Study of Enantioselective Epoxidation, Asymmetric Reduction and Synthesis of Bioactive Oligomeric Flavonoids

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Chapter 1: Synthesis of proanthocyanidins

1.1. Introduction

Anabolism and catabolism constitute important processes in living organisms, called metabolism. The process of building up protoplasm is called anabolism and breaking it down is called catabolism. Energy is consumed and released; physical and chemical changes take place in the life cycle of living organisms during metabolism. The substances, which are produced and degraded during these complex processes, are collectively known as metabolites.

Plant physiologists separate metabolism into two categories i.e. primary metabolism and secondary metabolism. All organisms possess similar metabolic pathways by which they synthesize and utilize certain essential chemical species: sugars, amino acids, common fatty acids, nucleotides and polymers derived from them (e.g. lipids, proteins and polysaccharides). This is known as primary metabolism and these compounds, which are essential for the survival and well being of the organisms, are called primary metabolites. Most organisms also utilize other metabolic pathways, producing compounds for the purposes other than primary physiological functions, these are secondary metabolites also known as natural products and the pathways for their synthesis and utilization constitute secondary metabolism. Many of these secondary metabolites found in plants, animals and micro-organisms possess pharmacological properties. Today many of these secondary metabolites are used to treat mild and serious human afflictions. Aspirin and menthol are two commonly used and widely recognized natural product drugs.

1.2. Introduction of monomeric flavonoids

The name flavonoids is derived from the Latin word "*Flavus*" which means Yellow, and these compounds are one of the biggest classes of secondary metabolites and designated plant-derived natural products with extreme diversity.[1] The diversity arises from differences in the oxidation state, skeletal modification, and oligomer formation. All the flavonoids have the

basic skeleton of 1,3-diphenylpropane (C_6-C_3-C_6) which constitute three rings (A, B, C) in the basic skeleton (Figure 1.1).

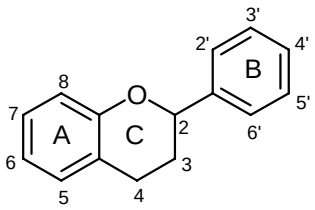


Figure 1.1: Basic skeleton of flavonoids.

1.3. Classes of flavonoids

The various classes of flavonoids are chalcones, flavones, flavanols, flavanone, flavanonols, flavans, catechins, flavandiols, and anthocyandins etc. The basic skeletons of the flavonoid classes are shown in (Figure 1.2). The chalcone is the starting unit of all the classes of flavonoids.

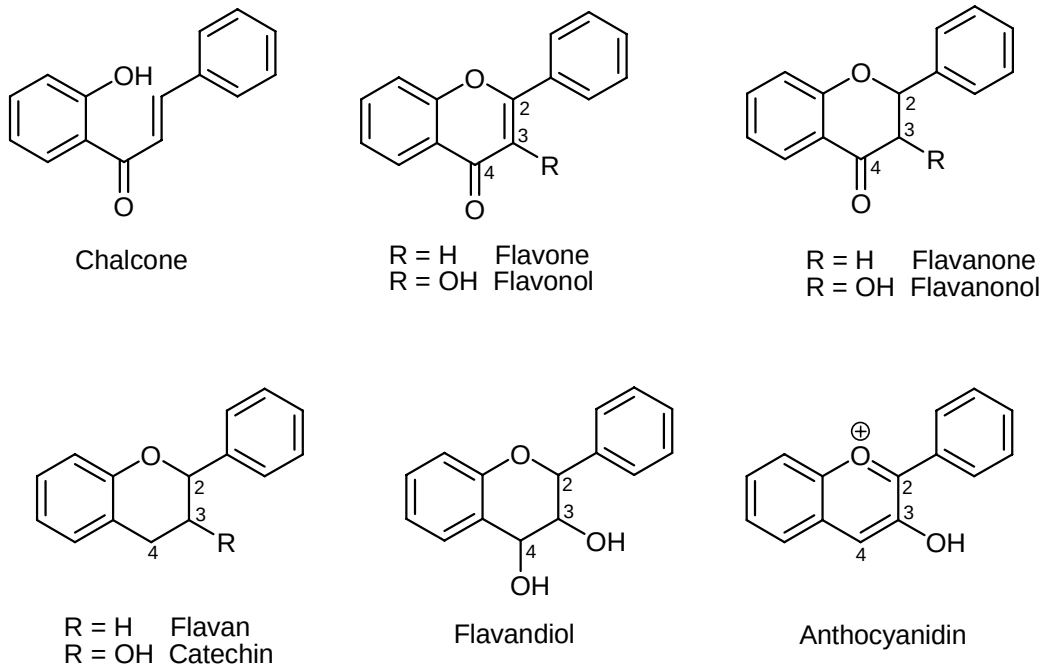


Figure 1.2: Structures of different classes of flavonoids.

A great number of different flavonoids are possible to be formed from derivatization of the basic skeleton, for example; glycosylation, methylation, hydroxylation or other modifications of this skeleton.[2] One key point would be the stereoselective elaboration of the C_4 position of the flavanol skeletons. This would have important relevance to the structural diversification in the biogenetic origin of complex polyphenols, such as oligomeric catechins.

An overview of different derivatives of different classes of flavonoids has been published by Harborne.[3,4,5,6]

1.4. Introduction to the proanthocyanidins

Proanthocyanidin (also known as oligomeric proanthocyanidin (OPC), leukocyanidin and leucoanthocyanin) is a specific class of flavonoids. It was discovered in 1936 by Professor Jacques Masquelier and called Vitamin P, although this name did not gain official category status and has since fallen out of usage. It was Masquelier who first developed techniques for the extraction of proanthocyanidins from certain plant species.

Proanthocyanidins can be found in many plants, most notably pine bark, grape seed, grape skin, and red wines of *Vitis vinifera*. However, bilberry, cranberry, black currant, green tea, black tea, and other plants also contain these flavonoids. The berries of chokeberry, specifically black chokeberry, have the highest measured concentrations of proanthocyanidin found in any plant to date.[7]

The proanthocyanidins presumably constitute the most ubiquitous group of all plant phenolics. Their exceptional concentrations in the barks and heartwoods of a variety of tree species have resulted in their commercial extraction with the initial objective of applying the extracts in leather manufacture.[8] They are also known as tannins, or condensed tannins, which are amorphous, rarely crystalline substances and are known for their astringent taste. They also have the ability to complex and to form precipitates with macromolecules such as proteins and polysaccharides, with alkaloids and with heavy metals.[9,10]

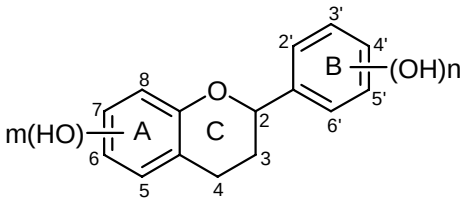
They are also known as leucoanthocyanidins which are monomeric compounds and are able to produce anthocyanidins by cleavage of a C–O bond on heating with mineral acid. Proanthocyanidins are oligomers/polymers which give anthocyanidins by cleavage of a C–C

bond under strongly acidic conditions in the presence of molecular oxygen. Together with the bi- and tri-flavonoids, they represent the two major classes of complex C_6-C_3-C_6 secondary metabolites. The bi- and tri-flavonoids are products of oxidative coupling of flavones, flavonols, dihydroflavonols, flavanones, isoflavones, aurones, chalcones, and 2-benzylbenzofuranones and thus consistently possess a carbonyl group at C_4 or its equivalent in every constituent flavanyl unit. The proanthocyanidins, on the contrary, usually originate by coupling at C_4 (C-ring) of an electrophilic flavanyl unit, presumably generated from a flavan-3,4-diol or a flavan-4-ol, most commonly to C_6 or C_6 (A-ring) of a nucleophilic flavanyl unit.[11] The proanthocyanidins have recently attracted a considerable amount of attention in the fields of nutrition, health and medicine. This is the result of a rapidly growing body of evidence suggesting that the proanthocyanidins may act as potent antioxidants and modulate key biological pathways *in vivo* in mammals.[12]

1.5. Classes of proanthocyanidins

There are a large number of classes of proanthocyanidins depending on the monomeric starting unit of the flavonoids. Some of the classes are shown (Table 1.1).

Table 1.1: Classes of proanthocyanidin.

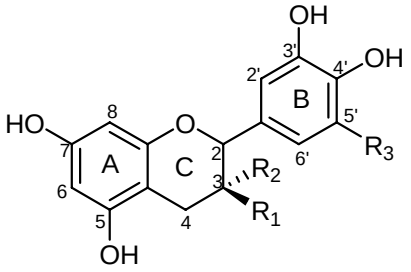


Class of proanthocynidin	Monomeric unit (2R:3S)	Substitution Pattern				
		5	7	3’	4’	5’
Procyanidin	Catechin	OH	OH	OH	OH	H
Prodelphindin	Gallocatechin	OH	OH	OH	OH	OH
Propelargonidin	Afzelechin	OH	OH	H	OH	H
Profisetindin	Fisetinidol	H	OH	OH	OH	H

1.5.1. Classes of procyanidin and prodelphindin

Procyanidins are the class of proanthocynidin which are abundant in nature and mainly comprise of (+)-catechin and (−)-epicatechin. For prodelphinidins, the main building blocks are (−)-gallocatechin and (+)-epigallocatechin. They are the monomeric units which build the proanthocyanidin and hence are called the building blocks for proanthocyaniodins (Table 1.2).

Table 1.2: Classes of procyanidins and prodelphindins with trivial names.



Trivial names	R_1	R_2	R_3	Configuration
(+)-Catechin	OH	H	H	2R:3S
(−)-Epicatechin	H	OH	H	2R:3R
(−)-Gallocatechin	OH	H	OH	2S:3R
(+)-Epigallocatechin	H	OH	OH	2R:3R

1.5.2. Nomenclature and trivial names of known procyanidin

The nomenclature system proposed by Hemingway[13] and extended by Porter[14] is applied consistently. Porter developed a nomenclature by considering the substitutions on the A and C-ring of the coupling units. He named the coupling unit, substituted at the C_4 position as the T-unit (top or upper unit) and the middle unit on which the substitution takes place at C_6 and C_8 as the M-unit (middle unit). The unit on which all the possible positions (C_4, C_6, C_8) for interflavanyl bonding used, is called the J-unit and the unit in which only one bond either on C_6 or C_8 is formed, is called as the B-unit (base unit). Here are the trivial names and Porter's nomenclature of some of the procyanidins (Table 1.3).

Table 1.3: Nomenclature of procyanidins according to Porter.

Trivial Names	**Porter Nomenclature**
Procyanidin **B_1**	Epicatechin-(4β→8)-catechin
Procyanidin **B_2**	Epicatechin-(4β→8)-epicatechin
Procyanidin **B_3**	Catechin-(4α→8)-catechin
Procyanidin **B_4**	Catechin-(4α→8)-epicatechin
Procyanidin **B_5**	Epicatechin-(4β→6)-epicatechin
Procyanidin **B_6**	Catechin-(4α→6)-catechin
Procyanidin **B_7**	Epicatechin-(4β→6)-catechin
Procyanidin **B_8**	Catechin-(4α→6)-epicatechin
Procyanidin **A_1**	Epicatechin-(2β→ O→7),(4β→8)-catechin
Procyanidin **A_2**	Epicatechin-(2β→ O→7),(4β→8)-epicatechin
Procyanidin **C_1**	Epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin
Procyanidin **C_2**	Catechin-(4α→8)-catechin-(4α→8)-catechin

1.6. Types of proanthocyanidins

There are different types of proanthocyanidins but the most abundant are A-types and B-types depending on the linkages between successive monomeric units. The linkage in proanthocyanidins is usually between the C_4 position of the ‘‘upper’’ unit and the C_8 position of the ‘‘lower’’ or ‘‘starter’’unit. α- or β-linkages can also occur between C_4 of the ‘‘upper’’ unit and C_6 or C_8 of the ‘‘lower’’ unit and thus give rise to different stereochemistry.[12,15]

1.6.1. A-type proanthocyanidins

In A-type proanthocyanidins, linkages occur between C_2 and C_4 of the T-unit (top or upper unit) and the oxygen at C_7 and position C_6 and C_8 of the B-unit (basic or lower unit). They are not as frequently isolated from plants as B-types. They have been considered as unusual structures. They have been found in plants as dimers, trimers, tetramers, pentamers and polymers (Figure 1.3).

A-type proanthocyanidins were shown to be the major components with antibacterial and antitherpeutic activity.[15]

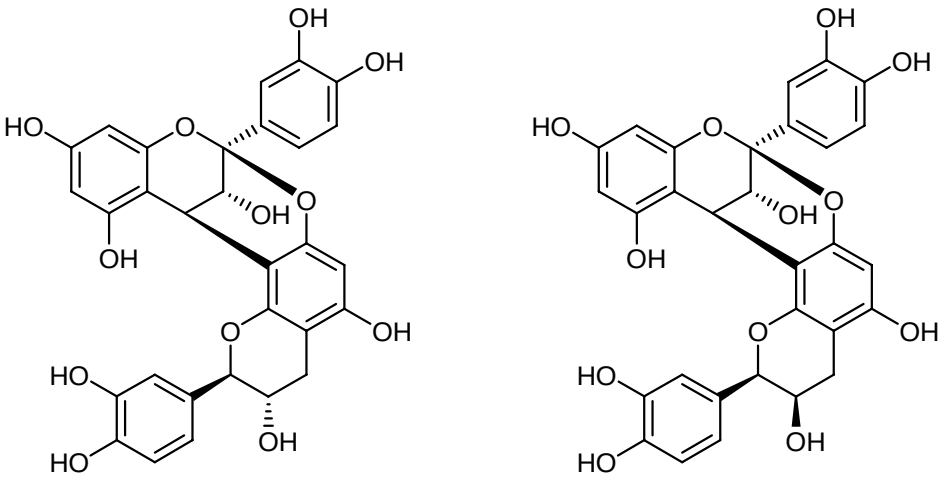
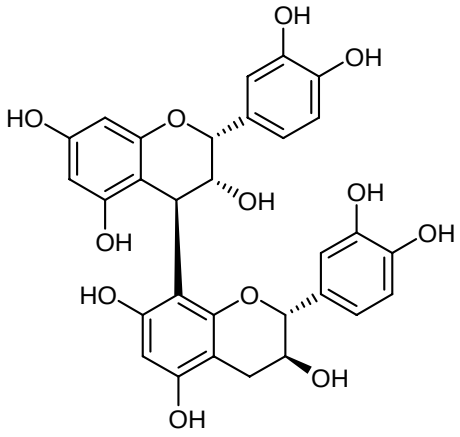


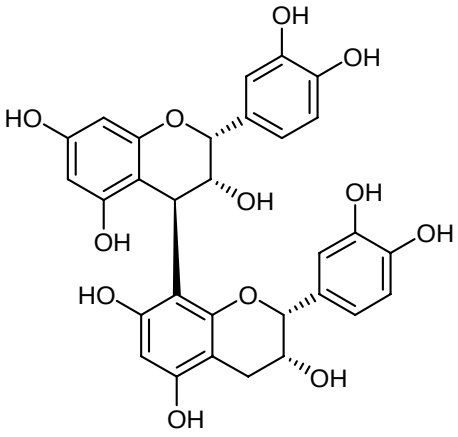
Figure 1.3: A-type proanthocyanidins.

1.6.2. B-type proanthocyanidins

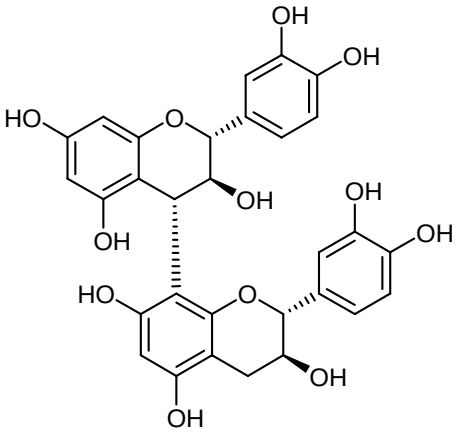
B-type proanthocyanidins are oligomers or polymers of flavan-3-ols characterized by a single interflavanyl linkage usually between C_4 of the ‘‘upper’’ extension units and C_8 or C_6 of the ‘‘lower’’ or ‘‘starter’’ unit. Proanthocyanidins B_1–B_4 differ only in the arrangement of (+)-catechin and (−)-epicatechin starter and extension units (Figure 1.4). B-types proanthocyanidin e.g. procyanidin C_2, and T_2 (Figure 1.5) due to a more extended phenolic system, are of major use in antioxidant activities.[15]



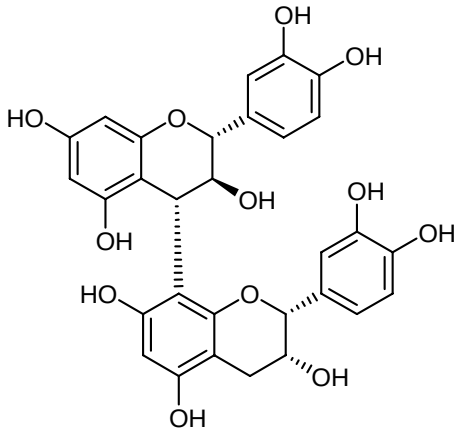
Procyanidin B_1



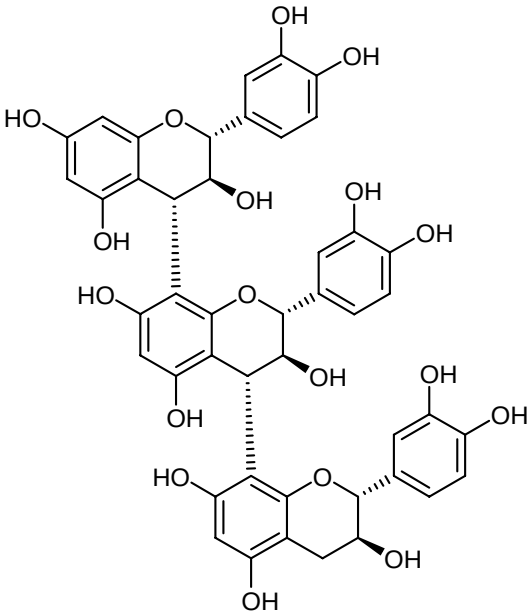
Procyanidin B_2



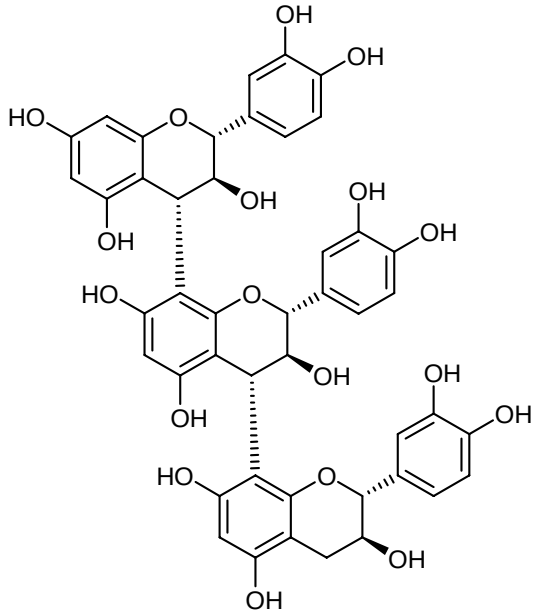
Procyanidin B_3



Procyanidin B_4



Procyanidin C_2



Prodelphinidin T_2

Figure 1.4: B-type proanthocyanidins.

1.7. Biosynthesis of (+)-catechin and (–)-epicatechin

Biosynthesis of proanthocyanidins is not easy because the potential substrates are not readily available, have multiple potential stereochemistries, and are readily oxidized in biological extracts. According to enzymological studies, in crude extracts from cell or tissue cultures, the flavanones are converted into dihydroflavonols by flavanone-3-hydroxylase (F3H). By the action of dihydroflavonol reductase (DFR) dihydroflavonols are further converted into leucoanthocyanidins i.e. into the corresponding flavan-3,4-diols and leucoanthocyanidin reductase (LAR). Leucoanthocyanidins are converted into (+)-flavan-3-ols and anthocyanidins by leucoanthocyanidin reductase (LAR) and anthocyanidin synthase (ANS) respectively.[15] Anthocyanidins are further converted into (−)-epi-flavan-3-ols and anthocyanins by anthocyanidin reductase (ANR) and anthocyanidin glycosyltransferase (GT) respectively (Scheme 1.1).

1.8. Formation of proanthocyanidin oligomers and polymers

Catechins and epicatechins are the most common starting units for the proanthocyanidins. 2,3-*cis*-(−)-Epicatechin is the predominant extention unit and is also more common in plants. Leucoanthocyanidins, flavan-3-ols and anthocyanidins are supposed to be converted into the corresponding quinone intermediate by the action of polyphenol oxidase (PPO). The quinones can then be converted into quinone methides or carbocations via flav-3-en-ols, or reduced to carbocations through coupled non-enzymatic oxidation.[15]

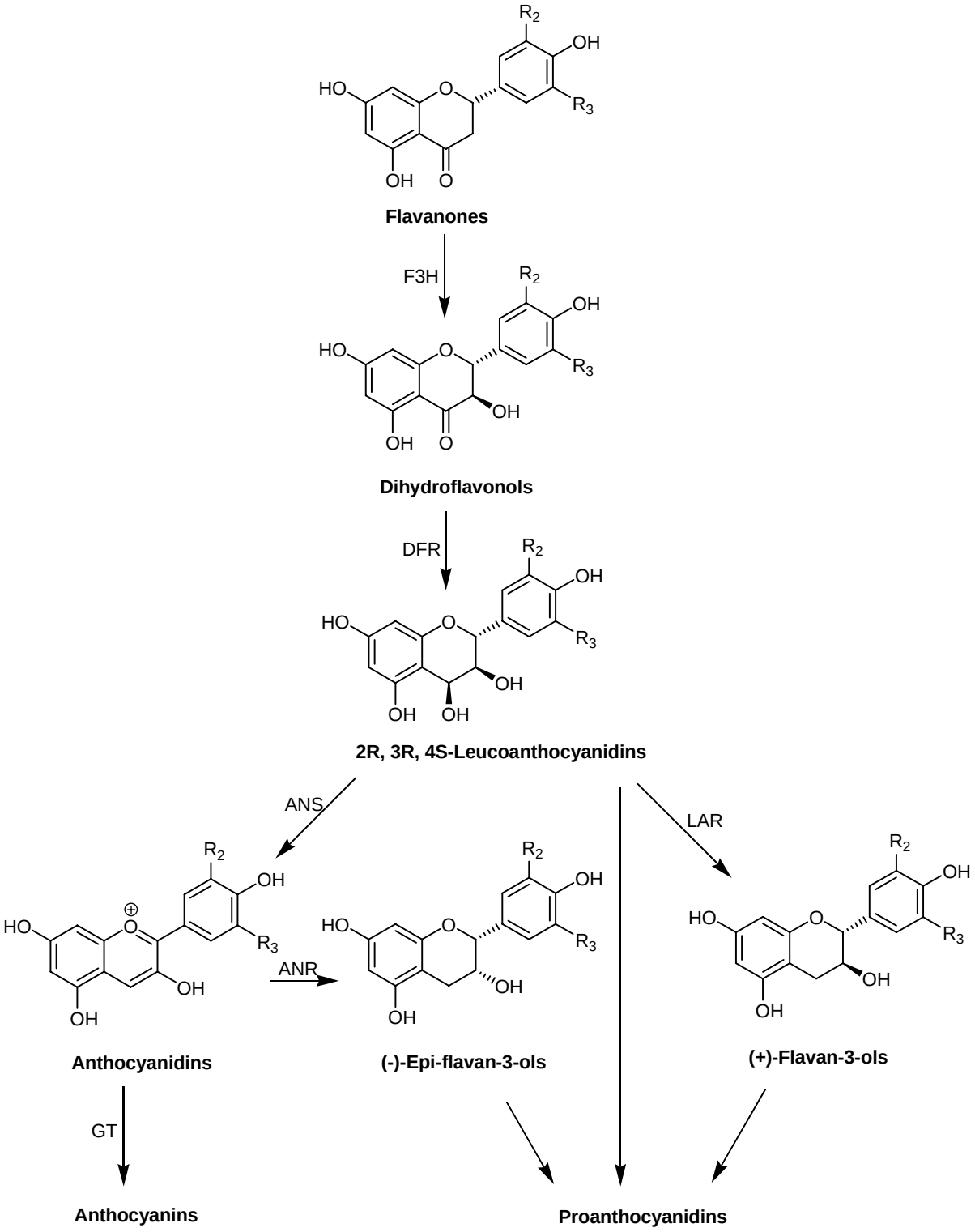
On the other hand, the anthocyanidins are converted into 2,3-*cis*-flavan-3-ols via anthocyanidin reductase (ANR) and lecuoanthocyanidins are converted into 2,3-*trans*-flavan-3-ols via leucoanthocyanidin reductase (LAR). Nucleophilic attack of 2,3-*cis*-flavan-3-ols (epicatechins) or 2,3-*trans*-flavan-3-ols (catechins) on the carbocations produce dimers and then oligomeric proanthocyanidins linked through C_4-C_6 or C_4-C_8 (Scheme 1.2).

There are three significant features:

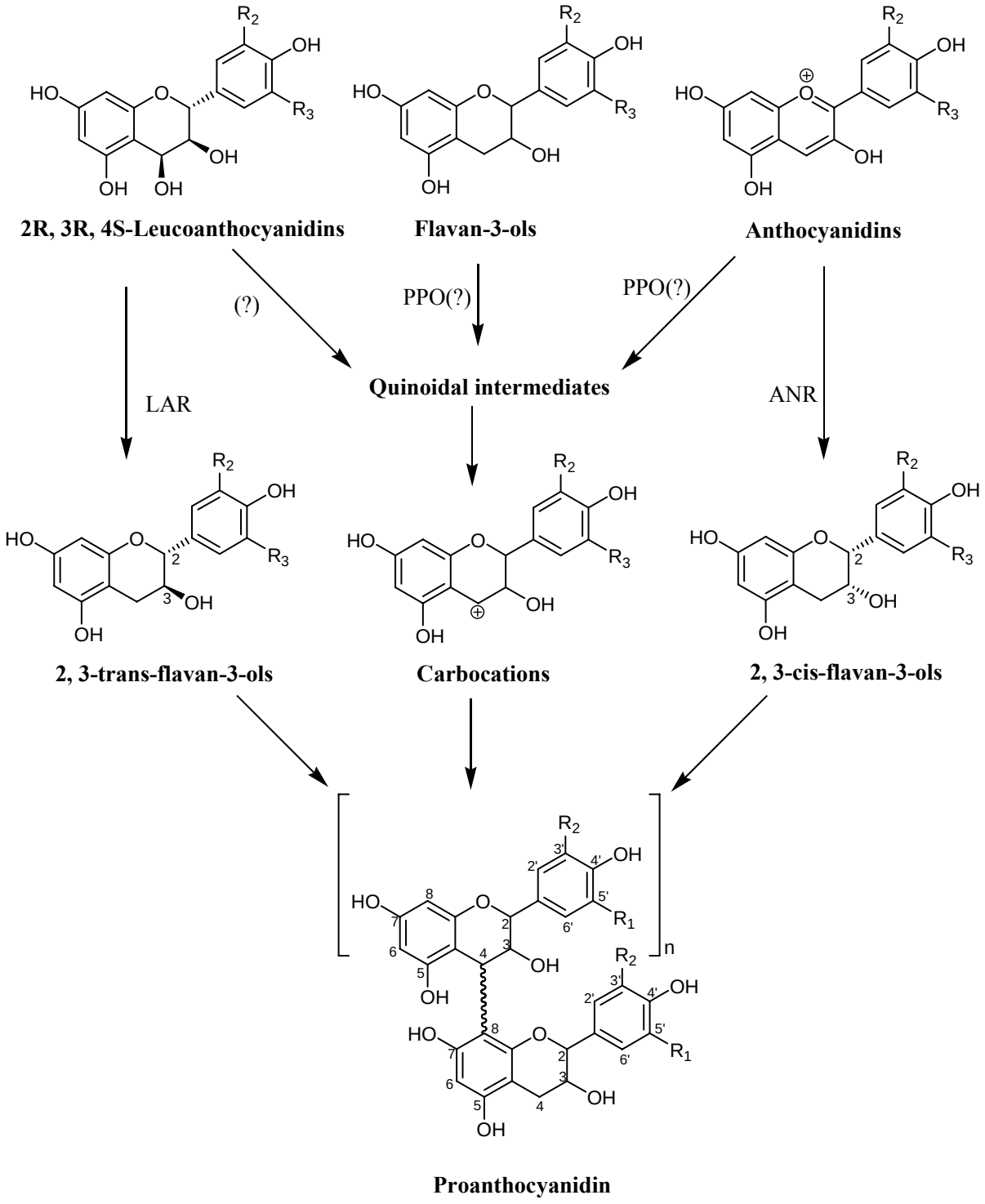
1. The utility of the C_4 position as building blocks of catechin and epicatechin series.

2. Their efficient activation by Lewis acids, such as $BF_3{\cdot}OEt_2$, allowing delivery of various nucleophiles at this position.

3. The stereochemistry of this substitution reaction.



Scheme 1.1: Biosynthesis of catechin and epicatechin.



Scheme 1.2: Biosynthesis of proanthocyanidins.

1.9. Human food and biological activities

Polyphenols have played a very important role in human life as ingredients of wine, tea, or herbal medicines but it became recently known that they also possess some very important biological functions at the molecular level. The specific interactions of polyphenols with biomolecules such as proteins exert powerful biological activities and have stimulated the search for new pharmaceutical entities derived from polyphenolic compounds.[9,16] These investigations are still being done as there is a difficulty in isolating these substances in pure form from natural sources, e.g., plant extracts. These sources generally produce mixtures of closely related compounds, not readily separable even with the aid of modern chromatographic and analytical methods. This difficulty offers an exciting challenge to organic synthesis for supplying valuable, homogeneous samples for biological testing. Among the polyphenol classes that have attracted recent interest are the condensed tannins (procyanidins), which have been identified as antiviral, antibacterial, and antitumor agents.[17]

Oligomeric proanthocyanidins may help to protect against the effects of internal and environmental stresses such as cigarette smoking and pollution, as well as supporting normal body metabolic processes. The effects may include depressing blood fat, lowering blood pressure, preventing blood vessel scleroses and preventing thrombus formation.[18]

Additionally, studies have shown that oligomeric proanthocyanidins may prevent cardiovascular disease by counteracting the negative effects of high cholesterol on the heart and blood vessels.

Some researchers also called these molecules pycnogenol. The main functions of proanthocyanidins are antioxidant activity and anti-mutagenic activity (to prevent chromosomal mutations). The most common antioxidants currently used are vitamin C and vitamin E. However, studies show that proanthocyanidin antioxidant capabilities are 20 times more powerful than vitamin C and 50 times more potent than vitamin E.[19]

Proanthocyanidins with unique molecular structure (A-type), isolated from cranberry fruit exhibit potent bacterial anti-adhesion activity.[20,21] Proanthocyanidins reduce histamine production naturally, and are used in the treatment of allergies.

Proanthocyanidins help to improve circulation by strengthening capillary walls. This is especially important for people with compromised circulatory systems, such as stroke victims, diabetics, arthritics, smokers, oral contraceptive users and people with general cardiovascular insufficiencies.

Proanthocyanidins inhibit the body's enzymes that break down collagen. Proanthocyanidins help collagen repair and rebuild correctly which can reverse damage done over the years by injury and free radical attack. The breakdown of collagen is what causes our skin to lose its elasticity which in turn causes wrinkles. Proanthocyanidins help to keep skin elastic, smooth and wrinkle-free. Proanthocyanidins are also taken as an oral cosmetic to help in the prevention of wrinkles.

Proanthocyanidins serve to protect against environmental toxins, such as radiation, pesticides, pollution, heavy metals, etc. The production of free radicals is increased because of today's environment. Tobacco smoke, alcohol, solvents, chemicals and more cause free radicals to form. Since proanthocyanidins eliminate free radicals, they help us to fight against the toxic effects of our environment.

Proanthocyanidins act as a natural, internal sunscreen. The sun's ultraviolet rays destroy up to 50 percent of our skin cells. Proanthocyanidins reduce this amount to approximately 15 percent. Inhibiting the daily effects, the sun's rays have on our skin, is our best defense against the aging of our skin.

1.10. Work plan

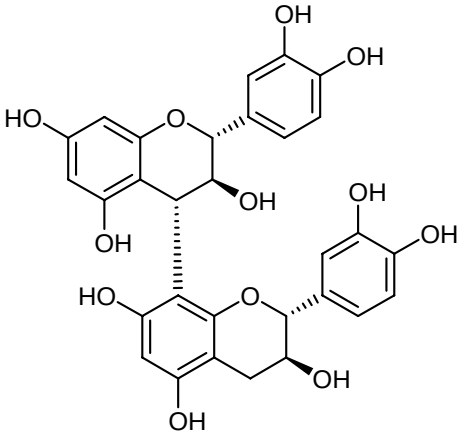
The oligomeric flavonoids are found in plants in the form of monomers, dimers, trimers and polymeric forms. They are present as mixtures of each other and with other compounds making it difficult to separate these molecules in large quantity in pure form, even with modern analytical techniques. This represents a challenge for chemists to synthesize these oligomeric flavonoids in large quantity and in pure form in order to study their roles in different fields of chemistry and biochemistry.

They form a part of human diet. It is estimated that at least one gram of flavonoids is ingested daily by everyone in the form of food stuffs, juices and wines etc.[22] They have powerful free radical scavenging activity and an anti-tumor-promoting effect.[11,23] They are also known as condensed tannins and have the ability to bind with biomolecules e.g. proteins. They display multiple biological activities that render them significant to health.[24] Some of the biological activities of proanthocyanidins are as follow.

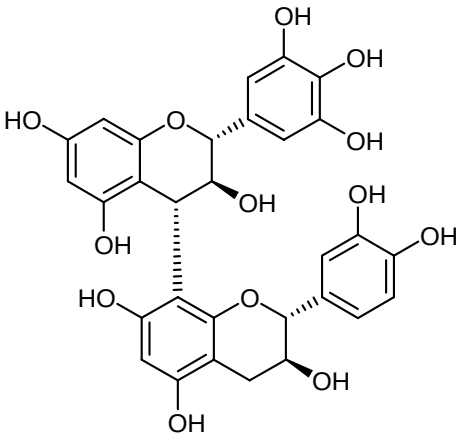
1. Boost immune system.
2. Protection from arteriosclerosis.
3. Enhance connective tissue health.
4. Reduce lipid peroxidation.
5. Boost the effects of vitamin C.
6. Lower cholesterol levels.
7. Reduce inflammation.
8. Reduce cancer risk.
9. Reduce risk of stroke and heart attack.
10. Effective antioxidant for brain and nerve tissue.
11. Possible arthritis reduction and relief.
12. Help to prevent inflammation of lung tissues.
13. Potential anti-aging benefits.
14. Reduction and repair of UV damage to cells.
15. Reduction of muscle cramps.
16. Potential for reduction of diabetic retinopathy.

Because of their number of biological activities and their use in human diet, we have planned to synthesize these oligomeric flavonoids in pure form and on gram scales in order to test them for certain biological activities as well as in food chemistry. The large quantity of these oligomeric flavonoids is also required to study their roles at the molecular level e.g. proteins. One of the major uses of these oligomeric flavonoids is that they are used as reference compounds in HPLC analysis of different food stuffs.

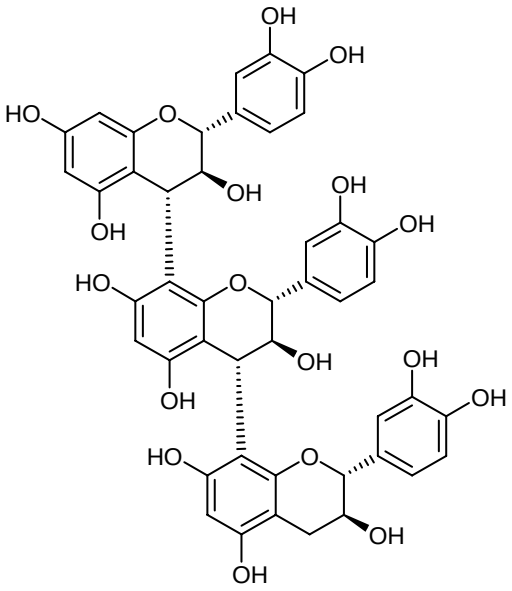
The work involved the synthesis of the following oligomeric flavonoids and to test them for different biological activities and their use in food chemistry i.e. human diet.



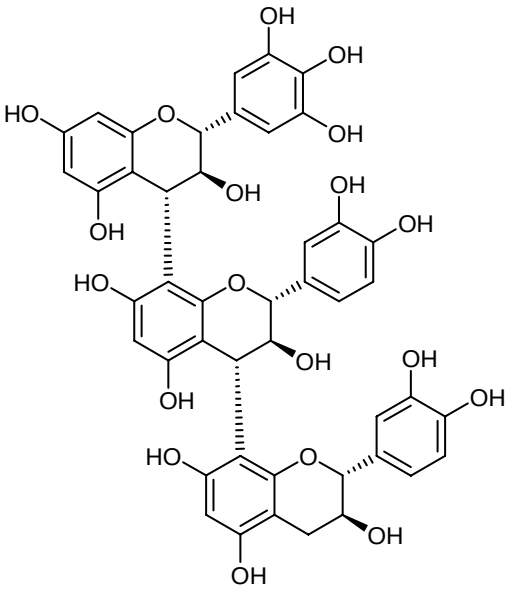
Procyanidin B_3



Prodelphinidin B_3



Procyanidin C_2



Prodelphinidin T_2

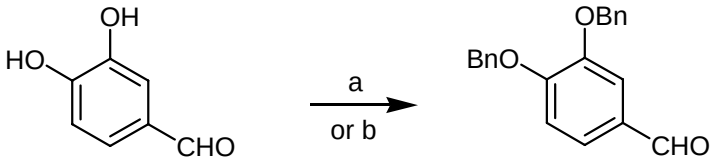
Figure 1.5: Sturtures of planned flavonoids.

1.11. Results and discussion

1.11.1. Synthesis of procyanidin B3 and C2

1.11.1.1. Synthesis of benzaldehyde 2

Benzyl chloride was used to protect 3,4-dihydroxy-benzaldehyde (**1)** in the presence of potassium carbonate as a weak base and DMF as a solvent.[25] The reaction proceeded smoothly in five hours at 150 °C with 77 % isolated yield (Scheme 1.3). In another reaction a better yield was obtained by adding tetrabutylammonium iodide in a catalytic amount to the reaction and the reaction was refluxed for 24h in acetone instead of DMF.[26] In the second procedure, the reaction time was longer but the workup of the reaction was easy, and no threat of removing DMF from the reaction mixture and loss of product in DMF during washing the reaction mixture. The isolated yield was 92 % in this case.



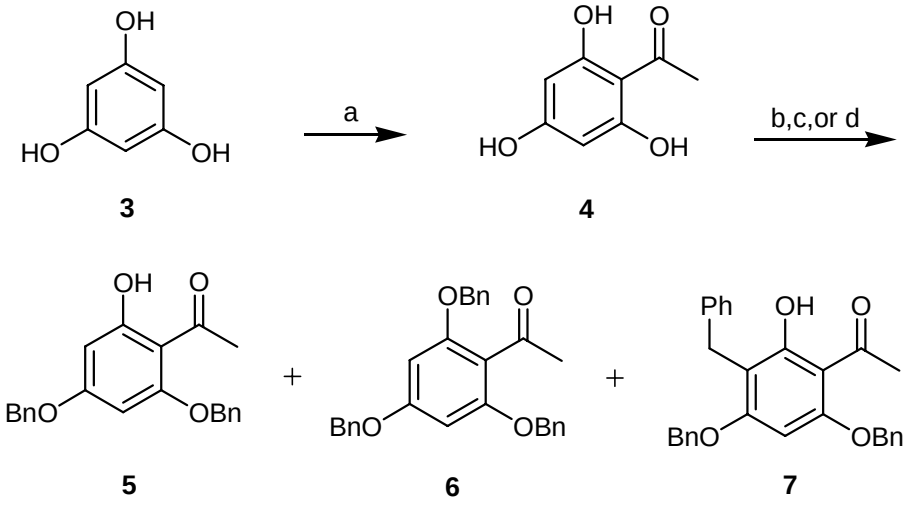
1 **2**

Scheme 1.3: Synthesis of benzaldehyde **2:** a) BnCl, K_2CO_3, DMF, 77 %; b) BnCl, K_2CO_3, acetone, TBAI, 92 %.

1.11.1.2. Synthesis of acetophenone 5

For the synthesis of the benzylated acetophenone **5**, phloroglucinol (**3**) was subjected to Friedel-Crafts acetylation.[27] Trihydroxyacetophenone (**4**) was obtained in 69 % isolated yield by treating equimolar amount of phloroglucinol **3** and acetic anhydride with 2.5 times molar excess of boron trifluoride solution in ether at 50-60 °C (Scheme 1.4). Trihydroxyacetphenone (**4**) was protected as the benzyl ether by adopting different solvents for reaction. First of all, the reaction was done in HMPA at 90-93 °C for 70 min.[28] We obtained the required dibenzylated acetophenone **5** in 70 % yield along with two side

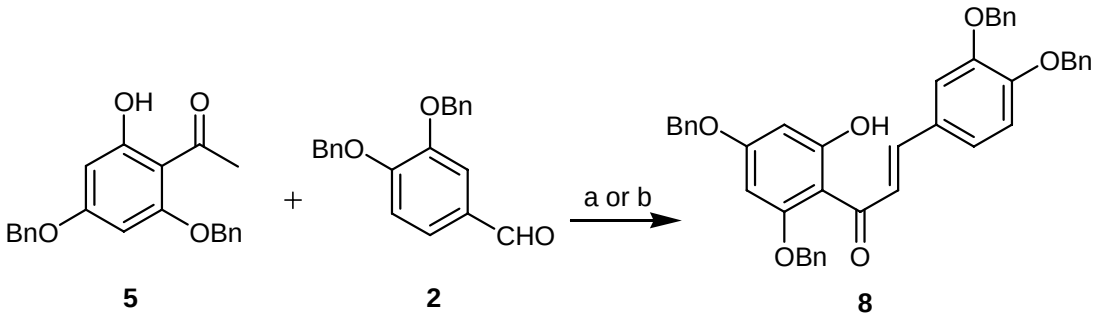
products, 5 % tribenzylated acetophenone **6** and 8 % C-benzylated **7** (Scheme 1.4). In this reaction, the temperature should not be too high as there is chelation between the keto group and hydroxyl group at the 2'or the 6'positions of trihydroxyacetophenone (**4**). By increasing the temperature of the reaction in the polar solvent, there is an increase in the possibility of breaking the chelation and thus the chance of formation of the side product **6** is increased. The C-benzylated side product **7** is simply Friedel-Crafts C-alkylation (Scheme 1.4). The other solvents for the reactions are acetone and DMF.[26] In acetone, the reaction was done at room temperature but no conversion into product was found. Due to the side products, we warmed the reaction mixture in DMF to a temperature between (60-70 °C) for 1.5h. It was observed that the yield of the required benzylated acetophenone **5** is increased to 83 % and no side product was observed.



Scheme 1.4: Synthesis of acetophenone **5:** a) Ac_2O, BF_3-Et_2O, 69 %; b) BnCl, K_2CO_3, HMPA, 70 %; c) BnCl, K_2CO_3, acetone, $^{+}NI^{-}(n\text{-}Bu)_4$; d) BnCl, K_2CO_3, DMF, 83 %.

1.11.1.3. Synthesis of chalcone 8

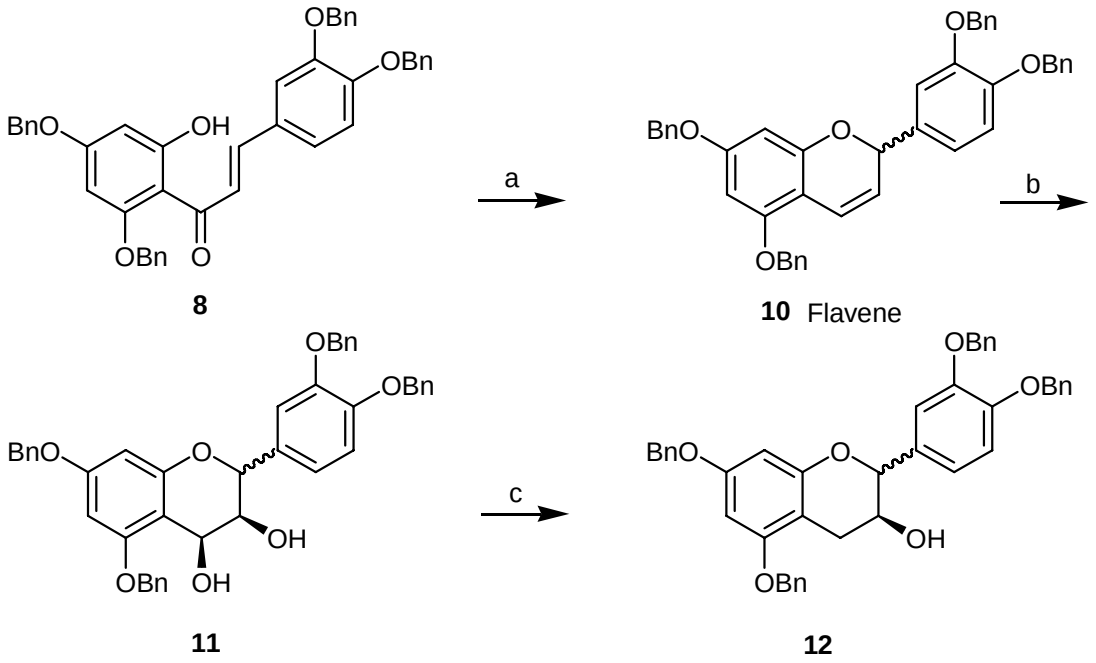
Tetrabenzylated chalcone **8** was obtained by the condensation reaction between equimolar amounts of benzylated acetophenone **5** and benzaldehyde **2** in dimethylforamide at room temperature using 60 % of sodium hydride dispersed in mineral oil The isolated yield was 82 %.[29] This reaction was also carried out by applying normal Claisen-Schmidt conditions, i.e using potassium hydroxide as the base in ethyl alcohol but the yield was only 20 % (Scheme 1.5).



Scheme 1.5: Synthesis of chalcone **8:** a) NAH, DMF, 82 %; b) KOH**,** ethanol, 20 %.

1.11.1.4. Synthesis of (±)-tetrabenzylated catechin 12

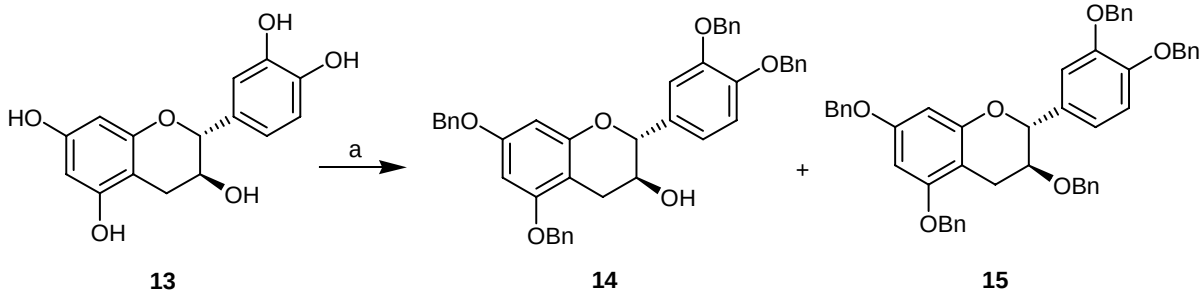
The benzylated chalcone **8** was treated with sodium borohydride in dimethoxy propane at 85 °C for 5-10 min. The reaction was monitored by TLC. When all of the chalcone was converted into unstable allylic alcohol, the reaction mixture was treated with a solution of boron trifluoride in dichloromethane for 25 min.[29] The flavene **10** was formed which was also observed to be unstable because of the ability to form an allylic cation as well as stabilized a methylenequinone by Claisen rearrangement. It was observed that flavene **10** starts decomposing after 5 h, and was thus immediately treated with osmium tetroxide (2.5 wt-% solution of osmium tetroxide in *t*-BuOH) in tetrahydrofuran for 8h to give racemic benzylated 3,4-diols **11** (Scheme 1.6). The dihydroxylation reaction proceeded in 45 % isolated yield. The yield of the reaction is low because some of the allylic alcohol formed was converted back to chalcone as we observed small percentage of chalcone **8** at the end. The other reason for the low yield may be due to the formation of a small amount of flavene **10** which decomposed during work up of the reaction and during the dihydroxylation reaction as well. The catechin tetrabenzyl ether **12** was obtained by deoxygenation effected by treating racemic benzylated 3,4-diols **11** with sodium cyanoborohydride in acetic acid for two days. The isolated yield of **12** was 78 %.



Scheme 1.6: Synthesis of (±)-tetrabenzylated catechin **12:** a) i) $NaBH_4$**,** DME; ii) BF_3-OEt_2; b) OsO_4, NMO, THF:H_2O (1:1), 45 %; c) $NaBH_3CN$, CH_3COOH, 78 %.

1.11.1.5. Synthesis of pure (+)-tetrabenzylated catechin

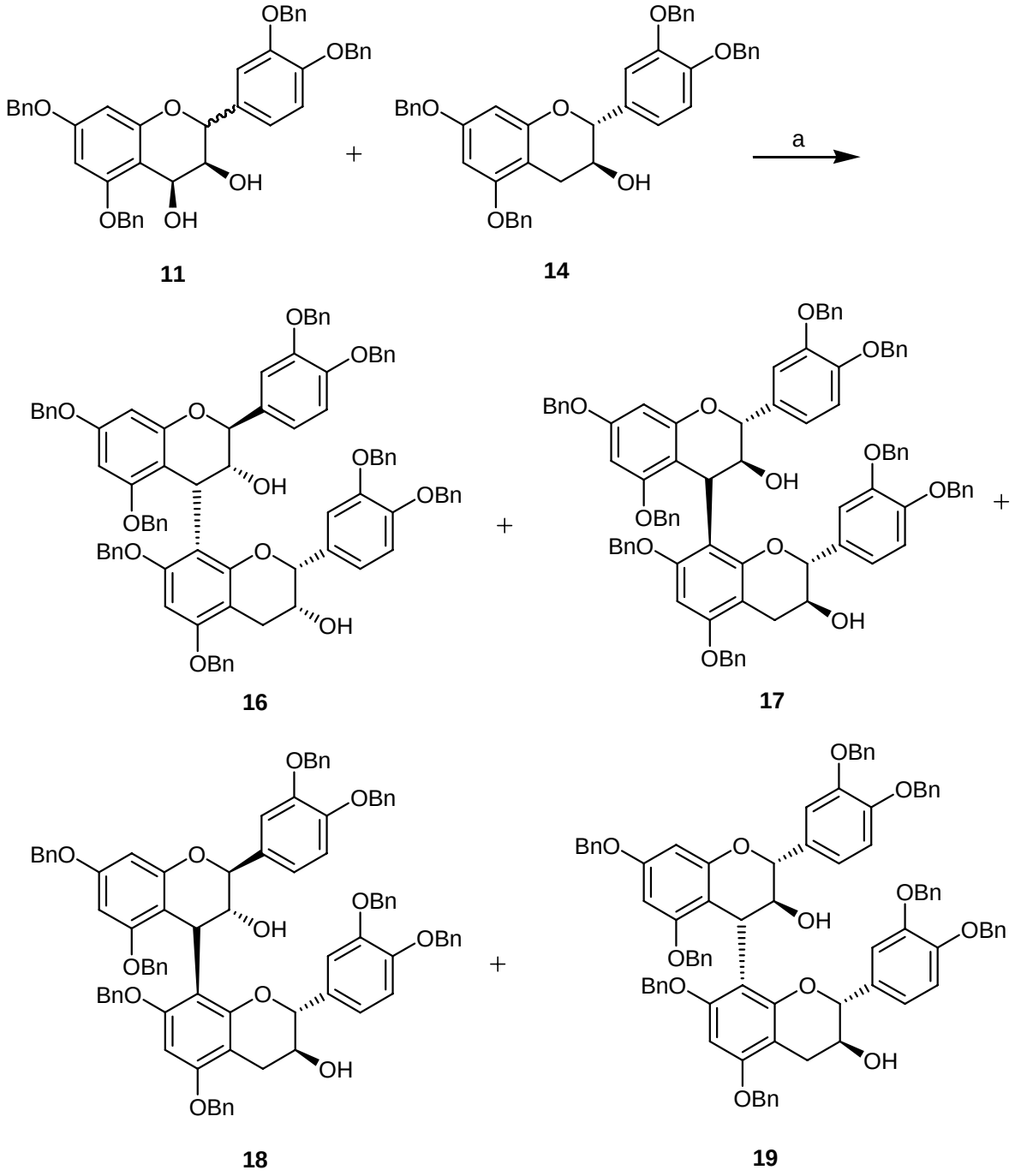
Tetrabenzyl ether of pure (+)-catechin **14,** which was needed for the coupling reaction with racemic catechin tetrabenzyl ether **12**, was prepared by treating the pure enantiomer of (+)-catechin (**13**) with benzyl chloride in the presence of K_2CO_3 in DMF at 120-130 °C.[30] The reaction was completed within 5h in 80 % yield along with 5 % pentabenzylated catechin **15** as side product (Scheme 1.7).



Scheme 1.7: Synthesis of (+)-tetrabenzylated catechin **14:** a) BnCl, K_2CO_3, DMF, 80 %.

1.11.1.6. Synthesis of procyanidin B_3

For the formation of dimer **19** which is known as benzylated procyanidine **B_3**, the mixture of tetrabenzyl ether of the pure (+)-catechin **14** and racemic tetrabenzylated 3,4-diols **11** was treated with two different Lewis acids.[31] In the condensation reaction, the mixture of both pure benzylated catechin **14** and racemic diol **11** was treated with $TiCl_4$ or TMSOTf in absolute dichloromethane at 0 °C for 5 min.[11] We were expecting only four separable products i.e. dimers **16-19** but a multitude of products were observed on TLC analysis (Scheme 1.8). These were not analyzed by spectroscopy techniques but from R_f-values one could observe that not only the dimers but also the trimers and higher oligomers of the catechin were formed in this reaction This is because there are mixtures of pure and racemic catechin which reacted with each another and also with other isomers to give dimers of different interflavanyl linkages. For higher oligomer, it is understandable that there are free electrophiles and nucleophiles in reaction mixture which reacted with one another to give higher oligomers. Higher oligomer formation can not be avoided completely but it could be minimised by adding the nucleophilic unit **14** in excess.



Scheme 1.8: Synthesis of tetrabenzylated procyanidin **B_3 19:** a) $TiCL_4$, CH_2Cl_2; b) TMSOTf, CH_2Cl_2.

1.11.1.7. Synthesis of procyanidin B_3 and C_2 from pure (+)-catechin (**13**)

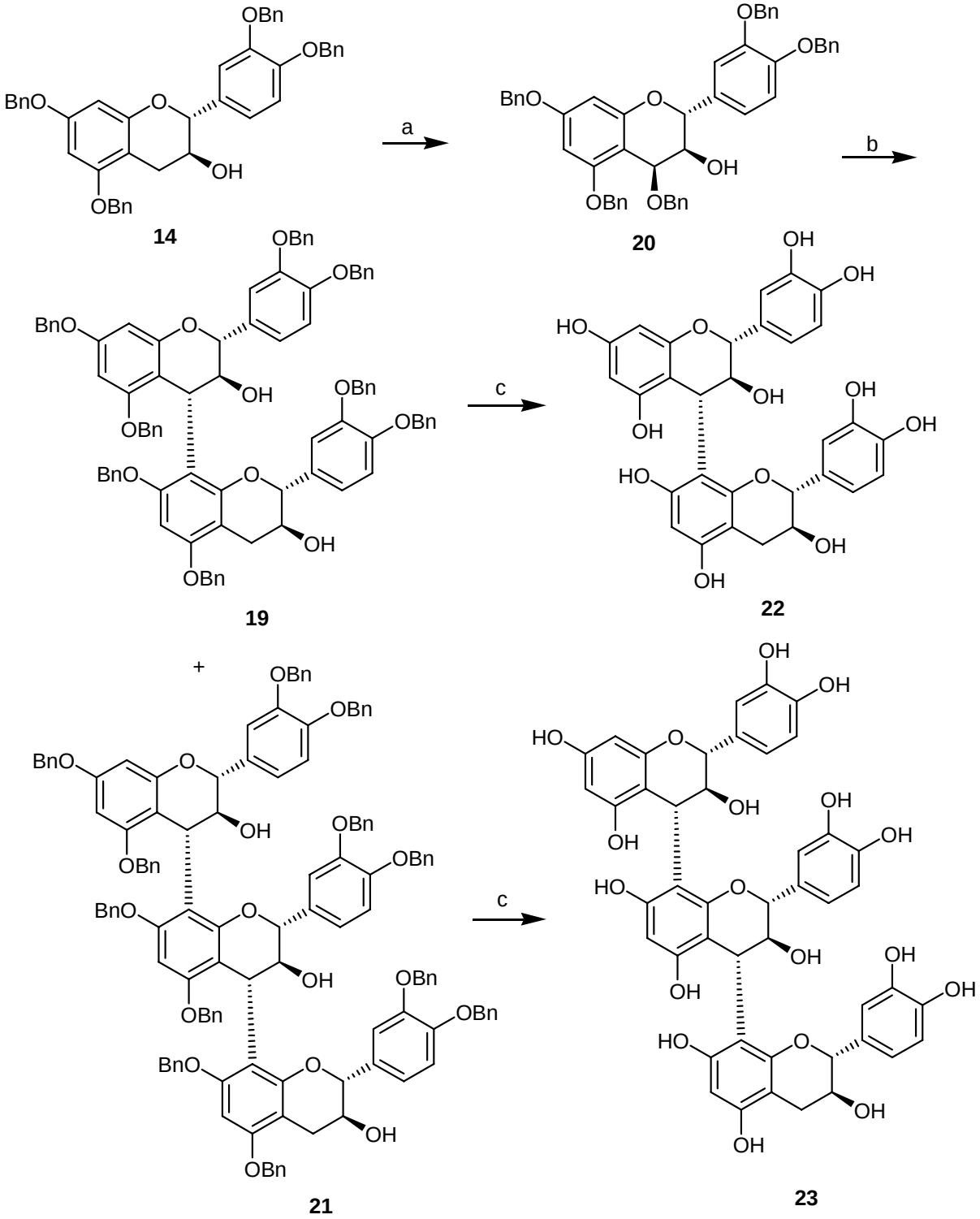
After the failure to synthesize proanthocyanidin B_3 with tetrabenzylated catechin**14** and racemic tetrabenzylated 3, 4-diols **11**, the synthesis of proanthocyanidin B_3 from pure (+) catechin was investigated. Pentabenzyloxyflavan-3-ol (**20**) was prepared by treating pure (+)-catechin tetrabenzyl ether **14** with DDQ in dichloromethane followed by nucleophilic attack of benzyl alcohol.[11] DDQ oxidation at the C_4 position was done at room temperature in 12 h with 82 % isolated yield (Scheme 1.9). Pentabenzyloxyflavan-3-ol (**20**) acts as an electrophile in the coupling reaction.

Benzylated procyanidine B_3 (**19**) was prepared by treating a mixture of pure tetrabenzylated catechin **14** (as a nucleophile) and pentabenzyloxyflavan-3-ol **20** (as an electrophile) with the Lewis acid TMSOTf in dichloromethane at 0 °C for 5 min.[11] The condensation is so fast that a mixture of dimer **19** (benzylated procyanidine B_3) and trimer **21** (benzylated procyanidine C_2) were formed in 80 % yield without complete consumption of starting material.[11] Condensation with $TiCl_4$ gave the same results but with 73 % isolated yield (Scheme 1.9).Use of 5 fold excess of nucleophilic moiety helped to avoid higher oligomer formation which is normal when equimolar amounts of electrophile and nucleophile were used.

In both condensations, there are two possible isomers at the C_4 position of the electrophile i.e. 4α or 4β flavanyl linkage. This linkage is controlled by the neighboring group participation of the OH present at the C_3. NMR studies showed two rotational isomers at C_4 to C_8 position. These rotamers are not separable and these are in the ratio of 2:1 in CD_3Cl. Condensation at lower temperature increased this ratio up to 55:1 but the isolated yield dropped to 30 %.

Procyanidine B3 (**22**) and procyanidin C_2 (**23**) were obtained by deprotection of the benzyl groups from dimer **19** and trimer **21**, respectively. This was done by hydrogenolysis using Pd/C, H_2. It was noted that this reagent is a little harsh for this type of molecule because a lot of benzylic positions are available. We observed the formation of monomeric catechin **13** along with dimer and trimer. This means that this procedure has also removed interflavanyl bond to yield the monomeric catechin (**13**).

Later we did the hydrogenolysis with Pearlman's catalyst i.e. $Pd(OH)_2$, H_2 which is a milder reagent and suitable for deprotection of catechin dimer and trimer to yield procyanidin B3 (**22**)and procyanidin C2 (**23**) (Scheme 1.9).

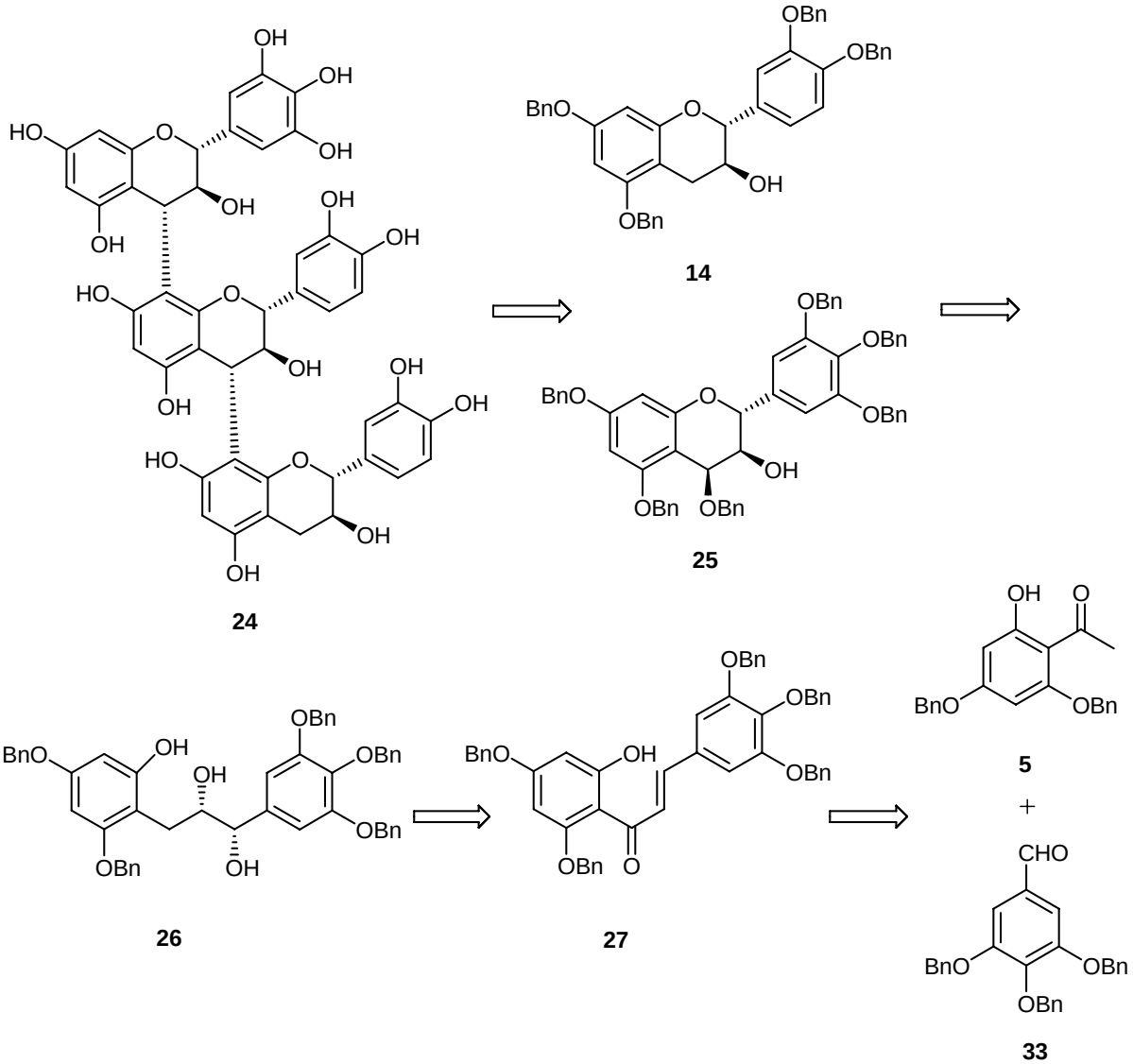


Scheme 1.9: Synthesis of procyanidin **B_3** (**22**) and procyanidin **C_2** (**23**) from (+)-catechin (**14**)**:** a) DDQ, BnOH, CH_2Cl_2, 82 %; b) **14**, TMSOTf, CH_2Cl_2, 80 %; c) $Pd(OH)_2$, H_2, 73 %.

1.12. Synthesis of Prodelphinidins B_3 and T_2

1.12.1. Retrosynthetic analysis for the synthesis of prodelphinidins B_3 and T_2

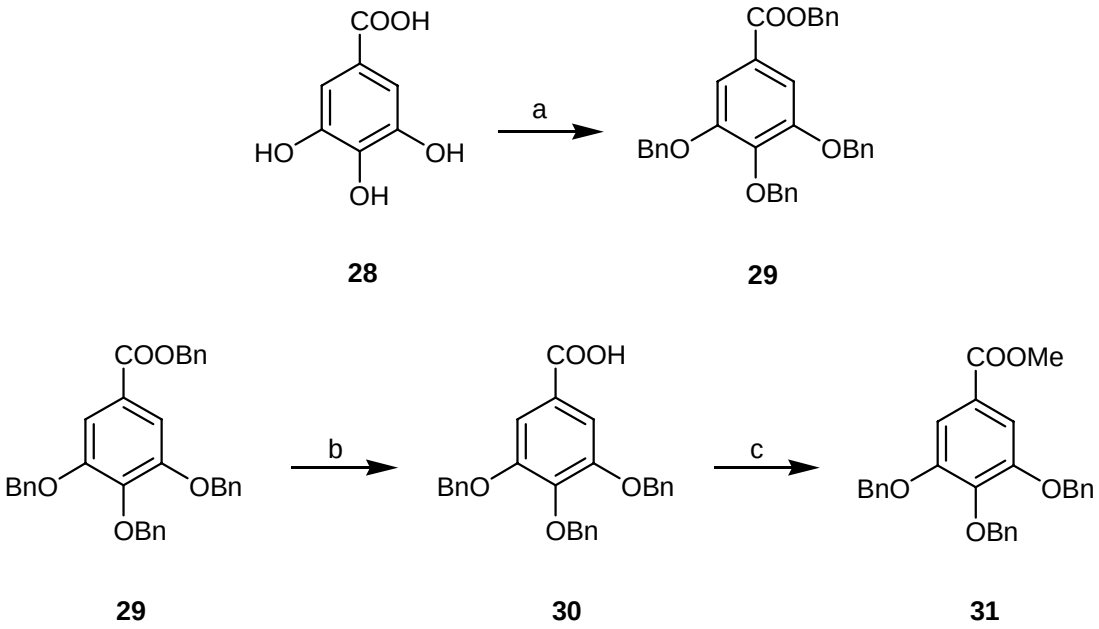
Retrosynthetic analysis suggested that prodelphinidin T_2 (**24**) can be obtained by the Lewis acid catalyzed condensation between electrophile **25** and nucleophile **14**. Nucleophile **14** can readily be obtained from catechin (**13**) and electrophile **25** can be obtained from diol **26** through cyclization. Diol **26** in turn can be obtained from chalcone **27** in two steps including decarbonylation and Sharpless asymmetric dihydroxylation. Chalcone **27** can be readily obtained by condensation between acetophenone **5** and aldehyde **33** (Scheme 1.10).



Scheme 1.10: Retrosynthetic analysis of prodelphinidin **T_2** (**24**).

1.12.2. Synthesis of benzylated esters 29 and 31

Benzyl tribenzyloxy benzoate **29** was prepared from gallic acid (**28**) by heating it for 12 h with benzyl chloride in the presence of K_2CO_3 in acetone. The reaction proceeded smoothly with 85% isolated yield.[32] The perbenzylated ester **29** was treated with 3N KOH in methanol and was refluxed to give 3,4,5-tribenzyloxy gallic acid (**30**). Methyl tribenzyloxy benzoate **31** was synthesized by simple esterification (Scheme 1.11). Tribenzyloxy gallic acid **30** was treated with concentrated sulphuric acid and absolute methanol under reflux for 5 h to give methyl tribenzyloxy benzoate **31** in 91 % yield.[33,34,35]



Scheme 1.11: Synthesis of benzyl ester **29** and methyl ester **31:** a) BnBr, K_2CO_3, acetone, reflux, 83 %; b) 3N KOH, CH_3OH, reflux, 12 h, 76 %; c) CH_3OH, H_2SO_4, 91 %.

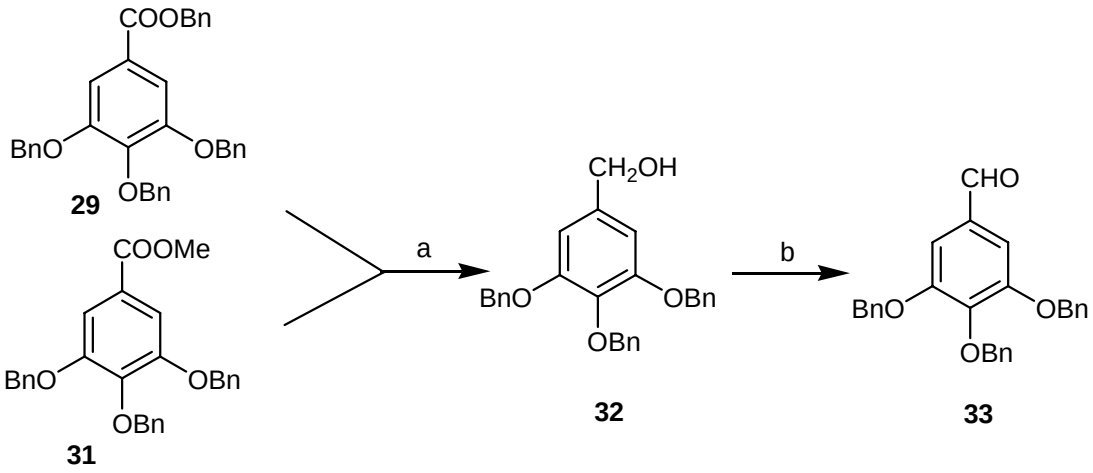
1.12.3. Synthesis of benzyl alcohol 32

Tribenzyloxy benzyl alcohol **32** was obtained by subjecting either benzyl tribenzyloxy benzoate **29** or methyl tribenzyloxy benzoate **31** to reduction separately by lithium aluminium hydride in tetrahydrofuran overnight at room temperature.[35,36] It was observed that the reduction proceeded quantitatively in both cases. But according to TLC analysis, it was

observed that the reduction of methyl tribenzyloxy benzoate **31** to tribenzyloxy benzyl alcohol **32** is faster than the reduction of benzyl tribenzyloxy benzoate **29** (Scheme 1.12).

1.12.4. Synthesis of benzaldehyde 33

Tribenzyloxybenzaldehyde **33** was obtained quantitatively by oxidation of tribenzyloxy benzylalcohol **32** by pyridinium chlorochromate[35] in dichloromethane at 0 °C for 6h (Scheme 1.12). The reaction was quantitative and product **33** was found to be stable.



Scheme 1.12: Synthesis of benzylated aldehyde **33:** a) $LiAlH_4$, THF, 85 %; b) PCC, CH_2Cl_2 86 %.

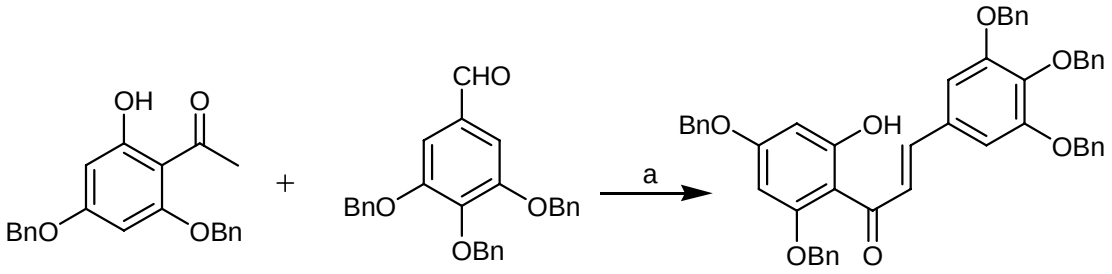
1.12.4. Synthesis of chalcone 27

The reaction was first carried out by applying normal Claisen-Schmidt conditions. Acetophenone **5** and benzaldehyde **33** were subjected to condensation using potassium hydroxide as the base in ethyl alcohol at room temperature for 2 days.[37,38,39,40] The yield of the product was 14 %. The reaction was also carried out by refluxing the mixture of benzylated acetophenone **5** and benzaldehyde **2** in methanol-KOH overnight but the isolated yield was not more than 20 % in this case[41](Scheme 1.13).

Pentabenzylated chalcone **27** was also obtained by refluxing the mixture of acetophenone **5** and benzaldehyde **33** in ethyl alcohol with the mixture of bases piperidine and pyridine (1.5:2)

(Scheme 1.13). The yield of the reaction was better (37 %) than normal Claisen-Schmidt condensation.[42,43]

In another reaction, pentabenzylated chalcone **27** was obtained by condensing equimolar amounts of benzylated acetophenone **5** and benzaldehyde **32** in DMF at temperature between 0-5 °C using 60% sodium hydride dispersed in mineral oil. The yield in this case was 60 %.[29] (Scheme 1.13). It would appear that the yield of formation of chalcone **27** is decreased as oxygenation on the phenolic rings is increased.



5 **33** **27**

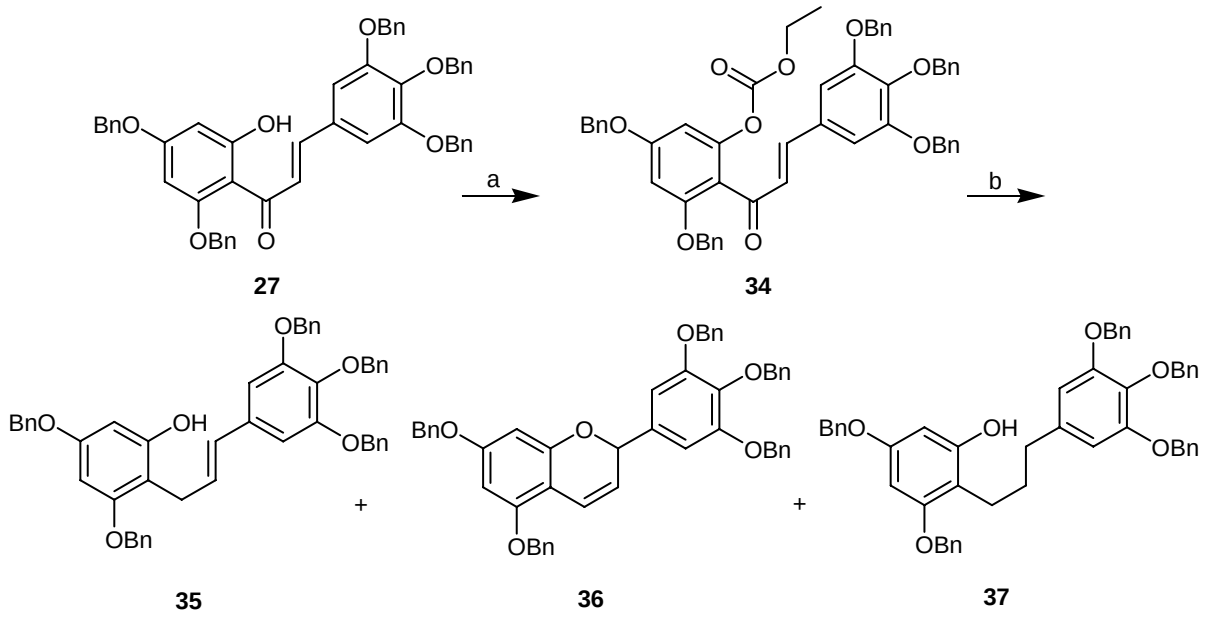
Scheme 1.13: Synthesis of chalcone **27:** a) KOH**,** ethanol, 14 %; b) KOH, MeOH, reflux, 20 %; c) Piperidine, pyridine, EtOH, 37 %; d) NAH, DMF, 72%.

1.12.5. Synthesis of pentabenzyloxy diphenyl propene 35

The 2'-hydroxy group of pentabenzylated chalcone **27** was protected as the ethyl carbonate **34** by treating chalcone **27** with ethyl chloroformate and triethylamine in anhydrous tetrahydrofuran at 0 °C for 1.5h.[41] Phenolic carbonates in α,β-unsaturated ketone systems are very good intermediates which are helpful in decarbonylation by reduction with sodium borohydride.[44] This is a mild method as compared to lithium aluminium hydride with $AlCl_3$. The carbonate intermediate **34** was reduced by sodium borohydride in water at 0°C for 5h to obtain propene **35** in 25 % isolated yield. In this reaction there was a large percentage of side products formed in which most of the chalcone was converted into flavene **36** and benzylated diphenylpropane **37** (Scheme 1.14).

Flavene **36** is formed due to Michael addition of the allylic alcohol formed in the reaction mixture and the substituted propane **37** is formed by the complete reduction of the chalcone

27. One reason for the side reactions and low yield is the solubility. The phenolic carbonate **34** having five benzyloxy groups has very low solubility in water at 0 °C. However, when the reaction was performed in a mixture of water and ethyl alcohol (1:3), the solubility was increased and the pentabenzyloxy diphenylpropene **35** was obtained in 46 % yield with a small percentage of the side products **36** and **37**.



Scheme 1.14: Synthesis of substituted propene **35:** a) anhyd. THF, Et_3N, ClCOOEt, 95%; b) Na BH_4, H_2O:EtOH (1:3), 46 %.

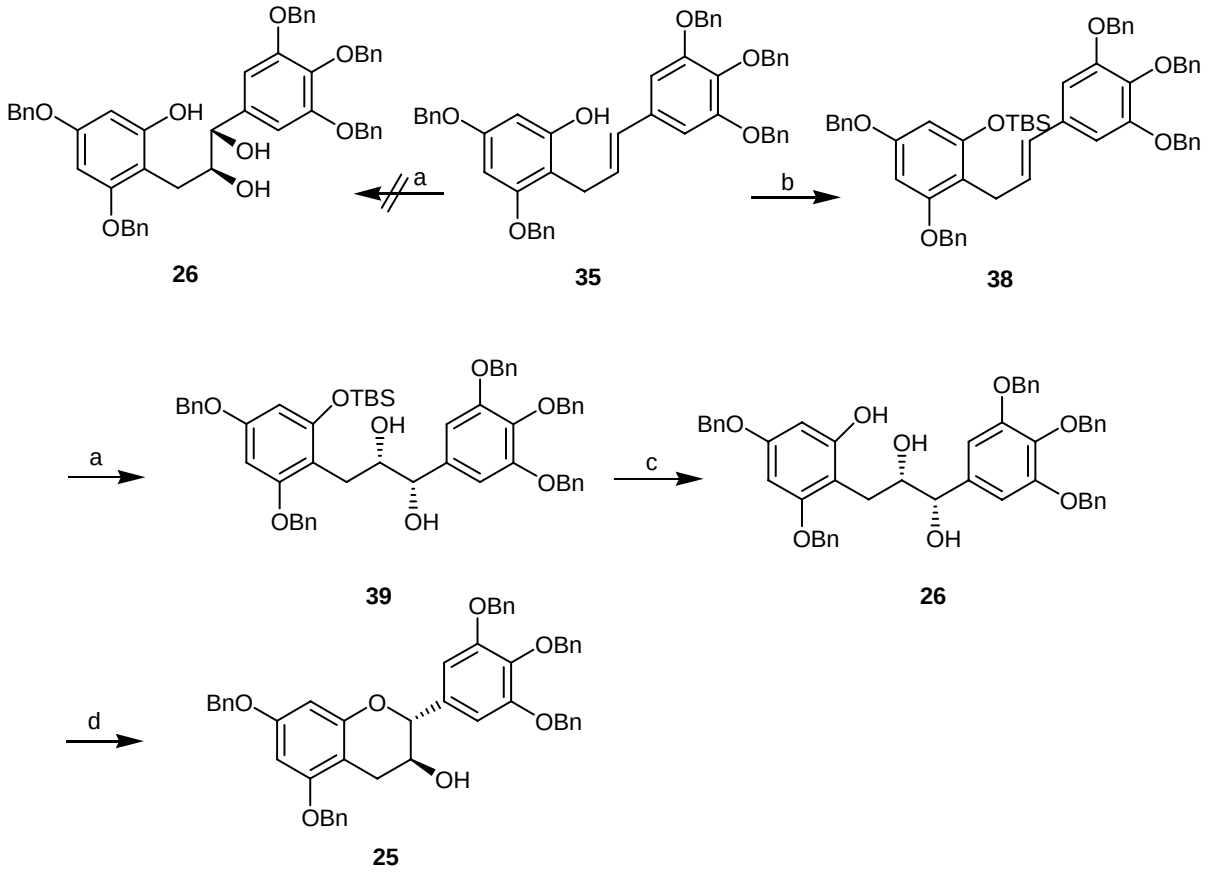
1.12.6. Synthesis of benzylated (–)-gallocatechin 25

Pentabenzylated diphenylpropene **35** was subjected to asymmetric dihydroxylation by treating it with AD mix-α. But there was no conversion observed even after two days.[41] The absence of the product may be explained due to possible interference by the free phenolic hydroxyl group present in propene **35** (Scheme 1.15).

TBS protected pentabenzylated diphenylpropene **38** was obtained in 95 % isolated yield by treating pentabenzylated diphenylpropene **35** with TBDMSCl and imidazole in DMF overnight.[41] TBS protected propene **38** was subjected to Sharpless asymmetric dihydroxylation by using AD mix-α. It was observed that by adding all the AD mix-α at once

was not the best procedure since starting material was still present. AD mix- α and methanesulphonamide were added in portions in order to complete the conversion of the propene **38** to benzylated diol **39** quantitatively[45] (Scheme 1.15).

Deprotection was achieved by treating the TBS protected diol **39** with tetrabutyl ammonium fluoride in anhydrous tetrahydrofuran to give benzylated deprotected triol **26**. Deprotection was necessary for the cyclization of the resulting triol **26** to benzylated gallocatechin **25**. Cyclization was carried out with the help of a standard Mitsunobu SN_2 type reaction.[46] Benzylated triol **26** was treated with diethyl azodicarboxylate and triphenyl phosphine in anhydrous tetrahydrofuran to afford the (–)-pentabenzylated gallocatechin **25** in 57 % isolated yield with inversion of stereochemistry at C_2 and C_3.(Scheme 1.15).



Scheme 1.15: Synthesis of benzylated gallocatechin **25:** a) AD-mix α, *t*-BuOH:H_2O(1:1), 85 %; b) TBDMSCl, imidazole, DMF, 95 %; c) TBAF, anhydrous, THF, 92 %; d) DEAD, Ph_3P, anhydrous THF, 57 %.

The prepared pentabenzyloxyflavan-3-ol (**25**) (benzylated (–)-gallocatechin) was subjected to DDQ oxidation at C_4 in dichloromethane followed by nucleophilic attack by benzyl alcohol to

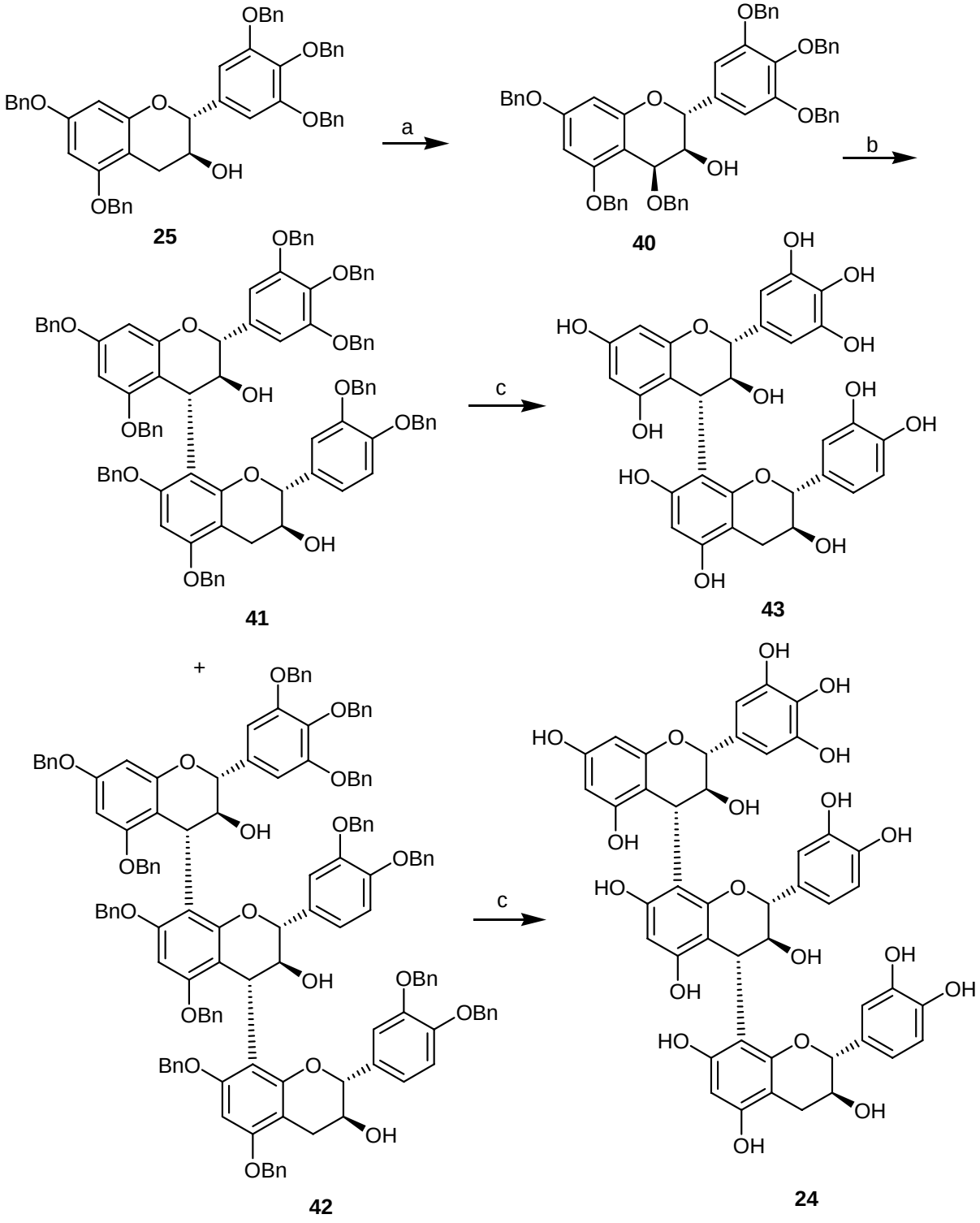
give hexabenzyloxyflavan-3-ol (**40**). DDQ oxidation [11] at C_4 was done at room temperature in 12 h with 73 % isolated yield (Scheme 1.16). Hexabenzyloxyflavan-3-ol (**40**) acts as an electrophile in the coupling reaction.

Benzylated prodelphinidin **B_3 41** was formed by subjecting a mixture of pure tetrabenzylated catechin **14** (as a nucleophile) and hexabenzyloxyflavan-3-ol (**40**) (as an electrophile) to Lewis acid TMSOTf in dichloromethane at 0 °C for 5 min.[29] In this rapid condensation, not only the dimer **19** as a major product, but also a trimer **42** as minor product was obtained in an overall 76 % yield, although the starting material was not completely consumed. Condensation with $TiCl_4$ gave the same results but with 70 % isolated yield (Scheme 1.16).Use of 4.5 fold excess of nucleophilic moiety **14** helped to avoid higher oligomer formation

In this kind of condensation, there could be two possible stereoisomers at C_4 of the electrophile. The interflavanyl linkage between C_4-C_8 and C_4-C_6 could be 4α→ C_8or 4β→8. This linkage is controlled by the neighbouring group participation of the OH present at C_3 of the electrophile. NMR studies showed that there are two rotational isomers at C_4. These rotamers are not separable and these are obtained in the ratio of 2:1 in CD_3Cl. Condensation at lower temperature increased this ratio up to 55:1 but the isolated yield dropped to 30 %.

Prodelphinidine B_3 (**43**) and prodelphinidine C_2 (**24**) were obtained by deprotection of the benzyl groups from dimer **41** and trimer **42**. This was first done by hydrogenolysis using Pd/C, H_2. It was observed that the condition was quite harsh for these molecules because we observed the monomeric catechin along with dimer and trimer. This means that it has also removed to some extent the interflavanyl bond to yield the monomeric catechin and the yield is also low.

Later we performed the hydrogenolysis with Pearlman's catalyst i.e. $Pd(OH)_2/H_2$ which is a milder reagent[47] and suitable for deprotection of catechin dimer and trimer to yield prodelphinidine B_3 (**43**) and prodelphinidine C_2 (**24**) in 73 % isolated yield (Scheme 1.16).



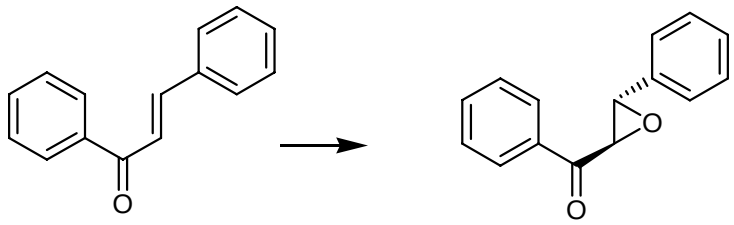
Scheme 1.16: Synthesis of procdelphinidin B_3 (**43**) and prodelphinidin C_2 (**24**) from (⁻)-benzylated gallocatechin **25:** a) DDQ, BnOH, CH_2Cl_2; b) **14**, TMSOTf, CH_2Cl_2; c) $Pd(OH)_2$, H_2.

Chapter 2: Asymmetric epoxidation of chalcones

2.1. Introduction

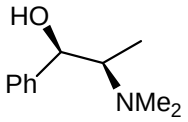
Chalcones are members of a class of secondary metabolites called flavonoids, which are widely distributed in higher plants. Chalcones are open chain C_6-C_3-C_6 flavonoids in which the two aromatic rings are joined by a three carbon, unsaturated carbony1 system. Fundamentally, chalcones can be considered to be derivatives of pheny1 styry1 ketones and are considered to be precursors of all classes of flavonoids.

The aim of this investigation is to prepare flavonoids via enantiomerically pure epoxides. Asymmetric epoxidation of electron-deficient olefins has gained widespread popularity amongst synthetic organic chemists. Most of the methods for enantioselective epoxidation of electron-deficient alkenes are essentially asymmetric variants of the Weitz-Scheffer[48] epoxidation using alkaline H_2O_2 which makes them selective for electron-deficient alkenes in the presence of other olefins.



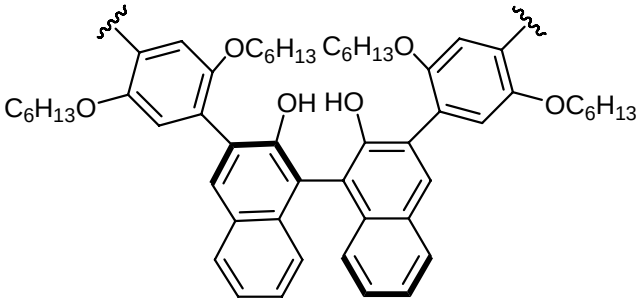
Chalcone Chlacone epoxide

Most of the methods for the asymmetric epoxidation of electron-deficient olefins e.g. chalcones rely on the use of chiral ligands, coordinated to the metal atom of metal peroxides. In 1996, Enders[49] disclosed that (*E*)-α,β-unsaturated ketones can be epoxidized in asymmetric fashion using stoichiometric quantities of diethyl zinc and chiral alcohols. A maximum of 61 % ee was obtained in the case of chalcone with 94 % conversion by using (1*R*,2*R*)-*N*-methylpseudoephedrine **44**.



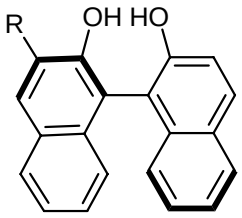
44

Pu and coworkers have developed a variant of catalytic zinc and ligands, using the modified polybinaphthyl **45**. In this process, oxygen is replaced as the stoichiometric oxidant by *tert*-butyl hydroperoxide (TBHP). The maximum ee obtained in case of chalcones was 79 % with 95 % conversion.[50]



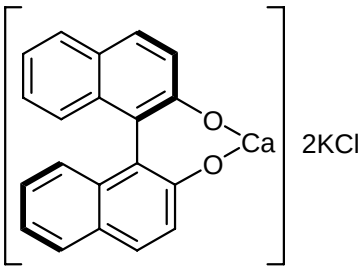
45

Shibasaki *et al.* have developed a series of complexes of the general form LnM_3 $(BINOL)_3$, where Ln = lanthanide metals, M= alkali metal. It was found that $LaNa_3$ $[(R)\text{-BINOL}]_3$ catalyses the epoxidation of the chalcone by *tert*-butyl hydroperoxide (TBHP) to afford (2*S*,3*S*)-epoxychalcone in 92%yield and 83 % ee. Later it was found that alkali metal-free complexes were also effective catalysts. The reaction of an equimolar mixture of (*R*)-BINOL **46** or **47** and $La(O\textit{i}Pr)_3$ in the presence of 4 Å molecular sieves generates a complex capable of catalyzing the asymmetric epoxidation of a range of (*E*)-enones. In this case, cumene hydroperoxide (CMHP) proved to be the most effective oxidant. Chalcone was epoxidized in 93 % yield and 83 % ee by this process.[51,52,53]



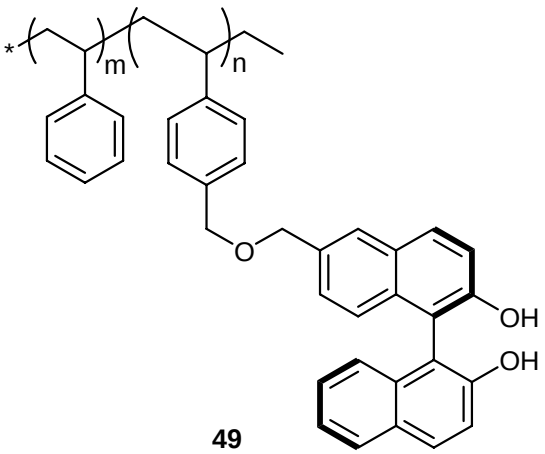
46 R=H
47 R=CH_2OH

Inanaga and coworkers investigated the effect of different additives. They found that triphenylphosphine oxide is the most effective oxidant which can raise the ee to 96 % with 99 % conversion of chalcones.[54] Kumarasawamy and co-workers[8,55,56] developed (*S*)-6,6'-diphenylbinol-Ca, an efficient chirally modified metal complex **48** for asymmetric epoxidation of α,β-unsaturated enones and obtained 90 % ee.



48

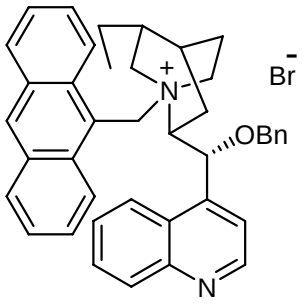
Jackson and coworkers[57] have reported the epoxidation of different chalcone derivatives using a metal peroxide. The best results are obtained using dibutyl magnesium, TBHP and (+)-diethyl tartrate as the ligand. The maximum ee was 94 % in this case. Sasai and co-workers[58] also developed the polymer-supported lanthanoide-BINOL complex **49** for the enantioselective epoxidation of α,β-unsaturated ketones and obtained up to 98 % ee.



49

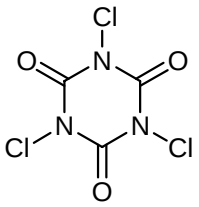
In the mid-1960s, phase transfer catalysis was developed. An organic salt such as a quaternary ammonium salt was used to transport inorganic ions into an organic phase. It is possible to induce asymmetry by using chiral ammonium salts in biphasic systems. The most common phase transfer reagents used for the asymmetric epoxidation of enones are alkylated *Cinchona* alkaloids (e.g. **50**). Different types of alkylated *Cinchona* alkaloids have been used by

Corey,[59] Lygo,[60,61,62,63] Yagi,[64] and Taylor.[65] They used NaOCl, KOCl, or H_2O_2 as oxidants. The ee obtained was 82-95 % with very good conversion of chalcones.



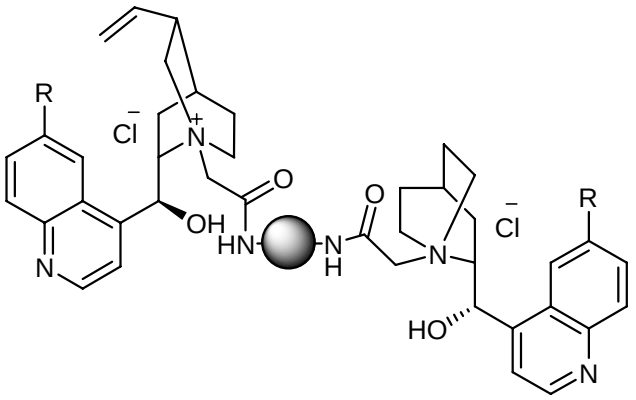
50

Liang and co-workers[66] used the C*inchona* alkaloid and trichloroisocyanuric acid **51** as a mild oxidant instead of the normally used NaOCl, KOCl, or H_2O_2 and obtained 99 % ee



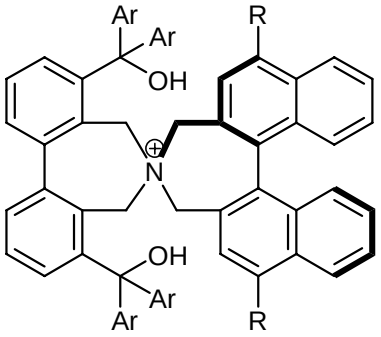
51

Adam and co-workers[67,68,69,70] used optically active hydroperoxides for the asymmetric Weitz-Scheffer epoxidation and controlled the enantioselectivity through metal-coordinated or hydrogen-bonded templates. Wang[71] used poly(ethylene glycol)-supported *Cinchona* ammonium salts **52** or **53** for catalytic symmetric epoxidation. Maruoka[72] and co-workers designed the new chiral phase-transfer catalyst **54** for highly enantioselective epoxidation of α,β-unsaturated ketones.



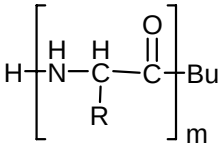
52 R = H

53 R = OMe



54 R = H

The use of synthetic peptides as stereoselective catalysts in organic reactions is an attractive alternative to the use of enzymes. In 1980, Julia[73] reported that poly-L-alanine **55** catalyzed asymmetric epoxidation of chalcone. The Julia reaction conditions were triphasic, consisting of the insoluble polyamino acid catalyst, an aqueous solution of NaOH and H_2O_2 and a solution of chalcone in an organic solvent. The important feature of the Julia-Colonna epoxidation was that the insoluble catalyst may be readily separated from the reaction products, washed and reused. Chalcone was epoxidized with polyamino acid catalyst in 93 % yield and 83 % ee.[74,75]



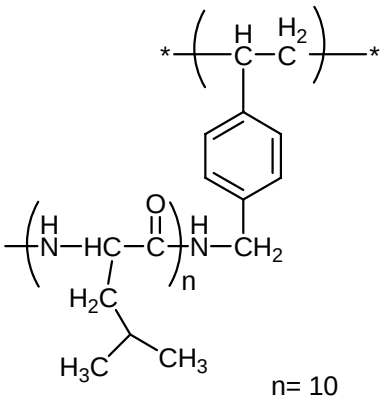
R = CH_3, m =10

55

The limitation of this reaction is the poor catalyst recycling. The low reactivity of reused catalyst has been overcome by Roberts and coworkers.[76-89] They developed biphasic systems which reduce the reaction times for chalcones to under 30 minutes. The first system is essentially anhydrous. The peroxide is delivered in the form of an anhydrous complex, typically urea-H_2O_2. Such complexes are stable and easy to handle and are safer than concentrated solutions of H_2O_2. The inorganic base NaOH, employed by Julia and Colonna, is replaced by the strong amidine base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the reaction is performed in an organic solvent such as anhydrous THF.

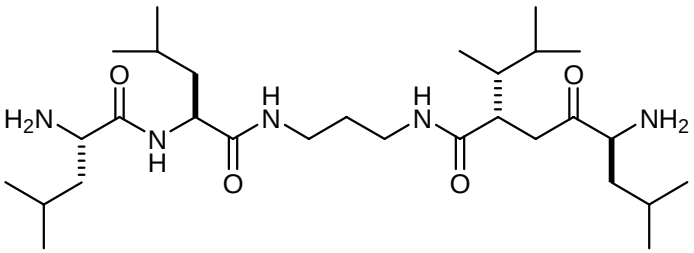
The disadvantage of this biphasic system is that it is more expensive than the triphasic system because it uses a rather more expensive oxidant and 1.5 equivalents of DBU. This condition is not ideal for large scale preparation. An alternative system used by Roberts and coworkers[90,91] employs inexpensive sodium percarbonate (NaPc) as both oxidant and base. The most effective solvent system is DME-water. This system also gives rates of reaction and enantioselectivities comparable to the DBU system. Chalcones were epoxidized in 92 % yield and 94 % ee in these processes.

In 1990, Itsuno[92,93,94] synthesized immobilized polymer-supported polyamino acid catalyst **56** for epoxidation of α,β-unsaturated ketones which proved to be good in non-aqueous media and obtained 99 % ee.



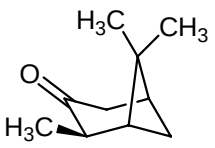
56 Polymer supported immobilized poly-L-leucin

Geller[95,96,97,98] noticed that by adding TBAB as a co-catalyst along with poly-L–leucin **57** it resulted in a dramatic acceleration of the reaction. Poly-L-leucine that had been polymerized at high temperature (ht-poly-L-leu) led to significantly more active catalysts as compared to the standard material.

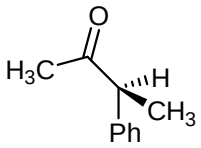


57

The first attempt to effect asymmetric epoxidation using chiral ketones **58** and **59** were reported by Curci[99] in the mid-1980s. In this case, the enantiomeric excess was only 9-12.5 %.

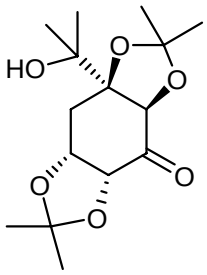


58

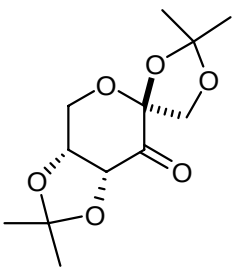


59

Recently chiral ketones, the precursors of corresponding dioxiranes, have been developed which will allow the epoxidations of a wide range of alkenes with good enantioselectivities. Different types of chiral ketones have been derived from (−)-quinic acid **60,** fructose **61**, and glucose, e.g. **62**, **63** and **64** by Shi and coworkers.[100,101,102,103,104,105,106,107,108,109,110,111] The most commonly used oxidants with chiral ketones are H_2O_2 and oxone in CH_3CN solution. Baeyer-Villiger reaction of the chiral ketones, from which the dioxiranes are derived, frequently competes with epoxidation especially for unreactive substrates. As a result, only a few chiral dioxiranes have been used successfully to epoxidize electron-deficient alkenes. Chalcone was epoxidized in 85 % yield and 96 % ee with chiral ketones.



60



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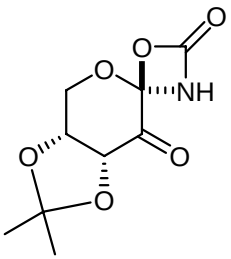
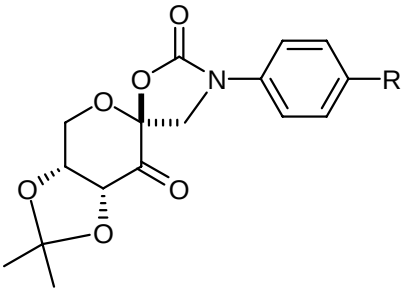


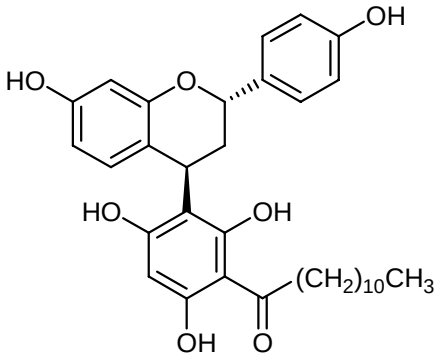
62



63 R = Me
64 R = Et

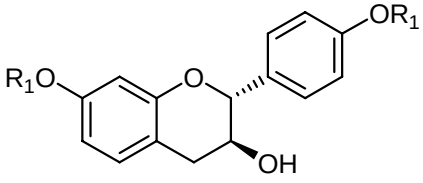
2.1. Strategic work plan

The aim of this work is try to improve the total synthesis of (+)-myristinin **A** (**65**) which is a natural DNA polymerase *β* inhibitor and potent DNA damaging agent.[41] In order to improve the total synthesis of (+)-myristinin A (**65)** in enantiomerically pure form, the synthesis of the flavan moiety **66** is important.



65 (+)-Myristinin A

For the synthesis of the flavan moiety **66**, we have developed a scheme based upon the epoxidation of chalcones. We also considered the study of the epoxidation of chalcones by applying different catalysts, followed by the transformation of these epoxy ketones to flavones.



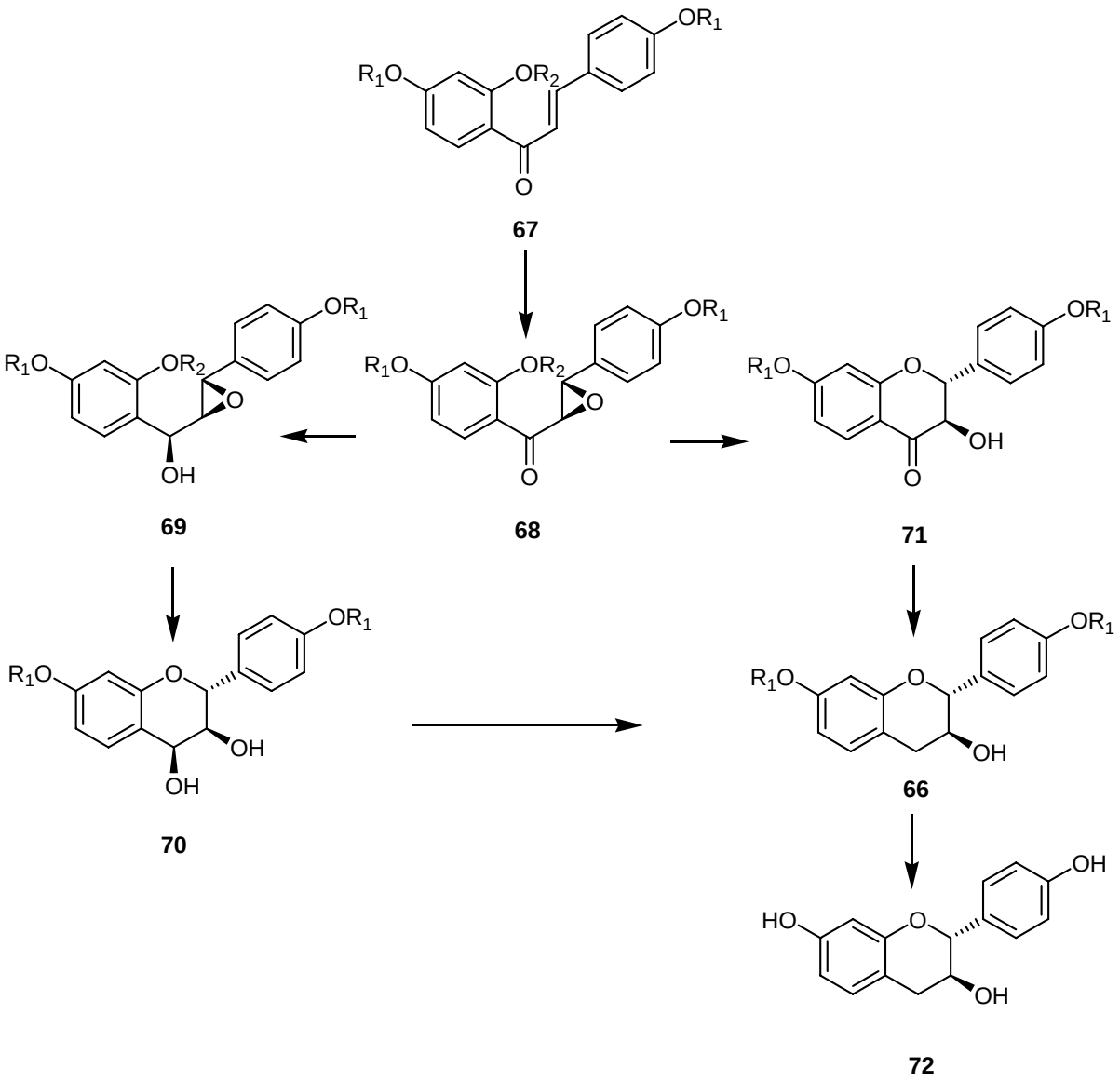
66

2.2.1. Asymmetric epoxidation of chalcones followed by cyclization

The synthesis of the flavan moiety was developed as shown in (Scheme 2.1). Protected chalcone **67** can be epoxidized by using different, chiral dioxiranes, chiral catalysts derived

from cinchonin or poly amino acids [48,49,50,51,52] to get epoxide **68**. The epoxide on the one hand can be reduced by using $ZnBH_4$[53,54] to get epoxy alcohol **69** and cyclization of the epoxy alcohol to give the *cis*-flavan-3,4-diol **70**, which on treatment with $NaBH_3CN$[29,112] will give rise to flavan-3-ol **66** (Scheme 2.1).

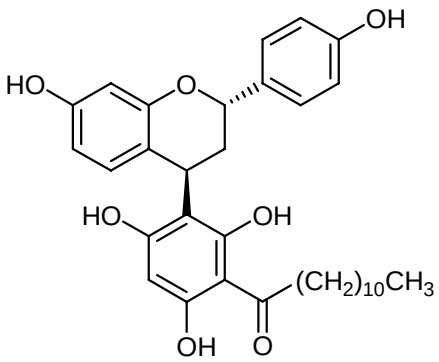
On the other hand, epoxide **68** can be cyclized by using methanolic hydrogen chloride in anhydrous methanol to get flavonol **71**[55] which on reduction, using $NaBH_4$ in acetic acid, gives flavan-3-ol **66**.[56,57] Final deprotection is expected to afforded the flavan-3-ol moiety **72** (Scheme 2.1).



Scheme 2.1: Synthetic plan of part A of myristinin A (**65**) by epoxidation followed by cyclization.

2.3. Known Synthesis of (+)-Myristinin A 65

Flavonoids are gaining much attention by chemists because of their biological activities, especially antibacterial, anticancer, and antiviral properties. (+)-Myristinin A (**65**) is a flavonoid isolated from *Myristica cinnamonea* by Sawadajoon and co-workers in 2002. (+)-Myristinin A (**65**) is known as a naturally occurring DNA polymerase *β* inhibitor and potent DNA damaging agent.[41]



65 (+)-Myristinin A

Hecht and coworkers[41]describe the synthesis of (+)-myristinin A (**65**) in 2005. Their synthetic scheme is shown below.

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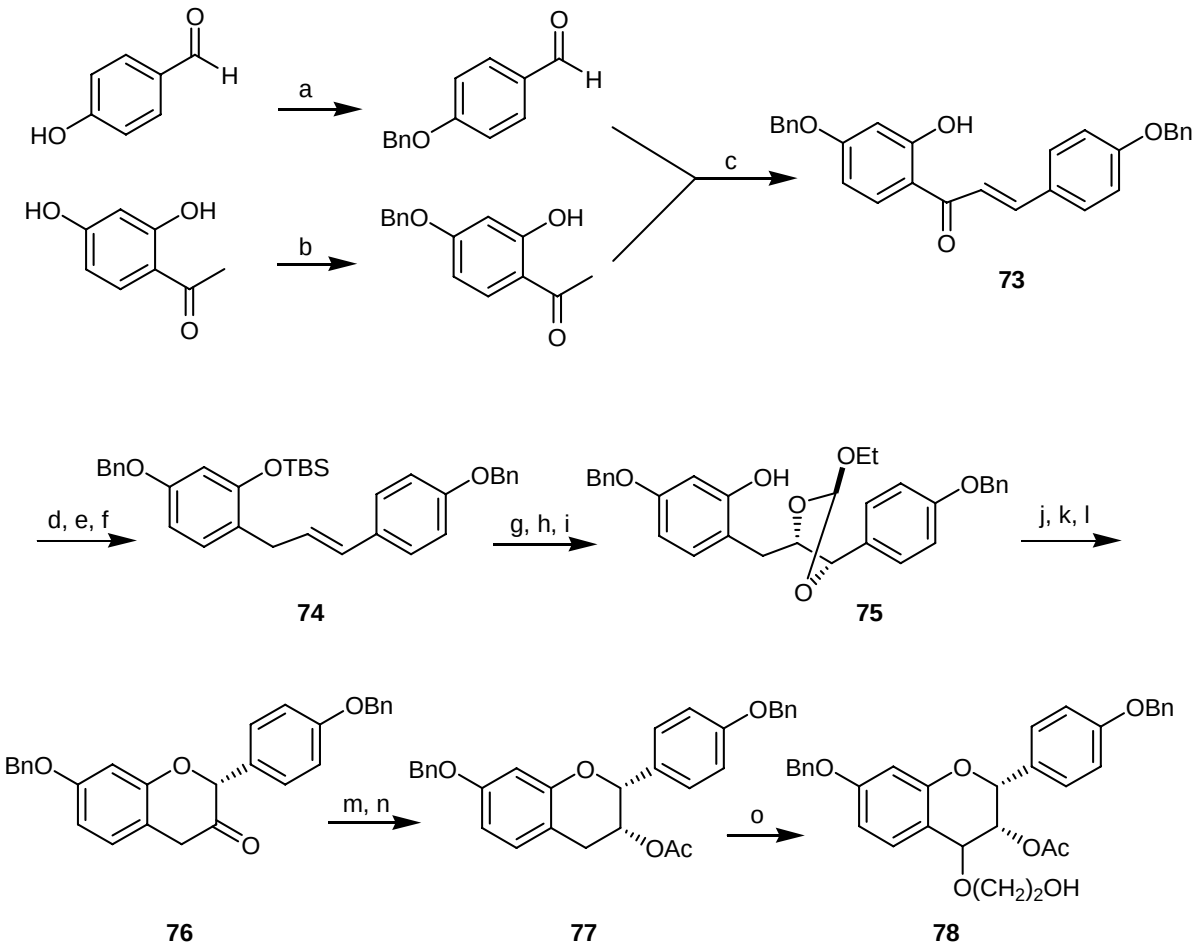
2.3.1. Synthesis of Part A, Flavan moiety 78

Their synthesis commenced with the protected benzaldehyde and acetophenone and their condensation into chalcone **73** in 97 % yield. Decarbonylation was done by using a mild method involving ethyl chloroformate and $NaBH_4$ in two-step process to afford substituted propene. The 2'-hydroxyl group of the propene was protected as the TBS-ether to give substituted 1,3-diphenylpropene **74**. Compound **74** was subjected to Sharpless asymmetric dihydroxylation using AD-mix α to give a diol. Treatment of the resulting diol with triethyl orthoformate in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) gave the ortho ester in 77% yield over two steps. TBAF in THF was used for the deprotection of the silyl ether to give phenol **75**. This phenol was treated with triethyl orthoformate and PPTS in dichloroethane at 60 °C to yield the intermediate 2,3-*trans*-pyran formate ester. Removal of the formate ester was done by treatment with K_2CO_3 in methanol to form a substituted flavan-3-ol, which was subjected to Dess-Martin periodinane oxidation to afford

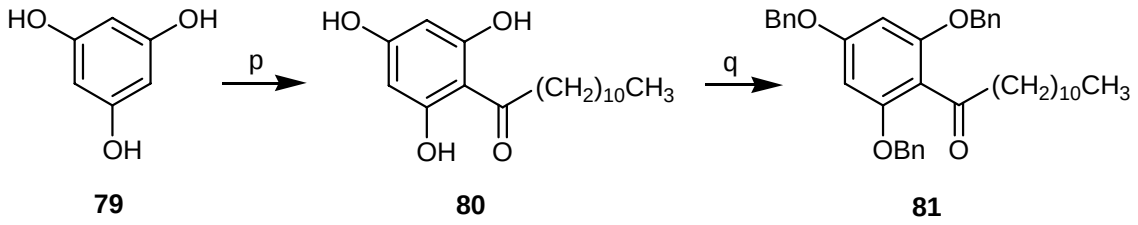
ketone **76**. Ketone **76** was reduced by using L-selectride in the presence of LiBr to afford the desired *cis* product which was acetylated using Ac_2O and NEt_3 to afford the acetylated product **77**. This was further subjected to DDQ oxidation and ethylene glycol in CH_2Cl_2 to afford part A of the molecule **78** (Scheme 2.2).



Scheme 2.2: Synthesis of part A of **78:** a) BnBr, K_2CO_3, DMF TBAI, RT; b) BnBr, K_2CO_3, MeCN , RT c) 40 % (w/v) KOH in MeOH, MeOH, reflux, 97 %; d) ethyl chloroformate, NEt_3, THF, 0 °C; e) $NaBH_4$, H2O, 74 %, 2 steps; f) TBDMSCl, imidazole, DMF, 100 %; g) AD-mix-α, methanesulfonamide, *t*-BuOH/H_2O (1:1), 84 %; h) $CH(OEt)_3$, cat. PPTS, CH_2Cl_2, 92 %; i) TBAF, THF, 100%; j) $CH(OEt)_3$, PPTS, $Cl(CH_2)_2Cl$, 60 °C, 89 %; k) K_2CO_3, THF/MeOH (1:1), 98%; l) Dess-Martin periodinane, CH_2Cl_2, 94 %; m) L-selectride, LiBr, THF, -78 °C, 78 %; n) Ac_2O, cat. DMAP, CH_2Cl_2, 93 %; o) DDQ, ethylene glycol, CH_2Cl_2, 79 %.

2.3.2. Synthesis of Part B 81

A solution of phloroglucinol **79** and lauric anhydride in THF was treated with BF_3-OEt_2 to give 1-(2,4,6-trihydroxyphenyl)dodecan-1-one **80** which was protected as the tribenzyl ether by using K_2CO_3 and benzyl bromide in DMF to give 1-(2,4,6-tribenzyloxyphenyl)dodecan-1-one **81** as the second part of the molecule (Scheme 2.3).

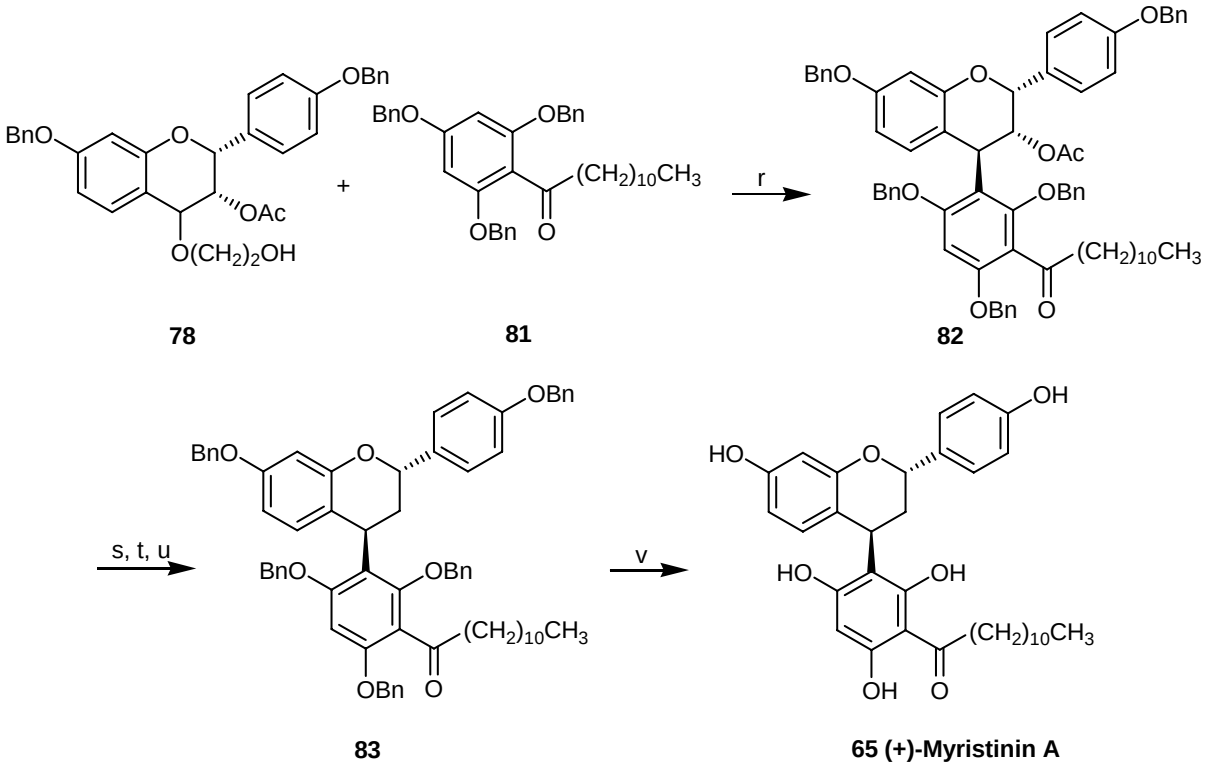


79 **80** **81**

Scheme 2.3: Synthesis of part B **81**: p) Lauric anhydride, BF_3-OEt_2, THF q) BnCl, K_2CO_3, DMF.

2.3.3. Coupling of Intermediates 78 and 81

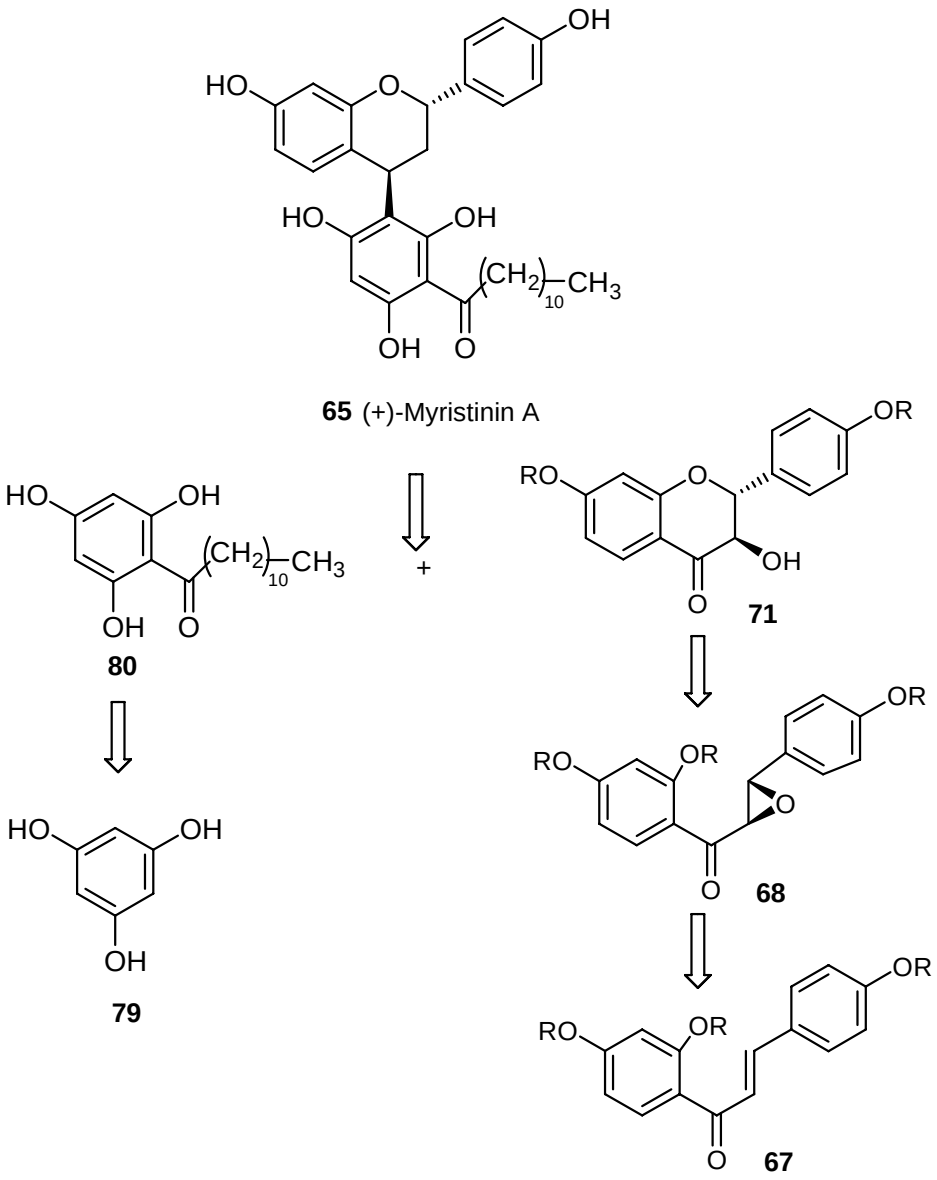
Lewis acid promoted condensation of **78** and **81** in THF gave the desired 2,4-*trans* isomer **82** in good yield (77 %). Deprotection of the acetate group was accomplished by treatment with K_2CO_3 in MeOH. The deprotected compound was subjected to thioacylation by reaction with phenyl phlorothionoformate in acetonitrile at 60 °C to give the desired deoxygenation precursor. This was refluxed immediately with $SnBu_3H$ in toluene in the presence of catalytic AIBN to give the deoxygenating product **83** (65%, three steps). Hydrogenolysis was smoothly done using Pearlman's catalyst ($Pd(OH)_2/H_2$) in THF/MeOH (1:1) to afford (+)-myristinin A (**65**) 75 % yield (Scheme 2.4).



Scheme 2.4: Coupling of Part A and Part B: r) TMSOTf, THF, -35 to -5 °C, 77 %; s) K_2CO_3, THF/MeOH (1:1), 100 %; t) PhOC(S)Cl, DMAP, MeCN, 50 °C; u) $SnBu_3H$, cat. AIBN, toluene, 100 °C, 65 %, 2 steps); v) $Pd(OH)_2/C$, H_2, THF/MeOH (1:1), 75 %.

2.4. Retrosynthetic analysis of (+)-myristinin (65)

Based on the epoxidation of chalcone, **67**, we suggest the following retrosynthetic analysis. Myristinin A (**65)** can be obtained by Lewis acid-catalysed condensation between **71** and **80**. **80** can further be achieved from phloroglucinol **79** and **71** can be formed from epoxide **68** through cyclization. Epoxide **68** in turn can be obtained from the epoxidation of chalcone **67** (Scheme 2.5).



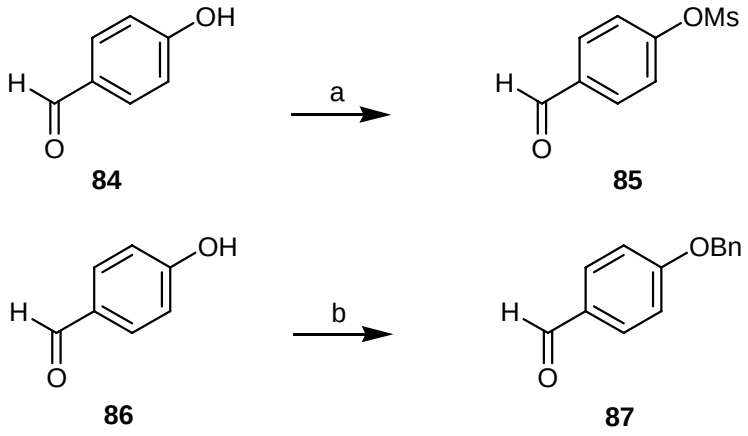
Scheme 2.5: Retrosynthetic analysis of (+)-myristinin A (**65**).

2.5. Results and discussion

2.5.1. Synthesis of chalcones for epoxidations

2.5.1.1 Synthesis of benzaldehydes 85, 87

4-Mesylbenzaldehyde **85** was prepared in good yield by treating 4-hydroxy benzaldehyde **84** with mesyl chloride in pyridine at room temperature for 4h.[113,114] 4-Benzyloxybenzaldehyde (**87**) was formed by subjecting 4-hydroxybenzaldehyde (**86**) to benzyl bromide and potassium carbonate in dimethylforamide in the presence of a catalytic amount of tetrabutylammonium iodide for 24 h at room temperature in quantitative yield[115] (Scheme 2.6).

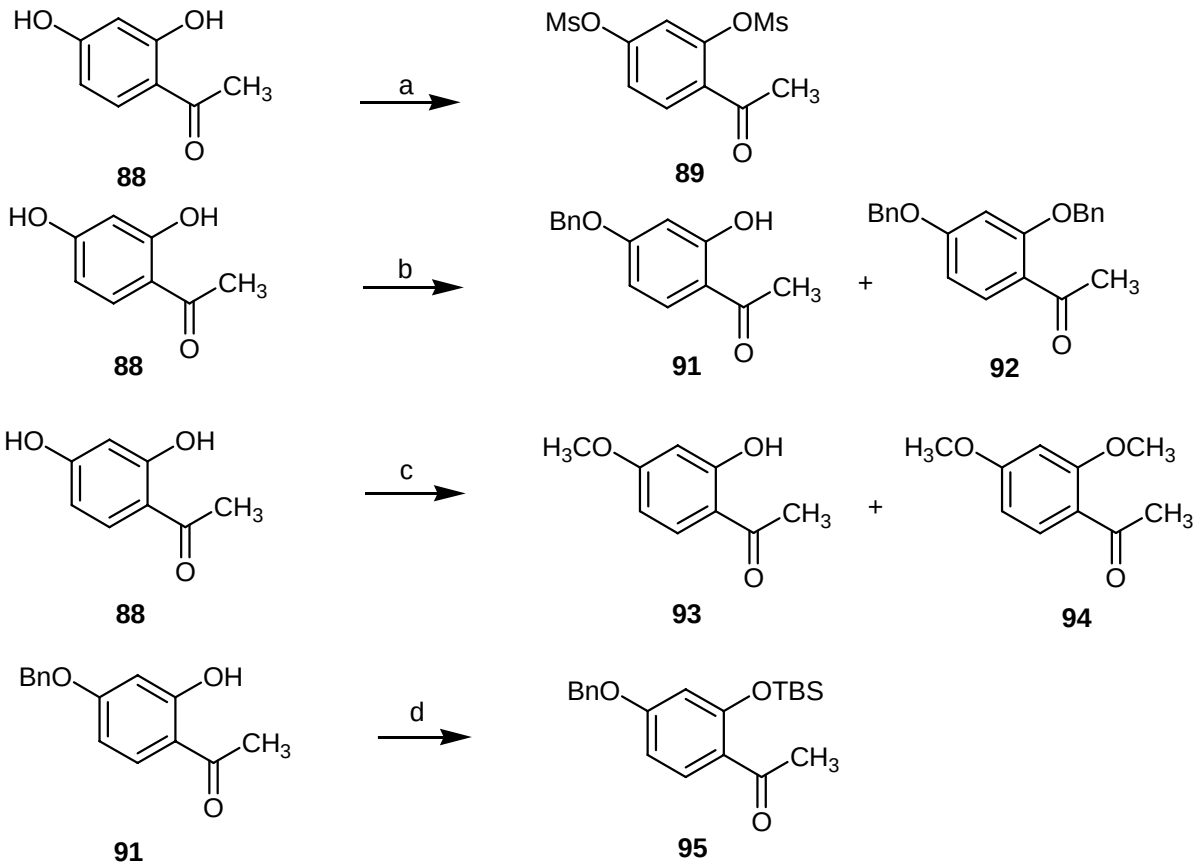


Scheme 2.6: Synthesis of benzaldehydes **85** and **87:** a) MsCl, pyridine, 75 %; b) BnBr, K_2CO_3, TBAI, 99 %.

2.5.1.2. Synthesis of acetophenones 89, 91, 93, 95

Acetophenone **89** was formed in good yield by treatment of dihydroxyacetophenone **88** with mesyl chloride in pyridine at room temperature for 6 h[113,114] (Scheme 2.7). An attempt to selectively mesylate only at the 4'-hydroxyl position of the dihydroxyacetophenone **88** to obtain monomesylated product failed. 4-Benzyloxy-2'-hydroxyacetophenone (**91**) was prepared by treating dihydroxyacetophenone **88** with benzyl bromide and potassium

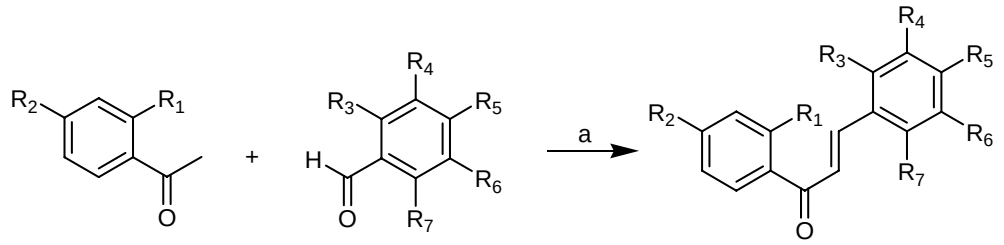
carbonate in acetonitrile under reflux for 1h (Scheme 3.12). The reaction was monitored by TLC. After 40min at reflux, it was observed that the formation of dibenzyloxy acetophenone **92** started. The isolated yield of the required **91** was 75 % along with 5 % **92** after the complete conversion of the reactant.[116] It was observed that by refluxing the acetophenone **88** with benzyl bromide in DMF, the side product **92** was isolated even in higher yield and the yield was decreased in DMF. This may be because of the polarity of the solvent used. 4'-Methoxy-2'-hydroxyacetophenone (**93**) was prepared by treating dihydroxyacetophenone **88** with dimethyl sulphate and potassium carbonate in acetone for 4h at room temperature in 91 % isolated yield along with 5 % of dimethoxy acetophenone **94** as a side product[117] (Scheme 3.12).The same reaction was also done in DMF and acetonitrile, but the yield was low in both the cases. The TBS protected acetophenone **95** was obtained in quantitative yield by treating acetophenone **91** with *tert*-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole (Scheme 2.7).[41]



Scheme 2.6: Synthesis of acetophenones **89, 91, 93, 95:** a) MsCl, pyridine, 82 %; b)BnBr, K_2CO_3, CH_3CN, 75 %; c) $(CH_3)_2SO_4$, K_2CO_3, acetone, 91 %; d) TBDMSCl, imidazole, DMF, 90 %.

2.6. Synthesis of methoxychalcones

The methoxy chalcones **106-112** were prepared by Claisen-Schmidt condensation between acetophenones **93, 96, 97, 98** and aldehydes **99-105**. The equimolar mixture of appropriate aldehyde and acetophenone in 95 % ethanol was treated with 60 % w/v of aqueous solution of KOH at 55 °C for two days (Scheme 2.8).[37,38,39,40,118]



93 R_1 = OH, R_2 = OCH_3

96 R_1 = H, R_2 = H

97 R_1 = OH, R_2 = H

98 R_1 = H, R_2 = OCH_3

99 R_3 - R_7 = H

100 R_3 = R_6 = OCH_3

101 R_3 = R_5 =R_7 = OCH_3

102 R_4 - R_5 = OCH_3

103 R_3 = R_4 =R_5 = OCH_3

104 R_5 = OCH_3

105 R_4 = R_5 =R_6 = OCH_3

106 R_1-R_7 = H

107 R_1 = OH, R_2-R_7 = H

108 R_2 = R_3 = R_6 = OCH_3, R_1 = R_4 = R_5 = R_7 = H

109 R_2 = R_3 = R_5 = R_7 = OCH3, R_1 = R_4 = R_6 = H

110 R_2 = R_4 = R_5 = OCH_3, R_1 = OH, R_3 = R_6 = R_7 = H

111 R_2 = R_3 = R_4 = R_5 = OCH_3, R_1 = OH, R_6 = R_7 = H

112 R_2 = R_5 = OCH_3, R_1 = OH, R_3 = R_4 = R_6 = R_7 = H

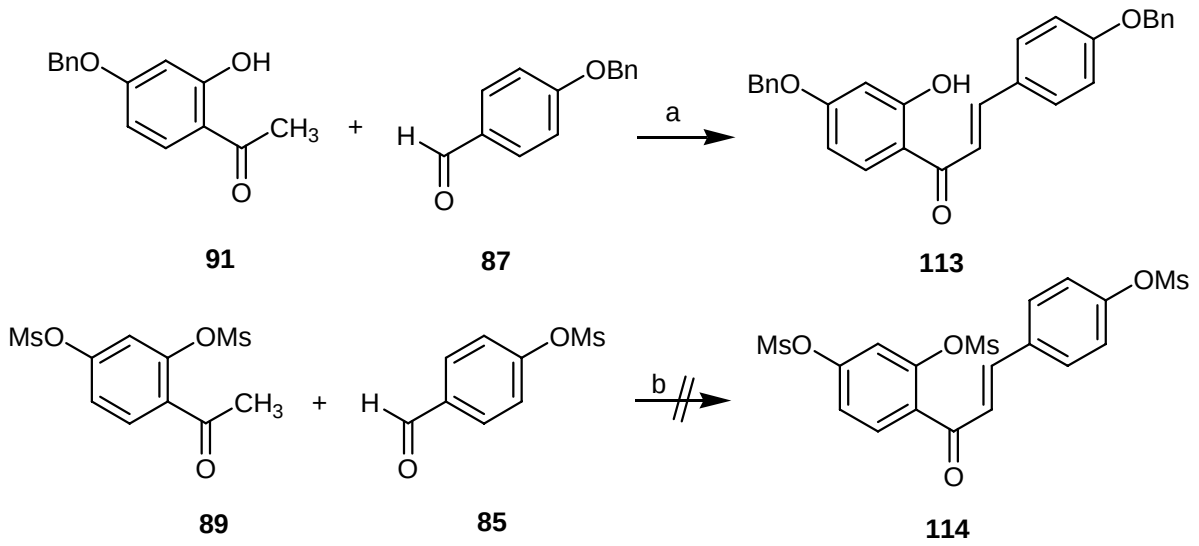
Scheme 2.8: Synthesis of methoxychalcones **106-112:** a) 60% w/v KOH, C_2H_5OH, 55 °C.

Different chalcones were prepared to evaluate their epoxidation. All of the chalcones were prepared in yields of 80 % and better. The best yield was obtained in case of chalcone **112** which was 87 % and the lowest yield was in case of chalcone **106** which was 81 %. The reason for the high yield may be the electron donating nature of the 4 and 4'-methoxy group present in the chalcone in the case of **112**. The lowest yield was because of the poor electron system in chalcone **106**. The yields of the chalcones are shown in tabular form (Table 2.1).

Table 2.1: Yields of the chalcones **106-112**.

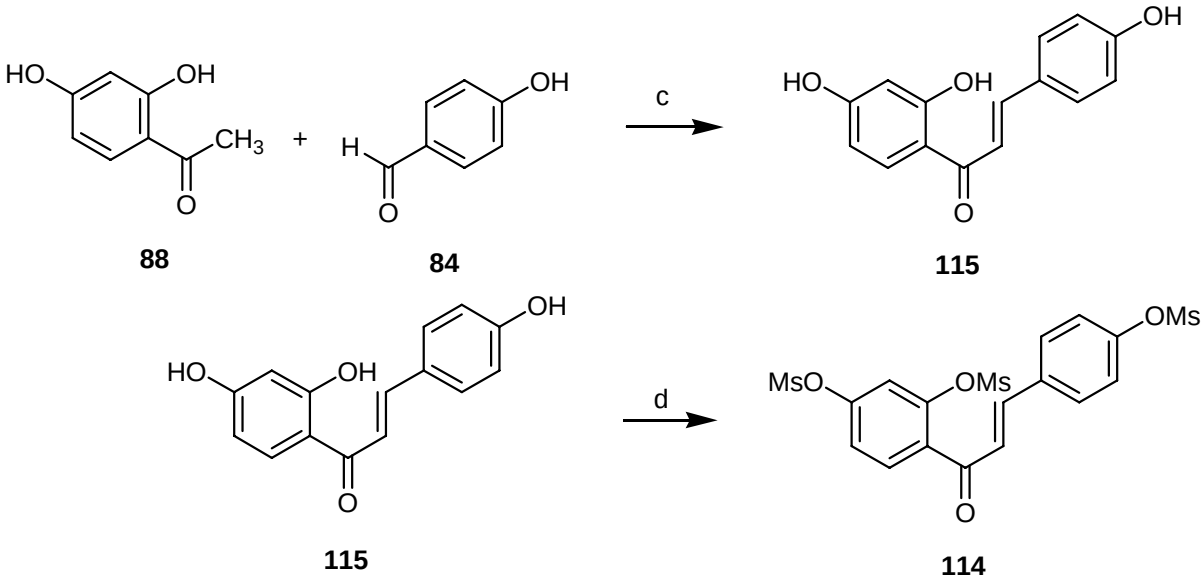
No. of Expt.	Acetophenone	Benzaldehyde	Chalcone	Yield %
1	96	99	106	81
2	97	99	107	83
3	98	100	108	83
4	98	101	109	86
5	93	102	110	82
6	93	103	111	85
7	93	104	112	87

Chalcone **113** was obtained in 94 % yield as a yellow solid by heating a mixture of acetophenone **91** and benzaldehyde **87** in methanol for 12h under reflux.[41] Preparation of chalcone **114** was attempted by reacting acetophenone **89** and benzaldehyde **85** in ethanol at room temperature. After 2 days, no product was observed. This mixture was then heated under reflux for 12 h, but even then no product was observed (Scheme 2.9). Acetophenone **89** and benzaldehyde **85** contain strong electron withdrawing groups which may be the reason for no reaction under this condition.



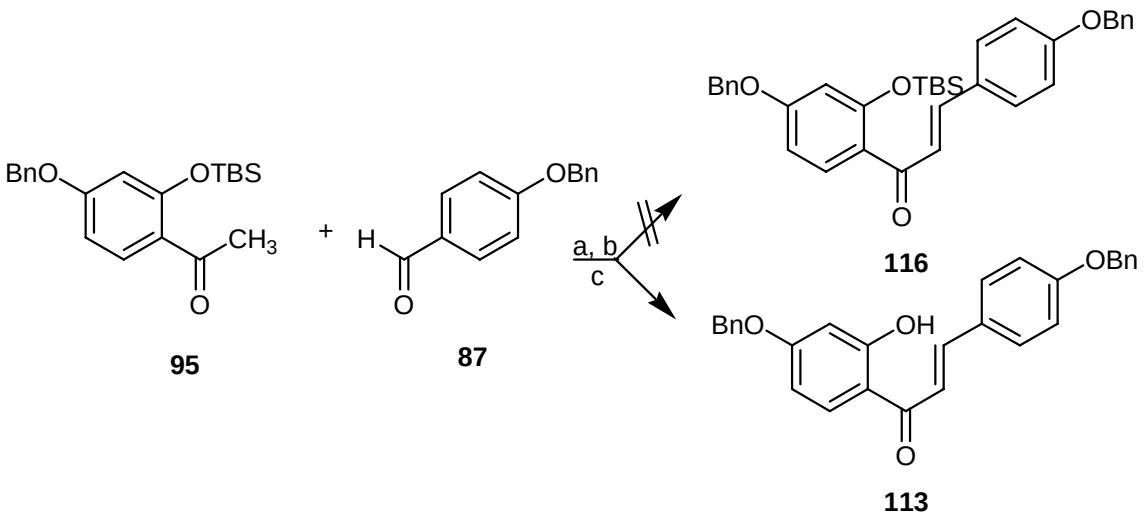
Scheme 2.9: Synthesis of chalcones **113** and **114:** a) KOH, MeOH, 94 %; b) KOH, C_2H_5OH, reflux, 12 h.

For the formation of chalcone **114**, chalcone **115** was firstly synthesized in 50% yield by subjecting a mixture of unprotected acetophenone **88** and aldehyde **84** to 60% potassium hydroxide in ethanol at 60 °C for 3 days.[115] Chalcone **115** was then treated with mesyl chloride and pyridine at room temperature to obtain **114** in 82% yield (Scheme 2.10). The mesylation reaction of trihydroxychalcone **115** was proceeded quantitatively.[113,114]



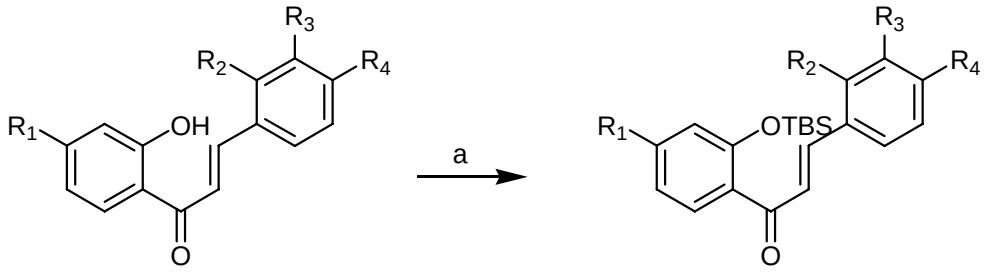
Scheme 2.10: Synthesis of chalcones **114** and **115:** a) KOH, C_2H_5OH, 50 %; b) MsCl, pyridine, 82 %.

Chalcone **116** could not be obtained under the different conditions applied. Under all the three conditions applied to a mixture of TBS-protected acetophenone **95** and benzaldehyde **87**, we obtained chalcone **113** and starting material **95** instead of chalcone **116**. This means that the TBS group is removed under all three conditions (Scheme 2.11). The reasons may be due to the instability of the TBS group under these strong basic conditions or the steric effects of the big TBS group did not allow the reaction to occur.[29,41]



Scheme 2.11: Synthesis of chalcone **116:** a) KOH, MeOH; b) KOH, C_2H_5OH, %; c) NaH, DMF.

Chalcones **107, 111, 114** were protected as TBS ethers by subjecting them to reaction with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide to obtain protected chalcones[41] **117-119** (Scheme 2.12). The reason for the slow reaction rate and the moderate yields in every case is due to the bulky TBS group.



107 R_1-R_4 = H

111 R_1-R_4 = OCH3

112 R_1=R_4 = OCH3
R_2=R_4= H

117 R_1-R_4 = H

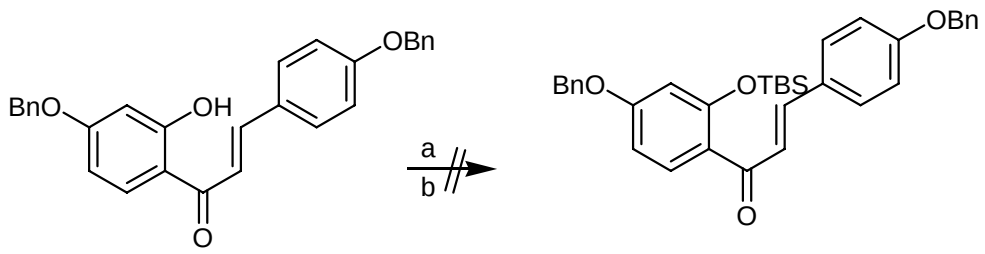
118 R_1-R_4 = OCH3

119 R_1=R_4 = OCH3
R_2=R_4= H

Scheme 2.12: TBS protection of chalcones **107, 111, 112:** a) TBDMSCl, imidazole, DMF.

Protection of chalcone **113** as the TBS ether was also attempted but could not be effected under the same conditions[41] (Scheme 2.13). We also tried to transform chalcone **113** to chalcone **116** by treating it with *tert*-butyldimethylsilyl triflate and 2,6-lutidine in dichloromethane but this reaction did not work.[119,120] The reason behind this may be due to

steric interaction between benzyloxy and *tert*-butyldimethylsilyl groups and the instability of the TBS group under the conditions applied.

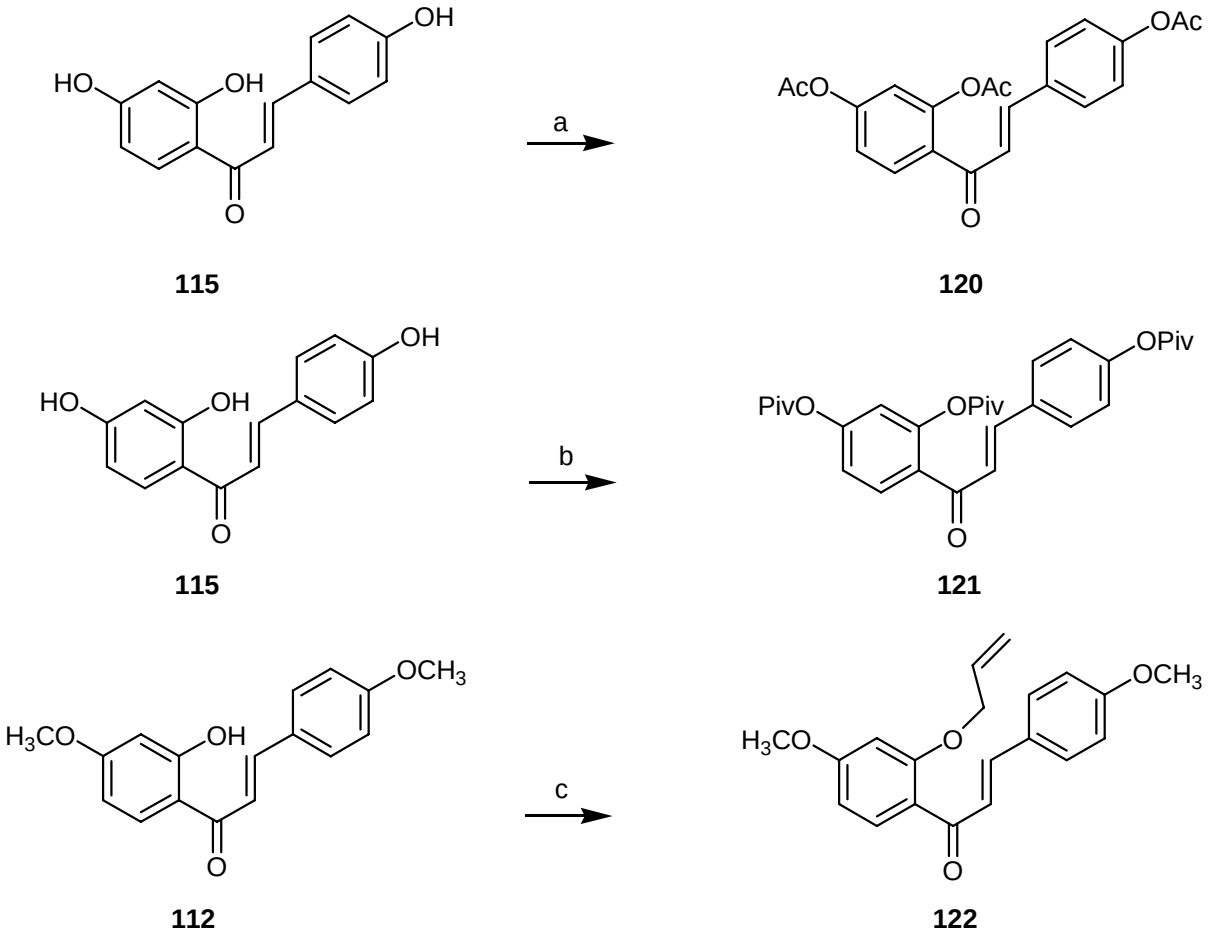


113 **116**

Scheme 2.13: TBS protection of chalcone **113:** a) TBDMSCl, DMF; b) TBDMS-Tf, 2,6-lutidin, CH_2Cl_2

Triacetylated chalcone **120** was prepared in quantitative yield by subjecting chalcone **115** to acetic anhydride in pyridine. Chalcone **115** was also converted into pivaloyl protected chalcone **121** by treating with pivaloyl chloride and pyridine in dichloromethane[121](Scheme 3.19).

Chalcone **112** was protected as the allyl ether **122** by reacting chalcone **112** with ally bromide and silver oxide in anhydrous toluene. The yield of the reaction was very low. But the yield of the allyl protection of chalcone **112** by treating it with potassium fluoride-alumina mixture (2:3) and allyl bromide in acetonitrile[122,123] was 85 %. There was no side product observed and the reaction time was also reduced (Scheme 2.14).



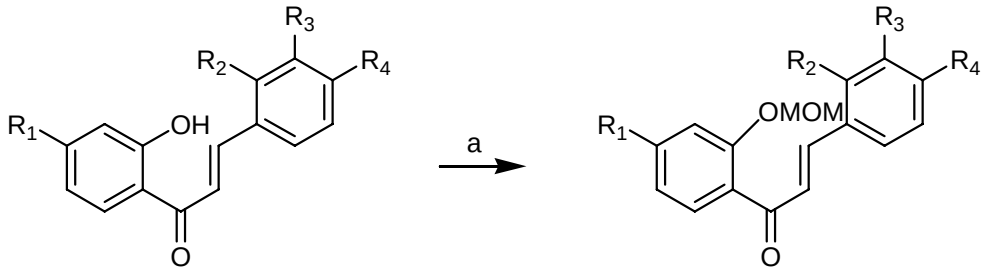
115 **120**

115 **121**

112 **122**

Scheme 2.14: Protection of chalcones**:** a) Ac_2O, Pyridine, 85 %; b) PivCl, pyridine, CH_2Cl_2, 65 %.; c) i) Ag_2O, allyl bromide, toluene, 55 %; or ii) KF-Al_2O_3, allyl bromide, CH_3CN, 85 %.

Chalcones **107**, **111-113** were protected as MOM ethers by treating them with methoxymethyl chloride and 1 M aqueous sodium hydroxide solution in dichloromethane in the presence of a catalytic amount of tetrabutylammonium chloride[124] to form the MOM-protected chalcones **123-126** in good yields (Scheme 2.15). All the reactions in case of MOM protection proceeded smoothly and in good yields.



107 R_1-R_4 = H

111 R_1-R_4 = OCH3

112 R_1=R_4 = OCH3
R_2=R_4= H

113 R_1=R_4 = OBn
R_2=R_4= H

123 R_1-R_4 = H

124 R_1-R_4 = OCH3

125 R_1=R_4 = OCH3
R_2=R_4= H

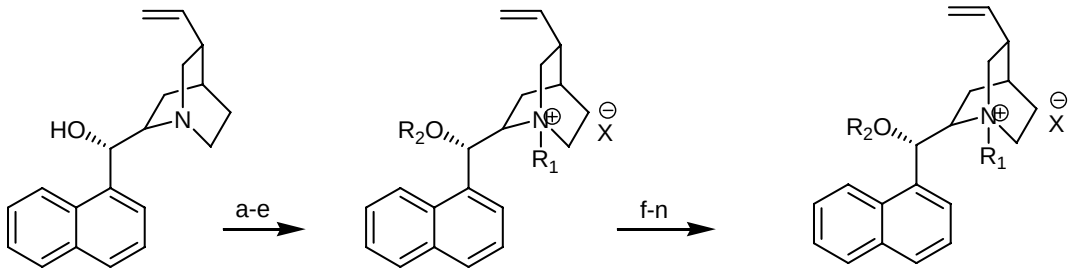
126 R_1=R_4 = OBn
R_2=R_4= H

Scheme 2.15: MOM protection of chalcones**:** a) MOMCl, 1N NaOH, CH_2Cl_2, TBACl.

2.7. Synthesis of catalysts for asymmetric epoxidation

2.7.1. Synthesis of phase transfer catalysts from (+)-cinchonine (127)

Different catalysts **127-141** were prepared from the (+)-cinchonine (**127**) for the epoxidation of the chalcones by treatment with different aryl halides (Scheme 3.2) under reflux to give *N*-alkyl cinchonium halides **128-132**[60].



127(+)-Cinchonine

128 R_1 = Bn, R_2 = H, X= Cl

129 R_1 = Bn, R_2 = H, X= Br

130 R_1 = 3-henylpropyl, R_2 = H, X= Br

131 R_1 = 2-Naphthyl, R_2 = H, X= Br

132 R_1 = *p*-OMeBn, R_2 = H, X= Cl

133 R_1 = R_2=Bn, X= Br

134 R_1 = Bn, R_2 = 3-phenylpropyl, X= Br

135 R_1 = Bn, R_2 = *p*-OMeBn, X= Br

136 R_1 = 3-phenylpropyl, R_2 = 3-phenylpropyl, X= Br

137 R_1 = 3-phenylpropyl, R_2 = Bn, X= Br

138 R_1 =2-Naphthyl, R_2 = Bn

139 R_1 =2-Naphthyl, R_2 = *p*-OMeBn

140 R_1 =R_2= *p*-OMeBn, X= Cl

141 R_1 = *p*-OMeBn, R_2 = Bn, X= Br

Scheme 2.16: Synthesis of phase transfer catalysts **128-141** from (+)-cinchonine (**127**)**:**
a) BnCl, toluene, reflux 48 h; b) BnBr, toluene, reflux 2h; c) 3-Phenylpropylbromide, toluene, reflux 8h; d) 2-Naphthylbromide, toluene, reflux, 4h; e) p-OMe-BnCl, toluene, reflux, 7h; f) **129**, BnBr, 50% NaOH, CH_2Cl_2, RT,2h; g) **129**, 3-phenylpropylbromide, 50% NaOH, CH_2Cl_2, RT, 4h; h) **129**, p-OMe-BnCl, 50% NaOH, CH_2Cl_2, RT, 2h; i) **130**, 3-phenylpropylbromide, 50% NaOH, CH_2Cl_2, RT, 2h; j) **130**, BnBr, 50% NaOH, CH_2Cl_2, RT, 2h; k) **131**, BnBr, 50% NaOH, CH_2Cl_2, RT, 2h; l) **131**, p-OMe-BnCl, 50% NaOH, CH_2Cl_2, RT, 2h; m) **132**, p-OMe-BnCl, 50% NaOH, CH_2Cl_2, RT, 2.5h; n) **132**, BnBr, 50% NaOH, CH_2Cl_2, RT, 2h

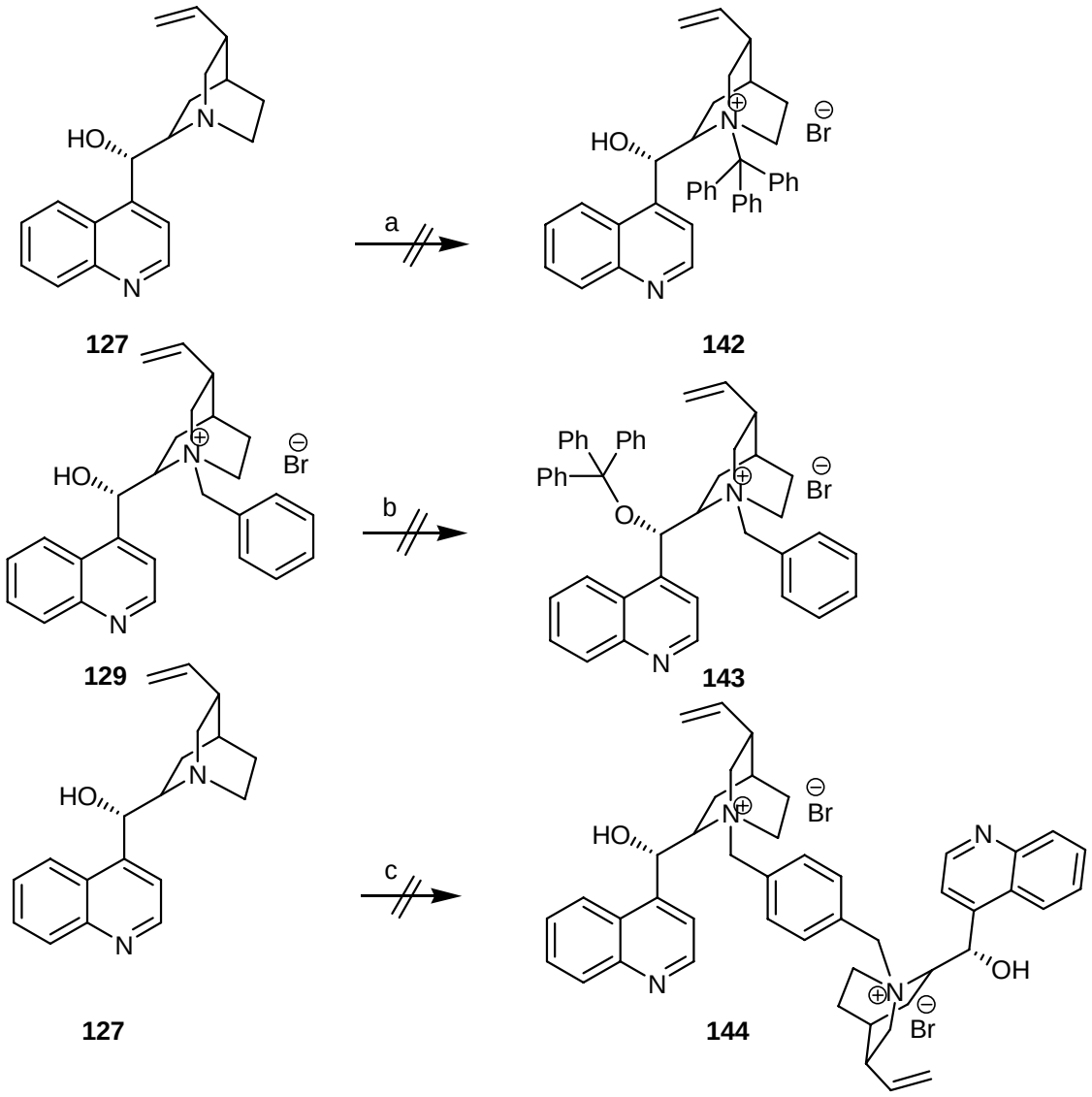
The free hydroxyl group present on the *N*-alkyl cinchonium halides **128-132** was subjected to etherification by treating it with different aryl halides to give *N*-alkyl, *O*-alkyl cinchonium halides **133-141** in quantitative yields.[60] It was observed that by protecting the free hydroxyl group the enantioselectivity increased. The catalysts with the free hydroxyl groups are stable towards oxidation and it may be due to hydrogen bonding between the hydroxyl group of the catalysts with substrate or oxidant used. Therefore the hydroxyl group was protected. It was observed that during the formation of *N*-alkyl cinchonium halides **128-132**, the reaction time with aryl chlorides was more than the aryl bromides and this is of course because of the reactivity of the halides (Scheme 2.16). In the etherification reaction, there is no great time difference between aryl chlorides and aryl bromides. All the reactions proceeded smoothly and in good yields. The enantioselectivity of the catalysts were mainly dependent on the aryl part of the catalysts.[125] The reaction conditions and the information about the reagents are given in Table 2.2.

Table 2.2: Synthesis of phase transfer catalysts.

No. Of Expt.	Starting Material	Reagents and Conditions	Product
1	127	a	128
2	127	b	129
3	127	c	130
4	127	d	131
5	127	e	132
6	129	f	133
7	129	g	134
8	129	h	135
9	130	i	136
10	130	j	137
11	131	k	138
12	131	l	139
13	132	m	140
14	132	n	141

The preparation of the catalysts **142**, **143, 144** was also attempted adopting the same procedure but was not successful (Scheme 3.3). The catalysts **142** and **143** were not formed which may be due to the steric effects of the trityl group and the second reason may be

because trityl bromide is not reactive enough in such kinds of reactions. The catalyst **144** was not formed, possibly be due to the effect of double salt formation.



Scheme 217: Synthesis of phase transfer catalysts **142-144:** a) trityl bromide, toluene, reflux 24 h; b) trityl bromide, 50% NaOH, CH_2Cl_2; c) p-xylene bromide, toluene, reflux.

2.7.2. Mechanism of the epoxidation with cinchonine quaternary ammonium salt

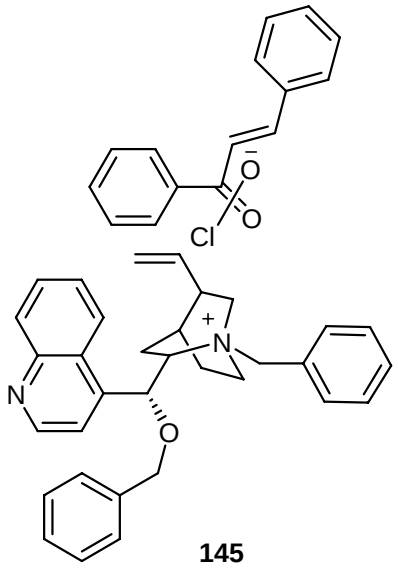
The mechanism of these reactions has been in detail studied by Corey[59] and has been thus clarified. The enantioselectivity of these reactions is controlled by the specific three dimensional arrangement of a contact ion pair. Normally with a contact ion pair, the nucleophilic site i.e. negatively charged species that have oxygen, is proximate to the

quaternary cationic centre i.e. positively charged nitrogen. The distance between these two species is controlled by the optimum van der Waals attractive interactions.

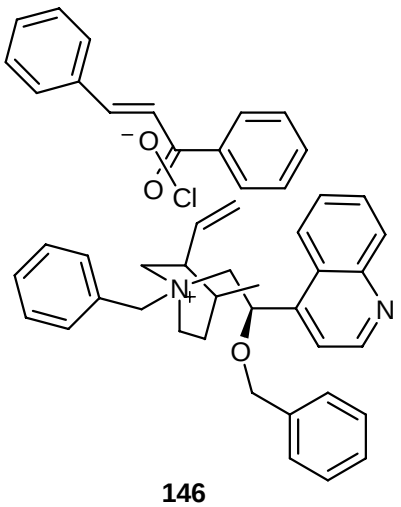
According to the stereo mechanistic details, the chiral cations (positively charged nitrogen atom) brings the oxidants (OCl^-) and α,β-enones into an appropriate three dimensional arrangement which allows the free selective conjugate addition of the ion-paired hypochlorite to the α, β-enones and lets the epoxidation proceed in an energetically and entropically favoured transition state.

If the aromatic ring attached to the carbonyl group of the α,β-enones is constrained to be co-planar with the carbonyl sigma plane, the enantioselectivity drops to a great extent. Sometimes the phenyl substituent and the carbonyl sigma plane are non-planar, i.e., out of л-conjugation, which can also be the reason for the low enantioselctivity.

As shown in **145** and **146** (Figure 2.1), the phenyl group is wedged between the ethylene and the quinoline ring and the carbonyl group is placed close to the positively charged nitrogen as allowed by van der Waals forces. The OCl^- ion is proximate to the β carbon of α,β-enones for conjugate addition. In facts the nucleophilic attack occurs by the negative charge developed at the carbonyl oxygen, which is stabilized by positively charged nitrogen.



145

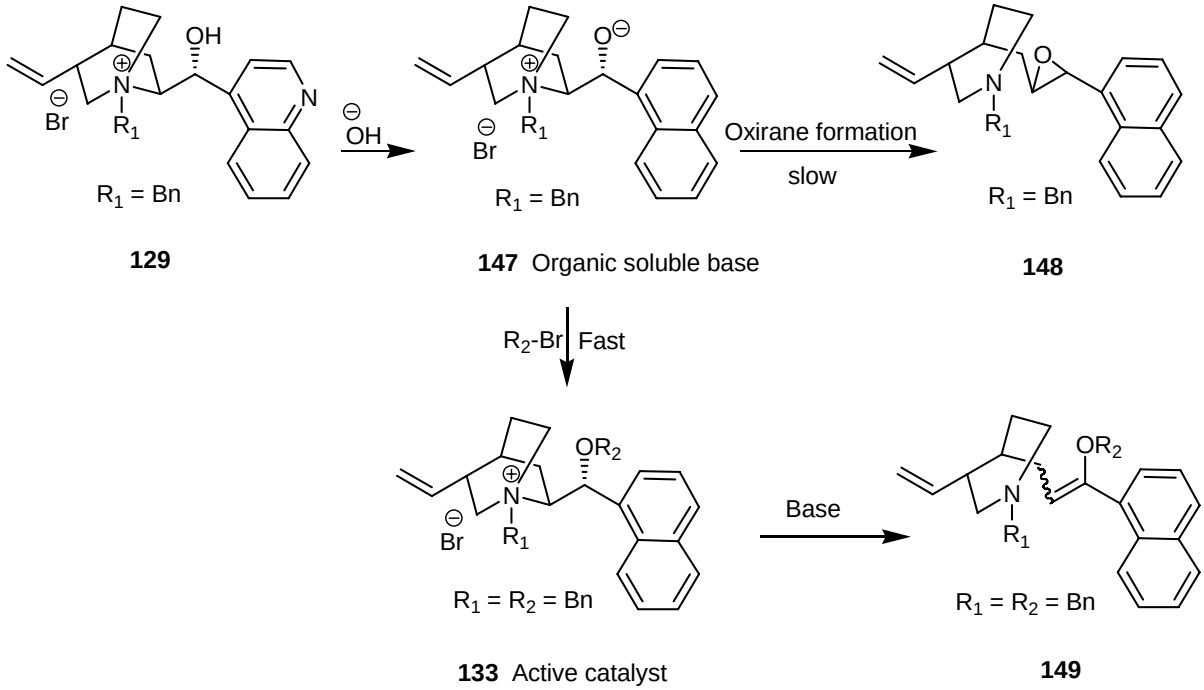


146

Figure 2.1: Mechanism of epoxidation with cinchonine quaternary ammonium salts.

2.7.3. Degradation of cinchonine catalyst

Degradation of catalyst was proposed by Merck.[126] Deprotonation of the initial catalyst **129** leads to zwitterion alkoxide **147** which could be degraded in two pathways. A slow fragmentation to form epoxide **148** and a faster alkylation to form **133,** followed by Hofmann's elimination to form **149**. This is illustrated in Scheme 2.18. The second *O* alkylation of the zwitterion alkoxide **147** occurs as soon as the alkyl halide is added, to form the active catalyst **133**, thus minimizing the effect of base-promoted racemization.

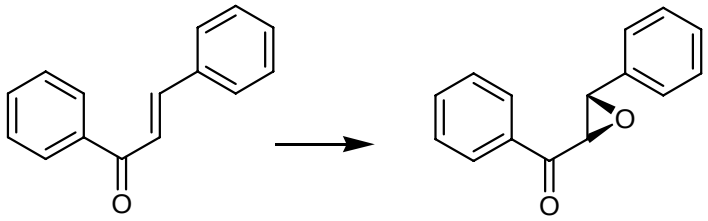


Scheme 2.18: Degradation of cinchonin catalyst.

2.7.4. Epoxidation of chalcones with cinchonin derived phase transfer catalysts

In order to check the effectiveness of the synthesized catalysts in Weitz-Scheffer epoxidations,[48] a number of experiments were performed at room temperature (Table 2.3). All the reactions were performed in toluene at room temperature by treating the chalcone **106** with 10 mol% of the phase transfer catalysts and 20 times excess of 13 % NaOCl as an oxidant. Different catalysts were used but the best catalyst found was **140** with enantioselectivity of 84 % ee (Table 2.3, entry 15).

Table 2.3: Enantioselctive epoxidation of chalcone **106** at room temperature.



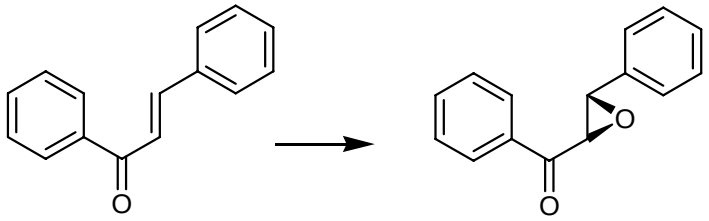
106 **Chalcone epoxide**

Expt.	Catalyst	Oxidant	Temp.	Time	Solvent	%yield	$[\alpha]_D$	% ee
1	128	13%NaOCl	RT	32h	Toluene	73	79,1	38
2	129	13%NaOCl	RT	25h	Toluene	82	87,5	42
3	130	13%NaOCl	RT	30h	Toluene	63	85,4	41
4	131	13%NaOCl	RT	23h	Toluene	87	101	62
5	132	13%NaOCl	RT	18h	Toluene	82	100,3	48
6	133	13%NaOCl	RT	12h	Toluene	80	149,2	72
7	134	13%NaOCl	RT	11h	Toluene	83	101,2	48
8	135	13%NaOCl	RT	10h	Toluene	85	164,8	80
9	136	13%NaOCl	RT	42h	Toluene	68	100	48
10	137	13%NaOCl	RT	15h	Toluene	71	130,3	62
11	138	13%NaOCl	RT	10h	Toluene	73	150,5	72
12	139	13%NaOCl	RT	22h	Toluene	65	164,3	80
13	140	t-BuOOH	RT	24h	Toluene	53	103,2	49
14	141	30%H2O2	RT	32h	Toluene	24	97,5	46
15	141	13%NaOCl	RT	10h	Toluene	84	173,9	84
16	140	13%NaOCl	RT	8h	Toluene	88	157,7	77

2.7.5. Effect of temperature change on epoxidation

We have also observed a temperature effect in the Weitz-Scheffer epoxidation with the synthesized catalysts. It was observed that with a decrease in temperature, the yield of the reaction also decreases but the reaction time and the enantioselectivity of the epoxide increases to a greater extent. The maximum enantioselectivity was observed in the case of catalyst **140** which was 90 % and the reaction was performed at -20 °C for 72 h (Table 2.4, entry 8). It was also observed that by adding 0.5 mol % additional catalyst after 24 h, there is an increase in the yield of the reaction and a decrease in the time of the reaction to some extent.

Table 2.4: Enantioselctive epoxidation of chalcone **106** and temperature effect.



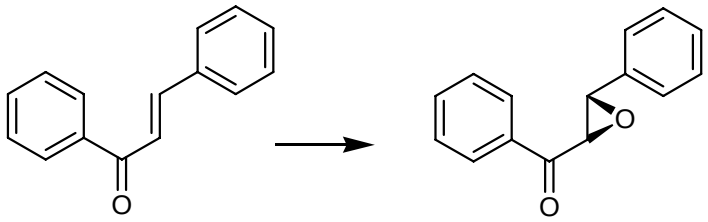
106 **Chalcone epoxide**

Expt.	Catalyst	Oxidant	Temp.	Time	%yield	$[\alpha]_D$	% ee
1	133	13%NaOCl	0 °C	30h	78	167,7	80
2	133	13%NaOCl	-10 °C	42h	67	169,9	81
3	135	13%NaOCl	0 °C	22h	73	173,4	84
4	135	13%NaOCl	-10 °C	29h	68	177,1	86
5	138	13%NaOCl	0 °C	15h	71	143,3	68
6	140	13%NaOCl	0 °C	24h	78	182,2	87
7	140	13%NaOCl	-10 °C	40h	75	184,5	89
8	140	13%NaOCl	-20 °C	72h	74	187,3	90
9	141	13%NaOCl	0 °C	20h	82	165,5	80

2.7.6. Effect of solvent polarity and oxidants in epoxidation

In case of using different solvents, it was observed that the use of polar solvents and also solvents in excess decreases the enantioselectivity of the epoxide e.g. there is a decrease in enantioselectivity observed in those cases where ethyl acetate and dichloromethane were used instead of toluene (Table 2.5). In the case of oxidants, 13% NaOCl is a very good oxidant along with toluene as solvents. The other oxidants used were 30% H_2O_2 and *t*-BuOOH but the enantioselectivity was decreased dramatically in these cases (Table 2.5).

Table 2.5: Enantioselctive epoxidation of chalcone **106**, solvent polarity and oxidant effect.



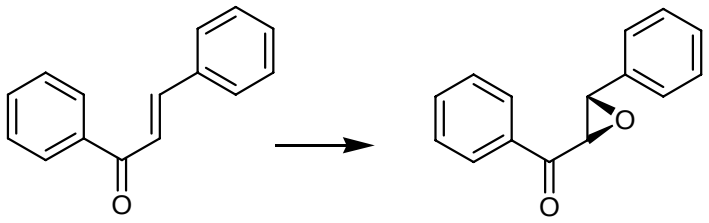
106 **Chalcone epoxide**

Expt.	Catalyst	Oxidant	Temp.	Solvent	Time	%yield	$[\alpha]_D$	% ee
1	133	30% H_2O_2	RT	CH_2CL_2	33h	54	116,9	56
2	133	t-BuOOH	RT	EtOAc	42h	52	127	61
3	135	t-BuOOH	RT	CH_2CL_2	22h	57	140	67
4	135	30% H_2O_2	RT	EtOAc	29h	49	148.2	71
5	138	30% H_2O_2	RT	CH_2CL_2	15h	52	133,3	64
6	140	30% H_2O_2	RT	CH_2CL_2	24h	61	156,9	75
7	140	13% NaOCl	RT	Toluene	10h	84	173,9	84
8	141	30% H_2O_2	RT	CH_2CL_2	72h	63	162,8	78
9	141	t-BuOOH	RT	EtOAc	20h	65	12945	62

2.7.7. Effect of the amount of catalyst in epoxidation

We have used different amounts of the catalysts in the epoxidation e.g. 10 mol %, 15 mol % and 20 mol %. It was observed that the use of more catalyst increases the rate of the reaction and yield but there is a decrease in the enantioselectivity. The use of 10 mol % catalyst in the epoxidation performed at room temperature was the best choice (Table 2.6).

Table 2.6: Enantioselctive epoxidation of chalcone **106** in toluene**,** amount of catalyst effect.



106 **Chalcone epoxide**

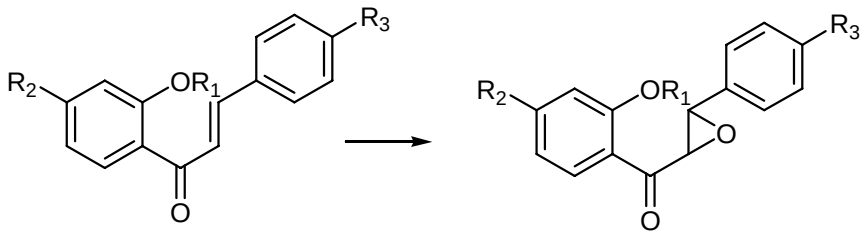
Expt.	Catalyst	Amount	Oxidant	Temp.	Time	%yield	$[\alpha]_D$	% ee
1	140	10 mol %	13%NaOCl	RT	10h	84	173,9	84
2	140	15 mol %	13%NaOCl	RT	8h	87	142,8	69
3	140	20 mol %	13%NaOCl	RT	22h	89	136,6	66

The catalysts derived from cinchonin were also tested against the synthesized substituted chalcones. But after doing different reactions, it was observed that these catalysts are not good for the substituted chalcones. The reason behind this is that these catalysts are good for electron deficient systems, but the methoxy substituted chalcones are electron rich. There is some enantioselectivity observed by using catalyst **129**, **133**, and **140** only with MOM-protected chalcones and an acceptable conversion to product was achieved (Table 2.7, entries 1, 2 & 8). In all other cases where there are methoxy groups, no conversion was observed after many days.

We converted the trihydroxychalcone **115** to both the acetyl and pivaloyl derivatives in order to make the system more electron deficient. It was observed that these groups are just too unstable under the conditions suitable for epoxidation. There is no epoxide observed with acetylated and pivaloylated chalcones (Table 2.7, entries 11, & 12)

We converted trihydroxy chalcone **115** into trimesylated chalcone **114**, which is a very electron deficient system with three mesylate groups. It was subjected to epoxidation with catalysts **140** and **141** where it was observed that the reaction was fast and complete in 5-8 h but no enantioselectivity was observed. The reason may be that the presence of mesyl groups poisoned the catalysts and that's why no enantioselectivity was observed (Table 2.7, entries 13, & 14).

Table 2.7: Enantioselctive epoxidation of substituted chalcones at room temperature.



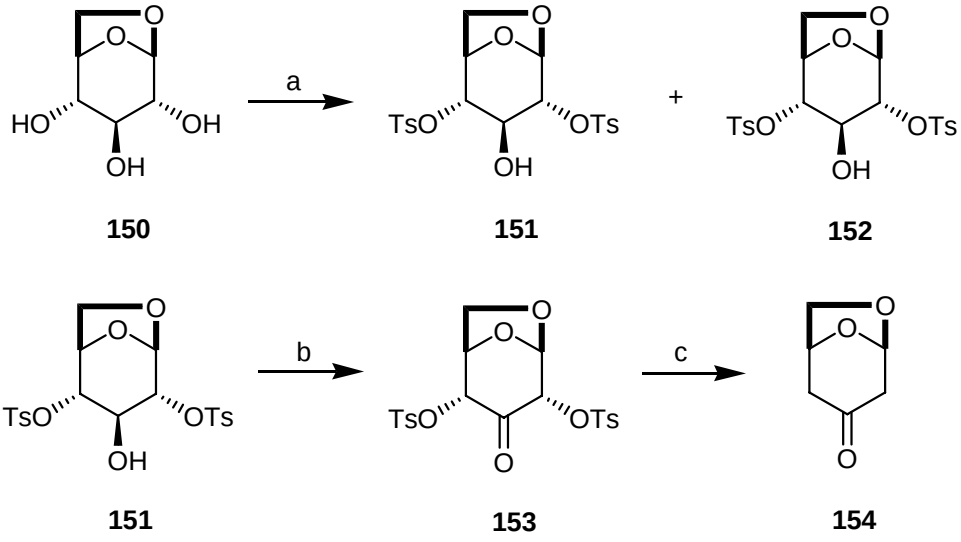
C E

Expt.	Catalyst	Oxidant	Time	R1	R2	R3	%Yield	$[\alpha]_D$
1	129	t-BuOOH	14h	MOM	H	H	83	-38.3
2	133	13%NaOCl	17h	MOM	H	H	73	-67.6
3	130	30% H_2O_2	3day	MOM	OMe	OMe	---	---
4	131	13%NaOCl	3day	TBS	OMe	OMe	---	---
5	132	13%NaOCl	3day	MOM	OMe	OMe	---	---
6	133	30% H_2O_2	2day	MOM	OMe	OMe	---	---
7	134	13%NaOCl	5day	TBS	OMe	OMe	---	---
8	140	13%NaOCl	17h	MOM	H	H	78	-73.5
9	140	30% H_2O_2	5day	MOM	OMe	OMe	---	---
10	141	30% H_2O_2	7day	MOM	OBn	OBn	---	---
11	140	13%NaOCl	12h	Ac	Ac	Ac	---	---
12	140	13%NaOCl	4day	Piv	Piv	Piv	---	---
13	140	13%NaOCl	5h	Ms	Ms	Ms	81	---
14	141	13%NaOCl	8h	Ms	Ms	Ms	68	---

2.8. Synthesis of chiral ketone catalysts derived from levoglucosan (150)

Chiral ketones have recently been used for epoxidation reactions. In order to test our epoxidation reaction, we have also thus tried to form new the chiral ketones **153** and **154** from the anhydrous sugar called levoglucosan (**150)**. Levoglucosan (**150)** was subjected to tosylation by treating it with tosyl chloride and pyridine at 0-10°C.[127] The reaction was monitored by TLC. After all the starting material was consumed; two products were observed i-e. ditosylated **151** which is the major product in 81 % isolated yield and the minor tritosylated side product **152** in 10 % isolated yield. The ditosylated **151** is required for the next oxidation reaction (Scheme 2.19).

Ditosylate **151** was oxidized by sodium bromate and acetic acid in acetonitrile. $RuCl_3$ was used as a catalyst for the reaction. Ditosylated ketone **153** was obtained in 90 % yield. Ketone **154** was obtained by removing the tolylsufonyl groups by subjecting ketone **153** to zinc dust in acetic acid treatment in tetrahydrofuran (Scheme 2.19). Before the detosylation, the activation of zinc dust is necessary which was done by stirring it with 1.5% HCL for 1h and then washing the solid with THF and then drying at 145 °C overnight.[127]



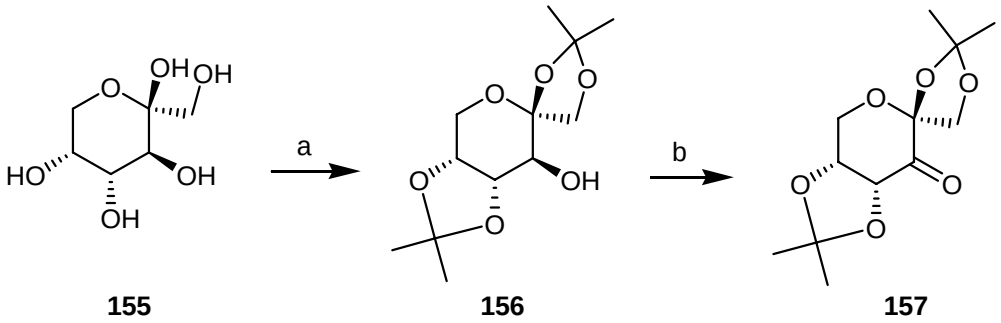
150 **151** **152**

151 **153** **154**

Scheme 2.19: Synthesis of chiral ketones **153** and **154** from anhydrosugar levoglucosan (**150):** a) TsCl, pyridine, 81 %; b) $NaBrO_3$, $RuCl_3.3H_2O$, CH_3COOH, CH_3CN, 80 %; c) Zn, NH_4OAc, THF, 85 %.

2.9. Synthesis of chiral ketone catalysts derived from D-Fructose (155)

Alcohol **156** was obtained by subjecting D-fructose (**155**) to acetonide protection. The reaction was done by treating fructose (**155**) with dimethoxypropane and perchloric acid in acetone at 0 °C for 6 h.[101] The reaction proceeded well but the yield of the reaction is under 60%. Chiral ketone **157** was obtained by oxidation of alcohol **156** by treating with pyridinium chlorochromate in CH_2Cl_2 in the presence of 3Å molecular sieves for 3 h. Ketone **157** was obtained in 86 % isolated yield (Scheme 2.20). This reaction was first done without molecular sieves but the yield is very low in that case. So the key point in this oxidation is the use of molecular sieves which keep the reaction conditions anhydrous. These molecular sieves should be pre-activated at 180-200 °C under vacuum for several hours.



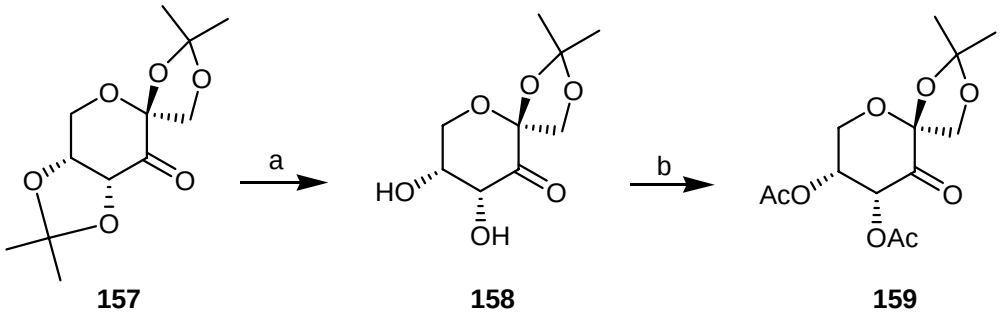
155 **156** **157**

Scheme 2.20: Synthesis of chiral ketones **157** from D-fructose (**155**)**:** a) DMP, $HClO_4$, acetone, 56 %; b) PCC, CH_2Cl_2, MS 3 Å, 86 %.

Dioxiranes generated in situ from chiral ketones **157** have been shown to be highly enantioselective for the asymmetric epoxidation of a variety of olefins.[128] However the epoxidation of substituted chalcones is still a question with these dioxiranes. The low reactivity of the ketone catalysts **157** was also a major obstacle for achieving asymmetric epoxidation in chalcones. Dioxiranes are electrophilic reagents, and react sluggishly with electron deficient olefins like chalcones. The other difficulty is the decomposition of the chiral ketones via Baeyer-Villiger oxidation.

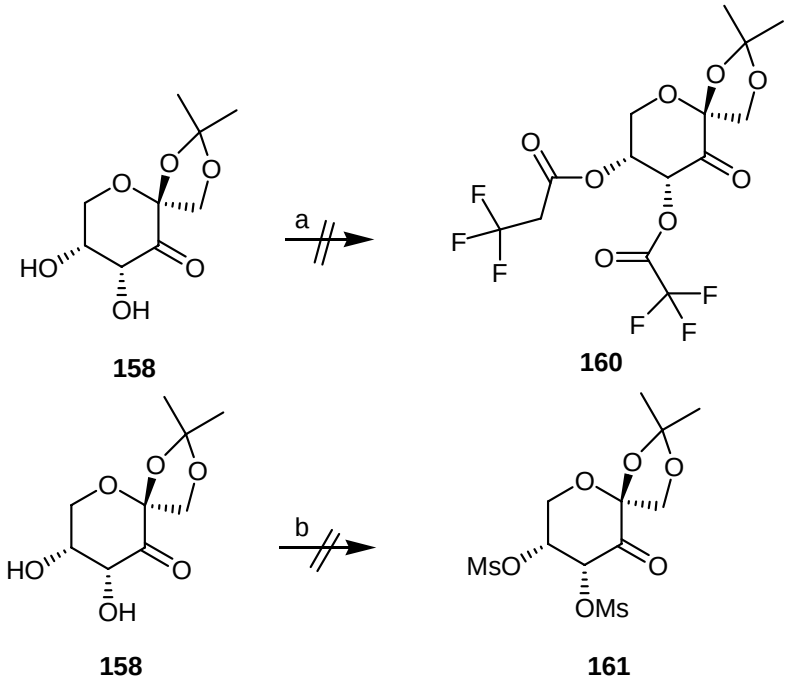
In order to enhance the reactivity of ketone **157,** the fused ketal of ketone **157** was replaced with more electron withdrawing groups.[128] Ketodiol **158** was obtained by treating ketone **157** with DDQ in acetonitril-H_2O (9:1) in 75 % yield. Ketodiol **158** was then subjected to

acetylation by treatment with acetic anhydride and *N,N*-dimethylaminopyridine in CH_2Cl_2 to give acetylated ketone **159** in 78 % isolated yield (Scheme 2.21).



Scheme 2.21: Synthesis of chiral ketones **159:** a) DDQ, CH_3CN-H_2O (9:1), 75 %; b) Ac_2O, DMAP, CH_2Cl_2, 78 %.

The formation of ketones **160** and **161** by introducing more electron deficient groups in the ketodiol **158**, were not successful. Treating **158** with trifluoroacetic anhydride proved to be unsuccessful. It was observed that **160** is unstable and can not be used as a precursor of dioxirane.



Scheme 2.22: Synthesis of chiral ketones **160** and **161:** a) TFAA, DMAP, CH_2Cl_2; b) MsCl DMAP, CH_2Cl_2.

Mesylated keton **161** was also attempted from ketodiol **158** by treating it with mesyl chloride and DMAP. It was observed that the mesylated product **161** decomposed immediately due to the two adjacent mesylate groups. An elimination reaction could also have occurred (Scheme 2.22).

2.9.1. Mechanism of the epoxidation with chiral ketones

The mechanism of the epoxidation through chiral dioxiranes was mainly studied by Shi and co-workers.[101,111,128] The ketone **157** is reacted with the oxidant used, mainly oxone, to form peroxysulfate ion alcohol **162**. Oxone is found to be the best oxidant with chiral ketones for the formation of dioxirane due to more active oxygen present. The active component in oxone is potassium peroxymonosulfate ($KHSO_5$). The peroxysulfate ion alcohol **162** reacts under basic conditions to remove the proton and form peroxysulfate ion alkoxide **163**. This alkoxide **163** would more efficiently form dioxirane **164**. Dioxirane **164** can react both with the alkene to give the epoxide and it can react with the peroxosulfate ion to regenerate the ketone **157**. Ketone **157** can be decomposed quickly that's why more amount of the ketone is required in order to get a good yield and enantioselectivity.

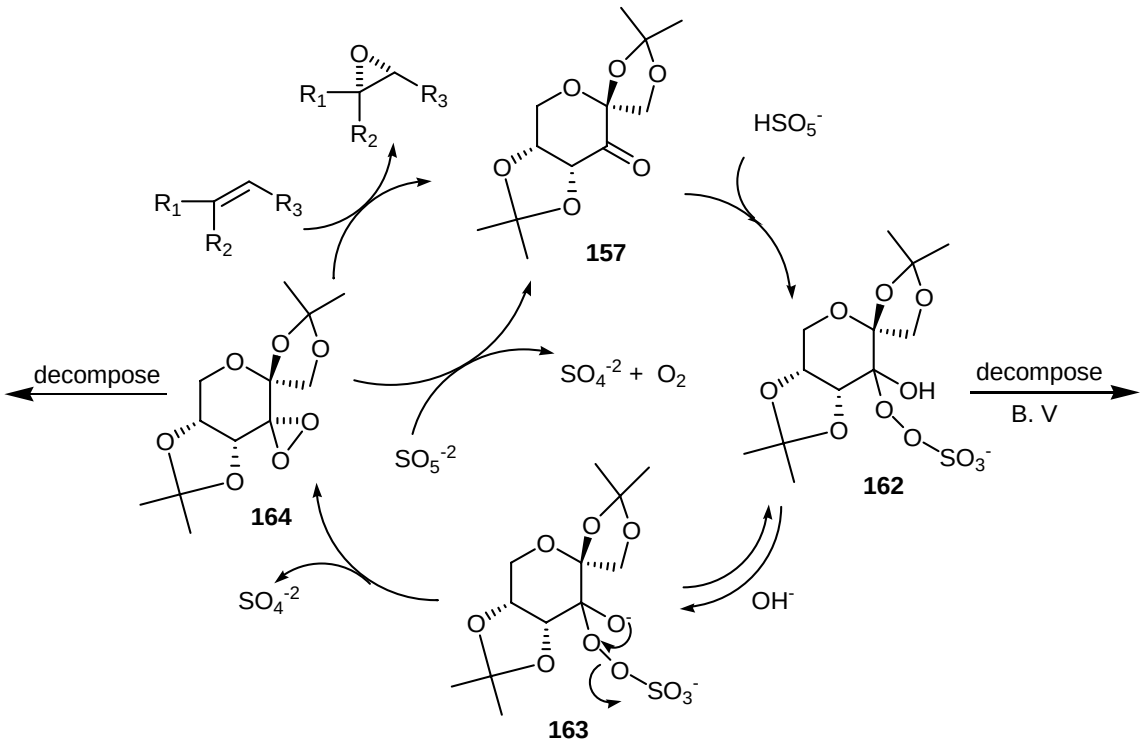


Figure 2.2: Mechanism of epoxidation by chiral dioxiranes.

Ketone **157** can be decomposed by Baeyer-Villiger oxidation of the compound **162** or it can be decomposed at the dioxiran **164** level especially when the alkene is non reactive. The mechanism is shown below (Figure 2.2).

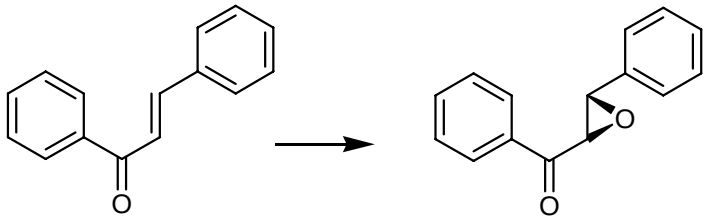
2.9.2. Epoxidation of chalcones with chiral ketones

After the failure of enantioselective epoxidation of substituted chalcones with catalysts derived from cinchonin, the epoxidation with the synthesized ketones **153, 154, 157** and **159** were studied. We thought that these ketones may be the precursors of chiral dioxiranes for substrate like chalcones. The ketones **157** and **159** are good candidates for the epoxidation of alkenes but not for the substituted chalcones. We have tested these ketones on chalcone by using different oxidants, e.g. oxone, 30% H_2O_2, and *t*-BuOOH in acetonitrile (Table 2.8).

In some cases, a small conversion was observed but no enantioselectivity at all. This means that these conversions did not happen due to the formation of chiral dioxiranes from these ketones (Table 2.8).

Chiral dioxiranes are also electrophilic reagents and react very slowly with the electron deficient molecules like chalcones. Sometimes this reaction is so slow that chiral ketones are decomposed either through Baeyer-Villiger oxidation before the formation of dioxirane or after the formation of dioxiranes. Sometimes the side reaction is favorable as the rate of the side reactions is greater than the original epoxidation reaction. This could also be the one reason of not getting chalcone epoxide with these chiral dioxiranes.

Table 2.8: Enantioselctive epoxidation of chalcone **106** in acetonitrile by chiral ketones.



106 **Chalcone epoxide**

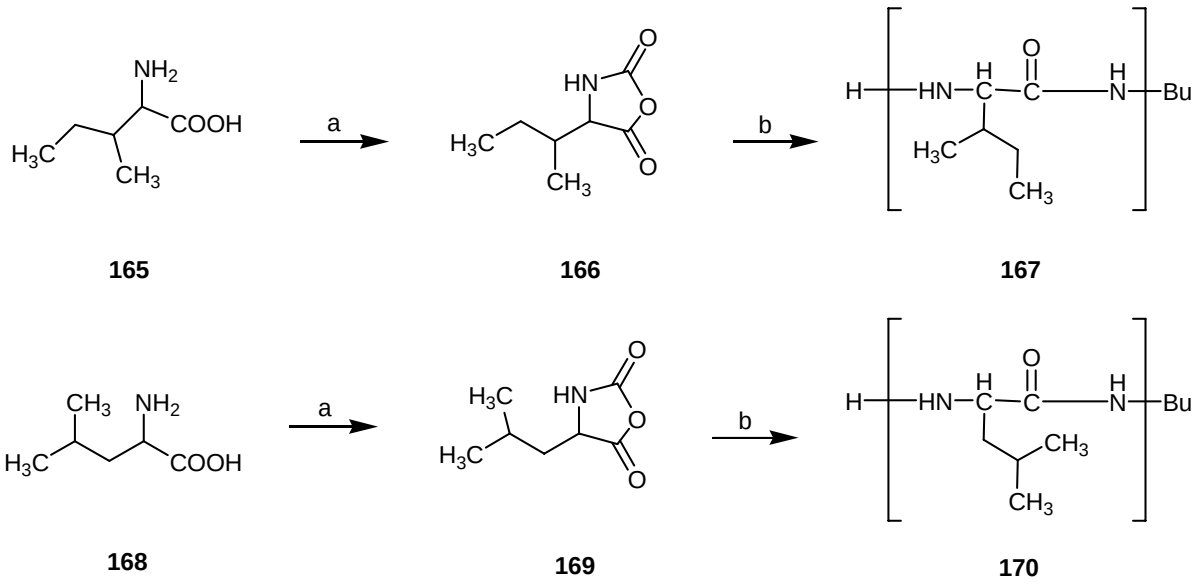
Expt.	Catalyst	Oxidant	Temp	Time	%yield	$[\alpha]_D$	% ee
1	153	Oxon	0 °C	30h	---	---	---
2	154	Oxon	RT	5day	10	---	---
3	154	30% H_2O_2	RT	3day	22	---	----
4	157	Oxon	RT	20	15	---	---
5	157	Oxon	0 °C	4day	10	---	---
6	157	30% H_2O_2	0 °C	24h	---	---	---
7	159	30% H_2O_2	RT	40h	30	---	---
8	159	t-BuOOH	RT	72h	---	---	---
9	159	Oxon	RT	20h	20	---	---

2.10. Synthesis of chiral amino acid catalysts for epoxidation

Catalsyts **167** and **170** were prepared from the amino acids L-isoleucine (**165**) and L-leucine (**168**) (Scheme 2.23). The *N*-carboxyanhydrides are usually synthesized by reaction of the corresponding α-amino acids with phosgene. The conventional procedure for the phosgenation of an amino acid involves passing gaseous phosgene through a suspension of the amino acid in a dry solvent such as dioxane or tetrahydrofuran until a clear solution is obtained.[129] But this process is difficult as gaseous phosgene is needed. L-isoleucin-*N*-carboxyanhydride **166** and L-leucine-*N*-carboxyanhydride **169** were prepared by treating L-isoleucin (**165**) and L-leucine (**168**) with trichloromethyl chloroformate and charcoal in tetrahydrofurane at 55 °C until the amnio acids dissolved completely. This method is easier and quantitative. These *N*-carboxyanhydrides are very sensitive to moisture.

Poly-L-isoleucine **167** and poly-L-leucine **170** were prepared from *N*-carboxyanhydrides **166** and **169** as reported.[73] The polymerization of the *N*-carboxy anhydrides **166** and **169** was performed with *n*-butylamine (molar ratio 10:1) to give polymers **167** and **170**. The molar ratio between *N*-carboxyanhydrides and *n*-butyl amine (10:1) controlled the degree of polymerization and it was assumed that by this molar ratio, the polymers contain an average of ten amino acids (Scheme 2.23).

It has been observed that the *N*-carboxyanhydrides are very sensitive to moisture that's why the use of absolute anhydrous solvent e.g. tetrahydrofuran is very necessary for the preparation of the *N*-carboxyanhydrides and also for the polymerization. In the presence of moisture, homo-polymerization occurred instead of co-polymerization.



165 **166** **167**

168 **169** **170**

Scheme 2.23: Synthesis of amino acid catalysts **167** and **170** from isoleucine (**165**) and leucine (**168**)**:** a) TCF, anhydrous THF, charcoal, 80 %; b) *n*-$BuNH_2$, CH_3CN, 83 %.

The catalysts **167** and **170** are very good for epoxidation and we obtained in enantioselectivity above 80 % with chalcone. The considerable drawbacks to this system are observed e.g.

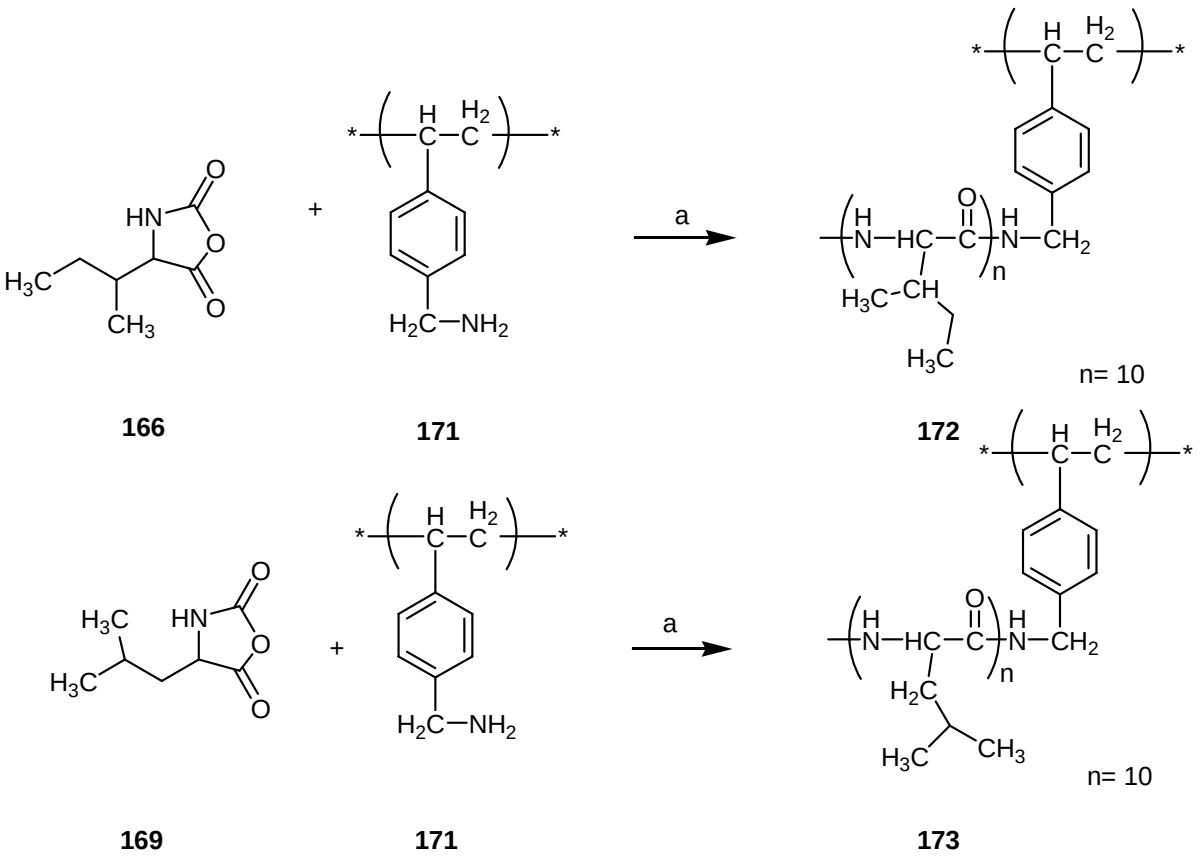
1. Difficulty in separating the paste-like polyamino acids

2. Recycling of the semisolid paste like polyamino acid.

3. There is loss of activity of the reused polyamino acids observed.

Polystyrene-co-diviny1benzene supported polyamino acids **172** and **173** can act as efficient chiral catalysts in the epoxidation of α, β-unsaturated carbonyl compounds with alkaline hydrogen peroxide to yield optically active epoxy ketones in 99 % ee.

Thus polymers **172** and **173** were synthesized according to the method of Itsuno.[92] Freshly prepared *N*-carboxyanhydrides of L-isoleucin **166** and L-leucine **169** were subjected to co-polymerization using polystyrene crosslinked with 2% divinyl benzene **171** as an initiator in anhydrous tetrahydrofuran at room temperature for 40 h to give polymer supported catalysts **172** and **173** in granular form (Scheme 2.24). It was observed that separation of the polymer-supported catalyst has been remarkably improved in this system, and they could be reused without a significant loss of activity.

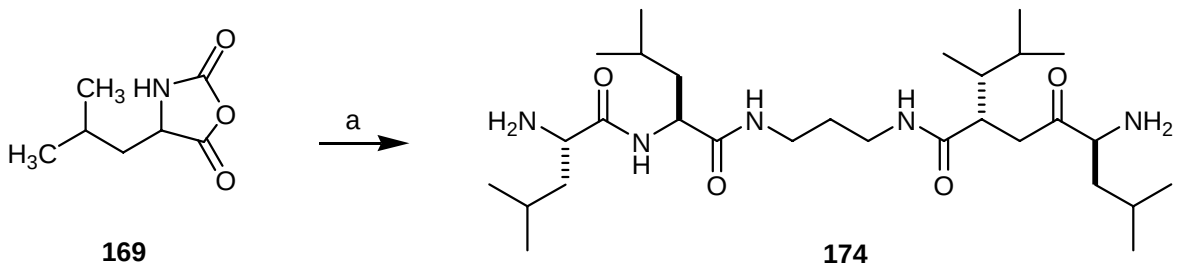


166 **171** **172**

169 **171** **173**

Scheme 2.24: Synthesis of amino acid catalysts **172** and **173** from *N*-carboxyanhydrides **166** and **169:** a) THF, %.

For the preparation of ht-poly-L-leu **174**, freshly prepared L-leucine *N*-carboxyanhydride **169** was treated with 1, 3-diaminopropane as an initiator in toluene at room temperature. Subsequently, the mixture was heated to reflux for 24 h to give hot polymer **174** (ht-poly-L-leu**)**.[97,98] This reaction proceeded smoothly and in good isolated yield. The ratio between *N*-carboxyanhydride **169** to initiator was 66:1 (Scheme 2.25).



169 **174**

Scheme 2.25: Synthesis of amino acid catalysts **174** from *N*-carboxyanhydride **169:** a) Toluene 1, 3-diaminopropane, 81 %.

2.10.1. Mechanism of the epoxidation with polyamino acids

The advancement of the Julia-Colonna reaction for the epoxidation enabled to explore the catalytic role of the polypeptide chain in imparting enantioselectivity.[82,83] Berkessel and co-workers showed that at least five amino acid residues are necessary for efficient and selective catalysis and the helicity of the peptides determines the configuration of the epoxide.

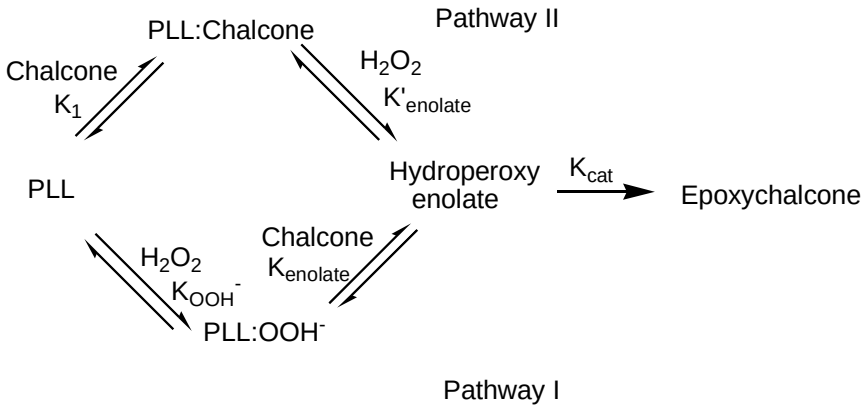
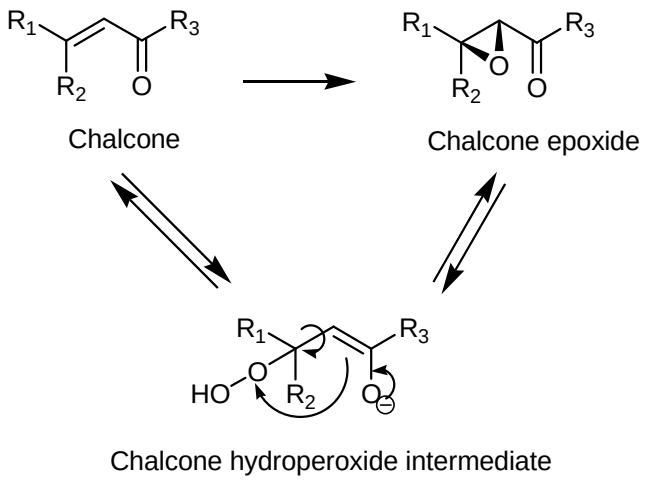


Figure 2.3: Mechanism of epoxidation by polyamino acids.

In situ monitoring kinetic analysis of the reaction suggested that the favoured route is the hydroperoxide route to hydroperoxy enolate and then to the corresponding epoxide. There are four different kinds of the catalytic intermediates.

i. PLL with no bound substrate.
ii. PLL bound chalcone i.e., the chalcones are bound to leucin with *N*-terminals.
iii. PLL bound with hydroperoxide ion.
iv. hydroperoxide-chalcone intermediate i.e., hydroperoxy enolate.

Kinetic studies showed that there is no bonding constant obtained with poly leucin. This means that bonding association of the PLL-chalcone must be an order weaker than bonding of PLL with hydroperoxide species. This means that the reaction proceeds through hydroperoxide pathway I. This is illustrated in Scheme 2.26.



Scheme 2.26: Mechanism of epoxidation via hydroperoxide formation.

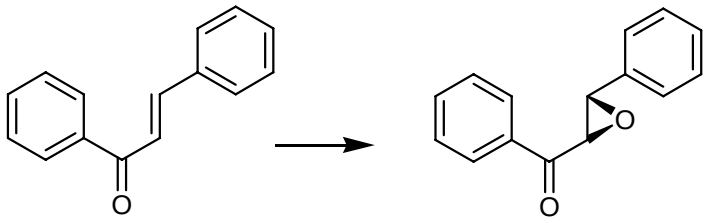
2.10.2. Epoxidation of chalcones with polyamino acids derived catalysts

Polyamino acids are also known in literature and are used in enantioselective epoxidation of chalcones. We have synthesized some of the catalysts **167, 170, 172, 173,** and **174** which have already been used in literature.[129,73] The epoxidaton of simple chalcone **106** was performed with polyamino acid catalysts and the source of oxygen is 30% H_2O_2 with NaOH. The reaction worked very well and more than 90 % ee was obtained (Table 2.9).

There is difficulty in recycling catalysts **167** and **170**.[92] Use of immobilized poly-L-isoleucine catalyst **172** and poly-L-leucine **173** by Itsuno was effective. These catalysts were synthesized by treating *N*-carboxyanhydrides with polystyrene crosslinked with 2 % divinyl benzene **171**. The epoxidation with catalyst **173** was accomplished within 40 min using (UHP/DBU) urea-hydrogen peroxide complex as a source of oxygen and DBU as an organic base with 93 % enantioselectivity. The oxidants 30 % H_2O_2/NaOH, and *t*-BuOOH/NaOH were used in triphasic systems and the UHP/DBU was used in a biphasic system (Table 2.9, entry 4).

Geller[97,98] used the triphasic system to epoxidize the chalcone and he used tetrabutylammonium bromide (TBAB) as co-catalyst. It was observed that by adding TBAB, there is marked decrease in the reaction time of the molecules like chalcone which reacts slowly (Table 2.9, entry 10).

Table 2.9: Enantioselctive epoxidation of chalcone **106** by polyamino acids.



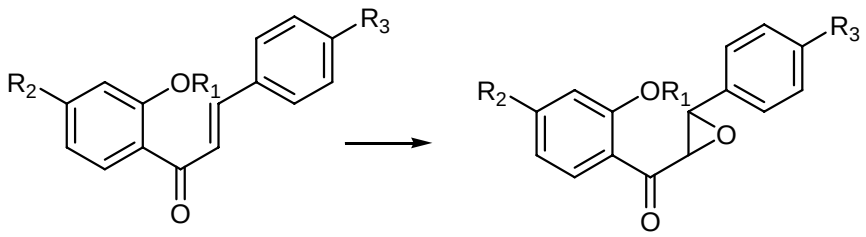
106 **Chalcone epoxide**

Expt.	Catalyst	Oxidant	Solvent	Temp.	Time	% yield	$[\alpha]_D$	%ee
1	167	30% H_2O_2 NaOH	CCl_4	RT	2day	72	173	84
2	170	30% H_2O_2 NaOH	CCl_4	RT	2day	73	171,9	83
3	170	UHP/DBU	CCl_4	RT	2day	54	161,5	78
4	172	UHP/DBU	CCl_4	RT	40 min	89	189,4	92
5	172	30% H_2O_2 NaOH	CCl_4	RT	20h	74	166,8	81
6	173	UHP/DBU	CCl_4	RT	55 min	90	193,5	93
7	173	t-BuOOH NaOH	CCl_4	RT	30h	23	86	42
8	173	30% H_2O_2 NaOH	CCl_4	RT	40h	30	181,2	88
9	174	30% H_2O_2	CCl_4	RT	72h	80	161,7	78
10	174	30% H_2O_2 TBAB	CCl_4	RT	14h	88	170	82

Again, the epoxidation of simple chalcone **106** was achieved excellently but we again observed a problem with substituted chalcones. Under the same conditions, there were poor ee observed in case of substituted chalcones. Only in case of catalysts **172** and **173**, some enantioselectivity of substituted chalcones with very poor conversion were observed (Table 2.10, entry 5, 6, 7 & 10). In the case of MOM-protected chalcone, there is some

enantioselectivity observed with catalyst **174** in the presence of TBAB as a co-catalyst (Table 2.10, entry 9).

Table 2.10: Enantioselctive epoxidation of substituted chalcones at room temperature.

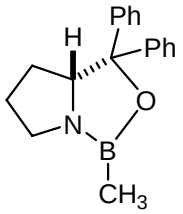


Expt.	Catalyst	Oxidant	Time	R1	R2	R3	%yield	$[\alpha]_D$
1	167	30% H_2O_2	14h	MOM	OMe	OMe	---	---
2	170	t-BuOOH	17h	MOM	OBn	OBn	---	---
3	170	30% H_2O_2	3day	TBS	OMe	OMe	---	---
4	172	30% H_2O_2	3day	MOM	OMe	OMe	---	---
5	172	UHP/DBU	3day	TBS	OMe	OMe	18	-97.3
6	173	UHP/DBU	2day	MOM	OMe	OMe	22	-129
7	173	30% H_2O_2	5day	MOM	OMe	OMe	18	-90,3
8	173	30% H_2O_2	5day	MOM	OBn	OBn	---	---
9	174	UHP/DBU	7dah	MOM	H	H	20	-117,3
10	174	30% H_2O_2	5day	MOM	OMe	OMe	12	-97,2

Chapter 3: Reduction of chalcones and cyclization

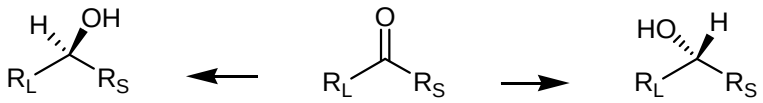
3.1. Introduction

In recent years, many papers describing the research on the enantioselective reduction of α, β-unsaturated ketones to obtain enantiomerically pure allylic alcohols have appeared in the literature. Allylic alcohols are very important precursors for synthesis of many natural products. The reagents used for the enantioselective reductions are made by the mixing of aluminium or boron hydrides and various chiral diols and amino alcohols.[130,131,132,133,134,135,136] For example, the catalyst **175** is known as the CBS-catalyst and is used for asymmetric reduction of simple ketones and α, β-unsaturated enones.[130,131,137]



175

During reduction, the nucleophile (hydride) can approach both the faces of the carbonyl group with an angle close to109° giving rise to a mixture of two isomers **A** and **B** which are mirror images of each other but not superimposable, and are thus enantiomers.



A **Ketone** **B**

Scheme 3.1: Reduction of ketones by chiral ligands.

To achieve the selectivity of one face of prochiral molecules with delivery of hydrides, lithium aluminium hydride, sodium borohydride and boron-tetrahydrofuran complex have been modified with optically active ligands. Some of the most familiar chiral ligands and chiral reducing agents used by different scientists are as follow (Figure 3.1).

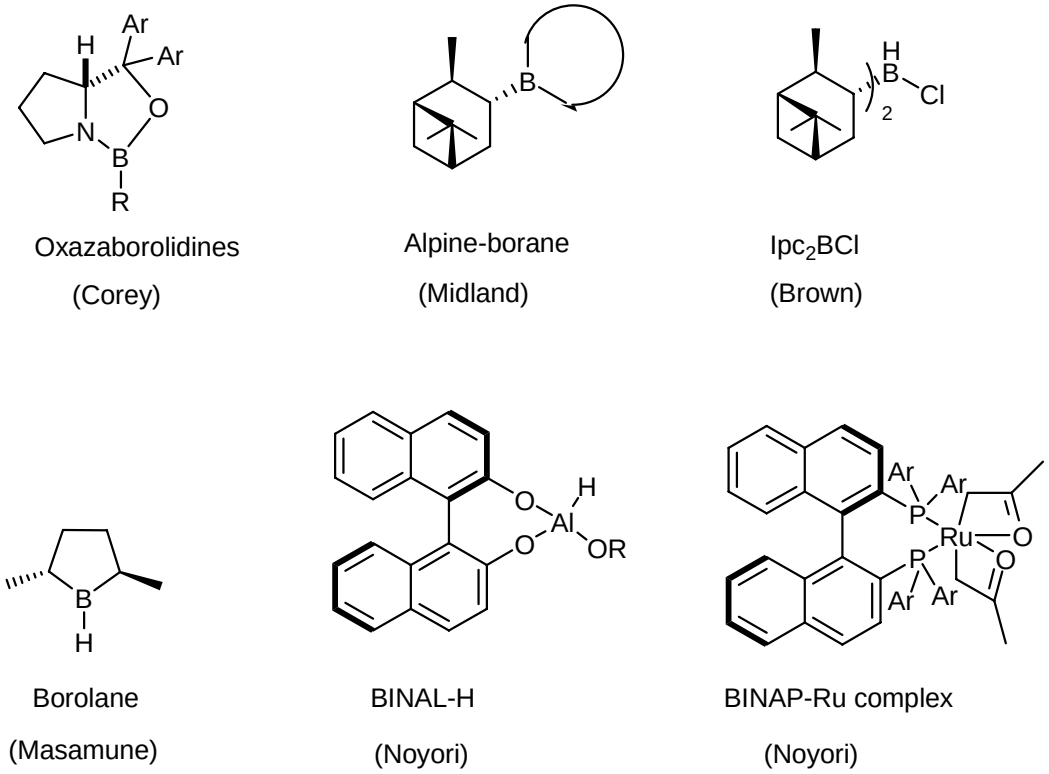
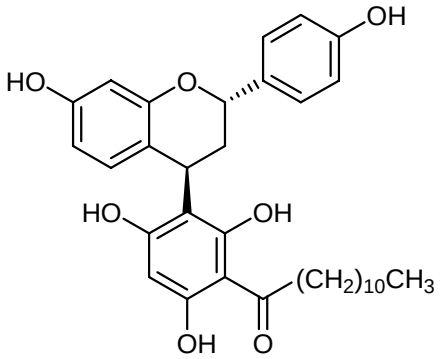


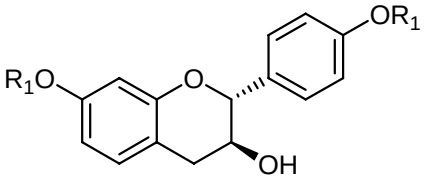
Figure 3.1: Chiral ligands used for enantioselective reduction.

3.2. Work plan

The plan of this work is to improve the total synthesis of (+)-myristinin A (**65**), which is a natural DNA polymerase *β* inhibitor and potent DNA damaging agent. In order to improve the overall synthesis, the synthesis of flavan moiety **66** is required. So the plan of this work is to synthesize the flavan moiety **66** in enantiomerically pure form from an allylic alcohol and then to couple this with appropriate partner to synthesize (+)-myristinin A (**65**). We have also planned to study the cyclization of the allylic alcohol to the flavene moiety.



65 (+)-Myristinin A



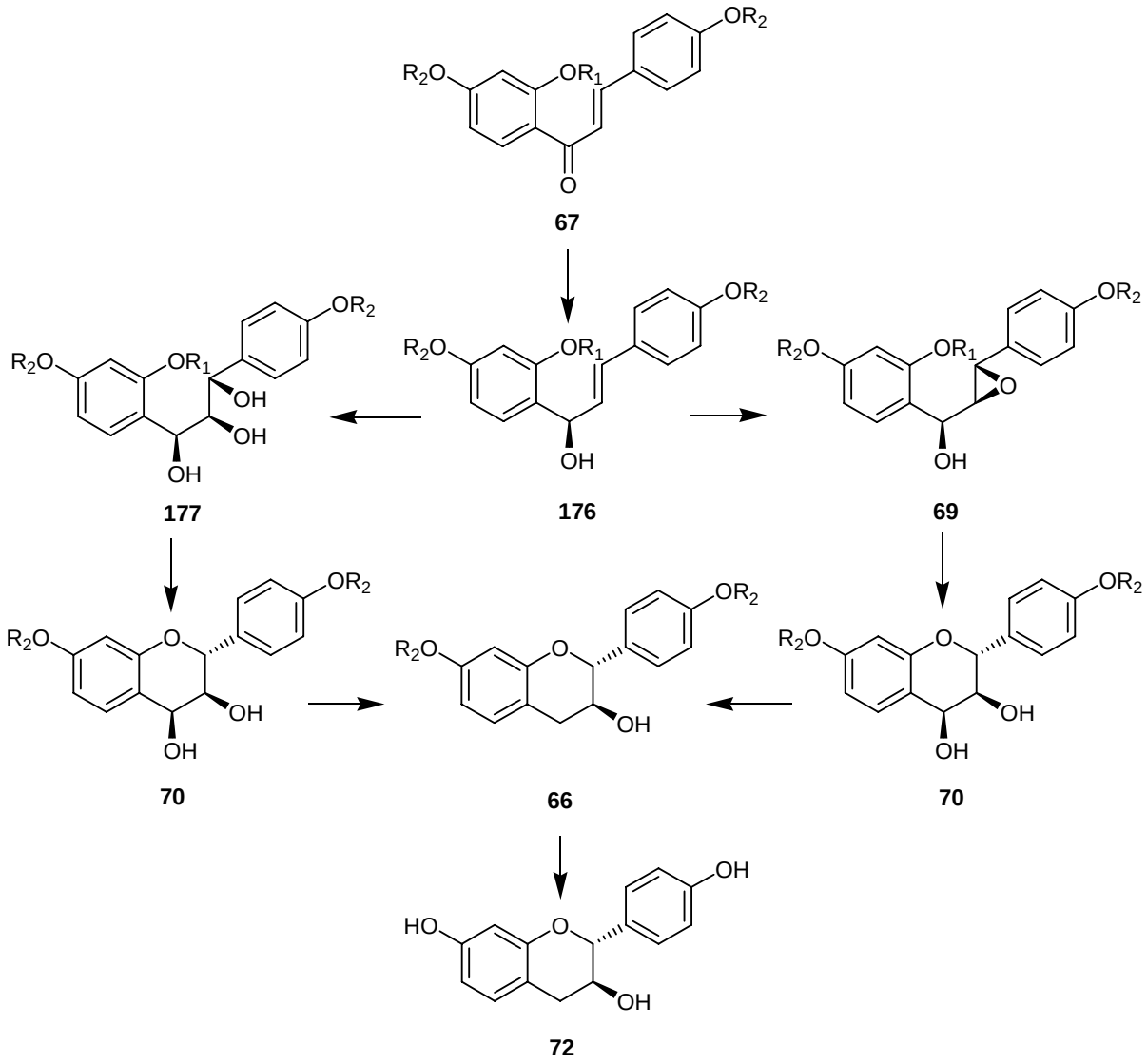
66

We have three routes to study these cyclization reactions of allylic alcohol to flavene or flavan moiety **66**. These routes are as follows.

3.2.1. Plan 1: Enantioselective reduction of ketone and Sharpless epoxidation

This plan is based on the enantioselective reduction of the chalcone followed by the epoxidation of the allylic alcohol. α,β-unsaturated ketones e.g. protected chalcone **67** can be enantioselectively reduced using iridium catalyst,[136] Corey-Bakshi-Shibata catalyst[130,131,132,137]] or Meerwein-Pondorf-Verley reduction[134] to obtain allylic alcohol **176**. The allylic alcohol **176** can be in one route subjected to Sharpless epoxidation[138,135,139] to get epoxy alcohol **69**. Cyclization of epoxy alcohol **69** should give *cis*-flavan-3,4-diol **70**. Deoxygenation can be achieved by treating it with $NaBH_3CN$[29,140] to give flavan-3-ol **66**. Final deprotection will afford the flavan-3-ol moiety **72** (Scheme 6).

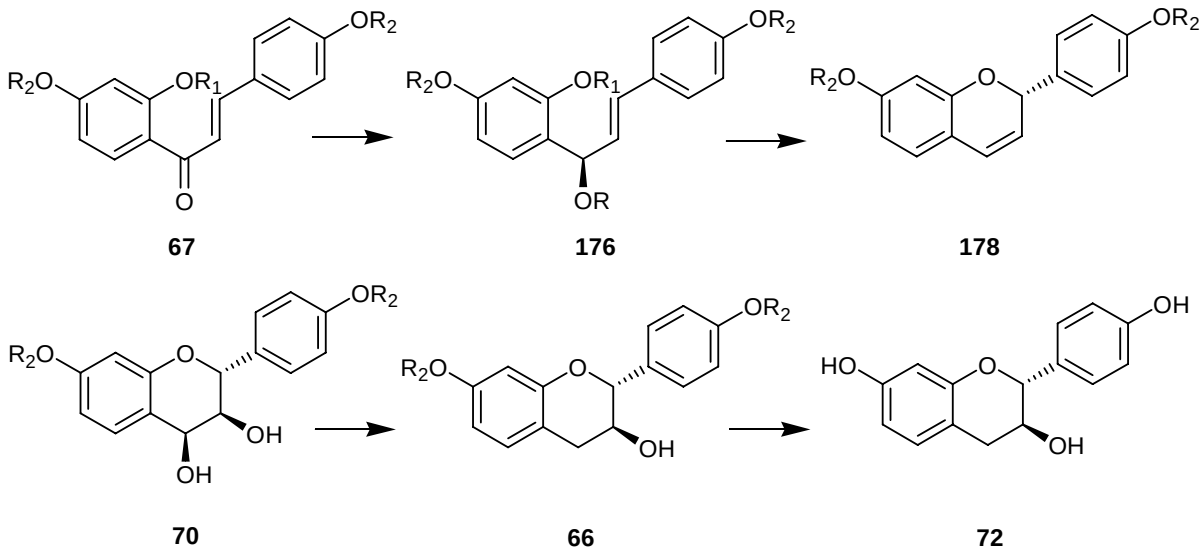
In an alternate route, the allylic alcohol **176** can be subjected to Sharpless dihydroxylation using AD mix-α to give triol **177**. Deprotection of the 2'-hydroxyl group followed by cyclization using Mitsunobu conditions should lead to *cis*-flavan-3, 4-diol **70**. This diol on treatment with $NaBH_3CN$[29,140] will give flavan-3-ol **66**. The flavan-3-ol moiety **72** can be achieved by final deprotection (Scheme 2).



Scheme 3.1: Synthesis of flavan moiety of (+)-myristinin A (**65**) by reduction and epoxidation.

3.2.2. Plan 2: Enantioselective reduction and SN_2 type reaction

In this route we envisage that chalcone **67** can be enantioselectively reduced to allylic alcohol **176** using either of the iridium catalyst[136] Corey-Bakshi-Shibata catalyst[130,131,132,137] or Meerwein-Pondorf-Verley reduction.[134] Deprotection of the 2'-hydroxy group and cyclization of the allylic alcohol by an SN_2, type reaction would afford flavene intermediate **178**, which can be subjected to Sharpless asymmetric dihydroxylation using AD mix-α. This should give *cis*-flavan-3, 4-diol **70** which on treatment with $NaBH_3CN$[29,140] will give rise to flavan-3-ol **66**. Final deprotection will give flavan-3-ol moiety **72** (Scheme 3.2).

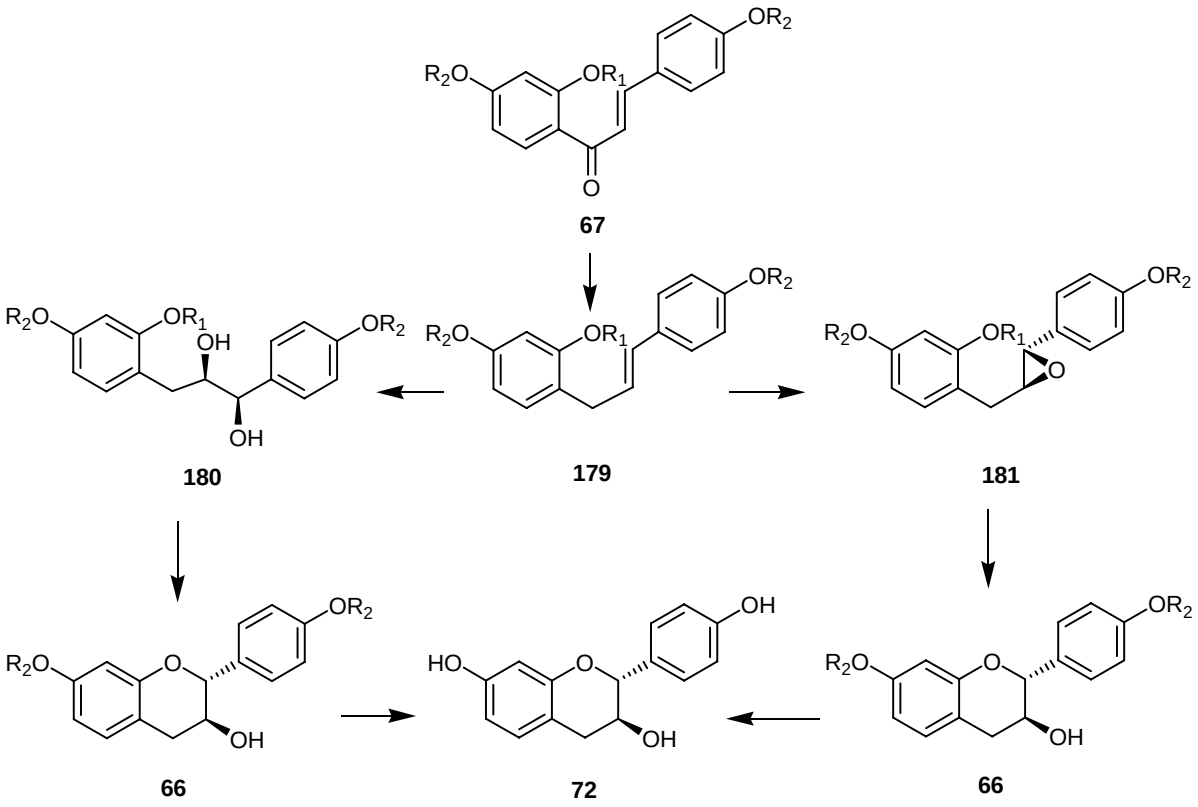


Scheme 3.2: Synthesis of flavan moiety of (+)-myristinin A (**65**) by reduction and SN_2 type Michael addition reaction.

3.2.3. Plan 3: Decarbonylation, asymmetric epoxidation or asymmetric dihydroxylation

In the final envisaged route, chalcone **67** can be reduced to the corresponding methylene analogue using a mild method involving ethyl chloroformate and $NaBH_4$ in a two step sequence followed by protection to obtain substituted 1,3-diphenylpropene **179**. The substituted propene **179** can be subjected to Sharpless asymmetric dihydroxylation to get diol **180**.[41] After deprotection, the product can be cyclized using the Mitsunobu reaction to produce flavan-3-ol **66**. Final deprotection will afford flavan-3-ol moiety **72**[46] (Scheme 8).

On the other hand, 1,3-diphenylpropene **179** can be epoxidized by using chiral ketones or catalysts derived from cinchonin or poly amino acids to get epoxide **181** which on cyclization should give flavan-3-ol **66**. Final deprotection will give flavan-3-ol moiety **72** (Scheme 3.3).

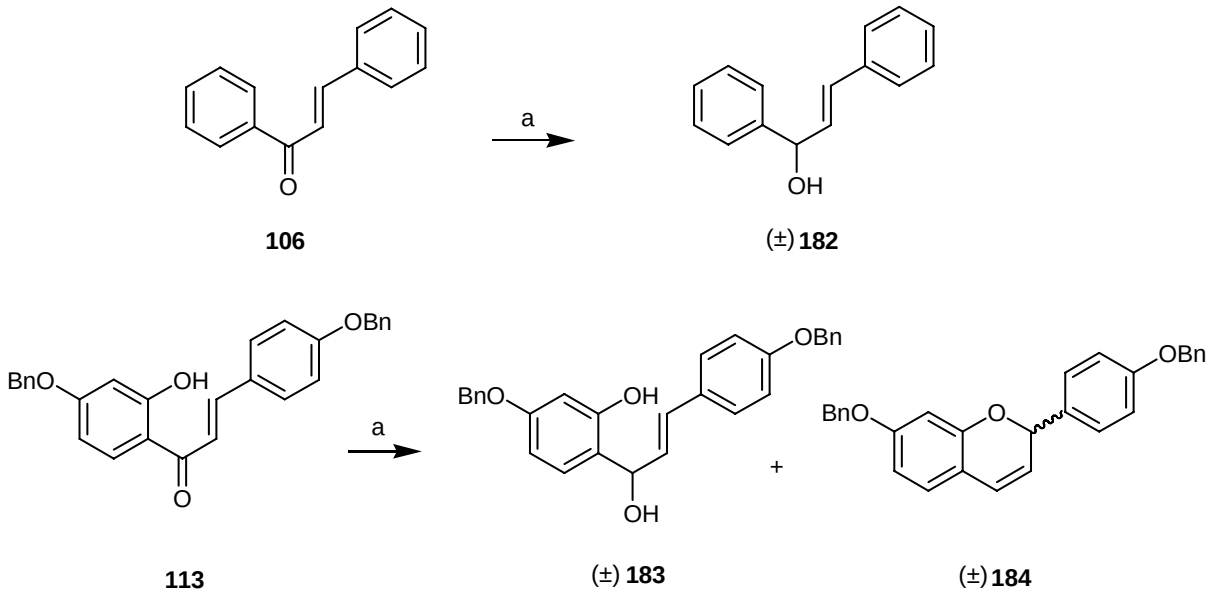


Scheme 3.3: Synthesis of flavan moiety of (+)-myristinin (**65**) by reduction followed by Sharpless asymmetric dihydroxylation.

3.3. Results and discussion

3.3.1. $NaBH_4$ reduction of chalcones

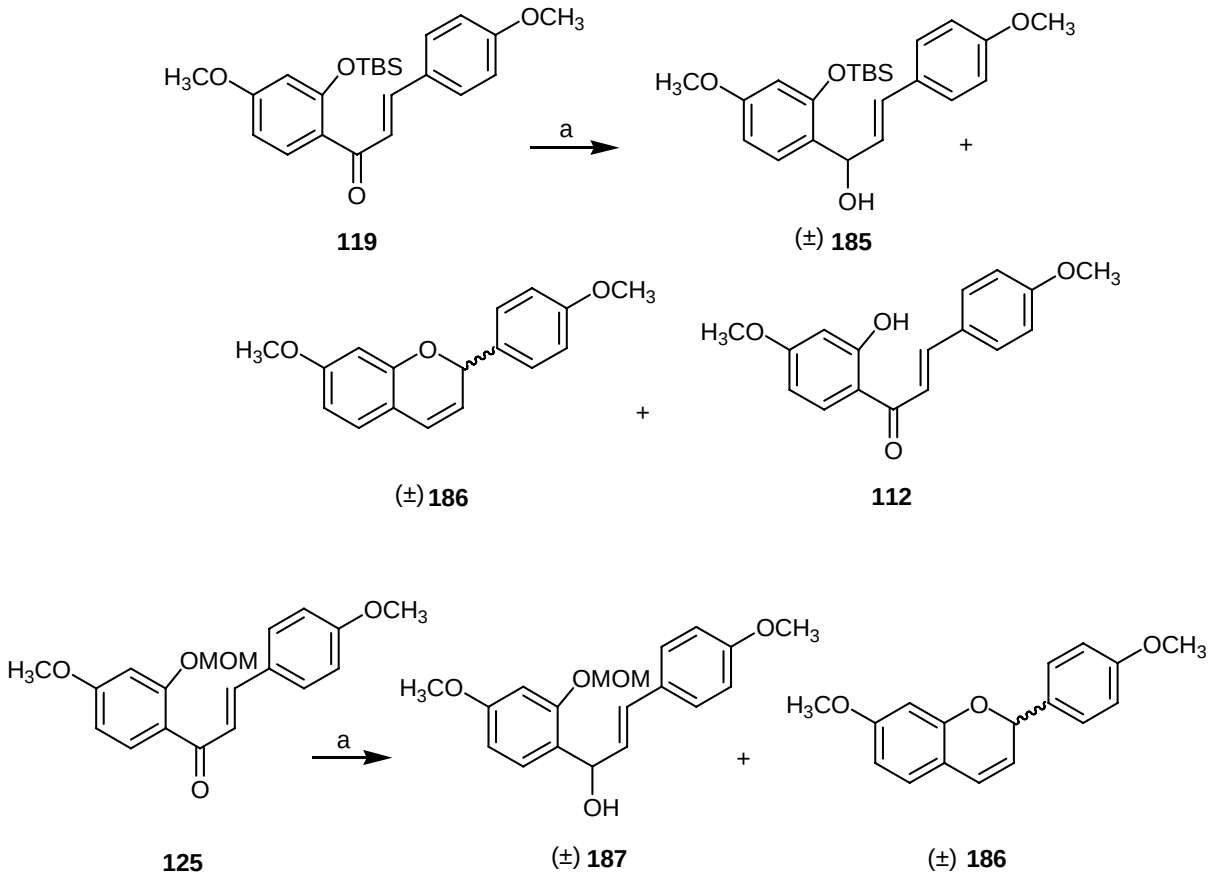
Racemic allylic alcohol **182** was obtained by reacting chalcone **106** with sodium borohydride in methanol at room temperature for 3 h.[141] In case of chalcone **106**, there is only one product i.e. **182** as there is no 2'-hydroxy group in the starting material but in case of chalcone **113**, allylic alcohol **183** along with racemic flavene **184** were obtained (Scheme 3.4). Both these products are unstable and decompose quickly. The cyclization to flavene **184** took place intramolecularly because the allylic alcohol **183** is a very good Michael acceptor and there is a free phenolic hydroxyl group which is prone to cyclization in this case.



Scheme 3.4: $NaBH_4$ reduction of chalcones **106** and **113:** a) $NaBH_4$, MeOH, 78 %.

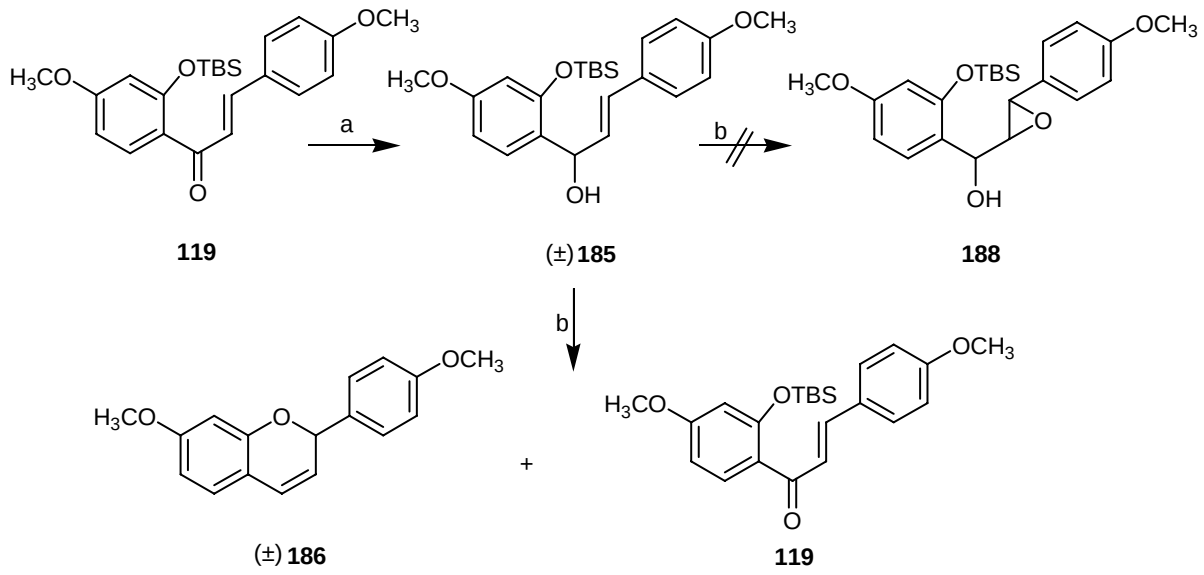
Certain chalcones were reduced with sodium borohydride after which we also tried to reduce these chalcones with chiral reagents. As it is clear from Scheme 3.4 that the free phenolic hydroxyl group presented a problem in that the allylic alcohol is quickly cyclized. We next protected different chalcones with different protecting groups and subjected these to sodium borohydride reduction. We used TBS-protected **119** and MOM-protected **125** chalcones for further studies (Scheme 3.5). In the first case, we obtained racemic allylic alcohols **185** along with racemic flavene **186**. Deprotected chalcone **112** was also observed in this case. In the

second case, racemic allylic alcohols **187** along with racemic flavene **186** were observed. It was observed that the allylic alcohols are not stable. In case of TBS-protected chalcone, we observed chalcone **112** because of the instability of the tertiary butyl dimethyl silyl group under these conditions.



Scheme 3.5: $NaBH_4$ reduction of chalcones **119** and **125:** a) $NaBH_4$, MeOH.

Next we tried to epoxidize the racemic allylic alcohol **185,** derived from TBS-protected chalcone **119** using Sharpless conditions to get hydroxy epoxide **188** (Scheme 3.6). We were of the idea of achieving kinetic separation to get the pure hydroxy epoxide but unfortunately this did not work and only racemic flavene **186** and TBS-protected chalcone **119** were obtained. The reason for no epoxidation may be the steric hindrance due to the *tert*-butyl dimethylsily group and the instability of the racemic allylic alcohol **185** which is converted back to chalcone **119**.

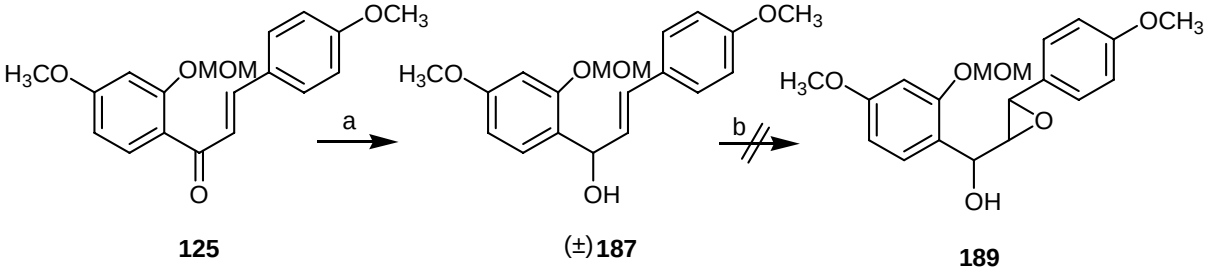


119 (±) **185** **188**

(±) **186** **119**

Scheme 3.6: $NaBH_4$ reduction of chalcone **119** and Sharpless epoxidation**:** a) $NaBH_4$, MeOH; b) L (+)-Diethyl tartrate, TBHP, CH_2Cl_2, Ti(O*i*Pr)$_4$.

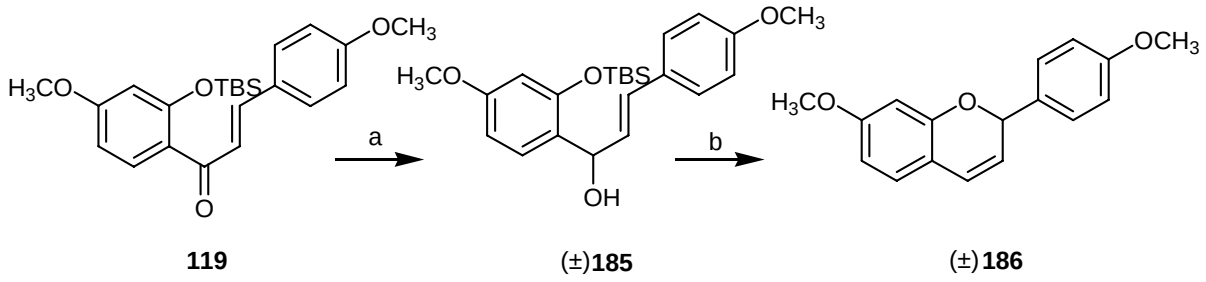
We also tried to epoxidize the racemic allylic alcohol **187**, derived from MOM-protected chalcone **125**, according to the Weitz-Scheffer epoxidation,[73] using phase transfer catalyst **133** and 13% NaOCl as an oxidant. But this also did not work and only the starting material **125** was obtained (Scheme 3.7).



125 (±) **187** **189**

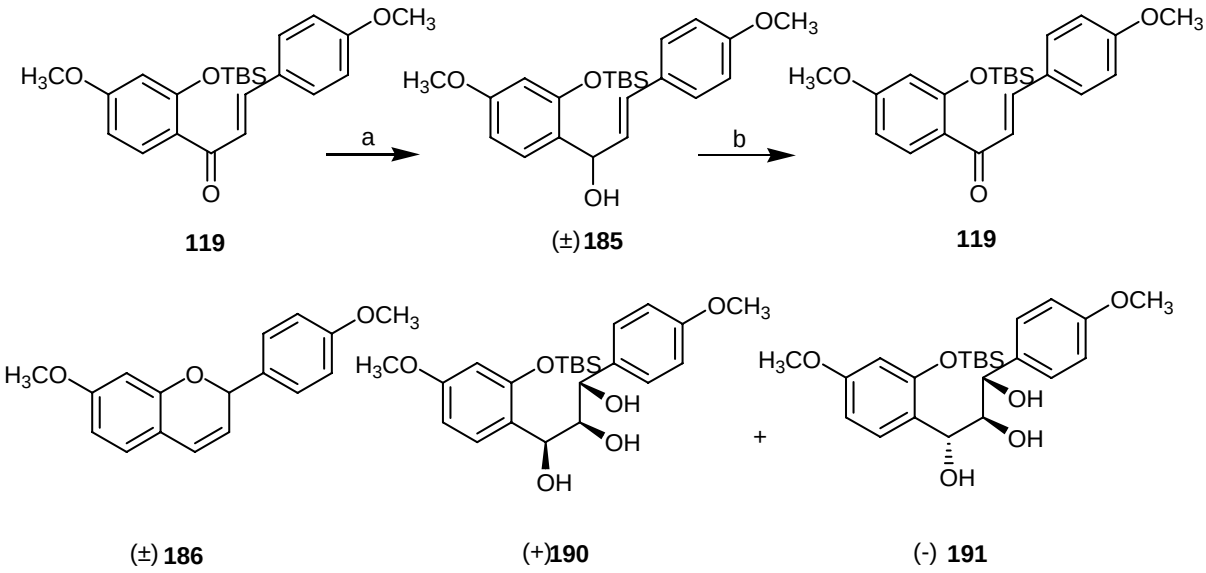
Scheme 3.7: $NaBH_4$ reduction of chalcones **125** and Weitz-Scheffer epoxidation**:** a) $NaBH_4$, MeOH; b) **133**, toluene, 13% NaOCl.

We next wished to investigate the cyclization of the TBS-protected allylic alcohol **185** to flavene **186**. Racemic allylic alcohol was formed from TBS-protected chalcone **119** by sodium borohydride reduction (Scheme 3.8). The allylic alcohol was deprotected by treating it with tetrabutylammonium fluoride in tetrahydrofuran. It was observed that allylic alcohol **185** was cyclised to racemic flavene **186** in 60 % yield.



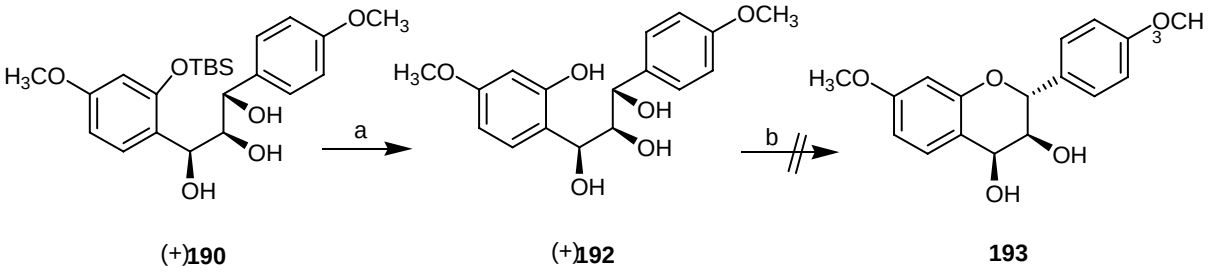
Scheme 3.8: $NaBH_4$ reduction of chalcone **119** and cyclization: a) $NaBH_4$, MeOH; b) TBAF, THF, 60 %.

The racemic allylic alcohol **185**, derived from TBS-protected chalcone **119** by sodium borohydride reduction, was then subjected to Sharpless dihydroxylation. The racemic allylic alcohol **185** was treated with AD mix-α in a mixture of *tert*-butanol and water (1:1) for 3 days[41] (Scheme 4.6). Two protected diastereomers i-e. triol **190** and triol **191** having very close R_f values were obtained. It was observed that the reaction was very slow and there was only 32 % conversion to the products. The slow reaction may be due to the steric hindrance of the *tert*-butyl dimethylsilyl groups with the ligands used. The yield of the reaction is low because of the instability of the racemic allylic alcohol **185,** since part of the allylic alcohol **185** was converted into flavene **186** and a part of it back to chalcone **119** (Scheme 3.9). Diastereoisomer **190** is 20 % and the diastereomer **191** is 12 %.



Scheme 4.6: $NaBH_4$ reduction of chalcone **119** and asymmetric dihydroxylation**:** a) $NaBH_4$, MeOH; b) AD-mix α, *tert*-BuOH:H_2O (1:1).

Tetraol **192** was obtained in quantitative yield by deprotecting the TBS group from **190** by treating it with tetrabutylammonium fluoride. Now the tetraol **192** was subjected to Mitsunobu reaction using diethyl azadicarboxylate and triphenylphosphine in anhydrous tetrahydrofurane,[46] but unfortunately cyclization did not work. This may be because of the two benzylic hydroxyl groups present in the molecule (Scheme 3.10).

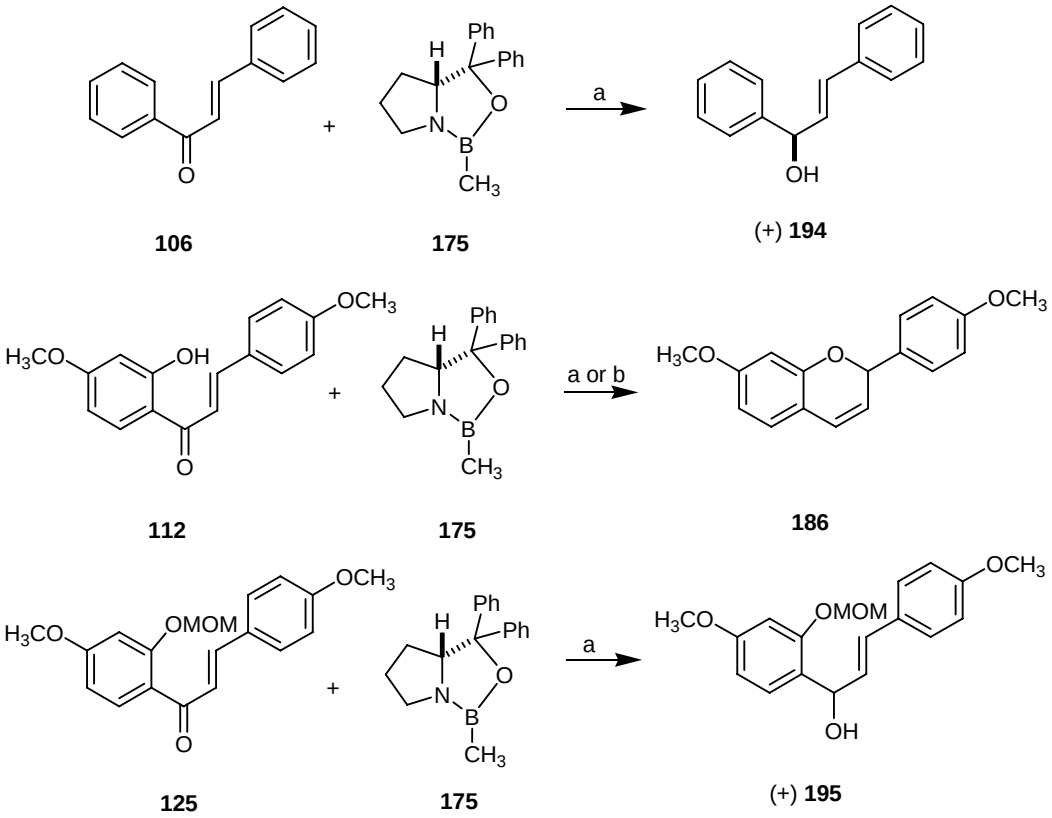


(+)**190** (+)**192** **193**

Scheme 3.10: Mitsunobu reaction: a) TBAF, THF, 90 %; b) DEAD, Ph_3P, anhyd. THF.

3.3.2. CBS- reduction of chalcones

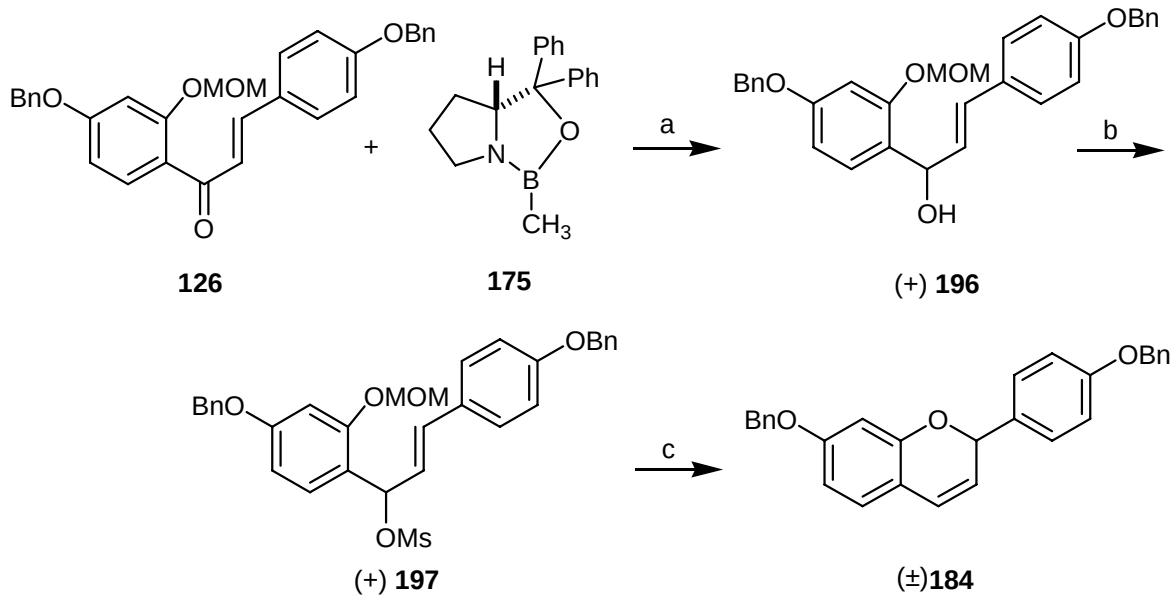
In order to study the cyclization reaction of chalcones, we performed chiral reductions using the CBS-catalyst. Allylic alcohol **194** was obtained from the reduction of chalcone **106** by chiral (*R*)-(+)-2-methyl-CBS-oxazaborolidine (**175**) in optically pure form.[137,142] We believed (Scheme 3.11) that the allylic alcohol having a free 2'-hydroxy will spontaneously undergo intramolecular cyclization to flavene **186**, as we observed in the $NaBH_4$-reduction. We wanted to use the internal chirality of the molecule and see how the cyclization proceeded. Chalcone **112** with the free 2'-hydroxy group was subjected to CBS-reduction in anhydrous tetrahydrofuran by treating with borane tetrahaydrofuran complex or dimethyl sulphide tetrahydrofuran complex. The chalcone **112** was reduced to the allylic alcohol which transformed into the racemic flavene **186** (Scheme 3.11). MOM-protected allylic alcohol **195** was obtained by subjecting MOM-protected chalcone **125** to CBS-reduction using borane tetrahydrofuran complex. It was observed that allylic alcohol **195** is a little more stable but not for a long time.



Scheme 3.11: CBS reduction of chalcones **106,112,125:** a) BH_3-THF, THF, 78 %. b) BH_3-$(CH_3)_2S$, THF, 55 %.

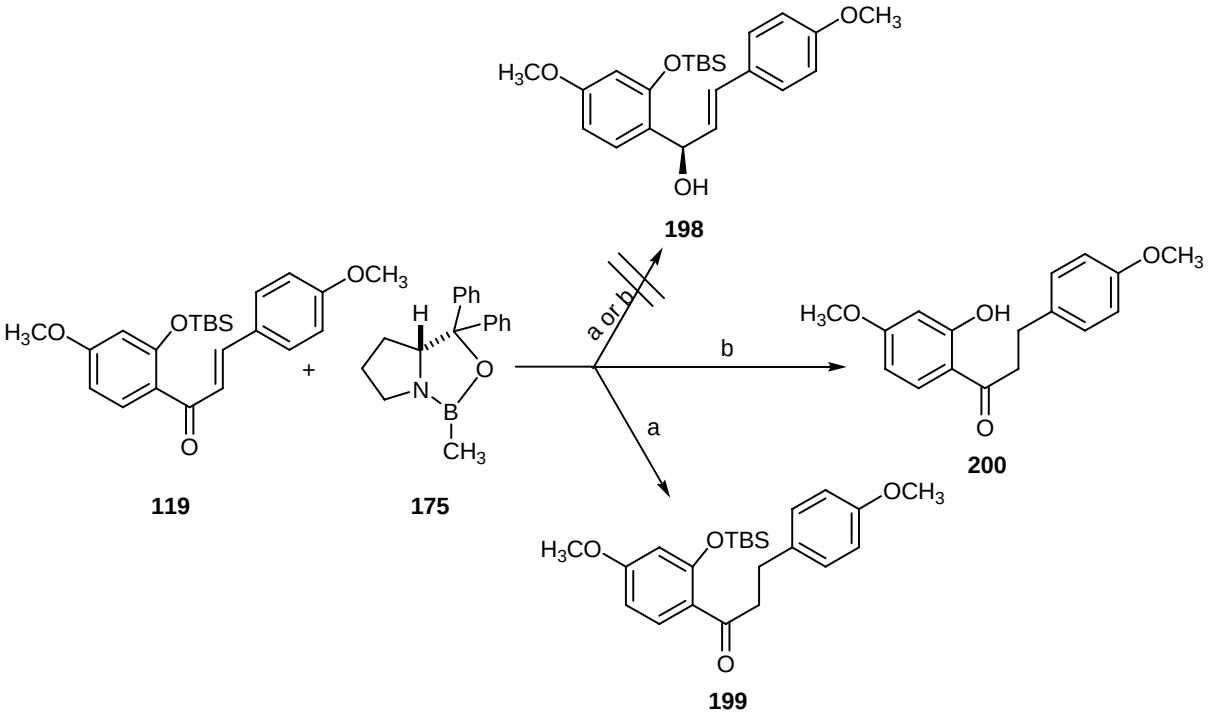
The moderate stability of the MOM-protected alcohol allylic **196** was encouraging for us to study its cyclization. MOM-protected allylic alcohol **196** was obtained by reacting MOM-protected chalcone **126** with (*R*)-(+)-2-methyl-CBS-oxazaborolidine (**175**) using the borane tetrahydrofuran complex.[137,142] Without further purification, allylic alcohol **196** was converted into allylic mesylate **197** using mesyl chloride and pyridine in dichloromethane.[143] The reaction was monitored by TLC (Scheme 3.12).

After the complete conversion of the allylic alcohol **196** to allylic mesylate **197,** deprotection of the MOM-group was followed by cyclization and was performed by 10 % hydrochloric acid in methanol[124] to give once again racemic flavene **184**. This means that the internal chirality of the molecule is unable to induce chirality at C_2 of the flavene **184** (Scheme 3.12).



Scheme 3.12: CBS reduction of chalcones **126:** a) BH_3-THF, THF; b) MsCl, pyridine, CH_2Cl_2; c) 10 % HCl/MeOH, 35 %.

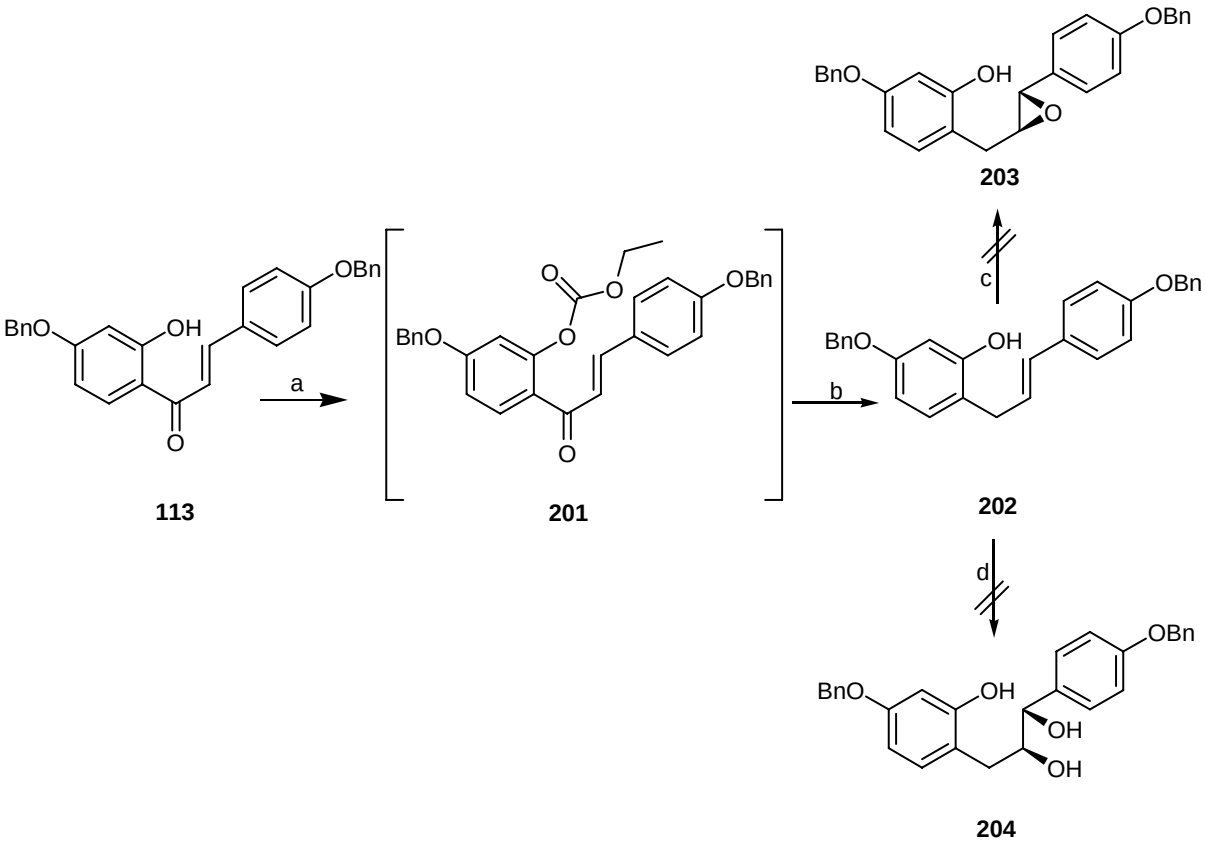
The unexpected results were obtained, when TBS-protected chalcone **119** was subjected to CBS-reduction using borane tetrahydrofurane complex and dimethyl sulphide tetrahydrofuran complex. Reaction with borane tetrahydrofurane complex afforded TBS-protected substituted propanone **199** instead of allylic alcohol **198**. The other reaction with dimethyl sulphide tetrahydrofuran complex yielded substituted propanone **200** (Scheme 3.13). The reason may be that the bulky TBS group hinders the reduction of ketone and allow the reagents to reduce double bond of the chalcone. In second case it was observed that the TBS ether was also not stable enough and that,s why the product **200** was obtained.



Scheme 3.13: CBS reduction of chalcone **119:** a) BH_3-THF, THF, 20 %; b) BH_3-$(CH_3)_2S$, THF, 31 %.

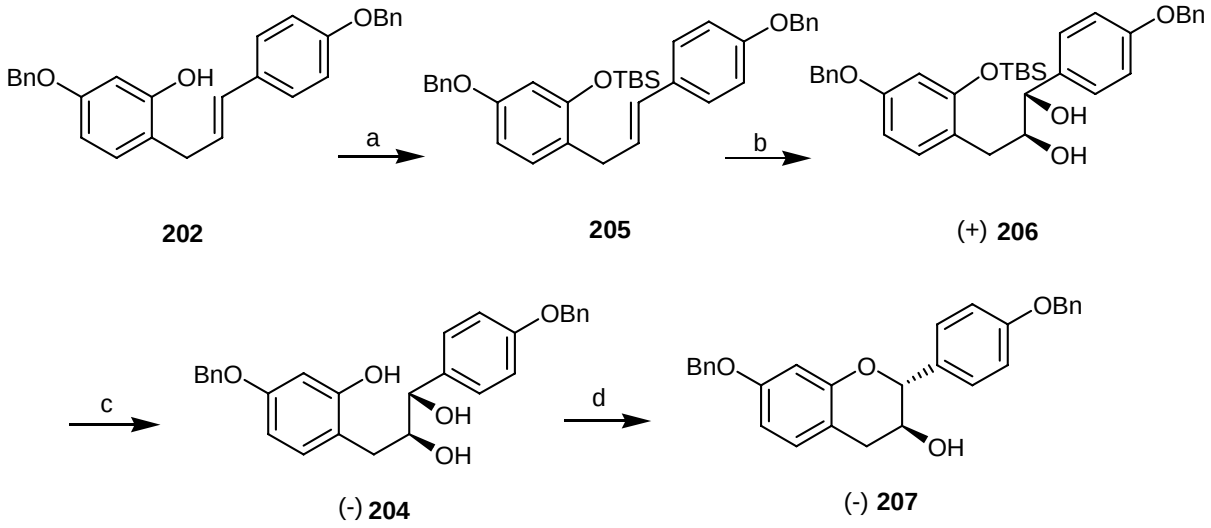
3.3.3 Decarbonylation of chalcone followed by asymmetric epoxidation or asymmetric dihydroxylation

The improved synthesis of flavan moiety was tried in another path. Claisen-Schmidt condensation between 4-benzoxy-2-hrdroxyacephenone **91** and 4-benzoxybenzaldehyde **87** was performed to afford chalcone **113** in quantitative yield. Deacarbonylation was done by employing mild method using NaBH4 in two steps sequence. In the first step chalcone **113** was converted into phenolic carbonate **201** which was then decarbonylated into substituted propene **202**. It was observed that by performing reaction at room temperature, the yield of the decarbonylated product is low due to the formation of racemic flavene **184**. In order to avoid the flavene formation and to improve the yield of the decarbonylated product **202**, the reaction was performed at 0-5 ^{0}C to afford alkene in 83% yield. Sharpless asymmetric dihadroxylation and asymmetric epoxidation using cinchonine catalyst **141** were attempeted in the presence of free phenolic hydroxyl to get compound **203** and **204** and proved unsuccessful.



Scheme 3.14: a) Anhyd. THF, Et_3N, ClCOOEt, 95%; b) i) Na BH_4, H_2O:EtOH (5:1) ii)dilHCl, 83 %; c) Cat.**141**, 13 % NaCl, toluene; d) AD-mix α, *t*-BuOH:H_2O(1:1).

Therefore the phenolic hydroxyl of the substituted prpene **202** was first protected as TBS ether using TBDMSCl and imidazole dimethylformamide to afford substituted TBS protected 1,3-diphenylpropene **205** in quantitative yield. Asymmetric dihydroxylation of protected 1,3-diphenylpropene **205** was proceeded smoothly with AD-mix α in tBuOH:H2O (1:1) to yield **206**. Instead of treating this diol with triethyl orthoformate in order to form ortho ester as done by Hecht and co-worker[41], we subjected diol to deprotection using TBAF to afford trihydroxy compound **204** which is ready for cyclization reaction. Cyclization was carried out with the help of a standard Mitsunobu SN_2 type reaction.[46] to afford 2,3-trans-flavan-3-ol **207** as white solid.



202 **205** (+) **206**

(-) **204** (-) **207**

Scheme 3.15: a) TBDMSCl, imidazole, DMF, 97 %; b) AD-mix α, *t*-BuOH:H_2O(1:1), 88 %; c) TBAF, anhydrous, THF, 98 %; d) DEAD, Ph_3P, anhydrous THF, 65 %.

Chapter 4: Experimental part

4.1. Instrumentations

Column chromatography: Silica gel 60 (230-400 mesh, 0.04-0.063 nm) from Merck.

Thin layer chromatography (TLC): Macherey-Nagel, Silica gel 60/F254. The compounds were visualized by irradiation with 254 or 366 nm light and/or using developing reagents: Solution of 10 g Cer-(IV)-sulfate, 25 g Molybdatophosphoric acid and 60 mL conc. H_2SO_4 in 960 mL water.

IR spectra: Nicolet FT-IR 510 p. The spectra were measured as KBr pellets or as thin films of neat compound. The absorptions are given in wave numbers (cm^{-1}).

Optical rotation: Perkin-Elmer Polarimeter 241 using standard cuvette (d = 10 cm) and Na lamp

(D-line, λ = 589 nm).

Mass spectra: Fison MD 800. Relative intensity is related to basis peak.

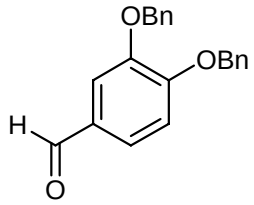
NMR spectra: BRUKER ARX 200, ARX 500. All spectra were recorded at room temperature (RT). ^{1}H-NMR and ^{13}C-NMR spectra the chemical shift values are given in ppm relative to $SiMe_4$. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Broad resonances are indicated broad (br).

Melting Point: Gallenkamp Melting point Apparatus, using one-side open capillary.

Purification of solvents: Purification of solvents was performed by standard methods.

4.2. Experimental part to chapter 1

4.1.1. 3,4-Bis(benzyloxy)benzaldehyde (2)



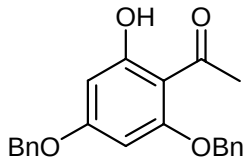
3,4-Dihdyroxybenzaldehyde **(1)** (1.00 g, 7.21 mmol), and benzyl bromide (2.88 g, 2 mL, 16.8mmol) were dissolved in DMF (20 ml). To this solution was added K_2CO_3 (2.00 g, 14.4 mol) and the mixture was stirred at 150 °C for 5 h. The reaction was monitored by TLC. The reaction mixture was cooled to 0 °C, and poured into Et_2O (100 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was removed using a rotary evaporator. After column chromatography, 3,4-bis(benzyloxy)benzaldehyde (**2**) was collected as a white solid in 77.7 % yield (1.8 g, 5.6 mmol).

Melting Point: 91-93 °C (Lit.[26] 88-89 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.20 (s, 2 H, 3-O*CH*$_2$Ph), 5.24 (s, 2 H, 4-O*CH*$_2$Ph), 7.00 (d, *J* = 8.2 Hz, 1 H, 5-H), 7.2-7.5 (m, 12 H, Ar-H), 9.80 (s, 1 H, CHO).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.1 (3-O*CH*$_2$Ph), 70.2 (4-O*CH*$_2$Ph), 111.6 (C-2), 112.4 (C-6), 126.1 (C-1), 126.6 (C-2), 126.8, 127.5, 127.6, 128, 129.8, 135.8, 136.1, (C-Ar) 148.6 (C-3), 153.6 (C-4), 190.2 (CHO).

4.2.2. 2,4-Bis(benzyloxy)-6-hydroxyacetophenone (5)



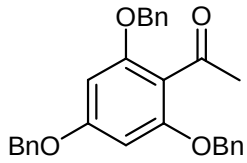
2,4,6-Trihydroxyacetophenone **(4)** (2.00 g, 12.00 mmol), benzyl bromide (3.30 g (3.00 mL, 26.00 mmol) were dissolved in DMF (20 mL). To this solution was added K_2CO_3 (2.00 g, 14.4 mol) and the mixture was stirred for 90 min. under an atmosphere of N_2 at 70 °C. The reaction was monitored by TLC with petroleum ether-ethyl acetate (3:1), R_f = 0.39) After removal of K_2CO_3, the filtrate was poured into ice-cold water and acidified to pH 4 with dil. HCl (100 mL). The mixture was then heated to 60-70 °C for 1 h to give a white precipitate. The precipitates were recrystallized from MeOH-Me_2CO (3:1) to give 2,4-bis(benzyloxy)-6-hydroxyacetophenone **(5)** in 83 % yield (3.5 g, 10.0 mmol) along with side products **6** and **7**.

Melting Point: 105-106 °C (Lit.[28] 100-102 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, CH_3), 5.06 (s, 2 H, 4-O*CH*$_2$Ph), 5.07 (s 2 H, 2-O*CH*$_2$Ph), 6.12 (d, *J* = 2.2 Hz, 1 H, 5-H), 6.19 (d, *J* = 2.2 Hz, 1 H, 3-H), 7.38-7.43 (m, 10 H, Ar-H), 14.02 (s, 1 H, 6-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 33.2 (CH_3), 70.2, (4-O*CH*$_2$PH), 71.1 (2-O*CH*$_2$Ph), 92.7 (C-5), 93.9 (C-3), 105.2 (C-1), 127.1, 127.7, 127.9, 128.3, 128.6, 128.9, 135.6, 135.9 (C-Ar), 162.0 (C-6), 165.1 (C-4), 167.5 (C-2), 203.1 (CO).

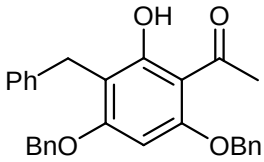
4.2.3. 2,4,6-Tris(benzyloxy)acetophenone (6)



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 5.13 (s, 2 H, 4-O*CH*$_2$Ph), 5.07 (s, 4 H, 2 (O*CH*$_2$Ph)), 6.12 (d, *J* = 2.2 Hz, 1 H, 5-H) 6.19 (d, *J* = 2.2 Hz, 1 H, 3-H), 7.33-7.42 (m, 10 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 32.3 (CH_3), 70.3 (4-O*CH*$_2$Ph), 70.7 (2(O*CH*$_2$Ph)), 93.7 (C-3, C-5), 115.4 (C-1), 127.1, 127.4, 127.9, 128.1, 128.5, 128.6, 136.4 136.5 (C-Ar), 157.2 (C-2, C-6), 161.1 (C-4), 201.2 (CO).

4.2.4. 3-Benzyl-2,4-bis(benzyloxy)-2-hydroxyacetophenone (7)

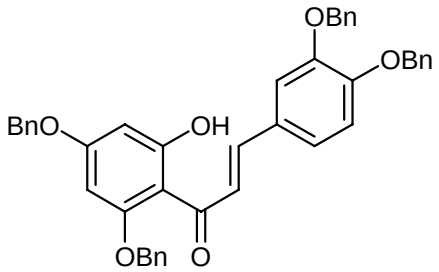


Melting Point: 121-122 °C (Lit.[29] 117 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 4.05 (s, 2 H, 3-*CH*$_2$Ph), 5.08 (s, 2 H, 6-O*CH*$_2$Ph), 5.12 (s, 2 H, 4-O*CH*$_2$Ph), 6.11 (s, 1 H, 5-H), 7.2-7.43 (m, 15 H, Ar-H), 14.21 (s, 1 H, 2-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 28.1 (3-*CH*$_2$Ph), 34.1 (CH_3), 70.1 (4-O*CH*$_2$Ph), 71.0 (6-O*CH*$_2$Ph), 88.7 (C-5), 108.4 (C-1), 111.2 (C-3), 125.4, 127.2, 127.8, 128.0, 128.1, 128.4, 128.6, 128.7, 128.8, 135.8, 136.2, 141.6, (C-Ar), 161.0 (C-6), 162.4 (C-4), 164.0 (C-2), 203.3 (CO).

4.2.5. 1-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-3-[3,4-bis(benzyloxy)phenyl]propenone (8)



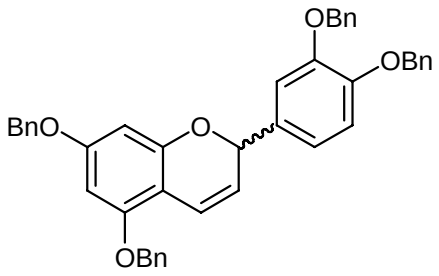
To a stirred solution of 2,4-bis(benzyloxy)-6-hydroxyacetophenone **(5)** (2.00 g, 6.00 mmol) in DMF (50 mL) was added NaH (60%), dispersed in mineral oil (1 g, 41.6 mmol) and then solution of 3,4-bis(benzyloxy)benzaldehyde **(2)** (1.90 g, 6.00 mmol in DMF (34 mL) was added drop wise over a period of 25 min at 0 °C. After stirring for 2 h at room temp, the reaction was carefully quenched with water (2 mL). DMF was evaporated under vacuum and the residue was dissolved in dichloromethane (200 mL) and was washed with water (100 mL) and brine (100 mL). The extract was concentrated and the residue was crystallized from ether to give 1-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-3-[3,4-bis(benzyloxy)phenyl]propenone **(8)** as yellow crystals in 81.6 % yield (3.21 g, 4.93 mmol).

Melting Point: 133-134 °C (Lit.[29] 137-138 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.92 (s, 4 H, 2 (O*CH*$_2$Ph)), 5.07 (s, 2 H, O*CH*$_2$Ph), 512 (s, 2 H, O*CH*$_2$Ph), 6.23 (d, *J* = 2.3 Hz, 1 H, 3'-H), 6.31 (d, *J* = 2.3 Hz, 1 H, 5'-H), 6.70 (s, 1 H, 2-H), 6.81 (d, *J* = 8.5 Hz, 1 H, 5-H), 6.87 (d, *J* = 8.5 Hz, 1 H, 6-H), 7.19-7.45 (m, 25 H, Ar-H), 7.66 (d, *J* = 14.7 Hz, 1 H, α-H), 7.78 (d, *J* = 14.7 Hz, 1 H, β-H), 14.21 (s, 1 H, 6'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.3 (4'-O*CH*$_2$Ph), 71.1 (3-O*CH*$_2$Ph), 71.3 (4-O*CH*$_2$Ph), 71.5 (O*CH2*Ph), 92.7 (C-5'), 95.2 (C-3'), 106.6 (C-1'), 114.7 (C-5), 115.4 (C-2), 122.4 (C-6), 125.9 (C-α), 127.2, 127.4, 127.7, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9 (C-Ar), 129.0 (C-1), 135.7, 136.0, 137.0 (C-Ar), 142.7 (C-β), 148.9 (C-3), 150.8 (C-4), 161.7 (C-6'), 165.2 (C-4'), 168.6 (C-2'), 192.6 (CO).

4.2.6. 5,7-Dibenzyloxy-2-[3,4-bis(benzyloxy)phenyl]-2*H*-chromene (10)

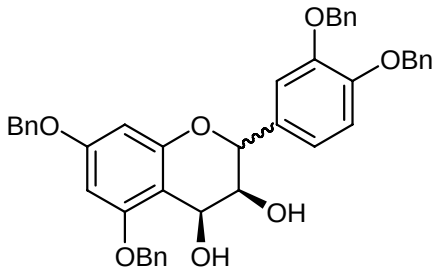


Chalcone **8** (2.00 g, 3.08 mmol) was dissolved in 1,2-dimethoxyethane (30 mL) at 85°C and $NaBH_4$ (120 mg, 3.14 mmol) was added. After 5-10 min (TLC monitoring) at 85 °C, the mixture was cooled at room temperature. The reaction mixture was then diluted with ethyl acetate (60 mL) and washed three times with brine (50 mL). The organic layer was dried over sodium sulphate before adding a solution of $BF_3{\cdot}OEt_2$ (0.038 mL) in CH_2Cl_2 (1 mL). After 35 minutes stirring at room temperature the dark orange solution was obtained which was washed 3 times with brine (50 mL), dried over sodium sulphate and concentrated to give flavene as an orange resin. Flavene **10** is unstable and that's why it was not further purified and subjected immediately to next reaction.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.99 (s, 2 H,O*CH*$_2$Ph), 5.03 (s, 2 H, O*CH*$_2$Ph), 5.05 (s, 2 H, O*CH*$_2$Ph), 5.09 (s, 2 H, O*CH*$_2$Ph), 5.53 (dd, *J* = 9.95, 3.29 Hz, 1 H, 3-H), 5.72 (dd, *J* = 3.24, 1.95 Hz, 1 H, 2-H), 6.13 (d, *J* = 2.17, 1 H, 8-H), 6.20 (d, *J* = 2.17, 1 H, 6-H), 6.69 (d, *J* = 8.4 Hz, 1 H, 5'-H), 6.73 (s, 2 H, 2'-H), 6.78 (d, *J* = 8.4 Hz, 1 H, 6'-H), 6.86 (dd, *J* = 9.86, 1.57 Hz, 1 H, 4-H), 7.25-7.41 (m, 25 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.1 (O*CH*$_2$Ph) 70.3 (O*CH*$_2$Ph), 70.7 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 77.0, (C-2), 93.9 (C-6), 95.2 (C-8), 105.0 (4a), 114.3 (C-3'), 114.9 (C-5'), 118.9 (C-4), 119.7 (C-3), 120.5 (C-6'), 127.2 (C-2), 127.3, 127.4, 127.5, 127.7, 127.9, 128.0, 128.4, 128.5 (C-Ar), 134.2 (C-1'), 136.7, 136.9, 137.2, 137.3 (C-Ar), 149.1 (C-3') 149.2 (C-4'), 154.9 (C-8a), 155.3 (C-5), 160.3 (C-7).

4.2.7. 2,3-*trans*-3,4-*cis*--5,7-Dibenzyloxy-2-[3,4-bis(benzyloxy)-phenyl]chroman-3,4-Diol (11)



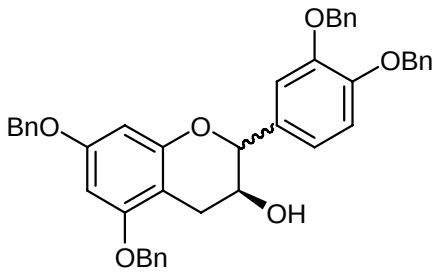
The flavene **10** was dissolved in THF (12 mL) and added to the mixture of *N*-methylmorpholine *N*-oxide (0.46 g, 2.14 mmol), water (1.2 mL), THF (16 mL) and OsO_4 (0.31 mL, 0.05 mmol) of a 2.5 wt-% solution in 2-methyl-2-propanol. After stirring 8 h at room temperature the pale yellow precipitating mixture was dissolved in CH_2Cl_2 (100 mL) and washed two times with an aqueous solution of $Na_2S_2O_3$ (10 g/100 mL). The organic layer was washed with water (100 mL) and brine (100 mL). Racemic diol **11** was crystallized from ether after dissolution in a minimum CH_2Cl_2 to obtain pure diol **11** as white crystals in 45 % yield (0.93 g, 1.39 mmol).

Melting Point: 177-179 °C (Lit.[29] 175 °C).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.8 (brs, OH), 4.09 (m, 1 H, 3-H), 4.69 (d, *J* = 3.4Hz, 1 H, 4-H), 4.96 (d, *J* = 12.0 Hz, 1 H, 2-H), 5.01 (s, 2 H, O*CH*$_2$Ph), 5.05 (s, 2 H, O*CH*$_2$Ph), 5.20 (s, 2 H, O*CH*$_2$Ph), 5.34 (s, 2 H, O*CH*$_2$Ph), 6.27 (d, *J* = 1.9 Hz, 1 H, 8-H), 6.32 (d, *J* = 1.9 Hz, 1 H, 6-H), 6.99 (d, *J* = 8.3 Hz, 1 H, 5'-H) 7.09 (dd, *J* = 8.3, 1.5 Hz, 1 H, 6'-H), 7.13 (d, *J* = 1.5 Hz, 1 H, 2'-H), 7.30-7.56 (m, 20 H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 61.5 (C-4), 70.2 (C-3), 70.1 (O*CH*$_2$Ph) 70.3 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 71.4 (O*CH*$_2$Ph), 76.6 (C-2), 94.1 (C-6), 94.6 (C-8), 105.2 (C-4a), 114.6 (C-2'), 115.1 (C-5'), 121.2 (C-6'), 127.2, 127.3, 127.4, 127.5, 127.7, 128.0, 128.1, 128.4, 128.6, 128.7 (C-Ar), 130.9 (C-1'), 136.4, 136.6, 137.2, 137.3 (C-Ar), 149.2 (C-3') 149.5 (C-4'), 156.0 (C-8a), 158.7 (C-5), 160.8 (C-7).

4.2.8. (±)(5,7-Dibenzyloxy-2-[3,4-bis(benzyloxy)phenyl]chroman-3-ol (12)



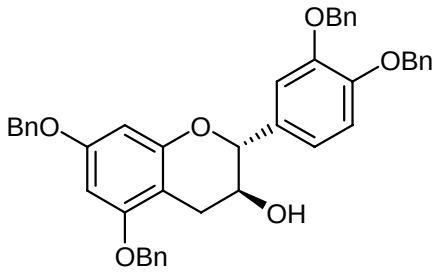
Racemic diol **11** (1.00 g, 1.51 mmol) was suspended in acetic acid (50 mL). $NaBH_3CN$ (1.52 g, 23.80 mmol) was carefully added to this suspension. After stirring for 2 days at room temperature, the acetic acid was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The crude extract was purified by column chromatography on silica gel using CH_2Cl_2/AcOEt (97:3) as eluent to afford racemic benzylated catechin **12** as white amorphous solid in 77.3 % yield (0.76 g, 1.16 mmol).

Melting Point: 129-130 °C (Lit.[10] 124-126 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.75 (dd, *J* = 16.4, 8.6 Hz,1 H, 4-H-α), 3.21 (dd, *J* = 16.4 and 5.5 Hz,1 H, 4-H-β), 4.09 (m, 1 H, 3-H), 4.69 (d, *J* = 8.3 Hz, 1 H, 2-H), 5.03 (s, 2 H, O*CH*$_2$Ph), 5.07 (s, 2 H, O*CH*$_2$Ph), 5.22 (s, 2 H, O*CH*$_2$Ph), 5.34 (s, 2 H, O*CH*$_2$Ph), 6.25 (d, *J* = 2.3 Hz, 1 H, 6-H), 6.32 (d, *J* = 2.3 Hz, 1 H, 8-H), 7.07 (d, *J* = 8.5 Hz, 1 H, 5'-H), 7.11 (dd, *J* = 8.5, 1.8 Hz, 1 H, 6'-H), 7.17 (d, *J* = 1.8 Hz, 1 H, 2'-H), 7.36-7.59 (m, 20 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 27.6 (C-4), 68.1 (C-3), 69.9 (O*CH*$_2$PH), 70.1 (O*CH*$_2$PH), 71.3 (O*CH*$_2$PH), 71.4 (O*CH*$_2$PH), 81.5 (C-2), 93.9 (C-6), 94.5 (C-8), 102.3 (C-4a), 114.1 (C-2'), 115.1 (C-5'), 120.5 (C-6'), 127.1, 127.2, 127.5, 127.8, 127.9, 128.4, 128.5, 128.6 (C-Ar), 131.1 (C-1'), 136.9, 137.0, 137.2 (C-Ar), 149.2 (C-3'), 149.4 (C-4'), 155.3 (C-8a), 157.8 (C-5), 158.8 (C-7).

4.2.9. (+)-3',4',5,7-Tetra-*O*-benzylcatechin (14)



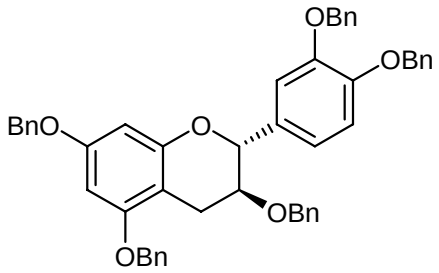
A stirred solution of (+)-catechin **(13)** (3.00 g, 10.33 mmol), benzyl chloride (6.62 g, 6.00 mL, 52.10 mmol) and K_2CO_3 (9 g, 65.10 mmol) in DMF (30 mL) was heated for 4 h at 120-130 °C (monitored by TLC). The mixture was poured into water (100 mL). The resulting solution was extracted with ethyl acetate (250 mL) and dried over sodium sulphate. Evaporation of the solvent gave a brown thick oil which was subjected to column chromatography on silica gel to obtain pure (+)-3',4',5,7-tetra-*O*-benzylcatechin **(14)** as a white in 79.8 % yield (5.3 g, 8.15 mmol) solid along with (+)-3',4',3,5,7-penta-*O*-benzylcatechin **(15)** as a side product.

Melting Point: 121-122 °C (Lit.[10] 124-126 °C).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.68 (dd, *J* = 16.4, 8.6 Hz,1 H, 4-H-α), 3.14 (dd, *J* = 16.4, 5.5 Hz,1 H, 4-H-β), 4.03 (m, 1 H, 3-H), 4.65 (d, *J* = 8.3 Hz, 1 H, 2-H), 5.01 (s, 2 H, O*CH*$_2$Ph), 5.05 (s, 2 H, O*CH*$_2$Ph), 5.19 (s, 2 H, O*CH*$_2$Ph), 5.20 (s, 2 H, O*CH*$_2$Ph), 6.23 (d, *J* = 2.5 Hz, 1 H, 6-H), 6.29 (d, *J* = 2.5 Hz, 1 H, 8-H), 6.98 (d, *J* = 8.5 Hz, 1 H, 5'-H), 7.01 (dd, *J* = 8.5, 2.1 Hz, 1 H, 6'-H), 7.05 (d, *J* = 2.1 Hz, 1 H, 2'-H), 7.28-7.48 (m, 20 H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.6 (C-4), 68.2 (C-3), 69.9 (O*CH*$_2$Ph), 70.1 (O*CH*$_2$Ph), 71.2 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 81.5 (C-2), 93.85 (C-6), 94.4 (C-8), 102.3 (C-4a), 113.9 (C-2'), 115.0 (C-5'), 120.6 (C-6'), 127.1, 127.2, 127.4, 127.5, 127.8, 127.8, 127.9, 128.4, 128.5, 128.5 (C-Ar), 130.9 (C-1'), 136.8, 136.9, 137.0, 137.1 (C-Ar) 149.1 (C-3'), 149.3 (C-4'), 155.2 (C-8a), 157.7 (C-5), 157.8 (C-7).

4.2.10. (+)-3',4',3,5,7-Penta-*O*-benzylcatechin (15)



Melting Point: 142-144 °C.

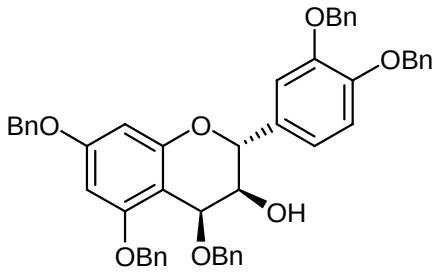
$[\alpha]_D$ = +29.7° (c = 1.0, MeOH), (Lit.[30] +32° (c = 1.0, MeOH).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.68 (dd, *J* = 16.3, 8.6 Hz,1 H, 4-H-α), 3.11 (dd, *J* = 16.3, 5.5 Hz,1 H, 4-H-β), 3.98 (m, 1 H, 3-H), 4.65 (d, *J* = 8.3 Hz, 1 H, 2-H), 5.04 (s, 2 H, O*CH*$_2$Ph), 5.07 (s, 2 H, O*CH*$_2$Ph), 5.14 (s, 4 H, O*CH*$_2$Ph), 5.19 (s, 2 H, O*CH*$_2$Ph), 6.29 (d, *J* = 2.5 Hz, 1 H, 6-H), 6.29 (d, *J* = 2.5 Hz, 1 H, 8-H), 6.98 (d, *J* = 8.5 Hz, 1 H, 5'-H),7.05 (dd, *J* = 8.5, 2.1 Hz, 1 H, 6'-H), 7.11 (d, *J* = 2.1 Hz, 1 H, 2'-H), 7.19-7.56 (m, 25 H, Ar-H).

4.2.11. [4,8]-2,3-trans-3,4-cis:2,3-trans-Octa-*O*-benzyl-bi-(+)-catechin (19)

(+)-Tetra-*O*-benzylated catechin **(14)** (323 mg, 0.50 mmol, 4.5 equiv.) and racemic 3,4-diol **11** (75 mg, 0.11 mmol) were dissolved in CH_2Cl_2 (20 mL). To this solution was added drop wise $TiCl_4$ (1M solution in CH_2Cl_2, 0.15 mL) at 0 °C. After stirring for 5 minutes at 0 °C, the reaction mixture was quenched with saturated sodium hydrogen carbonate (1 mL). The aqueous solution was extracted with chloroform (20 mL) and the organic phase was washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. After filtration of the organic phase, it was concentrated on rotary evaporator. Mixture of compounds including dimmer (procyanidin B_3), trimers and higher oligomers were observed after TLC analysis. These compounds are not analysed by chromatographic techniques.

4.2.12. (2S,3S,4S)-4,5,7,3',4'-Pentabenzyloxyflavan-3-ol (20)



To a solution of tetra-*O*-benzylcatechin **(14)** (500 mg, 0.78 mmol) and benzyl alcohol (0.80 mL, 7.60 mmol) in CH_2Cl_2 (6 mL) was added slowly DDQ (2 equiv., 140 mg, 0.61 mmol) at 0 °C. After stirring overnight at room temperature, 4-dimethylaminopyridine was added in excess to the solution at 0 °C and the mixture was stirred for another 30 minutes. The resulting mixture was filtered off. The filtrate was washed with water (50 mL) and brine (20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and resulting residue was subjected to silica gel column chromatography to give (2S,3S,4S)-4,5,7,3',4'-Pentabenzyloxyflavan-3-ol **(20)** as white foam in 82 % yield (491 mg, 0.64 mmol).

Melting Point: 127-128 °C (Lit.[11] 124-125 °C).

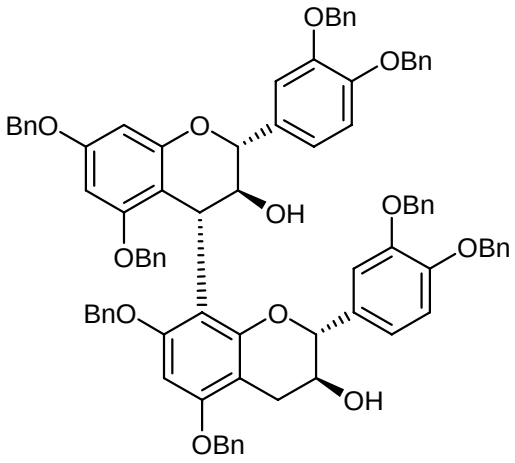
$[\alpha]_D$ = +53.7° (c = 0.48, $CHCl_3$), (Lit.[11] +56.4° (c = 0.48, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.35 (d, *J* = 9.7,1 H, 2-H), 3.90 (dt, *J* = 3.4, 9.7 Hz,1 H, 3-H), 4.66 (d, *J* = 11.5 Hz, 1 H, O*CH*$_2$Ph), 4.78 (d, *J* = 11.5 Hz, 1 H, O*CH*$_2$Ph), 4.96 (d, *J* = 3.4 Hz, 1 H, 4-H), 5.00 (d, *J* = 9.7 Hz, 1 H, O*CH*$_2$Ph), 5.01 (d, *J* = 11.2, 1 H, O*CH*$_2$Ph), 5.05 (d, *J* = 11.2, 1 H, O*CH*$_2$Ph), 5.13 (s, 4 H, O*CH*$_2$Ph), 6.18 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.28 (d, *J* = 2.2, 1 H, 6-H), 6.94 (d, *J* = 8.3, 1 H, 5'-H), 6.99 (dd, *J* = 2.0, 8.3 Hz, 1 H, 6'-H), 7.07 (d, *J* = 2.0 Hz, 1 H, 2'-H), 7.18-7.45 (m, 25 H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.3 (C-4), 67.8 (C-3), 69.8 (O*CH*$_2$Ph), 70.9 (O*CH*$_2$Ph), 71.5 (O*CH*$_2$Ph), 71.4 (O*CH*$_2$Ph), 71.7 (O*CH*$_2$Ph), 81.5 (C-2), 93.85 (C-6), 94.4 (C-8), 102.3 (C-4a), 113.9 (C-2'), 115.0 (C-5'), 120.6 (C-6'), 127.1, 127.2, 127.4, 127.5, 127.8, 127.8, 127.9, 128.4, 128.5, 128.5 (C-Ar), 130.9 (C-1'), 136.8, 136.9, 137.0, 137.1 (C-Ar) 149.1 (C-3'), 149.3 (C-4'), 155.2 (C-8a), 157.7 (C-5), 157.8 (C-7).

MS (EI, 70 eV): *m/z* (%) = 156 (44) $[M]^+$, 756.1 (4), 648 (30), 620 (12), 557 (15), 529 (28), 332 (19), 256 (22), 211 (19), 181 (62), 108.1 (100).

4.2.13. [4,8]-2,3-trans-3,4-cis:2,3-trans-Octa-*O*-benzyl-bi-(+)-catechin



(+)-Tetra-*O*-benzylcatechin **(14)** (323 mg, 0.50 mmol, 4.5 equiv.) and pentabenzylated catechin **20** (75 mg, 0.11 mmol) were dissolved in CH_2Cl_2 (20 mL). To this solution was added drop wise TMSOTf (0.5 M solution in CH_2Cl_2, 0.3 mL) at 0 °C. After stirring for 5 minutes at 0 °C, the reaction mixture was quenched with saturated sodium hydrogen carbonate (1 mL). The aqueous solution was extracted with chloroform (15 mL) and the organic phase was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. After filtration of the organic phase, it was concentrated on rotary evaporator. Mixture of dimer **19** (benzylated procyanidin B_3) and trimer **21** (benzylated procyanidin C_2) were obtained in 80 % yield which were isolated by column chromatography as pale yellow oils.

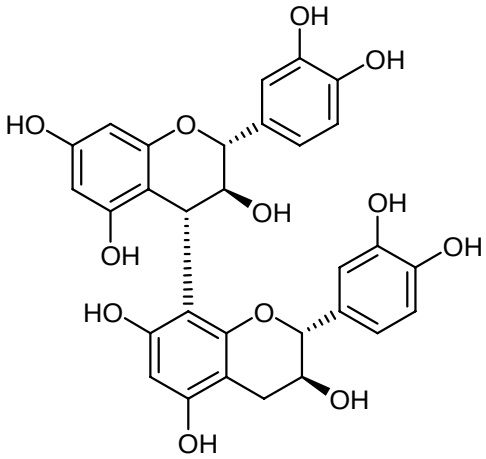
$[\alpha]_D = -101°$ (c = 0.80, $CHCl_3$), (Lit.[11] –106° (c = 0.80, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): Major isomer δ = 1.30–1.70 (m, 1.32 H, OH), 2.37 (dd, 0.66 H, *J* = 9.2, 16.3 Hz, 1 H, 4F-H-β), 3.04 (dd, *J* = 5.8, 16.3 Hz, 0.66 H, 4F-H-α), 3.58 (d, *J* = 8.8 Hz, 0.66 H, 2F-H), 3.61–3.67 (m, 0.66 H, 3F-H), 4.28 (dd, *J* = 8.8, 9.8 Hz, 0.66 H, 3C-H), 4.49 (d, *J* = 9.8 Hz, 0.66 H, 4C-H), 4.53 (d, *J* = 10.7 Hz, 0.66 H, O*CH*$_2$Ph), 4.66 (d, *J* = 8.8 Hz, 0.66H, 2C-H), 4.63–4.72 (m, 0.66 H, Ar-H), 4.79–4.83 (m, 1.32 H, Ar-H), 4.86-5.20 (m, 7.92 H, Ar-H), 6.09 (d, *J* = 2.4 Hz, 0.66 H, 6A-H), 6.17 (d, *J* = 2.4 Hz, 0.66 H, 8A-H), 6.23

(s, 0.66 H, 6D-H), 6.78 (dd, *J* = 2.0, 8.3 Hz, 0.66 H, 6'-H), 6.81–6.93 (m, 4.62 H, Ar-H), 6.97–7.01 (m, 1.32 H, 2',2-H), 7.11–7.15 (m, 1.32 H, Ar-H), 7.46–7.48 (m, 22.44 H, Ar-H).

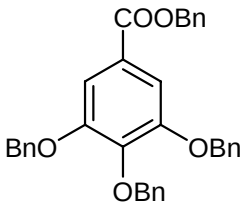
^{13}C-NMR (50 MHz, $CDCl_3$): Minor isomer δ = 1.30–1.70 (m, 0.68 H, OH), 2.64 (dd, *J* = 9.5, 16.3 Hz, 0.34 H, 4F-H-β), 3.16 (dd, *J* = 5.8, 16.3 Hz, 0.34 H, 4F-H-α), 3.61–3.67 (m, 0.34 H, 3F-H), 4.14 (dd, *J* = 8.2, 9.8 Hz, 0.34 H, 3C-H), 4.45 (d, *J* = 8.2 Hz, 0.34 H, 2F-H), 4.49 (d, *J* = 9.8 Hz, 0.34 H, 4C-H), 4.77 (d, *J* = 8.2 Hz, 0.34 H, 2C-H), 4.63–4.72 (m, 0.68 H, Ar-H), 4.79–4.83 (m, 0.68 H, Ar-H), 4.86-5.20 (m, 4.08 H, Ar-H), 6.00 (d, *J* = 2.4 Hz, 0.34 H, 6A-H), 6.08 (s, 0.34 H, 6D-H), 6.19 (d, *J* = 2.4 Hz, 0.34 H, 8A-H), 6.43 (dd, *J* = 2.0, 8.3 Hz, 0.34 H, 6'), 6.59 (d, *J* = 2.0 Hz, 0.34 H, 2'-H), 6.81–6.93 (m, 2.04 H, Ar-H), 7.46–7.48 (m, 11.9 H, Ar-H), 7.11–7.15 (m, 0.68 H, Ar-H).

4.2.14. Procyanidin-B_3



To a solution of benzylated catechin **19** (0.23 g, 0.18 mmol) in THF/MeOH/H_2O (20/1/1) was added 20% $Pd(OH)_2/C$ (10 mg) and stirred for 12 h at room temperature. When the TLC showed complete conversion, the mixture was filtered off and concentrated at reduced pressure to afford pale brown oil, which was purified by flash column chromatography using methanol to obtain procyanidin-B_3 **22** (73%) as an amorphous solid.

4.2.15. Benzyl-3,4,5-tribenzyloxybenzoate (29)



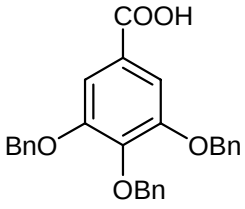
Gallic acid **(28)** (1.00 g, 5.88 mmol, 1 equiv.) was dissolved in dry acetone (60 ml). K_2CO_3 (3.60 g, 25.88 mmol, 4.4 equiv.) and benzyl bromide (3.1 ml, 4.4 g, 25.88 mmol, 4.4 equiv.) were added to the solution. The mixture was heated under stirring for 12 h. After adding water (200 ml), the mixture was extracted three times with ethyl acetate (50 mL). The solvent was removed on rotary evaporator under reduced pressure. The residual oil was crystallized with ethanol to yield the benzyl-3,4,5-tribenzyloxybenzoate **(29)** in 83 % yield (2.6g, 4.9 mmol).

Melting Point: 96 °C (Lit.[32] 93.5-94.5 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): 507 (s, 4 H, 2(O*CH*$_2$Ph)), 512 (s, 2 H, O*CH*$_2$Ph), 5.42 (s, 2 H, COO*CH*$_2$Ph), 6.51 (s, 2 H, 2, 6-H), 7.19-7.29 (m, 20 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 67.43 (COO*CH*$_2$Ph); 71.99 (O*CH*$_2$Ph); 75.82 (O*CH*$_2$Ph); 110.05 (C-2); 125.8, 125.9, 126.3, 126.8, 127, 4, 127.8, 127.9, 128.0, 128.1, 128.8, 129.0, 129.7, 137.3, 140.1153.23 (C-Ar); 166.41 (*COO*Bn)

4.2.16. 3,4,5-tribenzyloxy gallic acid (30)



The benzyl ester **(29)** (2.00 g, 3.78 mmol) was refluxed for 12 h in 3N KOH (20 mL) and methanol (100 mL). The mixture was then acidified with 3N HCl (pH 3-4) to give precipitates. The resulting precipitates were dissolved in ethyl acetate (150 mL) and washed

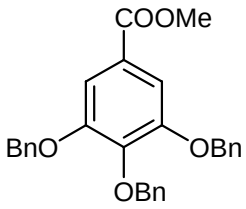
three times with water (150 mL). The organic phase was dried over Na_2SO_4. Recrystallization was done with methanol to afford white crystals in 76.7 % yield (1.30 g, 2.90 mmol)

Melting Point: 193-195 °C (Lit.[32] 193.5-193.7 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.15 (s, 4 H, O*CH*$_2$Ph), 5.17 (s, 2 H, O*CH*$_2$Ph) 7.27 (s, 2 H, 2, 6-H), 7.14-7.26 (m, 15 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 71.99 (O*CH*$_2$Ph), 75.86 (O*CH*$_2$Ph), 110.43 (C-2, C-6), 124.75, 127.5, 127.6, 127.8, 128.0, 128.1, 128.3, 128.6, 128.7, 128.9, 129.1, 129.2, 134.7, 138.3 (C-Ar).

4.2.17. Methyl-3,4,5-tribenzyloxybenzoate (31)



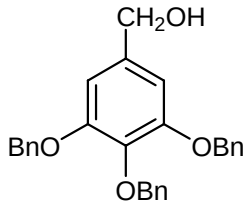
Conc. H_2SO_4 (5 mL) was added to the solution of 3,4,5-tribenzyloxybenzoic acid (10.00 g, 22.70 mmol) in absolute methanol (300 mL). The mixture was refluxed for 5 h. The reaction mixture was cooled and allowed to stand overnight at room temperature. The precipitates were formed which were crystallized (MeOH) to give the corresponding methyl ester as colourless needles in 91.1 % yield (9.4 g, 20.7 mmol).

Melting Point: 94-96 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, CH_3), 5.22 (s, 2 H, p-OCH_2Ph), 5.23 (s, 4 H, 2 (OCH_2Ph)), 6.71 (s, 2 H, 2, 6-H), 7.40 (m, 15 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 52.9 (CH_3), 71.8(O*CH*$_2$Ph), 71.9 (O*CH*$_2$Ph), 109.85 (C-2, C-6) 125.7 (C-1) 128.0, 128.4, 128.5, 128.6, 129.0, 137.1, 138.0, (C-Ar) 142.9 (C-4), 153.0 (C-3, C-5) 167.0 (*COO*)

4.2.18. 3,4,5-Tribenzyloxybenzylalcohol



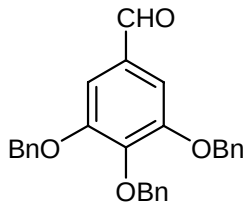
Methyl 3,4,5- tribenzyloxybenzoate **(31)** (1.00 g, 2.20 mmol) was suspended in dried warm THF (3.3 mL) and added drop wise to a suspension of lithium aluminium hydride (83 mg, 2.20 mmol) in 1 mL of THF. After stirring overnight, water (1 mL) was carefully added drop wise and then solution of sodium hydroxide (15 %, 1 mL), and then again water (2 mL) was added. The solid residue was obtained after filtration. THF (10 mL) was added to this solid material and heated to reflux followed by filtration of the warm solution. The combined THF extracts were evaporated under reduced pressure to give 3,4,5-tribenzyloxybenzyl alcohol **(32)** in 85 % yield (.8.00 g, 1.87 mmol).

Melting Point: 96-97 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.21 (br s, 1 H, OH), 4.56 (s, 2 H, *CH*$_2$OH), 5.11 (s, 2 H, O*CH*$_2$Ph), 5.14 (s, 4 H, 2 (O*CH*$_2$Ph)), 6.71 (s, 2 H, 2, 6-H), 7.30-7.52 (m, 15 H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 65.6 (*CH*$_2$OH) 71.5 (O*CH*$_2$Ph), 106.6 (C-2, C-6) 127.8, 128.3, 128.6, 128.9, 129.0, 128.9, 137.2, 137.5, 137.9 (C-Ar), 138.2 (C-4), 153.3 (C-3, C5).

4.2.19. 3,4,5-Tribenzyloxybenzaldehyde (33)



To a stirred suspension of pyridinium chlorochromate (813 mg, 1.90 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added 3,4,5-tribenzyloxybenzylalcohol **(32)** (1.00 g, 2.35 mmol) in CH_2Cl_2 (36

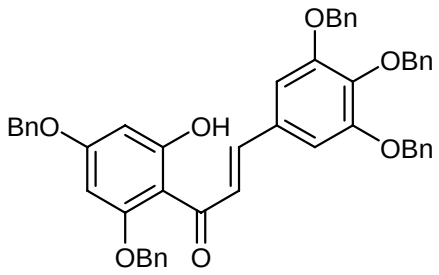
mL). The solution was stirred at 0 °C for 6 h. The suspension was filtered and washed by ether (60 mL). The organic layer was partitioned between ether (90 mL) and water (40 mL). The ether layers were combined, dried over $MgSO_4$ and evaporated to afford a residue. The residue was purified by chromatography to afford 3,4,5-tribenzyloxybenzaldehyde **(33)** in 86.8 % yield (700 mg, 1.65 mmol).

Melting Point: 100-101 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.20 (s, 2 H, O*CH*$_2$Ph), 5.21 (s, 4 H, 2 (OCH_2Ph)), 7.23-7.51 (m, 17 H, Ar-H), 9.79 (s, 1 H, CHO).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 71.6 (O*CH*$_2$Ph), 109.3 ((C-2, C-6)), 127.9, 128.4, 128.5, 128.6, 128.9, 129.0, 132.2, 136.8, 137.6 (C-Ar), 144.2, (C-4) 153.6 (C-3, C5), 191.4 (CHO).

4.2.20. 1-[2, 4-Bis(benzyloxy)-6-hydroxyphenyl]-3-[3,4,5-tris(benzyloxy)phenyl]propenone (27)



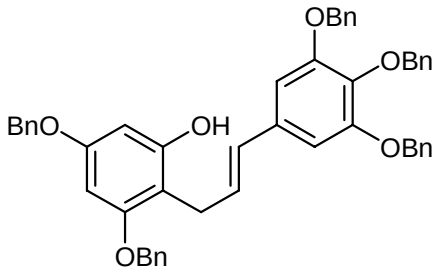
To a stirred solution of 2,4-bis(benzyloxy)-6-hydroxyacetophenone **(5)** (2.00 g, 5.70 mmol) in DMF (34 mL), NaH (60%), dispersed in mineral oil (1.00 g, 41.60 mmol) was added. The mixture was stirred 15 minutes at 0 °C. The solution of 3,4,5-tris(benzyloxy)benzaldehyde **(33)** (2.60 g, 5.70 mmol) in DMF (15 mL) was added drop wise over a period of 25 min at 0 °C. After stirring for 5 h at 0 °C, the reaction was carefully quenched with water (2 mL). The solvent was evaporated under vacuum, and the residue was dissolved in dichloromethane (200 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The extract was concentrated and the residue was crystallized from ether to give 1-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-3-[3,4,5-tris(benzyloxy)phenyl]propenone **(33)** as yellow crystals in 72 % yield (3.1 g, 4.11 mmol).

Melting Point: 148-149 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.89 (s, 4 H, O*CH*$_2$Ph), 5.13 (s, 4 H, O*CH*$_2$Ph), 6.23 (d, *J* = 2.4 Hz, 1 H, 3'-H), 6.31 (d, *J* = 2.4 Hz, 1 H, 5'-H), 6.70 (s, 2 H, 2,6-H), 7.16-7.49 (m, 25 H, Ar-H), 7.64 (d, *J* = 15.3 Hz, 1 H, α-H), 7.86 (d, *J* = 14.7 Hz, 1 H, β-H), 14.32 (s, 1H, 6'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.7 (4, 4'-O*CH*$_2$Ph), 71.4, (3, 5, 2'-O*CH*$_2$Ph), 95.5 (C-3', C-5'), 107.2 (C-1'), 108.6 (C-5), 114.4 (C-2), 121.4 (C-6), 125.9 (C-α) 127.4, 127.8, 128.1, 128.3, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2 (C-Ar), 131.0 (C-1), 136.1, 136.2, 137.2, 138.0, 140, 7 (C-Ar), 142.7 (C-β), 153.2 (C-3), 150.8 (C-4), 161.9 (C-6'), 165.6 (C-4'), 168.5 (C-2'), 193.0 (CO).

4.2.21. 1-[3,4,5-Tris(benzyloxyphenyl)]-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]propene (35)



Triethylamine (1.20 mL, 8.60 mmol) was added to a solution containing 1-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-3-[3,4,5-tris(benzyloxy)phenyl]propenone **(27)** (5.00 g, 6.63 mmol) in 45 mL of anhydrous THF. The reaction mixture was cooled to 0 °C in an ice bath and stirred for 10 minutes. Ethyl chloroformate (0.86 g, 0.75 mL, 7.83 mmol) was then added drop wise to this solution over a period of 20 minutes. The reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was filtered, and the precipitate obtained was washed with two 25-mL portions of THF. The filtrate was then added drop wise at 0 °C over a period of 45 min to a solution containing $NaBH_4$(1.0 g, 26.5 mmol in 40 mL of H_2O). The reaction mixture was then warmed to room temperature and stirred overnight. The reaction mixture was acidified with 1N HCl, diluted with H_2O (200 mL) and extracted with ether (3×250 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel column using ethyl acetate:

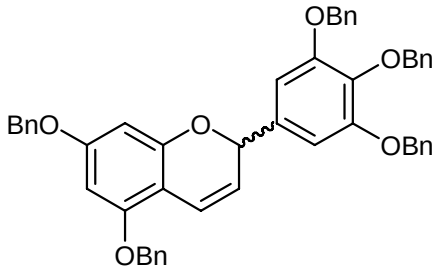
petrol ether (1:9). To afford 1-[3,4,5-tris(benzyloxyphenyl)]-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]propene **(35)** as colourless oil in 46.7 % yield (2.3 g, 3.10 mmol) along with two side products **36** and **37**.

Melting Point: 129-131 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.62 (d, *J* = 5.4 Hz, 2 H, CH_2), 5.03 (s, 2 H, 7-O*CH*$_2$Ph), 5.10 (s, 4 H, 3', 6'-O*CH*$_2$Ph),), 5.11(s, 4 H, 4',5-O*CH*$_2$Ph), 6.15-6.38 (m, 4 H, 2, 3, 6, 8-H), 6.70 (s, 2 H, 2', 6'-H), 7.31-7.55 (m, 25 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 32.0 (CH_2), 70.5 (7-O*CH*$_2$Ph), 70.7 (4'O*CH*$_2$Ph), 71.7 (3', 5', 5-O*CH*$_2$Ph), 94.1 (C-6), 95.5 (C-8), 106.4 (C-2', C-4'), 107.4 (C-4a) 127.3 (C-3), 127.7, 127.9, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.9, 128.9, 128.8, 128.9, 129.0, 129.6, 130.6, 133.3, 137.3, 137.6, 137.8, 138.2 (C-Ar), (C-4') 153.0 (C-5')153.3 (C-3'), 156.0 (*C*-OH), 158.4 (C-7), 159.2, (C-5).

5,7-Dibenzyloxy-2-[3,4,5-tris(benzyloxy)phenyl]-2*H*-chromene (36)



36

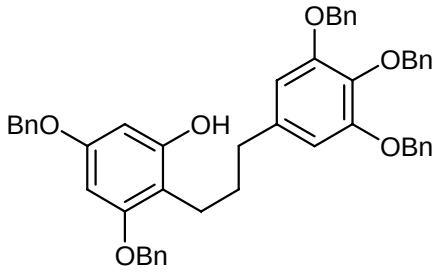
Melting Point: 105-107 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.99 (s, 2 H, O*CH*$_2$Ph), 5.03 (s, 2 H, O*CH*$_2$Ph), 5.05 (s, 4 H, O*CH*$_2$Ph), 5.09 (s, 2 H,O*CH*$_2$Ph), 5.53 (dd, *J* = 9.95, 3.29 Hz, 1 H, 3-H), 5.72 (dd, *J* = 3.24, 1.95 Hz, 1 H, 2-H), 6.13 (d, *J* = 2.17, 1 H, H-8), 6.20 (d, *J* = 2.17, 1 H, H-6), 6.78 (s, 2 H, 2', 6'-H), 6.86 (dd, *J* = 9.86 ,1.57 Hz, 1 H, 4-H), 7.25-7.41 (m, 25 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.1 (O*CH*$_2$Ph) 70.3 (O*CH*$_2$Ph), 70.7 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 77.0, (C-2), 93.9 (C-6), 95.2 (C-8), 105.0 (4a), 114.3 (C-2'),

114.9 (C-5'), 118.9 (C-4), 119.7 (C-3), 120.5 (C-6'), 127.2, 127.3, 127.4, 127.5, 127.7, 127.9, 128.0, 128.4, 128.5 (C-Ar), 134.2 (C-1'), 136.7, 136.9, 137.2, 137.3 (C-Ar), 149.1 (C-3') 149.2 (C-4'), 154.9 (C-8a), 155.3 (C-5), 160.3 (C-7).

1-[3,4,5-Tris(benzyloxyphenyl)]-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]propane (37)

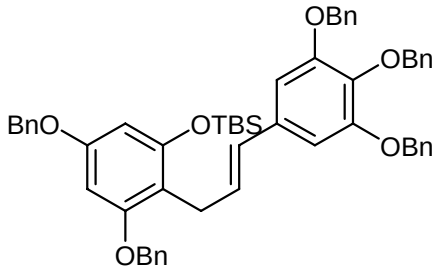


Melting Point: 102–103 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.28 (s, 6 H, Si $(CH_3)_2$), 1.11 (s, 9 H, Si-C$(CH_3)_3$), 1.93 (m, 2 H, 4-CH_2), 2.68 (t, *J* = 7.5, 2 H, 3-CH_2), 2.79 (t, *J* = 7.5, 2 H, 2-CH_2), 5.09 (s, 2 H, O*CH*$_2$Ph), 5.12 (s, 4 H, O*CH*$_2$Ph), 5.14 (s, 4 H, O*CH*$_2$Ph), 6.21 (d, *J* = 2.0, 1 H, 8-H),), 6.39 (d, *J* = 2.0, 1 H, 6-H),), 6.59 (s, 2 H, 2', 6'-H), 7.30-7.50 (m, 25 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.6 Si-$(CH_3)_2$), 18.3 (Si-*C*$(CH_3)_3$), 25.8 (Si-C(*CH*$_3$)$_3$), 26.8 (CH_2), 31.9 (CH_2) 70.5 (4', 7-O*CH*$_2$Ph), 71.7 (3', 5', 5-O*CH*$_2$Ph), 94.3 (C-6), 97.7 (C-8), 108.6 (C-2', C-4'), 115.0 (C-4a) 127.3 (C-3), 127.8, 127.9, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.8, 128.9., 128.9, 129.0, 129.6, 137.0, 133.6, 137.8, 137.9, 137.9, 138.6, 139.3 (C-Ar), (C-4') 152.8 (C-5')154.7 (C-3'), 158.1 (C-5), 158.4 (C-7).

4.2.22. 1-[3,4,5-Tris(benzyloxyphenyl)]-3-[2,4-bis(benzyloxy)-6- *tert*-butyldimethylsilyloxy]propene (38)



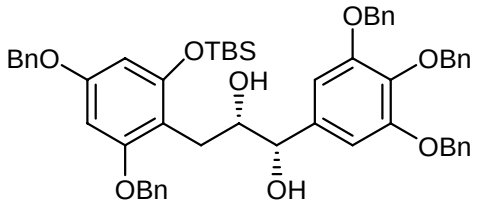
To a solution containing 1-[3,4,5-tris(benzyloxyphenyl)]-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]propene **(35)** (1.00 g, 1.35 mmol) in anhydrous DMF (12 mL) was added imidazole (275 mg, 4.05 mmol). The solution was stirred at room temperature for 5 minutes and TBDMSCl (0.305 g, 2.02 mmol) was then added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water (25 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column using ethyl acetate: petrol ether (1:9) to afford TBS protected propene **38** as a colourless solid in 94.8 % yield (1.1 g, 1.28 mmol).

Melting Point: 88-90 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.20 (s, 6 H, Si-$(CH_3)_2$), 1.00 (s, 9 H, Si-C$(CH_3)_3$), 3.52 (d, *J* = 4.9 Hz, 2 H, CH_2), 5.02 (s, 2 H, 7-O*C*H_2Ph), 5.05 (s, 4 H, 3', 6'-O*C*H_2Ph),), 5.10 (s, 4 H, 4',5-O*C*H_2Ph), 6.19-6.35 (m, 4 H, 2, 3, 6, 8-H), 6.60 (s, 2 H, 2', 6'-H), 7.30-7.47 (m, 25 H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = -4.0 Si-$(CH_3)_2$), 18.3 (Si-*C*$(CH_3)_3$), 25.8 (Si-C(*C*$H_3)_3$), 26.8 (C-4), 70.2 (7-O*C*H_2Ph), 70.1 (4'O*C*H_2Ph), 71.3 (3', 5', 5-O*C*H_2Ph), 93.9 (C-6), 98.5 (C-8), 105.9 (C-2', C-4'), 112.1 (C-4a) 127.3 (C-3), 127.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 128.9., 128.9, 129.0, 129.6, 130.6, 133.3, 137.1, 137.3, 137.6, 138.0 (C-C-Ar), 152.1(C-4') 153.8 (C-5')154.7 (C-3'), 158.1 (C-7), 158.4 (C-5).

4.2.23. (1*S*,2*S*)-3-[2,4-Bis(benzyloxy-6-(*tert*-butyldimethylsilyloxy)phenyl]-1-[3,4,5-tris(benzyloxyphenyl)- propan-1,2-diol (39)



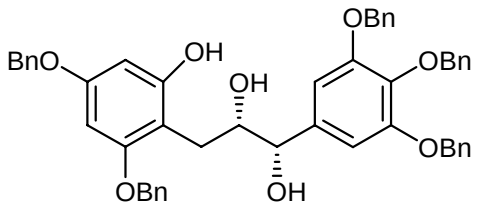
To a solution containing TBS-protected propene (1.00 g, 1.17 mmol) in 1:1 tBuOH-H_2O (12 mL) was added AD-mix α (1.65 g, 1.17 mmol) in portions. The heterogeneous mixture was cooled to 0 °C in an ice bath and methanesulfonamide (0.139 mg, 1.46 mmol) was also added in portions. To allow for complete dissolution of the starting material, chloroform (1 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 48 h. When the starting material was completely consumed (TLC monitored), the reaction was then quenched with sodium sulfite solution (2 mL) and diluted with ethyl acetate (150 mL) and water (150 mL). The organic layer was separated and washed with two 100 mL portions of 2M KOH followed by 100 mL of H_2O. The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column using ethyl acetate: petrol ether (1:9) to afford TBS protected diol **39** as colourless oil in 85 % yield (0.9 g, 1.01 mmol).

Melting Point: 193-195 °C (Lit.[32] 193.5–193.7 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 6 H, Si-CH_3), 0.19 (s, 3 H, Si-CH_3), 1.11 (s, 9 H, Si-C(CH_3)$_3$), 2.75 (dd, *J* = 14.8, 8.4 Hz, 1 H, 4-H-α), 2.90 (dd, *J* = 14.8 and 3.6 Hz, 1 H, 4-H-β), 3.92 (ddd, *J* = 8.4, 5.6, 3.6 Hz, 1 H, 3-H), 4.43 (d, *J* = 5.6 Hz, 1 H, 2-H), 4.89 (s, 2 H, O*CH*$_2$Ph), 4.95-5.05 (m, 8 H, O*CH*$_2$Ph), 6.21 (d, *J* = 2.0 Hz, 1 H, 8-H), 6.26 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.59 (s, 2 H, 2', 6'-H), 7.25-7.45 (m, 25 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.8 Si-(CH_3)$_2$), 18.5 (Si-*C*(CH_3)$_3$), 25.7 (Si-C(*CH*$_3$)$_3$), 26.9 (C-4), 70.0 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 79.4 (C-2), 82.1 (C-3) 93.9 (C-6), 98.5 (C-8), 105.9 (C-2', C-4'), 112.1 (C-4a) 127.3 (C-3), 127.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 128.9., 128.9, 129.0, 129.6, 130.6, 133.3, 137.1, 137.3, 137.6, 138.0 (C-Ar), (C-4') 152.8 (C-5')154.7 (C-3'), 158.1 (C-7), 158.4 (C-5).

4.2.24. (1S,2S)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-[3,4,5-tris(benzyloxyphenyl)-propan-1,2-diol (26)



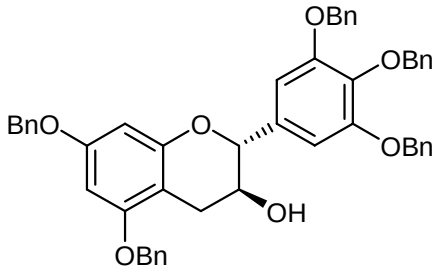
To a solution of TBS-protected Diol **39** (0.90 g, 1.01 mmol) in anhydrous THF (20 mL) was added tetra-*n*-butylammonium fluoride (300 mg, 0.95 mmol). The reaction mixture was stirred 1.5 h at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (5 mL). The reaction mixture was diluted with water (50 mL) and extracted with three portions of ethyl acetate (20 mL). The combined organic layer was washed with brine (25 mL) and water (25 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure to obtain brown residue which was purified by flash chromatography on a silica gel column to obtain triol **26** as colourless solid in 96.2 % yield (753 mg, 0.97 mmol).

Melting Point: 144-145 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ =), 2.75 (dd, *J* = 14.8, 8.4 Hz, 1 H, 4-H-α), 2.90 (dd, *J* = 14.8 and 3.6 Hz, 1 H, 4-H-β), 3.92 (ddd, *J* = 8.4, 5.6, 3.6 Hz, 1 H, 3-H), 4.43 (d, *J* = 5.6 Hz, 1 H, 2-H), 4.89 (s, 2 H, O*CH*$_2$Ph), 4.95-5.05 (m, 8H, O*CH*$_2$Ph), 6.21 (d, *J* = 2.0 Hz, 1 H, 8-H), 6.26 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.59 (s, 2 H, 2', 6'-H), 7.25-7.45 (m, 25 H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 26.9 (C-4), 70.0 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 75.3, 76.9, 77.1, 79.4 (C-2), 82.1 (C-3) 93.9 (C-6), 98.5 (C-8), 105.9 (C-2', C-4'), 112.1 (C-4a) 127.3 (C-3), 127.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 128.9., 128.9, 129.0, 129.6, 130.6, 133.3, 137.1, 137.3, 137.6, 138.0 (C-Ar), 152.1 (C-4') 152.8 (C-5')154.7 (C-3'), 158.1 (C-7), 158.4 (C-5).

4.2. 25. (–)-(2*S*,3R)-*trans*-5,7-Bis(benzyloxy)-2-[3,4,5-tris(benzyloxy)phenyl]chroman-3-ol (25)



To a solution of triol **26** (30 mg, 0.038 mmol) in anhydrous THF (2 mL) was added triphenylphosphine (15 mg, 0.057 mmol), The mixture was stirred for 10 minutes and diethylazodicarboxylate (0.01 mL, 0.057mmol) was then added drop wise to the reaction mixture. After stirring for 2.5 h at room temperature, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated on rotary evaporator to give white residue. The residue obtained was purified by silica gel column chromatography to afford gallocatechin **(25)** as white solid in 57.8 % yield (17 mg, 0.022 mmol).

Melting Point: 116-118 °C.

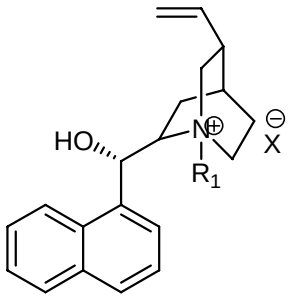
$[\alpha]_D$ = –8.96° (c = 1.0, $CHCl_3$), (Lit.[11] –7.21° (c = 1.0, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.76 (br s, 1 H, 3-OH), 2.75 (dd, *J* = 16.5, 9.0 Hz, 1 H, 4-H-α), 3.15 (dd, *J* = 16.5, 6.0 Hz, 1 H, 4-H-β), 4.01 (ddd, *J* = 9.0, 8.1, 6.0 Hz,1 H, 3-H), 4.65 (d, *J* = 8.1 Hz, 1 H, 2-H), 5.04 (s, 2 H, O*CH*$_2$Ph), 5.07, (s, 2 H, O*CH*$_2$Ph), 5.10 (s, 2 H, O*CH*$_2$Ph), 5.11 (s, 2 H, O*CH*$_2$Ph), 5.14 (s, 2 H, O*CH*$_2$Ph), 6.29 (d, *J* = 2.4 Hz, 1 H, 8-H), 6.34 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.78 (s, 2 H, 2', 6'-H), 7.30-7.55 (m, 25 H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 27.9 (C-4), 68.5 (C-3), 70.2 (O*CH*$_2$Ph), 70.4 (O*CH*$_2$Ph), 71.4 (O*CH*$_2$Ph), 82.1(C-2), 94.2 (C-8) , 94.6 (C-6), 102.6 (C-2'), 106.9 (C-6'), 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.0, 133.6, 137.1, 137.2, 138.0, 138.9 (C-Ar), 153.1 (C-4'), 153.3,(C-3') 155.4 (C-5), 158.0 (C-8a), 159.1 (C-7).

4.3. Experimental part to chapter 2

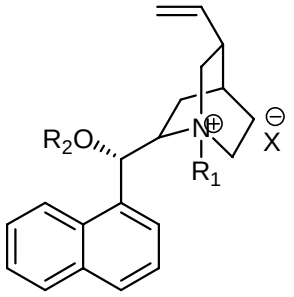
4.3.1. General procedure for the preparation of cinchonine catalysts (128-132)



128-132

A mixture of cinchonine (**127)** (1.00 g, 2.00 mmol) and corresponding aryl halides (5.78 mmol) was heated at reflux in toluene (25ml) under argon for 2-48h. The solution was then cooled to room temperature and the resulting precipitate filtered off. The residue was crystallized from chloroform-petroleum ether (1:3) to give salts **128-132** as solids. Reactions with aryl bromides were completed with in 2-5 h and reactions with aryl chlorides were completed with in 4-48 h.

4.3.2. General procedure for the preparation of cinchonin catalysts (133-141)

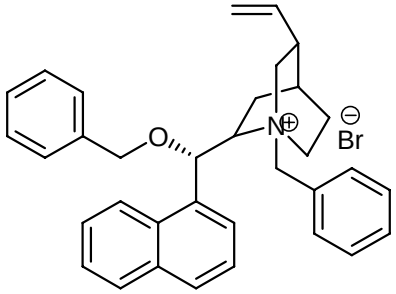


133-141

50 % aqueous sodium hydroxide (0.10 mL, 0.13 mmol) was added to a solution of salt (**128-132**) (0.38mmol) and corresponding aryl halides (1.10 mmol) in dichloromethane (3ml). The mixture was stirred vigorously for 1.5-5 h. Water (2 mL) was then added and the aqueous

layer was extracted with dichloromethane (5 mL). The combined organics were dried over magnesium sulphate, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography to afford corresponding catalyst.

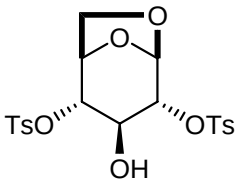
_N_, _O_-Dibenzylcinchonium bromide (133)



Melting Point: 218 °C (Lit.[131] 214-216 °C).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.48 (m, l H,), 1.82 (m, l H), 2.05 (br s, l H), 2.11-2.25 (m, 2 H), 2.57 (m, l H), 3.16 (m, 2 H), 4.11 (d, J = 11.8 Hz, l H), 4.18 (m, l H), 4.40 (l H, J = 11.6 Hz, d), 4.62 (m, l H), 4.87 (d, J = 11.6 Hz, 1 H), 4.92 (m, l H), 4.94 (d, J = 10.45 Hz, 1 H), 5.30 (d, J = 17.2 Hz, 1 H), 5.62-5.70 (m, l H), 6.19 (d, J = 11.7 Hz, 1 H), 6.25 (br s, l H), 7.37-7.65 (m, 8 H), 7.76 (d, J = 6.5 Hz, 2 H), 7.80 (t, J = 7.7 Hz, 2 H), 7.93 (m, 1 H), 8.15 (d, J = 8.4 Hz, 1 H), 8.76 (d, J = 8.15 Hz, 1 H); 9.02 (d, J = 4.2 Hz, 1 H).

4.3.3. 1,6-Anhydro-2,4-Di-*O*-tosyl-1,6-anhydro-β-D-*gluco*-pyranose (151)



Levoglucosan **(150)** (15.00 g, 92.60 mmol) was dissolved in anhydrous pyridine (100 mL). Tosyl chloride (38.80 g, 203.90 mmol) was added to the solution of levoglucosan at -10 °C in four portions, keeping the temperature below -5 °C. The reaction was stirred for 12 h at -5 °C. The reaction was monitored by TLC. After the complete conversion of the starting material, the reaction was quenched by adding water (10 mL) to the white suspension, and the reaction

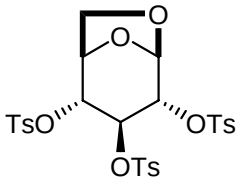
mixture was stirred for half an hour. Ethyl acetate (300 mL) was added, and the mixture was extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed two times with water (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated to obtain a residue. The residue was subjected to column chromatography to give ditosylate **151** in 81 % isolated yield (35.00 g, 76.22 mmol)along with tritosylate **152** in 10 % isolated yield

Melting Point: 122 °C (Lit.[132] 119-121 °C).

^{1}H-NMR (500 MHz, $CDCl_3$): = 2.46 (s, 3 H, Ar-*CH₃*), 2.47 (s, 3 H, Ar-*CH₃*), 2.94 (brs, 1 H, OH), 3.68 (dd, *J* = 7.8 Hz, *J* = 5.2 Hz, 1 H, 6a-H), 3.96 (brs, 1 H, 3-H), 4.02 (d, *J* = 7.8 Hz, 1 H, 6b-H), 4.22 (d, *J* = 3.0 Hz, 1 H, 2-H), 4.38 (d, *J* = 3.5 Hz, 1 H, 4-H), 4.65 (d, *J* = 5.2 Hz, 1 H, 5-H), 5.34 (s, 1 H, 1-H), 7.37 (m, 4 H, Ar-H), 7.78 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.82 (d. *J* = 8.3 Hz, 2 H, Ar-H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 26.5 (CH_3-Ar), 65.9 (C-6), 69.3 (C-3), 74.6 (C-5), 77.4 (C-2), 78.6 (C-4), 99.6 (C-1), 127.8, 127.9, 130.0, 130.1, 132.9, 133.1 145.4, 145.5 (C-Ar).

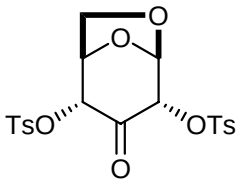
2,3,4-Tri-*O*-tosyl-1,6-anhydro-β-D-*gluco*-pyranose (152)



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 2.47 (s, 6 H), 3.69 (dd, dd, J = 8.2 and 5.7 Hz, 1 H), 4.04 (d, *J* = 8.4 Hz, 1 H), 4.15 (br d, J = 1.2 Hz, 1 H), 4.51 (br s, 1 H), 4.57-4.62 (m, 2 H,), 5.25 (br s, 1 H), 7.35 (m, 6 H), 7.68 (m, 4 H), 7.78 (m, 2 H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.63 (CH_3-Ar), 21.66 (CH_3-Ar), 21.69 (CH_3-Ar), 64.81, (C-6), 71.93 (C-3), 73.60 (C-4), 73.73 (C-2), 73.80 (C-5), 98.51, 127.87, 127.92, 128.11, 129.98, 130.01, 130.05, 131.77, 132.36, 132.67, 145.44, 145.50, 145.81 (C-Ar).

4.3.4. 1,6-Anhydro-2,4-di-*O*-tosyl-β-D-*ribo*-hexapyrano-3-ulose (153)



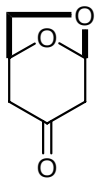
To a stirred solution of ditosylated levoglucosan **151** (10.00 g, 21.30 mmol) in CH_3CN (80 mL) were added glacial acetic acid (6.2 mL) and $RuCl_3$ $3H_2O$ (44 mg, 2.10 mmol) at 0 °C. The solution became dark brown. Solution of $NaBrO_3$ (2.1 g, 138 mmol in water 9.8 mL) was added to this dark brown solution over a period of 2.5 h, keeping the temperature below 8 °C. The resulting black mixture was stirred for 1.5 h at 0 °C and 2-propanol (1.0 mL) was added at 0 °C and reaction mixture was stirred for another 15 min. The reaction was poured into a mixture of ethyl acetate (85 mL) and 15 % aq. $Na_2S_2O_3$ (20 mL). The reaction mixture was stirred for 15 min, and the organic layer was separated and with water (20 mL), saturated sodium bicarbonate (2×50 mL), and water (20 mL). Ditosyl ketone was obtained in 80 % yield (8.00 g, 17.01 mmol).

$[\alpha]_D$ = –23.1° (c = 1.5, MeOH).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 6 H, 2 (Ar–CH3)), 3.83 (dd, *J* = 8.5, 5.0 Hz, 1 H, 6a-H), 3.92 (dd, *J* = 8.5 Hz, 1.0 Hz, 1 H, 6b-H), 4.52 (d, *J* = 1.2 Hz, 1 H, 2-H), 4.69 (d, *J* = 1.0 Hz, 1 H, 4-H), 4.90 (ddd, *J* = 5.0, 1.0, 1.0 Hz, 1 H, 5-H), 5.62 (d, *J* = 1.2, 1 H, 1-H), 7.33–7.38 (m, 4 H, Ar-H), 7.75–7.78 (m, 4 H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.6 (*CH3*–Ar), 21.7 (*CH3*–Ar), 66.7 (C-6), 77.3 (C-5), 77.6 (C-2), 79.0 (C-4), 101.3 (C-1), 127.9, 128.0, 128.1, 128.3, 129.9, 130.0, 132.5, 132.3, 145.3, 145.5 (C-Ar), 190.5 (CO).

4.3.5. 1,6-Anhydro-2,4-didesoxy-β-D-*glycero*-hexopyrano-3-ulose



Zinc dust (400 g) and 1.5 % aqueous HCl (800 mL) was mechanically stirred for 1.5 h at 20 °C. The aqueous layer was decanted, and the solids were washed with THF (2×800 mL). After filtration the solid was dried at 145 °C under vacuum overnight.

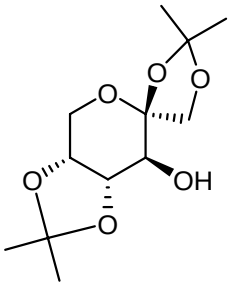
Activated zinc (53g, 810 mmol) was suspended in THF (220 mL) and crushed NH_4OAc (62 g, 810 mmol) was added to the suspension and mixture was stirred mechanically at 20 °C for 1h. The suspension was then cooled to 0 °C. The solution of ditosyl ketone (15 g, 32.10 mmol) in THF (65 mL) was added over 2.5 h with stirring, keeping the temperature below 5 °C. The reaction was warmed to 20 °C and stirred for 16 h. The suspension was filtered, and the salts were washed with THF (170 mL). Powdered potassium carbonate (15.5 g, 112.30 mmol) was added to the combined organic filtrates with stirring and aged at 20 °C for 22 h. The salts were filtered and washed with THF (80 mL). The combined organic filtrates were concentrated, and ketone was obtained as a solution in THF in 85 % yield (3.50 g, 27.34 mmol).

$[\alpha]_D = -105°$ (c = 0.81, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.42 (d, *J* = 16.8 Hz, 1 H, 4-Ha), 2.50 (m, 2 H, 2-H), 2.71 (ddd, *J*= 16.8 Hz, 5.0 Hz, 2.0 Hz, 1 H, 4-Hb), 3.76 (m, 1 H, 6-Ha), 3.80 (m, 1 H, 6-Hb), 4.79 (t, *J* = 5.0 Hz, 1 H, 5-H), 5.73 (t, *J* = 1.6 H, 1-H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 46.9 (C-4), 48.6 (C-2), 69.6 (C-6), 72.2 (C-5), 100.5 (C-1), 204.5 (C=O).

4.3.6. 1,2:4,5-Di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (156)

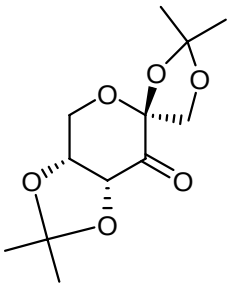


D-Fructose (36.00 g, 204.71 mmol) was suspended in acetone (700 mL), perchloric acid (60 %, 10 mL) and 2,2-dimethoxypropane (14.8 mL, 240.8 mmol) was added to a suspension at 0 °C (ice bath). After the reaction mixture was stirred under nitrogen at 0 °C for 7.5 h, concentrated ammonium hydroxide was added to pH 7-8 and the resulting solution was stirred for another 15 min. The solvent was removed under reduced pressure, and the solid residue was recrystallized from hexane-CH_2Cl_2 (4:1 v/v) to afford white needles of alcohol in 56 % isolated yield (30.32 g, 115.72 mmol).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 1.99 (d, J = 8.1 Hz, 1 H), 3.67 (dd, *J* = 8.1, 6.8 Hz, 1 H), 3.98 (d, *J* = 9.0 Hz, 1 H), 4.01 (dd, *J* = 13.2, 0.9 Hz, 1 H), 4.12 (dd, *J* = 13.2, 2.7 Hz, 1 H), 4.13 (dd, *J* = 6.8, 5.7 Hz, 1 H), 4.19 (d, *J* = 9.0 Hz, 1 H), 4.22 (ddd, *J* = 5.7, 2.7, 0.9 Hz, 1 H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 26.1 (CH_3), 26.4 (CH_3), 26.6 (CH_3), 28.1 (CH_3), 60.9 (C-6) 70.60 (C-3), 73.52 (C-7), 73.53 (C-5), 77.48 (C-6), 104.7 (C-2), 109.6 (C-8), 112.0 (C-9).

4.3.7. 1,2: 4,5-Di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (157)

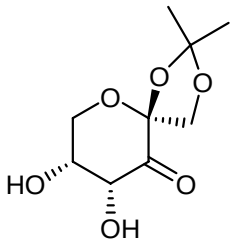


Alcohol (5.20 g, 20.00 mmol) was dissolved in dichloromethane (100 mL) and powdered 3 Å molecular sieves (22 g, activated at 180-200 °C under vacuum). PCC (11.64 g, 54.00 mmol) was added in portions over 15 min to the reaction mixture. The reaction mixture was stirred for 6 h under nitrogen. After TLC analysis, the reaction mixture was filtered off through celite and washed carefully with ether (200 mL). The filtrate was concentrated at reduced pressure to obtain residue which was purified by short silica gel column (hexane-ether, 1:1 v/v) to afford a white solid in 86% isolated yield. Crystallization was done with hexane CH_2Cl_2 to give white crystals of the ketone in 86 % yield (4.50 g, 17.45 mmol)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 6 H, 2(CH_3)$_2$), 1.46 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 4.00 (d, *J* = 9.5 Hz, 1 H), 4.12 (d, *J* = 13.4 Hz, 1 H), 4.39 (dd, *J* = 13.4, 2.2 Hz, 1 H), 4.55 (ddd, *J* = 5.7, 2.2, 1.0 Hz, 1 H), 4.61 (d, *J* = 9.5 Hz, 1 H), 4.73 (d, *J* = 5.7 Hz, 1 H),

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 25.9 (CH_3), 26.0 (CH_3), 26.4 (CH_3), 27.1 (CH_3),60.0 (C-6), 69.9 (C-4), 76.0 (C-7), 78.1 (C-5), 104.1 (C-9), 110.5 (C-8), 111.4 (C-2), 196.9 (CO).

4.3.8. 1,2-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (158)

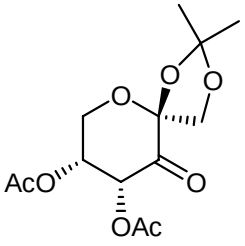


To a solution of ketone **157** (10.00 g, 38.80 mmol) in CH_3CN/H_2O (9/1) (130 mL) was added DDQ (0.91 g, 3.90 mmol) at room temperature. The reaction mixture was stirred at room temperature for 9 h. After the completion of the reaction (TLC monitored), the reaction mixture was concentrated and dissolved in EtOAc (100 mL). The organic solution was dried over sodium sulphate, filtered off and concentrated to give a residue which was purified by flash chromatography using hexane: ethyl acetate (1:0 to 1:1) to give diol as white solid in 75 % yield (6.50 g, 29.81 mmol).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 3H, CH_3), 1.54 (s, 3 H, CH_3), 3.99 (dd, *J* = 12.9, 2.4 Hz 1 H), 4.03 (d, *J* = 9.6 Hz, 1 H), 4.33 (d, J = 12.9 Hz, 1 H), 4.41 (m, 1 H), 4.71 (d, *J* = 9.5 Hz, 1 H), 4.74 (d, *J* = 4.0 Hz, 1 H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 26.1 (CH_3), 26.3 (CH_3), 63.2 (C-5), 69.5 (C-6), 73.8 (C-4), 74.1 (C-7), 104.3 (C-8), 113.5 (C-2), 198.9 (CO).

4.3.9. 4,5-Diacetyloxy-1,2-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (159)



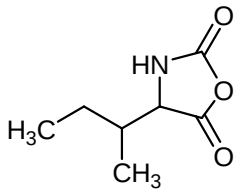
To a solution of diol (1.00 g, 4.58 mmol) and DMAP (120 mg, 0.93 mmol) in dry CH_2Cl_2 (42 mL) was added drop wise acetic anhydride (1.30 mL, 13.70 mmol) at 0 °C over a period of 20

min. Upon stirring at room temperature for 16 h (monitored by TLC), the reaction mixture was filtered through a short silica gel column. The filtrate was concentrated and the residue was purified by flash chromatography using hexane: ethyl acetate (1:1) to give ketone as white solid in 78% isolated yield (1.10 g, 3.64 mmol).

^{1}H-NMR (200 MHz, $CDCl_3$): 1.41 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3COO), 2.18 (s, 3 H, CH_3COO), 3.96 (dd, *J* = 13.2, 2.1 Hz 1 H), 3.99 (d, *J* = 9.6 Hz, 1 H), 4.44 (d, *J* = 13.2 Hz, 1 H), 4.70, (d, *J* = 9.6 Hz, 1 H), 5.60-5.62 (m, 1 H), 5.89 (d, *J* = 3.9 Hz, 1 H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 20.7 (CH_3COO), 21.1 (CH_3COO), 26.3 (CH_3), 26.7 (CH_3), 69.6 (C-6), 72.4 (C-4), 74.2 (C-5), 105.2 (C-7), 114.0 (C-8), 133 (C-2), 168.0 (COO), 182.1 (COO), 191.7 (CO)

4.3.10. L-Isoleucine-*N*-carboxyanhydride (166)

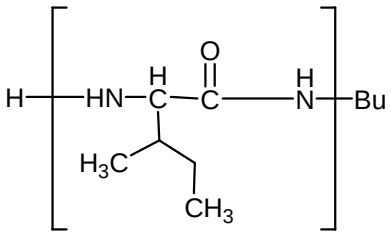


L-Isoleucine **(165)** (10.00 g, 76.23 mmol) and activated charcoal (0.30 g) were suspended in anhydrous tetrahydrofuran (100 mL). Trichloromethyl chloroformate (6.9 mL, 56.88 mmol) was added to the suspension with vigorous stirring. Stirring was continued and the temperature was gradually raised to 55 °C. After the complete dissolution of the amino acids, the solution was filtered off through celite placed on a glass filter. The filtrate was concentrated at 40 °C under reduced pressure to give pale yellow oil, which was crystallized from anhydrous hexane and crystallization was done twice from anhydrous diethyl ether-hexane to give colourless crystals of L-isoleucine-*N*-carboxyanhydride **(166)**.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.4 Hz, 3 H, 8-CH_3), 1.02 (d, *J* = 6.9, 3 H, 9-CH_3), 1.35 (m, 1 H, 7-Ha)**,** 1.50 (m, 1 H, 7-Hb), 1.94 (m, 1 H, 6-H), 4.29 (brs, 1 H, 4-H), 7.2 (br s, 1 H, NH)

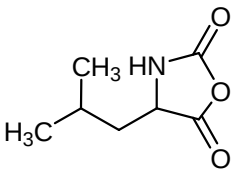
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 11.3 (C-8), 14.7 (C-9), 24.2 (C-7), 37.3 (C-6), 62.4 (C-4), 153.5 (CO, C-2), 168.9 (CO, C-5).

4.3.11. Poly L-isoleucine (167)



Freshly prepared L-isoleucin-*N*-carboxyanhydride **(166)** (4.00 g, 25.48 mmol) was dissolved in acetonitrile (100 mL) (dried over P_20_5). *n*-Butyl amin (0.25 mL, 2.54 mmol) was added to the solution and the reaction mixture was stirred for 4 days at room temperature until white solid appears. The solvent was removed under reduced pressure and the polymer collected was washed with diethyl ether and dried in vacuum.

4.3.12. L-Leucin-*N*-carboxyanhydride (169)



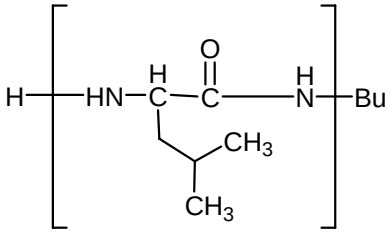
L-leucine **(168)** (10.00 g, 76.23 mmol) and activated charcoal (0.3 g) were suspended in tetrahydrofuran (100 mL). Trichloromethyl chloroformate (6.87 mL, 56.88 mmol) was then added to the suspension with vigorous stirring. Stirring was continued and the temperature was gradually raised to 55 °C. After the complete dissolution of the amino acids the solution was then filtered off through celite placed on a glass filter. The filtrate was concentrated at 40 °C under reduced pressure to give pale yellow oil, which was crystallized from anhydrous hexane and crystallization was done twice from anhydrous diethyl ether-hexane to give colourless crystals of the L-leucin-*N*-carboxyanhydride **(169)**.

Melting Point: 91-93 °C (Lit.[26] 88-89 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.98-1.09 (brs, 6 H, 8-CH_3, 9-CH_3), 1.79-184 (m, 3 H, 6-Ha, 6-Hb, 7-H) 1.80 (m, 1 H, 7-H), 4.38 (brs 1 H, 4-H), 7.32 (br s, 1 H, NH)

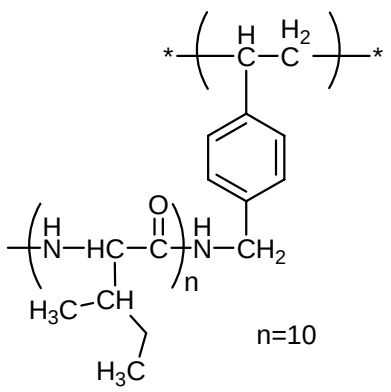
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 21.9 (C-7), 23.0 (C-8), 25.3 (C-9), 41.1 (C-6), 56.7 (C-4), 153.7 (CO, C-2), 170.7 (CO, C-5)

4.3.13. Poly-L-leucin (170)



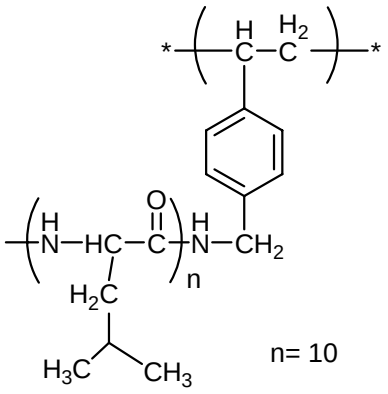
Freshly prepared L-Leucin-*N*-carboxyanhydride **(169)** (4.00 g, 25.48 mmol) was dissolved in 100 mL acetonitrile (dried over P_2O_5). *n*-Butyl amin (0.25 mL, 2.54 mmol) was added to the solution and the reaction mixture was stirred for 4 days at room temperature until white solid appears. The solvent was removed under reduced pressure and the polymer collected was washed with diethyl ether and dried in vacuum.

4.3.14. Immobilized poly-L-isoleucin (172)



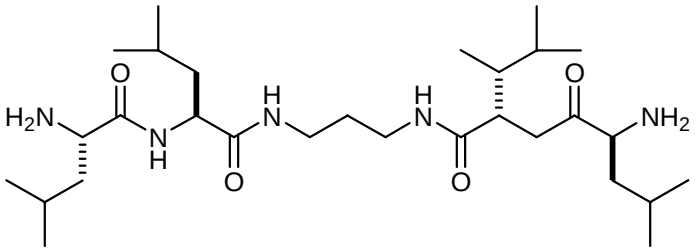
Aminomethylated polystyrene resin with 2 % divinyl benzene **171** (0.30 g, 1.10 mmol NH_2/g resin) was suspended in dry THF. The solution of freshly prepared L-isoleucine NCA **(166)** (6.00 g, 38.21 mmol) in THF (100 mL) was added to the suspension of polystyrene resin **171**. The solution was stirred at room temperature for 40 h. The resulting polymer beads were filtered off and washed with THF and methanol. The polymer was dried at 40 °C under vacuum for 24 h.

4.3.15. Immobilized-Poly-L-leucin (173)



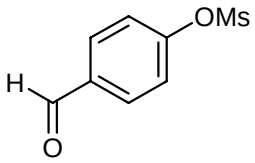
To the suspension of amino methylated polystyrene resin with 2 % divinyl benzene (0.3 g, 1.1 mmol NH_2/g resin) in dry THF was added a THF solution of freshly prepared L -leucine NCA (6 g, 38.2 mmol). The solution was stirred at room temperature for 40 h. The resulting polymer beads were filtered and washed with THF and methanol. The polymer **173** was dried at 40 °C under vacuum for 24 h.

4.3.16. Preparation of hot poly-L-leucine (174)



Freshly prepared L-leucine *N*-carboxyanhydride (10.00 g, 63.60 mmol) was dissolved in anhydrous toluene (150 mL) under argon at room temperature. The initiator 1,3-diaminopropane (0.071 g, 0.080 mL, 0.96mmol) was added to this homogeneous solution. The reaction mixture was gradually heated to 80 °C for 2 h. During this period CO_2 gas was liberated and stirring was maintained for 1 h at 80 °C. After cooling down to 60 °C, methanol (100 mL) was added and the heterogeneous reaction mixture was stirred for 1 h at 60 °C before the solid was filtered off. The polymer **174** was dried at 40 °C under vacuum for 24 h.

4.3.17. 4-Methansulfonyloxybenzaldehyde (85)



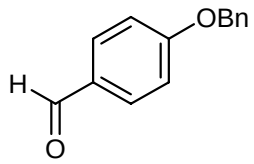
To a solution of 4-hydroxybenzaldehyde **(84)** (1.21 g, 9.80 mmol) in dry pyridine (10 mL), freshly distilled methanesulfonyl chloride (1.95 mL, 20.00 mmol) was added under ice bath. The reaction mixture was cooled to room temperature and was stirred for 4 h at room temperature. The mixture was poured into 10 % HCl (10 mL) solution and was extracted with ethyl acetate (3×15). The organic phase was washed with solution of sodium bicarbonate (10 mL) and brine (15 mL) and dried over $MgSO_4$. After filtration, the solvent was concentrated under reduced pressure to give oil which was purified by column chromatography to afford yellow crystals in 75 % yield.

Melting Point: 63 °C (Lit.[113] 60–61 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.25 (s, 3H, CH_3), 7.46 (d, *J* = 8.5 Hz, 2 H, 3, 5-H), 7.76 (d, *J* = 8.5 Hz, 1 H, 2, 6-H), 10.01 (s, 1 H, CHO).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 38.4 (CH_3), 123.0 (C-3, C-5), 132.0 (C-2, C-6), 135.4 (C-1), 153.7 (C-7), 191.0 (CHO).

4.3.18. 4-Benzyloxybenzaldehyde (87)



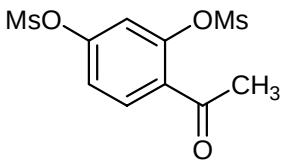
To a stirred suspension of K_2CO_3 (3.40 g, 24.60 mmol) in dry DMF (20 mL) at room temperature was added 4-hydroxybenzaldehyde **84** (2.00 g, 16.39 mmol) and TBAI (20 mg).The mixture was stirred for 30 min and then benzyl bromide (2.90 g, 2 mL, 16.66 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with water (5 mL) and extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with water (2 ×100 mL), brine and dried (Na_2SO_4). After filtration, the solvent was removed to give residue which was purified by silica gel column chromatography using PE/EtOAc (9:1) to give 4-benzyloxybenzaldehyde **87** as white solid in 99 % yield (3.45 g, 16.2 mmol).

Melting Point: 78 °C (Lit.[115] 78-79 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.16 (s, 2 H, OCH_2Ph), 7.1 (d, *J* = 8.1 Hz, 2 H, 3, 5-H), 7.19-7.30 (m, 5 H, Ar-H), 7.85 (d, *J* = 8.1 Hz, 2 H, 2, 6-H), 9.9 (s, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 71.3 (OCH_2Ph), 113.9 (3, 5-H), 127.7, 129.1 (C-1), 129.7, 130.5, 140.8 (C-Ar), 165.8 (C-4), 192.1 (CHO).

4.3.19. 2.4-Dimethansulfonyloxyacetophenone (89)



To a solution of 2,4-dihydroxyacetophenone **88** (1.20 g, 9.80 mmol) in dry pyridine (10 mL), freshly distilled methanesulfonyl chloride (1.95 mL, 20 mmol) was added under ice bath. The reaction mixture was cooled to room temperature was stirred for 4h at room temperature The mixture was poured into 10 % HCl (20 mL) solution and was extracted with ethyl acetate (3×25 mL). The organic phase was washed with solution of sodium bicarbonate (20 mL) and brine (20 mL) and dried over $MgSO_4$. After filtration, the solvent was concentrated under reduced pressure to give oil which was purified by column chromatography to afford yellow crystals of dimesylated acetophenone **89** in 82 % yield (2.50 g, 8.11 mmol).

Melting Point: 71-72 °C.

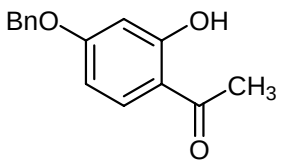
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, CH_3CO), 3.21 (s, 3 H, 2-O-SO_2CH_3), 3.26 (s, 3 H, 4-O-SO_2CH_3), 7.30 (d, *J* = 2.1 Hz, 3-H), 7.36 (dd, *J* = 8.0, 2.1 Hz, 5-H), 7.79 (d, *J* = 8.0 Hz, 1 H, 6-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 30.5 (CH_3CO), 38.3 (OSO_2CH_3), 38.8 (OSO_2CH_3), 118.2 (C-3), 121.3 (C-5), 132.1 (C-2, 4), 147.3 (C-1), 151.7 (C-6), 197.0 (CO).

MS (EI, 70 eV): *m/z* (%) = 308 (84) [M^+], 293 (99), 230 (12), 214 (100), 212 (32), 151 (12), 137 (70), 123 (21), 78 (38), 42 (46).

HREIMS: $C_{10}H_{12}O_7S_2$ 308.00244 (Calculated)
308.00252 (Found)

4.3.20. 4-Benzyloxy-2-dihydroxyacetophenone (91)



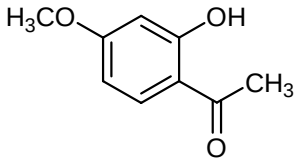
The mixture of 2,4-dihydroxyacetophenone **88** (3 g, 20 mmol), potassium carbonate (3.34 g, 24.00 mmol) were added in dry acetonitrile (40 mL) and was refluxed for 1.5 h. Benzyl bromide (2.85 mL, 24.00 mmol) in acetonitrile (10 mL) was then dropped to reaction mixture in a period of 25 min. The reaction mixture was refluxed for further 30 min and monitored by TLC. After cooling to room temperature, dichloromethane (150 mL) was added and washed with 5 % aqueous sodium hydroxide (50 mL) and three times with water (50 mL). The organic layer was dried with anhydrous sodium sulphate. After filtration, the solvent was removed under vacuum. The crude product was crystallized from acetone: hexane (1:2).

Melting Point: 115-116 °C (Lit.[116] 116-117 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 5.13 (s, 2 H, O*CH*$_2$Ph), 6.54 (s, 1 H, 3-H), 6.59 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.30-748 (m, 5 H, Ar-H), 7.70 (d, *J* = 7.9 Hz, 1 H, 6-H) 12.82 (s, 1 H, OH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 30.6 (CH_3), 71.1 (O*CH*$_2$Ph), 101.2 (C-3), 106.3 (C-5), 112.9 (C-6), 114.3 (C-1), 127.3, 129.0, 131.9 142.3 (C-Ar), 161.3 (C-2), 167.4 (C-4), 198.3 (CO).

4.3.21. 2-Hydroxy-4-methoxyacetophenone (93)



To a solution of 2,4-dihydroxyacetophenone **88** (3.00 g, 20.00 mmol), in acetone (50 mL) was added dimethyl sulfate (2.1 mL, 21.44 mmol) and potassium carbonate (4.1 g, 30.30 mmol). The mixture was stirred for 5 h. After completion of reaction (monitored by TLC) the solid

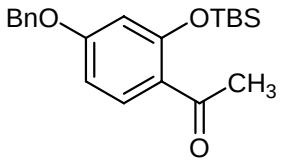
was filtered off and the evaporated. The residue obtained was subjected to chromatography over silica gel column using mixtures of petroleum ether–ethyl acetate (90:10) to give **93** (3 g, 91 %) as white solid.

Melting Point: 51 °C (Lit.[117] 49-50 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.38 (s, 1 H, 3'-Ar-H), 6.42 (d, *J* = 8.6, Hz, 1 H, 5'-H Ar), 7.61 (d, *J* = 8.6 Hz, 1 H, 6'-H Ar), 12.69 (s, 1H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 26.52 (CH_3CO), 55.8 (OCH_3), 101.2 (C-3), 107.8 (C-5), 114.2 (C-1), 132.7 (C-6), 165.5 (C-2), 166.4 (C-4), 202.9 (CO).

4.3.22. 4-Benzyloxy-2-*tert*-butyldimethylsilyloxyacetophenon (95)



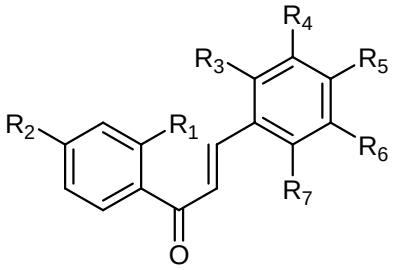
To a solution containing 2-hydroxy-4-benzyloxyacetophenon **91** (5.00 g, 20.60 mmol) in anhydrous DMF (150 mL) was added imidazole (4.00 g, 58.8 mmol) and TBDMSCl (5 g, 33.10 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was then poured into water (100 mL) and extracted with EtOAc (3×50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column using ethyl acetate: petrol ether (1:9) to give yellow solid of acetophenone **95** in 90 % yield.

Melting Point: 96-97 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.26 (s, 6 H, Si $(CH_3)_2$), 1.03 (s, 9 H, $SiC(CH_3)_3$), 2.61 (s, 3 H, $COCH_3$), 5.12 (s, 2 H, OCH_2Ph), 6.44 (d, *J* = 2.3 1 H, 3-H), 6.68 (dd, *J* = 8.8, 2.3 Hz, 1 H, 5-H), 7.30-7.47 (m, 5 H, Ar-H), 7.77 (d, *J* = 8.8 Hz, 1 H, 6-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -6.1 (Si $(CH_3)_2$), 18.9 (Si*C*$(CH_3)_3$), 26.33 (SiC(*CH_3)$_3$*), 31.7 (CH_3), 70.5 (O*CH_2*Ph), 106.9 (C-3), 108.4 (C-5), 124.4 (C-1), 127.7, 128.6, 129.1, 132.5, 136.7(C-6), 157.4 (C-2), 163.2 (C-4), 198.9 (CO).

4.3.23. General procedure for synthesis of methoxy chalcones



108 R_1-R_7 = H

109 R_1 = OH, R_2-R_7 = H

110 $R_2 = R_3 = R_6 = OCH_3$, $R_1 = R_4 = R_5 = R_7 = H$

111 $R_2 = R_3 = R_5 = R_7 = OCH3$, $R_1 = R_4 = R_6 = H$

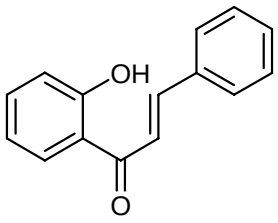
112 $R_2 = R_4 = R_5 = OCH_3$, $R_1 = OH$, $R_3 = R_6 = R_7 = H$

113 $R_2 = R_3 = R_4 = R_5 = OCH_3$, $R_1 = OH$, $R_6 = R_7 = H$

114 $R_2 = R_5 = OCH_3$, $R_1 = OH$, $R_3 = R_4 = R_6 = R_7 = H$

A mixture of equimolar amounts of corresponding acetophenones **95** and **98-100** (6.02 mmol) and benzaldehydes **101-107** (6.02 mmol) in 25 mL ethyl alcohol was warmed at 50 °C. The 50 % aqueous solution of NaOH (6ml) was added to the reaction mixture drop wise in a period of 30min. The reaction mixture was further stirred for 5 h at 50 °C. The stirring was closed and the reaction mixture was stayed for 24 h at room temperature. The yellow precipitates were formed. The reaction mixture was diluted with ice cold water (150 mL) until the yellow solid dissolved. The reaction mixture was acidified with diluted HCl (20 mL), maintaining the temperature at 0 °C. The precipitates formed are filtered off, dried and crystallized with aqueous ethanol to give corresponding chalcones **108-114**.

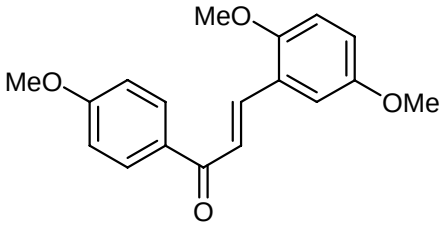
2'-Hydroxychalcone (107)



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.95-7.99 (m, 10 H, α-H, Ar-H), 8.01 (d, *J* = 15.5, 1 H, β-H), 13.9 (s, 1 H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 119.0 (3'-H), 119.2 (C-α), 120.4, 120.5, 129.0, 129.4, 130.0, 131.3, 135.0, 136.8 (C-Ar) 145.9 (C-β), 164.0 (C-2'), 194.1 (CO).

2,5,4'-Trimethoxychalcone (108)

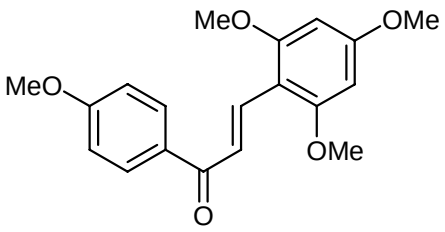


Melting Point: 102–103 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 3.H, OCH_3), 3.79 (s, 3.H, OCH_3), 3.80 (s, 3.H, OCH_3), 6.75-7.15 (m, 3 H, 3, 4, 6-H), 7.63 (d, *J* = 15.9 Hz, 1 H, α-H), 7.93 (dd, *J* = 8.8, 2.3 Hz, 2H, 3',5'-H), 7.98 (dd, *J* = 8.8, 2.3 Hz, 2 H, 2',6'-H), 8.11 (d, *J* = 15.9 Hz, 1 H, β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.9 (OCH_3), 56.1 (OCH_3), 56.4 (OCH_3), 112.3 (C-6), 114.7 (C-5'), 121.4 (C-α), 122.2 (C-2'), 131.3 (C-1'), 132.2 (C-6') 135.6 (C-β), 162.0 (C-2), 163.2 (C-5), 163.3 (C-4'), 191.1(CO).

2,4,6,4'-Tetramethoxychalcone (109)

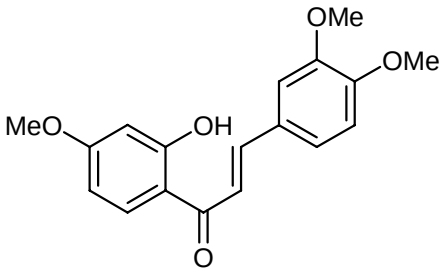


Melting Point: 148-150 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.86 (s, 3.H, OCH_3), 3.88 (s, 3.H, OCH_3), 3.91 (s, 6.H, 2 OCH_3), 6.14 (s, 2 H, 3,5-H), 6.14 (s, 2 H, 3,5-H), 6.96, (dd, *J* = 8.9, 2.0 Hz, 2 H, 3',5'-H) 7.90 (d, *J* = 15.9 Hz, 1 H, α-H), 8.06 (dd, *J* = 8.9, 2.0 Hz, 2H, 2',6'-H), 7.90 (d, *J* = 15.9 Hz, 1 H, β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.8 (OCH_3), 56.2 (OCH_3), 90.9 (C-3, C-5), 107.0 (C-1), 113.9 (C-3', C-5'), 122.2 (C-α), 131.0 (C-1'), 132.5 (C-6), 135.6 (C-β), 162.0 (C-2, C-6), 163.2 (C-4), 163.3 (C-4'), 190.8 (CO).

3,4,4'-Trimethoxy-2'-hydroxychalcone (110)

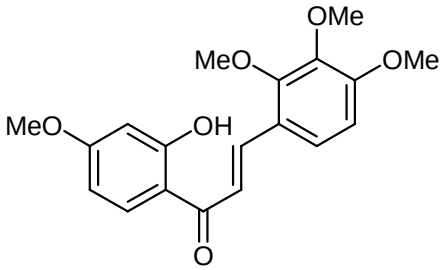


Melting Point: 154-155 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.89 (s, 3.H, OCH_3), 3.97 (s, 3.H, OCH_3), 4.0 (s, 3.H, OCH_3), 6.54 (dd, *J* = 8.8, 2.2, 1 H, 5'-H), 6.67 (d, *J* = 2.2, 1 H, 3'-H), 6.85 (d, *J* = 2.0, 1 H, 2-H), 6.89 (d, *J* = 8.3, 1 H, 5-H), 6.98 (dd, *J* = 8.3, 2.0, 1 H, 6-H), 7.43 (d, *J* = 15.9 Hz, 1 H, α-H),7.88 (d, *J* = 8.8, 1 H, 6'-H, 7.92 (d, *J* = 15.9 Hz, 1 H, β-H), 13.70 (s, 1 H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ =56.0 (OCH_3), 56.4 (OCH_3), 101,4 (C-3'), 108.0 (C-5'), 110.6 (C-2), 111.5 (C-5), 114.5 (C-1'), 118.4 (C-6), 123.7 (C-α), 128.2 (C-1), 131.5 (C-6'), 145.0 (C-β), 152.0 (C-2'), 166.4 (C-4), 167.0 (C-4'), 192.1(CO).

2,3,4,4'-Tetramethoxy-2'-hydroxychalcone (111)

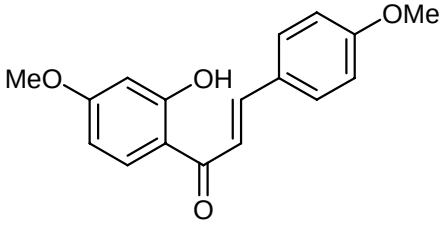


Melting Point: 142-143 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 3.H, OCH_3), 3.92 (s, 3.H, OCH_3), 3.94 (s, 3.H, OCH_3), 3.99 (s, 3.H, OCH_3), 6.49 (s, 1 H, 3'-H), 6.50 (d, *J* = 8.9 Hz, 1 H, 5'-H), 6.73 (d, *J* = 8.8, Hz 1 H, 5-H), 7.38 (d, *J* = 8.8 Hz, 1 H, 6-H), 7.64 (d, *J* = 15.6 Hz, 1 H, α-H), 7.84 (d, *J* = 8.9, Hz 1 H, 6'-H), 8.07 (d, *J* = 15.9 Hz, 1 H, β-H), 13.74 (s, 1 H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ =55.9 (OCH_3), 56.5 (OCH_3), 61.3 (OCH_3), 61.8 (OCH_3), 101.4 (C-3'), 107.9 (C-5'), 108.0 (C-1), 114.6 (C-1'), 119.8 (C-6), 122.3 (C-α), 124.6 (C-6'), 131.58 (C-4'), 140.2 (C-3), 142.9 (C-β), 154.33 (C-2), 156.3 (C-4), 166.3 (C-2'), 167.0 (C-4'), 192.6 (CO).

4,4'-Dimethoxy-2'-hydroxychalcone (112)

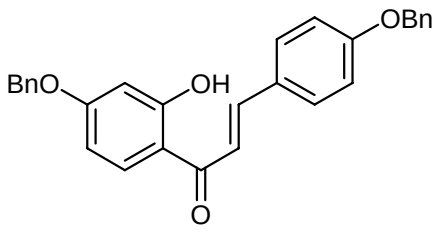


Melting Point: 91-93 °C (Lit.[121] 88-89 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 6 H, OCH_3), 6.49 (s, 1 H, 3'-H), 6.53 (d, *J* = 8.8, 1 H, 5'-H), 6.98 (d, *J* = 8.8 Hz, 2 H, 3, 5-H), 7.51 (d, *J* = 15.6 Hz, 1 H, α-H), 7.67 (d, *J* = 8.8 Hz, 2 H, 2, 6-H), 7.87 (d, *J* = 15.9 Hz, 1 H, β-H), 7.97 (d, *J* = 8.8, 1 H, 6'-H), 13.61 (s, 1 H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.8 (OCH_3), 55.9 (OCH_3), 101.4, (C-3') 108.0 (C-5'), 114.5 (C-3), 114.8 (C-1'), 118.1 (C-α), 127.9 (C-2), 130.7 (C-1), 131.5 (C-6'), 144.6 (C-β), 162.2 (C-4), 166.4 (C-2'), 167.0 (C-4'), 192.2 (CO).

4.3.24. 1-(4-Benzyloxy-2-hydroxyphenyl)-3-(4-benzyloxyphenyl)propenone (113)



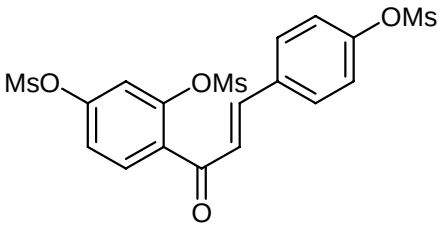
To a stirred suspension containing acetophenone **93** (5.0 g, 20.60 mmol) and aldehyde **90** (4.40 g , 41.20 mmol) in 80 mL of MeOH at 60 °C was added slowly 60 mL of 40 % (w/v) KOH in MeOH. The reaction mixture was heated to reflux overnight. After the bright yellow precipitates were formed, the reaction mixture was then cooled to room temperature, diluted with H_2O (200 mL) and extracted with ethyl acetate (3×500-mL). The combined organic layer was washed with H_2O (250-mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the chalcone as a bright yellow solid in 94 % yield (8.50 g, 19.4 mmol)

Melting Point: 136-137 °C (Lit.[41] 140-142 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = δ 5.15 (s, 2 H, OCH_2Ph), 5.16 (s, 2 H, OCH_2Ph), 6.60 (d, *J* = 2.1 Hz, 1 H, 3'-H), 6.73 (dd, *J* = 8.5, 2.1 Hz, 5'-H), 7.03 (d, *J* = 8.5 Hz, 6-H), 7.05 (d, *J* = 8.4 Hz, 2 H, 3, 5-H), 7.29-7.46 (m, 12 H, α-H, β-H, Ar-H), 7.64 (d, *J* = 8.4 Hz, 2 H, 2, 6-H), 13.62 (s, 1 H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.4 (O*CH*$_2$Ph), 70.5 (O*CH*$_2$Ph), 102.3 (C-3'), 108.4 (C-5'), 114.6 (C-3), 115.6 (C-1'), 118.1 (C-α), 127.8, 127.8, 128.0, 128.5, 128.6, 129.0, 130.7, 131.5, 136.2, 136.6 (C-Ar), 144.5 (C-β), 165.4 (C-4), 166.8 (C-2'), 192.1 (CO).

4.3.25. 2'4,4'-Trimethansulfonyloxychalcone (114)



To a stirred solution of 2,4,4'-trihydroxychalcone **115** (1.2 g, 9.80 mmol) in dry pyridine(10 mL), freshly distilled methanesulfonyl chloride (1.95 mL, 20 mmol) was added under ice bath. The reaction mixture was cooled to room temperature and was stirred for 10 h at room temperature. The reaction mixture was poured into 10 % HCl (20 mL) solution and was extracted with ethyl acetate (3 ×25 mL). The organic phase was washed with solution of sodium bicarbonate (15 mL) and brine (15 mL) and dried over $MgSO_4$. After filtration, the solvent was concentrated under reduced pressure to give oil which was purified by column chromatography to afford dark brown solid in 82 % yield (3.95 g, 8.06 mmol).
Melting Point: 106-107 °C.

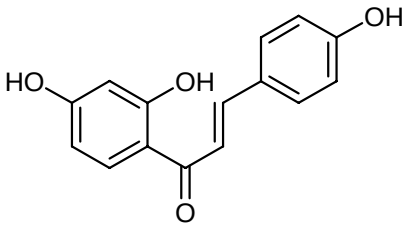
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.19 (s, 6H, 4, 4'-OSO_2CH_3), 3.25 (s, 3 H, 2'-OSO_2CH_3), 7.21 (d, *J* = 15.9 Hz, 1 H, α-H), 7.30-7.68 (m, 7 H, 3', 5', 2, 3, 5, 6, β-H), 7.74 (d, *J* = 8.5 Hz, 1 H, 6'-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 38.1 (OSO_2CH_3), 38.4 (OSO_2CH_3), 38.7 (OSO_2CH_3), 118.1 (C-3'), 121.5 (C-5'), 123.1 (C-3), 126.4 (C-α), 130.7 (C-2), 132.0 (C-1), 132.5 (C-1'), 133.8, (C-6'), 144.9 (C-β), 151.2 (C-4), 151.5 (C-2'), 171.5 (C-4'), 189.9 (CO).

MS (EI, 70 eV): *m/z* (%) = 490 (12) [M^+], 410 (100), 382 (10), 331 (45), 305 (14), 292 (10), 253 (18), 225 (37), 197 (18), 147 (9), 137 (16), 78 (22), 63 (10).

HREIMS: $C_{18}H_{18}O_{10}S_3$ 490.00620 (Calculated)
490.00589 (Found)

4.3.26. 2, 4, 4'-Trihydroxychalcone (115)

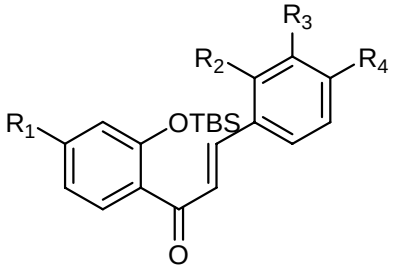


2,4-dihydroxyophenone (2.5 g, 16.40 mmol) and benzaldehyde (2.0 g, 16.40 mmol) were dissolved in ethanol (30 mL). Aqueous KOH (60 %; 30 mL) was added drop wise and the mixture was allowed to react at 60 °C for 3 days. Ice was added to the reaction mixture and acidified with dil. HCl (20 mL). The mixture was extracted three times with ethyl acetate (3 ×25 mL) and washed with water. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The residue obtained was subjected to column chromatography to afford the yellow crystals in 50 % yield.

Melting Point: 173-175 °C (Lit.[144] 179-181 °C).
^{1}H-NMR (200 MHz, $CDCl_3$): δ =6.35-6.60 (m, 2 H, 3',5'H), 6.95 (d, *J* = 9 Hz, 2 H, 3, 5-H), 7.75 (d, *J* = 9 Hz, 2H, 2, 6-H), 7.85 (s, 2 H, α-H, β-H), 8.10 (d, *J* = 9 Hz, 1 H, 6'-H), 13.67 (s, 1 H, 2'-OH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ =103.3 (C-3'), 108.2 (C-5'), 114.1 (C-1'), 116,3 (C-3), 117.8 (C-α), 127.1 (C-2), 131.3 (C-1), 132.8 (C-6'), 144.7 (C-β), 160.5 (C-4), 165.0 (C-2'), 167.1 (C-4'), 192.3 (CO).

4.3.27. General procedure for TBS-protection of chalcones (117-119)



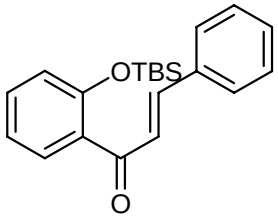
117 R_1-R_4 = H

118 R_1-R_4 = OCH3

119 R_1=R_4 = OCH3
R_2=R_4= H

To a solution containing 2'-hydroxy-chalcones **109, 113, 114** (20.6 mmol) in anhyd DMF (150 mL) was added imidazole (58.8 mmol) and TBDMSCl (33.1 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was then poured into of H_2O (100 mL) and extracted with three times with ethyl acetate (50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column using ethyl acetate: petrolether (1:7) to give corresponding corresponding TBS-protected chalcones **117, 118, 119**.

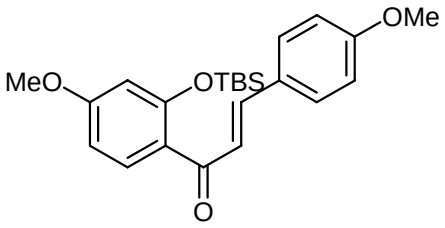
2-*tert*-Butyldimethylsilyloxychalcone (117)



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.21 (s, 6 H, 2(Si-CH_3), 0.94 (s, 9 H, C(CH_3)$_3$), 6.92-7.71 (m, 11 H, α-H, β-H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.80 (Si-CH_3), 18.59 (*C*(CH_3)$_3$, 26.0 ((C(*CH*$_3$)$_3$), 120.8 (C-2), 121.9 (C-5'), 127.5 (C-1'), 128.8 (C-3), 129.2 (C-α), 130.6 (C-1), 130.6 (C-6), 132.8 (C-3'), 135.3 (C-4), 143.6 (C-β), 154.4 (C-2'), 194.2(CO).

4,4'-Dimethoxy-2-*tert*-butyldimethylsilyloxychalcone (118)

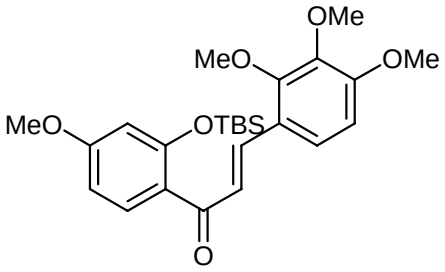


Melting Point: 79-80 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 6 H, Si-$(CH_3)_2$), 0.91 (s, 9 H, C$(CH_3)_3$), 3.82 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 6.40 (d, *J* = 2.4 Hz, 1 H, 3'-H), 6.60 (dd, *J* = 8.7, 2.4 Hz1 H, 5'-H), 6.98 (dd, *J* = 8.8, 2.0 Hz, 2 H, 3, 5-H), 7.30 (d, *J* = 15.8 Hz, 1 H, α-H), 7.53 (dd, *J* = 8.8, 2.0 Hz, 2 H, 2, 6-H), 7.61 (d, *J* = 8.7, 1 H, 6'-H), 7.63 (d, *J* = 15.9 Hz, 1 H, β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -4.1 (Si-CH_3), 18.2 ($C(CH_3)_3$, 25.7 (($C(CH_3)_3$), 55.3 (OCH_3), 55.4 (OCH_3), 106.3 (C-3'), 107.1 (C-5'), 114.2 (C-3), 125.1 (C-α), 125.6 (C-1'), 127.9(C-2),, 130.0 (C-1), 132.1(C-6'), 142.0 (C-β), 156.0(C-4), 161.2(C-2'), 163.2 (C-4'), 191.8 (CO).

2,3,4,4'-Tetramethoxy-2-*tert*-butyldimethylsilyloxychalcone (119)

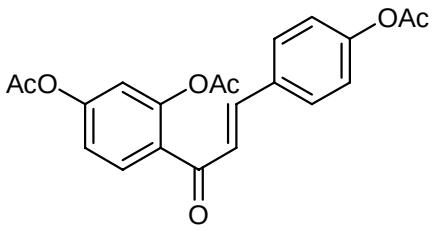


Melting Point: 138-140 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 6 H, Si-$(CH_3)_2$), 0.91 (s, 9 H, C$(CH_3)_3$), 3.82 (s, 3 H, OCH_3), 3.87 (s, 6 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.1 (d, *J* = 2.3 Hz, 1 H, 3'-H), 6.61 (dd, *J* = 8.7, 2.3 Hz1 H, 5'-H), 6.67 (d, *J* = 8.9, Hz, 2 H, 3, 5-H), 7.31 (d, *J* = 16.0 Hz, 1 H, α-H), 7.53 (dd, *J* = 8.9 Hz, 2 H, 2, 6-H),7.61 (d, *J* = 8.7, 1 H, 6'-H), 7.93 (d, *J* = 16.0 Hz, 1 H, β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.8 (Si-CH_3), 18.6 ($C(CH_3)_3$, 26.1 (($C(CH_3)_3$), 55.7 (OCH_3), 56.4 (OCH_3), 61.2 (OCH_3), 61.9 (OCH_3), 106.7 (C-3'), 107.5 (C-5'), 107.9 (C-5), 122.6 (C-1'), 123.3, 126.1 (C-α), 126.7 (C-1), 132.5 (C-6), 137.5 (C-3), 142.7 (C-β), 154.0 (C-2), 155.7 (C-4), 156.3 (C-2'), 163.5 (C-4'), 192.4 (CO).

4.3.28. 4,2',4'-Triacetyloxychalcone (120)



To a solution of 2',4,4'- trihydroxychalcone **115** (300 mg, 1.17 mmol) in pyridine (10 mL) was added acetic anhydride (1 mL, 10.53 mmol) at 0 °C drop wise over a period of 10 min. The reaction mixture was allowed to stir for 4 h at room temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice cold 10 % HCl solution (25 mL). The mixture was extracted with ethyl acetate (3×25). The organic phase was washed with solution of sodium bicarbonate (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give oil which was purified by column chromatography to afford yellow crystals in 85 % yield.

Melting Point: 88-90 °C.

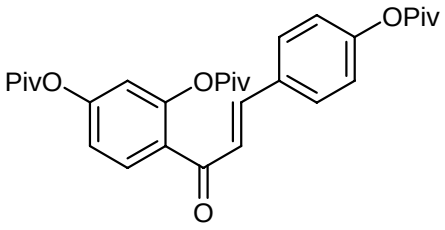
^{1}H-NMR (200 MHz, $CDCl_3$): δ =2.17 (s, 3H, 2'-$OCOCH_3$), 2.29 (s, 3H, 4-$OCOCH_3$), 2.30 (s, 6H, 4'-$(OCOCH_3)_2$), 7.02 (d, J = 2.2 Hz, 1 H, 3'-H), 7.10-7.18 (m, 4 H, 3, 5, 5',α-H), 7.50-7.61 (m, 3.H, 2, 6, β-H), 7.76(d, J = 8.5 Hz, 1 H, 6'-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 21.2 (CH_3COO), 21.4 (CH_3COO), 117.5 (C-3'), 119.6 (C-5'), 122.7 (C-α), 125.4 (C-3), 128.8 (C-1'), 129.9 (C-2), 131.1 (C-1), 132.5(C-6'), 144.5 (C-β), 150.0 (C-4), 152.9 (C-2'), 153.8 (C-4'), 168.9 (COO), 169.3 (COO), 169.4 (COO), 190.5 (CO).

MS (EI, 70 eV): *m/z* (%) = 382 (19) [M^+], 340 (36), 298 (50), 257 (72), 239 (12), 199 (9), 180 (14), 163 (26), 138 (74), 121 (67), 107 (20), 91 (10), 60 (11), 43 (100).

HREIMS:	$C_{21}H_{18}O_7$	382.10526	(Calculated)
		382.10510	(Found)

4.3.29. 4,2',4'-Triapivaloyloxychalcone (121)



To a stirred mixture of 2',4,4'- trihydroxychalcone **115** (300 mg, 1.17 mmol), DMAP (28 mg, 0.234 mmol) and pyridine (5 mL), was added a solution of pivaloyl chloride (1.29 mL, 10.53 mmol) in CH_2Cl_2 (2 mL) drop wise at 0 °C. The reaction mixture was allowed to stir for 24 h at room temperature. The reaction mixture was quenched with ice cold water and the extracted with CH_2CL_2 (2×15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give oil in 65 % yield.

Melting Point: 101-102 °C.

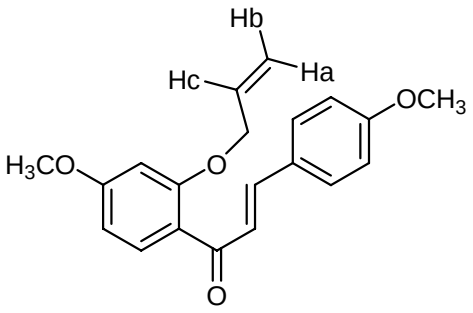
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.26 (s, 9 H, 2'-C(CH_3)$_3$), 1.36 (s, 9 H, 4-C(CH_3)$_3$), 1.39 (s, 9 H, 4'-C(CH_3)$_3$), 6.92-7.17 (m, 5 H, 3', 5', 3, 5, α-H), 7.49-7.72 (m, 4 H, 2, 6, 6',β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 27.3 (C(CH_3)$_3$), 27.4 (C(CH_3)$_3$),, 39.4 (C(CH_3)$_3$), 39.5 (C(CH_3)$_3$), 117.2 (C-3'), 119.4 (C-5'), 122.6 (C-3), 126.1 (α-C), 130.0 (C-1'), 130.5 (C-2), 132.2 (C-6'), 144.9 (β-C), 150.0 (C-4), 153.3 (C-2'), 153.9 (C-4'), 176.7 (COO), 177.1(COO), 191.5 (CO).

MS (EI, 70 eV): *m/z* (%) = 508 (86) [M^+], 424 (85), 423 (64), 340 (82), 323 (8), 257 (14), 256 (22), 227 (27), 163 (6), 137 (17), 107 (6), 85 (90), 57 (100).

HREIMS: $C_{30}H_{36}O_7$ 508.24609 (Calculated)
508.24624 (Found)

4.3.30. 2'-Allyloxy-4,4'-dimethoxychalcone (122)



124

Alumina was mixed with Potassium fluoride in water, and then the water was removed at 50-60 °C in a rotary evaporator. This impregnated alumina was further dried in a vacuum drying oven for several hours at 75°C. The typical alumina reagent used for alkylation pf phenols and alcohols was prepared at the weight ratio of 2:3 which corresponds to 1.15 mol of KF on 100 g of alumina.

A mixture of 1-[2'-Hydroxy-4-methoxyphenyl]-3-[4-methoxyphenyl]propen-1-one **112** (2.00 g, 7.00 mmol), allyl bromide (1.27 g, 1 mL, 10.50 mmol), and 40% potassium fluoride alumina (5.00 g, 35.00 mmol of KF) in 25 mL of CH_3CN (20 mL) was magnetically stirred at room temperature for 4 h. The solid material was filtered and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to afford yellow residue. Purification of the the residue was done by flash chromatography using petroleum ether-ethyl acetate (5:1) to afford yellow solid in 85 % yield.

Melting Point: 73-74 °C.

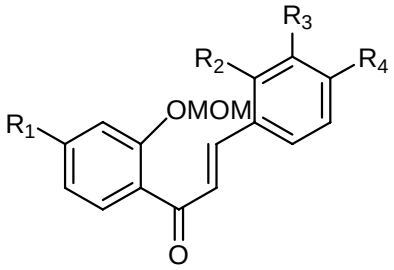
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.65 (dd, *J* = 5.0, 1.0 Hz, 2 H, CH_2), 5.32 (dd, *J* = 10.3, 1.3, 1 H, Ha), 5.47 (dd, *J* = 17.3, 1.3, 1 H, H_b), 5.99-6.16 (m, 1H, H_c), 6.50-6.62 (m, 2H, 3'-H, 5'-H), 6.91 (d, *J* = 8.7 Hz, 2 H, 3, 5-H), 7.43-7.66 (m, 3 H, 2, 6, α-H), 7.78 (d, *J* = 8.9 Hz, 1 H, 6'-H), 7.82 (d, *J* = 15.5 Hz, 1 H, β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 55.9 (OCH_3), 100.1 (C-3'), 106.1 (C-5'), 118.3 (C-3), 123.1 (C-α), 125.5 (C-1'), 128.5 (C-2), 130.4 (C-1), 133.2(C-6'),, 142.0 (C-β), 159.6 (C-4), 161.6(C-2'), 164.3 (C-4'), 190.8 (CO).

MS (EI, 70 eV): *m/z* (%) = 324 (50) [M^+], 283 (16), 227 (26), 191 (30), 151 (100), 121 (82), 83 (34), 41 (72), 28 (36).

HREIMS:	$C_{20}H_{20}O_4$	324.13617	(Calculated)
		324.13541	(Found)

4.3.31. General procedure for MOM-protected chalcones



123 R_1-R_4 = H

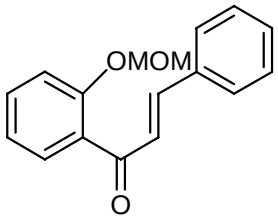
124 R_1-R_4 = OCH_3

125 R_1=R_4 = OCH3
R_2=R_4= H

126 R_1=R_4 = OBn
R_2=R_4= H

A mixture of 2'-hydroxylchalcones **107, 111, 112** and **113** (1.00 mmol), 1 N NaOH (10 mL) and CH_2Cl_2 (10 mL) was stirred at room temperature for 20 min. To this mixture was added tetrabutyl ammonium chloride (10 mg, 0.10 mmol) and stirred for another 20 min. A solution of methoxy methyl chloride (0.2 mL, 2.7 mmol) in CH_2Cl_2 (1 mL) was then added to the reaction mixture. The reaction mixture was stirred at room temperature for 4-8 h. The organic phase was washed with water (15 mL), dried over Na_2SO_4 and filtered off. The filtrate was concentrated under reduced pressure to give residue which was purified by column chromatography using ethyl acetate-petrol ether (2:8) to give corresponding MOM protected chalcones **123-126** as oils in good yields.

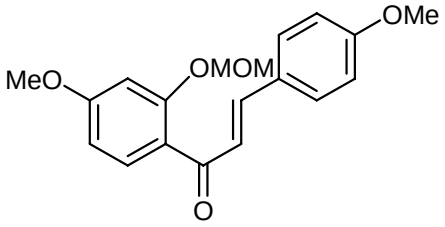
2'-Methoxymothoxychalcone (123)



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.42 (s, 3 H, OCH_3), 5.27 (s, 2 H, OCH_2O), 7.04- 7.73 (m, 11 H, α, β-H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.8 ($OCH_2O\mathit{CH_3}$), 95.2 ($O\mathit{CH_2}OCH_3$), 115.7 (3'-H), 122.4 (C-α), 127.5, 128.7, 129.3, 130.4, 130.7, 131.3, 133.0, 135.4 (Ar) 144.0 (C-β), 155.9 (C-2'), 193.7 (CO).

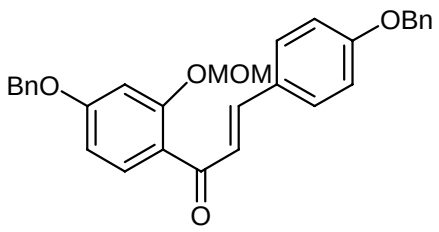
4,4'-Dimethoxy-2'-methoxymothoxychalcone (125)



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.49 (s, 3 H, $OCH_2O\mathit{CH_3}$), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.27 (s, 2 H, OCH_2), 6.62 (dd, *J* = 9.0, 2.5 Hz, 1H, 5-H), 6.72 (d, *J* = 2.5 Hz, 1H, 3-H), 6.96 (d, *J* = 9.0 Hz, 2 H, 3',5'-H), 7.51 (d, *J* = 16.0, 1 H, α-H),7.60 (d, *J* = 9.0 Hz, 1H, 6-H), 8.03 (d, *J* = 9.0, 2. H, 2',6'-H), 8.10 (d, *J* = 16.0, 1 H, β -H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.7 ($OCH_2O\mathit{CH_3}$),55.9 (OCH_3), 56.8 (OCH_3), 95.4 ($O\mathit{CH_2}OCH_3$) 102.0 (C-3'), 107.5 (C-5'), 114.7 (C-3), 123.6 (C-α), 125.3 (C-1'), 128.4 (C-2), 130.3 (C-1), 132.7 (C-6'), 142.0 (C-β), 158.0 (C-4), 161.7 (C-2'), 164.0 (C-4'), 191.5 (CO).

4,4'-Dibenzyloxy-2'-methoxymothoxychalcone (126)



Melting Point: 82-83 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.54 (s, 3 H, OCH_2OCH_3), 5.12 (s, 2H, OCH_2PH), 5.13 (s, 2 H, OCH_2PH), 5.28(s, 2 H, OCH_2OCH_3) 6.77, (dd, *J* = 8.6, 2.3 Hz, 1 H, 5'-H), 6.92 (d, *J* = 2.3 Hz, 1 H, 3'-H), 7.35-7.84 (m, 7 H, 2, 3, 5, 6,6', α-H and β-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 56.9 ($OCH_2O\mathit{CH_3}$), 70.5 ($O\mathit{CH_2}Ph$), 70.6 ($O\mathit{CH_2}Ph$), 95.5 ($O\mathit{CH_2}OCH_3$), 103.0 (C-3'), 108.3 (C-5'), 115.7 (C-3), 115.6 (C-1'), 125.5 (C-α), 127.9, 128.7, 129.1, 129.5, 130.4, 132.8, 136.8, 137.0, 142.6 (C-β), 158.1 (C-2') 160.9.5 (C-4), 163.2 (C-2'), 191.2 (CO).

MS (EI, 70 eV): *m/z* (%) = 480 (26) [M^+], 435 (33), 407 (28), 308 (12), 265 (8), 241 (32), 180 (24), 91 (100), 45 (48), 28(12).

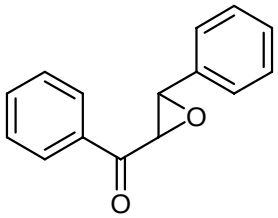
HREIMS:	$C_{31}H_{28}O_5$	480.19366	(Calculated)
		480.19362	(Found)

4.3.32. General Procedure for asymmetric epoxidation with cinchonine catalysts

To a solution of 1,3-diphenylprop-2-en-1-one (200 mg, 0.96 mmol) in toluene (6ml), was added cinchonin catalysts **141** (53 mg, 0.096 mmol). The reaction mixture was treated with 13 % aqueous sodium hypochlorite (1.29 mL, 20.7 mmol) and the mixture was stirred at room temperature for 8-48 h. After completion of the reaction, water (5ml) was added and the aqueous layer was extracted with ethyl acetate (2x10 mL). The combined organics were dried over sodium sulphate, filtered, and concentrated under reduced pressure. The residue was then

purified by passing through a pad of silica gel (1:1, ethyl acetate: petroleum ether) to afford (*E*)-2,3-epoxy-1,3-diphenylpropan-1-one in 80 % yield.

(*E*)-2,3-Epoxy-1,3-diphenylpropan-1-one



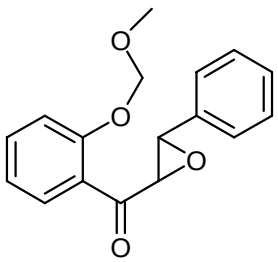
Melting Point: 75 °C (Lit.[61] 76-77 °C).

$[\alpha]_D = -185.7°$ (c = 2.73, THF), (Lit.[11] 195° (c = 2.73, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): 4.06 (d, *J* = 1.5Hz, 1 H, β-H), 4.29 (d, *J* = 1.5Hz, 1 H, α-H), 7.32-7.67 (m, 8 H, Ar-H), 7.93-8.04 (m, 2 H, Ar-H),

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 61.1 (C-β), 68.3 (C-α), 125.1-128.9 (C-Ar).

2'methoxymethoxy-2,3-epoxy-1,3-diphenylpropan-1-one



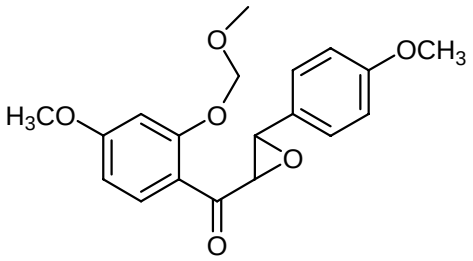
Melting Point: 88-89 °C (Lit.[124] 85-88 °C).

$[\alpha]_D = -167.62°$ (c = 1.0, MeOH).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.11 (s, 3 H, OCH_3), 4.03 (d, *J* = 1.8 Hz, β-H), 4.32 (d, *J* = 1.8 Hz, α-H), 4.83 (d, *J* = 7.0 Hz, 1 H, OCH_2O), 4.93 (d, *J* = 7 Hz, 1 H, OCH_2O), 7.0-7.54 (m, 8 H, Ar-H), 7.88 (dd, *J* = 7.5, 2 Hz, 6'-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 56.6 ($OCH_2O\mathit{CH_3}$), 60.2 (C-β), 65.3 (C-α), 94.8 ($O\mathit{CH_2}OCH_3$), 114.9, 122.4, 126.1, 126.9, 129.0, 129.2, 130.8, 135.1, 136.8 (C-Ar), 157.6 (C-2'), 195.1 (CO).

4,4'-Dimethoxy-2'methoxymethoxy-2,3-epoxy-1,3-diphenylpropan-1-one



Melting Point: 173-175 °C (Lit.[144] 179-181 °C).

$[\alpha]_D$ = –97.2° (c = 1.0,MeOH).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.11 (s, 3 H, $OCH_2\mathit{OCH_3}$), 3.81 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.91 (d, *J* = 1.9 Hz, 1 H, β-H), 4.29 (d, *J* = 1.9 Hz, 1 H, α-H), 4.80 (d, *J* = 7.0 Hz, 1 H, OCH_2O), 4.87 (d, *J* = 7.0 Hz, 1 H, OCH_2O), 6.60 (dd, *J* = 8.9, 2.0 Hz, 1 H, 5'-H), 6.63 (d, *J* = 2.0 Hz, 1 H, 3'-H), 6.90 (d, *J* = 9.0 Hz, 1 H, 3, 5-H), 7.27 (d, *J* = 9.0 Hz, 1 H, 2, 6-H), 7.85 (d, *J* = 8.9 Hz, 1 H, 6'-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.7 ($OCH_2\mathit{OCH_3}$), 56.0 (4'-OCH_3), 56.6 (4-OCH_3), 59.8 (β-C), 65.2 (α-C), 94.8 (OCH_2O), 100.7 (3'-C), 107.9 (5'-C), 114.1 (3-C), 114.4 (5-C), 119.9 (1'-C), 127.5 (1-C), 128.9 (2-C), 129.6 (6-C), 132 (6'-C), 159.7 (4-C), 160.5 (2'-C), 165.6 (4'-C), 193.1 (CO).

4.3.33. General procedure for asymmetric epoxidation with chiral ketones catalysts

For epoxidation reactions, all the flasks were prewashed with bicarbonate in order to avoid any metal contamination and dried in oven at 125 °C. In a three-neck round-bottom flask were added buffer (0.05 M $Na_2B_4O_7.10H_2O$ in 4 $\times 10^{-4}$ M aqueous Na_2(EDTA), anhydrous acetonitrile (15 mL), chalcone **106** (0.118 g, 1,00 mmol), tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol), and chiral ketone (0.0774 g, 0.3 mmol). The reaction mixture was cooled in ice bath. A solution of Oxone (0.85 g, 1.38 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 6.5 mL) and a solution of K_2CO_3 (0.8 g, 5.80mmol) in water (6.5 mL) were added drop wise through two separate addition funnels over a period of 1.5 h. The reaction was immediately quenched by addition of pentane and water. The mixture was extracted with pentane (3×30 mL), washed with brine, dried over Na_2SO_4, purified by flash chromatography to afford epoxide.

4.3.34. General procedure for asymmetric epoxidation with poly amino catalyst

The catalyst (400 mg) 0.1-0.9 mmol was added to a solution of chalcone (2.4 mmol) in toluene (6 g) and the mixture was stirred at room temp for 30 minutes. Then 4.4 mL of a solution of NaOH in H_2O_2 (0.08 g/ml) was added and the mixture was stirred at room temperature for the appropriate time (monitored by TLC). The insoluble catalyst is filtered off and washed with ether. Organic phase was washed with water (3 × 25 ml), dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give residue which was purified by column chromatography to give pure epoxide.

4.3.35. General procedure for asymmetric epoxidation with polymer supported immobilized poly amino catalyst

To a mixture of activated immobilized poly-L-isoleucine **172** or poly-L-leucine **172 (**800 mg) in THF (7.5 ml), was added urea hydrogen peroxide complex (1.2 eq) and DBU (1.4 eq). Chalcone (400 mg) was added to the slurry and the mixture was stirred at room temperature. After completion of the reaction, the catalyst was removed by filtration, rinsed with Et_2O (2×20 mL) and the filtrate was washed with water (20 mL). Drying (Na_2SO_4) of the solvent

and evaporation at reduced pressure to give crude product, which was purified by column chromatography and crystallized from ethanol.

4.3.36. General procedure for asymmetric epoxidation with hot poly amino acid catalyst with TBAB as co catalyst

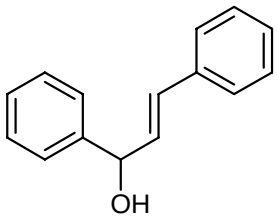
Tetrabutylammonium bromide (TBAB) (0.05 g, 1.70 mmol) poly-L-leucine (0.5 g, 0.05 mmol, 0.35) toluene (50 mL) and 5 M aqueous sodium hydroxide (4.10 mL) were added in a round bottom flask. After cooling to 15 °C, 30 % hydrogen peroxide (4.5 mL) was added at that temperature. The resulting heterogeneous mixture was warmed to 25 °C. This mixture was then kept at 25 °C for 1 hour before chalcone (5 g, 150 mmol 1.0 equiv.) was added as a solid. Subsequently, the reaction mixture was stirred for 20 hours in the dark at 25°C and diluted with ethyl acetate (150 mL) and quenched by addition of ice-cold 20 % aqueous $NaHSO_3$ solution (5 mL). After addition of water (50 mL) the layers were separated and organic layer containing epoxide. The aqueous layer containing insoluble poly-L-leucine. Poly- L -leucine was then filtered out and washed with ethyl acetate (20 mL).The combined organic layers were dried over sodium sulphate, filtered and concentrated under vacuum to afford solid. This material was crystallised from toluene (30 mL) to furnish epoxy ketone as a white solid.

4.4. Experimental part to chapter 3

4.4.1. General procedure for $NaBH_4$ reduction of the chalcones

Sodium borohydride (2.27 g, 60 mmol) was added in small portions to a stirred solution of chalcone (30 mmol) in methanol (100 ml). The solution was stirred for 1-5 h (monitored by TLC) and evaporated to dryness. The resulting residue was dissolved in ethyl acetate (150 ml). The organic solution was washed with water (2 x 50 ml), dried (Na_2SO_4), and evaporated to dryness to afford the allylic alcohol**s.**

(±)-1,3-Diphenylprop-2-enol (182)



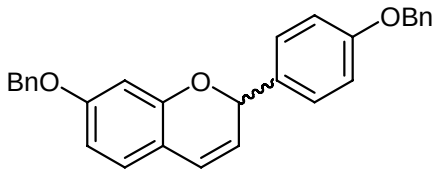
(±)

Melting Point: 53-54 °C (Lit.[141] 50-52 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ =2.44 (br s, 1 H, OH), 5.27 (d, *J* = 6 Hz, 1 H, *CH*-OH)), 6.26, (dd, *J* = 16, 6 Hz, 1 H, α-H) 6.60 (d, *J* = 16 Hz, 1 H, β-H), 7.25 (m, 10 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 75.0 (*CH*-OH), 126.4 (C-α), 126.7 (C-2'), 127.1 (C-2) 127.8 (C-4'), 128.6 (C-4), 130.6 (C-3'), 131.7 (C-β), 142.9 (C-1').

(±)-7-Benzyloxy-2-[4-benzyloxyphenyl]-2*H*-chromene (184)



(±)

Melting Point: 76-77 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.09 (s, 2 H, O*CH*$_2$Ph), 5.13 (s, 2 H, O*CH*$_2$Ph), 5.81 (dd, *J* = 9.8, 3.7 Hz, 1 H, 3-H), 5.97 (brs 1 H, 2-H), 6.62 (brs 1 H, 8-H), 6.68 (dd, *J* = 9.8, 1.9 Hz, 1 H, 4-H), 6.75 (d, *J* = 8.3 Hz, 1 H, 6-H), 7.05-20 (overlapped, 3 H, 5, 3', 5'-H), 7.41-7.72 (overlapped, 12 H, 2', 6' and Ar-H)

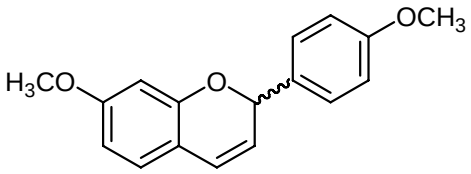
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.5 (O*CH*$_2$Ph), 70.9 (O*CH*$_2$Ph), 82.1 (C-2), 103.3 (C-8) 108.3 (C-6), 115.3 (C-4a), 115.4 (C-3'), 115.5 (C-4), 122.6 (C-3), 124.2 (C-2'), 127.8, 128.0, 128.4, 129.0, 129.1, 129.2, 129.9, 131.1, 133.8, 137.4, 137.4 (C-Ar) 154.9, 154.9 (C-4'), 159.4 (C-8a), 160.6 (C-7).

IR (Film): $\tilde{\nu}$ = 3027 (C−H), 2888 (C−H), 1610 (C=C), 1508 (CH_2), 1378 (C−H), 1166 (C−O), 1112 (C−O), 1027 (C−O).

MS (EI, 70 eV): *m/z* (%) = 420 (46) [M^+], 362 (5), 329 (38), 300 (60), 228 (54), 180 (12), 150 (14), 91 (100), 65 (62), 29 (28).

HREIMS:	$C_{29}H_{24}O_3$	420.17255	(Calculated)
		420.17254	(Found)

(±)-7-Methoxy-2-[4-methoxyphenyl]-2*H*-chromene (186)



(±)

Melting Point: 72-73 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.71 (dd, *J* = 9.5, 3.2 Hz, 1 H, 3-H), 5.87 (brs 1 H, 2-H), 6.40 (brs 1 H, 8-H), 6.49 (dd, *J* = 9.5, 1.8 Hz, 1 H, 4-H), 6.56 (d, *J* = 8.3 Hz, 1 H, 6-H), 6.91-7.03 (m, 3 H, 5, 3', 5'-H), 7.39-7.44 (overlapped, 2.H, 2', 6'-H).

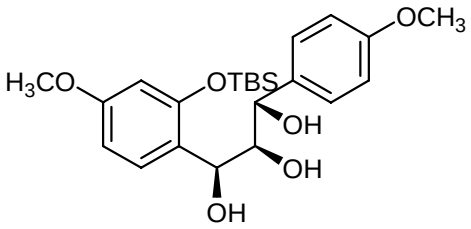
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 81.3 (C-2), 102.2 (C-8), 107.3 (C-6), 114.4 (C-4a), 115.1 (C-3'), 122.3 (C-4) 124.0 (C-3), 127.5 (C-2'), 129.0 (C-6), 133.4 (C-1'), 159.3 (C-8a), 160.1 (C-4'), 161.2 (C-7).

IR (Film): $\tilde{\nu}$ = 2931 (C−H), 2838 (C−H), 1610 (C=C), 1511 (CH_3), 1251 (C−H), 1170 (C−O), 1112 (C−O), 1025 (C−O).

MS (EI, 70 eV): *m/z* (%) = 268 (100) [M^+], 237 (66), 224 (26), 181 (12), 161 (78), 134 (60), 89 (12), 77 (13), 51 (6), 28 (21).

HREIMS:	$C_{23}H_{32}O_4Si$	268.10995	(Calculated)
		268.10995	(Found)

4.2. (+)-3-[4-Methoxy-6-(*tert*-butyldimethylsilyloxy)phenyl]-1-[4-methoxyphenyl)-propan-1,2,3-triol (190)



(+)

Sodium borohydride (190 mg, 5.02 mmol) was added in small portions to a stirred solution of 1-[2'-TBS protected-4-methoxyphenyl]-3-[4-methoxyphenyl]propen-1-one **119** (1 g, 2.51 mmol) in methanol (30 ml). The solution was stirred for 2 h and evaporated to dryness, and the residue taken up in ethyl acetate (15 ml). The organic solution was washed with water (2 × 10 ml), dried, and evaporated to dryness. This residue was not further purified due to instability of the allylic alcohol formed.

To a solution containing allylic alcohol (1.00 g, 2.50 mmol) in 25 mL of 1:1 tBuOH-H_2O (25 mL) was added AD mix-α (3.50 g,2.50 mmol). The heterogeneous slurry was cooled to 0 °C in an ice bath and methanesulfonamide (0.316 g, 3.30 mmol) was added. The reaction mixture was allowed to warm to room temperature for 2 days. The reaction mixture was then quenched with sodium sulphite and diluted with ethyl acetate (40 mL) and water (40 mL). The organic layer was separated and washed with 2 M KOH (2×25 mL) followed water (25 mL). The organic layer was then dried over $MgSO_4$ and concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column to afford TBS-protected triols **(+)-190** as white solid and **(−)-191** as pale yellow solid.

Melting Point: 104–105 °C.

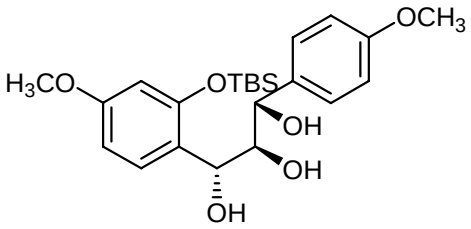
$[\alpha]_D$ = +26.7° (c = 1.0, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.24 (s,3 H, Si-CH_3), 0..25 (s,3 H, Si-CH_3), 0.99 (s, 9 H, Si-C(CH_3)$_3$), 2.81 (s, 1 H, OH), 3.16 (d, *J* = 2.7, 2 H, 2(OH)), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.5 (d, *J* = 2.7, 1 H, 3-H), 4.74 (d, *J* = 3.8,1 H, 4-H), 5.02 (d, *J* = 3.8,1 H, 2-H), 6.40

(d, *J* = 2.0, 1 H, 8-H), 6.57 (dd, *J* = 8.6, 2.0, 1 H, 6-H), 6.88 (d, *J* = 8.5, 1 H, 3', 5'-H), 7.24 (d, *J* = 8.5, 1 H, 2', 6'-H), 7.45 (d, *J* = 8.6, 1 H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = -3.8 (Si-CH_3), -3.5 (Si-CH_3), 18.5(Si-*C*$(CH_3)_3$), 26.1 (Si-C(*CH_3*)$_3$), 55.6 (OCH_3), 70.2 (C-1), 74.5 (C-3), 106.6 (C-2), 106.2 (C-3'), 114.2 (C-5'), 123.7 (C-1'), 128.1 (C-3), 129.1 (C-2), 133.5 (6'), 154.0 (C-2'), 159.5 (C-4), 160.3 (C-4')

(–)-3-[4-Methoxy-6-(*tert*-butyldimethylsilyloxy)phenyl]-1-[4-methoxyphenyl)- propan-1,2,3-triol (191)



(-)

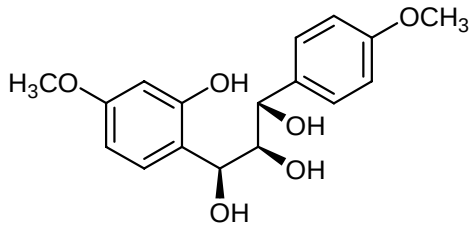
Melting Point: 90-91 °C.

$[\alpha]_D = -5.7°$ (c = 1.0, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.26 (s,3 H, Si-CH_3), 0.29 (s,3 H, Si-CH_3), 099 (s, 9 H, Si-C$(CH_3)_3$), 2.73 (d, *J* = 5.2, 1 H, OH), 3.50 (d, *J* = 7.6, 2 H, 2(OH)), 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.94 (d, *J* = 2.8, 1 H, 3-H), 4.80 (brs, 1 H, 4-H), 5.17 (brs, 1 H, 2-H 2-H), 6.41 (d, *J* = 2.1, 1 H, 8-H), 6.59 (dd, *J* = 8.7, 2.1, 1 H, 6-H), 6.85 (d, *J* = 8.4, 1 H, 3', 5'-H), 7.24 (d, *J* = 8.4, 1 H, 2', 6'-H), 7.45 (d, *J* = 8.7, 1 H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = -3.8 (Si-CH_3), -3.5 (Si-CH_3), 18.5 (Si-*C*$(CH_3)_3$), 26.1 (Si-C(*CH_3*)$_3$), 55.6 (OCH_3), 72.5 (C-1), 72.6 (C-3), 105.6 (C-2), 106.4 (C-3'), 114.1 (C-5'), 123.5 (C-1'), 127.8 (C-3), 128.4 (C-2), 133.8 (6'), 153.8 (C-2'), 159.3 (C-4), 160.3 (C-4')

4.4.3. (+)-3-[4-Methoxy-6-hydroxyphenyl]-1-[4-methoxyphenyl)- propan-1,2,3-triol (192)



(+)

To a solution containing Triol **190** (400 mg, 0.92 mmol) in anhydrous THF (4 mL) was added *tetra-n*-butylammonium fluoride (273 mg, 0.866 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (5 mL), diluted with H_2O (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine (15 mL) and H_2O (15 mL). The organic layer was dried over $MgSO_4$ and concentrated under diminished pressure to give residue. The residue was purified by flash chromatography on a silica gel column to afford **(+)-192** as a white solid.

Melting Point: 110-112 °C.

$[\alpha]_D$ = +21.7° (c = 1.0, $CHCl_3$).

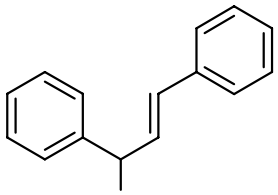
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.98 (brs, 4 H, 4 OH), 3.70 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.98 (t, *J* = 5.3, 1 H, 3-H), 4.52 (d, *J* = 5.3, 2 H, 1, 3-H), 6.32 (dd, *J* = 8.4, 2.4, 1 H, 6-H), 6.37 (d, *J* = 2.4, 1 H, 8-H), 6.78 (d, *J* = 8.5, 3', 5'-H), 6.80(d, *J* = 8.4, 1 H, 5-H), 7.10 (d, *J* = 8.5, 1 H, 2', 6'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.1 (OCH_3), 55.2 (OCH_3), 70.8 (C-1), 74.1 (C-3), 102.6 (C-2), 105.5 (C-3'), 113.7 (C-5'), 117.8 (C-1'), 128.1 (C-3), 130.5 (C-2), 132.8 (6'), 156.1 (C-2'), 159.1 (C-4), 160.5 (C-4').

4.4.4. General procedure for CBS reduction of the chalcones

To a stirred solution of (R)-2- methyl-CBS-oxazaborolidine (1M solution in toluene, 0.104 mmol) in dry THF (2 mL) was added $BH_3.OEt_2$ or BH_3-DMS (1.04 mmol) in an atmosphere of nitrogen. Solution of chalcone (1.04 mmol, in 0.2 mL THF) was added slowly over a period of 1.5 h using a syringe pump at 25 °C. Stirring of the reaction mixture at the same temperature was continued until all the chalcone disappeared (monitored by TLC). The reaction mixture was then quenched cautiously with methanol (0.5 mL). The reaction mixture was concentrated at reduced pressure to leave oil, which was purified by flash column chromatography on silica gel using ethyl acetate–petrol ether (1: 3) to give allylic alcohol.

(+)-1,3-Diphenylprop-2-enol (194)



(+)

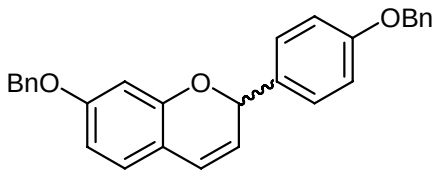
Melting Point: 55 °C (Lit.[141] 50-52 °C).

$[\alpha]_D$ = +13.5° (c = 1.0, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ =2.44 (br s, 1 H, OH), 5.27 (d, *J* = 6 Hz, 1 H, *CH*-OH)), 6.26, (dd, *J* = 16, 6 Hz, 1 H, α-H) 6.60 (d, *J* = 16 Hz, 1 H, β-H), 7.25 (m, 10 H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 75.0 (*CH*-OH), 126.4 (C-α), 126.7 (C-2'), 127.1 (C-2) 127.8 (C-4'), 128.6 (C-4), 130.6 (C-3'), 131.7 (C-β), 142.9 (C-1').

4.4.5. (±)-7-Benzyloxy-2-[4-benzyloxyphenyl]-2*H*-chromene (184)



(±)

To a stirred solution of (R)-2-methyl-CBS-oxazaborolidine (1M solution in toluene, 0.03 mL, 1.04 mmol) in dry THF was added $BH_3.OEt_2$ (89 mg, 0.1 mL, 0.104 mmol) in an atmosphere of nitrogen. Solution of chalcone **126** (0.5 g, 1.04 mmol, in 0.2 mL THF) was added slowly over a period of 1.5 h using a syringe pump at 25 °C. Stirring of the reaction mixture at the same temperature was continued until all the chalcone was converted in to allylic alcohol (monitored by TLC). The reaction mixture was then quenched cautiously with methanol (0.5 mL). The reaction mixture was concentrated at reduced pressure to leave allylic alcohol **196** as oil, which was unstable.

The unstable allylic alcohol **196** formed was directly subjected to mesylation. The allylic alcohol was dissolved in dichloromethane (10 mL). To this solution was added triethylamine (0.6 mL, 4.3026 mmol) and 4-dimethylaminopyridine (6 mg, 0.042 mmol) and the solution was stirred for 10 minutes. The mixture was cooled to -10 °C and methanesulfonyl chloride (0.4 mL, 4.08 mmol) was then added drop wise. The reaction mixture was warmed to room temperature and stirred for four hours. The reaction was quenched with 20 mL of 6 % aqueous HCl and extracted twice with CH_2C1_2 (20 mL). The combined organic extracts were washed twice with 6 % HCl (20 mL), three times with saturated $NaHCO_3$ (20 mL) and twice with saturated NaCl (20 mL). The organic phase was dried over Na_2SO_4, and evaporated to give mesylated product **197**. This product was not analyzed due to the instability of the product and subjected immediately to the next step for cyclization. TLC analysis showed already some of the conversion into flavene **184**.

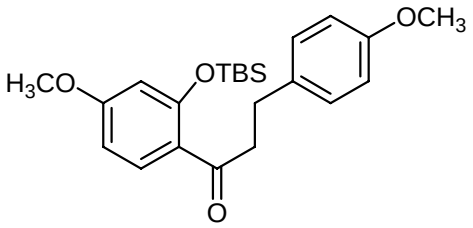
The mesylated product obtained was dissolved in methanol (3 mL) and 10 % HCl/MeOH (0.2 mL) was added. The reaction mixture was stirred at room temperature for 40 min. and was diluted with $CHCl_3$ (10 mL).The organic phase was washed with 5 % aq. $NaHCO_3$ and water.

The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give oil, which was purified to give flavene **184** as light yellow solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.09 (s, 2 H, O*CH*$_2$Ph), 5.13 (s, 2 H, O*CH*$_2$Ph), 5.81 (dd, *J* = 9.8, 3.7 Hz, 1 H, 3-H), 5.97 (brs 1 H, 2-H), 6.62 (brs 1 H, 8-H), 6.68 (dd, *J* = 9.8, 1.9 Hz, 1 H, 4-H), 6.75 (d, *J* = 8.3 Hz, 1 H, 6-H), 7.05-20 (overlapped, 3 H, 5, 3', 5'-H), 7.41-7.72 (overlapped, 12 H, 2', 6' and Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 70.5 (O*CH*$_2$Ph)70.9 (O*CH*$_2$Ph), 82.1 (C-2), 103.3 (C-8) 108.3 (C-6), 115.3 (C-4a), 115.4 (C-3'), 115.5 (C-4), 122.6 (C-3), 124.2 (C-2'), 127.8, 128.0, 128.4, 129.0, 129.1, 129.2, 129.9, 131.1, 133.8, 137.4, 137.4 (C-Ar) 154.9, 154.9 (C-4'), 159.4 (C-8a), 160.6 (C-7).

4.4.6. 1[4-Methoxy-6-(*tert*-butyldimethylsilyloxy)phenyl]-3-[4-methoxyphenyl)-propan-1-one (199)



To a stirred solution of (R)-2-methyl-CBS-oxazaborolidine (1M solution in toluene, 0.079 mL, 0.25 mmol) in dry THF (1 mL) was added $BH_3.OEt_2$ (0.23 mL, 2.5 mmol) in an atmosphere of nitrogen. Solution of chalcone **119** (1 g, 2.5 mmol, in 2 mL THF) was added slowly over a period of 1.5 h using a syringe pump at 25 °C. Stirring of the reaction mixture at the same temperature was continued until all the chalcone was disappeared (monitored by TLC). The reaction mixture was then quenched cautiously with methanol (0.5 mL). The reaction mixture was concentrated at reduced pressure to leave propanone **199** as solid instead of allylic alcohol **198**.

Melting Point: 70-72 °C.

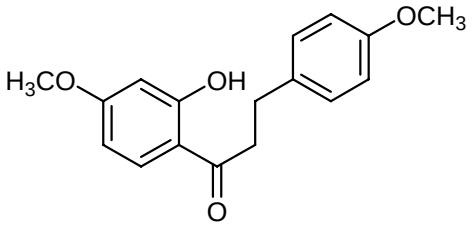
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.29 (s,6 H, $Si(CH_3)_2$), 0.99 (s, 9 H, $Si\text{-}C(CH_3)_3$), 3.00 (t, *J* = 8.4 Hz, 2 H, α-CH_2), 3.30 (t, *J* = 8.4 Hz, 2 H, β -CH_2), 3.81, (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.41 (d, *J* = 2.3, 1 H, 8-H), 6.59 (dd, *J* = 8.8, 2.3, 1 H, 6-H), 6.84 (d, *J* = 8.6, 1 H, 3', 5'-H), 7.15 (d, *J* = 8.6, 1 H, 2', 6'-H), 7.70 (d, *J* = 8.8, 1 H, 5-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.4 ($Si\text{-}CH_3$), -3.1 ($Si\text{-}CH_3$), 18.9 ($Si\text{-}C(CH_3)_3$), 26.3 ($Si\text{-}C(CH_3)_3$), 29.9 (β-C), 45.8 (α -C), 55.6 (OCH_3), 55.7 (OCH_3), 106.2 (C-3'), 107.2 (C-5'), 114.1 (C-3), 124.2 (C-1'), 129.7 (2'), 132.4 (C-6'), 134.1 (C-1), 157.0 (C-2'), 158.2 (C-4), 163.8 (C-4'), 200.7 (CO).

MS (EI, 70 eV): *m/z* (%) = 400 (8) [M^+], 344 (12), 343 (36), 279 (18), 239 (6), 219 (8), 184 (28), 149 (52), 121 (86), 97 (42), 75 (88), 57 (100).

HREIMS:	$C_{23}H_{32}O_4Si$	400.20700	(Calculated)
		400.20723	(Found)

4.4.7. 1[2-Hydroxy-4-methoxy-3-[4-methoxyphenyl)-propan-1-one (200)



To a stirred solution of (R)-2-methyl-CBS-oxazaborolidine (1M solution in toluene, 0.079 mL, 0.25 mmol) in dry THF (1 mL) was added $BH_3\text{-}S(CH_2)_2$ (0.23 mL, 2.4 mmol) in an atmosphere of nitrogen. Solution of chalcone **119** (0.5 g, 1.75 mmol, in 2 mL THF) was added slowly over a period of 1.5 h using a syringe pump at 25 °C. Stirring of the reaction mixture at the same temperature was continued until all the chalcone was disappeared (monitored by TLC). The reaction mixture was then quenched cautiously with methanol (0.5 mL). The reaction mixture was concentrated at reduced pressure to leave propanone **200** as oil instead of allylic alcohol **198**.

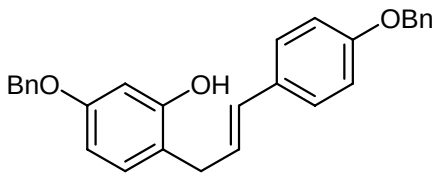
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.07 (t, *J* = 7.5 Hz, 2 H, α-CH_2), 3.20 (t, *J* = 7.5 Hz, 2 H, β-CH_2), 3.83, (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.43 (d, *J* = 2.4 Hz, 1 H, 8-H), 6.49 (dd, *J* = 8.7, 2.4 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.5, 1 H, 3', 5'-H), 7.22 (d, *J* = 8.5, 1 H, 2', 6'-H), 7.70 (d, *J* = 8.7, 1 H, 5-H), 12.98 (s, 1 H, 2'-OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 29.9 (β-C), 40.3 (α -C), 55.6 (OCH_3), 55.9 (OCH_3), 101.3 (C-3'), 108.0 (C-5'), 114.4 (C-3), 129.7 (C-1'), 131.9 (2'), 133.3 (C-6'), 134.1 (C-1), 158.5 (C-2'), 165.8 (C-4), 166.4 (C-4'),204.1 (CO).

MS (EI, 70 eV): *m/z* (%) = 286 (22) [M^+], 267 (6), 196 (17), 184 (40), 165 (30), 151 (60), 137 (40), 121 (56), 105 (84), 77 (100), 63 (22), 51 (48).

HREIMS:	$C_{17}H_{18}O_4$	286.12051	(Calculated)
		286.12037	(Found)

1-(4-Benzoxyphenyl)-3-(4-benzoxy-2-hydroxyphenyl)propene (202)



Triethylamine (2.49 mL, 17.90 mmol) was added to a solution containing 1-(4-Benzoxy-2-hydroxyphenyl)-3-(4-benzoxyphenyl)propenone (**113**) (6.00 g, 13.79 mmol) in 50 mL of anhydrous THF. The reaction mixture was cooled to 0 °C in an ice bath and stirred for 15 minutes. Ethyl chloroformate (1.79 g, 1.58 mL, 16.50 mmol) was then added drop wise to this solution over a period of 20 minutes. After the reaction mixture was stirred at 0 °C for 1.5 h, it was filtered, and the precipitate obtained was washed with two 20-mL portions of THF. The filtrate which is phenolic carbonat **201** was then added drop wise at 0 °C over a period of 45 min to a solution containing $NaBH_4$ (2.00 g, 58.00 mmol in 80 mL of H_2O). The reaction mixture was stirred at 0-5 °C overnight. It was acidified with 1N HCl, diluted with H_2O (200 mL) and extracted with ether (3×250 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel column using ethyl acetate: petrol ether (1:9) to afford

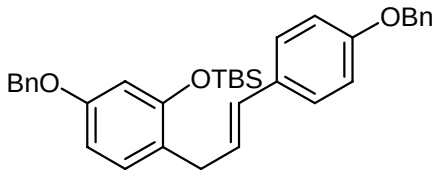
substituted propene **202** as colourless solid in 86 % yield (4.95 g, 11.73 mmol). It was observed that by performing reaction at room temperature 19 % (1.1 g, 2.61 mmol)

Melting Point: 106-107 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.53 (d, *J* = 6.3 Hz, 2 H, 3-H) 5.07 (s, 2 H, O*CH*$_2$Ph), 5.11 (s, 2 H, O*CH*$_2$Ph), 6.30, (m, 1 H, 2-H), 6.47 (br, 1 H, 1-H), 6.55 (dd, *J* = 8.5, 2.1 Hz, 1 H, 5'-H), 6.63 (br, I H, 3'-H), 6.98 (d, *J* = 8.2 Hz, 2 H, 3'', 5''-H), 7.10 (d, *J* = 8.2 Hz, 1 H, 6'-H), 7.29-7.54 (m, 12 H, 2'',6''-H, Ar-H),

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 34.1 (C-3), 70.4 (O*CH*$_2$Ph), 70.5 (O*CH*$_2$Ph), 103.4 (C-3'), 107.6 (C-5'), 115.3 (C-5''), 118.5 (C-3''), 127.8, 127.9, 128.4, 128.4, 129.0, 130.5, 131.2, 131.3, 136.2, 137.3, 137.4 (C-Ar), 155.4 (C-2'), 158.6 (C-4'), 159.2 (C-4'').

1-(4-Benzoxyphenyl)-3-(4-benzoxy-2-*tert*-butyldimethylsilyloxyphenyl)propene (205)

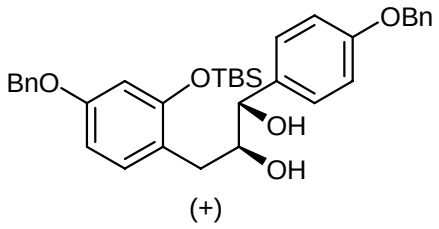


To a solution containing 1-(4-Benzoxyphenyl)-3-(4-benzoxy-2-hydroxyphenyl)propene (**202**) (2.00 g, 4.73 mmol) in anhydrous DMF (30 mL) was added imidazole (960 mg, 14.10 mmol). The solution was stirred at room temperature for 15 minutes and TBDMSCl (1.05 g, 6.96 mmol) was then added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column using ethyl acetate: petrol ether (1:9) to afford TBS protected propene **205** as colourless oil in 97 % yield (2.45 g, 4.57 mmol).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.28 (s, 6 H, Si-$(CH_3)_2$), 1.11 (s, 9 H, Si-C$(CH_3)_3$), 3.52 (d, *J* = 5.8 Hz, 2 H, 3-H) 5.11 (s, 2 H, O*CH*$_2$Ph), 5.13 (s, 2 H, O*CH*$_2$Ph), 6.32, (m, 1 H, 2-H), 6.53 (br, 1 H, 1-H), 6.67 (dd, *J* = 8.5, 2.1 Hz, 1 H, 5'-H), 6.63 (br, I H, 3'-H), 6.98 (d, *J* = 8.2 Hz, 2 H, 3'', 5''-H), 7.20 (d, *J* = 8.2 Hz, 6'-H), 7.32-7.59 (m, 12 H, 2'',6''-H, Ar-H),

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.60 Si-$(CH_3)_2$), 18.7 (Si-*C*$(CH_3)_3$), 26.2 (Si-C(*C*$H_3)_3$), 33.4 (C-3), 70.4 (O*C*H_2Ph), 70.6 (O*C*H_2Ph), 106.7 (C-3'), 107.6 (C-5'), 114.3 (C-5''), 115.1, (C-3''), 115.3 (C-2) 124.1 (C-1'), 127.6, 127.8, 127.9, 128.3, 128.7, 129.0, 129.8, 130.1, 130.3, 130.8, 131.4, 137.5, 135.6, (C-Ar), 154.5 (C-2'), 158.3 (C-4'), 158.5 (C-4'').

(2*S*,3*S*)-1-(4-Benzoxyphenyl)-3-(4-benzoxy-2-(*tert*-butyldimethylsilyloxy)phenyl)propan-1,2-diol (206)



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To a solution containing TBS-protected propene **205** (4.30 g, 8.00 mmol) in 1:1 tBuOH-H_2O (12 mL) was added AD-Mix α (11.2 g, 8.0 mmol) in portions. The heterogeneous mixture was cooled to 0 °C in an ice bath and methanesulfonamide (0.95 g, 10 mmol) was also added in portions. To allow for complete dissolution of the starting material, chloroform (0.5 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 16 h. When the starting material was completely consumed (TLC monitored), the reaction was then quenched with sodium sulfite solution (4 mL) and diluted with ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and washed with two 100 mL portions of 2M KOH followed by 100 mL of H_2O. The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column using ethyl acetate: petrol ether (1:3) to afford TBS protected diol **206** as colourless solid in 88 % yield (4.00 g, 7.00 mmol).

Melting Point: 66-68 °C.

$[\alpha]_D$ = +4.91° (c = 0.77, $CHCl_3$), (Lit.[41] +4.77° (c = 0.77, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 3 H, Si-CH_3), 0.19 (s, 3 H, Si-CH_3), 0.98 (s, 9 H, Si-C$(CH_3)_3$), 1.31 (br, 1 H, 1-OH), 1.67 (br, 1 H, 2-OH), 2.59 (dd, *J* = 8.2 and 6.7 Hz,1 H, 4-H-α), 2.71 (dd, *J* = 8.2 and 2.7 Hz, 1 H, 4-H-β), 3.89 (m, 1 H, 2-H), 4.50 (d, *J* = 6.1 Hz, 1 H, 1-H), 5.05 (s, 2 H, O*C*H_2Ph), 5.11 (s, 2 H, O*C*H_2Ph), 6.47, (d, *J* = 2.4 Hz, 1 H, 3'-H), 6.61

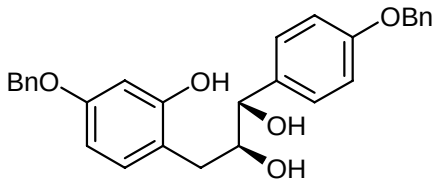
(dd, *J* = 8.3 Hz and 2.4 Hz, 1 H, 5'-H), 6.98, (d, *J* = 8.3 Hz, 1 H, 6'-H), 7.02 (m, 2 H, 3'',5''-H), 7.30-7.50 (m, 12 H, 2'',6''-H, Ar-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -3.7 Si-$(CH_3)_2$), 18.6 (Si-*C*$(CH_3)_3$), 26.2 (Si-C(*C*$H_3)_3$), 34.6 (C-3), 70.4 (O*C*H_2Ph), 70.5 (O*C*H_2Ph), 76.1 (C-2), 76.1 (C-1), 106.9 (C-3''), 107.9 (C-5''), 115.1 (C-3'), 121.3 (C-1'') 124.1 (C-1'), 127.6, 127.8, 127.7, 128.2, 128.4, 128.8, 129.9, 132.1, 133.7, 137.3, 137.5, (C-Ar), 154.8 (C-2'), 158.6 (C-4'), 158.7 (C-4'').

MS (EI, 70 eV): *m/z* (%) = 570 (14) [M^+], 536 (4), 494 (7), 357 (98), 327 (40), 299 (20), 225 (24), 213 (38), 197 (32), 121 (22), 91 (100), 73 (43).

HREIMS: $C_{35}H_{42}O_5Si$ 570.28015 (Calculated)
570.28040 (Found)

(2*S*,3*S*)-1-(4-Benzoxyphenyl)-3-(4-benzoxy-2-hydroxyphenyl)propan-1,2-diol (204)



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To a solution of TBS-protected Diol **206** (500 mg, 0.87 mmol) in anhydrous THF (16 mL) was added tetra-*n*-butylammonium fluoride (250 mg, 0.79 mmol). The reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (3 mL). The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine (25 mL) and water (25 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure to obtain brown residue which was purified by flash chromatography on a silica gel column to obtain triol **204** as colourless solid in 98 % yield (390 mg, 0.84 mmol).

Melting Point: 122-124 °C.

$[\alpha]_D = -1.28°$ (c = 1.0, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.55 (dd, *J* = 15.2 and 8.3 Hz,1 H, 4-H-α), 2.71 (dd, *J* = 14.2 and 6.1 Hz, 1 H, 4-H-β), 4.07 (br, 1 H, 2-H), 4.41 (d, *J* = 7.2 Hz, 1 H, 1-H), 5.04 (s, 2 H, O*CH*$_2$Ph), 5.11 (s, 2 H, O*CH*$_2$Ph), 6.47, (dd, *J* = 8.3 Hz and 2.4 Hz, 1 H, 5'-H), 6.62 (d, *J* = 8.3 Hz, 1 H, 3'-H), 6.69, (d, *J* = 8.7 Hz, 1 H, 5'-H), 7.04 (d, *J* = 8.7 Hz, 2 H, 3'',5''-H), 7.24-7.46 (m, 13 H, 6',2'',6''-H, Ar-H).

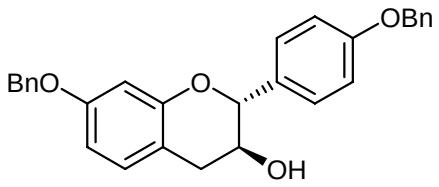
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 34.6 (C-3), 70.4 (O*CH*$_2$Ph), 70.5 (O*CH*$_2$Ph), 76.1 (C-2), 76.1 (C-1), 104.1 (C-3''), 107.3 (C-5''), 115.5 (C-3'), 117.1 (C-1'') 127.9 (C-1'), 127.6, 127.8, 127.7, 128.3, 128.5, 128.9, 129.0, 132.7, 133.8, 137.1, 137.5, (C-Ar), 157.1 (C-2'), 159.4 (C-4'), 159.6 (C-4'').

IR (Film): $\tilde{\nu}$ = 3426 (O−H), 3033 (C−H), 2892 (C−H), 1614 (C=C), 1509 (CH_2), 1440 (CH_2), 1286 (C−H), 1168 (C−H), 1024 (C−O).

MS (EI, 70 eV): *m/z* (%) = 456 (10) [M^+], 438 (60), 362 (16), 243 (36), 213 (97), 137 (50), 123 (58), 91 (100), 65 (25).

HREIMS:	$C_{29}H_{28}O_5$	456.19366	(Calculated)
		456.19335	(Found)

(2*R*,3*S*)-2-(4-Benzoxyphenyl)-7-benzoxychroman-3-ol (207)



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To a solution of triol **204** (260 mg, 0.56 mmol) in anhydrous THF (6 mL) was added triphenylphosphine (225 mg, 0.057 mmol), The mixture was stirred for 15 minutes and diethylazodicarboxylate (0.13 mL, 0.11 mmol) was then added drop wise to the reaction mixture. After stirring for 3 h at room temperature, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated on rotary evaporator to give white residue. The

residue obtained was purified by silica gel column chromatography to afford **207** as white solid in 65 % yield (165 mg, 0.36 mmol).

Melting Point: 96-98 °C.

$[\alpha]_D$ = –17.38° (c = 1.11, $CHCl_3$), (Lit.[41] –16.1° (c = 1.11, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.13 (br, 1 H, 3-OH), 2.94 (dd, *J* = 15.6, 9.0 Hz, 1 H, 4-H-α), 3.06 (dd, *J* = 15.6, 5.3 Hz, 1 H, 4-H-β), 4.13 (m, 1 H, 3-H), 4.65 (d, *J* = 8.0 Hz, 1 H, 2-H), 5.04 (s, 2 H, O*CH*$_2$Ph), 5.13, (s, 2 H, O*CH*$_2$Ph), 6.67 (dd, *J* = 8.1 Hz, 2.4 Hz, 2 H, 3',5'-H), 7.08 (m, 3 H, 5,6,8-H), 7.30-7.47 (m, 12 H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 32.5 (C-4), 68.6 (C-3), 70.4 (O*CH*$_2$Ph), , 82.1 (C-2), 107.6 137.2, 137.4, (C-Ar), 155.2, 158.9, 159.5.

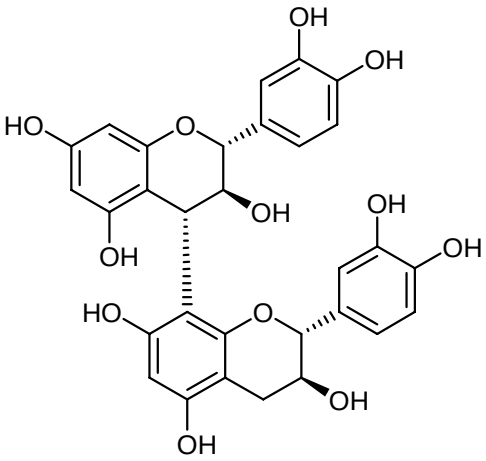
MS (EI, 70 eV): *m/z* (%) = 438 (98) [M^+], 362 (8), 347 (24), 226 (34), 213 (88), 107 (26), 91 (100), 65 (22).

HREIMS:	$C_{29}H_{26}O_4$	438.18311	(Calculated)
		438.18333	(Found)

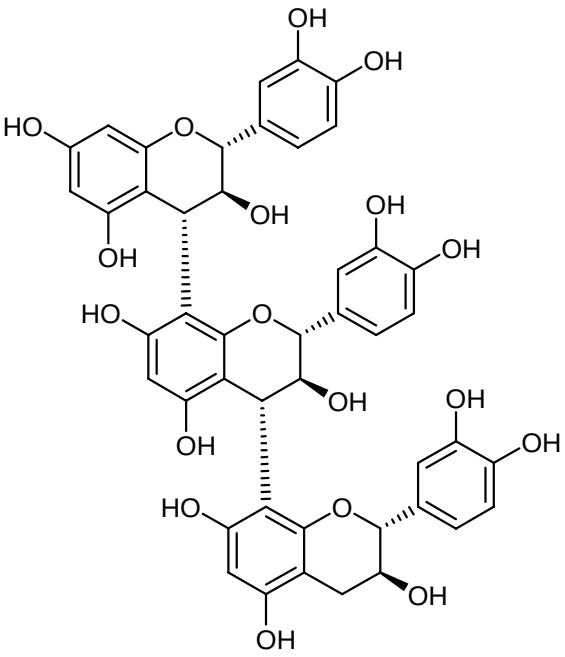
Chapter 5: Summary

In this work, the synthesis of biologically active proanthocyanidins was performed for better understanding of the fundamentals of structure-bioactivity relationship. In order to develop new agents for a more effective treatment of human diseases, the synthesis of the oligomeric flavonoids was investigated. These investigations could also open up new opportunities for other applications, such as targeted drug design and delivery.

Chapter 1 describes the synthesis of the bioactive oligomeric proanthocyanidins. The synthesis of the oligomeric procyanidins i.e. catechin dimer **(22)** and trimer **(23)** from racemic catechin has been attempted but it was proved to be unsuccessful. The synthesis of the known catechin dimer **(22)** and trimer **(23)** was then performed from pure (+)-catechin. These oligomeric flavonoids will help us to investigate their role at molecular level in biomolecules. These oligomeric flavonoids can be used as reference compounds in HPLC analysis of different food stuffs.

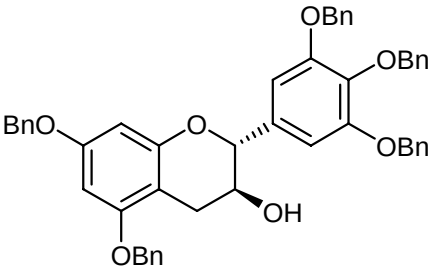


22



23

The total synthesis of the benzylated (–)-gallocatechin **(25)** has been done via different route and it was planned to synthesize different oligomers of prodelphinidins like prodelphindine B_3 **(43)** and T_2 **(24)** by using benzylated (–)-gallocatechin **(25)**.



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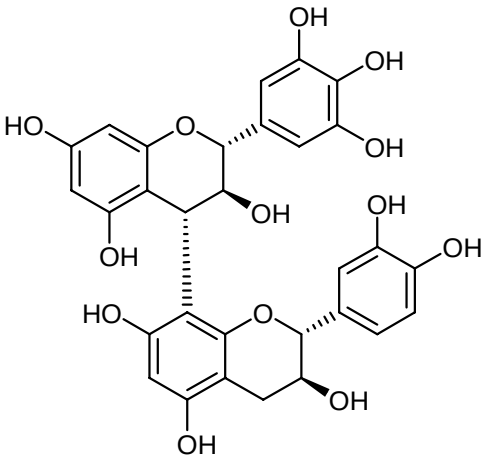

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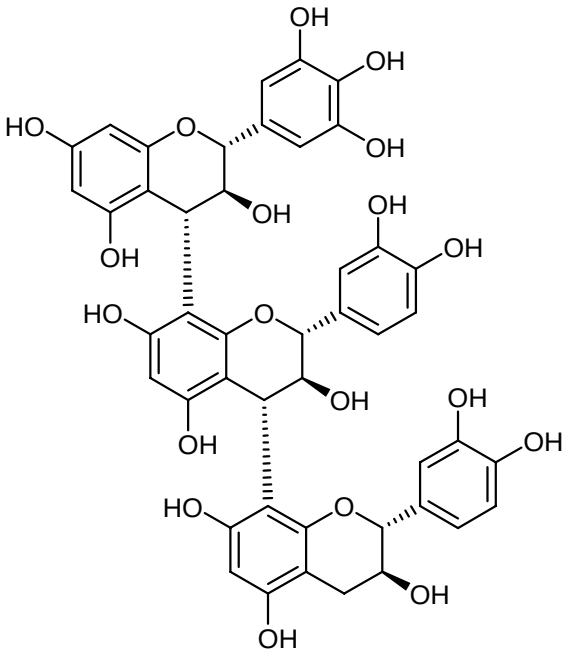


24

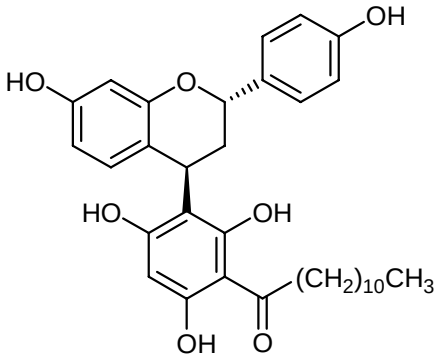
Chapter 2 gives an overview on enantioselective epoxidation of chalcones by using different catalysts. Three types of catalysts have been used to epoxidize the chalcone.

i. Catalysts derived from (+)-cinchonine.

ii. Catalysts derived from D-fructose and levoglucosan.

iii. Catalysts derived from polyamino acids.

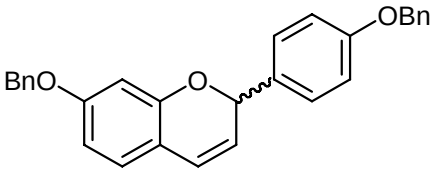
The aim of this work is try to improve the total synthesis of (+)-myristinin **A** (**65**) which is a natural DNA polymerase β inhibitor and potent DNA damaging agent. The maximum 93 % enantioselectivity in case of the unsubstituted chalcone with more than 80 % conversion was achieved. But in case of the substituted chalcones, the results were not satisfactory.



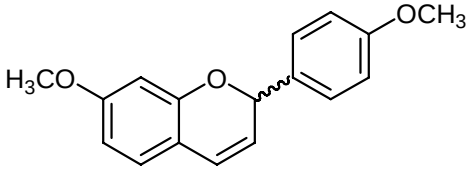
65 (+)-Myristinin A

Some new catalysts from (+)-cinchonin were prepared which showed respectable enantioselectivity with simple chalcone at low temperature but with substituted chalcones there was no enantioselectivity observed.

Chapter 3 presents the asymmetric reduction of chalcone into allylic alcohol. The reductions were performed by $NaBH_4$ and CBS catalyst. The allylic alcohols formed were subjected to cyclization in to flavene moieties. The main aim of this investigation was also to find out an alternative and short route to the total synthesis of the (+)-myristinin **A** (**65**) which is a natural DNA polymerase β inhibitor and potent DNA damaging agent. But in all cases, the allylic alcohol was cyclized in to racemic unstable flavene **184** or **186**.



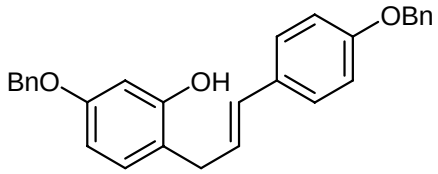
(±) **184**



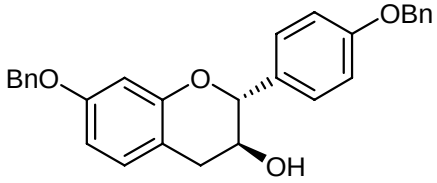
(±) **186**

The idea of using internal chirality of the molecule to induce chirality intramolecularly did not work and racemic product was obtained in all cases.

At the end of this work, the decarbonylation of the chalcone **113** have done by using mild reagent $NaBH_4$ in two step sequences to obtaine substituted propene **202**. Sharpless asymmetric dihydroxylation followed by cyclization using standard Mitsunobu reaction, the flave-3-ol **207** was obtaibed with required 2,3-trans stereochemistry in excellent enantioselectivity.



202



(-)-207

The synthesis of the flavan part of the myristinins A, B/C has been improved with excllent enantioselectivity. The yield of the substituted propene **202** was improved by optimizing the decarbonylation step in order to avoid the formation of the racemic flavene **184**. The number of the steps towards the total synthesis of the myristinins have been reduced by adopting different cyclization strategy. The excellent enantioselectivity of the 2,3-trans-flavan-3-ol **207** was obtained by using standard Mitsunobu reaction.

Chapter 6: Abbreviations

abs.	absolute
Ac	acetyl
Ar	aromatic
Bn	benzyl
Bzl	benzoyl
cat.	catalyst, catalytic
d	doublet
DME	1,2 dimethoxyethane
DMAP	dimethylaminopyridine
DMF	dimethylforamide
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
h.	hour(s)
HMPA	hexamethylphosphoramide
m.	multiplet
Me	methyl
MeOH	methanol
min.	minute
MOM	methoxymethyl
MOM	methoxymethyl
mp.	melting point
MS	mass spectrometry
Ms	mesyl
NMR	nuclear magnetic resonance spectroscopy
OBn	benzyloxy
OMe	methoxy
PE	petrolether
Ph	phenyl
PLL	poly-L-leucine
Piv	pivaloyl
q	quartet

s	singlet
t	triplet
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBACl	tetrabutylammonium chloride
TCF	trichloromethyl chloroformate
temp.	temperature
THF	tetrahydro furan
TLC	thin layer chromatography

Chapter 7: References

[1] K. Ohmori, N. Ushimaru, K. Suzuki, *Tetrahedron Letters* **2002**, *43*, 7753-7756.

[2] D. Strack, V. Wray, J. B. Harborne, P. M. Dey, *Methods in plant biochemistry* in *Plant phenolics* (Ed.: London Academic press), 1st. ed. **1989**, pp. 325-356.

[3] J. B. Harborne, T. J. Mabry, *The flavonoids* (Ed.: London Chapman and Hall) **1975**.

[4] J. B. Harborne, T. J Mabry, *The flavonoids, Advances in research* (Ed.: London Chapman and Hall) **1982**.

[5] J. B. Harborne, *The flavonoids, Advances in research since 1980* (Ed.: London Chapman and Hall) **1988**.

[6] J. B. Harborne, *The flavonoids, Advances in research since 1986* (Ed.: London Chapman and Hall) **1994**.

[7] X. Wu, L. Gu, R. L. Prior, S. McKay, *J. Agric. Food Chem.* **2004**, *52*, 7846-7856.

[8] D. Ferreira, P. J. Steynberg, g. D. Roux, V. E. Btandt, *Tetrahedron* **1992**, *48*, 1743-1803.

[9] S. Yoneda, H. Kawamoto, Nakatsubo., *J. Chem. Soc., Perkin Trans. 1* **1997**, 1025-1030.

[10] I. Tarascou, K. Barathieu, Y. Andre, I. Pianet, E. J. Dufourc, E. Fouquet, *Eur. J. Org. Chem.* **2006**, 5367-5377.

[11] A. Saito, N. Nakajima, A. Tanaka, M. Ubukata, *Tetrahedron* **2002**, *58*, 7829-7837.

[12] D. Ferreira, D. Slade, *Nat. Prod. Rep.* **2002**, *19*, 517-541.

[13] R. W. Hemingway, L. Y. Foo, L. J. Porter, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1209.

[14] J. B. Harborne, *L. J. Porter, in The flavonoids, advances in research since 1986* (Ed.: London Chapman and Hall) **1994**, p. 23.

[15] D. Y. Xie, R. A. Dixon, *Phytochemistry* **2006**, *66*, 2127-2144.

[16] J. J. Botha, D. Ferreira, G. D. Roux, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1235-1245.

[17] K. Ohmori, N. Ushimaru, K. Suzuki, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12002-12007.

[18] K. J. Murphy, *Am. J. Clinical Nutrition.* **2003**, *77*, 1466-1473.

[19] J. Shi, *J. Med. Food* **2003**, *6*, 291-299.

[20] R. G. Prior, L. Gu, *Phytochemistry* **2005**, *66*, 2264-2280.

[21] A. B. Howell, J. D. Reed, C. G. Krueger, R. Winterbottom, D. G. Cunningham, M. Leahy, *Phytochemistry* **2005**, *66*, 2281-2291.

[22] A. Saito, N. Nakajima, A. Tanaka, M. Ubukata, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1764-1767.

[23] A. Saito, N. Nakajima, A. Tanaka, M. Ubukata, *Tetrahedron Letters.* **2003**, *44*, 5449-5452.

[24] P. A. Kozikowski, W. Tückmantel, Y. Hu, *J. Org. Chem.* **2001**, *66*, 1287-1296.

[25] Y. Naito, M. Sugiura, Y. Yamaura, C. Fukaya, K. Yokoyama, Y. Nakagawa, T. Ikeda, M. Senda, T. Fujita, *Chem. Pharm. Bull.* **1991**, *39*, 1736-1745.

[26] C. C. Li, X. Z. Xie, D. Y. Zhang, H. J. Chen, Z. Yang, *J. Org. Chem.* **2003**, *68*, 8500-8504.

[27] N. N. Mateeva, N. R. Kode, K. K. Redda, *J. Hetereocyclic Chem.* **2002**, *39*, 1251-1258.

[28] M. Tsukayama, Y. Kawamura, H. Tamaki, T. Kubo, T. Horie, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 826-832.

[29] B. Nay, V. Arnaudinaud, J. Varcauteren, *Eur. J. Org. Chem.* **2001**, 2379-2384.

[30] T. Kikuchi, M. Nishimura, A. Hoshino, Y. Morita, S. Iida, N. Saito, T. Honda, *Heterocycles* **2003**, *60*, 1469-1475.

[31] V. Arnaudinaud, G. Nay, A. Nuhrich, G. Deffieux, M. J. Merillon, P. J. Monti, J. Vaercauteren, *Tetrahedron Lett.* **2001**, *42*, 1279-1281.

[32] F. berlin, P. Barthelemy, K. Ruiz, J. M. Lacombe, B. Pucci, *Helv. Chim. Acta* **2003**, *86*, 247-265.

[33] M. Fujita, M. Yamada, S. Nakajima, K. I. Kawal, M. Nagai, *Chem. Pharm. Bull.* **1984**, *32*, 2622-2627.

[34] G. Goetz, A. Fkyerat, N. Metais, M. Kunz, R. Tabacchi, R. Pezet, V. Pont, *Phytochemistry* **1999**, *52*, 759-767.

[35] Y. Zhao, X. Hao, W. Lu, J. Cai, H. Yu, T. Sevenet, F. Gueritte, *J. Nat. Prod.* **2002**, *65*, 902-908.

[36] G. J. Meuzelaar, M. C. A. van Valiet, L. Maat, R. A. Sheldon, *Eur. J. Org Chem.* **1999**, 2315-2321.

[37] C. Pouget, C. Fagnere, J.-P. Basly, A.-E. Besson, Y. Champavier, G. Habrious, A.-J. Chulia, *Pharmaceutical Research* **2002**, *19*, 286-291.

[38] A. Pelter, J. Bradshaw, R. F. Warren, *Phytochemistry* **1971**, *10*, 835-850.

[39] S. M. Ali, M. Ilyas, *J. Org. Chem.* **1986**, *51*, 5415-5417.

[40] J. A. N. Augustyn, B. C. B. Bezuidenhoudt, D. Ferreira, *Tetrahedron* **1990**, *46*, 2651-2660.

[41] D. J. Maloney, J.-Z. Deng, S. R. Starck, Z. Gao, S. M. Hecht, *J. Am. Chem. Soc.* **2005**, *127*, 4140-4141.

[42] T. N. Zaveri, *Org. Lett.* **2001**, *3*, 843-846.

[43] M. Tsukayama, Y. Kawamura, H. Tamaki, T. Kubo, T. Horie, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 826-832.

[44] N. Minami, S. Kijima, *Chem. Pharm. Bull.* **1979**, *27*, 1490-1494.

[45] L. Li, T. H. Chan, *Org. Lett.* **2001**, *3*, 739-741.

[46] S. S. Jew, Y. D. Lim, Y. S. Bae, A. H. Kim, H. J. Kim, J. Lee, G. H. Park, *Tetrahedron: Asymmetry* **2002**, *13*, 715-720.

[47] A. Saito, A. Tanaka, M. Ubukata, N. Nakajima, *Synlett.* **2004**, 1069-1073.

[48] E. Weitz, A. Scheffer, *Chem. Ber.* **1921**, *54*, 2344-2353.

[49] D. Enders, J. Zhu, G. Raabe, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1725-1728.

[50] H. Yu, X. Zheng, Z. Lin, Q. Hu, W. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 8149-8155.

[51] K. Yamada, T. Arai, H. Sasai, M. and Shibasaki, *J. Org. Chem.* **1998**, *63*, 3666-3672.

[52] S. Watanabe, Y. Kobayashi, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *Tetrahedron Letters.* **1998**, *39*, 7353-7356.

[53] M. Bougauchi, S. Watanabe, T. Arai, H. sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329-2330.

[54] K. Daikai, M. Kamaura, J. Inanaga, *Tetrahedron Letters.* **1998**, *39*, 7321-7322.

[55] G. Kumaraswamy, M. N. V. Sastry, N. Jena, K. R. Kumar, M. Vairamani, *Tetrahedro: Asymmetry.* **2003**, *14*, 3797-3803.

[56] G. Kumaraswamy, M. N. V. Sastry, N. Jena, *Tetrahedron Letters.* **2001**, *42*, 8515-8517.

[57] C. L. Elston, R. F. W. Jackson, S. J. F. MacDonald, P. J. Murray, *Angull. Chem. Int. Ed. Engl.* **1997**, *36*, 410-412.

[58] D. Jayaprakash, Y. Kobayashi, S. Watanabe, T. Arai, H. Sasai, *Tetrahedron: Asymmetry* **2003**, *14*, 1587-1592.

[59] Corey. E. J., F. Zhang, *Org. Lett.* **1999**, *1*, 1287-1290.

[60] B. Lygo, P. G. Wainwright, *Tetrahedron* **1999**, *55*, 6289-6300.

[61] B. Lygo, D. C. M. To, *Chem. Commun.* **2002**, 2360-2361.

[62] B. Lygo, P. G. Wainwright, *Tetrahedron Letters.* **1998**, *39*, 1599-1602.

[63] B. Lygo, D. C. M. To, *Tetrahedron Letters* **2001**, *42*, 1343-1346.

[64] T. Kato, M. Tanaka, M. Hoshikawa, M. Yagi, *Tetrahedron Letters.* **1998**, *39*, 7553-7556.

[65] G. Macdonald, L. Alcaraz, N. J. Lewis, K. J. R. :. Taylor, *Tetrahedron Letters.* **1998**, *39*, 5433-5436.

[66] J. Ye, Y. Wang, R. Liu, G. zhang, Q. Zhang, J. Chen, X. Liang, *Chem.Commun.* **2003**, 2714-2715.

[67] W. Adam, P. B. Rao, H. G. Degen, C. R. S. Moller, *Eur. J. Org. Chem.* **2002**, 630-639.

[68] W. Adam, P. B. Rao, H. G. Degen, C. Saha-Moeller, *J. Am. Chem. Soc.* **2000**, *122*, 5654-5655.

[69] W. Adam, P. B. Rao, H. G. Degen, C. Saha-Moeller, *Tetrahedron: Asymmetry* **2001**, *12*, 121-125.

[70] W. Adam, P. B. Rao, H. G. Degen, A. Levai, T. Patonay, C. Saha-Moeller, *J. Org. Chem.* **2002**, *67*, 259-264.

[71] J. Lv, X. Wang, J. Liu, L. Zhang, Y. Wang, *Tetrahedron: Asymmetry* **2006**, *17*, 330-335.

[72] T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844-6845.

[73] S. Julia, J. Masana, J. C. Vega, *Angew. Chem. Int. Ed.* **1980**, 929-931.

[74] S. Banfi, S. Colonna, H. Molinari, S. Julia, J. Guixer, *Tetrahedron* **1984**, *40*, 5207-5211.

[75] S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana, A. Alvarez, *Tetrahedron* **1983**, *39*, 1635-1641.

[76] A. P. Bentley, S. Bergeron, W. M. Cappi, E. D. Hibbs, B. M. Hursthouse, C. T. Nugent, R. Pulido, M. S. Roberts, E. L. Wu, *Chem. Commun.* **1997**, 739-740.

[77] L. Carde, H. Davies, P. T. Geller, M. S. Roberts, *Tetrahedron Letters.* **1999**, *40*, 5421-5424.

[78] W. P. Chen, A. L. Egar, M. B. Hursthouse, A. K. M. Malik, Mathews. J.E., S. M. Roberts, *Tetrahedron Letters.* **1998**, *39*, 8495-8498.

[79] R. J. J. Nel, P. S. van Heerden, H. van Rensburg, D. Ferreira, *Tetrahedron letters.* **1998**, *39*, 5623-5626.

[80] R. J. J. Nel, H. van Rensburg, P. S. van Heerden, J. Coetzee, D. Ferreira, *Tetrahedron* **1999**, *55*, 9727-9736.

[81] W. Kroutil, P. Mayon, M. E. Lasterra-Sanchez, S. J. Maddrell, S. M. Roberts, S. R. Thornton, C. J. Todd, M. Tuter, *Chem. commun.* **1996**, 845-846.

[82] S. P. Mthew, S. Gunathilagen, S. M. Roberts, D. G. Blackmond, *Org. Lett.* **2005**, *7*, 4847-4850.

[83] G. Carrea, S. Colonna, A. D. Meek, G. Ottolina, S. M. Roberts, *Chem. Commun.* **2004**, 1412-1413.

[84] D. R. Kelly, T. T. T. Bui, E. Caroff, A. F. Drake, S. M. Roberts, *Tetrahedron Letters* **2004**, *45*, 3885-3888.

[85] P. A. Bentley, R. W. Flood, S. M. Roberts, J. Skidmore, C. B. Smith, J. A. Smith, *Chem. Commun.* **2001**, 1616-1617.

[86] D. R. Kelly, S. M. Roberts, *Biopolymers (Pept Sci)* **2006**, *84*, 74-89.

[87] M. E. Lasterra-Sanchez, U. Felfer, P. Mayon, S. M. Roberts, S. R. Thornton, C. J. Todd, *J. Chem. Soc., Perkin Trans. 1* **1996**, 343-348.

[88] M. E. Lasterra-Sanchez, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1467-1468.

[89] P. A. Bentley, W. Kroutil, J. A. Littlechild, S. M. Roberts, *Chirality* **1997**, *9*, 198-202.

[90] F. J. Bickley, T. A. Gillmore, M. S. Roberts, J. Skidmore, A. Steiner, *J. Chem. Soc., Perkin Trans 1*. **2001**, 1109-1115.

[91] J. V. Allen, K. H. Drauz, W. R. Flood, S. M. Roberts, J. Skidmore, *Tetrahedron Letters*. **1999**, *40*, 5417-5420.

[92] S. Itsuno, M. Sakakura, K. Ito, *J. Org. Chem.* **1990**, *55*, 6047-6049.

[93] P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts, L. E. Wu, *Chem. Commun.* **1997**, 739-740.

[94] B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. Mccague, T. C. Nugent, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501-3507.

[95] T. Geller, A. Gerlach, C. M. Krüger, H. C. Militzer, *Tetrehedron Letters* **2004**, *45*, 5065-5067.

[96] T. Geller, C. M. Krüger, H. C. Militzer, *Tetrahedron Letters* **2004**, *45*, 5069-5071.

[97] A. Gerlach, T. Geller, *Adv. Synth. Catal.* **2004**, *346*, 1247-1249.

[98] T. Geller, A. Gerlach, C. M. Krüger, H. C. Militzer, *J. Molecular Catalysis A: Chemicals* **2006**, *251*, 71-77.

[99] S. E. Denmark, Z. C. Wu, *Synlett* **1999**, 847-859.

[100] X. Z. Wang, M. S. Miller, P. O. Anderson, Y. Shi, *J. Org. Chem.* **1999**, *64*, 6443-6458.

[101] X. Z. Wang, Y. Tu, M. Frohn, R. J. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

[102] L. Shu, Y. Shi, *Tetrahedron* **2001**, *57*, 5213-5218.

[103] X. Z. Wang, M. S. Miller, P. O. Anderson, Y. Shi, *J. Org. Chem.* **2001**, *66*, 521-530.

[104] L. Shu, Y. Shi, *J. Org. Chem.* **2000**, *65*, 8807-8810.

[105] A. G. Cao, X. Z. Wang, Y. Tu, Y. Shi, *Tetrahedron Letters.* **1998**, *39*, 4425-4428.

[106] Wang Z.X., Y. Shi, *J. Org. Chem.* **1997**, *62*, 8622-8623.

[107] M. Hickey, D. Goeddel, Z. Crane, Y. Shi, *Proceed. Natl. Acad. Sci.* **2004**, *101*, 5794-5798.

[108] D. Goeddel, L. Shu, Y. Yuan, O. A. Wong, B. Wang, Y. Shi, *J. Org. Chem.* **2006**, *71*, 1715-1717.

[109] M. X. Zhao, D. Goeddel, K. Li, Y. Shi, *Tetrahedron* **2006**, *62*, 8064-8068.

[110] M. X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377-5379.

[111] H. Tian, X. She, Y. Shi, *Org. Lett.* **2001**, *3*, 715-718.

[112] G. Kumaraswamy, N. Jena, M. N. V. Sastry, M. Padmaja, B. Markondaiah, *Adv. Synth. Catal.* **2005**, *347*, 867-871.

[113] P. C. M. MAO, J. F. Mouscadet, H. Leh, C. Auclair, L. Y. Hsu, *Chem. Pharm. Bull.* **2002**, *50*, 1634-1637.

[114] M. Humora, J. Quick, *J. Org. Chem.* **1979**, *44*, 1166-1168.

[115] R. R. Fernandes, M. S. Bodas, P. Kumar, *Tetrahedron* **2002**, *58*, 1223-1227.

[116] S. H. Jung, S. H. Cho, T. H. dang, J. H. Lee, J. H. Ju, M. K. Kim, Lee. S.H., Ryu. J.C., Kim. Y., *Eur. J. Med. Chem.* **2003**, *38*, 537-545.

[117] S. Venkateswarlu, G. K. Panchagnula, M. B. Guraiah, G. V. Subbaraju, *Tetrahedron* **2005**, *61*, 3013-3017.

[118] B. C. B. Bezuidenhoudt, E. V. Brandt, D. Ferreira, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1081-1087.

[119] E. J. Corey, H. Cho, C. Rücker, D. H. Hua, *Tetrahedron Letters* **1981**, *22*, 3455-3458.

[120] A. B. SmithIII, J. R. Empfielf, R. A. Rivero, H. A. Vaccaro, J. j. w. Duan, M. M. Sulikowski, *J. Am. Chem. Soc.* **1992**, *114*, 9419-9434.

[121] M. Orfanopoulos, I. Smonou, C. S. Foote, *J. Am. Chem. Soc.* **1990**, *112*, 3607-3614.

[122] H. Yin, R. W. Franck, S.-L. Chen, G. J. Quigley, L. Todarot, *J. Org. Chem.* **1992**, *57*, 644-651.

[123] T. Ando, J. Yamawaki, T. Kawate, S. Sumi, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2504-2507.

[124] H. Takahashi, Y. Kubota, H. Miyazaki, M. Onda, *Heterocycles* **1984**, *22*, 1147-1153.

[125] D. L. Hughes, U. H. Dolling, Ryan. K. M., E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.* **1987**, *52*, 4745-4752.

[126] M. J. O´Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507-4518.

[127] K. M. Belyk, Leonard. W. R. Jr., D. R. Bender, D. L. Hughes, *J. Org. Chem.* **2000**, *65*, 2588-2590.

[128] Y. X. Wu, X. She, Y. Shi, *J. Am. Chem. Soc.* **2002**, *124*, 8792-8793.

[129] R. Katakai, Y. Lizuka, *J. Org. chem.* **1985**, *50*, 715-716.

[130] J. E. Corey, K. R. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

[131] J. E. Corey, J. C. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.

[132] S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475-1504.

[133] T. Ohkuma, M. Koizumi, K. Muniz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6508-6509.

[134] M. Node, K. Nishide, Y. Shigeta, H. Shiraki, K. Obata, *J. Am. Chem. Soc* **2000**, *122*, 1927-1936.

[135] T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Letters.* **1981**, *22*, 4723-4726.

[136] C. Bianchini, E. Farnetti, L. Glendenning, M. Graziani, G. nardin, M. Peruzzini, E. Rocchini, F. Zanobini, *Organometallics* **1995**, *14*, 1489-1502.

[137] B. T. Cho, Y. S. Chum, *J. Chem. Soc., Perkin Trans. I* **1999**, 2095-2100.

[138] H. G. Roos, R. A. Donovan, *Tetrahedron: Asymmetry* **1999**, *10*, 991-1000.

[139] R. M. Hanson, K. B. Sharpless, *J. Org. Chem* **1986**, *51*, 1922-1925.

[140] B. Nay, V. Arnaudinaud, F. J. Peyrat, A. Nuhrich, G. Deffieux, M. J. Merillon, J. Vercauteren, *Eur. J. Org. Chem.* **2000**, 1279-1283.

[141] J. M. Dickinson, J. A. Murphy, C. W. Patterson, N. F. Wooster, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1179-1181.

[142] E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861-2863.

[143] V. Vaillancourt, M. R. Agharahimi, U. N. Sundram, O. Richou, D. J. Faulkner, K. F. Albizati, *J. Org. Chem.* **1991**, *56*, 378-387.

[144] J. J. P. Furlong, N. S. Nudelman, *J. Chem. Soc. Perkin Trans. II* **1988**, 1213-1217.