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The synthesis of ventiloquinone L, the monomer of cardinalin 3

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Readily available ethyl-4-acetoxy-6,8-dimethoxynaphthalene-2-carboxylate **27** was converted into 1-[3-allyl-4-(benzyloxy)-6,8-dimethoxy-2-naphthyl)-1-ethanol **31** in seven steps. Subjection of this compound to Wacker oxidation conditions provided 5-benzyloxy-7,9-dimethoxy-1,3-dimethyl-1*H*-benzo[*g*]isochromene **32** in good yield. Hydrogenation of the isochromene afforded (±)-*cis*-7,9-dimethoxy-1,3-dimethyl-1*H*-benzo[*g*]isochroman-5-ol **33** as the major product, which was readily converted into ventiloquinone L.

Introduction

The cardinalins (*e.g.* cardinalins 1–3, Fig. 1) are a series of biologically active pyranonaphthoquinone-type pigments isolated from a New Zealand toadstool, *Dermocybe cardinalis*,[1,2] that produces distinctive purple and orange fruit bodies. The simplest of this series of compounds is cardinalin 3 **3**, which is a dimer of another naturally occurring compound, ventiloquinone L **4**, isolated from *Ventilago goughii* (Rhamnaceae).[3] Cardinalin 3 **3** and ventiloquinone L **4** possess a *cis*-1,3-dimethylpyran ring fused to a naphthoquinone nucleus.

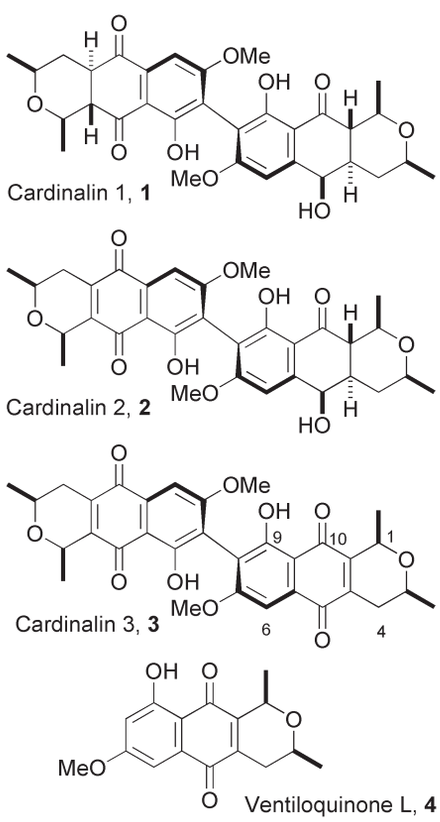

Fig. 1 Cardinalins 1–3 and ventiloquinone L.

While the synthesis of cardinalin 3 has yet to be achieved, there are two previously reported syntheses of ventiloquinone L.[4,5] The synthesis of the related 9-methyl ether, 7-methoxyeleutherin, has also been disclosed.[6,7] In this paper we wish to report our synthesis of ventiloquinone L, by describing three different approaches. The successful synthesis of ventiloquinone L was achieved in 13 steps and in an overall yield of 7.7% starting from commercially available 2,4-dimethoxybenzaldehyde.

Results and discussion

As a result of our experience in the synthesis of *trans*-1,3-dimethylisochromanes and the related naphtho[2,3-*c*]pyrans,[8–10] we believed that the synthesis of an analogue where the two methyl substituents on the pyran ring were *trans* (*e.g.* **5**) would be possible from the corresponding aromatic ester **6**. The aromatic ester **6** could in principle be synthesised from the substituted benzaldehyde **7** by traditional Stobbe condensation methodology as shown in Fig. 2. The aldehyde **7** could in turn be made from the substituted benzene precursor **8** by applying the benzopyran ring-forming reaction conditions described by Giles (KOBu^t, DMF, 80 °C)[11] and then subjecting the resulting styrene **9** to ozonolysis. By using these reaction conditions we believed that the pyran ring of **9** could be formed exclusively with the *trans*- rather than the required *cis*-stereochemistry found in the natural products.[12]

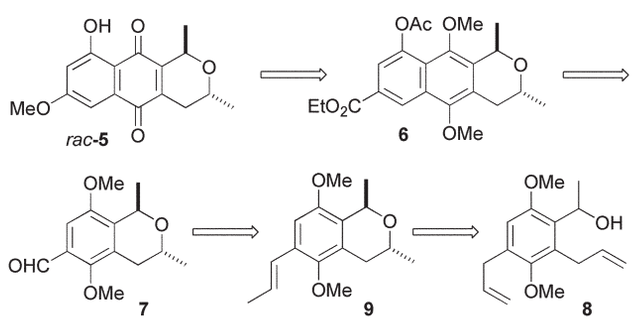

Fig. 2 Retrosynthesis of the ventiloquinone L analogue from a benzene precursor.

Readily available acetophenone **10**[13,14] was subjected to a Claisen rearrangement at 170 °C to afford a mixture of intermediate 2-allyl and 4-allyl acetophenones (Scheme 1). This mixture was alkylated with allyl bromide and then subjected to a second Claisen rearrangement to afford **11**. Methyl protection of phenol **11** afforded the desired pentasubstituted benzene **12**. Reduction of the ketone group of **12** yielded the required alcohol **8**. Subjecting the racemic alcohol **8** to modified Giles reaction conditions[11] (KOBu^t, *N*-methylpyrrolidinone, 100 °C) gave the desired isochromane **9** in good yield. At the same time the additional allyl substituent of **8** isomerised to afford the styrene **9**. As expected the stereochemistry of the isochromane **9** showed that the two methyl substituents were *trans*, with the C-1 methyl occupying a *pseudo*-axial position and the methyl at C-3 adopting an equatorial

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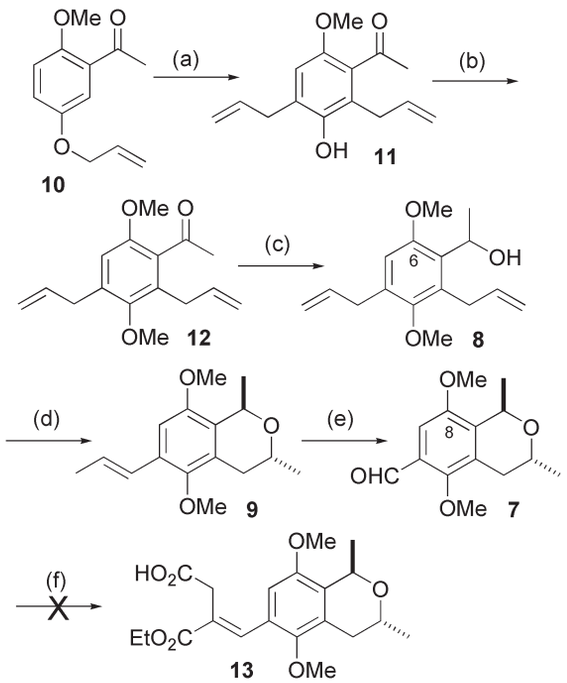


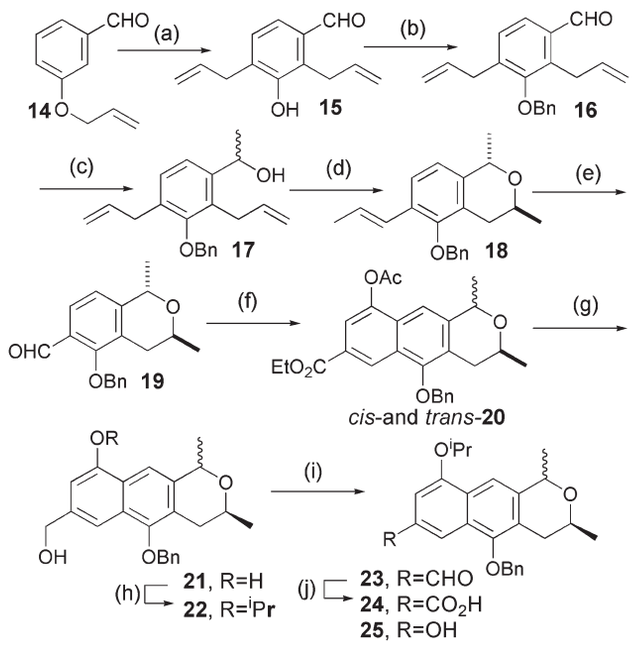
Scheme 1 *Reagents and conditions*: (a) (i) 170 °C, 12 h, 86%, (ii) allyl bromide, K_2CO_3, Me_2CO, reflux, 13 h, 97%; (iii) 160 °C, 7.5 h, 86%; (b) Me_2SO_4, K_2CO_3, Me_2CO, 17 h, reflux, 98%; (c) $LiAlH_4$, THF, rt, 16 h, 89%; (d) KOBu^t, *N*-methylpyrrolidinone, 100 °C, 30 min, 91%; (e) O_3–N_2, propanal–CH_2Cl_2, −94 °C, 7 min, 82%; (f) diethyl succinate, KOBu^t–^{t}BuOH, 100 °C.

orientation. Evidence for this was found in the ^{1}H NMR spectrum where, *inter alia*, the signal for H-3 was found as a multiplet between δ 3.90–4.10.[15] None of the related *cis*-pyran was isolated even when using extended reaction periods.

Careful ozonolysis of the styrene **9** in the presence of propanal to effect reductive ozonolysis[16] afforded aldehyde **7**, in good yield. This product was treated with diethyl succinate under Stobbe condensation conditions. However, all attempts to coerce the Stobbe condensation reaction to yield **13** failed and only starting material was recovered. We ascribe this to the fact that aldehyde **7** is too electron-rich as a result of the two electron-donating methoxy substituents on the benzene ring, resulting in diminished electrophilicity of the carbonyl group. In related work done by Meyers[17] the subsequent aromatic ring-forming reaction to afford the naphthalene was shown to be problematic.

It was felt that if the aldehyde of **7** was made less electron-rich the Stobbe condensation reaction and subsequent ring closure would proceed as expected. For example, if the aromatic oxygen at C-6 of **8** was absent this should provide **7** lacking the methoxy substituent at C-8. We could then attempt the Stobbe condensation. The required aromatic oxygen could be introduced at a later stage of the synthesis by oxidation. Therefore in a similar manner to that described previously, readily available 3-allyloxybenzaldehyde **14**[19] was subjected to a Claisen rearrangement at 180 °C to afford a mixture of intermediate 2-allyl and 4-allyl benzaldehydes. This mixture was again treated with allyl bromide and subjected to a second Claisen rearrangement to afford **15**. Benzyl protection of phenol **15** afforded **16** in excellent yield. The aldehyde **16** was then treated with methylmagnesium iodide to give alcohol **17**. We were now in a position to attempt to form the pyran ring using our modified conditions. We hoped that this reaction would not only afford the *trans*-pyran but also the *cis*-pyran as a result of less steric bulk at the C-8 position of the product **9**. However, based on literature precedent[18] we suspected that this reaction might be difficult to accomplish.

Gratifyingly, under our modified Giles conditions, compound **17** gave both the *trans*- and *cis*-1,3-dimethyl pyrans as predicted. However, the ratio of *cis*- to *trans*-1,3-dimethylpyran in the product **18** depended on how long the reaction was allowed to proceed. Thus pyran **18** was exclusively produced as the racemic 1,3-*trans*-dimethylisochromane if the reaction mixture was worked up after 10 min. If the reaction was left for 30 min about 70% of the 1,3-*cis*-dimethylpyran was formed. As before, in addition to pyran formation, isomerisation of the allyl substituent at C-6 took place to afford the styrene **18**. Ozonolysis of styrene **18** afforded aldehyde **19**, which was subjected to Stobbe condensation with diethyl succinate. In this case, the Stobbe condensation was successful, in accordance with our hypothesis. This was followed by an acetic anhydride-mediated ring closure to afford the naphtho[2,3-*c*]pyran **20**. This reaction was done on both the *trans*-1,3-dimethylpyran **19** as well as the mixture containing predominantly the *cis*-pyran **19** (Scheme 2). However, only the *trans*-naphthopyran **20** was fully characterised.



Scheme 2 *Reagents and conditions*: (a) (i) 180 °C, 24 h, 66%, (ii) allyl bromide, K_2CO_3, Me_2CO, reflux, 18 h, 100%, (iii) 180 °C, 18 h, 43%; (b) BnBr, K_2CO_3, Me_2CO, reflux, 18 h, 100%; (c) MeMgI–Et_2O–THF, 0 °C→rt, 82%; (d) KOBu^t, *N*-methylpyrrolidinone, 100 °C, 10 min, 94%, 100% *trans* (30 min, for 70% *cis*, 30% *trans*); (e) O_3–N_2, propanal–CH_2Cl_2, 7 min, −94 °C, 100%; (f) (i) diethyl succinate, KOBu^t–^{t}BuOH, reflux, 4 h, 97%, (ii) NaOAc–Ac_2O, 130 °C, 4 h, 75%; (g) $LiAlH_4$, THF, 0 °C→rt, 24 h, 93%; (h) ^{i}PrBr, K_2CO_3, Me_2CO, KI, reflux, 24 h, 95%; (i) 1,10-phenanthroline·H_2O, CuCl–benzene, K_2CO_3, reflux, O_2, 18 h, 80%; (j) MMPP, EtOH, rt, 24 h, 72%.

The plan at this stage was to use a series of functional group transformations to convert the ester at C-7 of **20** into the required methyl ether, while ensuring that the oxygen substituent at C-9 of **20** could eventually be converted into a phenol. Reduction of both esters of a mixture containing mainly *cis*-1,3-dimethylnaphthopyran **20** gave **21**. Selective transformation of the phenolic group into an isopropyl ether afforded **22**. It was clear from the ^{1}H NMR spectrum of **22** that the primary alcohol was still present. Oxidation of the alcohol function of **22** with copper(I) chloride in the presence of phenanthroline and oxygen gave the desired intermediate aldehyde **23** in good yield.[20] Unfortunately, Baeyer–Villiger oxidation of the aldehyde **23** followed by silica gel column chromatography unexpectedly and disappointingly afforded the acid **24**, instead of the desired naphthol **25**.[21] All other attempts (including modified Baeyer–Villiger oxidations) to convert the aldehyde into the desired naphthol failed and hence this route was abandoned.

At this stage we thought it might be easier to synthesise the naphthalene and then construct the pyran ring of ventiloquinone L as a last step, as shown in the retrosynthesis in Fig. 3. However, as before, it was realised that if an oxygen substituent was present at C-1 in a precursor such as **26** then in all likelihood the utilisation of the modified Giles methodology for the construction of the pyran ring of **4** would result in the formation of the *trans*-pyran and not the desired *cis*-pyran. Therefore the naphthalene **26** lacking an oxygen at C-1 was chosen as the target as we believed that the required quinone **4** could be made by oxidation from the appropriate naphthol.

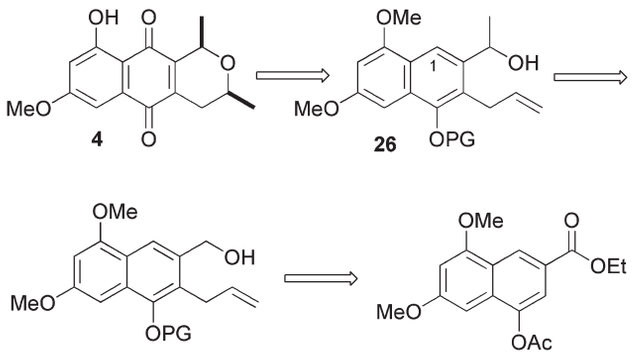
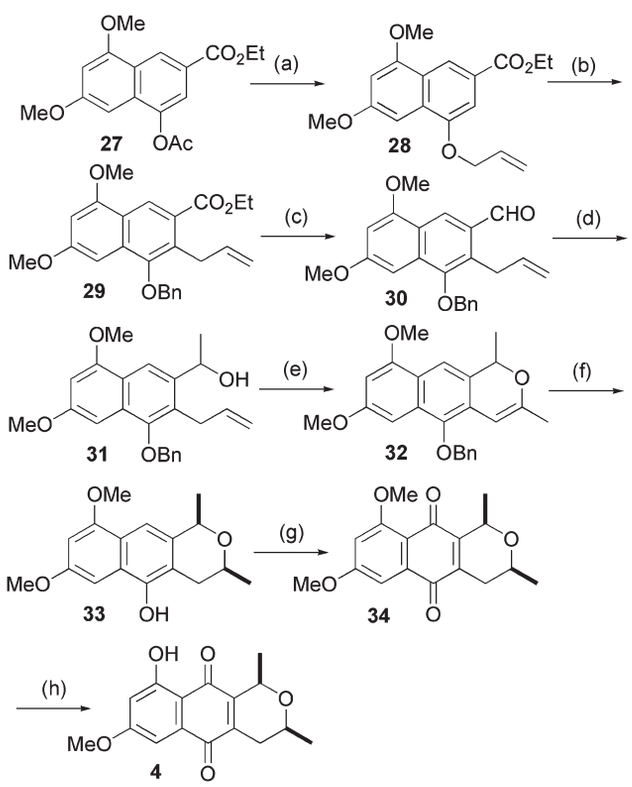


Fig. 3 Retrosynthesis of ventiloquinone L from a naphthalene precursor.

As described in the literature,[22,23] Stobbe condensation of 2,4-dimethoxybenzaldehyde followed by aromatic ring closure afforded the desired naphthalene **27**. Removal of the acetate protecting group of **27** with guanidine hydrochloride and KOBu^t yielded the desired intermediate naphthol in excellent yield.[24] Treatment of this naphthol with allyl bromide in boiling acetone in the presence of K_2CO_3 yielded **28**. Pyrolysis of **28** under our usual Claisen rearrangement reaction conditions followed by protection of the resultant naphthol as the benzyl ether provided **29** (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) (i) guanidine, EtOH–CH_2Cl_2, rt, 1 h, 95%, (ii) allyl bromide, K_2CO_3, Me_2CO, reflux, 16 h, 99%; (b) (i) DMF, 170 °C, 12 h, 75%, (ii) BnCl, KI, K_2CO_3, Me_2CO, 18 h, 100%; (c) (i) $LiAlH_4$, THF, 0 °C→rt, 18 h, 95%, (ii) PCC–Al_2O_3, CH_2Cl_2, rt, 8 h, 78%; (d) MeMgI–Et_2O–THF, 0 °C→rt, 8 h, 95%; (e) 10% $PdCl_2$–$CuCl_2{\cdot}H_2O$–DMF, rt, O_2, 3 h, 92%; (f) 10% Pd–C, H_2, CH_2Cl_2–dioxane, rt, 48 h, *cis*-35%; (g) 0.5 eq. salcomine, DMF, O_2, rt, 18 h, 90%; (h) BCl_3, CH_2Cl_2, −78 °C, 70%.

Reduction of the ester **29** followed by oxidation with PCC gave the desired aldehyde **30**. As before, Grignard addition of methylmagnesium iodide to **30** proceeded uneventfully to give racemic alcohol **31**. To our frustration, subjection of **31** to the Giles conditions for ring closure as well as our modified conditions did not provide the desired ring-closed pyran. However, exposure of **31** to Wacker type conditions[25] that we have utilised in our laboratories[26] gave the related isochromene **32** in an optimised yield of 92%. Treatment of **32** with 10% Pd/C under a hydrogen atmosphere resulted in the removal of the benzyl protecting group as well as reduction of the isochromene to yield the isochromane **33** as a mixture of *cis*- and *trans*-isomers in a ratio of 3 : 1 as indicated by ^{1}H NMR spectroscopy. Recrystallisation of the mixture yielded only the *cis*-pyran **33** in 35% yield over the two steps.

Oxidation of **33** with salcomine[27] gave the required known 7-methoxyeleutherin **34**.[6,7] Cleavage of the methoxy group at C-9 was accomplished with boron trichloride to afford the natural product ventiloquinone L **4**[3] in good yield. The reported spectroscopic data of our product agreed with that reported in the literature. Work is presently directed towards the coupling of ventiloquinone L to provide cardinalin 3.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-200, Bruker AVANCE 300 spectrometer or on a Bruker DRX-400 spectrometer at the frequency indicated. DEPT, C–H correlated and COSY spectra were run on some samples to enable a more complete assignment of signals. *J*-values are given in Hz. Infra-red spectra were recorded 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. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography. All solvents used for reactions and chromatography were distilled prior to use to remove residual non-volatiles. Anhydrous/oxygen-free solvents (THF and Et_2O) were obtained according to standard procedures. *N*-Methylpyrrolidinone was obtained from Fluka, supplied anhydrous, over molecular sieves. It was passed through a column packed with basic alumina above silica gel 60 just before use. Removal or concentration of solvent *in vacuo* implies the evaporation of solvent at 20–25 Torr utilising a rotary evaporator.

1-(5-Allyloxy-2-hydroxyphenyl)-1-ethanone

To a solution of 1-(2,5-dihydroxyphenyl)-1-ethanone (5.59 g, 36.7 mmol) in acetone (100 cm^3) was added allyl bromide (3.18 cm^3, 4.44 g, 36.7 mmol) and K_2CO_3 (5.08 g, 36.7 mmol). The mixture was heated at reflux under N_2 for 18 h. The reaction mixture was then allowed to cool to rt, filtered through Celite, and the filtrate concentrated *in vacuo*. The resultant light yellow oil was purified by column chromatography (30% EtOAc–hexane) leading to isolation of 1-[5-(allyloxy)-2-hydroxyphenyl]-1-ethanone (6.78 g, 96%), as a light yellow oil. Literature[14] (solid, mp 59–60 °C); ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 11.85 (1H, s, OH), 7.20 (1H, d, *J* 3.0, 6-H), 7.13 (1H, dd, *J* 9.0 and 3.0, 4-H), 6.91 (1H, d, *J* 9.0, 3-H), 6.12–5.98 (1H, m, $OCH_2CH{=}CH_2$), 5.44 (1H, dq, *J* 17.2 and 1.6, $OCH_2CH{=}CH_2$ *trans*), 5.34 (1H, dq, *J* 10.5 and 1.4, $OCH_2CH{=}CH_2$ *cis*), 4.52 (2H, dt, *J* 5.3 and 1.5, $OCH_2CH{=}CH_2$) and 2.60 (3H, s, $COCH_3$); ^{13}C NMR (50 MHz; $CDCl_3$) δ 204.0 (C=O), 156.8 (ArC–O), 150.6 (ArC–O), 133.1 ($OCH_2CH{=}CH_2$), 124.9 (3-C), 121.0 (ArC), 119.1 ($OCH_2CH{=}CH_2$), 117.9 (6-C), 114.9 (4-C), 69.8 ($OCH_2CH{=}CH_2$) and 26.7 ($COCH_3$); ν_{max}(film)/cm^{-1} 3082m (OH), 3020m (=CH), 2926m (C–H), 1673s (C=O), 1618s (C=C) and 1290s (C–O).

1-(5-Allyloxy-2-methoxyphenyl)-1-ethanone 10

To a solution of 1-(5-allyloxy-2-hydroxyphenyl)-1-ethanone (6.17 g, 32.1 mmol) in acetone (100 cm^3) was added dimethyl sulfate (9.11 cm^3, 12.2 g, 96.3 mmol) and K_2CO_3 (13.31 g, 96.30 mmol). The mixture was heated at reflux under N_2 for 72 h. The reaction mixture was then allowed to cool to rt, filtered through Celite and the filtrate concentrated *in vacuo*. The resultant light yellow oil was re-dissolved in EtOAc (100 cm^3) then washed with 12% v/v aqueous NH_3 (3 × 100 cm^3) until no further effervescence was observed. This was followed by washing with a 10% v/v solution of conc. $HCl_{(aq)}$ (3 × 100 cm^3) then H_2O until the aqueous layer was neutral. The organic layer was then dried with $MgSO_4$, filtered through Celite, the solvent removed *in vacuo* and the resultant oil purified by silica gel column chromatography (10% EtOAc–hexane) to afford the product **10** (4.75 g, 73%) as a colourless oil.[14] ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.30 (1H, d, *J* 3.2, 6-H), 7.04 (1H, dd, *J* 9.0 and 3.2, 4-H), 6.90 (1H, d, *J* 9.0, 3-H), 6.08–5.98 (1H, m, $OCH_2CH{=}CH_2$),

5.40 (1H, dq, *J* 17.2 and 1.6, $OCH_2CH{=}CH_2$ *trans*), 5.27 (1H, dq, *J* 10.5 and 1.4, $OCH_2CH{=}CH_2$ *cis*), 4.51 (2H, dt, *J* 5.3 and 1.5, $OCH_2CH{=}CH_2$), 3.86 (3H, s, OCH_3) and 2.64 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ 199.2 (C=O), 153.5 (ArC–O), 152.3 (ArC–O), 133.1 ($OCH_2CH{=}CH_2$), 121.0 (3-C), 120.9 (ArC), 117.6 ($OCH_2CH{=}CH_2$), 115.0 (6-C), 113.0 (3-C), 69.4 ($OCH_2CH{=}CH_2$), 55.9 (OCH_3) and 31.7 ($COCH_3$); ν_{max}(film)/cm^{-1} 3002w (=CH), 2943w (C–H), 1673s (C=O), 1580w (C=C) and 1281s (C–O).

1-(2,4-Diallyl-3-hydroxy-6-methoxyphenyl)-1-ethanone 11

1-(5-Allyloxy-2-methoxyphenyl)-1-ethanone **10** (4.75 g, 23.0 mmol) was heated at 170 °C under N_2 for 12 h. The resultant dark oil was allowed to cool to rt then purified by column chromatography (10% EtOAc–hexane) to afford a mixture of (2-allyl-3-hydroxyphenyl)-1-ethanone and (4-allyl-3-hydroxyphenyl)-1-ethanone (4.08 g, 86%) as a yellow-brown semisolid. No analysis was done apart from noting the difference in R_f value on TLC. To the solution of this intermediate (4.08 g, 19.8 mmol) in acetone (100 cm^3) was added allyl bromide (3.42 cm^3, 4.79 g, 39.6 mmol) and K_2CO_3 (5.47 g, 39.6 mmol). The mixture was heated at reflux under N_2 for 13 h. The reaction mixture was then allowed to cool, filtered through Celite and the filtrate concentrated *in vacuo*. The resultant oil was then purified by column chromatography (10% EtOAc–hexane) to afford (2-allyl-3-allyloxyphenyl)-1-ethanone and (4-allyl-3-allyloxyphenyl)-1-ethanone (4.73 g, 97%), as an orange-yellow oil. This material (4.30 g, 17.46 mmol) was heated at 160 °C under N_2 for 7.5 h. The resultant dark oil was allowed to cool to rt then purified by column chromatography (10% EtOAc–hexane) to afford the desired product **11** (3.72 g, 86%) as a light brown, viscous oil. Found M$^+$ 246.1263, $C_{15}H_{18}O_3$ requires M$^+$ 246.1260; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 6.61 (1H, s, 5-H), 6.05–5.89 (2H, m, 2 × $ArCH_2CH{=}CH_2$), 5.18–5.05 (4H, m, 2 × $ArCH_2CH{=}CH_2$), 5.01 (1H, s, OH), 3.76 (3H, s, OCH_3), 3.39 (2H, dt, *J* 6.2 and 1.6, $ArCH_2CH{=}CH_2$), 3.31 (2H, dt, *J* 6.2 and 1.6, $ArCH_2CH{=}CH_2$) and 2.47 (3H, s, $COCH_3$); ^{13}C NMR (50 MHz; $CDCl_3$) δ 205.4 (C=O), 149.9 (ArC–O), 146.6 (ArC–O), 136.0 and 135.8 (2 × $ArCH_2CH{=}CH_2$), 130.6 (ArC), 127.8 (ArC), 123.4 (ArC), 116.6 and 116.1 (2 × $ArCH_2CH{=}CH_2$), 111.3 (5-C), 56.0 (OCH_3), 35.4 and 32.5 (2 × $ArCH_2CH{=}CH_2$) and 31.4 ($COCH_3$); ν_{max}(film)/cm^{-1} 3509br (O–H), 3005w (=CH), 2938w (C–H), 1699s (C=O), 1638w and 1608w (C=C) and 1257s (C–O); *m*/*z* 246 (M$^+$, 15%), 231 (100), 190 (49) and 43 (21).

1-(2,4-Diallyl-3,6-dimethoxyphenyl)-1-ethanone 12

To a solution of the phenol **11** (1.16 g, 4.71 mmol) in acetone (100 cm^3) was added dimethyl sulfate (0.55 cm^3, 0.74 g, 5.9 mmol) and K_2CO_3 (0.81 g, 5.9 mmol). The mixture was heated at reflux under N_2 for 17 h. The reaction mixture was allowed to cool to rt, filtered through Celite and the filtrate concentrated on a rotary evaporator. The resultant oil was then re-dissolved in EtOAc (100 cm^3), washed with 12.5% aqueous NH_3 (2 × 100 cm^3) until no further effervescence was observed, followed by washing with a 10% v/v solution of conc. $HCl_{(aq)}$ (2 × 100 cm^3) and then H_2O until the aqueous layer was neutral. The organic layer was then dried with $MgSO_4$, filtered through Celite, the solvent removed *in vacuo* and the resultant oil purified by column chromatography (10% EtOAc–hexane) to afford the product **12** (1.20 g, 98%) as a yellow oil. Found M$^+$ 260.1410, $C_{16}H_{20}O_3$ requires M$^+$ 260.1412; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 6.64 (1H, s, 5-H), 6.04–5.80 (2H, m, 2 × $ArCH_2CH{=}CH_2$), 5.16–4.89 (4H, m, 2 × $ArCH_2CH{=}CH_2$), 3.78 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.42 (4H, 2 overlapping dt, *J* 11.8 and 1.7, 2 × $ArCH_2CH{=}CH_2$) and 2.46 (3H, s, $COCH_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 205.0 (C=O), 152.2 (ArC–O), 150.4 (ArC–O), 136.9 and 136.5 (2 × $ArCH_2CH{=}CH_2$), 134.7 (ArC), 130.8 (ArC), 130.4 (ArC), 116.3 and 115.6 (2 × $ArCH_2CH{=}CH_2$), 110.9 (5-C), 61.7 and 55.7 (2 × OCH_3), 34.2 and 32.4 (2 × $ArCH_2CH{=}CH_2$) and 30.6 ($COCH_3$); ν_{max}(film)/cm^{-1} 3005w (=CH), 2940m (C–H), 1701s (C=O), 1638w and 1598m (C=C) and 1248s (C–O); *m*/*z* 260 (M$^+$, 8%), 245 (100), 204 (49), 189 (12), 115 (10) and 43 (35).

1-(2,4-Diallyl-3,6-dimethoxyphenyl)-1-ethanol 8

To a solution of the ketone **12** (1.12 g, 4.30 mmol) in dry THF (30 cm^3), stirred at 0 °C under N_2, was added $LiAlH_4$ (0.24 g, 6.5 mmol) portion-wise, resulting in mild effervescence. The reaction mixture was then stirred at rt for 16 h. This was once again cooled to 0 °C and H_2O (0.50 cm^3), followed by a 3.75 M NaOH solution (0.50 cm^3) were added. After all the precipitate settled, $MgSO_4$ was added and the solution filtered through Celite, washing the Celite pad with EtOAc. Concentration of the filtrate *in vacuo* gave an oil which was purified by column chromatography (30% EtOAc–hexane) to afford the desired product **8** (1.00 g, 89%) as a very light yellow, viscous oil. Found M$^+$ 262.1578, $C_{16}H_{22}O_3$ requires M$^+$ 262.1569; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 6.66 (1H, s, 5-H), 5.99–5.96 (2H, m, 2 × $ArCH_2CH{=}CH_2$), 5.07–4.91 [5H, m, 2 × $ArCH_2CH{=}CH_2$ overlapping with $ArCH(OH)CH_3$], 3.85 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.51–3.40 (4H, m, 2 × $ArCH_2CH{=}CH_2$) and 1.51 [3H, d, *J* 6.6, $ArCH(OH)CH_3$]; ^{13}C NMR (100 MHz; $CDCl_3$) δ 153.9 (ArC–O), 150.4 (ArC–O), 137.0 and 136.9 (2 × $ArCH_2CH{=}CH_2$), 131.8 (ArC), 130.7 (ArC), 130.3 (ArC), 116.0 and 115.5 (2 × $ArCH_2CH{=}CH_2$), 111.2 (5-C), 67.2 [$ArCH(OH)CH_3$], 61.8 and 55.3 (2 × OCH_3), 34.1 and 30.3 (2 × $ArCH_2CH{=}CH_2$) and 23.4 [$ArCH(OH)CH_3$]; ν_{max}(film)/cm^{-1} 3565br (O–H), 3004m (=CH), 2977s (C–H), 1638m and 1601m (C=C) and 1231s (C–O); *m*/*z* 262 (M$^+$, 63%), 247 (100), 188 (99), 173 (13), 115 (12), 91 (10) and 43 (20).

(±)-*trans*-5,8-Dimethoxy-1,3-dimethyl-6-[(*E*)-1-propenyl]-1*H*-isochromane 9

To a solution of the alcohol **8** (1.40 g, 5.34 mmol) in distilled anhydrous *N*-methylpyrrolidinone (80 cm^3), stirred at 100 °C under N_2, was added sublimed $KOBu^t$ (1.79 g, 16.0 mmol), giving an instant dark brown colour. Stirring was continued for 30 min. The reaction mixture was allowed to cool down to rt, then poured into ice cold H_2O (150 cm^3). The product was extracted with CH_2Cl_2 (3 × 100 cm^3), the combined organic layers dried with $MgSO_4$, filtered through Celite and concentrated *in vacuo*. The bulk of the solvent (*N*-methylpyrrolidinone) was distilled off under vacuum and purification of the crude product by column chromatography (10% EtOAc–hexane) afforded desired product *rac-trans*-**9** (1.27 g, 91%) as white crystals, mp 92–93 °C (EtOAc–hexane). Found M$^+$ 262.1572, $C_{16}H_{22}O_3$ requires M$^+$ 262.1570; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 6.75 (1H, s, 7-H), 6.66 (1H, dq, *J* 14.6 and 1.6, $CH_3CH{=}CHAr$), 6.21 (1H, dq, *J* 14.6 and 6.6, $CH_3CH{=}CHAr$), 5.06 (1H, q, *J* 6.5, 1-H), 4.10–3.90 (1H, m, 3-H), 3.80 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.83 (1H, dd, *J* 16.9 and 3.2, 4-H *pseudo*-equatorial), 2.39 (1H, dd, *J* 16.9 and 10.8, 4-H *pseudo*-axial), 1.92 (3H, dd, *J* 6.6 and 1.6, $CH_3CH{=}CHAr$), 1.49 (3H, d, *J* 6.5, 1-CH_3) and 1.34 (3H, d, *J* 6.1, 3-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 152.1 (ArC–O), 148.8 (ArC–O), 129.2 (ArC), 128.4 (ArC), 128.3 (ArC), 126.6 ($CH_3CH{=}CHAr$), 126.0 ($CH_3CH{=}CHAr$), 106.4 (7-C), 68.7 (1-C), 62.6 (3-C), 61.1 (OCH_3), 55.6 (OCH_3), 31.0 (4-C), 22.3 (3-CH_3), 20.0 (1-CH_3) and 19.2 $CH_3CH{=}CHAr$); ν_{max}(film)/cm^{-1} 2971s (=CH), 2933s (C–H), 1602m and 1577w (C=C) and 1225s (C–O); *m*/*z* 262 (M$^+$, 24%), 248 (16), 247 (100), 161 (2), 115 (3), 91 (2) and 43 (6).

(±)-*trans*-5,8-Dimethoxy-1,3-dimethyl-1*H*-isochromane-6-carbaldehyde 7

Into the solution of *rac-trans*-**8** (0.60 g, 2.3 mmol) and propanal (0.66 cm^3, 0.53 g, 9.3 mmol) in CH_2Cl_2 (20 cm^3), stirred at −94 °C (partly frozen acetone bath), was bubbled N_2 and ozone simultaneously until all starting material was consumed (7 min, TLC monitoring). The bubbling of the gases was stopped and the reaction mixture allowed to warm up to rt. The solvent was then removed *in vacuo* and the resultant yellow semisolid purified by column chromatography (30% EtOAc–hexane). The product *rac-trans*-**7**, (0.46 g, 82%), was isolated as cream-white fluffy needles (mp 125–126 °C, CH_2Cl_2–hexane). Found M$^+$ 250.1215, $C_{14}H_{18}O_4$ requires M$^+$ 250.1205; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 10.34 (1H, s, CHO), 7.13 (1H, s, 7-H), 5.10 (1H, q, *J* 6.6, 1-H), 4.15–4.00 (1H, m, 3-H), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 2.89 (1H,

dd, *J* 16.9 and 3.3, 4-H pseudo-*equatorial*), 2.44 (1H, dd, *J* 16.9 and 10.7, 4-H pseudo-*axial*), 1.51 (3H, d, *J* 6.6, 1-CH_3) and 1.37 (3H, d, *J* 6.1, 3-CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 189.5 (C=O), 155.7 (ArC–O), 152.1 (ArC–O), 137.1 (ArC), 129.2 (ArC), 127.1 (ArC), 105.0 (7-C), 68.5 (1-C), 63.6 (3-C), 62.3 (OCH_3), 55.5 (OCH_3), 30.1 (4-C), 21.8 (3-CH_3) and 19.2 (1-CH_3); ν_{max}(film)/cm^{-1} 2973w (=CH), 2935w (C–H), 2905w and 2870w (CHO), 1685s (C=O), 1601s (C=C) and 1387 (C–O); *m*/*z* 250 (M^+, 39%), 236 (18), 235 (100), 202 (3), 191 (6), 174 (5), 145 (2) and 91 (4).

3-Allyloxybenzaldehyde 14

To a solution of *m*-hydroxybenzaldehyde (40.00 g, 327.6 mmol) in acetone (300 cm^3) was added allyl bromide (31.18 cm^3, 43.59 g, 360.3 mmol) and K_2CO_3 (49.80 g, 360.3 mmol). The mixture was stirred at reflux under N_2 for 18 h. After cooling down to rt, the mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The resultant oil was then purified by column chromatography (10% EtOAc–hexane) to afford the expected known product **14** (53.11 g, 100%) as a yellow oil.[19] ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 10.00 (1H, s, CHO), 7.49–7.42 (3H, m, 3 × ArH), 7.24–7.20 (1H, m, ArH), 6.13–6.04 (1H, m, OCH_2CH=CH_2), 5.46 (1H, dq, *J* 17.2 and 1.5, OCH_2CH=CH_2 *trans*), 5.34 (1H, dq, *J* 10.5 and 1.3, OCH_2CH=CH_2 *cis*) and 4.62 (2H, dt, *J* 5.3 and 1.5, OCH_2CH=CH_2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 192.0 (C=O), 159.0 (ArC–O), 137.8 (ArC), 132.6 (OCH_2CH=CH_2), 130.0 (ArCH), 123.4 (ArCH), 122.0 (ArCH), 117.9 (OCH_2CH=CH_2), 113.1 (ArCH) and 68.8 (OCH_2CH=CH_2).

2- and 4-Allyl-3-hydroxybenzaldehyde

The allyloxybenzaldehyde **14** (53.11 g, 327.5 mmol) was heated at 180 °C under N_2 for 24 h. The resultant dark oil was allowed to cool, resulting in crystallisation of the expected product mixture of the 2- and 4-allyl regioisomers, which was subsequently purified by column chromatography (30% EtOAc–hexane). The product, 2- and 4-allyl-3-hydroxybenzaldehyde mixture (34.85 g, 66%), was obtained as a crystalline, chromatographically inseparable mixture. Recrystallisation from CH_2Cl_2–hexane at −33 °C gave 2-allyl-3-hydroxybenzaldehyde as white needles (mp 102–103 °C, CH_2Cl_2–hexane).[19] Drying of the mother liquor gave a 4-allyl-3-hydroxybenzaldehyde-enriched mixture as a light brown oil.

2-Allyl-3-hydroxybenzaldehyde[19]. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 10.20 (1H, s, CHO), 7.46 (1H, dd, *J* 7.6 and 1.1, 4-H), 7.29 (1H, t, *J* 7.8, 5-H), 7.12 (1H, dd, *J* 7.9 and 1.1, 6-H), 6.09–6.00 (1H, m, $ArCH_2CH$=CH_2), 5.85 (1H, s, OH), 5.10 (1H, dq, *J* 10.2 and 1.6, $ArCH_2CH$=CH_2 *cis*), 5.02 (1H, dq, *J* 17.2 and 1.6, OCH_2CH=CH_2 *trans*) and 3.90 (2H, dt, *J* 5.8 and 1.5, ArCH_2CH=CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 193.1 (C=O), 154.9 (ArC–O), 135.9 ($ArCH_2CH$=CH_2), 135.1 (ArC), 127.8 (ArC), 127.6 (ArCH), 124.6 (ArCH), 121.5 (ArCH), 116.1 ($ArCH_2CH$=CH_2) and 28.5 (ArCH_2CH=CH_2).

2- and 4-Allyl-3-allyloxybenzaldehyde

To a solution of the mixture of 2- and 4-allyl-3-hydroxybenzaldehyde (34.85 g, 214.9 mmol) in acetone (150 cm^3) was added allyl bromide (20.46 cm^3, 28.60 g, 236.4 mmol) and K_2CO_3 (32.68 g, 236.5 mmol). The mixture was heated at reflux under N_2 for 18 h. After cooling down to rt, the reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The resultant oil was then purified by column chromatography (10% EtOAc–hexane) to afford the desired 2- and 4-allyl-3-allyloxybenzaldehyde (43.46 g, 100%) as an orange-yellow oil.

For analysis, pure 2-allyl-3-allyoxybenzaldehyde was prepared separately from 3-allyloxybenzaldehyde **14** under the same reaction conditions as before and then isolated as a yellow oil in quantitative yield. Found M^+ 202.0993, $C_{13}H_{14}O_2$ requires M^+ 202.0994. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 10.27 (1H, s, CHO), 7.47 (1H, dd, *J* 7.7 and 1.0, 4-H), 7.32 (1H, t, *J* 7.9, 5-H), 7.10 (1H, dd, *J* 8.2 and 1.0, 6-H), 6.09–5.97 (2H, m, $ArCH_2CH$=CH_2 and OCH_2CH=CH_2), 5.42 (1H, dq, *J* 17.3 and 1.5, OCH_2CH=CH_2 *trans*), 5.28 (1H, dq *J* 10.6 and 1.5, OCH_2CH=CH_2 *cis*), 5.00 (1H, dq, *J* 10.2 and 1.6, $ArCH_2CH$=CH_2 *cis*), 4.95 (1H, dq *J* 17.1 and 1.6, $ArCH_2CH$=CH_2 *trans*), 4.58 (2H, dt, *J* 5.0 and 1.6, OCH_2CH=CH_2) and 3.88 (2H, dt, *J* 8.0 and 1.6, ArCH_2CH=CH_2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 192.6 (C=O), 157.1 (ArC–O), 137.0 (OCH_2CH=CH_2), 135.5 (ArC), 133.3 ($ArCH_2CH$=CH_2), 131.7 (ArC), 127.8 (ArCH), 123.2 (ArCH), 117.8 (OCH_2CH=CH_2, or ArCH), 117.7 (ArCH or OCH_2CH=CH_2), 115.9 ($ArCH_2CH$=CH_2), 69.8 (OCH_2CH=CH_2) and 28.6 (ArCH_2CH=CH_2); ν_{max}(film)/cm^{-1} 3080w (=CH), 2926w (C–H), 2869w and 2731w (CHO), 1693s (C=O), 1636w and 1584s (C=C) and 1246s (C–O); *m*/*z* 202 (M^+, 63%), 161 (72), 133 (36), 131 (952), 115 (40), 105 (57), 91 (28), 77 (37) and 41 (100).

2,4-Diallyl-3-hydroxybenzaldehyde 15

The 2- and 4-allyl-3-allyloxybenzaldehyde mixture (43.46 g, 214.9 mmol) was heated at 180 °C under N_2 for 18 h. The now dark oil was allowed to cool to rt and purified by column chromatography (10% EtOAc–hexane), giving a brown, highly viscous oil that was further purified by recrystallisation (CH_2Cl_2–hexane) to afford the product **15** (18.71 g, 43%) as cream white crystals, mp 41–42 °C. Found M^+ 202.1000, $C_{13}H_{14}O_2$ requires M^+ 202.0994; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 10.14 (1H, s, CHO), 7.30 (1H, d, *J* 7.8, 6-H), 7.20 (1H, d, *J* 7.8, 5-H), 6.13–5.91 (2H, m, 2 × $ArCH_2CH$=CH_2), 5.52 (1H, s, OH), 5.23–4.98 (4H, m, 2 × $ArCH_2CH$=CH_2), 3.92 (2H, dt, *J* 5.8 and 1.8, ArCH_2CH=CH_2) and 3.48 (2H, dt, *J* 3.7 and 1.4, ArCH_2CH=CH_2); ^{13}C NMR (50 MHz; $CDCl_3$) δ 192.5 (C=O), 153.3 (ArC–O), 135.9 and 135.1 ($ArCH_2CH$=CH_2), 134.0 (ArC), 132.5 (ArC), 128.5 (ArCH), 127.3 (ArC), 125.1 (ArCH), 117.3 and 116.2 ($ArCH_2CH$=CH_2) and 35.5 and 28.8 (ArCH_2CH=CH_2); ν_{max}(film)/cm^{-1} 3489br (O–H), 3007w (=CH), 2978w (C–H), 2859w and 2725w (CHO), 1675s (C=O), 1602m and 1573m (C=C) and 1260m (C–O); *m*/*z* 202 (M^+, 68%), 187 (100), 173 (16), 131 (26), 91 (20) and 51 (10).

2,4-Diallyl-3-benzyloxybenzaldehyde 16

To a solution of the phenol **15** (1.36 g, 6.72 mmol) in acetone (75 cm^3) was added benzyl bromide (0.88 cm^3, 1.26 g, 7.40 mmol) and K_2CO_3 (1.02 g, 7.40 mmol). The mixture was stirred at reflux under N_2 for 18 h. After cooling to rt, the mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The resultant oil was purified column chromatography (10% EtOAc–hexane) to afford the product **16** (1.97 g, 100%) as a light yellow, viscous oil. Found M^+ 292.1467, $C_{20}H_{20}O_2$ requires M^+ 292.1463; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 10.18 (1H, s, CHO), 7.66 (1H, d, *J* 8.3, 6-H), 7.48–7.35 (5H, m, OCH_2PhH), 7.31 (1H, d, *J* 8.3, 5-H), 6.17–5.90 (2H, m, 2 × $ArCH_2CH$=CH_2), 5.16–4.85 (4H, m, 2 × $ArCH_2CH$=CH_2), 4.84 (2H, s, OCH_2Ph), 3.90 (2H, dt, *J* 5.4 and 1.8, ArCH_2CH=CH_2) and 3.52 (2H, dt, *J* 6.5 and 1.2, ArCH_2CH=CH_2); ^{13}C NMR (50 MHz; $CDCl_3$) δ 191.6 (C=O), 155.7 (ArC–O), 140.4 (ArC), 137.6 ($ArCH_2CH$=CH_2), 136.9 (ArC), 135.9 ($ArCH_2CH$=CH_2), 135.4 (ArC), 134.0 (ArC), 128.9 (ArCH), 128.6 (2 × ArCH), 128.1 (ArCH), 127.4 (2 × ArCH), 126.9 (ArCH), 116.9 and 116.0 ($ArCH_2CH$=CH_2), 75.9 (OCH_2Ph) and 34.5 and 29.9 (ArCH_2CH=CH_2); ν_{max}(film)/cm^{-1} 3078w (=CH), 2978w (C–H), 2866w and 2728w (CHO), 1691S (C=O), 1594m and 1570w (C=C) and 1248s (C–O); *m*/*z* 292 (M^+, 6%), 201 (12), 187 (6), 91 (100) and 51 (4).

1-[2,4-Diallyl-3-(benzyloxy)phenyl]-1-ethanol 17

Into a solution of methylmagnesium iodide [184.3 mmol, freshly prepared under Ar from methyl iodide (11.48 cm^3, 26.18 g, 184.5 mmol) and magnesium turnings (4.48 g, 184 mmol) in dry Et_2O (150 cm^3)], stirred at 0 °C, was added by cannula, a solution of the aldehyde **16** (21.57 g, 73.78 mmol) in dry THF (50 cm^3). The reaction mixture was allowed to warm up to rt over 8 h then cooled back to 0 °C and quenched with ice-cold H_2O, added drop-wise until all excess Grignard reagent was consumed. The resultant suspension was then extracted with EtOAc (3 × 100 cm^3). The combined

organic extracts were dried with $MgSO_4$, filtered through Celite and the filtrate concentrated *in vacuo*. Purification of the resultant yellow oil by column chromatography (10–30% EtOAc–hexane) afforded the product **17** (18.54 g, 82%), as a light yellow, viscous oil. Found M^+ 308.1776, $C_{21}H_{24}O_2$ requires M^+ 308.1776; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 7.46–7.31 (6H, m, 6-H overlapping with OCH_2PhH), 7.16 (1H, d, J 8.0, 5-H), 6.10–5.91 (2H, m, 2 × $ArCH_2CH{=}CH_2$), 4.95–4.80 [3H, m, $ArCH(CH_3)OH$ overlapping with OCH_2Ph], 5.14–4.96 (3H, m, 2 × $ArCH_2CH{=}CH_2$), 4.90 (1H, dq, J 15.3 and 1.9, one of $ArCH_2CH{=}CH_2$), 4.81 (2H, s, OCH_2Ph), 3.65–3.44 (4H, m, 2 × $ArCH_2CH{=}CH_2$), 1.95 (1H, br s, OH) and 1.44 [3H, d, J 6.4, $ArCH(CH_3)OH$]; ^{13}C NMR (50 MHz; $CDCl_3$) δ 155.0 (ArC–O), 144.0 (ArC), 137.9 ($ArCH_2CH{=}CH_2$), 137.5 (ArC), 137.1 ($ArCH_2CH{=}CH_2$), 132.2 (ArC), 129.6 (ArC), 129.0 (ArCH), 128.5 (2 × ArCH), 127.9 (ArCH), 127.4 (2 × ArCH), 121.3 (ArCH), 116.0 and 115.3 ($ArCH_2CH{=}CH_2$), 75.6 [$ArCH(CH_3)OH$], 66.1 (OCH_2Ph), 34.1 and 29.9 ($ArCH_2CH{=}CH_2$) and 24.4 [$ArCH(CH_3)OH$]; ν_{max}(film)/cm^{-1} 3381br (O–H), 3005w (=CH), 2976s (C–H), 1605w and 1573w (C=C) and 1258s (C–O); *m*/*z* 308 (M^+, 3%), 294 (12), 185 (10), 173 (7), 145 (5), 115 (4), 91 (100) and 65 (6).

(±)-*trans*-5-Benzyloxy-1,3-dimethyl-6-[(*E*)-1-propenyl]-1*H*-isochromane 18

To a solution of the alcohol **17** (2.44 g, 7.91 mmol) in anhydrous *N*-methylpyrrolidinone (100 cm^3), stirred at 100 °C under N_2, was added sublimed KOBu^t (2.66 g, 23.70 mmol), giving an instant dark brown colour. Stirring was continued for 10 min then the reaction mixture allowed to cool down to rt. This was then poured into ice H_2O (150 cm^3) and the product extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic layers were dried with $MgSO_4$, filtered through Celite and concentrated *in vacuo*. The bulk of the *N*-methylpyrrolidinone was then distilled off under vacuum and purification of the crude product by column chromatography (10% EtOAc–hexane) afforded the desired product *rac-trans*-**18** (2.29 g, 94%), as a yellow, viscous oil. Found M^+ 308.1780, $C_{21}H_{24}O_2$ requires M^+ 308.1776; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.49–7.27 (6H, m, OCH_2PhH overlapping with 7-H), 6.79 (1H, d, J 8.1, 8-H), 6.68 (1H, dd, J 15.9 and 1.6, $CH_3CH{=}CHAr$), 6.22 (1H, dq, J 15.9 and 6.6, $CH_3CH{=}CHAr$), 5.01 (1H, q, J 6.7, 1-H), 4.84 (1H, d, J 11.2, OCH_2Ph), 4.76, (1H, d, J 11.2, OCH_2Ph), 4.05–3.97 (1H, m, 3-H), 2.88 (1H, dd, J 16.6 and 3.2, 4-H *pseudo*-equatorial), 2.43 (1H, dd, J 16.6 and 6.8, 4-H *pseudo*-axial), 1.88 (3H, dd, J 6.6 and 1.6, $CH_3CH{=}CHAr$), 1.50 (3H, d, J 6.7, 1-CH_3) and 1.29 (3H, d, J 6.2, 3-CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 153.1 (ArC–O), 139.0 (ArC), 137.3 (ArC), 128.7 (CH), 128.3 (2 × ArCH), 128.1 (CH), 127.8 (2 × ArCH), 127.6 (CH), 127.0 (CH), 126.2 (CH), 123.6 (ArC), 121.0 (ArC), 75.3 (OCH_2Ph), 70.9 (1-C), 64.2 (3-C), 31.2 (4-C), 22.6 (1-CH_3), 21.9 (3-CH_3) and 19.4 ($CH_3CH{=}CHAr$); ν_{max}(film)/cm^{-1} 3032w (=CH), 2972s (C–H), 1582w and 1562w (C=C) and 1257s (C–O); *m*/*z* 308 (M^+, 16%), 293 (32), 217 (15), 173 (18), 145 (10), 91 (100) and 65 (5).

(±)-*trans*- and *cis*-5-(Benzyloxy-1,3-dimethyl-6-[(*E*)-1-propenyl]-1*H*-isochromane 18

Allowing epimerisation to afford a *rac-cis*-**18**-enriched mixture was accomplished by doing the same reaction (all amounts similar) but the reaction time was increased to 30 min. This led to isolation of a mixture of stereoisomers, containing *circa* 70% *rac-cis*-**18**. This was estimated from the integration for the signals for 3-H. For *rac-trans*-**18** 3-H, was at δ 4.05–3.97; for *rac-cis*-**18** 3-H, was at δ 3.80–3.73 ppm.

(±)-*trans*-5-Benzyloxy-1,3-dimethyl-1*H*-isochromane-6-carbaldehyde 19

Into the solution of the starting material *rac-trans*-**18** (2.29 g, 7.42 mmol) and propanal (2.68 cm^3, 2.16 g, 37.1 mmol) in CH_2Cl_2 (40 cm^3), stirred at −94 °C (partly frozen acetone bath), was bubbled N_2 and ozone simultaneously (separate inlets) until all starting material was consumed (7 min, TLC monitoring). The bubbling of the gases was stopped and the reaction mixture allowed to warm up to rt. Removal of the solvent *in vacuo* and purification of the resultant semisolid by column chromatography (30% EtOAc–hexane) afforded the product *rac-trans*-**19** (2.19 g, 100%) as a cream-white semisolid. Found M^+ 296.1421, $C_{19}H_{20}O_3$ requires M^+ 296.1412; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) δ 10.20 (1H, s, CHO), 7.67 (1H, d, J 8.1, 7-H), 7.41–7.39, (5H, m, OCH_2PhH), 6.79 (1H, d, J 8.1, 8-H), 5.06 (1H, q, J 6.9, 1-H), 5.05 (1H, J 11.2, OCH_2Ph), 4.91 (1H, d, J 11.2, OCH_2Ph), 4.09–3.96 (1H, m, 3-H), 2.94 (1H, dd, J 16.6 and 3.2, 4-H *pseudo*-equatorial), 2.48 (1H, dd, J 16.6 and 9.6, 4-H *pseudo*-axial), 1.54 (3H, d, J 6.9, 1-CH_3) and 1.34 (3H, d, J 6.2, 3-CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 189.7 (CHO), 159.6 (ArC–O), 148.0 (ArC), 135.9 (ArC), 128.7 (2 × ArCH), 128.7 (ArCH), 128.3 (2 × ArCH), 128.2 (ArC), 127.5 (ArC), 125.9 (ArCH), 121.8 (ArCH), 77.7 (OCH_2Ph), 70.7 (1-C), 63.6 (3-C), 30.4 (4-C), 21.8 (1-CH_3) and 21.2 (3-CH_3); ν_{max}(film)/cm^{-1} 3032w (=CH), 2974s (C–H), 2897w and 2874w (CHO), 1687s (C=O), 1601m and 1574w (C=C) and 1244m (C–O); *m*/*z* 296 (M^+, 3%), 281 (8), 163 (3), 91 (100), 84 (10), 65 (5) and 49 (14).

(±)-*trans*-Ethyl 9-acetoxy-5-benzyloxy-1,3-dimethyl-1*H*-benzo[*g*]isochromane-7-carboxylate 20

To a solution of the aldehyde *rac-trans*-**19** (4.21 g, 14.2 mmol) and diethyl succinate (5.91 cm^3, 6.19 g, 35.5 mmol) in dry ^{t}BuOH (100 cm^3) was added KOBu^t (3.99 g, 35.53 mmol). The mixture was stirred at reflux under N_2 for 4 h. The reaction mixture was allowed to cool, poured into ice H_2O (100 cm^3) and acidified to pH 3 with conc. $HCl_{(aq)}$. This was then extracted with EtOAc (3 × 100 cm^3), the combined organic layers dried with $MgSO_4$, filtered through Celite and the filtrate concentrated *in vacuo*. Purification of the resultant brown oil by column chromatography (30–50% EtOAc–hexane) led to isolation of the intermediate half-ester (5.87 g, 97%), as a light brown oil which was not characterised. To the Stobbe condensation product (5.87 g, 13.83 mmol), dissolved in acetic anhydride (80 cm^3) was added anhydrous sodium acetate (2.84 g, 34.6 mmol). The mixture was stirred at reflux under N_2 for 4 h. The reaction mixture was poured into ice H_2O (100 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic layers were then dried with $MgSO_4$, filtered through Celite and concentrated *in vacuo*. Purification of the resultant dirty-white solid by column chromatography (30% EtOAc–hexane) gave a pale brown solid which was purified further by crystallisation from EtOAc to afford the product *rac-trans*-**20** (4.65 g, 75%) as white granules, mp 183–184 °C. Found M^+ 448.1896, $C_{27}H_{28}O_6$ requires M^+ 448.1886; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) δ 8.77 (1H, d, J 1.0, 6-H), 7.78 (1H, d, J 1.5, 8-H), 7.55–7.53 (2H, m, 2 × ArH), 7.47–7.39 (3H, m, 3 × ArH), 7.35 (1H, br s, 10-H), 5.24 (1H, q, J 6.8, 1-H), 5.07 (1H, J 11.0, OCH_2Ph), 4.72, (1H, d, J 11.0, OCH_2Ph), 4.40 (2H, q, J 7.3, CH_3CH_2O), 4.08–4.02 (1H, m, 3-H), 3.12 (1H, dd, J 16.6 and 3.2, 4-H *pseudo*-equatorial), 2.58 (1H, dd, J 16.6 and 9.8, 4-H *pseudo*-axial), 2.48 (3H, s, CH_3COO), 1.62 (3H, d, J 6.8, 1-CH_3), 1.41 (3H, t, J 7.1, CH_3CH_2O–) and 1.34 (3H, d, J 6.2, 3-CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.2 (CH_3CO_2), 166.0 ($ArCO_2Et$), 153.2 (ArC–O), 146.7 (ArC–O), 142.0 (ArC), 136.8 (ArC), 128.6 (2 × ArCH), 128.5 (ArC), 128.4 (ArCH), 128.3 (2 × ArCH), 127.2 (ArC), 127.1 (ArC), 125.6 (ArC), 123.2 (6-C), 117.4 (8-C), 113.2 (10-C), 76.3 (OCH_2Ph), 70.7 (1-C), 63.8 (3-C), 61.2 (OCH_2CH_3), 30.9 (4-C), 22.6 (1-CH_3), 21.4 (3-CH_3), 21.0 (CH_3COO) and 14.3 (OCH_2CH_3); ν_{max}(film)/cm^{-1} 2852s (C–H, 1755m and 1716m (C=O), 1603w (C=C) and 1210m (C–O); *m*/*z* 448 (M^+, 10%), 356 (12), 314 (11), 271 (29), 149 (7), 91 (100) and 57 (6).

The following reactions are based on a *rac-cis*-**18**-enriched mixture of diastereomers. This was obtained from **17** using the KOBu^t-mediated ring closure, left for 30 min to allow epimerisation, and carrying the mixture of the stereoisomers thus isolated through ozonolysis (**18**→**19**), Stobbe condensation and intramolecular Friedel–Crafts acylation (**19**→**20**).

(±)-*cis*- and *trans*-5-Benzyloxy-7-hydroxymethyl-1,3-dimethyl-1*H*-benzo[*g*]isochroman-9-ol 21

To a solution of the (±)-*cis* and *trans* diester **20** (1.96 g, 4.37 mmol) in dry tetrahydrofuran (100 cm^3), stirred at 0 °C under N_2, was added $LiAlH_4$ (0.66 g, 17 mmol) portion-wise, resulting in mild effervescence. The cooling bath was removed and stirring continued at rt for 24 h. The reaction mixture was then cooled back to 0 °C and quenched with H_2O (0.66 cm^3) then NaOH solution (3.75 M, 0.66 cm^3) followed by more H_2O (2.00 cm^3). After total precipitation of the inorganic salts, the reaction mixture was filtered through Celite, the filtrate concentrated *in vacuo* and the resultant oil purified by column chromatography (30% EtOAc–hexane). The product **21** (1.96 g, 93%) was isolated as a white, crystalline solid that slowly turns light brown upon prolonged exposure to air. Recrystallisation from CH_2Cl_2 or EtOAc–hexane failed to give any pure *rac*-diastereomer and the data below is for the predominant *rac*-*cis*-product. Found M^+ 364.1666, $C_{23}H_{24}O_4$ requires M^+ 364.1675; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 9.10 (1H, OH), 7.81 (1H, s, 6-H), 7.75–7.31, (6H, m, OCH_2PhH overlapping with 10-H), 6.90 (1H, s, 8-H), 5.04–4.92 (3H, m, 1-H overlapping with OCH_2Ph), 4.69 (2H, s, 7-CH_2OH), 3.83–3.77 (1H, m, 3-H), 3.39, (1H, br s, 7-CH_2OH), 3.06 (1H, dd, *J* 16.5 and 2.3, 4-H *pseudo*-equatorial), 2.67–2.56 (1H, m, 4-H *pseudo*-axial), 1.68 (3H, d, *J* 6.4, 1-CH_3) and 1.38 (3H, d, *J* 6.2, 3-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 153.4 (ArC–O), 151.1 (ArC–O), 139.1 (ArC), 137.4 (ArC), 137.0 (ArC), 128.4 (2 × ArCH), 127.9 (ArCH), 128.8 (2 × ArCH), 127.7 (ArC), 124.6 (ArC), 124.2 (ArC), 113.4 (ArCH), 110.3 (ArCH), 107.2 (8-C), 74.8 (OCH_2Ph), 73.6 (1-C), 70.4 (3-C), 65.3 (7-CH_2OH), 31.7 (4-C), 22.0 (1-CH_3) and 21.9 (3-CH_3); ν_{max}(film)/cm^{-1} 3367br and 3172br (O–H), 2958w (=C–H), 2852w (C–H), 1606m and 1574w (C=C) and 1291s (C–O); *m*/*z* 364 (M^+, 24%), 273 (18), 272 (12), 230 (21), 229 (100), 212 (10), 199 (7) and 91 (62).

(±)-*cis*- and *trans*-(5-Benzyloxy-9-isopropyloxy-1,3-dimethyl-1*H*-benzo[*g*]isochroman-7-yl)methanol 22

To a solution of the racemic phenol diastereomers **21** (4.43 g, 12.2 mmol) in acetone (100 cm^3) were added isopropyl bromide (2.24 g, 18.2 mmol) and K_2CO_3 (2.52 g, 18.2 mmol). The mixture was heated at reflux under N_2 for 24 h. The reaction mixture was then allowed to cool to rt, filtered through Celite, and the filtrate concentrated *in vacuo*. The resultant light brown oil was purified by silica gel column chromatography (30% EtOAc–hexane). The product mixture *rac*-*cis*- and *rac*-*trans*-**22** (4.69 g, 95%), was isolated as a cream white, waxy solid. Recrystallisation from CH_2Cl_2 or EtOAc–hexane failed to give any pure *rac*-diastereomer. Presented below is the data for the predominant *rac*-*cis* diastereomer. Found M^+ 406.2139, $C_{26}H_{30}O_4$ requires 406.2144; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.81 (1H, s, 10-H), 7.53–7.36 (6H, m, OCH_2PhH, overlapping with 6-H), 5.03–4.97 (1H, m, 1-H), 4.99 (1H, d, *J* 11.3, OCH_2Ph), 4.92 (1H, d, *J* 11.3, OCH_2Ph), 4.74 [1H, sept, *J* 6.0, $(CH_3)_2CH$–O], 4.73 (2H, s, $ArCH_2OH$), 3.80–3.74 (1H, m, 3-H), 3.05 (1H, dd, *J* 16.6 and 2.8, 4-H *pseudo*-equatorial), 2.61 (1H, dd, *J* 16.5 and 11.0, 4-H *pseudo*-axial), 1.94 (1H, br s, $ArCH_2OH$), 1.69 (3H, d, *J* 6.4, 1-CH_3), 1.45 and 1.43 [each 3H, d, *J* 6.0, $(CH_3)_2CH$–O] and 1.34 (3H, d, *J* 6.1, 3-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 154.1 (ArC–O), 151.3 (ArC–O), 138.4 (ArC), 137.8 (ArC), 137.5 (ArC), 128.5 (2 × ArCH), 128.0 (ArCH), 127.9 (2 × ArCH), 127.6 (ArC), 125.8 (ArC), 125.1 (ArC), 113.6 (ArCH), 111.3 (ArCH), 105.0 (8-C), 75.1 (OCH_2Ph), 73.7 (1-C), 70.4 (3-C), 70.4 [$(CH_3)_2CH$–O] 66.1 ($ArCH_2OH$), 31.8 (4-C), 22.2 (1-CH_3), 22.1 [$(CH_3)_2CH$–O] and 22.0 (3-CH_3); ν_{max}(film)/cm^{-1} 3400br (O–H), 2974s (=CH), 2930w (C–H), 1497m (C=C) and 1302m (C–O). *m*/*z* 406 (M^+, 33%), 315 (41), 314 (11), 272 (25), 271 (100), 229 (79) and 91 (28).

(±)-*cis*- and *trans*-5-Benzyloxy-9-isopropyloxy-1,3-dimethyl-1*H*-benzo[*g*]isochromane-7-carbaldehyde 23

To a solution of the racemic alcohol diastereomers **22** (3.33 g, 8.19 mmol) in dry benzene (100 cm^3) was added 1,10-phenanthroline monohydrate (3.25 g, 16.4 mmol), copper(I) chloride (1.62 g, 16.4 mmol) and K_2CO_3 (2.26 g, 16.4 mmol). The reaction mixture stirred at 80 °C under oxygen, for 18 h. After the solution was cooled to rt, the solvent was removed *in vacuo* and replaced with CH_2Cl_2 (100 cm^3). This was then washed with an aqueous 25% NH_3 solution (3 × 100 cm^3) resulting in total dissolution and removal of the copper salt. Excess conc. $HCl_{(aq)}$ (50 cm^3) was then added, dissolving the phenanthroline as the hydrochloride. The layers were separated and the organic dried with K_2CO_3, filtered through Celite and the filtrate concentrated *in vacuo*. Purification of the resultant dark brown oil by silica gel column chromatography (30% EtOAc–hexane) led to the isolation of the product mixture *rac*-*cis*- and *rac*-*trans*-**23** (2.64 g, 80%) as a yellow, waxy solid. The spectral data of this mixture was very complicated and therefore *rac*-*trans* **23** was synthesised from *rac*-*trans* **18** using the following sequence; *trans*-**18→19→20→21→22→23**. None of the intermediates were characterised and this sequence gave *rac*-*trans*-**23** as yellow granules, mp 114.5–115.5 °C (CH_2Cl_2–hexane); Found M^+ 404.1989, $C_{26}H_{28}O_4$ requires M^+ 404.1988; ^1H NMR (400 MHz; $CDCl_3$; Me_4Si) δ 9.95 (1H, s, CHO), 8.03 (1H, s, 6-H), 7.81 (1H, s, 10-H), 7.52–7.38 (5H, m, OCH_2PhH), 7.20 (1H, s, 8-H), 5.27 (1H, q, *J* 6.7, 1-H), 5.10 (1H, d, *J* 11.3, OCH_2Ph), 4.99 (1H, d, *J* 11.3, OCH_2Ph), 4.85 [1H, sept, *J* 6.0, $(CH_3)_2CH$–O], 4.15–4.05 (1H, m, 3-H), 3.11 (1H, dd, *J* 16.5 and 2.9, 4-H *pseudo*-equatorial), 2.61 (1H, dd, *J* 16.5 and 9.8, 4-H *pseudo*-axial), 1.65 (3H, d, *J* 6.7, 1-CH_3) 1.47 [6H, d, *J* 6.0, $(CH_3)_2CH$–O] and 1.36 (3H, d, *J* 6.1, 3-CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 192.4 (CHO), 154.3 (ArC–O), 152.9 (ArC–O), 141.5 (ArC), 136.9 (ArC), 134.3 (ArC), 129.1 (ArC), 128.6 (2 × ArCH), 128.4 (ArCH), 128.0 (2 × ArCH), 127.2 (ArC), 125.6 (ArC), 123.1 (6-C), 114.9 (10-C), 99.9 (8-C), 76.1 (OCH_2Ph), 70.9 (1-C), 70.5 [$(CH_3)_2CH$–O], 63.7 (3-C), 31.0 (4-C), 22.7 (1-CH_3), 21.9 [$(CH_3)_2CH$–O] and 21.4 (3-CH_3); ν_{max}(film)/cm^{-1} 3032m (=CH), 2976w (C–H), 2875w and 2827w (CHO), 1690s (C=O), 1597m and 1573w (C=C) and 1134s (C–O); *m*/*z* 404 (M^+, 40%), 313 (21), 312 (20), 270 (20), 269 (95), 227 (67) and 91 (100).

(±)-*cis*-5-Benzyloxy-9-isopropyloxy-1,3-dimethyl-1*H*-benzo[*g*]isochromane-7-carboxylic acid 24

To a solution of the racemic mixture of aldehyde diastereomers **23** (0.82 g, 2.0 mmol) in ethanol (96%, 20 cm^3) stirred at 0 °C under N_2, was added magnesium monoperoxyphthalate hexahydrate (80%, 1.25 g, 2.03 mmol). The mixture was allowed to warm to rt over 24 h. A white precipitate formed over this period. The reaction mixture was poured into H_2O (100 cm^3) and extracted with EtOAc (3 × 100 cm^3). The combined organic layers were dried with $MgSO_4$, filtered through Celite and the filtrate concentrated *in vacuo*. Purification of the resultant white semisolid by column chromatography (30% EtOAc–hexane) led to the isolation of the *cis*-isopropyloxy-1,3-dimethyl-1*H*-benzo[*g*]isochromane-7-carboxylic acid **24** (0.61 g, 72%) as a white solid. Recrystallisation from CH_2Cl_2 gave white fluffy needles which decomposed at 210 °C. Found M^+ 420.1947, $C_{26}H_{28}O_5$ requires M^+ 420.1937; ^1H NMR (400 MHz; $CDCl_3$; Me_4Si) δ 8.56 (1H, s, 6-H), 7.88 (1H, s, 10-H), 7.58–7.38, (6H, m, OCH_2PhH overlapping with 8-H), 5.09–5.00 (3H, m, 1-H overlapping with OCH_2Ph), 4.85 [1H, sept, *J* 6.0, $(CH_3)_2CH$–O], 3.83–3.76 (1H, m, 3-H), 3.09 (1H, br d, *J* 16.2, 4-H *pseudo*-equatorial), 2.64 (1H, dd, *J* 16.2 and 9.7, 4-H *pseudo*-axial), 1.71 (3H, d, *J* 6.4, 1-CH_3), 1.51–1.48 [6H, m, $(CH_3)_2CH$–O] and 1.40 (3H, d, *J* 6.1, 3-CH_3); ν_{max}(film)/cm^{-1} 3375 (O–H), 2976m (=CH), 2932w (C–H), 1686s (C=O), 1576w (C=C) and 1116s (C–O); *m*/*z* 420 (M^+, 25%), 329 (12), 328 (10), 286 (14), 285 (65), (11), 243 (28), and 91 (100).

Ethyl-4-acetoxy-6,8-dimethoxynaphthalene-2-carboxylate 27

To a solution of 2,4-dimethoxybenzaldehyde (5.45 g, 32.8 mmol) and diethyl succinate (8.18 cm^3, 8.57 g, 49.2 mmol) in dry ^{t}BuOH (80 cm^3), stirred under N_2, was added $KOBu^t$ (5.52 g, 49.2 mmol).

The mixture was heated under reflux for 2 h then allowed to cool to rt, poured onto ice and acidified to pH 3 with conc. $HCl_{(aq)}$. The product thus precipitated was extracted into EtOAc (2 × 100 cm^3), the combined extracts dried with $MgSO_4$, filtered through Celite and the filtrate concentrated *in vacuo*. The resultant oil was purified by column chromatography (10% EtOAc–hexane) to give the desired half acid intermediate that was not characterised. To this intermediate Stobbe condensation product, dissolved in acetic anhydride (100 cm^3), was added anhydrous sodium acetate (6.72 g, 81.9 mmol) and the mixture heated at 140 °C under Ar for 2 h and then allowed to cool. Acetic anhydride was removed *in vacuo*, H_2O (100 cm^3) was added, and the product extracted with CH_2Cl_2 (3 × 100 cm^3). Drying of the combined extracts ($MgSO_4$), filtration through Celite and removal of the solvent *in vacuo* gave a dark brown semisolid which was purified by column chromatography (30% EtOAc–hexane, containing 2% v/v CH_2Cl_2) to give an orange-white solid which was recrystallised from EtOAc to give the desired product **27** (8.10 g, 77%) as yellow crystals (mp 157–158 °C, EtOAc, lit. 158–159 °C[22,23]); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 8.79 (1H, d, *J* 1.1, 1-H), 7.81 (1H, d, *J* 1.1, 3-H), 6.66 (1H, d, *J* 1.9, 5-H), 6.51 (1H, d, *J* 1.9, 7-H), 4.41 (2H, q, *J* 7.1, OCH_2CH_3), 3.97 (3H, s, OCH_3), 3.91 (1H, s, OCH_3), 2.45 (3H, s, CH_3CO_2) and 1.42 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 169.2 (CH_3CO), 166.2 ($ArCO_2Et$), 160.9 (ArC–O), 157.8 (ArC–O), 145.3 (ArC–O), 131.0 (ArC), 124.4 (ArC), 123.2 (1-C), 122.2 (ArC), 119.1 (3-C), 98.5 (5-C), 91.6 (7-C), 61.0 (OCH_2CH_3), 55.7 (OCH_3), 55.3 (OCH_3), 20.9 (CH_3CO_2) and 14.4 (OCH_2CH_3).

Ethyl 4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate

To a solution of guanidine hydrochloride (2.43 g, 25.4 mmol) in dry ethanol (40 cm^3), stirred at rt under Ar, was added KOBu^t (2.87 g, 25.6 mmol) and the resultant white suspension stirred for a further 30 min. To this mixture was added the acetate ester **27** (7.36 g, 23.1 mmol) in CH_2Cl_2 (40 cm^3) and stirring was continued for another 1.5 h. The reaction mixture was then poured into H_2O (100 cm^3), acidified to pH 4 with conc. $HCl_{(aq)}$ then extracted with EtOAc (3 × 100 cm^3). The combined extracts were dried with $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. Purification by column chromatography (30% EtOAc–hexane) followed by recrystallisation from EtOAc, gave ethyl 4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate[23] (6.07 g, 95%) as white, fluffy crystals, mp 186–187 °C (EtOAc, not reported previously). Found M^+ 276.0997, $C_{15}H_{16}O_5$ requires M^+ 276.0998; ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si) δ 10.33 (1H, s, OH), 8.22 (1H, d, *J* 1.1, 1-H), 7.39 (1H, d, *J* 1.1, 3-H), 7.06 (1H, d, *J* 2.0, 5-H), 6.66 (1H, d, *J* 2.0 7-H), 4.32 (2H, q, *J* 7.1, OCH_2CH_3), 3.96 (3H, s, OCH_3), 3.89 (3H, s, OCH_3) and 1.34 (3H, t, *J* 7.1 OCH_2CH_3); ^{13}C NMR (50 MHz; DMSO-d_6) δ 166.0 ($ArCOOEt$), 159.2 (ArC–O), 156.8 (ArC–O), 152.1 (ArC–O), 128.6 (ArC), 124.1 (ArC), 121.0 (ArCH), 115.0 (ArC), 107.7 (ArCH), 98.5 (5-C), 92.7 (7-C), 60.3 (OCH_2CH_3), 55.7 (OCH_3), 55.1 (OCH_3) and 14.1 (OCH_2CH_3); ν_{max}(film)/cm^{-1} 3367br (O–H), 2982w (=CH), 2839w (C–H), 1684m (C=O), 1520w (C=C) and 1150s (C–O); *m*/*z* 276 (M^+, 100%), 248 (30), 231 (22), 205 (19), 175 (6), 145 (6), 115 (15), 91 (6), 69 (9) and 43 (13).

Ethyl 4-allyloxy-6,8-dimethoxynaphthalene-2-carboxylate 28

Allyl bromide (3.09 cm^3, 4.32 g, 35.7 mmol) and K_2CO_3 (4.94 g, 35.7 mmol) were added to a solution of ethyl 4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate (6.58 g, 23.8 mmol) in acetone (100 cm^3). The mixture was stirred at reflux under Ar for 16 h, cooled to rt and filtered through Celite. The solvent was removed *in vacuo* and the resultant light brown oil purified by column chromatography (10% EtOAc–hexane). The product **28**[23] (7.46 g, 99%) was isolated as a cream-white solid. Recrystallisation from EtOAc–hexane gave cream-white needles, mp 69.5–70.5 °C (EtOAc–hexane, not reported in the literature); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 8.51 (1H, d, *J* 1.3, 1-H), 7.42 (1H, d, *J* 1.3, 3-H), 7.15 (1H, d, *J* 2.1, 5-H), 6.52 (1H, d, *J* 2.1, 7-H), 6.23–6.12 (1H, m, $OCH_2CH=CH_2$), 5.52 (1H, dq, *J* 17.3 and 1.5, $OCH_2CH=CH_2$ *trans*), 5.34 (1H, dq, *J* 10.5 and 1.5, $OCH_2CH=CH_2$ *cis*), 4.76 (2H, dt, *J* 5.2 and 1.5, $OCH_2CH=CH_2$), 4.42 (2H, q, *J* 7.1, OCH_2CH_3), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3) and 1.34 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 167.1 ($ArCOOEt$), 160.0 (ArC–O), 157.5 (ArC–O), 153.0 (ArC–O), 133.2 ($OCH_2CH=CH_2$), 129.8 (ArC), 124.5 (ArC), 121.6 (ArCH), 117.9 ($OCH_2CH=CH_2$), 117.5 (ArC), 105.6 (ArCH), 98.5 (5-C), 92.6 (7-C), 69.1 ($OCH_2CH=CH_2$), 60.8 (OCH_2CH_3), 55.6 (OCH_3), 55.4 (OCH_3) and 14.4 (OCH_2CH_3).

Ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate

To ethyl 4-allyloxy-6,8-dimethoxynaphthalene-2-carboxylate (4.33 g, 13.7 mmol), was added anhydrous DMF (5 cm^3) and the solution heated at 170 °C, under Ar, for 12 h. The now dark brown solution was allowed to cool to rt and purified by column chromatography (10% EtOAc–hexane) to afford ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate[23] (3.25 g, 75%) as a white solid which upon recrystallisation from EtOAc–hexane gave white granules, mp 118.5–119.5 °C (EtOAc–hexane, not reported in the literature); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 8.37 (1H, s, 1-H), 7.04 (1H, d, *J* 2.1, 5-H), 6.49 (1H, d, *J* 2.1, 7-H), 6.17–6.06 (1H, m, $ArCH_2CH=CH_2$), 5.69 (1H, s, OH), 5.23–5.17 (2H, m, $ArCH_2CH=CH_2$), 4.38 (2H, q, *J* 7.1, OCH_2CH_3), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.93–3.90 (2H, m, $ArCH_2CH=CH_2$) and 1.25 (3H, t, *J* 7.1 OCH_2CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 168.1 ($ArCOOEt$), 160.0 (ArC–O), 157.2 (ArC–O), 149.7 (ArC–O), 136.4 ($ArCH_2CH=CH_2$), 128.3 (ArC), 125.6 (ArC), 120.3 (ArC), 118.8 (ArC), 118.5 ($ArCH_2CH=CH_2$, or 1-C), 116.1 (1-C or $ArCH_2CH=CH_2$), 98.2 (5-C), 92.0 (7-C), 60.8 (OCH_2CH_3), 55.6 (OCH_3), 55.4 (OCH_3), 31.8 ($ArCH_2CH=CH_2$) and 14.3 (OCH_2CH_3).

Ethyl-3-allyl-4-benzyloxy-6,8-dimethoxynaphthalene-2-carboxylate 29

To a solution of ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate (2.68 g, 8.47 mmol) in acetone (80 cm^3) was added benzyl chloride (1.07 cm^3, 1.18 g, 9.34 mmol), K_2CO_3 (1.29 g, 9.33 mmol) and potassium iodide (1.55 g, 9.32 mmol), and the mixture stirred at reflux under Ar for 18 h. After cooling to rt, the mixture was filtered through Celite, the filtrate concentrated *in vacuo* and the resultant yellow oil purified by column chromatography (10% EtOAc–hexane) to give the product **29** (3.44 g, 100%) as a cream-white semisolid. Found M^+ 406.1757, $C_{25}H_{26}O_5$ requires M^+ 406.1780; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 8.55 (1H, s, 1-H), 7.56–7.36 (5H, m, OCH_2PhH), 6.91 (1H, d, *J* 2.0, 5-H), 6.47 (1H, d, *J* 2.0, 7-H), 6.15–6.02 (1H, m, $ArCH_2CH=CH_2$), 5.01–4.62 (4H, m, OCH_2Ph and $ArCH_2CH=CH_2$), 4.38 (2H, q, *J* 7.1, OCH_2CH_3), 4.03 (2H, dt, *J* 5.8 and 1.6, $ArCH_2CH=CH_2$), 3.97 (3H, s, OCH_3), 3.79 (3H, s, OCH_3) and 1.41 (3H, t, *J* 7.1 OCH_2CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 167.9 ($ArCOOEt$), 160.4 (ArC–O), 157.7 (ArC–O), 152.4 (ArC–O), 137.9 ($ArCH_2CH=CH_2$), 137.6 (ArC), 131.9 (ArC), 129.8 (ArC), 128.6 (2 × ArCH), 128.1 (ArCH), 127.6 (2 × ArCH), 126.2 (ArC), 122.1 (1-C), 120.7 (ArC), 114.8 ($ArCH_2CH=CH_2$), 97.5 (5-C), 92.7 (7-C), 76.0 (OCH_2Ph), 60.8 (OCH_2CH_3), 55.6 (OCH_3), 55.2 (OCH_3), 30.9 ($ArCH_2CH=CH_2$) and 14.3 (OCH_2CH_3); ν_{max}(film)/cm^{-1} 3076w (=CH), 2977w (C–H), 1714s (C=O), 1626s and 1594s (C=C) and 1252s (C–O); *m*/*z* 406 (M^+, 56%), 361 (7), 315 (100), 286 (31), 242 (82), 91 (47) and 65 (5).

(3-Allyl-4-benzyloxy-6,8-dimethoxy-2-naphthyl)methanol

To a solution of the ethyl naphthalene carboxylate **29** (2.60 g, 6.40 mmol) in dry THF (75 cm^3), stirred at 0 °C under Ar, was added $LiAlH_4$ (0.48 g, 13 mmol) portion-wise; mild effervescence was observed. The cooling bath was removed and the mixture stirred at rt for 18 h. The reaction mixture was re-cooled in an ice bath and quenched by slow addition of a dilute 10% aqueous HCl solution until no further effervescence was observed. After total precipitation of the salts, excess H_2O and acid were removed by addition

of K_2CO_3 (solid) and the solution was filtered through Celite. The filtrate was concentrated *in vacuo* and the resultant brown oil purified by column chromatography to afford (3-allyl-4-benzyloxy-6,8-dimethoxy-2-naphthyl)methanol (2.21 g, 95%) as a white semisolid. Found M^+ 364.1676, $C_{23}H_{24}O_4$ requires M^+ 364.1675; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.98 (1H, s, 1-H), 7.54–7.32 (5H, m, OCH_2PhH), 6.90 (1H, d, *J* 1.9, 5-H), 6.45 (1H, d, *J* 1.9, 7-H), 6.13–6.04 (1H, m, $ArCH_2CH{=}CH_2$), 5.03 (1H, dq, *J* 10.1 and 1.7, $ArCH_2CH{=}CH_2$ *cis*), 4.97 (2H, s, OCH_2Ph), 4.92 (1H, dq, *J* 17.2 and 1.7, $OCH_2CH{=}CH_2$ *trans*), 4.78 (2H, br s, $ArCH_2OH$), 3.93 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.72 (2H, dt, *J* 5.5 and 1.7, $ArCH_2CH{=}CH_2$) and 1.90 (1H, br s, OH); ^{13}C NMR (75 MHz; $CDCl_3$) δ 158.6 (ArC–O), 156.9 (ArC–O), 152.2 (ArC–O), 137.6 (ArC), 137.6 (ArC), 135.2 ($OCH_2CH{=}CH_2$), 129.4 (ArC), 128.6 (2 × ArCH), 128.3 (ArC), 128.0 (ArCH), 127.6 (2 × ArCH), 121.6 (ArC), 117.9 ($ArCH_2CH{=}CH_2$), 115.3 (ArC), 97.6 (5-C), 92.6 (7-C), 75.9 (OCH_2Ph), 63.8 ($ArCH_2OH$), 55.5 (OCH_3), 55.2 (OCH_3) and 30.3 ($ArCH_2CH{=}CH_2$); ν_{max}(film)/cm^{-1} 3419br (O–H), 3002w (=CH), 2936w (C–H), 1630s and 1603s (C=C) and 1203s (C–O); *m*/*z* 364 (M^+, 19%), 274 (20), 273 (100), 255 (36), 243 (18), 217 (21) and 91 (30).

3-Allyl-4-benzyloxy-6,8-dimethoxy-2-naphthaldehyde 30

Pyridinium chlorochromate (0.65 g, 3.02 mmol) was dissolved in dry acetonitrile (20 cm^3) and poured into neutral alumina (10.00 g). The suspension was dried *in vacuo* and to the solid was then added a solution of 3-allyl-4-benzyloxy-6,8-dimethoxy-2-hydroxymethylnaphthalene (1.00 g, 2.74 mmol) in CH_2Cl_2 (50 cm^3). The reaction mixture was left to stir under Ar at rt for 8 h. Filtration through Celite, concentration on a rotary evaporator and purification of the resultant yellow oil by column chromatography (30% EtOAc–hexane) gave the desired aldehyde **30** (0.78 g, 78%) as a white solid. Recrystallisation from EtOAc–hexane gave white needles, mp 94.5–95.0 °C (EtOAc–hexane). Found M^+ 362.1519, $C_{23}H_{22}O_4$ requires M^+ 362.1518; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 10.17 (1H, s, CHO), 8.49 (1H, s, 1-H), 7.54–7.37 (5H, m, OCH_2PhH), 6.92 (1H, d, *J* 2.0, 5-H), 6.49 (1H, d, *J* 2.0, 7-H), 6.18–6.09 (1H, m, $ArCH_2CH{=}CH_2$), 5.03 (1H, dq, *J* 10.2 and 1.7, $ArCH_2CH{=}CH_2$ *cis*), 4.99 (2H, s, OCH_2Ph), 4.94 (1H, dq, *J* 17.2 and 1.7, $ArCH_2CH{=}CH_2$ *trans*), 4.05 (2H, dt, *J* 5.6 and 1.7, $ArCH_2CH{=}CH_2$), 3.98 (3H, s, OCH_3) and 3.79 (3H, s, OCH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 192.3 (CHO), 161.6 (ArC–O), 158.2 (ArC–O), 152.4 (ArC–O), 137.7 (ArC), 137.6 (ArC), 133.2 ($ArCH_2CH{=}CH_2$), 130.2 (ArC), 129.3 (ArC), 128.6 (2 × ArCH), 128.2 (ArCH), 127.6 (2 × ArCH), 127.1 (ArC), 120.9 (C-1), 115.4 ($ArCH_2CH{=}CH_2$), 98.2 (5-C), 93.2 (7-C), 76.1 (OCH_2Ph), 55.7 (OCH_3), 55.3 (OCH_3) and 29.6 ($ArCH_2CH{=}CH_2$); ν_{max}(film)/cm^{-1} 3005w (=CH), 2938w (C–H), 2861w and 2723w (CHO), 1688s (C=O), 1622m (C=C) and 1156s (C–O); *m*/*z* 362 (M^+, 31%), 272 (19), 271 (100), 243 (40), 228 (24), 185 (11) and 91 (44).

1-(3-Allyl-4-benzyloxy-6,8-dimethoxy-2-naphthyl)-1-ethanol 31

To a solution of methylmagnesium iodide [freshly prepared from magnesium metal turnings (0.12 g, 4.9 mmol) and iodomethane (0.31 cm^3, 0.72 g, 5.1 mmol) in anhydrous Et_2O (40 cm^3)] stirred at 0 °C under Ar, was added a solution of 3-allyl-4-benzyloxy-6,8-dimethoxynaphthalene-2-carbaldehyde **30** (1.22 g, 3.37 mmol) in dry THF (20 cm^3). The resultant cloudy mixture was allowed to warm up to rt over 8 h, re-cooled to 0 °C and quenched with H_2O. This was then poured into H_2O (75 cm^3) and extracted with EtOAc (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. Purification of the resultant oil by column chromatography (30% EtOAc–hexane) gave the target alcohol (1.21 g, 95%) as a white solid. Recrystallisation from EtOAc–hexane gave white needles, mp 120.5–121.5 °C (EtOAc–hexane). Found M^+ 378.1831, $C_{24}H_{26}O_4$ requires M^+ 378.1831; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 8.17 (1H, s, 1-H), 7.54–7.36 (5H, m, OCH_2PhH), 6.90 (1H, d, *J* 2.0, 5-H), 6.46 (1H, d, *J* 2.0, 7-H), 6.15–6.06 (1H, m, $ArCH_2CH{=}CH_2$), 5.20 [1H, qd, *J* 6.4 and 3.1, $ArCH(CH_3)OH$, D_2O wash, q, *J* 6.4], 5.05 (1H, dq, *J* 10.2 and 1.8, $ArCH_2CH{=}CH_2$ *cis*), 4.98 (2H, s, OCH_2Ph), 4.91 (1H, dq, *J* 17.2 and 1.8, $ArCH_2CH{=}CH_2$ *trans*), 3.95 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.85–3.78 (1H, m, one of $ArCH_2CH{=}CH_2$), 3.66–3.59 (1H, m, one of $ArCH_2CH{=}CH_2$), 1.87 (1H, br d, *J* 3.1, OH) and 1.57 [3H, d, *J* 6.4, $ArCH(CH_3)OH$]; ^{13}C NMR (75 MHz; $CDCl_3$) δ 158.5 (ArC–O), 157.0 (ArC–O), 152.0 (ArC–O), 140.2 (ArC), 137.8 (ArC), 137.7 ($ArCH_2CH{=}CH_2$), 129.0 (ArC), 128.6 (2 × ArCH), 128.0 (ArCH), 127.6 (2 × ArCH), 127.4 (ArC), 121.9 (1-C), 115.4 (ArC), 114.6 ($ArCH_2CH{=}CH_2$), 97.5 (5-C), 92.5 (7-C), 75.9 (OCH_2Ph), 66.6 [$ArCH(CH_3)OH$], 55.5 (OCH_3), 55.2 (OCH_3), 30.0 ($ArCH_2CH{=}CH_2$) and 24.6 [$ArCH(CH_3)OH$]; ν_{max}(film)/cm^{-1} 3502br (O–H), 3001w (=CH), 2969w (C–H), 1629s and 1598s (C=C) and 1202s (C–O); *m*/*z* 378 (M^+, 22%), 288 (24), 287 (100), 269 (62), 231 (39) and 91 (21).

5-Benzyloxy-7,9-dimethoxy-1,3-dimethyl-1*H*-benzo[*g*]isochromene 32

To a solution of the alcohol **31** (1.52 g, 4.02 mmol) in DMF (20 cm^3), stirred at rt under oxygen, was added copper(II) chloride dihydrate (0.68 g, 4.0 mmol) and palladium(II) chloride (0.07 g, 0.40 mmol) in H_2O (10 cm^3). The resultant suspension, which turned black after a few min, was left to stir for 3 h. The reaction mixture was poured into H_2O (100 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered through Celite and the filtrate concentrated *in vacuo*. The resultant dark oil was purified by column chromatography (10% EtOAc–hexane) to afford the product **32** (1.39 g, 92%) as a white, waxy solid. Recrystallisation from 2-propanol gave white crystals, mp 97–98 °C (^{i}PrOH). Found M^+ 376.1674, $C_{24}H_{24}O_4$ requires M^+ 376.1675; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.50 (1H, s, 10-H), 7.44–7.22 (5H, m, OCH_2PhH), 6.78 (1H, d, *J* 2.1, 6-H), 6.29 (1H, d, *J* 2.1, 8-H), 5.91 (1H, s, 4-H), 5.18 (1H, q, *J* 6.4, 1-H), 4.88 (2H, s, OCH_2Ph), 3.82 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 1.88 (3H, s, 3-CH_3) and 1.58 (3H, d, *J* 6.4, 1-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 158.4 (ArC–O), 156.8 (ArC–O), 154.5 (ArC–O), 145.5 (ArC), 137.8 (ArC), 129.6 (ArC), 129.4 (ArC), 128.5 (2 × ArCH), 128.0 (ArCH), 127.9 (2 × ArCH), 122.0 (ArC), 120.9 (ArC), 112.4 (10-C), 96.8 (4-C), 95.8 (6-C), 92.6 (8-C), 75.7 (OCH_2Ph), 74.3 (1-C), 55.5 (OCH_3), 55.2 (OCH_3), 20.44 (1-CH_3) and 19.9 (3-CH_3); ν_{max}(film)/cm^{-1} 3030w (=CH), 2936m (C–H), 1651m, 1627s, 1605s and 1580m (C=C) and 1157s (C–O); *m*/*z* 376 (M^+, 19%), 286 (23), 285 (100), 267 (37), 167 (25), 149 (24), 71 (9) and 57 (18).

(±)-*cis*-7,9-Dimethoxy-1,3-dimethyl-1*H*-benzo[*g*]isochroman-5-ol 33

To a solution of the benzyloxyisochromene **32** (1.00 g, 2.66 mmol) in CH_2Cl_2–dioxane (3 : 1, 25 cm^3), stirred at rt under hydrogen (1 atm), was added Pd/C (0.10 g, 10% w/w) and stirring continued for 48 h. The reaction mixture was then filtered through Celite, the filtrate concentrated *in vacuo* and the resultant oil purified by column chromatography (10–30% EtOAc–hexane). This afforded the desired product **33** as a mixture (3 : 1 *cis* : *trans*) of diastereomers (0.39 g, 51%), as well as starting material (0.31 g). Recrystallisation of the product thus isolated from EtOAc–hexane gave solely *rac*-*cis*-**33** (0.27 g, 35%) as white leaflets which started subliming at 138 °C and melted at 178–179 °C. Found M^+ 288.1363, $C_{17}H_{20}O_4$ requires M^+ 288.1362; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.51 (1H, s, OH), 7.49 (1H, s, 10-H), 7.09 (1H, d, *J* 1.9, 6-H), 6.43 (1H, d, *J* 1.9, 8-H), 4.95 (1H, q, *J* 6.2, 1-H), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.90–3.81 (1H, m, 3-H), 2.95 (1H, dd, *J* 16.3 and 3.0, 4-H *pseudo*-equatorial), 2.61 (1H, dd, *J* 16.3 and 11.1, 4-H *pseudo*-axial), 1.65 (3H, d, *J* 6.2, 1-CH_3) and 1.35 (3H, d, *J* 6.2, 3-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 157.1 (ArC–O), 156.1 (ArC–O), 147.5 (ArC–O), 135.1 (ArC), 124.6 (ArC), 120.6 (ArC), 117.2 (ArC), 108.5 (10-C), 97.0 (6-C), 91.9 (8-C), 73.5 (1-C), 70.3 (3-C), 55.2 (OCH_3), 55.1 (OCH_3), 31.5 (4-C), 21.9 (1-CH_3) and 21.8 (3-CH_3); ν_{max}(film)/cm^{-1} 3401br (O–H), 2967s (=CH), 2932s (C–H), 1633m and 1602s (C=C) and 1152s (C–O); *m*/*z* 288 (M^+, 72%), 273 (100), 244 (26), 229 (11), 128 (6), 115 (8) and 43 (9).

(±)-*cis*-7,9-Dimethoxy-1,3-dimethyl-1*H*-benzo[*g*]isochromane-5,10-dione [7-methoxyeleutherin 34]

To a solution of the isochroman-5-ol, *rac*-**33** (0.30 g, 1.0 mmol) in DMF (5 cm^3), stirred at rt under an oxygen atmosphere, was added *N*,*N*′-bis(salicylidene)-ethylenediaminocobalt(II) hydrate (salcomine) (0.17 g, 0.52 mmol) and stirring was continued for 18 h. The reaction mixture was poured into ice H_2O (100 cm^3), acidified to pH 3 by drop-wise addition of conc. $HCl_{(aq)}$ and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered through Celite and the filtrate concentrated *in vacuo*. The resultant dark oil was purified by column chromatography (30% EtOAc–hexane) to afford the product *rac*-**34** (0.28 g, 90%) as an orange solid. Recrystallisation from EtOAc–hexane gave orange needles. ^1H and ^{13}C NMR spectra were in agreement with literature data.[6,7,28] ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 7.28 (1H, d, *J* 2.4, 6-H), 6.69 (1H, d, *J* 2.4, 8-H), 4.85–4.81 (1H, m, 1-H), 3.95 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.60–3.56 (1H, m, 3-H), 2.71 (1H, dt, *J* 18.2 and 2.6, 4-H *pseudo*-equatorial), 2.17 (1H, ddd, *J* 18.2, 10.2 and 3.8, 4-H *pseudo*-axial), 1.53 (3H, d, *J* 6.6 1-CH_3) and 1.35 (3H, d, *J* 6.2, 3-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 183.9 (C=O), 182.4 (C=O), 164.3 (ArC–O), 161.5 (ArC–O), 148.7 (ArC), 139.3 (ArC), 135.6 (ArC), 114.6 (ArC), 104.0 (6-C), 102.9 (8-C), 70.3 (1-C), 68.6 (3-C), 56.3 (OCH_3), 55.8 (OCH_3), 29.9 (4-C), 21.2 (1-CH_3) and 20.9 (3-CH_3).

(±)-*cis*-9-Hydroxy-7-methoxy-1,3-dimethyl-1*H*-benzo[*g*]isochromane-5,10-dione [Ventiloquinone L 4]

To a solution of *rac*-7-methoxyeleutherin **34** (0.30 g, 0.99 mmol) in anhydrous CH_2Cl_2 (30 cm^3), stirred at −78 °C under an Ar atmosphere, was added by syringe, a 1 M solution of BCl_3 in hexanes (1.98 cm^3, 1.98 mmol). The dark mixture was allowed to stir for 30 min, quenched with H_2O and allowed to warm up to rt. The mixture was then poured into H_2O (100 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered through Celite, the filtrate concentrated *in vacuo* and the resultant dark semisolid purified by column chromatography to afford the product (0.20 g, 70%) as an orange solid. Recrystallisation from CH_2Cl_2–hexane gave orange needles of the product **4**, that sublimed at 105 °C and melted at 117–118 °C. (Literature mp: enantiopure from natural source 126 °C, benzene–hexane).[3] ^1H and ^{13}C NMR spectroscopic data were in agreement with those previously reported. ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ 12.23 (1H, s, OH), 7.14 (1H, d, *J* 2.5, 6-H), 6.60 (1H, d, *J* 2.5, 8-H), 4.84–4.80 (1H, m, 1-H), 3.89 (3H, s, OCH_3), 3.60–3.56 (1H, m, 3-H), 2.73 (1H, dt, *J* 18.6 and 2.6, 4-H *pseudo*-equatorial), 2.22 (1H, ddd, *J* 18.6, 10.2 and 4.0, 4-H *pseudo*-axial), 1.58 (3H, d, *J* 6.6, 1-CH_3) and 1.36 (3H, d, *J* 6.2, 3-CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 187.4 (C=O), 183.0 (C=O), 165.6 (ArC–O), 164.2 (ArC–O), 146.7 (ArC), 143.2 (ArC), 133.2 (ArC), 109.5 (ArC), 107.6 (6-C), 106.1 (8-C), 69.8 (1-C), 68.6 (3-C), 56.0 (OCH_3), 30.6 (4-C) and 21.2 (1-CH_3 and 3-CH_3).

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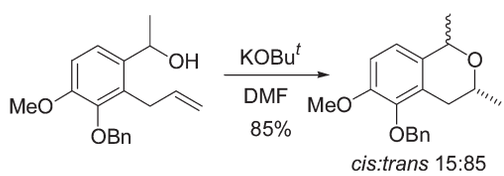

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