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Ring-closing metathesis in flavonoid synthesis, part 1: flavenes

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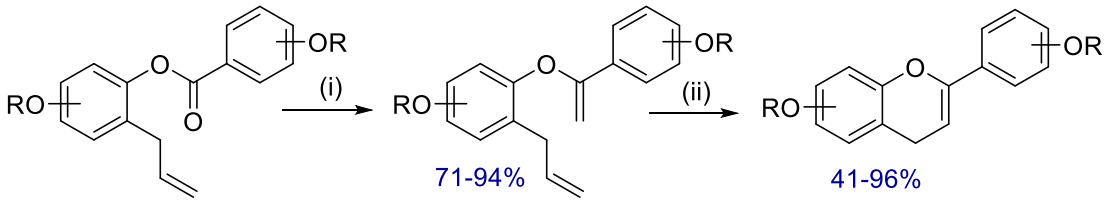
Abstract

Tebbe methylenation and ring-closing metathesis with Grubbs second generation catalyst were investigated as key steps in the synthesis of flav-2-enes with natural substitution patterns. The effect of aromatic substituents on the electron densities of the allyl and vinyl moieties and the effect thereof on methylenation and ring-closing metathesis, is discussed.



(i) $Cp_2TiCH_2ClAl(CH_3)_2$, (ii) $(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh$

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

Introduction

The flavonoid group is the most diverse group of secondary metabolites in plants. Based on two aryl rings linked by a 3-carbon chain, the basic flavonoid structure is commonly referred to as a C_6-C_3-C_6 skeleton. Though some flavonoids have an acyclic C_3 moiety, the vast majority of flavonoids are of the phenylchroman type. Depending on the position of the phenyl substituent (B-ring) on the heterocyclic ring (C-ring), the flavonoids are divided into three subclasses, *i.e.* the flavonoid subgroup **1** with a 2-phenyl substituent, and the isoflavonoids **2** and neoflavonoids **3** with this substituent at carbons 3 and 4, respectively.[1] Additional variety stem from the degree of unsaturation and oxidation of the heterocyclic ring, thus allowing for further sub-classification. A variety of substituents (*e.g.* hydroxy, methoxy, acetoxy and glycosyl) and substitution patterns contribute to further structural diversification and accompanying biological properties, *e.g.*, anti-cancer, anti-mutagenic, vasodilatory, anti-inflammatory, anti-allergenic, anti-microbial, anti-viral, neuroprotective, antioxidant, etc.[1]

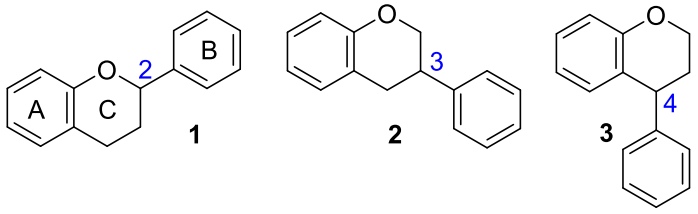
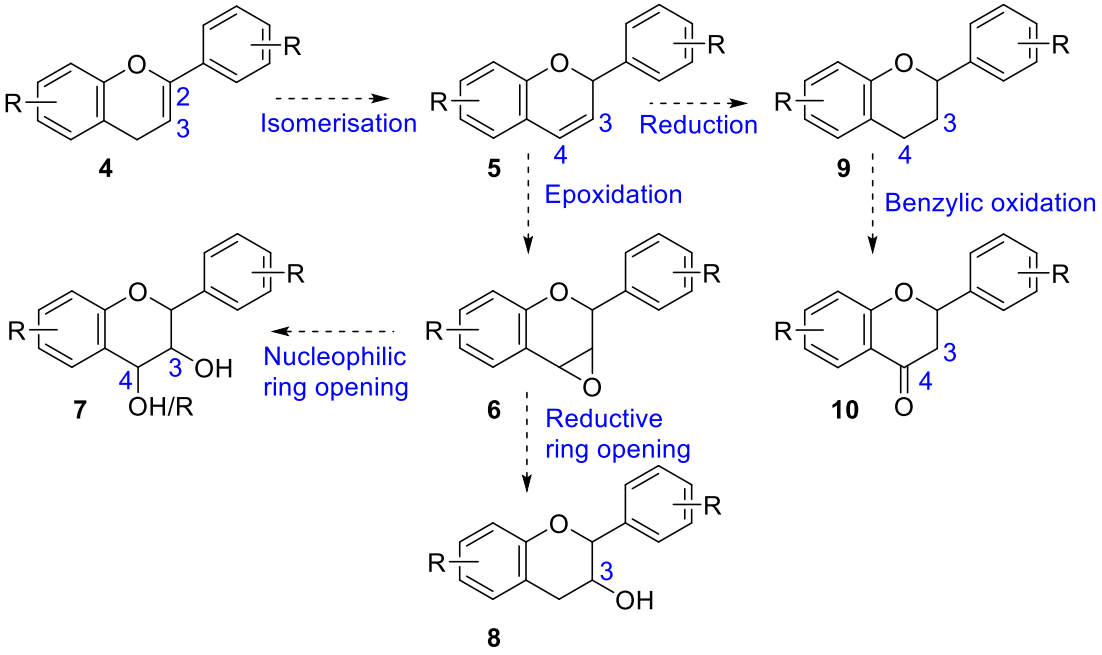


Chart 1. Basic skeletons of the flavonoid **1**, isoflavonoid **2** and neoflavonoid **3** subclasses.

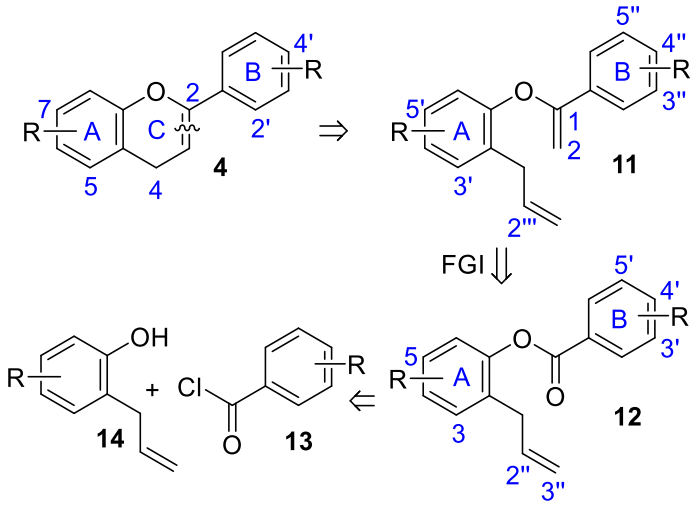
The flavonoid subgroup **1** is most commonly prepared via the chalcone (1,3-diaryl-2-propen-1-one) route. In this regard, the aldol condensation is the most prevalent, followed by Friedel-Crafts acylation, the Fries reaction, the Wittig reaction, Julia-Kocienski olefination or acid-catalysed condensation of benzaldehydes and phenylacetylenes. Catalytic methodologies exploited in the synthesis of flavonoids include the Suzuki-Miyaura, Heck and Sonogashira reactions.[2,3]

In alignment with modern catalytic methodologies in the synthesis of natural products, and as a continuation of our endeavours into the use of olefin metathesis as strategy for the formation of natural and other products,[4-6] we decided to investigate the possibility of applying ring closing metathesis to the preparation of flavonoids. Since this would imply unsaturation in the heterocyclic ring of the flavonoid unit, flav-2-enes **4**, which can then be advanced to the more stable flav-3-enes **5**[7-9] and/or other saturated and oxygenated analogues, were selected as target molecules to give entry into the series of flavonoid compounds (Scheme 1).



Scheme 1. Proposed flav-2-ene transformation into selected members of the flavonoid **1** subclass.

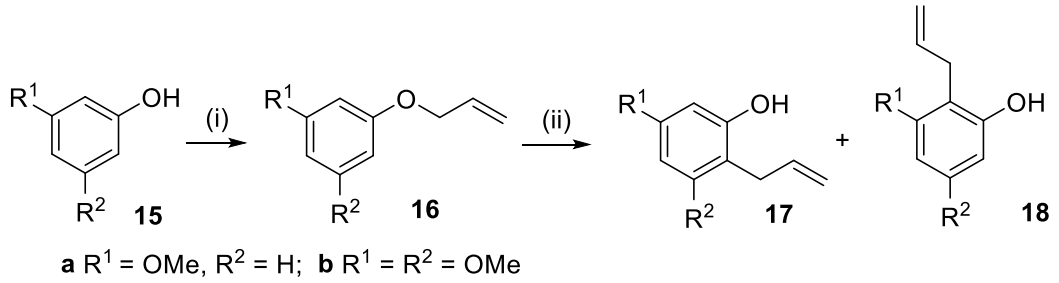
Herein, we disclose our results on the role of metathesis in the formation of flav-2-enes (2-phenyl-4*H*-chromenes) **4** with natural substitution patterns (Scheme 2). This investigation was inspired by the assembly of the benzochroman skeleton by the De Koning group[10] and is an extension of the application of ring-closing metathesis in the synthesis of the basic flavonoid and neoflavonoid skeletons previously reported by us.[4] The esterification of appropriately substituted 2-hydroxy allylbenzenes **14** with benzoyl chlorides **13** thus gave access to the 2-allylphenyl benzoates **12**, where after olefination and subsequent cross-metathesis gave various flav-2-enes **4** in good yield.



Scheme 2. Retrosynthetic approach to flav-2-enes (2-phenyl-4*H*-chromenes) **4** with natural substitution patterns. Note: *As the A- and B-rings of the flav-2-ene* ***4*** *originated from the allylbenzene* ***14*** *and benzoyl chloride* ***13****, respectively, the A/B ring labelling system was also applied to the intermediates*.

Results and Discussion

Though 2-hydroxy-allylbenzene (**17a**) is readily available, allylbenzenes **17** with substitution patterns typical to the A-ring of flavonoids, *i.e.* the so-called resorcinol (2,4-dioxygenation) and phloroglucinol (2,4,6-trioxygenation) substitution patterns, had to be prepared. This could be achieved by means of *O*-allylation of the relevantly substituted phenol via standard Williamson etherification (K_2CO_3, CH_3CN, reflux), followed by Claisen rearrangement (Scheme 3). Williamson etherification gave the desired *O*-allylated products, **16a**[11] and **16b**[12], in excellent yield (quantitative and 93%, respectively).



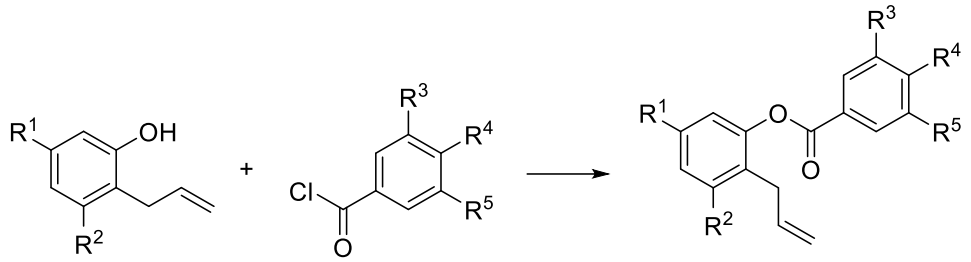
Scheme 3. (i) Allylbenzene, K_2CO_3, CH_3CN, reflux, (ii) 200 °C, 0 – 200 W, 3 × 15 min.

As an alternative to the Claisen rearrangement in high boiling solvents under conventional reflux (*ca* 8 h), microwave irradiation (200 W, 0–200 °C) allowed for a more environmentally friendly *O*-*C* rearrangement under neat conditions in only 45 minutes. The resorcinol-type *O*-allylbenzene rearranged to form the two *ortho C*-allyl isomers **17a**[11] and **18a**[11], respectively, in almost equal amounts (44% & 45%), whereas the phloroglucinol-type allylbenzene[13] **17b** was obtained in 88% yield.

With the appropriately substituted 2-hydroxy allylbenzenes **17** in hand, esterification of the unprotected hydroxy group with benzoyl chloride (**13a**), as well as analogues with 4-methoxy (**13b**), 3,4-dimethoxy (**13c**) and 3,4,5-trimethoxy (**13d**) substituents (corresponding to the common *p*-hydroxy-, catechol- and pyrogallol-type flavonoid B-rings), were accomplished in good yields (Table 1).

Tebbe methylenation was selected to convert the carbonyl into a terminal olefin.[14-16] As this step previously resulted in allyl methylation and selectivity could be improved by lowering the temperature,[4] the methylenation reaction on the first substrate **12aa** was initially performed at -40 °C. Although the desired 2-allylphenyl 1-(phenyl)vinyl ether (**11aa**) was obtained, the yield was low (9%) (Table 2, entry 1). The reaction mixture was subsequently allowed to warm up to room temperature from -40 °C, which led to a lower yield of only 5% (Table 2, entry 2). The reaction was therefore started at 0 °C, allowed to warm up to room temperature and eventually heated to reflux (66 °C) to give the desired product in 81% yield (Table 2, entry 3). With a high-yielding method in place, methylenation of the 2-allylphenyl benzoates **12** also gave access to 2-allylphenyl 1-(phenyl)vinyl ethers **11** with methoxy substituents on the 4- (**11ab**), 3,4- (**11ac**) and 3,4,5-positions (**11ad**) of the B-ring in combination with an unsubstituted A-ring (Table 2, entries 3-6), as well as derivatives that combine the 3,4- and 3,4,5-B-ring substitution with a resorcinol-type A-ring (5-substituted) (Table 2, entries 7 & 8). The method could unfortunately not be extended to the phloroglucinol-type A-ring compounds (Table 2, entries 9 & 10). Analogous methylenation options ($TiCp_2Cl_2$ with the Nysted reagent[17] and $TiCl_4$/Zn/$PbCl_2$ with CH_2Br_2[18]) also failed with these substrates (**12cc** & **12cd**).

Table 1. Benzoylation of 2-hydroxy allylbenzenes **17**



17a $R^1 = R^2 = H$
17b $R^1 = OMe$, $R^2 = H$
17c $R^1 = R^2 = OMe$

13a $R^3 = R^4 = R^5 = H$
13b $R^3 = R^5 = H$; $R^4 = OMe$
13c $R^3 = R^4 = OMe$, $R^5 = H$
13d $R^3 = R^4 = R^5 = OMe$

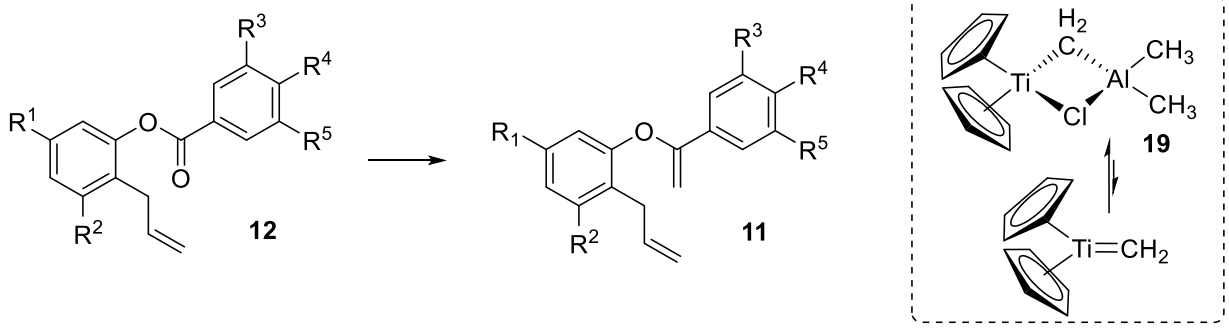
12aa $R^1 = R^2 = R^3 = R^4 = R^5 = H$
12ab $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$
12ac $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = OMe$
12ad $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = OMe$
12bc $R^1 = R^3 = R^4 = OMe$, $R^2 = R^5 = H$
12bd $R^1 = R^3 = R^4 = R^5 = OMe$, $R^2 = H$
12cc $R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = H$
12cd $R^1 = R^2 = R^3 = R^4 = R^5 = OMe$

Entry	Substrate	Substrate	Product	Yield (%)
1	**17a**	**13a**	**12aa**[4]	68[a]
2	**17a**	**13b**	**12ab**	74[a]
3	**17a**	**13c**	**12ac**	93
4	**17a**	**13d**	**12ad**	93
5	**17b**	**13c**	**12bc**	75
6	**17b**	**13d**	**12bd**	98
7	**17c**	**13c**	**12cc**	89
8	**17c**	**13d**	**12cd**	97

Reaction conditions: Pyridine, DMAP, DCM, reflux; [a] In these cases, acylation in pyridine/DMAP resulted in a gummy inseparable reaction mixture and *aq*. NaOH (2.0 M), rt was thus used.

As neither the B-ring nor the A-ring substitution patterns had a significant influence on the chemical shift of the carbonyl carbon (Table 3, δ_C 164.8–165.1) and thus the electronic properties of the carbonyl group, the failed methylenation of the phloroglucinol-type substrates, **12cc** and **12cd**, may be ascribed to the steric influence of the methoxy group *ortho* to the allyl group, most likely forcing the latter into a conformation that restricts interaction of the carbonyl with the Tebbe reagent. Oxygenation of the A-ring in the positions *para* and o*rtho* to the allyl group furthermore shielded the allylic H-2'' [Table 3, δ 5.94, 5.91 and 5.83 for 2-allylphenyl 3,4-dimethoxybenzoates **12ac**, **12bc** and **12cc** (line 6) and δ 5.96, 5.91 and 5.85 for 2-allylphenyl 3,4,5-trimethoxybenzoates **12ad**, **bd** and **cd** (line 8) with unsubstituted, 5-methoxy and 3,5-dimethoxy substituted A-rings, respectively], thus reflecting an increase in the electron density of the allyl double bond. A repelling interaction between the electron clouds of the Tebbe cyclopentadienyl rings and the electron-rich phloroglucinol-type allylbenzene **12** may also inhibit interaction between the titanium carbene and the carbonyl group.

Table 2. Tebbe methylenation of 2-allylphenyl benzoates **12**



aa $R^1 = R^2 = R^3 = R^4 = R^5 = H$
ab $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$
ac $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = OMe$
ad $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = OMe$

bc $R^1 = R^3 = R^4 = OMe$, $R^2 = R^5 = H$
bd $R^1 = R^3 = R^4 = R^5 = OMe$, $R^2 = H$
cc $R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = H$
cd $R^1 = R^2 = R^3 = R^4 = R^5 = OMe$

Entry	Substrate	Product	Yield (%)
1	**12aa**	**11aa**	9[a]
2	**12aa**	**11aa**	5[b]
3	**12aa**	**11aa**	81
4	**12ab**	**11ab**	71
5	**12ac**	**11ac**	94
6	**12ad**	**11ad**	85
7	**12bc**	**11bc**	87
8	**12bd**	**11bd**	75
9	**12cc**	**11cc**	0
10	**12cd**	**11cd**	0

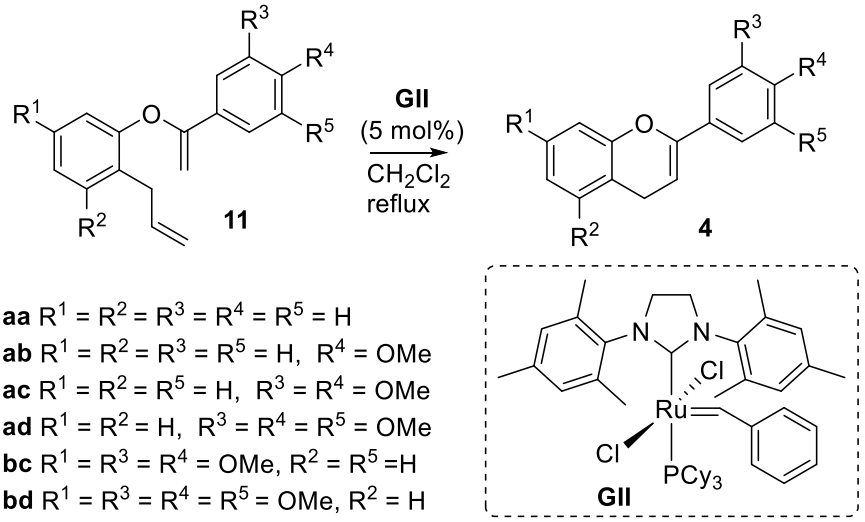
Reaction conditions: Substrate (400 mg), Tebbe reagent (0.5 M, 1.2–2.7 equiv.), THF (2 mL), 0 °C, 30 min, rt, 1 h, reflux, 2 h; [a] Tebbe reagent (2.0 equiv.), THF, -40 °C, 5 h; [b] Tebbe reagent (2.0 equiv.), THF, -40 °C, 4 h, rt, 6 h.

Table 3. ^{13}C and ^{1}H NMR chemical shifts (δ) of the carbonyl and allyl resonances of 2-allylphenyl benzoates **12** with resorcinol- and phloroglucinol-type A-rings in combination with catechol- and pyrogallol-type B-rings [600 MHz, $(CD_3)_2CO$] at 20 °C in relation to the yield of methylenation products **11**

	OMe		-		**11** Yield (%)	5-OMe		**11** Yield (%)	3,5-diOMe		**11** Yield (%)
1	-	CO	**12aa**	165.1	81						
2		H-2''		5.96							
3	4'	CO	**12ab**	164.8	71						
4		H-2''		5.95							
5	3',4'	CO	**12ac**	165.1	94	**12bc**	165.0	87	**12cc**	164.9	0
6		H-2''		5.94			5.91			5.83	
7	3',4',5'	CO	**12ad**	165.0	85	**12bd**	164.9	75	**12cd**	164.8	0
8		H-2''		5.96			5.91			5.85	

In the final step, ring-closing metathesis of the 2-allylphenyl 1-(phenyl)vinyl ethers **11**, catalysed by the Grubbs second generation catalyst (**GII**) in dichloromethane heated at reflux, gave the desired flav-2-enes **4** in acceptable to excellent yields (Table 4, 41–96%). The introduction of a 5-methoxy group to the A-ring resulted in a marked decrease in the efficiency of the metathesis reaction (Table 4, entry 3 vs 5 & entry 4 vs 6).

Table 4. Ring-closing metathesis of 2-allylphenyl 1-(phenyl)vinyl ethers (**11**)



aa $R^1 = R^2 = R^3 = R^4 = R^5 = H$
ab $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$
ac $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = OMe$
ad $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = OMe$
bc $R^1 = R^3 = R^4 = OMe$, $R^2 = R^5 = H$
bd $R^1 = R^3 = R^4 = R^5 = OMe$, $R^2 = H$

Entry	Substrate	Product	Yield (%)
1	**11aa**	**4aa**	92
2	**11ab**	**4ab**	87
3	**11ac**	**4ac**	96
4	**11ad**	**4ad**	96
5	**11bc**	**4bc**	76
6	**11bd**	**4bd**	41

When the vinyl methylene resonances of unsubstituted **11aa** and 4''-methoxy substituted 2-allylphenyl 1-(phenyl)vinyl ether **11ab** are compared, it is evident that the vinyl methylene carbon (C-2) of **11ab** is shielded (Table 5, lines 1 & 4: δ_C 89.2 vs 88.2 for **11aa** & **11ab**, respectively). The introduction of 3''- and 5''-methoxy substituents on the B-ring resulted in the deshielding of C-2 (Table 5, lines 4, 7 and 10: δ_C 88.2, 88.5 and 89.5 for **11ab**, **11ac** and **11ad**, respectively), thus reflecting the negative inductive effects of the 3''- and 5''-methoxy groups. A similar trend was observed for the analogous 2-allyl-5-methoxyphenyl 1-(phenyl)vinyl ethers **11bc** and **11bd**, with the vinyl methylene carbon of the 3'',4'',5''-trimethoxy derivative being deshielded with respect to that of the 3'',4''-dimethoxy analogue (Table 5, lines 7 & 10: δ_C 89.2 & 90.2 for **11bc** and **11bd**, respectively). This trend was emphasized by the shielding of the $=CH_2$ protons (H-2) of the *para* methoxy substituted 2-allylphenyl 1-(phenyl)vinyl ether **11ab** compared to those of the unsubstituted equivalent (Table 5, lines 2 & 5: δ_H 4.92, 4.16 vs 4.91, 4.03 for **11aa** & **11ab**, respectively) and the progressive deshielding thereof with the introduction of *meta* methoxy groups (Table 5, lines 5, 8 & 11: δ_H 4.91, 4.03; 4.95, 4.05; 5.02, 4.11 for **11ab**, **11ac** & **11ad**, respectively). The tendency was once again reciprocated with the variation of the B-ring substitution pattern of the 2-allylphenyl 1-(phenyl)vinyl ethers with the resorcinol-type A-ring, **11bc** and **11bd** (Table 5, lines 8 & 11: δ_H 4.97, 4.14; 5.04, 4.18 for **11bc** & **11bd**, respectively). The effect of substitution of the A-ring on the vinyl electron density was furthermore evident from the deshielding of the methylene

protons when a methoxy group was introduced to the 5' position (Table 5, line 7 & 10: 88.5 vs 89.2 for **11ac** & **11bc**; 89.5 and 90.2 for **11ad** & **11bd**, respectively), thus bearing evidence of the deactivating effect of a methoxy group *meta* to the vinyl ether moiety.

The yields obtained for the ring-closing metathesis products **4** proved to be related to the chemical shift of the vinyl methylene carbon and thus the electron density thereof. In the case of analogues with an unsubstituted A-ring, a decrease in yield was observed with the introduction of an activating *para* methoxy group into the B-ring and a subsequent increase in yield with the introduction of deactivating *meta* methoxy groups. The introduction of a 5'-methoxy group to the A-ring also resulted in a deshielding of the $=CH_2$ group with an accompanying decrease in yield.

Table 5. ^{13}C and ^{1}H NMR chemical shifts (δ) of the vinyl and allyl resonances of 2-allylphenyl 1-(phenyl)vinyl ethers **11** with unsubstituted and resorcinol-type A-rings in combination with unsubstituted, *p*-methoxy, catechol- and pyrogallol-type B-rings [600 MHz, $(CD_3)_2CO$] at 20 °C in relation to the yield of the ring-closing metathesis products **4**

			11	δ	**4** Yield (%)	**11**	δ	**4** Yield (%)
	B-ring OMe / A-ring OMe		-			5'		
1	-	$=\underline{C}H_2$	**11aa**	89.2	92			
2		$=C\underline{H}_2$		4.92, 4.16				
3		H-2'''		6.00				
4	4''	$=\underline{C}H_2$	**11ab**	88.2	87			
5		$=C\underline{H}_2$		4.91, 4.03				
6		H-2'''		6.00				
7	3'',4''	$=\underline{C}H_2$	**11ac**	88.5	96	**11bc**	89.2	76
8		$=C\underline{H}_2$		4.95, 4.05			4.97, 4.14	
9		H-2'''		6.01			5.98	
10	3'',4'',5''	$=\underline{C}H_2$	**11ad**	89.5	96	**11bd**	90.2	41
11		$=C\underline{H}_2$		5.02, 4.11			5.04, 4.18	
12		H-2'''		6.02			5.99	

Conclusions

Various flav-2-enes **4** with natural substitution patterns were prepared via Tebbe methylenation and ring-closing metathesis with Grubbs second generation catalyst (**GII**). A distinctive trend between the electron density of the phenyl allyl moiety and the yield of the methylenation products was observed. This suggested increased repulsion between the electron clouds of this moiety and the cyclopentadienyl rings of the Tebbe reagent to the extent that a phloroglucinol A-ring was not tolerated. Ring-closing metathesis was influenced negatively by an activating *p*-methoxy group and positively by deactivating *m*-methoxy groups on the B-ring. An A-ring methoxy group *meta* to the vinyl ether moiety deshielded the vinyl methylene, but shielded the *para* allyl, cumulating into an overall deleterious impact on metathesis. With the viability of this catalytic approach towards flav-2-enes **4** being demonstrated, problems with the phloroglucinol A-ring may be addressed by using alternative olefination method and metathesis catalysts. With the flav-2-ene **4** in hand, isomerization,

epoxidation, reduction and benzylic oxidation may give access to the various members of the flavonoid **1** subclass. The application of metathesis as common methodology towards the synthesis of the other two flavonoid subclasses, *i.e.* the iso- (**2**) and neoflavonoids (**3**), will be reported on in subsequent papers.

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 NMR spectra, and 77.16 ppm for $CDCl_3$ or 206.26 ppm for $(CD_3)_2CO$ in ^{13}C NMR spectra. 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[12]

K_2CO_3 (2.0 equiv.) was added to a mixture of phenol (1.0 equiv.) in dry CH_3CN (100 mL per 50 mmol substrate) under an Ar atmosphere. Allyl bromide (2.0 equiv.) was added slowly while the mixture was heated to reflux. Once deemed complete (TLC), the reaction mixture was allowed to cool to room temperature and the K_2CO_3 filtered off. The solvent and excess allyl bromide were removed in vacuo. The product was purified via PLC.

1-Allyloxy-3-methoxybenzene (16a). 1-Hydroxy-3-methoxybenzene (**15a**) (4.4 mL, 41 mmol), K_2CO_3 (11.93 g, 86.3 mmol), allyl bromide (7.0 mL, 81 mmol) yielded 1-allyloxy-3-methoxybenzene (**16a**) as a bright orange oil (6.56 g, quantitative yield); R_f 0.60 (hexanes/acetone 60:40); ^1H NMR (600 MHz, $CDCl_3$): δ 7.20 (1H, dd, *J* 8.2, 8.2 Hz, H-5), 6.56–6.54 (2H, m, H-4 & H-6), 6.53 (1H, dd, *J* 2.3, 2.3 Hz, H-2), 6.08 (1H, ddt, *J* 17.2, 10.5, 5.3 Hz, H-2'), 5.44 (1H, ddt, *J* 17.2, 1.4, 1.4 Hz, H-3'b), 5.32 (1H, ddt, *J* 10.5, 1.4, 1.4 Hz, H-3'a), 4.55 (2H, ddd, *J* 5.3, 1.4, 1,4 Hz, H-1'), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.9 (C-1/3), 159.9 (C-1/3), 133.4 (C-2'), 130.0 (C-5), 117.8 (C-3'), 107.0 (C-4/6), 106.5 (C-4/6), 101.3 (C-2), 68.9 (C-1'), 55.3 (-OMe); *m/z* (EI) 164 (M^+, 100%). The physical data correspond to those previously reported.[11]

1-Allyloxy-3,5-dimethoxybenzene (16b). 1-Hydroxy-3,5-dimethoxybenzene (**15b**) (3.91 g, 25.4 mmol), K_2CO_3 (9.11 g, 65.9 mmol), allyl bromide (5.4 mL, 62.0 mmol) yielded 1-allyloxy-3,5-dimethoxybenzene (**16b**) as a yellow oil (4.56 g, 93%); R_f 0.54 (hexanes/acetone 70:30); ^1H NMR (600 MHz, $CDCl_3$): δ 6.11 (2H, d, *J* 2.10 Hz, H-2 & H-6), 6.10–6.09 (1H, m, H-4), 6.05 (1H, ddt, *J* 17.3, 10.4, 5.6 Hz, H-2'), 5.41 (1H, ddt, *J* 17.3, 1.4, 1.4 Hz, H-3'b), 5.29 (1H, ddt, *J* 10.4, 1.4, 1.4 Hz, H-3'a), 4.49 (2H, ddd, *J* 5.6, 1.4, 1.4 Hz, H-1'), 3.77 (6H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$): δ 161.6 (C-3 & C-5), 160.6 (C-1), 133.3 (C-2'), 117.9 (C-3'), 93.7 (C-2 & C-6), 93.2 (C-4), 69.0 (C-1'), 55.4 (-OMe); *m/z* (EI) 194 (M^+, 100%). The physical data correspond to those previously reported.[12]

Claisen rearrangement

1-Allyloxybenzene (**16**) was irradiated with 200 W microwaves at 200 °C for 3 sessions of 15 min. each (neat), cooling the sample between sessions. The product was purified *via* PLC. The physical data of **17a**, **18a** and **17b** corresponded to those previously reported.[11,13]

1-Allyl-2-hydroxy-4-methoxybenzene (17a) and 1-Allyl-2-hydoxy-6-methoxybenzene (18a). 1-Allyloxy-3-methoxybenzene (**16a**) (0.50 g, 3.1 mmol) yielded 1-allyl-2-hydroxy-4-methoxybenzene (**17a**) as a light yellow oil (0.12 g, 44%): R_f 0.54 (hexanes/EtOAc, 90:10); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.01 (1H, d, *J* 8.3 Hz, H-6), 6.47 (1H, dd, *J* 8.3, 2.5 Hz, H-5), 6.43 (1H, d, *J* 2.5 Hz, H-3), 6.01 (1H, ddt, *J* 16.9, 10.4, 6.4 Hz, H-2'), 5.23 (1H, s, -OH), 5.17–5.13 (1H, m, H-3'a & H-3'b), 3.76 (3H, s, -OMe), 3.36 (2H, br. d, *J* 6.4 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$): *δ* 159.7 (C-4), 155.1 (C-2), 136.9 (C-2'), 131.0 (C-6), 117.5 (C-1), 116.4 (C-3'), 106.4 (C-5), 102.1 (C-3), 55.4 (-OMe), 34.6 (C-1'); *m/z* (EI) 164 (M^+, 100%) and 1-allyl-2-hydoxy-6-methoxybenzene (**18a**) as a light yellow oil (0.17 g; 45%): R_f 0.60 (hexanes/EtOAc 90:10); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.08 (1H, dd, *J* 8.6, 8.1 Hz, H-4), 6.51–6.50 (2H, m, H-3 & H-5), 5.99 (1H, ddt, *J* 17.2, 10.1, 6.3 Hz, H-2'), 5.15 (1H, s, -OH), 5.13–5.07 (2H, m, H-3'a & H-3'b), 3.81 (3H, s, -OMe), 3.48 (2H, ddd, *J* 6.3, 1.6, 1.6 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$): *δ* 158.4 (C-6), 155.3 (C-2), 136.5 (C-2'), 127.7 (C-4), 115.3 (C-3'), 113.7 (C-1), 108.9 (C-3/5), 103.4 (C-3/5), 55.9 (-OMe), 27.5 (C-1'); *m/z* (EI) 164 (M^+, 100%). The physical data correspond to those previously reported.

1-Allyl-2-hydroxy-4,6-dimethoxybenzene (17b). 1-Allyloxy-3,5-dimethoxybenzene (**16b**) (0.11 g, 0.57 mmol) yielded 1-allyl-2-hydroxy-4,6-dimethoxybenzene (**17b**) as a red-brown amorphous solid (0.1 g, 88%); R_f 0.31 (hexanes/EtOAc 90:10); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 6.11 (1H, d, *J* 2.4 Hz, H-3/5), 6.08 (1H, d, *J* 2.4 Hz, H-3/5), 5.96 (1H, ddt, *J* 17.3, 10.9, 5.9 Hz, H-2'), 5.25 (1H, s, -OH), 5.13–5.07 (2H, m, H-3'a & H-3'b), 3.78 (3H, s, -OMe), 3.76 (3H, s, -OMe), 3.39 (2H, ddd, *J* 5.9, 1.7, 1.7 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$): *δ* 159.9 (4°-C), 158.7 (4°-C), 155.9 (4°-C), 136.9 (C-2'), 115.4 (C-3'), 105.8 (C-1), 93.9 (C-3/5), 91.7 (C-3/5), 55.9 (-OMe), 55.3 (-OMe), 27.1 (C-1'); *m/z* (EI) 194 (M^+, 100%). The physical data correspond to those previously reported.

Benzoate synthesis in aqueous medium[19]

1-Allyl-2-hydroxybenzene (**17**) (1.0 equiv.) was dissolved in aq. NaOH (2.0 M, 40 mL). Benzoyl chloride (**13**) (2.0 equiv.) was added and the reaction mixture allowed to stir until the exothermic heat generation had ceased and the reaction mixture had cooled to rt. After completion of the reaction, the product was extracted into EtOAc (3 × 60 mL) and the solvent removed *in vacuo*.

2-Allylphenyl 4-methoxybenzoate (18ab). 1-Allyl-2-hydroxybenzene (**17a**) (0.5 mL, 4.0 mmol), 4-methoxybenzoyl chloride (**13b**) (1.3 mL, 9.6 mmol) yielded 2-allylphenyl 4-methoxybenzoate (**12ab**) as a colorless oil (0.74 g, 74%): R*f* 0.34 (hexanes/EtOAc 90:10); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 8.19 (2H, d, *J* 9.3 Hz, H-2' & H-6'), 7.32–7.29 (2H, m, Ar-H), 7.25–7.22 (1H, m, Ar-H), 7.20–7.18 (1H, m, Ar-H), 7.01 (2H, d, *J* 9.3 Hz, H-3' & H-5'), 5.95 (1H, ddt, *J* 16.8, 10.2, 6.6 Hz, H-2''), 5.07–5.02 (2H, m, H-3''), 3.90 (3H, s, -OMe), 3.38 (2H, br. d, *J* 6.6 Hz, H-1''); ^{13}C NMR (151 MHz, $CDCl_3$): *δ* 164.8 (C=O), 164.0 (C-4'), 149.3 (C-1), 136.0 (C-2''), 132.3 (C-2' & C-6'), 132.3 (C-2), 130.4 (Ar-C), 127.8 (Ar-C), 126.2 (Ar-C), 122.7 (Ar-C), 121.9 (C-1'), 116.3 (C-3''), 114.0 (C-3' & C-5'), 55.6 (-OMe), 34.8 (C-1''); HRMS(ES) *m/z* 291.1003 $[M + Na]^+$, $C_{17}H_{16}O_3Na^+$ requires 291.0992, found 291.1003.

Benzoate synthesis in anhydrous medium[20]

1-Allyl-2-hydroxybenzene (**17**) (1.0 equiv.), DMAP (0.2 equiv.) and dry pyridine (1.0 equiv.) were dissolved in dry DCM (15 mL) under Ar atmosphere. Benzoyl chloride (**7**) (2.0 equiv.) was added and the reaction mixture refluxed overnight. After completion of the reaction, the product was extracted into EtOAc (3 × 60 mL) and the solvent removed in *vacuo*. The product was purified *via* PLC.

2-Allylphenyl 3,4-dimethoxybenzoate (12ac). 1-Allyl-2-hydroxybenzene (**17a**) (0.5 mL, 3.8 mmol), DMAP (0.09 g, 0.7 mmol), pyridine (0.2 mL, 2.0 mmol), 3,4-dimethoxybenzoyl chloride (**13c**) (0.92 g, 4.6 mmol) yielded 2-allylphenyl 3,4-dimethoxybenzoate (**12ac**) as colorless needles (1.03 g, 93%): R*f* 0.20 (hexanes/EtOAc 90:10);

mp 92.0–93.2 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.85 (1H, dd, *J* 8.4, 2.1 Hz, H-6'), 7.68 (1H, d, *J* 2.1 Hz, H-2'), 7.36-7.30 (2H, m, Ar-H), 7.25 (1H, td, *J* 7.5, 1.3 Hz, Ar-H), 7.22 (1H, dd, *J* 8.1, 1.2 Hz, Ar-H), 7.12 (1H, d, *J* 8.4 Hz, H-5'), 5.94 (1H, ddt, *J* 16.8, 10.1, 6.6 Hz, H-2''), 5.06-4.98 (2H, m, H-3''), 3.92 (3H, s, -OMe), 3.90 (3H, s, -OMe), 3.37 (2H, br. d, *J* 6.6 Hz, H-1''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 165.1 (C=O), 155.1 (C-4'), 150.5 (C-1), 150.2 (C-3'), 137.1 (C-2''), 133.2 (C-2), 131.2 (Ar-C), 128.3 (Ar-C), 126.9 (Ar-C), 125.0 (C-6'), 123.8 (Ar-C), 122.5 (C-1'), 116.5 (C-3''), 113.3 (C-2'), 111.9 (C-5'), 56.3 (-OMe), 56.3 (-OMe), 35.4 (C-1''); HRMS(ES) *m/z* 321.1107 [M + Na]$^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1107.

2-Allylphenyl 3,4,5-trimethoxybenzoate (12ad). 1-Allyl-2-hydroxybenzene (**17a**) (0.5 mL, 4.0 mmol), DMAP (0.06 g, 0.5 mmol), pyridine (0.2 mL, 2.0 mmol), 3,4,5-trimethoxybenzoyl chloride (**13d**) (1.08 g, 4.7 mmol) yielded 2-allylphenyl 3,4,5-trimethoxybenzoate (**12ad**) as colorless needles (1.11 g, 93%): R*f* 0.21 (hexanes/EtOAc 90:10); mp 61.9–63.2 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.50 (2H, s, H-2' & H-6'), 7.37–7.33 (2H, m, Ar-H), 7.29–7.26 (1H, m, Ar-H), 7.25–7.23 (1H, m, Ar-H), 5.96 (1H, ddt, *J* 16.7, 10.1, 6.6 Hz, H-2''), 5.04–5.03 (2H, m, H-3''), 3.94 (6H, s, -OMe), 3.86 (3H, s, -OMe), 3.39 (2H, br. d, *J* 6.6 Hz, H-1''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 165.0 (C=O), 154.4 (C-3' & C-5'), 150.4 (C-1), 144.1 (C-4'), 137.1 (C-2''), 133.2 (C-2), 131.3 (Ar-C), 128.4 (Ar-C), 127.1 (Ar-C), 125.3 (C-1'), 123.66 (Ar-C), 116.49 (C-3''), 108.26 (C-2' & C-6'), 60.80 (-OMe), 56.69 (-OMe), 35.4 (C-1''); HRMS(ES) *m/z* 351.1200 [M + Na]$^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1200.

2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (12bc). 1-Allyl-2-hydroxy-4-methoxybenzene (**17b**) (0.44 g, 2.7 mmol), DMAP (0.10 g, 0.80 mmol), pyridine (0.2 mL, 2.0 mmol), 3,4-dimethoxybenzoyl chloride (**13c**) (0.76 g, 3.8 mmol) yielded 2-allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**12bc**) as colorless needles (0.66 g, 75%): R*f* 0.14 (hexanes/EtOAc 90:10). mp 96.3–97.2 °C. ^{1}H NMR [600 MHz, $(CD_3)_2CO$]; *δ*7.83 (1H, dd, *J* 8.5, 2.0 Hz, H-6'), 7.66 (1H, d, *J* 2.0 Hz, H-2'), 7.21 (1H, d, *J* 9.1 Hz, H-3), 7.11 (1H, d, *J* 8.5 Hz, H-5'), 6.85–6.82 (2H, m, H-4 & H-6), 5.91 (1H, ddt, *J* 17.0, 10.1, 6.6 Hz, H-2''), 5.01–4.95 (2H, m, H-3''), 3.93 (3H, s, 4'-OMe), 3.90 (3H, s, 3'-OMe), 3.80 (3H, s, 5-OMe), 3.28 (2H, br. d, *J* 6.6 Hz, H-1''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 165.0 (C=O), 160.0 (C-5), 155.0 (C-4'), 151.0 (C-1), 150.1 (C-3'), 137.5 (C-2''), 131.5 (C-3), 125.0 (C-2/6'), 124. 9 (C-2/6'), 122.5 (C-1'), 116.0 (C-3''), 113.3 (C-2'), 112.6 (C-4/6), 111.9 (C-5'), 109.4 (C-4/6), 56.3 (-OMe), 56.2 (-OMe), 55.8 (-OMe), 34.7 (C-1''); HRMS(ES) *m/z* 351.1206 [M + Na]$^+$,$C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1206.

2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (12bd). 1-Allyl-2-hydroxy-4-methoxybenzene (**17b**) (0.70 g, 1.8 mmol), DMAP (0.25 g, 2.1 mmol), pyridine (0.4 mL, 5.0 mmol), 3,4,5-trimethoxybenzoyl chloride (**13d**) (1.56 g, 6.76 mmol) yielded 2-allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**12bd**) as a colorless solid (1.48 g, 98%): R*f* 0.31 (hexanes/EtOAc 90:10); mp 93.5–94.2 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.47 (2H, s, H-2' & H-6'), 7.22 (1H, d, *J* 8.9 Hz, H-3), 6.86–6.83 (2H, m, H-4 & H-6) 5.91 (1H, ddt, *J* 16.7, 10.1, 6.5 Hz, H-2''), 5.03–4.97 (2H, m, H-3''), 3.92 (6H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.28 (2H, br. d, *J* 6.5 Hz, H-1''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 164.9 (C=O), 160.1 (C-5), 154.4 (C-3' & C-5'), 151.0 (C-1), 144.1 (C-4'), 137.6 (C-2''), 131.6 (C-3), 125.3 (C-2/1'), 124.9 (C-2/1'), 116.1 (C-3''), 112.8 (C-4/6),109.4 (C-4/6), 108.3 (C-2' & C-6'), 60.8 (-OMe), 56.7 (2× -OMe), 55.9 (-OMe), 34.8 (C-1''); HRMS(ES) *m/z* 381.1322 [M + Na]$^+$, $C_{20}H_{22}O_6Na^+$ requires 381.1309, found 381.1322.

2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (12cc). 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**17c**) (0.50 g, 1.4 mmol), DMAP (0.09 g, 0.7 mmol) and dry pyridine (0.2 mL, 2.0 mmol), 3,4-dimethoxybenzoyl chloride (**13c**) (0.67 g, 3.3 mmol) yielded 2-allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**12cc**) as pale yellow crystals (0.91 g, 89%): R*f* 0.11 (hexanes/EtOAc 90:10); mp 109.2–110.2 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.81 (1H, dd, *J* 8.4, 2.0 Hz, H-6'), 7.64 (1H, d, *J* 2.0 Hz, H-2'), 7.12 (1H, d, *J* 8.4 Hz, H-5'), 6.50 (1H, d, *J* 2.4 Hz, H-4/6), 6.44 (1H, d, *J* 2.4 Hz, H-4/6), 5.83 (1H, ddt, *J* 16.4, 10.0, 6.3 Hz, H-2''), 4.90–4.83 (2H, m, H-3''), 3.93 (3H, s, -OMe), 3.90 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.25 (2H, br. d, *J* 6.3 Hz, H-1''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 164.9 (C=O), 160.2 (4°-C), 159.8 (4°-C), 155.0 (4°-C), 151.6 (4°-C), 150.1 (4°-C),

137.2 (C-2''), 124.9 (C-6'), 122.5 (4°-C), 114.8 (C-3''), 113.8 (4°-C), 113.2 (C-2'), 111.8 (C-5'), 100.9 (C-4/6), 97.0 (C-4/6), 56.2 (2× -OMe), 56.2 (-OMe), 55.8 (-OMe), 28.5 (C-1''); HRMS(ES) *m/z* 381.1310 [M + Na]$^+$, $C_{20}H_{22}O_6Na^+$ requires 381.1314, found 381.1310.

2-Allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (12cd). 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**17c**) (0.37 g, 1.9 mmol), DMAP (0.07 g, 0.6 mmol), pyridine (0.2 mL, 2.0 mmol), 3,4,5-trimethoxybenzoyl chloride (**13d**) (0.89 g, 3.9 mmol) yielded 2-allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**12cd**) as a colorless solis (0.66 g, 97%): R*f* 0.25 (hexanes/EtOAc 90:10); mp 87.2–88.9 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.46 (2H, s, H-2' & H-6'), 6.51 (1H, d, *J* 2.4 Hz, H-4/6), 6.47 (1H, d, *J* 2.4 Hz, H-4/6), 5.85 (1H, ddt, *J* 16.3, 10.1, 6.2 Hz, H-2''), 4.93–4.87 (2H, m, H-3''), 3.91 (6H, s, -OMe), 3.86 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.27 (2H, br. d, *J* 6.2 Hz, H-1''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 164.8 (C=O), 160.3 (4°-C), 159.8 (4°-C), 154.3 (C-3' & C-5'), 151.6 (4°-C), 144.0 (C-4'), 137.2 (C-2''), 125.3 (4°-C), 115.0 (C-3''), 113.8 (4°-C), 108.1 (C-2' & C-6'), 100.8 (C-4/6), 97.1 (C-4/6), 60.8 (-OMe), 56.6 (-OMe), 56.3 (-OMe), 55.9 (-OMe), 28.6 (C-1''); HRMS(ES) *m/z* 411.1410 [M+ Na]$^+$,$C_{21}H_{24}O_7Na^+$ requires 411.1420, found 411.1410.

Vinyl ether synthesis

2-Allylphenyl benzoate (**12**) (1.0 equiv.) in THF (1–2 mL) was cooled to 0 °C and Tebbe reagent (**13**) (0.5 M, 2.0 equiv.) added. The mixture was allowed to stir at 0 °C for 30 min. where after it was allowed to reach rt and stirred for another hour. If the reaction did not run to completion at this stage, the reaction mixture was heated to 90 °C for an additional 2 hours. The reaction mixture was allowed to cool to rt and aq. NaOH (2.0 M, 1.0 mL) was added very slowly. Once the exothermic reaction subsided, the reaction mixture was dissolved in Et_2O (200 mL) and filtered through a column of activated basic Al_2O_3 (Sigma Aldrich Brockman I activated basic alumina, min. layer thickness: 0.11 mm, column length × width: 150 mm × 30 mm). The solvent was removed *in vacuo* and the crude reaction mixture purified *via* PLC.

2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (11ab).[21] 2-Allylphenyl 4-methoxybenzoate (**12ab**) (0.20 g, 0.77 mmol), Tebbe reagent (**19**) (3.0 mL, 1.5 mmol) yielded 2-allylphenyl 1-(4-methoxyphenyl)vinyl ether (**11ab**) as a yellow oil (0.14 g, 71%): R*f* 0.55 (hexanes/EtOAc 90:10); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.71 (2H, d, *J* 9.2 Hz, H-2'' & H-6''), 7.31 (1H, dd, *J* 7.6, 1.4 Hz, H-3'), 7.25 (1H, ddd, *J* 7.6, 7.6, 1.4 Hz, H-5'), 7.14 (1H, ddd, *J* 7.6, 7.6, 1.4 Hz, H-4'), 7.05 (1H, dd, *J* 7.6, 1.4 Hz, H-6'), 6.97 (2H, d, *J* 9.2 Hz, H-3'' & H-5''), 6.00 (1H, ddt, *J* 17.0, 10.1, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05–5.01 (1H, m, H-3'''a), 4.91 (1H, d, *J* 2.5 Hz, H-2), 4.03 (1H, d, *J* 2.5 Hz, H-2), 3.83 (3H, s, -OMe), 3.40 (2H, br. d, *J* 6.7 Hz, H-1'''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 161.4 (C-4''), 160.4 (4°-C), 154.3 (4°-C), 137.7 (C-2'''), 132.8 (4°-C), 131.4 (C-3'), 128.6 (C-5'), 127.7 (C-2'' & C-6''), 127.3 (C-1''), 125.4 (C-4'), 121.7 (C-6'), 116.3 (C-3'''), 114.6 (C-3'' & C-5''), 88.2 (C-2), 55.7 (-OMe), 34.8 (C-1'''); MS (EI) *m/z* 266 (M$^+$, 2%).

2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (11ac). 2-Allylphenyl 3,4-dimethoxybenzoate (**12ac**) (0.21 g, 0.69 mmol), Tebbe reagent (2.0 mL, 1.0 mmol) yielded 2-allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**11ac**) as a yellow oil (0.19 g, 94%): R*f* 0.37 (hexanes/acetone 80:20); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.34–7.32 (2H, m, H-2'' & H-6''), 7.31 (1H, dd, *J* 7.4, 1.6 Hz, H-3'), 7.25 (1H, ddd, *J* 8.0, 7.6, 1.6 Hz, H-5'), 7.14 (1H, ddd, *J* 7.6, 7.4, 1.3 Hz, H-4'), 7.05 (1H, dd, *J* 8.0, 1.3 Hz, H-6'), 6.97 (1H, d, *J* 8.7 Hz, H-5''), 6.01 (1H, ddt, *J* 17.0, 10.0, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05–5.02 (1H, m, H-3'''a), 4.95 (1H, d, *J* 2.5 Hz, H-2), 4.05 (1H, d, *J* 2.5 Hz, H-2), 3.84 (6H, s, -OMe), 3.40 (2H, br. d, *J* 6.7 Hz, H-1'''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.4 (C-1), 154.3 (C-1'), 151.2 (C-3''/4''), 150.1 (C-3''/4''), 137.7 (C-2'''), 132.7 (C-2'), 131.4 (C-3'), 128.8 (C-1''), 128.5 (C-5'), 125.3 (C-4'), 121.6 (C-6'), 119.0 (C-2''/6''), 116.2 (C-3'''), 112.3 (C-5''), 110.0 (C-2''/6''), 88.5 (C-2), 56.1 (-OMe), 34.8 (C-1'''); HRMS(ES) *m/z* 321.1457 [M + Na]$^+$, $C_{19}H_{20}O_3Na^+$ requires 319.1467, found 319.1457.

2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (11ad). 2-Allylphenyl 3,4,5-trimethoxybenzoate (**12ad**) (0.233 g, 0.708 mmol), Tebbe reagent (2.0 mL, 1.0 mmol) yielded 2-allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl

ether (**11ad**) as a yellow oil (0.20 g, 85%): R*f* 0.29 (hexanes/EtOAc 90:10); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.31 (1H, dd, *J* 7.7, 1.8 Hz, H-3'), 7.26 (1H, ddd, *J* 8.1, 7.7, 1.8 Hz, H-5'), 7.15 (1H, ddd, *J* 7.7, 7.7, 1.2 Hz, H-4'), 7.08 (2H, s, H-2'' & H-6''), 7.06 (1H, dd, *J* 8.1, 1.2 Hz, H-6'), 6.02 (1H, ddt, *J* 17.0, 10.1, 6.7 Hz, H-2'''), 5.08 (1H, ddt, *J* 17.0, 1.8, 1.8 Hz, H-3'''b), 5.05 (1H, ddt, *J* 10.1, 1.8, 1.8 Hz, H-3'''a), 5.02 (1H, d, *J* 2.6 Hz, H-2), 4.11 (1H, d, *J* 2.6 Hz, H-2), 3.86 (6H, s, -OMe), 3.76 (3H, s, -OMe), 3.41 (1H, br. d, *J* 6.7 Hz, H-1'''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.3 (C-1), 154.3 (4°-C), 154.2 (4°-C), 140.1 (4°-C), 137.7 (C-2'''), 132.7 (4°-C), 131.5 (C-1''), 131.5 (C-3'), 128.6 (C-5'), 125.5 (C-4'), 121.7 (C-6'), 116.2 (C-3'''), 103.9 (C-2'' & C-6''), 89.5 (C-2), 60.6 (-OMe), 56.5 (2× -OMe), 34.9 (C-1'''); HRMS(ES) *m/z* 351.1568 $[M + Na]^+$, $C_{20}H_{24}O_4Na^+$ requires 351.1572, found 351.1568.

2-Allyl-5-methoxyphenyl-1-(3,4-dimethoxyphenyl)vinyl ether (11bc). 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**12bc**) (0.27 g, 0.81 mmol), Tebbe reagent (2.0 mL, 1.0 mmol) yielded 2-allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**11bc**) as a yellow oil (0.23 g, 87%): R*f* 0.21 (hexanes/EtOAc 90:10); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.33–7.31 (2H, m, H-2'' & H-6''), 7.19 (1H, d, *J* 8.5 Hz, H-3'), 6.96 (1H, d, *J* 9.0 Hz, H-5''), 6.72 (1H, dd, *J* 8.5, 2.6 Hz, H-4'), 6.62 (1H, d, *J* 2.6 Hz, H-6'), 5.98 (1H, ddt, *J* 16.7, 10.0, 6.6 Hz, H-2'''), 5.07–5.03 (1H, m, H-3'''b), 5.03–4.99 (1H, m, H-3'''a), 4.97 (1H, d, *J* 2.4 Hz, H-2), 4.14 (1H, d, *J* 2.4 Hz, H-2), 3.84 (6H, s, 2× -OMe), 3.75 (3H, s, -OMe), 3.33 (2H, br. d, *J* 6.6 Hz, H-1'''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.4 (4°-C), 160.2 (4°-C), 155.1 (4°-C), 151.4 (4°-C), 150.3 (4°-C), 138.3 (C-2'''), 131.9 (C-3'), 128.9 (4°-C), 124.5 (4°-C), 119.2 (C-2''/6''), 115.9 (C-3'''), 112.5 (C-5''), 110.8 (C-4'), 110.3 (C-2''/6''), 107.4 (C-6'), 89.2 (C-2), 56.3 (2× -OMe), 55.8 (-OMe), 34.3 (C-1'''); HRMS(ES) *m/z* 349.1427 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1427.

2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (11bd). 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**12bd**) (0.20 g, 0.56 mmol), Tebbe reagent (3.0 mL, 1.5 mmol) yielded 2-allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**11bd**) as a yellow oil (0.15 g, 75%): R*f* 0.22 (hexanes/EtOAc 90:10); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.20 (1H, d, *J* 8.5 Hz, H-3'), 7.06 (2H, s, H-2'' & H-6''), 6.74 (1H, dd, *J* 8.5, 2.6 Hz, H-4'), 6.63 (1H, d, *J* 2.6 Hz, H-6'), 5.99 (1H, ddt, *J* 16.7, 10.0, 6.6 Hz, H-2'''), 5.07–5.00 (2H, m, H-3'''), 5.04 (1H, d, *J* 2.6 Hz, H-2), 4.18 (1H, d, *J* 2.6 Hz, H-2), 3.86 (6H, s, 2× -OMe), 3.76 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.32 (2H, br. d, *J* 6.6 Hz, H-1'''); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.4 (4°-C), 160.1 (4°-C), 155.0 (4°-C), 154.4 (C-3'' & C-5''), 140.1 (4°-C), 138.2 (C-2'''), 132.0 (C-3'), 131.6 (4°-C), 124.4 (4°-C), 115.9 (C-3'''), 111.0 (C-4'), 107.4 (C-6'), 104.0 (C-2'' & C-6''), 90.2 (C-2), 60.7 (-OMe), 56.6 (-OMe), 55.8 (-OMe), 34.3 (C-1'''); HRMS(ES) *m/z* 379.1322 $[M + Na]^+$, $C_{20}H_{20}O_6Na^+$ requires 379.1314, found 379.1322.

Flav-2-ene (4) synthesis *via* RCM

A solution of 2-allylphenyl 1-(phenyl)vinyl ether (**11**) (1.0 equiv.) and Grubbs II catalyst (5 mol%) in dry DCM (5 mL) was heated to reflux and allowed to stir overnight under Ar. After completion of the reaction, the product was directly purified *via* PLC.

4'-Methoxyflav-2-ene (4ab). 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**11ab**) (0.04 g, 0.2 mmol) yielded 4'-methoxyflav-2-ene (**4ab**) as colorless needles (0.03 g, 87%): R*f* 0.49 (hexanes/EtOAc 90:10); mp 102.3–105.1 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.66 (2H, d, *J* 8.8 Hz, H-2' & H-6'), 7.25–7.17 (1H, m, H-7), 7.13–7.11 (1H, br. d, *J* 7.2 Hz, H-5), 7.04–7.00 (2H, m, H-6 & H-8), 6.96 (2H, d, *J* 8.8 Hz, H-3' & H-5'), 5.54 (1H, dd, *J* 3.9, 3.9 Hz, H-3), 3.82 (3H, s, -OMe), 3.55 (2H, br. d, *J* 3.9 Hz, H-4); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.9 (C-4'), 152.9 (C-8a), 149.5 (C-2), 130.0 (C-5), 128.4 (C-7), 127.9 (C-1'), 126.6 (C-2' & C-6'), 124.2 (C-6/8), 120.8 (C-4a), 117.3 (C-6/8), 114.6 (C-3' & C-5'), 95.5 (C-3), 55.7 (-OMe), 24.8 (C-4); HRMS(AP) *m/z* 239.1082 $[M + H]^+$, $C_{16}H_{15}O_2^+$ requires 239.1072, found 239.1082.

3',4'-Dimethoxyflav-2-ene (4ac). 2-Allyl-3-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**11ac**) (0.09 g, 0.3 mmol) yielded 3',4'-dimethoxyflav-2-ene (**4ac**) as a yellow oil (0.08 g, 96%): R*f* 0.20 (hexanes/EtOAc 90:10); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.30–7.28 (2H, m, H-2' & H-6'), 7.20–7.17 (1H, m, H-7), 7.12 (1H, br. d, *J* 8.0 Hz,

H-5), 7.05–7.03 (1H, m, H-6), 7.01 (1H, dd, *J* 7.5, 1.2 Hz, H-8), 6.97 (1H, d, *J* 8.9 Hz, H-5'), 5.57 (1H, dd, *J* 3.9, 3.9 Hz, H-3), 3.87 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.55 (2H, br. d, *J* 3.9 Hz, H-4); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 152.9 (C-8a), 150.9 (C-3'/4'), 150.3 (C-3'/4'), 149.7 (C-2), 130.0 (C-5), 128.5 (C-7), 128.3 (C-1'), 124.3 (C-8), 120.9 (C-4a), 118.1 (C-2'/6'), 117.4 (C-6), 112.5 (C-5'), 109.4 (C-2'/6'), 95.9 (C-3), 56.3 (-OMe), 56.2 (-OMe), 24.9 (C-4). Note: *Compound decomposed before HRMS analysis was possible*.

3',4',5'-Trimethoxyflav-2-ene (4ad). 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)-vinyl ether (**11ad**) (0.08 g, 0.3 mmol) yielded 3',4',5'-trimethoxyflav-2-ene (**4ad**) as a yellow oil (0.07 g, 96%): R*f* 0.20 (hexanes/EtOAc 90:10); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.21–7.18 (1H, m, H-7), 7.14–7.12 (1H, m, H-5), 7.06–7.02 (4H, m, H-6, H-8, H-2' & H-6'), 5.66 (1H, dd, *J* 3.9, 3.9 Hz, H-3), 3.88 (6H, s, 2× -OMe), 3.75 (3H, s, -OMe), 3.57 (2H, br. d, *J* 3.9 Hz, H-4); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 154.4 (C-3' & C-5'), 152.8 (C-8a), 149.6 (C-2), 139.7 (C-4'), 130.9 (C-1'), 130.0 (C-5), 128.5 (C-7), 124.4 (C-8), 120.8 (C-4a), 117.4 (C-6), 103.1 (C-2' & C-6'), 97.2 (C-3), 60.7 (-OMe), 56.6 (2× -OMe), 24.9 (C-4); HRMS(ES) *m/z* 321.1100 $[M + Na]^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1100.

3',4',7-Trimethoxyflav-2-ene (4bc). 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**11bc**) (0.11 g, 0.34 mmol) yielded 3',4',7-trimethoxyflav-2-ene (**4bc**) as an orange oil (0.08 g, 76%): R*f* 0.31 (hexanes/acetone 80:20); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.29–7.27 (2H, m, H-2' & H-6'), 7.03–7.01 (1H, m, H-5), 6.97 (1H, d, *J* 8.7 Hz, H-5'), 6.64–6.61 (2H, m, H-6 & H-8), 5.57 (1H, dd, *J* 3.9, 3.9 Hz, H-3), 3.86 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.48 (2H, br. d, *J* 3.9 Hz, H-4); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.4 (C-7), 153.5 (C-8a), 150.9 (C-4'), 150.3 (C-3'), 149.4 (C-2), 130.4 (C-5), 128.2 (C-1'), 118.0 (C-2'/6'), 112.5 (C-4a), 112.4 (C-5'), 110.8 (C-6/8), 109.4 (C-2'/6'), 102.4 (C-6/8), 96.2 (C-3), 56.3 (-OMe), 56.2 (-OMe), 55.8 (-OMe), 24.3 (C-4); HRMS(ES) *m/z* 321.1109 $[M + Na]^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1109.

3',4',5',7-Tetramethoxyflav-2-ene (4bd). 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxy-phenyl)vinyl ether (**11bd**) (0.09 g, 0.30 mmol) yielded 3',4',5',7-tetramethoxyflav-2-ene (**4bd**) as an orange amorphous solid (0.03 g, 41%): R*f* 0.30 (hexanes/acetone 80:20); ^{1}H NMR [600 MHz, $(CD_3)_2CO$]: *δ* 7.03 (1H, d, *J* 8.3 Hz, H-5), 7.02 (2H, s, H-2' & H-6'), 6.65 (1H, d, *J* 2.5 Hz, H-8), 6.63 (1H, dd, *J* 8.3, 2.5 Hz, H-6), 5.65 (1H, dd, *J* 3.9, 3.9 Hz, H-3), 3.88 (6H, s, 2× -OMe), 3.78 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.48 (2H, br. d, *J* 3.9 Hz, H-4); ^{13}C NMR [151 MHz, $(CD_3)_2CO$]: *δ* 160.3 (C-4'/7), 154.3 (C-3' & C-5'), 153.3 (C-8a), 149.2 (C-2), 139.6 (C-4'/7), 130.8 (C-1'), 130.3 (C-5), 112.3 (C-4a), 110.8 (C-6), 103.0 (C-2' & C-6'), 102.4 (C-8), 97.4 (C-3), 60.6 (-OMe), 56.5 (2× -OMe), 55.7 (-OMe), 24.2 (C-4); HRMS(ES) *m/z* 351.1216 $[M + Na]^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1216.

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Supplementary Material

NMR spectra can be found online.

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