The application of organocatalytic Asymmetric Epoxidation

By

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Doctoral Thesis

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requirements for the award of Doctor of Philosophy

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Department of Chemistry

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Abstract

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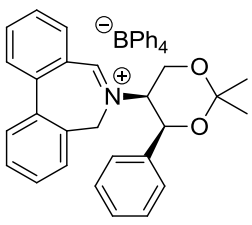
In the field of research of target natural product synthesis, catalytic asymmetric synthesis has become a vital tool to obtain enantiomerically pure compounds, and is often used in the synthesis of natural products as a key step.[1] For example, the asymmetric dihydroxylation was used in synthesis of gibberellic acid (GA_3)[2] by E. J. Corey, who was awarded the Nobel Prize for his developments in the theory and methodology of organic synthesis.[2]

This thesis is based on an ongoing research in the area of catalytic asymmetric synthesis that has been carried out in our group. Since 2005, metal-free catalytic asymmetric epoxidation using iminium salts such as **1** has been successfully employed to access chiral chromenes within the Page group. Iminium-catalysed asymmetric epoxidation methodology has been applied to the synthesis of levcromakalim, [3] *trans*-khellactone, and lomatin,[4] which are based on a chromene-type structure. In this thesis, we offer a detailed discussion on the influence of iminium salts on flav-3-ene derivatives and their stability under oxidative conditions. We were also able to successfully apply our methodology towards the enantioselective total synthesis of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **2**. The key epoxidation step proceeded in 70.4% ee and high yield, using chiral iminium salt catalyst **1** under aqueous conditions. The acid-catalysed epoxide ring-opening of epoxide **4** afforded *trans*-diol **3** in high yield.



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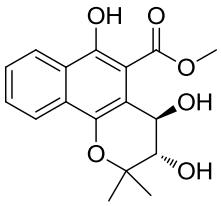

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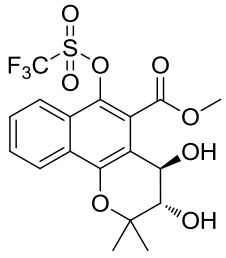

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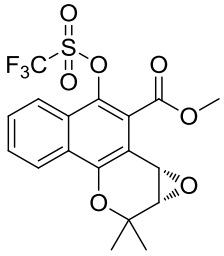

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[1] Koskinen, A. *Asymmetric Synthesis of Natural Products*,Chichester: John Wiley & Sons Ltd, Hampshire, **1995**. [2]Nicolaou. K. C.; Sorensen. J. E. *Classics In Total Synthesis*, Wiley-VCH, New York, **2008**.[3] Page, P. C. B.; Appleby, L. F.; Day, D. P.; Chan, Y.; Buckley, B. R.; Allin, S. M.; McKenzie, M. J. *Org. Lett.* **2009**, *11*, 1991.[4] Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375.

To my mother, wife and my daughters with all my love and respect

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Abbreviations

Ac	acetyl
Aq.	aqueous
Ar	aromatic
$[\alpha]_D$	Specific optical rotation at the sodium D Line
aq.	aqueous
Bn	benzyl
***n*-Bu**	normal butyl
***t*-Bu**	*tert*-butyl
***t*-BuOH**	*tert*-butanol
conc.	Concentrated
°C	degrees Celsius
cat.	catalyst (catalytic amount)
cm^{-1}	Wavenumber
CSA	camphorsulfonic acid
Δ	chemical shift
DCM	dichloromethane
DET	diethyl tartrate
DIAD	Diisopropyl azodicarboxylate
DMP	2,2-dimethoxypropane
DMSO-d_6	dimethylsulfoxide (deuteriated)
DMF	*N*,*N*-dimethylformamide
equiv.	equivalent(s)
ee	enantiomeric excess
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
h	hour(s)
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	infra-red
J	coupling constant
LDA	lithium diisopropylamide

LG	leaving group
M	molar
***m*-**	meta
***m*-CPBA**	meta-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
MHz	megahertz
mmol	millimole(s)
ml	millilitre(s)
min.	minutes
m.p.	melting point
m/z	mass to charge ratio
NaH	Sodium hydride
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
***P*-**	para
PCC	Pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
***i*-PrOH**	isopropanol
Ph_3P	triphenyl phosphine
***P*-TSA**	p-Toluenesulfonic acid
RT	room temperature
R	undefined group
SM	starting material
S_N2	nucleophilic substitution second order
S_N1	nucleophilic substitution first order
TEA	triethylamine
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TPPP	tetraphenylphosphonium monoperoxysulfate

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Chapter Two

Chapter Three

1.0 Introduction

1.1 Metabolism

Metabolism may be defined as the set of chemical reactions that occur in living organisms to enable all organisms to "live, grow and reproduce" by transforming and interconnecting a vast number of organic compounds. [1] Metabolism involves two processes: the process of building up protoplasm is called anabolism; for example, proteins are generated from amino acids: whilst breaking it down is called catabolism; for instance carbohydrates are broken down into sugar units.[1] Furthermore, plant physiologists separate metabolism into two categories: primary metabolism and secondary metabolism. [1] All organisms possess similar metabolic pathways by which they synthesize and utilise certain essential chemical species: carbohydrates, amino acids, and polymers derived from them (e.g. lipids, and proteins). [1] This is known as primary metabolism, and is essential for their survival and growth. In contrast to the compounds that are formed in primary metabolic pathways (primary metabolites), other organic compounds are not directly involved in the commonplace growth or development of organisms, which are precisely distributed in nature. Additionally they are produced by other metabolic pathways for different purposes than primary physiological functions; these are known as secondary metabolites, and the pathways for their synthesis and utilization constitute secondary metabolism. [1] Many of these secondary metabolites found in plants, animals and micro-organisms possess pharmacological properties. [1] Today many of these secondary metabolites are used to treat mild and serious human afflictions.[1] Aspirin and menthol are two commonly used and widely recognised natural product drugs. [1]

1.2 Some Natural Product Properties

Since the beginning of mankind, the use of natural compounds has continued to grow with the development of chemical methods. Conventional extraction methods of flower and plant essential oils, such as maceration, have been used to isolate compounds whose taste, colour and odour could fulfil various purposes. Healing creams and liquids were derived from plant extracts to prevent and cure diseases, and even reduce pain in all ancient cultures. For instance, *Xylocarpus granatum* Koenig (Meliaceae) used to be a well-known medicine in Southeast Asia for the treatment of diarrhoea, cholera, and fever.[2]

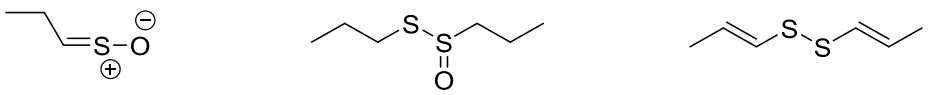
The name of the natural product is usually associated with the plant origin; for example, muscarine is derived from *Amania muscaria* (fly agaric). It can also be defined through the physiological action, as the natural product emetine causes vomiting (emetic). Although some aromatic compounds are very closely related in terms of structure, they can be very different in term of properties, such as taste, odour and colour. For example, strawberries and pineapples possess large amounts of furaneol, in contrast with cloudberries and canned mangoes, where a closely related structure is found (**Figure 1**). [2]

Furaneol
strawberries, pineapples

Methoxyfuraneol
cloudberries and canned mangoes

Figure 1

Also, the structural similarity of compounds issued from onions and their different properties is another illustration: the strong lachrymatory compound issued from enzyme activity, and the aroma compounds of fresh and boiled onions (**Figure 2**).[2]



lachrymatory

fresh onions

boiled onion

Figure 2

1.3 Chirality

Jean-Baptiste Biot conducted the first study of some natural isolates in polarized light in 1815. However, it was not until 1874 that Jacobus van't Hoff first suggested that tetrahedral carbon atoms carrying four different substituents could explain the phenomenon of optical isomers. Chirality is a property of molecules which do not possess any element of symmetry, are non-superimposable on their mirror images and possess a different spatial arrangement with the same constitution. Molecules that are mirror images of each other are termed enantiomers and have identical physical properties (e.g. m.p., NMR spectra and molecular weight, etc.), although each enantiomer rotates the plane of plane polarized light in opposite direction. For example, lemons and oranges share the same limonene enantiomer *R*, which gives a characteristic citrus flavour and odour. Two compounds related to limonene, *R*- and *S*-carvone, smell of spearmint and caraway, respectively (**Figure 3**).[2,3]

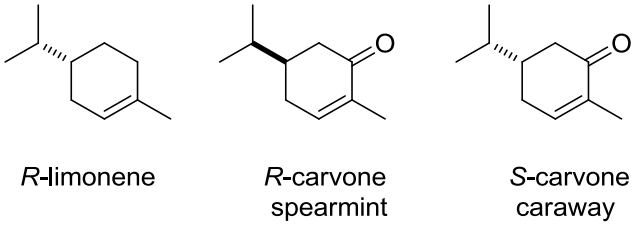
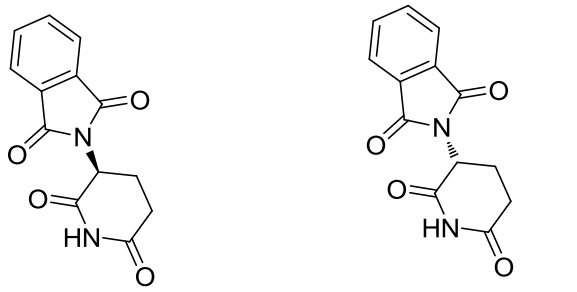


Figure 3: The two enantiomers of carvone and limonene.

As a synthetic chemist, the production of natural products, their derivatives and analogues by synthetic methods in an attempt to secure them in an enantiopure form is a vital element. The most striking example is the drug (±)-thalidomide, which was prescribed to pregnant women for morning sickness during the late 1950s. A dramatic increase of miscarriages and birth defects in mothers who were taking (±)-thalidomide occurred. It was later proven that while (*R*)-thalidomide **1** helped relieve morning sickness and was non-toxic, (*S*)-thalidomide **2** was potently teratogenic and caused severe birth defects (**Figure 4**).[2]



2 (*S*)-Thalidomide **1** (*R*)-Thalidomide

Figure 4: The two enantiomers of thalidomide

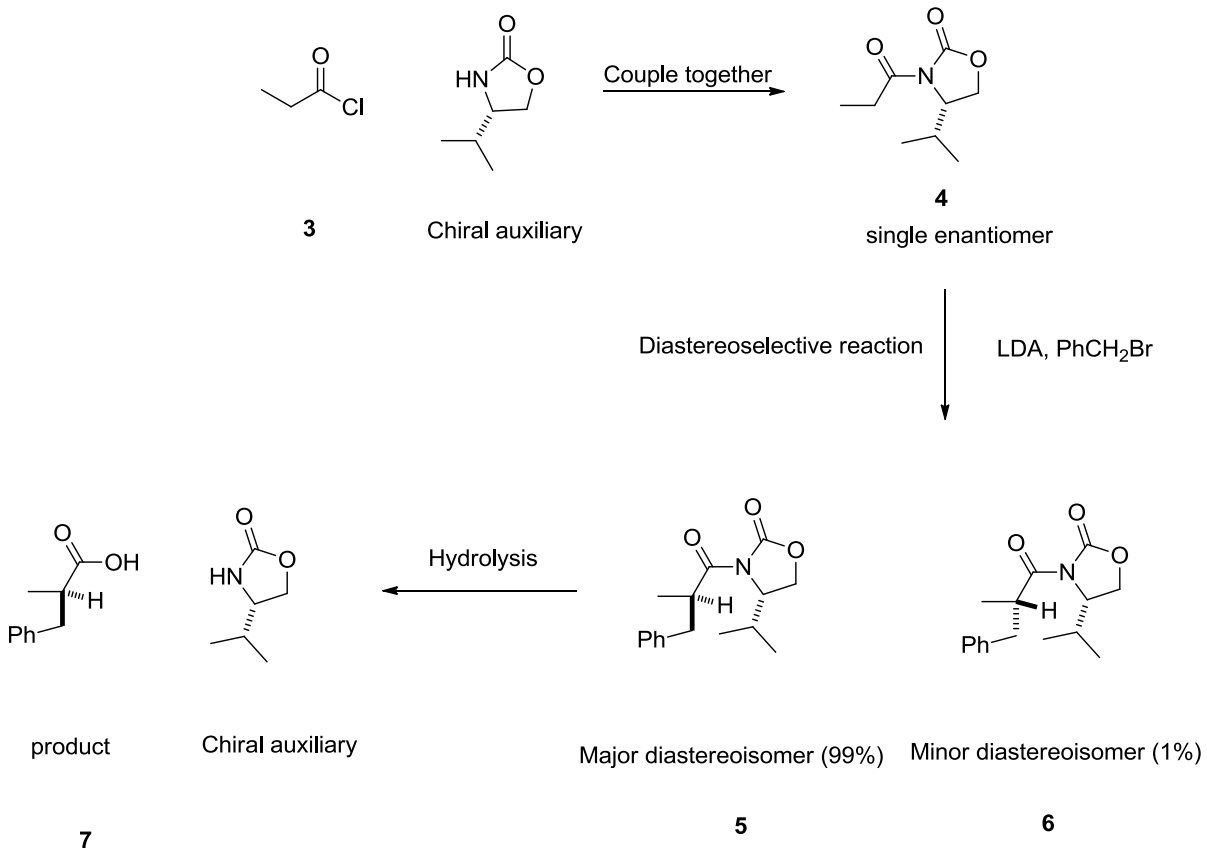
Therefore, as it becomes essential to obtain products in an enantiopure manner, the development of enantioselective techniques and methodologies to preferentially form a single enantiomer (or an enantioenriched mixture) are targeted.

1.4 Asymmetric synthesis

Asymmetric synthesis is defined as a chemical reaction which triggers chiral centres in the product in unequal amounts and thus delivers one of the isomers in excess over the other as a result of the influence of a chiral feature present in the substrate, reagent and/or catalyst. Asymmetric synthesis can also be accomplished using the following methods: chiral auxiliaries, synthesis using compounds from the chiral pool and asymmetric catalysis.[2,3]

1.4.1 Chiral auxiliaries

A chiral auxiliary is an enantiomerically pure compound that binds to a prochiral starting material.[4] Therefore, one single enantiomer is formed to influence the stereochemical outcome of a reaction creating one or more extra stereogenic centres, when the substrate undergoes a diastereoselective reaction. An illustration of the chiral auxiliary process is provided in **Scheme 1**.[4]

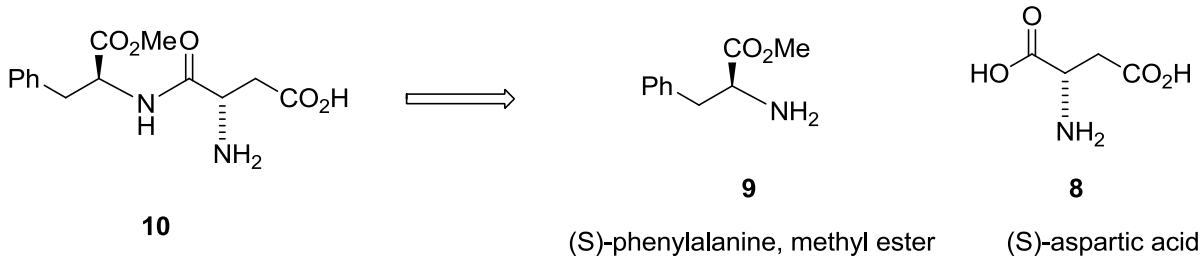


Scheme 1: Use of a chiral auxiliary to control the stereochemistry of **7**

Single enantiomer **4**, formed by the coupling reaction of a chiral auxiliary and **3**, reacts with benzyl bromide in presence of LDA, creating two possible diastereoisomeric products **5** and **6**. Diastereoisomer **5** is then subjected to a hydrolysis reaction which cleaves the enantiomerically enriched product **7** from the chiral auxiliary. [4]

1.4.2 Chiral pool synthesis

The chiral pool synthesis is the most facile approach for asymmetric synthesis. The simplicity of the chiral pool synthesis relies on cheap, and enantiomerically pure starting materials, such as carbohydrates and amino acids.[3] They are incorporated in a reaction without asymmetric induction to meet the chiral requirements of the target molecule. An obvious example of chiral pool synthesis is the preparation of artificial sweetener aspartame **10**. An economical synthetic route to manufacture aspartame is through the condensation reaction of (*S*)-aspartic acid **8** and (*S*)-phenylalanine methyl ester **9** (**Scheme 2**).[3]



Scheme 2: Synthesis of aspartame

1.4.3 Asymmetric catalysis

Asymmetric catalysis involves the generation of new asymmetric centres from prochiral centres in one simple transformation with the help of a chiral catalyst. The most widely used prochiral starting materials are alkenes and carbonyl group-containing substrates. One of the simplest and most effective asymmetric transformations of a prochiral olefin into a chiral product is the epoxidation reaction. Asymmetric epoxidation of olefins is the most direct and effective approach to synthesizing enantio-enriched epoxides, and many research efforts have been devoted to the development of efficient catalysts for this process, such as the Sharpless epoxidation.[2,4]

1.5 Epoxides

An epoxide, also known as oxirane, consists of a three-membered cycle which contains an oxygen atom and two carbon atoms **(Figure 5)**. [3] It is an unstable cyclic ether, because of the high ring strain coming from the 60° angle between the bonds in the three-membered ring.[3]

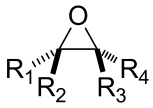
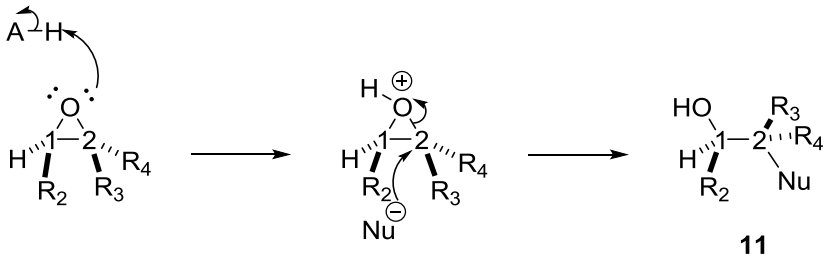
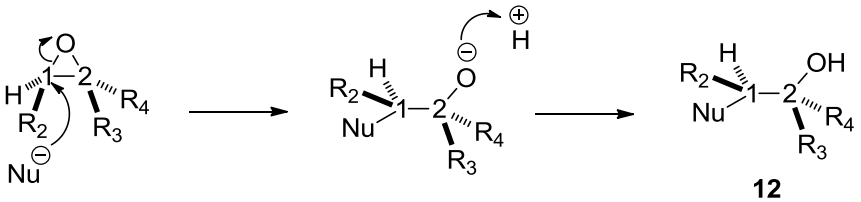


Figure 5. The epoxide.

Due to the strain present in the epoxide ring and the δ+ charge caused on the two carbon atoms by the electronegative oxygen atom, epoxides react as electrophiles; one of the electrophilic carbons attached to the oxygen can be easily targeted with various nucleophiles to relieve the substantial ring strain. This reactivity allows various chemical transformations of an epoxide into many 1,2-difunctionalized products such as **11** and **12**. An example of how either carbon can be targeted by acid or base catalysis is outlined below (**Scheme 3** and **Scheme 4**). [3]

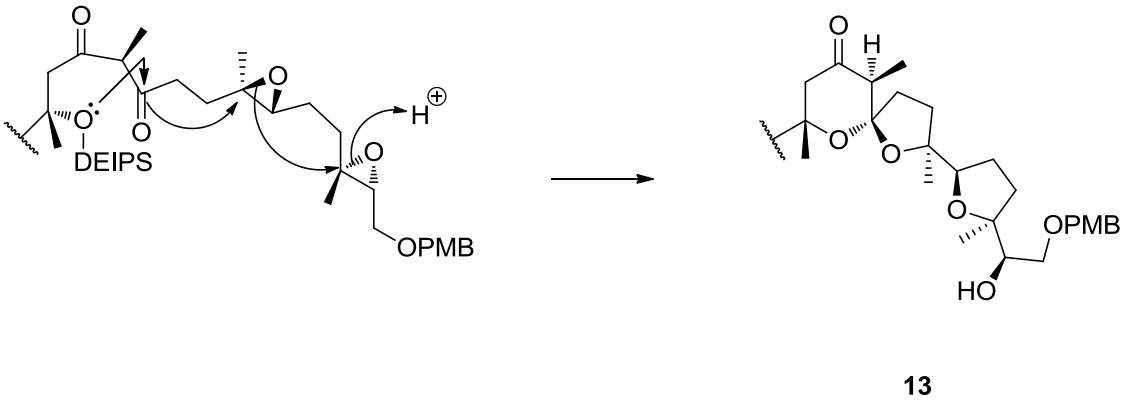


Scheme 3: Acid-catalysed ring opening of an epoxide: the nucleophile attacks the most substituted carbon in the epoxide



Scheme 4: Base-catalysed ring opening of an epoxide: the nucleophile attacks the least substituted carbon in the epoxide.

Indeed, a stereospecific ring-opening reaction in the presence of an acid is a constructive feature of the epoxide moiety and can be used to form complex natural products. For example, Paterson's synthesis of etheromycin made excellent use of an epoxide ring-opening/nucleophilic attack cascade strategy to efficiently construct the polycyclic ether skeleton **13** (**Scheme 5**).[5]



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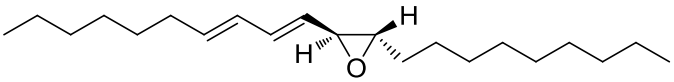
Scheme 5: Paterson's synthesis of etheromycin

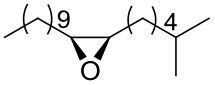
1.6 Epoxides in natural products

To gain a comprehensive picture of the importance of asymmetric epoxidation techniques, we should demonstrate the effect of biological responses from two enantiomers. For instance, (+)-disparlure **14** or (+)-(7*R*,8*S*)-*cis*-7,8-epoxy-2-methyl-octadecane is used as the active compound to lure the male gipsy moth, *Lymantria dispar* (L) into traps and, thus, reduce the growth and copulation of these destructive insects. Similarity, the male tussock moth, Orgyia (walker) responds to the (6*Z*,9*Z*,11*S*,12*S*)-11,12-epoxyhenicosa-6,9-diene *trans*-isomer (posticlure **15**), produced from the wingless females (**Figure 6**).[6,7]



15

posticlure



14

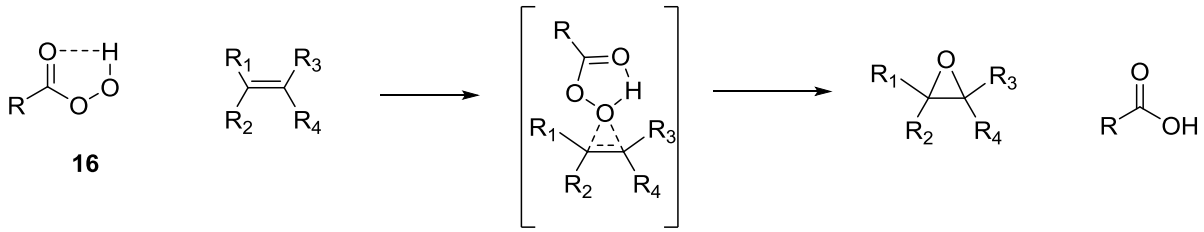
(+)-disparlure

Figure 6: Natural products containing an epoxide functional group: (+)-disparlure **14,** and posticlure **15**

1.7 Epoxidation techniques

1.7.1 Prilezhaev Epoxidation

Peroxycarboxylic acids **16** were recognized as epoxidizing agents of isolated carbon-carbon double bond by Prilezhaev in 1909.[8] Peroxycarboxylic acids **16** readily epoxidize alkenes *via* transition state **17** of the mechanism involving a nucleophilic attack on the peroxyacid oxygen-oxygen bond by the π-olefinic double bond (**Scheme 9**).[9] Recently, Houk reported theoretical work in support of a spiro transition state.[10] The reaction is stereospecific; the *E*- or *Z*- geometry of the alkene is retained in the epoxide product.[11]



Scheme 6: Use of peroxycarboxylic acids **16** in Prilezhaev's epoxidation of alkenes

In their study, Henbest[12] and Sharpless[13] have shown that there is a *syn*-hydroxy-stereodirecting effect in the example of allylic alcohols, meaning the epoxidation will take place preferentially on the face of the alkene bearing the hydroxyl group, because of hydrogen bonding with one of the oxygen of the peroxyacid (**Figure 7**)

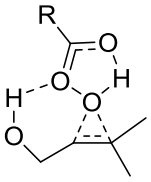
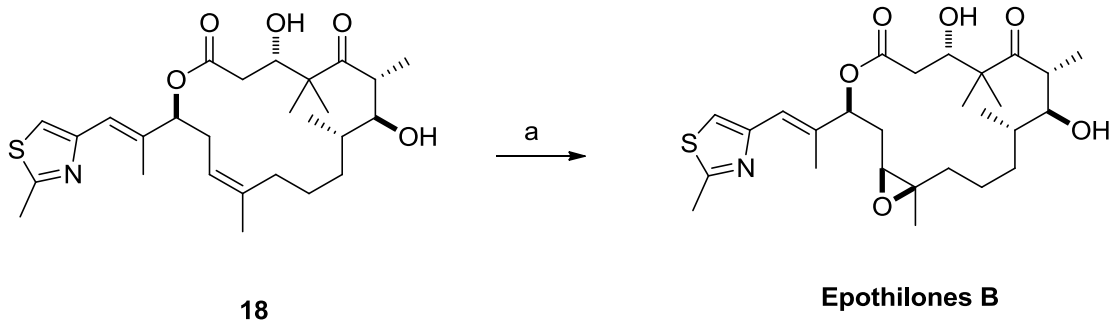


Figure 7: the peroxy-acid directed to more hindered face of alkene.

Mulzer's total syntheses of epothilones B is an example of the directing effect of the hydroxy group in the epoxidation of **18**. The Prilezhaev reaction was utilized to afford the *syn*-epoxide of the less hindered alkene (**Scheme 7**).



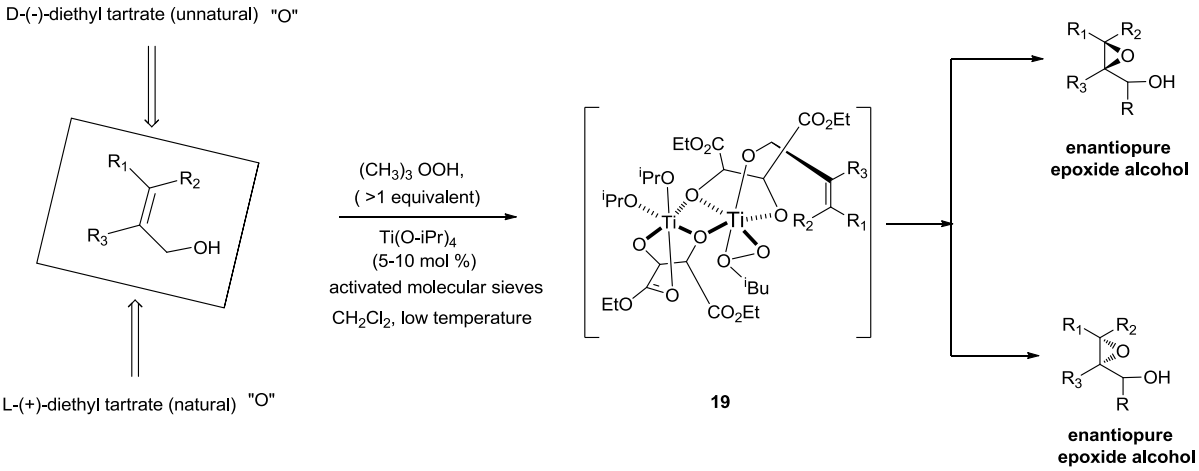
18 **Epothilones B**

Reagents and conditions: (a) *m*CPBA (1.5 equiv.), $CHCl_3$, –18 °C, 5h, 81%.

Scheme 7: Use of the Prilezhaev reaction in syntheses of epothilones B

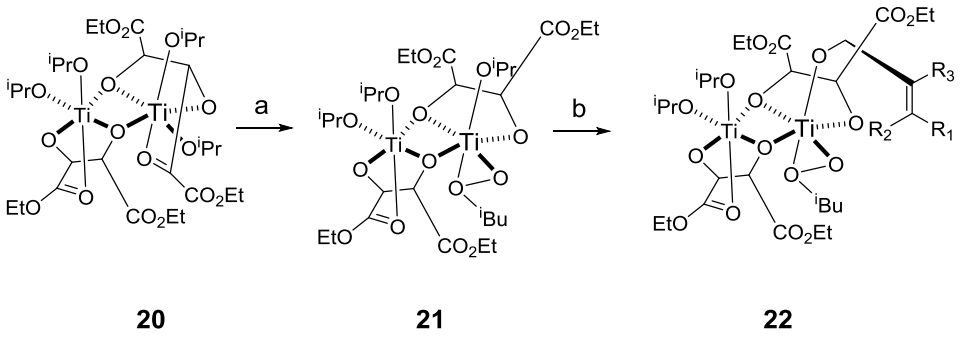
1.7.2 Sharpless Asymmetric Epoxidation

Sharpless and Katsuki invented a method to transform primary allylic alcohols into optically active epoxides in greater than 90% ee.[15] The Sharpless asymmetric epoxidation has been one of the most important discoveries of the last 30 years in asymmetric catalysis. The 2001 Nobel Prize was awarded to Professor Sharpless for a valuable contribution to chemistry and more particularly, asymmetric catalysis.[16,17] The key part of the procedure is the formation of an enantiomerically pure chiral complex, such as **19**, utilizing a hydroperoxide (usually *t*-BuOOH) as the oxidizing agent, 6-12 mol% of an enantiomerically pure dialkyl ester of tartaric acid (usually either diethyl tartrate) and titanium isopropoxide. When one of the isopropoxide groups is replaced with the allylic alcohol substrate, asymmetric epoxidation is achieved. The most important aspect of the system is the capability for the production of either enantiomer of the desired epoxy-alcohol by employing either enantiomer of the commercially available tartrate ester, which establishes the direction of the epoxidation in the reaction (**Scheme 8**).[18]



Scheme 8: Stereochemical outcome of the Sharpless epoxidation

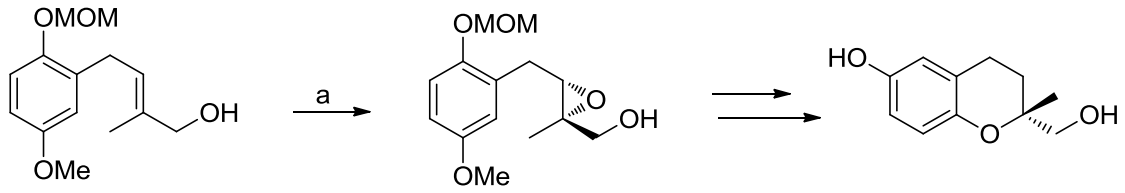
The mechanism of the Sharpless asymmetric epoxidation is shown below. The initial exchange of tetraisopropoxide ligands with the optically active diethyl tartrate results in the formation of the dimeric complex **20.**[13, 5] The nucleophilic substitution of the hydroperoxide on the metal centre allows the formation of **21**.[3] Coordination of the allylic alcohol to the metal then occurs, forming intermediate **22**, and delivery of the oxygen atom using the active catalyst follows (**Scheme 9**). [13,15,18]



Reagents and conditions: (a) ^{t}BOOH, (b) allylic alcohol

Scheme 9: Sharpless's epoxidation of allylic alcohols

The success in obtaining high enantioselectivities (93% ee) was utilized to prepare chroman-2-ylmethanol **25**, which is a key intermediate in the synthesis of α-tocopherol (Vitamin E). Sharpless asymmetric epoxidation of allylic alcohol **23**, using the natural L-(+)-diethyl tartrate, gave the enantiopure epoxide **24** in 85% yield (**Scheme 10**).[19]



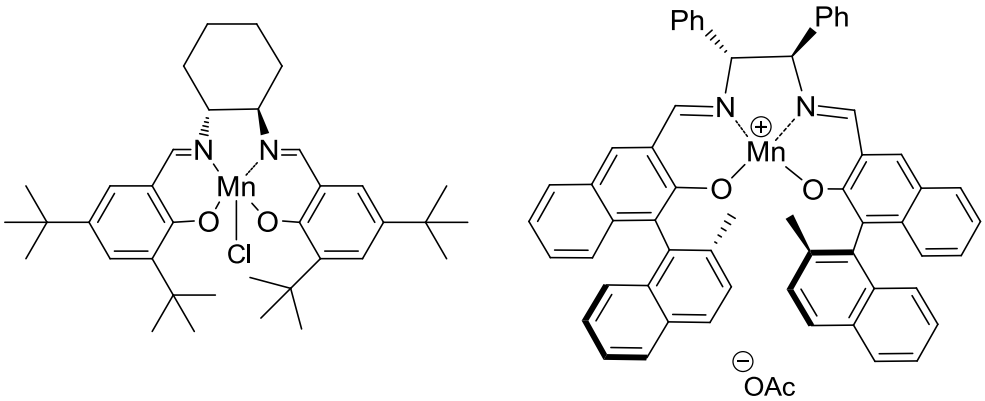
23 **24** **25**

Reagents and conditions: (a) ^{t}BOOH, Ti(OPr^{i})$_4$, L-(+)-diethyl tartrate, CH_2Cl_2, –24 °C, 20h, 85%.

Scheme 10: The Sharpless epoxidation as a key step in total synthesis of chroman-2-yl-methanol **25**

1.7.3 Jacobsen-Katsuki Epoxidation

Jacobsen reported manganese-salen complex catalyst **27** to be the most efficient catalyst for the enantioselective epoxidation of unfunctionalized olefins among over fifty ligand modifications.[20] Katsuki independently reported catalyst **28**, with a similar skeleton to **27** (**Figure 8**).[21] In general, such Mn(III)-based catalysts consist of a tetradentate salen-ligand complex. Unlike the Sharpless epoxidation, the Jacobsen-Katsuki epoxidation does not require the substrate to be an allylic alcohol. It is a transition metal-mediated epoxidation, and a host of oxidizing agents have been used (e.g. iodosylbenzene, sodium hypochlorite, Oxone™, hydrogen peroxide and *m*CPBA) for the oxidation of the manganese (III) metal centre into manganese (V). [22, 23, 24, 25, 26]



27 **28**

Figure 8: Jacobsen's and Katsuki's general catalyst structure, **27** and **28**, respectively.

The main difference lies in the substrate geometry: the Jacobsen epoxidation delivered the best results when *Z*-alkenes were used as substrates; while the Katsuki epoxidation performed effectively when *E*-alkenes were used as substrates.[22,23] Both can be used at very low catalyst loadings; it is common for 1 mol% loadings to be used, and *ees* in the isolated epoxides can be above 99%.[27] The reactions are not stereospecific, however. The active catalyst is a Mn(V)-oxo species, formed by the oxidation of the Mn(III)-salen complex, and is the most likely responsible intermediate for the oxygen transfer to the olefin.[25] However, the mechanisms described by Jacobsen and Katsuki to explain the enantioselectivity in the epoxidation process differ. Jacobsen's suggestion supports a 'top-on' approach to the axial oxygen, whereas Katsuki has suggested a 'side-on' approach (**Figure 9**). [23, 28]

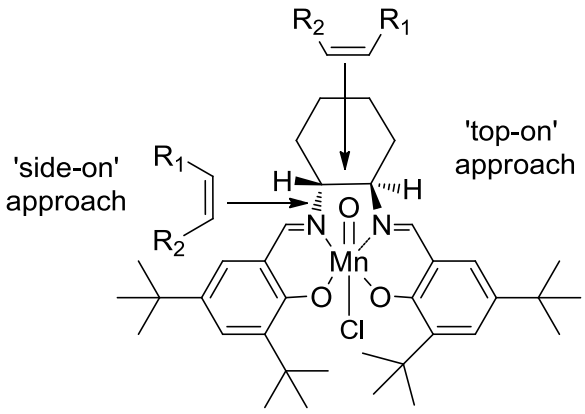
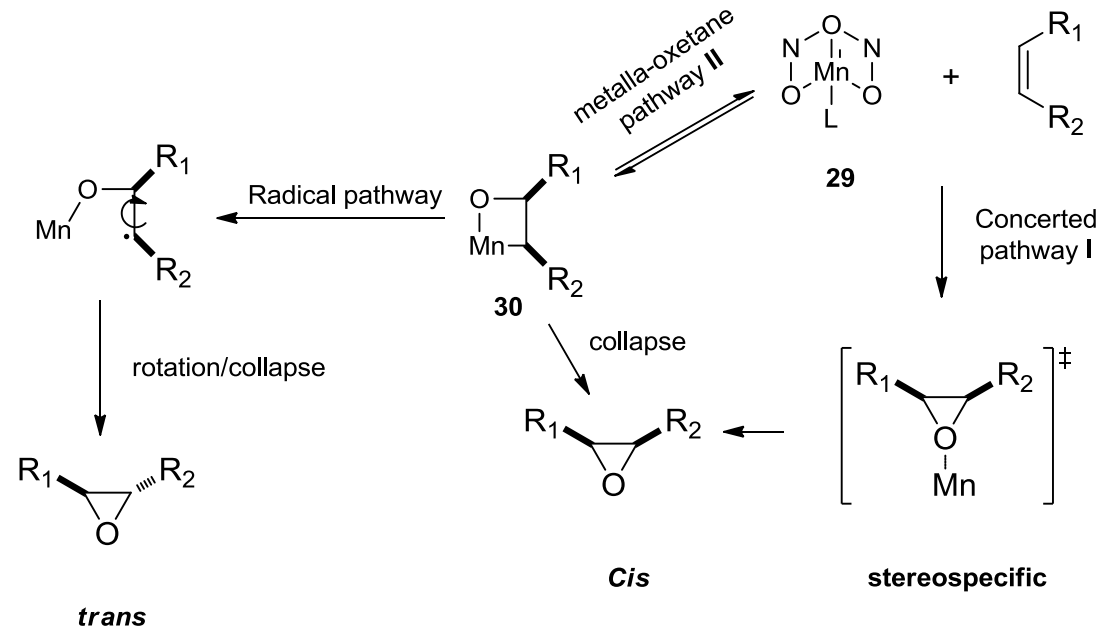


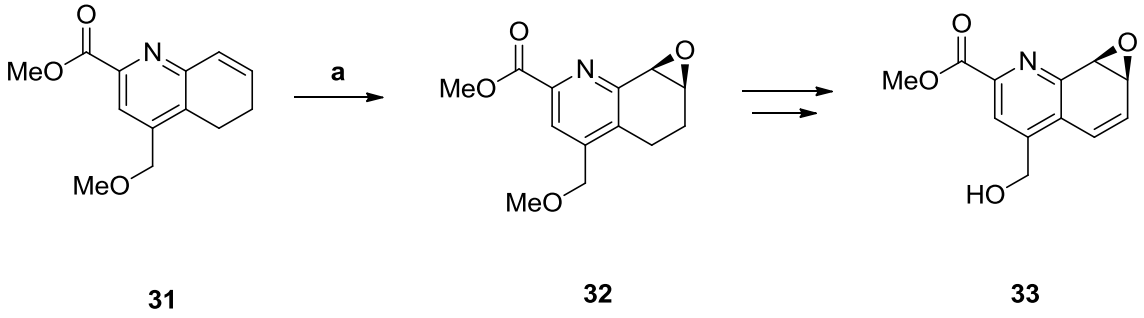
Figure 9: The two suggested approaches from Katsuki and Jacobsen

The mechanism has not been completely understood, and there are the three major mechanistic explanations for how the reaction proceeds. [.29] The first pathway **I** is a concerted reaction, much like the Prilezhaev epoxidation, where there is no C-C bond rotation around the intermediate species. [28.29] Thus, the reaction is stereospecific. The second pathway **II** is also stereospecific. [.29] However, in contrast to the first pathway, the reaction proceeds *via* a metalla-oxetane species **30**, which then collapses to give the epoxide with the same stereochemistry as the substrate. [27,28] The third pathway **III** is a radical pathway, where the mechanism suggests that the *tran*s-epoxide can be formed by a single electron transfer mechanism, due to C-C bond rotation around the intermediate species (**Scheme 11**). [23,27,28.29]



Scheme 11: Summary of proposed pathways of Katsuki and Jacobsen epoxidations

The importance of forming a chiral epoxide as the key step for the synthesis of pharmaceutical drugs can be illustrated: Hashimoto used Jacobsen's catalyst to prepare chiral epoxide **32**, a key intermediate in his synthesis of the dihydroquinoline core of Siomycin D_1 **33**, in 87% yield and 91% *ee* (**Scheme 12**).[30]

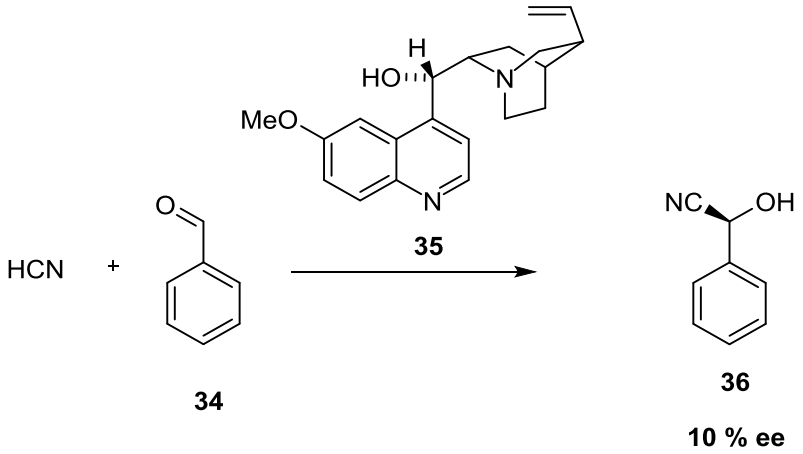


Reagents and conditions: (a) 4-phenylpyridine *N*-oxide (50 mol%), NaOCl (aq.), CH_2Cl_2, Jacobsen's Catalyst (5 mol%), r.t, 2.5h, 43%, 91% ee, 87%.

Scheme 12: Hashimoto's synthesis of the dihydroquinoline core of Siomycin D_1 utilising the Jacobsen-Katsuki epoxidation

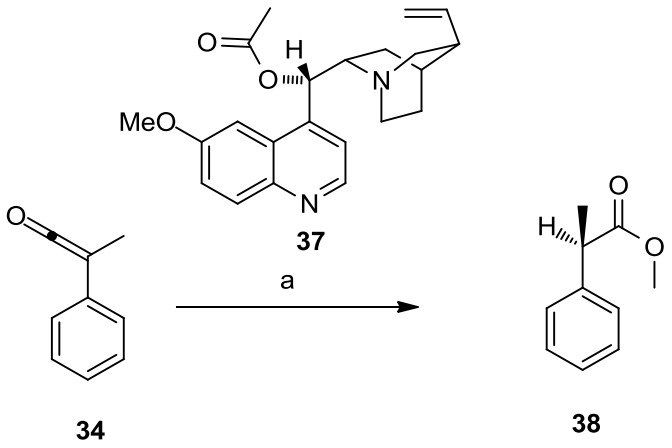
1.8 Organocatalysts

In contrast to metal-based epoxidation catalysts, organocatalysts are purely organic molecules, consisting of carbon, hydrogen, nitrogen, sulfur and phosphorus, and no transition metals are needed for the reaction to proceed.[31] The major advantages of organocatalysts lie in that they are inexpensive, readily available, not contaminated by metals, and usually non-toxic. As long as 90 years ago, an asymmetric organocatalytic reaction was reported by Fiske and Bredig. Their study discussed the addition of HCN to benzaldehyde **34** catalysed by quinine **35**, forming optically active cyanohydrin **36** in up to 10% *ee* (**Scheme 13**).[32]



Scheme 13: The formation of optically active cyanohydrins **36** from the first asymmetric organocatalytic reaction

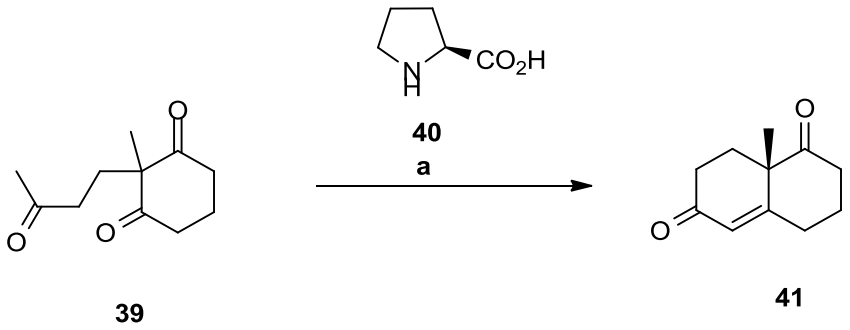
In 1960, Pracejus attempted to improve quinine as a catalyst. Pracejus reported the use of *O*-acetyl-quinine **37** with 1 mol% loading and 1.1 equivalents of methanol, in the addition to a ketene in toluene at −111 °C, to afford **38** in 93 % yield and 74% *ee* (**Scheme 14**).[33]



Reagents and conditions: (a) Methanol (1.1 equiv.), Toluene, –111 °C, 92%.

Scheme 14: The formation of optically active **38** by Pracejus, using *O*-acetyl- quinine

In the early 1970s and 1980s, Hajos and Parrish, alongside Wiechert, Sauer and Eder independently reported the use of chiral amines to catalyse enantioselective reactions.[34] For example, the asymmetric intramolecular aldol reaction of trione **39** was catalysed by L-proline **40**, leading to the formation of the unsaturated Wieland–Miescher Ketone **41**. [34]



Reagents and conditions: (a) **40** (3-47 mol%), CH_3CN, 80 °C ,R.T. 83%,71-93% *ee*.

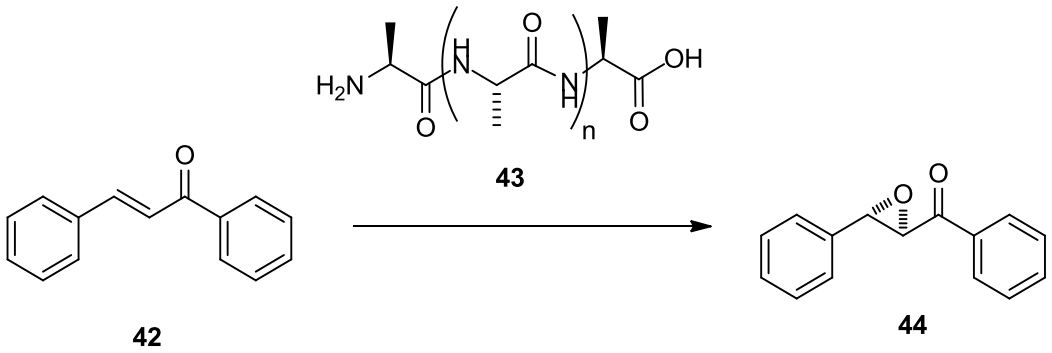
Scheme 15: Formation of the Wieland-Miescher ketone using L-proline

1.9 Non-Metal Catalysed Epoxidations

Today, organocatalysis, using such reagents as chiral dioxiranes, oxaziridines, amines and oxaziridiniums, forms a major part of the asymmetric epoxidation techniques available to modern synthetic chemists.

1.9.1 Juliá-Colonna epoxidation

Organocatalytic epoxidations of chalcone using poly-L-alanine **43** with H_2O_2 as the oxidizing agent were first reported by Juliá in 1980.[35] Poly-amino acid-catalysed epoxidation of chalcone **42** was achieved to afford **44** in heterogeneous triphasic conditions with excellent enantiomeric excesses (**Scheme 16**). [36] The major advantage of using a triphasic system is the insolubility of poly-L-alanine in an aqueous solution of sodium hydroxide, allowing simple separation and then re-use of the catalyst. [36] However, continuous recycling of catalyst leads to reduced enantioselectivities, due to catalyst degradation under basic conditions. It has been explained that the chain length required for high enantioselectivity should consist of a minimum of 10 to 30 amino-acid residues.[36]



Reagents and conditions: (a) H_2O_2/NaOH, Toluene or CH_2Cl_2, r.t., 85%, 93% *ee*.

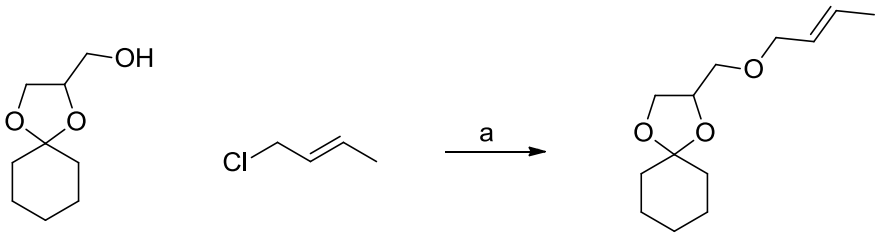
Scheme 16: Epoxidation of chalcone by Juliá using poly-L-alanine.

The capability of the triphasic system is limited, due to the reaction time required for the epoxidation of chalcone to occur (up to 24 h). Roberts used a biphasic reaction system to limit the reaction time to 30 minutes for chalcone. [37] This was achieved by replacing the oxidant H_2O_2 with urea-hydrogen peroxide, and the base with DBU, as both of them are soluble in organic solvents. Poly-L-leucine was used as the catalyst. [37]

1.9.2 Phase Transfer Catalysis

Phase transfer catalysis (PTC) is an important concept in organocatalytic reactions, where the catalyst acts as a phase transfer agent, allowing substances which are located in an immiscible phase to pass into an organic phase.[3] For example, alkylation of the acetal starting material **45** occurred using sodium hydroxide as the base in a water/dichloromethane biphasic

system.[3] Although sodium hydroxide is not soluble in dichloromethane, the tetraalkyl ammonium salt was employed to transfer the hydroxyl anion from the aqueous layer into the organic layer by forming $Bu_4N^+HO^-$, which is soluble in dichloromethane (**Scheme 17**).[3]



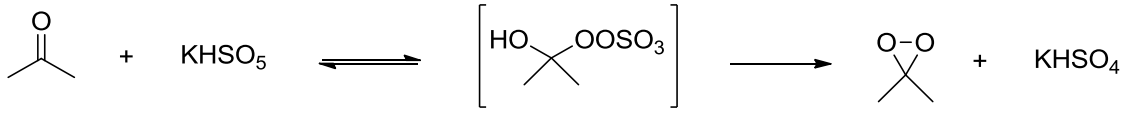
45 **46**

Reagents and conditions: (a) $Bu_4N^+ HSO_4^-$, NaOH, H_2O, CH_2Cl_2, 84%.

Scheme 17: Example of phase transfer catalysis

1.9.3 Chiral Dioxiranes as catalysts for asymmetric epoxidation.

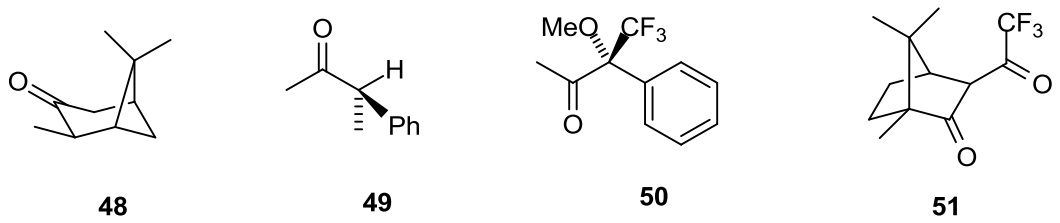
Dioxiranes **47** are three-membered ring systems that have a carbon and two oxygen atoms. Dioxiranes can be generated from ketones reacting *in-situ* with Oxone™, and are powerful and unstable oxidants.[3]



47

Figure 10: Generation of dioxiranes from ketones using Oxone™

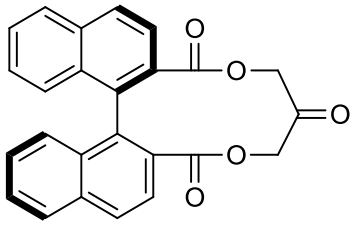
In 1984, the first example of asymmetric epoxidation using chiral ketone catalysts was reported by Curci (**Figure 11**).[38] Curci's initial work involved readily available ketones **48** and **49** with 1-methyl-1-cyclohexene as the substrate in a biphasic mixture of water and dichloromethane buffered to pH 7-8, with Bu_4NHSO_4 as a PTC. Drawbacks from the use of ketones **48** and **49** included poor epoxide ees (up to 12%), high catalyst loadings and poor reactivity.[38,39] Curci also investigated electron-deficient ketones **50** and **51**, and found these to be more reactive, but only moderate improvement in enantioselectivity were observed (13-20% *ee*, **Figure 11**).[38,39]



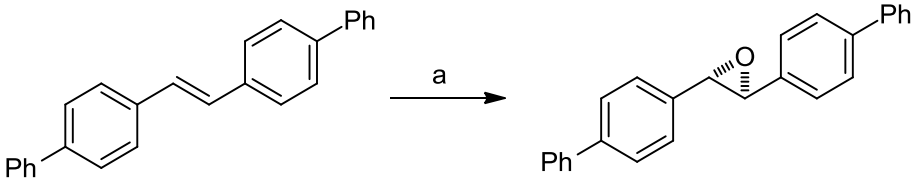
48 **49** **50** **51**

Figure 11: The chiral ketone catalysts developed by Curci between 1984 and 1995

In 1996, Yang was the first to develop an effective solution for the drawbacks of Curci's research. She introduced a new biphasic solvent system: acetonitrile-water, utilizing C2-symmetric binaphthalene-derived ketone **53**. Catalyst **53** was capable of enantiomeric excesses of up to 87% at a loading of only 10 mol% which was a huge improvement on Curci's ketone catalysts (**Scheme 18**).[40]



53



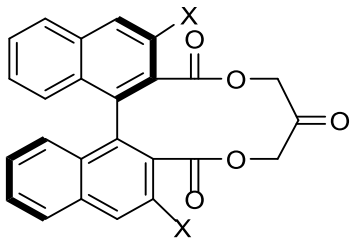
52 **54**

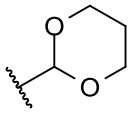
Reagents and conditions: (a) **53** (10 mol %), Oxone™ (5 equiv.), $NaHCO_3$ (15.5 equiv.), $MeCN/H_2O$, 0 °C, 80%, 87% *ee*.

Scheme 18: Dioxirane-mediated epoxidation protocol, using C_2 symmetric binaphthalene-derived catalyst

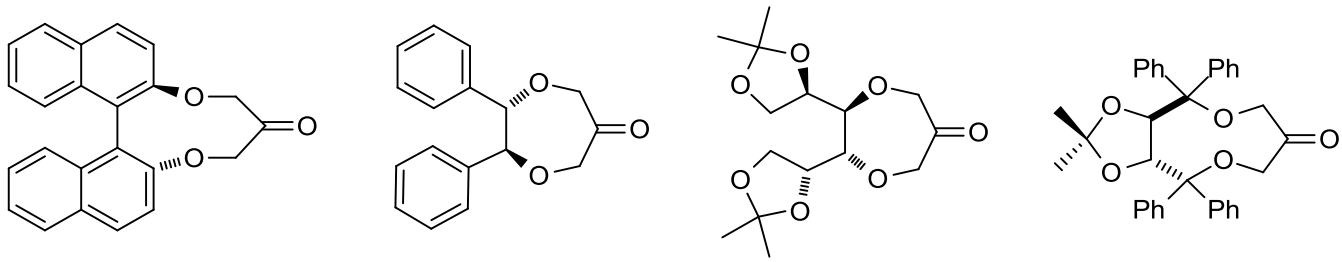
To further improve the reactivity of the C_2 symmetric binaphthalene-derived catalyst, structural modifications were necessary. Based on X-ray analysis, Yang suspected that the H-3 and H-3' atoms, which are closer to the chiral dioxirane moiety, behave as if the steric sensors in the oxygen transfer process. [41] By increasing the size of the groups at the 3 and 3' positions, Yang believed the selectivity of the process could be further improved. Consequently, higher enantioselectivities were indeed observed (**Table 1**).[41,42]

Table 1: Effect of the size of the steric sensor on the isolated *ee* of trans-stilbene oxide



X	ee
H	44%
Cl	76%
Br	75%
I	32%
Me	56%
CH_2OCH3	66%
$SiMe_3$	44%
	71%

Song [43] published chiral ketones **55**, and **56**, with oxygen atoms at the β-positions to the carbonyl group. However, these catalysts were not as selective; the ee did not exceed 53% for the epoxidation of *trans*-stilbene with 1 equivalent of the catalyst **55**. Adam also reported chiral ketones **57**, and **58**. They were able to afford *ee*'s similar to Song's ketones (**Figure 12**).[44]

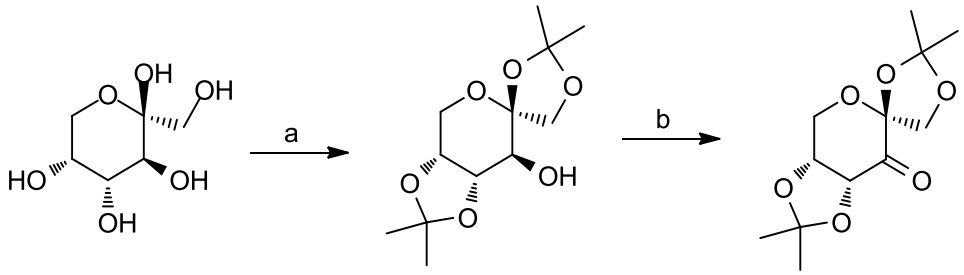


55 **56** **57** **58**

Figure 12: Catalysts developed by Song and Adam

1.9.3.1. Shi's fructose-derived ketone catalysts

In 1996, Shi reported the synthesis and use of D-fructose-derived ketone **61** for asymmetric epoxidation. Ketone **61** can be prepared from D-fructose **59** in two steps (**Scheme 19**).[45] Since then, this catalyst has been regarded as one of the most powerful and versatile organocatalytic asymmetric epoxidation catalysts. The key to success of the catalyst lies in the close proximity of the ketone and the stereogenic centres, significantly increasing the stereoinduction.[46]



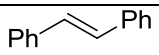
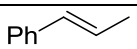
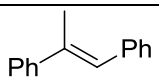
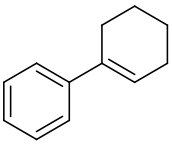
59 **60** **61**

Reagents and conditions: (a) acetone, $HClO_4$, 0 °C, 53%. (b) PCC, CH_2Cl_2, rt, 93%.

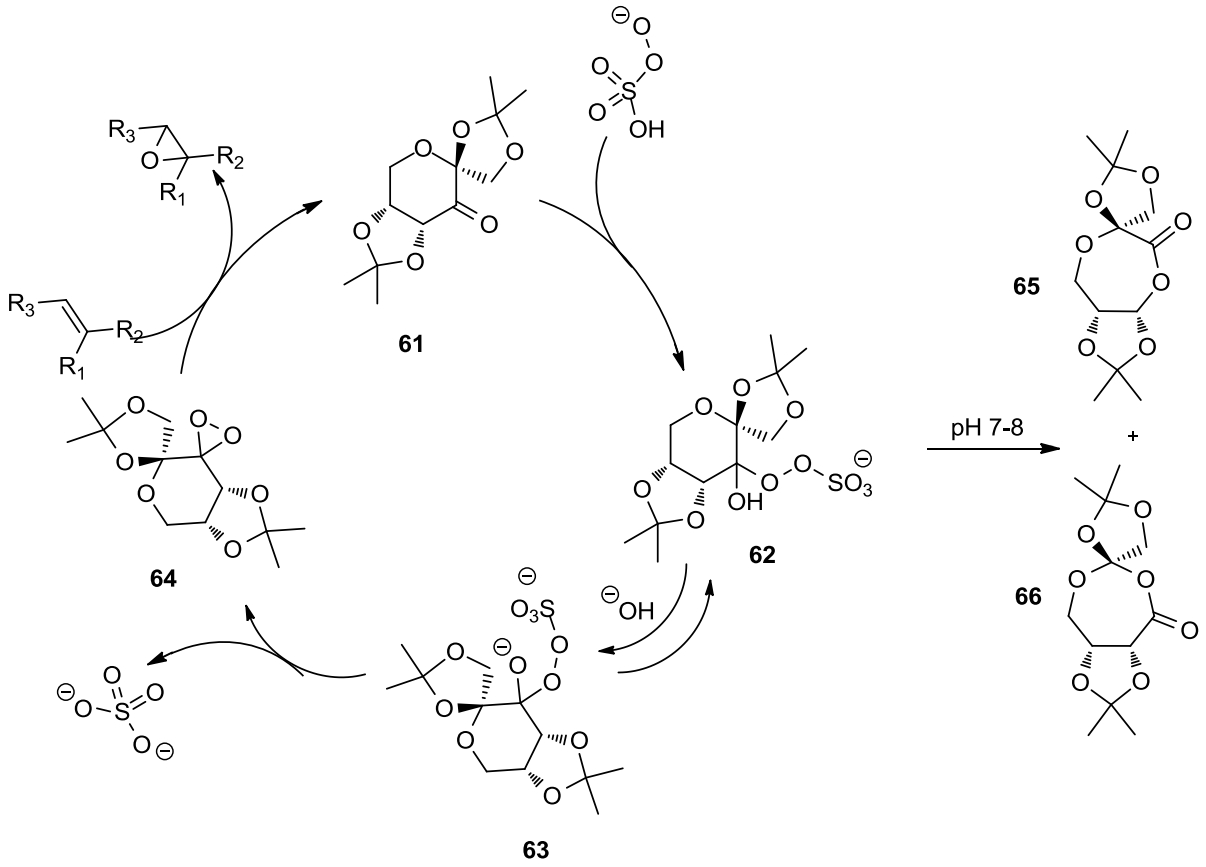
Scheme 19: Synthesis of Shi's D-fructose-derived ketone

Ketone **61** displayed high enantioselectivities for the asymmetric epoxidation of a range of unfunctionalized, *trans*- and trisubstituted olefins. For example, *trans*-stilbene oxide was obtained in 85% yield and 98% *ee* (**Table 2**). Low ees were, however, obtained for *cis*-disubstituted and terminal alkenes.[47]

Table 2 Shi's epoxidation of *trans*- and trisubstituted olefins with chiral ketone **61**

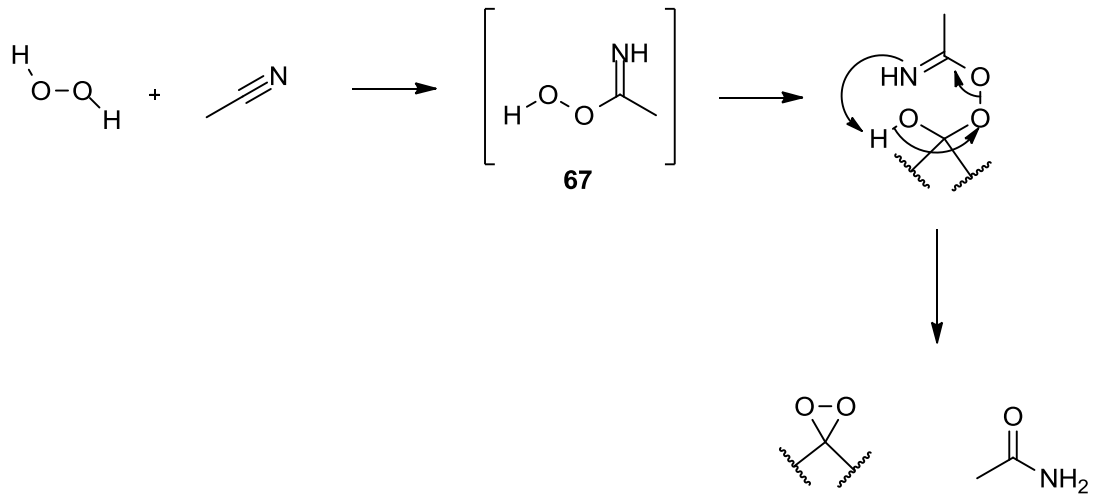
Substrate	Yield (%)	ee (%)
	85	98 (*R*,*R*)
	94	96 (*R*,*R*)
	89	96 (*R*,*R*)
	94	98 (*R*,*R*)

However, a problem identified by Shi was the requirement for ketone **61** to be used in high catalyst loadings for the complete conversion of alkene to the corresponding epoxide to occur. Shi studied the relationship between the effect of pH on the epoxidation reaction and the high catalyst loadings. The result of that study showed that the reaction run at pH 7-8 favours intermediate **62,** which is prone to a Baeyer-Villiger oxidation, affording corresponding lactones **65** & **66**. If the pH is increased to around 10, intermediate **63** is favoured and dioxirane **64** is generated (**Scheme 20**).[48]



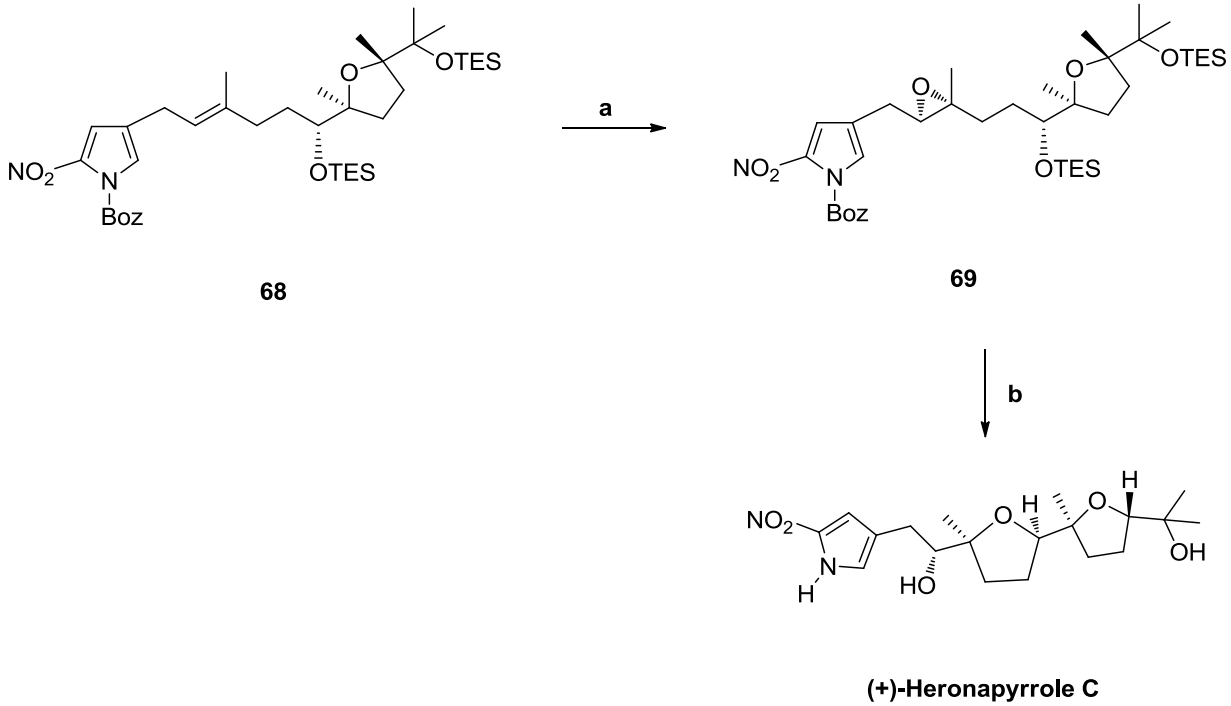
Scheme 20: Shi's catalytic cycle showing the Baeyer-Villiger decomposition pathway

Shi also reported the use of hydrogen peroxide as the oxidant. This system requires the use of acetonitrile, as peroxyimidic acid **67** is believed to be the active oxidant for generating the dioxirane (**Scheme 21**). High yields and enantioselectivities for a number of olefins were obtained.[49]



Scheme 21: Formation of the peroxyimidic acid **67**

The asymmetric synthesis of (+)-Heronapyrrole C was accomplished by Ding and co-workers: the alkene substrate **68** was exposed to Shi's ketone catalyst, forming key intermediate **69** in 82% yield. Ring-opening of the epoxide using an intramolecular nucleophile and deprotection of the *N*-Boz group led to the formation of the target molecule (**Scheme 22**).[50]

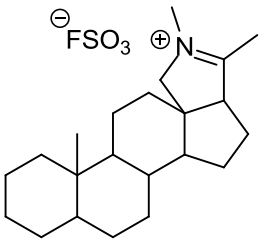


Reagents and conditions: (a) Shi catalyst, Oxone, K_2CO_3, MeCN/DME/buffer (1:2:2), 0 °C, 83%. (b) TBAF, THF, 0 °C to rt, 1h, then 50 °C, 0.5 h, 80%.

Scheme 22: Asymmetric synthesis of (+)-Heronapyrrole C using Shi's catalyst

1.10 Oxaziridinium salts as catalysts for asymmetric epoxidation

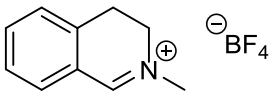
Oxaziridiniums species are three-membered rings, analogous to oxaziridines, which contain one oxygen, one carbon and one quaternized nitrogen atom.[3] Their reactivity is due to the presence of the quaternized nitrogen atom which increases their efficiency as oxygen transfer reagents to nucleophilic substrates. The first report of the existence of an oxaziridinium species was reported by Lusinchi's group in 1976.[51] The preparation of an oxaziridinium species was the result of a peroxyacid oxidation of the steroidal pyrrolinic iminium salt **70**.[51,52] Lusinchi demonstrated the capability of the oxaziridinium species for transferring oxygen to other nucleophilic substrates such as amines, sulfides, imines and alkenes (**Figure 13**).[53]



70

Figure 13: The first iminium salt

In an effort to develop a catalytic version of the reaction, Lusinchi and co-workers chose *N*-methyl-3,4-dihydroisoquinolinium tetrafluoroborate **71**[54] and Oxone™ as the oxidant for the epoxidation reaction of a range of unfunctionalized olefins (**Figure 14**).[55]



71

Figure 14: Model iminium salt

This work led to the iminium salt being used in catalytic amounts, generating the oxaziridinium by *in-situ* oxidation, avoiding extra synthetic steps (**Figure 15**).

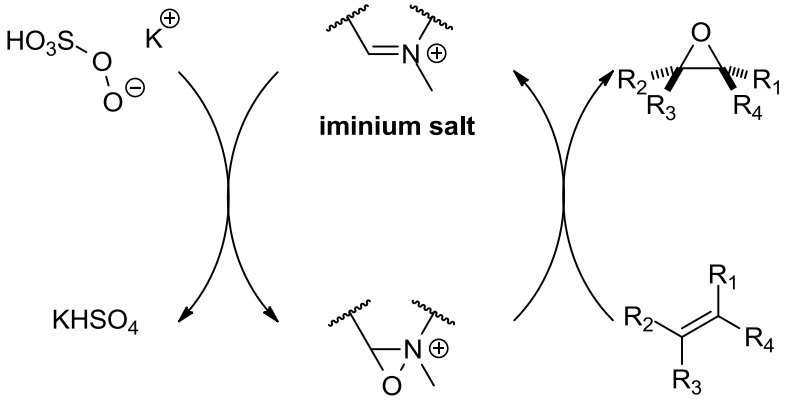
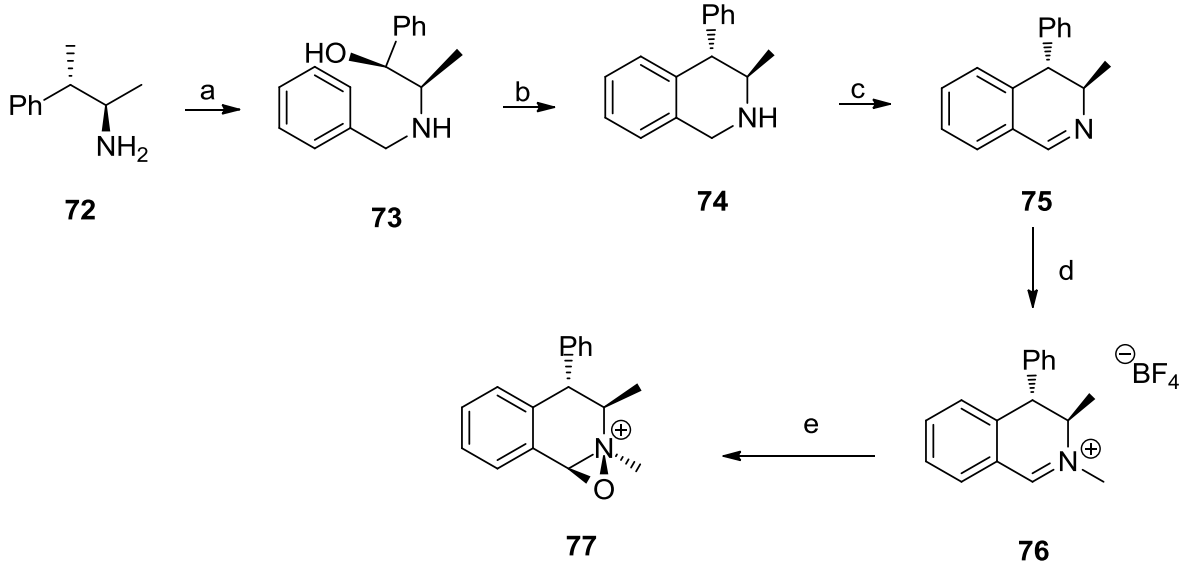


Figure 15: Catalytic cycle of the iminium/oxaziridinium salt with Oxone™

An initial investigation of enantiomerically pure iminium salts for their potential as catalysts was conducted by Lusinchi's group in 1993.[56] Lusinchi's group has produced the dihydroisoquinoline-derived oxaziridinium salt **77** as an oxygen transfer agent that exhibits respectable enantioselectivities in the epoxidation of olefins.[57,58] Salt **77** is derived from (1*S*,2*R*)-(+)-norephedrine **72** and is prepared in a five-step sequence. Importantly, they were also able to determine the structure of the oxaziridinium salt using X-ray crystallography (**Scheme 23**). [58]



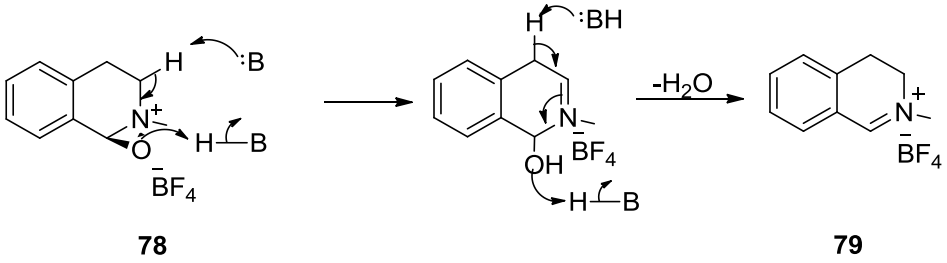
72 **73** **74** **75** **76** **77**

Reagents and conditions: (a) Benzaldehyde, $NaBH_4$, EtOH (b) CF_3CO_2H, H_2SO_4. (c) NaOCl, NaOMe (d) Me_3OBF_4, MeOH. (e) *m*CPBA, CH_2Cl_2 $NaHCO_3$.

Scheme 23: Chiral oxaziridinium salt isolated by Lusinchi

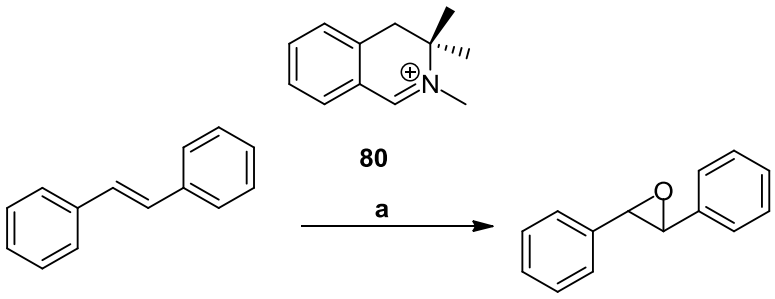
An initial reaction with 5 mol% of **76** and Oxone™ as the oxidant exhibited low enantioselectivities (35% *ee*) for the epoxidation of *trans*-stilbene.[58]

The catalytic oxaziridinium-mediated epoxidation is a highly efficient method. However, the issue of competing irreversible base-catalysed isomerization was addressed by Bohé. [59] Some common side reactions were observed in iminium salt-mediated epoxidation. They are identified as deleterious factors for the iminium salt catalytic process by reducing the catalytic efficiency of the epoxidation process: the loss of active oxygen from the intermediate oxaziridinium species **78** derived from the parent iminium catalysts can occur when the dihydroisoquinolinium **78** contains protons on the carbon α to the nitrogen. [59] The corresponding isoquinolinium salt **79** can be formed by dehydration. This is an acid-base pathway (**Scheme 24**). [59]



Scheme 24: Acid-base pathway

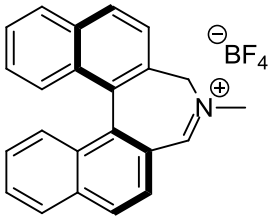
Bohé has aimed to improve the efficiency of the catalytic activity by removing the possibility of isomerization by dehydration. [59] A gradual increase in catalyst efficiency is reported when 3,3-disubstituted dihydroisoquinolium iminium salt **80** is utilized instead of the corresponding unsubstituted dihydroisoquinolinium catalyst, thus eliminating the base-catalysed isomerization (**Scheme 25**).[59] We have however never observed such processes in our iminium salt catalysts.



Reagents and conditions: (a) catalyst **80** (10 mol%), 7h, 100%.

Scheme 25: Bohé's improved 3,3-disubstituted-dihydroisoquinolinium catalyst **80**

Aggarwal reported the synthesis and the use of a binaphthalene-based catalyst **81**, which has an achiral methyl group as the nitrogen substituent, to achieve fair enantioselectivities (**Figure 16**).[60] 1-Phenylcyclohexene and *trans*-stilbene epoxidation reactions were carried out with 5 mol% of catalyst, Oxone™, and $NaHCO_3$ in a mixture of acetonitrile/water at room temperature, affording 1-phenylcyclohexene oxide and *trans*-stilbene oxide in 71% and 31% ee, respectively.[60]

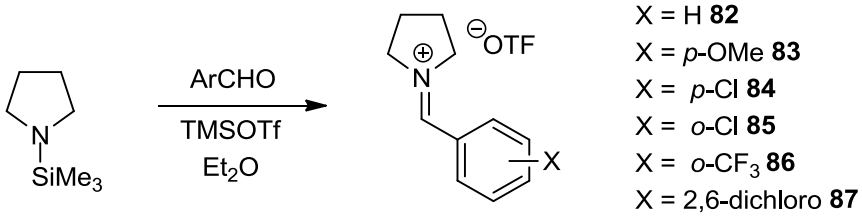


81

Figure 16

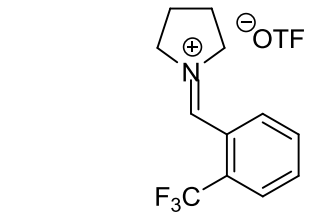
1.10.1 Armstrong's Exocyclic Iminium Salts

Armstrong was the first to explore a range of exocyclic iminium triflate salts and use them as epoxidation catalysts.[61,62] These salts were prepared by intermolecular condensation of *N*-trimethylsilyl pyrrolidine with various substituted aromatic aldehydes in the presence of trimethylsilyl triflate in anhydrous diethyl ether (**Scheme 26**).[61]

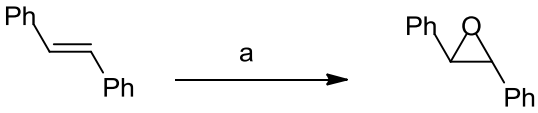


Scheme 26: Formation of Armstrong's exocyclic iminium triflate salts **82-87**

Armstrong found that catalyst **86**, bearing an *ortho*-trifluoromethyl group, catalysed the epoxidation of various olefins with 10 mol% loading, using Oxone™ and $NaHCO_3$ in a mixture of acetonitrile and water for 4 h at room temperature, affording the corresponding epoxides in 83% yield (**Scheme 27**).[61]



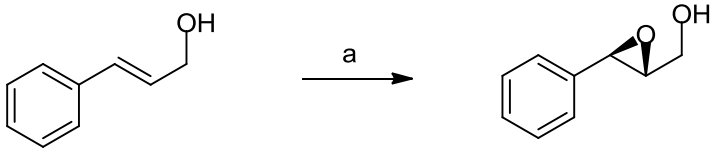
86



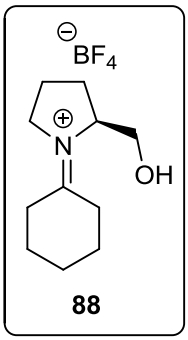
Reagents and conditions: (a) catalyst **86** (10 mol%), Oxone™ (2 equiv.), $NaHCO_3$ (4 equiv.), $MeCN/H_2O$ (99.6:0.4), rt, 4h, 83%.

Scheme 27

Likewise, in 2000, Komatsu studied ketiminium salts, derived from pyrrolidine and cyclohexanone in the presence of HBF_4 under Dean-Stark conditions, and attempted asymmetric epoxidation of a range of olefins.[63] The chiral ketiminium salt **88** was synthesised from L-prolinol, which afforded the epoxide of cinnamyl alcohol **89** in 39% *ee* (**Scheme 28**).[63]



89 **90**



88

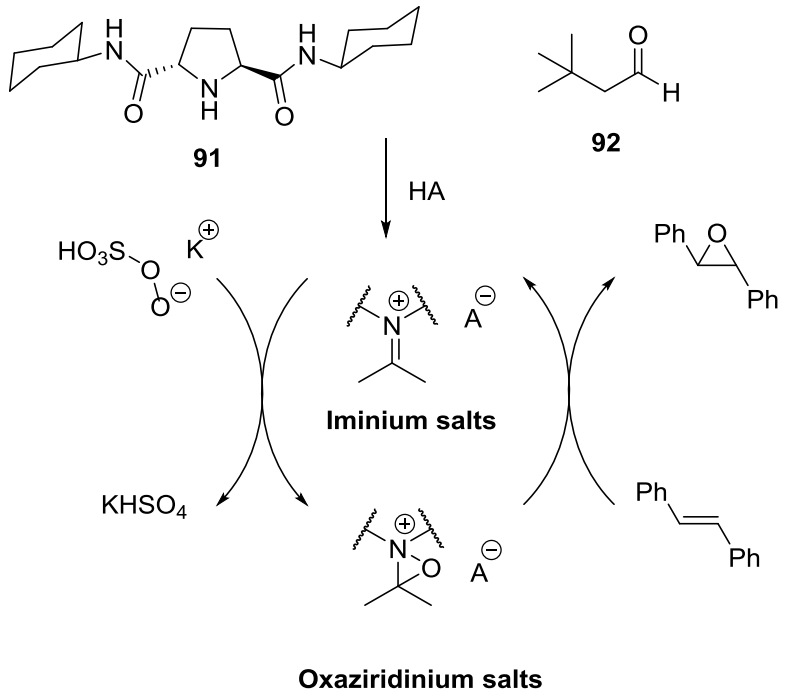
Reagents and conditions: (a) catalyst **88** (10 mol%), Oxone™ (1 equiv.), $NaHCO_3$ (4 equiv.), $MeCN/H_2O$ (98.7:1.3), 25 °C, 16h, 79%.

Scheme 28

1.10.2 Yang's chiral iminium salts

A direct method for the *in-situ* generation of chiral iminium salts involved the condensation of a secondary amine with either an aldehyde or a ketone.[64] This method allowed the screening of various iminium salts, under mild acidic conditions, without the need for purification. For example, amine **91** and aldehyde **92** (20 mol% loading for both **91** and **92**)

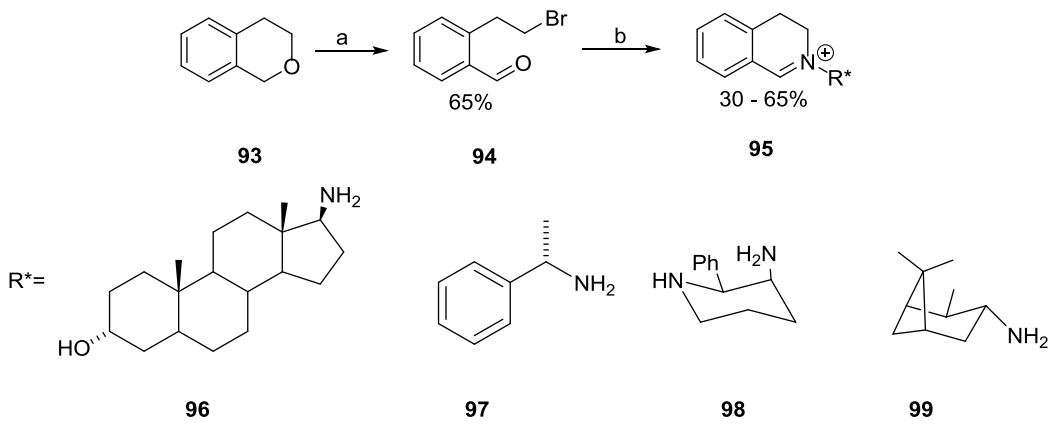
afforded good conversions using Oxone™ and $NaHCO_3$ in a mixture of acetonitrile and water, and gave *trans*-stilbene oxide in 65% *ee* (**Scheme 29**).[64]



Scheme 29: Yang's asymmetric epoxidation of *trans*-stilbene

1.10.3 Page's iminium salts

Page and co-workers have pursued a study based on cyclic chiral iminium salts containing the asymmetric centre in an exocyclic substituent on the iminium nitrogen. [65] This was expected to improve the potential enantioselectivity by bringing the enantiocontrolling asymmetric centres closer to the site of the oxygen transfer reaction. Thereby, Page has adopted a cognitive approach to design a class of chiral iminium salts bearing an exocyclic substituent at the nitrogen for the organocatalytic asymmetric epoxidation of olefins.[65] In 1998, Page revealed a synthetic route to facilitate the creation of a library of iminium salts, based on the reaction of primary amines with bromoaldehyde **94** to furnish dihydroisoquinolinium salts **95** (**Scheme 30**).[65]

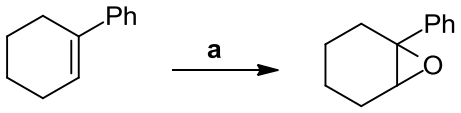


Reagents and conditions: (a) i) Br_2, CCl_4, reflux, 1h; b) HBr (conc.), reflux, 10 min, 65%; c) R*NH_2, $NaBPh_4$, EtOH, MeCN, 2h, 0°C to RT, 30-65 %

Scheme 30: Synthesis of dihydroisoquinolinium salts **95**

Dihydroisoquinolinium salt catalysts **96-99** were screened using model substrate 1-phenyl cyclohexene to gain insight into their reactivity and enantioselectivity. The *N*-isopinocamphenyl-derived catalyst **99** performed best and achieved *ee*s of up to 73% (**Table 3**).[65]

Table 3



Catalyst	Catalyst Loading/ (mol %)	Yield/ (%)	ee/ (%)
96	0.5	47	15
97	5	54	0
98	1	45	32
99	5	68	73

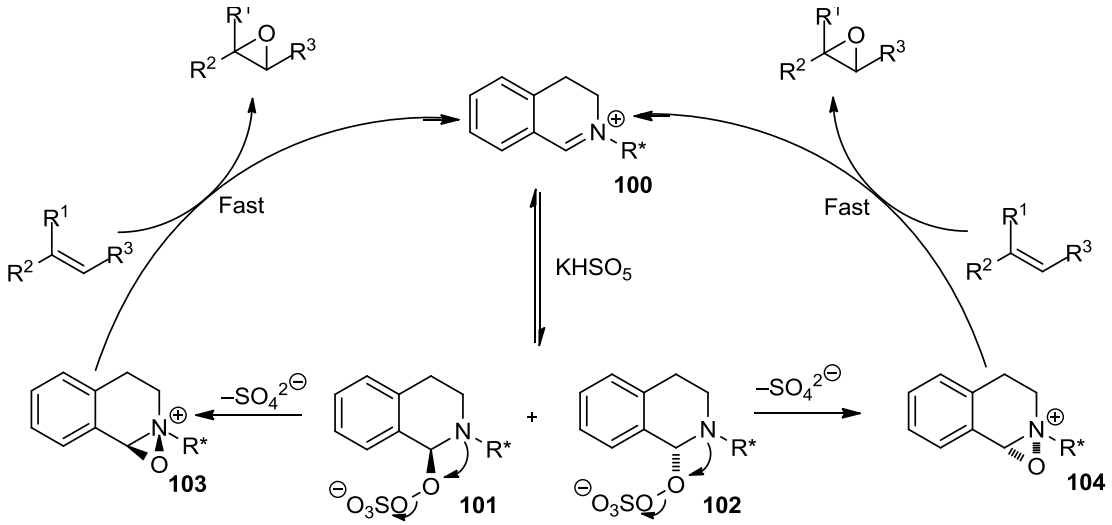
Reagents and conditions: (a) Iminium Salt, Oxone (2 equiv.), Na_2CO_3 (4 equiv.), $MeCN/H_2O$, 0°C

The process employed in the synthesis of the catalyst gained various advantages from the nature of the catalyst produced.[65] It involves simple synthetic steps, does not require chromatography and is easily scaled up (70 g). The bromide salts often are formed as oily products which are difficult to purify by conventional methods. This problem was solved by

anion exchange using the appropriate inorganic salts. Tetraphenylborate was used as counter-ion to obtain pure crystalline iminium salts.[65]

1.10.3.1 Mechanistic analysis

The catalytic asymmetric epoxidation of a simple alkene is thought to proceed through the proposed mechanism depicted below (**Scheme 31**).[66] Reversible nucleophilic attack of persulfate oxidant at the *si* or *re* face of the iminium species **100** leads to the formation of two diastereoisomeric species **101** or **102**.[66] Irreversible ring closure with concomitant expulsion of a sulfate anion delivers oxaziridinium species **103** and **104**, which is believed to be the rate-determining step under the reaction condtions.[66] Each diastereoisomer might then deliver the oxygen atom to either of the prochiral faces of the alkene substrate with a different degree of enantiocontrol.[66]



Scheme 31

Unfortunately, it is impossible to isolate the active oxaziridinium intermediate(s) due to its/their high reactivity and instability. Therefore, it is not fully understood whether one or both of the two oxaziridinium diastereoisomers **103** and **104** are involved in the process. [66] An early NMR study, however, showed the presence of only one diastereoisomer.

1.10.3.2 Catalytic oxidation conditions

1.10.3.2 .1 Effect of the solvent

Various solvents were tested by Page: dichloromethane gave the lowest reactivity, due perhaps to low solubility of Oxone™ in the organic phase. The best results were obtained when a biphasic acetonitrile/water system was used. It was reported that even at low catalyst loading (0.5 mol%) a significant increase of the rate of reaction was observed for a 1:1 mixture of acetonitrile and water without affecting epoxide ees.[66] For example, this solvent system was used in the asymmetric epoxidation of 1-phenylcyclohexene with tetraphenylborate iminium salt **99**, yielding 1-phenylcyclohexene oxide in 30% *ee* after 1 hour. However, at a higher catalyst loading (5 mol%), the use of any water/acetonitrile solvent system, using ratios from 1:9 to 9:1, led to full conversion in less than 20 minutes.[66] Thereby, this solvent system was found to be the best solvent system used, in terms of both enantioselectivity and reactivity. [66]

1.10.3.2 .2 Effect of Temperature

Page and co-workers attempted to carry out reactions below 0 °C, but were limited by the freezing point of water and by extent the solvent mixture. When employing an acetonitrile/water solvent system (1:1) at –10 °C, the biphasic mixture froze and the reaction rate decreased.[66] For example, at –10 °C with catalyst **99** and an acetonitrile/water mixture (3:1), 1-phenylcyclohexene oxide was obtained in 35% ee, while at 0 °C, phenylcyclohexene oxide was obtained in 40% ee. More importantly, this made little difference to the ee of the isolated epoxide. Negligible conversion to the epoxide was observed at between 27–32 °C, due to rapid decomposition of Oxone above room temperature. [66]

1.10.3.2 .3 Effect of Catalyst Loading

No epoxide was detected when the epoxidation reaction of 1-phenylcyclohexene in the absence of an iminium salt catalyst in an acetonitrile/water solvent system (1:1) at 0 ºC, with Oxone™ and sodium carbonate.[66] However, increasing catalyst loading from 0.1 to 6 mol%

was successful in improving the enantioselectivity of the epoxidation reaction; above 6 mol% only negligible improvement was observed. [66]

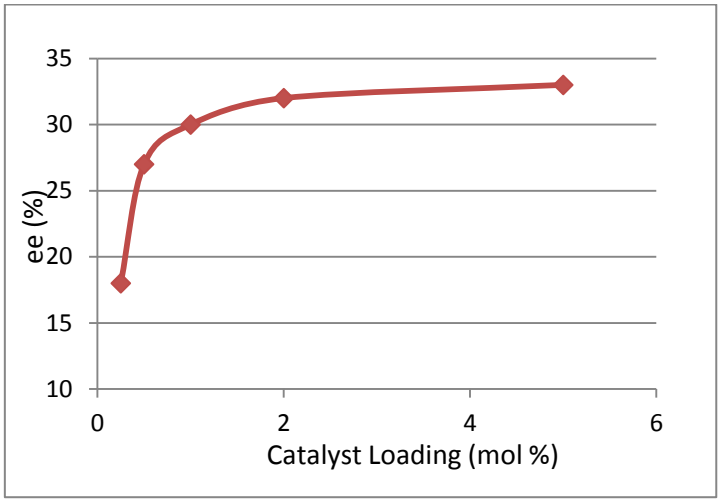
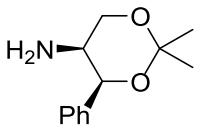


Figure 17: Effect of catalyst loading on the enantioselectivity of the asymmetric epoxidation of 1-phenylcyclohexene utilizing iminium salt **99**

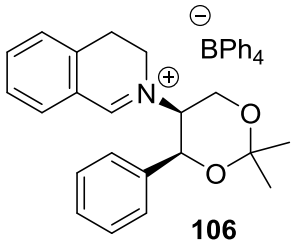
Since 1998, Page has made significant contributions towards designing iminium salts using a range of chiral amines in an attempt to potentially increase enantioselectivity. Page has introduced the dioxane-containing chiral amine **105**, which was proven to give better catalysts than amine **99**. Therefore, nowadays, amine **105** and derivatives are used exclusively in Page's most recent and successful catalyst designs (**Figure 18**). [67]



105

Figure 18: The dioxane-containing chiral amine **105**

Dihydroisoquinolinium salt **106** was used in the epoxidation of a range of simple alkenes, showing higher enantioselectivities, when compared to catalyst **99**.[67] For example, epoxidation of triphenylethylene was carried out using catalyst **106** (5 mol%) employing Oxone™ and sodium carbonate in an acetonitrile/water solvent system (1:1) at 0 °C, affording triphenylethylene oxide in 90% yield and 59% *ee* (compared with 100% yield and 5% ee when catalyst **99** was used under the same conditions). [67]

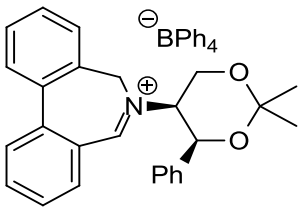


106

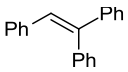
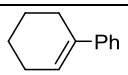
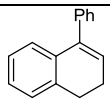
Figure 19

Further work was focused on the development of more selective catalysts, based on the replacement of the dihydroisoquinolinium moiety with a biphenyl structure, featuring a seven-membered ring system.[68] After screening various simple alkenes for asymmetric epoxidation, azepinium salt **107** was found to be more reactive in the epoxidation reaction than the six-membered ring dihydroisoquinolinium catalysts and demonstrated good enantiocontrol in the epoxidation process (**Table 4**).[68]

Table 4: Biphenyl-azepinium catalyst **107** prepared by Page and co-workers

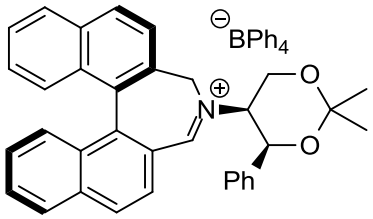


107

Catalyst	Time/min	conv/ (%)	ee/ (%)
	10	100	24
	3	90	59
	31	100	60
	3	41	41

Reagents and conditions (a) **107** (5 mol%), Oxone (2 equiv.), Na_2CO_3 (4 equiv.), MeCN/H_2O (1:1), 0 °C.

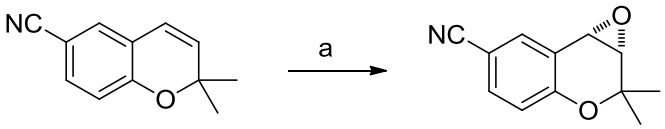
Page's group synthesised iminium salt catalyst **108** with a binaphthalene backbone (**Figure 20**).[69] The binaphthalene-azepinium salt **108** showed excellent enantioselectivities in the asymmetric epoxidation of 1-phenylcyclohexene (91% ee) and 4-phenyl-1,2-dihydronaphthalene (95% ee), while exhibiting poor enantioselectivities for 2-phenyl-2-propene (42% ee) and triphenylethylene (12% ee).[69]



108

Figure 20: Binaphthalene-azepinium catalyst prepared by Page and co-workers

Regarding the low solubility of Oxone™ in many organic solvents, Page's group conducted an investigation on the use of many stoichiometric oxidants under non-aqueous conditions. Tetraphenylphosphonium monoperoxysulfate (TPPP) turned out to possess a superior reactivity without any background epoxidation observed.[70] This positive finding was applied to develop a non-aqueous epoxidation system mediated by iminium salt catalysts.[70] Hence, performing the epoxidation reaction under the non-aqueous conditions at lower temperatures led to excellent enantioselectivities for the epoxidation of cyclic *cis*-disubstituted alkenes.[71] For example, 6-cyano-2,2-dimethylchromene oxide **110** was formed in a highly enantioselective fashion (97% ee) using iminium salt catalyst **107** (**Scheme 32**).[71]

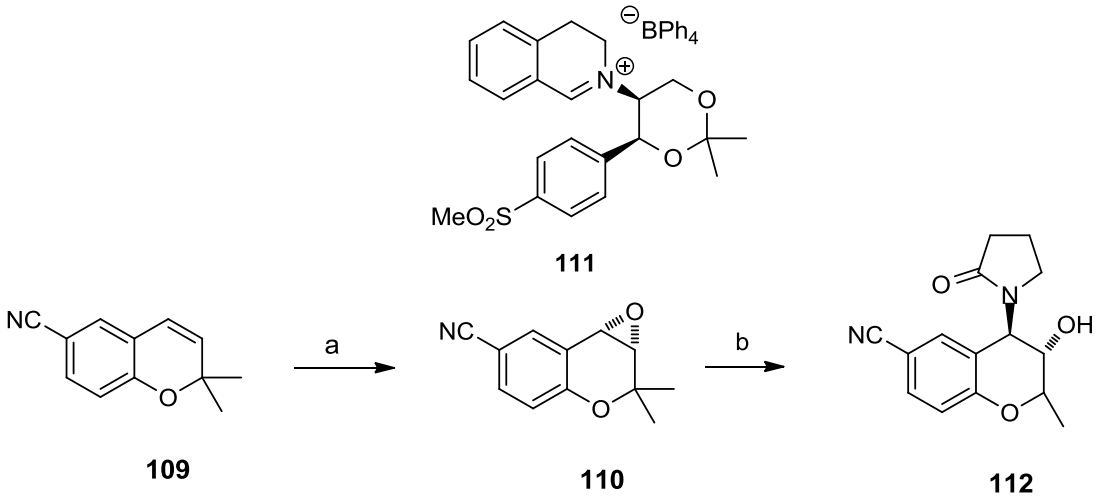


109 **110**

Reagents and conditions (a) Catalyst **107** (5 mol%), TPPP (2 equiv.), 20 h, 0 °C, 90%, 97% *ee*.

Scheme 32: Asymmetric epoxidation of **109** under non-aqueous conditions

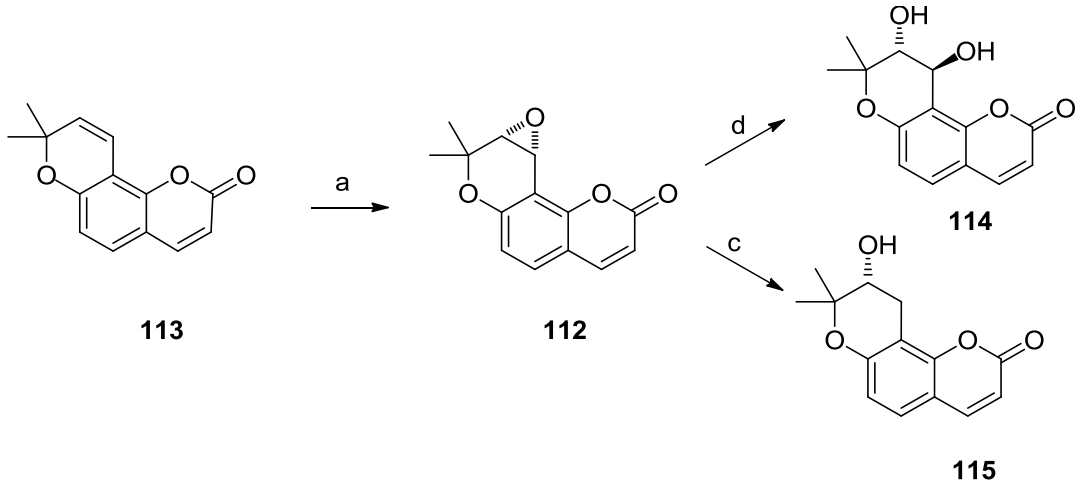
Subsequently, Page was able to use chiral iminium salts under non-aqueous conditions for the formation of epoxides in high enantioselectivity as the key step in the synthesis of natural products.[72] For example, in 2005, the total synthesis of anti-hypertensive agent levcromakalim **114** was achieved using an asymmetric epoxidation reaction mediated by **111** (**Scheme 33**).[72]



Reagents and conditions (a) Catalyst **111** (10 mol%), TPPP (2 equiv.), $CHCl_3$, 24 h, −40 °C, 85%, 97% ee; b) Pyrrolidin-2-one. NaH, DMSO, RT, 52%.

Scheme 33: Synthesis of levcromakalim **112**

Epoxide intermediate **110** was subjected to a ring-opening reaction using pyrrolidin-2-one to give levcromakalim.[72] Natural products *trans*-khellactone **114** and lomatin **115** were also prepared using an asymmetric epoxidation as the key step (**Scheme 34**).[73]



Reagents and conditions: (a) Catalyst **111** (10 mol%), TPPP (2 equiv.), $CHCl_3$, 24 h, −30 °C, 65%, 97% ee; d) 1M H_2SO_4 (aq.), acetone, RT, 95%. c) $NaBH_3CN$ (1 equiv.), $BF_3{\cdot}OEt$, THF, 0 °C, 92%.

Scheme 34: Total syntheses of *trans*-khellactone **114** and lomatin **115**

1.11 Kinetic resolution

In all living cells and organisms, complex processes naturally occur to synthesize chiral compounds that exist in an enantiomerically pure form, for instance, carbohydrates, proteins, and DNA in contrast with chemical reactions which usually produce racemic mixtures.[2] The racemic mixtures can then be separated into the two enantiomeric forms.[4] The process of separating a racemic mixture into its enantiomers is known as resolution.[4] One way of achieving separation is using a kinetic resolution. Kinetic resolution is a term defined as transformation of one of enantiomer faster than the other into the product in high enantiomeric purity, mediated by a chiral catalyst. The process depends on each enantiomer in the racemic mixture reacting at a different rate $K_R \neq K_S$ (**Figure 20**).[2,74]

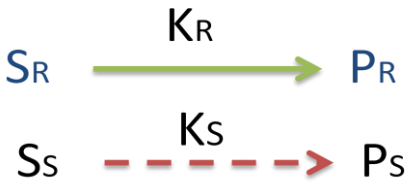


Figure 20

The selectivity factor (k_{rel}) is calculated by the equation reported by Kagan, which is related to the rate constant of the reaction of the R and S enantiomers, proceeding to a signal product. [74]

$$S = \frac{In\ (1-c)\ (1-ee)}{In\ (1-c)\ (1+ee)}$$

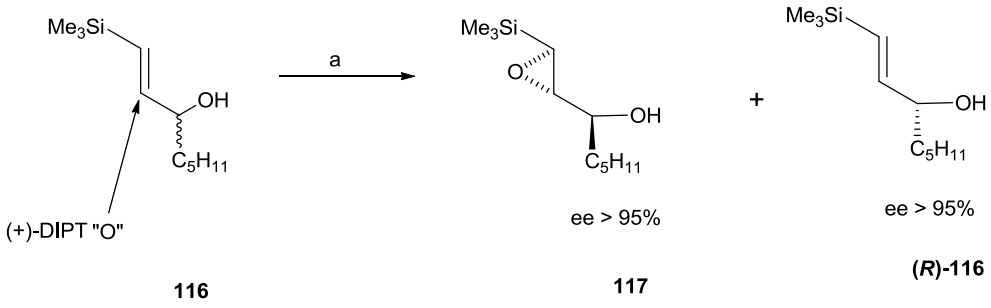
$S = K_{rel} = K_{fast}/K_{slow}$, ee = enantiomeric excess, c = conversion

1.11.1 The use of kinetic resolution in catalytic asymmetric epoxidation

The major advantages of a kinetic resolution process using asymmetric epoxidation lie in the following: racemic starting materials are cheap and readily available; a catalytic kinetic resolution can proceed at low loading; the catalyst is inexpensive and can be reused; and the unreacted substrate and product can be obtained with excellent enantioselectivities. [75]

1.11.2 Sharpless' kinetic resolution

An early report of a successful kinetic resolution using asymmetric epoxidation was published by Sharpless in 1981.[75] The asymmetric epoxidation reaction conditions previously reported were applied to a racemic allylic alcohol.[4] Although both enantiomers of the allylic alcohol can be epoxidized from the same face, the stereochemical outcome of the epoxidation of chiral allylic alcohols is settled by different rates of reaction for each enantiomer. For instance, racemic secondary allylic alcohols **116** that have one chiral centre at C1 (attached to the OH group) were tested under Sharpless epoxidation. One enantiomer is consequently expected to react faster than the other, if the rates of epoxidation of two enantiomers are fundamentally different.[4] Sharpless was able to obtain epoxide **117** and allylic alcohols in high enantioselectivity. Sharpless determined that the rate of epoxidation of (*S*)-**116** is 700 times higher than (*R*)-**116** (**Scheme 35**).[4]

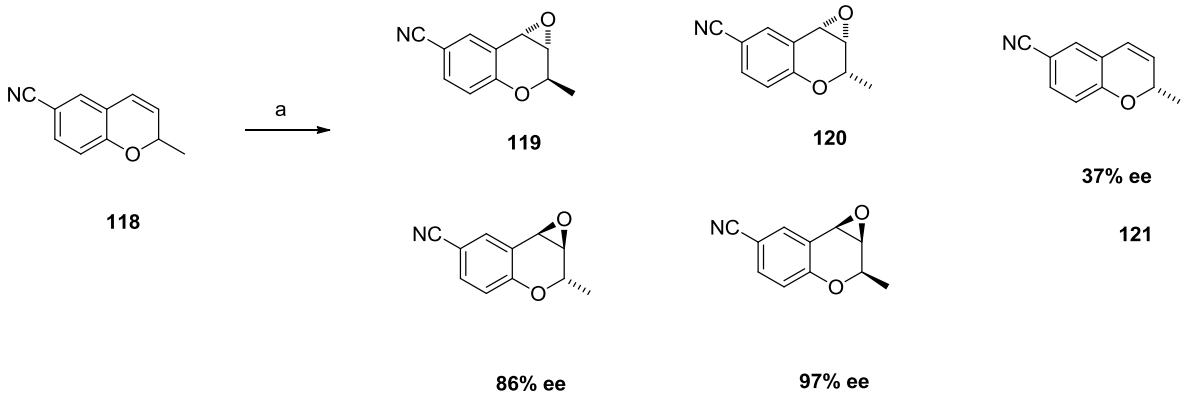


Reagents and conditions: (a) (+)-DIPT, $Ti(OPr^i)_4$,TBHP.

Scheme 35: Stereochemical outcome of the epoxidation of secondary allylic alcohols

1.11.3 Page's kinetic resolution

In 2013, Page first reported the kinetic resolution of racemic chromenes using an iminium salt-mediated epoxidation reaction.[77] The first example explored by Page, 6-cyano-2-methyl-chromene substrate **118**, was based on a 2-substituted benzopyran with the chiral centre at the C2 position. Chromene **118** was initially subjected to iminium salt-catalysed epoxidation, allowing a perceptive insight into the outcome of the kinetic resolution methodology.[77] The reaction was carried out with iminium salt **111** under non-aqueous conditions, affording the major epoxide diastereoisomer **119**, where the epoxide moiety is *trans* with regard to the methyl group at the C2 position, in 86% ee, the minor epoxide diastereoisomer **120** in 97% ee, and the unreacted starting material **121** in 37% ee (**Scheme 36**). [77]



Reagents and conditions: (a) iminium salt **111** (10 mol%), TPPP (4 equiv.), $CHCl_3$, –30 °C, 24 h (The upper structures of each pair are the major isomers in each case).

Scheme 36

Page was able to confirm the configuration of the major epoxide product by: 1) based on previous outcomes observed within the group for the epoxidation of prochiral olefins with catalyst **111**, the *si* face of the substrate appeared to be favoured; 2) the unreacted starting materials were recovered as enantioenriched mixtures and their optical rotations were matched by analogy with chiral chromenes of known absolute configuration and optical rotation which had been previously synthesized or isolated as single enantiomers (**Figure 21**).[77]

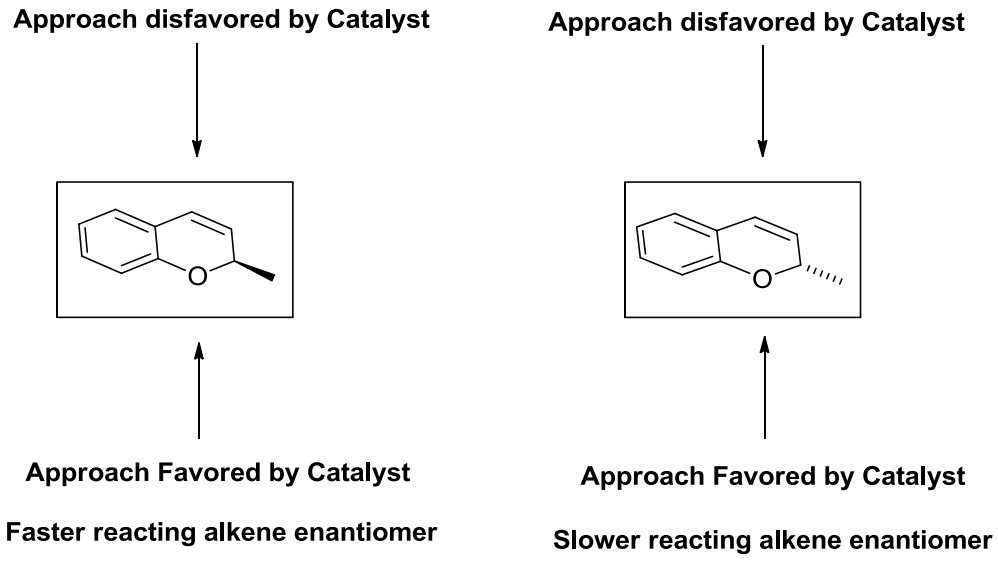
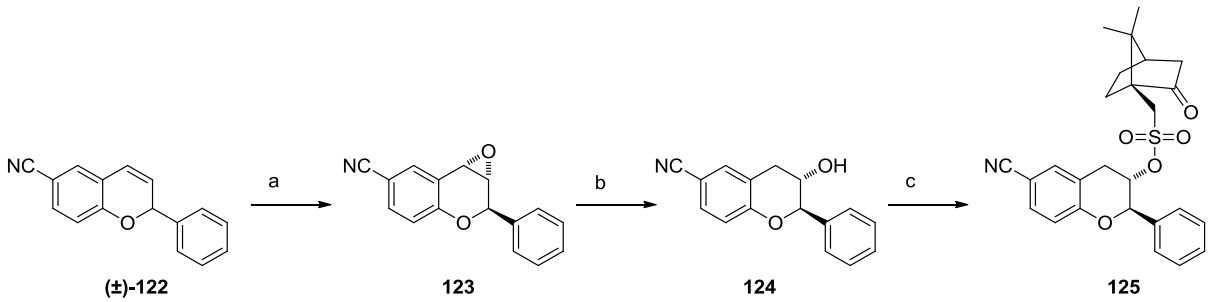


Figure 21

Increasing the size of the substituent at the C2 position, from methyl to phenyl, particularly favoured the formation of the major epoxide, where the epoxide moiety is *trans* with regards to the phenyl group without any observation of the c*is* analogue.[77] Importantly, the absolute configuration of the major epoxide enantiomer was confirmed by single crystal X-ray analysis of a sample of compound **125** (**Scheme 37**). [77]



Reagents and conditions: (a) Catalyst **111** (10 mol %), TPPP, $CHCl_3$, −30 °C, 24 h, 74 % ee; (b) Pd/C, H_2 (1 atm.), MeOH, RT, 20 min, quantitative; (c) (10*S*)-(+)-camphorsulfonyl chloride (1 equiv.), Et_3N (2 equiv.), toluene, RT, 24 h, 43%.

Scheme 37

1.12 Flavonoids

Phenolic compounds form one of the main classes of secondary metabolites and occur in a vast range of plants.[78,79] They possess a large number of structures with extreme diversity, for instance, benzoquinones, chromones, stilbenes, and flavonoids. [79] Phenolic compounds play a significant role in the organoleptic and nutritional qualities of fruit and vegetables.[78] Thus, certain colour and taste properties have been attributed to phenolic compounds in a number of plants and derivatives such as berries, tea, beer, grapes, olive oil, cocoa and coffee.[78,79,80] Among these compounds are flavonoids, which are generally termed to indicate a wide range of compounds and constitute one of the major classes of all plant secondary metabolites. Flavonoids are categorized by subclasses, which arise from a change in oxidation state, skeletal modification and oligomer formation.[81,82] They have the basic skeleton of 1,3-diphenyl propane (C_6-C_3-C_6), depending on the position of the linkage of the aromatic ring (ring C) to the benzopyran. Therefore flavonoids may be divided into three categories: flavonoids (2-phenylbenzopyrans) **126**, isoflavonoids (3-phenylbenzopyrans) **127**, and neoflavonoids **128** (**Figure 22**). These categories also possess similar biological activity.[81,82,83]

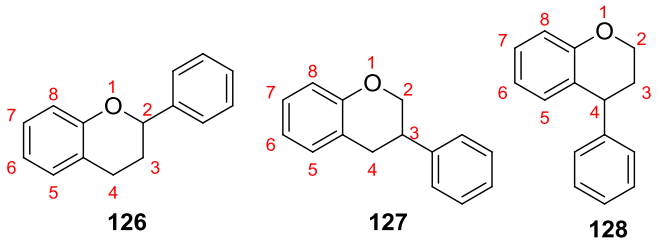


Figure 22: Structures of flavonoids **126**, isoflavonoids **127**, and the neoflavonoids **128**

1.12.1 2-Phenylbenzopyrans (C_6-C_3-C_6 backbone)

The degree of oxidation and saturation present in the heterocyclic C-ring and a basic chemical structure (C_6-C_3-C_6 backbone) are fundamental factors in the sub-division of 2-phenylbenzopyrans into the following groups **(Figure 23)**: [81]

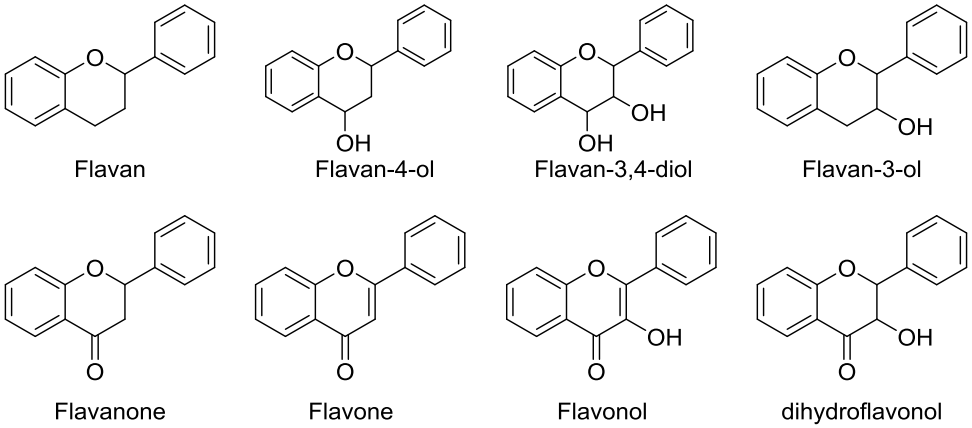


Figure 23

1.12.2 flavan-3-ol

Repeated condensation of flavan-3-ol results in the formation of a polymeric proantho-cyanidin, which may be defined as natural condensed tannin.[79,80] It exists as a mixture consisting of several 3-flavan-3-ols with different numbers of phenolic hydroxyl groups on the C ring. [80,84] Many flavan-3-ols have been identified and characterized according to the degree of hydroxylation of ring C; they are thought to have one (afzlechin/epiafzlechin), two (catechin/epicatechin), and three (gallocatechin/epigallocatechin) hydroxyl groups as well as different stereochemistry at the asymmetric carbon atoms in the heterocyclic ring C; examples include (+)-afzlechin, (−)-epiafzlechin, (+)-catechin, (−)-epicatechin, (−)-gallocatechin and (−)-epigallocatechin (EGC) (**Figure 24**). [79,80,84]

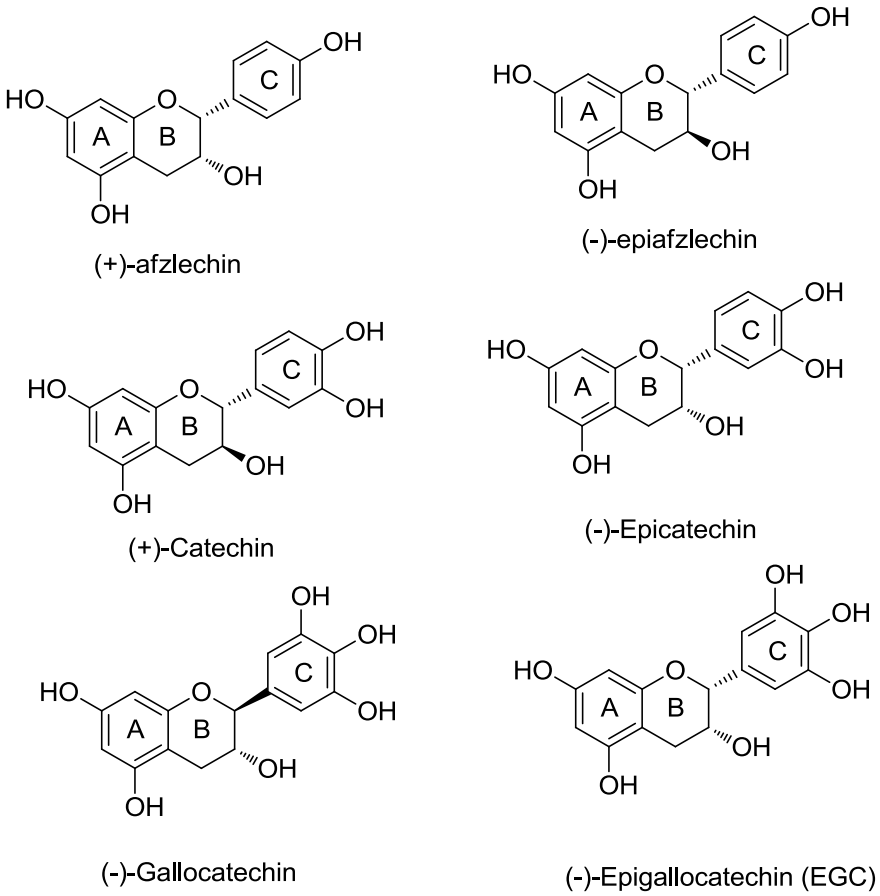
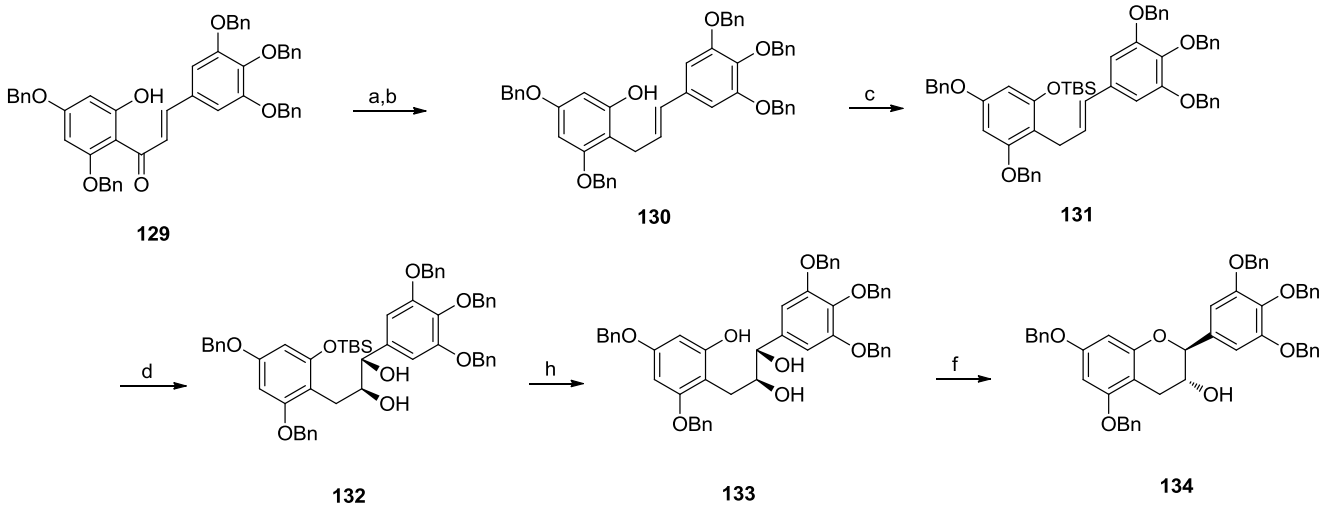


Figure 24: subclasses of flavan-3-ol

Although the majority of flavan-3-ols possess powerful antioxidant properties, many also have other biological activities attributed to them.[79] They show anticancer, antimutagenic, and immunomodulatory activities, promote cardiac recovery after ischamia, and inhibit bacterial adhesion to the urinary tract.[85,86]

1.12.3 Synthesis of (-)-Gallocatechin

The enantioselective synthesis of (−)-gallocatechin **134** was reported by Krohan.[87] Reduction of ketone **129** followed by dehydration using ethyl chloroformate and sodium borohydride led to the olefin **130** in 57% yield, followed by protection of hydroxyl group using *tert*-butyldimethylsilyl chloride.[87] A Sharpless asymmetric dihydroxylation of the double bond provided the key intermediate **132** in high enantiomeric purity (93.6% ee). Treatment of the TBS-ether **132** with tetrabutylammonium fluoride (TBAF) afforded the triol **133** in 92% yield. Cyclisation of the triol took place under Mitsunobu conditions, giving (−)-Gallocatechin **134** in 71% yield and 97.7% ee. [80,87]



Reagents and conditions: a) ClCOOEt, Et_3N, THF.; b) $NaBH_4$, H_2O–EtOH, 0–5 °C ,57%; c) TBSCl, DMF, imidazole, 93%; d) AD-mix α, *t*-BuOH–H_2O (1:1), 82%, 93.6% *ee*; h) TBAF, THF, r.t., 1.5h, 92%; f) DEAD, Ph_3P, THF, r.t., 3h,71%, 97.7% *ee*.

Scheme 38: Syntheses of (−)-Gallocatechin **134**

1.13 Introduction references

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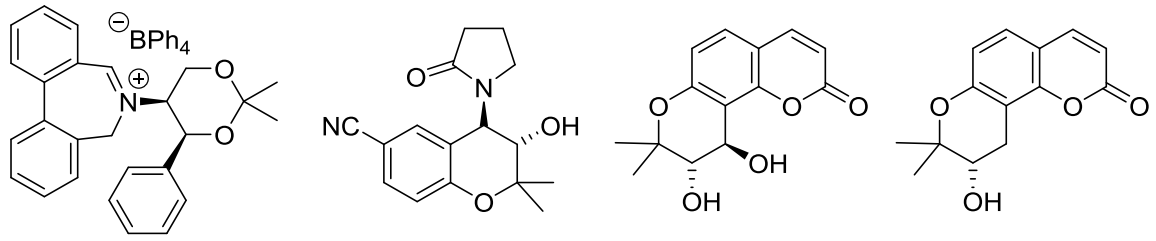
2.0 Results and discussion

2.1 Project Structural Analysis

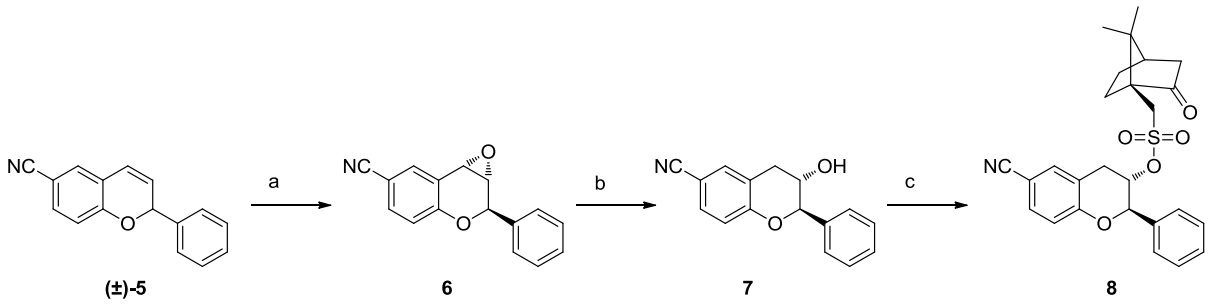
Chromenes are heterocyclic compounds and are potential targets for laboratory synthesis. They exhibit a broad range of pharmacological profiles, including anti-oxidant, anti-inflammatory, anti-cancer, and anti-HIV activity.[1] Preparation of racemic chromenes has been widely reported, although the number of examples of enantioselective synthesis of chromenes appears limited.[2,3] The asymmetric epoxidation reaction is a recently developed approach that can offer synthesis of optically active tetrahydropyrans in a highly enantioselective fashion.[4] Indeed, since 2005, metal-free catalytic asymmetric epoxidation using iminium salts such as **1** has been successfully employed to access chiral chromenes within the Page group. The iminium-catalysed asymmetric epoxidation methodology has been applied to the synthesis of levcromakalim **2**,[4] *trans*-khellactone **3**, and lomatin **4**,[1] which are based on a chromene-type structure (**Figure 1**).



1 levcromakalim **2** *trans*-khellactone **3** lomatin **4**

Figure 1: Chiral chromenes obtained using iminium salt catalysed epoxidation

We have also used Page's organocatalytic asymmetric epoxidation methodology towards the kinetic resolution of racemic chromene substrates. A successful protocol of kinetic resolution was developed by Page's group and involved the use of chiral iminium salts and the oxidant TPPP (Tetraphenylphosphonium monoperoxysulfate), soluble in organic solvents. [5] The aim of this study was to oxidize racemic alkenes, based on a chromene-type structure such as **5,** to afford epoxides in a diastereoselective and enantioselective fashion. The less reactive alkene enantiomer was also recovered in a low enantiomeric excess (14% ee) **Scheme 1**. [5]



Reagents and conditions: (a) Catalyst (10 mol %), TPPP, $CHCl_3$, -30 °C, 24 h, 74 % ee; (b) Pd/C, H_2 (1 atm.), MeOH, RT, 20 min, quantitative; (c) (10*S*)-(+)-camphorsulfonyl chloride (1 equiv.), Et_3N (2 equiv.), toluene, RT, 24 h, 43%.

Scheme 1: Oxidation of racemic chromene **5**.

Our group has a continuing interest in the application of the kinetic resolution to the flavan-3-ol family, with stereogenic centres at C2 and C3, which could be accessed through the selective oxidation of a racemic alkene using chiral iminium salts. This is due to the stereochemical outcome provided in the reaction described above (Scheme 1), which would allow us to access our target (-)-epigallocatechin (EGC) **9** from racemic alkene (±)-**10**. [6,7,8]

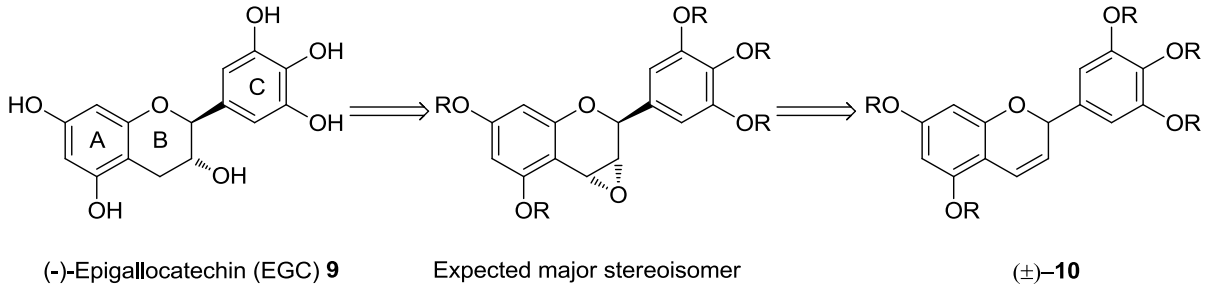
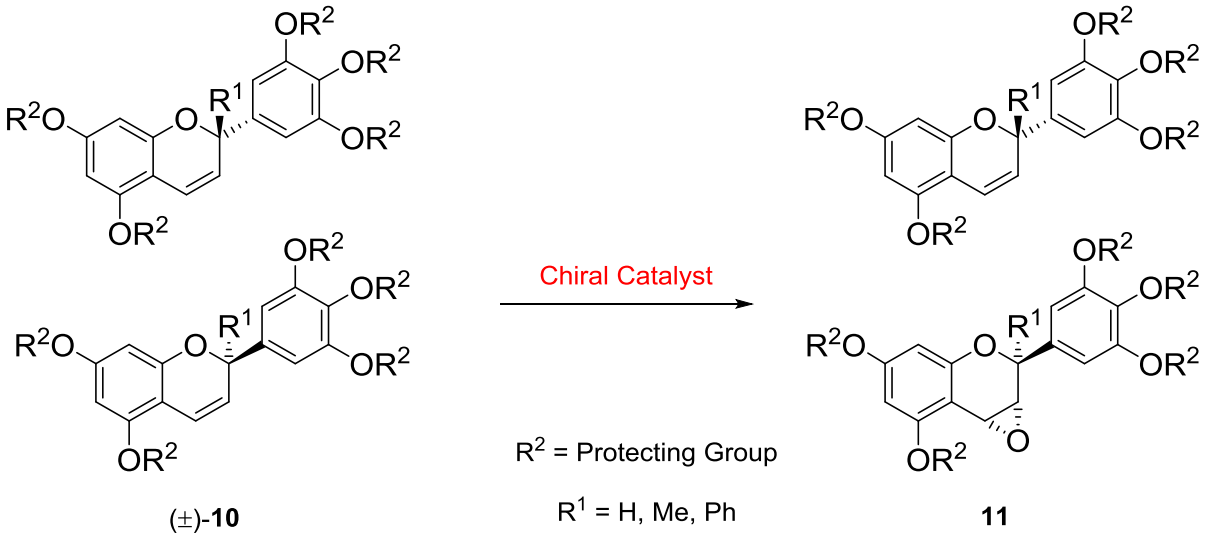


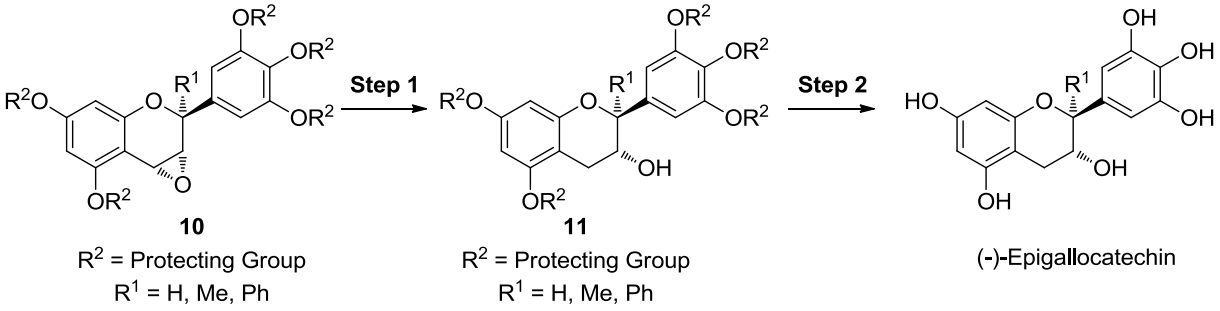
Figure 2: Retrosynthesis of epigallocatechin.

A concise enantioselective synthesis of chiral natural product **9** and its analogues was devised through a number of steps, including an asymmetric epoxidation reaction of a chromene-type structure as the key selective step. The absolute configuration of the stereogenic carbon atoms C-2 and C-3 from epigallocatechin and analogues will be accessed as shown below (**Scheme 2**) using chiral iminium salts as catalyst to transfer oxygen to the electron-rich racemic alkene **10**, where one enantiomer reacts faster than the other, resulting in the favoured formation of the chiral epoxide **11** with the desired configuration at C-2 and C-3.[5]



Scheme 2: Kinetic resolution of racemic alkene **10**

The preferential formation of one epoxide enantiomer **11** would be followed by a two-reaction sequence to form epigallocatechin (**Scheme 3**). The first step would be the reductive ring opening (Step 1) of the epoxide moiety followed by the removal of the protecting groups (Step 2).



Scheme 3: Synthesis of epigallocatechin and analogues

2.2 Synthesis of flav-3-ene A

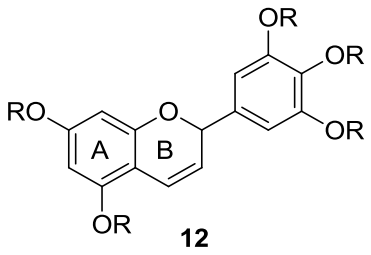
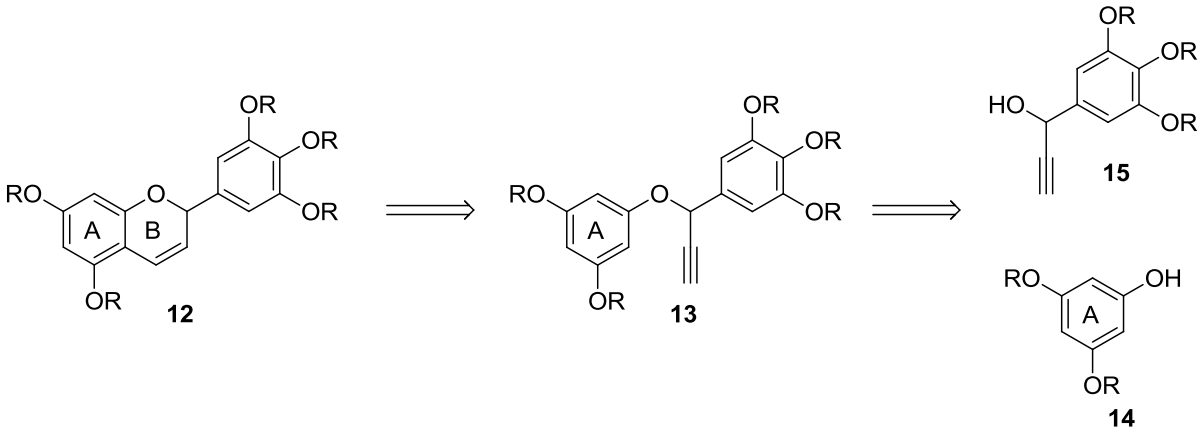


Figure 3: Targeted flav-3-enes.

Our concise approach for the synthesis of chromene **12** is based on an intramolecular Claisen rearrangement of propargylic ether **13**. During this process, aryl ethers are heated under reflux with a high boiling point solvent, such as ethylene glycol. The structure of the chromene is built by the linking of two ring fragments, namely A and B. Propargylic ether **13** can be potentially accessed through the condensation reaction of a phenol and a propargyl alcohol.[9] A synthetic route through which to form the aryl ethers can be achieved by nucleophilic attack of phenol **14** onto propargylic alcohol **15** in order to displace the alcohol moiety in the presence of acid (**Scheme 4**). [10, 11]

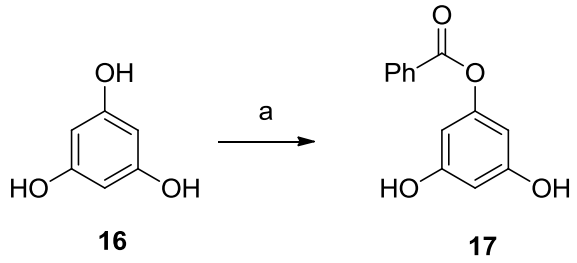


Scheme 4: Retrosynthetic approach towards **12**.

2.2.1.1 Synthesis of 3,5-dibenzyloxyphenol

Our initial target was 3,5-bis(benzyloxy)-phenol (Compound **14** where R=Bn). Attempts to obtain the desired bis-protected phenol from 1,3,5-benzenetriol **16** failed, with statistical mixtures obtained. Several studies have revealed that 3,5-dibenzyloxyphenol could be obtained through mono-protected 1,3,5-benzenetriol **17**. [12,13] The protected compound was

obtained using benzoyl chloride and pyridine in anhydrous tetrahydrofuran under reflux, giving benzoate **17** in 48% yield after three days (**Scheme 5**). [14]

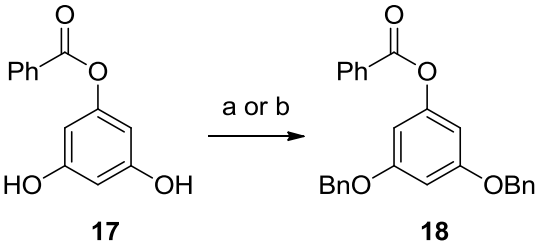


16 **17**

Reagents and conditions: (a) BzCl, pyridine, THF, reflux, 3 d, 48%.

Scheme 5: Mono-protection of 1,3,5-benzenetriol **16**.

The remaining hydroxyl groups were protected with benzyl groups. Compound **17** underwent the protection reaction using benzyl bromide and potassium carbonate in anhydrous tetrahydrofuran, affording **18** in 66% yield. When 18-crown-6 was also used, the reaction yield increased to 79%. [15]

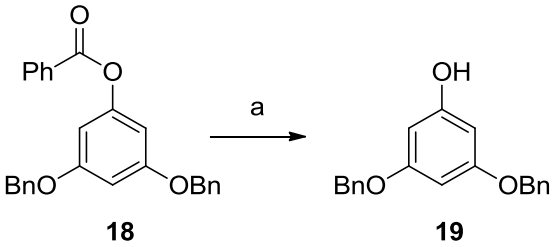


17 **18**

Reagents and conditions: (a) BnBr, K_2CO_3, THF, reflux, 24h, 66%; (b) BnBr, K_2CO_3, 18-crown-6, THF, reflux, 24h, 79%.

Scheme 6

Saponification of the benzoyl group using potassium hydroxide in methanol failed to yield **19**, with only starting material **18** recovered. [14] $LiAlH_4$ was then used to reduce the ester, leading to **19** in 68% yield.



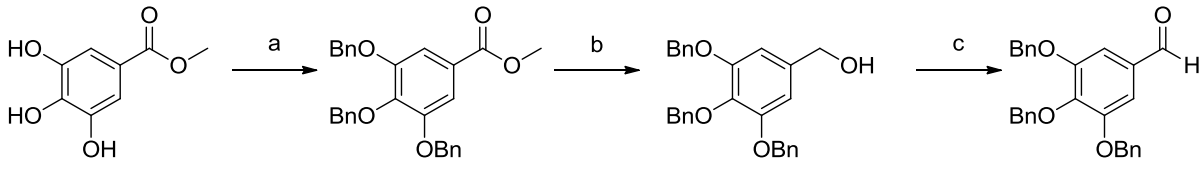
18 **19**

Reagents and conditions: (a) $LiAlH_4$, THF, overnight, 68%.

Scheme 7: Removal of the benzoyl protecting group

2.2.1.2 Synthesis of propargyl alcohol 24

During the next stage towards the synthesis of epigallocatechin, we attempted to prepare the C-ring fragment. Benzyl groups were chosen to mask the three nucleophilic and acidic hydroxyl groups of methyl 3,4,5-trihydroxybenzoate **20** to prevent any side reaction. This was achieved using a general method for the benzylation of phenols, involving a nucleophilic substitution reaction on benzyl bromide in the presence of K_2CO_3, and dimethylformamide to produce **21** in 89% yield. [16] Conversion of the ester to the corresponding alcohol was completed overnight, using $LiAlH_4$ in anhydrous tetrahydrofuran to give the desired compound **22** in 90% yield. Finally, the alcohol moiety was then oxidized to form the benzaldehyde **23** using PCC in 81% yield. [17]

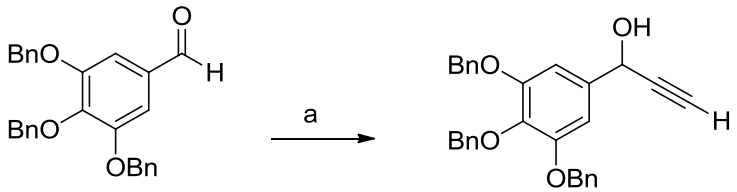


20 **21** **22** **23**

Reagents and conditions: (a) BnBr (4.5 equiv.), K_2CO_3 (3.3 equiv.), DMF, RT, overnight, 89%; (b) $LiAlH_4$ (1.55 equiv.), THF, 0 °C to RT, overnight, 90%; (c) PCC (1.5 equiv.), CH_2Cl_2, RT, overnight, 81%.

Scheme 8

Benzaldehyde **23** was subjected to the addition of a suitable organometallic reagent to synthesise racemic alcohol **24**. Propargylic alcohol **24** would play a significant role as a building block between ring C and rings A and B using a condensation reaction, and establishing the crucial C-O bond. The formation of secondary alcohol **24** containing a new carbon-carbon bond was achieved successfully using a Grignard reaction through the slow addition of ethynyl magnesium bromide to 3,4,5-*tris*-benzyloxy-benzaldehyde **23** under anhydrous conditions at −78 °C, yielding 66% of the desired compound as a yellow solid (**Scheme 9**). [18,19]



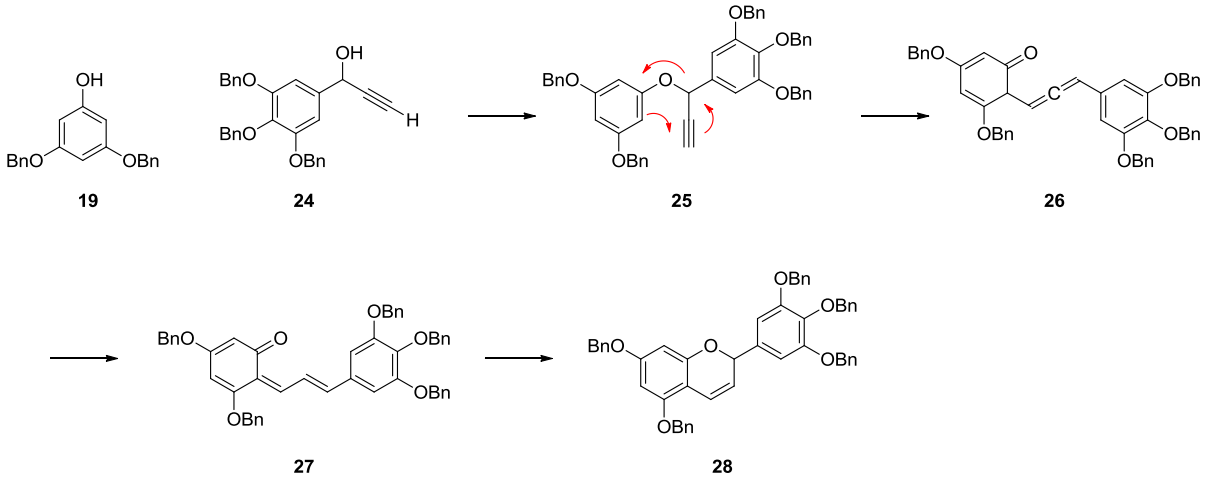
23 **24**

Reagents and conditions: (a) Ethynylmagnesium bromide (5 equiv.), NH_4Cl, THF, –78 °C, 2h, 66%.

Scheme 9

2.2.1.3 Synthesis of propargyl ether 25

A considerable amount of literature has been published in relation to the synthesis of chromenes.[19,20] For example, a simple and straightforward approach is the cyclo-condensation reaction of a phenol and a propargyl alcohol, which are easily accessible starting materials.[19] The proposed mechanism of the condensation reaction may be described as a sequence: firstly, 3,5-bis(benzyloxy)phenol **19** would be condensed with propargylic alcohol **24** to give propargyl ether **25** in the presence of an acid. During the second step, a Claisen rearrangement of propargyl ether **25** would occur to give allene **26**. Rearrangement of the allene moiety would give conjugated ketone **27**, and finally **3**-flav-3-ene **28** would be obtained through cyclization of **27**. [21]



Scheme 10: Proposed mechanism for the formation of alkene **28**.

According to the literature,[19,20,21] the synthesis of flav-3-enes can be achieved easily under acidic conditions (**Scheme 10**). The propargylic alcohol **24** was treated with phenol **19** in the presence of camphorsulfonic acid (0.05 equiv.) in anhydrous dichloromethane for 48 h at a room temperature. Unfortunately, no significant change in the reaction mixture was observed using ^{1}H NMR spectroscopic analysis, and only the starting materials were recovered. Increasing the amount of camphorsulfonic acid (0.1 equiv.) led to the formation of propargyl ether **25** in a moderate yield (28%) rather than flav-3-ene **28** (**chart 1**); and further yield increases were also observed as the amount of camphorsulfonic acid was increased.

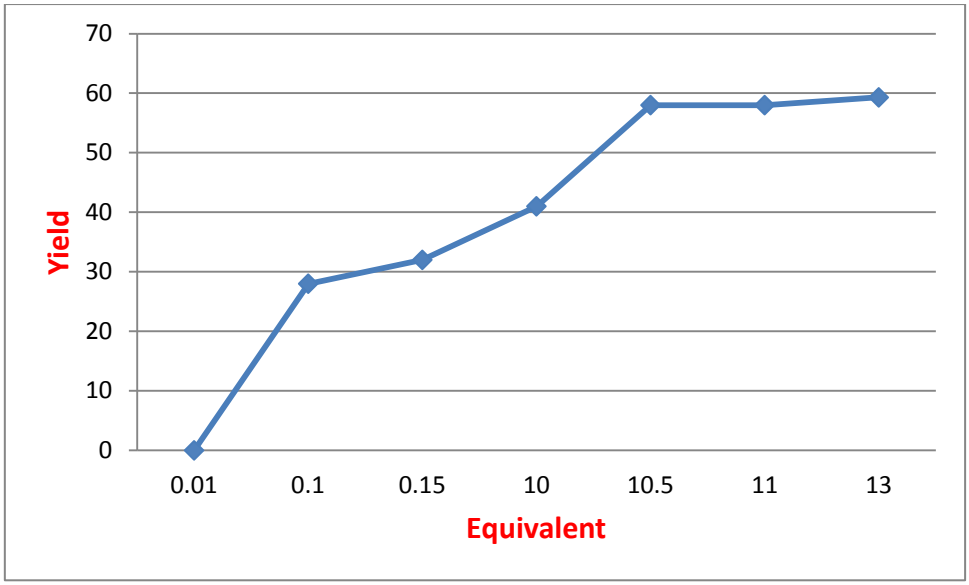
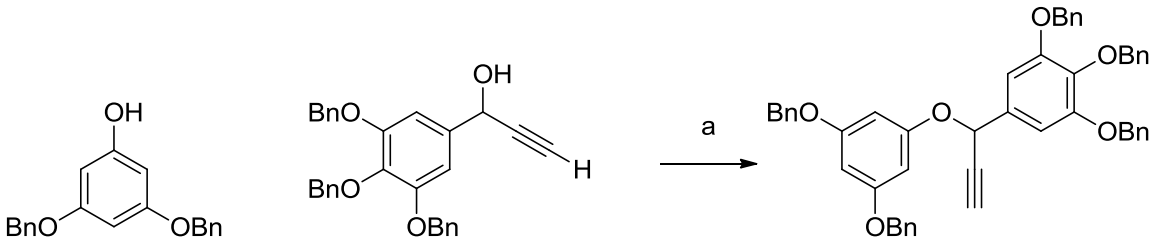


Chart 1: Optimisation of the synthesis of propargyl ether **25**

Relatively few methods have been described for the preparation of 2H-chromenes by one step condensation of a phenol and a propargyl alcohol using a Lewis acid as the catalyst. [19,22] The condensation reaction of 2-naphthol and a diaryl propargyl alcohol under acidic alumina catalysis to obtain diaryl-naphthopyrans in 32% yield has been reported.[23] In our hands, the condensation reaction occurred as a result of the treatment of the propargylic alcohol **24** with the phenol **19** in the presence of acidic alumina in toluene under reflux overnight, leading to propargyl ether **25** in 21% yield.

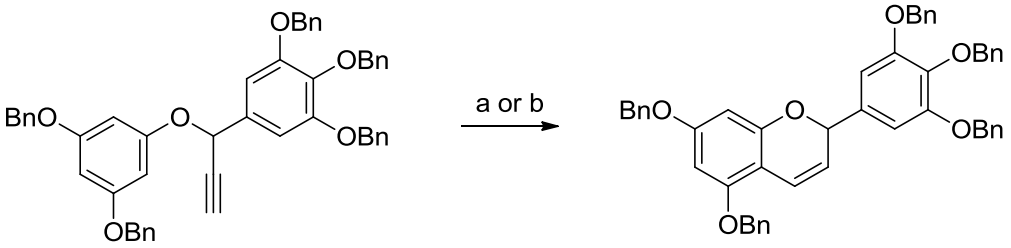


Reagents and conditions: (a) Al_2O_3, toluene, reflux, overnight, 21%.

Scheme 11

A Claisen rearrangement of the propargyl ether **25** into the corresponding chromene **28** was then attempted.[9,11] First, a high boiling point solvent, *N*,*N*-dimethylaniline, was used in order to promote a thermal Claisen rearrangement (**Table 1**).

Table 1: Thermal Claisen rearrangement attempts.



25 **28**

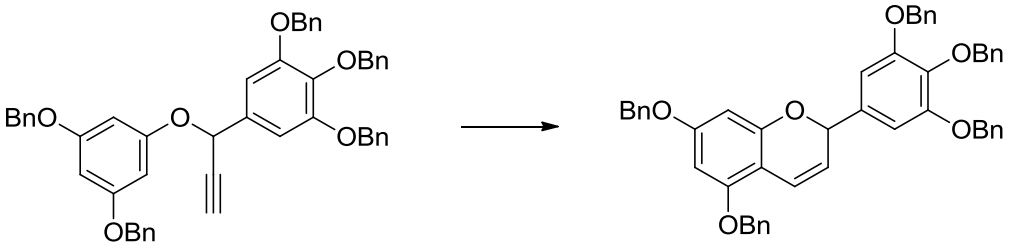
Conditions	Temp	Solvent	Time	Yield
a	Reflux	*N*,*N*-dimethylaniline	24 h	decomposition
b	150 °C	*N*,*N*-dimethylaniline	4 h	decomposition

Reagents and conditions: (a) *thermal reaction*; (b) *microwave-assisted synthesis.*

Unfortunately, the thermal rearrangement was unsuccessful and led to the decomposition of our starting material. A microwave-assisted synthesis was then attempted at a lower reaction temperature; only decomposition products were observed.

Another possible methodology involves the use of copper(I) chloride in the presence of copper as a catalyst to activate the alkyne moiety (**Table 2**). [11]

Table 2

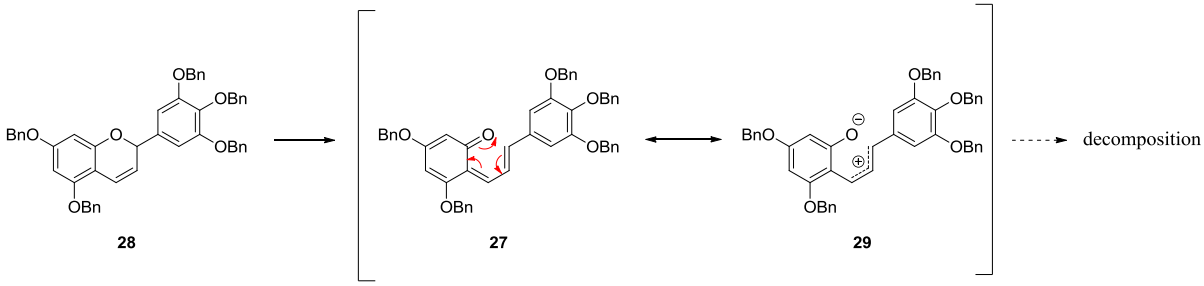


25 **28**

Entry	Temp.	Solvent	Catalysts	Time	Yield
1	Reflux	Toluene	Cu/CuCl	24 hours	decomposition
2	Reflux	Toluene	Cu/CuCl	24 hours	decomposition

Alkyne **25** was dissolved in toluene in presence of copper chloride and copper metal, and the reaction mixture was heated under reflux; as observed above, only decomposition products were observed under these reaction conditions. The instability of the flav-3-ene precursor under thermal conditions influenced the outcome of the Claisen rearrangement, regardless of

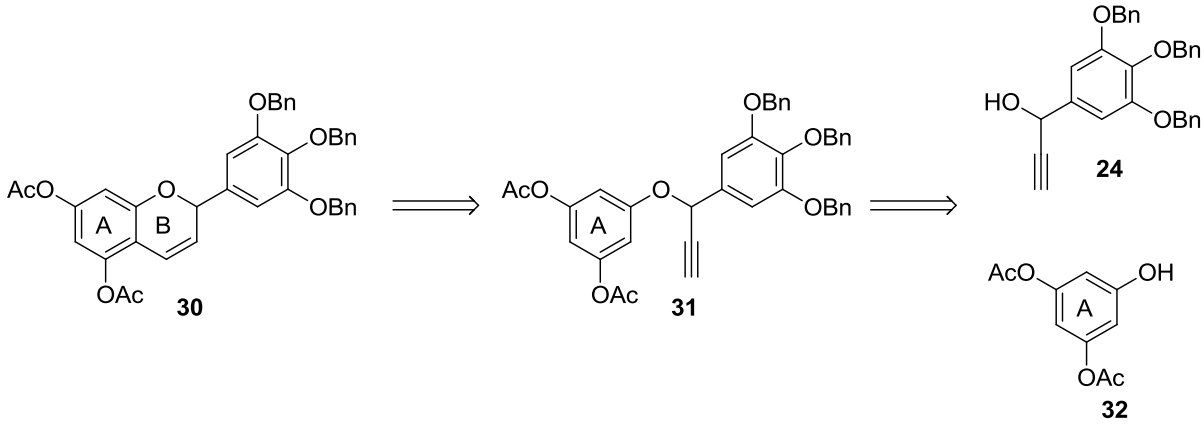
whether or not a Lewis acid was used. As reported in the literature, a possible degradation pathway involves the highly reactive orthoquinone methide **27**, which is in resonance with the corresponding allylic cation **29** (**Scheme 12**). [24,25]



Scheme 12: Possible degradation pathway

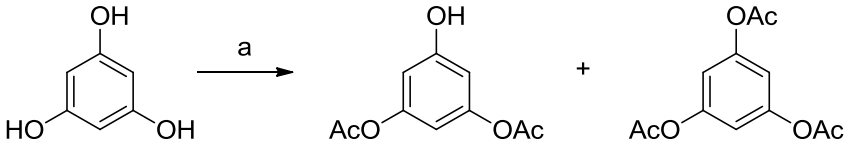
As the orthoquinone methide **27** is also a possible intermediate during the Claisen rearrangement of propargyl ether **25** (**Scheme 10**), a change of strategy was needed to improve the stability of the desired product. [24,25]

From a synthetic point of view, we believe the presence of highly electron-rich groups such as the benzyloxy groups on alkyne **25** may be destabilizing the flavene moiety. Replacing the benzyloxy with acetoxy groups would bring a reduced electron density into the conjugated π system to stabilize the flav-3-ene **30** or the corresponding orthoquinone methide intermediate. The synthesis would follow the same route as above, where a Claisen rearrangement of alkyne **31** would afford the desired flavene **30** (**Scheme 13**). Propargyl ether **31** can be prepared from the coupling of alkyne **24** and phenol **32**.



Scheme 13

3,5-Diacetoxyphenol **32** was prepared by treatment of phloroglucinol **16** with acetic anhydride in pyridine under reflux for 15h. The desired diacetoxy compound **32** was obtained in 58% yield, alongside the corresponding triacetoxy derivative **34** in 26% yield. [27]

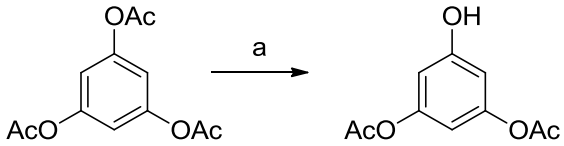


16 **32** **34**

Reagents and conditions: (a) Ac_2O, pyridine, reflux, 15h, [(**32**, 58%); (**34**, 26%)].

Scheme 14

Phloroglucinol triacetate **34** can be converted to the desired diacetate **32** using a simple saponification reaction. Indeed, compound **34** was dissolved in dimethylformamide followed by the addition of sodium hydride (0.5 equiv.) at 60 °C to afford phenol **32** in 53% yield. [28]

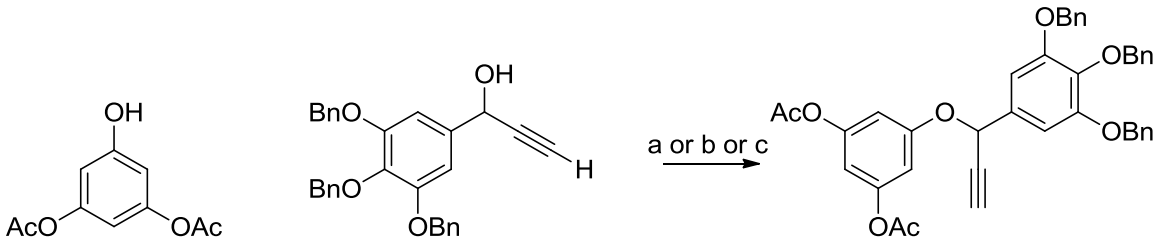


34 **32**

Reagents and conditions: (a) NaH, DMF, 60 °C, 4h, 53%.

Scheme 15

The acid-catalysed condensation of a phenol and a propargyl alcohol was then attempted to prepare the propargyl ether **31** (**Scheme 16**). 3,5-Diacetoxyphenol **32** and alkyne **24** were dissolved in anhydrous dichloromethane in the presence of camphorsulfonic acid for 18h to synthesise the propargyl ether **31** in 16% yield. [19,20]



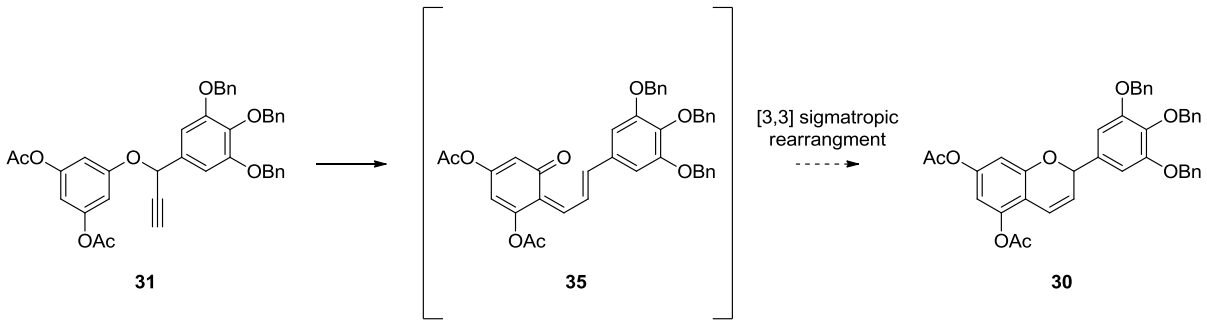
32 **24** **31**

Reagents and conditions: (a) camphorsulfonic acid, RT, CH_2Cl_2,18h, 16%; (b) DIAD, PPh_3, toluene, 0 °C to RT, 18h, 43%; (c) DIAD, PPh_3, THF, 0 °C to RT, 18h, 65%.

Scheme 16

As the yield obtained using the acid-catalysed methods were disappointing, another strategy was devised. A common way to form ethers involves the Mitsunobu reaction. [29] The phenol **32**, the propargyl alcohol **24** and triphenylphosphine were dissolved in anhydrous toluene at 0 °C, followed by the addition of diisopropyl azodicarboxylate (DIAD). TLC analysis showed that the propargyl ether **31** was gradually formed over 16 hours, and the desired product was obtained in 43% yield. When tetrahydrofuran was used in place of toluene, the yield was increased to 65%.

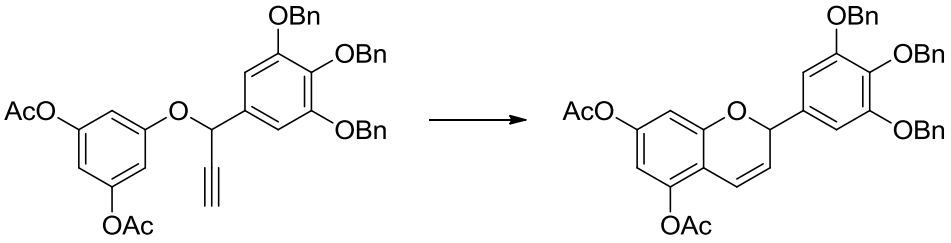
The final drive towards the target molecule was attempted as described above. The treatment of propargyl ether **31** with a high boiling solvent, such as *N*,*N*-dimethylaniline would be expected to afford the intermediate **35** through a Claisen rearrangement. Once formed, orthoquinone methide **35** would undergo a [3,3]-sigmatropic rearrangement, to give flav-3-ene **30** (**Scheme 17**). [9,11]



Scheme 17

When propargyl ether **31** was dissolved in *N*,*N*-dimethylaniline and the reaction mixture was heated at 180 °C, the desired chromene **30** was not obtained, but we were pleased to observe that no decomposition of the starting material had occurred. The reaction was also attempted using microwave-assisted synthesis for 6 h without any improvement. Likewise, in the presence of catalytic amounts of copper and copper chloride in toluene heated under reflux, propargyl ether **31** was the only compound detected using TLC and ^{1}H NMR spectroscopy. When compound **31** was submitted to microwave irradiation for 18 h, complete decomposition of the starting material was observed.

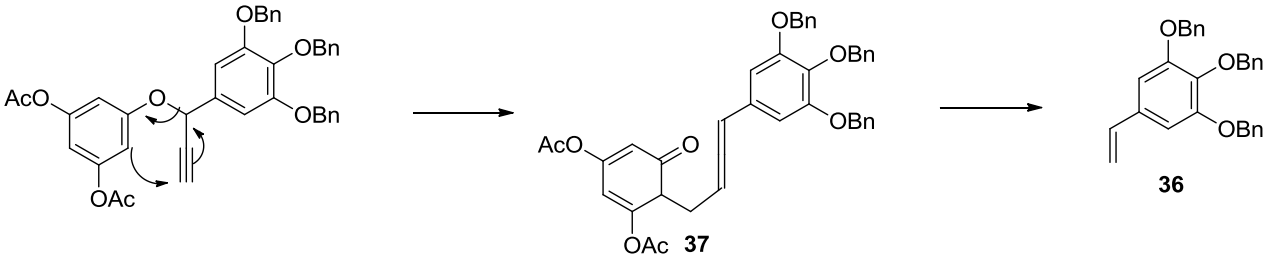
Table 3



31 **30**

Entry	Catalyst	Solvent	Temperature	Time	Conversion
1	-	*N*,*N*-dimethylaniline	180 °C	24h	SM
2	-	*N*,*N*-dimethylaniline	Microwave (180 °C)	6h	SM
3	-	*N*,*N*-dimethylaniline	Microwave (220 °C)	18h	decomposition
4	Cu/CuCl	Toluene	Reflux	24h	SM
5	$Pd(OAc)_2$	Toluene	Reflux	24h	10% (**36**)

A palladium-catalysed cyclization was also attempted: [30] the alkyne **31** and palladium acetate were dissolved in toluene and the mixture was heated under reflux. No starting material was detected after 24h. However, purification only yielded alkene **36** in 10% yield, presumably obtained through a palladium-catalysed rearrangement (**Scheme 18**).



Scheme 18: the formation of **36**

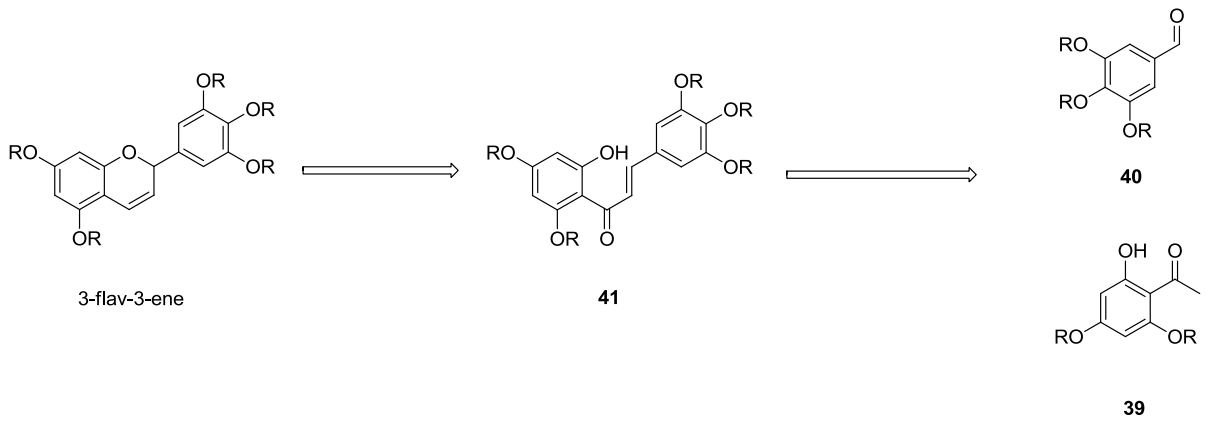
To the best of our knowledge, we do not have a rational explanation of the mechanism of the reaction. However, it is thought that the rearrangement occurs through complexation of allene **37**, with palladium. Oxidation of Pd(0) to Pd(II) may occur with coordination of Pd(0) with the allene generating a tetracoordinated Pd(0) complex containing both single carbon bonds bonded to the palladium centre.[11] Subsequently, the alkene **36** was obtained in 10% yield.

Evidence for the formation of compound **36** includes the presence of a terminal alkene moiety using ^{1}H, ^{13}C NMR and mass spectra analysis. Firstly, in the ^{1}H NMR spectrum, three sets of signals corresponding to protons on sp^2 carbons appeared as doublets of doublet with different *J* values (17.5, 10.8, 0.7) in 3 regions, confirming the presence of a terminal alkene. Using ^{13}C NMR spectroscopy, the sp^2 carbon atoms corresponding to the alkene moiety were observed at 137.9 and 112.1 ppm. Finally, a molecular ion at *m/z* 422.51 g/mol was observed using mass spectrometry, which matches the molecular weight of compound **36**.

2.3 Synthesis of flav-3-ene B

2.3.1 Retrosynthetic analysis

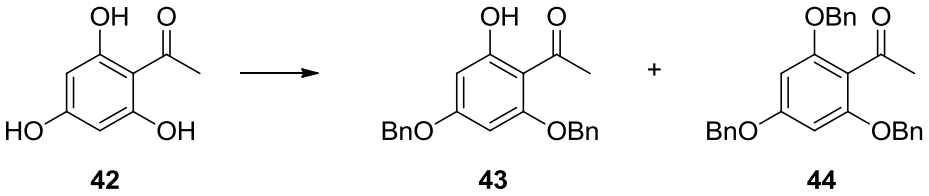
Another potential route towards the synthesis of flav-3-ene derivatives is outlined in the retrosynthetic approach below (**Scheme 19**). Flav-3-enes can be obtained through cyclization of the corresponding α,β-unsaturated ketones or chalcones **41**. One of the most convenient methods described is a base-mediated cyclization carried out in alcohol under reflux. The chalcone would be formed as a result of an intermolecular aldol condensation followed by dehydration. The aldol reaction is a two-step process: first, formation of the enolate at the α-carbon of the corresponding hydroxyacetophenones under basic conditions; then, addition of the enolate ion onto the electrophilic benzaldehyde to form the new carbon-carbon bond. Dehydration follows to generate the corresponding α,β-unsaturated ketone, such as **41**. [7, 32]



Scheme 19 Retrosynthetic analysis of 3-flav-3-ene

Benzylation using benzyl bromide (2 equiv.) was carried out as a preliminary experiment to protect 1-(2,4,6-trihydroxyphenyl) ethanone **42** using different bases in polar aprotic solvents (**Table 4**).[33,34,35,36] The ketone group was thought to sterically hinder one or both of the hydroxyl groups in the ortho position of compound **42**, hence preventing the reaction with benzyl bromide.

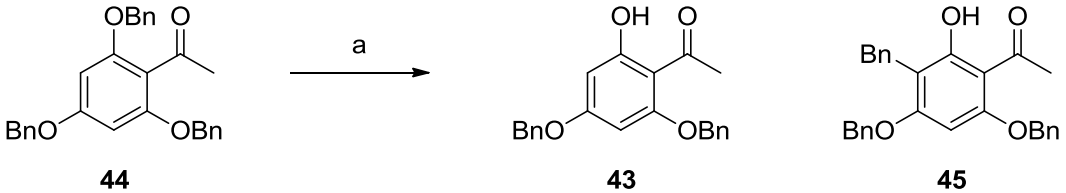
Table 4: Synthesis of ketone **43**.



	BnBr	Base	Solvent	Time	T (°C)	conversion
a	2 equiv.	K_2CO_3 (2 equiv.)	DMF	1.5 h	70	**43** (46%) / **44** (10%)
b	2.1 equiv.	K_2CO_3 (2 equiv.)	DMF	overnight	70	**43** (40%) / **44** (30%)
c	2.5 equiv.	K_2CO_3 (3 equiv.)	HMPA	overnight	90	**43** (26%) / **44** (60%)
d	2.15 equiv.	*n*-BuLi (2 equiv.)	THF	48 h	–76 to 0	**43** (56%)

However, when potassium carbonate was used as the base, significant amounts of the tribenzylated compound **44** were obtained alongside the desired ketone **43**. Increasing the reaction time also led to increased yields of **44** at the expense of the desired compound. When *n*-butyllithium was used at low temperature, the desired ketone **43** was obtained in 56% yield without the undesired side-product **44**.

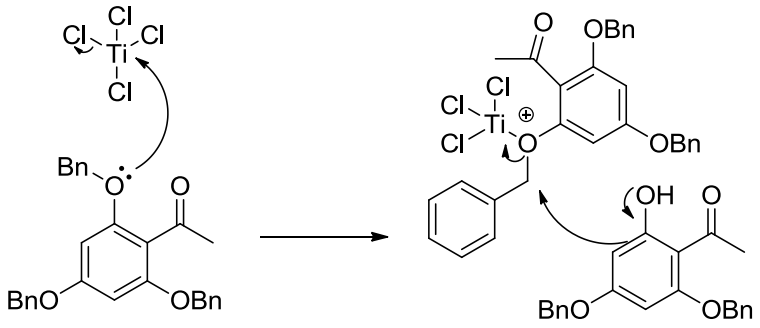
One way to increase the efficiency of the reaction would be to recycle compound **44** and convert it to the desired ketone **43**. The use of titanium tetrachloride has been reported to selectively remove one of the benzyl protecting groups in compound **44**.[15] Selective mono-deprotection of one of the benzyl groups of **44** was conducted in anhydrous dichloromethane using $TiCl_4$ at 0 °C for 1 hour, forming the desired compound **43** in 51% yield (**Scheme 20**).



Reagents and conditions: (a) $TiCl_4$ (0.7 equiv.), CH_2Cl_2, 1h, 0 °C, [(**43**, 51%); (**45**, 8%)].

Scheme 20

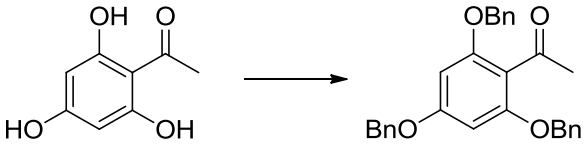
However, titanium tetrachloride may have activated the benzyl group towards intermolecular electrophilic aromatic substitution (**Scheme 21**), giving compound **45** in 8% yield. The outcome of the reaction was comparable to the result of a reaction reported in the literature. [15]



Scheme 21

In order to optimize the synthesis of **43** and to simplify purification, optimisation of the synthesis of **44** was attempted. The amounts of base and benzyl bromide were increased and ketone **44** was obtained in up to 90% yield (**Table 5**). [37]

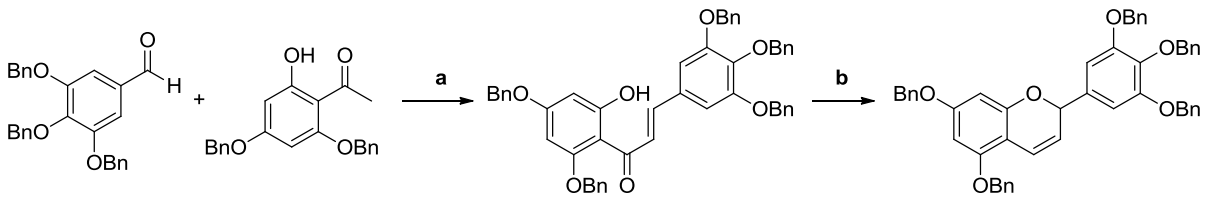
Table 5: Synthesis of ketone **42**.



42 **44**

	BnBr	**K_2CO_3**	**Solvent**	**Time**	**T (°C)**	**Yield**
a	4.5 equiv.	4.5 equiv.	DMF	24h	100	66%
b	6 equiv.	6 equiv.	DMF	24h	100	90%

The chalcone **46** was synthesized using an aldol condensation following a literature procedure. The treatment of acetophenone **43** and benzaldehyde **23** with sodium hydride in dimethylformamide gives the corresponding chalcone **46** in 55% yield. Sodium borohydride was then added to a dilute solution of the chalcone in a mixture of tetrahydrofuran and methanol (1:1) at room temperature resulting in the disappearance of the yellow colour. The reaction was then heated at 68 °C overnight affording flav-3-ene **28** in 14% yield. [32]

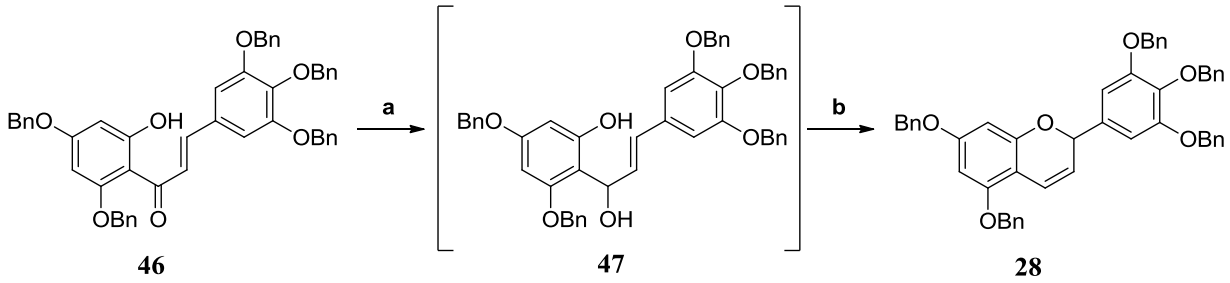


23 **43** **46** **28**

Reagents and conditions: (a) NaH (1.5 equiv.), DMF, R.T., 6h, 55 %; (b) $NaBH_4$ (1 equiv.), THF/MeOH, R.T. to reflux, overnight, 14%.

Scheme 22

Racemic flav-3-enes can also be prepared through direct cyclization of the corresponding chalcone using reducing agents followed by the addition of Lewis acids.[38] In an effort to improve the reaction yield, a stepwise process, where reduction of the ketone occurs followed by a Lewis acid-catalysed cyclization, was attempted (**Scheme 23**). Ketone **46** was reduced using sodium borohydride in a mixture of tetrahydrofuran and methanol. Removal of the solvents followed by an extraction yielded the alcohol **47** alongside some starting material. Literature precedents indicated that such a compound was prone to decomposition. Hence, the unpurified alcohol **47** was immediately redissolved in anhydrous dichloromethane and a catalytic amount of boron trifluoride etherate was added. Compound **28** was obtained in 21% yield.



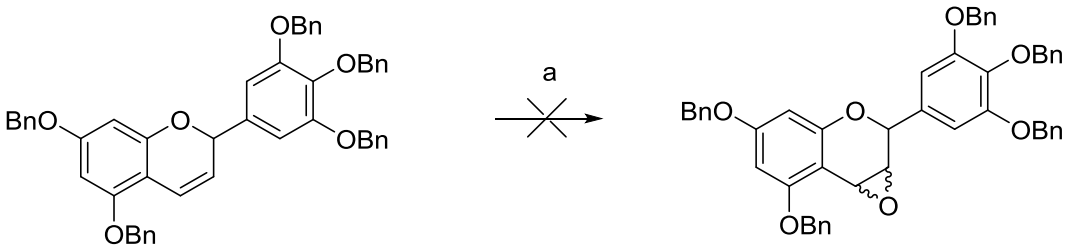
46 **47** **28**

Reagents and conditions: (a) $NaBH_4$ (1 equiv.), THF/MeOH, R.T., 2h; (b) BF_3,OEt (10 mol%), CH_2Cl_2, R.T., 3h, 21%.

Scheme 23

The epoxidation of flav-3-ene **28** was then attempted using *meta*-chloroperoxybenzoic acid with 4 equivalents of sodium hydrogen carbonate at 0 °C (**Scheme 24**). Unfortunately, neither the epoxide **48**, nor the starting material were observed using thin layer chromatography and ^1H NMR spectroscopy of the unpurified reaction mixture. The

instability of flav-3-ene **28** could explain the decomposition of the starting material under such conditions. [24,25]

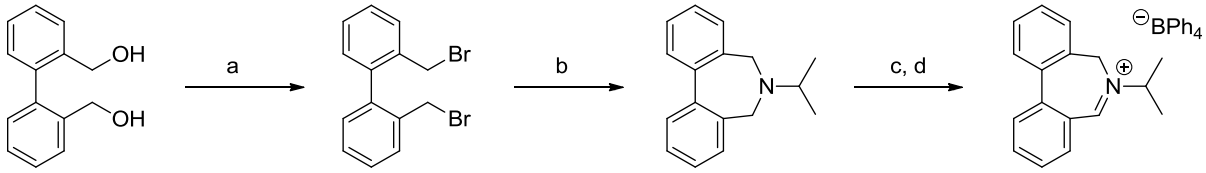


28 **48**

Reagents and conditions: (a) *m*-CPBA (2 equiv.), $NaHCO_3$ (4 equiv.), CH_2Cl_2, 0 °C, 10 min.

Scheme 24

In an attempt to utilize milder reaction conditions, the oxidizing agent was replaced by a tandem iminium salt/Oxone®. The chiral biphenyl iminium salt **52** was synthesised following a three-step procedure starting from 2,2'-biphenylmethanol **49** (**Scheme 25**).[39] The first step was an acid-catalysed displacement of the two hydroxyl groups of **46** using HBr (48% aq.) to give dibromo compound **50** in 90% yield. Formation of the azepine **51** was readily achieved using a 1:1 mixture of **50** and isopropylamine in acetonitrile under reflux overnight in the presence of K_2CO_3. The formation of the tetraphenylborate biphenyl iminium salt **51** was effected by exposure to NBS and subsequent anion exchange in 80% yield.



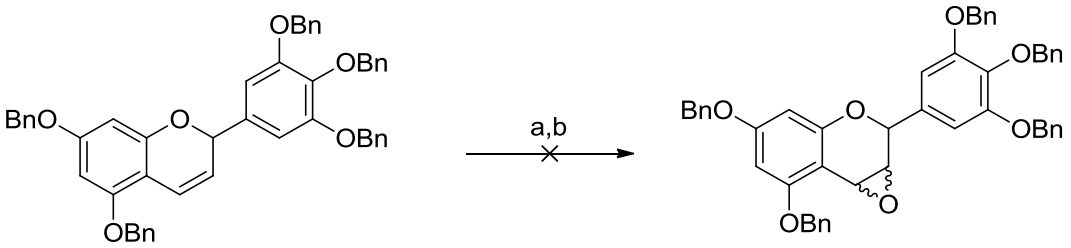
49 **50** **51** **52**

Reagents and conditions: (a) HBr (48% in H_2O), 100 °C, 1 h, 90 %; (b) Isopropylamine (1 equiv.), K_2CO_3 (3 equiv.), MeCN, reflux, overnight, 84%; (c) *N*-bromosuccinimide (1.2 equiv.), CH_2Cl_2, reflux, 3 h; (d) $NaBPh_4$, EtOH/MeCN, 5 min, 80% for the two steps.

Scheme 25

With the catalyst in hand, the epoxidation reaction was then attempted (**Table 6**). Unfortunately, the use of iminium salt-catalysed epoxidation also led to the decomposition of the starting material **28** and no epoxide was detected using spectroscopic analysis. The low stability of flav-3-ene **28**, which might well lead to the reactive orthoquinone which is in equilibrium with the corresponding allylic cation, during the reaction, could increase the decomposition rate of the starting material **28**.

Table 6: Epoxidation using iminium salt catalyst **52**.

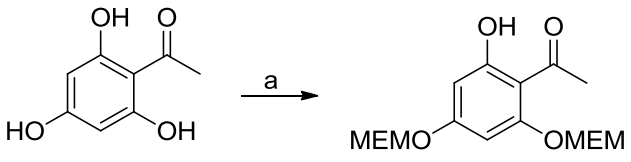


28 **48**

	Reaction conditions	Conversion
a	**52** (10 mol%), TPPP (2 equiv.), $CHCl_3$, - 20 °C, 24h.	Decomposition
b	**52** (10 mol%), Oxone® (2equiv.), $NaHCO_3$ (4 equiv.), MeCN/H_2O (10:1), 0 °C, 1h.	Decomposition

As mentioned above, flav-3-ene **28** is unstable under epoxidation conditions. Therefore, we must first find alternative protecting groups to increase the stability of the flavenes under oxidative conditions.

Selection of the most suitable protecting group for each hydroxyl moiety is essential, since it may hold the key to a successful oxidation of the flavene. The 2-methoxyethoxymethyl ether protecting group was introduced for their stability under mild conditions. [34] Treatment of 1-(2,4,6-trihydroxyphenyl) ethanone **42** with 2-methoxyethoxymethyl chloride (2.4 equiv.) in the presence of diisopropylamine (3 equiv.) in dichloromethane led to product **53** in 43% yield.[40] Using *N*,*N*-diisopropylethylamine under identical conditions led to increased solubility of reaction intermediates in dichloromethane, as exhibited by a quick change of reaction mixture colour from yellow into white over 25 min of stirring at room temperature, yielding 90% of compound **53**.

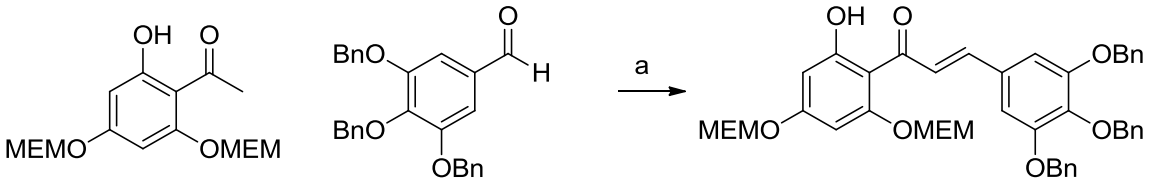


42 **53**

Reagents and conditions: (a) 2-Methoxyethoxymethyl chloride (2,4 equiv.), $(i\text{-}Pr)_2NEt$ (3 equiv.), CH_2Cl_2, R.T., overnight, 90 %.

Scheme 26

As described above, the aldol condensation is our preferred route towards the chalcone derivatives. Ketone **53** was dissolved in a solution of potassium hydroxide in ethanol. This was followed by the dropwise addition of benzaldehyde **23**. The aldol adduct underwent *in-situ* dehydration, leading to α,β-unsaturated chalcone **54** in 35% yield (**Scheme 27**).

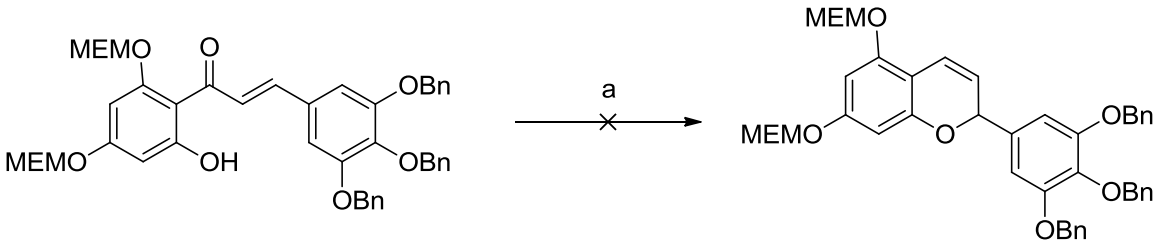


53 **23** **54**

Reagents and conditions: (a) KOH, EtOH, 35%.

Scheme 27

Slow addition of NaH to a solution of acetophenone **53** in DMF followed by addition of the aldehyde **23** resulted in the formation of the chalcone **54** in 70% yield. The reason for the improved yield was that the use of a stronger base increased the formation of the enolate derived from acetophenone **53**. As an initial attempt, the reduction of chalcone **54** using $NaBH_4$ was carried out in a mixture of tetrahydrofuran and ethanol under reflux to reduce the carbonyl group at the 3-position. TLC visualization revealed that full conversion of the starting material had occurred. However, the desired product **55** was not observed; similar results were obtained using $NaBH_4$ in a mixture of methanol and dichloromethane under reflux, with the starting material fully converted after two hours. As mentioned in the literature review, the alcohol intermediate has the tendency to cyclize *in-situ* to form the corresponding 3-flav-3-ene without the need for a catalyst. In an attempt to catalyse the cyclization, a few drops of boron trifluoride diethyl etherate were added to the reaction mixture; unfortunately, flav-3-ene **55** was not isolated and only degradation products were observed (**Scheme 28**).

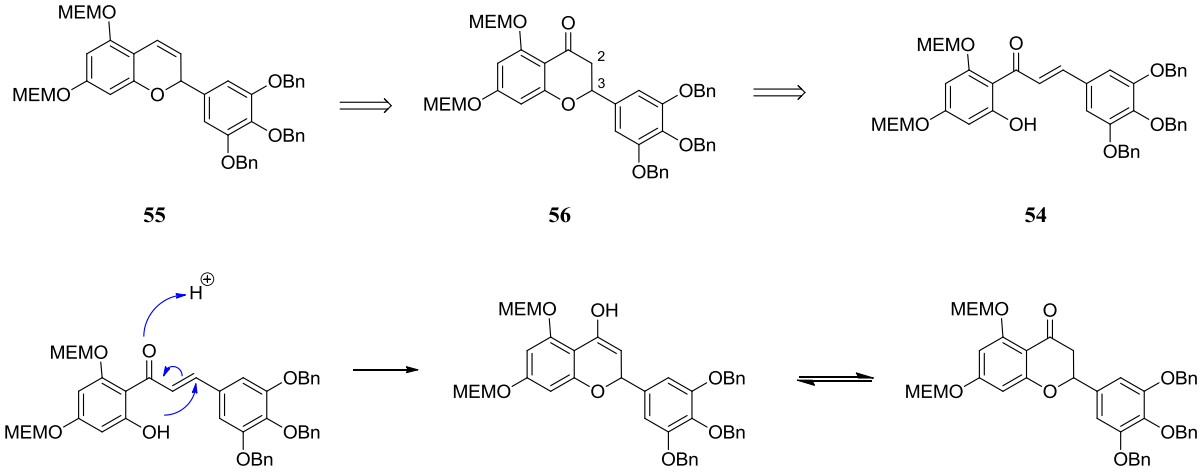


54 **55**

Reagents and conditions: (a) $NaBH_4$, MeOH, CH_2Cl_2 (1:10).

Scheme 28

Due to our repeated failed attempts to prepare **55,** an alternative shorter synthetic route to **55** was proposed (**Scheme 29**).

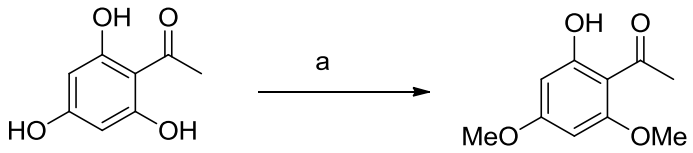


55 **56** **54**

Scheme 29

The fundamental features of chalcone **54** include an alkene moiety with an adjacent carbonyl group and a phenolic hydroxyl group. This could allow an acid-catalyzed intramolecular cyclization to occur giving ketone **56**. Following the reduction of the carbonyl group, which should lead to an alcohol *in-situ*, an elimination reaction could afford 3-flav-3-ene **55**.[41] The reaction was attempted in a solution of sodium acetate in ethanol under reflux for 2 days; the only product observed was the starting material **54**. A cyclization reaction was also performed under the same conditions in the presence of water (a few drops) to improve the solubility of sodium acetate, but no improvement was observed. We believe the problem with this approach was the lack of carbonyl group activation. An acid-catalysed reaction was then attempted: chalcone **54** was dissolved in a mixture of ethanol and HCl (0.2M) and heated under reflux overnight. Only starting material was recovered.

We next turned our attention to another potential protecting group: the methoxy group. 1-(2-Hydroxy-4,6-dimethoxyphenyl)ethanone **57** was synthesised according to literature methods. The general method for methylation of 2,4,6-trihydroxyacetophenone **42** involves treatment with dimethyl sulfate in acetone under reflux. The desired product is easily purified, giving ketone **57** in 90% yield. [42]

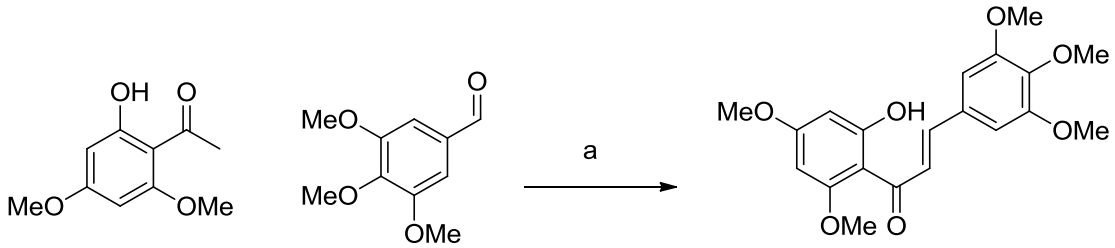


42 **57**

Reagents and conditions: (a) dimethyl sulfate (1.2 equiv.), K_2CO_3 (3 equiv.), acetone, reflux, overnight, 90%.

Scheme 30

An aldol reaction using ketone **57** and aldehyde **58** was then carried out to prepare the desired chalcone **59**. Acetophenone **57** and 3,4,5-trimethoxybenzaldehyde **58** were dissolved in a solution of potassium hydroxide in ethanol (1.0 g in 10 mL). The chalcone **59** was formed in 93% yield as a yellow solid and did not require further purification. [43]

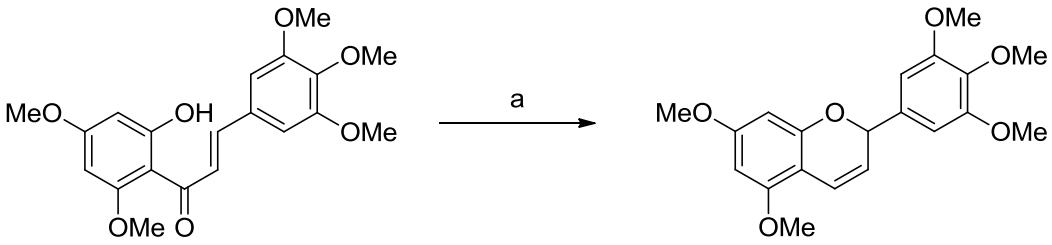


57 **58** **59**

Reagents and conditions: (a) KOH, ethanol, R.T., overnight, 93%.

Scheme 31

The cyclization of α,β-unsaturated ketone was achieved using $NaBH_4$ in propan-2-ol overnight, giving the desired flav-3-ene **60** in 20% yield (**Scheme 32**).

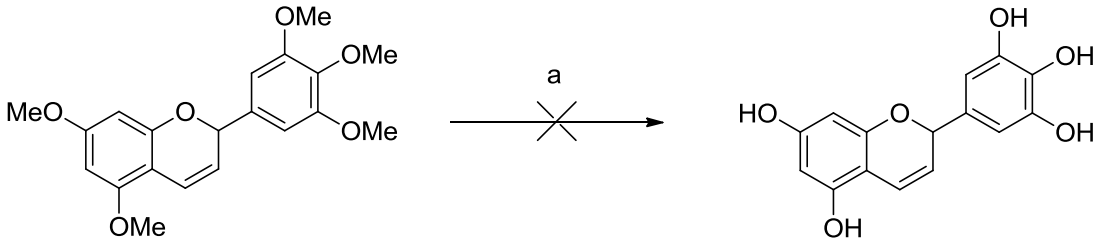


59 **60**

Reagents and conditions: (a) $NaBH_4$ (3 equiv.), 2-propanol, R.T., overnight, 20%.

Scheme 32

Epoxidation reactions were then carried out on flav-3-ene **60**. Both sets of conditions described above (**Table 6**) were used and the results were identical: only decomposition of the starting material was observed. Strongly electron-donating groups, such as methoxy and benzyloxy, on aromatic ring A increased the instability of flav-3-ene **60** under oxidative conditions, even when a mild iminium salt-mediated epoxidation was used. In an effort to stabilize the flav-3-ene under epoxidation conditions, the cleavage of the methoxy groups using boron tribromide was carried out to replace them by moderately activating groups, such as sulfonate and acetate groups. Compound **60** was dissolved in anhydrous dichloromethane at –78 °C and boron tribromide was added, the reaction mixture was then allowed to reach room temperature overnight. [44] Unfortunately, the deprotection failed and starting material was decomposed (**Scheme 33**).



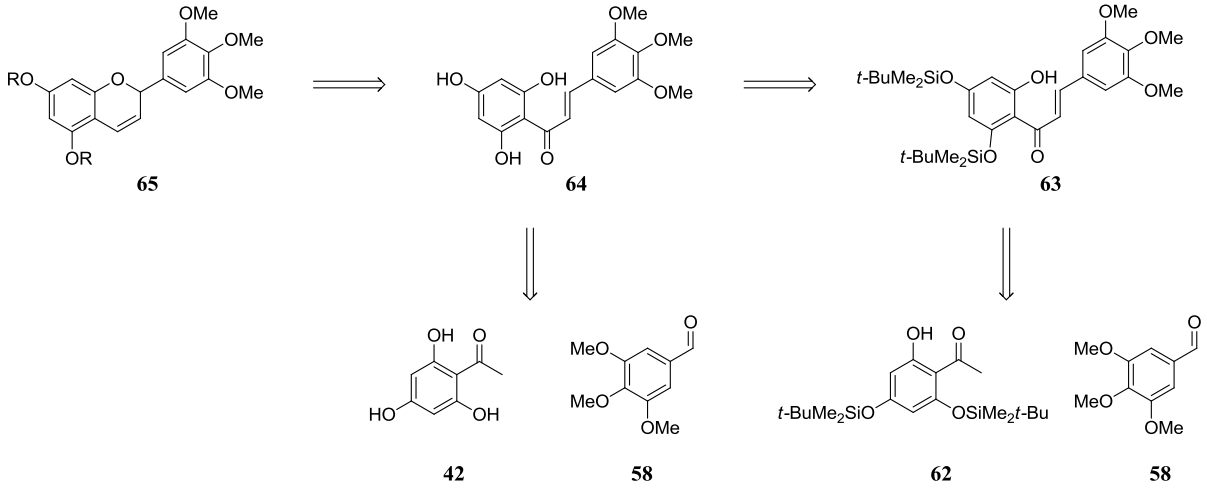
60 **61**

Reagents and conditions: (a) BBr_3 (7 equiv.), CH_2Cl_2, –78 °C to R.T., overnight.

Scheme 33

Because the cleavage of the methoxy groups did not occur and compound **61** was not isolated, alternative methods were attempted to install the desired groups on ring A of the flav-3-ene. Two possible routes were planned towards chalcone **64**: the first one involved an aldol condensation between benzaldehyde **58** and acetophenone **42**; the second route targeted silyl-protected chalcone **63**, prepared by aldol condensation of benzaldehyde **58** and phenone **62**. Removal of the silyl protecting groups should afford chalcone **64**. Then the key step in

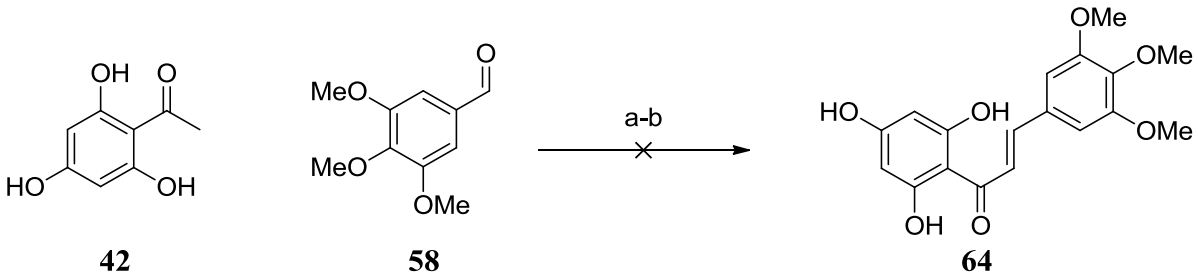
the synthesis, the ring closing of the flavene, could be attempted, followed by protection of the remaining hydroxyl groups. The protection could also be attempted before the ring-closing step (**Scheme 34**).



Scheme 34

The synthesis of chalcone **64** commenced with an aldol reaction between phenone **42** and 3,4,5-trimethoxybenzaldehyde **58**. However, using either KOH or $Ba(OH)_2$ as the base, no product was observed and the starting material was recovered (**Table 7**).[45] In the presence of hydroxyl groups in **42**, the formation of the enolate was probably disfavoured. We next turned our attention to the second possible route involving the use of silyl protecting groups.

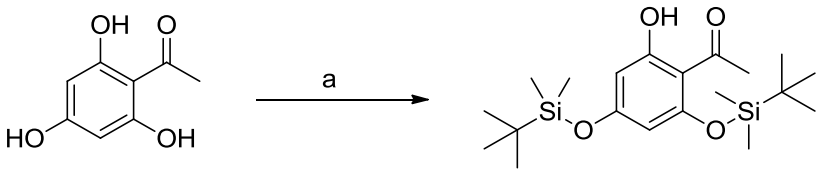
Table 7



42 **58** **64**

Entry	Base	Solvent	Temperature	Time	Conversion
a	KOH	Ethanol	80 °C	24 h	SM
b	$Ba(OH)_2$	Ethanol	R.T.	24 h	SM

The *t*-Butyldimethylsilyl moiety is a popular protecting group and is widely used among organic chemists. This is due to the fact that the protecting group is stable in the presence of basic reagents and is easily cleaved. Silyl-protected acetophenone **62** was prepared by treatment of 2,4,6-trihydroxyacetophenone **42** with *t*-butylchlorodimethylsilane and pyridine with a catalytic amount of 4-dimethylaminopyridine in dichloromethane in 90% yield (**Scheme 35**). [46,47]

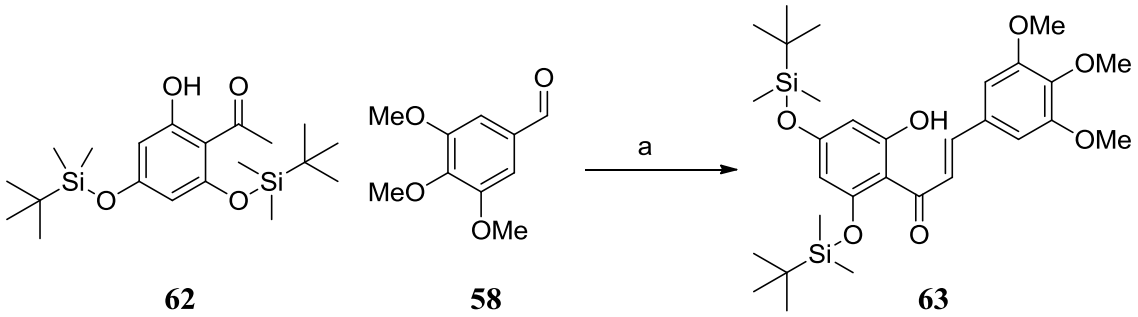


42 **62**

Reagents and conditions: (a) *t*-Butylchlorodimethylsilane (2.5 equiv.), pyridine (3 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, overnight, 90 %.

Scheme 35

After protection of two free phenolic hydroxyl groups, the reaction of **62** with 3,4,5-trimethoxybenzaldehyde **58** proceeded with the addition of NaH at room temperature, affording chalcone **63** in 21% yield (**Scheme 36**). [46]

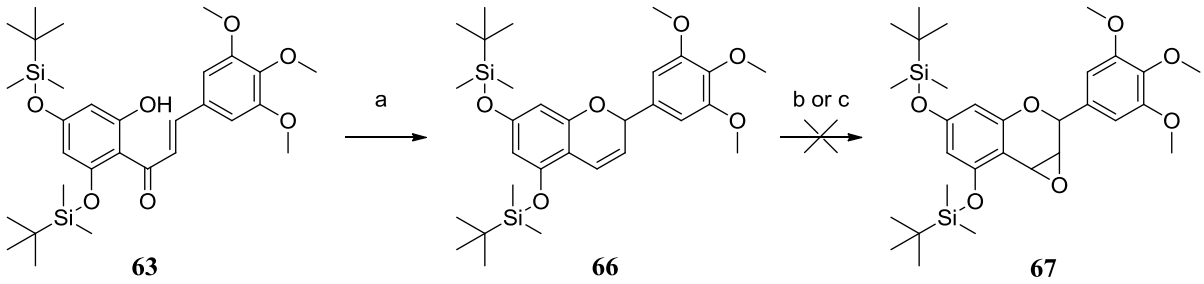


62 **58** **63**

Reagents and conditions: (a) NaH (0.8 equiv.), THF, R.T., 50 min, 21%.

Scheme 36

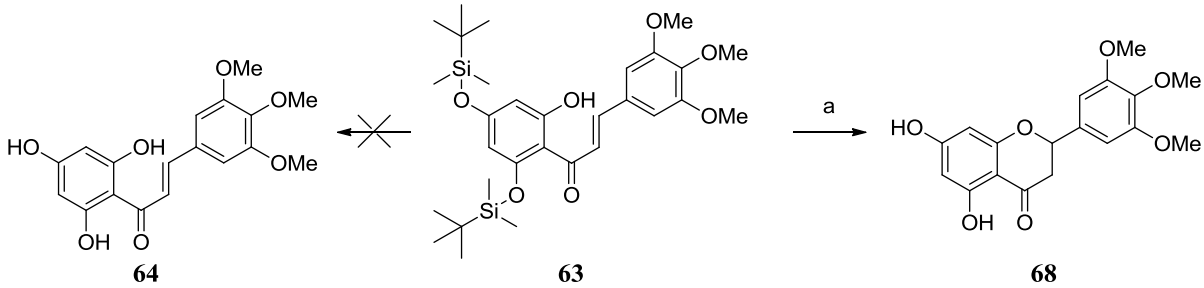
The desired key intermediate **63** having been obtained, we turned our attention to its cyclization. Reduction of compound **63** took place smoothly in a mixture of EtOH/ tetrahydrofuran (1:3) to give flav-3-ene **66** in a poor yield (10%). It should be noted that some decomposition of flav-3-ene **66** was observed by 1 hour after purification through column chromatography.[46] The epoxidation reactions were attempted using standard conditions, but perhaps, due to the observed instability of the alkene **66**, only decomposition of the starting material was observed (**Scheme 37**).



Reagents and conditions: (a) $NaBH_4$, EtOH/THF (1:2), 10 %; (b) *m*-CPBA (2 equiv.), $NaHCO_3$ (4 equiv.), CH_2Cl_2, 0 °C, 10 min; (c) Iminium salt **52**, Oxone, $MeCN/H_2O$ (1:0.1), 0 °C, 5 min.

Scheme 37

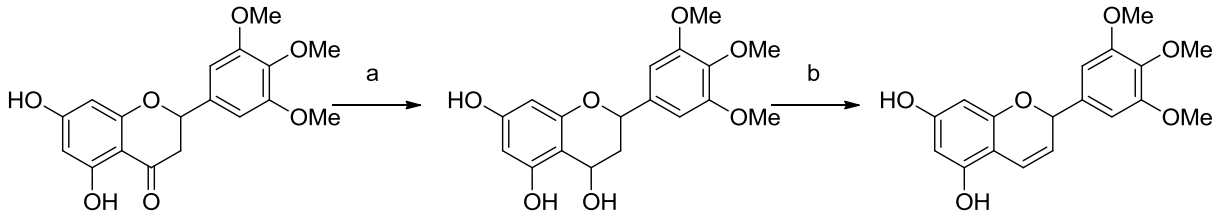
Due to the instability of compound **66**, we decided to interchange the protecting groups before the cyclization. We attempted to remove the silyl protecting groups of **63** using HBr in methanol under reflux. The reaction unexpectedly gave product **68**, rather than **64**, in excellent yield (97%) resulting from intramolecular cyclization in the presence of the strong acid (**Scheme 38**). [47]



Reagents and conditions: (a) MeOH/HBr(48 %), reflux, 97%, overnight.

Scheme 38

The formation of compound **68** provided us with an alternative pathway to the desired flav-3-ene. As mentioned above, a reduction followed by an *in-situ* dehydration (or a stepwise process) should afford the flav-3-ene **69** from flavanone **68**. Indeed, exposure of compound **68** to $NaBH_4$ in methanol under reflux furnished compound **69**, which then underwent dehydration to flav-3-ene **65** in the presence of camphorsulfonic acid in toluene under reflux for 1 hour (**Scheme 39**). [44]

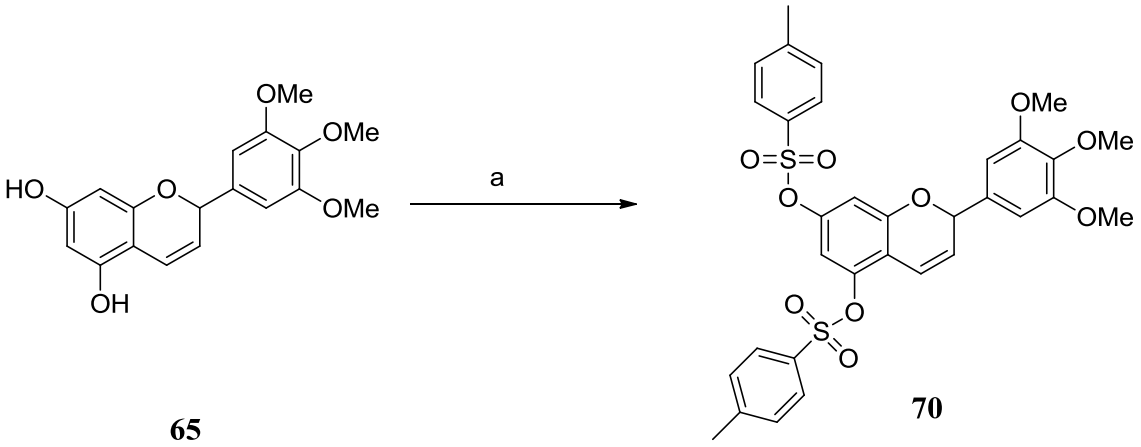


68 **69** **65**

Reagents and conditions: (a) $NaBH_4$ (3 equiv.), MeOH, reflux, 1h; (b) CSA (3 equiv.), toluene, reflux, 1h.

Scheme 39

The stage was then set to attempt to minimize the destabilization of the unpurified alkene **65** or the corresponding epoxide by installing moderately electron-donating group on ring A. We first turned our attention to the use of a sulfonate ester protecting groups. The treatment of compound **65** with K_2CO_3 and 4-toluenesulfonyl chloride in acetone under reflux furnished flav-3-ene **70** in 65% yield (**Scheme 40**). [47,48]

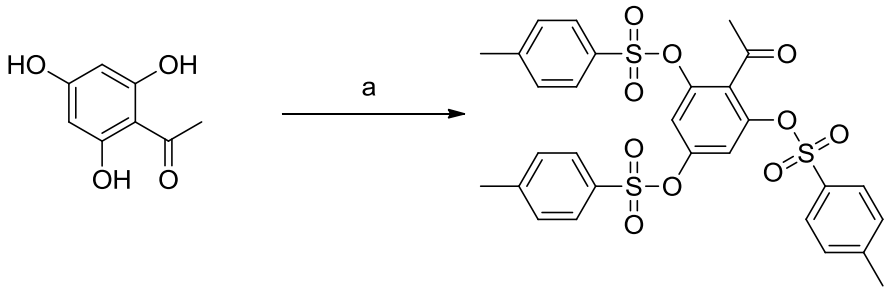


65 **70**

Reagents and conditions: (a) K_2CO_3 (4 equiv.), 4-toluenesulfonyl chloride (4 equiv.), acetone, reflux, overnight, 65%.

Scheme 40

Alternatively, flavene **70** could also be synthesized through a smaller number of steps. 2,4,6-trihydroxyacetophenone **42** was protected using K_2CO_3 and 4-toluenesulfonyl chloride in acetone under reflux, giving the tosylated compound **71** in 95% yield (**Scheme 41**).

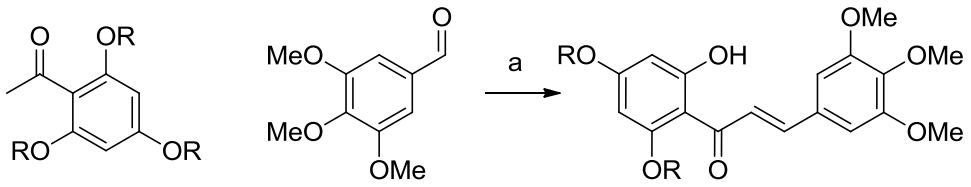


42 **71**

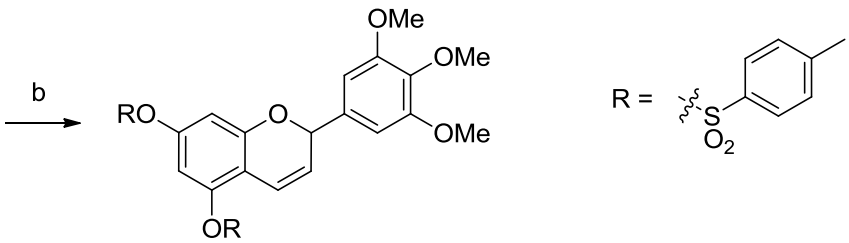
Reagents and conditions: (a) K_2CO_3 (4 equiv.), 4-toluenesulfonyl chloride (4 equiv.), acetone, reflux, overnight, 95%.

Scheme 41

A successful attempt was made to synthesize the compound **70**: Sodium hydride was utilized in anhydrous tetrahydrofuran: first, the aldol reaction occurred with concomitant mono-deprotection of a sulfonate ester to yield chalcone **72**. [48] Furthermore, the toluenesulfonate esters played a significant role in the stability of flavene **70** under the reaction conditions as compound **70** was obtained in high yield (98%), when **72** was treated with $NaBH_4$ in a mixture of ethanol and tetrahydrofuran (**Scheme 42**). [32,49]



71 **58** **72**



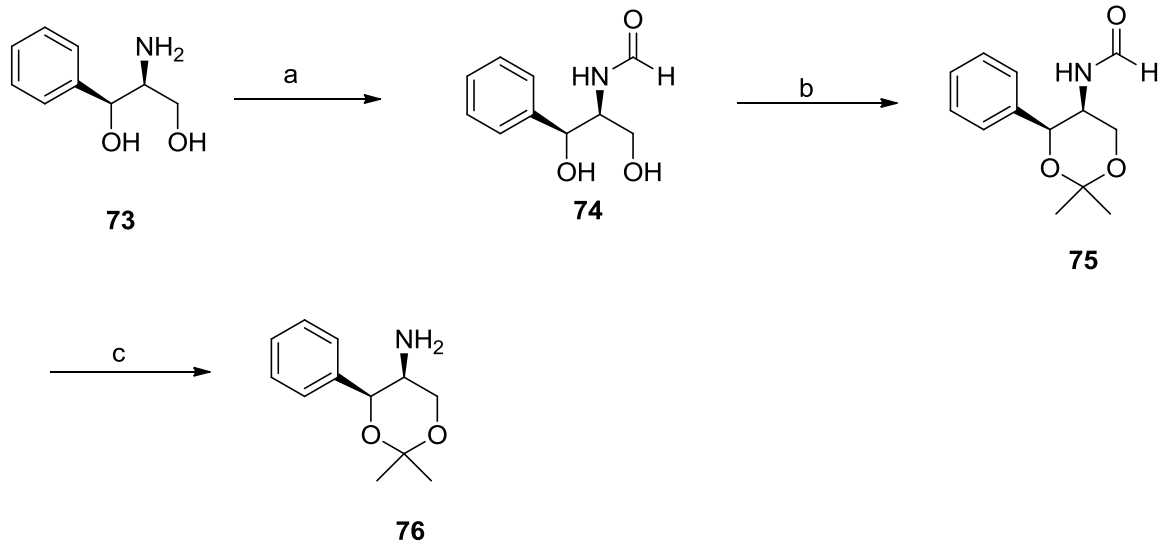
70

Reagents and conditions: (a) NaH (2.1 equiv.) THF, overnight, 22%; (b) $NaBH_4$, EtOH:THF (1:1), 50 °C, overnight, 98%.

Scheme 42

2.4 Catalyst synthesis

The amine used for the synthesis of catalyst **78** is (*S*)-(−)-2-amino-3-phenyl-1-propanediol **73**, which is commercially available. The procedure reported by Thomas was employed to offer protection of the amine groups as the formyl group was required prior to the acetonide protection of the diol moiety with acetone and 2,2-dimethoxypropane.[50] Sodium methoxide and methyl formate were added to amine **73** to achieve formylation, affording the intermediate **74** in quantitative yield. The acetonide generation was carried out immediately on compound **74** with 2,2-dimethoxypropane and camphorsulfonic acid in acetone to give acetal **75** in 77% yield. A solution of aqueous hydrazine monohydrate (80%) was used to remove the formyl protecting group by heating at reflux for 2 h to furnish **76** in 89% yield (**Scheme 43**).

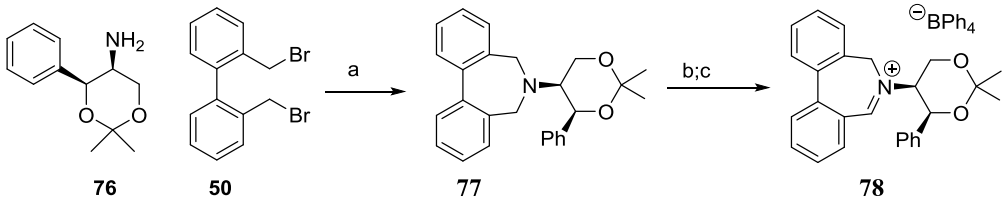


73 **74** **75** **76**

Reagents and conditions: (a) NaOMe (0.1 equiv.), MeOCHO (1.5 equiv.), MeOH, rt., 24h; (b) DMP (10 equiv.), CSA (0.15 equiv.), acetone, R.T., 4 h, 77% ; (c) Hydrazine monohydrate (98%), reflux, 2 h, 89%.

Scheme 43

Cyclocondensation of amine **76** with 2,2'-*bis*(bromomethyl)biphenyl **50** proceeded under basic conditions in acetonitrile under reflux for 24 h to form the amine **77**. The resulting amine was converted to the corresponding iminium bromide by addition of *N*-bromosuccinimide, followed by counter-ion exchange using sodium tetraphenylborate. Catalyst **78** was isolated and purified through recrystallization from hot ethanol in 78% yield (**Scheme 44**). [39]

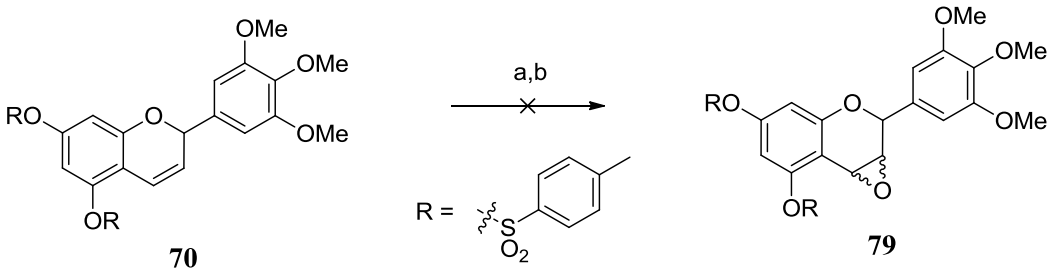


76 **50** **77** **78**

Reagents and conditions: (a) **76** (1 equiv.), **50** (1 equiv.), Cs_2CO_3 (2 equiv.), CH_3CN, reflux, 24 h (b) **77** (1 equiv.), NBS (1.1 equiv.), CH_2Cl_2, R.T., 6 h; (c) $NaBPh_4$ (1.1 equiv.) in minimum CH_3CN, EtOH, R.T., 10 min, 78%.

Scheme 44

Alkene **70** was subjected to a standard racemic epoxidation protocol, using *meta*-chloroperoxybenzoic acid and $NaHCO_3$ in anhydrous dichloromethane at 0 ºC for 24 h. The same reaction was also attempted in the absence of base. Unfortunately, no conversion to the epoxide product **79**, and only starting material, was observed by TLC and ^{1}H NMR spectral analysis.



70 **79**

Reagents and conditions: (a) *m*-CPBA (1 equiv.), $NaHCO_3$ (2 equiv.), CH_2Cl_2, 0 °C, 24 min; (b) *m*-CPBA (2 equiv.), CH_2Cl_2, 0 °C, 24 min.

Scheme 45

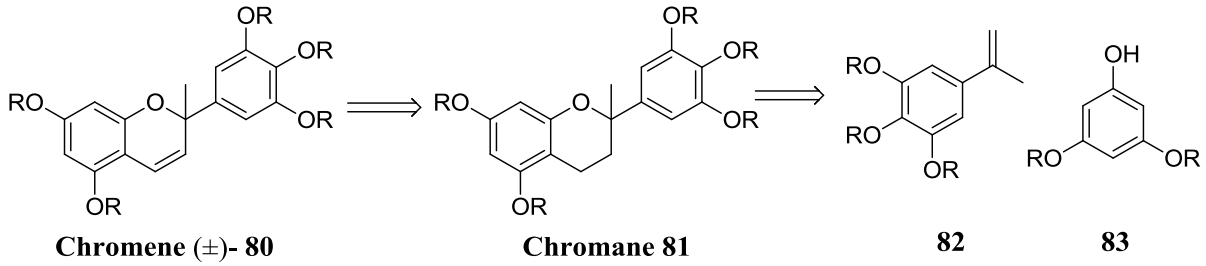
Epoxidation of alkene **70** also failed under the standard non-aqueous conditions with catalyst **78** at 0 and −20 ºC for 24 hours (**Table 5**). The low reactivity observed towards catalyst **78** and oxidant could be due to the presence of the sulfonyl protecting groups, which could deactivate the alkene moiety towards the oxidant.

Table 5

	Reaction conditions	**Conversion**
a	**78** (10 mol%), TPPP (2 equiv.), $CHCl_3$, −20 °C, 24h.	SM
b	**78** (10 mol%), TPPP (2 equiv.), $NaHCO_3$ (4 equiv.), MeCN 0 °C, 24h.	SM

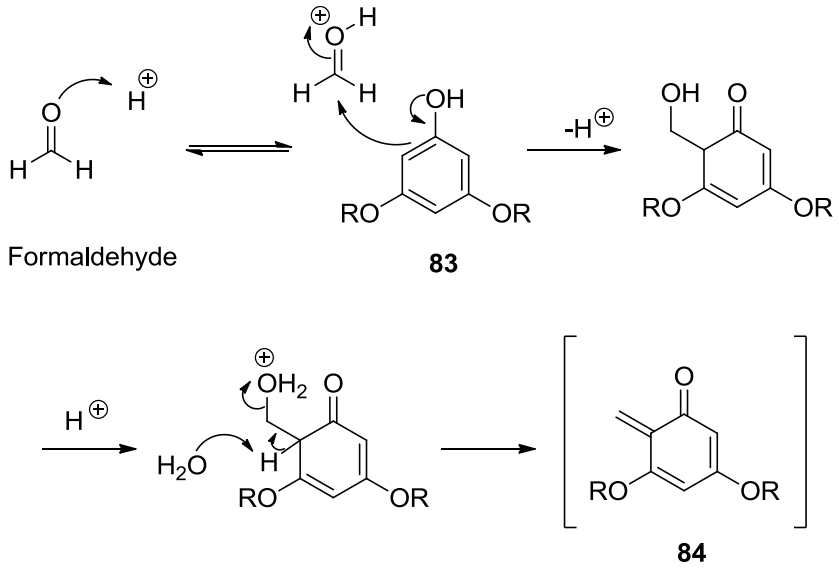
2.5 Synthesis of flav-3-ene analogues.

The major objective of our research is to synthesize epigallocatechin and its analogues. Thus, we turned our attention towards methyl group substitution at the C-2 positions. The underlying synthetic strategy is illustrated in **Scheme 46**, inspired by multicomponent reactions, which are defined as one-pot convergent reactions in which three or more starting materials react to form a product which contains portions of all the components after a cascade of elementary reactions.[51] Gu has recognized the potential for a one-pot, two step transformation to deliver chromane **81**, which is a key target towards the formation of chromene **80**.[52]



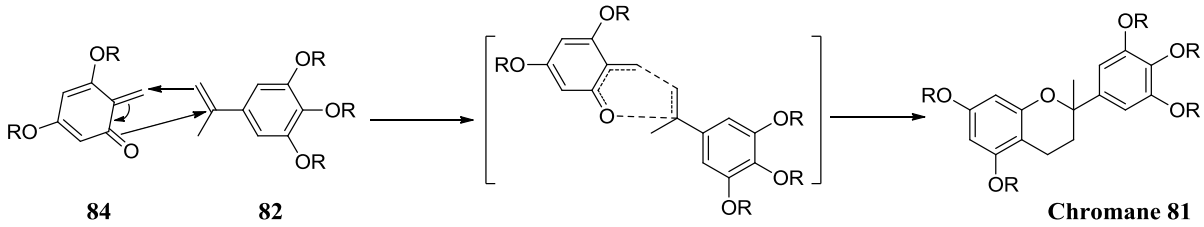
Scheme 46: Retrosynthesis of chromene (±)-**80**

Under acidic conditions, formaldehyde becomes an excellent electrophilic acceptor for aromatic electrophilic substitution. Condensation of protonated formaldehyde with the phenol **83** affords the formation of a new C-C bond, followed by dehydration to yield methylene intermediate **84** (**Scheme 47**). [52]



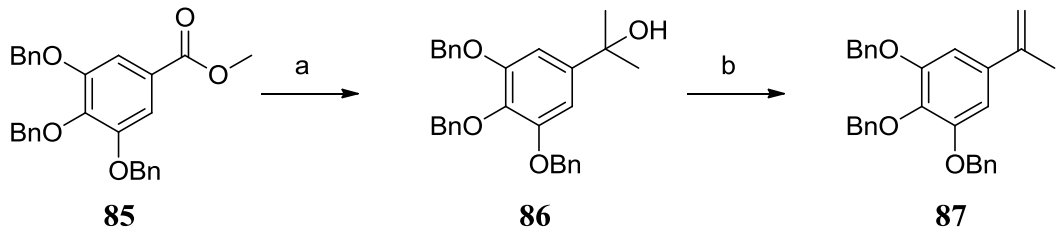
Scheme 47: Proposed mechanism for the formation of methylene intermediate **84**

The hetero-Diels–Alder reaction is the cyclocondensation of a 4π electron system with a 2π electron system, creating new carbon-carbon and carbon-oxygen bonds to form a six-membered ring in one efficient step. The scope and the utility of this intermolecular [4+2] hetero cycloaddition process in the literature for the formation of six-membered ring chromanes is limited. Gu reported that 2-substituted-5,6-benzochromanes could be formed by the trapping of methylene intermediates, such as **84**, with a suitable alkene under thermal conditions. Therefore, methylene intermediate **84** could undergo hetero-Diels–Alder reaction (**HDA**) with dienophile **82** for the facile construction of chromane **1 (Scheme 48)**. [52,53]



Scheme 48: Hetero-Diels–Alder reaction of intermediate 84 with dienophile **82**

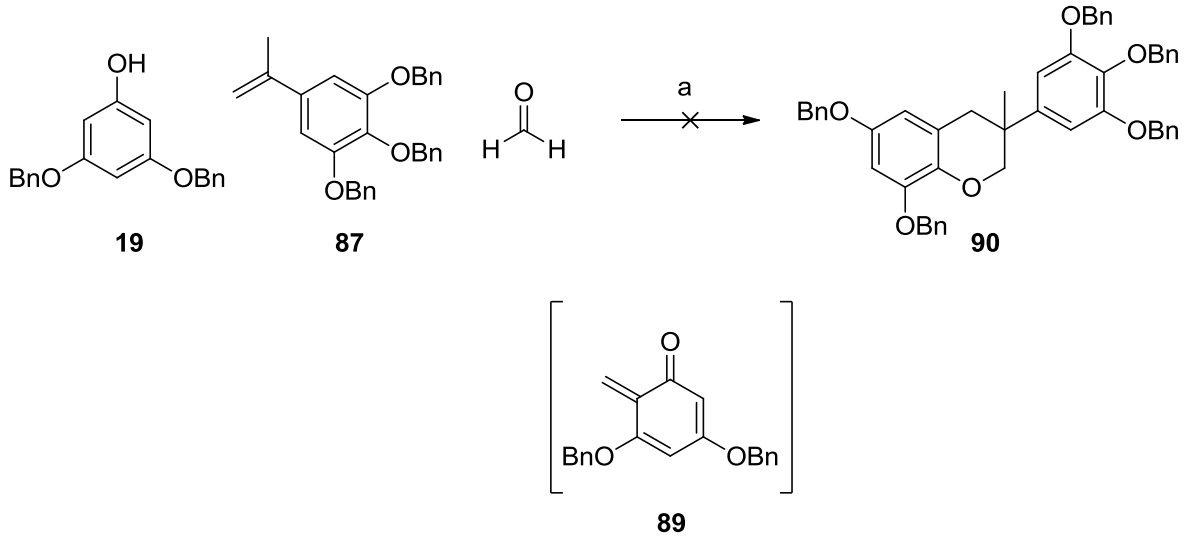
The reaction of Grignard reagents with esters is an important method to access tertiary alcohols, which are then frequently converted to the corresponding alkene in the presence of a base or an acid. Thus, large excesses of methylmagnesium bromide (3.0M in diethyl ether) were added to a solution of methyl 3,4,5-tris(benzyloxy)benzoate **6** at –78 °C to give tertiary alcohol **86** in 97% yield.[54] The treatment of a solution of 3,4,5-tris(benzyloxy)phenyl)propan-2-ol **86** in anhydrous toluene with camphorsulfonic acid induced dehydration providing the desired compound **87** in 71% yield (**Scheme 49**). [55]



Reagents and conditions: (a) MeMgBr (3 equiv.), THF, –78 °C to R.T., 17h, 97%; (b) camphorsulfonic acid (3 equiv.), toluene, reflux, 24h, 71%.

Scheme 49

In the key step towards the synthesis of chromanes, 3,5-bis(benzyloxy)phenol **19** and formaldehyde were dissolved in acetic acid in an attempt to give adduct **89**, followed by the addition of dienophile **87**.[52] The reaction mixture was then heated under reflux for three hours. Unfortunately, the reaction failed to give chromane **90** (**Scheme 50**).

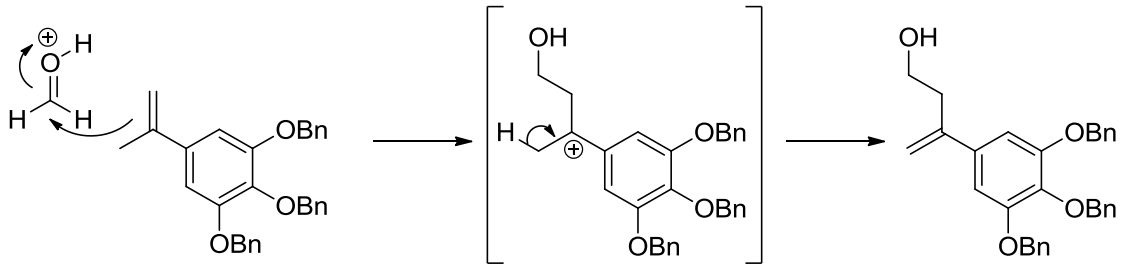


19 **87** **90** **89**

Reagents and conditions: (a) AcOH, 3h, reflux, 120 ˚C

Scheme 50: Hetero-Diels–Alder reaction using formaldehyde

The cause of the reaction failure was not specified. However, the failure might be due to a faster side reaction occurring between formaldehyde and electron-rich alkene **87**, rather than phenol **19**. Dienophile **87** possesses significant nucleophilic potential enhanced by the three activating benzyl groups. Furthermore, the intermediate carbocation **91** can be stabilized by the presence of two alkyl groups and a phenyl group. Deprotonation of carbocation **91** affords alkene **92 (Scheme 51)**. [56]

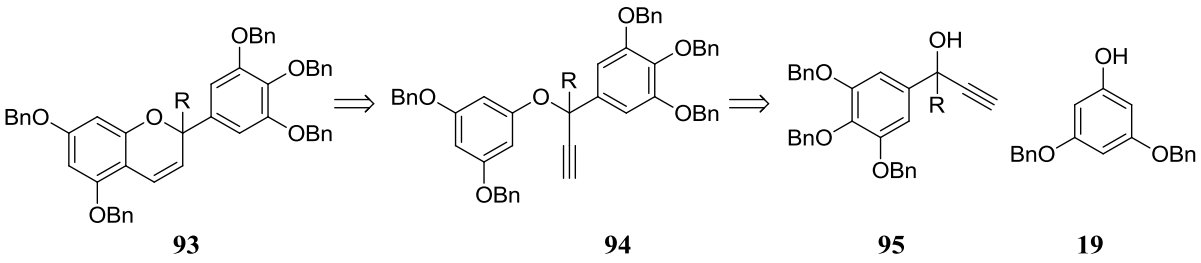


87 **91** **92**

Scheme 51: The formation of alcohol **92**

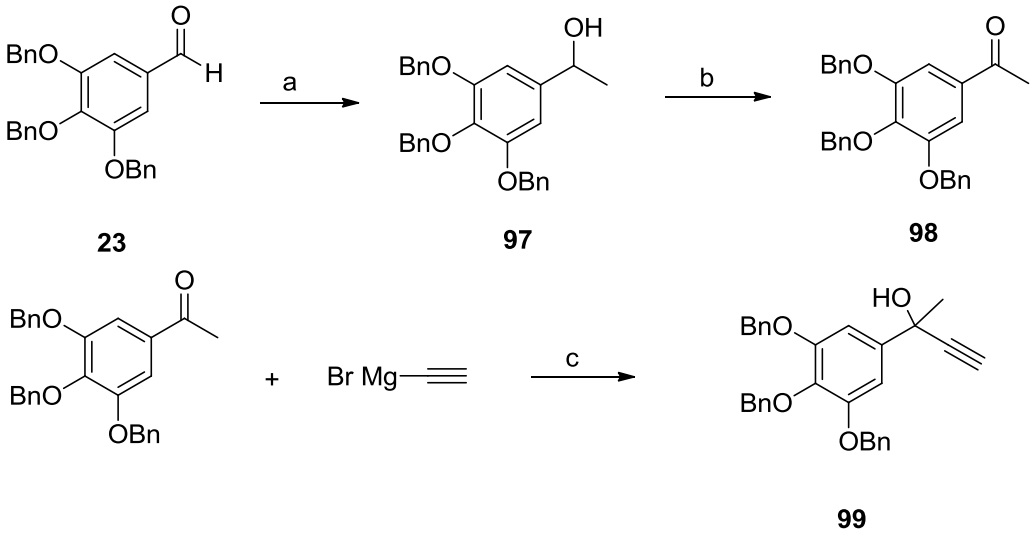
Another possibility for the synthesis of chromenes (or flav-3-enes), such as **93**, is through the rearrangement of suitable propargyl ethers, such as **94**; this pathway would also allow for many different substitution patterns and groups. A particularly interesting factor would be the potential for diverse groups to be inserted using different propargyl alcohols **95**. The rearrangement of propargylic ethers bearing electron-withdrawing groups into chromenes has

already been reported.[57] The desired propargyl ether could, in principle, be prepared by condensation of phenol **19** and propargyl alcohol **95** (**Scheme 52)**.



Scheme 52: Retrosynthesis of chromenes (±)-**14**

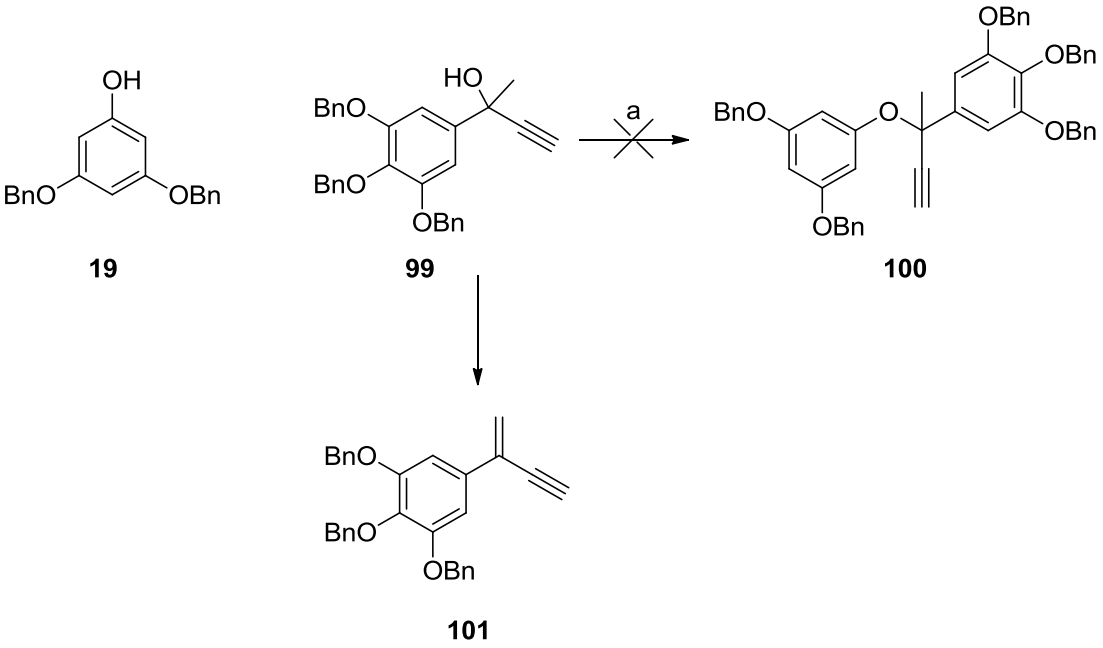
Initially, we decided to focus on the methyl series (such as **99**) to develop our methodology. The synthesis of propargylic alcohol **99** commenced with the addition of a Grignard reagent, methylmagnesium bromide (3.0M in diethyl ether), to a solution of 3,4,5-*tris*-(benzyloxy)-benzaldehyde **23** at 0 °C in anhydrous diethylether for 4 h. [58] The crude alcohol was purified by recrystallization using hexane at low temperature for 2 days, giving secondary alcohol **97** in 87% yield as a colourless solid. The alcohol moiety was then oxidized to the corresponding ketone **98** using PCC in 91% yield.[59] The ketone was treated with ethynyl magnesium bromide (3.5 equiv.) in anhydrous tetrahydrofuran to afford propargyl alcohol **99** in 55% yield. Increasing the amount of ethynyl magnesium bromide (5 equiv.) caused a decrease in the yield of **99** (down to 25%), and a complex mixture of unidentified products was observed (**Scheme 53**).[60]



Reagents and conditions: (a) MeMgBr (3 equiv.), Et_2O, 0 °C, 7h, 87%; (b) PCC (1.5 equiv.), CH_2Cl_2, 7h, R.T., 90%; (c) THF, NH_4Cl (aq.), 0 °C -R.T., 2h, 55%.

Scheme 53: Synthesis of propargyl alcohol **99**

With a methyl and ethyne group bearing centre in tertiary alcohol **99**, the formation of the corresponding carbocation might be expected to favour a reaction with a phenolic hydroxyl group from phenol **19**. Exposure of a mixture of the propargyl alcohol **99** and the phenol **19** in dichloromethane at 25 °C to a catalytic amount of camphorsulfonic acid for one hour did not result in the formation of propargyl ether **100** (**Scheme 54**). The propargyl alcohol **99** might, in principle, be converted into a tertiary carbocation, which is a common intermediate to both the E_1 elimination and the S_N1 reaction. The tertiary carbocation intermediate is sterically hindered which might prevent the S_N1 reaction from proceeding. Thus, the carbocation intermediate is probably more prone to an E1 reaction rather than the corresponding S_N1 reaction. Indeed, the E1 reaction is favoured leading to the alkene **101**. The ^{1}H NMR spectrum of the crude reaction mixture was compared with the ^{1}H NMR spectrum of the propargyl alcohol **99**: disappearance of both OH and methyl signals and appearance of alkene signals at 5.62 ppm and 5.75 ppm were observed (**Figure 4**).



Reagents and conditions: (a) Camphorsulfonic acid (10 mol.), CH_2Cl_2, 1h.

Scheme 54: synthesis of propargyl ether **100**

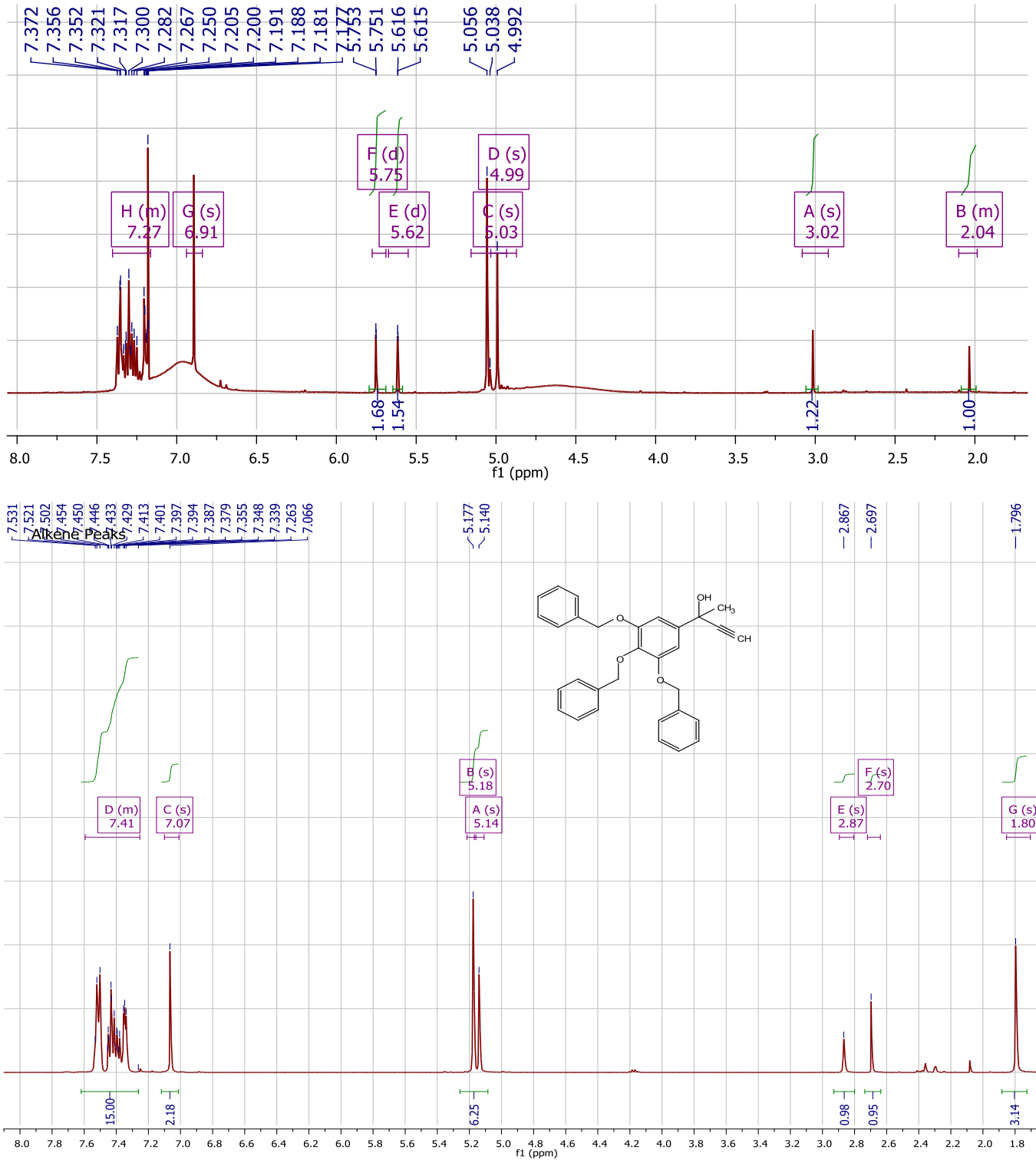
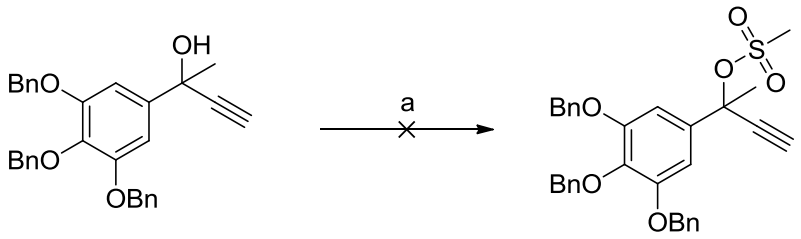


Figure 4: [1] H NMR spectra of the propargyl alcohol **99** and the crude reaction mixture

In an effort to avoid acid-catalysed dehydration of propargyl alcohol **99**, the conversion of the alcohol moiety into a good leaving group may speed up a S_N1 reaction with phenol **19**. However, all attempts to convert the propargyl alcohol into the corresponding chloride or bromide were unsuccessful, using hydrochloric acid, hydrobromic acid or thionyl chloride.[61,62] Furthermore, the treatment of propargyl alcohol **99** with methanesulfonyl chloride and triethylamine in dichloromethane in an attempt to form the methanesulfonyl ester **102** also failed (**Scheme 55**) and the starting material decomposed.[47]

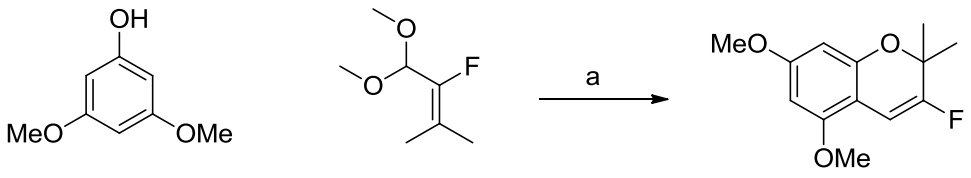


99 **102**

Reagents and conditions: (a) Methanesulfonyl chloride (1 equiv.), NEt_3 (1.1 equiv.), CH_2Cl_2, 0 °C, 0.45h.

Scheme 55: Attempts to form propargyl methanesulfonyl ester **102**

A literature search showed that the procedures reported by Crombie[63] and Camps[64] would be suitable to access the targeted chromenes. They reported that the condensation of α,β unsaturated carbonyl compounds in pyridine with phenols led to the formation of substituted benzopyrans in moderate to good yields. For example, cyclization occurred when phenol **103** was treated with an excess of dimethyl acetal **104** in pyridine, giving 2H-benzopyran **105** in 63% yield (**Scheme 56**).

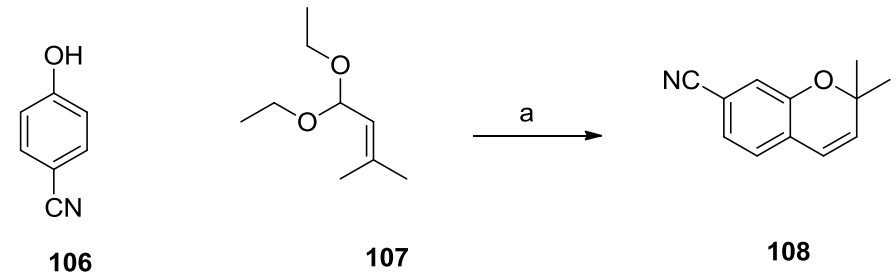


103 **104** **105**

Reagents and conditions: (a) pyridine, 140 °C, 2.5h, 63%.

Scheme 56

In 1995, North developed an excellent method for the synthesis of 2-substituted chromene structures: condensation of a phenol, such as **106**, with 3-methyl-2-butenal diethyl acetal **107** in the presence of an acid catalyst, such as fumaric acid, in *p*-xylene at 120 °C, results in the formation of 2-substituted chromenes, such as **108** (**Scheme 57**). [65]

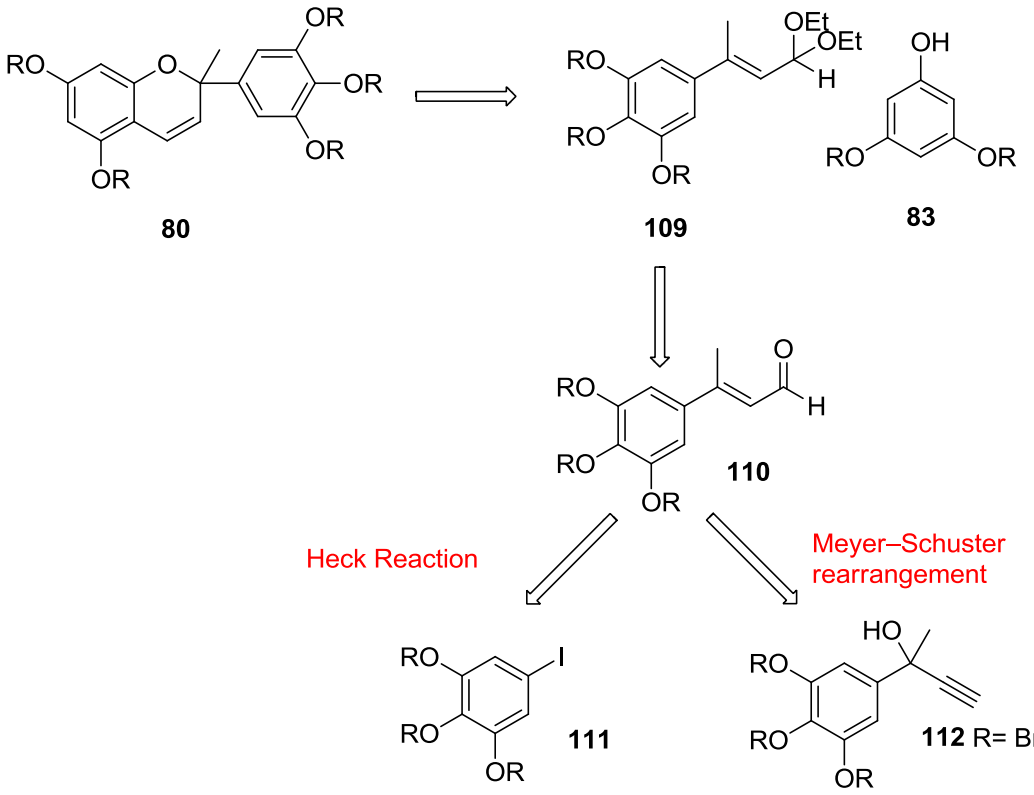


106 **107** **108**

Reagents and conditions: (a) Fumaric acid (0.13 equiv.), *p*-xylene, 120 °C, 6h, 79%.

Scheme 57: The conditions reported by North

The target chromene could be, in principle, obtained from acetal **109** and the corresponding phenol. As neither the desired acetal **109** nor the corresponding aldehyde **110** was commercially available, two strategies to access **110** were devised (**Scheme 58**). One potential route involves a Heck coupling between iodobenzene **111** and crotonaldehyde. The other potential route would allow us to use propargyl alcohols, such as **112**: a Meyer-Schuster rearrangement would lead to aldehyde **110**.

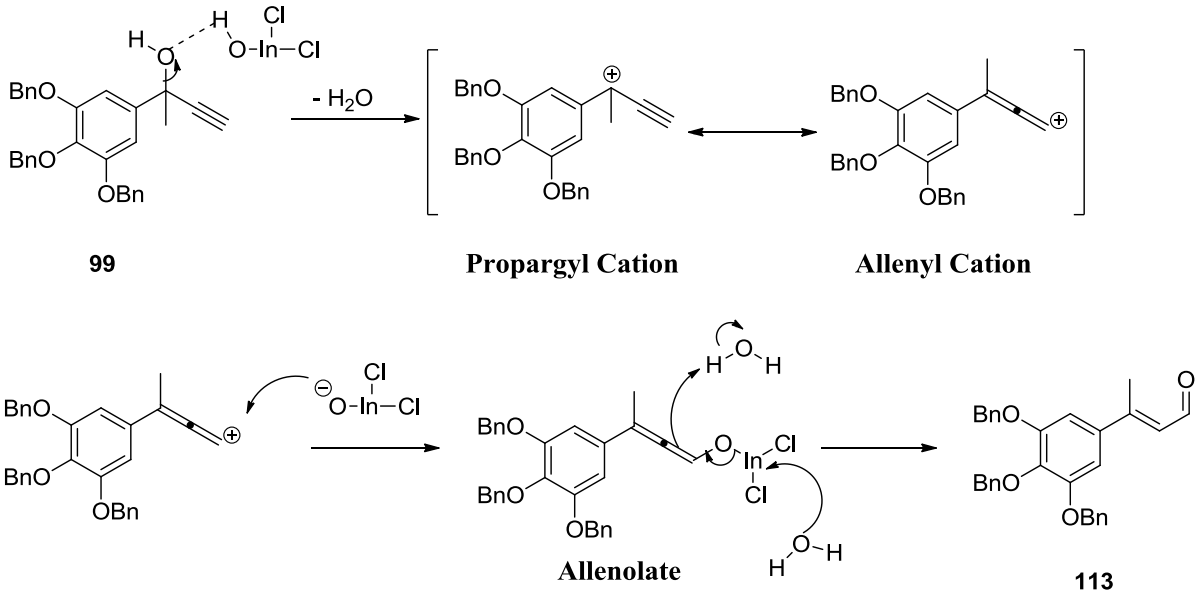


80 **109** **83** **110** **111** **112** R= Bn

Scheme 58: Retrosynthesis of acetal **30**

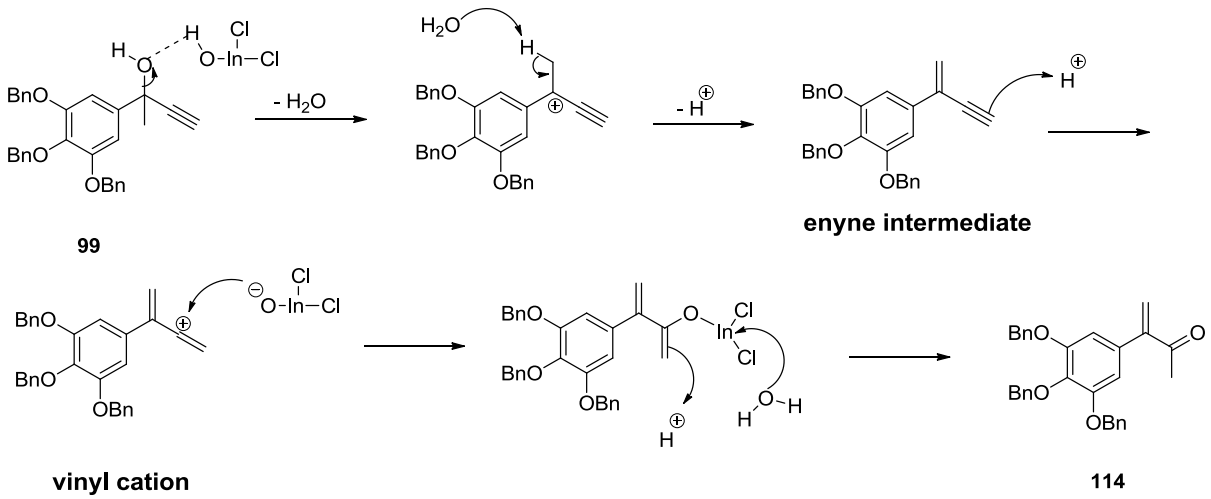
The Meyer-Schuster rearrangement involves a formal 1,3 shift of the hydroxyl moiety of the alkynol such as **99** followed by an internal redox-type process involving simultaneous oxidation of the resulting alcohol and reduction of the C≡C triple bond.[66,67] Recently,

transition metal-mediated Meyer-Schuster rearrangements have been used to synthesize α,β-unsaturated aldehydes. Indium (III) chloride and iron (III) chloride have showed a remarkable regioselectivity towards the Meyer-Schuster product in high yields. The strength of this later approach is a short reaction time and catalytic amounts of the water-compatible and inexpensive Lewis acids used under microwave irradiation and thermal activation.[68,69] The proposed mechanism for the Meyer–Schuster rearrangement is depicted in **Scheme 59**.



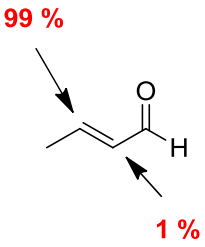
Scheme 59: The Meyer–Schuster rearrangement

Therefore, a reported procedure was followed: propargyl alcohol **99** (1 equiv.) was exposed to a catalytic amount of $InCl_3$ (1 mol%) in water under microwave irradiation at 160 °C. Despite increased amounts of catalyst and temperature, the desired compound was not detected. Iron (III) chloride (1.1 equiv.) was also utilized as the Lewis acid in tetrahydrofuran under reflux for 10 hours. No conversion of alcohol **99** was observed. Possible side reactions, such as the Rupe rearrangement or an elimination reaction, might occur due to the presence of a C–H bond in the β-position with respect to the alcohol group **(Scheme 60)**. [66,67] The Rupe rearrangement could be promoted under the Meyer–Schuster rearrangement conditions, and is another possible fate of the propargyl cation.[66] The Rupe rearrangement involves β-elimination of the propargyl cation, and therefore results in the formation of an enyne intermediate.[67] Subsequent protonation of the C≡C triple bond would lead to the formation of the vinyl cation, followed by tautomerization to afford **144**.[66,67]



Scheme 60: Possible side reactions

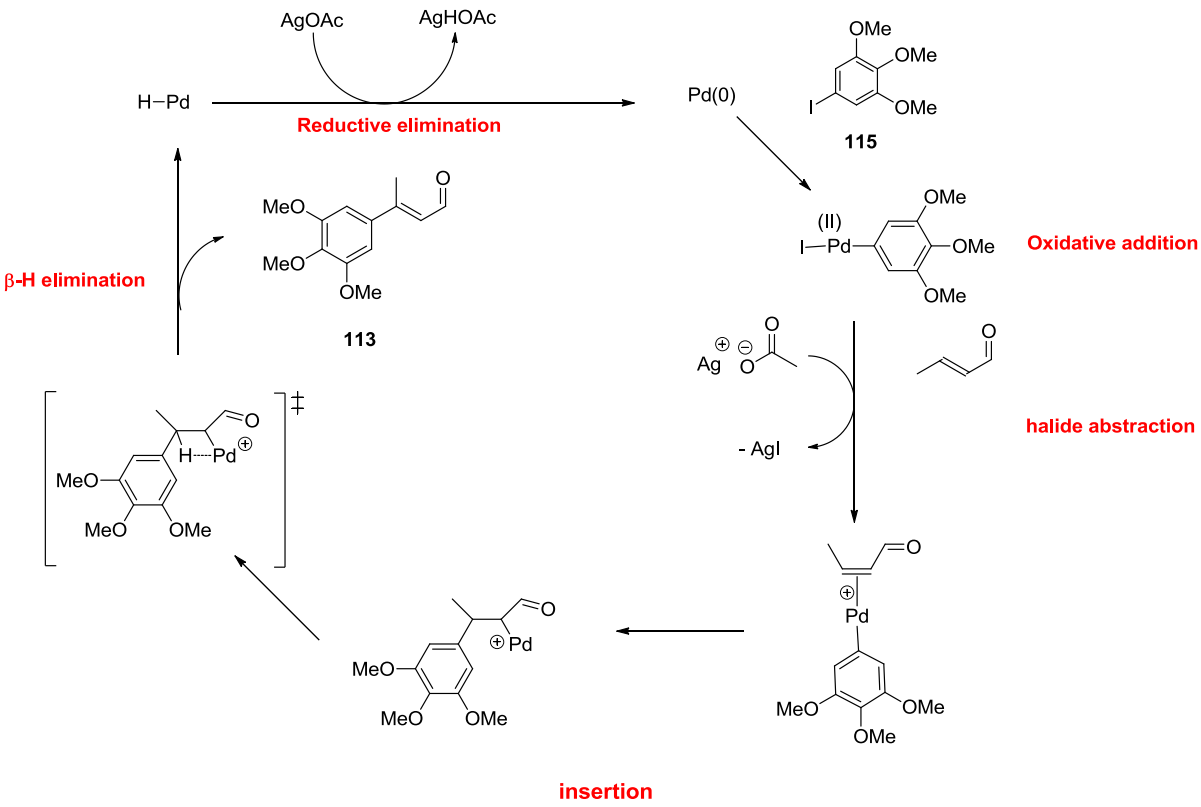
At this point, we decided to follow the other route to obtain α,β-unsaturated aldehyde **113**. The Heck reaction is a powerful tool for the preparation of disubstituted olefins from monosubstituted ones, discovered by T. Mizoroki and R.F. Heck independently in the late 1960s.[70] The regioselectivity observed when electron-deficient crotonaldehyde is used in a Heck coupling is particularly well-suited to our synthesis; under steric control, the addition occurs almost exclusively on carbon atom C3 (**Figure 5**).[71]



***trans*-Crotonaldehyde**

Figure 5: Regioselectivity of migratory insertion in the Heck coupling.

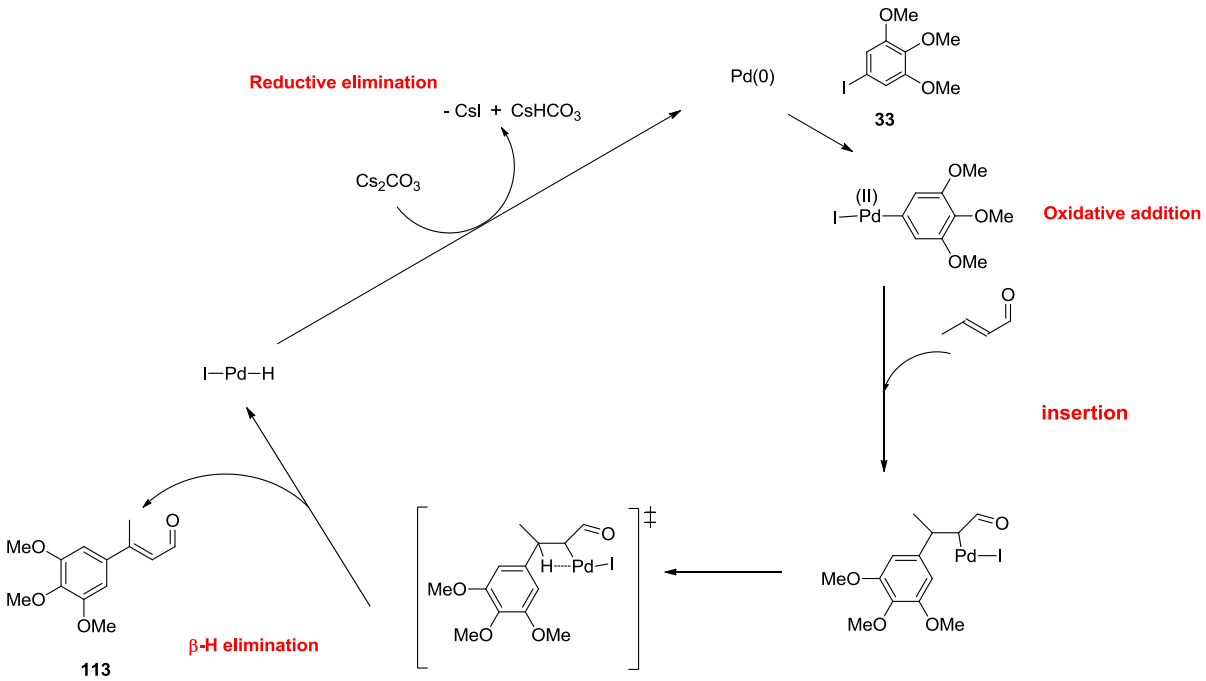
The Heck reaction proceeded by treatment of 5-iodo-1,2,3-trimethoxybenzene **115** (1 equiv.) and crotonaldehyde (1.2 equiv.) with palladium acetate (5 mol%) and silver acetate (2 equiv.) in acetonitrile under reflux for 19 hours giving aldehyde **113** in 44% yield (**Scheme 61**).[71,72]



Scheme 61: Cationic mechanism of Heck reaction

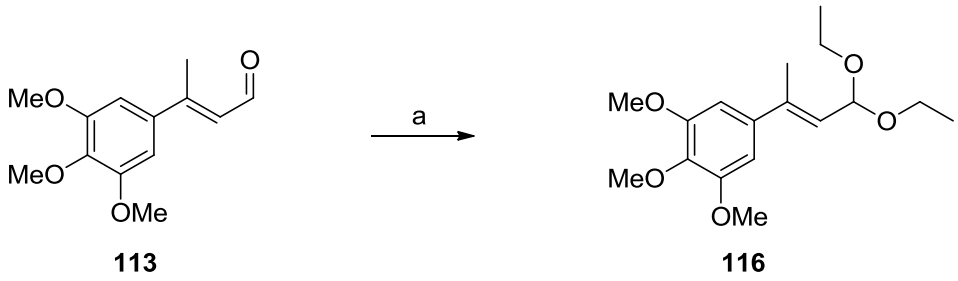
The Heck reaction follows a three-step mechanism. Firstly, oxidative addition occurs as the palladium inserts in the carbon-iodine bond to form an I-Pd(II)–Ph complex, followed by loss of the iodide using silver acetate. Secondly, after complexation of the alkene to the palladium centre, insertion of the palladium complex in the alkene bond occurs to form the new carbon-carbon bond. Finally, β-hydride elimination results in the formation of the product **113** and reductive elimination regenerates the palladium(0) centre.

It is interesting to note the change in the reaction yield when the Heck coupling proceeds through a neutral pathway. In the absence of silver acetate, the iodide remains attached to the metal centre using caesium carbonate (1.1 equiv.) as the base under the same conditions.[71] Indeed, a large increase in the yield was observed, and aldehyde **113** was obtained in 73% yield. The regiochemistry of the neutral pathway is governed by steric control, which affords the desired compound (**Scheme 62**).[72]



Scheme 62: Neutral pathway for Heck reaction

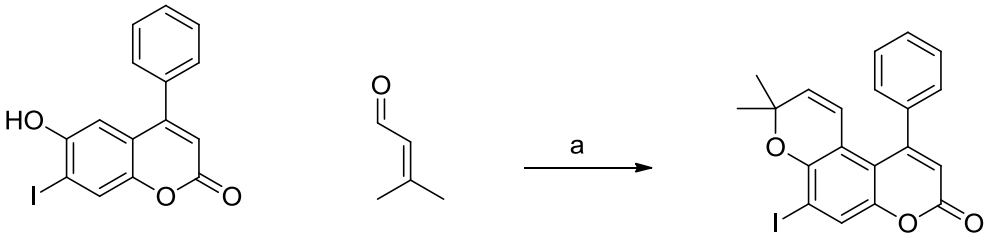
α,β-Unsaturated aldehyde **113** was submitted to acetalisation reaction conditions. [15] North's methodology has been utilised to synthesize various acetals within the group. The acetalization reaction was attempted with ammonium nitrate and triethylorthoformate in ethanol until full conversion of α,β-unsaturated aldehyde **113**, generally overnight. Unfortunately, the acetal **116** was found to be unstable and underwent rapid decomposition, even when stored at 0 °C for short periods of time (**Scheme 63**). [64]



Reagents and conditions: (a) $(EtO)_3CH$ (1.1 equiv.), NH_4NO_3 (0.25 equiv.), ethanol (4 mL), R.T., overnight.

Scheme 63

An examination of the literature[75] provided a relatively simple example to follow to synthesise the targeted chromenes without the requirement for an acetal group: cyclocondensation of an α,β-unsaturated aldehyde **117** and 5-hydroxycoumarin into chromene **118** was the key step for an elegant synthesis of pyranocoumarin derivatives which possess antiproliferative activity against breast cancer cell lines (**Scheme 64**). [75]

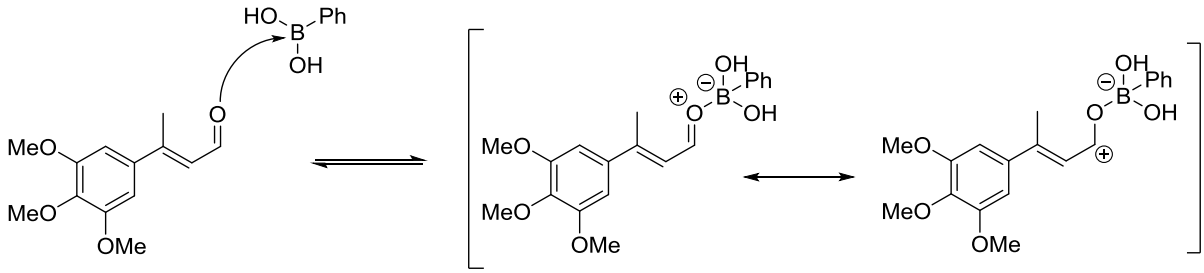


5-Hydroxycoumarin **117** **118**

Reagents and conditions: (a) **117** (1.5 equiv.), $PhB(OH)_2$ (1 equiv.), propionic acid (3 ml), toluene, 140 °C, 83%.

Scheme 64

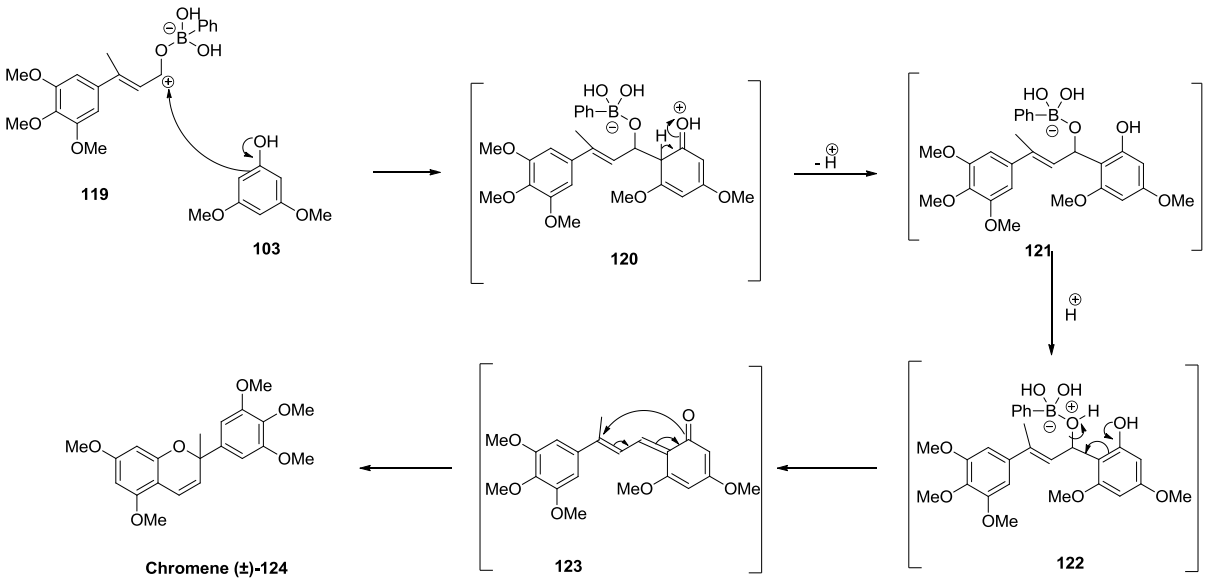
Thus, we attempted the procedure above for the formation of the desired chromene. Initially, the Lewis acid activation of the carbonyl group in compound **113** causes the formation of α-alkoxy-carbocation **119** due to the use of phenylboronic acid (**Scheme 65)**.



113 **119**

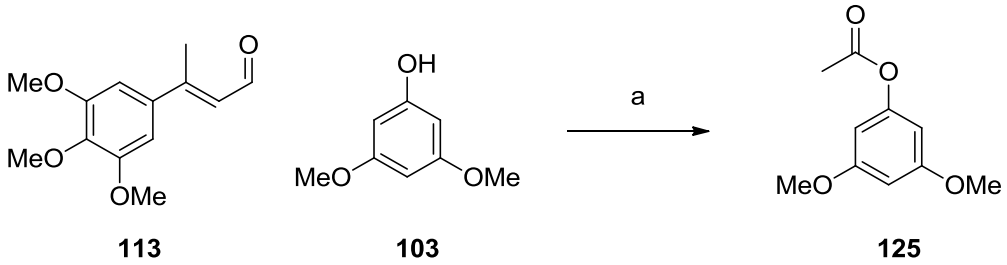
Scheme 65: The formation of α-alkoxy-carbocation **119**

We believe the mechanism of the reaction should follow this pathway: carbocation **119** reacts with phenol **103**, affording intermediate **120**. Rearomatization of **120** with loss of a proton then leads to compound **122**. Elimination of trihydroxy(phenyl)borate affords intermediate **123** and chromene **124** is obtained by [3,3]-electrocyclic rearrangement of **123** (**Scheme 66**).



Scheme 66: Proposed mechanism for synthesis of chromene (±)-**124**

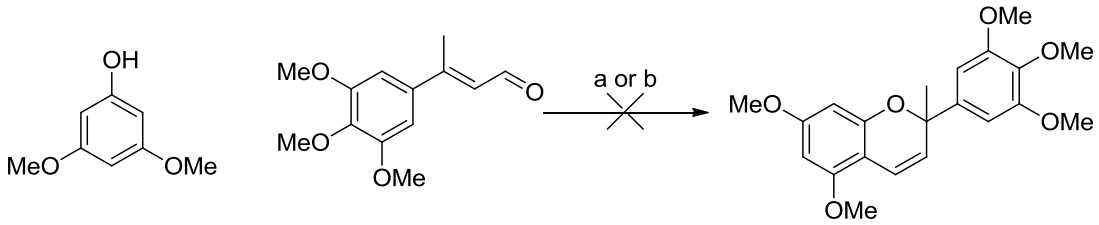
When the α,β-unsaturated aldehyde **113** was submitted to the cyclization reaction with phenol **103** in presence of acetic acid and phenylboronic acid in toluene under reflux overnight, the ester compound **125** was obtained in 90% yield.



Reagents and conditions: (a) **113** (1.5 equiv.), $PhB(OH)_2$ (1 equiv.), acetic acid (1 mL), toluene, reflux, 90%.

Scheme 67

In order to avoid the esterification of the phenol, acetic acid was replaced with Amberlyst, which is a strongly acidic cation exchange resin. However, cyclization did not occur under these conditions (**Scheme 68**).

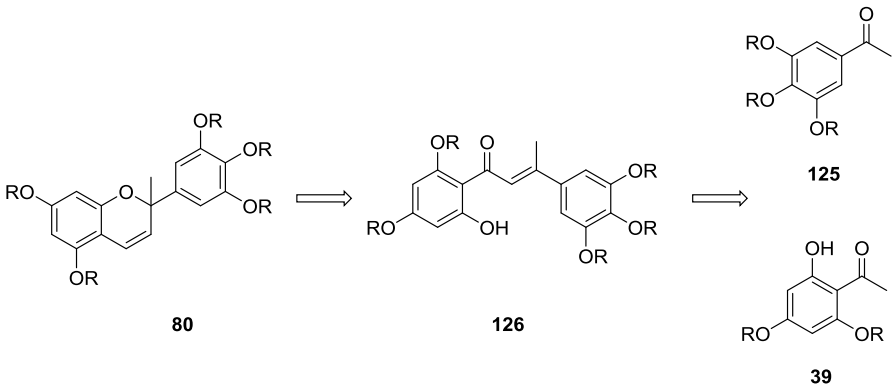


103 **113** Chromene (±)-**124**

Reagents and conditions: (a) **113** (1.5 equiv.), amberlyst, $PhB(OH)_2$ (1 equiv.), *p*-xylene, 140 °C, overnight; (b) **113** (3 equiv.) amberlyst, $PhB(OH)_2$ (2 equiv.), toluene, reflux, overnight.

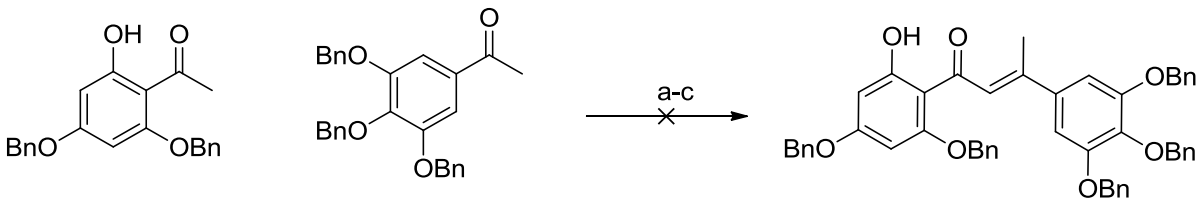
Scheme 68

In a further attempt to synthesize flav-3-ene **80** with a methyl analogue, we followed a promising route towards the synthesis of flav-3-ene derivatives as outlined in the retrosynthetic approach below (**Scheme 69**). Chalcones, such as **126**, would be prepared from ketones, such as **125**, through an aldol reaction with acetophenone **39. C**yclisation of the corresponding α,β-unsaturated ketones or chalcones **126** should lead to the formation of flav-3-enes, such as **80**.



Scheme 69: Retrosynthesis of racemic chromene **80**

Lithium diisopropylamide was used to generate the enolate of ketone **43** to attack compound **98** in an attempt to form chalcone **127**. The chalcone is a suitable precursor for the chromene **80** and could be submitted to a cyclization reaction to afford chromene **80** (**Scheme 70**). Unfortunately, due to the low quantity of base present, only starting material was observed due to a faster deprotonation of the phenolic hydroxyl rather than the desired formation of the enolate.[75] The reaction was also attempted using a larger quantity of base (3 equiv.) , giving only starting material.



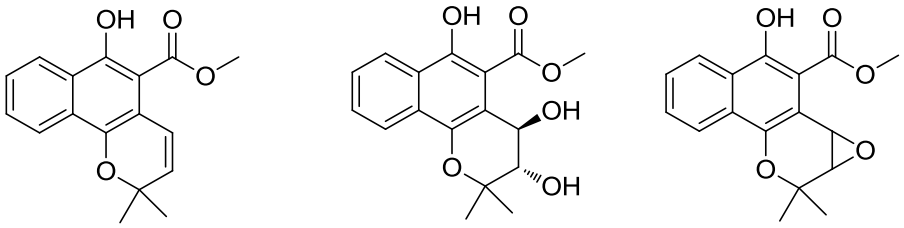
43 **98** **127**

Reagents and conditions: (a) **43** (1 equiv.), **98** (1 equiv.), LDA (2 equiv.), THF, 0 °C, overnight; (b) **43** (1 equiv.), **98** (1 equiv.), LDA (2 equiv.), THF, –20 °C, overnight; (c) **43** (1 equiv.), **98** (1 equiv.), LDA (3 equiv.), THF, –78 °C, overnight.

Scheme 70

2.6 Application of the Page asymmetric epoxidation in the synthesis of trans-3,4-dihydroxy-3,4-dihydromollugin.

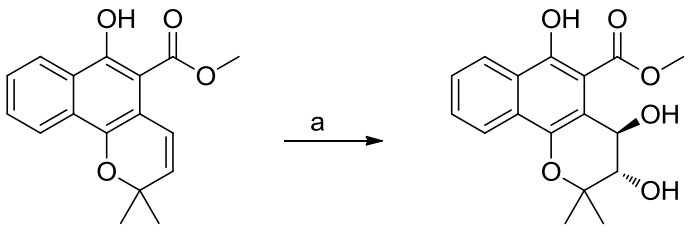
The root of the African medicinal plants, *Pentas longiflora* (Rubiaceae),[76] and *Rubia cordifolia*,[77] is the source of a benzochromene antibiotic: it contains mollugin **128** and its analogues *trans*-3,4-dihydroxy-3,4-dihydromollugin **129** and epoxymollugin **130**.[78,79] These plants appear to possess antitumour, antimutagenic, anti-leukaemia, anti-inflammatory, anti-colon cancer and antiallergic activities.[77,80] They are used to treat skin diseases such as pityriasis versicolor, itchy rashes, and malaria (mixed with milk), tapeworm, gonorrhea, and are used as a purgative in Kenya and Rwanda.[80,81]



128 **129** **130**

Figures 6: Mollugin and analogues

A reliable method for the synthesis of mollugin **128** was reported by Wang et al.[82] An intermolecular cyclization reaction was the key step in the formation of mollugin: 2-methyl-3-butenal and 1,4-dihydroxy-2-naphthoic acid were heated under reflux in the presence of benzene boronic acid and acetic acid in toluene, giving **128** in 91% yield. The synthesis of racemic *trans*-3,4-dihydroxy-3,4-dihydromollugin **129** was achieved in 31% yield by oxidation of mollugin using Oxone in a mixture of acetone/water in a 1:2 ratio for 12 h (**Scheme 71**).[76]

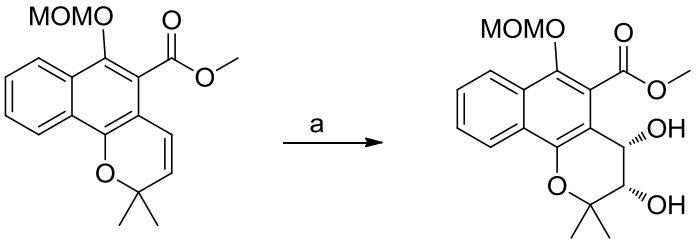


128 **129**

Reagent and conditions: a) Oxone (3 equiv.), acetone/water (1:2), 80 ˚C, 12h, 31%.

Scheme 71: The formation of racemic *trans*-3,4-dihydroxy-3,4-di-hydromollugin **129**

O-Methoxymethyl-(*3S,4S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **132** was prepared using a Sharpless asymmetric dihydroxylation of mollugin methoxymethyl ether in 30% yield and 86% ee (**Scheme 72**).[83]

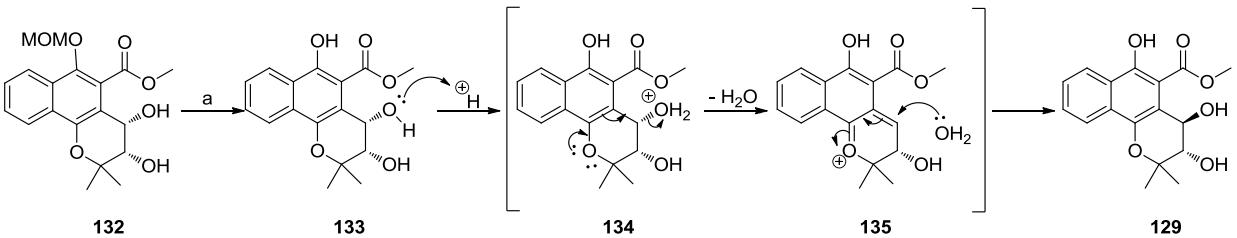


131 **132**

Reagent and conditions: a) AD-Mix β, K_2CO_3, $K_3F_2(CN)_6$, $K_2OsO_2(OH)_4$, $(DHQD)_2$-PHAL, *t*-BuOH:H_2O:THF (8:8:1) 0 ˚C to rt, 24h, 32%, 86% ee.

Scheme 72: The formation of *O*-methoxymethyl-(*3S,4S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **132**

Removal of the MOM group gave *cis*-diol **132** and *trans*-diol **129** in 60 and 20% yield, respectively. Indeed, when the deprotection of the MOM group was attempted using a large excess of hydrochloric acid, inversion of the configuration at the C4 position led to the formation of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **129**.[83] The author reasoned that a free hydroxyl group at position 4 was protonated and the resulting oxonium ion was displaced by an electron push mechanism starting from the lone pair of the pyranyl-oxygen. Thereby, *trans*-diol **129** was formed by nucleophilic attack on the reactive *ortho*-quinone methide intermediate **135** (**Scheme73**). Moreover, they commented that "the lower yields and side products are the drawbacks of this protocol"[83] and "routes were paved with difficulties".[82]



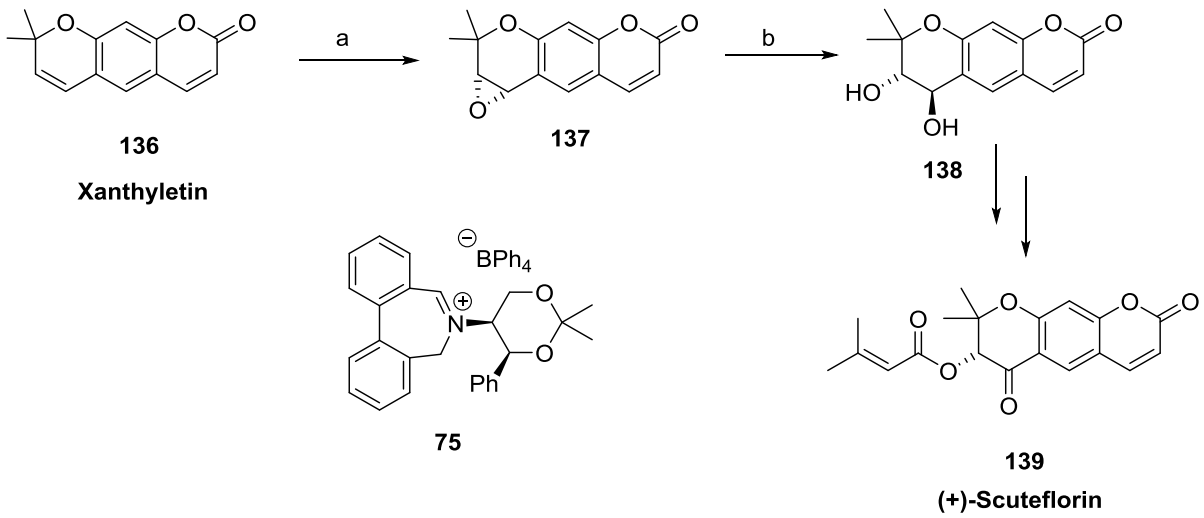
132 **133** **134** **135** **129**

Reagent and conditions: a) 6N HCl/THF (1:1), 0 ˚C to rt, 3h, 20%.

Scheme 73: The formation of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **129**

We have recently reported the highly enantioselective epoxidation of xanthyletin **136** in 99% ee as the key step towards the total synthesis of (+)-scuteflorin A **139**, using chiral iminium

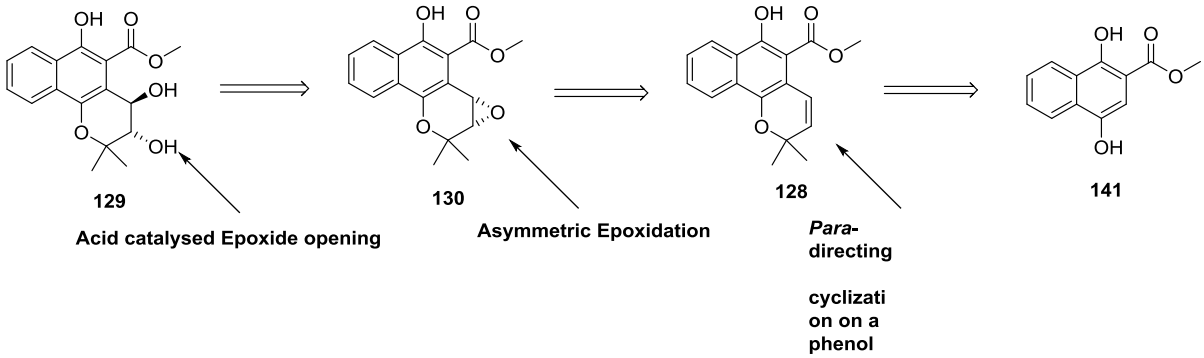
salt catalyst **75** under non-aqueous conditions. The acid-catalysed epoxide ring-opening of epoxide **136** afforded *trans*-diol **138** in high yield. Thus, we envisaged that the synthesis of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **129** could be effected by a similar epoxidation of mollugin **128** to install the stereocentres and functionality required. [84]



Reagent and conditions: (a) Catalyst **75** , TPPP, $CHCl_3$, −30 °C, 30 h, 97%, 99 % ee; (b) acetone/1 M H_2SO_4 (2:1), rt, 10 min, 60%.

Scheme74: Total synthesis of (+)-scuteflorin A using iminium-catalysed asymmetric epoxidation.

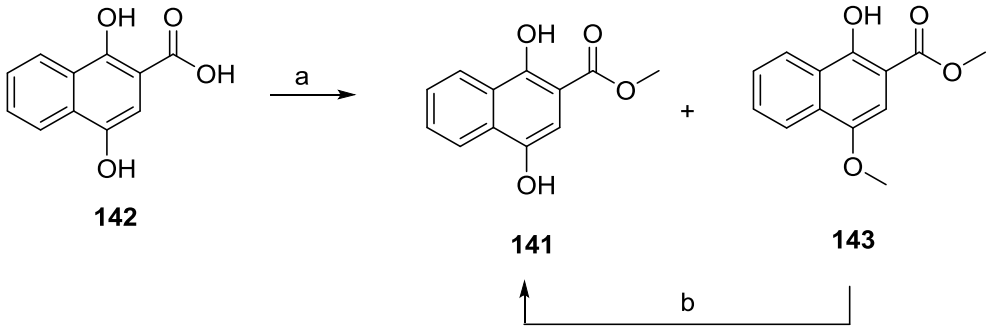
In our retrosynthetic analysis, *trans*-diol **129** could be derived in a straightforward manner from ring-opening of chiral epoxide **130**. Asymmetric epoxidation of cyclic *cis*-disubstituted mollugin **128** could secure the formation of enantioenriched epoxide intermediates **130**. Mollugin **128** could be accessed using Wang's methodology (**Scheme75**).



Scheme 75: Retrosynthetic analysis of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **129**.

2.6.1 Synthesis of mollugin

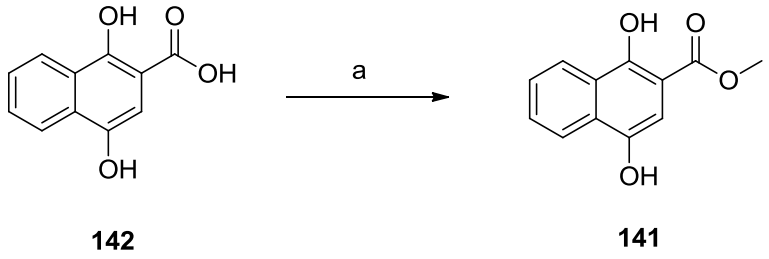
The first objective was the synthesis of 1,4-dihydroxynaphthalene-2-carboxylic ester **141**. Commercially available 1,4-dihydroxynaphthalene-2-carboxylic acid **142** was treated with sulfuric acid in methanol. Unfortunately, the desired product **141** was obtained in a very low yield (5%), alongside a major undesired product **143**, formed in 90% yield.[85] However, compound **143** can be converted to the desired 1,4-dihydroxynaphthalene-2-carboxylic ester **141** by demethylation of the methoxy group. Indeed, the treatment of a solution of **143** in anhydrous dichloromethane with aluminium chloride at 0 ºC produced the compound **141** in 91% yield (**Scheme76**).



Reagent and conditions: (a) CH_3OH, H_2SO_4, 8 h, 0 ºC-reflux, [**141** 5%; **143** 90%]; (b) $AlCl_3$ (2 equiv.), 0 ºC, 2 h, 91%.

Scheme 76: The synthesis of **141**

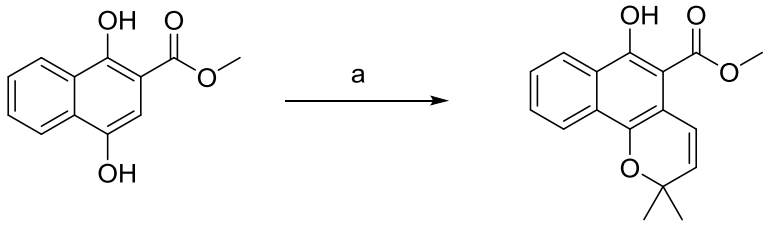
Another esterification method applied to 1,4-dihydroxynaphthalene-2-carboxylic acid resulted in the formation of the compound **141** in high yield: methyl iodide was used with anhydrous sodium hydrogen carbonate in dimethylformamide overnight at room temperature, giving **141** in 96% yield (**Scheme 77**).



Reagent and conditions: (a) MeI (1.5 equiv.), $NaHCO_3$ (1.2 equiv.), 0 ºC-rt, overnight, 96%.

Scheme 77: The formation of **141** in a high yield

It is then possible to achieve the synthesis of mollugin by *ortho*-directed cyclisation on a phenol with an enal species. Thus, the intermolecular phenylboronic acid-mediated cyclization of 3-methyl-2-butenal with **141** was achieved in 53% yield (**Scheme 78**).[85]

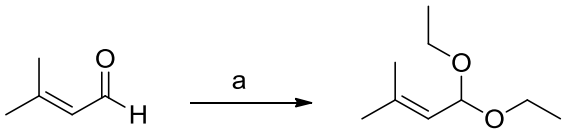


141 **129**

Reagent and conditions: (a) 3-Methyl-2-butenal (2.0 equiv.), $PhB(OH)_2$ (1.0 equiv.), toluene/AcOH, reflux, 17 h, 53%.

Scheme 78: Synthesis of mollugin

In order to improve the yield, we believed that the reaction could be carried out using North's procedure,[44] where a phenol is cyclized with an α,β-unsaturated acetal under basic conditions. In order to achieve that, α,β-unsaturated acetal **145** was initially formed by reacting aldehyde **144** and diethyl orthoformate in the presence of a catalytic amount of ammonium nitrate in anhydrous ethanol under nitrogen in 48% yield. The acetal was directly used after work up, due to its instability. (**Scheme 79**).

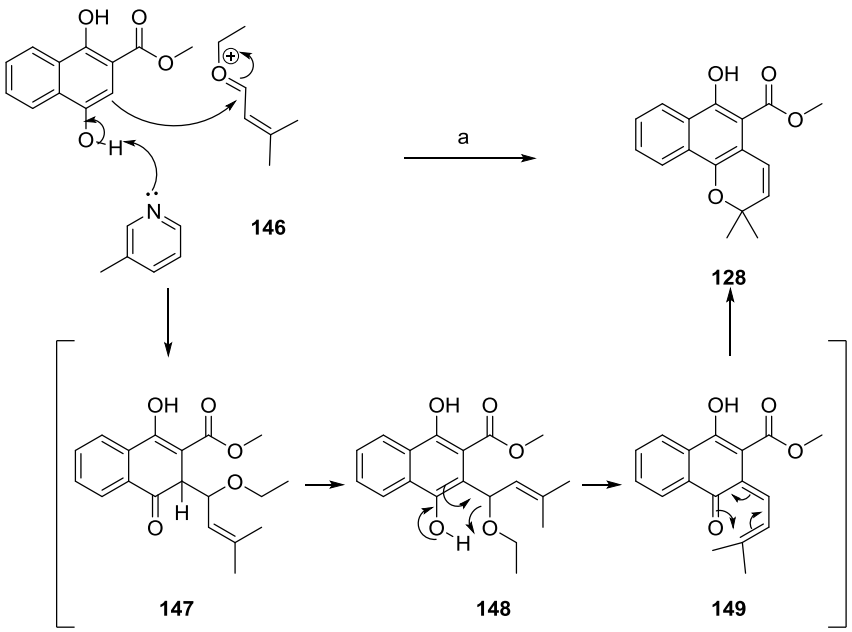


144 **145**

Reagent and conditions: (a) 3-Methyl-2-butenal (1 equiv.), NH_4NO_3 (0.25 equiv.), triethylorthoformate (1.2 equiv.) 0 ºC-rt, 24 h, 48%.

Scheme 79: Formation of the α-β-unsaturated acetal **145**

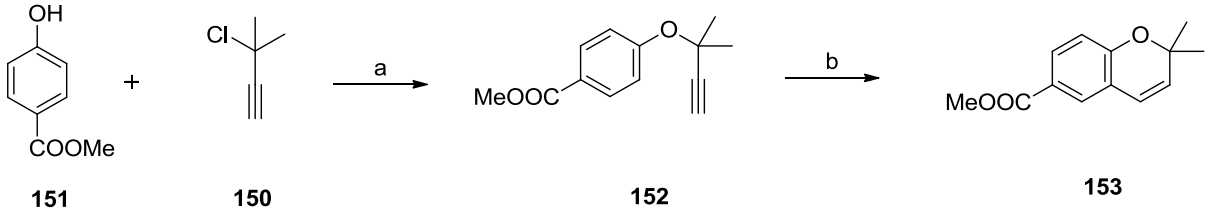
The cyclisation reaction using the α,β-unsaturated acetal **145** was carried out as described by North. Treatment of **141** with 3-picoline as the base in *p*-xylene resulted in the attack of oxocarbenium ion **146** to form dienone **147**. Elimination of ethanol led to *ortho*-quinone methide **149**. Finally, electrocyclic ring closure provided mollugin **128** in 64% yield.



Reagents and conditions: (a) **141** (1 equiv.), acetal **145** (1 equiv.), 3-picoline (0.25 equiv.), *p*-xylene, reflux, 24 h, 64%.

Scheme 80: Synthesis of mollugin **129** using North's procedure

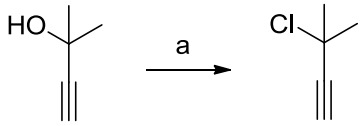
In an effort to increase the yield of mollugin **128**, alternative syntheses were sought. A promising study by Smith *et al*. involves the derivatization of methyl 4-hydroxybenzoate **151** with 3-chloro-3-methyl-1-butyne **150**, forming propargyl ether **152** which was then cyclised at high temperature in *N*,*N*-diethylaniline (**Scheme 81**).[86]



Reagents and conditions: (a) **151** (1 equiv.), 3-chloro-3-methyl-1-butyne **150** (3 equiv.), K_2CO_3 (1 equiv.), KI (1 equiv.), acetone, 49-53 ºC, 48 h, 79 %; (b) *N*,*N*-diethylaniline, 210 ºC, 97%.

Scheme 81: Synthesis of 6-carbomethoxychromene **153**

Hence, the synthesis of mollugin **128** commenced with the chlorination of commercially available 2-methyl-3-butyn-2-ol **154** using cold concentrated hydrochloric acid, forming **150** in 56% (**Scheme 82**).

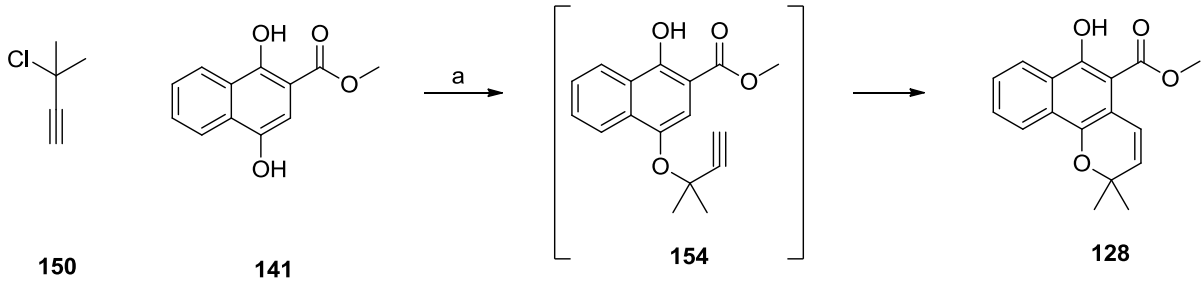


154 **150**

Reagents and conditions: (a) Methyl-3-butyn-2-ol **154** (3 equiv.), $CaCl_2$ (1 equiv.), CuCl (1 equiv.), Cu (3 mol%), HCl, 0 ºC, 1 h, 56 %.

Scheme 82: Chlorination of methyl-3-butyn-2-ol **154**

When starting materials **150** and **141**, a catalytic amount of copper powder, cuprous chloride and potassium carbonate were stirred at 53 ºC in acetone for 24h, mollugin **128** was produced in 19% yield (**Scheme 83**).[84] Interestingly, only product **128** was isolated alongside recovered starting material **141** (79% recovery)**.** Since **154** was found to be thermally unstable and to rearrange into **128**, the reaction conditions were modified by replacing acetone with toluene and increasing the temperature from 53 °C to reflux. Thereby, the desired product **128** was obtained in 81% yield.



150 **141** **154** **128**

Reagents and conditions: (a) 3-Chloro-3-methyl-1-butyne **150** (3.1 equiv.), CuCl (1 equiv.), Cu (5 mol%), K_2CO_3 (2 equiv.), KI (2 equiv.), acetone, 53 ºC, 24 h, 19 %.

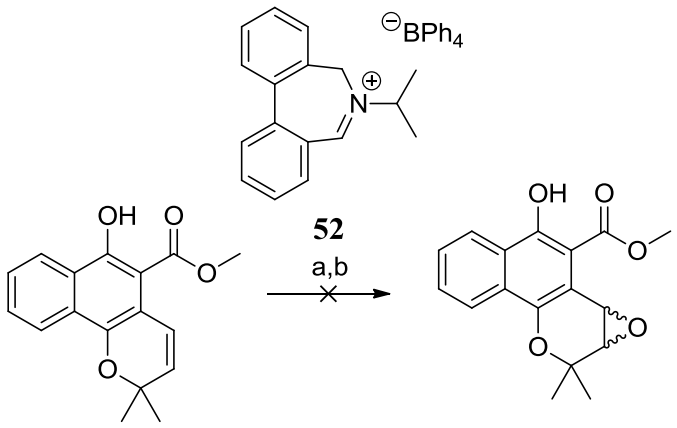
Scheme 83: **A**lternative route used for the synthesis of **128**

2.6.2 Synthesis of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin 129

2.6.2.1 Synthesis of racemic mollugin oxide 130

The synthesis of racemic mollugin oxide **130** was first attempted using standard epoxidation conditions. Unfortunately, *m*-CPBA oxidation of mollugin **128** in anhydrous dichloromethane was unsuccessful and decomposition of the starting material was observed. Non-chiral iminium salt **52** was also used to attempt the epoxidation of mollugin **128** in both aqueous and non-aqueous conditions, and only starting material was observed (**Table 7**).

Table 7: Standard epoxidation conditions

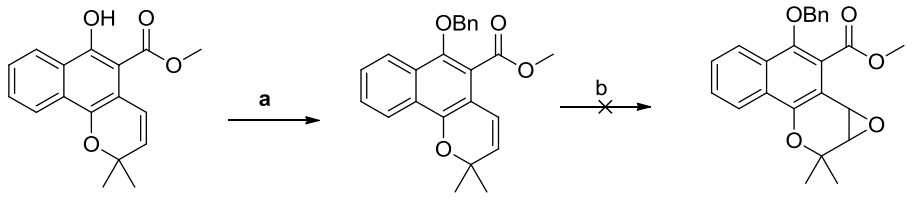


128 **130**

Conditions	Temp	Solvent	Time	Yield
a	0 °C	CH_2Cl_2	20 min	decomposition
b	0 °C	MeCN/H_2O (10:1)	24 h	SM

Reagents and conditions: (a) *m*-CPBA (1 equiv.), $NaHCO_3$ (2 equiv.); (b) **52** (10 mol%), $NaHCO_3$ (4 equiv.), Oxone™ (2 equiv.)

As the free phenolic hydroxyl was believed to interfere with our oxidation or destabilize the epoxide moiety, protection using a benzyl group was targeted. Benzyl bromide, mollugin, and potassium carbonate were mixed in dimethylformamide at 70 °C to give benzylated product **155** in 86% yield. Attempts to oxidise **155** using *m*-CPBA and sodium hydrogen carbonate in anhydrous dichloromethane led to decomposition (**Scheme 84**).



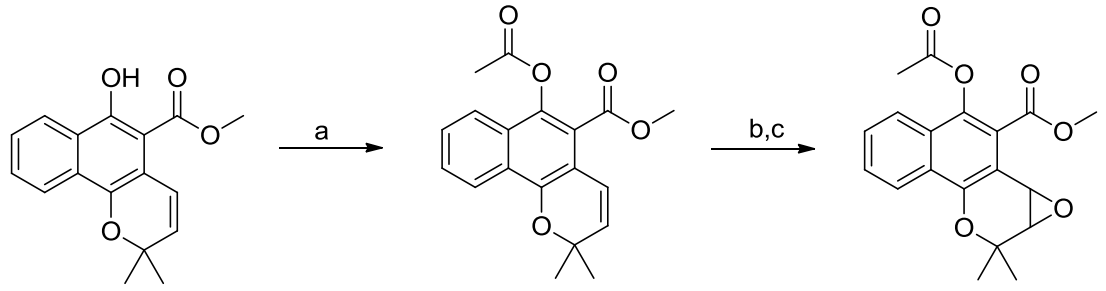
128 **155** **156**

Reagents and conditions: (a) BnBr (1.5 equiv.), K_2CO_3 (1.5 equiv.), DMF, 70 °C, 4h, 86%; (b) *m*-CPBA (1 equiv.), $NaHCO_3$ (2 equiv.), 0 °C, 50 min.

Scheme 84: Synthesis of **156**

It is possible, given these results, that strongly electron-donating groups can destabilize the epoxide moiety under standard epoxidation conditions. We then turned our attention towards milder electron-donating groups: acetylation of **128** was achieved using acetic anhydride and pyridine in anhydrous dichloromethane to give acetate **157** in 95% yield.[87] The formation of racemic epoxide **158** was successful utilizing *m*-CPBA and iminium salt **52** under aqueous conditions, affording epoxide **158** in 47% and 31% yield, respectively (**Table 8**). Unfortunately, we were unable to resolve the peaks corresponding to each enantiomer using chiral HPLC.

Table 8: Synthesis of racemic epoxide **158**.



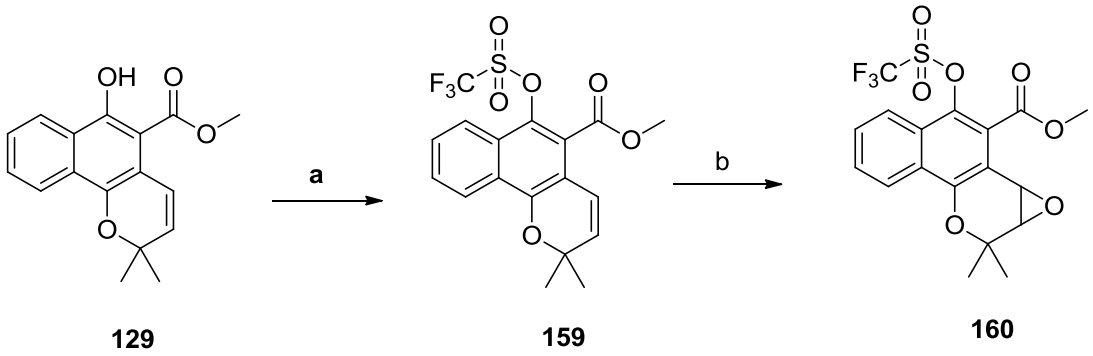
128 **157** **158**

Conditions	Temp	Solvent	Time	Yield
b	0 °C	CH_2Cl_2	20 min	47%
c	0 °C	MeCN/H_2O (10:1)	24 h	31%

Reagents and conditions: (a) Pyridine (19 equiv.), Ac_2O (19 equiv.), CH_2Cl_2, rt, overnight, 95%; (b) *m*-CPBA (1 equiv.), $NaHCO_3$ (2 equiv.); (c) **52** (10 mol%), $NaHCO_3$(4 equiv.), Oxone™ (2 equiv.).

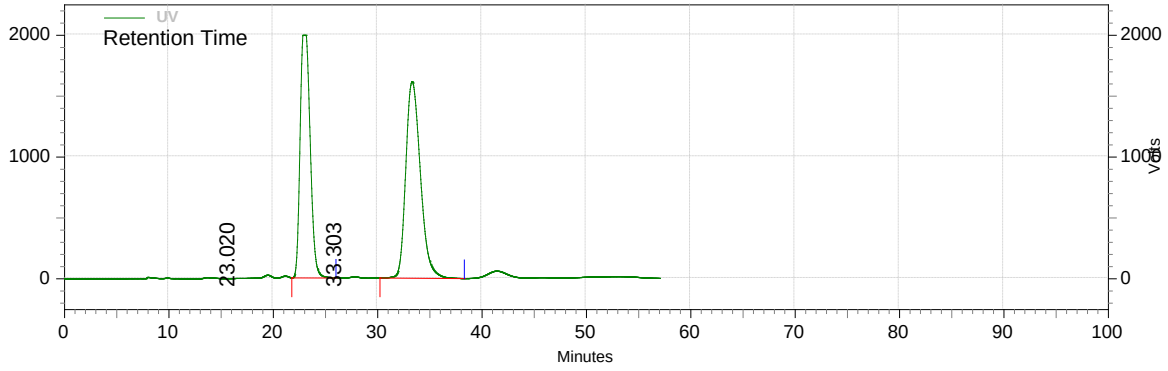
To overcome the poor separation of enantiomers of the racemic epoxide using HPLC, the installation of more polar protecting groups on the free phenolic hydroxyl of compound **128** was targeted. We first turned our attention towards the trifluoromethanesulfonate (or triflate)

group: treatment of mollugin **128** with triethylamine and trifluoromethanesulfonic anhydride in anhydrous dichloromethane afforded the desired product **159** in 98% yield.[88] The racemic epoxide **160** was prepared in 81% yield using *m*-CPBA (**Scheme 82**). Crucially, separation of the enantiomers the racemic product **160** was observed, and the chromatogram exhibited two peaks of not equal areas at 23 and 33 minutes with an acceptable resolution (**Figure 8**).



Reagents and conditions: (a) TEA (2 equiv.), $(CF_3SO_2)O$ (3 equiv.), DCM, 0 °C-RT, 24h, 91 %; (b) *m*-CPBA (1 equiv.), Na_2CO_3 (2 equiv.), 0 °C, 2 h, 81%.

Scheme 82: Synthesis of **160**



UV Results

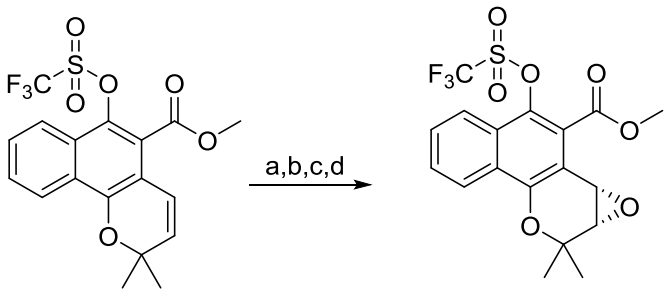
Retention Time	Area	Area %	Height	Height %
23.020	536527579	46.02	7973912	55.25
33.303	629307034	53.98	6458123	44.75
Totals	1165834613	100.00	14432035	100.00

Figure 8: Chromatogram of racemic **160**

2.6.2.2 Asymmetric epoxidation of 159

The synthesis of key non-racemic intermediate **160** was expected to require the use of the biphenyl-azepinium catalyst **74** prepared by our group. We screened catalyst **74** under aqueous conditions and non-aqueous conditions for asymmetric epoxidation of **159**. Somewhat surprisingly, epoxidation of **159** under non-aqueous conditions was unsuccessful at −30, −10 and 0 °C and the starting material was recovered in each case. However, under aqueous conditions, the reactivity of biphenyl catalyst **75** is excellent, and the desired epoxide was obtained in very high yields (**Table 9**).

Table 9: Synthesis of chiral epoxide **160**

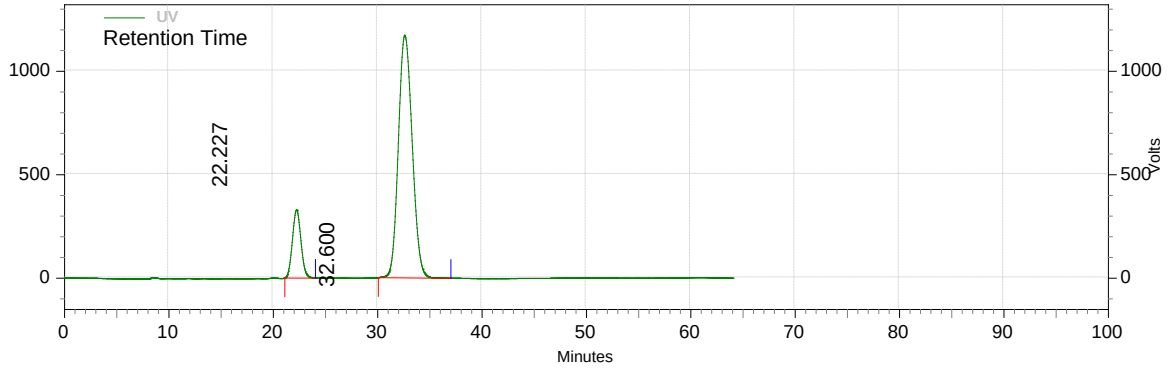


159 **160**

Conditions	Temp	Solvent	Time	Yield
a	−30 °C	$CHCl_3$	24 h	SM
b	−10 °C	$CHCl_3$	24 h	SM
c	0 °C	$CHCl_3$	24 h	SM
d	0 °C	MeCN/H_2O (10:1)	15 min	91%

Reagents and conditions: (a), (b), (c) catalyst **75** (10 mol%), TPPP (2 equiv.); (d) catalyst **75** (10 mol%), Na_2CO_3(5 equiv.), Oxone™ (2 equiv.).

Full conversion to (−)-(*S*,*S*)-epoxide **160** was observed after 15 min, and the product was isolated in 91% yield and 70.5% ee (**Figure 9)**. The absolute configuration at the C3 and C4 position was established as being (*S*), (*S*) for major enantiomer **160** based on the epoxidation of number of cyclic *cis*- chromene structures under aqueous conditions by our group, which their absolute configurations were determined by comparison of optical rotation with values reported in the literature. [4]

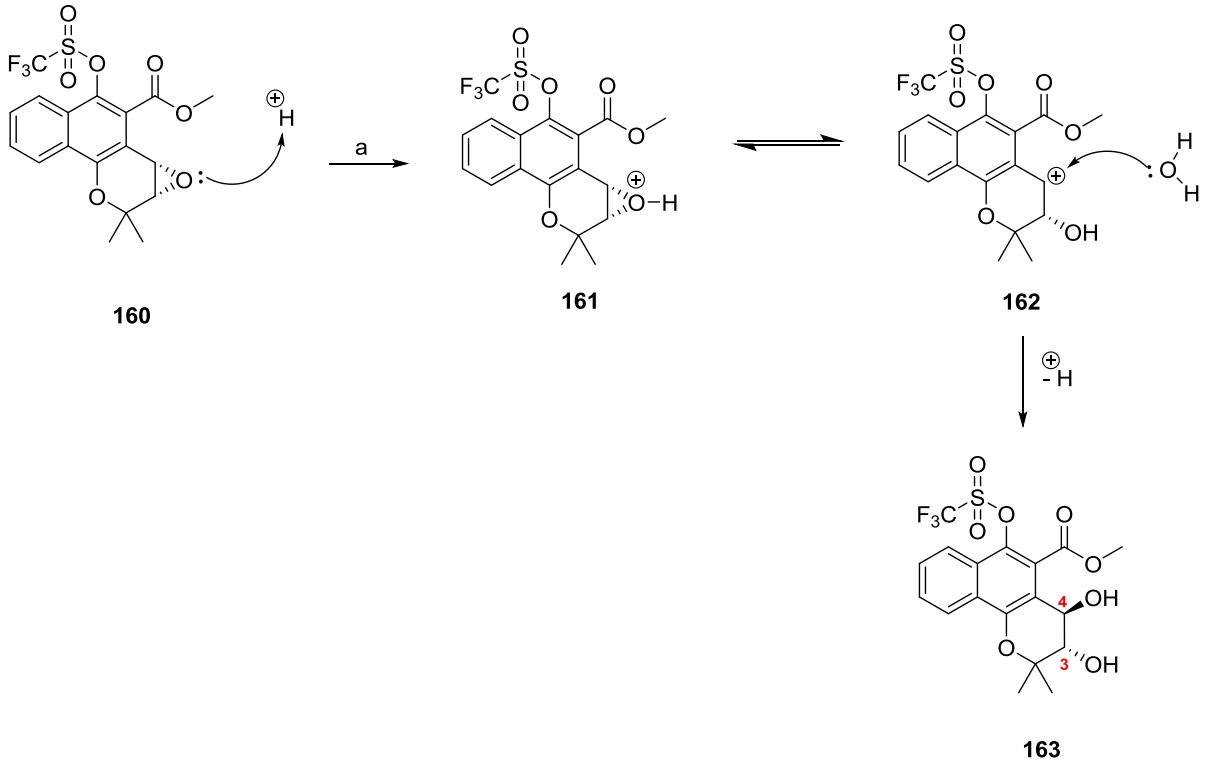


UV Results

Retention Time	Area	Area %	Height	Height %
22.227	74846313	14.75	1316297	21.90
32.600	432671896	85.25	4692895	78.10
Totals	507518209	100.00	6009192	100.00

Figures 9: Chromatogram of non-racemic **160**

The next step towards the synthesis of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **129** was the acid-catalysed ring-opening of the epoxide moiety to form the corresponding *trans*-diol as described above for the synthesis of (+)-scuteflorin A or *trans*-khellactone **117**.[84,56] The non-racemic epoxide **160** was treated with a mixture of acetone and 1M H_2SO_4 to yield (+)-(*3S,4R*)-*trans*-diol **163** in 74% yield (**Scheme 85**). Characteristic diol signals were observed using ^{1}H NMR spectra analysis: the protons at the C3 position (3.59 ppm, *J*=7.3 Hz), and C4 position (4.80 ppm, *J*=7.3 Hz). ^{19}F NMR data analysis also supported the presence of the trifluoromethanesulfonate group. High resolution mass spectrometry suggested that a molecular ion at m/z 468.092 g/mol was detected corresponding to a molecular ion matching **163**. Unfortunately, we were unable to obtain crystals suitable for X-ray analysis.

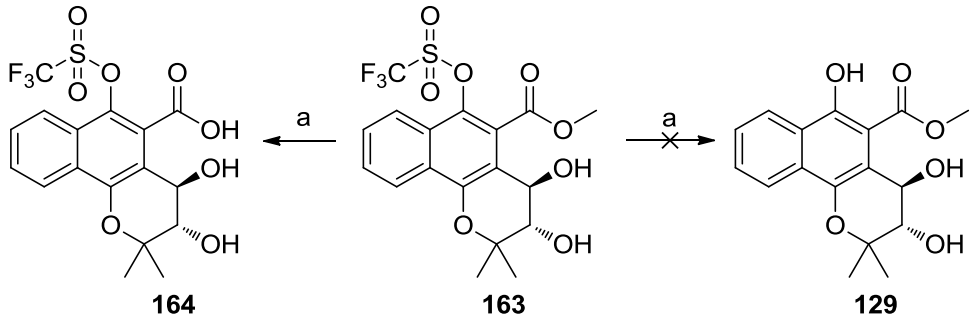


160 161 162 163

Reagents and conditions: (a) acetone/1M H_2SO_4 (2:1), RT, 1 h, 74%.

Scheme 85: Acid-catalysed ring-opening of the epoxide

The final stage is the removal of the trifluoromethanesulfonate group. Using potassium hydroxide in a mixture of water and ethanol (1:1), the reaction was heated under reflux for 30 min until complete disappearance of **163** was observed using TLC. [62] Unfortunately, compound **129** was not observed and hydrolysis of the methyl ester led to the formation of carboxylic acid **164**. The signal corresponding to the methyl ester group was absent when the ^{1}H NMR spectra of the crude reaction mixture was analysed, and the presence of the trifluoromethanesulfonate group was confirmed using ^{19}F NMR spectroscopy (**Scheme86**).

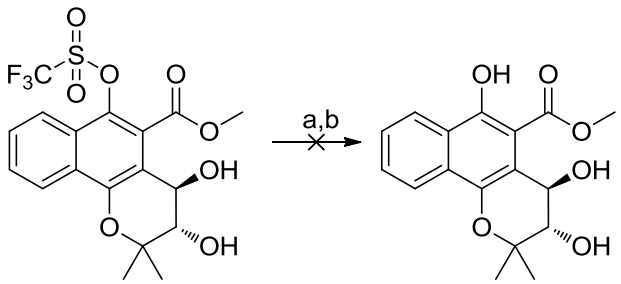


164 163 129

Reagents and conditions: (a) KOH (1 equiv.), H_2O/EtOH (1:1), reflux, 30 min.

Scheme 86: Attempt to remove the trifluoromethanesulfonate group

The cleavage reaction of the trifluoromethanesulfonate group was also attempted using 2 equivalents of tetraethylammonium hydroxide in dioxane. Thus, the disappearance of trifluoromethanesulfonate group was eventually observed using ^{19}F NMR spectroscopy, but the two signals corresponding to the diol moiety were not observed using ^{1}H NMR spectroscopy (**Scheme 87**).[89] We also attempted to remove the triflate group using caesium carbonate (3 equiv.) according to a literature procedure,[90] but no reaction was seen under these conditions after 19h, and **163** was recovered.



163 **129**

Reagents and conditions: (a) Et_4NOH (2 equiv.), dioxane, RT, 20 min; (b) Cs_2CO_3 (3 equiv.), PhMe, 0 °C, 19 h.

Scheme 87: Further attempts to remove the trifluoromethanesulfonate group

2.7 Conclusions

There is no doubt that the scope of academic and industrial organic synthesis has been deeply extended by developments in the field of asymmetric catalysis. At the beginning of this work, we challenged ourselves to develop a wide variety of reaction processes that could be used to synthesize flav-3-ene derivatives, and particularly the effect of a variety of protecting groups in stabilizing flav-3-ene derivatives. In all cases, I found that flav-3-ene containing protecting groups such as benzyloxy groups on the aromatic rings were unstable to the epoxidation reaction conditions. However, the toluenesulfonate moiety played a significant role in the stability of flav-3-ene under oxidative conditions. The findings of this study have important implications for the asymmetric epoxidation on flav-3-ene substrates.

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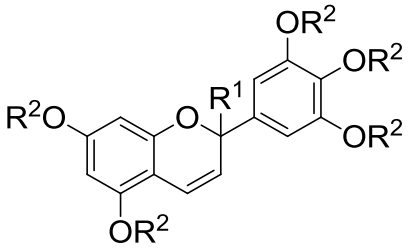
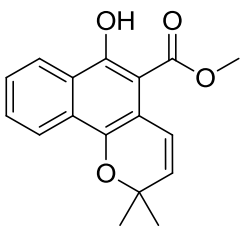


R^2 = Protecting Group

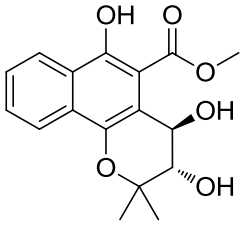
R^1 = H, Me, Ph

(±)-**10**

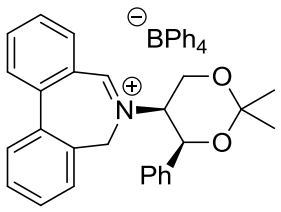
We have also used three straightforward approaches to synthesize mollugin **128**. The journey to synthesize *trans*-3,4-dihydroxy-3,4-dihydro-mollugin **129** in an enantioselective manner began with the employment of catalyst **75** to install an epoxide moiety. An acid-catalysed ring-opening of the epoxide was also successful and (+)-(*3S,4R*)-*trans*-diol **163** was obtained in 74% yield.



128



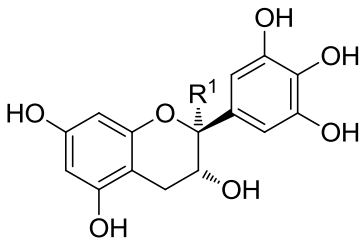
129



75

2.8 Future Work

We will undertake an extensive investigation of the effect of a variety of protecting groups on the stability of 3-flav-3-enes and their reactivity towards iminium salt catalysed epoxidation within our group. In addition, we will seek novel methods to synthesize 3-flav-3-ene analogues. This should allow us to use iminium salts to achieve enantioselective kinetic resolution as indicated at the beginning of this chapter. Moreover, it should permit us to gain access to polyphenol natural products, for example, the anti-cancer agent (−)-epigallocatechin.



R^1 = H, Me, Ph

(-)-Epigallocatechin

Despite our inability to observe any conversion to the desired *trans*-3,4-dihydroxy-3,4-dihydro-mollugin **129** from diol **163**, we will continue to seek to achieve the deprotection of the trifluoromethanesulfonate group within our group.

2.9 Results and Discussion References

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3.0 Experimental

3.1 General Experimental

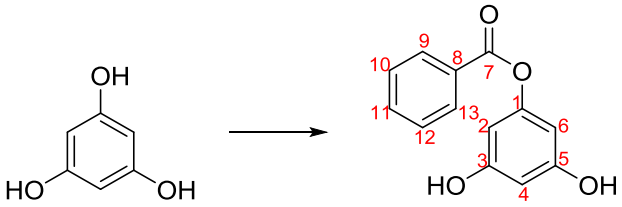
3.1.1 Physical Characterisation and Spectroscopic Techniques

Infrared spectra were acquired using a Perkin Elmer System 2000 FT-IR spectrophotometer. Solid samples were run as nujol mulls or as thin films of their solution in dichloromethane on sodium chloride plates. Liquid samples were run neat. ^{1}H and ^{13}C NMR spectra were measured respectively at 400.13 and 100.62 MHz using Varian Unity Plus (400 MHz) spectrometers, at 300.05 and 75.45 MHz using a Varian Gemini 200 (300 MHz) instrument, at 400.13 and 100.03 MHz using a 400 MHz Bruker Avance III 2 channel nanobay NMR spectrometer, or at 500.21 and 125.05 MHz using a Bruker Avance III 500 MHz NMR spectrometer. The solvent used for NMR spectroscopy was deuteriated chloroform unless stated otherwise, using tetramethylsilane as the internal reference. Chemical shifts are given in parts per million (ppm) and J values are given in Hertz (Hz). High resolution mass spectra were obtained from the EPSRC Mass Spectrometry Service at the University of Swansea. Melting points were recorded using a Büchi B-545 melting point instrument and are reported uncorrected. Optical rotation values were measured with a Bellingham and Stanley ADP-440 instrument, operating at λ=589 nm, corresponding to the sodium D line at the temperatures indicated. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used. Enantiomeric excesses were determined by Chiral High Performance Liquid Chromatography, (Chiral HPLC). HPLC samples were prepared by silica based chromatography. Data was recorded using Hitachi Elite LaChrom software fitted with a L2400 UV detector (256 nm unless stated otherwise), a L2300 column oven, a L2200 autosampler, a L2130 pump, and a Knaver Eurocel 01 5µm particle size column. All HPLC samples were run under hexane – isopropanol conditions.

Reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C, unless otherwise stated. Reaction solvents were obtained commercially dry, except dichloromethane, which was distilled from calcium hydride; tetrahydrofuran (THF) and diethyl ether (Et_2O), which were distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical.

3.2 Experimental Procedures Related to the Synthesis of flav-3-ene:

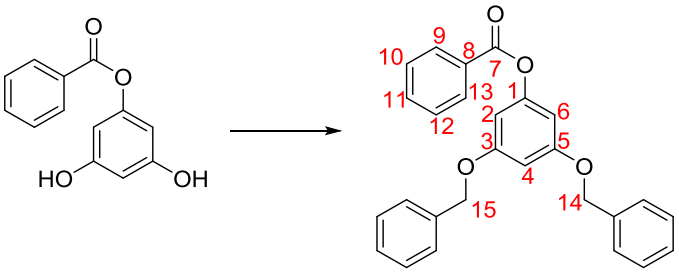
3.2.1 3,5-dihydroxyphenyl benzoate (17) [1]



Pyridine (1.26 mL, 15.7 mmol, 2 equiv.) was added to a solution of anhydrous phloroglucinol (1.0 g, 7.92 mmol) in anhydrous tetrahydrofuran (50 mL). Benzoylchloride (1.26 mL, 7.92 mL) in anhydrous tetrahydrofuran (20 mL) was added dropwise to the solution. The cloudy mixture was heated under reflux under nitrogen for 3 days. A solution of Cu_2SO_4 was poured into the cooled mixture. The resulting mixture was extracted with ethyl acetate (2×10 mL). The organic phase was washed with diluted aqueous HCl (1M, 2×5 mL), water (10 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude mixture was purified using silica gel column chromatography (1:3.5 ethyl acetate- petroleum ether) to afford compound **17** (0.88 g, 49%).

mp 75-78 °C; ν_{max} (neat)/cm^{-1} 3297, 3088, 3068, 1610, 1144.8; δ_H (400 MHz; *d6*-acetone) 6.26 (d, 2 H, *J* = 2.1 Hz, Ar***H***-2,6), 6.30 (t, 1 H, *J* = 2.1 Hz, Ar***H***-4), 7.65-7.70 (m, 2 H, Ar***H***-10,12), 7.67 (t, 1 H, *J* = 3.0 Hz, Ar***H***-11), 8.12 (m, 2 H, Ar***H***-9,13), 8.59 (s, 2 H, O***H***); δ_C (100 MHz; *d6*-acetone) 100.4 (***C***H-4), 100.9 (***C***H_2-2,6), 128.9 (***C***H_2-10,12), 130.0 (***C***H_2-9,13), 133.8 (***C***-8) 153.0 (***C***H-11), 159.2 (***C***-1), 162.0 (***C***$_2$-3,5), 164.5 (***C***O-7).

3.2.2 3,5-bis(Benzyloxy)phenyl benzoate (18) [2]

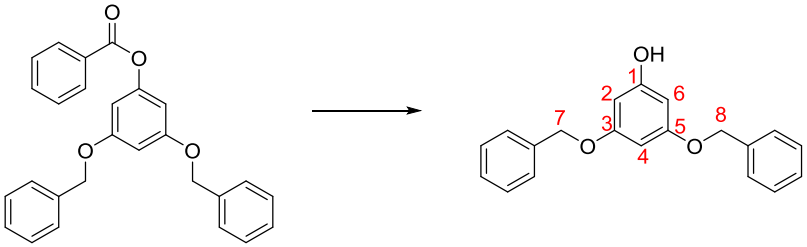


2-(3,5-Dihydroxyphenyl)-1-phenylethanone **17** (0.55 g, 2.4 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL). Potassium carbonate (0.99 g, 7.0 mmol) and 18-crown-6 (0.12 g, 0.2 equiv.) were added to the solution and the mixture was stirred at room temperature for 15 min. followed by the addition of benzyl bromide (0.65 mL, 5.5 mmol). The reaction was heated under reflux for three days under a nitrogen atmosphere. Water (5

mL) and diluted HCl (1M, 5 mL) were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3x20 mL) and the organic layer was washed with brine (5 mL), and diluted aqueous HCl (1M, 5 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvents were removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel (ethyl acetate : petroleum ether, 1:2). The product **18** was obtained as a yellow solid (0.86 g, 79%).

mp 97-100 °C; ν_{max} (neat)/cm^{-1} 2866, 1698, 1247, 712. δ_H (400 MHz; $CDCl_3$) 4.96 (s, 4 H, C_2***H***$_4$-14,15), 6.10 (d, 2 H, *J* = 2.1 Hz, Ar***H***-2,6), 6.22 (t, 1 H, *J* = 2.1 Hz, Ar***H***-4), 7.28-7.62 (m, 10 H, ***Ph***$_2C_2H_4O_2$), 7.47 (t, 2 H, *J* = 7.8 Hz, Ph***H***-10,12), 7.61 (t, 1H, *J* = 7.4 Hz, Ph***H***-11), 8.16 (m, 2 H, Ph***H***-9,13); δ_C (100 MHz; $CDCl_3$) 70.1 (***C***$_2H_4$-14,15), 95.0 (***C***H-4), 95.5 (***C***H_2-2,6), 127.8 (***C***H_2-10,12), 128.2, 128.7, 128.8, 129.4 (***Ph***$_2C_2H_4O_2$), 130.4 (***C***H_2-9,13), 134.1 (***C***-8), 136.9 (***C***H-11), 157.7 (***C***-1), 160.9 (***C***-3,5), 172.4 (**C**O-7).

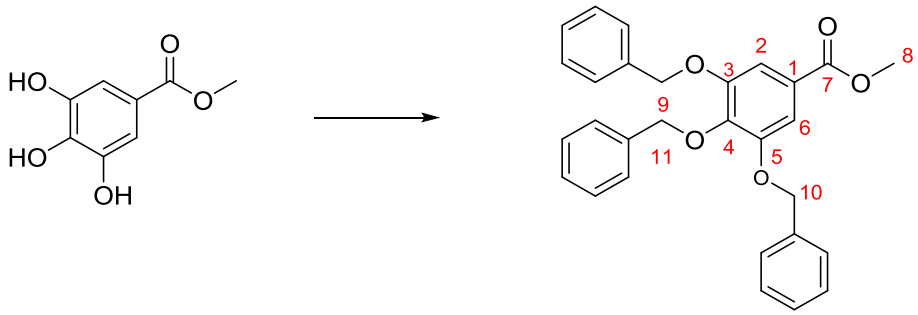
3.2.3 3,5-bis(Benzyloxy)phenol (19) [3]



3,5-*bis*(Benzyloxy)phenol (4.00 g, 9.75 mmol) was dissolved in anhydrous tetrahydrofuran (15 mL) and $LiAlH_4$ (1.85 g, 48.76 mmol) was cautiously added to the stirring solution under a nitrogen atmosphere at 0 °C (ice bath). The reaction was left overnight and followed by TLC (ethyl acetate/petroleum ether 1:4). The reaction was quenched by addition of water (10 mL) and washed using aqueous HCl (2M, 10 mL). The solution was washed using ethyl acetate, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel (ethyl acetate : petroleum ether, 1:5). The product **19** was obtained as a colourless solid (2.01 g, 68%).

mp 93-95 °C; ν_{max} (neat)/cm^{-1} 3292, 2863, 1148, 1042; δH (400 MHz; *d6*-acetone) 5.02 (s, 4 H, C_2***H***$_4$-7,8), 6.17 (d, 2 H, *J* = 2.0 Hz, Ph***H***-2,6), 7.20 (t, H, *J* = 2.1 Hz, Ph***H***-4), 7.18-7.49 (m, 10 H, ***Ph***$_2C_4H_4OPh$), 8.41 (s, 1 H, O***H*****);** δ_C (100 MHz; d6-acetone) 73.2 (***C***$_2H_4$-7,8), 95.0 (***C***H-4), 96.6 (***C***H_2-2,6) 127.8, 128.2, 128.8, 136.9 (***Ph***$_2C_2H_4OPh$), 157.6 (***C***-1), 160.9 (***C***-3,5).

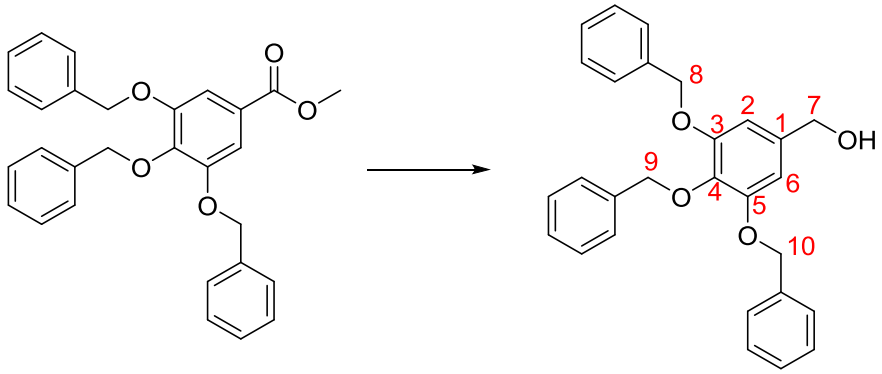
3.2.4 methyl 3,4,5-tris(Benzyloxy)benzoate (21) [4]



Benzyl bromide (10.32 mL, 90 mmol) was added to a mixture containing methyl 3,4,5-tris(benzyloxy)benzoate (5.00 g, 27 mmol) and K_2CO_3 (16.90 g, 122 mmol, in anhydrous dimethylformamide (60 mL). The reaction was stirred under a nitrogen atmosphere overnight at room temperature. After removing the organic solvent under reduced pressure, aqueous HCl (2M, 30 mL) was added to acidify the reaction mixture. The reaction was extracted with ethyl acetate (3×80 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate- petroleum ether, 5:1) to afford the desired compound as a colourless solid (10.94 g, 89%).

mp 160-163 °C; ν_{max} (neat)/cm^{-1} 2948, 2897, 1715, 1427, 1331, 1108, 751; δH (400 MHz; $CDCl_3$) 3.88 (s, 3 H, C***H***$_3$-8), 5.11 (s, 2 H, C***H***$_2$-11), 5.12 (s, 4 H, C_2***H***$_4$-9,10), 7.18-7.51 (m, 17 H, **A**r-H)**;** δ_C (100 MHz; $CDCl_3$) 52.5 (***C***H_3-8), 71.4 (***C***$_2H_4$-9.10), 75.3 (***C***H_2-11), 109.2 (***C***H-2,6) 125.4, 127.8, 128.16, 128.24, 128.3, 128.4, 128.8, 136.9, (***Ph***$_3C_6H_6O_3$Ph), 137.7 (***C***-1), 142.5 (***C***-4), 152.8 (***C***-3,5), 166.9 (***C***OH-7).

3.2.5 [3,4,5-Tris(Benzyloxy)phenyl]methanol (22) [4]

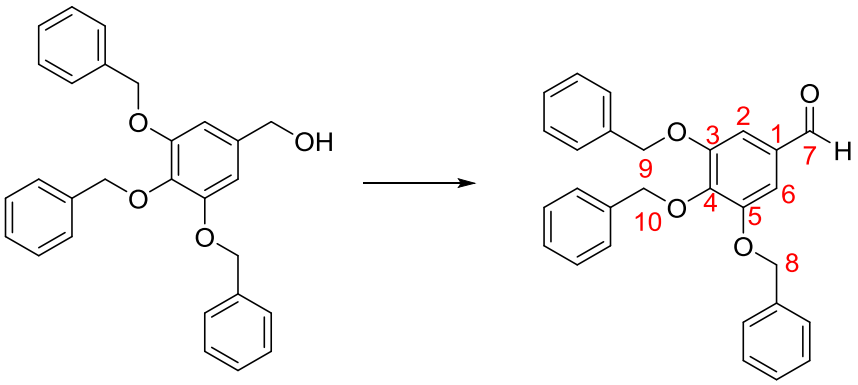


Methyl 3,4,5-tris(benzyloxy)benzoate **10** (5.00 g, 11.4 mmol) ester was dissolved in anhydrous tetrahydrofuran (40 mL) in an oven-dried 250 mL round-bottomed flask. $LiAlH_4$ (0.65 g, 17.1 mmol) was periodically added at 0 °C (ice bath), under a funnel of nitrogen. The

reaction was left to stir overnight. It was monitored by TLC with ethyl acetate and petroleum ether (R_f = 0.39). The reaction was quenched by the cautious addition of water (20 mL) followed by dilute aqueous HCl (1M, 20 mL). The reaction was stirred for a further 30 min. The mixture was extracted with diethyl ether (4x30 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (20 mL), brine (100 mL) and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure to give the desired compound as a colourless solid (4.18 g, 90%).

mp 163-165 °C; ν_{max} (neat)/cm^{-1} 3263, 2935, 1229, 1121, 734; δ_H (400 MHz; $CDCl_3$) 1.75 (s, 1 H, O***H***), 4.55 (s, 2 H, C***H***$_2$-**7**), 5.02 (s, 2 H, C***H***$_2$-9), 5.08 (s, 4 H, C_2***H***$_4$), 6.65 (s, 2 H, Ar***H***-2,6), 7.24-7.49 (m, 15 H, Ph_3C_2***H***$_6$O); δ_C (100 MHz; $CDCl_3$) 65.5 (***C***H_2-7), 71.3 (***C***$_2H_4$-8,10), 75.5 (***C***H_2-9), 106.4 (***C***H_2-2,6), 127.6, 128.0, 128.1, 128.4, 128.7, 128.8, 137.0, 137.3 (***Ph***$_3C_6H_6O_3$Ph), 137.7 (***C***-4), 138.0 (***C***-1), 153.1 (***C***$_2$-3,5).

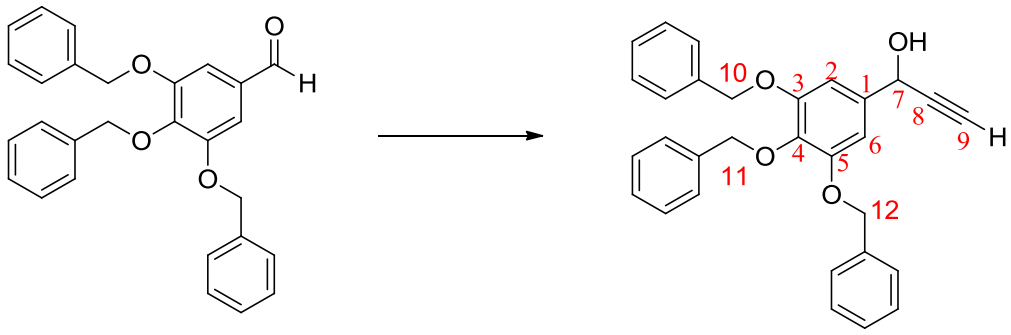
3.2.6 3,4,5-tris(Benzyloxy)benzaldehyde (23) [4]



3,4,5-*tris*(Benzyloxy)benzaldehyde (1.51 g, 3.54 mmol) was dissolved in dichloromethane. Pyridinium chlorochromate (2.27 g, 5.25 mmol) was added in one portion to the mixture. The reaction was stirred under a nitrogen atmosphere at a room temperature overnight and followed by TLC (ethyl acetate/petroleum ether, 3/1, R*f* = 0.53). Diethyl ether (50 mL) was added to precipitate out the chromium salts. The resulting suspension was filtered through a pad of celite, silica gel and sand. The solvents were removed under reduced pressure to give the desired aldehyde **23** as a colourless solid (1.22 g, 81%).

mp 156-158 °C; ν_{max} (neat)/cm^{-1} 2933, 1692, 1591, 1436, 1385, 1328, 1235, 1143, 1119; δH (400 MHz; $CDCl_3$) 5.16 (s, 4 H, C_2***H***$_4$-8,9), 5.19 (s, 2 H, C***H***$_2$-10), 7.20 (s, 2 H, Ar***H***-2,6), 7.24-7.51 (m, 15 H), 9.80 (s, 1 H, CO***H***-7); δ_C (100 MHz; $CDCl_3$) 72.7 (***C***$_2H_4$-8,9), 76.4 (***C***H_2-10), 112.2 (***C***H_2-2,6) 127.4, 128.4, 128.6, 128.80, 128.83, 129.0, 133.8, 137.1, (***Ph***$_3C_6H_6O_3$Ph), 138.8 (***C***-1), 144.6 (***C***-4), 156.2 (***C***$_2$-3,5), 196.0 (***C***OH-7).

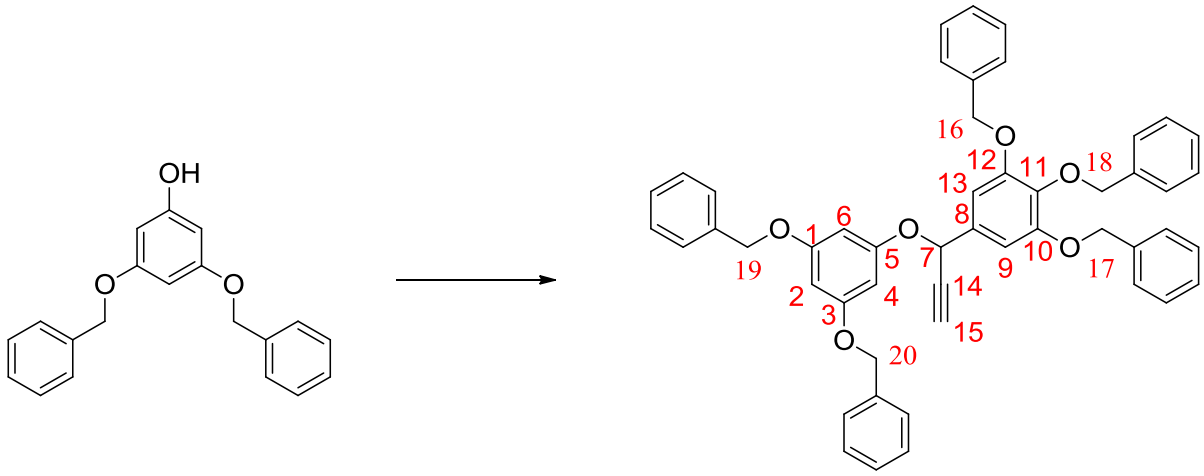
3.2.7 (3,4,5-Tris-benzyloxy-phenyl)-prop-2-yn-1-ol (24)



3,4,5-*tris*-Benzyloxybenzaldehyde **23** (0.25 g, 0.56 mmol) was dissolved in anhydrous tetrahydrofuran and the solution was cooled to – 78 °C. Ethynylmagnesium bromide (0.5M in THF, 6.00 mL) was cautiously added to the solution. The reaction was allowed to warm to room temperature, and left to stir for 2 hours. The reaction was quenched using a solution of NH_4Cl (5 mL). The excess THF was removed under reduced pressure. The residue was extracted with ethyl acetate (3×10 mL), washed with dilute aqueous HCl (1M, 5 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified using column chromatography on silica gel with ethyl acetate -petroleum ether (1:2) to give compound **24** as a yellow solid (241 mg, 91%).

mp 178-180 °C; ν_{max} (neat)/cm^{-1} 3303, 3019, 2867, 2140, 1331, 1124, 729; δ_H (400 MHz; $CDCl_3$) 2.19 (d, 1 H, *J* = 6.2 Hz, O***H***), 2.63 (d, 1 H, *J* = 2.2 Hz, C***H***-9), 5.02 (s, 2 H, C$\boldsymbol{H_2}$-11), 5.11 (s, 2 H, $C_2\boldsymbol{H_4}$-10,12), 5.33 (dd, 1 H, *J* = 6.2, 2.2 Hz, C***H***-7), 6.85 (s, 2 H, Ar***H***-2,6), 7.17-7.32 (m, 15 H, $\boldsymbol{Ph}_3C_3H_6O$); δ_C (100 MHz; $CDCl_3$) 64.3 (***C***H-7), 71.2 ($\boldsymbol{C}_2H_4$-10-12), 74.9 ($\boldsymbol{C}H_2$-11), 75.2 (***C***-9), 83.2 (***C***-8), 106.2 ($\boldsymbol{C}H_2$-2,6), 127.5, 127.8, 128.2, 128.5, 128.6, 128.7, 128.8, 135.6, ($\boldsymbol{Ph}_3C_3H_6O_3Ph$), 137.0 (***C***-1) 137.8 (***C***-4), 153.0 ($\boldsymbol{C}_2$-3,5); *m/z* found for $[M+NH_4]^+$: 468.2163; $[C_{30}H_{26}O_4+NH_4]^+$ requires 468.2169.

3.2.8 (((5-(1-(3,5-bis(Benzyloxy)phenoxy)prop-2-yn-1-yl)benzene-1,2,3-triyl)tris(oxy))tris(methylene))tribenzene (25)



Method A

The propargyl alcohol **24** (0.77 mmol, 350 mg) was dissolved in anhydrous dichloromethane and the resulting solution was added slowly into a dilute solution of camphorsulfonic acid (2.62 g, 10.5 equiv.) in anhydrous dichloromethane. The mixture changed to a light green colour. After 10 min, alcohol compound **19** (330 mg, 1.14 mmol) was added dropwise, and the reaction mixture turned into an apple red colour. The reaction was stirred for 48 hours. The solvent was evaporated under reduced pressure. The organic residue was dissolved in ethyl acetate (20 mL) and the organic layer was then washed with a solution of $NaHCO_3$ and brine (5 mL), dried using anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was recrystallised using toluene and the mother liquor was purified using flash chromatography on silica gel with toluene-ethyl acetate as eluent (35/1). The product **25** was obtained as a colourless powder (0.46 g, 58%).

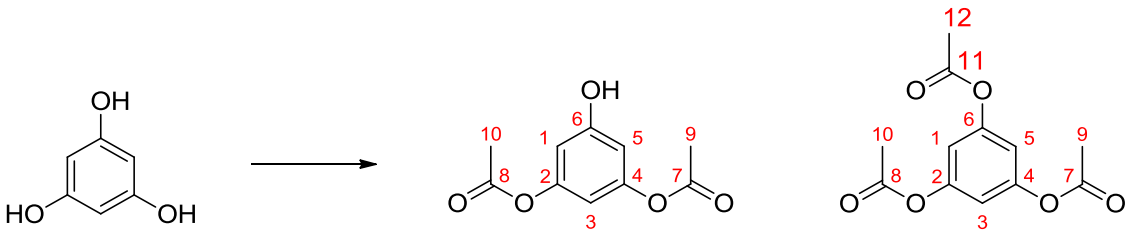
m.p. 200-202 °C; ν_{max} (neat)/cm^{-1} 2983, 2934, 2120, 1265, 738; δ_H (400 MHz, $CDCl_3$,): 2.56 (d, 1 H, *J* = 2.7 Hz, C***H***-15), 4.93-5.06 (m, 10 H, C_5***H***$_{10}$-16,17,18,19,20), 5.68 (d, 1 H, *J*= 2.7 Hz, C***H***-7), 6.24 (t, 1 H, *J* = 2.4 Hz, C***H***-2), 6.29 (d, 2 H, *J* = 2.4 Hz, C***H***$_2$-6,4), 6.76 (s, 2 H, C***H***$_2$-13,9), 7.08-7.69 (m, 25 H, ***Bn***$_5$$O_5$-16,17,18,19,20); δ_C (100MHz; $CDCl_3$), 70.3 (***C***H-7), 70.8 (***C***H_2-18), 71.2 (***C***$_2$$H_4$-16,17), 73.7 (***C***$_2$$H_4$-19,20), 75.5 (***C***-15), 83.9 (***C***H-14), 94.0 (***C***$_2$$H_2$-4,6), 96.4 (***C***H-2), 107.0 (***C***$_2$$H_2$-13,9), 127.7, 127.9, 128.41, 128.43, 128.7, 128.0, 128.5, 128.8, 128.9, 135.3, 136.9, 137.51, (***Ph***$_5$$C_5$$H_{10}$$O_5$$Ph_2$) 137.52, (***C***-8)138.1 (***C***-11), 152.9 (***C***$_2$-10,12), 156.4 (***C***$_2$-1,3), 156.9 (***C***H-5); *m/z* found for $[M+NH_4]^+$: 756.3320 $[C_{50}H_{42}O_6+NH_4]^+$ requires: 756.3320.

Method B

A suspension of the propargyl alcohol **14** (90 mg, 0.19 mmol), alcohol compound **8** (122 mg, 0.40 mmol) and acidic Al_2O_3 (1g) in anhydrous toluene (20 mL per g of acidic Al_2O_3) was heated under reflux for 24h. The apple red solution was allowed to cool, transferred to a separating funnel and extracted with dichloromethane (2 x 40 mL). The organic layers were combined and washed with a $NaHCO_3$ solution (40 mL, saturated aqueous) and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel with toluene-ethyl acetate as eluent (35/1) to furnish the title compound as a colourless powder (61 mg, 21%).

3.2.9 5-Hydroxy-1,3-phenylene diacetate (32) and benzene-1,3,5-triyl triacetate (34) [5]

Method A:



32 **34**

A solution of phloroglucinol (400 mg, 3.1 mmol) was dissolved in a mixture of pyridine and dichloromethane (2:1) and was stirred for 15 min under a nitrogen atmosphere. Acetic anhydride (0.6 mL, 6.3 mmol) was then added into the solution. The white solution turned yellow as the reaction was heated under reflux for 22h. After cooling, the solvent was removed *in vacuo* and water (16 mL) was added to the resulting residue. The aqueous phase was extracted with ethyl acetate (3×20 mL). The organic layer was washed with an aqueous solution of copper sulfate, brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by silica gel flash chromatography using ethyl acetate /light petroleum (1:2.5) to yield **23** as a colourless solid (380 mg, 58%) and **34** as a colourless solid (135 mg, 27%)

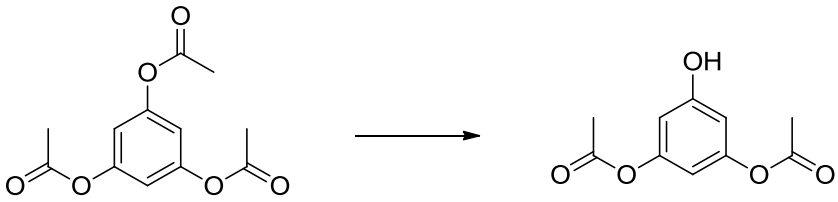
5-Hydroxy-1,3-phenylene diacetate 32:

mp 50-52 °C; ν_{max} (neat)/cm^{-1} 3288, 2967, 1608, 968; δH (500 MHz, $CDCl_3$): 2.12 (s, 6 H, $C_2\boldsymbol{H}_6$CO-9,10), 6.26 (d, 2 H, *J* = 2.0 Hz, $C_2\boldsymbol{H}_2$-1,5), 6.28 (t, 1 H, *J* = 2.0 Hz, C***H***-3), 6.69 (s, 1 H, CO***H***-6); δ_C (125 MHz, $CDCl_3$): 21.1 (***C***$_2$H$_6$CO-9,10), 107.0 (***C***$_2$H$_2$-1,5), 112.8 (***C***H-3) 151.1 (***C***$_2$O$_2$-2,4), 157.5 (***C***-6), 169.7 (***C***$_2$O$_2$-7,8).

Benzene-1,3,5-triyl triacetate 34:

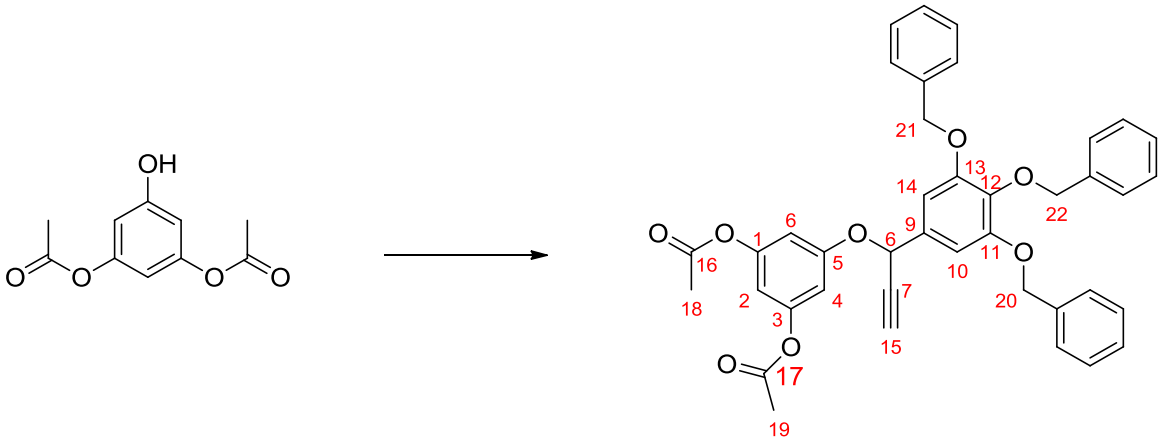
mp 35-37 °C; ν_{max} (neat)/cm^{-1} 2879, 1690, 1601, 832; δH (500 MHz, $CDCl_3$): 2.22 (s, 9 H, $C_3\boldsymbol{H}_9CO$-9,10,12), 6.26 (s, 3 H, $C_3\boldsymbol{H}_3$-1,3,5); δ_C (125 MHz, $CDCl_3$): 20.9 ($\boldsymbol{C}_3H_9CO$-9,10,12), 112.8 ($\boldsymbol{C}_3H_3$-1,3,5), 151.1 ($\boldsymbol{C}_3O_3$-2,4,6), 168.5 ($\boldsymbol{C}_3O_3$-7,8,11).

Method B:



Benzene-1,3,5-triyl triacetate **34** (100 mg, 0.39 mmol) was dissolved in dimethylformamide under a nitrogen atmosphere. Sodium hydride (6.6 mg, 0.27 mmol) was added into the solution, and the reaction mixture stirred for 1h followed by heating for 6h at 60 °C. After cooling, H_2O (4 mL) was added and the mixture heated under reflux for 30 min. The resulting solution was extracted with Et_2O (3× 20 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$and the solvents were removed under reduced pressure. The residue was purified by silica gel flash chromatography using ethyl acetate /Light petroleum (1:4) to yield **32** as a colourless solid (44 mg, 53%).

3.2.10 ((1-(3,4,5-tris(Benzyloxy)phenyl)prop-2-yn-1-yl)oxy)-1,3-phenylene diacetate (31)



Method A:

A solution of the propargyl alcohol **24** (200 mg, 0.44 mmol) and of phenol **32** (100 mg, 0.48 mmol) in anhydrous dichloromethane (6 mL) was added slowly into a solution of camphorsulfonic acid (0.44 g, 2 equiv.) in anhydrous dichloromethane under a nitrogen atmosphere. After 5 min, the reaction turned purple. The reaction was left to stir until it was

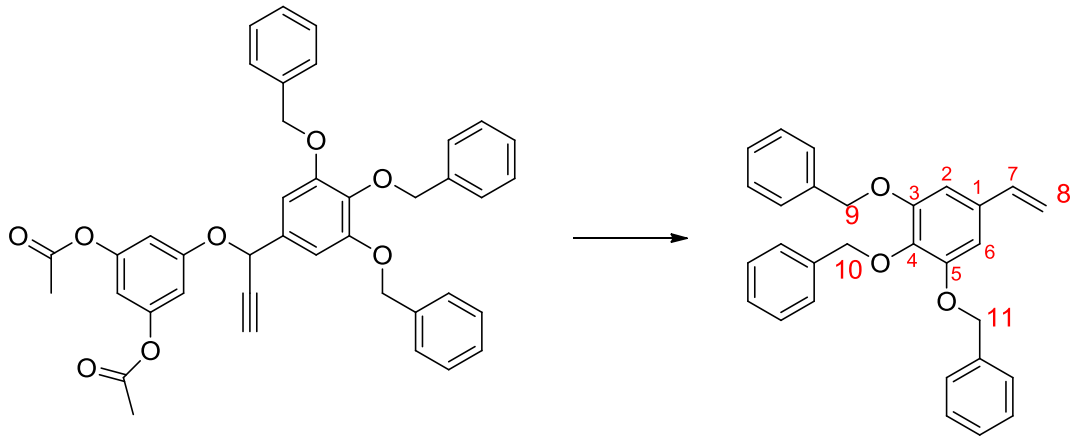
determined to have gone to completion by TLC. The reaction mixture was quenched by addition of water and transferred into a separating funnel containing saturated aqueous $NaHCO_3$ (6 mL). The mixture was extracted with dichloromethane (2x10 mL). The combined organic layers were washed with a $NaHCO_3$ solution, brine (5 mL) and dried using Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (ethyl acetate: toluene, 1:15) to give the title compound **18** as a brown oil (97 mg, 16%)

Method B:

The propargyl alcohol **24** (174 mg, 0.39 mmol), triphenylphosphine (101 mg, 0.39 mmol,) and the phenol **32** (89 mg, 0.42 mmol) were dissolved in anhydrous tetrahydrofuran under argon atmosphere at 0 °C. Diethyl azodicarboxylate (0.060 mL, 67 mg, 0.386 mmol) was then added dropwise. The reaction was stirred overnight at 0 °C. After evaporation of the solvent, the residue was dissolved in diethyl ether. The organic layer was washed with water (8 mL), brine (10 mL), dried over anhydrous $MgSO_4$ and the solvents evaporated under reduced pressure. Flash column chromatography on silica gel (ethyl acetate:toluene, 1:15) gave the desired compound as a brown oil (174 mg, 65%)

ν_{max} (neat)/cm^{-1} 2929, 2379, 2114, 1714, 1262, 861; δH (500 MHz, $CDCl_3$,): 2.25 (s, 6 H, $C_2\boldsymbol{H}_6$-17,18), 2.66 (d, 1 H, *J* = 2.1 Hz, C***H***-15), 4.96 (s, 2 H, C$\boldsymbol{H}_2$-22), 5.00 (s, 4 H, C2$\boldsymbol{H}_4$-20,21), 5.56 (d, 1 H, *J* = 2.1 Hz, C***H***-19), 6.64 (t, 1 H, *J* = 2.0 Hz, $C_2\boldsymbol{H}_2$-6,4), 6.51 (d, 2 H, *J* = 2.0 Hz, C***H***-2), 6.81 (s, 2 H, $C_2\boldsymbol{H}_4$-14,10), 7.21-7.34 (m,15 H); δ_C (125 MHz, $CDCl_3$): 21.0 ($\boldsymbol{C}_2H_6$-18,19), 70.5 (***C***H-6), 71.3 ($\boldsymbol{C}H_2$-22), 75.3 ($\boldsymbol{C}_2H_4$), 77.9 (***C***H-6), 80.2 (***C***-7), 107.2 ($\boldsymbol{C}_2H_4$-14,10), 107.4 ($\boldsymbol{C}_2H_4$-6,4), 109.2 (***C***H-2), 127.6, 127.9, 128.1, 128.3, 128.4, 128.6, 132.2, 137.0 ($\boldsymbol{Ph}_3C_3H_6O_3Ph$), 137.9 (***C***-9), 139.1 (***C***-12) 151.1 ($\boldsymbol{C}_2$-13,11), 153.0 ($\boldsymbol{C}_2$-1,3), 159.0 (***C***-5), 168.9 ($\boldsymbol{C}_2O_2$-19,18).

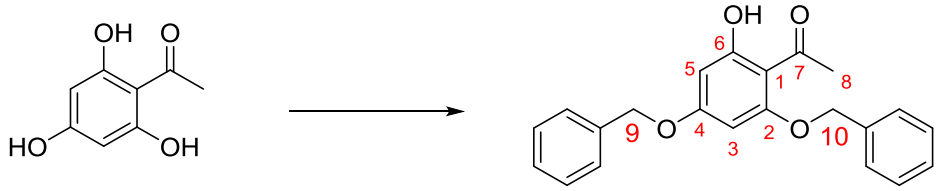
3.2.11 (((5-vinylbenzene-1,2,3-triyl)tris(oxy))tris(methylene))tribenzene (36)



Ether **31** (200 mg, 0.311 mmol) was dissolved in freshly distilled toluene (20 mL) under argon atmosphere at room temperature and palladium diacetate (15 mg, 0.05 mmol) was added. The reaction was heated under reflux overnight. The progress of the reaction was monitored by TLC. The palladium diacetate was filtered off on a pad of silica/celite, the solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (light petroleum ether:ethyl acetate 12:1), to furnish **36** as a colourless powder (174 mg, 10%).

mp 111-113 °C; ν_{max} (neat)/cm^{-1} 3068, 2990, 1272, 755; δH (500 MHz; $CDCl_3$) 4.99 (s, 2 H, C***H***$_2$-10), 5.05 (s, 4 H, C$_2$***H***$_4$-9,10), 5.11 (dd, 1 H, *J* = 10.8, 0.7 Hz, C***H***$_2$-8), 5.52 (dd, 1 H, *J* = 17.5, 0.7 Hz, C***H***$_2$-8), 6.50 (dd, 1 H, *J* = 17.5, 10.8 Hz, C***H***$_2$-7), 6.53 (s, 2 H, Ar***H***-2,6), 7.50 (m, 15 H, Bn***H***-9,10,11); δ_C (125 MHz, $CDCl_3$) 71.4 (***C***$_2$H$_4$-10,12), 75.3 (***C***H$_2$-11), 106.0 (***C***$_2$H$_2$-2,6), 112.1 (***C***H$_2$-8), 127.4, 127.8, 128.2, 128.5, 128.6, 128.8, 137.0, 137.2(***Ph***$_3$C$_3$H$_6$O$_3$Ph), 137.9 (***C***-7), 138.2 (***C***-4), 142.5 (***C***-1), 152.5 (***C***$_2$-3,5); *m/z* found for $[M+NH_4]^+$: 440.2216; $[C_{50}H_{42}O_6+NH_4]^+$ requires: 440.2216.

3.2.12 1-(2,4-bis(Benzyloxy)-6-hydroxyphenyl)ethanone (43) [4]



Method A

2,4,6-Trihydroxyacetophenone **42** (1.00 g, 5.96 mmol) was dissolved in dimethylformamide and anhydrous K_2CO_3 (1.64 g, 11.86 mmol) was added. The mixture was stirred for 10 minutes and benzyl bromide (1.41 mL, 11.86 mmol) was then added slowly. The reaction was heated for 1 hour at 80-85 °C. It was allowed to reach room temperature and the K_2CO_3 was filtered. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 mL). The organic layer was washed with water (20 mL), diluted aqueous HCl (1M, 10 mL), brine (5 mL) and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by silica gel flash chromatography (ethyl acetate/light petroleum ether 1:9) to afford the desired product **43** as a yellow solid (0.91 g, 46%).

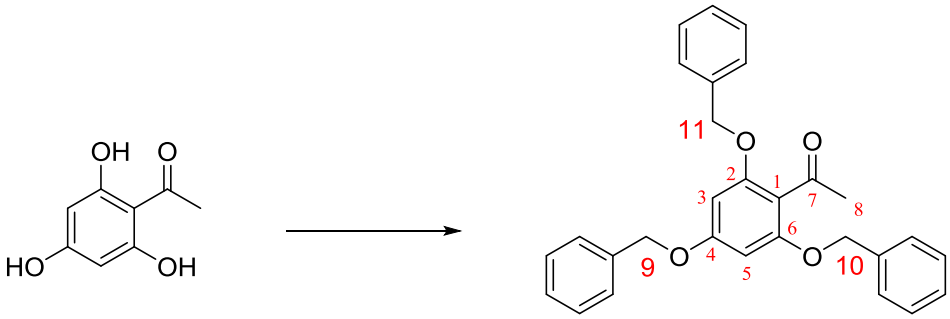
Rf= 0.25; mp 198-200 °C; ν_{max} (neat)/cm^{-1} 3450, 2836, 1731, 1246, 848; δH (400 MHz, $CDCl_3$): 2.55 (s, 3 H, C***H***$_3$CO-8), 5.01 (s, 2 H, C***H***$_2$-9), 5.03 (s, 2 H, C***H***$_2$-10), 6.09 (d, 1 H, *J*= 2.3 Hz, Ar-***H***-3), 6.16 (d, 1 H, *J* = 2.3 Hz, Ar***H***-5), 7.34-7.41 (m, 10 H, ***Ph***$_2$CH$_2$O$_2$-2,4); δ_C (100 MHz, $CDCl_3$): 33.6 (***C***H$_3$-8), 70.4 (***C***H$_2$O-9), 71.3 (***C***H$_2$O-10), 92.7 (***C***H-3), 94.9 (***C***H-5), 106.5 (***C***-1), 127.9, 128.2, 128.6, 128.7, 128.98, 129.05, 135.8, 136.1, (***Ph***$_2$C$_2$H$_6$O$_2$Ph), 162.2 (***C***-4), 165.3 (***C***-2), 167.8 (***C***OH-6), 203.4 (***C***-7); *m/z* found for $[M+H]^+$: 349.1435; $[C_{22}H_{20}O_6+ H]^+$: requires 349.1434

Method B

2,4,6-Trihydroxyacetophenone (300 mg, 1.78 mmol) was dissolved in tetrahydrofuran in an oven-dried round-bottomed flask under argon. The solution was cooled to −78 °C in a dry ice/acetone bath. *n*-Butyllithium (2.5 M, 1.5 mL, 3.5 mmol,) was added dropwise over 10 min directly into the solution. The reaction was stirred for 1 hour at −78 °C and benzyl bromide (0.42 mL, 0.61 g, 3.5 mmol) was slowly added. The reaction mixture was then allowed to reach to room temperature and was stirred overnight under argon. The reaction mixture was then cooled to −78 °C and a saturated aqueous ammonium chloride solution (5 mL) was added dropwise using a syringe. The solvents were removed under reduced pressure. The residue was dissolved in dichloromethane (3×10 mL), washed with dilute

aqueous HCl (1M, 5ml), and dried over anhydrous $MgSO_4$. The resulting compound was purified using flash column chromatography on silica-gel (ethyl acetate -light petroleum ether 1:3) to give the compound **43** as a colourless solid (347 mg, 46%).

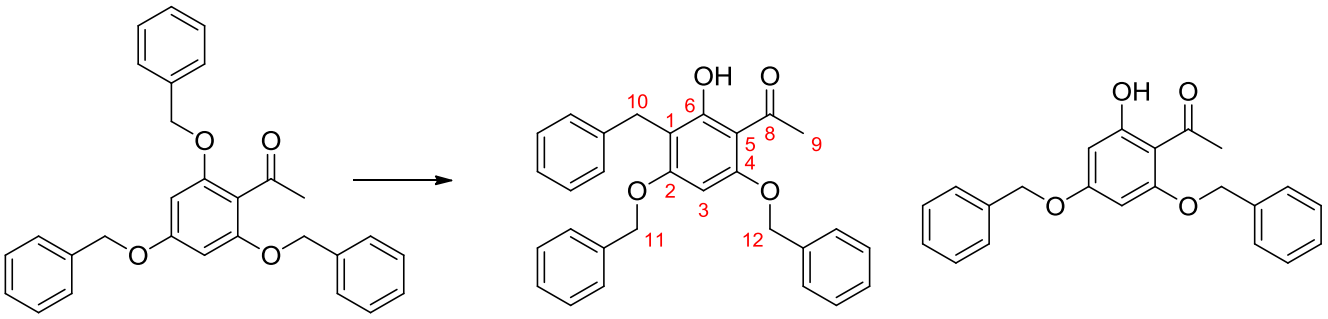
3.2.13 1-(2,4,6-tris(Benzyloxy)phenyl)ethanone (44) [4]



2,4,6-Trihydroxyacetophenone **42** (0.50 g, 2.97 mmol) was dissolved in anhydrous dimethylformamide (17 mL). Anhydrous K_2CO_3 (1.84 g, 17. 8 mmol) and benzyl bromide (2.11 mL, 17.8 mmol) were added to the mixture. The reaction was heated at 100 °C for 18h, and then allowed to cool to room temperature. The dimethylformamide was removed under reduced pressure and the oily residue was extracted using ethyl acetate (2×20 mL), the organic layers were combined, washed with dilute aqueous HCl (2M, 5 mL), brine and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (ethyl acetate : petroleum ether, 1:6) to afford the desired compound as a yellow liquid (1.17 g, 90%).

mp 207-209 $^{\circ}$C; ν_{max} (neat)/cm^{-1} 2853, 1721, 1248, 740; δH (400 MHz; $CDCl_3$) 2.40 (s, 3 H, C***H*****$_3$**-8), 4.96 (s, 2 H, C***H*****$_2$**-9), 5.01 (s, 4 H, C_2***H*****$_4$**-10,11), 6.20 (s, 2 H, Ar***H***-3,5), 6.65 (m, 15 H, ***Ph*****$_3$***C_3H_6*O); δ_C (100 MHz; $CDCl_3$) 32.8 (***C***H_3-8), 70.5 (***C***H_2-9), 70.8 (***C*****$_2$**H_4-11,10), 93.6 (***C***H_2-3,5), 115.2 (***C***-1), 127.3, 127.7, 128.2, 128.4, 128.8, 128.9, 136.6, 136.7, (***Ph***$_3C_3H_6O_3$Ph) 157.4 (***C***$_2$-2,6), 161.3 (***C***-4), 201.8 (***C***O-7).

3.2.14 1-(3-benzyl-4,6-bis(Benzyloxy)-2-hydroxyphenyl)ethanone (45) [7]

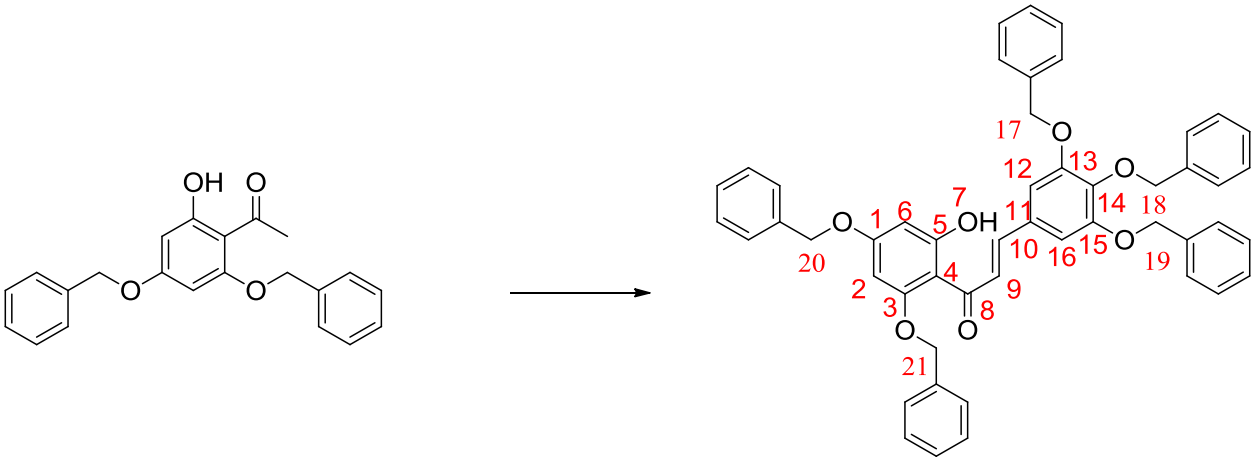


2,4,6-*tris*(Benzyloxy)phenyl)ethanone **44** (500 mg, 1.14 mmol) was treated with titanium(IV) chloride (0.087 ml, 151 mg) in freshly distilled dichloromethane at 0 ˚C. After 155 min of stirring, the mixture was slowly poured into a separating funnel containing aqueous saturated $NaHCO_3$. The organic layer was separated and washed with water and brine, dried anhydrous Mg_2SO_4 and concentrated under reduced pressure. The residue was crystallized from ether, and the mother liquor was purified by column chromatography on silica gel, using ethyl acetate/light petroleum (1:4) providing **43** (202 mg, 51%), and by-product **45** (39 mg, 8%).

Compound 45:

mp 214-216 ˚C; ν_{max} (neat)/cm^{-1} 3454, 2953, 1738, 1248, 818; δH (400 MHz, $CDCl_3$): 2.47 (s, 3 H, C***H***$_3$CO-9), 3.98 (s, 2 H, C***H***$_2$-10), 5.03 (s, 2 H, C***H***$_2$-11), 5.07 (s, 2 H, C***H***$_2$-12), 6.05 (s, 1 H, C***H***$_2$-3), 7.26-7.45 (m, 15 H).

3.2.15 (*2E*)-1-[2,4-Bis(Benzyloxy)-6-hydroxyphenyl]-3-[3,4,5-tris(benzyloxy)phenyl]-2-propen-1-one (46) [4]

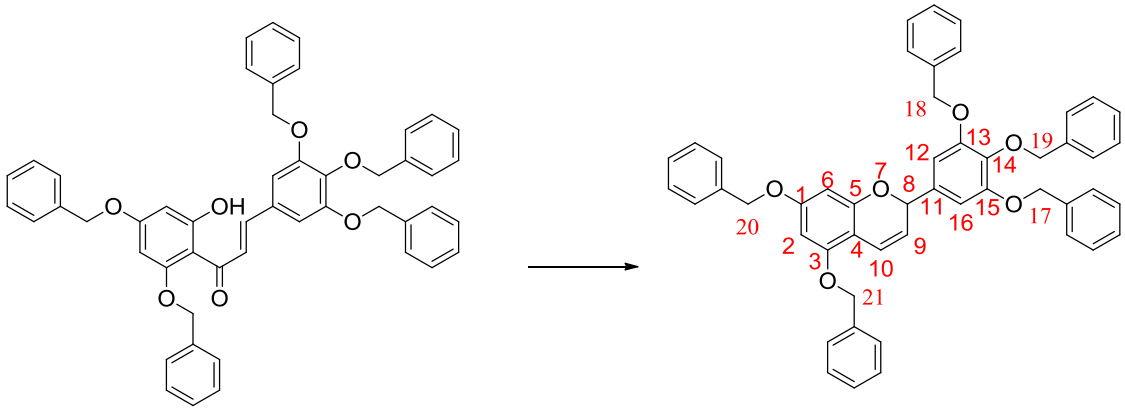


Compound **43** (370 mg, 1.06 mmol) was dissolved in dimethylformamide and NaH (38 mg, 1.6 mmol) was added. A solution of 3,4,5-tris(benzyloxy)benzaldehyde **32** (539 mg, 1.2 mmol) in dimethylformamide was then added dropwise over a 15 min period, and the

reaction stirred for a further 6 h at room temperature. Water (5 mL) was then added to quench any unreacted NaH, followed by removal of the solvents under reduced pressure. The resulting residue was dissolved in 20 mL of dichloromethane and washed with water (10 mL), dilute aqueous HCl (1M, 5 mL), and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was crystallized from ether to give **46** as a yellow solid (440 mg, 55%).

m.p. 234-236 °C; ν_{max} (neat)/cm^{-1} 3130, 1668, 1235, 1004, 937; (400 MHz, $CDCl_3$): 4.84 (s, 4 H, C***H***$_2$-20,21), 5.12 (s, 2 H, C***H***$_2$-18), 5.14 (s, 4 H, C***H***$_2$-17,19), 6.18 (d, 1 H, *J* = 2.4 Hz, C***H***-2), 6.25 (d, 1 H, *J* = 2.4 Hz, C***H***-6), 6.60 (s, 2 H, C***H***$_2$-12,16), 7.26-7.46 (m, 25 H, ***Ph***$_5$$CH_5O_5$-17,18,19,20,21), 7.66 (d, 1 H, *J* = 15.7 Hz, C***H***-9), 7.78 (d, 1 H, *J* = 15.7 Hz, C***H***-10); δ_C (100 MHz, $CDCl_3$): 71.0 (***C***H_2O-18), 71.3 (***C***$_2H_4$O-17,19), 75.2 (***C***$_2H_2$-20,21), 93.0 (***C***H-2), 95.1 (***C***H-6), 108.9 (***C***$_2H_2$-12,16), 110.0 (***C***-4), 125.3 (***C***H-9), 127.1, 127.2, 127.3, 127.4, 128.1, 128.2, 128.28, 128.32, 128.4, 128.6, 128.88, 130.77, (***Ph***$_5C_5H_{10}O_5$Ph), 131.8, (***C***-11), 136.8 (***C***-1), 137.3 (***C***-3), 140.3 (***C***H-10), 152.9 **(*C*-14)**, 153.3 (***C***-13,15), 168.2 (***C***OH-5), 191.0 (***C***=O).

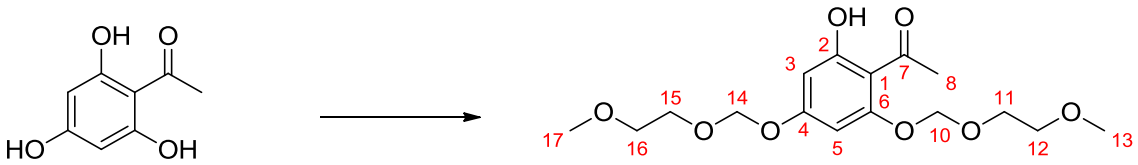
3.2.15 5,7-Bis(Benzyloxy)-2-[3,4,5-tris(benzyloxy)phenyl]-2H-chromene (28) [4]



Chalcone **46** (280 mg, 0.379 mmol) was dissolved in a mixture of tetrahydrofuran:methanol (2:1) at 0 ˚C and sodium borohydride (0.568 mmol, 21 mg) was added. The reaction was stirred over period of time (6 h) and then heated at 70 ˚C under a nitrogen atmosphere for 20 h, monitored by TLC until complete conversion of the starting material was observed. The solution was cooled and evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, the solvents removed under pressure and the residue was purified by silica gel flash column chromatography using ethyl acetate / petroleum ether (1:9) giving the desired compound as a colourless solid (38 mg, Rf 0.16, 14%).

m.p. 195-196 °C; ν_{max} (neat)/cm^{-1} 2972, 2876, 2043, 1964, 1138, 840, 661; δH (300 MHz, $CDCl_3$): 5.00 (s, 2 H, C***H***$_2$-19), 5.05 (s, 2 H, C***H***$_2$-20), 5.07 (s, 2 H, C***H***$_2$-21), 5.10 (s, 4 H, C_2***H***$_2$-17,18), 5.55 (dd, 1 H, *J* = 10.0, 3.0 Hz, C***H***-9), 5.74 (dd, 1 H, *J* = 3.0, 2.0 Hz, C***H***-8), 6.14 (d, 1 H, *J* = 2.0 Hz, C***H***-2), 6.24 (d, 1 H, *J* = 2.0 Hz, C***H***-6), 6.80 (s, 2 H, C_2***H***$_2$-12,16), 6.90 (dd, 1 H, *J* = 10.0, 2.0 Hz, C***H***-10), 7.26-7.46 (m, 25 H, ***Ph***$_5CH_5O_5$); δ_C (75 MHz, $CDCl_3$): 70.1 (Ph***C***H_2O-21), 70.2 (Ph***C***H_2O-20), 71.1 (Ph_2***C***$_2H_4$O-17,18), 75.2 (Ph***C***H_2O-19), 77.3 (***C***H-8), 93.9 (***C***H-2), 95.0 (***C***H-6), 104.9 (***C***$_2H_2$-12,16), 107.0 (***C***-4), 119.1 (***C***H-10), 119.9 (***C***H-9), 127.4, 127.6, 127.8, 127.9, 128.07, 128.14, 128.22, 128.23, 128.57, 130.5 136.7, 137.6, (***Ph***$_5C_5H_{10}O_5$Ph), 138.0, (***C***-11), 138.6 (***C***-5), 153.0 (***C***-13,15), 155.0 (***C***-14), 155.5 (***C***-3), 160.5 (***C***-1); *m/z* found for $[M+NH_4]^+$: 756.3319; $[C_{50}H_{42}O_6+NH_4]^+$ requires: 756.3320.

3.2.16 1-(2-hydroxy-4,6-bis((2-methoxyethoxy)methoxy)phenyl)ethanone (53)[8]



Method A:

2,4,6-Trihydroxyacetophenone monohydrate (600 mg, 3.5 mmol) was dissolved in anhydrous dichloromethane (15 mL) under a nitrogen atmosphere. The solution was cooled to 0 ˚C and diisopropylamine (1 mL, 8.4 mmol) was added. 2-Methoxyethoxymethyl chloride (1.7 mL, 9.8 mmol) was added into the mixture. The solution was stirred at 0 ˚C for the indicated time (16 h), and then left to stir at room temperature overnight. Water (10 mL) was then added and the aqueous layer was extracted with ethyl acetate (3×20 mL) and washed with dilute aqueous HCl (1M, 1mL). The combined organic layers were washed with water (3×10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether / ethyl acetate, 2:1) to give **53** as a colourless oily product (417 mg, 43%).

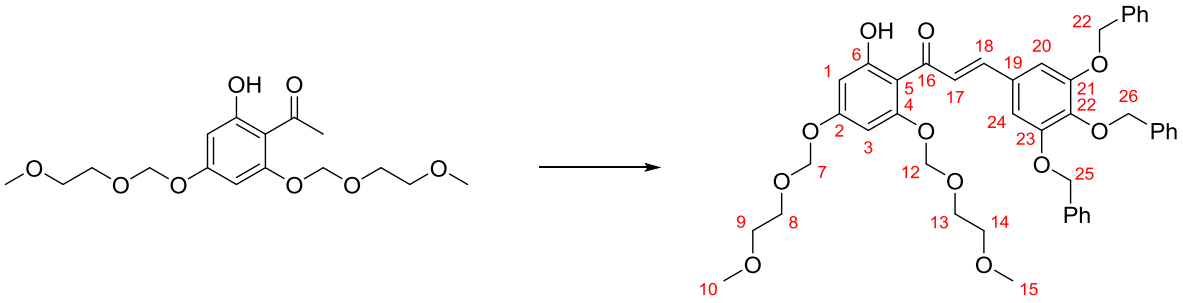
Method B:

2,4,6-Trihydroxyacetophenone monohydrate (850 mg, 5.0 mmol) and *N*,*N*-diisopropylethylamine (2.6 mL, 15 mmol) were dissolved in anhydrous dichloromethane (20 mL) under an atmosphere of argon and the reaction mixture was cooled to 0 ˚C. 2-Methoxyethoxymethyl chloride (1.3 mL, 12 mmol) was then added dropwise. The yellow

mixture was stirred at 0 ˚C over 60 min and then was allowed to stir overnight at room temperature. The solution was quenched with water (10 mL) and washed with dilute aqueous HCl (1M, 1mL). The aqueous layers were extracted with ethyl acetate (3x25 mL); the combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified through column chromatography on silica gel (ether petroleum / ethyl acetate, 2:1), to give the desired compound as a colourless oil (1.56 g, 90%).

ν_{max} (neat)/cm^{-1} 3289, 2946, 1578, 1441,1167, 889; δH (500 MHz, $CDCl_3$): 2.55 (s, 3 H, C***H***-8), 3.29 (s, 3 H, C***H***-13), 3.31 (s, 3 H, C***H***$_2$-17), 3.47 (t, 2 H, *J* = 4.4 Hz, C***H***-12), 3.50 (t, 2 H, *J* = 4.2 Hz, C***H***-16), 3.72 (t, 2 H, *J* = 4.4 Hz, C***H***-11), 3.76 (t, 2 H, *J* = 4.2 Hz, C***H***-15), 5.18 (s, 2 H, C***H***-10), 5.26 (s, 2 H, C***H***-14), 6.18 (d, 2 H, *J* = 2.3 Hz, C***H***-5), 6.19 (d, 2 H, *J* = 2.3 Hz, C***H***-3), 13.62 (s, 1 H, CO***H***-2); δ_C (125 MHz, $CDCl_3$): 32.4 (***C***H_3-8), 54.1 (***C***H_3-13), 58.0 (***C***H_3-17), 66.5 (***C***H_2-15), 67.2 (***C***H_2-11), 68.2 (***C***H_2-16), 68.6 (***C***H_2-12), 71.4 (***C***H_2-14), 71.7 (***C***H_2-10), 95.2 (***C***H-5), 96.7 (***C***H-3), 106.6 (***C***-1), 160.7 (***C***-6), 163.7 (***C***-4), 166.7 (***C***-2), 203.3 (***C***O-7).

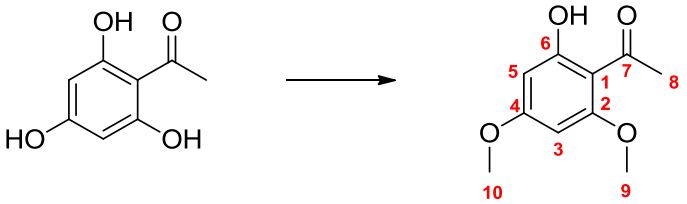
3.2.17 (E)-1-(2-hydroxy-4,6-bis((2-methoxyethoxy)methoxy)phenyl)-3-(3,4,5-tris(benzyloxy)phenyl)prop-2-en-1-one (54)



Compound **53** (750 mg, 2.17 mmol) was dissolved in anhydrous dimethylformamide. NaH (104 mg, 4.35 mmol) was then added. A solution of 3,4,5-tris(benzyloxy)benzaldehyde **23** (1.1 g, 2.60 mmol) in dimethylformamide was then added dropwise. The reaction mixture was then stirred overnight at room temperature. Water (5 mL) was used to quench any unreacted NaH, followed by the removal of the solvents under reduced pressure. The resulting residue was dissolved in ether (20 mL) and washed with water (10 mL), dilute aqueous HCl (1M, 1mL), and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (toluene/ethyl acetate, 3:1) to give **39** (1.14 g, 70%) as a pale yellow solid.

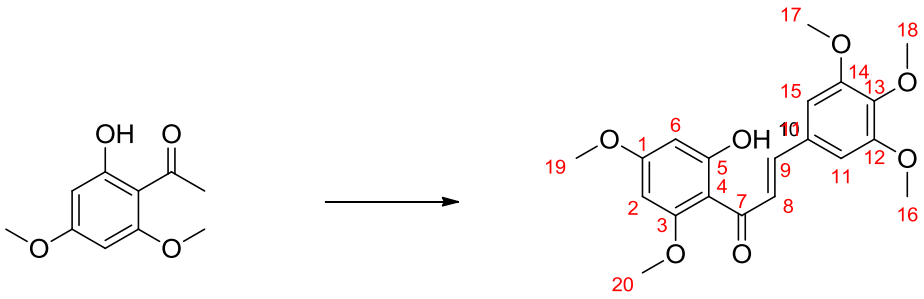
m.p. 145-147°C; ν_{max} (neat)/cm^{-1} 3626, 2851, 1992, 1713, 1026, 843; δH (500 MHz, $CDCl_3$): 3.20 (s, 3 H, C***H***-15), 3.31 (s, 3 H, C***H***-10), 3.41 (t, 2 H, *J* = 4.2 Hz, C***H***-14), 3.50 (t, 2 H, *J* = 4.4 Hz, C***H***-9), 3.71(t, 2 H, *J* = 4.2 Hz, C***H***-13), 3.77 (t, 2 H, *J* = 4.4 Hz, C***H***-8), 5.04 (s, 2 H, C***H***-26), 5.07 (s, 4 H, C***H***-22,25), 5.20 (s, 2 H, C***H***-12), 5.22 (s, 2 H, C***H***-7), 6.19 (d, 2 H, *J* = 2.3 Hz, C***H***-1), 6.26 (d, 2 H, *J* = 2.3 Hz, C***H***-3), 6.83 (s, 2 H, C***H***-20,24), 7.31 (m, 15 H, Ar***H***), 7.56 (d, 1 H, *J* = 15.5 Hz, C***H***-17), 7.66 (d, 1 H, *J* = 15.4 Hz, C***H***-18), 13.67 (s, 1 H, CO***H***-6); δ_C (125 MHz, $CDCl_3$,): 59.0 (***C***H_3-15), 59.1 (***C***H_3-10), 68.3 (***C***H_2-14), 68.8 (***C***H_2-9), 71.3 (***C***H_2-26), 71.5 (***C***H_2-22,25), 75.3 (***C***H_2-8) 77.0 (***C***H_2-13), 93.1 (***C***H-12), 94.3 (***C***H-7), 95.0 (***C***H-3), 97.6 (***C***H-1), 106.6 (***C***H-20,24), 107.6 (***C***H-5), 126.70 (***C***H-17), 126.75 (***C***-19), 127.4, 127.97, 128.05, 128.2, 128.58, 128.61, 130.99, 131.00 (***Ph***$_3C_3H_6O_3$Ph), 136.8 (***C***H-18), 142.3(***C***H-22), 153.1 (***C***-23,21), 159.8 (***C***-6), 163.5 (***C***-4), 167.2 (***C***-2), 192.7 (***C***=O); *m/z* found for $[M+H]^+$: 751.3110; $[C_{44}H_{46}O_{11}+H]^+$ requires: 751.3113.

3.2.18 1-(2-Hydroxy-4,6-dimethoxyphenyl)ethanone (57).[9]



2,4,6-Trihydroxyacetophenone (400 mg, 2.37 mmol) and K_2CO_3 (690 mg, 4.99 mmol) were dissolved in acetone (12 ml). The mixture was heated under reflux for 1 h under a nitrogen atmosphere. The reaction mixture was allowed to reach room temperature. Dimethylsulfate (0.33 mL, 448 mg, 3.55 mmol) was added and the solution stirred under a nitrogen atmosphere at 65 °C overnight. The solvents were evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed using a saturated solution of $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether /ethyl acetate (4:1) to afford **57** as a colourless solid (420 mg, 90%). m.p. 96-97 °C; ν_{max} (neat)/cm^{-1} 3453, 2951, 1731,1246, 1105, 831; δH (500 MHz, $CDCl_3$): 2.61 (s, 3 H, C***H***$_3$-8), 3.82 (s, 3 H, C***H***$_3$-9), 3.85 (s, 3 H, C***H***$_3$-10), 5.93 (d, 1 H, *J* = 2.3 Hz, Ar***H***-3), 6.06 (d, 1 H, *J* = 2.3 Hz, Ar***H***-5), 14.06 (s, 1 H, O***H***-6); δ_C (125 MHz, $CDCl_3$): 33.0 (***C***H_3-8), 55.6 (***C***$_2$H$_6$-9,10), 90.5 (***C***H-5), 93.5 (***C***H-3), 105.9 (***C***-1), 162.9 (***C***-2), 166.0 (***C***-4), 167.7 (***C***-6), 203.1 (***C***O-7).

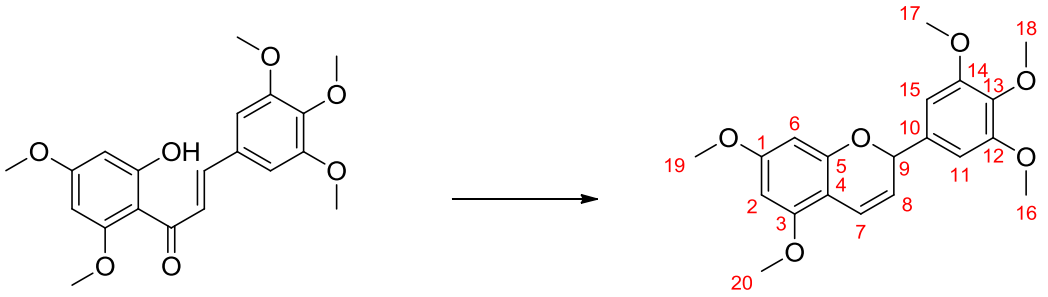
3.2.19 (2E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (59) [10]



Acetophenone **57** (720 mg, 3.68 mmol) and 3,4,5-trimethoxybenzaldehyde (930 mg, 4.78 mmol) were dissolved in ethanol (3 mL). The solution was heated at 80 °C and aqueous KOH (1 g KOH/10 mL EtOH) was added slowly. The reaction turned into a clear red solution and was left to stir at room temperature overnight. The mixture was acidified with concentrated dilute aqueous HCl (1M, 7mL) in an ice bath and the resulting precipitate filtered off, washed with cold water and cold ethanol. The yellow solid was purified by recrystallization with ethanol to yield chalcone **59** (1.27 g, 93%).

m.p. 201-203 °C; ν_{max} (neat)/cm^{-1} 3350, 3053, 2836, 1733, 1247, 739; δH (500 MHz, $CDCl_3$): 3.88 (s, 3 H, C***H***$_3$-19), 3.95 (m, 12 H, C$_4$***H***$_{12}$-16,17,18,20), 6.00 (d, 1 H, *J* = 2.0 Hz, Ar***H***-6), 6.15 (d, 1 H, *J* = 2.0 Hz, Ar***H***-2), 6.88 (s, 2 H, Ar***H***-11,15), 7.74 (d, 1 H, *J* = 15.5 Hz, C***H***-8), 7.84 (d, 1 H, *J* = 15.5 Hz, C***H***-9), 14.36 (s, 1 H, O***H***-5); δ_C (125 MHz, $CDCl_3$): 55.6 (***C***H$_3$-19), 55.8 (***C***H$_3$-18), 56.2 (***C***$_2$H$_6$-16.17), 61.0 (***C***H$_3$-20), 91.5 (***C***H-6), 93.9 (***C***H-2), 105.6 (***C***$_2$H$_2$-11,15), 106.3 (***C***-4), 126.9 (***C***H-8), 131.2 (***C***-10), 140.1 (***C***H-9), 142.4 (***C***-5), 154.4 (***C***$_2$-14,16), 162.4 (***C***-13), 166.3 (***C***-3), 168.5 (***C***-1), 192.4 (***C***O-7).

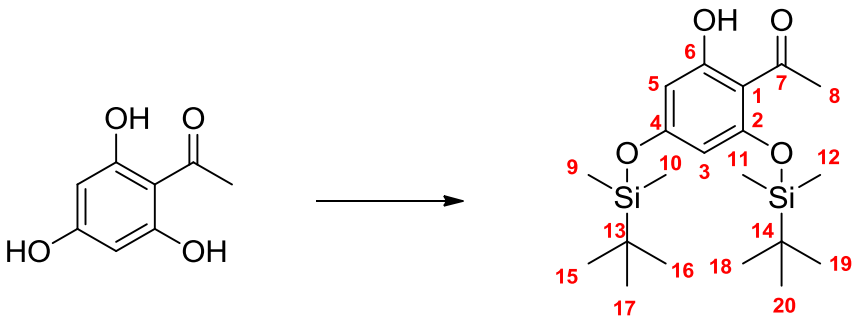
3.2.20 5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)-2H-chromene (60) [10]



Chalcone **59** (160 mg, 0.427 mmol) was dissolved in a mixture of anhydrous tetrahydrofuran and ethanol (10 mL). Sodium borohydride (64 mg, 1.7 mmol) was added and the mixture was then heated at 80 °C for 1 h. The reaction was then heated at 50 °C overnight. Dilute aqueous HCl (2M, 30 mL) was added and the resulting solution was allowed to stir for 30 min. The yellow mixture turned purple. The solvent was removed and the residue dissolved in ethyl acetate (50 mL), the organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue was then purified by column chromatography on silica gel (petroleum ether-ethyl acetate 5:1) to furnish **60** as a colourless powder (30 mg, 20%).

m.p. 178-180 °C; ν_{max} (neat)/cm^{-1} 3054, 2987, 2126, 1265,739; δH (500 MHz, $CDCl_3$): 3.77 (s, 3 H, C***H***$_3$-20), 3.95 (s, 3 H, C***H***$_3$-19), 3.87 (s, 3 H, C***H***$_3$-18), 3.88 (s, 6 H, C_2***H***$_6$-16,17), 5.61 (dd, 1 H, *J* = 9.9, 3.2 Hz, C***H***-8), 5.78 (dd, 1 H, *J* = 3.2, 2.0 Hz, C***H***-9), 6.07 (d, 1 H, *J* = 2.3 Hz, Ar***H***-2), 6.10 (d, 1 H, *J* = 2.3 Hz, Ar***H***-6), 6.73 (s, 2 H, Ar***H***-11,15), 6.84 (dd, 1 H, *J* = 9.9, 2.0 Hz, C***H***-7), δ_C (125 MHz, $CDCl_3$): 55.4 (***C***H$_3$-20), 55.6 (***C***H$_3$-19), 56.1 (***C***$_2$H$_6$-16.17), 60.8 (***C***H$_3$-18), 77.5 (***C***H-9), 91.9 (***C***H-2), 93.7 (***C***H-6), 104.3 (***C***$_2$H$_2$-11,15), 104.4 (***C***-4), 119.2 (***C***H-8), 119.7 (***C***H-7), 136.6 (***C***-10), 137.9 (***C***-5), 153.4 (***C***$_2$-14,12), 154.9 (***C***-13), 156.4 (***C***-3), 161.3 (***C***-1).

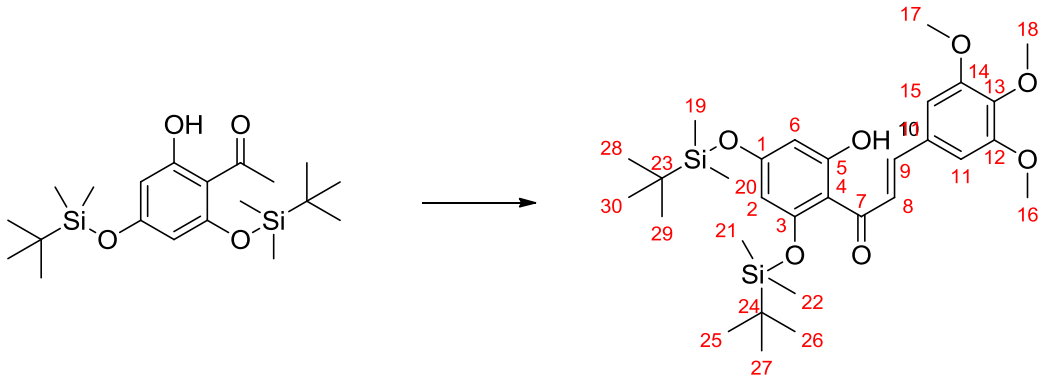
3.2.21 1-(2,4-Bis[dimethyl(2-methyl-2-propanyl)silyl]oxy}-6-hydroxyphenyl)ethanone (62) [11]



2,4,6-Trihydroxyacetophenone (300 mg, 1.78 mmol) was dissolved in anhydrous dichloromethane under a nitrogen atmosphere at room temperature. Triethylamine (0.75 mL, 5.34 mmol) and 4-dimethylaminopyridine (20 mg, 0.17 mmol) were added slowly. The mixture was stirred for 20 min and turned into a clear yellow solution. *tert*-Butylchlorodimethylsilane (600 mg, 3.9 mmol) was added. The reaction was stirred for 18 h at room temperature. The reaction was quenched with water (5 mL). The organic layer was washed with water (20 mL) and brine (5 mL), dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by silica gel flash chromatography using ethyl acetate/toluene (1/10) to furnish the desired product as a colourless oil (636 mg, 90%).

m.p. 156 °C; ν_{max} (neat)/cm^{-1} 3453, 2933, 1739, 1248, 1197, 985; δH (500 MHz, $CDCl_3$): 0.01 (s, 6 H, $SiC_2\boldsymbol{H}_6$-11,12), 0.12 (s, 6 H, $SiC_2\boldsymbol{H}_6$-9,10), 0.74 (s, 9 H, $C_3\boldsymbol{H}_9$-18,19,20), 0.74 (s, 9 H, $C_3\boldsymbol{H}_9$-15,16,17), 2.40 (s, 3 H, C$\boldsymbol{H}_3$-8), 5.62 (d, 1 H, J = 2.3 Hz, Ar$\boldsymbol{H}$-3), 5.80 (d, 1 H, J = 2.3 Hz, Ar$\boldsymbol{H}$-5), 13.31 (s, 1 H, O$\boldsymbol{H}$-5) δ_C (125 MHz, $CDCl_3$): -4.3 (Si$\boldsymbol{C}_2H_6$-11,12), -3.5 (Si$\boldsymbol{C}_2H_6$-9,10), 18.3 ($\boldsymbol{C}$-14), 18.9 ($\boldsymbol{C}$-13), 25.5 (Si$\boldsymbol{C}_3H_9$-18,19,20), 26.1 (Si$\boldsymbol{C}_3H_9$-15,16,17), 32.9 ($\boldsymbol{C}H_3$-8), 101.8 ($\boldsymbol{C}$H-5), 102.7 ($\boldsymbol{C}$H-3), 109.0 ($\boldsymbol{C}$-1), 159.5 ($\boldsymbol{C}$-2), 162.4 ($\boldsymbol{C}$-4), 166.4 ($\boldsymbol{C}$-6), 203.4 ($\boldsymbol{C}$O-10).

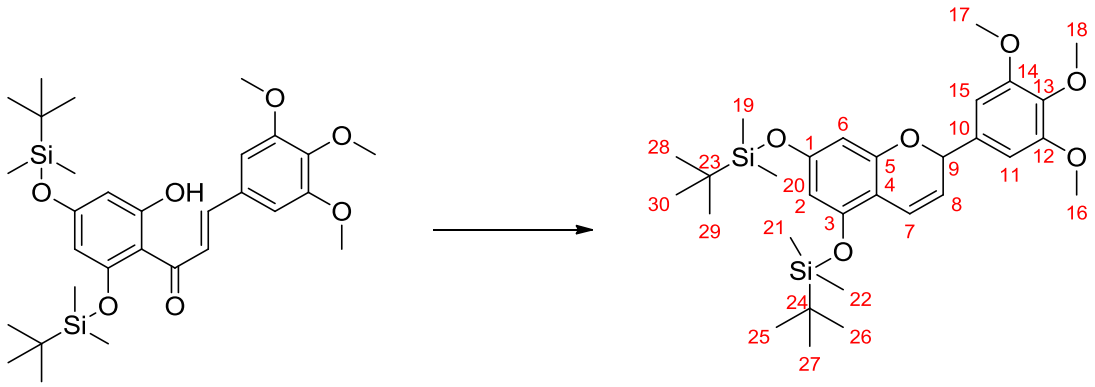
3.2.22 (E)-1-(2,4-bis((tert-butyldimethylsilyl)oxy)-6-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (63)



1-(2,4-*bis*((*tert*-Butyldimethylsilyl)oxy)-6-hydroxyphenyl)ethanone **62 (**250 mg ,0.63 mmol) and 3,4,5-trimethoxybenzaldehyde (185 mg, 0.94 mmol) were dissolved in anhydrous tetrahydrofuran at 0 ˚C. NaH (12 mg, 0.50 mmol) was then added and the reaction mixture stirred for 50 minutes at room temperature. The mixture was diluted with water, and extracted with dichloromethane (20 mL ×3). The organic layer was successively washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate, 8:1) to give yellow solid **63** (76 mg, 21%).

m.p. 113-115 °C; ν_{max} (neat)/cm^{-1} 3298, 2957,1646, 1604, 1318, 1143, 1091, 996; δH (500 MHz, $CDCl_3$): 0.01 (s, 6H, $SiC_2\boldsymbol{H}_6$-21,22), 0.12 (s, 6H, $SiC_2\boldsymbol{H}_6$-19,20), 0.71 (s, 9H, $C_3\boldsymbol{H}_9$-25,27,26), 0.76 (s, 9H, $C_3\boldsymbol{H}_9$-28,29,30), 3.67 (s, 6H, $C_2\boldsymbol{H}_6$-16,17), 3.68 (s, 3H, $C\boldsymbol{H}_3$-18), 5.67 (d, 1H, *J* = 2.30 Hz, Ar***H***-6), 5.88 (d, 1H, *J* = 2.30 Hz, Ar***H***-2), 6.61 (s, 2H, Ar***H***-11,15), 7.41 (d, 1H, *J* = 15.60 Hz, C***H***-8), 7.51 (d, 1H, *J* = 15.60 Hz, C***H***-9), 12.31 (s, 1H, O***H***-5) δ_C (125 MHz, $CDCl_3$): - 4.7 (Si***C***$_2H_6$-22,21), - 3.7 (Si***C***$_2H_6$-19,20), 18.2 (***C***-24), 18.6 (***C***-23), 25.5 (Si***C***$_3H_9$-25,26,27), 25.9 (Si***C***$_3H_9$-28,29,30), 56.1 (***C***$_2H_6$-16.17), 61.00 (***C***H_3-18), 102.2 (***C***H-6), 104.1 (***C***H-2), 105.8 (***C***$_2H_2$-11,15), 110.5 (***C***-4), 126.5 (***C***H-8), 130.7 (***C***-10), 140.1 (***C***H-9), 142.7 (***C***-13), 153.3 (***C***$_2$-14,16), 158.6 (***C***-3), 162.4 (***C***-1), 165.7 (***C***-5), 192.4 (***C***O-7); *m/z* found for $[M+H]^+$: 575.2850; $[C_{30}H_{46}O_7Si_2+H]^+$ requires: 575.2855.

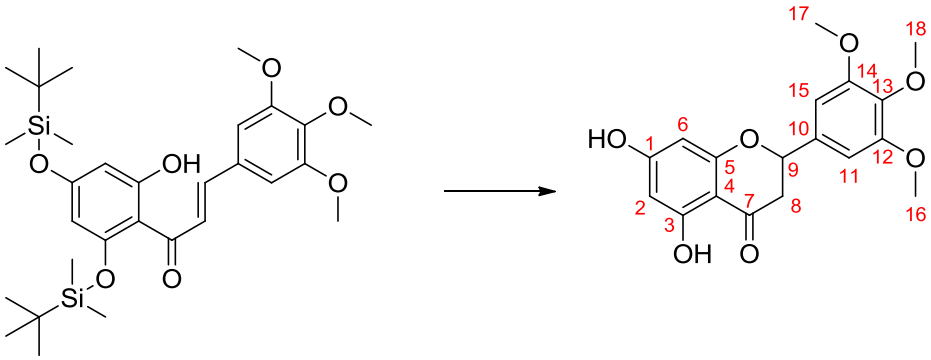
3.2.23 ((2-(3,4,5-trimethoxyphenyl)-2H-chromene-5,7-diyl)bis(oxy))bis(tert-butyldimethylsilane) (66)



A suspension of chalcone **63** (140 mg, 0.258 mmol) in a mixture of anhydrous tetrahydrofuran and ethanol (2/1: 10 mL) was heated at 90 °C for 5 min. Sodium borohydride (30 mg, 0.77 mmol) was added and the mixture was then heated at 90 °C for 10 min. a reaction was quenched with 30 mL of water and left to stir for 10 minute. After dilution with ethyl acetate (50 mL), the organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude residue was then purified by column chromatography, eluting with petroleum ether-dichloromethane (3:1), to furnish **63** as a beige powder (14 mg, 10%).

mp 98-101 °C; ν_{max} (neat)/cm^{-1} 2963, 2100, 1325, 1126, 1067, 1030, 818; δH (500 MHz, $CDCl_3$): 0.01 (s, 6H, $SiC_2\boldsymbol{H}_6$-21,22), 0.048 (s, 3H, C$\boldsymbol{H}_3$-20), 0.050 (s, 3H, C$\boldsymbol{H}_3$-19), 0.77 (s, 9H, $C_3\boldsymbol{H}_9$-25,27,26), 0.83 (s, 9H, $C_3\boldsymbol{H}_9$-28,29,30), 3.65 (s, 3H, C$\boldsymbol{H}_3$-18), 3.66 (s, 6H, $C_2\boldsymbol{H}_6$-16,17), 5.41 (dd, 1H, *J* = 9.9, 3.2 Hz, C***H***-8), 5.54 (m, 1H, C***H***-9), 5.74 (d, 1H, *J* = 2.2 Hz, Ar***H***-2), 5.85 (d, 1H, *J* = 2.2 Hz, Ar***H***-6), 6.50 (s, 2H, Ar***H***-11,15), 6.58 (dd, 1H, *J* = 9.9, 1.6 Hz, C***H***-7), δ_C (125 MHz, $CDCl_3$): - 4.3 (Si$\boldsymbol{C}_2H_6$-22,21), - 4.26 (Si$\boldsymbol{C}H_3$-20), - 4.23 (Si$\boldsymbol{C}H_3$-19), 18.2 (***C***-24), 18.3 (***C***-23), 25.6 (Si$\boldsymbol{C}_3H_9$-25,26,27), 25.7 (Si$\boldsymbol{C}_3H_9$-28,29,30), 56.0 ($\boldsymbol{C}_2H_6$-16.17), 60.7 ($\boldsymbol{C}H_3$-18), 77.3 (***C***H-9), 101.9 (***C***H-6), 104.2 (***C***H-2), 104.6 ($\boldsymbol{C}_2H_2$-11,15), 10.94 (***C***-4), 119.7 (***C***H-7), 120.3 (***C***H-8), 136.6 (***C***-10), 137.9 (***C***-5), 152.2 ($\boldsymbol{C}_2$-14,16), 153.3 (***C***-13), 154.8 (***C***-3), 156.82 (***C***-1).

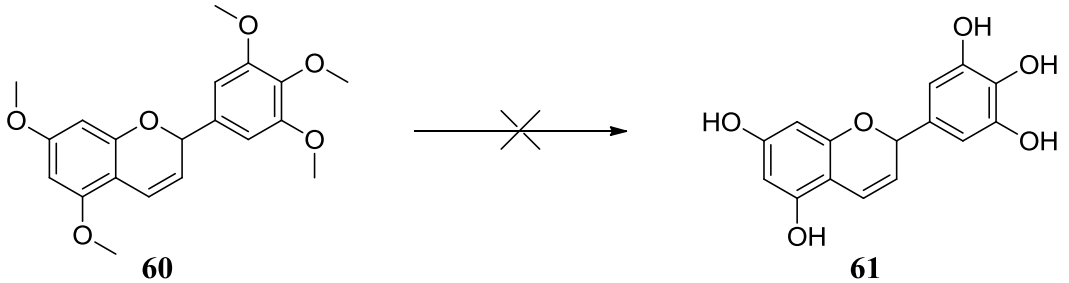
3.2.24 5,7-dihydroxy-2-(3,4,5-trimethoxyphenyl)chroman-4-one (68)



Chalcone **63** (130 mg, 2.26 mmol) was dissolved in a mixture of methanol (6 mL) and tetrahydrofuran (6 mL) at room temperature. Hydrogen bromide (48% in H_2O, 3 mL) was then added. The reaction was heated under reflux for 16 h. The organic solvents were evaporated under reduced pressure. The aqueous mixture was extracted with ethyl acetate (2x60 mL). The organic layer was washed with water (2x10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was flash chromatographed over a silica gel column, with ethyl acetate /petroleum ether (5:1) as eluent to afford the desired product (76 mg, 97%).

mp 263-265 °C; ν_{max} (neat)/cm^{-1} 3583, 3054, 1711, 915; δH (500 MHz, DMSO-d_6): 2.71 (dd, 1 H, *J* = 17.1, 2.9 Hz, C***H***$_2$-8), 3.03 (dd, 1 H, *J* = 17.1, 13.1 Hz, C***H***$_2$-8), 3.75 (s, 3 H, C***H***$_3$-18), 3.83 (s, 6 H, C_2***H***$_6$-16,17), 5.29 (dd, 1 H, *J* = 13.0, 2.9 Hz, C***H***-9), 5.28 (d, 1 H, *J* = 2.7 Hz, ***C***H-6), 5.30 (d, 1 H, *J* = 2.7 Hz, ***C***H-2), 6.66 (s, 2 H, Ar***H***-11,15), 10.30 (s, 1 H, O***H***-1), 11.99 (s, 1 H, O***H***-3), δ_C (125 MHz, DMSO-d_6): 43.4 (***C***H_2-8), 56.2 (***C***$_2H_6$-16.17), 60.6 (***C***H_3-18), 79.2 (***C***H-9), 95.6 (***C***H-6), 96.7 (***C***H-2), 102.2 (***C***-4), 103.5 (***C***$_2H_2$-11,15), 134.4 (***C***-10), 137.9 (***C***-5), 153.4 (***C***$_2$-14,16), 162.8 (***C***-13), 164.1 (***C***-3), 167.1 (***C***-1) 195.3 (***C***O-7); *m/z* found for $[M+H]^+$: 347.1127; $[C_{18}H_{18}O_7 + H]^+$ requires: 347.1125.

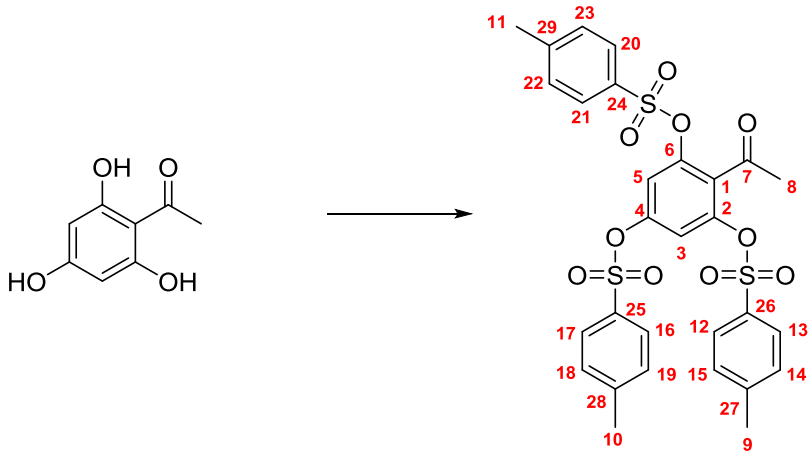
3.2.25 General procedure of demethylation for 5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)-2H-chromene. (61)



60 **61**

Compound **60** (400 mg, 1.11 mmol) was dissolved in anhydrous dichloromethane (10 mL) under argon. The solution was cooled to −78 °C. Boron tribromide (1M solution in dichloromethane, 0.6 mL, 3.34 mmol) was added dropwise using a syringe at −78 °C. The reaction mixture was allowed to stir for 1h at −78 °C. The reaction was then allowed to reach room temperature and left to stir overnight. Water (5 mL) was then added. The mixture was extracted with ethyl acetate (2x20 mL); the organic layers were combined and washed with water (2x10 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure.

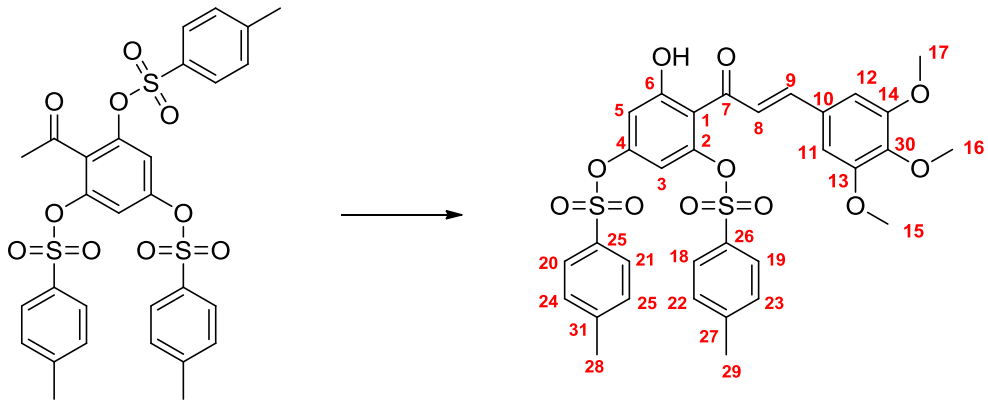
3.2.26 2-acetylbenzene-1,3,5-triyl tris(4-methylbenzenesulfonate) (71)



2,4,6-Trihydroxyacetophenone (1.0 g, 5.94 mmol) and K_2CO_3 (1.8 g, 13 mmol) were suspended in acetone. 4-Toluenesulfonyl chloride (3.4 g, 18 mmol) was then added to the reaction mixture. The mixture was heated under reflux for 24h under a nitrogen atmosphere. The reaction was allowed to reach room temperature and the solvent was evaporated under reduced pressure. Water was added and the resulting mixture was extracted with dichloromethane. The organic layer was washed with water (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) to afford compound **71** as a colourless solid (3.56 g, 95%).

m.p. 214-216 °C; ν_{max} (neat)/cm^{-1} 2979, 1707, 1368, 1144, 911, 848; δH (500 MHz, $CDCl_3$): 2.23 (s, 3 H, C***H***$_3$-8), 2.41 (s, 9 H, C***H***$_3$-9,10,11), 6.85 (s, 2 H, Ar***H***-3,5), 7.30 (d, 4 H, *J* = 7.5 Hz, C***H***$_2$-14,15,22,23), 7.35 (d, 2 H, *J* = 7.0 Hz, C***H***$_2$-18,19), 7.58 (d, 4 H, *J* = 7.5 Hz, C***H***$_2$-12,13,20,21), 7.66 (d, 2 H, *J* = 7.0 Hz, C***H***$_2$-17,16), δ_C (125 MHz, $CDCl_3$): 21.7 (***C***$_3$H$_9$-9,10,11), 31.5 (***C***H$_3$-8), 116.1 (***C***$_2$H$_2$-3,5), 128.3 (***C***$_4$H$_4$-12,13,20,21), 129.0 (***C***$_2$H$_2$-16,17), 130.22 (***C***$_4$H$_4$14,15,22,23), 130.29 (***C***$_2$H$_2$-18,19), 131.1 (***C***-28), 131.2 (***C***$_2$-27,29), 146.3 (***C***$_2$-24,26), 146.6 (***C***-25), 146.7 (***C***$_2$-2,6), 149.9 (***C***-4), 195.0 (***C***O-7).

3.2.27 (E)-5-hydroxy-4-(3-(3,4,5-trimethoxyphenyl)acryloyl)-1,3-phenylene bis(4-methylbenzenesulfonate) (72)

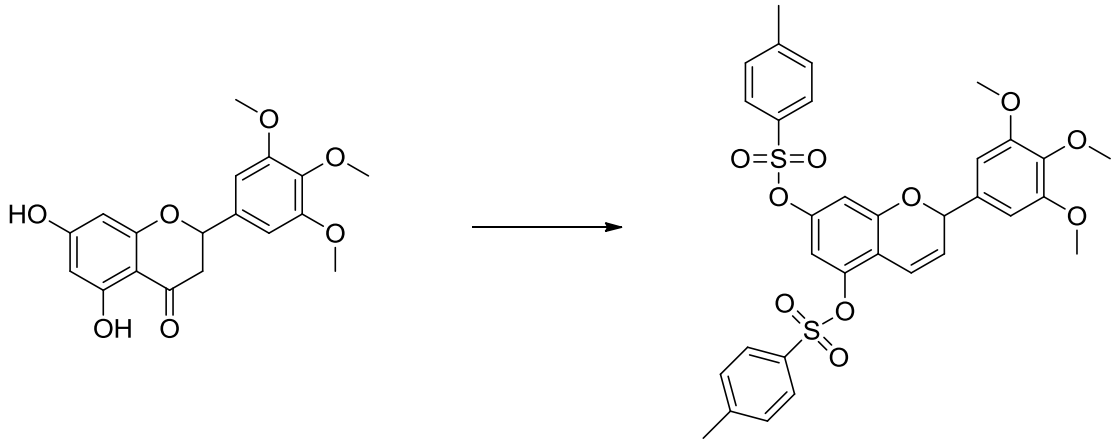


Compound **71** (1.00 g, 1.58 mmol) and 3,4,5-trimethoxybenzaldehyde (0.62 g, 3.17 mmol) were dissolved in anhydrous tetrahydrofuran under an argon atmosphere. NaH (0.08 mg, 3.16 mmol) was added in 2 times at room temperature. The reaction was stirred overnight at room temperature. Water (5 mL) was added into the reaction. The residue was dissolved in dichloromethane (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 1:1) to give **72** as a yellow oil (228 mg, 22%).

ν_{max} (neat)/cm^{-1} 3293, 1607, 1471, 1276, 1140, 869; δH (500 MHz, $CDCl_3$): 3.39 (s, 3 H, C***H***$_3$-29), 3.45 (s, 3 H, C***H***$_3$-28), 3.91 (s, 6 H, C***H***$_3$-15-17), 3.92 (s, 3 H, C_2***H***$_6$-16), 6.48 (d, 1 H, *J* = 2.4 Hz, Ar***H***-3), 6.51 (d, 1 H, *J* = 2.4 Hz, Ar***H***-5), 6.89 (s, 2 H, Ar***H***-11,12), 7.20 (d, 2 H, *J* = 8.4 Hz, C***H***$_2$-22-23), 7.35 (d, 2 H, *J* = 8.4 Hz, C***H***$_2$-18-19), 7.57 (d, 2 H, *J* = 8.7 Hz, C***H***$_2$-24-25), 7.61 (s, 1 H, C***H***-8), 7.70 (s, 1 H, C***H***-9), 7.73 (d, 2 H, *J* = 8.7 Hz, C***H***$_2$-20-21), 12.97 (s, 1 H, O***H***-6), δ_C (125 MHz, $CDCl_3$): 21.71 (***C***H_3-28), 21.74 (***C***H_3-29), 56.2 (***C***$_2H_6$-15,17), 61.0 (***C***H_3-16), 106.1 (***C***$_2H_2$-11,12), 108.2 (***C***H-5), 110.5 (***C***H-3), 114.2 (***C***-1), 124.4 (***C***H-8), 128.4 (***C***$_2H_2$-24-25), 128.6 (***C***$_2H_2$-22-23), 130.0 (***C***$_2H_2$-20,21), 130.1 (***C***$_2H_2$-18-19), 131.0 (***C***-27), 131.8 (***C***-31), 140.0 (***C***-26), 146.1 (***C***-35), 146.2 (***C***-4), 146.6 (***C***-2), 149.9 (***C***H-9), 153.4 (***C***$_2$-13,14), 153.5 (***C***-30), 164.5 (***C***-6), 191.8 (***C***-7); *m/z* found for $[M+H]^+$: 655.1299; $[C_{32}H_{30}O_{11}S_2+H]^+$ requires: 655.1302.

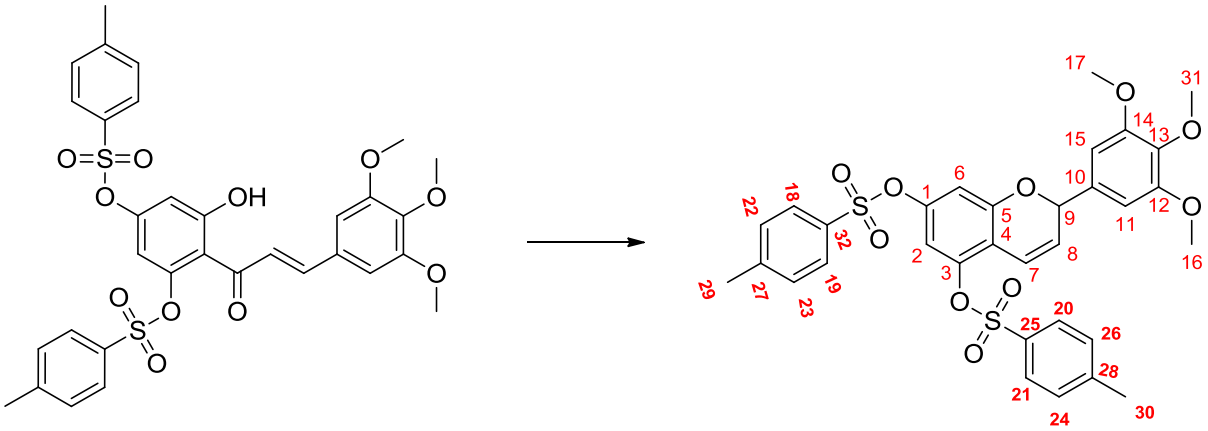
3.2.28 2-(3,4,5-trimethoxyphenyl)-2H-chromene-5,7-diyl-bis(4-methylbenzenesulfonate) (70)

Method A



Sodium borohydride powder (38 mg, 1.01 mmol) was added to a solution of **68** (112 mg, 0.33 mmol) in anhydrous Methanol. The reaction was heated under reflux until full conversion was observed by TLC analysis. The solvents were removed under reduced pressure. Anhydrous toluene was added to the residue and the flask was fitted with a Dean-Stark apparatus. The resulting solution was heated under reflux. Any MeOH remaining in the mixture was collected in the attached Dean-Stark apparatus. The mixture was allowed to cool to a room temperature and camphorsulfonic acid (234 mg, 1.01 mmol) was added. The reaction mixture was again heated to reflux and the water that evolved was collected in the Dean-Stark apparatus as the reaction proceeded for 1 h. The reaction was allowed to reach room temperature and the solvents removed under reduced pressure. The crude was re-dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$ followed by brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue **65** and K_2CO_3 (182 mg, 1.23 mmol) were dissolved in acetone. 4-Toluenesulfonyl chloride (234 mg, 1.23 mmol) was then added. The mixture was heated under reflux for 24h under a nitrogen atmosphere. The reaction mixture was allowed to reach room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with water (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) to afford the compound **70** as a colourless solid (140 mg, 65%).

Method B

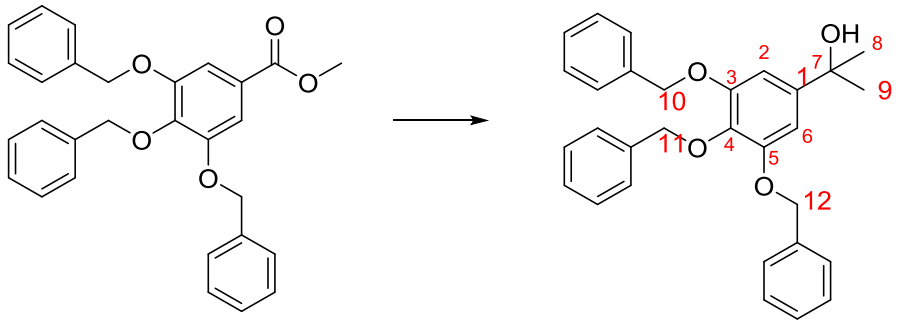


Sodium borohydride powder (346 mg, 9.16 mmol) was suspended in anhydrous tetrahydrofuran under argon at 0 °C. Compound **72** (200 mg, 3.05 mmol) was dissolved in a mixture of tetrahydrofuran/ethanol (2: 1) and the resulting solution was added to the sodium borohydride suspension. The reaction mixture was heated to reflux for 18h. The reaction was monitored by TLC until completion as observed. The solution was allowed to reach room temperature and the solvents were evaporated under reduced pressure. The residue was dissolved in diethyl ether and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the residue was purified by silica gel flash chromatography using ethyl acetate / petroleum ether (1:5) to give the title compound as a colourless solid (189 mg, Rf = 0.22, 97%).

m.p. 128-130 ˚C; ν_{max} (neat)/cm^{-1} 2925, 1938, 1464, 1030, 903; δH (500 MHz, $CDCl_3$): 2.36 (s, 3 H, C***H***$_3$-30), 2.37 (s, 3 H, C***H***$_3$-29), 3.74 (s, 3 H, C_2***H***$_6$-31) 3.77 (s, 6 H, C***H***$_3$-16,17), 5.71 (d, 1 H, *J* = 6.5 Hz, C***H***-9), 6.08 (dd, 1 H, *J* = 15.7, 6.5 Hz, C***H***-8), 6.17 (d, 1 H, *J* = 2.3 Hz, Ar***H***-2), 6.35 (d, 1 H, *J* = 2.3 Hz, Ar***H***-6), 6.40 (dd, 1 H, *J* = 15.7, 0.9 Hz, C***H***-7), 6.44 (s, 2 H, Ar***H***-11,15), 7.26 (m, 4 H, Ar***H***-22,23,24,26), 7.64 (m, 4 H, Ar***H***-18,19,20,21); δ_C (125 MHz, $CDCl_3$): 21.2 (***C***H_3-30), 21.7 (***C***H_3-29), 56.2 (***C***$_2H_6$-16,17), 60.8 (***C***H_3-31), 77.5 (***C***H-9), 104.5 (***C***$_2H_2$-11,15), 109.6 (***C***H-2), 109.7 (***C***H-6), 115.4 (***C***-4), 118.0 (***C***H-8), 125.4 (***C***H-7), 128.4 (***C***$_2H_2$-24-26), 129.4 (***C***$_2H_2$-22-23), 130.1 (***C***$_2H_2$-20,21), 131.9 (***C***$_2H_2$-18-19), 132.0 (***C***-28), 134.4 (***C***-27), 145.2 (***C***-25), 145.9 (***C***-32), 146.1 (***C***-5), 149.1 (***C***-13),153.5 (***C***$_2$-12,14), 154.2 (***C***-3), 158.0 (***C***-1).

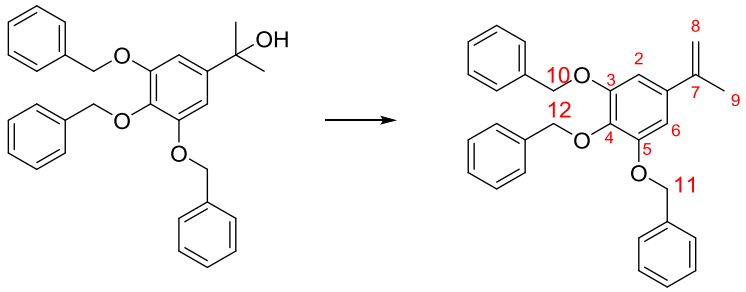
3.3 Experimental Procedures Related to the Synthesis of 3-flav-3-ene methyl analogues.

3.3.1 2-(3,4,5-tris(Benzyloxy)phenyl)propan-2-ol (86)



Methyl 3,4,5-tris-benzyloxybenzoate (1.00 g, 2.2 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and cooled to 0 °C under an argon atmosphere. Methylmagnesium bromide (3.0M in diethyl ether, 2.4 mL) was slowly added to the solution. After stirring for 2h at room temperature, the reaction mixture was quenched with diluted aqueous HCl (1M, 1mL). The reaction mixture was extracted with diethyl ether (3x30 mL), and the combined organic layers were washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with ethyl acetate-petroleum ether (1:4) to give the desired compound as a colourless solid (970 mg, 97% yield). mp 173-177 °C; ν_{max} (neat)/cm^{-1}3378, 2970, 1200, 731; δH (500 MHz; $CDCl_3$) 1.38 (s, 6 H, C_2***H***$_6$-8,9), 2.01(s, 1 H, CO*H*-7), 4.94 (s, 2 H, C***H***$_2$-11), 4.98 (s, 4 H, C_2***H***$_4$-10,12), 6.69 (s, 2 H, Ar***H***-2,6), 7.28 (m, 15 H, Bn***H***); δ_C (125MHz; $CDCl_3$) 31.8 (***C***$_2$$H_3$-8,9), 71.5 (***C***$_2$$H_4$-10,12), 72.6 (***C***$H_2$-11), 75.4 (***C***-7), 105.0 (***C***$_2$$H_2$-2,6), 127.7, 127.9, 128.0, 128.3, 128.6, 128.7, 137.3, 137.4 (***Ph***$_3$$C_3H_6O_3$Ph), 138.1 (***C***-1), 145.2 (***C***-4), 152.5 (***C***$_2$-3,5); *m/z* found for $[M+H]^+$: 455.2213; $[C_{30}H_{30}O_4+H]^+$ requires: 455.2217.

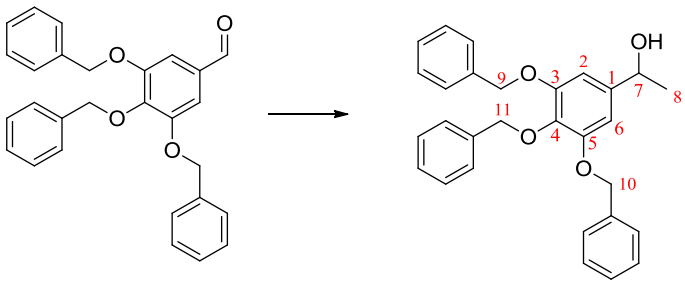
3.3.2 (((5-(prop-1-en-2-yl)benzene-1,2,3-triyl)tris(oxy))tris(methylene))tribenzene (87)



Camphorsulfonic acid (613 mg, 2.63 mmol) was added to a solution of **86** (400 mg, 0.87 mmol) in anhydrous toluene. The reaction was heated under reflux and followed by TLC until completion. The reaction was allowed to reach room temperature and the solvents were removed under reduced pressure. The crude mixture was re-dissolved in diethyl ether and washed with saturated aqueous NaOH followed by brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate -petroleum ether (1:8) to give the desired compound as a colourless solid (272 mg, 71% yield).

mp 167-169 °C; ν_{max} (neat)/cm^{-1} 3020, 2980, 1673, 1280, 980; δH (500 MHz; $CDCl_3$) 2.0 (d, 3 H, *J* = 0.6 Hz, C***H***$_3$-9), 4.95 (m, 1 H, C***H***-8), 4.98 (s, 2 H, C***H***$_2$-12), 4.94-4.95 (m, 1H, C***H***-8'), 5.05 (s, 4 H, C_2***H***$_4$-10,11), 5.16 (m, 1 H, C***H***-8), 6.69 (s, 2 H, Ar***H***-2,6), 7.27 (m, 15 H, Bn***H***); δ_C (125MHz; $CDCl_3$) 21.9 (***C***H_3-9), 71.5 (***C***$_2H_4$-10,11), 75.3 (***C***H_2-121), 106.0 (***C***$_2H_2$-2,6), 112.1 (***C***H_2-8), 127.5, 127.8, 127.9, 128.2, 128.5, 128.6, 137.0, 137.2 (***Ph***$_3C_3H_6O_3$Ph), 137.9 (***C***H-7), 139.4 (***C***-1), 143.0 (***C***-4), 152.5 (***C***$_2$-3,5); *m/z* found for $[M+H]^+$: 437.2112; $[C_{30}H_{28}O_3+H]^+$ requires: 437.2111.

3.3.1 3-(3,4,5-tris(Benzyloxy)phenyl)ethanol (97)

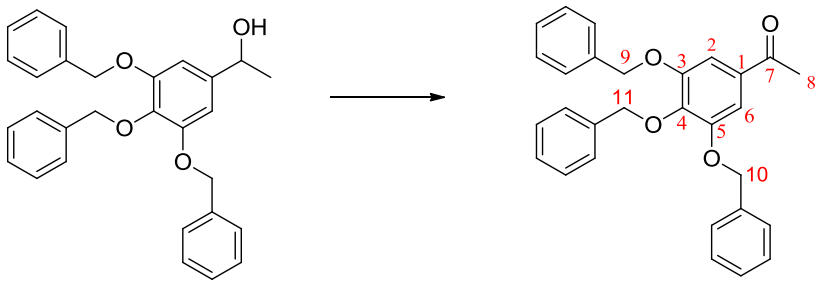


3,4,5-Tris-benzyloxybenzaldehyde (1 g, 2.35 mmol) was dissolved in diethylether (30 mL) and the solution was cooled to 0 °C. Methylmagnesium bromide (3.0M in diethyl ether, 2.4 mL, 3 equiv.) was cautiously added to the solution under a nitrogen atmosphere. The reaction was allowed to reach room temperature, and left to stir for 3h. The reaction was quenched

using a solution of NH_4Cl (10 mL). The excess of the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (3×20 mL), washed with diluted aqueous HCl (1M, 1mL), and dried over Mg_2SO_4. The resulting compound was triturated with petroleum ether to allow precipitation of a colourless solid. Filtration followed by a light petroleum wash and air drying gave compound **97** as a cottony solid (0.9 g, 87%).

mp 168-170 °C; ν_{max} (neat)/cm^{-1}, 3367, 3930, 2856, 1105, 936. δ_H (400 MHz; $CDCl_3$) 1.41 (d, 3 H, *J* = 6.4 Hz, C***H***$_3$-8), 1.96 (s, 1 H, O***H***-7), 4.75 (q, 1 H, *J* = 6.4 Hz, C***H***-7), 5.03(s, 2 H, C***H***$_2$-11), 5.09 (s, 4 H, C_2***H***$_4$-9,10), 6.66 (s, 2 H, Ar***H***-2,6), 7.38 (m, 15 H, Ar***H***); δ_C (100 MHz; $CDCl_3$) 25.4 (***C***H_3-8), 70.6 (***C***H-7), 71.4 (***C***$_2H_4$-9,10), 75.4 (***C***H_2-11), 105.2 (***C***$_2H_2$-2,6), 127.6, 127.9, 128.1, 128.3, 128.7, 128.8, 137.3, 137.8 (***Ph***$_3C_3H_6O_3$Ph), 138.0 (***C***-1), 141.8 (***C***-4), 153.0 (***C***$_2$-3,5); *m/z* found for $[M+NH_4]^+$: 458.2325; $[C_{29}H_{28}O_4+NH_4]^+$ requires: 458.2326.

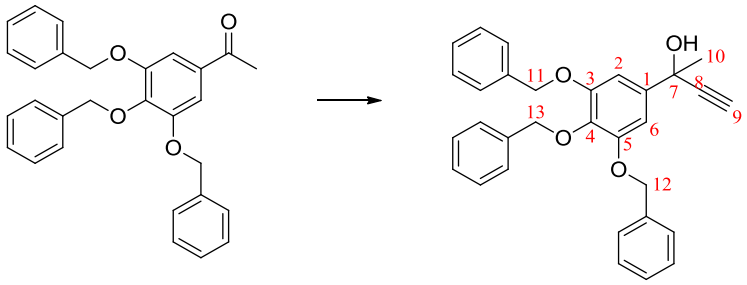
3.3.4 1-(3,4,5-tris(Benzyloxy)phenyl)ethanone (98)[12]



Pyridinium chlorochromate (3.0 g, 14 mmol) was dissolved in anhydrous dichloromethane at 0 °C under a nitrogen atmosphere. 3,4,5-Tris(benzyloxy)benzaldehyde (3.0 g, 6.8 mmol) was slowly added as a solution in anhydrous dichloromethane, the reaction mixture turned from orange to dark brown. The reaction mixture was allowed to reach room temperature, stirred for 7h, and followed by TLC (ethyl acetate/petroleum ether, 4/1, R*f* = 0.40) till complete consumption of the starting material. Diethyl ether (30 mL) was added to precipitate out the chromium salts and the solution was left stirring at 35 °C for 1 h. The reaction mixture was filtered through a pad of silica gel (middle) and celite (top, bottom). The solvents were removed under reduced pressure to give the desired compound as a colourless solid (2.7 g, 90%).

mp 167-168 °C; ν_{max} (neat)/cm^{-1} 2974, 1708, 1129, 817, 750 ; δ_H (400 MHz; $CDCl_3$) 2.34 (s, 3 H, C***H***$_3$-8), 4.98 (s, 4 H, C_2***H***$_4$-9,10), 5.00 (s, 2 H, C***H***$_2$-11, 2H), 7.10-7.29 (m, 17 H, Ar***H***); δ_C (100 MHz; $CDCl_3$) 26.7 (***C***H_3), 71.6 (***C***$_2H_6$-9,10), 75.4 (***C***H_2-11), 108.5 (***C***$_2H_2$-2,6), 127.8, 128.30, 128.36 , 128.5, 128.8, 128.9, 132.70, 136.9 (***Ph***$_3C_3H_6O_3$Ph), 137.6 (***C***-1) 143.1 (***C***-4), 152.9 (***C***$_2$-3,5), 197.1 (***C***O-7).

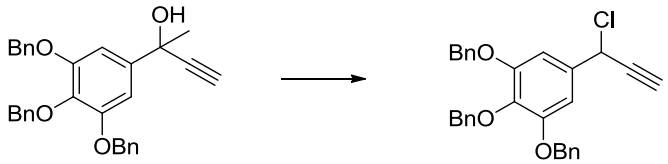
3.3.5 2-(3,4,5-tris(Benzyloxy)phenyl)but-3-yn-2-ol (99)



Compound **98** (580 mg, 1.3 mmol) was dissolved in a mixture of anhydrous tetrahydrofuran/diethylether and the solution was cooled to 0 °C. Ethynylmagnesium bromide (3.0M in tetrahydrofuran, 18.75 mL, 10 equiv.) was cautiously added to the solution. The reaction was allowed to reach room temperature, and left to stir for 2h. The reaction was quenched using a solution of NH_4Cl (5 mL). The solvents were removed under reduced pressure. Water was added and the mixture was extracted using dichloromethane (3×10 mL), and the combined organic layers washed with diluted aqueous HCl (1M, 1mL), dried over anhydrous Mg_2SO_4 and the solvents were removed under reduced pressure. The residue was purified using silica-gel column chromatography with ethyl acetate-petroleum ether (1:4) to give **99** as a yellow oil (0.33 g, 55%).

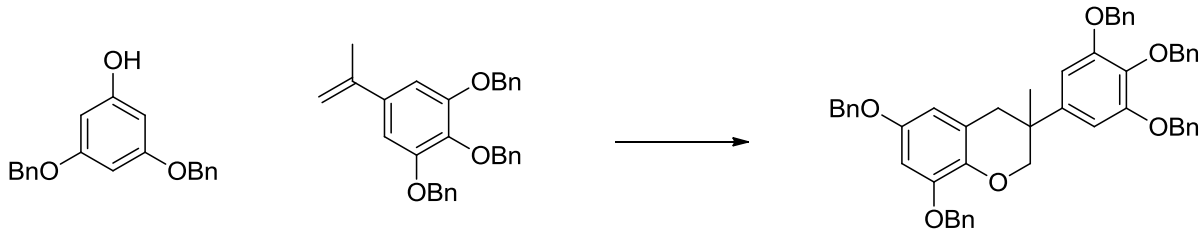
ν_{max} (neat)/cm^{-1} 3270, 2942, 2159, 1052, 986 δ_H (400 MHz; $CDCl_3$) 1.80 (s, 3 H, C***H***$_3$-10), 2.70 (s, 1 H, C***H***-9). 2.87 (s, 1 H, ***H***O-7), 5.14 (s, 2 H, C***H***$_2$-2), 5.17 (s, 4 H, C_2***H***$_4$-11,12), 7.07 (s, 2 H, Ar***H***-2,6), 7.26-7.52 (m, 15 H, Ar***H***); δ_C (100 MHz; $CDCl_3$) 33.5 (***C***H_3-10), 70.1 (***C***-7), 71.5 (***C***$_2H_4$-11,12), 73.5 (***C***H_2-13), 75.5 (***C***-9), 87.5 (***C***-8), 105.2 (***C***$_2H_2$-2,6), 127.9, 128.1, 128.2, 128.4, 128.5, 128.8, 128.9, 137.4 (***Ph***$_3C_3H_6O_3$Ph), 138.2 (***C***-1) 141.1 (***C***-4), 152.8 (***C***$_2$-3,5).

3.3.6 General procedure for chlorination or bromination



Hydrochloric acid (37% w/w, 1.1 equiv.), cuprous chloride (10 mol%), copper powder (10 mol%) were added to a 2L three neck flask at 0 °C; the reaction mixture was then purged with argon for 10 minutes. A solution of propargyl **24** alcohol (1 equiv.) in cold dichloromethane was added and the reaction was left to stir for 1 hour at 0 – 5 °C. The organic layer was separated, washed with cold water (3x30 mL), and a solution of $NaHCO_3$ (20 mL) and dried on magnesium sulfate.

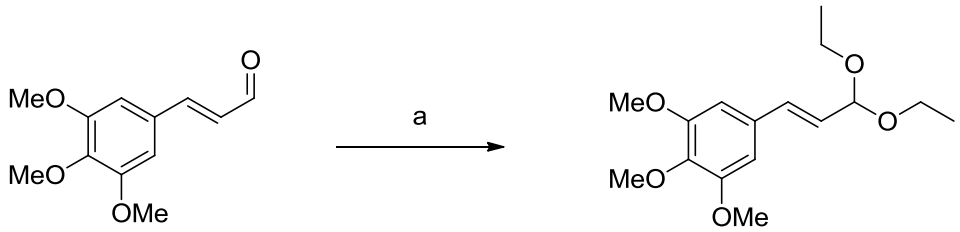
3.3.7 General procedure for the Hetero-Diels–Alder reaction



19 **87** **90**

Phenol **19** (1.3 equiv.) and formaldehyde (3 equiv.) were placed into an oven-dried flask, equipped with a stirrer bar under argon in acetic acid (1 mL). A solution of substituted alkene **87** in acetic acid (1 mL) was added. The mixture was stirred for 3 h at 100 °C. The reaction mixture was dissolved in ethyl acetate (3 mL) and neutralized with an aqueous solution of NaOH (2N). The upper organic phase was separated, and the bottom aqueous phase was extracted twice with ethyl acetate (2 mL). All organic phases were then combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The reaction mixture was then filtered and concentrated under reduced pressure, the crude oil was purified by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate.

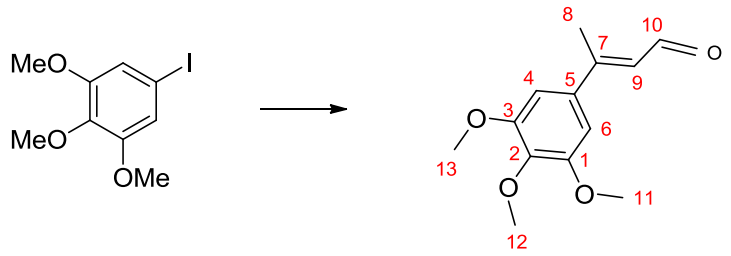
3.3.8 General procedure for acetalisation



42

The aldehyde **113** (1 equiv.) was dissolved in anhydrous ethanol (4 mL). Solid ammonium nitrate (0.25 equiv.) and triethylorthoformate (1.1 equiv.) were added directly to the solution. The solution was allowed to stir under a nitrogen atmosphere at room temperature for 24 h. The mixture was then quenched with saturated aqueous sodium hydrogen carbonate (4 mL). The acetal product was extracted three times using dichloromethane (10 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, and the organic solvents removed under reduced pressure. The reaction mixture was then filtered and concentrated under reduced pressure, the crude was purified by column chromatography, eluting with petroleum ether and ethyl acetate.

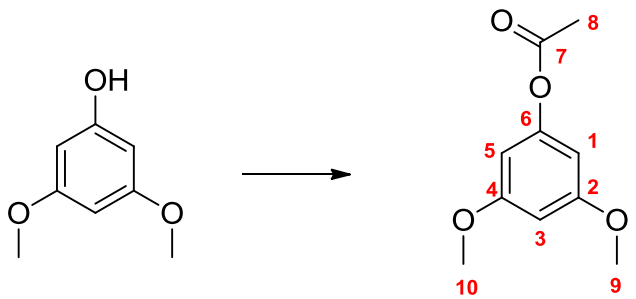
3.3.9 (*E*)-1,2,3-trimethoxy-5-(penta-2,4-dien-2-yl)benzene (113)



5-Iodo-1,2,3-trimethoxybenzene (120 mg, 0.4 mmol), AgOAc (136 mg, 0.81 mmol), and $Pd(OAc)_2$ (5 mol%) were dissolved in anhydrous acetonitrile in an oven-dried flask. The mixture was then purged with nitrogen for 10 min. Crotonaldehyde (0.04 mL, 0.48 mmol) was then added. The reaction temperature was stirred at 100 °C for 19 h. The reaction mixture was allowed to reach room temperature and the solvents were removed under reduced pressure. The residue was suspended in dichloromethane and the suspension was then filtered through a short pad of celite followed by several rinses using dichloromethane. The solution was then washed with water (3x10 mL), brine (10 mL), dried and the solvents removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (toluene/ethyl acetate, 3:1) to yield the desired compound as a pale yellow oil (42 mg, 44%).

ν_{max} (neat)/cm^{-1}3034, 2943, 1730, 1665, 1213, 732; δH (400 MHz, $CDCl_3$): 2.49 (d, 3 H, J = 1.2 Hz, C***H***$_3$-8), 3.82 (s, 3 H, C***H***$_3$-12), 3.83 (s, 6 H, C_2***H***$_6$-11-13), 6.30 (dq, 1 H, J = 7.9, 1.2 Hz, C***H***-9), 6.69 (s, 2 H, Ar***H***-4-6), 10.10 (d, 1 H, J = 7.9 Hz, CO***H***-10); δ_C (100 MHz, $CDCl_3$): 16.5 (***C***H_3-8), 56.4 (***C***$_2H_6$-11,13), 60.8 (***C***H_3-12), 103.8 (***C***$_2H_2$-4,6), 126.9 (***C***H-5), 136.1 (***C***H-9), 140.0 (***C***H-7), 153.5 (***C***-2), 157.5 (***C***-1,3) 191.2 (***C***O-10); *m/z* found for $[M+H]^+$: 237.1115; $[C_{13}H_{16}O_4+H]^+$ requires: 237.1121.

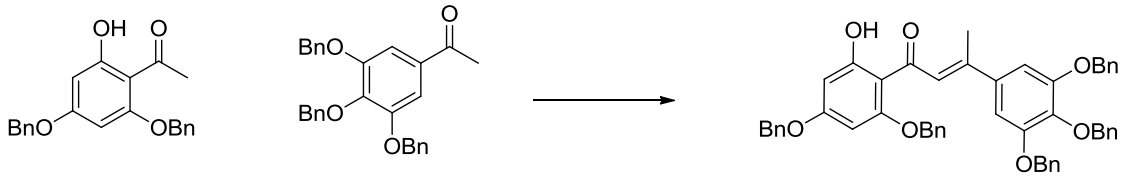
3,3.10 -dimethoxyphenyl acetate (125)[13]



Compound **113** (200 mg, 0.74 mmol) and 3,5-dimethoxyphenol (25 mg, 0.62 mmol) were dissolved in freshly distilled toluene in an oven-dried 50-mL flask fitted with a Dean-Stark apparatus. Phenylboronic acid (75 mg, 0.62 mmol) and glacial acetic acid (1 mL) were then

added. The reaction mixture was heated at 130 °C under a nitrogen atmosphere for 24 h. After cooling, the reaction mixture was quenched by addition of a saturated solution of $NaHCO_3$ (30 mL). The aqueous layers were extracted with ethyl acetate (3x10 mL) and the combined organic layers were washed with saturated NaCl (10 mL), dried over anhydrous $MgSO_4$ and the solvents were removed under reduced pressure. The residue was purified through column chromatography on silica gel (ether petroleum/ethyl acetate, 7:1), to give 8 as a yellow solid (28 mg, 90%); ν_{max} (neat)/cm^{-1}2943, 1707, 1151, 1026, 847; δH (400 MHz, $CDCl_3$): 2.20 (s, 3 H, C***H***$_3$-8), 3.70 (s, 6 H, C_2***H***$_6$-12), 6.19 (d, 2 H, *J* = 2.2 Hz, Ar***H***-5,1), 6.27 (t, 1 H, *J* = 2.2 Hz, Ar***H***-3), δ_C (100 MHz, $CDCl_3$): 20.1 (***C***H_3-8), 54.4 (***C***$_2H_6$-10,9), 97.2 (***C***H-3), 99.2 (***C***$_2H_2$-5,1), 151.2 (***C***-6), 160.1 (***C***-4,2), 168.3 (***C***O-7).

3,3.11 General procedure for Aldol reaction

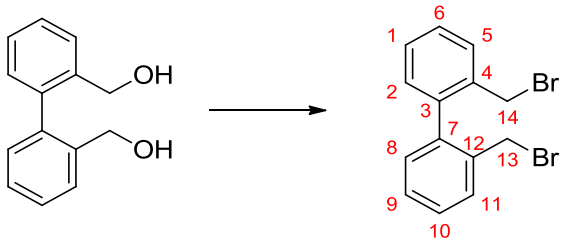


43 **98** **127**

LDA (1.1 equiv.) was added to a solution of **52** (1.1 equiv.) in anhydrous tetrahydrofuran at −78 °C over 15 min. The mixture was stirred for 30 min. A solution of **23** (1 equiv.) in anhydrous tetrahydrofuran at −78°C was added via cannula, over 10 minutes. The resulting solution was stirred at −78 °C for 1h and quenched by addition aqueous NH_4Cl (20 mL). The reaction mixture was extracted with diethyl ether (2 x 30 mL) and dried over anhydrous $MgSO_4$. After the solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 4:1).

3.4 Experimental procedures related to synthesis of iminium-salt catalyst

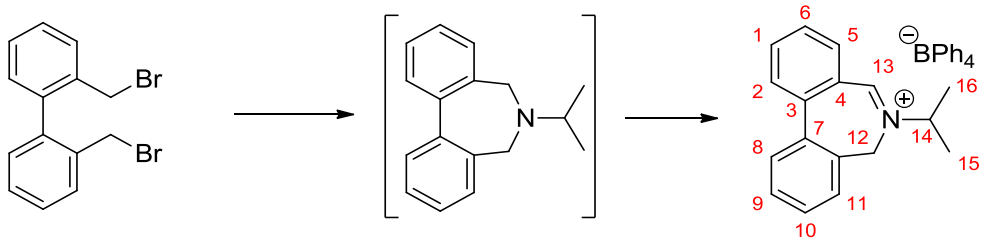
3.4.1 2,2'-bis(bromomethyl)-1,1'-biphenyl (50) [14]



2,2'-Biphenyldimethanol **49** (1 g, 4.67 mmol) was added to diluted HBr (48%, 25 mL) and the mixture heated under reflux until complete consumption of the starting material was observed by TLC. The reaction was allowed to cool to ambient temperature and diethyl ether (50 mL) added. The organic layer was washed with saturated brine (3 x 30 mL), saturated aqueous $NaHCO_3$ (3 x 30 mL), and water (3 x 30 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the desired product as colourless crystals (1.42 g, 90%).

mp 91-93 °C; ν_{max} (neat)/cm^{-1} 2940, 1673, 1427, 1673, 821, 612; δ_H (500 MHz; $CDCl_3$) 4.20 (d, 2H, *J* = 10.1 Hz, C***H***HBr-13,14), 4.36 (d, 2H, *J* = 10.1 Hz, CH***H***Br-13,14), 7.38 (dd, 2H, *J* = 7.5, 5.5 Hz, Ar***H***-6,10), 7.44-7.52 (m, 4H, Ar***H***-2,5,8,11), 7.64 (dd, 2H, *J* = 7.5, 5.5 Hz, Ar***H***-1,9). δ_c (125 MHz; $CDCl_3$) 32.1 (***C***$_2$$H_4$-13,14), 128.4, 128.8, 130.2, 130.8 (***Ar***H-1,2,6,5,8,9,10,11), 135.9 (***C***$_2$-3,7) 139.5 (***C***$_2$-4,12).

3.4.2 6-Isopropyl-5H-dibenzo[c,e]azepin-6-ium tetraphenylborate (52)

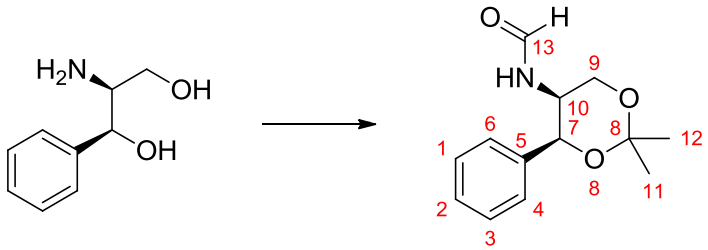


50 **51**

2,2'-bis-Bromomethylbiphenyl **50** (1.25 g, 3.67 mmol) and K_2CO_3 (1.52 g, 11 mmol) were added to stirred solution of isopropylamine (0.215 g, 0.311 ml, 3.67 mmol) in anhydrous acetonitrile (25 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was heated under reflux for 16 h. The solvent was removed under reduced pressure and the resulting residue dissolved in ethyl acetate (50 mL). The combined organic layers were washed with water (3 x 30 mL), and saturated brine (3 x 30 mL), and dried over anhydrous

$MgSO_4$. The solvents were removed under reduced pressure to yield the azepine in good purity as yellow foam **51**. N-Bromosuccinimide (0.9 g, 5.056mmol) was added to a stirred solution of azepine **51** (1 g, 4.213 mmol) in chloroform (10 mL) at ambient temperature. The reaction was monitored by TLC and once complete consumption of the azepine was observed, typically 15 min, the solvent was removed under reduced pressure to yield the iminium bromide salt intermediate. The salt was dissolved in ethanol (5 mL) and sodium tetraphenylborate (1.44 g, 4.213 mmol) was added in a minimal volume of acetonitrile. The reaction was allowed to stir at room temperature for 20 min. The solvents were removed under reduced pressure and dissolved in chloroform (25 mL). The combined organic layers were washed with water (3 x 10 mL), and saturated brine (3 x 10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resultant residue was recrystallized from ethanol to yield iminium salt catalyst **52** as a yellow powder (1.42 g, 90%), mp 131-134 °C; δ_H (400 MHz; DMSO-D_6) 1.41 (d, 6H, *J*=2.8 Hz, C_2***H***$_6$-15,16), 4.35 (s, 1H, C***H***H-12), 4.56 (sep, 2H, *J* = 2.8 Hz, C***H***-14), 5.12 (s, CH***H***-12), 6.76-7.18 (m, 20H, Ar***H***),7.60-8.05 (m, 8H, Ar***H***-1,2,5,6,8,9,10,11), 9.35 (s, 1H, N C***H***-13); δ_c (100 MHz; DMSO-D_6) 23.1 (***C***$_2$H$_6$-15,16), 52.61 (***C***H-14), 65.91 (***C***H_2-12), 119.1, 120.8, 122.1, 124.5 126.0, 128.9, 129.2, 129.8, 130.3, 130.7, 134.3, 134.8, 136.1, 137.5,141.1, 164.7 (***Ar***H), 167.6 (***C***H-13); *m/z* found for the iminium cation: 230.1430; $[C_{17}H_{18}N]^+$ requires 230.1430.

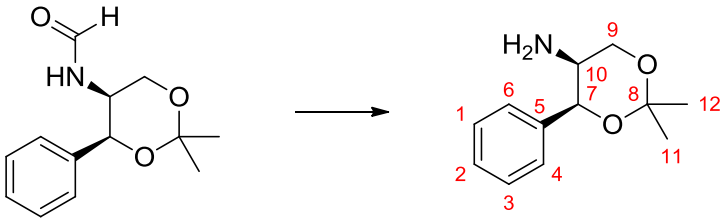
3.4.3 (*5S,6S*)-*N*-formyl-5-amino-6-phenyl-2,2-dimethyl-1,3-dioxane (75) [15]



Methyl formate (0.3 ml, 4.48 mmol) and sodium methoxide (0.016 ml, 0.30 mmol) were added to a solution of (1*S*,2*S*)–(+)–2-amino-1-phenyl-1,3-propanediol (0.5 g, 2.99 mmol), in anhydrous methanol. After 24h, the resulting solution was evaporated under reduced pressure to afford the formyl-protected amine (**74**) as a yellow oil. The oil was dissolved in acetone and camphorsulfonic acid (0.10 g, 0.45 mmol) and 2,2-dimethoxypropane (3.7 ml, 9.90 mmol) were added. The reaction mixture was again heated to reflux overnight. The reaction was allowed to reach room temperature and the solvents removed under reduced pressure to yield **75** as a yellow oil (0.54 g, 77%).

δ_H (500 MHz; $CDCl_3$), 1.48 (s, 3H, C***H***$_3$-12,), 1.52 (s, 3H, C***H***$_3$-11), 3.79 (dd, 1H, *J* = 10.5, 1.6 Hz, C***H***H-9) 4.17 (dd, 1H, *J* = 10.5, 1.6 Hz, CH***H***-9), 4.21 (d, 1H, *J* = 1.6 Hz, C***H***-10), 5.15 (s, 1H, C***H***-7), 6.48 (s, 1H, N***H***), 7.14- 7.27 (m, 5H, Ar***H***), 7.89 (s, 1H, C***H***-13). δ_c (125 MHz, $CDCl_3$) 17.5 (s, ***C***H_3-12), 28.7 (s, ***C***H_3-11), 44.4 (s, ***C***H-10), 63.6 (s, ***C***H-9), 70.6 (s, ***C***H-7), 98.9 (***C***-8), 124.2, 125.5, 126.6, 137.0, (***Ar***H-1,2,3,4,5,6), 159.5 (***C***=O-13).

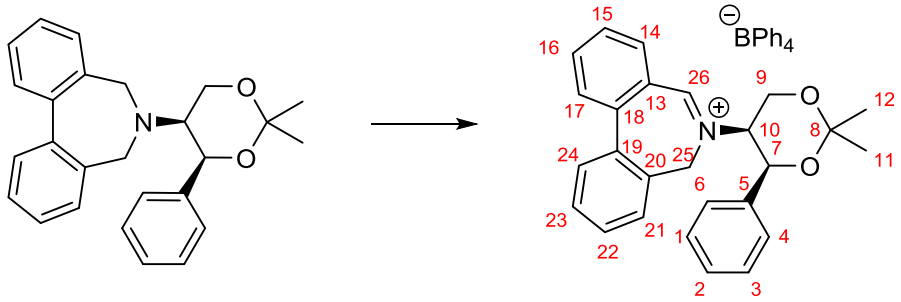
3.4.4 (*5S,6S*)-5-Amino-5-amino-6-phenyl-2,2-dimethyl-1,3-dioxane (76) [15]



The compound **75** (0.43 g, 1.827 mmol) was dissolved in aqueous hydrazine monohydrate (85%, 7 mL) and the mixture heated under reflux for 2 h. The reaction mixture was extracted with ethyl acetate (3x 10), and the combined organic layers were washed with water (2 x 20 mL) and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure to give the desired amine **76** as a yellow oil (0.33 g, 89%).

$[\alpha]^{20}_D$ +40.5 (c = 2.33, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3411, 2984, 1421, 1264, 896; δ_H (500 MHz; $CDCl_3$) 1.35 (s, 3H, C***H***$_3$-12,), 1.38 (s, 3H, C***H***$_3$-11), 2.53 (d, 1H, *J* = 1.3 Hz, C***H***-10), 3.69 (dd, 1H, *J* = 11.6, 1.3 Hz, C***H***H-9), 4.06 (dd, 1H, *J* = 11.6, 1.3 Hz, C***H***H-9), 4.89 (s, 1H, C***H***-7), 6.92- 7.43 (m, 5H, Ar***H***). δ_c (125 MHz, $CDCl_3$) 18.5 (***C***H_3-12), 29.9 (***C***H_3-11), 49.4 (***C***H-10), 65.8 (***C***H_2-9), 73.5 (***C***H-7), 98.8 (***C***-8), 125.5, 126.2, 127.1, 128.2 (***Ar***H-1,2,3,4,5,6).

3.4.5 (-)-6-[(*4S,5S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenzo[c,e]azepinium tetraphenylborate[16]



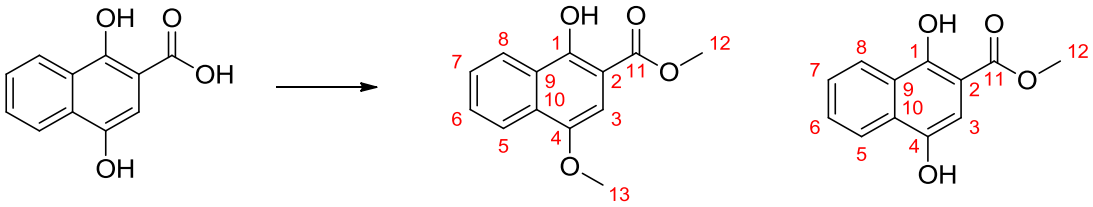
2,2'-bis(Bromomethyl)biphenyl **50** (0.32 g, 0.94 mmol) and (*5S,6S*)-5-Amino-5-amino-6-phenyl-2,2-dimethyl-1,3-dioxane **76** (0.19 g, 0.94 mmol) were dissolved in acetonitrile (21 mL). The mixture was stirred under a nitrogen atmosphere and Cs_2CO_3 (0.61 g, 1.88 mmol)

was added at room temperature. The reaction was submitted to reflux for 24 h, cooled, diluted with dichloromethane (30 mL), the resulting suspension was filtered into a separating funnel to remove Cs_2CO_3. The mixture was extracted with water (2x 50 mL), brine (2x 50 mL). The organic phase was separated, dried over $MgSO_4$ and the solvents were then removed under reduced pressure to give **77**. Amine **77** (0.51 g, 1.32) was then dissolved in anhydrous dichloromethane (10 mL), to which *N*-bromosuccinimide (0.25 g, 1.45 mmol) was added, and left to stir for 6 h. the solvent was removed under reduced pressure, and the remaining solid was re-dissolved in ethanol (5 mL). Sodium tetraphenylborate (0.5 g, 1.45 mmol) was dissolved in a minimum amount of acetonitrile and added to the stirring solution at room temperature. After 10 minutes, the reaction was stopped and excess organic solvents removed under reduced pressure. The resulting foam was then recrystallized from ethanol. The yellow solid was filtered off and washed with cold ethanol followed by petroleum ether affording **78** (0.33 g, 89%).

$[\alpha]^{20}_D$ -44.3 (c = 1.05, CH_3CN); ν_{max} (neat)/cm^{-1} 3411, 2984, 1421, 1264, 896; δ_H (500 MHz; Acetone-D^6) 1.79 (s, 3H, C***H***$_3$-12,), 1.83 (s, 3H, C***H***$_3$-11), 4.41 (d, 1H, *J* = 11.3 Hz, C***H***H-9), 4.73-4.70 (m, 1H, C***H***-10), 4.51 (d, 1H, *J* = 11.3 Hz, C***H***H-9),) 4.70-4.73 (m, 1H, C***H***-10), 4.80 (d, 1H, *J* = 12.1 Hz, C***H***H-25), 4.84 (d, 1H, *J* = 12.1 Hz, C***H***H-25), 5.96 (d, 1H, *J* = 2.6 Hz, C***H***-7), 6.75 (t, 4H, *J* = 7.3 Hz, Ar***H***), 6.90 (t, 8H, *J* = 7.3 Hz, Ar***H***), 7.20-7.25 (m, 8H, Ar***H***), 7.28-7.32 (m, 8H, Ar***H***), 7.42-7.53 (m, 4H, Ar***H***-14,15,21,22), 7.64-7.73 (m, 4H, Ar***H***-16,17,23,24), 8.01-8.11(m, 5H, Ar***H***-1,2,3,4,6), 9.09 (s, 1H, N*H*-26). δ_c (125 MHz, $CDCl_3$) 18.5 (***C***H_3-12), 28.7 (***C***H_3-11), 56.9 (***C***H_2-25), 61.4 (***C***H_2-9), 67.4 (***C***H-10), 71.8 (***C***H-7), 100.3 (***C***-8), 120.4, 124.1, 124.4, 124.5, 126.3, 126.4, 127.4, 127.9, 128.0, 128.2 128.4, 129.3, 129.4, 129.6**,** 132.6, 133.6, 135.0, 135.2, 142.5, 162.4 (***Ar***H), 170.98 (*C*H-26).

3.5 Experimental procedures related to synthesis of Synthesis of (*3S,4R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin 129

3.5.1 Methyl 1-hydroxy-4-methoxy-2-naphthoate (143) [17]



1,4-Dihydroxy-2-naphthoic acid (1.1 g, 5.38) was dissolved in methanol (12 ml) in a flask equipped with a stirring bar, and dilute aqueous H_2SO_4 (1M, 5mL)was then added slowly at 0 °C. The resulting brown solution was heated under reflux for 2 h. The reaction was quenched by the slow addition of water (6 ml). After removal of solvent, the mixture was dissolved in ethyl acetate (20 ml) and transferred to a separating funnel and washed with brine (10 ml). The organic layer was isolated and dried over anhydrous $MgSO_4$. The residue was purified through column chromatography (petroleum ether / ethyl acetate, 5:1), to give **143** as a white solid (1.12 g, 90%) and **141** as a yellow solid (58 mg, 5%)

Methyl 1-hydroxy-4-methoxy-2-naphthoate 143:

mp 130-132 °C; ν_{max} (neat)/cm^{-1} 3384, 2924, 1713, 1461, 846; δH (500 MHz, $CDCl_3$): 4.01 (s, 3 H, C***H***$_3$-12), 4.04 (s, 3 H, C***H***$_3$-13), 7. 14 (s, 1 H, C***H***-1), 7.60 (ddd, 1 H, *J* = 8.2, 6.9, 2.1 Hz, C***H***-6), 7.67 (ddd, 1 H, *J* = 8.2, 6.9, 2.1 Hz, C***H***-7), 8.23 (dd, 1 H, *J* = 8.2, 2.1 Hz, C***H***-8), 8.23 (dd, 1 H, *J* = 8.2, 2.1 Hz, C***H***-5), 11.65 (s, 1 H, O***H***-1); δ_C (125 MHz, $CDCl_3$): 52.3 (***C***H_3-12), 55.7 (***C***H_3-13), 100.4 (***C***H-3), 104.2 (***C***-2) 121.9, 123.8, 125.5, 126.4, 129.0, 129.8 (***Ar***H-5,6,7,8,9,10), 147.7 (***C***-1), 155.6 (***C***-4), 171.3 (***C***O-11).

Methyl 1,4-dihydroxy-2-naphthoate 141:

mp 151-153 °C; ν_{max} (neat)/cm^{-1} 3434, 2981, 1635, 1376, 929; δH (500 MHz, Acetone-D_6): 4.00 (s, 3 H, C***H***$_3$-12), 7.18 (s, 1 H, C***H***-1), 7.62 (t, 1 H, *J* = 7.6 Hz, C***H***-6), 7.67 (t, 1 H, *J* = 7.6 Hz, C***H***-7), 8.24 (d, 1 H, *J* = 8.3 Hz, C***H***-5), 8.36 (d, 1 H, *J* = 8.3 Hz, C***H***-8), 8.70 (s, 1 H, O***H***-4), 11.57 (s, 1 H, O***H***-1); δ_C (125 MHz, Acetone D_6): 52.8 (***C***H_3-12), 105.0 (***C***H-3), 105.6 (***C***-2) 123.1, 124.3, 126.3, 127.1, 129.5, 130.3 (***Ar***H-5,6,7,8,9,10), 145.8 (***C***-4), 155.1 (***C***-1), 172.0 (***C***O-11).

3.5.2 Methyl 1,4-dihydroxy-2-naphthoate 141:

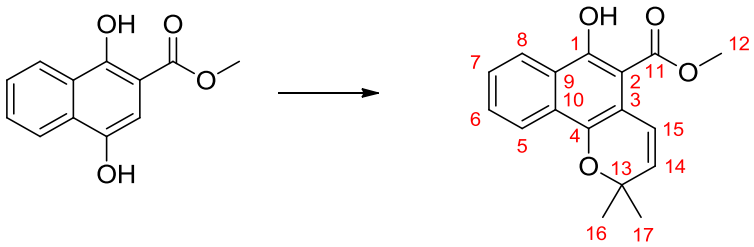
Method A

Compound **143** (0.43 g, 1.85 mmol) was suspended in anhydrous dichloromethane in an oven dried flask under a nitrogen atmosphere. $AlCl_3$ (0.49 g, 3.70 mmol) was then added at 0 °C**.** The mixture was stirred for 2h at 0 °C. The reaction was then quenched by slow addition of water (2 ml), followed by dilute aqueous HCl (1M, 1mL). The title compound was extracted from the aqueous layer with dichloromethane (3×10 ml). The combined organic layers were washed with brine (2×10 ml) and dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure to yield brown crude mixture. The mixture was purified through column chromatography (petroleum ether / ethyl acetate, 3:1), to give **141** as a yellow solid (0.36 g, 91%)

Method B

4-Dihydroxy-2-naphthoic acid (0.20 g, 0.9 mmol) and anhydrous $NaHCO_3$ (0.10 g, 1.1 mmol) were suspended in anhydrous dimethylformamide and the suspension was stirred for 30 minutes under a nitrogen atmosphere at room temperature. Methyl iodide (0.20 g, 0.09 ml, 1.4 mmol) was transferred using a syringe. The reaction was allowed to stir for 22 hours until all the starting material was consumed. The reaction was quenched with saturated brine (10 mL), dilute aqueous HCl (1M, 6mL). The reaction mixture was extracted with diethyl ether (30 ml × 3) and the organic phases were dried over anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. The residue was purified using flash column chromatography (petroleum ether / ethyl acetate, 4:1), to give **141** as a yellow solid (0.21 g, 96%).

3.5.3 Mollugin (128) [18]

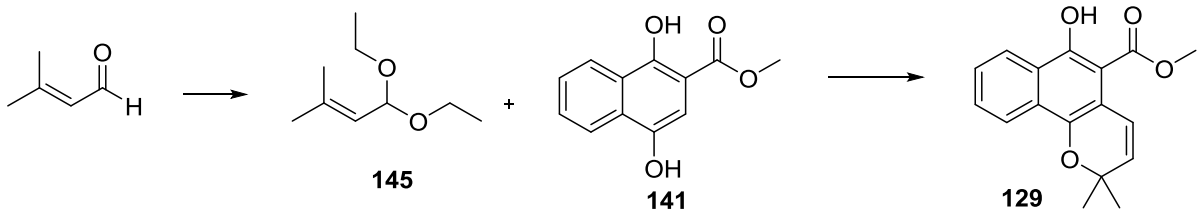


Method A

Phenylboronic acid (0.25g, 2.00 mmol) was added to a solution of methyl 1,4-dihydroxy-2-naphthoate (0.45g, 2.00 mmol) in toluene. Glacial acetic acid (3 mL) was added to the reaction mixture by syringe, and followed by a dropwise addition of 3-methyl-2-butenal (0.30 ml, 3.00 mmol). The reaction was heated under reflux with a Dean-Stark trap under a nitrogen atmosphere for 18 h. After cooling, the reaction mixture was quenched by addition of sodium bicarbonate (30 mL). The aqueous layers were extracted with ethyl acetate (30 ml × 3) and washed with brine (10 mL); the combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a brown solid. The residue was purified through column chromatography (petroleum ether / ethyl acetate, 11:1), to give **129** as a yellow solid (0.31 g, 56%).

mp 176-178 °C; ν_{max} (neat)/cm^{-1} 3435, 2986, 2305, 1712, 1264, 896; δH (500 MHz, $CDCl_3$): 1.45 (s, 6 H, C_2***H***$_6$-16,17), 3.91 (s, 3 H, C***H***$_3$-12), 5.59 (dd, 1 H, *J* = 10.0 Hz, C***H***-15), 7.03 (dd, 1 H, *J* = 10.0 Hz, C***H***-14), 7.41-7,45 (m, 1 H, C***H***-6), 7.51-7,54 (m, 1 H, C***H***-7), 8.09 (d, 1 H, *J* = 8.3 Hz, C***H***-8), 8.29 (d, 1 H, *J* = 8.3 Hz, C***H***-5), 12.10 (s, 1 H, O***H***-1); δ_C (125 MHz, $CDCl_3$): 26.87 (***C***$_3$H$_6$-16,17), 52.3 (***C***H$_3$-12), 74.5 (***C***-13), 102.2 (***C***-3), 112.5 (***C***-2), 121.9 (***C***H-15), 122.3, 124.0, 125.0, 126.3, 128.8, 129.0 (***Ar***H-5,6,7,8,9,10), 129.3 (***C***H-14), 141.5 (***C***-1), 156.5 (***C***-5), 172.53 (***C***O-11).

Method B

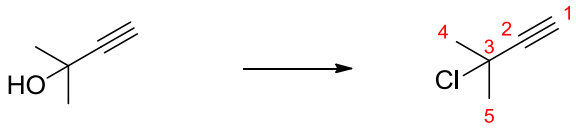


3-Methyl-2-butenal (1 ml, 10.3 mmol) was dissolved in anhydrous ethanol under an argon atmosphere. Solid ammonium nitrate (0.2 g, 2.5 mmol) and triethylorthoformate (2 ml, 12.36 mmol) were added directly to the solution at 0 ºC, which turned to a brown colour after 3 h.

The reaction mixture was allowed to stir under an argon atmosphere for 24 h. The reaction was filtered through a pad of celite and anhydrous Na_2SO_4, and the pad was washed through with diethyl ether. The solvents were removed under reduced pressure at 0 ºC to yield the compound **145** as brown oil (0.78 ml, 48%). The acetal **145** was used directly after preparation without further purification due to the instability of the acetal on silica. The required diethyl acetal (0.55 ml, 6.6 mmol) and methyl 1,4-dihydroxy-2-naphthoate **141** (1.43 g, 6.6 mmol) were dissolved in *p*-xylene (10 ml). The mixture was stirred under a nitrogen atmosphere for 20 min. 3-Picoline (0.16 ml, 1.65 mmol) was then added and the reaction was heated under reflux for 24h. During the reflux, the solution turned black. The solution was then allowed to reach room temperature. The mixture was dissolved in diethyl ether and washed with water. The organic layer was separated and charcoal was added. The mixture was filtered through a pad of celite to afford an oily residue. The crude residue was purified by column chromatography on silica gel (petroleum ether / ethyl acetate, 13:1), to give **129** as yellow solid (1.2 g, 56%).

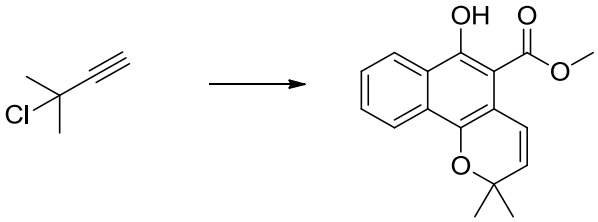
Method C

3.5.4 3-Chloro-3-methylbut-1-yne (150) [19]



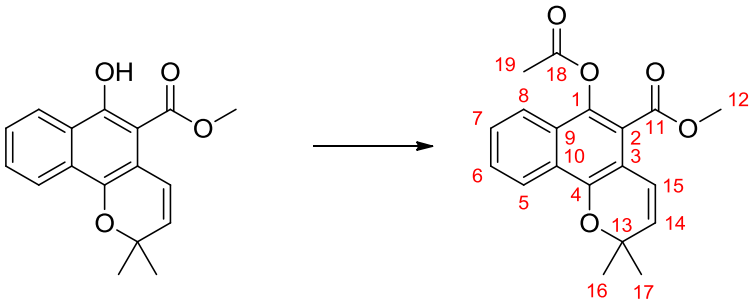
Calcium chloride (23.0 g, 209 mmol), cuprous chloride (20.0 g, 204 mmol) and copper powder (0.4 g, 6.67 mmol) were charged in a flask and cold HCl (37%, 250 mL) was added. The dark green solution was placed under an argon atmosphere and stirred at 0 °C for 5 min. While maintaining the reaction between 0 - 5 °C, 2-methyl-3-butyn-2-ol (65.0 mL, 667 mmol) was added slowly to the acidic solution. After complete addition of the alcohol, the reaction was stirred at 0 °C for 1 h. The biphasic reaction mixture was transferred to a separating funnel and the aqueous layer was removed. The remaining organic layer was then washed with dilute aqueous HCl (1M, 3 x 150 mL), cold water (2 x 150 mL) and saturated aqueous $NaHCO_3$ (150 mL). The remaining cloudy organic fraction was dried over anhydrous $MgSO_4$ and filtered to yield the compound as a clear colourless liquid (12.7 g, 56 %),; δ_H (500 MHz, $CDCl_3$): 1.86 (s, 6H, $C_2\boldsymbol{H}_6$-5,4), 2.63 (s, 1H, C***H***-1), δ_C (125 MHz, $CDCl_3$): 34.51 ($\boldsymbol{C}_2H_6$-5,4), 56.51 (***C***-3), 71.91 (***C***-2), 86.49 (***C***-1).

Mollugin (128)



Methyl 1,4-dihydroxy-2-naphthoate (0.53 g, 2.43 mmol), cuprous chloride (0.24 g, 2.43 mmol) and fine copper powder (7.7 mg, 0.12 mmol) were placed in a flame-dried flask, under a nitrogen atmosphere equipped with a condenser. Anhydrous toluene and K_2CO_3 (0.67 g, 4.86 mmol) were then added. The mixture was stirred vigorously and 3-chloro-3-methyl-but-1-yne (0.7 g, 7.38 mmol) was slowly added in one portion. The reaction was heated under reflux until the starting material was consumed by TLC (24h). The reaction was allowed to reach room temperature, and water (10 ml) was added. The solution was extracted with diethyl ether (3 × 15 ml). The ethereal layer was isolated and washed with saturated aqueous $NaHCO_3$ (10 ml) and brine (5 ml). The organic layer was dried over anhydrous $MgSO_4$ and removed under reduced pressure to yield yellow oil. The oil was purified by column chromatography on silica gel (petroleum ether / ethyl acetate, 9:1) to furnish **129** as a yellow powder (0.56 g, 81 %).

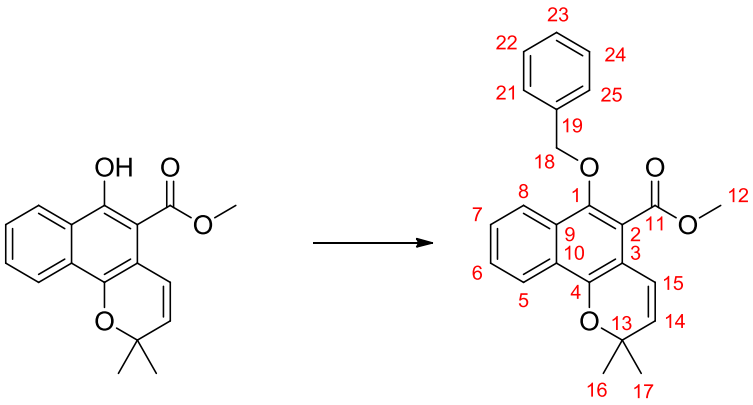
3.5.5 Methyl 6-acetoxy-2,2-dimethyl-2H-benzo[h]chromene-5-carboxylate (157)



Mollugin **129** (0.66 g, 2.3 mmol) was dissolved in anhydrous dichloromethane at room temperature. Acetic acid anhydride (4.16 ml, 44 mmol) and pyridine (3.5 ml, 44 mmol) were then added. The reaction was then allowed to stir overnight under an argon atmosphere. The reaction was quenched with a large amount of water and extracted with diethyl ether (3 x 50 mL). The organic phases were separated, combined, dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The residue was purified using flash column chromatography on silica gel (toluene / ethyl acetate, 10:1), to give **157** as a yellow oil (0.71 g, 95%).

ν_{max} (neat)/cm^{-1} 2952, 1976, 1759, 1338, 793; δH (400 MHz, $CDCl_3$): 1.43 (s, 6H, C_2***H***$_6$-16,17), 2.31 (s, 3H, C***H***$_3$-19), 3.84 (s, 3H, C***H***$_3$-12), 5.60 (d, 1H, *J* = 10.0 Hz, C***H***-15), 6.52 (d, 1H, *J* = 10.0 Hz, C***H***-14), 7.36-7.47 (m, 2H, Ar***H***$_2$-6,7), 7.36-7.47 (m, 1H, Ar***H***-8), 8.11-8.14 (m, 1H, Ar***H***-5); δ_C (100 MHz, $CDCl_3$): 20.6 (***C***H$_3$-19), 27.7 (***C***$_3$H$_6$-16,17), 52.4 (***C***H$_3$-12), 77.4 (***C***-13), 119.4 (***C***-3), 120.11 (***C***-2), 122.1 (***C***H-15), 122.4, 126.7 126.9, 127.3, 127.4, 129.7 (***Ar***H-5,6,7,8,9,10), 130.0 (***C***H-14), 139.0 (***C***-4), 146.8 (***C***-1), 166.1 (***C***O-18), 169.4 (***C***O-11); *m/z* found for $[M+NH_4]^+$: 344.1497; $[C_{19}H_{18}O_5+NH_4]^+$ requires 344.1492.

3.5.6 Methyl 6-(benzyloxy)-2,2-dimethyl-2H-benzo[h]chromene-5-carboxylate [20]

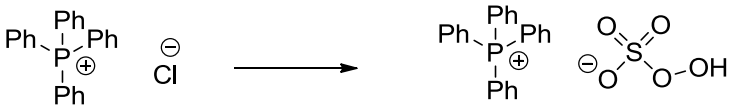


Mollugin (0.13 g, 0.45 mmol) and anhydrous K_2CO_3 (0.1 g, 0.7 mmol) were dissolved in dimethylformamide. Benzyl bromide (0.09 ml, 0.7 mmol) was then added. The resulting mixture was heated at 70 °C under a nitrogen atmosphere for 4 h. The reaction was then allowed to reach room temperature. Brine (10 mL) and dilute aqueous HCl (1M, 2 mL)were added and the solution was extracted with diethyl ether (2 x 50 ml). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether / ethyl acetate, 12:1) to give the compound **155** as a yellow solid (0.14 g, 86%).

mp 182-184 °C; ν_{max} (neat)/cm^{-1} 2952, 1765, 1718, 1133, 819; δH (400 MHz, $CDCl_3$): 1.42 (s, 6H, C_2***H***$_6$-16,17), 3.79 (s, 3H, C***H***$_3$-12), 5.01 (s, 2H, C***H***$_2$-18), 5.59 (d, 1H, *J* = 9.9 Hz, C***H***-15), 6.35 (d, 1H, *J* = 9.9 Hz, C***H***-14), 7.21-7.46 (m, 7H, Ar***H***$_7$-6,7,21,22,23,24,25), 7.94-8.00 (m, 1H, Ar***H***-8,), 8.07-8.17 (m, 1H, Ar***H***-5), δ_C (100 MHz, $CDCl_3$): 27.7 (***C***$_2$H$_6$-16,17), 52.4 (***C***H$_3$-12), 77.4 (***C***H$_2$-13), 77.8 (***C***H$_2$-18), 112.51 (***C***-3), 119.91 (***C***-2), 121.00 (***C***H-15), 122.5, 122.7, 127.8, 128.11, 128.18, 128.5, 126.81, 126.88, 126.90, 137.42 (***Ar***H), 130.29 (***C***H-14), 145.15 (***C***-4), 146.36 (***C***-1), 167.79 (***C***O-11).

3.5.7 Experimental procedures related to epoxidation reaction

3.5.7.1 Tetraphenylphosphonium monoperoxysulfate [21]



Oxone$^{(R)}$ triple salt ($2KHSO_5:KHSO_4:K_2SO_4$) (15 g, 48.8 mmol) was dissolved in cold deionised water (300 mL) at 10 °C. A solution of tetraphenylphosphonium chloride (15 g, 40.0 mmol) dissolved in cold dichloromethane (300 mL) was added. The biphasic mixture was left to stir for 30 min. The organic layer was separated and the organic phase was washed with deionised water. The organic layer was dried anhydrous $MgSO_4$ and filtered. Light petroleum was added until cloudiness developed, and the resulting solution was left in the freezer at –20 °C for 24 hours. A white precipitate of salt was filtered and measured to be 94% pure in peroxide, (12.87 g, 71%): ^{1}H NMR (500 MHz,$CDCl_3$): δ_H = 7.65 (s, Ar***H***,8H), 7.78 (s, 8H, Ar***H***), 7.89 (s, 4H, Ar***H***,), 9.08 (s, ***H***O-SO_4^-, 1H).

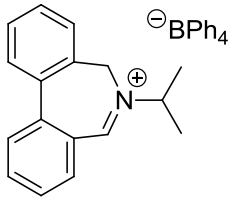
Purification of *meta*-Chloroperoxybenzoic acid

meta-Chloroperoxybenzoic acid was dissolved in diethyl ether at 0 °C. The organic layer was placed in separating funnel, washed with ice-cold water (2×10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduce pressure at 0 °C to yield a white solid.

3.5.7.2 General procedure for the formation of racemic epoxides with *m*-CPBA

meta-Chloroperoxybenzoic acid (1 equiv.) and $NaHCO_3$ (2 equiv.) were suspended in anhydrous dichloromethane at 0 °C. A solution of the desired alkene in dichloromethane was slowly added to the reaction mixture. The reaction was stirred until complete conversion of the alkene was observed by TLC. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ and the mixture transferred to a separating funnel. The organic layer was separated, washed with brine and saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure at room temperature. The residue was purified using column chromatography on silica gel typically eluting with light petroleum / ethyl acetate (10:1), buffered with 3% TEA.

3.5.7.3 General procedure for the formation of racemic epoxides with iminium salt 52.



52

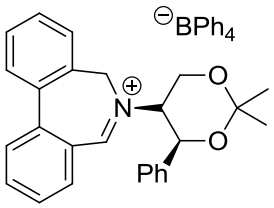
Method A

$NaHCO_3$ (4 equiv.) was dissolved to a mixture of acetonitrile/water (10:1) at 0 °C. Oxone™ (2 equiv.) was then added, followed by addition of the catalyst **52** (10 mol%) and the alkene (1 equiv.). The reaction was then left stirring, whilst being monitored by TLC. The reaction mixture was then diluted with diethyl ether and the resulting suspension filtered through a mixed pad of Na_2SO_3 and $MgSO_4$. The solvents were then removed and the residue was purified by column chromatography on silica gel, typically eluting with petroleum ether / ethyl acetate (10:1), buffered with 3% TEA.

Method B

Tetraphenylphosphonium monoperoxysulfate (2 equiv.) was added to a solution of the catalyst **52** (10 mol%) in anhydrous dichloromethane at −20 °C. After 5 min of stirring, the alkene (1 equiv.) dissolved in chloroform (1 mL) was slowly added. The mixture was stirred at −20 °C until complete conversion of the alkene was observed by TLC. The reaction mixture was then diluted with diethylether (10 mL) and the resulting suspension filtered through a mixed pad of Na_2SO_3 and $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel, typically eluting petroleum ether / ethyl acetate, buffered with 3% TEA.

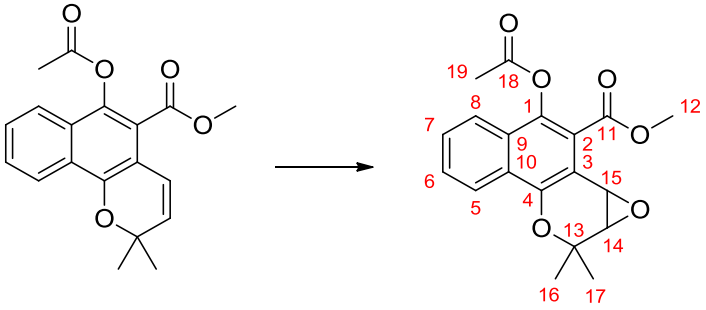
3.5.7.4 General procedure for the formation of chiral epoxides with iminium salt 78 under non-aqueous conditions.



78

The alkene (1 equiv.) was dissolved in chloroform and the resulting solution was allowed to cool down to the required temperature. Tetraphenylphosphonium monoperoxysulfate (2 equiv.) was added in one portion and the reaction mixture was stirred for 5 min. The catalyst **78** (10 mol%) was then added as a solid in small portions over 2 min. Consumption of the starting alkene was observed by TLC. The reaction mixture was allowed to reach 0 °C then was diluted with diethylether to precipitate out the excess Tetraphenylphosphonium monoperoxysulfate and the inorganic materials. The suspension was filtered through a thin pad of celite and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel, typically eluting with petroleum ether / ethyl acetate, buffered with 3% TEA.

3.5.8 Methyl-3-acetoxy-9,9-dimethyl-9,9a-dihydro-1aH-benzo[h]oxireno[2,3-c]chromene-2-carboxylate (158)

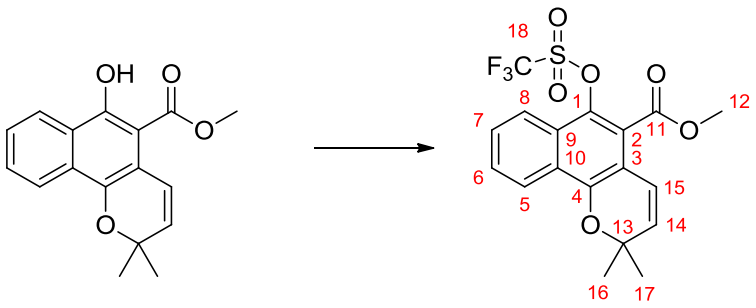


Oxone® (1.1 g, 1.8 mmol.), and $NaHCO_3$ (0.308 g, 3.7 mmol), were added to solution of alkene **157** (0.300 g, 0.9 mmol) in acetonitrile (1 mL) and water (0.1 mL).Catalyst **52** (0.05 g, 10 mol%) was then added at 0 °C. The crude product was purified using column chromatography on silica gel eluting with petroleum ether / ethyl acetate (12:1), buffered with 3% TEA, to yield the racemic epoxide **158** as a white solid (95 mg, 31%).

mp 147-150 °C; ν_{max} (neat)/cm^{-1} 2936, 1690, 1392, 1234, 779; δH (400 MHz, $CDCl_3$): 1.28 (s, 3H, C***H***$_3$-17), 1.64 (s, 3H, C***H***$_3$-16), 2.35 (s, 3H, C***H***$_3$-19), 3.50 (d, 1H, *J* = 4.5 Hz, C***H***-

14), 3.91 (s, 3H, C***H***$_3$-12), 4.26 (d, 1H, *J* = 4.5 Hz, C***H***-15), 7.45-7.56 (m, 2H, Ar***H***$_2$-6,7), 7.73-7.68 (m, 1H, Ar***H***-8), 8.11-8.17 (m, 1H, Ar***H***-5); δ_C (100 MHz, $CDCl_3$): 20.6 (***C***H_3-19), 25.5 (***C***$_3H_6$-16), 29.7 (***C***$_3H_6$-17), 48.2 (***C***H-14), 52.6 (***C***H_3-12), 62.8 (***C***H-15), 74.0 (***C***-13), 110.80 (***C***-3), 110.87 (***C***-2), 122.10, 122.14, 122.5, 127.3, 127.6, 128.0 (***Ar***H-5,6,7,8,9,10), 139.3 (***C***-4), 147.1 (***C***-1), 165.8 (***C***O-11), 169.3 (***C***O-11).

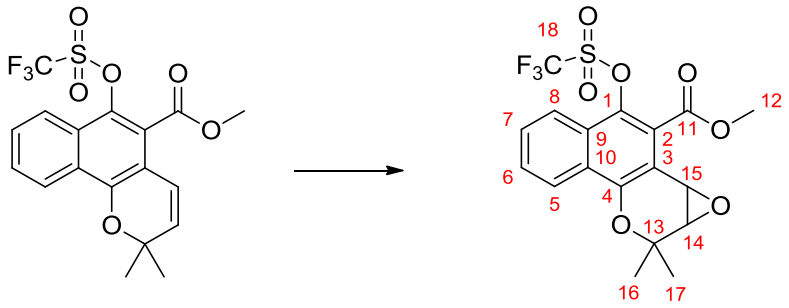
3.5.9 Methyl 2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-2H-benzo[h]chromene-5-carboxylate (159)



Mollugin **129** (0.45 g, 1.58 mmol) was dissolved in anhydrous dichloromethane (20 mL) at 0 °C under an argon atmosphere. Triethylamine (0.44 ml, 3.16 mmol) was then added. The resulting yellow solution was stirred for 20 min. Trifluoromethanesulfonic anhydride (0.8 ml, 4.74 mmol) was then added causing the reaction mixture to turn brown. After the addition was completed, the reaction was allowed to stir at room temperature for 24 h. The reaction was quenched by the slow addition of water (5 ml), the resulting biphasic mixture was transferred to separating funnel and the organic layer was separated, washed with brine (7 ml), dried over anhydrous Na_2SO_4 and filtered. The solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate (7:1) to give the compound **159** as a colourless oil (0.59 g, 91%).

ν_{max} (neat)/cm^{-1} 2976, 1724, 1149, 819, 751; δH (500 MHz, $CDCl_3$): 1.38 (s, 6H, C_2***H***$_6$-16,17), 3.86 (s, 3H, C***H***$_3$-12), 5.59 (d, 1H, *J* = 10.1 Hz, C***H***-15), 6.49 (d, 1H, *J* = 10.1 Hz, C***H***-14), 7.42-7.50 (m, 2H, Ar***H***$_2$-6,7), 7.88 (d, 1H, *J*= 8.1 Hz, Ar***H***-8), 8.09 (d, 1H, *J*= 8.4 Hz, Ar***H***-5); δ_F (471 MHz, $CDCl_3$): -73.34 (s, 3F, C***F***$_3$-18); δ_C (125 MHz, $CDCl_3$): 27.7 (***C***$_3H_6$-16,17), 52.4 (***C***H_3-12), 77.4 (***C***-13), 112.9 (***C***-3), 113.2, 114.8, 117.3, 119.9 (q, *J*= 317.5 Hz, ***C***F_3-18), 119.4 (***C***-2), 122.43 (***C***H-15), 121.6, 121.7, 126.55, 126.59, 127.9, 128.5 (***Ar***H-5,6,7,8,9,10), 130.7 (***C***H-14), 135.6 (***C***-4), 148.7 (***C***-1), 166.9 (***C***O-11); *m/z* found for $[M+NH_4]^+$: 434.0872; $[C_{18}H_{15}F_3O_6S+NH_4]^+$ requires 434.0872.

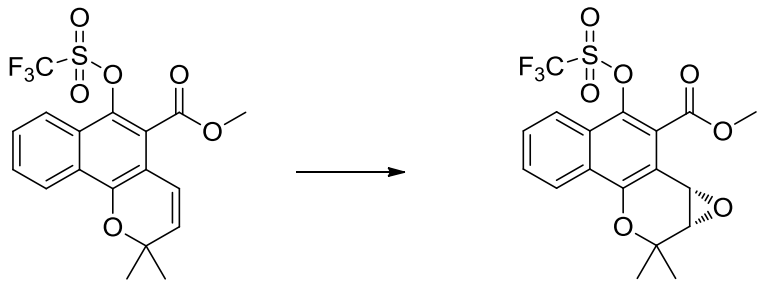
3.5.10 Methyl 9,9-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)-9,9a-dihydro-1aH-benzo[h]oxireno[2,3-c]chromene-2-carboxylate (160).



Na_2CO_3 (0.13 g, 1.24 mmol) was added to the solution of **157** (0.26 g, 0.62 mmol) in anhydrous dichloromethane at 0 °C. The solution of *m*-CPBA (0.1 g, 0.62 mmol) was slowly added at 0 °C. Complete conversion of alkene was observed by TLC (2 h). The residue was purified using column chromatography on silica gel eluting with petroleum ether / ethyl acetate (4:1), buffered with 3% TEA, to furnish the racemic epoxide **160** as a white solid (0.21 g, 81%).

mp 175-176 ˚C; ν_{max} (neat)/cm^{-1} 2976, 1724, 1149, 819, 751; δH (500 MHz, $CDCl_3$): 1.32 (s, 3H, C***H***$_3$-17), 1.65 (s, 3H, C***H***$_3$-16), 3.54 (d, 1H, *J* = 4.5 Hz, C***H***-14), 3.95 (s, 3H, C***H***$_3$-12), 4.37 (d, 1H, *J* = 4.5 Hz, C***H***-15), 7.54 (dd, 1 H, *J* = 8.1, 6.9, Hz, C***H***-6), 7.60 (dd, 1 H, *J* = 8.4, 6.9, Hz, C***H***-7), 7.98 (d, 1 H, *J* = 8.4 Hz, C***H***-8), 8.18 (d, 1 H, *J* = 8.1 Hz, C***H***-5); δ_F (471 MHz, $CDCl_3$): -73.18 (s, 3F, C***F***$_3$-18); δ_C (125 MHz, $CDCl_3$): 23.0 (***C***$_3$H$_6$-17), 25.6 (***C***$_3$H$_6$-16), 47.7 (***C***H-14), 53.6 (***C***H$_3$-12), 62.8 (***C***H-15), 74.6 (***C***-13), 111.2 (***C***-3) 114.7, 117.3, 119.8, 122.4 (q, *J*= 381.7 Hz, ***C***F$_3$-18), 121.8 (***C***-2), 122.6, 124.5, 127.2, 127.3, 128.2, 129.2 (***Ar***H-5,6,7,8,9,10), 135.8 (***C***-4), 149.1 (***C***-1), 164.6 (***C***O-11); *m/z* found for $[M+H]^+$: 433.0558; $[C_{18}H_{15}F_3O_7S+H]^+$ requires 433.0563.

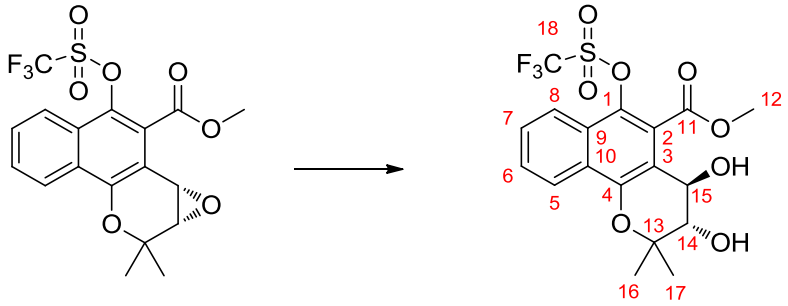
3.5.11 (*1S,9S*)-methyl 9,9-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)-9,9a-dihydro-1aH-benzo[h]oxireno[2,3-c]chromene-2-carboxylate (160).



Water (0.2 mL), acetonitrile (2 mL) and Na_2CO_3 (0.19 g, 1.80 mmol) were placed to a test-tube in an ice-bath at 0 °C. The mixture was stirred for 2 min, followed by Oxone® (0.44 g,

0.72 mmol) and the catalyst **78** (0.25g, 10 mol%) were added. After 5 min, a solution of alkene **159** (0.15 g, 0.36 mmol) in acetonitrile was added dropwise. The mixture was stirred at 0 °C until complete conversion of the alkene was observed by TLC (15 min). The reaction mixture was then diluted with diethylether (5 mL), the resulting suspension was filtered through a mixed pad of celite and Na_2SO_3. The solvents were removed under reduced pressure. The epoxide **160** was obtained by flash column chromatography on silica gel eluting with petroleum ether / ethyl acetate (7:1), containing 3% TEA. (0.14 g, 91%), $[\alpha]^{20}_D$ -17 (c = 0.12, $CHCl_3$); Chiral HPLC trace (99.5:0.5, hexane:iso-propanol, flow rate; 0.5 mL/min); 22.22 min (14.75 %), 32.60 min (85.25 %).

3.5.12 (*3S,4R*)-methyl 3,4-dihydroxy-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate (163)

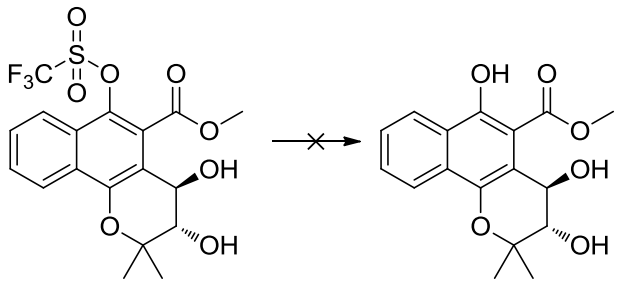


Compound **160** (83 mg, 0.91 mmol) was dissolved in acetone (1 mL) at room temperature. Diluted sulfuric acid (1M, 0.5 ml) was added dropwise to the solution, and the mixture was stirred for 1h. The reaction was monitored by TLC till the starting material had been completely consumed. The reaction mixture was neutralized to pH 7 using $NaHCO_3$. The solution was diluted with dichloromethane (10 ml) and water (5 ml). The organic layer was isolated and the aqueous was further extracted with dichloromethane (10 ml). The combined organic extracts were washed with brine (20 ml), and dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure. The residue was purified through column chromatography on silica gel using petroleum ether / ethyl acetate (1:1), to afford **161** as a white solid (68 mg, 74%).

$[\alpha]^{20}_D$ +11.4 (c = 0.22, $CHCl_3$); mp 186-188 ˚C; ν_{max} (neat)/cm^{-1} 3283, 2850, 1765, 1230, 893; δH (500 MHz, $CDCl_3$): 1.27 (s, 3H, C***H***$_3$-17), 1.46 (s, 3H, C***H***$_3$-16), 3.59 (d, 1H, *J* = 7.3 Hz, C***H***-14), 3.86 (s, 3H, C***H***$_3$-12), 3.87 (s, 1H, O***H***-14), 3.91 (s, 1H, O***H***-15), 4.80 (d, 1H, *J* = 7.3 Hz, C***H***-15), 7.54-7.49 (m, 1 H, C***H***-6), 7.65-7.66 (m, 1 H, C***H***-7), 7.91 (d, 1 H, *J* = 8.4 Hz, C***H***-8), 8.10 (d, 1 H, *J* = 8.1Hz, C***H***-5); δ_F (471 MHz, $CDCl_3$): -73.22 (s, 3F, C***F***$_3$-18); δ_C

(125 MHz, $CDCl_3$): 19.4 (***C***$_3$H$_6$-16), 25.7 (***C***$_3$H$_6$-17), 53.2 (***C***H$_3$-12), 68.6 (***C***H-14), 75.5 (***C***H-15), 79.4 (***C***-13), 114.2 (***C***-3) 114.7, 117.2, 119.8, 122.3 (q, *J*= 380.2 Hz, ***C***F$_3$-18), 121.7 (***C***-2), 123.0, 123.7, 126.6, 126.7, 128.1, 128.9 (***Ar***H-5,6,7,8,9,10), 135.9 (***C***-4), 148.1 (***C***-1), 166.8 (***C***O-11); *m/z* found for $[M+NH_4]^+$: 468.0925; $[C_{18}H_{17}F_3O_8S+NH_4]^+$ requires 468.0934.

3.5.13 General procedure for the deprotection of trifluoromethanesulfonate (129).



Method A

163 (1 equiv.) was dissolved in mixture of water/ethanol (1:1). The solution was stirred at room temperature under a nitrogen atmosphere for 10 min. Potassium hydroxide (1 equiv.) was added. After 10 min, the reaction was heated under reflux for 30 min. The reaction was allowed to cool down and then was neutralized to pH 7 using diluted HCl (1M, 0.5 ml). The solution was extracted with ethyl acetate (3×10 ml), the organic layers were combined, washed with brine (10 ml), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure.

Method B

163 (1 equiv.) was dissolved in dioxane and diluted Et_4NOH (2 equiv.) was then added under an argon atmosphere at room temperature. The solution was stirred until complete consumption of the starting material was observed by TLC. The reaction mixture was diluted with dichloromethane (20 ml), washed with diluted HCl (1M, 1 ml) water (10 ml) and brine (5 ml). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure.

Method C

To a solution of **163** (1 equiv.) in toluene (5 mL) was added Cs_2CO_3 (3 equiv.). The reaction was heated at 80 ˚C) during 19 h. The crude mixture was quenched with ethyl acetate (10 mL) and a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (2 ×10 mL). Organic layers were then combined, dried over anhydrous MgSO4 and concentrated under reduced pressure.

3.6 Experimental Section Reference

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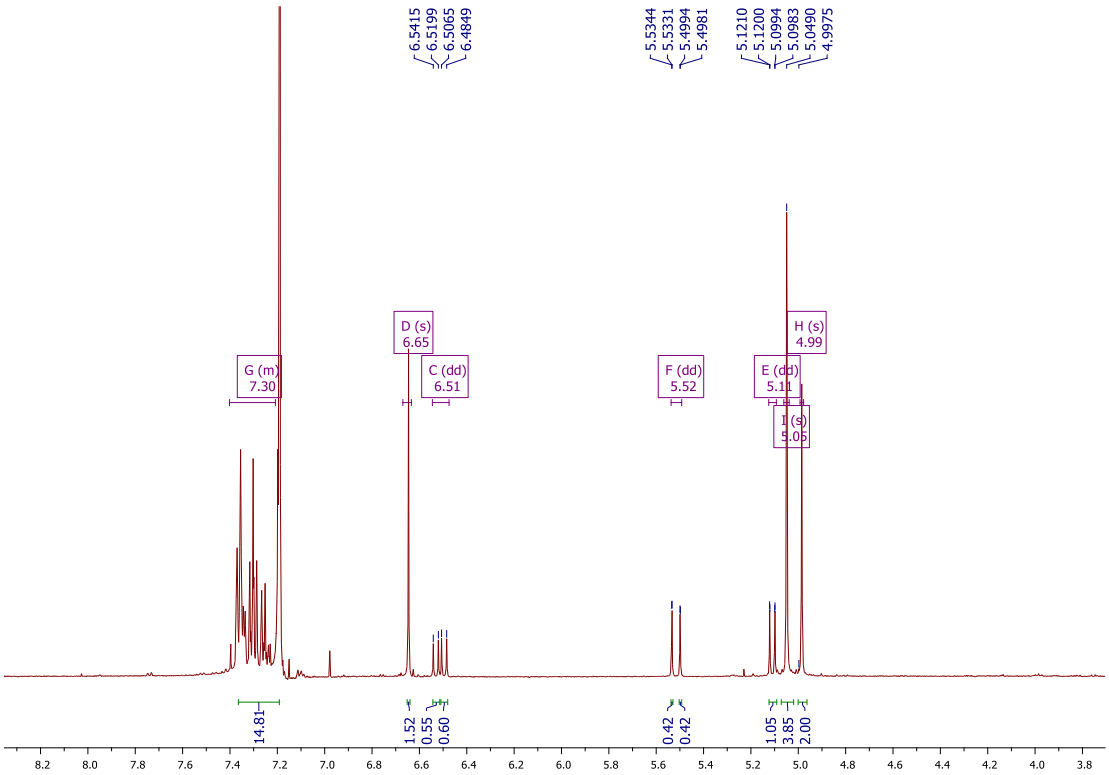
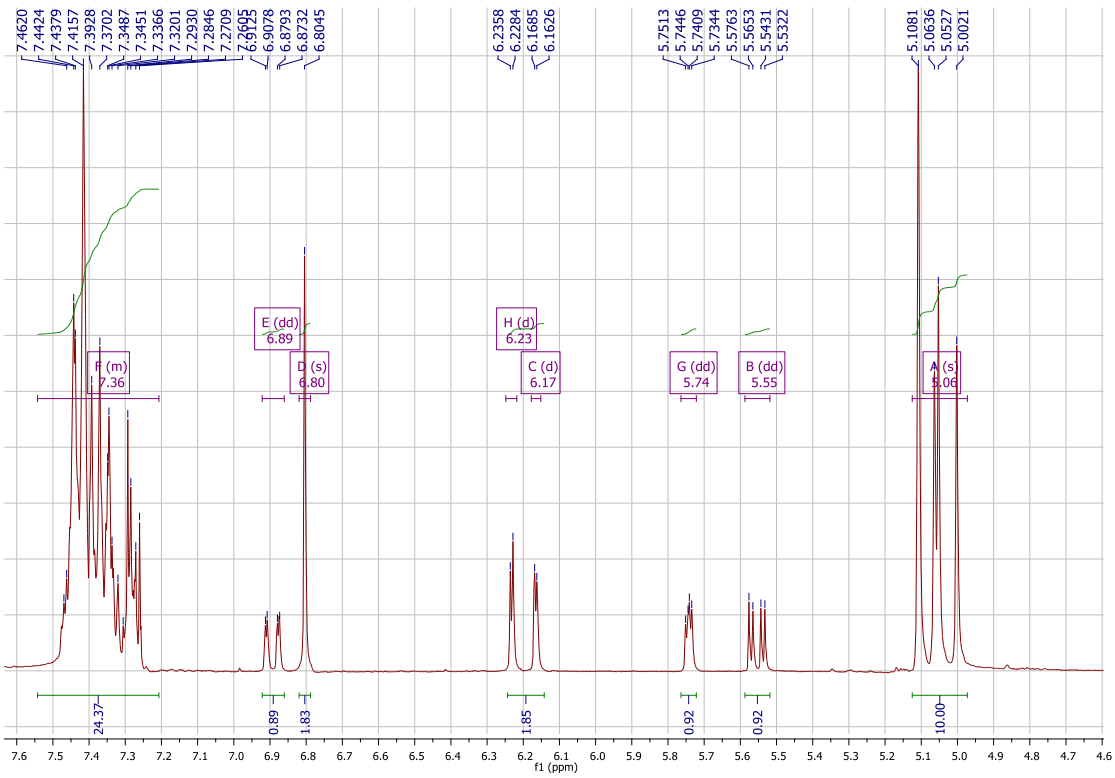
^{1}H NMR spectra of **36**



^{1}H NMR spectra of **28**



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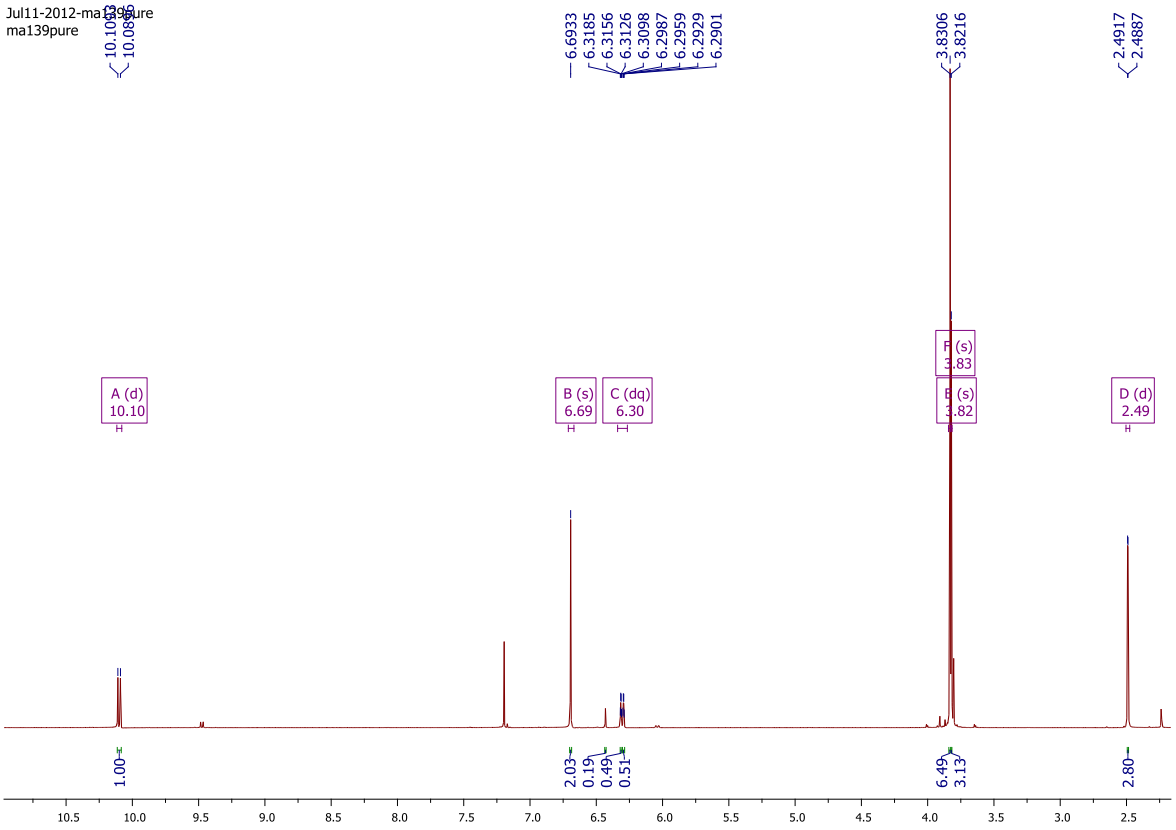
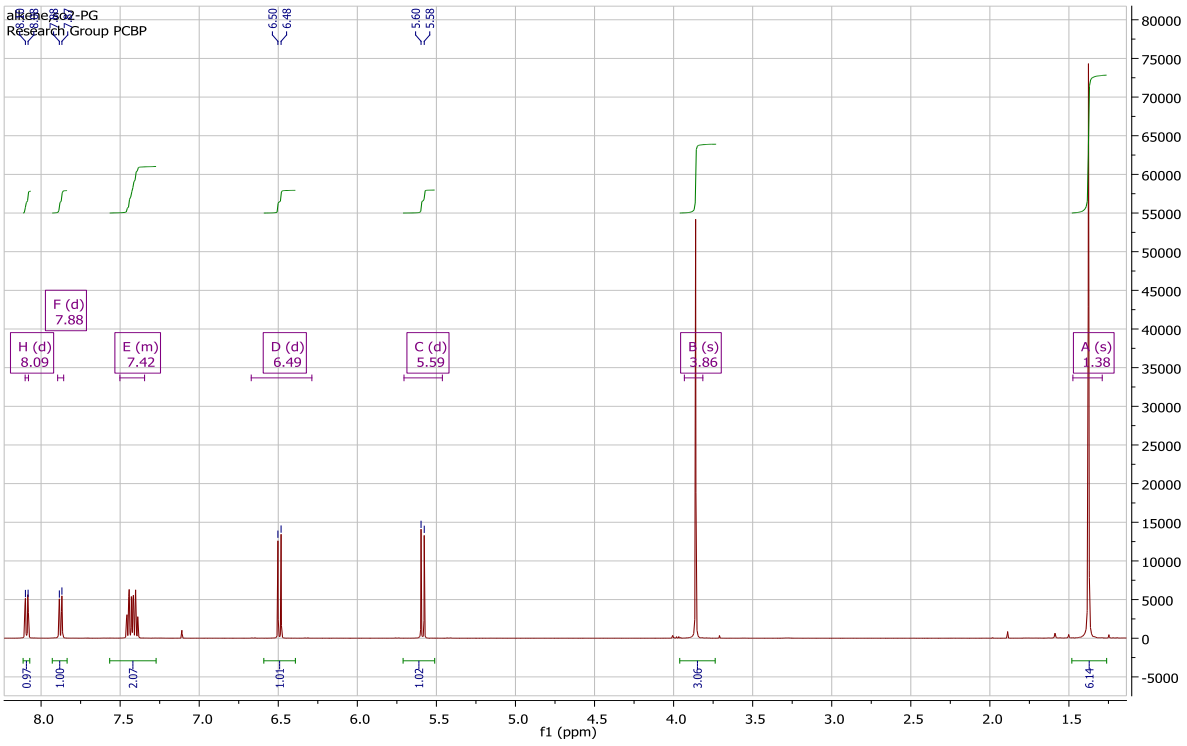


^{1}H NMR spectra of **159**



^{1}H NMR spectra of **160**