup>+</sup>, MeOH, 16 h, 0 °C [0% (**147**), 6% (**148**)].

Due to the scale dependant nature of the reduction of the *tert*-butyl ester **169** to the corresponding aldehyde **149**, four, 100 milligram reactions were set up in parallel. It was hoped that this would provide enough material so as to attempt the coupling reaction with phloroglucinol (**9**) on a sufficient scale such that a significant amount of the desired products might be produced and isolated. The reactions were carefully monitored by TLC, as previous attempts led to formation of the over-reduced product. As such, the reactions were deemed to be complete after stirring for 1.5 h at -78 °C, whereupon they were quenched with a saturated aqueous solution of Rochelle's salt (potassium sodium tartrate) and then pooled into a single flask. After extraction of the crude reaction mixture with ether, the combined organic extracts were concentrated *in vacuo*, and immediately dissolved in methanol. This solution was then added to a methanolic suspension of Dowex 50WX8-400-H<sup>+</sup> ion exchange resin and phloroglucinol (**9**). The molar ratio of the aldehyde **149** to phloroglucinol (**9**) was approximately 6.6:1. As per the mechanistic rationale put forth by Snider and co-workers, six equivalents of the aldehyde **149** is the minimum amount for this reaction to proceed to completion.

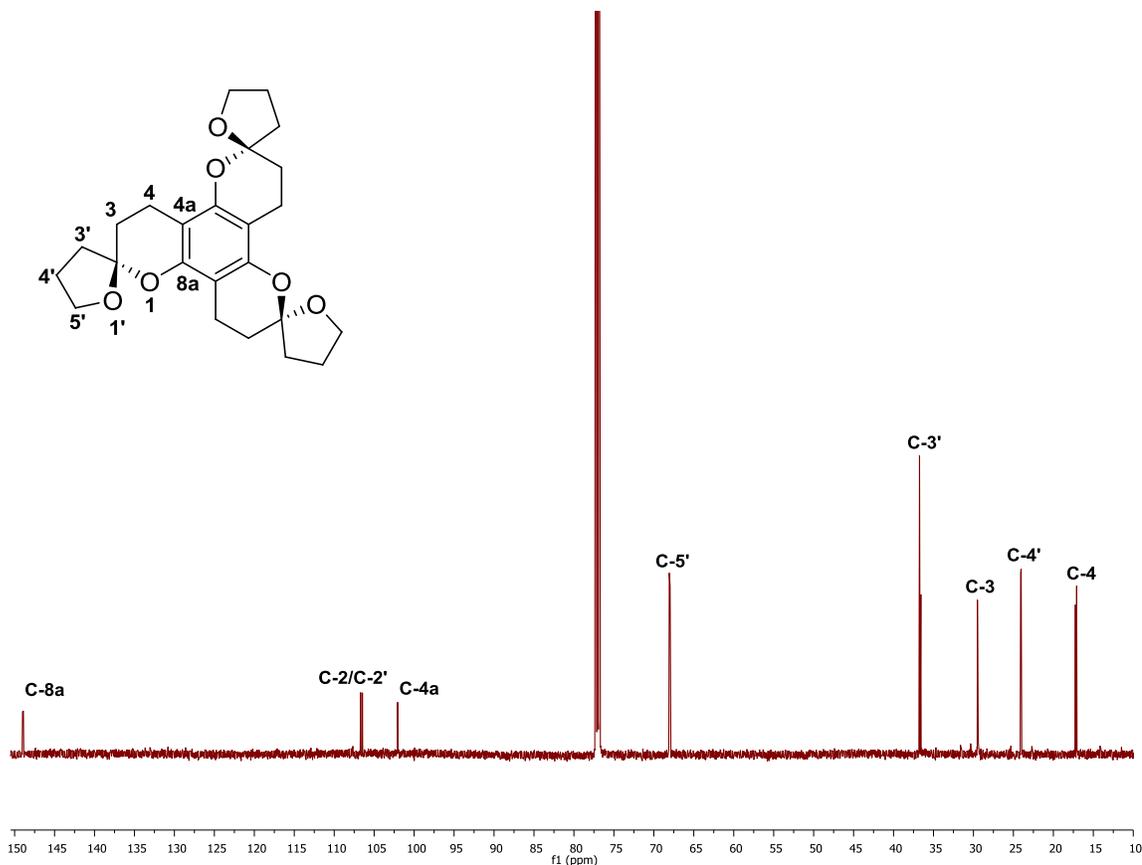
In a manner similar to the synthesis of the xyloketal A analogue (±)-**130** discussed above (section 3.2.3), only the unsymmetrical *tris*-adduct (±)-**148** was observed upon

work-up and purification. Moreover, no *mono*- or *bis*-adducts containing the [5,6]-spiroacetal ring system were isolated. The high resolution mass spectrum of the adduct ( $\pm$ )-**148** exhibited a peak at  $m/z$  415.2102 amu, which was consistent with the protonated molecular ion for a compound with a molecular formula of  $C_{24}H_{30}O_6$ , which in turn corresponded to either of the desired products ( $\pm$ )-**147** or ( $\pm$ )-**148**. Through the use of 1D and 2D NMR spectroscopic methods, all of the methylene proton signals for this unsymmetrical *tris*-adduct ( $\pm$ )-**148** were assigned. Moreover, all of the observed signals were consistent with the assignments made for the *mono*-[5,6]-spiroacetal ( $\pm$ )-**180**. The  $^1H$  NMR spectrum of the unsymmetrical *tris*-[5,6]-spiroacetal ( $\pm$ )-**148** with all of the protons assigned is shown below (**Figure 3.3.5.1**). The only key difference between the signals manifested by the *mono*-[5,6]-spiroacetal ( $\pm$ )-**180** and those of the *tris*-[5,6]-spiroacetal ( $\pm$ )-**148**, was the coalescence of the signals corresponding to the protons labelled *H*-4, which in this case were evident as a multiplet centred at  $\delta$  2.66 ppm.



**Figure 3.3.5.1**  $^1\text{H}$  NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of  $(\pm)$ -analogue  $[(\pm)\text{-148}]$ .

The  $^{13}\text{C}$  NMR spectrum of the *tris*-[5,6]-spiroacetal  $(\pm)\text{-148}$ , shown below, clearly indicates the unsymmetrical nature of this compound (**Figure 3.3.5.2**). As with the previous xyloketal A analogue  $(\pm)\text{-130}$ , each signal consists of three closely grouped peaks. These groupings however, add up to the total number of carbons for a single ring system, the chemical shifts of which are consistent with the previous assignment made for the *mono*-[5,6]-spiroacetal  $(\pm)\text{-180}$  ring system.



**Figure 3.3.5.2**  $^{13}\text{C}$  NMR spectrum (150 MHz,  $\text{CDCl}_3$ ) of  $(\pm)$ -analogue  $[(\pm)\text{-148}]$ .

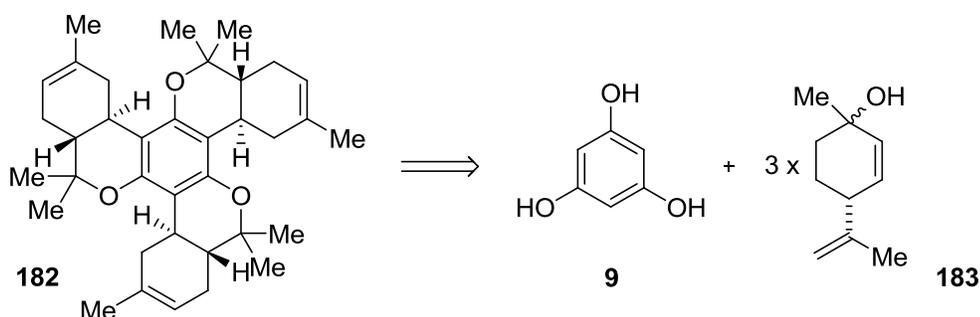
### 3.4 Synthesis of Chimeric Xyloketal A Analogue Containing the Ring System of $\Delta^8$ -Tetrahydrocannabinol

#### 3.4.1 Retrosynthetic Analysis of Xyloketal A Analogue (182) and Overview of the Cannabinoids

The optimized set of reaction conditions for the total synthesis of xyloketal A (**15**, **Scheme 1.4.5.5**) were derived from the work of Razdan *et al.*, and so an obvious choice for a potential carbon-based electrophilic species to further probe the limits of phloroglucinol's (**9**) susceptibility to triple EAS reactions, was *p*-mentha-2,8-dien-1-ol (**183**, **Scheme 3.4.1.1**). This compound found previous use as a precursor in Razdan's synthesis of  $\Delta^9$ -tetrahydrocannabinol (**185**,  $\Delta^9$ -THC) and  $\Delta^8$ -tetrahydrocannabinol (**186**,  $\Delta^8$ -THC).<sup>21</sup> The key reactions involved the coupling of *p*-mentha-2,8-dien-1-ol (**183**)

with olivetol (**190**) via an electrophilic aromatic substitution reaction and subsequent intramolecular etherification reaction (*vide infra*; **Scheme 3.4.1.2**). In this case, it was proposed that three or more equivalents of *p*-mentha-2,8-dien-1-ol (**183**) could be used to decorate a single phloroglucinol (**9**), the result of which would be the xyloketal A analogue **182** (**Scheme 3.4.1.1**).

**Scheme 3.4.1.1 Retrosynthetic Analysis of Xyloketal A Analogue (182) Containing the  $\Delta^8$ -THC Ring System**

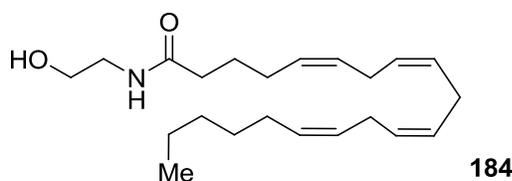


The proposed synthesis of the analogue **182** would involve a triple electrophilic aromatic substitution reaction of phloroglucinol (**9**) with *p*-mentha-2,8-dien-1-ol (**183**), upon treatment with an appropriate acid. The desired  $C_3$ -symmetric product would contain seven rings, six stereogenic centres and possess three sets of the tetrahydrocannabinol (**185** or **186**) ring system. As such, the following is a brief overview of the cannabinoid class of natural products.

The Cannabinoids are a class of lipophilic ligands that activate the eponymous cannabinoid receptors.<sup>62</sup> These receptors are part of the super-family of transmembrane G-protein coupled receptors. There are two types,  $CB_1$  located in the basal ganglia and limbic system, and  $CB_2$ , which are involved in the immune system and are concentrated in the spleen. The cannabinoids themselves are divided into three classes;

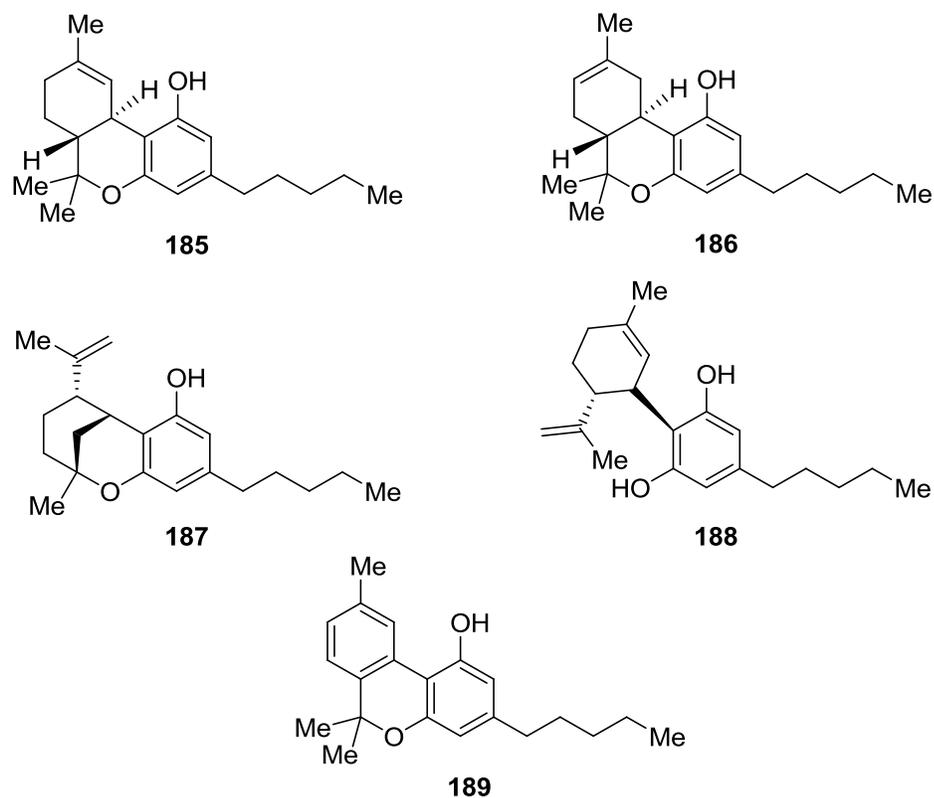
endocannabinoids, plant cannabinoids and synthetic cannabinoids. In humans all of these compounds fall into a wider class of signalling lipids called N-acylethanolamides. The endogenous version of these compounds is thought to differ from other neurotransmitters, in that they are made on demand and are not stored in vesicles. In addition, they undergo retrograde signalling, which differs from the standard signalling pathway in that they are produced in the post-synaptic cleft and travel to the pre-synaptic cleft.

An example of an endogenous cannabinoid is arachinoylethanolamine (also called anandamide, which is derived from the Sanskrit word for bliss), a compound derived from arachadonic acid (**Figure 3.4.1.1**).<sup>62</sup>



**Figure 3.4.1.1 Structure of the endogenous cannabinoid arachidonoyl ethanolamine (184).**

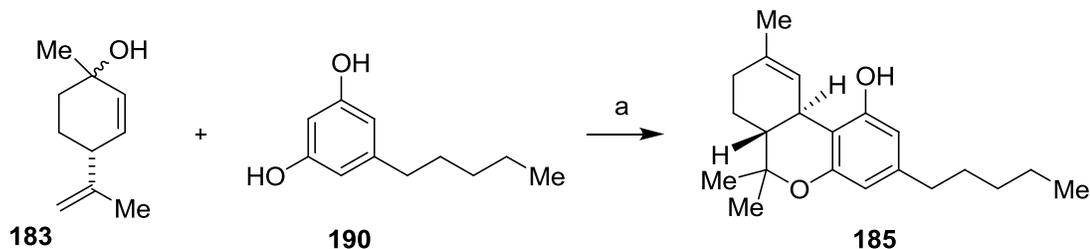
To date, eighty-five naturally occurring cannabinoids have been isolated from the *cannabis* plant. The most abundant of these are listed below (**Figure 3.4.1.2**).<sup>63</sup> Of note,  $\Delta^9$ -tetrahydrocannabinol (**185**) and  $\Delta^8$ -tetrahydrocannabinol (**186**) have been shown to mimic the endogenous cannabinoid arachinoylethanolamine (**184**) and act as a partial agonist of the CB<sub>1</sub> receptor. Indeed, the molecular structure of the endogenous cannabinoid arachinoylethanolamine (**184**) is similar in several key features to the molecular structures of  $\Delta^9$ -THC (**185**) and  $\Delta^8$ -THC (**186**).



**Figure 3.4.1.2** Molecular structures of the naturally-occurring cannabinoids,  $\Delta^9$ -tetrahydrocannabinol (185),  $\Delta^8$ -tetrahydrocannabinol (186), iso- $\Delta^9$ -tetrahydrocannabinol (187), cannabidiol (188) and cannabinol (189).

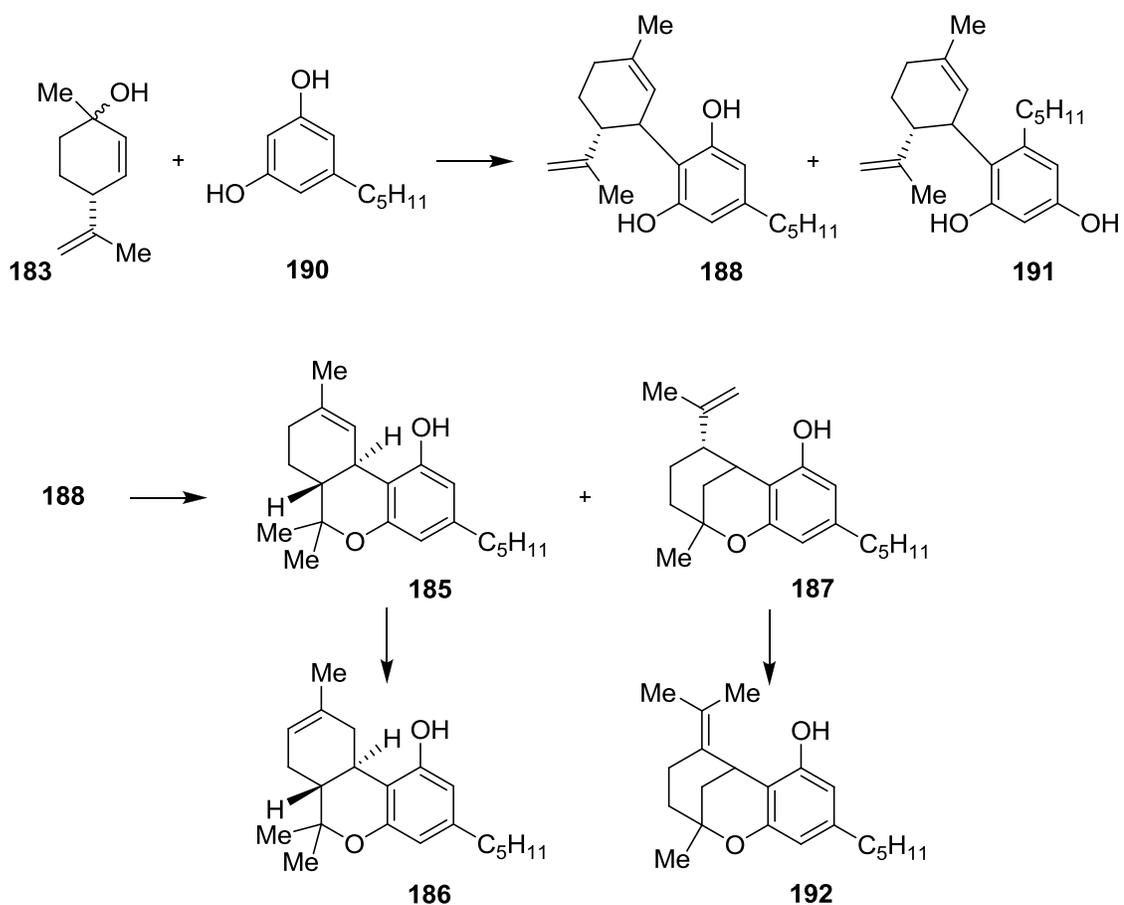
In 1974, Razdan and co-workers completed a total synthesis of the plant cannabinoid (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol (also called  $\Delta^1$ -tetrahydrocannabinol according to older nomenclature) in one step from *p*-mentha-2,8-dien-1-ol (183) and olivetol (190) (Scheme 3.4.1.2).<sup>21</sup>

**Scheme 3.4.1.2 Razdan's Total Synthesis of (-)-*trans*- $\Delta^9$ -Tetrahydrocannabinol (185)<sup>21</sup>**



Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{MgSO}_4$ , MeCN, 0 °C, 1.5 h (50%).

This work represented the first asymmetric synthesis from the two starting materials mentioned above, where the major product was (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol. Up until this point, condensation of these substances, catalyzed by either weak or strong acids, resulted in a mixture of, among other products, (-)-cannabidiol (**188**) and (-)-*trans*- $\Delta^8$ -tetrahydrocannabinol (**186**).<sup>21</sup> Razdan and co-workers purported that the use of 1% boron trifluoride diethyl etherate in the presence of magnesium sulfate led to the preferential formation of the  $\Delta^9$ -tetrahydrocannabinol regioisomer (**185**) over the thermodynamically more stable  $\Delta^8$ -tetrahydrocannabinol (**186**). Notably, the authors also concluded that subsequent isomerisation from  $\Delta^9$ -THC to  $\Delta^8$ -THC in the presence of *para*-toluene sulfonic acid in refluxing benzene, provided a cleaner method for the preparation of the latter regioisomer, as opposed to the previously prescribed condensation of *p*-mentha-2,8-dien-1-ol (**183**) and olivetol (**190**) in the absence of magnesium sulfate.



**Figure 3.4.1.3** Razdan and co-worker's synthesis of cannabinoids (**185-188** and **191-192**).

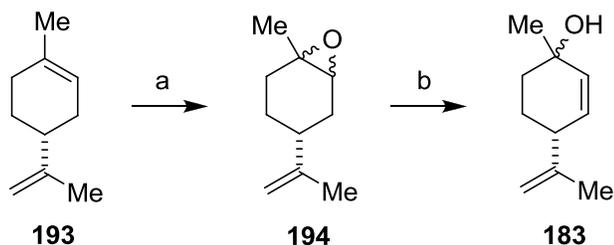
Due to the observation that the resulting product profile, depending on the reaction conditions, could be quite complicated, Razdan and co-workers carried out a detailed mechanistic study of the pathways that led to each respective compound formed under the various conditions (**Figure 3.4.1.3**). First, the initial coupling of *p*-mentha-2,8-dien-1-ol (**183**) with olivetol (**190**), led to formation of the so-called normal cannabidiol (*n*-CBD, **188**) and abnormal cannabidiol (*abn*-CBD, **191**), in a ratio of 1:2, when less than 0.5% boron trifluoride diethyl etherate or wet *para*-toluene sulfonic acid was used. Under varying sets of conditions normal cannabidiol (*n*-CBD, **188**) could be converted to

$\Delta^9$ -THC (**185**) and *iso*- $\Delta^9$ -THC (**187**), and subsequently, under more forcing conditions, these could be converted to  $\Delta^8$ -THC (**186**) and the *iso*- $\Delta^9$ -THC regioisomer **192**. In a similar fashion, the corresponding products, formed from the reaction of the abnormal cannabidiol (*abn*-CBD, **191**), were also isolated. During the course of this study, the authors determined that normal cannabidiol (*n*-CBD, **188**) and abnormal cannabidiol (*abn*-CBD, **191**) were in equilibrium, and could be formed interchangeably *via* a retro-Friedel-Crafts reaction. This observation was borne out in the ratio of  $\Delta^9$ -THC (**185**), formed from normal cannabidiol (*n*-CBD, **188**), to the abnormal cannabidiol (**191**) derived, *abn*- $\Delta^9$ -THC (not shown), which was determined to be 3:1. Considering that these were formed from a 2:1 mixture of abnormal cannabidiol (*abn*-CBD, **191**) to normal cannabidiol (*n*-CBD, **188**), this indeed implies that the normal and abnormal cannabidiols (**188** and **191**) can interconvert. From these and other product ratios, Razdan and co-workers inferred the relative rates of formation of these cannabidiol precursors, and used these arguments to rationalize the formation of the desired  $\Delta^9$ -THC (**185**) as the major product under the optimized conditions.<sup>21</sup>

### 3.4.2 Synthesis of *p*-Mentha-2,8-diene Precursor (**183**) for the Preparation of the THC Ring System

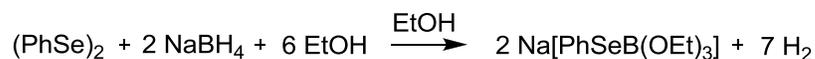
In order to test whether the chimeric xyloketal A-THC analogue (**182**) could be successfully synthesised, the required precursor, *p*-mentha-2,8-dien-1-ol (**183**), was prepared according to known literature procedures (**Scheme 3.4.2.1**).<sup>64</sup>

**Scheme 3.4.2.1** Synthesis of *p*-Mentha-2,8-diene (**183**)<sup>64</sup>



Reagents and conditions: (a) *m*-CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min (36%); (b) (i) PhSeSePh, NaBH<sub>4</sub>, EtOH, reflux, 2 h, (ii) H<sub>2</sub>O<sub>2</sub>, THF, rt, 15 h (53%).

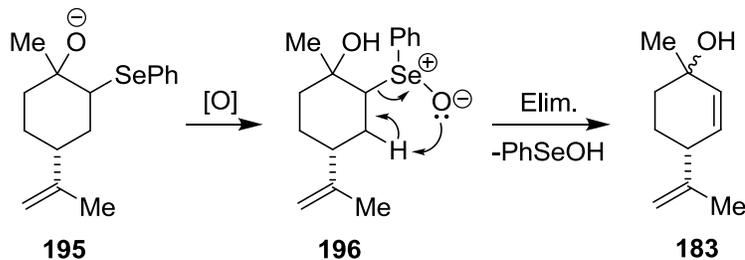
In preliminary attempts, (+)-limonene (**193**) was converted to the epoxide **194**, a compound which subsequently was purchased from Aldrich. This mixture of *cis*- and *trans*-epoxide **194** was then converted to the diene **183** *via* nucleophilic attack of the reduced selenide species (Na[PhSeB(OEt)<sub>3</sub>]), which is formed according to the following equation (**Figure 3.4.2.1**).<sup>65</sup>



**Figure 3.4.2.1** Formation of active selenide species prepared from diphenyl diselenide for the preparation of diene (**183**).<sup>65</sup>

Subsequent oxidation of the selenium moiety with hydrogen peroxide followed by an elimination reaction of intermediate **196**, yielded the desired product (**183**) in satisfactory yield (**Scheme 3.4.2.2**).<sup>66</sup>

### Scheme 3.4.2.2 Mechanistic Rationale for Formation of *p*-Mentha-2,8-diene (183)<sup>66</sup>



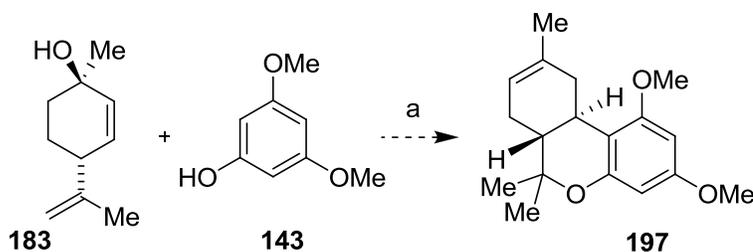
### 3.4.3 Reaction of *p*-Mentha-2,8-diene (183) with 3,5-Dimethoxyphenol (143)

As described above, depending on the reaction conditions, an array of potential products could form as a result of an electrophilic aromatic substitution reaction of *p*-mentha-2,8-dien-1-ol (183) and olivetol (190). Whereas the use of phloroglucinol (9) instead of olivetol (190) precludes the formation of the set of potential products derived from abnormal cannabidiol (*abn*-CBD, 191), the five possible products that were derived from a “normal” coupling of *p*-mentha-2,8-dien-1-ol (183) with olivetol (190), could have led to a multitude of products when applied to a substrate such as phloroglucinol (9). Indeed, each set of fused rings in the proposed THC-based xyloketal A analogue (182) could, in principle, form as either a  $\Delta^8$ - or  $\Delta^9$ -tetrahydrocannabinol (186 and 185) or additionally as either of the two possible *iso*-tetrahydrocannabinols (187 and 192). The target ring system for the preparation of the  $C_3$ -symmetric version of this *tris*-adduct would be derived from  $\Delta^8$ -tetrahydrocannabinol (185), the thermodynamically most stable version of this ring system.

A report by Kraatz and co-workers in 1976 outlined the synthesis of a small number of  $\Delta^8$ -THC analogues from *p*-mentha-2,8-dien-1-ol (183) and phloroglucinol (9) as well as *mono*- and *di*-alkylated phloroglucinol (9) derivatives.<sup>67</sup> Thus, in order to

ascertain the feasibility of preparing the xyloketal A-THC analogue **182**, the readily-available 3,5-dimethoxyphenol (**143**) was chosen as a suitable model compound for the preparation of a hitherto unknown adduct containing a single  $\Delta^8$ -THC ring system. However, despite repeated attempts, none of the desired adduct **197** could be isolated from the complex mixture of products that was thus obtained (**Scheme 3.4.3.1**).

**Scheme 3.4.3.1** Attempted Synthesis of  $\Delta^8$ -THC Model Compound (**197**) using *p*-Mentha-2,8-diene (**183**)

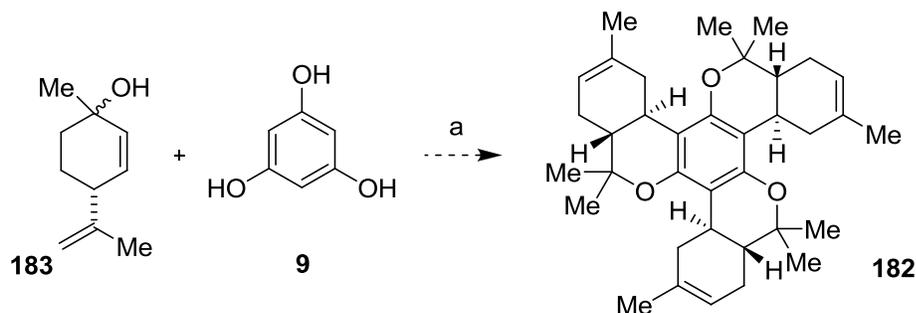


Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{MgSO}_4$ , ether,  $0^\circ\text{C}$ , 5h (complex mixture).

**3.4.4** Reaction of Phloroglucinol (**9**) with *p*-Mentha-2,8-dien-1-ol (**183**)

Undeterred by the above result, the proposed triple electrophilic aromatic substitution reaction of phloroglucinol (**9**) with *p*-mentha-2,8-dien-1-ol (**183**) was undertaken per the method outlined by Razdan and co-workers in their synthesis of  $\Delta^9$ -THC (**185**, **Scheme 3.4.4.1**).

**Scheme 3.4.4.1 Attempted Synthesis of Xyloketal A Analogue (182)**



Reagents and conditions: (a) See below: Table 3.4.4.1.

**Table 3.4.4.1 Reagents and Conditions Corresponding to Scheme 3.4.4.1**

entry	acid	acid equiv.	(183) equiv.	solvent	temp.	time	result
1	BF <sub>3</sub> •OEt <sub>2</sub>	1	4.4	ether	0 °C	5 h	complex mixture
2	BF <sub>3</sub> •OEt <sub>2</sub>	0.1	6	ether	0 °C	5 h	complex mixture
3	BF <sub>3</sub> •OEt <sub>2</sub>	1	6	ether	0 °C	5 h	complex mixture
4	BF <sub>3</sub> •OEt <sub>2</sub>	2	6	ether	0 °C	5 h	complex mixture
5	BF <sub>3</sub> •OEt <sub>2</sub>	6	6	CH <sub>2</sub> Cl <sub>2</sub>	0 °C	5 h	complex mixture
6	PTSA	12	6	CH <sub>2</sub> Cl <sub>2</sub>	0 °C	5 h	complex mixture

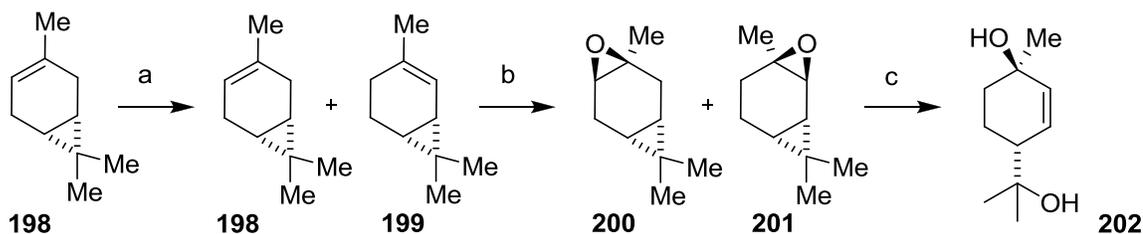
The first set of conditions employed here was taken from Pettigrew and co-worker's optimized conditions for the synthesis of the xyloketal A (**15**) ring system. As this led to a complex mixture of products, in the next attempt, a catalytic amount of acid was used. Upon repeated attempts to affect this transformation however, none of the desired product was isolable from the extremely complex mixture of products that were produced under each set of conditions. This was despite the fact that the <sup>1</sup>H NMR spectrum of the crude material manifested a broad peak at  $\delta$  5.38 ppm. This signal is

consistent with the alkene peak reported for  $\Delta^8$ -THC (**186**) as opposed to the corresponding peak at  $\delta$  6.30 ppm for  $\Delta^9$ -THC (**185**). In addition, the mass spectra (CI) of these crude mixtures displayed base peaks at  $m/z$  529 amu, which corresponded to the protonated molecular ion of the desired adduct **182** (C<sub>36</sub>H<sub>49</sub>O<sub>3</sub>).

### 3.4.5 Synthesis of (+)-*p*-Menth-2-ene-1,8-diol (**202**): An Alternative Substrate for Reaction with Phloroglucinol (**9**)

A literature search for alternate substrates to affect the desired transformation led to the discovery of the following process chemistry preparation of diol **202** (Scheme 3.4.5.1).<sup>68</sup>

#### Scheme 3.4.5.1 Synthesis of (+)-*p*-Menth-2-ene-1,8-diol (**202**)<sup>68</sup>



Reagents and conditions: (a) *t*-BuOK, DMSO, 100 °C, 12 h [**198**:**199** (2:3)]; (b) peracetic acid, CH<sub>2</sub>Cl<sub>2</sub>, NaHCO<sub>3</sub> (aq), 10 °C, 12 h; (c) H<sub>2</sub>O, AcOH (cat.), EtOAc, 0 °C, 8 h [61% from 2-carene (**199**)].

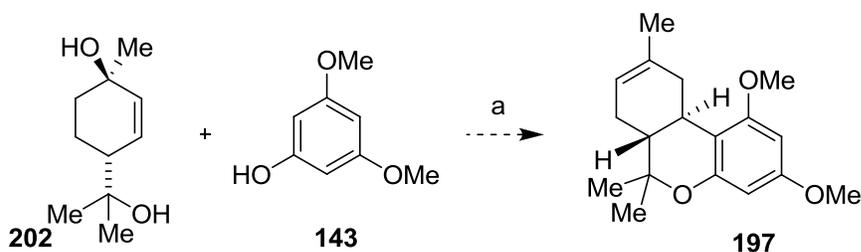
This procedure was developed by Cabaj and co-workers as a means to prepare kilogram quantities of the diol **202**. In our hands, this procedure was easily replicated on a gram scale and the diol **202** was isolated in pure crystalline form. The first step of this method involved a thermal isomerisation of 3-carene (**198**) under basic conditions to its regioisomer 2-carene (**199**). Of note, 2-carene (**199**) costs \$9810 per mole whereas 3-carene (**198**) costs \$319 per mole from Aldrich. The dimethylsulfoxide in this case acts to sequester the potassium ion, and thus greatly increases the basicity of the *tert*-butoxide.<sup>69</sup> This led to a 3:2 mixture of 2-carene (**199**) and 3-carene (**198**). Peracetic

acid was then added to this mixture over 8 h *via* a syringe pump, at approximately 10 °C. Upon work-up, the crude mixture was dissolved in ethyl acetate and to this was added an aqueous solution of acetic acid. This in turn led to the isolation of diol **202** in pure crystalline form and in good yield. Indeed, the advantage of this last step lies in the fact that only the epoxide **201**, derived from 2-carene (**199**), is susceptible to the acid-mediated ring-opening reaction, thus leading to a single diol product.

### 3.4.6 Synthesis of Model Compounds Containing the $\Delta^8$ -THC Ring System (203-205)

Using the alternative substrate, (+)-*p*-menth-2-ene-1,8-diol (**202**), attempts were made to prepare the 3,5-dimethoxyphenol-derived model compound **197**. Once again however, the reaction led to the formation of a complex mixture of products (**Scheme 3.4.6.1**).

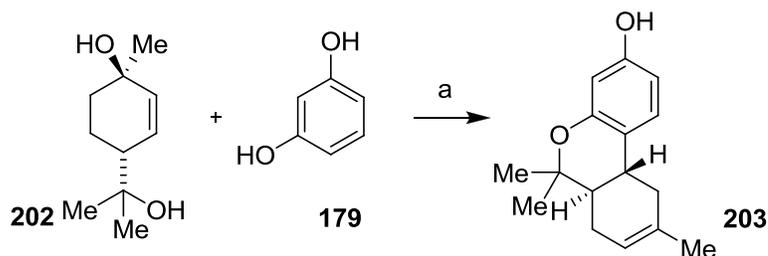
#### Scheme 3.4.6.1 Attempted Synthesis of $\Delta^8$ -THC Model Compound (**197**) Using (+)-*p*-Menth-2-ene-1,8-diol (**202**)



Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{MgSO}_4$ , ether, 0 °C, 5-12 h or PTSA (0.1 equiv.), PhH, reflux, 5 h (complex mixture).

Although 3,5-dimethoxyphenol (**143**) proved an ineffective platform for constructing the  $\Delta^8$ -THC ring system, it was envisioned that a less hindered phenol might accommodate the desired transformation. Thus, resorcinol (**179**) was employed in the preparation of the known  $\Delta^8$ -THC derivative **203** (**Scheme 3.4.6.2**).<sup>70</sup>

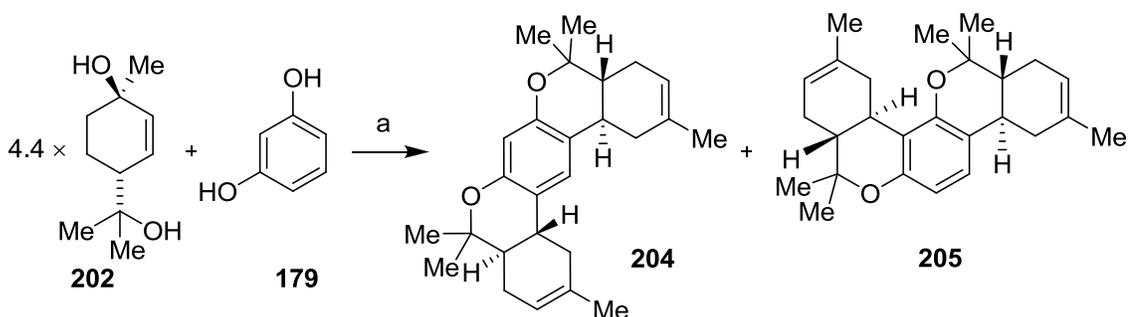
### Scheme 3.4.6.2 Synthesis of the *mono*- $\Delta^8$ -THC Derivative (**203**)<sup>70</sup>



Reagents and conditions: (a) PTSA (0.1 equiv.), PhH, reflux, 5 h (32%).

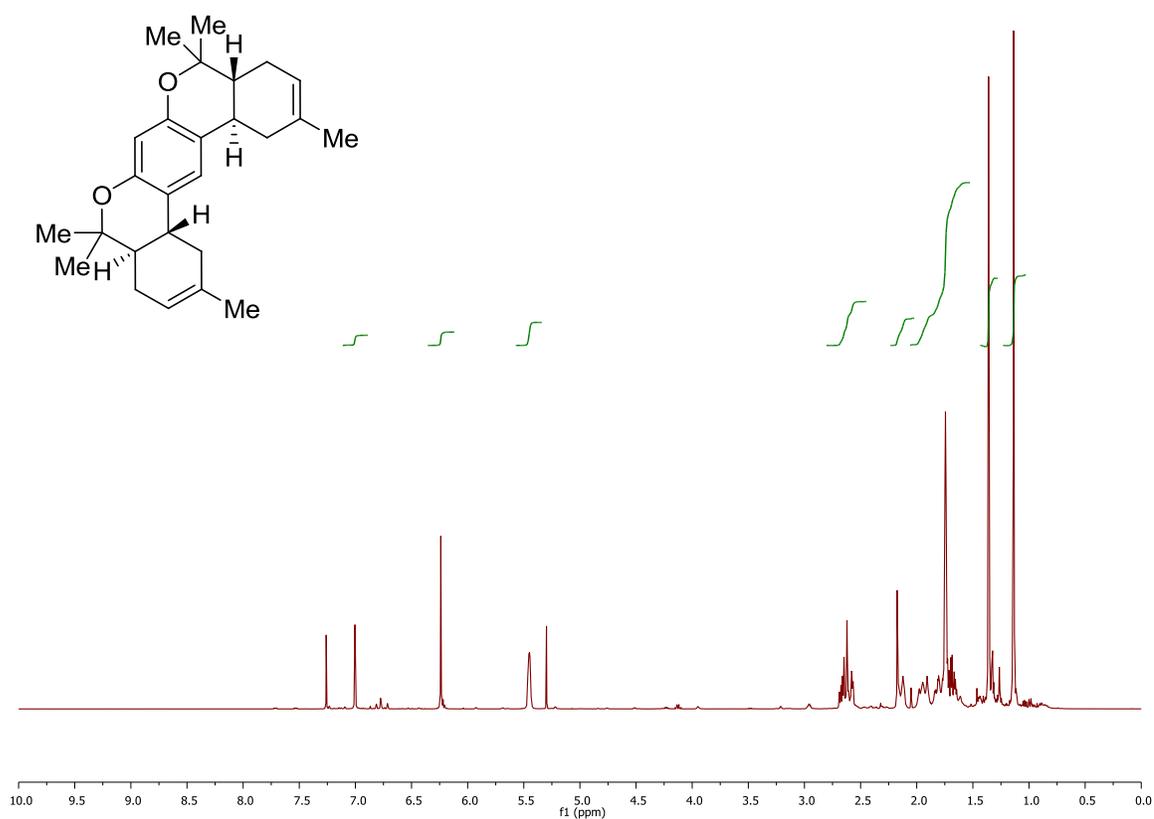
This model compound was prepared using a slightly modified version of Razdan and co-worker's conditions for the preparation of this as well as of other  $\Delta^8$ -THC analogues.<sup>70</sup> This method was then applied to the synthesis of the novel *bis*-adducts **204** and **205** in good yield (Scheme 3.4.6.3). Notably, these *bis*-adducts were isolated in yields that were in the upper range of those reported for other THC analogues, as these are typically quite low.<sup>71</sup> Moreover, compounds containing two sets of the  $\Delta^8$ -THC ring-system have only been reported on three occasions, and were in every case prepared from 5-substituted resorcinols.<sup>72-74</sup>

### Scheme 3.4.6.3 Synthesis of the Model Compounds (**204**) and (**205**) Containing the *bis*- $\Delta^8$ -THC ring System



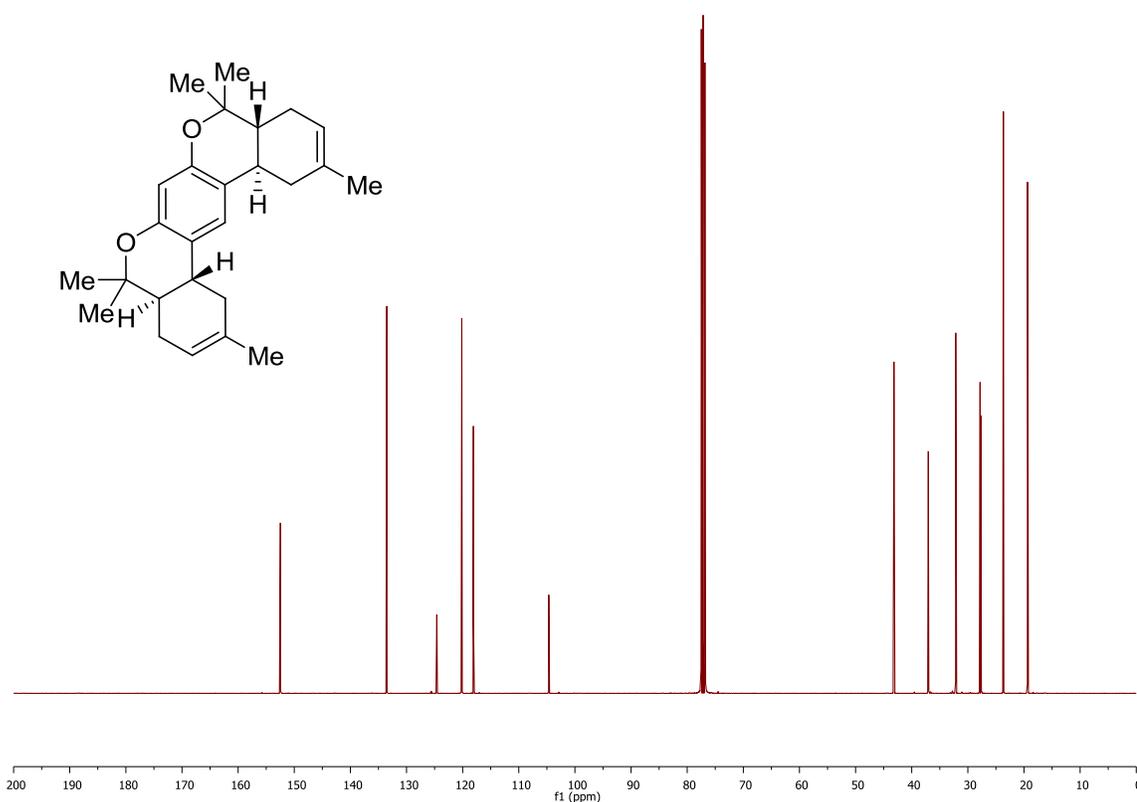
Reagents and conditions: (a) PTSA (0.4 equiv.), PhH, reflux, 5 h [74% {**204**:**205** (1.7:1)}].

The ratio of the  $C_2$ -symmetric adduct **204** to the unsymmetrical adduct **205** was determined to be 1.7:1, and these compounds were separable by flash chromatography. Due perhaps to the excess of the diol precursor **202** that was employed here, none of the *mono*- $\Delta^8$ -THC derivative **203** was observed. The high-resolution mass spectra of the adducts **204** and **205** exhibited peaks at  $m/z$  379.2637 and 379.2640 amu, which corresponded to the protonated molecular ions for these compounds and moreover, were consistent with their predicted molecular formulae ( $C_{26}H_{34}O_2$ ). The  $^1H$  NMR spectrum of the  $C_2$ -symmetric derivative **204**, manifested signals which corresponded to those exhibited by a single  $\Delta^8$ -THC ring system (**Figure 3.4.6.1**).<sup>64,75</sup>



**Figure 3.4.6.1**  $^1H$  NMR spectrum (600 MHz,  $CDCl_3$ ) of  $\Delta^8$ -THC model compound (**204**).

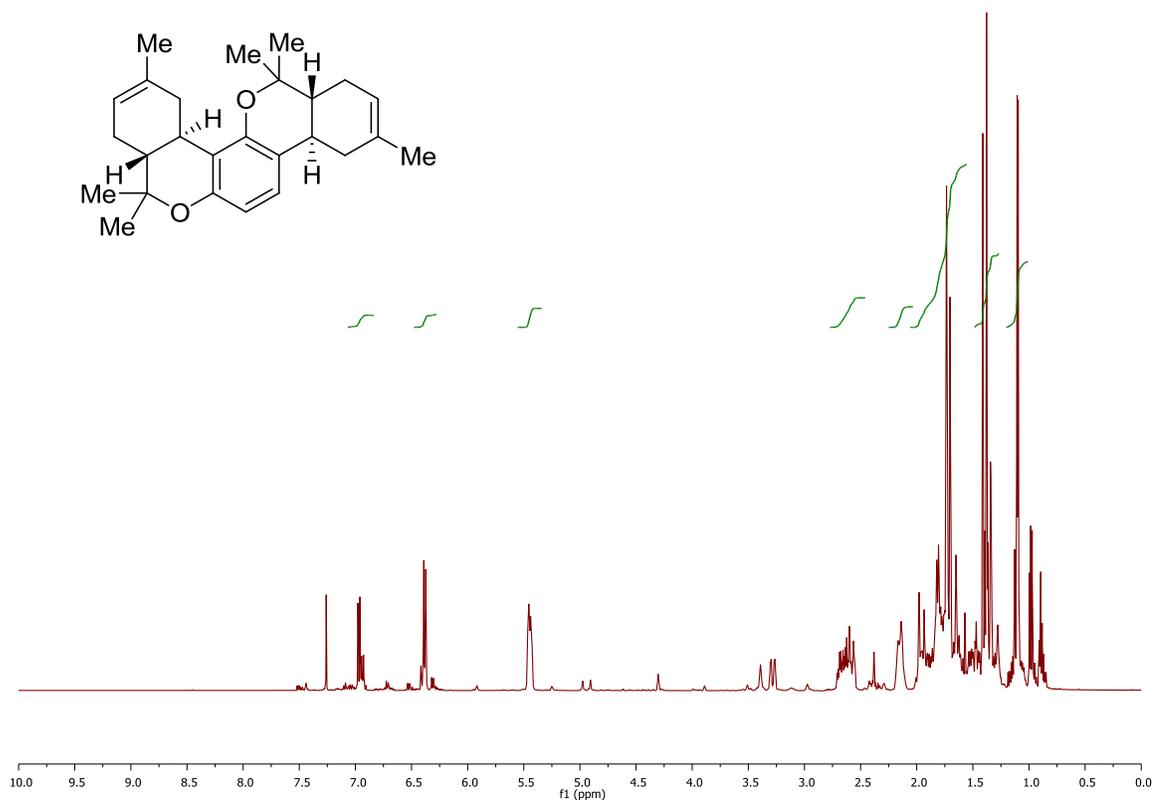
In addition, the  $^{13}\text{C}$  NMR spectrum of this compound exhibited fourteen peaks, consistent with the  $C_2$ -symmetry of its proposed structure (**Figure 3.4.6.2**). All of the observed peaks for this adduct were consistent with data reported for the  $\Delta^8$ -THC ring system.<sup>64,75</sup> A detailed discussion of all the signals in both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra corresponding to the  $\Delta^8$ -THC ring system is included in the following section (**3.4.7**). Of note, the peak at  $\delta$  76.9 ppm is embedded in the solvent peak and is therefore not visible.



**Figure 3.4.6.2**  $^{13}\text{C}$  NMR spectrum (150 MHz,  $\text{CDCl}_3$ ) of  $\Delta^8$ -THC model compound (204).

The unsymmetrical adduct **205** produced much more complicated  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, displaying signals corresponding to two sets of the  $\Delta^8$ -THC ring system.

Moreover, this derivative proved extremely difficult to purify and was somewhat unstable (Figure 3.4.6.3).



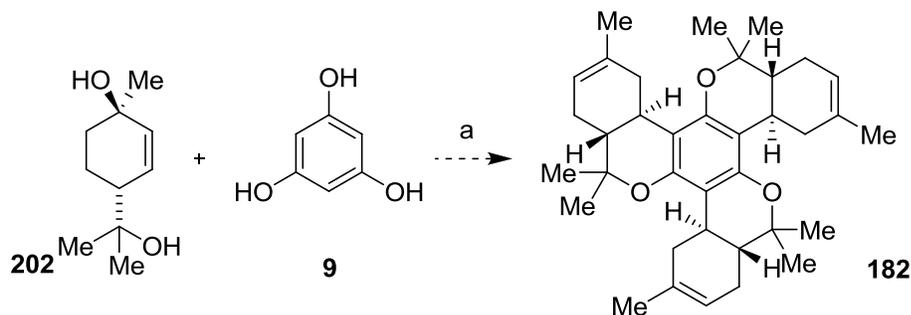
**Figure 3.4.6.3**  $^1\text{H}$  NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of  $\Delta^8$ -THC model compound (205).

### 3.4.7 Reaction of Phloroglucinol (9) with (+)-*p*-Menth-2-ene-1,8-diol (202)

Now that satisfactory reaction conditions for the construction of compounds that contain multiple sets of the  $\Delta^8$ -THC ring system had been identified, the synthesis of the  $\text{C}_3$ -symmetric, chimeric xyloketal  $\Delta^8$ -tetrahydrocannabinol **182** was recommended. In the first attempt, four equivalents of diol **202** were reacted with phloroglucinol (**9**) in the

presence of boron trifluoride diethyl etherate. However, this led to a complex mixture of products from which the target compound **182** could not be isolated (**Scheme 3.4.7.1**).

**Scheme 3.4.7.1 Attempted Synthesis of Xyloketal A Analogue (182) Using Diol (202)**



Reagents and conditions: (a) See below: Table 3.4.7.1.

**Table 3.4.7.1 Reagents and Conditions Corresponding to Scheme 3.4.7.1**

entry	acid	acid equiv.	(202) equiv.	solvent	temp.	time	result
1	BF <sub>3</sub> ·OEt <sub>2</sub>	0.4	4	ether	0 °C → rt	o/n	complex mixture
2	BF <sub>3</sub> ·OEt <sub>2</sub>	0.6	6	ether	0 °C → rt	o/n	complex mixture
3	BF <sub>3</sub> ·OEt <sub>2</sub>	0.6	6	benzene	0 °C → rt	o/n	complex mixture
4	BF <sub>3</sub> ·OEt <sub>2</sub>	1	6	THF	0 °C → rt	16 h	complex mixture
5	PTSA	0.3	3	benzene	reflux	5 h	<b>complex mixture; Quinone [210 (40%)]</b>
6	PTSA	0.6	6	CH <sub>2</sub> Cl <sub>2</sub>	0 °C	5 h	complex mixture
7	PTSA	0.6	6	THF	-78 °C → rt	4 h	complex mixture
8	PTSA	1.2	12	benzene	reflux	5 h	complex mixture

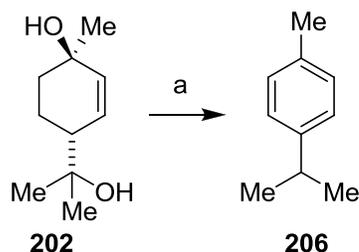
9	PTSA	0.1	7	benzene	reflux	1 h/2 h	complex mixture
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In subsequent experiments, the equivalents of diol **202** were increased to six, and both ether and benzene were employed as the reaction solvent (**Table 3.4.7.1; entries 2-3**). In the final experiment performed in the presence of boron trifluoride diethyl etherate, a stoichiometric amount of this acid was used, the result of which was also a complex mixture of products. In addition, experiments undertaken in the presence of PTSA similarly led to complex mixtures of products from which none of the desired xyloketal A- $\Delta^8$  THC analogue **182** could be isolated (**entries 5-9**). Mass spectra (CI) of these crude mixtures displayed base peaks at  $m/z$  529 amu, corresponding to the protonated molecular ion of species with a molecular formula consistent with the target compound **182** (C<sub>36</sub>H<sub>49</sub>O<sub>3</sub>). Efforts to isolate individual compounds from these mixtures by flash chromatography produced fractions that appeared as a single spot by TLC. In addition to standard NMR spectroscopy techniques, total correlation spectroscopy experiments were performed on these fractions, the results of which supported the hypothesis that these were mixtures of compounds that contained key spectroscopic features associated with the  $\Delta^8$ -THC ring system.\* This suggests that mixtures of triple adducts had formed in these reaction that contained the THC ring system, but hitherto have been extremely resistant to isolation and purification. Of note, when PTSA was employed as the acid promoter, significant amounts of *para*-cymene (**206**) were produced, ostensibly as the product of a side reaction of the diol **202** (**Scheme 3.4.7.2**).

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\* Total correlation spectroscopy experiments were performed under the auspices of Jeffrey Mowat.

### Scheme 3.4.7.2 Side Reaction of the Diol (**202**) Producing *p*-Cymene (**206**)

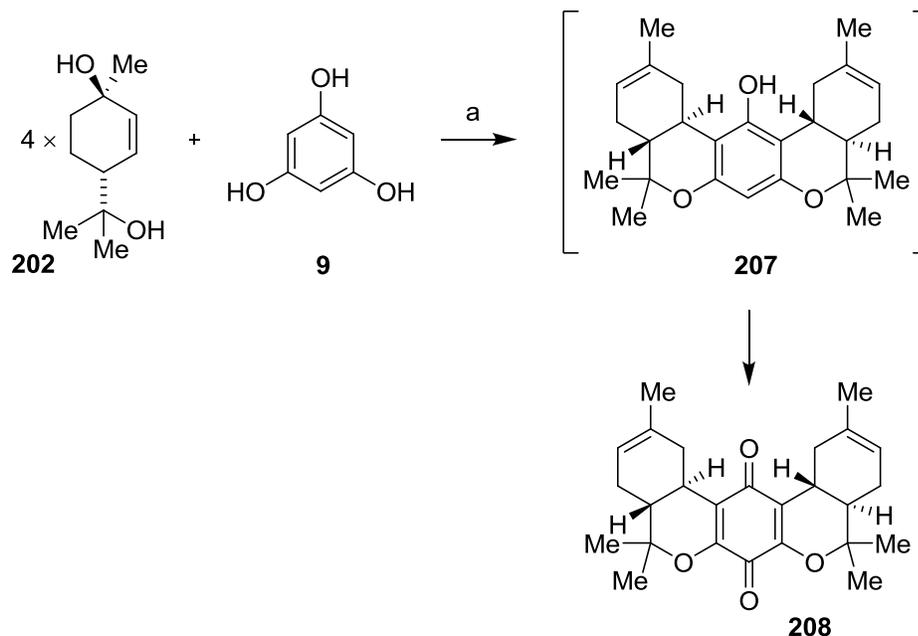


Reagents and conditions: (a) PTSA, benzene, reflux.

Interestingly, when only three equivalents of the diol precursor (**202**) were used (**Table 3.4.7.1; entry 5**), the array of products produced was greatly attenuated, and the  $C_2$ -symmetric quinone **208** was isolated (**Scheme 3.4.7.3**). In order to circumvent the formation of this quinone byproduct, the equivalents to the diol **202**, in the presence of PTSA, were increased (**entries 6-9**). In addition, the solutions in which these reactions were carried out were degassed for 30 min. in order to minimize the oxygen present in the system. Indeed, while these measures largely prevented any formation of the quinone **208**, they did not have any effect as regards the isolation of the *tris*-adduct **182**.

At this point the focus of this investigation shifted to the serendipitous production of the novel quinone byproduct **208**. When the equivalents of the diol **202** were increased to four, in the presence of PTSA, the yield of this compound was increased to 51%.

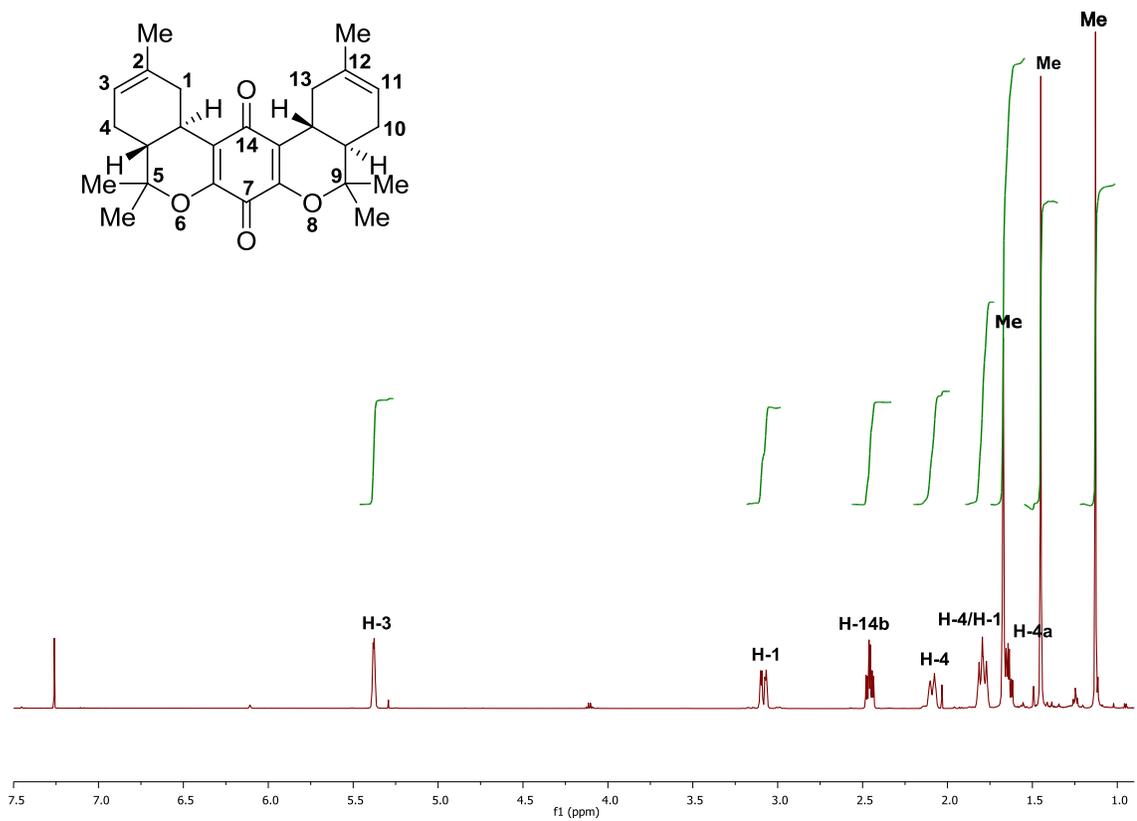
### Scheme 3.4.7.3 Synthesis of the Quinone (208)



Reagents and conditions: (a) PTSA, PhH, reflux, 5 h (51%).

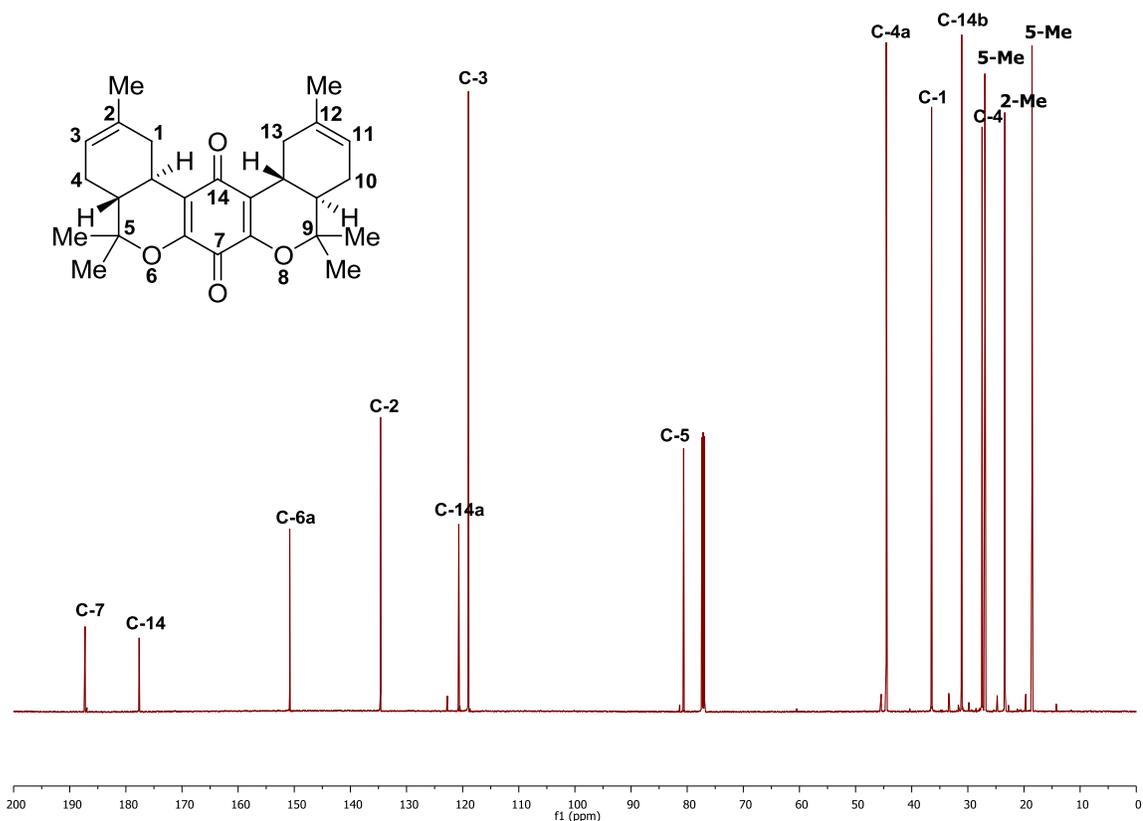
This product was isolated as a bright yellow, waxy solid, the ultraviolet-visible spectrum of which displayed two absorptions at  $\lambda_{\text{max}}$  305 ( $\epsilon = 14497$ ) and 418 ( $\epsilon = 408$ ) nm. The high resolution mass spectrum of this adduct exhibited a prominent peak at  $m/z$  409.2363 amu, that corresponded to the protonated molecular ion for the quinone **208** (molecular formula:  $\text{C}_{26}\text{H}_{32}\text{O}_4$ ). The molecular structure of this compound was determined using  $^1\text{H}$ ,  $^{13}\text{C}$ , COSY, HSQC and HMBC NMR spectroscopy. Of interest, these spectra exhibited signals corresponding to the molecular structure of a single  $\Delta^8$ -THC ring system. This served as confirmation of the  $C_2$ -symmetry exhibited by this compound. For simplicity, only the numbering of one ring system is included in each spectrum (**Figure 3.4.7.1** and **Figure 3.4.7.2**). The doublet at  $\delta$  5.38 ppm in the  $^1\text{H}$  NMR spectrum was assigned to the proton at position 3 (labelled *H*-3), and was confirmed using reported literature values for related compounds.<sup>64,75</sup> The remaining peaks in the

$^1\text{H}$  NMR spectrum were assigned through interpretation of the COSY and HMBC NMR spectra.



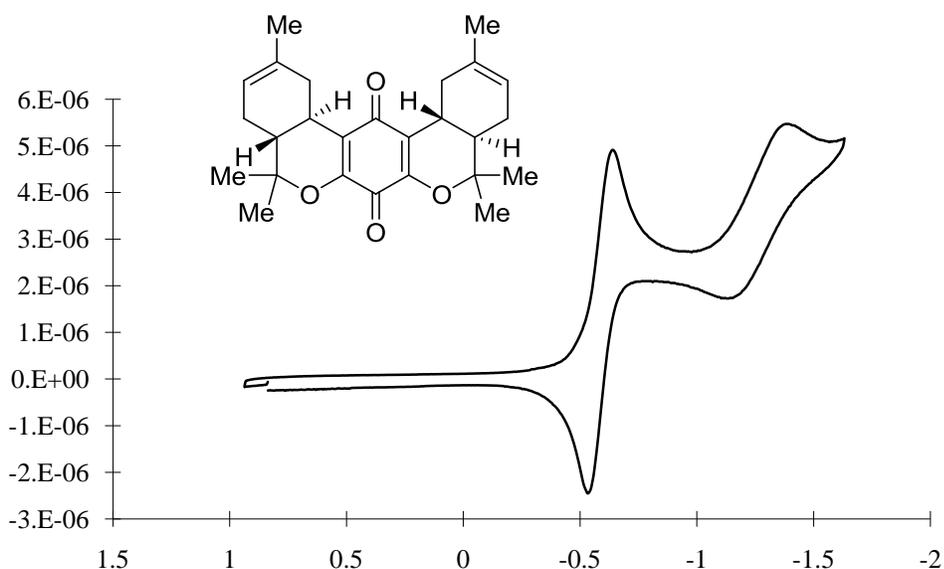
**Figure 3.4.7.1**  $^1\text{H}$  NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of quinone (208).

Of note, the  $^{13}\text{C}$  NMR spectrum exhibits two distinct peaks in the carbonyl region at  $\delta$  177.6 and 187.3 ppm. The latter signal is assigned to C-7, and its chemical shift, downfield relative to the other quinone carbonyl carbon, is attributed to its proximity to the ring oxygens.



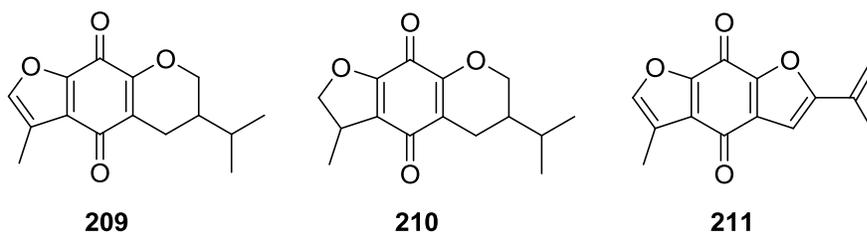
**Figure 3.4.7.2** <sup>13</sup>C NMR spectrum (150 MHz, CDCl<sub>3</sub>) of quinone (**208**).

In order to investigate the electrochemical properties of the quinone **208**, a cyclic voltammogram was obtained (**Figure 3.4.7.3**). The sample was run in dichloromethane, with ferrocene employed as an internal standard. The resultant curve exhibits two cathodic polarographic waves, E<sub>1</sub> and E<sub>2</sub>, which correspond to the formation of the quinone radical anion (Q<sup>•-</sup>) and the quinone dianion (Q<sup>2-</sup>), respectively. This result is consistent with the CV data reported for quinones where the experiment was performed in dry, neutral, aprotic solvents.<sup>76</sup>



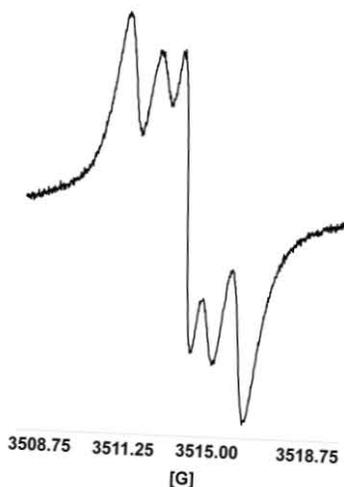
**Figure 3.4.7.3** Cyclic voltammogram of quinone (**208**) in  $\text{CH}_2\text{Cl}_2$  ( $E_{1/2}^0 = -0.587 \text{ V}$ ).

The oxidation of phenols of the type transiently produced here (intermediate **207**, **Scheme 3.4.7.3**) to their corresponding quinone is not unknown, however, it typically requires the aid of a catalyst such as Fremy's salt [potassium nitrosodisulfonate;  $\text{K}_4(\text{ON}(\text{SO}_3)_2)_2$ ] or oxygen gas and the organometallic reagent salcomine.<sup>77,78</sup> Moreover, very few examples of quinones of this type, which contain heterocycles with the oxygen heteroatoms in this arrangement are known. The natural product scabequinone (**209**) and its derivatives comprise the closest related compounds (**Figure 3.4.7.4**).<sup>79</sup>



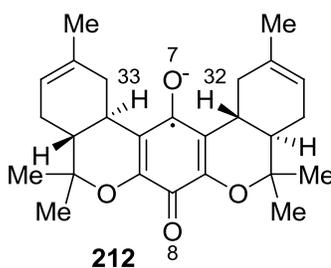
**Figure 3.4.7.4** Molecular structures of ( $\pm$ )-scabequinone (**209**) and derivatives (**210**) and (**211**).<sup>79</sup>

In a preliminary investigation, the quinone **208** was reduced with one equivalent of cobaltocene, and an EPR spectrum of the reduced anion was obtained (**Figure 3.4.7.5**). The resultant spectrum was consistent with those reported for quinone radicals.<sup>80-82</sup>



**Figure 3.4.7.5** EPR spectrum of the reduced quinone anion (**212**).

In addition, density functional theory calculations of a reduced anion of quinone **208** predicted spin densities on *O*-7 and *O*-8 of 20 and 31%, respectively, and 0.2% on both *H*-32 and *H*-33 (**Figure 3.4.7.6**).<sup>†</sup>



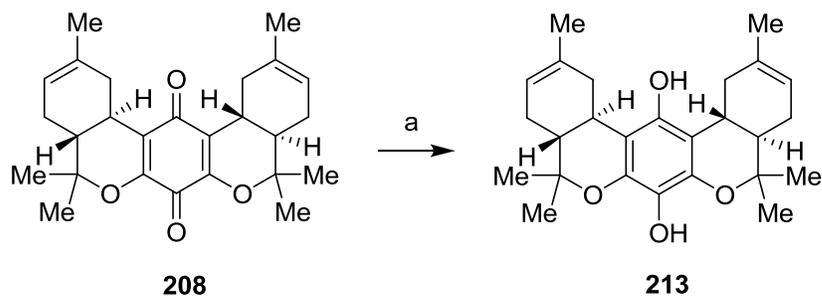
**Figure 3.4.7.6** Density functional theory calculations of the reduced anion (**212**) of quinone (**208**): Calculated spin densities: *O*-7 = 20%; *O*-8 = 31%; *H*-32 = 0.2%; *H*-33 = 0.2%.

<sup>†</sup> DFT calculations were performed by Dr. Tim Storr using Gaussian 03, Revision C.02, M. J. Frisch *et al.* Gaussian, Inc., Wallingford CT, 2004.

The minor amounts of predicted spin density on the protons adjacent to *O*-7, labelled here as *H*-32 and *H*-33, supported the hypothesis that coupling of these protons with the radical of the reduced quinone anion **212**, could have given rise to the pattern that was observed in the EPR spectrum (**Figure 3.4.7.5**). Moreover, the larger calculated spin density on the oxygen labelled *O*-8, could be rationalized based on this oxygen's proximity to the two adjacent oxygen heteroatoms (**Figure 3.4.7.6**). Subsequent experiments to confirm these assertions however, were not pursued.

In order to further explore the chemistry of quinone **208**, it was reduced with sodium borohydride to the hydroquinone **213** using a known literature procedure.<sup>83</sup> However, this species rapidly converted back to the quinone **208** upon work-up (**Scheme 3.4.7.4**).

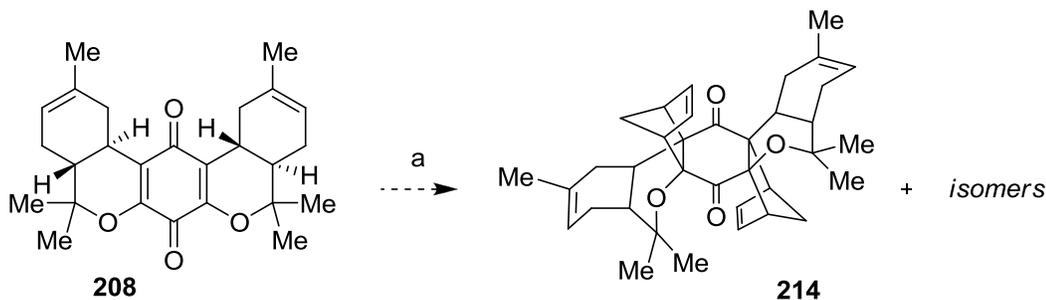
#### Scheme 3.4.7.4 Reduction of Quinone (208)



Reagents and conditions: (a) NaBH<sub>4</sub>, THF, MeOH, 0.5 h, rt (reverted to quinone **208** upon work-up).

Finally, several experiments were undertaken to affect a double Diels-Alder reaction of quinone **208** using freshly cracked cyclopentadiene (**Scheme 3.4.7.5**, the anticipated *endo* product is shown).<sup>84</sup> It was anticipated that formation of the desired Diels-Alder adducts would result in a loss of the bright yellow colour associated with quinone **208** and its solutions.

**Scheme 3.4.7.5 Attempted Diels-Alder Reaction of Quinone (208) [*Endo* Product (214) Shown]**



Reagents and conditions: (a) Cyclopentadiene (20 equiv.), benzene, sealed tube, 2 days, 210 °C and cyclopentadiene (20 equiv), xylenes, sealed tube, 2 days, 270 °C and cyclopentadiene (20 equiv), benzene, microwave, 5 min, 34 PSI, 190 °C (no reaction).

This was not observed however, and no evidence for the production of a reaction product was obtained upon preliminary attempts to affect this Diels-Alder reaction. As a result, this investigation was not pursued any further.

### 3.5 Conclusions

Three novel carbon based electrophilic species **133**, **149** and **183/202** were identified as potential precursors for the synthesis of complex polycyclic  $C_3$ -symmetric xyloketal A analogues. All three of these targets were successfully prepared according to known literature procedures. The hitherto unknown  $\alpha,\beta$ -unsaturated alcohol **134** was coupled to phloroglucinol (**9**) via a triple electrophilic aromatic substitution reaction with subsequent acetal formation reactions to afford the complex polycyclic adduct [(±)-**130**] in a single diastereoselective synthetic operation. The *tris*-benzannulated spiroacetal [(±)-**148**] was prepared as a single diastereoisomer from the aldehyde **149** via a complex reaction sequence. The third carbon centred electrophilic species **183/202**, when reacted with phloroglucinol (**9**), led to a complex mixture of adducts with the isolation and

purification of the desired  $C_3$ -symmetric xyloketal A- $\Delta^8$ -THC analogue **182**, remaining elusive. A future set of experiments regarding the synthesis of this target molecule could involve the preparation of the *mono*-, *bis*- and finally the desired *tris*-adduct **182** in a sequential manner. An interesting result of this study was the isolation of the novel  $C_2$ -symmetric quinone **208** *via* a spontaneous oxidation reaction of the phenol **207**, which contained two sets of the  $\Delta^8$ -THC ring system.

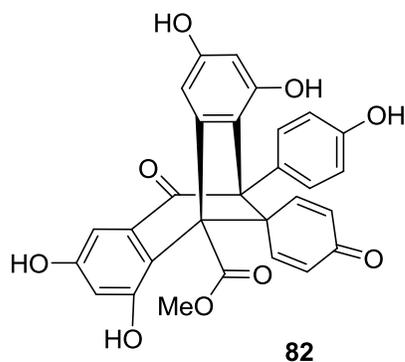
## Chapter 4:

### *Results and Discussion: Progress Towards the Total Synthesis of Hopeanol*

#### 4.1 Introduction to the Natural Product Hopeanol (82)

##### 4.1.1 Biological Activity, Biosynthetic Pathway, and the Total Synthesis of Hopeanol (82) by Nicolaou *et al.*

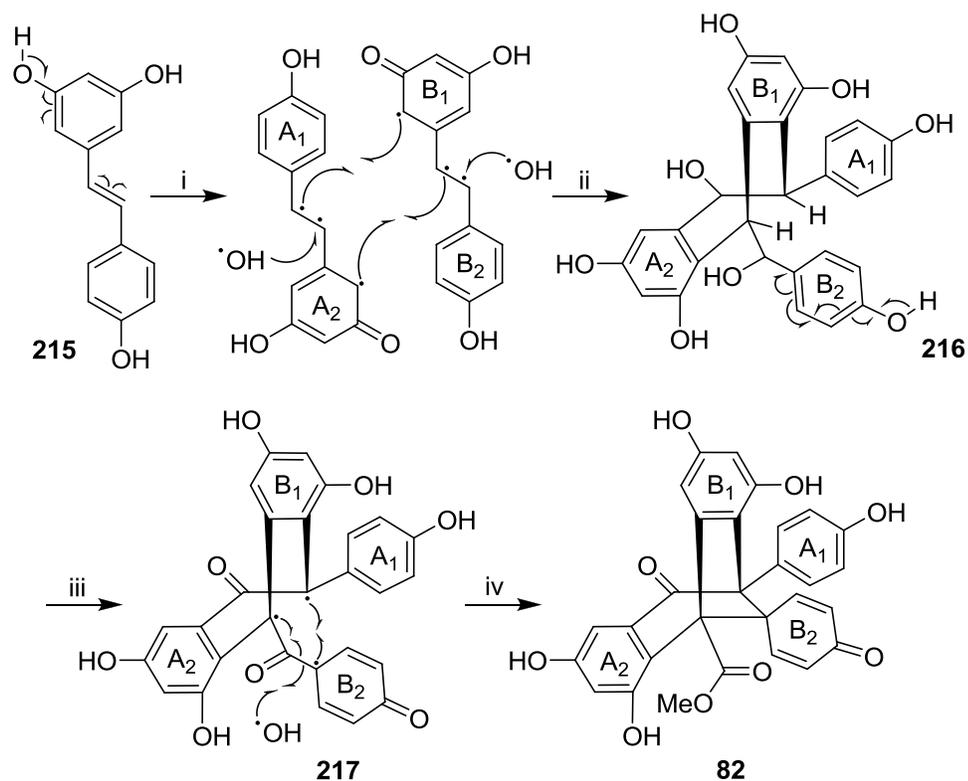
This chapter concerns a discussion of an approach towards the total synthesis of the natural product hopeanol (**82**). This substance was isolated in 2006 by Tan and co-workers from the bark of the dipterocarpaceous plant species *Hopea Exalata*.<sup>85</sup> Hopeanol (**82**) exhibits remarkable cytotoxic activity. Most notably, when tested against KB cancer cell lines, hopeanol (**82**) registered an IC<sub>50</sub> of  $0.52 \pm 0.04$   $\mu\text{M}$ . Indeed, when compared to the IC<sub>50</sub> values of 5-fluorouracil, a clinically prescribed antitumor drug, hopeanol (**82**) demonstrated a stronger inhibitory effect in all cell lines tested.<sup>85</sup> This significant biological activity notwithstanding, hopeanol's (**82**) novel structure made it an attractive target for synthesis.



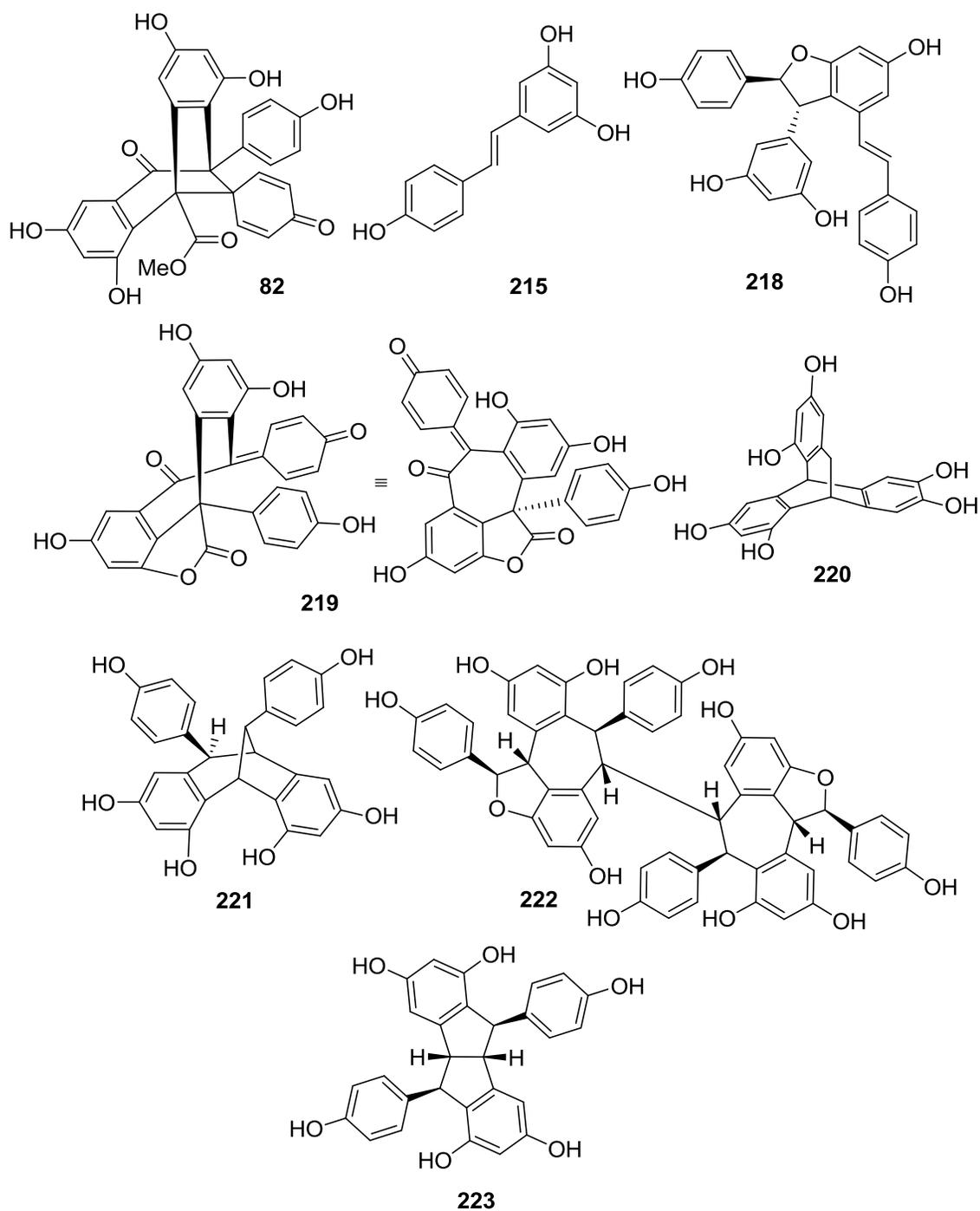
**Figure 4.1.1.1 Molecular structure of the natural product hopeanol (82).**

Hopeanol (**82**) is a member of the polyphenol class of secondary metabolites (**Figure 4.1.1.2**).<sup>86</sup> Specifically, this molecule is believed to be a constituent of an expanding group of natural products that are derived from oligomerization of the highly abundant natural product, resveratrol (**215**) which has itself been isolated from seventy two different plants.<sup>87</sup> A biosynthetic pathway has been proposed for hopeanol (**82**) that proceeds *via* a dimerization of resveratrol through a series of radical species (**Scheme 4.1.1.1**).<sup>85</sup> The first step of this process is thought to involve the homolytic cleavage of the stilbene double bond and one of the phenolic double bonds, followed by the aforementioned dimerization leading to intermediate **216**. Subsequent oxidation of the hydroxyl groups and migration of the B<sub>2</sub> ring of intermediate **217**, followed by an esterification reaction of the resultant carboxylic acid moiety (not shown), would result in the natural product, hopeanol (**82**).

**Scheme 4.1.1.1 Proposed Biosynthesis of Hopeanol (84) from Resveratrol (215)<sup>85</sup>**



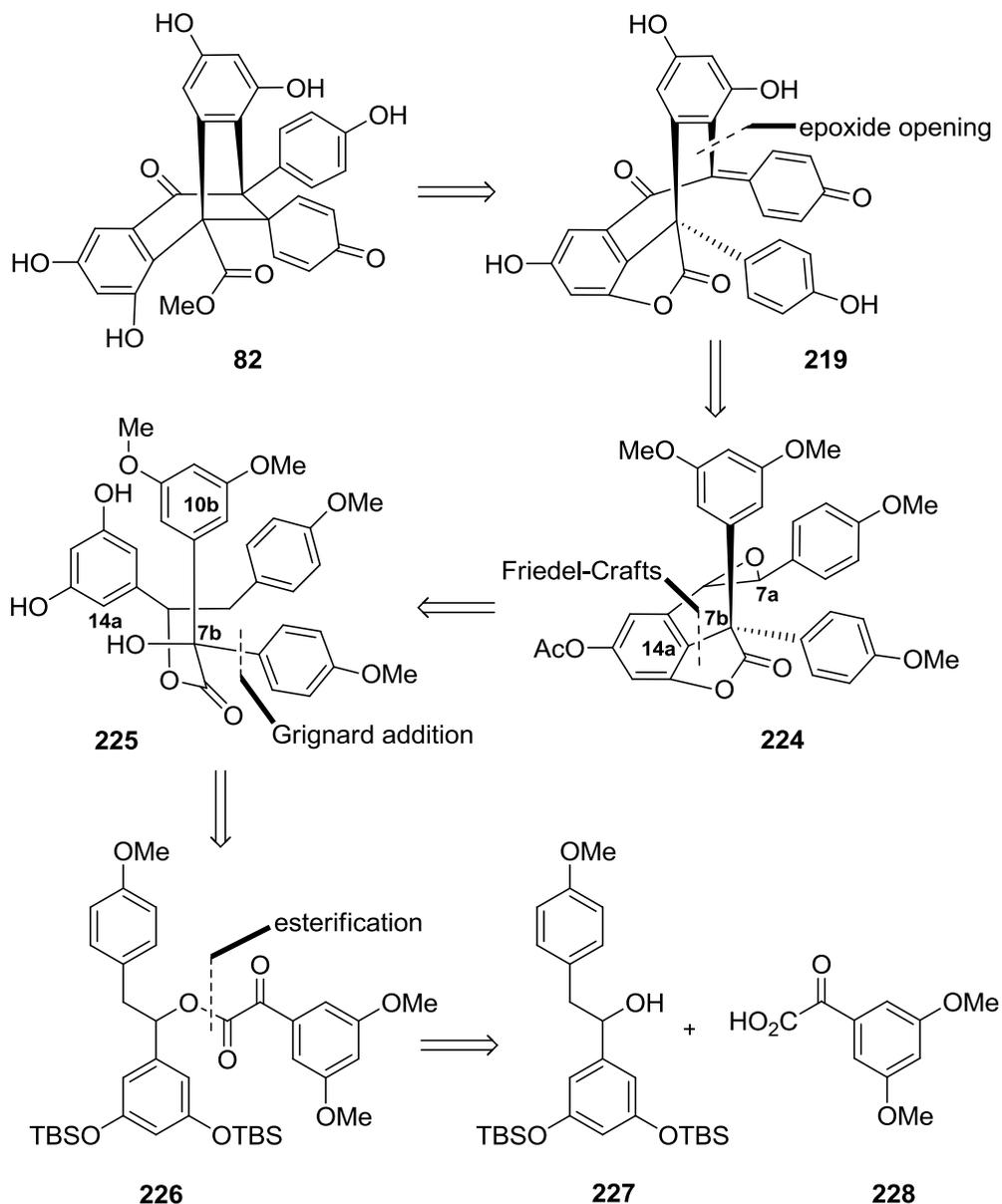
Recently, Snyder and co-workers have developed a modular method for the preparation of nine structurally related members of the resveratrol (**215**) class of secondary metabolites, including cassigarol (**220**), and ampelopsin F (**221**), from a common precursor.<sup>87</sup>



**Figure 4.1.1.2** Molecular structures of resveratrol-derived oligomers: hopeanol (82), resveratrol (215),  $\epsilon$ -viniferin (218), hopeahainol A (219), cassigarol B (220), ampelopsin F (221), hopeaphenol (222) and pallidol (223).<sup>87,88</sup>

Notwithstanding the interest resveratrol-based natural products (**215**) have garnered recently, to date only one total synthesis of hopeanol (**82**) has been reported.<sup>88,89</sup> This synthesis, which was completed in 2010 by Nicolaou and co-workers, employed a strategy which took advantage of an interconversion reaction of ( $\pm$ )-hopeanol (**82**) and the related natural product ( $\pm$ )-hopeahainol A (**219**). Indeed, hopeanol (**82**) is believed to be the biosynthetic precursor to hopeahainol A (**219**, **Scheme 4.1.1.2**).

**Scheme 4.1.1.2 Nicolaou and Co-worker's Retrosynthetic Analysis of Hopeanol (82) and Hopeahainol A (219)**<sup>88,89</sup>

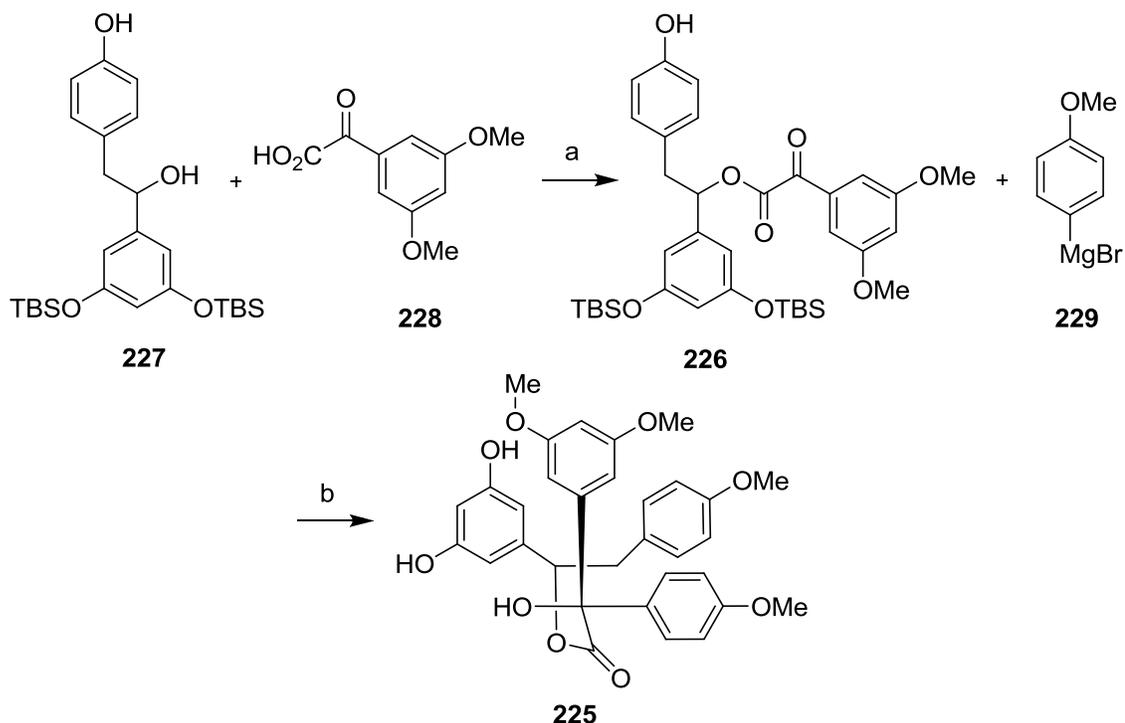


Thus, the primary target, hopeahainol A (**219**), was sought according to the strategy outlined above (**Scheme 4.1.1.2**). In the penultimate step, hopeahainol A (**219**) would be generated *via* a ring-opening reaction, resulting in the formation of a carbon-carbon bond between C7a and C10b. The advanced intermediate **224** could in turn be formed *via* a Friedel-Crafts electrophilic aromatic substitution reaction leading to the

carbon-carbon bond between C14a and C7b. The starting point for this strategy, Nicolaou and co-worker's surmised, could involve an esterification reaction of precursors **227** and **228**, followed by an addition of a Grignard reagent formed from 4-bromoanisole.

The first step therefore, involved the preparation of the benzylic alcohol **227**, formed from the coupling reaction of 3,5-*bis*(OTBS)phenyl lithium and *p*-methoxyphenylacetaldehyde. This product was then esterified with 3,5-dimethoxy- $\alpha$ -oxophenylacetic acid (**228**), to afford the  $\alpha$ -keto ester **226**. Subsequent reaction with methoxyphenylmagnesium bromide (**229**), followed by cleavage of the silyl ether protecting groups, led to the hydroxyl ester precursor **225** in 79% yield as a 1:1 mixture of diastereoisomers (**Scheme 4.1.1.3**).

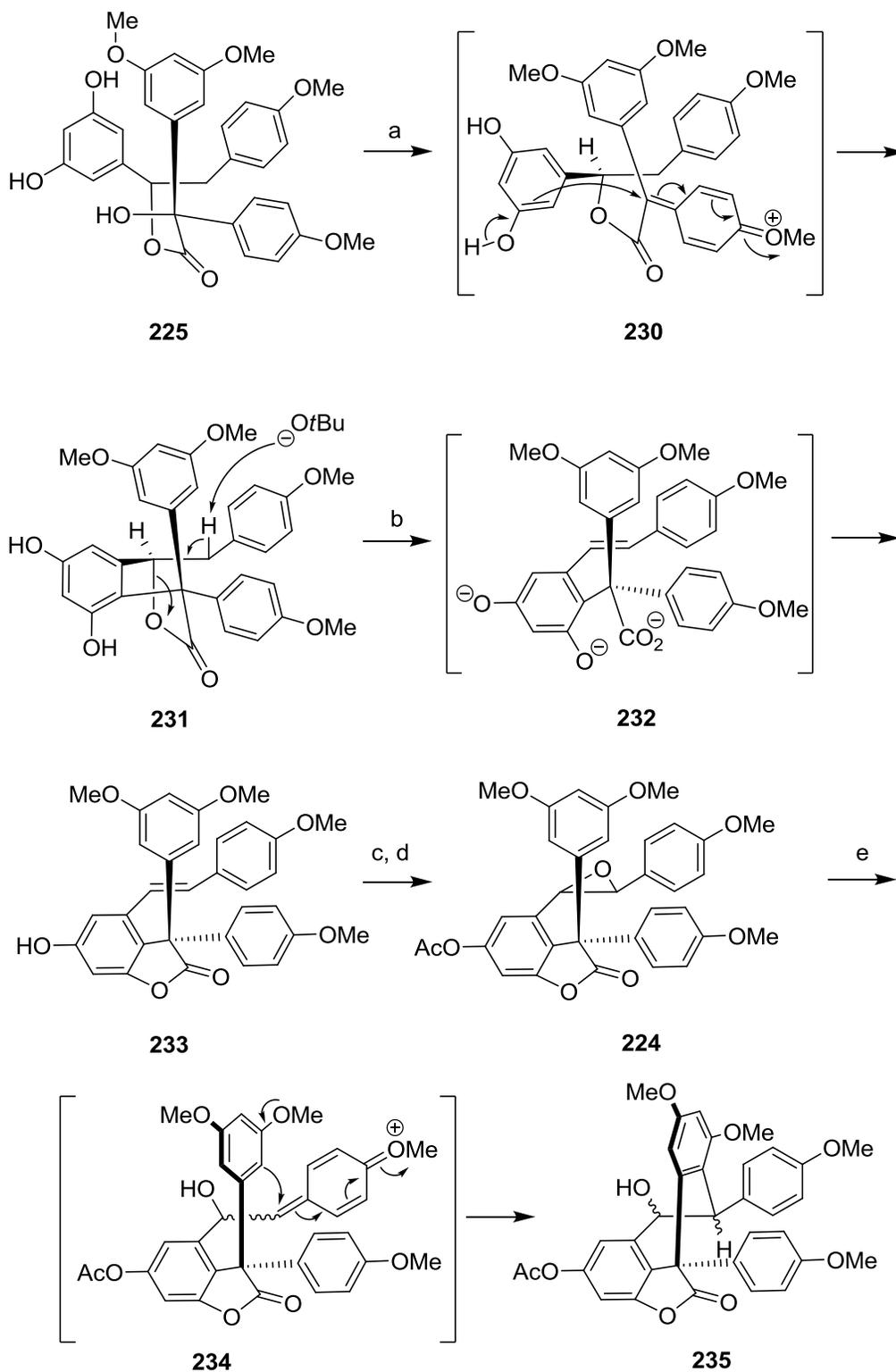
**Scheme 4.1.1.3 Nicolaou and Co-worker's Synthesis of Hydroxy Ester Precursor (225)<sup>88,89</sup>**



Reagents and conditions: (a) **228** (1.5 equiv.), DCC (2.3 equiv.), DMAP (0.3 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 12 h (95%); (b) **229** (0.2 M in THF, 1.3 equiv.), THF, -10 °C, 10 min then TBAF (1.0 M in THF, ) 0 °C, 30 min (79%, *ca.* 1:1 mixture of diastereoisomers).

On stirring this tetracyclic intermediate **225** in the presence *para*-toluene sulfonic acid, the pentacyclic species **233** was produced as a mixture of diastereoisomers (d.r. = 2:4:1). The authors postulated that the observed change in the diastereoisomeric ratio (from dr = 1:1 for **225** to dr = 2:4:1 for **233**), on completion of this reaction, was directed by the intermediate **230**. This was not however, considered a shortcoming in the overall synthetic strategy, as the stereocentre in question would disappear in the following step. This hypothesis was borne out upon subsequent treatment with potassium *tert*-butoxide, which led to a single isomer of compound **233** *via* intermediate **232**. Protection of the free phenol, epoxidation and finally treatment with tin (IV) chloride in dichloromethane resulted in the advanced intermediate **235** (Scheme 4.1.1.4).

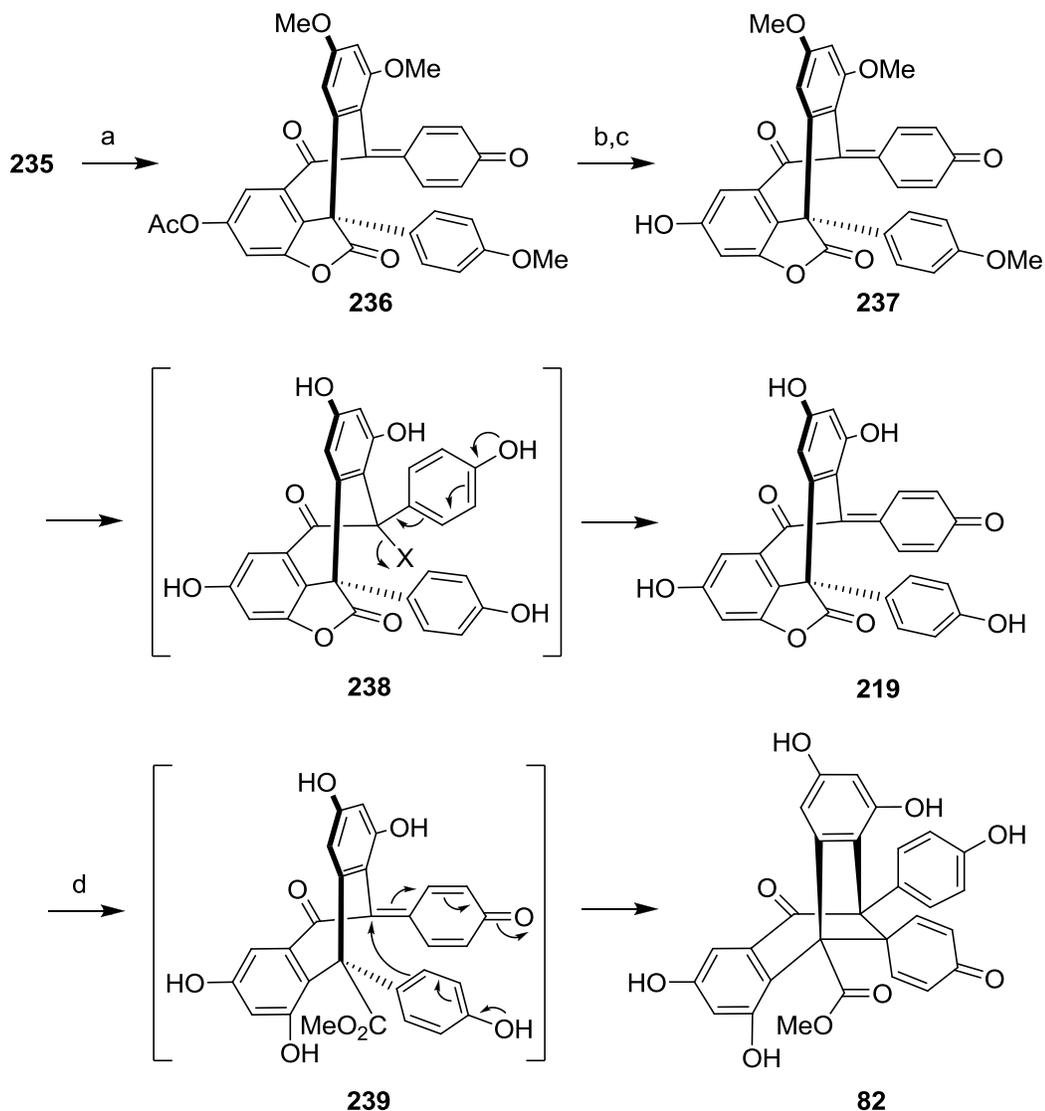
**Scheme 4.1.1.4 Nicolaou and Co-worker's Synthesis of Hexacyclic Intermediate (235)<sup>88,89</sup>**



Reagents and conditions: (a) PTSA (3.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 48 h (65%, *ca.* 2:4:1 mixture of diastereoisomers); (b) KO<sup>t</sup>Bu (1.0 M in THF, 5.0 equiv.), THF, 0 to 25 °C, 4 h, then sat. aq. NH<sub>4</sub>Cl (76%); (c) Ac<sub>2</sub>O (1.5 equiv.), DMAP (0.1 equiv.), pyridine, 0→25 °C, 1 h (quant.); (d) *m*CPBA (77% *wt/wt*, 4.0 equiv.), NaHCO<sub>3</sub> (6.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min (*ca.* 1:1 mixture of diastereoisomers); (e) SnCl<sub>4</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, -40→-20 °C, 20 min (62%, over two steps, *ca.* 2:1 mixture of diastereoisomers).

Oxidation of this key hexacyclic precursor **235**, followed by removal of the acetate, and complete demethylation in the presence of boron tribromide, led to the reactive intermediate **238**, which in turn collapsed to the natural product hopeahainol A (**219**, Scheme 4.1.1.5).

**Scheme 4.1.1.5 Nicolaou and Co-worker's Total Synthesis of Hopeahainol A (**219**) and Hopeanol (**82**)<sup>88,89</sup>**



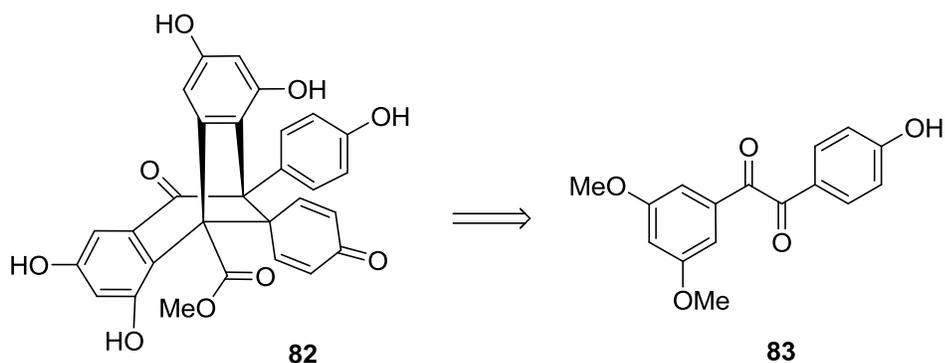
Reagents and conditions: (a) IBX (10 equiv.), DMSO, 25 °C, 24 h (66%); (b) sat. aq. NaHCO<sub>3</sub>, MeOH, 25 °C, 1 h (quant.); (c) BBr<sub>3</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 18 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, -78→-20 °C, 24 h (84%); (d) NaOMe (1.0 equiv.), MeOH, 25 °C, 60 h (80%).

Finally, the target molecule, hopeahainol A [(±)-**219**] was converted to the natural product hopeanol [(±)-**82**] upon treatment with sodium methoxide. More recently Nicolaou and co-worker's reported an asymmetric version of the total syntheses of both enantiomers of hopeahainol A (**219**) and hopeanol (**82**), using similar methods.<sup>89</sup>

#### 4.1.2 A Synthetic Strategy for the Total Synthesis of Hopeanol (82)

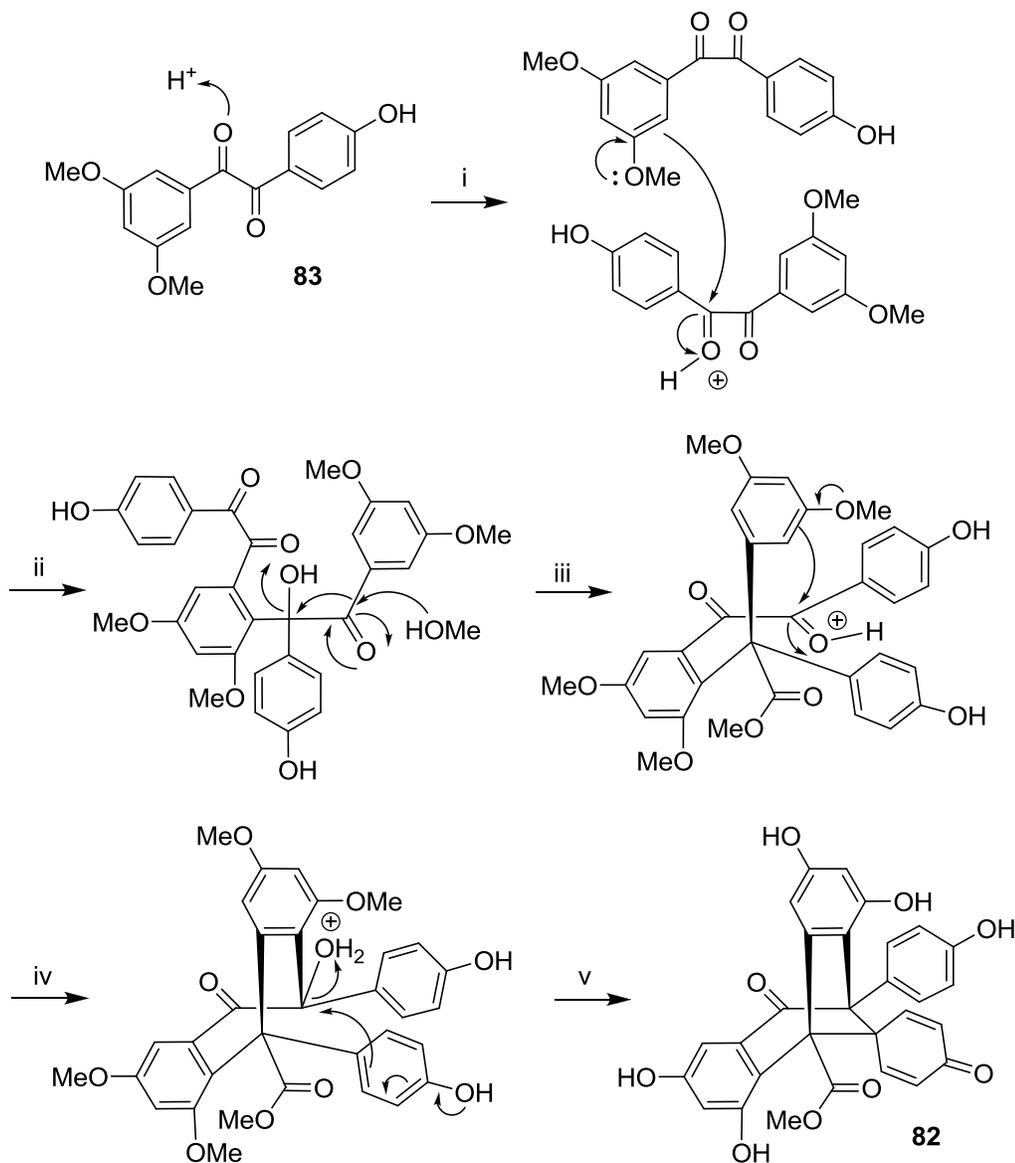
An in depth retrosynthetic analysis of hopeanol (**82**), with its proposed biosynthetic pathway from resveratrol (**215**) as inspiration, resulted in the 1,2-diketone **83** being proffered as a potential reactive precursor to this natural product (**Scheme 4.1.2.1**).

##### Scheme 4.1.2.1 Retrosynthetic Analysis of Hopeanol (82)



In the forward sense, the 1,2-diketone **83** could act as a surrogate for resveratrol (**215**) and undergo an EAS induced dimerization reaction. Subsequent rearrangements upon treatment with an appropriate acid, in the presence, or followed by the addition of methanol, would afford the natural product hopeanol (**82**, **Scheme 4.1.2.2**).

**Scheme 4.1.2.2 Proposed Mechanism for the Synthesis of Hopeanol (82)**



The first step in this proposed cascade reaction would involve activation of one of the carbonyls by an acid, followed by an intermolecular electrophilic aromatic substitution reaction of the more electron-rich trisubstituted aromatic ring of another diketone (**Scheme 4.1.2.2**; steps i and ii). A Friedel-Crafts alkylation reaction of this type has been shown to proceed with indoles and electron deficient  $\alpha$ -keto esters.<sup>90</sup> The next step in this sequence would involve a 1,2-aryl shift, following the nucleophilic attack of

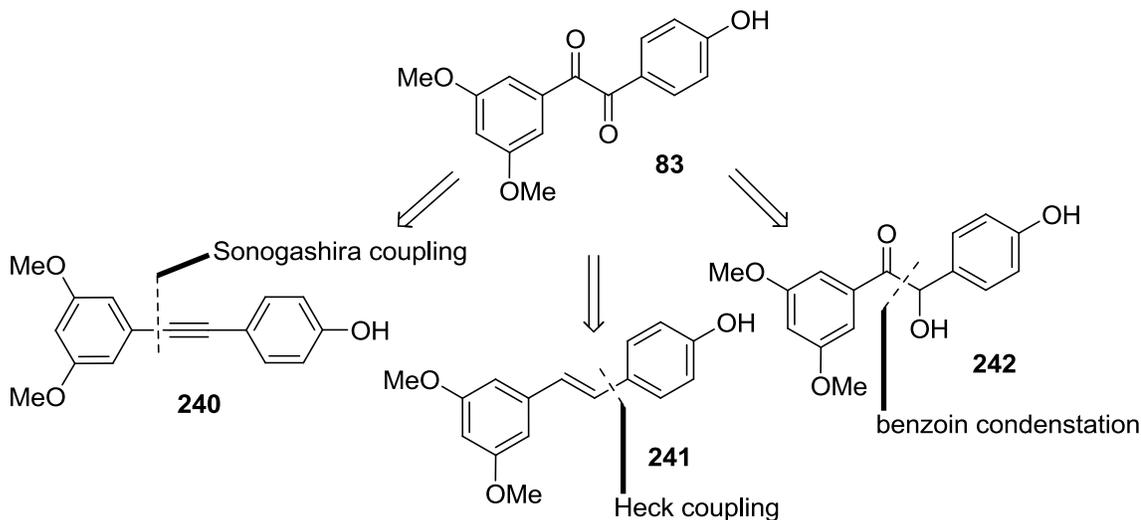
methanol on the hydroxy carbonyl moiety; a critical rearrangement in this sequence, which has been shown to proceed in a variety of circumstances (step iii).<sup>91-94</sup> The final stages of this sequence would require two sequential electrophilic aromatic substitution reactions, the last of which would result in a permanent loss of aromaticity in one of the rings in the final compound, and a demethylation reaction, to afford hopeanol (**82**, steps iv and v). Thus, in order to test this hypothesis, the synthesis of the requisite 1,2-diketone **83** was undertaken. This synthesis and the subsequent attempts to prepare hopeanol (**82**) *via* the proposed route are discussed in the following sections.

## 4.2 Synthesis of Diketone Precursor (**83**)

### 4.2.1 Retrosynthetic Analysis of the 1,2-Diketone Precursor (**83**)

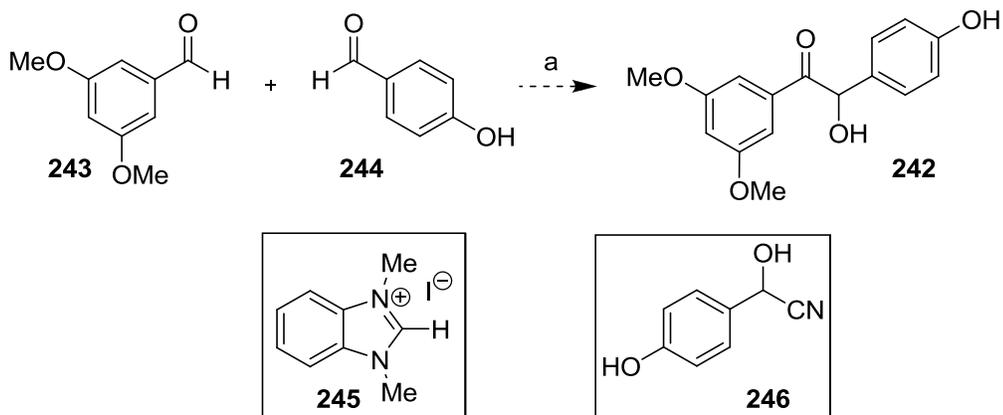
Several strategies were considered for the preparation of the key diketone precursor **83**, all of which would involve an oxidation reaction as the ultimate step. The penultimate precursor, the tolan **240** could in theory be prepared *via* Sonogashira coupling reactions of appropriately substituted iodobenzenes and phenylacetylenes. Similarly, the resveratrol derivative **241** could be synthesized *via* a Heck coupling reaction of its corresponding halide and stilbene precursors (**Scheme 4.2.1.1**).

**Scheme 4.2.1.1 Various Retrosynthetic Analyses of the 1,2-Diketone Precursor (83)**



The most concise of these strategies would involve a benzoil condensation of 3,5-dimethoxybenzaldehyde (**243**) and 4-hydroxybenzaldehyde (**244**), which in principle, would lead to the  $\alpha$ -hydroxyketone **242**. This species could then be oxidized to the desired 1,2-diketone precursor **83**. The initial set of reagents and conditions to prepare the  $\alpha$ -hydroxyketone **242**, were derived from the standard reported conditions for the so-called benzoil condensation; a catalytic amount of sodium or potassium cyanide in a mixture of ethanol and water.<sup>95</sup> After several attempts however, and in the presence of increasing equivalents of the cyanide catalyst, only a small amount of the cyano alcohol **246** was isolated. In addition, several attempts using the imidazolium catalyst **245** also proved ineffective (Scheme 4.2.1.2).<sup>96</sup>

**Scheme 4.2.1.2 Attempted Synthesis of  $\alpha$ -Hydroxy Ketone (**242**) via the Benzoin Condensation**



Reagents and conditions: (a) See below: Table 4.2.1.1.

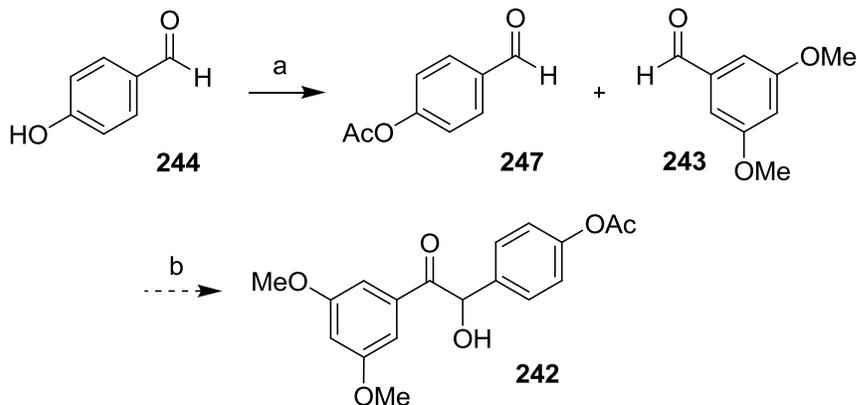
**Table 4.2.1.1 Reagents and Conditions Corresponding to Scheme 4.2.1.2**

entry	catalyst	equiv.	solvent	temp.	time	result
1	NaCN	0.3	EtOH/H <sub>2</sub> O (2:1)	reflux	24 h	no reaction
2	NaCN	1	EtOH/H <sub>2</sub> O (2:1)	reflux	24 h	no reaction
3	NaCN	5	EtOH/H <sub>2</sub> O (2:1)	reflux	24 h	<b>[246 (18%)]</b>
4*	<b>(245)</b>	0.1	MeOH	reflux	28 h	no reaction

\*NaOMe (0.2 equiv.) was used to activate catalyst.

At this point the phenol moiety of 4-hydroxybenzaldehyde (**244**) was converted to the corresponding acetate **247**.<sup>97</sup> This was undertaken as a preventative measure for the possibility that this free phenol moiety could be quenching the active catalyst, thus prohibiting the requisite condensation reaction. However, when the freshly prepared 4-acetoxybenzaldehyde (**247**) and 3,5-dimethoxybenzaldehyde (**243**) were subjected to the benzoin reaction conditions, no reaction was observed (**Scheme 4.2.1.3**).

**Scheme 4.2.1.3 Reaction of 4-Acetoxybenzaldehyde (247) and 3,5-Dimethoxybenzaldehyde (243)**

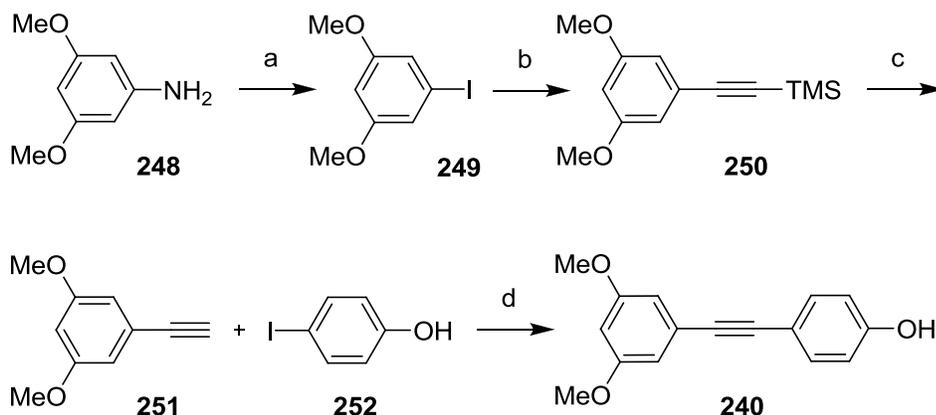


Reagents and conditions: (a) Ac<sub>2</sub>O (3 equiv.), pyridine (3 equiv.), DMAP (0.1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h (quant.); (b) 245 (0.1 equiv.), NaOMe (0.2 equiv.), MeOH, reflux, 2 days (no reaction).

**4.2.2 Synthesis of the 1,2-Diketone Precursor via the Tolan (240)**

While an exhaustive investigation of all of the possible conditions to affect the benzoin condensation was not undertaken, these preliminary experiments indicated that, in terms of expediency, the alternate strategy involving the perhaps more reliable Sonogashira coupling chemistry, might prove more fruitful over the short term. Thus, the initial strategy was abandoned in favour of the somewhat longer route involving a series of Sonogashira coupling reactions, which had previously been shown to work in the synthesis of 1,2-diketones of this type (Scheme 4.2.2.1).<sup>98</sup>

### Scheme 4.2.2.1 Synthesis of Tolan (240)

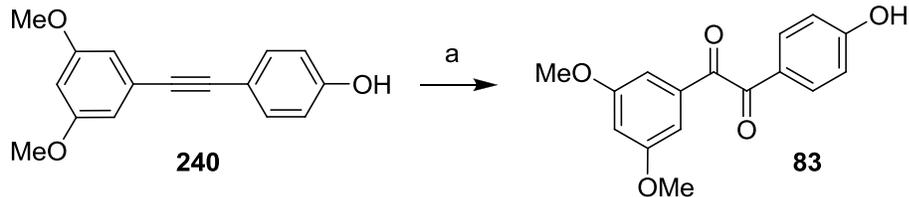


Reagents and conditions: (a)  $\text{NaNO}_2$ ,  $\text{HCl}$ ,  $\text{KI}$ ,  $\text{H}_2\text{O}$ ,  $0\text{ }^\circ\text{C}$ , 12 h (55%); (b) TMS-acetylene,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ,  $\text{CuI}$ ,  $\text{NEt}_3$ ,  $\text{PPh}_3$ ,  $80\text{ }^\circ\text{C}$ , 2 days (93%); (c) TBAF,  $\text{THF}$ ,  $\text{rt}$ , 15 min (92%); (d)  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ,  $\text{CuI}$ ,  $\text{NEt}_3$ ,  $\text{PPh}_3$ ,  $80\text{ }^\circ\text{C}$ , 3 days (85%).

Using known literature procedures, 3,5-dimethoxyphenylacetylene (**251**) was prepared from commercially-available 3,5-dimethoxyaniline (**248**).<sup>99</sup> The first step of this sequence involved a Sandmeyer reaction which converted 3,5-dimethoxyaniline (**248**) to 3,5-dimethoxyiodobenzene (**250**) in moderate yield. A Sonogashira coupling reaction of this aryl halide with trimethylsilylacetylene, followed by TBAF-mediated deprotection of the trimethyl silyl moiety and finally a second Sonogashira coupling reaction of 3,5-dimethoxyphenylacetylene (**251**) and 4-iodophenol (**252**), afforded the desired tolan **240** in excellent yield.

A literature search indicated several potential procedures to oxidize a tolan triple bond to a 1,2-diketone.<sup>98,100-102</sup> The most closely related and straightforward sets of conditions were tested from among the possible prescribed procedures. The two successful entries employed iodine or palladium (II) chloride to activate the triple bond, with dimethylsulfoxide serving as both solvent and oxidant (**Scheme 4.2.2.2**; **Table 4.2.2.1**; **entries 1 and 2**).

### Scheme 4.2.2.2 Oxidation of the Tolans (240) to the 1,2-Diketone Precursor (83)



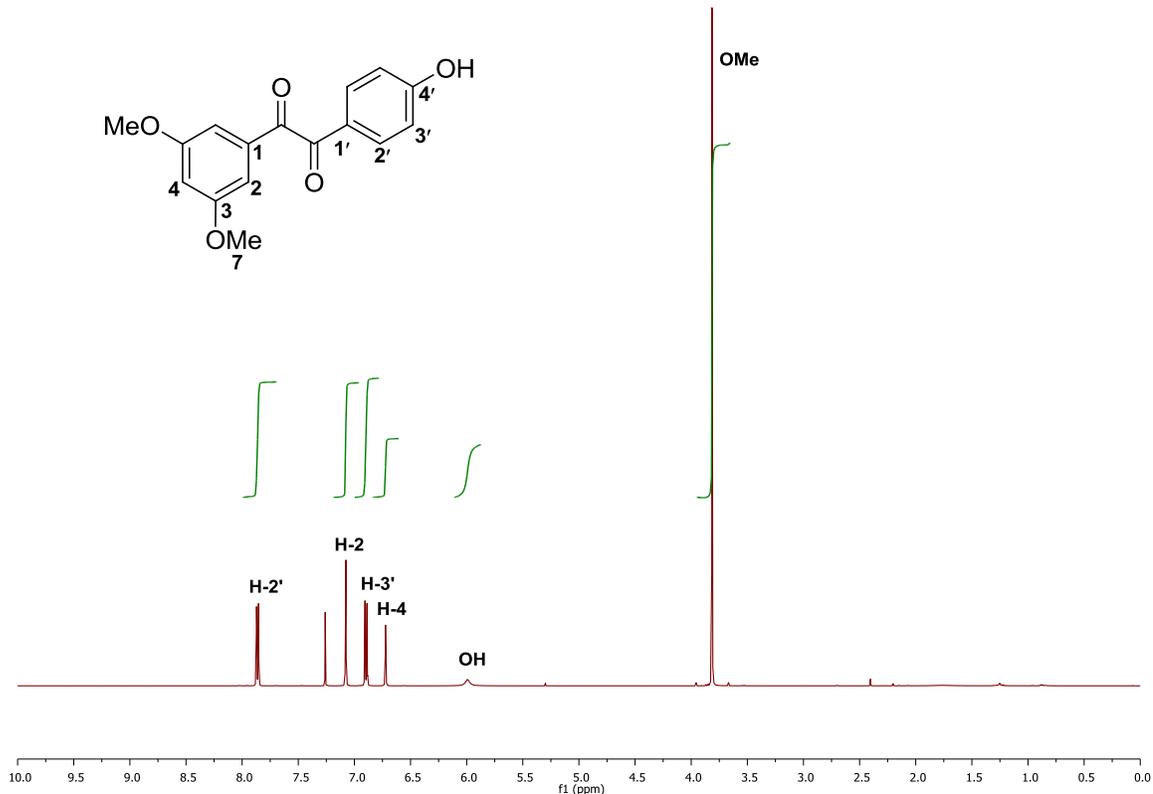
Reagents and conditions: Reagents and conditions: (a) See below: Table 4.2.2.1.

**Table 4.2.2.1 Reagents and Conditions Corresponding to Scheme 4.2.2.2**

entry	reagent (equiv.)	solvent	temp.	time	yield (83) (%)
1*	I <sub>2</sub> (1.1)	DMSO	140 °C	24 h	54
2	PdCl <sub>2</sub> (0.1)	DMSO	140 °C	24 h	48
3	FeCl <sub>3</sub> (0.1)	DMSO	140 °C	24 h	0
4	KMnO <sub>4</sub> /CuSO <sub>4</sub> ·5H <sub>2</sub> O	DCM/H <sub>2</sub> O/ <i>t</i> -BuOH	200 °C	24 h	0

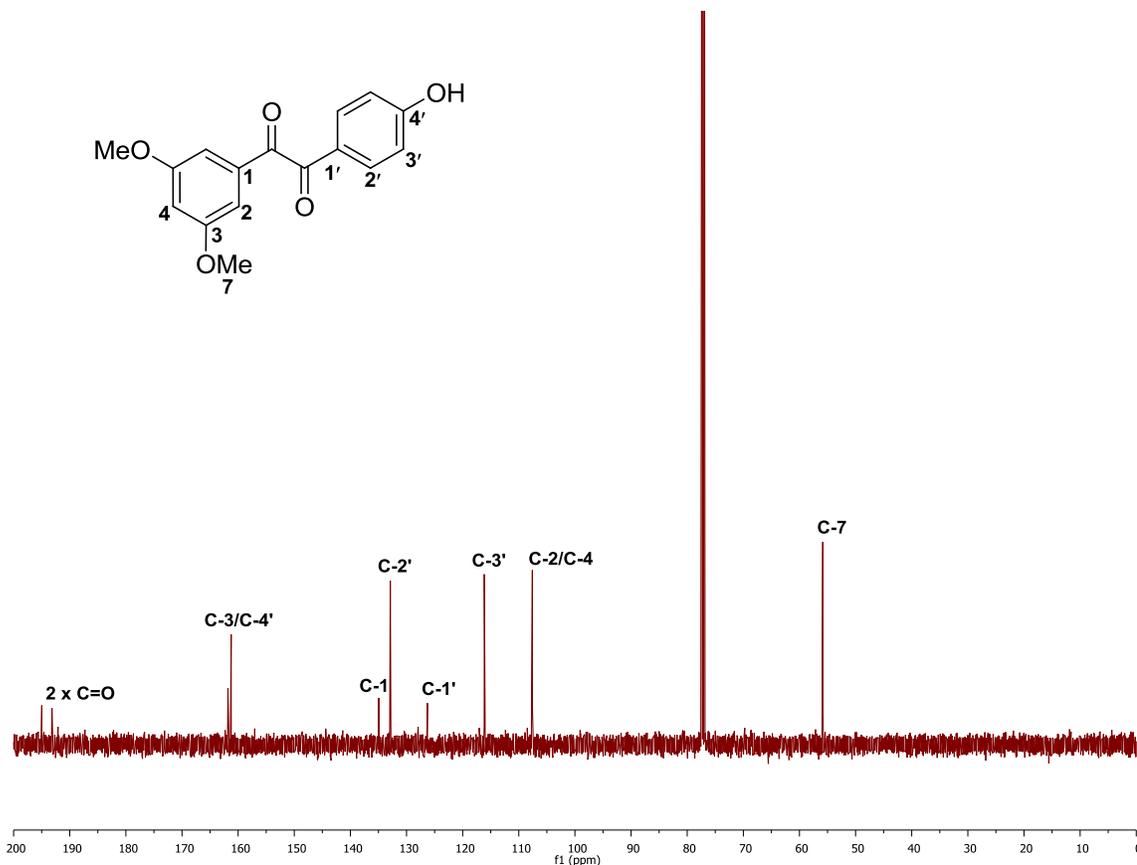
\*No increase in yield when subjected to longer reaction times up to 72 hours.

The infrared spectrum of this product displayed two absorptions at 1679 and 1607 cm<sup>-1</sup>. These are consistent with those reported for the carbonyl stretches of benzils.<sup>103</sup> In addition, the high resolution mass spectrum of this compound exhibited a base peak at *m/z* 287.0919 amu, which corresponded to the protonated molecular ion of the diketone **83** and is consistent with its predicted molecular formula (C<sub>16</sub>H<sub>14</sub>O<sub>5</sub>). The molecular structure of this adduct was confirmed using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The triplet at δ 6.72 ppm in the <sup>1</sup>H NMR spectrum was assigned to the proton between the two methoxy groups, as this was the only signal that would integrate to one proton (*H*-4) (**Figure 4.2.2.1**). The proton labelled *H*-2 was assigned to the doublet at δ 7.08 ppm. This left the remaining aromatic signals, namely the doublets at δ 6.90 and 7.86 ppm, to be assigned to *H*-3' and *H*-2', respectively.



**Figure 4.2.2.1**  $^1\text{H}$  NMR spectrum (600 MHz,  $\text{CDCl}_3$ ) of the 1,2-diketone (**83**).

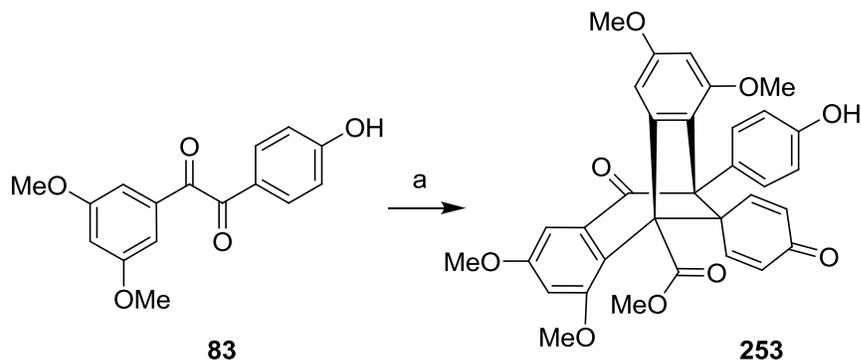
The  $^{13}\text{C}$  NMR displayed eleven peaks, which was expected for the diketone **83**. The peak at  $\delta$  55.9 ppm was assigned to the methoxy carbon ( $\text{C-7}$ ), and the peaks at  $\delta$  107.6 and 107.7 ppm were consistent with the signals arising from carbons positioned *ortho* to a methoxy group on an aromatic ring. Moreover, the peak observed at  $\delta$  116.1 ppm, was consistent with a carbon positioned *ortho* to a phenol group, and was thus assigned to  $\text{C-3}'$ . The carbons labelled  $\text{C-3}$  and  $\text{C-4}'$  were assigned to the signals at  $\delta$  161.2 and 161.8 ppm, while the two carbonyl peaks appeared at  $\delta$  193.2 and 195.0 ppm, respectively. The remaining carbons, labelled  $\text{C-1}'$ ,  $\text{C-2}'$  and  $\text{C-1}$  were assigned to the peaks at  $\delta$  126.3, 132.9 and 135.0 ppm, respectively (**Figure 4.2.2.2**).



**Figure 4.2.2.2**  $^{13}\text{C}$  NMR spectrum (150 MHz,  $\text{CDCl}_3$ ) of the 1,2-diketone (**83**).

With a method for the preparation of gram quantities of the diketone precursor **83** in place, conditions to affect the proposed series of cascade reactions leading to a total synthesis of hopeanol (**82**) were pursued. Thus, an extensive series of Lewis and protic acids were tested to see if the diketone **83** could undergo a dimerization reaction, and potentially rearrange to form the tetramethyl hopeanol analogue **253**, or another advanced, structurally-related intermediate (**Scheme 4.2.2.3**).

**Scheme 4.2.2.3 Attempted Synthesis of Tetramethyl Hopeanol Analogue (253)**



Reagents and conditions: Reagents and conditions: (a) See below: Table 4.2.2.2.

**Table 4.2.2.2 Reagents and Conditions Corresponding to Scheme 4.2.2.3**

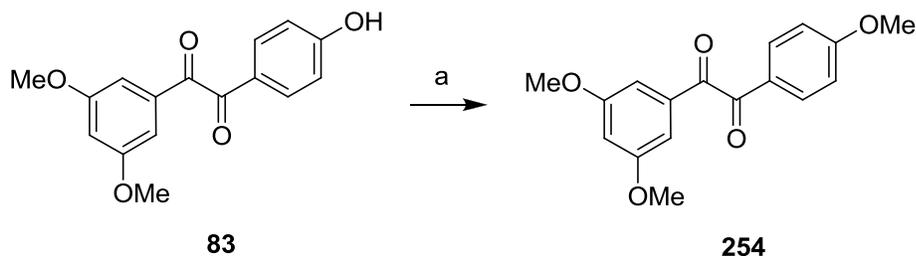
entry	acid	mol % (acid)	solvent	temp.	time	result
1	none	none	MeOH	rt→reflux	3 days	no reaction
2	PPTS	20	MeOH	rt→reflux	4 days	no reaction
3	PPTS	40	MeOH	rt→reflux	4 days	no reaction
4	PPTS	20	benzene	rt→reflux	4 days	no reaction
5	PTSA	20	MeOH	rt→reflux	4 days	no reaction
6	H <sub>2</sub> SO <sub>4</sub>	20	MeOH	rt→reflux	4 days	no reaction
7	TfOH	20	MeOH/CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	4 days	no reaction
8	BF <sub>3</sub> ·OEt <sub>2</sub>	20	MeOH	rt→reflux	4 days	no reaction
9	InCl <sub>3</sub>	20	MeOH	rt→reflux	4 days	no reaction
10	InCl <sub>3</sub>	20	CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	4 days	no reaction
11	AlCl <sub>3</sub>	20	CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	4 days	no reaction
12	TiCl <sub>4</sub>	20	CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	0.5 days	decomposition
13	TFA	20	CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	4 days	no reaction
14	SnCl <sub>4</sub>	20	CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	4 days	no reaction
15	ZnCl <sub>2</sub> *	20	CH <sub>2</sub> Cl <sub>2</sub>	rt→reflux	4 days	no reaction

\*Added as a 1.0 M solution in ether.

As a control, the diketone **83** was stirred in methanol in the absence of any acid as a means to establish its baseline reactivity. However, after stirring this solution at reflux for three days, no reaction was observed. Subsequently, a series of protic acids of increasing strengths were tested, however, in all cases no reaction was observed (**entries 2-7**). Following these experiments, the Lewis acids, boron trifluoride diethyl etherate and indium (III) chloride were tested with methanol as the solvent. Once again however, no reaction was observed (**entries 8-9**). At this point, the solvent employed in these test reactions was changed to dichloromethane. It was hoped that this solvent might accommodate the required EAS reaction, and lead to an unrearranged dimerization product (*cf.* **Scheme 4.1.2.2**), which could be subjected to subsequent reactions that would lead to hopeanol (**82**) in a more step-wise manner. Indeed, as with all prior experiments, none of the acids employed in this way led to any reaction products (**entries 10-15**).

Due to the apparent intransigence of the diketone **83** towards reaction conditions that favour electrophilic aromatic substitution reactions, the phenol moiety was converted to its corresponding methyl ether (**254**). This was carried out in order to mitigate any confounding effects that the free phenol might have in regard to the initial proposed EAS reaction with the ketone functionality (**Scheme 4.2.2.4**).

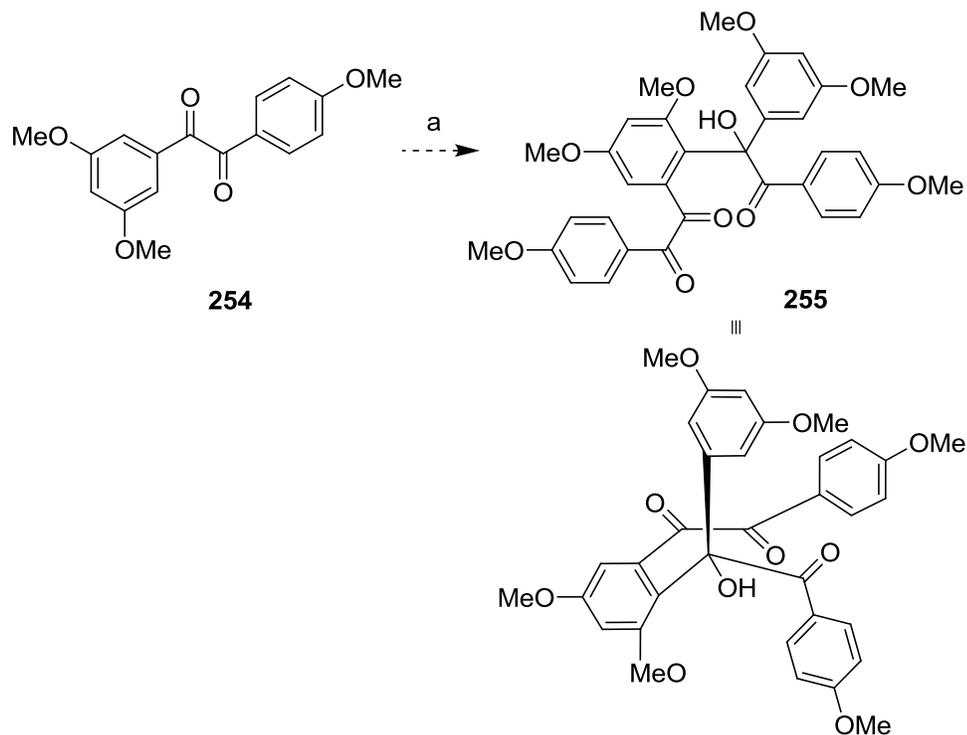
#### Scheme 4.2.2.4 Methylation of 1,2-Diketone Precursor (83)



Reagents and conditions: (a) MeI (20 equiv.), K<sub>2</sub>CO<sub>3</sub> (5 equiv.), acetone, reflux, 1 h (94%).

This methylation reaction was carried out according to a known literature procedure, resulting in the methyl ether **254**, in excellent yield as a bright yellow solid.<sup>89</sup> Subsequently, a series of acids were tested in aprotic solvents in the hopes of facilitating the initial proposed EAS induced dimerization reaction of, in this case, the fully methylated 1,2 diketone **254** (Scheme 4.2.2.5).

**Scheme 4.2.2.5 Attempted Dimerization of Fully-Methylated 1,2-Diketone (254)**



Reagents and conditions: (a) See below: Table 4.2.2.3.

**Table 4.2.2.3 Reagents and Conditions Corresponding to Scheme 4.2.2.5**

entry	acid (20 mol %)	solvent	temp.	time	result
1	AlCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	4 days	no reaction
2	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	4 days	no reaction
3	BF <sub>3</sub> •OEt <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	4 days	no reaction
4	PTSA	CH <sub>2</sub> Cl <sub>2</sub>	rt	4 days	no reaction
5	ZnCl <sub>2</sub> (1.0M in ether)	CH <sub>2</sub> Cl <sub>2</sub>	rt	4 days	no reaction
6	TiCl <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0 °C→reflux	4 days	no reaction
7	SnCl <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0 °C→rt	4 days	no reaction
8	SnCl <sub>4</sub>	toluene	0 °C→reflux	4 days	no reaction
9	TFA (neat)	none	rt	4 days	no reaction

The first acid tested in this series of experiments was aluminum (III) chloride, a Lewis acid which is known to promote EAS reactions.<sup>104</sup> The following experiments employed acids of varying strength, none of which had any observable effect. The final entry involved the use of neat trifluoroacetic acid, which has been shown to facilitate multiple tandem EAS reactions.<sup>105</sup> Once again however, no reaction was observed.

### 4.3 Conclusions

The 1,2-diketone **83** was identified as a potential precursor to the natural product hopeanol (**82**). *En route* to the preparation of this target compound, 3,5-dimethoxyaniline (**248**) was converted, *via* a Sandmeyer reaction, to 3,5-dimethoxyiodobenzene (**249**). This compound was then converted to 3,5-dimethoxy-1-phenylacetylene (**251**) in excellent yield *via* a Sonogashira reaction. Subsequently, a second Sonogashira reaction of this adduct **251** with 4-iodophenol (**252**) afforded the tolan **240**. The 1,2-diketone **83** was then successfully prepared by two methods in good overall yield. The corresponding methyl ether **254** was then prepared, and both of these compounds (**83** and **254**) were subjected to an extensive series of acid promoters in attempts to affect, either in whole or in part, the proposed transformation. As no reaction was observed under any of the reaction conditions that were tested here, in so far as the proposed electrophilic aromatic substitution reaction is concerned, it has been determined that this molecule is not a suitable precursor to hopeanol (**82**).

## Chapter 5:

### *Experimental Procedures and Characterization Data*

#### 5.1. General Experimental Details

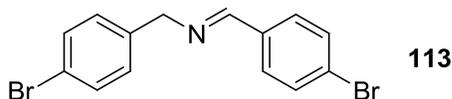
All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, *N,N'*-diisopropylamine, hexamethylphosphoramide, 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.<sup>106</sup> Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography (“flash chromatography”) was carried out using Merck silica gel 60 (230 to 400 mesh).<sup>107</sup> Melting points were measured on a Mel-temp Electrothermal capillary melting point apparatus and are uncorrected. Proton and carbon nuclear magnetic resonance spectra (<sup>1</sup>H and <sup>13</sup>C NMR, respectively) were recorded using a Bruker Avance 600 spectrometer equipped with a QNP or TCI cryoprobe (operating frequencies: <sup>1</sup>H, 600 MHz; <sup>13</sup>C, 150 MHz), a Bruker Avance 500 spectrometer (operating frequencies: <sup>1</sup>H, 500 MHz; <sup>13</sup>C, 125 MHz), or a

Bruker Avance 400 spectrometer (operating frequencies:  $^1\text{H}$ , 400 MHz;  $^{13}\text{C}$ , 100 MHz), at ambient temperature unless stated otherwise. Chemical shifts ( $\delta$ ) 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 ( $\text{CDCl}_3$ ) were 7.26 and 77.16 ppm for  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, respectively. The reference values used for deuterated methanol ( $\text{CD}_3\text{OD}$ ) were 3.31 and 49.00 ppm, respectively. The reference values used for deuterated dimethylsulfoxide [ $(\text{CD}_3)_2\text{SO}$ ] were 2.50 and 39.52 ppm, respectively. Infrared spectra (IR) were recorded as either KBr pellets (KBr), evaporated films (ef) or as films (neat) using a MB-series Bomem/Hartman and Braun Fourier transform spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Varian 4000 GC/MS mass spectrometer. The mode of ionization used was chemical ionization (CI) with methanol. Matrix-assisted laser desorption/ionization Time-of-Flight mass spectra (MALDI-TOF) were recorded on a PerSeptive Biosystems Voyager-DE mass spectrometer using 2,5-dihydroxybenzoic acid as the matrix. High-resolution mass spectra were recorded in positive ion-mode with an ESI ion source on an Agilent<sup>TM</sup> Time-of-Flight LC/MS mass spectrometer. Cyclic voltammetry (CV) was performed on a PAR-263A potentiometer, equipped with a silver wire reference electrode, a platinum disk working electrode and a Pt counter electrode with either 0.1 M  $\text{Bu}_4\text{NClO}_4$  or  $\text{Bu}_4\text{NPF}_6$  solutions in  $\text{CH}_2\text{Cl}_2$  or  $\text{CH}_3\text{CN}$ . Ferrocene was used as an internal standard. EPR spectra were collected using a Bruker EMXplus spectrometer operating with a premiumX X-band (9.5 GHz) microwave bridge. The sample was placed in a quartz capillary for measurements. EPR spectra were simulated with a Bruker WINEPR and

Simfonia software package. Optical rotations were measured on a Perkin Elmer polarimeter 341 at 589 nm.

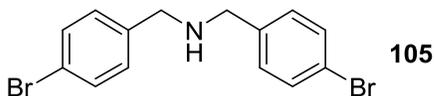
## 5.2 Experimental Procedures and Characterization Data Concerning Chapter 2

### 5.2.1 4-Bromo-N-[(4-bromophenyl)methylene]benzenemethanamine [4-bromobenzylidene-4-bromobenzylamine] (**113**)<sup>34</sup>



A mixture of 4-bromobenzaldehyde (**112**) (2.59 g, 14.0 mmol) and 4-bromobenzylamine hydrochloride (**111**) (3.11 g, 14.0 mmol) in toluene (300 mL) was heated at reflux in a Dean-Stark apparatus for 48 h. The reaction mixture was then filtered whilst hot, rinsed with benzene and the filtrate was concentrated *in vacuo*. The crude *title compound* **113** (5.25 g) was carried forward without purification to the next step.

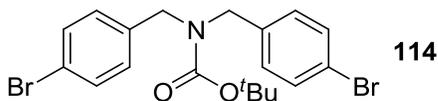
### 5.2.2 *bis*(4-Bromobenzyl)amine [4,4'-dibromodibenzylamine] (**105**)<sup>34</sup>



To a solution of crude imine **113** (5.25 g, ~14.0 mmol) in tetrahydrofuran:methanol (1:1, 260 mL) at room temperature was added sodium borohydride (1.06 g, 28.0 mmol). The reaction mixture was stirred for 15 h and then an aqueous solution of hydrochloric acid (7.2 M, 100 mL) was added dropwise, followed by an aqueous solution of potassium hydroxide (5 M, 200 mL). The reaction mixture was extracted with dichloromethane (3 x 100 mL) and the combined organic extracts were then washed with water (3 x 100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using ether:hexanes (1:1) as the eluant to afford the *title compound* **105** (4.46 g, 90% over two steps) as a colourless low melting solid.  $R_f = 0.31$ , ether:hexanes (1:1); **M.p.** 42-45 °C,

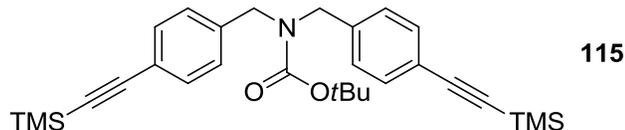
chloroform (lit.<sup>34</sup> 46-48 °C); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.65 (1H, br, NH), 3.74 (4H, s, 2 x ArCH<sub>2</sub>), 7.21 (4H, d, J = 8.4 Hz, 4 x ArH), 7.45 (4H, d, J = 8.5 Hz, 4 x ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 52.2, 120.6, 129.7, 131.3, 139.1; IR (neat) 2917, 2828, 1591, 1486, 1456, 1403, 1097, 1070, 1011, 807 cm<sup>-1</sup>; MS (CI) m/z (rel. intensity) 354 [M(2 x <sup>79</sup>Br) + H, 20], 356 [M(<sup>79</sup>Br + <sup>81</sup>Br) + H, 38] and 358 [M(2 x <sup>81</sup>Br) + H, 16], 186 (9), 188 (8), 169 (100), 171 (99); HRMS Calcd. for C<sub>14</sub>H<sub>14</sub>Br<sub>2</sub>N (M + H); 353.9491. Found; 353.9488.

### 5.2.3 *tert*-Butyl bis(4-bromobenzyl)carbamate (**114**)<sup>35</sup>



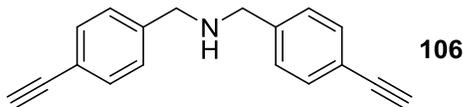
To a solution of *bis*(4-bromobenzyl)amine (**105**) (1.03 g, 2.90 mmol) in methanol (20 mL) was added triethylamine (0.60 mL, 4.30 mmol) and di-*tert*-butyldicarbonate (0.80 mL, 3.48 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. The crude product was purified by flash chromatography using dichloromethane:hexanes (1:1) as the eluant to afford the *title compound* **114** (1.17 g, 92%) as a colourless oil. R<sub>f</sub> = 0.61, hexanes:ether (1:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.48 (9H, s, 3 x CH<sub>3</sub>), 4.27 (2H, br, ArCH<sub>2</sub>), 4.35 (2H, br, ArCH<sub>2</sub>), 7.05 (2H, br, 2 x ArH), 7.09 (2H, br, 2 x ArH), 7.44 (4H, d, J = 8.4 Hz, 4 x ArH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 28.5, 48.8, 49.1, 80.6, 121.3, 129.1, 129.8, 131.8, 136.9, 155.9; IR (neat) 2977, 2930, 1688, 1488, 1455, 1401, 1243, 1164, 1071, 1011 cm<sup>-1</sup>; MS (CI) m/z (rel. intensity) 454 [M(2 x <sup>79</sup>Br) + H, 0.3], 456 [M(<sup>79</sup>Br + <sup>81</sup>Br) + H, 1), 458 [M(2 x <sup>81</sup>Br) + H, 0.3], 398 (48), 400 (100), 402 (49), 354 (19), 356 (37), 358 (17); HRMS Calcd. for C<sub>19</sub>H<sub>21</sub>Br<sub>2</sub>NNaO<sub>2</sub> (M + Na); 475.9831. Found; 475.9840.

#### 5.2.4 *tert*-Butyl bis[4-((trimethylsilyl)ethynyl)benzyl]carbamate (**115**)<sup>35</sup>



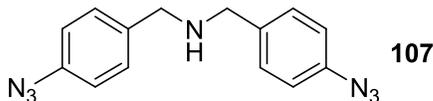
To a solution of *tert*-butyl bis(4-bromobenzyl)carbamate (**114**) (2.27 g, 5.00 mmol) in freshly distilled triethylamine (30 mL) was added *tetrakis*(triphenylphosphine)palladium(0) (290 mg, 0.25 mmol), copper iodide (5.0 mg, 0.26 mmol), and trimethylsilylacetylene (3.10 mL, 22.3 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 4 days and was then allowed to cool room temperature. The reaction mixture was then diluted with water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using dichloromethane:hexanes (1:1) as the eluant to afford the *title compound* **115** (2.24 g, 91%) as a colourless oil.  $R_f = 0.29$ , dichloromethane:hexanes (1:1);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.25 (18H, s, 6 x  $\text{CH}_3$ ), 1.46 (9H, s, 3 x  $\text{CH}_3$ ), 4.28 (2H, br,  $\text{ArCH}_2$ ), 4.39 (2H, br,  $\text{ArCH}_2$ ), 7.08 (2H, br, 2 x  $\text{ArH}$ ), 7.13 (2H, br, 2 x  $\text{ArH}$ ), 7.42 (4H, d,  $J = 8.2$  Hz, 4 x  $\text{ArH}$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  0.1, 28.5, 49.5, 80.6, 94.4, 105.0, 122.2, 127.2, 128.0, 132.3, 138.4, 156.0; **IR** (neat) 2963, 2159, 1697, 1506, 1456, 1404, 1366, 1249, 1163, 865  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 490 ( $\text{M} + \text{H}$ , 5), 390 (100), 187 (8); **HRMS** Calcd. for  $\text{C}_{29}\text{H}_{40}\text{NO}_2\text{Si}_2$  ( $\text{M} + \text{H}$ ); 490.2592. Found; 490.2590.

### 5.2.5 *bis*(4-Ethynylbenzyl)amine (106)



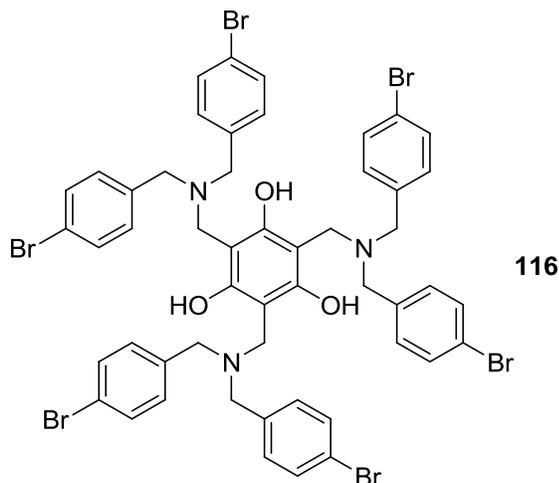
To a stirred solution of *tert*-butyl *bis*[4-{(trimethylsilyl)ethynyl}benzyl]carbamate (**115**) (2.24 g, 4.57 mmol) in methanol (30 mL) was added potassium carbonate (2.70 g, 19.5 mmol). The reaction mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The crude residue was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was then dissolved in trifluoroacetic acid (40 mL) and stirred at room temperature for 15 min. The reaction mixture was then poured onto crushed ice (60 mL), basified with a saturated aqueous solution of sodium bicarbonate and then extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude residue was purified by flash chromatography using ethyl acetate:hexanes (1:1) as the eluant to afford the *title compound* **106** (985 mg, 88%) as a colourless oil.  $R_f = 0.42$ , ethyl acetate:hexanes (4:1);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.63 (1H, br, *NH*), 3.07 (2H, s, 2 x *CCH*), 3.79 (4H, s, 2 x *ArCH}\_2*), 7.30 (4H, d,  $J = 8.1$  Hz, 4 x *ArH*), 7.47 (4H, d,  $J = 8.1$  Hz, 4 x *ArH*);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  52.9, 77.1, 83.7, 120.8, 128.2, 132.3, 141.2; **IR** (ef) 3289, 3029, 2917, 2828, 2106, 1505, 1455, 1410, 1359, 1231, 1203, 1099, 1018, 823  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 246 (*M* + *H*, 100), 144 (4), 130 (4), 115 (11); **HRMS** Calcd. for  $\text{C}_{18}\text{H}_{16}\text{N}$  (*M* + *H*); 246.1277. Found; 246.1269.

### 5.2.6 *bis*(4-Azidobenzyl)amine (**107**)



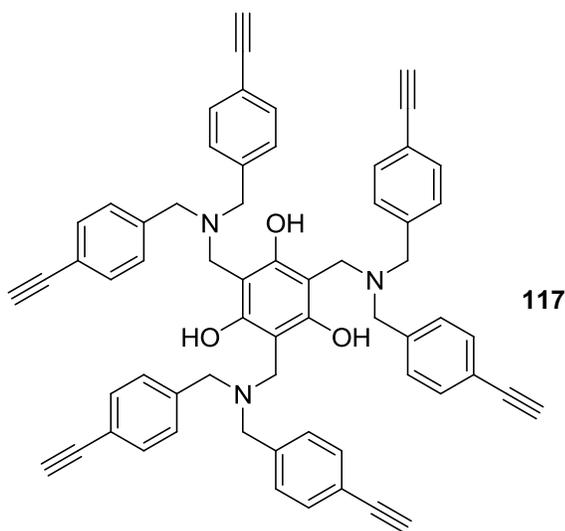
To a solution of *bis*(4-bromobenzyl)amine (**105**) (501 mg, 1.41 mmol) in ethanol: water (7:3, 8 mL) was added sodium azide (400 mg, 6.15 mmol), copper iodide (53 mg, 0.28 mmol), sodium ascorbate (28 mg, 0.14 mmol) and *N,N'*-dimethylethylenediamine (0.05 mL, 0.46 mmol). The reaction mixture was stirred at reflux for 12 h, allowed to cool to room temperature and then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using ether:hexanes (5:2) as the eluant to afford the *title compound* **107** (362 mg, 93%) as a yellow solid.  $R_f = 0.30$ , ethyl acetate:hexanes (4:1);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.59 (1H, br, NH), 3.77 (4H, s, 2 x  $\text{ArCH}_2$ ), 7.00 (4H, d,  $J = 8.5$  Hz, 4 x  $\text{ArH}$ ), 7.32 (4H, d,  $J = 8.6$  Hz, 4 x  $\text{ArH}$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  52.6, 119.1, 129.7, 137.2, 138.9; **IR** (KBr) 2823, 2410, 2113, 1605, 1581, 1506, 1289, 1129, 1014, 827  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 280 (M + H, 1), 252 (3), 106 (100), 132 (40); **HRMS** Calcd. for  $\text{C}_{14}\text{H}_{14}\text{O}_7$  (M + H); 280.1305. Found; 280.1311.

### 5.2.7 2,4,6-tris[*bis*(4-Bromobenzyl)amino]methylphloroglucinol (**116**)



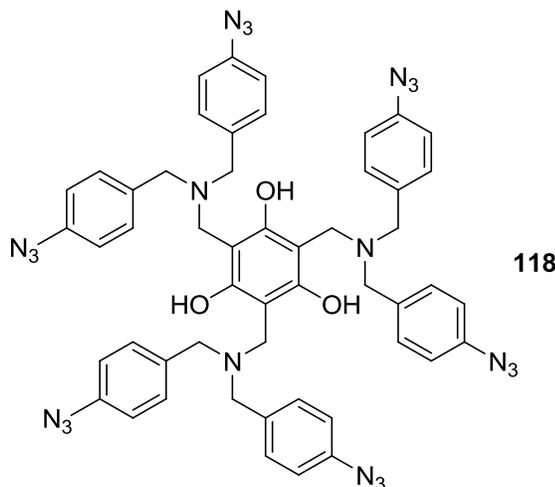
To a solution of *bis*(4-bromobenzyl)amine (**105**) (465 mg, 1.31 mmol) and phloroglucinol (**9**) (51 mg, 0.40 mmol) in ethanol (30 mL), was added an aqueous formaldehyde solution (0.12 mL, 37% w/v, 1.40 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h and the resultant precipitate was then collected by filtration. The filter-cake was washed with cold ethanol (3 x 15 mL) and dried *in vacuo* to afford the *title compound* **116** (286 mg, 64%) as a white powder. **M.p.** 130-133 °C (ethanol); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 3.53 (12H, s, 6 x CH<sub>2</sub>), 3.71 (6H, s, 3 x CH<sub>2</sub>), 7.13 (12H, d, *J* = 8.4 Hz, 12 x ArH), 7.44 (12H, d, *J* = 8.4 Hz, 12 x ArH), 11.13 (3H, br, 3 x OH); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 49.2, 57.3, 99.4, 121.8, 131.3, 131.9, 136.0, 155.9; **IR** (KBr) 2928, 2835, 1633, 1592, 1488, 1453, 1377, 1351, 1259, 1121, 1072, 1012, 908 cm<sup>-1</sup>; **MS** (ESI) *m/z* (rel. intensity) 1221.9 [M(6 x <sup>79</sup>Br) + H, 0], 1223.9 [M(5 x <sup>79</sup>Br + <sup>81</sup>Br) + H, 4], 1225.5 [M(4 x <sup>79</sup>Br + 2 x <sup>81</sup>Br) + H, 11], 1227.9 [M(3 x <sup>79</sup>Br + 3 x <sup>81</sup>Br) + H, 17], 1229.9 [M(2 x <sup>79</sup>Br + 4 x <sup>81</sup>Br) + H, 12], 1231.9 [M(1 x <sup>79</sup>Br + 5 x <sup>81</sup>Br) + H, 5], 614.4346 (45), 355.9488 (100); **HRMS** Calcd. for C<sub>51</sub>H<sub>46</sub>Br<sub>6</sub>N<sub>3</sub>O<sub>3</sub> (M + H); 1227.8582. Found; 1227.8558.

### 5.2.8 2,4,6-tris[*bis*(4-Ethynylbenzyl)amino]methylphloroglucinol (**117**)



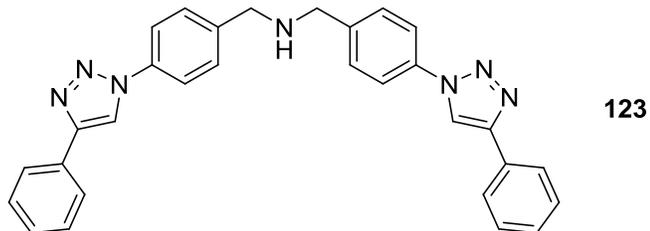
To a solution of *bis*(4-ethynylbenzyl)amine (**106**) (468 mg, 1.91 mmol) and phloroglucinol (**9**) (60 mg, 0.47 mmol) in ethanol (30 mL), was added an aqueous formaldehyde solution (0.20 mL, 37% w/v, 2.40 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h and the resultant precipitate was then collected by filtration. The filter-cake was washed with cold ethanol (3 x 15 mL) and dried *in vacuo* to afford the *title compound* **117** (200 mg, 48%) as a beige powder. **M.p.** decomp. (ethanol); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 3.06 (6H, s, 6 x CCH), 3.57 (12H, s, 6 x CH<sub>2</sub>), 3.73 (6H, s, 3 x CH<sub>2</sub>), 7.23 (12H, d, *J* = 8.2 Hz, 12 x ArH), 7.44 (12H, d, *J* = 8.1 Hz, 12 x ArH), 11.12 (3H, br, 3 x OH); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 53.6, 57.8, 77.7, 83.4, 99.9, 121.3, 129.4, 132.2, 137.8, 156.0; **IR** (KBr) 3289, 2927, 2834, 2107, 1629, 1506, 1457, 1366, 1119, 1098, 909 cm<sup>-1</sup>; **MS** (ESI-MS) *m/z* (rel. intensity) 898 (M + H, 100); **HRMS** Calcd. for C<sub>63</sub>H<sub>52</sub>N<sub>3</sub>O<sub>3</sub> (M + H); 898.4403. Found; 898.3984.

### 5.2.9 2,4,6-tris[*bis*(4-Azidobenzyl)amino]methyl]phloroglucinol (**118**)



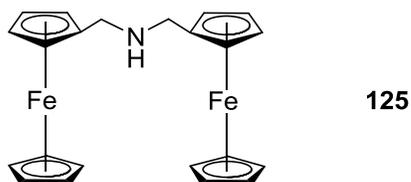
To a solution of *bis*(4-azidobenzyl)amine (**107**) (649 mg, 2.30 mmol) and phloroglucinol (**9**) (67 mg, 0.53 mmol) in ethanol (30 mL), was added an aqueous formaldehyde solution (0.20 mL, 37% w/v, 2.40 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h and the resultant precipitate was then collected by filtration. The filter-cake was washed with cold ethanol (3 x 15 mL) and dried *in vacuo* to afford the *title compound* **118** (518 mg, 80 %) as an orange powder.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.55 (12H, s, 6 x  $\text{CH}_2$ ), 3.77 (6H, s, 3 x  $\text{CH}_2$ ), 6.98 (12H, d,  $J = 8.3$  Hz, 12 x  $\text{ArH}$ ), 7.25 (12H, d,  $J = 8.3$  Hz, 12 x  $\text{ArH}$ ), 11.25 (3H, br, 3 x  $\text{ArOH}$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  49.1, 57.2, 99.4, 119.2, 131.0, 133.7, 139.3, 155.9; **IR** (KBr) 2925, 2834, 2410, 2117, 1633, 1606, 1506, 1379, 1507, 1288, 1116, 909  $\text{cm}^{-1}$ ; **MS** (ESI)  $m/z$  (rel. intensity) 1000.4 ( $\text{M} + \text{H}$ , 26), 500.7 (100); **HRMS** Calcd. for  $\text{C}_{51}\text{H}_{46}\text{N}_{21}\text{O}_3$  ( $\text{M} + \text{H}$ ); 1000.4087. Found; 1000.4067.

### 5.2.10 *bis*[4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzyl]amine (**123**)



A suspension of *bis*(4-azidobenzyl)amine (**107**) (196 mg, 0.70 mmol), copper iodide (27 mg, 0.14 mmol), and sodium ascorbate (28 mg, 0.14 mmol) in tetrahydrofuran (5 mL) was stirred for 16 h at room temperature. The resultant precipitate was collected by filtration, washed with cold tetrahydrofuran (3 x 15 mL) and then dried *in vacuo* to afford the crude *title compound* **123** (298 mg, 88%) as a cream coloured solid. Partial data:  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.93 (4H, s, 2 x  $\text{CH}_2$ ), 7.39 (2H, t,  $J = 7.1$  Hz, 2 x  $\text{ArH}$ ), 7.47 (4H, t,  $J = 7.4$  Hz, 4 x  $\text{ArH}$ ), 7.56 (4H, d,  $J = 7.8$  Hz, 4 x  $\text{ArH}$ ), 7.78 (4H, d,  $J = 8.1$  Hz, 4 x  $\text{ArH}$ ), 7.92 (4H, d,  $J = 8.1$  Hz, 4 x  $\text{ArH}$ ), 8.19 (2H, s, 2 x  $\text{trzH}$ ); **MS** (ESI)  $m/z$  (rel. intensity) 484.2 ( $\text{M} + \text{H}$ , 100).

### 5.2.11 *bis*(Ferrocenylmethyl)amine (**125**)

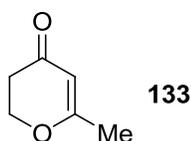


To a solution of ferrocenecarboxaldehyde (**126**) (1.50 g, 7.01 mmol) and ammonium acetate (5.50 g, 71.4 mmol) in methanol, was added sodium cyanoborohydride (1.23 g, 19.6 mmol). The reaction mixture was stirred for 48 h at room temperature and was then acidified with concentrated hydrochloric acid to  $\text{pH} < 2$ . The resultant mixture was concentrated *in vacuo*, diluted with water (20 mL), and then

washed with ether (2 x 20 mL). The aqueous extract was then basified with an aqueous solution of potassium hydroxide (45% w/v), saturated with sodium chloride and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using dichloromethane:hexanes:methanol (5:4:1) as the eluant to afford the *title compound* **125** (1.08 g, 40%) as pale yellow solid.  $R_f = 0.28$ , dichloromethane:hexanes:methanol (5:4:1); **M.p.** 189-192 °C, dichloromethane (lit.<sup>108</sup> 188-189 °C, ethanol); **<sup>1</sup>H NMR** (500 MHz, CD<sub>3</sub>OD)  $\delta$  3.73 (4H, s, 2 x CH<sub>2</sub>), 3.16 (10H, s, 10 x ArH), 4.21 (4H, apparent t,  $J = 1.8$  Hz, 4 x ArH), 4.30 (4H, apparent t,  $J = 1.8$  Hz, 4 x ArH); **<sup>13</sup>C NMR** (125 MHz, CD<sub>3</sub>OD)  $\delta$  48.4, 69.7, 69.8, 70.6, 82.5; **IR** (KBr) 3094, 3061, 2934, 2696, 2666, 2556, 1533, 1452, 1433, 1397, 1322, 1236, 1104, 1041, 1001, 820 cm<sup>-1</sup>; **MS** (ESI-MS.)  $m/z$  (rel. intensity) 414 (M + H, 100); **HRMS** Calcd. for C<sub>22</sub>H<sub>24</sub>Fe<sub>2</sub>N (M + H); 414.0603. Found; 414.0589.

### 5.3 Experimental Procedures and Characterization Data Concerning Chapter 3

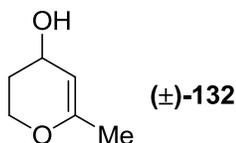
#### 5.3.1. 2-Methyl-5,6-dihydro-4H-pyran-4-one (133)<sup>42</sup>



A solution of acetylacetone (10.3 mL, 100 mmol) in tetrahydrofuran (20 mL) was added dropwise to a suspension of sodium hydride (3.60 g, 60% in mineral oil, 120 mmol) and hexamethylphosphoramide (15.0 mL, 86.2 mmol) in tetrahydrofuran (150 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and then *n*-butyllithium (48.0 mL, 2.5 M in hexanes, 120 mmol) was added dropwise and the resultant mixture

was stirred for 30 min at 0 °C. Dry paraformaldehyde powder (6.03 g, 200 mmol) was then added and the reaction mixture was stirred at room temperature for 2 h. Hydrochloric acid (3 M, ~150 mL) was then added until a pH = 2 was obtained. The resultant mixture was stirred for an additional 2.5 h and was then extracted with ether (3 x 150 mL). The combined organic extracts were subsequently washed with brine (300 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ethyl acetate:hexanes (1:4) as the eluant to afford the *title compound* **133** (5.78 g, 52%) as a colourless liquid.  $R_f = 0.26$ , ether:hexanes (95:5);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.99 (3H, s,  $\text{CH}_3$ ), 2.50 (2H, t,  $J = 6.9$  Hz,  $\text{CH}_2$ ), 4.45 (2H, t,  $J = 6.9$  Hz,  $\text{CH}_2$ ), 5.33 (1H, s,  $\text{CH}$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.2, 35.6, 68.0, 105.4, 174.7, 192.2; **IR** (neat) 2968, 2886, 1665, 1609, 1467, 1403, 1353, 1199, 1164, 1073, 1044, 984  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 113 ( $\text{M} + \text{H}$ , 100); **HRMS** Calcd. for  $\text{C}_6\text{H}_9\text{O}_2$  ( $\text{M} + \text{H}$ ); 113.0597. Found; 113.0599.

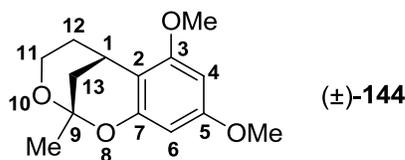
### 5.3.2 (4*RS*)-2-Methyl-5,6-dihydro-4*H*-pyran-4-ol [(±)-**132**]



A solution of the ketone **133** (1.00 g, 8.92 mmol) in ether (10 mL) was added dropwise to a suspension of lithium aluminum hydride (676 mg, 17.8 mmol, 2 equiv.) in ether (25 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min. and was then re-cooled to 0 °C. Water (0.6 mL), an aqueous solution of sodium hydroxide (15 wt%, 0.6 mL), and water (1.8 mL) were then added in succession and the resultant mixture was filtered through a plug of celite. The filter-cake was

washed with ether (3 x 15 mL) and the combined filtrates were concentrated *in vacuo* to afford the *title compound* ( $\pm$ )-**132** (1.03 g, quant.) as a clear liquid. This material proved to be unstable to purification (kugelrohr distillation or flash chromatography on silica gel) and to storage. Thus, the crude *title compound* ( $\pm$ )-**132** (>95% pure) was used immediately in subsequent experiments.  $R_f = 0.34$ , ether:hexanes (95:5);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.65 (3H, s,  $\text{CH}_3$ ), 1.66-1.69 (1H, m,  $\text{OCH}_2\text{CHH}$ ), 1.70-1.79 (1H, m,  $\text{OCH}_2\text{CHH}$ ), 2.98 (1H, br,  $\text{OH}$ ), 3.87 (1H, apparent td,  $J = 11.4, 2.7$  Hz,  $\text{OCCH}_3\text{CHCHOH}$ ), 3.95-4.03 (2H, m,  $\text{OCH}_2$ ), 4.63 (1H, d,  $J = 4.9$  Hz,  $\text{OCCH}$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.0, 31.0, 59.8, 62.0, 99.0, 154.3; **IR** (neat) 3370, 2956, 2924, 2881, 1670, 1466, 1429, 1391, 1298, 1254, 1224, 1166, 1079, 1019, 977, 951, 872  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 115 ( $\text{M} + \text{H}$ , 10), 97 (100).

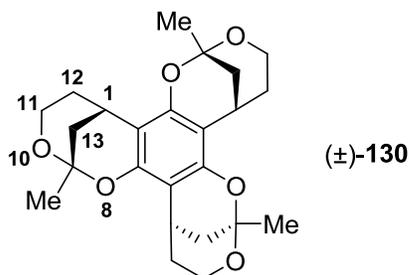
### 5.3.3 (*RS*)-3,5-Dimethoxy-9-methyl-8,10-dioxatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene [( $\pm$ )-**144**]



To a suspension of 3,5-dimethoxyphenol (**143**) (560 mg, 3.63 mmol, 1.1 equiv.), the alcohol **132** [prepared from the corresponding ketone **133** (370 mg, 3.30 mmol, 1 equiv.)] and anhydrous magnesium sulfate (500 mg) in tetrahydrofuran (25 mL) was added boron trifluoride diethyl etherate (0.40 mL, 3.18 mmol) dropwise at 0 °C. The reaction mixture was stirred for 5 h at 0 °C and was then filtered through a plug of celite. The filter-cake was washed with tetrahydrofuran (2 x 15) and the combined filtrates were washed with water (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes

(4:1) as the eluant to afford the *title compound* ( $\pm$ )-**144** (103 mg, 13%) as a colourless oil.  $R_f = 0.44$ , ether:hexanes (1:2);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45-1.50 (1H, m, 12-*CHH*), 1.51 (3H, s,  $\text{CH}_3$ ), 1.71 (1H, ddd,  $J = 12.7, 3.7, 1.9$  Hz, 13-*CHH*), 1.95 (1H, apparent tdd,  $J = 12.9, 5.5, 3.4$  Hz, 12-*CHH*), 2.01 (1H, dd,  $J = 12.7, 2.8$  Hz, 13-*CHH*), 3.42-3.45 (1H, m, 1-*CH*), 3.63 (1H, apparent td,  $J = 12.5, 3.1$  Hz, 11-*CHH*), 3.73 (1H, apparent dd,  $J = 11.9, 5.4$  Hz, 11-*CHH*), 3.76 (3H, s,  $\text{OCH}_3$ ), 3.77 (3H, s,  $\text{OCH}_3$ ), 6.07 (1H, d,  $J = 2.3$  Hz, *ArH*), 6.10 (1H, d,  $J = 2.4$  Hz, *ArH*);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  23.0, 28.0, 29.7, 34.6, 55.4, 55.5, 60.5, 91.5, 92.1, 97.6, 105.9, 157.2, 157.3, 159.8; **IR** (neat) 2992, 2940, 2840, 1620, 1592, 1496, 1450, 1382, 1354, 1213, 1102, 1048, 871  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 251 ( $\text{M} + \text{H}$ , 100); **HRMS** Calcd. for  $\text{C}_{14}\text{H}_{19}\text{O}_4$  ( $\text{M} + \text{H}$ ); 251.1278. Found; 251.1274.

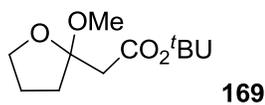
### 5.3.4 (*RS*)-*tris*-Benzannulated acetal [( $\pm$ )-**130**]



To a suspension of phloroglucinol (**9**) (130 mg, 1.03 mmol, 1 equiv.), the alcohol **132** [prepared from the corresponding ketone **133** (1.00 g, 8.92 mmol, 9 equiv)] and anhydrous magnesium sulfate (500 mg) in tetrahydrofuran (75 mL) was added boron trifluoride diethyl etherate (1.30 mL, 10.4 mmol) dropwise at 0 °C. The reaction mixture was stirred for 16 h at room temperature and was then filtered through a plug of celite. The filter-cake was washed with tetrahydrofuran (2 x 50 mL), and the combined filtrates were then washed with water (100 mL), dried over anhydrous sodium sulfate and

concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (4:1) as the eluant to afford the *title compound* ( $\pm$ )-**130** (294 mg, 71%) as a white solid.  $R_f = 0.39$ , ether:hexanes (1:2); **M.p.** 219-221 °C, ether:hexanes (4:1);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41-1.47 (2H, m, 2 x 12-*CHH*), 1.49 (6H, s, 2 x  $\text{CH}_3$ ), 1.51 (3H, s,  $\text{CH}_3$ ), 1.57-1.63 (1H, m, 12-*CHH*), 1.68-1.75 (3H, m, 2 x 12-*CHH* + 12-*CHH*), 1.91-2.05 (6H, m, 3 x 13- $\text{CH}_2$ ), 3.44-3.48 (1H, m, 1-*CH*), 3.52-3.60 (3H, 11-*CHH* + 2 x *CH*), 3.61-3.78 (5H, m, 2 x 11-*CHH* + 2 x 11-*CHH* + 11-*CHH*);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  22.93, 22.98, 23.15, 28.02, 28.04, 28.07, 29.68, 29.82, 34.54, 34.63, 34.72, 60.60, 60.62, 60.67, 97.29, 97.47, 103.13, 103.20, 103.26, 151.16, 151.17, 151.25; **IR** (ef) 2986, 2942, 2888, 1614, 1455, 1380, 1354, 1303, 1248, 1206, 1144, 1005, 900  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 415 ( $\text{M} + \text{H}$ , 100), 371(8); **HRMS** Calcd. for  $\text{C}_{24}\text{H}_{31}\text{O}_6$  ( $\text{M} + \text{H}$ ); 415.2115. Found; 415.2109.

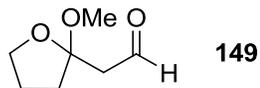
**5.3.5 *tert*-Butyl 2-(2-methoxytetrahydrofuran-2-yl)acetate [1,1-dimethylethyl tetrahydro-2-methoxy-2-furanacetate] (169)<sup>55</sup>**



To a solution of *N,N'*-diisopropylamine (4.0 mL, 27 mmol) in tetrahydrofuran at -78 °C was added a solution of *n*-butyllithium (10.4 mL, 2.5 M in hexanes, 26 mmol). The solution was stirred at 0 °C for 1 h, and was then cooled to -78 °C. A solution of *tert*-butylacetate (3.6 mL, 27 mmol) in tetrahydrofuran (8 mL) was then added dropwise and the resultant mixture was stirred at -78 °C for 2 h. A solution of  $\gamma$ -butyrolactone (2.0 mL, 26 mmol) in tetrahydrofuran (12 mL) was then added dropwise and the reaction mixture was allowed to warm to -30 °C and was then stirred for 2 h. A saturated aqueous solution of ammonium chloride (80 mL) was then added and the reaction mixture was

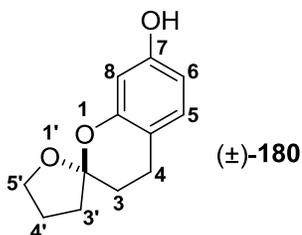
extracted with ether (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue (7.2 g) was then dissolved in methanol (200 mL) and Dowex-H<sup>+</sup> (1.02 g) was added. The resultant mixture was stirred at room temperature for 12 h, and then filtered through a plug of celite. The filter-cake was washed with methanol (2 x 50 mL) and the filtrates were then concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (3:7) as the eluant to afford the *title compound* **169** (3.49 g, 66% over two steps) as a colourless oil. **R<sub>f</sub>** = 0.31, ether:hexanes (3:7); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.41 (3H, s, 3 x CH<sub>3</sub>), 1.81-1.93 (1H, m, CHH), 1.98-2.08 (3H, m, CHH + CH<sub>2</sub>), 2.47 (1H, d, *J* = 13.9 Hz, CCHHCO<sub>2</sub>*t*-Bu), 2.85 (1H, d, *J* = 13.9 Hz, CCHHCO<sub>2</sub>*t*-Bu), 3.20 (3H, s, OCH<sub>3</sub>), 3.78-3.89 (2H, m, OCH<sub>2</sub>); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  24.3, 28.0, 36.5, 41.4, 48.6, 67.6, 80.6, 107.0, 169.0; **IR** (ef) 2981, 2876, 1737, 1481, 1370, 1215, 1145, 1048, 930 cm<sup>-1</sup>; **MS** (CI) *m/z* (rel. intensity) 185 (18), 129 (100), 111 (49), 57 (19); **HRMS** Calcd. for C<sub>11</sub>H<sub>20</sub>NaO<sub>4</sub> (M + Na); 239.1254. Found; 239.1247.

**5.3.6 (2-Methoxy-tetrahydrofuran-2-yl)acetaldehyde [tetrahydro-2-methoxy-2-furanacetaldehyde] (149)<sup>55</sup>**



To a solution of the ester **169** (102 mg, 0.47 mmol) in ether (4 mL) was added diisobutylaluminum hydride (1 mL, 1 M in dichloromethane, 1.0 mmol) dropwise at -78 °C. The reaction mixture was stirred for 1.5 h and then a saturated aqueous solution of Rochelle's salt (6 mL) was added. The resultant suspension was allowed to warm to room temperature and was stirred for 1 h. The reaction mixture was then extracted with ether (3 x 10 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. This material proved extremely unstable to purification (kugelrohr distillation or flash chromatography on silica gel) and to storage. Thus, the crude *title compound* **149** was used immediately in subsequent experiments.  $R_f = 0.47$ , ether:hexanes (1:1).

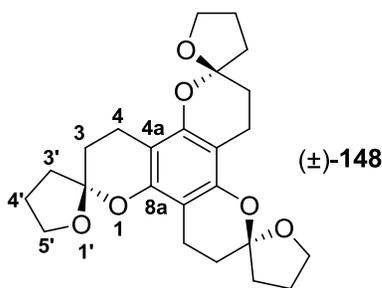
**5.3.7 (RS)-3,4-Dihydrospiro[1-benzopyran-2,2'-oxolane]-7-ol [(±)-180]**



To a suspension of resorcinol (**179**) (53 mg, 0.48 mmol) and Dowex-H<sup>+</sup> (10 mg) in methanol (8 mL) was added a solution of the aldehyde **149** [prepared from the corresponding ester **169** (100 mg, 0.46 mmol)] in methanol (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 16 h and was then filtered through a plug of celite. The filter-cake was washed with methanol (2 x 10 mL) and the combined filtrates were

concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (1:1) as the eluant to afford the *title compound* ( $\pm$ )-**180** (27 mg, 29%) as a colourless oil.  $R_f = 0.44$ , ether:hexanes (1:1);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  1.79-1.93 (1H, m, 3'-CHH), 1.93-2.09 (3H, m, 3-CH<sub>2</sub> + 4'-CHH), 2.14-2.36 (2H, m, 3'-CHH + 4'-CHH), 2.67 (1H, dt,  $J = 16.0, 5.0$  Hz, 4-CHH), 2.90-3.02 (1H, m, 4-CHH), 3.91-4.03 (1H, m, 5'-CHH), 4.05-4.14 (1H, m, 5'-CHH), 4.86 (1H, s, OH), 6.27 (1H, d,  $J = 2.6$  Hz, 8-ArH), 6.35 (1H, dd,  $J = 8.2, 2.6$  Hz, 6-ArH), 6.91 (1H, d,  $J = 8.2$  Hz, 5-ArH);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  22.2, 24.1, 30.1, 37.0, 68.3, 103.9, 106.9, 108.1, 114.1, 129.9, 153.8, 155.0; **IR** (ef) 3378, 2956, 2895, 1625, 1596, 1459, 1297, 1241, 1225, 1154, 1133, 1083, 1024, 993  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 207 (M + H, 71), 189 (8), 97 (100); **HRMS** Calcd. for  $\text{C}_{12}\text{H}_{14}\text{NaO}_3$  (M + Na); 229.0835. Found; 229.0838.

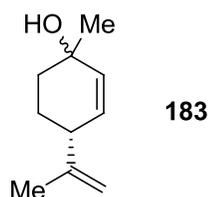
### 5.3.8 (*RS*)-*tris*-Benzannulated-[5,6]-spiroacetal [( $\pm$ )-**148**]



A solution of the aldehyde **149** [prepared from the corresponding ester **169** {4 x (100 mg, 0.46 mmol)} in four separate reactions] in methanol (4 mL) was added dropwise to a suspension of phloroglucinol (**9**) (51 mg, 0.40 mmol) and Dowex-H<sup>+</sup> (60 mg) in methanol (4 mL) at 0 °C. The reaction mixture was stirred for 16 h at 0 °C and then filtered through a plug of celite. The filter-cake was washed with methanol (2 x 10 mL) and the combined filtrates were concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (1:1) as the eluant to afford the

*title compound* ( $\pm$ )-**148** (10 mg, 6%) as a colourless oil.  $R_f = 0.28$ , ether:hexanes (1:2);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  1.77-1.86 (3H, m, 3 x 3'-CHH), 1.89-2.03 (9H, m, 3 x 3-CH<sub>2</sub> + 3 x 4'-CHH), 2.09-2.28 (6H, m, 3 x 3'-CHH + 3 x 4'-CHH), 2.58-2.73 (6H, m, 3 x 4-CH<sub>2</sub>), 3.91-4.00 (3H, m, 3 x 5'-CHH), 4.00-4.10 (3H, m, 3 x 5'-CHH);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  17.20, 17.23, 17.35, 24.12, 24.14, 24.21, 29.53, 29.57, 29.61, 36.70, 36.87, 68.08, 68.18, 68.21, 102.09, 102.14, 102.18, 106.59, 106.68, 106.81, 149.01, 149.08, 149.12; **IR** (ef) 2952, 2880, 1617, 1459, 1354, 1306, 1250, 1138, 1105, 1082, 1023, 944, 910, 868  $\text{cm}^{-1}$ ; **MS** (ESI-MS)  $m/z$  (rel. intensity) 415 (M + H, 100), 331 (8); **HRMS** Calcd. for  $\text{C}_{24}\text{H}_{31}\text{O}_6$  (M + H); 415.2115. Found; 415.2102.

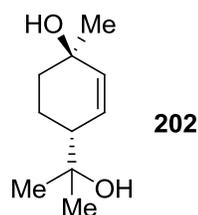
### 5.3.9 (+)-*p*-Mentha-2,8-dien-1-ol (**183**)<sup>64</sup>



To a solution of diphenyldiselenide (5.5 mL, 18 mmol) in ethanol (17 mL) was added sodium borohydride (1.32 g, 34.9 mmol) in small portions over 5 min at room temperature. The resultant suspension was stirred for 20 min (until colourless), and then a solution of (+)-limonene oxide (2.7 mL, 17 mmol, a mixture of *cis*- and *trans*- isomers) in ethanol (6.5 mL) was added dropwise. The reaction mixture was stirred at reflux for 2 h and was then allowed to cool to room temperature. An aqueous solution of hydrochloric acid (30 mL, 1 M) was then added and the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was

dissolved in tetrahydrofuran (200 mL), and hydrogen peroxide (17 mL, 30% *w/w*) was added dropwise at 0 °C. The resultant mixture was stirred at reflux for 2 h, and then left at room temperature for 16 h. Water (100 mL) was then added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (200 mL), brine (200 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ethyl acetate:hexanes (2:3) as the eluant to afford the *title compound* **183** (1.33 g, 53%) as a colourless liquid.  $R_f = 0.34$ , ether:hexanes (1:1);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  1.29 (3H, s,  $\text{CH}_3$ ), 1.51-1.58 (1H, m,  $\text{HOCCH}_2\text{CHH}$ ), 1.62-1.68 (1H, m,  $\text{HOCCHH}$ ), 1.73 (3H, s,  $\text{CH}_3$ ), 1.76-1.81 (1H, m,  $\text{HOCCH}_2\text{CHH}$ ), 1.86-1.92 (1H, m,  $\text{HOCCHH}$ ), 2.73 (1H, m,  $\text{HOCCH}_2\text{CH}_2\text{CH}$ ), 4.66 (1H, m,  $\text{CHCCHH}$ ), 4.78 (1H, m,  $\text{CHCCHH}$ ), 5.64 (1H, ddd,  $J = 10.1, 2.1, 1.2$  Hz,  $\text{HOCCH}$ ), 5.70 (1H, ddd,  $J = 10.1, 2.2, 0.9$  Hz,  $\text{HOCCHCH}$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0, 25.0, 29.5, 36.8, 43.6, 67.6, 110.7, 132.3, 134.1, 148.3;  $\text{IR}$  (neat) 3371, 2967, 2936, 2866, 1717, 1644, 1451, 1372, 1198, 1106, 1008, 951, 907, 889  $\text{cm}^{-1}$ ;  $\text{MS}$  (CI)  $m/z$  (rel. intensity) 153 ( $\text{M} + \text{H}$ , 7), 135 (100);  $\text{HRMS}$  Calcd. for  $\text{C}_{10}\text{H}_{17}\text{O}$  ( $\text{M} + \text{H}$ ); 153.1274. Found; 153.1271.

### 5.3.10 (+)-*p*-Menth-2-ene-1,8-diol (**202**)<sup>68</sup>

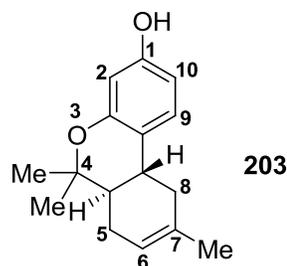


To a stirred suspension of potassium *tert*-butoxide (7.3 g, 65 mmol) in dimethylsulfoxide (17 mL, 240 mmol) was added 3-carene (**198**) (23 mL, 150 mmol). The reaction mixture was stirred at 100 °C for 12 h and was then allowed to cool to room

temperature. Water (17 mL) was then added dropwise and the reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was filtered through a short pad of silica gel using hexanes:ethyl acetate (9:1) as the eluant to afford a crude mixture of 2- and 3-carene (**199** and **198**, respectively) [19.3 g, ~3:2 (by crude NMR)]. A solution of this mixture in dichloromethane (26 mL) was then added to a solution of sodium bicarbonate (34.9 g, 415 mmol) in water (97 mL) at ~10 °C. Peracetic acid (42 mL, 32 wt.% in dilute acetic acid) was then added over 6 h, and the resultant mixture was stirred at ~10 °C for 1 h. An aqueous solution of sodium thiosulfate (35 mL, 15 % w/v) was then added dropwise and the reaction mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (200 mL) and water (2 x 200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was diluted with ethyl acetate (200 mL) and an aqueous solution of acetic acid (2.1 M, 7.0 mL) was then added dropwise at ~10 °C. The reaction mixture was stirred for 23 h at ~10 °C and then concentrated *in vacuo*. The crude residue was diluted with ethyl acetate (100 mL) and then concentrated *in vacuo* to approximately half the original volume (~50 mL). The solution was then cooled to ~10 °C and heptane was slowly added until crystal formation was observed. The slurry was then left in a freezer (-20 °C) for 24 h. The resultant crystals were collected by filtration, washed with a cold mixture of heptane:ethyl acetate (3:1, 3 x 30 mL) and dried *in vacuo* to afford the *title compound* **202** (5.06 g, 20% over three steps) as a white crystalline solid.  $R_f = 0.25$ , ethyl acetate:hexanes (4:1); **M.p.** 112-114 °C, heptanes:ethyl acetate [lit.<sup>68</sup> 115 °C];  $^1\text{H}$

**NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.16 (3H, s, CH<sub>3</sub>), 1.21 (3H, s, CH<sub>3</sub>), 1.28 (3H, s, CH<sub>3</sub>), 1.36-1.45 (1H, m, HOCCH<sub>2</sub>CHH), 1.65 (1H, apparent td,  $J = 12.9, 3.0$  Hz, HOCCHHCH<sub>2</sub>), 1.81-1.90 (1H, m, HOCCH<sub>2</sub>CHH), 1.90-1.99 (1H, m, HOCCHHCH<sub>2</sub>), 2.13-2.20 (1H, m, HOCH<sub>2</sub>CH<sub>2</sub>CH), 5.68-5.78 (2H, apparent AB<sub>q</sub>, HOCCHCH); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  23.1, 26.2, 28.0, 28.4, 38.4, 47.1, 69.6, 72.8, 128.0, 136.7; **IR** (KBr) 3353, 2969, 2935, 1402, 1378, 1365, 1195, 1177, 1144, 1123, 1097, 1006, 980 cm<sup>-1</sup>; **MS** (CI)  $m/z$  (rel. intensity) 153 (14), 135 (22), 95 (100); **HRMS** Calcd. for C<sub>10</sub>H<sub>18</sub>NaO<sub>2</sub> (M + Na); 193.1199. Found; 193.1198.

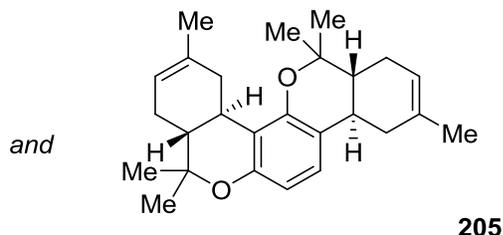
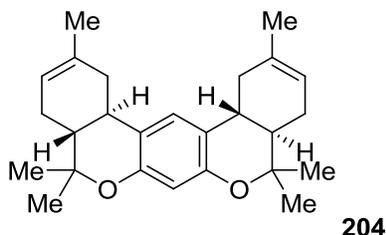
**5.3.11 (4a*R*,8a*R*)-4,4,7-Trimethyl-4a,5,8,8a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol (203)**<sup>70</sup>



To a solution of the diol **202** (141 mg, 0.826 mmol) and resorcinol (**179**) (110 mg, 1.00 mmol) in benzene (15 mL) was added *para*-toluene sulfonic acid monohydrate (16 mg, 0.083 mmol) at room temperature. The reaction mixture was heated at reflux in a Dean-Stark apparatus for 5.5 h, and was then allowed to cool to room temperature. The resultant mixture was diluted with ether (15 mL), and then washed with a saturated aqueous solution of sodium bicarbonate (15 mL), water (15 mL) and brine (15 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the *title compound* **203** (110 mg, 45%) as a yellow solid.  $R_f = 0.31$ , hexanes:ether (2:1); **M.p.** 130-132 °C, chloroform [lit.<sup>70</sup> 137-138 °C]; **<sup>1</sup>H NMR** (500

MHz, CDCl<sub>3</sub>)  $\delta$  1.15 (3H, s, CH<sub>3</sub>), 1.38 (3H, s, CH<sub>3</sub>), 1.64-1.72 (1H, m, 4a-CH), 1.73 (3H, s, CH<sub>3</sub>), 1.75-1.86 (1H, m, 5 or 8-CHH), 1.87-1.98 (1H, m, 5 or 8-CHH), 2.10-2.19 (1H, m, 5-CHH), 2.52-2.70 (2H, m, 8-CHH + 8a-CH), 5.07 (1H, s, OH), 5.46 (1H, d,  $J = 1.9$  Hz, 6-CH), 6.30 (1H, d,  $J = 2.6$  Hz, ArH), 6.40 (1H, dd,  $J = 2.6, 8.4$  Hz, ArH) 7.06 (1H, dd,  $J = 0.8, 8.4$  Hz, ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  19.3, 23.6, 27.6, 27.7, 32.0, 36.9, 43.0, 77.5, 103.9, 107.8, 118.5, 120.1, 127.8, 133.5, 154.1, 155.0; IR (KBr) 3375, 2900, 1622, 1596, 1509, 1443, 1373, 1169, 1108, 1041, 993 cm<sup>-1</sup>; MS (CI)  $m/z$  (rel. intensity) 245 (M + H, 100), 189 (6); HRMS Calcd. for C<sub>16</sub>H<sub>21</sub>O<sub>2</sub> (M + H); 245.1536. Found; 245.1538.

**5.3.12 5,5,9,17,21,21-Hexamethyl-4,22-dioxapentacyclo[12.8.0.0<sup>3,12</sup>.0<sup>6,11</sup>.0<sup>15,20</sup>]docosa-1(14),2,8,12,17-pentaene [(4a*R*,9a*R*,13a*R*,14b*R*)-2,5,5,9,9,12-hexamethyl-1,4,4a,5,9,9a,10,13,13a,14b-decahydrobenzo[*c*]isochromeno[4,3-*g*]chromene] (204) and 5,9,9,17,21,21-hexamethyl-10,22-dioxapentacyclo[12.8.0.0<sup>2,11</sup>.0<sup>3,8</sup>.0<sup>15,20</sup>]docosa-1(14),2(11),5,12,17-pentaene (205)**



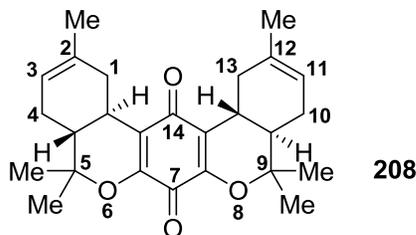
To a stirred solution of the diol **202** (340 mg, 2.00 mmol) and resorcinol (**179**) (50 mg, 0.45 mmol) in benzene (40 mL) at room temperature was added *para*-toluene sulfonic acid monohydrate (38.0 mg, 0.200 mmol). The reaction mixture was heated at reflux in a Dean-Stark apparatus for 5 h and was then allowed to cool to room temperature. The resultant mixture was diluted with ether (40 mL) and washed with a saturated aqueous solution of sodium bicarbonate (40 mL), water (40 mL) and brine (40 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using dichloromethane:hexanes (7:3) as the eluant to afford a mixture (1.7:1) of the *title compounds* **204** (79 mg, 46%) and **205** (47 mg, 27%) as colourless oils.

*Title compound 204*:  $R_f = 0.45$ , dichloromethane:hexanes (7:3);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.14 (6H, s, 2 x  $\text{CH}_3$ ), 1.36 (6H, s, 2 x  $\text{CH}_3$ ), 1.63-1.72 (2H, m, 2 x  $\text{CHCHCCO}$ ), 1.74 (6H, s, 2 x  $\text{CH}_3$ ), 1.79-1.87 (2H, m, 2 x  $\text{CHHCHCHH}$ ), 1.95 (2H, m, 2 x  $\text{CH}_3\text{CCHCH}_2$ ), 2.15 (2H, td,  $J = 5.0, 11.0$  Hz, 2 x  $\text{CHCHCCO}$ ), 2.62 (4H, dd,  $J = 4.5, 15.4$  Hz, 2 x  $\text{CH}_3\text{CCH}_2$ ), 5.45 (2H, d,  $J = 1.8$  Hz, 2 x  $\text{CH}_3\text{CCHCH}_2$ ), 6.24 (1H, s,

ArH), 7.00 (1H, s, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4, 23.7, 27.7, 27.8, 32.2, 37.0, 43.2, 76.9, 104.7, 118.1, 120.2, 124.6, 133.5, 152.5; IR (neat) 2975, 2929, 1625, 1579, 1494, 1579, 1493, 1448, 1384, 1370, 1299, 1216, 1115  $\text{cm}^{-1}$ ; MS (CI)  $m/z$  (rel. intensity) 379 (M + H, 100), 339 (80); HRMS Calcd. for  $\text{C}_{26}\text{H}_{35}\text{O}_2$  (M + H); 379.2632. Found; 379.2640.

*Title compound 205*:  $R_f$  = 0.65, dichlorormethane:hexanes (7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (3H, s,  $\text{CH}_3$ ), 1.11 (3H, s,  $\text{CH}_3$ ), 1.38 (3H, s,  $\text{CH}_3$ ), 1.41 (3H, s,  $\text{CH}_3$ ), 1.70 (3H, s,  $\text{CH}_3$ ), 1.74 (3H, s,  $\text{CH}_3$ ), 2.06-2.22 (3H, m), 2.51-2.76 (3H, m), 5.44-5.45 (2H, m), 6.38 (1H, d,  $J$  = 8.4 Hz), 6.97 (1H, d,  $J$  = 8.5 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.5, 19.6, 23.7, 23.8, 27.6, 27.7, 27.8, 28.2, 32.31, 32.32, 36.2, 37.1, 42.9, 45.4, 76.5, 77.1, 109.2, 114.1, 117.1, 119.2, 120.0, 125.1, 133.8, 135.6, 152.4, 152.9; IR (neat) 2973, 1738, 1609, 1587, 1481, 1443, 1383, 1370, 1263, 1189, 1109, 1090, 1038  $\text{cm}^{-1}$ ; MS (CI)  $m/z$  (rel. intensity) 379 (M + H, 100), 339 (18); HRMS Calcd. for  $\text{C}_{26}\text{H}_{35}\text{O}_2$  (M + H); 379.2632. Found; 379.2637.

### 5.3.13 (4a*R*,9a*R*,13a*R*,14b*R*)-2,5,5,9,9,12-Hexamethyl-1,4a,5,9a,10,13,13a,14b-octahydrobenzo[*c*]isochromeno[4,3-*g*]chromene-7,14(4*H*,9*H*)-dione (**208**)

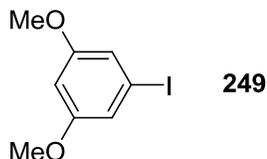


To a stirred solution of the diol **202** (440 mg, 2.60 mmol) and phloroglucinol (**9**) (82 mg, 0.65 mmol) in benzene (30 mL) at room temperature was added *para*-toluene sulfonic acid monohydrate (50 mg, 0.26 mmol). The reaction mixture was heated at

reflux in a Dean-Stark apparatus for 5 h and was then allowed to cool to room temperature. The resultant mixture was diluted with ether (30 mL), and then washed with a saturated aqueous solution of sodium bicarbonate (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using hexanes:ethyl acetate (8:1) as the eluant to afford the *title compound* **208** (128 mg, 48%) as a bright yellow amorphous solid.  $R_f = 0.29$ , hexanes:ethyl acetate (8:1); **M.p.** 105-108 °C, hexanes:ethyl acetate;  $[\alpha]_D^{20} = -908.5$  (*c* 1.0, chloroform); **UV-Vis**  $\lambda_{\max}$  (chloroform) 305 ( $\epsilon = 14497$ ), 418 ( $\epsilon = 408$ ) nm; **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  1.13 (6H, s, 2 x CH<sub>3</sub>), 1.45 (6H, s, 2 x CH<sub>3</sub>), 1.61-1.66 (2H, m, 2 x 4a-CH), 1.67 (6H, s, 2 x CH<sub>3</sub>), 1.79 (4H, m, 2 x 1-CHH + 2 x 4-CHH), 2.09 (2H, d, *J* = 14.6 Hz, 2 x 4-CHH), 2.46 (2H, td, *J* = 5.0, 11.0 Hz, 2 x 14b-CH), 3.08 (2H, dd, *J* = 4.5, 15.4 Hz, 2 x 1-CHH), 5.38 (2H, d, *J* = 3.7 Hz, 2 x 3-CH); **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>)  $\delta$  18.6, 23.4, 27.0, 27.5, 31.1, 36.5, 44.6, 80.7, 119.0, 120.7, 134.7, 150.9, 177.6, 187.3; **IR** (KBr) 2983, 1690, 1631, 1590, 1227, 1192, 1162, 1112, 1071, 1054 cm<sup>-1</sup>; **MS** (CI) *m/z* (rel. intensity) 409 (M + H, 100); **HRMS** Calcd. for C<sub>26</sub>H<sub>33</sub>O<sub>4</sub> (M + H); 409.2373. Found; 409.2363.

## 5.4 Experimental Procedures and Characterization Data Concerning Chapter 4

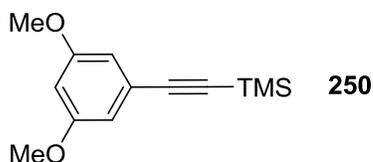
### 5.4.1 3,5-Dimethoxyiodobenzene (**249**)<sup>99</sup>



A solution of sodium nitrite (2.44 g, 35.4 mmol) in water (20 mL) was added dropwise to a suspension of 3,5-dimethoxyaniline (**248**) (4.53 g, 29.5 mmol) in aqueous

hydrochloric acid (15% v/v, 20 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and then a solution of potassium iodide (5.95 g, 35.8 mmol) in water (20 mL) was added dropwise. The mixture was stirred at room temperature for 16 hours and was then extracted with ether (3 x 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bisulfite (100 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using dichloromethane:petroleum ether (3:7) as the eluant to afford the *title compound* **249** (4.31 g, 55%) as a white solid.  $R_f = 0.51$ , ether:hexanes (1:1); **M.p.** 67-69 °C, chloroform (lit.<sup>109</sup> 72-74.5 °C); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.76 (6H, s, 2 x CH<sub>3</sub>), 6.40 (1H, t,  $J = 2.2$  Hz, ArH), 6.86 (2H, d,  $J = 2.2$  Hz, 2 x ArH); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  55.6, 94.2, 100.8, 115.9, 161.2; **IR** (KBr) 3069, 2948, 2823, 1709, 1584, 1469, 1415, 1295, 1197, 1160, 1016, 938, 854 cm<sup>-1</sup>; **MS** (CI)  $m/z$  (rel. intensity) 265 (M + H, 100), 138 (8); **HRMS** Calcd. for C<sub>8</sub>H<sub>10</sub>IO<sub>2</sub> (M + H); 264.9720. Found; 264.9722.

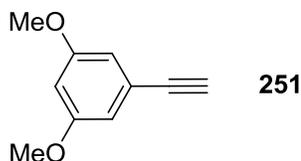
#### 5.4.2 1-(3,5-Dimethoxyphenyl)-2-trimethylsilylacetylene (**250**)<sup>99</sup>



To a solution of 3,5-dimethoxyiodobenzene (**249**) (4.01 g, 15.2 mmol) in triethylamine (125 mL) was added *bis*(triphenylphosphine)palladium(II) dichloride (526 mg, 0.75 mmol), copper iodide (114 mg, 0.60 mmol), and triphenylphosphine (79 mg, 0.30 mmol) at room temperature. The resultant mixture was stirred for 15 min and then trimethylsilylacetylene (2.4 mL, 17.4 mmol) was added. The reaction mixture was stirred at 50 °C for 2 days and then was concentrated *in vacuo*. The crude residue was purified

by flash chromatography using dichloromethane:petroleum ether (3:7) as the eluant to afford the *title compound* **250** as a white solid.  $R_f = 0.4$ , ether:hexanes (4:1); **M.p.** 54-55 °C, dichloromethane;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.27 (9H, s, 3 x  $\text{CH}_3$ ), 3.76 (6H, s, 2 x  $\text{CH}_3$ ), 6.44 (1H, t,  $J = 2.3$  Hz, ArH), 6.63 (2H, d,  $J = 2.3$  Hz, 2 x ArH);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03, 55.4, 93.7, 102.3, 105.2, 109.7, 124.4, 160.5; **IR** (KBr) 3091, 3065, 2952, 2837, 2165, 2142, 1956, 1601, 1455, 1420, 1325, 1257, 1195, 1154, 1063, 979  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 235 (M + H, 100); **HRMS** Calcd. for  $\text{C}_{13}\text{H}_{19}\text{O}_2\text{Si}$  (M + H); 235.1149. Found; 235.1144.

#### 5.4.3 3,5-Dimethoxy-1-phenylacetylene (**251**)<sup>99</sup>



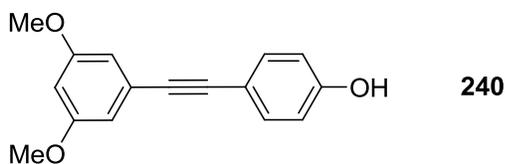
**Method A:** A solution of tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 5.0 mL) was added to a solution of 1-(3,5-dimethoxyphenyl)-2-trimethylsilylacetylene (**250**) (3.26 g, 13.9 mmol) in tetrahydrofuran (75 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min and then filtered through a short pad of silica gel to afford the *title compound* **251** (2.07 g, 92 %) as a white crystalline solid.

**Method B:** To a solution of 1-(3,5-dimethoxyphenyl)-2-trimethylsilylacetylene (**250**) (3.10 g, 13.2 mmol) in methanol (150 mL) was added potassium carbonate (2.10 g, 15.2 mmol). The reaction mixture was stirred at room temperature for 24 h and was then concentrated *in vacuo*, diluted with water (100 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate

and concentrated *in vacuo*. The crude residue was purified by flash chromatography using dichloromethane:hexanes (1:1) as the eluant to afford the *title compound* **251** (1.86 g, 87%) as a white crystalline solid.

*Title compound 251*:  $R_f$  = 0.54, ether:hexanes (1:1); **M.p.** 41-42 °C, chloroform (lit.<sup>110</sup> 44-46 °C);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.10 (1H, s, CCH), 3.74 (6H, s, 2 x  $\text{CH}_3$ ), 6.46 (1H, t,  $J$  = 2.4 Hz, ArH), 6.65 (2H, d,  $J$  = 2.4 Hz, 2 x ArH);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  55.5, 76.9, 83.7, 102.3, 110.0, 123.5, 160.6; **IR** (KBr) 3289, 2960, 2838, 2155, 1598, 1457, 1420, 1346, 1322, 1297, 1251, 1206, 1065  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 163 (M + H, 100); **HRMS** Calcd. for  $\text{C}_{10}\text{H}_{11}\text{O}_2$  (M + H); 163.0754. Found; 163.0748.

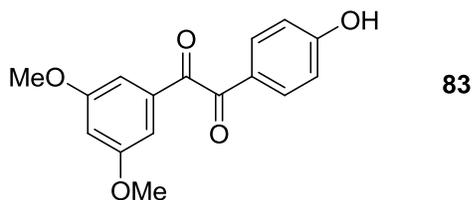
#### 5.4.4 4-[(3,5-Dimethoxyphenyl)ethynyl]phenol (**240**)



To a solution of 4-iodophenol (**252**) (1.60 g, 7.30 mmol) in triethylamine (100 mL) was added *bis*(triphenylphosphine)palladium(II) dichloride (252 mg, 0.360 mmol), copper iodide (55 mg, 0.290 mmol) and triphenylphosphine (38 mg, 0.150 mmol) at room temperature. The resultant mixture was stirred at room temperature for 20 min and then a solution of 3,5-dimethoxy-1-phenylacetylene (**251**) (1.40 g, 8.60 mmol) in triethylamine (100 mL) was added. The reaction mixture was stirred at 70 °C for 2 days and was then allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (3:2) as the eluant to afford the *title compound* **240** (1.55 g, 85%) as a red solid.  $R_f$  = 0.31, ether:hexanes

(3:2); **M.p.** 105-107 °C, chloroform; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.80 (6H, s, 2 x OCH<sub>3</sub>), 5.88 (1H, br, OH), 6.48 (1H, t, *J* = 2.3 Hz, ArH), 6.72 (2H, d, *J* = 2.3 Hz, 2 x ArH), 6.82 (2H, d, *J* = 8.8 Hz, 2 x ArH), 7.43 (2H, d, *J* = 8.8 Hz, 2 x ArH); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 55.6, 88.1, 89.2, 101.7, 109.4, 115.2, 115.7, 125.0, 133.4, 156.1, 160.4; **IR** (KBr) 3408, 3004, 2938, 2840, 2210, 1595, 1513, 1453, 1421, 1357, 1347, 1255, 1205, 1156, 1063, 834 cm<sup>-1</sup>; **MS** (CI) *m/z* (rel. intensity) 255 (M + H, 100); **HRMS** Calcd. for C<sub>16</sub>H<sub>15</sub>O<sub>3</sub> (M + H); 255.1016. Found; 255.1022.

#### 5.4.5 3,5-Dimethoxy-4'-hydroxybenzil (83)



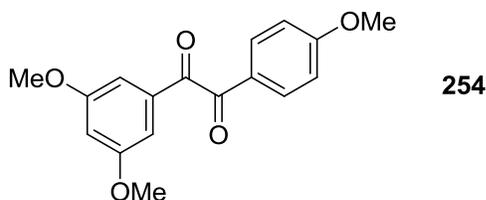
**Method A:** To a solution of 4-[(3,5-dimethoxyphenyl)ethynyl]phenol (**240**) (3.35 g, 13.2 mmol) in dimethylsulfoxide (150 mL) was added palladium (II) chloride (235 mg, 1.33 mmol). The reaction mixture was stirred at 140 °C for 48 h and was then allowed to cool to room temperature. The mixture was diluted with water (300 mL) and then extracted with ether (3 x 100 mL). The combined organic extracts were washed with water (300 mL) and brine (300 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (3:1) as the eluant to afford the *title compound* **83** (2.25 g, 60%) as an orange powder.

**Method B:** To a solution of 4-[(3,5-dimethoxyphenyl)ethynyl]phenol (**242**) (136 mg, 0.530 mmol) in dimethylsulfoxide (50 mL) was added iodine (149 mg, 0.590 mmol).

The reaction mixture was stirred at 140 °C for 48 h and was then allowed to cool to room temperature. The mixture was diluted with an aqueous solution of sodium thiosulfate (1% w/v, 100 mL) and then extracted with ether (3 x 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (3:1) as the eluant to afford the *title compound 83* (82 mg, 54%) as an orange powder.

*Title compound 83*:  $R_f = 0.31$ , ether:hexanes (3:1); **M.p.** 142-146 °C, chloroform;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.81 (6H, s, 2 x  $\text{CH}_3$ ), 5.99 (1H, br, OH), 6.72 (1H, t,  $J = 2.3$  Hz, ArH), 6.90 (2H, d,  $J = 8.8$  Hz, 2 x ArH), 7.08 (2H, d,  $J = 2.3$  Hz, 2 x ArH), 7.86 (2H, d,  $J = 8.8$  Hz, 2 x ArH);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  55.9, 107.6, 107.7, 116.1, 126.3, 132.9, 135.0, 161.2, 161.8, 193.2, 195.0; **IR** (KBr) 3358, 2936, 2841, 1679, 1607, 1515, 1469, 1065, 1039, 923  $\text{cm}^{-1}$ ; **MS** (CI)  $m/z$  (rel. intensity) 287 (M + H, 63), 255 (2), 165 (100), 121 (3); **HRMS** Calcd. for  $\text{C}_{16}\text{H}_{15}\text{O}_5$  (M + H); 287.0914. Found; 287.0919.

#### 5.4.6 3,4',5-Trimethoxybenzil (254)



To solution of the dione **83** (521 mg, 1.82 mmol) in acetone (20 mL) was added potassium carbonate (1.26 g, 9.10 mmol) and methyl iodide (2.3 mL, 36.9 mmol) at room temperature. The reaction mixture was stirred at reflux for 1 h and was then allowed to

cool to room temperature. The mixture was diluted with water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography using ether:hexanes (4:1) as the eluant to afford the *title compound* **254** (512 mg, 94%) as a bright yellow solid. **R<sub>f</sub>** = 0.48, ether:hexanes (3:1); **M.p.** 92-93 °C (ether:hexanes); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 3.81 (6H, s, 2 x CH<sub>3</sub>), 3.88 (3H, s, CH<sub>3</sub>), 6.71 (1H, t, *J* = 2.3 Hz, ArH), 6.96 (2H, d, *J* = 9.0 Hz, 2 x ArH), 7.08 (2H, d, *J* = 2.3 Hz, 2 x ArH), 7.92 (2H, d, *J* = 8.9 Hz, 2 x ArH); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 55.78, 55.79, 107.49, 107.54, 114.5, 126.2, 132.5, 135.1, 161.2, 165.1, 193.1, 194.8; **IR** (KBr) 3014, 8936, 2841, 1669, 1590, 1513, 1466, 1425, 1314, 1284, 1210, 1160, 1039, 1024, 925 cm<sup>-1</sup>; **MS** (CI) *m/z* (rel. intensity) 301 (M + H, 100), 165 (87), 135 (4); **HRMS** Calcd. for C<sub>17</sub>H<sub>17</sub>O<sub>5</sub> (M + H); 301.1071. Found; 301.1073.

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