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PAPER

$Bi(OTf)_3$-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 novobiocin[2] 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 xanthones[6] and an antimycobacterial benzofurochroman **3**[7] (selected examples are shown in Fig. 1).

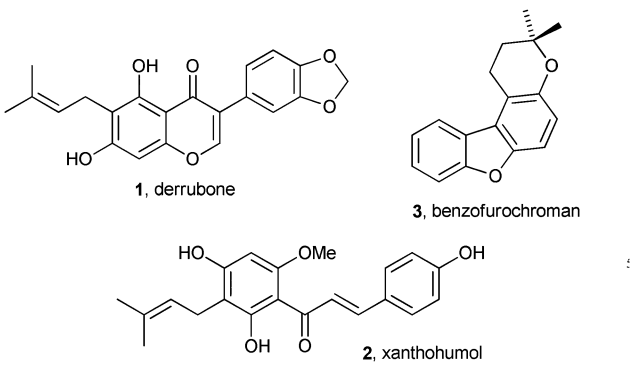
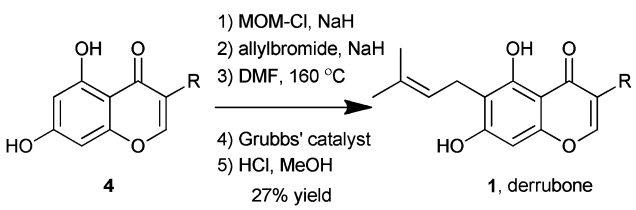


Fig. 1 Selected examples.

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 prenyltranferases NphB and SCO7190 as biocatalysts.[10]

The isoflavone core of derrubone **4** was achieved in an elegant three-step synthesis from commercially available starting materials in 64% yield, without the need for 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 $AlCl_3$,[11] phosphoric acid,[12] Amberlyst®

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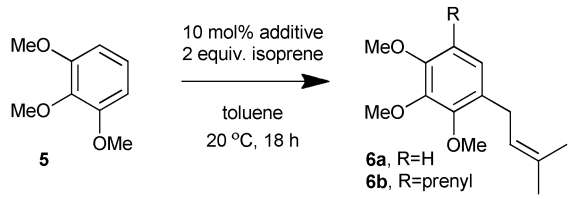
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and ^{1}H NMR and ^{13}C NMR spectra, as well as selected 2D NMR data for compound **18**. See DOI: 10.1039/c1ob05365e

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



		Conversion (%)		
Entry	Additive	**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	$BF_3{\cdot}OEt_2$	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 ^{1}H NMR of the crude reaction mixture after it had been passed through a plug of silica gel.

15,[13] $CpMoCl(CO)_3$,[14] $ZnCl_2$/AcOH,[15] $BF_3{\cdot}OEt_2$,[16] zeolites,[17] Ag(OTf),[18] $Sc(OTf)_3$–ionic liquid,[19] $Cu(OTf)_2$–bipy[20] catalysts, Me_3SiI[21] 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 Me_3SiI 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.

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 $ZrCl_4$ or $AlCl_3$ (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). $BF_3{\cdot}OEt_2$ gave the mono-product **6a** selectively, although the conversion was lower (entry 8). Both $BF_3{\cdot}OEt_2$[16b] and $Sc(OTf)_3$[19] 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 $(4\text{-}ClC_6H_4O)_3P(AuCl)$ and $AgBF_4$ in 65% yield after 16 h at room temperature.[26]

Table 2 The effect of additives[a]

			Isolated yields (%)		
Entry	Additive	Time/h	**5**	**6a**	**6b**
1	None	1.25	0	62	20
2[b]	None	1.5	10	68	23
3	20 μL H_2O	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 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 4 Å molecular sieves was detrimental to the reaction, whilst the addition of H_2O 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 ($Bi(OTf)_3{\cdot}4H_2O$) 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.

The use of anhydrous or reagent grade toluene did not affect the reaction (entries 1 and 2, Table 2); however, with the addition of H_2O, 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 AgOTf[18] 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.

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

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.

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). 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 derivates 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** (Fig. 2).†

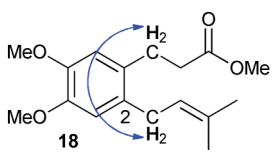
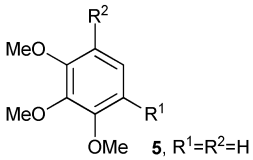
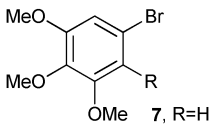
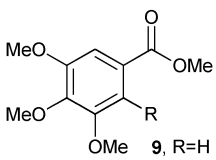
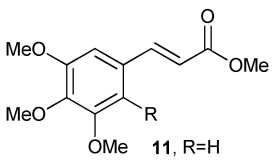
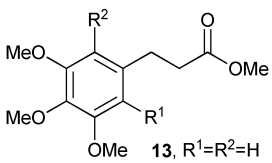
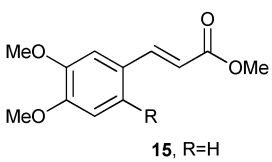
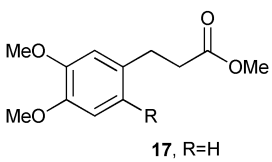


Fig. 2 Key NOESY correlation between highlighted protons.

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 ^{1}H 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.

Table 4 Prenylation of various aryl ethers with isoprene and $Bi(OTf)_3$[a]

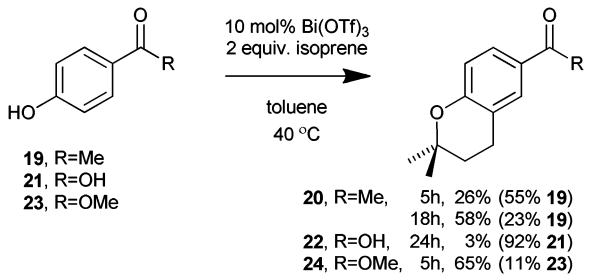
Entry	Arene	Reaction time/h	Product(s) (% yield) sm/mono/bis[b]
1[c]	 **5**, R^1=R^2=H	1.25	—/62 (**6a**)/20 (**6b**)
2	 **7**, R=H	7	50/44 (**8**)/—
3	 **9**, R=H	5	85/15 (**10**)/—
4	 **11**, R=H	4	18/47 (**12**)/—
5	 **13**, R^1=R^2=H	1.5	—/58 (**14a**)/30 (**14b**)
6	 **15**, R=H	6	57/17 (**16**)/—
7	 **17**, R=H	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 R^1 = prenyl R^2 = H, and bis refers to R^1 = R^2 = prenyl. [c] Entry 1, Table 2.

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.

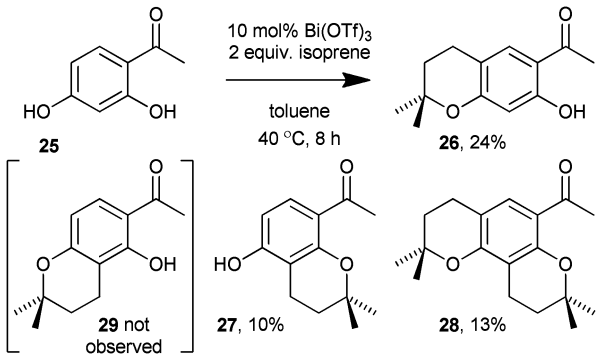
Treatment of the methyl ketone **19** with 10 mol% $Bi(OTf)_3$ and isoprene at 40 °C gave the cyclised product **20** directly in 26% yield after 5 h, with the recovery of 55% of unreacted phenol **19** (Scheme 2). Leaving the reaction for 18 h, however, gave the



Scheme 2 Prenylation of phenol derivatives.

cyclised product **20** in 58% yield 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**.

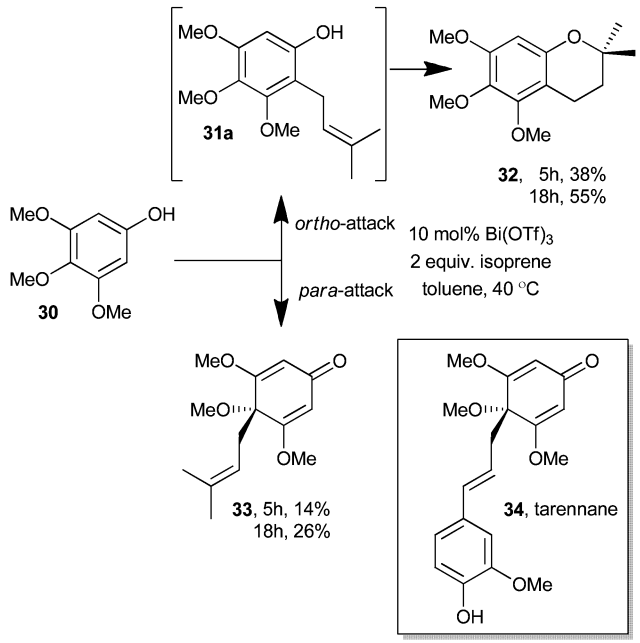
Reaction of 2,4-dihydroxyacetophenone **25** with isoprene in the presence of $Bi(OTf)_3$ gave a mixture of compounds **26** (24%), **27** (10%) and **28** (13%) (Scheme 3). A different mixture of possible products was observed when this reaction was catalysed with H_3PO_4, as chromans **26** (14%), **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.* H_3PO_4).[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 $HCl/AlCl_3$,[32] $BF_3{\cdot}OEt_2$.[33] clay,[30b] zeolites[17] 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 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** to our reaction conditions gave the cyclised chroman **32** directly in 55% yield after 18 h (Scheme 4).

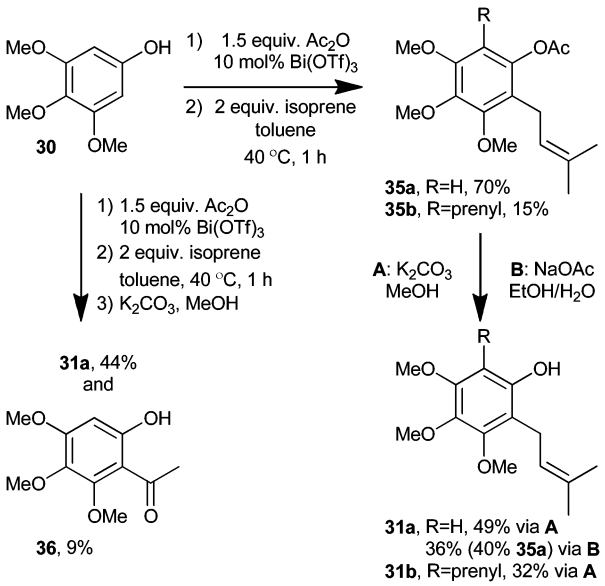


Scheme 4 Prenylation of phenol **30**.

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-360[17] 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 K_2CO_3, 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 H_2O_2 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 Ac_2O in the presence of 1 mol% $Bi(OTf)_3$ in 98% yield after 5 min at room temperature.[37] Incorporation of Ac_2O 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).

Removal of the acetal group was achieved under standard conditions using K_2CO_3 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 K_2CO_3 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%)



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

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 $BF_3{\cdot}OEt_2$[41] and in similar systems in the presence of $Bi(OTf)_3$.[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 micrOTOF™ 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 Parrain[43] 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®, washed 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.

^{1}H 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, ArO*Me*), 3.88 (3H, s, ArO*Me*), 3.70 (3H, s, CO_2Me), 2.93 (2H, t, J 7.5 Hz, ArCH_2) and 2.64 (2H, t, J 7.5 Hz, CH_2CO_2Me); **^{13}C 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

$Bi(OTf)_3$ (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–Et_2O 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; **^{1}H 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, C*H*=CMe_2), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 3.87 (3H, s, OMe), 3.31 (2H, d, *J* 7.5 Hz, ArCH_2), 1.77 (3H, br s, CH=C$Me_A$$Me_B$) and 1.77 (3H, br s, CH=C$Me_A$$Me_B$); **^{13}C 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 6.67 (1H, s, ArH), 5.25 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe_2), 3.91 (3H, s, OMe), 3.83 (6H, s, OMe), 3.27 (4H, d, *J* 7.0 Hz, ArCH_2) and 1.74 (12H, d, *J* 1.5 Hz, CH=CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{19}H_{29}O_3$ 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–Et_2O 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–Et_2O 70 : 30] 0.63; **IR** ν_{max} (thin film) 2935, 1590, 1482, 1452, 1430, 1396, 1313, 1270, 1237, 1195, 1156, 1113, 1045 and 1019; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 6.87 (1H, s, ArH), 5.12 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe_2), 3.84, (6H, s, OMe), 3.82 (3H, s, OMe), 3.42, (2H, d, *J* 7.0 Hz, ArCH_2), 1.79 (3H, br s, CH=C$Me_A$$Me_B$) and 1.68 (3H, d, *J* 1.0 Hz, CH=C$Me_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{14}H_{19}{}^{79}BrNaO_3$ 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–Et_2O 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 7.17 (1H, s, ArH), 5.12 (1H, triplet of septets, *J* 6.5 and 1.5 Hz, C*H*=CMe_2), 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, $ArCH_2$), 1.75 (3H, d, *J* 0.5 Hz, CH=C$Me_A$$Me_B$) and 1.66 (3H, d, *J* 1.0 Hz, CH=C$Me_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{16}H_{23}O_5$ requires MH^+ 295.1546.

Methyl *E*-3-(3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)-phenyl)propenoate (12). Following the general procedure, ester **11** (504 mg, 2 mmol) gave, after 4 h and subsequent column chromatography [silica, PE–Et_2O 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 7.92 (1H, d, *J* 15.5 Hz, C*H*=CHCO$_2$Me), 6.87 (1H, s, ArH), 6.26 (1H, d, *J* 15.5 Hz, CH=C*H*CO$_2$Me), 5.02 (1H, t, *J* 6.5 Hz, C*H*=CMe_2), 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, ArCH_2), 1.81 (3H, s, CH=C$Me_A$$Me_B$) and 1.67 (3H, s, CH=C$Me_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{18}H_{24}NaO_5$ 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–Et_2O 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–Et_2O 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 6.53 (1H, s, ArH), 5.08–5.04 (1H, m, C*H*=CMe_2), 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, ArCH_2CH=CMe_2), 2.93–2.89 (2H, m, Ar$CH_2CH_2CO_2$Me) 2.60–2.56 (2H, m, CH_2CO_2Me), 1.79 (3H, br s, CH=C$Me_A$$Me_B$) and 1.71 (3H, d, *J* 1.0 Hz, CH=C$Me_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{18}H_{26}NaO_5$ requires MNa^+ 345.1678.

Bis-product (14b). R_f [PE–Et_2O 80 : 20] 0.51; **IR** ν_{max}(thin film) 2948, 2933, 1740 (C=O), 1463, 1416, 1334, 1195, 1170, 1096, 1048 and 982; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 5.10–5.06 (2H, m, C*H*=C$Me_A$$Me_B$), 3.91 (3H, s, OMe), 3.85 (6H, s, OMe), 3.72 (3H, s, OMe), 3.36 (4H, d, *J* 6.5 Hz, ArCH_2CH=CMe_2), 2.93–2.89 (2H, m, Ar$CH_2CH_2CO_2$Me), 2.50–2.46 (2H, m, CH_2CO_2Me), 1.79 (6H, d, *J* 1.0 Hz, CH=C$Me_A$$Me_B$) and 1.71 (6H, d, *J* 1.0 Hz, CH=C$Me_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{23}H_{35}O_5$ requires MH^+ 391.2485.

Methyl *E*-3-(4,5-dimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)-propenoate (16). Following the general procedure, ester **15** (446 mg, 2 mmol) gave, after 6 h and subsequent column chromatography [silica, PE–Et_2O 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 7.95 (1H, d, *J* 16.0 Hz, C*H*=CHCO$_2$Me), 7.05 (1H, s, ArH), 6.68 (1H, s, ArH), 6.24 (1H, d, *J* 16.0 Hz, CH=C*H*CO$_2$Me), 5.16 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe_2), 3.87 (3H, s, OMe), 3.87 (3H, s, OMe), 3.78 (3H, s, OMe), 3.40 (2H, d, *J* 7.0 Hz, ArCH_2), 1.76 (3H, br s, CH=C$Me_A$$Me_B$) and 1.71 (3H, d, *J* 1.0 Hz, CH=C$Me_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{17}H_{22}NaO_4$ requires MNa^+ 313.1416.

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–Et_2O gradient from 100 : 0 to 90 : 10], the mono-product **18** (376 mg, 64%) as a colourless oil.

R_f [PE–Et_2O 50 : 50] 0.32; **IR** ν_{max} (thin film) 2934, 2851, 1737 (C═O), 1516, 1458, 1361, 1271, 1209 and 1093; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 6.69 (1H, s, ArH), 6.69 (1H, s, ArH), 5.21 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*═CMe_2), 3.85 (3H, s, OMe), 3.85 (3H, s, OMe), 3.69 (3H, s, OMe), 3.29 (2H, d, *J* 7.0 Hz, ArCH_2CH═CMe_2), 2.92–2.88 (2H, m, Ar$CH_2CH_2CO_2$Me), 2.59–2.55 (2H, m, CH_2CO_2Me), 1.75 (3H, br s, CH═C$Me_A$$Me_B$) and 1.74 (3H, br s, CH═$CMe_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{17}H_{25}O_4$ requires MH^+ 293.1753.

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–Et_2O–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-Et_2O 70 : 30] 0.63; **Mp** 89–93 °C (from CH_2Cl_2); **IR** ν_{max} (thin film) 2976, 1670 (C═O), 1537, 1498, 1419, 1358, 1289, 1265, 1156 and 1117; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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–CH_2), 2.54 (3H, s, COMe), 1.84 (2H, t, *J* 6.5 Hz, C3–CH_2) and 1.37 (6H, s, CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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–CH_2), 1.84 (2H, t, *J* 7.0 Hz, C3–CH_2) and 1.36 (6H, s, CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{12}H_{15}O_3$ requires MH^+ 207.1021.

Consistent with the spectroscopic data previously reported.[49]

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–Et_2O 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-Et_2O 70 : 30] 0.61; **IR** ν_{max} (thin film) 2975, 2948, 1716 (C═O), 1613, 1581, 1493, 1437, 1290, 1263, 1155 and 1118; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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–CH_2), 1.82 (2H, t, *J* 7.0 Hz, C3–CH_2) and 1.34 (6H, s, CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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]

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 the 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.

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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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–CH_2), 2.70 (3H, s, COMe), 1.80 (2H, t, *J* 7.0 Hz, C3–CH_2) and 1.33 (6H, s, CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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–CH_2), 2.64 (3H, s, COMe), 1.87 (2H, t, *J* 7.0 Hz, C3–CH_2) and 1.43 (6H, s, CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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). **IR** ν_{max} (thin film) 2974, 2933, 1662 (C═O), 1603, 1579, 1457, 1357, 1298, 1258, 1178, 1154, 1120 and 1096; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 7.48 (1H, s, C5–ArH), 2.70 (2H, t, *J* 7.0 Hz, C4–CH_2), 2.60 (2H, t, *J* 7.0 Hz, C10–CH_2), 2.56 (3H, s, COMe), 1.76 (2H, t, *J* 7.0 Hz, C9–CH_2), 1.76 (2H, t, *J* 7.0 Hz, C3–CH_2), 1.35 (6H, s, C(8)–CMe_2) and 1.32 (6H, s, C2–CMe_2); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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–Et_2O 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). R_f [PE-Et_2O 80 : 20] 0.52; **IR** ν_{max} (thin film) 2973, 2937, 1611, 1489, 1460, 1413, 1324, 1203, 1158, 1131, 1098, 1045 and 1013; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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–CH_2), 1.73 (2H, t, *J* 7.0 Hz, C3–CH_2), 1.30 (3H, s, C2–C$Me_A$$Me_B$) and 1.28 (3H, s, C2–$CMe_A$$Me_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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). R_f [PE–EtOAc 40 : 60] 0.50; **Mp** 106–109 °C (from CH_2Cl_2); **IR** ν_{max} (thin film) 2934, 2852, 1659 (C=O), 1625, 1597, 1459, 1374, 1240, 1215, 1163, 1078 and 888; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 5.56 (2H, s, C2/C6–CH), 4.66 (1H, triplet of septets, *J* 7.5 and 1.5 Hz, C*H*=CMe$_2$), 3.73 (6H, s, C3/C5–OMe), 3.08 (3H, s, C4–OMe), 2.67 (2H, d, *J* 7.5 Hz, CH_2CH=CMe$_2$), 1.56 (3H, br s, CH=C*Me*$_A$Me$_B$) and 1.52 (3H, br s, CH=CMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{14}H_{21}O_4$ 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–Baltork,[37] Ac_2O (283 µl, 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 µl, 4 mmol) was added to the solution and the tube was sealed and the reaction heated at 40 °C for 1 h. Column chromatography [silica, PE–Et_2O 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). R_f [PE–Et_2O 80 : 20] 0.37; **IR** ν_{max} (thin film) 2937, 1767 (C=O), 1608, 1490, 1456, 1408, 1368, 1339, 1206, 1122, 1075 and 1042; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 6.38 (1H, s, C6–ArH), 5.06 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe$_2$), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.80 (3H, s, OMe), 3.17 (2H, d, *J* 7.0 Hz, ArCH_2), 2.27 (3H, s, Ac), 1.73 (3H, br s, CH=C*Me*$_A$Me$_B$) and 1.66 (3H, d, *J* 1.0 Hz, CH=CMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{16}H_{23}O_5$ requires MH^+ 295.1546.

Bis-product (35b). R_f [PE–Et_2O 80 : 20] 0.61; **IR** ν_{max} (thin film) 2935, 1765 (C=O), 1600, 1463, 1416, 1367, 1346, 1204, 1097,. 1048 and 982; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 5.08 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe$_2$), 3.87 (3H, s, C4–OMe), 3.82 (6H, s, C3/5–OMe), 3.16 (4H, broad s, ArCH_2), 2.52 (3H, s, Ac), 1.73 (6H, d, *J* 1.0 Hz, CH=C*Me*$_A$Me$_B$) and 1.73 (6H, d, *J* 1.0 Hz, CH=CMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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 $C_{21}H_{30}NaO_5$ requires MNa^+ 385.1991.

General procedure: deacetylation of aromatic acetates

Method A: Following a procedure reported by Bates *et al.* but at a different concentration,[38] K_2CO_3 (2 equiv.) was added to a solution of the acetate (1 equiv.) in MeOH (5 mL mmol^{-1}) at room temperature and the reaction was stirred for 2 h. The suspension was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with saturated brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Column chromatography [silica, PE–EtOAc gradient from 100 : 1 to 75 : 25] afforded the phenol product.

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/H_2O (10 : 1, 5.5 mL mmol^{-1}) and the reaction heated at reflux for 5 h. After cooling, the reaction was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic fractions were combined, washed with saturated brine (15 mL), dried over anhydrous Na_2SO_4, 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 6.20 (1H, s, C6–ArH), 5.70 (1H, s, OH), 5.19 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe$_2$), 3.83 (3H, s, OMe), 3.79 (3H, s, OMe), 3.72 (3H, s, OMe), 3.31 (2H, d, *J* 7.0 Hz, ArCH_2), 1.78 (3H, d, *J* 1.0 Hz, CH=C*Me*$_A$Me$_B$) and 1.70 (3H, d, *J* 1.0 Hz, CH=CMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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 $C_{14}H_{20}NaO_4$ 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; **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 5.59 (1H, s, OH), 5.21 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, C*H*=CMe$_2$), 3.85 (3H, s, C4–OMe), 3.84 (6H, s, C3/5–OMe), 3.34 (4H, d, *J* 7.0 Hz, ArCH_2), 1.80 (6H, d, *J* 1.0 Hz, CH=C*Me*$_A$Me$_B$) and 1.72 (6H, d, *J* 1.0 Hz, CH=CMe$_A$*Me*$_B$); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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; $C_{19}H_{29}O_4$ 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] Ac_2O (283 µl, 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 µl, 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 K_2CO_3 (552 mg, 4 mmol) was added. The reaction was stirred for 50 min at room temperature and then quenched with saturated aqueous NH_4Cl (30 mL) and extracted

with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, 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). **^{1}H NMR** δ_H (400 MHz, $CDCl_3$) 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); **^{13}C NMR** δ_C (100 MHz, $CDCl_3$) 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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