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Ring-closing metathesis in flavonoid synthesis, part 2: neoflav-3-enes

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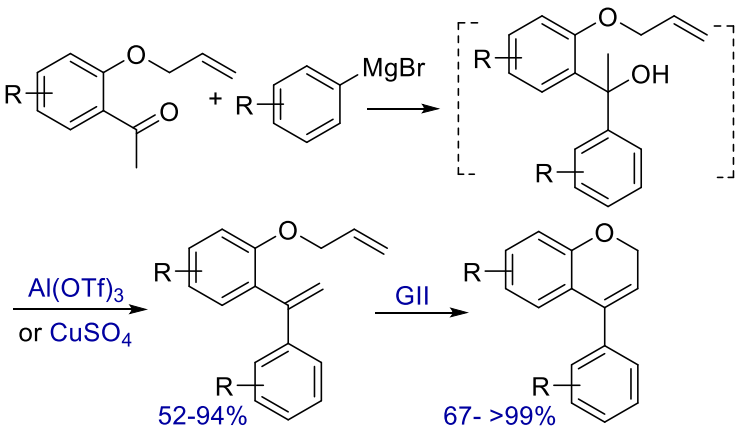
Abstract

A series of neoflav-3-enes with a variety of natural substitution patterns was prepared from 1-(allyloxy)-2-[1-(aryl)vinyl]benzenes by Grubbs second generation (GII) catalyst-promoted ring-closing metathesis (67 - 99% yield). The 1-(allyloxy)-2-[1-(phenyl)vinyl]benzene substrates were accessible in yields of 52 – 94% from the corresponding 2-(allyloxy)acetophenones via a Grignard reaction and Lewis acid-promoted dehydration, either in a one pot process in the presence of $Al(OTf)_3$ or in consecutive steps with $CuSO_4$ as dehydrating agent.



Keywords: Flavonoid, neoflavene, Grignard, aluminium triflate, metathesis, Grubbs catalyst

Introduction

The flavonoids, which are characterized by a C_6-C_3-C_6 skeleton, i.e. two aryl rings linked by a three-carbon chain, are important privileged compounds with anti-cancer, anti-mutagenic, vasodilatory, anti-inflammatory, anti-allergenic, anti-microbial, anti-viral, neuroprotective and antioxidant activities, amongst others.[1] The flavonoids are further subdivided into three subclasses, i.e. the flavonoids (**1**), isoflavonoids (**2**) and neoflavonoids (**3**), depending on the position of the attachment of the B-ring to the heterocycle (Chart 1).

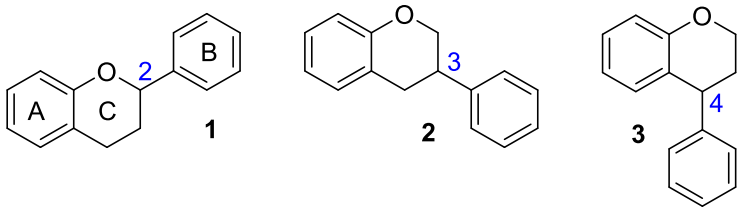
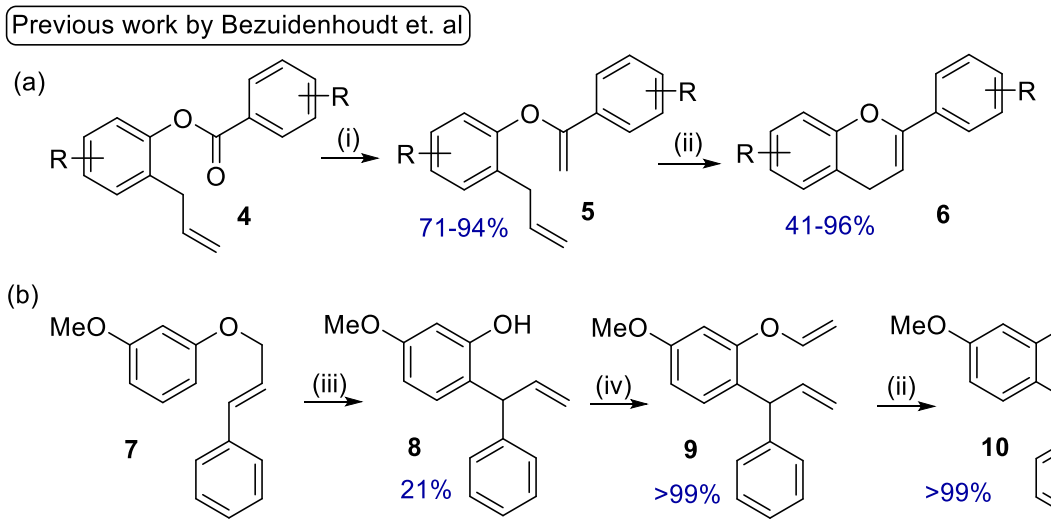


Chart 1. Basic skeleton for the flavonoid (**1**), isoflavonoid (**2**) and neoflavonoid (**3**) subclasses of the flavonoids.

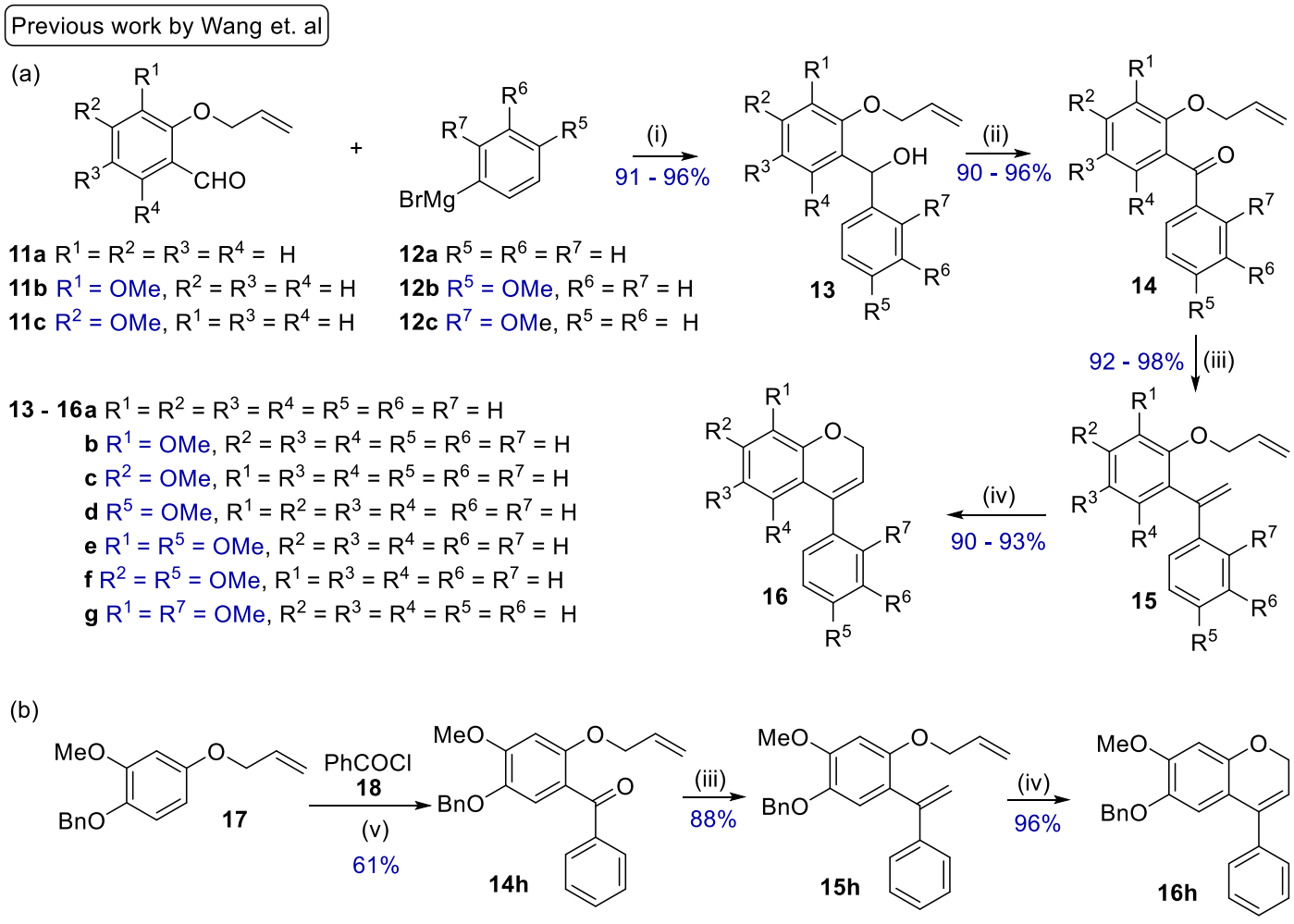
Whereas both the flavonoid (**1**) and isoflavonoid (**2**) subclasses may be prepared from chalcones (1,3-diaryl-2-propen-1-ones),[2-11] classical synthetic methodology towards neoflavonoids (**3**) mostly rely on the preparation of 4-arylcoumarins,[12] which require the availability of suitably substituted 3-oxo-3-arylpropanoates or arylpropiolates (Von Pechmann condensation of highly activated phenols),[13-17] 3-arylacrylonitriles (Houben-Hoesch reaction with phenols)[18,19] or 2-hydroxybenzophenones (Perkin reaction with anhydrides or acyl halides,[13,16] olefination[20] or alkoxyacetylide addition – cycloisomerization[12]). Modern catalytic methods towards neoflavonoids, on the other hand, require suitably substituted coumarins (oxidative Heck reaction with arylboronic acids),[21] coumarins with electron-withdrawing groups on position 4 (e.g. Suzuki coupling with arylboronic acids,[22-24] Ullmann coupling with aryl halides,[25] palladium-catalyzed coupling with triarylbismuth[26]), *ortho*-hydroxy or -methoxycinnamates (Heck reaction with aryl halides),[27] 3-arylpropiolates or aryl 3-arylpropiolates (transition metal catalyzed inter- and intramolecular hydroarylation),[12,28] or 2-(1-phenylvinyl)phenols (cyclocarbonylation and -carboxylation).[12] Alternatively, neoflavonoids (**3**) may be reached through the preparation of neoflav-3-enes, which are commonly synthesized by either (i) heat or Lewis acid induced cyclization of aryl 3-arylprop-2-ynyl ethers[29-32] or (ii) mercury mediated coupling of a phenolic entity and a chromene.[13]

In our endeavours to find benign, catalytic methodologies towards the synthesis of flavonoids, we recently reported a ring-closing metathesis strategy for the preparation of flav-2-enes (**6**) displaying natural substitution patterns (Scheme 1a).[33] We previously also reported on the preparation of the 7-methoxy derivative of neoflav-2-ene (**10**)[34] by means of a Claisen rearrangement, vinylation and subsequent ring-closing metathesis with Grubbs second generation catalyst (**GII**). The yield of the Claisen rearrangement step was unacceptably low, though (21%) (Scheme 1b).[34]

In an alternative approach, Wang and co-workers[35,36] prepared a limited series of neoflav-3-enes (**16**) through the **GII**-catalyzed ring-closing metathesis of 1-(allyloxy)-2-[1-(phenyl)vinyl]benzenes (**15**), which in turn could be obtained by Wittig methylenation of the corresponding benzophenones (**14**). The benzophenone (**14**) was obtained through either the Grignard reaction of 2-allyloxybenzaldehydes (**11**) and subsequent MnO_2 oxidation, or the Friedel-Crafts acylation of an allylether (**17**) (Scheme 2).

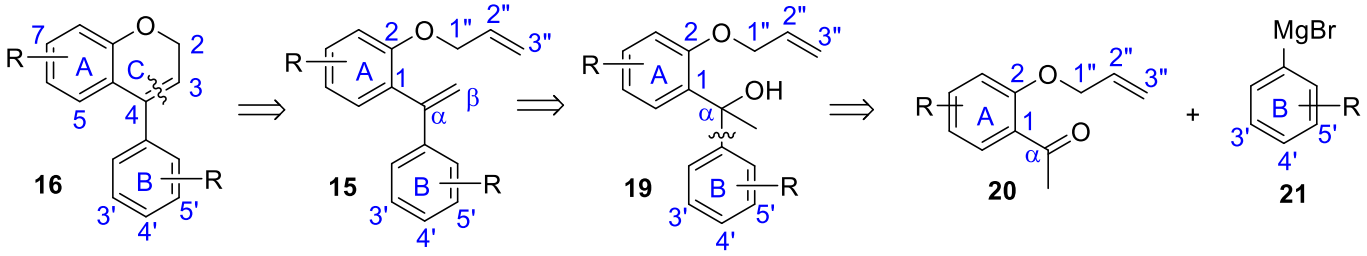


Scheme 1. The preparation of flav-2-enes (**6**) and 7-methoxyneoflav-2-ene (**10**) with ring-closing metathesis as key step: (i) $Cp_2TiCH_2ClAl(CH_3)_2$ (0.5 M, 1.2 – 2.7 eq.), THF (2 mL), 0 °C, 30 min., rt, 1h, reflux, 2h; (ii) **GII** (5 mol %), CH_2Cl_2, reflux; (iii) *N*,*N*-dimethylaniline, 193 °C; (iv) $Cu(OAc)_2$, $Sn(vinyl)_4$, O_2, MeCN, rt.



Scheme 2. The preparation of neoflav-3-enes (**16**) with ring-closing metathesis as key step: (i) THF, rt, 2h; (ii) MnO_2, CH_2Cl_2, rt, 5h; (iii) PPh_3CH_3Br, KOtBu, THF, 0 °C; (iv) **GII,** CH_2Cl_2, reflux; (v) ZnO, rt.

A variety of acetophenones are commercially available and we anticipated that the required 1,1-diarylethenes (**15**) could be prepared from 2-allyloxy-acetophenones (**19**) by means of a domino Grignard reaction and $Al(OTf)_3$-catalysed dehydration sequence (Scheme 3).[37]

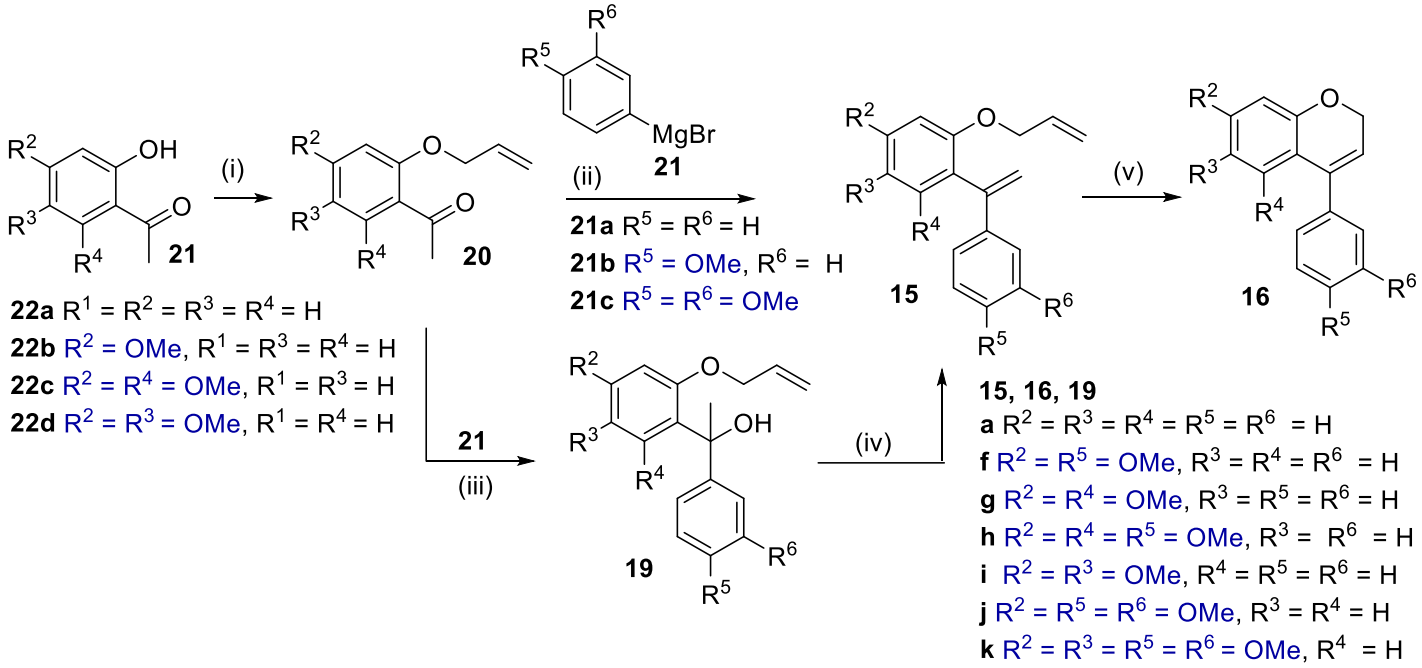


Scheme 3. Retrosynthetic approach to neoflav-3-enes (**16**). The A/B ring labelling system of neoflav-3-enes (**16**) was also applied to the intermediates.

Herein we thus would like to report on the application of a domino Grignard reaction – Lewis acid-catalysed dehydration sequence, and ring-closing metathesis, to the preparation of a series of neoflav-3-enes (**16**) (Scheme 4) with natural substitution patterns.

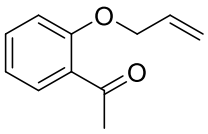
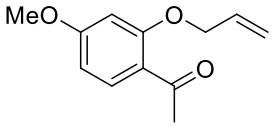
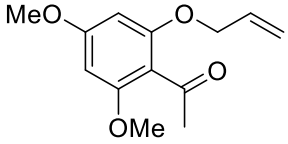
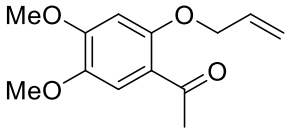
Results and Discussion

Allylation of suitably substituted acetophenones (**22**) gave a series of 2-allyloxy-acetophenones (**20**) in good to excellent yields (Scheme 4, Table 1, 74 – 99%).



Scheme 4. Reaction conditions: (i) **22**, K_2CO_3, allyl bromide, reflux; (ii) **20**, $Al(OTf)_3$, -30 °C, 30 min; **21**, -30 °C – rt; (iii) **20**, **21**, -60 °C; (iv) **19**, anhydrous $CuSO_4$, hexanes, reflux; (v) **15**, **GII** (5 mol %), CH_2Cl_2, reflux.

Table 1. Preparation of 2-allyloxy-acetophenones (**20**) via allylation of suitably substituted acetophenones (**22**)

Entry	Reactant	Product	Yield (%)
1	**22a**	 **20a**	96
2	**22b**	 **20b**	96
3	**22c**	 **20c**	74
4	**22d**	 **20d**	99

Reaction conditions: **22**, K_2CO_3, allylbromide, CH_3CN, reflux

With the 2-allyloxy-acetophenones (**20**) in hand, an $Al(OTf)_3$-activated one-pot domino Grignard – elimination reaction[37] (**20**, $Al(OTf)_3$, THF, -30 °C, 30 min., then **21**, -30 °C – rt) gave a series of 1-(allyloxy)-2-[1-(phenyl)vinyl]benzenes (**15**) in acceptable to excellent yields (Table 2, rows 2 – 5, 52 – 94%).

Interestingly, no unsubstituted 1-(allyloxy)-2-(1-phenylvinyl)benzene (**15a**) could be obtained under these conditions, though the pre-elimination product, 1-[2-(allyloxy)phenyl]-1-phenylethan-1-ol (**19a**), was obtained in 44% yield when aluminium triflate was excluded from the reaction mixture (Table 2, row 1). The Grignard product of 2-allyloxy-acetophenones **20b** and **20d** with 3,4-dimethoxyphenylmagnesium bromide (**21c**) also resisted dehydration and gave the diphenylethan-1-ols **19j** and **19k** in 50 and 4% yield, respectively (Table 2, rows 6 and 7). The reaction of **20b** and **21c** at room temperature without the addition of $Al(OTf)_3$, furnished diphenylethan-1-ol **19j** in 32% yield and the Grignard reaction with $Al(OTf)_3$ was thus repeated at -60 °C. Neither the diphenylethan-1-ol (**19j**), nor the 1-(allyloxy)-2-[1-(phenyl)vinyl]benzene (**15**), was obtained under these conditions. However, the Grignard reaction at -60 °C without $Al(OTf)_3$ gave 1-[2-(allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19j**) in 60% yield (Table 2, row 6). Extending the low temperature Grignard reaction without $Al(OTf)_3$ to acetophenone **20d** and 3,4-dimethoxyphenylmagnesium bromide (**21c**), also furnished the desired 1,1-diarylethan-1-ol, 1-[2-(allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19k**), in high yield (Table 2, row 7, 80%). Subsequent dehydration of the 1,1-diarylethan-1-ols (**19**) by anhydrous $CuSO_4$[38] in refluxing hexane, gave the 1-(allyloxy)-2-[1-(phenyl)vinyl]benzenes (**15**) in good yield (Table 2, rows 6 and 7, 75 and 64% yield of **15j** and **15k**, respectively). The final step, ring-closing metathesis with **GII** in refluxing dichloromethane, gave the desired neoflav-3-enes (**16**) in 67% to quantitative yield (Table 2).

Whereas a phloroglucinol-type A-ring had a negative impact on the Grubbs second generation (**GII**) catalyst-promoted ring-closing metathesis reactions of 2-allylphenyl 1-(phenyl)vinyl ethers (**5**) to form flav-2-enes (**6**) (Scheme 1),[33] the corresponding neoflav-3-ene (**16g**) was formed in quantitative yield from the 1-(allyloxy)-2-[1-(phenyl)vinyl]benzene derivative, **15g** (Table 2, row 3). Yields of above 90% were obtained for the ring-closing metathesis reactions of substrates with no, one or two alkoxy substituents (Table 2, rows 1 – 3; also refer to

Scheme 2 and Wang et. al[36]), but decreased with the introduction of additional alkoxy substituents (Table 2, rows 5-7). No correlation could, however, be observed between the yields and the NMR chemical shifts, and thus the electronic properties, of the vinyl or allyl moieties of the 1-(allyloxy)-2-[1-(phenyl)vinyl]benzene substrates (**15**) or products (**16**). This suggests that other factors, such as sterics and/or pi-stacking with the catalyst mesitylene rings, have to play the determining role in the efficiency of the ring-closing metathesis step.

Table 2. The preparation of neoflav-3-enes (**16**) via the Grignard reaction of 2-allyloxy-acetophenones (**20**) with arylmagnesium bromides (**21**) and dehydration to give the 1,1-diarylethan-1-ols (**19**) and 1-(allyloxy)-2-[1-(phenyl)vinyl]benzenes (**15**), or **15** directly in one pot, followed by ring-closing metathesis

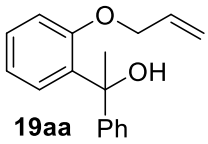
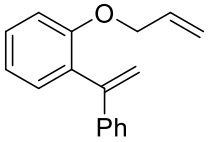
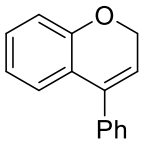
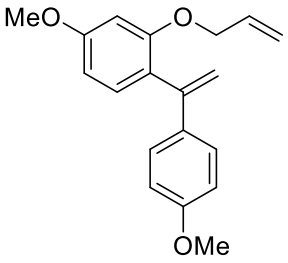
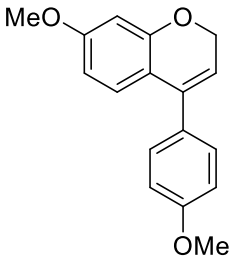
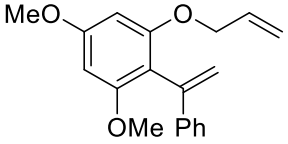
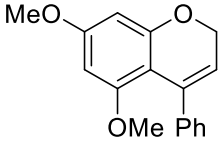
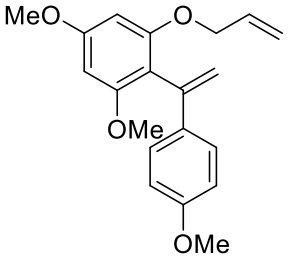
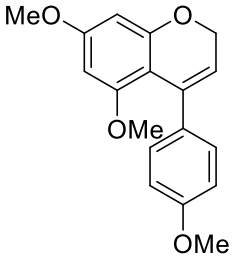
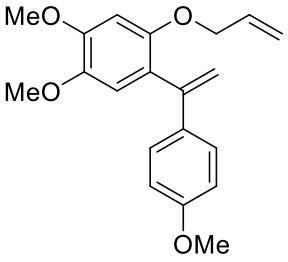
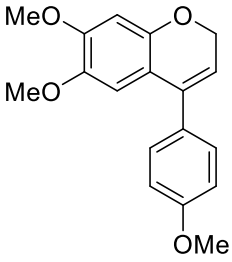
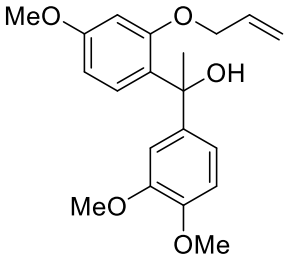
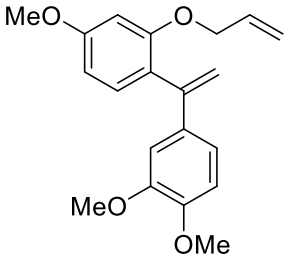
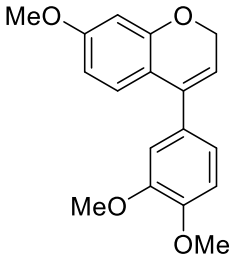
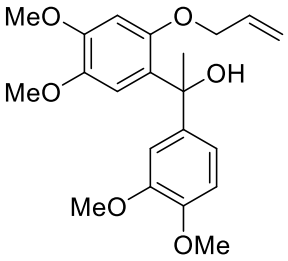
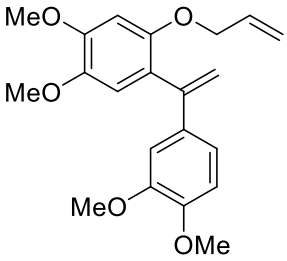
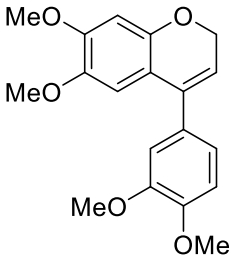
	20	**21**	**19**, Yield (%)	**15**, Yield (%)	**16**, Yield (%)
1	**20a**	**21a**	 **19aa** 44[a]	 **15a** -	 **16a** 93
2	**20b**	**21b**	-	 **15f** 66	 **16f** 95
3	**20c**	**21a**	-	 **15g** 94	 **16g** >99
4	**20c**	**21b**	-	 **15h** 65	 **16h** 73
5	**20d**	**21b**	-	 **15i** 52	 **16i** 79

Table 2. Continued

	20	**21**	**19**, Yield (%)	**15**, Yield (%)	**16**, Yield (%)
6	**20b**	**21c**			
			19j 50, 32,[a] 0,[b] 60[c]	**15j** 75[d]	**16j** 67
7	**20d**	**21c**			
			19k 4, 80[c]	**15k** 64[d]	**16k** 72

Reaction conditions for the one-pot preparation of **15**, or **19** and then **15**: **20**, $Al(OTf)_3$, THF, -30 °C, 30 min., then **21**, -30 °C – rt; [a]rt, without $Al(OTf)_3$; [b]-60 °C; [c]-60 °C, without $Al(OTf)_3$,[d]**19**, $CuSO_4$, hexanes, reflux; Reaction conditions for the preparation of **16**: **15**, **GII** (5 mol %), CH_2Cl_2, reflux

Conclusions

A series of neoflav-3-enes (**16**) with natural substitution patterns could be prepared from 1-(allyloxy)-2-[1-(phenyl)vinyl]benzenes (**15**) by means of ring-closing metathesis with Grubbs second generation catalyst in good to excellent yields. The 1-(allyloxy)-2-[1-(phenyl)vinyl]benzene substrates (**15**) were accessible from the corresponding 2-(allyloxy)acetophenones (**20**) *via* a Grignard reaction and Lewis acid-promoted dehydration, either in one pot in the presence of $Al(OTf)_3$ or in consecutive steps with $CuSO_4$ as dehydrating agents.

This study, in conjunction with a recent paper on flav-2-enes (**6**),[33] demonstrate the preparation of neoflavonoid (**3**) and flavonoid (**1**) representatives with natural substitution patterns from readily available starting materials by ring-closing metathesis as common methodology.

Experimental Section

General. NMR-spectroscopy was performed on a Bruker AM 600 FT-spectrometer at 20 °C (unless specified to the contrary) with either $CDCl_3$ (deuterochloroform) or $(CD_3)_2CO$ (deuterated acetone) as solvent. Chemical shifts are reported in parts per million (ppm) with the solvent peak at 7.26 ppm for $CDCl_3$ or 2.06 ppm for $(CD_3)_2CO$ in ^1H, and 77.16 ppm for $CDCl_3$ or 206.26 ppm for $(CD_3)_2CO$ in ^{13}C NMR experiments. 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. Alternatively, MS was performed with a Matrix Assisted Laser Desorption Ionization Time-Of-Flight (MALDI-TOF) Bruker Microflex LRF20 in either the positive or negative mode with the minimum laser power required to observe signals. High resolution MS (EI-MS, 70 eV) was performed by PMBMS, University of KwaZulu-Natal. Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP3) apparatus and are uncorrected. Microwave reactions were carried out in a CEM Discover® SP microwave reactor utilising the dynamic irradiation program (fixed temperature, variable power) with continuous cooling and the power set to a maximum of 200 W.

Williamson ether synthesis[39]

K_2CO_3 (2.0 eq.) was added to a solution of the phenol (1.0 eq.) in dry CH_3CN (100 mL per 50 mmol substrate) under an Ar atmosphere. Allyl bromide (2.0 eq.) was added slowly while the mixture was heated to reflux. Once the reaction was deemed complete, the reaction mixtures were allowed to cool to rt, the K_2CO_3 filtered off and the solvent and excess allyl bromide removed *in vacuo.* The pure products were obtained *via* PLC.

2'-Allyloxyacetophenone (**20a**).[40] 2'-Hydroxyacetophenone (**22a**) (0.4 mL, 4 mmol), K_2CO_3 (1.13 g, 8.14 mmol, 2. eq.) and allyl bromide (0.6 mL, 7 mmol, 1.8 eq.) yielded 2'-allyloxyacetophenone (**20a**) as a yellow oil (0.62 g, 96%); R_f: 0.37 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.65 (1H, dd, *J* 7.8, 1.9 Hz, H-6'), 7.48 (1H, ddd, *J* 8.4, 8.3, 1.9 Hz, H-4'), 7.13 (1H, br. d, *J* 8.4 Hz, H-3'), 7.01 (1H, ddd, *J* 8.3, 7.8, 1.0 Hz, H-5'), 6.15 (1H, ddt, *J* 17.3, 10.6, 5.4 Hz, H-2''), 5.47 (1H, ddt, *J* 17.3, 1.5, 1.5 Hz, H-3''b), 5.30 (1H, ddt, *J* 10.6, 1.5, 1.5 Hz, H-3''a), 4.72 (2H, ddd, *J* 5.4, 1.5, 1.5 Hz, H-1''), 2.57 (3H, s, -C$\underline{H_3}$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 199.2 (C-1), 158.8 (C-2'), 134.3 (C-4'), 134.2 (C-2''), 130.7 (C-6'), 129.7 (C-1'), 121.5 (C-5'), 118.3 (C-3''), 114.2 (C-3'), 70.2 (C-1''), 32.1 (-$\underline{C}H_3$); *m/z* (EI) 176 (M^+, 7%).

2'-Allyloxy-4'-methoxyacetophenone (**20b**).[41] 2'-Hydroxy-4'-methoxyacetophenone (**22b**) (1.07 g, 5.20 mmol), K_2CO_3 (1.89 g, 13.7 mmol, 2.6 eq.) and allyl bromide (1.1 mL, 13 mmol, 2.4 eq.) yielded 2'-allyloxy-4'-methoxyacetophenone (**20b**) as a light yellow solid (1.27 g, 96%); R_f: 0.36 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.74 (1H, d, *J* 8.7 Hz, H-6'), 6.65 (1H, d, *J* 2.3 Hz, H-3'), 6.60 (1H, dd, *J* 8.7, 2.3 Hz, H-5'), 6.18 (1H, ddt, *J* 17.3, 10.7, 5.4 Hz, H-2''), 5.50 (1H, ddt, *J* 17.3, 1.5, 1.5 Hz, H-3''b), 5.33 (1H, ddt, *J* 10.7, 1.5, 1.5 Hz, H-3''a), 4.75 (2H, ddd, *J* 5.4, 1.5, 1.5 Hz, H-1''), 3.87 (3H, s, -O$\underline{Me}$), 2.53 (3H, s, -C$\underline{H_3}$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 196.7 (C-1), 165.5 (C-4'), 161.1 (C-2'), 134.3 (C-2''), 133.0 (C-6'), 122.1 (C-1'), 118.4 (C-3''), 106.9 (C-5'), 100.1 (C-3'), 70.3 (C-1''), 56.1 (-O$\underline{Me}$), 32.3 (-$\underline{C}H_3$); *m/z* (EI) 206 (M^+, 34%).

2'-Allyloxy-4',6'-dimethoxyacetophenone (**20c**).[42] 2'-Hydroxy-4',6'-dimethoxyacetophenone (**22c**) (0.69 g, 3.5 mmol), K_2CO_3 (1.38 g, 9.99 mmol, 2.9 eq.) and allyl bromide (0.7 mL, 8 mmol, 2 eq.) yielded 2'-allyloxy-4',6'-dimethoxyacetophenone (**20c**) as a yellow oil (0.61 g, 74%); R_f: 0.22 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 6.26 (2H, s, H-3' and H-5'), 6.03 (1H, ddt, *J* 17.3, 10.6, 5.0 Hz, H-2''), 5.40 (1H, ddt, *J* 17.3, 1.7, 1,7 Hz, H-3''b), 5.23 (1H, ddt, *J* 10.6, 1.7, 1.7 Hz, H-3''a), 4.59 (2H, ddd, *J* 5.0, 1.7, 1.7 Hz, H-1''), 3.83 (3H, s, -O$\underline{Me}$), 3.79 (3H, s, -O$\underline{Me}$), 2.36 (3H, s, -C$\underline{H_3}$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 200.3 (C-1), 163.1 (C-4'/6'), 158.9 (C-4'/6'), 157.7 (C-2'), 134.4 (C-2''), 117.4 (C-3''), 115.1 (C-1'), 92.8 (C-3'/5'), 91.9 (C-3'/5'), 69.9 (C-1''), 56.2 (-O$\underline{Me}$), 55.9 (-O$\underline{Me}$), 32.6 (-$\underline{C}H_3$); *m/z* (EI) 236 (M^+, 22%).

2'-Allyloxy-4',5'-dimethoxyacetophenone (20d). 2'-Hydroxy-4',5'-dimethoxyacetophenone (**22d**) (0.82 g, 3.5 mmol), K_2CO_3 (1.72 g, 12.4 mmol, 3.4 eq.) and allyl bromide (1.0 mL, 12 mmol, 3.3 eq.) yielded 2'-allyloxy-4',5'-dimethoxyacetophenone (**20d**) as *light yellow needles* (0.97 g, quantitative yield); R_f: 0.28 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.34 (1H, s, H-3'/6'), 6.80 (1H, s, H-3'/6'), 6.18 (1H, ddt, *J* 17.3, 10.6, 5.5 Hz, H-2''), 5.49 (1H, ddt, *J* 17.3, 1.5, 1.5 Hz, H-3''b), 5.32 (1H, ddt, *J* 10.6, 1.5, 1.5 Hz, H-3''a), 4.76 (2H, ddd, *J* 5.5, 1.5, 1.5 Hz, H-1''), 3.91 (3H, s, -O$\underline{Me}$), 3.79 (3H, s, -O$\underline{Me}$), 2.54 (3H, s, -C$\underline{H_3}$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 196.3

(C-1), 155.6 (4°-C), 155.4 (4°-C), 144.4 (C-4'/5'), 134.6 (C-2''), 120.2 (C-1'), 118.3 (C-3''), 113.6 (C-3'/6'), 99.6 (C-3'/6'), 71.2 (C-1''), 56.5 (-OMe), 56.4 (-OMe), 32.5 (-CH_3); *m/z* (EI) 236 (M^+, 46%).[43]

Allyloxy phenylvinyl benzene synthesis *via* the Wittig reaction

A suspension of MTPPB (1.5 eq.) and *t*-BuOK (1.5 eq.) in anhydrous THF (10.0 mL) under argon was cooled to 0 °C and stirred for 15 minutes. 2-Allyloxybenzophenone (1.0 eq.) was added to this mixture which was gradually warmed to rt. After completion of the reaction (TLC), a saturated solution of aq. NH_4Cl (60.0 mL) was added and the product extracted into Et_2O (3 x 60.0 mL), dried over Na_2SO_4, the solvent removed *in vacuo* and the pure product obtained *via* PLC purification.

1-(Allyloxy)-2-(1-phenylvinyl)benzene (**15a**).[36] 2-Allyloxybenzophenone (**14a**) (0.51 g, 2.6 mmol), MTPPB (1.13 g, 3.16 g, 1.2 eq.) and *t*-BuOK (0.36 g, 3.2 mmol, 1.3 eq.) yielded 1-(allyloxy)-2-(1-phenylvinyl)benzene (**15a**) as a yellow oil (0.48 g, 96%): R_f: 0.56 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.36 – 7.32 (1H, m, H-5), 7.31 – 7.28 (4H, m, H-2', 6', 3' and 5'), 7.28 – 7.23 (2H, m, H-3 and H-4'), 7.03 – 7.00 (2H, m, H-4 and H-6), 5.70 (1H, d, *J* 1.5 Hz, H-β), 5.67 (1H, ddt, *J* 7.3, 10.6, 4.8 Hz, H-2''), 5.28 (1H, d, *J* 1.5 Hz, H-β), 5.03 (1H, ddt, *J* 17.3, 1.8, 1.8 Hz, H-3''b), 4.98 (1H, ddt, *J* 10.6, 1.8, 1.8 Hz, H-3''a), 4.39 (2H, ddd, *J* 4.8, 1.8, 1.8 Hz, H-1''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 157.0 (C-1), 148.8 (C-α), 142.4 (C-1'), 134.3 (C-2''), 132.2 (C-2), 131.9 (C-3), 130.1 (C-4'), 128.9 (C-2' and C-6'), 128.1 (C-5), 127.2 (C-3' and C-5'), 121.6 (C-4), 116.4 (C-3''), 115.5 (C-β), 113.6 (C-6), 69.3 (C-1''); *m/z* (EI) 236 (M^+, 3%).

Allyloxy phenylvinyl benzene synthesis *via* an Al(OTf)$_3$ enhanced Grignard reaction[37]

A mixture of 2'-allyloxyacetophenone (1.0 eq.) and $Al(OTf)_3$ (1.0 eq.) in Et_2O (10.0 mL) was stirred at -30 °C for 30 min. under Ar where after the Grignard reagent in Et_2O (3.0 M, 2.0 eq.) was added. The temperature was allowed to increase to rt. while stirring continued. Once the reaction was deemed complete (TLC), the reaction was quenched with aq. NH_4Cl (50.0 mL) and the product extracted into EtOAc (3 x 60.0 mL). The organic layer was dried over Na_2SO_4, the solvent removed *in vacuo* and the product purified *via* PLC.

2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**15f**).[36] 2'-Allyloxy-4'-methoxyacetophenone (**20b**) (0.17 g, 0.82 mmol), $Al(OTf)_3$ (0.47 g, 0.99 mmol, 1.2 eq.) and 4-methoxyphenylmagnesium bromide (**21b**) (0.7 mL, 3.0 M, 2.6 eq.) yielded 2-(allyloxy)-4-methoxy-1-[1-(4-methoxy-phenyl)vinyl]benzene (**15f**) as a yellow oil (0.19 g, 66%): R_f: 0.49 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.22 (2H, d, *J* 8.8 Hz, H-2' and H-6'), 7.14 (1H, d, *J* 9.2 Hz, H-6), 6.85 (2H, d, *J* 8.8 Hz, H-3' and H-5'), 6.57 (1H, dd, *J* 9.2, 2.3 Hz, H-5), 6.57 (1H, d, *J* 2.3 Hz, H-3), 5.72 (1H, ddt, *J* 17.3, 10.7, 4.7 Hz, H-2''), 5.54 (1H, d, *J* 1.7 Hz, H-β), 5.12 (1H, d, *J* 1.7 Hz, H-β), 5.07 (1H, ddt, *J* 17.3, 1.9, 1.9 Hz, H-3''b), 5.01 (1H, ddt, *J* 10.7, 1.9, 1.9 Hz, H-3''a), 4.40 (1H, ddd, *J* 4.7, 1.9, 1.9 Hz, H-1''), 3.82 (3H, s, -OMe), 3.78 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.8 (C-4), 160.2 (C-4'), 158.0 (C-2), 147.9 (C-α), 135.2 (C-1'), 134.3 (C-2''), 132.4 (C-6), 128.4 (C-2' and C-6'), 125.0 (C-1), 116.5 (C-3''), 114.2 (C-3' and C-5'), 113.3 (C-β), 105.8 (C-3/5), 100.9 (C-3/5), 69.4 (C-1''), 55.7 (-OMe), 55.6 (-OMe); *m/z* (EI) 296 (M^+, 28%).

1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**15g**). 2'-Allyloxy-4',6'-dimethoxyacetophenone (**20c**) (0.22 g, 0.91 mmol), $Al(OTf)_3$ (0.88 g, 1.8 mmol, 2.0 eq.) and phenylmagnesium bromide (**21a**) (0.6 mL, 3.0 M, 2.0 eq.) yielded 1-(allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**15g**) as a *yellow oil* (0.25 g, 94%): R_f: 0.42 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.34 – 7.31 (2H, m, H-2' and H-6'), 7.27 – 7.23 (2H, m, H-3' and H-5'), 7.22 – 7.18 (1H, m, H-4'), 6.32 (1H, d, *J* 2.2 Hz, H-4/6), 6.30 (1H, d, *J* 2.2 Hz, H-4/6), 5.87 (1H, d, *J* 1.7 Hz, H-β), 5.81 (1H, ddt, *J* 17.3, 10.6, 4.7 Hz, H-2''), 5.22 (1H, ddt, *J* 17.3, 1.7, 1.7 Hz, H-3''b), 5.13 (1H, d, *J* 1.7 Hz, H-β), 5.06 (1H, ddt, *J* 10.6, 1.7, 1.7 Hz, H-3''a), 4.45 (2H, ddd, *J* 4.7, 1.7, 1.7 Hz, H-1''), 3.84 (3H, s, -OMe), 3.67 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.8 (C-3/5), 159.8 (C-3/5), 158.5 (C-1), 142.5 (C-1'), 142.4 (C-α), 134.6 (C-2''), 128.8 (C-3' and C-5'), 127.7 (C-4'), 126.7 (C-2' and C-6'), 116.5 (C-3'' and C-β), 113.3 (C-2), 93.0 (C-4/6), 92.0 (C-4/6), 69.6 (C-1''), 56.1 (-OMe), 55.7 (-OMe); *m/z* (EI) 296 (M^+, 26%); HR-MS (ES) *m/z* 319.1307 $[M + Na]^+$, $C_{19}H_{20}O_3Na^+$ requires 319.1310, found 319.1307.

1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**15h**). 2'-Allyloxy-4',6'-dimethoxyacetophenone (**20c**) (0.21 g, 0.87 mmol), $Al(OTf)_3$ (0.42 g, 0.88 mmol, 1.0 eq.) and 4-methoxyphenylmagnesium bromide (**21b**) (1.0 mL, 3.0 M, 3.5 eq.) yielded 1-(allyloxy)-3,5-dimethoxy-2-[1-(4-methoxy-phenyl)vinyl]benzene (**15h**) as a *yellow oil* (0.18 g, 65%): R_f: 0.41 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.24 (2H, d, *J* 8.9 Hz, H-2' and H-6'), 6.81 (2H, d, *J* 8.9 Hz, H-3' and H-5'), 6.30 (1H, d, *J* 2.2 Hz, H-4/6), 6.29 (1H, d, *J* 2.2 Hz, H-4/6), 5.84 (1H, ddt, *J* 17.3, 10.6, 4.7 Hz, H-2''), 5.76 (1H, d, *J* 1.6 Hz, H-β), 5.23 (1H, ddt, *J* 17.3, 1.8, 1.8 Hz, H-3''b), 5.07 (1H, ddt, *J* 10.6, 1.8, 1.8 Hz, H-3''a), 4.98 (1H, d, *J* 1.6 Hz, H-β), 4.45 (2H, ddd, *J* 4.7, 1.8, 1.8 Hz, H-1''), 3.84 (3H, s, -OMe), 3.76 (3H, s, -OMe), 3.68 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.7 (C-3/5), 159.9 (C-3/5/4'), 159.7 (C-3/5/4'), 158.5 (C-1), 141.8 (C-α), 134.8 (C-1'), 134.7 (C-2''), 127.9 (C-2' and C-6'), 116.5 (C-3''), 114.4 (C-β), 114.1 (C-3' and C-5'), 113.6 (C-2), 93.0 (C-4/6), 92.1 (C-4/6), 69.6 (C-1''), 56.1 (-OMe), 55.7 (-OMe), 55.5 (-OMe); *m/z* (EI) 326 (M^+, 94%); HR-MS (ES) *m/z* 349.1416 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1416.

1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**15i**). 2'-Allyloxy-4',5'-dimethoxyacetophenone (**20d**) (0.21 g, 0.89 mmol), $Al(OTf)_3$ (0.41 g, 0.86 mmol, 1.0 eq.) and 4-methoxyphenylmagnesium bromide (**21b**) (2.0 mL, 3.0 M, 6.7 eq.) yielded 1-(allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**15i**) as a *yellow oil* (0.15 g, 52%): R_f: 0.30 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.24 (2H, d, *J* 8.8 Hz, H-2' and H-6'), 6.85 (2H, d, *J* 8.8 Hz, H-3' and H-5'), 6.82 (1H, s, H-3/6), 6.73 (1H, s, H-3/6), 5.70 (1H, ddt, *J* 17.2, 10.7, 5.0 Hz, H-2''), 5.55 (1H, d, *J* 1.6 Hz, H-β), 5.16 (1H, d, *J* 1.6 Hz, H-β), 5.08 (1H, ddt, *J* 17.2, 1.8, 1.8 Hz, H-3''b), 5.00 (1H, ddt, *J* 10.7, 1.8, 1.8 Hz, H-3''a), 4.36 (2H, ddd, *J* 5.0, 1.8, 1.8 Hz, H-1''), 3.85 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.77 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 160.2 (C-4'), 151.5 (C-4/5), 150.9 (C-1), 147.8 (C-α), 144.5 (C-4/5), 135.1 (C-1'), 134.9 (C-2''), 128.6 (C-2' and C-6'), 124.2 (C-2), 116.6 (C-3/6), 116.5 (C-3''), 114.2 (C-3' and C-5'), 113.6 (C-β), 101.5 (C-3/6), 70.8 (C-1''), 57.0 (-OMe), 56.4 (-OMe), 55.6 (-OMe); *m/z* (EI) 326 (M^+, 48%); HR-MS (ES) *m/z* 349.1418 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1418.

Synthesis of 1-[2-(allyloxy)phenyl]-1-phenylethan-1-ols *via* the Grignard reaction

A mixture of 2'-allyloxyacetophenone (1.0 eq.) and 3,4-dimethoxyphenylmagnesium bromide (0.5 M, 2.0 eq.) in THF (2.0 mL) was stirred at -60 °C for 3 hours where after the temperature was allowed to increase to rt. while stirring continued overnight. Once the reaction was deemed complete (TLC), the reaction was quenched with aq. NH_4Cl (50.0 mL) and the product extracted into EtOAc (3 x 60.0 mL). The organic layer was dried and the solvent removed under reduced pressure. The reaction mixture was purified *via* PLC.

1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19j**). 2'-Allyloxy-4'-methoxyacetophenone (**20b**) (0.11 g, 0.53 mmol) and 3,4-dimethoxyphenylmagnesium bromide (**21c**)[44] (2.0 mL, 0.5 M, 1.8 eq.) yielded 1-[2-(allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19j**) as a *yellow oil* (0.11 g, 60%): R_f: 0.19 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 59a): δ 7.48 (1H, d, *J* 8.4 Hz, H-6'), 7.03 (1H, d, *J* 2.1 Hz, H-2''), 6.79 (1H, d, *J* 8.4 Hz, H-5''), 6.75 (1H, dd, *J* 8.4, 2.1 Hz, H-6''), 6.56 (1H, dd, *J* 8.4, 2.5 Hz, H-5'), 6.55 (1H, d, *J* 2.5 Hz, H-3'), 5.76 (1H, ddt, *J* 17.3, 10.4, 5.1 Hz, H-2'''), 5.15 (1H, ddt, *J* 17.3, 1.5, 1.5 Hz, H-3'''b), 5.11 (1H, ddt, *J* 10.4, 1.5, 1.5 Hz, H-3'''a), 4.50 (1H, s, -OH), 4.44 (1H, ddd, *J* 13.0, 5.1, 1.5 Hz, H-1'''a), 4.35 (1H, ddd, *J* 13.0, 5.1, 1.5 Hz, H-1'''b), 3.79 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.73 (3H, s, -OMe), 1.80 (3H, s, -CH_3); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 59b): δ 161.0 (C-4'), 157.7 (C-2'), 149.6 (C-3''), 148.8 (C-4''), 143.8 (C-1''), 134.1 (C-2'''), 129.8 (C-1'), 128.2 (C-6'), 118.5 (C-6''), 117.5 (C-3'''), 112.0 (C-5''), 110.9 (C-2''), 105.2 (C-5'), 101.6 (C-3'), 75.7 (C-1), 69.8 (C-1'''), 56.1 (-OMe), 56.1 (-OMe), 55.6 (-OMe), 30.4 (-CH_3); HR-MS (ES) *m/z* 367.1520 $[M + Na]^+$, $C_{20}H_{24}O_5Na^+$ requires 367.1516, found 367.1520.

1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19k**). 2'-Allyloxy-4',5'-dimethoxyacetophenone (**20d**) (0.83 g, 0.35 mmol) and 3,4-dimethoxyphenylmagnesium bromide (**21c**) (2.0 mL, 0.5 M, 2.8 eq.) yielded 1-[2-(allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19k**) as a *yellow oil* (0.11

g, 80%): R_f: 0.14 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.03 (1H, d, *J* 2.0 Hz, H-2''), 6.98 (1H, s, H-6'), 6.71 (1H, d, *J* 8.4 Hz, H-5''), 6.66 (1H, dd, *J* 8.4, 2.0 Hz, H-6''), 6.52 (1H, s, H-3'), 5.68 – 5.61 (1H, m, H-2'''), 5.15 – 5.10 (2H, m, H-3'''a and H-3'''b), 4.57 (1H, s, -OH), 4.31 (1H, br. dd, *J* 12.5, 5.7 Hz, H-1'''a), 4.07 (1H, br. dd, *J* 12.5, 5.7 Hz, H-1'''b), 3.87 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.82 (3H, s, -OMe), 1.81 (3H, s, -CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ 150.5 (C-2'), 148.9 (C-4'/4''), 148.4 (C-3'), 147.5 (C-4'/4''), 143.0 (C-5'), 143.0 (C-1''), 132.9 (C-2'''), 128.2 (C-1'), 117.9 (C-3'''), 117.3 (C-6''), 111.7 (C-6'), 110.4 (C-5''), 108.7 (C-2''), 100.6 (C-3'), 75.9 (C-1), 70.8 (C-1'''), 57.0 (-OMe), 56.2 (-OMe), 55.97 (-OMe), 55.94 (-OMe), 30.4 (-CH_3); HR-MS (ES) *m/z* 397.1629 $[M + Na]^+$, $C_{21}H_{26}O_6Na^+$ requires 397.1627, found 397.1629.

Allyloxy phenylvinyl benzene synthesis *via* dehydration with $CuSO_4$

A mixture of the tertiary alcohol (1.0 eq.) and anhydrous $CuSO_4$ (4.0 eq.) was heated to reflux in dehydrated hexane overnight. After completion of the reaction, the mixture was washed with distilled H_2O (30.0 mL) and the product extracted into EtOAc (3 x 30.0 mL). The organic layer was dried and the solvent removed under reduced pressure. The reaction mixture was purified *via* PLC.

2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**15j**). 1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19j**) (0.11 g, 0.33 mmol), $CuSO_4$ (0.21 g, 1.3 mmol, 3.9 eq.) yielded 2-(allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**15j**) as a *yellow oil* (0.08 g, 75%): R_f : 0.30 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.15 (1H, d, *J* 8.7 Hz, H-6), 6.95 (1H, d, *J* 2.0 Hz, H-2'), 6.84 (1H, d, *J* 8.3 Hz, H-5'), 6.77 (1H, dd, *J* 8.3, 2.0 Hz, H-6'), 6.59 – 6.56 (2H, m, H-3 and H-5), 5.77 – 5.70 (1H, m, H-2''), 5.56 (1H, d, *J* 1.6 Hz, H-β), 5.14 (1H, d, *J* 1.6 Hz, H-β), 5.08 (1H, br. d, *J* 17.3, 1.7 Hz, H-3''b), 5.02 (1H, br. d, *J* 10.5, 1.7 Hz, H-3''a), 4.43 – 4.40 (2H, m, H-1''), 3.82 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.75 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.6 (C-4), 158.0 (C-2), 150.0 (C-3'/4'), 149.9 (C-3'/4'), 147.9 (C-α), 135.6 (C-1'), 134.3 (C-2''), 132.3 (C-6), 124.9 (C-1), 120.1 (C-6'), 116.4 (C-3''), 113.5 (C-β), 112.2 (C-5'), 111.4 (C-2'), 105.7 (C-5), 100.8 (C-3), 69.3 (C-1''), 56.08 (-OMe), 56.07 (-OMe), 55.6 (-OMe); HR-MS (ES) *m/z* 349.1418 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1418.

1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**15k**). 1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**19k**) (0.10 g, 0.27 mmol) and $CuSO_4$ (0.19 g, 1.2 mmol, 4.5 eq.) yielded 1-(allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**15k**) as a *yellow oil* (0.06 g, 64%): R_f: 0.26 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 6.96 (1H, d, *J* 2.1 Hz, H-2'), 6.86 (1H, d, *J* 8.4 Hz, H-5'), 6.81 (1H, s, H-3/6), 6.79 (1H, dd, *J* 8.4, 2.1 Hz, H-6'), 6.74 (1H, s, H-3/6), 5.72 (1H, ddt, *J* 17.3, 10.6, 4.9 Hz, H-2''), 5.58 (1H, d, *J* 1.6 Hz, H-β), 5.17 (1H, d, *J* 1.6 Hz, H-β), 5.09 (1H, ddt, *J* 17.3, 1.7, 1.7 Hz, H-3''b), 5.01 (1H, ddt, *J* 10.6, 1.7, 1.7 Hz, H-3''a), 4.38 (2H, ddd, *J* 4.9, 1.7, 1.7 Hz, H-1''), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.77 (3H, s, -OMe), 3.76 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 151.6 (4°-C), 150.9 (4°-C), 150.2 (4°-C), 150.0 (4°-C), 147.9 (C-α), 144.5 (C-4), 135.7 (C-1'), 135.0 (C-2''), 124.2 (C-2), 120.3 (C-6'), 116.6 (C-3/6), 116.5 (C-3''), 113.8 (C-β), 112.3 (C-5'), 111.7 (C-2'), 101.6 (C-3/6), 70.9 (C-1''), 57.0 (-OMe), 56.4 (-OMe), 56.2 (-OMe), 56.2 (-OMe); HR-MS (ES) *m/z* 379.1523 $[M + Na]^+$, $C_{21}H_{24}O_5Na^+$ requires 379.1521, found 379.1523.

Neoflavene synthesis *via* RCM

A solution of the allyloxy phenylvinyl benzene (**15**) (1.0 eq.) and Grubbs II catalyst (5 mol %) in dry DCM (10.0 ml) was heated to reflux and allowed to continue stirring overnight. After completion of the reaction, the solvent was removed under reduced pressure and the product purified *via* PLC.

Neoflav-3-ene (**16a**).[45] 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**15a**) (0.18 g, 0.72 mmol) yielded neoflav-3-ene (**16a**) as a yellow oil (0.14 g, 93%): R_f: 0.67 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.45 – 7.41 (2H, m, H-2' and H-6') , 7.40 – 7.37 (1H, m, H-4'), 7.36 – 7.33 (2H, m, H-3' and H-5'), 7.19 – 7.15 (1H, m, H-7), 6.97 (1H, dd, *J* 7.6, 1.6 Hz, H-5), 6.88 – 6.85 (2H, m, H-6 and H-8), 5.88 (1H, t, *J* 4.0 Hz, H-3), 4.82 (2H, d, *J* 4.0 Hz, H-2); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 156.0 (C-8a), 139.2 (C-1'), 137.7 (C-4), 130.2 (C-7), 129.5 (C-4'), 129.4 (C-

3' and C-5'), 128.8 (C-2' and C-6'), 126.5 (C-5), 124.5 (C-4a), 122.0 (C-3/6), 121.6 (C-3/6), 117.1 (C-8), 65.9 (C-2); *m/z* (EI) 207 ([M-H]$^+$, 100%).

4',7-Dimethoxyneoflav-3-ene (**16f**).[44] 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**15f**) (0.05 g, 0.2 mmol, 1.0 eq.) yielded 4',7-dimethoxyneoflav-3-ene (**16f**) as a beige oil (0.04 g, 95%): R_f: 0.38 (hexanes:A 7:3); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.27 (2H, d, *J* 8.8 Hz, H-2' and H-6'), 6.98 (2H, d, *J* 8.8 Hz, H-3' and H-5'), 6.93 (1H, d, *J* 8.0 Hz, H-5), 6.49 – 6.46 (2H, m, H-6 and H-8), 5.68 (1H, t, *J* 4.0 Hz, H-3), 4.78 (2H, d, *J* 4.0 Hz, H-2), 3.84 (-OMe), 3.79 (-OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.7 (C-7), 160.5 (C-4'), 157.4 (C-8a), 137.2 (C-4), 131.6 (C-1'), 130.5 (C-2' and C-6'), 127.4 (C-5), 117.9 (C-4a), 117.5 (C-3), 114.7 (C-3' and C-5'), 107.6 (C-6/8), 102.8 (C-6/8), 66.1 (C-2), 55.7 (-OMe), 55.7 (-OMe); *m/z* (EI) 268 (M$^+$, 100%).

5,7-Dimethoxyneoflav-3-ene (**16g**).[46] 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**15g**) (0.13 g, 0.43 mmol) yielded 5,7-dimethoxyneoflav-3-ene (**16g**) as a yellow oil (0.12 g, quantitative yield): R_f : 0.34 (hexanes:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.31 – 7.27 (2H, m, H-3' and H-5'), 7.27 – 7.23 (1H, m, H-4'), 7.19 – 7.17 (2H, m, H-2' and H-6'), 6.23 (1H, d, *J* 2.4 Hz, H-6/8), 6.19 (1H, d, *J* 2.4 Hz, H-6/8), 5.71 (1H, t, *J* 4.7 Hz, H-3), 4.57 (2H, d, *J* 4.7 Hz, H-2), 3.81 (-OMe), 3.41 (-OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 162.5 (C-7), 159.2 (C-8a), 158.6 (C-5), 142.0 (C-1'), 137.5 (C-4), 128.3 (Ar-C), 127.8 (Ar-C), 127.4 (C-4'), 118.7 (C-3), 107.5 (C-4a), 95.0 (C-6/8), 94.0 (C-6/8), 65.4 (C-2), 55.7 (-OMe), 55.5 (-OMe); *m/z* (EI) 268 (M$^+$, 100%); HR-MS (ES) *m/z* 291.0995 [M + Na]$^+$, $C_{17}H_{16}O_3Na^+$ requires 291.0997, found 291.0995.

4',5,7-Trimethoxyneoflav-3-ene (**16h**). 1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**15h**) (0.03 g, 0.1 mmol) yielded 4',5,7-trimethoxyneoflav-3-ene (**16h**) as an *orange oil* (0.02 g, 73%): R_f : 0.36 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.11 (2H, d, *J* 8.8, H-2' and H-6'), 6.86 (2H, d, *J* 8.8, H-3' and H-5'), 6.21 (1H, d, *J* 2.4 Hz, H-6), 6.19 (1H, d, *J* 2.4 Hz, H-8), 5.67 (1H, t, *J* 4.7 Hz, H-3), 4.54 (2H, d, *J* 4.7 Hz, H-2), 3.81 (3H, s, -OMe), 3.81 (3H, s, -OMe), 3.45 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 162.5 (C-7), 159.7 (C-5), 159.4 (C-4'), 158.8 (C-8a), 137.1 (C-4), 134.3 (C-1'), 128.9 (C-2' and C-6'), 117.6 (C-3), 113.7 (C-3' and C-5'), 107.6 (C-4a), 95.0 (C-6/8), 94.1 (C-6/8), 65.4 (C-2), 55.8 (-OMe), 55.6 (-OMe), 55.5 (-OMe); *m/z* (EI) 298 (M$^+$, 100%); HR-MS (ES) *m/z* 595.2320 [M$^+$]-dimer, $C_{36}H_{35}O_8^+$ requires 595.2332, found 595.2320.

4',6,7-Trimethoxyneoflav-3-ene (**16i**).[47] 1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**15i**) (0.07 g, 0.2 mmol) yielded 4',6,7-trimethoxyneoflav-3-ene (**16i**) as a yellow oil (0.05 g, 79%): R_f : 0.28 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.31 (2H, d, *J* 8.7 Hz, H-2' and H-6'), 7.00 (2H, d, *J* 8.7 Hz, H-3' and H-5'), 6.61 (1H, s, H-5), 6.56 (1H, s, H-8), 5.72 (1H, t, *J* 4.1 Hz, H-3), 4.72 (2H, d, *J* 4.1 Hz, H-2), 3.85 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.62 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 160.6 (C-4'), 151.5 (C-8a), 150.9 (C-7), 144.6 (C-6), 137.5 (C-4), 131.6 (C-1'), 130.5 (C-2' and C-6'), 117.5 (C-3), 116.6 (C-4a), 114.8 (C-3' and C-5'), 111.6 (C-5), 102.0 (C-8), 65.9 (C-2), 57.1 (-OMe), 56.2 (-OMe), 55.7 (-OMe); *m/z* (EI) 298 (M$^+$, 100%).

3',4',7-Trimethoxyneoflav-3-ene (**16j**). 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**15j**) (0.05 g, 0.2 mmol) yielded 3',4',7-trimethoxyneoflav-3-ene (**16j**) as a *yellow oil* (0.03 g, 67%): R_f : 0.33 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 6.99 (2H, d, *J* 8.3 Hz, H-5 and H-5'), 6.90 (1H, d, *J* 2.0 Hz, H-2'), 6.88 (1H, dd, *J* 8.3, 2.0 Hz, H-6'), 6.48 (1H, dd, *J* 8.3, 2.5 Hz, H-6), 6.46 (1H, d, *J* 2.5 Hz, H-8), 5.72 (1H, t, *J* 4.0 Hz, H-3), 4.78 (2H, d, *J* 4.0 Hz, H-2), 3.85 (3H, s, -OMe), 3.82 (3H, s, -OMe), 3.79 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 161.7 (C-7), 157.3 (C-8a), 150.2 (C-3' and C-4'), 137.4 (C-4), 132.0 (C-1'), 127.5 (C-5/5'), 121.6 (C-6'), 117.8 (C-4a), 117.5 (C-3), 113.1 (C-2'), 112.6 (C-5/5'), 107.6 (C-6'), 102.7 (C-8), 66.1 (C-2), 56.1 (-OMe), 56.1 (-OMe), 55.7 (-OMe); HR-MS (ES) *m/z* 321.1103 [M + Na]$^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1103.

3',4',6,7-Tetramethoxyneoflav-3-ene (**16k**). 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**15k**) (0.05 g, 0.1 mmol) yielded 3',4',6,7-tetramethoxyneoflav-3-ene (**16k**) as an *orange-brown oil* (0.03 g, 72% yield): R_f: 0.27 (hexanes:acetone 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 7.01 (1H, d, *J* = 8.7 Hz, H-5'), 6.94 – 6.91 (2H, m, H-2' and H-6'), 6.67 (1H, s, H-5), 6.57 (1H, s, H-8), 5.75 (1H, t, *J* 4.1 Hz, H-3), 4.72 (2H, d, *J* 4.1 Hz,

H-2), 3.85 (3H, s, -OMe), 3.83 (6H, s, -OMe), 3.64 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 151.3 (C-8a), 150.8 (C-7), 150.2 (C-3'/4'), 150.1 (C-3'/4'), 144.5 (C-6), 137.6 (C-4), 131.9 (C-1'), 121.6 (C-2'/6'), 117.5 (C-3), 116.4 (C-4a), 113.0 (C-2'/6'), 112.6 (C-5'), 111.3 (C-5), 101.9 (C-8), 65.8 (C-2), 56.9 (-OMe), 56.2 (-OMe), 56.1 (-OMe), 56.1 (-OMe); HR-MS (ES) *m/z* 351.1208 $[M + Na]^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1208.

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Supplementary Material

NMR spectra can be found online in the supplementary material.

References

1. Nabavia, S. M.; Šamecb, D.; Tomczykc, M.; Milellad, L.; Russod, D.; Habtemariame, S.; Suntarf, I.; Rastrellig, L.; Dagliah, M.; Xiaoi, J.; Giampierij, F.; Battinoj, M.; Sobarzo-Sanchezk, E.; Nabavim, S. F.; Yousefin, B.; Jeandeto, P.; Xup, S.; Shirooieq, S. *Biotechnol. Adv.* **2020**, *38*, 107316. https://doi.org/10.1016/j.biotechadv.2018.11.005
2. Gomes, M. N.; Muratov, E. N.; Pereira, M.; Peixoto, J. C.; Rosseto, L. P.; Cravo, P. V. L.; Andrade, C. H.; Neves, B. J. *Molecules* **2017**, *22*, 1210. https://doi.org/10.3390/molecules22081210
3. Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. *Chem Rev*. **2017**, *117* (12), 7762–7810. https://doi.org/10.1021/acs.chemrev.7b00020
4. Ollis, W. D.; Ormand, K. L.; Redman, B. T.; Roberts, R. J.; Sutherland, I. O. *J. Chem. Soc. C Org.* **1970**, *1*, 125. https://doi.org/10.1039/J39700000125
5. McKillop, A.; Swann, B. P.; Ford, M. E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95* (11), 3641–3645. https://doi.org/10.1021/ja00792a029
6. Nógrádi, M.; Szöllösy, Á. *Liebigs Ann.* **1996**, 305.
7. Thanigaimalai, P.; Yang, H.-M.; Sharma, V. K.; Kim, Y.; Jung, S.-H. *Bioorg. Med. Chem.* **2010**, *18* (12), 4441–4445. https://doi.org/10.1016/j.bmc.2010.04.075
8. Kawamura, Y.; Maruyama, M.; Tokuoka, T.; Tsukayama, M. *Synthesis* **2002**, *17*, 2490–2496. https://doi.org/10.1055/s-2002-35617
9. Van Rensburg, H.; Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1997**, *53* (41), 14141–14152. https://doi.org/10.1016/S0040-4020(97)00916-2
10. Bhrara, S. C.; Jain, A. C.; Seshadri, T. R. *Tetrahedron* **1964**, *20* (5), 1141–1149. https://doi.org/10.1016/S0040-4020(01)98981-1
11. Bhrara, S. C.; Jain, A. C.; Seshadri, T. R. *Tetrahedron* **1965**, *21* (5), 963–967. https://doi.org/10.1016/0040-4020(65)80034-5

12. Jung, J.-W.; Kim, N.-J.; Yun, H.; Han, Y. T. *Molecules* **2018**, *23*, 2417. https://doi.org/10.3390/molecules23102417
13. Donnelly, D. M. X.; Boland, G. In *The Flavonoids - Advances in Research Since 1986*; Harborne, J. B., Chapman and Hall Ltd.: London, 1994; pp 239–248.
14. Ollis, W. D.; Redman, B. T.; Roberts, R. J.; Sutherland, I. O.; Gottlieb, O. R. *Chem. Commun. (Londen)* **1968**, 1392–1393. https://doi.org/10.1039/C19680001392
15. Von Pechmann, H. *Chem. Ber.* **1884**, *17* (1), 929–936. https://doi.org/10.1002/cber.188401701248
16. Hwang, I.-T.; Lee, S.-A.; Hwang, J.-S.; Lee, K.-I. *Molecules* **2011**, *16* (8), 6313–6321. https://doi.org/10.3390/molecules16086313
17. Potdar, M. K.; Rasalkar, M. S.; Mohile, S. S.; Salunkhe, M. M. *J. Mol. Catal. Chem.* **2005**, *235* (1–2), 249–252. https://doi.org/10.1016/j.molcata.2005.04.007
18. Sato, K.; Amakasu, T. *J. Org. Chem.* **1968**, *33* (6), 2446–2450. https://doi.org/10.1021/jo01270a060
19. Das Gupta, A. K.; Paul, M. S. *J. Indian Chem. Soc.* **1970**, *47*, 1017–1018.
20. Ahluwalia, V. K.; Singh, D.; Singh, R. P. *Monatsh. Chem.* **1985**, *116* (6–7), 869–872. https://doi.org/10.1007/BF00809163
21. Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.* **2012**, *48* (24), 2985–2987. https://doi.org/10.1039/C2CC18150A
22. Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J.; Rea, M. D. *Synth. Commun.* **1999**, *29* (15), 2719–2730. https://doi.org/10.1080/00397919908086434
23. Garazd, M. M.; Garazd, Y. L.; Khilya, V. P. *Chem. Nat. Compd.* **2005**, *41* (3), 245–359. https://doi.org/10.1007/s10600-005-0126-7
24. Eguchi, T.; Hoshino, Y.; Ayame, A. *Bull. Chem. Soc. Jpn.* **2002**, *75* (3), 581–585. https://doi.org/10.1246/bcsj.75.581
25. Lei, J.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2004**, No. 13, 2364–2368. https://doi.org/10.1055/s-2004-832818
26. Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *Eur. J. Org. Chem.* **2010**, *2010* (20), 3945–3955. https://doi.org/10.1002/ejoc.201000134
27. Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. *Adv. Synth. Catal.* **2005**, *347* (2–3), 308–312. https://doi.org/10.1002/adsc.200404297
28. Sharma, D.; Reddy, C. B.; Shil, A. K.; Saroach, R. P.; Das, P. *Mol. Divers.* **2013**, *17* (4), 651–659. https://doi.org/10.1007/s11030-013-9461-y
29. Iwai, I.; Ide, J. *Chem. Pharm. Bull. (Tokyo)* **1963**, *11* (8), 1042–1049. https://doi.org/10.1248/cpb.11.1042
30. Allan, J.; Robinson, R. *J. Chem. Soc. Trans.* **1924**, *125* (0), 2192–2195. https://doi.org/10.1039/CT9242502192
31. Shao, Q.; Huang, Y. *Chem. Commun.* **2015**, *51* (30), 6584–6586. https://doi.org/10.1039/C5CC01407G
32. Arcadi, A.; Blesi, F.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Marinelli, F. *Org. Biomol. Chem.* **2012**, *10* (48), 9700–9708. https://doi.org/10.1039/C2OB26763B
33. Pieterse, T.; Marais, C.; Bezuidenhoudt, B. C. B. *Arkivoc* **2022**, 2022, 98-113.

https://doi.org/10.24820/ark.5550190.p011.733
34. Miller, B. J.; Pieterse, T.; Marais, C.; Bezuidenhoudt, B. C. B. *Tetrahedron Lett.* **2012**, *53* (35), 4708–4710. https://doi.org/10.1016/j.tetlet.2012.06.094
35. Li, S.-R.; Chen, L.-Y.; Tsai, J.-C.; Tzeng, J.-Y.; Tsai, I.-L.; Wang, E.-C. *Tetrahedron Lett.* **2007**, *48*, 2139 – 2141. https://doi.org/10.1016/j.tetlet.2007.01.117
36. Li, S.-R.; Chen, H.-M.; Chen, P.-Y.; Tsai, J.-C.; Chen, L.-Y.; Wang, E.-C.; Huang, Y.-T.; Wei, Y.-C.; Lu, P.-J. *J. Chin. Chem. Soc.* **2008**, *55* (4), 923–932. https://doi.org/10.1002/jccs.200800137
37. Pieterse, T.; Visser, M.; Marais, C.; Bezuidenhoudt, B. C. B. *Synlett* **2016**, *27*, 1541-1546. https://doi.org/10.1055/s-0035-1561401
38. Hoffman, R. V.; Bishop, R. D.; Fitch, P. M.; Hardenstein, R. *J. Org. Chem*. **1980**, *45*, 917 – 919. https://doi.org/10.1021/jo01293a030
39. Holmes, P.; White, D. E.; Wilson, I. H. *J. Chem. Soc. Resumed* **1950**, 2810. https://doi.org/10.1039/JR9500002810
40. Huang, K.-S.; Li, S.-R.; Wang, Y.-F.; Lin, Y.-L.; Chen, Y.-H.; Tsai, T.-W.; Yang, C.-H.; Wang, E.-C. *J. Chin. Chem. Soc.* **2005**, *52* (1), 159–167. https://doi.org/10.1002/jccs.200500025
41. Kato, E.; Kawabata, J. *Bioorg. Med. Chem. Lett.* **2010**, *20* (15), 4333–4336. https://doi.org/10.1016/j.bmcl.2010.06.077
42. Wootton, R. C. R. Ph.D Thesis, University of Salford, UK, 2000.
43. HR-MS analysis was not obtained for **20d**, but subsequent intermediates and products were fully characterized.
44. Sivaraman, B.; Aidhen, I. S. *Eur. J. Org. Chem.* **2010**, *2010* (26), 4991–5003. https://doi.org/10.1002/ejoc.201000532
45. Liu, G.; Lu, X. *Tetrahedron* **2008**, *64* (30–31), 7324–7330. https://doi.org/10.1016/j.tet.2008.05.056
46. Cai, X.; Pan, Y.; Wang, C.; Qian, G.; Rong, Z. *Tetrahedron Lett.* **2020**, *61*, 151993. https://doi.org/10.1016/j.tetlet.2020.151993
47. Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J.; Nesbitt, K. *Tetrahedron* **2001**, *57*, 413 – 423. https://doi.org/10.1016/S0040-4020(00)00955-8