New Methodology for the Biomimetic Synthesis of Flavan-3,4-diols and Derivatives.

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Jeanette van Jaarsveldt

Supervisor: Prof. B.C.B. Bezuidenhoudt

Co-supervisor: Dr. J.H. van Tonder

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DECLARATION of AUTHENTICITY

I, the undersigned, declare that this dissertation, 'New Methodology for the Biomimetic Synthesis of Flavan-3,4-diols and Derivatives', is my own original work, gathered and employed for the fulfilment of the objectives of this study and that each source of information used has been acknowledged by means of a complete reference. This dissertation has not been submitted previously for any degree or examination at any university.

Jeanette van Jaarsveldt

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Pretoria, South Africa

TABLE OF CONTENTS

ABREVIATIONS

A	acetone
AcOH	acetic acid
ADHD	attention deficit/hyperactive disorder
AD-mix-α	asymmetric dihydroxylation mix-α
AD-mix-β	asymmetric dihydroxylation mix-β
Aib	α-aminobutyric acid
AIBN	azobisisobutyronitrile
APTESi	(3-aminopropyl)triethoxysilane
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthylene
BINOL	binaphthyl
BOC	di-tert-butyl dicarbonate
BQC	quinidine benzylchloride
BQdC	quinine benzylchloride
br	broad (spectral)
C	chloroform (chromatography)
CD	compact disc
CHP	chiral hydroperoxides
CMHP	cumene hydroperoxide
d	doublet (spectral); day(s)
dAA	cyclic α,α-disubstituted amino acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCFC	dry-column flash chromatography
DCM	dichloromethane
dd	doublet of doublets (spectral)
de	diastereomeric excess
δ	chemical shift in ppm
DEPT	distortionless enhancement by polarisation transfer
DET	(+)-diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron-impact
EIMS	electron-impact ionization mass spectroscopy
eq	equivalent
EtOAc	ethyl acetate
FCC	flash column chromatography
FID	flame ionization detector
g	gram
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
H	hexanes
h	hour(s)

HMBC	heteronuclear multiple-bond correlation
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
Hz	hertz
IPA	isopropyl alcohol/propan-2-ol
i-PLL	polymer supported poly-L-leucine
J spin-spin	coupling constant (NMR spectroscopy)
LA	Lewis acid
LAB	lithium aminoborohydride
LDL	low density lipoproteins
lit.	literature value
m	multiplet (spectral); milli
m/z	mass-to-charge ratio
M^+	parent molecular ion
m-CPBA	*meta*-chloroperbenzoic acid
MHz	mega hertz
min	minute(s)
MOM	methoxymethyl ether
m.p.	melting point
MPV	Meerwein-Ponndorf-Verley
MS	mass spectrometry
MW	microwave
n.p.	no product
NaDCCA	sodium dichloroisocyanurate
NaOAc	sodium acetate
NaPc	sodium percarbonate
n-BuLi	*n*-Butyllithium
NCS	*N*-chlorosuccinimide
NDDH	1,3-dichloro-5,5-dimethylhydantoin
NHMDS	*N*-sodiohexamethyldisilazane
NMO	*N*-morpholine oxide
NMR	nuclear magnetic resonance
PAA	poly(amino acid)
PCC	pyridinium chlorochromate
Ph	phenyl
PhIO	iodosylbenzene
PLA	poly-L-alanine
PLC	preparative thin-layer chromatography
PLL	poly-L-leucine
PLLSiCat	silica-supported poly-L-leucine catalyst
ppm	parts per million
PTC	phase transfer catalyst
q	quartet (spectral)
rBAL	recombinant benzaldehyde lyase
RF	response factors
R*f*	retention factor (chromatography)
RM	reaction mixture
RT	retention time (chromatography)
RT	room temperature
s	singlet (spectral)
Sat. Sol.	saturated solution
t	triplet (spectral)
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols
TBAB	tetra-*n*-butylammonium bromide
TBHP	*tert*-butylhydroperoxide

TBTH	tributyltin hydride
TCCA	trichloroisocyanuric acid
THF	tetrahydofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
Tol	toluene
Torr	unit of pressure
TPAP	tetrapropylammonium perruthenate
TS	transition state
UHP	urea-hydrogen peroxide
W	watts

LITERATURE REVIEW

"Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more and fear less."

- Marie Curie

CHAPTER 1

INTRODUCTION

1.1 Importance of Flavonoids

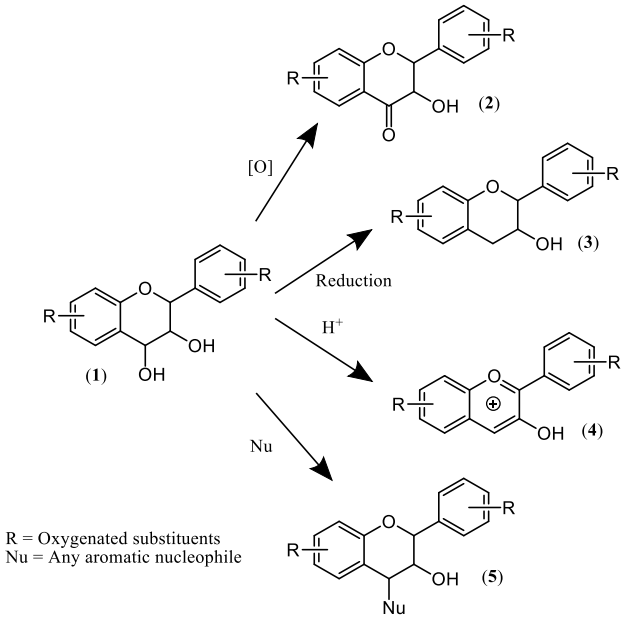
It has long been known that the vivid colours of fruit and flowers is attributed to the presence flavonoids, however, in recent years it became clear that these polyphenolic compounds have a more vital role to play in plant physiology.[1] Since flavonoid structures/classes differ in oxygenation pattern and saturation, (cf. section 2.2) over 9000 different compounds of this family have been isolated to date.[2–5] Although these compounds are abundant in almost all natural and dietary material, it is the promising properties towards mankind's wellbeing exhibited by flavonoids that has led to the tremendous interest into these compounds. In recent years scientists have turned to various flavonoids to explain some of the health benefits associated with diets rich in fruit, vegetables and red wine.[3,6]

Since flavonoids exhibit a remarkable number of pharmacological properties (cf. section 2.4) that include antioxidant,[7] anti-inflammatory[8,9] and antimicrobial activities,[8,10] a great deal of work has been done on the medicinal and therapeutic application of these compounds for the prevention and/or treatment of cancer,[11,12] neurodegenerative,[7,8] cardiovascular,[13] diabetes,[14,15] as well as other age related[7] and chronic diseases.[7,14]

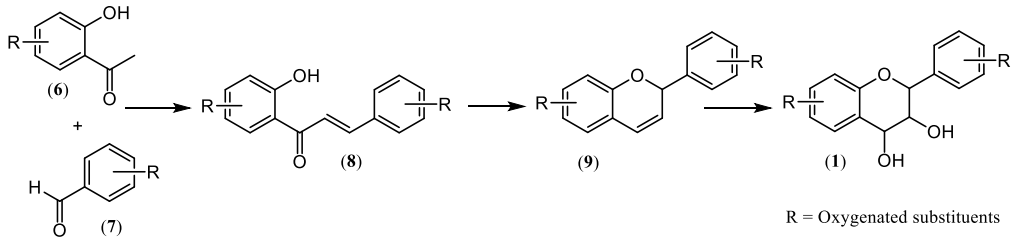
1.2 Aim of Research Project

Although flavonoids have been established as physiologically important compounds, studies on the biological activities and applications of these analogues are largely restricted to compounds that are obtainable from natural sources in sufficient quantities to allow for testing and administering to patients. As a consequence, progress in this field of study (in vitro and in vivo) is hampered by the difficulties and inaccessibility to ward pure flavonoid units in sufficient quantities and enantiomerically pure form at a reasonable cost.[16] To alleviate these restrictions, the synthesis of enantiomerically pure flavonoid monomers with all naturally occurring substitution patterns has become a top-class subject for academic research. Many of the existing methodologies towards the stereoselective synthesis of these compounds are, however, expensive, tedious and require the utilization of stoichiometric quantities of often poisonous reagents (cf. chapter 3),[4] so the development of novel catalytic methods towards the synthesis of flavonoids that are not readily available is highly sought-after.

In order to address these issues and possibly open a single route to the synthesis of many monomeric flavonoid classes (**2-4)** as well as related oligomers (**5**; Scheme 1.1), it was decided to investigate the possibility of utilizing flavan-3,4-diols (**1**) in this regard. Since chalcones (**8**) are already established as the key starting material in the synthesis of many flavonoids and are readily available through aldol condensation of the appropriately substituted acetophenones (**6**) and aldehydes (**7**), this substrate was selected as central reactant to be transformed into the target flavan-3,4-diols (Scheme 1.2). Furthermore, the novel methodology must comprise of as few process steps as possible and be amendable to allow for the synthesis of enantiomerically pure monomers by the simple addition of a relatively cheap reagent or preferably readily available chiral catalyst.



Scheme 1.1: Flavonoids available through flavan-3,4-diols transformations.



Scheme 1.2: Envisaged synthesis of flavan-3,4-diols as precursors to other flavonoids.

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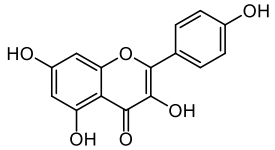
CHAPTER 2

THE FLAVONOIDS

2.1 Introduction

Plant and fungus secondary metabolites include a prominent class of polyphenolic derivatives, namely flavonoids, this term found its origin from the Latin word "flavus" meaning yellow.[1,2] It has been estimated that more than 9000 compounds, with a basic flavonoid structure, had been isolated to date from natural resources, while several others have been synthesised.[2,3] In recent years it has been realised that these ubiquitous compounds are not only responsible for the attractive colours of fruits and flowers, but have a major ecological function as well. They play a crucial part in the protection of plants against insect attacks, microbial infection, oxidative stress and growth regulation.[1–4] For example, some plants synthesise flavonoids [e.g. kaempferol (**10**)] to act as a sunscreen when exposed to harmful UV-B radiation.[1] The "French paradox", a term coined by French epidemiologists in the 1980's, first led to the increased study of the nutritional and therapeutic values of flavonoids. This ensued after population studies indicated that a Mediterranean diet (overgenerous intake of dietary sources high in flavonoids) and the consumption of red wine can be inversely correlated to mortality from cardiovascular diseases in certain countries.[3,5] Thus it was found that flavonoids not only are beneficial for plant health, but their cumulative beneficial properties (cf. section 2.4) for human consumption make them one of the most studied classes of bioactive compounds found in food.[4,6]



(**10**) Kaempferol

2.2 Structure Variation

2.2.1 Monomeric Flavonoids

Most flavonoids comprise of a fifteen-carbon skeleton, with the three-carbon bridge, which can either be acyclic of heterocyclic, flanked by two aromatic rings (C_6-C_3-C_6).[1,7,8] The so-called minor flavonoids (Figure 2.1) chalcones (**11**), *retro*-chalcones (**12**) and dihydrochalcones (**13**), are acyclic in nature and, apart from aromatic oxygenation pattern, may also show differences in the oxygenation of either the α- or β-position (**14-16**).[7]

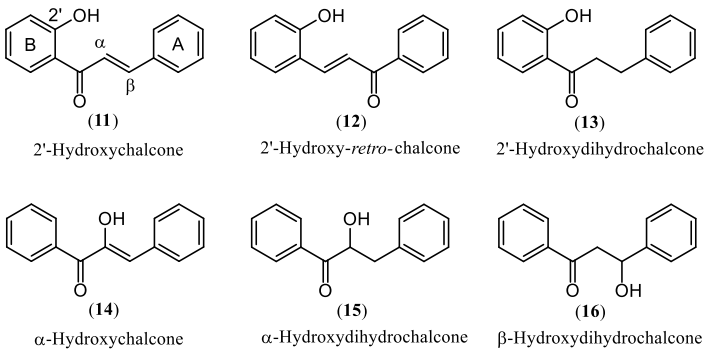


Figure 2.1: Basic structures of acyclic flavonoids.

While it is generally accepted that chalcones are the biomimetic precursors to cyclic flavonoids,[7,8] chalcones can either form a five or six membered heterocyclic ring leading to benzofuran derivatives, like aurone (**17**) and auronol (**18**) or benzopyran derivatives (Figure 2.2). The benzopyran derivatives may be subdivided according to the position of the phenyl substituent (B-ring) where a B-ring in the 2-position would lead to a flavonoid skeleton (**19**) and 3- and 4-substituted derivatives to isoflavonoids (**20**) and neoflavonoids (**21**), respectively.[7,8]

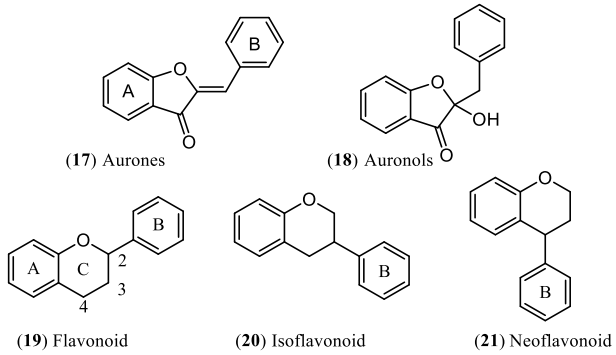


Figure 2.2: Basic skeleton of heterocyclic flavonoid classes.

In turn, each of the three classes of flavonoids can be divided into sub-classes based on the degree of unsaturation and oxygenation present in the heterocyclic C-ring. The sub-classes of flavonoids are depicted in Figure 2.3, where the C-ring can either be completely saturated (flavan, **19**) or unsaturated between C-2 and C-3 (flav-2-ene, **22**) or C-3 and C-4 (flav-3-ene, **23**). Further oxidation of flavenes produces intensely coloured anthocyanidins (**24**) with a flavylium cation framework.[7,8] Similarly, the saturated C-ring can also contain hydroxy substituents at C-3 (flavan-3-ol, **25**), or C-4 (flavan-4-ol, **26**) or both of these carbons (flavan-3,4-diol, **27**). Combining the varying degrees of oxygenation and oxidation of the C-ring leads to compounds such as flavanones (**28**), that contains a carbonyl group at C-4 and dihydroflavonols (**29**), having an additional 3-hydroxy function. The presence of a double bond between C-2 and C-3 of flavanones generates flavone compounds (**30**) and flavonols (**31**), if a hydroxy group is also present at the unsaturated 3-carbon.[7,8]

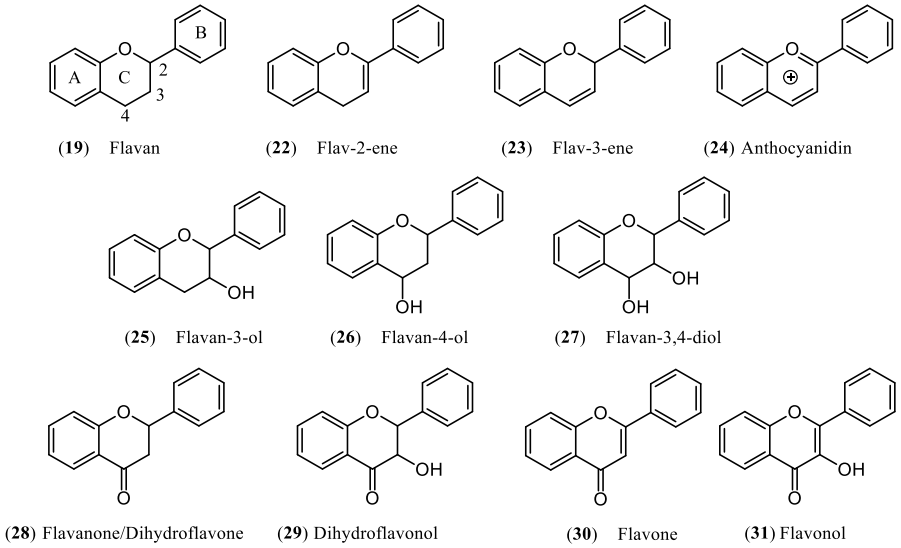


Figure 2.3: Sub-classes of flavonoids.

The degree of oxygenation of the A- and B-rings of flavonoids is also important as compounds with unsubstituted aromatic rings do not usually occur in nature.[7,8] Generally, either one, two or three oxygen substituents are present on either or both of the A- and/or B-rings where the arrangement of the di- or trihydroxy units determine the classification of the moiety (Figure 2.4, **32**-**35**).[8]

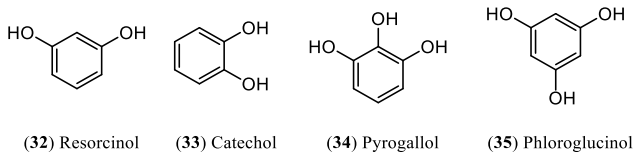


Figure 2.4: Hydroxylation patterns of naturally occurring compounds.

The phloroglucinol substitution pattern (**35**) is generally found on the A-ring with the other ring containing either a catechol substitution pattern (e.g. quercetin, **36**), a *p*-oxygenated substituent [e.g. kaempferol (**10)** or apigenin (**37**)], or even a pyrogallol substitution pattern (e.g. myricetin, **38**). The remaining substitution patterns, i.e. resorcinol (**32**), catechol (**33**) and pyrogallol (**35**), can be present on either or both of the aromatic rings with fisetin[9] (**39**) and melanoxetin[10] (**40**) being examples of compounds with a resorcinol or pyrogallol A-ring, respectively. Additional oxygenation on the A- (i.e. C-6 and C-8) and B-rings (i.e. C-2' and C-6') are also found, but are restricted to certain plant families (e.g. **41** or **42**).[8,11] Alkylation, *O*- or *C*, is another common feature of many flavonoids (Figure 2.5), with one or more methyl groups being attached to the oxygen functions of several compounds [e.g. *O*-methylated derivatives of apigenin (**37**) and fisetin (**39**)]. Alkylation, however, is not limited to methyl groups and may vary from higher carbon number alkyl groups (e.g. prenyl, **43**) to sugar moieties and even more complex ring systems attached to the phenolic moiety (e.g. *p*-dioxane system, **44**).[8] Anthocyanidins are usually isolated as glycosides form, which is termed anthocyanins.

Examples of *O*-glycosides are naringin (**45**) and neohesperidin (**46**), which are known to give grapefruit and other citrus fruit their typical bitter taste,[12–14] while vitexin (**47**), a *C*-glycoside, is commonly found in Cannabis species.[15]

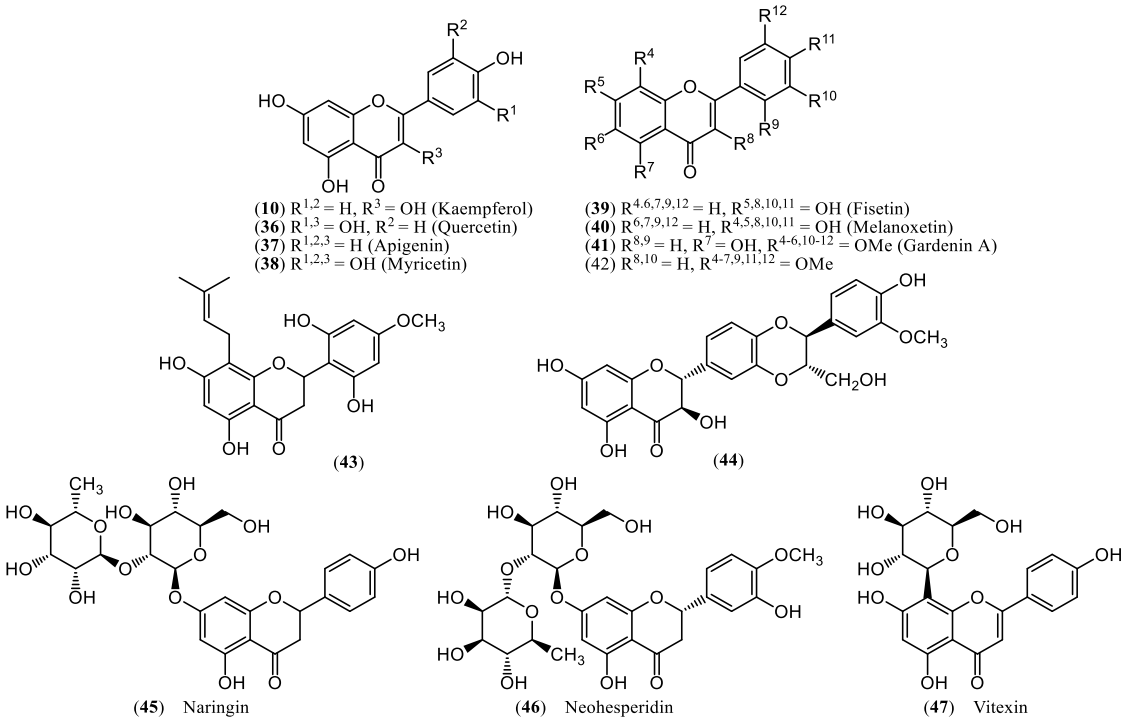


Figure 2.5: Naturally occurring flavonoid compounds.

Depending on the oxidation state of the heterocyclic ring, flavonoid molecules may contain stereogenic centres at C-2, C-3 & C-4 and may the absolute configuration be included into the trivial name of the compound.[8] Catechin (**48**), for example, represents a compound with 2,3-*trans*-relative configuration and (2*R*,3*S*)-absolute configuration (Figure 2.6). The 2,3-*cis*-diastereoisomer (**49**) of catechin has the prefix 'epi'- added to the name, while the less common enantiomers of these compounds, (**50**) and (**51**), are designated by the prefix 'ent'-.[8,16]

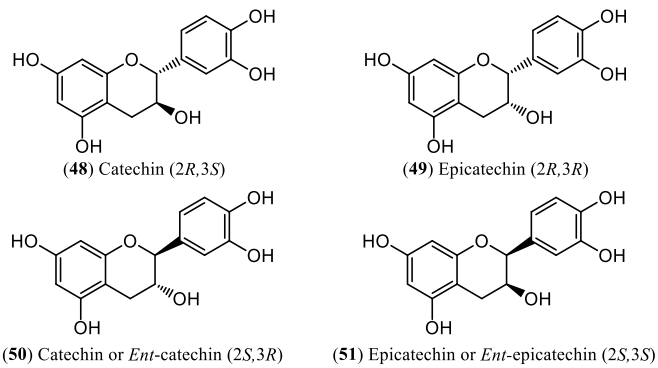


Figure 2.6: Differentiation between stereoisomers of catechin.

2.2.2 Oligomeric Flavonoids

Oligomeric flavonoids are compounds consisting of two or more flavanyl units linked by C-C or C-O bonds. Bi- and tri-flavonoids consist of two and three monomeric units, respectively, and are products of oxidative coupling between basic flavanyl units possessing a carbonyl group at C-4 (Figure 2.7).[8,17] Since the isolation of the first biflavonoid, ginkgetin (**52**), from *Ginko biloba* L. in 1929, the number of isolated biflavonoids has increased tremendously as these compounds are widely distributed in nature.[18] The configurational and conformational possibilities are endless with the most commonly observed types being flavone–flavone (**53**-**55**), flavone–flavonol, and flavanone–flavone analogues.[18,19]

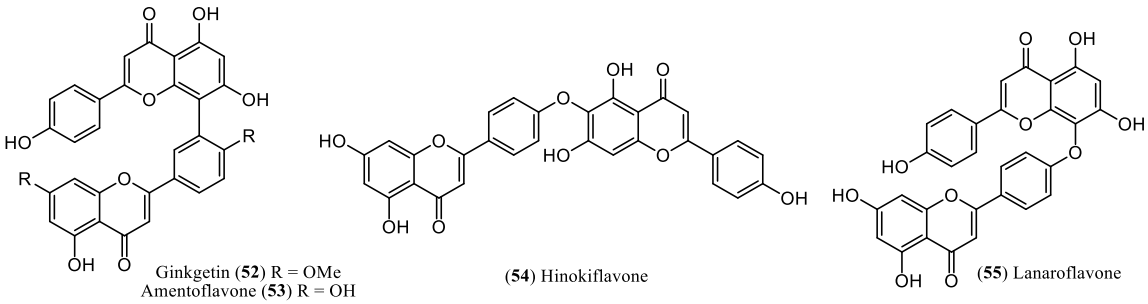


Figure 2.7: Examples of structure variations in biflavonoids.

Oligomeric proanthocyanidins, also called condensed tannins, represent the second subdivision of oligomeric flavonoids and was coined due to the fact that treatment of these polymers with a strong acid would generate anthocyanidins by cleavage of a C-C bond.[8,17] Thus, in contrast to biflavonoids, proanthocyanidins are generated through C-C and/or C-O couplings from the heterocyclic C-ring usually at C-4 of an electrophilic flavanyl unit [generated from flavan-4-ols (**26**) or flavan-3,4-diols (**27**)] to the A-ring (i.e. C-8 of C-6) of a nucleophilic analogue [e.g. flavan-3-ol (**25**)].[8,17] Depending on the position and type of bond(s), proanthocyanidins can be differentiated as A-(**56**) or B-type (**57**) compounds or both (**58**) (Figure 2.8).

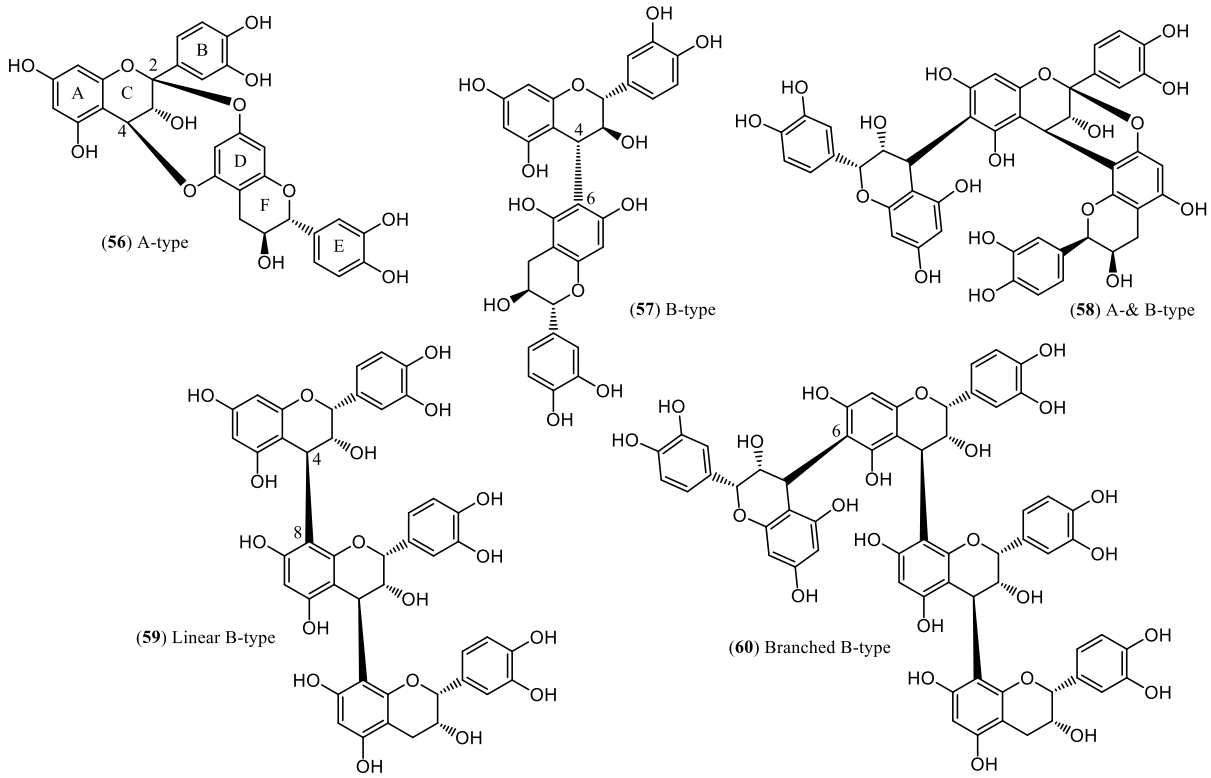
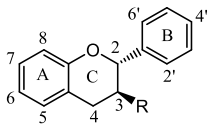


Figure 2.8: Examples of the structural variation in proanthocyanidins.

The B-type oligomers are the simpler of the two classes and have a single bond from C-4 of the 'upper' unit to either C-8 (the so-called 4→ 8 compounds) or C-6 (the so-called 4 → 6 compounds) of the 'lower' or propagating flavanyl unit (**57**). The A-type compounds (**56**) display an additional unusual ether linkage between C-2 of the '-upper' unit and an A-ring hydroxy substituent of the 'lower' unit. Each of these types can also include more than two basic units forming up to hexamers or larger.[20] Some oligomeric proanthocyanidin trimers or higher oligomers may contain only (4 → 8) bonds, the linear compounds (**59**), while other analogues may display a mixture of (4 → 8) and (4 → 6) linkages, the branched isomers (**60**).[16,21] Like monomeric flavonoids and bioflavonoids the hydroxylation patterns of the A-, B- and C-rings of proanthocyanidins may vary considerably, so these condensed tannins are further classified in terms of the monomeric unit's hydroxylation pattern as listed in Table 2.1.[16,21] In order to also include the absolute configuration at the point of binding (C-4) between the different monomeric units in the name and since the *R* and *S* descriptors may lead to ambiguities (the substitution pattern of the aromatic rings may determine the priorities of the groups attached to the stereogenic centre) with the orientation of the 4-substituent, a system analogous to that used in carbohydrate chemistry was invoked to indicate the α or β orientation of the 4-aryl substituent, for example, compound (**57**) will be named catechin-(4α→6)-catechin and (**59**) epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin.[16,17,21,22]

Table 2.1: Trivial names and hydroxylation pattern of (2*R*,3*S*) monomeric units and the proanthocyanidin classes.[16,21]



Class	Monomeric Unit	Hydroxylation Patterns	No.
Flavan-3-ols (R = OH)			
Proguibourtindin	Guibourtinidol	4',7	**61**
Profisetinidin	Fisetinidol	3',4',7	**62**
Prorobinetinidin	Robinetinidol	3',4',5',7	**63**
Proteracacidin	Oritin	4',7,8	**64**
Promelacacidin	Prosopin	3',4',7,8	**65**
Propelargonidin	Afzelechin	4',5,7	**66**
Procyanidin	Catechin	3',4',5,7	**48**
Prodelphinidin	Gallocatechin	3',4',5',5,7	**67**
Flavans (R = H)			
Proapigeninidin	Apigeniflavan	4',5,7	**68**
Proluteolinidin	Luteoliflavan	3',4',5,7	**69**
Protricetinidin	Tricetiflavan	3',4'5',5,7	**70**

2.3 Sources of Flavonoids

2.3.1 Dietary Sources

As both monomeric and oligomeric flavonoids make up a large part of plant secondary metabolites and are present in virtually all plant material, especially the photosynthesising plant cells, those compounds make up an integral part of human and animal diets.[4,23] Flavonoids are generally responsible for taste and colour in food products like red wine, coffee, fruit and spices.[4,23] Consequently, their widespread distribution and cumulative benefits when consumed make them one of the most studied bioactive compound classes found in dietary sources (Table 2.2).[4,6,23] Natural dietary sources contain complex mixtures of polyphenols, while the concentration and classes of flavonoids are influenced by genetic (e.g. species) and environmental factors (e.g. light, ripeness).[23–25] Commercially available dietary sources may contain flavonoids if the product contains any natural flavours or colourings or is made from plant material, depending on the method of preparation.[23,24]

Table 2.2: Dietary sources of different flavonoids.[4,17,23–30]

Class	Flavonoid	Dietary Sources
Minor flavonoids	chalconaringenin (**71**), phloretin (**72**)	tomatoes, pears, strawberries, bearberries, wheat products, turmeric, ginger
Flavonol	kaempferol (**10**), quercetin (**36**), myricetin (**38**), rutin (**73**)	apples, peaches, hops-based products, onion, red wine, olive oil, berries, grapefruit, fruit juices, spices, green tea, grapes, tomatoes, potatoes, broccoli, squash, cucumbers, lettuce, berries, nuts, persimmons, chilli, rocket, watercress
Flavone	luteolin (**74**), apigenin (**37**), chrysin (**75**)	fruit skins, red wine, red & green pepper, tomato skins, cocoa-based products, celery, broccoli, parsley, thyme, dandelion, chamomile tea, carrots, olive oil, peppermint, rosemary, thyme, oregano, cereals, chilli, honey
Flavanone	naringenin (**76**), hesperidin (**77**), naringin (**45**), neohesperidin (**46**)	citrus fruits, grapefruits, lemons, oranges, lime, lemon juice, mint
Flavan-3-ol	catechins (**48**), epicatechins (**49**), gallocatechin (**78**), epigallocatechin (**79**)	cocoa-based products, tea leaves, oolong tea, black tea, green tea, apricots, cherries, apples, bananas
Anthocyanidin	cyanidin (**80**), delphinidin (**81**), peonidin (**82**)	cherries, berries, strawberry, cranberries, plums, sweet potatoes, red grapes, red wine, tea, radishes, black current
Oligomeric flavonoids	theaflavin (**83**), **56**, **58**	black tea, cranberries, peanut skins, red wine, cocoa-based products, apples, pecan nuts, peaches, cinnamon, berries, apple ciders

While minor flavonoids, e.g. phloretin[24] (**71**) and chalconaringenin[25] (**72**) are usually found in food as different glycosides, flavonols, e.g. kaempferol (**10**), quercetin (**36**) and myricetin (**38**), are the most abundant naturally occurring flavonoid subgroup and are present in concentrations of up to 6.5 g/L in the skins of fruit.[4,23,25] Even in commercial products like red wine and tea these compounds can be present in concentrations of 30 to 45 mg/L.[25] Natural flavone glycosides, like luteolin (**74**), apigenin (**37**) & chrysin (**75**), usually contain a 5-hydroxy group together with hydroxylation at C-7 and/or C-3' and/or C-4', and are predominantly found in leaves, flowers and fruit of plants and was also isolated from several vegetables species.[24,29]

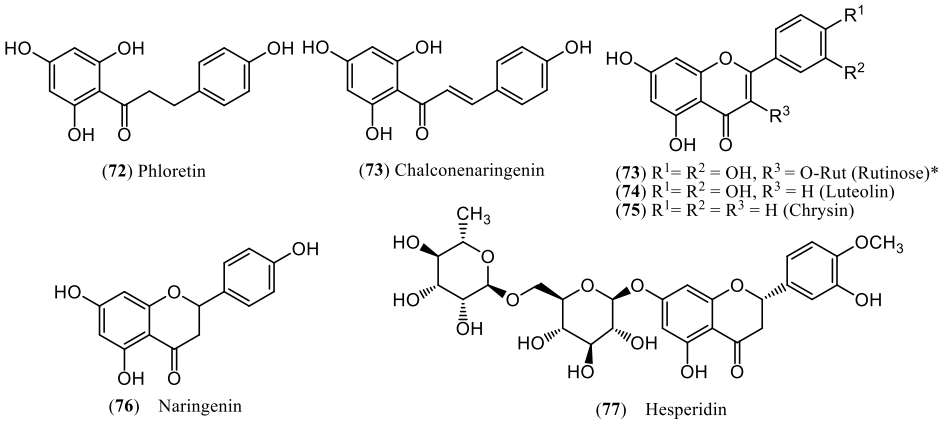


Figure 2.9: Examples of naturally occurring minor and heterocyclic flavonoids.

*Rutinose = α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose

Flavanones, present in citrus are responsible for the bitter taste of the fruit and fruit products.[23,24] Orange juice, for example, can contain 470-761 mg/L of hesperidin (**77**), whereas, in the whole fruit it can be up to five times that of a single glass of juice, with the solid parts of the fruit having the highest flavanone concentration.[25] Water-soluble anthocyanidins are best known as plant pigments of red, blue and purple in the flowers and fruit of the plants. The colour of these compounds in the plant parts depends on the pH in the environment of the compound, the hydroxylation pattern of the particular analogue and the level of alkylation (e.g. methylation).[4,24,25] Occurring primarily as glycosides, anthocyanins are also widely distributed in natural dietary sources and may therefore make up an integral part of the human diet.[25] Cyanidin (**80**), delphinidin (**81**) and peonidin (**82**) are some of the anthocyanidins widely present in fruit skins, vegetables and red wine.[24,25] Fifteen different anthocyanins, for example, have been isolated from French wines, which can contain up to 350 mg of anthocyanin analogues per litre, while blackcurrant or black berries can contain 2-4 g/kg (fresh weight) of these compounds.[23,25]

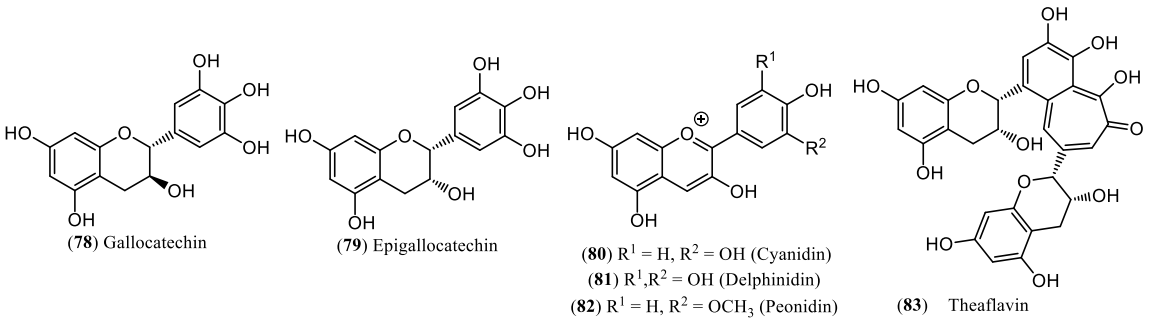


Figure 2.10: Flavonoid compounds found in tea, wine and other commercial products.

Flavan-3-ols like catechin and epicatechin (**48** & **49**) are present in fruit like apricots and cherries, whereas, gallocatechin (**78**), epigallocatechin (**79**) and their gallate derivatives are mainly found in tea (catechin concentration in green tea can be up to 800 mg/L).[25] Oligomeric flavonoids, e.g. **56** and **58**, occur naturally in cranberries and peanut skins, while almond skins may contain polymers of

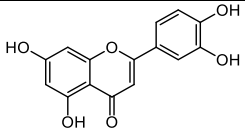
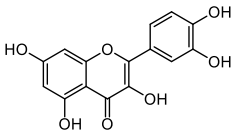
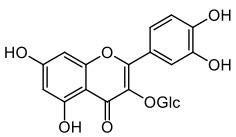
procyanidin, propelargonidin and prodelphinidin classes (Table 2.1), while these compounds are also responsible for the bitter taste of cocoa-products.[16,17,25] Proanthocyanidins consisting of 4 to 11 monomeric units are also found in commercial products like apple ciders, wine, beer and tea.[25]

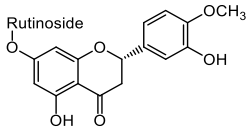
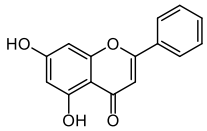
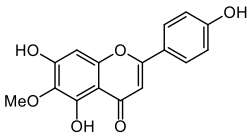
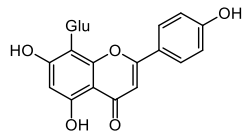
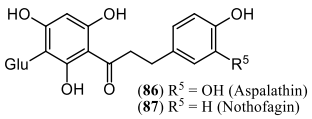
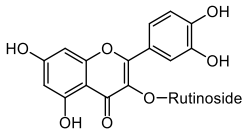
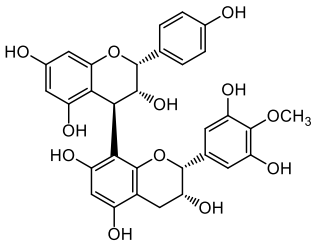
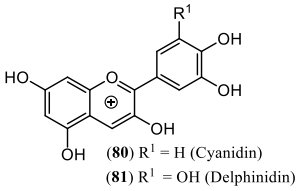
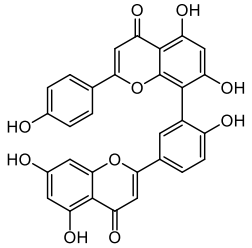
Owing to varying degrees of polymerization of monomeric flavan-3-ol units (e.g. catechin) during the fermentation of tea leaves, green, oolong or black tea can be produced.[31] The tea originating from the least fermented leaves, i.e. green tea, contains the highest concentration of monomeric flavan-3-ols, while black tea being the most fermented, has a lower concentration of flavan-3-ol monomers and high amounts of dimers like theaflavin (**83**) and other tannins which are formed during the fermentation process.[27,31] A similar process occurs during the aging of wine, where anthocyanidins, flavanols and other flavonoid monomers form various complex structures resulting in distinctive tastes and smells of the different wine brands.[23,25,32]

2.3.2 Medicinal Plants

Plants have been used for treatment of various afflictions by indigenous populations (e.g. Africa, China and India) since the dawn of civilization.[2,4,33] The improvement of analytical methods and the ever rising number of studies on medicinal plants in recent years have shown that the complexity and variety of compounds (e.g. flavonoids) isolated from medicinal plants are contributing factors to their potential therapeutic and physiological properties.[4,33,34] Some plants containing flavonoids and their medicinal applications are listed in Table 2.3.[4,35–41]

Table 2.3: Medicinal plants containing flavonoids.[4,35–41]

Plant	Family	Flavonoid	Structure	Treatment
Aloe vera	Asphodelaceae	Luteolin (**74**)		Burns, cuts, insect bites, skin irritation,
Cannabis sativa	Compositae	Quercetin (**36**)		Epilepsy, migraine, asthma, fatigue, insomnia, rheumatism
Psidium guajava	Myrtaceae	Quercetin (**36**)		Diarrhoea, diabetes, fever, cough, ulcers, malaria
Adansonia digitata	Malvaceae	Quercetin glucoside (**84**)		Fever, diarrhoea, hiccups, haemoptysis

Mentha longifolia	Lamiaceae	Hesperidin (**77**)		Coughs, asthma, colds, headache, indigestion, urinary tract infections
Oroxylum indicum	Bignoniaceaea	Chrysin (**75**)		Gastric ulcers, tumors, diabetes, respiratory diseases
Saussurea involucrata	Asteraceae	Hispidulin (**85**)		Swelling, acne, arthritis, bronchitis
Passiflora incarnate	Passifloraceae	Vitexin (**47**)		Insomnia, anxiety, sedation
Aspalathus linearis	Fabaceae	Aspalathin (**86**), Nothofagin (**87**) & Rutin (**73**)	 	Colic, dermatitis, indigestive problems
Elaeodendron transvaalense	Celastraceae	Ouratea proanthocyanidin A (**88**)		Fever, stomach ache/cramps, diarrhoea
Rhoicissus tridentata	Vitaceae	Cyanidin (**80**) & Delphinidin (**81**)		Stomach ailments, infertility
Xerophyta retinervis	Velloziaceae	Amentoflavone (**53**)		Asthma, nose bleeds, pain

2.4 Biological Activity

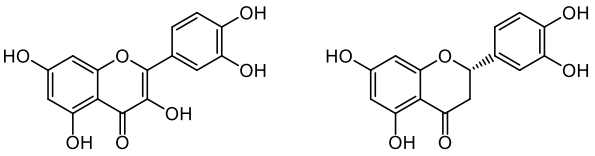
Many flavonoids may act as antimicrobial or feeding repellents as flavonoids are often produced as a result of pathogenic attacks, while other activities such as antioxidant, photoreceptor, visual attractors, growth regulatory and light screening activities have also been ascribed to these compounds.[1,4,23,24] Many flavonoid classes (including oligomeric proanthocyanidins and biflavonoids) have been determined to be biologically active in humans and animals, exhibiting in vitro pharmacological properties which include cardioprotective,[28] neuroprotective,[25,26] anti-inflammatory,[26,42] anticancer,[43,44] antibacterial,[45] antifungal,[46] antiviral,[26] anti-allergic[47] and antioxidant activities.[2,4,23–25,48–50]

2.4.1 Antioxidant Activity

Recent studies have indicated that many chronic diseases are related to oxidative stress, induced by free radicals;[4,24,25] thus the antioxidant ability of flavonoids have received wide attention when compared to the other biological activities of these compounds.[4,24,25] The antioxidant activity of flavonoids can be divided into different modes of action, i.e. the suppression of radical formation by either inhibiting key enzymes involved in radical generation (e.g. lipid peroxidase), or by the chelation to metals (e.g. Fe, Cu).[2,4,23,25] Alternatively flavonoids can also scavenge free radicals directly which increases the response and protection of natural antioxidant defences and, in this way, protecting against chronic diseases.[4,24]

The configuration, substitution and total number of hydroxy groups of a polyphenol influence the efficacy of its antioxidant properties. In this regard, it has been determined that a catechol B-ring leads to the most effective antioxidants.[4,23,24,51] This has been ascribed to the capability of the B-ring to stabilise radicals (e.g. hydroxy, peroxy and peroxynitrite) via donating a proton and electron to the oxygen radical, resulting in the formation of the relatively less reactive flavonoid radical.[4,23–25,51] This hypothesis was supported by the observed decrease in radical scavenging capacity upon alkylation (e.g. methylation or glycosylation) of the free hydroxy groups.[4,23,51] Studies with superoxide anions and peroxynitrite radicals also indicated proanthocyanidin oligomers to be more effective than monomeric flavonoids in antioxidant potency.[4,50]

Quercetin (**36**), for example, is a potent antioxidant known for its iron-chelating properties and displays the ability to inhibit enzymes, e.g. xanthine oxidase.[4,24,26] Eriodictyol (**89**), found in thyme and lemons, inhibits superoxide anion production and lipid peroxidation and therefore protects red blood cells against oxidative haemolysis.[52]

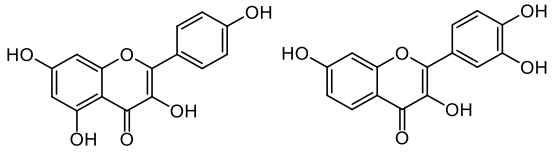


(**36**) Quercetin (**89**) Eriodictyol

Figure 2.11: Flavonoids exhibiting antioxidant activity.

2.4.2 Anticarcinogenic Activity

Since many fruit and vegetables are rich in flavonoids and may help in preventing the onset of cancer, the chemopreventative properties of these foods have been ascribed to the flavonoid contents.[2,4,23,49] The anti-mutagenic and anticancer properties of flavonoids seem to stem from their ability to efficiently inhibit oxidative damage to cells,[23] so it is not surprising that quercetin (**36**), well known for its antioxidant abilities, is inversely associated with the incidence of prostate, lung, stomach and breast cancer.[4,50] A study by Srivastava et al.[53] found that quercetin (**36**) and some biflavonoids induce apoptosis in breast and leukemic cancer cells and that flavonoids like fisetin (**39**) and kaempferol (**10**) not only induce apoptosis in cancer cells, but also enhance the effects of anti-tumor agents like cisplatin.[4,43,44,50]



(**10**) Kaempferol (**39**) Fisetin

Figure 2.12: Anti-carcinogenic flavonoid compounds.

2.4.3 Anti-Inflammatory Activity

Flavonoids with a C-2 double bond may also impact on the immune system to reduce inflammatory responses by affecting key enzymes giving rise to these analgesic and anti-inflammatory effects.[4,25] Kang et al.[42] found the flavonoids, naringin (**45**) and hesperidin (**77**) isolated from bitter oranges, to block the signalling pathways (i.e. mitogen-activated protein kinase and nuclear factor-kappa B) associated with inflammatory responses and thus supresses the production of the key enzymes (e.g. cyclo-oxygenase, lipoxygenase) responsible for the formation of pro-inflammatory agents.[2,24,26,42] Biflavonoids, in particular, have exhibited great analgesic activity, which may lead to the development of superior anti-inflammatory agents.[50] As a result, flavonoids can be used to treat diseases known to induce inflammatory responses, for example, gout, leukemia, sepsis, asthma, arthritis, sclerosis and systemic lupus erythematosus,[33,49,50,54] with flavonoids such as amentoflavone (**53**), for example, being effective in the treatment of psoriasis.[24,51,55]

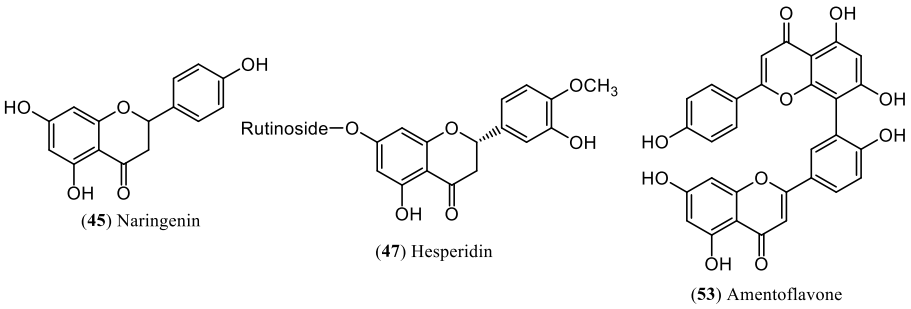


Figure 2.13: Flavonoids exhibiting anti-inflammatory activity.

2.4.4 Antiviral, Antibacterial & Antimicrobial Activity

As flavonoids are plant secondary metabolites usually produced in response to stress (e.g. oxidative, microbial attack), compounds like flavones, flavonol glycosides, flavanones and chalcones show antiviral and antibacterial activity towards a wide range of micoorganisms.[1,4] Although most polyphenols display some antibacterial properties, biflavonoids, e.g. amentoflavone (**53**) and derivatives isolated form *Garcinia livingstonei*, are particularly potent against *Escherichia coli* (*E. coli*) and other bacteria.[2,50] The proanthocyanidin **58**, commonly found in cranberry juice, is effective in the prevention of urinary tract infections,[17] while other proanthocyanidins are used to treat infections such as pancreatitis, reduce pain severity, and vomiting.[49] Condensed tannins, e.g. ouratea proanthocyanidin A (**88**), are also effective in the treatment of diarrhoea and as an antiseptic and detoxifying agent.[35]

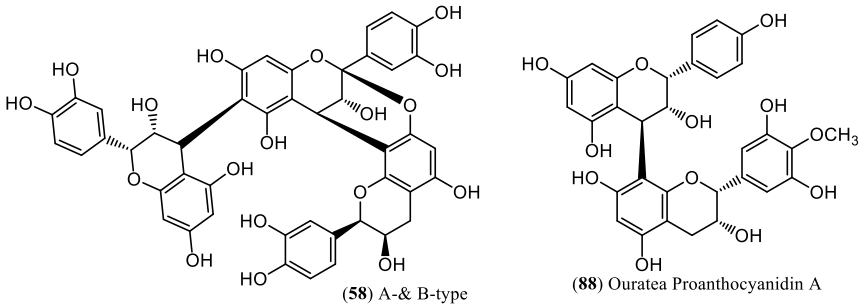


Figure 2.14: Oligomeric flavonoids showing antibacterial activity.

In addition to antibacterial activity, the catechins in green tea have also been proven to inhibit the replication of the influenza virus,[2,4] while compounds such as quercetin (**36**), robustaflavone (**90**), rutin (**73**), apigenin (**37**) and naringin (**45**) have shown in vitro activity against hepatitis B, rabies, herpes, HIV and polio viruses.[2,4,26,49,50] More in vivo studies are, however, required to fully assess the potential of flavonoids as antiviral drugs.[24,26]

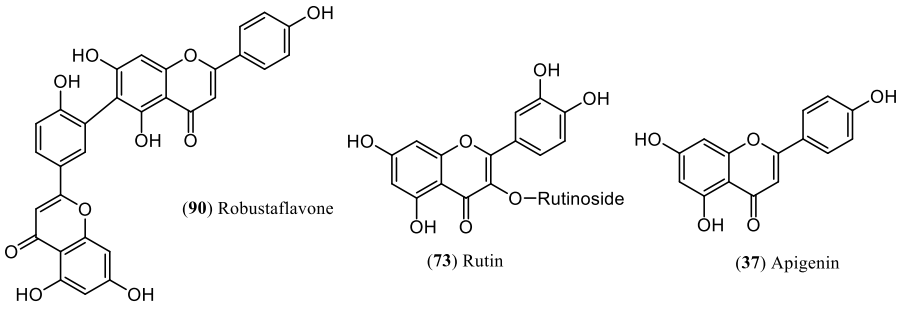


Figure 2.15: Flavonoids exhibiting antiviral activity.

2.4.5 Cardioprotective Activities

Epidemiological studies, where in it was found that elevated red wine consumption reduces the incidence of coronary heart disease, provided support for the so-called "French Paradox",[28,49] while it was also established that the consumption of tea may lower the risk of atherosclerosis, coronary heart disease and also protect against strokes.[23] The ability of flavonoids to prevent cardiovascular diseases may be associated with the radical scavenging properties of these compounds, which prevent oxidation of low density lipoproteins (LDL) and also by inhibiting the growth of atherogenic plaque.[23,26,49] Since flavonoids inhibit the cyclo-oxygenase and lipoxygenase pathways, these compounds are also powerful antithrombotic agents (in vitro and in vivo).[26] It has been found that a daily intake of 30 mg of flavonoids, e.g. naringenin (**76**) and apigenin (**37**), decreases the risk of myocardial infarction by 50% compared to a lower intake of 20 mg, indicating that the consumption of flavonoids was cardioprotective.[2]

2.4.6 Hepatoprotective and Gastrointestinal Activities

Hepatoprotective activity [44] (ability to prevent damage to the liver) has been attributed to a number of flavonoids, e.g. rutin (**73**), catechin (**48**), apigenin (**37**), quercetin (**36**), so these compounds can be used to treat hepatobiliary dysfunction and as a choleretic drug [metochalcone (**91**)].[4,23,57,58] Other clinical investigations indicated that flavonoids can be used as potent remedies for gastrointestinal problems such as loss of appetite, nausea, abdominal pain, stomach and intestine discomfort, as a result of improving conditions of the digestive tract tissue after the intake of these polyphenols.[4,23,25]

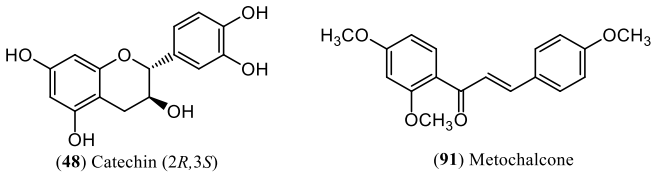


Figure 2.16: Flavonoids used to treat hepatobiliary dysfunction.

2.4.7 Flavonoids and Diseases

While malaria is one of the most common diseases in subtropical and tropical countries with parasite strains which have become increasingly resistant towards multiple drugs ,e.g. *Plasmodium falciparum* (*P. falciparum*), a natural source to combat this disease would make an important contribution towards the health of communities in these areas.[59,60] In an in vitro study, Lim et al.[60] found 6-methylflavanone (**92**) and 4'-methoxydihydrochalcone (**93**) to show a 100% growth inhibition of the *P. falciparum* parasite. Other studies identified biflavonoids, like lanaroflavone (**55**), to possess high antimalarial activities.[50,61]

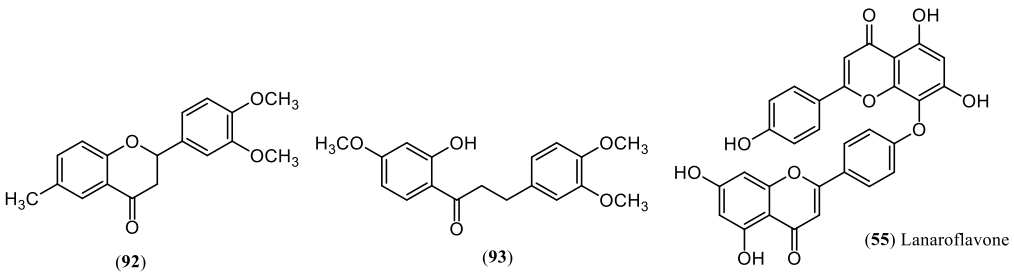


Figure 2.17: Bioflavonoids exhibiting anti-malaria activity.

Since diabetes mellitus represents one of the most prevalent diseases in the world, many flavonoids have been evaluated for antidiabetic properties and an inverse relationship between free hydroxy groups present in the molecule and its activity have been found.[19,51] Oligomeric flavonoids, like amentoflavone (**53**), showed potential in the treatment of insulin resistant (type 2) diabetes.[19,49] Monomeric flavonoids found in green tea, i.e. epicatechin (**49**), may also act as active insulin receptors to reduce the harmful effects of diabetes.[62]

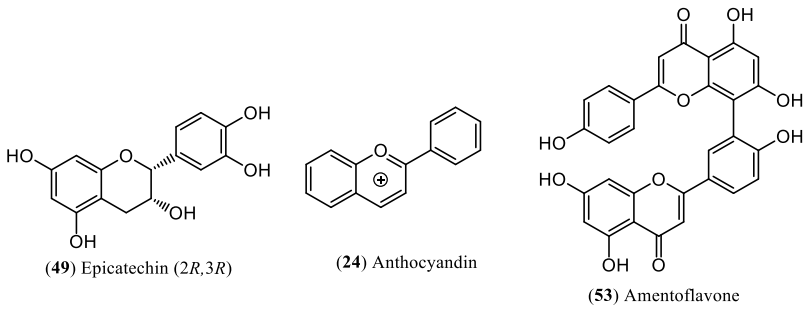


Figure 2.18: Flavonoids beneficial for the prevention of diabetes.

Since oxidative stress plays a key role in the risk of dementia and flavonoids are known to cross the blood-brain barrier,[25,26] polyphenols in apple juice and red wine were reported as having the potential to limit the progress of Alzheimer's and Parkinson's diseases, as well as, improve memory and reduce the risk of dementia.[25,26] Quercetin (**36**) and rutin (**73**), for example, act as neuroprotective agents to

relieve the symptoms of mild Alzheimer's disease by inhibiting key enzymes in the central nervous system.[24] Other flavonoids, e.g. anthocyanin (**24**), naringenin (**76**) and hesperidin (**77**), display anticholinesterase activity which also assists in the treatment of Alzheimer's disease.[24,25,51,63] The consumption of tea showed antiosteoporotic effects, so women who consumed tea measured higher bone density when compared to women who did not drink tea.[26] Oligomeric proanthocyanidins like those extracted from grape seeds or pine trees (i.e. Pycnogenol®) have also been correlated to the improvement of wound healing[64] and asthma symptoms,[65] as well as aiding in the treatment of migraine and attention deficit/hyperactive disorder (ADHD).[33,49]

2.6 Conclusion

Owing to the seemingly unlimited structural diversity of flavonoids, these compounds play a very important role not only in the physiology of plants, but also in their defence mechanisms. The medicinal potential of these compounds became more evident in recent years as frequent application in traditional remedies was described. As a result, these natural compounds are indispensable components of nutraceutical, pharmaceutical, medicinal, and cosmetic applications and important sources for the discovery and development of novel drugs to aid the prevention and treatment of chronic diseases.

2.7 References

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CHAPTER 3

STEREOSELECTIVE SYNTHESIS OF MONOMERIC FLAVONOIDS

3.1 Introduction

A considerable number of innovative drug discoveries and modern medications find their origin in natural products, which can be ascribed to the plant-based foundation of traditional medicine and therapies.[1] The realisation that naturally occurring secondary metabolites, e.g. flavonoids, have major health-promoting properties and physiological activities (cf. section 2.4), has brought on an immense expansion in natural product chemistry.[1,2] The focal point of natural product chemistry has, however, shifted even further in recent years towards the synthesis of enantiomerically pure compounds. It took over a century, since its discovery in 1848 by Louis Pasteur,[3,4] to recognize the crucial role of chirality not only in the animal and plant kingdoms, but in the agricultural, chemical and pharmaceutical industries as well.[3] The realisation that chirality is an integral part of life has come at a great expense as, for years, some drugs, such as beta blockers for cardiovascular disease,[5] were administered as racemic mixtures. Physiological interaction of enantiomers can vary considerably as the body contains a copious amount of homochiral compounds (e.g. enzymes, proteins) that selectively interact with a specific enantiomer, resulting in a different response and effect for each stereoisomer.[3]

The enantioselective synthesis of flavonoids, e.g. the introduction of stereogenicity into prochiral precursors such as chalcones, has received limited attention from the chemistry community, while the studies of oligoflavonoids, as well as the in vitro and in vivo studies of the properties of flavonoids, are hampered by the inaccessibility of enantiomerically pure monomeric flavonoids.[6] A number of flavonoids (viz. α- and β-hydroxydihydrochalcones, dihydroflavonols, flavan-3-ols, flavan-3,4-diols, isoflavans and pterocarpans) and their intermediates (e.g. chalcone epoxides) have, however, been synthesised successfully in reasonable yields and enantiomeric purity during the last quarter-century.[7]

3.2 Enantioselective Epoxidation of Chalcones

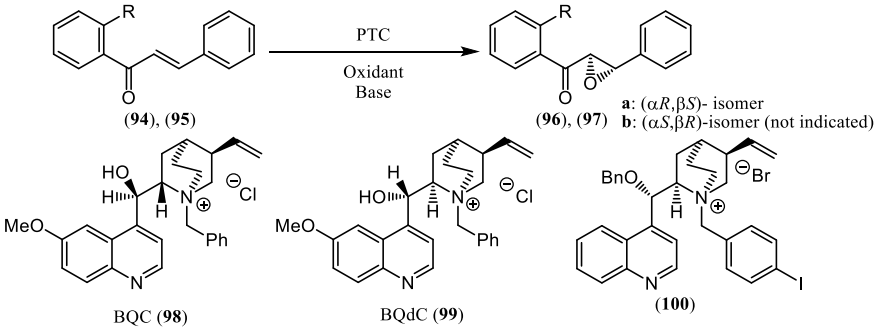
While chalcone derivatives are freely accessible through the aldol condensation reactions and although the condensation can be performed under acidic conditions, the base-catalysed Claisen-

Schmidt adaptation represent the standard method for the synthesis of these compounds as the acidic pathway often leads to racemic flavanones as secondary products.[7] As key intermediates in the synthesis of many flavonoids, the stereoselective epoxidation of chalcones plays a crucial role in the introduction of chirality to other acyclic and heterocyclic flavonoids and has thus received considerable attention in recent years.

3.2.1 Quaternary Ammonium Salts as Phase Transfer Catalysts (PTC)

Wynberg and co-workers[8,9] were the first to report the preparation of optically active *trans*-chalcone epoxides under Weitz-Scheffer epoxidation conditions (30% aq. NaOH/H_2O_2/toluene) in the presence of a chiral quinidine or quinine derived quaternary ammonium salt as PTC. The stereoselective epoxidation of unsubstituted (**94**) and 2'-methoxychalcone (**95**) utilizing quinine benzyl chloride (BQC, **98**) and quinidine benzyl chloride (BQdC, **99**) as chiral catalysts gave high yields (ca. 92 - 99%), but low optical purities for both substrates (ee; ca. 21-48%; Table 3.1, entry 1-5). The enantiomer obtained from the BQC reactions revealed a (-)-rotation whereas the BQdC derived product gave the (+)-enantiomer.[8] Absolute configurations were later established by Wynberg and Marsman[10] to be α*R*,β*S* and α*S*,β*R* for the (-)- and (+)-enantiomers, respectively. By employing *N*-[(4-substituted)benzyl]cinchoninium bromides as PTC (dibutyl ether, LiOH and H_2O_2), Arai and co-workers[11] were able to show that an electron-withdrawing substituent on the 4-position of the *N*-benzyl unit improves the efficacy of the system to 84% ee and 97% yield for the unsubstituted chalcone (**94**) with *N*-(4-iodobenzyl)cinchoninium (**100**), (Table 3.1, entry 6).

Table 3.1: Stereoselective synthesis of chalcone epoxide with H_2O_2 as oxidant and various PTC's.

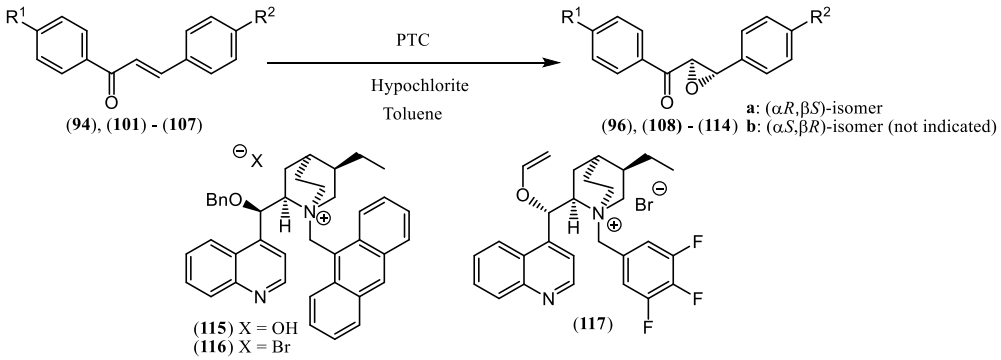


Entry	PTC	Chalcone	R	Epoxide	Yield (%)	ee (%)
[a] **1**[8,10]	BQC(**98**)	**94**	H	**96a**	99	24[d]
[a] **2**[8,10]	BQdC(**99**)	**94**	H	**96b**	-[e]	23[d]
[a] **3**[8,10]	BQdC(**99**)	**95**	OMe	**97b**	-[f]	21[d]
[a] **4**[8,10]	BQC(**98**)	**95**	OMe	**97a**	-[f]	25
[b] **5**[9]	BQC(**98**)	**95**	OMe	**97a**	92	48
[c] **6**[11]	**100**	**94**	H	**96b**	97	84

Reagents and conditions: [a] PTC (1 mol%), toluene, NaOH, 30% H_2O_2, RT, 24 h. [b] PTC (1 mol%), toluene, NaOH, 30% H_2O_2, 21 ° C, 18 h. [c] PTC (5 mol%), dibutyl ether, LiOH, 4 °C, 36-37 h. [d] ee values calculated from the reported optical rotation. [e] Yield only given as high. [f] Yield not reported.

Concurrently, Lygo and Wainwright[12] evaluated *N*-anthracenyl derivatives, e.g. **115**, as PTC during the oxygenation of α,β-unsaturated ketones with aq. NaOCl and found that unsubstituted (**94**), 4-methoxy- (**101**), 4'-nitro- (**105**) and 4'-bromochalcones (**107**) gave good yields and moderate ee's (Table 3.2, entries 1, 6, 11 & 15). They also ascertained that the enantioselectivity of the reaction is not only altered by derivatization of the PTC, but also by altering the *O*-substituents of the catalyst. By reducing the catalyst loading from 10 to 1 mol% and increasing the NaOCl stoichiometry (from 11 to 15%) Lygo and To[13] were able to improve the yield for unsubstituted chalcone (**94**) to 98% when reactions were performed in toluene as solvent (entry 2). These reaction conditions, however, had no effect on the ee (entries 2, 12 & 16) for all substrates.[13,14]

Table 3.2: Stereoselective epoxidation of *trans*-chalcones with hypochlorite and altered PTC's.

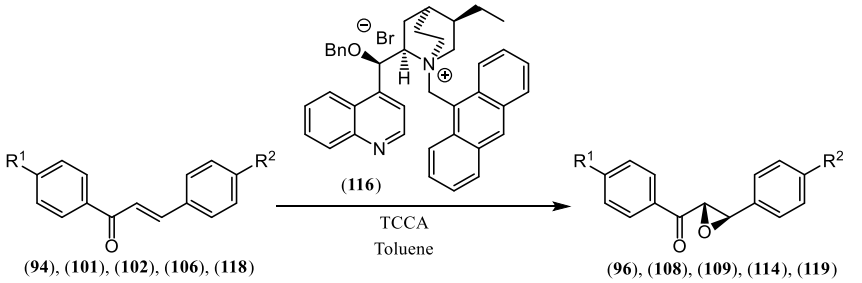


Entry	PTC	Chalcone	R^1	R^2	Epoxide	Yield (%)	ee (%)
[a] **1**[12]	**115**	**94**	H	H	**96b**	90	86
[b] **2**[13]	**115**	**94**	H	H	**96b**	98	86
[c] **3**[15]	**117**	**94**	H	H	**96a**	95	80
[d] **4**[15]	**117**	**94**	H	H	**96a**	82	91
[e] **5**[16]	**116**	**94**	H	H	**96b**	96	93
[a] **6**[12]	**115**	**101**	H	OMe	**108b**	87	82
[d] **7**[15]	**117**	**102**	OMe	H	**109a**	90	91
[e] **8**[16]	**116**	**101**	H	OMe	**108b**	70	95
[d] **9**[15]	**117**	**103**	Me	H	**110a**	71	92
[e] **10**[16]	**116**	**104**	H	Me	**111b**	70	94
[a] **11**[12]	**115**	**105**	NO_2	H	**112b**	85	83
[b] **12**[14]	**115**	**105**	NO_2	H	**112b**	85	86
[d] **13**[15]	**117**	**106**	H	NO_2	**113a**	95	92
[e] **14**[16]	**116**	**106**	H	NO_2	**113b**	90	94
[a] **15**[12]	**115**	**107**	Br	H	**114b**	99	88
[b] **16**[13]	**115**	**107**	Br	H	**114b**	93	88
[e] **17**[16]	**116**	**107**	Br	H	**114b**	92	93

Reagents and conditions: [a] PTC (10 mol%), 11% aq. NaOCl (2 eq), 25 °C, 48 h. [b] PTC (1 mol%), 15% aq. NaOCl (2 eq), 25 °C, 12-24h. [c] PTC (5 mol%), 11% aq. NaOCl (10 eq), RT, 48 h. [d] PTC (5 mol%), 11% aq. NaOCl (10 eq), 0 °C, 24-48 h. [e] PTC (10 mol%), KOCl (8 M), -40 °C, 12 h.

Yoo et al.[15] evaluated the *N*-(2,3,4-trifluorobenzyl)hydrocinchonine-derived (**117**) as PTC in the epoxidation process and found it to be effective in the preparation of (α*R*,β*S*)-epoxyketones in high optical purities. The transformation of unsubstituted chalcone (**94**) as well as 4'-methoxy (**102**), 4'-methyl (**103**) and 4-nitro (**106**) substituted chalcones were also effective and produced the epoxides in high ee's and good yields when performed at 0 °C compared to ambient reaction temperatures (Table 3.2, entries 3 vs. 4 and 7, 9 & 13). Corey and Zhang[16] substituted the NaOCl for its potassium equivalent (KOCl) in combination with bromide PTC (**116**), which allowed for the transformation to be performed at -40 °C. The cryogenic temperature further improved the ee's for the unsubstituted (**94**), 4'-bromo- (**107**), 4-methyl- (**104**), 4-methoxy- (**101**), 4-nitrochalcone (**106**) to ca. 94% (entries 5, 8, 10, 14 & 17). Ye and co-workers[17,18] generated KOCl in situ, by reacting trichloroisocyanuric acid (TCCA) with KOH, and preformed the epoxidation reactions in the presence *N*-anthracenylmethylcinchonidine bromide catalysts (**116**). Although results were similar for the unsubstituted chalcone (**94**; Table 3.2, entry 1 vs. Table 3.3, entry 1) when compared with those reported by Lygo and Wainwright[12] (vide supra), it was established that the reaction was also possible under solid-liquid biphasic conditions with 4'-methoxy- (**102**) and 4-chlorochalcone (**118**) displaying superior results (Table 3.3, entries 2 & 5). For 4-methoxychalcone (**101**) under liquid-liquid conditions, however, monochlorinated products were observed along with unreacted starting material (entry 3).

Table 3.3: Stereoselective epoxidation of *trans*-chalcone derivatives under liquid-liquid and solid-liquid biphasic conditions.[17,18]



a: (α*R*,β*S*)-isomer (not indicated)
b: (α*S*,β*R*)-isomer

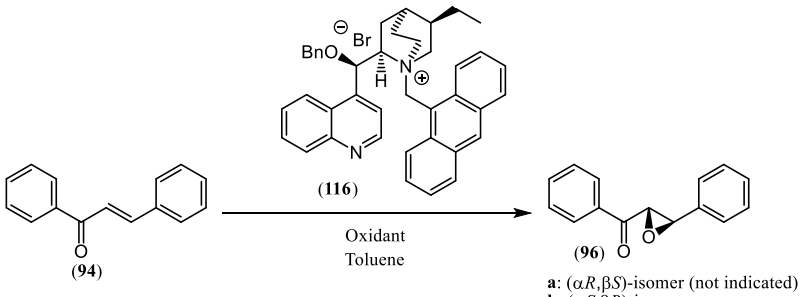
Entry [a]	Chalcone	R^1	R^2	Epoxide	Method A [b]		Method B [c]	
					Yield (%)	ee (%)	Yield (%)	ee (%)
1	**94**	H	H	**96b**	90	89	90	87
2	**102**	OMe	H	**109b**	82	90	86	91
3	**101**	H	OMe	**108b**	0	-	80	91
4	**106**	H	NO_2	**113b**	83	96	76	93
5	**118**	H	Cl	**119b**	97	84	94	89

Reagents and conditions: [a] PTC (10 mol%), TCCA (1 eq), 0 °C, 7 - 24 h. [b] 50% aq. KOH (6 eq). [c] Solid KOH (6 eq).

Alternative oxidant precursors which were evaluated by Lygo et al.[14] were sodium dichloroisocyanurate (NaDCCA), 1,3-dichloro-5,5-dimethylhydantoin (NDDH) and *N*-chlorosuccinimide (NCS). Although high ee's (88-90%) and conversions (80-95%) were

achievable for unsubstituted chalcone (**94**; Table 3.4, entries 1-3) in the presence of all the aforementioned oxidants, only 20% conversion was obtained in the presence of NCS (entry 4).

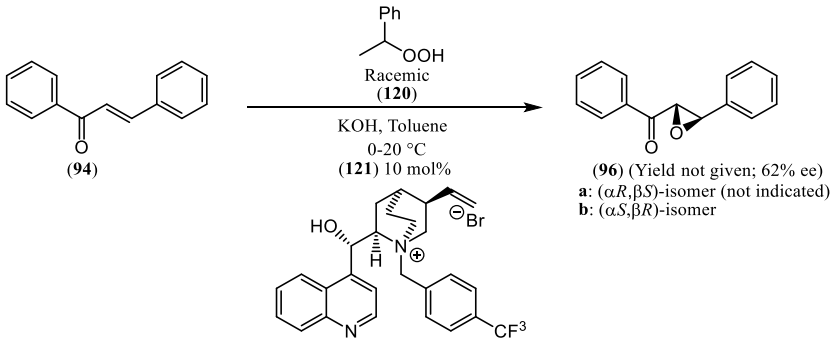
Table 3.4: Oxidant survey for stereoselective epoxidation of trans-chalcone.[14]



Entry [a]	Oxidant	Time (h)	Epoxide	Conversion (%)	ee (%)
1	TCCA	15	**96b**	95	89
2	NaDCCA	24	**96b**	95	88
3	NDDH	24	**96b**	80	86
4	NCS	48	**96b**	20	90

Reagents and conditions: [a] PTC (1 mol%), 50 % aq. KOH, 0 °C.

As is evident from the above discussion, it appears that hypochlorite is the superior oxidant for stereoselective epoxidation of **94** when compared to H_2O_2 (Table 3.1) especially for the cryogenic KOCl system (Table 3.2). Apart from the hypochlorite and H_2O_2 system, other oxidants have also been explored in combination with PTC's. Adam et al.[19] returned to peroxides as oxidant and evaluated (1-phenyl)ethyl hydroperoxide (**120**), as a racemic mixture, in combination with KOH in the presence of the non-alkylated cinchonidine-derived PTC (**121**) in toluene, but no real improvement in ee values were reported (Scheme 3.1).

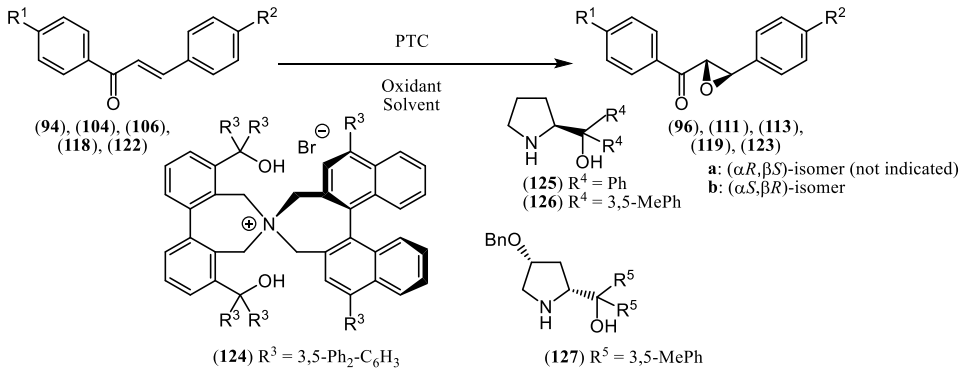


Scheme 3.1: Stereoselective epoxidation of unsubstituted chalcone with a novel hydroperoxide.[19]

Some non-cinchonidine based ammonium salts have also been reported for the epoxidation of chalcones. For example, the *N*-spiroammonium PTC (**124**), containing a diarylmethanol moiety, exhibited excellent enantioselectivity (up to 96%) during the epoxidation of unsubstituted (**94**), 4-chloro (**118**) and 4'-chlorochalcone (**122**) (Table 3.5, entries 1-3).[20] Lattanzi[21,22] and Zhao et al.[23] utilized amino alcohols (e.g. L-or D-proline) as a bifunctional catalyst during the epoxidation of α,β-

enones. Employing a more sterically encumbered catalysts (**126** vs. **125**) not only increased the chiral induction (entry 4 vs. 5), but also reduced the catalyst loading from 30 to 20 mol%.[21,22] Furthermore, Zhao et al.[23] illustrated that the C-2 and C-4 configurations of these catalysts have a profound influence on the enantioselectivity of the reaction and showed that a *cis*-benzyloxy moiety at C-4 (**127**) improved both enantioselectivity and reactivity (entry 6). Chalcones with either electron-donating or electron-withdrawing substituents were converted with both **126** and **127** PTC into epoxides in high ee's (entries 7-12). However, **127** seemed to induce a higher degree of enantioselectivity compared to **126,** but in a lower overall chemical yield (entries 5, 7, 9, 11 vs 6, 8, 10, 12).

Table 3.5: Stereoselective epoxidation of *trans*-chalcones with non-cinchonidine based ammonium salts.[20–24]



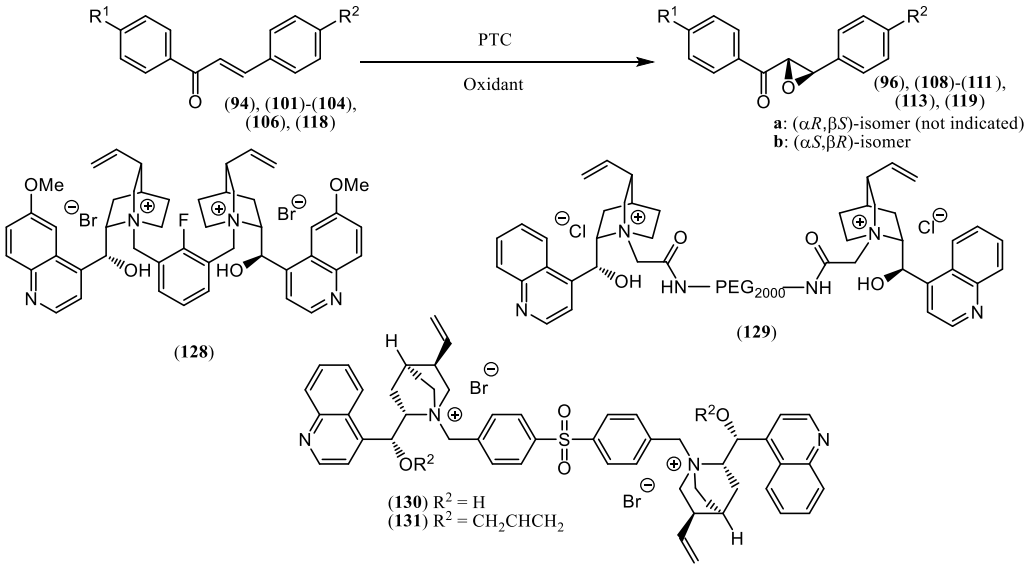
Entry	PTC	Chalcone	R^1	R^2	Epoxide	Yield (%)	ee (%)
[a] **1**[20]	**124**	**94**	H	H	**96b**	99	96
[a] **2**[20]	**124**	**118**	H	Cl	**119b**	99	96
[a] **3**[20]	**124**	**122**	Cl	H	**123b**	99	93
[b] **4**[21]	**125**	**94**	H	H	**96a**	72	75
[c] **5**[22]	**126**	**94**	H	H	**96a**	90	91
[b] **6**[23]	**127**	**94**	H	H	**96b**	75	94
[c] **7**[22]	**126**	**104**	H	Me	**111a**	75	90
[b] **8**[23]	**127**	**104**	H	Me	**111b**	72	94
[c] **9**[22]	**126**	**118**	H	Cl	**119a**	81	92
[b] **10**[23]	**127**	**118**	H	Cl	**119b**	76	96
[c] **11**[22]	**126**	**106**	H	NO_2	**113a**	90	82
[b] **12**[23]	**127**	**106**	H	NO_2	**113b**	90	94

Reagents and conditions: [a] PTC (3 mol%), 13% aq. NaOCl, toluene, 0 °C, 24-48 h. [b] PTC (30 mol%), TBHP (1.2 eq), hexane, RT, 94-190 h. [c] PTC (20 mol%), TBHP (1.2 eq), hexane, 4 °C, 112-178 h.

Jew et al.[25] combined dimeric ammonium salts, e.g. **128**, with surfactants (e.g. Triton X-100, span® 20 and Tergitol NP 9) and were able to improve selectivity and reduce reaction times without the need for sub-zero temperatures. PTC **128** in the presence of span® 20 (sorbitan monolaurate) was identified as the most promising system for unsubstituted (**94**), 4'-methoxy- (**102**) and 4'-methylchalcone (**103**), which were all converted into their respective epoxides in high yield (ca. 95-96%) and ee (ca. 97-

99%) (Table 3.6, entries 1, 5 & 6). Wang et al.[26] investigated soluble dimeric cinchonidine and quinine PTC's anchored to diacetamido-PEG_{2000} chloride (**129**), but could not obtain ee's higher than 86% (entry 2), while Ashokkumar et al.[27] found dimeric PTC's **130** and **131** to yield similar reactivity and selectivity for all the 4-methoxy (**101**), 4-methyl (**104**), 4-chloro (**118**) and 4-nitro (**106**) substituted chalcones (entries 3, 4, 7-12).

Table 3.6: Stereoselective epoxidation of *trans*-chalcones with dimeric ammonium salts.



Entry	PTC	Chalcone	R^1	R^2	Epoxide	Yield (%)	ee (%)
[a] **1**[25]	**128**	**94**	H	H	**96b**	95	99
[b] **2**[26]	**129**	**94**	H	H	**96a**	90	86
[c] **3**[27]	**130**	**101**	H	OMe	**108a**	95	97
[c] **4**[27]	**131**	**101**	H	OMe	**108a**	95	98
[a] **5**[25]	**128**	**102**	OMe	H	**109b**	95	99
[a] **6**[25]	**128**	**103**	Me	H	**110b**	96	97
[c] **7**[27]	**130**	**104**	H	Me	**111a**	94	92
[c] **8**[27]	**131**	**104**	H	Me	**111a**	94	94
[c] **9**[27]	**130**	**118**	H	Cl	**119a**	98	98
[c] **10**[27]	**131**	**118**	H	Cl	**119a**	98	99
[c] **11**[27]	**130**	**106**	H	NO_2	**113a**	92	95
[c] **12**[27]	**131**	**106**	H	NO_2	**113a**	92	96

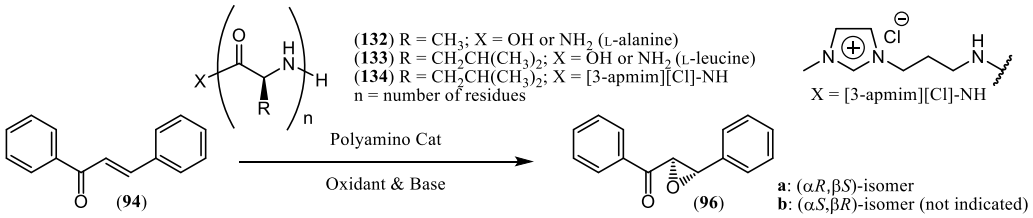
Reagents and conditions: [a] PTC (1 mol%), Span® 20 (1 mol%), 30% H_2O_2 (10 eq), 50% aq. KOH (1 eq), diisopropyl ether (iPr_2O), RT, 1.5-4 h. [b] PTC (50 mol%), 70% *t*-BuOOH, KOH (1 M), DCM, 0 °C, 48 h. [c] PTC (3 mol%), H_2O_2, 10% aq. Cs_2CO_3, toluene, RT, 4.5 h.

Upon comparing these dimeric PTC's it would appear that dimeric catalysts can reduce the reaction time drastically (from 7 - 48 h to just 1.5 - 4.5 h) compared to any of the aforementioned monomeric PTC or non-cinchonidine based ammonium salts. Although promising yields and ee's were obtained with quaternary ammonium catalysts in the epoxidation of α,β-unsaturated ketones, like chalcones, none of the substrates used in these studies were compounds with naturally occurring substitution patterns.

3.2.2 Poly(amino Acid) Catalysed Epoxidation Systems

Juliá and co-workers[28] utilized poly(amino acids) (PAA), such as poly-L-alanine (**132**, PLA), as stereoselective catalysts in stereoselective epoxidation of chalcones. Utilizing these insoluble amino acid catalysts in a triphasic system, with aq. NaOH, H_2O_2 and an organic solvent (toluene) containing the substrate, provided a promising yield (ca. 85%) and ee (ca. 93%) for unsubstituted chalcone (**94**) (Table 3.7, entry 1). Subsequently, Colonna et al.[29] found a linear relationship between the degree of stereoselective induction and the chain length of the poly(amino acid) with the optimal length being between 10 and 30 amino acid residues. Although it was found that these gel-like catalysts may be recycled after separation from the reaction mixture by filtration, the recycled catalyst showed a severe loss of stereoselectivity due to catalyst degradation under the prevailing alkaline conditions.[29] Itsuno et al.[30] addressed this limitation by utilizing a polymer-supported poly(amino acid), e.g. poly(styrene-co-divinylbenzene)-supported poly-L-leucine (**133**, i-PLL), as chiral catalyst and was able to improve both the yield and ee for the unsubstituted (**94**) (Table 3.7, entry 2). Not only could the i-PLL catalyst be recycled multiple times without significant activity loss, but with a lower degree of polimerization (less than 10 amino acid residues) favourable ee's (ca. 80-88%) could still be achieved.

Table 3.7: Stereoselective epoxidation with poly(amino acid) catalysts.



Entry	Epoxide	Yield (%)	ee (%)
[a] **1**[28]	**96a**	85	93
[b] **2**[30]	**96a**	94	97
[c] **3**[31]	**96a**	100	>95
[d] **4**[32]	**96a**	*>99* [l]	96
[e] **5**[32]	**96a**	92	89
[f] **6**[32]	**96a**	87	94
[g] **7**[33]	**96a**	96	95
[h] **8**[33]	**96a**	99	95
[i] **9**[34]	**96a**	*>99* [l]	94
[j] **10**[35]	**96a**	*100* [l]	≥93
[k] **11**[36]	**96a**	91	95

Reagents and conditions: [a] PLA (10 mol%), aq.NaOH (4 eq), 30% H_2O_2 (30 eq), toluene, RT, 48 h. [b] i-PLL (1 meq), see note a. [c] i-PLL (10 mol%), DBU (1.2 eq), UHP (1.2.eq), dry THF, 30 min. [d] i-PLL (10 mol%), NaPc (1.5 eq), H_2O-DME, RT, 20 min. [e] i-PLL (2 mol%), see note c. [f] i-PLL (2 mol%), see note d. [g] [3-apmim]Cl-PLL (20 mol%), NaPc (1.5 eq), H_2O-DME, RT, 2 h. [h] Recycled catalyst (7th time), 15 min, see note i. [i] PLL (11 mol%), TBAB (11 mol%), aq. NaOH (5M, 4.2 eq), 30% H_2O_2 (28.5 eq), toluene, RT, 1.5 h. [j] PLLSiCat (2.5 mol%, one eq based on one amino acid chain), 50 min, see note c. [k] AP-PLL-silica gel (10 mol%), NaPc (1.6 eq), DME-H_2O, RT, 4 h. [l] Italicised values refer to conversion.

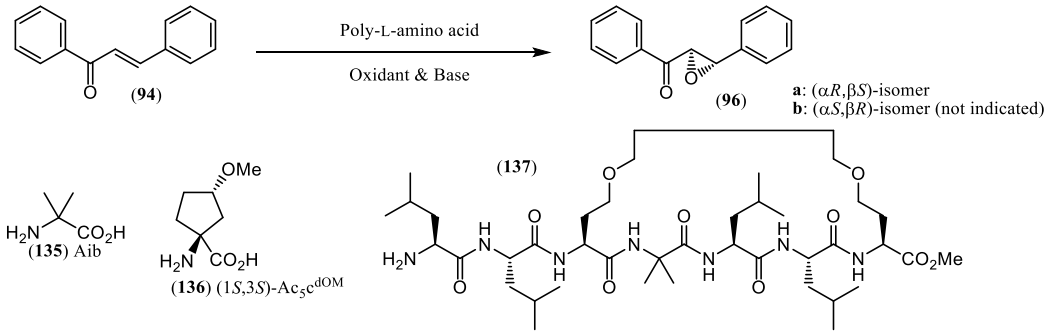
By utilizing a non-aqueous system {polymer-supported poly-L-leucine (i-PLL), urea-hydrogen peroxide (UHP), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF} Roberts and co-workers[31] improved the Juliá-Colonna conditions and were able to obtain the epoxide **96**a in quantitative yield and high ee (ca. 95%) within 30 minutes (Table 3.7, entry 3). Nevertheless, the utilization of DBU and UHP led to a more expensive system, thus Roberts et al.[32] reverted to sodium percarbonate (NaPc) as both base and oxidant in a water/1,2-dimethoxyethane (DME) solvent mixture. These conditions offered excellent enantioselectivities (96%, entry 4) and a lower catalyst loading (10 vs. 2 mol%, based on a single amino acid as catalytic unit) without any decrease in enantioselectivity (entry 5 vs 6).[32] By utilizing an imidazolium-modified PLL catalyst [**134**, (3-apmim)Cl-PLL], Tang et al.[33] could eliminate any preactivation required by the Roberts' NaPc system and obtained ee's of (95%) for the chalcone epoxide **96a** even after seven cycles (entry 7 & 8). Although the Roberts system improved and simplified catalyst recycling, the Juliá-Colonna triphasic system was still preferred for large-scale industrial work. Owing to this Geller et al.[34] made significant reactivity improvements by introducing a PTC (e.g. tetra-*n*-butylammonium bromide, TBAB) to the catalyst system and were able to epoxidize **94** in 99% conversion with 94% ee in only 1.5 h (entry 9).

Finally, Roberts and co-workers[35] introduced silica-supported poly-L-leucine (PLLSiCat) catalysts, which simplified the separation process of the catalyst from the product mixture and were able to obtain complete conversion and high ee (93%) for unsubstituted chalcone (**94**; Table 3.7, entry 10). By first polymerizing the amino acid and then grafting it onto (3-aminopropyl)triethoxysilane (APTESi) activated silica gel, Tang and co-workers[36] were able to form a stable AP-PLL-silica gel catalyst, which could be recycled up to six times without any noticeable decrease in ee (entry 11). Through the addition of a nucleophilic solvent-soluble polymer (diamino-PEG) as initiator during catalyst polymerization process, Roberts et al.[37] were able to generate the first Juliá-Colonna type THF-soluble PAA catalyst {e.g. H-[(L-Leu)$_n$NH-PEG$_x$-NH(L-Leu)]$_n$} which resulted in high ee's (ca. 95-98%) for **96a**.[37–39]

Juliá et al.[29] postulated that an α-helical structure of poly(amino acids) is necessary for efficient catalytic activity and that the terminus of the catalyst had some effect on the selectivity of the reaction. FT-IR and molecular modelling studies showed that catalysts with four or more residual amino acid units adopted an α-helical structure and thus indicated that the *N*-terminus plays a pivotal role in the selectivity of the reaction for both solid-phase bound and 'free' PLL catalysts.[37–39] By altering the peptide of the *N*-terminus form L- to D-Leu [e.g. H-(L-Leu)$_{20}$R to H-(D-Leu)$_5$(L-Leu)$_{15}$R], Roberts and co-workers[40,41] were able to provide further support for the fact that the *N*-terminus directs and determines the stereochemical outcome of the reaction, since the preferred product was changed from the (2*R*,3*S*) to the (2*S*,3*R*)-enantiomer.

Since it was found that an α-helical structure of the poly(amino acid) is an important factor during the chiral induction process Ohkata et al.[42] incorporated a helix-inducer [α-aminobutyric acid (**135**; Aib)] during the preparation of their catalyst and reported oligo-L-leucine (e.g. Boc-L-Leu_6-Aib-L-Leu_6-OBzl) prepared in this way to give **96a** in an excellent ee of 94% (Table 3.8, entry 1). Tanaka et al.[43] found that a cyclic α,α-disubstituted amino acid (dAA) catalyst {e.g. R-[L-Leu-L-Leu-(1*S*,3*S*)-Ac_5c^{dOM}(**136**)]$_3$-OMe} gave better enantioselectivity when the *N*-terminus was unprotected [i.e R = H vs. BOC, entry 2 vs. 3], while they were also able to reduce the catalyst loading from 25 to 5 mol%. Demizu et al.[44] developed a stapled helical L-Leu-based catalyst that contains four Aib residues, promoting the helical structure with a cross-linked subunit ensuring a right-handed (*P*) helix. Tethering the L-Leu rich peptides to L-homoserine (L-Hse) resulting in catalyst **137**, they were able to obtain **96a** in quantitative yield and almost complete enantiomeric purity (entry 4).

Table 3.8: Enantioselective epoxidation of chalcone with modern PAA catalysts.



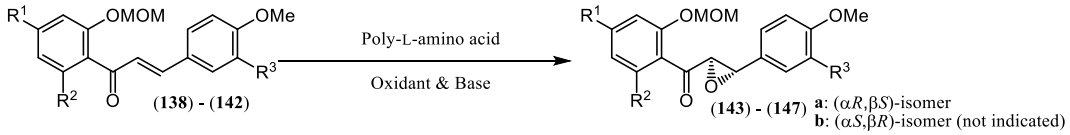
Entry	Chalcone	Epoxide	Yield (%)	ee (%)
[a] **1**[42]	**94**	**96a**	73	94
[b] **2**[43]	**94**	**96a**	98	82
[c] **3**[43]	**94**	**96a**	99	98
[d] **4**[44]	**94**	**96a**	99	>99

Reagents and condition: [a] Boc-L-Leu_6-Aib-L-Leu_6-OBzl (4 mol%), DBU (6 eq), UHP (1.3 eq), THF, RT, 24 h. [b] Boc-[L-Leu-L-Leu-(1*S*,3*S*)-Ac_5c^{dOM}]$_3$-OMe (25 mol%), DBU (5.6 eq), UHP (1.1 eq), THF, 0 °C –RT, 24 h. [c] H-[L-Leu-L-Leu-(1*S*,3*S*)-Ac_5c^{dOM}]$_3$-OMe (5 mol%), see note b. [d] **137** (10 mol%), see note b.

Although several authors reported various alterations and improvements to the poly(amino acid) epoxidation catalyst system (vide supra), all of these investigations were limited by the fact that only unsubstituted, mono- or disubstituted chalcones were subjected to the epoxidation reaction. Both triphasic and biphasic systems were therefore successfully extended to 2' protected chalcones (**138 - 142**) displaying naturally occurring oxygenation patterns by Ferreira and co-workers.[7,45–49] Although the triphasic system (NaOH, H_2O_2, CCl_4) with poly-L-alanine catalyst afforded the (α*R*,β*S*)-chalcone epoxides (**143 - 147**) in moderate to good yields (ca. 79-99%) and ee's (ca. 49-86%) (Table 3.9, entries 1-5), the utilization of the adapted biphasic system (i-PLL, DBU, UHP, THF) resulted in higher ee values (ca. 53-95%) for almost all substrates (entries 6-10). Epoxidation reactions with the poly-D-amino acid catalyst were also successful in yielding the opposite (α*S*,β*R*)-enantiomer of the

chalcone epoxides, albeit with somewhat inferior yield and ee's when compared to the L-amino acid catalyst (ee values between 49-74% for the Juliá procedure and 50-90% for the biphasic procedure). Expanding the substrate scope highlighted the effect of the substitution pattern of the chalcone on the enantioselectivity and yield of the reaction, since substrates (**141** and **142**) containing a phloroglucinol B-ring gave low ee's (ca. 53-70%) and yields (ca. 21-97%) (entries 4, 5, 9 & 10).[47,48,49]

Table 3.9: Stereoselective epoxidation of chalcones exhibiting oxygenation patterns of naturally occurring flavonoids with poly(L-amino acid).

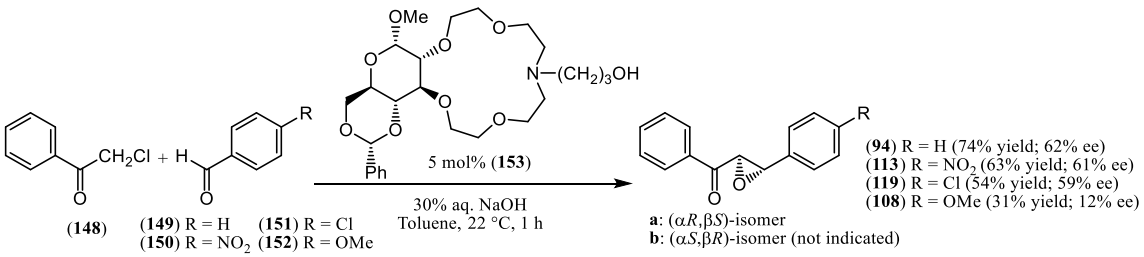


Entry	Chalcone	R^1	R^2	R^3	Epoxide	Yield (%)	ee (%)
[a] **1**[47]	**138**	H	H	H	**143a**	99	84
[a] **2**[47]	**139**	OMe	H	H	**144a**	98	86
[a] **3**[47]	**140**	OMe	H	OMe	**145a**	99	67
[a] **4**[47]	**141**	OMe	OMe	H	**146a**	97	70
[a] **5**[47]	**142**	OMe	OMe	OMe	**147a**	79	49
[b] **6**[48,49]	**138**	H	H	H	**143a**	71	85
[b] **7**[48,49]	**139**	OMe	H	H	**144a**	80	95
[b] **8**[48,49]	**140**	OMe	H	OMe	**145a**	64	88
[b] **9**[49]	**141**	OMe	OMe	H	**146a**	36	60
[b] **10**[49]	**142**	OMe	OMe	OMe	**147a**	21	53

Reagents and condition: [a] PLA: chalcone (1:1; m/m), NaOH (6 M), 30% H_2O_2, CCl_4, 36-96 h. [b] i-PLL: chalcone (2:1; m/m), DBU (1.4 eq), UHP (1.2 eq), dry THF, 48-96 h.

3.2.3 Chiral Crown Ethers as PTC

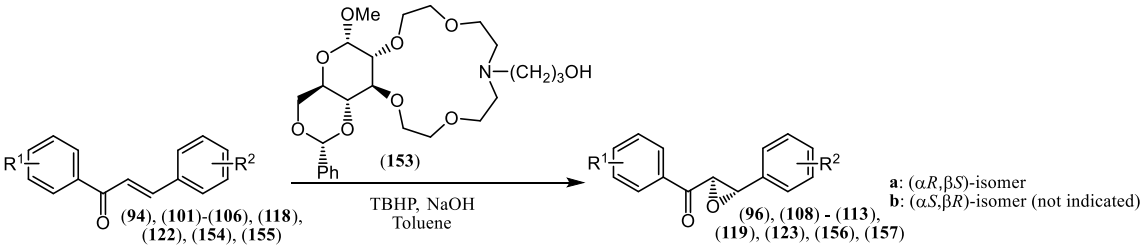
The exploration of sugar-based crown ether catalysts (**153**) on the Michael addition and Darzens condensation reactions (Scheme 3.2) resulted in the enantioselective epoxidation of *trans*-chalcones (**94**, **108**, **113** and **119**).[50] After testing a series of lariat ether catalysts (*N*-substituents containing electron-donating heteroatom)[50,51] containing various monosaccharide units (e.g. α-D-galactopyranoside-, α- and β-D-glucopyranoside-based), it was established that the enantioselectivity was significantly affected by not only the sugar moiety, but also by the *N*-substituents. It was furthermore shown that the α-D-glucopyranoside-based catalyst with acetal (CH-Ph) protected hydroxy groups and a hydroxypropyl *N*-substituent, i.e. **153**, resulted in optimum chiral induction (78% yield and 73% ee) for unsubstituted chalcone (**94**) (Table 3.10, entry 1).[51–53]



Scheme 3.2: Synthesis of α,β-epoxyketones through Darzens condensation.[50]

Over the years Bakó and co-workers[52–56] found that lowering the reaction temperature from RT to 2 °C affected the ee positively (Table 3.10, entries 1-3) and were able to obtain the epoxides of chalcones containing chloro, methoxy, methyl and nitro substituents (entries 6-13) during their investigations. Molecular modelling studies indicated that the nucleophilic addition of the peroxy anion to the β-carbon of the chalcone to be the configuration determining step of the reactions.[55] By varying the substituent position Bakó and co-workers,[52–56] were able to show that superior ee's could be obtained for the *para*-substituted (**122**) compounds compared to the *ortho*-(**154**) and *meta*-(**155**) substituted analogues (entries 4-6),[56] with the lowest ee values for those with *ortho*-substituents. Electron-donating groups gave better yields but not better ee's compared to the electron-withdrawing analogues (entry 6 vs. 8), while moving the substituents from the B to the A-ring also resulted in lower ee's (entries 7-13).[56]

Table 3.10: Stereoselective epoxidation of *trans*-chalcone with α-D-glucopyranoside-based PTC.

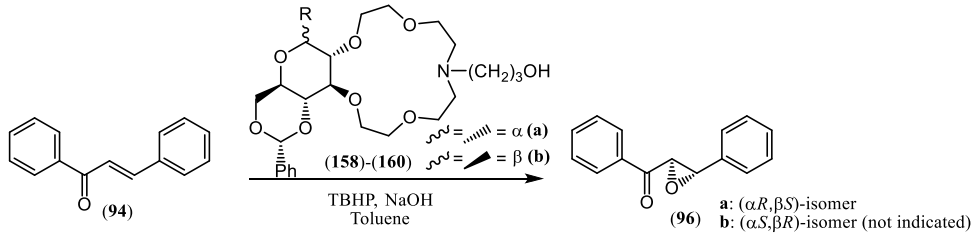


Entry [a]	Chalcone	R^1	R^2	Epoxide	Time (h)	Yield (%)	ee (%)
[b] **1**[52]	**94**	H	H	**96a**	1	78	73
[c] **2**[53,54]	**94**	H	H	**96a**	1	50	92
[d] **3**[56]	**94**	H	H	**96a**	1	82	94
[d] **4**[56]	**154**	*o*-Cl	H	**156a**	3	65	69
[d] **5**[56]	**155**	*m*-Cl	H	**157a**	2	68	79
[d] **6**[56]	**122**	*p*-Cl	H	**123a**	2	71	97
[d] **7**[56]	**118**	H	*p*-Cl	**119a**	2	78	83
[d] **8**[56]	**103**	*p*-Me	H	**110a**	2	81	92
[d] **9**[56]	**104**	H	*p*-Me	**111a**	2	88	86
[d] **10**[56]	**102**	*p*-OMe	H	**109a**	3	58	95
[d] **11**[56]	**101**	H	*p*-OMe	**108a**	2	79	85
[d] **12**[56]	**105**	*p*- NO_2	H	**112a**	2	63	96
[d] **13**[56]	**106**	H	*p*-NO_2	**113a**	1	52	63

Reagents and conditions: [a] PTC (7 mol%), TBHP (2 eq), 20% aq. NaOH (3.5 eq), toluene. [b] Temp: RT. [c] Temp: 4 °C. [d] Temp: 2 °C.

Additionally, Bakó et al.[57] investigated the catalytic effect of α-(**158a – 160a**) and β-alkyloxy (**158b** – **160b**) (methoxy, ethoxy and *i*-propoxy) substituents on C-1 of the sugar moiety and found that a size increase of the C-1 substituent led to a decrease in ee (Table 3.11, entries 4-6). Furthermore, α-anomers were found to generate higher stereoselective induction compared to the β-anomers (entries 1-3 vs 4-6).

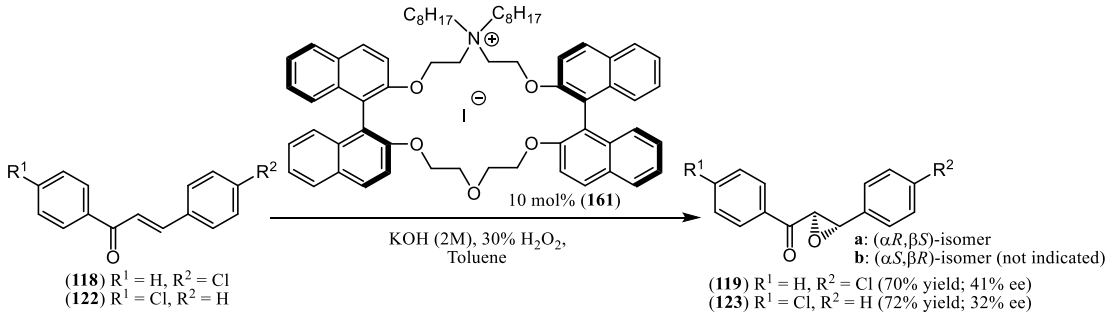
Table 3.11: Stereoselective epoxidation of *trans*-chalcone with C-1 substituted crown ethers.[57]



Entry	Catalyst	R	Yield (%)	ee (%)
1	**158a**	α-OMe	82	94
2	**159a**	α-OEt	96	94
3	**160a**	α-O*i*Pr	93	93
4	**158b**	β-OMe	87	84
5	**159b**	β-OEt	93	78
6	**160b**	β-O*i*Pr	86	73

Reagents and conditions: [a] PTC (7 mol%), TBHP (2 eq), 20% aq. NaOH (3.5 eq), toluene, RT, 1 h.

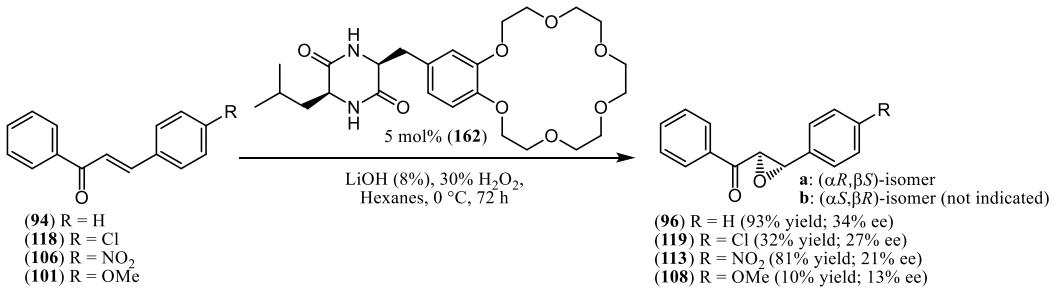
As crown ether catalysts gave a few promising yields and ee's compared to quaternary ammonium salts, Hori et al.[58] investigated a novel azacrown ether-type chiral quaternary ammonium salt (**161**), which would function as a surfactant and as chiral recognition molecule. The ee's obtained, however, were disappointing and did not improve on results obtained from the existing quaternary ammonium or crown ether PTC's for 4-chloro- (**118**) and 4'-chlorochalcones (**122**) (Scheme 3.3).[58]



Scheme 3.3: Stereoselective epoxidation of *trans*-chalcone with a novel PTC.[58]

Bérubé and Voyer[59] prepared and tested a cyclic dipeptide based supramolecular chiral catalyst (*cis*-**162**) on various *para*-substituted chalcones (Scheme 3.4). Although, L-DOPA-derived crown ethers were combined with the L-leucine derived catalyst in an attempt to enhance enantioselectivity the ee's

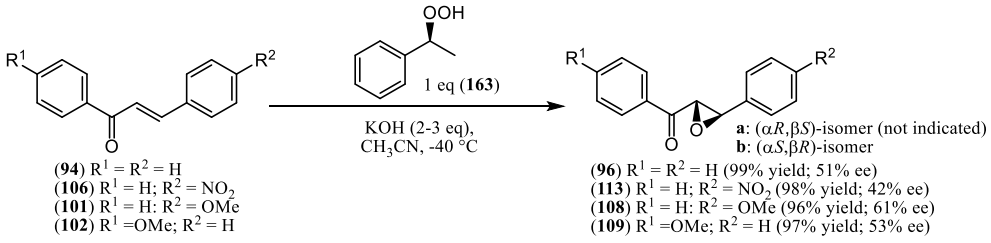
obtained were low compared to the aforementioned studies. Even though the use of crown ether PTC's resulted in promising yields, only a few examples of moderate to good ee's were obtained. Furthermore, epoxidation of substrates resembling naturally occurring chalcones, e.g. 4-methoxychalcone (**101**), gave low to moderate yields and only one promising ee of ca. 95% (Table 3.10, entry 10).



Scheme 3.4: Stereoselective epoxidation with crown-ether-modified cyclic dipeptide PTC.[59]

3.2.4 Chiral Peroxides and Dioxiranes

Optically active peroxides, e.g. *S*-(-)-(1-phenyl)ethyl hydroperoxide (**163**), have been evaluated for the stereoselective epoxidation of α,β-unsaturated ketones by Adam et al.[60] Although the yields were high (ca. 96-99%), the ee's obtained were moderate to low (ca. 42-61 %) for the 4-nitro (**106**), 4-methoxy (**101**), 4'-methoxy (**102**) and unsubstituted chalcone (**94**) (Scheme 3.5). The study, however, established that the metal ion of the inorganic base plays a pivotal role in the chiral induction process through a template effect between the substrate and the hydroperoxide. Zilbeyaz et al.[61] developed and tested a series of *p*-substituted phenylethyl hydroperoxides as enantioselective oxidants in the stereoselective Wietz-Scheffer epoxidation of **94**. Although these hydroperoxides led to quantitative conversion they did, however, not improve the enantioselectivity with ee's below 44%.

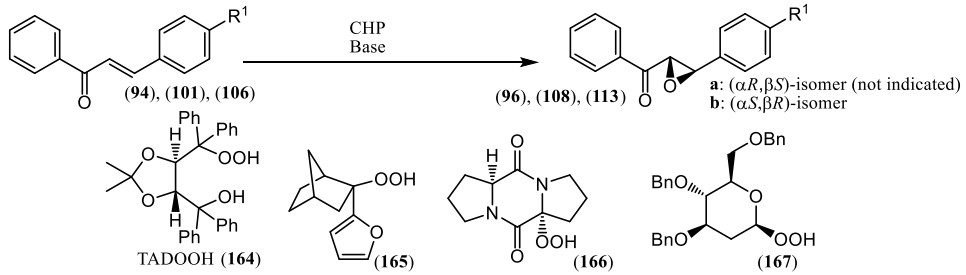


Scheme 3.5: Chiral epoxidation with optically active peroxide.[60]

Replacing one OH group on TADDOL with an OOH group, Seebach and Aoki[62] were able to prepare a stable crystalline hydroperoxy alcohol viz. TADOOH (**164**), which when reacted with sub-stoichiometric amounts of *n*-butyllithium (BuLi) at low temperatures (e.g. -78 °C) led to a 98% ee and 80% yield of the unsubstituted chalcone epoxide (**96b**) with a dominant (2*S*,3*R*)-epoxide configuration (Table 3.12, entry 1). The development of a tertiary hydroperoxide derived from

(+)-norcamphor (**165**) by Lattanzi et al.[63] in recent years led to no significant improvement in the enantioselectivity of the products during the stereoselective epoxidation of chalcones with low ee values (ca. 42-45%) obtained for a series of substituted *E*-chalcones (entries 2-4). Diketopiperazine-derived hydroperoxide (**166**)[64] also yielded a low ee (ca. 37%) for unsubstituted chalcone (**94**; entry 5) and although glycosyl hydroperoxide (**167**)[65] gave higher ee (ca. 95%) for the same substrate (entry 6) both chiral hydroperoxides (CHP), **166** and **167**, required extended the reaction times when compared to the (+)-norcamphor (**165**) system.[64,65]

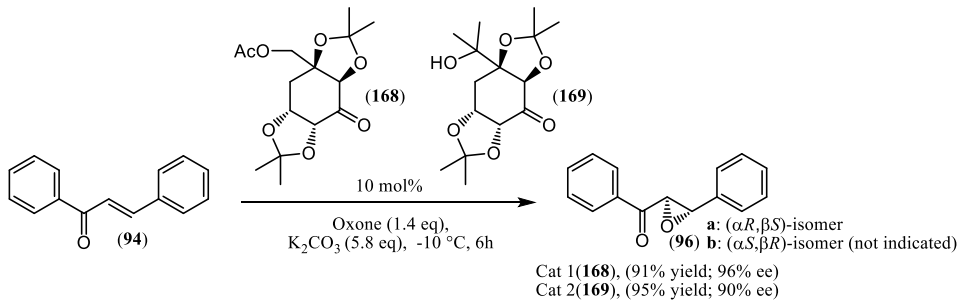
Table 3.12: *E*-chalcone epoxidation by employment of novel hydroperoxides.[62,63]



Entry [a]	Chalcone	R^1	Epoxide	Yield (%)	ee (%)
[a] **1**[62]	**94**	H	**96b**	80	98
[b] **2**[63]	**94**	H	**96a**	66	43
[b] **3**[63]	**106**	*p*-NO_2	**113a**	98	45
[b] **4**[63]	**101**	*p*-OMe	**108a**	30	42
[c] **5**[64]	**94**	H	**96a**	84	37
[d] **6**[65]	**94**	H	**96b**	-[e]	95

Reagents and conditions: [a] TADOOH (**164**) (1.5 eq), *n*-BuLi (1.1 eq), THF, -78 °C, 120 h. [b] **165** (1.1 eq), *n*-BuLi (1.2 eq), THF, -20 °C, 1-3 h. [c] **166** (1.1 eq), DBU (1.2 eq), THF, 0 °C, 6 d. [d] **167** (1.5 eq), NaOH (1.5 eq), dry toluene, RT, 3-6 d. [e] Yields not reported.

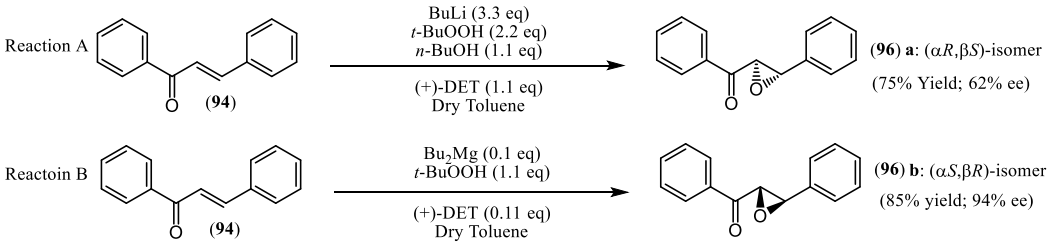
As dioxiranes are powerful and versatile oxygen transfer agents, epoxidations mediated by these compounds may be stereoselective if chiral ketones are used for the preparation of the oxidant. Recently, Shi and co-workers[66–68] were able to utilize the in situ generated dioxiranes derived from (-)-quinic acid (**168** and **169**), in the epoxidation of the unsubstituted chalcone (**94**) and were able to obtain the products in good ee (ca. 90-96%) and yield (ca. 91-95%) (Scheme 3.6). Although stereoselective epoxidation with dioxiranes gave good results, the formation of the dioxiranes are complicated by the competing Baeyer-Villiger oxidation, so many ketones are unreactive in this regard. Furthermore, while novel efficient chiral dioxiranes have been reported for the stereoselective epoxidation of electron-deficient olefins, hardly any have been employed for the epoxidation of chalcone substrates.[69–72]



Scheme 3.6: Epoxidation of unsubstituted chalcone with chiral dioxiranes.[66,67]

3.2.5 Metal Complex Based Epoxidation Catalysts

Several methods for the stereoselective epoxidation of electron-deficient alkenes utilizing chiral ligand-metal peroxide systems have been reported with a number of metals [e.g. Zn, Li, Mg and various lanthanides] and ligands [e.g. binaphthyl (BINOL), diethyl tartrate and prolinols]. Jackson et al.[73] established that di-*tert*-butyl peroxide, generated in situ from *tert*-butyl hydroperoxide (TBHP) and *n*-BuLi, gave an acceptable ee (ca. 62%) in the presence of lithium butoxide and (+)-diethyl tartrate (DET) for unsubstituted chalcone (**94**, Scheme 3.7, Reaction A). Exchanging BuLi for the more commercially available dibutylmagnesium (Bu_2Mg) provided a more enantioselective system in which the number of equivalents of the reagent could be significantly decreased (ee of ca. 94%; Reaction B).

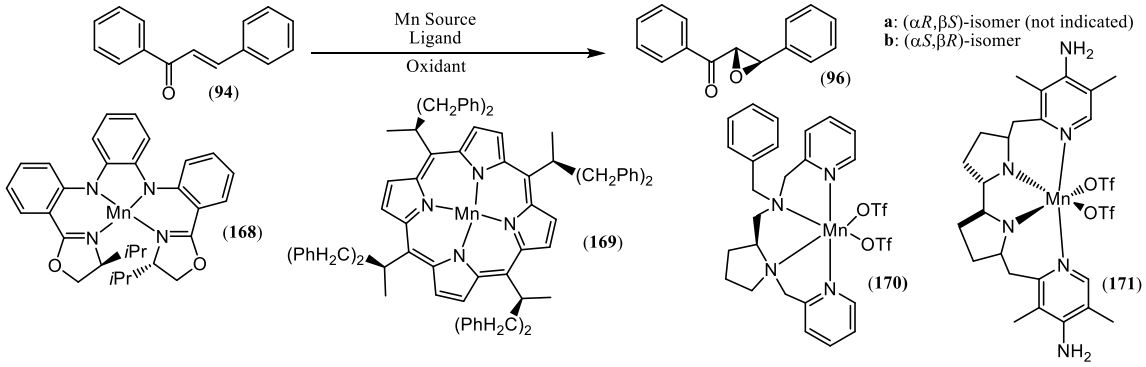


Scheme 3.7: Diethyl tartrate-metal peroxide system.[73]

Zinc-mediated stereoselective epoxidations with diethylzinc (Et_2Zn), O_2 and a chiral alcohol, reported by Enders et al.,[74] were only applied to unsubstituted chalcone (**94**) and gave the epoxide (**96a**) in 61% ee and 94% yield. In an attempt to improve on the Enders system, Pu et al.[75] investigated a chiral poly-BINOL zinc-mediated system and found that although the enantioselectivity of the reaction increased (71% ee), the yields were much lower (ca. 41%). The change from O_2 to stoichiometric amounts of TBHP improved the yield for the unsubstituted chalcone (**94**) and led to the isolation of the epoxide (**96a**) in 74% ee and 95% yield, while Dötz and Minatti[76,77] using a BINOL-Et_2Zn system with cumene hydroperoxide (CMHP) as oxidant were able to improve the yield to 99% and 76% ee for the unsubstituted chalcone (**94**).

Various groups have developed and tested novel non-heme or porphyrin inspired catalysts with an array of metals (e.g. Mn, Yb, Co), Goa et al.[78] reported a porphyrin-based catalyst (**168**) {prepared from $Mn(OTf)_2$ and a tetradentate N_4 ligand} and obtained the unsubstituted chalcone epoxide (**96b**) in a 50% ee and 5% yield (Table 3.13, entry 1). A novel chiral porphyrin Mn complex (**169**), developed by Sakthipriya and Ananthi,[79] improved on Goa's unsubstituted chalcone (**94**) results with a 90% ee and yield being obtained when iodosylbenzene (PhIO) was utilized as oxidant (entry 2). The groups of Sun[80–82] and Bryliakov[83–87] tested non-porphyrinic/heme Mn Based catalysts, (**170**) and (**171**), prepared from $Mn(OTf)_2$ and tetradentate N_4 ligands, which yielded the unsubstituted chalcone epoxide (**96a**) in a 90% ee and 96% yield (entry 3) and 98% ee with a quantitative yield (entry 4), respectively. Furthermore, Bryliakov and co-workers[83–87] found that an improvement in the electron-donating ability of the substituents of the ligand ultimately led to an increases in the enantioselectivity of the reactions.

Table 3.13: Stereoselective epoxidation of chalcone with Mn-tetradentate N_4 catalysts.

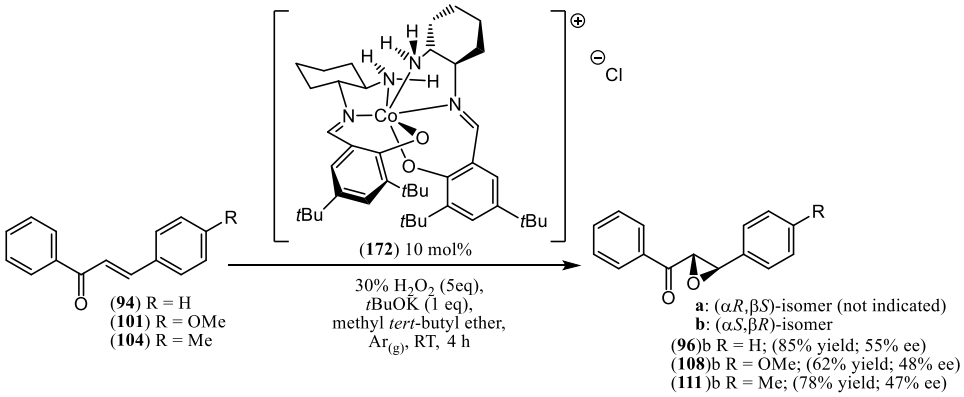


Entry	Epoxide	Yield (%)	ee (%)
[a] **1**[78]	**96b**	5	50
[b] **2**[79]	**96** [c]	90	90
[d] **3**[87]	**96a**	96	90
[e] **4**[82]	**96a**	100	98

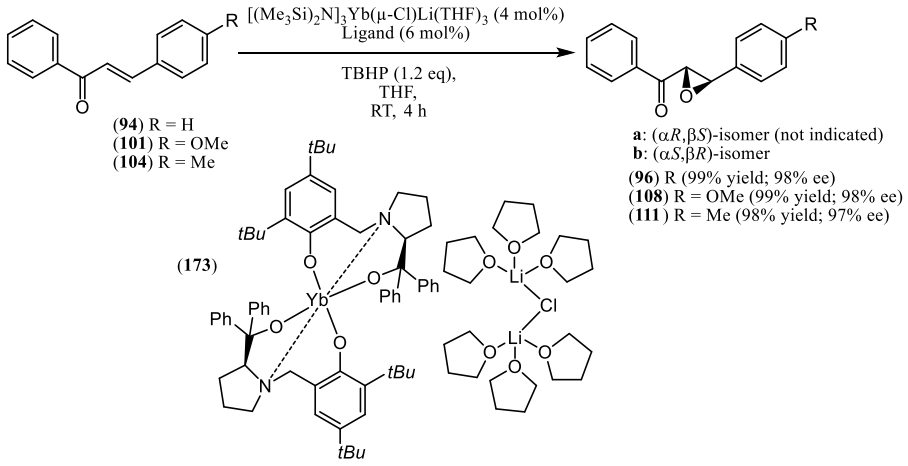
Reagents and conditions: [a] $Mn(OTf)_2$ (0.2 mol%), ligand (0.2 mol%) [catalyst (**168**)], 50% H_2O_2 (1 eq), HOAc (5 eq), CH_3CN, 0 °C, 1 h. [b] $MnCl_2 \cdot 4H_2O$ (10 mol%), ligand (10 mol%) [catalyst (**169**)], PhIO (1 eq), $CHCl_2$, RT, 2 h. [c] Configuration only given as *S*. [d] **170** (2 mol%), CMHP (2 eq), 2-ethylhexanoic acid (5 eq), CH_3CN, 0 °C, 2 h. [e] **171** (0.2 mol%), 30% H_2O_2 (1.3 eq), 2-ethylhexanoic acid:CH_3CN (1:5 v/v), -30 °C, 2 h.

Subsequent studies showed that a positively charged octahedral Co(III) complex (**172**) could catalyse the stereoselective epoxidation of an array of *p*-substituted *trans*-chalcones, e.g. 4-OMe (**101**), 4-Me(**104**), under phase transfer conditions with H_2O_2 as oxidant, although ee's were in the range of 44-55% and yields in the order of 85% (Scheme 3.8).[88] Yao, Zhao and co-workers[89,90] tested an in situ generated heterobimetallic catalyst (**173**) {prepared from rare-earth metal amides, e.g. $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$, in the presence of phenoxy-functionalized chiral prolinols} for the enantioselective epoxidation of α,β-unsaturated ketones. After utilization of TBHP as oxidant,

they were able to obtain the unsubstituted (**96b**), 4-methoxy (**108b**) and 4-methylchalcone (**111b**) epoxides in high yields (97-99%) and ee's (97-98%) (Scheme 3.9).



Scheme 3.8: Metal catalysed epoxidation of *p*-substituted chalcones.

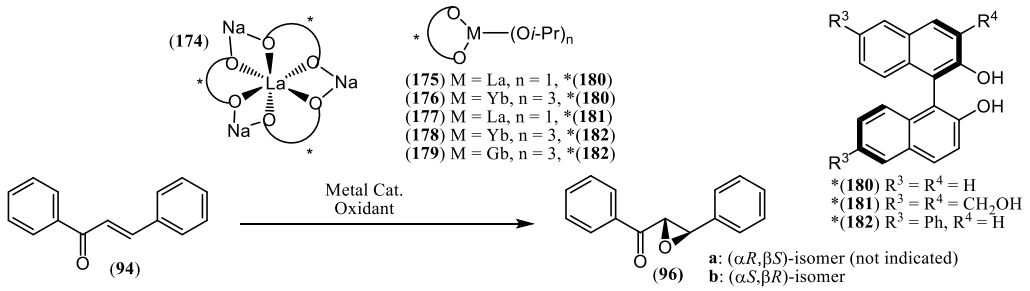


Scheme 3.9: Stereoselective chalcone epoxidation with novel Yb-prolinol catalysts.

BINOL and lanthanide alkoxide systems (Ln-BINOL) with alkyl hydroperoxides represent one of the general methods for the catalytic stereoselective epoxidation of electron-deficient olefins.[91] Shibasaki et al.[92] developed two types of catalyst systems with one based on a bimetallic $LnM_3[(R)\text{-BINOL}]_3$ (Ln = lanthanide, M = Alkali metal) and the other one being alkali-metal-free. Utilizing $LaNa_3[(R)\text{-BINOL}]_3$ catalyst (**174**) and *tert*-butyl hydroperoxide (TBHP) as oxidant they were able to obtain the (2*S*,3*R*)-epoxychalcone (**96b**) in 92% yield and 83% ee (Table 3.14, entry 1), but this system was not successfully extended to other (*E*)-enones, e.g. *trans*-1-phenyl-2-buten-1-one. The alkali-metal-free catalysts, e.g. La(O*i*-Pr)-BINOL (**175**), used in combination with CMHP as oxidant, on the other hand, were successful in the epoxidation of a wide range of (*E*)-enones and yielded similar ee's (ca. 83%) for **96b** (entry 2). During these investigations both ytterbium and lanthanum catalysts were tested revealing that the optimum lanthanide was dependant on the nature of the enone with La and

CMHP being the best combination for aryl ketones and Yb with TBHP being more effective for alkyl ketones.[92]

Table 3.14: Epoxidation of chalcones with metal-BINOL systems.



Entry	Catalyst	Epoxide	Yield (%)	ee (%)
[a] **1**[92]	$LaNa_3$[(*R*)-BINOL]$_3$ (**174**)	**96b**	92	83
[b] **2**[92]	La(O*i*-Pr)-BINOL (**175**)	**96b**	93	83
[c] **3**[93]	Yb(O*i*-Pr)$_3$-BINOL (**176**)	**96b**	99	81
[d] **4**[94]	La(O*i*-Pr)-BINOL (**175**)	**96b**	99	96
[e] **5**[95]	La(O*i*-Pr)-BINOL (**175**)	**96b**	99	96
[f] **6**[92]	La(O*i*-Pr)-3-hydroxymethyl-BINOL (**177**)	**96b**	93	91
[g] **7**[96]	Yb(O*i*-Pr)$_3$-6,6'-diphenyl-BINOL (**178**)	**96a**	91	97
[h] **8**[97]	Gb(O*i*-Pr)$_3$-6,6'-diphenyl-BINOL (**179**)	**96a**	95	95

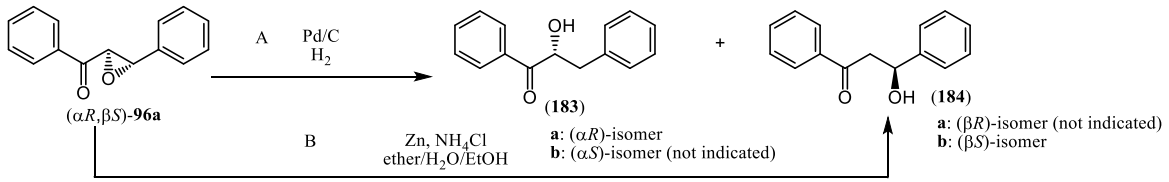
Reagents and conditions: [a] $LaNa_3$[(*R*)-BINOL]$_3$ (**174**) (10 mol%), TBHP (2 eq), THF, RT, 10 h. [b] La(O*i*-Pr)-BINOL (**175**) (5 mol%), CMHP (1.5 eq), MS 4Å, THF, RT, 6 h. [c] Yb(O*i*-Pr)$_3$-BINOL (**176**) (5 mol%), H_2O (5 eq), TBHP (1.5 eq), MS 4Å, THF, RT, 1 h. [d] La(O*i*-Pr)-BINOL (**175**) (5 mol%), Ph_3P=O (15 mol%), TBHP (1.5 eq), MS 4Å, THF, RT, 0.5 h. [e] La(O*i*-Pr)-BINOL (**175**) (5 mol%), Ph_3As=O (15 mol%), TBHP (1.2 eq), MS 4Å, THF, RT, 0.25 h. [f] La(O*i*-Pr)-3-hydroxymethyl-BINOL (**177**) (5 mol%), CMHP (2 eq), THF, RT, 7 h. [g] Yb(O*i*-Pr)$_3$-6,6'-diphenyl-BINOL (**178**) (5 mol%), CMHP (2 eq), THF, 0 °C, 8 h. [h] Gb(O*i*-Pr)$_3$-(*S*)-6,6'-diphenyl-BINOL (**179**) (5 mol%), CMHP (2 eq), THF, RT, 8 h.

The addition of stoichiometric quantities of water to the Yb-BINOL system greatly improved the reaction and gave the unsubstituted chalcone epoxide (**96b**) in a quantitative yield and high ee (Table 3.14, entry 3).[93] Inanaga et al.[94] further extended the investigation into the effect of other additives on the Shibasaki's La-BINOL system and found that the addition of, for example Ph_3P=O, not only allowed for decreased reaction times, but also stabilised the chiral La-complex. The addition of triphenylarsine oxide (Ph_3As=O) also resulted in increased catalyst activity even with reduced catalyst amounts and gave results comparable to the Ph_3P=O system (entry 5).[95] Various substituents on the BINOL ligand, e.g. 3-hydroxymethyl (**181**), 6,6'-diphenyl (**182**), have also been investigated and provided better enantioselectivity than BINOL itself, with yields of 91-95% and ee's of 91-97% being obtained (entry 6-8).[92,96,97] Qian et al.[96,97] extended the evaluation to other chalcone derivatives, e.g. 4-methoxy (**101**), and were able to obtain the epoxides in ca. 85-91% yield and ee's up to 91% with La and Gd based catalysts, while Kumaraswamy et al.[98] tested a novel Ca-6,6'-diphenyl-BINOL catalyst on chalcone substrates (e.g. **94**, **103**, **104**), but found disappointingly lower yields and ee's (60-82% and 22-80%, respectively).

Polymeric heterogeneous BINOL catalysts formed from Ln-(O*i*-Pr)$_3$ (Ln =Yb/La) were found to promote unsubstituted chalcone (**94**) epoxidation in high yield (95%) but low ee (35%),[99] while Sasai et al. were also able to improve the enantioselectivity of the reactions through usage of a polymer-supported Ln-BINOL complex [98% ee obtained for (**96b**)].[100] Attempts towards the optimization of the epoxidation reaction conditions for the La(O*i*-Pr)$_3$: BINOL: $Ph_3P{=}O$ (in a 1:1:3 ratio) by Inanaga and co-workers[101,102] allowed for an efficient and practical method to obtain chalcone epoxides in high optical purities with ee's up to >99% and 99% yields for unsubstituted (**94**) and 4'-methoxychalcone (**102**).

3.3 α- and β-Hydroxydihydrochalcones

During determination of the absolute configuration of chalcone epoxides, Marsman and Wynberg[10] were the first to prepare the α-hydroxydihydrochalcone (**183**) stereoselectively through catalytic hydrogenation (Pd/C) of (-)-(α*R*,β*S*)-(**96a**) (Scheme 3.10, Reaction A). They also performed the reduction over zinc dust and were able to obtain the (+)-(β*S*)-β-hydroxydihydrochalcone (**184**) for the first time (Reaction B).

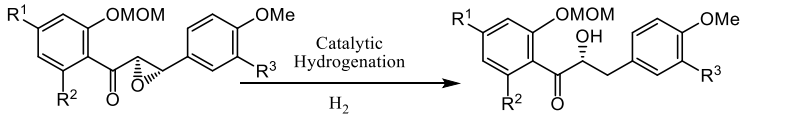


Scheme 3.10: Preparation of α- and β-hydroxydihydrochalcone.[10]

Utilizing the versatile poly(amino acid) epoxidation methodology (cf. section 3.2.2), Ferreira and co-workers[45,46] extended the catalytic hydrogenation procedure to a series of novel chalcone epoxides, affording α-hydroxydihydrochalcones (**185** - **189**) in acceptable to good yields, with very little to no observable drop (from the epoxide) in enantioselectivity. Treatment of (+)-(α*S*,β*R*)- and (-)-(α*R*,β*S*)-chalcone epoxides (**143** - **147**) with either Pd/C or Pd/$BaSO_4$ afforded the (-)-(α*S*)- and (+)-(α*R*)-α-hydroxydihydrochalcones, respectively, in moderate ee's (ca. 14-76%) and yields (ca. 40-92%) (Table 3.15).

Ferreira and co-workers[48,49] also extended the most general method for regioselective reductive ring opening of α,β-epoxyketones to a series of chalcone epoxides with naturally occurring oxygenation patterns to afford the corresponding β-hydroxydihydrochalcones through treatment of the epoxides with tributyltin hydride (TBTH) and azobisisobutyronitrile (AIBN) and were able to obtain the β-hydroxydihydrochalcones (**190** - **194**) in excellent yields (ca. 70-90%) and moderate to high ee's (ca. 47-91%) (Table 3.16).

Table 3.15: Synthesis of α-hydroxydihydrochalcones through catalytic hydrogenation.[45,46]



(**143**)-(**147**)
a: (α*R*,β*S*)
b: (α*S*,β*R*) (not indicated)

(**185**)-(**189**)
a: (α*R*)-isomer
b: (α*S*)-isomer (not indicated)

Entry	Epoxide	R^1	R^2	R^3	Product	Yield (%)	ee (%)
[a] **1**	**143a**	H	H	H	**185a**	51	61
[a] **2**	**143b**	H	H	H	**185b**	72	48
[a] **3**	**144a**	OMe	H	H	**186a**	88	76
[a] **4**	**144b**	OMe	H	H	**186b**	70	52
[b] **5**	**145a**	OMe	H	OMe	**187a**	42	61
[b] **6**	**145b**	OMe	H	OMe	**187b**	40	16
[c] 7	**146a**	OMe	OMe	H	**188a**	- [d]	24
[c] **8**	**146b**	OMe	OMe	H	**188b**	- [d]	19
[b] **9**	**147a**	OMe	OMe	OMe	**189a**	- [d]	14
[b] **10**	**147b**	OMe	OMe	OMe	**189b**	- [d]	16

Reagents and conditions: [a] $Pd/BaSO_4$, MeOH, RT, 3-5 h. [b] 10% Pd/C, EtOH, 20 min. [c] 5% Pd/C, EtOH, 20 min. [d] Not reported.

Table 3.16: β-Hydroxydihydrochalcones by regioselective reductive ring opening of chalcone epoxides.[48,49]

(**143**)-(**147**)
a: (α*R*,β*S*)
b: (α*S*,β*R*) (not indicated)

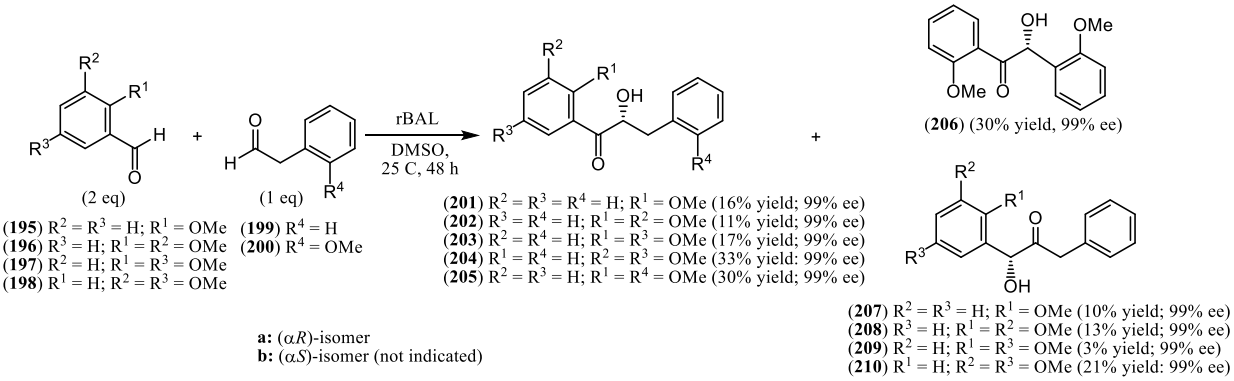
(**190**)-(**194**)
a: (β*R*)-isomer
b: (β*S*)-isomer (not indicated)

Entry [a]	Epoxide	R^1	R^2	R^3	Product	Yield (%)	ee (%)
1	**143a**	H	H	H	**190a**	73	85
2	**143b**	H	H	H	**190b**	70	80
3	**144a**	OMe	H	H	**191a**	83	91
4	**144b**	OMe	H	H	**191b**	90	88
5	**145a**	OMe	H	OMe	**192a**	78	84
6	**145b**	OMe	H	OMe	**192b**	81	85
7	**146a**	OMe	OMe	H	**193a**	79	55
8	**146b**	OMe	OMe	H	**193b**	76	61
9	**147a**	OMe	OMe	OMe	**194a**	83	48
10	**147b**	OMe	OMe	OMe	**194b**	78	47

Reagents and conditions: [a] TBTH (3 eq), AIBN (1 eq), dry benzene, N_2, reflux, 1 h.

Sanchez-Gonzalez and Rosazza[103] more recently reported the stereoselective preparation of only (*R*)-α-hydroxydihydrochalcones (**201a** – **205a**) through utilization of a mixed aromatic acyloin condensation with recombinant benzaldehyde lyase (BAL) and were able to synthesise several B-ring mono- and disubstituted (*R*)-α-hydroxydihydrochalcones in >99% ee but low yields (ca. 11-21%)

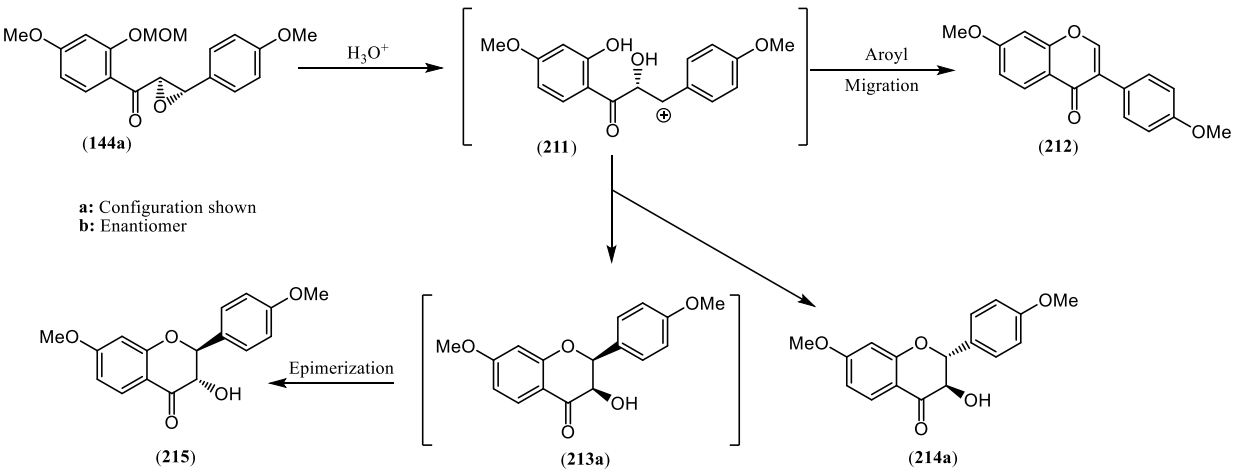
(Scheme 3.11). The loss in yield could be ascribed to the formation of other ketone products and the phenyacetaldehyde undergoing self-condensation (**206**) or α-hydroxydihydrochalcone isomer (**207 - 210**) being formed.



Scheme 3.11: Stereoselective-enzyme catalysed synthesis of B-ring substituted (*R*)-α-hydroxydihydrochalcones.

3.4 Dihydroflavonols

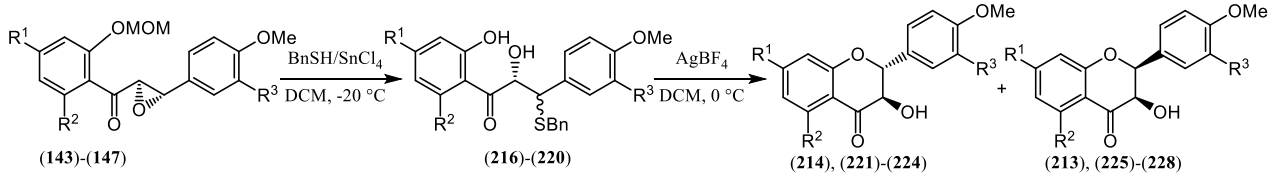
Since dihydroflavonols (**29**) may be viewed as potential electrophiles in the preparation of oligomeric flavonoids, these compounds have received considerable attention from a synthetic point of view and racemic mixtures of these analogues were prepared through application of Algar-Flynn-Oyamada and Wheeler reactions.[104,105] The acid catalysed cyclization of chalcone epoxides towards dihydroflavonol stereoisomers (**213** and **214**) are complicated by acid catalysed aroyl migration resulting in the formation of the competing isoflavone (**212**) as well as rapid C-3 epimerization of the less stable (2*S*,3*R*)-2,3-*cis*-4',7-dimethoxydihydroflavonol (**213**) under the acidic conditions (Scheme 3.12).[106]



Scheme 3.12: Limitations of acid catalysed cyclization towards dihydroflavonols.

In order to eliminate isoflavone formation, Van Rensburg et al.[47] embarked on a strategy of nucleophilic opening of the epoxide ring before deprotection of the 2'-OH group and cyclization in order to obtain the target dihydroflavonol. Thus, treatment of the chalcone epoxide with a phenylmethanethiol-tin(IV) chloride ($BnSH/SnCl_4$) system in DCM gave the corresponding α-hydroxy-β-benzylsulfanyldihydrochalcones (**216 - 220**) in diastereomeric mixtures with yields ranging from 86 to 93% for an assortment of substituted chalcone epoxides. Subsequent removal of the benzyl mercaptan entity with the thiophilic Lewis acid (L.A.), silver tetrafluoroborate ($AgBF_4$), at 0 °C gave the 2,3-*trans*-dihydroflavonols (**214**, **221**-**224**) in good overall yields (ca. 61-86%) and reasonable ee's (ca. 44-84%) (Table 3.17). The *trans*-dihydroflavonols were throughout accompanied by small quantities of the rare *cis*-diastereomers (**213**, **225** -**228**).

Table 3.17: Dihydroflavonol synthesis through β-benzylsulfanyl-α-hydroxydihydrochalcones.



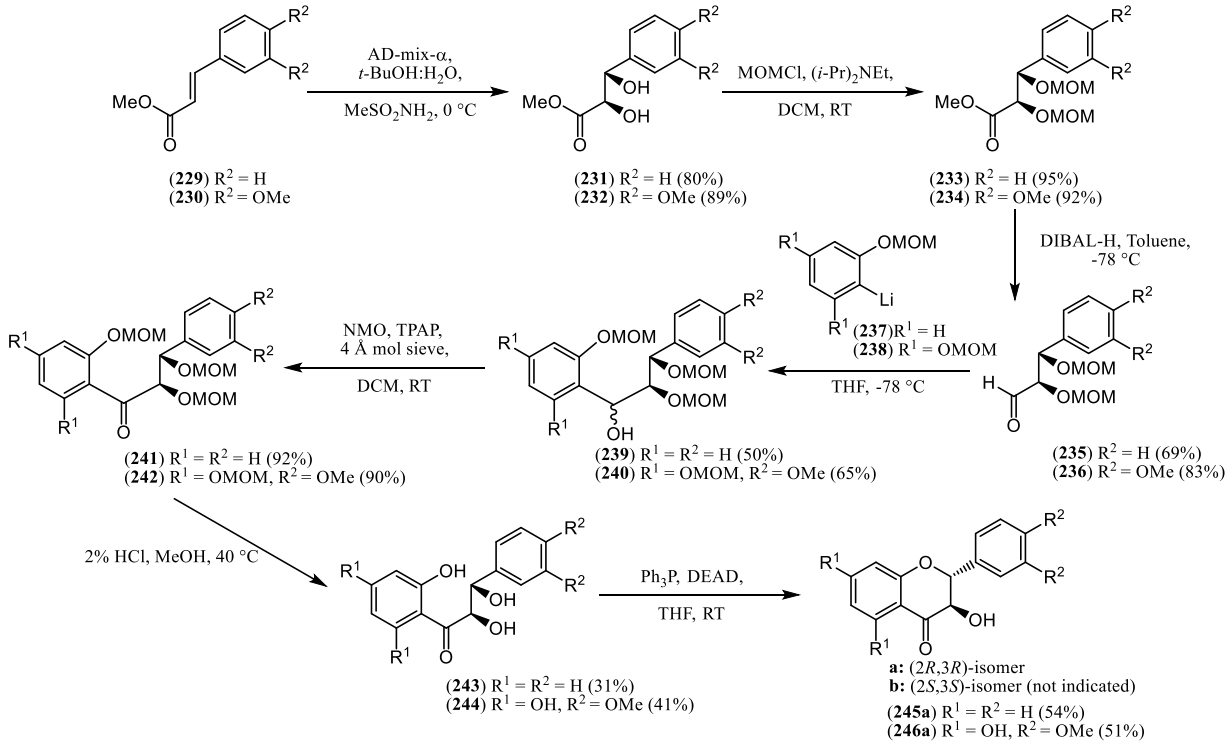
a: Configuration as shown
b: Enantiomer (not indicated)

Entry [a]	CE[b]	R^1	R^2	R^3	DHC[c]	DHF[d]	Yield (%)	ee (%)[e]	*trans:cis*
1	**143a**	H	H	H	**216**	**221a/225a**	86	83	93:7
2	**143b**	H	H	H	**216**	**221b/225b**	83	69	94:6
3	**144a**	OMe	H	H	**217**	**214a/213a**	71	84	79:21
4	**144b**	OMe	H	H	**217**	**214b/213b**	72	75	83:17
5	**145a**	OMe	H	OMe	**218**	**222a/226a**	81	68	85:15
6	**145b**	OMe	H	OMe	**218**	**222b/226b**	79	58	86:14
7	**146a**	OMe	OMe	H	**219**	**223a/227a**	65	69	78:22
8	**146b**	OMe	OMe	H	**219**	**223b/227b**	64	53	84:16
9	**147a**	OMe	OMe	OMe	**220**	**224a/228a**	61	47	82:18
10	**147b**	OMe	OMe	OMe	**220**	**224b/228b**	63	44	80:20

Reagents and conditions: [a] $AgBF_4$ (5 eq), DCM, 0 °C, 12 h. [b] CE = Chalcone Epoxide. [c] DHC = β-benzylsulfanyl-α-hydroxydihydrochalcones. [d] DHF = Dihydroflavonols. [e] ee determined for *trans*-isomer.

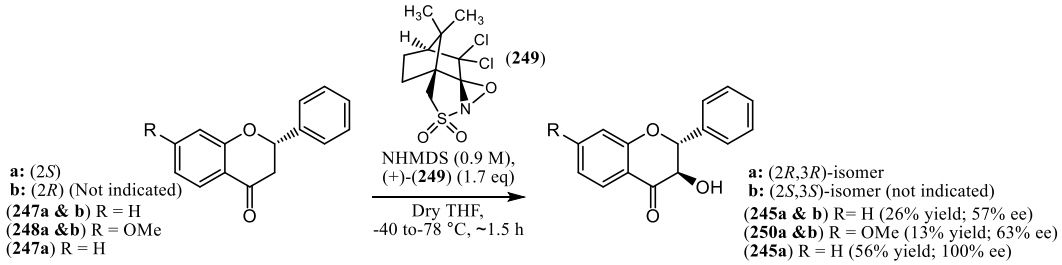
Jew et al.[107] reported a multistep method for the synthesis of (2*R*,3*R*)-dihydroflavonols that entailed Sharpless stereoselective dihydroxylation of the methyl cinnamate derivatives (**229** and **230**) as key chiral induction step (Scheme 3.13). The catalytic stereoselective dihydroxylation with AD-mix-α gave highly optically pure (2*R*,3*S*)-diols, **231** and **232**, in high yields (ca. 80-89%) and 99% ee. Protection of the newly formed hydroxy function followed by diisobutylaluminium hydride (DIBAL-H) reduction of the esters (**233** and **234**) to the corresponding aldehydes (**235** and **236**) and subsequent alkylation with the aryllithium analogues (**237** and **238**), led to the 1,3-diarylpropantriol derivatives (**239** and **240**), which could be oxidized in high yields (ca. 90-92%) to the dihydroxyketone analogues

(**241** and **242**) by treatment with *N*-methylmorpholine (NMO) and tetrapropylammonium perruthenate (TPAP). Finally, deprotection of the OH groups and intramolecular Mitsunobu reaction afforded the (2*R*,3*R*)-2,3-*trans*-dihydroflavonols, **245a** and **246a**, in high optical purity (99% ee) and acceptable yields (ca. 51-54%).



Scheme 3.13: Multistep procedure for the enantioselective synthesis of dihydroflavonols.

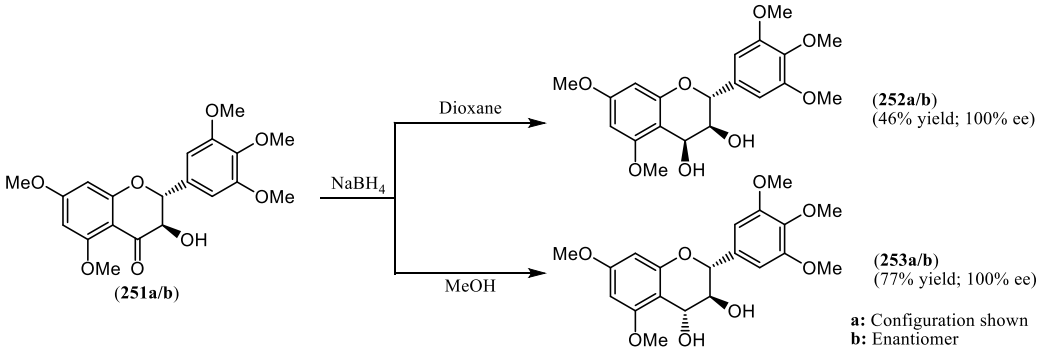
The most recent attempt at the symmetric synthesis of dihydroflavonols was reported by Bezuidenhoudt et al.[108] and was accomplished through stereoselective α-hydroxylation of flavanones with *N*-sodiohexamethyldisilazane (NHMDS) and (+)-(8,8-dichlorocamphorylsulfonyl)oxaziridine (**249**) in dry THF (Scheme 3.14). The hydroxylation of racemic flavanone mixtures (**247** and **248**) gave ee's up to 57-63%, but low yields (ca. 13-26%) with the 2,3-*trans*-(2*R*,3*R*) configuration being dominant. Performing the same oxidation procedure on enantiopure flavanone (**247**) resulted in the formation of only the *trans*-(2*R*,3*R*)-stereoisomer (**245a**) in a 56% yield and 100% diastereomeric excess (de) with a 100% ee (Scheme 3.14).



Scheme 3.14: Stereoselective α-hydroxylation of flavanones.[108]

3.5 Flavan-3,4-diols

The obvious approach towards the synthesis of enantiomerically enriched flavan-3,4-diols (**252**/**253**) would be through the reduction of dihydroflavonols (**251**). In this regard, either of the two C-4 epimers could be obtained in high de (ca. 100%) and moderate to low yields (ca. 46–77%) when reduced with sodium borohydride ($NaBH_4$) in either an aprotic (e.g. 1,4-dioxane) or protic (e.g. MeOH) solvent (Scheme 3.15). This has remained the first option for the stereoselective synthesis of these compounds.[109,110]

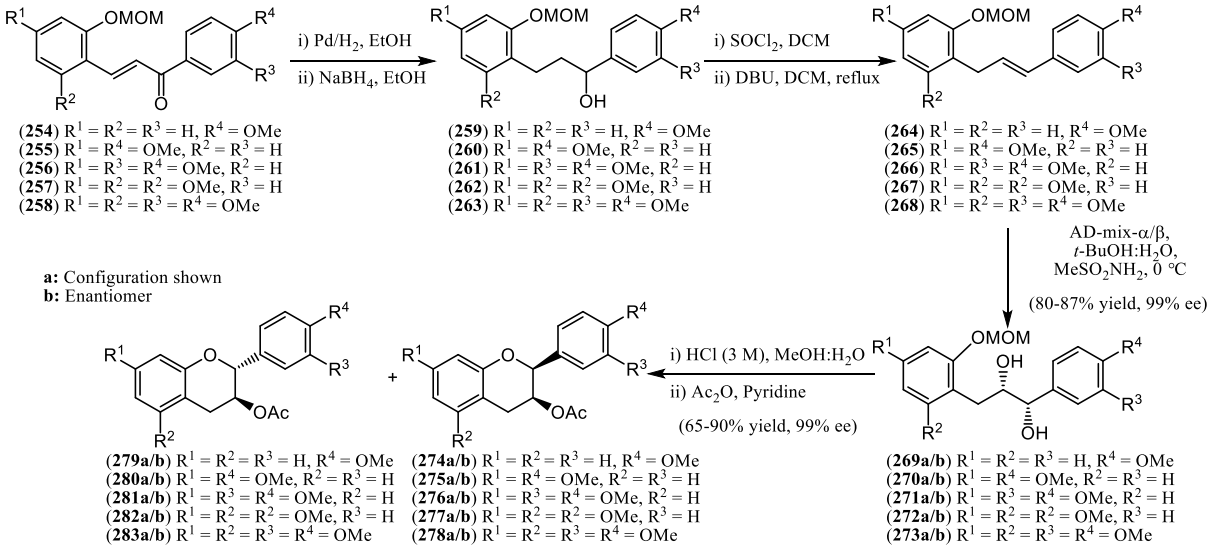


Scheme 3.15: Reductive transformations of dihydroflavonols.[110]

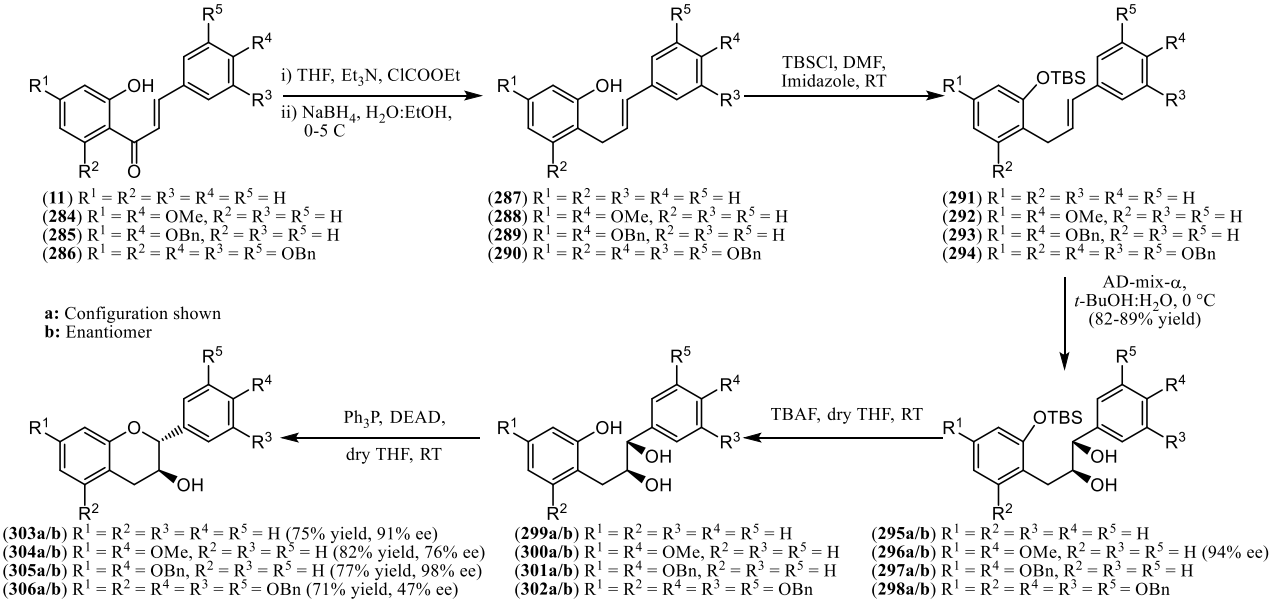
3.6 Flavan-3- and 4-ols

Flavan-3-ols are important as nucleophiles in oligomeric flavonoid preparations (cf. section 2.2.2) and as such have received a good deal of attention from a synthetic point of view. While these compounds are readily available in high yield (ca. 93%) via sodium cyanoborohydride ($NaBH_3CN$) reduction of flavan-3,4-diols,[111] or dihydroflavonols through consecutive reduction with lithium aluminium hydride ($LiAlH_4$) and catalytic hydrogenation over Pd/C,[7] these approaches are still dependent on the availability of the dihydroflavonols in high optical purity. Thus, Ferreira and co-workers[112,113] and Krohn et al.[114] addressed stereocontrol in the flavan-3-ol at C-2 and C-3 by transforming a series of *retro*-chalcones (**254** - **258**) into 1,3-diarylpropenes (**264** - **268**), which were subsequently subjected to stereoselective dihydroxylation through application of the Sharpless stereoselective dihydroxylation methodology, with either AD-mix-α or -β, which afforded the

corresponding propan-1,2-diol enantiomers (**269a/b - 273a/b**) in acceptable yields and high ee's. Acid catalysed cyclization of the aforementioned compounds (**269 - 273**) by Ferreira and co-workers[112,113] yielded a *trans*:*cis* (ca. 3:1) mixture of the flavan-3-ol derivatives (**274 - 283**) in 65-90% yields and 99% ee (Scheme 3.16). Krohn et al.,[114] on the other hand, effected the cyclization through the application of Mitsunobu methodology and were able to obtain the 2,3-*trans*-flavan-3-ols (**303 - 306**) in high yields (ca. 71 – 82%) and acceptable ee's (ca. 47 – 98%) (Scheme 3.17).

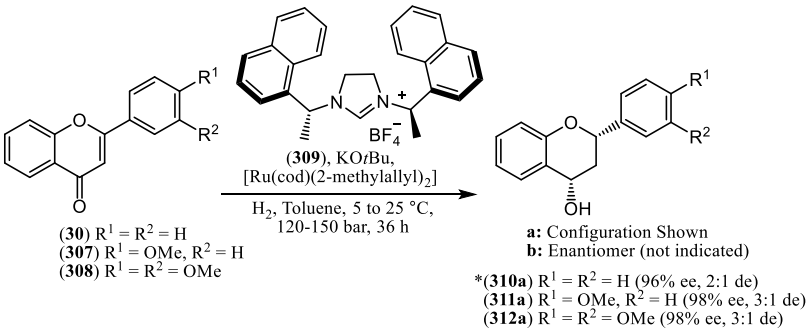


Scheme 3.16: Ferreira's methodology for the enantioselective synthesis of flavan-3-ols.



Scheme 3.17: Krohn's methodology for the 1,3-diarylpropene based enantioselective preparation of flavan-3-ols.

Since flavan-4-ols (**26**) are not widely utilized in the synthesis of other flavonoids, the stereoselective synthesis of these compounds has received little attention. However, Glorius et al.[115] reported the enantioselective hydrogenation of flavones over a ruthenium *N*-heterocyclic carbene (NHC) (**309**) system and were able to obtain the unsubstituted (**310**), 4'-methoxy- (**311**) and 3',4'-dimethoxyflavan-4-ols (**312**) in diastereomeric mixtures dominated by the 1,4-*cis*-isomer and with high ee (ca. 96 - 98%) and quantitative yields (Scheme 3.18).



Scheme 3.18: Ru-catalysed hydrogenation of flavones.

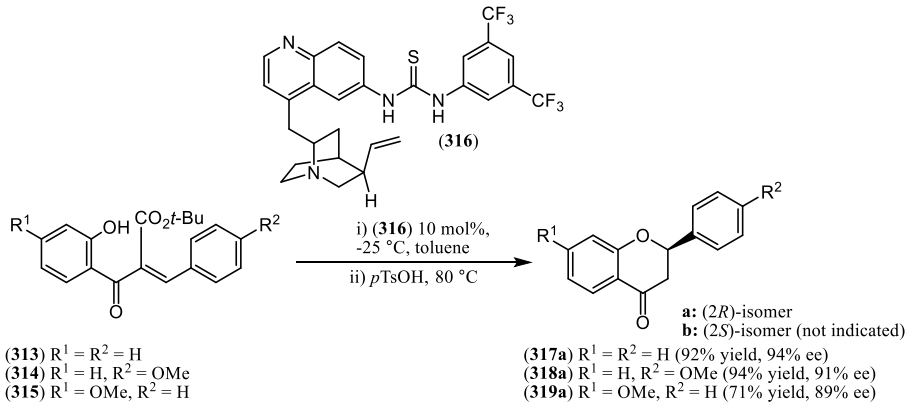
* *NOTE*: Full conversion in all cases, with the major product being the cis-isomer.

3.7 Selective Formation of the C-2 Stereocenter: Enantioselective Formation of Flavanones and Flavans

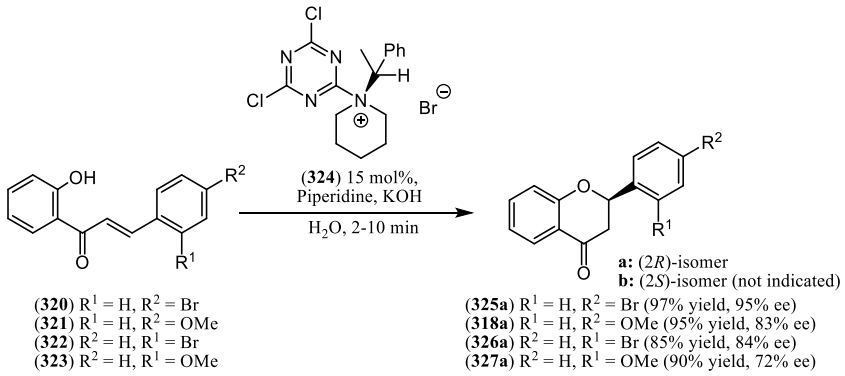
Although flavanones represent one of the most common naturally occurring flavonoid classes (cf. section 2.3), only a few stereoselective methods for the preparation of enantio-enriched flavanones have been developed.[116] Most of the existing stereoselective methodologies include intramolecular *oxa*-Michael addition reactions of 2'-hydroxychalcones. With the addition of a chiral organocatalyst, Wang et al.[117] developed a one-pot procedure for the synthesis of 6-fluoroflavanone from the corresponding aldehyde and acetophenone catalysed by (*S*)-pyrrolidinyltetrazole, but were only able to obtain a 51% ee and 22% yield. Recently, Hinterman and Dittmer[118] reported a cinchona alkaloid derived quaternary ammonium salt as catalyst for the enantioselective synthesis of flavan-4-one (**317**), but could only obtain relatively low enantioselectivity (55%).

Through the introduction of an activating 2-alkoxycarbonyl group [e.g. *tert*-butyl ester (CO_2t-Bu)] at C-2 of the chalcone substrate, Scheidt et al.[119] were able to improve enantioselectivity of the cyclization reaction when a chiral thiourea (**316**) was used as catalyst. Application of this methodology towards the synthesis of the unsubstituted (**317**), 4'-methoxy- (**318**) and 7-methoxyflavanone (**319**) led to these products being isolated in high yields (ca. 71-94%) and good to excellent ee's (ca. 89-94%) (Scheme 3.19). Awasthi et al.[116] showed that with a chiral (*S*)-triazine based organocatalyst (**324**) and small alterations in the reaction conditions, the enantioselective

outcome of the reaction could be improved to (ca. 72 – 95%) for B-ring *ortho*- and *para*-substituted flavanones (**318**, **325** - **327**) (Scheme 3.20).

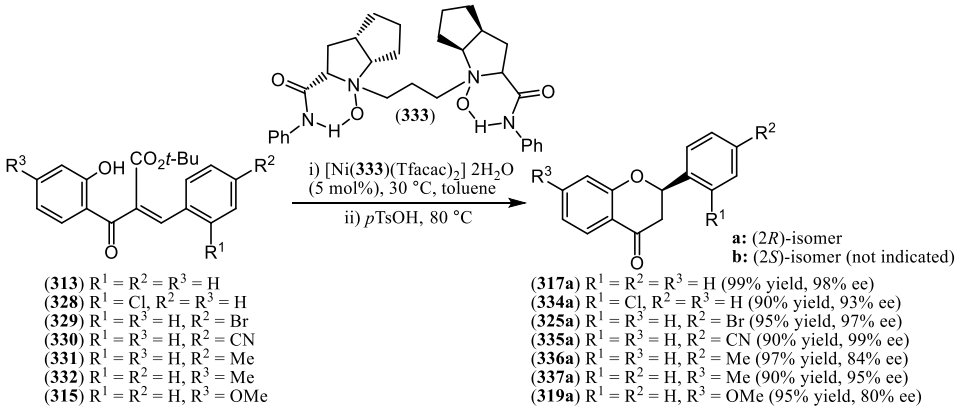


Scheme 3.19: Stereoselective synthesis of flavanones from activated 2'-hydroxychalcones.

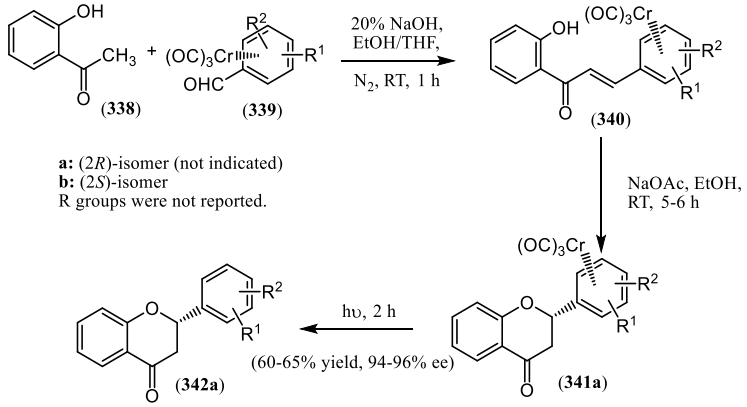


Scheme 3.20: Stereoselective synthesis of flavanones catalysed by (*S*)-Triazine-based catalyst.

The cyclization of C-α ester activated 2'-hydroxychalcones in the presence of a chiral *N*,*N*'-dioxide nickel(II) complex with **333** as ligand, reported by Feng et al.,[120] facilitated the cyclization of a wide variety of chalcone analogues (**313**, **315**, **328** - **332**) in 90-99% yield and up to 99% ee's (Scheme 3.21). Synthesising the chalcones from the corresponding tricarbonyl (η^6-arylbenzaldehyde)chromium(0) complexes (**339**) and *o*-hydroxyacetophenone (**338**), allowed for the cyclization of sterically hindered chalcone derivatives (**340**), providing flavanones (**342**) in high enantioselectivity (ca. 94-96% ee) and 60-65% yield (Scheme 3.22).[121]



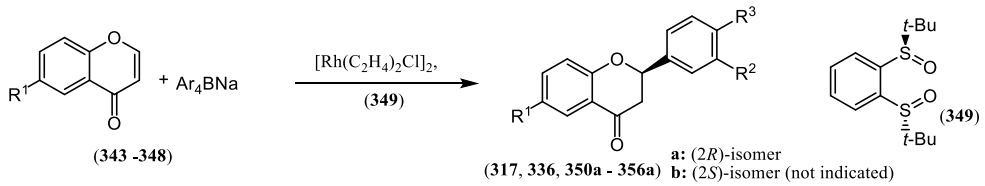
Scheme 3.21: Metal-catalysed stereoselective flavanone synthesis from activated 2'-hydroxychalcones.



Scheme 3.22: Stereoselective flavanone synthesis with tricarbonyl (η^6-arylbenzaldehyde)chromium(0).

Some groups also reported the use of rhodium catalysts to facilitate the stereoselective 1,4-addition of tetraarylborate complexes and arylboronic acids to chromones (**343 - 348**).[122–124] In this regard, Liao et al.[122] were able to effect the addition of sodium tetraphenylborates (Ar_4BNa) to 6-substituted chromones (**343 - 348**) by utilizing an (*R*,*R*)-1,2-bis(*tert*-butylsulfinyl)benzene (**349**) based rhodium catalyst and were able to prepare only the (*R*)-flavanones with 6-methyl- (**350**), 6-methoxy- (**351**), 6-halogen- (**352 - 354**), 3'-methyl- (**355**), 3'-chloro- (**356**) and 4'-methyl- (**336**) substituents in moderate to good yields (ca. 58 – 75%) and 97 – 99% ee's (Table 3.18).

Table 3.18: Rh-catalysed stereoselective 1,4-addition of sodium tetraarylborates to chromones.[122]

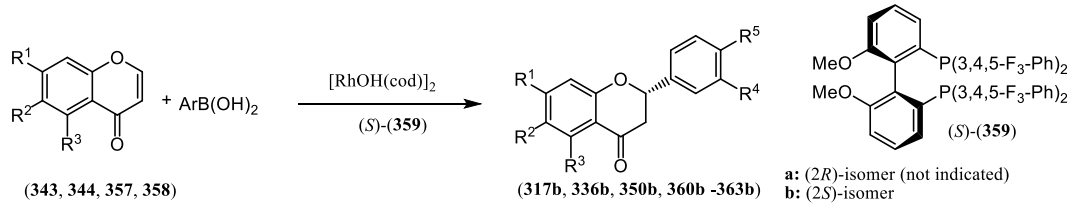


Entry [a]	Chromone	R^1	R^2	R^3	Flavanone	Yield (%)	ee (%)
1	**343**	H	H	H	**317a**	75	> 99
2	**344**	Me	H	H	**350a**	62	99
3	**345**	OMe	H	H	**351a**	68	>99
4	**346**	Cl	H	H	**352a**	71	>99
5	**347**	F	H	H	**353a**	58	99
6	**348**	Br	H	H	**354a**	63	> 99
7	**343**	H	Me	H	**355a**	64	98
8	**343**	H	Cl	H	**356a**	25	97
9	**343**	H	H	Me	**336a**	70	>99

Reagents and conditions: [a] $[Rh(C_2H_4)_2Cl]_2$/(*R*,*R*)-(**349**) (5 mol% Rh), Ar_4BNa (4 eq), DCM/H_2O (15:1, v/v), 40 °C, 24 h.

By utilizing a rhodium catalyst bearing a (6,6'-dimethoxybiphenyl-2,2'-diyl)bis[bis-(3,4,5-trifluoro-phenyl)phosphine] (MeO-F_{12}-BIPHEP) (**359**) as chiral ligand and arylboronic acids [$ArB(OH)_2$] as nucleophiles, the group of Korenaga and Sakai[123] were able to prepare the (*S*)-6- (**350**) and -7-mono-(**363**) and disubstituted flavanones (**362**) with *meta*- (**353** and **360**) and *para*-substituents (**361** and **336**) on the B-ring in 80 to 90% yield and 99% ee (Table 3.19) and could also extend their methodology to the preparation of the naturally occurring flavanones (*R*)-(**363a**) and (*S*)-pinostrobin (**363b**) (entry 8).

Table 3.19: Korenaga and Sakai's methodology towards the stereoselective synthesis of flavanones.[123]

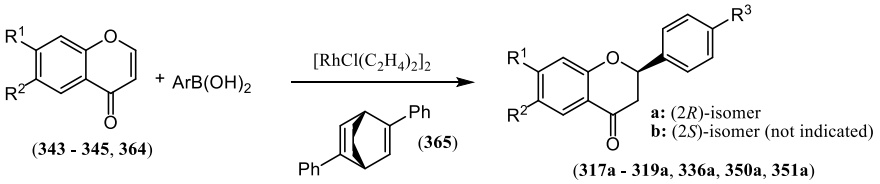


Entry	Chromone	R^1	R^2	R^3	R^4	R^5	Flavanone[d]	Yield (%)	ee (%)
1 [a]	**343**	H	H	H	H	H	**317b**	95	99
2 [a]	**343**	H	H	H	OMe	H	**360b**	90	>99
3 [a]	**343**	H	H	H	F	H	**353b**	80	>99
4 [a]	**343**	H	H	H	H	Me	**336b**	82	99
5 [a]	**343**	H	H	H	H	F	**361b**	80	>99
6 [a]	**344**	H	Me	H	H	H	**350b**	87	>99
7 [a]	**357**	Me	Cl	H	H	H	**362b**	90	>99
8 [b]	**358**	OMe	H	OH	H	H	**363b**	90	>99

Reagents and conditions: [a] $[RhOH(cod)]_2$/(*S*)-(**359**) (3 mol% Rh), $ArB(OH)_2$ (3.5-12 eq), DCM/H_2O, 20-40 °C, 1-3 h. [b] (1) $[RhOH(cod)]_2$/(*S*)-(**359**) (0.5 mol% Rh), $PhB(OH)_2$ (8 eq), toluene/H_2O, 60 °C, 1-3 h. (2) $AlCl_3$, CH_3CN, reflux 3 h.

Wang et al.[124] employed the commercially available chiral diene (*R*,*R*)-Ph-bod {(1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene} (**365**) as chiral inducing agent on the rhodium catalyst complex and were able to synthesise a series of (*R*)-flavanones (**317**, **336**, **350**, **351**, **366**, **367**) in 97 - 99% ee and 66 – 94% yield (Table 3.20). Although the catalyst systems differ in solvent, ligand, metal source and temperature, all groups have reported ee's up to 99% with excellent yields (ca. 70-90%) for a broad range of substituted flavanones.

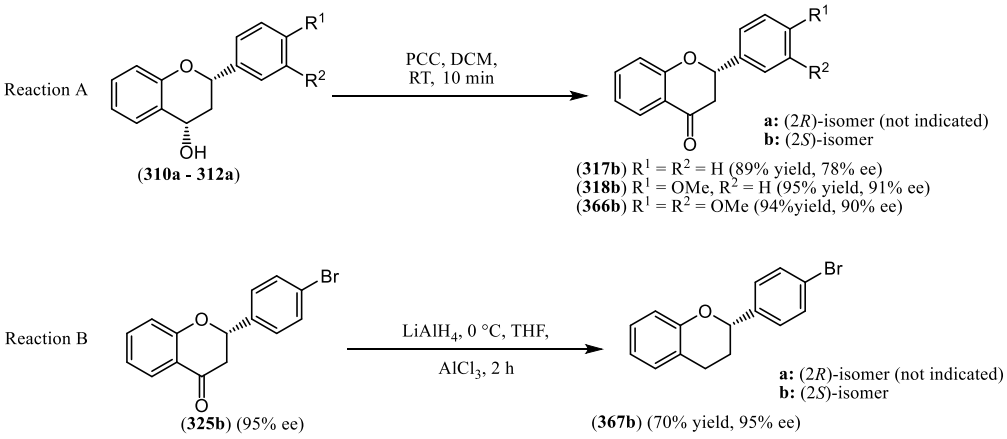
Table 3.20: Rh-catalysed stereoselective synthesis of flavanones from chromones.[124]



Entry [a]	Chromone	R^1	R^2	R^3	Flavanone[d]	Yield (%)	ee (%)
1	**343**	H	H	H	**317a**	94	>99
2	**345**	H	OMe	H	**351a**	76	>99
3	**364**	OMe	H	H	**319a**	81	98
4	**343**	H	H	OMe	**318a**	86	99
5	**344**	H	Me	H	**350a**	81	99
6	**343**	H	H	Me	**336a**	90	>99

Reagents and conditions: [a] $[Rh(C_2H_4)_2Cl]_2$ (10 mol% Rh), (*R*,*R*)-(**365**) (1.1 eq), $ArB(OH)_2$ (3 eq), dioxane/H_2O (9:1), KOH (1 eq), 90 °C, 22 h.

Since many flavonoid compounds can easily be transformed into other classes of flavonoids, the enantio-enriched flavan-4-ols mentioned in section 3.6 may be used in the preparation of the corresponding flavanones through selective oxidation of the C-4 secondary alcohol moiety without compromising the integrity of the C-2 stereocenter.[115] Applying pyridinium chlorochromate (PCC) oxidation to **310** – **312**, gave the corresponding (*S*)-flavanones (**317**, **318** and **366**) in high yields (89-95%) and excellent ee's (78-91%) (Scheme 3.23, Reaction A). Finally, Awasthi et al.[116] demonstrated that through simple reductive transformation of the (*S*)-4'-bromoflavanone (**325**), the corresponding flavan (**367**) could be obtained in a good yield (70%) without loss in enantiomeric excess (95%) (Scheme 3.23, Reaction B).



Scheme 3.23: Simple transformations towards the formation of chiral flavonoids.

3.8 Conclusions

Although enantiomeric purity has received an increased attention, the majority of the research in the stereoselective of flavonoid monomers has been done on the stereoselective epoxidation of chalcones. The unsubstituted chalcone and various electron-donating or -withdrawing substituted analogues have been successfully epoxidized in low to high yields and ee's with PTC, metal based catalysts, crown ethers and chiral peroxides. However, epoxidation of chalcones with naturally occurring substitution patterns have predominantly been epoxidized in the presence of poly(amino acids) in moderate to good yields and ee's. The chiral induction during the synthesis of chalcone epoxides further allowed for the synthesis of optically active α- and β-hydroxydihydrochalcones through catalytic hydrogenation and reductive ring opening methodologies and although the yields and ee's were low for the α-hydroxydihydrochalcones, results for its isomer were somewhat more promising with higher ee's being obtained for all substrates.

As chiral induction was and is possible for acyclic flavonoids, cyclization methodologies towards dihydroflavonols were attempted on these enantiomerically enriched compounds and resulted in promising yields and ee's. Other research groups utilized Sharpless stereoselective dihydroxylation methodologies to generate enantiomerically enriched acyclic 1,3-diarylpropantriols that could be used to synthesise other classes of flavonoids, including dihydroflavonols and flavan-3-ols. The synthesis of optically active flavan-4-ols and flavanones was recently attempted with similar methodologies to those used for the chiral induction for chalcone epoxides (e.g. metal based catalyst, PTC) and provided these compounds in high optical purity and yields.

Nonetheless, despite all these promising methodologies, there is only one currently known method towards the synthesis of enantiopure flavan-3,4-diols. Should it therefore be possible to generate a more extensive range of isomers and substituted flavan-3,4-diols, could it provide a gateway to a plethora of flavonoids (monomeric and oligomeric).

3.9 References

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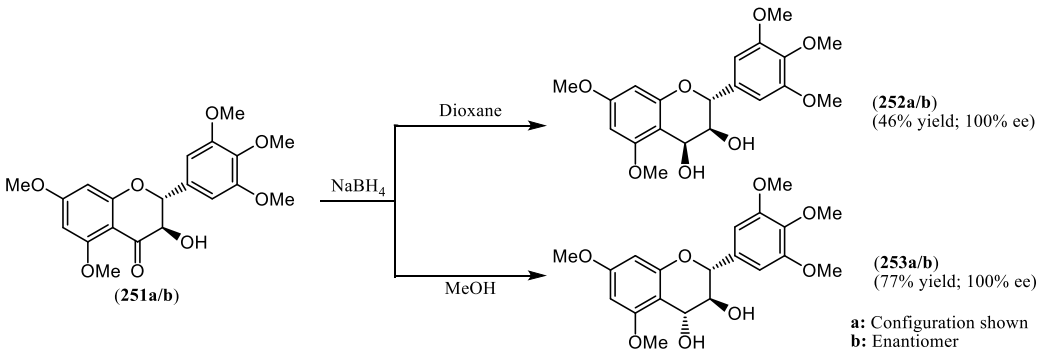
CHAPTER 4

DISCUSSION

4.1 Introduction

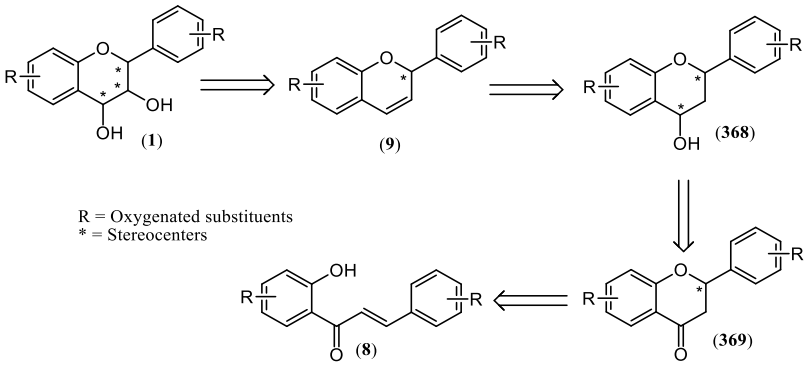
As indicated in Section 2.4, flavonoids are important biological compounds with several beneficial properties for human beings. In vivo and in vitro studies of the beneficial effects of these compounds are, however, limited to compounds with substitution patterns obtainable from natural sources. Furthermore, the majority of the methods implemented towards the stereoselective preparation of flavonoids entail the production of these compounds in low yields and ee's or employ expensive or not readily available catalysts, like poly(amino acids) that is difficult to synthesise, and/or metal catalysts (e.g. Rh or Pd), making them less attractive.

Since flavan-3,4-diols are key intermediates in the synthesis of monomeric and oligomeric flavonoids, it was decided to investigate a simple efficient route towards these compounds that could be amended to the stereoselective synthesis of flavan-3,4-diols. The stereoselective epoxidation of electron-deficient olefins have received attention and these reactions are capable of producing optically active epoxides that could be transformed into dihydroflavonols (**251**) and eventually flavan-3,4-diols (**252**/**253**) by reduction of the 4-carbonyl group (cf. section 3.5 and Scheme 4.1). The preparation of enantiomerically pure dihydroflavonols (**251**) in this way, however, represents a tedious process that includes between five and seven steps and often lead to substandard yields and ee's for a number of compounds (e.g. phloroglucinol containing compounds). The challenges and limitations associated with this methodology therefore served as an additional impetus into the development of improved technology for the preparation of flavan-3,4-diols (**1**) in acceptable enantiomeric purity and yields.



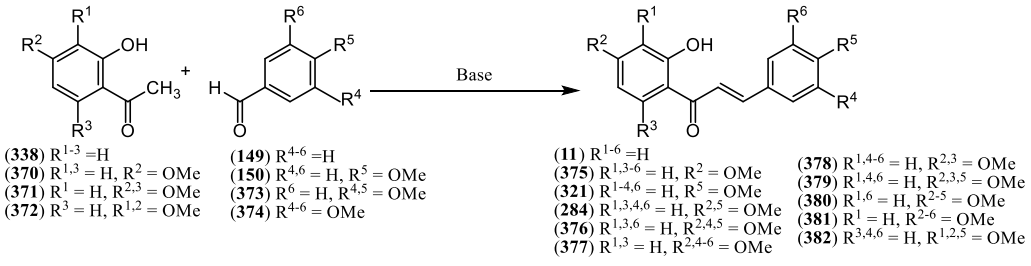
Scheme 4.1: Reductive transformations of dihydroflavonols.

It was thus envisioned that if flav-3-enes (**9**), obtainable by cyclization of chalcones (**8**), followed by reductive elimination of the oxygen function, could be converted stereoselectively into the corresponding flavan-3,4-diols (**1**) in high yield (Scheme 4.2) and only a few process steps by application of a chiral catalyst, the new methodology could make an important contribution towards these compounds becoming available for biological testing in all possible substitution patterns at a reasonable cost. However, before chiral induction could be attempted, an epoxidation process with the potential to be changed into stereoselective methodology, had to be developed.



Scheme 4.2: Retrosynthesis of flavan-3,4-diols from readily available starting materials.

The first objective of the current investigation, therefore, was to prepare a series of substituted 2'-hydroxychalcones (**8**) that could be cyclized to the corresponding flavanones (**369**), reduced (**368**) and dehydrated to the target series of flav-3-enes (**9**) (Scheme 4.3). Although chalcones are generally available by aldol condensation between acetophenones (**387**, **370** – **372**) and benzaldehydes (**149**, **150**, **373** and **374**), several reagent systems have been reported for this reaction with yields generally varying between ca. 50 and 90%.[1–3] In order to find the best reagents and optimum conditions for the preparation of the envisaged 2'-hydroxychalcones (**11**, **284**, **321**, **375** – **382**) (Scheme 4.3), an evaluation of the different reagents and experimental conditions for the synthesis of chalcones were embarked upon.



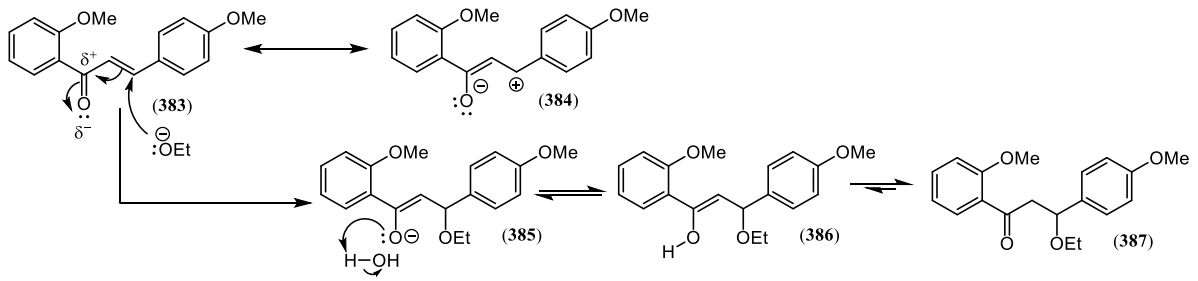
Scheme 4.3: Substitution pattern of 2'-hydroxychalcones to be synthesised.

4.2 Aldol Condensation Reactions

4.2.1 Optimization of Aldol Condensation Conditions

To ensure a simpler purification process and to facilitate a clean reaction without the presence of a free 2'-OH group, the investigation was started with the aldol condensation between 2'-methoxyacetophenone (**388**) and *p*-anisaldehyde (**150**) under the standard conditions of KOH catalysis in a polar protic solvent.[4] Treatment of an ethanol solution of 2'-methoxyacetophenone (**388**) and *p*-anisaldehyde (**150**) with solid KOH gave the expected chalcone (**383**) in 77% yield after acidic work-up and purification by PLC (Table 4.1, entry 1). The structure of the chalcone was confirmed by NMR spectroscopy (^{1}H and ^{13}C NMR), where the β- and α-resonances (δ_H 7.57 & 7.24, respectively) indicated a *trans*-configuration (d, J = 15.81 Hz) (Plate 1A), and mass spectrometry (MS), which indicated the presence of a molecular ion at *m/z* 268 (M^+, 51%).

The chalcone (**383**) was accompanied by another product (**387**) in a 2% yield with R_f 0.28 (H:EtOAc, 9:1). The ^{1}H NMR spectrum (Plate 2A) of this compound indicated no typical chalcone double bond resonances, while the presence of an ethoxy group in the molecule was evident as indicated by two methylene multiplets at δ_H 3.36-3.31 and 3.31-3.25 and a methyl resonance at δ_H 1.09 (t, J = 7.02 Hz). The spectrum further revealed two geminal coupled protons alpha to a carbonyl group (δ_H 3.48, J = 8.33, 16.53 Hz and 3.24, J = 5.01, 16.53 Hz) as well as a methine proton (δ_H 4.85, J = 5.01, 8.33 Hz), thus the additional product from the reaction could be identified as the β-ethoxy-2',4-dimethoxydihydrochalcone (**387**). ^{13}C NMR and DEPT experiments (Plates 2C & 2B) confirmed the presence of a carbonyl (δ_C 200.4) and two CH_2 carbons (δ_C 64.2 & 52.6), while high-resolution mass spectrometry (HRMS) revealed a sodium adduct molecular ion at *m/z* 337.1416 ($[M + Na]^+$), calculated for $C_{19}H_{22}O_4Na$: 337.1416. The formation of the side-product (**387**) is explicable in terms of Michael addition[5] of some of the in situ generated ethoxide to the β-carbon of the newly formed chalcone (**383**) (Scheme 4.4).

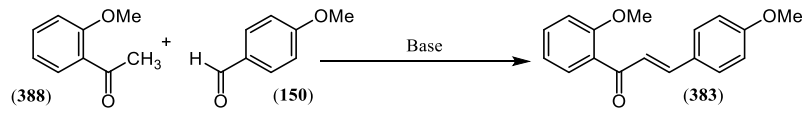


Scheme 4.4: Michael addition under KOH conditions.

Since van der Westhuizen et al.[3] reported a high yielding (90%) method that utilizes the polar aprotic solvent, 1,4-dioxane, during the synthesis of chalcones, the KOH procedure was repeated in dioxane

in order to improve on the chalcone yield. However, when the solvent was changed to dioxane the yield dropped to only 7% (Table 4.1, entry 2). Changing the conditions to aq. NaOH (40%) at 40 °C in ethanol and dioxane showed the same trend as the reactions at RT, with chalcone yields of 78% and 9%, respectively being obtained (Table 4.1, entries 3 and 4).

Table 4.1: Preparation of 2',4-dimethoxychalcone under various reaction conditions.

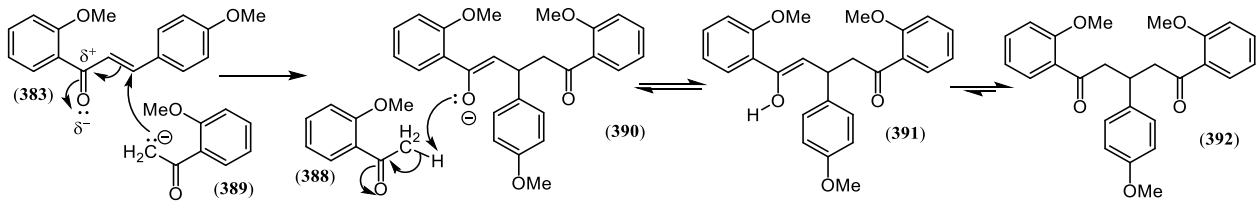


Entry	Method [a]	Reaction Time (h)	Product Yield (%)	Side-Product	Yield (%)
1	A (KOH, EtOH, RT)	24	77	**387**	2
2	B (KOH, dioxane, RT)	24	7	-	-
3	C (aq. NaOH, EtOH, 40 °C)	20	78	-	-
4	D (aq. NaOH, dioxane, 40 °C)	20	9	-	-
5	E (NaH, DMF, RT)	1	52	**392**	8
6	F (aq. NaOH, dioxane, 50 °C, MW)	1	1	-	-
7	G (aq. NaOH, EtOH, 50 °C, MW)	1	69	**387** **392**	Trace 29
8	H (aq. NaOH, EtOH, 128 °C, MW)	1	0	**403** **399** **398**	3 36 48

[a] Reagents and conditions: Method A: solid KOH (4.8 eq), EtOH, RT; Method B: solid KOH (4.8 eq), dioxane, RT; Method C: aq. NaOH (50%), EtOH, 40 °C; Method D: aq. NaOH (50%), dioxane, 40 °C; Method E: NaH (1.5 eq), dry DMF, Ar, RT; Method F: aq. NaOH (50%) dioxane, MW (100 W), 50 °C; Method G: aq. NaOH (50%) EtOH, MW (100 W), 50 °C; Method H: aq. NaOH (50%), EtOH, MW (200 W), 128 °C.

Moving away from the base catalysed reaction to stoichiometric formation of the nucleophile, the acetophenone (**388**) was treated with sodium hydride under anhydrous conditions (dry DMF, Ar) for 30 min, before addition of the anisaldehyde (**150**). While the chalcone (**383**) was obtained in moderate yield (52%) (Scheme 4.1, entry 5), these conditions also led to the formation of another side-product (8%, R_f 0.13, H:EtOAc, 8:2). The ^{1}H NMR spectrum in (C_6D_6) (Plate 3A) of the side-product (**392**), again showed no characteristic chalcone double bond resonances, but three methoxy groups and twelve aromatic signals [δ_H 7.73 (J = 7.73 Hz), 7.18 (J = 8.52 Hz), 7.02 (J = 7.62, 8.32 Hz), 6.72 (J = 8.52 Hz), 6.69 (J = 7.62, 7.73 Hz), 6.38 (J = 8.32 Hz)], i.e. three aromatic rings. The ^{1}H NMR spectrum further revealed two methylene signals at δ_H 3.55 (2H, dd, J = 7.21, 16.37 Hz) and 3.45 (2H, dd, J = 7.21, 16.37 Hz) as well as a methine proton at δ_H 4.35-4.29 (1H, m), while the ^{13}C NMR spectrum (in C_6D_6) (Plate 3C) confirmed the presence of a carbonyl moiety (δ_C 200.3). It could therefore be concluded that the side-product was the 1,3,5-triarylpentane-1,5-dione, viz. 1,5-*bis*(2'-methoxyphenyl)-3-(4''-methoxyphenyl)pentane-1,5-dione (**392**). The 1,5-diketone structure (**392**) of the side-product was confirmed by HRMS analysis where a sodium adduct molecular ion at *m/z* 441.1678 $[M + Na]^+$ (calculated for $C_{26}H_{26}O_5Na$: 441.1677) was observed. The formation of the

1,5-diketone (**392**) could again be ascribed to Michael addition of the in situ generated acetophenone anion (**389**) to the chalcone, thus explaining the somewhat reduced yield of the target chalcone (Scheme 4.5).



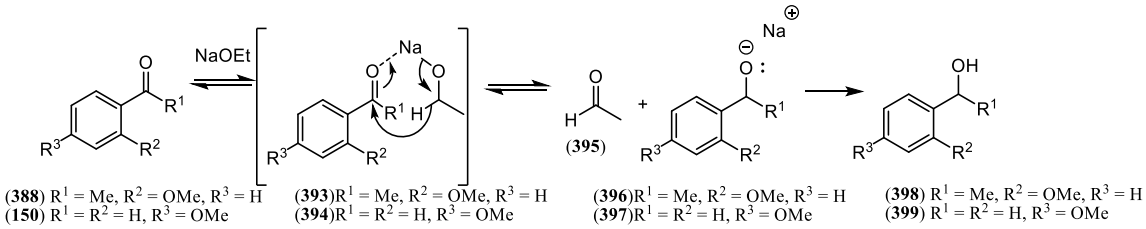
Scheme 4.5: Michael addition of acetophenone anion to the chalcones.

Since microwave (MW) irradiation generally increases reaction rates[6] and the reactions with NaOH at higher temperatures resulted in promising yields, it was subsequently decided to evaluate the effect of MW heating (100W) on this aldol condensation reaction. At 50 °C, in both EtOH and dioxane, a similar trend was observed as for the reactions under conditions of external heating with a lower yield found for the reaction in dioxane (69% vs. 1%; Table 4.1, entries 6 and 7). Interestingly, in this instance the EtOH reaction produced both Michael addition products (**387** and **392**), with the 1,5-diketone (**392**) the major side-product (29%). The formation of the diketone (**392**) as major side-product in the ethanol reaction is probably explicable in terms of the acetophenone anion (**389**) being the softer nucleophile so it will preferentially attack the soft β-position of the α,β-unsaturated electrophile.

As the yield of the reaction in ethanol proved to be superior to that of the reaction in dioxane and it was considered that the diketone formation could be minimized by even shorter reaction times, the reaction in ethanol was repeated under MW heating at 128 °C (200 W). The reaction, however, did not yield chalcone (**383**) or any of the previously found secondary products (**387** and **392**), but two alcohol side-products (**398**) and (**399**) and the dihydrochalcone (**403**) in 48, 36 and 3% yield, respectively. The benzylic alcohol side-product structures (**398** and **399**) were assigned on the basis of the expected aromatic resonances [δ_H 7.29 (2H, d, *J* = 8.61 Hz), 6.89 (2H, d, *J* = 8.61 Hz) for (**399**) and 7.34 (1H, dd, *J* = 1.77, 7.48 Hz), 7.25 (1H, dt, *J* = 1.77, 8.10 Hz), 6.97 (1H, td, *J* = 0.82, 7.48 Hz), 6.89 (1H, br d, *J* = 8.10 Hz) for (**398**), respectively] and methoxy resonances [δ_H 3.81 (3H, s) and 3.87 (3H, s), respectively] in the ^{1}H NMR spectra (Plates 6A and 7A), while the absence of a carbonyl function was evident from the ^{13}C NMR spectra (Plates 6C and 7C). The structure of the 2',4-dimethoxydihydrochalcone (**403**) could be determined from the ^{1}H NMR spectrum (Plate 8A) where the resonances from the two methylene groups [3.27 and 2.97 each 2H, each t, *J* = 7.79 Hz] were clearly visible. MS analysis of all three products (**399**), (**398**) and (**403**) yielded the

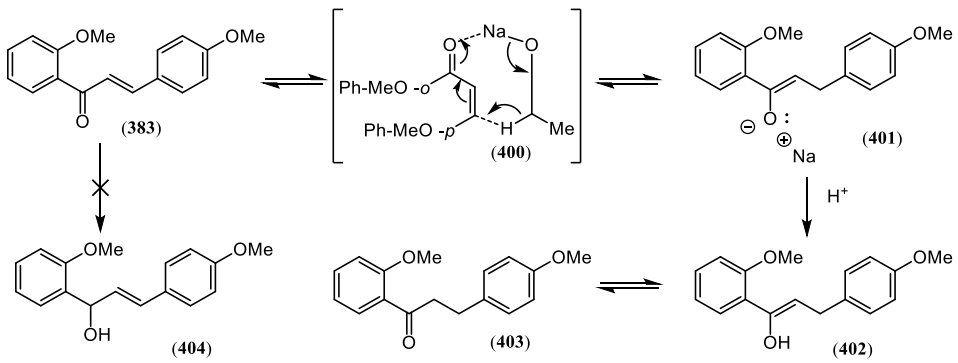
corresponding molecular ions [*m/z* 138 (M^+, 100%), 152 (M^+, 30%) and 270 (M^+, 34%), respectively]; thus confirming the envisaged structures.

While the origin of the reduced products **398**, **399** and **403** are not fully understood at this stage, it would appear as if a Meerwein-Ponndorf-Verley (MPV)[7] type reduction between the ethoxide and benzaldehyde/acetophenone could be the cause of the reduction of the carbonyl compounds. Although MPV reductions are usually performed with aluminium alkoxides and isopropanol as hydrogen donor, Zuidema et al.[8] reported the utilization of NaOH in MPV reductions, so it is possible that a six-membered Lewis salt-transition states (**393**/**394**)[9,10] led to hydrogen transfer from the ethoxide to the carbonyl entity of the aldehyde and the ketone, leading to the formation of the two benzylic alcohols obtained from the reaction at the elevated temperature (Scheme 4.6).



Scheme 4.6: Suggested mechanism of the MPV type reduction of the carbonyl compounds.

The presence of the dihydrochalcone provides evidence that the aldol condensation actually occurred to some extent and it was interesting to note that at the higher reaction temperature, the chalcone (**383**) was not attacked by the ethoxide in a Michael addition fashion, but was rather reduced through a possible eight-membered transition state (TS) (**400**) hydride transfer mechanism (Scheme 4.7). Since MPV reduction reactions usually require refluxing conditions due to the energy needed for the hydride transfer process, it could be concluded that the refluxing conditions are not ideal for aldol condensation reactions especially when an inorganic metal base like NaOH is employed.



Scheme 4.7: Proposed mechanism for the MPV reduction of the chalcone.

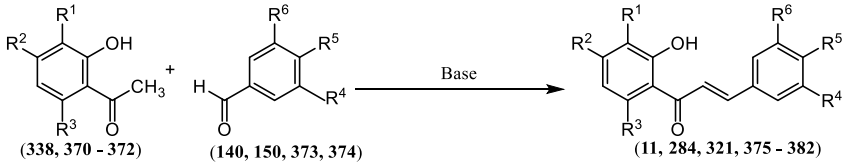
Upon comparing the reactions in dioxane and ethanol it is evident that a polar protic solvent facilitates the aldol condensation, while a polar aprotic solvent such as dioxane leads to low yields even at elevated temperatures or under MW conditions. It also seems that although the rise in temperature accelerates the aldol condensation, it increases the possibility of secondary product formation or the onset of reduction reactions. Furthermore, no significant improvement from solid KOH at RT to aq. NaOH at 40 °C warranted the use of higher temperature as both reactions produced the chalcone (**383**) in high yields (77 and 78%, respectively) within 20-24 hours. The use of NaH, on the other hand, drastically shortens the reaction time to 1 h without any temperature increase and although the presence of 1,5-*bis*(2'-methoxyphenyl)-3-(4''-methoxyphenyl)pentan-1,5-dione (**392**) lowered the yield, it provides a viable option for chalcone synthesis under short reaction times. Therefore, it was subsequently decided to evaluate the NaH and KOH procedures for the synthesis of a series of 2'-hydroxychalcones.

4.2.2 Preparation of 2'-Hydroxychalcones

A series of 2'-hydroxychalcones with varying natural product substitution patterns was, therefore, prepared by the utilization of the NaH and KOH procedures mentioned in the previous section. Method A [solid addition of KOH to a mixture of the corresponding benzaldehyde (**140**, **150**, **373**, **374**) and acetophenone (**338**, **370 - 372**) in ethanol] produced low to moderate yields (21 – 82%) of all chalcones (**11**, **284**, **321**, **375 - 382**) after acidic work-up and recrystallization from an ethanol/water mixture (1:1) (Table 4.2). This method, however, often needed days (1-7 d) to reach near completion as the equilibrium was never fully driven to consume the limiting reagent (acetophenone). The structures of all chalcones were unambiguously confirmed by EIMS, m.p. and NMR spectroscopic (^{1}H, ^{13}C and 2D) analyses (Table 4.3).

Upon comparing the reactions between benzaldehydes (**140**, **150**, **373**, **374**) and the acetophenones (**338**, **370 - 372**), it was found that an increase in the oxygenation of the B-ring could be correlated to an increase in product yield, with the more reactive phloroglucinol derivative (**371**) giving the best yield of 82% (Table 4.2, entry 7). On the other hand, when the resorcinol or phloroglucinol B-ring remains constant and the oxygenation of the A-ring increases the opposite was found, i.e. yields followed a slightly decreasing trend with the addition of methoxy groups (entries 4-6 and 8-10). This tendency could probably be ascribed to the increase of electron density on the aromatic ring as the number of methoxy substituents increase resulting in a decrease in the electrophilicity of the formyl group. It was also interesting to note that the phloroglucinol substituted acetophenone (**371**) produced a higher yield when compared to the resorcinol and pyrogallol analogues (**370**) and (**372**) (65, 71 and 41%, respectively) for this particular method (entries 4, 8 and 11).

Table 4.2: Preparation of various 2'-hydroxychalcones.



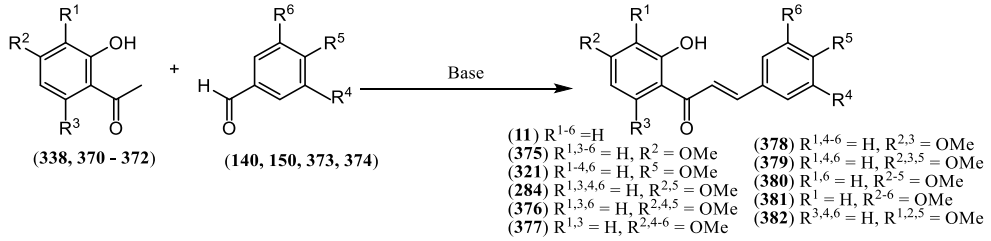
(338, 370 - 372) (140, 150, 373, 374) (11, 284, 321, 375 - 382)

Entry	Chalcone	R^1	R^2	R^3	R^4	R^5	R^6	Method A [a]		Method B [b]	
								Reaction Time (d)	Yield (%)	Reaction Time (h)	Yield (%)
1	**11**	H	H	H	H	H	H	6	60	1	63
2	**375**	H	OMe	H	H	H	H	1	74	1	57
3	**321**	H	H	H	H	OMe	H	2	80	1	94
4	**284**	H	OMe	H	H	OMe	H	7	65	2	92
5	**376**	H	OMe	H	OMe	OMe	H	7	62	1.5	82
6	**377**	H	OMe	H	OMe	OMe	OMe	7	54	2	72
7	**378**	H	OMe	OMe	H	H	H	1	82	1	98
8	**379**	H	OMe	OMe	H	OMe	H	7	71	0.5	99
9	**380**	H	OMe	OMe	OMe	OMe	H	7	74	1.5	96
10	**381**	H	OMe	OMe	OMe	OMe	OMe	7	21	1.5	94
11	**382**	OMe	OMe	H	H	OMe	H	7	41	0.5	99

Reagents and conditions: [a] Method A: solid KOH (4.8 eq), EtOH, RT; [b] Method B: NaH (1.5 eq), dry DMF, Ar, RT.

Method B with NaH in anhydrous DMF and preformation of the acetophenone anion allowed for completion of the reaction within 30 min to 2 h and produced most of the chalcones in high yields (57-99%) after acidification and precipitation from the reaction mixture. Similar trends to the KOH procedure were observed upon comparing the product yields of method A with that of method B, however, with this method both phloroglucinol- and pyrogallol-substituted acetophenones (**371** & **372**) gave higher yields compared to the resorcinol (**370**) analogues (99 vs. 92%) (Table 4.2, entries 4, 8 and 11). This procedure further supported the need for an activated A-ring during the condensation reactions as the unsubstituted or deactivated ring (**149**) resulted in lower yields than the substrates containing a *p*-substituent (**150**) for both methods (entries 1 vs. 3). In general, the NaH procedure was found to produce higher yields in a shorter amount of time without the need for recrystallization compared to the KOH procedure.

Table 4.3: Diagnostic Data for the structure elucidation of 2'-hydroxychalcones.

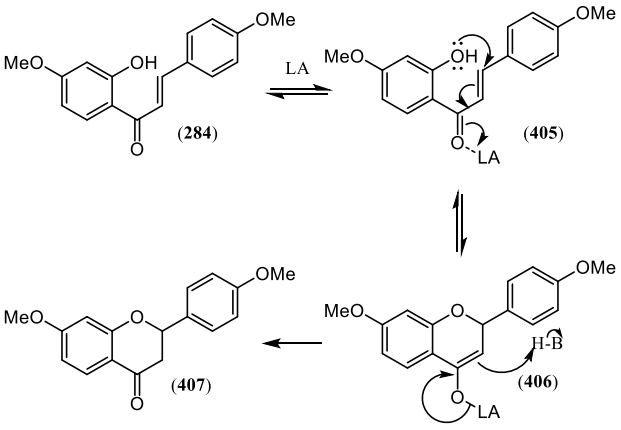


Entry	Chalcone	^{1}H NMR [a]				EIMS (m/z)	m.p. (Lit.) (°C) [b]
		δ (H-α)	δ (H-β)	*J* (Hz)	Plate		
1	**11**	7.67	7.93	15.48	9A	224 (M^+, 78%)	88.6-90.3 (88)
2	**375**	7.59	7.90	15.47	10A	253 (M^+, 26%)	107.1-108.4 (107-108)
3	**321**	7.54	7.90	15.21	11A	254 (M^+, 60%)	92.4-93.7 (95-96)
4	**284**	7.46	7.87	15.37	12A	284 (M^+, 83%)	107.6-109.5 (114-116)
5	**376**	7.43	7.84	15.34	13A	314 (M^+, 60%)	160.9-161.5 (157-159)
6	**377**	7.45	7.80	15.36	14A	344 (M^+, 72%)	122.8-132.5 (118-119)
7	**378**	7.90	7.79	15.61	15A	284 (M^+, 67%)	90.5-91.7 (91-92)
8	**379**	7.77	7.80	15.56	16A	314 (M^+, 100%)	112.6-114.7 (109-110)
9	**380**	7.80	7.75	15.50	17A	344 (M^+, 77%)	155.8-157.5 (151-153)
10	**381**	7.79	7.70	15.49	18A	374 (M^+, 60%)	184.7-186.8 (181-182)
11	**382**	7.44	7.85	15.36	19A	314 (M^+, 87%)	132.1-134.1 (131-132)

[a] multiplicity of both α- and β-H are doublets (d); [b] m.p. determined for products recrystallized from EtOH:H_2O (1:1).

4.3 Flavanone Synthesis

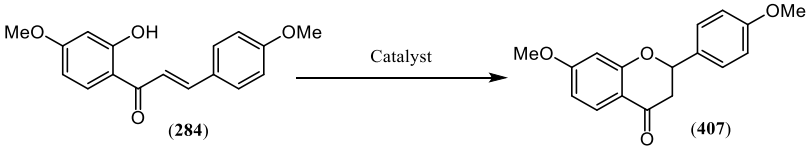
With all the chalcone substrates in hand, attention was subsequently turned towards the formation of the heterocyclic C-ring of the flavonoid entities, before reduction and dehydration would lead to the envisaged flav-3-enes (**9**) (Scheme 4.2). Since it has been reported that the cyclization of 2'-hydroxychalcones (**8**) towards the corresponding flavanone (**369**) or the flavone (**368**) can be catalysed by Lewis acids (LA) like $ZnCl_2$[11] or $InCl_3$[12] and Bezuidenhoudt et al.[13] reported aluminium triflate [$Al(OTf)_3$] to be an efficient recyclable catalyst for the construction of C-O bonds through direct nucleophilic substitution, it was subsequently decided to evaluate the utilization of this oxophilic LA as catalyst during the cyclization of the 2'-hydroxychalcones (Scheme 4.8).



Scheme 4.8: Lewis acid-catalyzed flavanone synthesis

The 2'-hydroxy-4,4'-dimethoxychalcone (**284**) was therefore treated with $Al(OTf)_3$ in acetonitrile at RT. Since TLC indicated no product formation after a few hours at RT, the temperature was increased to 40 °C, 60 °C and eventually refluxing conditions before any product formation could be detected (TLC). Keeping the reaction at reflux for 24 h eventually gave the flavanone (**407**) in 24% yield accompanied by unreacted chalcone (**284**) (15%) after extraction and PLC (Table 4.4, entry 1). The structure of 4',7-dimethoxyflavanone (**407**) was confirmed by NMR spectroscopy (^{1}H and ^{13}C, Plates 20A and 20C) where H-2 was observed at δ_H 5.42 (dd, *J* = 2.85, 13.32 Hz) and the geminal 3-C$\underline{H}_2$ protons at δ_H 3.06 (dd, *J* = 13.32, 16.83 Hz) and 2.80 (1H, dd, *J* =2.85, 16.83 Hz). Furthermore, the resonance of the carbonyl functionality was observed at δ_C 191.0 and the $\underline{C}H_2$ carbon at δ_C 44.3 in the ^{13}C NMR spectrum, while GC-MS showed a molecular ion at *m/z* 284 (M^+, 11%).

Table 4.4: Synthesis of 4',7-dimethoxyflavanone through various cyclization procedures.



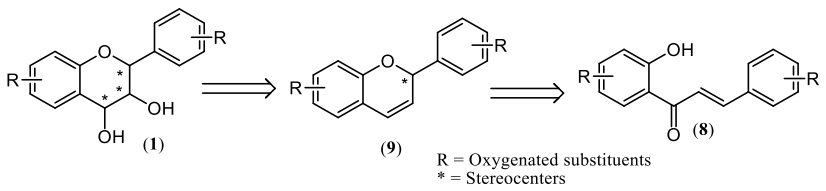
Entry	Method [a]	Heating	Catalyst	Time (h)	Yield (%)
1	Method A	Conventional	$Al(OTf)_3$	24	24
2	Method B	Conventional	NaOAc	24	56
3	Method C	MW	NaOAc	1	42
4	Method D	MW	$Al(OTf)_3$	1	11
5	Method E	MW	$Bi(OTf)_3$	1	24
6	Method F	MW	$La(OTf)_3$	1	5
7	Method G	MW	$Cu(OTf)_2$	1	24
8	Method H	MW	$Cu(OTf)_2$	2	21

[a] Reagents and conditions: Method A: $Al(OTf)_3$ (10 mol%), CH_3CN, reflux; Method B: NaOAc (2eq), EtOH:H_2O (10:1), reflux; Method C: NaOAc (2 eq), EtOH:H_2O (10:1), 150 W, 128 °C; Method D: $Al(OTf)_3$ (10 mol%), CH_3CN, 150 W, 132 °C; Method E: $Bi(OTf)_3$ (10 mol%), CH_3CN, 150 W, 132 °C; Method F: $La(OTf)_3$ (10 mol%), CH_3CN, 150 W, 132 °C; Method G: $Cu(OTf)_2$ (10 mol%), CH_3CN, 150 W, 132 °C; Method H: $Cu(OTf)_2$ (10 mol%), CH_3CN, 150 W, 132 °C.

To be able to compare the $Al(OTf)_3$ catalysed cyclization of the chalcones with standard literature procedures[4,14,15] the reaction was repeated over the conventional catalyst, sodium acetate, in ethanol/water for 24 h under reflux conditions. In this instance the flavan-4-one (**407**) could be isolated in 56% yield after purification by PLC (Table 4.4, entry 2). In an attempt to increase the reaction rate and maybe reduce side-product formation, the reactions with $Al(OTf)_3$ and NaOAc were repeated under MW conditions[6] (150 W, 1 h). Flavanone formation, however, dropped to 11 and 42% yields, respectively (entries 3 and 4) under these conditions.

As the yields obtained for the reactions catalysed by $Al(OTf)_3$ were lower than that found for the conventional NaOAc procedure, it was subsequently decided to also evaluate less acidic or weaker LA, like bismuth triflate [$Bi(OTf)_3$], in the faster MW procedure. Employing $Bi(OTf)_3$ resulted in a higher yield of 24% (Table 4.4, entry 5), however, when moving to a metal with a larger ionic radius like lanthanum (La) that should theoretically be even less acidic, the yield dropped to only 5% indicating that the optimum metal must lie between Al^{3+} and Bi^{3+} (entry 6). Since copper triflate [$Cu(OTf)_2$] has a smaller ionic radius and charge on the metal, it should theoretically give an LA that lies between Al and Bi so this catalyst was subsequently tested in the reaction under MW irradiation conditions (150 W, 1 h). A disappointing yield of only 24% (entry 7), still lower than that of the conventional sodium acetate process, was found and it was decided to increase the MW irradiation time for the $Cu(OTf)_2$ procedure to 2 h. This adaption, however, did not increase the yield and produced the flavanone (**407**) in a low 21% yield after PLC.

Since cyclization by metal triflates did not produce promising yields with an array of unidentifiable products being observed and although a number of LA's could still be evaluated, an advanced literature survey indicated the existence of a more direct route towards flav-3-enes (**9**) through reductive cyclization of 2'-hydroxychalcones (**8**) with sodium borohydride (Scheme 4.9),[16–22] so the flavanone approach was consequently abandoned.

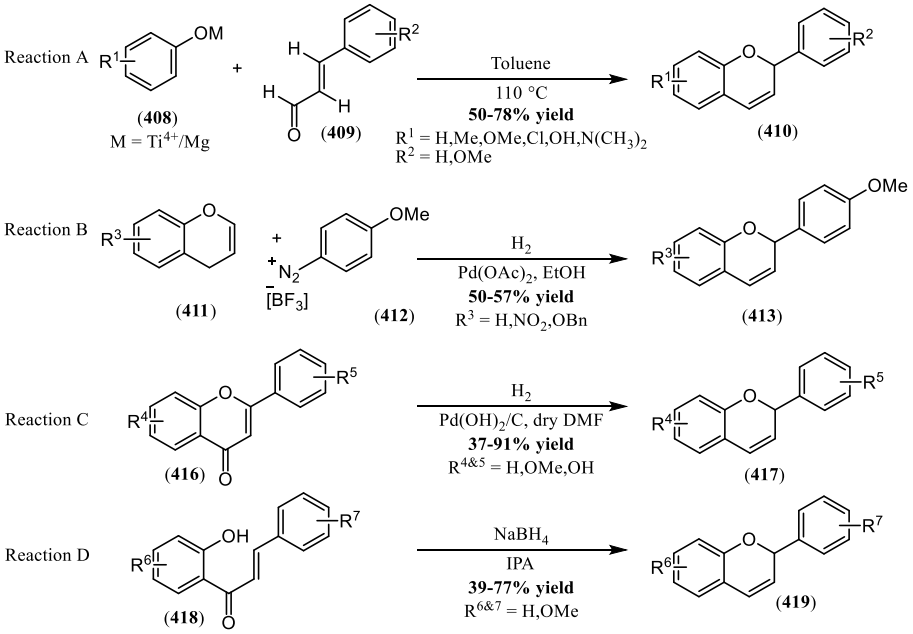


Scheme 4.9: Alternative retrosynthesis route towards flavan-3,4-diols.

4.4 Preparation of Flav-3-enes

4.4.1 Optimization of Flav-3-ene Preparation

Flavenes are rarely isolated from natural sources due to their high reactivity[23–25] and as flav-3-enes (**9**) may act as intermediates in the synthesis of other monomeric and dimeric flavonoid species, a number of synthetic routes for the preparation of these analogues have been reported (Scheme 4.10). However, most of these reported procedures include metal phenoxides (**408**) condensed with α,β-unsaturated compounds (**409**)[26] (Scheme 4.10, Reaction A), or in Heck arylation reactions with arenediazonium salts (**412**)[27] (Reaction B) or expensive metal catalysts that are utilized in simple hydrogenation reactions of flavones (**416**)[28] (Reaction C) that make these routes less favourable. Since the corresponding 2'-hydroxychalcones (**418**) were available and Clark-Lewis and co-workers[16,25] reported the direct formation of flav-3-enes by reductive cyclization of these analogues with $NaBH_4$ in moderate yields (Scheme 4.10, Reaction D), this method for the preparation of the envisaged flav-3-enes was selected for the current investigation. Although the basic methodology were reported by several authors, multiple procedural variations have been documented, so it was decided to start the investigation by finding the optimum reaction conditions with the preparation of 4',7-dimethoxyflav-3-ene (**420**).[17–19]

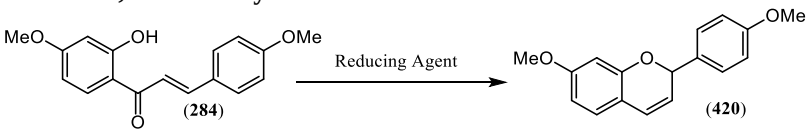


Scheme 4.10: Reported procedures for the preparation of flav-3-enes.

Since Zaveri[17] performed the reductive cyclization in a mixture of THF and ethanol (2:1) at 65 °C, these conditions were used for the first reaction, but only 9% of the target flav-3-ene (**420**) could be isolated after 30 min of reaction time, although TLC indicated complete consumption of the starting material (Table 4.5, entry 1). The structure of the flav-3-ene (**420**) was confirmed by ^{1}H NMR data

(Plate 21A) where an ABX system with three doublets of doublets at δ_H 6.50 (J = 1.62, 9.81 Hz), 5.83 (J = 1.62, 3.39 Hz) and 5.65 (J = 3.39, 9.81 Hz), corresponding to H-4, H-2 and H-3, respectively, were observed. EIMS confirmed the structure of the product by displaying a molecular ion at *m/z* 267 (M^+, 53%). Increasing the reaction time to 17 h (at 65 °C) had a limited effect on the yield which increased to 14% (entry 2), while lowering the temperature to 25 °C generated the flavene (**420**) in a yield of 36% (after 17 h) (entry 3). Although the first temperature reduction improved the yield, another decrease in temperature to 0 °C had the inverse effect and led to a decrease in yield (17%) after 6 h (entry 4). A prolonged reaction time of 24 h at this temperature resulted in an even worse reaction as only 6% of the product (**420**) could be isolated (entry 6).

Table 4.5: Preparation of 4',7-dimethoxyflav-3-ene under various conditions.



Entry	Method [a]	Solvent	Temp. (°C)	Reducing Agent	Time	Yield (%)
1	Method A	THF:EtOH	65	$NaBH_4$	30 min	9
2	Method B	THF:EtOH	65	$NaBH_4$	17 h	14
3	Method C	THF:EtOH	25	$NaBH_4$	17 h	36
4	Method D	THF:EtOH	0	$NaBH_4$	6 h	17
5	Method E	THF:EtOH	0	$NaBH_4$	24 h	6
6	Method F	THF	25	$NaBH_4$	17 h	4
7	Method G	Dry THF	25	$(CH_3)_2$-LAB	5 h	26
8	Method H	IPA	75-RT	$NaBH_4$	overnight	12
9	Method I	IPA	75-RT	$NaBH_4$ (sat. sol.)	overnight	66

Reagents and conditions: [a] Methods A-E: chalcone (1 eq), $NaBH_4$ (4 eq), THF:EtOH (2:1). Method D: chalcone (1 eq), $NaBH_4$ (4 eq). Method G: chalcone (1 eq), $(CH_3)_2$-LAB = $LiBH_3N(CH_3)_2$ (4 eq), Ar. Method H: chalcone (1 eq), $NaBH_4$ (3 eq). Method I: chalcone (1 eq), sat. sol. $NaBH_4$.

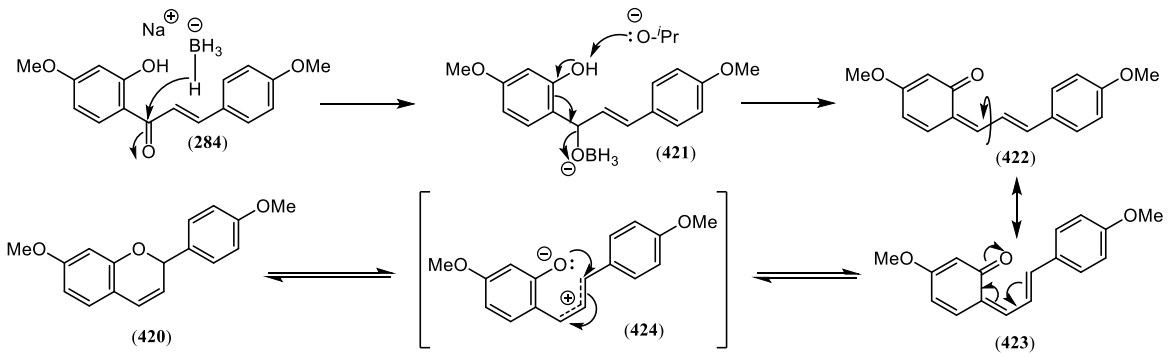
Since all the yields were not even close to acceptable for the second step of a multiple step synthetic process, more attention was required in order to improve this reaction. Owing to the fact that most of the procedures reported for $NaBH_4$ reductive cyclizations included either ethanol or IPA as solvent and it is well documented that $NaBH_4$ may be decomposed by alcohols like methanol,[29,30] it was decided to determine if an alcohol solvent is needed for the reaction. The reaction at 25 °C (Table 4.5, entry 3) was therefore repeated in THF only, but the product yield dropped to ca. 4% (entry 6). Since it was observed that the $NaBH_4$ did not dissolve that well in the THF and this could be the cause for the disappointing yield, it was decided to switch to a reducing agent that would be soluble in THF, but that would react similarly to $NaBH_4$. Although LAB reagents (lithium aminoborohydride reagents) are known to be of similar reactivity than lithium aluminium hydride,[31] and as it was reported by Zhang et al.[32] that harsher reducing agents such as $LiAlH_4$ did not produce the flav-3-ene in high yields but rather a complex mixture of products, it was nevertheless decided to

evaluate lithium dimethylaminoborohydride [$(CH_3)_2$-LAB or $LiBH_3N(CH_3)_2$] in dry THF under Ar atmosphere, a 26% yield of the target flavene (**420**) was obtained in 5 h (entry 7).

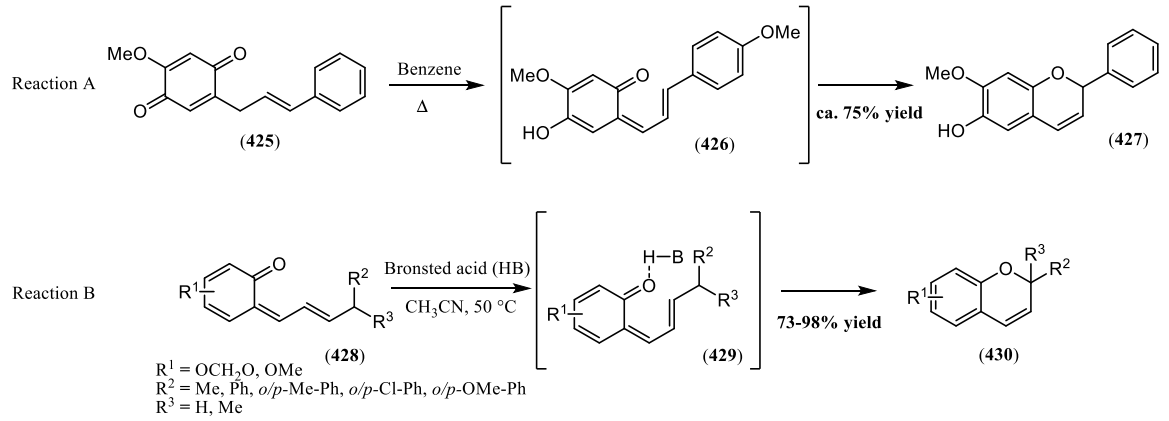
Owing to this dismal result (only 26% yield), it was decided to continue the investigation with $NaBH_4$, but rather use one of the sterically demanding alcohols, isopropanol (IPA) or *t*-butyl alcohol, as solvent, even though $NaBH_4$ has a low solubility in these solvents. To counter the lower solubility the temperature could be raised to 60 °C.[30] Although two procedures were reported for the $NaBH_4$ reaction in IPA, the procedure according to Devakaram et al.,[18,19] where the solid $NaBH_4$ is added in small portions to a hot solution of the chalcones, was followed as first attempt. 2'-Hydroxy-4,4'-dimethoxychalcone (**284**) was therefore dissolved in hot IPA and the reducing agent added in portions, which generated a white precipitate (ppt) when cooled to RT and the reaction mixture left to stir overnight. After acidification (10% HOAc) of the reaction mixture and purification by PLC, the flav-3-ene (**420**) was obtained in only 12% yield (Table 4.5, entry 8). When utilizing the procedure reported by Clark-Lewis and co-workers[16,25] a hot saturated $NaBH_4$ solution was added to a hot solution of the chalcone (**284**), both in IPA, resulting in a white ppt to be formed again and the mixture left overnight at RT. The ppt was subsequently dissolved in $CHCl_3$ [under inert atmosphere, with an O_2 scrubber (section 5.9)] and the resulting milky solution boiled for 10 min turning the reaction mixture pink in colour. Addition of 10% HOAc solution resulted in a dark red mixture, which was refluxed for 2 h generating a light yellow solution containing the crude product when neutralized and concentrated. Finally, recrystallization from MeOH, led to the pure 4',7-dimethoyxflav-3-ene (**420**) to be obtained in 66% yield (entry 9).

The fact that the target flavene could be obtained in this way in good yield probably indicated that the initially formed borate complex required the addition of acid and heat to be fully decomposed and to drive the reaction towards cyclization; thus quenching the reaction with an excess acetone[33] (as can be done for most carbonyl reductions) or acid alone is insufficient and could account for the lower yields found for the previous procedures. Any attempts towards structure determination of the initially formed borate complex were unsuccessful. Since the allylic/benzylic alcohol is the initial reduction product with hydride reagents[34–36] and according to the reduction mechanism proposed by Clark-Lewis and Skingle,[25] it can be assumed that the first step in the mechanism entails generation of the allylic alcohol borate complex (**421**). Furthermore, as $NaBH_4$ also generates the alkoxide from the solvent medium, the alcoholate probably deprotonates the 2'-hydroxy function of the chalcones, which can assist in the dissociation of the borate with the formation of two possible rotational isomers of the vinyl *o*-quinone methide (**422** and **423**). Since the quinone methides **426** and **429**, respectively, have been postulated as key intermediate for the cyclization of 2-cinnamyl-5-methoxy-1,4-benzoquionone (**425**)[23] (Scheme 4.12, Reaction A) and proven to produce the chromene (**430**), when treated with Brønsted acid (Reaction B),[37] it could be concluded that the extremely labile quinone methide

intermediates **422** and **423** are probably also the intermediates in the formation of the target flav-3-ene (**420**) during the current investigation (Scheme 4.11).



Scheme 4.11: Possible mechanism for the formation of the flav-3-ene.

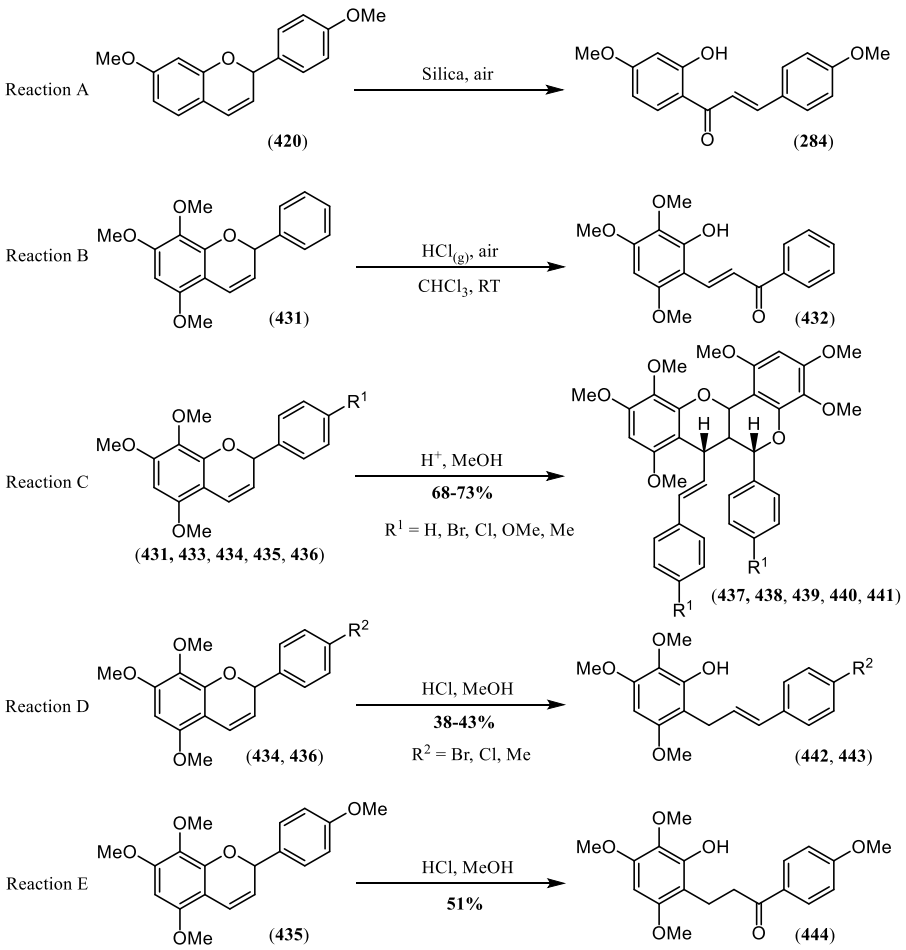


Scheme 4.12: Postulated quinone methides formed during the preparation of flav-3-ene and chromene compounds.

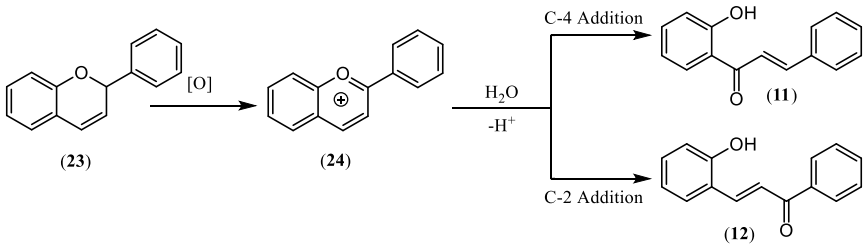
The low flav-3-ene (**420**) yields obtained during some of the previous preparation attempts (Table 4.5, entries 1-9), may also be due to the fact that flav-3-enes are extremely reactive and sensitive to acid, silica, light and air; all of which have been well documented over the years.[23,24,38–42] The decomposition of the chalcone starting material during chromatography (Scheme 4.13, Reaction A) probably explains some of the low yields obtained during the early preparation attempts (Table 4.5), while the much better yields obtained with the last method (Method I) may be at least in part ascribed to the fact that crystallization was used to obtain the pure product.[18,19]

The observed instability of flav-3-enes may be due to a "Claisen type" rearrangement to the labile *o*-quinone methide (**423**) which is in equilibrium with its carbocation (**424**) and can lead to a number of reactions and products. The instability of the flav-3-enes are not only the result of the transformation into the quinone methide, but the alkene moiety is also highly susceptible to cycloaddition reactions[43] with 1,3-dipolar and electrophilic reagents which has been utilized in

cyclopropanations and γ-lactonizations.[44–46] The instability and high reactivity of flav-3-enes was demonstrated by the transformation of 5,7,8-trimethoxyflav-3-ene (**431**), isolated from *Uvaria dependens*, into the *retro*-chalcone (**432**) by exposure to air, while it could also be induced by treating the flav-3-ene with HCl in air (Scheme 4.13, Reaction B).[23,24] Dimerization of flav-3-enes may also occur under acidic conditions (TFA, HCl or HOAc) leading to compounds like dependensin (**437**, R^1 = H), (Scheme 4.13, Reaction C), but with substituents in certain positions on the flavene nucleus and depending on the acid used, *o*-cinnamylphenols (**442**/**443**) or dihydrochalcone (**444**) (Reactions D and E) may also be prodcued.[18,19] A flavylium ion (**24**) could be a plausible intermediate in reactions such as A, D and E (Scheme 4.13), as the simple oxidation and addition of water to either C-4 or C-2 would lead to the corresponding chalcone (**11**) or *retro*-chalcone (**12**), respectively (Scheme 4.14).



Scheme 4.13: Acid sensitivity of flav-3-enes.

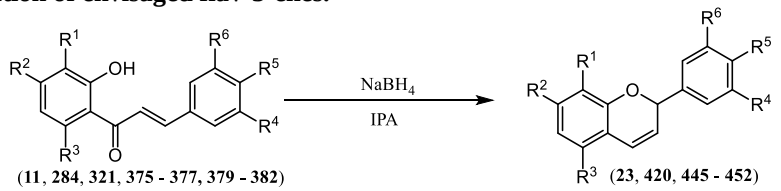


Scheme 4.14: Possible formation of chalcones through flavylium ion intermediates.

4.4.2 Preparation of Envisaged Flav-3-ene Series

As the best procedure was determined and experience about the instability of the flav-3-enes obtained, the proven $NaBH_4$ reduction in IPA procedure was applied to the direct preparation of the envisaged series of flav-3-enes (**23**, **420**, **445** - **452**) with different oxygenation patterns (Table 4.6) in 42-77% yields. As these compounds readily decompose and purification via chromatography often gave low yields, recrystallization from either MeOH or EtOH was always the first choice method of purification. If crystals could not be obtained, the crude products were subjected to dry-column flash chromatography (DCFC) or FCC with 1% TEA in the eluent, while ensuring that the product had a limited time on the silica. Furthermore, due to the sensitivity of the flavenes, the yellow oily compounds were stored under O_2 free Ar atmosphere in the dark at freezer temperatures (ca. -20 °C), while the crystalline products were stored in a desiccator over P_2O_5 under vacuum in the dark and at fridge temperatures (ca. -5 to 0 °C). All products were unambiguously identified with NMR (^1H, ^{13}C, DEPT and 2D), EIMS, m.p. (where possible). The structure of the novel 3',4',7-trimethoxyflav-3-ene (**447**) was confirmed with HRMS, where a sodium adduct molecular ion at *m/z* 321.1100 [$(M + Na)^+$] was found (calculated for $C_{18}H_{18}O_4Na$: 321.1103) (Table 4.7).

Table 4.6: Preparation of envisaged flav-3-enes.



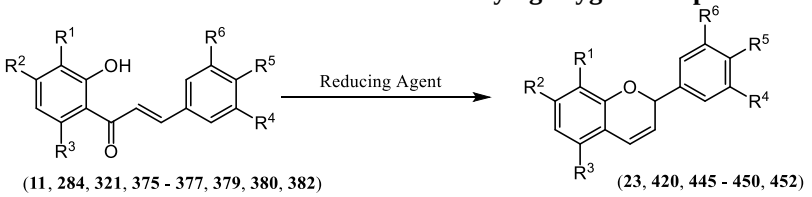
(**11**, **284**, **321**, **375 - 377**, **379 - 382**) (**23**, **420**, **445 - 452**)

Entry [a]	Chalcone	R^1	R^2	R^3	R^4	R^5	R^6	Flav-3-ene	Yield (%)*
1	**11**	H	H	H	H	H	H	**23**	62[b]
2	**375**	H	OMe	H	H	H	H	**445**	61[c]
3	**321**	H	H	H	H	OMe	H	**446**	42[c]
4	**284**	H	OMe	H	H	OMe	H	**420**	66[d]
5	**376**	H	OMe	H	OMe	OMe	H	**447**	77[c]
6	**377**	H	OMe	H	OMe	OMe	OMe	**448**	64[d]
7	**379**	H	OMe	OMe	H	OMe	H	**449**	75[c]
8	**380**	H	OMe	OMe	OMe	OMe	H	**450**	64[d]
9	**381**	H	OMe	OMe	OMe	OMe	OMe	**451**	-
10	**382**	OMe	OMe	H	H	OMe	H	**452**	76[d]

[a] Reagents and conditions: (1) sat. $NaBH_4$, IPA (30 mL/$g_{chalcone}$), overnight, (2) 10% HOAc in $CHCl_3$ (10 mL/$g_{chalcone}$), reflux (2-4 h). * Purification method: [b] FCC [hexanes:toluene (3:7), 1% TEA], [c] DCFC (toluene, 1% TEA), [d] recrystallization MeOH:H_2O or EtOH:H_2O (1:1),

Upon comparing the results obtained, it is evident that as the oxygenation on the A-ring increases from unsubstituted (**23**) to resorcinol (**420**) to phloroglucinol (**450**) or pyrogallol (**452**) the yield increases (Table 4.6, entry 1, 4, 7 and 10). Conversely, as oxygenation on the B-ring increases the flavene becomes more unstable resulting in lower yields (Table 4.6, entries 3 and 6) indicating an inverse correlation between degree of oxygenation and the yield. This increase in instability culminated in the fact that the penta-substituted flavene (**451**) could not be isolated at all and only unidentifiable side-products became available after purification via recrystallization or FCC (Table 4.6, entry 9). The formation of these side-products is likely due to the susceptibility of the C-2 functionality towards oxidation, thus converting the product into the corresponding flavylium cation (Scheme 4.14). This conversion would occur more rapidly as the electron density of the B-ring increases,[47] thus a compound such as **451** with an electron rich pyrogallol-type B-ring would easily oxidize towards the suspected intermediate.

Table 4.7: Diagnostic structural data for flav-3-enes with varying oxygenation patterns.

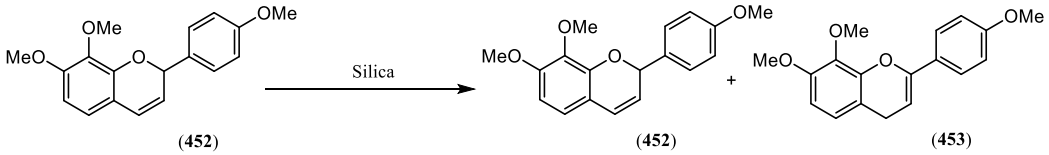


(**11**, **284**, **321**, **375 - 377**, **379**, **380**, **382**) (**23**, **420**, **445 - 450**, **452**)

Entry	Flavenes	^{1}H NMR				EIMS (m/z)	m.p. (Lit.) (°C) [b]
		δ (ppm)	m	*J* (Hz)	Plate		
1	**23**	6.58 (H-4) 5.97 (H-2) 5.84 (H-3)	dd dd dd	1.63, 9.84 1.63, 3.39 3.39, 9.84	22A	208 (M^+, 87%)	-
2	**445**	6.51 (H-4) 5.90 (H-2) 5.68 (H-3)	ddd dd dd	0.45, 1.89, 9.83 1.89, 3.38 3.38, 9.83	23A	237 (M^+, 100%)	-
3	**446**	6.55 (H-4) 5.88 (H-2) 5.79 (H-3)	dd dd dd	0.99, 9.84 0.99, 3.42 3.42, 9.84	24A	238 (M^+, 88%)	-
4	**420**	6.50 (H-4) 5.83 (H-2) 5.65 (H-3)	dd dd dd	1.62, 9.81 1.62, 3.39 3.39, 9.81	21A	267 (M^+, 53%)	78.9-79.0 (79-81)
5	**447**	6.51 (H-4) 5.82 (H-2) 5.65 (H-3)	dd dd dd	1.88, 9.82 1.88, 3.29 3.29, 9.82	25A	298 (M^+, 30%)	-
6[a]	**448**	6.51 (H-4) 5.81 (H-2) 5.64 (H-3)	dd dd dd	1.59, 9.79 1.59, 3.16 3.16, 9.79	26A	327 (M^+, 21%)	89.7-91.1
7	**449**	6.82 (H-4) 5.79 (H-2) 5.60 (H-3)	dd dd dd	1.82, 9.95 1.82, 3.49 3.49, 9.95	27A	297 (M^+, 4%)	-
8	**450**	6.82 (H-4) 5.77 (H-2) 5.59 (H-3)	dd dd dd	1.60, 9.92 1.60, 3.35 3.35, 9.92	28A	328 (M^+, 100%)	118.3-119.5 (119.5)
9	**452**	6.52 (H-4) 5.88 (H-2) 5.73 (H-3)	dd dd dd	1.44, 9.85 1.44, 3.77 3.77, 9.85	29A	298 (M^+, 100%)	72.8-74.3 (75.5)

The instability of the flav-3-enes under chromatographic conditions was confirmed by TLC (not preparative) of the recrystallized 4',7,8-trimethoxyflavene (**452**) which indicated the presence of two products, even when the eluent contained 1% TEA. Thus, to determine what the additional product was, a small amount of recrystallized product (**452**) was "purified" via PLC, which resulted in the collective isolation of both the flav-3-ene (**452**) and flav-2-ene (**453**) in a ratio of 1:0.2 (Scheme 4.15). The two compounds were easily distinguished by ^{1}H NMR data (Plate 30) as the heterocyclic protons

of the flav-2-ene (**453**) were displayed as an A_2X multiplet system [δ_H 5.41 (1H, dd, *J* = 3.72, 3.72 Hz) and 3.49 (2H, dd, *J* = 0.35, 3.72 Hz)] and the equivalent protons of the flav-3-ene (**452**) analogues as a set of ABX multiplets at much lower field [δ_H 6.50 (1H, dd, *J* = 1.55, 9.86 Hz), 5.88 (1H, dd, *J* = 1.55, 3.81 Hz), 5.71 (1H, dd, *J* = 3.81, 9.86 Hz)]. This is not surprising as prototropic rearrangement and isomerization to the flav-2-ene has been suggested as possible intermediate in the dimerization and decomposition of the flav-3-ene towards the inverted dihydrochalcones (**444**).[19,48,49]

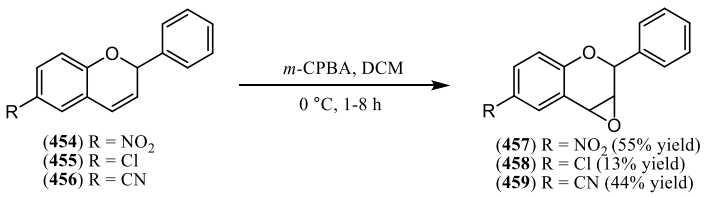


Scheme 4.15: Isomerization of flav-3-ene.

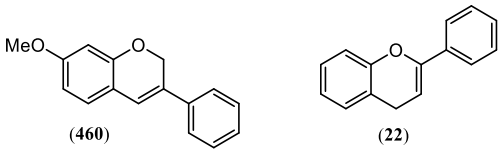
4.5 Epoxidation Reactions

4.5.1 Introduction

As the series of flav-3-enes were now in hand, attention was subsequently turned towards the epoxidation of these compounds with the ultimate goal of preparing the epoxide in high enantiomeric excess in order for these products to be converted into flavan-3,4-diol equivalents. Although *m*-CPBA has been used in the epoxidation of flav-3-enes containing electron-withdrawing groups attached to the A-ring (**454** - **456**) and yields of 13-55% obtained (Scheme 4.16),[50] literature also indicated that methoxy substituted isoflav-3-ene (**460**) and flav-2-ene (**22**) did not produce epoxides when treated with this reagent.[51] Since these compounds (**460** and **22**) were decomposed when treated with *m*-CPBA or gave no reaction, it was decided to investigate the utilization of other strong non-acidic oxidants in the epoxidation of the envisaged oxygenated flav-3-enes (**23**, **420**, **445** – **450**, **452**) during the current study.



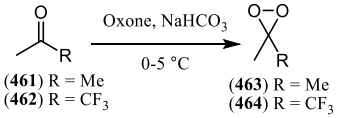
Scheme 4.16: Literature example of the epoxidation of flav-3-enes.



(**460**) (**22**)

Figure 4.1: Examples of flavene compounds unsuccessfully epoxidized with *m*-CPBA.

As dioxiranes are highly reactive oxidants that are capable of oxidizing alkenes in high chemo-, regio- and diastereoselectivity[52] under basically neutral conditions, this type of reagent was selected as oxidant in the current investigation, despite the fact that oxidation of heteroatoms (e.g. N, S, Si, O, Mn) with these reagents have also been reported.[52–54] Dioxiranes are, furthermore, readily generated from commercially available ketones (e.g. acetone) and potassium monoperoxysulfate ($2KHSO_5 \bullet K_2SO_4 \bullet KHSO_4$, Oxone®,Curox®, or Caroate®) and can be prepared and used in situ or after purification by distillation as a solution in the parent ketone. As the oxidation reactions with distilled dioxirane solutions are strictly performed under neutral conditions, the possibility of the highly reactive flav-3-ene epoxides being transformed into other analogues would also be minimized if these reagents are used for these reactions. Utilizing dioxirane compounds as reagents in these reactions would also have the added advantage that these reactions can easily be converted into enantioselective epoxidation reactions through the addition of a chiral catalyst to the reaction mixture[55–57] or the use of a chiral ketone for the preparation of the dioxirane.[58,59] The possibility of utilizing a wide variety of ketones containing electron-donating (e.g. acetone) as well as electron-withdrawing substituents (e.g. hexafluoropropanone) and therefore dioxiranes of varying reactivity [e.g. (**463**) and (**464**)] during the epoxidation reactions[52,60–62] added further impetus into the selection of these reagents as oxidants during the current investigation, thus providing yet another motive to study these oxidants further as a small alteration could lead to chiral induction.



(**461**) R = Me
(**462**) R = CF_3

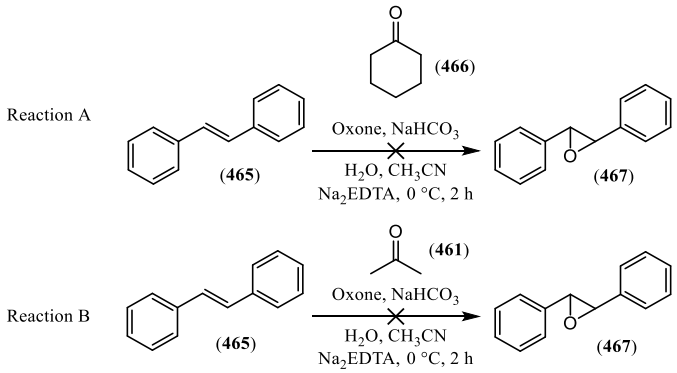
(**463**) R = Me
(**464**) R = CF_3

Scheme 4.17: DMDO (463) and TFD (464).

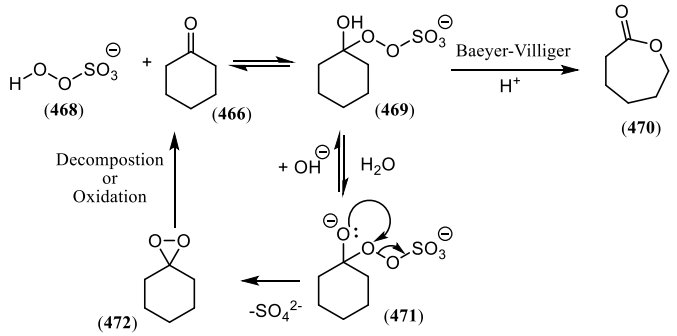
4.5.2 In Situ Generated DMDO and Epoxidation Reactions

Since the successful epoxidation of *trans*-stilbene with dioxiranes have been reported,[62,63] it was decided to use this compound as model substrate to start the investigation, while it was also decided to utilize the more convenient in situ conditions for generating the dioxirane as it would allow for the utilization of a wider range of ketones. The investigation was therefore started by applying the monophasic procedure for in situ preparation of dioxirane from cyclohexanone (**466**), as reported by

Yang et al.,[64] to the epoxidation of *trans*-stilbene (**465**). No reaction, however, occurred with only the starting material being isolated (Scheme 4.18, Reaction A) after 2 h at 0 °C. Since it was thought that the competing Baeyer-Villiger reaction[61,65] might have led to the decreased the amount of available ketone present in the solution (Scheme 4.19), it was decided to change the ketone to acetone (**461**) as that was the exact in situ epoxidation system reported by Shi et al.[65] for the preparation of stilbene oxide, but again no epoxidation could be detected (Scheme 4.18, Reaction B).



Scheme 4.18: Treatment of *trans*-stilbene with in situ generated dioxiranes from cyclohexanone and acetone.



Scheme 4.19: Cyclohexanone dioxirane formation and competing Baeyer-Villiger reaction.

Although the failure of the reaction was somewhat surprising, literature revealed that several variables such as the rate of Oxone® addition,[66] pH of the reaction mixture (controlled by the addition of solid $NaHCO_3$ to Oxone®)[52,67,68] and the presence or absence of a phase transfer catalyst like tetrabutylammonium hydrogen sulphate,[62,63,69] might have had an influence on the outcome of the reaction. Furthermore, since it is well known that aqueous in situ conditions can only be applied to reactions where both substrates and the product are tolerant of aqueous conditions[60] and it has been shown that epoxides of precocene I (**485**)[70–72] and methoxy substituted isoflav-3-ene (**460**) or flav-2-enes (**22**)[51] are extremely sensitive to basic and acidic conditions, it was decided to continue the investigation by using a neutral[55] distilled solution of DMDO in an appropriate solvent.

4.5.3 Isolation of DMDO and Epoxidation Reactions

Although the isolation of volatile DMDO in an acetone solution has been reported, several experimental set-ups[60,73–77] for this preparation have been described and dilute solutions (ca. 0.04-0.12 M) are usually obtained.[52,67,73] The distillation process can also make it difficult to control the water content of the DMDO solution and although the solutions drying procedures have been described, they are not always reliable and often diluted the concentrations even further.[73,75,78] The well-formulated procedure by Murray and Singh,[77] which involves the simultaneous portion-wise addition of solid Oxone® and an acetone-water mixture to a vigorously stirred cooled (ice-bath) aqueous solution of $NaHCO_3$ and acetone under N_2 atmosphere was therefore used during the first attempt at the preparation of the DMDO solution (Figure 4.2, left). The volatile DMDO was distilled over, collected in a cooled (-78 °C) receiving flask under reduced pressure (100-80 Torr) and stored in the freezer. Since only 13 mL of the DMDO solution was obtained and not the reported ca. 62-76 mL, it was decided to change the preparation procedure to that reported by Adam et al.[75] (150 mL, 0.09-0.11 M solution) which excluded the slow addition of the acetone-water mixture and the inert atmosphere (Figure 4.2, right).

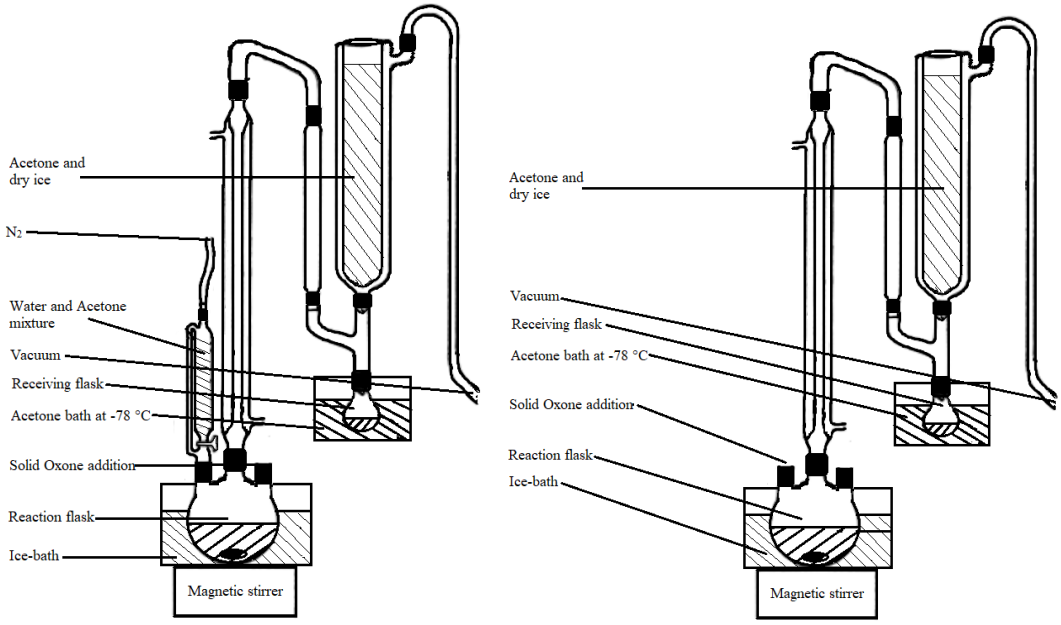


Figure 4.2: Different DMDO preparation set-ups.

The procedure and set-up alterations did, however, not improve the DMDO yield as only 10 mL of 0.13 M solution was obtained [standardized by GC analysis of a thioanisole oxidation process (section 5.10.2, Method A)]. Since literature also indicated that the decreased yield could be due to decomposition of the Oxone®[79] and that it could be addressed by with the presence of EDTA,[80] the

DMDO synthesis was repeated in the presence of a 2% EDTA solution, but this alteration had no significant positive effect on the yield of DMDO generated.

Despite, the small amounts of DMDO obtained by all the previous methods, it was decided to continue with the epoxidation study and establish whether the envisaged flav-3-enes could actually be epoxidized successfully with this oxidant and come back to the improvement of the preparation procedure at a later stage. Since Adam et al.[55] reported the enantioselective epoxidation of 6-cyano-2,2-dimethylchromene (**474**) in DCM with Jacobsen's Mn(III) salen catalyst (**473**) and DMDO, it was decided to repeat this epoxidation without the addition of the chiral catalyst as starting point in the current investigation. Thus treatment of a cooled (ice-bath) 6-cyano-2,2-dimethylchromene (**474**) solution in DCM with DMDO, followed by solvent removal and purification by FCC gave the 6-cyano-2,2-dimethylchromane oxide (**475**) in 91% yield after only 1 h at RT. The structure of the product was confirmed by ^{1}H NMR spectroscopy (Plate 31A) where the two doublets for the heterocyclic C-ring were clearly visible at δ_H 3.91 (1H, d, J = 4.33 Hz, H-4) and 3.53 (1H, d, J = 4.33 Hz, H-3), while EIMS indicated a molecular ion at *m/z* 201 (M^+, 61%).

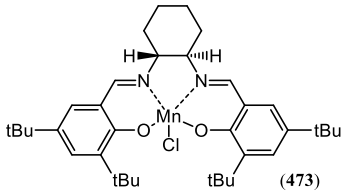
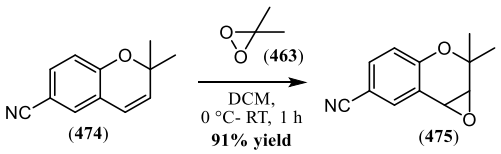
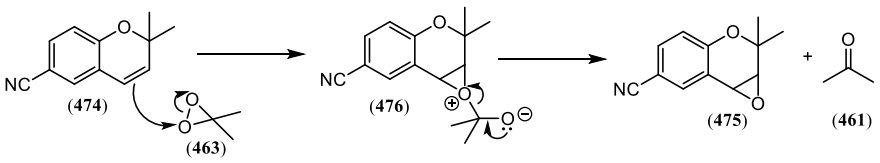


Figure 4.3: (*R*,*R*)-Jacobsen's Mn(III) salen catalyst.



Scheme 4.20: DMDO epoxidation of 6-cyano-2,2-dimethylchromene.

It has been well established that the olefin oxidation by dioxiranes occur via a concerted electrophilic reaction mechanism[60,81] and that the epoxidation reaction is initiated by nucleophilic attack of the double bond onto one of the slightly positively charged dioxirane oxygens. The epoxide is subsequently generated by the elimination of acetone from the zwitterion (**476**) (Scheme 4.21).



Scheme 4.21: Concerted mechanism for chromene oxidation with DMDO.

Despite the fact that a concerted mechanism for the dioxirane epoxidation of alkenes is generally accepted, two mechanistic TS, i.e. the so-called spiro-TS (**477**) and planar-TS (**478**), have been proposed for this transformation. Several studies, however, supported the spiro-TS (Figure 4.4),[52,60,82–85] as this TS leads to a stabilizing secondary orbital interaction between the non-bonding orbital of the dioxirane oxygen and the π^* orbitals of the alkene, which is not possible in the planar-TS (Figure 4.4). However, recent investigations into the reactivity and stability of the ketone reactant indicated that the ketone substituents could alter the competition between the two TS, thus affecting the isomeric outcome of the reaction.[85]

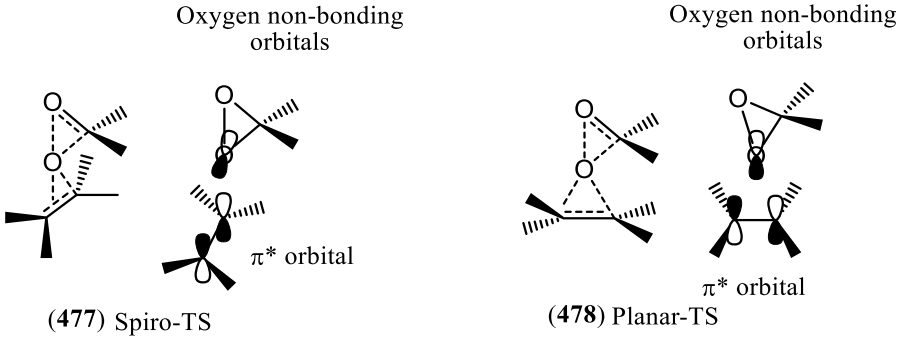
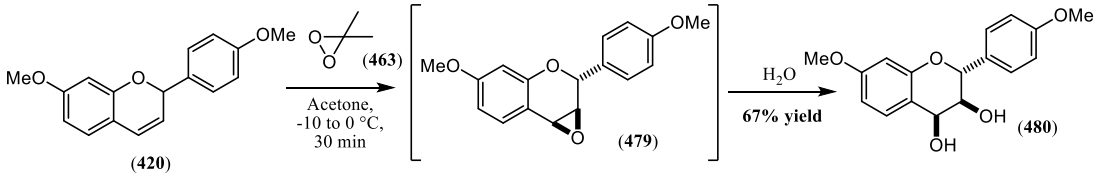


Figure 4.4: Mechanistic transition states of DMDO and olefins.

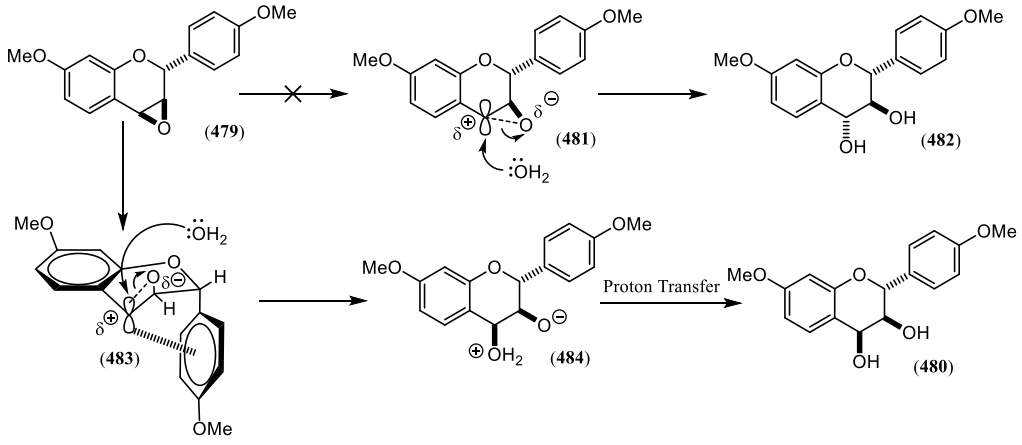
Nonetheless, as the model substrate resulted in promising yields, the investigation was subsequently extended to the epoxidation of 4',7-dimethoxyflav-3-ene (**420**). Since it was suspected that the epoxide from this flav-3-ene might be a more labile than that obtained from the electron-poor cyanodimethylchromene (**474**) and DCM might be slightly acidic, the solvent was changed to acetone. After rapid addition of the DMDO to a cooled (-10 °C) solution of the substrate (**420**) in acetone, followed by stirring at 0 °C for 30 min, the solvent was evaporated under reduced pressure and the crude product purified by PLC to obtain, not the epoxide, but the 2,3-*trans*-3,4-*cis* diastereoisomer of 4',7-flavan-3,4-diol (**480**) in 67% yield (Scheme 4.22). The structure of the product (**480**) was confirmed by ^{1}H NMR data (Plate 32A), which indicated, apart from the expected aromatic signals [δ_H .40 (2H, d, *J* = 8.63 Hz, H-2'&6'), 7.25 (1H, d, *J* = 8.49 Hz, H-5), 6.96 (2H, d, *J* = 8.63 Hz, H-3'&5'), 6.58 (1H, dd, *J* = 2.46, 8.49 Hz, H-6), 6.46 (1H, d, *J* = 2.46 Hz, H-8)], three heterocyclic resonances at δ_H 4.98 (1H, d, *J* = 9.71 Hz), 4.74 (1H, d, *J* = 3.55 Hz) and 4.02 (1H, dd, *J* = 3.55, 9.71 Hz) as well as two hydroxy protons at δ_H 2.67 (1H, br s) and 2.25 (1H, br s). The presence of the hydroxy resonances was confirmed by the addition of deuterium oxide (D_2O) to the NMR solvent,

which led to the collapse of these signals. A molecular ion at *m/z* 302 (M^+, 5%) in the EIMS spectrum gave further credence to the structure of the proposed product. The 2,3-*trans*-3,4-*cis* configuration followed from the coupling constants of the heterocyclic protons, which were in good agreement with literature values for the 2-,3- and 4-protons of this compound [δ_H 5.02 (d, *J* = 9.7 Hz, H-2), 4.64 (d, *J* = 3.6 Hz, H-4) and 3.97 (dd, *J* = 3.6, 9.7 Hz, H-3)].[86,87]



Scheme 4.22: DMDO epoxidation of 4',7-dimethoxyflav-3-ene.

Despite the fact that the epoxide was not obtained from the reaction, the formation of the observed flavan-3,4-diol (**480**) was not surprising and explicable in terms of nucleophilic attack from a water molecule (present in the wet acetone) to the electrophilic 4-position of the epoxide. The 2,3-*trans*-relative configuration of the diol product (**480**) is also obvious as it could be expected that the bulky 2-phenyl substituent would render epoxidation to the opposite face of the flav-3-ene double bond more favourable, so epoxide (**479**) would be formed as the main product, if not exclusively (Scheme 4.22). The observed 3,4-*cis* relative configuration of the diol product (**480**), however warrants some further commenting, as it could be expected that the initially formed flavan epoxide (**479**) would be attacked by the water molecule in an S_N2 fashion from the less hindered face opposite to the epoxide ring, thus leading to the 3,4-*trans* diol product (**480**) (Scheme 4.23).[81] Since this was not observed, it might be that the incipient C-4 carbocation is stabilized by interaction with the π-electrons of the phenolic B-ring (**483**), which would render attack to that face of the C-ring as less favourable (Scheme 4.23).[88,89]



Scheme 4.23: Possible B-ring interaction and stabilization of carbocation.

Even though the epoxidation reaction was successful, the DMDO handling and storage were found to be rather problematic as DMDO is extremely volatile and has a life time at RT of only a few minutes to 24 h.[90,91] Although it has been reported that DMDO can be stored in a freezer (-20 °C) away from light and heavy metals for at least a week,[64,73,92–94] it was found during the current study that after a night in the freezer, the concentration had already decreased dramatically. Owing to these difficulties, it was decided to rather prepare the DMDO and use it immediately, so storage of the DMDO solution could be avoided.

4.5.4 DMDO Distilled Directly into the Reaction Mixtures

4.5.4.1 Set-up and Standardization

The ability to directly distil the DMDO solution into the epoxide mixture would depend on the ability to produce the solution repeatedly at the same quantity and concentration, thus this aspect of the preparation subsequently received some attention. To adapt the quantity of DMDO produced to the size of the envisaged epoxidation reactions, the volume of the DMDO set-up was reduced from that described in the previous section 4.5.3 (Table 4.8, entries 1 en 2), while the vacuum system was also removed in order to avoid any loss of DMDO due to possible entrainment (Figure 4.5, left). The previous preparation (Table 4.8, entries 2) was therefore repeated with half of the reagents and yielded 11 mL of a 0.01 M (0.15 mmol) solution (Table 4.8, entry 3) (standardization see section 5.10.2, Method B). In an attempt to reduce any possible loss of DMDO during opening of the flask for portion-wise addition of Oxone®, a solid addition flask was added to the reaction set-up (Figure 4.5, right). This alteration resulted in a substantial increase in yield and 11 mL of a 0.03 M (0.30 mmol) solution could be obtained (Table 4.8, entry 4). As a final attempt at increasing the quantity of DMDO formed, a slight vacuum (130 Torr) was added to the end of the set-up (Figure 4.6), which led to an increase in DMDO production to 12 mL of a 0.12 M (1.5 mmol) solution, while half of the reagent quantities of the previous procedure were again used (Table 4.8, entries 4 vs. 5). In order to see if the latest procedure would be repeatable, the process was subsequently executed again, in duplicate, and an average of 11 mL of a 0.11 M (1.3 mmol) solution was obtained for all three efforts (Table 4.8, entry 6-8), which was in good agreement with literature procedures where ca. 0.04-0.12 M solutions were obtained.[52,67,73]

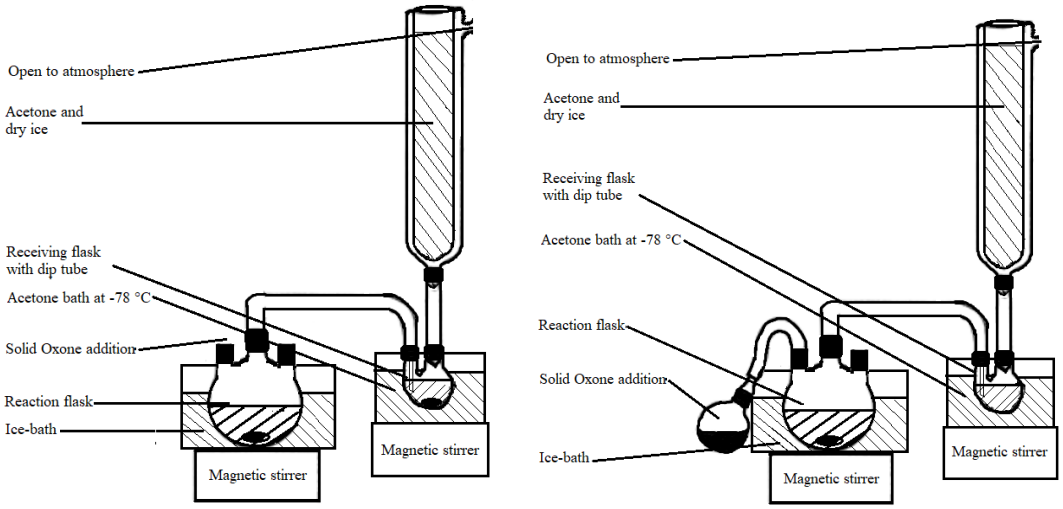


Figure 4.5: Alterations to the DMDO set-up.

Table 4.8: Concentration of isolated DMDO.

Entry	Method [a]	Acetone (mol)	Oxone® (mol)	DMDO (mmol)	Concentration DMDO (M) [b]
1	A	1.5	0.3	ND	ND
2	B	2.6	0.2	1.30	0.13
3	C	1.4	0.1	0.15	0.01
4	D	1.4	0.1	0.3	0.03
5	E	0.7	0.05	1.5	0.12
6	E	0.7	0.05	1.1	0.10
7	E	0.7	0.05	1.2	0.11
8 (avg 5-6)	E	0.7	0.05	1.3	0.11

[a] Reagents and conditions: Method A: Figure 4.2, left (N_2 & vacuum 100-80 Torr), H_2O (140 mL), $NaHCO_3$ (1.14 mol) ; Method B: Figure 4.2, right (vacuum 100-80 Torr), H_2O (254 mL), $NaHCO_3$ (0.7 mol); Method C: Figure 4.5, left, H_2O (130 mL), $NaHCO_3$ (0.35 mol); Method D: Figure 4.5, right (solid addition flask), H_2O (130 mL), $NaHCO_3$ (0.35 mol); Method E: Figure 4.6 (vacuum 130 Torr), H_2O (65 mL), $NaHCO_3$ (0.18 mol). [b] Standardization with GS-MS analysis of thioanisole oxidation process (section 5.10.2, Method B).

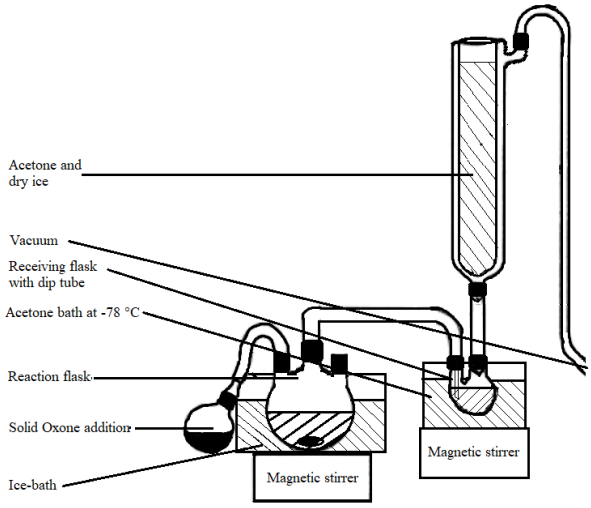
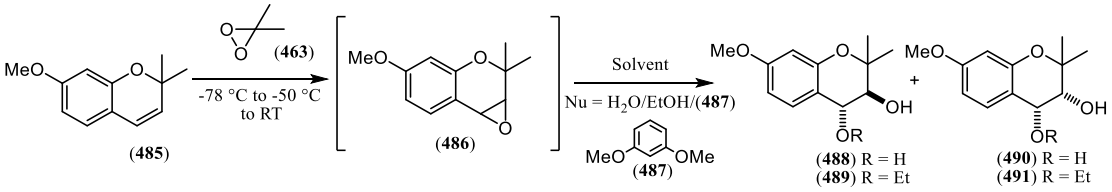


Figure 4.6: Final DMDO set-up for epoxidation reactions.

4.5.4.2 Epoxidation of 7-Methoxy-1,1-dimethylchromene (Precocene I)

As the flav-3-ene substrates were not easy to prepare and highly decomposable, it was decided to test the process of direct addition of distilled DMDO to the substrate on a model compound, i.e. 7-methoxy-1,1-dimethylchromene [precocene I (**485**)], that would have properties similar to that of the envisaged flavenes. Owing to the fact that the epoxide might not be stable and may react with some nucleophilic species present leading to several side-products, the first epoxidation reaction was performed in the presence of *m*-dimethoxybenzene (**487**) with the idea that the labile epoxide might be trapped by the nucleophilic resorcinol derivative. Treatment of a precocene I (**485**) and *m*-dimethoxybenzene (**487**) solution in DCM with DMDO (prepared according to the latest procedure) at –78 °C for 1 h and allowing it to stir overnight at RT, followed by solvent evaporation under reduced pressure and purification by PLC, however, did not give any product containing an aromatic substituent, but rather the two chroman-3,4-diols (**488** and **490**) collectively isolated (R_f 0.11; H:C, 9:1, 1% TEA) in 36% yield (Table 4.9, entry 1). The structures **488** and **490** were established from their ^{1}H NMR spectra (Plate 33A), with resonances at δ_H 4.46 (1H, d, *J* = 8.38 Hz, H-4) and 3.52 (1H, d, *J* = 8.38 Hz, H-3) for (**488**) and δ_H 4.73 (1H, br s, H-4) and 3.64 (1H, br s, H-3) for (**490**). The relative configurations, which could be assigned as 3,4-*trans*-(**488**) and 3,4-*cis*-(**490**) by comparison to reported literature values,[72,95] further indicating that the diastereoisomers were formed in a ratio of 3:2 (*trans*:*cis*) (Table 4.10, entry 1). The structure was further confirmed by EIMS where a molecular ion at *m/z* 223 (M^+, 16%) was clearly visible.

Table 4.9: Epoxidations of precocene I with DMDO.



Entry	Method [a]	Nu	Solvent	Products	Yield (%)	Ratio (*trans*:*cis*)
1	A	*m*-DMB (**487**)	DCM	(**488**) and (**490**)	36[b]	3:2 [d]
				(**489**) and (**491**)	43[c]	2:1
2	B	EtOH	DCM	(**488**) and (**490**)	46	2:1[d]
				(**489**) and (**491**)	28[b]	6:1
3	C	H_2O	Acetone	(**488**) and (**490**)	77	2:1[d]

[a] Reagents and conditions: Method A: *m*-DMB = *m*-dimethoxybenzene (**487**) (2 eq), DCM; Method B: EtOH (2 eq), DCM; Method C: H_2O, acetone. [b] Collectively isolated. [c] Collective yield from isolated masses. [d] Determined by ^{1}H NMR of isolated diastereometic mixture.

The two *trans*-(**488**) and *cis*-diols (**490**) were accompanied by two additional products (**489** and **491**) with R_f 0.28 and 0.33 (H:C, 9:1, 1% TEA) in 28 and 15% yields (Table 4.9, entry 1). These structures were identified with ^{1}H NMR experiments (Plates 34A and 35A) as the 4-ethoxy-substituted products, as the expected aromatic resonances [δ_H 7.30 (1H, d, *J* = 8.53 Hz, H-5), 6.61 (1H, dd, *J* = 2.51, 8.53 Hz, H-6) and 6.56 (1H, d, *J* = 2.51 Hz, H-8) for **489** and 7.31 (1H, d, *J* = 8.54 Hz, H-5), 6.64 (1H, dd, *J* = 2.51, 8.54 Hz, H-6) and 6.58 (1H, d, *J* = 2.51 Hz, H-8) for **491**] were accompanied by further characteristic resonances at δ_H 4.32 (1H, d, *J* = 7.27 Hz, H-4), 3.68 (1H, dd, *J* = 4.81, 7.27 Hz, H-3), 3.33-3.24 (2H, m, $OC\underline{H}_2CH_3$) and 1.01 (3H, t, *J* = 6.98 Hz, $OCH_2C\underline{H}_3$) for (**489**) and 4.18 (1H, d, *J* = 4.29 Hz, H-4), 3.60 (1H, d, *J* = 4.29 Hz, H-3), 3.52-3.43 (2H, m, $OC\underline{H}_2CH_3$) and 1.12 (3H, t, *J* = 6.99 Hz, $OCH_2C\underline{H}_3$) for (**491**) were displayed. ^{13}C and DEPT experiments (Plates 34/35C and 34/35B) also confirmed the presence of CH_2 and CH_3 carbons at δ_C 64.5 or 64.7 ($O\underline{C}H_2CH_3$) and 16.0 or 15.5 ($OCH_2\underline{C}H_3$) for **489** and **491**, respectively. HRMS and EIMS of the compound displayed sodium adduct molecular ion at *m/z* 275.1265 $[M + Na]^+$ (calculated for $C_{14}H_{20}O_4Na$: 275.1259) and 251 (M^+, 18%), respectively, that was in good accordance with the suggested structure. Each geometric isomer was distinguished in accordance to the Karplus equation[96] as vicinal hydrogens with a larger dihedral angle, i.e. the *trans*-isomer, produce a larger coupling constant (*J*) compared to a smaller dihedral angle, i.e. *cis*-isomer, that would generate a small *J* value (Table 4.10). Compounds, **489** and **491**, were therefore unequivocally assigned as 3,4-*trans*-4-ethoxy-7-methoxy-2,2-dimethylchroman-3-ol and the 3,4-*cis*-4-ethoxy-7-methoxy-2,2-dimethylchroman-3-ol structures, respectively.

Table 4.10: Diagnostic data for heterocyclic C-ring of 3-chromanol products.

Entry	Product	MS (*m/z*)	^{1}H NMR		
			δ (ppm)	***J* (Hz)**	**Plate**
1	**488**	223 (M^+, 16%)	4.46 (d, H-4) 3.52 (d, H-3)	8.38	33A
2	**490**		4.73 (br s, H-4) 3.64 (br s, H-3)	-	33A
3	**489**	251 (M^+, 18%)	4.32 (d, H-4) 3.68 (dd, H-3)	7.27 7.27, 4.81	34A
4	**491**	275.1265 $[M + Na]^+$	4.18 (d, H-4) 3.60 (d, H-3)	4.29	35A

Since no reaction between the resorcinol dimethylether (**487**) and the in situ formed chromene epoxide (**486**) was detected, it could be concluded that the nucleophilicity of the aromatic entity was not high enough to affect the ring opening of the epoxide at the prevailing sub-zero temperatures. In the absence of a potent nucleophile, the incipient carbocation at C-4 of the chromane entity therefore reacted with water from the DMDO preparation process that was entrained to the receiving reaction

flask during the preparation of the DMDO solution; thus leading to the formation of the *cis*-(**490**) and *trans*-diols (**488**). Although the formation of the diols **488** and **490** could be explained in this way, the formation of the two 4-ethoxy analogues **489** and **491** were more problematic as no ethanol was added to the reaction work-up. A close investigation of the composition of the DCM used, however, indicated it to be stabilized by ethanol,[97] so the 4-ethoxy substituted chromanols could be attributed to the ethanol attacking the incipient 4-carbocation, leading to the *cis*- and *trans*-4-ethoxy products, (**489**) and (**491**), respectively.

The *trans*:*cis* isomer ratios of 3:2 and 2:1 for the diol and 4-ethoxychromanol, respectively, indicated the expected preferential S_N2 type *anti* attack of the nucleophile on the epoxide, while some degree of S_N1 substitution is also evident from the fact that some of the 3,4-*cis*-isomer were indeed formed in both instances. The preferential formation of the 3,4-*trans*-isomers **488** and **489** in both these substitution reactions taken in conjunction with the fact that only the 3,4-*cis*-isomer (**480**) was obtained during the opening of the flav-3-ene epoxide (**479**), serves as additional support of the idea that the quasi axial B-ring of the flavene interacts in some way with the incipient 4-carbocation, thus shielding that face of the molecule from nucleophilic attack and forcing *anti* attack on the epoxide (Scheme 4.23).

In order to prove that the ethanol in the DCM actually led to the 4-ethoxychromanols being formed, the reaction in DCM was repeated with the addition of ethanol (2 eq). Under these conditions, however, an increase (46 vs. 36%) in the formation of the chroman-3,4-diols (**488** and **489**) and a decrease (43 vs. 28%) for the 4-ethoxychromanols (**489** and **491**) were obtained (Table 4.9, entry 2). Although this at first seemed strange and unexpected, it must be kept in mind that anhydrous ethanol was not used and thus the concentration of water in the DCM mixture was also increased during this reaction. The fact that the diastereometic ratio (de) shifted even more towards the *trans*-isomer (2:1 and 6:1, respectively) for both the diol and 4-ethoxychromanol (**488** and **489**) indicated an enhancement of the S_N2 process over the S_N1 equivalent when an excess of the nucleophile is present. Finally, since water proved to be a more potent nucleophile when compared to ethanol, it was finally decided to repeat the epoxidation reaction in (wet) acetone rather than DCM, which gave only the *cis*- and *trans*-3,4-diols (**488**) and (**490**) in a combined yield of 77%, with the *trans*-isomer as the major isomer (Table 4.9, entry 3).

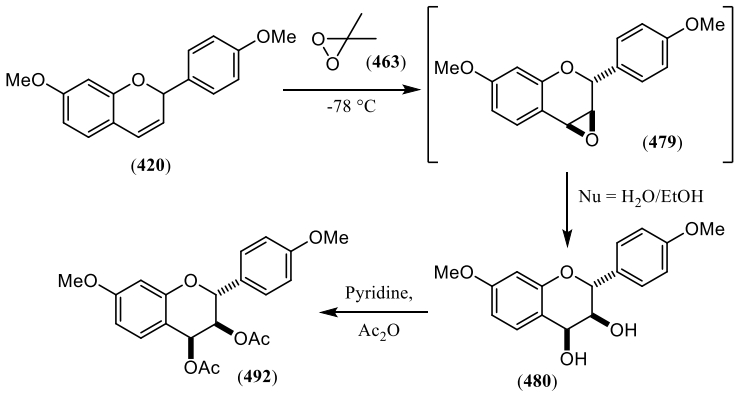
4.5.4.3 Epoxidation of Flav-3-enes

Since the model substrate provided evidence that the new DMDO set-up would be a viable option for the formation of at least the flavan-3,4-diols in acceptable yields, attention was subsequently turned towards the epoxidation of the available series of substituted flav-3-enes. As the oxidation of the 4',7-dimethoxyflav-3-ene (**420**) with prepared or isolated DMDO (section 4.5.3) generated only one

diastereoisomer of the product in an acceptable yield of 67% in only 30 min at 0 °C (Table 4.11, entry 1), the same substrate was used to determine whether the reaction with the DMDO distilled directly into the reaction mixture would afford the same promising results.

In an attempt to improve the yield and as it was suspected that a substantial amount of product is lost during separation, it was decided that protection of the hydroxy groups might be beneficial to the separation process on silica. It was further decided to acetylate the OH groups before separation, so the reaction was repeated with DMDO distilled directly into the reaction mixture. After completion of the reaction and solvent evaporation under reduced pressure, acetic anhydride and pyridine (ratio of 1:2) was added to the crude product. After 2 h at 40 °C, precipitation of the product and purification by PLC gave the expected 2,3-*trans*-3,4-*cis*-3,4-diacetoxy-4',7-dimethoxyflavan (**492**), but in a low yield of 42% (Table 4.11, entry 2). The structure of the product was confirmed by the ^{1}H NMR data (Plate 36A) where two acetoxy methyl resonances at δ_H 2.13 [3H, s, 4-OC(O)C<u>H</u>$_3$] and 1.84 [3H, s, 3-OC(O)C<u>H</u>$_3$], as well as the expected heterocyclic proton signals [δ_H 6.16 (1H, d, *J* = 3.50 Hz, H-4), 5.44 (1H, dd, *J* = 3.50, 10.35 Hz, H-3) and 5.22 (1H, d, *J* = 10.35 Hz, H-2)] were clearly visible, while the relative configuration of the suggested structures could be assigned by comparison of the coupling constants (*J*) of the heterocyclic C-ring protons with literature values (Table 4.12).[86,87,96,98–106] The proposed structure was also confirmed by carbonyl carbon resonances at δ_C 170.6 and 169.4 in the ^{13}C NMR spectrum (Plate 36C) and the expected molecular ion at *m/z* 386 (M^+, 3%) in the EIMS.

Table 4.11: Various epoxidation procedures of 4',7-dimethoxyflav-3-ene.



Entry	Method[a]	Nu	Temp (°C)	Time	Solvent	Product	Yield (%)
1	A	H_2O	-10 to 0	30 min	Acetone	**480**	67
2	B	H_2O	-78 to RT	Overnight	Acetone	**492**	42
3	C	H_2O	-78 to RT	Overnight	Acetone	**480**	91
4	D	H_2O	-78 to RT	15 min	Acetone	**480**	90

[a] Reagents and conditions: Method A: Isolated DMDO, acetone, 30 min at 0 °C. Method B: Distilled DMDO, acetone, overnight at RT, 2) pyridine, DMAP, Ac_2O, 40 °C, 2 h. Method C: Distilled DMDO, acetone, overnight at RT. Method D: Distilled DMDO, acetone, 15 min at RT.

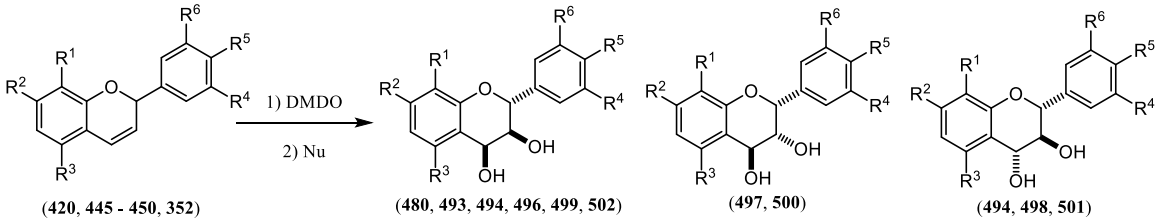
As the yield proved to be on the low side and it could be that some of the product was lost during the acetylation process, it was subsequently decided to repeat the reaction, but without the derivatization process, which led to the 2,3-*trans*-3,4-*cis*-4',7-dimethoxyflavan-3,4-diol (**480**) obtained in an excellent yield of 91% after removal of the solvent without any further purification (Table 4.11, entry 3). Although the directly distilled DMDO procedure gave promising yields, the reaction time was prolonged to ensure complete reaction with the nucleophile (H_2O), however, the reaction with the isolated DMDO resulted in an acceptable yield being obtained (Table 4.11, entry 1) at a higher temperature and after a shorter reaction time. Thus, the reaction was repeated with the reaction flask being removed from the acetone-bath (at -78 °C) directly after the DMDO was distilled over and left to stir for 15 min (where after TLC indicated completion of the reaction) and the solvent removed under reduced pressure, which gave compound **480** in 90% yield (Table 4.11, entry 4). As this procedure generated results similar to those obtained at lower temperatures and longer reaction times, it was decided to utilize these reaction conditions for the epoxidation of all the other methoxy substituted flav-3-enes (**445** – **450**, **352**).

In order to assess the effect of substitution pattern on the epoxidation reaction, the optimized reaction conditions were subsequently applied to the series of flav-3-enes prepared in section 4.4. As the 4',7-dimethoxyflav-3-ene (**420**) gave high yields, it was decided to start the investigation with the less oxygenated substrates, 7-methoxy- (**445**) and 4'-methoxyflav-3-ene (**446**), respectively. Thus, treatment of 7-methoxyflav-3-ene (**445**) and 4'-methoxyflav-3-ene (**446**) with DMDO under the aforementioned conditions, followed by reaction with water, afforded the expected 2,3-*trans*-3,4-*cis*-7-methoxyflavan-3,4-diol (**493**) and 2,3-*trans*-3,4-*cis*- and 2,3-*trans*-3,4-*trans*-4'-methoxyflavan-3,4-diols (**494** and **495**), respectively, albeit in drastically decreased yields of only 34 and 44% (Table 4.13, entry 1 and 2 vs. 3). The structures of the products **493**, **494** and **495** were confirmed by their ^{1}H NMR spectra (Plates 37A and 39A), which, apart from the expected aromatic proton resonances, indicated the presence of three heterocyclic protons, and by EIMS (Table 4.14, entries 1 and 2), while the relative configuration of all the products could be assigned by comparison of the coupling constants (*J*) of the heterocyclic C-ring protons with literature values (Table 4.12).

Table 4.12: Spin-spin coupling constants (*J*) for 2-, 3- and 4-protons for the four possible diastereoisomers of flavan-3,4-diols and derivatives reported in literature.[86,87,96,98–106]

Entry	Configuration	Flavan-3,4-diol		3,4-Diacetoxyflavan	
		$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)	$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)
1	2,3-*trans*-3,4-*cis*	9.0-10.2	3.5-4.1	9.5-10.5	3.0-4.0
2	2,3-*trans*-3,4-*trans*	9.9-10.2	7.2-8.5	7.4-11.1	5.2-8.0
3	2,3-*cis*-3,4-*trans*	0.9	2.5	0.9-3.0	2.5-2.8
4	2,3-*cis*-3,4-*cis*	1.0	4.8	1.0-1.2	3.9-4.2

Table 4.13: Flavan-3,4-diols obtained during the epoxidation reactions of the substituted flav-3-enes.

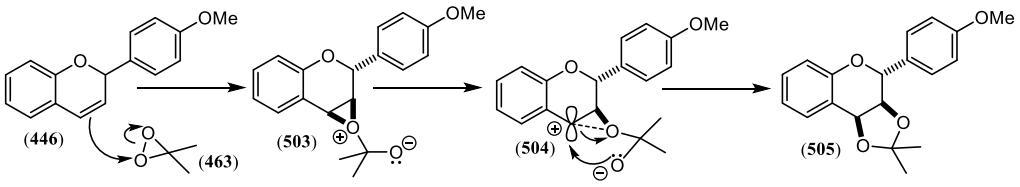


(**420**, **445 - 450**, **352**) (**480**, **493**, **494**, **496**, **499**, **502**) (**497**, **500**) (**494**, **498**, **501**)

Entry	Flavene	R^1	R^2	R^3	R^4	R^5	R^6	Product (ratio)	Yield (%)
1	**445**	H	OMe	H	H	H	H	**493**	34
2	**446**	H	H	H	H	OMe	H	**494**, **495** (3:1)[a]	44
3	**420**	H	OMe	H	H	OMe	H	**480**	90
4	**447**	H	OMe	H	OMe	OMe	H	**496**, **497**, **498** (6:1.4:1)[b]	88
5	**448**	H	OMe	H	OMe	OMe	OMe	**499**, **500**, **501** (4:1.4:1)[a]	69
6	**452**	OMe	OMe	H	H	OMe	H	**502**	61
7	**449**	H	OMe	OMe	H	OMe	H	n.p.[c]	n.p.[c]
8	**450**	H	OMe	OMe	OMe	OMe	H	n.p.[c,d]	n.p.[c,d]

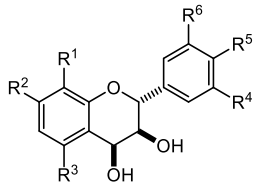
[a] de ratio determined by ^{1}H NMR of isolated diastereomeric mixture. [b] de ratio determined by ^{1}H NMR of RM. [c] n.p. = no product isolated under standard reaction conditions. [d] Obtained after quenching the reaction mixture at -40 °C with DMSO (vide infra).

The epoxidation of the 4'-methoxyflav-3-ene (**446**) also yielded 4% of an unexpected side-product [R_f 0.53 (H:EtOAc, 8:2, 1% TEA)]. The ^{1}H NMR spectrum of this compound (**505**) (Plate 38) displayed two methyl resonances at δ_H 1.56 and 1.49 in addition to the expected heterocyclic [δ_H 5.14 (1H, d, *J* = 5.53 Hz, H-4), 4.54 (1H, d, *J* = 9.84 Hz, H-2), 4.34 (1H, dd, *J* = 5.53, 9.84 Hz, H-3)] and aromatic [δ_H 7.48 (1H, dd, *J* = 1.44, 7.58 Hz, H-5), 7.42 (2H, d, *J* = 8.68 Hz, H-2'&6'), 7.28 (1H, ddd, *J* = 1.44, 7.24, 8.19 Hz, H-7), 7.05 (1H, td, *J* = 1.02, 7.58 Hz, H-6), 7.00 (1H, br d, *J* = 8.19 Hz, H-8) and 6.96 (2H, d, *J* = 8.68 Hz, H-3'&5')] signals. Since no OH resonances could be detected by deuterium exchange, it was decided that the additional product could be the isopropylidene derivative of the flavan-3,4-diol (**494**). The proposed structure of the side-product (**505**) was confirmed by the presence of a molecular ion at *m/z* 312 (M^+, 15%) in the mass spectrum and could be explained in terms of nucleophilic attack of the DMDO oxygen onto the incipient C-4 carbocation of the flavan unit as indicated in Scheme 4.24.

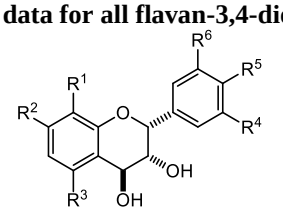


Scheme 4.24: Proposed mechanism for the formation of the side-product during the epoxidation reaction of the 4'-methoxyflav-3-ene.

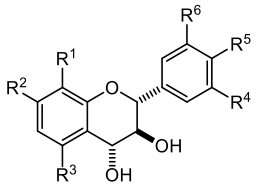
Table 4.14: Diagnostic ^{1}H NMR and MS data for all flavan-3,4-diols isolated.



(**480**, **493**, **494**, **496**, **499**, **502**, **506**)



(**497**, **500**)



(**495**, **498**, **501**)

Entry	3,4-Diol (Plate)	MS (*m/z*)[a]	H	^{1}H NMR Resonances (ppm)		
				trans,cis	***cis,trans***	***trans,trans***
				δ [m, *J*(Hz)]	**δ [m, *J*(Hz)]**	**δ [m, *J*(Hz)]**
1	**493** (37A)	272 (M^+, 20%)	H-2 H-3 H-4	5.05 (d, 9.52) 4.04 (dd, 3.57, 9.52) 4.74 (d, 3.57)	-	-
2	**494/495** (39A)	272 (M^+, 16%)	H-2 H-3 H-4	5.04 (d, 9.44) 4.09 (ddd, 3.78, 5.43, 9.44) 4.83 (dd, 3.38, 3.78)	-	4.83 (d, 9.91) 3.93 (ddd, 2.45, 8.44, 9.91) 4.93 (dd, 5.14, 8.44)
3	**480** (32A)	302 (M^+, 5%)	H-2 H-3 H-4	4.98 (d, 9.71), 4.02 (dd, 3.55, 9.71) 4.74 (d, 3.55)	-	-
4[b]	**496** (40A)	332 (M^+, 7%)	H-2 H-3 H-4	4.99 (d, 9.80), 4.04 (ddd, 2.94, 5.99, 9.80) 4.79 (dd, 2.94, 3.02)	-	-
5	**499/500/ 501** (41A)	362 (M^+, 18%)	H-2 H-3 H-4	4.96 (d, 9.85) 4.04 (dd, 3.50, 9.85) 4.78 (d, 3.50)	5.21 (br s) 4.03 (br d, 2.88) 4.67 (d, 2.88)	4.76 (d, 9.93) 3.91 (dd, 8.18, 9.93) 4.85 (br d, 8.18)
6	**502** (42A)	332 (M^+, 4%)	H-2 H-3 H-4	5.03 (d, 9.37) 3.97 (dd, 3.61, 9.37) 4.71 (d, 3.61)	-	-
7	**506** (44A)	362 (M^+, 8%)	H-2 H-3 H-4	4.91 (d, 10.26) 3.84 (dd, 3.69, 10.26) 4.86 (d, 3.69)	-	-

[a] Molecular ions were determined with EIMS. [b] Only one diastereoisomer could be fully purified and characterised.

Extending the investigation to the epoxidation (under conditions of distilled DMDO in acetone) of the 7-methoxyflav-3-ene with catechol (**447**) and pyrogallol (**448**) B-ring substitution, resulted in mixtures of 2,3-*trans*-3,4-*cis* (**496** and **499**, respectively), 2,3-*cis*-3,4-*trans*- (**497** and **500**, respectively) and 2,3-*trans*-3,4-*trans*-3,4-diols (**498** and **501**, respectively) being obtained in 88 and 69% yields, respectively, and ratios of 6:1.4:1 and 4:1.4:1 (Table 4.13, entries 4 and 5). The structures of these products (**496 - 451**) were elucidated on the basis of their ^{1}H NMR spectra (Plates 40A and 41A), which showed heterocyclic resonances and molecular ions as indicated in Table 4.14 and confirmed by ^{13}C NMR (Plates 40C and 41C). Repeating the epoxidation reaction (distilled DMDO in acetone) on the flavan-3-ene (**452**) with a higher oxygenated A-ring resulted in only the 2,3-*trans*-3,4-*cis*-4',7,8-trimethoxyflavan-3,4-diol (**502**) being formed in a 61% yield (Table 4.13, entry 6) as well as the corresponding isopropylidene derivative (**507**) in a 9% yield.

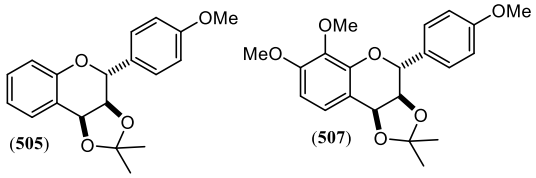
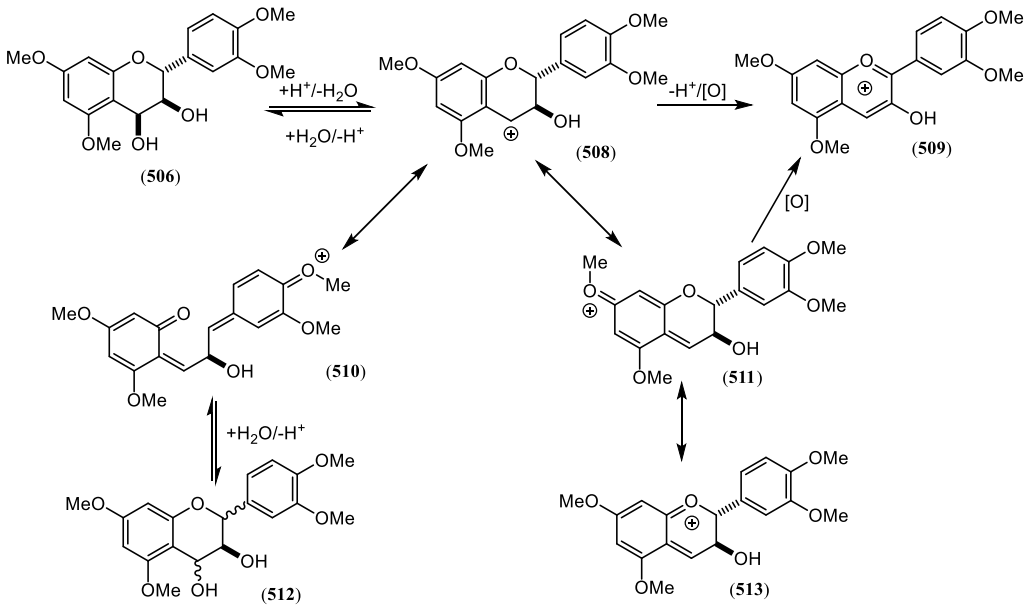


Figure 4.7: Isolated isopropylidene derivatives.

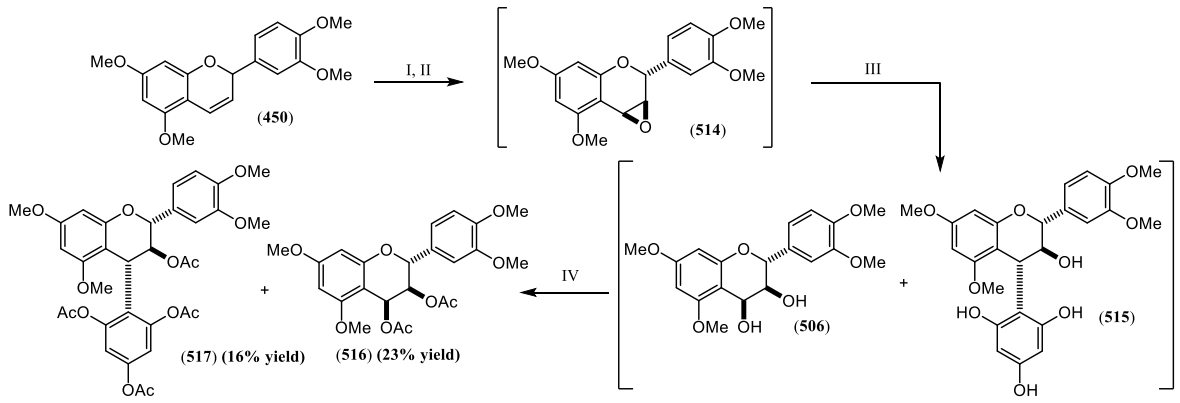
The structure of the isopropylidene derivative (**507**) was confirmed by ^{1}H NMR (Plate 43A), which indicated the presence of three heterocyclic protons [Table 4.14, entry 6 and at δ_H 5.11 (d, J = 5.49 Hz, H-4), 4.57 (d, J = 9.70 Hz, H-2) and 4.30 (1dd, J = 5.49, 9.70 Hz, H-3), respectively], while the spectrum of (**507**) also contained the signals from two methyl groups at δ_H 1.55 (3H, s, CH_3) and 1.48 (3H, s, CH_3). Final confirmation of the structures came from MS where the molecular ions at *m/z* 332 (M^+, 4%) and 372 (M^+, 22%), respectively, were clearly visible, as well as the ^{13}C NMR spectrum (Plate 43C) of (**507**) indicating aliphatic carbons signals at δ_C 109.2 [$\underline{C}(CH_3)_2$], 28.6 (CH_3) and 26.1 (CH_3).

Increasing the oxygenation level of the flavene A-ring to a phloroglucinol substitution pattern (**449** and **450**), however, resulted in a bright red reaction mixture once the mixture reached room temperature with no target product being observable by TLC, NMR or from the reaction mixture upon work-up and purification. Since it is well documented that leucoanthocyanidins (flavan-3,4-diols) are readily oxidized to form coloured anthocyanidins, which may consist of an array of resonance structures arising from the corresponding quinone methide structures (Scheme 4.25)[107–109] and dioxiranes are known to readily oxidize secondary,[110] benzyl[111] or epoxy alcohols[112] and *vic*-diols,[113] it was hypothesized that the failure of the epoxidation of the phloroglucinol substrates might be attributed to the fact that these highly oxygenated substrates are prone to further oxidation and stable C-4 carbocations, which could lead to inseparable mixtures of charged products like anthocyanidins.



Scheme 4.25: Quinone methide resonance structures of anthocyanidins or carbocations.

Since the formation of highly reactive quinone methide intermediates and/or over-oxidation could be the reason for the substrates with a phloroglucinol A-ring to provide no identifiable product(s), it was decided to see if the incipient or formal carbocation electrophile could not be trapped by a stable carbon-carbon bond to an aromatic nucleophile, which would then lead to the formation of a 4-aryl substituted product. As highly reactive free phenolic nucleophiles, such as phloroglucinol, are prone to oxidation it was further decided to quench the excess oxidant with DMSO at a sub-zero temperature before addition of the nucleophile. The epoxidation of 3',4',5,7-tetramethoxyflav-3-ene (**450**) was therefore repeated in the standard way, but after 1 hour at -78 and -40 °C, respectively, DMSO (5 eq) was added and the reaction mixture stirred for another hour, before the phloroglucinol nucleophile (2 eq) was added, where after the mixture was allowed to slowly reach RT and stirred overnight. Once concentrated, it was noticed that the crude product mixture contained a small amount of a white ppt, which was subsequently filtered off and identified by ^{1}H NMR (Plate 44A) and EIMS (Table 4.14, entry 7) as the 2,3-*trans*-3,4-*cis*-3',4',5,7-tetramethoxyflavan-3,4-diol (**506**) (9% yield). In order to simplify the purification process of the filtrate, the solvent was removed by distillation under reduced pressure and the mixture acetylated (Ac_2O, pyridine, DMAP, 40 °C, 3 h) to obtain two products R_f 0.42 and 0.28 (H:EtOAc, 1:1, 1% TEA) in 23 and 16% yield, respectively, after PLC (Scheme 4.26).

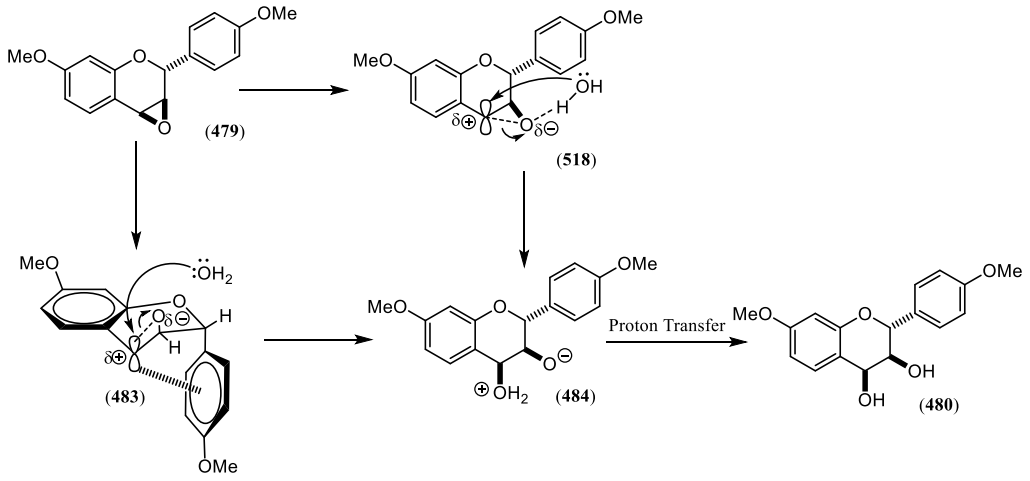


Scheme 4.26: Epoxidation of 3',4',5,7-tetramethoxyflav-3-ene. Reagents and conditions: I) DMDO, -78 to -40 °C, 1 h; II) DMSO, -40 °C, 1 h; III) H_2O & phloroglucinol (**35**, 2eq); IV) Pyridine, Ac_2O, DMAP, 40 °C, 3 h

The ^{1}H NMR spectrum (Plate 45A) of the first product (R_f 0.42) showed resonances characteristic of a flavan-3,4-diol albeit at lower field [δ_H 6.42 (1H, d, *J* = 3.67 Hz, H-4), 5.40 (1H, dd, *J* = 3.67, 10.92 Hz, H-3), 5.10 (1H, d, *J* = 10.92 Hz, H-2)], which was accompanied by two acetoxy signals at δ_H 2.12 [3H, s,4-OC(O)CH_3], 1.82 [3H, s, 3-OC(O)CH_3] whereas a molecular ion at (*m/z*) 446 (M^+, 3%) confirmed this product to be the 2,3-*trans*-3,4-*cis*-3,4-diacetoxy-3',4',5,7-tetramethoxyflavan (**516**). In addition to the expected aromatic [δ_H 7.03 (1H, dd, *J* = 1.91, 8.26 Hz, H-6'), 6.98 (1H, d, *J* = 1.91 Hz, H-2'), 6.86 (1H, d, *J* = 8.26 Hz, H-5'), 6.15 (1H, d, *J* = 2.36 Hz, H-6/8), 6.01 (1H, d, *J* = 2.36 Hz, H-6/8)] and heterocyclic resonances [δ_H 5.78 (1H, dd, *J* = 9.12, 10.03 Hz, H-3), 4.79 (1H, d, *J* = 10.03 Hz, H-2), 4.60 (1H, d, *J* = 9.12 Hz, H-4)], the ^{1}H NMR spectrum (Plate 46A) of the second product (R_f 0.28) indicated the presence of four acetoxy groups {δ_H 2.35, 2.23, 1.93, 1.67 [3H, s, 3/2"/4"/6"-OC(O)CH_3]} as well as two aromatic doublets δ_H 6.88 (1H, d, *J* = 2.29 Hz, H-3"/5") and 6.77 (1H, d, *J* = 2.29 Hz, H-3"/5"), so this product could be identified as the 2,3-*trans*-3,4-*trans*-3-acetoxy-4-(2",4",6"-triacetoxyphenyl) -3',4',5,7-tetramethoxyflavan (**517**). The structure of the phloroglucinol coupled product (**517**) was confirmed by its ^{13}C NMR spectrum (Plate 46C) which indicated four carbonyl groups (δ_C 169.0, 168.5, 168.4, 167.8) as well as extra aromatic [δ_C 148.8 (C-2"/6"), 148.6 (C-2"/6"), 129.1 (C-4"), 124.0 (C-1"), 114.6 (C-3"/5"), 113.4 (C-3"/5")] and methyl signals {δ_C 21.3, 21.2, 20.7, 20.4 [3/2"/4"/6"-OC(O)CH_3]}, while a molecular ion at (*m/z*) 638 (M^+, 3%) was also found in the mass spectrum.

While it has been established that the flavan-3,4-diols can be formed from the corresponding flav-3-enes in moderate to excellent yields (ca. 35 - 90%) by DMDO oxidation, the relative configuration of the different (preferred) product(s) vary quite substantial for the different flavenes and warrants some comments. The preferred formation of the 2,3-*trans*-3,4-*cis* relative configuration of the flavan-3,4-diols originating from all the flav-3-enes (**420**, **445 – 448**, **450** and **452**) may be an indication that the B-ring shields that specific face of the incipient carbocation from attack by the nucleophile, resulting in the 2,4-*trans*-product being formed preferentially (Scheme 4.23 or Scheme 4.27). It is, however, also possible that hydrogen bonding between the partially negatively charged epoxide oxygen and the

attacking water molecule directs the water nucleophile to the same face of the incipient/formal carbocation as the epoxide ring (Scheme 4.27). Since all the flavenes (**420**, **445**, **447**, **448** and **450**) with an electron rich resorcinol or phloroglucinol type A-ring gave the 2,3-*trans*-3,4-*cis*-flavan-3,4-diols (**480**, **493**, **502** and **506**) as only or major product (Table 4.13, entries 1-6), it may also be that the highly strained epoxide ring opens with the formation of a C-4 carbocation which is stabilized through some degree of quinone methide formation. Hydrogen bonding between the attacking water molecule and the alkoxide anion and/or B-ring participation then leads to the preferred formation of the 3,4-*cis*-products. Since the 3,4-*cis* isomers are seen as the thermodynamic, and thus preferred products, through delocalization of the A-ring electron density into the orthogonal C-4 σ* orbital in the 3,4-diol,[114–117] the preferred formation of the 3,4-*cis* products may be considered as due to these compounds being the more stable products. However, since the reactions were performed under conditions of kinetic control (-78 °C to RT) and an equilibrium between the 3,4-diol and epoxide is highly unlikely, this argument seems to be flawed and not a plausible explanation for the observed product distribution.



Scheme 4.27: Possible shielding or nucleophile directing interactions leading towards the formation of 3,4-*cis*-relative configuration.

As it was found by Mthembu[118] that a more electron rich catechol or pyrogallol B-ring enhances the stabilization of the C-4 carbocation during attack of nucleophiles and it was observed during the current investigation that the B-ring oxygenated substrates (**446** - **448**) gave the 3,4-*trans*-products together with the 3,4-*cis*-analogues, it could be envisaged that the C-4 carbocation is also stabilized through a quinone methide type structure involving the B-ring oxygens (**510**) as indicated in Scheme 4.25. Since a B-ring quinone methide type structure (**510**) would render shielding of C-4 by the B-ring impossible, the possibility of water attacking onto the α- and β-faces of the double bond at C-4 would become equally possible, thus leading to a 50:50 mixture of the *cis*- and *trans*-diols. The possibility of B-ring quinone methide involvement in the resulting relative configuration of the 3,4-

diol is further corroborated by the isolation of C-2 epimerised products (2,3-*cis*-isomers) from the reactions of flav-3-enes with a catechol (**447**) or pyrogallol (**448**) B-ring substitution pattern.

Finally, the 3,4-*trans*-relative configuration of the 4-arylflavan-3-ol derivative (**517**) is probably explicable in terms of an S_N2 type substitution of the OH of the 3,4-*cis*-diol. Although phloroglucinol is known to be an excellent nucleophile, substitution of the 4-hydroxy group of flavan-3,4-diols usually happens at room or elevated temperatures with the formation of both the 3,4-*cis*- and 3,4-*trans*-products, with the *trans*-isomer being the main product,[119] so the fact that only the *trans*-isomer was obtained indicates that the temperature was not high enough to generate the free carbocation or quinone methide, therefore an S_N2 process was followed during the substitution reaction.

4.6 Conclusion and Future Work

The aim of this project, i.e. the development of novel methodology for the epoxidation of flav-3-enes, required the availability of these flav-3-enes and it was envisaged that those compounds could be made from the corresponding 2'-hydroxychalcones. Thus the different methodologies (KOH or aq. NaOH in EtOH or dioxane, NaH/DMF) for the preparation of chalcones from acetophenones and benzaldehydes were subsequently evaluated and it was found that the anhydrous NaH system not only required shorter reaction times (ca. 0.5–2 h), but also gave the chalcone products in near quantitative yields for a number of oxygenated substitution patterns. Cyclization towards the corresponding flavanone to be reduced and dehydrated to the flavenes, however, did not produce substantial yields despite the evaluation of several Lewis acids and other systems [NaOAc/EtOH; $Al(OTf)_3$, $Bi(OTf)_3$, $La(OTf)_3$ and $Cu(OTf)_2$ all in CH_3CN] under conventional heating as well as MW conditions, so it was decided to alter the methodology to the reductive cyclization of 2'-hydroxychalcones.

Although a number of reagent systems and conditions (e.g. $NaBH_4$ in THF/EtOH or IPA) have been reported for the direct transformation of 2'-hydroxychalcones into flav-3-enes, only dissolving the chalcone in hot IPA before the addition of a hot saturated solution of $NaBH_4$ in IPA generated repeatable and moderate to good yields (ca. 42-77%) for a series of flav-3-enes, after the borated complex was fully decomposed with 10% HOAc in $CHCl_3$ under inert refluxing conditions. Utilizing these optimized conditions, a series of methoxy substituted flav-3-enes, which were highly reactive and had to be purified either by DCFC or crystallization and stored under argon at sub-zero temperatures, could be prepared and subjected to the epoxidation process.

While first attempts at the epoxidation centred around distilling the acetone-dimethyldioxirane (DMDO) mixture from the aqueous Oxone®-carbonate solution and adding the acetone solution of the DMDO to the flavene, it was found that the direct distillation of DMDO into an acetone solution of

the flavene at -78 °C followed by removal of the flask form the sub-zero temperatures and allowing the reaction to be completed at room temperature (15 min), gave moderate to excellent yields of the oxygenated flavan-3,4-diols (ca. 34-90%), which were formed after hydrolysis of the epoxide intermediates. Even the flavene with an electron-rich phloroglucinol A-ring could be epoxidized and transformed into the 3,4-diol in ca. 32% yield in this way, while it was also demonstrated that the epoxide/3,4-diol could be attacked successfully by a phenolic nucleophile, leading to the direct formation of the 4-aryl substituted flavan-3-ol in 16% yield. Granting the yield of this 4-aryl substituted product was still low, optimization of the reaction parameters for the preparation of 4-aryl substituted flavan-3-ols may lead to a one-step process for the formation for 4-aryl substituted flavan-3-ols as well as oligomeric proanthocyanidins from flav-3-enes and a two-step process for the preparation of these compounds from the readily available chalcones.

In all cases, the epoxidation reaction resulted in excellent diastereoselectivities being achieved and 3,4-*cis*-products were almost exclusively formed. Since the ultimate aim of the methodology would be the enantioselective synthesis of flavan-3,4-diols and the diastereoselectivity of the reactions were excellent, it is envisaged that controlling the absolute configuration at C-2 of the flavenes would lead to the overall process becoming enantioselective, so future work will centre around finding a chiral agent or base capable of selectively directing the cyclization to one face of the allyl alcohol during formation of the flav-3-ene. Other possible methods towards enantioselective preparation of flavan-3,4-diols may also be based on the utilization of either a chiral catalyst, such as Jacobsen's Mn(III) salen, or the use of a chiral ketone during the dioxirane synthesis and might lead to a resolution process for the procurement of flavonoid analogues in high optical purity.

4.7 References

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CHAPTER 5

EXPERIMENTAL

5.1 Chromatography

5.1.1 Thin-Layer Chromatography (TLC)

Qualitative TLC was conducted on aluminium backed "Macherey-Nagel Alugram® Xtra Sil G/UV_{254}" plates (0.2 mm layer) divided into 2.5 x 5.0 cm strips. Eluent ratios are given as v/v and R_f values noted where observed in these qualitative TLC assessments.

5.1.2 Preparative Thin-Layer Chromatography (PLC)

PLC was carried out on either glass plates (20 x 20 cm) coated with Merck Kieselgel 60 PF_{254} (ca. 1.0 mm) which was air-dried overnight at room temperature (RT) or on aluminium backed "Macherey-Nagel Alugram® Xtra Sil G/UV254" plates (20 x 20 cm, 0.2 mm layer). The crude product (5 – 20 mg) was applied to each plate and developed in the appropriate eluent (ratios given as v/v). Bands were distinguished under UV-light (254 nm) and removed by means of solvation with acetone. All solvent was removed under reduced pressure at ca. 25-30 °C.

5.1.3 Flash Column Chromatography (FCC)

FCC was conducted on 100 g of "Macherey-Nagel Silica 60 (0.063 – 0.2 mm)" for every 1 g of crude product in a glass column. Air was removed of by elution with the appropriate solvent under N_2-pressure (ca. 50 kPa). The crude product was dissolved in a minimum amount of eluent (ratios given as v/v) and loaded onto the column. The purified product was recovered by elution under N_2-pressure with the appropriate eluent and collected in fractions. Corresponding fractions were combined and evaporated under reduced pressure at ca. 30 °C.

5.1.4 Dry-column Flash Chromatography (DCFC)

A glass Buchner funnel fitted with a sintered glass disc was charged with 80 g of "Macherey-Nagel Silica 60 (0.063 – 0.2 mm)" for every 1 g of crude product. The silica was levelled and compacted by hand after which the silica was wetted with appropriate eluent. After each solvent addition the solvent fraction was removed with suction, taking care not to allow the silica to crack. The crude product was dissolved in a minimum amount of eluent (ratios given as v/v) and loaded. Additions of the

appropriate solvent(s) in fractions lead to the recovery of the purified product. Corresponding fractions were combined and evaporated under reduced pressure at ca. 25 °C.

5.1.5 Gas Chromatography with Flame Ionization Detection (GC)

GC analysis was conducted on a Shimadzu gas chromatograph (GC-2010) fitted with an auto-sampler unit (AOC-20i+s) and a flame ionization detector (FID). Separation was attained using hydrogen ($H_{2(g)}$) as carrier gas at a constant velocity of 40 cm/sec on a J&W HP-5 capillary column (0.25 μm film thickness, 0.32 mm ID, 30 m). Injection port and detector temperatures were set as 230 and 250 °C, respectively. Temperature-programs are reported were relevant.

Quantification was carried out by single point internal standard protocol with a known amount of dodecane included in all relevant experiments as internal standard. Response factors (RF) were calculated using the equation below.

$$RF = \frac{Area\ IS\ \times Mole\ DA}{Mole\ IS\ \times Area\ DA}$$

5.1.6 Gas Chromatography-Mass Spectrometry (GC-MS)

GC-MS analysis was conducted on a Shimadzu gas chromatograph (GC-2010) fitted with an electron-impact (EI) mass spectrometer (GC-MS-QP-2010) and an auto-sampler injection unit (AOC-20i). Separation was achieved on a J&W DB-5ms capillary column (0.25 μm film thickness, 0.32 mm ID, 30 m) utilizing helium (He) as carrier gas at a constant velocity of 27.5 cm/sec.

5.2 Spectroscopic and Spectrometric Methods

5.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

All NMR spectra were recorded on a 400 MHz AVANCE III NMR spectrometer using a 5 mm BBI H-BB-D probe or 600 MHz AVANCE II NMR spectrometer using a 5 mm DUAL 13C-1H/D probe both with z-gradients and operating at 25 °C (293 K) with either deuterochloroform ($CDCl_3$), deutarated acetone (C_3D_6O) or deuterobenzene (C_6D_6) as solvent. Chemical shift values are given in parts per million (ppm) on the δ-scale, whereas coupling constants are given in Hz. All residual solvent peaks and common impurities are listed below (Tables 5.1 & 5.2). Additional experiments utilized for structural elucidation and resonance assignment were distortionless enhancement by polarisation transfer (DEPT) at a 135° angle, heteronuclear single-quantum correlation (HSQC) and heteronuclear multiple-bond correlation (HMBC). The ^{1}H NMR of either the reaction mixture or the isolated diastereomeric mixture was used to determine the diastereomeric ration (de) and the

resonances of the free flavan-3,4-diol hydroxy groups confirmed by the addition of deuterium oxide (D_2O) in an appropriate solvent.

Table 5.1: NMR Solvent Residual Peaks.[1,2]

Solvent	Residual Resonance (^1H)	Residual Resonance (^{13}C)
$CDCl_3$	7.26 ppm	77.16 ppm
C_3D_6O	2.05 ppm	29.84 & 206.26 ppm
C_6D_6	7.16 ppm	128.06 ppm

Table 5.2: Standard Chemical Shift of Common Impurities.[1,2]

Impurity	m[a]	$CDCl_3$		C_3D_6O		C_6D_6	
		^1H (ppm)	^{13}C (ppm)	^1H (ppm)	^{13}C (ppm)	^1H (ppm)	^{13}C (ppm)
H_2O	s	1.56	-	2.84	-	0.04	-
Grease	m	0.86		0.87		0.92	
	br s	1.26	29.76	1.29	30.73	1.36	30.21
Silicone Grease	s	0.07	1.04	0.13	1.40	0.29	1.38
[b, c] Plasticiser			14.2				
	m	0.95-0.80	22.8	0.96-0.83		1.01-0.79	
	s	1.26	29.5	1.29	-	1.36	-
	s	1.44	29.8	-		-	
			32.0				
Triethylamine	t	1.03	11.61	0.96	12.49	0.93	12.35
	q	2.53	46.25	2.45	47.07	2.40	46.77
[d] Triethylammonium salt	t	1.31-1.41	8.64	-	-	-	-
	q	3.01-3.12	45.88				

[a] m = multiplicity of resonance. [b] See Plate 47. [c] Only commonly seen resonance indicated. [d] See Plate 48

5.2.2 Mass Spectrometry (MS)

5.2.2.1 Electron-Impact Ionization (EIMS)

EIMS analysis was conducted on a Shimadzu gas chromatograph (GC-2010) fitted with a mass spectrometer (GC-MS-QP-2010) by means of the direct sample inlet unit (DI-2010).

5.2.2.2 High-Resolution Mass Spectrometry (HRMS)

HRMS analyses were conducted at the University of KwaZulu-Natal (UKZN), Pietermaritzburg, South Africa.

5.3 Melting Points (m.p.)

Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP3) apparatus and are uncorrected.

5.4 Microwave (MW) Irradiation

Reactions were carried out in a CEM Discover® SP microwave reactor utilizing the dynamic irradiation program (fixed temperature, variable power) with continuous cooling and stirring.

5.5 Anhydrous Solvents

Anhydrous DMF was bought from Sigma-Aldrich. Dynamic drying of heptane was done through a small column of activated basic alumina (Sigma-Aldrich Brockman I basic alumina, 20% v/v). Pyridine was dried passively over KOH.

5.6 Oxygen Free Argon

5.6.1 Preparation of Catalyst Bed

Argon used during specified reductive cyclization reactions towards the flav-3-ene were passed through a catalyst bed obtained from Sigma-Aldrich Chromium(VI)oxide 99.9% and Merck Silica Gel 40 (0.2 - 0.5 mm) and prepared as follows; Aqueous CrO_3 (50 g in 1.5 L H_2O) was added to silica gel (1 kg). The contents were thoroughly mixed, before the water was decanted off and the silica dried overnight at 120 °C.

5.6.2 Activation and Regeneration of Catalyst Bed

Activation and regeneration of the catalyst was achieved by using a "CTF 12/65/550 Wire Wound Tube Furnace" to heat the column to 500 °C while vented with O_2. After a while the O_2 was replaced

with Ultra High Purity (UHP) N_2 for 10 min, before switching to UHP CO. The column was vented with UHP CO until a colour change from orange to blue was observed. Finally the column was cooled to room temperature while being vented with UHP N_2.

5.7 Chalcone Synthesis

5.7.1 General Procedures for Aldol Condensation

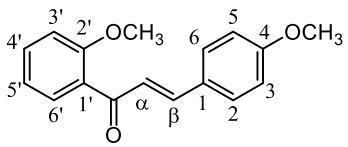
Method A:[3] Acetophenone (1 eq) and benzaldehyde (1.1 eq) were dissolved in EtOH or 1,4-dioxane (7 mL/mmol$_{acetophenone}$) and cooled (ice-bath, only reactions in EtOH) for 15 min before freshly ground KOH (4.8 eq) was added, turning the reaction mixture (RM) light yellow. The RM was stirred for 24 h to 7 days at RT. Once the reaction was completed or equilibrium reached (TLC), the RM was acidified with sat. NH_4Cl solution (lithmus/pHydrion® INSTA-CHEK 0-13) and any organic material extracted into EtOAc. The organic layer was neutralized with sat. $NaHCO_3$, washed with H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure the crude product was recrystallized from an EtOH and H_2O mixture where possible.

Method B:[4] Dry heptane (0.13 mL/mmol NaH) was added to NaH (60% dispersion in mineral oil, 1.5 eq) under argon ($Ar_{(g)}$) and the mixture stirred for 5-10 min at RT. Anhydrous DMF (3.47 mL/mmol$_{NaH}$) was then added and the white suspension cooled (ice-bath) for 10 - 15 min. A solution of acetophenone (1 eq) in anhydrous DMF (1.2 mL/mmol$_{acetophenone}$) was slowly added, via a syringe, to the cool solution, turning the RM light yellow. After the mixture stirred for 30 min in an ice-bath, a solution of benzaldehyde (1 eq) in anhydrous DMF (1.2 mL/mmol$_{benzaldehyde}$) was added slowly via syringe. The resulting orange mixture was left to stir, slowly reaching RT, for 30 min to 2 h. The reaction was followed in 30 min intervals (TLC) and once completed, the RM was poured over crushed ice and acidified with 3M HCl, until pH 7 (pHydrion® INSTA-CHEK 0-13), while vigorously stirred. The yellow suspension was stirred for an additional 30 min, where after the yellow solid was collected by suction filtration, thoroughly rinsed with water and suction dried to afford the wanted compound, unless specified otherwise.

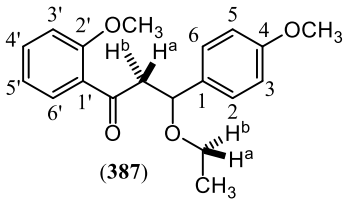
5.7.2 Preparation of 2',4-Dimethoxychalcone (**383**)

Method A: Performed according to general aldol condensation Method A; KOH (0.270 g, 4.8 mmol) was added to a cooled (ice-bath) solution of 2'-methoxyacetophenone (0.153 g, 1 mmol) and *p*-anisaldehyde (0.146 g, 1.1 mmol) in EtOH (7 mL). After KOH addition the RM stirred at RT for 24 h. The crude product was then subjected to purification by PLC (H:EtOAc, 9:1), producing two products with R_f of 0.17 and 0.28 in yields of 77% (0.211 g) and 2% (0.005 g), respectively.

- 2',4-Dimethoxychalcone (**383**)[5] Yellow paste; R_f 0.17 (H:EtOAc, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 1A) δ ppm 7.59 (1H, dd, *J* = 1.78, 7.49 Hz, H-6'), 7.57 (1H, d, *J* = 15.81 Hz, H-β), 7.53 (2H, d, *J* = 8.75 Hz, H-2&6), 7.45 (1H, ddd, *J* = 1.78, 7.49, 8.38 Hz, H-4'), 7.24 (1H, d, *J* = 15.81 Hz, H-α), 7.03 (1H, td, *J* = 0.73, 7.49 Hz, H-5'), 6.99 (1H, br d, *J* = 8.38 Hz, H-3'), 6.91 (2H, d, *J* = 8.75 Hz, H-3&5), 3.88 (3H, s, 2'-OC<u>H</u>$_3$), 3.83 (3H, s, 4-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 1C) δ ppm 193.3 (<u>C</u>O), 161.6 (C-4), 158.0 (C-2'), 143.5 (C-β), 132.6 (C-4'), 130.3 (C-6'), 130.2 (C-2&6), 129.7 (C-1), 127.9 (C-1'), 125.1 (C-α), 120.8 (C-5'), 114.5 (C-3&5), 111.7 (C-3'), 55.9 (2'-O<u>C</u>H$_3$), 55.5 (4-O<u>C</u>H$_3$); MS (*m/z*): 268 (M^+, 51%).


(**383**)

- *<u>β-Ethoxy-2',4-dimethoxydihydrochalcone</u>* (**387**) Colourless oil; R_f 0.28 (H:EtOAc, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 2A) δ ppm 7.61 (1H, dd, *J* = 1.67, 7.57 Hz, H-6'), 7.45-7.41 (1H, m, H-4'), 7.28 (2H, d, *J* = 8.61 Hz, H-2&6), 6.98 (1H, br t, *J* = 7.57 Hz, H-5'), 6.93 (1H, br d, *J* = 8.34 Hz, H-3'), 6.87 (2H, d, *J* = 8.61 Hz, H-3&5), 4.85 (1H, dd, *J* = 5.01, 8.33 Hz, H-β), 3.86 (3H, s, 2'-OC<u>H</u>$_3$), 3.80 (3H, s, 4-OC<u>H</u>$_3$), 3.48 (1H, dd, *J* = 8.33, 16.53 Hz, H-α^b), 3.36-3.31 (1H, m, C<u>H</u>$_2^{a/b}$), 3.31-3.25 (1H, m, C<u>H</u>$_2^{a/b}$), 3.24 (1H, dd, *J* = 5.01, 16.53 Hz, H-α^a), 1.09 (3H, t, *J* = 7.02 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 2C) δ ppm 200.4 (<u>C</u>O), 159.1 (C-4), 158.5 (C-2'), 134.6 (C-1), 133.4 (C-4'), 130.5 (C-6'), 128.9 (C-1'), 128.0 (C-2&5), 120.8 (C-5'), 113.9 (C-3&5), 111.5 (C-3'), 77.7 (C-β), 64.2 ($\underline{C}H_2CH_3$), 55.6 (2'-O<u>C</u>H$_3$), 55.4 (4-O<u>C</u>H$_3$), 52.6 (C-α), 15.4 ($CH_2\underline{C}H_3$); GC-MS (*m/z*): 314 (M^+, 1%), 284 (M^+, 30%), 165 (M^+, 64%), 135 (M^+, 100%), 77 (M^+, 24%); HRMS (*m/z*): $[M + Na]^+$ calculated for $C_{19}H_{22}O_4Na$: 337.1416; found, 337.1416.


(**387**)

<u>Method B:</u> Performed according to general aldol condensation Method A; KOH (0.275 g, 4.9 mmol) was added to a solution of 2'-methoxyacetophenone (0.153 g, 1 mmol) and *p*-anisaldehyde (0.148 g, 1.1 mmol) in 1,4-dioxane (7 mL) at RT. After KOH addition, the RM was stirred at RT for 24 h. The crude product was subjected to purification by means of PLC (H:EtOAc, 9:1) producing the title compound (**383**) in only 7% (0.019 g) yield.

<u>Method C:</u>[6] 50% aq. NaOH solution (5 mL) was added to a hot (40 °C) mixture of 2'-methoxyacetophenone (0.153 g, 1 mmol, 1 eq) and *p*-anisaldehyde (0.168 g, 1.2 mmol, 1.2 eq) in EtOH (10 mL). After stirring for 20 hours, at temperature, the resulting yellow solution was acidified with sat. NH_4Cl solution (lithmus/pHydrion® INSTA-CHEK 0-13) and the organic material extracted into EtOAc (3 x 15 mL). The organic layer was neutralized with sat. $NaHCO_3$, washed with H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure the crude product was subjected to

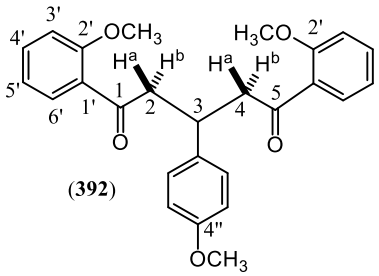
purification by means of PLC (H:EtOAc, 8:2) producing a compound with an R_f 0.26 in a yield of 78% (0.211 g) which was further identified as the title compound (**383**).

- 2',4-Dimethoxychalcone (**383**)[5] Yellow paste; R_f 0.26 (H:EtOAc, 8:2); see the above section 5.7.2, Method A for characterization.

Method D:[6] Performed according to the procedure above (Method C) in dioxane (10 mL). A yield of 9% (0.024 g) was obtained for the title compound (**383**) after purification by means of PLC (H:EtOAc, 8:2) .

Method E: Performed according to general aldol condensation Method B; Heptane (0.2 mL) was added to NaH (0.063 g, 1.6 mmol) under inert atmosphere (Ar). Anhydrous DMF (5.2 mL) was then added and as soon as the suspension in DMF was cooled, 2'-methoxyacetophenone (0.153 g, 1 mmol) in DMF (1.2 mL) was added. After 30 min a solution of *p*-anisaldehyde (0.136 g, 1 mmol) in DMF (1.2 mL) was added slowly. The reaction was stopped after 1 hour and the brown RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) where after any organic material was extracted into EtOAc. The organic layer was neutralized with sat. $NaHCO_3$ and washed sufficiently with H_2O. After the solvent was removed under reduced pressure the crude product was subjected to purification by PLC (H:EtOAc, 8:2). The title compound (**383**) was obtained in 52% (0.134 g) yield with an R_f 0.26 and was accompanied by a compound with a R_f 0.13 in a 8% (0.018 g) yield.

- *1,5-Bis(2'-methoxyphenyl)-3-(4''-methoxyphenyl)-pentane-1,5-dione* (**392**) Yellow solid; R_f 0.13 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, C_6D_6, Plate 3A) δ ppm 7.73 (2H, br d, *J* = 7.73 Hz, H-6'), 7.18 (2H, d, *J* = 8.52 Hz, H-2''&6''), 7.02 (2H, br dd, *J* = 7.62, 8.32 Hz, H-4'), 6.72 (2H, d, *J* = 8.52 Hz, H-3''&5''), 6.69 (2H, br dd, *J* = 7.62, 7.73 Hz, H-5'), 6.38 (2H, br d, *J* = 8.32 Hz, H-3'), 4.35-4.29 (1H, m, H-3), 3.55 (2H, dd, *J* = 7.21, 16.37 Hz, H-2$^{a/b}$&4$^{a/b}$), 3.45 (2H, dd, *J* = 7.21, 16.37 Hz, H-2$^{a/b}$&4$^{a/b}$), 3.28 (3H, s, 2'-OCH_3), 3.17 (6H, s, 4''-OCH_3); ^{13}C NMR (151 MHz, C_6D_6, Plate 3C) δ ppm 200.3 (CO), 158.59 (C-4''), 158.52 (C-2'), 137.4 (C-1''), 132.8 (C-4'), 130.8 (C-6'), 129.8 (C-1'), 129.1 (C-2''&6''), 120.9 (C-5'), 114.1 (C-3''&5''), 111.5 (C-3'), 55.0 (2'-OCH_3), 54.7 (4''-OCH_3), 50.9 (C-2&4), 37.2 (C-3); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 4A) δ ppm 7.47 (2H, dd, *J* = 1.65, 7.62 Hz, H-6'), 7.43-7.39 (2H, m, H-4'), 7.10 (2H, d, *J* = 8.62 Hz, H-2''&6''), 6.93 (2H, br dd, *J* = 7.41, 7.62 Hz, H-5'), 6.92 (2H, d, *J* = 8.37 Hz, H-3'), 6.76 (2H, d, *J* = 8.62 Hz, H-3''&5''), 3.87 (1H, p, *J* = 7.36 Hz, H-3), 3.85 (6H, s, 2'-OCH_3), 3.75 (3H, s, 4''-OCH_3), 3.35 (2H, dd, *J* = 7.36, 16.46 Hz, H-2$^{a/b}$ &4$^{a/b}$), 3.31 (2H, dd, *J* = 7.36, 16.46 Hz, H-



(**392**)

2$^{a/b}$&4 $^{a/b}$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 4C) δ ppm 201.5 (CO), 158.36 (C-2'), 158.01 (C-4''), 136.8 (C-1''), 133.3 (C-4'), 130.4 (C-6'), 128.9 (C-1'), 128.7 (C-2''&6''), 120.8 (C-5'), 113.7 (C-3''&5''), 111.5 (C-3'), 55.6 (2''-OCH_3), 55.3 (4''-OCH_3), 50.4 (C-2&4), 36.8 (C-3); ^{1}H NMR (600 MHz, $CDCl_3$, 58 °C, Plate 4F) δ ppm 7.45 (2H, dd, *J* = 1.79, 7.68 Hz, H-6'), 7.39 (2H, ddd, *J* = 1.79, 7.32, 8.34 Hz, H-4'), 7.10 (2H, d, *J* = 8.69 Hz, H-2''&6''), 6.93 (2H, ddd, *J* = 0.82, 7.32, 7.68 Hz, H-5'), 6.92 (2H, br d, *J* = 8.34 Hz, H-3'), 6.76 (2H, d, *J* = 8.69 Hz, H-3''&5''), 3.88 (1H, p, *J* = 7.20 Hz, H-3), 3.85 (6H, s, 2'-OCH_3), 3.75 (3H, s, 4''-OCH_3), 3.36 (2H, dd, *J* = 7.20, 16.27 Hz, H-2$^{a/b}$&4$^{a/b}$), 3.31 (2H, dd, *J* = 7.20, 16.27 Hz, H-2$^{a/b}$&4$^{a/b}$); ^{1}H NMR (600 MHz, C_3D_6O, Plate 5) δ ppm 7.49-7.45 (2H, m, H-4'), 7.39 (2H, dd, *J* = 1.64, 7.59 Hz, H-6'), 7.13 (2H, d, *J* = 8.61 Hz, H-2''&6''), 7.11 (2H, br d, *J* = 8.37 Hz, H-3'), 6.95 (2H, br dd, *J* = 7.47, 7.59 Hz, H-5'), 6.77 (2H, d, *J* = 8.61 Hz, H-3''&5''), 3.90 (6H, s, 2'-OCH_3), 3.86 (1H, p, *J* = 7.25 Hz, H-3), 3.72 (3H, s, 4''-OCH_3), 3.32 (4H, d, *J* = 7.25 Hz, H-2&4); HRMS (*m/z*): $[M + Na]^+$ calculated for $C_{26}H_{26}O_5Na$: 441.1677; found, 441.1678.

Method F:[7] 50% aq. NaOH solution (5 mL) was added to a mixture of 2'-methoxyacetophenone (0.153 g, 1 mmol, 1 eq) and *p*-anisaldehyde (0.168 g, 1.2 mmol, 1.2 eq) in 1,4-dioxane (10 mL). The RM was irradiated with MW (100 W) for 1 hour at 50 °C, resulting in a light yellow RM. The resulting solution was acidified with sat. NH_4Cl solution (lithmus/pHydrion® INSTA-CHEK 0-13) and the organic material extracted into EtOAc (3 x 15 mL). The organic layer was neutralized with sat. $NaHCO_3$, washed with H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure the crude product was subjected to purification by means of PLC (H:EtOAc, 9:1) yielding 1% (0.003 g) of the title compound (**383**).

Method G:[7] Performed according to the above procedure (Method F) in EtOH (10 mL) resulting in a red RM after MW irradiation and three compounds with an R_f 0.11, 0.25 and 0.44 (H:EtOAc, 7:3) in respective yields of 29% (0.051 g), 69% (0.188 g) and trace amounts (0.002 g).

- *1,5-bis(2'-methoxyphenyl)-3-(4''-methoxyphenyl)pentane-1,5-dione* (**392**) Yellow solid; R_f 0.11 (H:EtOAc, 7:3); see the above section 5.7.2, Method B for characterization.

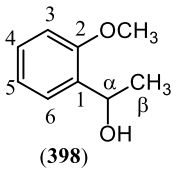
- 2',4-Dimethoxychalcone (**383**)[5] Yellow paste; R_f 0.25 (H:EtOAc, 7:3); see the above section 5.7.2, Method A for characterization.

- *β-Ethoxy-2',4-dimethoxydihydrochalcones* (**387**) Colourless oil; R_f 0.44 (H:EtOAc, 7:3); see the above section 5.7.2, Method A for characterization.

Method H:[7] Performed according to the above procedure (Method F) in ethanol and irradiated with MW (200 W) for 1 h at a temperature of 128 °C, the resulting brown RM gave 0% yield of the title

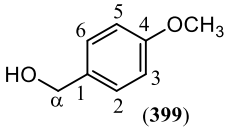
compound (**383**). Three products were obtained after purification with the R_f 0.13, 0.17 and 0.22 in yields of 48% (0.074 g), 36% (0.05 g) and 3% (0.008 g), respectively.

- 2-Methoxy-α-methylbenzyl alcohol (**398**)[8] Yellow oil; R_f 0.13 (H:EtOAc, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 6A) δ ppm 7.34 (1H, dd, *J* = 1.77, 7.48 Hz, H-6), 7.25 (1H, dt, *J* = 1.77, 8.10 Hz, H-4), 6.97 (1H, td, *J* = 0.82, 7.48 Hz, H-5), 6.89 (1H, br d, *J* = 8.10 Hz, H-3), 5.12-5.08 (1H, m, H-α), 3.87 (3H, s, OC<u>H</u>$_3$), 2.66 (1H, d, *J* = 4.09 Hz, O<u>H</u>), 1.51 (3H, d, *J* = 6.54 Hz, C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 6C) δ ppm 156.7 (C-2), 133.6 (C-1), 128.4 (C-4), 126.2 (C-6), 120.9 (C-5), 110.6 (C-3), 66.7 (C-α), 55.4 (2-O<u>C</u>H$_3$), 23.0 (β-<u>C</u>H$_3$); MS (*m/z*): 152 (M^+, 30%).



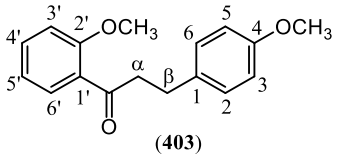
(**398**)

- 4-Methoxybenzyl alcohol (**399**)[9] Colourless oil; R_f 0.17 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 7A) δ ppm 7.29 (2H, d, *J* = 8.61 Hz, H-2&6), 6.89 (2H, d, *J* = 8.61 Hz, H-3&5), 4.61 (2H, d, *J* = 4.66 Hz, C<u>H</u>$_2$), 3.81 (3H, s, OC<u>H</u>$_3$), 1.75 (1H, br s, O<u>H</u>); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 7C) δ ppm 159.4 (C-4), 133.3 (C-1), 128.8 (C-2&6), 114.1 (C-3&5), 65.2 (α-<u>C</u>H$_2$), 55.4 (4-O<u>C</u>H$_3$); MS (*m/z*): 138 (M^+, 100%).



(**399**)

- 2',4-Dimethoxydihydrochalcone (**403**)[10] Light yellow transparent needles; R_f 0.22 (H:EtOAc, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 8A) δ ppm 7.68 (1H, dd, *J* = 1.80, 7.64 Hz, H-6'), 7.45 (1H, ddd, *J* = 1.80, 7.51, 8.37 Hz, H-4'), 7.15 (2H, d, *J* = 8.63 Hz, H-2&6), 7.00 (1H, td, *J* = 0.85, 7.51 Hz, H-5'), 6.84 (1H, br d, *J* = 8.37 Hz, H-3'), 6.84 (2H, d, *J* = 8.63 Hz, H-3&5), 3.88 (3H, s, 2'-OC<u>H</u>$_3$), 3.79 (3H, s, 4-OC<u>H</u>$_3$), 3.27 (2H, t, *J* = 7.79 Hz, H-α), 2.97 (2H, t, *J* = 7.79 Hz, H-β); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 8C) δ ppm 202.0 (<u>C</u>O), 158.6 (C-2'), 158.0 (C-4), 133.9 (C-1), 133.5, (C-4'), 130.4 (C-6'), 129.5 (C-2&6), 128.5 (C-1'), 120.8 (C-5'), 113.9 (C-3&5), 55.6 (2'-O<u>C</u>H$_3$), 55.4 (4-O<u>C</u>H$_3$), 45.8 (C-α), 39.7 (C-β); EIMS (*m/z*): 270 (M^+, 34%).

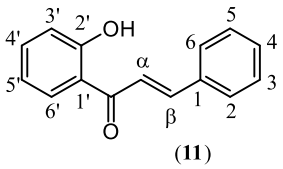


(**403**)

5.7.3 Preparation of 2'-Hydroxychalcone (**11**)

Method A: Performed according to general aldol condensation Method A; KOH (6.00 g, 0.107 mol) was added to a cooled (ice-bath) solution of 2'-hydroxyacetophenone (3.03 g, 0.022 mol) and benzaldehyde (2.62 g, 0.025 mol) in EtOH (147 mL). After addition of the reagents, the RM stirred at RT for 6 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O), producing the title compound (**11**) in a 60% (2.99 g) yield.

- 2'-Hydroxychalcone (**11**)[11] Bright yellow needles; R_f 0.70 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 9A) δ ppm 12.81 (1H,s, OH), 7.93 (1H, d, *J* = 15.48 Hz, H-β), 7.93 (1H, dd, *J* = 1.56, 8.13 Hz, H-6'), 7.67 (1H, d, *J* = 15.48 Hz, H-α), 7.68-7.66 (2H, m, H-2&6), 7.51 (1H, ddd, *J* = 1.56, 7.26, 8.46 Hz, H-4'), 7.45-7.44 (3H, m, H-3,4&5), 7.04 (1H, dd, *J* = 1.03, 8.46 Hz, H-3'), 6.95 (1H, ddd, *J* = 1.03, 7.26, 8.13 Hz, H-5'); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 9C) δ ppm 193.9 (CO), 163.8 (C-2'), 145.6 (C-β), 136.6 (C-4'), 134.8 (C-1), 131.1 (C-4), 129.8 (C-6'), 129.2 (C-3&5), 128.8 (C-2&6), 120.3 (C-α), 120.2 (C-1'), 119.0 (C-3'), 118.8 (C-5'); m.p. 88.6-90.3 °C (recrystallized from EtOH:H_2O, Lit.[12] 88 °C); EIMS (*m/z*): 224 (M^+, 78%).



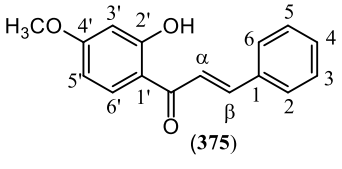
(**11**)

Method B: Performed according to general aldol condensation Method B; Heptane (0.7 mL) was added to NaH (0.195 g, 8.1 mmol) under $Ar_{(g)}$. Anhydrous DMF (19 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxyacetophenone (0.404 g, 3.7 mmol) in DMF (4 mL) was added. After 30 min a solution of *p*-anisaldehyde (0.393 g, 3.7 mmol) in DMF (4 mL) was added slowly. The reaction was stopped after 1 h and the red RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13), allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O to yield the title compound (**11**) in 63% (0.515 g) yield.

5.7.4 Preparation of 2'-Hydroxy-4'-methoxychalcone (**375**)

Method A: Performed according to general aldol condensation Method A; KOH (0.820 g, 14.6 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4'-methoxyacetophenone (0.501 g, 3.0 mmol) and benzaldehyde (0.324 g, 3.1 mmol) in EtOH (30 mL). After addition of the reagents, the RM stirred at RT for 24 h. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**375**) in a 74% (0.565 g) yield.

- 2'-Hydroxy-4'-methoxychalcone (**375**)[13] Bright yellow needles; R_f 0.31 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 10A) δ ppm 13.45 (1H, s, OH), 7.90 (1H, d, *J* = 15.47 Hz, H-β), 7.85 (1H, d, *J* = 8.80 Hz, H-6'), 7.67 (2H, dd, *J* = 3.05, 6.49 Hz, H-2&6), 7.59 (1H, d, *J* = 15.47 Hz, H-α), 7.46-7.43 (3H, m, H-3,4&5), 6.49 (1H, dd, *J* = 2.47, 8.80 Hz, H-5'), 6.49 (1H, d, *J* = 2.47 Hz, H-3'), 3.87 (3H, s, 4'-OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 10C) δ ppm 192.0 (CO), 166.9 (C-2'), 166.4 (C-4'), 144.5 (C-β), 134.9 (C-1), 131.4 (C-6'), 130.8 (C-4), 129.1 (C-3&5), 128.7 (C-2&6), 120.5 (C-α), 114.2 (C-1'), 107.9 (C-5'), 101.2 (C-3'), 55.7 (4'-OCH_3); m.p. 107.1-108.4 °C (recrystallized from EtOH:H_2O, Lit.[14] 107-108 °C); EIMS (*m/z*): 253 (M^+, 26%).



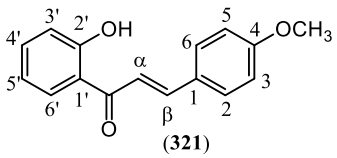
(**375**)

Method B: Performed according to general Aldol condensation Method B; Heptane (0.7 mL) was added to NaH (0.160 g, 6.7 mmol) under $Ar_{(g)}$. Anhydrous DMF (4 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4'-methoxyacetophenone (0.499 g, 3.0 mmol) in DMF (4 mL) was added. After 30 min a solution of benzaldehyde (0.324 g, 3.0 mmol) in DMF (4 mL) was added slowly. The reaction was stopped after 1 h and the pink-red RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**375**) in 57% (0.433 g) yield.

5.7.5 Preparation of 2'-Hydroxy-4-methoxychalcone (**321**)

Method A: Performed according to general Aldol condensation Method A; KOH (1 g, 17.8 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxyacetophenone (0.498 g, 3.7 mmol) and *p*-anisaldehyde (0.548 g, 4.0 mmol) in EtOH (9 mL). After addition the RM stirred at RT for 2 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**321**) in a 80% (0.753 g) yield.

- 2'-Hydroxy-4-methoxychalcone (**321**)[15] Yellow/orange small needles; R_f 0.47 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 11A) δ ppm 12.94 (1H, s, OH), 7.92 (1H, dd, *J* = 1.56, 7.68 Hz, H-6'), 7.90 (1H, d, *J* = 15.21 Hz, H-β), 7.63 (2H, d, *J* = 8.73 Hz, H-2&6), 7.54 (1H, d, *J* = 15.21 Hz, H-α), 7.57 (1H, ddd, *J* = 1.56,7.59, 8.33 Hz, H-4'), 7.02 (1H, dd, *J* = 0.71, 8.33 Hz, H-3'), 6.95 (2H, d, *J* = 8.73 Hz, H-3&5), 6.96-6.92 (1H, m, H-5'), 3.86 (3H, s, 4-OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 11C) δ ppm 193.8 (CO), 163.7 (C-2'), 162.2 (C-4), 145.5 (C-β), 136.3 (C-4'), 130.7 (C-2&6), 129.7 (C-6'), 127.5 (C-1), 120.3 (C-1'), 118.9 (C-5'), 118.7 (C-3'), 117.8 (C-α), 114.7 (C-3&5), 55.6 (4-OCH_3); m.p. 92.4-93.7 °C (recrystallized from EtOH:H_2O, Lit.[15] 95-96 °C); EIMS (*m/z*): 254 (M^+, 60%).



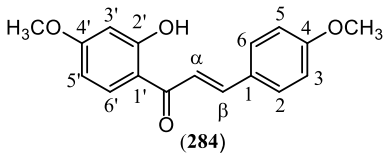
(**321**)

Method B: Performed according to general Aldol condensation Method B; Heptane (0.7 mL) was added to NaH (0.199 g, 8.2 mmol) under $Ar_{(g)}$. Anhydrous DMF (19 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxyacetophenone (0.504 g, 3.7 mmol) in DMF (4 mL) was added. After 30 min a solution of *p*-anisaldehyde (0.504 g, 3.7 mmol) in DMF (4 mL) was added slowly. The reaction was stopped after 1 h and the red RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**321**) in 94% (0.877 g) yield.

5.7.4 Preparation of 2'-Hydroxy-4,4'-dimethoxychalcone (**284**)

Method A: Performed according to general aldol condensation Method A; KOH (6.502 g, 0.116 mol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4'-methoxyacetophenone (4.006 g, 0.024 mol) and *p*-anisaldehyde (3.693 g, 0.027 mol) in EtOH (80 mL). After addition of the reagents, the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**284**) in a 65% (4.452 g) yield.

- 2'-Hydroxy-4,4'-dimethoxychalcone (**284**)[13] Bright yellow small needles; R_f 0.46 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 12A) δ ppm 13.57 (1H, s, OH), 7.87 (1H, d, *J* = 15.37 Hz, H-β), 7.83 (1H, d, *J* = 8.66, H-6'), 7.62 (2H, d, *J* = 8.69 Hz, H-2&6), 7.46 (1H, d, *J* = 15.37 Hz, H-α), 6.95 (2H, d, *J* = 8.69 Hz, H-3&5), 6.50 (1H, dd, *J* = 2.48, 8.66 Hz, H-5'), 6.48 (1H, d, *J* = 2.48 Hz, H-3'), 3.870(3H, s, 4/4'-OCH_3), 3.865 (3H, s, 4/4'-OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 12C) δ ppm 192.0 (CO), 166.8 (C-2'), 166.2 (C-4'), 161.9 (C-4), 144.4 (C-β), 131.2 (C-6'), 130.5 (C-2&6), 127.7 (C-1), 118.0 (C-α), 114.6 (C-3&5), 114.3 (C-1'), 107.7 (C-5'), 101.2 (C-3'), 55.7 (4/4'-OCH_3), 55.6 (4/4'-OCH_3); m.p. 107.6-109.5 °C (recrystallized from EtOH:H_2O, Lit.[14] 114-116 °C); EIMS (*m/z*): 284 (M^+, 83%).



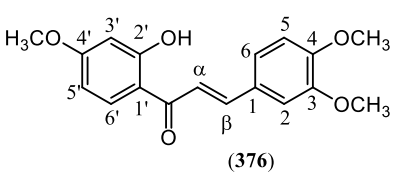
(**284**)

Method B: Performed according to general Aldol condensation Method B; Heptane (1.2 mL) was added to NaH (0.319 g, 13.3 mmol) under $Ar_{(g)}$. Anhydrous DMF (14 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4'-methoxyacetophenone (0.996 g, 6 mmol) in DMF (7 mL) was added. After 30 min a solution of *p*-anisaldehyde (0.817 g, 6 mmol) in DMF (7 mL) was added slowly. The reaction was stopped after 2 h and the red RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**284**) in 92% (1.569 g) yield.

5.7.5 Preparation of 2'-Hydroxy-3,4,4'-trimethoxychalcone (**376**)

Method A: Performed according to general aldol condensation Method A; KOH (1.632 g, 29.1 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4'-methoxyacetophenone (1.011 g, 6 mmol) and 3,4-dimethoxybenzaldehyde (1.203 g, 6.7 mmol) in EtOH (20 mL). After addition of the reagents, the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**376**) in a 62% (1.181 g) yield.

- 2'-Hydroxy-3,4,4'-trimethoxychalcone (**376**)[16] Yellow needles; R_f 0.25 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 13A) δ ppm 13.54 (1H, s, O<u>H</u>), 7.841 (1H, d, *J* = 15.34 Hz, H-β), 7.838 (1H, d, *J* = 8.40 Hz, H-6'), 7.43 (1H, d *J* = 15.34 Hz, H-α), 7.25 (1H, dd, *J* = 1.88, 8.32 Hz, H-6), 7.16 (1H, d, *J* = 1.88 Hz, H-2), 6.91 (1H, d, *J* = 8.32 Hz, H-5), 6.49 (1H, dd, *J* = 2.45, 8.40 Hz, H-5'), 6.47 (1H, d, *J* = 2.45 Hz, H-3'), 3.96 (3H, s, 3-OC<u>H</u>$_3$), 3.94 (3H, s, 4-OC<u>H</u>$_3$), 3.86 (3H, s, 4'-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 13C) δ ppm 191.9 (<u>C</u>O), 166.8 (C-2'), 166.2 (C-4'), 151.7 (C-4), 149.4 (C-3), 144.7 (C-β), 131.3 (C-6'), 127.9 (C-1), 123.5 (C-6), 118.2 (C-α), 114.3 (C-1'), 111.3 (C-5), 110.4 (C-2), 107.8 (C-5'), 101.2 (C-3'), 56.16 (4-O<u>C</u>H$_3$), 56.15 (3-O<u>C</u>H$_3$), 55.7 (4'-O<u>C</u>H$_3$); m.p. 160.9-161.5 °C (recrystallized from EtOH:H_2O, Lit.[17] 157-159 °C); EIMS (*m/z*): 314 (M^+, 60%).

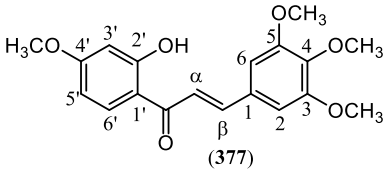

(**376**)

<u>Method B:</u> Performed according to general Aldol condensation Method B; Heptane (0.6 mL) was added to NaH (0.172 g, 7.1 mmol) under $Ar_{(g)}$. Anhydrous DMF (16 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4'-methoxyacetophenone (0.510 g, 3.1 mmol) in DMF (4 mL) was added. After 30 min a solution of aldehyde (0.543 g, 3.0 mmol) in DMF (4 mL) was added slowly. The reaction was stopped after 2 h and the RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**376**) in 82% (0.775 g) yield.

<u>5.7.6 Preparation of 2'-Hydroxy-3,4,4',5-tetramethoxychalcone (**377**)</u>

<u>Method A:</u> Performed according to general aldol condensation Method A; KOH (1.686 g, 30 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4'-methoxyacetophenone (1.001 g, 6 mmol) and 3,4,5-trimethoxybenzaldehyde (1.305 g, 6.7 mmol) in EtOH (43 mL). After addition the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**377**) in a 54% (1.115 g) yield.

- 2'-Hydroxy-3,4,4',5-tetramethoxychalcone (**377**)[17] Bright yellow fine powder; R_f 0.24 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 14A) δ ppm 13.46 (1H, s, O<u>H</u>), 7.83 (1H, d, *J* = 8.85 Hz, H-6'), 7.80 (1H, d, *J* = 15.36 Hz, H-β), 7.45 (1H, d, *J* = 15.36 Hz, H-α), 6.87 (2H, s, H-2&6), 6.49 (1H, dd, *J* = 2.44, 8.85 Hz, H-5'), 6.48 (1H, d, *J* = 2.44 Hz, H-3'), 3.93 (3H, s, 3&5-OC<u>H</u>$_3$), 3.91 (3H, s, 4-OC<u>H</u>$_3$), 3.86 (3H, s, 4'-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 14C) δ ppm 191.8 (<u>C</u>O), 166.9 (C-2'), 166.3 (C-4'), 153.6 (C-3&5), 144.7 (C-β), 140.8 (C-4), 131.3 (C-6'), 130.4 (C-1), 119.6 (C-α),


(**377**)

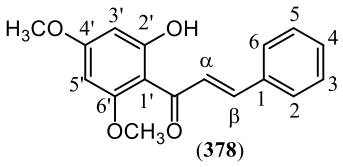
114.2 (C-1'), 107.9 (C-5'), 106.0 (C-2&6), 101.2 (C-3'), 61.2 (4-O<u>C</u>H$_3$), 56.4 (3&5-O<u>C</u>H$_3$), 55.7 (4'-O<u>C</u>H$_3$); m.p. 122.8-132.5 °C (recrystallized from EtOH:H$_2$O, Lit.[17] 118-119 °C); EIMS (*m/z*): 344 (M$^+$, 72%).

<u>Method B:</u> Performed according to general Aldol condensation Method B; Heptane (0.6 mL) was added to NaH (0.177 g, 7.4 mmol) under Ar$_{(g)}$. Anhydrous DMF (16 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4'-methoxyacetophenone (0.504 g, 3 mmol) in DMF (4 mL) was added. After 30 min a solution of 3,4,5-trimethoxybenzaldehyde (0.607 g, 3.1 mmol) in DMF (4 mL) was added slowly. The reaction was stopped after 1.5 h and the RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H$_2$O yielding the title compound (**377**) in 72% (0.749 g) yield.

<u>5.7.7 Preparation of 2'-Hydroxy-4',6'-dimethoxychalcone (**378**)</u>

<u>Method A:</u> Performed according to general aldol condensation Method A; KOH (0.732 g, 13.0 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4',6'-dimethoxyacetophenone (0.494 g, 2.52 mmol) and benzaldehyde (0.292 g, 2.75 mmol) in EtOH (12 mL). After addition the RM stirred at RT for 24 h. The crude product was then subjected to purification by recrystallization (EtOH:H$_2$O) producing the title compound (**378**) in a 82% (0.585 g) yield.

- <u>2'-Hydroxy-4',6'-dimethoxychalcone (**378**)</u>[18] Yellow/orange small needles; R$_f$ 0.44 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, CDCl$_3$, Plate 15A) δ ppm 14.29 (1H, s, O<u>H</u>), 7.90 (1H, d, *J* = 15.61 Hz, H-α), 7.79 (1H, d, *J* = 15.61 Hz, H-β), 7.61 (2H, dd, *J* = 1.56, 7.66 Hz, H-2&6), 7.43-7.38 (3H, m, H-3,4&5), 6.11 (1H, d, *J* = 2.37 Hz, H-3'), 5.97 (1H, d, *J* = 2.37 Hz, H-5'), 3.92 (3H, s, 4'/6'-OC<u>H</u>$_3$), 3.84 (3H, s, 4'/6'-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, CDCl$_3$, Plate 15C) δ ppm 192.8 (<u>C</u>O), 168.6 (C-2'), 166.4 (C-4'/6'), 162.7 (C-4'/6'), 142.5 (C-β), 135.7 (C-1), 130.2 (C-4), 129.0 (C-3&5), 128.5 (C-2&6), 127.7 (C-α), 106.5 (C-1'), 94.0 (C-3'), 91.4 (C-5'), 56.0 (4'/6'-O<u>C</u>H$_3$), 55.7 (4'/6'-O<u>C</u>H$_3$); m.p. 90.5 - 91.7 °C (recrystallized from EtOH:H$_2$O, Lit.[17] 91-92 °C); EIMS (*m/z*): 284 (M$^+$, 67%).



(**378**)

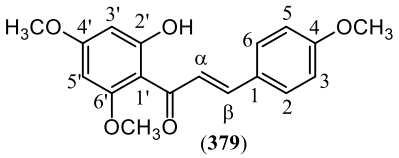
<u>Method B:</u> Performed according to general Aldol condensation Method B; Heptane (0.5 mL) was added to NaH (0.144 g, 6 mmol) under Ar$_{(g)}$. Anhydrous DMF (13 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4',6'-dimethoxyacetophenone (0.507 g, 2.6 mmol) in DMF (3 mL) was added. After 30 min a solution of benzaldehyde (0.272 g, 2.6 mmol) in DMF (3 mL) was added slowly. The reaction was stopped after 1 h and the orange RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate.

The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**378**) in 98% (0.712 g) yield.

5.7.8 Preparation of 2'-Hydroxy-4,4',6'-trimethoxychalcone (**379**)

Method A: Performed according to general aldol condensation Method A; KOH (1.475 g, 26.3 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4',6'-dimethoxyacetophenone (1.005 g, 5.1 mmol) and *p*-anisaldehyde (0.783 g, 5.8 mmol) in EtOH (36 mL). After addition the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**379**) in a 71% (1.143 g) yield.

- 2'-Hydroxy-4,4',6'-trimethoxychalcone (**379**)[19] Bright Yellow needles; R_f 0.36 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 16A) δ ppm 14.42 (1H, s, O<u>H</u>), 7.80 (1H, d, *J* = 15.56 Hz, H-β), 7.77 (1H, d, *J* = 15.56 Hz, H-α), 7.55 (2H, d, *J* = 8.77 Hz, H-2&6), 6.92 (2H, d, *J* = 8.77 Hz, H-3&5), 6.10 (1H, d, *J* = 2.37 Hz, H-3'), 5.95 (1H, d, *J* = 2.37 Hz, H-5'), 3.90 (3H, s, 6'-OC<u>H</u>$_3$), 3.84 (3H, s, 4-OC<u>H</u>$_3$), 3.82 (3H, s, 4'-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 16C) δ ppm 192.7 (<u>C</u>O), 168.5 (C-2'), 166.1 (C-4'), 162.6 (C-6'), 161.5 (C-4), 142.6 (C-β), 130.2 (C-2&6), 128.4 (C-1), 125.2 (C-α), 114.5 (C-3&5), 106.5 (C-1'), 93.9 (C-3'), 91.3 (C-5'), 55.9 (6'-O<u>C</u>H$_3$), 55.6 (4/4'-O<u>C</u>H$_3$), 55.5 (4/4'-O<u>C</u>H$_3$); m.p. 112.6-114.7 °C (recrystallized from EtOH:H_2O, Lit.[17] 109-110 °C); EIMS (*m/z*): 314 (M^+, 100%).



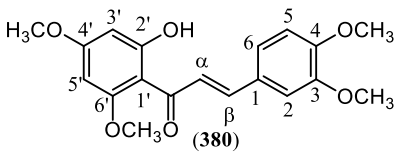
(**379**)

Method B: Performed according to general Aldol condensation Method B; Heptane (0.5 mL) was added to NaH (0.146 g, 6.1 mmol) under $Ar_{(g)}$. Anhydrous DMF (13 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4',6'-dimethoxyacetophenone (0.505 g, 2.6 mmol) in DMF (3 mL) was added. After 30 min a solution of *p*-anisaldehyde (0.347 g, 2.5 mmol) in DMF (3 mL) was added slowly. The reaction was stopped after 30 min and the RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**379**) in 99% (0.806 g) yield.

5.7.9 Preparation of 2'-Hydroxy-3,4,4',6'-tetramethoxychalcone (**380**)

Method A: Performed according to general aldol condensation Method A; KOH (1.681 g, 30 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4',6'-dimethoxyacetophenone (1.004 g, 6 mmol) and 3,4-dimethoxybenzaldehyde (1.203 g, 6.7 mmol) in EtOH (43 mL). After addition the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**380**) in a 74% (1.153 g) yield.

- 2'-Hydroxy-3,4,4',6'-tetramethoxychalcone (**380**)[20]



(**380**)

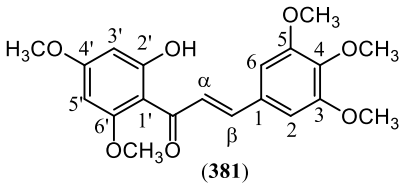
Yellow to orange needles; R_f 0.17 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 17A) δ ppm 14.39 (1H, s, O<u>H</u>), 7.80 (1H, d, *J* = 15.50 Hz, H- α), 7.75 (1H, d, *J* = 15.50 Hz, H- β), 7.21 (1H, dd, *J* = 1.89, 8.30 Hz, H-6), 7.12 (1H, d, *J* = 1.89 Hz, H-2), 6.89 (1H, d, *J* = 8.30 Hz, H-5), 6.11 (1H, d, *J* = 2.35 Hz, H-3'), 5.96 (1H, d, *J* = 2.35 Hz, H-5'), 3.94 (3H, s, 3-OC<u>H</u>$_3$), 3.93 (3H, s, 4-OC<u>H</u>$_3$), 3.91 (3H, s, 6'-OC<u>H</u>$_3$), 3.83 (3H, s, 4'-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 17C) δ ppm 192.6 (<u>C</u>O), 168.5 (C-2'), 166.2 (C-4'), 162.6 (C-6'), 151.2 (C-4), 149.3 (C-3), 142.8 (C-β), 128.8 (C-1), 125.6 (C-α), 122.8 (C-6), 111.3 (C-5), 110.7 (C-2), 106.5 (C-1'), 94.0 (C-3'), 91.4 (C-5'), 56.1 (3/4/6'-O<u>C</u>H$_3$), 56.0 (3/4/6'-O<u>C</u>H$_3$), 55.9 (3/4/6'-O<u>C</u>H$_3$), 55.7 (4'-O<u>C</u>H$_3$); m.p. 155.8-157.5 °C (recrystallized from EtOH:H_2O, Lit.[17] 151-153 °C); EIMS (*m/z*): 344 (M^+, 77%).

<u>Method B:</u> Performed according to general Aldol condensation Method B; Heptane (0.5 mL) was added to NaH (0.140 g, 5.8 mmol) under $Ar_{(g)}$. Anhydrous DMF (13 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4',6'-dimethoxyacetophenone (0.509 g, 2.6 mmol) in DMF (3 mL) was added. After 30 min a solution of 3,4-dimethoxybenzaldehyde (0.430 g, 2.6 mmol) in DMF (3 mL) was added slowly. The reaction was stopped after 1.5 h and the RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**380**) in 96% (0.856 g) yield.

<u>5.7.10 Preparation of 2'-Hydroxy-3,4,4',5,6'-pentamethoxychalcone (**381**)</u>

<u>Method A:</u> Performed according to general aldol condensation Method A; KOH (1.395 g, 25 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-4',6'-dimethoxyacetophenone (1.001 g, 5.1 mmol) and 3,4,5-trimethoxybenzaldehyde (1.101 g, 5.6 mmol) in EtOH (36 mL). After addition the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H_2O) producing the title compound (**381**) in a 21% (0.4029 g) yield.

- 2'-Hydroxy-3,4,4',5,6'-pentamethoxychalcone (**381**)[21]



(**381**)

Bright yellow needles; R_f 0.14 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 17A) δ ppm 14.31 (1H, s, O<u>H</u>), 7.79 (1H, d, *J* = 15.49 Hz, H-α), 7.70 (1H, d, *J* = 15.49 Hz, H-β), 6.83 (2H, s, H-2&6), 6.11 (1H, d, *J* = 2.35 Hz, H-3'), 5.96 (1H, d, *J* = 2.35 Hz, H-5'), 3.91 (6H, s, 3&5-OC<u>H</u>$_3$), 3.90 (3H, s, 6'-OC<u>H</u>$_3$), 3.89 (3H, s, 4-OC<u>H</u>$_3$), 3.83 (3H, s, 4'-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 17C) δ ppm 192.5 (CO), 168.6 (C-2'), 166.3 (C-4'), 162.5 (C-6'), 153.5 (C-3&5), 142.5 (C-β), 140.2

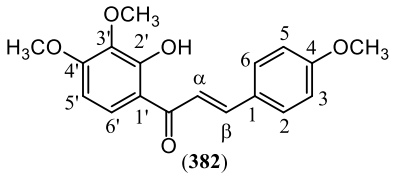
(C-4), 131.3 (C-1), 127.1 (C- α), 106.5 (C-1'), 105.7 (C-2&6), 94.0 (C-3'), 91.5 (C-5'), 61.1 (4-O<u>C</u>H$_3$), 56.3 (3&5-O<u>C</u>H$_3$), 55.9 (6'-O<u>C</u>H$_3$), 55.7 (4'-O<u>C</u>H$_3$); m.p. 184.7-186.8 °C (recrystallized from EtOH:H$_2$O, Lit.[21] 181-182 °C); EIMS (*m/z*): 374 (M$^+$, 60%).

<u>Method B:</u> Performed according to general Aldol condensation Method B; Heptane (0.5 mL) was added to NaH (0.138 g, 5.7 mmol) under Ar$_{(g)}$. Anhydrous DMF (10 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4',6'-dimethoxyacetophenone (0.504 g, 2.6 mmol) in DMF (3 mL) was added. After 30 min a solution of 3,4,5-trimethoxybenzaldehyde (0.504 g, 2.6 mmol) in DMF (3 mL) was added slowly. The reaction was stopped after 1.5 h and the RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate. The ppt was filtered under vacuum and washed sufficiently with H$_2$O yielding the title compound (**381**) in 94% (0.903 g) yield.

<u>5.7.11 Preparation of 2'-Hydroxy-3',4,4'-trimethoxychalcone (**382**)</u>

<u>Method A:</u> Performed according to general aldol condensation Method A; KOH (0.686 g, 12.2 mmol) was added to a cooled (ice-bath) solution of 2'-hydroxy-3',4'-dimethoxyacetophenone (0.501 g, 2.6 mmol) and *p*-anisaldehyde (0.390 g, 2.9 mmol) in EtOH (30 mL). After addition the RM stirred at RT for 7 d. The crude product was then subjected to purification by recrystallization (EtOH:H$_2$O) producing the title compound (**382**) in a 41% (0.333 g) yield.

- <u>2'-Hydroxy-3',4',4-trimethoxychalcone (**382**)</u>[22]



(**382**)

Orange/yellow plates; R$_f$ 0.20 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, CDCl$_3$, Plate 19A) δ ppm 13.34 (1H, s, O<u>H</u>), 7.85 (1H, d, *J* = 15.36 Hz, H-β), 7.67 (1H, d, *J* = 9.07 Hz, H-6'), 7.59 (2H, d, *J* = 8.71 Hz, H-2&6), 7.44 (1H, d, *J* = 15.36 Hz, H-α), 6.93 (2H, d, *J* = 8.71 Hz, H-3&5), 6.51 (1H, d, *J* = 9.07 Hz, H-5'), 3.93 (3H, s, 3'-OC<u>H</u>$_3$), 3.91 (3H, s, 4'-OC<u>H</u>$_3$), 3.84 (3H, s, 4-OC<u>H</u>$_3$); ^{13}C NMR (151 MHz, CDCl$_3$, Plate 19C) δ ppm 192.6 (<u>C</u>O), 162.0 (C-4), 158.5 (C-3'), 158.4 (C-2'), 144.7 (C-β), 136.8 (C-4'), 130.5 (C-2&6), 127.5 (C-1), 126.0 (C-6'), 117.8 (C-α), 115.8 (C-1'), 114.6 (C-3&5), 102.9 (C-5'), 60.7 (4'-O<u>C</u>H$_3$), 56.2 (3'-O<u>C</u>H$_3$), 55.5 (4-O<u>C</u>H$_3$); m.p. 132.1-134.1 °C (recrystallized from EtOH:H$_2$O, Lit.[17] 131-132 °C); EIMS (*m/z*): 314 (M$^+$, 87%).

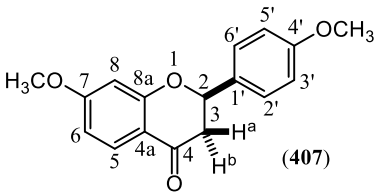
<u>Method B:</u> Performed according to general Aldol condensation Method B; Heptane (0.5 mL) was added to NaH (0.164 g, 6.8 mmol) under Ar$_{(g)}$. Anhydrous DMF (13 mL) was then added and as soon as the suspension in DMF was cooled, 2'-hydroxy-4',6'-dimethoxyacetophenone (0.504 g, 2.6 mmol) in DMF (3 mL) was added. After 30 min a solution of *p*-anisaldehyde (0.347 g, 2.5 mmol) in DMF (3 mL) was added slowly. The reaction was stopped after 30 min and the red RM poured over ice and acidified with 3M HCl (lithmus/pHydrion® INSTA-CHEK 0-13) allowing the product to precipitate.

The ppt was filtered under vacuum and washed sufficiently with H_2O yielding the title compound (**382**) in 99% (0.803 g) yield.

5.8 Cyclization Towards 4',7-Dimethoxyflavan-4-one (407)

Method A:[23] 2'-Hydroxy-4',4-dimethoxychalcone (**284**) (0.101 g, 0.4 mmol) and $Al(OTf)_3$ (0.019 g, 0.04 mmol, 10 mol%) was dissolved in CH_3CN (2 mL) and subsequently refluxed for 24 h. After the RM cooled it was concentrated under reduced pressure after the RM cooled. The organic material was extracted into EtOAc (2 x 10 mL), washed with brine, followed by H_2O, dried over Na_2SO_4 and concentrated under reduced pressure at 30 °C. Purification of the crude product with PLC (H:EtOAc, 8:2) yielded the 4',7-dimethoxyflavanone (**407**) (0.024 g, 24%) and chalcone (**284**) (0.015 g, 15%).

- 4',7-Dimethoxyflavanone (**407**)[24] Light yellow solid; R_f 0.27 (H:C, 6:4); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 20A) δ ppm 7.87 (1H, d, *J* = 8.83 Hz, H-5), 7.40 (2H, d, *J* = 8.67 Hz, H-2'&6'), 6.96 (2H, d, *J* = 8.67 Hz, H-3'&5'), 6.61 (1H, dd, *J* = 2.39, 8.83 Hz, H-6), 6.48 (1H, d, *J* = 2.39 Hz, H-8), 5.42 (1H, dd, *J* = 2.85, 13.32 Hz, H-2), 3.834 (3H, s, 4'-OC$\underline{H}_3$), 3.829 (3H, s, 7-OC$\underline{H}_3$), 3.06 (1H, dd, *J* = 13.32, 16.83 Hz, H-3^a), 2.80 (1H, dd, *J* =2.85, 16.83 Hz, H-3^b); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 20C) δ ppm 191.0 (C-4), 166.3 (C-7), 163.8 (C-8a), 160.1 (C-4'), 131.0 (C-1'), 128.9 (C-5), 127.9 (C-2'&6'), 115.0 (C-4a), 114.4 (C-3'&5'), 110.3 (C-6), 101.1 (C-8), 79.9 (C-2), 55.8 (4'/7-O$\underline{C}$H$_3$), 55.5 (4'/7-O$\underline{C}$H$_3$), 44.3 (C-3); GC-MS (*m/z*): 284 (M^+, 11%).



(**407**)

Method B:[3,25,26] NaOAc (0.092 g, 1.1 mmol, 2 eq) in H_2O (1.3 mL) was added to 2'-hydroxy-4',4-dimethoxychalcone (**284**) (0.150 g, 0.53 mmol) in EtOH (13 mL) and subsequently refluxed for 24 h. After the RM cooled the solvent was evaporated in vacuum and the organic material extracted into Et_2O (2 x 25 mL). The organic layers were combined and washed with H_2O, dried over Na_2SO_4 and concentrated in vacuum at RT. Purification of the crude product with PLC (H:C, 6:4) yielded the 4',7-dimethoxyflavanone (**407**) (0.084 g, 56%).

Method C:[7] A mixture of NaOAc (0.093 g, 1.1 mmol, 2 eq) in H_2O (1.3 mL) and 2'-hydroxy-4',4-dimethoxychalcone (**284**) (0.151 g, 0.53 mmol) in EtOH (13 mL) was subjected to MW irradiation (150 W, 128 °C) for 1 h. The solvent was evaporated in vacuum and the organic material extracted into Et_2O (2 x 25 mL). After the organic layers were combined, washed with H_2O and dried over Na_2SO_4 the crude product was concentrated in vacuum at RT. Purification of the crude product with PLC (H:C, 6:4) yielded the 4',7-dimethoxyflavanone (**407**) (0.084 g, 42%).

Method D:[7] 2'-Hydroxy-4',4-dimethoxychalcone (**284**) (0.099 g, 0.4 mmol) and $Al(OTf)_3$ (0.017 g, 0.04 mmol, 10 mol%) was dissolved in CH_3CN (2 mL) and subjected to MW irradiation (150 W, 132 °C) for 1 h. The RM was concentrated under reduced pressure after the RM cooled. The organic material was extracted into EtOAc (2 x 10 mL), washed with brine, followed by H_2O, dried over Na_2SO_4 and concentrated under reduced pressure at 30 °C. Purification of the crude product with PLC (H:EtOAc, 8:2) yielded the 4',7-dimethoxyflavanone (**407**) (0.011 g, 11%).

- 4',7-Dimethoxyflavanone (**407**)[24] Light yellow solid; R_f 0.39 (H:EtOAc, 8:2); see above section 5.8, Method A for characterization.

Method E: Performed according to the above procedure (Method D) with $Bi(OTf)_3$ (0.024 g, 0.04 mmol, 10 mol%) and 2'-Hydroxy-4',4-dimethoxychalcone (**284**) (0.100 g, 0.4 mmol) and subjected to MW irradiation (150 W, 132 °C) for 1 h. Purification of the crude product with PLC (H:EtOAc, 8:2) yielded the 4',7-dimethoxyflavanone (**407**) (0.0236 g, 24%).

Method F: Performed according to the above procedure (Method D) with $La(OTf)_3$ (0.021 g, 0.04 mmol, 10 mol%) and 2'-Hydroxy-4',4-dimethoxychalcone (**284**) (0.103 g, 0.4 mmol) and subjected to MW irradiation (150 W, 132 °C) for 1 h. Purification of the crude product with PLC (H:EtOAc, 8:2) yielded the 4',7-dimethoxyflavanone (**407**) (0.006 g, 5%).

Method G: Performed according to the above procedure (Method D) with $Cu(OTf)_2$ (0.013 g, 0.04 mmol, 10 mol%) and 2'-Hydroxy-4',4-dimethoxychalcone (**284**) (0.104 g, 0.4 mmol) and subjected to MW irradiation (150 W, 132 °C) for 1 h. Purification of the crude product with PLC (H:EtOAc, 8:2) yielded the 4'7-dimethoxyflavanone (**407**) (0.025 g, 24%).

Method H: Performed according to the above procedure (Method D) with $Cu(OTf)_2$ (0.015 g, 0.04 mmol, 10 mol%) and 2'-Hydroxy-4',4-dimethoxychalcone (**284**) (0.113 g, 0.4 mmol) and subjected to MW irradiation (150 W, 132 °C) for 2 h. Purification of the crude product with PLC (H:EtOAc, 8:2) yielded the 4'7-dimethoxyflavanone (**407**) (0.0235 g, 21%).

5.9 Reductive Cyclization of 2'-Hydroxychalcones Towards Flav-3-enes

5.9.1 General Procedure

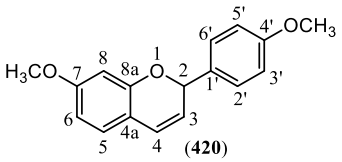
Method:[27] A hot (75 °C) saturated solution of $NaBH_4$ in isopropyl alcohol (IPA) (50 mL/g_{NaBH_4}) was added in small aliquots (2 mL) to a hot solution of the appropriate 2'-hydroxychalcone in IPA (30 $mL/g_{chalcone}$) until the solution was colourless or TLC indicated the complete consumption of the starting material. The RM was then allowed to stir at RT overnight, after which the solvent was removed under reduced pressure at 25 °C. Chloroform (20 $mL/g_{chalcone}$) was then added to the white

borate complex under Ar atmosphere (O_2 scrubber, section 5.6) and gently boiled (50-55 °C) for 10 min before the addition of 10% HOAc in $CHCl_3$ (10 mL/$g_{chalcone}$). After the a gentle reflux for 2-4 h under Ar atmosphere an excess of potassium carbonate was added and the suspension was evaporated under reduced pressure at 25 °C. The solid residue was filtered out and washed with Et_2O and the filtrate concentrated under reduced pressure at 25 °C before purification was attempted.

5.9.2 Preparation of 4',7-Dimethoxyflav-3-ene (**420**)

Method A:[28] $NaBH_4$ (0.056 g, 1.5 mmol, 4 eq) was added to a solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.106 g, 0.4 mmol) dissolved in THF (6 mL) and EtOH (3 mL). The solution was heated to a gentle reflux (65 °C) for 30 min, after which TLC indicated no starting material. After the RM cooled to RT, an excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. The RM was then evaporated to dryness and dissolved in DCM (3 x 25 mL) washed with brine, H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure at 25 °C, the crude product was subjected to purification by PLC (H:EtOAc; 8:2, 1% TEA), giving the title compound (**420**) in a 9% (0.009 g) yield.

- 4',7-Dimethoxyflav-3-ene (**420**)[29] White solid; R_f 0.56 (H:EtOAc, 8:2, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 21A) δ ppm 7.38 (2H, d, *J* = 8.69 Hz, H-2'&6'), 6.92 (1H, d, *J* = 8.30 Hz, H-5), 6.89 (2H, d, *J* = 8.69 Hz, H-3'&5'), 6.50 (1H, dd, *J* = 1.62, 9.81 Hz, H-4), 6.42 (1H, dd, *J* = 2.45, 8.30 Hz, H-6), 6.36 (1H, d, *J* = 2.45 Hz, H-8), 5.83 (1H, dd, *J* = 1.62, 3.39 Hz, H-2), 5.65 (1H, dd, *J* = 3.39, 9.81 Hz, H-3), 3.80 (3H, s, 4'/7-OCH_3), 3.74 (3H, s, 4'/7-OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 21C) δ ppm 161.0 (C-7), 159.9 (C-4'), 154.5 (C-8a), 133.1 (C-1'), 128.8 (C-2'&6'), 127.3 (C-5), 123.8 (C-4), 122.1 (C-3), 114.9 (C-4a), 114.2 (C-3'&5'), 107.1 (C-6), 102.0 (C-8), 77.1 (C-2), 55.4 (4'&7-OCH_3); m.p. 78.9-79.0 °C (Lit.[14] 79-81 °C); EIMS (*m/z*): 267 (M^+, 53%).



Method B:[28] $NaBH_4$ (0.107 g, 2.8 mmol, 4 eq) was added to a solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.201 g, 0.7 mmol) dissolved in THF (12 mL) and EtOH (6 mL). The solution was heated to a gentle reflux (65 °C) for 17 h and yielded a yellow RM. After the RM cooled to RT an excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. The RM was then evaporated to dryness yielding a yellow solid and dissolved in DCM (3 x 25 mL) washed with brine, H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure at 25 °C the crude product was subjected to purification by PLC (H:EtOAc; 8:2, 1% TEA) giving the title compound (**420**) in a 14% (0.027 g) yield.

Method C: $NaBH_4$ (0.801 g, 21.2 mmol, 4 eq) was added to a hot (75 °C) solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (1.472 g, 5.2 mmol) dissolved in THF (100 mL) and EtOH (50 mL), where after the RM was allowed to stir at 25 °C for 17 h. An excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. After the crude product was dried completely under reduced pressure at 25 °C, the organic material was extracted into DCM washed with brine, H_2O and dried over Na_2SO_4. The crude product was subjected to purification by FCC (H:DCM; 6:4, 1% TEA) and further with PLC (H:DCM, 1:1, 1% TEA), after concentrated under reduced pressure at 25 °C and gave the title compound (**420**) in 36% (0.495 g) yield.

- 4',7-Dimethoxyflav-3-ene (**420**)[29] White solid; R_f 0.46 (H:DCM; 6:4, 1% TEA) and 0.47 (H:DCM, 1:1, 1% TEA); see above section 5.9.2, Method A for full characterization.

Method D: $NaBH_4$ (0.057 g, 1.5 mmol, 4 eq) was added to a solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.100 g, 0.4 mmol) dissolved in THF (6 mL) and EtOH (3 mL). The solution was stirred at 0 °C for 6 h, after which TLC indicated no starting material. An excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. The RM was then evaporated to dryness and dissolved in DCM (3 x 25 mL) washed with brine, H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure at 25 °C the crude product was subjected to purification by PLC (H:EtOAc; 8:2, 1% TEA and MeOH) giving the title compound (**420**) in a 17% (0.016 g) yield.

Method E: $NaBH_4$ (0.055 g, 1.5 mmol, 4 eq) was added to a solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.102 g, 0.4 mmol) dissolved in THF (6 mL) and EtOH (3 mL). The solution was stirred at 0 °C for 24 h, after which TLC indicated no starting material. An excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. The RM was then evaporated to dryness and dissolved in DCM (3 x 25 mL) washed with brine, H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure at 25 °C the crude product was subjected to purification by PLC (H:EtOAc; 8:2, 1% TEA and MeOH) giving the title compound (**420**) in a 6% (0.006 g) yield.

Method F: $NaBH_4$ (0.056 g, 1.5 mmol, 4 eq) was added to a solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.104 g, 0.4 mmol) dissolved in THF (9 mL) and stirred at 25 °C for 17 h. An excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. The RM was then evaporated to dryness and dissolved in DCM (3 x 25 mL) washed with brine, H_2O and dried over Na_2SO_4. Once concentrated under reduced pressure at 25 °C the crude product was subjected to purification by PLC (H:EtOAc; 8:2, 1% TEA and MeOH) giving the title compound (**420**) in a 4% (0.004 g) yield.

Method G:[30] $(CH_3)_2$-LAB $[LiBH_3N(CH_3)_2]$ (1.0 mL, 1.4 mmol, 4 eq) was slowly added to a solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.1 g, 0.4 mmol) in anhydrous THF (2 mL) and allowed to stir at 25 °C for 5 h. An excess amount of acetone was added to quench the reaction, removed under reduced pressure and the process repeated two more times. After the crude product was evaporated to dryness the organic material was extracted into Et_2O, washed with water and dried over Na_2SO_4. Once concentrated under reduced pressure the crude product was subjected to purification by PLC (H:EtOAc, 8:2, 1% TEA) which gave the title compound (**420)** in a 26% (0.0243 g) yield.

Method H:[14,31] Small portions of $NaBH_4$ (0.080 g, 2.1 mmol, 3 eq) was added to a hot (75 °C) solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (0.201 g, 0.7 mmol) in IPA (18 mL), where after the RM was allowed to cool to RT and left to stir overnight. The solvent was then partially evaporated under reduced pressure at 25 °C, ice was added and the resulting solution was acidified using 10% HOAc until pH 5 (lithmus/pHydrion® INSTA-CHEK 0-13). The solution was extracted with DCM, neutralized with sat. $NaHCO_3$ and the organic layer washed with brine, water and dried over Na_2SO_4. The crude product was subjected to purification by PLC (H:EtOAc, 8:2, 1% TEA), after concentration under reduced pressure and produced the title compound (**420**) in a 12% (0.023 g) yield.

Method I: Performed according to general flav-3-ene synthesis method; A hot sat. sol. $NaBH_4$ (7 x 2mL) was added to a hot solution of 2'-hydroxy-4,4'-dimethoxychalcone (**284**) (1.005 g, 4 mmol) in IPA (30 mL). After stirring overnight at RT the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (20 mL) for 10 min turning the solution pink. A 10% HOAc in $CHCl_3$ solution (10 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 2 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure, where after the title compound (**420)** was recrystallized from MeOH in a 66% (0.623 g) yield.

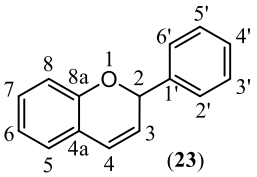
- 4',7-Dimethoxyflav-3-ene (**420**)[29] White solid; m.p. 78.9-79.0 °C (Lit.[14] 79-81 °C); see above section 5.9.2, Method A for full characterization.

5.9.3 Preparation of Flav-3-ene (**23**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (3 x 2 mL) was added to a hot solution of 2'-hydroxychalcone (**11**) (0.996 g, 4 mmol) in IPA (30 mL). After stirring overnight at RT the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (20 mL) for 10 min turning the solution pink. A 10% HOAc in $CHCl_3$ solution (10 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under

reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure. The crude product was purified by FCC (H:Tol, 3:7, 1% TEA) giving a 62% (0.575 g) yield for the title compound (**23**).

- Flav-3-ene (**23**)[32] Yellow sticky oil; R_f 0.75 (H:EtOAc, 9:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 22A) δ ppm 7.51 (2H, dd, *J* = 1.35, 7.20 Hz, H-2'&6'), 7.42 (2H, dd, *J* = 7.20, 7.67 Hz, H-3'&5'), 7.37 (1H, dd, *J* = 1.35, 7.67 Hz, H-4'), 7.16 (1H, ddd, *J* = 1.56, 7.84, 8.06 Hz, H-7), 7.06 (1H, dd, *J* = 1.56, 7.43 Hz, H-5), 6.92 (1H, ddd, *J* = 0.99, 7.43, 7.84 Hz, H-6), 6.86 (1H, br d, *J* = 8.06 Hz, H-8), 6.58 (1H, dd, *J* = 1.63, 9.84 Hz, H-4), 5.97 (1H, dd, *J* = 1.63, 3.39 Hz, H-2), 5.84 (1H, dd, *J* = 3.39, 9.84 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 22C) δ ppm 153.3 (C-8a), 141.0 (C-1'), 129.6 (C-7), 128.8 (C-3'&5'), 128.5 (C-4'), 127.1 (C-2'&6'), 126.7 (C-5), 125.0 (C-3), 124.1 (C-4), 121.4 (C-4a), 121.3 (C-6), 116.1 (C-8), 76.9 (C-2); EIMS (*m/z*): 208 (M^+, 87%).

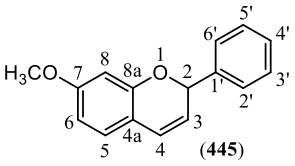


(**23**)

5.9.4 Preparation of 7-Methoxyflav-3-ene (**445**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (3 x 2 mL) was added to a hot solution of 2'-hydroxy-4'-methoxychalcone (**375**) (0.514 g, 2 mmol) in IPA (15 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (10 mL) for 10 min turning the solution pink. A 10% HOAc in $CHCl_3$ solution (5 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure, purification by DCFC (Tol, 1% TEA) gave the title compound (**445**) in 61% (0.292 g) yield.

- 7-Methoxyflav-3-ene (**445**)[33] Yellow sticky oil residue/gum; R_f 0.86 (Tol, 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$, Plate 23A) δ ppm 7.47 (2H, dd, *J* = 1.55, 6.82 Hz, H-2'&6'), 7.39 (2H, dd, *J* = 6.82, 7.30 Hz, H-3'&5'), 7.34 (1H, dd, *J* = 1.55, 7.30 Hz, H-4'), 6.94 (1H, d, *J* = 8.25 Hz, H-5), 6.51 (1H, ddd, *J* = 0.45, 1.89, 9.83 Hz, H-4), 6.45 (1H, dd, *J* = 2.49, 8.25 Hz, H-6), 6.42 (1H, br d, *J* = 2.49 Hz, H-8), 5.90 (1H, dd, *J* = 1.89, 3.38 Hz, H-2), 5.68 (1H, dd, *J* = 3.38, 9.83 Hz, H-3), 3.76 (3H, s, O<u>C</u>H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, Plate 23C) δ ppm 161.0 (C-7), 154.5 (C-8a), 141.1 (C-1'), 128.8 (C-3'&5'), 128.5 (C-4'), 127.4 (C-5), 127.1 (C-2'&6'), 123.8 (C-4), 122.0 (C-3), 114.8 (C-4a), 107.1 (C-6), 101.9 (C-8), 77.4 (C-2), 55.42 (O<u>C</u>H$_3$); EIMS (*m/z*): 237 (M^+, 100%).

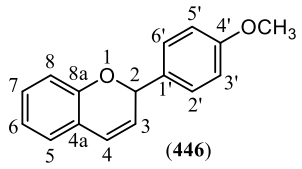


(**445**)

5.9.5 Preparation of 4'-Methoxyflav-3-ene (**446**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (3 x 2 mL) was added to a hot solution of 2'-hydroxy-4-methoxychalcone (**321**) (0.511 g, 2 mmol) in IPA (15 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (10 mL) for 10 min, turning the solution yellow. A 10% HOAc in $CHCl_3$ solution (5 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure. Purification of the crude product by DCFC (Tol, 1% TEA) gave the title compound (**446**) in a 42% (0.200 g) yield.

- 4'-Methoxyflav-3-ene (**446**)[34] Yellow sticky oily residue/gum; R_f 0.56 (H:EtOAc, 9:1, 1% TEA) and 0.86 (Tol, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 24A) δ ppm 7.39 (2H, d, *J* = 8.62 Hz, H-2'&6'), 7.11 (1H, ddd, *J* = 0.97, 7.42, 8.00 Hz, H-7), 7.02 (1H, dd, *J* = 0.97, 7.36 Hz, H-5), 6.90 (2H, d, *J* = 8.62 Hz, H-3'&5'), 6.87 (1H, br dd, *J* = 7.36, 7.42 Hz, H-6), 6.77 (H, br d, *J* = 8.00 Hz, H-8), 6.55 (1H, dd, *J* = 0.99, 9.84 Hz, H-4), 5.88 (1H, dd, *J* = 0.99, 3.42 Hz, H-2), 5.79 (1H, dd, *J* = 3.42, 9.84 Hz, H-3), 3.81 (3H, s, $OC\underline{H}_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 24C) δ ppm 159.9 (C-4'), 153.2 (C-8a), 133.0 (C-1'), 129.5 (C-7), 128.8 (C-2'&6'), 126.6 (C-5), 125.1 (C-3), 124.2 (C-4), 121.5 (C-4a), 121.2 (C-6), 116.2 (C-8), 114.1 (C-3'&5'), 76.9 (C-2), 55.4 ($O\underline{C}H_3$); EIMS (*m/z*): 238 (M^+, 88%).

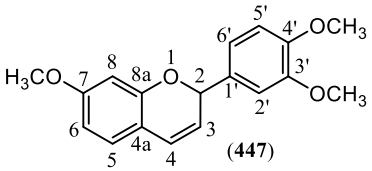


(**446**)

5.9.6 Preparation of 3',4',7-Trimethoxyflav-3-ene (**447**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (8 x 2 mL) was added to a hot solution of 2'-hydroxy-3',4',4-trimethoxychalcone (**376**) (1.00 g, 3.2 mmol) in IPA (30 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (20 mL) for 10 min turning the solution bright pink. A 10% HOAc in $CHCl_3$ solution (10 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure. Purification of the crude product by DCFC (Tol, 1% TEA) gave the title compound (**447**) in a 77% (0.734 g) yield.

- *3',4',7-Trimethoxyflav-3-ene* (**447**) Yellow sticky oily residue/gum; R_f 0.58 (Tol, 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$, Plate 25A) δ ppm 7.01 (1H, d, *J* = 1.99 Hz, H-2'), 6.99 (1H, dd, *J* = 1.99, 8.15 Hz, H-6'), 6.93 (1H, d, *J* = 8.28 Hz, H-5), 6.85 (1H, d, *J* = 8.15 Hz, H-5'), 6.51 (1H, dd, *J* = 1.88, 9.82 Hz, H-4), 6.43 (1H, dd, *J* = 2.48, 8.28 Hz, H-6), 6.38 (1H, d, *J* = 2.48 Hz, H-8), 5.82 (1H, dd, *J* = 1.88, 3.29 Hz, H-2), 5.65 (1H, dd, *J* = 3.29, 9.82 Hz, H-3), 3.870 (3H, s, 3'/4'-OC$\underline{H}_3$), 3.867 (3H, s, 3'/4'-OC$\underline{H}_3$), 3.74 (3H, s, 7-OC$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$, Plate 25C) δ ppm 161.0 (C-7), 154.4 (C-8a), 149.3 (C-3'/4'), 149.2 (C-3'/4'), 133.4 (C-1'), 127.3 (C-5), 124.0 (C-4), 122.0 (C-3), 119.9 (C-6'), 114.8 (C-4a), 111.1 (C-5'), 110.6 (C-2'), 107.1 (C-6), 101.9 (C-8), 77.4 (C-2), 56.02 (3'/4'-O$\underline{C}H_3$), 55.96 (3'/4'-O$\underline{C}H_3$), 55.4 (7-O$\underline{C}H_3$); EIMS (*m/z*): 298 (M^+, 30%); HRMS (*m/z*): $[M + Na]^+$ calculated for $C_{18}H_{18}O_4Na$: 321.1103; found, 321.1100.

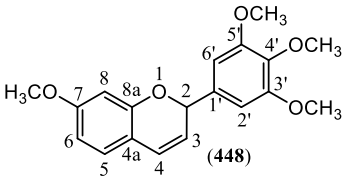


(**447**)

5.9.7 Preparation of 3',4',5',7-Tetramethoxyflav-3-ene (**448**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (7 x 2 mL) was added to a hot solution of 2'-hydroxy-3',4',4,5'-tetramethoxychalcone (**377**) (0.502 g, 1.5 mmol) in IPA (15 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (10 mL) for 10 min turning the solution pink. A 10% HOAc in $CHCl_3$ solution (5 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 4 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure, where after the title compound (**448**) was recrystallized form EtOH:H_2O (1:1) in a 64% (0.307 g) yield.

- 3',4',5',7-Tetramethoxyflav-3-ene (**448**)[35] Off-white plates; R_f 0.47 (H:EtOAc, 8:2, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 26A) δ ppm 6.94 (1H, d, *J* = 8.29 Hz, H-5), 6.69 (2H, s, H-2'&6'), 6.51 (1H, dd, *J* = 1.59, 9.79 Hz, H-4), 6.44 (1H, dd, *J* = 2.50, 8.29 Hz, H-6), 6.41 (1H, d, *J* = 2.50 Hz, H-8), 5.81 (1H, dd, *J* = 1.59, 3.16 Hz, H-2), 5.64 (1H, dd, *J* = 3.16, 9.79 Hz, H-3), 3.85 (3H, s, 3'&5'-OC$\underline{H}_3$), 3.84 (3H, s, 4'-OC$\underline{H}_3$), 3.76 (3H, s, 7-OC$\underline{H}_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 26C) δ ppm 161.1 (C-7), 154.5 (C-8a), 153.6 (C-3'&5'), 138.2 (C-4'), 136.6 (C-1'), 127.4 (C-5), 124.2 (C-4), 121.9 (C-3), 114.8 (C-4a), 107.3 (C-6), 104.5 (C-2'&6'), 102.0 (C-8), 77.8 (C-2), 60.9 (4'-O$\underline{C}H_3$), 56.3 (3'&5'-O$\underline{C}H_3$), 55.5 (7-O$\underline{C}H_3$); m.p. 89.7-91.1 °C; EIMS (*m/z*): 327 (M^+, 21%).

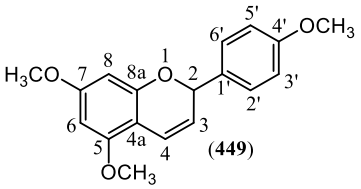


(**448**)

5.9.8 Preparation of 4',5,7-Trimethoxyflav-3-ene (**449**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (6 x 2 mL) was added to a hot solution of 2'-hydroxy-4,4',6'-trimethoxychalcone (**379**) (1.001 g, 3.2 mmol) in IPA (30 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (20 mL) for 10 min turning the solution dark pink/purple. A 10% HOAc in $CHCl_3$ solution (10 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure, where after the crude product was subjected to purification by DCFC (Tol, 1% TEA) and gave the title compound (**449**) in a 75% (0711 g) yield.

- 4',5,7-Trimethoxyflav-3-ene (**449**)[35] Yellow sticky oil/gum; R_f 0.60 (Tol, 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$, Plate 27A) δ ppm 7.39 (2H, d, *J* = 8.64 Hz, H-2'&6'), 6.89 (2H, d, *J* = 8.64 Hz, H-3'&5'), 6.82 (1H, dd, *J* = 1.82, 9.95 Hz, H-4), 6.03 (2H, s, H-6&8), 5.79 (1H, dd, *J* = 1.82, 3.49 Hz, H-2), 5.60 (1H, dd, *J* = 3.49, 9.95 Hz, H-3), 3.81 (3H, s, 4'/5/7-OC<u>H</u>$_3$), 3.80 (3H, s, 4'/5/7-OC<u>H</u>$_3$), 3.74 (3H, s, 4'/5/7-OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, Plate 27C) δ ppm 161.3 (C-5/7), 159.8 (C-4'), 156.3 (C-5/7), 155.0 (C-8a), 133.1 (C-1'), 128.9 (C-2'&6'), 119.9 (C-3), 118.9 (C-4), 114.1 (C-3'&5'), 104.6 (C-4a), 93.9 (C-6/8), 91.9 (C-6/8), 76.9 (C-2), 55.7 (4'/5/7-O<u>C</u>H$_3$), 55.44 (4'/5/7-O<u>C</u>H$_3$), 55.41 (4'/5/7-O<u>C</u>H$_3$); EIMS (*m/z*): 297 (M^+, 4%).

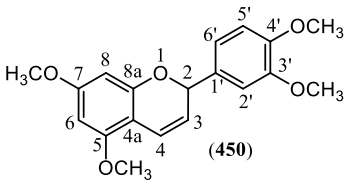


(**449**)

5.9.9 Preparation of 3',4',5,7-Tetramethoxyflav-3-ene (**450**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (8 x 2mL) was added to a hot solution of 2'-hydroxy-3',4,4',6'-tetramethoxychalcone (**380**) (0.500 g, 1.5 mmol) in IPA (15 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (10 mL) for 10 min turning the solution purple. A 10% HOAc in $CHCl_3$ solution (5 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure, where after the title compound (**450**) was recrystallized from EtOH:H_2O (1:1) in a 64% (0.337 g) yield.

- 3',4',5,7-tetramethoxyflav-3-ene (**450**)[27] Orange plates; R_f 0.34 (H:EtOAc, 8:2, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 28A) δ ppm 7.01 (1H, d, *J* = 1.84 Hz, H-2'), 7.00 (1H, dd, *J* = 1.84, 8.14 Hz, H-6'), 6.84 (1H, d, *J* = 8.14 Hz, H-5'), 6.82 (1H, dd, *J* = 1.60, 9.92 Hz, H-4), 6.04 (1H, d, *J* = 2.16 Hz, H-8), 6.03 (1H, d, *J* = 2.16 Hz, H-6), 5.77 (1H, dd, *J* = 1.60, 3.35 Hz, H-2), 5.59 (1H, dd, *J* = 3.35, 9.92 Hz, H-3), 3.873 (3H, s, 3'/4'-OC$\underline{H}_3$), 3.868 (3H, s, 3'/4'-OC$\underline{H}_3$), 3.80 (3H, s, 5-OC$\underline{H}_3$), 3.73 (3H, s, 7-OC$\underline{H}_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 28C) δ ppm 161.4 (C-7), 156.4 (C-5), 155.0 (C-8a), 149.3 (C-3'), 149.2 (C-4'), 133.5 (C-1'), 120.0 (C-6'), 119.9 (C-3), 119.1 (C-4), 111.1 (C-5'), 110.7 (C-2'), 104.6 (C-4a), 93.9 (C-8), 92.0 (C-6), 77.3 (C-2), 56.1 (3'/4'-O$\underline{C}H_3$), 56.0 (3'/4'-O$\underline{C}H_3$), 55.7 (C-5), 55.5 (C-7); m.p. 118.3-119.5 °C (Lit.[27] 119.5 °C); EIMS (*m/z*): 328 (M^+, 100%).

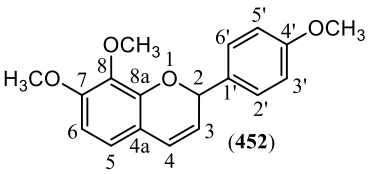


(**450**)

5.9.10 Preparation of 4',7,8-Trimethoxyflav-3-ene (**452**)

Method: Performed according to general flav-3-ene synthesis method; A hot (75 °C) sat. $NaBH_4$ (4 x 2mL) was added to a hot solution of 2'-hydroxy-3',4,4'-trimethoxychalcone (**382**) (0.498 g, 1.6 mmol) in IPA (15 mL). After stirring overnight at RT, the solvent was evaporated under reduced pressure at 25 °C and the borate complex gently boiled under Ar atmosphere in $CHCl_3$ (10 mL) for 10 min turning the solution pink. A 10% HOAc in $CHCl_3$ solution (5 mL) was slowly added to a slightly cooled RM and then refluxed under Ar for 3 h, where after an excess K_2CO_3 was added and the solvent evaporated under reduced pressure. The solid residue was dissolved in Et_2O, filtered and the filtrate concentrated under reduced pressure, where after the title compound (**452**) was recrystallized from MeOH:H_2O (1:1) in a 76% (0.360 g) yield.

- 4',7,8-Trimethoxyflav-3-ene (**452**)[22] White glistening plates; R_f 0.44 (H:EtOAc, 8:2, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 29A) δ ppm 7.38 (2H, d, *J* = 8.70 Hz, H-2'&6'), 6.86 (2H, d, *J* = 8.70 Hz, H-3'&5'), 6.72 (1H, d, *J* = 8.37 Hz, H-5), 6.52 (1H, dd, *J* = 1.44, 9.85 Hz, H-4), 6.43 (1H, d, *J* = 8.37 Hz, H-6), 5.88 (1H, dd, *J* = 1.44, 3.77 Hz, H-2), 5.73 (1H, dd, *J* = 3.77, 9.85 Hz, H-3), 3.82 (3H, s, 7-O$\underline{C}H_3$), 3.78 (3H, s, 4'-O$\underline{C}H_3$), 3.67 (3H, s, 8-O$\underline{C}H_3$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 29C) δ ppm 159.8 (C-4'), 153.9 (C-7), 146.4 (C-8a), 137.5 (C-8), 132.5 (C-1'), 128.8 (C-2'&6'), 123.8 (C-4), 122.6 (C-3), 121.1 (C-5), 116.6 (C-4a), 114.0 (C-3'&5'), 104.2 (C-6), 76.6 (C-2), 61.0 (7-O$\underline{C}H_3$), 56.1 (4'-O$\underline{C}H_3$), 55.4 (8-O$\underline{C}H_3$); m.p. 72.8-74.3 °C (Lit.[27] 75.5 °C); EIMS (*m/z*): 298 (M^+, 100%).



(**452**)

5.10 Dimethyldioxirane

5.10.1 Set up and Procedure

Method A:[36] See Figure 5.1 for set up, three neck reaction flask connected to receiving flask, through two condensers, equipped with a cold condenser (acetone and dry ice) which is further connected to the vacuum; Under inert atmosphere (Ar) Oxone® (180 g, 0.29 mol) was added in portions to a cooled (ice-bath) mixture of water (80 mL), acetone (50 mL, 0.68 mol) and $NaHCO_3$ (96 g, 1.14 mol), simultaneously an additional mixture of acetone (60 mL, 0.82 mol) and water (60 mL) was added dropwise over a 30 min period. The RM was vigorously stirred throughout the reaction and after complete addition of regents a slight vacuum (100-80 Torr) was applied, collecting a 13 mL yellow solution of dimethyldioxirane (DMDO) in acetone in the cooled (dry ice and acetone bath) receiving flask and stored in the freezer.

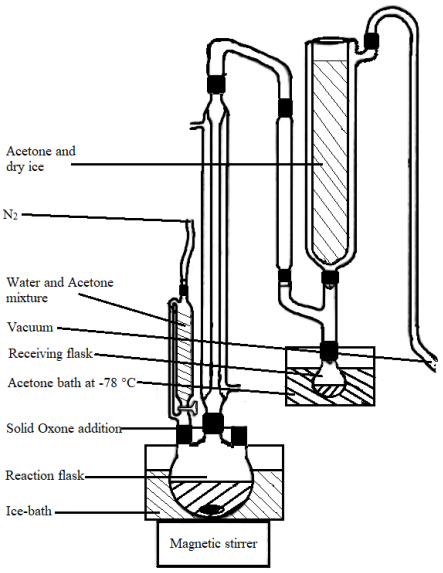


Figure 5.1

Method B:[37] See Figure 5.2 for set up, three neck reaction flask connected to receiving flask equipped with a cold condenser (acetone and dry ice) which is further connected to the vacuum; Oxone® (120 g, 0.2 mol) was added in portions over 3 min intervals to a cooled (ice-bath) mixture of water (254 mL), acetone (192 mL, 2.6 mol) and $NaHCO_3$ (58 g, 0.7 mol) while vigorously stirred throughout addition. About 5 min after complete addition of the reagents a slight vacuum was applied (ca. 100-80 Torr) and ice-bath removed from the reaction flask and the RM left to stir at RT for 2 h (until bubbling subsided). A 10 mL (1.3 mmol, 0.13 M) yellow solution of dimethyldioxirane (DMDO) in acetone was collected in the cooled (-78 °C) receiving flask and stored in the freezer, DMDO standardized via Method A of section 5.9.2.

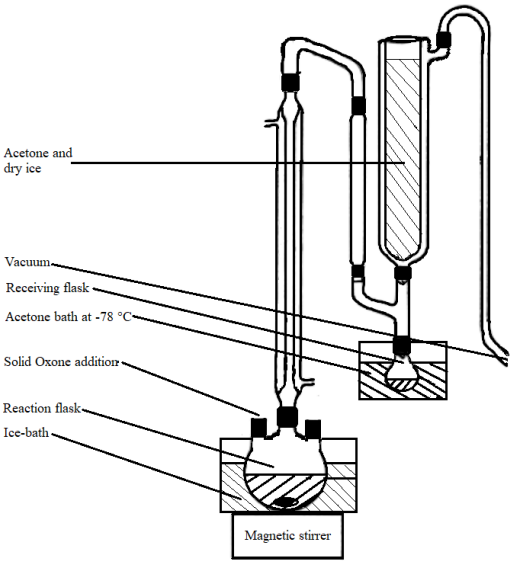


Figure 5.2

Method C:[38,39] Set up volume reduced, see Figure 5.3, three neck reaction flask was directly connected, with a u-bent glass tube and a dip tube, to the receiving flask equipped with a cold condenser (acetone and dry ice). Oxone® (60 g, 0.10 mol) was added in portions over 3 min intervals to a cooled (ice-bath) mixture of water (130 mL), distilled acetone (100 mL, 1.36 mol) and $NaHCO_3$ (29 g, 0.35 mol) while vigorously stirred throughout addition of the Oxone®. About 5 min after complete addition of the Oxone®, the ice-bath was removed from the reaction flask and the RM left to stir at RT for 2 h (until bubbling subsided). An 11 mL (0.15 mmol, 0.01 M) yellow solution of DMDO in acetone was collected in the cooled (-78 °C) receiving flask with DMDO standardized via Method B of section 5.9.2.

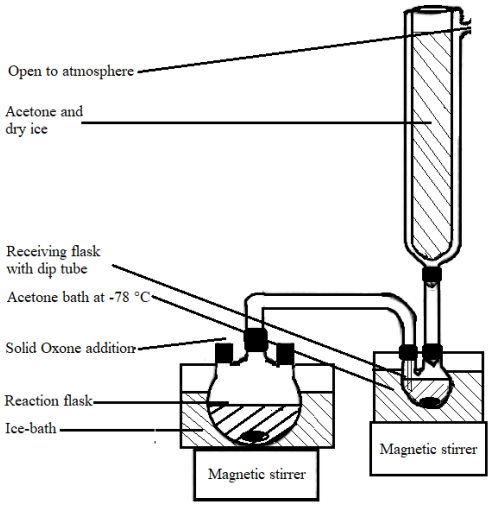


Figure 5.3

Method D:[37] For alteration in set up see Figure 5.4, three neck reaction flask equipped with a solid addition flask was directly connected, with a u-bend glass tube and a dip tube, to the receiving flask equipped with a cold condenser (acetone and dry ice). Performed according to Method C; A yellow solution of DMDO (11 mL, 0.3 mmol, 0.03 M) in acetone was collected in the cooled (-78 °C) receiving flask with DMDO standardized via Method B of section 5.9.2.

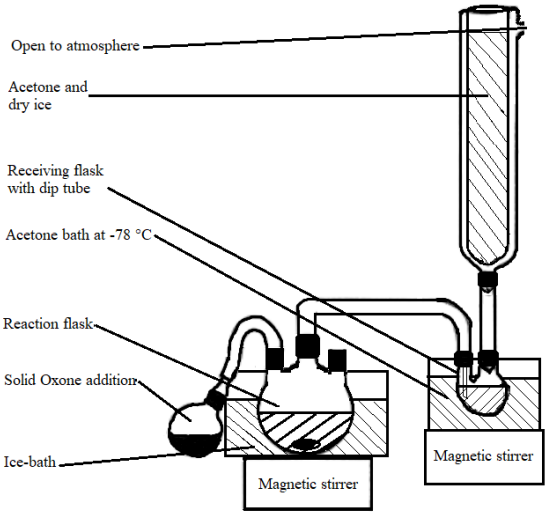


Figure 5.4

Method E: For set up see Figure 5.5, three neck reaction flask equipped with a solid addition flask was directly connected, with a u-bend glass tube and a dip tube, to the receiving flask equipped with a cold condenser (acetone and dry ice) and linked to the vacuum. Oxone® (30 g, 0.05 mol) was added in portions over 3 min intervals to a cooled (ice-bath) mixture of water (65 mL), distilled acetone (50 mL, 0.68 mol) and $NaHCO_3$ (15 g, 0.18 mol) while vigorously stirred throughout addition. About 5 min after complete addition of Oxone®, a slight vacuum was applied (130 Torr) for 1 h (until bubbling subsided). At the same time the ice-bath was removed from the reaction flask and left to stir at RT for a few minutes and a yellow solution of DMDO in acetone was collected in the cooled (-78 °C) receiving flask. Procedure was repeated three times and DMDO standardized via Method B of section 5.9.2 to obtain the average mmol/concentration reported.

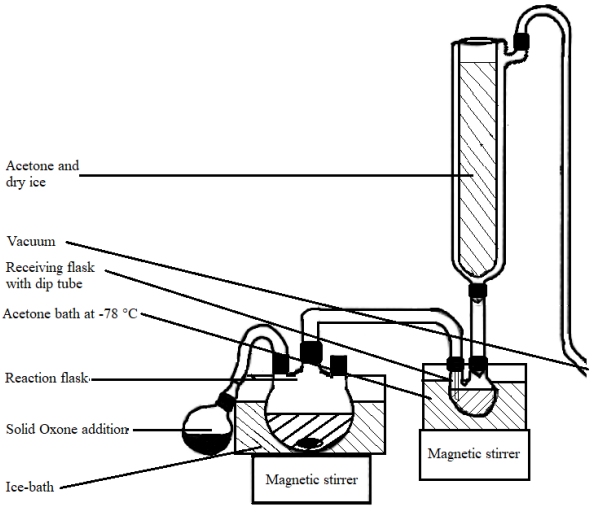


Figure 5.5

1) Volume: 12 mL; n: 1.5 mmol; Concentration: 0.12 M

2) Volume: 11 mL; n: 1.1 mmol; Concentration: 0.10 M

3) Volume: 11 mL; n: 1.2 mmol; Concentration: 0.11 M

Average: n: 1.3 mmol and Concentration: 0.11 M

5.10.2 DMDO Standardization

Method A:[36] Standard solutions of both thioanisole and dodecane were prepared in acetone with a concentration of 0.2 M. The DMDO concentration/mol was determined in triplicate, by combining 1 mL of each solution (DMDO, thioanisole and dodecane) in a vial and stirred. After a few minutes, GC analysis was carried out on 1 µL of solution, with the response factors (RF) predetermined (section 5.1.5) and the quantity of DMDO obtained was determined by measuring the thiol concentration/mol before and after oxidation. See Table 5.3 for GC program and retention times.

Method B: Receiving flask contained thioanisole (0.10 g, 0.8 mmol) and dodecane (0.14 g, 0.8 mmol) in DCM (2.5 mL) equipped with a magnetic stirrer. Reaction was carried out as mentioned in DMDO methods C to E, aliquots (1 mL) of the RM before and after oxidation was analysed by GC on 1 µL of solution, with the response factors (RF) predetermined (section 5.1.5), the mol DMDO

obtained was determined by measuring the thiol concentration/mol before and after oxidation in triplicate. See Table 5.3 for GC program and retention times.

Table 5.3: GC program for DMDO standardization.[a]

Ramp (°C/min)	Temperature (°C)	Hold time (min)
-	70	5
10	160	1
25	250	2

[a] Retention times observed: Sulfide, 7.42 min; dodecane, 9.80 min; sulfoxide, 11.87 min; sulfone 12.79 min.

5.11 Epoxidation Reactions

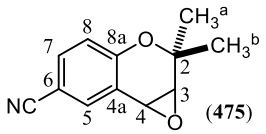
5.11.1 General Procedures

Method: Performed with set up and procedure of Method E, section 5.10.1; DMDO (3.3 eq) solution was distilled over to a cooled (-78 °C) receiving flask containing a solution of either a corresponding flav-3-ene or chromene (1 eq) and the appropriate nucleophile (2 eq) in either DCM or acetone (30 mL/g_{SM}). Reaction was allowed to stir at -78 °C for 1 h while under vacuum (130 Torr) where after any further temperature alterations and purification methods are further specified below.

5.11.2 Epoxidation of 6-Cyano-2,2-dimethylchromene (**474**)

Method:[40] DMDO (7 mL, 0.19 M) was rapidly added to a cooled (ice-bath) stirred solution of 6-cyano-2,2-dimethylchromene (0.0995 g, 0.54 mmol) in DCM (2.5 mL). The RM was allowed to slowly reach RT and stirred for 1 h where after the solvent was removed under reduced pressure at 25 °C. Purification by FCC (H:EtOAc, 8:2, 1% TEA) gave a compound with an R_f 0.36 in a 91% (0.0998 g) yield.

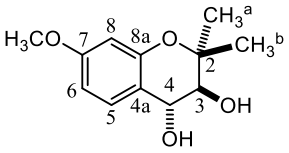
- 6-Cyano-2,2-dimethylchromane oxide (**475**)[41] Off-white crystals; R_f 0.36 (H:EtOAc, 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 31A) δ ppm 7.65 (1H, d, *J* = 1.80 Hz, H-5), 7.52 (1H, dd, *J* = 1.80, 8.47 Hz, H-7), 6.86 (1H, d, *J* = 8.47 Hz, H-8), 3.91 (1H, d, *J* = 4.33 Hz, H-4), 3.53 (1H, d, *J* = 4.33 Hz, H-3), 1.59 (3H, s, $CH_3^{a/b}$), 1.29 (3H, s, $CH_3^{a/b}$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 31C) δ ppm 156.6 (C-8a), 134.5 (C-7), 133.9 (C-5), 121.2 (C-4a), 119.2 (C-8), 118.9 (CN), 104.5 (C-6), 74.8 (C-2), 62.4 (C-3), 50.0 (C-4), 25.6 ($CH_3^{a/b}$), 23.2 ($CH_3^{a/b}$); EIMS (*m/z*): 201 (M^+, 61%).



5.11.3 Epoxidation of Precocene I (**485**)

Method A: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of precocene I (0.095 g, 0.5 mmol) and dimethylresorcinol (0.145 g, 1 mmol, 2 eq) in DCM (3 mL). The RM was kept at -78 °C for 1 h, where after vacuum was removed and the RM left at -50 °C for 1 h, after which the RM was allowed to slowly reach RT and stirred overnight at RT. Once TLC indicated the depletion of the starting material, the solvent was removed under reduced pressure at 25 °C and the crude product was subjected to purification via PLC (H:C, 9:1, 1% TEA), which provided two off-white products with R_f 0.28 and 0.33 in yields of 28 (0.037 g) and 15% (0.020 g), respectively. These products were accompanied by 3,4-*cis*-(**490**) and 3,4-*trans*-7-methoxy-2,2-dimethylchroman-3,4-diols (**488**), R_f 0.11 (H:C, 9:1, 1% TEA), collectively isolated in 36% (0.042 g) as a yellow oil (in a ratio of 1:3).

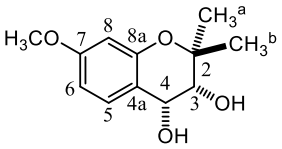
- 3,4-*trans*-7-Methoxy-2,2-dimethylchroman-3,4-diol (**488**)[42]



(**488**)

Yellow to orange oil; R_f 0.11 (H:C, 9:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 33A) δ ppm 7.28 (1H, d, *J* = 8.56 Hz, H-5), 6.52 (1H, dd, *J* = 2.41, 8.56 Hz, H-6), 6.32 (1H, d, *J* = 2.41 Hz, H-8), 4.46 (1H, d, *J* = 8.38 Hz, H-4), 3.75 (3H, s, OCH_3), 3.52 (1H, d, *J* = 8.38 Hz, H-3), 3.29 (1H, br s, $OH^{3/4}$), 2.95 (1H, br s, $OH^{3/4}$), 1.45 (3H, s, $CH_3^{a/b}$), 1.19 (3H, s, C), 1.19 (3H, s, $CH_3^{a/b}$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 33C) δ ppm 160.9 (C-7), 153.5 (C-8a), 128.3 (C-5), 115.7 (C-4a), 108.1 (C-6), 101.35 (C-8), 78.7 (C-2), 76.9 (C-3), 69.8 (C-4), 55.4 (OCH_3), 26.7 ($CH_3^{a/b}$), 19.0 ($CH_3^{a/b}$); EIMS (*m/z*): 223 (M^+, 16%).

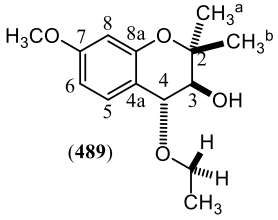
- 3,4-*cis*-7-Methoxy-2,2-dimethylchroman-3,4-diol (**490**)[43]



(**490**)

Yellow to orange oil; R_f 0.11 (H:C, 9:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 33A) δ ppm 7.37 (1H, d, *J* = 8.56 Hz, H-5), 6.55 (1H, dd, *J* = 2.44, 8.56 Hz, H-6), 6.35 (1H, d, *J* = 2.44 Hz, H-8), 4.73 (1H, br s, H-4), 3.74 (3H, s, OCH_3), 3.64 (1H, br s, H-3), 2.90 (1H, br s, $OH^{3/4}$), 2.59 (1H, br s, $OH^{3/4}$), 1.46 (3H, s, $CH_3^{a/b}$), 1.27 (3H, s, $CH_3^{a/b}$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 33C) δ ppm 160.8 (C-7), 153.3 (C-8a), 129.7 (C-5), 114.5 (C-4a), 108.6 (C-6), 101.41 (C-8), 78.2 (C-2), 71.7 (C-3), 65.2 (C-4), 55.4 (OCH_3), 24.8 ($CH_3^{a/b}$), 23.6 ($CH_3^{a/b}$); EIMS (*m/z*): 223 (M^+, 16%).

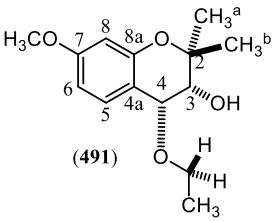
- *3,4-trans-4-Ethoxy-7-methoxy-2,2-dimethylchroman-3-ol* (**489**)



Off-white solid; R_f 0.28 (H:C, 9:1, 1% TEA); ^{1}H NMR (600 MHz, C_6D_6, Plate 34A) δ ppm 7.30 (1H, d, *J* = 8.53 Hz, H-5), 6.61 (1H, dd, *J* = 2.51, 8.53 Hz, H-6), 6.56 (1H, d, *J* = 2.51 Hz, H-8), 4.32 (1H, d, *J* = 7.27 Hz, H-4), 3.68 (1H, dd, *J* =

4.81, 7.27 Hz, H-3), 3.52-3.43 (2H, m, OC<u>H</u>$_2$CH$_3$), 3.14 (3H, s, OC<u>H</u>$_3$), 2.03 (1H, d, *J* = 4.81 Hz, O<u>H</u>), 1.44 (3H, s, C<u>H</u>$_3^{a/b}$), 1.25 (3H, s, C<u>H</u>$_3^{a/b}$), 1.12 (3H, t, *J* = 6.99 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (151 MHz, C_6D_6, Plate 34C) δ ppm 161.3 (C-7), 154.6 (C-8a), 129.8 (C-5), 114.5 (C-4a), 108.5 (C-6), 101.9 (C-8), 78.5 (C-2), 77.3 (C-4), 73.5 (C-3), 64.5 (O<u>C</u>H$_2$CH$_3$), 54.8 (O<u>C</u>H$_3$), 26.2 (<u>C</u>H$_3^{a/b}$), 20.4 (<u>C</u>H$_3^{a/b}$), 16.0 (OCH$_2$<u>C</u>H$_3$); HRMS (*m/z*): [M + Na]$^+$ calculated for $C_{14}H_{20}O_4Na$: 275.1259; found, 275.1265; EIMS (*m/z*): 251 (M$^+$, 18%).

- <u>*3,4-cis-4-Ethoxy-7-methoxy-2,2-dimethylchroman-3-ol*</u> (**491**)



Off-white solid; R_f 0.33 (H:C, 9:1, 1% TEA); ^{1}H NMR (600 MHz, C_6D_6, Plate 35A) δ ppm 7.31 (1H, d, *J* = 8.54 Hz, H-5), 6.64 (1H, dd, *J* = 2.51, 8.54 Hz, H-6), 6.58 (1H, d, *J* = 2.51 Hz, H-8), 4.18 (1H, d, *J* = 4.29 Hz, H-4), 3.60 (1H, d, *J* = 4.29 Hz, H-3), 3.33-3.24 (2H, m, OC<u>H</u>$_2$CH$_3$), 3.27 (3H, s, OC<u>H</u>$_3$), 1.56 (3H, s, CH$_3^{a/b}$), 1.15 (3H, s, CH$_3^{a/b}$), 1.01 (3H, t, *J* = 6.98 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (151 MHz, C_6D_6, Plate 35C) δ ppm 161.5 (C-7), 154.8 (C-8), 130.4 (C-5), 112.4 (C-4a), 108.2 (C-6), 101.6 (C-8), 77.6 (C-2), 73.3 (C-4), 68.8 (C-3), 64.7 (O<u>C</u>H$_2$CH$_3$), 54.8 (O<u>C</u>H$_3$), 24.6 (<u>C</u>H$_3^{a/b}$), 24.3 (<u>C</u>H$_3^{a/b}$), 15.5 (OCH$_2$<u>C</u>H$_3$); HRMS (*m/z*): [M + Na]$^+$ calculated for $C_{14}H_{20}O_4Na$: 275.1259; found, 275.1265; EIMS (*m/z*): 251 (M$^+$, 18%).

<u>Method B:</u> Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of precocene I (0.1 g, 0.5 mmol) and EtOH (0.06 mL, 1 mmol, 2 eq) in DCM (3 mL). The RM was kept at -78 °C for 1 h after vacuum was removed and a further hour at -50 °C, after which the RM was allowed to slowly reach RT and stirred overnight at RT where after TLC indicated the depletion of the starting material. After removal of the solvent under reduced pressure at 25 °C the crude product was subjected to purification via PLC (H:EtOAc, 8:2, 1% TEA) and gave the off-white minor and major products, of *3,4-cis-4-Ethoxy-7-methoxy-2,2-dimethylchroman-3-ol* (**491**) (4%, 0.006 g) and *3,4-trans-4-Ethoxy-7-methoxy-2,2-dimethylchroman-3-ol* (**489**) (24%, 0.039 g), accompanied by 3,4-*cis*-(**490**) and 3,4-*trans*-7-methoxy-2,2-dimethylchroman-3,4-diol (**488**) in a 46% yield (0.067 g) collectively isolated as a yellow oil (in a ratio of 1:2).

- <u>3,4-*trans*-7-Methoxy-2,2-dimethylchroman-3,4-diol (**488**)</u>[42] Yellow to orange oil; R_f 0.11 (H:EtOAc, 8:2); see the above section 5.11.3, Method A for characterization.

- <u>3,4-*cis*-7-Methoxy-2,2-dimethylchroman-3,4-diol (**490**)</u>[43] Yellow to orange oil; R_f 0.11 (H:EtOAc, 8:2); see the above section 5.11.3, Method A for characterization.

- <u>*3,4-trans-4-Ethoxy-7-methoxy-2,2-dimethylchroman-3-ol* (**489**)</u> Off-white solid; R_f 0.39 (H:EtOAc, 8:2); see the above section 5.11.3, Method A for characterization.

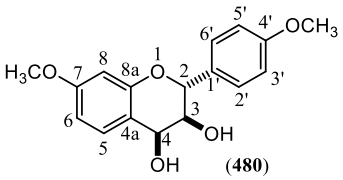
- *3,4-cis-4-Ethoxy-7-methoxy-2,2-dimethylchroman-3-ol* (**491**) Off-white solid; R_f 0.47 (H: EtOAc, 8:2); see the above section 5.11.3, Method A for characterization.

Method C: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of precocene I (0.1 g, 0.5 mmol) in acetone (3 mL). The RM was kept at -78 °C for 1 h after vacuum was removed and a further hour at -50 °C, after which the RM was allowed to slowly reach RT and stirred overnight at RT where after TLC indicated the depletion of the starting material. After removal of the solvent under reduced pressure at 25 °C, the crude product was subjected to purification via PLC (H:EtOAc, 8:2, 1% TEA) and gave 3,4-*cis*-(**490**) and 3,4-*trans*-7-methoxy-2,2-dimethylchroman-3,4-diol (**488**) in a 77% (0.103 g) collective yield as a yellow oil (in a ratio of 1:2).

5.11.4 Preparation of 4',7-Dimethoxyflavan-3,4-diol (**480**)

Method A:[44] DMDO (11 mL, ca. 0.07-0.09 M, ca. 2 eq) was rapidly added into a cooled (-10 °C) stirred solution of 4',7-dimethoxyflav-3-ene (**420**) (0.101 g, 0.4 mmol) in acetone (1 mL) and allowed to slowly reach 0 °C. After 30 min at 0 °C TLC indicated depletion of starting material and solvent was removed under reduced pressure at 25 °C. Purification by PLC (C, 1% TEA) generated one diastereoisomer of the title compound (**480**) in a 67% (0.072 g) yield.

- 2,3-*trans*-3,4-*cis*-4',7-Dimethoxyflavan-3,4-diol (**480**)[45]



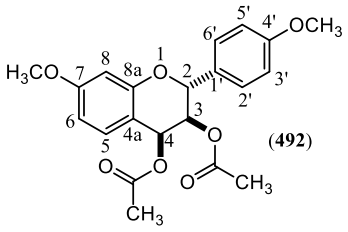
(**480**)

Off-white solid; R_f 0.44 (C, 1% TEA) and 0.11 (H:EtOAc, 7:3, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 32A) δ ppm 7.40 (2H, d, *J* = 8.63 Hz, H-2'&6'), 7.25 (1H, d, *J* = 8.49 Hz, H-5), 6.96 (2H, d, *J* = 8.63 Hz, H-3'&5'), 6.58 (1H, dd, *J* = 2.46, 8.49 Hz, H-6), 6.46 (1H, d, *J* = 2.46 Hz, H-8), 4.98 (1H, d, *J* = 9.71 Hz, H-2), 4.74 (1H, d, *J* = 3.55 Hz, H-4), 4.02 (1H, dd, *J* = 3.55, 9.71 Hz, H-3), 3.82 (3H, s, 4'-OCH_3), 3.76 (3H, s, 7-OCH_3), 2.67 (1H, br s, $OH^{3/4}$), 2.25 (1H, br s, $OH^{3/4}$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 32C) δ ppm 161.5 (C-7), 160.2 (C-4'), 155.5 (C-8a), 131.7 (C-5), 129.5 (C-1'), 129.1 (C-2'&6'), 114.6 (C-4a), 114.4 (C-3'&5'), 108.9 (C-6), 101.2 (C-8), 76.4 (C-2), 71.2 (C-3), 66.1 (C-4), 55.5 (4'&7-OCH_3); EIMS (*m/z*): 302 (M^+, 5%).

Method B: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 4',7-dimethoxyflav-3-ene (**420**) (0.097 g, 0.4 mmol) in acetone (3 mL). The RM was kept at -78 °C overnight where after it was allowed to slowly reach RT and TLC indicated the depletion of the starting material. After solvent removal, under reduced pressure, the RM was subjected to acetylation. Two drops of dried pyridine and one drop acetic anhydride were added for 1 mg of crude product, where after the solution was heated for 2 h at 40 °C. The RM was poured over ice and the ppt filtered off and thoroughly washed with H_2O. The

precipitate was subjected to purification via PLC (H:EtOAc:MeOH, 6:3:1, 1% TEA) and gave a product with a R_f 0.78 in a 42% (0.059 g) yield.

- 2,3-*trans*-3,4-*cis*-3,4-Diacetoxy-4',7-dimethoxyflavan (**492**)[46]



(**492**)

Colourless oil; R_f 0.78 (H:EtOAc:MeOH, 3:3:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 36A) δ ppm 7.37, (2H, d, *J* = 8.68 Hz, H-2'&6'), 7.19 (1H, d, *J* = 8.58 Hz, H-5), 6.91 (2H, d, *J* = 8.68 Hz, H-3'&5'), 6.55 (1H, dd, *J* = 2.48, 8.58 Hz, H-6), 6.47 (1H, d, *J* = 2.48 Hz, H-8), 6.16 (1H, d, *J* = 3.50 Hz, H-4), 5.44 (1H, dd, *J* = 3.50, 10.35 Hz, H-3), 5.22 (1H, d, *J* = 10.35 Hz, H-2), 3.82 (3H, s, 4'-OC$\underline{H}_3$), 3.76 (3H, s, 7-OC$\underline{H}_3$), 2.13 [3H, s, 4-OC(O)C$\underline{H}_3$], 1.84 [3H, s, 3-OC(O)C$\underline{H}_3$]; ^{13}C NMR (151 MHz, $CDCl_3$, Plate 36C) δ ppm 170.6 (4-O$\underline{C}$(O)CH_3), 169.4 (3-O$\underline{C}$(O)CH_3), 161.9 (C-7), 160.1 (C-4'), 155.9 (C-8a), 131.8 (C-5), 128.9 (C-2'&6'), 128.8 (C-1'), 114.0 (C-3'&5'), 111.1 (C-4a), 108.9 (C-6), 101.2 (C-8), 74.9 (C-2), 70.0 (C-3), 66.4 (C-4), 55.5 (7-O$\underline{C}H_3$), 55.4 (4'-O$\underline{C}H_3$), 21.3 (4-OC(O)$\underline{C}H_3$), 20.6 (3-OC(O)$\underline{C}H_3$); EIMS (*m/z*): 386 (M^+, 3%).

Method C: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 4',7-dimethoxyflav-3-ene (**420**) (0.097 g, 0.4 mmol) in acetone (3 mL). The RM was kept at -78 °C overnight where after it was allowed to slowly reach RT and TLC indicated the depletion of the starting material. Removing the solvent under reduced pressure gave the 2,3-*trans*-3,4-*cis*-4',7-dimethoxyflavan-3,4-diol (**480**) in a 91% (0.099 g) yield (see Method A mentioned above for characterization).

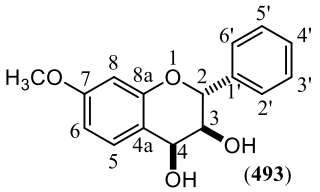
Method D: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 4',7-dimethoxyflav-3-ene (**420**) (0.096 g, 0.4 mmol) in acetone (3 mL). The RM was kept at -78 °C for the duration of the DMDO addition where after the receiving flask was removed from the acetone bath and allowed to stir at RT for 15 min where after TLC indicated complete consumption of starting material. Removing the solvent under reduced pressure gave the 2,3-*trans*-3,4-*cis*-4',7-dimethoxyflavan-3,4-diol (**480**) in a 90% (0.097 g) yield (see Method A mentioned above for characterization).

5.11.5 Preparation of 7-Methoxyflavan-3,4-diol (**493**)

Method: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 7-methoxyflav-3-ene (**445**) (0.105 g, 0.4 mmol) in acetone (3 mL). The RM was kept at -78 °C for the duration of the DMDO addition where after the receiving flask was removed from the acetone bath and allowed to stir at RT for 15 min where after TLC indicated complete consumption of starting material. After removing the solvent under reduced

pressure, purification via PLC (H:EtOAc, 8:2, 1% TEA) gave one diastereoisomer of the title compound (**493**) in a 34% (0.041 g) yield.

- 2,3-*trans*-3,4-*cis*-7-Methoxyflavan-3,4-diol (**493**)[47,48]



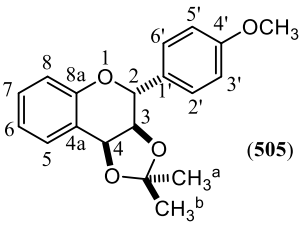
(**493**)

White solid; R_f 0.19 (H:EtOAc, 8:2, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 37A) δ ppm 7.48 (2H, dd, *J* = 1.37, 7.10 Hz, H-2'&6'), 7.43 (2H, dd, *J* = 7.10, 7.43 Hz, H-3'&5'), 7.41-7.37 (1H, m, H-4'), 7.27 (1H, d, *J* = 8.47 Hz, H-5), 6.59 (1H, dd, *J* = 2.49, 8.47 Hz, H-6), 6.48 (1H, d, *J* = 2.49 Hz, H-8), 5.05 (1H, d, *J* = 9.52 Hz, H-2), 4.74 (1H, *J* = 3.57 Hz, H-4), 4.04 (1H, dd, *J* = 3.57, 9.52 Hz, H-3), 3.77 (3H, s, 7-OCH_3), 2.62 (1H, br s, 3/4-OH), 2.24 (1H, br s, 3/4-OH); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 37C) δ ppm 161.5 (C-7), 155.4 (C-8a), 137.7 (C-1'), 131.6 (C-5), 129.0 (C-4'), 128.9 (C-3'&5'), 127.7 (C-2'&6'), 114.6 (C-4a), 108.9 (C-6), 101.2 (C-8), 76.9 (C-2), 71.3 (C-3), 65.9 (C-4), 55.5 (7-OCH_3); EIMS (*m/z*): 272 (M^+, 20%).

5.11.6 Preparation of 4'-Methoxyflavan-3,4-diol (**494**/**495**)

Method: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 4'-methoxyflav-3-ene (**446**) (0.100 g, 0.4 mmol) in acetone (3 mL). The RM was kept at -78 °C for the duration of the DMDO addition where after the receiving flask was removed from the acetone bath and allowed to stir at RT for 15 min, TLC indicated complete consumption of starting material. After removing the solvent under reduced pressure and purification via PLC (H:EtOAc, 8:2, 1% TEA) a white solid with R_f 0.53 (H:EtOAc, 8:2, 1% TEA) in a 4% (0.005 g) yield was obtained. It was accompanied by 2,3-*trans*-3,4-*cis*-4'-methoxyflavan-3,4-diol (**494**) and 2,3-*trans*-3,4-*trans*-4'-methoxyflavan-3,4-diol (**495**), collectively isolated as a white solid in a 44% yield (0.050 g) (ratio of 3:1); R_f 0.28 (H:EtOAc, 8:2, 1% TEA); EIMS (*m/z*): 272 (M^+, 16%).

- 2,3-*trans*-3,4-*cis*-3,4-*O*-Isopropylidene-4'-methoxyflavan* (**505**)[47,48]

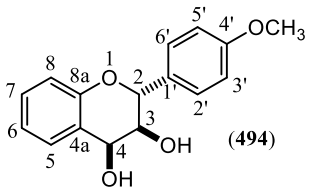


(**505**)

White solid; R_f 0.53 (H:EtOAc, 8:2, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 38) δ ppm 7.48 (1H, dd, *J* = 1.44, 7.58 Hz, H-5), 7.42 (2H, d, *J* = 8.68 Hz, H-2'&6'), 7.28 (1H, ddd, *J* = 1.44, 7.24, 8.19 Hz, H-7), 7.05 (1H, td, *J* = 1.02, 7.58 Hz, H-6), 7.00 (1H, br d, *J* = 8.19 Hz, H-8), 6.96 (2H, d, *J* = 8.68 Hz, H-3'&5'), 5.14 (1H, d, *J* = 5.53 Hz, H-4), 4.54 (1H, d, *J* = 9.84 Hz, H-2), 4.34 (1H, dd, *J* = 5.53, 9.84 Hz, H-3), 3.83 (3H, s, 4'-OCH_3), 1.56 (3H, s, $CH_3^{a/b}$), 1.49 (3H, s, $CH_3^{a/b}$); EIMS (*m/z*): 312 (M^+, 15%).

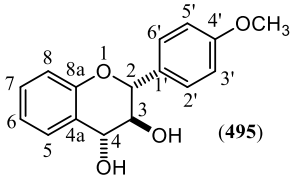
NOTE:* Due to an insufficient quantity ^{13}C experiment was not successful, refer to (507**).

- 2,3-*trans*-3,4-*cis*-4'-Methoxyflavan-3,4-diol (**494**)[47,48]



White solid; R_f 0.28 (H:EtOAc, 8:2, 1% TEA);[1]H NMR (600 MHz, $CDCl_3$, Plate 39A) δ ppm 7.42 (2H, d, *J* = 8.62 Hz, H-2'&6'), 7.39 (1H, dd, *J* = 1.56, 7.57 Hz, H-5), 7.28 (1H, ddd, *J* = 1.56, 8.21, 8.48 Hz, H-7), 7.00 (1H, ddd, *J* = 0.98, 7.57, 8.48 Hz, H-6), 6.97 (2H, d, *J* = 8.62 Hz, H-3'&5'), 8.21 (1H, br d, *J* = 8.21 Hz, H-8), 5.04 (1H, d, *J* = 9.44 Hz, H-2), 4.83 (1H, dd, *J* = 3.38, 3.78 Hz, H-4), 4.09 (1H, ddd, *J* = 3.62, 5.43, 9.44 Hz, H-3), 3.84 (3H, s, OCH_3), 2.62 (1H, d, *J* = 3.38, Hz, 4-OH), 2.08 (1H, d, *J* = 5.43 Hz, 3-OH); [13]C NMR (151 MHz, $CDCl_3$, Plate 39C) δ ppm 160.3 (C-4'), 154.4 (C-8a), 131.97 (C-5), 130.5 (C-7), 129.5 (C-1'), 129.1 (C-2'&6'), 122.3 (C-4a), 121.4 (C-6), 117.1 (C-8), 114.50 (C-3'&5'), 76.5 (C-2), 71.2 (C-3), 66.3 (C-4), 55.53 (OCH_3); EIMS (*m/z*): 272 (M^+, 16%).

- 2,3-*trans*-3,4-*trans*-4'-Methoxyflavan-3,4-diol* (**495**)[47,48]



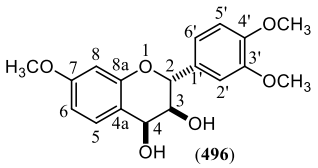
White solid; R_f 0.28 (H:EtOAc, 8:2, 1% TEA); [1]H NMR (600 MHz, $CDCl_3$, Plate 39A) δ ppm 7.55 (1H, br d, *J* = 7.85 Hz, H-5), 7.44 (2H, d, *J* = 8.67 Hz, H-2'&6'), 7.22 (1H, ddd, *J* = 1.36, 7.80, 8.17 Hz, H-7), 7.03 (1H, ddd, *J* = 0.80, 7.80, 7.85 Hz, H-6), 6.98 (2H, d, *J* = 8.67 Hz, H-3'&5'), 6.88 (1H, dd, *J* = 0.80, 8.17 Hz, H-8), 4.93 (1H, dd, *J* = 5.14, 8.44 Hz, H-4), 4.83 (1H, d, *J* = 9.91 Hz, H-2), 3.93 (1H, ddd, *J* = 2.45, 8.44, 9.91 Hz, H-3), 3.84 (3H, s, OCH_3), 2.47 (1H, d, *J* = 5.14 Hz, 4-OH), 1.93 (1H, d, *J* = 2.45 Hz, 3-OH); [13]C NMR (151 MHz, $CDCl_3$, Plate 39C) δ ppm 129.4 (C-7), 129.2 (C-2'&6'), 127.4 (C-5), 121.6 (C-6), 116.4 (C-8), 114.55 (C-3'&5'), 80.4 (C-2), 74.3 (C-3), 71.8 (C-4), 55.54 (OCH_3); EIMS (*m/z*): 272 (M^+, 16%).

***** *NOTE:* Due to the low concentration of the 2,3-*tran*-3,4-*trans* isomer (**495**) it's quaternary carbons could not be assigned.

5.11.7 Preparation of 3',4',7-Trimethoxyflavan-3,4-diol (**496 - 498**)

Method: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 3',4',7-trimethoxyflav-3-ene (**447**) (0.100 g, 0.4 mmol) in acetone (3 mL). The RM was kept at -78 °C for the duration of the DMDO addition where after the receiving flask was removed from the acetone bath and allowed to stir at RT for 15 min where after TLC indicated complete consumption of starting material. [1]H NMR of the RM indicated the possibility of the presence of three diastereoisomers viz. 2,3-*trans*-3,4-*cis*- (**496**), 2,3-*cis*-3,4-*trans*-(**497**) and 2,3-*trans*-3,4-*trans*-3',4',7-trimethoxyflavan-3,4-diol (**498**) in a de ratio of 6:1.4:1, respectively. However, after removing the solvent under reduced pressure the product was recrystallized form EtOH:H_2O (1:1) to give only the 2,3-*trans*-3,4-*cis*-diastereoisomer of the title compound in 88% (0.101 g) yield.

- 2,3-*trans*-3,4-*cis*-3',4',7-Trimethoxyflavan-3,4-diol (**496**)[49]



(**496**)

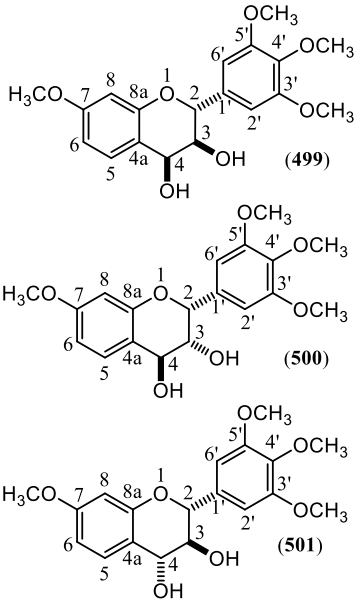
Small off-white crystals; R_f 0.44 (C, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 40A) δ ppm 7.27 (1H, d, *J* = 8.60 Hz, H-5), 7.04 (1H, dd, *J* = 1.78, 8.18 Hz, H-6'), 7.01 (1H, d, *J* = 1.78 Hz, H-2'), 6.92 (1H, d, *J* = 8.18 Hz, H-5'), 6.59 (1H, dd, *J* = 2.43, 8.60 Hz, H-6), 6.48 (1H, d, *J* = 2.43 Hz, H-8), 4.99 (1H, d, *J* = 9.80 Hz, H-2), 4.79 (1H, dd, *J* = 2.94, 3.02 Hz, H-4), 4.04 (1H, ddd, *J* = 2.94, 5.99, 9.80 Hz, H-3), 3.91 (3H, s, 3′/4'-OCH_3), 3.90 (3H, s, 3′/4'-OCH_3), 3.77 (3H, s, 7-OCH_3), 2.63 (1H, d, *J* = 3.02 Hz, 4-OH), 2.18 (1H, d, *J* = 5.99 Hz, 3-OH); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 40C) δ ppm 161.5 (C-7), 155.5 (C-8a), 149.8 (C-3'/4'), 149.6 (C-3'/4'), 131.8 (C-5), 129.8 (C-1'), 120.6 (C-6'), 114.6 (C-4a), 111.4 (C-5'), 110.5 (C-2'), 108.9 (C-6), 101.3 (C-8), 76.7 (C-2), 71.2 (C-3), 66.1 (C-4), 56.14 (3′/4'-OCH_3), 56.09 (3′/4'-OCH_3), 55.5 (7-OCH_3); EIMS (*m/z*): 332 (M^+, 7%).

5.11.8 Preparation of 3',4',5',7-Tetramethoxyflavan-3,4-diol (**499 - 501**)

Method: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 3',4',5',7-tetramethoxyflav-3-ene (**450**) (0.100 g, 0.3 mmol) in acetone (3 mL). The RM was kept at -78 °C for the duration of the DMDO addition after which the receiving flask was removed from the acetone bath and allowed to stir at RT. After 15 min the starting material was completely consumed (indicated via. TLC). Removal of the solvent under reduced pressure and purification via PLC (H:EtOAc, 6:4, 1% TEA) gave 2,3-*trans*-3,4-*cis*-(**499**), 2,3-*cis*-3,4-*trans*-(**500**) and 2,3-*trans*-3,4-*trans*-3',4',5',7-tetramethoxyflavan-3,4-diol (**501**)[50] collectively isolated as a white solid in a de ratio of 4:1.4:1, respectively

- 2,3-*trans*-3,4-*cis*- (**499**), 2,3-*cis*-3,4-*trans*- (**500**) and 2,3-*trans*-3,4-*trans*-3',4',5',7-Tetramethoxyflavan-3,4-diol* (**501**)[50] White solid (formed in a ratio 1:1.4:1); R_f 0.05 (H:EtOAc, 1:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 41A) δ ppm 7.42 [0.2H, br d, *J* = 8.57 Hz, H-5, (**501**)], 7.27 [1H, d, *J* = 8.24 Hz, H-5, (**499**)], 7.26 [0.3H, d, *J* = 8.41 Hz, H-5, (**500**)], 6.76 [0.6H, s, H-2'&6', (**500**)], 6.70 [2.4H, s, H-2'&6', (**499**) and (**501**)], 6.63-6.60 [0.5H, m, H-6, (**500**) and (**501**)], 6.59 [1.6H, dd, *J* = 2.49, 8.24 Hz, H-6, (**499**)], 6.58 [0.3H, d, *J* = 2.48 Hz, H-8, (**500**)], 6.48 [1H, d, *J* = 2.49 Hz, H-8, (**499**)], 6.44 [0.2H, d, *J* = 2.47 Hz, H-8, (**501**)], 5.21 [0.3H, br s, H-2, (**500**)], 4.96 [1H, d, *J* = 9.85 Hz, H-2, (**499**)], 4.85 [0.2H, br d, *J* = 8.18 Hz, H-4, (**501**)], 4.78 [1H, d, *J* = 3.50 Hz, H-4, (**499**)], 4.76 [0.2H, d, *J* = 9.93 Hz, H-2, (**501**)], 4.67 [0.3H, d, *J* = 2.88 Hz, H-4, (**500**)], 4.04 [1.4H, dd, *J* = 3.50, 9.85 Hz, H-3, (**499**)], 4.03 [0.3H, br d, *J* = 2.88 Hz, H-3, (**500**)], 3.90 [0.2H, dd, *J* = 8.18, 9.93 Hz, H-3, (**501**)], 3.89 [2H, s, 3'&5'-OCH_3, (**500**)], 3.87 [7.6H, s, 3'&5'-OCH_3, (**499**) and (**501**)], 3.85 [1H, s, 4'-OCH_3, (**500**)], 3.842 [3H, s, 4'-OCH_3, (**499**)], 3.840 [0.7H, s, 4'-OCH_3, (**501**)], 3.80

[1H, s, 7-OCH_3, (**500**)], 3.77 [3H, s, 3'&5'-OCH_3, (**499**)], 3.76 [0.7H, s, 7-OCH_3, (**501**)], 2.74 [0.4H, br s, 3/4-OH, (**500**)], 2.42 [0.9H, br s, 3/4-OH, (**499**)], 1.87 [0.2H, br s, 3/4-OH, (**501**)], 1.65 [0.9H, br s, 3/4-OH, (**499**)], 1.60 [0.3H, br s, 3/4-OH, (**500**)], 0.94 [br s, 3/4-OH, (**501**)]; ^{13}C NMR (151 MHz, $CDCl_3$, Plate 41C) δ ppm 161.5 [C-7, (**499**)], 161.4 [C-7, (**500**)], 160.7 [C-7, (**501**)], 155.3 [C-8a, (**499**)], 155.2 [C-8a, (**500**)], 154.8 [C-8a, (**501**)], 153.69 [C-3'&5', (**500**)], 153.67 [C-3'&5', (**501**)], 153.66 [C-3'&5', (**499**)], 138.5 [C-4', (**500**)/(**501**)], 138.4 [C-4', (**499**)], 137.8 [C-4', (**500**)/(**501**)], 133.3 [C-1', (**500**)], 133.1 [C-1', (**499**)], 132.6 [C-1', (**501**)], 132.0 [C-5, (**500**)], 131.8 [C-5, (**499**)], 128.3 [C-5, (**501**)], 115.9 [C-4a, (**501**)], 114.6 [C-4a, (**499**)], 113.8 [C-4a, (**500**)], 109.5 [C-6, (**500**)], 109.0 [C-6, (**499**)], 108.8 [C-6, (**501**)], 104.7 [C-2'&6', (**499**)], 104.6 [C-2'&6', (**501**)], 103.5 [C-2'&6', (**500**)], 101.6 [C-8, (**500**)], 101.3 [C-8, (**499**)], 101.1 [C-8, (**501**)], 81.3 [C-2, (**501**)], 77.0 [C-2, (**499**)], 74.9 [C-2, (**500**)], 74.4 [C-3, (**501**)], 71.5 [C-4, (**501**)], 71.3 [C-3, (**500**)], 71.2 [C-3, (**499**)], 67.5 [C-4,(**500**)], 66.1 [C-4, (**499**)], 61.0 [4'-OCH_3, (**500**)/(**501**)], 60.9 [4'-OCH_3, (**499**) and (**500**)/(**501**)], 56.4 [3'&5'-OCH_3, (**500**)/(**501**)], 56.3 [3'&5'-OCH_3, (**499**) and (**500**)/(**501**)], 55.6 [7-OCH_3, (**500**)/(**501**)], 55.5 [7-OCH_3, (**499**) and (**500**)/(**501**)]; EIMS (*m/z*): 362 (M^+, 18%).

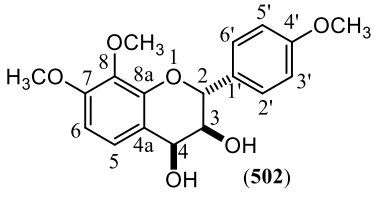


* *NOTE:* Due to a lower concentration, the quaternary carbons of **500** and **501** were assumed to be in the general area of the main product's resonances, with the smaller resonance being the lesser diastereoisomer (**501**).

5.11.9 Preparation of 4',7,8-Trimethoxyflavan-3,4-diol (**502**)

Method: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 4',7,8-trimethoxyflav-3-ene (**452**) (0.100 g, 0.3 mmol) in acetone (3 mL). The RM was kept at -78 °C for the duration of the DMDO addition where after the receiving flask was removed from the acetone bath and allowed to stir at RT for 15 min where after TLC indicated complete consumption of starting material. Two products were obtained, after solvent removal under reduced pressure and purification via PLC (H:EtOAc, 1:1, 1% TEA), with the R_f 0.11 and 0.81 in yields of 61% (0.068 g) and 9% (0.011 g), respectively.

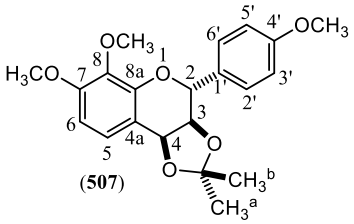
- 2,3-*trans*-3,4-*cis*-4',7,8-Trimethoxyflavan-3,4-diol (**502**)[51]



White solid; R_f 0.11 (H:EtOAc, 1:1, 1% TEA); ^1H NMR (600 MHz, $CDCl_3$, Plate 42A) δ ppm 7.37 (2H, d, *J* = 8.68 Hz,

H-2'&6'), 7.04 (1H, d, *J* = 8.60 Hz, H-5), 6.92 (2H, d, *J* = 8.68 Hz, H-3'&5'), 6.58 (1H, d, *J* = 8.60 Hz, H-6), 5.03 (1H, d, *J* = 9.37 Hz, H-2), 4.71 (1H, d, *J* = 3.61 Hz, H-4), 3.97 (1H, dd, *J* = 3.61, 9.37 Hz, H-3), 3.84 (3H, s, 7-OCH_3), 3.804 (3H, s, 4'-OCH_3), 3.797 (3H, s, 8-OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 42C) δ ppm 160.0 (C-4'), 153.8 (C-7), 148.3 (C-8a), 136.9 (C-8), 129.8 (C-1'), 128.9 (C-2'&6'), 125.2 (C-5), 116.7 (C-4a), 114.2 (C-3'&5'), 105.5 (C-6), 76.5 (C-2), 71.1 (C-3), 66.1 (C-4), 60.9 (8-OCH_3), 56.3 (7-OCH_3), 55.4 (4'-OCH_3); EIMS (*m/z*): 332 (M^+, 4%).

- 2,3-*trans*-3,4-*cis*-3,4-*O*-Isopropylidene-4',7,8-trimethoxyflavan (**507**)[52]



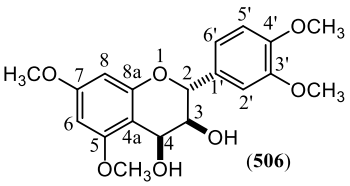
(**507**)

White solid; R_f 0.81 (H:EtOAc, 1:1, 1% TEA); ^1H NMR (600 MHz, $CDCl_3$, Plate 43A) δ ppm 7.44 (2H, d, *J* = 8.67 Hz, H-2'&6'), 7.16 (1H, d, *J* = 8.62 Hz, H-5), 6.95 (2H, d, *J* = 8.67 Hz, H-3'&5'), 6.66 (1H, d, *J* = 8.62 Hz, H-6), 5.11 (1H, d, *J* = 5.49 Hz, H-4), 4.57 (1H, d, *J* = 9.70 Hz, H-2), 4.30 (1H, dd, *J* = 5.49, 9.70 Hz, H-3), 3.87 (3H, s, 7-OCH_3), 3.822 (3H, s, 4'/8-OCH_3), 3.821 (3H, s, 4'/8-OCH_3), 1.55 (3H, s, $CH_3^{a/b}$), 1.48 (3H, s, $CH_3^{a/b}$); ^{13}C NMR (151 MHz, $CDCl_3$, Plate 43C) δ ppm 159.9 (C-4'), 153.7 (C-7), 149.5 (C-8a), 137.8 (C-8), 130.1 (C-1'), 128.8 (C-2'&6'), 125.3 (C-5), 114.6 (C-4a), 114.1 (C-3'&5'), 109.2 [$\underline{C}(CH_3)_2$], 106.4 (C-6), 77.7 (C-2), 75.9 (C-3), 71.6 (C-4), 61.1 (4'/8-OCH_3), 56.4 (7-OCH_3), 55.4 (4'/8-OCH_3), 28.6 ($CH_3^{a/b}$), 26.1 ($CH_3^{a/b}$); EIMS (*m/z*): 372 (M^+, 22%).

5.11.10 Preparation of 3',4',5,7-Tetramethoxyflavan-3,4-diol (**506**)

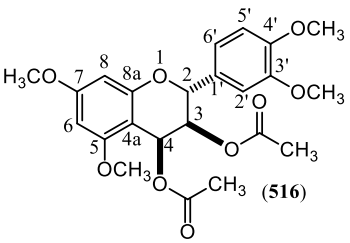
Method: Performed according to general epoxidation method; DMDO was distilled into a cooled (-78 °C) receiving flask containing a solution of 3',4',5,7-tetramethoxyflav-3-ene (**450**) (0.100 g, 0.3 mmol) in acetone (3 mL, wet). The RM was kept at -78 °C for 1 h after the vacuum was broken and a further hour at -40 °C, after which TLC indicated the depletion of the starting material. The reaction was quenched with DMSO (0.108 g, 1.4 mmol, 5 eq) at -40 °C. After an hour, phloroglucinol (0.078 g, 0.6 mmol, 2 eq) was added to the RM and stirred at RT overnight. After concentration under reduced pressure, white ppt in crude product was filtered out and washed with ethanol giving the 2,3-*trans*-3,4-*cis*-3',4',5,7-tetramethoxyflavan-3,4-diol (**506**) in a 9% (0.010 g) yield. The remaining crude product was subjected to acetylation as two drops of dried pyridine and one drop of acetic acid anhydride were added for each mg of crude product and heated (40 °C) for 3 h. After pouring the RM over ice, the ppt was filtered out and thoroughly washed with water. Purification of the ppt by PLC (H:EtOAc, 1:1, 1% TEA) gave two products with R_f 0.42 and 0.28 (H:EtOAc, 1:1, 1% TEA) in 16% (0.011 g) and 23% (0.015 g) yields, respectively.

- 2,3-*trans*-3,4-*cis*-3',4',5,7-Tetramethoxyflavan-3,4-diol (**506**)[53]



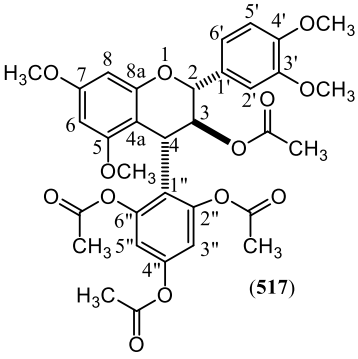
White solid; R_f 0.61 (C, 1% TEA); ^{1}H NMR (600 MHz, C_3D_6O & D_2O, Plate 44A) δ ppm 7.09 (1H, d, *J* = 1.94 Hz, H-2'), 7.02 (1H, dd, *J* = 1.94, 8.22 Hz, H-6'), 6.94 (1H, d, *J* = 8.22 Hz, H-5'), 6.13 (1H, d, *J* = 2.27 Hz, H-6), 5.97 (1H, d, *J* = 2.27 Hz, H-8), 4.91 (1H, d, *J* = 10.26 Hz, H-2), 4.86 (1H, d, *J* = 3.69 Hz, H-4), 3.84 (1H, dd, *J* = 3.69, 10.26 Hz, H-3), 3.813 (3H, s, 5-OCH_3), 3.806 (6H, s, 3'&5'-OCH_3), 3.73 (3H, s, 7-OCH_3); ^{13}C NMR (151 MHz, C_3D_6O & D_2O, Plate 44C) δ ppm 162.4 (C-7), 160.7 (C-5), 156.8 (C-8a), 150.1 (C-4'), 149.9 (C-3'), 132.6 (C-1'), 121.6 (C-6'), 112.8 (C-2'), 112.2 (C-5'), 106.2 (C-4a), 93.6 (C-8), 92.2 (C-6), 77.2 (C-2), 71.2 (C-3), 62.0 (C-4), 56.1 (3'&5'-OCH_3), 55.9 (5-OCH_3), 55.6 (7-OCH_3); EIMS (*m/z*): 362 (M^+, 8%).

- 2,3-*trans*-3,4-*cis*-3,4-Diacetoxy-3',4',5,7-tetramethoxyflavan (**516**)[54]



Light yellow oil; R_f 0.42 (H:EtOAc, 1:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 45A) δ ppm 7.00 (1H, dd, *J* = 1.95, 8.24 Hz, H-6'), 6.95 (1H, d, *J* = 1.95 Hz, H-2'), 6.87 (1H, d, *J* = 8.24 Hz, H-5'), 6.42 (1H, d, *J* = 3.67 Hz, H-4), 6.10 (2H, s, H-6&8), 5.40 (1H, dd, *J* = 3.67, 10.92 Hz, H-3), 5.10 (1H, d, *J* = 10.92 Hz, H-2), 3.894, (3H, s, 3'/4'-OCH_3), 3.893 (3H, s, 3'/4'-OCH_3), 3.78 (3H, s, 5/7-OCH_3), 3.76 (3H, s, 5/7-OCH_3), 2.12 [3H, s,4-OC(O)CH_3], 1.82 [3H, s, 3-OC(O)CH_3]; ^{13}C NMR (151 MHz, $CDCl_3$, Plate 45C) δ ppm 170.2 [4-O<u>C</u>(O)CH_3], 169.4 [3-O<u>C</u>(O)CH_3], 162.7 (C-5/7), 159.7 (C-5/7), 156.7 (C-8a), 149.7 (C-4'), 149.2 (C-3'), 129.1 (C-1'), 120.9 (C-6'), 111.1 (C-5'), 110.6 (C-2'), 100.6 (C-4a), 93.1 (C-6/8), 92.5 (C-6/8), 75.0 (C-2), 720.0 (C-3), 62.1 (C-4), 56.101 (3'/4'-OCH_3), 56.059 (3'/4'-OCH_3), 55.9 (5/7-OCH_3), 55.6 (5/7-OCH_3), 21.2 [4-OC(O)<u>C</u>H_3], 20.6 [3-OC(O)<u>C</u>H_3]; EIMS (*m/z*): 446 (M^+, 3%).

- 2,3-*trans*-3,4-*trans*-3-Acetoxy-4-(2",4",6"-triacetoxyphenyl)-3',4',5,7-tetramethoxyflavan (**517**)[55]



White solid; R_f 0.28 (H:EtOAc, 1:1, 1% TEA); ^{1}H NMR (600 MHz, $CDCl_3$, Plate 46A) δ ppm 7.03 (1H, dd, *J* = 1.91, 8.26 Hz, H-6'), 6.98 (1H, d, *J* = 1.91 Hz, H-2'), 6.88 (1H, d, *J* = 2.29 Hz, H-3"/5"), 6.86 (1H, d, *J* = 8.26 Hz, H-5'), 6.77 (1H, d, *J* = 2.29 Hz, H-3"/5"), 6.15 (1H, d, *J* = 2.36 Hz, H-6/8), 6.01 (1H, d, *J* = 2.36 Hz, H-6/8), 5.78 (1H, dd, *J* = 9.12, 10.03 Hz, H-3), 4.79 (1H, d, *J* = 10.03 Hz, H-2), 4.60 (1H, d, *J* = 9.12 Hz, H-4), 3.90 (3H, s, 3'/4'-OCH_3), 3.88 (3H, s, 3'/4'-OCH_3), 3.72 (3H, s, 5/7-OCH_3), 3.37 (3H, s, 5/7-OCH_3), 2.35 [3H, s, 3/2"/4"/6"-OC(O)CH_3], 2.23 [3H, s, 3/2"/4"/6"-OC(O)CH_3], 1.93 [3H, s, 3/2"/4"/6"-OC(O)CH_3], 1.67 [3H, s, 3/2"/4"/6"-OC(O)CH_3]; ^{13}C NMR (151 MHz, $CDCl_3$, Plate 46C) δ ppm 169.0 [3/2"/4"/6"-O<u>C</u>(O)CH_3], 168.5 [3/2"/4"/6"-

O<u>C</u>(O)CH_3], 168.4 [3/2"/4"/6"-O<u>C</u>(O)CH_3], 167.8 [3/2"/4"/6"-O<u>C</u>(O)CH_3], 160.3 (C-5/7), 159.1 (C-5/7), 156.5 (C-8a), 149.8 (C-1'), 149.7 (C-3'/4'), 149.0 (C-3'/4'), 148.8 (C-2"/6"), 148.6 (C-2"/6"), 129.1 (C-4"), 124.0 (C-1"), 120.7 (C-6'), 114.6 (C-3"/5"), 113.4 (C-3"/5"), 111.0 (C-5'), 110.8 (C-2'), 105.5 (C-4a), 94.2 (C-6/8), 93.9 (C-6/8), 80.5 (C-2), 72.7 (C-3), 56.1 (3'/4'-OCH_3), 56.0 (3'/4'-OCH_3), 55.6 (5/7-OCH_3), 55.5 (5/7-OCH_3), 36.7 (C-4), 21.3 [3/2"/4"/6"-OC(O)<u>C</u>H_3], 21.2 [3/2"/4"/6"-OC(O)<u>C</u>H_3], 20.7 [3/2"/4"/6"-OC(O)<u>C</u>H_3], 20.4 [3/2"/4"/6"-OC(O)<u>C</u>H_3]; EIMS (*m/z*): 638 (M^+, 3%).

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