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A Synthetic Approach to the Biflavonoids Chamaejasmine and Isochamaejasmine

Verna B. Baron

A synthetic approach to the biflavonoids chamaejasmine and isochamaejasmine

By

Verna B. Baron

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By

Verna B. Baron

Approved:

_____

Keith T. Mead
(Director of Dissertation)

_____

Joseph P. Emerson
(Committee Member)

_____

T. Keith Hollis
(Committee Member)

_____

Debra Ann Mlsna
(Committee Member)

_____

Todd E. Mlsna
(Committee Member)

_____

Stephen C. Foster
(Graduate Coordinator)

_____

R. Gregory Dunaway
Professor and Dean
College of Arts & Sciences

Name: Verna B. Baron

Date of Degree: December 13, 2014

Institution: Mississippi State University

Major Field: Chemistry

Major Professor: Keith T. Mead

Title of Study: A synthetic approach to the biflavonoids chamaejasmine and isochamaejasmine

Pages in Study: 101

Candidate for Degree of Doctor of Philosophy

Biflavonoids form a ubiquitous class of compounds in nature, which are well known for their numerous medicinal benefits. Biflavonoids such as chamaejasmine and isochamaejasmine have been shown to exhibit pharmacological activity such as anitidiabetic, anti-malaria, anti- HIV, anticancer etc. Biflavanones, chamaejasmine and isochamaejasmine are dimers of the flavanone narigenin at the C-3 position, which gives them a rare 3/3″ C – C linkage. They are structurally similar in that they both have four stereocenters. The difference between these two compounds is the stereochemistry at the C-2″ and C-3″. In this study, installation of each of these stereocenters will be targeted at different stages of the synthesis.

Installation of the stereocenters at C-2 and C-3 was achieved through the cyclopropanation of a 2-aryl-*2H*-chromene, followed by the tin (II) triflate catalyzed rearrangement of the cyclopropane into a gamma-lactone. This gamma-lactone provided the core structure for one of the flavanone units in the targeted biflavonoids, as well as providing the building block for the second flavanone unit.

For the construction of the second flavanone unit the gamma-lactone was transformed into a chalcone precursor, which served as the platform for the installation of the other two stereocenters in the biflavonoids. The construction of the chalcone precursor was achieved first through the synthesis of an alpha-benzylidene lactone. Several attempts were made to open this alpha-benzylidene lactone via the addition of an aryllithium, which proved to be a challenge. This problem was resolved through the opening of the alpha-benzylidene lactone via reduction with Red-Al, subsequent formation of an aldehyde, and then addition of the aryllithium to the aldehyde. Successful synthesis of the chalcone precursor was achieved through the oxidation of the product of the aryllithium addition, albeit in a modest yield (43 %).

Herein, studies related towards the synthesis of chamaejasmine and isochamaejasmine are presented.

Keywords: biflavonoids, biflavanones, chamaejasmine, isochamaejasmine, cyclopropanation

DEDICATION

To my parents (Nelson & Philipa Baron) and siblings (Hendo, Aileen, Nevo and Jason)

for their continual love, support and encouragement.

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LIST OF ABBREVIATIONS

ABSA	4-acetamidobenzenesulfonyl azide
Ar	aryl
BAIB	[bis(acetoxy)-iodo]benzene
Bn	benzyl
Bu_2 BOTf	dibutylboryl trifluoromethanesulfonate
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum Hydride
DIPEA	diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulphoxide
DNP	dinitrophenylhydrazine
EC_{50}	effective concentration to induce 50% death
Et	ethyl

Et_2O	diethyl ether
EtOAc	ethyl acetate
FPRL1	formyl peptide receptor-like 1
HeLa	human cervical carcinoma
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration of a substance
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium Diisoproyl amine
LHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
Ms	mesyl
NR	no reaction
p-ABSA	4-acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
PMA	phosphomolybdic Acid
ppm	parts per million
q	quartet

Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
Rh_2(*s*-TBSP)$_4$	tetrakis[1-[(4-*tert*-butylphenyl)sulfonyl]-(2*R*)-pyrrolidinecarboxylate]dirhodium(II)
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
^{t}Bu	*tert*- butyl
^{t}BuLi	*tert*- butyllithium
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylendiamine

CHAPTER I

INTRODUCTION

1.1 Biflavonoids

Biflavonoids are polyphenolic compounds that form an important class of compounds in nature. They are basically dimers of flavonoids (chalcones, flavones, flavanones, flavanols, etc.) linked by either a C – C or a C – O – C linkage (Figure 1.1). Since the connecting linkage may occur at several different positions a wide variety of flavonoid-flavonoid combinations exist. However, biflavonoids are prevalent in only a few plant species. Biflavonoids are of growing interest in the medicinal field due to their exhibition of a wide spectrum of pharmacological benefits which includes, but are not limited to, antioxidant,[1-2] anticancer,[3-5] anti-inflammatory,[6-7] and antiviral. [8-9]

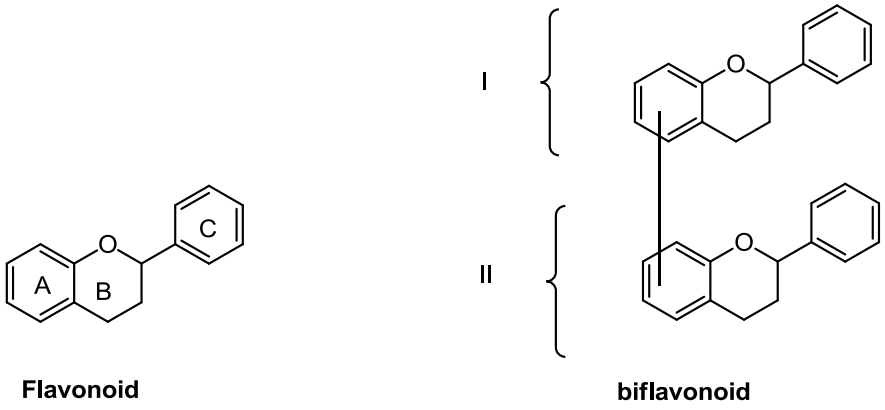


Figure 1.1 Basic scaffold of flavonoids and biflavonoids

These bioactive compounds, though not widely distributed, occur in a wide variety of fruits, vegetables and plants. Since the isolation of the first biflavonoid, ginkgetin, from the leaves of the tree *Ginkgo biloba L.,* the number of biflavonoids isolated and characterized has significantly grown.[10]

Stellera chamaejasme L. is one plant from which these biflavonoids have been isolated. Commonly known as *Langdu* in Chinese traditional herbal medicine, it is widely distributed in the northern and southwestern parts of China and Nepal and has been used in the treatment of scabies, skin ulcers, solid tumors and tuberculosis.[11-12] These known therapeutic effects have led to great interest into the isolation of several bioactive compounds found in *Stellera chamaejasme L*.[13-17] The biflavonoids, chamaejasmine and isochamaejasmine, which contain the rare 3, 3″ – linkage between dimers, are two such compounds isolated from the roots of *Stellera chamaejasme L*. Typical C-3/C-3″ biflavonoids like these have been found to have various biological activities such as antifungal,[18] anticancer,[19] antiviral (HIV[20] & hepatitis B[14]) and antimalarial.[21]

1.2 Chamaejasmine

Chamaejasmine was first isolated from *Stellera Chamaejasme L*. in 1979 by Hung and Zhang.[22] Subsequently, several 3/3" biflavonoids, including its *meso* isomer isochamaejasmine,[23] have been isolated from *Stellera Chamaejasme L*., as well as other plant species. Chamaejasmine **1** is a C_2 symmetric dimer of the flavonoid naringenin **2** at C-3 with four stereocenters, having the geometry of *trans- trans* at C-2/C-3 and C-2″/ C-3″ (Figure 1.2).

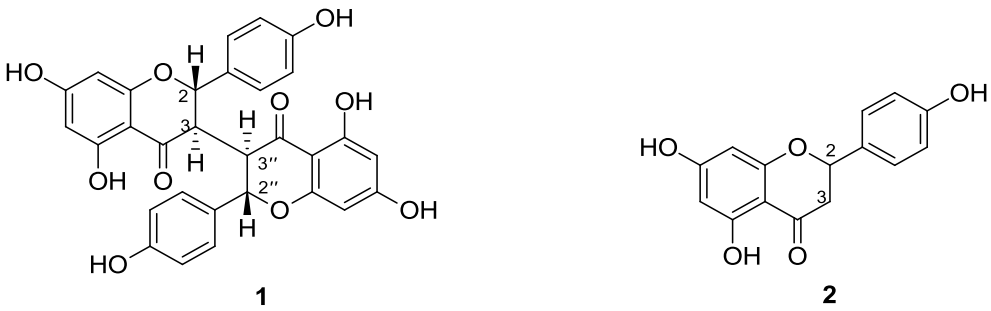
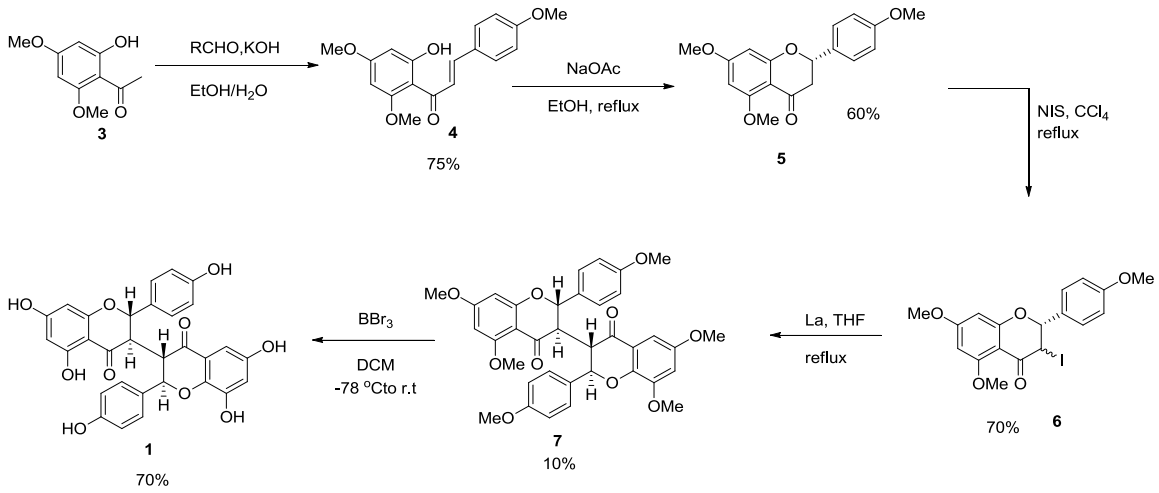


Figure 1.2 Structures of chamaejasmine **1** and naringenin **2**

Chamaejasmine, is of significant medicinal interest due to its demonstrated biological activities.[24-29] It has been shown to be active against several cancer cell lines. In one case it was shown to inhibit cell proliferation (IC_{50} = 4 –16 μm) when its anticancer activity was evaluated against the breast cancer line, MDA-MB-231.[27] Screening chamaejasmine against the human lung adenocarcinoma, demonstrated its ability to inhibit the growth of A549 cells in a time dependent manner, with an IC_{50} value of 7.72 μM after 72 hrs of treatment.[26] Both of these preceding bioactivities of chamaejasmine strongly suggests that it can be used as a chemotherapeutic agent. Chamaejasmine has not only been shown to be an anticancer agent but also has been shown to inhibit aldose reductase,[28] a key role player in the complications, like neuropathy and retinopathy, associated with diabetes.

Bao-Chun *et al.* were able to achieve the first synthesis of *dl*- chamaejasmine via a biomimetric synthetic strategy (Scheme 1.1).[30] In this approach, 2′-hydroxy acetophenone **3** was treated with *p*- anisaldehyde in the presence of potassium hydroxide to produce 2′- hydroxy chalcone **4**. The chalcone was then cyclized to flavanone **5** with the use of sodium acetate. Treatment of flavanone **5** with *N*-iodosuccinimide yielded 3-

iodoflavanone **6**, the key intermediate in the synthesis. The key step in the synthesis was achieved by the dimerization of **6** in the presence of lanthanum. This reductive dimerization yields the racemic-chamaejasmine hexamethyl ether **7** in 10 % yield as well as several by-products. The major of these isolable products (Figure 1.3) were chalcone **4** (25 %), flavone **8** (20 %) and flavanone **5** (5 %). Global demethylation of **7** with excess tribromide boron yielded the desired *dl*- chamaejasmine with an overall yield of 22 %.



Scheme 1.1 Biomimetic synthesis of racemic chamaejasmine

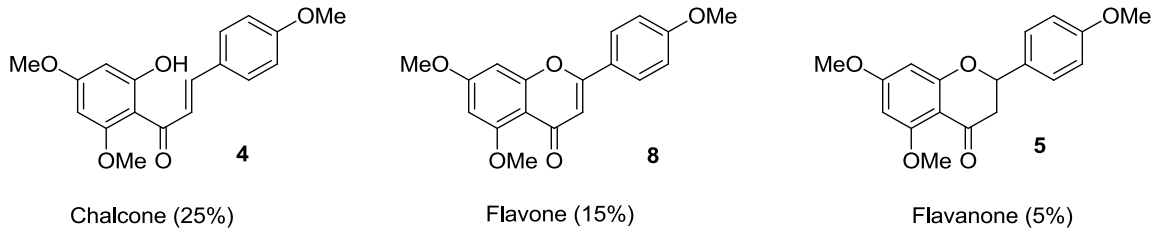
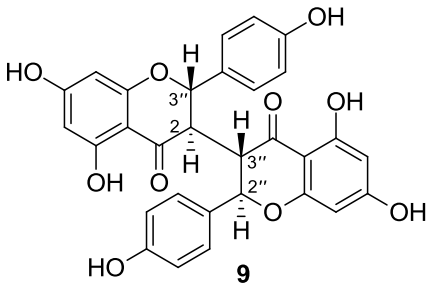


Figure 1.3 By-products from the reductive dimerization

While this synthetic route to chamaejasmine may be considered to be a concise route (5 steps) it suffers from a poor overall yield. Our approach, as will be discussed in a subsequent section, will allow for the synthesis of chamaejasmine as well as, the synthesis of its *meso*- isomer isochamaejasmine.

1.3 Isochamaejasmine

Isochamaejasmine **9** (Figure 1.4) is one of the stereoisomers of chamaejasmine, differing only by the stereochemistry at C-2″ and C-3″. Like its isomer chamaejasmine, it has been of great interest in the medicinal field.[31-33] Isochamaejasmine has been found to have antimicrobial and antiparasitic activity. In the screening of it against the *Plasmodium falciparum*, a species that causes malaria, it was found to have moderate antiplasmodial activity with an IC_{50} of 7.3 ± 3.8 μm, while having a relatively low cytotoxicity (CC_{50} 29.0 ± 10.9 μm).[33] Isochamaejasmine, has also been shown to have anticancer activity: it has been found to stimulate the activation of NF-κB in the human cervical cancer cell line HeLA, with an EC_{50} of 3.23 μm, independently of FPRL1.[32] This activation of NF-κB indicates that isochamaejasmine can affect cancer cells while having little effect on normal cells; a key problem with prevalent aniticancer drugs.



9

Figure 1.4 Structure of isochamaejasmine

Unlike chamaejasmine, isochamejasmine has not been synthesized previously. Efforts made during this study were targeted towards the synthesis of both of these bioactive compounds via a common intermediate (section 1.4). Synthesis of these molecules will allow for the greater exploration of their medicinal benefits, since isolation of these compounds is extremely tedious. A typical isolation protocol[34] of these compounds involves several extraction procedures, using a variety of solvent conditions, followed by preparative HPLC and then preparative TLC or flash column chromatography. This protocol yields ~10 mg of the desired compound after starting with 1 kg of the plant material. Thus synthesis of these compounds will provide means to generate greater quantities of these compounds, in a less tedious manner, which could lead to further exploration of their medicinal properties.

1.4 Retrosynthesis

As discussed in the previous section chamaejasmine and isochamaejasmine by their respective stereochemistry at C-2″ and C-3″ (Figure 1.5). It is envisioned that these stereocenters (C-2″ and C-3″) may be set by the cyclization of chalcone precursors **10** (Scheme 1.2).

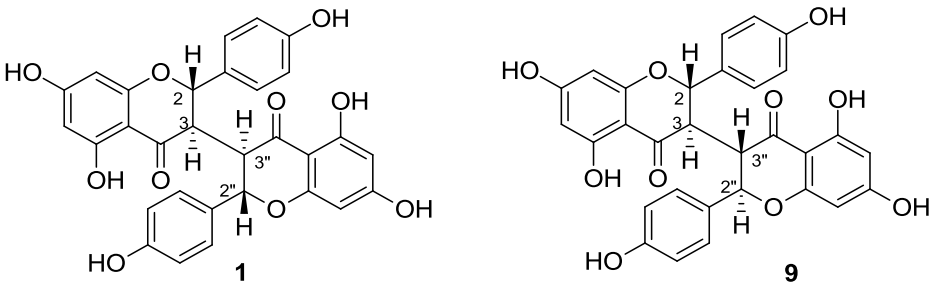
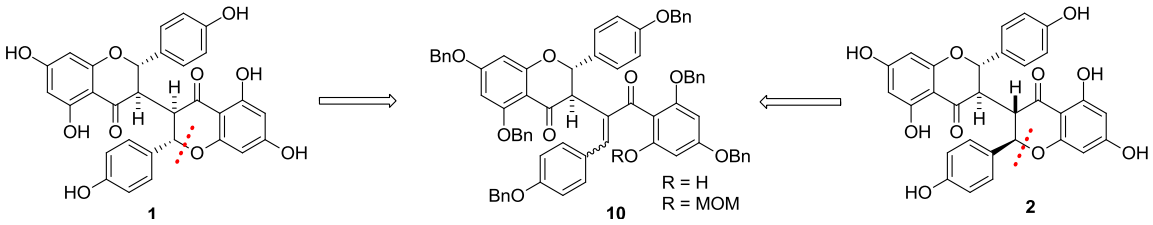


Figure 1.5 Structural differences between chamaejasmine and isochamaejasmine

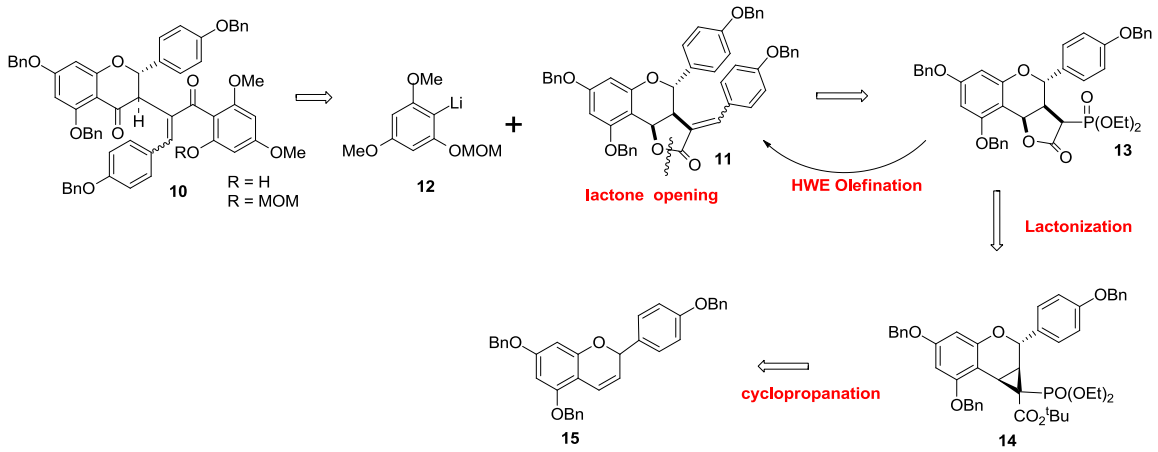
Using the notion that chalcones tend to cyclize with complete trans-selectivity,[35] it can be hypothesized that different geometric configurations of the enone moiety of chalcone precursor **10** would result in the formation of different products. That is, the cyclisation of *Z* or *E*-chalcones would result in the formation of *trans* products with opposite stereochemistry at C-2″ and C-3″.



Scheme 1.2 Chalcone precursor for the synthesis of chamaejasmine and isochamaejasmine

Utilizing a retrosynthetic approach (Scheme 1.3) the chalcone precursor can be synthesized via lithiation of α-benzylidene lactone **11** using known aryllithium **12**. The α-benzylidene lactone can be synthesized by a Horner – Wadsworth – Emmons (HWE) olefination. It is at this stage of the synthesis that the geometric configuration of the chalcone will be determined. Yu and coworkers have demonstrated that the stereochemical outcome of a HWE olefination on α-phosphono lactones can be controlled by the application of different reaction conditions.[36] *Z*-Olefins were selectively obtained (90:1, *Z*/*E*) by treatment of α-phosphono lactones with KHMDS and then rapidly warming to room temperature. On the other hand, applying the same conditions but warming slowly to room temperature resulted in selective formation of *E*-olefins (~70:1,

E/*Z*). Successful application of these reaction conditions to our α-phosphono lactone would provide the necessary framework for our E/Z-desired chalcone precursor.



Scheme 1.3 Proposed retrosynthetic approach to chalcone precursor

The α-phosphono lactone **13** required for this HWE olefination can be prepared by the rearrangement of cyclopropane **14** via a γ- lactonization reaction. Methodology developed within our laboratory has demonstrated that 2-aryl cyclopropanes rearrange[37] to γ- lactones in decent yields (53- 75%) by treatment with a Lewis acid, such as $Sn(OTf)_2$. 2-Aryl cyclopropane **14** may be synthesized via the cyclopropanation of 2-aryl-*2H*-chromene **15**. It has been demonstrated that cyclopropanation of 2-aryl-*2H*-chromenes leads to exclusive formation of a single diastereomer.[38] In this diastereoselective cyclopropanation the cyclopropane adds anti to the aryl group, resulting in a *trans* configuration (Figure 1.6). By successfully applying these conditions to our chromene, stereocenters at C-2 and C-3 will be installed.

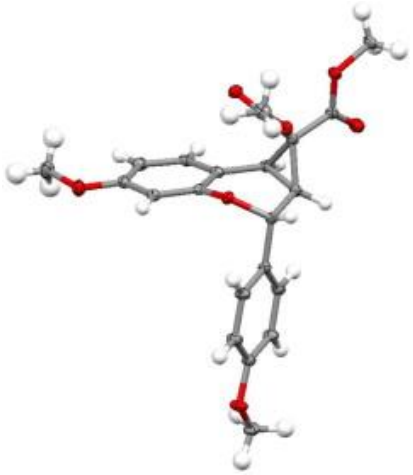


Figure 1.6 Crystal structure of typical cyclopropane adapted from ref.[38]

The chromene, a well-known synthetic scaffold, may be synthesized from the required chalcone in a one pot protocol developed by Ashihara and coworkers.[39]

The ensuing chapters focus on efforts made towards the synthesis of the desired chalcone precursor, as previously described. In the final section of chapter 2, the hypothesis that *E*/*Z*-chalcones results in different products, thereby yielding either chamaejasmine or isochamaejasmine, is evaluated.

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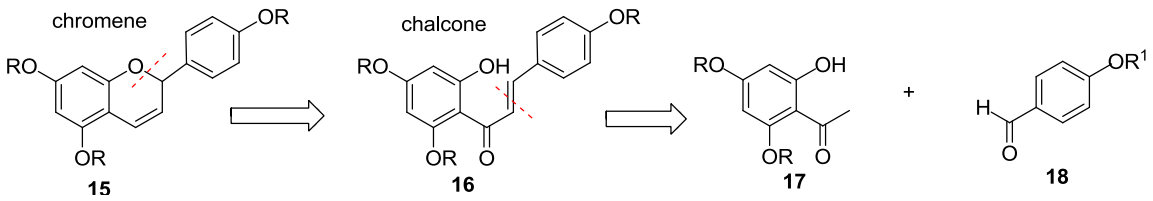
CHAPTER II

RESULTS AND DISCUSSION

2.1 Synthesis of Chromene

Chromenes (*2H*-benzopyran derivatives) are privileged scaffolds in drug discovery, due to their occurance to a wide array of bioactive natural products.[1-3] In our study, towards the synthesis of isochamaejasmine as chamaejasmine, the chromene will serve as the building block for one of the flavanone units found in these biflavonoids. Chromene **15** will be synthesized via the cyclisation of chalcone **16**, which in turn will be synthesized via a Claisen-Schmidt condensation reaction. (Scheme 2.1)

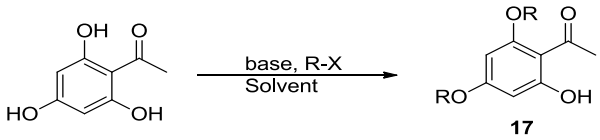


Scheme 2.1 Retrosynthetic analysis of chromene **15**

Prior to synthesizing chalcone **16**, several 2′-hydroxyacetophenones were protected (Table 2.1). The protective group utilized was initially selected based on: 1) relative ease of removal; a task that will be essential in the final stages of the synthesis of these biflavonoids and 2) the ability to survive a multi-step synthesis. Preparation of the

respective 2′-hydroxyacetophenone were all conducted by the treatment of commercially available 2′,4′,6′-trihydroxyacetophenone with a base in the presence of the respective alkyl halide using established literature procedures,[4-6] yielding the protected 2′-hydroxy acetophenones **17a-c** in good to excellent yields (70– 87 %).

Table 2.1 Protection of 2′-hydroxyacetophenone

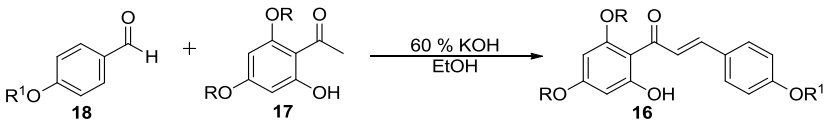


17

Product	R	% Yield
17a	Bn	71
17b	MOM	70
17c	Me	87

With the protected 2′-hydroxyacetophenones in hand, a Claisen-Schmidt condensation reaction was conducted to form 2′-hydroxychalcones **16a-c** (Table 2.2). The methyl-protected chalcone **16c** was synthesized under standard conditions of mixing the acetophenone and the corresponding, commercially available benzaldehyde **18** in ethanol, in the presence of a large excess of 60 % KOH solution. For entries **16a** and **16b,** an alternate procedure had to be used for the synthesis since the respective acetophenones were insoluble in ethanol. These chalcones were successfully synthesized by refluxing of corresponding acetophenone and the benzaldehyde in DMF, in the presence of NaH.

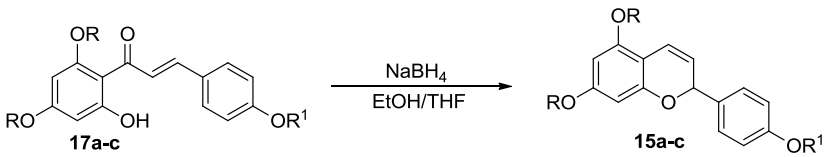
Table 2.2 Synthesis of 2′-hydroxychalcones



Product	R	R^1	% Yield
16a	Bn	Bn	88
16b	MOM	Bn	47
16c	Me	Me	83

The chalcones were then converted into the corresponding 2-aryl-*2H*-chromenes by the reduction of the carbonyl group followed by cyclization (Table 2.3). This conversion was conducted by refluxing the chalcone in a 2:1 mixture of THF:EtOH in the presence of $NaBH_4$.[7] This protocol is preferred to the alternate methods of 2-aryl-*2H*-chromene synthesis since the chromene is obtained in one step and the reaction is typically completed within 30 mins to 1 hour. The chromenes were prepared in decent yields using this method, with the exception of the MOM-protected chromene (Table 2.3, entry 2), which decomposed rapidly during purification, even when purification was conducted using neutral or basic alumina.

Table 2.3 Synthesis of 2-aryl-*2H*-chromenes

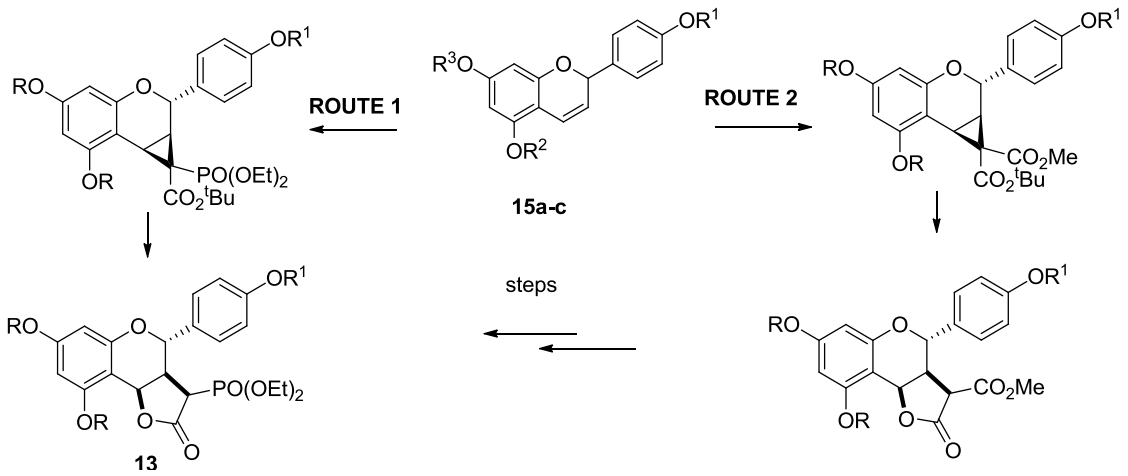


Entry	Product	R	R^1	% Yield
1	15a	Bn	Bn	53
2	15b	MOM	Bn	11
3	15c	Me	Me	73

Chromenes have a tendency to decompose quickly,[8] owing to their susceptibility to oxidation; thus work- up and purification were done as quickly as possible. Furthermore, synthesized chromenes were used immediately for the next stage of the synthesis. If the chromene needed to be stored, it was stored at low temperatures (-5 to -10 ^{o}C) and was used within 3-5 days.

2.2 Synthesis of α-phosphono lactone 13

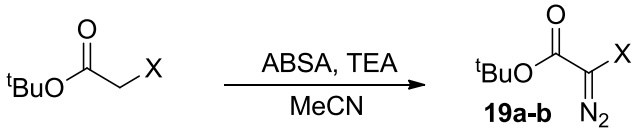
Once the chromene had been synthesized, synthesis of α-phosphono lactone **13** was attempted. Two approaches were considered in the formation of **13** (Scheme 2.2). In both approaches the chromene would be converted to a cyclopropane, which will then undergo a rearrangement reaction to produce a γ-lactone. The approaches differ by the choice of diazo derivative that will be used for the cyclopropanation reaction. If route 1 was successful, it would produce a direct route to the α-phosphono lactone, through the cyclopropanation of the chromene, followed by the rearrangement of that cyclopropane. However, if route 1 is unsuccessful in yielding the desired product, the α-phosphono lactone may be obtained by an indirect route (route 2). In route 2, following the rearrangement reaction a decarboxylation would be necessary prior to the synthesis of the α-phosphono lactone.



Scheme 2.2 Approach to α-phosphono lactone

Prior to conducting the cyclopropanation reaction the two different diazos were prepared via a Regitz diazotization,[9] by treating the respective commercially available starting material with *p*-acetamidobenzenesulfonyl azide (Table 2.4).

Table 2.4 Synthesis of diazo



Diazo	X	% Yield
19a	CO_2Me	87
19b	$PO(OEt)_2$	54

With the diazo derivatives in hand the cyclopropanation reactions were then conducted via route 2, using optimized conditions of a methodology developed in our lab.[10] Chromenes **15a-c** were treated with diazo derivative **19a** in the presence of Rh_2(*s*-TBSP)$_4$ (Table 2.5). This reaction was conducted by the slow addition of a solution of the diazo derivative to a solution of the respective chromene and the catalyst. Addition of the

diazo derivative too quickly or too slowly leads to excessive dimerization of the diazo derivative or decomposition of the chromene respectively.

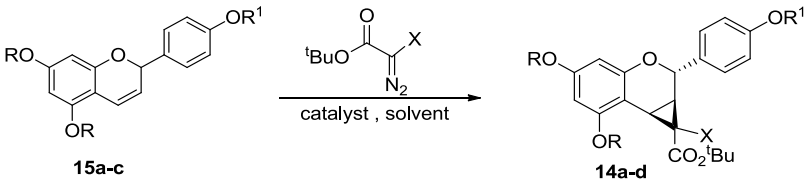
This reaction was first attempted using the benzyl-protected chromene. The benzyl group was the first choice of protective group due to its ability to be cleaved under neutral conditions (reduction with H_2 gas over Pd/C catalyst), thereby eliminating the risk of the deprotection step interfering with other functional groups within the compound. However, this reaction was unsuccessful (Table 2.5, entry 1), since only dimerized product, the chromene and decomposed chromene were recovered from the reaction. The lack of reactivity of the diazo towards the benzyl-protected chromene could be attributed to the bulkiness of the benzyl protective group and its ability to freely rotate. These attributes possibly lead to an unfavorable interaction between the chromene and the incoming rhodium carbenoid species.

The protective group was then changed to a smaller group that could just as easily be cleaved, using relatively mild conditions. Therefore, the next reaction was conducted using the MOM-protected chromene **15b**. Unfortunately, the same results were obtained (Table 2.5, entry 3). These results could be explained for the same reasons as for **15a**, as well as the fact that this chromene is much more unstable than the others (only isolated in 11 % yield, Table 2.3). As a result of instability it is possible that the rate of chromene decomposition may also play a role in the lack of reactivity.

Next, the cyclopropanation reaction was attempted using methyl-protected chromene **15c**, which contains the smallest protective group (Table 2.5, entry 4). Gratifyingly, success was achieved as the desired cyclopropane **14d** was attained in a 64 % yield as a single diastereomer. As explained in section 1.4, the crystal structure

obtained from these types of cyclopropanes indicates that the cyclopropane ring adds anti to the aryl group at the 2- position of the pyran- moiety.[11] This successful cyclopropanation reaction therefore installs the chiral centers present in the targeted biflavonoids at C-2 and C-3.

Table 2.5 Cyclopropanation of *2H*-chromenes



15a-c 14a-d

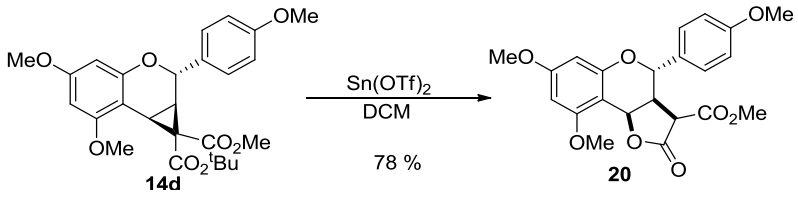
Entry	Product	R^1	R	X	Catalyst	Solvent	% Yield
1	14b	Bn	Bn	CO_2Me	Rh_2(*S*-TBSP)$_4$	DCM	---[a]
2	14c	Bn	MOM	CO_2Me	Rh_2(*S*-TBSP)$_4$	DCM	---[a]
3	14d	Me	Me	CO_2Me	Rh_2(*S*-TBSP)$_4$	DCM	64
4	14a	Me	Me	PO(OEt)2	CuI	Toluene	NR

[a] only the decomposition of starting material and dimerization observed

The methyl-protected chromene was then used to attempt the cyclopropanation with diazo derivative **19b**, which would produce the α-phosphono lactone **13** directly. A different protocol was used for this, since it was already demonstrated in our lab that cyclopropanation of 2-aryl-*2H*-chromenes using compound **19b** under such conditions were unsuccessful.[10] A protocol used by Igor and co-workers for the cyclopropanation using highly electron withdrawing diazo derivatives was then applied to our chromene.[12] In this protocol chromene **15a** and the diazo derivative **19b** were refluxed in toluene in the presence of CuI as a catalyst (Table 2.5, entry 4). Unfortunately, no indication of product was observed as only the starting materials (**14d** and **19b**) were recovered from the reaction.

Typically in cyclopropanation reactions the observance of dimerized product in contrast to cyclopropane formation is a clear indication that the carbene/carbenoid species, which is necessary for the reaction to occur, is being generated. The dimerized product was not observed in this reaction; therefore it is safe to suggest that this reaction condition failed due to the inability of the CuI catalyst to generate the pivotal carbenoid species, resulting in the lack of cyclopropanated product. This route to the α-phosphono lactone was therefore abandoned and the longer route was pursued.

Cyclopropane **14d** was then treated with $Sn(OTf)_2$ which resulted in the rearrangement of the cyclopropane into γ-lactone **20** in a 78 % yield (Scheme 2.3). This rearranged product maintains the anti- stereochemistry as the preceding cyclopropane, which has been confirmed in our lab by means of an X-ray crystal structure.[13]

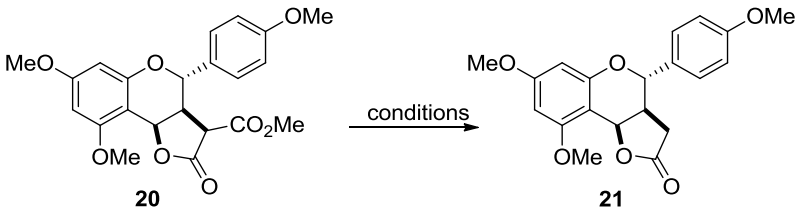


Scheme 2.3 Rearrangement of cyclopropane to γ-lactone.

With this rearranged product in hand several attempts were then made to synthesize lactone **21** (Table 2.6). Initially, it was thought to use conventional methods of refluxing in the presence of aqueous acid to effect this transformation. However, after careful consideration this route was not pursued, due to the lability of the choman-framework, as well as the lactone moiety, to acidic conditions. Basic conditions for the decarboxylation reaction were then attempted, but unfortunately this proved futile (Table

2.6, entry 1). Therefore, Krapcho's method for the dealkoxycarbonylation of esters with α-electron withdrawing substituents was implemented (Table 2.6, entries 2-5).[14-15] This protocol occurs under relatively mild conditions and thus can tolerate a wide array of functional groups and protective groups. Refluxing a solution of the lactone **20** in anhydrous DMF, in the presence of sodium iodide, proved to be the most successful of these methods; yielding the desired product in a 91 % yield (Table 2.6, entry 5).

Table 2.6 Decarboxylation of lactone

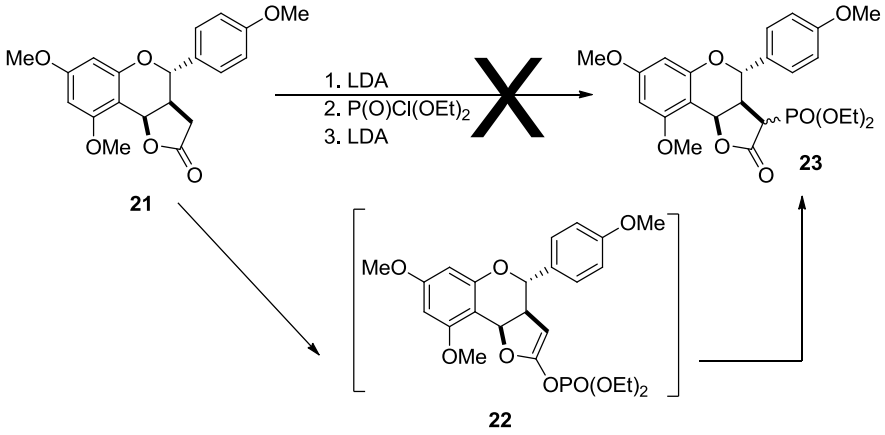


Entry	Conditions	% Yield
1	1. 1 M KOH. MeOH, overnight 2. Toluene reflux 2hrs	---[a]
2	NaCl, wet DMSO, reflux 2hrs	50
3	NaCl, Dry DMSO heat 1.5 hrs	76
4	NaCl, wet DMF reflux 2hrs	---[a]
5	NaI, DMF reflux 5hrs	91

[a]decomposition of starting material

With lactone **21** in hand, attempts were made for the synthesis of the α-phosphono lactone, using a protocol developed by Wiemer and coworkers.[16] This method was selected in preference to the alternate choice of the classical Arbuzov reaction for two main reasons: 1) use of the Arbuzov's protocol would require the formation of an α-bromo lactone, which may be problematic and 2) even if the bromination was successful, phosphonation would necessitate a S_N2 reaction which may again be problematic owing to the sterically hindered lactone. Wiemer's protocol allows for the direct synthesis of the α-phosphono lactone from lactone **21** via the formation of an enolate.

Initial attempts at synthesizing the phosphono lactone using this protocol began with the use of diethyl chlorophosphate as the phosphorylating agent (Scheme 2.4). In this protocol the lactone was treated with LDA followed by the phosphorylating agent to generate vinyl phosphate **22**.[17] This vinyl phosphate was then treated with LDA, which promotes the rearrangement of the vinyl phosphate to the required α- phosphono lactone **23**. To much dismay, this attempt was did not produce compound **23**.

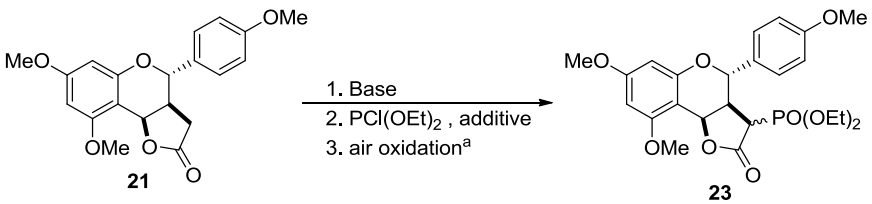


Scheme 2.4 Diethyl chlorophosphate approach to α- phosphono lactone

Another protocol developed by the same group, which employs the use of diethyl chlorophosphite as the phosphorylating agent, was then pursued.[18] The results obtained for this protocol are summarized in Table 2.7. Following the unmodified literature procedure, the lactone **21** was first treated with LDA followed by diethyl chlorophosphite (entry 1), yielding the desired product as a mixture of diastereomers, in a meager 24.2 % yield. It was then thought to implement additives in an attempt to improve the reaction yield. As is evident in entries 2 and 3, the use of the additives, HMPA and TMEDA

respectively, did improve the yield. LHMDS was then employed as a base, to see whether changing the base would also improve the yield. In fact, when LHMDS was used in the presence of TMEDA, the yield obtained was the highest of all reactions attempted (entry 5). This yield was comparative to literature examples of sterically hindered lactones, thus no further optimizations were done for this reaction.

Table 2.7 Phosphonation of lactone using diethyl chlorophosphite

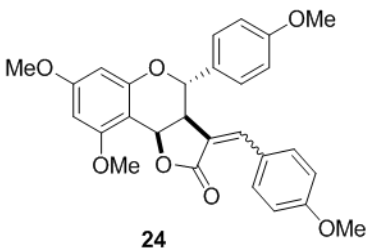


Entry	Base	Additive	% Yield
1	LDA	none	24.2
2	LDA	HMPA	31
3	LDA	TMEDA	34
4	LHMDS	none	24
5	LHMDS	TMEDA	43

[a] air oxidation: reaction flask was left opening to the atmosphere stirring overnight

2.3 Synthesis of α-benzylidene lactones 24

With the α-phosphono lactone **23** in hand, attempts were made to synthesize the *E* and *Z* isomer of the key intermediate, α-methylene lactone **24** (Figure 2.1). Initial attempts to synthesize this lactone began with an employment of a HWE olefination approach by treatment of the α-phosphono lactone with an aldehyde in the presence of base (section 2.3.1). Since this synthetic route did not yield the desired product, an aldol reaction approach had to be implemented (section 2.3.2).

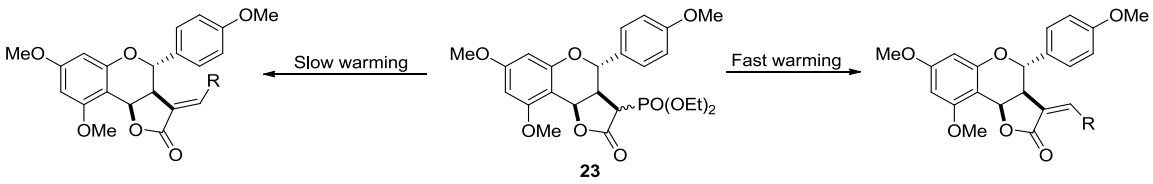


24

Figure 2.1 Key intermediate, α-benzylidene lactone to be synthesized

2.3.1 HWE approach to α-benzylidene lactone

Initial conditions applied for HWE olefination were implemented to stereoselectively generate the *E* and *Z* isomer of the α-benzylidene lactone. In this protocol, the α-phosphono lactone was treated with KHMDS, followed by treatment with 18-crown-6-ether and *p*-anisaldehdye. The stereochemical outcome of the reaction is dependent on how quickly the reaction is warmed to room temperature following the addition of the reagents (Scheme 2.5). It has been demonstrated that application of the HWE reaction using these reaction conditions on α-phosphono lactones followed by slow warming leads exclusively to the *E*-isomer, while fast warming leads to the *Z*-isomer.[19]



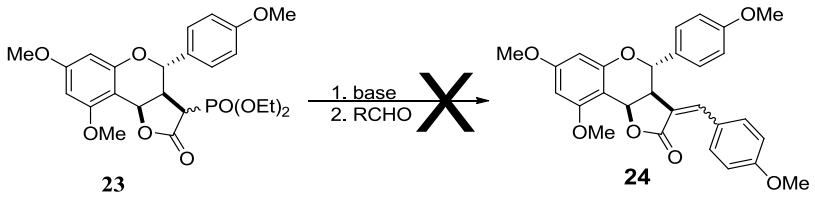
23

Scheme 2.5 HWE approach to α-benzylidene lactone

Unfortunately, application of this protocol to our phosphono lactone, resulted in only α-phosphono lactone **23** being recovered (Table2.8, entries 1 & 2). Alternate bases,

which are typically employed in HWE olefinations, were then employed. Regrettably, these methods were also unsuccessful (Table 2.8, entries 3 & 4).

Table 2.8 Horner Emmons Olefination of phosponate ester



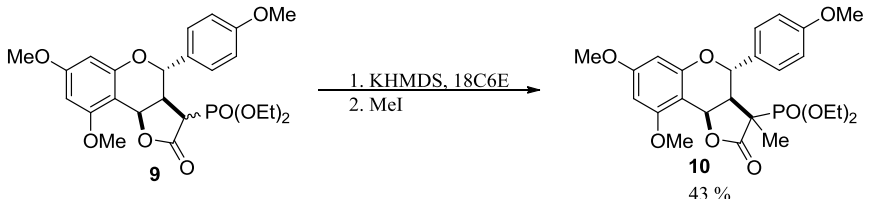
23 24

Entry	Conditions	Yield
1	1. KHMDS,18C6E -78°C 2. RCHO -78°C 3. Slow waming[a] to RT	NR
2	1. KHMDS, 18C6E -78°C 2. RCHO -78°C 3. Fast waming[b] to RT	NR
3	NaH, THF, reflux	NR
4	K_2CO_3, reflux	NR

[a] Slow warming: reaction was started at -78 °C in a covered dewar flask. After the addition of the aldehyde the covering of the flask was removed and the reaction was allowed to slowly come to room temperature. [b] Fast warming: after the addition of the aldehyde the reaction flask was immediately removed from the dewar flask and placed in a water bath at 30 °C.

With unsuccessful application of the HWE olefination conditions to our lactone **23**, it was then concluded that lack of production of the desired product could be attributed to no formation of the required enolate. The α-phosphono lactone was therefore treated with KHMDS, followed by treatment with 18-crown-6-ether and MeI. Successful methylation of the α-phosphono lactone would be a strong indicator that the enolate is being generated under these reaction conditions. Indeed the methylation was successful, albeit in a low 43 % yield (Scheme 2.6). This proved that the enolate was indeed

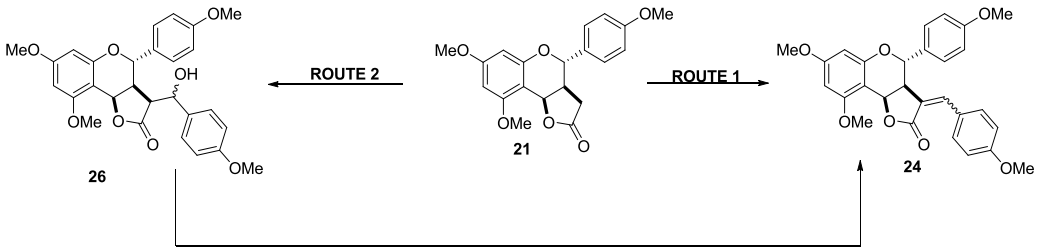
generated under these conditions, thus the failed reactivity with *p*-anisaldehyde, a much bigger electrophile than MeI, could be attributed to steric hindrance.



Scheme 2.6 Methylation of α-phosphono lactone

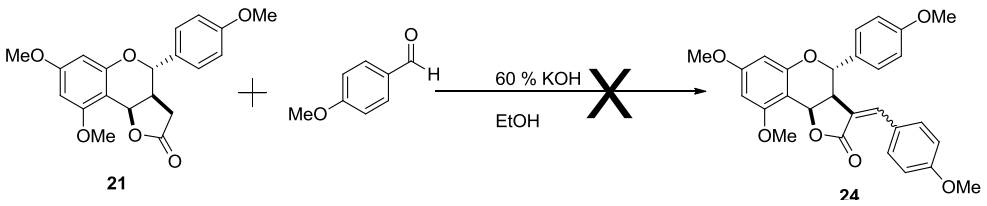
2.3.2 Aldol approach to enone

Since the HWE reaction was unsuccessful, an alternate strategy towards the synthesis of α- benzylidene lactone **24** was taken. In this approach an aldol condensation methodology would be pursued. If the aldol condensation reaction does not yield the required α-benzylidene lactone (route 1); an indirect approach (route 2) could be taken, where the aldol product would be first generated and subsequent mesylation and elimination would fabricate the desired product (Scheme 2.7).



Scheme 2.7 Aldol approach to α-benzylidene lactone

For direct α-benzylidene lactone synthesis, standard conditions for aldol condensation reactions were applied. Treatment of a solution of lactone **21** and *p*-anisaldehyde with 60 % KOH in ethanol and stirring overnight, resulted in no formation of the desired product (Scheme 2.8). Lactone **21** was consumed in the reaction, however only *p*-methoxybenzoic acid and *p*-anisaldehyde were recovered from the reaction. Since this direct route was futile, the viability of route **2** was then investigated.

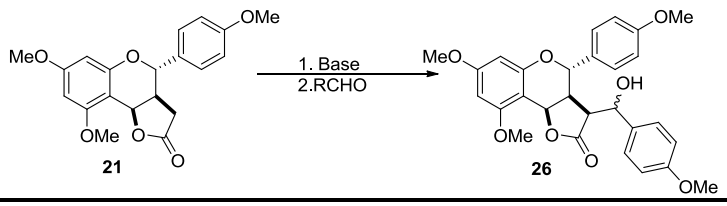


Scheme 2.8 Aldol condensation synthesis of α- benzylidene lactone

In pursuit of the second route, several reaction conditions were applied for the formation of aldol product **26** (Table 2.9). Initial conditions that were applied were geared towards the diastereoselective synthesis of **26**. Lactone **21** was therefore treated with dibutyl boron triflate in the presence of Hünig's base at -78 ^{o}C, followed by the addition of *p* -anisaldehyde. This Mukaiyama aldol reaction has been shown to yield a single diastereomer when applied to lactones.[20] Upon warming the reaction to room temperature after stirring at 0 ^{o}C for 2 hours, as described in the literature, no formation of product was observed (Table 2.9, entry 1). The reaction was repeated under the same conditions but was quenched at -78 ^{o}C instead. This change in reaction conditions resulted in the isolation of the product in an 8.3 % yield as a single diastereomer (Table 2.9, entry 2).

The lactone was then treated with LHMDS and then *p*- anisaldehyde to produce **26**. Warming the reaction to room temperature after the addition of *p*-anisaldehyde resulted in an improved yield of 25 % (Table 2.9, entry 3). The reaction was repeated but was quenched at -78 ºC instead. To much delight, this resulted in the isolation of the aldol product in a 76 % yield as an inseparable mixture of diastereomers (Table 2.9, entry 4). KHMDS was also applied to see if this would have resulted in a higher yield, however a much lower yield was obtained (Table 2.9, entry 6).

Table 2.9 Conditions employed in the synthesis of aldol **26**

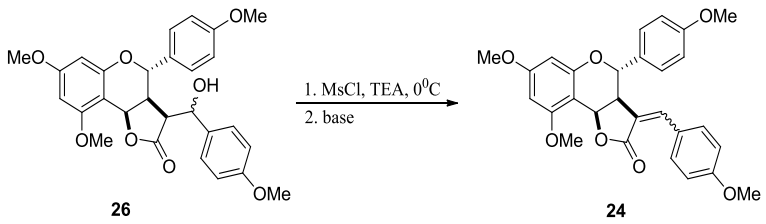


Entry	Conditions	% Yield
1	1. Bu_2 BOTf, DIPEA -78 ºC to RT 2. RCHO 0ºC to RT	---[a]
2	1. Bu_2 BOTf, DIPEA -78 ºC 2. RCHO -78ºC; quench at -78 ºC	8.3[b]
3	1. LHMDS -78ºC 2. RCHO ; -78ºC to RT	25
4	1. LHMDS -78ºC 2. RCHO -78ºC; quench at -78 ºC	76
5	1. LHMDS -78ºC 2. Bu_2 BOTf, DIPEA -78 ºC 3. RCHO; quench at -78 ºC	14[b]
6	1. KHMDS -78ºC 2. RCHO -78ºC; quench at -78 ºC	26

[a] decomposition of starting material; [b]single diastereomer isolated

Aldol product **26** was then converted to α-benzylidene lactone **24** in a one pot two-step sequence. Aldol product **26** was first mesylated by treatment with methanesulfonyl chloride and triethylamine. This was followed by elimination of the nascent mesylate by treatment with a base. When the mesylate of **26** was treated with potassium *tert*-butoxide, the desired product was isolated in a 62 % yield in an *E*/*Z* ratio of 5:2 (Table 2.10, entry 1). DBU was the next base used for the elimination of the mesylate, since Kang and coworkers, in a protocol to generate α-benzylidene lactones from the aldol product of γ- lactones, demonstrated the exclusive formation of the *E*-isomer in several cases.[21] Treatment of our mesylate with DBU, while it did not lead to the exclusive formation of the *E*-isomer, significantly improved the yield to 82 %, with an *E*/*Z* ratio of 3:2 (Table 2.10, entry 2).

Table 2.10 Synthesis of α-benzylidene lactone



26 24

Entry	Base	% Yield	E/Z ratio[a]
1	KO^{t}Bu	62	5:2
2	DBU	82	3:2

[a]determined by NMR

The ratio of *E*/*Z*-isomers was determined from the integration of the vinyl proton. The vinyl proton for the *E*-isomer occurs as a singlet at δ = 7.53 ppm, while the corresponding signal of the *Z*-isomer occurs more upfield at δ = 5.89 ppm (Figure 2.2).

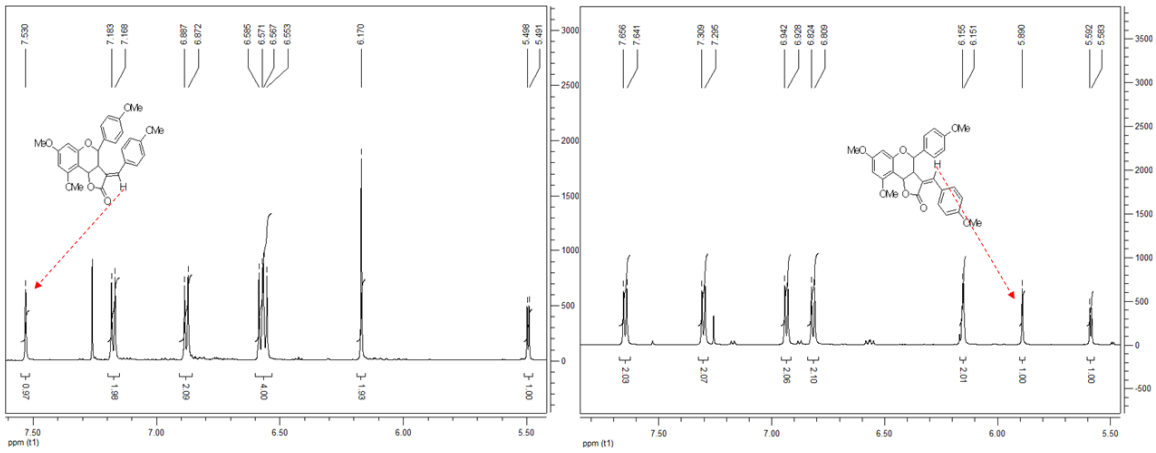


Figure 2.2 Chemical shift differences between *E* and *Z* α-methylene lactone **24**[a]

This mixture of stereoisomers was difficult to separate via conventional flash column chromatography, even when using different solvent systems such as; hexane/EtOAc, hexane/Et_2O and DCM/MeOH. Efforts made to separate them by using a silver impregnate silica column were also unsuccessful. As a result, the olefin product was carried to subsequent steps of the synthesis as a mixture, with the anticipation that a successful separation would be feasible at a later stage in the synthesis.

2.4 Lactone ring opening

With the α-benzylidene lactone in hand, attention was turned towards the synthesis of the chalcone precursor **27** (Figure 2.3). Lactone ring opening via a lithiation reaction proved to be more difficult than anticipated. As a result several different approaches had to be employed towards the synthesis of the chalcone precusor.

[a] Spectra for pure isomers were obtained by collection of the 1st and last fraction

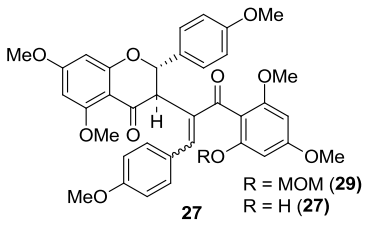
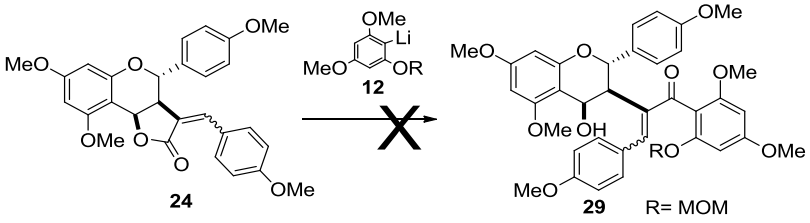


Figure 2.3 Targeted chalcone precursor to biflavonoids

2.4.1 Direct approach: Reaction of lactone with aryllithium 12

In the initial attempt made to synthesize the chalcone precursor, α-benzylidene lactone **24** was treated with known[22] aryllithium **12** at -78 ºC (Scheme 2.9). Unfortunately, only starting material was recovered from the reaction. Presumably the lack of reactivity could be attributed to the sterically hindered α-benzylidene lactone being unsusceptible to attack by a large nucleophile, as is the case of the aryl lithium used.

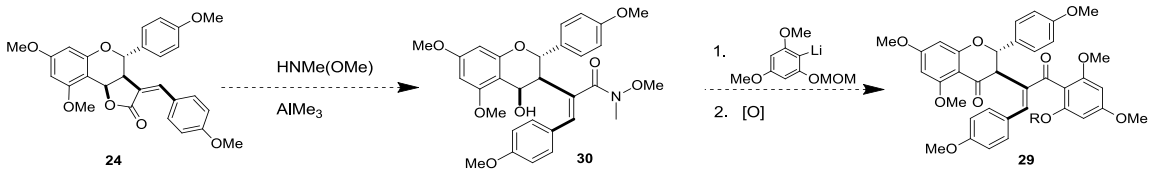


Scheme 2.9 Attempted approach to chalcone precursor

2.4.2 Weinreb amide approach

Since the direct approach to the acylation was did not yield the desired product, a Weinreb amide approach was then attempted (Scheme 2.10). In this approach the α-benzylidene lactone **24** would be treated with HNMe(OMe) in the presence of a Lewis

acid to give Weinreb amide **30**. Generation of Weinreb amides from similar α-benzylidene lactones has been previously accomplished by the treatment of α-benzylidene lactones with an amine in the presence of $AlMe_3$.[23] This Weinreb amide can then be treated with aryllithium **12** followed by oxidation to give chalcone **29**.



Scheme 2.10 Proposed Weinreb amide approach

In order to synthesize Weinreb amide **30** standard conditions were initially applied: α-methylene lactone **24** was treated with *N, O*-dimethylhydroxylamine in the presence of trimethylaluminium as the Lewis acid (Table 2.11, entry 1). Unfortunately, the desired product was not observed. After a survey of the literature, other methods were attempted. These methods present a slight modification to the Weinreb methodology, and have been shown to significantly improve the yield of Weinreb amides derived from lactones. [24-25] Unfortunately, application of these methods to our lactone also proved futile in yielding the desired product (Table 2.9 entries, 2 & 3).

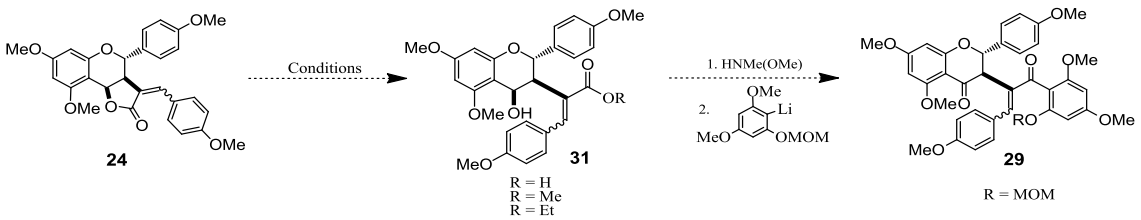
Table 2.11 Conditions employed in the synthesis of Weinreb amide **30**.

ENTRY	Conditions	Yield
1	$AlMe_3$	NR
2	$AlMe_2Cl$	NR
3	Dibal-H	NR

With the unsuccesful attempts at opening the α-benzylidene lactone via the direct lithiation approach and the Weinreb amide approach, it was concluded that sterics may have played a role in the lack of formation of the desired product. That is, the sterically hindered α-benzylidene lactone was not susceptible to attack by large nucleophiles. As a result, it was thought that use of a much smaller nucleophile might achieve the ring opening. Therefore, the next reactions that were attempted involved the α-benzylidene lactone ring opening via basic and acidic conditions.

2.4.3 Base/ acid catalyzed opening of the lactone 24

In this approach basic or acidic conditions would be used to initiate the lactone ring opening into either the ester or acid, dependent on conditions used (Scheme 2.11). The ester or the acid produced by lactone ring opening could be converted into a Weinreb amide and then reacted with the aryllithium to produce the desired chalcone precursor **29**. Alternately, this could be achieved in one-pot. The one-pot conversion of either acids or esters directly to ketones via the *in situ* generation of Wienreb amides has been reported in literature.[26-28]

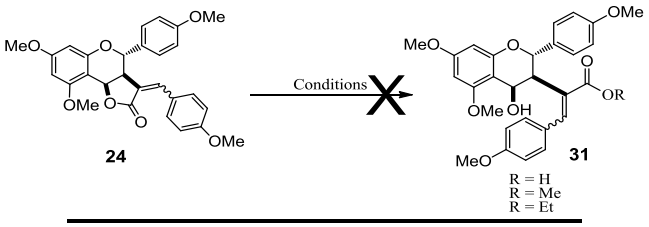


Scheme 2.11 Proposed base/ acid catalyzed approach to chalcone **29**

Several different bases were employed to attempt the base catalyzed lactone ring opening (Table 2.12). Unfortunately, all conditions attempted were unfruitful. When using lithium hydroxide as the base, it was noticed while tracking the reaction by TLC that the starting material was consumed prior to work-up and purification by flash column chromatography. However, when the reaction was worked-up and purified, only starting material was recovered, indicating the product had converted back into the starting material upon work-up. This may be due to the facile recyclization of the hydroxy acid produced by the base catalyzed ring opening. γ-Lactones are known to have a high rate of ring closure due to their relatively low activation energy.[29] Furthermore, this observation could possibly be explained by the Thorpe – Ingold effect, where it is known that the presence of quaternary carbons in an alkyl chain tends to increase the rate of cyclization.[30]

In light of this facile recyclization, attempts were made to afford the formation of the hydroxyl-acid by utilizing an alkoxide, such as sodium methoxide (Table 2.12, entry 4 & 5) or sodium ethoxide (Table 2.12, entry 5), in the opening of the lactone. Unfortunately, these attempts were also unfruitful. It has been demonstrated that treatment of the crude hydroxyl-acid with a methylating reagent, such as methyl iodide or dimethylsulfate, has prevented the unwanted recyclization.[31,32] Application of these conditions to our lactone were also unsuccessful (Table 2.12, entries 7 & 8).

Table 2.12 Conditions applied for the basic/ acidic lactone ring opening

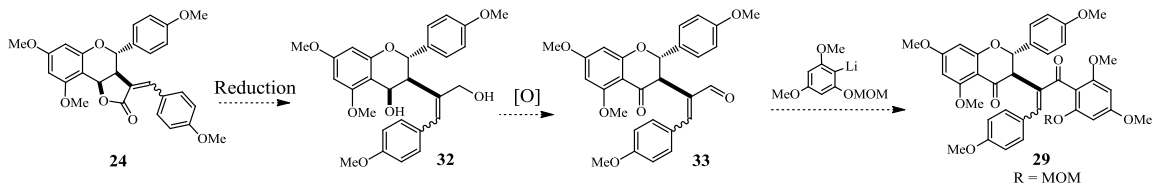


ENTRY	Conditions	Yield
1	Et_3N, MeOH	---[a]
2	NaOH, MeOH	---[a]
3	LiOH, MeOH	---[a]
4	MeONa, MeOH	---[a]
5	MeONa, THF	---[a]
6	EtONa, EtOH	---[a]
7	1. LiOH, MeOH 2. MeI, DMF	---[a]
8	1. LiOH, THF 2. Me_2SO_4, DMSO	---[a]
9	H_2SO_4, H_2O/ THF	---[a]

[a] Starting material was recovered upon work-up

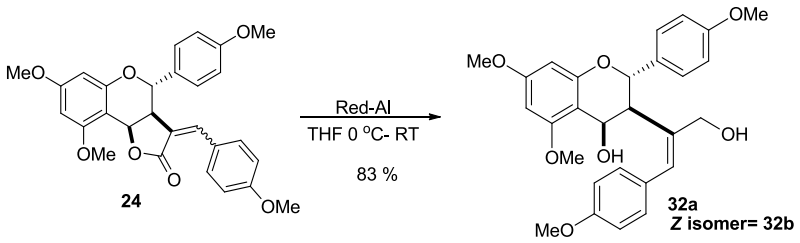
2.4.4 Reduction of lactone approach to chalcone precursor

Since the acidic/basic approach did not yield the desired product, an alternate approach was embarked upon (Scheme 2.12). This approach involved reduction of the α-benzylidene lactone to diol **32**, followed by oxidation to **33**. Treatment of keto-aldehyde **33** with the aryllithium followed by oxidation should give the target chalcone **29**. It is anticipated that the greater reactivity of the aldehyde versus the less reactive and more sterically hindered ketone, should ensure exclusive addition of the aryllithium to the aldehyde and not the ketone, with the use of one equivalent of the aryllithium.



Scheme 2.12 Reduction approach to chalcone **29**

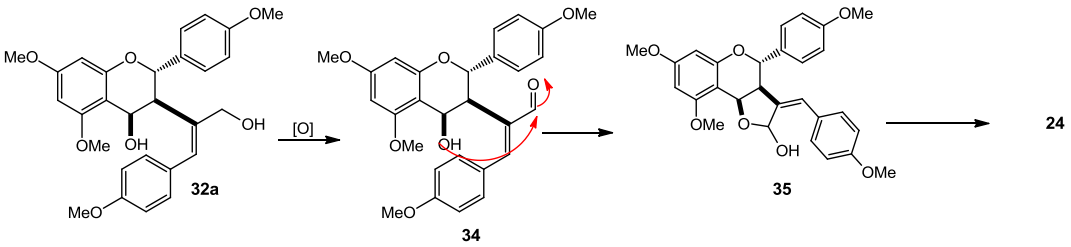
Lithium aluminum hydride (LAH) was used In the initial attempt of the reduction of the α-benzylidene lactone. However, the reaction never went to completion, even when the reaction was stirred for 2 days in the presence of a large excess of LAH. The reducing agent was then changed to Red-Al, which yielded diol **32** in an 83 % yield (Scheme 2.13). Fortuitously at this stage of the synthesis the *E* and *Z* isomers were separable by conventional flash column chromatography.



Scheme 2.13 Reduction of α-benzylidene lactone to diol

With diol **32** in hand, oxidation to the keto-aldehyde **33** was attempted. Initially, it was thought that concurrent oxidation of the alcohols present in the diol **32** would be the best course of action since asynchronous oxidation may lead to the oxidation of the primary alcohol first. This may then be followed by undesired intramolecular cyclization of the secondary alcohol onto the nascent aldehyde, forming a hemiacetal **34**, which can

be further oxidized to α-benzylidene lactone **24** (Scheme 2.14). Thus, the diol was treated with two equivalents of the respective oxidizing agent, with the exception of the application of MnO_2, which typically requires a much larger fold excess (10 – 20 eq) of the oxidant for successful oxidation.



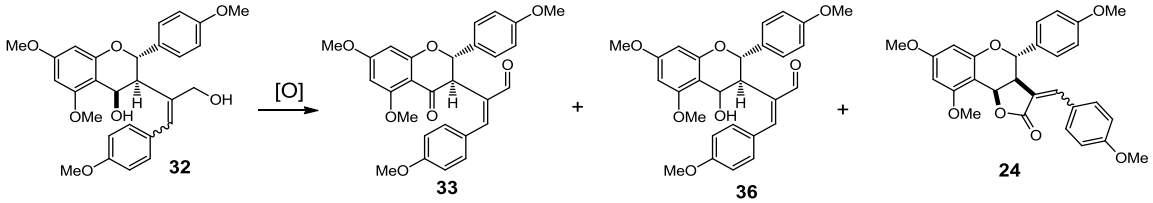
Scheme 2.14 Intramolecular cyclization caused by asynchronous oxidation

Initially, well-known conditions for concurrent oxidations were applied (Table 2.13, entries 1 & 2). Applications of these conditions, PCC and Swern oxidative conditions, resulted in the decomposition of the diol. MnO_2 was then applied for the oxidation, since it has been known to oxidize both allylic and benzylic alcohols (Table 2.13, entry 3). Unfortunately, when diol **32a** was treated with MnO_2, only α-benzylidene lactone **24** was obtained in a 51 % yield (Table 2.13, entry 3).

IBX, another reagent commonly used for the oxidation of benzylic and allylic alcohols, was then applied. In that case, no reaction occurred as only diol **32a** was recovered from the reaction (Table 2.13, entry 4). With the use of DDQ the desired keto-aldehyde was not obtained. However, hydroxy-aldehyde **36** was obtained, albeit in a low 32 % yield (Table 2.13, entry 5). It should be noted that the intramolecular cyclization to

hemiacetal **35** followed by the oxidation could not be avoided, even with the use of one equivalent of DDQ; as the α-benzylidene lactone **24** was also isolated in a 28 % yield.

Table 2.13 Oxidative conditions for synthesis of intermediate **7**.

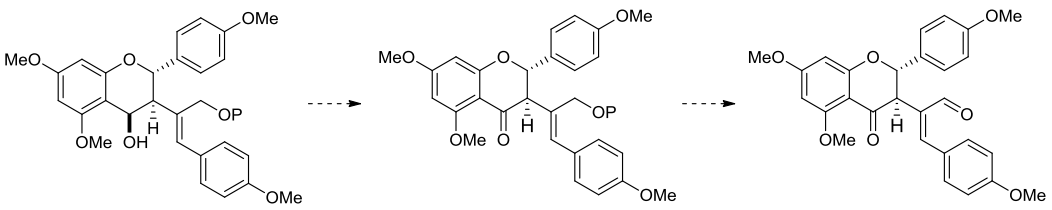


		% Yield		
Entry	**Conditions**	**33**	**36**	**24**
1	PCC[a]	N.O[b]	N.O	N.O
2	Swern[a]	N.O	N.O	N.O
3	MnO2	N.O	N.O	51
4	IBX	N.O	N.O	N.O
5	DDQ	N.O	32	28

[a] decomposition of starting material [b] N.O = not observed

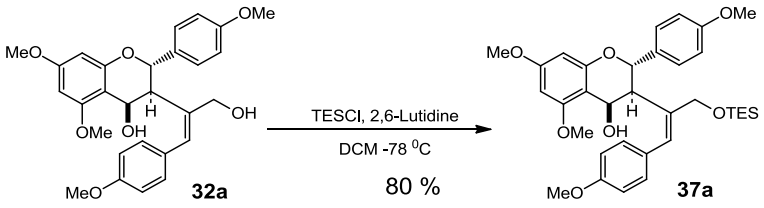
2.4.4.1 Protection/deprotection approach to keto–aldehyde 33

Alas, the direct approach to keto-aldehyde **33** was not as successful as anticipated, thus a protection/deprotection strategy had to be utilized (Scheme 2.15). Firstly, it was thought to selectively protect the allylic alcohol of the diol as a triethyl silyl (TES) group. The TES group was selected as the protective group of choice since it has been demonstrated that it can be converted directly to an aldehyde or a ketone by the application of Swern oxidation conditions. Once the allylic alcohol is protected, the benzylic alcohol can then be oxidized. Deprotection and oxidation should yield the desired keto-aldehyde. The keto- aldehyde can then be treated with the respective aryllithium followed by oxidation to yield the required chalcone.



Scheme 2.15 Protection /deprotection approach to chalcone precursor

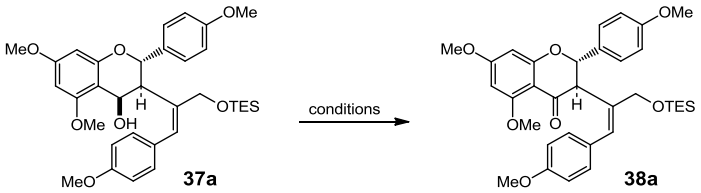
Selective protection[33] of the allylic alcohol of diol **32a**, was achieved by the addition of 2,6-lutidine and TESCl to a solution of the diol in DCM , yielding mono (TES) ether **37a** in an 80 % yield (Scheme 2.16).



Scheme 2.16 Selective TES protection of allylic alcohol of diol

With successful selective protection of the allylic alcohol, several conditions were then attempted for the oxidation of the benzylic alcohol. These results have been summarized in Table 2.14. Application of IBX and manganese dioxide, resulted in no observable reaction as only compound **37a** was recovered from the reaction. Auspiciously, when Dess-Martin periodinane (DMP) was used for the oxidation, the desired ketone **38a** was obtained in a 77 % yield.

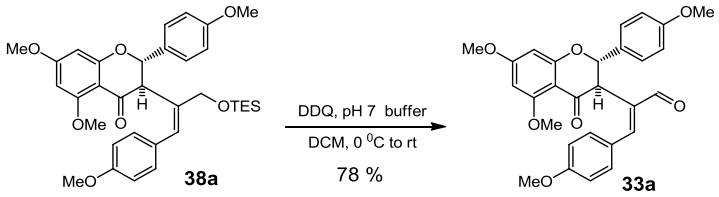
Table 2.14 Oxidative conditions applied for oxidation of benzylic alcohol in **37a**.



Entry	Oxidant	% Yield
1	MnO_2	NR
2	Swern	---[a]
3	IBX	NR
4	DMP	77

adecomposition

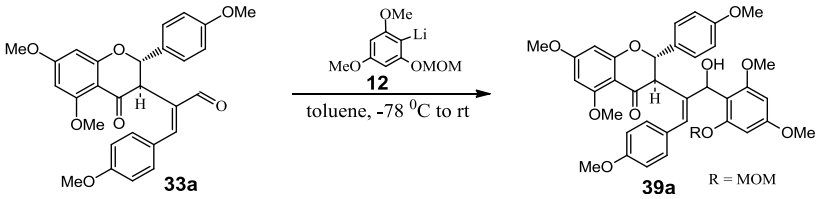
For the deprotection of the TES ether, DDQ was implemented, which has been shown to have the ability of converting electron-rich silyl ethers directly into aldehydes.[34] Thus a solution of ketone **38a** at 0 ^{o}C was treated with DDQ (Scheme 2.17) and then warmed to room temperature. The desired keto-aldehyde was isolated in a 78 % yield.



Scheme 2.17 Synthesis of keto-aldehyde

With keto-aldehyde **33a** in hand, the lithiation reaction was attempted. The aryllithium to be used for this lithiation was first prepared by the protection of 3,5-dimethoxyphenol as a MOM ether under standard conditions. The MOM ether was then treated with *tert*- butyllithium at -78 ^{o}C which produced *ortho-lithiated* MOM ether **12**.[22]

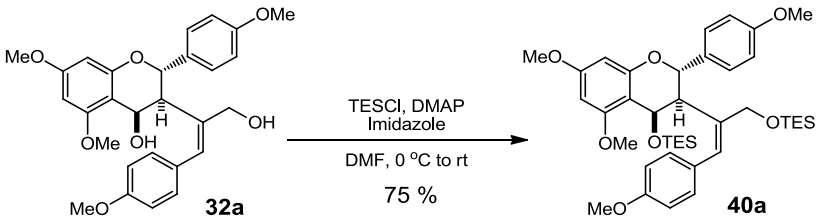
The freshly prepared aryllithium was then titrated into the solution of the keto-aldehyde **33a** in toluene at -78 ^{o}C and monitored by TLC. Maintaining the temperature at -78 ^{o}C, resulted in no product formation. The reaction mixture was then slowly warmed to room temperature which resulted in multiple spots appearing on TLC. Upon work-up and purification the desired lithiated product **39a** was isolated in a disappointing 16 % yield (Scheme 2.18).



Scheme 2.18 Lithiation of Keto- aldehyde **33a**

2.4.4.2 Bis (TES) Ether protected diol approach to chalcone precursor

With such a low yield obtained with the keto-aldehyde, it was then thought to alter the protocol to ensure that only one carbonyl moiety was present (the aldehyde). Thus the diol **32a** was treated with DMAP, imidazole and TESCl, which yielded bis (TES) ether **40a** in a 75 % yield (Scheme 2.19).



Scheme 2.19 Bis (TES) ether synthesis

With the bis (TES) ether in hand attempts were then made to selectively remove the allylic TES ether. These results have been summarized in Table 2.15. Swern oxidative conditions have been shown to convert allylic TES directly to a carbonyl group in the presence of other TES ethers, [35] therefore this was the first method used to attempt this transformation. Implementation of Swern conditions for this selective deprotection/oxidation resulted in multiple spots being observed on TLC (Table 2.15, entry 1). Only one of these isolated spots showed trace presence of the aldehyde by NMR analysis, with a characteristic chemical shift at 9.6 ppm. This method was therefore abandoned and an alternate protocol was sought.

A survey of the literature found that DDQ[34] has also been used to convert TES ethers directly to the carbonyl group. Thus, bis (TES) ether **40a** was treated with DDQ at 0 ^{o}C. The mixture was then warmed to room temperature and monitored for completion. After stirring for 7 hours at room temperature the starting material was still present; therefore an additional 1 equivalent of DDQ was added and the reaction was stirred for a further 2 hours. This resulted in aldehyde **41a** being isolated in a 42 % yield. However, α-benzylidene lactone **24a** was also isolated in a 31 % yield (Table 2.15, entry 2).

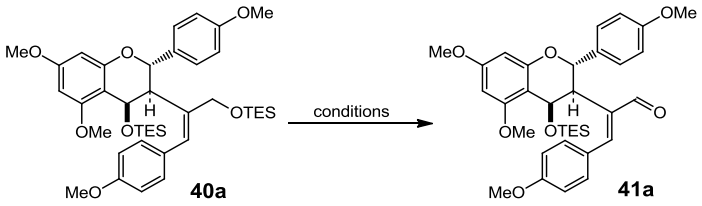
The α-benzylidene lactone formation resulted from the use of excess DDQ. Addition of the 1st equivalent was successful in oxidizing the allylic TES ether to aldehyde **41a**, while addition of the 2nd equivalent resulted in deprotection of the benzylic TES ether, followed by intramolecular cyclization onto the nascent aldehyde and the oxidation to give the α-benzylidene lactone (see Scheme 2.14).

The reaction was then repeated using just 1 equivalent of DDQ; after stirring for 7 hours at room temperature starting material was still present, thus the reaction was left to

stir overnight. This resulted in complete decomposition of the starting material as well as the desired product that was formed, indicating that the reaction time was too long (Table 2.15, entry 3).

The reaction was then repeated, and the reaction was quenched at the 7 hour mark, in spite of the fact that starting material was still present. In this case the desired product was isolated in a 62 % yield; a 79 % yield when the recovered starting material is taken into consideration (Table 2.15, entry 4). Even with the use of 1 equivalent DDQ the side product formed from this reaction, α-benzylidene lactone **24**, could not be avoided, as it was also isolated in a 7.4 % yield.

Table 2.15 Oxidative conditions applied to compound **40a**



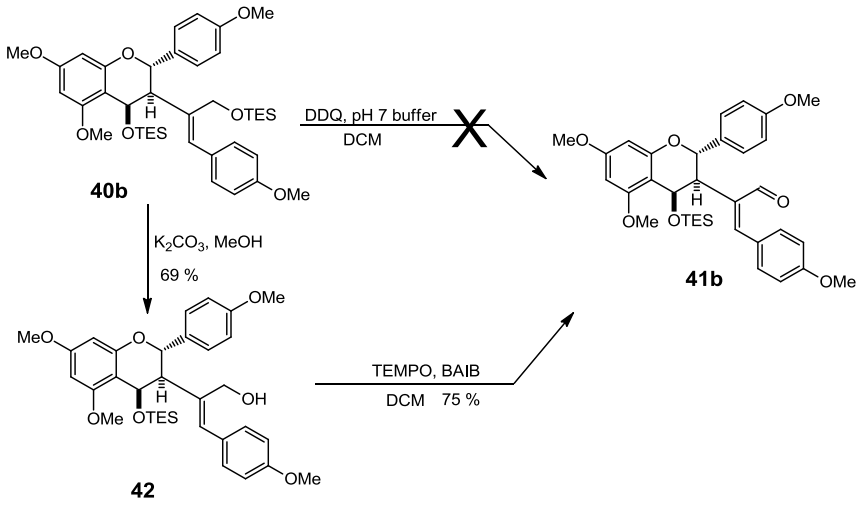
40a **41a**

ENTRY	OXIDANT	EQ	REACTION TIME	% YIELD
1	$(COCl)_2$	1	2 hrs	---[a]
2	DDQ	2	7 hrs	42 (31)[b]
3	DDQ	1	16 hrs	---[c]
4	DDQ	1	7 hrs	62(79)[c]

[a] trace; [b] yield of α-benzylidene lactone **24**; [c] decomposition; [d] yield based on recovered **40a**

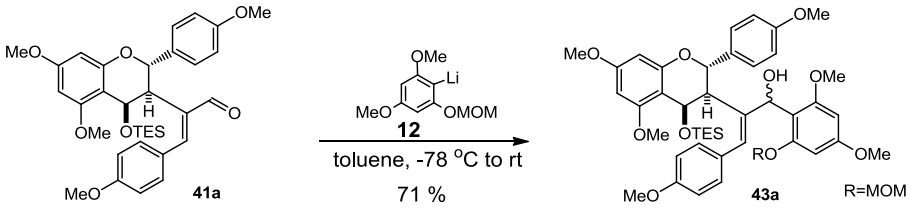
Applying these same conditions for sequential deprotection and oxidation to the aldehyde for the *Z*-isomer **40b** resulted in no formation the desired product. As a result, a two–step protocol had to be applied to *Z*-bis (TES) ether **40b** for the synthesis of *Z*-aldehyde **41b** (Scheme 2.20). In this protocol the primary TES group **40b** was selectively cleaved[36] by treatment with K_2CO_3 in MeOH, which furnished primary alcohol **42** in a 69

% yield. Subsequent treatment of **42** with MnO_2 produced the desired aldehyde **41b** in a 68 % yield. Application of TEMPO/BAIB, for the oxidation of the allylic alcohol, increased the yield to 75 %.



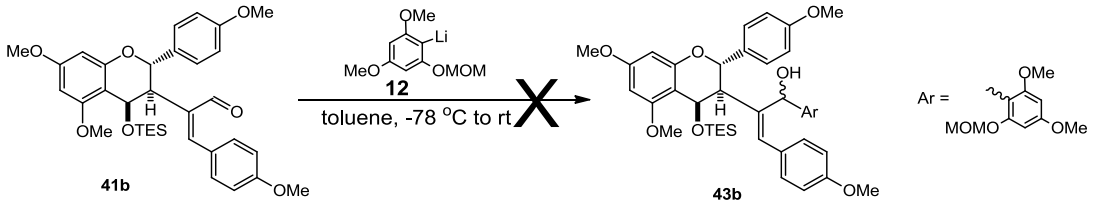
Scheme 2.20 Strategy implemented for the synthesis of *Z*-aldehyde **41b**

The lithiation reaction was then attempted with aldehyde **41a** which successfully yielded the desired product as a mixture of epimers in a 71 % yield (Scheme 2.21). The complications seen with the lithiation reaction utilizing keto-aldehyde **33a** were not observed (section 2.4.4.1).



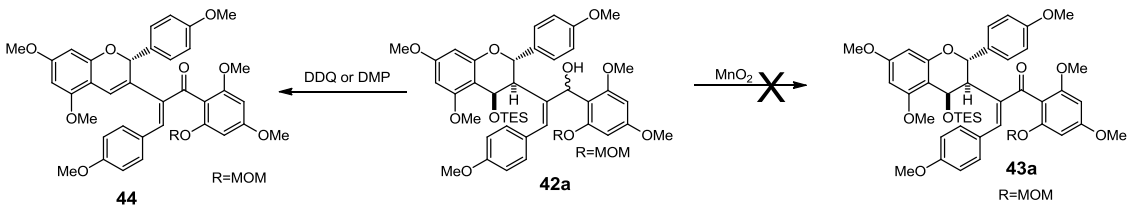
Scheme 2.21 Lithiation of aldehyde **41a**

Disenchantingly, application of these reaction conditions to the *Z*-isomer resulted in no formation of the desired product as only aldehyde **41b** was recovered from the reaction (Scheme 2.22). Failure of the lithiation reaction may be attributed to steric crowding of Z-aldehyde **41b**, which in turn prevents attack of the aldehyde by the bulky lithiating reagent **12**.



Scheme 2.22 Lithiation of *z*-aldehyde **41b**

With alcohol **42a** in hand, attempts were made to synthesize chalcone **43a** via the oxidation of the allylic alcohol (Scheme 2.23). Unfortunately, all conditions applied to achieve this were futile. Use of MnO_2 resulted only in the recovery of alcohol **42a**, even when 20–30 equivalents of the oxidant was used and the reaction was stirred for 3 days. Implementation of DDQ or DMP, resulted in the elimination of the TES protective group, yielding chromene **44** (Scheme 2.23) as the major product of the reaction. In the case of use of DMP, the desired chalcone **43a** was also obtained in a 26 % yield.



Scheme 2.23 Oxidative conditions applied for the synthesis of chalcone **43**

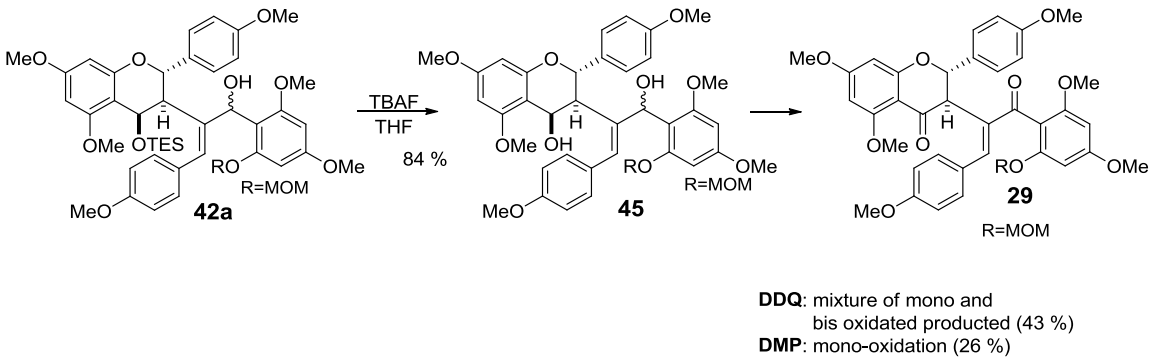
With the possibility of the elimination of the TES protective group in mind, it was then thought that a better route would be to first deprotect the TES group, then concurrently oxidize both of the alcohols present in the diol produced (Scheme 2.24). Therefore, allylic alcohol **42a** was treated with TBAF, which gave diol **45** in an 83 % yield.

Concomitant oxidation of both the benzylic and allylic alcohols was then attempted. This oxidation was not straightforward: use of MnO_2 resulted in no reaction; when DMP was used, even though 2 equivalents were used, only one of the alcohols in diol **45** was oxidized (26 % yield); application of DDQ resulted in a mixture of the mono-oxidated and bis-oxidated product (~ 43 % yield of inseparable mixture). [b] Swern oxidative conditions were also applied, but this resulted in decomposition of the diol. Sequential oxidation of the diol, by 1st using DMP and then DDQ or vice versa, also proved futile.

Difficulties with the concomitant oxidation of both alcohols in diols have been reported in literature. In one such case the oxidation was achieved by sequential treatment

[b] Product formed was confirmed by HRMS

of the diol with DMP and then Jones' reagent.[37] In our case the use of such a strongly acidic reagent (Jones' reagent) is not applicable.



Scheme 2.24 Synthesis of chalcone precursor

The deprotection of the MOM group was then attempted using the inseparable mixture of the mono/bis-oxidated product. Unfortunately, attempts made to remove the MOM group using standard condition for MOM deprotection (*p*-toluenesulfonic acid in MeOH and HCl in methanol), resulted in the decomposition of the starting material.

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CHAPTER III

CONCLUSION & FUTURE PERSPECTIVES

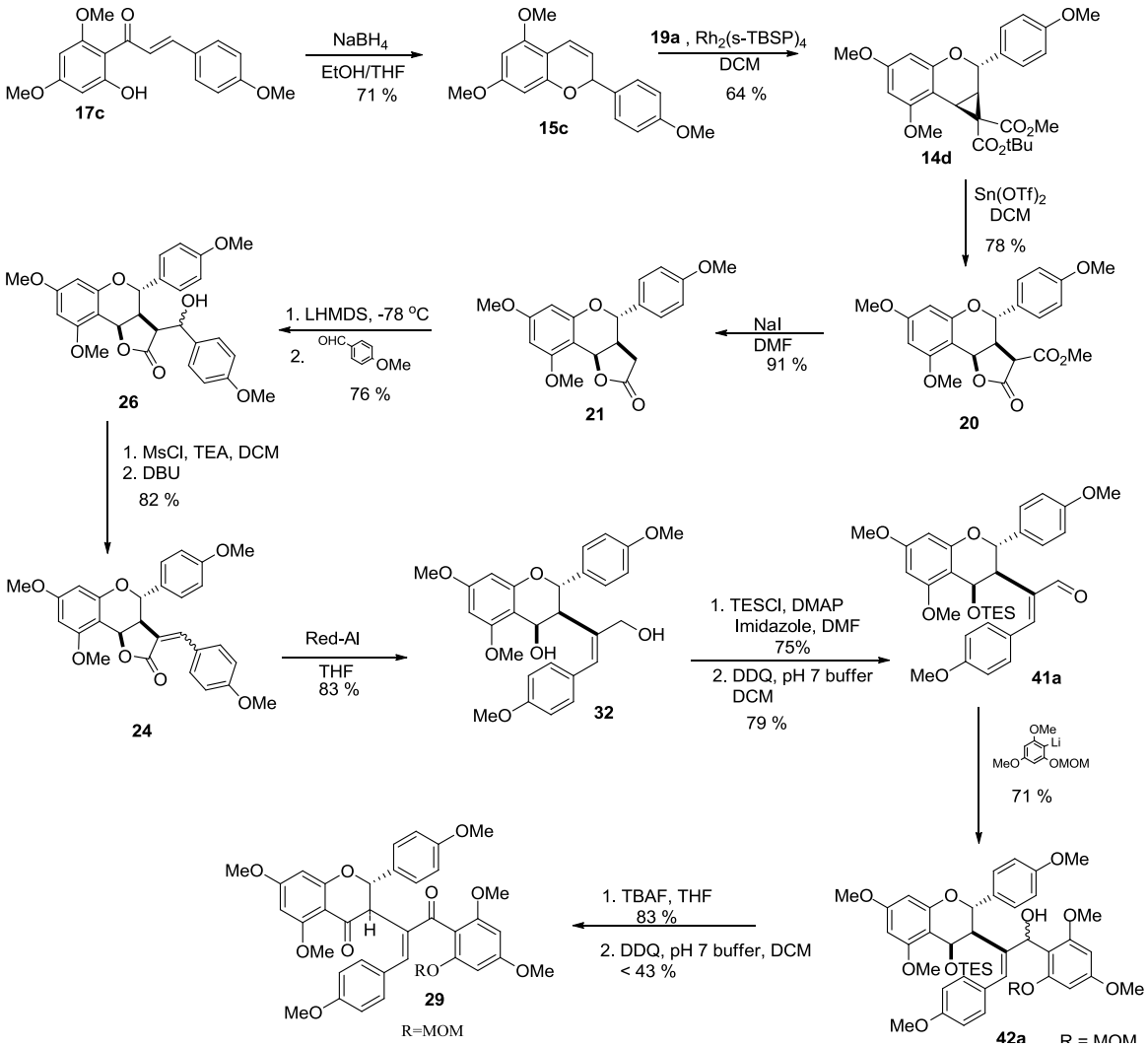
In this study a synthetic route towards the synthesis of chamaejasmine and isochamaejasmine, each containing four stereogenic centers, has been developed. The strategy applied for this synthesis has been depicted in Scheme 3.1. The goals of this dissertation were as follows:

I: Install stereocenters at C-2 and C-3

II: Synthesize *E*/*Z* chalcone precursors to the biflavonoids

III: Test the hypothesis that E/Z chalcones cyclize with complete *trans* selectivity and yield *trans* products with opposing stereochemistry.

Goal I was achieved through the cyclopropanation of chromene **15c** followed by rearrangment into γ-lactone **20**. This created the framework for one of the flavanone units in these biflavonoids, in addition to the building block to the 2nd flavanone unit. In order to accomplish goal II, γ-lactone **20** was transformed into aldol product **26**. Aldol product **26** was then converted into α-benzylidene lactone **24**. This conversion produced the desired *E*/*Z* configuration for the chalcone precursor. Lactone ring opening, formation of an aldehyde, followed by addition of aryllithium **12** and oxidation furnished the desired *E*-chalcone precursor **29**. Efforts made to synthesize the *Z*-chalcone precursor using the same strategy were futile.

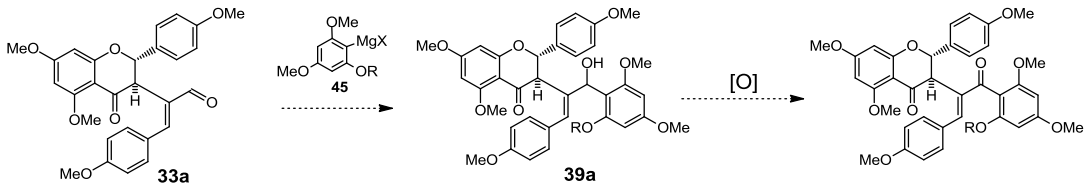


Scheme 3.1 Overall strategy to the synthesis of chalcone precursor **29**

The oxidation reaction to yield *E*-chalcone precursor **29** from a diol was a challenge and only furnished the desired chalcone in less than 43 % yield as a mixture of the desired product, as well as the mono oxidized product. Therefore, an alternate strategy needs to be implemented in order to obtain the chalcone precursor in an improved yield.

One such approach would involve revisiting the keto-aldehyde strategy discussed in section 2.4.4.1. In this strategy, the addition of the aryllithium to the aldehyde only

yielded the desired product in a 16 % yield, due to the multiple side reactions. This yield may be improved through the use of alternate reagents instead of the very reactive aryllithium. Less reactive reagents such as Grignard, Gilman and organozinc reagents may be implemented for the addition (Scheme 3.2). These methods would ensure the need to oxidize only one alcohol to produce the desired chalcone precursor, thereby eliminating the issue of the mixture of products obtained when oxidizing the diol.



Scheme 3.2 Alternate strategy to chalcone precursor

Another issue which arose from the protocol used to form the chalcone precursor was the deprotection of the MOM group in compound **29**. Attempts made to deprotect the MOM group resulted in the decomposition of **29**. As a result of this goal III in this study was not accomplished.

Utilizing the alternate strategy proposed above (Figure 3.2) goal III could be accomplished by allowing the protective group (R) used in arylating reagent **45** to be varied. As a result, protective groups other than MOM that could be removed under milder conditions (non-acidic conditions) can be implemented in the arylating reagent **45** used in the addition to the aldehyde **33a**. Research is ongoing to test the viability of this route in synthesizing the desired chalcone precursor in a decent yield.

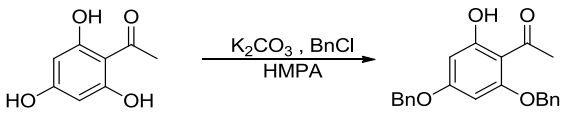
CHAPTER IV

EXPERIMENTAL PROCEDURES

4.1 General experimental methods

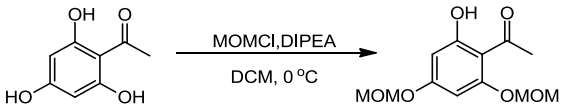
All reactions were performed using oven-dried glassware under inert atmosphere (Ar or N_2). Reactions were monitored by TLC using Sorbent Technology silica gel TLC plates (UV 254) and PMA, $KMnO_4$ or DNP for visualization. Column chromatography was performed on silica gel using mixtures of hexane and EtOAc as the eluting solvents unless otherwise noted. Flash purification of compounds was conducted using Biotage-Isolera™ One. Anhydrous DMSO, DMF, and toluene were purchased from Sigma Aldrich in a SureSeal™ bottle and used without further purification. Other solvents and reagents (such as THF, DCM, Et_3N, and acetonitrile) were dried over sodium benzophenone ketyl or calcium hydride and distilled before use. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance 300 or 600 MHz instrument in $CDCl_3$ and data are reported as chemical shift (δ) in ppm from tetramethylsilane as an internal standard. For ^{13}C NMR spectra data are reported as δ in ppm from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$, 77.16 ppm). Samples of new compounds were submitted to Mississippi State University for HRMS analysis. Melting points were determined with a Barnstead International MEL-TEMP melting point apparatus and are uncorrected. Note: Compounds that have been previously characterized have citations after their chemical name.

4.2 Synthesis of diprotected acetophenones



Scheme 4.1 Synthesis of 1-(2,4-bis(benzyloxy)-6-hydroxyphenyl)ethanone (**17a**)[1]

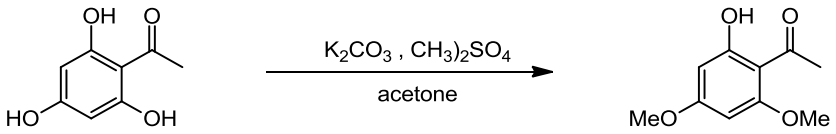
To a solution of 2,4,6-trihydroxyacetophenone (1.05 g, 5.680 mmol) in HMPA (7 mL) was added potassium carbonate (2.24 g, 16.08 mmol) and benzyl chloride (1.36 mL, 10.80 mmol). The resulting suspension was stirred under reflux overnight. The reaction mixture was then poured into ice water and acidified to pH 2 with 6 M HCl. The mixture was then extracted with EtOAc (x 3) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography. Yield: 1.4 g, 71 %; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): 14.00 (s, 1H), 7.43-7.34 (m, 10H), 6.15 (d, J = 2.3 Hz, 1H), 6.10 (d, J = 2.3 Hz, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 2.57 (s, 3H)



Scheme 4.2 Synthesis of 1-(2-hydroxy-4,6-bis(methoxymethoxy)phenyl)ethanone (**17b**)[2]

To a solution of 2,4,6-trihydroxyacetophenone (500 mg, 2.680 mmol) in DCM (6 mL) at 0 °C was slowly added DIPEA (1.32 mL, 7.580 mmol). The reaction mixture was stirred for 20 minutes before chloromethyl methyl ether (0.48 mL, 6.32 mmol) was added

dropwise. After stirring at room temperature for 2 hours the reaction mixture was quenched with deionized water and the aqueous layer was extracted with DCM (3x, 10 mL). The combined organic layers were then washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. Yield: 482 mg, 70 %; clear oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.74 (s, 1H), 6.23 (s, 2H), 5.26 (s, 2H), 5.16 (s, 2H), 3.52 (s, 3H), 3.46 (s, 3H), 2.63 (s, 3H).



Scheme 4.3 Synthesis of 1-(2-hydroxy-4,6-dimethoxyphenyl)ethanone (**17c**)[3]

To a solution of 2,4,6-trihydroxyacetophenone (10.11 g, 54.2 mmol) in dry acetone (214 mL) was added K_2CO_3 (14.98 g, 107.8 mmol) and dimethylsulfate (10.3 mL, 108.4 mmol). The reaction was refluxed for 5 hours, after which it was cooled to room temperature and poured into ice water (200 mL). The resulting white precipitate was filtered and washed with cold water. Yield: 9.25 g, 87 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.02 (s, 1H), 6.06 (d, J = 2.21 Hz, 1H), 5.93 (d, J = 2.21 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.61 (s, 3H).

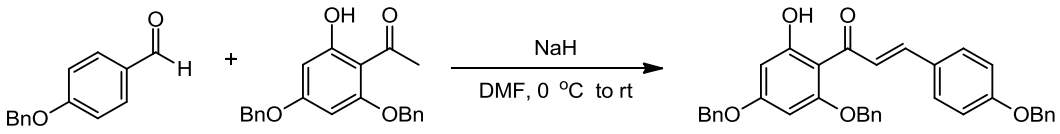
4.3 Synthesis of 2′- hydroxychalcones

4.3.1 Procedure A

To a solution of the 2′-hydroxyacetophenone (1.4 g, 4.04 mmol) and *p*-anisaldehyde (0.939 g, 4.42 mmol) in anhydrous DMF (20 mL) at 0 °C was added NaH (397 mg, 16.54 mmol). The resulting solution was warmed to room temperature and stirred overnight. The reaction mixture was diluted with H_2O and extracted with EtOAc (3x, 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure leaving a solid residue, which was recrystallized from 100% MeOH.

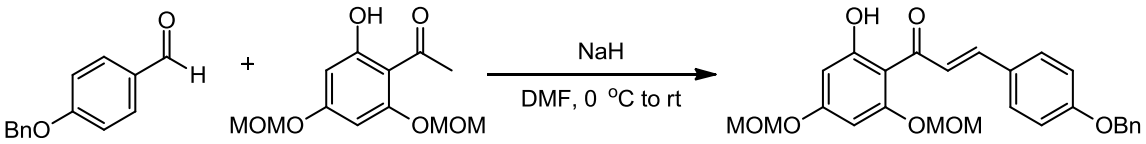
4.3.2 Procedure B

To a solution of 2′ - hydroxyacetophenone (1.00 g, 5.09 mmol) and *p*-anisaldehyde (0.62 mL, 5.09 mmol) in ethanol (20 mL) was added a solution of potassium hydroxide (4 mL, 107 mmol, 60% w/w). After stirring at room temperature overnight, the reaction was neutralized with saturated NH_4Cl and extracted with EtOAc (x3). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$ The solvent was removed under reduced pressure leaving a solid residue, which was recrystallized from 100% MeOH.



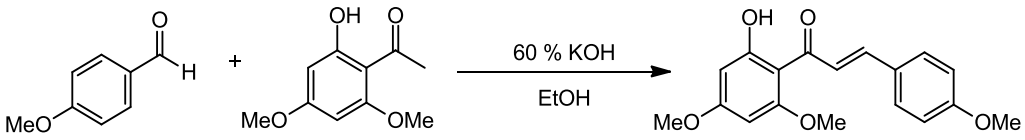
Scheme 4.4 Synthesis of (*E*)-3-(4-(benzyloxy)phenyl)-1-(2,4-bis(benzyloxy)-6-hydroxyphenyl)prop-2-en-1-one (**18a**)[4]

Synthesized via procedure A. Yield: 1.93 g, 88%; yellow solid; m.p. 133.7-136.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 14.7 (s, 1H), 7.81-7.78 (d, J = 15.5 Hz, 1H), 7.71-7.68 (d, J = 15.5 Hz, 1H), 7.50-7.36 (m, 15H), 7.00-6.99 (d, J = 8.5 Hz, 2H), 6.78-6.77 (d, J = 8.4 Hz, 2H), 6.22 (s, 1H), 6.17 (s, 1H), 5.10 (s, 2H), 5.08 (s, 2H), 5.05 (s, 2H).



Scheme 4.5 Synthesis of (*E*)-3-(4-(benzyloxy)phenyl)-1-(2-hydroxy-4,6-bis(methoxymethoxy)phenyl)prop-2-en-1-one (**18b**)[5]

Synthesized by procedure A. Yield: 48 %; yellow solid; m.p. 103 °C – 105 °C. ; ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.94 (s, 1H),7.84 (d, J = 15.5 Hz, 1H), 7.80 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 7.1 Hz, 2H), 7.41 (d, J = 7.3 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.32 (d, J = 2.3 Hz, 1H), 6.25 (d, J=2.3 Hz, 1H), 5.29 (s, 2H), 5.19 (s, 2H), 5.12(s, 2H), 3.53 (s, 3H) 3.48 (s, 3H).

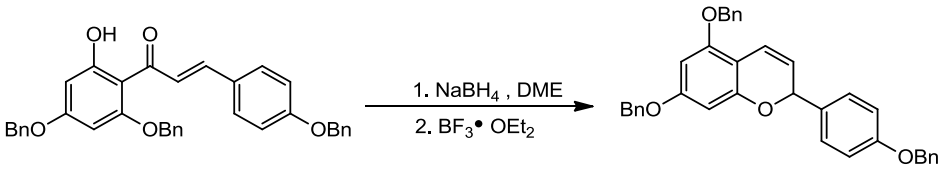


Scheme 4.6 Synthesis of (*E*)-1-(2-hydroxy-4, 6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**18c**)[6]

Synthesized by procedure B. Yield: 1.33 g, 83 %; yellow solid; m.p. 112 °C – 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.36 (s, 1H), 7.90 (d, J = 15.6 Hz, 1H), 7.80 (d, J =

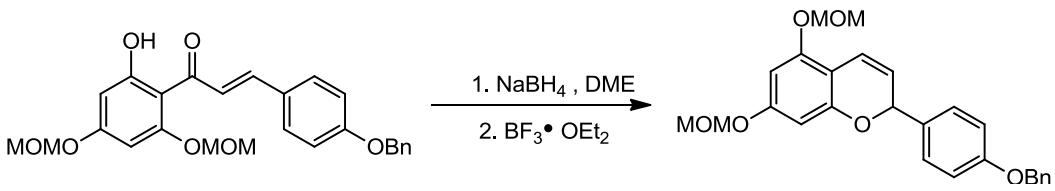
15.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.11 (d, *J* = 2.3 Hz, 1H), 5.97 (d, *J* = 2.3 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 2.40 (s, 3H).

4.4 Synthesis of Chromenes



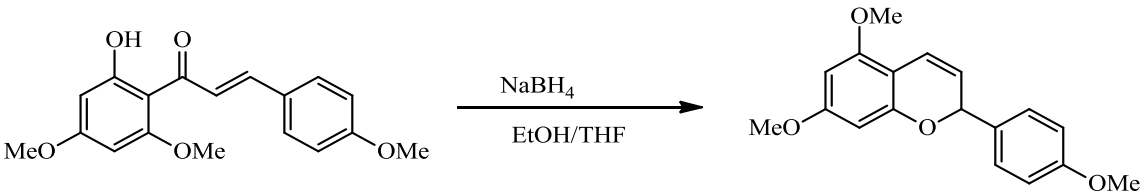
Scheme 4.7 Synthesis of 5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-2*H*-chromene (**15a**)[4]

To a solution of chalcone (200 mg, 0.369 mmol) in DME (4 mL) was added $NaBH_4$ (14 mg, 0.423 mmol). The mixture was then stirred for 5 mins at 85 ºC. After cooling to room temperature the mixture was diluted with EtOAc and washed with brine (x3). The organic layer was dried over anhydrous Na_2SO_4 and was filtered. A solution of boron trifluoride ethyl etherate (50 µL, 0.4051 mmol) in DCM (200 µL) was added and the resulting mixture was stirred for 30 minutes at room temperature. The solution was washed with brine (x3) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on neutral alumina. Yield: 100 mg, 55 %; clear oil; ^{1}H NMR (300 MHz, $CDCl_3$;) δ 7.40-7.32 (m, 18 H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.89 (dd, *J* = 9.9, 1.4 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 6.12 (d, *J* = 2.1 Hz, 1H), 5.78 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.61 (dd, *J* = 9.9, 3.5 Hz, 1H), 5.05 (s, 2H), 5.01 (s, 2H), 4.94 (s, 2H).



Scheme 4.8 Synthesis of 2-(4-(benzyloxy)phenyl)-5,7-bis(methoxymethoxy)-2H-chromene (**15b**)

To a solution of chalcone (180 mg, 0.399 mmol) in DME (4 mL) was added $NaBH_4$ (15.4 mg, 0.408 mmol). The mixture was stirred for 5 mins at 85 ^oC. After cooling to room temperature the mixture was diluted with EtOAc and washed with brine (x3). The organic layer was dried over anhydrous Na_2SO_4 and was filtered. A solution of boron trifluoride ethyl etherate (50 µL, 0.4051 mmol) in DCM (200 µL) was added and the resulting mixture was stirred for 30 minutes at room temperature. The solution was washed with brine (x3) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on neutral alumina. Yield: 20 mg, 12%; clear oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 7H), 6.98 (d, J = 8.7 Hz, 2H), 6.85 (dd, J =10.0, 1.3 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 6.24 (d, J = 2.1 Hz, 1H), 5.81-5.79 (m, 1H), 5.64 (dd, J = 10.0, 3.4 Hz, 1H), 5.18 (s, 2H), 5.10 (s, 2H), 5.08 (s, 1H,), 3.51 (s, 3H), 3.45 (s,3H).

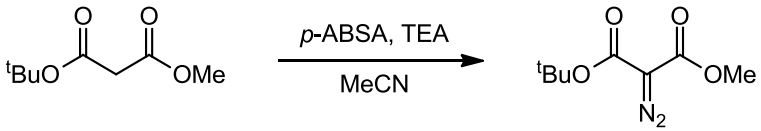


Scheme 4.9 Synthesis of 5,7-dimethoxy-2-(4-methoxyphenyl)-2H-chromene (**15c**)[7]

To a solution of chalcone (150 mg, 0.477 mmol) in a 2:1 THF/EtOH mixture (9 mL) was added $NaBH_4$ (36.1 mg, 0.954 mmol)). The mixture was heated to reflux until completion (1 hour). The solvents were removed and the residue was dissolved in a 1:1 DCM/H_2O (10 mL) and was stirred at room temperature. After stirring for 10 minutes the layers were separated and the aqueous was layer was extracted with DCM (x3). The combined organic layers was then washed with brine and dried over anhydrous Na_2SO_4.

Yield: 104 mg, 73 %; yellow oil; ^{1}H NMR ($CDCl_3$; 300MHz) δ 7.37 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 9.9, 1.8 Hz, 1H), 6.01 (s, 2H), 5.78 (dd, J = 3.5, 1.8 Hz, 1H), 5.60 (dd, J = 9.9, 3.5 Hz,1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H).

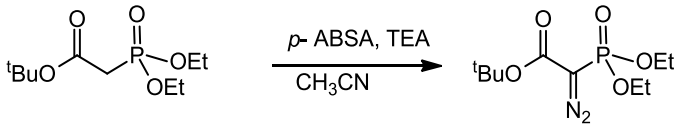
4.5 Synthesis of Diazo



Scheme 4.10 Synthesis of 1-*tert*-butyl 3-methyl 2-diazomalonate (**19a**)[8]

To a solution of *tert*- butyl methyl malonate (0.97 mL, 5.74 mmol) in acetonitrile (42 mL), was added *p*- acetoamidobenzenesulfonyl azide (1.58 g, 6.58 mmol). The reaction mixture was cooled at 0 ^{oC} for 15 minutes, then Et_3N (2.7 mL, 19.57 mmol) was added. The mixture was stirred for an additional 15 minutes at 0 ^{oC} before it was warmed room temperature and stirred overnight. The solvent was removed and the residue was washed with a 1:1 solution of Et_2O/ petroleum ether several times. The solvent was removed under reduced pressure and the residue was purified by flash column

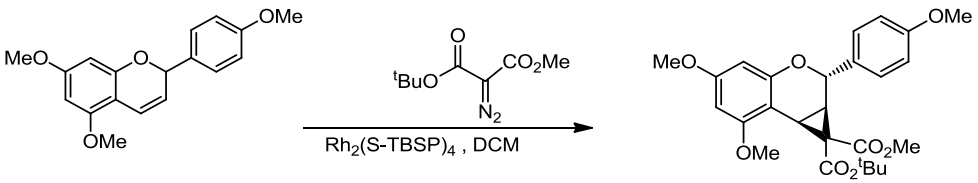
chromatography. Yield: 951 mg, 83%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 1.49 (s, 9H).



Scheme 4.11 Synthesis of *tert*-butyl 2-diazo-2-(diethoxyphosphoryl)acetate (**19b**)[9]

To a stirred solution of tert-butyl 2-(diethoxyphosphoryl)acetate (0.1 ml, 0.426 mmol) in dry THF (1 mL) was added a mixture of NaH (12.3 mg, 0.511 mmol) and *p*-acetoamidobenzenesulfonyl azide (123 mg, 0.511 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 10 mins at 0 °C and then stirred for an additional 10 min at room temperature. Ether (2 mL) and water (2 mL) were then added to the reaction mixture and it was extracted with Et_2O. The organic layer as then washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue as purified by flash column chromatography. Yield: 63.8 mg, 54 %, colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23- 4.15 (m, 4 H), 1.50 (s, 9H), 1.39 (t, J = 7.1 Hz, 6H).

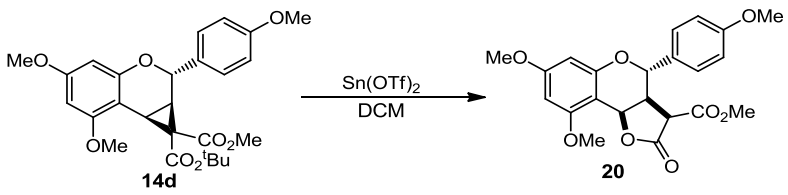
4.6 Synthesis of cyclopropane 14d



Scheme 4.12 Synthesis of 1-*tert*-butyl 1-methyl 5,7-dimethoxy-2-(4-methoxyphenyl)-1a,2-dihydrocyclopropa[c]chromene-1,1(7b*H*)-dicarboxylate (**14d**)[7]

To a solution of chromene (175 mg, 0.546 mmol) and Rh_2(*S*-TBSP)$_4$ in DCM (5 mL) was added a solution of *tert*-butyl methyl malonate diazo (347 mg, 1.73 mmol) in DCM (3.3 mL) via syringe pump over a period of 3-4 hours. After the addition was complete the reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using Et_2O/hexane system as the eluent. Yield: 170 mg; 66%; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.10 (d, *J* = 2.2 Hz, 1H), 5.84 (d, *J* = 2.2 Hz, 1H), 5.49 (s, 1H).

4.7 Rearrangement of cyclopropane

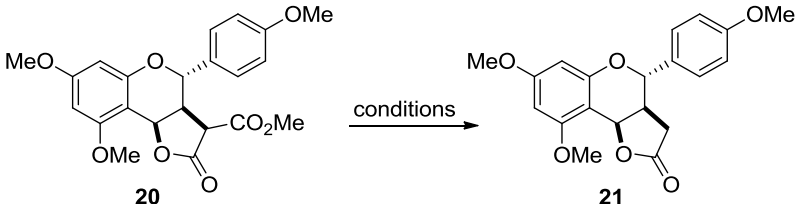


Scheme 4.13 Synthesis of methyl 7,9-dimethoxy-4-(4-methoxyphenyl)-2-oxo-3,3a,4,9b-tetrahydro-2*H*-furo[3,2-c]chromene-3-carboxylate (**20**)[7]

To a solution of cyclopropane (51 mg, 0.108 mmol) in dry DCM (2.2 mL) at 0 °C was added tin(II) triflate (23 mg, 0.054 mmol). The resulting solution was allowed to warm up to room temperature overnight. It was then quenched with water and the layers were separated. The aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography. Yield: 45 mg, 78 %, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.6 Hz, 2H), 6.98

(d, J = 8.6 Hz, 2H), 6.14 (d, J = 2.1 Hz, 1H), 6.10 (d, J = 2.1 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (s, 6H), 3.29 (dd, J = 11.5, 4.9 Hz), 1H), 3.23 (s, 1H).

4.8 Decarboxylation of lactone



Scheme 4.14 Synthesis of 7,9-dimethoxy-4-(4-methoxyphenyl)-3,3a,4,9b-tetrahydro-2*H*-furo[3,2-c]chromen-2-one (**21**)

4.8.1 Procedure A

To a solution of lactone (54 mg, 0.1300 mmol) in DMF (2 mL) was added sodium iodide (58 mg, 0.387 mmol). Afte refluxing for 5 hours the solvent was removed under reduced pressure. The residue was then dissolved in water the extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by flash column chromatography. Yield: 42 mg; 91 %; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, J = 8.6 Hz, 2H) 6.96-6.94 (d, J=8.6 Hz, 2H), 6.14 (d, J = 2.1Hz, 2H), 6.11 (d, J = 2.1 Hz, 2H), 5.60 (d, J = 4.8 Hz, 1H), 4.55 (d, J=11.5 Hz, 1H), 2.86-2.82 (m, 1H) , 2.78 (dd, J = 17.8, 7.9 Hz, 1H), 2.25 (d, J = 17.8 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): δ 175.4, 162.5, 160.5, 160.2, 157.5, 129.2, 129.1, 114.3, 99.9, 93.1, 92.4, 72.2, 55.8, 55.4, 55.3,

39.1, 32.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_6$, 357.1333; found, 357.1328.

4.8.2 Procedure B

To a solution of lactone (453.6 mg, 1.095 mmol) in anhydrous DMSO (62 mL) was added NaCl (96.1 mg, 1.643 mmol). After heating the mixture for 1.5 hours, the mixture was cooled to room temperature and distilled water was added. It was then extracted with EtOAc (x3) and the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by flash column chromatography. Yield: 295.1 mg, 76 %; yellow oil.

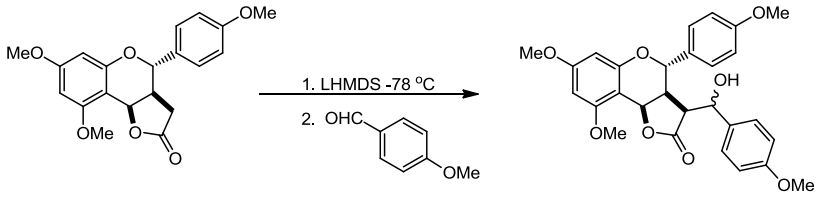
4.9 Synthesis of α-phosphono lactone 23

Scheme 4.15 Synthesis of diethyl (7,9-dimethoxy-4-(4-methoxyphenyl)-2-oxo-3,3a,4,9b-tetrahydro-2*H*-furo[3,2-*c*]chromen-3-yl)phosphonate (**23**)

To a solution of lactone (22 mg, 0.0617 mmol) in THF (0.5 mL) at -78 °C was added LHMDS (0.13 mL, 0.1300 mmol, 1M in THF). After stirring the solution at that temperature for 2 hours TMEDA (20 µL, 0.13 mmol) and diethylchlorophosphite (20 µL, 0.1390 mmol) was added and the reaction mixture was allowed to warm to room temperature over 3 hours. The reaction was then quenched by the slow addition of 1 M acetic acid in Et_2O (2 mL). The resulted mixture was filtered through a celite pad and the

pad was washed with Et_2O. After concentration under reduced pressure the residue was stirred overnight (the flask was left open to air). The mixture was dissolved in Et_2O, washed with saturated $NaHCO_3$ and brine respectively and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. Yield: 13 mg, 43 % mixture of diastereomers; clear oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37(d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.14 (d, J = 2.2 Hz, 1H), 6.09 (d, J = 2.2 Hz, 1H), 5.90 (d, J = 2.1 Hz, 1H), 4.53 (d, J = 5.0 Hz, 1H), 4.17-4.01 (m, 4H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.25-3.20 (m, 1H) 2.74 (d, J = 24.7, 1H), 1.31 (t, J = 7.1, 3 H), 1.23 (t, J = 7.0, 3H).

4.10 Synthesis of Aldol product 26



Scheme 4.16 Synthesis of 3-(hydroxy(4-methoxyphenyl)methyl)-7,9-dimethoxy-4-(4-methoxyphenyl)-3,3a,4,9b-tetrahydro-2*H*-furo[3,2-*c*]chromen-2-one (**26**)

To a solution of lactone (295.1 mg, 0.8276 mmol) in THF (2 mL) was added LHMDS (1.65 mL, 1.65 mmol, 1 M in THF) at -78 °C. After stirring for 2 hours at that temperature, *p*- anisaldehyde (200 µL, 1.65 mmol) was added. The solution was stirred for an additional 2 hours at -78 °C, after which the reaction was quenched by the addition of saturated aqueous NH_4Cl and warmed to room temperature. The resulted mixture was then extracted with EtOAc (x3). The combined organic layers were washed with brine

and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. Yield: 308.5 mg mixture of diastereomers, 76 %; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 8.3 Hz, 2H), 6.11 (s, 1H), 6.03 (s, 1H), 5.76 (d, *J* = 5.5 Hz, 1H), 5.31 (s, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 2.83 (dd, *J* = 11.5, 5.5 Hz,1H), 2.46 (s, 1H), 2.25 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 177.2, 162.2, 160.8, 159.6, 158.8, 157.3, 132.7, 128.8, 128.1, 125.8, 113.8, 113.7, 100.3, 99.9, 93.0, 92.4, 77.2, 72.9, 72.7, 55.7, 55.3, 55.1, 55.1, 52.5, 39.1; **other diastereomer**: δ 6.97 (d, *J* = 7.7 Hz, 2H), 6.95 (d, *J* = 7.68 Hz, 2H), 6.77 (d, *J* = 7.7 Hz, 2H), 6.72 (d, *J* = 7.7 Hz, 2H), 6.10 (s, 1H), 6.04 (s, 1H), 5.50 (d, *J* = 5.3 Hz, 1H), 4.91 (d, *J* = 9.0 Hz, 1H), 4.42 (d, *J* = 10.9 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.22 (s, 1H), 2.59 (d, *J* = 9.1, 1H), 2.56 (dd, *J* = 10.8, 5.4 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 177.0, 162.5, 160.6, 160.0, 159.6, 157.2, 131.7, 129.0, 128.2, 127.6, 114.1, 114.0, 99.7, 93.1, 92.5, 76.7, 72.3, 71.5, 55.8, 55.4, 55.3, 55.2, 51.3, 41.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_6$, 493.1857; found, 493.1855.

4.11 Synthesis α-benzylidene lactone 24

26 24

Scheme 4.17 Synthesis of (*E*)-7,9-dimethoxy-3-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-3,3a,4,9b-tetrahydro-2H-furo[3,2-c]chromen-2-one (**24**)

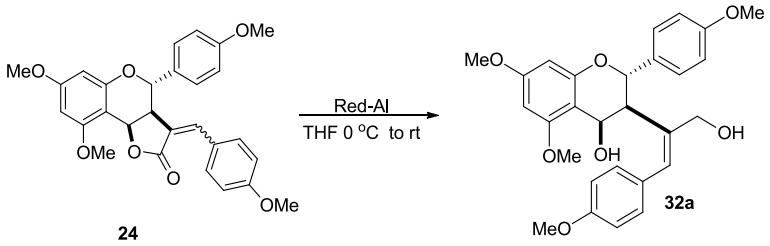
4.11.1 Procedure A

To a solution of aldol product **26** (308.5 mg, 0.6264 mmol) in DCM (4 mL) at 0 ^{o}C was added mesylchloride (98 µL, 1.261 mmol) and Et_3N (437 µL, 3.135 mmol). After stirring at room temperature for 1 hour, the reaction mixture was cooled to 0 ^{o}C and DBU (668 µL, 3.129 mmol) was added. The reaction was warmed to room temperature and stirred overnight. It was then diluted by the addition of distilled water and the layers were separated. The aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the residue purified by flash column chromatography. Yield: 242.9 mg, 82%; yellow oil. ***E*- alkene**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J*= 8.6 Hz, 2H), 6.17 (s, 2H), 5.5 (d, *J* = 4.7 Hz, 1H), 4.59 (d, *J* =10.8 Hz, 1H), 3.88 (s, 1H), 3.79 (s,1H), 3.77(s, 1H), 3.63 (s, 1H); ^{13}C NMR (600 MHz, $CDCl_3$): 172.0, 162.5, 160.7, 160.3, 159.7, 157.5, 139.8, 131.0, 129.4, 128.2, 126.2, 122.5, 113.6, 113.6, 99.9, 93.1, 92.5, 76.7, 70.1, 55.8, 55.4, 55.2, 55.0, 44.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{28}H_{26}NaO_7$, 497.1571; found, 497.1623. ***Z*- alkene**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.16 (s, 2H), 5.90 (s, 1H), 5.60 (d, 5.1 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 3.88 (s, 1H), 3.85 (s,1H), 3.81 (s, 1H), 3.78 (s, 1H), 3.23 (dd, *J* = 11.0, 5.0 Hz, 1H); ^{13}C NMR (600 MHz, $CDCl_3$): 168.7, 162.4, 160.9, 160.8, 160.0, 157.6, 143.2, 133.0, 129.5, 129.1, 126.1, 121.3, 113.9, 113.5, 100.2, 93.1, 92.6, 77.6, 69.2, 55.8, 55.4, 55.4, 55.3, 48.5.

4.11.2 Procedure B

To a solution of of aldol product **26** (27 mg, 0.0548 mmol) in DCM (0.5 mL) at 0 ^{o}C was added Et_3N (38 µL, 0.2726 mmol) and mesylchloride (9 µL, 0.1096). The mixture was warmed to room temperature and stirred for 1 hour. It was then quenched by the addition of distilled water. The layers were separated and the aqueous phase was extracted with DCM. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was the removed *in vacuo* and the residue dissolved in dry THF (7 mL). Potassium *tert*-butoxide (19 mg, 0.169 mmol) was then added and the mixture was refluxed until reaction was complete, as indicated by TLC. After completion the reaction mixture was diluted with distilled water and was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography. Yield: 16.2 mg, 62 %; pale yellow oil.

4.12 Synthesis of diol 32



Scheme 4.18 Synthesis of 3-(3-hydroxy-1-(4-methoxyphenyl)prop-1-en-2-yl)-5,7-dimethoxy-2-(4-methoxyphenyl)chroman-4-ol (**32**)

Red-Al (0.66 mL, 2.046 mmol, 60% weight in toluene) was added dropwise to a solution of α- benzylidene lactone **24** (242.9 mg, 0.5119 mmol) in THF (4.2 mL) at 0 ^{o}C.

The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction mixture was then cooled to 0 ^{o}C and a saturated solution of Rochelle's salt was added dropwise. The layers were separated and the organic layer was washed with a saturated solution of Rochelle's salt. The combined aqueous layers were extracted with Et_2O (x3), followed by washing of the combined organic layers with brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography. Yield: 203.9 mg (Z Isomer: 73.5 mg; *E* isomer: 124.7 mg; mix (5.7 mg), 83 %; clear oil. ***E* Isomer**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.55 (s, 1H), 6.10 (d, *J* = 2.2 Hz , 1H), 6.02 (d, *J* = 2.2 Hz, 1H), 5.35 (d, *J* = 11.1 Hz, 1H), 5.12 (d, *J* = 3.3 Hz), 4.11 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (d, *J* = 12.4 Hz, 1H), (s, 3H), 3.71 (s, 3H), 3.58 (dd, *J* = 11.0, 3.42 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): δ 161.4, 159.8, 158.8, 158.5, 155.9, 138.0, 134.8, 130.2, 129.8, 129.5, 129.4, 113.8, 113.7, 105.9, 93.1, 91.7, 75.8, 65.1, 64.1, 60.3, 55.6, 55.3, 55.2, 55.1, 44.3; HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{28}H_{30}O_7$, 478.1992; found, 478.1963.

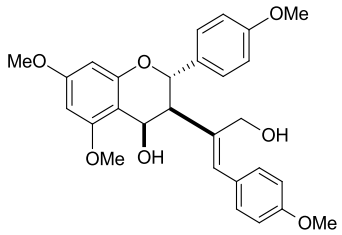
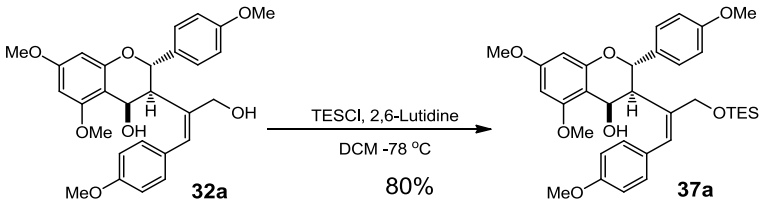


Figure 4.1 (*Z*)-3-(3-hydroxy-1-(4-methoxyphenyl)prop-1-en-2-yl)-5,7-dimethoxy-2-(4-methoxyphenyl)chroman-4-ol (**32b**)

Z Isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.47 (s, 1H), 5.40 (d, *J* = 11.2 Hz, 1H), 5.11 (d, *J* = 3.4 Hz, 1H), 3.88 (s, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.15 (dd, *J* = 11.2, 3.2 Hz); ^{13}C NMR (600MHz, $CDCl_3$): δ 161.5, 159.9, 158.9, 158.7, 155.9, 136.7, 135.3, 130.4, 130.4, 129.5, 129.1, 113.9, 113.5, 105.9, 93.2, 91.7, 75.6, 64.9, 58.2, 55.6, 55.4, 55.2, 52.7; HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{28}H_{30}O_7$, 478.1992; found, 478.1963.

4.13 Synthesis of mono (TES) Ether



Scheme 4.19 Synthesis of (*E*)-5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-ol (**37a**)

To a solution of diol **32a** (23.3 mg, 0.0487 mmol), in dry DCM (16 mL) at - 78 °C, was added a solution of TESCl (50 µL, 0.2979 mmol) and 2,6-lutidine (60 µL, 0.5152 mmol) in dry DCM (1 mL) via syringe. After stirring at - 78 °C temperature for 3 hours, the reaction was quenched by the addition of a saturated solution of aqueous NH_4Cl. The mixture was extracted with DCM (x3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography. Yield: 23.2 mg, 80%; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.4 Hz,

2H), 6.83 (d, J = 8.4 Hz, 2H), 6.51 (s, 1H), 6.09 (s, 1H), 5.98 (s, 1H), 5.45 (d, J = 11.2 Hz, 1H), 5.14 (s, 1H), 4.73 (s, 1H), 4.33 (d, J = 12.1, 1H), 3.88 (s, 3H), 3.81 (s, 6H), 3.77 (s, 1H), 3.69 (s, 1H), 3.59 (dd, J = 11.3, 1.59 Hz), 0.96 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 7.9 Hz, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 163.7, 162.5, 161.7, 161.2, 158.4, 140.0, 136.3, 133.2, 132.6, 132.4, 132.1, 116.6, 116.5, 109.1, 95.4, 94.4, 77.9, 68.1, 66.1, 58.5, 58.0, 58.0, 47.1, 9.5, 7.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{34}H_{44}NaO_7Si$, 615.2749; found, 615.2721.

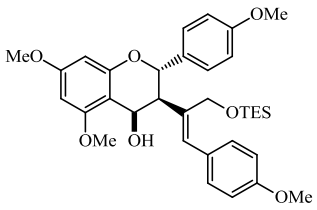
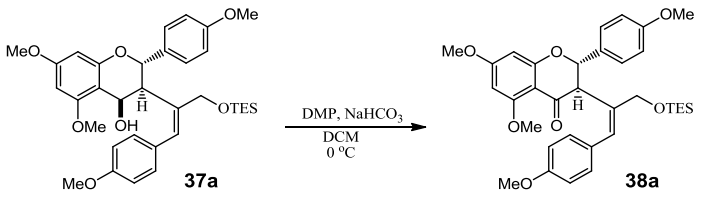


Figure 4.2 (*Z*)-5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-one (**37b**)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.49 (s, 1H), 6.11 (d, J = 2.3 Hz, 1H), 6.08 (d, J = 2.3 Hz, 1H), 5.49 (d, J = 11.5 Hz, 1H), 5.10 (d, J = 2.5 Hz, 1H), 3.99 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.69 (s, 1H), 3.28 (dd, J = 11.5, 2.5 Hz), 0.96 (t, J = 8.0 Hz, 9H), 0.62 (q, J = 7.7 Hz, 6H); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{34}H_{44}NaO_7Si$, 615.2749; found, 615.2721.

4.14 Synthesis of ketone 38



Scheme 4.20 Synthesis of (*E*)-5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-one (**38a**)

To a suspension of mono (TES) ether **37a** (24 mg, 0.0405 mmol), and $NaHCO_3$ (119.1 mg, 1.4178 mmol) in dry DCM (11.2 mL) at 0 °C was added DMP (34.3 mg, 0.0809 mmol); in two portions over 15 minutes. After stirring at room temperature for 5 hours the reaction mixture was cooled to 0 °C and quenched by the slow addition of saturated $NaHCO_3$ (10 mL) and $Na_2S_2O_5$ (10 mL). The resulting mixture was stirred for 5 minutes at 0 °C and then for 30 minutes at room temperature. The layers were then separated and the aqueous phase was extracted with DCM (x3). The combined organic layers were then washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography. Yield: 18.5 mg, 77 %; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.06 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.63 (s, 1H), 6.10 (d, J = 2.1 Hz, 1H), 6.04 (d, J = 2.1 Hz, 1H), 5.49 (d, J = 12.6 Hz, 1H), 4.30 (d, J = 12.6 Hz, 1H), 4.22 (d, J = 13.6 Hz, 1H), 4.19 (d, J = 13.5 Hz, 1H), 3.9 (s, 3H), 3.804 (s, 3H), 3.793 (s, 3H), 3.767 (s, 3H), 0.91 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9, 6H); ^{13}C NMR ($CDCl_3$; 600MHz): δ 190.2, 165.5, 164.8, 162.4, 159.9, 158.4, 134.3, 129.9, 129.8, 129.6, 129.4, 129.3, 113.6, 113.4, 106.2, 93.3, 93.2, 81.9, 64.6, 56.0, 55.5,

55.3, 55.2, 53.4, 6.7, 4.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{34}H_{43}O_7Si$, 591.2773; found, 591.2762.

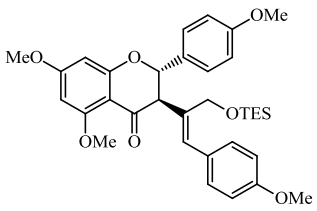


Figure 4.3 (*Z*)-5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-one (**38b**)

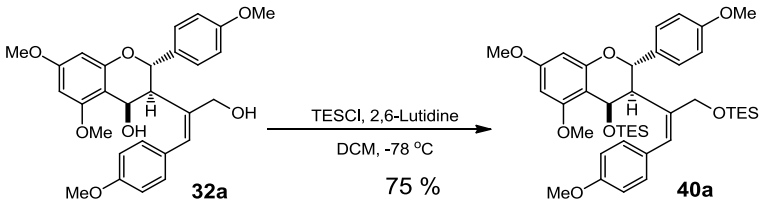
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.14 (d, *J* = 2.2 Hz, 1H), 6.09 (d, *J* = 2.2 Hz, 1H), 6.01 (s, 1H), 5.74 (d, *J* = 11.1 Hz, 1H), 4.38 (d, *J* = 12.3 Hz, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 3.88 (s, 3H), 3.81(s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.76 (s, 1H), 0.87-0.84 (t, *J* = 7.9 Hz, 9H), 0.54-0.50 (q, *J* = 7.9 Hz, 6H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{34}H_{43}O_7Si$, 591.2773; found, 591.2762.

4.15 Synthesis of keto-aldehyde 33a

Scheme 4.21 (*E*)-2-5,7-dimethoxy-2-(4-methoxyphenyl)-4-oxochroman-3-yl)-3-(4-methoxyphenyl)acrylaldehyde (**33**)

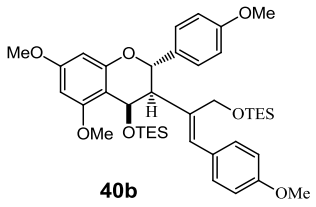
To a solution of ketone (20.7 mg, 0.0351 mmol), in dry DCM (1.2 mL) at 0 °C was added phosphate pH 7 buffer (0.11 mL) and DDQ (9.6 mg, 0.0423 mmol). The resulting mixture was warmed to room temperature and stirred until completion as indicated by TLC (7 hours). The mixture was then quenched by the addition of saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with DCM (x3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the reddish residue was purified by flash column chromatography. Yield: 12.9 mg, 78 %; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.42 (s, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 6.73 (d, J = 8.1 Hz, 2H), 6.12 (s,1H), 6.10 (s, 1H), 5.96 (d, J = 12.0 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 3.90 (s, 1H), 3.83 (s, 1H), 3.80 (s, 1H), 3.77 (s, 1H); ^{13}C NMR (600 MHz, $CDCl_3$): 194.0, 188.9, 165.9, 165.2, 162.7, 160.6, 159.9, 155.0, 130.2, 129.3, 128.6, 126.8, 114.0, 113.7, 93.5, 93.4, 80.9, 56.2, 55.6, 55.3, 55.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{28}H_{27}O_7$, 475.1751; found, 475.1733.

4.16 Synthesis of bis (TES) Ether 40



Scheme 4.22 Synthesis of (*E*)-((5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-yl)oxy)triethylsilane (**40a**)

TESCl (184 µL, 1.0962 mmol) was added dropwise to a solution of diol (124.7 mg, 0.2607 mmol), imidazole (110 mg, 1.6157 mmol), and 4-DMAP (12.7 mg, 0.1039 mmol) in dry DMF (8 mL) at 0 ºC. The reaction mixture was then warmed to rt and stirred overnight. It was then poured into a saturated solution of $NaHCO_3$ and extracted with Et_2O (x3). The organic layer was then washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by flash column chromatography. Yield: 138.6 mg, 75 %; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): 7.11 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.82-6.81 (m, 4H), 6.65 (s, 1H), 5.99 (s, 1H), 5.93 (s, 1H), 5.49 (d, *J* =11.6 Hz, 1H), 5.22 (s, 1H), 4.73 (d, *J* = 15.8 Hz, 1H), 3.91 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 3.792 (s, 3H), 3.784 (s, 3H), 3.680 (s, 3H), 3.46 (d, *J* = 11.6 Hz, 1H), 0.90 (t, *J* = 7.7 Hz, 9H), 0.85 (t, *J* = 7.6 Hz, 9H), 0.63-0.53 (m, 6H), 0.463 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (600 MHz, $CDCl_3$): 161.1, 159.8, 157.8, 157.7, 155.9, 139.3, 130.9, 130.8, 129.8, 129.7, 125.1, 113.8, 113.7, 106.8, 92.8, 90.6, 75.3, 64.8, 55.3, 55.2, 55.1, 54.8, 43.7, 6.9, 6.7, 5.0, 4.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{40}H_{50}NaSi_2$, 729.3613; found, 729.3606.

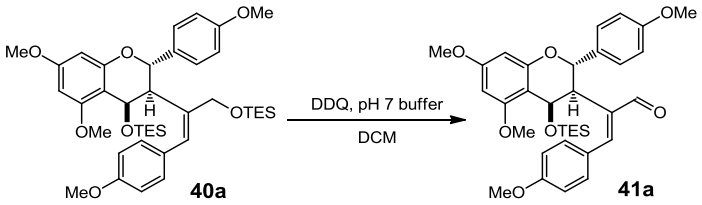


40b

Figure 4.4 (*E*)-((5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-yl)oxy)triethylsilane (**40b**)

^{1}H NMR (600 MHz, $CDCl_3$): 7.37 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 8.1 Hz, 2H), 6.40 (s, 1H), 6.07 (s, 1H), 6.02 (s, 1H), 5.615 (d, J = 11.3 Hz, 1H), 5.19 (s, 1H), 4.19 (d, J = 11.3 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.073 (d, J = 11.7 Hz, 1H), 0.86-0.59 (m, 18H), 0.59-0.532 (m, 6H), 0.50-0.46 (m, 6H). ^{13}C NMR (600 MHz, $CDCl_3$): 160.9, 159.2, 158.1, 157.8, 155.8, 136.0, 132.5, 131.1, 130.1, 129.7, 129.6, 113.4, 113.3, 108.0, 92.9, 90.5, 76.8, 62.4, 61.6, 55.2, 55.1, 54.6, 46.1, 7.0, 6.7, 5.1, 4.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{40}H_{50}NaSi_2$, 729.3613; found, 729.3606.

4.17 Synthesis of *E*-aldehyde 41a

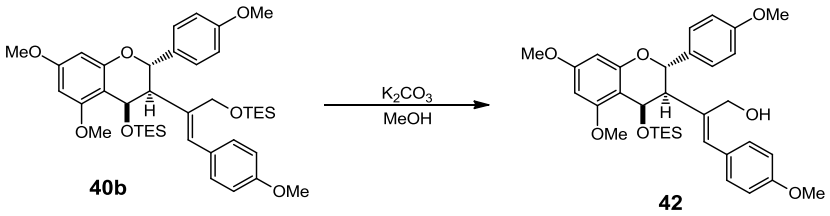


Scheme 4.23 Synthesis of ((*E*)-2-(5,7-dimethoxy-2-(4-methoxyphenyl)-4-((triethylsilyl)oxy)chroman-3-yl)-3-(4-methoxyphenyl)acrylaldehyde (**41a**)

To a solution of bis-protected triethylsiyl ether **40a** (36.4 mg, 0.0515 mmol) in DCM at 0 ºC was added DDQ (12.8 mg, 0.0564 mmol) and phosphate pH 7 buffer (0.18 mL). The solution was warmed to room temperature and monitored for completion. Upon completion saturated $NaHCO_3$ was added and the layers were separated. The aqueous phase was extracted with Et_2O (x3). The combined organic layers were then washed with brine and dried over $MgSO_4$. The solvent was then removed under reduced pressure and

the residue was purified by flash column chromatography. Yield: 20.7 mg 68 % (79 %)[c] ; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.57 (s. 1H), 7.30 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.77 (d, *J* = 7.9 Hz, 2H), 6.14 (d, *J* = 11.0 Hz, 1H), 6.05 (s, 2H), 5.20 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.66 (d, *J* = 10.9 Hz, 1H), 0.85 (t, *J* = 8.0, 9 H), 0.62-0.49 (m, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): 193.0, 161.3, 160.3, 159.7, 159.7, 158.4, 145.2, 131.2, 130.7, 129.6, 114.4, 113.8, 106.3, 92.9, 91.0, 74.8, 64.1, 59.7, 55.3, 55.2, 55.2, 54.7, 6.9, 4.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{34}H_{43}O_7Si$, 591.2773; found, 591.2721.

4.18 Selective deprotection of 1^0 TES ether



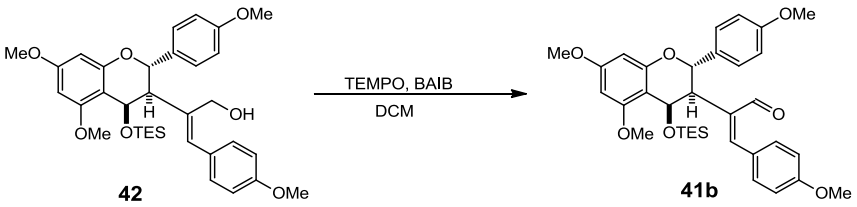
Scheme 4.24 Synthesis of (*Z*)-2-(5,7-dimethoxy-2-(4-methoxyphenyl)-4-((triethylsilyl)oxy)chroman-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-ol (**42**)

To a solution of bis (TES) ether (15.1 mg, 0.0213 mmol) in methanol (3.4 mL) at 0 ^{o}C was added K_2CO_3 (23 mg, 0.1664 mmol). The mixture was warmed to rt and stirred overnight. After stirring overnight, starting material was still present, therefore an additional K_2CO_3 (20 mg) was added and the reaction mixture was stirred for an additional 2 hours. It was then diluted by the addition of distilled water (4 mL) and brine (4 mL) and extracted with EtOAc (x3). The combined organic layers were washed with

[c] Yield based on recovered starting material

brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography. Yield: 8.7 mg, 69 %; ^{1}H NMR (600 MHz, $CDCl_3$): 7.367 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.46 (s, 1H), 6.07 (d, J = 2.2 Hz, 1H), 6.03 (d, J = 2.3 Hz, 1H), 5.66 (d, J = 11.6 Hz, 1H), 5.22 (d, J = 1.9 Hz, 1H), 4.00 (d, J = 12.2 Hz, 1H), 3.96 (d, J = 12.2 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.02 (dd, J = 11.6, 1.9 Hz, 1H), 0.87 (t, J = 8.0 Hz, 9H), 0.61-0.57 (m, 3H), 0.54-0.50 (m, 3H); ^{13}C NMR (600MHz, $CDCl_3$): 161.5, 159.5, 157.8, 156.1, 137.0, 133.6, 130.1, 129.4, 113.8, 113.5, 106.6, 93.0, 90.7, 75.8, 64.1, 60.1, 59.8, 55.3, 55.2, 55.2, 54.8, 51.0, 6.9, 4.9,; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{34}H_{44}NaSi$, 615.2749; found, 615.2721.

4.19 Synthesis of *Z*-aldehyde

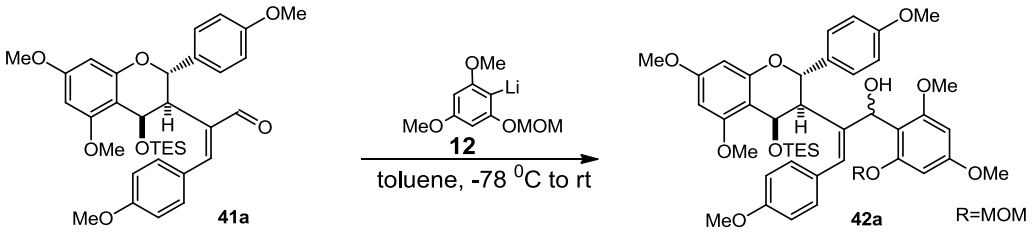


Scheme 4.25 Synthesis of ((*Z*)-2-(5,7-dimethoxy-2-(4-methoxyphenyl)-4-((triethylsilyl)oxy)chroman-3-yl)-3-(4-methoxyphenyl)acrylaldehyde (**41b**)

To a solution of primary alcohol **42** (16 mg, 0.0270 mmol) in DCM (0.25 ml) at rt was added TEMPO (0.42 mg, 0.003 mmol) and BAIB (17.4 mg, 0.0540 mmol). The reaction mixture was monitored for completion as indicated by TLC (2 hours). The reaction mixture was then diluted by the addition of DCM and washed with saturated $Na_2S_2O_3$. The aqueous phase was then extracted with DCM (x3). The combined organic

layers were washed with $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. Yield: 11.3 mg, 71 %; ^{1}H NMR (600 MHz, $CDCl_3$): 9.59 (s, 1H), 7.61 (s, 1H) 7.29 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.06 (d, J = 2.3 Hz, 1H), 6.02 (d, J = 2.3 Hz, 1H), 5.55 (d, J = 11.8 Hz, 1H), 5.01 (d, J = 2.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.71 (dd, J = 11.8, 2.2 Hz, 1H), 0.83 (t, J = 8.0 Hz, 9H), 0.58-0.47 (m, 6H); ^{13}C NMR (600MHz, $CDCl_3$): 191.7, 161.1, 160.5, 159.5, 158.0, 155.8, 150.4, 137.0, 131.5, 131.4, 129.5, 126.5, 113.8, 113.8, 106.1, 92.9, 90.8, 76.3, 61.6, 55.3, 55.2, 55.2, 54.7, 40.7, 7.0, 5.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ $C_{34}H_{43}O_7Si$, 591.2773; found, 591.2721.

4.20 Lithiation of aldehyde 41a



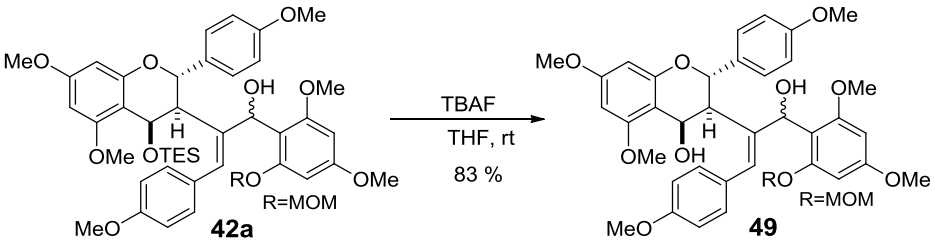
Scheme 4.26 (*E*)-2-(5,7-dimethoxy-2-(4-methoxyphenyl)-4-((triethylsilyl)oxy)chroman-3-yl)-1-(2,4-dimethoxy-6-(methoxymethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-ol (**42a**)

To a solution of aldehyde **41a** (24.5 mg, 0.0415 mmol) in toluene (0.3 mL) at – 78 ^{o}C, was added a freshly prepared solution of aryllithium **12**[d] (0.41 mL, 0.303 M in toluene, 0.1242 mmol). The reaction mixture was stirred at -78 ^{o}C for 15 mins and then

[d] For preparation of aryllithium see ref.[10]

warmed to -50 °C over 30 mins and then to rt over 2 hours. The reaction was then quenched by the addition of a saturated solution of NH_4Cl and extracted with EtOAc (x3). The combined organic layers were then washed brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. Yield: 23.1 mg as a mixture of inseparable diastereomers, 71 %; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{44}H_{56}NaO_{11}Si$, 811.3490; found, 811.3447.

4.21 Deprotection of TES ether



Scheme 4.27 Synthesis of (*E*)-3-(3-(2,4-dimethoxy-6-(methoxymethoxy)phenyl)-3-hydroxy-1-(4-methoxyphenyl)prop-1-en-2-yl)-5,7-dimethoxy-2-(4-methoxyphenyl)chroman-4-ol (**49**)

To a solution of alcohol **42a** (44.2 mg, 0560 mmol) in dry THF (2.8 mL) at rt, was added TBAF (84 µL, 1.0 M in THF, 0.084 mmol). The reaction mixture was stirred at rt until completion (1.5 hours). It was then quenched by the addition of a saturated solution of $NaHCO_3$ and extracted with DCM (x3). The combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated under removed pressure. The resulting residue was purified by flash column chromatography. Yield: 31.6 mg as an

inseparable mixture of diastereomers, 84 %; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{38}H_{42}NaO_{11}$, 697.2625; found, 697.2591.

4.22 References

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APPENDIX A

^{1}H NMR AND ^{13}C NMR SPECTRA FOR ALL NEW COMPOUNDS