Chapter 2

Diastereoselective Synthesis of *trans*-4-Arylchroman-3-ols via Ar–C Bond-Forming Intramolecular Friedel–Crafts Epoxide-Arene Cyclization Reaction and Its Applications in the Synthesis of *cis*-4-Arylchroman-3-ols and Chroman-Fused 2,3-Dihydrobenzofuran

Work of this Chapter has resulted in the following two publications:

1. Devi, R., Kalita, T., and Das, S. K. Brønsted acid-catalysed intramolecular ring opening of 2-(aryloxymethyl)-3-aryloxiranes leading to *trans*-4-arylchroman-3-ols: scope and limitation. *RSC Advances*, 5:39692-39696, 2015. (communication)
2. Devi, R., Gogoi, D., Bora, P., and Das, S. K. Synthesis of diverse catechin congeners via diastereoselective intramolecular epoxy-arene cyclization. *Tetrahedron*, 72(32):4878-4888, 2016. (full paper)

2.1. Introduction

Chroman-3-ol **1** (Figure 2.1) is a ubiquitous structural unit in a large number of biologically important natural products and synthetic compounds ─ selected examples being flavon-3-ols **2** [1], 4-arylflavan-3-ols **3** [1], 6a-hydroxypterocarpans such as variabilin **4** [2], and compound **5** (a selective 5-HT_2 receptor agonist) [3]. Compounds bearing the chroman-3-ol structural unit exert a broad spectrum of biological activities; some of them essentially very much important, such as antioxidant, anticancer, antifungal, antiarteriosclerotic, and antibacterial effects [4]. One of the important structural features of flavon-3-ols **2**, as evidenced by their representative members catechin **2a**, epicatechin **2b**, gallocatechin **2c**, and epigallocatechin **2d**, is that they all bear highly electron-rich aryl rings. Another common feature of these molecules is that they all undergo oxidative oligomerization *in vivo* through the 4-position of the chroman ring, and hence potential bioaccessibility of the parent flavon-3-ols is reduced [4]. Along this line, we hypothesized that with the congeneric 4-arylchroman-3-ols **4** (Figure 2.1), oxidative oligomerization would be suppressed, and the relevant biological activities might be retained/improved. To the best of our knowledge, 4-arylchroman-3-ols have never been isolated from nature although there has been a recent report of isolation of their derivatives [5]. We believed that synthesis of all stereoisomers of this class of molecules would benefit in their evaluation as bioactive scaffolds. An equally enthralling inspiration for their synthesis lied in their probable application in the synthesis of chroman-based polycyclic molecules (*vide infra*).

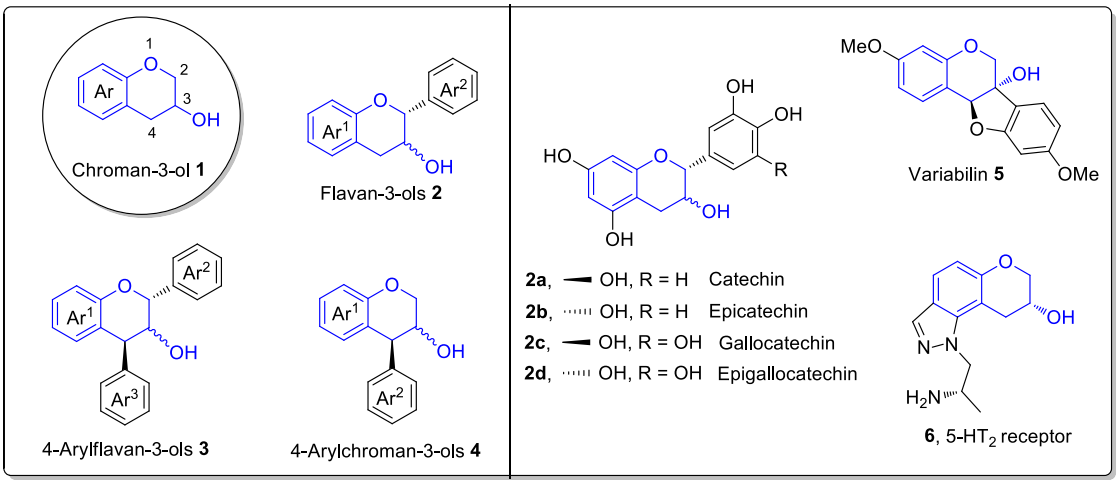
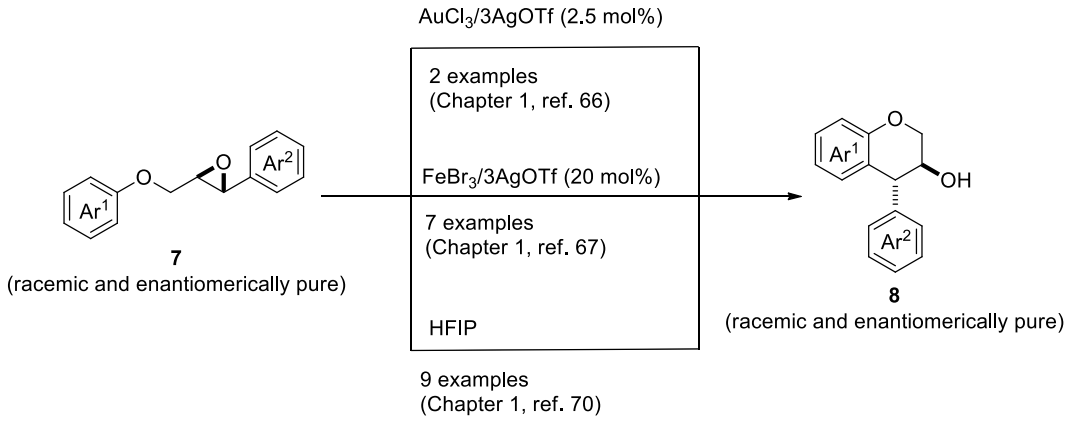


Figure 2.1. General structures of chroman-3-ol, flavon-3-ols, 4-arylflavan-3-ols, and 4-arylchroman -3-ols and representative examples of biologically important chroman-3-ols

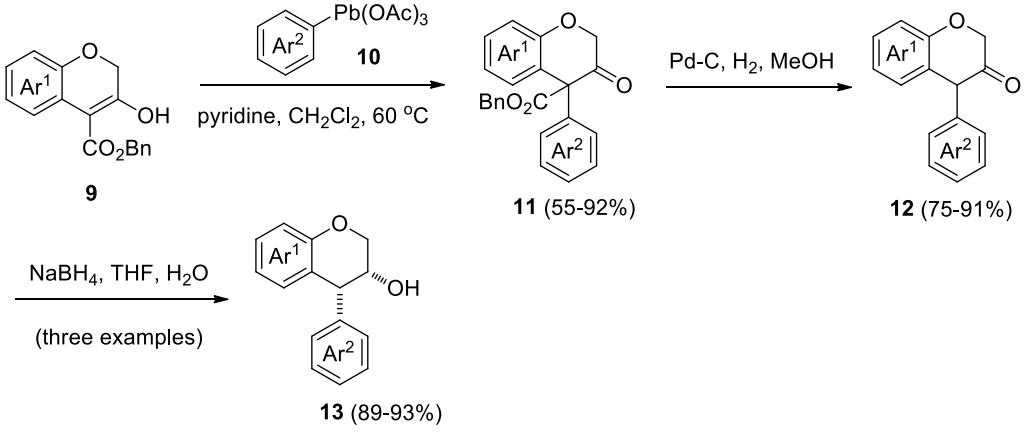
2.2. Literature Known Methods to Access 4-Arylchroman-3-ols

In sharp contrast to the well-explored chemistry and biology of **2**, the synthetic and bio-evaluation studies of **4** has not yet been explored systematically. As shown in Scheme 2.1, racemic and enantiomerically pure *trans*-4-arylchroman-3-ols **8** have been synthesized via intramolecular Friedel-Crafts epoxide-arene cyclization (IFCEAC) of *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7** (for details, see **Chapter 1, Section 1.7.1.1**).



Scheme 2.1. **Summary of previous efforts on the synthesis of *trans*-4-arylchroman-3-ols by IFCEAC**

Finet et al. reported the synthesis of three *cis*-4-arylchroman-3-ols as intermediate compounds while synthesizing a series of neoflavenes [6]. In their approach, reaction of 4-benzyloxycarbonyl-2*H*-1-benzopyran-3(4*H*)-ones **9** with 1.1 molar equivalent of aryllead(IV) triacetates **10** in the presence of 3 molar equivalents of pyridine in anh. chloroform at 60 ºC afforded chroman derivatives **11** in 55-92% yields (Scheme 2.2). Subsequently, decarboxylative hydrogenolysis of **11** provided 4-arylchroman-3-ones **12** in 75-91% yields.

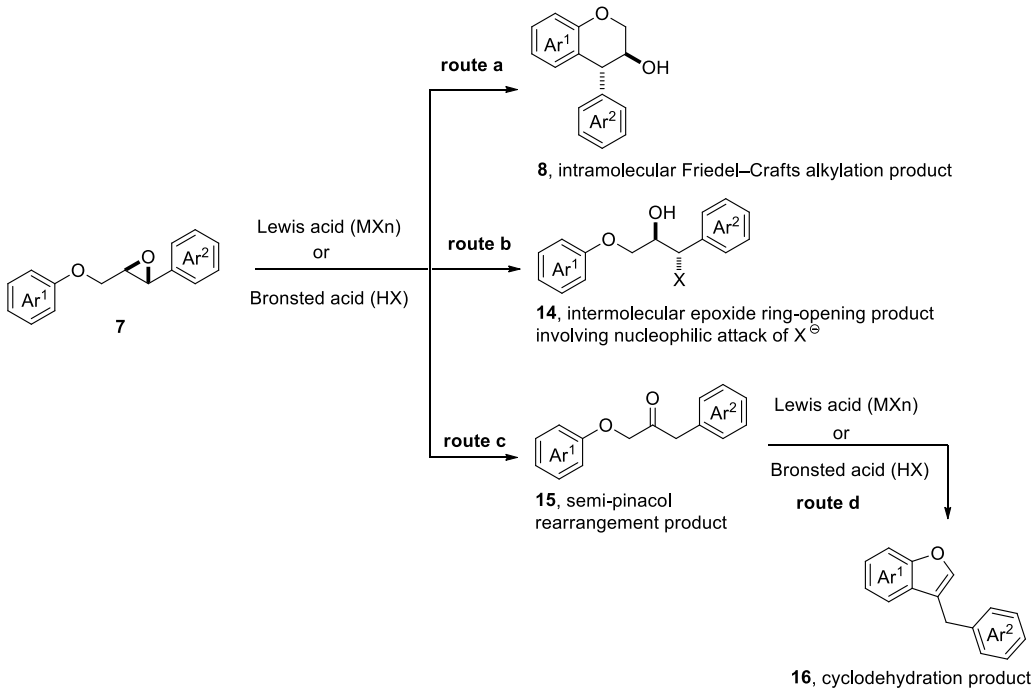


Scheme 2.2. Diastereoselective synthesis of *cis*-4-arylchroman-3-ols by Finet et al.

Finally, they converted only three of the synthesized 4-arylchroman-3-ones into the corresponding *cis*-4-arylchroman-3-ols **13** by a completely diastereoselective $NaBH_4$ reduction in THF and water.

2.3. Background and Objectives

Before we discuss about drawbacks of these known methods of synthesizing *trans*-4-arylchroman-3-ols **8** from the corresponding *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7** (Scheme 2.1), it is worth mentioning the synthetic challenges associated with this transformation. On the basis of the literature precedence, one can envision four different reaction pathways from *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7** in the presence of a Brønsted/Lewis acid catalyst/promoter (Scheme 2.3).



Scheme 2.3. Possible reaction pathways of *trans*-2-aryl-3-(aryloxymethyl)oxiranes

The epoxide ring of **7** can experience an intramolecular nucleophilic attack by the tethered arene to furnish desired **8** via a 6-(arene-*endo*)-*endo*-epoxide cyclization (Scheme 2.3, route a). For such a reaction, the tethered arene ring must be sufficiently electron rich. Alternatively, with an electron poor tethered arene group, ligand from the Lewis acid or conjugate base of the Brønste acid may force **7** to undergo intermolecular epoxide ring-opening reaction to yield **14** (Scheme 2.3, route b), or furnish the corresponding ketones **15** via a semi-pinacol rearrangement (Scheme 2.3, route c).

Ketones **15** might also undergo *in situ* cyclodehydration reaction to afford the corresponding 2,3-dihydrobenzofurans **16** (Scheme 2.3, route d).

As discussed in the Section 2.2, it is clear that transition metal-based Lewis acid catalysts can be efficiently used to obtain *trans*-4-arylchroman-3-ols **8** from the corresponding *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7**. However, one of the drawbacks of transition metal-based catalysts is the requirement of strict anh. conditions. This necessitates the inclusion of some special attention to handle very small amount of the catalyst used in the synthetic procedures, and hence carrying these reaction on large-scale applications may be wearisome. In this regard, identification of transition-metal-free conditions is important because such procedures generally have other obvious advantages in terms of cost, nontoxicity and environmental compatibility.

These limitations have recently been overcome successfully with the use of HFIP as a reaction medium in the IFCEAC reaction (*vide supra*) ─ however, the use of a specialized and expensive Brønsted acid like this particular fluorinated alcohol can be considered as an obstacle for the extensive use of this method. We postulated that this issue could potentially be overcome by the use of easily accessible Brønsted acids involving transition-metal-free condition. Another notable feature of these reported methods is that the Ar^2 ring of synthesized *trans*-4-arylchroman-3-ols typically has been limited to only phenyl and 4-bromophenyl rings, thus significantly limiting the application of this method in organic synthesis. Moreover, until now there has been no report of the synthesis of this class of molecules with free phenolic-OH group on both the aryl rings (Ar^1 and Ar^2) ─ an important requirement for displaying relevant biological activity, and further structural elaboration toward more complex molecules. On the other hand, although synthetic route developed by Finet and co-workers could provide *cis*-4-arylchroman-3-ols efficiently (Scheme 2.2), no asymmetric version of this methodology has yet been developed.

The above-described drawbacks prompted us to initiate a systematic study on the synthesis of 4-arylchroman-3-ols using an alternative catalyst system. In particular, the aims of the research work described in this chapter were:

(i) to synthesize diverse *trans*-4-arylchroman-3-ols by a Brønsted acid catalyzed and operationally simple method under transition-metal-free conditions,

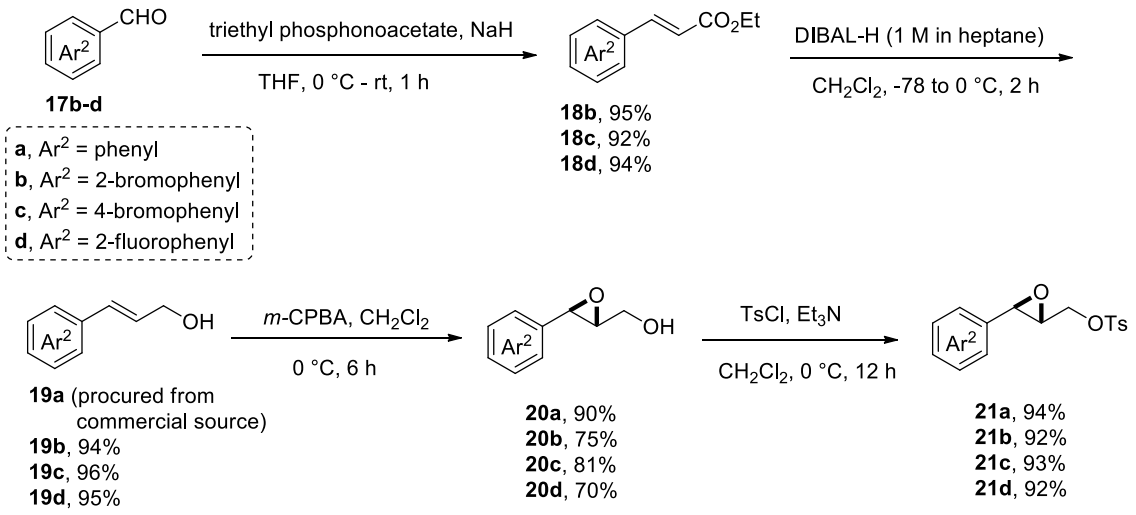
(ii) to develop new route to access *cis*-4-arylchroman-3-ols, and

(iii) to utilize *trans*/*cis*-4-arylchroman-3-ols to construct chroman-based tetracyclic molecules.

2.4. Results and Discussion

2.4.1. Synthesis of *trans*-2-Aryl-3-(aryloxymethyl)oxirane)

To assemble a series of *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7** required for the study, first we synthesized four racemic *trans*-3-arylglycidols **20a-d** following well-established literature procedures (Scheme 2.4). Thus, Horner–Wadsworth–Emmons (HWE) olefination of benzaldehydes **17b-d** with triethyl phosphonoacetate and NaH in THF followed by DIBAL-H reduction of the resulting *trans*-ethyl cinnamates **18b-d** in CH_2Cl_2 produced the corresponding *trans*-cinnamyl alcohol **19b-d**. Next, epoxidation of **19a-d** (**19a** was procured from commercial source) with *m*-CPBA in CH_2Cl_2 furnished *trans*-3-arylglycidols **20a-d** which were then tosylated with TsCl in the presence of Et_3N in CH_2Cl_2 to afford the corresponding epoxy tosylates **21a-d**.



Scheme 2.4. Synthesis of tosylates of *trans*-3-arylglycidols

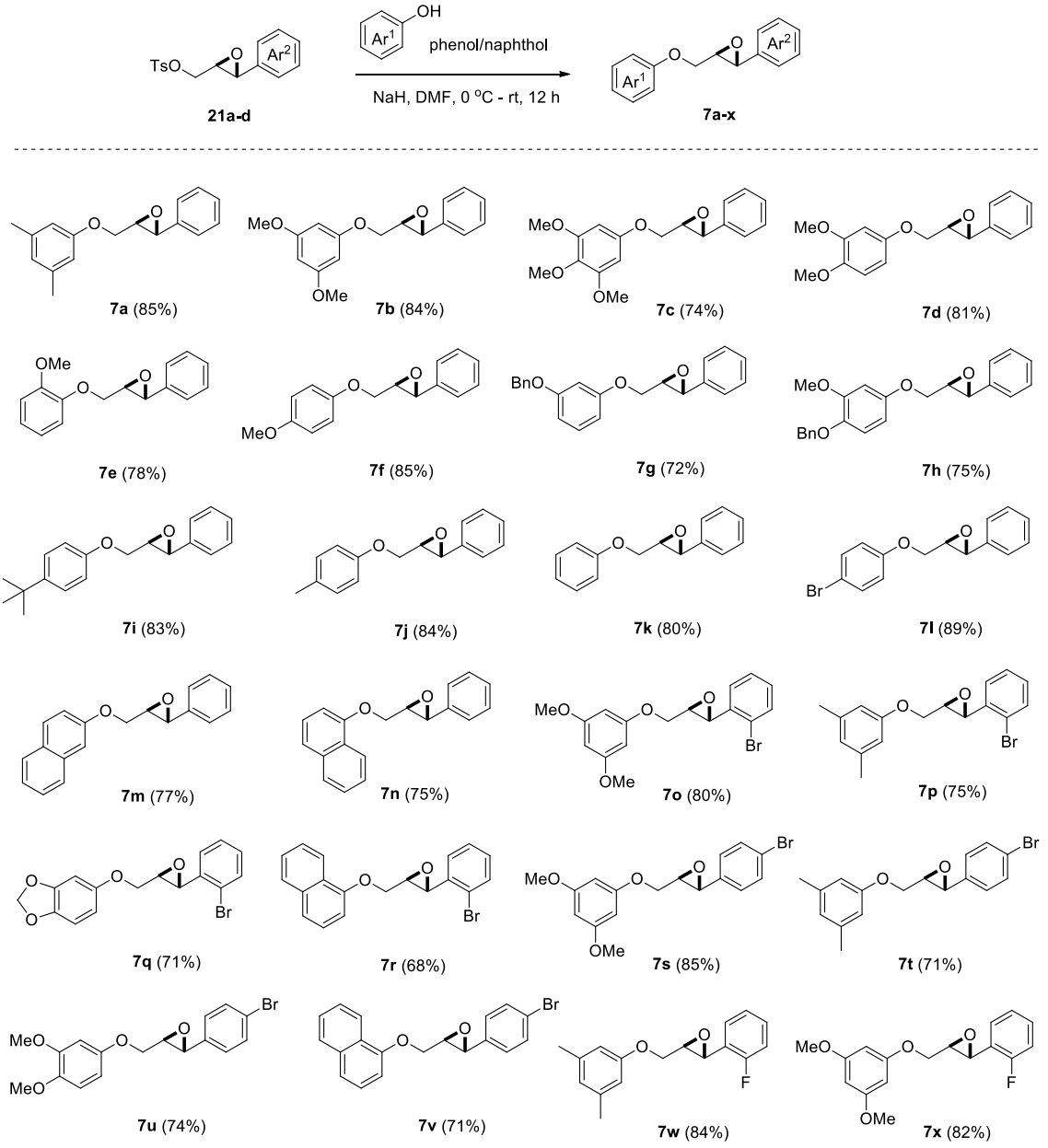
With epoxy tosylates **21a-d** in hand, we next conducted alkylation of different phenols/naphthols (1.0 equiv) with **21a-d** (1.05 equiv) in the presence of NaH (1.5 equiv) in anh. DMF to obtain *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7a-x** (Table 2.1). These reactions were very much clean, furnishing the desired products in high isolated yields.

2.4.2. Screening of Reaction Conditions for the IFCEAC Reaction

Our optimization study commenced with the IFCEAC of **7a** in the presence of readily available Brønsted acids (Table 2.2). Thus, a solution of **7a** in AR grade MeCN

containing 20 mol% of *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$) as Brønsted acid catalyst was heated at 70 °C for 30 min in an open atmosphere.

Table 2.1. Synthesis of *trans*-2-aryl-3-(aryloxymethyl)oxiranes[a,b]

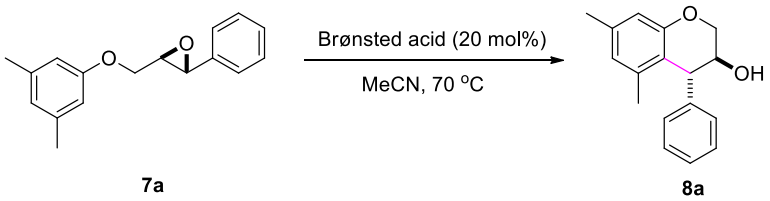


[a]Reaction conditions: phenol/naphthol (1.0 mmol), **21** (1.05 mmol) and NaH (1.5 mmol) in 3 mL anh. DMF. [b]The percentage values shown in parentheses indicate the respective isolated yields after column chromatography

The desired product, *trans*-5,7-dimethyl-4-phenylchroman-3-ol **8a**, was obtained in 80% isolated yield (Table 2.2, entry 1). A comparable product yields (76-78%; entries 2-4) were obtained upon changing the catalyst from $TsOH \cdot H_2O$ to methanesulfonic acid

(MsOH), (±)-camphorsulfonic acid (CSA) or 2,4-dinitrobenzenesulfonic acid (DNBSA). However, when stronger Brønsted acids like TFA, H_2SO_4, TfOH and Tf_2NH were tested, lower yields of 60-65% were obtained (entries 5-8). On the other hand, employment of $HBF_4{\cdot}OMe_2$ gave a yield of 76% (entry 9) in this transformation.

Table 2.2. Survey of common Brønsted acid catalysts for the IFCEAC of 7a[a]



7a **8a**

entry	Brønsted acid (20 mol%)	time	yield (%)[b]
1	$TsOH{\cdot}H_2O$	30 min	80
2	MsOH	30 min	78
3	**(±)**-CSA	30 min	76
4	DNBSA	30 min	78
5	TFA	30 min	65
6	H_2SO_4	30 min	60
7	TfOH	30 min	64
8	Tf_2NH	30 min	66
9	$HBF_4{\cdot}OMe_2$	30 min	76
10	H_3PO_4	30 min	50
11	AcOH	5 h	trace
12	PhOH	8 h	0
13	Amberlite IR 120[c]	2 h	0
14	none	h	0

[a]Reaction conditions: **7a** (0.4 mmol), acid catalyst (20 mol%), MeCN (10 mL) at 70 °C.

[b]Isolated yields after column chromatography. [c]50 mg of the catalyst was used

While low yield (50%) was also observed with H_3PO_4 (entry 10), the reaction failed to provide **8a** when we conducted the reaction with much weaker acid AcOH (entry 11) or phenol (entry 12), even after running it for a longer period of time. It is noteworthy that use of heterogeneous Brønsted acid Amberlite IR 120 was also ineffective (entry 13). Predictably, the reaction did not proceed in the absence of a catalyst (entry 14).

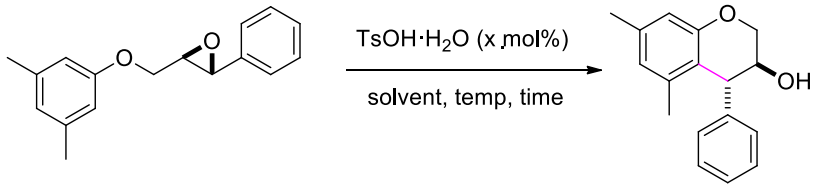
Although the optimization studies revealed an almost equal efficiency of sulfonic acids $TsOH·H_2O$, MsOH, **(±)**-CSA and DNBSA, we picked $TsOH·H_2O$ as the Brønsted acid catalyst, due to its low cost and ease in handling, for further optimization of the reaction conditions.

Subsequently, we examined the effect of solvents, catalyst loading and temperature on the IFCEAC of **7a** leading to **8a** using 20 mol% of $TsOH·H_2O$ as catalyst (Table 2.3). We found that all these factors influence the efficiency of the cyclization. For example, use of THF and 1,4-dioxane as reaction medium failed to provide **8** (Table 2.3, entries 1 and 2) while halogenated solvents like $CHCl_3$ and $ClCH_2CH_2Cl$ (DCE) furnished relatively lower yields of **8** (entries 3 and 4) in comparison to that obtained in MeCN. However, same yield was obtained when the reaction was carried in $MeNO_2$ (entry 5). But toluene provided significantly higher yield (entry 6) compared to MeCN or $MeNO_2$. Use of toluene/DCE mixture (4:1) resulted in better yield (entry 7); but lower than that obtained in toluene. Interestingly, when we conducted the reaction in toluene/MeCN (4:1), the result was an enhanced yield of 94% (entry 8). This superior outcome might be due to the increased solubility of TsOH in toluene/ MeCN compared to that in toluene alone. Use of anh. toluene/MeCN (4:1) in the presence of 4 Å molecular sieves under an argon atmosphere did not improve the yield (entry 9). So maintenance of strict anh. conditions was not necessary for our protocol.

Moreover, with toluene/MeCN (4:1) as a reaction medium, the screening of $TsOH·H_2O$ loading indicated that yield of the reaction was diminished when it was used in less than 20 mol% (Table 2.3, entries 10-12). Interestingly, stoichiometric amount of $TsOH·H_2O$ in the same solvent system generated uncharacterizable side-products (none of which was detected with 20 mol% catalyst loading) possibly through the decomposition, oligomerization or polymerization of the starting material, lowering the yield significantly (entry 13). Additionally, we found that the reaction was also influenced by temperature. Using 20 mol % of $TsOH·H_2O$ as catalyst and toluene/MeCN (4:1) as a reaction medium, the reaction was poor yielding at rt (Table 2.3, entry 14). On the other hand, when we carried out the reaction at 82 °C instead of 70 °C, yield was slightly diminished (entry 15). Based on the above results, it was evident that this transformation was best carried out using $TsOH·H_2O$ (20 mol%) as catalyst in toluene/MeCN (4:1) at 70 °C for 30 min. It is noteworthy to mention that this transformation was regio- and stereoselective because only diastereomerically pure *trans*

isomer **8a** was isolated. The molecular structure was confirmed by comparing the NMR data of **8a** with the reported data [7,8].

Table 2.3. Influence of solvent, catalyst loading and temperature on the IFCEAC of 7a leading to the formation of 8a[a]



7a **8a**

entry	solvent	cat (mol%)	temp (°C)	time (min)	yield (%)[b]
1	THF	20	70	120	0
2	1,4-dioxane	20	70	120	0
3	$CHCl_3$	20	70	30	55
4	DCE	20	70	30	66
5	$MeNO_2$	20	70	30	80
6	toluene	20	70	30	90
7	toluene/DCE (4:1)	20	70	30	84
8[b]	**toluene/MeCN (4:1)**	**20**	**70**	**30**	**94**
9[c]	toluene/MeCN (4:1)	20	70	30	94
10	toluene/MeCN (4:1)	1	70	360	15
11	Toluene/MeCN (4:1)	5	70	120	50
12	toluene/MeCN (4:1)	10	70	60	75
13	toluene/MeCN (4:1)	100	70	30	85
14	toluene/MeCN (4:1)	20	rt	30	10
15	toluene/MeCN (4:1)	20	82	30	91

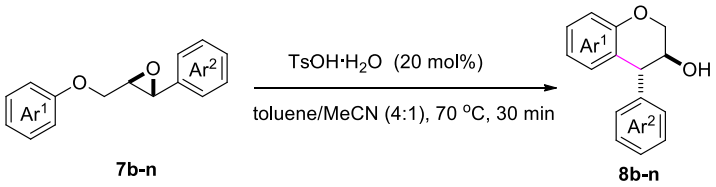
[a]Reaction conditions: **7a** (0.4 mmol), Brønsted acid catalyst (20 mol%), AR grade solvent (10 mL), open atmosphere. [b]Isolated yields after silica gel column chromatography. [c]The entry highlighted in bold indicates the optimal reaction conditions. [c]Dried (anh.) solvents were employed in the presence of 4 Å MS under argon atmosphere.

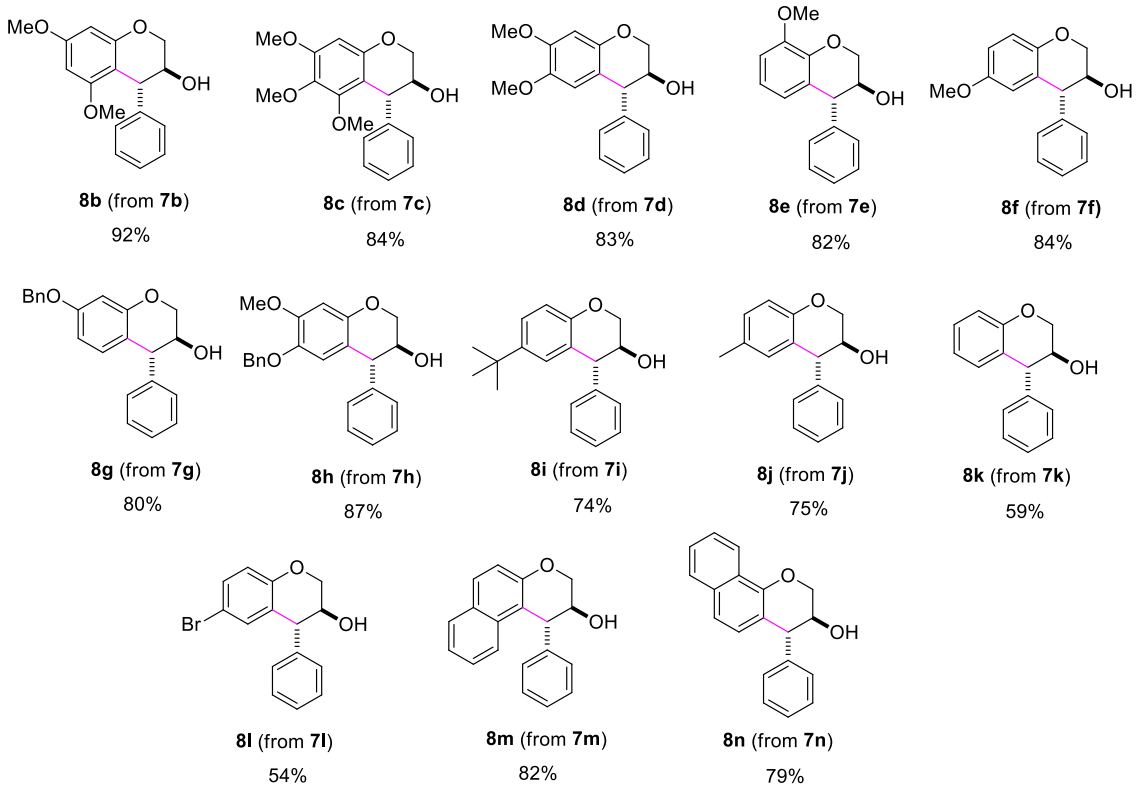
2.4.3. TsOH·H_2O-Catalyzed IFCEAC of *trans*-2-Aryl-3-(aryloxymethyl)oxiranes 7b-x Leading to the Formation of (±)-*trans*-4-Phenylchroman-3-ols 8b-x

Upon the establishment of viable reaction conditions, we next sought to determine the scope of the reaction in terms of demonstrating the impact of the electronic nature of the

Ar^1 group while keeping the Ar^2 group as the unsubstituted phenyl group (Ar^2 = phenyl). Thus, we subjected *trans*-2-aryl-3-(aryloxymethyl)oxiranes **7b-n** to the IFCEAC under the optimized reaction conditions. The result is summarized in the Table 2.4.

Table 2.4. TsOH·H_2O-catalyzed IFCEAC of trans-2-aryl-3-(aryloxymethyl) oxiranes 7b-n leading to the formation of (±)-*trans*-4-arylchroman-3-ols 8b-n[a,b]





[a]All reactions were conducted by heating a solution of **7b-n** (0.4 mmol) and TsOH·H_2O (20 mol %) in a mixture of toluene (8 mL) and MeCN (2 mL) at 70 °C for 30 min. [b]The percentage values indicate the respective isolated yields after column chromatography.

It clearly indicates that substrates **7b-f** with methoxy-substituted phenyl groups such as 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3,4-dimethoxyphenyl, 2-methoxyphenyl, and 4-methoxyphenyl groups underwent the diastereoselective IFCEAC to give products **8b-f** in good to high yields (Table 2.4, list of products, first row). Noteworthy is that, owing to the presence of higher nucleophilic site on the 3,5-

dimethoxyphenyl group (Ar^1 ring), the cyclization of **7b** was high yielding (92%) compared to other methoxy-substituted phenyl ring (Ar^1 ring) bearing starting materials **7c-f**.

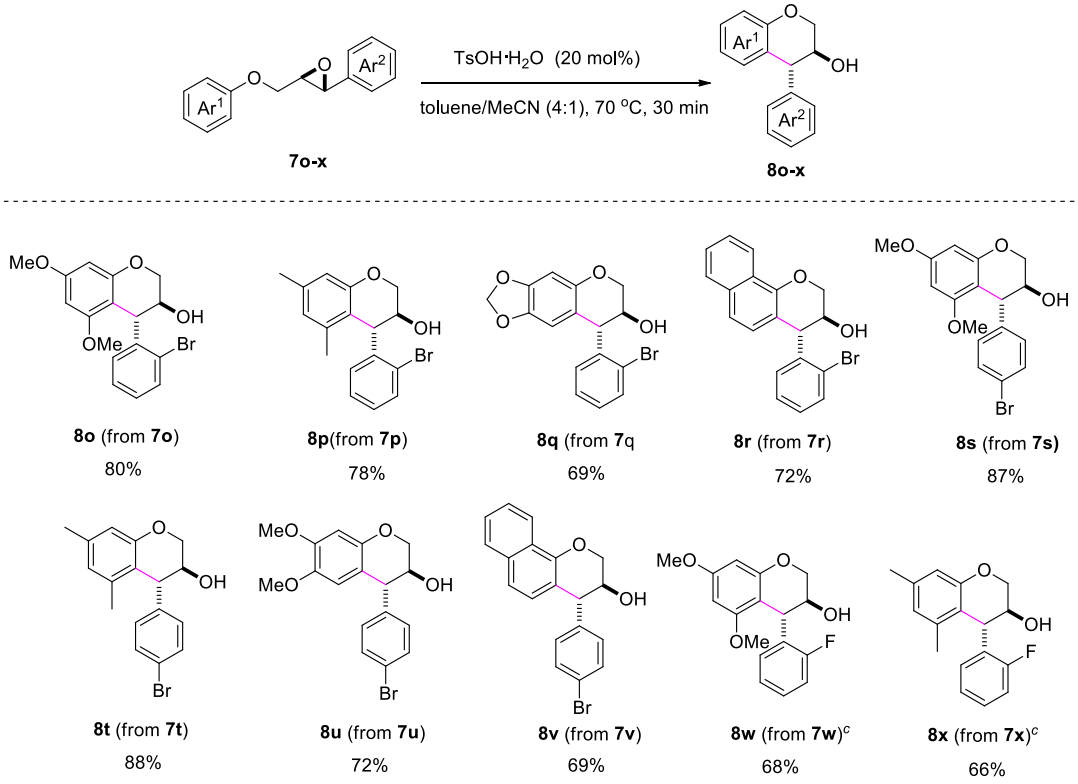
Although the reactions leading to **8b-f** were satisfactory, removal of the methyl groups would be required to access biologically relevant *trans*-4-arylchroman-3-ols with free phenolic-OH group(s) on the Ar^1 ring. To avoid the potentially harsh Lewis or Brønsted acidic conditions (e.g., BBr_3, HBr etc.), which are commonly used for demethylation of –OMe group, suitable protecting group for phenolic-OH group(s) must be introduced (on the Ar^1 ring) which must not interfere with the IFCEAC but must be sufficiently stable and easily removable at the end. Toward that objective, we synthesized and subjected two benzyloxy-substituted phenyl ring containing substrates **7g** and **7h** for this transformation (Table 2.4). To our delight, both of them gave good yields of expected products. This is in sharp contrast to a previous report on IFCEAC [9] in which the metal-based Lewis acid catalysts were very sensitive to –OBn group, resulting in decomposition of glycidyl ether substrates possibly through strong coordination of metal-based Lewis acid catalysts to benzyloxy group. To overcome this difficulty, suitable thiourea derivative was introduced which could moderate the Lewis acidity, thus enabling the product formation in good yields.

Meanwhile, substrates **7i** and **7j** bearing alkyl-substituted Ar^1 groups also provided the corresponding products in good yields. However, substrate **7k** with the unsubstituted phenyl group (Ar^1 = phenyl) furnished **8k** in the low yield of 59%. Similar poor yield was observed in the reactions with substrate **7l** bearing a 4-bromophenyl substituent as the Ar^1 ring, furnishing product **8l**. Consequently, the reaction with substrates bearing electron poorer Ar^1 rings, such as 4-chlorophenyl and 4-fluorophenyl, were not investigated. Nonetheless, naphthalyl group bearing substrates **7m** and **7n** provided products **8m** and **8n**, respectively in satisfactory yields.

The poor yields with the substrates bearing less nucleophilic Ar^1 fragments might be proposed to occur from the undesired side-reactions as described in Scheme 2.3. However, keeping in mind the electron-rich nature of Ar^1 ring in naturally occurring 3-chromanols and their derivatives, it is evident that this method of synthesizing *trans*-4-arylchroman-3-ols containing electron-rich Ar^1 group is a fairly good method. Moreover, all reactions were carried out in open air with AR-grade toluene and MeCN, making this transformation very reliable and operationally simple. Therefore, this procedure should favorably complement the existing ones.

We next inspected the feasibility of the reaction on substrates **7o-x** encompassing the Ar^2 as a halophenyl ring (Table 2.5). Under the optimized reaction conditions, substrates **7o-v** encompassing an *ortho*/*para*-bromophenyl moiety as the Ar^2 group successfully produced the desired products **8o-v** (Table 2.5).

Table 2.5. TsOH·H_2O-catalyzed IFCEAC of *trans*-2-aryl-3-(aryloxymethyl) oxiranes 7o-x leading to the formation of (±)-*trans*-4-arylchroman-3-ols 8o-x[a,b]



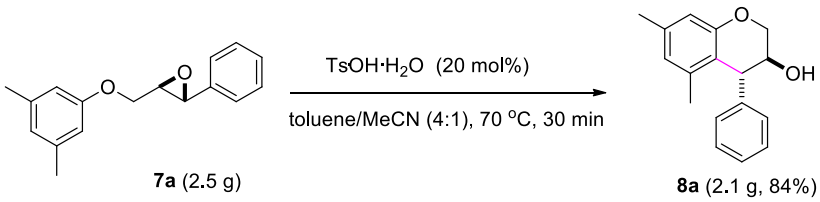
[a]Unless otherwise noted, all the reactions were conducted by heating a solution of **7o-x** (0.4 mmol) and TsOH·H_2O (20 mol %) in a mixture of toluene (8 mL) and MeCN (2 mL) at 70 °C for 30 min. [b]The percentage values indicate the respective isolated yields after column chromatography. [c]Reactions were run for 1 h instead of 30 min.

trans-4-Arylchroman-3-ols **8o** and **8p** were obtained from the corresponding substrates in 80 and 78% yields, respectively. Substrates **7q** and **7r** also furnished the corresponding products in satisfactory yields of 69 and 72% yields, respectively. The presence of an inductively electron-withdrawing *ortho*-bromo-substituent on the Ar^2 ring undoubtedly created a noticeable decrease in yields; although the desired regio- and stereoselectivity was uninterrupted. Notably, these products have not been reported in the literature by previously reported synthetic procedures for this IFCEAC or any other synthetic methodologies. As expected, substrates **7s-v** containing a *para*-bromophenyl

moiety exhibited better results compared to their *ortho* counterparts. For example, the product yield from substrate **7o** was 80% whereas substrate **7s** offered 87% yield. It is worthwhile to mention that the products with bromine substituent could be potentially used to introduce additional functionalities and generate molecular complexity and diversity. Next we turned our attention to *ortho*-fluorophenyl containing substrates **7w** and **7x**. However, with these two substrates, reaction rate decreased substantially and reactions were incomplete within 30 min, although they proceeded to completion after 1 h with decreased yields, presumably due to the much stronger electron-withdrawing effect of the *ortho*-fluoro substituent.

2.4.4. Upscaling of the Reaction: Gram-Scale Synthesis of 8a

Until now, syntheses of *trans*-4-arylchroman-3-ols were carried out with only small amounts of substrates. To show the practical utility of this protocol, an upscale to the gram-level was essential. In this aspect, the gram-scale synthesis of *trans*-4-arylchroman-3-ol **8a** was examined. As shown in Scheme 2.5, the reaction of 2.5 g of **7a** under the optimized reaction conditions proceeded smoothly and delivered the corresponding product **8a** in 84% yield without a significant loss of efficiency (yield on small scale: 94%, Table 2.3, entry 8). Successful upscaling of the reaction at gram scale demonstrated its synthetic practicality.

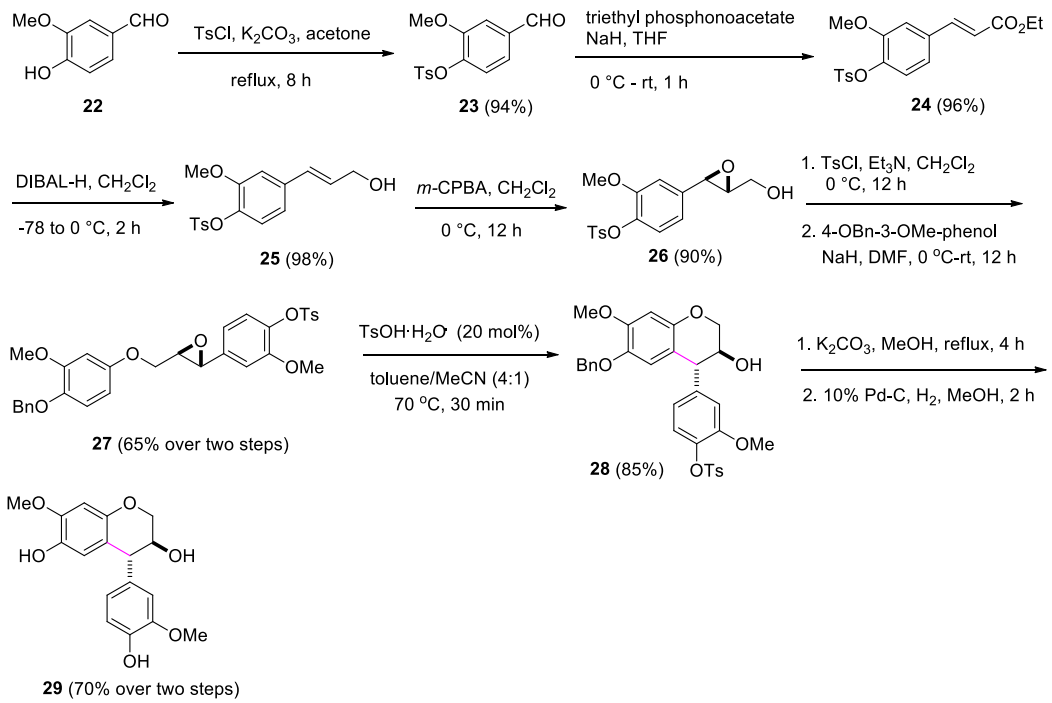


Scheme 2.5. Gram-scale synthesis of racemic 8a

2.4.5. Synthesis of *trans*-4-Arylchroman-3-ol with Free Phenolic–OH Groups on Ar^1 and Ar^2 Rings

Our next effort was to apply the present methodology to the synthesis of *trans*-4-arylchroman-3-ol containing phenolic-OH substituted-Ar^1 ring. However, execution of this plan was not as straightforward as it might appear at first glance. *trans*-3-Arylglycidols derived from parent *E*-cinnamyl alcohol or electron-withdrawing group-substituted *E*-cinnamyl alcohols can be readily synthesized and are stable—but those from *ortho*/*para*-alkoxy-substituted cinnamyl alcohols are difficult to prepare or are

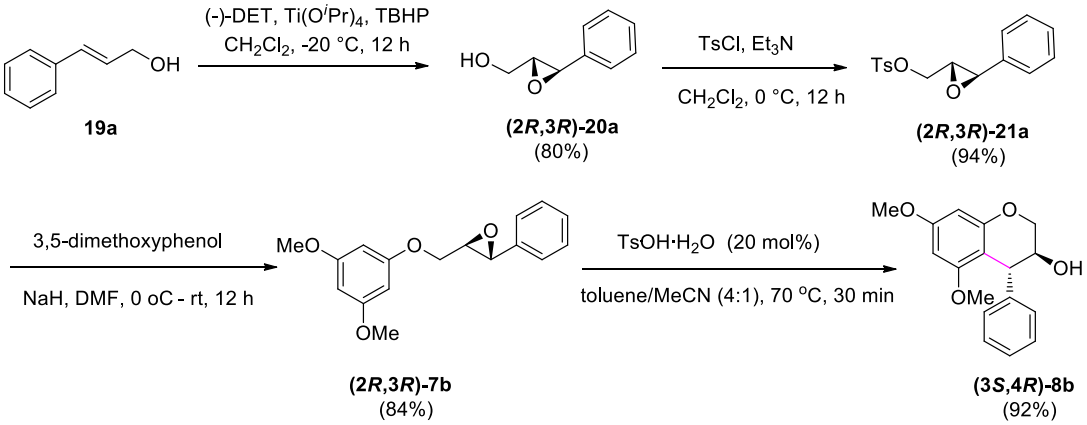
unstable due to intermolecular epoxide ring-opening by the *in situ* generated *m*-chlorobenzoic acid under *m*-chloroperbenzoic acid (*m*-CPBA)-mediated epoxidation condition [10]. The scenario is not much different with the popular Sharpless asymmetric epoxidation or any other common epoxidation methods [10]. During efforts to address this, it occurred to us that the *ortho*/*para*-tosyloxy-substituted *E*-cinnamyl alcohols could be epoxidized efficiently [11], enabling the introduction of –OH or –OR substituent on the aryl Ar^2 ring. Thus, following a literature procedure, vanillin **22** was converted to *E*-allylic alcohol **25** via a three-step reaction sequence involving sequential tosylation, HWE olefination and DIBAL-H reduction (Scheme 2.6) [11]. Next, *m*-CPBA-mediated epoxidation of **25** produced epoxy alcohol **26**, which after tosylation, was subjected to NaH-mediated etherfication with 4-benzyloxy-3-methoxyphenol to produce glycidyl ether **27**. Compound **27** was then subjected to IFCEAC under the optimized reaction conditions to obtain compound **28** in 85% yield. Finally, a two-step reaction sequence of detosylation of **28** with K_2CO_3 in refluxing methanol and subsequent debenzylation of the resulting product with Pd-C and H_2 gas provided *trans*-4-arylchroman-3-ol **30** bearing free phenolic –OH on both Ar^1 and Ar^2 rings.



Scheme 2.6. Synthesis of *trans*-4-arylchroman-3-ol with free phenolic –OH groups

2.4.6. Asymmetric Version of the Developed Methodology

Next, we turned our attention to develop an asymmetric version of the developed IFCEAC. Thus, enantiomerically enriched epoxy alcohol **(2*R*,3*R*)-20a** was synthesized using Sharpless asymmetric epoxidation ((-)-DET, Ti(O*i*Pr)$_4$, TBHP) as the source of chirality (Scheme 2.7). Next, compound (**2*R*,3*R*)-20a** was converted into epoxy tosylate (**2*R*,3*R*)-7b** following the steps described in 2.4. IFCEAC reaction of (**2*R*,3*R*)-7b** under the optimized reaction conditions furnished **(3*S*,4*R*)-8b**. The stereospecific nature of this reaction was confirmed by comparison of the specific rotation values of compound **(3*S*,4*R*)-8b** with literature value (see the Experimental Section for more details).

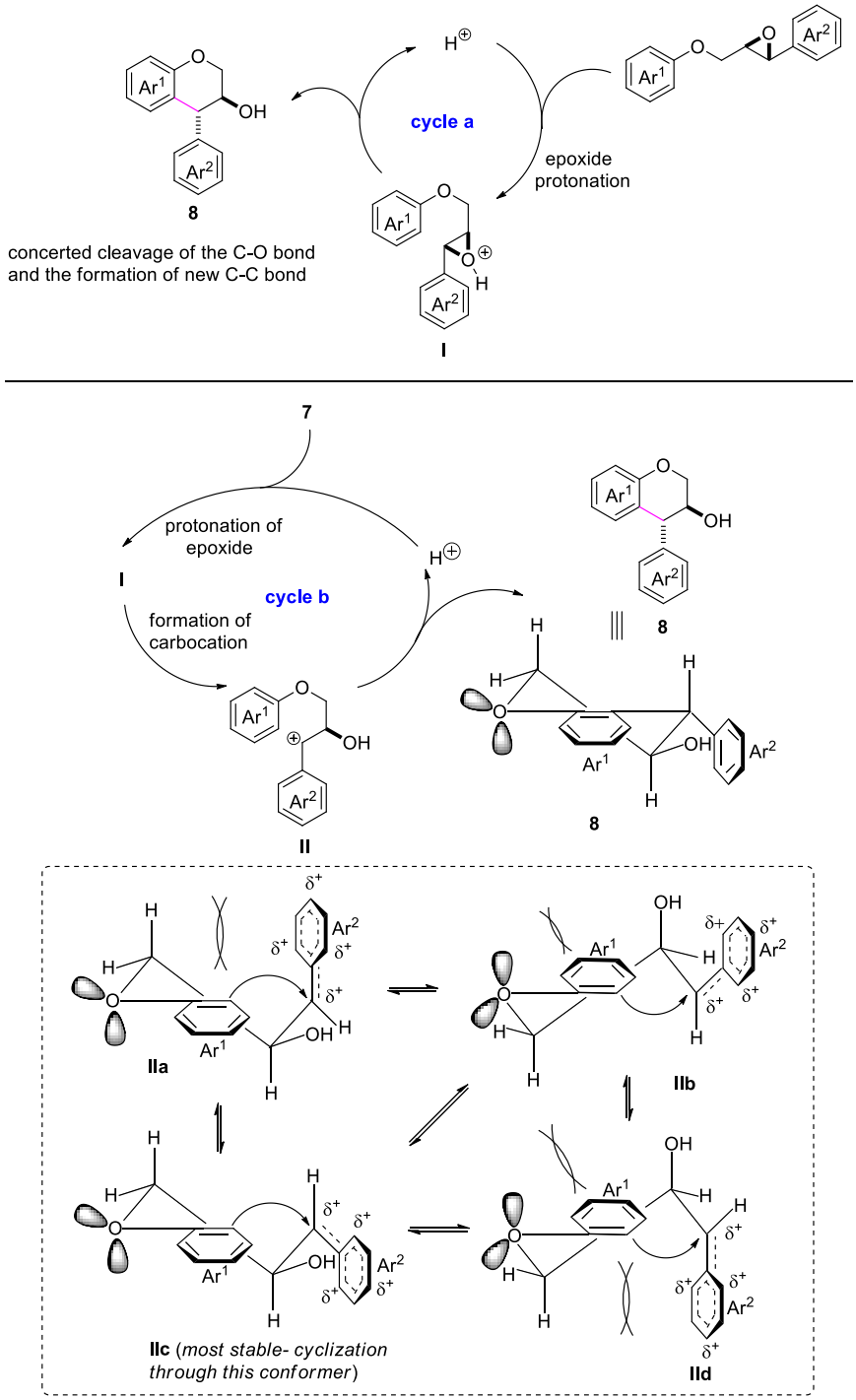


Scheme 2.7. Confirmation of the enantiospecific nature of the developed IFCEAC

2.4.7. Proposed Reaction Mechanism

A mechanistic rationalization for the formation of the *trans*-4-arylchroman-3-ols via TsOH·H_2O catalyzed IFCEAC of *trans*-2-aryl-3-(aryloxymethyl)oxiranes, which was in agreement with our observations is proposed in Scheme 2.8. The first step, unquestionably, must be the activation of epoxide **7** through protonation to give protonated epoxide **I**. Subsequent nucleophilic attack of the Ar^1 group to **I** could happen in a concerted process or step-wise manner. As suggested by Qu et al. [8], *trans*-4-arylchroman-3-ol **8** could be obtained from **7** via 6-(arene-*endo*)-*endo*-*tet*-epoxide cyclization (cycle a, Scheme 2.8) through the concerted process. This concerted epoxide-ring opening might be more operational with substrates with electron-drawing group on the *ortho* or *para* position of the Ar^2 ring. Simultaneously, we hypothesized that in the presence of acid catalyst, **I** could also experience ring-opening to form more stable benzylic carbocation intermediate **II** (cycle b). This should be more realistic with

substrates bearing electron-donating group on the *ortho* and/or *para* position of the Ar^2 ring.



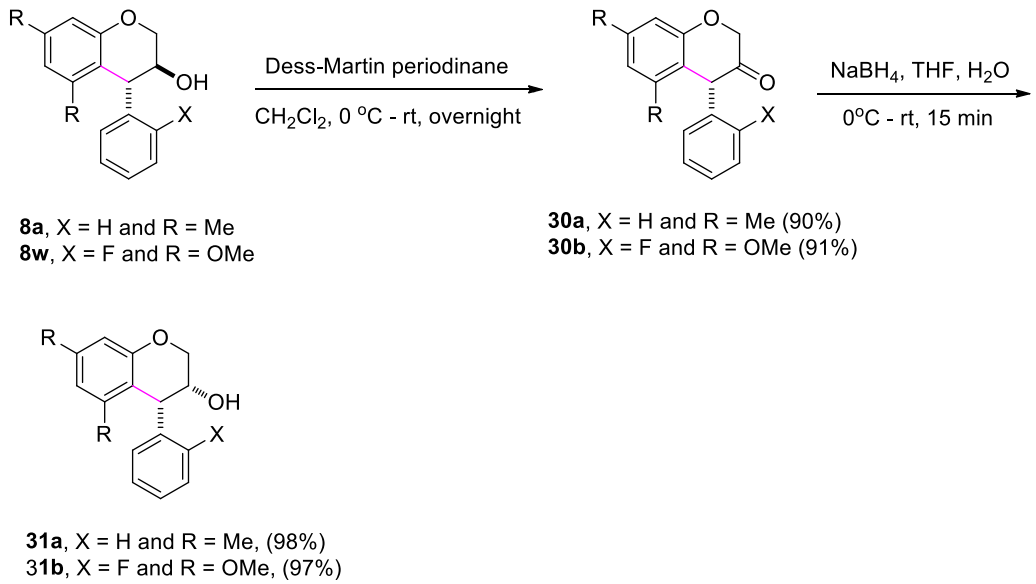
Scheme 2.8. Proposed mechanisms for the *trans*-diastereoselectivity in the TsOH·H_2O catalyzed IFCEAC of *trans*-2-aryl-3-(aryloxymethyl)oxiranes

Four conformers **IIa-c** are possible for the intermediate carbocation **II**, and among them the conformer **IIc** has all substituents in the pseudoequatorial positions and hence

might predominate over others [12]. Subsequent cyclization by a 6-*exo*-*trig* mode could afford *trans*-4-arylchroman-3-ol **8**.

2.4.8. Application of *trans*-4-Arylchroman-3-ols: Synthesis of *cis*-4-Arylchroman-3-ols from the Corresponding *trans*-Isomers

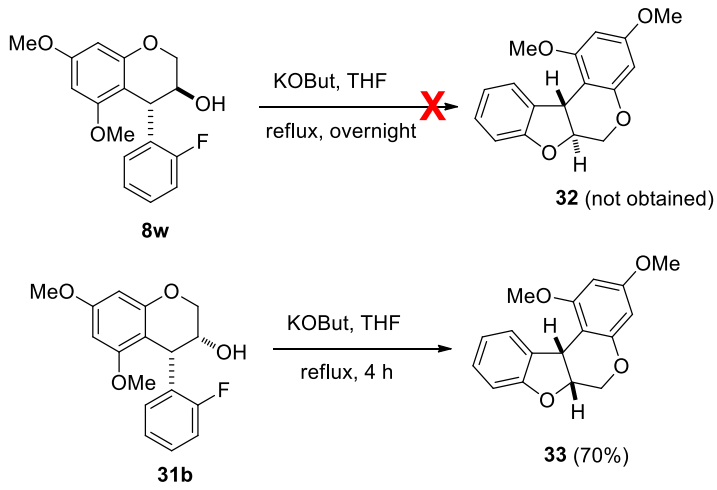
trans-4-Arylchroman-3-ols derived from IFCEAC have not been converted previously to the corresponding *cis* isomers. We turned our attention to develop a methodology for this transformation with selective substrates **8a** and **8w**. Classical Mitsunobu inversion was not effective to achieve this purpose. Delightfully, however, Dess-Martin oxidation of **8a** and **8w** followed by simple $NaBH_4$ reduction of the resulting chromanones (**30a** and **30b**, respectively) furnished *cis*-4-arylchroman-3-ols **31a** and **31b**, respectively, with complete diastereoselectivity (Scheme 2.9) [6]. The reduction processes appeared to be very fast and clean (showed only one spot on TLC from the crude reaction mixture), yielding the corresponding products in very high yields. Further TLC analysis indicated that, the *trans*-isomer **8a** (Table 2.3, entry 8) and the corresponding *cis*-isomer **31a** (obtained from this reduction process, Scheme 2.9) showed small but definite difference in R_f values, with the *cis*-isomer being less polar. From the synthesis point of view, this two-step epimerization process appeared to be very much attractive because of complete diastereoselectivity and high overall yield.



Scheme 2.9. Two-step epimerization of *trans*-4-arylchroman-3-ols 8a and 8w

2.4.9. Application of *cis*-4-Arylchroman-3-ols: Synthesis of a Chroman-Fused 2,3-Dihydrobenzofuran System

Finally, to demonstrate the synthetic utility of 4-arylchroman-3-ols in the synthesis of chroman-based polycyclic molecules, we treated *trans*-4-arylchroman-3-ol **8w** with KOBu^t in THF under reflux condition (Scheme 2.10). Unfortunately, it resulted in the recovery of unreacted starting material, and the corresponding polycyclic product **32** was not obtained. The failure to access compound **32** by this transformation involving an S_NAr mechanism might be due to the unfavorable *trans* stereochemistry at the 6,5-ring junction. A confirmation of this assumption came from the next experiment. When the corresponding *cis*-isomer **31b** was subjected to this intramolecular S_NAr under the above-mentioned reaction conditions, we could successfully obtain chroman-fused 2,3-dihydrobenzofuarn **33** having a *cis* stereochemistry at the 6,5-ring junction.



Scheme 2.10. Synthesis of a chroman-fused 2,3-dihydrobenzofuran 33

2.5. Conclusion

In summary, a systematic synthetic study of diverse *trans*-4-arylchroman-3-ols was made via TsOH·H_2O (20 mol%)-catalyzed diastereoselective intramolecular Friedel-Crafts epoxide-arene cyclization. The protocol involved conducting reactions in AR-grade toluene/MeCN under open air, did not require strict anh. conditions, and avoided the use of expensive Lewis/ Brønsted acids. Remarkably, exposure of arylglycidyl ethers to a strong Brønsted acid like TsOH·H_2O in AR-grade toluene/MeCN did not generate the corresponding diols through hydrolysis, or the resulting *trans*-4-arylchroman-3-ols did not suffer from dehydration to the corresponding chromene derivatives. The exact

nature of this fundamentally unique reaction (stepwise vs concerted) could vary depending on the substrate; however, the synthetic effectiveness was clearly evident, with *trans*-4-arylchroman-3-ols being prepared in moderate to high yields with complete regio- and diastereoselectivity. This method also allowed scale-up from milligram- to gram-scale. Furthermore, this methodology was suitable for the introduction of phenolic-OH groups on both the aromatic rings, thereby creating opportunities for the synthesis of complex molecules. Finally, we could develop a methodology to convert *trans*-4-arylchroman-3-ols to their corresponding *cis*-isomers, and demonstrated the potential for further transformations by synthesizing a chroman-fused 2,3-dihydrobenzofuran derivative. Such a combination of two privileged structural motifs is highly relevant for drug discovery and development.

2.6. Experimental Section

2.6.1. General Remarks

All dry reactions were carried out under nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Commercial reagents were used without further purification unless otherwise stated. Progress of reactions was monitored by TLC on pre-coated Merck silica gel plates (60F-254). Visualization of reactants and products was accomplished with UV light. Column chromatography was performed over silica gel (60–120 mesh) procured from Merck using freshly distilled solvents. ^{1}H NMR and ^{13}C NMR spectra were run on a JEOL 400 MHz spectrometer in $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (*J* values) are given in hertz (Hz). Chemical shifts are expressed in parts per million (ppm). Optical rotations were measured by a Rudolph Autopol V polarimeter. Elemental analyses were carried out with a Perkin-Elmer CHN analyzer. Melting points were measured on a Büchi 535 melting point apparatus. The values are not corrected.

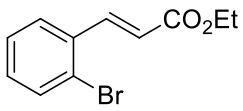
2.6.2. Preparation of Compounds

Synthesis of *trans*-3-Arylglycidyl Tosylates (Scheme 2.4)

General procedure A: synthesis of *trans*-ethyl cinnamates 18b-d from benzaldehydes 17b-d by Horner–Wadsworth–Emmons (HWE) olefination

Triethylphosphonoacetate (11.9 mL, 60 mmol) was added to a stirred suspension of NaH (2.5 g, 65 mmol) in anh. THF (70 mL) at 0 °C under nitrogen atmosphere. The mixture was allowed to warm to rt, and after 30 min was re-cooled to 0 °C. A solution of an appropriate aromatic aldehyde (50 mmol) in THF (70 mL) was added to the reaction mixture, and the resulting mixture was stirred at rt for 1 h. The reactant mixture was quenched by aq. saturated NH_4Cl solution (50 mL), and diluted with diethyl ether (100 mL). The organic layers was separated and then washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by a silica gel column chromatography (0-5% EtOAc in hexanes).

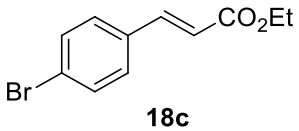
***(E)*-Ethyl 3-(2-bromophenyl)acrylate(18b):**



18b

Following **general procedure A**, 2-bromobenzaldehyde **17b** (9.25 g, 50 mmol) was subjected to the HWE olefination reaction. The crude product was purified by a silica gel column chromatography (0-5% EtOAc in hexanes) to obtain compound **18b** as a colorless oil. Yield: 95% (12.11 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 15.9 Hz, 2H), 7.62-7.58 (m, 2H), 7.31-7.21 (m, 2H), 6.38 (d, *J* = 15.7 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.35 (q, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 142.8, 134.5, 133.4, 131.1, 127.7, 127.6, 125.2, 121.1, 60.6, 14.2. Spectral data were consistent with the literature data [13].

***(E)*-Ethyl 3-(4-bromophenyl)acrylate (18c):**

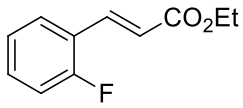


18c

Following **general procedure A**, 4-bromobenzaldehyde **17c** (9.25 g, 50 mmol) was subjected to the HWE olefination reaction. The crude product was purified by a silica gel column chromatography (0-5% EtOAc in hexanes) to obtain compound **18c** as a colorless oil. Yield: 92% (11.73 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 15.9 Hz, 1H), 7.35-7.51 (m, 4H), 6.38 (d, *J* = 15.9 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* =

7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ166.7, 143.2, 133.4, 132.1, 129.5, 124.5, 119.0, 60.7, 14.4. Spectral data were consistent with the literature data [13].

(*E*)-Ethyl 3-(2-fluorophenyl)acrylate (18d):



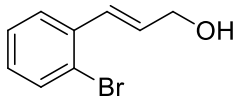
18d

Following **general procedure A**, 2-fluorobenzaldehyde **17d** (6.205 g, 50 mmol) was subjected to the HWE olefination reaction. The crude product was purified by a silica gel column chromatography (0-5% EtOAc in hexanes) to obtain compound **18d** as a colorless oil. Yield: 94% (9.59 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 16.2 Hz, 1 H), 7.53 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.38-7.28 (m, 1H), 7.17-7.05 (m, 2H), 6.53 (d, *J* = 16.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 161.2 (d, *J* = 252.3 Hz), 137.1 (d, *J* = 2.92 Hz), 131.5 (d, *J* = 8.7 Hz), 128.9 (d, *J* = 2.9 Hz), 124.3 (d, *J* = 3.6 Hz), 122.4 (d, *J* = 11.7 Hz), 120.7 (d, *J* = 6.6 Hz), 116.1 (d, *J* = 21.7 Hz), 60.5, 14.2. Spectral data were consistent with the literature data [14].

General procedure B: DIBAL-H reduction of *trans*-ethyl cinnamates 18b-d

To a stirred solution of an appropriate *trans*-unsaturated ester (1.0 equiv, 19.6-25.74 mmol) in anh. CH_2Cl_2 (50 mL) at -78 °C under nitrogen atmosphere was added DIBAL-H (1.0 M in heptane, 2.2 equiv) dropwise. The resulting solution was then allowed to slowly warm to 0 °C and stirred for 2 h at this temperature. The reaction was quenched by careful addition of small amount of methanol and then allowed to warm to room temperature. Saturated aq. potassium sodium tartrate (50 mL) and EtOAc (100 mL) were added and the mixture was stirred vigorously for 1 hour. The phases were then separated and the aqueous phase was extracted with EtOAc (50 x 2 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by a silica gel column chromatography (5-15% EtOAc in hexanes).

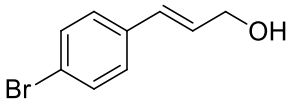
(*E*)-3-(2-Bromophenyl)prop-2-en-1-ol (19b):



19b

Following **general procedure B**, compound **18b** (5.0 g, 19.6 mmol) was reduced by DIBAL-H. The crude product was purified by a silica gel column chromatography (5-15% EtOAc in hexanes) to obtain compound **19b** as a colorless gum. Yield: 94% (3.92 g); R_f: 0.23 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ7.52 (d, *J* = 8.0 Hz, 1H), 7.48 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 6.93 (d, *J* = 15.5 Hz, 1H), 6.28 (dt, *J* = 16.0, 5.5 Hz, 1H), 4.33 (d, *J* = 5.0 Hz, 2H), 2.48 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.6, 133.0, 131.7, 129.6, 129.0, 127.6, 127.2, 123.7, 63.5. Spectral data were in consistent with the literature data [15].

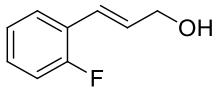
(*E*)-3-(4-Bromophenyl)prop-2-en-1-ol (19c):



19c

Following **general procedure B**, compound **18c** (5.0 g, 19.6 mmol) was reduced by DIBAL-H. The crude product was purified by a silica gel column chromatography (5-15% EtOAc in hexanes) to obtain compound **19c** as a white solid. Yield: 96% (4.0 g); R_f: 0.21 (silica gel, 25% EtOAc in hexanes); mp: 66-68 °C {Lit. mp: 65-67 °C} [16]; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.44 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.56 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.34 (dt, *J* = 16.0, 5.5 Hz, 1H), 4.31 (t, *J* = 4.6 Hz, 2H), 1.62 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 131.9, 130.0, 129.6, 128.2, 121.6, 63.7. Spectral data were consistent with the literature data [16].

(*E*)-3-(2-Fluorophenyl)prop-2-en-1-ol (19d):



19d

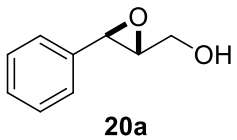
Following **general procedure B**, compound **18d** (5.0 g, 25.74 mmol) was reduced by DIBAL-H. The crude product was purified by a silica gel column chromatography (5-15% EtOAc in hexanes) to obtain compound **19d** as a colorless gum. Yield: 95% (3.72

g); R_f: 0.25 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.21 (m, 1H), 7.10 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.04 (ddd, *J* = 1.2, 8.2, 10.8 Hz, 1H), 6.78 (d, *J* = 16.1 Hz, 1H), 6.45 (td, *J* = 5.6, 16.1 Hz, 1H), 4.35 (dd, *J* = 1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (d, *J* = 249.4 Hz), 131.2 (d, *J* = 4.6 Hz), 128.9 (d, *J* = 8.5 Hz), 127.5 (d, *J* = 3.8 Hz), 124.5 (d, *J* = 12.2 Hz), 124.1 (d, *J* = 3.6 Hz), 123.4 (d, *J* = 3.4 Hz), 115.7 (d, *J* = 22.0 Hz), 63.8. Spectral data were consistent with the literature data [17].

General procedure C: *m*-chloroperbenzoic acid (*m*CPBA)-mediated epoxidation of *E*-cinnamylalcohola 19a-d:

To a stirred solution of *E*-cinnamyl alcohol **19** (10 mmol) in CH_2Cl_2 (25 mL) was added *m*CPBA (77% purity, 3.32 g, 15 mmol) at 0 °C. The reaction mixture was stirred at rt for 6 h. The mixture was diluted with CH_2Cl_2 (50 mL) and then washed successively with aq. solutions of Na_2SO_3 (25 mL), $NaHCO_3$ (25 mL) and brine (25 mL). The organic layers was separated and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by a silica gel column chromatography (5-20% EtOAc in hexanes).

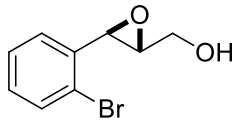
***trans*-(±)-3-Phenyloxiran-2-yl)methanol (20a):**



20a

Following **general procedure C**, compound **19a** (1.34 g, 10.0 mmol) was epoxidized by *m*CPBA. The crude product was purified by a silica gel column chromatography (5-25% EtOAc in hexanes) to obtain compound **20a** as a colorless gum. Yield: 90% (1.35 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5H); 4.01 (dd, *J* = 12.7, 2.9 Hz, 1H); 3.90 (d, *J* = 2.2 Hz, 1H); 3.74 (dd, *J* = 12, 6.8 Hz, 1H); 3.21 (td, *J* = 4.1, 2.2 Hz, 1H); 2.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ136.6, 128.5, 128.3, 125.7, 62.5, 61.2, 55.6. Spectral data were consistent with the literature data [18-20].

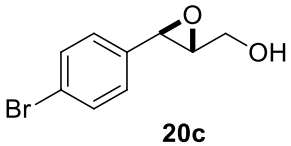
***trans*-(±)-3-(2-Bromophenyl)oxiran-2-yl)methanol (20b):**



20b

Following **general procedure C**, compound **19b** (2.13 g, 10.0 mmol) was epoxidized by *m*-CPBA. The crude product was purified by a silica gel column chromatography (5-25% EtOAc in hexanes) to obtain compound **20b** as a colorless gum. Yield: 75% (1.72 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35-7.25 (m, 2H), 7.21-7.15 (m, 1H), 4.19 (d, *J* = 2.1 Hz, 1H), 4.10 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.87 (dd, *J* = 12.9, 3.9 Hz, 1H), 3.10-3.07 (m, 1H), 2.21 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ136.2, 132.0, 129.2, 127.5, 126.1, 122.2, 62.1, 61.4, 55.4. Spectral data were consistent with the literature data [9].

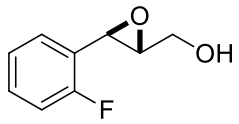
***trans*-(±)-3-(4-Bromophenyl)oxiran-2-yl)methanol (20c):**



20c

Following **general procedure C**, compound **19c** (2.13 g, 10.0 mmol) was epoxidized by *m*CPBA. The crude product was purified by a silica gel column chromatography (5-25% EtOAc in hexanes) to obtain compound **20c** as a colorless gum. Yield: 81% (1.86 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.04 (dd, *J* = 2.4 Hz, 13.2 Hz, 1H), 3.90 (d, *J* = 2 Hz, 1H), 3.80 (dd, *J* = 3.2 Hz, 12.8 Hz, 1H), 3.16–3.18 (m, 1H), 2.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 131.6, 127.3, 122.2, 62.4, 60.9, 54.9; Spectral data were consistent with the literature data [21].

***trans*-(±)-3-(2-Fluorophenyl)oxiran-2-yl)methanol (20d):**



20d

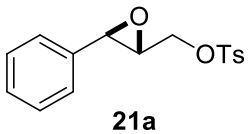
Following **general procedure C**, compound **19d** (1.52 g, 10.0 mmol) was epoxidized by *m*CPBA. The crude product was purified by a silica gel column chromatography (5-25% EtOAc in hexanes) to obtain compound **20d** as a colorless gum. Yield: 70% (1.18

g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.03 (m, 4H), 4.21 (d, *J* = 2 Hz, 1H), 4.07 (ddd, *J* = 12.8, 5.6, 2.4 Hz, 1H), 3.82 (ddd, *J* = 8.4, 7.2, 4.0 Hz, 1H), 3.25–3.23 (m, 1H), 2.23 (dd, *J* = 7.2, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (d, *J* = 245 Hz), 129.5 (d, *J* = 8 Hz), 126.2 (d, *J* = 3 Hz), 124.3 (d, *J* = 3 Hz), 124.0 (d, *J* = 12 Hz), 115.2 (d, *J* = 20 Hz), 61.7, 61.2, 50.2 (d, *J* = 6 Hz); Spectral data were consistent with the literature data [21].

General Method D: tosylation of *trans*-3-arylglycidols 20a-d:

To a stirred solution of *trans*-3-arylglycidol **20** (7.0 mmol) in CH_2Cl_2 (50 mL) at 0 ^{o}C was added triethylamine (1.5 mL, 10.47 mmol) followed by tosyl chloride (2 g, 10.47 mmol) and kept in the refrigerator for 12 h. The reaction mixture was diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (100 mL) and dried over anh. Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (2-15% EtOAc/hexanes).

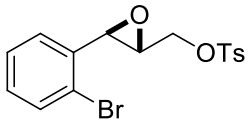
(±)-*trans*-3-Phenyloxiran-2-yl)methyl 4-methylbenzenesulfonate (21a):



21a

Following **general procedure D**, compound **20a** (1.05 g, 7.0 mmol) was subjected to the tosylation reaction. The crude product was purified by a silica gel column chromatography (2-15% EtOAc in hexanes) to obtain compound **21a** as a white solid. Yield: 94% (2.00 g); mp: 65–66 °C (lit. mp: 68–69 °C) [22]; R_f: 0.52 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.38–7.31 (m, 5H), 7.23-7.20 (m, 2H), 4.36 (dd, *J* = 11.5, 3.6 Hz, 1H), 4.14 (dd, *J* = 11.5, 5.7 Hz, 1H), 3.77 (d, *J* = 2.0 Hz, 1H), 3.26-3.23 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ145.3, 135.6, 132.7, 130.0, 128.7, 128.6, 128.0, 125.8, 69.5, 58.6, 58.4, 21.7. The spectroscopic and physical data were in agreement with literature data [22].

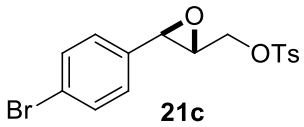
(±)-*trans*-3-(2-Bromophenyl)oxiran-2-yl)methyl 4-methylbenzenesulfonate (21b):



21b

Following **general procedure D**, compound **20b** (1.60 g, 7.0 mmol) was subjected to the tosylation reaction. The crude product was purified by a silica gel column chromatography (2-15% EtOAc in hexanes) to obtain compound **21b** as a white solid. Yield: 92% (2.47 g); mp: 120–122 °C; R_f: 0.57 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.30-7.27 (m, 1H), 7.19-7.15 (m, 2H), 4.46 (dd, *J* = 11.4, 3.2 Hz, 1H), 4.10 (dd, *J* = 11.5, 5.9 Hz, 1H), 4.01 (d, *J* = 2.0 Hz, 1H), 3.12-3.09 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 135.2, 132.6, 132.2, 129.9, 129.7, 127.9, 127.7, 126.2, 122.4, 69.4, 58.2, 55.9, 21.6; Anal. calcd for $C_{16}H_{15}BrO_4S$: C, 50.14; H, 3.94, found: C, 50.19; H, 3.96.

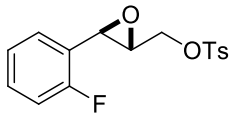
(±)-*trans*-3-(4-Bromophenyl)oxiran-2-yl)methyl 4-methylbenzenesulfonate (21c):



21c

Following **general procedure D**, compound **20c** (1.60 g, 7.0 mmol) was subjected to the tosylation reaction. The crude product was purified by a silica gel column chromatography (2-15% EtOAc in hexanes) to obtain compound **21c** as a white solid. Yield: 93% (2.49 g); R_f: 0.52 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 4.31 (dd, *J* = 11.4, 3.8 Hz, 1H), 4.15 (dd, *J* = 11.4, 5.3 Hz, 1H), 3.73 (d, *J* = 1.7 Hz, 1H), 3.20-3.16 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ145.2, 134.7, 132.7, 131.8, 130.0, 128.0, 127.3, 122.6, 69.0, 58.6, 55.9, 21.7. The spectroscopic and physical data were in agreement with literature data [7].

(±)-*trans*-3-(2-Fluorphenyl)oxiran-2-yl)methyl 4-methylbenzenesulfonate (21d):



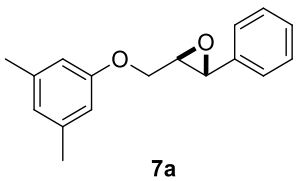
21d

Following **general procedure D**, compound **20d** (1.18 g, 7.0 mmol) was subjected to the tosylation reaction. The crude product was purified by a silica gel column chromatography (2-15% EtOAc in hexanes) to obtain compound **21d** as a white solid. Yield: 92% (2.07 g); mp: 117–119 °C; R_f: 0.56 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32-7.26 (m, 1H), 7.14-7.10 (m, 2H), 7.07-7.02 (m, 1H), 4.39 (dd, *J* = 11.4, 3.2 Hz, 1H), 4.12 (dd, *J* = 11.4, 5.5 Hz, 1H), 4.01 (d, *J* = 2.3 Hz, 1H), 3.28-3.25 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (d, *J* = 248.2 Hz), 145.1, 132.5, 129.93 (d, *J* = 8.6 Hz), 129.94, 127.9, 126.1 (d, *J* = 3.8 Hz), 124.4 (d, *J* = 3.8 Hz), 122.9 (d, *J* = 12.5 Hz), 115.3 (d, *J* = 21.1 Hz), 69.3, 57.9, 50.9 (d, *J* = 6.7 Hz), 21.6; Anal. calcd for $C_{16}H_{15}FO_4S$: C, 59.62; H, 4.69, found: C, 59.72; H, 4.64.

General method E: synthesis of *trans*-2-aryl-3-(aryloxymethyl)oxiranes 7a-x by the alkylation of penols/naphthols with epoxy tosylates 21a-d (Table 2.1):

To a stirred suspension of sodium hydride (36 mg, 1.5 mmol) in DMF (3 mL), a solution of phenol/naphthol (1.0 mmol) in anh. DMF (5 mL) was added at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 5 min, and a solution of racemic epoxy tosylates **21a-d** (1.05 mmol) in DMF (5 mL) was added dropwise. The solution was stirred for an additional 12 h at rt. The reaction was terminated by the addition of 10% aqueous ammonium chloride (10 mL) and diethyl ether (50 mL) was added. The organic layer was separated, washed by brine (50 mL), dried over Na_2SO_4 and filtered. After filtration, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (5-15% EtOAc/hexanes).

(±)-*trans*-2-((3,5-Dimethylphenoxy)methyl)-3-phenyloxirane (7a):

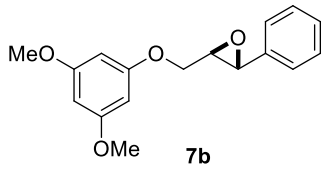


7a

Following **general procedure E**, alkylation of 3,5-dimethylphenol (122 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7a** as a colorless oil. Yield: 85% (216 mg); R_f: 0.57 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.33 (m, 5H), 6.51-6.60 (m, 3H), 4.21 (dd, *J* = 3.1,

11.2 Hz, 1H), 4.03 (dd, *J* = 5.3, 11.2 Hz, 1H), 3.84 (d, *J* = 2.0 Hz, 1H), 3.30-3.33 (m, 1H), 2.26 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.7, 136.8, 128.7, 128.5, 125.9, 123.2, 112.6, 67.9, 60.4, 56.4, 21.6. The spectroscopic and physical data were in agreement with literature data [7].

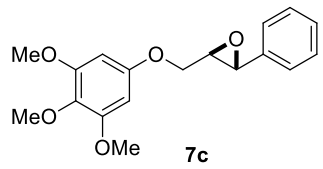
(±)-*trans*-2-((3,5-Dimethoxyphenoxy)methyl)-3-phenyloxirane (7b):



7b

Following **general procedure E**, alkylation of 3,5-dimethoxyphenol (154 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7b** as a colorless oil. Yield: 84% (241 mg); R_f: 0.45 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5H), 6.20-6.10 (m, 1H), 4.26 (dd, *J* = 3.1, 11.1 Hz, 1H), 4.05 (dd, *J* = 5.2, 11.1 Hz, 1H), 3.88 (d, *J* = 2.1 Hz, 1H), 3.74 (s, 6H), 3.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 160.2, 136.4, 128.4, 128.3, 125.6, 93.5, 93.4, 67.9, 60.0, 56.2, 55.2. The spectroscopic and physical data were in agreement with literature data [7].

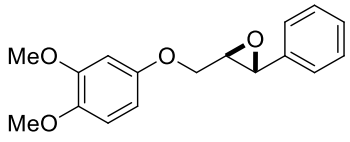
(±)-*trans* -2-((3,4,5-Trimethoxyphenoxy)methyl)-3-phenyloxirane (7c):



7c

Following **general procedure E**, alkylation of 3,4,5-trimethoxyphenol (184 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7c** as a colorless gum. Yield: 74% (234 mg); R_f: 0.41 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 6.22 (s, 2H), 4.29 (dd, *J* = 3.1, 11.1 Hz, 1H), 4.11 (dd, *J* = 5.2, 11.2 Hz, 1H), 3.91 (d, *J* = 2.0 Hz, 1H), 3.84 (s, 6H), 3.79 (s, 3H), 3.40-3.38 (m, 1H); Anal. calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37, found: 68.22; H, 6.44.

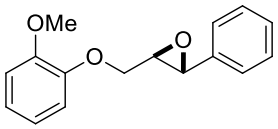
(±)-*trans*-2-((3,4-Dimethoxyphenoxy)methyl)-3-phenyloxirane (7d):



7d

Following **general procedure E**, alkylation of 3,4,-dimethoxyphenol (154 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7d** as a colorless semi-solid. Yield: 81% (232 mg); R_f: 0.44 (silica gel, 15% EtOAc in hexanes); Compound **7d** was used for the next step without characterization.

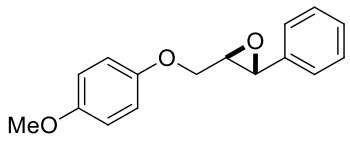
(±)-*trans* -2-((2-Methoxyphenoxy)methyl)-3-phenyloxirane (7e):



7e

Following **general procedure E**, alkylation of 2-methoxyphenol (124 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7e** as a colorless gum. Yield: 78% (200 mg); R_f: 0.49 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 7.01-6.90 (m, 4H), 4.40 (dd, *J* = 2.3, 11.3 Hz, 1H), 4.20 (dd, *J* = 5.5, 11.7 Hz, 1H), 3.91 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 3H), 3.47-3.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 147.8, 136.5, 128.4, 128.3, 125.7, 122.0, 120.8, 114.4, 111.9, 69.4, 60.3, 56.4, 55.7; Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29, found: C, 75.18; H, 6.30.

(±)-*trans* -((4-Methoxyphenoxy)methyl)-3-phenyloxirane (7f):

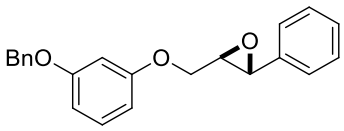


7f

Following **general procedure E**, alkylation of 4-methoxyphenol (124 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7f** as a colorless solid. Yield: 85% (217 mg); mp: 140-142 °C (lit. mp: 142-143 °C);[7] R_f: 0.49 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 6.91-6.81 (m, 4H), 4.26 (dd, *J* = 3.1, 11.2 Hz, 1H), 4.08 (dd, *J* = 5.1, 11.2 Hz, 1H), 3.90-3.88 (m, 1H), 3.76 (s, 3H), 3.39-3.35 (m, 1H) ; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 154.3,

152.7, 136.6, 128.6, 128.4, 125.7, 115.8, 114.7, 68.7, 60.4, 56.4, 55.7. The spectroscopic and physical data were in agreement with literature data [7].

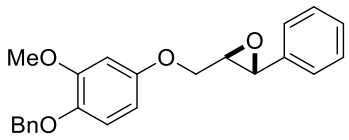
(±)-*trans* -2-((3-(Benzyloxy)phenoxy)methyl)-3-phenyloxirane (7g):



7g

Following **general procedure E**, alkylation of 3-benzyloxyphenol (200 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7g** as a light yellow semi-solid. Yield: 72% (239 mg); R_f: 0.53 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.30 (m, 10H), 7.25-7.19 (m, 1H), 6.65-6.56 (m, 3H), 5.06 (s, 3H), 4.31 (dd, *J* = 3.2, 11.0 Hz, 1H), 4.11 (dd, *J* = 5.5, 11.4 Hz, 1H), 4.11 (dd, *J* = 5.5, 11.4 Hz, 1H), 3.92 (d, *J* = 2.3 Hz, 1H), 3.41-3.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 159.6, 136.8, 136.4, 128.9, 128.5, 128.4, 127.9, 127.4, 125.7, 107.6, 107.0, 102.0, 69.9, 67.8, 60.1, 56.2; Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06, found: C, 79.62; H, 6.14.

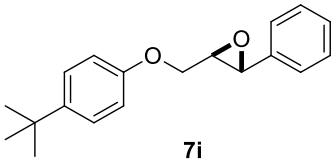
(±)-*trans* -2-((4-(Benzyloxy)-3-methoxyphenoxy)methyl)-3-phenyloxirane (7h):



7h

Following **general procedure E**, alkylation of 4-benzyloxy-3-methoxyphenol (230 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7h** as a light yellow semi-solid. Yield: 75% (271 mg); R_f: 0.51 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.30 (m, 10H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 6.38 (dd, *J* = 2.7, 8.6 Hz, 1H), 5.10 (s, 3H), 4.28 (dd, *J* = 3.2, 11.3 Hz, 1H), 4.08 (dd, *J* = 5.4, 11.3 Hz, 1H), 3.91 (d, *J* = 2.3 Hz, 1H), 3.40-3.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 150.8, 142.8, 137.4, 136.4, 128.5, 128.4, 127.4, 125.7, 111.5, 104.1, 101.4, 72.0, 68.4, 60.3, 56.3, 55.9; Anal. calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12, found: C, 76.27; H, 6.21.

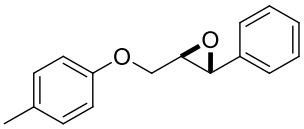
(±)-*trans*-2-((4-(*tert*-Butyl)phenoxy)methyl)-3-phenyloxirane (7i):



7i

Following **general procedure E**, alkylation of 4-*tert*-butylphenol (150 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7i** as a colorless solid. Yield: 83% (234 mg); mp: 149-151 °C (lit. mp: 152-153 °C) [7]; R_f: 0.58 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.38 (m, 7H), 6.87-6.90 (m, 2H), 4.29 (dd, *J* = 3.3, 11.2 Hz, 1H), 4.12 (dd, *J* = 5.1, 11.2 Hz, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 3.37-3.40 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 144.1, 136.6, 128.6, 128.4, 126.4, 125.8, 114.2, 68.0, 60.4, 56.4, 34.1, 31.6. The spectroscopic and physical data were in agreement with literature data [7,8].

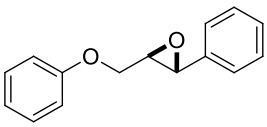
(±)-*trans*-2-Phenyl-3-((*p*-tolyloxy)methyl)oxirane (7j):



7j

Following **general procedure E**, alkylation of *p*-cresol (108 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7j** as colorless solid. Yield: 84% (202 mg); Compound **7j** was used for the next step without characterization.

(±)-*trans*-2-(Phenoxymethyl)-3-phenyloxirane (7k):

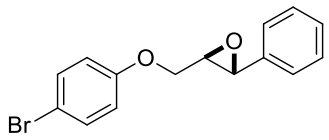


7k

Following **general procedure E**, alkylation of phenol (94 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7k** as a colorless solid. Yield: 80% (181 mg); mp: 131-133 °C (lit. mp: 129-130 °C) [7,8]; R_f: 0.52 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.38 (m, 7H), 6.94-7.0 (m, 3H), 4.32 (dd, *J* = 3.2, 11 Hz, 1H), 4.14 (dd, *J* = 5.1, 11 Hz, 1H), 3.91 (d, *J* = 2.0 Hz, 1H), 3.39-3.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 136.5, 129.6, 128.6,

128.4, 125.7, 121.3, 114.7, 67.9, 60.3, 56.4. The spectroscopic and physical data were in agreement with the literature data [7,8].

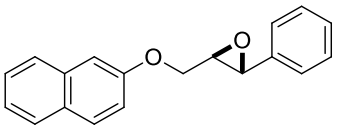
(±)-*trans*-2-((4-Bromophenoxy)methyl)-3-phenyloxirane (7l):



7l

Following **general procedure E**, alkylation of 4-bromophenol (173 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7l** as a colorless solid. Yield: 89% (272 mg); mp: 115-117 °C (lit. mp: 117-118 °C) [8]. R_f: 0.54 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.40 (m, 5H), 6.83–6.86 (m, 2H), 4.32 (dd, *J* = 3.0, 10.8 Hz, 1H), 4.10 (dd, *J* = 5.4, 10.8 Hz, 1H), 3.92 (d, *J* = 2.4Hz, 1H), 3.39–3.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 136.3, 132.3, 128.6, 128.5, 125.7, 116.5, 113.5, 68.1, 60.0, 56.2. The spectroscopic and physical data were in agreement with the literature data [8].

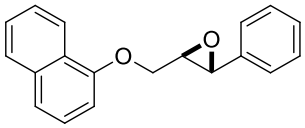
(±)-*trans*-2-((Naphthalen-2-yloxy)methyl)-3-phenyloxirane (7m):



7m

Following **general procedure E**, alkylation of 2-naphthol (144 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7m** as a colorless gum. Yield: 77% (213 mg); mp: 109-111 °C (lit. mp: 108-109 °C) [8]; R_f: 0.55 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (m, 3H), 7.45 (m, 1H), 7.30 (m, 6H), 7.20 (m, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 4.33 (dd, *J* = 11.0, 3.0 Hz, 1H), 4.12 (dd, *J* = 11.0, 5.3 Hz, 1H), 3.90 (d, *J* = 1.9 Hz, 1H), 3.39 (dd, *J* = 4.5, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 136.5, 134.4, 129.6, 129.2, 128.6, 128.4, 127.7, 126.8, 126.5, 125.7, 123.9, 118.8, 107.0, 67.9, 60.2, 56.4. The spectroscopic and physical data were in agreement with the literature data [6,8].

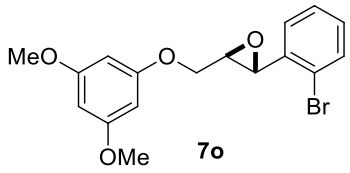
(±)-*trans*-2-((Naphthalen-1-yloxy)methyl)-3-phenyloxirane (7n):



7n

Following **general procedure E**, alkylation of 1-naphthol (144 mg, 1.0 mmol) with epoxy tosylate **21a** (319 mg, 1.05 mmol) was performed to obtain compound **7n** as a colorless semi-solid. Yield: 75% (207 mg); R_f: 0.55 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24(d, *J* = 8.5 Hz, 1H), 7.73(d, *J* = 6.5 Hz, 1H), 7.44-7.38 (m, 3H), 7.31-7.17 (m, 6H), 6.77 (d, *J* = 7.5 Hz, 1H), 4.42 (dd, *J* = 2.0, 11.0 Hz, 1H), 4.25 (dd, *J* = 5.0, 11.0 Hz, 1H), 3.94 (d, *J* = 2.0 Hz, 1H), 3.48-3.37 (m, 1H); Anal. calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84, found: C, 82.66; H, 5.76.

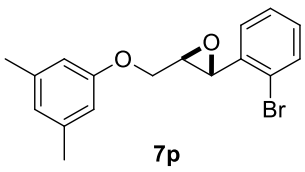
(±)-*trans*-2-(2-Bromophenyl)-3-((3,5-dimethoxyphenoxy)methyl)oxirane (7o):



7o

Following **general procedure E**, alkylation of 3,5-dimethoxyphenol (154 mg, 1.0 mmol) with epoxy tosylate **21b** (402 mg, 1.05 mmol) was performed to obtain compound **7o** as a colorless semi-solid. Yield: 80% (292 mg); R_f: 0.47 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.33-7.16 (m, 3H), 6.15 (d, *J* = 1.8 Hz, 2H), 6.12-6.11 (m, 1H), 4.42 (dd, *J* = 2.3, 11.0 Hz, 1H), 4.19 (d, *J* = 1.8 Hz, 1H), 4.08 (dd, *J* = 5.9, 11.4 Hz, 1H), 3.77 (s, 6H), 3.25-3.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 160.3, 136.1, 132.2, 129.4, 127.6, 126.3, 122.4, 93.5, 67.9, 59.8, 55.9, 55.4; Anal. calcd. for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69, found: C, 55.82; H, 4.72.

(±)-*trans*-2-(2-Bromophenyl)-3-((3,5-dimethylphenoxy)methyl)oxirane (7p):

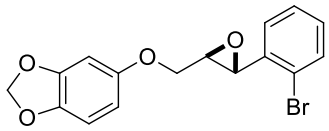


7p

Following **general procedure E**, alkylation of 3,5-dimethylphenol (122 mg, 1.0 mmol) with epoxy tosylate **21b** (402 mg, 1.05 mmol) was performed to obtain compound **7p** as a light yellow gum. Yield: 75% (250 mg); R_f: 0.58 (silica gel, 15% EtOAc in

hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.32-7.26 (m, 2H), 7.19-7.14 (m, 1H), 6.62 -6.60 (m, 3H), 4.40 (dd, *J* = 2.7, 11.5Hz, 1H), 4.18 (d, *J* = 2.3 Hz, 1H), 4.10 (dd, *J* = 5.5, 11.4 Hz, 1H), 3.24-3.21 (m, 1H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 139.2, 136.2, 132.2, 129.4, 127.6, 126.3, 123.0, 122.4, 112.4, 112.5, 67.7, 60.4, 55.9, 21.4; Anal. calcd. for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14, found: C, 61.21; H, 5.09.

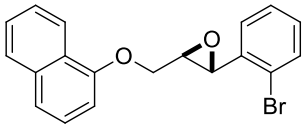
(±)-*trans*-5-((3-(2-Bromophenyl)oxiran-2-yl)methoxy)benzo[d][1,3]dioxole (7q):



7q

Following **general procedure E**, alkylation of sesamol (138 mg, 1.0 mmol) with epoxy tosylate **21b** (402 mg, 1.05 mmol) was performed to obtain compound **7q** as a white solid; Yield: 71% (248 mg); mp: 87-88 ^{o}C; R_f: 0.47 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.33-7.16 (m, 3H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.40 (dd, *J* = 2.3, 8.2 Hz, 1H),5.92 (s, 2H), 4.37 (dd, *J* = 2.7, 11.4 Hz, 1H), 4.17 (d, *J* = 1.8 Hz, 1H), 4.05 (dd, *J* = 5.5, 11.4 Hz, 1H), 3.23-3.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 148.2, 142.0, 136.1, 132.2, 129.4, 127.6, 126.3, 122.4, 107.9, 105.9, 101.2, 98.4, 68.9, 59.9, 55.9; Anal. calcd. for $C_{16}H_{13}BrO_4$: C, 55.04; H, 3.75, found: C, 55.14; H, 3.66.

(±)-*trans*-2-(2-Bromophenyl)-3-((naphthalen-1-yloxy)methyl)oxirane (7r):

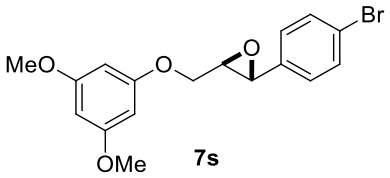


7r

Following **general procedure E**, alkylation of 1-naphthol (144 mg, 1.0 mmol) with epoxy tosylate **21b** (402 mg, 1.05 mmol) was performed to obtain compound **7r** as a colorless gum. Yield: 68% (242 mg); R_f: 0.56 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 10.0 Hz, 1H), 7.80 (d, *J* = 9.6 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.52-7.32 (m, 6H), 7.22-7.18 (m, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 4.60 (dd, *J* = 2.7, 11.0 Hz, 1H),), 4.36 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.31 (d, *J* = 2.3 Hz, 1H), 3.40-3.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 136.2, 134.5, 132.3, 129.5,

127.7, 127.4, 126.5, 126.3, 125.7, 125.6, 125.3, 122.4, 122.0, 120.9, 105.0, 68.1, 59.9, 56.1; Anal. Calcd. for $C_{19}H_{15}BrO_2$: C, 64.24; H, 4.26, found: C, 64.28; H, 4.35.

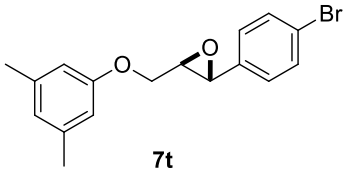
(±)-*trans*-2-(4-Bromophenyl)-3-((3,5-dimethoxyphenoxy)methyl)oxirane (7s):



7s

Following **general procedure E**, alkylation of 3,5-dimethoxyphenol (154 mg, 1.0 mmol) with epoxy tosylate **21c** (402 mg, 1.05 mmol) was performed to obtain compound **7s** as a colorless solid; Yield: 85% (310 mg); mp: 69-71 °C (lit. mp: 73-74 °C) [7]. R_f: 0.45 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.12 (s, 3H), 4.27 (dd, *J* = 3.2, 11.2 Hz, 1H), 4.09 (dd, *J*= 5.1, 11.2 Hz, 1H), 3.88 (d, *J* = 1.7 Hz, 1H), 3.76 (s, 6H), 3.30-3.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 160.2, 135.6, 131.7, 127.3, 122.3, 93.6, 93.5, 67.6, 60.1, 55.7, 55.4. The spectroscopic and physical data were in agreement with the literature data [7].

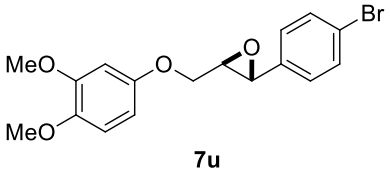
(±)-*trans*-2-(4-Bromophenyl)-3-((3,5-dimethylphenoxy)methyl)oxirane (7t):



7t

Following **general procedure E**, alkylation of 3,5-dimethylphenol (122 mg, 1.0 mmol) with epoxy tosylate **21c** (402 mg, 1.05 mmol) was performed to obtain compound **7t** as a light yellow liquid; Yield: 71% (237 mg); R_f: 0.59 (silica gel, 15% EtOAc in hexanes); Compound **7j** was immediately used for the next step without characterization.

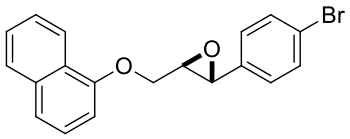
(±)-*trans*-2-(4-Bromophenyl)-3-((3,4-dimethoxyphenoxy)methyl)oxirane (7u):



7u

Following **general procedure E**, alkylation of 3,4-dimethoxyphenol (154 mg, 1.0 mmol) with epoxy tosylate **21c** (402 mg, 1.05 mmol) was performed to obtain compound **7u** as a white semi-solid; Yield: 74% (270 mg); R_f: 0.46 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J*=8.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H),6.34 (dd, *J* = 3.0, 9.0 Hz, 1H), 4.18 (dd, *J* = 3.0, 11.0 Hz, 1H), 4.01 (dd, *J* = 4.5, 11.0 Hz, 1H), 3.79-3.75 (m, 7H), 3.24 (d, *J* = 1.5 Hz, 1H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 149.9, 144.0, 135.6, 131.7, 127.3, 122.3, 111.6, 104.0, 101.2, 68.2, 60.4, 56.4, 55.8, 55.7; Anal. calcd for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69, found: C, 55.88; H, 4.62.

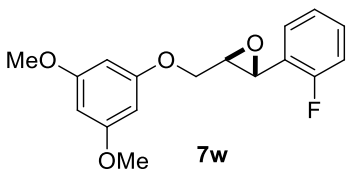
(±)-*trans*-2-(4-Bromophenyl)-3-((naphthalen-1-yloxy)methyl)oxirane (7v):



7v

Following **general procedure E**, alkylation of 1-naphthol (144 mg, 1.0 mmol) with epoxy tosylate **21c** (402 mg, 1.05 mmol) was performed to obtain compound **7v** as a white solid; Yield: 76% (270 mg); mp.: 144-145 ^{o}C; R_f: 0.58 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.27 (m, 1H), 7.80 (d, *J* = 2.3 Hz, 1H), 7.51-7.45 (m, 5H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.48 (dd, *J* = 3.2, 11.0 Hz, 1H), 4.31 (dd, *J* = 5.0, 11.0 Hz, 1H), 3.97 (d, *J* = 1.8 Hz, 1H), 3.48-3.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 135.7, 134.6, 131.7, 127.5, 127.4, 126.6, 125.7, 125.6, 125.4, 122.3, 121.9, 121.0, 105.1, 67.9, 60.3, 55.8; Anal. Calcd for $C_{19}H_{15}BrO_2$: C, 64.24; H, 4.26, found: C, 64.29; H, 4.34.

(±)-*trans*-2-((3,5-Dimethoxyphenoxy)methyl)-3-(2-fluorophenyl)oxirane (7w):

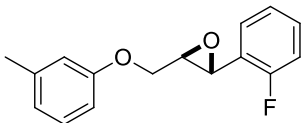


7w

Following **general procedure E**, alkylation of 3,5-Dimethoxyphenol (154 mg, 1.0 mmol) with epoxy tosylate **21d** (338 mg, 1.05 mmol) was performed to obtain compound **7w** as a colorless gum; Yield: 84% (250 mg); R_f: 0.49 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.02 (m, 4H), 6.13-6.10 (m, 3H), 4.33

(dd, *J* = 2.7, 11.0 Hz, 1H), 4.19 (d, *J* = 1.8 Hz, 1H), 4.06 (dd, *J* = 5.5, 11.4 Hz, 1H), 3.76 (s, 6H), 3.39-3.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 161.4 (d, *J* = 247.3 Hz), 160.2, 159.5, 155.4, 129.6 (d, *J* = 7.7 Hz), 126.1 (d, *J* = 3.8 Hz), 124.3 (d, *J* = 2.9 Hz), 123.8 (d, *J* = 12.5 Hz),115.2 (d, *J* = 21.1 Hz), 93.51, 93.48, 67.8, 59.5, 55.28, 55.30, 50.6 (d, *J* = 7.7 Hz),; Anal. calcd. for $C_{17}H_{17}FO_4$: C, 67.10; H, 5.63, found: C, 67.56; H, 5.73.

(±)-*trans*-2-((3,5-Dimethylphenoxy)methyl)-3-(2-fluorophenyl)oxirane (7x):



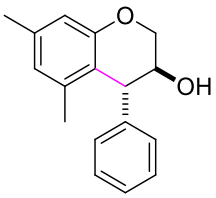
7x

Following **general procedure E**, alkylation of 3,5-dimethylphenol (122 mg, 1.0 mmol) with epoxy tosylate **21d** (338 mg, 1.05 mmol) was performed to obtain compound **7x** as a colorless gum; Yield: 84% (229 mg); R_f: 0.58 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.03 (m, 4H), 6.63-6.59 (m, 3H), 4.33 (dd, *J* = 3.0, 11.2 Hz, 1H), 4.19 (d, *J* = 1.7 Hz, 1H), 4.10 (dd, *J* = 5.2, 11.2 Hz, 1H), 3.39-3.36 (m, 1H), 2.29 (s, 3H); Anal. calcd. for $C_{17}H_{17}FO_2$: C, 74.98; H, 6.29, found: C, 74.87; H, 6.20.

General procedure F: synthesis of (±)-*trans*-4-arylchroman-3-ols 8a-x by TsOH·H_2O-catalyzed IFCEAC of (±)-*trans*-2-aryl-3-(aryloxymethyl)oxiranes (Table 2.2):

To a stirred solution of (±)-*trans*-2-aryl-3-(aryloxymethyl)oxiranes **7** (0.4 mmol) in AR grade toluene (8 mL) and MeCN (2 mL) was added TsOH.H_2O (16 mg, 0.084 mmol). The resulting mixture was then heated at 70 °C. When the reaction was completed (approx. 30 min), the mixture was cooled to room temperature, and then poured in beaker containing EtOAc (25 mL) and saturated aq. $NaHCO_3$ solution (25 mL) with vigorous stirring. The organic layer was separated and the aq. layer was extracted by EtOAc (20 x 2mL). The combined organic layers were washed with brine (50 mL) and dried over anh. Na_2SO_4. After filtration, the solution was evaporated to anh.ness under reduced pressure. The residue was subjected to silica gel column chromatography (with 5-20% EtOAc/hexanes) to afford the desired (±)-*trans*-4-arylchroman-3-ol 8a-x.

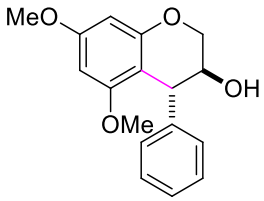
(±)-*trans*-5,7-Dimethyl-4-phenylchroman-3-ol (8a):



8a

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7a** (102 mg, 0.4 mmol) was performed to obtain compound **8a** as a white solid. Yield: 94% (239 mg); mp: 125-126 °C (lit. mp: 127-128 °C) [7]. R_f: 0.45 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.66 (s, 1H), 6.64 (s, 1H), 4.13 (m, 1H), 4.05-4.04 (m, 1H), 4.01-3.96 (m, 2H), 2.28 (s, 4H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 142.6, 139.2, 138.0, 128.7, 128.5, 126.7, 124.5, 116.0, 114.9, 69.9, 64.4, 46.5, 21.1, 18.9; Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13, found: C, 80.36; H, 7.19. The physical and spectral data are in well agreement with the literature reported data [7,8].

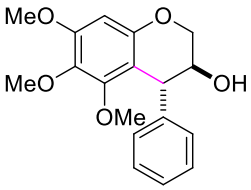
(±)-*trans*-5,7-Dimethoxy-4-phenylchroman-3-ol (8b):



8b

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7b** (115 mg, 0.4 mmol) was performed to obtain compound **8b** as a white solid; Yield: 92% (263 mg); mp: 101-102 °C (lit. mp: 100-101°C) [7]. R_f: 0.39 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 2H), 7.19-7.16 (m, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 4.22 (m, 1H), 4.02-3.92 (m, 3H), 3.78 (s, 3H), 3.55 (s, 3H), 2.1 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 159.6, 154.9, 143.3, 128.3, 128.0, 126.3, 101.6, 92.8, 92.3, 69.2, 64.9, 55.4, 55.2, 43.2; Anal. calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34, found: C, 71.40; H, 6.36. The physical and spectral data are in well agreement with the literature reported data [7,8].

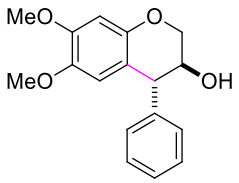
(±)-*trans*-5,6,7-Trimethoxy-4-phenylchroman-3-ol (8c):



8c

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7c** (127 mg, 0.4 mmol) was performed to obtain compound **8c** as a white semi-solid. Yield: 84% (106 mg); R_f: 0.35 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 3H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.31 (s, 1H), 4.23 (m, 1H), 3.99 (m, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 149.8, 143.8, 136.6, 128.3, 128.1, 126.5, 106.9, 95.5, 69.1, 64.9, 60.6, 60.1, 55.7, 44.1; Anal. calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37, found: C, 68.41; H, 6.39.

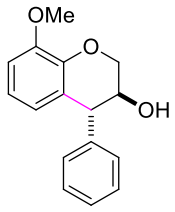
(±)-*trans*-6,7-Dimethoxy-4-phenylchroman-3-ol (8d):



8d

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7d** (115 mg, 0.4 mmol) was performed to obtain compound **8d** as a White semi-solid. Yield: 83% (95 mg); mp: 118-119 ^{o}C; R_f: 0.40 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.19 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.49 (s, 1H), 6.33 (s, 1H), 4.09-4.06 (m, 1H), 4.03 (d, *J* = 2.0 Hz, 2H), 3.98-3.93 (m, 1H), 3.88 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 147.9, 143.8, 142.8, 128.9, 128.5, 126.8, 113.1, 111.9, 100.2, 69.9, 66.2, 56.2, 55.7, 49.3; Anal. calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34, found: C, 71.25; H, 6.42.

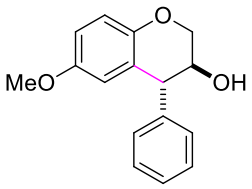
(±)-*trans*-8-Methoxy-4-phenylchroman-3-ol (8e):



8e

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7e** (103 mg, 0.4 mmol) was performed to obtain compound **8e** as a white solid. Yield: 82% (85 mg); mp: 140-142 ^{o}C; R_f: 0.45 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.02 (m, 5H), 6.73-6.68 (m, 2H), 6.39 (d, *J* = 7.4 Hz, 1H), 4.13-3.99 (m, 4 H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 142.5, 130.2, 129.0, 128.6, 128.4, 126.9, 122.8, 120.7, 109.4, 69.4, 66.8, 55.7, 49.7; Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29, found: C, 75.07; H, 6.32.

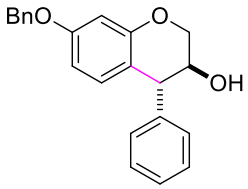
(±)-*trans*-6-Methoxy-4-phenylchroman-3-ol (8f):



8f

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7f** (103 mg, 0.4 mmol) was performed to obtain compound **8f** as a white solid. Yield: 84% (86 mg); mp: 114-115 °C (lit. mp: 115-116 °C) [7]; R_f: 0.53 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.30-7.25 (m, 1H), 7.18-7.16 (m, 2H), 6.89 (d, *J* = 9.1 Hz, 1H), 6.79 (dd, *J* = 3.0, 9.1 Hz, 1H), 6.42 (d, *J* = 2.9 Hz, 1H), 4.15 (d, *J* = 10.5 Hz, 1H), 4.09-4.12 (m, 2H), 3.99-3.97 (m, 1H), 3.67 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 153.9, 148.0, 142.5, 129.0, 128.6, 126.9, 122.5, 117.2, 115.2, 114.6, 69.7, 66.5, 55.5, 50.2; Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29, found: C, 74.91; H, 6.22. The physical and spectral data are in well agreement with the literature reported data [7,8].

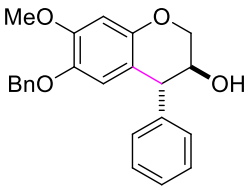
(±)-*trans*-7-(Benzyloxy)-4-phenylchroman-3-ol (8g):



8g

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7g** (133 mg, 0.4 mmol) was performed to obtain compound **8g** as a colorless semi-solid; Yield: 80% (106 mg); R_f: 0.48 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.24 (m, 8H), 7.14-7.12 (m, 2H), 6.76 (dd, *J* = 9.1 Hz, 1H), 6.55-6.53 (m, 2H), 5.02 (s, 2H), 4.16-3.96 (m, 4H), 2.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 154.8, 142.7, 136.8, 131.8, 129.0, 128.6, 128.5, 127.9, 127.5, 127.0, 114.3, 109.2, 102.0, 69.9, 69.7, 66.7, 49.5; Anal. calcd. for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06, found: C, 79.59; H, 6.11.

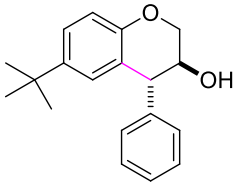
(±)-*trans*-6-(Benzyloxy)-7-methoxy-4-phenylchroman-3-ol (8h):



8h

Following general procedure F, TsOH·H_2O-catalyzed IFCEAC of **7h** (145 mg, 0.4 mmol) was performed to obtain compound **8h** as a colorless semi-solid. Yield: 87% (126 mg); R_f: 0.41 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 8H), 7.13-7.07 (m, 2H), 6.49 (s, 1H), 6.37 (s, 1H), 4.90 (s, 2H), 4.12-3.93 (m, 4H), 3.85 (s, 3H), 2.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 148.6, 142.8, 142.6, 137.1, 130.0, 128.9, 128.6, 128.3, 127.7, 127.5, 126.9, 117.0, 100.6, 71.8, 69.9, 66.6, 55.9, 49.6; Anal. calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12, found: C, 76.28; H, 6.05.

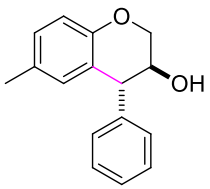
(±)-*trans*-6-(*tert*-Butyl)-4-phenylchroman-3-ol (8i):



8i

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7i** (113 mg, 0.4 mmol) was performed to obtain compound 8i as a white solid. Yield: 74% (84 mg); mp: 108-109 °C (lit. mp: 110-111 °C) [7]; R_f: 0.52 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.21 (m, 4H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.15-4.08 (m, 3H), 4.08-3.99 (m, 1H), 1.98 (bs, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 144.1, 142.9, 129.1, 128.7, 128.1, 127.9, 125.3, 120.8, 116.0, 70.1, 66.5, 50.2, 34.1, 31.1; Anal. calcd. for $C_{19}H_{22}O_2$: C, 80.52; H, 7.59, found: C, 80.57; H, 7.53. The physical and spectral data are in well agreement with the literature reported data [7,8].

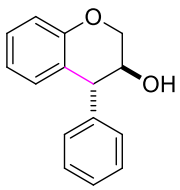
(±)-*trans*-6-Methyl-4-phenyl-chroman-3-ol (8j):



8j

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7j** (96 mg, 0.4 mmol) was performed to obtain compound **8j** as a white solid. Yield: 75% (72 mg); mp: 102-103 ^{o}C*;* R_f: 0.48 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.11 (m, 5H), 6.98-6.95 (m, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.67 (br s, 1H), 4.15-4.04 (m, 3H), 3.998-3.95 (m, 1H), 2.17 (s, 3H), 2.01 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 142.7, 131.4, 130.2, 129.1, 128.9, 128.6, 126.9, 121.5, 116.3, 69.8, 66.5, 50.1, 20.4; Anal. calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71, found: C, 79.92; H, 6.78.

(±)-*trans*-4-Phenyl-chroman-3-ol (8k):

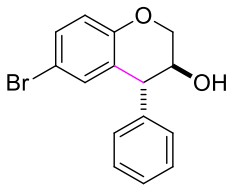


8k

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7k** (90 mg, 0.4 mmol) was performed to obtain compound **8k** as a white solid. Yield: 59% (54 mg); mp: 122-123 °C (lit. mp: 120-121 °C) [7]; R_f: 0.46 (silica gel, 30% EtOAc in hexanes); ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.35-7.13 (m, 6H), 6.92- 6.84 (m, 3H), 4.18 (dd, *J* = 2.1, 11.0 Hz, 1H), 4.09 (m, 2H), 4.02-3.98 (m, 1H), 2.08 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 142.6, 131.3, 129.1, 128.5, 128.2, 127.1, 122.1, 121.2, 116.6, 69.7, 66.7, 50.1; Anal. calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24, found: C, 79.68; H, 6.19. The physical and spectral data are in well agreement with the literature reported data [7,8].

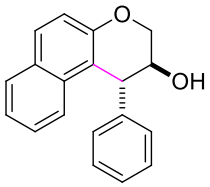
(±)-*trans*-6-Bromo-4-phenyl-chroman-3-ol (8l):



8l

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7l** (122 mg, 0.4 mmol) was performed to obtain compound **8l** as a white solid; Yield: 59% (54 mg); mp: 118-119 °C (lit. mp: 120-121 °C) [8]; R_f: 0.50 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.19 (m, 4H), 7.07 (d, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.18 (d, *J* = 2.1, 10.9 Hz, 1H), 4.11-3.97 (m, 3H), 1.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 141.9, 139.8, 137.1, 129.0, 129.0, 127.5, 124.8, 119.0, 83.5, 69.4, 66.5, 49.9*;* Anal. calcd. for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29, found: C, 59.10; H, 4.21. The physical and spectral data are in well agreement with the literature reported data [8].

(±)-*trans*-1-Phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-2-ol (8m):

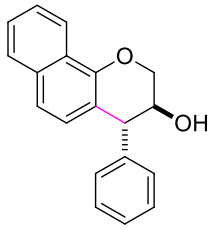


8m

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7m** (111 mg, 0.4 mmol) was performed to obtain compound **8m** as a white solid. Yield: 82% (90 mg); mp: 130-131 ^{o}C; R_f: 0.53 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.23 (m, 1H), 7.72-7.70 (m, 1H), 7.48-7.42 (m, 2H), 7.31-7.08 (m, 6H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.24-4.21 (m, 1H), 4.14-4.05 (m, 3H), 2.38 (bs, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 149.3, 142.8, 133.6, 129.2, 128.7, 128.5, 127.4, 127.0, 126.3, 125.6, 124.8, 121.8, 120.8,115.2, 69.9, 66.7, 50.1; Anal. calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84, found: C, 82.52; H, 5.89. The physical and spectral data are in well agreement with the literature reported data [6,8].

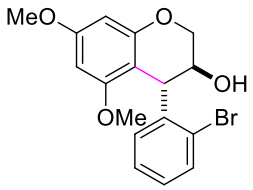
(±)-*trans*-4-Phenyl-3,4-dihydro-2*H*-benzo[*h*]chromen-3-ol (8n):



8n

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7n** (111 mg, 0.4 mmol) was performed to obtain compound **8n** as a white solid. Yield: 79% (87 mg); R_f: 0.52 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.73 (m, 2H), 7.48–7.45 (m, 1H), 7.30-7.15 (m, 8H), 4.68 (br s, 1H), 4.22–4.14 (m, 3H), 2.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 143.0, 133.4, 129.8, 129.3, 128.5, 126.8, 126.7, 123.5, 122.9, 118.5, 111.7, 69.7, 64.8, 45.9; Anal. calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84, found: C, 82.66; H, 5.89.

(±)-*trans*-4-(2-Bromophenyl)-5,7-dimethoxychroman-3-ol (8o):

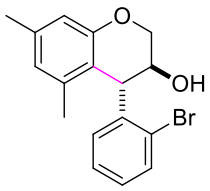


8o

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7o** (146 mg, 0.4 mmol) was performed to obtain compound **8o** as a white solid. Yield: 80% (116 mg); mp: 158-159 ^{o}C; R_f: 0.39 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, J = 1.4, 7.8 Hz, 1H), 7.15-7.03 (m, 2H), 6.75 (dd, J = 1.4, 7.8 Hz, 1H), 6.15 (d, J = 2.3 Hz, 1H), 6.06 (d, J = 2.3 Hz, 1H), 4.51 (m, 1H), 4.10-4.04 (m, 2H), 3.92-3.89 (m, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 1.87 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 155.3, 141.8, 132.8, 129.9, 128.1, 127.3, 124.5, 101.3, 92.8, 92.4, 66.7,

64.9, 55.5, 55.3, 43.1; Anal. calcd. for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69, found: C, 55.99; H, 4.57.

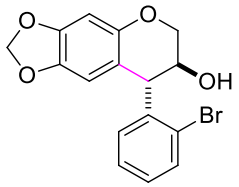
(±)-*trans*-4-(2-Bromophenyl)-5,7-dimethylchroman-3-ol (8p):



8p

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7p** (133 mg, 0.4 mmol) was performed to obtain compound **8p** as a white solid. Yield: 78% (104 mg); mp: 121-122 ^oC; R_f: 0.54 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.17-7.07 (m, 2H), 6.72 (dd, *J* = 1.4, 7.8 Hz, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 4.46 (m, 1H), 4.11-4.05 (m, 2H), 3.96-3.93 (m, 1H), 2.29 (s, 3H), 1.84 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 141.0, 138.8, 138.2, 133.0, 130.4, 128.5, 127.7, 124.7, 124.6, 115.7, 114.8, 67.1, 64.3, 45.9, 21.0, 18.5; Anal.Calcd for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14. Found: C, 61.39; H, 5.17.

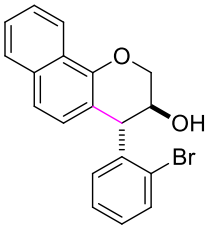
(±)-*trans*-8-(2-Bromophenyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-7-ol (8q):



8q

Following **general procedure F**, TsOH·H_2O-catalyzed **IFCEAC** of **7q** (140 mg, 0.4 mmol) was performed to obtain compound **8q** as a colorless semi-solid. Yield: 69% (96 mg); mp: 121-122 ^oC; R_f: 0.38 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.23-7.08 (m, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.49 (s, 1H), 6.28 (s, 1H), 5.92 (s, 2H), 4.43 (m, 1H), 4.15-3.95 (m, 3H), 2.15 (s, 1H); Anal. calcd. for $C_{16}H_{13}BrO_4$: C, 55.04; H, 3.75, found: C, 55.07; H, 3.66.

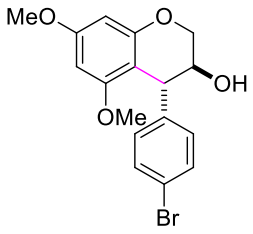
(±)-*trans*-4-(2-Bromophenyl)-3,4-dihydro-2*H* benzo[h]chromen-3-ol (8r):



8r

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7r** (142 mg, 0.4 mmol) was performed to obtain compound **8r** as a pale yellow semi-solid. Yield: 72% (102 mg); R_f: 0.54 (silica gel, 30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 9.1 Hz, 1H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.63 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.53-7.48 (m, 2H), 7.37 (d, *J* = 8.7 Hz, 1H),7.17-7.07 (m, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.75 (dd, *J* = 1.8, 7.8 Hz, 1H), 4.64 (m, 1H), 4.32-4.15 (m, 3H), 2.50 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 133.6, 133.0, 128.54, 128.51, 127.6, 127.4, 126.4, 125.6, 125.0, 124.7, 121.7, 121.1, 114.0, 67.7, 65.8, 48.7; Anal. Calcd. for $C_{19}H_{15}BrO_2$: C, 64.24; H, 4.26, Found: C, 64.31; H, 4.29.

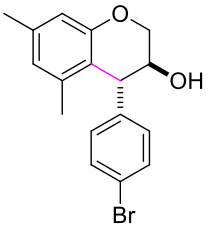
(±)-*trans*-4-(4-Bromo-phenyl)-5,7-dimethoxy-chroman-3-ol (8s):



8s

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7s** (146 mg, 0.4 mmol) was performed to obtain compound **8s** as a white solid. Yield: 87% (127 mg); mp: 76-77 °C (lit. mp: 77-78 °C) [7]. R_f: 0.38 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 6.14 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 4.16 (m, 1H), 4.02-3.95 (m, 2H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 2.30 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 159.5, 155.0, 142.5, 131.4, 129.7, 120.2, 101.3, 92.9, 92.4, 69.0, 64.9, 55.4, 55.3, 42.8; Anal. calcd. for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69, found: C, 55.99; H, 4.61. The physical and spectral data are in well agreement with the literature reported data [7].

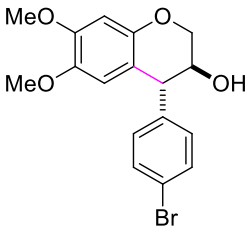
(±)-*trans*-4-(4-Bromo-phenyl)-6,7-dimethoxy-chroman-3-ol (8t):



8t

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7t** (133 mg, 0.4 mmol) was performed to obtain compound 8t as a White solid. Yield: 72% (105 mg); mp: 89-90 ^oC; R_f: 0.56 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.49 (s, 1H), 6.29 (s, 1H), 4.06 (d, *J* = 10.1 Hz, 1H), 4.01-3.99 (m, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 1.83 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 144.1, 141.9, 131.7, 130.6, 120.9, 112.8, 111.3, 100.3, 69.8, 66.2, 56.2, 55.8, 48.9; Anal. calcd. for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69, found: C, 55.97; H, 4.78.

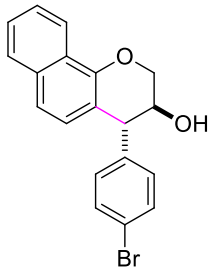
(±)-*trans*-4-(4-Bromo-phenyl)-5,7-dimethyl-chroman-3-ol (8u):



8u

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7u** (146 mg, 0.4 mmol) was performed to obtain compound **8u** as a white solid. Yield: 88% (117 mg); mp: 86-87 ^oC; R_f: 0.35 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 6.8 Hz, 1H), 4.07 (m, 1H), 4.03-3.99 (m, 2H), 3.92-88 (m, 1H), 2.28 (s, 3H), 1.97 (br s, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 141.7, 139.1, 138.4, 131.9, 130.3, 124.7, 115.5, 115.08, 69.7, 64.3, 46.0, 21.2, 18.9; Anal. calcd. for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14, found: C, 61.37; H, 5.31.

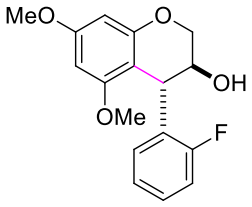
(±)-*trans*-4-(4-Bromo-phenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-3-ol (8v):



8v

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7v** (142 mg, 0.4 mmol) was performed to obtain compound **8v** as a white solid. Yield: 69% (98 mg); mp: 128-129 ^oC; R_f: 0.49 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 8.26-8.23 (m, 1H), 7.77-7.75 (m, 1H), 7.51-7.47 (m, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 4.28-4.21 (m, 1H), 4.23-4.11 (m, 3H), 2.43 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 141.9, 133.6, 131.8, 130.8, 128.2, 127.4, 126.5, 125.7, 124.8, 121.8, 121.1, 114.7, 69.8, 66.7, 49.5; Anal. calcd for $C_{19}H_{15}BrO_2$: C, 64.24; H, 4.26, found: C, 64.29; H, 4.38.

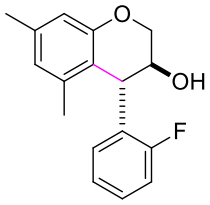
(±)-*trans*-4-(2-Fluorophenyl)-5,7-dimethoxychroman-3-ol (8w):



8w

Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7w** (109 mg, 0.4 mmol) was performed to obtain compound **8w** as a white solid. Yield: 68% (82 mg); mp: 146-147 ^oC; R_f: 0.51 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.23-7.17 (m, 1H), 7.09-7.04 (m, 1H), 6.99 (td, *J* = 7.3, 1.4 Hz, 1H), 6.75 (td, *J* = 7.8, 1.8 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 6.10 (d, *J* = 2.7 Hz, 1H), 4.52 (m, 1H), 4.11-4.05 (m, 2H), 3.93 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 2.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (d, *J* = 246.3 Hz), 160.4, 159.5, 155.4, 130.1 (d, *J* = 13.4 Hz), 129.7 (d, *J* = 4.8 Hz), 128.1 (d, *J* = 8.6 Hz), 124.0 (d, *J* = 2.9 Hz), 115.1 (d, *J* = 22.0 Hz), 100.5, 92.9, 92.4, 67.1, 65.3, 55.5, 55.3 (d, *J* = 1.9 Hz), 37.0; Anal. calcd. for $C_{17}H_{17}FO_4$: C, 67.10; H, 5.63, found: C, 67.05; H, 5.72.

(±)-*trans*-4-(2-Fluorophenyl)-5,7-dimethylchroman-3-ol (8x):



8x

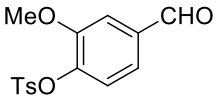
Following **general procedure F**, TsOH·H_2O-catalyzed IFCEAC of **7x** (122 mg, 0.4 mmol) was performed to obtain compound **8x** as a white solid; Yield: 66% (71 mg); mp: 132-133 ^oC; R_f: 0.40 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.19 (m, 1H), 7.10-6.97 (m, 2H), 6.70-6.64 (m, 3H), 4.43 (m, 1H), 4.11-4.04 (m, 2H), 3.96-3.93 (m, 1H), 2.29 (s, 4H), 1.89 (s, 3H); Anal. calcd. for $C_{17}H_{17}FO_2$: C, 74.98; H, 6.29, found: C, 75.08; H, 6.18.

Large scale synthesis of compound 8a (Scheme 2.5):

Following **general procedure F**, the reaction of 2.5 g of **7a** under the optimized reaction conditions delivered the corresponding product **8a** in 84% (2.1 g) yield.

Preparation of a *trans*-4-arylchroman-3-ol with free phenolic–OH groups on the two arene rings (Scheme 2.6):

4-Formyl-2-methoxyphenyl-4-methylbenzenesulfonate (23):

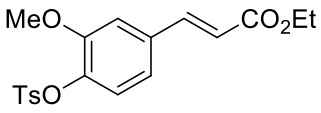


23

To a stirred solution of vanillin **22** (5.0 g, 32.86 mmol) in acetone (50 mL) was added K_2CO_3 (9.1 g, 65.7 mmol). After stirring the reaction mixture for 10 min at rt, TsCl (7.52 g, 39.4 mmol) was added to it. The reaction mixture was then heated at reflux temperature for 8 h and then cooled to rt, filtered and concentrated under reduced pressure. The resulting residue was re-dissolved in EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (5-25% ethyl acetate in hexanes) to give **23** (9.46 g, 94 %) as a white solid; mp: 124–126 °C (lit. mp: 125–128 °C) [11]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.46–7.28 (m, 5 H), 3.63 (s, 3 H), 2.4 (s, 3 H); ^{13}C NMR (100 MHz): δ 190.8,

152.4, 145.4, 142.8, 135.6, 132.6, 129.4, 128.4, 124.4, 124.2, 110.9, 55.6, 21.6. The physical and spectral data matched with the literature data [11].

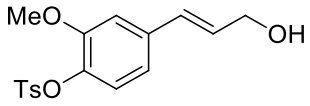
Ethyl (*E*)-3-(3-methoxy-4-tosyloxyphenyl)-2-propenoate (24):



24

Following **general procedure A**, aldehyde **23** (7.66 g, 25 mmol) was subjected to the HWE olefination reaction. The crude product was purified by a silica gel column chromatography (5-20% EtOAc in hexanes) to obtain compound **24** as a colorless oil. Yield: 96% (9.03 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 4.22 (q, *J* = 7.5 Hz, 2H), 3.58 (s, 3H), 2.43 (s, 3H), 1.32 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 151.9, 145.2, 143.2, 139.5, 134.3, 132.9, 129.3, 128.5, 124.2, 120.7, 119.2, 111.4, 60.5, 55.5, 21.6, 14.2. The physical and spectral data matched with the literature data [11].

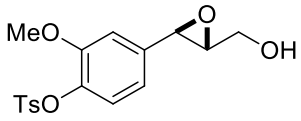
(*E*)-3-(3-Methoxy-4-tosyloxyphenyl)-2-propen-1-ol (25):



25

Following **general procedure B**, compound **24** (5.0 g, 13.28 mmol) was reduced by DIBAL-H. The crude product was purified by a silica gel column chromatography (5-30% EtOAc in hexanes) to obtain compound **25** as a colorless gum. Yield: 98% (4.36 g); R_f: 0.46 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.29 (dt, *J* = 16.0, 6.0 Hz, 1H), 4.32–4.28 (m, 2H), 3.54 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 145.0, 137.7, 136.8, 133.1, 129.8, 129.7, 129.3, 128.6, 123.9, 118.8, 110.2, 63.3, 55.4, 21.6. The physical and spectral data matched with the literature data [11].

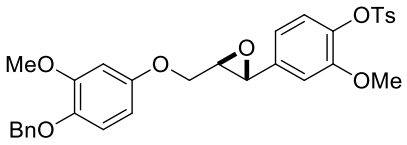
(±)-*trans*-3-(Hydroxymethyl)oxiran-2-yl)-2-methoxyphenyl 4-methylbenzene sulfonate (26):



26

Following **general procedure C**, compound **25** (3.34 g, 10.0 mmol) was epoxidized by *m*-CPBA. The crude product was purified by a silica gel column chromatography (5-25% EtOAc in hexanes) to obtain compound **26** as a colorless semi-solid. Yield: 90% (3.15 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 8.3 Hz, 3 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 6.82 (dd, *J* = 2.2, 8.3 Hz, 1 H), 4.05-3.95 (m, 1 H), 3.86 (d, *J* = 2.2 Hz, 1 H), 3.82-3.72 (m, 1 H), 3.57 (s, 3 H), 3.14-3.10 (m, 1 H), 2.44 (s, 3 H), 1.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 144.9, 138.0, 136.8, 133.0, 129.2, 128.3, 123.8, 117.8, 109.2, 62.5, 60.8, 55.4, 54.8, 29.5. The physical and spectral data matched with the literature data [11].

(±)-3-((4-(Benzyloxy)-3-methoxyphenoxy)methyl)oxiran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (27):



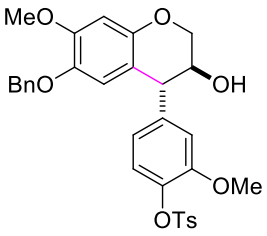
27

Following **general procedure D**, epoxy alcohol **26** (500 mg, 1.43 mmol) was subjected to the tosylation reaction. The crude product was recrystallized from EtOAc/hexane to obtain the corresponding pure epoxy tosylate as white solid (647 mg) which was used for the next step without further purification and characterization.

Following **general procedure E**, alkylation of 4-benzyloxy-3-methoxyphenol (281 mg, 1.22 mmol) with the epoxy tosylate (647 mg, 1.28 mmol), obtained from the above-mentioned reaction, was performed to obtain compound **27** as a colorless semi-solid. Yield: 65% (523 mg); R_f: 0.59 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75(d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.37-7.29 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.84 (dd, *J* = 1.9, 8.3 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.33 (dd, *J* = 2.8, 8.7 Hz, 1H), 5.08 (s, 2H), 4.25 (dd, *J*

= 3.2, 11.2 Hz, 1H), 4.06 (dd, *J* = 5.0, 11.2 Hz, 1H), 3.86 (s, 4H), 3.56 (s, 3H), 3.30-3.27 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 152.1, 150.9, 145.0, 142.9, 138.3, 137.4, 136.7, 133.2, 129.4, 128.6, 128.5, 127.8, 127.4, 124.0, 118.1, 115.4, 109.2, 104.1, 101.3, 72.0, 68.1, 60.4, 55.9, 55.8, 55.6, 55.6, 21.6; Anal. calcd. for $C_{31}H_{30}O_8S$: C, 66.18; H, 5.37, found: C, 66.08; H, 5.44.

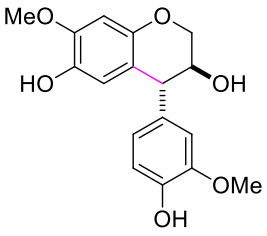
(±)-*trans*-4-(6-(Benzyloxy)-3-hydroxy-7-methoxychroman-4-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (28):



28

Compound **28** was prepared according to the **general procedure F**, starting from **27** (0.5 g, 0.88 mmol). Column chromatography: 10-20% ethyl acetate in hexanes as elution gradient. Yield: 85% (425 mg); light yellow semi-solid; R_f: 0.39 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.31-7.26 (m, 8H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.57 (s, 1H), 6.47 (s, 1H), 6.31 (s, 1H), 4.96-4.88 (m, 2H), 4.05 (dd, *J* = 3.2 and 11.2 Hz, 1H), 3.99-3.90 (m, 3H), 3.85 (s, 3H), 3.49(s, 3H), 2.43 (s, 3H), 2.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 150.2, 148.6, 145.0, 142.7, 137.3, 137.0, 133.4, 129.4, 128.5, 128.4, 127.8, 127.4, 123.8, 121.0, 116.9, 113.0, 111.7, 100.6, 71.8, 69.7, 66.7, 55.9, 55.6, 49.6, 21.6; Anal. calcd. for $C_{31}H_{30}O_8S$: C, 66.18; H, 5.37, found: C, 66.26; H, 5.42.

(±)-*trans*-4-(4-Hydroxy-3-methoxyphenyl)-7-methoxychroman-3,6-diol (29):



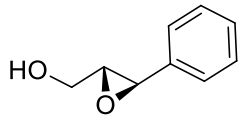
29

To a solution of compound **28** (0.3 g, 0.53mmol) in MeOH (5 mL) was added K_2CO_3 (371 mg, 2.65mmol) and the mixture heated at reflux temperature for 4 h. Methanol was

removed in a rotary evaporator and the resulting residue was dissolved in beaker containing EtOAc (50 mL) and 1 M HCl (50 mL) and stirred vigorously. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated to obtain a light brown semi-solid which was used for the next step without further purification. This detosylated product was then dissolved in EtOAc (50 mL) and purged with nitrogen by repeated filling and deflating of a nitrogen balloon. 10% Pd-C (50 mg) was added to this solution. After degassing under reduced pressure, the flask was purged with hydrogen using a rubber balloon. After stirred at rt and normal pressure under the hydrogen atmosphere for 2 h, the reaction solution was suction-filtered using Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (10-30% EtOAc in hexanes) to obtain compound **29** (118 mg, 70% over the two steps) as brown semi-solid. R_f: 0.25 (silica gel, 60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, J = 8.1 Hz, 1H), 6.68-6.60 (m, 2H), 6.44 (s, 1H), 6.40 (s, 1H), 5.61 (br s, 1H), 5.22 (br s, 1H), 4.50 (m, 1H), 4.15-4.09 (m, 2H), 3.96-3.89 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 2.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 146.7, 146.3, 144.7, 140.1, 134.3, 122.0, 115.5, 114.4, 113.9, 111.1, 99.5, 70.0, 66.9, 55.9, 49.8; Anal. calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70, found: C, 64.72; H, 5.61.

IFCEAC with chiral substrate (Scheme 2.7):

Synthesis of (2*R*,3*R*)-3-phenyloxiran-2-yl)methanol {(2*R*,3*R*)-20a}:

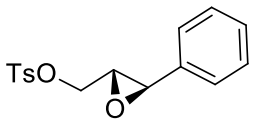


(2*R*,3*R*)-20a

A mixture of activated 3Å molecular sieves (0.9 g) and 50 mL of anh. CH_2Cl_2 was cooled to −10 °C. Diethyl D-(-)-tartrate (0.5 g, 2.4 mmol), $Ti(O^iPr)_4$ (0.45 g, 1.6 mmol), and ^{t}BuOOH (7.8 mL, 48 mmol 6.2 M in CH_2Cl_2) were added sequentially. The resulting suspension was stirred for 20 min at this temperature. Then, the mixture was cooled to −20 °C and cinnamyl alcohol **19a** (4.35 g, 32.5 mmol in 10 mL of CH_2Cl_2) was added with stirring over a time period of 15 min. Stirring was continued for 12 h at -20 °C. The reaction mixture was then allowed to come to 0 °C and quenched with water (10 mL). Next, the mixture was treated with 2.5 mL of a 30% aqueous solution of sodium

hydroxide saturated with sodium chloride and was stirred for 10 min. The aqueous layer was separated and washed with CH_2Cl_2 (2×40 mL). Combined organic layers were dried with anh. Na_2SO_4 and concentrated under reduced pressure. The resulting lite yellow liquid was purified by column chromatography (5-20% EtOAc in hexanes) as colorless gum (896 mg, 80%); $[\alpha]^{27}_D$ = +48.2 (c 2.25, $CHCl_3$) {lit. $[\alpha]^{27}_D$ = -49.6 (c 2.4, $CHCl_3$) for **(2*S*,3*S*)-20a**} [20]. The spectroscopic data were identical with the racemic substrate **20a**.

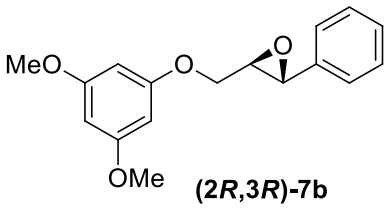
Synthesis of ((2*R*,3*R*)-3-Phenyloxiran-2-yl)methyl 4-methylbenzenesulfonate {(2*R*,3*R*)-21a}:



(2*R*,3*R*)-21a

Following the synthesis of racemic **21a**, **(2*R*,3*R*)-21a** was synthesized from **(2*R*,3*R*)-20a**. $[\alpha]^{27}_D$ = +44.6 (c = 2.5, $CHCl_3$); {lit. $[\alpha]^{27}_D$ = −41.7 (c = 1.27, $CHCl_3$) [22] and $[\alpha]^{27}_D$ = −45.0 (c = 2.5, $CHCl_3$) [23] for the **(2*S*,3*S*))-21a**}; yield and spectral data of **(2*R*,3*R*)-21a** were identical with that of racemic **21a**.

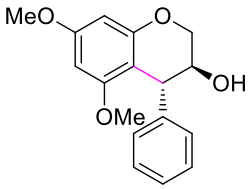
Synthesis of (2*R*,3*R*)-2-((3,5-Dimethoxyphenoxy)methyl)-3-phenyloxirane {(2*R*,3*R*)-7b}:



(2*R*,3*R*)-7b

Following the synthesis of racemic **7b**, **(2*R*,3*R*)-7b** was synthesized from **(2*R*,3*R*)-21a** and 3,5-dimethoxyphenol. $[\alpha]^{27}_D$ = +52.4 (c = 1.0, $CHCl_3$); {lit. $[\alpha]^{27}_D$ = +52.6 (c = 1.2, $CHCl_3$) [7] and $[\alpha]^{20}_D$ = +54.0 (c = 1.0, $CHCl_3$) [8]}; yield and spectral data of **(2*R*,3*R*)-7b** were identical with that of racemic **7b**.

Synthesis of (3*S*,4*R*)-5,7-Dimethoxy-4-phenylchroman-3-ol{(3*S*,4*R*)-8b}:

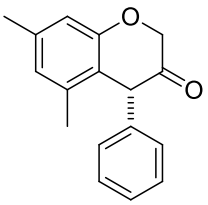


(3*S*,4*R*)-8b

Following the synthesis of racemic **8b**, **(3*S*,4*R*)-8b** was synthesized from **(2*R*,3*R*)-7b**. $[\alpha]^{27}_{D}$ = +51.5 (c = 1.0, $CHCl_3$); {lit. $[\alpha]^{27}_{D}$ = +52.3 (c = 1.1, $CHCl_3$) [7] and $[\alpha]^{20}_{D}$ = +53.0 (c = 1.0, $CHCl_3$) [8]}; yield and spectral data of **(3*S*,4*R*)-8b** were identical with that of racemic **8b**.

Conversion of *trans*-4-arylchroman-3-ols to the corresponding *cis*-4-arylchroman-3-ols (Scheme 2.9):

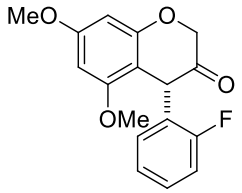
(±)-5,7-Dimethyl-4-phenylchroman-3-one (30a):



30a

To a stirred solution of (±)-*trans*-5,7-dimethyl-4-phenylchroman-3-ol **8a** (254 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (504 mg, 1.18 mmol) at 0 ^{o}C and the resulting solution was stirred at rt for 12 h. The reaction mixture was quenched with a saturated solution of Na_2SO_3 and $NaHCO_3$ (15 mL each). The reaction mixture was passed through a pad of celite. The combined organic phase was dried over anh. Na_2SO_4, and chromatographed on silica gel column (2-10% EtOAc in hexanes) to get **30a** (228 mg, 90%) as colorless gum. R_f: 0.58 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 3H), 7.18 (d, *J* = 7.4 Hz, 2H), 6.83 (s, 1H), 6.79 (s, 1H), 4.84 (s, 1H), 4.61 (d, *J* = 17.8 Hz, 1H), 4.33 (d, *J* = 17.8 Hz, 1H), 2.35 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 154.5, 138.8, 137.7, 135.6, 128.9, 127.8, 127.5, 126.0, 119.9, 116.1, 71.6, 53.5, 21.1, 18.4; Anal. calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39, found: C, 80.88; H, 6.50.

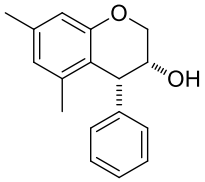
(±)-4-(2-Fluorophenyl)-5,7-dimethoxychroman-3-one (30b):



30b

Starting from compound **8w** (305 mg, 1 mmol), the title compound was isolated as colorless gum in the same manner as described for compound **30a**. Yield: 91% (278 mg); R_f: 0.48 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.17 (m, 1H), 7.10-6.99 (m, 3H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 5.21 (s, 1H), 4.66 (dd, *J* = 16.9, 0.9 Hz, 1H), 4.41 (dd, *J* = 16.9, 1.3 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 160.9, 160.7 (d, *J* = 247.1 Hz), 158.4, 156.0, 129.9 (d, *J* = 5.2 Hz), 128.8 (d, *J* = 7.8 Hz), 125.6 (d, *J* = 15.6 Hz), 124.1, 115.6 (d, *J* = 20.8 Hz), 72.4, 55.6, 55.4, 43.5; Anal. calcd. for $C_{17}H_{15}FO_4$: C, 67.54; H, 5.00, found: C, 67.59; H, 5.07.

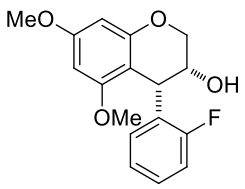
(±)-*cis*-5,7-Dimethyl-4-phenylchroman-3-ol (31a):



31a

To a stirred solution of **30a** (101 mg, 0.4 mmol) in THF (5 mL) and water (1 mL), was added $NaBH_4$ (75 mg, 2.0 mmol) at 0 ^oC. The mixture was stirred at room temperature for 30 min and then quenched by addition of saturated aq. solution of NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (2×20 mL), washed brine (40 mL) and dried over Na_2SO_4. After filtration, the solution was evaporated to anh.ness under reduced pressure. The residue was subjected to silica gel column chromatography (with 5-20% EtOAc in hexanes) to obtain **31a** as white solid. Yield: 98% (99 mg); R_f: 0.47 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.17 (m, 3H), 7.04 (d, *J* = 6.6 Hz, 2H), 6.54 (s, 1H), 6.50 (s, 1H), 4.26-4.22 (m, 2H), 3.93-3.89 (m, 1H), 3.67 (t, *J* = 10.5 Hz, 1H), 2.19 (s, 4H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 138.1, 138.0, 130.3, 128.5, 127.3, 123.9, 117.8, 114.5, 65.5, 64.4, 44.9, 21.0, 19.0; Anal. calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13, found: C, 80.32; H, 7.19.

(±)-*cis*-4-(2-Fluorophenyl)-5,7-dimethoxychroman-3-ol (31b):

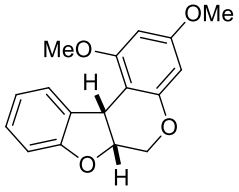


31b

Starting from compound **30b** (100 mg, 0.33 mmol), the title compound was prepared in same manner as described for compound **31a**. Yield: 97% (98 mg); light yellow gum; R_f: 0.42 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.18 (m, 1H), 7.09-6.99 (m, 2H), 6.86 (td, *J* = 7.4, 1.3 Hz, 1H), 6.13 (d, *J* = 2.3 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 4.82 (d, *J* = 5.9 Hz, 1H), 4.38-4.33 (m, 1H), 4.05-4.01 (m, 1H), 3.86 (t, *J* = 10.1 Hz, 1H), 3.79 (s, 3H), 3.55 (s, 3H), 2.02 (br, s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (d, *J* = 243.5 Hz), 160.4, 158.6, 155.9, 130.7 (d, *J* = 4.8 Hz), 128.1 (d, *J* = 8.6 Hz), 127.1 (d, *J* = 14.4 Hz), 123.6 (d, *J* = 2.9 Hz), 114.7 (d, *J* = 23.0 Hz), 102.6, 92.7, 92.1, 65.4, 64.9, 55.4 (d, *J* = 1.9 Hz), 55.2 (d, *J* = 1.9 Hz), 34.8; Anal. calcd. for $C_{17}H_{17}FO_4$: C, 67.10; H, 5.63, found: C, 67.18; H, 5.57.

Preparation of Chroman-Fused 2,3-Dihydrobenzofuran (Scheme 2.10)

***rel*-(6a*R*,11b*R*)-1,3-Dimethoxy-6a,11b-dihydro-6*H*-benzofuro[2,3-*c*]chromene (33):**



33

To a solution of compound **31b** (60 mg, 0.19 mmol) in THF (5 mL) was added KOBu^t (33 mg, 0.29 mmol) under nitrogen atmosphere. The resulting mixture was then refluxed for 3 h. After cooling to rt, the reaction mixture was quenched by adding H_2O (5 mL) and then extracted with EtOAc (20 mL). The combined organic phase was dried over anh. Na_2SO_4, concentrated, and chromatographed (5-15% EtOAc in hexanes) on silica gel column to get **33** (38 mg, 70%) as white solid. R_f: 0.61 (silica gel, 30% EtOAc in hexanes); mp: 109-110 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.8 Hz, 1H), 7.11-7.07 (m, 1H), 6.82-6.78 (m, 2H), 6.17 (d, *J* = 2.3 Hz, 1H), 6.09 (d, *J* = 2.3 Hz, 1H),

5.17-5.13 (m, 1H), 4.84 (d, *J* = 9.1 Hz, 1H), 4.39 (dd, *J* = 3.7 and 11.9 Hz, 1H), 4.00 (dd, *J* = 2.7 and 11.9 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 159.0, 158.5, 130.9, 128.3, 126.2, 120.9, 109.6, 105.7, 99.9, 94.3, 93.0, 79.8, 66.7, 55.3, 55.4, 36.3; Anal. calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67, found: C, 71.89; H, 5.72.

2.7. References

[1] Ellis, G. P. and Lockhart, I. M. Chromenes, Chromanones, and Chromones. In *The Chemistry of Heterocyclic Compounds*, volume 31, pages 1-1196. Wiley-VCH, 2007.

[2] Goel, A., Kumar, A., and Raghuvanshi, A. Synthesis, Stereochemistry, Structural Classification, and Chemical Reactivity of Natural Pterocarpans. *Chemical Reviews*, 113(3):1614-1640, 2012.

[3] May, J. A., Sharif, N. A., McLaughlin, M. A., Chen, H. H., Severns, B. S., Kelly, C. R., and Dean, T. R. Ocular Hypotensive Response in Nonhuman Primates of (8*R*)-1-[(2*S*)-2-Aminopropyl]-8,9-dihydro-7*H*-pyrano[2,3-*g*]indazol-8-ol a Selective 5-HT2 Receptor Agonist. *Journal of Medicinal Chemistry*, 58(22):8818-8833, 2015.

[4] Aron, P. M. and Kennedy, J. A. Flavan-3-ols: nature, occurrence and biological activity. *Molecular Nutrition & Food Research*, 52(1):79-104, 2008.

[5] Andrianasolo, E. H., Haramaty, L., Rosario-Passapera, R., Bidle, K., White, E., Vetriani, C., and Lutz, R. Ammonificins A and B, Hydroxyethylamine Chroman Derivatives from a Cultured Marine Hydrothermal Vent Bacterium, *Thermovibrio ammonificans*. *Journal of Natural Products*, 72(6):1216-1219, 2009.

[6] Donnelly, D. M. X., Finet, J. P., Guiry, P. J., and Nesbitt, K. Synthesis of neoflavenes by ligand coupling reactions with aryllead triacetates. *Tetrahedron*, 57(2):413-423, 2001.

[7] Marcos, R., Rodríguez-Escrich, C., Herrerias, C. I., and Pericàs, M. A. Metal-Mediated Cyclization of Aryl and Benzyl Glycidyl Ethers: A Complete Scenario. *Journal of the American Chemical Society*, 130(50):16838-16839, 2008.

[8] Li, G.-X. and Qu, J. Friedel–Crafts alkylation of arenes with epoxides promoted by fluorinated alcohols or water. *Chemical Communications*, 2010(46):2653-2655, 2010.

[9] Liu, Y., Li, X., Lin, G., Xiang, Z., Xiang, J., Zhao, M., and Yang, Z. Synthesis of

Catechins via Thiourea/$AuCl_3$-Catalyzed Cycloalkylation of Aryl Epoxides. *The Journal of Organic Chemistry*, 73(12):4625-4629, 2008

[10] Li, L. Q., Li, M. M., Wang, K., and Qin, H. B. Total synthesis of (±)-brazilin and formal synthesis of (±)-brazilein,(±)-brazilide A using *m*-CPBA. *Tetrahedron Letters*, 54(45):6029-6031, 2013.

[11] Yadav, J. S., Pandurangam, T., Reddy, V. V. B., and Reddy, B. V. S. Total Synthesis of Rhoiptelol B. *Synthesis*, 2010(24):4300-4306, 2010.

[12] Rondot, C., Retailleau, P., and Zhu, J. Synthesis of Protected Chiral Vicinal Diaminoalcohols by Diastereoselective Intramolecular Benzylic Substitution from Bistrichloroacetimidates. *Organic Letters*, 9(2):247-250, 2007.

[13] Lu, J. and Toy, P. H. Organocatalytic Decarboxylative Doebner-Knoevenagel Reactions between Arylaldehydes and Monoethyl Malonate Mediated by a Bifunctional Polymeric Catalyst. *Synlett*, 2011(12):1723-1726, 2011.

[14] Basu, B., Das, S., Das, P., Mandal, B., Banerjee, D., and Almqvist, F. Palladium Supported on a Polyionic Resin as an Efficient, Ligand-Free, and Recyclable Catalyst for Heck, Suzuki-Miyaura, and Sonogashira Reactions. *Synthesis*, 2009(07):1137-1146, 2009.

[15] Kim, E., Koh, M., Lim, B. J., and Park, S. B. Emission Wavelength Prediction of a Full-Color-Tunable Fluorescent Core Skeleton, 9-Aryl-1,2-dihydropyrrolo[3,4-*b*]indolizin-3-one. *Journal of the American Chemical Society*, 133(17):6642-6649, 2011

[16] Davis, M. C. and Groshens, T. J. Synthesis of *p*-Quinquephenyl from *E*,*E*-1,4-Bis(4-bromophenyl)-1,3-butadiene. *Synthetic Communications*, 41(2):206-218, 2010.

[17] Petersen, M. Å., Mortensen, M. A., Cohrt, A. E., Petersen, R., Wu, P., Fleury-Brégeot, N., and Clausen, M. H. Synthesis of 1, 4, 5 trisubstituted γ-lactams via a 3-component cascade reaction. *Bioorganic & Medicinal chemistry*, 23(11):2695-2698, 2015.

[18] Gao, Y., Klunder, J. M., Hanson, R. M., Masamune, H., Ko, S. Y., and Sharpless, K. B. Catalytic Asymmetric Epoxidation and Kinetic Resolution: Modified Procedures Including in Situ Derivatization. *Journal of the American Chemical Society*, 109(19):5765-5780, 1987.

[19] Li, X. and Borhan, B. Prompt Determination of Absolute Configuration for Epoxy

Alcohols via Exciton Chirality Protocol. *Journal of the American Chemical Society*, 130(48):16126-16127, 2008.

[20] Balamurugan, R., Kothapalli, R. B., and Thota, G. K. Gold-Catalysed Activation of Epoxides: Application in the Synthesis of Bicyclic Ketals. *European Journal of Organic Chemistry*, 2011(8):1557-1569, 2011.

[21] Xu, M. H., Tu, Y. Q., Tian, J. M., Zhang, F. M., Wang, S. H., Zhang, S. H., and Zhang, X. M. Asymmetric epoxidation of α,β-unsaturated aldehydes catalyzed by a spiro-pyrrolidine-derived organocatalyst. *Tetrahedron: Asymmetry*, 27(6):294-300, 2016.

[22] Patel, A. R., Hu, X. G., Lawer, A., Ahmed, M. I., Au, C., Jwad, R., and Hunter, L. Scalable, stereoselective syntheses of α, β-difluoro-γ-amino acids. *Tetrahedron*, 72(23):3305-3317, 2016.

[23] Brunner, H. and Sicheneder, A. Synthesis of Optically Active Phosphanes via Sharpless Epoxidation. *Angewandte Chemie, International Edition*, 100(5):730-731, 1988

[24] Ebisawa, M., Ueno, M., Oshima, Y., and Kondo, Y. Synthesis of dictyomedins using phosphazene base catalyzed diaryl ether formation. *Tetrahedron Letters*, 48(50):8918-8921, 2007.

2.8. NMR Spectra of Selected Compounds

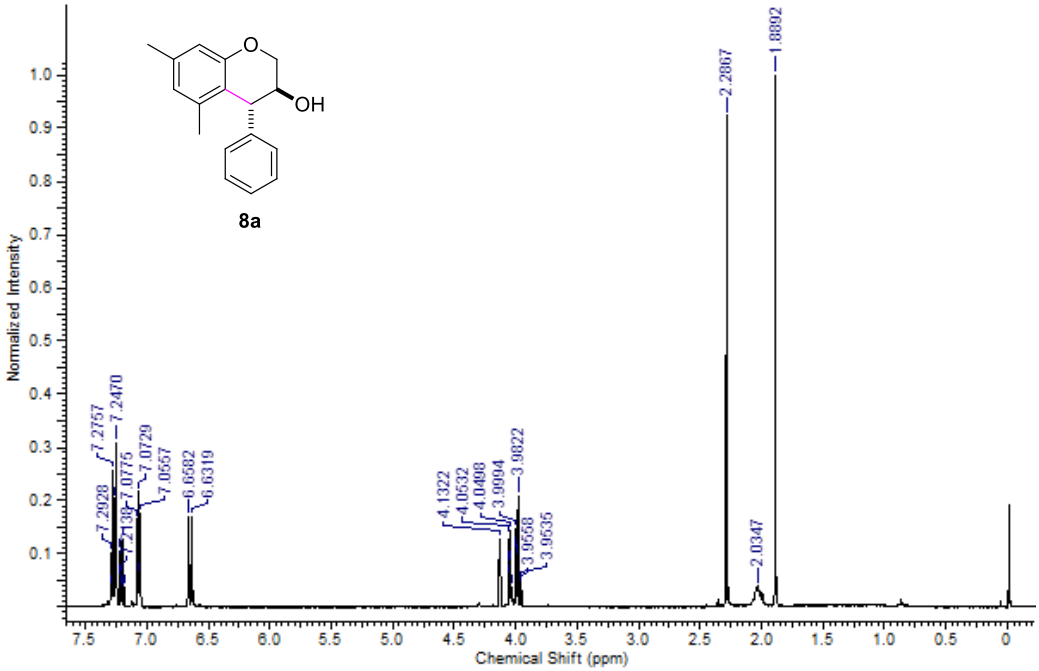


Figure 2.2. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 8a

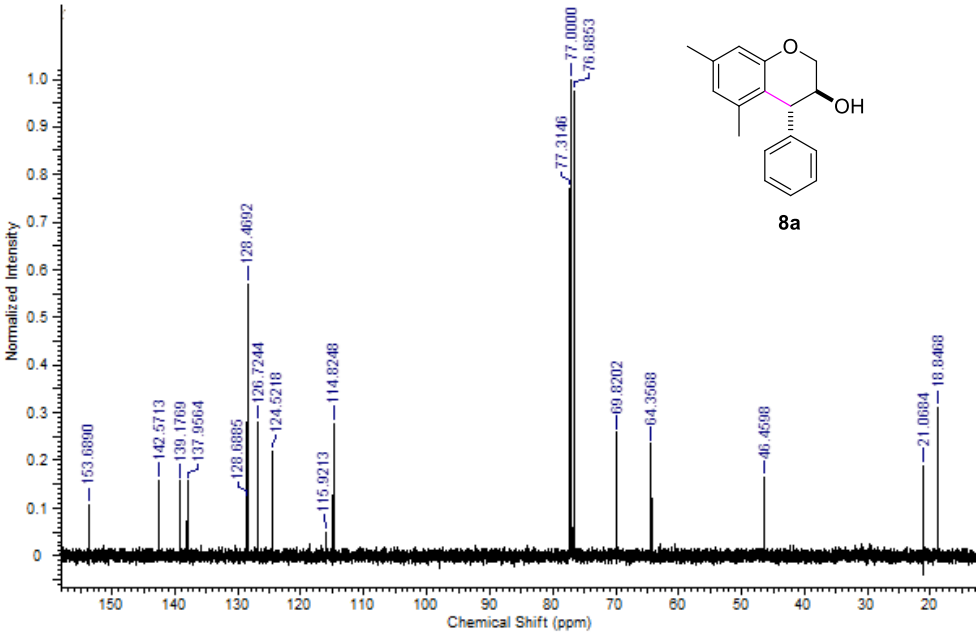


Figure 2.3. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 8a

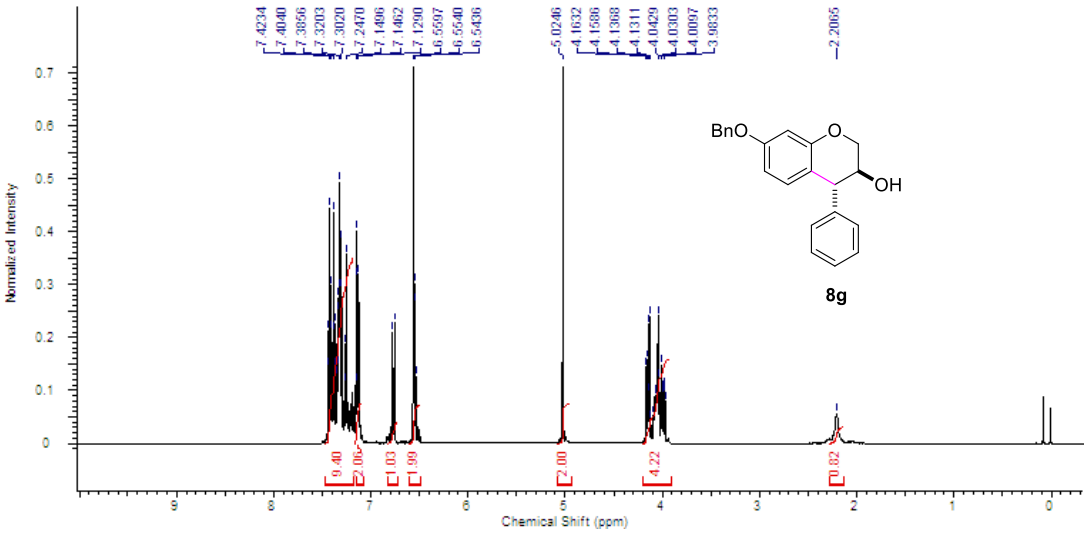


Figure 2.4. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 8g

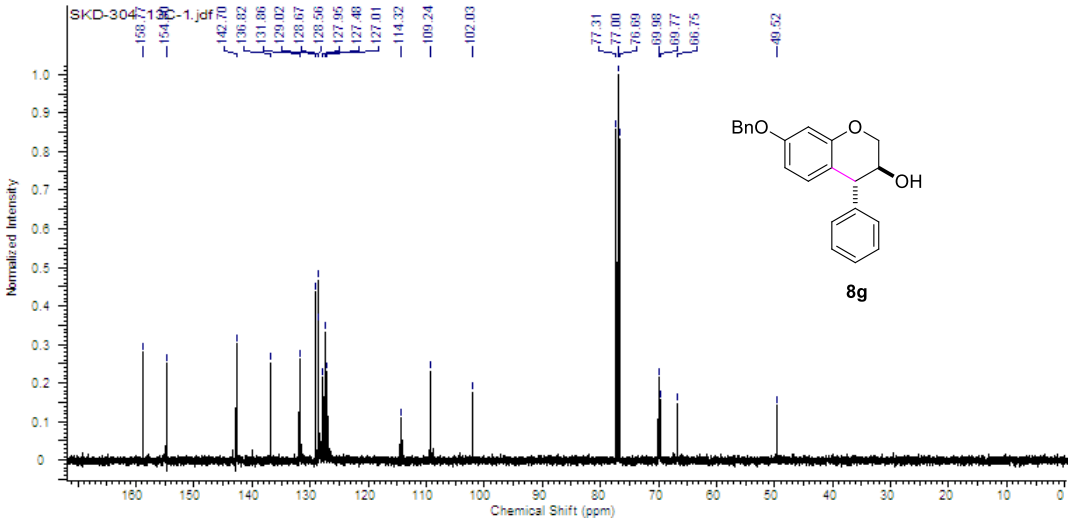


Figure 2.5. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 8g

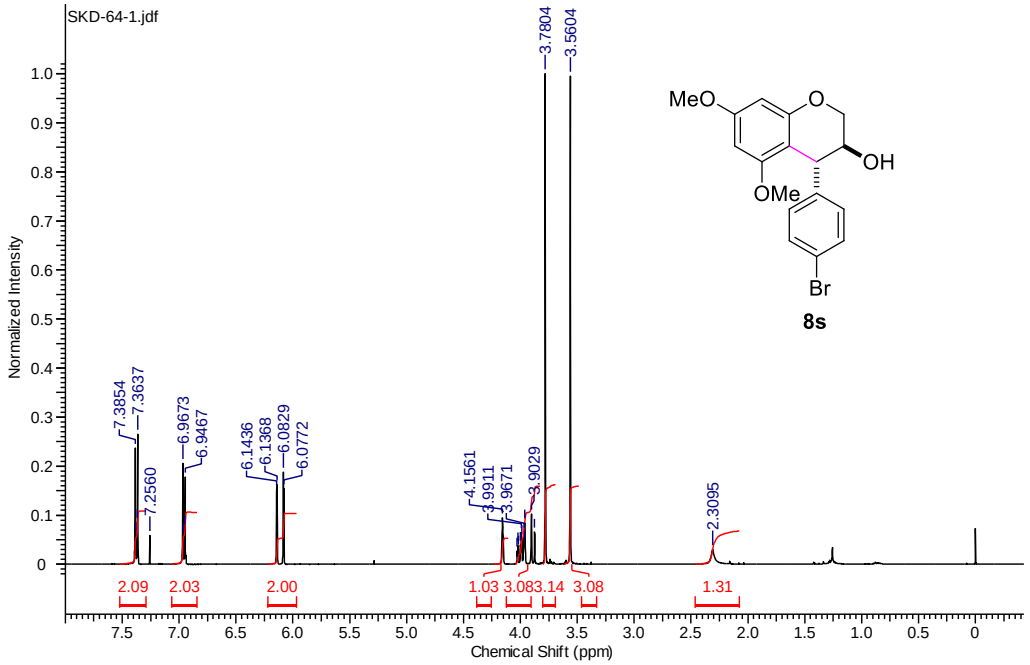


Figure 2.6. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 8s

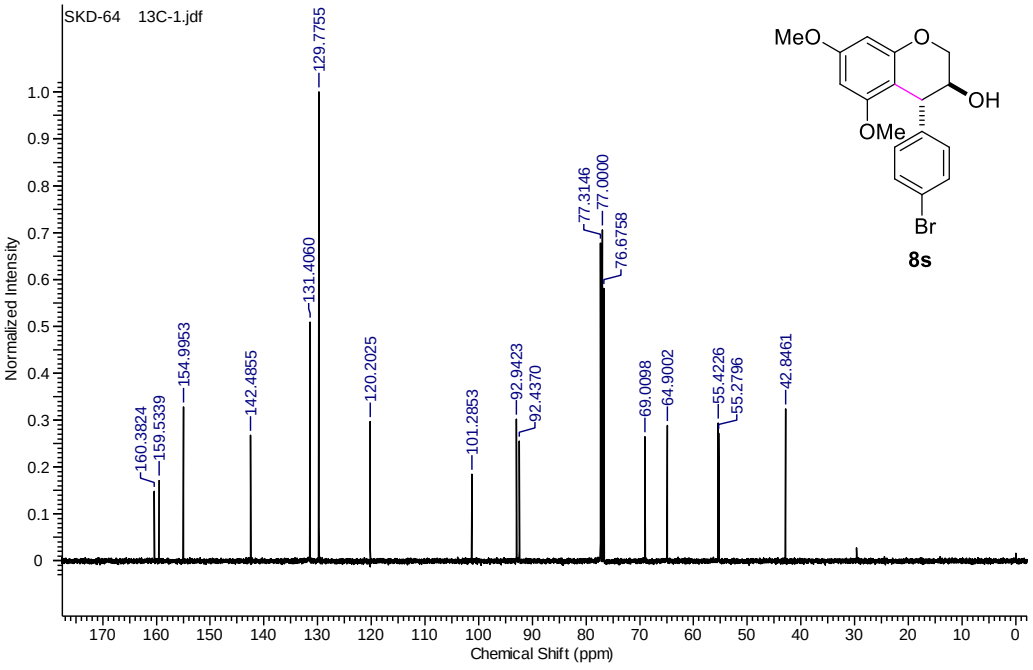


Figure 2.7. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 8s

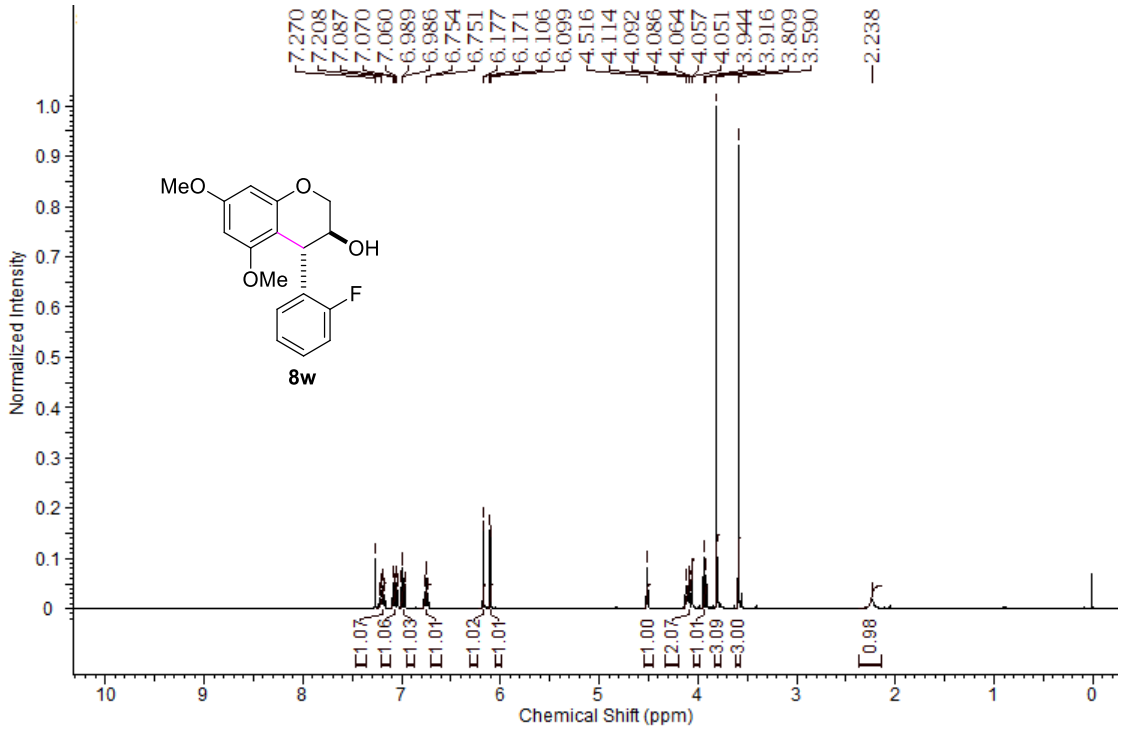


Figure 2.8. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 8w

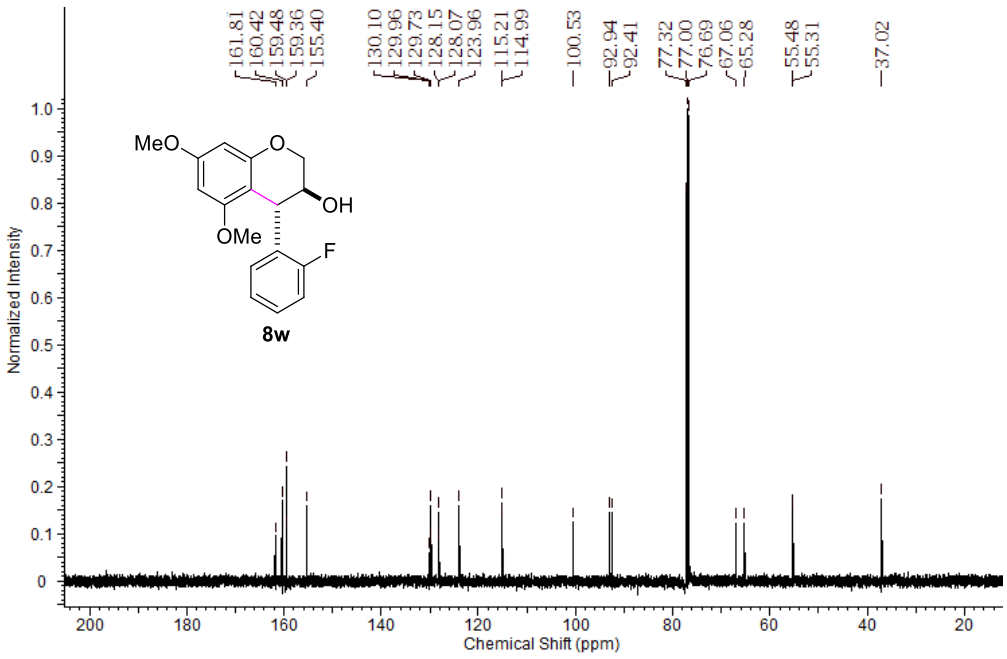


Figure 2.9. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 8w

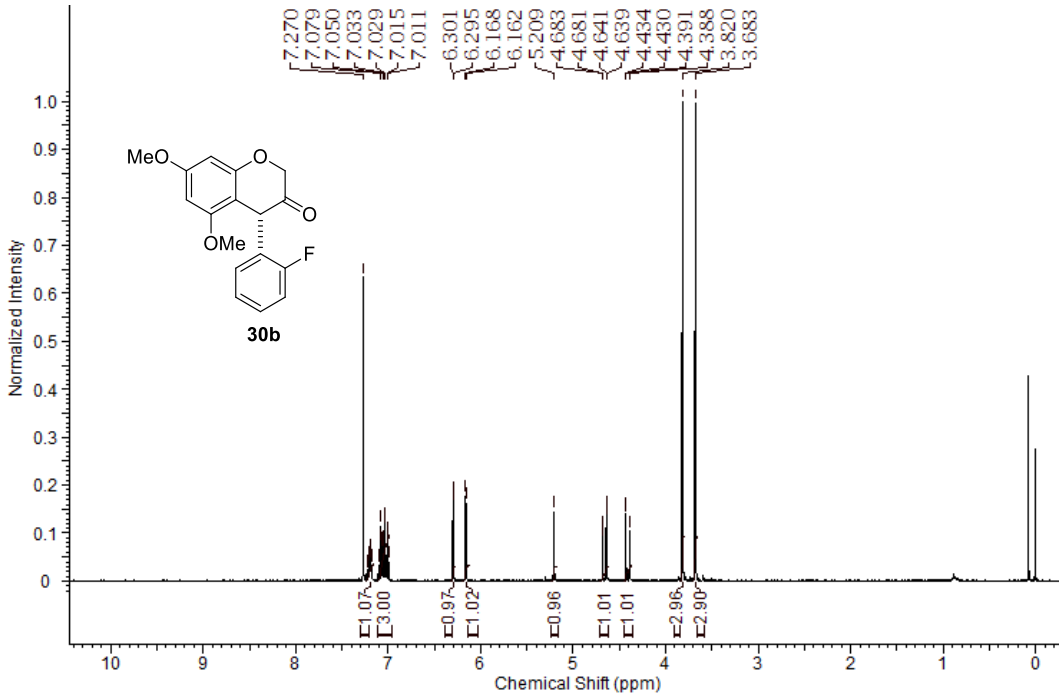


Figure 2.10. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 30b

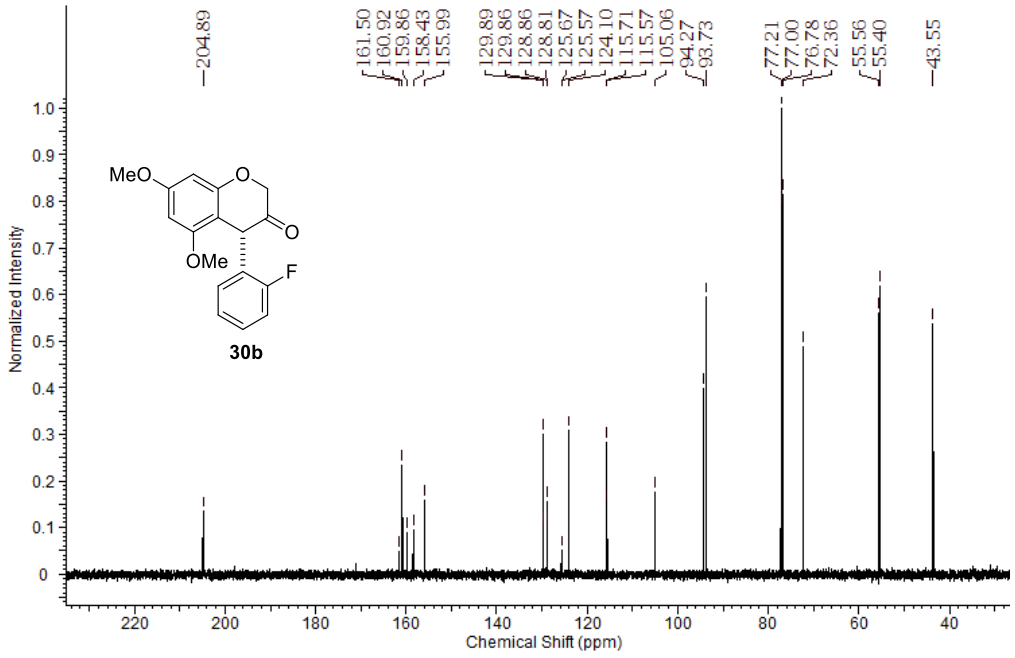


Figure 2.11. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **30b**

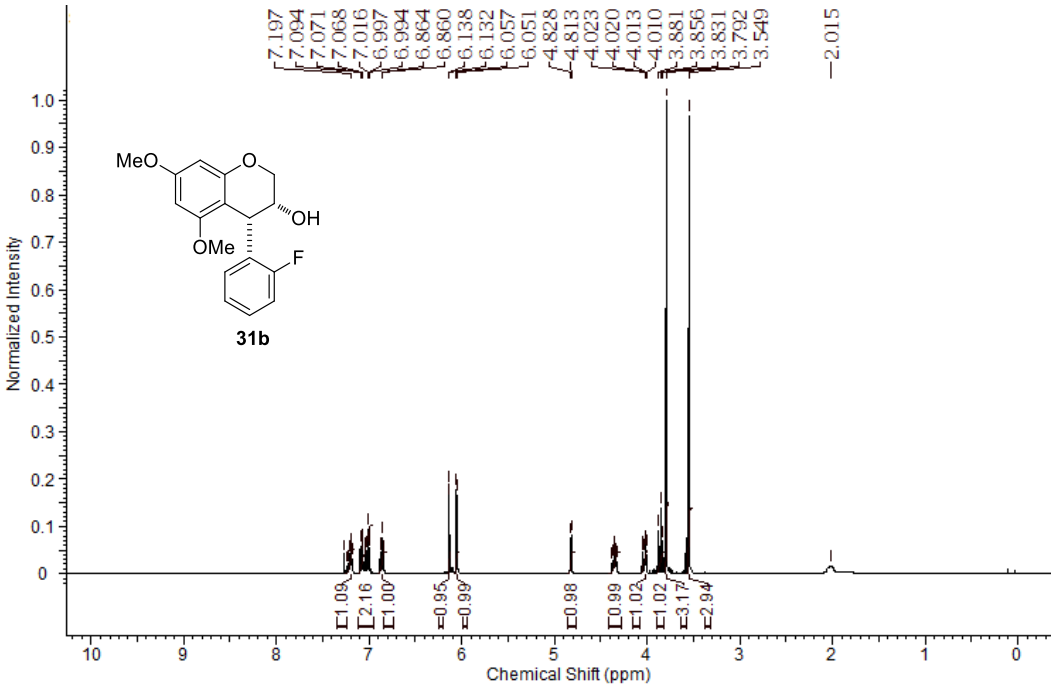


Figure 2.12. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 31b

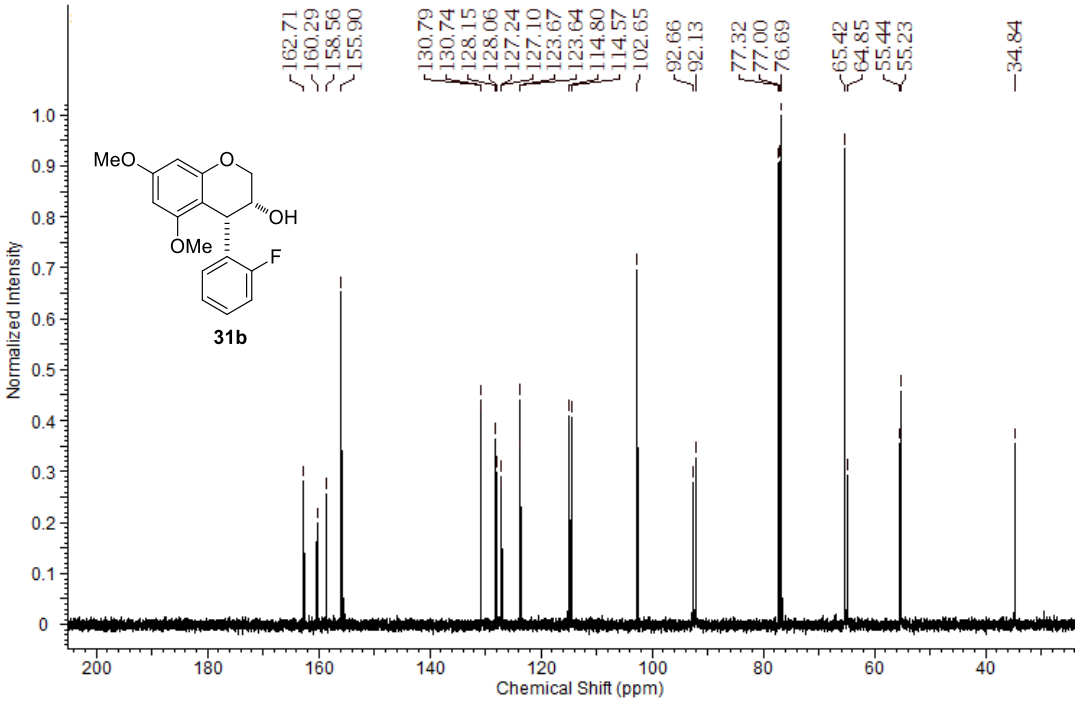


Figure 2.13. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 31b

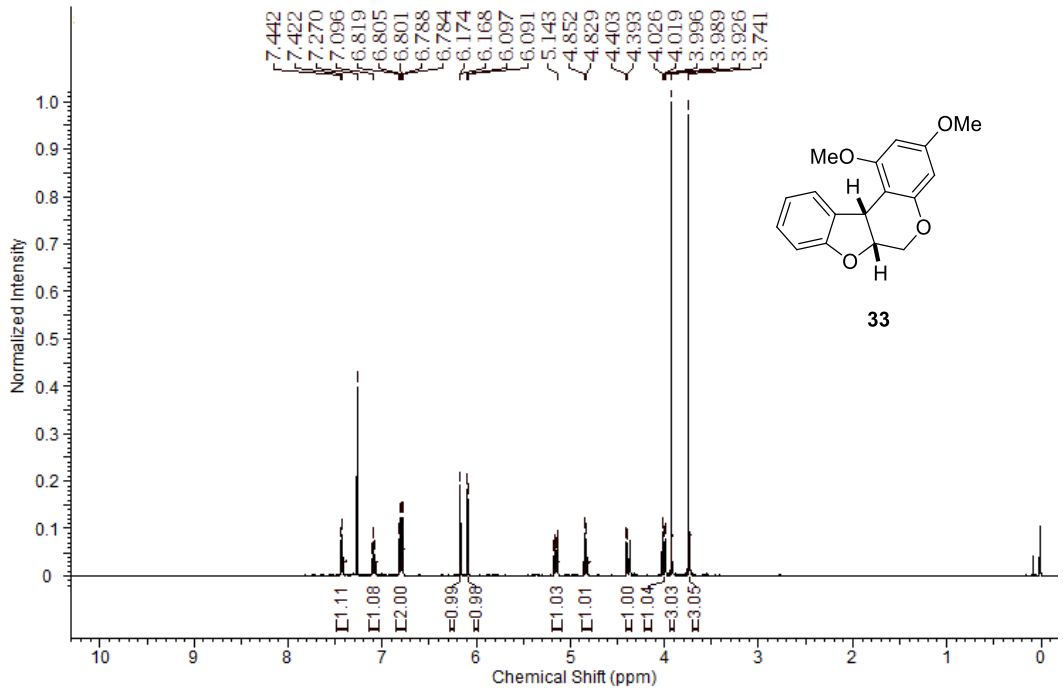


Figure 2.14. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 33

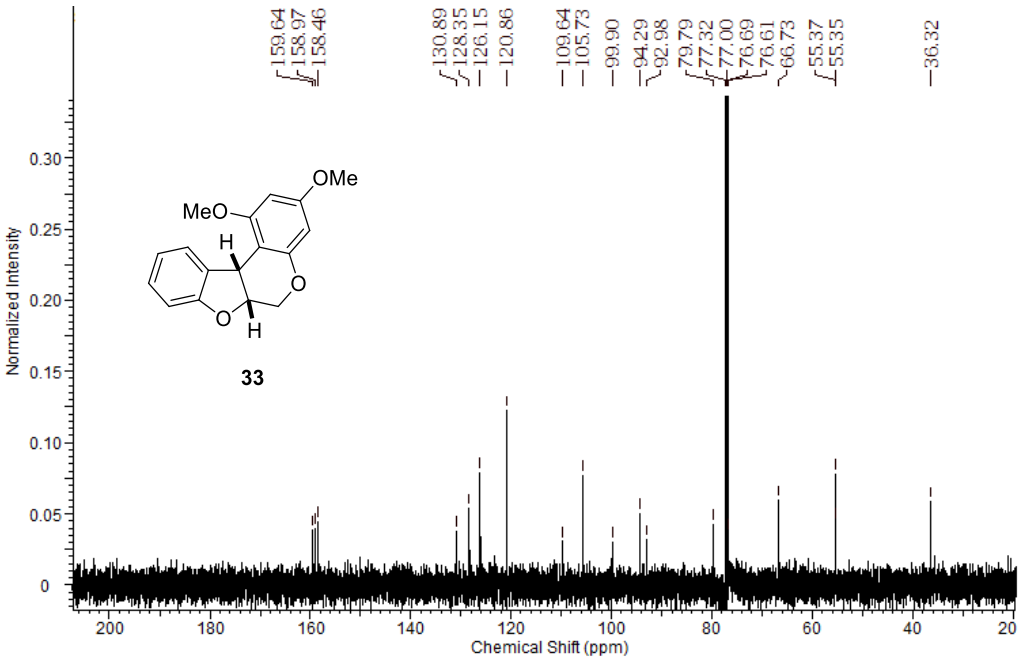


Figure 2.15. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 33