Syntheses of isochromane analogues of the michellamines and korupensamines

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Syntheses of the oxygen analogues **6**, **7** and **8** of the michellamines **1** and korupensamines **2** are described. Racemic 5-iodo-6,8-dimethoxy-*trans*-1,3-dimethylisochromane **10** was synthesised in eleven steps from 2,4-dimethoxybenzaldehyde in an overall yield of 51%. The isopropoxy analogue **11** was synthesised in a similar manner. Isochromane **10** was coupled using Suzuki methodology with 4-isopropoxy-5-methoxy-7-methylnaphthalene-1-boronic acid **9** to produce **7** in 96% yield. This was converted in good yield into the desired product **6** by oxidative dimerisation followed by reduction of the cross-conjugated ene-dione intermediate **45**.

Introduction

The michellamines (*e.g.*, michellamine B, **1**) are a growing class of novel naphthylisoquinoline alkaloids isolated from the tropical liana *Ancistrocladus korupensis*, found in the Cameroon.[1] These compounds are of interest to the scientific community as they show activity against the Human Immunodeficiency Virus (HIV).[2] In addition, as a result of their intriguing structures, chemists have been interested in the synthesis of these molecules and a number of groups have published total syntheses or approaches to their synthesis.[3]

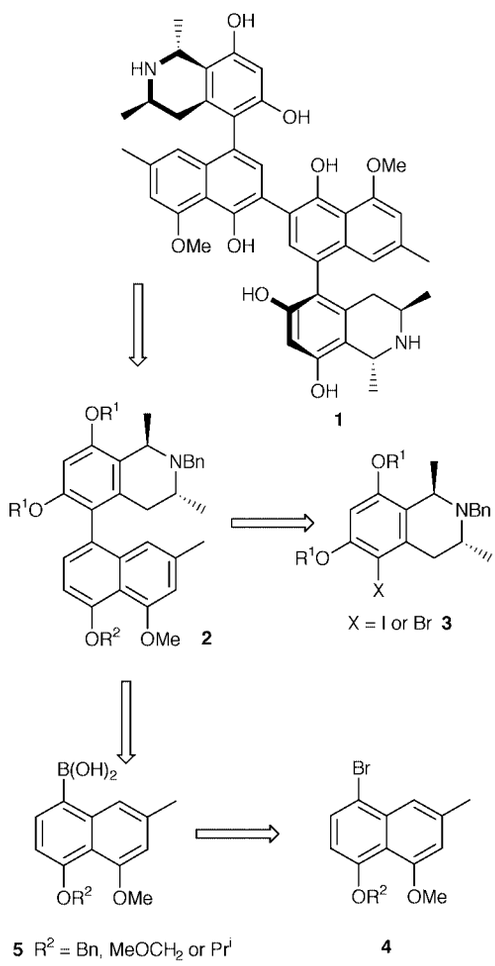
Most of the published syntheses rely on the dimerisation of a (5)-naphthylisoquinoline such as **2**, which in turn is constructed from a suitably protected tetrahydroisoquinoline precursor, *e.g.* **3**. Isoquinoline **3** is invariably made by means of a Bischler–Napieralski cyclisation.[4] The bromonaphthalene **4** is a key intermediate in several reported syntheses.[3e,p,5] The biaryl axis is then formed between **3** and various naphthalene boronic acids such as **5**, which are themselves prepared from the brominated precursor **4**. The formation of the biaryl axis has been accomplished using both Suzuki[3a–d,h–j,l,o,q] and Stille[3e,p] coupling procedures, with the Suzuki methodology[6] used more frequently. Removal of R^2 from the diastereoisomeric biaryl products **2**, dimerisation and deprotection of the remaining phenolic groups result in formation of the michellamines, *e.g.* **1**. The biaryl products **2**, the 'monomers' of the michellamines, are also found in Nature and are known as the korupensamines.[7] They do not show activity against the HIV, but do show biological activity against the malaria parasite, *Plasmodium falciparum*.

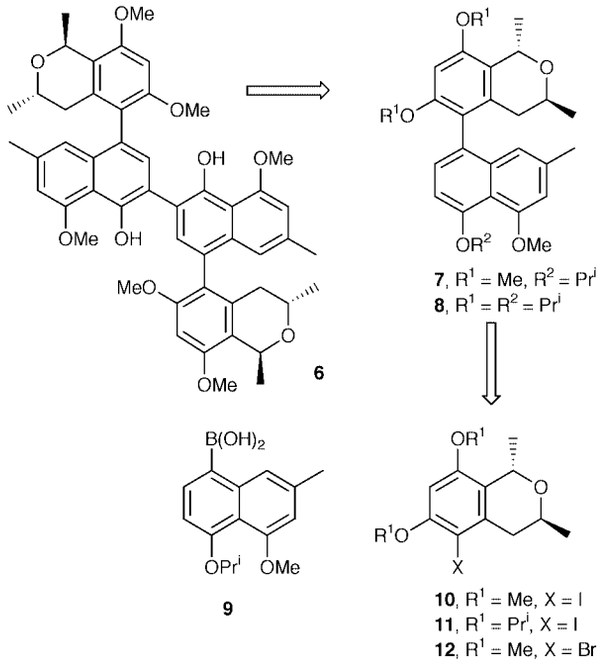
As a result of the activities associated with natural products such as the michellamines, the National Cancer Institute (NCI) of the USA has encouraged researchers to synthesise analogues of these naturally occurring compounds,[8] and several have been reported.[9] Most of the analogues prepared have unnatural biaryl linkages in which the isoquinoline and naphthalene moieties are joined at sites other than those found in **1**. In this paper we report in full on a synthesis of racemic methoxy- and isopropoxy-isochromane analogues of the korupensamines (**7** and **8**) as well as the methoxylated michellamine oxygen analogue **6**. Preliminary details have previously appeared in a communication.[10]

Results and discussion

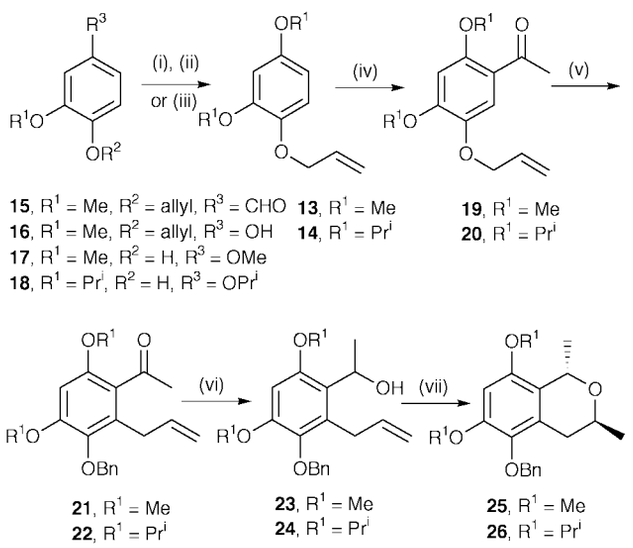
Retrosynthesis of **6** takes the obvious structural symmetry of the target into account, and leads to **7**. This important intermediate was in turn disconnected to give isochromane **10** and the naphthalene **9**. In **10**, the phenolic groups are protected as their methyl ethers, but we also chose to prepare the analogue **11** possessing isopropyl protecting groups, as it was hoped that these groups could be selectively removed when required to afford phenolic analogues of **6**.[11]

We elected to synthesise the desired isochromanes **10** and **11** from 1-allyloxy-2,4-dimethoxybenzene **13** and its isopropoxy analogue **14**. The bromide analogue **12** was also prepared from





13. 1-Allyloxy-2,4-dimethoxybenzene **13** was synthesised either from vanillin through the intermediacy of **15** and **16** or from 2,4-dimethoxybenzaldehyde[12] *via* **17**;[13] both routes involve Baeyer–Villiger oxidation of the aldehyde group as shown in Scheme 1. Although vanillin is cheaper, the second route was



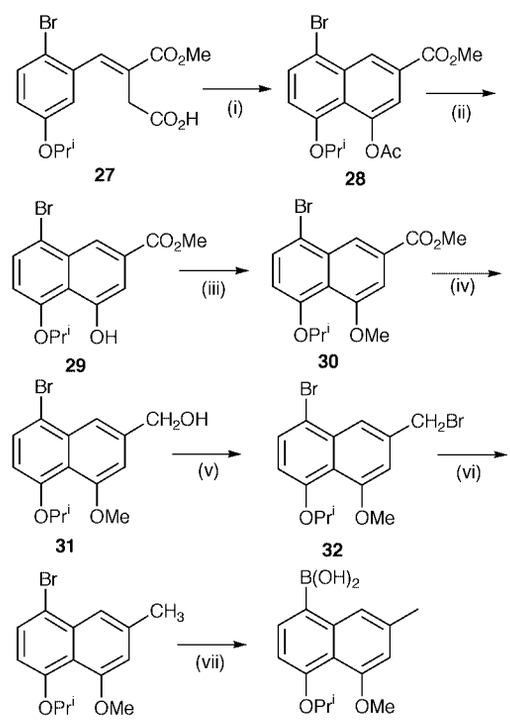
Scheme 1 *Reagents and conditions*: For **15** ⟶ **16** ⟶ **13** (i) MMPP (magnesium monoperoxyphthalic acid hexahydrate) silica gel, MeOH (64%); (ii) $(MeO)_2SO_2$, K_2CO_3, Me_2CO (92%); (iii) $H_2C{=}CHCH_2Br$, K_2CO_3, Me_2CO (96%) (**17** ⟶ **13**) (or 94%) (**18** ⟶ **14**); (iv) AcOH, TFAA, CH_2Cl_2 (66%) (**13** ⟶ **19**) (or 94%) (**14** ⟶ **20**); (v) (a) 160 °C; (b) $PhCH_2Br$, K_2CO_3, Me_2CO (2 steps) (82%) (**19** ⟶ **21**) (or 79%) (**20** ⟶ **22**); (vi) $LiAlH_4$, Et_2O (94%) (**21** ⟶ **23**) (or 93%) (**22** ⟶ **24**); (vii) $KOBu^t$, DMF, (94%) (**23** ⟶ **25**) (or 85%) (**24** ⟶ **26**).

the method of choice as the intermediate products were formed in higher yields and were easier to handle. Compound **14** was synthesised from 2,4-diisopropoxybenzaldehyde, which is readily made by Vilsmeier–Haack formylation of 1,3-diisopropoxybenzene.[14] Following the same steps as outlined for the formation of **13**, 2,4-diisopropoxybenzaldehyde was converted into **14** *via* **18** in good overall yields (62%). With both **13** and **14** in hand, the acetyl functionality was introduced by treatment with a mixture of acetic acid and trifluoroacetic anhydride at ambient temperature to yield **19** (66%) and **20** (94%).[15] The location of the acetyl group in both products was unambiguous, as the ^{1}H NMR spectra showed, *inter alia*, two singlets (*i.e.*, no *ortho* or *meta* coupling) at δ 7.45 and 6.50 for **19** and δ 7.44 and 6.50 for **20**.

Efficient conversion (*ca.* 80%) of both **19** and **20** into **21** and **22**, respectively, was achieved by heating the compounds neat at 160 °C (to induce a Claisen rearrangement) and protecting the resulting phenols as benzyl ethers. Reduction of **21** and **22** gave the racemic alcohols **23** and **24** (both in 93–94% yield).

Utilising methodology developed by Giles *et al.*,[16] we converted both of these alcohols into the desired racemic *trans*-1,3-dimethylisochromanes **25** and **26** by treatment with potassium *tert*-butoxide in DMF at 75 °C. Evidence for the formation of the *trans*-product in both cases was again obtained from the ^{1}H NMR spectra. It has been shown that 3-H for *trans*-1,3-dimethylisochromanes occurs upfield ($\delta \approx 4$) in relation to the *cis*-isomer ($\delta \approx 3.8$).[17] In these examples, the ^{1}H NMR spectra showed 3-H for **25** as a multiplet at δ 3.99–3.91, and for the isopropyl analogue **26** as a multiplet at δ 3.98–3.93. The relative stereochemistry was confirmed by an X-ray crystal-structure determination on compound **36**, prepared later in the synthetic sequence.

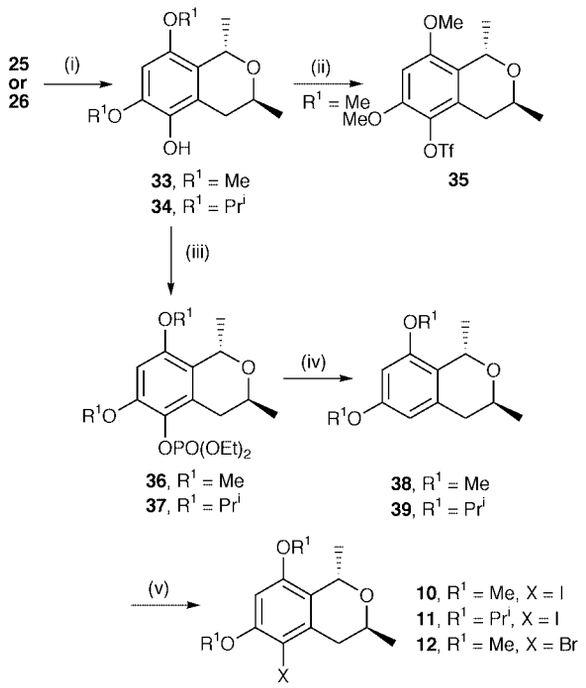
The naphthalene **9** required for the coupling with the isochromane moiety was synthesised using standard methodology. 2-Bromo-5-isopropoxybenzaldehyde[18] was treated with dimethyl succinate in the presence of potassium *tert*-butoxide to give the intermediate Stobbe condensation product **27** as a mixture of geometrical isomers (60 : 40). This was treated with acetic anhydride and sodium acetate[19] to give the naphthalene **28**. The overall yield of this two-step sequence was 49%. Following a series of functional-group manipulations[3e] (**28** ⟶ **29** ⟶ **30** ⟶ **31** ⟶ **32**), 5-bromo-8-isopropoxy-1-methoxy-3-methylnaphthalene **4** was obtained. Conversion into the corresponding naphthaleneboronic acid **9** was accomplished in high yield by sequential treatment of **4** with *n*-butyllithium at −78 °C and triisopropyl borate followed by hydrolysis as outlined in Scheme 2.



Scheme 2 *Reagents and conditions*: (i) Ac_2O, NaOAc (74%); (ii) KOH–MeOH (95%); (iii) $(MeO)_2SO_2$, K_2CO_3, Me_2CO (99%); (iv) $LiAlH_4$, Et_2O (98%); (v) $(CBrCl_2)_2$, PPh_3, CH_2Cl_2 (86%); (vi) L-Selectride, CH_2Cl_2 (100%); (vii) (a) *n*-BuLi, THF, −78 °C; (b) $B(OPr^i)_3$, aq. NH_4Cl, not purified.

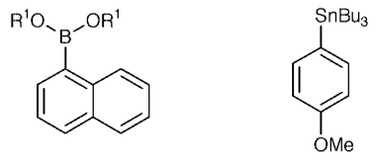
With the synthesis of both the isochromane skeleton and the naphthalene accomplished, it was necessary to modify functional groups to allow for efficient coupling of the two moieties. In particular, the benzyl ether at C-5 in both isochromanes **25** and **26** must be converted into a functional group suitable for coupling with the naphthalene **9**. While the specific choice of functional group was not obvious at this stage, it was clear that hydrogenolysis of the benzyl group was an essential first step. Removal of the benzyl protecting group was accomplished with either 10% palladium on charcoal or palladium black under a hydrogen atmosphere to give a quantitative yield of both **33** and **34**. The isochromane ring, itself a benzylic ether, was unaffected during this reaction.

Phenol **33** was converted into triflate **35** by treatment with triflic anhydride in the presence of pyridine (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) 10% Pd/C, MeOH, H_2 (100%) (**25** ⟶ **33**) and (**26** ⟶ **34**); (ii) Tf_2O, $CHCl_3$, pyridine (88%); (iii) $(EtO)_2POCl$, NaH, THF (100%) (**33** ⟶ **36**) (or 81%) (**34** ⟶ **37**); (iv) K, NH_3, −78 °C (100%) (**36** ⟶ **38**) (or 91%) (**37** ⟶ **39**); (v) Ag_2SO_4, I_2, EtOH (94%) (**38** ⟶ **10**) and (**39** ⟶ **11**); or Br_2, AcOH–$CHCl_3$ (93%) (**38** ⟶ **12**).

Attempted coupling reactions with two model systems, 1-naphthylboronic acid **40**[20] and tributyl-(4-methoxyphenyl)-stannane **42**,[21] were unsuccessful. This is probably due to the electron-rich nature of the isochromane, which makes it more difficult for palladium(0) to be inserted between the triflate oxygen and carbon in the aromatic ring.[22] Hence we chose to replace the benzyloxy group with a halogen before attempting coupling reactions. For isochromane **25**, this was done by using an uneventful high yielding deoxygenation sequence,[23] **25** ⟶ **33** ⟶ **36** ⟶ **38**, which proceeded overall in quantitative yield. An X-ray crystal structure[24] of **36** provided conclusive evidence of the structure of the molecule and verified the 1,3-*trans*-dimethyl stereochemistry of the pyran ring. Isochromane **38** was converted into both the bromide **12** and iodide **10** using bromine in acetic acid or iodine and silver(I) sulfate[25] in yields of 93 and 94%, respectively. A similar sequence of reactions was used for converting the isopropoxyisochromane **34** into iodide **11** *via* **37** and **39**. The regiochemistry of all three products **10**, **11** and **12** was confirmed by NOE experiments. Irradiation of the single aromatic proton showed enhancement of both methoxy groups in **10** and **12**, while irradiation of **11** showed enhancement of both isopropoxy groups.



40, R^1=H
41, R^1= -Me_2CCMe_2-

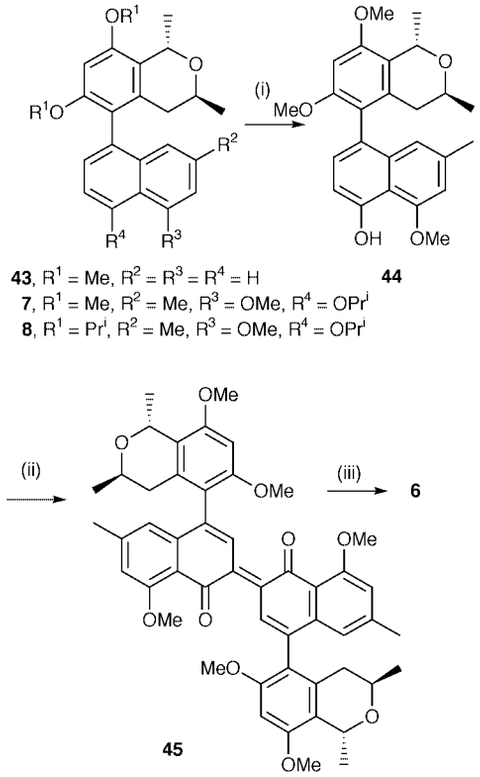
42

The stage was now set to couple the halogenated isochromanes **10**–**12** with the substituted naphthaleneboronic acid **9** using the palladium-mediated Suzuki reaction.[6] However, we considered it prudent to optimise reaction conditions by first performing some model reactions with readily accessible aromatic boronic acids before committing our more valuable naphthaleneboronic acid **9**. Treatment of bromoisochromane **12** with 1-naphthylboronic acid **40** in the presence of 10 mol% tetrakis(triphenylphosphine)palladium(0) in toluene and of aq. sodium bicarbonate[3f] under argon gave a 28% yield of the desired product **43** as a mixture of diastereoisomers (ratio: 66 : 34), which arise from the creation of a stereogenic axis. Clear evidence for the formation of two diastereoisomers came from the ^1H and ^{13}C NMR spectra, which showed doubling of virtually all the signals. In addition, the high-resolution mass spectrum showed the expected molecular ion at M^+ 348.1717 ($C_{23}H_{24}O_3$ requires *M*, 348.1725). As the yield of **43** was low the reaction was repeated using the method of Coudret.[26] Reaction of **12** with 1-naphthylboronic acid pinacol ester **41**[27] and dichloro-[1,1′-bis(diphenylphosphino)ferrocene]palladium(0) gave a very disappointing yield (14%) of the desired product **43**. Hence, at this stage it was decided that all future work on these reactions would be done on the iodinated isochromanes **10** and **11**, as literature precedent indicated that iodine is the best halogen for Suzuki coupling reactions.[3f]

After much experimentation, iodoisochromane **10** and naphthylboronic acid **9** were treated with 20 mol% tetrakis(triphenylphosphine)palladium(0) in DMF under argon with tribasic potassium phosphate[28] to give the desired biaryl compound **7** in an excellent yield of 96%. Doubling of signals in both the ^1H NMR and ^{13}C NMR spectra showed clearly that the product had been formed as a mixture of two diastereoisomers (59 : 41). The ^1H NMR spectrum showed a number of differences on the isochromane moiety as compared with that of the precursor **10**, the most significant being the shift of the aromatic singlet (7-H) from δ 6.34 to δ 6.99 and 6.97 for the diastereomeric products. Additionally, the two 4-H protons, which appeared as double doublets at δ 2.74 and 2.35 in **10**, appeared in the product **7** as multiplets at δ 2.15–2.03 and 1.88–1.81.

Under the same conditions, coupling **11** with **9** gave the desired product **8** in a disappointing yield of 15%. Even in the presence of an oxygen scavenger, 2,6-di-*tert*-butyl-4-methylphenol,[29] the yield could not be improved. Nevertheless, compounds **7** and **8** are both oxygen analogues of the korupensamines—the first on record.

Selective removal of the isopropyl group of **7** with boron trichloride yielded the naphthol **44**. This was treated with silver(I) oxide to afford **45** (Scheme 4). This purple compound was not characterised fully, but subjected to hydrogenation on a palladium–charcoal catalyst to yield the desired oxygen analogue of the michellamines **6** in good yield. The product was produced as a mixture of racemic diastereoisomers. This represents the first synthesis of an isochromane analogue of the michellamines. We are currently investigating the separation of these six possible diastereoisomers, after which biological evaluation of these new michellamine analogues will be undertaken. Furthermore, synthesis of the isochromane building blocks as pure enantiomers will also reduce the number of diastereoisomeric options in the final product, and this comparatively straightforward task is also under investigation.



Scheme 4 *Reagents and conditions*: (i) BCl_3, −78 °C, CH_2Cl_2 (51%); (ii) Ag_2O, 0.2% Et_3N, $CHCl_3$ (100%); (iii) H_2, Pd/C (75%).

Experimental

^1H and ^{13}C NMR spectra were recorded either on a Bruker AC-200 or 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. *J*-Values are given in Hz. NMR spectroscopic assignments with the same superscript may be interchanged. IR 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 analyses were 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 were distilled prior to use.

4-Allyloxy-3-methoxybenzaldehyde 15

Allyl bromide (39.8 g, 0.33 mol) and potassium carbonate (90.0 g, 0.65 mol) were added to a solution of vanillin (22.0 g, 0.145 mol) in dry DMF (500 cm^3). The reaction mixture was heated under nitrogen at 70 °C for 50 h. After filtration and removal of the solvent *in vacuo*, the reside was purified by column chromatography (10% ethyl acetate–hexane) to give the *product* **15** as a clear yellow oil (27.5 g, 99%) which solidified (mp 27–29 °C) (Found: M^+, 192.0793. $C_{11}H_{12}O_3$ requires *M*, 192.0786); ν_{max}(film)/cm^{-1} 3080m (=CH_2), 3030m (=CH), 1683s (C=O), 1586s (ArC=C), 1267s and 1032m (C–O–C) and 995s (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 9.85 (1H, s, CHO), 7.43 (1H, dd, *J* 8.7 and 1.9, 6-H), 7.41 (1H, d, *J* 1.9, 2-H), 6.98 (1H, d, *J* 8.7, 5-H), 6.16–6.02 (1H, m, 2′-H), 5.50–5.31 (2H, m, 3′-H_2), 4.71 (2H, br dt, *J* 5.4 and 1.4, 1′-H_2) and 3.94 (3H, s, OCH_3); δ_C (50.32 MHz; $CDCl_3$) 190.7 (C=O), 153.3, 149.7 (2 × ArC–O), 132.1 (2′-C), 130.0 (1-C), 126.4 (6-C), 118.6 (3′-C), 111.8 (2-C), 109.1 (5-C), 69.6 (1′-C) and 55.8 (OCH_3); *m*/*z* (EI) 192 (M^+, 100%), 177 (6), 151 (63), 95 (43), 77 (19), 65 (10) and 41 (32).

4-Allyloxy-3-methoxyphenol 16

Magnesium monoperoxyphthalic acid hexahydrate (MMPP) (51.0 g, 0.10 mol) was added to a solution of the benzaldehyde **15** (16.6 g, 0.086 mol) in dry methanol (200 cm^3), under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred under nitrogen for 55 h, during which time a pink precipitate formed. An additional portion of MMPP (10 g) was added and the reaction mixture was stirred for a further 15 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (20% ethyl acetate–hexane), to afford the *phenol* **16** as a dark red-brown oil (9.91 g, 64%) (Found: M^+, 180.0774. $C_{10}H_{12}O_3$ requires *M*, 180.0786); ν_{max}(film)/cm^{-1} 3417br (OH), 3086m (=CH_2), 2844m (OCH_3), 1601s and 1510m (ArC=C), 1211s and 1016m (C–O–C) and 994s (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.74 (1H, d, *J* 8.6, 5-H), 6.46 (1H, d, *J* 2.8, 2-H), 6.33 (1H, dd, *J* 8.6 and 2.8, 6-H), 6.17–5.95 (2H, m, 2′-H and OH), 5.40–5.19 (2H, m, 3′-H_2), 4.51 (2H, br dt, *J* 5.6 and 1.4, 1′-H_2) and 3.76 (3H, s, OCH_3); δ_C (50.32 MHz; $CDCl_3$) 150.9, 150.4 and 141.5 (3 × ArC–O), 133.6 (2′-C), 117.8 (3′-C), 115.6 (5-C), 106.0 (2-C), 100.8 (6-C), 71.1 (1′-C) and 55.6 (OCH_3); *m*/*z* (EI) 180 (M^+, 34%), 139 (100), 111 (26), 93 (12), 69 (6), 65 (8) and 41 (11).

1-Allyloxy-2,4-dimethoxybenzene 13

Dimethyl sulfate (11.8 cm^3, 0.13 mol) and potassium carbonate (20.0 g, 0.14 mol) were added to a solution of 4-allyloxy-3-methoxyphenol **16** (5.45 g, 0.03 mol) in distilled acetone (250 cm^3). The reaction mixture was heated at reflux under a nitrogen atmosphere for 18 h. The acetone was removed *in vacuo* after which water (100 cm^3) and diethyl ether (100 cm^3) were added. The organic phase was separated, and washed successively with aq. ammonia (10% v/v; 3 × 100 cm^3), water (100 cm^3), hydrochloric acid (10% v/v; 100 cm^3) and water (100 cm^3). The organic solvent was dried ($MgSO_4$), and removed *in vacuo* to yield the crude material, which was purified by column chromatography (5% ethyl acetate–hexane) to give the *triether* **13** (5.39 g, 92%) as a clear oil (Found: M^+, 194.0934. $C_{11}H_{14}O_3$ requires *M*, 194.0943); ν_{max}(film)/cm^{-1} 2820m (OCH_3), 1610m and 1583m (ArC=C), 1503m (C=C), 1210vs and 1043s (C–O–C) and 983s and 917m (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.81 (1H, d, *J* 8.7, 6-H), 6.51 (1H, d, *J* 2.9, 3-H), 6.36 (1H, dd, *J* 8.7 and 2.9, 5-H), 6.18–5.95 (1H, m, 2′-H), 5.37 (1H, dd, *J* 17.3 and 1.5, 3′-H), 5.25 (1H, dd, *J* 10.5 and 1.5, 3′-H), 4.53 (2H, br dt, *J* 5.5 and 1.5, 1′-H_2) and 3.84 and 3.75 (each 3H, s, OCH_3); δ_C (50.32 MHz; $CDCl_3$; Me_4Si) 154.6, 150.5 and 142.1 (3 × ArC–O), 133.7 (2′-C), 117.5 (3′-C), 114.8 (6-C), 102.9 (3-C), 100.3 (5-C), 70.7 (1′-C) and 55.7 and 55.4 (2 × OCH_3); *m*/*z* (EI) 194 (M^+, 32%), 153 (100), 125 (40) and 91 (28).

2,4-Dimethoxyphenol 17

Magnesium monoperoxyphthalic acid hexahydrate (26.8 g, 0.054 mol) was added portionwise to a solution of 2,4-dimethoxybenzaldehyde (6.00 g, 0.036 mol) in methanol (250 cm^3), under a nitrogen atmosphere at 0 °C. The reaction mixture was warmed to room temperature and stirred under nitrogen for 48 h, during which time the mixture went a bright pink colour. The reaction mixture was then filtered to remove the precipitate. The precipitate was washed with an excess of ethyl acetate and then the organic filtrates were combined and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (10–20% ethyl acetate–hexane) to afford the *phenol* **17** (4.90 g, 88%) as a yellow oil (bp 129 °C, 10 mmHg; lit.,[13] 129 °C, 10 mmHg); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.82 (1H, d, *J* 8.6, 6-H), 6.49 (1H, d, *J* 2.8, 3-H), 6.38 (1H, d, *J* 8.6 and 2.8, 5-H), 5.53 (1H, br s, OH) and 3.84 and 3.75 (each

3H, s, OCH_3); δ_C (50.32 MHz; $CDCl_3$) 153.5, 147.0 and 139.7 (3 × ArC–O), 114.1 (6-C), 104.2 (3-C), 99.4 (5-C) and 55.8 and 55.7 (2 × OCH_3).

1-Allyloxy-2,4-dimethoxybenzene 13 (alternative preparation)

Allyl bromide (18.6 cm^3, 26.0 g, 0.21 mol) and potassium carbonate (29.7 g, 0.21 mol) were added to a solution of 2,4-dimethoxyphenol **17** (13.3 g, 0.086 mol) in dry acetone (200 cm^3). The reaction mixture was heated at reflux under nitrogen for 18 h. The potassium carbonate was removed by filtration and the solvent was removed *in vacuo*. Purification by column chromatography (10–20% ethyl acetate–hexane) afforded the *product* **13** as a clear yellow oil (16.01 g, 96%). Spectral data of this compound were identical to those obtained from 4-allyloxy-3-methoxyphenol **16**.

5-Allyloxy-2,4-dimethoxyacetophenone 19

Trifluoroacetic anhydride (TFAA) (3.3 cm^3, 4.9 g, 0.023 mol) and glacial acetic acid (1.3 cm^3, 1.4 g, 0.023 mol) were pre-mixed in a glass vial and the mixture added to a solution of 1-allyloxy-2,4-dimethoxybenzene **13** (3.49 g, 0.018 mol) in dry dichloromethane (100 cm^3). The reaction mixture was then stirred under nitrogen for 60 h. Water (50 cm^3) was added and solid sodium hydrogen carbonate was added portionwise until effervescence had decreased. The reaction mixture was then stirred for 1 h before being extracted with dichloromethane (3 × 30 cm^3), and the organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (20% ethyl acetate–hexane) yielded the *ketone* **19** as a white crystalline material (2.80 g, 66%), mp 82.5–83.5 °C (from hexane–ethyl acetate) and starting material (0.59 g, 17% recovery) (Found: M^+, 236.1036. C, 66.02; H, 6.76. $C_{13}H_{16}O_4$ requires *M*, 236.1049. C, 66.07; H, 6.83%); ν_{max}(KBr pellet)/cm^{-1} 2835w (OCH_3), 1760s (C=O), 1667s and 1613s (ArC=C), 1507 (C=C), 1287s and 1027s (C–O–C) and 975m (=CH); δ_H (200 MHz; $CDCl_3$) 7.45 (1H, s, 6-H), 6.50 (1H, s, 3-H), 6.16–5.96 (1H, m, 2′-H), 5.41 (1H, dd, *J* 17.3 and 1.5, 3′-H), 5.28 (1H, dd, *J* 10.4 and 1.5, 3′-H), 4.58 (2H, br dt, *J* 5.5 and 1.5, 1′-H), 3.94 and 3.91 (each 3H, s, OCH_3) and 2.58 (3H, s, $COCH_3$); δ_C (50.32 MHz; $CDCl_3$) 197.0 (CO), 155.7, 154.4 and 141.8 (3 × ArC–O), 133.1 (2′-C), 119.0 (1-C), 118.1 (3′-C), 114.9 (6-C), 96.4 (3-C), 70.2 (1′-C), 56.0 and 56.0 (2 × OCH_3) and 32.0 ($CO\mathit{C}H_3$); *m*/*z* (EI) 236 (M^+, 41%), 195 (100), 43 (58) and 41 (18).

2-Allyl-3-benzyloxy-4,6-dimethoxyacetophenone 21

5-Allyloxy-2,4-dimethoxyacetophenone **19** (3.29 g, 0.014 mol) was heated at 160 °C for 23 h under a nitrogen atmosphere. An NMR spectrum of the crude product confirmed that conversion to the phenol had occurred. The reaction mixture was cooled to room temperature and acetone (200 cm^3), potassium carbonate (9.6 g, 0.070 mol) and benzyl bromide (8.3 cm^3, 0.070 mol) were added. The reaction mixture was then heated under nitrogen at reflux for 18 h. After cooling, filtration of the inorganic solids and evaporation of the solvent under vacuum, the residue was purified by column chromatography (5–10% ethyl acetate–hexane) to afford the *ketone* **21** as a clear, colourless oil (3.71 g, 82%) (Found: M^+, 326.1512. $C_{20}H_{22}O_4$ requires *M*, 326.1518); ν_{max}(film)/cm^{-1} 3004m (=CH), 2840m (OCH_3), 1691s (C=O), 1594 (ArC=C), 1250s (C–O–C), 1003m and 913m (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.48–7.32 (5H, m, Ph), 6.43 (1H, s, 5-H), 5.95–5.75 (1H, m, 2′-H), 4.98–4.87 (2H, m, 3′-H_2), 4.90 (2H, s, OCH_2), 3.89 and 3.81 (each 3H, s, OCH_3), 3.42 (2H, br dt, *J* 6.2 and 1.6, 1′-H_2) and 2.45 (3H, s, $COCH_3$); δ_C (50.32 MHz; $CDCl_3$) 204.6 (CO), 154.0, 153.3, 140.0 (3 × ArC–O), 137.7 (ArC–C), 136.9 (2′-C), 131.8 (ArC–C), 128.3, 127.9, 127.8 (3 × PhC), 124.0 (ArC–C), 115.5 (3′-C), 95.1 (5-C), 74.9 (OCH_2), 55.9 and 55.8 (2 × OCH_3), 32.6 ($COCH_3$) and 30.5 (1′-C); *m*/*z* (EI) 326 (M^+, 14%), 235 (100), 217 (37), 91 (57) and 43 (83).

1-(2-Allyl-3-benzyloxy-4,6-dimethoxyphenyl)ethanol 23

Lithium aluminium hydride (0.53 g, 0.014 mol) was added to a solution of ketone **21** (2.27 g, 6.96 mmol) in dry diethyl ether (40 cm^3) and the reaction mixture was stirred under argon for 18 h. Methanol (10 cm^3) was added carefully, followed by water (40 cm^3), and the aqueous phase was extracted with ethyl acetate (3 × 20 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*, after which the residue was purified by column chromatography (10% ethyl acetate–hexane), to yield the *alcohol* **23** as a clear oil (2.14 g, 94%) (Found: M^+, 328.1666. $C_{20}H_{24}O_4$ requires *M*, 328.1675); ν_{max}(film)/cm^{-1} 3600br (OH), 1600s (ArC=C) and 1000s (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.48–7.29 (5H, m, Ph), 6.49 (1H, s, 5-H), 6.00–5.82 (1H, m, 2′-H), 5.02 (1H, dd, *J* 10.2 and 1.6, 3′-H), 4.94 (1H, dd, *J* 17.2 and 1.6, 3′-H), 4.87 and 4.91 (each 1H, d, *J* 10.9, OCH_2), 3.88 and 3.87 (each 3H, s, OCH_3), 3.88–3.81 (1H, br m, $CHCH_3$), 3.50–3.43 (2H, m, 1′-H_2) and 1.51 (3H, d, *J* 6.6, CH_3); δ_C (50.32 MHz; $CDCl_3$) 154.1, 151.9 and 140.1 (3 × ArC–O), 137.9 (ArC–C), 136.8 (2′-C), 131.3 (ArC–C), 128.3, 127.9 and 127.7 (3 × PhC), 124.0 (ArC–C), 115.4 (3′-C), 96.2 (5-C), 74.9 (OCH_2), 67.0 (CHOH), 55.9 and 55.5 (2 × OCH_3), 30.3 (1′-C) and 23.7 (CH_3); *m*/*z* (EI) 328 (M^+, 19%) 237 (66), 219 (100) and 91 (45).

5-Benzyloxy-6,8-dimethoxy-*trans*-1,3-dimethylisochromane 25

Sublimed potassium *tert*-butoxide (1.50 g, 13.4 mmol) was added to a solution of the alcohol **23** (1.10 g, 3.35 mmol) in dry DMF (50 cm^3). The reaction mixture was stirred under argon at 75 °C for 90 min. Water (20 cm^3) and diethyl ether (20 cm^3) were added and the mixture was extracted sequentially with diethyl ether (3 × 50 cm^3), dichloromethane (3 × 40 cm^3) and ethyl acetate (20 cm^3). The organic solvents were combined, dried ($MgSO_4$) and evaporated under vacuum. Subsequent purification by column chromatography (5% ethyl acetate–hexane) afforded the *isochromane* **25** (1.03 g, 94%) as a clear oil (Found: M^+, 328.1681. $C_{20}H_{24}O_4$ requires *M*, 328.1675); ν_{max}(film)/cm^{-1} 2842m (OCH_3), 1604s and 1568m (ArC=C), 1230m, 1088s and 808m (C–O–C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.48–7.30 (5H, m, Ph), 6.39 (1H, s, 7-H), 5.04 (1H, q, *J* 6.5, 1-H), 4.91 (2H, s, OCH_2), 3.99–3.91 (1H, m, 3-H), 3.87 and 3.80 (each 3H, s, OCH_3), 2.78 (1H, dd, *J* 17.0 and 3.3, 4-H *pseudo*-equatorial), 2.28 (1H, dd, *J* 17.0 and 10.8, 4-H *pseudo*-axial), 1.47 (3H, d, *J* 6.5, 1-CH_3) and 1.27 (3H, d, *J* 6.1, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$) 151.7, 151.1 and 138.7 (3 × ArC–O), 138.0 and 128.7 (2 × ArC–C), 128.3, 128.1 and 127.8 (3 × PhC), 120.3 (ArC–C), 94.8 (7-C), 74.3 (OCH_2), 68.0 (1-C), 62.4 (3-C), 56.1 and 55.4 (2 × OCH_3), 30.8 (4-C), 21.9 (1-CH_3) and 19.7 (3-CH_3); *m*/*z* (EI) 328 (M^+, 18%), 237 (100), 193 (88), 165 (17) and 91 (13).

2,4-Diisopropoxyphenol 18

DMF (13.1 cm^3, 12.4 g, 0.17 mol) and anhydrous phosphoryl trichloride (7.9 cm^3, 13.0 g, 0.085 mol) were added to a solution of 1,3-diisopropoxybenzene[14] (16.4 g, 84.6 mmol) in toluene (15 cm^3). The reaction mixture was stirred at 0 °C for 30 min and the bright yellow mixture was then heated at 120 °C for 2 h under nitrogen. During this time the colour of the reaction changed from yellow to deep red. The reaction mixture was poured into aq. sodium hydroxide (250 cm^3 of 10% NaOH and 100 cm^3 of ice) with stirring and the mixture was subsequently extracted with dichloromethane (3 × 100 cm^3). The organic phase was washed with water (2 × 100 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The resultant black residue was purified by silica gel column chromatography (10% ethyl acetate–hexane) to afford *2,4-diisopropoxybenzaldehyde* as an orange oil (18.1 g, 96%) (Found: M^+, 222.1256. $C_{13}H_{18}O_3$ requires *M*, 222.1253);

ν_{max}(film)/cm^{-1} 1682s (C=O), 1602s and 1573m (ArC=C), 1386m and 1375m [CH_3, $CH(CH_3)_2$] and 1261s (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 10.31 (1H, s, CHO), 7.78 (1H, d, *J* 8.7, 6-H), 6.47 (1H, dd, *J* 8.7 and 2.2, 5-H), 6.43 (1H, d, *J* 2.2, 3-H), 4.66–4.59 [2H, m, 2 × C*H*$(CH_3)_2$], 1.39 [6H, d, *J* 6.0, $CH(CH_3)_2$] and 1.36 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (100.63 MHz; $CDCl_3$) 188.2 (CHO), 164.4 and 162.2 (2 × ArC–O), 129.9 (6-C), 119.3 (1-C), 106.9 (5-C), 101.0 (3-C), 70.8 and 70.1 [2 × *C*H$(CH_3)_2$] and 21.7 [2 × CH(*C*$H_3)_2$]; *m*/*z* (EI) 222 (M^+, 29%), 180 (12), 138 (100), 109 (4) and 43 (14).

2,4-Diisopropoxybenzaldehyde (16.9 g, 75.8 mmol) was dissolved in distilled methanol (100 cm^3) and the solution was cooled in an ice-bath. Magnesium monoperoxyphthalic acid hexahydrate (MMPP) (56.3 g, 0.11 mol) was added gradually to the stirred solution over a period of 20 min. The solution was left to stir for 60 h at room temperature under nitrogen. The solution, which changed from pale yellow to pink, was filtered and then solvent was removed *in vacuo*. The resultant red oil was purified by column chromatography (10% ethyl acetate–hexane). The *phenol* **18** was isolated as a yellow oil (10.07 g, 63%) (Found: M^+, 210.1242. $C_{12}H_{18}O_3$ requires *M*, 210.1256); ν_{max} (film)/cm^{-1} 4000br (OH), 1594s, (ArC=C), 1385m and 1373m [C–CH_3, $CH(CH_3)_2$], 1284s (C–O–C) and 1001s and 987s (C–O, C–OH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.80 (1H, d, *J* 8.7, 6-H), 6.49 (1H, d, *J* 2.7, 3-H), 6.37 (1H, dd, *J* 8.7 and 2.7, 5-H), 5.70 (1H, br s, OH), 4.46 and 4.36 [each 1H, sept, *J* 6.1, 2 × C*H*$(CH_3)_2$] and 1.27 and 1.26 [each 6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 151.0, 144.8 and 140.7 (3 × ArC–O), 114.1 (6-C), 107.7 (3-C), 104.0 (5-C), 71.1 and 70.5 [2 × *C*H$(CH_3)_2$] and 21.7 and 21.6 [2 × CH(*C*$H_3)_2$]; *m*/*z* (EI) 210 (M^+, 77%), 168 (27) and 126 (100).

1-Allyloxy-2,4-diisopropoxybenzene 14

2,4-Diisopropoxyphenol **18** (10.0 g, 47.8 mmol) was dissolved in acetone (400 cm^3). Anhydrous potassium carbonate (16.5 g, 0.12 mmol) and allyl bromide (10.3 cm^3, 14.4 g, 0.12 mol) were added and the stirred solution was heated at reflux under a nitrogen atmosphere for 24 h. Excess of anhydrous potassium carbonate (16.5 g, 0.12 mol) and allyl bromide (10.3 cm^3, 14.4 g, 0.12 mol) were added and the solution was heated at reflux under a nitrogen atmosphere for a further 24 h. The solution was then filtered and the solvent removed *in vacuo*. The resultant yellow oil was purified by column chromatography (5% ethyl acetate–hexane). The *triether* **14** was isolated as a yellow oil (11.17 g, 94%) (Found: M^+, 250.1556. $C_{15}H_{22}O_3$ requires *M*, 250.1569); ν_{max}(film)/cm^{-1} 1612m and 1584m (ArC=C), 1382m and 1372m (–CH_3), 1241s (C–O–C), 1167m (–CH_3) and 1000s and 929m (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.81 (1H, d, *J* 8.8, 6-H), 6.52 (1H, d, *J* 2.9, 3-H), 6.40 (1H, dd, *J* 8.8 and 2.9, 5-H), 6.04 (1H, ddt, *J* 17.2, 10.5 and 5.2, 2′-H), 5.37 (1H, dd, *J* 17.2 and 1.6, 3′-H), 5.22 (1H, dd, *J* 10.5 and 1.6, 3′-H), 4.52–4.38 [4H, m, 1′-H_2 and 2 × C*H*$(CH_3)_2$], 1.34 [6H, d, *J* 6.1, $CH(CH_3)_2$] and 1.29 [6H, d, *J* 6.0, $CH(CH_3)_2$]; δ_C (100.63 MHz; $CDCl_3$) 152.8, 149.0 and 143.7 (3 × ArC–O), 134.1 (2′-C), 116.8 (3′-C[a]), 116.7 (6-C[a]), 107.4 (3-C[b]), 106.8 (5-C[b]), 71.6 and 71.1 [2 × *C*H$(CH_3)_2$], 70.4 (1′-C) and 22.1 and 22.0 [2 × CH(*C*$H_3)_2$]; *m*/*z* (EI) 250 (M^+, 11%), 209 (3), 194 (11), 179 (2), 167 (14), 125 (100) and 110 (70).

5-Allyloxy-2,4-diisopropoxyacetophenone 20

Acetic trifluoroacetic anhydride was pre-formed by adding glacial acetic acid (0.33 cm^3, 0.35 g, 5.8 mmol) to stirred TFAA (0.81 cm^3, 1.0 g, 4.8 mmol) and the mixture was then added to a solution of 1-allyloxy-2,4-diisopropoxybenzene **14** (1.2 g, 4.8 mmol) in dichloromethane (20 cm^3) under argon. The solution was stirred for 72 h and gradually darkened to a purple-blue colour. Water (20 cm^3) and dichloromethane (50 cm^3) were added to the solution, and the excess acid was neutralised by careful addition of solid sodium hydrogen carbonate during 2 h until no further effervescence was observed. The mixture was extracted with dichloromethane (6 × 50 cm^3) and this extract was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resultant residue was purified by column chromatography (5–10% ethyl acetate–hexane) to afford the *ketone* **20** as a dark oil (1.30 g, 94%) (Found: M^+, 292.1971. $C_{17}H_{24}O_4$ requires *M*, 292.1675); ν_{max}(film)/cm^{-1} 1762s (C=O), 1655 (ArC=C), 1409m (CH_3, CH_3CO), 1384m and 1373m (–CH_3), 1021m (C–O–C) and 999m and 916m (=CH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.44 (1H, s, 6-H), 6.50 (1H, s, 3-H), 6.13–5.96 (1H, m, 2′-H), 5.46–5.20 (2H, m, 3′-H_2), 4.65–4.53 [4H, m, 2 × C*H*$(CH_3)_2$ and 1′-H_2], 2.60 (3H, s, $COCH_3$) and 1.39 [12H, d, *J* 6.1, 4 × $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 197.5 (C=O), 153.6, 152.8 and 143.0 (3 × ArC–O), 133.4 (2′-C), 120.9 (1-C), 117.1 (3′-C), 116.2 (6-C), 102.6 (3-C), 71.8 and 71.2 [2 × *C*H$(CH_3)_2$], 70.4 (1′-C), 32.2 ($COCH_3$) and 22.0 and 21.9 [2 × CH(*C*$H_3)_2$]; *m*/*z* (EI) 292 (M^+, 17%), 277 (4), 250 (3), 235 (2), 209 (7), 167 (100), 149 (77) and 41 (60).

2-Allyl-3-benzyloxy-4,6-diisopropoxyacetophenone 22

Ketone **20** (1.00 g, 3.42 mmol) was heated in an oil-bath at 160 °C for 24 h under an argon atmosphere until NMR spectroscopy showed that the Claisen rearrangement was complete. Acetone (50 cm^3), benzyl bromide (2.9 g, 17.0 mmol) and anhydrous potassium carbonate (2.4 g, 17.0 mmol) were added and the reaction mixture was heated at reflux, under an argon atmosphere, for 17 h. After cooling, the solution was filtered and the solvent was removed *in vacuo*. The resulting brown oil was purified by column chromatography (hexane, and then 5% ethyl acetate–hexane) to afford the *ketone* **22** as a clear yellow oil (1.03 g, 79%) (Found: M^+, 382.2139. $C_{24}H_{30}O_4$ requires *M*, 382.2144); ν_{max}(film)/cm^{-1} 1692s (C=O), 1591vs (ArC=C), 1421m (–CH_3, CH_3CO), 1373m (–CH_3), 1218s (C–O–C), 1172m and 1160m (–CH_3) and 999m and 912m (=CH); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.47–7.30 (5H, m, Ph), 6.42 (1H, s, 5-H), 5.90–5.80 (1H, m, 2′-H), 4.96–4.90 (2H, m, 3′-H_2), 4.91 (2H, s, OCH_2), 4.58 [1H, sept, *J* 6.1, C*H*$(CH_3)_2$], 4.46 [1H, sept, *J* 6.1, C*H*$(CH_3)_2$], 3.42 (2H, br dt, *J* 6.2 and 1.5, 1′-H), 2.46 (3H, s, $COCH_3$), 1.37 [6H, d, *J* 6.1, $CH(CH_3)_2$] and 1.31 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (100.63 MHz; $CDCl_3$) 204.9 (CO), 151.9, 151.2 and 141.4 (3 × ArC–O), 137.9 (ArC–C), 137.0 (2′-C), 131.9 (ArC–C), 128.2, 127.9 and 127.7 (3 × PhC), 125.8 (ArC–C), 115.3 (3′-C), 100.9 (5-C), 74.7 (CH_2), 71.3 and 71.1 [2 × *C*H$(CH_3)_2$], 32.6 ($COCH_3$), 30.6 (1′-C) and 22.0 and 22.0 [2 × CH(*C*$H_3)_2$]; *m*/*z* (EI) 382 (M^+, 52%), 291 (28), 249 (15), 207 (100), 165 (7), 91 (59) and 41 (13).

1-(2-Allyl-3-benzyloxy-4,6-diisopropoxyphenyl)ethanol 24

Lithium aluminium hydride (0.20 g, 5.2 mmol) was added over a period of 10 min to a solution of ketone **22** (1.00 g, 2.61 mmol) in diethyl ether (100 cm^3). The reaction mixture was then stirred under an argon atmosphere for 2 h. Methanol (10 cm^3) was added carefully, followed by water (20 cm^3). The mixture was then extracted with diethyl ether (3 × 50 cm^3), which was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resultant yellow oil was purified by column chromatography (10% ethyl acetate–hexane) to afford the *alcohol* **24** as a clear yellow oil (0.93 g, 93%) (Found: M^+, 384.2303. $C_{24}H_{32}O_4$ requires *M*, 384.2301); ν_{max}(film)/cm^{-1} 3547br (OH), 2867m (OCH_2), 1594s, (ArC=C), 1385s and 1371s [–CH_3, $CH(CH_3)_2$], 1271s (C–O–C, ArC–O–C) and 993s and 909m (=CH); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.48–7.30 (5H, m, Ph), 6.48 (1H, s, 5-H), 6.00–5.88 (1H, m, 2′-H), 5.04–4.88 (4H, m, 3′-H_2 and OCH_2Ph), 4.61 [1H, sept, *J* 6.1, C*H*$(CH_3)_2$], 4.53 [1H, sept, *J* 6.1, C*H*$(CH_3)_2$], 4.02 (1H, br s, OH), 3.73 (1H, q, *J* 6.4, C*H*CH_3), 3.51–3.30 (2H, m, 1′-H_2), 1.53 (3H, d, *J* 6.6, CHCH_3) and 1.42–1.32 [12H, m, 2 × $CH(CH_3)_2$]; δ_C (100.63 MHz; $CDCl_3$) 151.6, 149.6 and 141.3 (3 × ArC–O), 138.0 (ArC–C), 136.9 (2′-C), 131.6 (ArC–C), 128.2, 127.9 and 127.7 (3 × PhC),

125.1 (ArC–C), 115.4 (3′-C), 101.3 (5-C), 74.8 (OCH_2), 71.5 and 71.0 [2 × $CH(CH_3)_2$], 67.2 (CHOH), 30.5 (1′-C), 23.7 ($CHCH_3$) and 22.3, 22.2, 22.1 and 21.9 [2 × $CH(CH_3)_2$]; *m/z* (EI) 384 (M^+, 14%), 293 (58), 251 (13), 209 (36), 191 (100), 163 (15), 91 (58) and 43 (14).

5-Benzyloxy-6,8-diisopropoxy-*trans*-1,3-dimethylisochromane 26

Sublimed potassium *tert*-butoxide (1.52 g, 13.5 mmol) was added to a solution of the alcohol **24** (1.30 g, 3.38 mmol) in DMF (20 cm^3). The reaction mixture was stirred under argon at 75 °C for 10 min. Water (50 cm^3) and ice (10 cm^3) were added and the mixture was extracted with diethyl ether (3 × 50 cm^3). The organic phases were combined, dried ($MgSO_4$), and evaporated under vacuum. Subsequent column chromatography (5% ethyl acetate–hexane) afforded the *isochromane* **26** (1.11 g, 85%) as a clear oil (Found: M^+, 384.2307. $C_{24}H_{32}O_4$ requires *M*, 384.2301); ν_{max}(film)/cm^{-1} 1600m (ArC=C), 1373m and 1360m [–CH_3, $CH(CH_3)_2$], 1217m (C–O–C) and 1122s, 1066m and 813m (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.47–7.30 (5H, m, Ph), 6.37 (1H, s, 7-H), 5.01 (1H, q, *J* 6.6, 1-H), 4.93 (2H, s, OCH_2), 4.55–4.44 [2H, m, 2 × $CH(CH_3)_2$], 3.98–3.93 (1H, m, 3-H), 2.76 (1H, dd, *J* 17.0 and 3.3, 4-H *pseudo*-equatorial), 2.30 (1H, dd, *J* 17.0 and 10.8, 4-H *pseudo*-axial), 1.48 (3H, d, *J* 6.6, 1-CH_3), 1.35 (3H, d, *J* 6.0, 3-CH_3), 1.34 [6H, d, *J* 6.1, $CH(CH_3)_2$], 1.29 [3H, d, *J* 6.9, $CH(CH_3)CH_3$] and 1.27 [3H, d, *J* 7.1, $CH(CH_3)CH_3$]; δ_C (100.63 MHz; $CDCl_3$) 149.6, 148.9 and 140.3 (3 × ArC–O), 138.2 and 128.8 (2 × ArC–C), 128.3, 128.1 and 127.8 (3 × PhC), 122.1 (ArC–C), 101.1 (7-C), 74.2 (OCH_2), 71.8 and 69.9 [2 × $CH(CH_3)_2$], 68.3 (1-C), 62.4 (3-C), 31.0 (4-C), 22.4, 22.3, 22.2 and 22.1 (2 × $CH(CH_3)_2$[a]), 21.9 (1-CH_3[a]) and 19.8 (3-CH_3); *m/z* (EI) 384 (M^+, 18%), 293 (54), 251 (37), 209 (100), 167 (57), 91 (56) and 43 (32).

Methyl 4-acetoxy-8-bromo-5-isopropoxy-2-naphthoate 28

A solution of 2-bromo-5-isopropoxybenzaldehyde[18] (2.97 g, 0.12 mmol) and dimethyl succinate (2.14 g, 0.15 mmol) in dry *tert*-butyl alcohol (10 cm^3) was added to a boiling solution of freshly sublimed potassium *tert*-butoxide (1.51 g, 13.4 mmol) in dry *tert*-butyl alcohol (40 cm^3) over a period of 15 min. The reaction mixture was heated under reflux for a further 45 min, then allowed to cool, diluted with water (50 cm^3) and acidified with conc. hydrochloric acid. The organic material was extracted into toluene (3 × 100 cm^3) and the solvent removed by evaporation under reduced pressure. Diethyl ether (100 cm^3) and saturated aq. sodium hydrogen carbonate (20 cm^3) were added to the resultant oil. The organic phase was separated and the aqueous phase washed a further two times with diethyl ether (2 × 100 cm^3). The aqueous phase was then made acidic with conc. hydrochloric acid and the resulting mixture extracted with diethyl ether (3 × 100 cm^3), which was then dried ($MgSO_4$), and removed under vacuum. The residue was purified by column chromatography (20% ethyl acetate–hexane) to afford the intermediate acid **27** as a mixture of geometrical isomers (60:40). The *product* **27** was a pale yellow oil which hardened into an opaque yellow semi-solid (2.88 g, 66%) (Found: M^+, 356.0268. $C_{17}H_{17}BrO_5$ requires *M*, 356.0259); ν_{max}(film)/cm^{-1} 3200–3100br (COO–H), 1701m (CO_2Me), 1659s (CO_2H), 1601 (ArC=C), 1368m [CH_3, $CH(CH_3)_2$], 1241s (C–O) and 706m (C–Br); δ_H [200 MHz; $CO(CD_3)_2$] (assignments in brackets are for the minor geometrical isomer) 7.80 (7.72) (1H, s, C*H*=C) 7.55 (7.29) (1H, d, *J* 8.8, 3-H), 7.04 (6.83) (1H, d, *J* 3.0, 6-H), 6.90 (6.75) (1H, dd, *J* 8.8 and 3.0, 4-H), 4.58 (4.47) [1H, sept, *J* 6.0, $CH(CH_3)_2$], 3.82 (3H, s, CO_2CH_3), (3.63) 3.44 (2H, s and d, *J* 0.6, CH_2) and 1.29 [6H, d, *J* 6.0, $CH(CH_3)_2$]; δ_C [50.32 MHz; $CO(CD_3)_2$] 172.3, 168.0 (168.0) (2 × C=O), 158.3 (157.9) (ArC–O), (141.5) 141.1 (3-C), 136.9 (1-C[a]), 134.4 (133.9) (6-C), 129.1 (HC=*C*[a]), (119.6) 119.4 (4-C[b]), 117.7 (117.3) (H*C*=C[b]), 71.0 (70.9) [*C*H(CH$_3$)$_2$], 52.6 (CO_2CH_3), 34.0 (CH_2) and 22.1 [$CH(CH_3)_2$]; *m/z* (EI) 358, 356 (M^+, 9%), 277 (20), 235 (100), 191 (18) and 43 (16).

The intermediate acid **27** (0.670 g, 1.88 mmol) and anhydrous sodium acetate (0.027 g, 3.29 mmol) were dissolved in acetic anhydride (15 cm^3) and were heated at reflux for 6 h. The reaction mixture was allowed to cool and diluted with water (20 cm^3) and diethyl ether (20 cm^3). Saturated aq. sodium hydrogen carbonate was then added with stirring until effervescence had ceased. The aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were then dried ($MgSO_4$), and removed *in vacuo*. The *naphthoate* **28** (0.53 g, 74%) was obtained as a yellow crystalline material, mp 108–109 °C (from hexane–ethyl acetate), after purification by column chromatography (5% ethyl acetate–hexane) (Found: M^+, 380.0255. $C_{19}H_{17}BrO_5$ requires *M*, 380.0259); ν_{max}(film)/cm^{-1} 1716s (C=O), 1600m (ArC=C), 1267s (C–O–C), 1213s (C–O) and 693m (C–Br); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.86 (1H, d, *J* 1.7, 1-H), 7.71 (1H, d, *J* 8.6, 7-H), 7.68 (1H, d, *J* 1.7, 3-H), 6.83 (1H, dd, *J* 8.6 and 0.4, 6-H), 4.68 [1H, sept, *J* 6.0, $CH(CH_3)_2$], 3.98 (3H, s, CO_2CH_3), 2.38 (3H, s, $COCH_3$) and 1.40 [6H, d, *J* 6.0, $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 169.5 (OAc[a]), 165.9 (CO_2Me[a]), 153.4 (5-C[b]), 147.2 (4-C[b]), 134.1 (8a-C), 131.1 (7-C[c]), 128.7 (2-C), 128.4 (1-C[c]), 123.5 (4a-C), 119.7 (3-C), 114.3 (8-C), 110.6 (6-C), 70.8 [*C*H(CH$_3$)$_2$], 52.4 (CO_2CH_3), 21.7 [$CH(CH_3)_2$] and 21.3 ($COCH_3$); *m/z* (EI) 382, 380 (M^+, 60%), 340, 338 (38), 298, 296 (100), 267, 265 (38), 240, 238 (56), 217 (31) and 158 (35).

Methyl 8-bromo-5-isopropoxy-4-methoxy-2-naphthoate 30

Potassium hydroxide (0.28 g, 5.0 mmol) in methanol (10 cm^3) was added to a solution of ester **28** (1.59 g, 4.17 mmol) in methanol (100 cm^3) and the reaction mixture was stirred for 1 h under argon. The methanol was removed *in vacuo* and the organic material dissolved in toluene (50 cm^3). The organic phase was washed with water (3 × 100 cm^3) and then with hydrochloric acid (1 M; 100 cm^3). The organic phase was then evaporated *in vacuo* to afford the *intermediate naphthol* **29** (1.34 g, 95%) as a yellow solid, mp 103–109 °C, which was not purified further (Found: M^+, 338.0151. $C_{15}H_{15}BrO_4$ requires *M*, 338.0153); ν_{max}(film)/cm^{-1} 3360br (OH), 1720s (C=O), 1600m and 1567 (ArC=C), 1280s (C–O–C), 1227s (C–O, ArC–OH) and 1100s (C–O); δ_H (200 MHz; $CDCl_3$; Me_4Si) 9.86 (1H, s, OH), 8.37 (1H, d, *J* 1.6, 1-H), 7.61 (1H, d, *J* 8.4, 7-H), 7.45 (1H, d, *J* 1.6, 3-H), 6.71 (1H, d, *J* 8.4, 6-H), 4.81 [1H, sept, *J* 6.1, $CH(CH_3)_2$], 3.97 (3H, s, CO_2CH_3) and 1.50 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 166.7 (CO_2CH_3), 155.5 (4-C[a]), 153.8 (5-C[a]), 134.0 (8a-C), 130.3 (7- and 2-C[b]), 120.8 (1-C[b]), 118.9 (4a-C), 115.9 (8-C), 110.7 (3-C[c]), 108.8 (6-C[c]), 73.5 [*C*H(CH$_3$)$_2$], 52.3 (CO_2CH_3) and 21.9 [$CH(CH_3)_2$]; *m/z* (EI) 340, 338 (M^+, 65%), 298, 296 (100) and 217 (14).

Dimethyl sulfate (1.0 cm^3, 1.3 g, 0.11 mol) and potassium carbonate (1.5 g, 0.11 mol) were added sequentially to a solution of the foregoing naphthol **29** (0.77 g, 2.3 mmol) in acetone (100 cm^3). The reaction mixture was heated at reflux under an argon atmosphere for 18 h. The acetone was removed *in vacuo* after which water (100 cm^3) and diethyl ether (100 cm^3) were added. The organic phase was washed successively with aq. ammonia (10%; 3 × 100 cm^3), water (100 cm^3), hydrochloric acid (10% v/v; 100 cm^3) and water (100 cm^3). The organic solvent was dried ($MgSO_4$), and evaporated *in vacuo* to yield a crude material, which was purified by column chromatography (5% ethyl acetate–hexane) to give the *ether* **30** (0.79 g, 99%) as thin white crystals, mp 102–103 °C (from CH_2Cl_2–hexane) (Found: M^+, 352.0300. $C_{16}H_{17}BrO_4$ requires *M*, 352.0310); ν_{max}(film)/cm^{-1} 1728vs (OCO), 1589m (ArC=C), 1368s [CH_3, $CH(CH_3)_2$], 1282vs and 1256s (C–O) and 1163m [CH_3, $CH(CH_3)_2$]; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.56 (1H, d, *J* 1.4, 1-H), 7.70 (1H, d, *J* 8.4, 7-H), 7.45 (1H, d, *J* 1.4, 3-H), 6.87 (1H, d, *J* 8.4, 6-H), 4.53 [1H, sept, *J* 6.0, $CH(CH_3)_2$], 4.00 and 3.99

(each 3H, s, CO_2CH_3 and OCH_3) and 1.40 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 166.9 (CO_2CH_3), 157.7 (5-C[a]), 155.0 (4-C[a]), 134.4 (8a-C), 131.1 (7-C[b]), 128.8 (2-C), 122.8 (1-C[b]), 122.6 (4a-C), 115.5 (8-C), 114.8 (6-C), 105.8 (3-C), 73.3 [$CH(CH_3)_2$], 56.4 (OCH_3), 52.4 (CO_2CH_3) and 21.9 [$CH(CH_3)_2$]; *m*/*z* (EI) 354, 352 (M^+, 27%), 312, 310 (100), 297, 295 (24), 253, 251 (9) and 172 (9).

(8-Bromo-5-isopropoxy-4-methoxy-2-naphthyl)methanol 31

Lithium aluminium hydride (0.020 g, 0.56 mmol) was added to a solution of compound **30** (0.200 g, 0.56 mmol) in dry diethyl ether (5 cm^3) and the mixture was stirred under an argon atmosphere for 1 h. The mixture was filtered through a short Celite column and the solvent was removed *in vacuo* to yield the *alcohol* **31** (0.18 g, 98%) as a clear oil, with identical spectroscopic properties to those reported in the literature[3e] (Found: M^+, 324.0364. $C_{15}H_{17}BrO_3$ requires *M*, 324.0361); ν_{max}(film)/cm^{-1} 3600m (OH, free), 3347br (OH, hydrogen bonded), 2833m (C–H, OCH_3), 1587s and 1573s (ArC=C) and 1266s (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.64 (1H, d, *J* 0.8, 8-H), 7.61 (1H, d, *J* 8.3, 2-H), 6.83 (1H, d, *J* 0.8, 6-H), 6.74 (1H, d, *J* 8.3, 3-H), 4.76 (2H, br s, CH_2OH), 4.49 [1H, sept, *J* 6.1, $CH(CH_3)_2$], 3.90 (3H, s, OCH_3), 2.42 (1H, br s, OH) and 1.39 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (100.625 MHz; $CDCl_3$) 157.4 (4-C[a]), 154.8 (5-C[a]), 140.4 (7-C), 134.8 (8a-C), 130.6 (2-C), 119.9 (4a-C), 117.4 (8-C), 114.4 (1-C), 113.0 (6-C), 105.9 (3-C), 73.3 [$CH(CH_3)_2$], 65.3 (CH_2OH), 56.3 (OCH_3) and 21.9 [$CH(CH_3)_2$]; *m*/*z* (EI) 326, 324 (M^+, 31%), 284, 282 (100), 269, 267 (19), 203 (6) and 115 (20).

5-Bromo-3-bromomethyl-8-isopropoxy-1-methoxynaphthalene 32

1,2-Dibromotetrachloroethane (0.48 g, 1.47 mmol) was added to a solution of alcohol **31** (0.478 g, 1.47 mmol) and triphenylphosphine (0.39 g, 1.47 mmol) in dichloromethane (10 cm^3). The reaction mixture was stirred under argon at room temperature for 30 min, after which the solvent was removed *in vacuo*. Column chromatography (5% ethyl acetate–hexane) afforded the *product* **32** (0.49 g, 86%) as a white solid, with identical spectroscopic properties to those reported in the literature.[3e] Mp 124–126 °C (from acetone) (lit.,[3e] 126 °C, from acetone); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.80 (1H, d, *J* 1.6, 4-H), 7.65 (1H, d, *J* 8.4, 6-H), 6.89 (1H, d, *J* 1.6, 2-H), 6.79 (1H, d, *J* 8.4, 7-H), 4.63 (2H, s, CH_2Br), 4.51 [1H, sept, *J* 6.1, $CH(CH_3)_2$], 3.97 (3H, s, OCH_3) and 1.39 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 158.0 (8-C[a]), 155.1 (1-C[a]), 136.9 (3-C), 134.8 (4a-C), 131.0 (6-C), 120.4 (8a-C), 120.0 (4-C), 114.3 (5-C), 113.7 (2-C), 107.5 (7-C), 73.3 [$CH(CH_3)_2$], 56.4 (OCH_3), 34.0 (CH_2Br) and 22.0 [$CH(CH_3)_2$].

5-Bromo-8-isopropoxy-1-methoxy-3-methylnaphthalene 4

L-Selectride (1 M in tetrahydrofuran; 0.26 cm^3, 0.26 mmol) was added dropwise to a stirred solution of dibromide **32** (0.100 g, 0.26 mmol) in dry dichloromethane (5 cm^3) under an argon atmosphere at 0 °C. The reaction mixture was stirred for a further 2 h, after which the solvent was removed *in vacuo*. Purification by column chromatography afforded the *naphthalene* **4** (0.08 g, 100%) as a white solid, with identical spectroscopic properties to those reported in the literature.[3e] Mp 74–76 °C (from propan-2-ol) (lit.,[3e] 78 °C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.62–7.58 (1H, m, 4-H), 7.60 (1H, d, *J* 8.3, 6-H), 6.72–6.68 (1H, m, 2-H), 6.70 (1H, d, *J* 8.3, 7-H), 4.49 [1H, sept, *J* 6.1, $CH(CH_3)_2$], 3.92 (3H, s, OCH_3), 2.49 (3H, d, *J* 0.5, $ArCH_3$) and 1.37 [6H, d, *J* 6.1, $CH(CH_3)_2$]; δ_C (50.32 MHz; $CDCl_3$) 157.1 (8-C[a]), 154.9 (1-C[a]), 137.6 (3-C), 135.0 (4a-C), 130.3 (6-C), 119.4 (4-C), 118.9 (8a-C), 113.8 (5-C), 112.2 (2-C[b]), 109.4 (7-C[b]), 73.1 [$CH(CH_3)_2$], 56.4 (OCH_3), 22.1 ($ArCH_3$) and 22.0 [$CH(CH_3)_2$].

6,8-Dimethoxy-*trans*-1,3-dimethylisochroman-5-ol 33

Method A. 10% Palladium on carbon (0.07 g, 10% by mass) was added to a solution of isochromane **25** (0.656 g, 2.00 mmol) in dry methanol (40 cm^3) and the mixture was stirred at room temperature under a hydrogen pressure of one atmosphere. After 4 h the mixture was filtered through a small Celite plug and the solvent was removed *in vacuo* to afford the *isochromanol* **33** as a dark oil (0.48 g, 100%) (Found: M^+, 238.1193. $C_{13}H_{18}O_4$ requires *M*, 238.1205); ν_{max}(film)/cm^{-1} 3300br (OH), 1626s (ArC=C), 1260s and 1087s (C–O–C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.39 (1H, s, 7-H), 5.07 (1H, q, *J* 6.5, 1-H), 4.55 (1H, br s, OH), 4.15–3.95 (1H, m, 3-H), 3.86 and 3.77 (each 3H, s, OCH_3), 2.81 (1H, dd, *J* 17.0 and 3.4, 4-H *pseudo*-equatorial), 2.36 (1H, dd, *J* 17.0 and 10.8, 4-H *pseudo*-axial), 1.48 (3H, d, *J* 6.5, 1-CH_3) and 1.33 (3H, d, *J* 6.1, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$) 148.5, 144.3 and 136.4 (3 × ArC–O), 120.9 and 120.5 (2 × ArC–C), 93.8 (7-C), 68.1 (1-C), 62.2 (3-C), 56.2 and 55.8 (2 × OCH_3), 30.1 (4-C), 21.9 (1-CH_3) and 19.7 (3-CH_3); *m*/*z* (EI) 238 (M^+, 24%), 223 (100), 208 (14) and 193 (7).

Method B. A small scoop of palladium black (≈ 0.050 g) in water was washed with methanol (2 × 20 cm^3) followed by dry methanol (2 × 2 cm^3). (**CAUTION:** dry palladium black is very pyrophoric and the catalyst must stay wet with solvent.) A formic acid–methanol mixture (10%; 2 cm^3) was added and the reaction mixture was stirred vigorously for 10 min. The benzyl-protected compound **25** (0.088 g, 0.27 mmol) was added to the catalyst in a formic acid–methanol mixture (10%; 2 cm^3) and the reaction mixture was stirred for 45 min at ambient temperature under an argon atmosphere. The palladium black was removed by filtration and the catalyst was washed with methanol (2 × 20 cm^3). The solvent was removed *in vacuo* to afford the *isochromanol* **33** as a dark oil (0.064 g, 100%). Spectral data for this product were identical to those obtained in method A.

6,8-Dimethoxy-*trans*-1,3-dimethylisochroman-5-yl trifluoromethanesulfonate 35

Dry pyridine (0.27 cm^3, 0.26 g, 3.3 mmol) was added to a solution of isochromanol **33** (0.71 g, 3.00 mmol) in dry chloroform (20 cm^3) under an argon atmosphere in a Schlenk tube. This mixture was added through a cannula to a Schlenk tube containing trifluoromethanesulfonic anhydride (0.95 g, 3.30 mmol), forming a purple-red reaction mixture. The reaction mixture was then stirred for 18 h under argon. Ice–water (10 cm^3) were added and the water layer was extracted with chloroform (3 × 10 cm^3), which was separated, dried ($MgSO_4$), and removed *in vacuo*. Column chromatography (dichloromethane) yielded the *triflate* **35** as a white semi-solid (0.98 g, 88%) (Found: M^+, 370.0699. $C_{14}H_{17}F_3O_6S$ requires *M*, 370.0698); ν_{max}(KBr pellet)/cm^{-1} 1618m and 1589m (ArC=C), 1207vs and 1135vs (R–SO_2–OR), 1086s (C–O–C) and 763m (C–F, CF_3); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.46 (1H, s, 7-H), 5.03 (1H, q, *J* 6.6, 1-H), 4.11–3.96 (1H, m, 3-H), 3.87 and 3.83 (each 3H, s, OCH_3), 2.77 (1H, dd, *J* 16.8 and 3.3, 4-H *pseudo*-equatorial), 2.44 (1H, dd, *J* 16.8 and *J* 10.6, 4-H *pseudo*-axial), 1.47 (3H, d, *J* 6.6, 1-CH_3) and 1.33 (3H, d, *J* 6.1, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$) 155.0 and 150.1 (2 × ArC–O), 128.8 (5-C), 121.8 and 120.7 (2 × ArC–C), 118.6 (q, *J* 320.2, CF_3), 94.1 (7-C), 67.8 (1-C), 61.9 (3-C), 56.0 and 55.5 (2 × OCH_3), 30.5 (4-C), 21.6 (1-CH_3) and 19.4 (3-CH_3); *m*/*z* (EI) 370 (M^+, 22%), 355 (100), 237 (72), 222 (22), 207 (22) and 193 (95).

6,8-Dimethoxy-*trans*-1,3-dimethylisochroman-5-yl diethyl phosphate 36

Isochromanol **33** (0.18 g, 0.76 mmol) was added to a suspension of sodium hydride (50% in oil; 0.044 g, 0.91 mmol) in THF (5 cm^3) and the mixture was stirred for 20 min under an argon atmosphere. Diethyl phosphorochloridate (0.12 cm^3, 0.91

mmol) was added dropwise by syringe and the mixture was stirred under argon for 20 h. Diethyl ether (50 cm^3) was added and the organic phase was washed with aq. sodium hydroxide (10% *m*/*v*; 3 × 20 cm^3). The organic solvent was dried ($MgSO_4$), and removed *in vacuo* to give a light yellow residue. This compound was subjected to column chromatography (50% ethyl acetate–hexane to 10% methanol–hexane) to give the *phosphate ester* **36** (0.28 g, 100%) as a light pink solid, mp 74.5–75.5 °C (from chloroform) (Found: C, 54.28; H, 7.32; M^+, 374.1483. $C_{17}H_{27}O_7P$ requires C, 54.54; H, 7.32%; *M*, 374.1494); ν_{max}(KBr pellet)/cm^{-1} 1618 (ArC=C), 1280s (P=O), 1225m (C–O–C, ArC–O–C), 1050s (P–O–CAr) and 1032vs and 825w (P–O–C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.38 (1H, s, 7-H), 5.04 (1H, q, *J* 6.5, 1-H), 4.29–4.20 (2H, m, C$H_2$$CH_3$), 4.18–3.98 (3H, m, C$H_2$$CH_3$ and 3-H), 3.87 and 3.80 (each 3H, s, OCH_3), 2.89 (1H, dd, *J* 17.0 and 3.2, 4-H *pseudo*-equatorial), 2.46 (1H, dd, *J* 17.0 and 10.9, 4-H *pseudo*-axial) and 1.48–1.29 (12H, m, 1- and 3-CH_3 and 2 × $OCH_2C$$H_3$); δ_C (50.32 MHz; $CDCl_3$) (values in brackets refer to minor diastereomer) 152.6 (152.5) (149.4), 149.4, 131.3 and (131.1) (3 × ArC–O), 127.5, (127.5), 120.1 and (120.0) (2 × ArC–C), (94.3), 94.3 (7-C), 67.7 (1-C), 64.2, (64.0), (63.1) and 63.0 (2 × OCH_2), 61.9 (3-C), 55.9 and 55.2 (2 × OCH_3), 30.7 (4-C), 21.6 (1-CH_3), 19.4 (3-CH_3), 16.0 (15.9), 15.8 and (15.7) (2 × $OCH_2$$CH_3$); *m*/*z* (EI) 374 ($M^+$, 13%), 359 (100) and 205 (32).

6,8-Dimethoxy-*trans*-1,3-dimethylisochroman 38

Phosphate **38** (0.28 g, 0.75 mmol) was dissolved in diethyl ether (5 cm^3) and added to a stirred solution of liquid ammonia (50 cm^3) at −78 °C. Potassium metal was added in small pieces until a dark blue colour persisted for 15 min. Excess of ammonium chloride was then added and propan-2-ol (50 cm^3) was added to destroy excess of potassium metal. The ammonia was allowed to evaporate overnight and water (20 cm^3) was added to the mixture. The aqueous layer was extracted with diethyl ether (5 × 20 cm^3), which was dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography gave the *isochromane* **38** as a clear oil (0.17 g, 100%) (Found: M^+, 222.1268. $C_{13}H_{18}O_3$ requires *M*, 222.1256); ν_{max}(film)/cm^{-1} 2850m (OCH_3), 1608m and 1600 (ArC=C) and 1212s and 1090s (C–O–C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.29 (1H, d, *J* 2.3, 5-H), 6.21 (1H, d, *J* 2.3, 7-H), 5.03 (1H, q, *J* 6.5, 1-H), 4.16–4.00 (1H, m, 3-H), 3.78 (6H, s, 2 × OCH_3), 2.68–2.49 (2H, m, 4-H_2), 1.48 (3H, d, *J* 6.5, 1-CH_3) and 1.30 (3H, d, *J* 6.1, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$) 158.9 and 156.5 (2 × ArC–O), 135.1 and 120.6 (2 × ArC–C), 104.0 (5-C), 96.3 (7-C), 68.3 (1-C), 62.6 (3-C), 55.2 and 55.1 (2 × OCH_3), 36.4 (4-C), 21.8 (1-CH_3) and 19.8 (3-CH_3); *m*/*z* (EI) 222 (M^+, 18%), 207 (100), 192 (6) and 177 (6).

5-Bromo-6,8-dimethoxy-*trans*-1,3-dimethylisochromane 12

Isochromane **38** (0.155 g, 0.70 mmol) was dissolved in a mixture of chloroform (5 cm^3) and acetic acid (5 cm^3) and the solution was cooled to 0 °C under an atmosphere of argon. Bromine (0.036 cm^3, 0.11 g, 0.70 mmol) was dissolved in acetic acid (2.5 cm^3) and added slowly by syringe to the stirred solution. After 105 min, water (10 cm^3) was added and the mixture was extracted with chloroform (3 × 20 cm^3). The organic layer was washed successively with water (2 × 10 cm^3), saturated aq. sodium bicarbonate (10 cm^3) and brine (10 cm^3). After drying of the organic phase ($MgSO_4$), the solvent was removed *in vacuo* and the *product* **12** was obtained after column chromatography as a clear oil (0.19 g, 93%) (Found: M^+, 300.0353. $C_{13}H_{17}{}^{79}BrO_3$ requires *M*, 300.0361); ν_{max}(film)/cm^{-1} 2850m (OCH_3), 1598m and 1575m (ArC=C) and 1212vs and 1078m (C–O–C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.38 (1H, s, 7-H), 5.04 (1H, q, *J* 6.6, 1-H), 4.14–3.92 (1H, m, 3-H), 3.89 and 3.82 (each 3H, s, OCH_3), 2.83 (1H, dd, *J* 17.3 and 3.5, 4-H *pseudo*-equatorial), 2.37 (1H, dd, *J* 17.3 and 10.9, 4-H *pseudo*-axial), 1.47 (3H, d, *J* 6.6, 1-CH_3) and 1.34 (3H, d, *J* 6.1, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$) 155.2 and 154.9 (2 × ArC–O), 134.7 and 122.3 (2 × ArC–C), 104.4 (5-C), 94.2 (7-C), 67.9 (1-C), 62.6 (3-C), 56.3 and 55.3 (2 × OCH_3), 36.9 (4-C), 21.7 (1-CH_3) and 19.5 (3-CH_3); *m*/*z* (EI) 302, 300 (M^+, 11%), 287, 285 (100), 221 (4) and 206 (7).

5-Iodo-6,8-dimethoxy-*trans*-1,3-dimethylisochromane 10

Sublimed iodine (0.23 g, 0.89 mmol) and silver(I) sulfate (0.28 g, 0.89 mmol) in absolute ethanol (10 cm^3) were added dropwise to a stirred solution of **38** (0.17 g, 1.08 mmol) in absolute ethanol (10 cm^3). Additional absolute ethanol (10 cm^3) was used to wash residues from the dropping funnel into the reaction mixture. The mixture was stirred under argon at room temperature for 3 h, during which time the mixture colour changed from an orange to a bright yellow. The precipitate was filtered off, and washed with ethanol (20 cm^3). The organic solvent was then removed under vacuum and replaced with dichloromethane (10 cm^3) to give a bright yellow solution. This solution was washed successively with aq. sodium hydroxide (10% m/v; 20 cm^3) and water (20 cm^3). The organic phase was separated, dried ($MgSO_4$), and then evaporated *in vacuo*. Purification by flash chromatography afforded the *iodide* **10** as a white solid (0.25 g, 94%), mp 111–112 °C (from ethanol; sublimes above 85 °C and goes green with time) (Found: M^+, 348.0221. $C_{13}H_{17}IO_3$ requires *M*, 348.0222); ν_{max}(KBr pellet)/cm^{-1} 2850w (OCH_3), 1600m and 1566 (ArC=C) and 1215s, 1171m, 1069s and 816m (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.34 (1H, s, 7-H), 5.02 (1H, q, *J* 6.6, 1-H), 4.08–4.03 (1H, m, 3-H), 3.87 and 3.83 (each 3H, s, OCH_3), 2.74 (1H, dd, *J* 17.0 and 3.5, 4-H *pseudo*-equatorial), 2.35 (1H, dd, *J* 17.0 and 10.8, 4-H *pseudo*-axial), 1.46 (3H, d, *J* 6.6, 1-CH_3) and 1.35 (3H, d, *J* 6.1, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) 157.1 and 156.5 (2 × ArC–O), 137.5 and 122.9 (2 × ArC–C), 93.5 (7-C), 82.2 (5-C), 68.0 (1-C), 63.1 (3-C), 56.4 and 55.3 (2 × OCH_3), 42.3 (4-C), 21.7 (1-CH_3) and 19.5 (3-CH_3); *m*/*z* (EI) 348 (M^+, 16%) and 333 (100).

6,8-Diisopropoxy-*trans*-1,3-dimethylisochroman-5-ol 34

10% Palladium on carbon (0.11 g; 10% by mass) was added to a solution of isochromane **26** (1.09 g, 2.83 mmol) in dry methanol (50 cm^3) and the mixture was stirred at room temperature in an autoclave at a hydrogen pressure of one atmosphere. After 2 h the mixture was filtered through a small Celite plug and the solvent was removed *in vacuo* to afford the *isochromanol* **34** (0.82 g, 100%) as a brown oily, low melting solid (Found: M^+, 294.1844. $C_{17}H_{26}O_4$ requires *M*, 294.1831); ν_{max}(film)/cm^{-1} 3547br (OH), 1617s (ArC=C), 1383m and 1373m [CH_3, CH-$(CH_3)_2$], 1244m (C–O–C), 1121vs (C–OH) and 1100m, 1064m and 814m (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.35 (1H, s, 7-H), 5.36 (1H, s, OH), 5.03 (1H, q, *J* 6.6, 1-H), 4.47 [1H, sept, *J* 6.1, C$H$$(CH_3)_2$], 4.39 [1H, sept, *J* 6.0, C$H$$(CH_3)_2$], 4.07–4.02 (1H, m, 3-H), 2.79 (1H, dd, *J* 17.0 and 3.4, 4-H *pseudo*-equatorial), 2.36 (1H, dd, *J* 17.0 and 10.9, 4-H *pseudo*-axial), 1.49 (3H, d, *J* 6.6, 1-CH_3), 1.36–1.32 [12H, m, 2 × CH(CH_3)$_2$] and 1.26 (3H, d, *J* 6.0, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) 146.3, 142.0 and 137.7 (3 × ArC–O), 122.3 and 120.8 (2 × ArC–C), 99.1 (7-C), 72.2 and 70.5 [2 × CH$(CH_3)_2$], 68.4 (1-C), 62.2 (3-C), 30.3 (4-C), 22.3, 22.3, 22.1 and 22.0 [2 × CH(CH_3)$_2$[a]], 22.0 (1-CH_3[a]) and 19.8 (3-CH_3); *m*/*z* (EI) 294 (M^+, 34%), 279 (57), 237 (56), 195 (100) and 167 (10).

6,8-Diisopropoxy-*trans*-1,3-dimethylisochroman-5-yl diethyl phosphate 37

Sodium hydride (60% in oil; 0.13 g, 3.24 mmol) was added to a solution of isochromanol **34** (0.79 g, 2.7 mmol) in THF (50 cm^3) and the mixture was stirred for 20 min under an argon atmosphere. Diethyl phosphorochloridate (0.43 cm^3, 0.51 g, 3.0 mmol) was added dropwise by syringe and the mixture was

stirred at room temperature for 20 h. Diethyl ether (50 cm^3) was added and the organic phase was washed successively with aq. sodium hydroxide (10% *m*/*v*; 3 × 20 cm^3) and water (50 cm^3). The organic layer was dried ($MgSO_4$), and removed *in vacuo* to give a light yellow residue. This was purified by column chromatography (50% ethyl acetate–hexane to 10% methanol–hexane) to give the *phosphate ester* **37** as a clear oil (0.93 g, 81%) (Found: M^+, 430.2111. $C_{21}H_{35}O_7$ requires *M*, 430.2120); ν_{max} (film)/cm^{-1} 2860w (OCH_2), 1610m (ArC=C), 1367m (CH_3), 1295m (P=O), 1124s (C–O–C) and 1035s (P–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.36 (1H, s, 7-H), 5.00 (1H, q, *J* 6.5, 1-H), 4.54–4.44 [2H, m, 2 × C*H*(CH_3)$_2$], 4.28–4.21 (4H, m, 2 × C$H_2$$CH_3$), 4.05–4.00 (1H, m, 3-H), 2.90 (1H, dd, *J* 16.9 and 3.1, 4-H *pseudo*-equatorial), 2.46 (1H, dd, *J* 16.9 and 10.9, 4-H *pseudo*-axial), 1.47 (3H, d, *J* 6.6, 1-CH_3), 1.37–1.33 (15H, m, 5 × CH_3), 1.31 (3H, d, *J* 6.1, CH_3) and 1.29 (3H, d, *J* 6.0, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) (values in parentheses refer to the minor stereoisomer) 150.5 (150.4), 147.4 (147.4) (132.3) and 132.2, (3 × ArC–O), 127.8 (127.8) and 121.3 (2 × ArC–C), 99.0 (7-C), 71.1 and 69.8 [2 × *C*H(CH_3)], 67.9 (1-C), (64.0), 63.9, 63.9 and (63.9) (2 × O*C*$H_2$$CH_3$), 62.0 (3-C), 30.9 (4-C), 21.9 (1-CH_3[a]), 21.9, 21.8, 21.8 and 21.7 [2 × CH(*C*H_3)$_2$[a]], 19.4 (3-CH_3[a]) and 15.9 and 15.9 (2 × OCH_2*C*H_3); *m*/*z* (EI) 430 (M^+, 31%), 415 (62), 373 (100), 331 (33) and 43 (20).

6,8-Diisopropoxy-*trans*-1,3-dimethylisochromane 39

Liquid ammonia (50 cm^3) was distilled into a solution of isochromane **37** (0.53 g, 1.23 mmol) in diethyl ether (5 cm^3) at −78 °C. Potassium metal was added in small pieces until a dark blue colour persisted for 15 min. Excess of ammonium chloride was then added and propan-2-ol (50 cm^3) was added to destroy excess of potassium metal. The ammonia was allowed to evaporate overnight and water (50 cm^3) was added to the mixture. The aqueous layer was extracted with diethyl ether (3 × 50 cm^3), which was dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography gave the *isochromane* **39** as a clear oil (0.31 g, 91%) (Found: M^+, 278.1875. $C_{17}H_{26}O_3$ requires *M*, 278.1882); ν_{max}(film)/cm^{-1} 1610s and 1591 (ArC=C), 1383m and 1372m [CH_3, CH(CH_3)$_2$] and 1204m, 1069s and 829m (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.25 (1H, d, *J* 2.1, 5-H), 6.18 (1H, d, *J* 2.1, 7-H), 5.00 (1H, q, *J* 6.6, 1-H), 4.53–4.45 [2H, m, 2 × C*H*(CH_3)$_2$], 4.09–4.04 (1H, m, 3-H), 2.62–2.51 (2H, m, 4-H_2), 1.48 (3H, d, *J* 6.6, 1-CH_3), 1.34–1.31 [9H, m, CH(C*H*$_3$)-CH_3, CH(C*H*$_3$)$_2$], 1.30 [3H, d, *J* 6.0, CH(C*H*$_3$)CH_3] and 1.28 (3H, d, *J* 6.1, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) 157.0 and 154.6 (2 × ArC–O), 135.1 and 121.1 (2 × ArC–C), 106.0 (5-C), 99.5 (7-C), 69.8 and 69.5 [2 × *C*H(CH_3)$_2$], 68.5 (1-C), 62.6 (3-C), 36.5 (4-C), 22.2, 22.1, 22.1 and 21.8 [2 × *C*H(*C*H_3)$_2$[a]], 21.8 (1-CH_3[a]) and 19.8 (3-CH_3); *m*/*z* (EI) 278 (M^+, 18%), 263 (100), 221 (40), 179 (89) and 43 (17).

5-Iodo-6,8-diisopropoxy-*trans*-1,3-dimethylisochromane 11

Sublimed iodine (0.30 g, 1.19 mmol) and silver(I) sulfate (0.37 g, 1.19 mmol) in absolute ethanol (15 cm^3) were added dropwise to a stirred solution of **39** (0.30 g, 1.08 mmol) in absolute ethanol (25 cm^3). After 3 h the reaction mixture was treated in the same manner as for **10** to afford, after purification by flash chromatography (10% ethyl acetate–hexane), the *iodide* **11** as a colourless oil (0.41 g, 94%) (Found: M^+, 404.0851. $C_{17}H_{25}IO_3$ requires *M*, 404.0848); ν_{max}(film)/cm^{-1} 1586s and 1560s (ArC=C), 1380s and 1373s [CH_3, CH(CH_3)$_2$], 1212s, 1105s and 1071 (C–O–C) and 614m (C–I); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.34 (1H, s, 7-H), 4.99 (1H, q, *J* 6.6, 1-H), 4.58–4.43 [2H, m, 2 × C*H*(CH_3)$_2$], 4.11–4.01 (1H, m, 3-H), 2.73 (1H, dd, *J* 17.0 and 3.6, 4-H *pseudo*-equatorial), 2.35 (1H, dd, *J* 17.0 and 10.9, 4-H *pseudo*-axial), 1.48 (3H, d, *J* 6.6, 1-CH_3), 1.40–1.33 [12H, m, 2 × CH(C*H*$_3$)$_2$] and 1.30 (3H, d, *J* 6.0, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) 155.7 and 154.4 (2 × ArC–O), 137.8 and 124.4 (2 × ArC–C), 99.2 (7-C), 85.2 (5-C), 72.6 and 69.8 [2 × *C*H(CH_3)$_2$], 68.3 (1-C), 63.2 (3-C), 42.7 (4-C), 22.2, 22.2, 22.0 and 21.9 [2 × CH(*C*H_3)$_2$[a]], 21.8 (1-CH_3[a]) and 19.6 (3-CH_3); *m*/*z* (EI) 404 (M^+, 36%), 389 (100), 347 (70), 305 (92) and 178 (7).

6,7-Dimethoxy-*trans*-1,3-dimethyl-5-(1-naphthyl)isochromane 43

Method 1. Bromide **12** (0.090 g, 0.30 mmol), 1-naphthylboronic acid **40** (0.10 g, 0.60 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.03 mmol, 10 mol%) were added under a stream of argon to a Pyrex culture tube. Degassed toluene (1.5 cm^3) and saturated aq. sodium bicarbonate (1.5 cm^3) were added and the tube was sealed. The tube was then heated at 110 °C for 20 h, and then allowed to cool to ambient temperature. Brine (10 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 5 cm^3). The organic extracts were combined, dried ($MgSO_4$), and then the solvent was removed *in vacuo*. Purification of the residue by preparative thin-layer chromatography (PLC) (5% ethyl acetate–hexane) afforded the *biaryl compound* **43** as a brown oil (0.029 g, 28%) (diastereomeric ratio 66:34), naphthalene (0.020 g, 26%) and unreacted bromoisochromane **12** (0.033 g, 37%) (Found: M^+, 348.1717. $C_{23}H_{24}O_3$ requires *M*, 348.1725); ν_{max}(film)/cm^{-1} 3055w (ArC–H), 2837w (C–H, OCH_3), 1597s (ArC=C), 1485m (ArC–C) and 1210s, 1087s and 1070m (C–O–C); δ_H (400 MHz; $CDCl_3$) (assignments in brackets are for the minor diastereoisomer) 7.90–7.84 (2H, m, 2 × ArH), 7.55–7.24 (5H, m, 5 × ArH), 6.49 (1H, s, 7-H), 5.18–5.14 (1H, m, 1-H), 3.90–3.80 (1H, m overlapping with OCH_3, 3-H) (3.92), 3.91 (3H, s, OCH_3) (3.61), 3.60 (3H, s, OCH_3), 2.25–2.17 (1H, m, 4-H *pseudo*-equatorial), 1.93–1.87 (1H, m, 4-H *pseudo*-axial), 1.56 (1.55) (3H, d, *J* 6.5, 1-CH_3) and 1.07 (1.04) (3H, d, *J* 6.1, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) (156.8), 156.7, 155.8 (3 × ArC–O), 135.1, 134.6 (134.5), 133.7 (133.7), 132.7 (4a-, 1′-, 4a′-, 8a′-C), 128.2 (128.2), 128.0 (127.6), 127.3 (125.9) (125.8), 125.8, 125.7 (125.6), 125.6, 125.6 and (125.5) (7 × ArC–H), 120.4 (120.3) 120.2 and 120.1 (8a- and 5-C), 93.3 (93.3) (7-C), 68.4 (68.3) (1-C), 62.8 (62.7) (3-C) (56.1), 56.0 and 55.3 (2 × OCH_3), 34.7 (33.8) (4-C), 21.8 (21.7) (1-CH_3) and 20.0 (19.9) (3-CH_3); *m*/*z* (EI) 348 (M^+, 75%), 334 (100) and 166 (45).

Method 2. Isochromane **12** (0.050 g, 0.17 mmol) and 1-naphthylboronic acid pinacol ester **41** (0.063 g, 0.25 mmol) were dissolved in DMF (3 cm^3) in a Schlenk tube under an argon atmosphere. The reaction mixture was degassed with argon for a further 30 min. Dichloro-[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)][30] (0.006 g, 0.0083 mmol, 5 mol%) and degassed aq. sodium carbonate (2 M; 0.42 cm^3, 0.083 mol) were added, forming a white precipitate which dissolved when heated at 80 °C for 18 h. Water (10 cm^3) was added and the reaction mixture was extracted with diethyl ether (3 × 10 cm^3). The organic phase was separated and washed sequentially with water (10 cm^3), brine (10 cm^3) and water (10 cm^3), before being dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by PLC (5% ethyl acetate–hexane) afforded the desired *naphthylisochromane* **43** (8.0 mg, 14% based on bromoisochromane **12**) (diastereomeric ratio 58:42), racemic 1,1′-binaphthyl (21.0 mg, 66% based on boronic ester **41**) and debrominated pyran **38** (17.0 mg, 46% based on bromoisochromane **12**). The product **43** was identical to that synthesized by Method 1.

5-(4-Isopropoxy-5-methoxy-7-methyl-1-naphthyl)-6,8-dimethoxy-*trans*-1,3-dimethoxyisochromane 7

The bromonaphthalene **4** (0.10 g, 0.32 mmol) was dissolved in dry THF (5 cm^3) and the solution was cooled to −78 °C under an argon atmosphere. *n*-Butyllithium (1.4 M; 0.27 cm^3, 0.38 mmol) was added by syringe over a period of 10 min and the solution became yellow. After stirring of the mixture for a further 7 min, triisopropyl borate (0.22 cm^3, 0.95 mmol) was

added by syringe and the mixture was stirred at −78 °C for a further 5 min. The reaction mixture was then warmed to room temperature over a period of 18 h. Saturated aq. ammonium chloride (10 cm^3) and ice (10 cm^3) were added and the reaction mixture was stirred for a further 10 min before being extracted successively with diethyl ether (2 × 10 cm^3) and dichloromethane (2 × 10 cm^3). The organic phases were combined, dried ($MgSO_4$), and the solvent removed under vacuum to afford a residue of 4-isopropoxy-5-methoxy-7-methyl-1-naphthylboronic acid **9** which was used without further purification and without delay.

The boronic acid **9** (assume 0.31 mmol) was transferred to a small round-bottomed flask with DMF (1 cm^3) and oxygen was excluded by three freeze–thaw cycles. The flask was sealed and transferred to an argon tent. Iodide **10** (0.054 g, 0.15 mmol), tribasic potassium phosphate (K_3PO_4) (0.10 g, 0.48 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.036 g, 0.031 mmol, 20 mol% based on iodide **10**) were added sequentially under flowing argon. The flask was sealed, and then heated, with stirring, under an argon atmosphere at 100 °C for 65 h. The mixture was then cooled and brine (10 cm^3) was added. The reaction mixture was extracted with diethyl ether (4 × 10 cm^3), which was dried ($MgSO_4$), and removed *in vacuo*. Purification by column chromatography (5–20% ethyl acetate–hexane) afforded the *biaryl compound* **7** as a dark oil (0.069 g, 96%) (diastereoisomeric ratio 60:40) (Found: M^+, 450.2411. $C_{28}H_{34}O_5$ requires *M*, 450.2406); ν_{max}(film)/cm^{-1} 2837w (CH, OCH_3), 1583vs (ArC=C), 1372s [–CH_3, $CH(CH_3)_2$], 1277s (C–O–C), 1175s [–CH_3, $CH(CH_3)_2$] and 1110s and 812m (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) (assignments in brackets are for the minor diastereoisomer) 6.99 (6.97) (1H, d, *J* 7.9, 2′-H) (6.83), 6.82 (1H, d, *J* 7.9, 3′-H), 6.68–6.66 and 6.60–6.55 (2H, m, 6′-H and 8′-H), 6.40 (1H, s, 7-H), 5.09 (5.07) (1H, q, *J* 6.5, 1-H), (4.51) 4.51 [1H, sept, *J* 6.1, C*H*$(CH_3)_2$], (3.86) 3.86 (3H, s, OCH_3), 3.86–3.83 (1H, m overlapping with OCH_3, 3-H), 3.84 (3.83) (3H, s, OCH_3), 3.55 (3.54) (3H, s, OCH_3), (2.25) 2.23 (3H, s, $ArCH_3$), 2.12 (1H, dd, *J* 17.1 and 3.3, 4-H *pseudo*-equatorial), (2.06) (1H, d, *J* 17.1, 4-H *pseudo*-equatorial), (1.85) (1H, dd, *J* 17.1 and 7.3, 4-H *pseudo*-axial), 1.83 (1H, d, *J* 17.1, 4-H *pseudo*-axial), (1.48) 1.47 (3H, d, *J* 6.5, 1-CH_3), (1.36) 1.35 [6H, d, *J* 6.1, $CH(CH_3)_2$] and (1.00) 0.98 (3H, d, *J* 6.1, 3-CH_3); δ_C (100.63 MHz; $CDCl_3$) 157.1 (157.1), 156.9 (156.8), 155.5, 154.3 and (154.3) (4 × ArC–O), 136.6 (136.5), 135.8 (135.6), 135.0 (134.9) and 128.5 (4 × ArC–C), 128.1 (2′-C), 127.1 (127.2), 121.3 (121.2) (120.3) and 120.0 (3 × ArC–C), (117.9), 117.8 (8′-C^a), 111.5 (111.4) (3′-C^a), 108.9 (108.9) (6′-C^a), 93.5 (93.5) (2 × 7-C), 72.6 (72.6) [2 × *C*$H(CH_3)_2$], 68.3 (68.3) (1-C), 62.8 (3-C), (56.5) 56.4, 56.2 (56.2) and 55.2 (3 × OCH_3), (34.6) 33.6 (4-C), 22.3 (22.2) ($ArCH_3{}^b$), 22.0 [$CH(CH_3)_2{}^b$], 21.7 (21.7) (1-CH_3) and 20.0 (20.0) (3-CH_3); *m*/*z* (EI) 450 (M^+, 74%), 435 (18), 408 (13), 393 (100) and 196 (32).

When this experiment was conducted with bromoisochromane **12** rather than the iodide **10**, a lower yield of biaryl **7** was obtained (24%) (diastereomeric ratio 60:40).

6,8-Diisopropoxy-5-(4-isopropoxy-5-methoxy-7-methyl-1-naphthyl)-*trans*-1,3-dimethylisochromane 8

2,6-Di-*tert*-butyl-4-methylphenol (0.054 g, 0.25 mmol), tribasic potassium phosphate (0.22 g, 0.11 mmol) and tetrakis-(triphenylphosphine)palladium(0) (0.081 g, 0.07 mmol, 20 mol%) were placed in a two-necked flask. The vessel was purged with argon and iodide **11** (0.142 g, 0.35 mmol) and boronic acid **9** (0.192 g, 0.70 mmol) were added sequentially in degassed DMF (2 × 1 cm^3). The dropping funnel was washed with degassed DMF (0.5 cm^3) and the reaction mixture was stirred and heated at 100–105 °C under argon for 94 h. During this time the reaction mixture colour changed from a dark green to a bright blue and finally became a dark purple. The reaction mixture was cooled to ambient temperature, diluted with brine (10 cm^3) and extracted with diethyl ether (4 × 10 cm^3). The organic layers were then combined, dried ($MgSO_4$), and the solvent removed *in vacuo*. Column chromatography (5–20% ethyl acetate–hexane) and subsequent PLC (5% ethyl acetate–hexane) afforded the *biaryl compound* **8** as a yellow oil (0.026 g, 15% based on iodide **11**, diastereomeric ratio 62:38) (Found: M^+, 506.3020. $C_{32}H_{42}O_5$ requires *M*, 506.3032); ν_{max}(film)/cm^{-1} 2860m (C–H, OCH_2), 1584s (ArC=C) and 1274m (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) (assignments in brackets are for the minor diastereoisomer) 7.09 (7.05) (1H, d, *J* 7.9, 2′-H), 6.90 (6.85) (1H, d, *J* 7.9, 3′-H), 6.78 (6.69) (1H, br s, 8′-H^a), 6.64 (6.63) (1H, d, *J* 1.3, 6′-H^a), 6.56 (1H, s, 7-H), 5.13 (5.12) (1H, d, *J* 6.6, 1-H), 4.65–4.53 [2H, m, 2 × C*H*$(CH_3)_2$], 4.03 [1H, sept, *J* 6.0, C*H*$(CH_3)_2$], 4.00–3.95 (1H, m, 3-H), 3.95 (3H, s, OCH_3), (2.32) 2.31 (3H, 2 × s, 7′-CH_3), 2.23 (1H, dd, *J* 17.1 and 3.1, 4-H *pseudo*-equatorial), (2.19–2.14) (1H, m, 4-H, *pseudo*-equatorial), 2.00–1.93 (1H, m, 4-H *pseudo*-axial), (1.57) 1.55 (3H, d, *J* 6.6, 1-CH_3) and 1.44–0.87 [21H, m, 3 × $CH(CH_3)_2$ and 3-CH_3]; δ_C (100.63 MHz; $CDCl_3$) (156.8), 156.8, 155.3 (155.2) (153.9), 153.9 (153.4) and 153.3 (4 × ArC–O), 136.8 (136.6), 135.4 (135.2), 134.9 and (134.8) (3 × ArC–C), (128.7) 128.4 (2′-C), 127.9 (127.8), 123.6 (123.4) (122.0) and 121.8 (3 × ArC–C), 118.1 (118.0) (8′-C^a), 117.8 (ArC–C), 112.2 (112.1) (3′-C), (108.4) 108.4 (6′-C^a), 100.4 (100.3) (7-C), 72.9 (72.8), 72.3 (72.2) (69.6) and 69.4 [3 × *C*$H(CH_3)_2$], (68.6) 68.5 (1-C), 62.8 (3-C) (56.3), 56.2 (OCH_3), (34.9) 34.5 (4-C), 22.3–21.7 [3 × $CH(CH_3)_2$, $ArCH_3$, 1-CH_3] and (20.0) 20.0 (3-CH_3); *m*/*z* (EI) 506 (M^+, 100%), 491 (52), 449 (64), 407 (33), 365 (27) and 183 (31).

4-(6,8-Dimethoxy-*trans*-1,3-dimethylisochroman-5-yl)-8-methoxy-6-methyl-1-naphthol 44

Isopropyl-protected naphthol **7** (0.050 g, 0.11 mmol) was dissolved in dry dichloromethane (5 cm^3) and the solution was cooled to −78 °C under an argon atmosphere. Boron trichloride (1 M; 0.33 cm^3, 0.33 mmol) was added dropwise over a period of 5 min. The reaction mixture was stirred for 30 min, during which time it assumed a dark red colour. The mixture was then warmed to room temperature and methanol (2 cm^3) was added. The solvent was removed under vacuum and the residue was purified by column chromatography (5–20% ethyl acetate–hexane) to afford the *phenol* **44** as a brown oil (0.023 g, 51%) (diastereoisomeric ratio 66:34) (Found: M^+, 408.1944. $C_{25}H_{28}O_5$ requires *M*, 408.1937); ν_{max}(film)/cm^{-1} 3407br (OH), 1616s and 1589s (ArC=C) and 1257s, 1092m, 1079s, 1049m and 834m (C–O–C); δ_H (200 MHz; $CDCl_3$; Me_4Si) (assignments in brackets are for the minor diastereoisomer) 9.40 (9.39) (1H, s, OH), 7.11 (7.06) (1H, d, *J* 7.9, 3-H), 6.87 (6.86) (1H, d, *J* 7.9, 2-H), 6.69–6.67 (1H, m, 5-H^a), 6.63–6.59 (1H, m, 7-H^a), 6.48 (1H, s, 7′-H), 5.17 (5.14) (1H, q, *J* 6.6, 1-H), 4.06 (3H, s, OCH_3), 4.05–3.80 (1H, m, overlapping with OCH_3, 3′-H), 3.92 (3H, s, OCH_3), 3.63 (3.62) (3H, s, OCH_3), (2.33) 2.32 (3H, d, *J* 0.7, $ArCH_3$), 2.24 (1H, dd, *J* 17.0 and 3.3, 4′-H *pseudo*-equatorial), (2.20) (1H, dd, *J* 17.0, 4′-H *pseudo*-equatorial), 1.98–1.84 (1H, m, 4′-H *pseudo*-axial), (1.56) 1.55 (3H, d, *J* 6.6, 1-CH_3) and (1.09) 1.07 (3H, d, *J* 6.1, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$) 156.2, 153.8 and 146.0 (3 × ArC–O), 136.0, 135.5, 135.0 and 130.0 (4 × ArC–C), 129.6 (3-C), 124.8, 120.0 and 118.5 (3 × ArC–C), 118.6 (5-C^a), (109.6), 109.4 (2-C^a), 106.3 (7-C^a), 93.4 (7′-C), 68.3 (1′-C), 62.8 (3′-C) (56.2), 56.2, 56.0 and 55.2 (3 × OCH_3), (34.6) 33.7 (4′-C), 22.2 ($ArCH_3$), 21.7 (1′-CH_3) and 19.9 (3′-CH_3); *m*/*z* (EI) 408 (M^+, 54%), 393 (100) and 349 (7).

4′,4″-Bis(6,8-dimethoxy-1,3-*trans*-dimethylisochroman-5-yl)-8′,8″-dimethoxy-6′,6″-dimethyl-2′,2″-bi-(1′-naphthol) 6

(a) Dimerisation. Phenol **44** (0.015 g, 0.037 mmol) was dissolved in freshly dried chloroform (3 cm^3) containing triethyl-

amine (0.2%). Silver(I) oxide (0.15 g, 10 mass equiv.) was added and the mixture was stirred under air for 9 days in the dark until all the starting material had been consumed with an extra portion of silver(I) oxide (0.10 g) added after 2 days. During this time the reaction mixture assumed a dark purple colour. The mixture was filtered through a short Celite plug and the solvent was removed *in vacuo*. The residue was purified by column chromatography (5% methanol–dichloromethane) to afford the intermediate *ene-dione* **45** (0.016 g, 100%) as a dark, purple semi-solid (Found: M^+, 812.3551. $C_{50}H_{52}O_{10}$ requires *M*, 812.3561); *m*/*z* (EI) 812 (M^+, 100%) and 391 (17).

(b) Reduction. *Method 1.*—10% Palladium on carbon (0.016 g, 1 mass equiv.) was added to a solution of the foregoing ene-dione **45** (0.016 g) in a dichloromethane (2.5 cm^3)–methanol (2.5 cm^3) mixture. The mixture was stirred at ambient temperature under hydrogen (1 atm) for 120 min. The catalyst was removed by filtration through a short Celite column in a Pasteur pipette. An additional amount of the dichloromethane–methanol mixture (50 : 50; 10 cm^3) was used to wash the Celite. The fractions were combined and the solvent removed *in vacuo* to afford a yellow, semi-solid compound (0.014 g) that went oily after a short period of time. The compound was further purified on C_{18} reversed-phase silica (methanol) to yield the *product* **6** as a semi-solid (0.012 g, 75% over two steps). Over a period of time the solid darkened to a deep purple colour (Found: M^+, 814.3717. $C_{50}H_{54}O_{10}$ requires *M*, 814.3717); ν_{max}(film)/cm^{-1} 3372br (OH), 2830w (C–H, OCH_3) and 1240s and 1081s (C–O–C); δ_H (400 MHz; $CDCl_3$; Me_4Si) (assignments in brackets are for the minor diastereoisomer) (unprimed and triply primed locants refer to the isochromane ring carbons) 9.83–9.73 (2H, m, 1′-OH and 1″-OH), 7.35–7.30 (2H, m, 3′-H and 3″-H), 6.91–6.69 (2H, m, 7′-H and 7″-H[a]), 6.65–6.60 (2H, m, 5′- and 5″-H), 6.47 (2H, s, 7- and 7‴-H[a]), 5.17–5.14 (2H, m, 1- and 1‴-H), 4.03 (4.03) (6H, s, 6- and 6‴-OCH_3[b]), 3.97–3.86 (2H, m overlapping with OCH_3s, 3- and 3‴-H), 3.90 (6H, s, 8- and 8‴-OCH_3[b]), 3.63 (6H, s, 8′- and 8″-OCH_3), 2.45–2.30 (2H, m, 4- *pseudo*-equatorial and 4‴-H *pseudo*-equatorial), 2.35, (2.34), (2.33), 2.32 (6H, 4 × s, 6′- and 6″-$ArCH_3$), 2.04–1.90 (2H, m, 4- *pseudo*-axial and 4‴-H *pseudo*-axial), 1.57–1.52 (6H, m, 1- and 1‴-CH_3) and 1.12–1.08 (6H, m, 3- and 3‴-CH_3); δ_C (100.63 MHz; $CDCl_3$) 157.0 (157.0) (8′- and 8″-C), 156.5, 156.5 (6-C and 6‴-C), 155.4 (155.4) (8- and 8‴-C), 150.6 (150.6) (1′- and 1″-C), 135.2 (6′- and 6″-C[c]), 135.1 (4a′- and 4a″-C[c]), (135.0) 134.9 (3′- and 3″-C), 132.8 (132.7) (4a- and 4a‴-C), (124.1) 124.0 (4′- and 4″-C), (120.3) 120.2 (5- and 5‴-C[d]), 120.0 (120.0) (5′- and 5″-C[d]), 118.6 (2′- and 2″-C[d]), 118.4 (8a′- and 8a″-C), (113.6) 113.5 (8a- and 8a‴-C), 106.3 (7′- and 7″-C), (93.6) 93.4 (7- and 7‴-C), 68.3 (68.3) (1- and 1‴-C), (62.9) 62.8 (3- and 3‴-C), 56.2 (56.2) (6- and 6‴-OCH_3[e]), 56.1 (56.0) (8- and 8‴-OCH_3[e]), 55.2 (8′- and 8″-OCH_3), 33.7 (4- and 4‴-C), 22.1 (6′ and 6″-CH_3), 21.7 (3- and 3‴-CH_3) and 20.0 (1- and 1‴-CH_3); *m*/*z* (EI) 816.3782 (18%) $(M + 2H)^+$, 815.3748 (57) $(M + H)^+$, 814 (M^+, 100) and 392 (22); *m*/*z* (ES) 853.3 (50%) $(M + K)^+$, 837.5 (100) $(M + Na)^+$, 815.5 (76) $(M + H)^+$, 771.5 (48) and 407.3 (20).

Method 2. The foregoing ene-dione **45** (16 mg, 0.019 mmol) was dissolved in methanol (25 cm^3) and irradiated (GEC Alsthom 1500 W 230 V Visible Light) for 4 min with stirring of the solution during which time the reaction mixture's colour changed from a dark purple to a clear yellow. The solvent was removed *in vacuo* and the residue was purified by column chromatography (5–30% ethyl acetate–hexane) to afford the product **6** as a yellow oil (0.007 g, 46%). The product **6** had the same spectroscopic properties as the product obtained from Method 1.

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References and notes

1 Reviews: (*a*) G. Bringmann and F. Pokorny, in *The Alkaloids. Chemistry and Pharmacology*, ed. G. A. Cordell, Academic Press, San Diego, 1995, Vol. 46, ch. 4, pp. 127–271; (*b*) G. Bringmann, R. Walter and R. Weirich, in *Houben-Weyl: Methods of Organic Chemistry*, ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Georg Thieme Verlag, Stuttgart and New York, 1995, Vol. E21a, pp. 567–586.

2 (*a*) J. B. McMahon, M. J. Currens, R. J. Gulakowski, R. W. Buckheit, Jr., C. Lackman-Smith, Y. F. Hallock and M. R. Boyd, *Antimicrob. Agents Chemother.*, 1995, **39**, 484; (*b*) J. G. Supko and L. Malspeis, *Antimicrob. Agents Chemother.*, 1995, **39**, 9; (*c*) M. Boyd, Y. F. Hallock, J. H. Cardellina II, K. P. Manfredi, J. W. Blunt, J. B. McMahon, R. W. Buckheit, Jr., G. Bringmann, M. Schäffer, G. M. Cragg, D. W. Thomas and J. G. Jato, *J. Med. Chem.*, 1994, **37**, 1740; (*d*) K. P. Manfredi, J. W. Blunt, J. H. Cardellina II, J. B. McMahon, L. L. Pannell, G. M. Cragg and M. R. Boyd, *J. Med. Chem.*, 1991, **34**, 3402.

3 Some recent syntheses: (*a*) T. R. Hoye, M. Chen, B. Hoang, L. Mi and O. P. Priest, *J. Org. Chem.*, 1999, **64**, 7184; (*b*) T. Watanabe and M. Uemura, *Chem. Commun.*, 1998, 871; (*c*) G. Bringmann, R. Götz, P. A. Keller, R. Walter, M. R. Boyd, F. Lang, A. Garcia, J. J. Walsh, I. Tellitu, K. V. Bhaskar and T. R. Kelly, *J. Org. Chem.*, 1998, **63**, 1090; (*d*) P. D. Hobbs, V. Upender and M. I. Dawson, *Synlett*, 1997, 965; (*e*) G. Bringmann, R. Götz, S. Harmsen, J. Holenz and R. Walter, *Liebigs Ann.*, 1996, 2045; (*f*) T. R. Hoye and M. Chen, *J. Org. Chem.*, 1996, **61**, 7940; (*g*) P. Chau, I. R. Czuba, M. A. Rizzacasa, G. Bringmann, K.-P. Gulden and M. Schäffer, *J. Org. Chem.*, 1996, **61**, 7101; (*h*) V. Upender, D. J. Pollart, J. Liu, P. D. Hobbs, C. Olsen, W.-R. Chao, B. Bowden, J. L. Crase, D. W. Thomas, A. Pandey, J. A. Lawson and M. I. Dawson, *J. Heterocycl. Chem.*, 1996, **33**, 1371; (*i*) T. R. Hoye and L. Mi, *Tetrahedron Lett.*, 1996, **37**, 3097; (*j*) P. D. Hobbs, V. Upender, J. Liu, D. J. Pollart, D. W. Thomas and M. I. Dawson, *Chem. Commun.*, 1996, 923; (*k*) A. V. R. Rao, M. K. Gurjar, D. V. Ramana and A. K. Chheda, *Heterocycles*, 1996, **43**, 1; (*l*) T. Watanabe, K. Kamikawa and M. Uemura, *Tetrahedron Lett.*, 1995, **36**, 6695; (*m*) B. N. Leighton and M. A. Rizzacasa, *J. Org. Chem.*, 1995, **60**, 5702 and references therein; (*n*) G. Bringmann, S. Harmsen, J. Holenz, T. Geuder, R. Götz, P. A. Keller, R. Walter, Y. F. Hallock, J. H. Cardellina II and M. R. Boyd, *Tetrahedron*, 1994, **50**, 9643; (*o*) T. R. Kelly, A. Garcia, F. Lang, J. J. Walsh, K. V. Bhaskar, M. R. Boyd, R. Götz, P. A. Keller, R. Walter and G. Bringmann, *Tetrahedron Lett.*, 1994, **35**, 7621; (*p*) G. Bringmann, R. Götz, P. A. Keller, R. Walter, P. Henschel, M. Schäffer, M. Stäblein, T. R. Kelly and M. R. Boyd, *Heterocycles*, 1994, **39**, 503; (*q*) T. R. Hoye, M. Chen, L. Mi and O. P. Priest, *Tetrahedron Lett.*, 1994, **35**, 8747; (*r*) G. Bringmann, R. Weirich, H. Reuscher, J. R. Jansen, L. Kinzinger and T. Ortmann, *Liebigs Ann. Chem.*, 1993, 877.

4 (*a*) T. Kametani, in *The Total Synthesis of Natural Products*, ed. J. ApSimon, John Wiley & Sons, Inc., New York, 1977, Vol. 3, pp. 1–272; (*b*) M. D. Rozwadowska, *Heterocycles*, 1994, **39**, 903.

5 T. R. Hoye and L. Mi, *J. Org. Chem.*, 1997, **62**, 8586.

6 (*a*) General reviews: (i) S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263; (ii) G. Bringmann, R. Walter and R. Weirich, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 977; (*b*) Suzuki coupling reviews: (i) A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178; (ii) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (iii) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 1998, pp. 49–97; (iv) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.

7 Y. F. Hallock, K. P. Manfredi, J. W. Blunt, J. H. Cardellina II, M. Schäffer, K.-P. Gulden, G. Bringmann, A. Y. Lee, J. Clardy, G. François and M. R. Boyd, *J. Org. Chem.*, 1994, **59**, 6349.

8 Announcement in *J. Nat. Prod.*, 1992, **55**, 1018.

9 (*a*) G. Bringmann, M. Wenzel, T. R. Kelly, M. R. Boyd, R. J. Gulakowski and R. Kaminsky, *Tetrahedron*, 1999, **55**, 1731 and references therein; (*b*) H. Zhang, D. E. Zembower and Z. Chen, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2687; (*c*) ref. 3*h*.

10 C. B. de Koning, J. P. Michael and W. A. L. van Otterlo, *Tetrahedron Lett.*, 1999, **40**, 3037.

11 C. F. Carvallio, A. V. Russo and M. V. Sargent, *Aust. J. Chem.*, 1985, **38**, 777.
12 A. H. Sommers, R. J. Michaels, Jr. and A. W. Weston, *J. Am. Chem. Soc.*, 1952, **74**, 5546.
13 R. I. Meltzer and J. Doczi, *J. Am. Chem. Soc.*, 1950, **72**, 4986.
14 (*a*) J. H. Gardner and J. R. Stevens, *J. Am. Chem. Soc.*, 1947, **69**, 3086; (*b*) H. H. Hodgson and H. Clay, *J. Chem. Soc.*, 1932, 869.
15 (*a*) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 1951, 718; (*b*) R. G. F. Giles, S. C. Yorke, I. R. Green and V. I. Hugo, *J. Chem. Soc.*, *Chem. Commun.*, 1984, 554.
16 R. G. F. Giles, I. R. Green, V. I. Hugo and P. R. K. Mitchell, *J. Chem. Soc.*, *Chem. Commun.*, 1983, 51.
17 C. B. de Koning, R. G. F. Giles and I. R. Green, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 2743.
18 2-Bromo-5-isopropoxybenzaldehyde was prepared by bromination of 3-hydroxybenzaldehyde (R. Pschorr, *Justus Liebig's Ann. Chem.*, 1912, **391**, 23) followed by protection of the phenol by reaction with isopropyl bromide and potassium carbonate as also described in refs. 3*e* and 3*p*.
19 E. Brenna, C. Fuganti and S. Serra, *Tetrahedron*, 1998, **54**, 1585.
20 (*a*) K. Smith, *Organometallic Compounds of Boron*, Chapman & Hall, London, New York, 1985, pp. 94 and 118; (*b*) W. König and W. Scharrnbeck, *J. Prakt. Chem.*, 1930, **128**, 153.
21 J. K. Stille, A. M. Echavarren, R. M. Williams, J. A. Hendrix, B. A. Merrill and L. E. Overman, *Org. Synth.*, 1993, **71**, 97.
22 A. M. Gilbert and W. D. Wulff, *J. Am. Chem. Soc.*, 1994, **116**, 7449.
23 (*a*) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 1955, 522; (*b*) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, 1973, **38**, 2314.
24 The results of the single X-ray crystal study confirmed the structure. Empirical formula $C_{17}H_{27}O_7P$; monoclinic; C_2/c; $a = 19.798$, $b = 11.232$, $c = 19.333$ Å. These results will be reported in full elsewhere: L. Cook, C. B. de Koning, J. P. Michael and W. A. L. van Otterlo, manuscript in preparation.
25 W.-W. Sy, *Tetrahedron Lett.*, 1993, **34**, 6223.
26 (*a*) C. Coudret, *Synth. Commun.*, 1996, **26**, 3543 and personal communication; (*b*) M. H. Todd, S. Balasubramanian and C. Abell, *Tetrahedron Lett.*, 1997, **38**, 6781.
27 (*a*) M. Murata, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 1997, **62**, 6458; (*b*) B. Schilling and D. E. Kaufmann, *Eur. J. Org. Chem.*, 1998, 701.
28 T. Watanabe, N. Miyaura and A. Suzuki, *Synlett*, 1992, 207.
29 (*a*) C. Coudret and V. Mazenc, *Tetrahedron Lett.*, 1997, **38**, 5293; (*b*) personal communication, B. H. Lipshutz, University of California, Santa Barbara.
30 T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158.

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