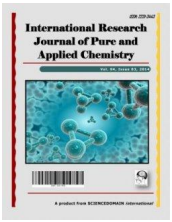

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Flavans: Synthetic Strategies: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author OM designed the study, wrote the Introduction and section 1 of the Discussion, Author NK wrote the Discussion, Conclusion and format of References. Both authors read and approved the final manuscript.

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ABSTRACT

Flavans consist of the 2-phenylchroman structural unit found naturally in the plant kingdom. They are important compounds due to their various pharmacological properties, such as anticarcinogenic, anti-inflammatory, antioxidant, antimalarial, antiviral properties and chemopreventive potential for *Helicobacter pylori* peptic ulcers. Because the flavans are only minutely available from natural sources improved synthesis of flavans are desirable to obtain sufficient quantities for biological testing. Thus, this review article aims at describing the synthetic protocols which exist in the literature. From the surveyed literature 153 synthetic flavans, flavens, isoflavan, neoflavans and anthocyanins were reported.

Keywords: Flavans; flavens; anthocyanins; isoflavan; synthesis; chalcones.

ABBREVIATIONS

$BF_3.Et_2O$ = Boron trifluoride diethyl etherate
$NaBH_4$ = Sodium borohydride
AcOH = Acetic acid
$LiAlH_4$ = Lithium aluminium hydride

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Co12 = Human colon carcinoma cell line
P-388 cell line = Murine lymphocytic leukemia cell line
SGC-7901 = Gastric carcinoma,
BEL-7402 = Hepatic carcinoma cell line
HL-60 = Acute promyelocytic leukemia cell line
MTT = 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
$Pd(OAc)_2$ = Palladium (II) acetate
Et_3N = Triethyl amine
CuI = Copper (I) iodide
KO^tBu = Potassium tert-butoxide
DMF = Dimethylformamide
$NaBH_3CN$ = Sodium cyanoborohydide
PhBr = Bromobenzene
$BrCH_2CH_2Br$ = 1,2-Dibromoethane
n-Bu_4NHSO_4 = Tetrabutylammonium hydrogen sulfate
$Pd(OH)_2$ = Palladium (II) hydroxide
n-BuLi = n-Butyllithium
DEAD = Diethyl diazenedicarboxylate
rt = Room temperature
AD-mix α = Asymmetric dihydroxylation mixture of reagents where phthalazine adduct contains dihydroquinine
$MeSO_2NH_2$ = Methyl sulfonamide
TBAF = Tetra-n-butylammonium fluoride
$EtC(OEt)_3$ = 1,1,1-Triethoxypropane
PPTS = Pyridinium p-toluenesulfonate
TEA = Triethyl amine
PTC = Phase transfer catalyst
Bi(OTf) = Bismuth triflate or bismuth (III) trifluoromethanesulfonate
TBDPSI = t-Butyldiphenylsilyl ether
9-BBN = 9-Borabicyclo[3.3.1]nonane

1. INTRODUCTION

Flavan are an omnipresent 2-phenylchroman structural unit of the C_6-C_3-C_6 type, 2-phenyl-3,4-dihydro-2*H*-chromene nucleus found in flavonoids. They are natural products distributed in the plant kingdom with >17 000 natural flavans isolated [1]. The well-studied flavans are the flavan-3-ols of which their natural occurrences and biological activities were presented in a 2008 review article [1]. Flavans are found in foods such as red wines, green teas, apples, pears, and cocoa products. They exhibit interesting biological and pharmacological activities [2a-h] and high degree of structural diversity depending on the type of constitutive units.

The well-known flavans from green tea (*Camellia sinensis*) are (+)-catechin (**1**), (-)-epicatechin (**2**), (-)-epigallocatechin (**3**) which possess various biological properties such as anticarcinogenic, anti-inflammatory, antioxidant and immunomodulatory properties, inhibition of bone resorption [3,4]. The green tea potent antioxidants are (-)-epicatechin gallate (**4**) and (-)-epigallocatechin gallate (**5**) [5]. The synthetic strategies towards catechins and related tea polyphenols were reviewed by Asakawa and co-workers [6]. The lesser known important natural flavans are 7-hydroxy-3′,4′-methylenedioxyflavan (**6**) from *Zephyranthes flava* which is traditionally used to cure diabetes, ear and chest disorders and viral infections [7], 4′,6-dichloroflavan (**7**) hinders rhinovirus replication *in vitro* [8], morusyunnansin E (**8**) exhibits potent inhibitory activity on mushroom tyrosinase [9], whereas (*S*)-equol (**9**) is believed to be a dietary phytoestrogen through binding to the estrogen receptor b (ERb) which is 13 times more potent than the unnatural (*R*)-isomer [10,11]. (*S*)-Equol is a metabolite of soy isoflavone, daidzein whose transformation was assisted by intestinal bacteria such as gut microflora [12,13], 3'-hydroxyequol has shown potential to prevent hormone-related cancer [14]. Vestitol (**10**) displays anti-inflammatory, antimicrobial activities and has chemo-preventive potential for peptic ulcers in *H-Pylori* infected individuals [15,16]. The fully substituted sideroxylonal B (**11**) from *Eucalyptus sideroxylon* exhibits antibacterial [17, 18] and antitumor properties [19]. 7-O-gallyltriceflavan (**12**) exhibits antiviral properties [20] while

Griffinord E (**13**) shows antimalarial activity [21]. The natural flavans **1**-**13** are shown in Figure 1.

Flavans have attracted the attention of many synthetic chemists and a number of synthetic protocols have been developed for their synthesis due to their pharmacological importance. Thus this review describes the synthetic strategies reported for the synthesis of flavan and their analogues. This would assist to identify the most biologically important flavans and their simpler and efficient synthetic methods. Hence, enabling the future targeted synthesis of flavans.

2. DISCUSSION

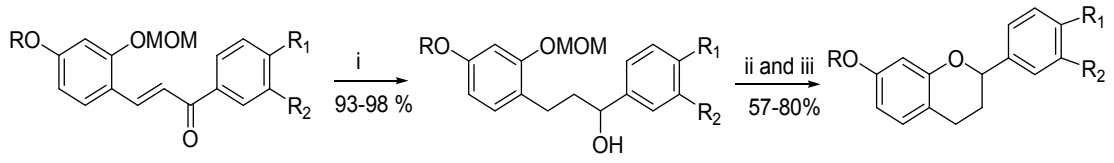
2.1 Flavans

Li and co-workers have described the synthesis of flavans (**6** and **16**) starting from a chalcone (**14**). The reduction of the chalcone using Raney nickel followed by the $BF_3.Et_2O$ assisted cyclization in protic media formed the benzopyran ring of natural flavans as depicted in Scheme 1 [22]. Flavan (**16**) is an antifeedant chemical constituent of *Stypandra grandis* and *Lycoris raliata* [23]. Xue and co-workers have utilized a similar protocol to accomplish the synthesis of *Dracaena cinnabari* [24,25] isolated flavans (**23**-**25**) starting from salicylaldehyde (**17**) as shown in Scheme 2. The α,β-unsaturated ketone function of the chalcone was reduced by H_2/Pd, which usually reduces C=C double bonds [25].

Our group have also accomplished the synthesis of an array of flavans (**30**-**34**) [26,27]. Contrary to reduction methods using H_2/Pd and H_2/Raney Nickel in Scheme 1 and 2, Our group used $NaBH_4$ to reduce chalcones [26] to the corresponding alcohols, which were cyclized into flavans (**30**-**34**) [27,28] as shown in Scheme 3. $NaBH_4$ here reduced the C=C double bond, it is a reagent which is normally used for carbonyl group reductions. Recently, we have demonstrated the versatility of our methods by reducing 2-thienylchalcones (**37**) to alcohols (**38**), which were cyclized to flavans [2-(thiophen-2-yl)chroman] bearing an electron rich thiophene ring (**39**, **40**) [29] as depicted in Scheme 4.

The reduction of *o*-hydroxychalcones with $LiAlH_4/AlCl_3$ affords *trans*-cinnamylphenol chromophore [30]. The cinnamylphenols were photocyclized to flavans *via* irraditions of the substrate in benzene inside a pyrex tube using a 125W Hg lamp (Scheme 5) [31]. Alternatively, flavan **43** was synthesized in higher yields by the Clemmenson reduction of flavanone [30,31], Scheme 6.

Zang and co-workers accomplished the synthesis of natural flavan racemates (**52**-**54**), *via* the Pd-C catalyzed hydrogenation / hydrogenolysis of flavones as described in Scheme 7. The esterification of the phenol with benzoic chloride followed by the Baker-Venkataraman rearrangement affords 1,3-diketones (**49**). To complete the synthesis the 1,3-diketone forms the natural flavone (**51**) after treatment with acetic acid, and the subsequent hydrogenation/hydrogenolysis catalyzed by Pd-C yields the racemic flavans (**52**-**54**) [32]. The two flavans, 2(*S*)-7,8,3′,4′,5′-pentamethoxyflavan (**52**) and 2(*S*)-5′-hydroxy-7,8,3′,4′-tertramethoxyflavan (**53**), had been isolated from the roots of *Muntingia calabura.* These natural flavonoids exhibited cytotoxic activity against human colon carcinoma Co12 and murine lymphocytic leukemia P-388 cell lines [33]. The synthetic analogues were assessed for anti-proliferative activity against human cancer cell lines, SGC-7901 gastric carcinoma, BEL-7402 hepatic carcinoma, HeLa cervical carcinoma, and HL-60 acute promyelocytic leukemia, by MTT assay. The flavan (**52**) exhibited 1.6-5.7 more potency than cisplatin, while (**53**) showed moderate activities [32].



14 **15** **6** R= H, R_1, R_2 = OCH_2O
16 R= Me, R_1= OH, R_2 = H

i) H_2/Raney Ni (W-2), EtOH; ii) $BF_3.Et_2O$, 1,4-dioxane, 1.5h; iii) HCl, MeOH, reflux

Scheme 1: Li et al. synthesis of flavans

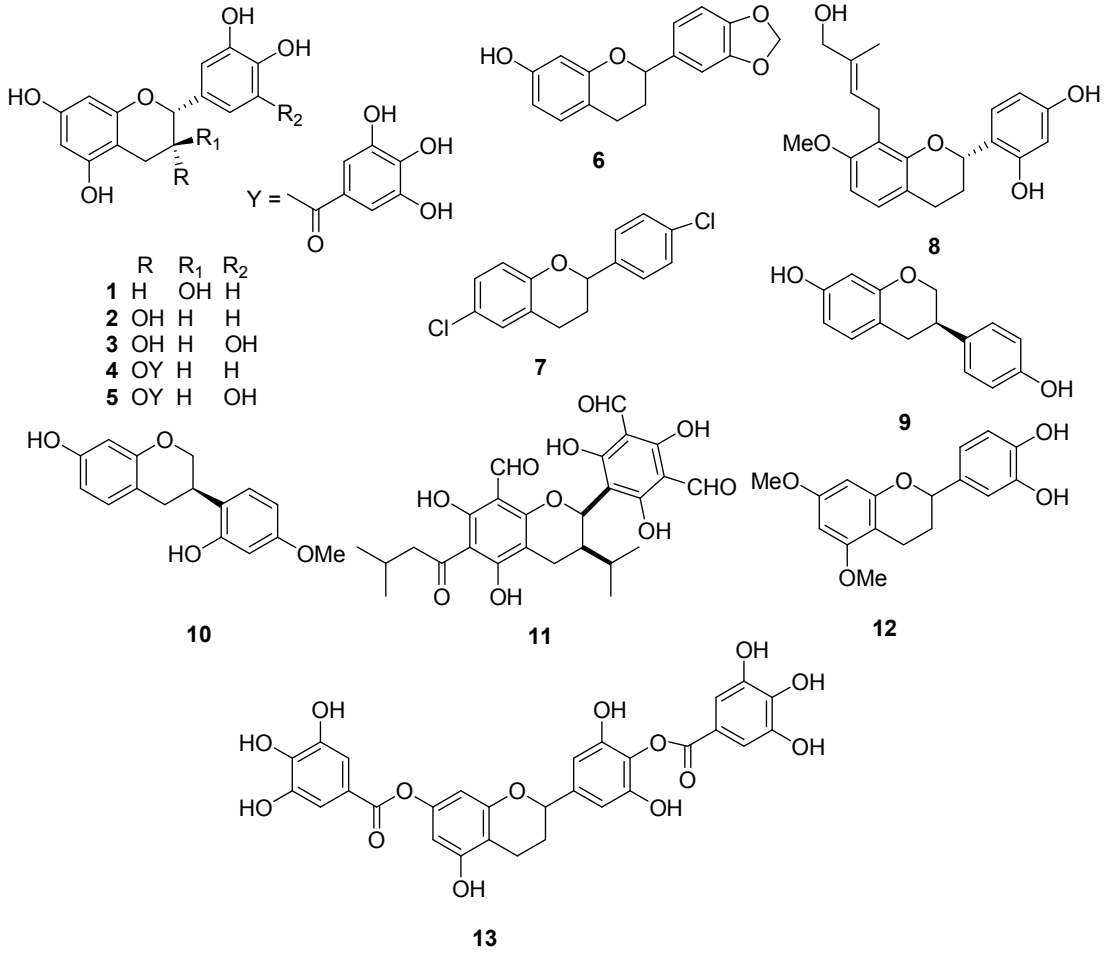
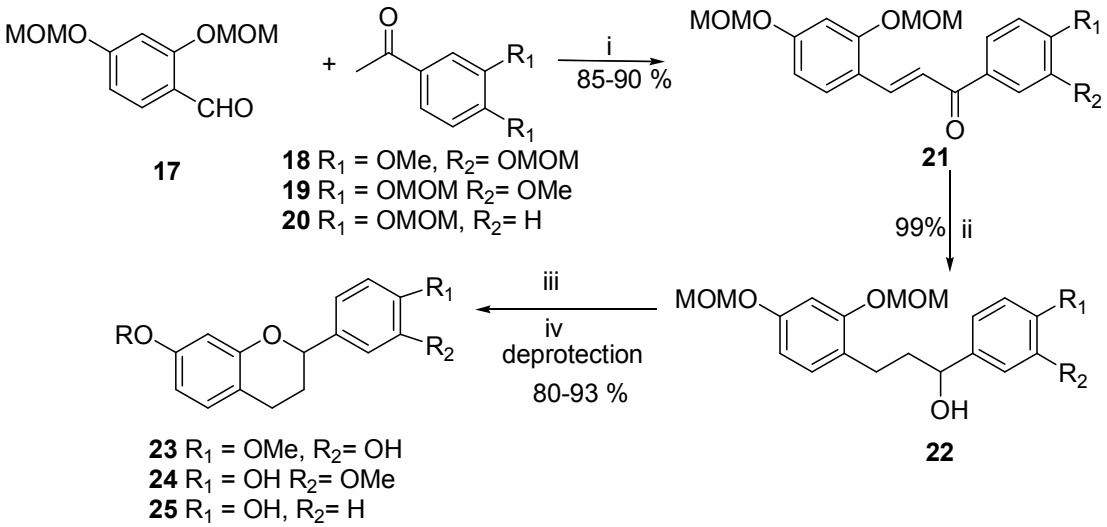
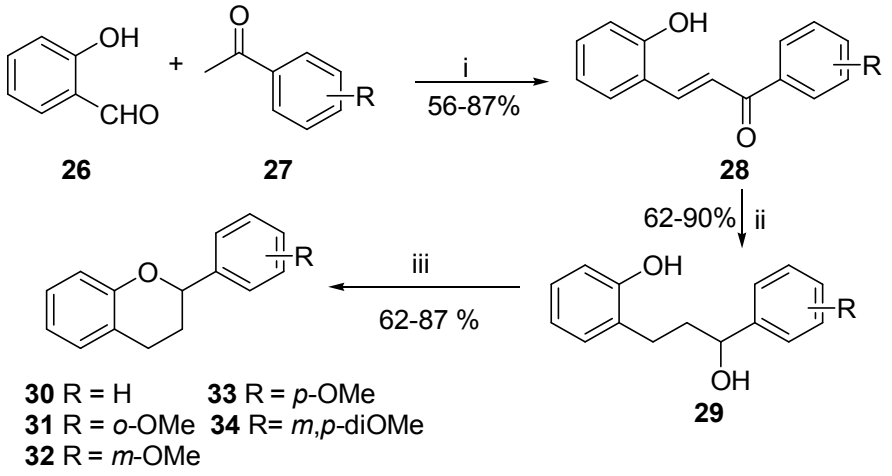


Figure 1: Some naturally occuring bioactive flavans



Reagents and conditions: i) KOH, MeOH, rt; ii) H_2/Pd-C (5%), EtOH, rt; iii) $BF_3.Et_2O$, 1,4-dioxane, rt; iv) HCl, MeOH.

Scheme 2: Xue et al. synthesis of flavans.



26 **27** **28** **29**

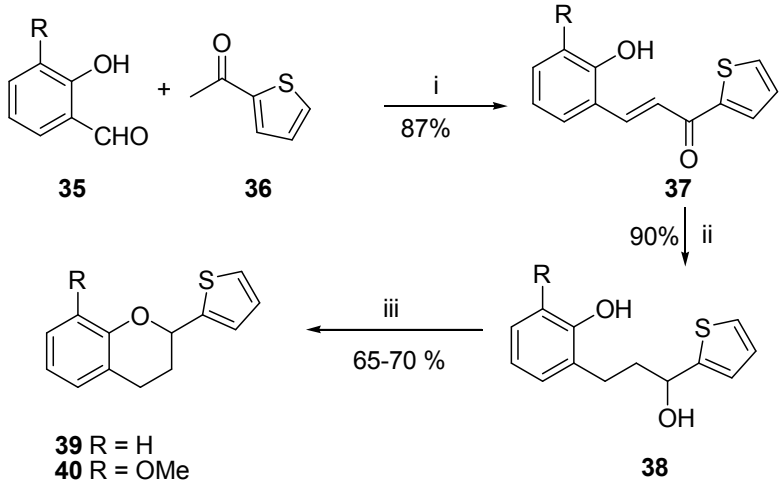
30 R = H **33** R = *p*-OMe
31 R = *o*-OMe **34** R= *m*,*p*-diOMe
32 R = *m*-OMe

Reagents and conditions: i) NaOH, EtOH, 2h, 60 ^{o}C; ii) $NaBH_4$, MeOH, rt, 0.5h; iii) AcOH, reflux.

Scheme 3: Mazimba et al. synthesis of flavans.

Suchand and co-workers [34] reported a three step protocol for the sysnthesis of flavans. Firstly, the intermolecular [Pd] catalyzed C-C bond formation between 2-bromoiodobenzene (**55**) and allylic alcohols (**56**) affords dihydrochalcones (**57**). The dyhydrochalcones (**57**) were reduced to secondary alcohols (**58**) using $NaBH_4$. The third step was the intramolecular [Pd]-catalyzed C–O bond formation which cyclizes the 2º alcohols (**58**) into the chroman ring (**59**-**67**). But, the [Pd] catalysis was inferior in yields (0-62%) [35,36] and formed back the ketone moiety of dihydrochalcones (**57**) as the minor product (9-65%). Whereas, the [Cu]-catalyzed C-O bond formations were found to exclusively form flavans (**59**-**67**) in good yield (68-85%) as shown in Scheme 8 [34].

The Suchand and co-workers protocol was extended to the synthesis of flavans substituted at C-2 (**69**-**76**) as described in Scheme 9. The strategy involved the reaction of dihydrochalcones (**57**) and Grignard reagent [34]. Ramulu and co-workers showed the versatility of the [Pd] and [Cu]-catalysed construction of C-C and C-O bonds in the synthesis of flavans by preparing flavans (**77**-**85**) [37] shown in Fig. 2.

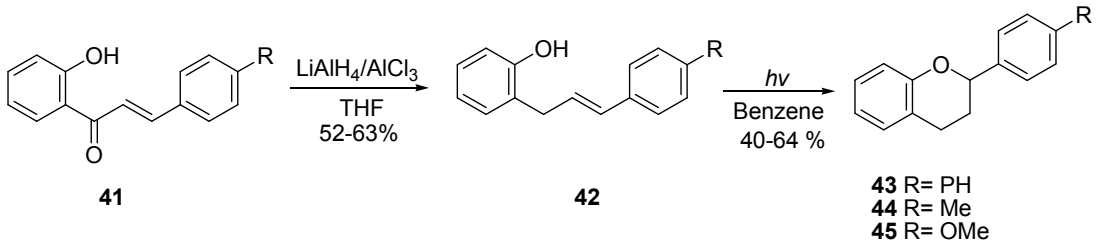


35 **36** **37** **38**

39 R = H
40 R = OMe

Reagents andconditions: i) NaOH, Grind; ii) $NaBH_4$, MeOH, rt, 0.5h; iii) AcOH, reflux.

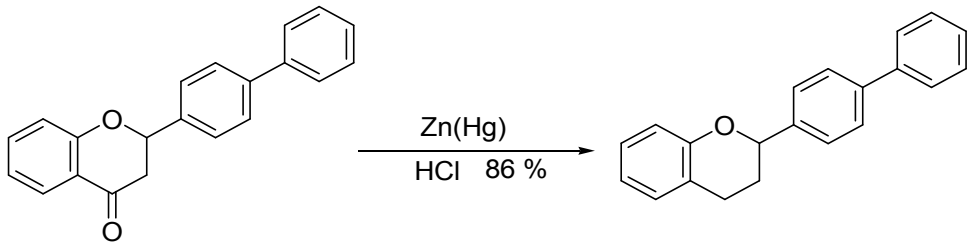
Scheme 4: Mazimba's synthesis of 2-(thiophen-2-yl)chroman



41 **42**

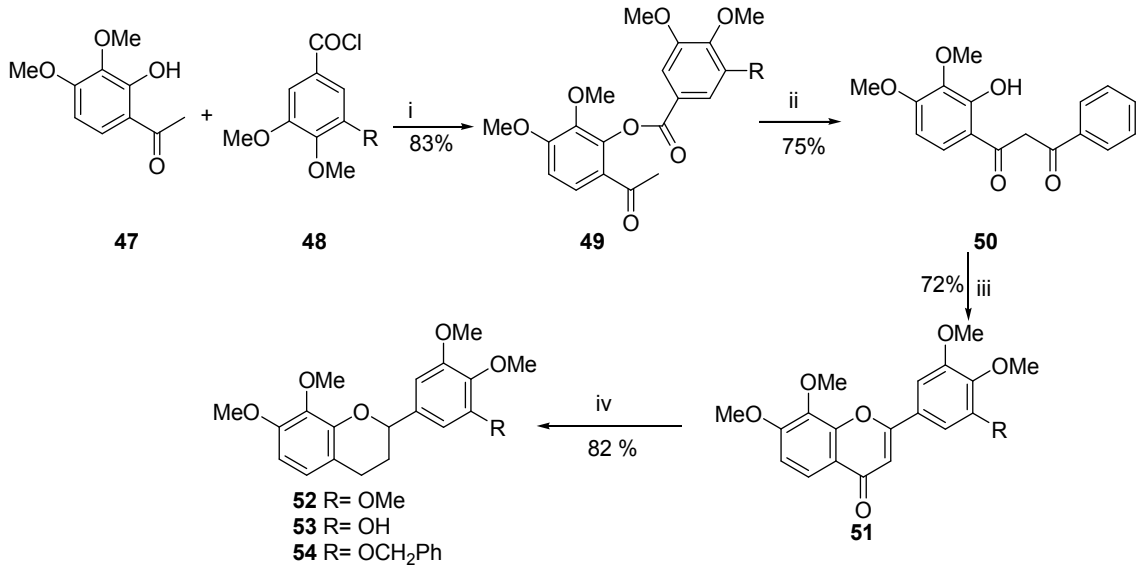
43 R= PH
44 R= Me
45 R= OMe

Scheme 5: Photocyclization of cinnamylphenols to flavans



46 **43**

Scheme 6 Clemmensen reduction of flavanone to flavans



47 **48** **49** **50** **51**

52 R= OMe
53 R= OH
54 R= OCH_2Ph

Reagents and conditions: i)dry pyridine, 110^oC, 1h; ii) pyridine, NaOH, rt, 4h; iii) CH_3COOH, 6h; iv) H_2, Pd-C, $CH_3COOC_2H_5$, rt, 12h; v) H_2, Pd-C, CH_3OH, rt, 24 h.

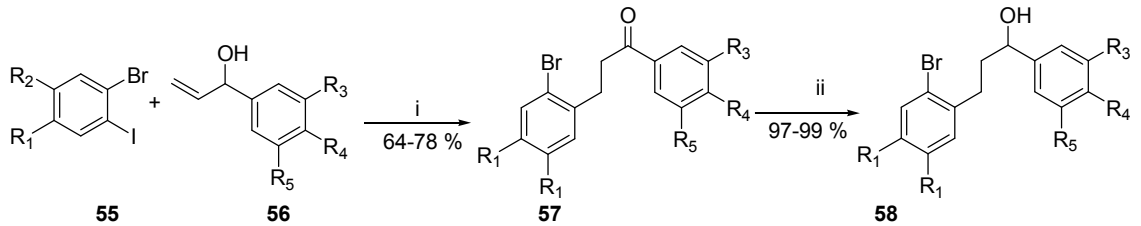
Scheme 7: Zhang et al. synthesis of flavans.

A multi-component reactions between phloroglucinol (**86**), styrene (**87**) and formaldehyde (**89**) in the presence of a heterogeneous solid catalyst directly furnished flavans (**89**; Scheme 10) shown in Fig. 3. Besides silica-$HClO_4$, other catalyst that efficiently assisted the reaction were silica-$FeCl_3$, $HClO_4$ and Amberlyst-IR-50 [38].

Flavens **102**-**104** were synthesized by the reduction of flavylium perchlorate (**101**) using magnesium bromide, while reduction using sodium borohydride or sodium cyanoborohydride afforded flavens **105**-**109** [39]. Further reactions of flavens with sodium cyanoborohydride afforded the corresponding flavans **110**-**114** shown in Scheme 11. These reactions were successful only for flavens bearing electron donating groups in ring B at positions C-2' and C-4' [39]. The ring B electron donating groups permit the resonance stabilization of the positive charge placed at C-2 before being quenched by

a hydride ion. The reaction of flav-2-ens of type 115 with alcohols in the presence of Lewis acid yields 2-alkoxyflavans **118**-**120**, which were subsequently reduced to flavans (**121**-**123**) using $NaBH_3CN$ in Scheme 12 [39].

5,7-Dihydroxy-4´-methoxyflavan (**130**) was synthesized in a total of seven steps from 3,5-bis(benzyloxy)phenol (**124**) by Machado and coworkers [40]. *O*-allylation of phenol **124** using allyl bromide yields an allylic ether **125**, which under thermal conditions undergoes a Claisen rearrangement to furnish a phenol (**126**). Esterification of **126** using 1,2-dibromoethane in K_2CO_3/acetone with subsequent base elimination under phase transfer catalysis furnished diene (**127**). 4*H*-chromene ring (**128**) was obtained from diene **127** through ring closure assisted by the Grubbs-2 catalyst. Heck reaction of compound **128** with 2-MeOPh-N_2BF_4 followed by ring closing metathesis furnished flav-3-en (**129**). Palladium-catalyzed hydrogenation-hydrogenolysis afforded 5,7-dihydroxy-4´-methoxyflavan (**130**) (Scheme 13) [40]. Flavan **130** has been isolated from *Faramea guianensis* and shows significant *in vitro* leishmanicidal activity [41].

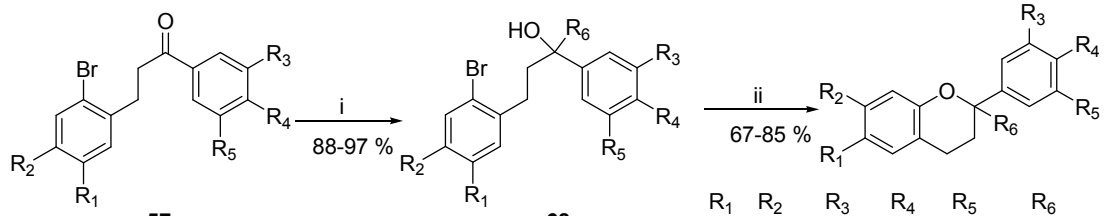


55 **56** **57** **58**

	R_1	R_2	R_3	R_4	R_5
59	H	H	OMe	H	H
60	H	H	OMe	OMe	H
61	H	H	OMe	OMe	OMe
62	H	H	OCH_2-	OCH_2-	H
63	OMe	H	OMe	H	H
64	OMe	H	OMe	OMe	H
65	OMe	H	OMe	OMe	OMe
66	OMe	H	OCH_2-	OCH_2-	H
67	H	OMe	OMe	H	H

Reagents and conditions: i) 3 mol % $Pd(OAc)_2$, Et_3N, MeCN, 80 ^oC; ii) $NaBH_4$, MeOH, rt; iii) 20 mol% CuI, 2,2-bipyridyl (20 mol %), KO^{t}Bu, DMF, 120 ^oC

Scheme 8: [Pd] catalyzed C-C and [Cu]-catalysed C-O bond formations in the synthesisis of flavans



57 **68**

	R_1	R_2	R_3	R_4	R_5	R_6
69	H	H	OMe	H	H	Me
70	H	H	OMe	OMe	H	Me
71	H	H	OMe	OMe	OMe	Me
72	H	H	OCH_2-	OCH_2-	H	Me
73	OMe	H	OMe	H	H	Me
74	OMe	H	OMe	OMe	OMe	Me
75	OMe	H	OCH_2-	OCH_2-	H	CH_2CH_2
76	H	OMe	OMe	H	H	Me

Reagents and conditions: i) R_6MgX, THF, -10 ^oC-rt; ii) 20 mol% CuI, 2,2-bipyridyl (20 mol %), KO^{t}Bu, DMF, 120 ^oC

Scheme 9: Grignard reagents C-C and [Cu]-catalysed C-O bond formations in the synthesis of flavans

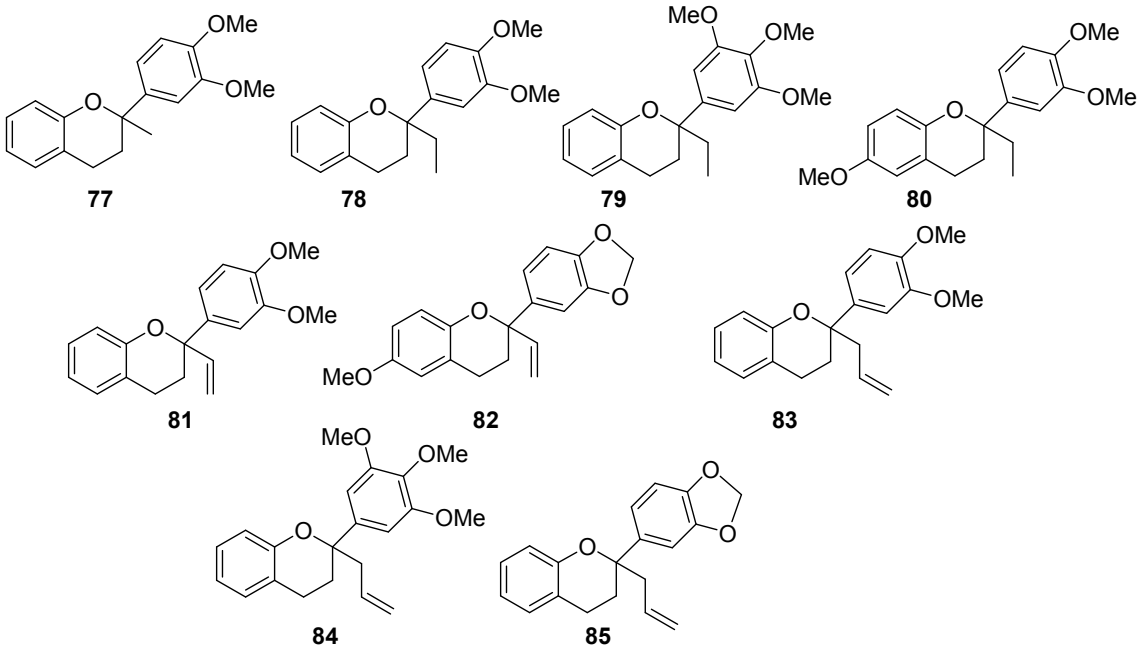
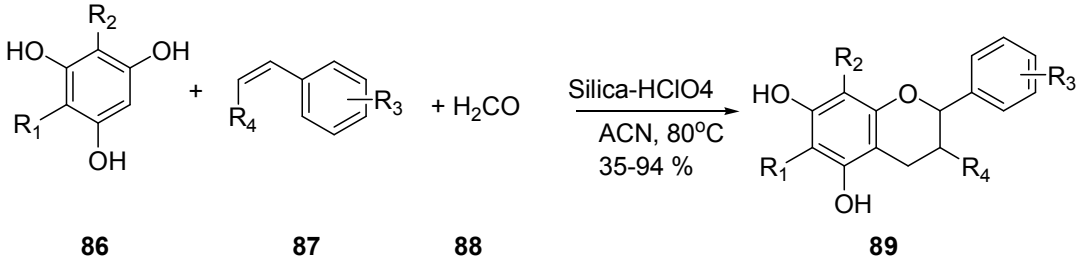


Figure 2: Flavans reported by Ramulu et al. (37)



Scheme 10: Bharate et al. MCR in the synthesis of flavans

Hodgetts and co-workers have reported a synthetic strategy towards flavans in which the intermolecular and intramolecular Mitsunobu reactions were the keys steps. The intermolecular Mitsunobu reaction between 2-bromophenol (**131**) and (*R*)-3-chloro-1-phenyl-1-propanol (**132**) under standard inversion conditions afforded (*S*)-phenyl ether (**133**). Cyclization was accomplished in the presence of *n*-butyllithium [42] to furnish enantiomerically pure flavans as shown in Scheme 22. Tephrowatsin E (**138**) is a natural flavan isolated from *Tephrosia watsoniana* [43].

The one pot cyclization and *in situ* functionalization of the Mitsunobou reaction ether product was probed. The first addition of *n*-butylithium was selective towards the *ortho*-bromo metal exchange which leads to the formation of the flavan ring affording 6-bromo-2-phenylchroman. Further addition of the organolithium reagent forms a chromanyllithium by the second halogen-metal exchange. Quenching of the electrophile accomplishes the one pot synthesis of flavans (**140**-**144**) as described in Scheme 15 [42].

The synthesis of enantiomerically pure 4',6-dichloroflavan (BW683C) (**7**) was achieved starting from the asymmetric reduction of suitable prochiral ketone, 3,4′-dichloropropiophenone (**145**) with (*R*)-oxazaborolidine and borane [42, 44] as described in Scheme 16.

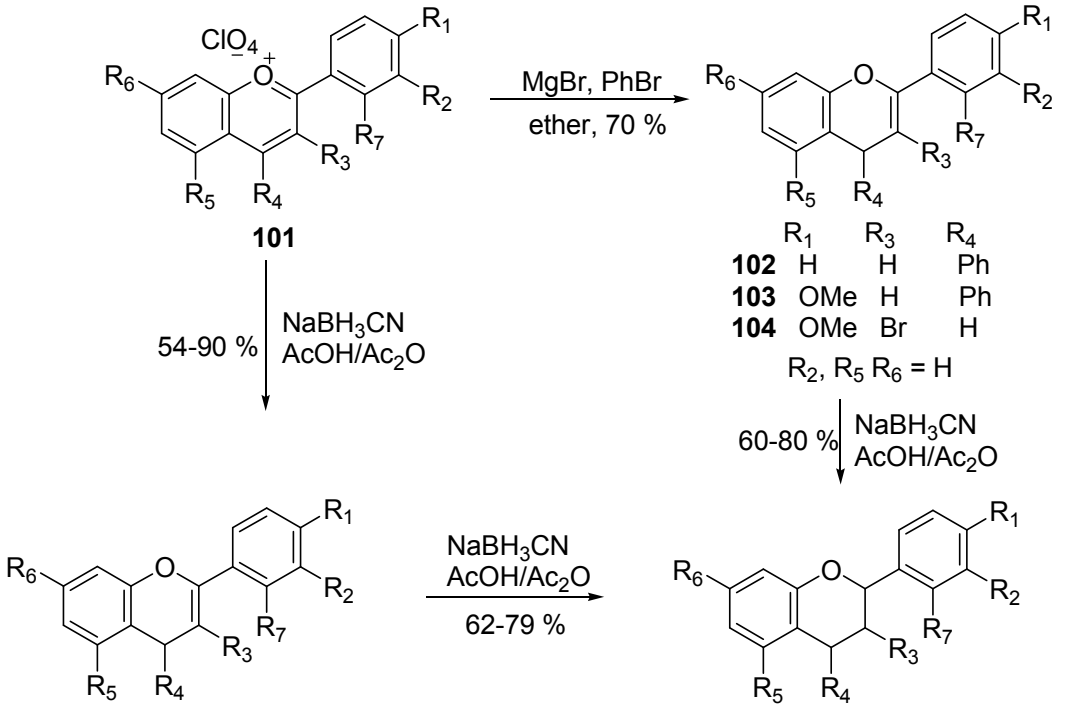
2.2 C2, C3-substituted Flavan Derivatives

Deodhar and co-workers [45] described the synthesis of 4-arylflavans (**153**) from flavanone (**151**) which was derived *via* the condensation reaction of resacetophenone (**148**) and 4-

hydroxybenzaldehyde (**149**). The acetylated flavanone (**151**) furnished 7,4′-diacetoxyflavan-4-ol (**152**) after the palladium-catalyzed hydrogenation. The OH-group was substituted with an aryl group in the presence of $BF_3.OEt_2$ yielding equal mixtures of *cis* and *trans*-flavans (**153**) after KOH hydrolysis of the acetyl group [45].

The condensation reaction of phenols and secondary alcohols in the presence of $BF_3.OEt_2$ to form ethers [46] was applied to the synthesis of 4α-aryloxyflavans. The synthesis of 4α-aryloxyflavans (**155**-**161**) was accomplished by reactions of phenol with flavan-4β-ols (**154**) catalyzed by boron trifluoride in ether, Scheme 25 [47,48]. *p*-Cresol resulted in the highest yield (70%) for 4α-aryloxyflavans. Catalysis using alcoholic hydrogen chloride or toluene-*p*-sulphonic acid yields 4-arylflavans (**162**-**164**) [47,49]. The thermal decomposition of flavan-4β-yl phenyl carbonates (**165**) of flavan-4β-ol yielded 4α-aryloxyflavans (**155**-**161**) [50,47] without producing 4-arylflavans (Scheme 18). The disadvantage for these synthetic methods were concomitant formation of 4α-aryloxyflavans and 4-arylflavans, which needed separation, and failure to work with 7-methoxy or 3-hydroxy substituted flavan-4-ols.

Thus, a synthetic method based on the opening of flav-3-ene epoxides (**166**) with phenols and phenolates ions was reported. The phenols ring opening reaction affords 2,3-*cis*-3,4-*cis*- (**167**) and 2,3-*trans*-3,4-*cis*-(**169**) 4-aryloxyflavan-3-ols while the phenolate ions yields 2,3-*cis*-3,4-*trans*-(**168**) and 2,3-*trans*-3,4-*trans*-(**171**) 4-aryloxyflavan-3-ols as shown in Scheme 19 [48]. The phenols *cis*-openning of the epoxide ring occurs by the ion-pair mechanism [51] to exclusively give 3,4-*cis*-stereochemistry, while the phenolate reaction is an SN2 mechanism that leads to 3,4-trans stereochemistry.



	R_1	R_3	R_4
102	H	H	Ph
103	OMe	H	Ph
104	OMe	Br	H

	R_1	R_2	R_3	R_4	R_5	R_6
105	H	H	H	H	H	H
106	NO_2	H	H	H	H	H
107	OMe	H	H	H	H	H
108	OMe	OMe	H	H	OMe	OMe
109	R_{1-6} = H, R_7 = OMe					

	R_1	R_2	R_3	R_4	R_5	R_6
110	H	H	H	H	H	H
111	OMe	H	H	Ph	H	H
112	OMe	H	H	H	H	H
113	OMe	OMe	H	H	OMe	OMe
114	R_{1-6} = H, R_7 = OMe					

Scheme 11: Synthesis of flavans *via* reduction of flavylium salts

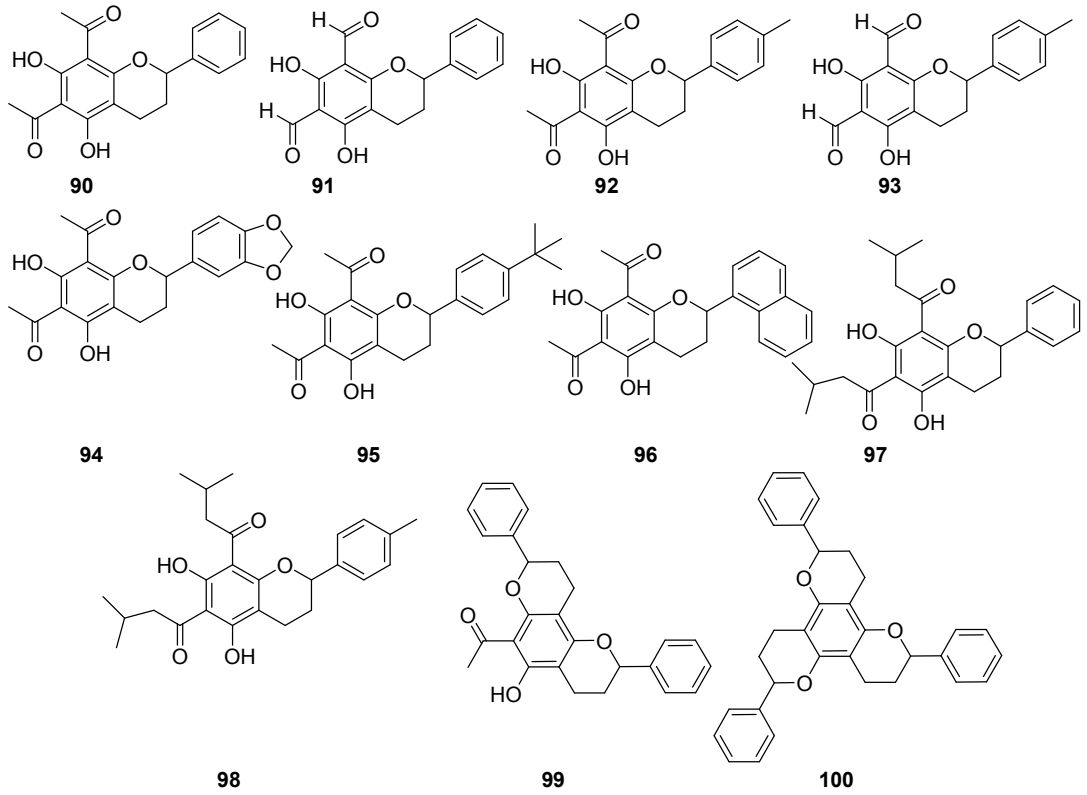
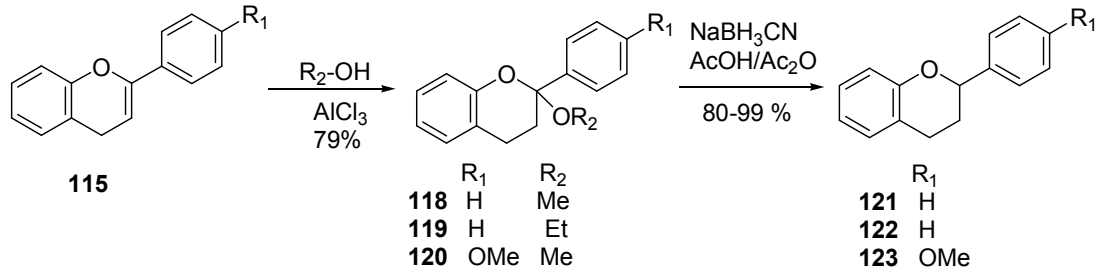


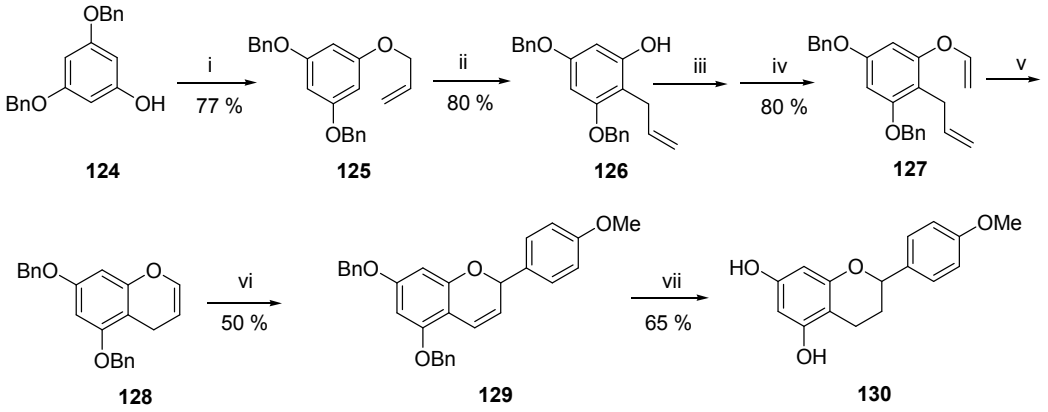
Figure 3: Flavans reported by Bharate and co-workers



Scheme 12: Flavan synthesis from flavens

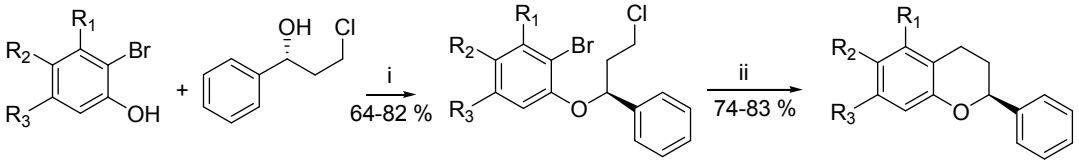
When Zhang and co-workers attempted to reduce the orthogonally protected chalcones (**178**) to the olefin, cinnamylphenol derivative (**182**) the formation of flavene (**180**) was observed [52]. Apparantly the flavene was formed due to the pre-mature quenching of the reaction with acid, since the reduction of the carbonyl group with $NaBH_4/CeCl_3$ rapidly formed the alcohol intermediate (**179**), while the conversion to the olefin was a much slower step. The intermediate *E*-configuration of the double bond favors the acid catalyzed intramolecular cyclization to form the flavene (**180**), while the olefin (**182**) was formed after prolonged stirring. The olefin (**182**) was transformed into flavan-3-ol (**187**) and flavan-3-one (**188**) as described in Scheme 20 [52]. Ten examples of compound type (**187**) and (**188**) were reported, while flavan-3-ol (**187**) is also a derivative of (-)-epicatechin (**2**). The racemic diol (**181**) was accomplished by the dihydroxylation of flavene (**180**) using a non-asymmetric dihydroxylation protocol [52, 53].

The tetramethyl ether of melacacidin was synthesized by the hydrogenation of 7,8,3′,4′-tetramethylflavonol (**189**) over Raney nickel to furnish *tetra*-*O*-methylmelacacidin (**190**) shown in Scheme 21 [54]. (2*R*,3*R*,4*R*)-Melacacidin is a natural flavan-3,4-diol obtained from *Acacia species* and has shown to have moderate allergenic properties [55].



Reagents and conditions: i) Allyl bromide, K_2CO_3, acetone, 60 °C, 15 h; ii) 230 °C, 1 h; iii) $BrCH_2CH_2Br$, K_2CO_3, acetone, 60 °C, 38 h; iv) 50 % aq. NaOH, *n*-Bu_4NHSO_4, benzene, 1 h; v) Grubbs-2 Ru-catalyst, toluene , 60 °C, 10 min; vi) 2-MeOPh-N_2BF_4, $Pd(OAc)_2$, 2,6-*di*-*t*-butyl-4-methylpyridine, EtOH, 55 °C, 20 min (over two steps); vii) H_2, $Pd(OH)_2$, THF/MeOH, 25 °C, 5 h.

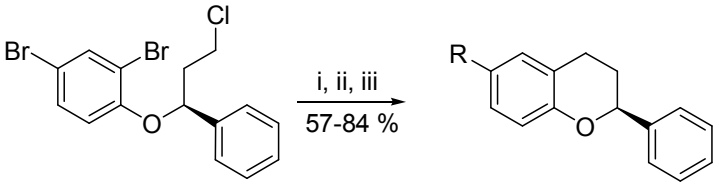
Scheme 13: Machado *et al*. synthesis of *F. guianensis* flavan



	R_1	R_2	R_3
134	H	H	H
135	H	Me	H
136	H	Cl	H
137	-$(CH)_4$-		H
138	OMe	H	OMe

Reagents and conditions: i) PPh_3, DEAD, THF, rt.; ii) *n*-BuLi, THF, -50 ^oC to rt.

Scheme 14: Mitsunobu reaction in the synthesis of flavans

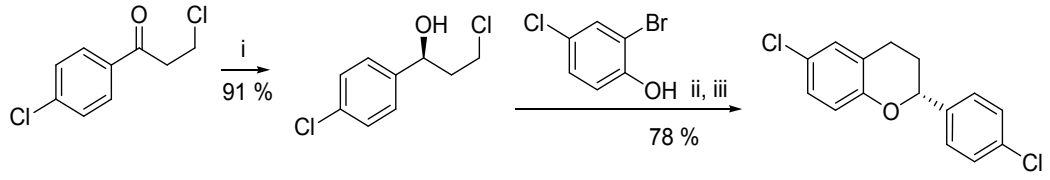


139

	E	R
140	None	Br
141	DMF	CHO
142	$CO_{2(g)}$	CO_2H
143	$(CH_2O)_n$	CH_2OH
144	MeI	Me

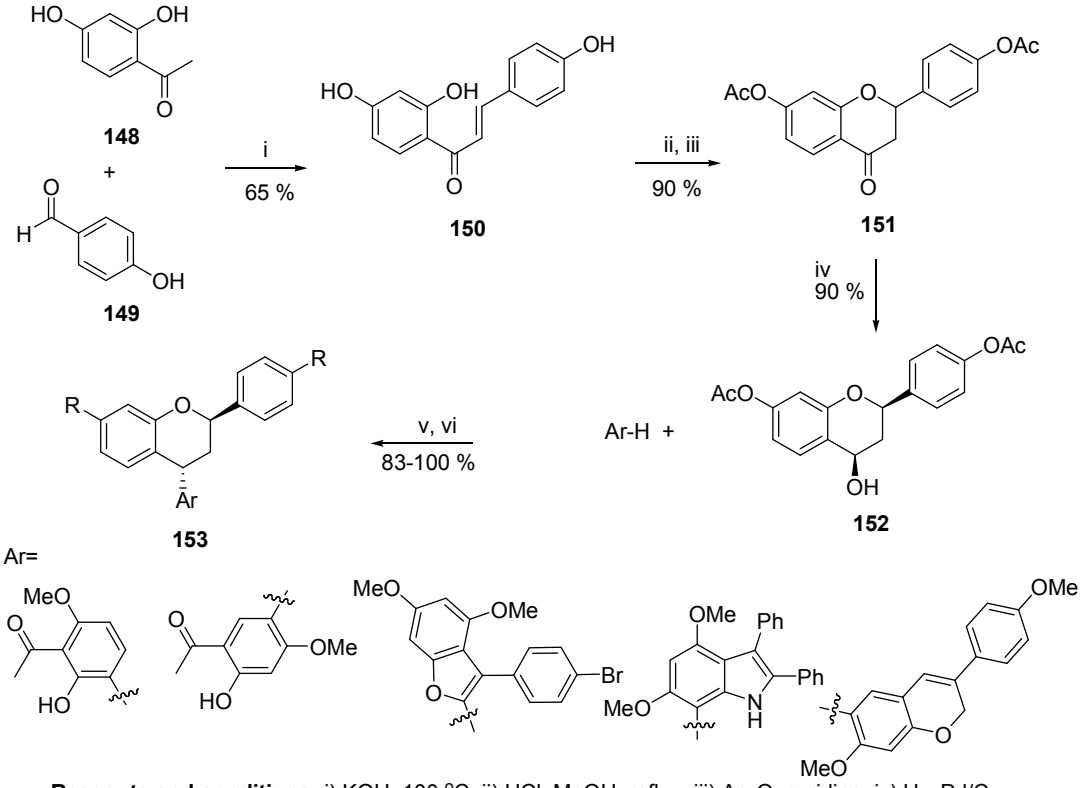
Reagents and conditions: i) *n*-BuLi, THF, -50 ^oC to rt; ii) *n*-BuLi; iii) E (electrophile), -50 ^oC to rt.

Scheme 15: Mitsunobu reaction one pot cyclization and fuctionalization into flavans



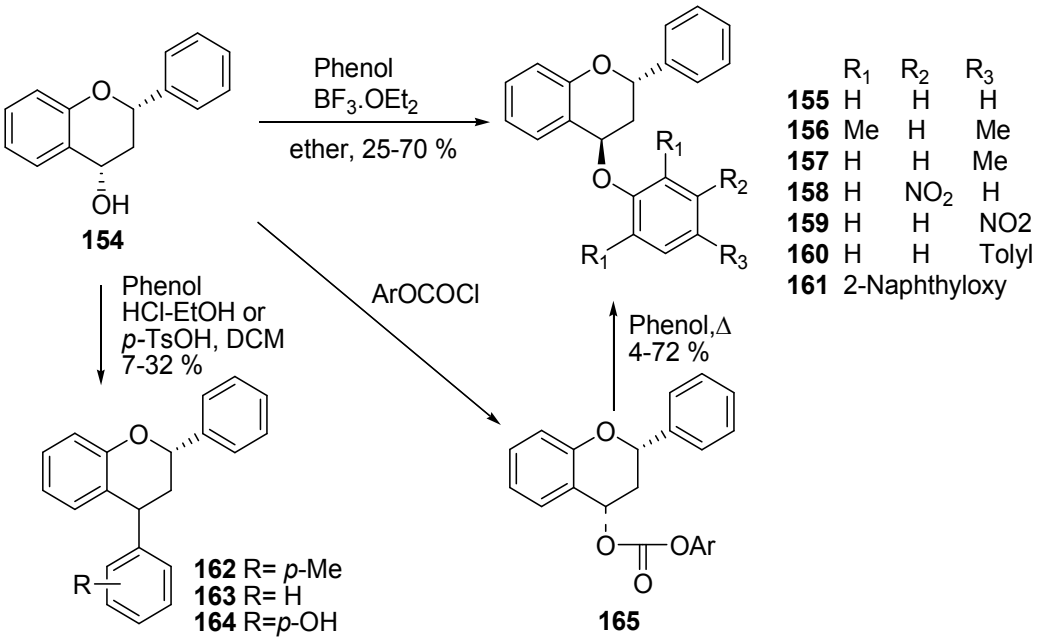
Reagents and conditions: i) BH_3, (*R*)-oxazaborolidine, THF, 0 ^oC; ii) PPh_3, DEAD, THF, rt; iii) *n*-BuLi, THF, -50 ^oC to rt.

Scheme 16: Synthesis of 4',6-dichloroflavan

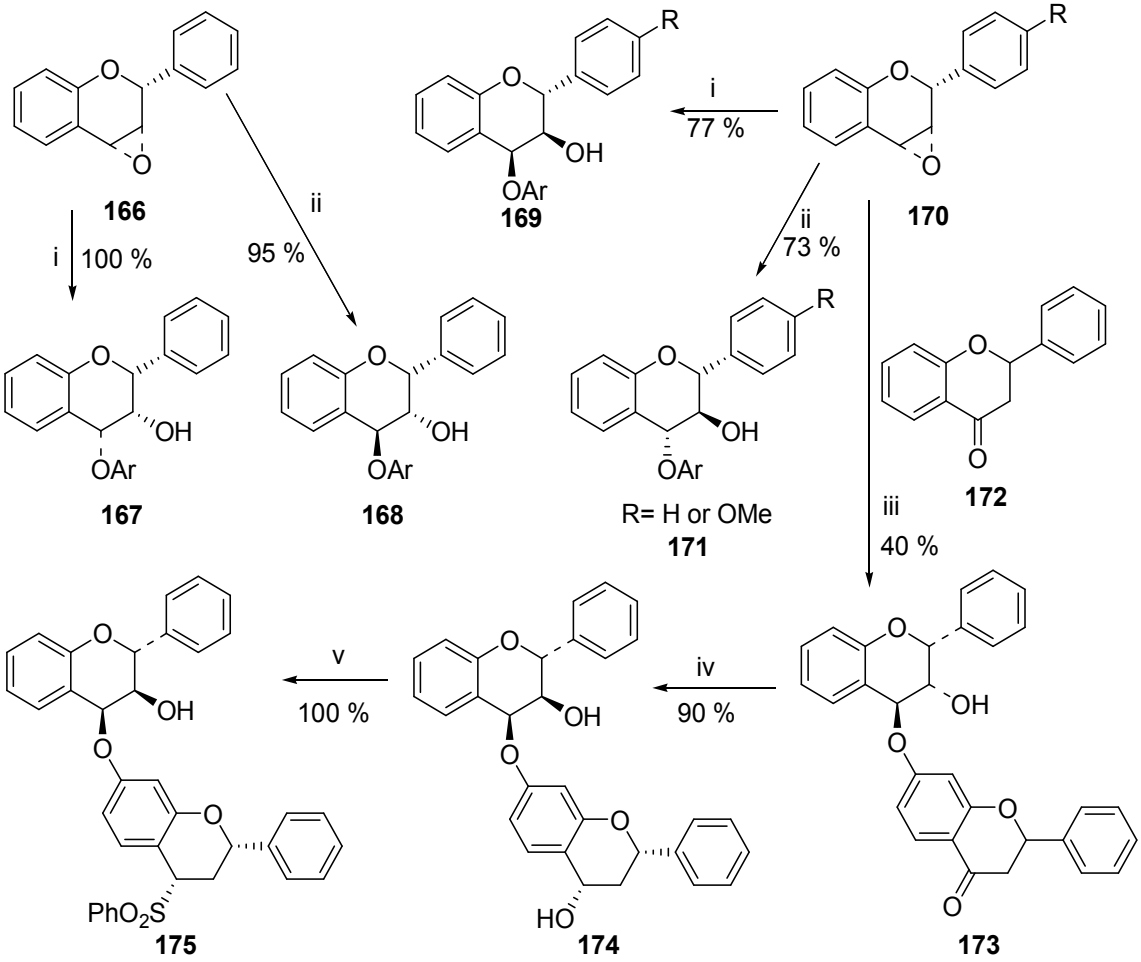


Reagents and conditions: i) KOH, 100 ^{o}C; ii) HCl, MeOH, reflux; iii) Ac_2O, pyridine; iv) H_2, Pd/C, EtOH v) $BF_3.OEt_2$, DCM, rt; vi) KOH, MeOH.

Scheme 17: Deodhar and co-workers synthesis of 4-arylflavans



Scheme 18: Synthesis of 4-arylflavans and 4-aryloxyflavans



Reagents and Conditions: i) ArOH; ii) ArO- Na+; iii) $CHCl_3$; iv) $NaBH_4$, MeOH-$CHCl_3$; v) $PhSO_2H$, HOAc, EtOH

Scheme 19: Synthesis of 4-aryloxyflavans from 2,3-*cis* and 2,3-*trans*-flav-3-ene

The Clark-Lewis group reported the synthesis of four sets of racemates (**193**, **197**, **199**-**200**) of flavan-3,4-diols in Scheme 22. The *cis*-*cis* racemate (**193**) was obtained from flavanol **192** by Raney-Ni hydrogenation [56,57]. The reduction of 2,3-*trans*flavandiols (**198**) with $LiAlH_4$ furnished 2,3-*trans*, 3,4-*cis*-racemate (**199**) and 2,3-*trans*, 3,4-*trans*-racemate (**200**). The least accessible leucoanthocyanidins racemic form was synthesized by the reduction of the 3-bromoflavanone (**195**) into 3-bromoflavan-4-ol (**196**) with $NaBH_4$. The treatment of 3-bromoflavan-4-ol (**196**) with potassium acetate in acetic anhydride afforded the 2,3-*cis*-3,4-*trans* racemate (**197**) as described in Scheme 22 [58]. The acetic anhydride was used for the acetylation of the racemate obtained with KOAc-EtOH which was an oil, while its diacetate was a solid. The ^1H NMR was used to assign the configurations and the heterocyclic ring was found to adopt a half-chair conformation. The coupling constants were distinctive for 2H, 3H and 4H in flavan-3-diols as *cis* [$J_{2ax\text{-}3eq}$=0.9-1 Hz and $J_{3eq\text{-}4ax}$=3.3-3.9 Hz] and *trans* [$J_{2ax\text{-}3ax}$=7.1-10 Hz, $J_{3ax\text{-}4ax}$=5.8-7.5 Hz and $J_{3eq\text{-}4eq}$=0-1 Hz] [56,58].

Machado and coworkers synthesized 4′-methoxyflav-3-en (**205**) from phenol (**201**) in a total of five steps [40,59]. Phenol (**201**) (R = H) was reacted with allyl bromide in the presence of K_2CO_3 and acetone followed by thermal Claisen rearrangement to compound **202**. *O*-allylation of compound (**202**) with tetravinyltin in acetonitrile, catalyzed by copper (II) acetate furnished allyl ether (**203**). Ring closure metathesis using Grubbs-2 catalyst afforded chromene (**204**) and the Heck-Matsuda arylation with Ar-N_2BF_4 using

palladium (II) acetate catalyst furnished 4′-methoxyflav-3-en (**205**) as depicted in Scheme 23. $Pd_2(dba)_3dba$ equally worked as a catalyst but at slightly elevated temperature of 65ºC to furnish 4′-methoxyflav-3-en (**205**) in 54% [59,60].

Mewett and coworkers [61] synthesized flavan-3-ols, (**211**, **212**), starting from the reaction of acetophenone (**206**) and benzaldehyde (**207**) (Sche**m**e 24). The first key step was the reduction of the chalcone with $NaBH_4$ to afford (*E*)-1,3-diarylpropene (**209**). The reported $NaBH_4$-H_2O/H^+ reduction system was selective towards C=O reduction only, similar to $LiAlH_4/AlCl_3$-THF [30], but was in utter-contrast to reductions using H_2/Pd-C [25] and $NaBH_4$-MeOH systems [26,29,34] which reduced both the C=C and C=O bonds. After the MOM protection of free OH, asymmetric dihydroxylation of the (*E*)-1,3-diarylpropene (**209**) double bond using AD-mix-β afforded (1*R*,2*R*)-*syn*-diol (**210**) (AD-mix-α equally works to give (1*S*,2*S*)- *syn*-diol. The deprotection and cyclisation [62] furnished a mixture of *cis*- and *trans*-flavan-3-ols, (**211**-**212**), in a ratio of 1:3 respectively [61]. In chalcone reductive protocols the hydroxyl group is derived from the C=O reduction [29], and cyclization afford flavans while in this protocol the cyclization step yields C-3 hydroxy substituted flavans (flavan-3-ol), due to the presence of 1,2-diols moiety.

The dimethyldioxirane (DMD), oxidation of flavan-4α-ol and flavans (**213**) derivatives affords the corresponding C-2 hydroxy derivatives (**213**, **215**) in good yields [63,64], Scheme 25. Treatment of compound (**214**) with silica gel eliminates the acetic acid to give flavene (**216**). The flavane with the 4-*equatorial* acetoxy is more stable. On the other hand the dehydration of flavan (**215**) requires $POCl_3$ at 50ºC. The differences have been ascribed to the fact that the presence of the *axial* acetoxy group in hydroxylated intermediate (**218**) weakens the hydrogen bonding between the C-2 hydroxy group and the benzyl ethereal oxygen, which favors dehydration [63,65]. The flavylium ion, anthocyanin (**217**) was obtained after the treatment of flavene (**216**) with HCl, whereas mild oxidants were required for transformations of flavene (**219** and **220**) [63].

The reaction of nucleophiles (alcohols or amines) with flavan-4-ols or flavan-4-halides affords the corresponding 4-substituted flavans. A series of 4α-halogenoflavans (**223**-**227**) were obtained via SN^2 substitution reaction of flavan-4β-ol (**222**) with phosphorous halide, Scheme 26. The 4α-halogenoflavans were reported to have a 2,4-*trans* configuration based on ^{1}H-NMR interpretations, $J_{2,3}$ =13-14 Hz and $J_{3,4}$ = 6-6.5 Hz. An attempt to recrystallize the 4α-chloroflavan (**223**) from methanol led to the substitution of the halide by the MeO^- ion (**229**). The action of arylphenols on 4α-halogenoflavan gave the desired product albeit at lower yields (20-30%) and inversion of configuration. Improved yields 40-50% for the 4β-arylflavans (**230**-**235**) were accomplished using stoicheiometric amount of a phase transfer catalyst, PTC (benzyltri-*n*-butylammonium bromide) as shown in Scheme 27. Flavan-4β-yl sulphides (**238**, **239**) were synthesized by the action of thiophenolate nucleophile on 4α-chloroflavan (**223**) (Scheme 28), while 4-aminoflavans (**240**-**244**) were synthesized using amino group nucleophiles [66-69] as described in Scheme 29.

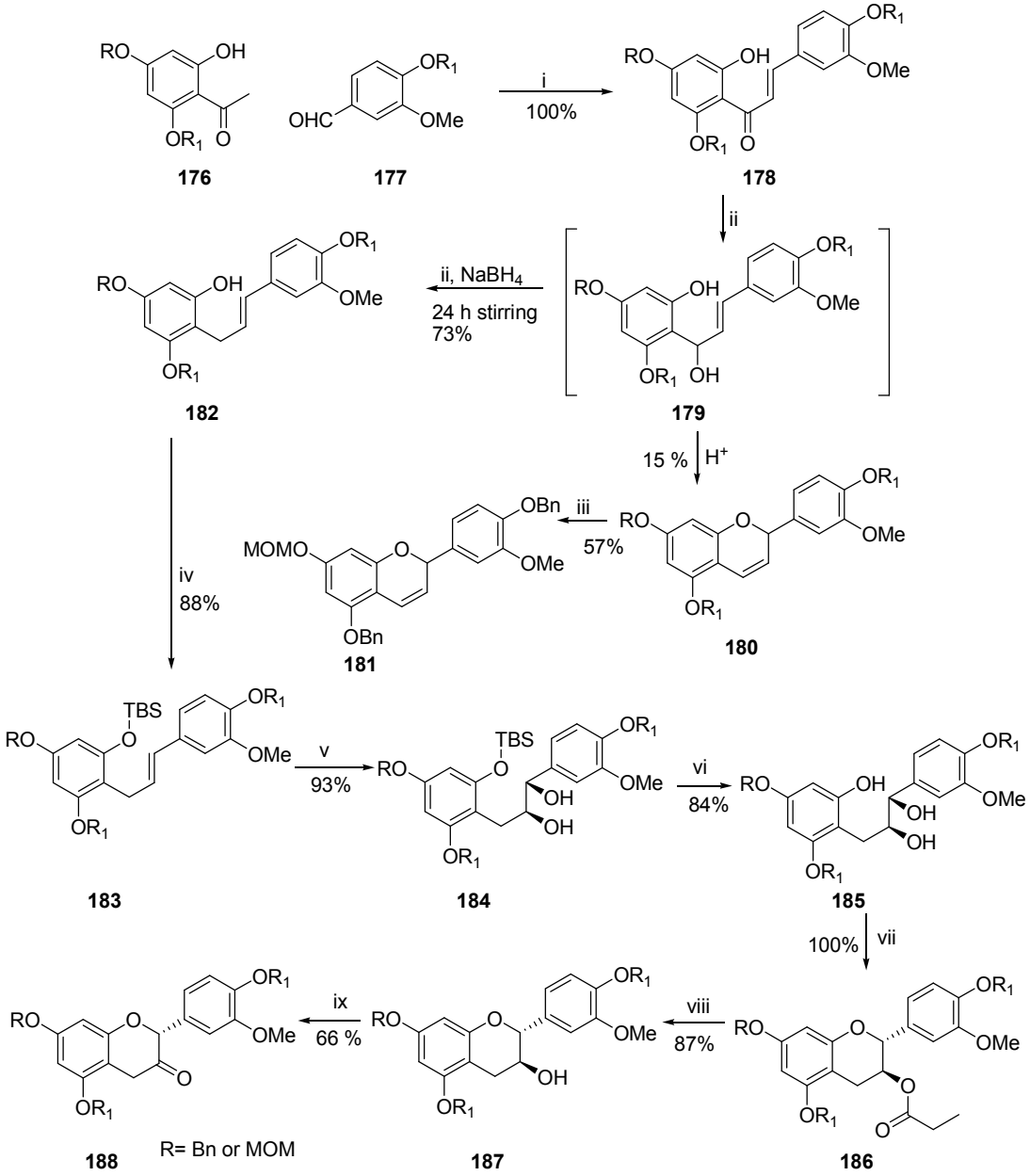
Flavylium salts were reduced to flavenes in various ways. Lithium aluminium hydride is generally used for the preparation of flav-2-ens unsubstituted at C2' and C3 (**246**), and flav-3-ens substituted at C3 and C2' (**247**-**248**; Scheme 30) [70]. Mixture of flav-2-ens (**249**) and flav-3-enes (**250**) were obtained for flavylium ions bearing electron donating groups at C-2', which render $LiAlH_4$ a less useful reducing agent [71].

The catalytic reduction of 3,5,7,2′,4′-pentamethoxyflavylium chloride (**251**) with Pd-$BaSO_4$ furnished 3,5,7,2′,4′-pentamethoxyflavan (**252**; Scheme 31) [72], which is a derivative of cyanomaclurin (3,5,7,4′-tetrahydoxyflavan) [73]. Cyanomaclurin (**253**) is a constituent of *Atorcapus* species and exhibit antibacterial and tyrosinase inhibitor activity [74,75].

An efficient bromination of flav-2-ens (**254**) with *N*-bromosuccinimide in methanol occurred more rapidly than substitution into the aromatic moiety to give 2,3-*cis*-2methoxy-3-bromoflavans (**255**). The reduction of flavans (**255**) with *tri*-*n*-butylin hydride removed the bromine atom to afford 2-methoxyflavans (**257**-**259**), while the removal of the methoxy group was achieved by using $LiAlCl_4$ to yield 3-bromoflavane (**256**). The 3-bromoflavanes (**256**) gave the corresponding 2-methoxyflavanes (**257**-**259**) after treatment with silver nitrate in methanol as shown in Scheme 32 [39,76].

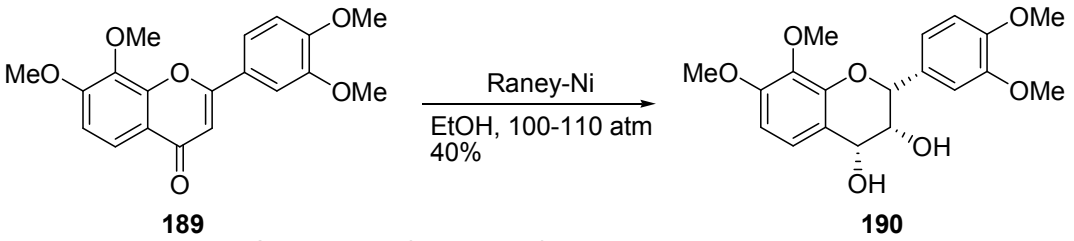
Gharpute and co-workers [77] reported a mild protocol for the synthesis of flavans (**263**-**266**)

using in situ generated quinone methide (*o*-QMs) (**262**), which undergoes a [4+2] cycloaddition reaction with styrene (**261**) and non-aryl vinylogous systems such as acrylates as shown in Scheme 33 and Figure 4. The *o*-QMs were generated from o-hydroxy bisbenzylic alcohols (**260**) using (±)-binolphosphoric acid (BPA) and the reaction required a 1:1 equivalent of styrene (261) for an efficient hetero Diels-Alder reaction [77-79]. The BPA catalyzed reaction had a diastereoselectivity (3:1) favouring the cis isomer, while Bi(OTf)3 catalyst produced a racemic mixture (1:1) though at the same yields [77].



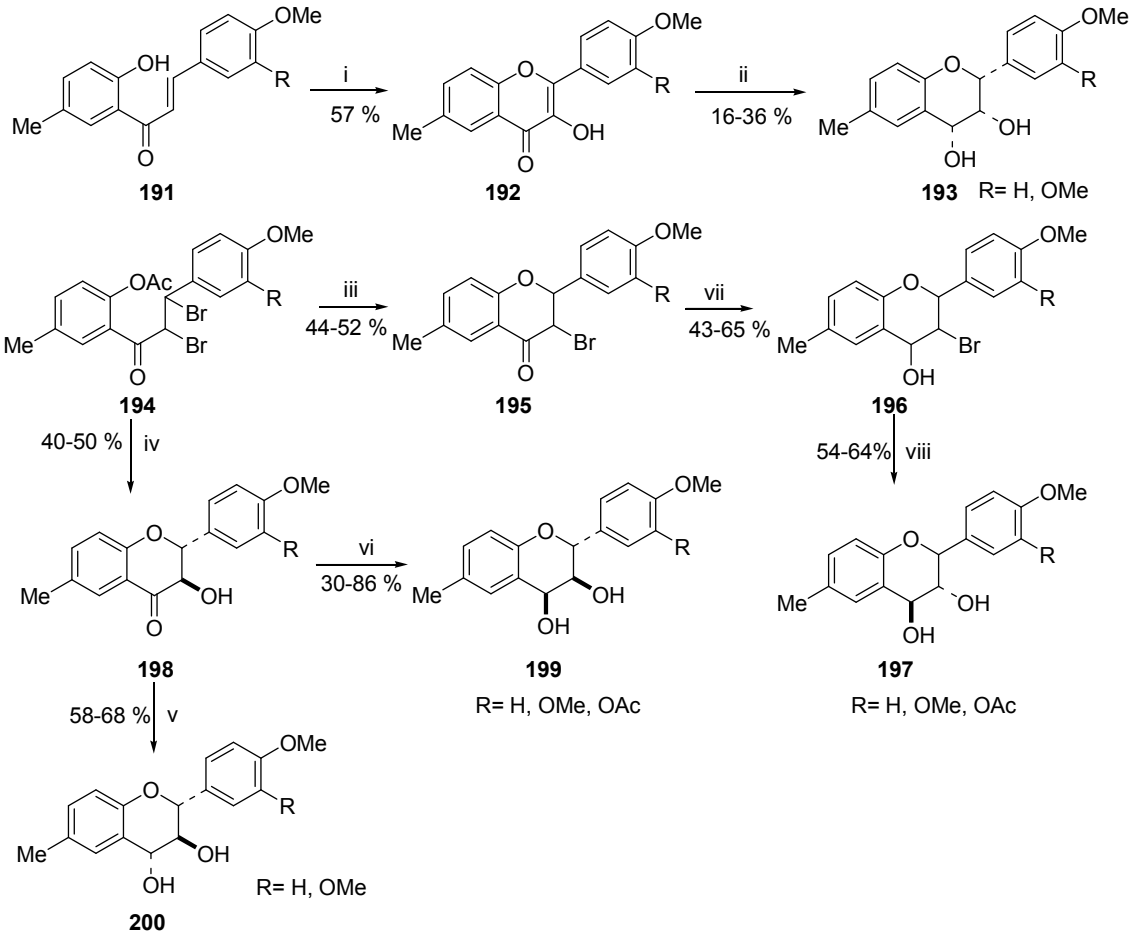
Reagents and conditions: i) NaH, Heptane/DMF; ii) $NaBH_4$, $CeCl_3.7H_2O$, THF/EtOH, 0^oC; iii) $K_3Fe(CN)_6$, K_2CO_3, $OsCl_3.H_2O$, quinuclidine, methane sulfonamide, *t*-butanol/H_2O/THF, rt, 18 h then $NaBH_3CN$-HOAc, 50^oC, 2h; iv) TBDMSCl, imidazole, DMF; v) AD-mix-a, $MeSO_2NH_2/K_2CO_3$, *t*-BuOH/water/THF, 0 ^oC; vi) TBAF, AcOH, THF, 0 ^oC; vii) $EtC(OEt)_3$, PPTS, DCM, 65^oC; viii) K_2CO_3, MeOH; ix) Dess–Martin periodinane, DCM, rt.

Scheme 20: Zhang et al. chalcone reduction and synthesis of flavanes, flavan-3-one and flavan-3-ol



189 **190**

Scheme 21: Synthesis of melacacidin tetramethyl ether



191 **192** **193** R= H, OMe

194 **195** **196**

198 **199** **197**

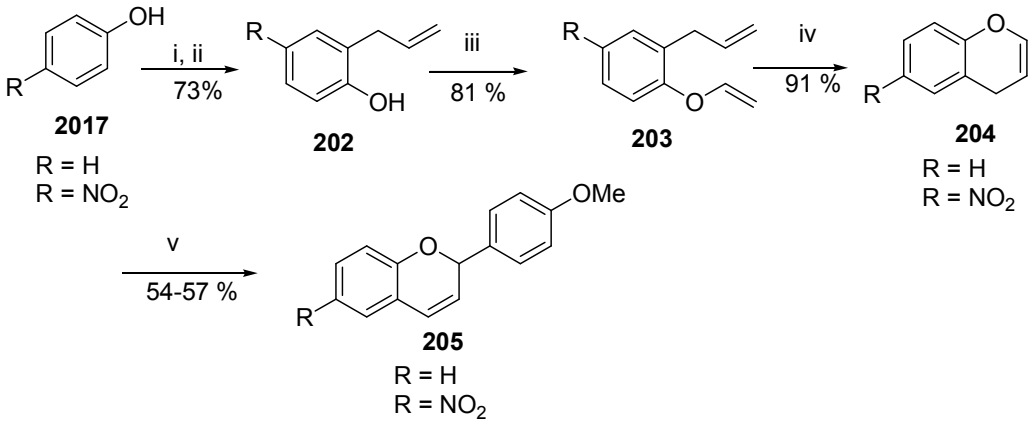
R= H, OMe, OAc R= H, OMe, OAc

200

Reagents and Conditions: i) H_2O_2-OH^-; ii) Raney-Ni, EtOH, 100 atm, 90^oC, 14h; iii) HCl, EtOH-H_2O, 4h iv) Br_2, CCl_4, $COMe_2$, 15 min; v) $LiAlH_4$, THF, 0^oC, 1h; vi) $LiAlH_4$, $AlCl_3$, THF, 0^oC, 1h; vii) $NaBH_4$, MeOH, 2 days, 0^oC or $LiAlH_4$, THF, 1h, 0^oC; viii) KOAc, AcOH, Ac_2O.

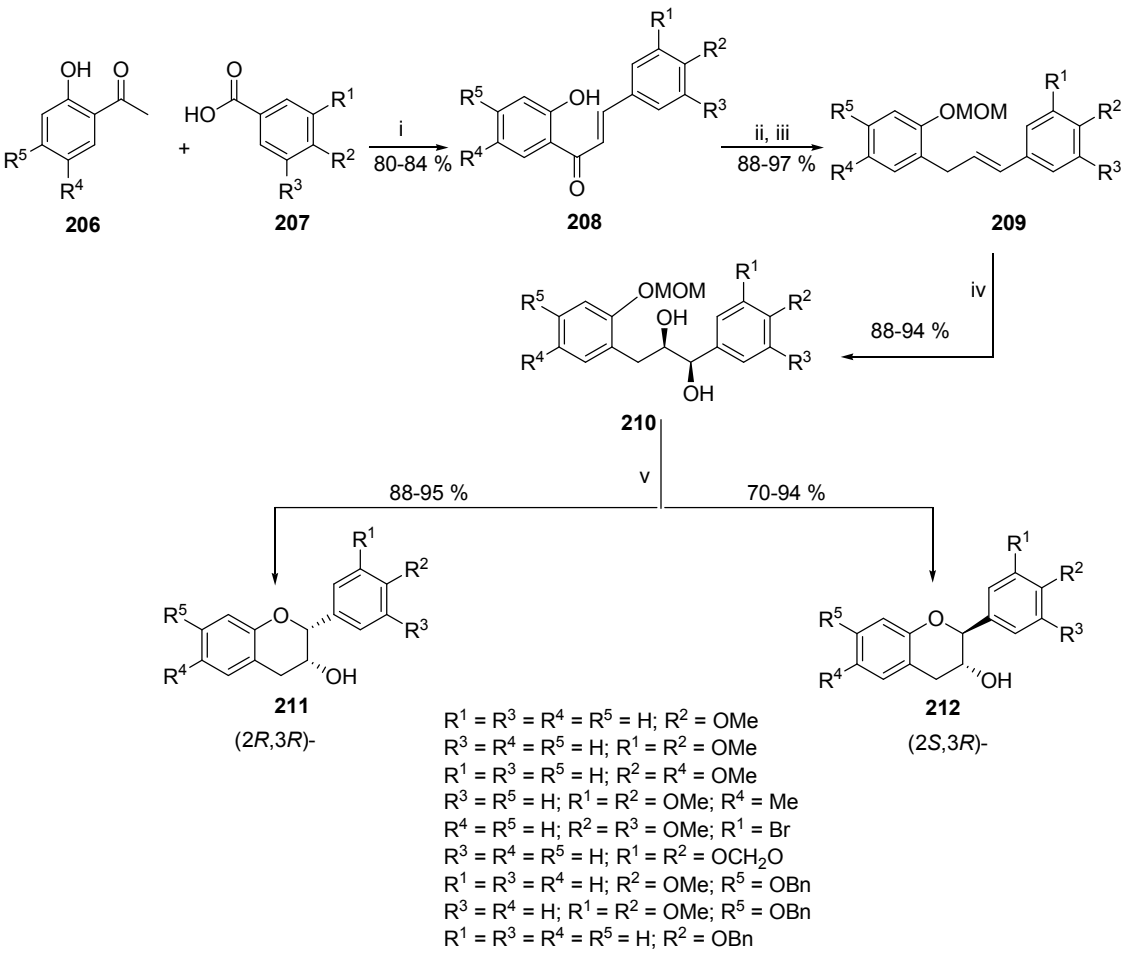
Scheme 22: Synthesis of flavan-3,4-diol racemates

Gharpure and co-workers applied the hetero Diels-Alder reaction of *o*-quinone with styrene to the synthesis of Myristinins A and B/C [77]. Myristinins A (**279**) and B/C are natural neoflavans isolated from *Myristica cinnamomea*, *Knema elegans* and *Horsfieldia amygdaline* [80,81] showing anti-inflammatory, antifungal and are both potent DNA-damaging agent and DNA polymerase β inhibitors [80-83]. The total synthesis of Myristinins A and B/C reported by Gharpure and co-workers in Scheme 34 [77] is shorter than the lengthy strategy reported by Hecht and co-workers [80,81].



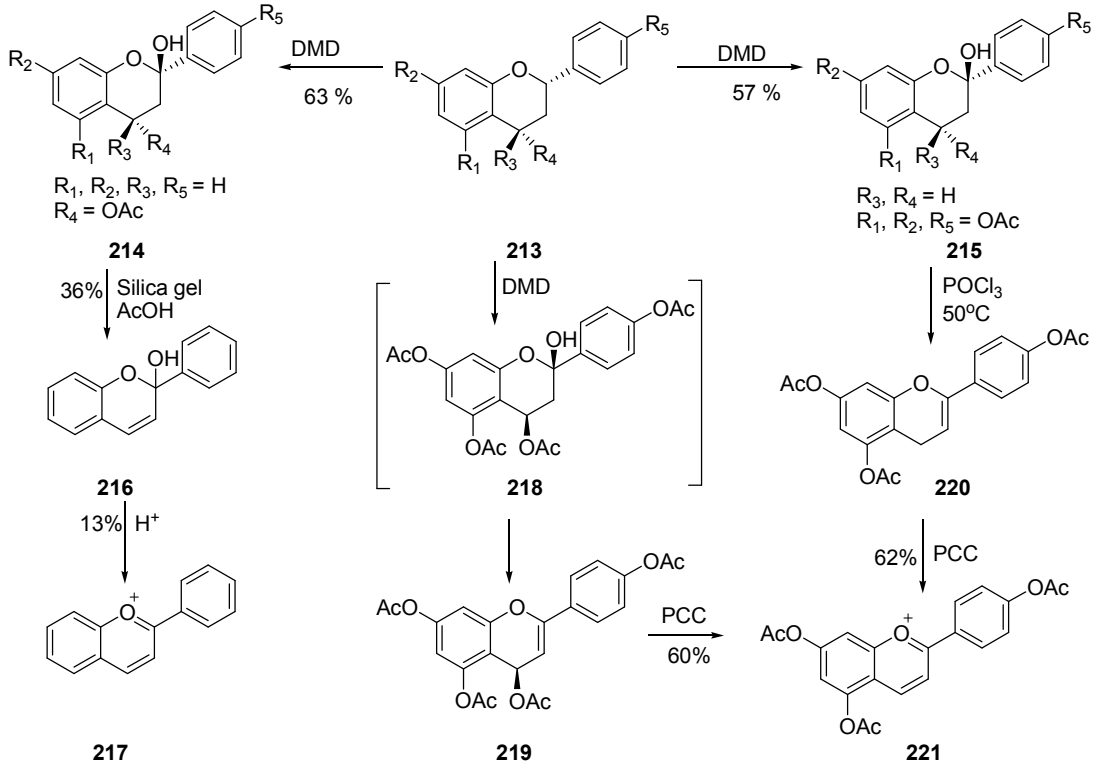
Reagents and conditions: i) K_2CO_3, allyl bromide, acetone, 60 °C; ii) Δ (180-240 °C), neat; iii) $Cu(OAc)_2$, $Sn(CH=CH_2)_4$, O_2, MeCN, 25 °C, 24 h; iv) Grubb's second generation Ru-catalyst, toluene, 60 °C, 1 h; v) Ar-N_2BF_4, $Pd(OAc)_2$, 2,6-di-t-butyl-4-methylpyridine, EtOH, 55 °C, 2.5 h.

Scheme 23: Machado et al. synthesis of 4'-methoxyflav-3-en

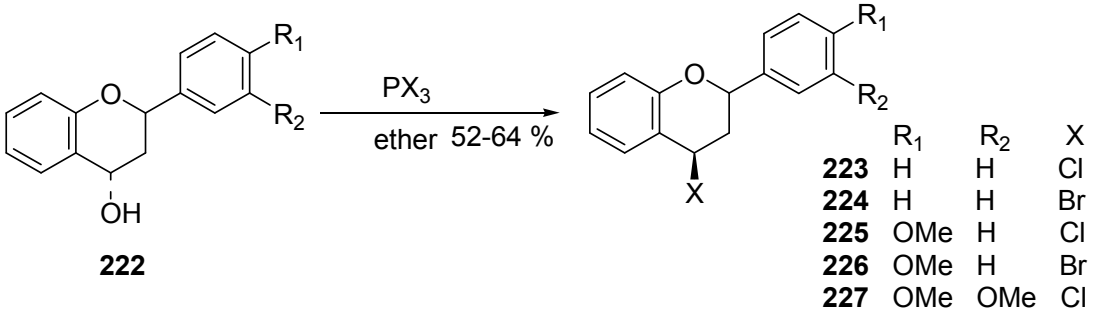


Reagents and conditions: i) KOHaq/ EtOH; ii) $EtCO_2Cl$/TEA/THF, then $NaBH_4/H_2O$, then H^+; iii) MOMCl/(*i*-Pr)$_2$NEt/THF; iv) AD-mix-β or AD-mix-α/$MeSO_2NH_2$, H_2O/BuOH, 0-4 °C; v) HCl/MeOH-H_2O.

Scheme 24: Mewett and coworkers synthesis of flavan-3-ols



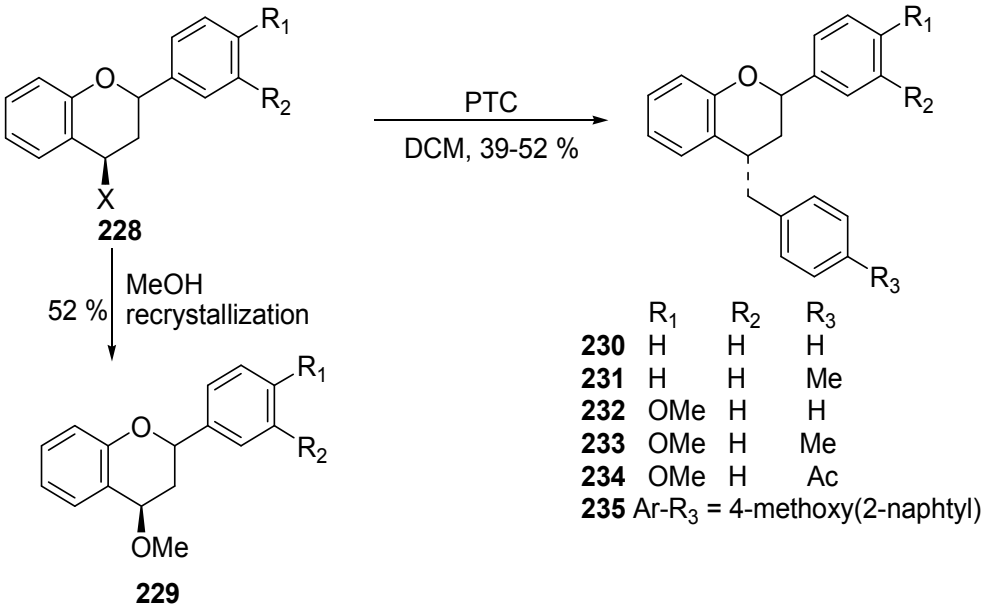
Scheme 25: Hydroxylation and oxidation of flavans



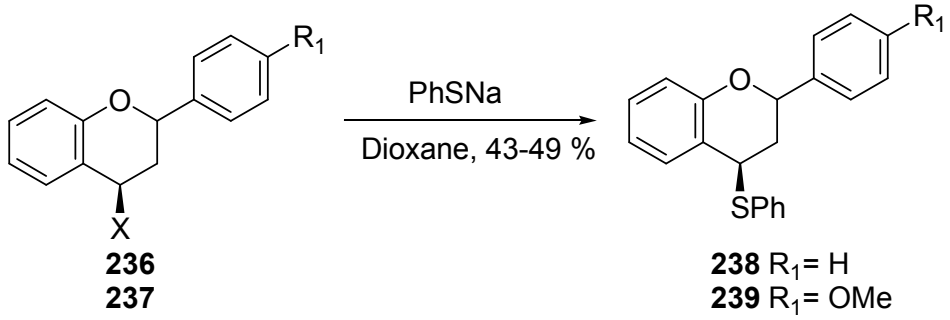
Scheme 26: Synthesis of 2,4-*trans*-4- halogenoflavans

The strategy begun by deriving the *o*-QM precursor (**272**), iodoalcohol (**271**) from the addition of diiodide to an aldehyde (**270**). The *o*-QM undergoes a [4+2] cycloaddition with styrene to furnish arylflavan in good diastereoselectivity (*cis*:*trans*; 9:1). The arylflavan stabilized by styrene dienophile reacted with ethyl vinyl ether (**275**) under Heck reaction conditions to afford ketone **276**. Ketone **276** was reported to be difficult in forming an enolate ion due to steric hindrance, but repeat generation of ketone **276** enolate ions using *t*-BuOK and alkylation with *n*-decyl iodide accomplished the synthesis of Myristinin A (**279**) [79] as depicted in Scheme 34.

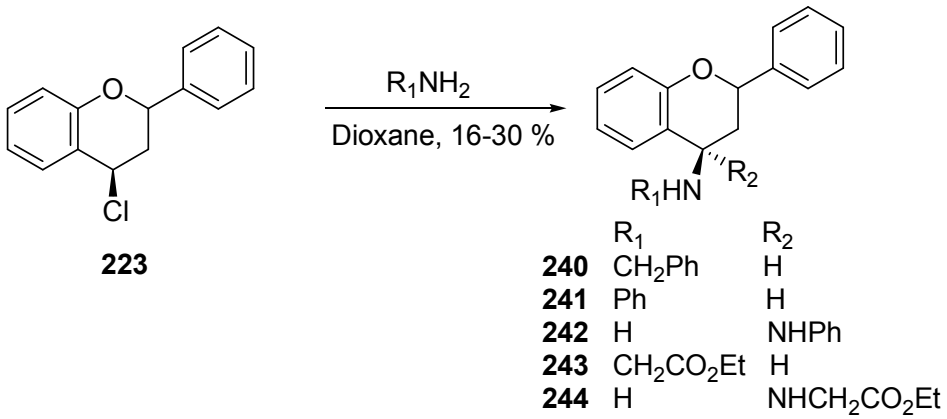
Suchand and co-workers presented the neoflavan synthesis based on the intramolecular [Cu]-catalyzed C–O bond formation from the precursor diphenylalcohols. The synthesis starts with the Lewis acid promoted Friedel-Crafts Michael addition of electron rich phenols (**281**) onto the double bond of the cinnamate ester (**280**) to furnish a β-diaryl ester (**282**). Preferential electrophilic aromatic bromination of the electron rich aromatic ring at the β-diaryl ester, followed by reduction of the ester furnished the required precursor alcohols (**284**). The cyclization using intramolecular [Cu]-catalyzed C–O bond formation was successful and furnished neoflavans (**285**) shown in Scheme 35 and Fig. 5 in good yields [84].



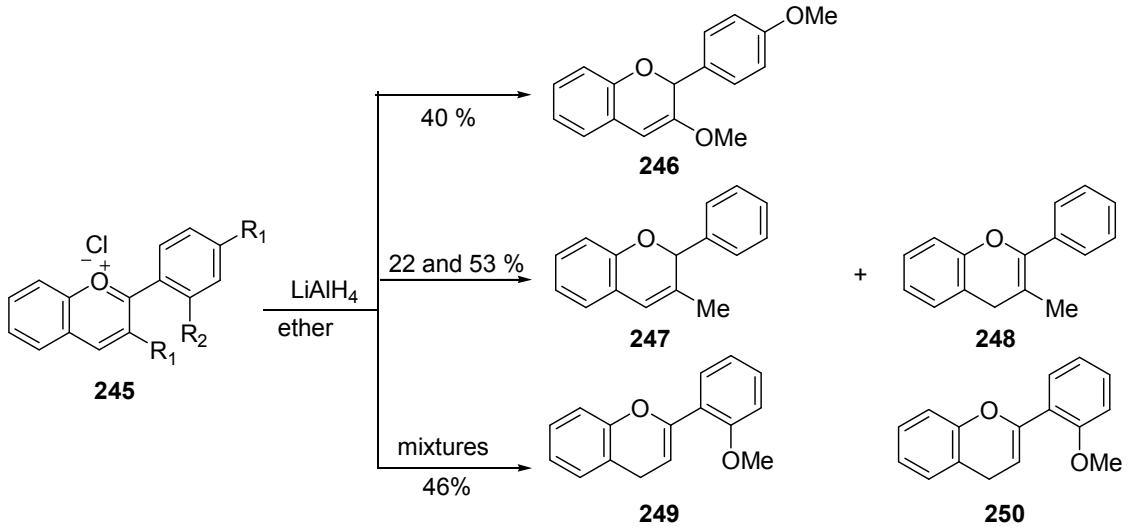
Scheme 27: Synthesis of 2,4-*cis*-4- arylflavans



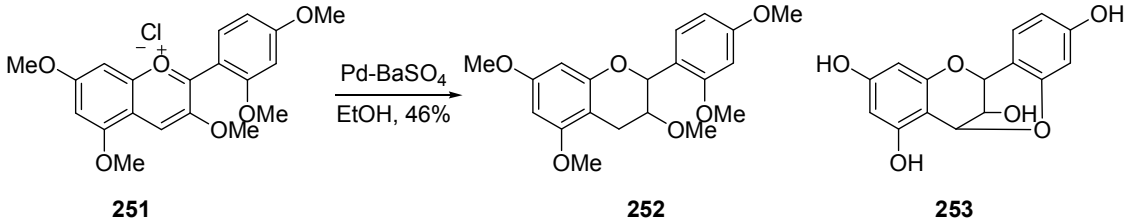
Scheme 28: Flavan-4α-yl sulphides synthesis



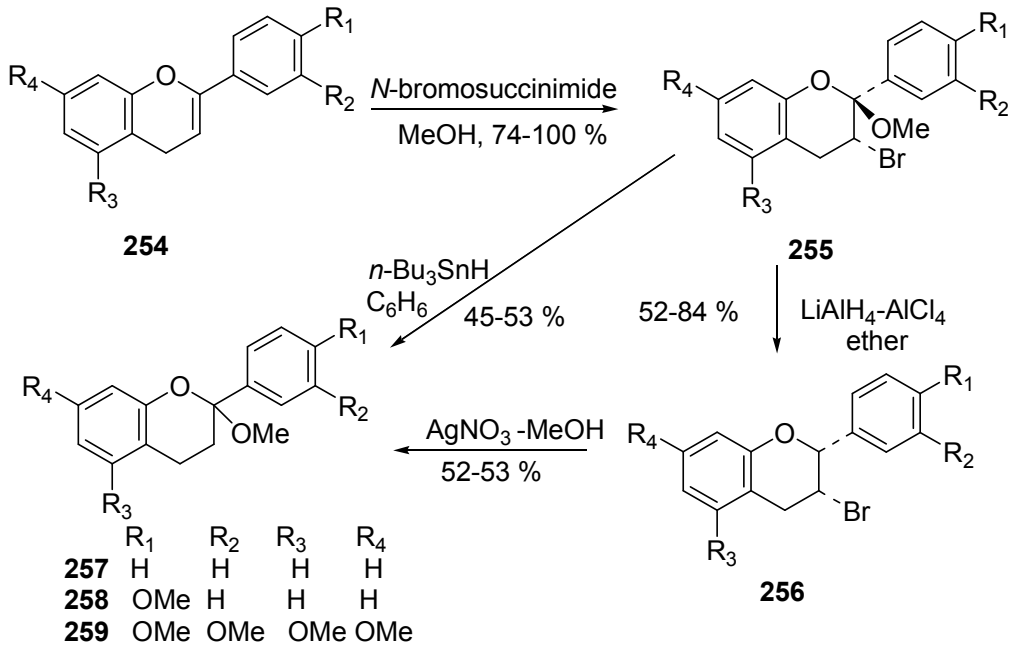
Scheme 29: Synthesis of 4-aminoflavans



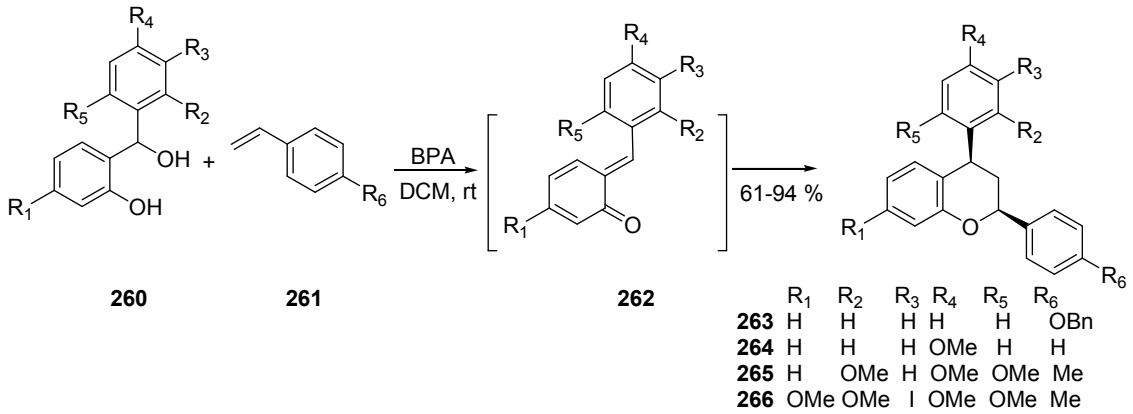
Scheme 30: Reduction of flavylium ions with $LiAlH_4$



Scheme 31: Synthesis of pentamethoxyflavan



Scheme 32: Synthesisi of 2-methoxyflavan and 3-bromoflavans



Scheme 33: Synthesis of flavans using [4+2] cycloaddition of *o*-QMs and styrene

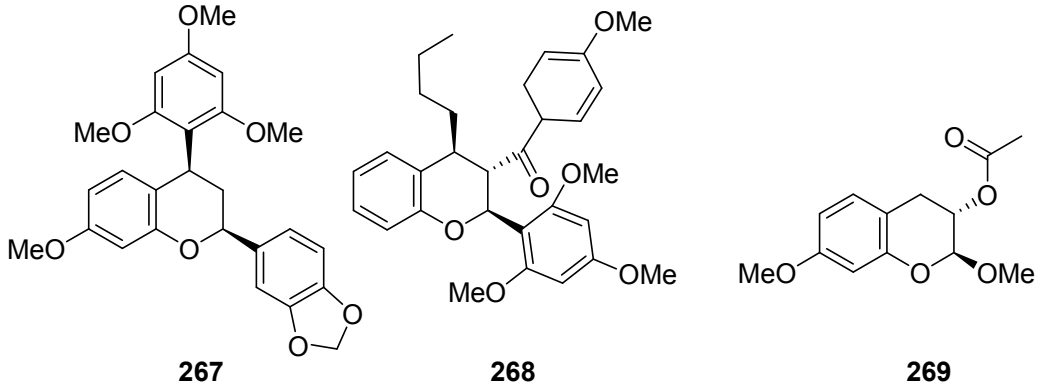


Figure 4: Flavane derivatives reported by Gharpure and co-workers

The synthesis of [3.3.1]-bicyclic ketals was accomplished by the Pd(II)-catalyzed asymmetric 1,4-conjugate addition of organoboron reagent [85], 2-hydroxyphenylboronic acid (**294**) to chalcones (**293**). The 2-hydroxyphenyl palladium metal complex (**295**) was generated *in situ via* the transmetalation of 2-hydroxyphenylboronic acid (**294**), with the chiral Pd(ii)-complex [generated from $Pd(PhCN)_2Cl_2$ and ligand (*R*)-3,5-xyly-BINAP, **L3**]. The palladium complex **295** act as a *bis*(nucleophile) in the construction of the chiral flavan heteroannular ketals shown in Scheme 36 [86]. The products were reported in higher enantio-selectivities and the substituent on the chalcones only affected the yields. Besides the flavanone reductions utilizing inorganic catalyst reductions, the application of biocatalysts has also been reported. Three day biotransformation of (*S*)-flavanone (**317**) with yeast of the genus *Candida wiswanathi* KCh 120 enabled the enantioselective reduction of the ketone functional group to give (2*S*,4*S*)-*cis*-flavan-4-ol (38%, 95%) (**318**) and (2*R*,4*S*)-*trans*-flavan-4-ol (51%, 92% ee) (**319**) as shown in Scheme 37. The reductions by the yeast species were (*S*)-one selective. The (*R*)-flavanone was ineffectively reduced by *Saccharomyces brasiliensis* KCh 905 to afford (2*S*,4*R*)-*trans*-flavan-4-ol (12%, 91% ee) and (2*R*,4*R*)-*cis*-flavan-4-ol (7%, 22% ee) [87].

2.3 Isoflavans

Deodhar and co-workers [45] used the procedure for the synthesis of flavans (**152**) (Scheme 17) to the construction of isoflavans **325** from isoflavanol (**323**) [88,89] as described in Scheme 38. *Trans*-4-aryl/heteroarylisoflavans were synthesized in good to excellent yields and bearing various substituents [45].

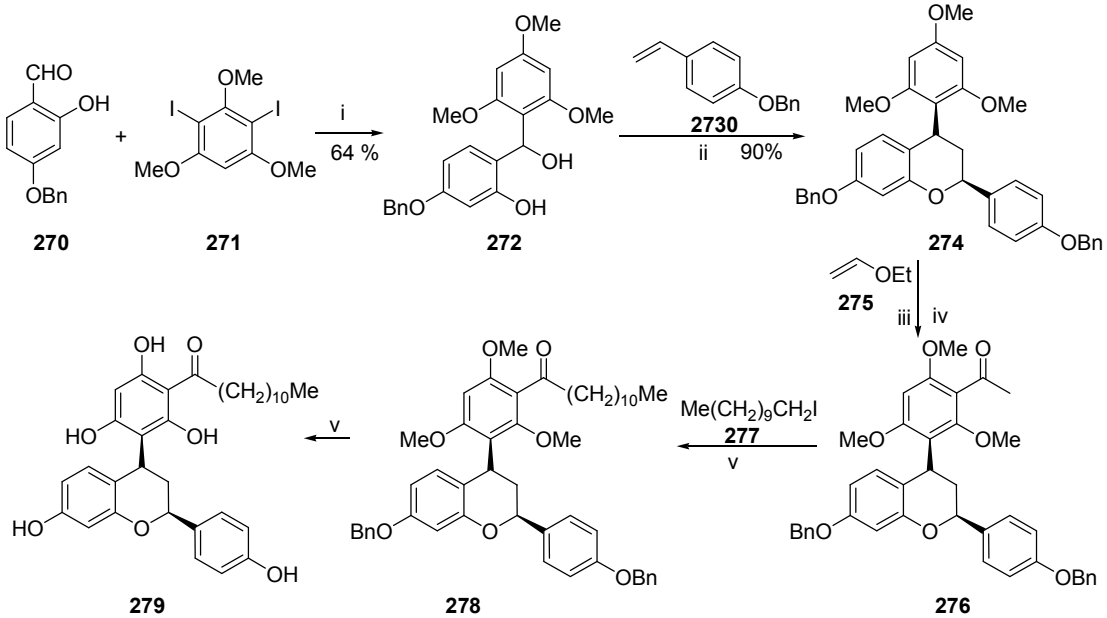
Takashima and co-workers outlined the synthesis of natural flavans, (*S*)-equol, (*R*)-sativan and (*R*)-vestitol using allylic substitution [90]. The (*S*)-equol synthesis was offset by the Wittig reaction between the phosphonium salt derived from arylaldehyde and the protected 2-hydroxypropanal (**326**). The aldehyde was synthesized from ethyl-(*S*)-lactate (**329**). The Wittig product was the *cis*-olefin (**332**), which

after deprotection and esterification afforded the key intermediate, picolinate (**333**) in 94% ee (*cis*:*trans*: 14:1). The allylic substitution of (*S*)-picolinate with the copper reagent produced the *anti* SN^2 *trans* olefin product which when subjected to OsO_4-catalyzed dihydroxylation gave a polar diol of **335**. The cleavage of the diol by $NaIO_4$ and *in situ* reduction of the resulting aldehyde with $NaBH_4$ affords an alcohol, which was brominated to obtain compound **335**. The cyclization of **335** yields (*S*)-equol (**9**) in 91% ee after demethylations using BBr_3 [90-92] as depicted in Scheme 39. The synthesis of (*S*)-equol was previously reported in a similar manner from (*S*)-picolinate with yields of 74% and 99% ee [93]. The first total synthesis of (*S*)-equol was reported by Heemstra and co-workers in an overall yield of 9.8%. Their six step protocol key step was the Evans alkylation [94] to form the stereocenter and an intramolecular etherification to generate the benzopyran ring, which was deprotected to furnish (*S*)-equol as shown in Scheme 41 [95].

For the synthesis of (*R*)-sativan, the intermediate (*R*)-picolinate was synthesized from ethyl-(*R*)-lactate using similar reactions described in Scheme 38. The synthetic protocol for (*R*)-sativan differs with that of (*S*)-equol at the deprotection and cyclization steps. The protecting benyl group was removed by H_2-Pd/C catalyst and cyclization with Mitsunobu reagent, PPh_3 and DEAD constructed the benzopyran ring of (*R*)-sativan (**344**) as shown in Scheme 41 [90,96-98].

The synthetic strategy towards (*R*)-vestitol (**10**) was similar to that of (*R*)-sativan (**344**), but the copper reagent utilized was derived from the Grignard reagent 2-MOMO-4-$MeOC_6H_3MgBr$. The final step was the deprotection of the MOM group with HCl in MeOH (Scheme 42) to furnish (*R*)-vestitol in 90% ee [90,92,99].

Gharpure and coworkers reported the synthesis of isoflavans using *in situ* generated o-quinone methides (*o*-QM) as heterodiene in the [4+2] Diels-Alder cycloaddition reaction shown in Scheme 43. The required *o*-acetotoxymethylphenol (**347**) was prepared from the salicyladehyde derivative (**348**) reduction, while the arylenol ethers (**348**) were synthesized *via* Wittig reaction on an arylaldehyde (**347**).



Reagents and conditions: i) *n*-BuLi, THF, -78 ^oC; ii) BPA, DCM; iii) $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 110 ^oC; iv) HCl; v) *t*-BuOK, THF, 0 ^oC-rt.

Scheme 34: Synthesis of Myristinin A

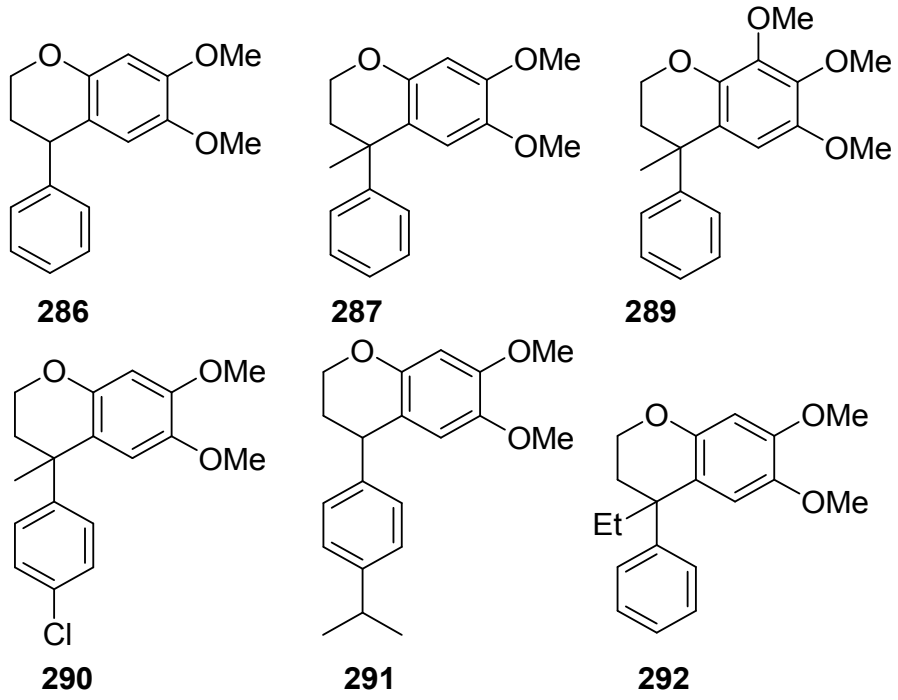
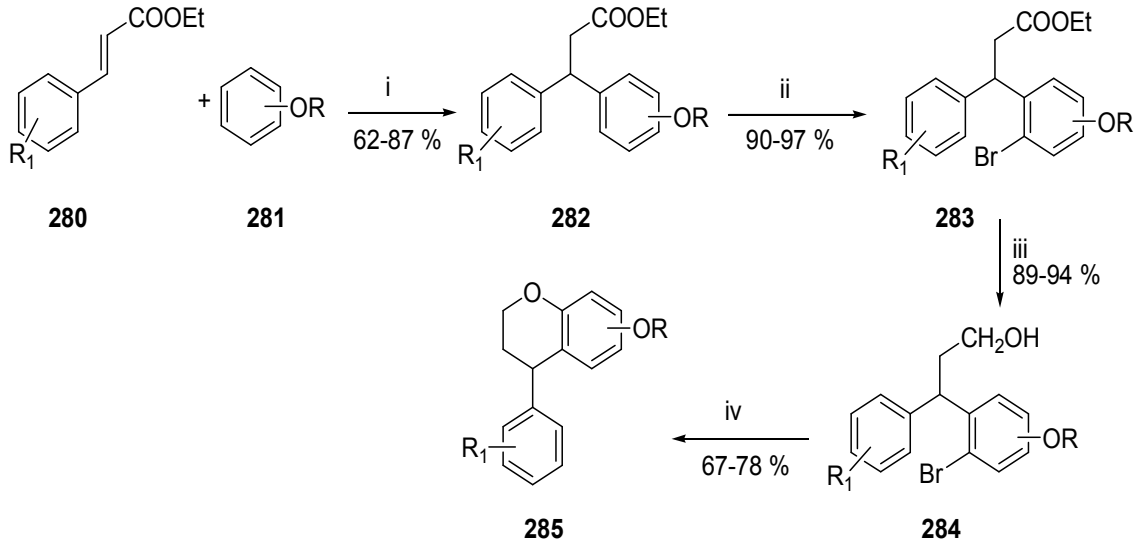
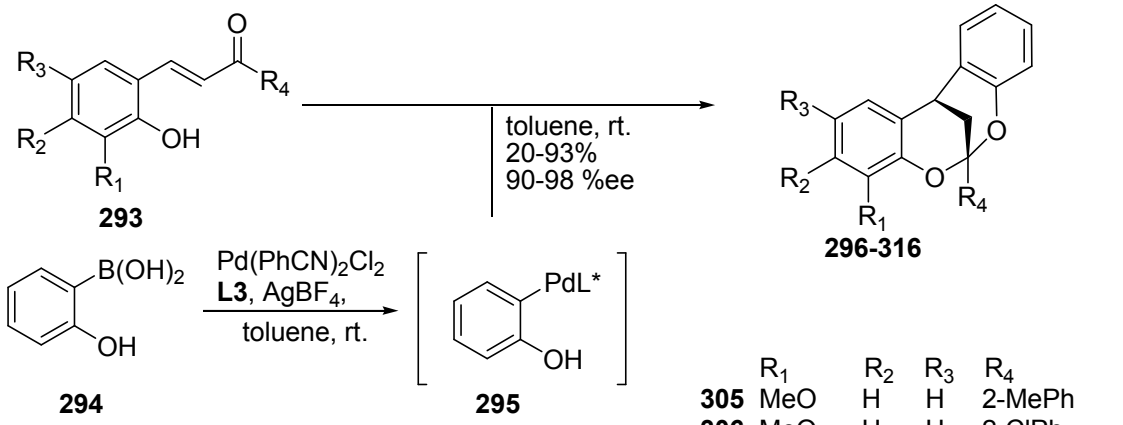


Figure 5 Neoflavans reported by Suchand and co-workers



Reagents and conditions: i) $FeCl_3$, DCE, rt, 12h; ii) Br_2, DCM, 0^oC, 3h; iii) LAH, Et_2O, 0^oC, 1h; iv) CuI, 2,2'-bipy. *t*-BuKO, DMF, 120 ^oC, 24h.

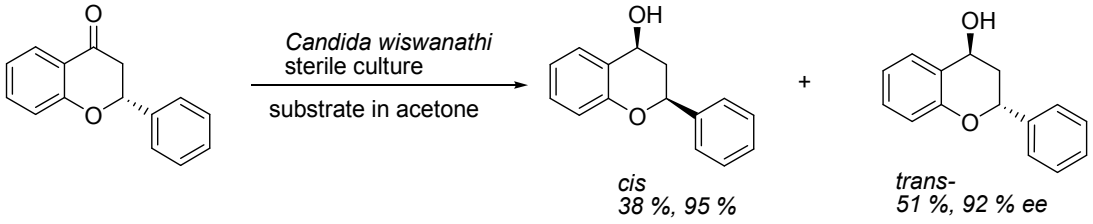
Scheme 35: [Cu]-catalyzed C-O bond formation in the synthesis of neoflavans



	R_1	R_2	R_3	R_4
296	MeO	H	H	Ph
297	H	MeO	H	Ph
298	H	H	MeO	Ph
299	H	H	OH	Ph
300	H	H	Me	Ph
301	H	H	F	Ph
302	H	H	Cl	Ph
303	H	H	Br	Ph
304	H	H	NO_2	Ph

	R_1	R_2	R_3	R_4
305	MeO	H	H	2-MePh
306	MeO	H	H	2-ClPh
307	MeO	H	H	2-BrPh
308	MeO	H	H	3-ClPh
309	MeO	H	H	4-ClPh
310	MeO	H	H	4-FPh
311	MeO	H	H	4-CF_4 Ph
312	MeO	H	H	4-MePh
313	MeO	H	H	4-MeOPh
314	MeO	H	H	3,4-diMePh
315	H	H	H	Ph
316	H	H	H	C_4H_4S

Scheme 36: Synthesis of flavan heteroannular ketals



Scheme 37: Biotransformations of flavanone to flavan-4-ols

The Diels Alder reaction of diene, o-quinone methides (*o*-QM; **351**) generated from o-acetotoxymethylphenol and the dienophile, arylenol ethers (**348**) afforded diastereomeric mixture of isoflavan acetals (**352**). Reductive elimination of the methoxy group afforded isoflavans (**353**) in poor to excellent yields as shown in Scheme 43 [100].

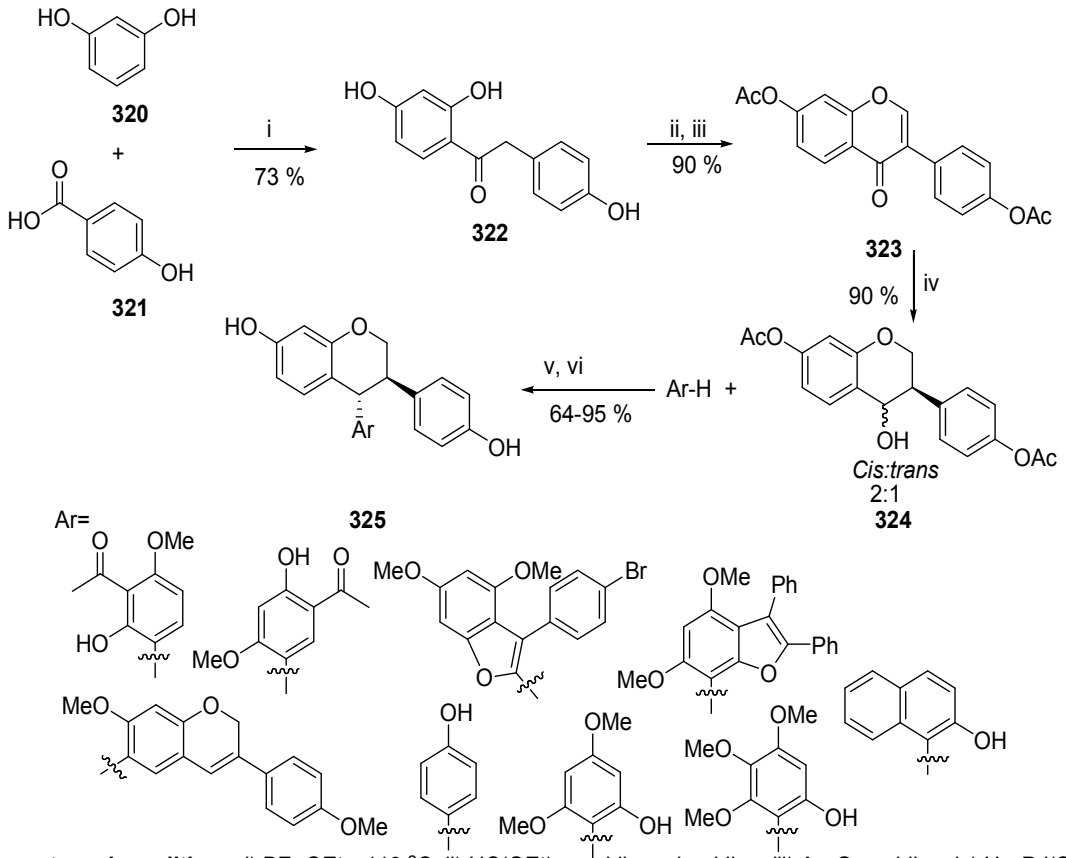
Natural isoflavans were prepared by de-protecting compounds (**353**-**364** in Scheme 43) using H2/Pd-C in ethylacetate. Compound **363** and 364 furnished equol (**340**) and vestitol (**10**) in 83 and 87 % yield respectively. Compound **362** methoxy groups were removed using pyridinium hydrochloride to give 3'-hydroxyequol (**9**) in 65% yield [100].

Versteeg and co-workers reported the synthesis of isoflavans using the Evans chiral auxilliary alkylation. The acylation of the trimethylsilyl ethers of chiral auxiliary, (4*S*,5*R*)-(+)- and (4*R*,5*S*)-(-)-imidazolidin-2-ones (**365**) with phenylacetyl chlorides (**367**) affords *N*-acyl imidazolidinones (**368**). The LICA (lithium isopropylcyclohexylamide) generated enolate ion of *N*-acyl imidazolidinones were alkylated in good yields giving only one diastereoisomer (**369**; *de* 84-90%). The reduction of the alkylation products into arylpropanols followed by the cyclization afford isoflavans (**371**). The cyclization after the activation of the hydroxyl group gives lower yields (46-60%) when NaH was used, but higher yields (73-95%) were observed when Mitsunobou conditions were employed [101,97]

as shown in Scheme 44. The reports indicated that the alkylation step had preferential formation of the *Z*-enolate. Thus, the alkylation was directed to the face of the enolate opposite the phenyl moiety on the chiral auxiliary and the configuration of the isoflavans were stated to be 3*R* or 3*S* [94,101]. The C-3 configuration of the isoflavans were determined by that of chiral auxiliary. (4*S*,5*R*)-(+)-imidazolidin-2-ones affords the 3*S*-isoflavans while the (4*R*,5*S*)-(-)-imidazolidin-2-ones yields the 3*R* isomers [101,97].

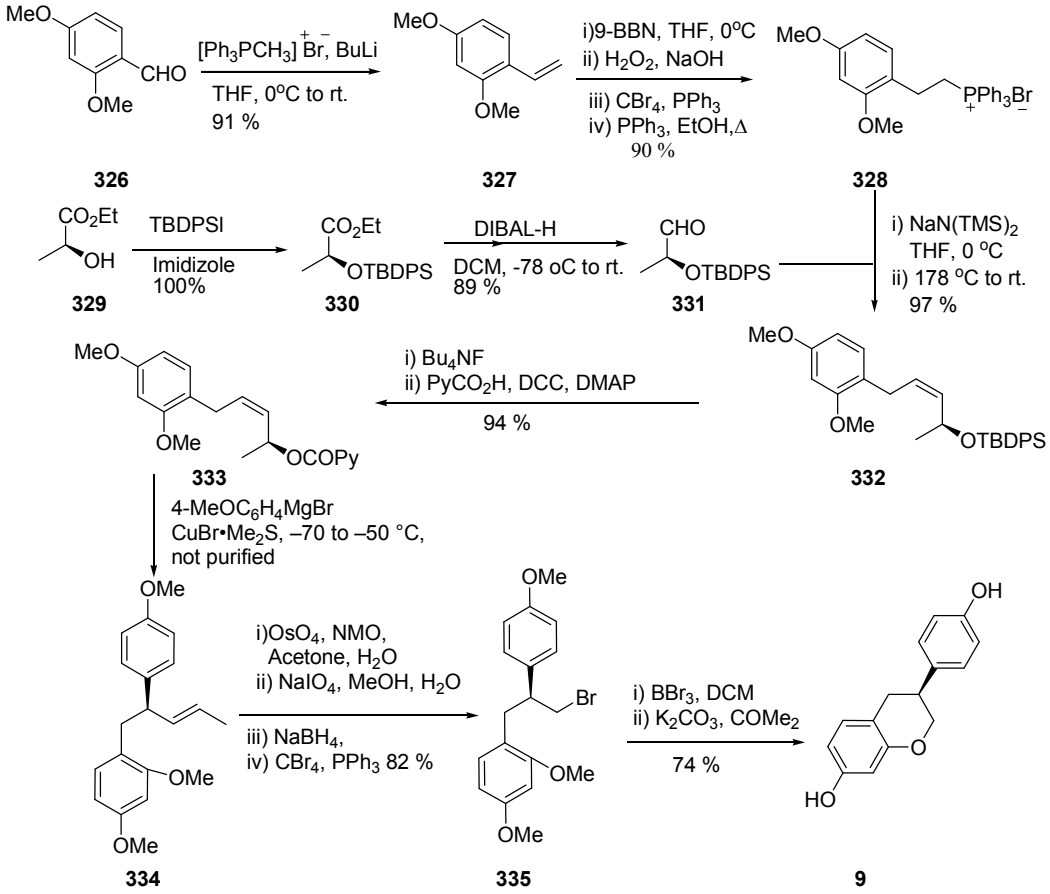
Glabridin (**386**) is a natural isoflavan from the licorice of *Glycyrrhiza glabra*. Glabridin has been found to be responsible for the licorice antioxidative effect and also inhibit the tyrosinase-dependent melanin biosynthesis [102,103]. The synthetic strategy towards (±)-Glabridin was outlined by Yoo and Nahm [104] as described in Scheme 45.

The heartwood of *Dalbergia nitidula* contains the natural isoflavan oligomer, (3*S*,4*S*)-3,4-trans-4-[(3*S*)-6',7-dihydroxy-4'-methoxyisoflavan-3'-yl]-2',7-dihydroxy-4-methoxy-isoflavan (**388**). The synthesis of the [4,3']-*bi*-isoflavan was accomplished by the condensation of (+)-vestitol (**10**) with (+)-medicarpin (**387**) as the elctrophile. The pterocarpan (**389**) reacted with phenolic electrophiles (**390**-**391**) to furnish 4-arylisoflavan and dimers shown in Scheme 46 and 47 [105].

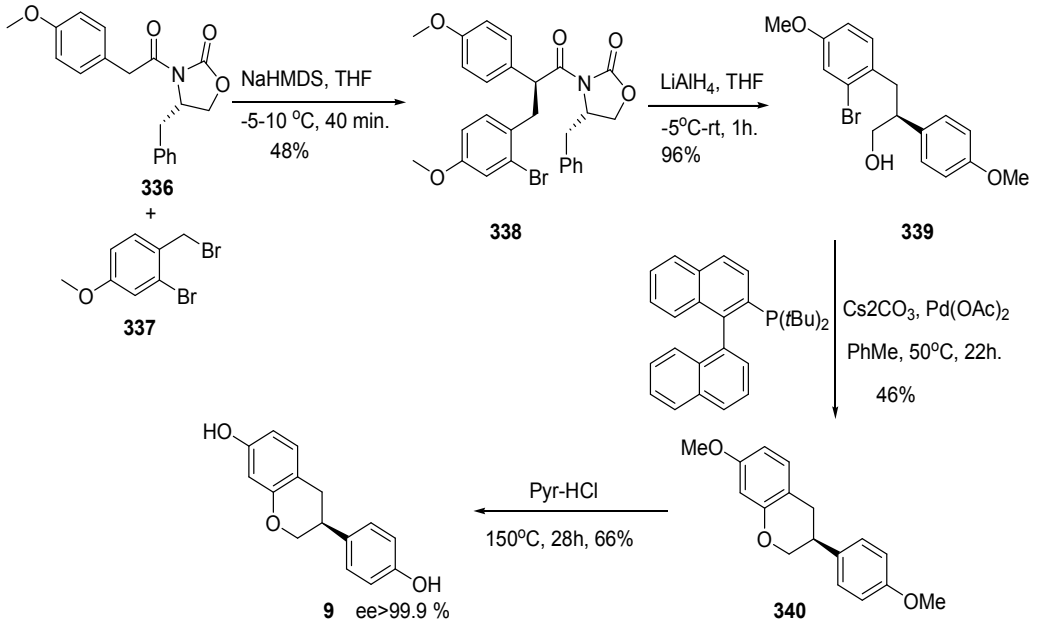


Reagents and conditions: i) $BF_3.OEt_2$, 110 ^oC; ii) $HC(OEt)_3$, pyridine, piperidine; iii) Ac_2O, pyridine; iv) H_2, Pd/C, EtOH; v) $BF_3.OEt_2$, DCM, rt.; vi) KOH, MeOH.

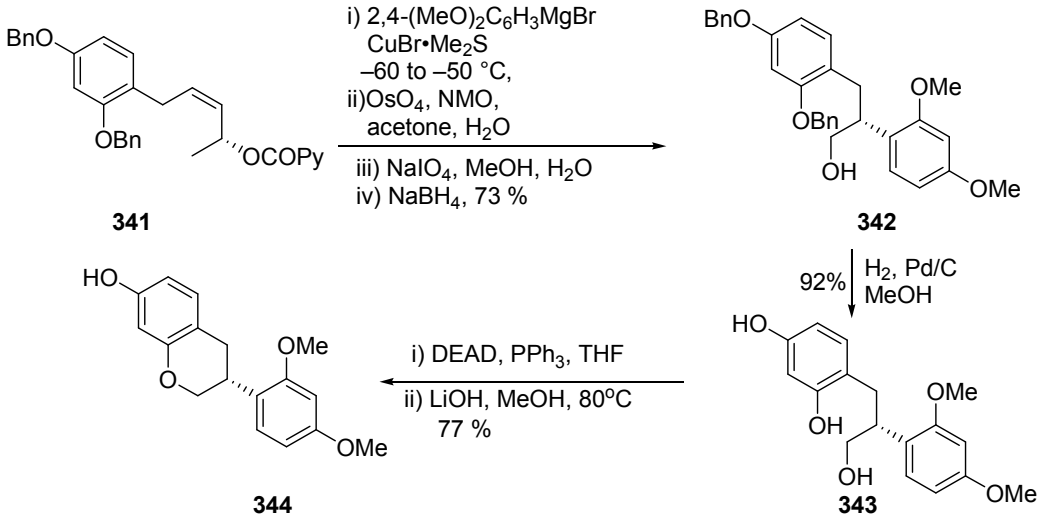
Scheme 38: Deodhar and co-workers synthesis of 4-arylisoflavans



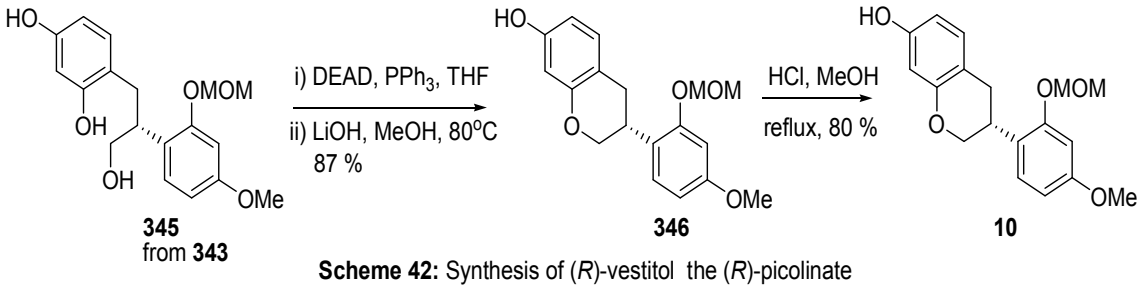
Scheme 39: Synthesis of (*S*)-equol



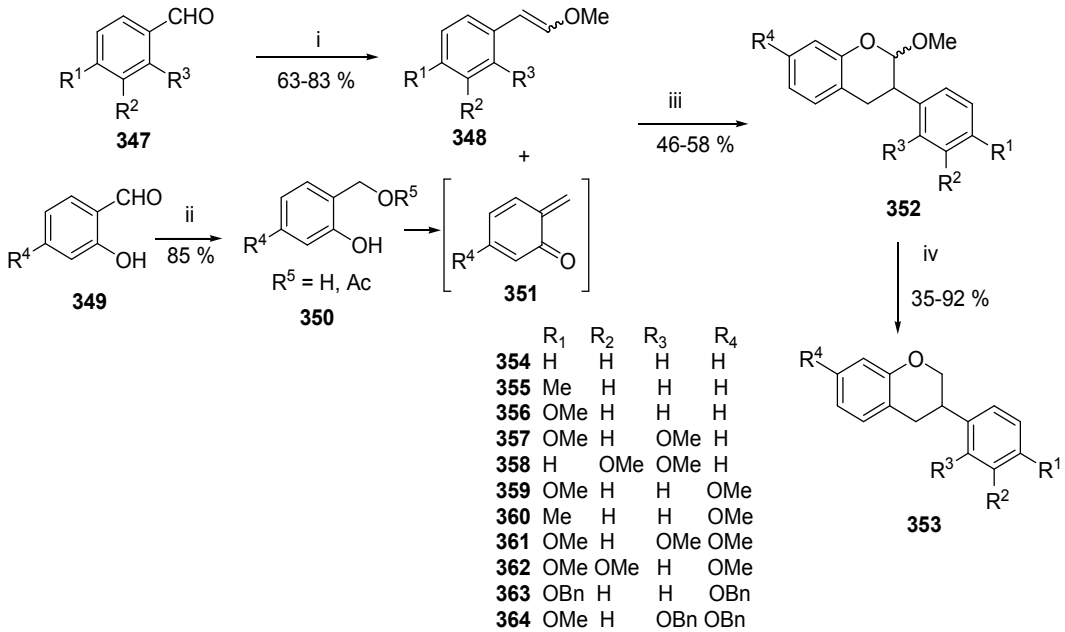
Scheme 40: Synthesis of (*S*)-equol via Evans alkylation



Scheme 41: Synthesis of (*R*)-sativan the (*R*)-picolinate

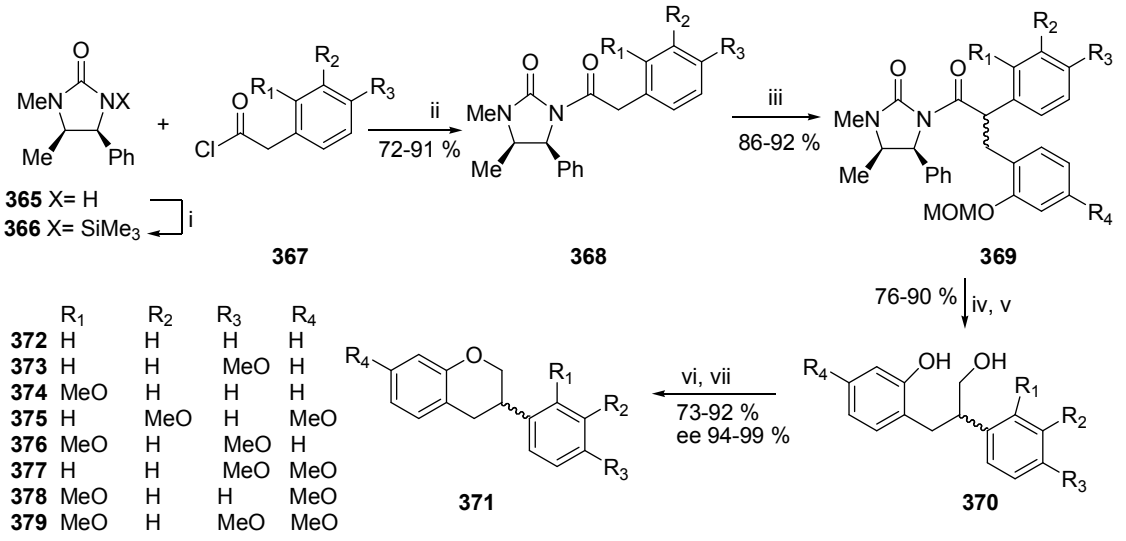


Scheme 42: Synthesis of (*R*)-vestitol the (*R*)-picolinate



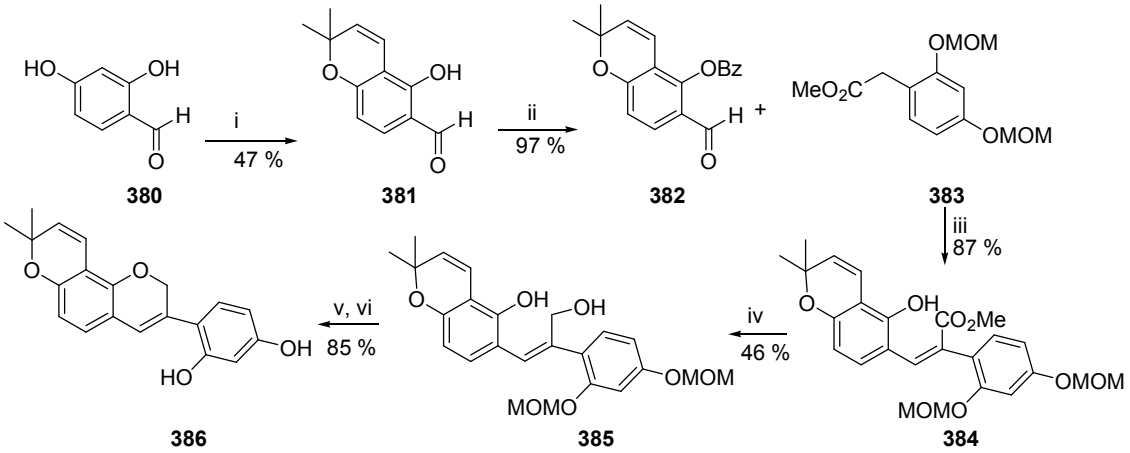
Reagents and conditions: i) Ph_3P CH_2OMeCl, LiHMDS, THF, 0 ºC; ii) NaBH4, MeOH, rt.; then AcCl, Py, DCM, 0 °C to rt.; iii) PhH, 80 ºC or PhMe, 115 ºC; iv)Et_3SiH, $BF_3.OEt_2$, DCM, 0°C

Scheme 43: Isoflavan synthesis using DA reaction between *o*-QM and arylenol ethers



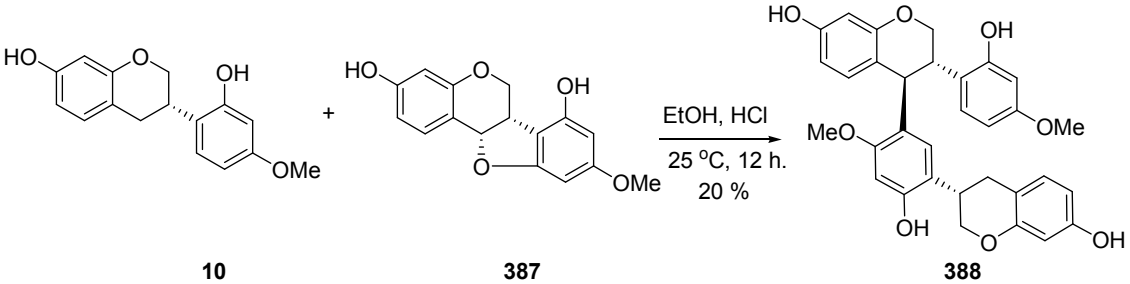
Reagents and conditions: i) BuLi, Ph_3CH, THF, 0 "C; then Me_3SiCl, -78 ^oC to rt; ii) tetrabutylammonium fluoride, MeCN, rt; iii) LICA, 2-O-methoxymethylbenzyl bromide, THF-DCM, -40 ^oC; iv) $LiAlH_4$, THF, -24 ^oC to rt; v) HCl, MeOH, reflux; vi) BrsCl, pyridine, DCM, rt; vii) PPh_3, DEAD, THF, rt.

Scheme 44: Synthesis of isoflavans using chiral auxilliary

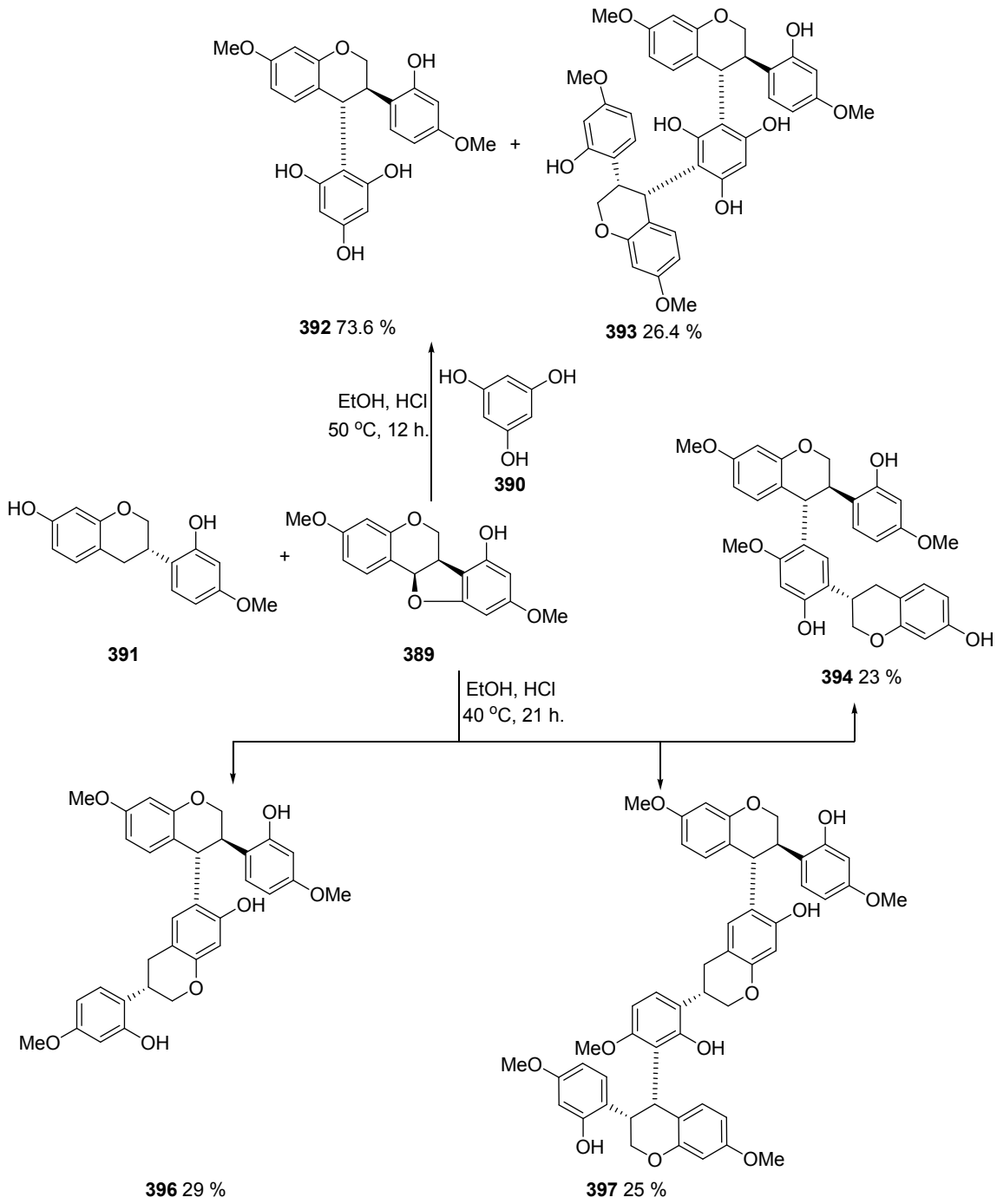


Reagents, conditions: i) $(CH_3)_2C=CHCHO$, $MgSO_4$/py; ii) $BzCl/CH_2Cl_2$, TEA, 0 °C; iii) LDA, THF, -78 °C; iv) $LiBH_4$, THF, reflux; v) PPh_3, DEAD, THF; vi) TsOH, i-PrOH, reflux.

Scheme 45: Synthesis of isoflavan: Glabridin



Scheme 46: Synthesis of [4,3′]-*bi*-isoflavan



Scheme 47: Synthesis of isoflavan oligormers from reaction of a pterocarpan with phenolics

3. CONCLUSION

As mentioned earlier on, flavans are important compounds containing the 2-phenylchroman moiety. They have been reported to possess anticancer, anti-inflammatory, antioxidants and antimicrobial properties. As such, numerous efforts have been directed towards their syntheses. Among the many methods reported, the common methods for their preparations include; (i). Reduction of flavanone and flavone with Raney-Ni, $NaBH_4$ or H_2/Pd (ii) cyclisation of

2-(3-hydroxy-3-phenylpropyl)phenol derived from chalcones via reduction using $NaBH_4$ or H_2/Pd (iii). Reduction of anthocyanins with $NaBH_3CN$ in $AcOH/Ac_2O$ or with MgBr/PhBr followed by $NaBH_3CN$, (iv). Reactions of flav-2-enes with alcohols in Lewis acid with subsequent reduction with $NaBH_3CN$, (v). Condensation of phenols with secondary alcohols in $BF_3.OEt_2$ to 4α-aryloxyflavans and (vi). bromination of flav-2-enes with *N*-bromosuccinimide. Neoflavans were synthesized by the intramolecular [Cu]-catalyzed cyclization of 3-(2-bromophenyl)-3-phenylpropan-1-ol. Isoflavans are isomers of flavans in which the 2-phenyl ring has shifted to position 3. Hence, methods for their syntheses are similar to those for flavans with with the addition of the intramolecular etherification of 3-bromo-2-(4-methoxyphenyl)propyl)-2,4-dimethoxybenzene with good ee. Flavens, on the other hand have a C=C double bond at either position 2 or 3. They are mainly synthesized through (i). Reduction of anthocyanins, (ii). Reduction of chalcones and (iii) hydroxylation of flavans with BMD followed by oxidation with $POCl_3$ to flav-2-enes. Anthocyanins are generally synthesized via hydroxylation of flavans with subsequent oxidation. This report has presented the synthesis of flavans, isoflavans, neoflavans, flavens and anthocyanins.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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