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Ring-closing metathesis in flavonoid synthesis, part 3: isoflavenes

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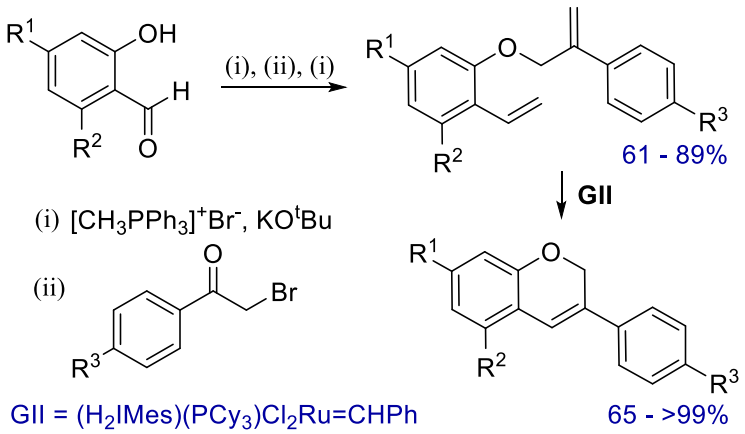
Abstract

Isoflav-3-enes with natural substitution patterns were prepared in two steps from readily available starting materials by means of a one-pot Wittig methylenation – etherification – Wittig methylenation, followed by ring-closing metathesis catalyzed by the Grubbs second generation catalyst. This included the preparation of a series of five novel 1-[(2-phenylallyl)oxy]-2-vinylbenzenes in good yields (61 – 89%). Olefin metathesis thus affords a common strategy for the synthesis of all three flavonoid subclasses, i.e. the flavonoids, neoflavonoids and isoflavonoids.



Keywords: Flavonoid, phenylchroman, isoflavene, methylenation, metathesis, Grubbs catalyst

Introduction

The isoflavonoids is a subclass of the flavonoids, with the flavonoids being a large and diverse group of secondary metabolites in plants and, more interestingly, medicinal lead compounds with anti-cancer, anti-mutagenic, vasodilatory, anti-inflammatory, anti-allergenic, anti-microbial, anti-viral, neuroprotective and antioxidant activities, amongst others.[1] The three flavonoid subclasses, i.e. the flavonoids, isoflavonoids and neoflavonoids (Figure 1), share the basic flavonoid C_6-C_3-C_6 skeleton (which refers to two aryl rings being linked by a 3-carbon chain), but differ in the position of attachment of the aryl substituent (B-ring) to the heterocyclic ring (C-ring).[1]

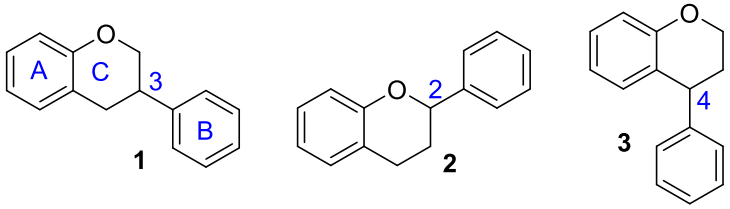
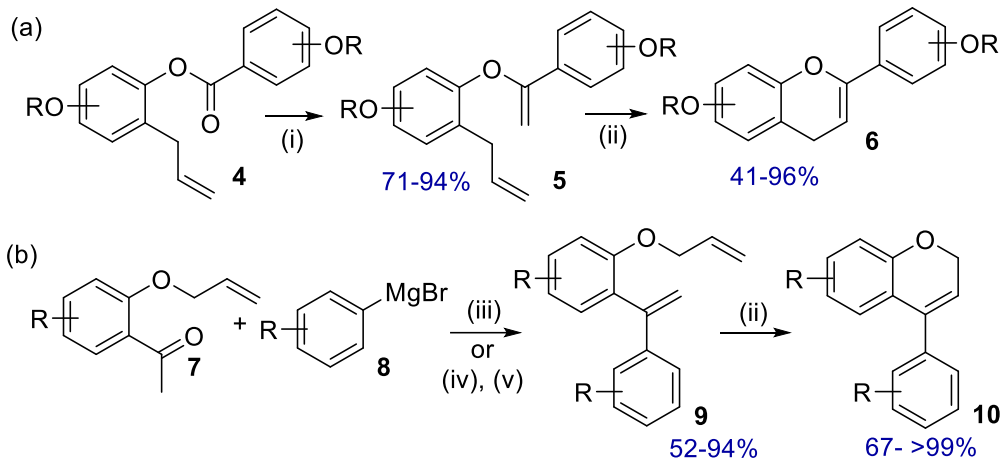


Figure 1. The basic isoflavan (**1**), flavan (**2**) and neoflavan (**3**) skeletons of the isoflavonoid, flavonoid and neoflavonoid subclasses of the flavonoids.

Isoflavonoids have classically been prepared by the formylation of 2'-hydroxydeoxybenzoins,[2-7] Tl(III) catalysed oxidative rearrangement of chalcones[8-12] or acid-catalysed rearrangement of chalcone epoxides.[13-15] Whereas the formylation of deoxybenzoins is restricted to a few substrates with the appropriate substitution patterns, by atom economy and harsh or corrosive reaction conditions, chalcones are typically prepared by means of the aldol condensation, thus generating stoichiometric amounts of waste originating from the base. The acid-catalysed rearrangement of chalcone epoxides is not only unselective, forming isoflavones, dihydroflavonols and flavonols, but also low in yield. Furthermore, though the Tl(III)-based oxidative rearrangement of chalcones gives the isoflavones in good yields and is the standard method for the preparation of isoflavonoids, thallium salts are toxic and not suitable for use in the synthesis of pharmaceuticals.

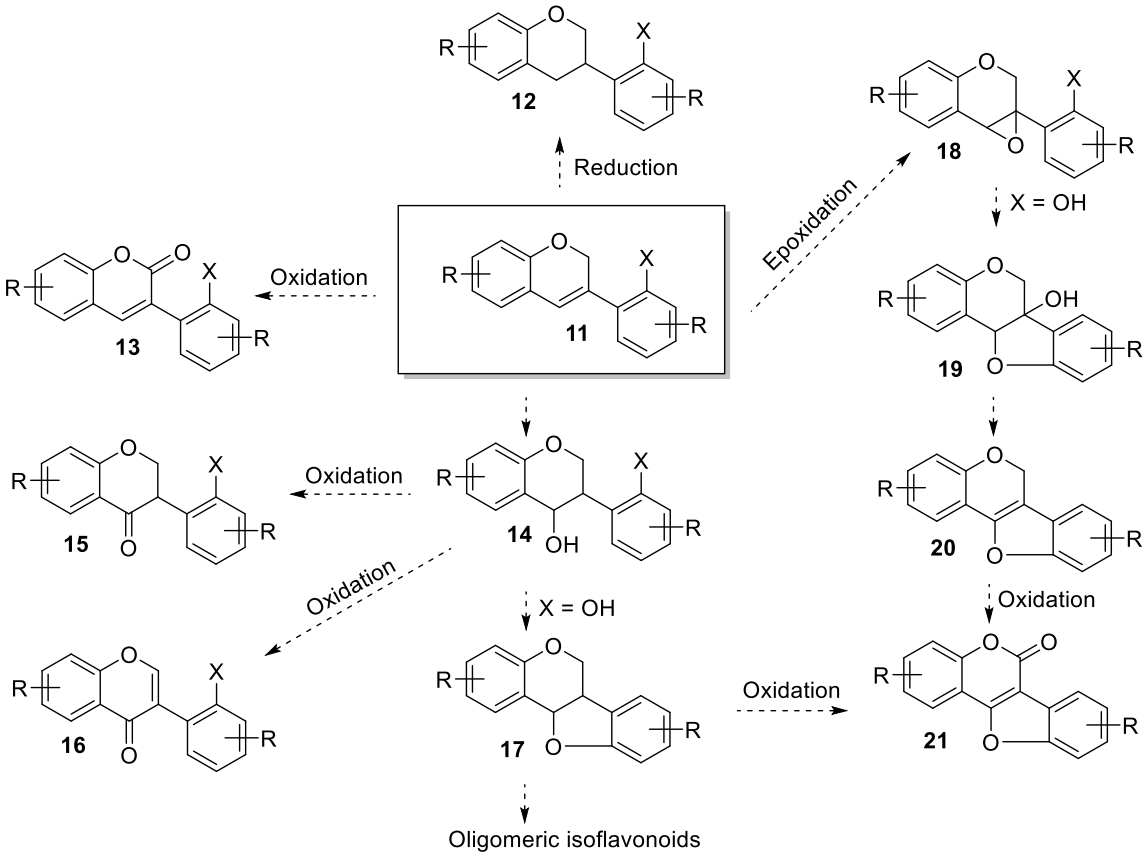
More benign and environmentally friendly catalytic methods for the preparation of isoflavonoids (**1**) include Suzuki cross-coupling between 3-bromochromones and arylboronic acids,[16,17] Negishi coupling of 3-halochromones and arylzinc bromides,[18] the Wacker-Cook oxidative cyclisation of α-methylenedeoxybenzoins,[19] gold(I) catalysed annulation of phenylacetylenes and salicylaldehydes[20,21] and the intramolecular Heck reaction of 1-iodo-2-[(2-phenylallyl)oxy]benzenes.[22]

We recently reported on the application of ring-closing metathesis to the synthesis of flav-2-enes (2-phenyl-4*H*-chromenes) (**6**) and neoflav-3-enes (4-phenyl-2*H*-chromenes) (**10**) as representatives of the flavonoids[23] and neoflavonoids[24] (Scheme 1). In this paper, we elaborate on the ring-closing metathesis theme and report the synthesis of isoflav-3-enes (3-phenyl-*2H*-chromenes) (**11**).



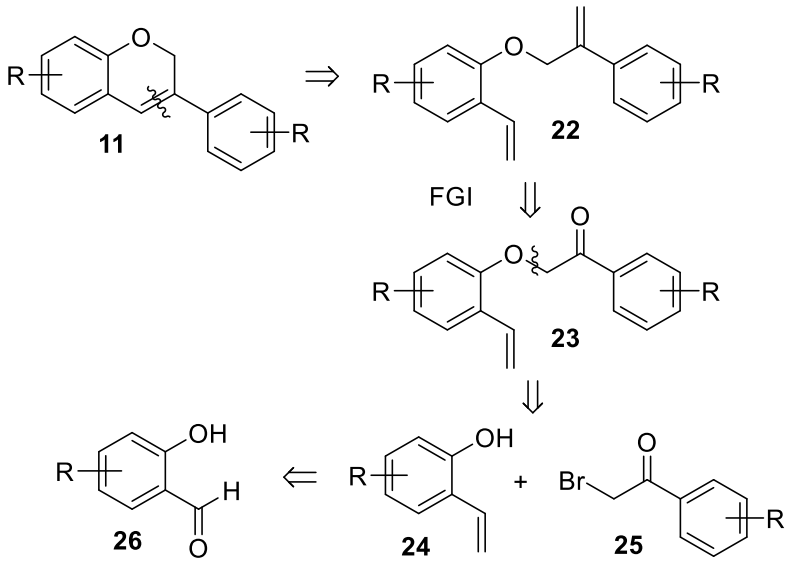
Scheme 1. The synthesis of flav-2-enes (**6**) and neoflav-3-enes (**10**) with ring-closing metathesis as key step. Reaction conditions: (i) Tebbe reagent (0.5 M, 1.2 – 2.7 eq.), THF (2 mL), 0 °C, 30 min., rt, 1 h, reflux, 2 h; (ii) **GII** (5 mol %), CH_2Cl_2, reflux; (iii) $Al(OTf)_3$ (1 eq.), Et_2O, -30 °C – rt; (iv) THF, -60 °C - rt; (v) anhydrous $CuSO_4$, hexane, reflux.

Whereas flav-2-enes (**6**) and neoflav-3-enes (**10**) are key intermediates in the synthesis of flavonoids and neoflavonoids, respectively, isoflav-3-enes (**11**) can serve as intermediates to several classes of isoflavonoids, e.g. isoflavans (**12**), 3-arylcoumarins (**13**), isoflavanones (**15**), isoflavones (**16**), pterocarpans (**17**) and pterocarpenes (**20**) (Scheme 2).[4]



Scheme 2. Possible transformation of isoflav-3-enes (**11**) into other classes of isoflavonoids.

Our strategy towards isoflav-3-enes (**11**) entails the methylenation of a 2-hydroxybenzaldehyde (**26**), etherification of the 2-vinylphenol (**24**) with an α-haloacetophenone (**25**), methylenation of the 1-phenyl-2-(2-vinylphenoxy)ethan-1-one (**23**) and, finally, ring-closing metathesis. Though Tebbe methylenation, as was utilised in the synthesis of flav-2-enes (**6**) (Scheme 1a), would also be an option in this case, a shorter three-step one pot Wittig methylenation – etherification – Wittig methylenation[25] was chosen (Scheme 3).



Scheme 3. Retrosynthetic approach to isoflav-3-enes (**11**) with natural substitution patterns.

Li et al.[25] reported a one pot Wittig methylenation – etherification – Wittig methylenation strategy for the preparation of 7-benzyloxy-4'-methoxyisoflav-3-ene (**27**) (Figure 2). We herein report on the extension and modification of this elegant strategy to afford a series of substituted isoflav-3-enes.

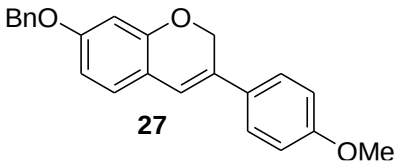
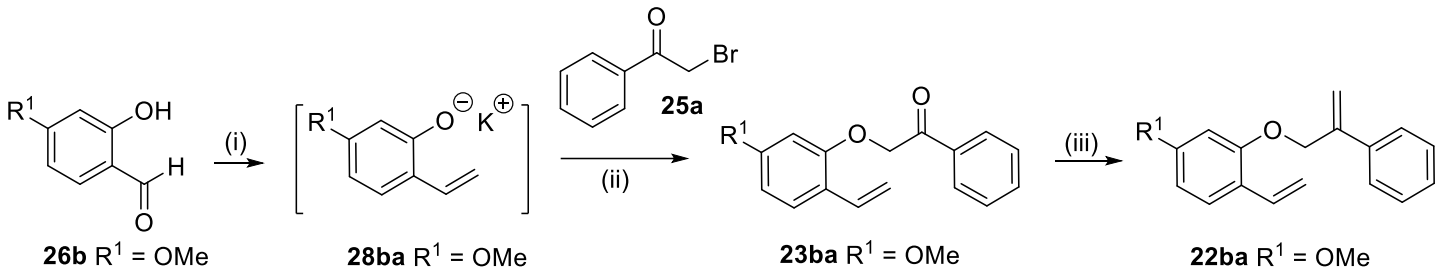


Figure 2. 7-Benzyloxy-4'-methoxyisoflav-3-ene (**27**).

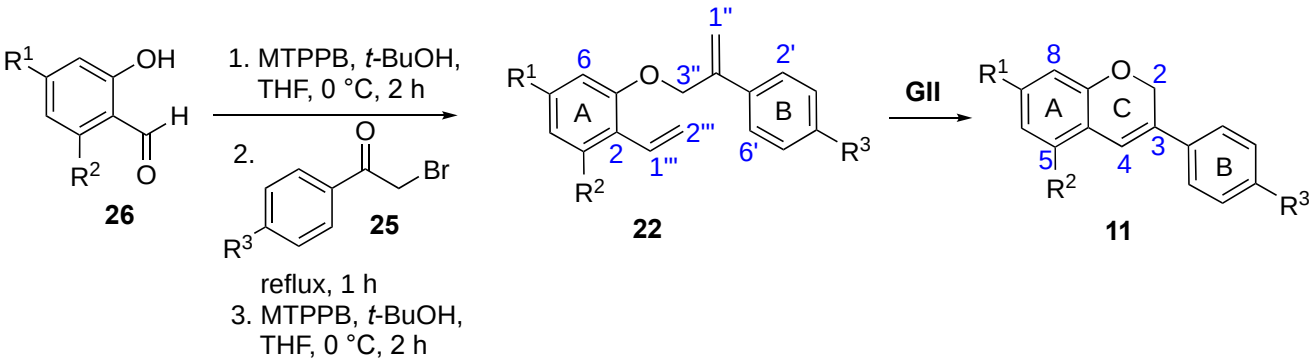
Results and Discussion

By following the one-pot three-step protocol reported by Li et al.,[25] the Wittig reaction of 2-hydroxy-4-methoxybenzaldehyde (**26b**) with methylenetriphenylphosphorane (1.2 eq.) (derived from methyltriphenylphosphonium bromide (MTPPB) and *t*-BuOK in THF at 0 °C), etherification with bromoacetophenone (**25a**) (1.2 eq.) at reflux and another Wittig reaction ($PPh_3=CH_2$, 1.2 eq.) at 0 °C, afforded 4-methoxy-2-[(2-phenylallyl)oxy]-1-vinylbenzene (**22ba**) in 35% yield (Scheme 4, Table 1, entry 1). By increasing the equivalents of the Wittig reagent in the last step to two, the yield of the desired 4-methoxy-2-[(2-phenylallyl)oxy]-1-vinylbenzene (**22ba**) was increased to 89% (Table 1, entry 2).



Scheme 4. The synthesis of a model 1-aryl-2-(2-vinylaryloxy)ethan-1-one (**23**) and 1-[(2-phenylallyl)oxy]-2-vinylbenzene (**22**) by means of Wittig methylenation and etherification. Reaction conditions: (i) MTPPB (1.2 eq.), *t*-BuOK (1.2 eq.), THF, 0 °C, 15 min.; **26**, *t*-BuOK (1.2 eq.), THF, 0 °C, 2 h; (ii) **28**, **25** (1.2 eq.), THF, reflux, 1 h; (iii) MTPPB (1.2 eq. or 2 eq.), *t*-BuOK (1.2 eq. or 2 eq.), THF, 0 °C, 15 min., then **23**, 0 °C – rt.

A series of five novel 1-[(2-phenylallyl)oxy]-2-vinylbenzenes (**22**) was thus prepared in good yield (61 – 89%) by the application of the optimized one pot Wittig methylenation – etherification – Wittig methylenation strategy (Scheme 5, Table 1).



Scheme 5. The preparation of 1-[(2-phenylallyl)oxy]-2-vinylbenzenes (**22**) by means of a one-pot Wittig methylenation – etherification - Wittig methylenation and isoflav-3-enes (**11**) by ring-closing metathesis.

Table 1. The preparation of 1-[(2-phenylallyl)oxy]-2-vinylbenzenes (**22**) by means of a one-pot Wittig methylenation – etherification - Wittig methylenation sequence

	26	**25**	Substitution		**22**	Yield (%)
1	**26a**	**25b**	$R^1 = R^2 = H$	R^3 = OMe	**22ab**	35[a]
2	**26a**	**25b**	$R^1 = R^2 = H$	R^3 = OMe	**22ab**	89
3	**26b**	**25a**	R^1 = OMe, $R^2 = H$	$R^3 = H$	**22ba**	63
4	**26b**	**25b**	R^1 = OMe, $R^2 = H$	R^3 = OMe	**22bb**	61
5	**26c**	**25a**	$R^1 = R^2$ = OMe	$R^3 = H$	**22ca**	76
6	**26c**	**25b**	$R^1 = R^2$ = OMe	R^3 = OMe	**22cb**	70

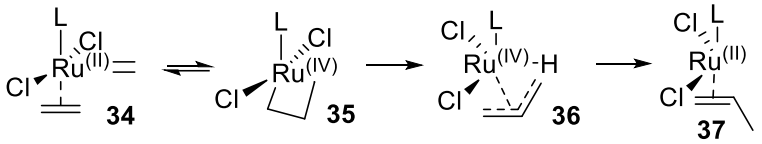
Reaction conditions: (i) Preparation of $Ph_3P{=}CH_2$: *t*-BuOK (1.2 eq.), THF, 0 °C, MTPPB (1.2 eq.), 15 min.; (ii) benzaldehyde **26** (1.0 eq.), *t*-BuOK (1.2 eq.), THF, 0 °C, 2 h; (iii) reflux, 2-bromoacetophenone **25** (1.2 eq., dropwise), 1 h ; (iv) 0 °C, $Ph_3P{=}CH_2$ (2.0 eq.), 2 h. [a]$Ph_3P{=}CH_2$ (1.2 eq.) in step (iv)

With the 1-[(2-phenylallyl)oxy]-2-vinylbenzenes (**22**) in hand, ring-closing metathesis of **22ab** catalysed by the Grubbs second generation catalyst (**GII**) (5 mol %) in refluxing dichloromethane (Scheme 5),[26] afforded 4'-methoxy-isoflav-3-ene (**11ab**) in 86% yield (Table 2, entry 1). 7-Methoxy-isoflav-3-ene (**11ba**) and 4',7-dimethoxyisoflav-3-ene (**11bb**) could be obtained in quantitative and 57% yield, respectively, under similar conditions (Table 2, entries 2 and 3). However when the phloroglucinol-type 2-[(2-phenylallyl)oxy]-2-vinylbenzenes **22ca** and **22cb** were subjected to these metathesis conditions, no conversion took place even after 72 hours. To increase the reaction temperature, the solvent was therefore replaced by toluene. Under these conditions, 5,7-dimethoxyisoflav-3-ene (**11ca**) was obtained in 67% yield (Table 2, entry 4), but still no trace of 4',5,7-trimethoxyisoflav-3-ene (**11cb**) was observed. Replacing the Grubbs second generation catalyst with the Hoveyda-Grubbs catalyst also failed to effect ring-closing metathesis of substrate (**22cb**). Janse van Rensburg et al.[27] previously ascribed the deactivation of Grubbs catalysts to β-hydride transfer and the formation of ruthenium hydride species (Scheme 6). Additives such as 1,4-benzoquinone,[28] phenol[29] and *p*-cresol[30,31] are known to increase the catalyst life-time and to alter the catalyst activity. 1,4-Benzoquinone (0.2 eq.) was therefore added to the reaction mixture of **22cb** and **GII** in refluxing toluene to obtain the desired 4',5,7-trimethoxyisoflav-3-ene (**11cb**) in 65% yield (Table 2, entry 5).

Table 2. The preparation of isoflav-3-enes (**11**) from 1-[(2-phenylallyl)oxy]-2-vinylbenzenes (**22**) by ring-closing metathesis

	26	**25**	Substitution		**11**	Yield (%)
1	**26a**	**25b**	$R^1 = R^2 = H$	R^3 = OMe	**11ab**	86
2	**26b**	**25a**	R^1 = OMe, $R^2 = H$	$R^3 = H$	**11ba**	>99
3	**26b**	**25b**	R^1 = OMe, $R^2 = H$	R^3 = OMe	**11bb**	57
4	**26c**	**25a**	$R^1 = R^2$ = OMe	$R^3 = H$	**11ca**	67[b]
5	**26c**	**25b**	$R^1 = R^2$ = OMe	R^3 = OMe	**11cb**	65[c]

Reaction conditions: **GII** (5 mol %), CH_2Cl_2, reflux; [b]**GII** (5 mol %), toluene, reflux; [c]**GII** (5 mol %), 1,4-benzoquinone (0.2 eq.), toluene, reflux



L = PCy_3, IMes

Scheme 6. Catalyst deactivation by β-hydride transfer as proposed by Janse van Rensburg et al.[27]

Conclusions

A series of five novel 1-[(2-phenylallyl)oxy]-2-vinylbenzenes (**22**) were prepared in good yield (61 – 89%) after slight modifications to the one pot Wittig methylenation – etherification – Wittig methylenation strategy previously reported by Li et al.[25] (larger excess of methylenetriphenylphosphorane in the third step). Subsequent ring-closing metathesis with Grubbs second generation catalyst (**GII**) gave access to the corresponding isoflav-3-enes (**11**), with more drastic conditions being required for compounds with a

phloroglucinol type substitution pattern (higher temperature; 1,4-benzoquinone as additive). Various isoflav-3-enes (**11**) with natural substitution patterns could be accessed.

The application of metathesis towards the synthesis of the three flavonoid subclasses, i.e. the flavonoids[23] (**2**), neoflavonoids[24] (**3**) and isoflavonoids (**1**), has thus been successfully demonstrated and offers a common methodology towards the synthesis of all three flavonoid subclasses.

Experimental Section

General. NMR-spectroscopy was performed on a Bruker AM 600 FT-spectrometer at, unless specified to the contrary, 20 °C with $CDCl_3$ (deuterochloroform) or $(CD_3)_2CO$ (deuterated acetone) as solvent. Chemical shifts are reported in parts per million (ppm) with the solvent peak for proton spectra at 7.26 ppm for $CDCl_3$ and 2.06 ppm for $(CD_3)_2CO$ and 77.16 ppm for $CDCl_3$ and 206.26 ppm for $(CD_3)_2CO$ on the δ-scale in carbon spectra, whereas coupling constants are given in Hz. Mass spectrometry was performed by means of electron impact (EI) ionization on a Shimadzu GC-MS QP-2010 fitted with a J & W DB-5ms capillary column (0.25 µm film thickness, 0.32 mm ID, 30 m), helium as carrier gas at a linear velocity of 27.5 cm/s and an injector temperature of 250 °C. Injections were made in the split mode. The initial column temperature of 50 °C was kept for 3 min, where after it was increased to 250 °C at 10 °C/min and kept at this temperature for the rest of the analysis. High resolution MS (HR-MS) was performed by PMBMS, University of KwaZulu-Natal. Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP3) apparatus and are uncorrected.

Vinyl benzene synthesis.[25] A suspension of methyltriphenylphosphonium bromide (MTPPB) (1.2 eq.) and *t*-BuOK (1.2 eq.) in anhydrous THF (5.0 mL) under argon was cooled to 0 °C and stirred for 15 minutes. A mixture of benzaldehyde (1.0 eq.) and *t*-BuOK (1.2 eq.) in THF (5.0 mL) was added and the resulting mixture stirred at 0 °C for 2 h. The reaction mixture was then heated to reflux and a solution of bromoacetophenone (1.2 eq.) in anhydrous THF (2.0 mL) added dropwise and stirred for 1 h. The reaction mixture was cooled to 0 °C again and transferred to a solution of MTPPB (1.2 eq.) and *t*-BuOK (1.2 eq.) in anhydrous THF (5.0 mL) already stirred at 0 °C for 15 min. The resulting mixture was left to continue stirring at 0 °C for 2 h after which it was quenched with aq. NH_4Cl (60.0 mL). The product was extracted into EtOAc (3 x 60.0 mL), the extract dried over Na_2SO_4, the solvent removed in *vacuo* and the product purified *via* PLC.

1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**22ab**). MTPPB (1.18 g, 3.30 mmol, 2.0 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 2.0 eq.), 2-hydroxybenzaldehyde (**26a**) (0.20 g, 1.6 mmol), *t*-BuOK (0.23 g, 2.1 mmol, 1.3 eq.), 2-bromo-4'-methoxyacetophenone (**25b**) (0.46 g, 2.0 mmol, 1.2 eq.), MTPPB (1.17 g, 3.28 mmol, 2.0 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 2.0 eq.) yielded 1-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**22ab**) as a *yellow oil* (0.39 g, 89%): R_f: 0.63 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.54 – 7.50 (1H, m, H-3), 7.51 (2H, d, *J* 9.0, H-2' and H-6'), 7.27 – 7.24 (1H, m, H-5), 7.11 (1H, dd, *J* 8.3, 1.0 Hz, H-6), 7.00 (1H, dd, *J* 17.8, 11.2 Hz, H-1'''), 6.96 – 6.94 (1H, m, H-4), 6.93 (2H, d, *J* 9.0 Hz, H-3' and H-5'), 5.73 (1H, dd, *J* 17.8, 1.6 Hz, H-2'''b), 5.57 – 5.56 (1H, m, H-1''), 5.41 – 5.40 (1H, m, H-1''), 5.16 (1H, dd, *J* 11.2, 1.6 Hz, H-2'''a), 4.98 (2H, br. s, H-3''), 3.80 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 160.6 (C-4'), 156.7 (C-1), 143.8 (C-2''), 132.4 (C-1'''), 131.5 (C-1'), 129.8 (C-5), 128.0 (C-2' and C-6'), 127.5 (C-2), 127.0 (C-3), 121.7 (C-4), 114.6 (C-3' and C-5'), 114.4 (C-2'''), 113.5 (C-6), 113.0 (C-1''), 70.7 (C-3''), 55.6 (-OMe); *m/z* (EI) 266 (M^+, 54%); HR-MS (AP) *m/z* 267.1394 ($[M+H]^+$), $C_{18}H_{18}O_2^+$ requires 267.1385, found 267.1394.

4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**22ba**). MTPPB (1.14 g, 3.19 mmol, 1.2 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 1.2 eq.), 2-hydroxy-4-methoxybenzaldehyde (**26b**) (0.41 g, 2.7 mmol, 0.8 eq.), *t*-BuOK (0.38 g, 3.4 mmol, 1.3 eq.), 2-bromoacetophenone (**25a**) (0.86 g, 4.3 mmol, 1.6 eq.), MTPPB (2.29 g, 6.41 mmol, 2.4 eq.), *t*-BuOK (0.72 g, 6.4 mmol, 2.4 eq.) yielded 4-methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**22ba**) as a *yellow oil* (0.44 g, 63%): R_f: 0.62 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.60 – 7.57 (2H, m, H-2' and H-6'), 7.45 (1H, d, *J* 8.4 Hz, H-6), 7.40 – 7.37 (2H, m, H-3' and H-5'), 7.35 – 7.31 (1H, m, H-4'), 6.90 (1H, dd, *J* 17.8, 11.2 Hz, H-1'''), 6.71 (1H, d, *J* 2.4 Hz, H-3), 6.55 (1H, dd, *J* 8.4, 2.4 Hz, H-5), 5.68 – 5.67 (1H, m, H-1''), 5.60 (1H, dd, *J* 17.8, 1.6 Hz, H-2'''b), 5.55 – 5.53 (1H, m, H-1''), 5.03 (2H, br. s, H-3''), 5.02 (1H, dd, *J* 11.2, 1.6 Hz, H-2'''a), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.6 (C-4), 157.6 (C-2), 144.5 (C-1'/2''), 139.1 (C-1'/2''), 132.0 (C-1'''), 129.3 (C-3' and C-5'), 128.7 (C-4'), 127.8 (C-6), 126.8 (C-2' and C-6'), 120.4 (C-1), 114.9 (C-1''), 111.9 (C-2'''), 106.5 (C-5), 100.3 (C-3), 70.5 (C-3''), 55.6 (-OMe); HR-MS (AP) *m/z* 267.1384 ($[M+H]^+$), $C_{18}H_{18}O_2^+$ requires 267.1385, found 267.1384.

4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**22bb**). MTPPB (0.94 g, 2.6 mmol, 1.7 eq.), *t*-BuOK (0.30 g, 2.5 mmol, 0.9 eq.), 2-hydroxy-4-methoxybenzaldehyde (**26b**) (0.23 g, 1.5 mmol), *t*-BuOK (0.18 g, 1.6 mmol, 1.1 eq.), 2-bromo-4'-methoxyacetophenone (**25b**) (0.37 g, 1.6 mmol, 1.1 eq.), MTPPB (0.95 g, 2.7 mmol, 1.8 eq.), *t*-BuOK (0.32 g, 2.9 mmol, 1.9 eq.) yielded 4-methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**22bb**) as a *colourless oil* (0.27 g, 61%): R_f: 0.13 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.51 (2H, d, *J* 8.5 Hz, H-2' and H-6'), 7.45 (1H, d, *J* 8.5 Hz, H-6), 6.96 – 6.90 (1H, m, H-1'''), 6.92 (2H, d, *J* 8.5 Hz, H-3' and H-5'), 6.69 (1H, d, *J* 2.4 Hz, H-3), 6.54 (1H, dd, *J* 8.5, 2.4 Hz, H-5), 5.61 (dd, *J* 17.8, 1.6 Hz, H-2'''b), 5.58 (1H, br. s H-1''), 5.43 – 5.42 (1H, m, H-1''), 5.04 (1H, dd, *J* 11.2, 1.6 Hz, H-2'''a), 4.97 (2H, br. s, H-3''), 3.79 (3H, s, -OMe), 3.78 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.6 (C-4), 160.4 (C-4'), 157.6 (C-2), 143.6 (C-2''), 132.0 (C-1'''), 131.3 (C-1'), 128.1 (C-2' and C-6'), 127.9 (C-6), 120.4 (C-1), 114.5 (C-3' and C-5'), 113.1 (C-1''), 112.0 (C-2'''), 106.4 (C-5), 100.3 (C-3), 70.6 (C-3''), 55.6 (-OMe), 55.4 (-OMe); *m/z* (EI) 296 (M^+, 100%). **22bb** was used in the next step without further characterization (see **11bb**).

1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**22ca**). MTPPB (0.71 g, 2.0 mmol, 1.3 eq.), *t*-BuOK (0.23 g, 2.0 mmol, 1.3 eq.), 2-hydroxy-4,6-dimethoxybenzaldehyde (**26c**) (0.29 g, 1.6 mmol), *t*-BuOK (0.23 g, 2.0 mmol, 1.3 eq.), 2-bromoacetophenone (**25a**) (0.40 g, 2.0 mmol, 1.3 eq.), MTPPB (1.2 g, 3.3 mmol, 2.1 eq.), *t*-BuOK (0.36 g, 3.2 mmol, 2.0 eq.) yielded 1,5-dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**22ca**) as a *yellow oil* (0.36 g, 76%): R_f: 0.51 (hexanes:acetone 6:4); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.57 – 7.54 (2H, m, H-2' and H-6'), 7.38 – 7.35 (2H, m, H-3' and H-5'), 7.33 – 7.30 (1H, m, H-4'), 6.86 (1H, dd, *J* 17.9, 12.0 Hz, H-1'''), 6.39 (1H, d, *J* 2.3 Hz, H-4), 6.26 (1H, d, *J* 2.3 Hz, H-6), 5.87 (1H, dd, *J* 17.9, 3.0 Hz, H-2'''b), 5.66 – 5.64 (1H, m, H-1''), 5.53 – 5.52 (1H, m, H-1''), 5.10 (1H, dd, *J* 12.0, 3.0 Hz, H-2'''a), 5.01 (2H, br. s, H-3''), 3.82 (3H, s, -OMe), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.3 (C-1), 160.5 (C-5), 159.2 (C-3), 144.5 (C-2''), 139.2 (C-1'), 129.2 (C-3' and C-5'), 128.8 (C-4'), 127.9 (C-1'''), 126.8 (C-2' and C-6'), 115.7 (C-2'''), 115.1 (C-1''), 108.8 (C-2), 92.7 (C-4), 91.8 (C-6), 70.8 (C-3''), 55.9 (-OMe), 55.5 (-OMe); *m/z* (EI) 296 (M^+, 97%); HR-MS (ES) *m/z* 319.1309 $[M + Na]^+$, $C_{19}H_{20}O_3Na^+$ requires 319.1310, found 319.1309.

1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**22cb**). MTPPB (0.71 g, 2.0 mmol, 1.2 eq.), *t*-BuOK (0.22 g, 2.0 mmol, 1.2 eq.), 2-hydroxy-4,6-dimethoxybenzaldehyde (**26c**) (0.30 g, 1.7 mmol), *t*-BuOK (0.22 g, 2.0 mmol, 1.2 eq.), 2-bromo-4'-methoxyacetophenone (**25b**) (0.46 g, 2.0 mmol, 1.2 eq.), MTPPB (1.18 g, 3.30 mmol, 2.0 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 2.0 eq.) yielded 1,5-dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**22cb**) as a *yellow oil* (0.38 g, 70%); R_f: 0.63 (hexanes:acetone 6:4); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.51 (2H, d, *J* 8.8 Hz, H-2' and H-6'), 6.93 (2H, d, *J* 8.8 Hz, H-3' and H-5'), 6.85 (1H, dd, *J* 18.0, 12.3 Hz, H-1'''), 6.39 (1H, d, *J* 2.3 Hz, H-4/6), 6.27 (1H, d, *J* 2.3 Hz, H-4/6), 5.86 (1H, dd, *J* 18.0, 3.0 Hz, H-2'''b), 5.57 (1H, br. s, H-1''), 5.43 – 5.41 (1H, m, H-1''), 5.09 (1H, dd, *J* 12.3, 3.0 Hz, H-2'''a), 4.99 (2H,

br. s, H-3''), 3.84 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.5 (C-5), 160.7 (C-1/4'), 160.7 (C-1/4'), 159.5 (C-3), 144.0 (C-2''), 131.6 (C-1'), 128.2 (C-2' and C-6'), 128.1 (C-1'''), 115.8 (C-2'''), 114.6 (C-3' and C-5'), 113.4 (C-1''), 109.0 (C-2), 92.9 (C-4/6), 91.9 (C-4/6), 71.2 (C-3''), 56.0 (-OMe), 55.7 (-OMe), 55.6 (-OMe); HR-MS (ES) *m/z* 349.1414 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1410, found 349.1414.

Isoflavene synthesis *via* RCM.[26] A solution of vinyl ether (1.0 eq.) and Grubbs II catalyst (5 mol %) in dry DCM or toluene (5.0 – 10.0 mL) was heated to reflux and allowed to stir overnight. After completion of the reaction, the product was directly purified *via* PLC. Alternatively, a solution of vinyl ether (1.0 eq.), Grubbs II catalyst (5 mol %) and 1,4-benzoquinone (10 mol %) in dry toluene (5.0 – 10.0 mL) was heated to reflux. After completion of the reaction, the product (in solvent) was directly purified *via* PLC.

4'-Methoxyisoflav-3-ene (**11ab**). 1-{[2-(4-Methoxy-phenyl)allyl]oxy}-2-vinylbenzene (**22ab**) (0.34 g, 1.3 mmol), DCM (5.0 mL) yielded 4'-methoxyisoflav-3-ene (**11ab**) as a beige amorphous solid (0.26 g, 86%); R_f : 0.46 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.50 (2H, d, *J* 8.9 Hz, H-2' and H-6'), 7.13 (1H, dd, *J* 7.4, 1.6 Hz, H-5), 7.11 (1H, ddd, *J* 8.0, 7.7, 1.6 Hz, H-7), 6.97 (2H, d, *J* 8.9 Hz, H-3' and H-5'), 6.90 (1H, ddd, *J* 7.7, 7.4, 1.2 Hz, H-6), 6.87 (1H, br. s, H-4), 6.80 (1H, br. d, *J* 8.0 Hz, H-8), 5.15 (1H, s, H-2), 5.14 (1H, s, H-2), 3.82 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 160.7 (C-4'), 154.0 (C-8a), 132.4 (C-3), 129.7 (C-1'), 129.4 (C-5/7), 127.7 (C-5/7), 126.9 (C-2' and C-6'), 124.2 (C-4a), 122.3 (C-6), 118.7 (C-4), 116.0 (C-8), 115.0 (C-3' and C-5'), 67.5 (C-2), 55.6 (-OMe); *m/z* (EI) 238 (M^+, 100%). The physical data corresponded to those previously reported.[32]

7-Methoxyisoflav-3-ene (**11ba**). 4-Methoxy-2-[(2-phenylallyl)oxy]-1-vinylbenzene (**22ba**) (0.20 g, 0.67 mmol), DCM (5.0 mL) yielded 7-methoxyisoflav-3-ene (**11ba**) as a white solid (0.18 g, quantitative yield): R_f : 0.53 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.55 – 7.53 (2H, m, H-2' and H-6'), 7.43 – 7.40 (2H, m, H-3' and H-5'), 7.33 – 7.31 (1H, m, H-4'), 7.11 (1H, d, *J* 8.3 Hz, H-5), 6.97 (1H, br. s, H-4), 6.53 (1H, dd, *J* 8.3, 2.4 Hz, H-6), 6.44 (1H, d, *J* 2.4 Hz, H-8), 5.18 (1H, s, H-2), 5.17 (1H, s, H-2), 3.80 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.9 (C-7), 155.6 (C-8a), 137.8 (C-1'), 129.6 (C-3), 129.5 (C-3' and C-5'), 128.9 (C-5), 128.5 (C-4'), 125.4 (C-2' and C-6'), 120.5 (C-4), 117.1 (C-4a), 108.2 (C-6), 102.1 (C-8), 67.7 (C-2), 55.7 (-OMe); *m/z* (EI) 238 (M^+, 100%). The physical data corresponded to those previously reported.[33]

4',7-Dimethoxyisoflav-3-ene (**11bb**). 4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**22bb**) (0.26 g, 0.84 mmol), DCM (5.0 mL) yielded 4',7-dimethoxyisoflav-3-ene (**11bb**) as a yellow oil (0.13 g, 57%): R_f : 0.28 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.48 (2H, d, *J* 8.9 Hz, H-2' and H-6'), 7.07 (1H, d, *J* 8.3 Hz, H-5), 6.97 (2H, d, *J* 8.9 Hz, H-3' and H-5'), 6.84 (1H, br. s, H-4), 6.51 (1H, dd, *J* 8.3, 2.5 Hz, H-6), 6.42 (1H, d, *J* 2.5 Hz, H-8), 5.13 (1H, br. s, H-2), 5.13 (1H, br. s, H-2), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.6 (C-7), 160.4 (C-4'), 155.4 (C-8a), 130.2 (C-1'), 129.4 (C-3), 128.5 (C-5), 126.7 (C-2' and C-6'), 118.6 (C-4), 117.4 (C-4a), 115.0 (C-3' and C-5'), 108.1 (C-6), 102.1 (C-8), 67.7 (C-2), 55.7 (-OMe), 55.7 (-OMe); *m/z* (EI) 268 (M^+, 100%). The physical data corresponded to those previously reported.[33]

5,7-Dimethoxyisoflav-3-ene (**11ca**). 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**22ca**) (0.11 g, 0.34 mmol), toluene (5.0 mL) yielded 5,7-dimethoxyisoflav-3-ene (**11ca**) as a yellow amorphous solid (0.07 g, 67%): R_f : 0.57 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.52 – 7.49 (2H, m, H-2' and H-6'), 7.42 – 7.38 (2H, m, H-3' and H-5'), 7.31 – 7.27 (1H, m, H-4'), 7.12 (1H, br. s, H-4), 6.19 (1H, d, *J* 2.2 Hz, H-6/8), 6.11 (1H, d, *J* 2.2 Hz, H-6/8), 5.10 (1H, s, H-2), 5.10 (1H, s, H-2), 3.87 (3H, s, -OMe), 3.80 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 162.5 (C-5/7), 157.7 (C-5/7), 156.2 (C-8a), 138.2 (C-1'), 129.6 (C-3' and C-5'), 128.2 (C-4'), 127.5 (C-3), 125.3 (C-2' and C-6'), 115.6 (C-4), 106.6 (C-4a), 94.4 (C-6/8), 92.7 (C-6/8), 67.5 (C-2), 56.1 (-OMe), 55.8 (-OMe); *m/z* (EI) 268 (M^+, 84%). The physical data corresponded to those previously reported.[34]

4',5,7-Trimethoxyisoflav-3-ene (**11cb**). 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**22cb**) (0.13 g, 0.40 mmol), toluene (5.0 mL), benzoquinone (0.01, 0.09 mmol, 0.2 eq) yielded 4',5,7-

trimethoxyisoflav-3-ene (**11cb**) as a yellow oil (0.08 g, 65%): R_f: 0.34 (hexanes:acetone 7:3). ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.46 (2H, d, *J* 8.8 Hz, H-2' and H-6'), 7.01 – 6.99 (1H, m, H-4), 6.97 (2H, d, *J* 8.8 Hz, H-3' and H-5'), 6.18 (1H, d, *J* 2.2 Hz, H-6), 6.09 (1H, dd, *J* 2.2, 0.5 Hz, H-8), 5.07 (1H, s, H-2), 5.07 (1H, s, H-2), 3.86 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 162.0 (C-5/7), 160.2 (C-4'), 157.4 (C-5/7), 155.8 (C-8a), 130.6 (C-1'), 127.2 (C-3), 126.5 (C-2' and C-6'), 114.9 (C-3' and C-5'), 113.5 (C-4), 106.7 (C-4a), 94.3 (C-8), 92.6 (C-6), 67.5 (C-2), 56.0 (-OMe), 55.7 (-OMe), 55.6 (-OMe); *m/z* (EI) 298 (M^+, 100%). The physical data corresponded to those previously reported.[35]

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Supplementary Material

NMR spectra can be found online in the supplementary material.

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