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The synthesis of isochroman-4-ols and isochroman-3-ols: models for naturally occurring benzo[*g*]isochromanols

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Abstract—The synthesis of isochromanes containing hydroxy substituents at the 4- and 3-positions has been achieved. The key step for the synthesis of the isochroman-4-ols entailed an oxidative mercury mediated ring closure of 2-(prop-1-enyl)phenylmethanol derivatives, while in the synthesis of the isochroman-3-ols the key step involved ozonolysis of 2-(prop-2-enyl)phenylmethanol derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Moore[1] has postulated that many quinones are biologically active because they are able to act as bioreductive alkylating agents. Examples include the naturally occurring naphthoquinone nanaomycin D **1**,[2] as well as compounds such as granaticin B **2**[3] and griseusin A **3**.[4] Not only do these compounds contain a naphthoquinone skeleton, but they all have oxygen substituents at the C-4 position, a feature that is believed to be important for these compounds to behave as bioreductive alkylating agents.[1] Benzo[*g*]isochromane quinones possessing an oxygen substituent at C-3 also show biological activity, and it is probable that this results from them functioning as bioreductive alkylating agents. Compounds that fall into this class include fusarubin **4**[5] and marticin **5**[6] (Fig. 1).

To date, a number of methods have been developed for the construction of isochromanes and benzo[*g*]isochromane systems containing an oxygen substituent at the 4- or 3-position.[7] In this paper, we report on two different approaches to the synthesis of both 4- and 3-isochromanols, **6**–**11**. Part of this work has been reported as a communication[8] (Fig. 2).

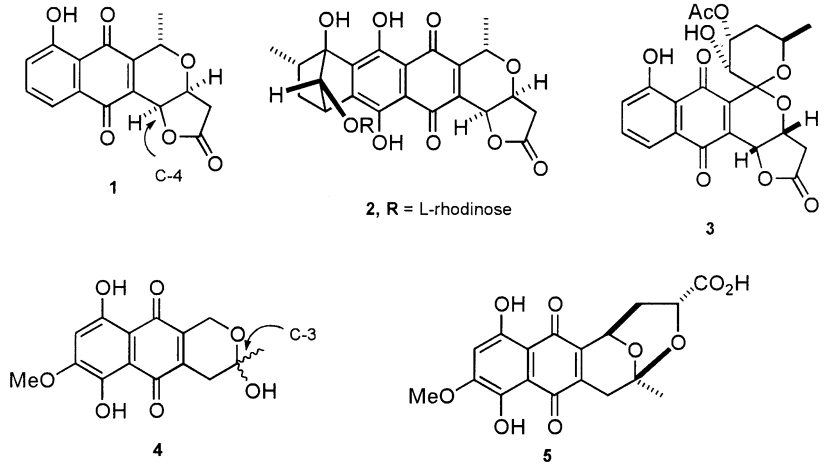

Figure 1.

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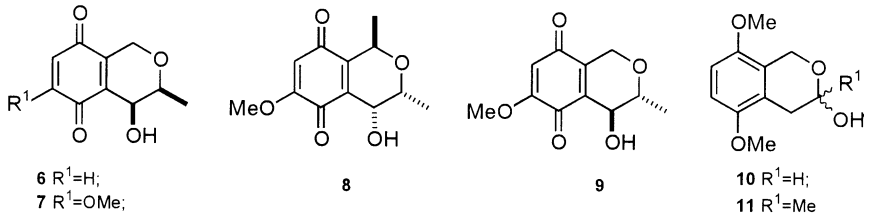


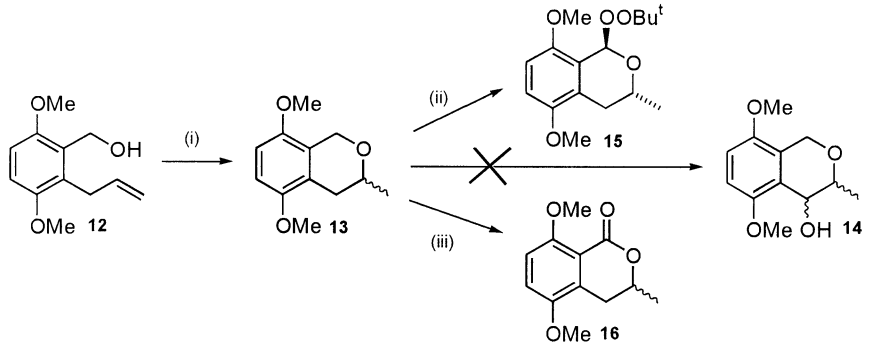
Figure 2.

2. Results and discussion

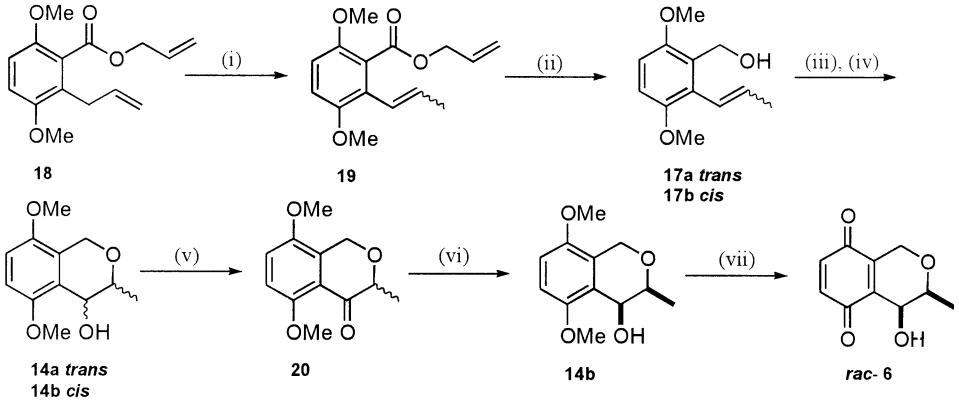
2.1. Synthesis of isochroman-4-ols

It has been demonstrated[9] that treatment of alcohol **12** with potassium *t*-butoxide in DMF affords the isochromane **13**. As a starting point for this work it was thought that **13** could be hydroxylated to the required product **14**, as precedent exists in the corresponding benzo[*g*]isochromane series.[10] However, attempts by a variety of methods[11] failed to produce the required hydroxylated isochromane **14** from **13** and only led to the recovery of starting material or gave an intractable mixture of products. As shown in Scheme 1 two of the attempted methods afforded characterizable, but undesired products. Treatment of isochromane **13** with *t*-butyl hydroperoxide and chromium(VI) oxide[12] yielded the hydroperoxide **15** in 68% yield. The high resolution mass spectrum showed a molecular ion at *m/z* 296.1615 ($C_{15}H_{24}O_5$ requires 296.1624) and the ^{1}H NMR spectrum showed, inter alia, a singlet at δ 1.34 integrating for nine protons. It was clear that oxidation had taken place at C-1 as a singlet was now observed at δ 6.19 while the two signals at C-4 were still present as a doublet of doublets at δ 1.42 and 2.32. The orientation of the newly introduced substituent at C-1 is unclear but it is believed to adopt a pseudoaxial position. By contrast, treatment of **13** with oxygen and with simultaneous irradiation from a 250 W-mercury lamp through a quartz filter afforded the lactone **16** in low yield. Both of these reactions could be useful for the synthesis of natural products containing an isocoumarin nucleus, but these products were not desirable for our purposes.

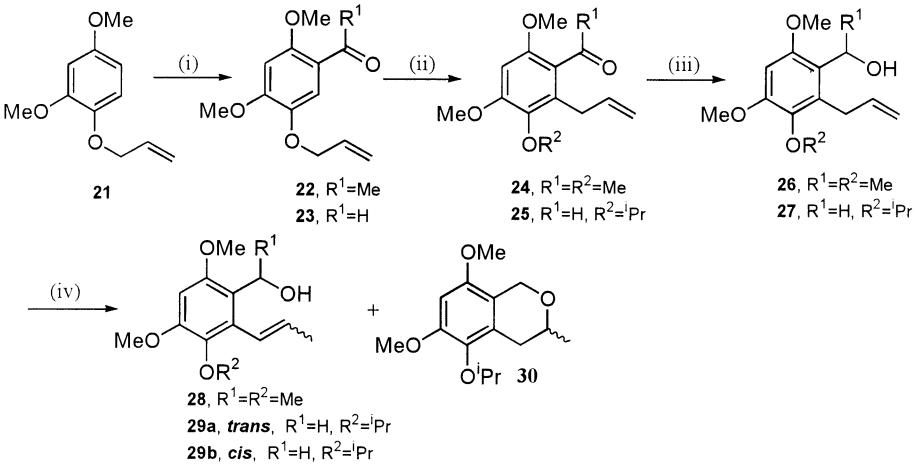
We next chose to examine oxidative ring closures on the related styrene precursor **17**, the synthesis of which is shown in Scheme 2. Treatment of ester **18**[9] with potassium



Scheme 1. *Reagents and conditions*: (i) KOBu^t, DMF, 60°C, 10 min, 82%; (ii) CrO_3, CH_2Cl_2, ^{t}BuOOH, 12 h, 68%; (iii) O_2, $CHCl_3$, $h\nu$, 1 h, 20%.



Scheme 2. *Reagents and conditions*: (i) KOBu^t, DMF, rt, 15 min, 99%; (ii) $LiAlH_4$, Et_2O, 12 h, 98%; (iii) $Hg(OAc)_2$, THF, 15 min; (iv) $NaBH_4$, DMF, O_2, 86%; (v) PCC, CH_2Cl_2, 74%; (vi) $LiAlH_4$, Et_2O, 80%; (vii) AgO, HNO_3, dioxane, 89%.

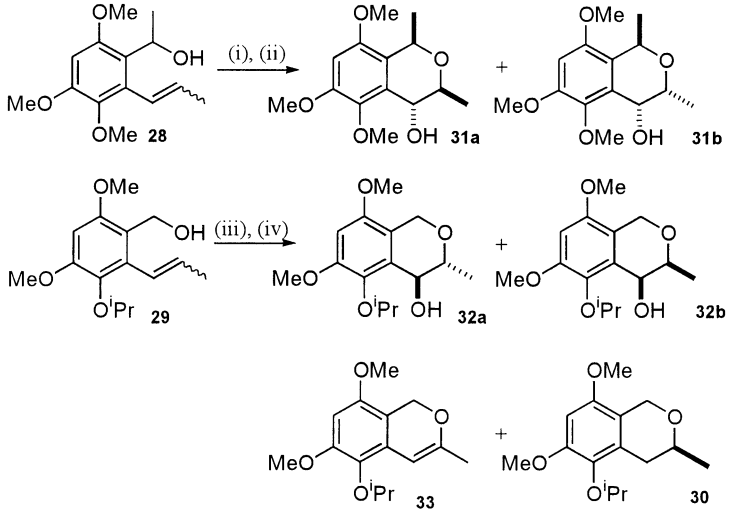


Scheme 3. *Reagents and conditions*: (i) **21**→**22**, AcOH/TFAA, CH_2Cl_2, 67%; **21**→**23**, DMF, $POCl_3$, toluene, 2 h, 95%; (ii) **22**→**24**, (a) 170°C, (b) $(MeO)_2SO_2$, K_2CO_3, Me_2CO, 95%; **23**→**25**, (a) DMF, reflux, (b) ^{i}PrBr, K_2CO_3, Me_2CO, 97%; (iii) **24**→**26**, $LiAlH_4$, Et_2O, 74%; **25**→**27**, $LiAlH_4$, Et_2O, 99%; (iv) **26** **28**, $PdCl_2(MeCN)_2$, 98%; **27**→**29** and **30** KOBu^t, DMF, rt, 15 min, 79% **29** and 15% **30**.

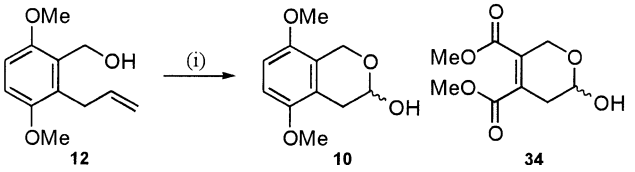
t-butoxide in DMF at room temperature gave **19** almost exclusively as the *trans*-styrene (99% as estimated by ^{1}H NMR spectroscopy). The ^{1}H NMR spectrum showed, inter alia, a doublet of quartets at δ 6.47 (J=16.0 and 1.7 Hz), assigned to the benzylic proton. Reduction of **19** with lithium aluminium hydride afforded the desired styrene **17** in 98% yield. The stage was now set to attempt oxidative ring closures. Optimum conditions involved treatment of alcohol **17** in THF with 1.1 mol equiv. of mercury(II) acetate.[13] This was followed by removal of the THF and reduction of the intermediate acetoxymercuri-isochromane with sodium borohydride in an oxygenated solution of DMF. The desired products **14a** and **14b** (ratio: 1:1) were obtained as a mixture of diastereoisomers in a combined yield of 86%. The mixture of products **14** could be oxidized to ketone **20** using pyridinum chlorochromate in CH_2Cl_2 in 74% yield. This ketone was subsequently reduced with lithium aluminium hydride to afford isochroman-4-ol **14b** as a single diastereoisomer. The ^{1}H NMR spectrum clearly showed the *syn* relationship between H-3 and H-4 with a coupling constant of 1.8 Hz. Isochromane **14b** was then oxidized with silver(II) oxide[14] to afford the first desired quinone **6**, in 89% yield.

More highly substituted analogs of **6** were prepared from allyl ether **21**, the synthesis of which we have recently described.[15] Treatment of **21** with trifluoroacetic acid in the presence of acetic acid afforded the acetophenone **22** in 67% yield,[15] as shown in Scheme 3. Alternatively, exposure of **21** to $POCl_3$ and DMF afforded aldehyde **23** in 95% yield. Claisen rearrangements of **22** and **23** afforded phenols that were not isolated but directly protected as the methyl ether **24**[16] and as the isopropyl ether **25**, respectively. Each product was then reduced in turn with lithium aluminium hydride to afford the desired alcohols **26**[15] and **27** in good yield. Exposure of **26** to palladium(II) chloride–bisacetonitrile[17] gave **28**. Careful treatment of **27** with potassium *t*-butoxide in DMF for 15 min provided **29**, as a 2:1 mixture of *trans*- and *cis*-isomers, together with a small amount of **30**.

As shown in Scheme 4, treatment of **28** with mercury(II)



Scheme 4. *Reagents and conditions*: (i) $Hg(OAc)_2$, THF, 15 min; (ii) $NaBH_4$, NaBr, DMF, O_2, 23% **31a** and 22% **31b**; (iii) $Hg(OAc)_2$, THF, 15 min; (iv) $NaBH_4$, DMF, O_2, 26% **32a**, 22% **32b**, 4% **33** and 25% **30**.



Scheme 5. *Reagents and conditions*: (i) O_3, MeOH, −40°C, (b) Zn, AcOH, 53%; with longer exposure to O_3 formation of **34** was noted.

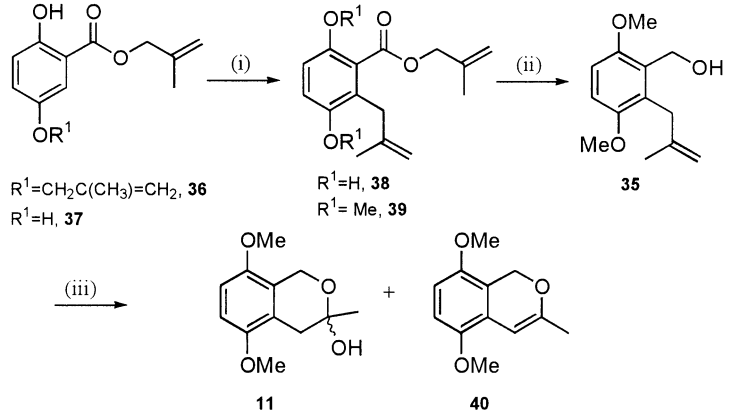
acetate, sodium borohydride and oxygen in DMF afforded a racemic mixture of *cis*-1,3-dimethyl and *trans*-1,3-dimethyl isochroman-4-ols **31a** and **31b**, respectively (45% combined yield, in an approximate ratio of 1:1). The coupling constants derived from the ^{1}H NMR spectrum of **31a** showed that H-3 and H-4 were *anti* to each other (J=8.6 Hz) while in isochromanol **31b** the same two protons were *syn* to each other (J=1.7 Hz). Under the same conditions, alcohol **29** was converted into **32a** and **32b** (combined yield 48%, in an approximate ratio of 1:1) together with isochromane **30** and what is believed to be isochromene **33**. The formation of **30** is ascribed to inefficient oxygenation during the reaction, while **33** could be formed by loss of water from either **32a** or **32b**. Oxidation of **31b**, **32a** and **32b** with silver(II) oxide afforded quinones **8**, **9** and **7**, respectively.

2.2. Synthesis of isochroman-3-ols

While working on the synthesis of isochroman-4-ols it came to our attention that a simple and quick entry to the synthesis of isochroman-3-ols could be accomplished by treatment of **12** with ozone, which would give the corresponding aldehyde. The aldehyde would be in equilibrium with hemiacetal **10**, which contains the isochroman-3-ol skeleton (Scheme 5). In principle, this route could be applied to the synthesis of naturally occurring compounds such as marticin **4** and fusarubin **5**. Treatment of alcohol **12** with ozone for approximately 2 min followed by treatment with zinc in acetic acid afforded the desired isochroman-3-ol **10** in an optimized yield of 53%. The reaction time for the ozonolysis was critical, as exposure of the substrate **12** for longer periods led to the formation of substantial amounts of **34**, showing that electron-rich aromatic rings are also susceptible to oxidation with ozone. It was clear from ^{1}H NMR spectroscopy that product **10** had been formed since apart from the obvious signals two doublets of doublets at δ 2.65 and 2.94 (J=17.1 and 5.2 Hz and J=17.1 and 3.7 Hz), assigned to 4-H, were present. The doublet of doublet of doublets at δ 5.30 (J=5.2, 4.2 and 3.7 Hz) was assigned to H-3, also indicating coupling to the hydroxy proton. The ^{1}H NMR spectrum of **34** showed no signals in the aromatic region, but it was clear that the hydroxy pyran ring system was still present. The high-resolution mass spectrum showed the required molecular ion at 216.0629 ($C_9H_{12}O_6$ requires 216.0634).

The next objective was to attempt the same reaction on the methallyl equivalent **35** in order to access the 3-methylisochroman-3-ol skeleton **11** of fusarubin **5**. Treatment of 2,5-dihydroxybenzoic acid with 1.8 mol equiv. of potassium carbonate and excess methallyl chloride afforded the desired bismethallylated compound **36** in 50% yield and the monomethallylated compound **37** in 36% yield (Scheme 6). These were easily separated by chromatography. Unfortunately, we were unable to improve the yield of **36** further. Compound **36** was heated at 180°C for 18 h, after which the intermediate hydroquinone **38** was immediately protected by treatment with dimethyl sulfate and potassium carbonate in boiling acetone to give the bis(methyl ether) **39** in 33% over two steps. Finally, ester **39** was reduced with lithium aluminium hydride to give **35**. Exposure of alkene **35** to ozone with careful monitoring every 15 s followed by quenching the reaction with excess dimethyl sulfide afforded the desired isochroman-3-ol **11** in 81% yield. Two doublets at δ 2.67 and 2.91 (J=17.2 Hz) were present in the ^{1}H NMR spectrum and were assigned to H-4. A three-proton singlet at δ 1.53 for the additional methyl group at C-3 was also evident. A minor product of this reaction (18%) was the isochromene **40**. Again it was clear from the ^{1}H NMR spectrum that this product had formed as a one-proton signal at δ 5.79 assigned to the benzylic styryl proton was observed. By comparison, attempts to make **11** by Wacker oxidation[18] of alcohol **12** with a catalytic amount of palladium(II) chloride and copper(II) chloride in DMF gave, at best, the desired hemiacetal **11** in 29% yield, with the major product being isochromene **40** (50%).

In summary, two novel methods have been developed for the synthesis of isochroman-4-ols and isochroman-3-ols. At



Scheme 6. *Reagents and conditions*: (i) (a) 180°C, (b) $(MeO)_2SO_2$, Me_2CO, K_2CO_3, 33%; (ii) $LiAlH_4$, Et_2O, 90%; (iii) (a) From **35**, O_3, MeOH, −40°C, (b) Me_2S, 81% **11** and 18% **40**.

present we are in the process of developing these methods for the synthesis of naturally occurring compounds containing this structural motif, viz. nanaomycin D **1** and fusarubin **4**.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded either on a Bruker AC-200, or on a Bruker DRX-400 spectrometer at the frequency indicated. DEPT, CH-correlated and HMBC spectra were run on some samples to enable complete assignments of all the signals. NMR spectral assignments with the same superscript may be interchanged. *J*-Values are given in Hz. Infra-red spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer, or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Elemental analysis was performed on a Perkin–Elmer 2400 CHN Elemental Analyser. Macherey–Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography, and Macherey–Nagel Kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography was distilled prior to use.

3.1.1. 1-*t*-Butylperoxy-5,8-dimethoxy-3-methylisochromane 15. A 25 cm^3 round-bottomed flask was charged with chromium trioxide (8.9 mg, 0.09 mmol), dichloromethane (5 cm^3) and *t*-butyl hydroperoxide (70% in *t*-BuOH, 1.0 cm^3, 0.937 g, 7.3 mmol). The mixture was allowed to stir for 2 min before 5,8-dimethoxy-3-methylisochroman **13**[9] (230 mg, 1.11 mmol) was added, and stirring was continued at ambient temperature under an air atmosphere for 12 h. The reaction was then quenched with water (5 cm^3) and extracted with dichloromethane (4×20 cm^3). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. Chromatography of the residue (eluant 5% ethyl acetate/hexane) to remove traces of starting material afforded 1-*t*-butylperoxy-5,8-dimethoxy-3-methylisochroman **15** as clear to off-white crystals (233 mg, 68%). R_f 0.58 (20% EtOAc/hexane); mp 75–77°C; IR ($CHCl_3$): ν_{max}=1590 cm^{-1} (m, C=C), 1020 (s, C–O); ^{1}H NMR (200 MHz): δ_H=1.34 [9H, s, OOC(CH_3)$_3$], 1.42 (3H, d, *J*=6.3 Hz, 3-CH_3), 2.32 (1H, dd, *J*=17.5 and 11.5 Hz, 4-H_aH_b), 2.78 (1H, dd, *J*=17.5 and 3.6 Hz, 4-H_aH_b), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.41 (1H, dqd, *J*=11.5, 6.3 and 3.6 Hz, 3-H), 6.19 (1H, s, 1-H), 6.68 (1H, d, *J*=8.9 Hz, 7-H)[a], 6.77 (1H, d, *J*=8.9 Hz, 6-H)[a]; ^{13}C NMR (50 MHz): δ_C=21.3 (3-CH_3), 26.5 [OOC(CH_3)$_3$], 29.7 (C-4), 55.6 (OCH_3), 55.6 (OCH_3), 62.2 (C-3), 80.5 [OO*C*(CH_3)$_3$], 96.6 (C-1), 108.0 (C-7)[a], 110.4 (C-6)[a], 120.0 (C-8a)[b], 126.2 (C-4a)[b], 150.5 (C-8)[c], 151.4 (C-5)[c]; MS (EI): *m*/*z* (%): 296 (M$^+$, 2), 222 (11), 208 (12), 207 (100), 192 (10), 179 (13), 58 (19), 43 (19), 32 (76), 28 (98); HRMS calcd for $C_{16}H_{24}O_5$ M 296.1624, found 296.1615.

3.1.2. 5,8-Dimethoxy-3-methylisocoumarin 16. 5,8-Dimethoxy-3-methylisochroman **13** (196 mg, 0.94 mmol) was dissolved in dry chloroform (15 cm^3) in a quartz vessel. Oxygen was bubbled through the solution, which was irradiated with light from a 250 W-mercury lamp for 1 h. The reaction mixture was then washed with a 10% aqueous hydrochloric acid solution and then with a 15% aqueous sodium hydroxide solution. The separated organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. Chromatography (eluant 40% ethyl acetate/hexane) afforded 5,8-dimethoxy-3-methylisocoumarin **16** as a yellow solid (42 mg, 20%). Mp 67–69°C (lit.[19] 69–70°C); IR ($CHCl_3$): ν_{max}=1720 cm^{-1} (s, C=O), 1610 (m, C=C); ^{1}H NMR (200 MHz): δ_H=1.49 (3H, d, *J*=6.3 Hz, 3-CH_3), 2.57 (1H, ddd, *J*=16.9, 11.7 and 0.6 Hz, 4-H_aH_b), 3.15 (1H, dd, *J*=16.9 and 2.9 Hz, 4-H_aH_b), 3.82 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.50 (1H, dqd, *J*=11.7, 6.3 and 2.9 Hz, 3-H), 6.86 (1H, d, *J*=9.1 Hz, 6-H)[a], 7.04 (1H, d, *J*=9.1 Hz, 7-H)[a].

3.1.3. *trans*-Prop-2-enyl 3,6-dimethoxy-2-(prop-1-enyl)-benzoate 19. Prop-2-enyl 3,6-dimethoxy-2-(prop-2-enyl)-benzoate **18**[9] (1.223 g, 4.67 mmol) was dissolved in DMF (45 cm^3). Potassium *t*-butoxide (1.05 g, 9.36 mmol) was added to the stirred solution. The yellow solution turned black after 2 min. The reaction was stirred for 15 min at room temperature under a nitrogen atmosphere. The reaction was quenched with water (100 cm^3) and the aqueous phase was thoroughly extracted with diethyl ether (5×40 cm^3). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography (eluant 10% ethyl acetate/hexane) afforded *trans*-prop-2-enyl 3,6-dimethoxy-2-(prop-1-enyl)benzoate (with traces of the *cis* product) **19** as a yellow oil (1.211 g, 99%). R_f=0.33 (15% EtOAc/hexane); IR (film): ν_{max}=1734 cm^{-1} (s, C=O), 1648 and 1591 (m, C=C); ^{1}H NMR (400 MHz): δ_H=1.84 [3H, dd, *J*=6.6 and 1.7 Hz, =CH(CH_3)], 3.77 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.79 (2H, ddd, *J*=5.8, 1.4 and 1.4 Hz, COOCH_2CH=), 5.26 (1H, ddd, *J*=10.4, 2.8 and 1.4 Hz, =CH_aH$_b$), 5.40 (1H, ddd, *J*=17.2, 2.8 and 1.4 Hz, =CH$_a$$H_b$), 5.99 (1H, ddt, *J*=17.2, 10.4 and 5.8 Hz, COOCH$_2$C*H*=), 6.16 [1H, dq, *J*=16.0 and 6.6 Hz, =C*H*(CH$_3$)], 6.40 (1H, dq, *J*=16.0 and 1.7 Hz, ArCH=), 6.73 (1H, d, *J*=9.0 Hz, 5-H)[a], 6.84 (1H, d, *J*=9.0 Hz, 4-H)[a]; ^{13}C NMR (100 MHz): δ_C=19.2 [=CH(*C*H$_3$)], 56.0 (OCH_3), 56.3 (OCH_3), 65.7 (COO*C*H$_2$CH=), 109.9 (=*C*H$_2$)[a], 112.1 (C-5)[a], 118.5 (C-4)[a], 123.9 (C-2)[b], 124.1 [=*C*H(CH$_3$)], 125.9 (C-1)[b], 131.5 (ArCH=)[c], 131.9 (COOCH$_2$*C*H=)[c], 150.1 (C-6)[d], 151.5 (C-3)[d], 167.7 (CO); MS (EI): *m*/*z* (%): 263 (M+1, 14), 262 (M$^+$, 82), 221 (100), 205 (39), 193 (54), 178 (20), 150 (25), 149 (21), 91 (11), 41 (15); HRMS calcd for $C_{15}H_{18}O_4$ M 262.1205, found 262.1208.

3.1.4. *trans*-[3,6-Dimethoxy-2-(prop-1-enyl)phenyl]-methanol 17a and *cis*-[3,6-dimethoxy-2-(prop-1-enyl)-phenyl]methanol 17b. Prop-2-enyl 3,6-dimethoxy-2-(prop-1-enyl)benzoate **19** (2.79 g, 10.5 mmol) in dry diethyl ether (40 cm^3) was added to a stirred suspension of lithium aluminium hydride (0.80 g, 21 mmol) in dry diethyl ether (40 cm^3). The reaction was stirred under a nitrogen atmosphere for 12 h. The reaction mixture was successively treated with water (0.8 cm^3), aqueous sodium hydroxide (15%, 0.8 cm^3) and water (2.4 cm^3). The aqueous phase

was extracted with diethyl ether (3×100 cm^3) and the combined ether layers were dried with anhydrous magnesium sulfate. The residue obtained upon evaporation of ether under reduced pressure was purified by column chromatography (eluant 40% ethyl acetate/hexane) to afford [3,6-dimethoxy-2-(prop-1-enyl)phenyl]methanol **17a** and **17b** (2.16 g, 98%) as a yellow oil (68:32 ratio, respectively; estimated by NMR spectroscopy). R_f 0.38 (30% EtOAc/hexane); IR (film): ν_{max}=3370 cm^{-1} (s, OH), 1640 and 1600 (m, C=C); ^{1}H NMR (200 MHz) **17a**: δ_H=1.93 [3H, dd, *J*=6.7 and 1.7 Hz, =CH(CH_3)], 2.2 (1H, br s, OH), 3.78 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.77 (2H, s, ArCH_2OH), 5.98 [1H, dq, *J*=16.0 and 6.7 Hz, =C*H*(CH_3)], 6.47 (1H, dq, *J*=16.0 and 1.7 Hz, ArCH=), 6.72 (1H, d, *J*=9.0 Hz, 5-H), 6.78 (1H, d, *J*=9.0 Hz, 4-H); **17b**: δ_H=1.52 [3H, dd, *J*=6.7 and 1.7 Hz, =CH(CH_3)], 2.2 (1H, br s, OH), 3.77 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.67 (2H, s, ArCH_2OH), 5.98 [1H, dq, *J*=11.2 and 6.7 Hz, =C*H*(CH_3)], 6.35 (1H, dq, *J*=11.2 and 1.7 Hz, ArCH=), 6.79 (2H, s, 4-H and 5-H); ^{13}C NMR (50 MHz) **17a**: δ_C=19.1 [=CH(*C*H_3)], 55.7 (OCH_3), 56.0 (OCH_3), 58.3 ($ArCH_2OH$), 108.6 (C-5)[a], 110.1 (C-4)[a], 124.0 [=*C*H(CH_3)], 127.8 (C-2)[b], 128.9 (C-1)[b], 132.4 (ArCH=), 151.4 (C-3)[c], 152.5 (C-6)[c]; **17b**: δ_C=14.6 [=CH(*C*H_3)], 55.6 (OCH_3), 56.0 (OCH_3), 58.9 ($ArCH_2OH$), 109.1 (C-5)[a], 110.0 (C-4)[a], 123.8 [=*C*H(CH_3)], 128.3 (C-2)[b], 128.9 (C-1)[b], 129.7 (ArCH=), 151.2 (C-3)[c], 152.2 (C-6)[c]; MS (EI): *m*/*z* (%): 209 (M+1, 13), 208 (M^+, 100), 179 (17), 177 (22), 175 (30), 165 (60), 161 (21), 147 (18), 121 (22), 115 (33), 107 (20), 105 (37), 103 (26), 91 (61), 77 (54); HRMS calcd for $C_{12}H_{16}O_3$ M 208.1099, found 208.1108.

3.1.5. (3*R,4*S**)-5,8-Dimethoxy-3-methylisochroman-4-ol 14a and (3*R**,4*R**)-5,8-dimethoxy-3-methylisochroman-4-ol 14b.** *cis*- and *trans*-[3,6-Dimethoxy-2-(prop-1-enyl)]-phenylmethanol **17a** and **17b** (364 mg, 1.75 mmol) were dissolved in dry THF (20 cm^3). To this was added mercury(II) acetate (669 mg, 2.10 mmol) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 15 min. The solvent was evaporated under reduced pressure; the residue was dissolved in DMF (15 cm^3) and transferred into a pressure-equalizing dropping funnel. Sodium borohydride (165 mg, 4.37 mmol) was suspended in DMF (15 cm^3), and the suspension was thoroughly purged with oxygen (20 min). To this was added dropwise over a period of 15 min the mercuric salt solution in DMF. The gray suspension was stirred for a further 1 h, at which time the solution was clear, with droplets of mercury evident at the bottom of the reaction vessel. (This does not always occur, and the reaction needs to be monitored by TLC.) The solvent was removed in vacuo and the residue subjected to column chromatography (eluant 10% ethyl acetate/hexane) to afford *trans*-diastereomer (3*R**,4*S**)-5,8-dimethoxy-3-methylisochroman-4-ol **14a** as white crystals (177 mg, 45%). R_f 0.49 (30% EtOAc/hexane); mp 60–61°C (white needles, hexane/dichloromethane); IR ($CHCl_3$): ν_{max}=3438 cm^{-1} (m, OH), 1604 (m, C=C), 1035 (s, C–O); ^{1}H NMR (400 MHz): δ_H=1.41 (3H, d, *J*=6.2 Hz, 3-CH_3), 3.66 (1H, dq, *J*=7.5 and 6.2 Hz, 3-H), 3.74 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.59 (1H, d, *J*=16.0 Hz, ArC$H_a$$H_b$O), 4.59 (1H, d, *J*=7.5 Hz, 4-H), 4.80 (1H, d, *J*=16.0 Hz, $ArCH_a$$H_b$O), 6.67 (1H, d, *J*=8.9 Hz, 6-H)[a], 6.72 (1H, d, *J*=8.9 Hz, 7-H)[a]; ^{13}C NMR (100 MHz): δ_C=18.2 (3-CH_3), 55.4 (OCH_3), 55.6 (OCH_3), 63.4 (C-1)[a], 68.1 (C-4)[a], 74.5 (C-3)[a], 108.5 (C-6)[b], 108.6 (C-7)[b], 125.5 (C-8a)[c], 125.8 (C-4a)[c], 149.2 (C-8)[d], 151.6 (C-5)[d]; MS (EI): *m*/*z* (%): 224 (M^+, 19), 181 (13), 180 (100), 179 (11), 165 (36), 149 (8), 91(9), 77 (9), 43 (9); HRMS: calcd for $C_{12}H_{16}O_4$ M 224.1049, found 224.1036.

Further elution (30% ethyl acetate/hexane) afforded the *cis*-diastereomer (3*R**,4*R**)-5,8-dimethoxy-3-methylisochroman-4-ol **14b** as white crystals (161 mg, 41%). R_f 0.31 (30% EtOAc/hexane); mp 68–70°C (white cubes, hexane); IR ($CHCl_3$): ν_{max}=3403 cm^{-1} (m, OH), 1605 (m, C=C), 1060 (m, C–O); ^{1}H NMR (200 MHz): δ_H=1.43 (3H, d, *J*=6.5 Hz, 3-CH_3), 2.12 (1H, br s, OH), 3.67 (1H, qd, *J*=6.5 and 1.8 Hz, 3-H), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.55 (1H, d, *J*=16.1 Hz, ArC$H_a$$H_b$O), 4.56 (1H, d, *J*=1.8 Hz, 4-H), 4.93 (1H, d, *J*=16.1 Hz, $ArCH_a$$H_b$O), 6.72 (2H, s, 6-H and 7-H); ^{13}C NMR (50 MHz): δ_C=16.7 (3-CH_3), 55.5 (OCH_3), 55.8 (OCH_3), 62.7 (C-1)[a], 64.9 (C-4)[a], 73.8 (C-3)[a], 108.3 (C-6)[b], 109.1 (C-7)[b], 124.7 (C-8a)[c], 126.0 (C-4a)[c], 149.2 (C-8)[d], 151.5 (C-5)[d]; MS (EI): *m*/*z* (%): 224 (M^+, 28), 181 (13), 180 (100), 179 (54), 165 (37), 149 (10), 91 (12), 77 (9), 43 (8); HRMS: calcd for $C_{12}H_{16}O_4$ M 224.1049, found 224.1038.

3.1.6. (±)-5,8-Dimethoxy-3-methylisochroman-4-one 20. A diastereomeric mixture of 5,8-dimethoxy-3-methylisochroman-4-ols **14a** and **14b** (240 mg, 1.07 mmol) was dissolved in dichloromethane (15 cm^3) and cooled to −10°C. A dispersion of pyridinium chlorochromate (1.04 g, 4.80 mmol) and celite (1.04 g) was added to the solution. The orange suspension was stirred for 12 h, after which it was filtered, the solvent evaporated under reduced pressure and the residue purified by column chromatography (eluant 20% ethyl acetate/hexane) to afford 5,8-dimethoxy-3-methylisochroman-4-one **20** as an off-white solid (176 mg, 74%). Mp 143–145°C; IR ($CHCl_3$): ν_{max}= 1710 cm^{-1} (s, C=O), 1599 (m, C=C), 1032 (m, C–O); ^{1}H NMR (200 MHz): δ_H=1.49 (3H, d, *J*=6.6 Hz, 3-CH_3), 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.15 (1H, qd, *J*=6.6 and 1.0, 3-H), 4.68 (1H, dt, *J*=16.2 and 1.0 Hz, 1-$H_a$$H_b$), 5.09 (1H, d, *J*=16.2 Hz, 1-$H_a$$H_b$), 6.85 (1H, d, *J*=9.1 Hz, 6-H)[a], 7.03 (1H, d, *J*=9.1 Hz, 7-H)[a]; ^{13}C NMR (50 MHz): δ_C= 16.0 (CH_3), 55.9 (OCH_3), 56.2 (OCH_3), 62.8 (C-1), 78.2 (C-3), 110.8 (C-6)[a], 116.4 (C-7)[a], 119.0 (C-8a)[b], 132.4 (C-4a)[b], 148.0 (C-8)[c], 153.9 (C-5)[c], 194.9 (C-4); MS (EI): *m*/*z* (%): 222 (M^+, 85), 178 (100), 177 (29), 163 (53), 148 (21), 121 (41), 120(41); HRMS calcd for $C_{12}H_{14}O_4$ M 222.0892, found 222.0881.

3.1.7. (3*R,4*R**)-5,8-Dimethoxy-3-methylisochroman-4-ol 14b.** A solution of isochroman-4-one **20** (196 mg, 0.88 mmol) in dry tetrahydrofuran (5 cm^3) was added to a suspension of lithium aluminium hydride (40 mg, 1.05 mmol) in dry tetrahydrofuran (5 cm^3). The suspension was stirred at ambient temperature under a nitrogen atmosphere for 5 h. The reaction mixture was treated successively with water (0.1 cm^3), aqueous sodium hydroxide (15%, 0.1 cm^3) and water (0.3 cm^3). The white precipitate was removed by filtration, and the solution was concentrated under reduced pressure. Column chromatography of the residue afforded (3*R**,4*R**)-5,8-dimethoxy-3-methylisochroman-4-ol **14b** (176

mg, 89%) as white crystals identical in all respects with the material described above.

3.1.8. (3*R,4*R**)-4-Hydroxy-3-methylisochromane-5,8-quinone 6.** (3*R**,4*R**)-5,8-Dimethoxy-3-methylisochroman-4-ol **14b** (122 mg, 0.54 mmol) was dissolved in dioxane (6 cm^3) and silver(II) oxide (337 mg, 2.72 mmol) was added to the solution. Nitric acid (6 M) was added dropwise to the stirred suspension until all the silver(II) oxide was consumed, resulting in an orange solution. The solution was stirred for a further 2 min and quenched with water (15 cm^3). The aqueous phase was extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. Column chromatography of the residue (eluant 30% ethyl acetate/hexane) afforded (3*R**,4*R**)-4-hydroxy-3-methylisochromane-5,8-quinone **6** (94 mg, 89%) as a red–brown solid. R_f 0.50 (50% EtOAc/hexane); IR ($CHCl_3$): ν_{max}=3419 cm^{-1} (s, br, OH), 1651 (vs, C=O), 1610 (w, C=C), 1054 (m, C–O); ^{1}H NMR (400 MHz): δ_H=1.40 (3H, d, *J*=6.5 Hz, 3-CH_3), 2.45 (1H, d, *J*=6.2 Hz, 4-OH), 3.61 (1H, dq, *J*=6.5 and 2.0 Hz, 3-H), 4.34 (1H, dd, *J*=18.9 and 1.8 Hz, ArCH_aH_b), 4.37 (1H, ddd, *J*=6.2, 2.0 and 1.8 Hz, 4-H), 4.70 (1H, d, *J*=18.9 Hz, ArCH_aH_b), 6.76 (1H, d, *J*=10.2 Hz, 6-H)[a], 6.81 (1H, d, *J*=10.2 Hz, 6-H)[a]; ^{13}C NMR (100 MHz): δ_C=16.0 (3-CH_3), 61.0 (C-3)[a], 63.0 (C-1)[a], 73.5 (C-4), 136.3 (C-6)[b], 136.5 (C-7)[b], 139.0 (C-8a)[c], 141.1 (C-4a)[c], 185.9 (C-8)[d], 186.3 (C-5)[d]; MS (EI): *m/z* (%): 194 (M^+, 3), 150 (100), 122 (27), 121 (22), 95 (14), 94 (21), 82 (10), 66 (19); HRMS calcd for $C_{10}H_{10}O_4$ M 194.0579, found 194.0571.

3.1.9. 2,4-Dimethoxy-5-(prop-2-enyloxy)benzaldehyde 23. 2,4-Dimethoxy-1-(prop-2-enyloxy)benzene **21**[15] (5.36 g, 27.63 mmol) was dissolved in dry toluene (7 cm^3) and the solution was cooled to 0°C. DMF (4.1 cm^3, 4.0 g, 55.3 mmol) and phosphorus(V) oxychloride (3.1 cm^3, 5.1 g, 33.2 mmol) were added, and the solution was stirred under a nitrogen atmosphere at 0°C for 20 min. The yellow solution was heated at reflux for 2 h, turning progressively to dark yellow, then orange and finally black. The solution was allowed to cool and poured into ice slurry of aqueous sodium hydroxide (10%, 50 cm^3). The aqueous layer was extracted with dichloromethane (3×100 cm^3). The combined organic extracts were dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography (eluant 20% ethyl acetate/hexane) afforded 2,4-dimethoxy-5-(prop-2-enyloxy)benzaldehyde **23** (5.82 g, 95%) as a yellow solid. R_f 0.37 (30% EtOAc/hexane); mp 154–156°C; IR (film): ν_{max}=2854 cm^{-1} (s, CHO), 1657 (m, C=O), 1605 (m, C=C), 1037 (m, C–O); ^{1}H NMR (200 MHz): δ_H=3.92 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.57–4.61 (2H, m, OCH_2C=), 5.26–5.46 (2H, m, =CH_2), 6.00–6.18 (1H, m, C*H*=CH_2), 6.49 (1H, s, 3-H), 7.34 (1H, s, 6-H), 10.30 (1H, s, CHO); ^{13}C NMR (50 MHz): δ_C=56.1 (OCH_3), 56.2 (OCH_3), 70.1 (O*C*H_2C=), 96.0 (C-3), 111.3 (=CH_2), 117.3 (C-1), 118.4 (C-6), 132.8 (*C*H=CH_2), 142.4 (C-5), 156.2 (C-4)[a], 158.7 (C-2)[a], 187.9 (CHO); MS (EI): *m/z* (%): 222 (M^+, 32), 181 (100), 153 (63), 151 (100), 125 (9), 110 (5), 109 (4); HRMS calcd for $C_{12}H_{14}O_4$ M 222.0892, found 222.0894.

3.1.10. 3-Isopropoxy-4,6-dimethoxy-2-(prop-2-enyl)benzaldehyde 25. 2,4-Dimethoxy-5-(prop-2-enyloxy)benzaldehyde **23** (1.120 g, 5.05 mmol) was dissolved in DMF (10 cm^3) and heated at reflux with stirring under a nitrogen atmosphere for 20 h. The solution was allowed to cool and a further 40 cm^3 of DMF was added to the solution. 2-Bromopropane (2.4 cm^3, 3.1 g, 25.2 mmol) and potassium carbonate (3.49 g, 25.2 mmol) were added and the resulting suspension was stirred at 80°C under a nitrogen atmosphere for 12 h. The reaction mixture was allowed to cool, filtered, and the solvent removed under reduced pressure. Column chromatography of the residue afforded 3-isopropoxy-4,6-dimethoxy-2-(prop-2-enyl)benzaldehyde **25** (1.29 g, 97%) as a yellow oil. R_f 0.60 (40% EtOAc/hexane); IR (film): ν_{max}=2787 cm^{-1} (w, CHO), 1686 (s, C=O); ^{1}H NMR (400 MHz): δ_H=1.24 [6H, d, *J*=6.2 Hz, OCH(CH_3)$_2$], 3.86 (2H, ddd, *J*=6.0, 1.6 and 1.6 Hz, ArCH_2), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.35 [1H, sept, *J*=6.2 Hz, OC*H*(CH_3)$_2$], 4.89–4.97 (2H, m, =CH_2), 5.91 (1H, ddt, *J*=17.1, 10.2 and 6.0 Hz, C*H*=CH_2), 6.40 (1H, s, 5-H), 10.43 (1H, s, CHO); ^{13}C NMR (100 MHz): δ_C=22.3 [OCH(*C*H_3)$_2$], 30.2 (Ar*C*H_2), 55.6 (OCH_3), 56.0 (OCH_3), 74.8 [O*C*H(CH_3)$_2$], 94.1 (C-5), 114.7 (=CH_2), 116.1 (C-1), 137.0 (*C*H=CH_2), 137.0 (C-2), 138.9 (C-3), 158.3 (C-4)[a], 161.0 (C-6)[a], 190.1 (CHO); MS (EI): *m/z* (%): 264 (M^+, 52), 222 (46), 221 (63), 207 (100), 193 (28), 189 (16), 173 (34); HRMS calcd for $C_{15}H_{20}O_4$ M 264.1362, found 264.1369.

3.1.11. [3-Isopropoxy-4,6-dimethoxy-2-(prop-2-enyl)-phenyl]methanol 27. 3-Isopropoxy-4,6-dimethoxy-2-(prop-2-enyl)benzaldehyde **25** (1.453 g, 5.50 mmol) was dissolved in dry diethyl ether (50 cm^3) and added to a stirred suspension of lithium aluminium hydride (420 mg, 11.0 mmol) in dry diethyl ether (20 cm^3). The gray suspension was stirred at ambient temperature, under a nitrogen atmosphere, for 12 h. The reaction mixture was treated successively with water (0.40 cm^3), aqueous sodium hydroxide (15%, 0.4 cm^3) and water (1.3 cm^3), and stirred for 10 min. The white precipitate was removed by filtration and the filtrate was dried with magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography of the residue (eluant 30% ethyl acetate/hexane) afforded [3-isopropoxy-4,6-dimethoxy-2-(prop-2-enyl)-phenyl]methanol **27** as a clear oil (1.453 g, 99%). R_f 0.46 (40% EtOAc/hexane); IR (film): ν_{max}=3441 cm^{-1} (m, br, OH), 1637 and 1597 (m, C=C); ^{1}H NMR (200 MHz): δ_H= 1.25 [6H, d, *J*=6.2 Hz, OCH(CH_3)$_2$], 2.2 (1H, br s, OH), 3.58 (2H, dt, *J*=5.7 and 1.8 Hz, ArCH_2CH=), 3.85 (6H, 2×s, each OCH_3), 4.35 [1H, sept, *J*=6.2 Hz, OC*H*(CH_3)$_2$], 4.63 (2H, s, ArCH_2OH), 4.87–5.05 (2H, ddt, *J*=17.1, 10.2 and 5.7 Hz, =CH_2), 5.97 (1H, m, C*H*=CH_2), 6.43 (1H, s, 5-H); ^{13}C NMR (50 MHz): δ_C=22.5 [OCH(*C*H_3)$_2$], 30.7 (Ar*C*H_2CH=), 55.8 (2×OCH_3), 57.3 (ArCH_2OH), 74.7 [O*C*H(CH_3)$_2$], 95.3 (C-5), 115.1 (=CH_2), 120.2 (C-1)[a], 133.5 (C-2)[a], 137.8 (*C*H=CH_2), 138.7 (C-3), 152.9 (C-4)[b], 154.4 (C-6)[b]; MS (EI): *m/z* (%): 266 (88), 224 (100), 223 (46), 207 (25), 191 (36), 69 (16); HRMS calcd for $C_{15}H_{22}O_4$ M 266.1518, found 266.1523.

3.1.12. 1-{3,4,6-Trimethoxy-2-[(*E*)-1-propenyl]phenyl}-1-ethanol 28. Alcohol **26**[15] (252 mg, 1.0 mmol) in dry dichloromethane (50 cm^3) was treated with palladium(II)

chloride bisacetonitrile (15 mg) and stirred under argon at 25°C for 3 h. Removal of the palladium salt by flash chromatography (eluant 20% ethyl acetate/hexane) afforded the *trans*-conjugated alcohol **28** (248 mg, 98%) as a low melting semi-solid. R_f 0.40 (20% EtOAc/hexane); IR (nujol); ν_{max}=3536 cm^{-1} (m, OH), 1594 (s, C=C); ^1H NMR (400 MHz): δ_H=1.52 [3H, d, J=6.6 Hz, ArCH(CH_3)], 1.92 [3H, dd, J=6.5, and 1.8 Hz, =CH(CH_3)], 2.3 (1H, br s, OH), 3.68 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.05 [1H, m, CH(OH)], 5.79 (1H, dq, J=16.0, 1 and 6.5 Hz, =CHCH$_3$), 6.40 (1H, dq, J=16.0 and 1.8 Hz, 1ArCH=), 6.48 (1H, s, 6-H); ^{13}C NMR (100 MHz): δ_C= 19.0 (CHCH$_3$), 23.9 (=CHCH$_3$), 55.7 (OCH_3), 56.1 (OCH_3), 60.2 (OCH_3), 67.3 [CH(OH)], 96.6 (C-6), 123.5 (C-2), 124.0 (=CHCH$_3$), 132.2 (ArCH=), 140.8 (C-4)[a], 151.6 (C-1)[a], 154.0 (C-5)[a]; MS (EI): m/z (%): 252 (100), 234 (15), 219 (40), 207 (45), 91 (20), 77 (15), 43 (50); (Calcd for $C_{14}H_{20}O_4$: C, 66.7; H, 7.9%. Found: C, 66.6, H, 7.7%).

3.1.13. *trans*-[3-Isopropoxy-4,6-dimethoxy-2-(prop-1-enyl)-phenyl]methanol 29a, *cis*-[3-isopropoxy-4,6-dimethoxy-2-(prop-1-enyl)phenyl]methanol 29b and (±)-5-isopropoxy-6,8-dimethoxy-3-methylisochromane 30. [3-Isopropoxy-4,6-dimethoxy-2-(prop-2-enyl)phenyl]methanol **27** (521 mg, 1.96 mmol) was dissolved in DMF (25 cm^3). Potassium *t*-butoxide (220 mg, 1.96 mmol) was added and the resulting black solution was stirred under a nitrogen atmosphere, at ambient temperature for 15 min. The reaction mixture was quenched with water (30 cm^3) and thoroughly extracted with diethyl ether. The combined ether extracts were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography of the residue (eluant 10% ethyl acetate/hexane) afforded (±)-5-isopropoxy-6,8-dimethoxy-3-methylisochroman **30** as white crystals (78 mg, 15%). R_f 0.76 (30% EtOAc/hexane); IR ($CHCl_3$); ν_{max}=1610 cm^{-1} (m, C=C), 1120 (s, C–O); ^1H NMR (400 MHz): δ_H=1.25 [3H, d, J=6.2 Hz, OCH(CH_3)$_a$(CH$_3$)$_b$], 1.26 (3H, d, J=6.2 Hz, OCH(CH$_3$)$_a$(CH_3)$_b$], 1.35 (3H, d, J=6.2 Hz, 3-CH$_3$), 2.39 (1H, dd, J=16.8 and 10.6 Hz, 4-CH_aH$_b$), 2.85 (1H, ddd, J=16.8, 2.9 and 1.1 Hz, 4-CH$_a$$H_b$), 3.62–3.67 (1H, dddd, J=10.6, 6.2, 2.9 and 1.1 Hz, 3-H), 3.77 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.36 [1H, sept, J=6.2 Hz, OCH(CH$_3$)$_2$], 4.57 (1H, ddd, J=15.4, 1.1 and 1.1 Hz, 1-CH_aH$_b$), 4.86 (1H, d, J=15.4 Hz, 1-CH$_a$$H_b$), 6.35 (1H, s, 7-H); ^{13}C NMR (100 MHz): δ_C=21.6 (3-CH$_3$), 22.5 [OCH(CH$_3$)$_a$(CH$_3$)$_b$], 22.6 [OCH(CH$_3$)$_a$(CH$_3$)$_b$], 31.4 (C-4), 55.4 (OCH_3), 56.1 (OCH_3), 64.2 (C-1), 70.2 [OCH(CH$_3$)$_2$], 74.2 (C-3), 94.7 (C-7), 115.6 (C-8a)[a], 129.4 (C-4a)[a], 137.9 (C-5), 151.1 (C-6), 151.2 (C-8).

Further elution (30% ethyl acetate/hexane) yielded *trans*-[3-isopropoxy-4,6-dimethoxy-2-(prop-1-enyl)phenyl]methanol **29a** and *cis*-[3-isopropoxy-4,6-dimethoxy-2-(prop-1-enyl)-phenyl]methanol **29b** (64:36, respectively, by NMR ratio, 79%) as a yellow oil. R_f 0.42 (40% EtOAc/hexane); IR (film): ν_{max}=3491 cm^{-1} (m, br, OH), 1588 (s, C=C), 1110 (s, C–O); ^1H NMR (400 MHz) **29a**: δ_H=1.22 [6H, d, J=6.2 Hz, OCH(CH_3)$_2$], 1.91 (3H, dd, J=6.5 and 1.8 Hz, =CHCH_3), 2.3 (1H, br s, OH), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.22 [1H, sept, J=6.2 Hz, OCH(CH$_3$)$_2$], 4.68 (2H, s, ArCH_2OH), 6.04 (1H, dq, J=16.0 and 6.5 Hz, =CHCH$_3$), 6.36–6.51 (2H, m, ArCH= and 5-H); **29b**: δ_H=1.19 [6H, d, J=6.2 Hz, OCH(CH_3)$_2$], 1.54 (3H, dd, J=6.8 and 1.7 Hz, =CHCH_3), 2.3 (1H, br s, OH), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.15 [1H, sept, J= 6.2 Hz, OCH(CH$_3$)$_2$], 4.60 (2H, s, ArCH_2OH), 5.90 (1H, dq, J=11.3 and 6.8 Hz, =CHCH$_3$), 6.36–6.51 (2H, m, ArCH= and 5-H); ^{13}C NMR (100 MHz) **29a**: δ_C=18.9 (=CHCH$_3$), 22.3 [OCH(CH$_3$)$_2$], 55.8 (OCH_3)[a], 55.9 (OCH_3)[a], 57.8 (ArCH$_2$OH)[a], 75.0 [OCH(CH$_3$)$_2$], 95.4 (C-5), 119.1 (C-4), 124.9 (=CHCH$_3$), 132.3 (ArCH=), 134.5 (C-3), 138.5 (C-2), 152.8 (C-1)[b], 154.5 (C-6)[b]; **29b**: δ_C=14.9 (=CHCH$_3$), 22.3 [OCH(CH$_3$)$_2$], 55.7 (OCH_3)[a], 55.8 (OCH_3)[a], 58.2 (ArCH$_2$OH)[a], 75.1 [OCH(CH$_3$)$_2$], 95.5 (C-5), 119.4 (C-4), 124.4 (=CHCH$_3$), 129.4 (ArCH=), 132.5 (C-3), 138.3 (C-2), 152.9 (C-1)[b], 154.1 (C-6)[b]; MS (EI): m/z (%): 266 (82), 224 (87), 223 (37), 209 (20), 207 (33), 206 (42), 205 (87), 191 (100), 181 (50), 177 (22), 175 (40), 161 (21), 91 (25), 77 (32), 65 (20), 43 (44), 41 (50); HRMS calcd for $C_{15}H_{22}O_4$ M 266.1518, found 266.1512.

3.1.14. (1*R,3*S**,4*R**)-5,6,8-Trimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-isochroman-4-ol 31a and (1*R**,3*R**,4*R**)-5,6,8-trimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-isochroman-4-ol 31b.** Alcohol **28** (280 mg, 1.11 mmol) in THF (25 cm^3) was treated with mercury(II) acetate (424 mg, 1.33 mmol) at 25°C and stirred for 30 min, after which time sodium bromide (136 mg, 1.33 mmol) in hot methanol (10 cm^3, 50°C) was added and stirring was continued for an additional 30 min. Removal of the solvents by rotary evaporation at 40°C gave a residue which was dissolved in DMF (25 cm^3). This was added dropwise to a slurry of sodium borohydride (84 mg, 2.22 mmol) in DMF (12 cm^3) into which dry oxygen had previously been bubbled for 5 min. Passage of oxygen was continued for an additional 3 h after addition. Removal of the solvent at 50°C under reduced pressure afforded a gray semi-solid which was mixed with water (40 cm^3) and the resulting suspension was extracted with dichloromethane and the residue obtained was subjected to chromatography (eluant 30% ethyl acetate/hexane) to yield pyran **31a** (65 mg, 22%) as white crystals; mp 111–112°C (hexane), R_f 0.45 (30% EtOAc/hexane); IR (nujol): ν_{max}=3512 cm^{-1} (m, OH), 1604 (s, C=C); ^1H NMR (400 MHz) δ_H=1.45 (3H, d, J= 6.2 Hz, 3-CH$_3$), 1.49 (3H, d, J=6.6 Hz, 1-CH$_3$), 3.44 (1H, dq, J=8.6 and 6.2 Hz, pseudoaxial 3-H), 3.80 (3H, s, OCH_3), 3.90 (6H, s, 2×OCH_3), 4.58 (1H, d, J=8.6 Hz, pseudoaxial 4-H), 4.59 (1H, s, D_2O exchangeable, pseudoequatorial 4-OH), 4.85 (1H, dq, J=6.6 and 1.0 Hz, pseudoaxial 1-H), 6.46 (1H, s, 7-H); ^{13}C NMR (100 MHz) δ_C=18.6 (3-CH$_3$), 21.7 (1-CH$_3$), 55.6 (OCH_3), 56.1 (OCH_3), 61.1 (OCH_3), 69.6 (C-4), 71.1 (C-1), 73.5 (C-3), 96.6 (C-7), 121.2 (C-8a)[a], 132.8 (C-4a)[a], 140.5 (C-5), 151.1 (C-6)[b], 152.4 (C-8)[b]; MS (EI): m/z (%): 268 (100), 250 (10), 235 (95), 209 (50), 191 (30); (Calcd for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5%. Found: C, 62.5; H, 7.6%).

Further elution afforded isochromanol **31b** (78 mg, 26%) as white crystals; mp 100–101°C (hexane), R_f 0.45 (30% EtOAc/hexane); IR (nujol): ν_{max}=3458 cm^{-1} (m, OH), 1616 (m, C=C); ^1H NMR (400 MHz) δ_H=1.40 (3H, d, J=6.2 Hz, 3-CH$_3$), 1.47 (3H, d, J=6.6 Hz, 1-CH$_3$), 1.8 (1H, br s, D_2O exchangeable, pseudoequatorial 4-OH), 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s,

OCH_3), 4.05 (1H, dq, J=6.2 and 1.7 Hz, pseudoaxial 3-H), 4.53 (1H, d, J=1.7 Hz, pseudoequatorial 4-H), 5.04 (1H, q, J=6.6 Hz, 1-H), 6.48 (1H, s, 7-H); ^{13}C NMR (100 MHz) δ_C=16.9 (3-CH_3), 18.3 (1-CH_3), 55.6 (OCH_3), 56.2 (OCH_3), 61.6 (OCH_3), 62.9 (C-4), 66.3 (C-1), 68.4 (C-3), 96.6 (C-7), 119.7 (C-8a)[a], 130.8 (C-4a)[a], 140.7 (C-5), 151.5 (C-6 and C-8); MS (EI): *m/z* (%): 268 (100), 250 (30), 235 (95), 209 (50), 191 (40); (Calcd for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5%. Found: C, 62.5; H, 7.3%).

3.1.15. (3*R,4*S**)-5-Isopropoxy-6,8-dimethoxy-3-methylisochroman-4-ol 32a, (3*R**,4*R**)-5-isopropoxy-6,8-dimethoxy-3-methylisochroman-4-ol 32b, (±)-5-isopropoxy-6,8-dimethoxy-3-methylisochromane 30 and 5-isopropoxy-6,8-dimethoxy-3-methylisochromene 33.** A mixture of *cis*- and *trans*-[3-isopropoxy-4,6-dimethoxy-2-(prop-1-enyl)phenyl]methanol **29** (431 mg, 1.62 mmol) was dissolved in dry THF (20 cm^3). Mercury(II) acetate (620 mg, 1.94 mmol) was added to the solution and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 15 min. The solvent was evaporated under reduced pressure; the residue was dissolved in DMF (15 cm^3) and transferred into a pressure-equalizing dropping funnel. Sodium borohydride (123 mg, 3.24 mmol) was suspended in DMF and the solution was purged thoroughly with oxygen (20 min). The mercuric salt solution in DMF was added dropwise over a period of 15 min. The gray suspension was stirred for a further 1 h, at which time the solution was clear, with droplets of mercury evident at the bottom of the reaction vessel. (This does not always occur and the reaction needs to be monitored by TLC.) The solvent was removed in vacuo and the residue subjected to column chromatography (eluant 10% ethyl acetate/hexane) to afford an inseparable mixture of (±)-5-isopropoxy-6,8-dimethoxy-3-methylisochromane **30** and 5-isopropoxy-6,8-dimethoxy-3-methylisochromene **33** [125 mg, 25%) and (16 mg, 4%), respectively, by NMR spectroscopy ratio], as a white solid. The signals for **30** could be identified by comparison to authentic material. The signals for isochromene **33** could not be fully assigned owing to the small quantity of **33** present in the mixture, but were distinguished by analogy with isochromene **40**.

Further elution (20% ethyl acetate/hexane) afforded (3*R**,4*S**)-5-isopropoxy-6,8-dimethoxy-3-methylisochroman-4-ol **32a** (109 mg, 24%) as a white solid. R_f 0.56 (30% EtOAc/hexane); IR ($CHCl_3$): ν_{max}=3400 cm^{-1} (m, br, OH), 1610 (s, C=C), 1035 (s, C–O); ^{1}H NMR (400 MHz): δ_H=1.23 (3H, d, J=6.2 Hz, 3-CH_3), 1.40 [3H, d, J=6.2 Hz, OCH(CH_3)$_a$(CH_3)$_b$], 1.42 (3H, d, J=6.2 Hz, OCH(CH_3)$_a$(CH_3)$_b$], 3.56 (1H, dq, J=7.8 and 6.2 Hz, 3-H), 3.78 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.50 (1H, s, OH), 4.55 (1H, dd, J=15.4 and 1.0 Hz, PhCH_aH$_b$O), 4.58 (1H, dd, J=7.8 and 1.0 Hz, 4-H), 4.55–4.59 [obscured by signals at 4.55 and 4.58, 1H, OCH(CH_3)$_2$], 4.77 (1H, d, J=15.4 Hz, PhCH_aH$_b$O), 6.41 (1H, s, 7-H); ^{13}C NMR (100 MHz): δ_C=18.3 [OCH(CH_3)$_a$(CH_3)$_b$], 22.1 (3-CH_3), 22.9 [OCH(CH_3)$_a$(CH_3)$_b$], 55.4 (OCH_3), 56.0 (OCH_3), 63.8 (C-1), 69.6 (C-4), 74.6 (C-3), 75.3 [OCH(CH_3)$_2$], 95.9 (C-7), 116.1 (C-8a)[a], 131.6 (C-4a)[a], 138.3 (C-5), 150.9 (C-6)[b], 151.2 (C-8)[b]; MS (EI): *m/z* (%): 222 (M^+, 100), 196 (30), 195 (32), 181 (15), 180 (32), 179 (84), 151 (13); HRMS calcd for $C_{15}H_{22}O_5$ M 282.1467, found 282.1456.

The last set of fractions (eluant 30% ethyl acetate/hexane) afforded (3*S**,4*S**)-5-isopropoxy-6,8-dimethoxy-3-methylisochroman-4-ol **32b** as a white solid (91 mg, 20%). R_f 0.32 (30% EtOAc/hexane); IR ($CHCl_3$): ν_{max}=3400 cm^{-1} (m, br, OH), 1602 (s, C=C), 1070 (s, C–O); ^{1}H NMR (400 MHz): δ_H=1.22 [3H, d, J=6.2 Hz, OCH(CH_3)$_a$(CH_3)$_b$], 1.38 (3H, d, J=6.2 Hz, OCH(CH_3)$_a$(CH_3)$_b$], 1.42 (3H, d, J=6.4 Hz, 3-CH_3), 2.3 (1H, br s, OH), 3.65 (1H, dq, J=6.4 and 1.5 Hz, 3-H), 3.78 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.51 (1H, d, J=15.6 Hz, PhCH_aH$_b$O), 4.56 (1H, d, J=1.5 Hz, 4-H), 4.63 [1H, sept, J=6.2 Hz, OCH(CH_3)$_2$], 4.86 (1H, d, J=15.6 Hz, PhCH_aH$_b$O), 6.45 (1H, s, 7-H); ^{13}C NMR (100 MHz): δ_C=16.7 [OCH(CH_3)$_a$(CH_3)$_b$], 22.1 [OCH(CH_3)$_a$(CH_3)$_b$], 22.3 (3-CH_3), 55.4 (OCH_3), 56.1 (OCH_3), 63.4 (C-4), 64.4 (C-1), 73.7 (C-3), 74.8 [OCH(CH_3)$_2$], 96.6 (C-7), 115.2 (C-8a)[a], 131.3 (C-4a)[a], 139.4 (C-5), 151.0 (C-6)[b], 151.4 (C-8)[b]; MS (EI): *m/z* (%): 282 (M^+, 25), 222 (100), 196 (27), 195 (83), 181 (18), 180 (30), 179 (77); HRMS calcd for $C_{15}H_{22}O_5$ M 282.1467, found 282.1469.

3.1.16. (1*R,3*R**,4*S**)-4-Hydroxy-6-methoxy-1,3-dimethylisochromane-5,8-dione 8.** To a solution of isochromanol **31b** (26 mg, 0.097 mmol) in acetonitrile (2 cm^3) was added water (0.7 cm^3). The mixture was added dropwise to cerium(IV) ammonium nitrate (106 mg, 0.20 mmol) in water (1.0 cm^3). Stirring was continued for an additional 20 min, after which water (30 cm^3) was added and the yellow emulsion was extracted with dichloromethane. The residue obtained after evaporation of the solvent under reduced pressure was subjected to chromatography (eluant 40% ethyl acetate/hexane) to yield quinone **8** as a solid; mp 134–136°C. R_f 0.30 (40% EtOAc/hexane); IR (nujol): ν_{max}=3350 cm^{-1} (br m, OH), 1668 (s, C=C), 1640 (s, C=C); ^{1}H NMR (400 MHz): δ_H=1.37 (3H, d, J=6.2 Hz, 3-CH_3), 1.45 (3H, d, J=6.6 Hz, 1-CH_3), 3.83 (3H, s, 6-OCH_3), 3.94 (1H, dq, J=6.6 and 2.1 Hz, pseudoaxial 3-H), 4.38 (1H, d, J=2.1 Hz, pseudoequatorial 4-H), 4.87 (1H, q, J=6.2 Hz, 1-H), 5.91 (1H, s, 7-H); ^{13}C NMR (100 MHz): δ_C=16.1 (3-CH_3), 18.1 (1-CH_3), 56.3 (OCH_3), 61.0 (C-3), 66.6 (C-1), 67.2 (C-4), 107.7 (C-7), 137.0 (C-8a)[a], 145.2 (C-4a)[a], 158.4 (C-6), 181.2 (8-CO)[b], 186.1 (5-CO); HRMS calcd for $C_{12}H_{14}O_5$ M 238.0842, found 238.0838. (Calc. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9%. Found: C, 60.7; H, 5.7%).

3.1.17. (3*R,4*R**)-4-Hydroxy-6-methoxy-3-methylisochromane-5,8-quinone 7.** (3*R**,4*S**)-5-Isopropoxy-6,8-dimethoxy-3-methylisochroman-4-ol **32b** (52 mg, 0.184 mmol) was dissolved in dioxane (5 cm^3). Silver(II) oxide (114 mg, 0.925 mmol) was added to the solution. Nitric acid (6 M) was added dropwise to the suspension until all the silver(II) oxide had been consumed and an orange solution resulted. The reaction mixture was quenched with water (10 cm^3) and extracted with dichloromethane (3×10 cm^3). The combined extracts were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography of the residue afforded (3*R**,4*R**)-4-hydroxy-6-methoxy-3-methylisochroman-5,8-quinone **7** as an orange–brown solid (15 mg, 37%). R_f 0.43 (50% EtOAc/hexane); ^{1}H NMR (200 MHz): δ_H=1.40 (3H, d, J=6.2 Hz, 3-CH_3), 1.8 (1H, br s, 4-OH), 3.56 (1H, dq, J= 7.6 and 6.2 Hz, 3-H), 3.84 (3H, s, OCH_3), 4.43 (1H, dd,

J=19.8 and 2.7 Hz, 1-H_aH_b), 4.43 (overlaps with signal at 4.43, 1H, ddd, J=7.6, 2.7 and 2.4 Hz, 4-H), 4.64 (1H, dd, J=19.8 and 2.4 Hz, 1-H_aH_b), 5.90 (1H, 2, 7-H); MS (EI): m/z (%): 224 (M^+, 8), 181 (23), 180 (100), 179 (20), 152 (28), 149 (19), 122 (25), 85 (22), 83 (33), 81 (21), 71 (77), 69 (79), 59 (57), 58 (29), 57 (38), 56 (21), 55 (53), 53 (21), 45 (34), 43 (74); HRMS calcd for $C_{11}H_{12}O_5$ M 224.0685, found 224.0673.

3.1.18. (3*R,4*S**)-4-Hydroxy-6-methoxy-3-methylisochromane-5,8-quinone 9.** (3*R**,4*R**)-5-Isopropoxy-6,8-dimethoxy-3-methylisochroman-4-ol **32a** (100 mg, 0.354 mmol) was dissolved in dioxane (5 cm^3). Silver(II) oxide (219 mg, 1.77 mmol) was added to the solution. Nitric acid (6 M) was added dropwise to the suspension until all the silver(II) oxide had been consumed and an orange solution resulted. The reaction mixture was quenched with water (10 cm^3) and extracted with dichloromethane (3×10 cm^3). The combined extracts were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography of the residue afforded (3*R**,4*S**)-4-hydroxy-6-methoxy-3-methylisochromane-5,8-quinone **9** as an orange–red solid (55 mg, 69%). R_f 0.33 (50% EtOAc/hexane); ^{1}H NMR (200 MHz): δ_H=1.39 (3H, d, J=6.4 Hz, 3-CH_3), 2.42 (1H, br s, 4-OH), 3.59 (1H, dq, J=6.4 and 1.9 Hz, 3-H), 3.85 (3H, s, OCH_3), 4.34 (1H, dd, J=19.1 and 1.7 Hz, 1-H_aH_b), 4.40 (overlaps with signal at 4.34, 1H, dd, J=1.9 and 1.7 Hz, 4-H), 4.72 (1H, d, J=19.1 Hz, 1-H_aH_b), 5.96 (1H, 7-H); ^{13}C NMR (50 MHz): δ_C=15.9 (3-CH_3), 56.4 (OCH_3), 60.8 (C-1), 63.2 (C-4), 73.6 (C-3), 107.2 (C-7), 137.3 (C-8a)[a], 141.8 (C-4a)[a], 158.7 (C-6), 180.6 (C-8)[b], 186.1 (C-5)[b]; MS (EI): m/z (%): 224 (M^+, 1), 180 (100), 165 (18), 152 (18), 122 (22), 95 (40), 69 (49); HRMS calcd for $C_{11}H_{12}O_5$ M 224.0685, found 224.0677.

3.1.19. 5,8-Dimethoxyisochroman-3-ol 10 and dimethyl 3,6-dihydro-2-hydroxy-2*H*-pyran-4,5-dicarboxylate 34. *Method A*. [3,6-Dimethoxy-2-(prop-2-enyl)]phenylmethanol **12** (206 mg, 0.99 mmol) was dissolved in methanol (10 cm^3) and cooled to −40°C. Oxygen containing ozone was passed through the solution for periods of 15 s, and the reaction was monitored by TLC each time. When TLC indicated that total conversion of starting material had occurred (~2 min), glacial acetic acid (1.5 cm^3) and zinc dust (0.1 g) were added and the solution was warmed to ambient temperature. The mixture was filtered with suction and the methanol removed under reduced pressure. Water (10 cm^3) was added and the aqueous layer was extracted with dichloromethane (3×10 cm^3). The organic layer was separated dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. Chromatography (eluant 20% ethyl acetate/hexane) afforded 5,8-dimethoxyisochroman-3-ol **10** (222 mg, 53%) as white crystals. Mp 115–117°C (hexane/CH_2Cl_2); IR ($CHCl_3$): ν_{max}=3500 cm^{-1} (m, br, OH), 1620 (m, C=C), 1040 (w, C–O); ^{1}H NMR (200 MHz): δ_H=2.65 (1H, dd, J=17.1 and 5.2 Hz, 4-H_aH_b), 2.94 (1H, dd, J=17.1 and 3.7 Hz, 4-H_aH_b), 3.27 (1H, d, J=4.2 Hz, 3-OH), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.73 (1H, d, J=15.9 Hz, 1-H_aH_b), 4.94 (1H, d, J=15.9 Hz, 1-H_aH_b), 5.30 (1H, ddd, J=5.1, 4.2 and 3.7 Hz, 3-H), 6.62 (1H, d, J=8.9 Hz, 7-H)[a], 6.67 (1H, d, J=8.9 Hz, 6-H)[a]; ^{13}C NMR (50 MHz): δ_C=29.2 (C-4), 55.4 (OCH_3), 55.6 (OCH_3), 60.3 (C-1), 92.1 (C-3), 107.1 (C-7)[a], 107.9 (C-6)[a], 121.2 (C-8a)[b], 123.5 (C-4a)[b], 149.1 (C-8)[c], 151.2 (C-5)[c]; MS (EI): m/z (%): 211 (8), 210 (M^+, 69), 192 (3), 177 (4), 164 (100), 149 (61), 134 (6), 121 (15), 91 (18), 87 (15), 74 (25); HRMS calcd for $C_{11}H_{14}O_4$ M 210.0892, found 210.0890.

Method B. [3,6-Dimethoxy-2-(prop-2-enyl)]phenylmethanol **12** (412 mg, 1.98 mmol) was dissolved in methanol (20 cm^3) and cooled to −40°C. Oxygen containing ozone was passed through the solution for 5 min, after which ozone was no longer absorbed, as indicated by the liberation of iodine from a solution of potassium iodide at the reactor exit. Glacial acetic acid (3 cm^3) and zinc dust (0.2 g) were added and the solution was warmed to ambient temperature. The mixture was filtered with suction and the methanol removed under reduced pressure. Water (10 cm^3) was added and the aqueous layer was extracted with dichloromethane (3×10 cm^3). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. Chromatography (eluant 20% ethyl acetate/hexane) afforded 5,8-dimethoxyisochroman-3-ol **10** (176 mg, 42%) as white crystals. Further elution (20% ethyl acetate/hexane) afforded dimethyl 3,6-dihydro-2-hydroxy-2*H*-pyran-4,5-dicarboxylate **34** (45 mg, 10%) as a yellow oil. IR (film): ν_{max}=3436 cm^{-1} (w, br, OH), 1728 (vs, C=O), 1604 (w, C=C), 1060 and 1044 (C–O); ^{1}H NMR (200 MHz): δ_H=2.42 (1H, ddd, J=18.2, 6.1 and 3.0 Hz, 3-H_aH_b), 2.66 (1H, ddd, J=18.2, 6.9 and 3.0 Hz, 3-H_aH_b), ~3.7 (obscured, 1H, m, OH), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.36 (1H, ddd, J=17.3, 3.0 and 3.0 Hz, 6-H_aH_b), 4.55 (1H, ddd, J=17.3, 3.0 and 3.0 Hz, 6-H_aH_b), 5.27 (1H, dd, J=6.9 and 6.1 Hz, 2-H); ^{13}C NMR (50 MHz): δ_C=31.6 (C-3), 52.3 (OCH_3) 52.5 (OCH_3), 60.2 (C-6), 90.2 (C-2), 131.6 (C-5)[a], 132.2 (C-4)[a], 165.6 (CO), 167.3 (CO); MS (EI): m/z (%): 216 (M^+), 185 (28), 184 (23), 155 (50), 152 (25), 140 (24), 139 (90), 127 (24), 123 (27), 112 (22), 111 (41), 83 (54), 59 (48), 53 (36), 43 (29), 41 (23), 39 (21), 28 (46); HRMS calcd for $C_9H_{12}O_6$ M 216.0634, found 216.0629.

3.1.20. 2-Methylprop-2-enyl 2-hydroxy-5-(2-methylprop-2-enyloxy)benzoate 36 and 2-methylprop-2-enyl 2,5-dihydroxybenzoate 37. 2,5-Dihydroxybenzoic acid (3.83 g, 35.8 mmol) was dissolved in distilled acetone (300 cm^3). 3-Chloro-2-methylpropene (methallyl chloride) (10.6 cm^3, 9.72 g, 107.3 mmol, 3 equiv.), potassium carbonate (8.91 g, 64.5 mmol) and potassium iodide (594 mg, 3.58 mmol) were added to the solution. The resulting mixture was heated at reflux, with stirring, under a nitrogen atmosphere for 12 h. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography (eluant 2.5% ethyl acetate/hexane) to afford 2-methylprop-2-enyl 2-hydroxy-5-(2-methylprop-2-enyloxy)benzoate **36** (4.69 g, 50%) as a yellow oil. R_f 0.84 (30% EtOAc/hexane); IR ($CHCl_3$): ν_{max}=3223 cm^{-1} (w, br, OH), 1686 (s, CO), 1617 (s, C=C), 1084 (m, C–O); ^{1}H NMR (200 MHz): δ_H=1.82 [3H, s, $COOCH_2C(CH_3)$=][a], 1.84 [3H, s, $OCH_2C(CH_3)$=][a], 4.39 [2H, s, $OCH_2C(CH_3)$=], 4.76 [2H, s, $COOCH_2C(CH_3)$=], 4.99–5.09 (4H, m, 2×=CH_2), 6.91 (1H, d, J=9.1 Hz, 3-H), 7.11 (1H, dd, J=9.1 and 3.1 Hz, 4-H), 7.37 (1H, d, J=3.1 Hz, 6-H), 10.37 (1 H, s, OH, D_2O

exchangeable); ^{13}C NMR (50 MHz): δ_C=19.3 [OCH$_2$C(*C*H$_3$)=][a], 19.4 [COOCH$_2$C(*C*H$_3$)=][a], 68.3 [COO*C*H$_2$C(CH$_3$)=], 72.5 [O*C*H$_2$C(CH$_3$)=], 111.9 (C-1), 112.9 [COOCH$_2$C(CH$_3$)=*C*H$_2$][b], 113.4 [OCH$_2$C(CH$_3$)=*C*H$_2$][b], 113.5 (C-6), 118.4 (C-3), 124.5 (C-4), 139.3 [COOCH$_2$*C*(CH$_3$)=][c], 140.8 [OCH$_2$*C*(CH$_3$)=][c], 151.0 (C-5)[d], 156.2 (C-2)[d], 169.4 (CO); MS (EI): *m/z* (%): 262 (M$^+$, 24), 207 (14), 135 (13), 135 (12), 55 (100); HRMS calcd for $C_{15}H_{18}O_4$ M 262.1205, found 262.1205. Further elution (eluant 30% ethyl acetate/hexane) led to the isolation of 2-methylprop-2-enyl 2,5-dihydroxybenzoate **37** (2.68 g, 36%) as white plates. R_f 0.56 (30% EtOAc/hexane); mp 45–47°C; IR (CHCl$_3$): ν_{max}=3397 cm^{-1} (s, OH) and 3250 (br shoulder, OH), 1686 (s, CO), 1622 (m, C=C); ^{1}H NMR (200 MHz): δ_H 1.82 [3H, s, COOCH$_2$C(C*H*$_3$)=], 4.74 [2H, d, *J*=0.5 Hz, COOC*H*$_2$C(CH$_3$)=], 4.96–5.07 (2H, m, =CH$_2$), 6.1 (1H, br s, 5-O*H*, D$_2$O exchangeable), 6.87 (1H, d, *J*=8.9 Hz, 3-H), 7.03 (1H, dd, *J*=8.9 and 3.0 Hz, 4-H), 7.34 (1H, d, *J*=3.0 Hz, 6-H), 10.36 (1H, s, 2-O*H*, D$_2$O exchangeable); ^{13}C NMR (100 MHz): δ_C=19.3 [OCH$_2$C(*C*H$_3$)=][a], 68.5 [COO*C*H$_2$C(CH$_3$)=], 112.2 (C-1), 113.6 [COOCH$_2$C(CH$_3$)=*C*H$_2$][b], 114.8 (C-6)[b], 118.4 (C-3), 124.2 (C-4), 139.1 [COOCH$_2$*C*(CH$_3$)=], 147.9 (C-5)[d], 155.5 (C-2)[d], 169.4 (CO); MS (EI): *m/z* (%): 208 (M$^+$, 46), 137 (47), 136 (100), 108 (12), 81 (12), 55 (65), 53 (12), 52 (12); HRMS calcd for $C_{11}H_{12}O_4$ M 208.0736, found 208.0749.

3.1.21. 2-Methylprop-2-enyl 3,6-dimethoxy-2-(2-methylprop-2-enyl)benzoate 39. 2-Methylprop-2-enyl 2-hydroxy-5-(2-methylprop-2-enyloxy)benzoate **36** (1.286 g, 4.91 mmol) was heated in the absence of solvent at 180°C under a nitrogen atmosphere for 18 h. After cooling, acetone (40 cm^3) was added. Dimethyl sulfate (2.3 cm^3, 3.09 g, 24.5 mmol) and potassium carbonate (3.39 g, 24.5 mmol) were added to the black solution. The reaction mixture was heated at reflux under a nitrogen atmosphere for 18 h. After cooling and filtration, the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (50 cm^3) and successively washed with aqueous ammonia (25%, 3×50 cm^3), dilute hydrochloric acid (2×50 cm^3) and water (50 cm^3). The ether layer was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography of the residue afforded 2-methylprop-2-enyl 3,6-dimethoxy-2-(2-methylprop-2-enyl)-benzoate **39** as a yellow oil (430 mg, 33%). IR (film): ν_{max}=1734 cm^{-1} (s, COO), 1657 and 1607(w, C=C), 1074 (s, C–O); ^{1}H NMR (200 MHz): δ_H=1.71 [3H, d, *J*=0.5 Hz, COOCH$_2$C(C*H*$_3$)=], 1.79 [3H, s, ArCH$_2$C(C*H*$_3$)=], 3.35 [2H, s, ArC*H*$_2$C(CH$_3$)=], 3.75 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 4.46–4.47 [1H, m, ArCH$_2$C(CH$_3$)=C*H*$_a$H$_b$], 4.69 [2H, s, COOC*H*$_2$C(CH$_3$)=] 4.69–4.73 [overlaps with signal at 4.69, 1H, m, ArCH$_2$C(C*H*$_3$)=CH$_a$*H*$_b$], 4.94–4.96 [1H, m, COOCH$_2$C(CH$_3$)=C*H*$_a$H$_b$], 5.08–5.09 [1H, m, COOCH$_2$C(CH$_3$)=CH$_a$*H*$_b$], 6.75 (1H, d, *J*=9.0 Hz, 4-H), 6.85 (1H, d, *J*=9.0 Hz, 5-H); ^{13}C NMR (50 MHz): δ_C=19.4 [COOCH$_2$C(*C*H$_3$)=], 22.7 [ArCH$_2$C(*C*H$_3$)=], 34.5 [Ar*C*H$_2$C(CH$_3$)=], 56.1 (OCH$_3$), 56.2 (OCH$_3$), 68.4 [COO*C*H$_2$C(CH$_3$)=], 109.7 [ArCH$_2$C(CH$_3$)=*C*H$_2$], 110.7 [COOCH$_2$C(CH$_3$)=*C*H$_2$], 112.3 (C-4)[a], 113.5 (C-5)[a], 125.5 (C-1)[b], 127.0 (C-2)[b], 139.7 [COOCH$_2$*C*(CH$_3$)=], 143.6 [ArCH$_2$*C*(CH$_3$)=], 150.2 (C-3)[c], 151.8 (C-6)[c], 167.4 [*C*OOCH$_2$C(CH$_3$)=]; MS (EI): *m/z* (%): 290 (M$^+$, 58), 235 (69), 219 (37), 191 (22), 176 (37), 149 (100), 57 (32), 55 (27); HRMS calcd for $C_{17}H_{22}O_4$ M 290.1518, found 290.1519.

3.1.22. [3,6-Dimethoxy-2-(2-methylprop-2-enyl)phenyl]-methanol 35. 2-Methylprop-2-enyl 3,6-dimethoxy-2-(2-methylprop-2-enyl)benzoate **39** (430 mg, 1.64 mmol) was dissolved in dry diethyl ether (20 cm^3). A suspension of lithium aluminium hydride (250 mg, 6.58 mmol) in diethyl ether (20 cm^3) was added to the solution. The gray suspension was stirred at ambient temperature under a nitrogen atmosphere for 16 h. The reaction mixture was successively treated with water (0.25 cm^3), aqueous sodium hydroxide (15%, 0.25 cm^3) and water (0.25 cm^3). The white precipitate was filtered off, and the solution was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography of the residue (eluant 20% ethyl acetate/hexane) afforded [3,6-dimethoxy-2-(2-methylprop-2-enyl)phenyl]methanol **35** as a clear oil (327 mg, 90%). R_f 0.41 (30% EtOAc/hexane); IR (film): ν_{max}=3420 cm^{-1} (s, br, OH), 1640 and 1600 (m, C=C), 1060 (m, C–O); ^{1}H NMR (200 MHz): δ_H=1.79 [3H, t, *J*=0.6 Hz, ArCH$_2$C(C*H*$_3$)=], 2.6 (1H, br s, OH), 3.46 [2H, s, ArC*H*$_2$C(CH$_3$)=], 3.73 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 4.33–4.34 (1H, m, =C*H*$_a$H$_b$), 4.63 (2H, s, ArC*H*$_2$OH), 4.71–4.74 (1H, m, =CH$_a$*H*$_b$), 6.72 (1H, d, *J*=9.0 Hz, 4-H), 6.79 (1H, d, *J*=9.0 Hz, 5-H); ^{13}C NMR (50 MHz): δ_C=22.9 [ArCH$_2$C(*C*H$_3$)=], 33.1 [Ar*C*H$_2$C(CH$_3$)=], 55.5 (OCH$_3$)[a], 56.0 (OCH$_3$)[a], 57.2 (ArCH$_2$OH)[a], 108.7 (=CH$_2$)[b], 110.0 (C-4)[b], 110.5 (C-5)[b], 128.1 (C-1)[c], 129.0 (C-2)[c], 145.5 [ArCH$_2$*C*(CH$_3$)=], 151.8 (C-3)[d], 152.1 (C-6)[d]; MS (EI): *m/z* (%): 222 (M$^+$, 100), 204 (18), 189 (54), 179 (22), 175 (15), 174 (14), 173 (14), 149 (12), 91 (15), 77 (12), 43 (12); HRMS calcd for $C_{13}H_{18}O_3$ M 222.1256, found 222.1259.

3.1.23. 5,8-Dimethoxy-3-methylisochroman-3-ol 11 and 5,8-dimethoxy-3-methylisochromene 40. *Method A*. [3,6-Dimethoxy-2-(2-methylprop-2-enyl)phenyl]methanol **35** (227 mg, 1.02 mmol) was dissolved in methanol (20 cm^3) and cooled to -40°C. Oxygen containing ozone was passed through the solution for approximately 1 min, after which ozone was no longer absorbed, as indicated by the liberation of iodine from a solution of potassium iodide at the reactor exit. Dimethyl sulfide (0.15 cm^3, 127 mg, 2.04 mmol) was added; the solution was warmed to ambient temperature and stirred for 30 min. The reaction mixture was concentrated under reduced pressure. The residue was subjected to column chromatography (eluant 5% ethyl acetate/hexane) to afford 5,8-dimethoxy-3-methylisochromene **40** as white crystals (38 mg, 0.184 mmol, 18%). R_f 0.65 (20% EtOAc/hexane); mp 52–53°C (hexane/CH$_2$Cl$_2$); IR (CHCl$_3$): ν_{max}=1610 cm^{-1} (m, C=C), 1599 (w, C=C), 1039 (m, C–O); ^{1}H NMR (400 MHz): δ_H=1.85 (3H, d, *J*=0.9 Hz, 3-CH$_3$), 3.66 (3H, s, OCH$_3$), 3.68 (3H, s, OCH$_3$), 5.04 (2H, s, ArCH$_2$O), 5.79 (1H, d, *J*=0.9 Hz, 4-H), 6.50 (1H, d, *J*=8.9 Hz, 7-H)[a], 6.58 (1H, d, *J*=8.9 Hz, 6-H)[a]; ^{13}C NMR (100 MHz): δ_C=19.7 (3-CH$_3$), 55.7 (OCH$_3$), 56.0 (OCH$_3$), 63.4 (C-1), 95.3 (C-4), 108.0 (C-6)[a], 110.0 (C-7)[a], 115.8 (C-4a)[b], 122.1 (C-8a)[b], 146.7 (C-3)[c], 148.8 (C-5)[c], 154.7 (C-8)[c]; MS (EI): *m/z* (%): 206 (M$^+$, 100), 205 (29), 191 (72), 176 (10); HRMS calcd for $C_{12}H_{14}O_3$ M 206.0943, found 206.0946.

Further elution (20% ethyl acetate/hexane) afforded 5,8-dimethoxy-3-methylisochroman-3-ol **11** as a white needles (185 mg, 81%). R_f=0.38 (30% EtOAc/hexane); mp 107–109°C; IR (film): ν_{max}=3470 cm^{-1} (m, br, OH), 1615 (m, C=C), 1070 (w, C–O); ^{1}H NMR (200 MHz): δ_H=1.55 (3H, s, 3-CH_3), 2.67 (1H, d, J=17.2 Hz, 4-H_aH_b), 2.91 (1H, d, J=17.2 Hz, 4-H_aH_b), 2.92 (1H, s, 3-OH), 3.74 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.78 (2H, s, $ArCH_2O$), 6.59 (1H, d, J=9.0 Hz, 7-H)[a], 6.64 (1H, d, J=9.0 Hz, 6-H)[a]; ^{13}C NMR (50 MHz): δ_C=23.0 (3-CH_3), 28.8 (C-4), 55.3 (OCH_3), 55.5 (OCH_3), 58.8 (C-1), 94.3 (C-3), 106.9 (C-7)[a], 107.6 (C-6)[a], 121.3 (C-8a)[b], 123.0 (C-4a)[b], 149.1 (C-8)[c], 151.1 (C-5)[c]; MS (EI): *m/z* (%): 224 (M^+, 39), 207 (5), 206 (6), 191 (5), 181 (6), 164 (100), 149 (61), 91 (21), 77 (18), 65 (10); HRMS calcd for $C_{12}H_{14}O_3$ M 224.1049, found 224.1051.

Method B. [3,6-Dimethoxy-2-(prop-2-enyl)]phenylmethanol **12** (160 mg, 0.77 mmol) was dissolved in a water/DMF mixture (1:1, 3 cm^3). Palladium(II) chloride (14 mg, 0.08 mmol) and copper(II) chloride (103 mg, 0.77 mmol) were added to the solution. Oxygen was bubbled through the reaction mixture, which was stirred at ambient temperature for 2 h. The reaction mixture was filtered, concentrated under reduced pressure and the residue was subjected to column chromatography (eluant 5% ethyl acetate/hexane) to afford 5,8-dimethoxy-3-methylisochromene **40** as white crystals (79 mg, 50%). Further elution (20% ethyl acetate/hexane) afforded 5,8-dimethoxy-3-methylisochroman-3-ol **11** as a yellow oil (50 mg, 29%); characterization as above.

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