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Bi(OTf)₃-catalysed prenylation of electron-rich aryl ethers and phenols with isoprene: a direct route to prenylated derivatives

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Electron-rich aryl ethers and phenols react with isoprene (2-methylbuta-1,3-diene) in the presence of catalytic Bi(OTf)₃ at 40 °C to afford the corresponding prenylated or 2,2-dimethylchroman products, respectively, in moderate to good yields. This transformation offers a convenient and expedient entry to prenylated derivatives of electron-rich aromatics that often display enhanced biological activities. The methodology has been employed in the efficient synthesis of a biologically active natural product and related compounds.

Introduction

A large number of biologically active compounds possess one or more prenyl groups and/or the related 2,2-dimethylchroman unit.¹ Selected examples include novobiocin² and derrubone **1**,³ which have anti-tumour activity through the inhibition of heat-shock protein (Hsp90), xanthohumol **2** which displays anti-inflammatory and anti-cancer activity,⁴ the antioxidant vitamin E,⁵ cytotoxic and antiplasmodial xanthonols⁶ and an antimycobacterial benzofurochroman **3**⁷ (selected examples are shown in Figure 1).

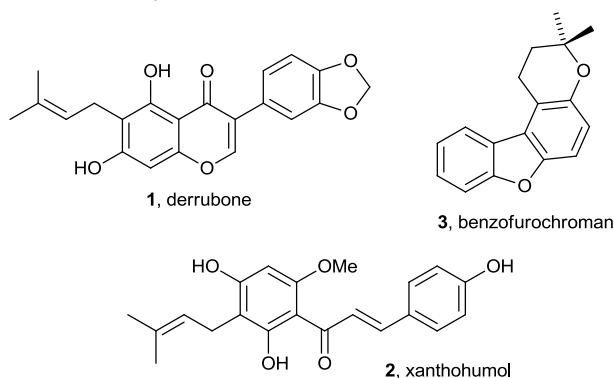
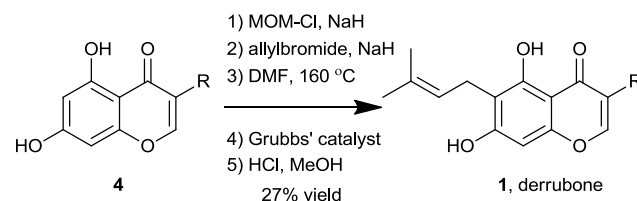


Figure 1 Selected examples

Due to a variety of factors, prenylation can often lead to enhanced biological activities compared to the non-prenylated precursors,^{1,8} although the position of substitution is also an important aspect.^{1a} Owing to the potential for improved activity and its presence in many biologically active compounds, a number of chemical syntheses of prenylated phenols have been reported. *ortho*-Prenylation of phenols has been achieved using various methods,⁹ including directed *ortho*-metallation, metal-halogen exchange, phenoxide *ortho*-C-alkylation, Claisen rearrangement, Friedel-Crafts-like prenylation and conjugate addition to *para*-quinone.^{9a} Of particular interest to the present study is the Bi(OTf)₃-catalysed [1,3] rearrangement of aryl prenyl ethers to afford prenylated phenols and chroman derivatives.^{9b} Chemoenzymatic syntheses have also been reported using prenyltransferases NphB and SCO7190 as biocatalysts.¹⁰

The isoflavone core of derrubone **4** was achieved in a elegant three-step synthesis from commercially available

starting materials in 64% yield, without the need of protecting groups.^{3b} Unfortunately direct prenylation under various conditions gave the *O*-prenyl derivative as the major product. The synthesis of derrubone **1** was achieved indirectly by: 1) selective MOM-protection of the isoflavone core at 7-OH, 2) *O*-allylation at 5-OH, 3) Claisen rearrangement, 4) cross-metathesis using Grubbs' second-generation catalyst with 2-methyl-2-butene to provide the prenyl group and 5) MOM-deprotection in 27% yield over 5 steps (Scheme 1).



Scheme 1 Synthesis of derrubone (R=3,4-methylenedioxyphenyl)^{3b}

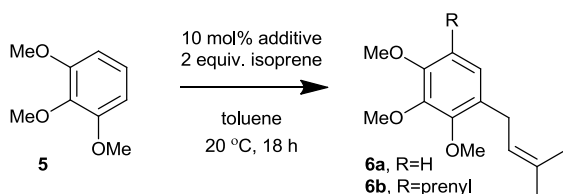
The reaction of unprotected phenols with isoprene (2-methylbuta-1,3-diene) affords the corresponding 2,2-dimethylchromans and has been reported with various Lewis and Brønsted acids, such as AlCl₃,¹¹ phosphoric acid,¹² Amberlyst[®] 15,¹³ CpMoCl(CO)₃,¹⁴ ZnCl₂/AcOH,¹⁵ BF₃·OEt₂,¹⁶ zeolites,¹⁷ Ag(OTf),¹⁸ Sc(OTf)₃-ionic liquid,¹⁹ Cu(OTf)₂-bipy²⁰ catalysts, Me₃SiI²¹ and HI.^{21a} In many cases, the *ortho*-prenylated phenol initially generated cyclises under the reaction conditions to afford the chroman. Sartori, however, described the reaction of phenols and isoprene using a zeolite HSZ-360 catalyst that gave selectively either the prenylated phenol derivative at 80 °C or the corresponding chroman at 120 °C.¹⁷ Sharma also reported the selective synthesis of *C*-prenylated phenols using Me₃SiI generated *in situ* or HI.^{21a}

Although there are many reports of the reaction of phenols with isoprene, there are very few examples of the equivalent reaction with aryl ethers.^{17,22} The prenylation of aryl ethers with allylic alcohols or activated derivatives is much more common.^{9,23} We now describe the direct prenylation of electron-rich aryl ethers, phenols and acetates with isoprene under mild reaction conditions, to afford selectively the corresponding prenylated aryl ether, 2,2-dimethylchroman and *C*-prenylated phenol products respectively.

Results and Discussion

During the course of our investigations into the synthesis of biologically active compounds, we discovered that Bi(OTf)₃ catalysed the reaction between electron-rich aryl ethers with isoprene to generate the prenylated product under mild conditions. Bi(OTf)₃ is a commercially available, easy-to-handle Lewis acid that has been used to catalyse a variety of reactions,²⁴ including aromatic sulfonation and Friedel-Crafts acylation.^{24a,25} We examined the effect of various Lewis acids to catalyse the reaction between 1,2,3-trimethoxybenzene **5** and isoprene and the results are shown in Table 1.

Table 1 Prenylation of 1,2,3-trimethoxybenzene **5**^a



Entry	Additive	Conversion (%)		
		5	6a	6b
1	None	100	-	-
2	ZrCl ₄		Unidentified mixtures	
3	AlCl ₃		Unidentified mixtures	
4	Yb(OTf) ₃	100	-	-
5	Zn(OTf) ₂	100	-	-
6	Sc(OTf) ₃	58	42	-
7	Bi(OTf) ₃	11	70	19
8	BF ₃ ·OEt ₂	65	35	-

^a Reactions were performed on 0.5 mmol scale in 2.5 mL of anhydrous toluene with 2 equiv. isoprene at 20 °C for 18 h, with 10 mol% additive where used. Conversions were determined by ¹H NMR of the crude reaction mixture after it had been passed through a plug of silica gel.

There was no observable reaction in the absence of an acid catalyst (entry 1, Table 1), whilst complicated mixtures of compounds were obtained with either ZrCl₄ or AlCl₃ (entries 2 and 3). Of the triflate salts, no reaction was observed with Yb(OTf)₃ and Zn(OTf)₂ however Sc(OTf)₃ gave some prenylated product **6a** but Bi(OTf)₃ afforded the best results (entries 4-7). BF₃·OEt₂ gave the mono-product **6a** selectively, although the conversion was lower (entry 8). Both BF₃·OEt₂^{16b} and Sc(OTf)₃¹⁹ have previously been used in the reaction of isoprene with a phenol but not with an aryl ether. The prenylated product **6a** has also been obtained by the gold(I)-catalysed reaction of 1,2,3-trimethoxybenzene **5** with dimethylallene in the presence of (4-ClC₆H₄O)₃P(AuCl) and AgBF₄ in 65% yield after 16 h at room temperature.²⁶

The effect of temperature on the reaction was investigated at 40 °C and 60 °C, in addition to the results obtained at 20 °C (given in Table 1). It was concluded that the optimum temperature was 40 °C, which was then used throughout.

Bi(OTf)₃ could either act as a source of TfOH or as a Lewis acid. Previous reports that used Bi(OTf)₃ have shown that the addition of 4Å molecular sieves was detrimental to the reaction, whilst the addition of H₂O had little effect, suggesting that TfOH was the active species.²⁷ Moreover, the addition of a sterically hindered base (2,6-di-*tert*-butyl-4-methylpyridine; DTBMP) was found to inhibit the Bi(OTf)₃-

catalysed transformation.^{27a,28} Similarly, no difference in reactivity was observed in the Bi(OTf)₃-catalysed Mannich-type reaction between the anhydrous and the hydrated form (Bi(OTf)₃·4H₂O) of the catalyst.²⁹ The effect of these additives were examined in the reaction between 1,2,3-trimethoxybenzene **5** and isoprene at 40 °C and the results are shown in Table 2.

Table 2 The effect of additives^a

Entry	Additive	Time (h)	Isolated yields (%)		
			5	6a	6b
1	None	1.25	0	62	20
2^b	None	1.5	10	68	23
3	20 μL H ₂ O	5	5	63	13
4^c	DTBMP	6	87	7	0

^a Reactions were all performed on 2 mmol scale in 10 mL of anhydrous toluene at 40 °C with 2 equiv. isoprene and 10 mol% Bi(OTf)₃. ^b Non-anhydrous Reagent Grade toluene used. ^c 33 mol% DTBMP = 2,6-Di-*tert*-butyl-4-methylpyridine was used.

The use of anhydrous or reagent-grade toluene did not affect the reaction (entries 1 and 2, Table 2), however, with the addition of H₂O, the reaction required 5 h to achieve similar yields (entry 3). The presence of the sterically hindered base DTBMP severely hindered the reaction (entry 4) and these results are consistent with previous reports that suggest Bi(OTf)₃ is a source of TfOH.²⁷⁻²⁹ Although TfOH has been suggested as an active catalytic species in the reaction of phenols with isoprene using AgOTf¹⁸ or Cu(OTf)₂-bipy catalyst,²⁰ in both cases the authors suggest the metal also plays an important role as a Lewis acid.

Mixtures of mono- and bis-prenylated products were observed, as the initial mono-prenylated product **6a** is more reactive than the starting material due to increased electron-donation. We investigated the effect of various equivalents of isoprene in the reaction and the results are shown in Table 3.

Table 3 The effect of isoprene^a

Entry	Equiv.	Time (h)	Isolated yields (%)		
			5	6a	6b
1	1.1	2	22	50	7
2	1.5	1.5	8	65	2
3^b	2	1.25	0	62	20
4	3	1.25	0	41	36

^a Reactions were all performed on 2 mmol scale in 10 mL of anhydrous toluene at 40 °C with 10 mol% Bi(OTf)₃. ^b Entry 1, Table 2.

As expected, increased equivalents of isoprene afford more of the bis-prenylated product **6b**. Two equivalents of isoprene gave complete conversion of the starting material and good levels of the mono- and bis-prenylated products (entry 3, Table 3), so this was used with various phenolic ethers and the results are shown in Table 4.

5-Bromo-1,2,3-trimethoxybenzene **7** was less reactive than trimethoxybenzene **5** and required 7 h to afford the mono-prenylated product **8** in 44% yield, together with 50% unreacted starting material, presumably due to the steric and electronic influences of the bromo substituent (entry 2, Table 4). The reactivity was further diminished with a methyl ester substituent, affording the prenylated ester **10** in only 15% yield and 85% recovered starting material after 5 h (entry 3).

Table 4 Prenylation of various aryl ethers with isoprene and Bi(OTf)₃^a

Entry	Arene	Reaction time (h)	Product(s) (% yield) sm / mono / bis ^b
1 ^c		1.25	- / 62 (6a) / 20 (6b)
2		7	50 / 44 (8) / -
3		5	85 / 15 (10) / -
4		4	18 / 47 (12) / -
5		1.5	- / 58 (14a) / 30 (14b)
6		6	57 / 17 (16) / -
7		6	- / 64 (18) / -

^a Reactions were all performed on 2 mmol scale in 10 mL of anhydrous toluene at 40 °C with 2 equiv. isoprene and 10 mol% Bi(OTf)₃. ^b sm refers to recovered starting material, mono product is either R=prenyl or R¹=prenyl R²=H and bis refers to R¹=R²=prenyl. ^c Entry 1, Table 2.

3,4,5-Trimethoxyacetophenone and 3,4,5-trimethoxybenzaldehyde (not shown) only gave unidentified mixtures of compounds when subjected to the reaction conditions. The cinnamic methyl ester **11** gave an improved yield, affording mono-prenylated product **12** in 47% yield after 4 h (entry 4). An increase in reactivity was observed with the removal of conjugation, as the dihydrocinnamic methyl ester **13** gave both the mono- and bis-prenylated products in 58% (**14a**) and 30% (**14b**) yields respectively after only 1.5 h (entry 5).

The dimethoxy derivatives were less reactive and required longer reaction times. As previously observed, the unsaturated cinnamate derivative **15** was less reactive than the saturated methyl ester **17** and gave the mono-prenylated products in 17% (**16**) and 64% (**18**) yields respectively (entries 6 and 7). Only the products from prenylation at C2 were obtained, as

determined by NOESY correlations between the methylene protons indicated in ester **18** (Figure 2).[†]

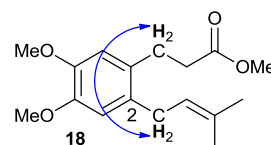


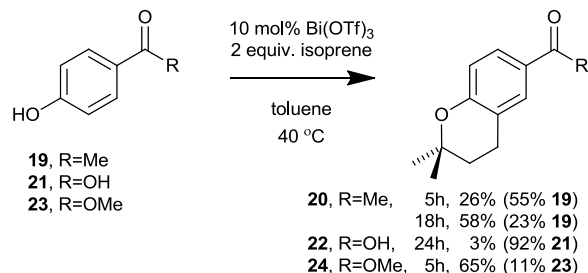
Figure 2 Key NOESY correlation between highlighted protons

The mono-methoxycinnamic esters were also investigated and were the least reactive in this series (results not shown). Methyl 4-methoxycinnamate did not show any conversion after 6 h and although methyl 4-methoxydihydrocinnamate appeared to afford the mono-prenylated product by ¹H NMR, it was a minor component in an inseparable mixture by column chromatography with unreacted starting material.

These results demonstrate the possibility of selective and direct prenylation of electron-rich aryl ethers present in various biologically active compounds, such as flavonoids and chalcones,^{1a,c-h} which could exhibit improved activities.

Application to phenols

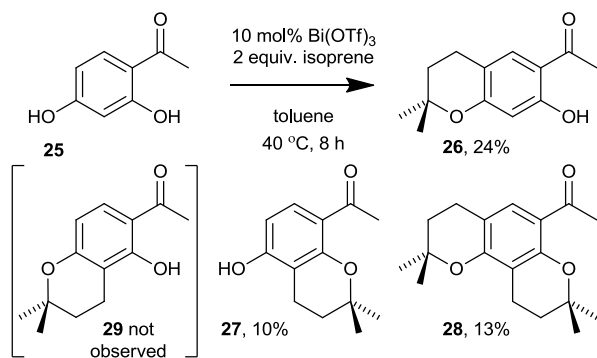
Substituted phenols were subjected to the optimised reaction conditions reported in Table 4 and the results are shown in Scheme 2 below.



Scheme 2 Prenylation of phenol derivatives

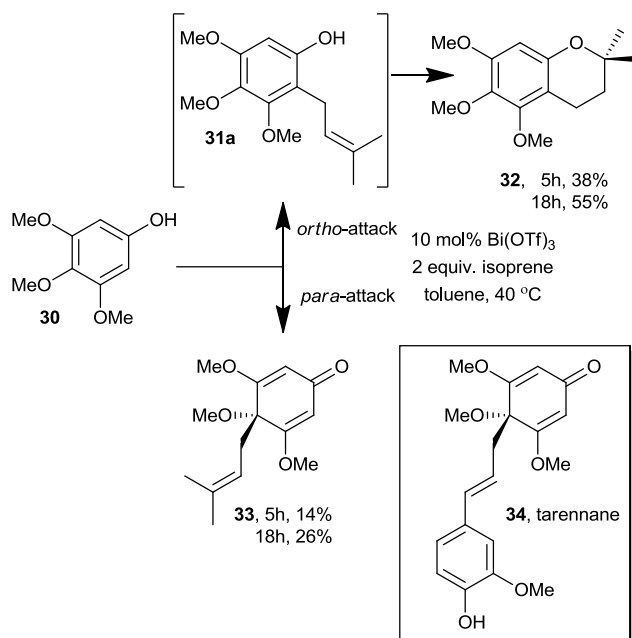
Treatment of the methyl ketone **19** with 10 mol% Bi(OTf)₃ and isoprene at 40 °C gave the cyclised product **20** directly in 26% yield after 5 h, with the recovery of 55% of unreacted phenol **19** (Scheme 2). Leaving the reaction for 18 h, however, gave the cyclised product **20** in 58% with 23% of recovered starting material. The carboxylic acid **21** gave the corresponding chroman **22** in only 3% yield, with 92% unreacted starting material even after 24 h. The methyl ester **23** however gave the chroman derivative **24** in 65% yield after 5 h, together with 11% of unreacted phenol **23**.

Reaction of 2,4-dihydroxyacetophenone **25** with isoprene in the presence of Bi(OTf)₃ gave a mixture of compounds **26** (24%), **27** (10%) and **28** (13%) (Scheme 3). A different mixture of possible products was observed when this reaction was catalysed with H₃PO₄, as chromans **26** (14%), **28** (5%) and **29** (17%) were obtained.^{12b}


Scheme 3 Prenylation of resorcinol **25**

The chromans obtained in Schemes 2 and 3 could be generated by the initial formation of the *O*-prenyl aryl ether and subsequent rearrangement to the corresponding *C*-prenylated product,^{9,17,20,30} which has been previously reported with Bi(OTf)₃.^{9b,31} However, since the results obtained *vide supra* demonstrate that the presence of a free phenolic OH is not necessary for prenylation, the reaction presumably occurs through direct *C*-alkylation of the arene by a Friedel-Crafts-type capture of the carbocation generated by the protonation of isoprene by TfOH (*cf.* H₃PO₄).^{12a,12d} Cyclisation of the *ortho*-prenylated phenol under the reaction conditions would then afford the observed 2,2-dimethylchroman product, which has been previously achieved with HCl/AlCl₃,³² BF₃·OEt₂,³³ clay,^{30b} zeolites¹⁷ as well as Bi(OTf)₃.^{9b,31}

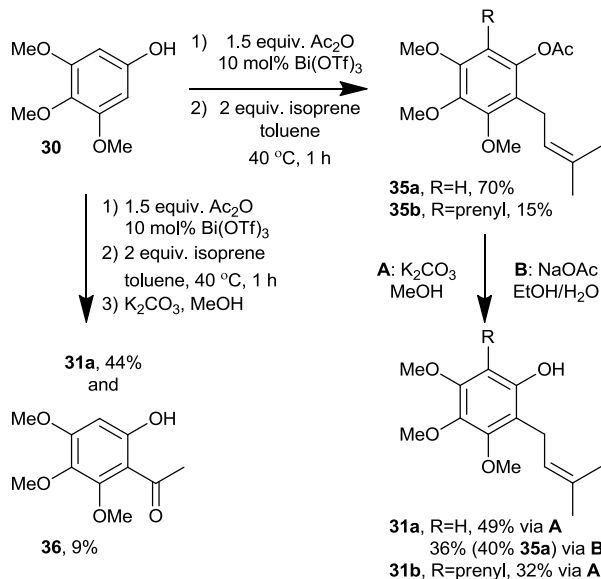
The prenylated phenol **31a** has been isolated from the leaves and stems of *Piper clarkii* and displays anti-invasive activity against human MCF-7/6 breast carcinoma cells.³⁴ Sartori previously reported that the reaction of 3,4,5-trimethoxyphenol **30** with isoprene in the presence of a zeolite catalyst gave the prenylated phenol **31a** in 40% yield at 80 °C


Scheme 4 Prenylation of phenol **12**

or the corresponding chroman **32** at 120 °C.¹⁷ Youn also reported the synthesis of chroman **32** using a Sc(OTf)₃-ionic liquid catalyst system.¹⁹ Submission of the free phenol **30** under our reaction conditions gave the cyclised chroman **32** directly in 55% yield after 18 h (Scheme 4).

As previously described, the reaction presumably proceeds *via* the *ortho*-prenylated phenol **31a**, which undergoes cyclisation under the reaction conditions to afford the chroman **32** (Scheme 4). The dienone **33**, resulting from attack at the *para*-position with respect to the phenol OH, was also isolated from the reaction mixture in 26% yield. Only the chroman **32** was previously reported in the reaction of phenol **30** and isoprene catalysed by using zeolite HSZ-360¹⁷ or Sc(OTf)₃ in ionic liquid.¹⁹ A similar transformation was, however, observed in the reaction between 3,4,5-trimethoxyphenol **30** and 3-chloro-3-methylbut-1-yne with K₂CO₃, which gave the corresponding ether in addition to the related dienone from *para*-attack.³⁵ It is of great interest that the dienone **33** is structurally similar to tarennane **34**, a natural product isolated from the whole plant of *Tarenna attenuata* that displays potent antioxidant activities against H₂O₂ damage.³⁶

To prevent formation of the chroman and synthesise selectively the *ortho*-prenylated phenol **31a**, we investigated the protection of the phenol group *in situ*. Phenol has been efficiently acetylated by Ac₂O in the presence of 1 mol% Bi(OTf)₃ in 98% yield after 5 min at room temperature.³⁷ Incorporation of Ac₂O to our optimised reaction conditions resulted in the initial protection of the phenol **30** which, upon the addition of isoprene, gave the desired prenylated product **35a** as the acetate in 70% yield, together with the bis-product **35b** in 15% yield, in a one-pot transformation (Scheme 5).


Scheme 5 One and two-step synthesis of **31a**

Removal of the acetal group was achieved under standard conditions using K₂CO₃ in MeOH (Method A) to afford the mono-prenylated phenol **31a** in 49% yield and the bis-prenylated derivative **31b** in only 32% yield (Scheme 5). The cleavage of aromatic acetates using K₂CO₃ in MeOH gave

high yields of related Plicatin B (89%)³⁸ and the 8-prenyl isomer of derrubone (90%),^{3b} although variable results were also reported (15-67%) with other similar substrates.³⁹

Narender recently reported the use of NaOAc in the deacetylation of structurally related aromatic acetates in high yields.⁴⁰ However, treatment of the acetate **35a** with NaOAc in aqueous EtOH for 5 h (Method **B**), as described by Narender,⁴⁰ gave the desired phenol **31a** in only 36% yield, together with 40% recovered starting material. A one-pot transformation from phenol **30** was also investigated and gave the prenylated phenol **31a** in 44% yield (Scheme 5). The acetophenone derivative **36** was also isolated in 9% yield, which is obtained from a Fries rearrangement of the aromatic acetate and has been reported with $\text{BF}_3 \cdot \text{OEt}_2$ ⁴¹ and in similar systems in the presence of $\text{Bi}(\text{OTf})_3$.^{31,42}

Conclusions

The procedure described here represents a novel and practical Friedel-Crafts-type prenylation of electron-rich aryl ethers and phenols under mild reaction conditions using readily available and atom-efficient isoprene. The reaction of the acetate-protected phenol demonstrates that this substituent is also an effective substrate in the reaction and can be used to afford selectively the *ortho*-prenylated phenol without the formation of the chroman. The application of this methodology to the efficient synthesis of a natural product (**31a**) and non-natural analogues (**33** and **31b**) is also reported.

Many biologically active compounds possess an electron-rich aromatic core. Since prenylation can lead to enhanced activities, the transformation described herein could find applications in medicinal chemistry programmes, increasing the number of compounds available for screening. The mild reaction conditions, predictable selectivity and functionality generated makes this reaction a very useful medicinal chemistry tool. The formation of C–C and C–O bonds in the presence of an inexpensive and easy-to-handle catalyst under mild reaction conditions is also worthy of note.

Experimental

General

NMR spectra were obtained on Varian Mercury VX (400 MHz) or Bruker Avance III (400 MHz) spectrometers. The chemical shifts are recorded in parts per million (ppm) with reference to tetramethylsilane. The coupling constants *J* are quoted to the nearest 0.5 Hz and are not corrected. Mass spectra were obtained on a micrOTOFTM from Bruker Daltonics. Melting points were obtained using a Reichert-Jung heated-stage microscope. Infrared spectra were recorded on a Perkin-Elmer Spectrum RXI FT-IR system and all values are recorded in cm^{-1} . PE refers to petroleum ether, bp 40–60 °C.

Methyl 3,4,5-trimethoxybenzoate **9**, methyl *E*-3-(3,4,5-trimethoxyphenyl)propenoate **11**, methyl 3-(3,4,5-trimethoxyphenyl)propanoate **13**, methyl *E*-3-(3,4-dimethoxyphenyl)propenoate **15** and methyl 4-hydroxybenzoate **23** were all synthesised from their corresponding carboxylic acids following the procedure reported by Parrain⁴³ and gave

samples that were consistent with the spectroscopic data reported for **9**,⁴⁴ **11**,⁴³ **13**,⁴⁵ **15**⁴⁶ and **23**.⁴⁷

Methyl 3-(3,4-dimethoxyphenyl)propanoate (**17**)

10% Palladium on carbon (50 mg, 0.05 mmol) was added to a vigorously stirred solution of methyl 3,4-dimethoxycinnamate (819 mg, 3.69 mmol) in EtOH (20 mL). After 3 cycles of purging the flask with N_2 then a vacuum, the flask was put under an atmosphere of H_2 . After 2 h, the mixture was filtered through Celite[®], washing thoroughly with EtOH, then the solvent removed under reduced pressure to afford the methyl propionate **17** (821 mg, 99%) as a colourless oil without need for further purification.

¹H NMR δ_{H} (400 MHz, CDCl_3) 6.84 (1H, d, *J* 8.5 Hz, C5-ArH), 6.77 (1H, dd, *J* 8.5 and 2.0 Hz, C6-ArH), 6.76 (1H, d, *J* 2.0 Hz, C2-ArH), 3.90 (3H, s, ArOMe), 3.88 (3H, s, ArOMe), 3.70 (3H, s, CO₂Me), 2.93 (2H, t, *J* 7.5 Hz, ArCH₂) and 2.64 (2H, t, *J* 7.5 Hz, CH₂CO₂Me); ¹³C NMR δ_{C} (100 MHz, CDCl_3) 173.4, 149.0, 147.6, 133.2, 120.1, 111.8, 111.4, 56.0, 55.9, 51.6, 36.0 and 30.6.

Consistent with the spectroscopic data previously reported.⁴⁸

General procedure: Formation of prenylated and chroman compounds

$\text{Bi}(\text{OTf})_3$ (136 mg, 0.2 mmol) was added to a vigorously stirred solution of the arene (2 mmol) and isoprene (400 μl , 4 mmol) in anhydrous toluene (10 mL) in a thick-walled pressure tube at room temperature under Ar. The tube was sealed and the reaction heated at 40 °C for between 75 min and 24 h and the crude reaction mixture (often dark purple/black in colour) was applied directly to a silica gel chromatography column to afford the purified product(s). Representative reactions have also been performed in a conventional round-bottomed flask with a tightly fitted stopper to afford similar results.

1,2,3-Trimethoxy-4-(3-methylbut-2-en-1-yl)benzene (**6a**) and 2,3,4-trimethoxy-1,5-bis(3-methylbut-2-en-1-yl)benzene (**6b**)

Following the general procedure, 1,2,3-trimethoxybenzene **5** (336 mg, 2 mmol) gave, after 75 min and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10], the mono-product **6a** (292 mg, 62%) and the bis-product **6b** (122 mg, 20%) as colourless oils.

Mono-product (**6a**)

IR ν_{max} (thin film) 2936, 1599, 1495, 1464, 1416, 1294, 1256, 1096 and 1017; ¹H NMR δ_{H} (400 MHz, CDCl_3) 6.86 (1H, d, *J* 8.5 Hz, ArH), 6.64 (1H, d, *J* 8.5 Hz, ArH), 5.28 (1H, triplet of septets, *J* 7.5 and 1.5 Hz, CH=CMe₂), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 3.87 (3H, s, OMe), 3.31 (2H, d, *J* 7.5 Hz, ArCH₂), 1.77 (3H, br s, CH=CMe_AMe_B) and 1.77 (3H, br s, CH=CMe_AMe_B); ¹³C NMR δ_{C} (100 MHz, CDCl_3) 152.0, 151.8, 142.4, 132.0, 127.9, 123.5, 123.3, 107.4, 60.7, 60.7, 56.0, 28.2, 25.7 and 17.7.

Consistent with the spectroscopic data previously reported.²⁶

Bis-product (6b)

IR ν_{\max} (thin film) 2965, 2931, 1479, 1460, 1411, 1325, 1235, 1092, 1065 and 1015; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 6.67 (1H, s, ArH), 5.25 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, *CH*=CMe₂), 3.91 (3H, s, OMe), 3.83 (6H, s, OMe), 3.27 (4H, d, *J* 7.0 Hz, ArCH₂) and 1.74 (12H, d, *J* 1.5 Hz, CH=CMe₂); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 149.8, 146.3, 132.0, 130.3, 124.2, 123.3, 60.8, 60.6, 28.4, 25.7 and 17.8; **MS** (+ESI) *m/z* 305 (MH⁺, 9%); **HRMS** (+ESI) Found MH⁺, 305.2103; C₁₉H₂₉O₃ requires MH⁺ 305.2117.

1-Bromo-3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)benzene (8)

Following the general procedure, the aryl bromide **7** (494 mg, 2 mmol) gave, after 7 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 95:5], the product **8** (275 mg, 44%) as a colourless oil in addition to recovered starting material **7** (246 mg, 50%).

R_f [PE-Et₂O 70:30] 0.63; **IR** ν_{\max} (thin film) 2935, 1590, 1482, 1452, 1430, 1396, 1313, 1270, 1237, 1195, 1156, 1113, 1045 and 1019; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 6.87 (1H, s, ArH), 5.12 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, CH=CMe₂), 3.84, (6H, s, OMe), 3.82 (3H, s, OMe), 3.42, (2H, d, *J* 7.0 Hz, ArCH₂), 1.79 (3H, br s, CH=CMe_AMe_B) and 1.68 (3H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 152.6, 152.1, 142.0, 131.8, 128.1, 122.1, 117.9, 112.0, 61.1, 60.7, 56.2, 29.3, 25.7 and 18.1; **MS** (+ESI) *m/z* 315 (MH⁺, 97%), 317 (MH⁺, 100) and 337 (MNa⁺, 23); **HRMS** (+ESI) Found MNa⁺, 337.0400; C₁₄H₁₉⁷⁹BrNaO₃ requires MNa⁺ 337.0415.

Methyl 3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)benzoate (10)

Following the general procedure, ester **9** (452 mg, 2 mmol) gave, after 5 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 95:5], the product **10** (87 mg, 15%) as a colourless oil in addition to ester **9** (384 mg, 85%).

IR ν_{\max} (thin film) 2939, 1723 (C=O), 1594, 1491, 1455, 1431, 1401, 1337, 1222, 1154, 1115 and 1055; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.17 (1H, s, ArH), 5.12 (1H, triplet of septets, *J* 6.5 and 1.5 Hz, CH=CMe₂), 3.91 (3H, s, OMe), 3.86 (3H, s, OMe), 3.86 (3H, s, OMe), 3.82 (3H, s, OMe), 3.62 (2H, d, *J* 6.5 Hz, ArCH₂), 1.75 (3H, d, *J* 0.5 Hz, CH=CMe_AMe_B) and 1.66 (3H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 168.0, 152.3, 151.0, 145.7, 131.1, 130.7, 125.2, 123.8, 109.7, 61.0, 60.7, 56.1, 52.0, 25.9, 25.7 and 17.9; **MS** (+ESI) *m/z* 295 (MH⁺, 29%) and 317 (MNa⁺, 12); **HRMS** (+ESI) Found MH⁺, 295.1551; C₁₆H₂₃O₅ requires MH⁺ 295.1546.

Methyl E-3-(3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)propanoate (12)

Following the general procedure, ester **11** (504 mg, 2 mmol) gave, after 4 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10], the mono-product **12** (302 mg, 47%) as a colourless oil in addition to ester **11** (90

mg, 18%).

IR ν_{\max} (thin film) 2937, 1719 (C=O), 1631, 1592, 1566, 1487, 1409, 1347, 1289, 1254, 1168, 1124; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.92 (1H, d, *J* 15.5 Hz, CH=CHCO₂Me), 6.87 (1H, s, ArH), 6.26 (1H, d, *J* 15.5 Hz, CH=CHCO₂Me), 5.02 (1H, t, *J* 6.5 Hz, CH=CMe₂), 3.89 (3H, s, OMe), 3.86 (3H, s, OMe), 3.83 (3H, s, OMe), 3.79 (3H, s, OMe), 3.42 (2H, d, *J* 6.5 Hz, ArCH₂), 1.81 (3H, s, CH=CMe_AMe_B) and 1.67 (3H, s, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 167.4, 151.9, 151.7, 144.2, 142.6, 131.6, 129.0, 128.6, 123.1, 118.0, 105.3, 61.0, 60.8, 55.9, 51.6, 25.7, 25.0 and 17.9; **MS** (+ESI) *m/z* 343 (MNa⁺, 11%); **HRMS** (+ESI) Found MNa⁺, 343.1508; C₁₈H₂₄NaO₅ requires MNa⁺ 343.1521.

Methyl 3-(3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)propanoate (14a) and methyl 3-(3,4,5-trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)phenyl)propanoate (14b)

Following the general procedure, ester **13** (508 mg, 2 mmol) gave, after 90 min and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 80:20], the mono-product **14a** (376 mg, 58%) and the bis-product **14b** (233 mg, 30%) as colourless oils.

Mono-product (14a)

R_f [PE-Et₂O 80:20] 0.27; **IR** ν_{\max} (thin film) 2935, 1739 (C=O), 1599, 1578, 1494, 1453, 1406, 1338, 1283, 1239, 1196, 1121, 1073 and 1042; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 6.53 (1H, s, ArH), 5.08-5.04 (1H, m, CH=CMe₂), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 3.71 (3H, s, OMe), 3.33 (2H, d, *J* 6.5 Hz, ArCH₂CH=CMe₂), 2.93-2.89 (2H, m, ArCH₂CH₂CO₂Me) 2.60-2.56 (2H, m, CH₂CO₂Me), 1.79 (3H, br s, CH=CMe_AMe_B) and 1.71 (3H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 173.4, 152.1, 151.5, 140.9, 134.2, 131.1, 126.2, 123.8, 108.4, 60.9, 60.7, 56.0, 51.6, 35.5, 28.3, 25.6, 25.2 and 17.8; **MS** (+ESI) *m/z* 345 (MNa⁺, 24%); **HRMS** (+ESI) Found MNa⁺, 345.1661; C₁₈H₂₆NaO₅ requires MNa⁺ 345.1678.

Bis-product (14b)

R_f [PE-Et₂O 80:20] 0.51; **IR** ν_{\max} (thin film) 2948, 2933, 1740 (C=O), 1463, 1416, 1334, 1195, 1170, 1096, 1048 and 982; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 5.10-5.06 (2H, m, CH=CMe_AMe_B), 3.91 (3H, s, OMe), 3.85 (6H, s, OMe), 3.72 (3H, s, OMe), 3.36 (4H, d, *J* 6.5 Hz, ArCH₂CH=CMe₂), 2.93-2.89 (2H, m, ArCH₂CH₂CO₂Me), 2.50-2.46 (2H, m, CH₂CO₂Me), 1.79 (6H, d, *J* 1.0 Hz, CH=CMe_AMe_B) and 1.71 (6H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 173.4, 150.3, 144.8, 133.0, 131.1, 129.5, 124.0, 60.8, 60.4, 51.5, 34.9, 25.7, 25.6, 24.8 and 17.8; **MS** (+ESI) *m/z* 391 (MH⁺, 20%); **HRMS** (+ESI) Found MH⁺, 391.2652; C₂₃H₃₅O₅ requires MH⁺ 391.2485.

Methyl E-3-(4,5-dimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)propanoate (16)

Following the general procedure, ester **15** (446 mg, 2 mmol) gave, after 6 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10], the mono-product **16**

(100 mg, 17%) as a colourless oil.

IR ν_{\max} (thin film) 2934, 1715 (C=O), 1602, 1514, 1458, 1268, 1167 and 1102; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.95 (1H, d, *J* 16.0 Hz, CH=CHCO₂Me), 7.05 (1H, s, ArH), 6.68 (1H, s, ArH), 6.24 (1H, d, *J* 16.0 Hz, CH=CHCO₂Me), 5.16 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, CH=CMe₂), 3.87 (3H, s, OMe), 3.87 (3H, s, OMe), 3.78 (3H, s, OMe), 3.40 (2H, d, *J* 7.0 Hz, ArCH₂), 1.76 (3H, br s, CH=CMe_AMe_B) and 1.71 (3H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 167.7, 151.0, 147.6, 142.1, 135.5, 132.6, 125.0, 122.9, 116.3, 112.6, 109.0, 56.0, 55.9, 51.5, 31.8, 25.7 and 17.9; **MS** (+ESI) *m/z* 313 (MNa⁺, 9%); **HRMS** (+ESI) Found MNa⁺, 313.1424; C₁₇H₂₂NaO₄ requires MNa⁺ 313.1416.

15 Methyl 3-(4,5-dimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)propanoate (18)

Following the general procedure, ester **17** (448 mg, 2 mmol) gave, after 6 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10], the mono-product **18** (376 mg, 64%) as a colourless oil.

R_f [PE-Et₂O 50:50] 0.32; **IR** ν_{\max} (thin film) 2934, 2851, 1737 (C=O), 1516, 1458, 1361, 1271, 1209 and 1093; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 6.69 (1H, s, ArH), 6.69 (1H, s, ArH), 5.21 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, CH=CMe₂), 3.85 (3H, s, OMe), 3.85 (3H, s, OMe), 3.69 (3H, s, OMe), 3.29 (2H, d, *J* 7.0 Hz, ArCH₂CH=CMe₂), 2.92-2.88 (2H, m, ArCH₂CH₂CO₂Me), 2.59-2.55 (2H, m, CH₂CO₂Me), 1.75 (3H, br s, CH=CMe_AMe_B) and 1.74 (3H, br s, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 173.4, 147.5, 147.2, 132.1, 131.7, 130.4, 123.4, 113.0, 112.7, 56.0, 55.9, 51.5, 35.5, 31.3, 27.8, 25.7 and 17.9; **MS** (+ESI) *m/z* 293 (MH⁺, 15%) and 315 (MNa⁺, 27); **HRMS** (+ESI) Found MH⁺, 293.1723; C₁₇H₂₅O₄ requires MH⁺ 293.1753.

35 1-(2,2-Dimethylchroman-6-yl)ethanone (20)

Following the general procedure, phenol **19** (272 mg, 2 mmol) gave, after 18 h and subsequent column chromatography [silica, PE-Et₂O-EtOAc gradient from 100:0:0 to 85:15:0 then 50:0:50], the chroman **20** (235 mg, 58%) as a white solid in addition to phenol **19** (62 mg, 23%).

R_f [PE-Et₂O 70:30] 0.63; **Mp** 89-93 °C (from CH₂Cl₂); **IR** ν_{\max} (thin film) 2976, 1670 (C=O), 1537, 1498, 1419, 1358, 1289, 1265, 1156 and 1117; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.75 (1H, d, *J* 2.5 Hz, C5-ArH), 7.73 (1H, dd, *J* 8.5 and 2.5 Hz, C7-ArH), 6.81 (1H, d, *J* 8.5 Hz, C8-ArH), 2.83 (2H, t, *J* 6.5 Hz, C4-CH₂), 2.54 (3H, s, COMe), 1.84 (2H, t, *J* 6.5 Hz, C3-CH₂) and 1.37 (6H, s, CMe₂); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 196.9, 158.6, 130.5, 129.4, 128.3, 120.7, 117.2, 75.5, 32.5, 26.9, 26.2 and 22.4.

Consistent with the spectroscopic data previously reported.^{16b}

2,2-Dimethylchroman-6-carboxylic acid (22)

Following the general procedure, phenol **21** (276 mg, 2 mmol) gave, after 24 h and subsequent column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60], the chroman **22** (14 mg, 3%) as a white solid in addition to phenol **21** (254

mg, 92%).

IR ν_{\max} (thin film) 2975, 1681 (C=O), 1608, 1578, 1443, 1411, 1324, 1296, 1265, 1156 and 1120; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.86 (1H, d, *J* 2.0 Hz, C5-ArH), 7.84 (1H, dd, *J* 8.5 and 2.0 Hz, C7-ArH), 6.82 (1H, d, *J* 8.5 Hz, C8-ArH), 2.84 (2H, t, *J* 7.0 Hz, C4-CH₂), 1.84 (2H, t, *J* 7.0 Hz, C3-CH₂) and 1.36 (6H, s, CMe₂); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 172.1, 159.1, 132.4, 129.9, 120.8, 120.7, 117.4, 75.6, 32.5, 26.9 and 22.3; **MS** (+ESI) *m/z* 207 (MH⁺, 100%) and 229 (MNa⁺, 45); **HRMS** (+ESI) Found MH⁺, 207.1033; C₁₂H₁₅O₃ requires MH⁺ 207.1021.

Consistent with the spectroscopic data previously reported.⁴⁹

70 Methyl 2,2-dimethylchroman-6-carboxylate (24)

Following the general procedure, phenol **23** (304 mg, 2 mmol) gave, after 5 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 85:15] the chroman **24** (285 mg, 65%) as a white solid in addition to phenol **23** (32 mg, 11%).

R_f [PE-Et₂O 70:30] 0.61; **IR** ν_{\max} (thin film) 2975, 2948, 1716 (C=O), 1613, 1581, 1493, 1437, 1290, 1263, 1155 and 1118; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.78 (1H, d, *J* 2.0 Hz, C5-ArH), 7.76 (1H, dd, *J* 8.5 and 2.0 Hz, C7-ArH), 6.77 (1H, d, *J* 8.5 Hz, C8-ArH), 3.86 (3H, s, OMe), 2.80 (2H, t, *J* 7.0 Hz, C4-CH₂), 1.82 (2H, t, *J* 7.0 Hz, C3-CH₂) and 1.34 (6H, s, CMe₂); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 167.1, 158.3, 131.6, 129.1, 121.5, 120.6, 117.2, 75.3, 51.7, 32.6, 26.9 and 22.3. Consistent with the spectroscopic data previously reported.^{12c}

85 1-(7-Hydroxy-2,2-dimethylchroman-6-yl)ethanone (26), 1-(5-hydroxy-2,2-dimethylchroman-8-yl)ethanone (27) and 1-(2,2,8,8-tetramethyl-2,3,4,8,9,10-hexahydropyrano[2,3-*f*]-chromen-6-yl)ethanone (28)

Following general procedure, phenol **25** (304 mg, 2 mmol) gave, after 8 h and subsequent column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30], the chroman products **26** (105 mg, 24%) as a white solid, **27** (46 mg, 10%) as a white solid and **28** (77 mg, 13%) as a colourless oil.

95 Chroman (26)

Mp 115-118 °C (from EtOAc); lit.^{12b} 118-119 °C; **IR** ν_{\max} (thin film) 2937, 2957, 1867, 1647 (C=O), 1612, 1495, 1369, 1288, 1280, 1161, 1118, 1058 1020 and 885; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 12.30 (1H, s, OH), 7.41 (1H, s, C5-ArH), 6.28 (1H, s, C8-ArH), 2.71 (2H, t, *J* 7.0 Hz, C4-CH₂), 2.70 (3H, s, COMe), 1.80 (2H, t, *J* 7.0 Hz, C3-CH₂) and 1.33 (6H, s, CMe₂); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 202.3, 162.8, 161.4, 132.2, 113.9, 112.7, 104.6, 75.9, 32.7, 26.4, 26.1 and 21.7. Consistent with the spectroscopic data previously reported.^{12b,50}

Chroman (27)

Mp 165-170 °C (from EtOAc); **IR** ν_{\max} (thin film) 3172, 2974, 2931, 1638 (C=O), 1583, 1433, 1362, 1277, 1217, 1157, 1119 and 1051; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 7.68 (1H, d, *J* 8.5 Hz, C7-ArH), 7.20 (1H, broad s, OH), 6.47 (1H, d, *J* 8.5 Hz, C6-ArH), 2.74 (2H, t, *J* 7.0 Hz, C4-CH₂), 2.64 (3H, s, COMe),

1.87 (2H, t, J 7.0 Hz, C3-CH₂) and 1.43 (6H, s, CMe₂); ¹³C NMR δ_C (100 MHz, CDCl₃) 199.7, 159.2, 156.4, 129.9, 120.3, 108.5, 107.0, 75.3, 32.2, 31.6, 26.9 and 17.0.

Chroman (28)

⁵ IR ν_{\max} (thin film) 2974, 2933, 1662 (C=O), 1603, 1579, 1457, 1357, 1298, 1258, 1178, 1154, 1120 and 1096; ¹H NMR δ_H (400 MHz, CDCl₃) 7.48 (1H, s, C5-ArH), 2.70 (2H, t, J 7.0 Hz, C4-CH₂), 2.60 (2H, t, J 7.0 Hz, C10-CH₂), 2.56 (3H, s, COMe), 1.76 (2H, t, J 7.0 Hz, C9-CH₂), 1.76 (2H, t, J 7.0 Hz, C3-CH₂), 1.35 (6H, s, C(8)-CMe₂) and 1.32 (6H, s, C2-CMe₂); ¹³C NMR δ_C (100 MHz, CDCl₃) 198.6, 156.2, 153.8, 129.2, 120.0, 111.9, 109.4, 75.3, 74.7, 32.8, 32.3, 31.8, 27.1, 26.8, 21.7 and 17.2.

Consistent with the spectroscopic data previously reported.^{12b}

5,6,7-Trimethoxy-2,2-dimethylchroman (32) and 3,4,5-trimethoxy-4-(3-methylbut-2-en-1-yl)-cyclohexa-2,5-dienone (33)

Following the general procedure, phenol **30** (368 mg, 2 mmol) gave, after 18 h and subsequent column chromatography [silica, PE-Et₂O gradient from 100:0 to 85:15 then PE-EtOAc gradient from 50:50 to 30:70], the chroman product **32** (279 mg, 55%) as a colourless oil and the dienone **33** (132 mg, 26%) as a white solid.

Chroman (32)

³⁰ R_f [PE-Et₂O 80:20] 0.52; IR ν_{\max} (thin film) 2973, 2937, 1611, 1489, 1460, 1413, 1324, 1203, 1158, 1131, 1098, 1045 and 1013; ¹H NMR δ_H (400 MHz, CDCl₃) 6.15 (1H, s, C8-ArH), 3.87 (3H, s, C6-OMe), 3.79 (3H, s, C5-OMe), 3.78 (3H, s, C7-OMe), 2.63 (2H, t, J 7.0 Hz, C4-CH₂), 1.73 (2H, t, J 7.0 Hz, C3-CH₂), 1.30 (3H, s, C2-CMe_AMe_B) and 1.28 (3H, s, C2-CMe_AMe_B); ¹³C NMR δ_C (100 MHz, CDCl₃) 152.4, 151.4, 150.0, 135.4, 106.7, 96.6, 74.0, 61.0, 60.5, 55.8, 32.4, 26.7, 26.7 and 17.0.

Consistent with the spectroscopic data previously reported.¹⁹

Dienone (33)

⁴⁰ R_f [PE-EtOAc 40:60] 0.50; M_p 106-109 °C (from CH₂Cl₂); IR ν_{\max} (thin film) 2934, 2852, 1659 (C=O), 1625, 1597, 1459, 1374, 1240, 1215, 1163, 1078 and 888; ¹H NMR δ_H (400 MHz, CDCl₃) 5.56 (2H, s, C2/C6-CH), 4.66 (1H, triplet of septets, J 7.5 and 1.5 Hz, CH=CMe₂), 3.73 (6H, s, C3/C5-OMe), 3.08 (3H, s, C4-OMe), 2.67 (2H, d, J 7.5 Hz, CH₂CH=CMe₂), 1.56 (3H, br s, CH=CMe_AMe_B) and 1.52 (3H, br s, CH=CMe_AMe_B); ¹³C NMR δ_C (100 MHz, CDCl₃) 187.3, 169.4, 136.3, 115.7, 104.3, 79.4, 56.0, 52.5, 35.6, 25.7 and 17.6; MS (+ESI) m/z 253 (MH⁺); HRMS (+ESI) Found MH⁺, 253.1427; C₁₄H₂₁O₄ requires MH⁺ 253.1440.

3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)-phenyl acetate (35a) and 3,4,5-trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)-phenyl acetate (35b)

Incorporating the procedure reported by Mohammadpoor-

⁵⁵ Baltork,³⁷ Ac₂O (283 μ l, 3 mmol) was added to a rapidly stirred suspension of Bi(OTf)₃ (136 mg, 0.2 mmol) and phenol **30** (368 mg, 2 mmol) in anhydrous toluene (10 mL) in a thick-walled pressure tube at room temperature under Ar. After 5 min, isoprene (400 μ l, 4 mmol) was added to the solution and ⁶⁰ the tube was sealed and the reaction heated at 40 °C for 1 h. Column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10] gave the mono-prenylated product **35a** (414 mg, 70%) and the bis-prenylated product **35b** (108 mg, 15%) as colourless oils.

Mono-product (35a)

⁶⁵ R_f [PE-Et₂O 80:20] 0.37; IR ν_{\max} (thin film) 2937, 1767 (C=O), 1608, 1490, 1456, 1408, 1368, 1339, 1206, 1122, 1075 and 1042; ¹H NMR δ_H (400 MHz, CDCl₃) 6.38 (1H, s, C6-ArH), 5.06 (1H, triplet of septets, J 7.0 and 1.5 Hz, CH=CMe₂), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.80 (3H, s, OMe), 3.17 (2H, d, J 7.0 Hz, ArCH₂), 2.27 (3H, s, Ac), 1.73 (3H, br s, CH=CMe_AMe_B) and 1.66 (3H, d, J 1.0 Hz, CH=CMe_AMe_B); ¹³C NMR δ_C (100 MHz, CDCl₃) 169.5, 152.3, 151.7, 144.5, 140.5, 131.3, 122.7, 120.1, 102.4, 61.0, 60.8, 56.0, 25.6, 23.5, 20.8 and 17.7; MS (+ESI) m/z 295 (MH⁺, 24%), 317 (MNa⁺, 20); HRMS (+ESI) Found MH⁺, 295.1533; C₁₆H₂₃O₅ requires MH⁺ 295.1546.

Bis-product (35b)

⁸⁰ R_f [PE-Et₂O 80:20] 0.61; IR ν_{\max} (thin film) 2935, 1765 (C=O), 1600, 1463, 1416, 1367, 1346, 1204, 1097, 1048 and 982; ¹H NMR δ_H (400 MHz, CDCl₃) 5.08 (2H, triplet of septets, J 7.0 and 1.5 Hz, CH=CMe₂), 3.87 (3H, s, C4-OMe), 3.82 (6H, s, C3/5-OMe), 3.16 (4H, broad s, ArCH₂), 2.52 (3H, s, Ac), 1.73 (6H, d, J 1.0 Hz, CH=CMe_AMe_B) and 1.73 (6H, d, J 1.0 Hz, CH=CMe_AMe_B); ¹³C NMR δ_C (100 MHz, CDCl₃) 169.3, 150.3, 144.8, 143.2, 131.3, 123.7, 122.7, 61.0, 60.6, 25.6, 24.1, 20.6 and 17.8; MS (+ESI) m/z 363 (MH⁺, 5%) and 385 (MNa⁺, 14); HRMS (+ESI) Found MNa⁺, 385.1975 C₂₁H₃₀NaO₅ requires MNa⁺ 385.1991.

General Procedure: Deacetylation of aromatic acetates

⁹⁵ **Method A:** Following a procedure reported by Bates *et al.* but at a different concentration,³⁸ K₂CO₃ (2 equiv.) was added to a solution of the acetate (1 equiv.) in MeOH (5 mL/mmol) at room temperature and the reaction was stirred for 2 h. The suspension was quenched with saturated aqueous NH₄Cl (30 mL) and extracted with EtOAc (3 \times 15 mL). The combined organic fractions were washed with saturated brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent ¹⁰⁰ removed under reduced pressure. Column chromatography [silica, PE-EtOAc gradient from 100:1 to 75:25] afforded the phenol product.

¹⁰⁵ **Method B:** Following a procedure reported by Narender *et al.*,⁴⁰ NaOAc (10 equiv.) was added to a solution of the acetate (1 equiv.) in EtOH/H₂O (10:1, 5.5 mL/mmol) and the reaction heated at reflux for 5 h. After cooling, the reaction was diluted with H₂O (15 mL) and extracted with EtOAc (3 \times 15 mL). The organic fractions were combined, washed with

saturated brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed under reduced pressure. Column chromatography [silica, PE-EtOAc gradient from 100:1 to 75:25] afforded the phenol product.

3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenol (31a)

Following Method A, acetate **35a** (411 mg, 1.4 mmol) gave the phenol **31a** (173 mg, 49%) as a yellow amorphous solid. Following Method B, acetate **35a** (132 mg, 0.45 mmol) gave the phenol **31a** (41 mg, 36%) as a yellow amorphous solid, in addition to acetate **35a** (53 mg, 40%).

R_f [PE-EtOAc 75:25] 0.25; **IR** ν_{\max} (thin film) 3392, 2963, 1935, 1607, 1505, 1463, 1415, 1357, 1237, 1197, 1164, 1126, 1082, 1040 and 993; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 6.20 (1H, s, C6-ArH), 5.70 (1H, s, OH), 5.19 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, CH=CMe₂), 3.83 (3H, s, OMe), 3.79 (3H, s, OMe), 3.72 (3H, s, OMe), 3.31 (2H, d, *J* 7.0 Hz, ArCH₂), 1.78 (3H, d, *J* 1.0 Hz, CH=CMe_AMe_B) and 1.70 (3H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 151.9, 151.9, 150.9, 136.1, 133.6, 122.6, 113.0, 96.6, 61.2, 61.0, 55.9, 25.7, 22.8 and 17.8; **MS** (+ESI) *m/z* 253 (MH⁺ 100%) and 275 (MNa⁺, 92); **HRMS** (+ESI) Found MNa⁺, 275.1272 C₁₄H₂₀NaO₄ requires MNa⁺ 275.1259.

Consistent with the spectroscopic data previously reported.^{34b}

3,4,5-Trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)phenol (31b)

Following Method A, acetate **35b** (100 mg, 0.27 mmol) gave the phenol **31b** (28 mg, 32%) as a colourless oil.

IR ν_{\max} (thin film) 3461, 2964, 2933, 1605, 1462, 1418, 1357, 1256, 1171, 1097, 1051 and 987; **¹H NMR** δ_{H} (400 MHz, CDCl₃) 5.59 (1H, s, OH), 5.21 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, CH=CMe₂), 3.85 (3H, s, C4-OMe), 3.84 (6H, s, C3/5-OMe), 3.34 (4H, d, *J* 7.0 Hz, ArCH₂), 1.80 (6H, d, *J* 1.0 Hz, CH=CMe_AMe_B) and 1.72 (6H, d, *J* 1.0 Hz, CH=CMe_AMe_B); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 150.1, 149.2, 140.3, 133.4, 122.6, 116.8, 61.1, 60.9, 25.8, 23.1 and 17.8; **MS** (+ESI) *m/z* 321 (MH⁺, 50%); **HRMS** (+ESI) Found MH⁺, 321.2066; C₁₉H₂₉O₄ requires MH⁺ 321.2066.

3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenol (31a) and 1-(6-hydroxy-2,3,4-trimethoxyphenyl)ethanone (36)

Incorporating the procedure reported by Mohammadpoor-Baltork,³⁷ Ac₂O (283 μ l, 3 mmol) was added to a rapidly stirred suspension of Bi(OTf)₃ (136 mg, 0.2 mmol) and phenol **30** (368 mg, 2 mmol) in anhydrous toluene (10 mL) in a thick-walled pressure tube at room temperature under Ar. After 5 min, isoprene (400 μ l, 4 mmol) was added to the solution and the tube was sealed and the reaction heated at 40 °C for 4 h. The solvent was removed and following the procedure reported by Bates *et al.*,³⁸ the residue was dissolved in MeOH (10 mL) and K₂CO₃ (552 mg, 4 mmol) was added. The reaction was stirred for 50 min at room temperature and then quenched with saturated aqueous NH₄Cl (30 mL) and extracted with CH₂Cl₂ (3 \times 30 mL). The combined organic fractions were washed with saturated brine (30 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed

under reduced pressure. Column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30] gave the mono-prenylated product **31a** (223 mg, 44%), consistent with the spectroscopic data reported, in addition to the acetophenone product **36** (39 mg, 9%) as colourless oils.

Acetophenone product (36)

¹H NMR δ_{H} (400 MHz, CDCl₃) 13.39 (1H, s, OH), 6.22 (1H, s, C5-ArH), 3.97 (3H, s, OMe), 3.87 (3H, s, OMe), 3.76 (3H, s, OMe) and 2.63 (3H, s, COMe); **¹³C NMR** δ_{C} (100 MHz, CDCl₃) 203.3, 161.9, 160.1, 155.2, 134.8, 108.5, 96.1, 61.0, 60.9, 56.0 and 31.8.

Consistent with the spectroscopic data previously reported.⁴¹

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Notes and references

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- † Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data and ¹H NMR and ¹³C NMR spectra, as well as selected 2D-NMR data for compound **18**. See DOI: 10.1039/b000000x/
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