Progress Towards the Synthesis of Flavone Derivatives

by

David C. Carroll

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

BIOCHEMISTRY AND MOLECULAR BIOLOGY

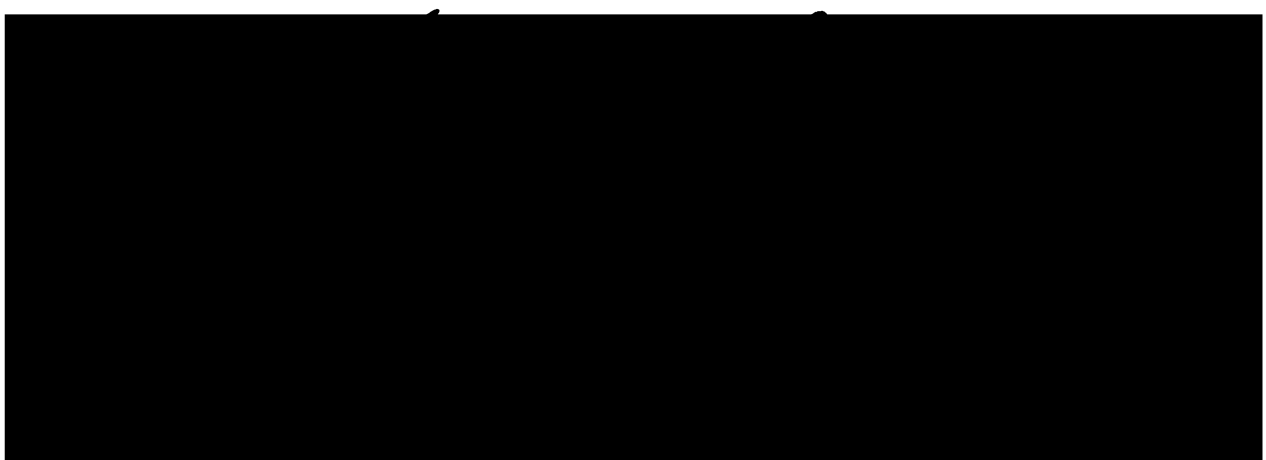
in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco



Date University Librarian

Table of Contents page

List of Figures and Schemes page

Figures

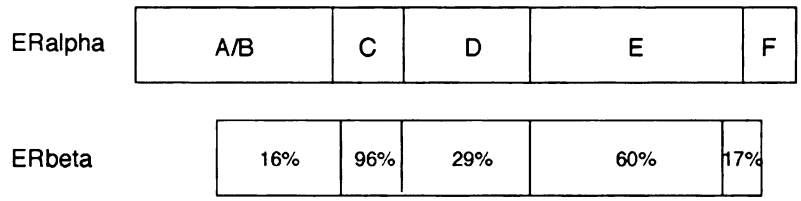
Schemes

Progress Towards the Synthesis of Flavone Derivatives

Chapter 1. Introduction

The estrogen receptors (ER-α and ER-β) are ligand inducible transcription factors which play a pivotal role in many developmental and reproductive processes.(1-5) Like other nuclear receptors, the two ERs have a modular structure consisting of a N-terminal, DNA-binding (DBD), and ligand-binding (LBD) domain (**figure 1**). Both ER subtypes share considerable homology in the DBD and LBD (96% and 60% respectively), but vary considerably in the C-terminal and N-terminal regions.(6-8) The ligand bound ER activates target genes by binding to estrogen response elements (EREs) either directly or through protein-protein interactions and for full activation requires activation function-1 (AF-1) in the A/B domain and activation function-2 (AF-2) in the LBD which recruits a p160/p300 coactivator protein complex to the promoter.(9, 10) The coactivator complex helps mediate strong transcriptional activation through chromatin modification and interactions with the basal transcription machinery.(11, 12) The roles each ER subtype have in normal and pathological processes (such as breast cancer and osteoporosis) are presently unclear. ER-β and ER-α knockout mice suggest that both subtypes have different physiological functions.(1, 3-5, 13-17)

Figure 1: Structural comparison of rat ER-α and ER-β.

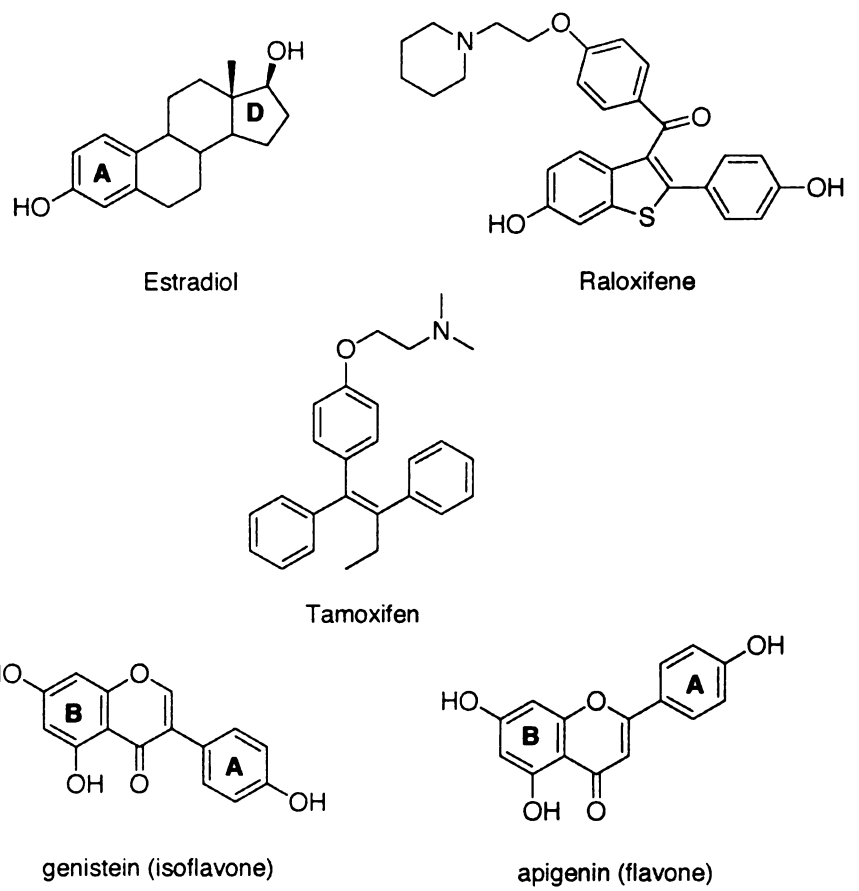


In addition to the endogenous ligand estradiol, several non-steroidal ligands such as tamoxifen and raloxifene have been shown to bind the ER and mediate transcription of ER responsive genes (**figure 2**). However, unlike the pure ER activating effects of estradiol, these compounds can positively and negatively regulate the ER in a tissue specific manner and are referred to as selective estrogen receptor modulators (SERM's).(18) The molecular basis of SERM tissue-specific ER mediated activity is currently unclear but is thought to involve several factors including differences in ER subtype activity and cell type distribution, target gene promoter context, and coactivator availability.

In addition to these synthetically derived SERM's, many naturally occurring compounds also exhibit interesting estrogenic activity. The flavonoids are a group of structurally related compounds many of which possess estrogenic activity. Isoflavones and flavones are two important members of the flavonoid family of phytoestrogens and are found in large quantities in soy beans and derived products (**figure 2**).(19) Epidemiological studies show a strong correlation between the prevention of many ER linked diseases and the

estrogenic effects of isoflavones and flavones obtained through the consumption of soy products.(20)

Figure 2: Structures of selected ER ligands.



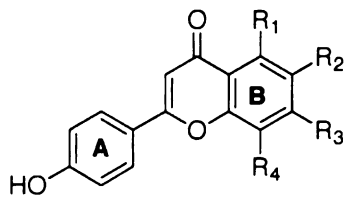
Identification of compounds that have ER subtype-selective activity will be useful tools for evaluating the distinct roles that ER-α and ER-β play in the diverse target tissues in which estrogens act. However, to date no high affinity ER-β selective ligands have been reported. One goal of my project was to synthesize ligands selective for ER-β. Good candidate structures for this endeavor were discovered in evaluation of the flavonoids.

A great deal of research in the ER field has been conducted on the isoflavone genistein. This natural compound has been shown to have a 20 – 30 fold binding preference for ER-β.(21) (22) In contrast, little is known about the binding and ER activity of flavones. Apigenin has been the most studied member of the flavones, and like genistein, has been shown to have a preference for binding ER-β.(21) But a comprehensive investigation of the binding preferences of a variety of hydroxysubstituted flavones is lacking. In order to study the interaction of flavones with the ER, it was necessary to synthesize a variety of flavones. The remainder of this thesis describes efforts to synthesize a number of polyhydroxylated flavones and an approach to using the flavone structure as a core with which to create derivatives.

Chapter 2. Synthetic Plan for Flavones

2.1 Choice of Synthetic Approach. The various polyhydroxylated flavones chosen for synthesis are described in **figure 3**. The flavone derivatives chosen for synthesis would enable us to examine the affect that the number and position of hydroxyl groups in the B-ring have on ER binding.

Figure 3: Polyhydroxylated flavone target compounds.

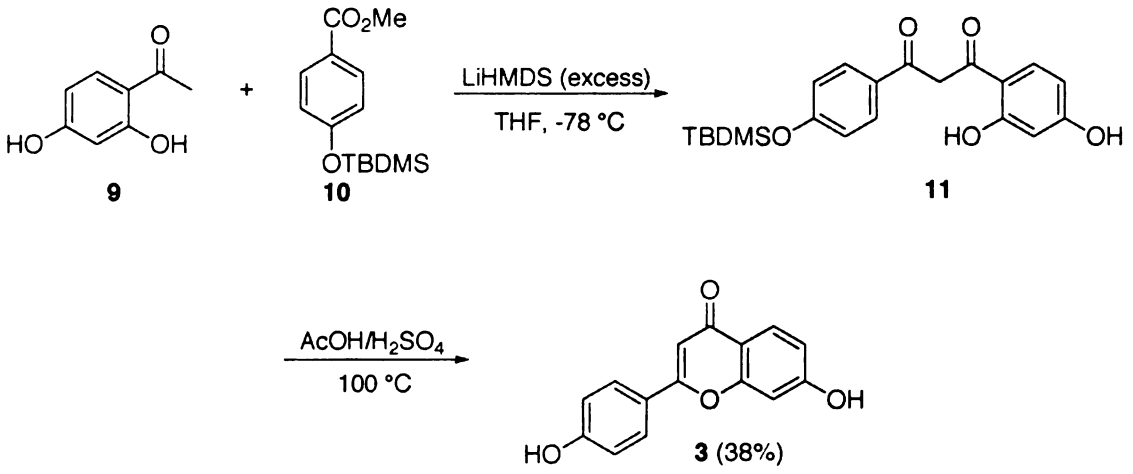


Compound	R_1	R_2	R_3	R_4
1	OH	H	H	H
2	H	OH	H	H
3	H	H	OH	H
4	H	H	H	OH
5	OH	H	OH	OH
6	H	OH	OH	H
7	H	H	OH	OH
8	H	OH	H	OH

A number of synthetic approaches to flavones have been described in the literature.(23-28) A suitable synthetic approach to this class of compounds must be expeditious and allow the use of diverse and easily accessible starting materials such that a number of different flavones can be created from a common route. A first synthetic attempt to flavones involved a two-step procedure as outlined in **scheme 1** for the synthesis of 4',7-dihydroxyflavone (**3**).(29) This process required the deprotonation of 2',4'-dihydroxyacetophenone (**9**) with an excess of lithium bis(trimethylsilyl)amide (LiHMDS) and subsequent

addition of the enolate to methyl 4-(t-butyldimethylsilyloxy)benzoate (**10**) to provide dione **11**. The crude dione was then subjected to a mixture of glacial acetic acid (AcOH) and concentrated H_2SO_4 to give the desired dihydroxyflavone **3**.

Scheme 1: Two-step synthesis of flavones.



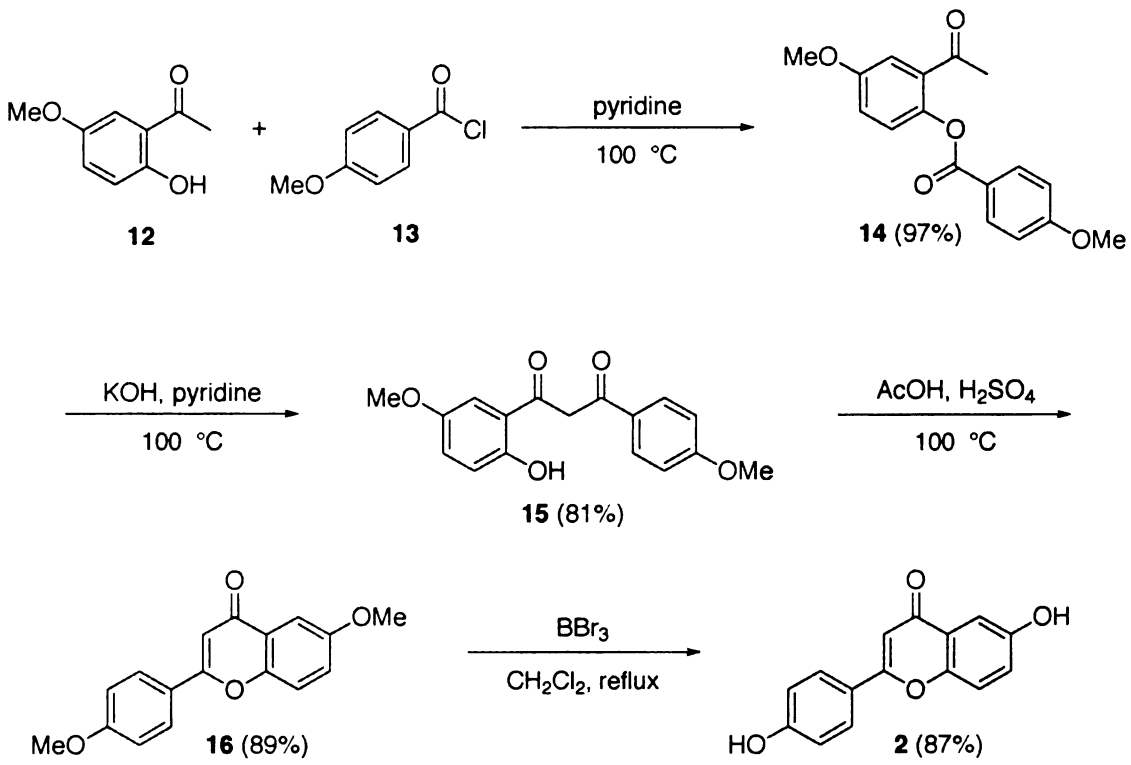
In theory this is a very rapid and simple approach to a variety of flavones, but in practice it proved to be unreliable and low yielding. One difficulty encountered was the production of a number of unwanted products. This made the isolation and purification of the desired flavone very challenging. Analysis of the reaction mixture by thin layer chromatography (TLC) showed that the first step in the reaction was the source of the side products. Therefore, attempts were made to purify the crude dione prior to the acid induced cyclization step. Unfortunately the dione was not able to be isolated with ample purity. Varying factors such as rate and order of addition of LiHMDS, temperature, and reaction

times as a means of optimizing the first step of the reaction were unsuccessful. Therefore another route to flavones was pursued.

A search of the literature provided a more reliable though longer method for the production of flavones involving the Baker-Venkataraman rearrangement as a key step.(30-31) This approach to flavones is illustrated in **scheme 2** for the synthesis of 4',6-dihydroxyflavone (**2**). Coupling of 2'-hydroxy-5'-methoxyacetophenone (**12**) and p-anisoylchloride (**13**) in pyridine gave 5-methoxy-2-(4'-methoxybenzoyloxy)acetophenone (**14**). In the presence of pyridine and KOH, **14** underwent the Baker-Venkataraman rearrangement to give dione **15**. Subjecting **15** to a mixture of AcOH and H_2SO_4 resulted in a cyclization/dehydration reaction to form 4',6-dimethoxyflavone (**16**). The desired hydroxyflavone **2** was obtained by removal of the methyl protecting groups using BBr_3.

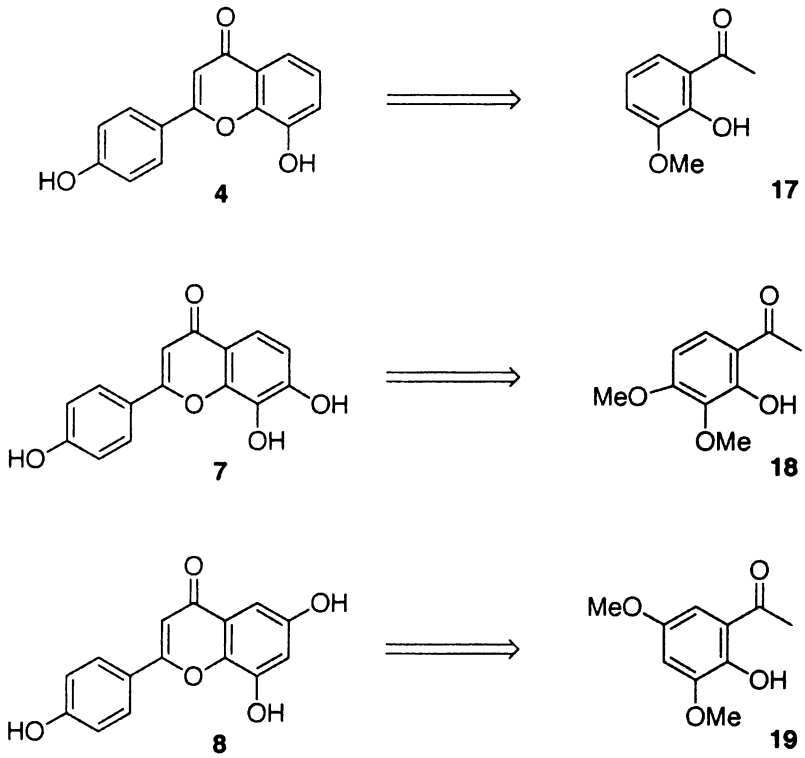
This method for flavone synthesis though requiring more steps proved to be more reliable and higher yielding than the two-step procedure illustrated in **scheme 1**. In addition, the reactions were generally completed within 10 minutes, and the purification of the intermediate compounds was simple and rapid. All compounds could be precipitated out of the reaction mixture and collected by suction filtration. One draw back of this procedure is the requirement that all hydroxyl groups except the 2'-hydroxy group on the acetophenone starting material be protected.

Scheme 2: Second synthetic approach to flavones.



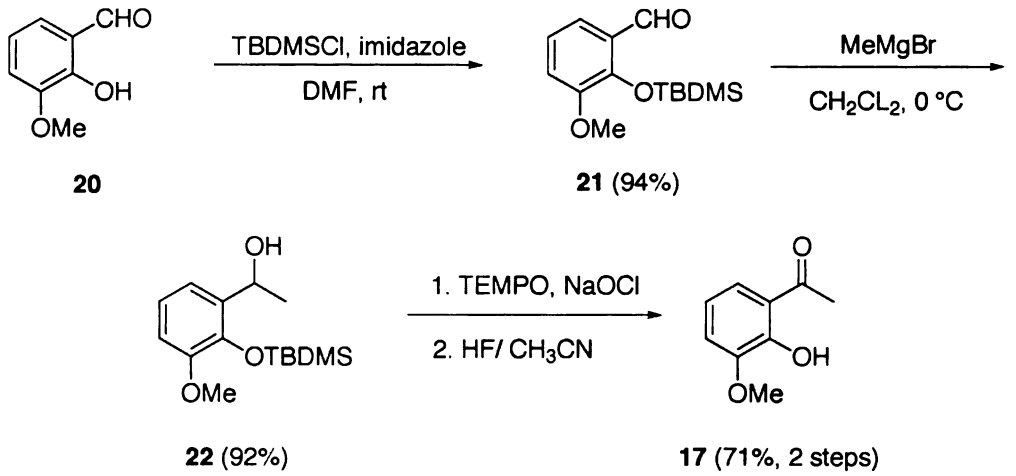
2.2 Synthesis of Acetophenone Derivatives. Unfortunately, not all methoxy substituted 2'-hydroxyacetophenone starting reagents necessary to synthesize the flavones illustrated in **figure 3** were commercially available. Therefore, synthesis of several acetophenone derivatives was required, and these are shown in **figure 4**.

Figure 4: Acetophenone derivatives requiring synthesis.



The synthetic route to acetophenone **17** is given in **scheme 3**. Protection of o-vanillin (**20**) with t-butyldimethylsilylchloride (TBDMSCl) gave benzaldehyde **21** in high yield. This benzaldehyde was then treated with methylmagnesium bromide to afford alcohol **22**. Oxidation of **22** with NaOCl and catalytic TEMPO followed by HF induced deprotection of the silyl protected alcohol gave 2'-hydroxy-3'-methoxyacetophone (**17**).(33)

Scheme 3: Synthesis of 2'-hydroxy-3'-methoxyacetophenone.



20

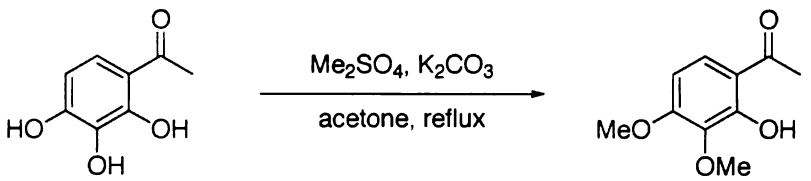
21 (94%)

22 (92%)

17 (71%, 2 steps)

The acetophone required for the synthesis of flavone **7** was made in one step from 2',3',4'-trihydroxyacetophenone (**23**) (**scheme 4**). Treatment of **23** with two equivalents of dimethyl sulfate gave a mixture of mono-, di-, and tri-methoxyacetophenones. The major product was 2'-hydroxy-3',4'-dimethoxyacetophenone (**18**) which was easily separated from the undesired products by flash chromatography.

Scheme 4: Synthesis of 2'-hydroxy-3',4'-dimethoxyacetophenone.

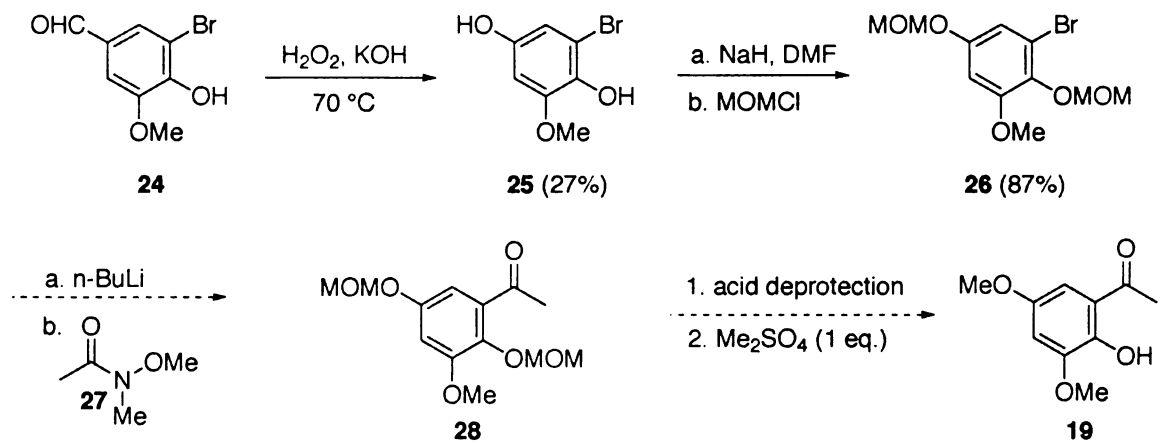


23

24 (64%)

Synthesis of acetophenone **19** is ongoing and has proven to be rather difficult. An outline for synthesis of **19** is shown in **scheme 5**. The main difficulty in the synthesis has been the Baeyer-Villiger oxidation of 4-bromovanillin (**24**) to hydroquinone **25** using a basic solution of H_2O_2. Yields of **25** have consistently been very low despite published reports that this exact transformation under the same conditions provides **25** in yields greater than 90%.(34) (35) Attempts to improve yields of **25** by varying reaction conditions (temp., time, equivalents of reagents, etc.) were unsuccessful. The difficulty experienced in forming **25** is in agreement with a report that m-hydroxysalicylaldehyde does not undergo Baeyer-Villiger oxidation under these conditions.(36) Compound **24** was also resistant to Baeyer-Villiger oxidation under acidic conditions using perbenzoic acids.(37)

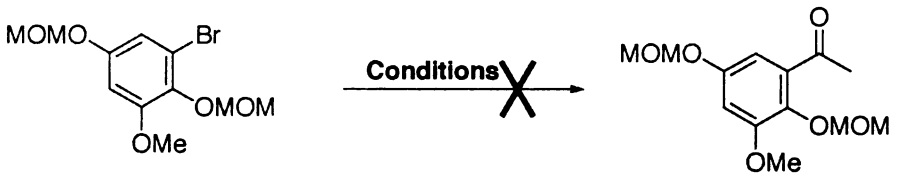
Scheme 5: Synthetic route to 2'-hydroxy-3',5'-dimethoxyacetophenone.



The small amounts of hydroquinone **25** obtained were carried forward in the synthesis by protection of the alcohols as methoxymethyl ethers (MOM). The next step (**scheme 5**) involves a metal-halogen exchange and addition of the resulting organometallic reagent onto a suitable electrophile such as Weinreb amide **27**.(38) (39)

Despite several attempts, this transformation has not been achieved (**scheme 6**). The lack of reaction is attributed to the low efficiency of the metal-halogen exchange since the majority of the starting material is recovered and only minor amounts of compound **31** are present even after quenching the reaction with water. The ideal conditions for this exchange to occur in high yield are still under investigation. Though some phenyl anion was formed, it did not react with amide **27**. This lack of reaction was attributed to the decreased electrophilicity of amides compared to other carbonyl electrophiles. However, substituting more reactive electrophiles such as ethyl acetate (EtOAc), acetyl chloride (AcCl), and acetic anhydride (Ac_2O) in place of **27** did not result in a reaction. Despite the use of anhydrous solvents, dried glassware, and dried reagents, moisture is likely to be the source of the difficulties. Clearly, more work needs to be conducted to optimize the efficiency of the metal-halogen exchange and exclude moisture.

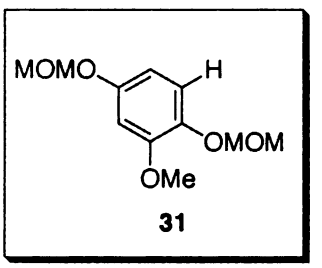
Scheme 6: Attempts at lithium-halogen exchange.



29 **30**

Conditions

Metal Source/Temperature	Electrophile
1. n -BuLi (1 or 2 eq.), -78 °C	**27**, EtOAc, AcCl, or Ac_2O
2. n-BuLi (1 or 2 eq.), 0 °C	"
3. t-BuLi (1 or 2 eq.), -78 °C	"
4. t-BuLi (1 or 2 eq.), 0 °C	"
5. Mg^0, rt	"



31

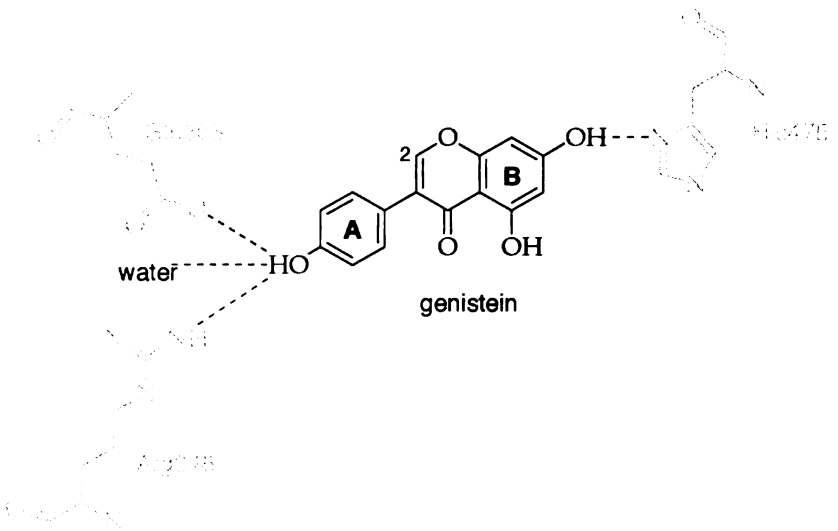
Chapter 3. Derivatization of Flavones

Estrogen receptor ligands which possess ER subtype selectivity and/or tissue context specific activity are important tools to aid in understanding the diverse roles the ER's play in normal and pathological processes. We decided to investigate using the flavone core structure as a scaffold to create derivatives which may have novel and interesting biological activity.

3.1 Choosing a position to derivatize. The interesting biological characteristics of SERM's such as raloxifene and tamoxifen are attributed to extensions which are attached to a stilbene-like core. Crystal structures of these compounds bound to the LBD show that these extensions poke out of the ligand binding pocket between helices 3 and 11 to disrupt the position of helix 12, a key component of AF-2.(40-42) A logical plan for derivatization of flavones would be to choose a position for extensions off the flavone scaffold which would mirror the positioning of the AF-2 disrupting extensions branching off the stilbene-like cores of known SERM's.

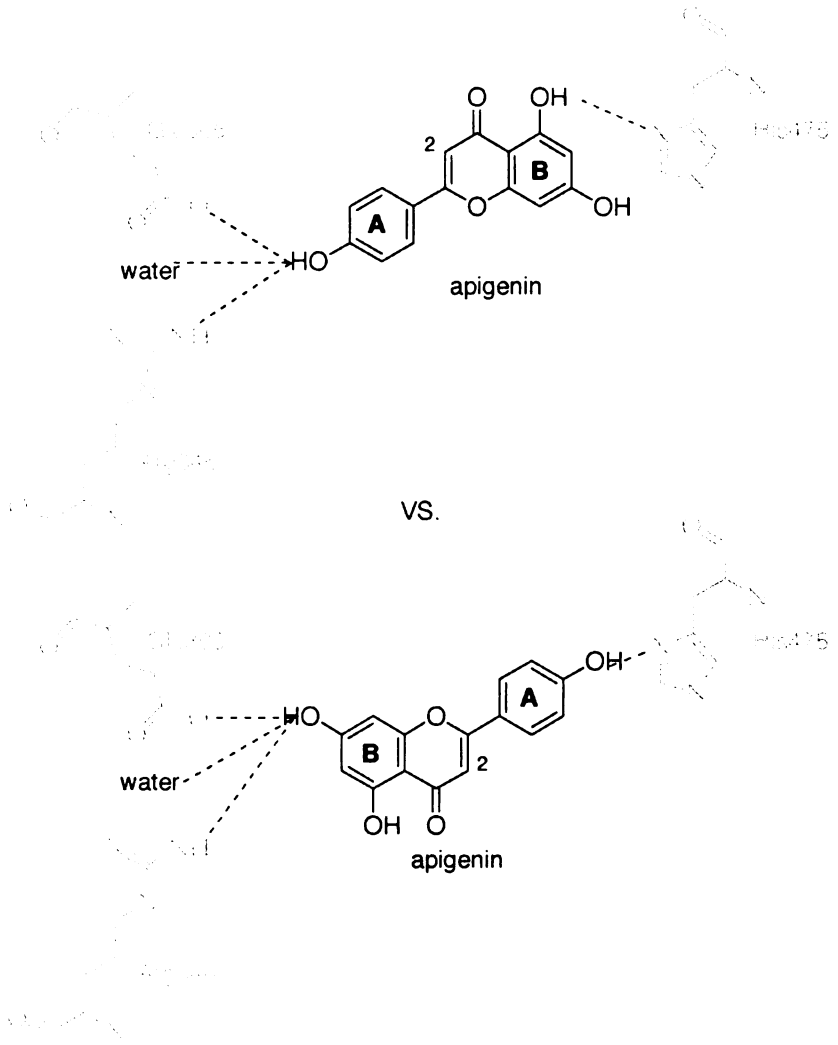
The crystal structure of the isoflavone genistein bound to the LBD of ER-β has been solved, and a simplified illustration of the key hydrogen bonding interactions of genistein with residues lining the ligand binding pocket of ER-β is shown in **figure 5**.

Figure 5: Key interactions of genistein with residues lining the ligand binding pocket (LBP) of ER-β.



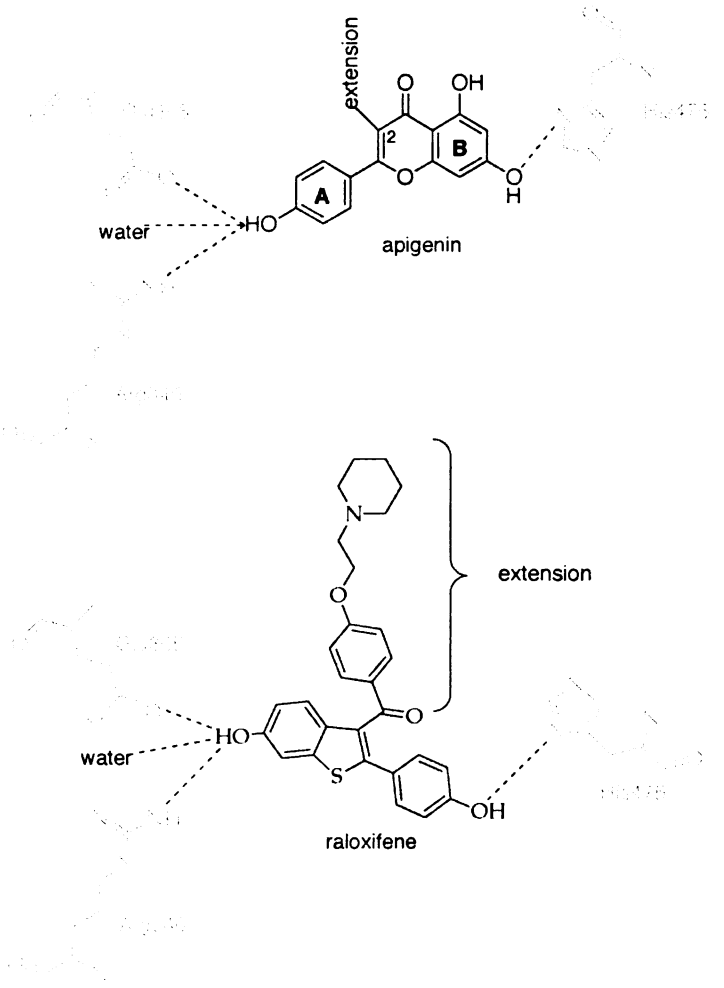
Though a crystal structure detailing the binding mode of flavones to the ER's does not exist, it is reasonable to assume that flavones such as apigenin bind to the ER in a manner similar to genistein. Two hypothetical ER binding orientations of apigenin are shown in **figure 6**. The first orientation resembles the binding mode of genistein with the A-ring hydroxyl making contacts with key residues (Glu305 and Arg346) in the ligand binding pocket. The second hypothetical binding mode of apigenin shows participation of B-ring hydroxyl groups in the same hydrogen bonding interactions. The latter orientation is unlikely since it's been shown that polyhydroxylation of the portion of ER ligands which interact with Glu353 and Arg394 diminishes binding. For example, an additional hydroxyl group in the A-ring of estrogen decreases binding to less than 19% .(43)

Figure 6: Two hypothetical binding orientations of apigenin in LBD of ER-β.



A comparison of the hypothetical binding of apigenin with the published binding mode of raloxifene to ER-β provides insight on what position of flavones to derivatize. Placing substituents off C-2 of the flavone core should roughly mimic the piperidine containing extension of raloxifene (**figure 7**). Therefore efforts to derivatize this portion of the flavone core were pursued.

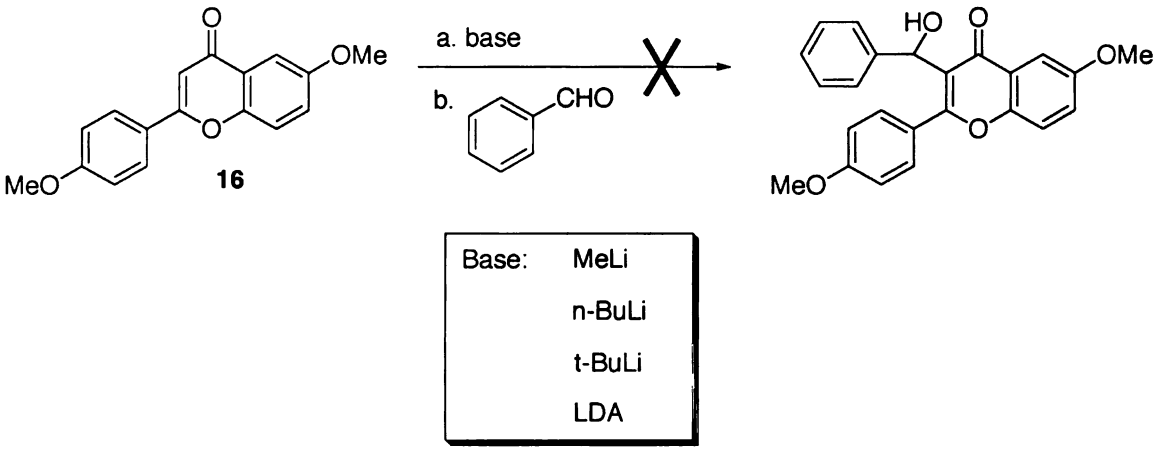
Figure 7: Comparison of the binding mode of Raloxifene with hypothetical binding mode of apigenin in LBD of ER-β.



3.2 Derivatization of C-2 of the Flavone Scaffold. Substitution of the C-2 hydrogen atom with other atoms has been reported in the literature.(44-47) One

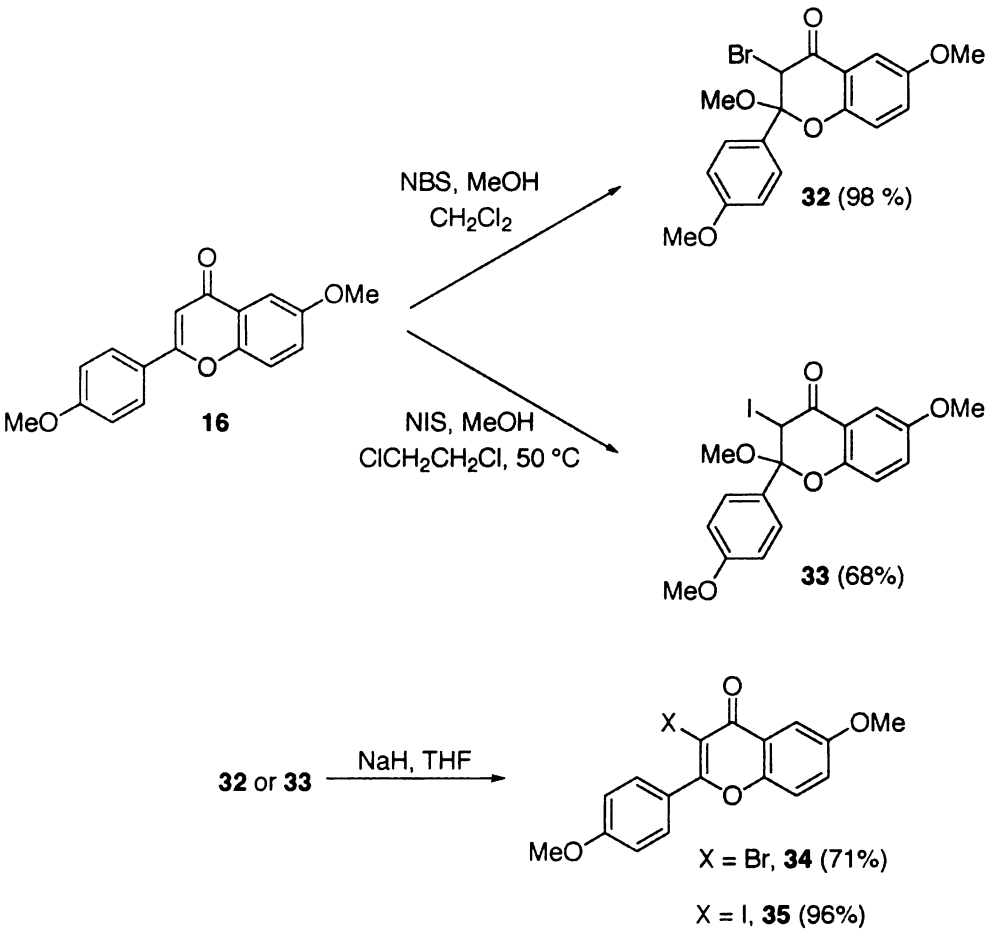
method consists of deprotonating the flavone at C-2 through the use of a strong base. Attempts to deprotonate C-2 with a number of bases trap the resulting anion with benzaldhyde were not successful (**scheme 7**).

Scheme 7: Attempts to deprotonate C-2 of 4',6-dimethoxyflavone.



Another method consisted of replacing the C-2 hydrogen with a halogen atom. Subjecting flavone **16** to N-halosuccinimide in methanol gave 2-halo-1,4',6-trimethoxyflavanones **32** and **33** (**scheme 8**).(47,48) In the presence of a non-nucleophilic base such as sodium hydride, elimination of methoxide from **32** and **33** took place to give the C-2 halogen substituted flavones **34** and **35**.

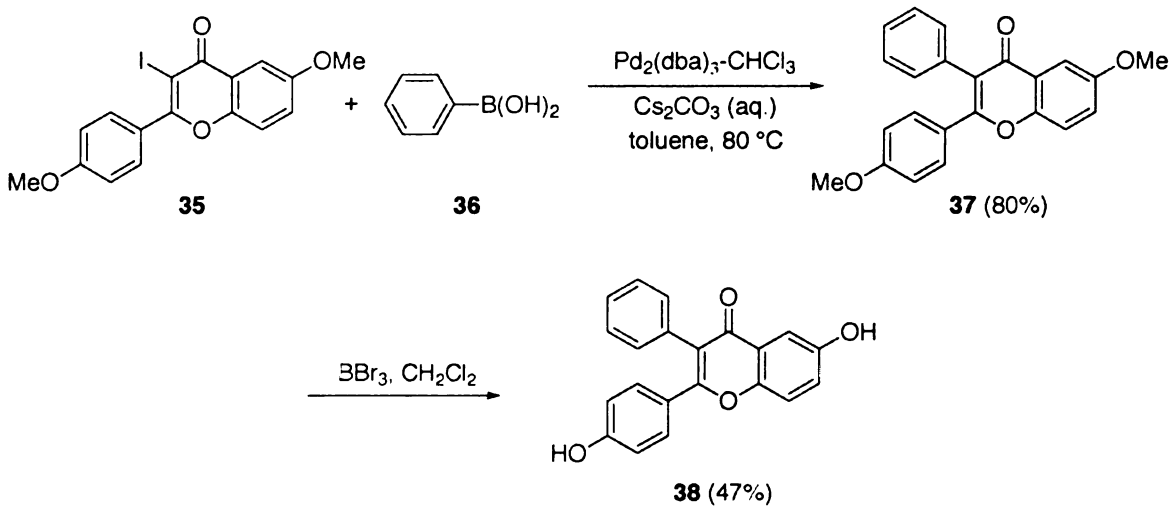
Scheme 8: Replacement of C-2 hydrogen with a halogen atom.



With **34** and **35** in hand, a couple of options existed for further elaboration of the flavone core. Attempts to form a C-2 anion via lithium halogen exchange with subsequent addition of the anion to an electrophile were not successful. Though this procedure has been reported to work, this method of flavone elaboration was not explored beyond initial investigations.(46) Instead, a more versatile and promising method of derivatizing 2-halogenated flavones using Pd-mediated cross coupling reactions was pursued.(49)

Investigations for utilizing Pd-mediated cross-coupling reactions such as the Suzuki coupling with compounds **34** and **35** are still in the early stages. Though not exhaustively explored, the coupling of phenylboronic acid (**36**) with bromoflavone **34** was not successful. This coupling with **36** was accomplished with the more reactive iodoflavone **35** (**scheme 9**). Deprotection of the ring hydroxyl groups with BBr_3 afforded 4',6-dihydroxy-2-phenylflavone (**38**).

Scheme 9: Pd-mediated cross coupling-reaction.



35 **36** **37** (80%)

38 (47%)

Chapter 4. Future Directions.

4.1 Chemistry. The syntheses of all target compounds listed in **figure 3** have not been completed. In order to complete flavone **8**, more work needs to be done to synthesize the appropriate starting material, acetophenone **19**. In addition, hydroxyflavones **1**, **4**, **5**, and **7** are one step away from completion; they are all protected as methyl ethers. Subjecting the methyl ethers of these compounds to BBr_3 will provide the desired hydroxy flavones.

The Pd-mediated cross-coupling reaction appears to be a good way to easily access a number of C-2 substituted flavones. More derivatives need to be synthesized using this approach.

4.2 Biology. The binding properties of target compounds (**figure 3**) to both ER subtypes need evaluation. Competitive binding to the ER between target compounds and radiolabeled estradiol can be used to determine binding constants.

Chapter 5. Experimental Section

5.1 General information.

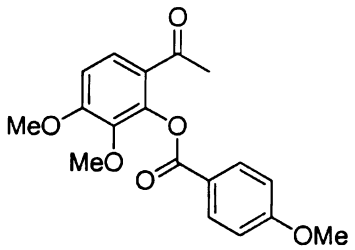
All anhydrous solvents were purchased in Sure/Seal™ bottles from Aldrich®. Starting materials were purchased from commercial sources and were used without further purification unless otherwise noted. Unless noted differently, all reactions were carried out under an atmosphere of Argon and stirred with a magnetic stirring bar. The argon was passed through a column of NaOH and Drierite® (anhydrous $CaSO_4$) prior to use. Inorganic salts used as washes or to quench reaction mixtures are saturated aqueous solutions unless indicated otherwise. Reactions were performed at room temperature unless noted otherwise. Reaction flasks were either dried in a 120 °C oven for 12 h, or they were flame dried just prior to use. All syringes were dried in a 120 °C oven for at least 12 h and cooled in a desiccator containing Drierite® and anhydrous P_2O_5 before use.

All reactions were monitored by thin-layer chromatography (TLC) on Alugram® Sil G/UV_{254} precoated aluminum-backed plates. Flash chromatography was performed using 200 – 400 mesh, 60Å silica gel purchased from Aldrich®.

^1H NMR and ^{13}C NMR spectra were recorded with a Varian-INOVA 400 MHz spectrometer, and chemical shifts are reported in parts per million (ppm) and are referenced to $CHCl_3$ present in $CDCl_3$ (7.26 ppm) or tetramethylsilane (0.00 ppm) unless otherwise noted. Coupling constants are expressed in Hertz.

5.2 Experimentals.

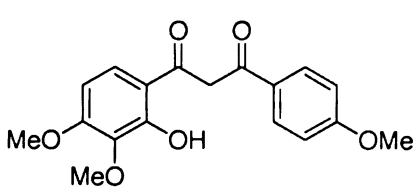
General procedure used to synthesize methoxy-2-(4'-methoxybenzoyloxy) acetophenone derivatives.



A solution of p-anisoyl chloride (0.670 g, 3.93 mmol), 2'-hydroxy-3',4'-dimethoxy acetophenone (0.700 g, 3.57 mmol), and anhydrous pyridine (1.5 mL) was heated at 100 °C for 10 min. The reaction mixture was cooled slightly and a solution of 1:1 methanol/water (v/v, 3 mL) was added. Pale white crystals formed upon further cooling to 0 °C which were collected on a Büchner funnel and rinsed with a cold (0 °C) solution of 1:1 methanol/water (v/v). The solid was was dried by heating under reduced pressure to provide 3,4-dimethoxy-2-(4'-methoxybenzoyloxy) acetophenone which was used without further purification (1.16 g, 97%). ^{1}H NMR: δ 8.20 (d, 2, J = 8.8), 7.68 (d, 1, J = 8.8), 7.01 (d, 2, J = 8.8), 6.89 (d, 1, J = 8.8), 3.95 (s, 3), 3.90 (s, 3), 2.49 (s, 3). ^{13}C NMR: δ 195.9, 164.3, 164.1, 157.2, 144.6, 141.5, 132.5, 125.8, 125.0, 121.4, 114.0, 109.1, 60.9, 56.1, 55.5, 29.9.

Spectra for other methoxy-2-(4'-methoxybenzoyloxy)acetophenone derivatives are located at the end of the Experimental Section.

General procedure used to synthesize 1-(4'-methoxyphenyl)-3-(2''-hydroxy-methoxyphenyl)-1,3-propanediones.

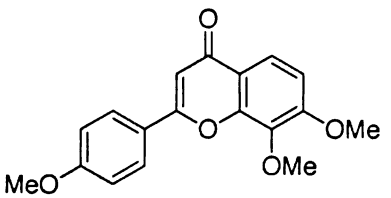


Powdered KOH (0.380 g, 6.77 mmol) was added to a 100 °C solution of 3,4-dimethoxy-2-(4'-methoxybenzoyloxy)acetophenone (1.10 g, 3.33 mmol) and

anhydrous pyridine (5.5 mL). During 10 minutes of heating, a bright yellow precipitate formed. After removal from the oil bath, glacial acetic acid (1.8 mL), absolute ethanol (6.0 mL), and water (3.6 mL) were added to the reaction mixture causing the solids to dissolve. Cooling to 0 °C gave bright yellow needle-like crystals which were collected on a Büchner funnel, washed with cold (0 °C) 1:1 ethanol/water (v/v), and dried by heating under reduced pressure. This provided the desired product, 1-(4'-methoxyphenyl)-3-(2''-hydroxy-3'',4''-dimethoxy)-1,3-propanedione, which was used without further purification (0.867 g, 81%). NMR analysis of the product shows the dione is in equilibrium with enol tautomers. ^{1}H NMR: δ 12.40 (s), 12.21 (s), 8.00 (d, J = 8.8), 7.88 (d, J = 8.8), 7.59 (d, J = 9.2), 7.52 (d, J = 8.8), 6.94 – 6.97 (m), 6.65 (s), 6.50 (d, J = 8.8), 4.50 (s), 3.93 (s), 3.92 (s), 3.91 (s), 3.87 (s). ^{13}C NMR: δ 198.7, 194.0, 191.8, 176.6, 164.1, 163.0, 158.9, 157.9, 157.3, 156.9, 136.8, 131.3, 129.1, 128.6, 127.7, 125.9, 124.5, 115.1, 114.2, 114.0, 113.9, 103.3, 103.0, 90.8, 60.6, 56.1, 56.0, 55.5, 55.4, 50.1.

Spectra for other 1-(4'-methoxyphenyl)-3-(2''-hydroxy-methoxyphenyl)-1,3-propanedione derivatives are located at the end of the Experimental Section.

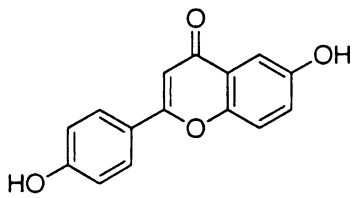
General procedure used to synthesize methoxy substituted flavones.



A suspension of glacial acetic acid (AcOH) (3.4 mL) and , 1-(4'-methoxyphenyl)-3-(2''-hydroxy-3'',4''-dimethoxy)-1,3-propanedione (0.300 g, 0.954 mmol) was heated at 100 °C while 20% H_2SO_4/AcOH (v/v, 0.67 mL) was added dropwise. A thick yellow precipitate formed within 2 minutes. After 10 minutes the reaction mixture was poured into water (20 mL) and a floculant white solid precipitated out of solution. The solid was collected on a Büchner funnel and washed with water. The white solid was dissolved in CH_2Cl_2 (100 mL), and the organic layer was washed with water, $NaHCO_3$, and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product, 4',7,8-trimethoxyflavone, was obtained as a white solid which was used without further purification (0.263 g, 89%). ^{1}H NMR: δ 7.95 (d, 1, J = 8.8), 7.91 (d, 2, J = 8.8), 7.04 (d, 1, J = 8.8), 7.03 (d, 2, J = 8.8), 6.68 (s, 1), 4.04 (s, 3), 4.00 (s, 3), 3.88 (s, 3). ^{13}C NMR: δ 177.9, 162.9, 162.3, 156.5, 150.4, 136.8, 127.8, 124.1, 120.9, 118.6, 114.4, 109.7, 105.4, 61.5, 56.4, 55.4.

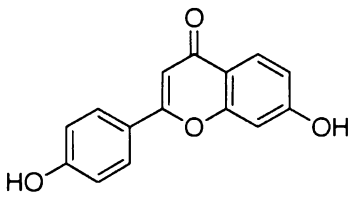
Spectra for other methoxy substituted flavones are located at the end of the Experimental Section.

General procedure used to synthesize hydroxy substituted flavones.



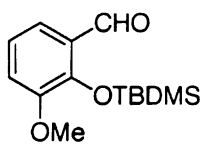
A solution of BBr_3 (1 M in CH_2Cl_2, 29 mL, 29 mmol) was added dropwise to a refluxing mixture of 6,4'-dimethoxyflavone (2.0 g, 7.1 mmol) and anhydrous 1,2-dichloroethane. The dark yellow reaction mixture was stirred at reflux overnight. The reaction mixture was cooled (0 °C) and slowly quenched with methanol. The product mixture was concentrated in vacuo with flash silica gel. The silica absorbed crude product was applied to the top of a column of silica gel. The product was eluted using 5% methanol/ CH_2Cl_2 to give 4',6-dihydroxyflavone as a pale yellow solid (1.6 g, 87%). ^1H NMR (d_6-DMSO): δ 7.93 (d, 2, J = 8.8), 7.61 (d, 1, J = 8.8), 7.31 (d, 1, J = 3.2), 7.23 (dd, 1, J = 9.2, 2.8), 6.93 (d, 2, J = 8.8), 6.78 (s, 1). ^{13}C NMR (d_6-DMSO): δ 176.8, 162.7, 160.7, 154.6, 149.2, 128.2, 124.2, 122.7, 121.8, 119.6, 115.9, 107.5, 103.9.

Spectra for other hydroxy substituted flavones are located at the end of the Experimental Section.

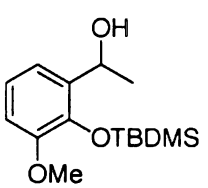


4',7-dihydroxyflavone. A solution of lithium bis(trimethylsilyl)amide (1 M solution in THF, 13.5 mL, 13.5 mmol) was added dropwise over 15 min to a well stirred cold (-78 °C) solution of 2',4'-dihydroxyacetophenone (0.50 g, 3.2 mmol) in anhydrous THF (16 mL). The reaction mixture was then warmed (-20 °C) and stirred for 2 h. After cooling again (-78 °C) a solution of methyl 4-(t-butyldimethylsilyloxy)benzoate (0.88 g, 3.3 mmol) in anhydrous THF (1.6 mL) was added. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched with HCl (0.6 M, 70 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was dissolved in glacial acetic acid (11.5 mL) and heated (100 °C) while 20% H_2SO_4/AcOH (v/v, 2.3 mL) was added dropwise. After 10 minutes the reaction mixture was poured into water and a brown precipitate formed which was collected on a Büchner funnel and rinsed with cold (0 °C) water. The crude product mixture was purified over flash silica gel (CH_2Cl_2 ramped to 5% methanol/CH_2Cl_2) to give the product as a pale yellow solid (0.324 g, 38%). ^1H NMR (d_6-DMSO): δ 7.91 (d, 2, J = 8.8), 7.86 (d, 1, J = 8.4), 6.89 – 6.97 (m, 4),

6.72 (s,1). ^{13}C NMR (d_6-DMSO): δ 176.2, 162.5, 162.4, 160.6, 157.3, 128.1, 126.4, 121.8, 116.1, 115.8, 114.7, 104.4, 102.4.

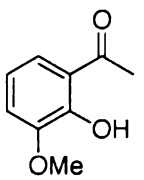


2-{(t-butyldimethylsilyl)oxy}-3-methoxybenzaldehyde. To a solution of o-vanillin (3.00 g, 19.7 mmol) in anhydrous DMF (10 mL) was added t-butyldimethylsilylchloride (4.14 g, 27.5 mmol) and imidazole (2.98 g, 43.7 mmol). The reaction mixture was stirred overnight and was then poured into a separatory funnel containing water (200 mL). The aqueous layer was extracted with ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to provide a colorless oil. The crude product mixture was purified over flash silica gel (hexanes ramped to 4% ethyl acetate/hexanes) to give a white solid (4.96 g, 94%). ^1H NMR: δ 10.52 (s, 1), 7.39 (d, 1, J = 8.0), 7.05 (d, 1, J = 8.0), 6.96 (t, 1, J = 8.4), 3.84 (s, 3), 1.01 (s, 9), 0.09 (s, 6). ^{13}C NMR: δ 190.3, 150.8, 149.2, 127.9, 121.21, 119.1, 116.9, 55.2, 25.9, 18.9, -4.2.



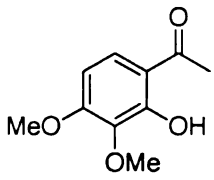
1-[2-{(t-butyldimethylsilyl)oxy}-3-methoxyphenyl]ethanol. To a cold (0 °C) solution of 2-{(t-butyldimethylsilyl)oxy}-3-methoxybenzaldehyde (2.15 g, 7.61

mmol) in anhydrous CH_2Cl_2 (35 mL) was added dropwise methyl magnesium bromide (1 M in butyl ether, 10.0 mL). After 1 hour the reaction mixure was quenched with water. The organic layer was saved and the aqueous layer made slightly acidic (pH = 5). The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. The crude product mixture was purified over flash silica gel (10% ramped to 25% ethyl acetate/hexanes) to give a white solid (1.97 g, 92%). ^1H NMR: δ 7.03 (d, 1, J = 8.0), 6.93 (t, 1, J = 8.0), 6.78 (d, 1, J = 8.0), 5.27 – 5.35 (m, 1), 3.79 (s, 3), 1.47 (d, 3, J = 6.4), 1.01 (s, 9), 0.21 (s, 3), 0.20 (s, 3). ^{13}C NMR: δ 149.5, 136.7, 121.2, 119.0, 117.4, 110.3, 64.7, 54.7, 26.1, 23.0, 18.9, -3.8.



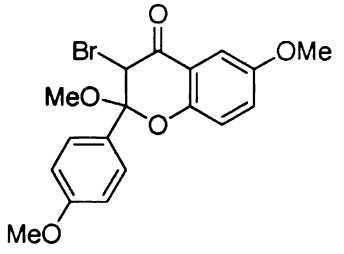
2'-hydroxy-3'-methoxyacetophenone. A solution of NaOCl (commercial bleach, ~0.7 M, 16.6 mL) and $NaHCO_3$ (0.84 g) was added dropwise to a vigorously stirred and cold (0 °C) mixture of 1-[2-{(t-butyldimethylsilyl)oxy}-3-methoxyphenyl]ethanol (1.51 g, 5.3 mmol), TEMPO (17.0 mg, 0.10 mmol), and KBr (1.08 g, 9.1 mmol) in CH_2Cl_2 (15 mL) so as to maintain the temperature below 10 °C. After completion of the addition, the reaction mixture was stirred for an additional 15 minutes and then poured into a separatory funnel. The reaction mixture was then washed with 10% HCl containing 125 mg KI/10mL (10 mL),

10% $Na_2S_2O_3$ (10 mL), and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil which was used without further purification (1.35 g). To the crude product mixture was added a 19:1 solution of acetonitrile/HF (48%) (v/v). The reaction mixture was stirred for 2 hours and then quenched with $NaHCO_3$ and diluted with ether. The aqueous layer was made slightly acidic (pH = 5) and further extracted with ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a pale yellow oil. Purification of the crude product mixture over flash silica gel (4% ethyl acetate/hexanes) provided the desired product as a white solid (0.631 g, 71% for two steps). ^1H NMR: δ 12.57 (s, 1), 7.35 (d,1, J = 8.4), 7.07 (d, 1, J = 8.4), 6.85 (t, 1, J = 8.0), 3.91 (s, 3), 2.64 (s, 3). ^{13}C NMR: δ 204.9, 152.8, 148.9, 121.8, 119.7, 118.2, 117.0, 56.2, 27.0.

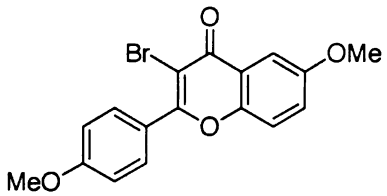


2'-hydroxy-3',4'-dimethoxyacetophenone. Dimethyl sulfate (1.20 mL, 12.6 mmol) was added dropwise over an hour to a mixture of 2',3',4'-trihydroxyacetophenone (1.00 g, 5.94 mmol) and anhydrous K_2CO_3 (1.60 g, 11.6 mmol) in acetone (dried over $MgSO_4$, 60 mL). Upon completion of the addition, the reaction mixture was heated at reflux overnight. The solvent was then removed in vacuo and the resulting tan solid was suspended in water and made slightly acidic (pH = 5). Extraction with ether followed by drying with Na_2SO_4 and

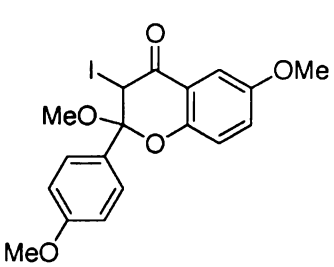
concentration in vacuo gave a tan solid which was purified by flash chromatography (5% ramped to 10% ethyl acetate/hexanes) (0.74 g, 64%). ^{1}H NMR: δ 12.56 (s, 1), 7.50 (d, 1, J = 9.2), 3.94 (s, 3), 3.89 (s, 3), 2.58 (s, 3). ^{13}C NMR: δ 203.2, 158.5, 157.1, 136.5, 127.0, 115.3, 102.9, 60.7, 56.1, 26.4.



2-bromo-1,4',6-trimethoxyflavanone. To a suspension of 4',6-dimethoxyflavone in anhydrous methanol (2.6 mL) and anhydrous CH_2Cl_2 (1.3 mL) was added N-bromosuccinimide (0.190 g, 1.07 mmol). The reaction mixture was stirred for 4 hours and then the solvent was removed in vacuo. The crude product was purified over flash silica gel to provide a tan oil (0.188 g, 98%). ^{1}H NMR: δ 7.58 (d, 2, J = 8.8), 7.43 (d, 1, J = 3.2), 7.21 (dd, 1, J = 8.8, 3.2), 7.12 (d, 1, J = 8.8), 7.00 (d, 2, J = 8.8), 4.38 (s, 1), 3.87 (s, 3), 3.85 (s, 3), 3.01 (s, 3). ^{13}C NMR: δ 186.6, 160.4, 154.9, 149.8, 128.3, 127.8, 125.2, 119.3, 118.6, 113.7, 108.5, 105.1, 55.8, 55.3, 51.8, 50.4.

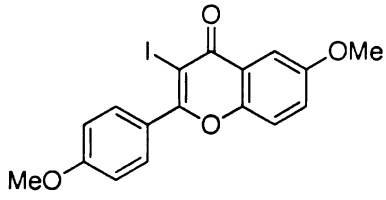


2-bromo-4',6-dimethoxyflavone. Sodium hydride (60% oil dispersion, 2.0 mg, 0.050 mmol) was added to a cold solution (0 °C) of 2-bromo-1,4',6-trimethoxyflavanone (17 mg, 0.043 mmol) in anhydrous THF (0.60 mL). The reaction mixture was stirred overnight and then quenched with water and diluted with ethyl acetate. The aqueous layer was further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a white solid. Purification over flash silica gel (5% ethyl acetate/hexanes) gave the product as a white powder (15 mg, 96%). ^1H NMR: δ 7.87 (d, 2, J = 8.8), 7.63 (d, 1, J = 3.2), 7.44 (d, 1, J = 8.8), 7.29 (dd, 1, J = 9.2, 3.2), 7.04 (d, 2, J =8.8), 3.93 (s, 3), 3.90 (s, 3). ^{13}C NMR: δ 173.1, 161.7, 161.5, 157.3, 150.5, 131.2, 125.1, 124.2, 122.4, 119.3, 113.7, 107.9, 105.4, 56.0, 55.5.



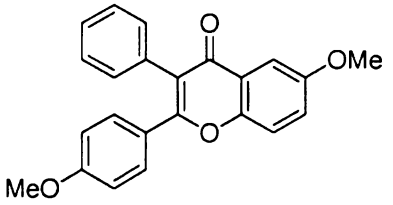
2-iodo-1,4',6-trimethoxyflavanone. To a heated (50 °C) solution of 4',6-dimethoxyflavone (82 mg, 0.29 mmol) in anhydrous 1,2-dichloroethane (1.0 mL)

was added N-iodosuccinimide (0.137 g, 0.609 mmol) followed by anhydrous methanol (1.0 mL). The dark red reaction mixture was stirred overnight and then diluted with CH_2Cl_2 and washed with 10% $Na_2S_2O_3$ and brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a yellow solid. Purification of the crude product mixture over flash silica gel provided the product as a white solid (89 mg, 68%, or 96% based on recovered starting material). ^1H NMR: δ 7.56 (d, 2, J = 8.8), 7.44 (d, 1, J = 3.2), 7.19 (dd, 1, J = 9.2, 3.2), 7.12 (d, 1, J = 9.2), 6.99 (d, 2, J = 8.8), 4.76 (s, 3), 3.86 (s, 3), 3.84 (s, 3), 2.99 (s, 3). ^{13}C NMR: δ 188.0, 160.3, 154.9, 149.4, 128.8, 128.2, 124.9, 119.2, 118.4, 113.6, 108.5, 105.6, 55.8, 55.2, 52.7, 32.6.

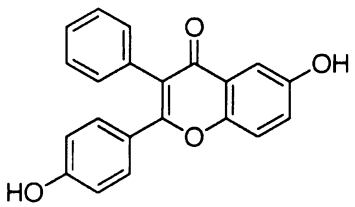


2-iodo-4',6-dimethoxyflavone. Sodium hydride (60% oil dispersion, 13 mg, 0.34 mmol) was added to a cold solution (0 °C) of 2-iodo-1,4',6-trimethoxyflavanone (85 mg, 0.193 mmol) in anhydrous THF (0.60 mL). The reaction mixture was stirred overnight and then quenched with water and diluted with CH_2Cl_2. The aqueous layer was made acidic and further extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a white solid. Purification over flash silica gel

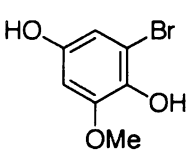
(5% ethyl acetate/hexanes) gave the product as a white powder (57 mg, 71%). ^{1}H NMR: δ 7.78 (d, 2, J = 8.8), 7.60 (d, 1, J = 2.8), 7.41 (d, 1, J = 8.8), 7.28 (dd, 1, J = 8.8, 2.8), 7.02 (d, 2, J = 8.8), 3.91 (s, 3), 3.90 (s, 3). ^{13}C NMR: δ 174.4, 170.0, 161.5, 157.2, 150.6, 131.3, 127.2, 124.1, 120.4, 119.0, 113.5, 105.6, 86.8, 55.9, 55.4.



4',6-dimethoxy-2-phenylflavone. To a solution of 2-iodo-4',6-dimethoxyflavone (30 mg, 0.074 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (1.0 mg) in anhydrous toluene (0.50 mL) was added concurrently a solution of phenylboronic acid (11 mg, 0.090 mmol) dissolved in ethanol (0.150 mL) and cesium carbonate (2 M aqueous solution, 0.083 mL). The reaction mixture was heated (80 °C) over night and then diluted with ethyl acetate. The organic layer was washed with NH_4Cl and the aqueous layer back extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a yellow solid which was purified over flash silica gel (10% ramped to 30% ethyl acetate/hexanes) (24 mg, 80%). ^{1}H NMR: δ 7.64 (d, 1, J = 3.2), 7.46 (d, 2, J = 8.8), 7.23 – 7.34 (m, 8), 6.77 (d, 2, J = 8.8), 3.91 (s, 3), 3.79 (s, 3). ^{13}C NMR: δ 177.1, 161.1, 160.8, 156.8, 150.8, 133.5, 131.2, 131.1, 128.3, 127.4, 125.5, 124.0, 123.5, 121.3, 119.3, 113.5, 105.4, 55.9, 55.3.

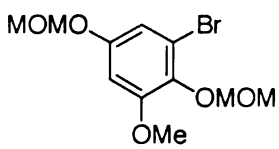


4',6-dihydroxy-2-phenylflavone. A solution of BBr_3 (1 M in CH_2Cl_2, 0.30 mL, 0.29 mmol) was added dropwise to a solution 4',6-dimethoxy-2-phenylflavone (24 mg, 0.067 mmol) and anhydrous CH_2Cl_2 (0.50 mL). The dark orange reaction mixture was stirred for 2 h. The reaction mixture was slowly quenched with methanol and concentrated in vacuo. The silica absorbed crude product was applied to the top of a column of silica gel. Purification of the crude product mixture over flash silica gel provided the product as a white powder (10 mg, 47%). ^{1}H NMR (d_6-DMSO): δ 7.58 (d, 2, J = 8.8), 7.15 – 7.38 (m, 8), 6.65 (d, 2, J = 8.8), 3.38 (br s, 2). ^{13}C NMR(d_6-DMSO): δ 175.8, 161.2, 159.0, 154.8, 149.1, 133.8, 131.2, 131.1, 127.9, 127.1, 123.5, 123.4, 123.0, 120.2, 119.6, 114.9, 107.8.



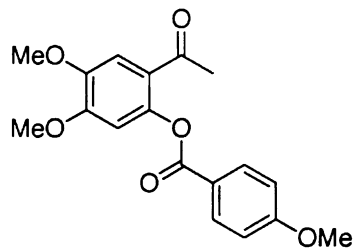
1-bromo-2,5-dihydroxy-3-methoxybenzene. 5-bromovanillin (2.06 g, 8.66 mmol) was treated with KOH (1 N, 9.13 mL) and H_2O_2 (3%, 20 mL) and the resulting dark purple reaction mixture was stirred for 20 h at 75 °C. The reaction

was made acidic by the addition of acetic acid and extracted with ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a brown oil. The residue was dissolved in hot water and cooled to rt. An amorphous brown solid formed and was collected by filtration (0.0508 g, 27%). ^1H NMR: δ 6.59 (s, 1), 6.42 (s,1), 5.48 (s, 1), 4.42 (s, 1), 3.88 (s, 3).

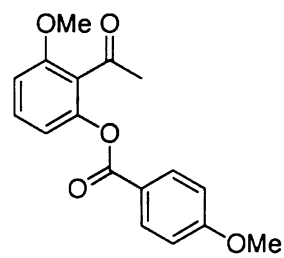


1-bromo-2,5-bis{(methoxymethy)oxy}-2-methoxybenzene. To hexanes washed NaH (60% oil dispersion, 40 mg prewash weight, 1.0 mmol) was added a cold (0 °C) solution of 1-bromo-2,5-dihydroxy-3-methoxybenzene (54 mg, 0.25 mmol) in anhydrous DMF (4.0 mL). After stirring for 5 min, chloromethylmethylether (tech. grade, 0.18 mL, 2.4 mmol) was added dropwise and the reaction mixture warmed to rt. The reaction mixture was quenched with methanol and water and then extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a yellow oil. Purification of the crude reaction mixture over flash silica gel gave the product as a colorless oil (67 mg, 87%). ^1H NMR: δ 6.86 (d, 1, J = 2.8), 6.57 (d, 1, J = 2.8), 5.11 (s, 2), 5.09 (s,2), 3.82 (s, 3), 3.65 (s, 3), 3.47 (s, 3). ^{13}C NMR: δ 154.2, 153.8, 138.3, 117.7, 111.6, 101.4, 98.7, 94.9, 57.9, 56.1, 56.0.

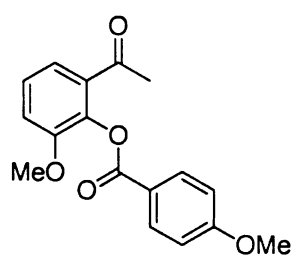
5.3 Additional Spectra Data.



4,5-dimethoxy-2-(4'-methoxybenzoyloxy)acetophenone. ^{1}H NMR: δ 7.86 (d, 2, J = 8.8), 7.57 (s,1), 7.02 (d, 2, J = 8.8), 6.98 (s,1), 6.70 (s, 1), 4.01 (s, 3), 3.99 (s, 3), 3.89 (s, 3). ^{13}C NMR: δ 177.6, 162.8, 162.2, 154.3, 152.2, 147.5, 127.7, 124.3, 117.3, 114.4, 105.8, 104.5, 99.7, 56.4, 56.2, 55.5.

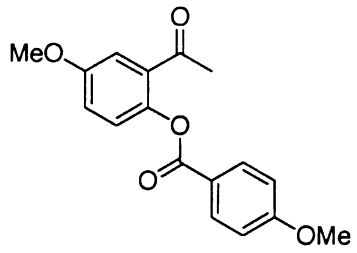


6-methoxy-2-(4'-methoxybenzoyloxy)acetophenone. ^{1}H NMR: δ 8.09 (d, 2, J = 8.8), 7.38 (t, 1, J = 8.8), 6.96 (d, 2, J= 8.8), 6.84 – 6.87 (m, 2), 3.98 (s, 3), 3.88 (s, 3), 2.49 (s, 3). ^{13}C NMR: δ 200.6, 164.5, 164.0, 157.3, 147.9, 132.8, 132.4, 130.8, 121.3, 115.3, 113.9, 108.5, 56.0, 55.5, 31.7.

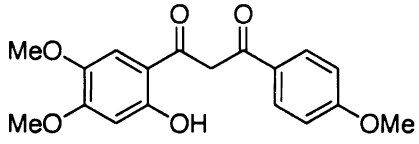


3-methoxy-2-(4'-methoxybenzoyloxy)acetophenone. ^{1}H NMR: δ 8.18 (d, 2, J = 8.8), 7.41 (d, 1, J = 8.0), 7.29 (t, 1, J = 8.0), 7.16 (d, 1, J = 8.0), 7.00 (d, 2, J =

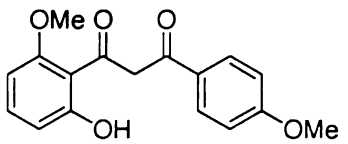
8.8), 3.90 (s, 3), 3.83 (s, 3), 2.52 (s, 3). ^{13}C NMR: δ 197.8, 164.0, 152.0, 139.3, 132.9, 132.6, 126.3, 121.4, 121.1, 115.9, 113.9, 60.4, 56.3, 55.5, 30.4.



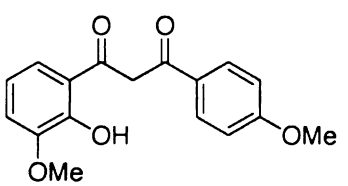
5-methoxy-2-(4'-methoxybenzoyloxy)acetophenone. ^{1}H NMR: δ 8.16 (d, 2, J = 8.8), 7.34 (d, 1, J = 2.8), 7.10 – 7.14 (m, 2), 7.0 (d, 2, J = 8.8), 3.90 (s, 3), 3.86 (s, 3), 2.52 (s, 3). ^{13}C NMR: δ 197.4, 165.1, 164.1, 157.2, 143.1, 132.4, 132.0, 124.9, 121.5, 119.3, 114.0, 55.8, 55.5, 30.1.



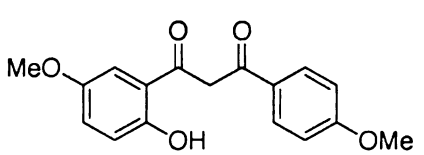
1-(4'-methoxyphenyl)-3-(2"-hydroxy-4",5"-dimethoxy)-1,3-propanedione. ^{1}H NMR: δ 12.46 (s), 12.4 (s), 8.04 (d, J = 8.8), 7.90 (d, J = 8.8), 7.26 (s), 7.12 (s), 6.94 – 6.99 (m), 6.56 (s), 6.48 (s), 6.43 (s), 4.48 (s), 3.92 (s), 3.91 (s), 3.90 (s), 3.88 (s), 3.87 (s), 3.85 (s). ^{13}C NMR: δ 196.9, 193.4, 191.8, 176.5, 164.2, 162.9, 160.7, 159.9, 157.3, 156.3, 142.2, 131.5, 128.6, 126.1, 114.1, 114.0, 111.6, 110.5, 110.1, 101.1, 100.5, 90.6, 56.9, 56.5, 56.2, 56.1, 55.5, 51.1.



1-(4'-methoxyphenyl)-3-(2''-hydroxy-6''-methoxy)-1,3-propanedione. ^{1}H NMR: δ 12.54 (s), 7.85 (d, J = 8.8), 7.88 (d, J = 8.8), 7.27 – 7.33 (m), 6.97 (d, J = 8.8), 6.60 (d, J = 8.4), 6.43 (d, J = 8.4), 4.53 (s), 3.95 (s), 3.89 (s). ^{13}C NMR: δ 201.0, 196.5, 193.6, 193.0, 177.8, 165.1, 163.7, 163.0. 160.7, 160.2, 136.6, 134.7, 130.4, 129.6, 128.8, 114.1, 113.9, 111.1, 101.8, 101.1, 96.8, 55.9, 55.5, 55.4, 55.0.

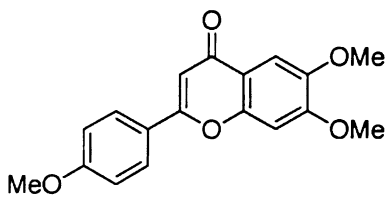


1-(4'-methoxyphenyl)-3-(2''-hydroxy-3''-methoxy)-1,3-propanedione. ^{1}H NMR: δ 12.33 (s), 12.20 (s), 7.99 (d, J = 8.8), 7.92 (d, J = 8.8), 7.38 (d, J = 8.0), 7.04 (d, J = 8.0), 6.98 (d, J = 8.8), 6.86 (t, J = 8.0), 6.78 (s), 4.59 (s), 3.92 (s), 3.90 (s), 3.89 (s), 3.88 (s). ^{13}C NMR: δ 194.6, 178.0, 163.3, 152.6, 149.2, 131.2, 128.9, 125.9, 122.1, 119.7, 119.2, 118.6, 118.3, 117.5, 116.0, 114.2, 114.1, 91.6, 56.2, 55.5.

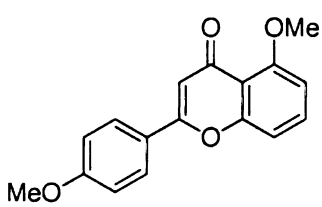


1-(4'-methoxyphenyl)-3-(2''-hydroxy-5''-methoxy)-1,3-propanedione. ^{1}H NMR: δ 11.68 (s), 11.59 (s), 8.00 (d, J = 8.8), 7.90 (d, J = 8.8), 7.28 (d, J = 3.2),

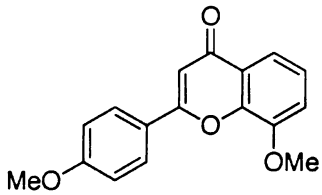
7.20 (d, J = 3.2), 7.08 (dd, J = 9.2, 3.2), 6.97 (d, J = 8.8), 6.93 (d, J = 9.2), 6.68 (s), 4.56 (s), 3.88 (s), 3.87 (s), 3.83 (s). ^{13}C NMR: δ 194.3, 178.0, 163.2, 156.5, 151.9, 131.3, 128.8, 125.8, 125.2, 122.6, 119.4, 118.8, 114.1, 114.0, 113.2, 111.9, 91.0, 56.1, 55.5.



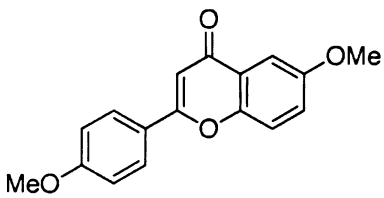
4',6,7-trimethoxyflavone. ^{1}H NMR: δ 7.86 (d, 2, J = 8.8), 7.57 (s, 1), 7.02 (d, 2, J = 8.8), 6.98 (s, 1), 6.70 (s, 1), 4.01 (s, 3), 3.99 (s, 3), 3.89 (s, 3). ^{13}C NMR: δ 177.6, 162.8, 162.2, 154.3, 152.2, 147.5, 127.7, 124.3, 117.3, 114.4, 105.8, 104.5, 99.7, 56.4, 56.3, 55.5.



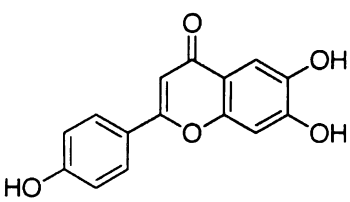
4',5-dimethoxyflavone. ^{1}H NMR: δ 7.84 (d, 2, J = 8.8), 7.55 (t, 1, J = 8.4), 7.12 (d, 1, J = 8.4), 7.01 (d, 2, J = 8.8), 6.82 (d, 1, J = 8.4), 6.65 (s,1), 4.00 (s, 3), 3.88 (s, 3). ^{13}C NMR: δ 178.2, 162.1, 161.0, 159.6, 158.1, 133.4, 127.6, 123.6, 114.4, 114.3, 110.0, 107.6, 106.3, 56.4, 55.4.



4',8-dimethoxyflavone. ^{1}H NMR: δ 7.92 (d, 2, J = 8.8), 7.76 (d, 1, J = 8.0), 7.30 (t, 1, J = 8.0), 7.17 (d, 1, J = 8.0), 7.01 (d, 2, J = 8.8), 6.74 (s, 1), 4.02 (s, 3), 3.88 (s, 3). ^{13}C NMR: δ 178.3, 162.9, 162.3, 149.0, 146.5, 128.0, 124.9, 124.6, 124.1, 116.4, 114.4, 114.2, 105.9, 56.3, 55.4.



4',6-dimethoxyflavone. ^{1}H NMR: δ 7.87 (d, 2, J = 8.8), 7.59 (d, 1, J = 3.2), 7.48 (d, 1, J = 9.2), 7.27 (dd, 1, J = 9.2, 3.2), 7.02 (d, 2, J = 8.8), 6.74 (s, 1), 3.91 (s, 3), 3.89 (s, 3). ^{13}C NMR: δ178.2, 163.2, 162.3, 156.9, 151.0, 127.9, 124.5, 124.1, 123.5, 119.4, 114.4, 105.5, 104.9, 55.9, 55.5.

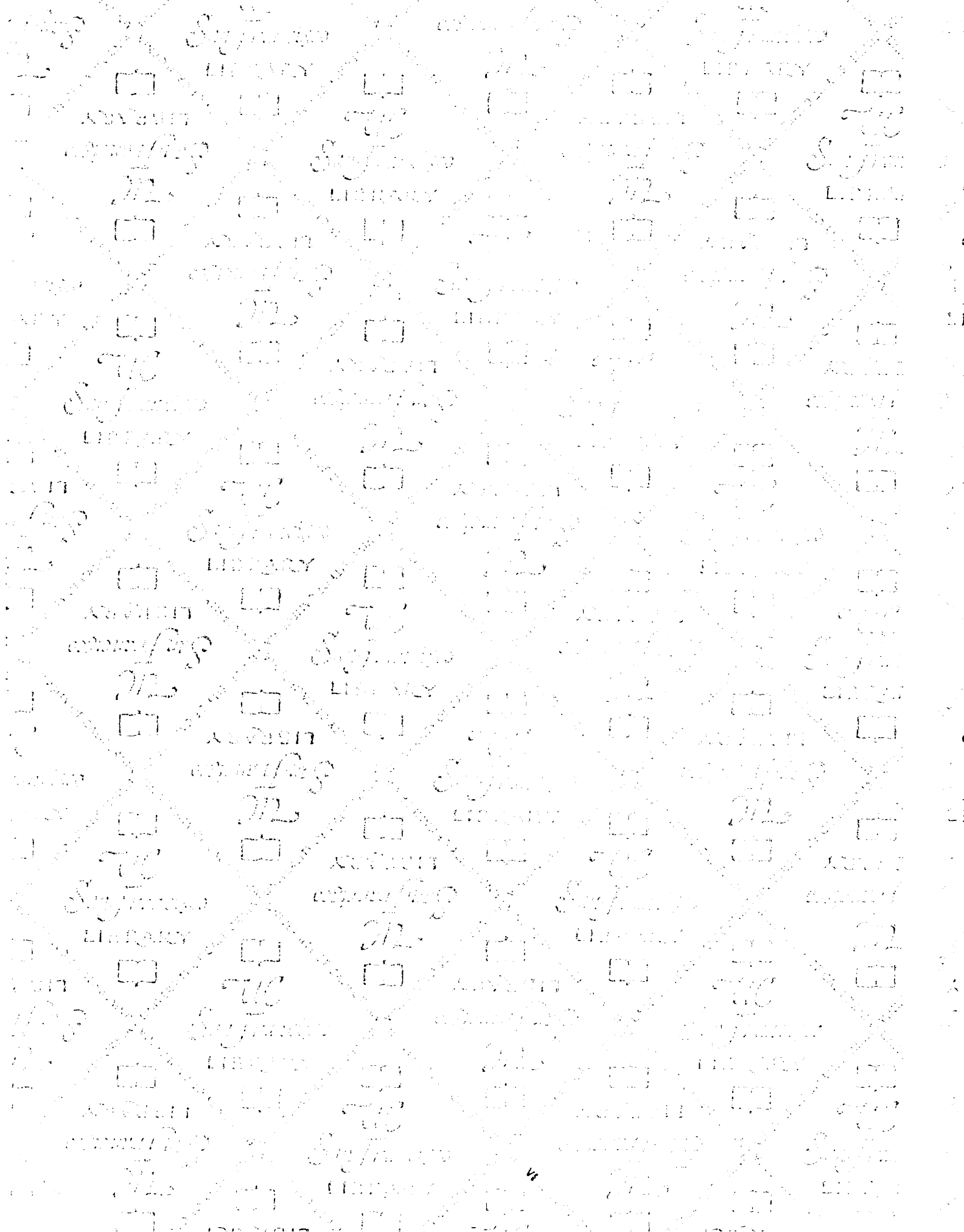


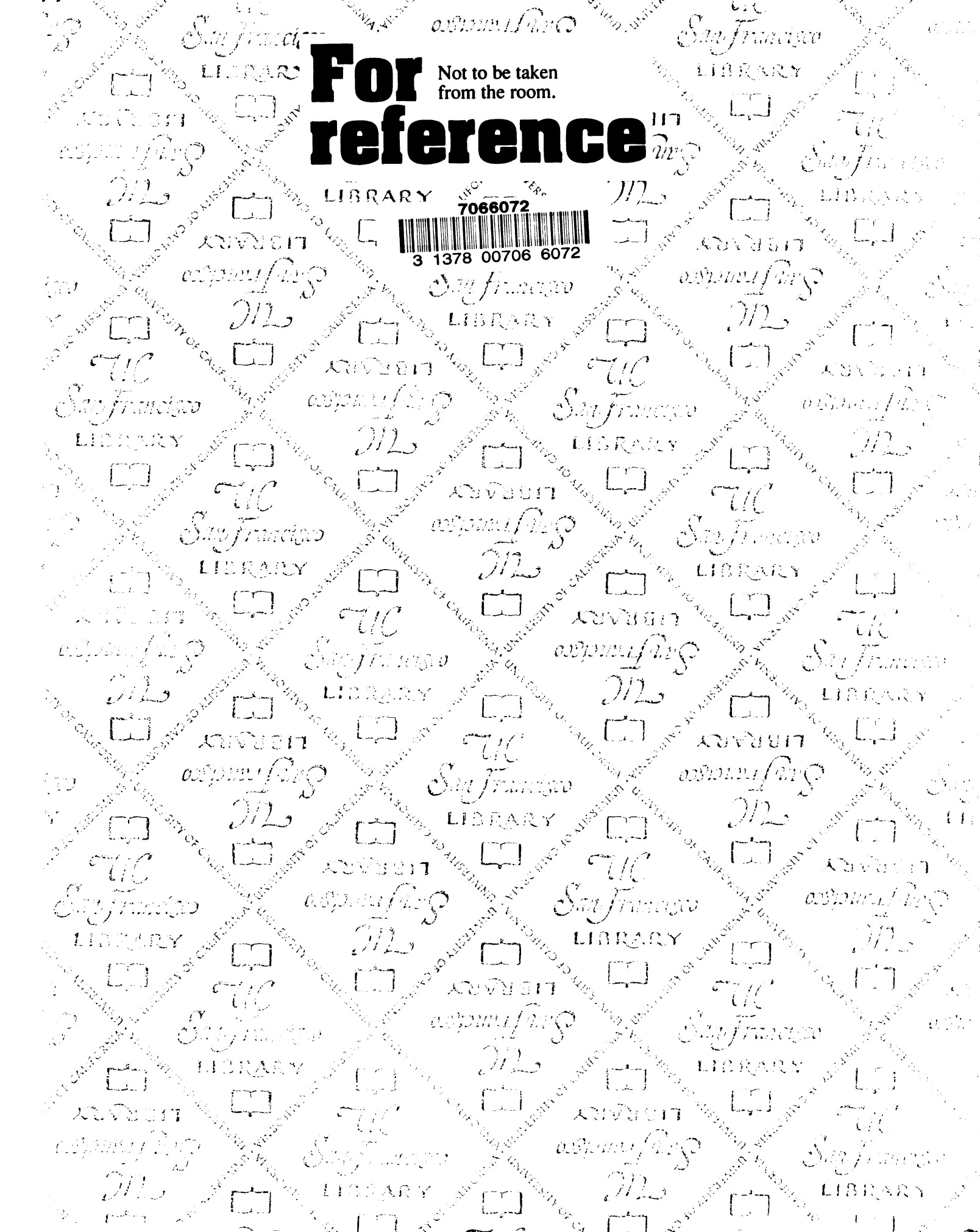
4',6,7-trihydroxyflavone. ^{1}H NMR (d_6-DMSO): δ 7.87 (d, 2, J = 8.8), 7.28 (s, 1), 6.99 (s, 1), 6.91 (d, 2, J = 8.8). ^{13}C NMR (d_6-DMSO): δ 176.5, 162.3, 160.6, 152.3, 150.9, 144.7, 128.1, 122.2, 116.1, 107.8, 104.0, 103.3,

Chapter 6. References

1. K. S. Korach, *Science* **266**, 1524-7 (1994).
2. M. Y. Farhat, M. C. Lavigne, P. W. Ramwell, *Faseb J* **10**, 615-24 (1996).
3. E. P. Smith *et al.*, *N Engl J Med* **331**, 1056-61 (1994).
4. J. H. Krege *et al.*, *Proc Natl Acad Sci U S A* **95**, 15677-82 (1998).
5. J. F. Couse *et al.*, *Science* **286**, 2328-2330 (1999).
6. R. V. Weatherman, R. J. Fletterick, T. S. Scanlan, *Annu Rev Biochem* **68**, 559-581 (1999).
7. G. G. Kuiper, J. A. Gustafsson, *FEBS Lett* **410**, 87-90 (1997).
8. G. B. Tremblay *et al.*, *Mol Endocrinol* **11**, 353-65 (1997).
9. L. Klein-Hitpass, M. Schorpp, U. Wagner, G. U. Ryffel, *Cell* **46**, 1053-1061 (1986).
10. Y. Umayahara *et al.*, *J Biol Chem* **269**, 16433-42 (1994).
11. J. Torchia, C. Glass, M. G. Rosenfeld, *Curr Opin Cell Biol* **10**, 373-83 (1998).
12. C. K. Glass, M. G. Rosenfeld, *Genes Dev* **14**, 121-141 (2000).
13. D. B. Lubahn *et al.*, *Proc Natl Acad Sci U S A* **90**, 11162-6 (1993).
14. S. Ogawa, D. B. Lubahn, K. S. Korach, D. W. Pfaff, *Proc Natl Acad Sci U S A* **94**, 1476-81 (1997).
15. P. J. Shughrue, D. B. Lubahn, A. Negro-Vilar, K. S. Korach, I. Merchenthaler, *Proc Natl Acad Sci U S A* **94**, 11008-12 (1997).
16. S. K. Das *et al.*, *Proc Natl Acad Sci U S A* **94**, 12786-91 (1997).
17. Z. Weihua *et al.*, *Proc Natl Acad Sci U S A* **97**, 5936-41 (2000).
18. J. I. MacGregor, V. C. Jordan, *Pharmacol Rev* **50**, 151-96 (1998).
19. P. A. Murphy, *Food Technol* **36**, 62-64 (1982).
20. M. S. Kurzer, X. Xu, *Annu Rev Nutr* **17**, 353-81 (1997).
21. G. G. Kuiper *et al.*, *Endocrinology* **139**, 4252-63 (1998).
22. G. G. Kuiper *et al.*, *Endocrinology* **138**, 863-70 (1997).
23. A. Fougerousse, E. Gonzalez, R. Brouillard, *J Org Chem* **65**, 583-6 (2000).
24. E. S. Wu *et al.*, *J Med Chem* **30**, 788-92 (1987).
25. E. S. Wu *et al.*, *J Med Chem* **32**, 183-92 (1989).
26. E. S. Wu *et al.*, *J Med Chem* **35**, 3519-25 (1992).
27. K. Thakkar, R. L. Geahlen, M. Cushman, *J Med Chem* **36**, 2950-5 (1993).
28. O. Prakash, s. Pahuja, R. M. Moriarty, *Synthetic Communications* **20**, 1417-1422 (1990).
29. D. Nagarathnam, M. Cushman, *J Org Chem* **56**, 4484-4887 (1991).
30. D. E. Zembower, H. Zhang, *J Org Chem* **63**, 9300-9305 (1998).
31. W. Baker, R. Robinson, *J Chem Soc*, 1981-1986 (1925).
32. W. Baker, *J Chem Soc*, 1381-1389 (1933).
33. P. L. Anelli, C. Biffi, s. Quici, *J Org Chem* **52**, 2559-2562 (1986).

34. H. W. Dorn, W. H. Warren, J. L. Bullock, *J Am Chem Soc* **61**, 144-147 (1939).
35. J. Zhu, R. Beugelmans, A. Bigot, G. P. Singh, M. Bois-Choussy, *Tet Let* **34**, 7401-7404 (1993).
36. H. D. Dakin, *Catechol (pyrocatechol)*. H. Gilman, Ed., Org Synth (John Wiley & Sons, Inc., New York, 1941), vol. 1.
37. Y. Ogata, Y. Sawaki, *J Org Chem* **34**, 3985-3991 (1969).
38. S. Nahm, S. M. Weinreb, *Tet Lett* **22**, 3815-3818 (1981).
39. G. Majetich, Y. Zhang, *J Am Chem Soc* **116**, 4979-4980 (1994).
40. A. M. Brzozowski *et al.*, *Nature* **389**, 753-8 (1997).
41. A. C. Pike *et al.*, *Embo J* **18**, 4608-4618 (1999).
42. M. Dowsett, *Acta Oncol* **35**, 91-5 (1996).
43. G. M. Anstead, K. E. Carlson, J. A. Katzenellenbogen, *Steroids* **62**, 268-303 (1997).
44. M. Marder *et al.*, *Bioorg Med Chem Lett* **7**, 2003-2008 (1997).
45. B. D. M. Cunningham, M. D. Threadgill, P. W. Groundwater, I. L. Dale, J. A. Hickman, *Anti-cancer Drug Design* **7**, 365-384 (1992).
46. A. M. Costa, F. M. Dean, M. A. Jones, R. S. Varma, *J Chem Soc Perkin Trans 1*, 799-808 (1985).
47. T. G. C. Bird, B. R. Brown, I. A. Stuart, W. R. Tyrrell, *J Chem Soc Perkin Trans 1*, 1831-1846 (1983).
48. J. R. Shelton, C. Cialdella, *J Org Chem* **23**, 1128-1133 (1958).
49. N. Miyaura, A. Suzuki, *Chem Rev* **95**, 2457-2483 (1995).




For reference
Not to be taken from the room.
LIBRARY
7066072
3 1378 00706 6072