

**An Efficient Route for the Synthesis of Flavans Using
Sequential One-pot Jeffery Heck Coupling and Reduction
as Key Protocol**

A Project Report

Submitted to the Department of Chemistry
Indian Institute of Technology, Hyderabad
As part of the requirements for the degree of

MASTER OF SCIENCE

By

Nishu Rana

(Roll No. CY14MSCST11009)

Under the supervision of

Dr. G. Satyanarayana



भारतीय प्रौद्योगिकी संस्थान हैदराबाद
Indian Institute of Technology Hyderabad

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY HYDERABAD
INDIA
APRIL, 2016

Declaration

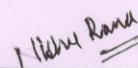
I hereby declare that the matter embodied in this report is the result of investigation carried out by me in the Department of Chemistry, Indian Institute of Technology Hyderabad under the supervision of **Dr. G. Satyanarayana**.

In keeping with general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.



Signature of the Supervisor

Dr. G. Satyanarayana
Associate Professor
Department of Chemistry
Indian Institute of Technology Hyderabad
Ordnance Factory Estate, Yeddumallaram



(Signature of the Student)

Nishu Rana

(Name of the Student)

CY14MSCST11009

(Roll No.)

Approval Sheet

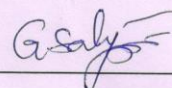
This thesis entitled "*An Efficient Route for the Synthesis of Flavans Using Sequential One-pot Jeffery Heck Coupling and Reduction As Key Protocol*" by Nishu Rana is approved for the degree of Master of Technology from IIT Hyderabad.



Prof. Faiz Ahmed Khan
Examiner
Department of Chemistry
Indian Institute of Technology
Hyderabad-502285, India
April 2016



Dr. D. S. Sharada
Examiner
Department of Chemistry
Indian Institute of Technology
Hyderabad-502285, India
April 2016



Dr. G. Satyanarayana
Adviser
Department of Chemistry
Indian Institute of Technology
Hyderabad-502285, India
April 2016

Acknowledgements

I express my profound gratitude to my project supervisor Dr. G. Satyanarayana for his invaluable guidance and constant encouragement throughout my project. It has been a great privilege and honor to be associated with him.

I sincerely thank, “Department of Chemistry of Indian Institute of Technology (IIT) Hyderabad”, for providing all the necessary facilities. My special thanks to the Head of the Department Dr. M. Deepa. I sincerely thank all the faculty members of the department, for their timely assistance and their constant encouragement. I sincerely thank to all my teachers throughout my academic career. I sincerely thank all my lab members for their constant help and valuable suggestions during my stay in the lab. I am grateful to Niharika Pedireddi for her constant help and support. I sincerely thank Dr. A. Gopi Krishna Reddy and Mr. Karu Ramesh Varma for their constant help and providing me with all the spectral data. My hearty thanks to Mr. Devarapalli Ravi Kumar and Mr. Suchand Basuli for their constant motivation. My acknowledgement will be incomplete without mentioning the encouragement and mental support by my dearest friend Neha Mehalwar. I also thank to all my seniors at IIT Hyderabad for their constant valuable help. I also thank to all my friends and my classmates for their support.

Dedicated to

My Beloved Parents and My Loving Brother

Abstract

Synthetic protocol like domino one-pot methods were found to be very economical and environment friendly as they devoid of isolation of intermediates. These protocols result in minimizing the wastage of chemicals and reagents and hence have attracted much attention from synthetic chemists as they help in constructing multiple bonds in a single-pot. The transition-metal-catalyzed reactions have gained much popularity in this area as they involve construction of bonds sequentially in a single loading of the starting materials.

Herein, we propose a facile approach for the synthesis of flavans starting from aryl allylic alcohols and iodophenols in a sequential one-pot fashion in which [Pd]-catalyzed C-C bond formation via Jeffery Heck reaction and sodium borohydride reduction form the key steps for the formation of alcohols. The diol precursors obtained were subjected to FeCl₃ mediated intramolecular cyclization to give different functionalized flavans in good yields.

Contents

1.1 Introduction	1
1.2 Biological and pharmacological activities.....	2
1.3 Background.....	3
1.4 Results and discussion	6
1.5 Conclusion	16
1.6 Experimental section	17
1.7 References and notes	38

An Efficient Route for the Synthesis of Flavans Using Sequential One-pot Jeffery Heck Coupling and Reduction as Key Protocol

1.1 INTRODUCTION:

Domino one-pot synthetic method has emerged as one of the most efficient and powerful tools¹ in organic synthetic field. A domino reaction is a method in which two or more bond forming transformations under the same reaction conditions without adding any supplementary catalysts and reagents.² This strategy results in the minimization of labour work and reduction in the wastage of resources. The development of such sustainable and low cost protocols has attracted attention in synthetic organic chemistry.

Flavans are a set of naturally occurring biologically active polyphenols known to be flavanoids, possessing a 2-phenylchroman core with a wide range of biological activities. Naturally occurring polyphenols and their derivatives constitute a large family of plant metabolites which are found to have powerful antioxidant activities.³ Flavans are of great interest because they exhibit useful medicinal, pharmacological and biological activities⁴ such as antiviral, antibacterial,⁵ antioxidant, antiarthritic, protein kinase, prostaglandin-synthesis inhibition,⁶ DNA synthesis/cell cycle arrest, topoisomerase inhibition,⁷ anticancerous,⁸ immune-stimulating, vasodilatory,⁹ anticarcinogenic,¹⁰ antiviral, antiallergic and cytotoxic activities. The flavanoids comprise a huge class of compounds, widely present in plants, containing numerous phenolic hydroxyl groups attached as glycosidic rings deliberating antioxidant activity.¹¹ Flavans cover a wide range of naturally occurring compounds which play an important role in plant growth, fruit bearing, blossoming, bacteria defense etc. The chemical structure of flavan constitutes of 15 carbon atoms, two benzene rings joined by a linear three carbon chain. Owing to such interesting structural diversity and promising biological properties, this class of natural products has attracted much attention from the synthetic chemists and

provided a platform for development of new synthetic methodologies for the synthesis of flavans.

1.2 BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES:

Flavans have attracted appreciable attention due to the presence of a chroman core which is responsible for many crucial biological, pharmacological and chemoprotective activities.¹² There are numerous natural products reported comprising the flavan core and conferring various biological activities. The compound (2*S*)-2'-hydroxy-7,8,3',4',5'-pentamethoxyflavan (**1**) is known to have cytotoxic and anticancer activity.¹³ (±)-5,4'-dihydroxy-7,3'-dimethoxyflavan (**2**) has been used as antimicrobial against *Candida albicans*.¹⁴ 7,4'-dihydroxyflavan (**3**) showed fungi toxic activity against *Botrytis cinerea* and *Cladosporium herbarum*.¹⁵ (±)-7-Hydroxy-3',4'-Methylene dioxyflavan (**4**)¹⁶ and its 7-glycosidic linkage has been used for curing diabetes, ear and chest ailments and act as antiviral agent (Figure 1).

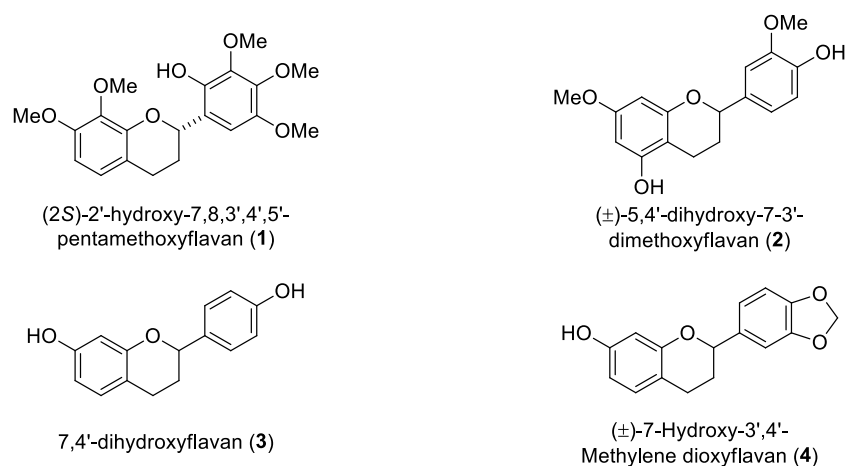


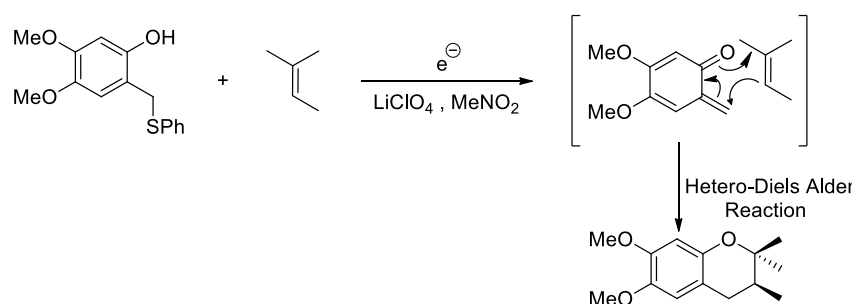
Figure 1: Representative examples of natural products with flavan as core structure.

1.3 BACKGROUND STUDIES:

The recent explosion of interest in the synthesis of flavans is due to its unique structural features and interesting biological activities. There are considerable synthetic strategies reported in the literature for the synthesis of flavans

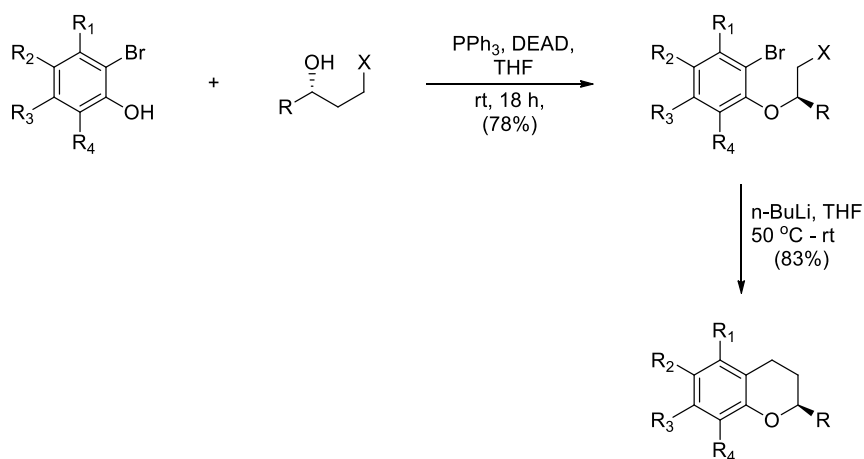
core skeleton. These include intra- and intermolecular Mitsunobu reaction,¹⁷ acid-catalyzed cyclization,¹⁸ reduction of flavanones¹⁹ or flav-2-enes²⁰ etc. Among them reductive deoxygenation of the flavanone and protic acid-catalyzed cyclization to give the benzopyran ring are common approaches, but these approaches typically suffer from poor yields and harsh reaction conditions. Some milder conditions include synthesis of chromans in which RuCl₃/AgOTf is used as an intramolecular hydroarylation catalyst.²¹ There are many more synthetic methods reported in the literature.

In one report, Chiba et al. in 1999, had reported chromane skeleton²² by intramolecular hetero-diels alder reaction of *in-situ* generated *o*-quinomethane and alkenes (Scheme 1).



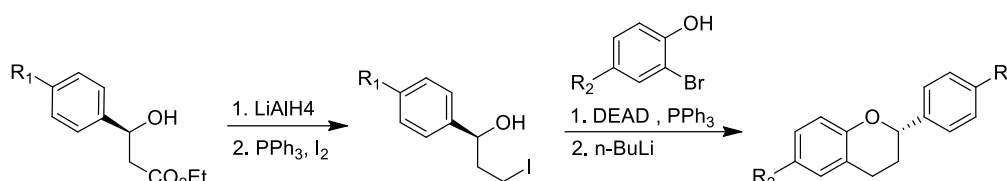
Scheme 1: Intramolecular diels-alder reaction of in-situ generated *o*-quinomethane and alkenes for flavan synthesis.

In 2005, Hodgetts et al. has designed efficient strategy in which intermolecular Mitsunobu reaction of substituted 2-bromophenol and a homochiral propanol, followed by lithiation and then intramolecular SN² results in the cyclization to give 2-substituted chroman skeleton (Scheme 2).²³



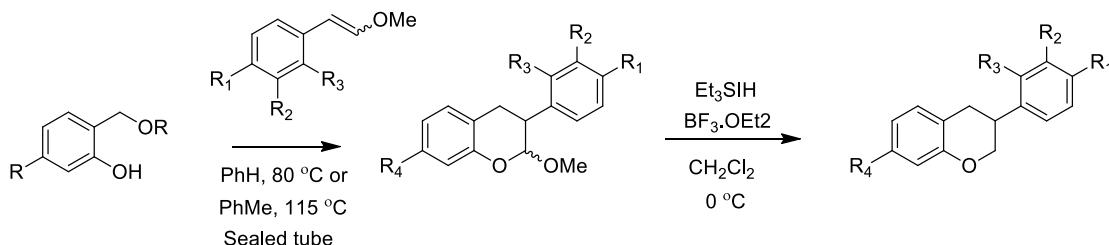
Scheme 2: Synthesis of flavans from substituted 2-bromophenol and homochiral propanol.

For further development of intermolecular Mitsunobu reaction for synthesizing the flavan core skeleton, in 2008, Park et al. investigated the catalytic asymmetric dehydration of β -hydroxy esters²⁴ followed by the intermolecular Mitsunobu reaction with substituted 2-bromophenols and obtained enantiorich flavan derivatives (Scheme 3).



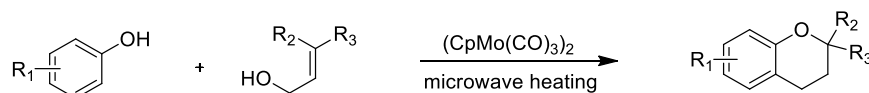
Scheme 3: Intermolecular Mitsunobu reaction with substituted 2-bromophenol.

In 2008, Gharpure et al. has also reported an efficient strategy for the synthesis of isoflavans from o-quinone methides and aryl-substituted enol ethers via Diels-Alder reaction followed by the reductive cleavage of the acetal group (Scheme 4).²⁵



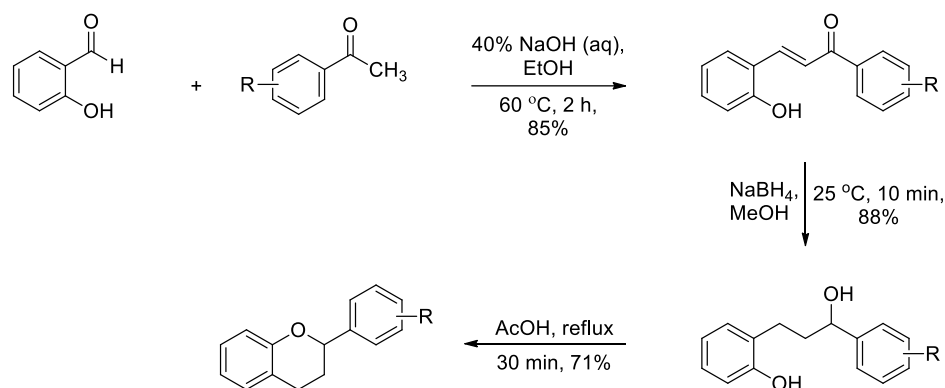
Scheme 4: Synthesis of isoflavans from o-quinomethides and aryl-substituted enol ethers.

In 2009, Yamamoto et al. has proposed the synthesis of chromans from phenols and allylic alcohols under microwave heating conditions via [3,3] cyclocoupling and using molybdenum complexes as the catalyst.²⁶ These cyclocoupling reactions suffered from the drawbacks due to the selectivity problems and they are limited only to *ortho/para* phenols (Scheme 5).²⁷



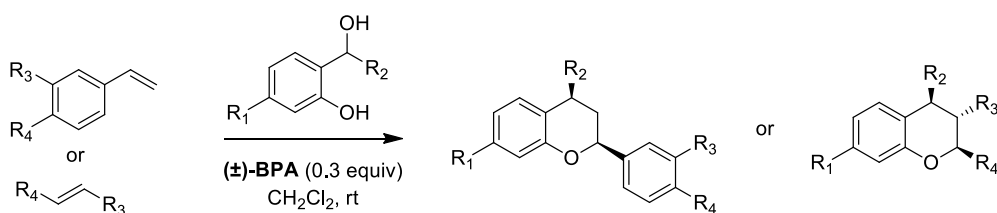
Scheme 5: Synthesis of flavans via [3,3] cyclocoupling and using molybdenum complexes as catalyst.

In another report, in 2011 Mazimba et al. had designed flavan skeleton by the aldol condensation of salicylaldehyde and acetophenone to give chalcone. The chalcone was further reduced with NaBH₄ in methanol and acetic acid mediated intramolecular cyclization gave the requisite flavan (Scheme 6).²⁸



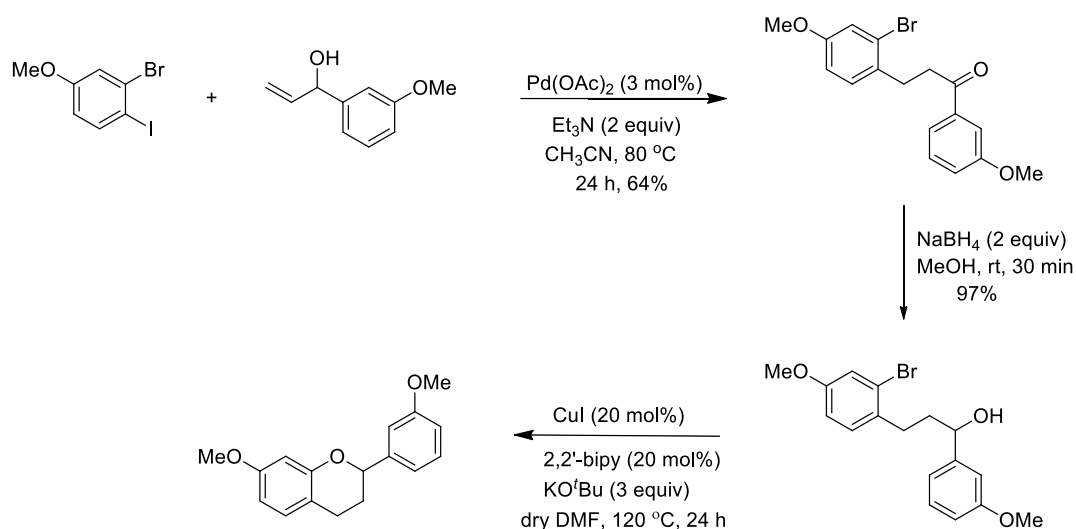
Scheme 6: Aldol condensation followed by reduction and acid mediated cyclization.

In recent years, so many strategies have been reported for the synthesis of flavans. In 2013, Gharpure et al. in continuation to his interest in flavan skeletons had designed a methodology for the synthesis of biologically active 2,4-diarylbenzopyrans in which [4+2] cycloaddition of olefin and o-quinone methides generated from alcohols by using (\pm)-binolphosphoric acid was the key step (Scheme 7).²⁹



Scheme 7: Synthesis of flavan core skeleton via [4+2] cycloaddition of o-quinomethides and olefins.

Due to our interest in transition-metal-catalysis, recently, we have disclosed an efficient strategy for flavans³⁰ and neoflavans³¹ involving copper-catalyzed intramolecular Buchwald-Hartwig cross coupling as the key step (Scheme 8).

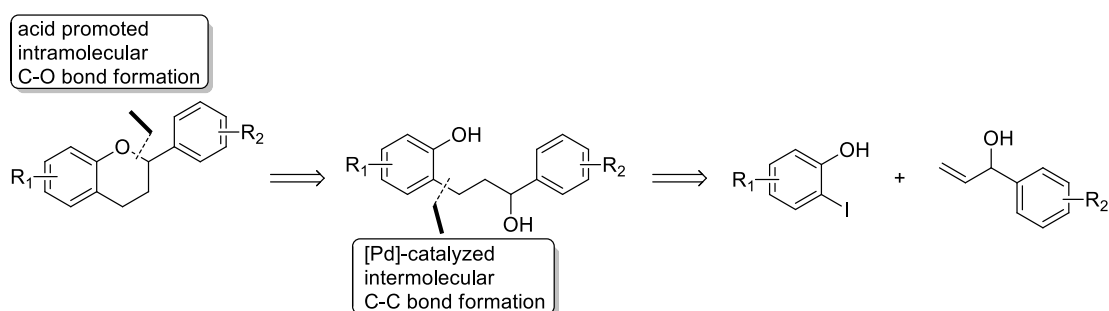


Scheme 8: Represents intramolecular [Cu]-catalyzed flavan synthesis.

With this background literature, herein, we report a new efficient and simple synthetic route for the synthesis of functionalized flavans.

1.4 RESULTS AND DISCUSSIONS:

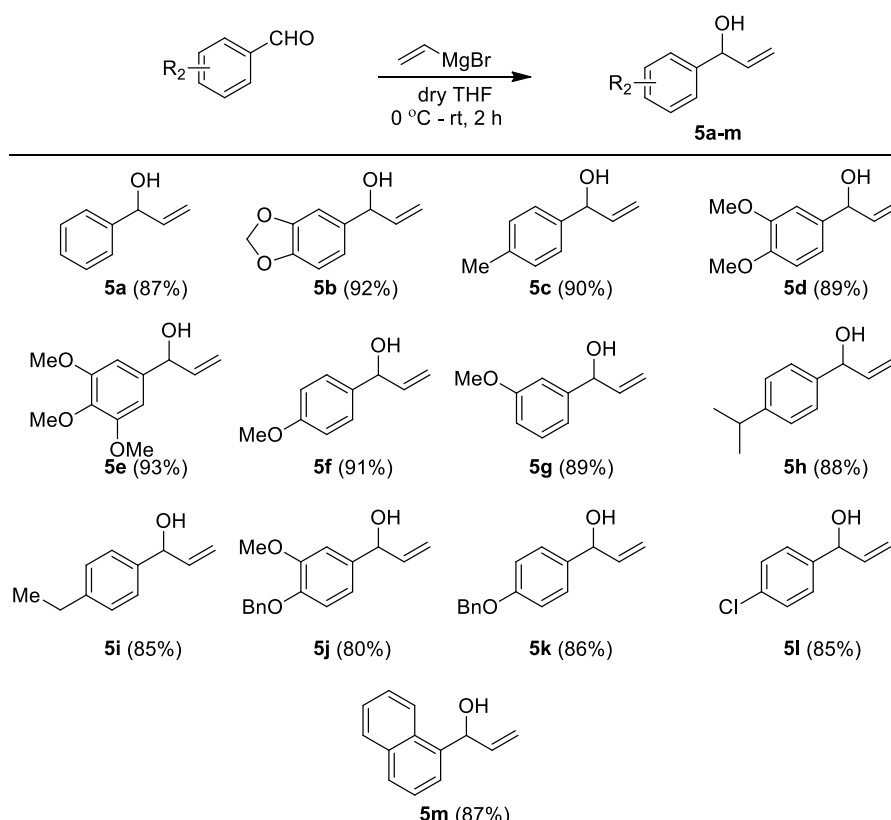
In continuation to our lab interest to work in acid mediated transformations, we designed a strategy for the preparation of flavans shown in the retrosynthetic analysis (Scheme 9). We propose an intramolecular Lewis acid mediated C–O bond formation as the key step from the secondary alcohols derived from the aryl allylic alcohols and iodophenols via [Pd]-catalyzed Jeffery-Heck reaction followed by the reduction strategy (Scheme 9).



Scheme 9: Retrosynthetic analysis of flavan.

To initiate the proposed work, the aryl allylic alcohols **5** were prepared by using standard Grignard addition of vinylmagnesium bromide on the commercially available aromatic aldehydes. Using this protocol, several substituted aryl allylic alcohols **5** were obtained in excellent yields (Table 1).

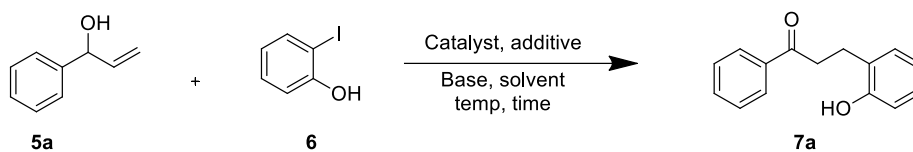
Table 1: Formation of aryl allylic alcohols **5** from corresponding benzaldehydes by using vinylmagnesium bromide Grignard reaction.



With the required aryl allylic alcohols **5**, we proceeded for the planned Jeffery Heck reaction between alcohol **5a** and 2-iodophenol **6** under various conditions to result in dihydrochalcone **7**. Various reaction conditions were explored in order to find out the best reaction conditions by varying base, solvent, temperature conditions and reaction time, which are summarized in the Table 2. Initially we began our trials with the reported conditions by using standard reported Jeffery-Heck conditions using [Pd]-catalyst and a base in the presence of an additive. As anticipated, the product **7a** was obtained albeit in moderate yield (Table 2, entry 1). To improve the yield, we increased the temperature; however,

disappointingly, the yield of product **7a** was not improved (Table 2, entry 2). As an alternative, we changed the solvent to DMF, but it resulted in the decomposition of the starting material and furnished the product **7a** in very poor yield (Table 2, entry 3). When triethylamine was used as base in absence of additive, with acetonitrile as solvent, the product **7a** was obtained in slightly better yields with large amount of starting material (Table 2, entry 4). Hence, for the complete conversion, we further increased the reaction time and found that the yield was poor (Table 2, entry 5). Also in solvent DMF at 100 °C for 24 h, the yield was not improved (Table 2, entry 6). To our delight, in the same DMF solvent at 100 °C for longer reaction times (72 h), the product **7a** was obtained in very good yields (Table 2, entry 7). On the other hand, using other bases such as Cs₂CO₃ and DIPA, gave poor and fair yields of the product **7a**, respectively (Table 2, entries 9 & 10).

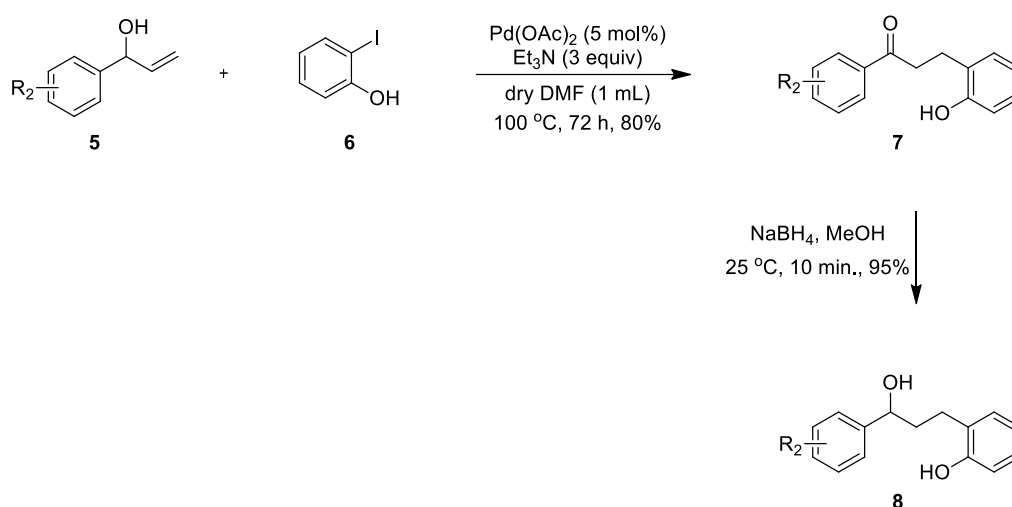
Table 2: Optimizations of [Pd]-catalyzed Jeffery-Heck reaction between aryl allylic alcohol **5** and 2-iodophenol **6**.



Entry	Catalyst (5 mol %)	Additive (1.1 equiv)	Base (3 equiv)	Solvent (1 mL)	Time (h)	Temp (°C)	Yield (%) ^a
1	Pd(OAc) ₂	TEBAC	NaHCO ₃	CH ₃ CN	24	50	40 ^b
2	Pd(OAc) ₂	TEBAC	NaHCO ₃	CH ₃ CN	24	80	39 ^b
3	Pd(OAc) ₂	TEBAC	NaHCO ₃	DMF	24	100	10 ^b
4	Pd(OAc) ₂	–	Et ₃ N	CH ₃ CN	24	80	45 ^b
5	Pd(OAc) ₂	–	Et ₃ N	CH ₃ CN	40	80	31
6	Pd(OAc) ₂	–	Et ₃ N	DMF	24	100	43 ^b
7	Pd(OAc)₂	–	Et₃N	DMF	72	100	80
8	Pd(OAc) ₂	–	Cs ₂ CO ₃	DMF	72	100	24
9	Pd(OAc) ₂	–	(ⁱ Pr) ₂ NH	DMF	72	100	67

^a Isolated yields of chromatographically pure products. ^b No complete conversion; starting material was also isolated.

By implementing the standardized conditions (Table 2, entry 7), various substituted dihydrochalcones **7** were accomplished under [Pd]-catalysis. Dihydrochalcones **7** were then subjected to NaBH₄ reduction in methanol to furnish the corresponding secondary alcohols **8**. The products **8** were obtained in near quantitative (95 to 97%) yields (Scheme 10). These alcohols were confirmed by IR & NMR spectroscopic techniques.

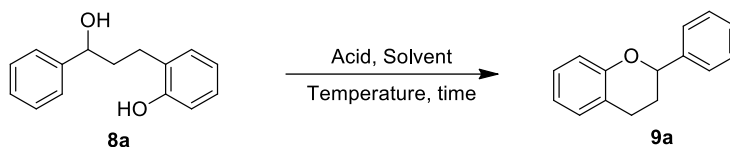


Scheme 10: Synthesis of diols **8** via ketones **7** using aryl allylic alcohols **5** and 2-iodophenol **6**.

Having the key synthetic precursors **8** in hand, we implemented various acids for the C–O bond formation to yield the required flavans **9**. The explored reaction conditions to identify best optimized conditions are summarized in Table 3. Due to our interest in Lewis acid mediated cyclization reactions, initially, we decided to treat the secondary alcohol **8a** with anhydrous AlCl₃. Thus, the secondary alcohol **8a** was treated with anhydrous AlCl₃ in dry DCM at ambient and ice temperatures as well. However, the reaction leads to the decomposition of the starting material and hence, neither product **9a** nor the starting material **8a** was recovered (Table 3, entries 1 & 2). While, keeping all the reaction conditions constant but at decreased temperature to –40 °C, interestingly, furnished the product **9a** exclusively albeit in poor yield (Table 3, entry 3). On the other hand, the reaction with other acids such

as TFA and $\text{BF}_3 \cdot \text{OEt}_2$ at low temperature proved ineffective (Table 3, entries 4 & 5). Gratifyingly, anhydrous FeCl_3 furnished the product **9a** in fair yield (Table 3, entry 6). Furthermore, when the reaction was carried out by increasing temperature to -20 °C with the same anhydrous FeCl_3 , gave the product **9a** even in good yield (Table 3, entry 7) when compared to that conducted at -40 °C.

Table 3: Attempts of acid mediated intramolecular cyclization of diol **8a**.



Entry	Acid	Solvent (4 mL)	Temp (°C)	Time (min)	Yield of 9a (%) ^a
1	AlCl_3 (1.2 equiv)	Dry DCM (4)	rt	10	– ^b
2	AlCl_3 (1.2 equiv)	Dry DCM (4)	0	10	– ^b
3	AlCl_3 (1.2 equiv)	Dry DCM (4)	-40	10	41
4	TFA (.15 equiv)	Dry DCM (4)	-40	10	– ^b
5	$\text{BF}_3 \cdot (\text{OEt})_2$ (1.5 equiv)	Dry DCM (4)	-40	10	– ^b
6	FeCl_3 (1.2 equiv)	Dry DCM (4)	-40	120	68
7	FeCl_3 (1.2 equiv)	Dry DCM (4)	-20	90	72

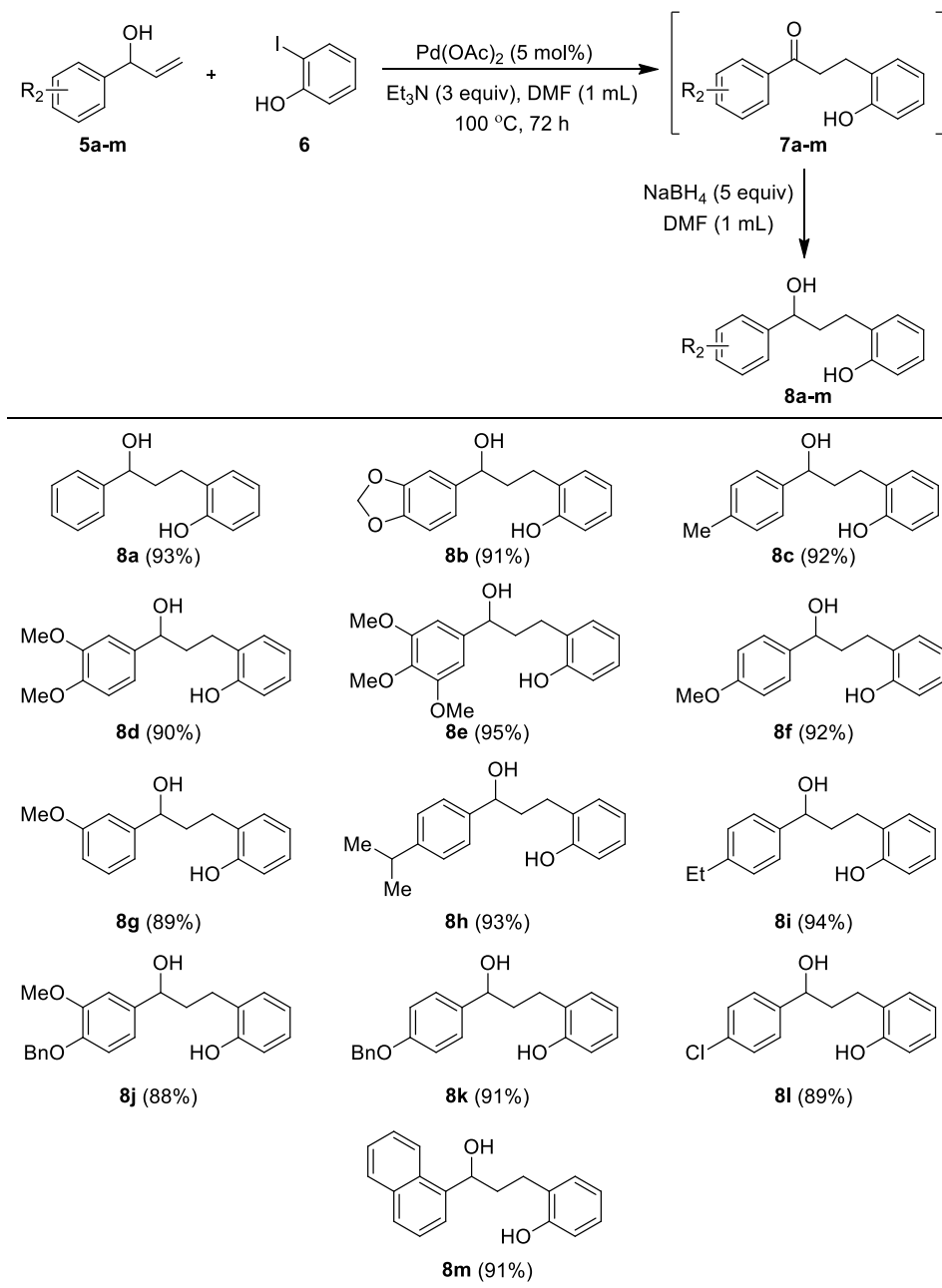
^aIsolated yields of chromatographically pure products. ^bRepresents that starting material decomposed.

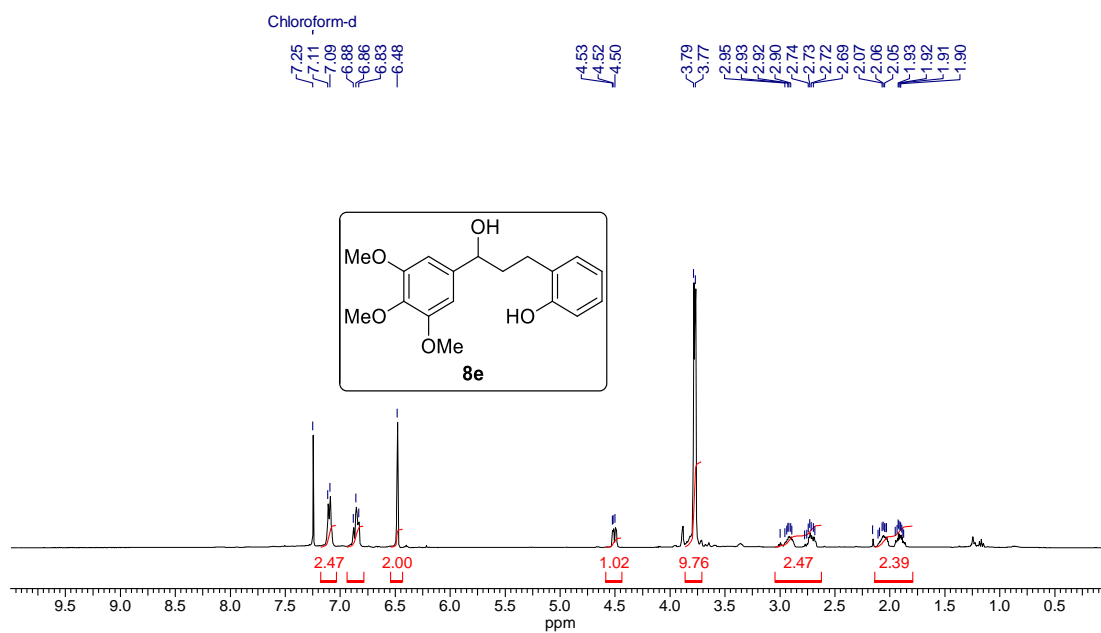
Further, to make our strategy more efficient and sustainable, we explored sequential one-pot [Pd]-catalyzed coupling, reduction and acid mediated cyclization protocol to for the direct synthesis of flavans **9**, starting from aryl allylic alcohols **5** and 2-iodophenol. However, we ended up in obtaining poor yields of flavans **9** (i.e. 15-20%). Several attempts were made to improve the yield of this one-pot strategy; yet, no improvement in the yields was noticed.

Therefore, we decided to explore the possibility to make the secondary alcohols **8** in one-pot fashion (i.e. [Pd]-catalyzed coupling and reduction protocol in a single-pot). Thus, after confirming the formation of Jeffery-Heck products **7** from TLC, *in-situ* the reaction mixture was reduced with NaHB_4 with additional amount of solvent (DMF) to make sure that proper stirring is maintained. Gratifyingly, the

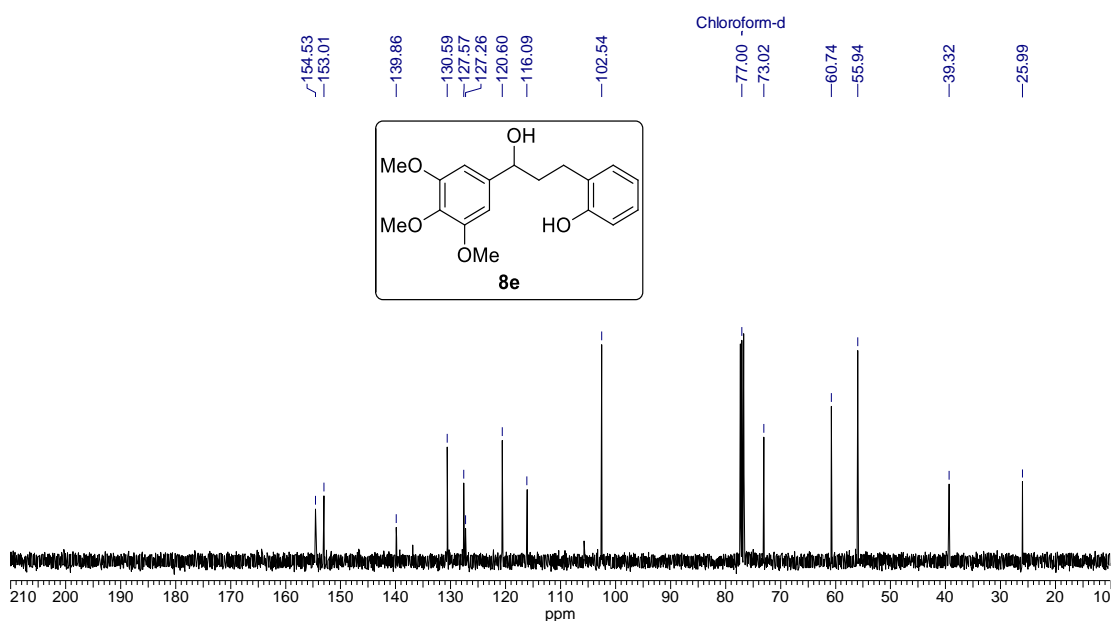
protocol was quite successful and furnished the secondary alcohols **8a-8m**, in good to excellent yields (Table 4). These secondary alcohols **8a-8m** were fully characterized by spectroscopic techniques ($^1\text{H-NMR}$ and $^{13}\text{C-NMR}$, IR and Mass Spectrometry).

Table 4: Secondary alcohols **8a-8m** obtained from corresponding aryl allylic alcohols **5a-5m** and 2-iodophenol **6** in sequential one-pot method.





$^1\text{H-NMR}$ (400 MHz) spectrum of **8e** in CDCl_3



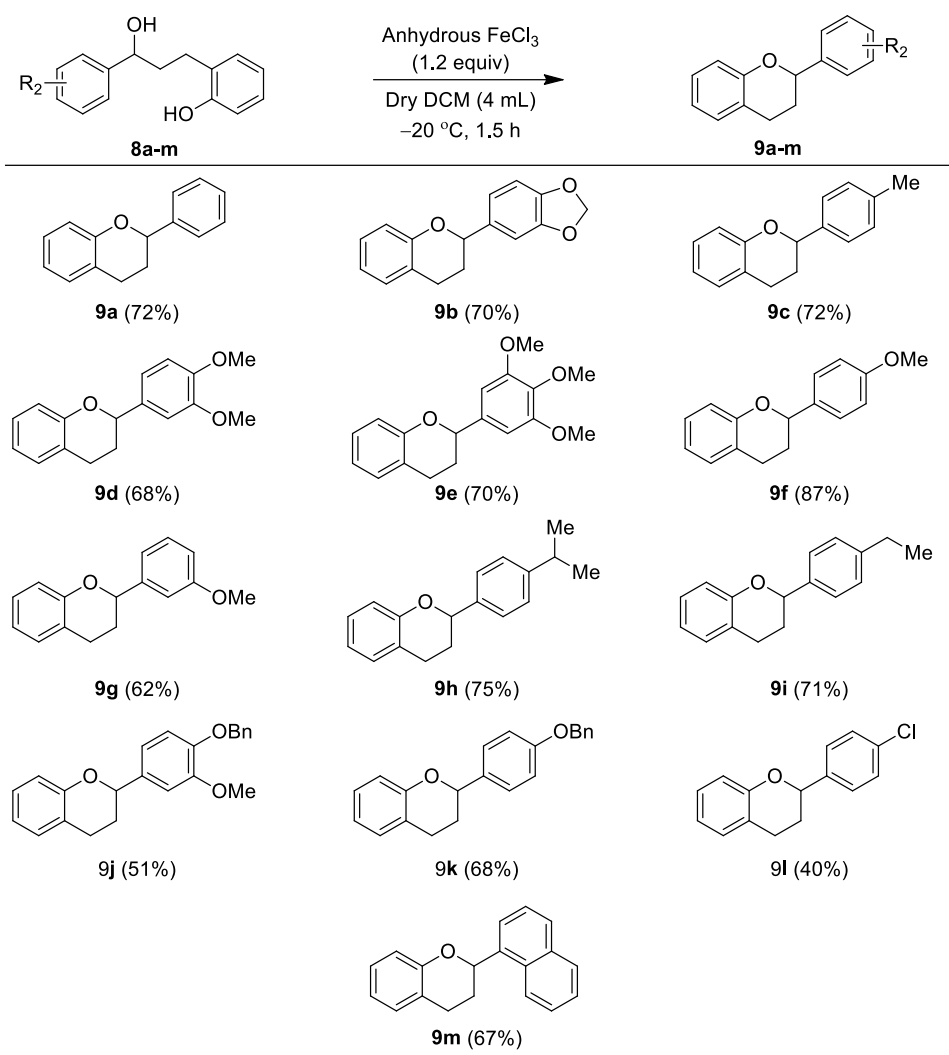
$^{13}\text{C-NMR}$ (100 MHz) spectrum of **8e** in CDCl_3

The chemical structure of secondary alcohol **8e** was confirmed from its spectral data. The strong and broad adsorption peak in IR spectra at $\nu_{\text{max}}=3287\text{ cm}^{-1}$ is due to O–H stretching. The lack of stretching frequency for C=O near 1680 cm^{-1} confirmed that dihydrochalcone **7e** had been reduced to secondary alcohol **8e**. Further the skeletal of secondary alcohol **8e** was established by its $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. The presence of six aromatic hydrogens in **8e** was confirmed by the doublet of doublet for two aromatic hydrogens at $\delta=7.10\text{ ppm}$ with coupling constant $J=7.3$ and

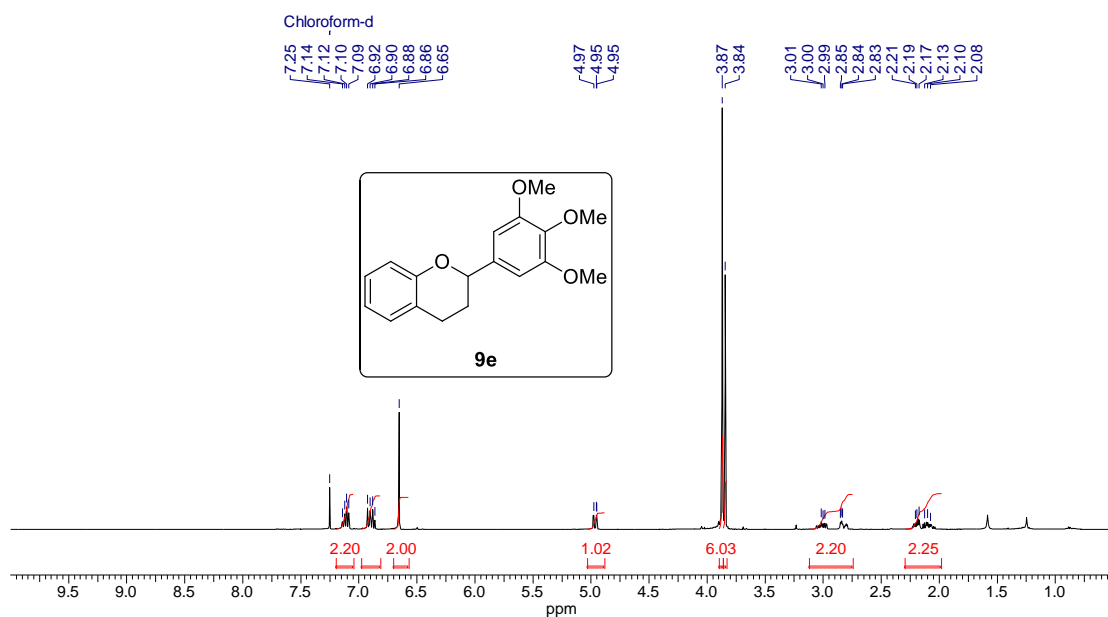
7.3 Hz, multiplet for another two aromatic hydrogens in the range of $\delta=6.88\text{--}6.83$ ppm and singlet at $\delta=6.48$ ppm for two aromatic hydrogens adjacent to methoxy groups. The doublet of doublet at $\delta=4.53\text{--}4.49$ ppm with coupling constants $J=10.3$ and 3.4 Hz was evident for the coupling of $-\text{CH}$ hydrogen with adjacent $-\text{CH}_2$ group hydrogens, attached to hydroxyl group. The chemical shifts for three methoxy groups attached to aromatic ring was found as singlets at $\delta=3.79, 3.78, 3.77$ ppm. The presence of two $-\text{CH}_2$ groups in **8e** was seen as multiplets in the range of $\delta=3.01\text{--}2.68$ and $2.11\text{--}1.87$ ppm. The presence of 11 lines in aromatic ^{13}C -NMR in the range of $\delta=154.5\text{--}102.6$ ppm confirmed 12 aromatic carbon atoms. The chemical shift for $-\text{CH}$ carbon atom was found to be at $\delta=73.1$ ppm. The three substituted methoxy carbon atoms were confirmed by presence of two lines at $\delta=60.8$ and 56.0 (for 2 carbon atoms) ppm and presence of triplets at $\delta=39.4, 26.1$ ppm confirmed the presence of two $-\text{CH}_2$ groups. HR-MS (ESI⁺) m/z calculated for $[\text{C}_{18}\text{H}_{23}\text{O}_5]^+=[\text{M}+\text{H}]^+$: 319.1540; found: 319.1544.

Finally, to check the scope and applicability for the cyclization reaction to give the target flavans **9**, the diols **8** were treated under optimized reaction conditions [i.e. anhydrous FeCl_3 (1.2 equiv) in dry DCM (4 mL) at -20 °C for 1.5 h, Table 3, entry 7]. To our delight, the method was found amenable and furnished flavans **9a-9m** in fair to good yields (Table 5). Significantly, this strategy was successful for the concise synthesis of flavans **9a-9m** with electron deactivating to electron rich substituents on the aromatic ring.

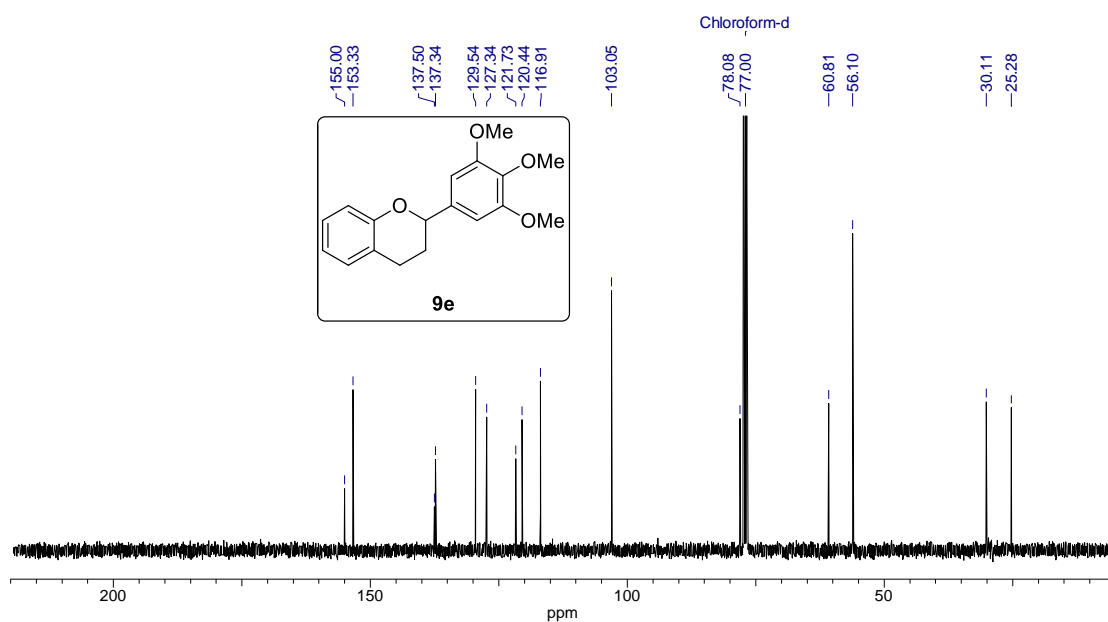
Table 5: FeCl_3 mediated cyclization of diol precursors **8a-8m** obtained in one-pot method to give corresponding flavans **9a-9m**.



The cyclized products **9** were confirmed by spectroscopic techniques (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, HRMS spectroscopy).



$^1\text{H-NMR}$ (400 MHz) of compound **9e** in CDCl_3



$^{13}\text{C-NMR}$ (100 MHz) of compound **9e** in CDCl_3

The cyclized product **9e** obtained was confirmed due to the strong adsorption peak at $\nu_{\text{max}}=1047\text{ cm}^{-1}$ for the C–O stretching. The lack of stretching frequency for O–H near 3287 cm^{-1} confirmed that diol precursor had been cyclized to flavan **9e**. Further the skeletal of flavan **9e** was established by its $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. In $^1\text{H-NMR}$, the presence of the doublet of doublet for two aromatic –CH at $\delta=7.12\text{ ppm}$ ($J=7.3$ and 7.3 Hz), doublet at $\delta=7.09\text{ ppm}$ ($J=7.3\text{ Hz}$) for aromatic –CH,

doublet at $\delta=6.91$ ppm ($J=7.8$ Hz) for aromatic $-\text{CH}$, doublet of doublet at $\delta=6.88$ ($J=7.8$ and 7.3 Hz) for two aromatic $-\text{CH}$, and singlet at $\delta=6.65$ ppm for two aromatic hydrogens adjacent to methoxy groups confirmed the presence of six aromatic hydrogens in **9e**. The doublet of doublet at $\delta=4.98\text{--}4.95$ ppm ($J=10.3$ and 2.4 Hz) was evident for $-\text{CH}$ hydrogen with adjacent to oxygen atom. The presence of singlets at $\delta=3.87$ and 3.81 ppm for six hydrogens of two methoxy and three hydrogen the third methoxy substituent in **9e**. The presence of two $-\text{CH}_2$ groups in **9e** was observed as multiplets in the range of $\delta=3.10\text{--}2.75$ and $2.25\text{--}2.00$ ppm. The presence of five singlets at $\delta=155.0, 153.3, 137.5, 137.3, 121.7$ ppm in ^{13}C -NMR were observed for six aromatic carbon atoms, doublets at $\delta=129.5, 127.3, 120.4, 116.9$ and 103.0 ppm for six aromatic carbon atoms attached to hydrogen and the doublet at $\delta=78.1$ ppm for $-\text{CH}$ carbon atom adjacent to oxygen in **9e**. The quartets at $\delta=60.8$ and 56.1 (for 2 carbon atoms) ppm for three substituted methoxy carbon atoms attached to the aromatic ring and the presence of triplets at $\delta=30.1, 25.3$ ppm two $-\text{CH}_2$ groups confirmed the structure of flavan **9e**. HR-MS (ESI⁺) m/z calculated for $[\text{C}_{18}\text{H}_{21}\text{O}_4]^+=[\text{M}+\text{H}]^+$: 371.1434; found: 371.1430. Therefore, based on the above mentioned spectral data, the flavan analogue **9e** obtained by our strategy was confirmed.

1.5 CONCLUSIONS:

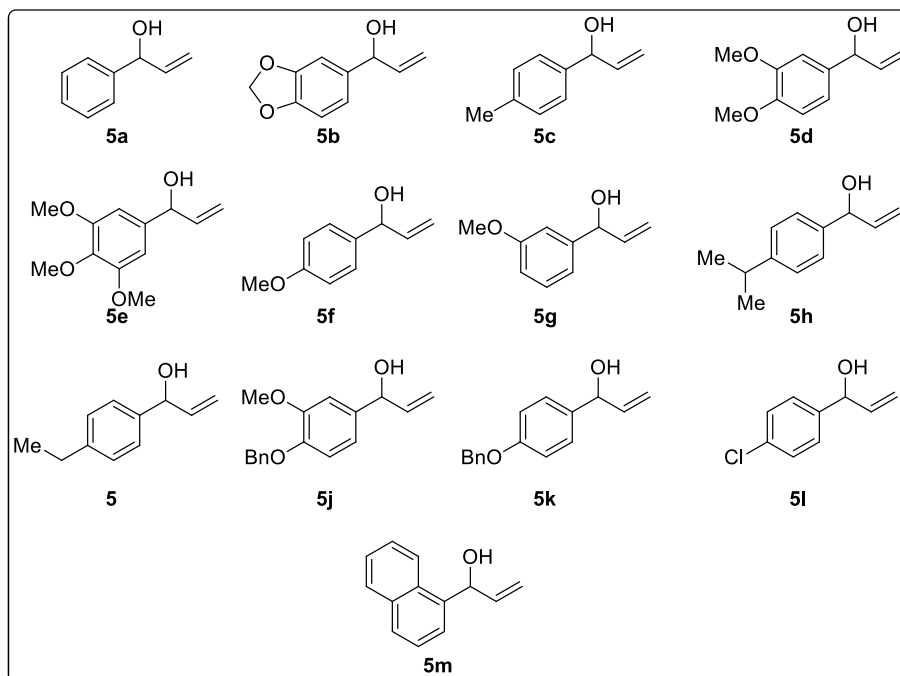
In summary, we have described an efficient and concise strategy for the synthesis flavans of biological relevance. Intermolecular [Pd]-catalyzed C–C bond formation followed by sodium borohydride mediated reduction were accomplished as a key sequential one-pot strategy. An intramolecular FeCl_3 mediated C–O bond formation gave the target flavans. Flavans show interesting biological and therapeutic properties. The described strategy requires mild reaction conditions. Hence, this methodology is significant and susceptible for the synthesis of a number of flavan analogues in good yields.

1.6 EXPERIMENTAL SECTION:

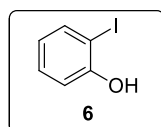
General:

IR spectra were recorded on a Bruker Tensor 37 (FT-IR) spectrophotometer. ^1H -NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in CDCl_3 ; chemical shifts (δ in ppm) and coupling constants (J in Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_{\text{H}} = 0.00$ ppm) or CHCl_3 ($\delta_{\text{H}} = 7.25$ ppm). ^{13}C -NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at 295 K in CDCl_3 ; chemical shifts (δ in ppm) are reported relative to CHCl_3 [$\delta_{\text{C}} = 77.00$ ppm (central line of triplet)]. In the ^{13}C -NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^1H -NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet, septd = septet of doublets. The assignment of signals was confirmed by ^1H , ^{13}C CPD and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF using multimode source. All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a mixture of petroleum ether and ethyl acetate as eluents. Reactions were generally run under an argon or nitrogen atmosphere. $\text{Pd}(\text{OAc})_2$ (with purity 98%), 2-iodophenol (with purity 99%), triethylamine (with purity 99%) and NaBH_4 (with purity 99%) were purchased from Sigma-Aldrich and used as received. 1M vinylmagnesium bromide in THF (with purity 99%) was purchased from local commercial sources and used as received. All solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C, THF was dried over sodium metal, whereas DMF was dried over calcium hydride and acetonitrile was dried over P_2O_5 . Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

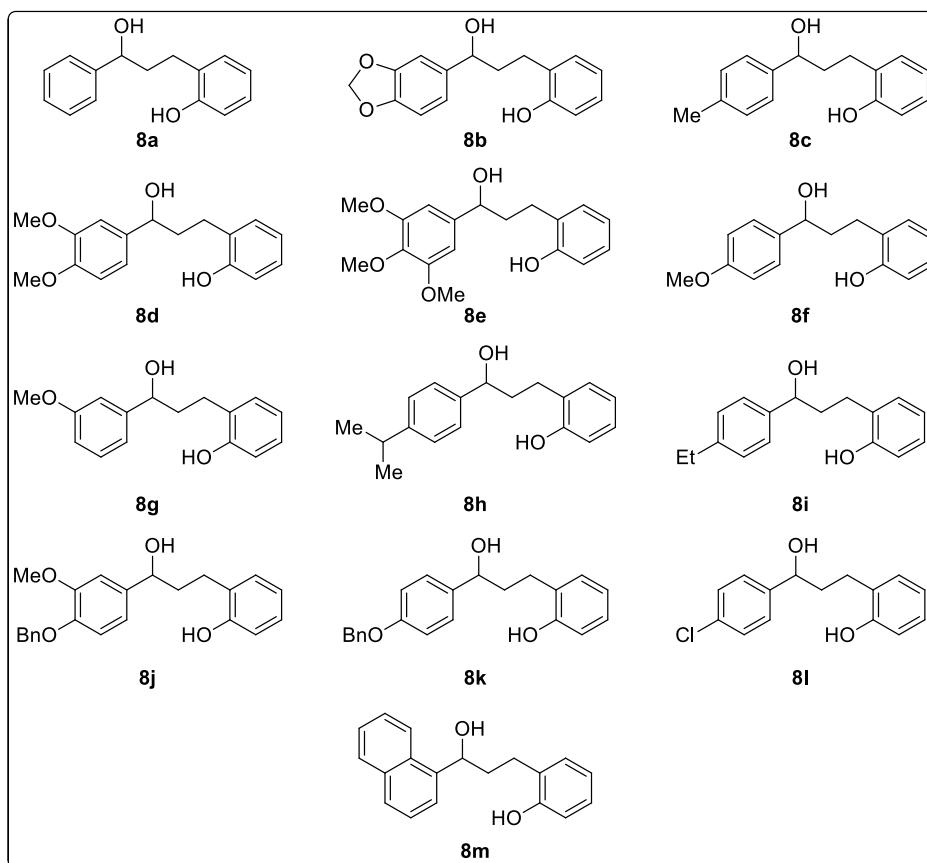
The following aryl allylic alcohols **5a-5m** were obtained from corresponding substituted benzaldehyde compounds by using vinyl magnesium bromide Grignard reaction. These aryl allylic alcohols are reported in the literature.²⁷



2-Iodophenol **6** is commercially available.

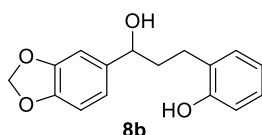


The diols **8a-8m** in one-pot were synthesized via Jeffery Heck reaction followed by sodium borohydride reduction. Compounds **8a**, **8f**, **8g** are reported in the literature.¹⁹



GP-1 (General procedure for the synthesis of 2-(3-hydroxy-3-phenylpropyl)phenols 8): In an oven dried Schlenk under nitrogen atmosphere, were added aryl allylic alcohol **5** (100 mg, 1equiv), 2-iodophenol **6** (197 mg, 1.2 equiv), Pd(OAc)₂ (5.0 mg, 3 mol%) and trimethylamine (226.6 mg, 3 equiv) followed by dry DMF (1 mL). The resulted reaction mixture was stirred at 100 °C for 72 h. Progress of the reaction was monitored by TLC till the reaction is completed. To the *in-situ* cooled reaction mixture at 0 °C, NaBH₄ (3 equiv) and DMF (1 mL) were added and stirred the reaction mixture at room temperature for 3 h. Completion of the reduction monitored by TLC. Then, the mixture was quenched with the aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na₂SO₄), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohols **8a-8m**.

GP-2 (General procedure for the synthesis of 2-phenylchroman 9): In an oven dried Schlenk under nitrogen atmosphere, were added diols **8a-8m** (1 equiv) followed by DCM (2-4 mL). The reaction mixture was cooled to $-20\text{ }^{\circ}\text{C}$ and then anhydrous FeCl_3 (1.2 equiv) was added. The resulted reaction mixture was stirred for 1.5 h at $-20\text{ }^{\circ}\text{C}$. Progress of the reaction was monitored by TLC till the reaction is completed. Then, the mixture was quenched by the addition of aqueous NaHCO_3 solution and then extracted with dichloromethane ($3 \times 15\text{ mL}$). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the flavans **9a-9m**.



2-(3-(benzo[d][1,3]dioxol-5-yl)-3-hydroxypropyl)phenol (8b): GP-1 was carried out with aryl allylic alcohol **5b** (112 mg, 1 equiv) and 2-iodophenol (197 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (141.9 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the diol **8b** (155.3 mg, 91%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 80:20), $R_f(\mathbf{5b})=0.70$, $R_f(\mathbf{8b})=0.30$, UV detection].

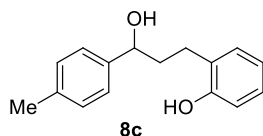
IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}}=3058, 2985, 1511, 1488, 1433, 1288, 1272, 1264, 1137, 896, 735, 708\text{cm}^{-1}$.

^1H NMR (CDCl_3 , 400 MHz): $\delta=7.13\text{--}7.08$ (t, 2H, $J=6.7\text{ Hz}$, Ar-H), 6.88–6.82 (dd, 2H, $J=7.3\text{ Hz}$, Ar-H), 6.81 (s, 1H, Ar-H), 6.71 (s, 2H, Ar-O-CH₂-O), 5.91 (s, 1H, Ar-H), 4.53–4.49 (dd, 1H, $J=10.3$ and 3.4 Hz , Ar-CH-OH), 2.93–2.66 (m, 2H), 2.08–1.85 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): $\delta=155.0$ (s, Ar-C), 147.8 (s, Ar-C), 147.2 (s, Ar-C), 135.6 (s, Ar-C), 129.5 (d, Ar-CH), 127.4 (d, Ar-CH), 120.4 (d, Ar-CH), 119.6 (d,

Ar-CH), 119.5 (d, Ar-CH), 116.9 (d, Ar-CH), 108.2 (d, Ar-CH), 106.8 (d, Ar-CH), 101.1 (t, 2H), 77.7 (d, Ar-CH-OH), 30.0 (t, CH₂), 25.2 (t, CH₂) ppm.

HR-MS (ESI+) m/z calculated for [C₁₆H₁₇O₄]⁺=[M+H]⁺: 273.1121; found 273.1120.



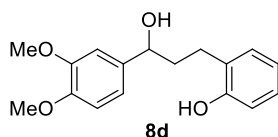
2-(3-hydroxy-3-(p-tolyl)propyl)phenol (8c): GP-1 was carried out with aryl allylic alcohol **5c** (150 mg, 1 equiv) and 2-iodophenol (267.6 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (192.6 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the diol **8c** (150.4 mg, 92%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 80:20), *R_f*(**5c**)=0.70, *R_f*(**8c**)=0.40, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3022, 2921, 2851, 1487, 1455, 1231, 1109, 1103, 1098, 1072, 809, 750 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.18 (d, 2H, *J*=7.8 Hz, Ar-H), 7.13–7.09 (m, 4H, Ar-H), 6.87 (t, 2H, *J*=7.8 Hz, Ar-H), 4.59–4.55 (dd, 1H, *J*=10.3 and 3.4 Hz, Ar-CH-OH), 2.98–2.68 (m, 2H, CH₂), 2.32 (s, 3H, Ar-CH₃), 2.14–1.86 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =154.6 (s, Ar-C), 140.8 (s, Ar-C), 137.6 (s, Ar-C), 130.6 (d, Ar-CH), 129.3 (d, 2C, 2 × Ar-CH), 127.7 (d, 2C, 2 × Ar-CH), 127.1 (s, Ar-C), 125.8 (d, Ar-CH), 120.7 (d, Ar-CH), 116.3 (d, Ar-CH), 72.8 (d, Ar-CH-OH), 39.3 (t, CH₂), 26.0 (t, CH₂), 21.1 (q, Ar-CH₃) ppm.

HR-MS (ESI+) m/z calculated for [C₁₆H₁₉O₂]⁺=[M+H]⁺: 243.1380; found 243.1382.



2-(3-(3,4-dimethoxyphenyl)-3-hydroxypropyl)phenol (8d): GP-1 was carried out with aryl allylic alcohol **5d** (100 mg, 1 equiv) and 2-iodophenol (136 mg, 1.2 equiv)

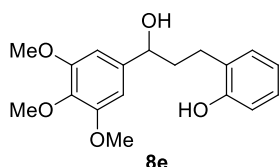
in dry DMF (1 mL) followed by reduction with sodium borohydride (97.9 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the diol **8d** (133.6 mg, 90%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 70:30), $R_f(\mathbf{5d})=0.70$, $R_f(\mathbf{8d})=0.40$, UV detection].

IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}}=3062$, 2992, 1521, 1284, 1147, 1052, 1023, 999, 745, 718, 701 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta=7.14\text{--}7.10$ (dd, 2H, $J=7.3$ and 7.3 Hz, Ar-H), 6.89–6.77 (m, 5H, Ar-H), 4.56–4.52 (dd, 1H, $J=10.3$ and 3.4 Hz, Ar-CH-OH), 3.84 (s, 3H, Ar-OCH₃), 3.83 (s, 3H, Ar-OCH₃), 2.98–2.68 (m, 2H, CH₂), 2.12–1.89 (m, 2H, CH₂) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): $\delta=154.6$ (s, Ar-C), 148.9 (s, Ar-C), 148.5 (s, Ar-C), 136.4 (s, Ar-C), 130.7 (d, Ar-CH), 127.7 (d, Ar-CH), 127.2 (s, Ar-C), 120.7 (d, Ar-CH), 118.1 (d, Ar-CH), 116.3 (d, Ar-CH), 110.9 (d, Ar-CH), 108.9 (d, Ar-CH), 72.8 (d, Ar-CH-OH), 55.9 (q, Ar-OCH₃), 55.8 (q, Ar-OCH₃), 39.2 (t, CH₂), 26.1 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for $[\text{C}_{17}\text{H}_{21}\text{O}_4]^+=[\text{M}+\text{H}]^+$: 289.1434; found 289.1432.



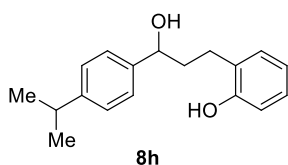
2-(3-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl)phenol (8e**):** GP-1 was carried out with aryl allylic alcohol **5e** (100 mg, 1 equiv) and 2-iodophenol (117.8 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (84.8 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 70:30) furnished the diol **8e** (134.8 mg, 95%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 60:40), $R_f(\mathbf{5e})=0.80$, $R_f(\mathbf{8e})=0.40$, UV detection].

IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}}=3287$, 3032, 2957, 2924, 2868, 1583, 1487, 1454, 1381, 1236, 1153, 1015, 830, 752 cm^{-1} .

¹H NMR (CDCl₃, 400 MHz): δ=7.10 (dd, 2H, *J*=7.3, Ar-H), 6.88–6.83 (m, 2H, Ar-H), 6.48 (s, 2H, Ar-H), 4.53–4.49 (dd, 1H, *J*=10.3 and 3.4 Hz, Ar-CH-OH), 3.79 (s, 3H, Ar-OCH₃), 3.78 (s, 3H, Ar-OCH₃), 3.77 (s, 3H, Ar-OCH₃), 3.01–2.68 (m, 2H, CH₂), 2.11–1.87 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=154.5 (s, Ar-C), 153.1 (s, Ar-C), 153.0 (s, Ar-C), 139.9 (s, Ar-C), 139.8 (s, Ar-C), 130.7 (d, Ar-CH), 127.6.8 (d, Ar-CH), 127.3 (s, Ar-C), 127.2 (s, Ar-C), 120.7 (d, Ar-CH), 116.2 (d, Ar-CH), 102.6 (d, 2 × Ar-CH), 73.1 (d, Ar-CH-OH), 60.8 (q, Ar-OCH₃), 56.0 (q, 2C, 2 × Ar-OCH₃), 39.4 (t, CH₂), 26.1 (t, CH₂) ppm.

HR-MS (ESI⁺) *m/z* calculated for [C₁₈H₂₃O₅]⁺=[M+H]⁺: 319.1540; found: 319.1544.



2-(3-hydroxy-3-(4-isopropylphenyl)propyl)phenol (8h): GP-1 was carried out with aryl allylic alcohol **5h** (100 mg, 1 equiv) and 2-iodophenol (149.9 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (141.9 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the diol **8h** (142.6 mg, 93%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 80:20), *R_f*(**5h**)=0.70, *R_f*(**8h**)=0.30, UV detection].

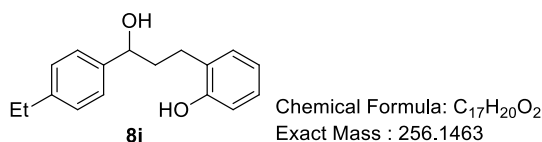
IR (MIR-ATR, 4000–600 cm⁻¹): *v*_{max}=3314, 2929, 1610, 1511, 1454, 1243, 1175, 1031, 831, 754 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ=7.19–7.13 (dd, 4H, *J*=8.3 and 7.8 Hz, Ar-H), 7.09–7.06 (t, 2H, *J*=6.8 Hz, Ar-H), 6.86–6.78 (m, 2H, Ar-H), 4.56–4.52 (dd, 1H, *J*=10.3 and 3.4 Hz, Ar-CH-OH), 2.93–2.66 (m, 3H, CH), 2.09–1.88 (m, 2H, CH₂), 1.22 (d, 3H, CH₃), 1.20 (d, 3H, CH₃), ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=154.4 (s, Ar-C), 148.4 (s, Ar-C), 141.1 (s, Ar-C), 130.6 (d, Ar-CH), 127.6 (d, Ar-CH), 127.3 (s, Ar-C), 126.6 (d, 2C, 2 × Ar-CH),

125.9 (d, 2C, 2 × Ar-CH), 120.8 (d, Ar-CH), 116.3 (d, Ar-CH), 72.9 (d, Ar-CH-OH), 39.3 (t, CH₂), 33.8 (d, CH), 26.1 (t, CH₂), 24.0 (q, 2C, 2 × CH₃) ppm.

HR-MS (ESI+) m/z calculated for [C₁₈H₂₃O₂]⁺=[M+H]⁺: 271.1693; found 271.1692.



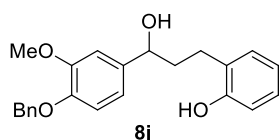
2-(3-(4-ethylphenyl)-3-hydroxypropyl)phenol (8i): GP-1 was carried out with aryl allylic alcohol **5i** (100 mg, 1 equiv) and 2-iodophenol (162.9 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (117.9mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the diol **8i** (148.5 mg, 94%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 80:20), *R_f*(**5i**)=0.70, *R_f*(**8i**)=0.40, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3054, 2964, 2927, 1733, 1510, 1455, 1373, 1244, 1045, 732, 703 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.21 (d, 2H, *J*=8.3 Hz, Ar-H), 7.16–7.10(dd, 4H, *J*=7.8 and 8.3 Hz, Ar-H), 6.90–6.80 (m, 2H), 4.60–4.56 (dd, 1H, *J*=10.3 and 3.4 Hz, Ar-CH-OH), 2.97–2.70 (m, 2H, CH₂), 2.66–2.60 (q, 2H, CH₂), 2.17–1.89 (m, 2H, CH₂), 1.23 (t, 3H, CH₃), ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =154.5 (s, Ar-C), 143.8 (s, Ar-C), 141.0 (s, Ar-C), 127.3 (s, Ar-C), 130.6 (d, 2C, 2 × Ar-CH), 128.0 (d, 2 × Ar-CH), 127.6 (d, Ar-CH), 125.9 (d, 2 × Ar-CH), 120.7 (d, Ar-CH), 116.3 (d, Ar-CH), 72.9 (d, Ar-CH-OH), 39.3 (t, CH₂), 28.5 (t, CH₂), 26.1 (t, CH₂), 15.6 (q, Ar-CH₂-CH₃), ppm.

HR-MS (ESI+) m/z calculated for [C₁₇H₂₁O₂]⁺=[M+H]⁺: 257.1536; found 257.1536.



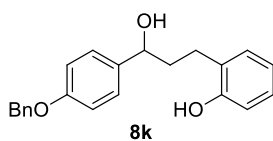
2-(3-(4-(benzyloxy)-3-methoxyphenyl)-3-hydroxypropyl)phenol (8j): GP-1 was carried out with aryl allylic alcohol **5j** (150 mg, 1 equiv) and 2-iodophenol (146.7 mg, 1.2 equiv) in dry DMF (1.5 mL) followed by reduction with sodium borohydride (105.5 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 70:30) furnished the diol **8j** (170.1 mg, 88%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 70:30), $R_f(\mathbf{5j})=0.80$, $R_f(\mathbf{8j})=0.50$, UV detection].

IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}}=3054, 2935, 1593, 1512, 1453, 1421, 1264, 1137, 1024, 896, 731, 702 \text{ cm}^{-1}$.

^1H NMR (CDCl_3 , 400 MHz): $\delta=7.41$ (d, 2H, $J=7.3$ Hz, Ar-H), 7.36–7.26 (m, 3H, Ar-H), 7.11 (t, 1H, $J=7.8$ Hz, Ar-H), 6.88–6.74 (m, 5H, Ar-H), 5.11 (s, 2H, Ar-H), 4.55–4.51 (dd, 1H, $J=10.3$ and 3.4 Hz, Ar-CH-OH), 3.84 (s, 3H, Ar-OCH₃), 2.96–2.68 (m, 2H, CH₂), 2.12–1.86 (m, 2H, CH₂) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): $\delta=154.6$ (s, Ar-C), 149.7 (s, Ar-C), 147.7 (s, Ar-C), 137.0 (s, Ar-C), 130.6 (d, Ar-CH), 127.2 (s, Ar-C), 128.5 (d, 2C, 2 \times Ar-CH), 127.8 (d, Ar-CH), 127.7 (d, Ar-CH), 127.3 (d, 2C, 2 \times Ar-CH), 120.7 (d, Ar-CH), 118.0 (d, Ar-CH), 116.3 (d, Ar-CH), 113.9 (d, Ar-CH), 109.6 (d, Ar-CH), 72.8 (d, Ar-CH-OH), 71.1 (t, CH₂), 56.0 (q, Ar-OCH₃), 39.2 (t, CH₂), 26.0 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for $[\text{C}_{23}\text{H}_{25}\text{O}_4]^+=[\text{M}+\text{H}]^+$: 365.1747; found 365.1646.



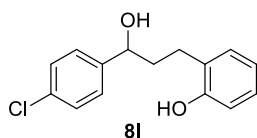
2-(3-(4-(benzyloxy)phenyl)-3-hydroxypropyl)phenol (8k): GP-1 was carried out with aryl allylic alcohol **5k** (150 mg, 1 equiv) and 2-iodophenol (165 mg, 1.2 equiv) in dry DMF (1.5 mL) followed by sodium borohydride (118.7 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the diol **8k** (180.8 mg, 91%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 70:30), $R_f(\mathbf{5k})=0.80$, $R_f(\mathbf{8k})=0.40$, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3316, 3035, 2923, 1612, 1585, 1522, 1489, 1453, 1243, 1178, 1032, 836, 755, 718 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.42–7.30 (m, 5H, Ar-H), 7.21 (d, 2H, J =8.8 Hz, Ar-H), 7.14–7.09 (m, 2H, Ar-H), 6.93–6.88 (m, 4H, Ar-H), 5.03 (s, 2H, Ar-H), 4.56–4.53 (dd, 1H, J =10.3 and 3.4 Hz, Ar-CH-OH), 2.96–2.68 (m, 2H, CH₂), 2.12–1.85 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =158.3 (s, Ar-C), 154.6 (s, Ar-C), 136.8 (s, Ar-C), 136.2 (s, Ar-C), 130.6 (d, Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 128.0 (d, Ar-CH), 127.7 (d, 2C, 2 × Ar-CH), 127.1 (s, Ar-C), 125.8 (d, 1C, Ar-CH), 120.7 (d, Ar-CH), 116.3 (d, Ar-CH), 72.8 (d, Ar-CH-OH), 39.3 (t, CH₂), 26.0 (t, CH₂), 21.1 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for [C₂₂H₂₃O₃]⁺=[M+H]⁺: 335.1642; found 335.1640.



2-(3-(4-chlorophenyl)-3-hydroxypropyl)phenol (8I): GP-1 was carried out with aryl allylic alcohol **5I** (100 mg, 1 equiv) and 2-iodophenol (156.7 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (112.8 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 80:20) furnished the diol **8I** (137.5 mg, 89%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 70:30), R_f (**5I**)=0.80, R_f (**8I**)=0.50, UV detection].

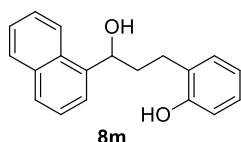
IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3023, 2933, 2855, 1488, 1480, 1456, 1239, 1152, 1106, 1078, 1049, 996, 923, 825, 806, 753, 711 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.29 (d, 2H, J =8.8 Hz, Ar-H), δ =7.23 (d, 2H, J =8.8 Hz, Ar-H), 7.14–7.09 (m, 2H, Ar-H), 6.90–6.82 (m, 2H, Ar-H), 4.59–4.56 (dd, 1H, J =10.3 and 3.4 Hz, Ar-CH-OH), 2.96–2.68 (m, 2H, CH₂), 2.08–1.86 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =154.3 (s, Ar-C), 142.4 (s, Ar-C), 133.4 (s, Ar-C), 130.6 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 127.8 (d, Ar-CH), 127.2 (d, 2C, 2 ×

Ar-CH), 126.9 (s, Ar-C), 120.9 (d, Ar-CH), 116.1 (d, Ar-CH), 72.3 (d, Ar-CH-OH), 39.4 (t, CH₂), 25.8 (t, CH₂) ppm.

HR-MS (ESI+) m/z calculated for [C₁₅H₁₆ClO₂]⁺=[M+H]⁺: 245.0728; found 245.0726.



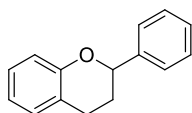
2-(3-hydroxy-3-(naphthalen-1-yl)propyl)phenol (8m): GP-1 was carried out with aryl allylic alcohol **5m** (100 mg, 1 equiv) and 2-iodophenol (143.5 mg, 1.2 equiv) in dry DMF (1 mL) followed by reduction with sodium borohydride (104 mg, 5 equiv) in additional DMF (1 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the diol **8m** (137.5 mg, 91%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 80:20), *R_f*(**5m**)=0.90, *R_f*(**8m**)=0.60, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3315, 2918, 2849, 1593, 1489, 1456, 1377, 1240, 1176, 1064, 1039, 1001, 799, 778, 754 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.83 (t, 1H, *J*=7.3 Hz, Ar-H), 7.80–7.74 (dd, 2H, *J*=7.8 Hz, Ar-H), 7.61 (d, 1H, *J*=7.3 Hz, Ar-H), 7.47–7.40 (m, 3H, Ar-H), 7.17–7.13 (m, 2H, Ar-H), 6.91 (t, 2H, *J*=6.8 Hz, Ar-H), 5.40–5.36 (dd, 1H, *J*=10.3 and 3.4 Hz, Ar-CH-OH), 3.11–2.76 (m, 2H, CH₂), 2.23–2.14 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =154.6 (s, Ar-C), 139.5 (s, Ar-C), 133.7 (s, Ar-C), 130.6 (d, Ar-CH), 130.0 (s, Ar-C), 128.9 (d, Ar-CH), 128.2 (d, Ar-CH), 127.8 (d, 2C, 2 × Ar-CH), 126.2 (d, Ar-CH), 125.6 (d, Ar-CH), 125.4 (s, Ar-C), 122.8 (d, Ar-CH), 122.6 (d, Ar-CH), 120.9 (d, Ar-CH), 116.3 (d, Ar-CH), 69.8 (d, Ar-CH-OH), 38.3 (t, CH₂), 26.1 (t, CH₂) ppm.

HR-MS (ESI+) m/z calculated for [C₁₉H₁₉O₂]⁺=[M+H]⁺: 279.1380; found 279.1379.



9a

2-phenylchromane (9a): GP-2 was carried out with diol **8a** (84 mg, 1 equiv), dry DCM (3 mL) and anhydrous FeCl₃ (71.6 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 99:1) furnished the flavan **9a** (58.3 mg, 72%) as a white solid, which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 98:2), *R_f*(**8a**)=0.05, *R_f*(**9a**)=0.80, UV detection].

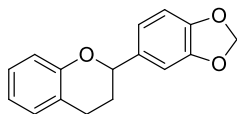
M. P.: 45–46 °C.

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3022, 2849, 1581, 1487, 1454, 1302, 1232, 1068, 751, 573 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.46–7.32 (m, 5H, Ar-H), 7.17–7.10 (m, 2H, Ar-H), 6.95–6.88 (m, 2H, Ar-H), 5.10–5.07 (dd, 1H, *J*=10.3 and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.06–2.78 (m, 2H, CH₂), 2.26–2.06 (m, 2H, CH₂) ppm. .

¹³C NMR (CDCl₃, 100 MHz): δ =155.1 (s, Ar-C), 141.7 (s, Ar-C), 129.6 (d, Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, Ar-CH), 126.0 (d, 2C, 2 × Ar-CH), 121.8 (s, Ar-C), 120.3 (d, Ar-CH), 117.0 (d, Ar-CH), 77.8 (d, Ar-CH-CH₂-CH₂), 30.0 (t, CH₂), 25.1 (t, CH₂) ppm.

HR-MS (ESI⁺) *m/z* calculated for [C₁₅H₁₅O]⁺=[M+H]⁺: 211.1117; found 211.1115



9b

2-(benzo[d][1,3]dioxol-5-yl)chromane (9b): GP-2 was carried out with diol **8b** (100 mg, 1 equiv), dry DCM (3 mL) and anhydrous FeCl₃ (71.3 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the flavan **9b** (65.1 mg, 70%) as a white solid, which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 97:3), *R_f*(**8b**)=0.05, *R_f*(**9b**)=0.80, UV detection].

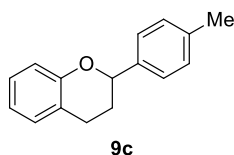
M. P.: 198–199 °C

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3031, 2853, 1610, 1500, 1410, 1320, 1162, 1050, 830, 588 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.15–7.09 (dd, 2H, J =8.3 and 7.3 Hz, Ar-H), 6.95 (s, 1H, Ar-H), 6.91–6.87 (d, 2H, J =7.8 Hz, Ar-H), 5.97 (s, 2H, Ar-O-CH₂-O), 4.99–4.96 (dd, 1H, J =10.3 and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.04–2.80 (m, 2H, Ar-O-CH-CH₂-), 2.21–2.03 (m, 2H, Ar-O-CH-CH₂-CH₂-) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =155.0 (s, Ar-C), 147.8 (s, Ar-C), 147.2 (s, Ar-C), 135.6 (s, Ar-C), 129.5 (d, Ar-CH), 127.4 (d, Ar-CH), 120.4 (d, Ar-CH), 119.6 (d, Ar-CH), 119.5 (d, Ar-CH), 116.9 (d, Ar-CH), 108.2 (d, Ar-CH), 106.8 (d, Ar-CH), 101.1 (t, 2H, Ar-O-CH₂-O), 77.7 (d, Ar-CH-CH₂-CH₂), 30.0 (t, CH₂), 25.2 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for [C₁₆H₁₅O₃]⁺=[M+H]⁺: 255.1016; found 255.1018.



2-(*p*-tolyl)chromane (9c): GP-2 was carried out with diol **8c** (167 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl₃ (134.3 mg, 1.2 equiv) at –20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the flavan **9c** (89.5 mg, 72%) as a white solid which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 97:3), R_f (**8c**)=0.05, R_f (**9c**)=0.80, UV detection].

M. P.: 92–93 °C.

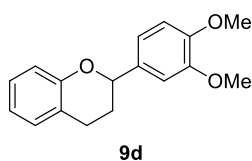
IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3054, 2923, 1514, 1487, 1233, 1072, 893, 701, cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.35 (d, 2H, J =7.8 Hz, Ar-H), 7.22 (d, 2H, J =7.8 Hz, Ar-H), 7.16–7.10 (dd, 2H, J =8.3 and 7.3 Hz, Ar-H), 6.94–6.88 (m, 4H, Ar-H),

5.07–5.04 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.06–2.79 (m, 2H, CH₂), 2.39 (s, 3H, Ar-CH₃), 2.25–2.06 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): $\delta=155.2$ (s, Ar-C), 138.7 (s, Ar-C), 137.5 (s, Ar-C), 129.6 (d, Ar-CH), 129.2 (d, 2C, 2 \times Ar-CH), 127.3 (d, Ar-CH), 126.0 (d, 2C, 2 \times Ar-CH), 121.8 (s, Ar-C), 120.3 (d, Ar-CH), 117.0 (d, Ar-CH), 77.7 (d, Ar-CH-CH₂-CH₂), 29.9 (t, CH₂), 25.2 (t, CH₂), 21.2 (q, Ar-CH₃) ppm.

HR-MS (ESI+) m/z calculated for [C₁₆H₁₇O]⁺=[M+H]⁺: 225.1274; found 225.1272.



2-(3,4-dimethoxyphenyl)chromane (9d): GP-2 was carried out with diol **8d** (120 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl₃ (81.1 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:5) furnished the flavan **9d** (76.2 mg, 68%) as a white solid, which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 93:7), $R_f(\mathbf{8d})=0.10$, $R_f(\mathbf{9d})=0.80$, UV detection].

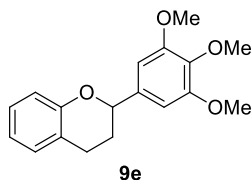
M. P.: 98–99 °C

IR (MIR-ATR, 4000–600 cm⁻¹): $\nu_{max}=2988$, 2891, 1800, 1707, 1480, 1360, 1110, 1050, 860, 780 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): $\delta=7.14$ – 7.09 (dd, 2H, $J=7.3$ and 6.8 Hz, Ar-H), 6.98 (s, 1H, Ar-H), 6.96 (d, 2H, $J=1.9$ Hz, Ar-H), 6.92–6.86 (m, 3H, Ar-H), 5.01–4.98 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.90 (s, 3H, Ar-OCH₃), 3.89 (s, 3H, Ar-OCH₃), 3.05–2.79 (m, 2H, CH₂), 2.21–2.07 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): $\delta=155.1$ (s, Ar-C), 149.0 (s, Ar-C), 148.7 (s, Ar-C), 134.2 (s, Ar-C), 129.6 (d, Ar-CH), 127.3 (d, Ar-CH), 121.7 (s, Ar-C), 120.3 (d, Ar-CH), 118.5 (d, Ar-CH), 116.9 (d, Ar-CH), 111.0 (d, Ar-CH), 109.3 (d, Ar-CH), 77.8 (d, Ar-CH-CH₂-CH₂), 56.0 (q, Ar-OCH₃), 55.9 (q, Ar-OCH₃), 30.0 (t, CH₂), 25.3 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for [C₁₇H₁₉O₃]⁺=[M+H]⁺: 271.1329; found 271.1337.



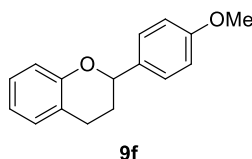
2-(3,4,5-trimethoxyphenyl)chromane (9e): GP-2 was carried out with diol **8e** (80 mg, 1 equiv), dry DCM (3 mL) and anhydrous FeCl₃ (48.9 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 93:7) furnished the flavan **9e** (52.8 mg, 70%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**8e**)=0.10, R_f(**9e**)=0.90, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3368, 3026, 2890, 1603, 1501, 1486, 1440, 1241, 1036, 933, 811, 699 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.12 (dd, 1H, *J*=7.3 and 7.3 Hz, Ar-H), 7.09 (d, 1H, *J*=7.3 Hz, Ar-H), 6.91 (d, 1H, *J*=7.8 Hz, Ar-H), 6.88 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 6.65 (s, 2H, 2 × Ar-H), 4.98–4.95 (dd, 1H, *J*=10.3 and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.87 (s, 6H, 2 × Ar-OCH₃), 3.81 (s, 3H, Ar-OCH₃), 3.10–2.75 (m, 2H, CH₂), 2.25–2.00 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =155.0 (s, Ar-C), 153.3 (s, 2C, 2 × Ar-C), 137.5 (s, Ar-C), 137.3 (s, Ar-C), 129.5 (d, Ar-CH), 127.3 (d, Ar-CH), 121.7 (s, Ar-C), 120.4 (d, Ar-CH), 116.9 (d, Ar-CH), 103.0 (d, 2C, 2 × Ar-CH), 78.1 (d, Ar-CH-CH₂-CH₂), 60.8 (q, Ar-OCH₃), 56.1 (q, 2C, 2 × Ar-OCH₃), 30.1 (t, CH₂), 25.3 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for [C₁₈H₂₁O₄]⁺=[M+H]⁺: 371.1434; found: 371.1430.



2-(4-methoxyphenyl)chromane (9f): GP-2 was carried out with diol **8f** (101.5 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl₃ (76.5 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:5) furnished the flavan **9f** (82.1 mg, 87%) as a white solid, which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 93:7), $R_f(\mathbf{8f})=0.10$, $R_f(\mathbf{9f})=0.80$, UV detection].

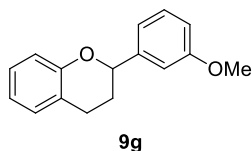
M. P.: 85–86 °C

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3024, 2851, 1582, 1487, 1233, 1072, 995, 567 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.36 (d, 2H, $J=8.8$ Hz, Ar-H), 7.12 (dd, 1H, $J=7.8$ and 7.3 Hz, Ar-H), 7.09 (d, 1H, $J=7.3$ Hz, Ar-H), 6.93 (d, 2H, $J=8.8$ Hz, Ar-H), 6.90 (d, 1H, $J=7.3$ Hz, Ar-H), 6.88 (d, 1H, $J=7.3$ and 7.3 Hz, Ar-H), 5.01 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.82 (s, 3H, Ar-OCH₃), 3.15–2.75 (m, 2H, CH₂), 2.25–2.00 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =159.3 (s, Ar-C), 155.2 (s, Ar-C), 133.8 (s, Ar-C), 129.5 (d, Ar-CH), 127.4 (d, Ar-CH), 127.3 (d, 2C, 2 × Ar-CH), 121.8 (s, Ar-C), 120.2 (d, Ar-CH), 116.9 (d, Ar-CH), 113.9 (d, 2C, 2 × Ar-CH), 77.5 (d, Ar-CH-CH₂-CH₂), 55.3 (q, Ar-OCH₃), 29.8 (t, CH₂), 25.3 (t, CH₂) ppm.

HR-MS (ESI⁺) m/z calculated for [C₁₆H₁₇O₂]⁺=[M+H]⁺: 241.1223; found 241.1223.



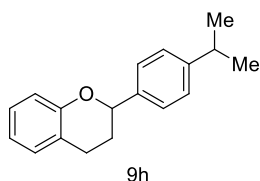
2-(3-methoxyphenyl)chromane (9g): GP-2 was carried out with diol **8g** (120 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl₃ (73.1 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 93:7) furnished the flavan **9g** (69.2 mg,

62%) as a semi solid [TLC control (petroleum ether/ethyl acetate 93:7), $R_f(\mathbf{8g})=0.10$, $R_f(\mathbf{9g})=0.80$, UV detection].

IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}}=2920, 2840, 1514, 1234, 703, 588 \text{ cm}^{-1}$. ^1H NMR (CDCl_3 , 400 MHz): $\delta=7.31$ (t, 1H, $J=8.3$ Hz, Ar-H), 7.16–7.09 (m, 2H, Ar-H), 7.02 (d, 2H, $J=7.8$ Hz, Ar-H), 6.94–6.87 (m, 3H, Ar-H), 5.07–5.04 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH- $\text{CH}_2\text{-CH}_2$), 3.83 (s, 3H, Ar-OCH₃), 3.05–2.78 (m, 2H, CH₂), 2.24–2.06 (m, 2H, CH₂) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): $\delta=159.7$ (s, Ar-C), 155.0 (s, Ar-C), 143.3 (s, Ar-C), 129.6 (d, Ar-CH), 129.5 (d, Ar-CH), 127.4 (d, Ar-CH), 121.8 (s, Ar-C), 120.4 (d, Ar-CH), 118.3 (d, Ar-CH), 116.9 (d, Ar-CH), 113.3 (d, Ar-CH), 111.6 (d, Ar-CH), 77.6 (d, Ar-CH- $\text{CH}_2\text{-CH}_2$), 55.3 (q, Ar-OCH₃), 29.9 (t, CH₂), 25.1 (t, CH₂) ppm.

HR-MS (ESI+) m/z calculated for $[\text{C}_{16}\text{H}_{17}\text{O}_2]^+=[\text{M}+\text{H}]^+$: 241.1223; found 241.1223.

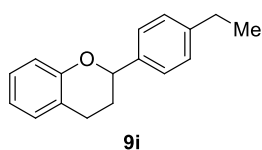


2-(4-isopropylphenyl)chromane (9h): GP-2 was carried out with diol **8h** (105 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl_3 (62.2 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 97:3) furnished the flavan **9h** (73.5 mg, 75%) as a semi-solid [TLC control (petroleum ether/ethyl acetate 97:3), $R_f(\mathbf{8h})=0.05$, $R_f(\mathbf{9h})=0.90$, UV detection].

IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}}=3037, 2923, 2852, 1456, 1234, 1050, 737, 568 \text{ cm}^{-1}$.

^1H NMR (CDCl_3 , 400 MHz): $\delta=7.35$ (d, 2H, $J=8.3$ Hz, Ar-H), 7.24 (d, 2H, $J=8.3$ Hz, Ar-H), 7.13–7.07 (dd, 2H, $J=8.3$ and 7.3 Hz, Ar-H), 6.91–6.84 (m, 2H, Ar-H), 5.03–5.00 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH- $\text{CH}_2\text{-CH}_2$), 3.03–2.78 (m, 2H, CH₂), 2.82–2.76 (m, 1H, CH), 2.21–2.04 (m, 2H, CH₂), 1.26 (d, 3H, CH₃), 1.24 (d, 3H, CH₃), ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=155.2 (s, Ar-C), 148.5 (s, Ar-C), 139.0 (s, Ar-C), 129.6 (d, Ar-CH), 127.3 (d, Ar-CH), 126.6 (d, 2C, 2 × Ar-CH), 126.1 (d, 2C, 2 × Ar-CH), 121.8 (s, Ar-C), 120.3 (d, Ar-CH), 117.0 (d, Ar-CH), 77.8 (d, Ar-CH-CH₂-CH₂), 33.9 (d, CH), 29.8 (t, CH₂), 25.3 (t, CH₂), 24.1 (q, CH₃), 24.0 (q, CH₃), ppm.
HR-MS (ESI+) m/z calculated for [C₁₈H₂₁O]⁺=[M+H]⁺: 253.1587; found 253.1586.



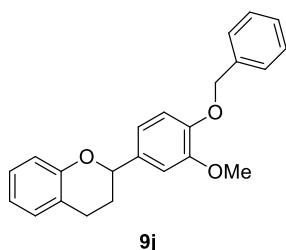
2-(4-ethylphenyl)chromane (9i): GP-2 was carried out with diol **8i** (105 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl₃ (62.2 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the flavan **9i** (73.2 mg, 75%) as a white solid which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 97:3), *R_f*(**8i**)=0.05, *R_f*(**9i**)=0.80, UV detection].
M. P.: 56–57 °C.

IR (MIR-ATR, 4000–600 cm⁻¹): *v*_{max}=3020, 2924, 2850, 1582, 1487, 1455, 1302, 1232, 1048, 751 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ=7.34 (d, 2H, *J*=8.3 Hz, Ar-H), 7.22 (t, 2H, *J*=8.3 Hz, Ar-H), 7.13–7.07 (dd, 2H, *J*=7.8 and 7.3 Hz, Ar-H), 6.91–6.85 (dd, 2H, *J*=8.3 and 7.3 Hz, Ar-H, Ar-O-CH), 5.04–5.01 (dd, 1H, *J*=10.3 and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.03–2.76 (m, 2H, CH₂), 2.68–2.63 (q, 2H, CH₂), 2.22–2.04 (m, 2H, CH₂), 1.24 (s, 3H, Ar-CH₃), ppm.

¹³C NMR (CDCl₃, 100 MHz): δ=155.2 (s, Ar-C), 143.9 (s, Ar-C), 138.9 (s, Ar-C), 129.5 (d, Ar-CH), 128.0 (d, 2C, 2 × Ar-CH), 127.3 (d, Ar-CH), 126.1 (d, 2C, 2 × Ar-CH), 121.8 (s, Ar-C), 120.3 (d, Ar-CH), 116.9 (d, Ar-CH), 77.8 (d, Ar-CH-CH₂-CH₂), 29.8 (t, CH₂), 28.6 (t, CH₂), 25.2 (q, Ar-CH₃), ppm.

HR-MS (ESI+) m/z calculated for [C₁₇H₁₉O]⁺=[M+H]⁺: 239.1430; found 239.1430.



2-(4-(benzyloxy)-3-methoxyphenyl)chromane (9j): GP-2 was carried out with diol **8j** (80.3 mg, 1 equiv), dry DCM (3 mL) and anhydrous FeCl₃ (44.9 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 93:7) furnished the flavan **9f** (38.8 mg, 51%) as a white solid which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 93:7), $R_f(\mathbf{8j})=0.05$, $R_f(\mathbf{9j})=0.80$, UV detection].

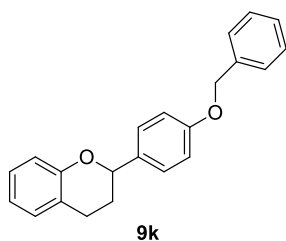
M. P.: 91–92 °C.

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3028, 2848, 1581, 1487, 1259, 1223, 1052, 1025, 852, 736 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.45 (d, 2H, $J=7.8$ Hz, Ar-H), 7.37 (t, 2H, $J=6.8$ Hz, Ar-H), 7.30 (t, 1H, $J=7.8$ Hz, Ar-H), 7.14–7.08 (m, 2H, Ar-H), 7.00 (s, 1H, Ar-H), 6.92–6.86 (m, 4H, Ar-H), 5.17 (s, 2H, Ar-H), 5.00–4.97 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.91 (s, 3H, Ar-OCH₃), 3.04–2.78 (m, 2H, CH₂), 2.21–2.05 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =155.1 (s, Ar-C), 149.7 (s, Ar-C), 147.8 (s, Ar-C), 137.2 (s, Ar-C), 134.8 (s, Ar-C), 129.5 (d, Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 127.8 (d, Ar-CH), 127.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 121.8 (s, Ar-C), 120.4 (d, Ar-CH), 118.4 (d, Ar-CH), 116.9 (d, Ar-CH), 113.9 (d, Ar-CH), 109.9 (d, Ar-CH), 77.8 (d, Ar-O-CH), 71.1 (t, Ar-CH-CH₂-CH₂), 56.0 (q, Ar-OCH₃), 29.9 (t, CH₂), 25.3 (t, CH₂) ppm.

HR-MS (ESI+) m/z calculated for [C₂₃H₂₃O₃]⁺=[M+H]⁺: 347.1642; found 347.1643.



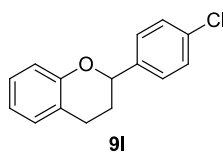
2-(4-(benzyloxy)phenyl)chromane (9k): GP-2 was carried out with diol **8k** (160 mg, 1 equiv), dry DCM (5 mL) and anhydrous FeCl₃ (97.9 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:5) furnished the flavan **9k** (102.6 mg, 68%) as a white solid which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 95:5), *R_f*(**8k**)=0.10, *R_f*(**9k**)=0.80, UV detection].

M. P.: 83–84 °C.

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3032, 2851, 1581, 1487, 1272, 1229, 1055, 1025, 791, 751, 696 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ =7.47–7.33 (m, 7H, Ar-H), 7.16–7.10 (dd, 2H, *J*=7.3 and 7.3 Hz, Ar-H), 7.02 (d, 2H, *J*=8.3 Hz, Ar-H), 6.93–6.88 (dd, 2H, *J*=7.8 and 6.4 Hz, Ar-H), 5.10 (s, 2H, Ar-H), 5.04–5.01 (dd, 1H, *J*=10.3 and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.05–2.97 (m, 2H, CH₂), 2.23–2.06 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =158.5 (s, Ar-C), 155.2 (s, Ar-C), 137.0 (s, Ar-C), 134.1 (s, Ar-C), 129.6 (d, Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 128.0 (d, Ar-CH), 127.5 (d, 2C, 2 × Ar-CH), 127.4 (d, 2C, 2 × Ar-CH), 127.3 (d, Ar-CH), 120.3 (d, Ar-CH), 117.0 (d, Ar-CH), 114.9 (d, 2C, 2 × Ar-CH), 77.5 (d, Ar-CH-CH₂-CH₂), 70.1 (t, Ar-O-CH₂-O), 29.8 (t, CH₂), 25.3 (t, CH₂) ppm.

HR-MS (ESI+) *m/z* calculated for [C₂₂H₂₁O₂]⁺=[M+H]⁺: 317.1536; found 317.1535.



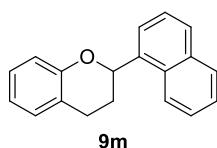
2-(4-chlorophenyl)chromane (9l): GP-2 was carried out with diol **8l** (66 mg, 1 equiv), dry DCM (3 mL) and anhydrous FeCl₃ (49.3 mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 93:7) furnished the flavan **9l** (24.6 mg, 40%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), *R_f*(**8l**)=0.05, *R_f*(**9l**)=0.70, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3020, 2850, 1583, 1457, 1232, 1050, 891, 751 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =7.35 (s, 4H, Ar-H), 7.14–7.07 (m, 2H, Ar-H), 6.90–6.86 (m, 2H, Ar-H), 5.05–5.02 (dd, 1H, *J*=10.3 and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.03–2.75 (m, 2H, CH₂), 2.21–1.99 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): δ =154.8 (s, Ar-C), 140.2 (s, Ar-C), 133.5 (s, Ar-C), 129.6 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 127.4 (d, Ar-CH), 127.3 (d, 2C, 2 × Ar-CH), 120.5 (d, Ar-CH), 116.9 (d, Ar-CH), 77.0 (d, Ar-CH-CH₂-CH₂), 29.9 (t, CH₂), 24.9 (t, CH₂) ppm.

HR-MS (ESI+) *m/z* calculated for [C₁₅H₁₄ClO]⁺=[M+H]⁺: 245.0728; found 245.0726.



2-(naphthalen-1-yl)chromane (9m): GP-2 was carried out with diol **8m** (105.5 mg, 1 equiv), dry DCM (4 mL) and anhydrous FeCl₃ (73.8mg, 1.2 equiv) at -20 °C for 1.5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:5) furnished the flavan **9m** (71.04 mg, 72%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 97:3), *R_f*(**8m**)=0.05, *R_f*(**9m**)=0.80, UV detection].

IR (MIR-ATR, 4000–600 cm⁻¹): ν_{max} =3051, 2927, 1581, 1456, 1302, 1231, 1111, 799, 732, 582 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ =8.09 (d, 1H, *J*=8.8 Hz, Ar-H), 7.93 (dd, 1H, *J*=7.3 and 6.3 Hz, Ar-H), 7.88 (d, 1H, *J*=8.3 Hz, Ar-H), 7.76 (d, 1H, *J*=7.3 Hz, Ar-H),

7.59–7.52 (m, 3H, Ar-H), 7.23–7.19 (m, 2H, Ar-H), 7.04–6.96 (m, 2H, Ar-H), 5.85–5.82 (dd, 1H, $J=10.3$ and 2.4 Hz, Ar-CH-CH₂-CH₂), 3.20–2.87 (m, 2H, CH₂), 2.48–2.24 (m, 2H, CH₂) ppm.

¹³C NMR (CDCl₃, 100 MHz): $\delta=155.3$ (s, Ar-C), 137.0 (s, Ar-C), 133.8 (s, Ar-C), 130.3 (s, Ar-C), 129.7 (d, Ar-CH), 129.0 (d, Ar-CH), 128.4 (d, Ar-CH), 127.5 (d, 2C, 2 \times Ar-CH), 126.2 (d, Ar-CH), 125.6 (d, Ar-CH), 125.5 (s, Ar-C), 123.5 (d, Ar-CH), 123.1 (d, 2C, 2 \times Ar-CH), 122.0 (d, Ar-CH), 120.5 (d, Ar-CH), 117.1 (d, Ar-CH), 75.1 (d, Ar-CH-CH₂-CH₂), 29.1 (t, CH₂), 25.6 (t, CH₂) ppm.

HR-MS (ESI+) m/z calculated for [C₁₉H₁₇O]⁺=[M+H]⁺: 261.1274; found 261.127

1.7 References and Notes:

-
1. Poudel, T. N.; Lee, Y. R. *Org. Biomol. Chem.* **2014**, *12*, 919.
 2. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
 3. a) White, T. J. *Sci. Food Agric.* **1957**, *8*, 377. b) Anderson, B. M.; Noble, C. J. *Agric. Food Chem.* **1977**, *25*, 28
 4. a) Takasugi, M.; Kumagai, Y.; Nagao, S.; Masamune, T.; Shirata, A.; Takahashi, K. *Chem. Lett.* **1980**, 1459. b) Sahai, R.; Agarwal, S. K.; Rastogi, R. P. *Phytochemistry* **1980**, *19*, 1560. c) Ghosal, S.; Saini, K. S.; Sinha, B. N. *J. Chem. Res.* **1983**, 330, 2601. d) Bauker, D. J.; Selway, J. W. T.; Batchelor, T. F.; Tisadale, M.; Caldwell, I. C.; Young, D. A. B. *Nature* **1981**, 292, 369. e) E. Merck A. G., Netherlands Patent Appl. 61614, 645. d), April 21, 1967; Ger. Appl. Oct. 20, 1965; *Chem. Abstr.* **1968**, *68*, 68885b. f) Takasugi, M.; Niino, N.; Nagao, S.; Aivetai, M.; Masamune, T.; Shirata, A.; Takahashi, K. *Chem. Lett.* **1984**, 689. g) Bhattacharya, S. K.; Ghosal, S.; Chaudhuri, R. K.; Sanyal, A. K. *J. Pharm. Sci.* **1972**, *61*, 1838.
 5. Ho, C. T.; Chen, Q.; Shi, H.; Zhang, K. Q.; Rosen, R. T., Antioxidative effect of polyphenol extract prepared from various Chinese teas. *Prev. Med.* **1992**, *21*, 520.

-
6. Lindahl, M.; Tagesson, C. Selective inhibition of groups II phospholipase A2 by quercetin. *Inflammation* **1993**, *17*, 573.
 7. Evans, C. A.; Miller, N. J.; Paganga, G. *Free Radical biology and medicine* **1996**, *7*, 933.
 8. Chang, W. S.; Lee, Y. J.; Lu, F. J.; Chiang, H. C. Inhibitory effects of flavonoids on xanthine oxidase. *Anticancer Res.* **1993**, *13*, 2165.
 9. Elliott, A. J.; Scheiber, S. A.; Thomas, C.; Pardini, R. S. Inhibition of glutathione reductase by flavonoids. A structure-activity study. *Biochem. Pharmacol.* **1992**, *44*, 1603.
 10. Middleton, E.; Kandaswami, C. Effects of flavonoids on immune and inflammatory functions. *Biochem. Pharmacol.* **1992**, *43*, 1167.
 11. Cody, B.; Middleton, E.; Harborne, J.B., eds. *Plant flavonoids in biology and medicine*. New York: Alan Liss; **1986**, 15.
 12. a) Abdel-Razik, A. F.; Nassar, M. I.; El-Khrisy, E. D. A.; Dawidar, A. A. M.; Mabry, T. J. *Fitoterapia*, **2005**, *76*, 762. b) Morikawa, T.; Xu, F. M.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull.* **2006**, *54*, 1530. c) Li, L. J.; Zhang, Y.; Zhang, P.; Pi, H. F.; Ruan, H. L.; Wu, J. Z. *J. Asian Nat. Prod. Res.* **2011**, *13*, 367. e) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, *3*, 465. f) Veitch, N. C.; Grayer, R. *J. Nat. Prod. Rep.* **2011**, *28*, 1626.
 13. Kaneda, N.; Pezzuto, J. M.; Soejarto, D. D.; Kinghorn, A. D.; Farnsworth, N. R. *J. Nat. Prod.* **2012**, *75*, 82.
 14. Garo, E.; Maillard, M.; Antus, S.; Mavi, S.; Hostettmann, K. *Phytochemistry* **1996**, *43*, 1265.
 15. Meksuriyen, D.; Cordell, G. A. *J. Sci. Soc. Thailand* **1988**, *14*, 3.
 16. Ghosal, S.; Singn, S. K.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 151.
 17. Hodgetts, K. J. *Tetrahedron* **2005**, *61*, 6860.
 18. Xue, J.; Zhang, X.; Chen, X.; Zhang, Y. Li. *Synthetic Commun.* **2003**, *33*, 3527.
 19. (a) Oyama, K.; Kondo, T. *J. Org. Chem.* **2004**, *69*, 5240. (b) Jimenez, M. C.; Miranda, M. A.; Tormos, R. *Tetrahedron* **1997**, *53*, 14729.
 20. Bird, T. G. C.; Brown, B. R.; Stuart, I. A.; Tyrrell, A. W. R. *J. Chem. Soc.* **1983**, *8*, 1831.
 21. Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.
 22. Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *Chem. Commun.* **1999**, 691.

-
23. Hodgetts, K. J. *Tetrahedron* **2005**, *61*, 6860.
24. Choi, E. T.; Lee, M. H.; Kim, Y.; Park, Y. S. *Tetrahedron* **2008**, *64*, 1515.
25. S. J. Gharpure, S. J.; Sathiyarayananand, A. M.; Jonnalagadda, P. *Tetrahedron* **2008**, *49*, 2974.
26. Yamamoto, Y.; Itonaga, K. *Org. Lett.* **2009**, *11*, 717.
27. a) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. b) Yamamoto, Y.; Itonaga, K. *Org. Lett.* **2009**, *11*, 717.
28. Mazimba, O.; Masesane, I. B.; Majinda, R. R. *Tetrahedron* **2011**, *52*, 6716.
29. S. J. Gharpure, S. J.; Sathiyarayananand, A. M.; Vuram, P. K. *RSC Adv.* **2013**, *3*, 18279.
30. Ramulu, B. V.; Mahendar, L.; Krishna, J.; Reddy, A. G. K.; Satyanarayana, G. *Tetrahedron* **2013**, *69*, 8305.
31. Suchand, B.; Mrithunjoy, K.; Krishna, J. *RSC Adv.* **2014**, *4*, 13941.