CHAPTER III

TOTAL FACILE SYNTHESIS OF BIOACTIVE ISOFLAVONOIDS

3.1 INTRODUCTION

Isoflavonoids represent a large class of natural products and exhibit remarkably diverse biological properties. They are found in many plants and are especially abundant in *Leguminosae* family, such as soya, lentils, chick pea, fenugreek, clovers and alfafa [85]. Compounds with isoflavonoid as the core structure have been shown to possess antioxidant [86, 87], antitumor [88, 89], anticataract [90], anti-inflammatory [91] and antifertility [92] activity. Some isoflavonoids are well-known as tyrosine kinase inhibitor [93]. Recent studies have also revealed that isoflavonoids bind to G-protien couple receptors, including serotonin, dopamine, δ-opiate and benzodiazepine receptors [94].

Concerning with their remarkably rich biological activities and excellent pharmacological properties, isoflavonoids have been the target of a grate deal of research into their synthesis.

As aforementioned in previous chapter, eight isolated substances (**D1-D8**) were obtained from the dichloromethane extract of *D. oliveri* heartwood. Among them, **D5**, (±)-mucronulatol, displayed the significant radical scavenging effect on DPPH radical with IC_{50} value 0.32 mM as well as the highest antifungal activity against *F. oxysporum* at the minimum amount required for the inhibition of fungal growth on TLC of 0.5 μg. **D7**, (±)-violanone, showed moderate scavenging activity towards DPPH radical with IC_{50} value 0.48 mM and antifungal activity against *F. oxysporum* at the minimum amount required for the inhibition of fungal growth on TLC of 1 μg. In addition, **D5** and **D7** displayed cytotoxicity against human hepatocellular carcinoma (HepG2) with IC_{50} values of 3.7 and 4.7 μg/mL, respectively. Furthermore, **D7** also showed high cytotoxicity against diamondback moth and mosquito larvae with LC_{50} values of 92 and 121 ppm, respectively. Nevertheless, **D5** and **D7** obtained in limited quantitative yield (4.5×10^{-3}% and 9.5×10^{-3}% based on the dried heartwoods (4 kg), respectively). As a result, subsequent biological studies have been very limited. Various biological activities of isolated

substances mainly with the same reason have not been established due to its scarce natural abundance.

Therefore, to complete structure activity relationship study, (±)-mucronulatol (**D5**) and (±)-violanone (**D7**) were selected to synthesize as a representative of isoflavan and isoflavanone, respectively. Furthermore, 7-hydroxy-3',4'-dimethoxy-isoflavone was also synthesized as a representative of isoflavone.

3.1.1 Literature Review

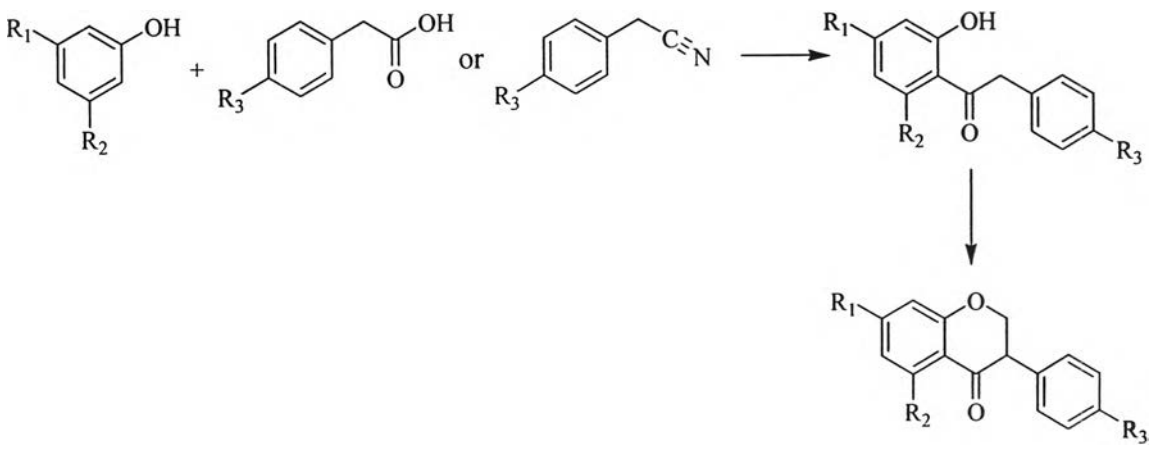
3.1.1.1 Synthetic Routes to Isoflavones

Many different procedures exist for the preparation of isoflavones can be categorized to one of the following general methods:

- The addition of a one-carbon unit to a deoxybenzoin and subsequent ring closure
- The oxidative conversion of chalcones
- The rearrangement of flavanones
- The arylation of chromanone moiety

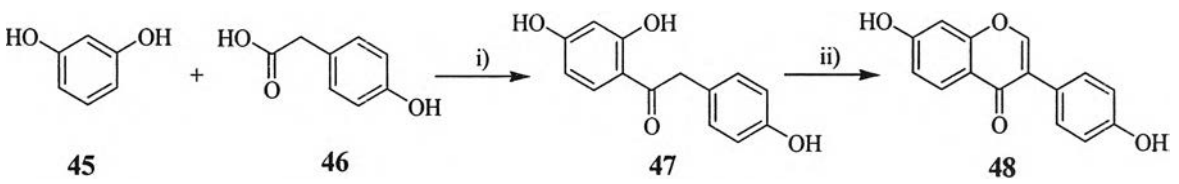
(a) *via* deoxybenzoin

The general synthetic route for isoflavonoids generally involves the condensation of an appropriate phenol with either a substituted phenyl acetic acid or benzyl nitrile. This gives deoxybenzoin which then undergoes formylation and finally cyclization to give isoflavonoid [95].



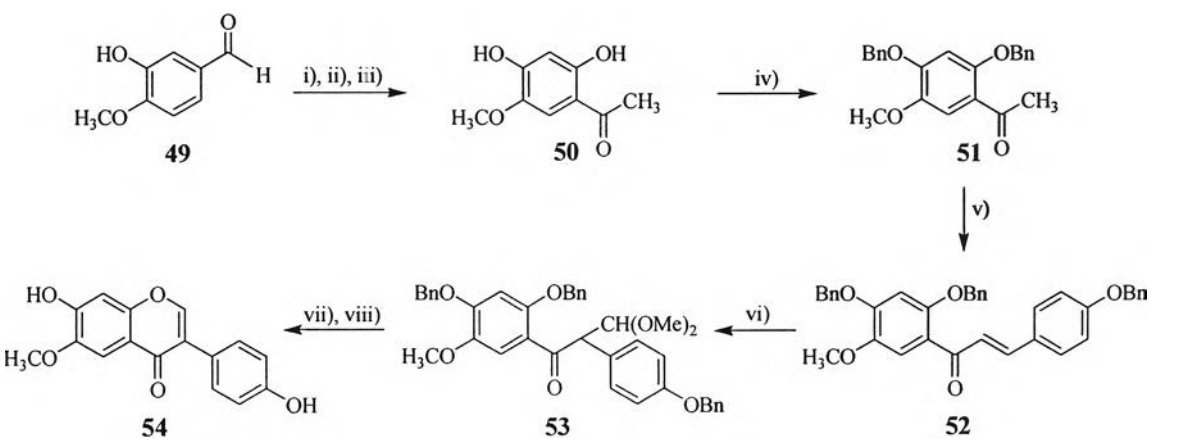
Spath and Lederer [96] reported that minute amount of isoflavone derivatives could be obtained through the reaction of *o*-hydroxydeoxybenzoins with ethylformate and sodium. Later, the procedure was improved by Venkataraman and co-workers [97, 98] to receive isoflavones in moderate to good yield with necessary protection of all hydroxyl groups except the 2-hydroxyl group prior to performing the reaction in order to prevent ring formylation and consequent polymerization.

Recently, daidzein (**48**), the soy isoflavones, was synthesized by Oldfield and co-workers [95]. Condensation of the resorcinol (**45**) and *p*-hydroxyphenylacetic acid (**46**) was carried out in neat $BF_3.OEt_2$, giving the deoxybenzoin intermediate (**47**). The formylation cyclization step was achieved using dimethylformamide dimethylacetal in DMF.



i) $BF_3.Et_2O$; ii) $DMF.(OMe)_2$, DMF

Furthermore, in 2004 Zhang and Botting [99] reported the synthesis of glycitein, another soy isoflavone. This procedure involved the reaction of 2,4-dihydroxy-5-methoxyacetophenone (**50**) *via* acetylation of isovanillin (**49**) with acetyl chloride followed by a Baeyer-Villiger reaction, selective hydrolysis and finally a BF_3 catalyzed Fries rearrangement. An aldol reaction using 4-benzyloxybenzaldehyde gave a chalcone (**52**) and then thallium (III) mediated oxidative rearrangement, deprotection and cyclization provided glycitein (**54**).



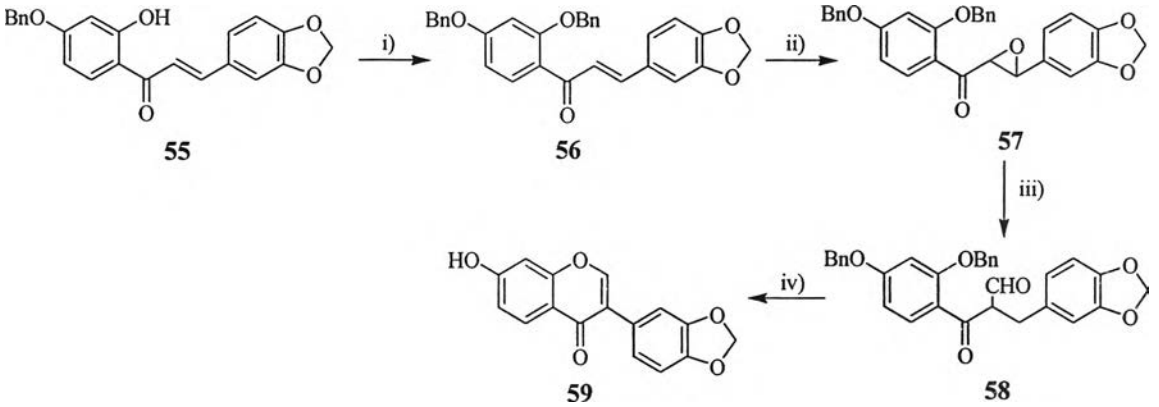
i) CH_3COCl, Et_3N, THF/Et_2O; ii) *m*-CPBA, CH_2Cl_2, reflux, then $NaHCO_3$, EtOH; iii) $BF_3.OEt_2$, 70°C; iv) BnBr, K_2CO_3, acetone, reflux; v) H_3CO-C$_6$H$_4$-CHO, KOH, MeOH/THF; vi) $Tl(NO_3)_2.3H_2O$, $HC(OMe)_3$, MeOH; vii) H_2, 5% Pd/C, MeOH/Acetone; viii) MeOH, conc HCl, reflux

(b) *via* chalcones

Synthesis of isoflavones usually involves ring closure of benzyl phenyl kenone [100], the preparation of which is often unsatisfactory [101] or unsuccessful. The generally more accessible chalcones can be converted into isoflavones *via* chalcone epoxides [102-104] or by the oxidative rearrangement of chalcone [105-107]. Chalcones are readily obtained by condensation of aromatic acetophenone with aromatic aldehydes.

- *via* chalcone epoxidation

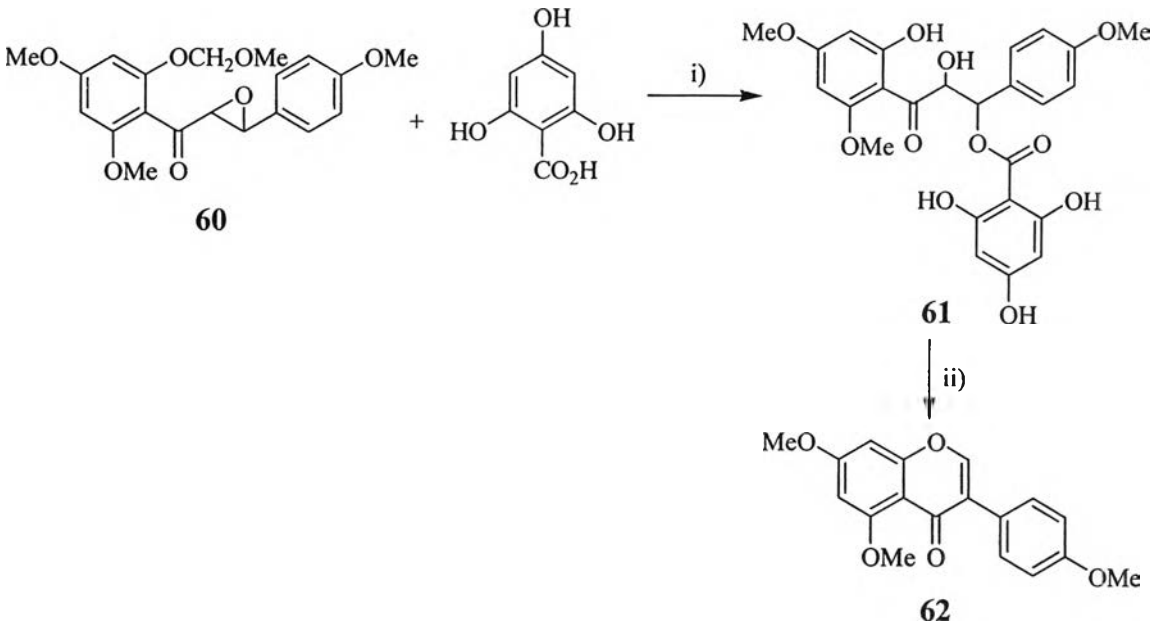
In 1963, Jain and co-workers [102-104] synthesized isoflavones by BF_3 catalyzed rearrangement of 2-benzyloxychalcone epoxides. The application of this method to the synthesis of pseudoptigenin (**59**) is shown below:



i) BnBr, K_2CO_3, acetone, reflux; ii) 30% H_2O_2, NaOH; iii) $BF_3.OEt_2$, benzene; iv) AcOH, HCl

The 2'-hydroxy group of chalcone (**55**) was protected by benzylation and following epoxidation with H_2O_2. BF_3-catalyzed rearrangement of the chalcone epoxide (**57**) receieved the α-formyldeoxybenzoin (**58**) which in the presence of acid underwent benzyl group cleavage and ring closure to obtain pseudoptigenin (**59**).

Moreover, Westhuizen and co-workers [105] reported the reaction of a chalocon epoxide (**60**) with 2,4,6-trihydroxybenzoic acid to give the β-ester (**61**). Acid treatment of (**61**) provided 4',5,7-trimethoxyisoflavone (**62**) in 25% an overall yield.

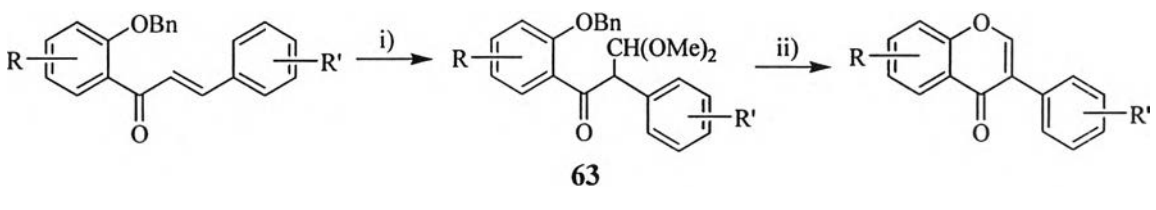


i) $(CH_3)_2CO$, RT, 1 h; ii) TsOH, benzene, Δ, 1 min

- *via* oxidative rearrangement of chalcone

The oxidative rearrangement of chalcones has been widespread application for the synthesis of isoflavones, for examples:

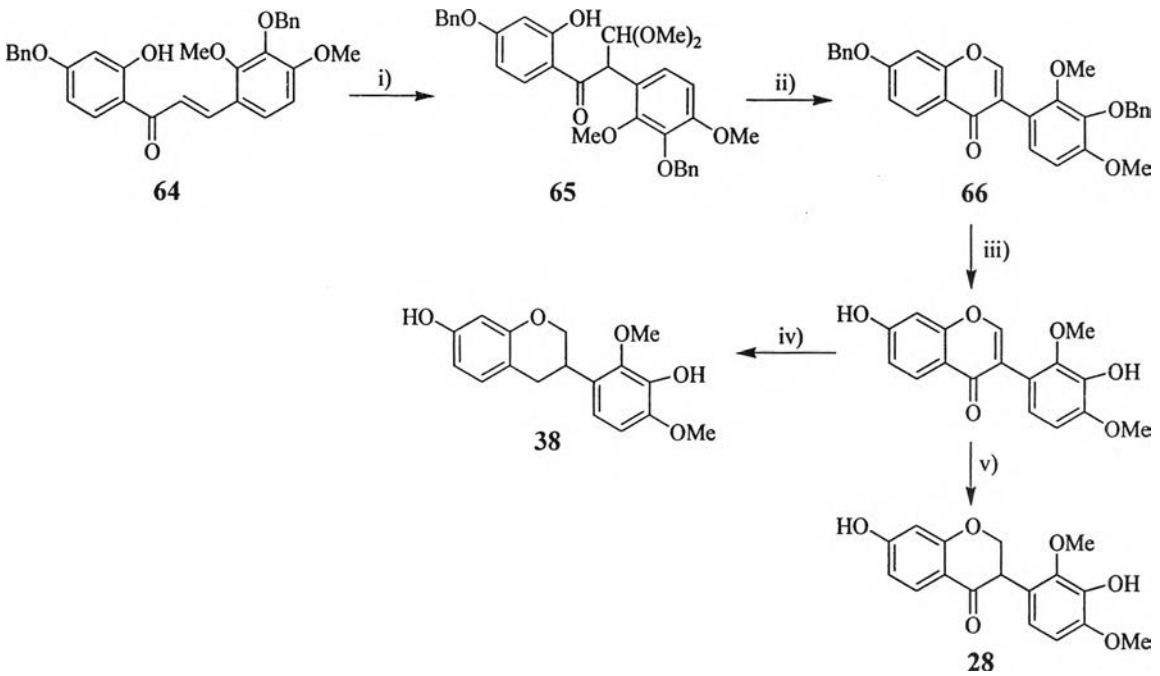
Ollis and co-workers [106-108] disclosed that isoflavones could be synthesized by the oxidative rearrangement of fully protected chalcones with thallium (III) acetate. The initial product was a 1,2-diaryl-3,3-dimethylpropan-1-one (**63**) which after deprotection and hydrolysis provided the isoflavone in moderate yield.



i) $Tl(OAc)_3$, $HC(OMe)_3$, MeOH, Δ , 100 h; ii) H_2, Pd/C; iii) HCl, MeOH

Later, Mckillop and co-workers [109] found that thallium (III) nitrate (TTN) was more efficient than the triacetate for the rearrangement of simple chalcone to 1,2-diaryl-3,3-dimethoxyprapan-1-ones. The reaction was usually complete within a few minutes at room temperature, whereas, thallium (III) triacetate required up to 100 h at 65°C. In addition, Farkas and co-workers [110] extended this improved reaction to the synthesis of isoflavones and found that simple unprotected 2'-hydroxychalcones could be smoothly converted by TTN into 1,2-diaryl-3,3-dimethoxyprapan-1-ones and that

acid catalyzed ring closure of the acetal provided the corresponding isoflavones. For example, mucronulatol (**38**) and violanone (**28**) were conveniently prepared by the oxidative rearrangement of 2'-hydroxychalcone (**64**) with TTN in MeOH into 1-(2-hydroxyphenyl)-3,3-dimethoxy-2-phenylpropane-1-one (**65**) followed by cyclization to give isoflavone derivative (**66**). Finally, deprotection and following with catalytic hydrogenation in the presence of acetic acid gave mucronulatol (**38**) or hydrogenation in acetone on palladium charcoal catalyst yielded violanone (**28**).



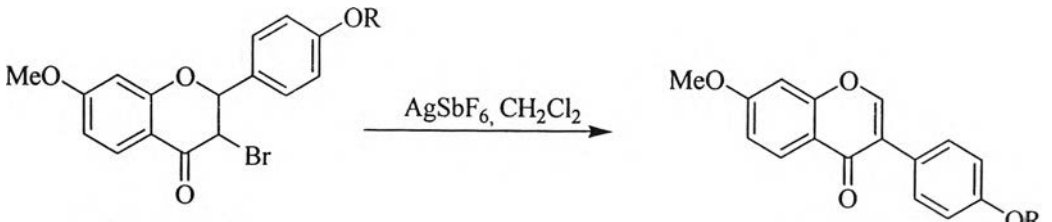
i) TTN, MeOH; ii) HCl, MeOH; iii) H_2, Pd/C; iv) H_2, Pd/C, AcOH; v) H_2, Pd/C, acetone

However, the utilization of the above method was unsatisfied since reactions proceeded in very poor yield with those chalcones, possibly due to their highly insoluble in MeOH.

(c) The rearrangement of flavanones

- with silver hexafluoroantimonate ($AgSbF_6$)

Pelter and co-workers [111] exposed that treating 3-bromoflavanones (**67a**) and (**67b**) with silver hexafluoroantimonate in CH_2Cl_2 yielded the corresponding isoflavones (**68a**) and (**68b**), respectively, in moderate yield *via* 2,3-aryl migration.

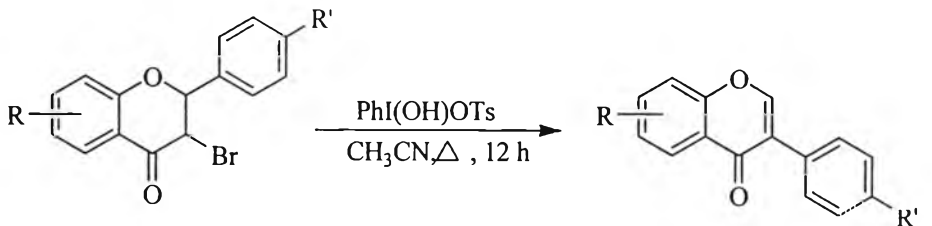


67a R = H
67b R= Me

68a R = H
68b R= Me

- with [hydroxyl(tosyloxy)iodo]benzene (PhI(OH)OTs)

Oxidative rearrangement of flavanone (**69**) occurred with stiochiometric of [hydroxyl(tosyloxy)iodo]benzene in refluxing acetonitrile generating the corresponding isoflavones (**70**) in good yield (72-80%) [112].



69 **70**

- with thallium (III) salts

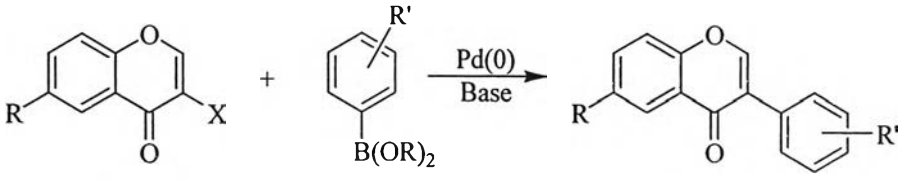
Isoflavones have been obtained by oxidative rearrangement of flavanones using thallium (III) toluene-*p*-sulphonate in propionitrile [113, 114], TTN in acetonitrile [114], TTN in MeOH-$CHCl_3$ containing 70% perchloric acid [115] and thallium (III) perchlorate in acetonitrile or dimethoxyethane [116]. Each of these methods suffered however in requiring the use of stoichiometric quantities of toxic thallium salts.

(d) The arylation of a chromanone moiety

Although the aforementioned methods could produce isoflavones individually in good yield, they were not efficient for synthesis of a series of isoflavones with different substituted groups at 3-position. Therefore, to dissolve this problem a series of 3-aryl isoflavones derivatives could be efficiently synthesized by using arylation of chromanone reaction.

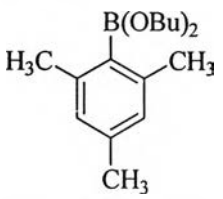
- with $ArB(OH)_2$ or $ArB(OBu)_2$

The palladium catalyzed cross coupling reaction of 3-bromochromones (**71**) [117] and 3-iodochromones (**72**) [118] with arylboronic acids or its butyl ester afforded isoflavones in moderate to good yield (47-98%). The reaction was found to be sensitive to steric effects: arylation with dibutyl mesitylboronate (**73**) gave a low yield of isoflavone (**74**) after a long reaction time (48 h under reflux condition).



71 X = Br
72 X = I

R = H, Bu



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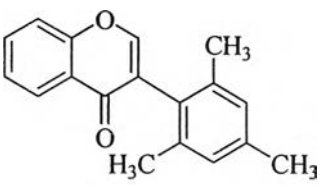

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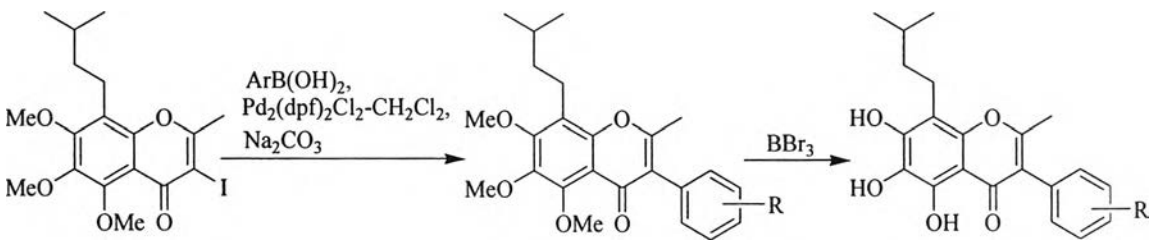
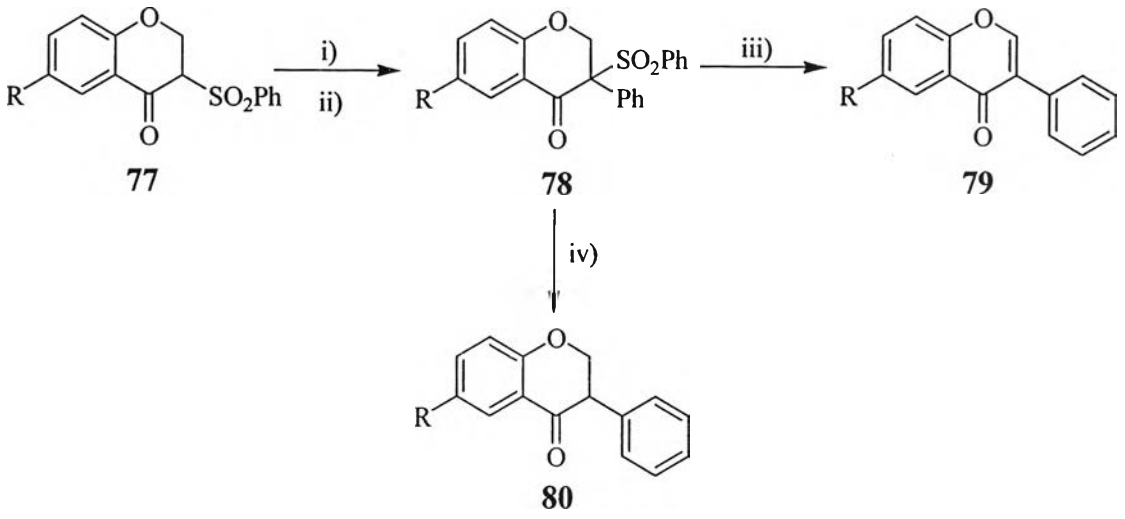
Recently, Ding and Wang [85] reported the synthesis of analogues of 3-aryl-8-isobutyl-5,6,7-trihydroxy-2-methyl-4*H*-chromen-4-one (**76**) *via* Suzuki coupling reaction of 3-iodo-8-isobutyl-5,6,7-trimethoxy-2-methyl-4*H*-chromen-4-one (**75**) with different aryl boronic acids.



75 **76**

- with organobismuth reagents

The phenylation of 3-phenylsulfonylchroman-4-ones (**77**) with tripheylbismuth carbonate yielded isoflavones (**79**) and isoflavanone (**80**) after oxidative and reductive removal respectively of the phenylsulphonyl group from 3-phenyl-3-phenylsulphonylchroman-4-on intermediates (**78**) [119, 120].

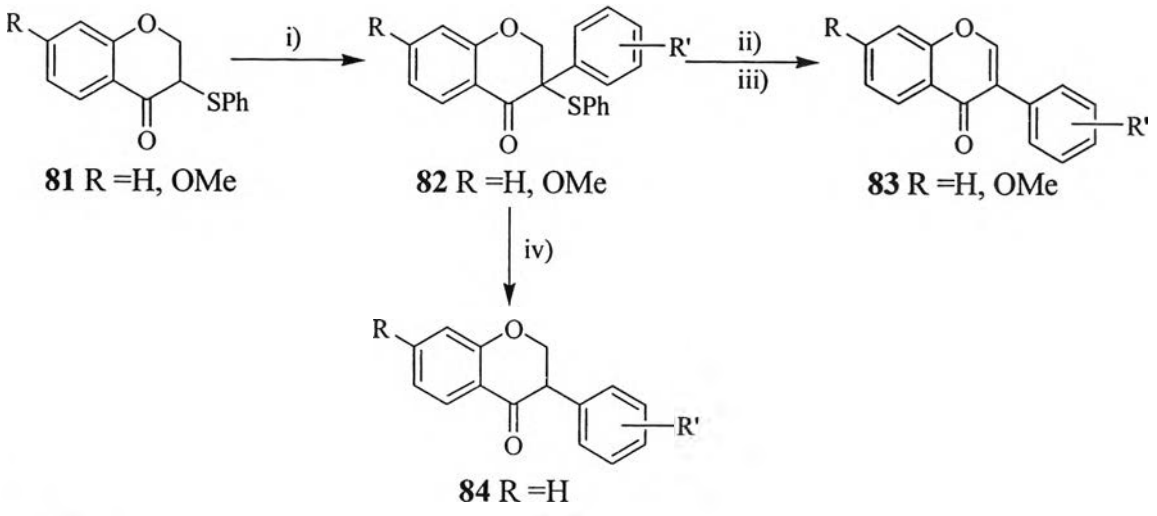


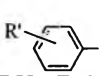
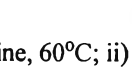
i) KH,THF; ii) Ph_3BiCO_3, reflux; iii) $AlCl_3$, CH_2Cl_2, RT; iv) Zn, HOAc, refulx 1h

In spite of the organobismuth mediated ligand coupling route to isoflavonoids was good yield, this method was severely limited with regards to natural product synthesis because of the lack of availability of suitably substituted arylbismuth reagents.

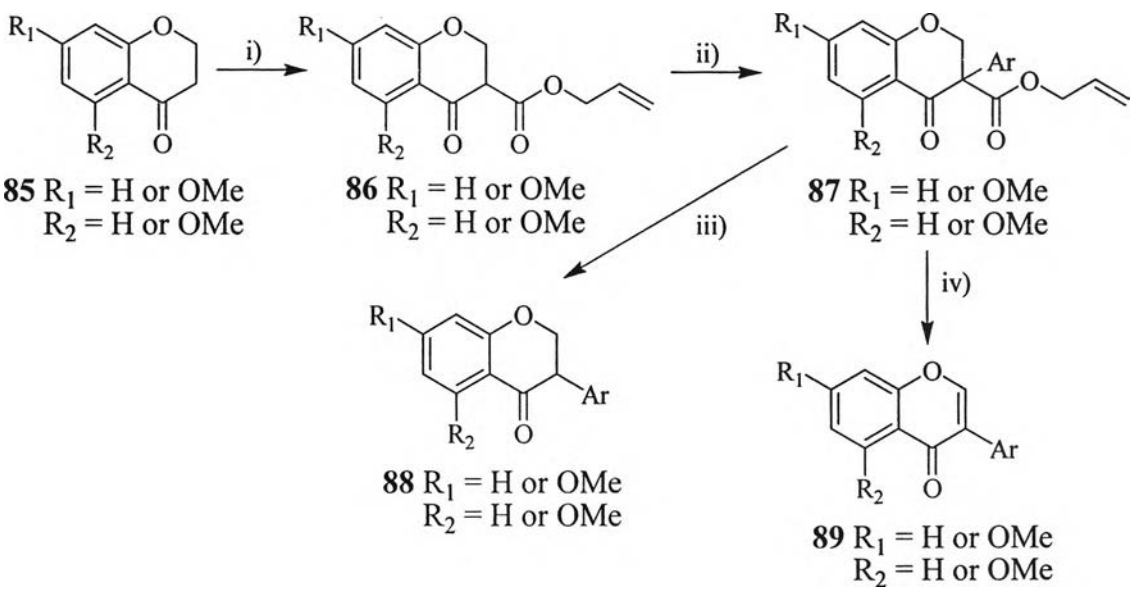
- with arylleadtriacetate $ArPb(OAc)_3$

Arylation of 3-(phenylthio)-chroman-4-ones (**81**) with a range of aryllead (IV) triacetate gave a series of 3-aryl-3-(phenylthio)-chroman-4-ones (**82**). Removal of the phenylthio group by oxidation with dimethyldioxirane and subsequent thermal elimination lead to the corresponding isoflavones (**83**). Isoflavanones (**84**) were also obtained from (**82**) by reduction with nickel boride [121].



i)  $Pb(OAc)_3$, $CHCl_3$, pyridine, 60°C; ii)  , acetone, rt; iii) toluene, reflux; iv) $NiCl_2$, $NaBH_4$, EtOH, H_2O, reflux

In addition, Donnelly and co-workers [122, 123] reported arylation of ring-A substituted and unsubstituted 3-allyloxycarbonylchroman-4-ones with aryllead (IV) triacetate followed by selective catalytic dealloxycarbonylation afforded the corresponding isoflavanones or isoflavones in high overall yield.



i) LHMDS, $NCCO_2CH_2CHCH_2$, THF, -78°C; ii) $ArPb(OAc)_3$, $CHCL_3$, pyridine, iii) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, rt, 72 h; iv) $Pd(OAc)_2$, DPPE, MeCN, reflux, 4 h

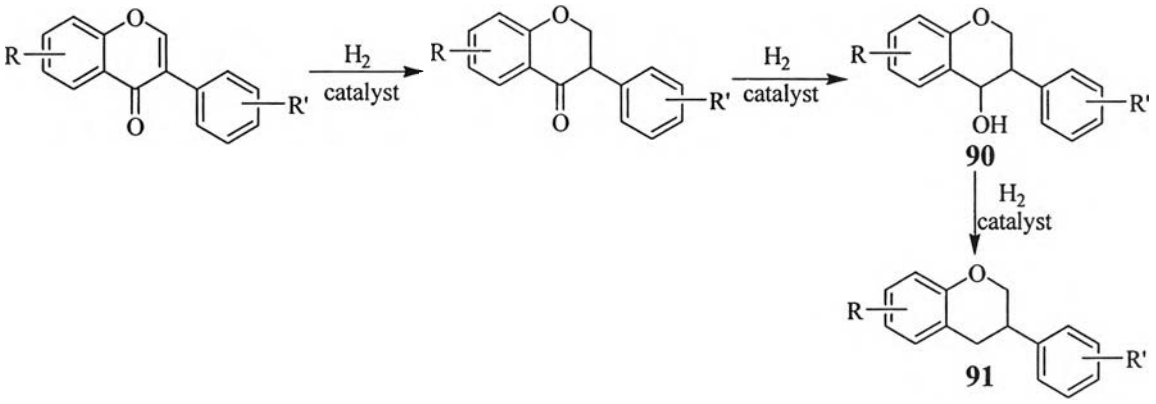
3.1.1.2 Synthetic Routes to Isoflavanones

The synthetic routes to isoflavanones are not as numerous as their isoflavones analogues but are quite similar in approach and many distribute a common pathway. The various approaches can be classified under the following heading for discussion:

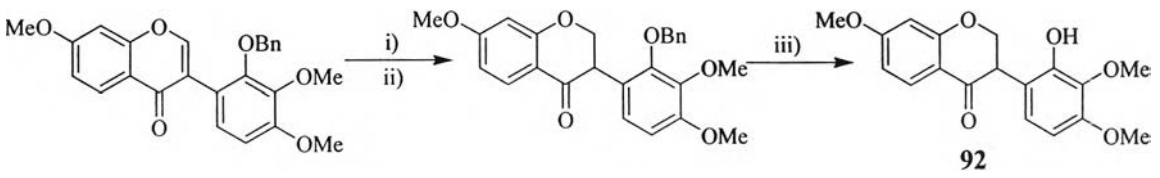
- The reduction of isoflavones
- The oxidation of isoflavans
- *via* deoxybenzoins
- Arylation methods

(a) The reduction of isoflavones

Isoflavanones are frequenty synthesized by hydrogenation of isoflavones using noble metal catalyst. PtO_2 [124] and Pd-C [125] are routinely employed but the process must be monitored carefully to avoid-reduction to isoflavan-4-ols (**90**) and isoflavans (**91**).



In 1981, Antus and co-workers [126] reported the synthesis of 2'-hydroxy-3',4',7-trimethoxyisoflavanones (**92**), a constituent of *Myroxylon peruiferum* [127], by reduction with diisobutylaluminium hydride (DIBAH) in THF-toluene.



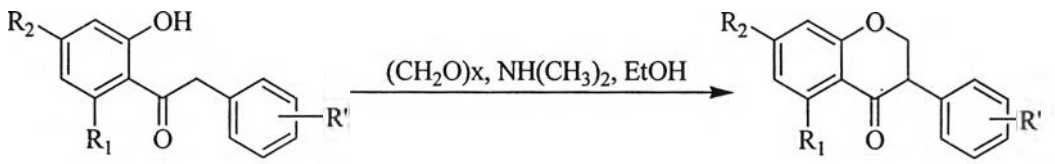
i) (i-$C_4H_9)_2AlH$, toluene,THF, -65°C; ii) MeOH, rt; iii) H_2, Pd-C

(b) The oxidation of isoflavans

Whalley and co-workers [128, 129] reported that the oxidation of isoflavans with potassium permanganate yielded isoflavanones in low to moderate yield. Later, Bretenach and co-workers [130] found that much better yields were obtained when 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in MeOH was used to oxidize fully protected isoflavans.

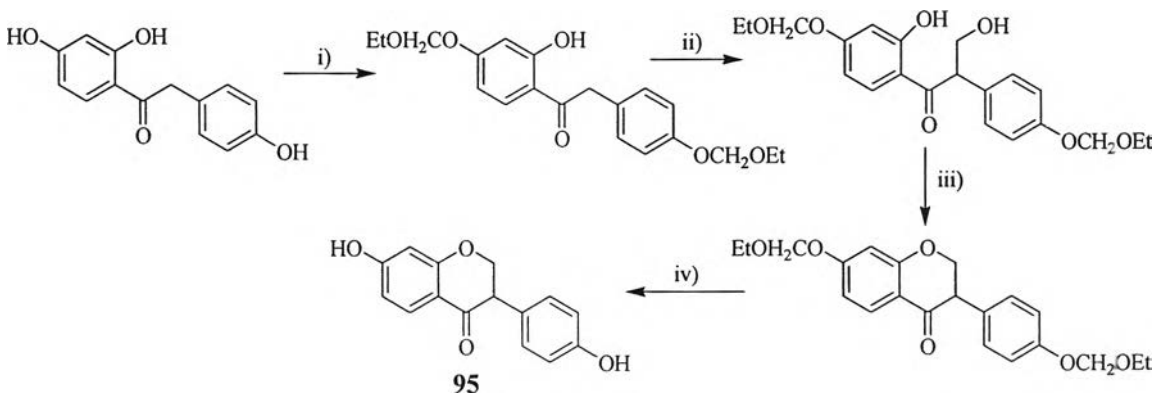
(c) *via* deoxybenzoin

Gandhidasan and co-workers [131] reported the synthesis of isoflavanones (**94**) using the Mannich reaction of 2'-hydroxydeoxybenzoins (**93**) with paraformaldehyde in refluxing ethanol in the presence of secondary amines such as piperidine, dimethylamine or diethylamines.



93 **94**

The synthesis of hydroxyisoflavanones has been efficiently accomplished using ethoxymethyl chloride as the methylene source [132, 133]. The application of this method to the synthesis of dihydrodaidzein (**95**) is depicted as shown below [133]:

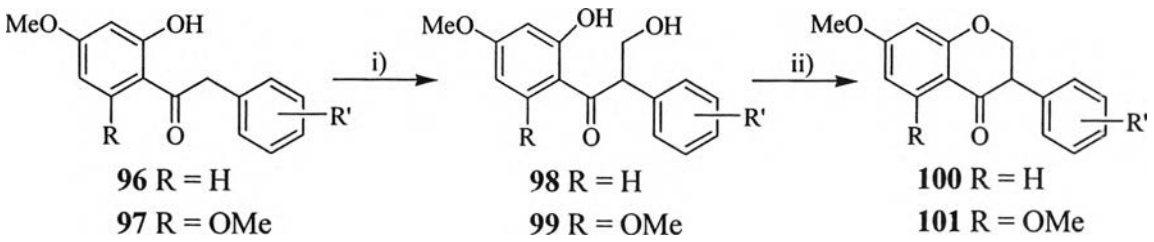


95

i) $EtOCH_2Cl$, K_2CO_3, $MeCO_2$, rt; ii) $EtOCH_2Cl$, K_2CO_3, $MeCO_2$, 60-70°C; iii) Na_2CO_3,40% aq. EtOH; iv) 10% MeOH-HCl

2'-Hydroxybenzoins (**96**, **97**) with a phloroglucinol unit in ring-A were converted to the corresponding α-hydroxymethyldeoxybenzoin (**98**, **99**) on treatment with formaldehyde in a $CHCl_3$-K_2CO_3 biphase system which easily cyclized to the

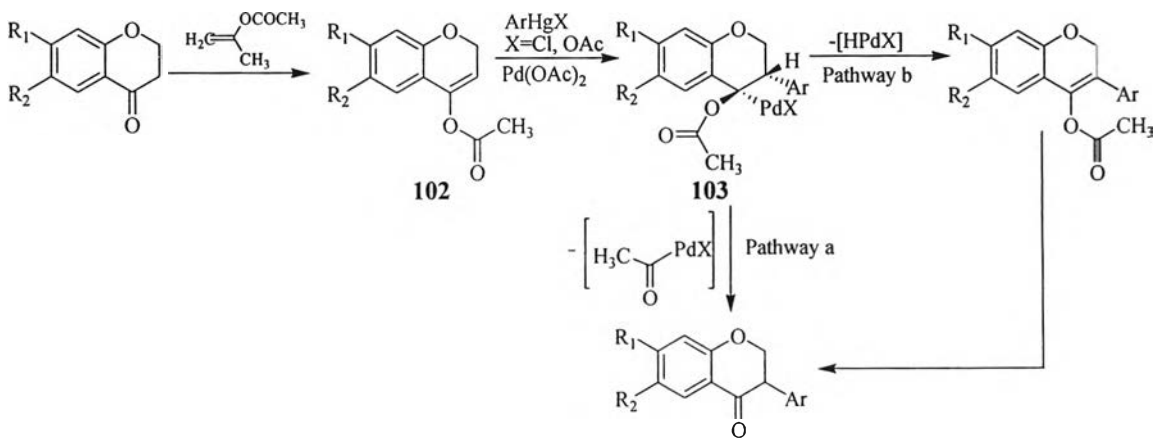
corresponding isoflavanones (**100**, **101**) on treatment with diethylamine in refluxing ethanol [134].



i) HCHO, $CHCl_3$, aq K_2CO_3; ii) Et_2NH, EtOH, reflux

(d) Arylation method

The synthetic routes to isoflavanone using arylation method are quite similar synthetic routes to isoflavone which aforementioned discussion in Section 3.1.1.1. Moreover, the Heck reaction of chroman-4-one enol ester (**102**) with arylpalladium compounds afforded isoflavanone in good yield (60-75%) [135]. The arylpalladium compounds were generated *in situ* from the reaction of arylmercuric chloride or aryl mercuric acetate with palladium acetate. The arylation reaction was believed to proceed by the *cis*-addition of an arylpalladium compound to the chromene double bond of (**102**) with the aryl group addition to the least hindered C-3 position to give the intermediate (**103**). The required isoflavanone was then obtained by elimination of palladium with an acetyl group (pathway a) or by a *trans*-palladium hydride elimination and subsequent hydrolysis (pathway b).



3.1.1.3 Synthetic Routes to Isoflavans

Farkas and co-workers [110, 136] reported the synthesis of mucronulatol *via* oxidative rearrangement of chalcones with TTN as aforementioned discussion in Section 3.1.1.1.

In addition, isoflavans were frequently synthesized by hydrogenation of isoflavanones using noble metal catalysts as aforementioned discussion in Section 3.1.1.2.

According to the above-mentioned evidence of many existing synthesis routes, TTN mediated rearrangement of chalcones has seen wide spread application to the synthesis of isoflavonoids. An example of this procedure was the synthesis of violanone and mucronulatol as aforementioned in Section 3.1.1.1. However, that method had limitations, not the least of which was the use of stoichiometric quantities of toxic TTN. Moreover, the reaction was susceptible to the nature of the substituents: in the case of a 2'-hydroxy-4',5',6'-trioxygenated chalcone, ring-A oxidation by TNN in MeOH gave a quinine monoacetate [137-139]. Finally, the yields of isolated isoflavonoids are often low because nitric acid generated from TTN during reaction causes the hydrolysis of labile acetate group [140] or the formation of unwanted nitro by-products [141].

In this research, selected isoflavonoids were synthesized using arylation of a common α-phenylthiocarbonyl intermediate with aryllead reagents as a key step afforded a direct, efficient and selective entry into the synthesis of isoflavanones, isoflavones and isoflavans. Moreover, for the synthesis of the naturally occurring isoflavonoids, this method is more general than the described phenylations of 3-hydroxymethylene- and 3-ethyloxalyl-chroman-4-one with various pentavalent triphenylbismuth derivatives [120] or 3-phenylsulfonylchroman-4-ones with triphenylbismuth carbonate [119]. However, these latter methods suffer from the limited range of available polyalkoxyphenylbismuth derivatives as opposed to the wide range of easily accessible polyalkoxyphenyllead derivatives.

Furthermore, the synthesis of violanone, mucronulatol and 3',7-dihydroxy-2',4'-dimethoxyisoflavone using aryllation of activated chroman-4-one with aryllead (IV) triacetate was addressed the first time in chemical literature.

In addition, the aryllation of chroman-4-one with aryllead (IV) triacetate is also efficient for synthesis of a series of isoflavonoids with different substituents on ring-B.

3.1.2 The Goal of This Research

According to the biological results of isolated substances from CH_2Cl_2 extract of the heartwoods of *D. oliveri*, **D5**, (±)-mucronulatol, showed the interesting radical scavenging effect on DPPH radical and antifungal activity against *F. oxysporum*. **D7**, (±)-violanone, in addition displayed moderate scavenging activity toward DPPH radical and antifungal activity against *F. oxysporum*. Furthermore, **D5** and **D7** displayed cytotoxicity against human hepatocellular carcinoma (HepG2). **D7** also showed high cytotoxicity against diamondback moth and mosquito larvae. Therefore, the goal of this chapter can be summarized as:

1. To synthesize the selected isoflavonoids such as mucronulatol, violanone and 3',7-dihydroxy-2',4'-dimethoxyisoflavone
2. To explore the biological activities of synthesized compounds

3.2 EXPERIMENTAL

3.2.1 Instruments and Equipment

Melting points were taken on a Büchi B-540 capillary apparatus and are uncorrected. NMR spectra were obtained on a Bruker AC 300 spectrometer. Chemical shifts (δ) are reported in ppm for a solution of the compound in $CDCl_3$ with internal reference Me_4Si and *J*-values in hertz. Elemental analyses were performed at the Laboratoire de Microanalyse of the Centre National de la Recherche Scientifique, Vernaison. Separation by column chromatography was performed using Merck Kieselgel 60 (70-230 mesh).

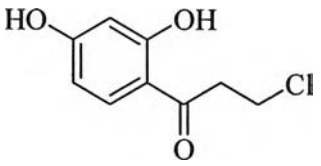
3.2.2 Chemicals

Ether refers to diethyl ether and petroleum spirit refers to the fraction with distillation range 40-65°C. All solvents were purified by standard techniques; the solvents were distilled under dry argon atmosphere: THF and Et_2O in the presence of sodium and benzophenone, and CH_2Cl_2 in the presence of P_2O_5. All chemicals and organic solvents were commercially available and were used as supplied.

3.2.3 Synthesis of Isoflavonoids using the Arylation of Chromanone Moiety

3.2.3.1 Preparation of Activated Chromanone

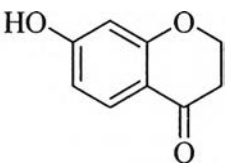
3-Chloro-1-(2,4-dihydroxyphenyl)-propane-1-one (**P1**)



At 0°C, under Ar, to a solution of resorcinol (10.10 g, 100 mmol) in dry Et_2O (100 mL) was injected 3-chloropropionylchloride (9.55 mL, 100 mmol). Under a vigorous stirring, a solution of $AlCl_3$ (33.34 g, 100 mmol) in dry Et_2O (100 mL) was slowly added drop by drop over 1 h. The resulting mixture was warmed up to room temperature, stirred over 0.5 h at this temperature, refluxed for 1 h, and then stirred at room temperature overnight. The mixture was poured into an acidic solution (10% HCl 100 mL) and then extracted with Et_2O (3 x 150 mL). The solvent was distilled off under reduce pressure to afford **P1** [142] as orange oil which was used in the next step.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.54 (*s*, 1H), 7.60 (1H, d, J = 8.5 Hz, H6), 6.36-6.41 (2H, m, H3, H5), 3.89 (2H, t, J = 6.8 Hz, -C$\underline{H_2}$Cl) and 3.38 (2H, t, J = 6.8 Hz, -COC$\underline{H_2}$-).

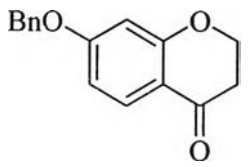
7-Hydroxy-4-chromanone (**P2**)



To a stirred solution of 2M NaOH (100 mL) at 5°C was added **P1** in one portion. The solution was warmed to room temperature over 2 h and then re-cooled to 5°C, and the pH was adjusted to 2 with 6M H_2SO_4. The mixture was extracted with Et_2O (3 x 50 mL), washed with brine, dried over anh Na_2SO_4 and filtered. The solvent was distilled off under reduce pressure to afford **P2** (16.49 g, quantitative yield) as yellow solid, m.p. 140.5-141.0°C (lit, m.p. 145°C) [142].

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 9.40 (1H, *s*), 7.12 (1H, d, *J* = 8.5 Hz, H5), 6.56 (1H, dd, *J* = 2.3, 8.5 Hz, H6), 6.39 (1H, d, *J* = 2.3 Hz, H8), 4.53 (2H, t, *J* = 6.4 Hz, H2) and 2.69 (2H, t, *J* = 6.6 Hz, H3).

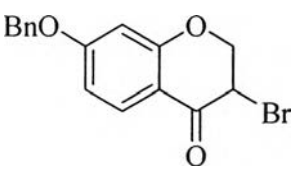
7-Benzyloxy-4-chromanone (**P3**)



Under Ar, K_2CO_3 (27.64 g, 200 mmol) was added to a solution of benzyl bromide (14.35 mL, 120 mmol) and **P2** (16.40 g, 100 mmol) in dry acetone (200 mL). The reaction mixture was refluxed for overnight and then filtered. The filtrate was evaporated to dryness. The residue was extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with 10% NaOH solution, water and dried over anh Na_2SO_4. The solvent was distilled off under reduce pressure to afford yellow solid which was washed with EtOH. Filtrate was evaporated to dryness and further purified by column chromatography using Et_2O: pentane (4:6) as eluent to obtain **P3** (13.29 g, 52 %) as pale yellow solid, m.p.102.1-103.2°C (lit, m.p.103-104°C) [143].

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.84 (1H, d, *J* = 8.7 Hz, H5), 7.34-7.41 (5H, m, Ph), 6.65 (1H, d, *J* = 8.9 Hz, H6), 6.48 (1H, s, H8), 5.09 (2H, s, -OCH_2Ph), 4.50 (2H, t, *J* = 6.9 Hz, H2) and 2.74 (2H, t, *J* = 6.9 Hz, H3).

3-Bromo-7-benzyloxy-2,3-dihydro-4H-1-benzopyran-4-one (**P4**)

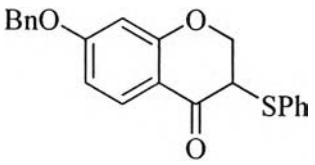


Under Ar, to a refluxing mixture of copper (II) bromide (7.81 g, 33.46 mmol) in EtOAc (15 mL) was added a solution of **P3** (5.00 g, 19.46 mmol) in anh $CHCl_3$ (30 mL). The resulting mixture was refluxed with vigorous stirring for overnight. The insoluble copper (I) bromide which formed was filtered off and washed through with

EtOAc. The solvent was distilled off under reduce pressure to afford brown sticky liquid which purified by crystallization with CH_2Cl_2 and EtO_2. The filtrate was evaporated to dryness and then purified by column chromatography using CH_2Cl_2 as eluent to obtain **P4** [144] (4.23 g, 66%) as white solid, m.p. 108.9-109.8°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89 (1H, d, J = 8.9 Hz, H5), 7.34-7.41 (5H, m, Ph), 6.72 (1H, dd, J = 2.3, 8.9 Hz, H6), 6.54 (1H, d, J = 2.3 Hz, H8), 5.29 (2H, s, -OC$\underline{H}_2$Ph) and 4.55-4.66 (3H, m, H2 and H3).

7-Benzyloxy-3-phenylthio-2,3-dihydro-4H-1-benzopyran-4-one (**P5**)



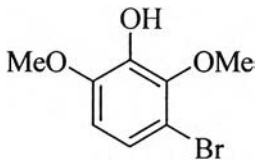
Thiophenol (1.29 mL, 12.64 mmol) was dissolved with stirring in dry THF (30 mL) and the resultant solution was cooled to 0°C prior to the addition of NaH (0.51 g, 12.64 mmol). After standing for 30 min at 0°C, a solution of **P4** (4.13 g, 12.39 mmol) in dry THF (60 mL) was added dropwise over a period of 30 min at 0°C. The reaction mixture was then brought to room temperature, stirred for 10 min and filtered through celite. The filtrate was washed with dil HCl and water and dried over anh Na_2SO_4. The solvent was removed *in vacuo* to give yellow oil which was purified by column chromatography using Et_2O-pentane (3:7) as eluent to obtain **P5** (3.98 g, 89%) as white solid, m.p. 79°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.87 (1H, d, J = 8.9 Hz, H5), 7.29-7.54 (10H, m, 2 x Ph), 6.69 (1H, dd, J = 2.3, 8.9 Hz, H6), 6.49 (1H, d, J = 2.3 Hz, H8), 5.09 (2H, s, OC$\underline{H}_2$Ph), 4.61 (1H, dd, J = 3.9, 11.7 Hz, H2*ax* or H2*eq*), 4.50 (1H, dd, J = 6.4, 11.7 Hz, H2*ax* or H2*eq*) and 4.02 (1H, dd, J = 3.9, 6.4 Hz, H3).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 186.5 (1C, C, C4), 165.0 (1C, C, C7), 162.5 (1C, C, C9), 135.6 (1C, C), 132.8 (2C, CH), 131.9 (1C, C), 129.8 (1C, CH, C5), 128.9 (2C, CH), 128.5 (2C, CH), 128.1 (1C, CH), 127.9 (1C, CH), 127.3 (2C, CH), 113.8 (1C, CH, C6), 110.8 (1C, C, C10), 101.4 (1C, CH, C8), 70.4 (1C, CH_2, O$\underline{C}H_2$Ph), 70.1 (1C, CH_2, C2) and 50.9 (1C, CH, C3).

3.2.3.2 Preparation of Aryllead (IV) Triacetate Derivatives

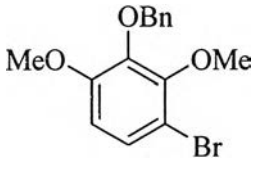
3-Bromo-2,6-dimethoxyphenol (**P6**)



At -20°C, under Ar, to a solution of 2,6-dimethoxyphenol (10.00 g, 64 mmol) in anh $CHCl_3$ was added a solution of Br_2 (3.26 mL, 64 mmol) in anh $CHCl_3$ drop by drop over 1 h. The reaction mixture was poured into ice water and then extracted with $CHCl_3$ (3 x 150 mL).The combined organic layers were washed with brine, water and dried over anh Na_2SO_4. The solvent was distilled off under reduce pressure to afford **P6** (15.05 g, quantitative yield) as brown liquid (lit, b.p.120°C at 4 mm Hg) [145].

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.02 (1H, d, J = 8.9 Hz, H4), 6.57 (1H, d, J = 8.9 Hz, H5), 5.63 (1H, s, OH), 3.92 (3H, s, OMe) and 3.88 (3H, s, OMe).

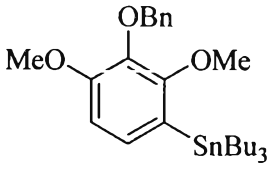
2-Benzyloxy-4-bromo-1,3-dimethoxybenzene (**P7**)



K_2CO_3 (17.70 g, 128 mmol) was added to a solution of benzyl bromide (9.21 mL, 77 mmol) and **P6** (14.88 g, 64 mmol) in dry acetone (150 mL). The reaction mixture was refluxed for overnight and then filtered. The filtrate was evaporated to dryness. The residue was extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with 10% NaOH solution, water and dried over anh Na_2SO_4. The solvent was distilled off under reduce pressure to afford orange oil which was purified by distillation to obtain **P7** (19.77 g, 96%), as yellow oil, b.p. 150°C at 5 x 10^{-3} mm Hg (lit, b.p. 159-164°C at 0.2 mm Hg) [146].

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32-7.51 (5H, m, Ph), 7.23 (1H, d, J = 8.9 Hz, H5), 6.60 (1H, d, J = 8.9 Hz, H6), 5.03 (2H, s, -OC$\underline{H_2}$Ph), 3.90 (3H, s, OMe) and 3.82 (3H, s, OMe).

(3-Benzyloxy-2,4-dimethoxyphenyl)-tributylstannane (**P8**)

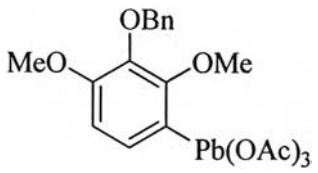


Under Ar, *n*-butyllithiun (2.5 M solution in hexane, 20.14 mL, 50.35 mmol) was added over 15 min to a well stirred solution of **P7** (13.56 g, 41.96 mmol) in dry THF (80 mL) at -78°C and the resulting mixture was stirred at this temperature for 30 min. Tributylchlorostannane (13.66 mL, 50.35 mmol) was then added with stirring over 5 min at -78°C. After stirring for 20 min at this temperature, the reaction mixture was poured into a saturated NH_4Cl solution (32 mL) then water was added and a mixture was extracted with Et_2O. The Et_2O extract was washed with brine, dried over anh Na_2SO_4 and the solvent was removed to afford yellow oil (27.13 g, crude) which was purified by distillation to give **P8** (20.14 g, 90%) as yellow oil (b.p. >180°C at 10^{-3} mm Hg).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32-7.50 (5H, m, Ph), 7.01 (1H, d, J = 7.9 Hz, H5), 6.69 (2H, d, J = 7.9 Hz, H4 and H6), 5.00 (2H, s, -OC$\underline{H}_2$Ph), 1.47-1.53 (6H, m, 3 x CH_2), 1.27-1.39 (6H, m, 3 x CH_2), 1.00-1.24 (6H, m, 9 x CH_2) and 0.89 (9H, t, J = 7.4 Hz, 3 x CH_3).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 158.1 (1C, C, C2), 154.7 (1C, C, C4), 140.0 (1C, C, C1'), 137.7 (1C, C, C3), 131.0 (1C, CH, C6), 128.2 (2C, 2 x CH, C3' and C5'), 128.1 (2C, 2 x CH, C2' and C6'), 127.4 (1C, CH, C4'), 125.8 (1C, C, C1), 108.0 (1C, CH, C5), 74.7 (1C, CH_2, -O$\underline{C}H_2$Ph), 60.7 (1C, CH_3, OMe), 55.8 (1C, CH_3, OMe), 29.1 (3C, 3 x CH_2), 27.3 (3C, 3 x CH_2), 13.6 (3C, 3 x CH_2) and 9.8 (3C, 3 x CH_3).

3-Benzyloxy-2,4-dimethoxyphenyllead triacetate (**P9**)



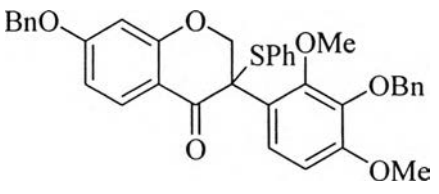
Under Ar, a solution of 3-benzyloxy-2,4-dimethoxy-tributylstannane (4.27 g, 8.00 mmol) in dry $CHCl_3$ (30 mL) was quickly added drop by drop to a mixture of lead tetraacetate (3.90 g, 8.80 mmol) and mercuric acetate (0.13 g, 0.40 mmol) in dry $CHCl_3$ (50 mL). The reaction mixture was heated at 40°C for 3 h after this time filtered through celite and solvent was concentrated under reduce pressure to a small volume. Petroleum ether was added and the solution was kept overnight at -15°C. The precipitate was collected, washed with petroleum Et_2O and dried to give **P9** (4.14 g, 82 %) as brown powder, m.p. 160.8-162.0°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.49 (1H, d, J = 9.1 Hz, H5), 7.33-7.44 (5H, m, Ph), 6.84 (1H, d, J = 9.1 Hz, H6), 5.03 (2H, s, -OCH_2Ph), 4.02 (3H, s, OMe), 3.88 (3H, s, OMe) and 2.11 (9H, s, 3 x CH_3).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 180.0 (3C, C), 157.8 (1C, C), 152.9 (1C, C), 147.3 (1C, C), 141.4 (1C, C), 137.2 (1C, C), 128.8 (2C, 2 x CH), 128.7 (2C, 2 x CH), 128.6 (1C, CH), 126.7 (1C, CH), 109.3 (1C, CH), 75.8 (1C, CH_2), 62.5 (1C, CH_3, OMe), 56.9 (1C, CH_3, OMe) and 20.9 (3C, 3 x CH_3).

3.2.3.3 Preparation of 3-Aryl-3-phenylthio-2,3-dihydro-4*H*-1-benzopyran-4-one

7-Benzyloxy-3-(3-benzyloxy2,4-dimethoxyphenyl)-3-phenylthio-2,3-dihydro-4H-1-benzopyran-4-one (**P10**)



Under Ar, dry pyridine (0.78 mL, 9.64 mmol) was added to a stirred mixture of **P5** (1.06 g, 2.92 mmol) and **P9** (2.20 g, 3.51 mmol) in dry $CHCl_3$ (30 mL) (1.0 mL per 0.6 mmol of substrate) and the resultant mixture was refluxed at 55°C for

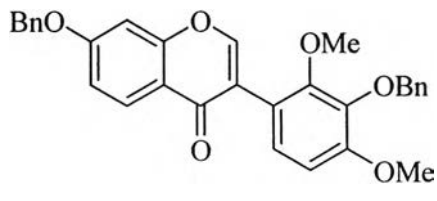
overnight. After this time the reaction mixture was diluted with $CHCl_3$ (150 mL) and washed with 6% H_2SO_4 (150 mL). The organic layer was retained and the aq layer was extracted with $CHCl_3$. All the organic layers were combined, filtered through celite, dried over anh Na_2SO_4 and the solvent was evaporated. The residue was dissolved with hot ethanol and added 10% NaOH. After that extracted with CH_2Cl_2, dried over anh Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography by using Et_2O-pentane (4:6) as eluent to give **P10** (0.89 g, 51 %) as yellow solid, m.p. 50.7-52.8°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.86 (1H, d, *J* = 8.9 Hz, H6'), 7.74 (1H, d, *J* = 8.7 Hz, H5), 7.10-7.40 (15H, m, 3 x Ph), 6.67 (1H, d, *J* = 8.9 Hz, H5'), 6.64 (1H, dd, *J* = 2.3, 8.7 Hz, H6), 6.47 (1H, d, *J* = 2.3 Hz, H8), 5.04 (2H, s, OC$\underline{H_2}$Ph), 4.93 (2H, dd, *J* = 10.9, 15.3 Hz, OC$\underline{H_2}$Ph), 4.84 (1H, d, *J* = 12.1 Hz, H2*ax* or H2*eq*), 4.15 (1H, d, *J* = 12.1 Hz, H2*ax* or H2*eq*), 3.80 (3H, s, OMe) and 3.67 (3H, s, OMe).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 185.2 (1C, C, C4), 164.4 (1C, C, C7), 161.6 (1C, C, C9), 154.3 (1C, C, C2'), 151.7(1C, C, C4'), 141.1 (1C, C, C3'), 137.2 (1C, C) 136.0 (1C, C), 135.4 (2C, 2 x CH), 130.5 (1C, CH, C6'), 129.8 (1C, CH), C5), 18.6 (2C, 2 x CH), 128.5 (1C, CH), 128.3 (2C, 2 x CH), 128.2 (2C, 2 x CH), 128.1 (1C, CH), 128.0 (2C, 2 x CH), 127.9 (1C, CH), 127.5 (2C, 2 x CH), 125.3 (1C, C), 122.0 (1C, C, C10), 114.3 (1C, C, C1'), 110.5 (1C, CH, C6), 106.4 (1C, CH, C5'), 101.5 (1C, CH, C8), 74.6 (1C, CH_2), 73.4 (1C, CH_2), 70.2 (1C, CH_2), 62.6 (1C, C, C3), 60.0 (1C, CH_3, OMe) and 55.9 (1C, CH_3, OMe).

3.2.3.4 Preparation of 3-Aryl-4*H*-1-benzopyran-4-one *via* Desulphurization of 3-Aryl-3-phenylthio-4*H*-1-benzopyran-4-one using *m*-CPBA

7-Benzyloxy-3-(3-benzyloxy-2,4-dimethoxyphenyl)-4H-1-benzopyran-4-one (**P11**)



m-CPBA (67 mg, 0.387 mmol) in dry EtOAc (10 mL) was added to a solution of **P10** (78 mg, 0.129 mmol) in dry EtOAc (8 mL) at 0°C. The solution was stirred at room temperature and reaction was followed by TLC. The solvent was removed *in*

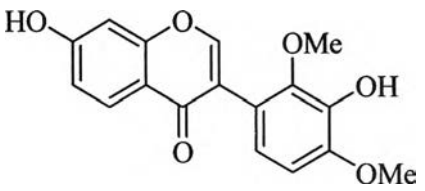
vacuo yielding a crude product which was purified by preparative chromatography using CH_2Cl_2-EtOH (9.98:0.02) as eluent. The product obtained was then boiled in toluene to remove the phenylsulfoxide group. The reaction was checked by TLC until starting material was completely disappeared. The solvent was evaporated to give **P11** (0.038 g, 59 %) as yellow solid, m.p. 143-145°C (lit, m.p. 145-147°C [110]).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (1H, d, J = 8.9 Hz, H5), 7.91 (1H, s, H2), 7.31-7.54 (10H, m, 2 x Ph), 7.08 (1H, d, J = 8.7 Hz, H5'), 7.07 (1H, dd, J = 2.3, 8.9 Hz, H6), 6.95 (1H, d, J = 2.3 Hz, H8), 6.75 (1H, d, J = 8.7 Hz, H6'), 5.18 (2H, s, OC$\underline{H_2}$Ph), 5.07 (2H, s, OC$\underline{H_2}$Ph), 3.88 (3H, s, OMe) and 3.81 (3H, s, OMe).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 174.8 (1C, C, C4), 162.0 (1C, C, C7), 156.9 (1C, C, C9), 153.3 (1C, CH, C2), 152.7 (1C, C, C4'), 151.5 (1C, C, C2'), 140.4 (1C, C, C3'), 136.7 (1C, C, OCH$_2\underline{Ph}$), 134.8 (1C, C, OCH$_2\underline{Ph}$), 127.8 (2C, 2 x CH), 127.4 (1C, CH), 127.3 (4C, 4 x CH), 126.9 (2C, CH), 126.5 (2C, 2 x CH), 125.2 (1C, C, C3), 121.2 (1C, CH, C6'), 117.6 (1C, C, C10), 117.5 (1C, C1'), 113.9 (1C, CH, C6), 106.5 (1C, CH, C5'), 100.3 (1C, CH, C8), 74.2 (1C, CH_2, O$\underline{C}H_2$Ph), 69.5 (1C, CH_2, O$\underline{C}H_2$Ph), 60.3 (1C, CH_3, OMe) and 55.1 (1C, CH_3, OMe).

3.3.2.5 Preparation of Isoflavone

7-Hydroxy-3-(3-hydroxy-2,4-dimethoxyphenyl)chromen-4-one (**P12**)



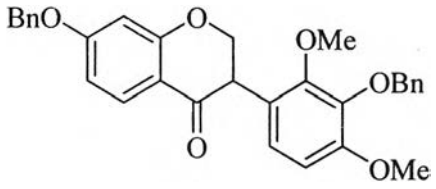
HBr (47% in water, 10 mL) was added to **P11** (0.022 g, 0.070 mmol). The resultant was refluxed at 50°C for overnight. After that the reaction mixture was evaporated to a small volume and extracted with CH_2Cl_2. All the organic layer was dried over anh Na_2SO_4 and concentrated to give **P12** (0.011 g, 95%) as yellow solid, m.p. 253°C (lit, 251-252°C [127]).

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 9.60 (1H, s, OH), 8.07 (1H, d, J = 8.7 Hz, H5), 8.00 (1H, s, H2), 7.53 (1H, s, OH), 7.03 (1H, dd, J = 2.3 and 8.7 Hz, H6), 6.93 (1H, d, J = 2.3 Hz, H8), 6.78 (2H, s, H5' and H6'), 3.89 (3H, s, OMe) and 3.77 (3H, s, OMe).

^{13}C-NMR (300 MHz, acetone-d_6) δ (ppm): 175.5 (1C, C, C4), 163.0 (1C, C, C7), 158.7 (1C, C, C9), 154.0 (1C, CH, C2), 149.5 (1C, C, C4'), 147.0 (1C, C, C2'), 140.2 (1C, C, C3'), 128.2 (1C, CH, C5), 123.4 (1C, C, C3), 121.6 (1C, CH, C6'), 120.0 (1C, C, C1'), 118.3 (1C, C, C10), 115.3 (1C, CH, C6), 107.1 (1C, CH, C5'), 103.0 (1C, CH, C8), 60.1 (1C, CH_3, OMe) and 56.4 (1C, CH_3, OMe).

3.2.3.6 Preparation of 3-Aryl-2,3-dihydro-4*H*-1-benzopyran-4-one *via* Desulphurisation of 3-Aryl-3-phenylthio-4*H*-1-benzopyran-4-one using Nickel Boride

7-Benzyloxy-3-(3-benzyloxy-2,4-dimethoxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one (**P13**)



P10 (0.60 g, 0.99 mmol) and nickel chloride hexahydrate (5.66 g, 23.81 mmol) in EtOH (150 mL) was stirred under Ar and treated dropwise with a solution of NaH (0.75, 19.84 mmol) in water (10 mL). The formation of black precipitate was observed. The mixture was then heated under reflux for 4 h. The reaction mixture was filtered through celite and the filter cake was washed with EtOH. The combined filtrates were evaporated to small bulk and extracted with Et_2O. The ether solution was dried over anh Na_2SO_4 and concentrated to give yellow oil which was purified by column chromatography using Et_2O-pentane (4:6) as eluent to give **P13** (0.42 g, 86%) as brown sticky syrup.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.94 (1H, d, J = 8.7 Hz, H5), 7.31-7.50 (10H, m, 2 x Ph), 6.83 (1H, d, J = 8.7 Hz, H6'), 6.70 (1H, dd, J = 2.3, 8.7 Hz, H6), 6.65 (1H, d, J = 8.7 Hz, H5'), 6.53 (1H, d, J = 2.3 Hz, H8), 5.11 (2H, s, OC$\underline{H}_2$Ph), 5.01 (2H, s, OC$\underline{H}_2$Ph), 4.59 (1H, dd, J = 10.9, 11.7 Hz, H2*ax* or H2*eq*), 4.47 (1H, dd, J = 5.7, 10.9 Hz, H2*ax* or H2*eq*), 4.18 (1H, dd, J = 5.5, 11.8 Hz, H3), 3.84 (3H, s, OMe) and 3.83 (3H, s, OMe).

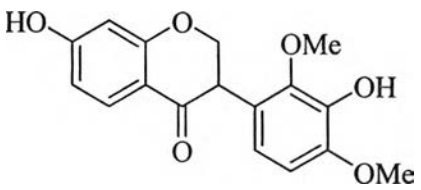
^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 191.5 (1C, C, C4), 164.8 (1C, C, C7), 163.7 (1C, C, C9), 153.7 (1C, C, C2'), 152.4 (1C, C, C4'), 141.2 (1C, C, C3'), 137.5 (1C, C), 135.9 (1C, C), 129.3 (1C, CH, C5), 128.6 (2C, CH), 128.2 (5C, CH), 127.8

(1C, CH), 127.4 (2C, CH), 124.6 (1C, CH, C6'), 121.4 (1C, C, C1'), 115.5 (1C, C, C10), 110.4 (1C, CH, C6), 107.5 (1C, CH, C5'), 101.7 (1C, CH, C8), 74.9 (1C, CH_2), 71.4 (1C, CH_2), 70.2 (1C, CH_2), 61.0 (1C, CH_3, OMe), 56.0 (1C, CH_3, OMe) and 48.1 (1C, CH, C3).

3.2.3.7 Preparation of Isoflavanone

7-Hydroxy-3-(3-hydrloxy-2,4-dimethoxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one

(P14)



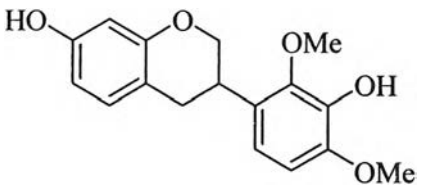
HBr (47% in water, 10 mL) was added to **P13** (0.23 g, 0.49 mmol). The resultant was refluxed at 50°C for 22 hr. After that the reaction mixture was evaporated to a small volume and extracted with CH_2Cl_2. All the organic layer was dried over anh Na_2SO_4 and concentrated to give brown sticky liquid which was purified by column chromatography using Et_2O-pentane (9:1) as eluent to give **P14** (0.148 g, 95%) as white crystal, m.p. 200.4-202.4°C (lit, m.p. 200-204°C [43, 110, 127, 147]).

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.81 (1H, d, J = 8.5 Hz, H5), 6.71 (1H, d, J = 8.5 Hz, H6'), 6.64 (1H, d, J = 8.1 Hz, H5'), 6.62 (1H, dd, J = 2.3, 8.5 Hz, H6), 6.44 (1H, d, J = 2.3 Hz, H8), 4.61 (1H, dd, J = 11.0, 11.5 Hz, H2*ax*), 4.48 (1H, dd, J = 5.5, 11.0 Hz, H2*eq*), 4.15 (1H, dd, J = 5.5, 11.5 Hz, H3), 3.86 (3H, s, OMe) and 3.81 (3H, s, OMe).

^{13}C-NMR (300 MHz, acetone-d_6) δ (ppm): 191.3 (1C, C, C4), 164.9 (1C, C, C7), 164.7 (1C, C, C9), 149.1 (1C, C, C2'), 146.9 (1C, C, C4'), 140.3 (1C, C, C3'), 130.0 (1C, CH, C5), 123.1 (1C, C, C1'), 120.4 (1C, CH, C6'), 115.8 (1C, C, C10), 111.2 (1C, CH, C6), 107.4 (1C, CH, C5'), 103.5 (1C, CH, C8), 72.1 (1C, CH_2, C2), 60.1 (1C, CH_3, OMe), 56.5 (1C, CH_3, OMe) and 48.9 (1C, CH, C3).

3.2.3.8 Preparation of Isofavan

7-Hydroxy-3-(3-hydrloxy-2,4-dimethoxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-ol (**P15**)



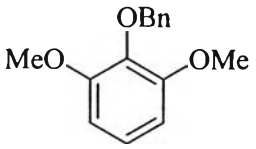
Under Ar, 10% Pd/C (20 mg, 2% by weight of substrate) was added to a stirred solution of **P13** (0.078 g, 0.159 mmol) in EtOH (10 mL). The mixture was stirred at room temperature and the reaction was checked by TLC until starting material was completely disappeared. The reaction mixture was filtered through celite and washed with acetone. The combined filtrates were evaporated to give **P15** (quantitative yield) as white crystal, m.p. 221-224°C (lit, m.p. 227-229°C [72, 110, 136, 148]).

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.90 (1H, d, J = 8.3 Hz, H5), 6.74 (1H, d, J = 8.5 Hz, H5'), 6.67 (1H, d, J = 8.5 Hz, H6'), 6.39 (1H, dd, J = 2.3, 8.3 Hz, H6), 6.31 (1H, d, J = 2.3 Hz, H8), 4.20 (1H, ddd, $J_{H2eqH4eq}$ = 1.9 Hz, J_{HeqH3} = 3.5 Hz, $J_{HeqH2ax}$ = 10.3 Hz, H2*eq*), 3.95 (1H, t, $J_{H2axH2eq}$ = J_{H2axH3} = 10.3 Hz, H2*ax*), 3.88 (3H, s, OMe), 3.84 (3H, *s*, OMe), 3.46 (1H, ddd, J_{H3H2eq} = 3.5 Hz, J_{H3H4eq} = 5.9 Hz, J_{H3H2ax} = 10.3 Hz, H3), 2.92 (1H, dd, J_{H4axH3} = 10.9 Hz, $J_{H4axH4eq}$ = 15.6 Hz, H4*ax*) and 2.80 (1H, ddd, J_{H4eqH3} = 5.4 Hz, $J_{H4eqH2eq}$ = 10.9 Hz, $J_{H4eqH4ax}$ = 15.6 Hz, H4*eq*).

^{13}C-NMR (300 MHz, acetone-d_6) δ (ppm): 157.8 (1C, C, C7), 156.3 (1C, C, C9), 148.7 (1C, C, C2'), 147.0 (1C, C, C4'), 140.6 (1C, C, C3'), 131.2 (1C, CH, C5), 128.4 (1C, C, C1'), 117.6 (1C, CH, C6'), 114.5 (1C, C, C10), 109.1 (1C, CH, C6), 108.2 (1C, CH, C5'), 103.9 (1C, CH, C8), 71.2 (1C, CH_2, C2), 61.1 (1C, CH_3, OMe), 56.7 (1C, CH_3, OMe), 33.0 (1C, CH, C3) and 32.3 (1C, CH_2, C4).

3.2.4 Synthesis of Isoflavone *via* Deoxybenzoin

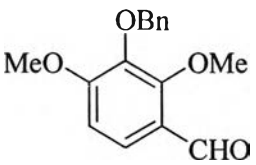
2-Benzyloxy-1,3-dimethoxybenzene (**S1**)



Under Ar, to a solution of 2,6-dimethoxyphenol (40.00 g, 0.259 mol) and benzyl chloride (37 mL, 0.312 mol) in dry THF was added, in small solid portion, NaH 60% in oil (12.48 g, 0.312 mol). After the addition, the mixture was refluxed for 12 h, then poured into water (100 mL) and extracted with Et_2O (3 x 50 mL). The combinated organic layers were successively washed with 10% aq NaOH solution (3 x 30 mL) and brine, and then dried over anh Na_2SO_4. Solvent was removed and the residue was purified by distillation under reduce pressure to afford **S1** (50.89 g, 80%) as a colorless oil, b.p. 140°C/10^{-3} mmHg (lit, 178-180°C/7 mmHg [148(a), 149]).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50 (2H, d, J = 8.1 Hz, H2' and H6'), 7.28-7.37 (3H, m, H3', H4' and H5'), 6.99 (1H, t, J = 8.3 Hz, H4), 6.57 (2H, d, J = 8.3 Hz, H5 and H6), 5.01 (2H, s, OCH_2Ph) and 3.82 (6H, s, OMe).

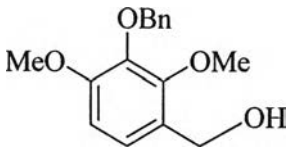
3-Benzyloxy-2,4-dimethoxybenzaldehyde (**S2**)



Under Ar, at 0-5°C, to a solution of **S1** (31.30 g, 0.128 mol) in DMF (22 mL, 0.282 mol) was added dropwise over 3 h of phosphoryl chloride (30 mL, 0.32 mol). Stirring was continued at room temperature for an additional 1 h and then at 70°C for 4 h. The reaction was checked by TLC until starting material was completely disappeared. The mixture was cooled, poured into ice water (200 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with 10% aq NaOH (3 x 40 mL) and brine, dried over anh Na_2SO_4 and solvent was distilled off. Residue was left under reduce pressure at 60°C using oil pump to remove impurities to afford **S2** (12.50 g, 36%) as colorless oil [148(a), 149].

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 10.25 (1H, s, HCO) 7.62 (1H, d, J = 8.8 Hz, H6), 7.49 (2H, d, J = 8.1 Hz, H2' and H6'), 7.33-7.41 (3H, m, H3', H4' and H5'), 6.76 (1H, d, J = 8.8 Hz, H5), 5.04 (2H, s, OCH_2Ph), 4.02 (3H, s, OMe) and 3.91 (3H, s, OMe).

3-Benzyloxy-2,4-dimethoxybenzylalcohol (**S3**)

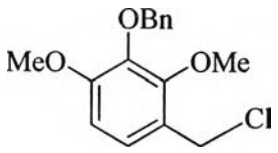


To a solution of **S2** (12.50 g, 46 mmol) in a mixture of EtOH and water (3:1) (65 mL) was added by solid fraction $LiBH_4$ (0.60 g, 27 mmol). After the addition, stirring was continued for 30 minutes. The mixture was poured into aqueous saturated NH_4Cl solution (150 mL) and extracted with Et_2O (3 x 40 mL). The extracts were washed with brine and dried over anh Na_2SO_4. The solvent was distilled off under reduce pressure and the residue was purified by column chromatography using Et_2O-pentane (6:4) as eluent to afford **S3** (12.25 g, 97%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.49 (2H, d, J = 7.6 Hz, H2' and H6'), 7.31-7.40 (3H, m, H3', H4' and H5'), 6.99 (1H, d, J = 8.4 Hz, H6), 6.64 (1H, d, J = 8.4 Hz, H5), 5.02 (2H, s, OCH_2Ph), 4.62 (2H, d, J = 5.3 Hz, CH_2OH), 3.95 (3H, s, OMe), 3.84 (3H, s, OMe) and 2.08 (1H, s, OH).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 153.8 (1C, C, C4 or C2), 152.1 (1C, C, C2 or C4), 141.0 (1C, C, C1'), 137.6 (1C, C, C3), 128.3 (2C, CH, C2' and C6'), 128.2 (2C, CH, C3' and C5'), 127.9 (1C, CH, C4'), 126.9 (1C, C, C1), 123.6 (1C, CH, C6), 107.2 (1C, CH, C5), 75.1 (1C, CH_2, OCH_2Ph), 61.4 (1C, CH_2, CH_2OH), 61.2 (1C, CH_3, OMe) and 56.0 (1C, CH_3, OMe).

3-Benzyloxy-2,4-dimethoxybenzylchloride (**S4**)

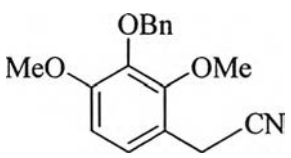


Under Ar, to a solution of **S3** (10.65 g, 38.80 mmol) in dry Et_2O (30 mL) was added dropwise over 20 min of thionyl chloride (5.66 mL, 77.60 mmol). Stirring was continued for 30 min then a mixture was washed with aq saturated Na_2CO_3 solution (4 x 30 mL). The combined aqueous layers were extracted with Et_2O (2 x 30 mL) and the extracts were washed with brine and dried over anh Na_2SO_4. The solvent was distilled off under reduce pressure without heating to afford **S4** (10.92 g, 96%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50 (2H, d, J = 8.1 Hz, H2' and H6'), 7.32-7.41 (3H, m, H3', H4' and H5'), 7.06 (1H, d, J = 8.6 Hz, H6), 6.66 (1H, d, J = 8.6 Hz, H5), 5.02 (2H, s, O$\underline{C}H_2$Ph), 4.62 (2H, s, $\underline{C}H_2$Cl), 3.99 (3H, s, OMe) and 3.84 (3H, s, OMe).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 154.4 (1C, C, C4 or C2), 152.3 (1C, C, C2 or C4), 141.0 (1C, C, C1'), 137.4 (1C, C, C3), 128.1 (2C, CH, C2' and C6'), 128.0 (2C, CH, C3' and C5'), 127.7 (1C, CH, C4'), 125.0 (1C, C, C1), 123.6 (1C, CH, C6), 107.2 (1C, CH, C5), 74.8 (1C, CH_2, O$\underline{C}H_2$Ph), 61.4 (1C, CH_3, OMe), 55.7 (1C, CH_3, OMe) and 41.5 (1C, CH_2, $\underline{C}H_2$Cl).

3-Benzyloxy-2,4-dimethoxybenzylcyanide (**S5**)



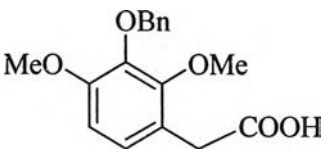
Under Ar, to a solution of **S4** (8.10 g, 27.70 mmol) in DMF (40 mL) was added finely reduced KCN (2.0 g, 30.70 mmol) in solid portion. The mixture was stirred at 50°C for 2 days then poured into water (150 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anh Na_2SO_4. The solvent was distilled off under reduce pressure and the residue was purified by

column chromatography using Et_2O-pentane (4:6) as eluent to afford **S5** (6.2 g, 79%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48 (2H, d, J = 7.6 Hz, H2' and H6'), 7.32-7.40 (3H, m, H3', H4' and H5'), 7.02 (1H, d, J = 8.6 Hz, H6), 6.66 (1H, d, J = 8.6 Hz, H5), 5.01 (2H, s, $OC\underline{H}_2Ph$), 3.96 (3H, s, OMe), 3.84 (3H, s, OMe) and 3.65 (2H, s, $C\underline{H}_2CN$)

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 153.9 (1C, C, C4 or C2), 151.4 (1C, C, C2 or C4), 140.8 (1C, C, C1'), 137.1 (1C, C, C3), 128.0 (2C, CH, C2' and C6'), 127.9 (2C, CH, C3' and C5'), 127.7 (1C, CH, C4'), 123.6 (1C, CH, C6), 118.2 (1C, C, CN or C1), 116.1 (1C, C, C1 or CN), 107.1 (1C, CH, C5), 74.8 (1C, CH_2, $O\underline{C}H_2Ph$), 60.7 (1C, CH_3, OMe), 55.7 (1C, CH_3, OMe) and 18.0 (1C, CH_2, $\underline{C}H_2CN$)

3-Benzyloxy-2,4-dimethoxybenzoic acid (**S6**)



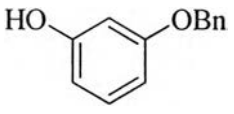
To a solution of **S5** (4.60 g, 16.20 mmol) in EtOH (50 mL) was added quickly drop by drop a 40% aq NaOH solution (25 mL). After addition, the mixture was refluxed for 3 h, and then EtOH was removed under vacuum. The residue was added with water (200 mL) and washed with Et_2O (4 x 30 mL). The aqueous layer was acidified by conc HCl until pH 1, and then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried over anh Na_2SO_4 and the solvent was distilled off under reduce pressure to afford **S6** (3.34 g, 68%) as sticky light yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48 (2H, d, J = 7.9 Hz, H2' and H6'), 7.36 (2H, t, J = 7.9 Hz, H3' and H5'), 7.33 (1H, t, J = 7.9 Hz, H4'), 6.91 (1H, d, J = 8.5 Hz, H6), 6.63 (1H, d, J = 8.5 Hz, H5), 5.01 (2H, s, $OC\underline{H}_2Ph$), 3.90 (3H, s, OMe), 3.84 (3H, s, OMe) and 3.62 (2H, s, $C\underline{H}_2COOH$).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 178.0 (1C, C, $\underline{C}OOH$), 153.4 (1C, C, C4 or C2), 152.1 (1C, C, C2 or C4), 140.9 (1C, C, C1'), 137.5 (1C, C, C3), 128.1 (2C, CH, C2' and C6'), 128.0 (2C, CH, C3' and C5'), 127.7 (1C, CH, C4'), 125.0 (1C, CH,

C6), 119.9 (1C, C, C1), 107.2 (1C, CH, C5), 74.9 (1C, CH_2, O$\underline{C}H_2$Ph), 55.8 (1C, CH_3, OMe), 53.4 (1C, CH_3, OMe) and 35.2 (1C, CH_2, $\underline{C}H_2$COOH).

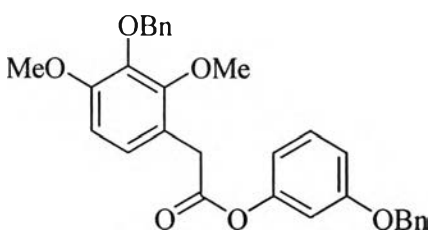
3-Benzyloxyphenol (**S7**)



Under Ar, to a suspension of resorcinol (4.40 g, 40 mmol) and K_2CO_3 (11.04 g, 80 mmol) in dry acetone (100 mL) was injected benzyl chloride (4.60 mL). The resulting mixture was refluxed overnight, and then acetone was distilled off under reduced pressure. The residue was poured into water and extracted with Et_2O. The combined organic layers were dried over anh Na_2SO_4 and the solvent was distilled off under reduce pressure. The residue was purified by column chromatography using Et_2O-pentane (3:7) as eluent to afford **S7** (5.80 g, 73%) as light yellow needles, m.p. 49°C (lit, m.p. 49°C [150]).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29-7.44 (5H, m, Ph), 7.12 (1H, t, J = 8.1 Hz, H5), 6.56 (1H, dd, J = 2.3, 8.1 Hz, H4), 6.47 (1H, t, J = 2.3 Hz, H2), 6.42 (1H, dd, J = 2.3, 8.1 Hz, H6), 5.02 (2H, s, OC$\underline{H}_2$Ph) and 4.88 (1H, s, OH).

(3-Benzyloxy-2,4-dimethoxyphenyl)-acetic acid 3-benzyloxy-phenyl ester (**S8**)



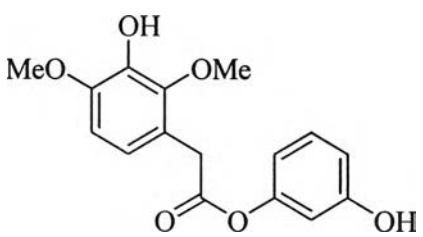
Under Ar, to a solution of **S6** (1.51 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise of oxalyl chloride (0.65 mL, 7.5 mmol). The resulting mixture was refluxed for 2 h, allowed to cool to room temperature then concentrated under reduced pressure (10^{-3} mmHg). A solution of acetyl chloride residue in freshly distilled THF (20 mL) was added dropwise to a solution of phenolates (**S7**) (to a solution of (**S7**) (1.10 g, 5.50 mmol) in dry THF (10 mL) was added NaH, 60% dispersion in mineral oil (0.24 g, 6.0 mmol) and the mixture was stirred at room temperature for 30

minutes). After the addition, the mixture was refluxed for 2 h, allowed to cool to room temperature then added with CH_2Cl_2 (100 mL). The resulting solution was washed successively with saturated aq Na_2CO_3 solution (4 x 30 mL) and brine, and then dried over anh Na_2SO_4. The solvent was distillated off under reduced pressure to afford **S8** (2.30 g, quantitative yield) as light yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30-7.53 (11H, m, 2 x Ph and H5'), 6.99 (1H, d, J = 8.4 Hz, H6), 6.84 (1H, dd, J = 2.5, 8.1 Hz, H4'), 6.79 (1H, t, J = 2.5 Hz, H2'), 6.72 (1H, dd, J = 2.5, 8.1 Hz, H6'), 6.66 (1H, d, J = 8.4 Hz, H5), 5.03 (4H, s, 2 x OCH_2Ph), 3.92 (3H, s, OMe), 3.83 (3H, s, OMe) and 3.81 (2H, s, CH_2COOH).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 170.0 (1C, C, CO), 159.4 (1C, C), 153.4 (1C, C), 152.1 (1C, C), 151.7 (1C, C), 140.9 (1C, C), 137.4 (1C, C), 136.4 (1C, C), 129.5 (1C, CH), 128.3 (2C, 2 x CH), 128.0 (2C, 2 x CH), 127.9 (2C, 2 x CH), 127.7 (1C, CH), 127.6 (1C, CH), 127.2 (2C, 2 x CH), 124.8 (1C, CH), 119.9 (1C, C), 113.8 (1C, CH), 112.0 (1C, CH), 108.4 (1C, CH), 107.1 (1C, CH), 74.7 (1C, CH_2), 69.8 (1C, CH_2), 60.8 (1C, CH_3, OMe), 55.7 (1C, CH_3, OMe) and 35.5 (1C, CH_2).

(3-Hydroxy-2,4-dimethoxyphenyl)-acetic acid 3-hydroxyphenyl ester (**S9**)



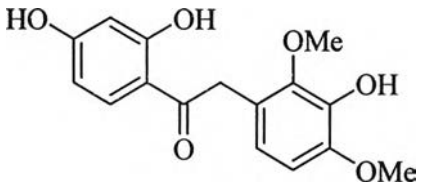
A suspension of **S8** (2.30 g, 5 mmol) and 10% Pd/C (100 mg, 4% weight) in absolute EtOH (30 mL) was stirred under hydrogen atmosphere at room temperature for 2 h. The mixture was added with acetone (50 mL) and filtered through a short pad of celite. Evaporation of the filtrate under reduced pressure and purification of residue by column chromatography using Et_2O-pentane (7:3) as eluent afford **S9** (1.15 g, 81%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.19 (1H, t, J = 8.1 Hz, H5'), 6.78 (1H, d, J = 8.5 Hz, H6), 6.66 (2H, dd, J = 2.0, 8.1 Hz, H4' and H6'), 6.63 (1H, d,

J = 8.5 Hz, H5), 6.59 (1H, t, J = 2.0 Hz, H2'), 5.58 (1H, s, OH), 5.27 (1H, s, OH), 3.94 (3H, s, OMe), 3.89 (3H, s, OMe) and 3.81 (2H, s, $\underline{C}H_2COO$).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 171.0 (1C, C, $\underline{C}OO$), 157.2 (1C, C, C3'), 151.6 (1C, C, C1'), 147.5 (1C, C, C4 or C2), 145.4 (1C, C, C2 or C4), 138.6 (1C, C, C3), 129.7 (1C, CH, C5'), 120.5 (1C, CH, C6), 120.1 (1C, C, C1), 113.1 (1C, CH, C6' or C4'), 112.9 (1C, CH, C4' or C6'), 109.0 (1C, CH, C2'), 106.3 (1C, CH, C5), 60.4 (1C, CH_3, OMe), 56.1 (1C, CH_3, OMe) and 35.7 (1C, CH_2, $\underline{C}H_2COO$).

1-(2,4-Dihydroxyphenyl)-2-(3-hydroxy-2,4-dimethoxyphenyl)ethanone (**S10**)

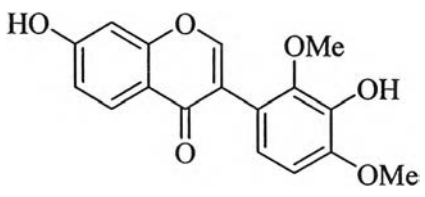


Under Ar, to a solution of **S9** (0.70 g, 2.40 mmol) in dry CH_2Cl_2 (2 mL) was quickly injected dropwise of $BF_3.OEt_2$ (8 mL). The mixture was heated at 80°C for 3 h, allowed to cool to room temperature, poured into water (100 mL), and then extracted with CH_2Cl_2 (3 x 30 mL). The extracts were washed with brine, dried over anh Na_2SO_4 and the solvent was removed under vacuum to afford **S10** (0.70 g, quantitative yield) as light yellow plates, m.p. 152°C (lit. m.p.153°C [72]).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.80 (1H, d, J = 9.2 Hz, H6'), 6.69 (1H, d, J = 8.3 Hz, H6), 6.62 (1H, d, J = 8.3 Hz, H5), 6.37 (1H, dd, J = 1.9, 9.2 Hz, H5'), 6.36 (1H, d, J = 1.9 Hz, H3), 6.03 (1H, s, OH), 5.60 (1H, s, OH), 4.18 (2H, s, $\underline{C}H_2CO$), 3.87 (3H, s, OMe) and 3.86 (3H, s, OMe).

^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 203.0 (1C, C, $\underline{C}O$), 165.0 (1C, C, C4' or C2'), 163.7 (1C, C, C2' or C4'), 147.2 (1C, C, C4 or C2), 144.9 (1C, C, C2 or C4), 138.5 (1C, C, C3), 132.7 (1C, CH, C6'), 120.7 (1C, C, C1), 120.6 (1C, CH, C6), 113.0 (1C, C, C1'), 108.4 (1C, CH, C5'), 106.6 (1C, CH, C5), 103.3 (1C, CH, C3'), 60.5 (1C, CH_3, OMe), 56.0 (1C, CH_3, OMe) and 38.7 (1C, CH_2, $\underline{C}H_2CO$).

7-Hydroxy-3-(3-hydroxy-2,4-dimethoxyphenyl)chromen-4-one (**P12**)



Under Ar, to a solution of **S10** (120 mg, 0.41 mmol) in anh DMF (2 mL) was injected dropwise of $BF_3.OEt_2$ (0.314 mL, 2.46 mmol). After heating to 50°C, methanesulfonyl chloride (0.096 mL, 1.44 mmol) was added, and then the resulting mixture was refluxed for 2 h and allowed to cool to room temperature. The reaction mixture was poured into 10% aq Na_2CO_3 solution (100 mL), washed with Et_2O (3 x 20 mL), acidified with conc HCl until pH 1, then extracted with $CHCl_3$ (4 x 20 mL). The combined organic layers were washed with brine and dried over anh Na_2SO_4. The solvent was evaporated off and the residue was purified by column chromatography using CH_2Cl_2-EtOH (10:1) as eluent to afford **P12** (63 mg, 51%) as pale yellow needles, m.p. 254°C (lit, 251-252°C [72, 127]).

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 9.69 (1H, s, OH), 8.06 (1H, d, J = 8.7 Hz, H5), 7.99 (1H, s, H2), 7.59 (1H, s, OH), 7.01 (1H, d, J = 2.3 and 8.7 Hz, H6), 6.92 (1H, d, J = 2.3 Hz, H8), 6.77 (2H, s, H5' and H6'), 3.89 (3H, s, OMe) and 3.77 (3H, s, OMe).

^{13}C-NMR (300 MHz, acetone-d_6) δ (ppm): 175.7 (1C, C, C4), 163.2 (1C, C, C7), 158.9 (1C, C, C9), 154.1 (1C, CH, C2), 149.7 (1C, C, C4'), 147.2 (1C, C, C2'), 140.4 (1C, C, C3'), 128.4 (1C, CH, C5), 123.6 (1C, C, C3), 121.8 (1C, CH, C6'), 120.1 (1C, C, C1'), 118.5 (1C, C, C10), 115.5 (1C, CH, C6), 107.3 (1C, CH, C5'), 103.2 (1C, CH, C8), 60.3 (1C, CH_3, OMe) and 56.5 (1C, CH_3, OMe).

3.2.5 Biological Activity

3.2.5.1 Cytotoxicity Test

- Cell Cultures

Human epithelial mammary HBL100 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), penicillin/streptomycin and L-glutamine, maintained in a humidified incubator at 37°C with 5% carbon dioxide.

- **Survival Assay** [151]

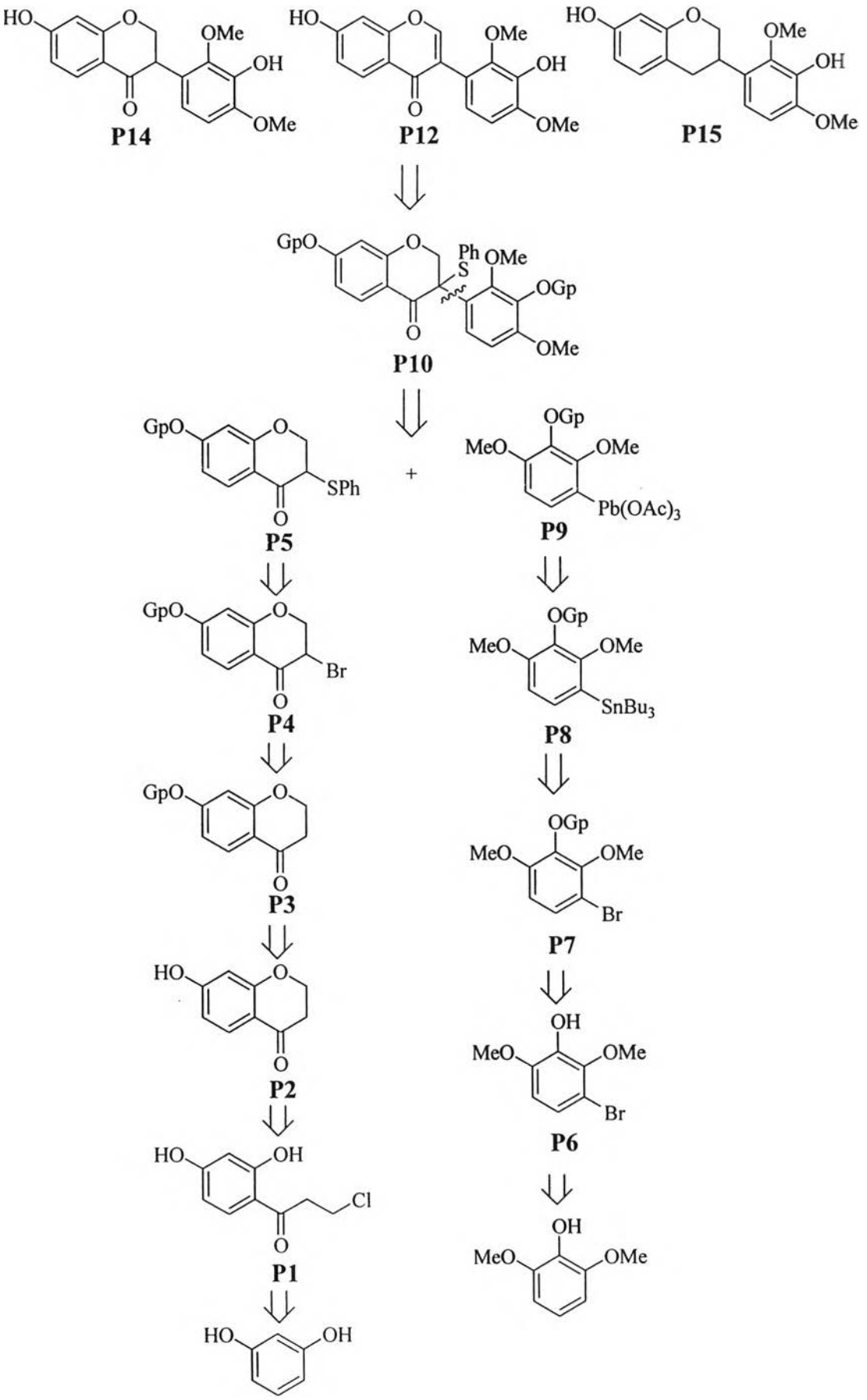
Human Epithelial Mammary HBL100 cells were grown at 37°C in a humidified atmosphere containing 5% carbon dioxide in DMEM medium, supplemented with 10% fetal bovin serum, penicillin/streptomycin and *L*-glutamine. The cytotoxicity of the test compounds was assessed using a cell proferation assay developed by Promega (CellTiter 96 AQuepus one solution cell proliferation assay). Briefly, 3 x 10^4 exponentially growing cells were seeded in 96-well microculture plates with various drugs concentrations (100 nM, 1, 5, 10, 30 and 50 μM) in a volume of 150 μL. After 72 h incubation at 37°C, 150 μL of the MTT solution (0.5 mg/1 mL medium culture) was added to each well, and then the samples were incubated for a further 2 h at 37°C. Each drugs concentration was tested in triplicate. Plates were analyzed on a Metertech ∑960. (IC_{50}: Drug concentration that inhibits the growth of HBL 100 cells by 50% after incubation in liquid medium for 72 h.)

3.3 RESULTS AND DISCUSSION

In this research, (±)-mucronulatol (**D5**) and (±)-violanone (**D7**) isolated from the CH_2Cl_2 extract of *D. oliveri* heartwood and displayed high and moderate antioxidant and antifungal activity against *Fusarium oxysporum*, respectively. Furthermore, **D5** and **D7** displayed cytotoxicity against human hepatocellular carcinoma (HepG2). **D7** also showed high cytotoxicity against diamondback moth and mosquito larvae. They were synthesized from a common intermediate prepared by arylation of 3-phenylthiochroman-4-one derivative with aryllead (IV) triacetate. Furthermore, 3',7-dihydroxy-2',4'-dimethoxyisoflavone, a representative of isoflavone group was also synthesized using arylation of 3-phenylthiochroman-4-one derivative with aryllead (IV) triacetate and addition of a one carbon unit to a deoxybenzoin (*via* deoxybenzoin).

3.3.1 Synthesis of Isoflavonoids using Arylation Reaction

3',7-Dihydroxy-2',4'-dimethoxy-isoflavone, -isoflavanone and -isoflavan were retrosynthetically disconnected using arylation reaction as shown in Scheme 3.1.



Scheme 3.1 Retrosynthesis of three selected isoflavonoids using arylation

According to the retrosynthetic approach shown in Scheme 3.1, the common intermediate for the synthesis of three target molecules was **P10**. Strategic disconnection of the proposed intermediate **P10** at C3-C1' bond provided the appropriate precursor **P5** and aryllead (IV) triacetate (**P9**).

P5 was planned to synthesize from **P4** *via* nucleophilic substitution. **P4** could be obtained using α-bromination reaction of protected chroman-4-one (**P3**) which could be achieved from chroman-4-one (**P2**). The intramolecular cyclization of **P1** should reach **P2** without any problem, while. Ketone (**P1**) could be attained using Friedel-Craft acylation of resorcinol and 3-chloropropionylchloride.

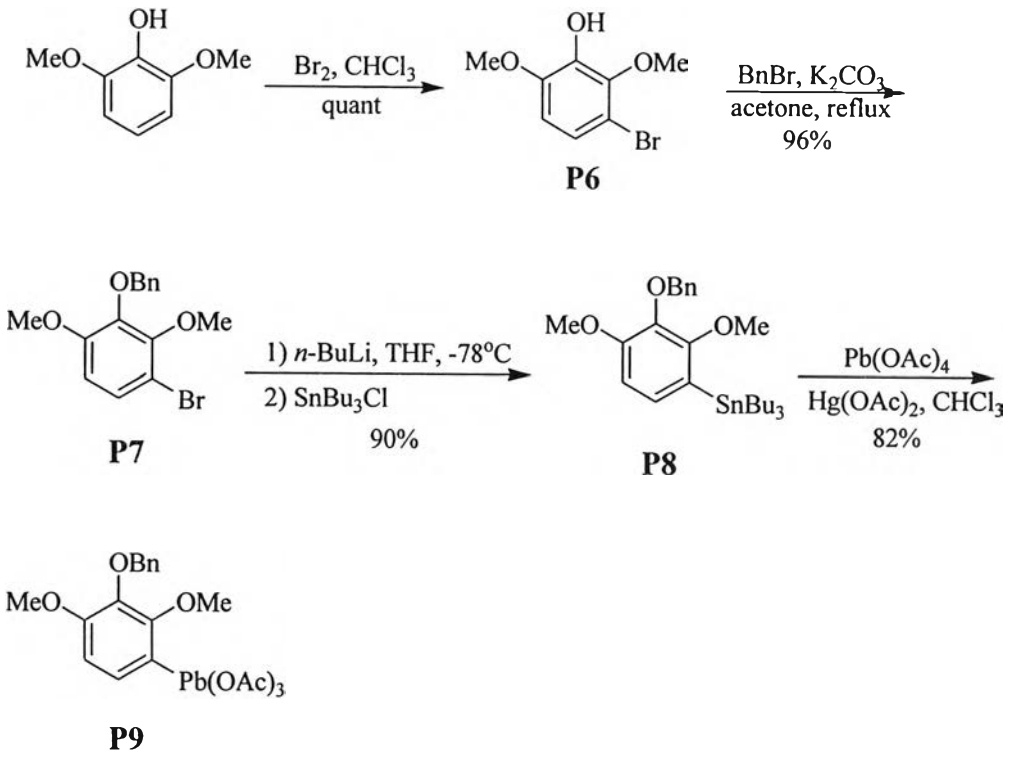
Aryllead (IV) triacetate (**P9**) would be prepared by tin-lead exchange reaction between aryltributylstannane (**P8**) and lead (IV) tetraacetate. Aryltributylstannane (**P8**) was planned to be gained from the reaction between chlorotributylstannane and aryllithium from the corresponding arylbromide containing a protected 3-hydroxy substitutent (**P7**). Protected arylbromide (**P7**) should be synthesized from arylbromide (**P6**) *via* electrophilic substitution. Finally, arylbromide (**P6**) should be obtained using bromination reaction of 2,6-dimthoxyphenol.

The synthesis of target isoflavone (**P12**) could eventually be accomplished by using oxidation reaction of phenylthio group into sulfoxide followed by thermal elimination and deprotection, respectively whereas, the target isoflavanone (**P14**) could be acquired by reduction and deprotection, respectively. Hydrogenation either the target isoflavone or isoflavanone would provide the target isoflavan (**P15**).

Synthesis of Aryllead (IV) Triacetate

An appropriate aryllead (IV) triacetate was prepared by tin-lead exchange between aryltrialkyltin and lead tetraacetate according to the protocol reported by Donnelly and co-workers [122, 152]. This procedure in addition opened the gateway for the synthesis of a wide range of isoflavanones and isoflavones, including highly hindered systems as the 2',4',6'-trisubstituted phenyl derivative in high yield.

The synthesis of aryllead (IV) triacetate is shown in Scheme 3.2.



Scheme 3.2 Synthesis of aryllead (IV) triacetate

The preparation of aryllead (IV) triacetate could be achieved in 4 steps as shown in Scheme 3.2. Using 2,6-dimethoxyphenol as a starting material, **P6** was quantitatively obtained by bromination reaction. The protection of hydroxyl group as benzyl group was carried out in the presence of benzyl bromide and K_2CO_3 in acetone giving **P7** in excellent yield (96%). Aryltributylstannane (**P8**) was achieved in excellent yield (90%) from the reaction of chlorotributylstannane and aryllithium formed from arylbromide and *n*-BuLi in THF. Finally, in the last step of the synthesis of aryllead (IV) triacetate, **P8** was converted into aryllead (IV) triacetate (**P9**) in good yield (82%) by tin-lead exchange between **P8** and lead (IV) tetraacetate in the presence of a catalytic amount of $Hg(OAc)_2$ in $CHCl_3$. The ^{1}H-NMR spectrum (Figure 3.1) of **P9** displayed two *ortho* coupled protons at δ 7.49 (d, J = 9.1 Hz, H5) and 6.84 (d, J = 9.1 Hz, H6). The signals at δ 7.35-7.44 (m) were assigned to five aromatic protons. The signal at δ 5.03 was ascribed to two protons of methylene group. The presence of two methoxy groups was detected at δ 3.88 and 4.02. This spectrum also demonstrated the singlet signal of nine protons at δ 2.11 indicated the presence of three methyl groups. The ^{13}C-NMR spectrum (Figure 3.2) of **P9** displayed the characteristic of three carbonyl groups at δ 180.0, two methoxy groups at 62.5 and 56.9 and three methyl groups at δ 20.9. Five quaternary carbons (δ 157.8, 152.9,

147.3, 141.4 and 137.2), seven aromatic carbons (δ 128.8 (2C), 128.7 (2C), 128.6, 126.7 and 109.3) and methylene carbon (δ 75.8) were observed.

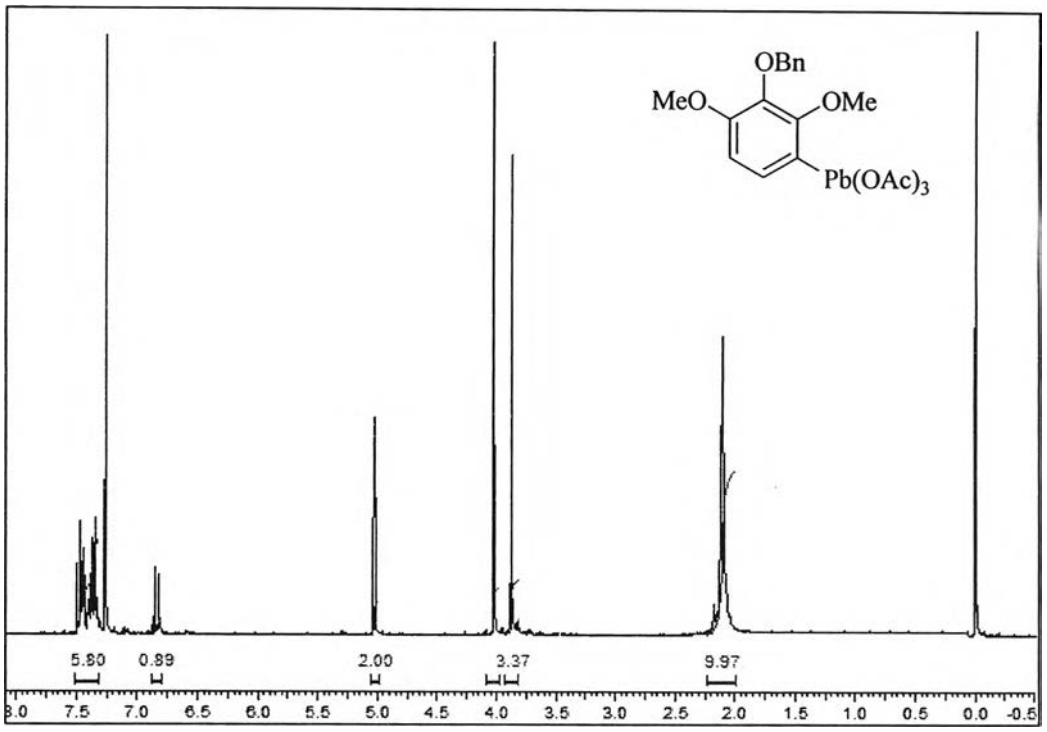


Figure 3.1 The ^{1}H-NMR spectrum of **P9**

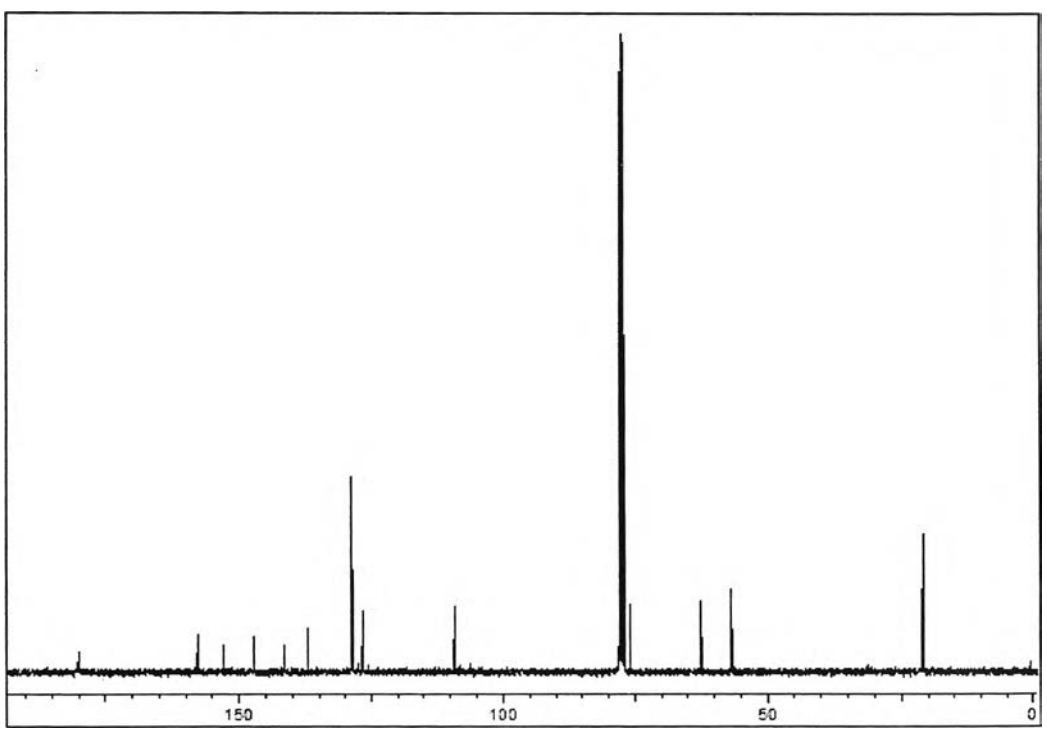
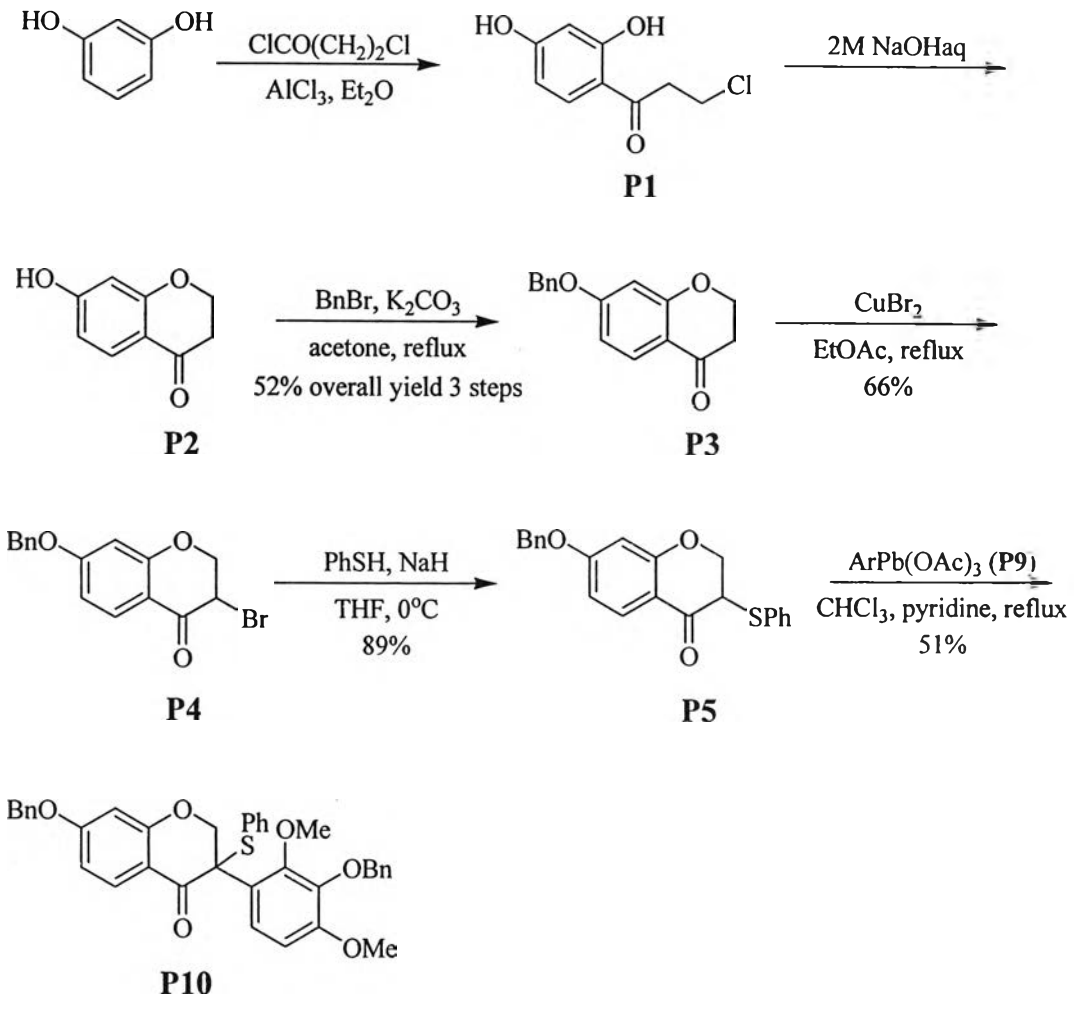


Figure 3.2 The ^{13}C-NMR spectrum of **P9**

Synthesis of Intermediate P10

The synthesis of the common intermediate **P10** for three target isoflavonoids using arylation reaction is demonstrated in Scheme 3.3.



Scheme 3.3 Synthesis of intermediate **P10**

Firstly, the common intermediate for three target isoflavonoids, 3-aryl-3-phenylthiochroman-4-one (**P10**), was prepared in six steps as described in Scheme 3.2. Using resorcinol as the starting material, ketone (**P1**) was obtained by Friedel-Craft acylation with chloropropionyl chloride in the presence of $AlCl_3$ as Lewis acid catalyst. Intramolecular cyclization of **P1** in basic condition afforded chroman-4-one (**P2**). **P2** was protected as benzyl group to yield protected chroman-4-one (**P3**) in 52% yield for 3 steps. α-Bromination of **P3** with cooper (II) bromide in EtOAc at reflux condition generated **P4** in 66% yield. Activation of a carbonyl group in **P4** by an

α-arylthio substitutent was proceeded with thiophenol and NaH in THF at 0°C to obtain **P5** in good yield (89%).

The ^{1}H-NMR spectrum of **P5** (Figure 3.3) disclosed two *ortho* coupled protons at δ 7.87 (d, J = 8.9 Hz, H5) and 6.69 (dd, J = 2.3, 8.9 Hz, H6) and *meta* coupled proton at 6.49 (d, J = 2.3 Hz, H8). Ten aromatic protons were detected at δ 7.29-7.54 (m). The signal at δ 5.09 was ascribed to two protons of methylene group adjusted aromatic. The proton signals at δ 4.61 (dd, J = 3.9, 11.7 Hz) and 4.50 (dd, J = 6.4, 11.7 Hz) were assigned to protons at H2 and 4.02 (dd, J = 3.9, 6.4 Hz) was ascribed to proton at H3. The ^{13}C-NMR spectrum of **P5** (Figure 3.4) signified carbonyl carbon (δ 186.5), five quaternary carbons (δ 165.0 (C7), 162.5 (C9), 135.6, 131.9 and 110.8 (C10) and fourteen methine carbons (δ 132.8 (2 x CH), 129.8 (C5), 128.9 (2 x CH), 128.5 (2 x CH), 128.1, 127.9, 127.3 (2 x CH), 113.8 (C6), 101.4 (C8) and 50.9 (C3). Moreover, two peaks indicative of methylene carbons at δ 70.4 (O<u>C</u>H$_2$Ph), and 70.1 (C2) were observed.

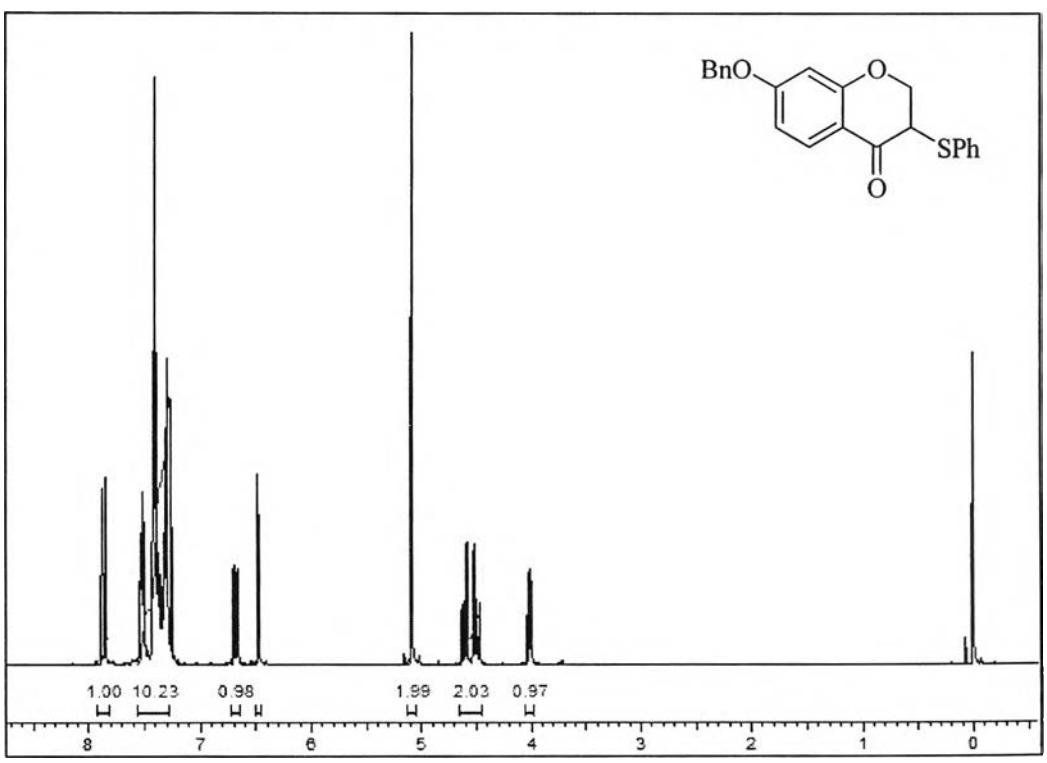


Figure 3.3 The ^{1}H-NMR spectrum of **P5**

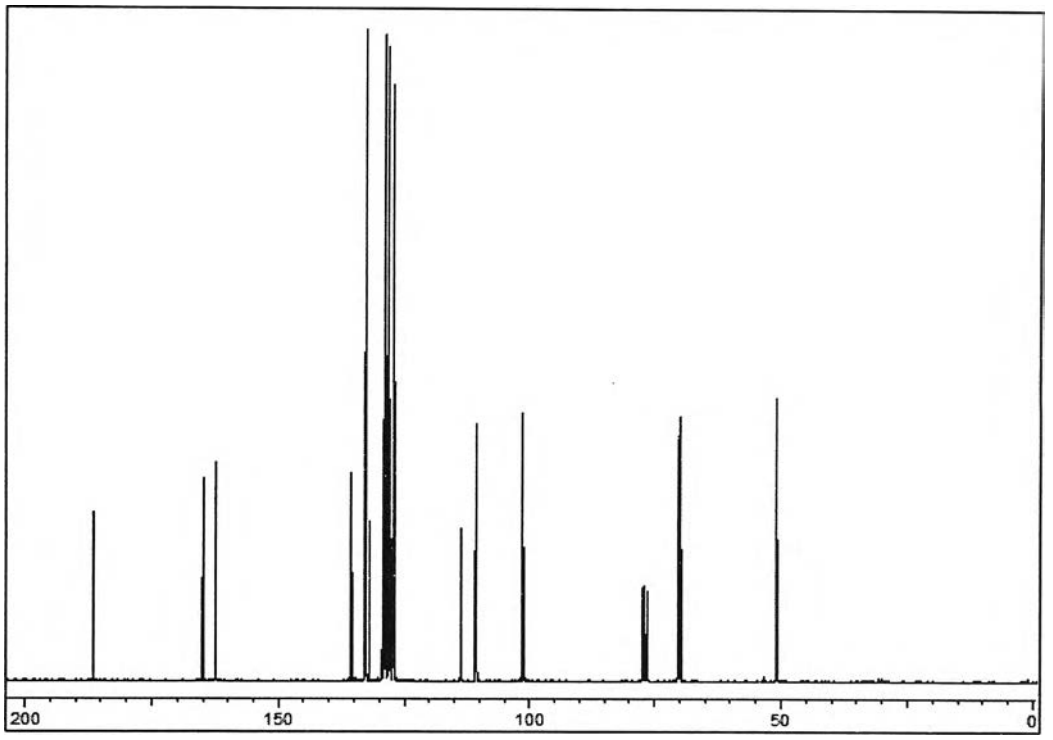


Figure 3.4 The ^{13}C-NMR spectrum of **P5**

The preparation of intermediate **P10** involved the arylation reaction of **P5** and **P9**. The ^{1}H-NMR spectrum of **P10** (Figure 3.5) presented four *ortho* coupled protons at δ 7.86 (d, J = 8.9 Hz, H6'), 7.74 (d, J = 8.7 Hz, H5), 6.67 (d, J = 8.9 Hz, H5'), 6.64 (dd, J = 2.3, 8.7 Hz, H6) and *meta* coupled proton at δ 6.47 (1H, d, J = 2.3 Hz, H8). Fifteen aromatic protons were detected at δ 7.10-7.40 (*m*). The signal at δ 5.04 and 4.93 was ascribed to two protons of methylene group adjusted aromatic. The proton signals at δ 4.84 (d, J = 12.1 Hz), 4.15 (d, J = 12.1 Hz) were assigned to protons at H2. The presence of two methoxy groups was detected at δ 3.80 and 3.67. The ^{13}C-NMR spectrum of **P10** (Figure 3.6) displayed carbonyl carbon (δ 185.2), eleven quaternary carbons (δ, 164.4 (C7), 161.6 (C9), 154.3 (C2'), 151.7 (C4'), 141.1 (C3'), 137.2, 136.0, 125.3, 122.0 (C10), 114.3 (C1') and 62.6 (C3) and twenty one methine carbons (δ 135.4 (2 x CH), 130.5 (C6'), 129.8 (C5), 18.6 (2 x CH), 128.5, 128.3 (2 x CH), 128.2 (2 x CH), 128.1, 128.0 (2 x CH), 127.9, 127.5 (2 x CH), 110.5 (C6), 106.4 (C5'), 101.5 (C8) and 74.6. Moreover, two peaks indicative of methylene carbons at δ 73.4 and 70.2 and two methyl groups at δ 60.0 and 55.9 were observed.

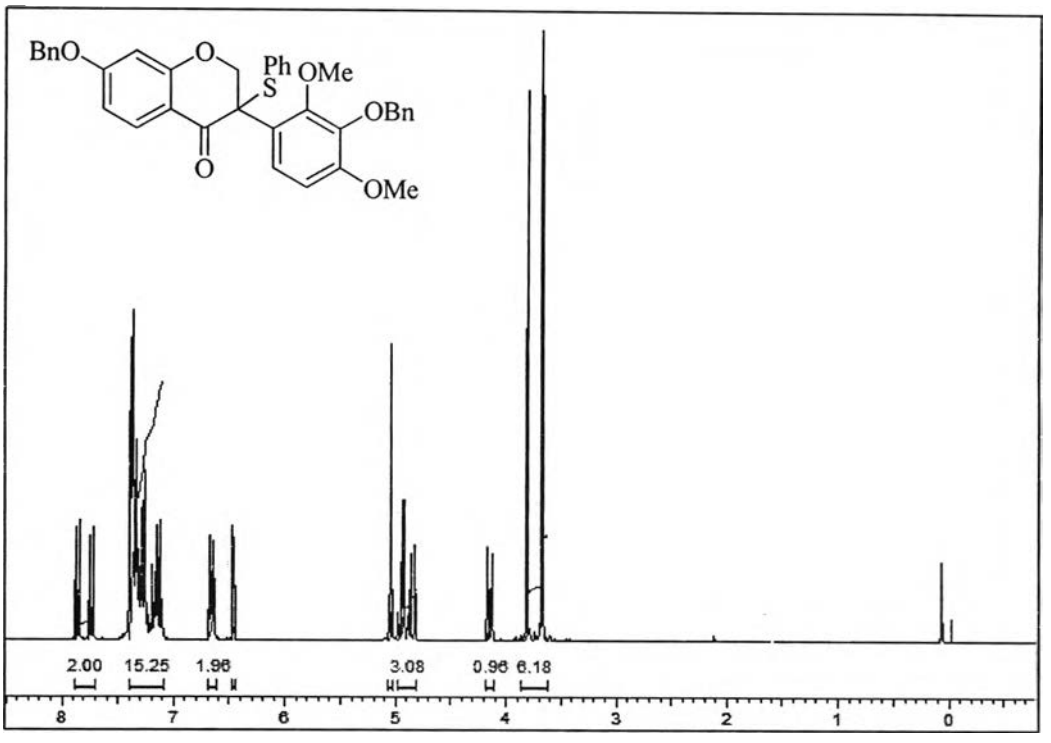


Figure 3.5 The ^{1}H-NMR spectrum of **P10**

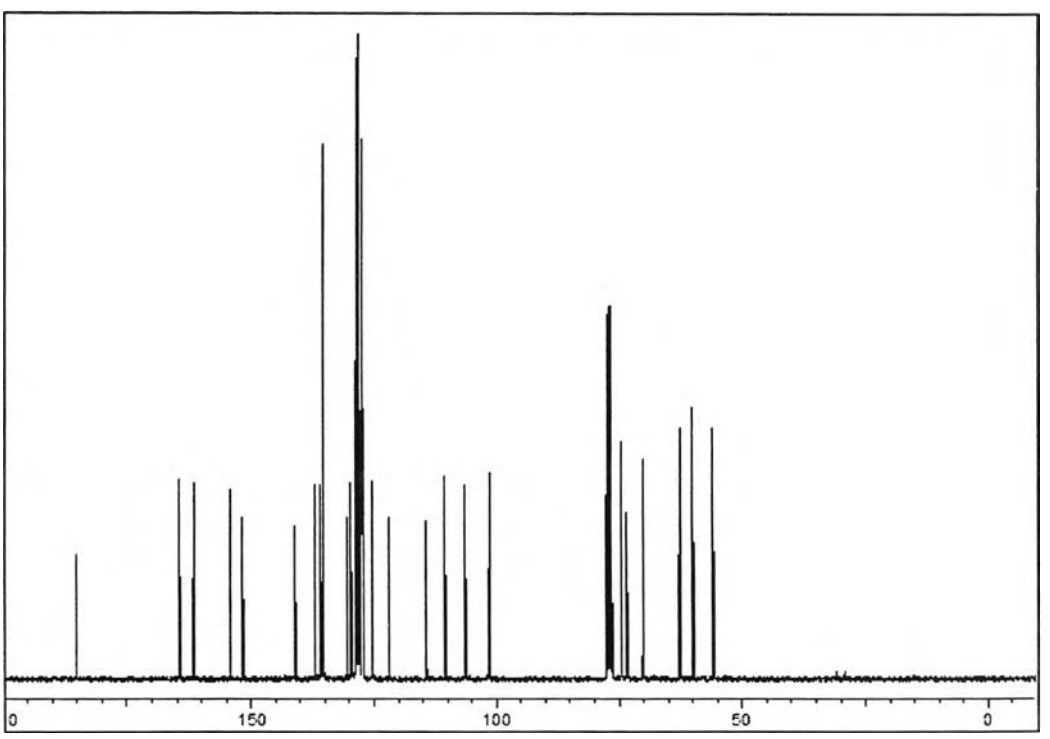
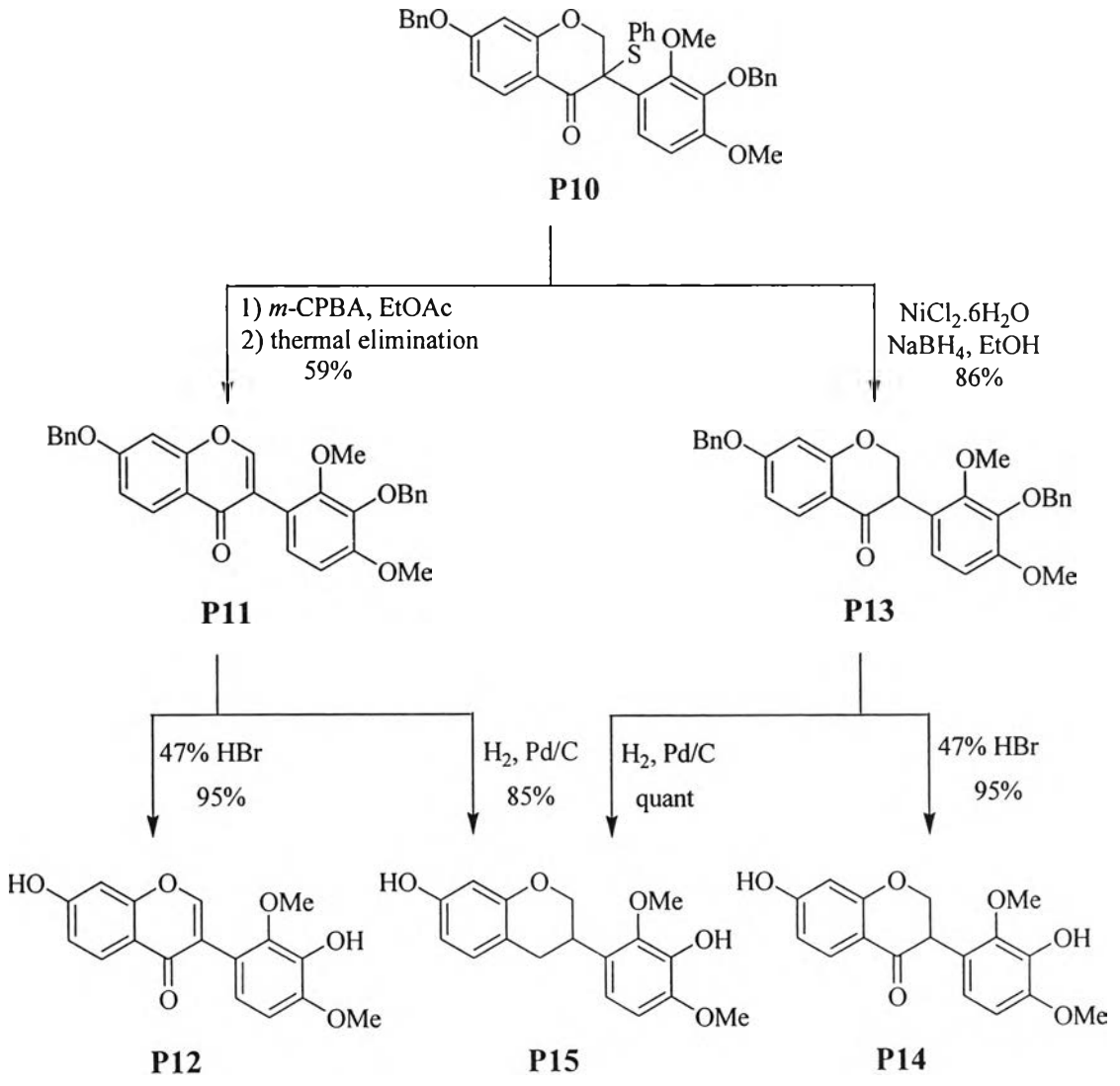


Figure 3.6 The ^{13}C-NMR spectrum of **P10**

Synthesis of Three Target Isoflavonoids

P10 as an intermediate precursor for the synthesis of three target molecules could be converted to isoflavone or isoflavanone by *m*-CPBA oxidation followed by thermal elimination or reduction, respectively. Whereas isoflavan could be obtained by hydrogenation either from the target isoflavone or isoflavanone.

Oxidation of **P10** with *m*-CPBA in EtOAc followed by thermal elimination led to the protected isoflavone (**P11**) in yield of 59%. The benzyl group in **P11** could be removed easily in 47% HBr to produce **P12** in excellent yield (95%). Whereas the reduction of **P10** with excess nickel boride in EtOH led to the protected isoflavanone (**P13**) in good yield (86%). Deprotection of **P13** with 47% HBr yielded **P14** in excellent yield (95%). **P15** could be accomplishly obtained in good to excellent yield (85%-quantitative) by hydrogenation either from the protected isoflavone (**P11**) or isoflavanone (**P13**) as shown in Scheme 3.4.



Scheme 3.4 Synthesis of three target isoflavonoids

The ^{1}H-NMR spectrum of **P12** (Figure 3.7) showed two *ortho* coupled protons at δ 8.07 (d, J = 8.7 Hz, H5) and 7.03 (1H, dd, J = 2.3 and 8.7 Hz, H6) and *meta* coupled proton at δ 6.93 (1H, d, J = 2.3 Hz, H8). The singlet proton signal at δ 8.00 was assigned to olefinic proton at H2. The broad singlet signal at δ 6.78 was ascribed to proton at H5' and H6'. The presence of two hydroxyl groups were detected at δ 9.60 and 7.53 and two methoxy groups were also detected at δ 3.89 and 3.77. The ^{13}C-NMR spectrum of **P12** (Figure 3.8) displayed carbonyl carbon (δ 175.5), eight quaternary carbons (δ, 163.0 (C7), 158.7 (C9), 149.5 (C4'), 147.0 (C2'), 140.2 (C3'), 123.4 (C3), 120.0 (C1') and 118.3 (C10) and six methine carbons (δ 154.0 (C2), 128.2 (C5), 121.6 (C6'), 115.3 (C6), 107.1 (C5') and 103.0 (C8). Moreover, two peaks indicative of methyl group at δ 60.1 and 56.4 were observed.

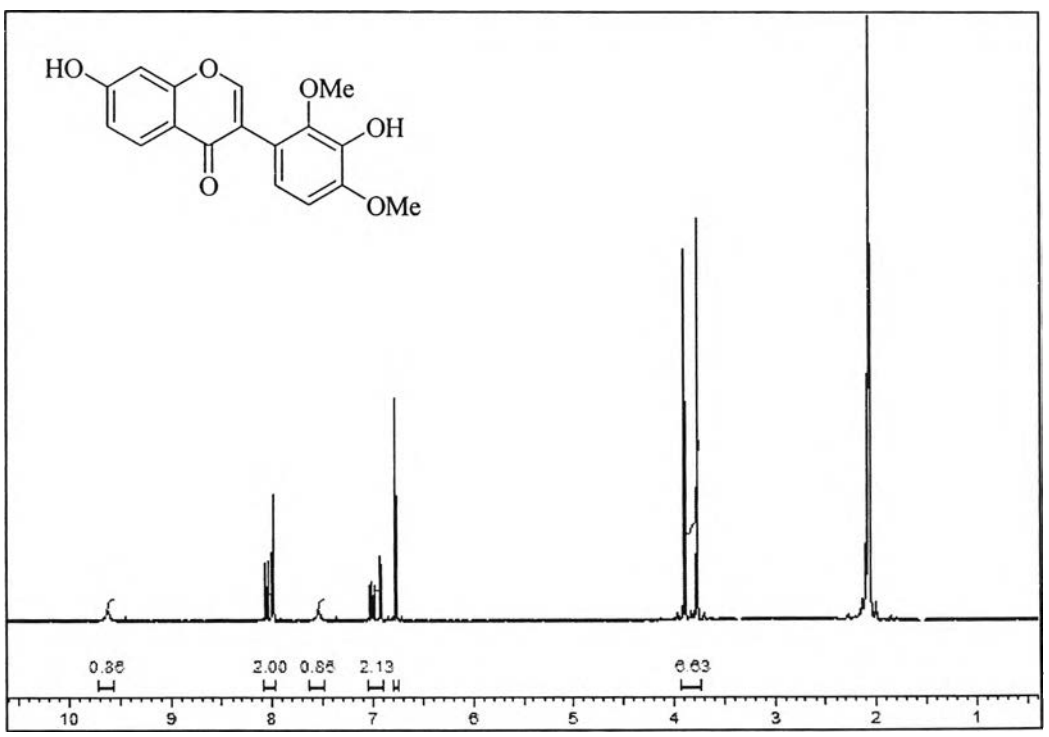


Figure 3.7 The ^{1}H-NMR spectrum of **P12**

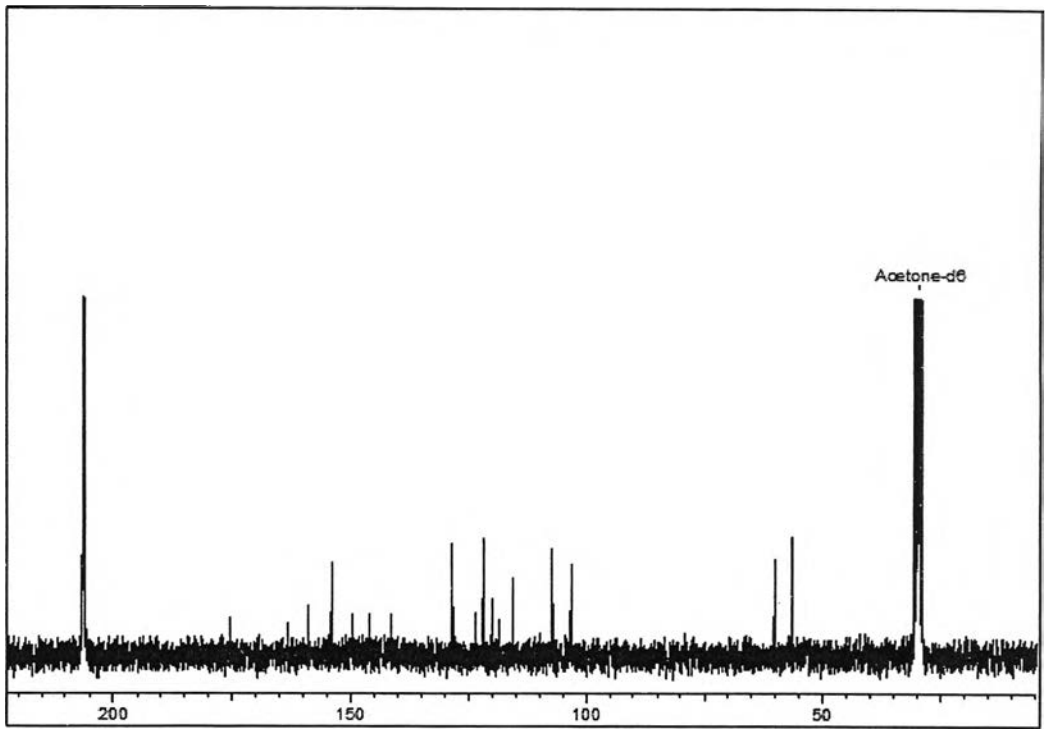


Figure 3.8 The ^{13}C-NMR spectrum of **P12**

The ^{1}H-NMR spectrum of **P14** (Figure 3.9) revealed four *ortho* coupled protons at δ 7.81 (d, *J* = 8.5 Hz, H5), 6.71 (d, *J* = 8.5 Hz, H6'), 6.64 (d, *J* = 8.1 Hz, H5') and 6.62 (dd, *J* = 2.3, 8.5 Hz, H6) and *meta* coupled proton at 6.44 (d, *J* = 2.3 Hz, H8). The three double doublet signals at δ 4.61 (*J* = 11.0, 11.5 Hz), 4.48 (*J* = 5.5, 11.0 Hz) and 4.15 (*J* = 5.5, 11.5 Hz) were assigned to proton at H2*ax*, H2*eq* and H3, respectively. The presence of two methoxy groups was detected at δ 3.86 and 3.81. The ^{13}C-NMR spectrum of **P14** (Figure 3.10) displayed carbonyl carbon (δ 191.3), seven quaternary carbons (δ 164.9 (C7), 164.7 (C9), 149.1 (C2'), 146.9 (C4'), 140.3 (C3'), 123.1 (C1') and 115.8 (C10), six methine carbons (δ 130.0 (C5), 120.4 (C6'), 111.2 (C6), 107.4 (C5'), 103.5 (C8) and 48.9 (C3) and one methylene carbon (δ 72.1). The signal of two methoxy groups was detected at δ 60.1 and 56.5.

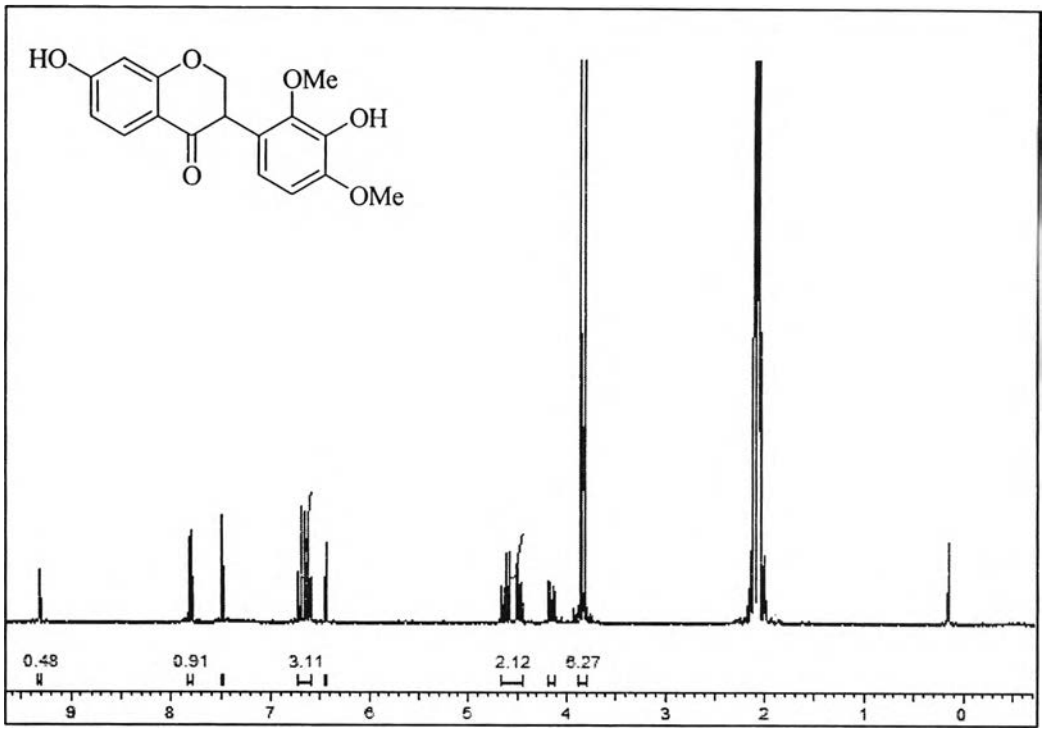


Figure 3.9 The ^{1}H-NMR spectrum of **P14**

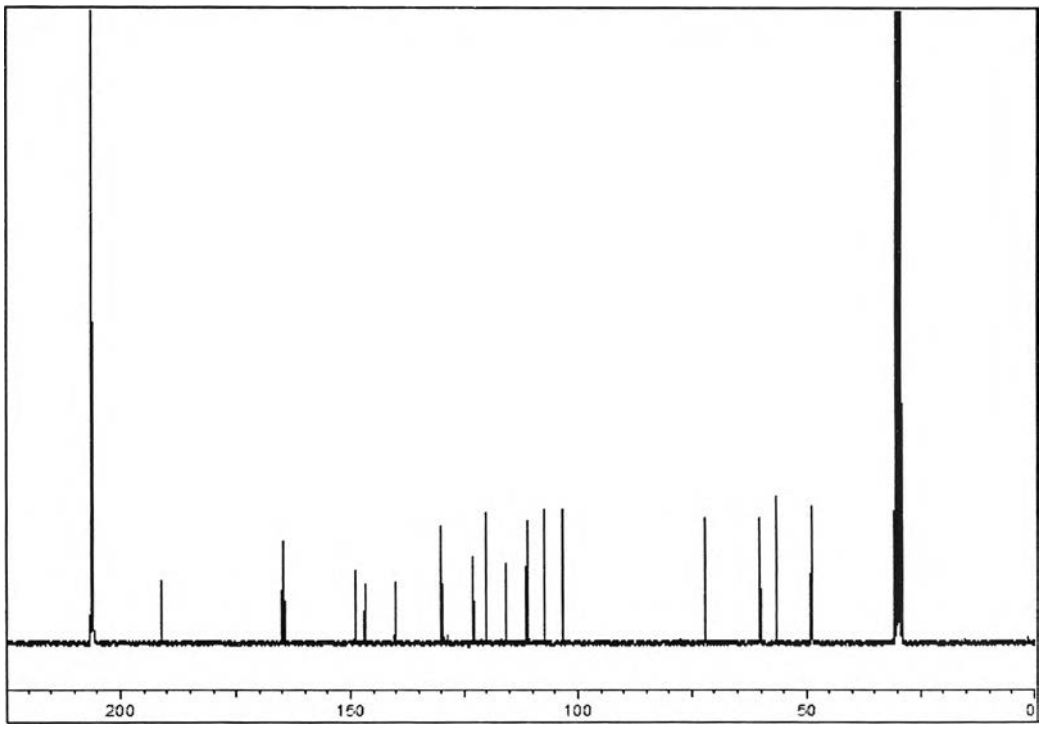


Figure 3.10 The ^{13}C-NMR spectrum of **P14**

The ^{1}H-NMR spectrum of **P15** (Figure 3.11) showed four *ortho* coupled protons at δ 6.90 (d, J = 8.3 Hz, H5), 6.74 (d, J = 8.5 Hz, H5'), 6.67 (d, J = 8.5 Hz, H6') and 6.39 (dd, J = 2.3, 8.3 Hz, H6) and *meta* coupled proton at 6.31 (d, J = 2.3 Hz, H8). The signal at δ 4.20 (ddd, J = 1.9, 3.5, 10.3 Hz), 3.95 (t, J = 10.3 Hz), 2.92 (dd, J = 10.9, 15.6 Hz) and 2.80 (ddd, J = 5.4, 10.9, 15.6 Hz,) were assigned to two methylene protons at H2*eq*, H2*ax*, H4*ax* and H4*eq*, respectively. The presence of methine proton at H3 was detected at δ 3.46 (ddd, J = 3.5, 5.9, 10.3 Hz). The two single signals at δ 3.88 and 3.84 were ascribed to two methoxy groups. The ^{13}C-NMR spectrum of **P15** (Figure 3.12) disclosed seven quaternary carbons (δ 157.8 (C7), 156.3 (C9), 148.7 (C2'), 147.0 (C4'), 140.6 (C3'), 128.4 (C1') and 114.5 (C10), six methane carbons (δ 131.2 (C5), 117.6 (C6'), 109.1 (C6), 108.2 (C5'), 103.9 (C8) and 33.0 (C3) and two methylene carbon (δ 71.2 (C2) and 32.3 (C4)). The signal of two methoxy groups was detected at δ 61.1 and 56.7. The presence of two methoxy groups was detected at δ 61.1 and 56.7.

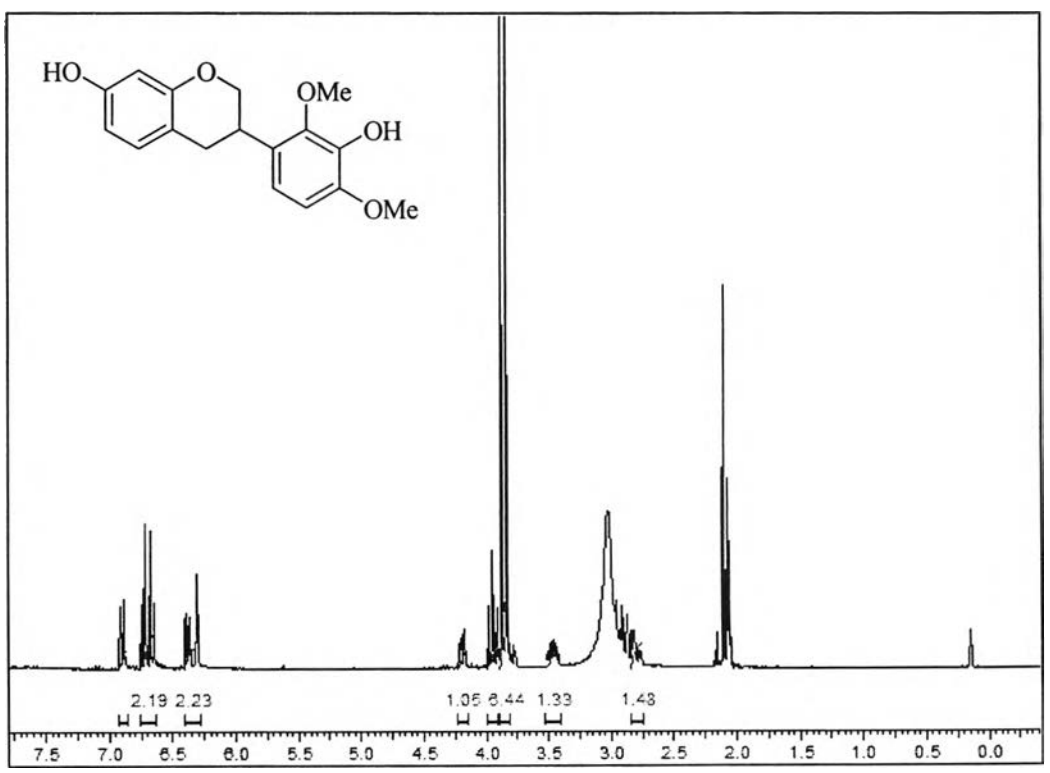


Figure 3.11 The ^{1}H-NMR spectrum of **P15**

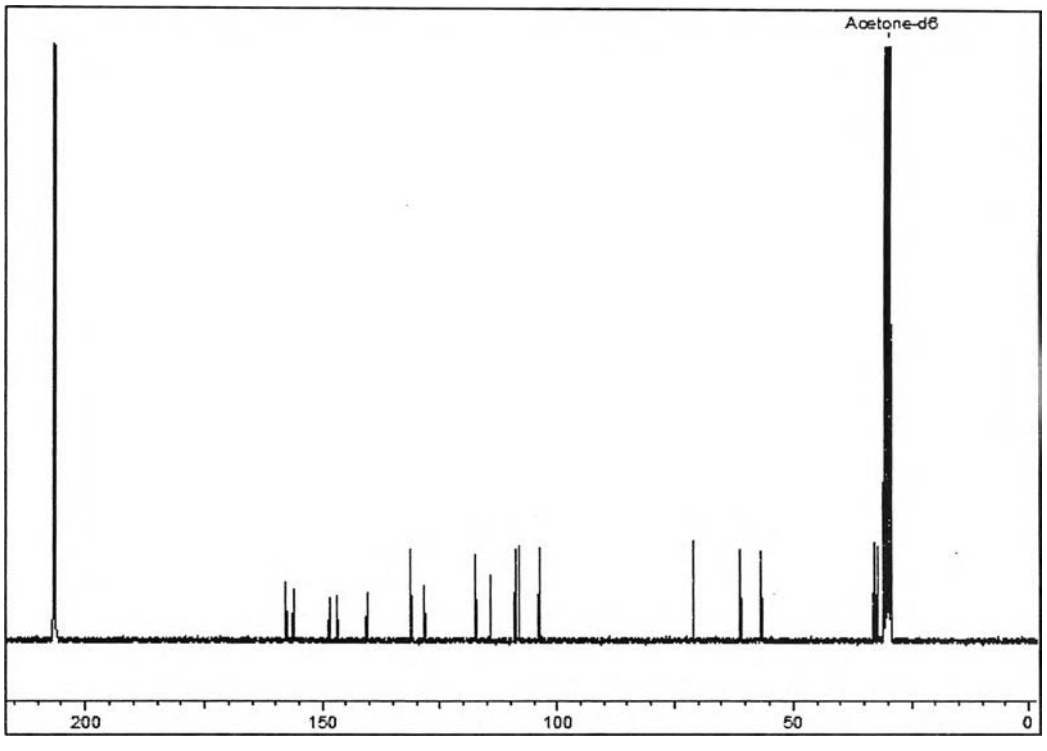
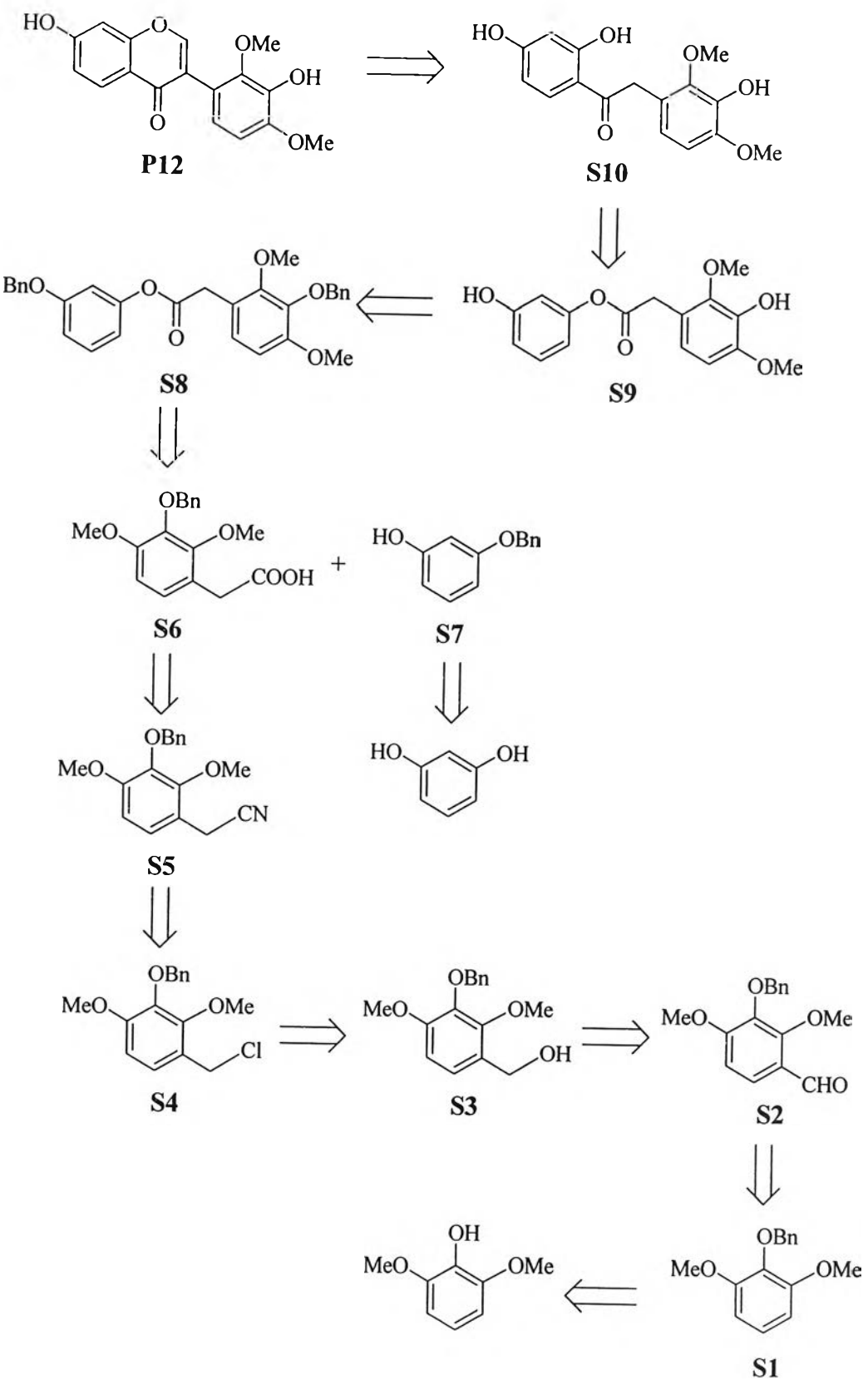


Figure 3.12 The ^{13}C-NMR spectrum of **P15**

3.3.2 Synthesis of Isoflavone using Deoxybenzoin

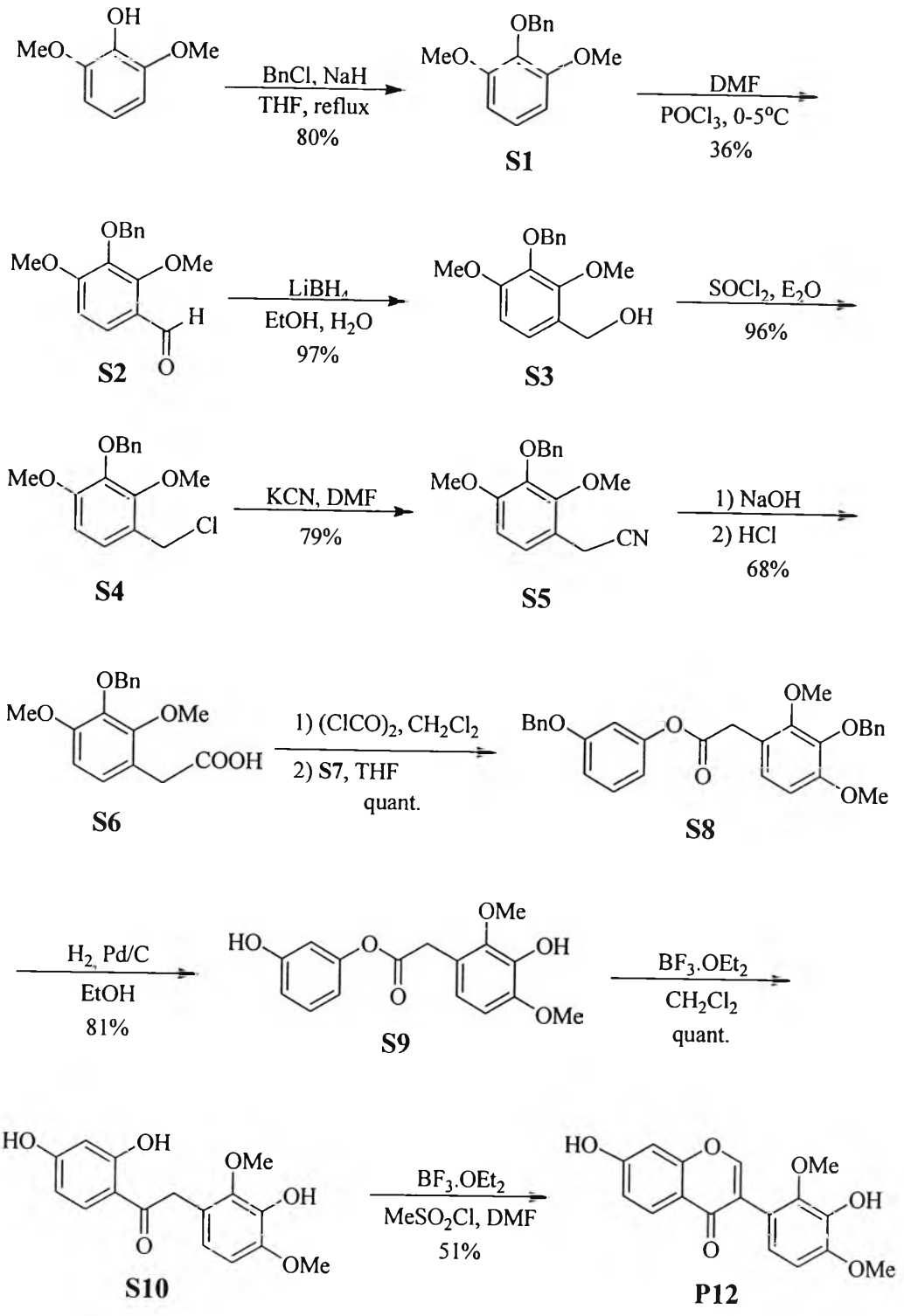
In addition, 3',7-dihydroxy-2',4'-dimethoxyisoflavone (**P12**) was also prepared using the addition of a one carbon unit to a deoxybenzoin (*via* deoxybenzoin). Retrosynthesis of **P12** is shown in Scheme 3.5.



Scheme 3.5 Retrosynthesis of **P12** *via* deoxybenzoin

According to the retrosynthesis approach in Scheme 3.5, the target isoflavone (**P12**) was planned to synthesize from deoxybenzoin (**S10**) *via* α-formylation followed by cyclization. Deoxybenzoin (**S10**) was manipulated using Fries rearrangement of ester (**S9**) derived from protected ester (**S8**). **S8** should be synthesized from the esterification of acid chloride derived from arylacetic acid (**S6**) and 3-benzyloxyphenol (**S7**). Arylacetic acid (**S6**) should be prepared from benzylchloride (**S4**) *via* nucleophilic substitution with cyanide and subsequently by hydroxylation and acidification of benzylcyanide (**S5**). **S4** was prepared *via* chlorination of benzyl alcohol (**S3**) derived from the reduction of benzaldehyde (**S2**). **S2** was gained from formylation of benzene (**S1**) which was obtained from the benzylation of 2,6-dimethoxyphenol.

The total synthesis of 3',7-dihydroxy-2',4'-dimethoxyisoflavanone (**P12**) *via* deoxybenzoin is shown Scheme 3.6.



Scheme 3.6 Total synthesis of 3',7-dihydroxy-2',4'-dimethoxyisoflavone *via* deoxybenzoin

According to total synthesis of 3',7-dihydroxy-2',4'-dimethoxyisoflavone (**P12**) in Scheme 3.6, the target molecule was prepared in 10 steps from 2,6-dimethoxyphenol. Firstly, the protection of hydroxyl group using benzylchloride and NaH in THF introduced benzyl ether (**S1**) in good yield (80%). The formylation to benzaldehyde (**S2**) was then carried out with $POCl_3$ in DMF in low yield (36%). Reduction of aldehyde to alcohol was achieved using $LiBH_4$ in EtOH giving benzyl alcohol (**S3**) in 97% yield. The chlorination of **S3** was subsequently carried out using $SOCl_2$ in Et_2O, yielding benzyl chloride (**S4**) in 96% yield. Cyanation with KCN in DMF was the next step performed to give benzylcyanide (**S5**) in 79% yield, followed by hydrolysis in basic condition and acidification to obtain aryl acetic acid (**S6**) in 68% yield. Ester **S8** was achieved in excellent yield after chlorination using oxalylchloride followed by condensation with 3-benzyloxyphenol (**S7**) in THF. Hydrogenation to remove the benzyl ether provided ester **S9** in 81% yield. Treatment of ester **S9** with $BF_3.OEt_2$ gave deoxybenzoin **S10** in quantitative yield implied that a Fries rearrangement had taken place. Finally, in the last step of the synthesis, this deoxybenzoin (**S10**) was converted to the ring closure isoflavone by condensation with DMF in the presence of methanesulfonylchloride and $BF_3.OEt_2$ yielding **P12** in 51% yield.

In this research, isoflavonoid compounds could be synthesized using arylation of α-phenylthiochroman-4-one with aryllead (IV) triacetate. Isoflavone could be synthesized by two routes. The first route was arylation of α-phenylthiochroman-4-one with lead (IV) tetraacetate; alternatively, the ring closure of deoxybenzoin.

The synthesis of isoflavonoid compounds using arylation of α-phenylthiochroman-4-one derivatives with aryllead (IV) triacetate allowed the selective synthesis of a wide variety of isoflavonoids bearing different types of substituents present in natural products. Whereas the synthesis of isoflavone using ring closure of deoxybenzoin could not be possible to synthesize those kinds of isoflavones. In addition, aryllead (IV) triacetates could be selectively prepared in high yield by tin-lead exchange between aryltrialkyltin and lead (IV) tetraacetate. As presented in this work, the synthesis of isoflavonoids using arylation of α-phenylthiochroman-4-one derivatives with aryllead (IV) triacetate was carried out in 8 steps, whereas using ring closure of deoxybenzoin was completed in 10 steps.

3.3.3 Cytotoxicity Test of Three Synthetic Compounds

Three synthetic compounds were further examined for cytotoxicity was carried out by follow the protocols described in Section 3.2.5. Three synthetic compounds were applied to determine drug concentration required to inhibit the growth of HBL100 cells by 50% after incubation in the culture medium for 72 h. The calculated IC_{50} values against the human epithelial mammary (HBL100) cells are presented in Table 3.1.

Table 3.1 Cytotoxicity test activity of synthetic compounds

Substance	HBL100 IC_{50} (μM)
P12	>50
P14	>50
P15	5.21

Among all synthetic compounds, **P15** showed high cytotoxicity against human epithelial mammary (HBL100) cells with IC_{50} value of 5.21 μM whereas the other substances were inactive (IC_{50} > 50 μM).

3.4 CONCLUSION

Total synthesis of 3',7-dihydroxy-2',4'-dimethoxy-isoflavanone and -isoflavan, biological active constituents from extract of *D. oliveri* heartwoods, was accomplished using arylation of α-phenylthiochroman-4-one with aryllead (IV) triacetate reagent as a key step. 3',7-Dihydroxy-2',4'-dimethoxyisoflavone, a representative of isoflavone, was also synthesized by 2 routes. The first route was similar to the synthesis of 3',7-dihydroxy-2',4'-dimethoxy-isoflavanone and -isoflavan. Alternatively, 3',7-dihydroxy-2',4'-dimethoxyisoflavone could be synthesized by using ring closure of the corresponding deoxybenzoin.

Concerning with arylation of α-phenylthiochroman-4-one with aryllead (IV) triacetate, three target isoflavonoids were prepared in 8 steps from resorcinol by Friedel-Craft reaction to obtain ketone **P1**, followed by intramolecular cyclization in basic condition to afford chroman-4-one **P2** in 52% yield for 3 steps. Protection of

hydroxyl group with benzyl group followed by bromination and nucleophilic substitution reaction with thiophenyl group acquired 7-benzyloxy-3-phenylthio-chraman-4-one (**P5**). Next step was arylation with 3-benzyloxy-2,4-dimethoxyphenyllead (IV) triacetate (**P9**) to achieve the corresponding α-aryl-α-phenylthiochroman-4-one **P10**. Reduction of **P10** with excess nickel boride yield the corresponding isoflavanone **P13** in 86% yield whereas oxidation of **P10** with *m*-CPBA gave the corresponding isoflavone **P11** in moderate yield. After deprotection of **P11** and **P13** under acidic condition, 3',7-dihydroxy-2',4'-dimethoxy-isoflavone (**P12**) and -isoflavanone (**P14**) were attained in excellent yield, respectively. Hydrogenation of either the corresponding isoflavone **P11** or isoflavanone **P13** yielded 3',7-dihydroxy-2',4'-dimethoxy-isoflavan (**P15**) in good to excellent yield. The total yield of 3',7-dihydroxy-2',4'-dimethoxy-isoflavone (**P12**), -isoflavanone (**P14**) and -isoflavan (**P15**) over 8 steps reaction was 9%, 13% and 8-13%, respectively based on the starting material.

The synthesis of 3',7-dihydroxy-2',4'-dimethoxyisoflavone (**P12**) *via* deoxybenzoin was accomplished in 10 steps from 2,6-dimethoxyphenol as starting material. Firstly, protection of a hydroxyl group with benzyl group followed by benzylation and then reduction aldehyde to alcohol to obtain benzyl alcohol **S3**. The next step was chlorination, cyanation and hydrolysis, respectively to give arylacetic acid **S6** which was converted to ester **S8** by chlorination and condensation with 4-benzyloxyphenol, respectively. After deprotection and Fries rearrangement, deoxybenzoin **S10** was obtained in quantitative yield. Finally, 3',7-dihydroxy-2',4'-dimethoxyisoflavone (**P12**) was obtained in moderate yield by condensation with DMF in the presence of methanesulfonylchloride and $BF_3.OEt_2$. The total yield of 3',7-dihydroxy-2',4'-dimethoxyisoflavone (**P12**) over 10 steps reaction was 6% based on 2,6-dimethoxyphenol as starting material.

The synthesis of isoflavonoids using arylation of chroman-4-one with aryllead (IV) triacetate is efficient for synthesis of a series of isoflavonoids with different substituents on ring-B. In addition, the synthesis of 3',7-dihydroxy-2',4'-dimethoxy-isoflavone, -isoflavanone and -isoflavan using arylation of chroman-4-one with aryllead (IV) triacetate was addressed for the first time.

The ring closure step for the synthesis of 3',7-dihydroxy-2',4'-dimethoxyisoflavone by oxidative rearrangement of chalcones with TTN [110] was reported. This method, however, required a hydroxyl protection except for that at

2'-position in order to avoid the formation of unwanted products. The synthesis of 3',7-dihydroxy-2',4'-dimethoxyisoflavone *via* deoxybenzoin according to the present work did not require hydroxyl protection for the ring closure step. Moreover, the oxidative rearrangement of chalcones with TTN proceeded in very poor yield with those chalcones possibly due to their highly insoluble in MeOH. The reported also suffered in requiring the use of stoichiometric quantities of toxic thallium salts.

Three synthetic compounds were further examined for cytotoxicity against human epithelial mammary (HBL100) cells. **P15** displayed high cytotoxicity against HBL100 cells with IC_{50} value of 5.21 μM whereas the other compounds were inactive (IC_{50} > 50 μM).