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. Selected examples include novobiocin$^7$ and derrubone 1, 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$^5$ and an antimycobacterial benzofurochroman $^3$ (selected examples are shown in Figure 1).

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.$^{15}$ 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,$^7$ 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 SCOT7190 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.$^{10}$ 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-butenel to provide the prenyl group and 5) MOM-deprotection in 27% yield over 5 steps (Scheme 1).

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$^0$ 15,$^{13}$ CpMoCl(CO)$_3$,$^{14}$ ZnCl$_2$/AcOH,$^{15}$ BF$_3$/OEt$_2$,$^{16}$ zeolites,$^{17}$ Ag(OTf)$_2$,$^{18}$ Sc(OTf)$_3$-ionic liquid,$^{19}$ Cu(OTf)$_2$-bipy,$^{20}$ catalysts, Me$_2$Si$^{21}$ and H$_2$.$^{21a}$ 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$_2$Si generated in situ or H$_2$.$^{21a}$

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.

![Scheme 1 Synthesis of derrubone (R=3,4-methylenedioxyphenyl)$^{10}$](image-url)
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, including aromatic sulfonation and Friedel-Crafts acylation. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>ZrCl$_3$</td>
<td>Unidentified mixtures</td>
</tr>
<tr>
<td>3</td>
<td>AlCl$_3$</td>
<td>Unidentified mixtures</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)$_3$</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Zn(OTf)$_2$</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Sc(OTf)$_3$</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>Bi(OTf)$_3$</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>BF$_3$·OEt$_2$</td>
<td>65</td>
</tr>
</tbody>
</table>

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.

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$_3$ 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$_3$·OEt$_2$ gave the mono-product 6a selectively, although the conversion was lower (entry 8). Both BF$_3$·OEt$_2$ and Sc(OTf)$_3$ 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-CIC$_6$H$_4$O)$_3$P(AuCl) and AgBF$_4$ in 65% yield after 16 h at room temperature.

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 H$_2$O had little effect, suggesting that TfOH was the active species. Moreover, the addition of a sterically hindered base (2,6-di-tert-butyl-4-methylpyrididine; DTBMP) was found to inhibit the Bi(OTf)$_3$-catalysed transformation. 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)$_3$·4H$_2$O) of the catalyst. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Isolated yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1.25</td>
<td>5 6a 6b</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>1.5</td>
<td>10 68 25</td>
</tr>
<tr>
<td>3</td>
<td>20 µL H$_2$O</td>
<td>5</td>
<td>5 63 13</td>
</tr>
<tr>
<td>4</td>
<td>DTBMP</td>
<td>6</td>
<td>87 7 0</td>
</tr>
</tbody>
</table>

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)$_3$. Non-anhydrous Reagent Grade toluene was used. 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 H$_2$O, 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. 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, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv.</th>
<th>Time (h)</th>
<th>Isolated yields (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>1.1</td>
<td>2</td>
<td>22 50 7</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
<td>8 65 2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.25</td>
<td>0 62 20</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1.25</td>
<td>0 41 36</td>
</tr>
</tbody>
</table>

a Reactions were all performed on 2 mmol scale in 10 mL of anhydrous toluene at 40 °C with 10 mol% Bi(OTf)$_3$. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene</th>
<th>Reaction time (h)</th>
<th>Product(s) (% yield)</th>
<th>sm / mono / bis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1.25</td>
<td>50 / 44 (8) / –</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>7</td>
<td>50 / 44 (8) / –</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>5</td>
<td>85 / 15 (10) / –</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4</td>
<td>18 / 47 (12) / –</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1.5</td>
<td>– / 58 (14a) / 30 (14b)</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>6</td>
<td>57 / 17 (16) / –</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>6</td>
<td>– / 64 (18) / –</td>
<td>–</td>
</tr>
</tbody>
</table>

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. sm refers to recovered starting material, mono product is either R=prenyl or R₁=prenyl R₂=H and bis refers to R₁=R₂=prenyl. Entry 1, Table 2.

3,4,5-Trimethoxyacetophenone and 3,4,5-trimethoxy-benzaldehyde (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, 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.\(^{12b}\)
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, which has been previously reported with Bi(OTf)$_3$. 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 TIOH (cf. H$_3$PO$_4$). 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$_3$, BF$_3$·OEt$_2$, clay, zeolites as well as Bi(OTf)$_3$.

The prenylated phenol 31a has been isolated from the leaves and stems of Piper clarkii and displays anti-invasive activity against human MCF-7/16 breast carcinoma cells. 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. Youn also reported the synthesis of chroman 32 using a Sc(OTf)$_3$-ionic liquid catalyst system. Substitution of the free phenol 30 to 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 dieneone 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 or Sc(OTf)$_3$ in ionic liquid. A similar transformation was, however, observed in the reaction between 3,4,5-trimethoxyphenol 30 and 3-chloro-3-methylbut-1-ylene with K$_2$CO$_3$, which gave the corresponding ether in addition to the related dieneone from para-attack. It is of great interest that the dieneone 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$_2$O$_2$ damage.

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$_2$O in the presence of 1 mol% Bi(OTf)$_3$ in 98% yield after 5 min at room temperature. Incorporation of Ac$_2$O 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$_2$CO$_3$ 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$_2$CO$_3$ in MeOH gave...
high yields of related Plicatin B (89%)\(^3\) and the 8-prenyl isomer of derrubone (90%)\(^3\), although variable results were also reported (15-67%) with other similar substrates.\(^3\) Narendran 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 Narendran,\(^40\) 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 acetoephene derivative 36 was also isolated in 9% yield, which is obtained from a Fries rearrangement of the aromatic acetate and has been reported with 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 microOTOF™ 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)propanoate 11, methyl 3-(3,4,5-trimethoxyphenyl)propanoate 13, methyl E-3-(3,4-dimethoxyphenyl)-propanoate 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,\(^44\)\(^11\) 13,\(^45\) 15\(^46\) and 23.\(^27\)

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\(^49\), 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.

\(^1\)H NMR \(\delta_H\) (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, \(J_{2.0 \ Hz, \ C2-ArH}\)), 3.87 (3H, s, ArOMe), 2.93 (2H, t, \(J_{7.5 \ Hz, \ ArCH2}\)) and 2.64 (2H, t, \(J_{7.5 \ Hz, \ CH2-CO2Me}\)); \(^13\)C NMR \(\delta_C\) (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-EtO\(_2\)O 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 \(v_{max}\) (thin film) 2936, 1599, 1495, 1464, 1416, 1294, 1256, 1096 and 1017; \(^1\)H NMR \(\delta_H\) (400 MHz, CDCl\(_3\)) 6.66 (1H, d, \(J_{8.5 \ Hz, \ ArH}\)), 6.64 (1H, d, \(J_{8.5 \ Hz, \ ArH}\)), 5.28 (1H, triplet of septets, \(J_{7.5 \ and \ 1.5 \ Hz, \ CH=CMe3}\)), 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, \(CH=CMerMe2B\)) and 1.77 (3H, br s, \(CH=CMerMe2B\)); \(^13\)C NMR \(\delta_C\) (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.\(^26\)
**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-EtO gradient from 0:0 to 95:5], the product 8 (275 mg, 44%) as a colourless oil in addition to recovered starting material 7 (246 mg, 50%).

**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-EtO 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%).

**Bis-product (6b)**

- **IR** ν<sub>max</sub> (thin film) 2965, 2931, 1479, 1460, 1411, 1235, 1092, 1065 and 1015; **1H NMR** δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 6.67 (1H, s, ArH), 5.25 (2H, triplet of septets, J = 7.0 and 1.5 Hz, H<sub>CH=CM<sub>2</sub></sub>), 3.91 (3H, s, OMe), 3.83 (6H, s, OMe), 3.27 (4H, d, J = 7.0 Hz, ArCH<sub>2</sub>) and 1.74 (12H, d, J 1.5 Hz, CH=CM<sub>2</sub>);
- **13C NMR** δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>, 9%); **HRMS** (ESI) Found MH<sup>+</sup>, 305.2103;
- C<sub>18</sub>H<sub>20</sub>O<sub>3</sub> requires MH<sup>+</sup> 305.2117.

**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-EtO 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)**

- **IR** ν<sub>max</sub> (thin film) 2935, 1739 (C=O), 1599, 1578, 1494, 1453, 1406, 1338, 1283, 1239, 1196, 1121, 1073 and 1042; **1H NMR** δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 6.53 (1H, s, ArH), 5.08-5.04 (1H, m, CH=CM<sub>2</sub>), 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<sub>2</sub>CH=CM<sub>2</sub>), 2.93-2.89 (2H, m, ArCH<sub>2</sub>CH=COOMe) 2.60-2.56 (2H, m, CH=COOMe), 1.79 (3H, br s, CH=CM<sub>2</sub>Me<sub>2</sub>), 1.71 (3H, d, J 1.0 Hz, CH=CM<sub>2</sub>Me<sub>2</sub>);
- **13C NMR** δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 173.3, 151.1, 151.2, 149.0, 134.2, 131.2, 126.2, 123.3, 108.4, 60.9, 60.7, 56.1, 51.6, 35.5, 28.3, 25.6, 25.2 and 17.8; **MS** (ESI) m/z 345 (MNa<sup>+</sup>, 24%); **HRMS** (ESI) Found MNa<sup>+</sup>, 345.1661; C<sub>18</sub>H<sub>20</sub>NaO<sub>3</sub> requires MNa<sup>+</sup> 345.1678.

**Bis-product (14b)**

- **IR** ν<sub>max</sub> (thin film) 2948, 2933, 1740 (C=O), 1463, 1416, 1334, 1195, 1170, 1096, 1048 and 982; **1H NMR** δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 5.10-5.06 (2H, m, CH=CM<sub>2</sub>Me<sub>2</sub>), 3.91 (3H, s, OMe), 3.85 (6H, s, OMe), 3.72 (3H, s, OMe), 3.36 (4H, d, J 6.5 Hz, ArCH<sub>2</sub>CH=CM<sub>2</sub>), 2.93-2.89 (2H, m, ArCH<sub>2</sub>CH=COOMe), 2.50-2.46 (2H, m, CH=COOMe), 1.79 (6H, d, J 1.0 Hz, CH=CM<sub>2</sub>Me<sub>2</sub>);
- **13C NMR** δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 173.4, 150.3, 148.8, 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<sup>+</sup>, 20%); **HRMS** (ESI) Found MH<sup>+</sup>, 391.2652; C<sub>22</sub>H<sub>24</sub>O<sub>4</sub> requires MH<sup>+</sup> 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-EtO gradient from 100:0 to 90:10], the mono-product 16 (302 mg, 47%) as a colourless oil in addition to ester 11 (90 mg, 18%).
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-EtOAc gradient from 100:0 to 90:10], the mono-product 18 (376 mg, 64%) as a colourless oil.

IR νmax (thin film) 2934, 1715 (C=O), 1602, 1514, 1458, 1268, 1167 and 1102; 1H NMR δH (400 MHz, CDCl3) 7.95 (1H, d, J 16.0 Hz, CH=CH2), 7.05 (1H, s, ArH), 6.68 (1H, s, ArH), 6.24 (1H, d, J 16.0 Hz, CH=CH2O2Me), 5.16 (1H, triplet of septets, J 7.0 and 1.5 Hz, CH=CMe2), 3.87 (3H, t, OMe), 3.78 (3H, s, OMe), 3.40 (2H, d, J 7.0 Hz, ArCH2), 1.76 (3H, br s, CH3), 1.24 (3H, t, J 7.0 Hz, CH2Me), 1.37 (3H, s, Me2); 13C NMR δC (100 MHz, CDCl3) 171.2, 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 313 (MNa+, 9%); HRMS (+ESI) Found MNa+ 313.1424; C13H22NaO4 requires MNa+ 313.1416.

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-EtOAc gradient from 100:0 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%).

IR νmax (thin film) 2976, 1670 (C=O), 1537, 1498, 1419, 1358, 1289, 1265, 1156 and 1106; 1H NMR δH (400 MHz, CDCl3) 7.75 (1H, d, J 2.5 Hz, C5-ArH), 7.21 (3H, s, C6-ArH), 7.05 (1H, t, J 8.5 Hz, C3-ArH), 2.83 (2H, t, J 7.0 Hz, C4-CH2), 2.45 (2H, s, COMe), 1.84 (2H, t, J 6.5 Hz, C3-CH2) and 1.37 (6H, s, CMe2); 13C NMR δC (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.

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 νmax (thin film) 2975, 1681 (C=O), 1608, 1578, 1443, 1411, 1324, 1296, 1156 and 1120; 1H NMR δH (400 MHz, CDCl3) 7.86 (1H, d, J 2.0 Hz, C5-ArH), 7.84 (1H, d, 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-C3H2) and 1.36 (6H, s, CMe2); 13C NMR δC (100 MHz, CDCl3) 171.2, 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 MNa+ 207.1033; C12H10O3 requires MH+ 207.1021.

Consistent with the spectroscopic data previously reported.

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-EtOAc 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%).

IR νmax (thin film) 2975, 2948, 1716 (C=O), 1613, 1581, 1493, 1437, 1290, 1263, 1155 and 1118; 1H NMR δH (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, CH2Me2); 13C NMR δC (100 MHz, CDCl3) 167.1, 158.3, 131.6, 129.1, 121.5, 120.6, 117.2, 53.7, 51.3, 32.6, 26.9 and 22.3.

Consistent with the spectroscopic data previously reported.

1-(7-Hydroxy-2,2-dimethylchroman-6-yl)ethanone (26), 1-(5-hydroxy-2,2-dimethylchroman-6-yl)ethanone (27) and 1-(2,2,8,8-tetramethyl-2,3,4,8,9,10-hexahydropyran-2,3,6-carboxylates (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 νmax (thin film) 2937, 2957, 1867, 1647 (C=O), 1612, 1495, 1369, 1288, 1280, 1161, 1118, 1058 1020 and 885; 1H NMR δH (400 MHz, CDCl3) 12.30 (1H, s, OH), 7.41 (1H, s, C5-ArH), 6.28 (1H, s, C6-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, CH2Me2); 13C NMR δC (100 MHz, CDCl3) 202.3, 162.8, 161.4, 132.2, 113.9, 112.7, 104.6, 75.9, 32.7, 26.4 and 21.7.

Consistent with the spectroscopic data previously reported.

Chroman (27)

Mp 165-170 °C (from EtOAc); IR νmax (thin film) 3172, 2974, 2931, 1638 (C=O), 1583, 1433, 1362, 1277, 1217, 1157, 1119 and 1051; 1H NMR δH (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, 7.0 Hz, C3-CH3) and 1.43 (6H, s, CMe3); 13C NMR δc (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)

IR vmax (thin film) 2974, 2933, 1662 (C=O), 1603, 1579, 1457, 1357, 1298, 1258, 1178, 1154, 1120 and 1096; 1H NMR δH (400 MHz, CDCl3) 7.48 (1H, s, C5-ArH), 2.70 (2H, t, J 7.0 Hz, C4-CH2), 2.50 (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-CH3), 1.35 (6H, s, C(8)-CMe2) and 1.32 (6H, s, C2-CMe2); 13C NMR δc (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-EtOAc 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)

Rf [PE-EtOAc 80:20] 0.52; IR vmax (thin film) 2973, 2937, 1611, 1489, 1460, 1413, 1324, 1203, 1158, 1131, 1094, 1045 and 1013; 1H NMR δH (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-CH3), 1.30 (3H, s, C2-CMe2Me8) and 1.28 (3H, s, C2-CMe2Me9); 13C NMR δc (100 MHz, CDCl3) 152.4, 151.4, 150.0, 135.4, 106.7, 96.6, 74.0, 61.0, 55.8, 32.4, 26.7 and 17.0.

Consistent with the spectroscopic data previously reported.19

Dienone (33)

Rf [PE-EtOAc 40:60] 0.50; Mp 106-109 °C (from CH2Cl2); IR vmax (thin film) 2934, 2852, 1659 (C=O), 1625, 1597, 1459, 1374, 1240, 1215, 1163, 1078 and 888; 1H NMR δH (400 MHz, CDCl3) 5.56 (2H, s, C2-ArH), 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=CH2), 1.56 (3H, br s, CH=CM3e8) and 1.52 (3H, br s, CH=CM3e9); 13C NMR δc (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; C13H12O2 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 Mohamadpoor-
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%).

Acetophenone product (36)

1H NMR δH (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 δC (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.34b

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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


