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Synthesis of oxygenated 4-arylisoflavans and 4-arylflavans

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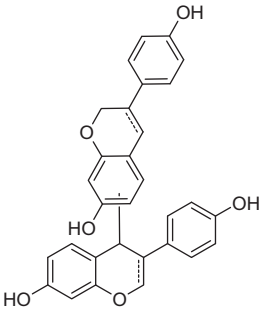
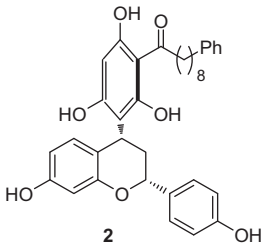
ABSTRACT

Oxygenated 4-arylisoflavans and 4-heteroarylisoflavans were synthesized in good yields via $BF_3{\cdot}OEt_2$ catalyzed arylation reactions of 4′,7-diacetoxyisoflavan-4-ol **8** with activated aryl and heteroaryl compounds. These reactions were found to produce stereoselectively the trans isomers. Similar reactions of 4′,7-diacetoxyflavan-4-ol **16** afforded the corresponding 4-arylflavans and 4-heteroarylflavans as mixtures of cis/trans isomers.

The flavonoids are a very well known family of natural products.[1–3] They are found extensively throughout the plant kingdom and play a vital role in the ecology of plants. They have received considerable attention on account of their medicinal properties,[4] such as antioxidant,[5] anti-inflammatory,[6] gastroprotective,[7] antiviral,[8] antimutagenic,[9] topoisomerase II inhibitory,[10] protein kinase C inhibitory,[11] and cytotoxic activities.[12–14] Kumar and Heaton have demonstrated that dimeric isoflavonoid compounds with the general formulae as depicted in **1** show potent anticancer activity toward a variety of cancer cell lines.[15] Similar biologically active compounds can be found in the 4-arylflavan series as well. For example, Hecht et al.[16] have described compound **2** and its atropisomer as potent DNA polymerase β inhibitors.



1



2

Although there are several examples of naturally occurring dimeric flavonoids with potent activity against various pathogenic conditions, their use as medicaments has been severely limited due to their low abundance in plant material, tedious methods of extraction and purification, and unavailability of appropriate biological data. The development of efficient synthetic methodologies to generate these systems is therefore necessary in order to exploit fully their medicinal potential.

4-Arylflavanoids have been previously synthesized[17–19] by condensation of isoflavanols with phenols in the presence of aluminum trichloride, through treatment of isoflavanones with Grignard reagents and subsequent hydrogenation, through the reaction of 4-haloflavans with potassium salts of phenolic compounds and by reactions of flavans with 4-benzylthioflavans in the presence of silver tetrafluoroborate. However, these methodologies cannot be easily adopted for the synthesis of highly oxygenated flavones or isoflavones due to their low yields, and structure activity studies have shown that the oxygenation pattern is very important for biological activity.

Herein we report the efficient synthesis of oxygenated 4-arylisoflavans and 4-arylflavans via the acid-catalyzed reaction of isoflavonols and flavanols with activated aromatic and heteroaromatic compounds.

The precursor to the targeted 4-arylisoflavones, diacetoxyisoflavanol **8**, was synthesized in four steps using standard isoflavone synthetic methods[20] as outlined in Scheme 1. Resorcinol (**3**) was reacted with 4-hydroxyphenylacetic acid (**4**) in the presence of boron trifluoride-diethyl etherate ($BF_3{\cdot}OEt_2$) to give deoxybenzoin **5** in 73% yield. Deoxybenzoin **5** was then cyclized by heating with triethyl orthoformate in the presence of pyridine and piperidine to give daidzein (4′,7-dihydroxyisoflavone) (**6**) in 67% yield. Daidzein (**6**) was acetylated using acetic anhydride/pyridine prior to catalytic hydrogenation with palladium on carbon in order to prevent

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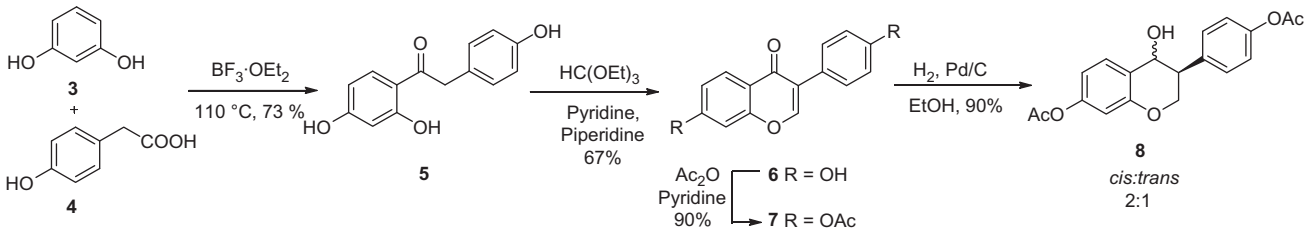
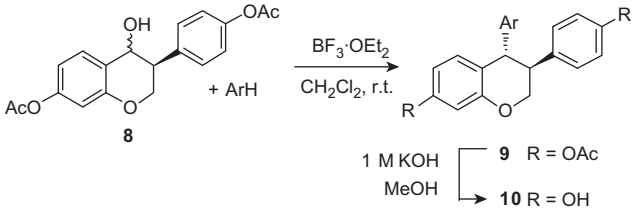
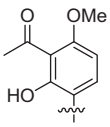
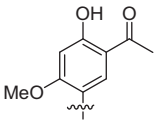
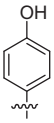
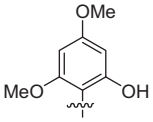
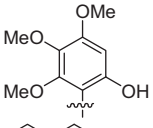
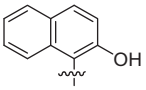
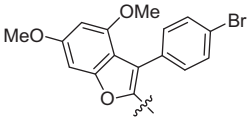
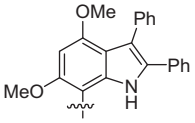
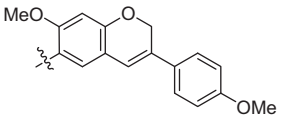


Scheme 1.



Scheme 2.

Table 1
Synthesis of 4-aryl and 4-heteroarylisoflavans

Entry	Ar	Isoflavan			
		9	Yield (%)	**10**	Yield (%)
1		**9a**	67	**10a**	84
2		**9b**	28	**10b**	95
3		**9c**	29	**10c**	94
4		**9d**	46	**10d**	64
5		**9e**	81	**10e**	68
6		**9f**	65	**10f**	80
7		**9g**	43	**10g**	83
8		**9h**	75	**10h**	80
9		**9i**	77	**10i**	74

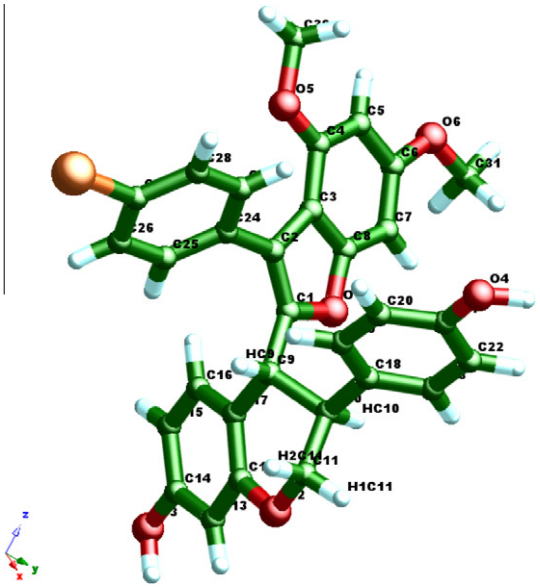
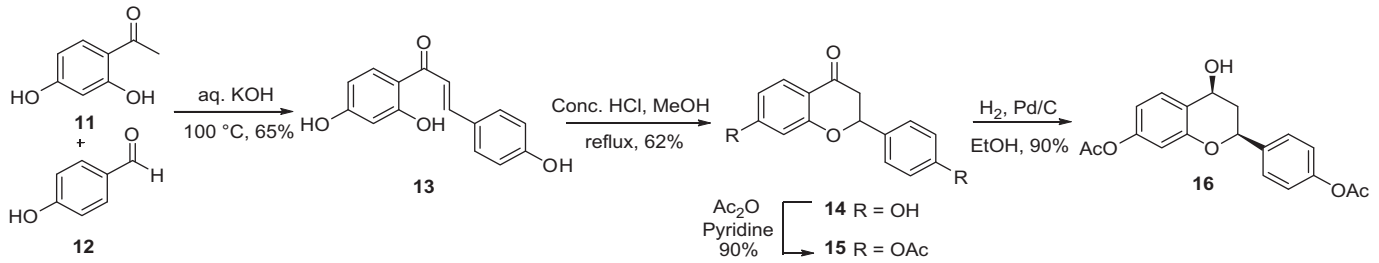


Figure 1. ORTEP diagram of 4-heteroarylisoflavan 10 g.

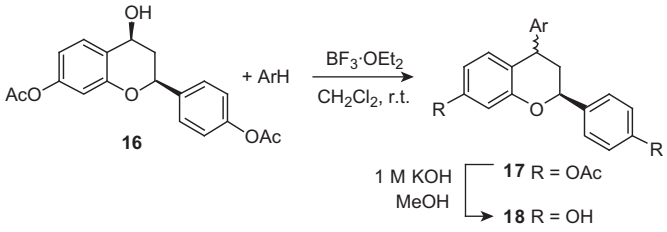
self coupling of the isoflavanol when later preparing the 4-aryl systems. 4′,7-Diacetoxyisoflavan-4-ol **8** was obtained in 90% yield as a 2:1 *cis*:*trans* mixture of isomers, which was not separated, as determined by ^{1}H NMR spectroscopy.

Isoflavanol **8** was then reacted with 2-hydroxy-6-methoxyacetophenone in the presence of $BF_3{\cdot}OEt_2$ at room temperature for 1 h.[21] After aqueous work-up, the crude product was column chromatographed to give isoflavan **9a** in 67% yield (Scheme 2, Table 1, entry 1). The *trans* stereochemistry of the product was established on the basis of the coupling constant of 7.2 Hz between the H3 and H4 protons, and there was a noted absence of any NOE correlation between the H3 and H4 protons. Substitution of the acetophenone *ortho* to the hydroxyl group was established through the presence of an NOE correlation between the methoxy group and its adjacent aromatic proton, indicating a C4–C3″ connection between the isoflavan and 2-hydroxy-6-methoxyacetophenone units. The corresponding 4′,7-dihydroxy analogue **10a** was subsequently prepared in 84% yield by hydrolyzing the acetoxy groups using 1 M KOH solution.

Exclusive formation of the *trans* product was an interesting outcome because it was expected that the incoming nucleophile could possibly attack from either side of the carbocation intermediate, and as a result produce a mixture of *cis* and *trans* isomers. Formation of the *trans* product only is therefore rationalized by the presence of the C3 aryl group, which directs the attack of the incoming nucleophile to the opposite side of the intermediate carbocation due to steric hindrance. Thus the $BF_3{\cdot}Et_2O$-catalyzed arylation reaction was found to be stereoselective and although a mixture of *cis* and *trans* isomers of the starting isoflavanol **8** was employed, only the *trans* product was obtained in good yield.



Scheme 3.



Scheme 4.

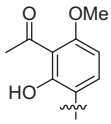
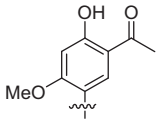
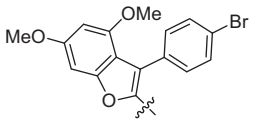
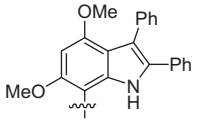
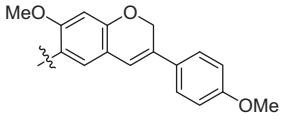
Isoflavanol **8** underwent acid-catalyzed substitution reactions with other activated phenolic compounds to give similarly only the *trans* isomers of 4-arylflavans **9b** and **9c** in good yields (Table 1, entries 2 and 3). Phenols with bulky substituents *ortho* to the most activated position gave the corresponding 4-arylisoflavans **9d–f** as a mixture of atropisomers due to restricted rotation around the C4–C1″ bond (Table 1, entries 4–6). This caused broadening of some peaks in the ^{1}H NMR spectra and additional peaks for some of the carbon atoms in the ^{13}C NMR spectra. With these results in hand, the reaction of isoflavanol **8** with activated heterocyclic compounds such as benzofurans, indoles, and isoflavenes was investigated. The resulting 4-heteroarylisoflavans **9g–i** were obtained as the *trans* isomers in 74–83% yields (Table 1, entries 7–9).

The *trans* 4-arylisoflavans and 4-heteroarylisoflavans were subsequently hydrolyzed using 1 M KOH to give the corresponding 4′,7-dihydroxyisoflavans in 64–95% yields. The stereochemistry of compound **10g** was further confirmed by X-ray crystallography as shown in Figure 1.[22]

With these encouraging results, this methodology was extended to the synthesis of 4-arylflavans. The diacetoxyflavanol precursor **16** was synthesized in 4 steps starting from resacetophenone (**11**) (Scheme 3). 4,2′,4′-Trihydroxychalcone **13** was synthesized by the condensation of resacetophenone (**11**) with 4-hydroxybenzaldehyde (**12**) in the presence of excess KOH.[23] Chalcone **13** was then cyclized by heating under reflux in concentrated HCl before being acetylated using acetic anhydride/pyridine to give diacetoxyflavanone **15**. Finally, catalytic hydrogenation using Pd/C in THF gave *cis*-diacetoxyflavanol **16** in 90% yield.

Flavanol **16** was condensed with 2-hydroxy-6-methoxyacetophenone and 2-hydroxy-4-methoxyacetophenone in the presence of $BF_3{\cdot}OEt_2$ at room temperature for 1 h. (Scheme 4, Table 2, entries 1 and 2). However, in this case the reactions were not found to be stereoselective and gave almost equal mixtures of both *cis* and *trans* isomers of compounds **17a** and **17b**. The *cis*/*trans* isomers had the same R_f value on TLC and were very difficult to separate

Table 2
Synthesis of 4-aryl and 4-heteroarylflavans

Entry	Ar	Flavan			
		17	Yield (%)	**18**	Yield (%)
1		**17a**	67	**18a** *trans* **18b** *cis*	97 85
2		**17b**	37	**18c** *trans* **18d** *cis*	87 100
3		**17c**	24	**18e** *trans*	83
4		**17d**	69	**18f** *trans*	95
5		**17e**	73	**18g** *trans*	92

using flash column chromatography. Small quantities of the pure isomers were eventually obtained after repeated column chromatography purification and were subsequently hydrolyzed using 1 M KOH to give corresponding 4′,7-dihydroxyflavans **18a–d**.

The lack of stereoselectivity observed in the flavan system can be rationalized by the fact that the C2 phenyl group is further away from the intermediate cationic carbon than in the previously described isoflavan system. As a result, the incoming nucleophile is free to attack from either face of the carbocation, which leads to a mixture of *cis* and *trans* isomers being produced.

Flavanol **16** was similarly condensed with an activated benzofuran, indole, and isoflavene in the presence of $BF_3{\cdot}OEt_2$ to give 4-heteroaryl analogues **17c–e** as 1:1 mixtures of *cis* and *trans* isomers (Table 2, entries 3–5). However, in these cases only the *trans* isomer could be isolated in pure form after column chromatography. With the slightly lower R_f value, the *cis* isomer could not adequately be separated from the *trans* isomeric product to allow for complete characterization. Hydrolysis of the *trans* isomers using 1 M KOH afforded the corresponding *trans* 4′,7-dihydroxyflavans **18e–g** in good yields.

In conclusion, $BF_3{\cdot}OEt_2$-catalyzed reactions of 4′,7-diacetoxyisoflavan-4-ol **8** with activated aryl and heteroaryl compounds gave *trans* 4-arylisoflavans and 4-heteroarylisoflavans in good yields in a single step. The related reaction of 4′,7-diacetoxyflavan-4-ol **16** under similar conditions gave the corresponding 4-arylflavans and 4-heteroarylflavans as mixtures of *cis*/*trans* isomers.

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21. *Representative procedure for compound* ***9a****:* To a stirred solution of isoflavanol **8** (500 mg, 1.46 mmol) and 2-hydroxy-6-methoxyacetophenone (242 mg, 1.61 mmol) in CH_2Cl_2 (25 ml) was added $BF_3{\cdot}OEt_2$ (10 drops). The mixture was stirred at r.t. for 2 h then quenched with H_2O (25 ml). The aqueous layer was extracted with CH_2Cl_2 (25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Chromatography (SiO_2, 25% EtOAc/hexane) gave the title compound **9a** as a white solid (480 mg, 67%). mp 138–140 °C; Found: C, 68.36; H, 5.64. Anal. Calculated for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3COO), 2.60 (s, 3H, CH_3COO), 2.68 (s, 3H, CH_3CO), 3.42 (m, 1H, H3), 3.83 (s, 3H, CH_3O), 4.23 (m, 2H, H2), 4.69 (d, J = 7.2 Hz, 1H, H4), 6.27 (d, J = 8.6 Hz, 1H, H5″, 6.54 (dd, J = 8.3, 2.3 Hz, 1H, H6), 6.66 (d, J = 2.3 Hz, 1H, H8), 6.75 (d, J = 8.3 Hz, 1H, H5), 6.96 (d, J = 8.7 Hz, 2H, H3′, H5′), 6.97 (d, J = 8.6 Hz, 1H, H6″), 7.30 (d, J = 8.7 Hz, 2H, H2′, H6′), 13.77 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 20.9, 21.0, 33.6, 39.9, 43.0, 55.4, 68.6, 100.7, 109.6, 110.7, 114.0, 121.6, 122.0, 128.7, 130.7, 136.4, 138.3, 149.4, 149.9, 155.2, 160.3, 162.1, 169.2, 169.3, 205.3; UV (MeOH): λ_{max} 206 nm (ε 49509 $cm^{-1}M^{-1}$), 275 (14429), 344 (4233); IR (KBr): ν_{max} 3452, 2930, 1760, 1613, 1496, 1463, 1428, 1368, 1317, 1244, 1207, 1146, 1111, 1088, 1035, 1017, 911, 801 cm^{-1}; MS (TOF-ESI) m/z Calcd for $C_{28}H_{26}O_8Na$ $(M + Na)^+$ 513.15. Found 513.12.
22. Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 882494 (**10g**). The X-ray crystal structure was obtained by Donald Craig, Crystallography Laboratory, UNSW Analytical Centre, Sydney, Australia.
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