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o-Quinone methide based approach to isoflavans: application to the total syntheses of equol, 3′-hydroxyequol and vestitol

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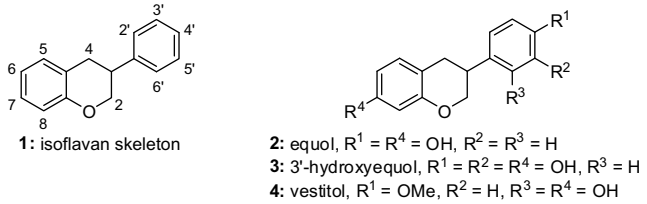
Abstract

A concise strategy is developed for the synthesis of isoflavans employing a Diels–Alder reaction between *o*-quinone methides and aryl-substituted enol ethers followed by reductive cleavage of the acetal group. The method is extended towards the total syntheses of equol, 3′-hydroxyequol and vestitol.

Keywords: *o*-Quinone methides; Diels–Alder reaction; Isoflavonoids; Equol; Hydroxyequol; Vestitol

Polyphenolic compounds have recently attracted considerable interest in the field of nutrition, health and medicine.[1] Isoflavans (**1**) represent a relatively smaller subgroup of isoflavonoids (Fig. 1), and show a wide array of physiological activity. Interestingly, not only laevorotatory and dextrorotatory but also racemic isoflavonoids are obtained from natural sources. Due to the antioxidant properties associated with them, isoflavans have been implicated in the treatment of free radical mediated disorders such as cancer, and Alzheimer's, Parkinson's and cardiovascular diseases.[2,3] Soy isoflavonoids, in particular equol (**2**),[4] have attracted increasing attention for their phytoestrogenic activity[5] and potential use in menopausal hormone replacement therapy[6] as well as in the treatment of breast cancer.[7] 3′-Hydroxyequol (**3**) is a metabolite of genistein and along with the other isoflavan metabolites has shown potential to prevent hormone-related cancer and cardiovascular diseases.[8] Vestitol (**4**) and related isoflavans are thought to be useful chemo preventive agents for peptic ulcer or gastric cancer in *H-Pylori* infected individuals[9] and exhibit phytoalexin properties,[10] resulting in a considerable increase in demand for these 'green medicines'. In fact, the biological activity of some of the plants used in traditional medicines has been attributed to isoflavonoids. In spite of this diverse biological activity, unlike flavonoids, naturally occurring isoflavans and their analogues have received considerably less attention from synthetic chemists. Partial syntheses of equol (**2**), vestitol (**4**) and related isoflavans were achieved by hydrogenation of the corresponding isoflavanone derivatives.[11] 4-Chromenesulfones were shown to provide the isoflavan skeleton via conjugate addition of aryllithium and subsequent sulfone manipulation.[12] For enantioselective syntheses of equol (**2**), an enantioselective alkylation and either a Mitsunobu reaction[13] or an intramolecular Buchwald etherification[14] were used as key steps for assembly of the chroman ring. However, a general strategy which will give rapid access to various isoflavans is still lacking.



1: isoflavan skeleton

2: equol, $R^1 = R^4 = OH$, $R^2 = R^3 = H$
3: 3'-hydroxyequol, $R^1 = R^2 = R^4 = OH$, $R^3 = H$
4: vestitol, $R^1 = OMe$, $R^2 = H$, $R^3 = R^4 = OH$

Fig. 1. The isoflavan skeleton and various examples.

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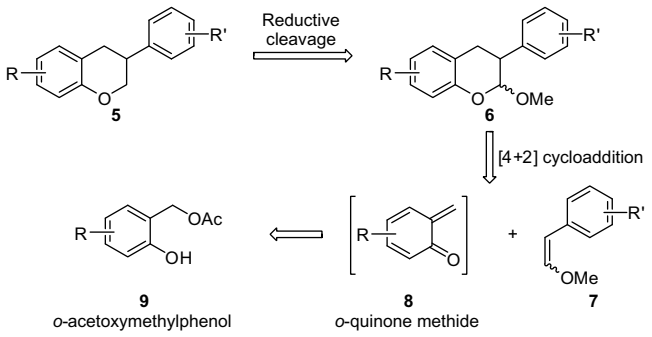
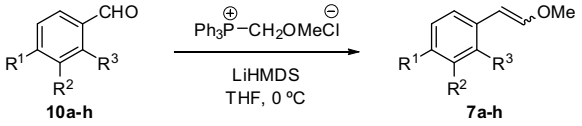
o-Quinone methides (*o*-QMs) have been found to be useful heterodienes in the [4+2] cycloaddition reaction, particularly for the synthesis of benzopyrans, and several methods have been developed for the generation of these extremely reactive intermediates in a controlled manner.[15] They have also been applied in the synthesis of various natural products including flavonoids.[16] However, to the best of our knowledge, there are no reports on the utility of these reactions for the synthesis of isoflavans. Herein, we now describe a concise, general protocol for the synthesis of biologically active isoflavans and their analogues employing the [4+2] cycloaddition reaction of *o*-QMs with aryl-substituted enol ethers followed by reductive removal of the methoxy group from the intermediate acetal moiety.

We envisaged that the isoflavan backbone **5** could be obtained by reductive removal of the methoxy acetal linkage of **6** using a Lewis acid and trialkylsilane (Scheme 1).[17] Acetal **6** in turn could be rapidly assembled by a [4+2] cycloaddition of aryl-substituted enol ether **7** with *o*-QM **8** generated in situ from *o*-acetoxymethylphenol derivative **9**. The requisite enol ether **7** can be readily prepared by a methoxymethylene Wittig reaction on an aldehyde whereas *o*-acetoxymethylphenol **9** could be obtained from an appropriate salicylaldehyde derivative.

To begin with, the synthesis of aryl substituted enol ethers **7** was undertaken (Scheme 2). Thus, treatment of



Scheme 1.

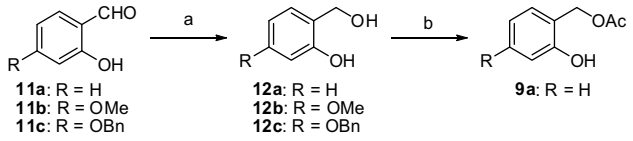


Scheme 2.

Table 1

Entry	Aldehyde	R^1	R^2	R^3	Product	Yield[a] (%)
1	**10a**	H	H	H	**7a**	76
2	**10b**	OMe	H	H	**7b**	72
3	**10c**	Me	H	H	**7c**	68
4	**10d**	OMe	H	OMe	**7d**	83
5	**10e**	H	OMe	OMe	**7e**	71
6	**10f**	OMe	H	OBn	**7f**	80
7	**10g**	OBn	H	H	**7g**	70
8	**10h**	OMe	OMe	H	**7h**	63

[a] A ca. 1:1 mixture of geometrical isomers (by ^{1}H NMR) was obtained.

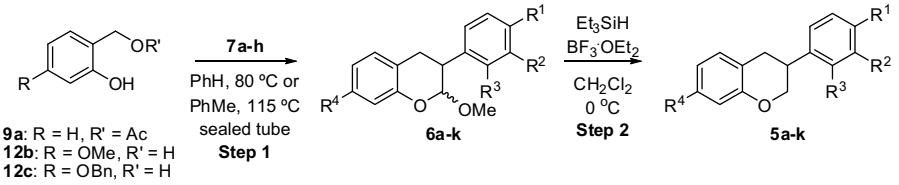


Scheme 3. Reagents, conditions and yields: (a) $NaBH_4$, MeOH, rt, 89% (for **12a**), 92% (for **12b**) 95% (for **12c**); (b) AcCl, Py, CH_2Cl_2, 0 °C to rt, 85%.

substituted benzaldehydes **10a–h** with methoxymethylene(triphenyl)phosphorane furnished enol ethers **7a–h**, respectively, in good yields as a ca. 1:1 mixture of geometrical isomers (Table 1).[18]

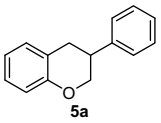
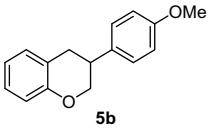
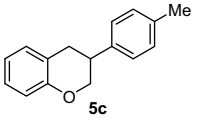
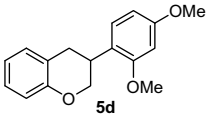
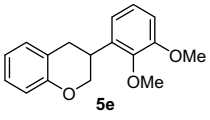
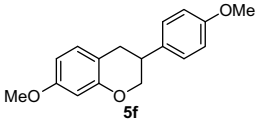
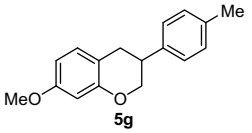
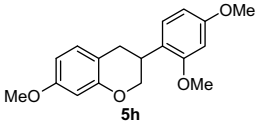
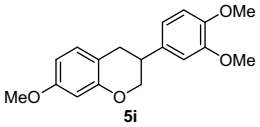
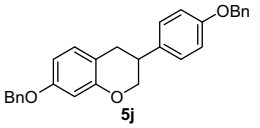
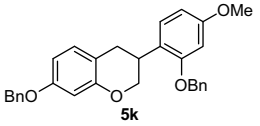
Synthesis of *o*-QM precursors **9** started from readily available aldehydes **11a–c**. Thus, the reduction of aldehydes **11a–c** with sodium borohydride gave the corresponding alcohols **12a–c** in excellent yields (Scheme 3). Treatment of alcohol **12a** with acetyl chloride and pyridine according to Baldwin's protocol yielded the *o*-acetoxymethylphenol **9a**.[19] The attempted selective acylation of alcohols **12b–c** however was found to provide a complex mixture of products in our hands, so we decided to study the [4+2] reaction of alcohols **12b–c** directly.

Having both the diene precursors **9a** and **12b–c** and the dienophiles **7a–h** in hand, we turned our attention to the synthesis of isoflavans **5** (Scheme 4). Thus, phenol **9a** was mixed with 5 equiv of enol ether **7b** in benzene, and the mixture was heated in a sealed tube at 80 °C for 24 h to furnish acetal **6b** as a mixture of diastereomers in 52% yield. It is worth mentioning here that the majority (ca. 70%) of the unreacted enol ether **7b** could also be recovered. Reductive removal of the methoxy group from acetal **6b** was accomplished using $BF_3{\cdot}OEt_2$ and triethylsilane to give isoflavan **5b** in excellent yield (Table 2, entry 2).[20]



Scheme 4.

Table 2

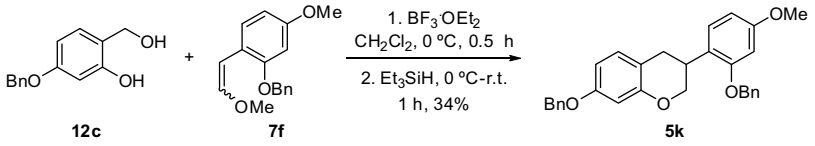
Entry	*o*-QM precursor	Enol ether	Yield[a] (%)		Isoflavan
			Step 1[b]	Step 2	
1	**9a**	**7a**	48	68	 **5a**
2	**9a**	**7b**	52	92	 **5b**
3	**9a**	**7c**	58	80	 **5c**
4	**9a**	**7d**	52	75	 **5d**
5	**9a**	**7e**	46	85	 **5e**
6	**12b**	**7b**	57[c]	65	 **5f**
7	**12b**	**7c**	52[c]	65	 **5g**
8	**12b**	**7d**	48[c]	35	 **5h**
9	**12b**	**7h**	52[c]	68	 **5i**
10	**12c**	**7g**	55[c]	75	 **5j**
11	**12c**	**7f**	52[c]	62	 **5k**

[a] Yield refers to chromatographically purified material.
[b] In all the cases, a ca. 1:1 diastereomeric mixture of acetals was obtained.
[c] The reaction was conducted in toluene at 115 °C.

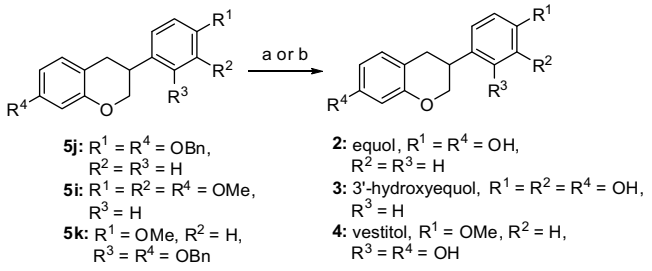
Delighted by the successful synthesis of isoflavan **5b**, we decided to study the scope of this reaction sequence. The Diels–Alder reaction of acetate **9a** with enol ethers **7a–e** proceeded smoothly to furnish the cycloadducts **6a–e**, respectively, in moderate yields as ca. 1:1 mixtures of diastereomers (entries 1–5). The reaction of alcohol **12b** with enol ether **7b** under similar conditions of thermolysis in benzene was found to be sluggish and even after prolonged reaction times (48 h) gave acetal **6f** in poor yield only. However, changing the solvent from benzene to toluene and conducting the reaction at 115 °C improved the efficiency of the reaction, and acetal **6f** was obtained in 57% yield (entry 6). Acetals **6g–k** were synthesized in moderate yields following this new protocol (entries 7–11). No special effort was made to separate the diastereomeric acetals **6a–k** as in the subsequent step the acetal stereocentre was lost. However, in all the cases at least one of the diastereomers could be cleanly separated and characterized unambiguously. It is noteworthy that we did not observe any regioisomeric flavan derivatives in any of these reactions. The reductive removal of the methoxy group of acetals **6a–k** using $BF_3{\cdot}OEt_2$ and triethylsilane was uneventful, and isoflavans **5a–k** were obtained in good to excellent yields in all the cases. Incidently, isoflavan **5f** has been converted to equol **2**, so its synthesis here constitutes a formal synthesis of equol **2**.[14]

It is known in the literature that Lewis acids can catalyze the formation and [4+2] cycloaddition reaction of *o*-QMs with a variety of dienophiles.[21] We reasoned that in our case, the Lewis acid should be able to catalyze both the steps namely [4+2] cycloaddition and the reductive removal of the methoxy group of the acetal moiety in a 'one-pot' transformation. To test this hypothesis, we subjected the phenol **12c** and enol ether **7f** to treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C (Scheme 5). After completion of the cycloaddition step (TLC monitoring), we added triethylsilane in the same pot. Gratifyingly, isoflavan **5k** was obtained in 34% yield which even though low compares favourably with the two-step yield obtained earlier. The added advantage here is a considerable reduction in the overall reaction time.

Having demonstrated the scope of the *o*-QM cycloaddition followed by the reductive removal of the acetal moiety for the formation of the isoflavan skeleton, we turned our attention to using this strategy for the synthesis of the natural isoflavans equol (**2**), 3′-hydroxyequol (**3**) and vestitol (**4**). Thus, deprotection of the benzyl ethers of **5j** and **5k** using H_2/10% Pd/C in ethyl acetate furnished equol (**2**) and vestitol (**4**), respectively, in excellent yields (Scheme 6). The data for the synthetic samples were found to be in good agreement with the reported values.[11a,14] On the other hand, when isoflavan **5i** was subjected to treatment with pyridinium hydrochloride at 150 °C, 3′-hydroxyequol (**3**) was obtained in 65% yield. This constitutes the first total synthesis of 3′-hydroxyequol (**3**).



Scheme 5.



Scheme 6. Reagents, conditions and yields: (a) H_2/10% Pd/C, EtOAc, 24 h, 83% (for **2**), 87% (for **4**); (b) pyridinium hydrochloride, 150 °C, 65% (for **3**).

In conclusion, we have developed a general and concise strategy for the synthesis of the isoflavan skeleton based on a [4+2] cycloaddition of *o*-QMs with aryl-substituted enol ethers followed by reductive removal of the acetal moiety. We have also demonstrated that the isoflavans can be synthesized in a single pot operation with reduction in the overall reaction time with comparable efficiencies. Further, the method is applied to the total syntheses of equol (**2**), 3′-hydroxyequol (**3**) and vestitol (**4**). The method developed is amenable to the synthesis of various analogues of the isoflavonoid family, and further studies are underway in our laboratory in this direction.

Representative experimental procedure: A solution of *o*-acetoxymethylphenol **9a** (183 mg, 1.10 mmol) and enol ether **7b** (900 mg, 5.50 mmol) in benzene (2 ml) at 80 °C was stirred in a sealed tube under nitrogen for 26 h (TLC monitoring). Evaporation of the benzene under reduced pressure gave a brown oily residue which was purified by silica gel column chromatography using ethyl acetate–hexanes (1:50) as eluent to give a diastereomeric mixture of acetal **6b** (156 mg, 52%) as a sticky solid.

To a cooled (0 °C), magnetically stirred solution of **6b** (58 mg, 0.22 mmol) and triethylsilane (0.15 ml, 0.93 mmol) in dry CH_2Cl_2 (5 ml) was added $BF_3{\cdot}OEt_2$ (0.07 ml, 0.55 mmol) dropwise. The reaction mixture was then allowed to warm to rt slowly over a period of 30 min. The reaction mixture was quenched using saturated aq $NaHCO_3$ (2 ml) and extracted with ethyl acetate (3×10 ml). The combined organic extracts were washed with brine, dried (anhyd. Na_2SO_4) and filtered. Evaporation of the solvent under reduced pressure and purification of the residue by silica gel column chromatography using ethyl acetate–hexanes (1:50) as eluent furnished isoflavan **5b** (48 mg, 92%) as a white solid which was recrystallized from boiling hexanes–CH_2Cl_2.

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20. All the compounds exhibited spectral data consistent with their structures. Melting point, IR, NMR (^{1}H and ^{13}C) and HRMS spectral data for some of the compounds are as follows: *Acetal* **6b**: IR (neat) 2920, 2839, 1612, 1504, 1454, 1302, 1235, 1179, 1116, 1073, 1033, 990, 824, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.08 (m, 4H), 6.94–6.87 (m, 2H), 6.83–6.79 (m, 2H), 5.08 (d, $J = 3.6$ Hz, 1H), 3.76 (s, 3H), 3.50 (s, 3H), 3.28 (dd, $J = 15.8$, 6.7 Hz, 1H), 3.24–3.21 (m, 1H), 2.89 (dd, $J = 15.8$, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 158.66 (C), 152.25 (C), 133.29 (C), 129.25 (CH), 128.84 (2C, CH), 127.54 (CH), 122.28 (C), 121.33 (CH), 117.11 (CH), 114.18 (2C, CH), 102.37 (CH), 55.96 (CH_3), 55.37 (CH_3), 41.19 (CH), 28.39 (CH_2); HRMS (ESI, M^++H) calcd for $C_{17}H_{19}O_3$, 271.1334; found, 271.1330. *Isoflavan* **5b**: mp 78–80 °C; IR (neat) 2924, 1612, 1505, 1455, 1312, 1239, 1181, 1113, 1030, 825, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.21–7.10 (m, 4H), 6.93–6.87 (m, 4H), 4.35 (ddd, $J = 10.6$, 3.6, 1.9 Hz, 1H), 4.01 (t, $J = 10.6$ Hz, 1H), 3.82 (s, 3H), 3.27–3.18 (m, 1H), 3.10–2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 158.76.(C), 154.42 (C), 133.47 (C), 129.91 (CH), 128.43 (2C, CH), 127.53 (CH), 122.19 (C), 120.48 (CH), 116.66 (CH), 114.32 (2C, CH), 71.20 (CH_2), 55.42 (CH_3), 37.84 (CH), 32.66 (CH_2); HRMS (ESI, M^++Na) calcd for $C_{16}H_{16}O_2Na$, 263.1048; found, 263.1043.
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