Bidirectional racemic synthesis of the biologically active quinone cardinalin 3

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Readily available 2,2′,6,6′-tetramethoxy-1,1′-biphenyl was transformed in 14 synthetic steps into the natural product cardinalin 3 using a bidirectional approach. One of the key steps was the formation of the *cis*-1,3-dimethylnaphtho[2,3-*c*]pyran ring. (±)-1,1′-[6,6′-Diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-diyl]diethanol was treated with O_2 in the presence of $CuCl_2$ and catalytic $PdCl_2$ to afford 5,5′-bis(benzyloxy)-7,7′,9,9′-tetramethoxy-1,1′,3,3′-tetramethyl-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene. Hydrogenation of this compound afforded 7,7′,9,9′-tetramethoxy-*cis*-1,3-*cis*-1′,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene-5,5′-diol in quantitative yield, which was converted in 3 steps to cardinalin 3.

Introduction

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

While the synthesis of cardinalin 3 has yet to be achieved, there are three previously reported syntheses of ventiloquinone L.[4–6] In principle, the dimerization of ventiloquinone L should provide cardinalin 3, but in our hands this proved to be problematic.[5] Therefore we sought an alternative approach.

The use of bidirectional synthesis has been used to assemble a number of compounds that contain two equal halves.[7a] For instance, a recent example is the synthesis of the central amino acid component of chloptosin **5**, a relatively complex natural product (Fig. 2).[7b] This approach has also been used for the assembly of biaryl naphthalenes.[7c,7d]

In this paper we wish to report on the bidirectional synthesis of cardinalin 3 **3**. The successful synthesis of cardinalin 3 was achieved in 14 steps and in an overall yield of 2.3% starting from readily available 2-iodo-1,3-dimethoxybenzene.

Results and discussion

As a result of our inability to convert ventiloquinone L **4** into cardinalin 3 **3** using oxidative coupling methodology,[5] we reasoned that the biaryl axis could be constructed at an early stage of the synthesis. We postulated that thereafter, using a bidirectional

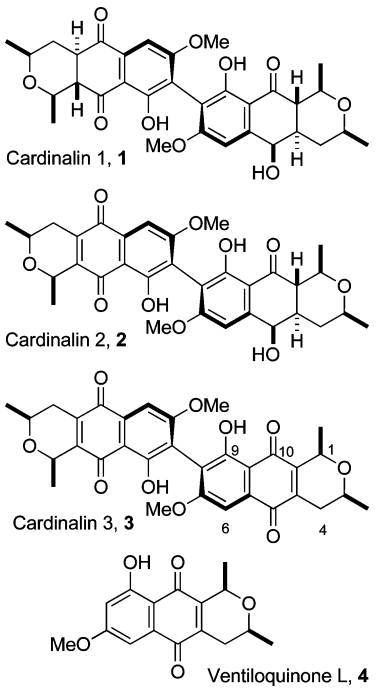

Fig. 1 Cardinalins 1–3 and ventiloquinone L.

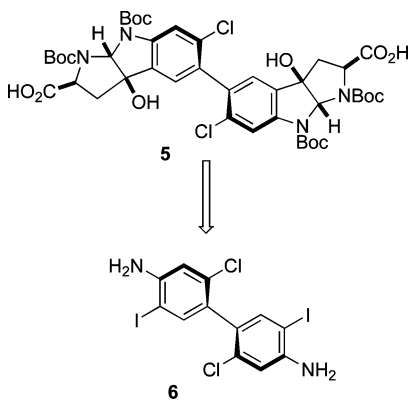

Fig. 2 Bidirectional synthesis of the central amino acid of chloptosin.

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synthetic approach, methodology we had used previously could be used to synthesize cardinalin 3 **3**.

Starting from readily available 2-iodo-1,3-dimethoxybenzene **7**[8] it was found that the highest yielding way to convert this compound into the desired biaryl **8** was using literature Ullmann type chemistry.[9] As shown in Scheme 1, an *in situ* formation of 2-litho-1,3-dimethoxybenzene was readily accomplished and reaction of this with CuI in the presence of **7** yielded the desired product **8** in excellent yield. Hence the desired biaryl bond had now been formed at an early stage of the synthesis.

We now were set to try all the remaining reactions in the synthesis in a bidirectional manner. All attempts using traditional Vilsmeier–Haack conditions to form the bis-aldehyde **9** were either unsuccessful, low yielding, or gave mixtures of the desired product and the mono-formylated product. By contrast, using the conditions developed by Rieche and co-workers[10] the product **9** was formed in excellent yields. We were now in a position to attempt the formation of the second aromatic ring to make the biaryl naphthalene **10**. Therefore **9** was subjected to Stobbe condensation conditions with diethyl succinate. This was followed by an acetic anhydride-mediated ring closure to afford the desired naphthalene **10** in 60% yield over the two steps.

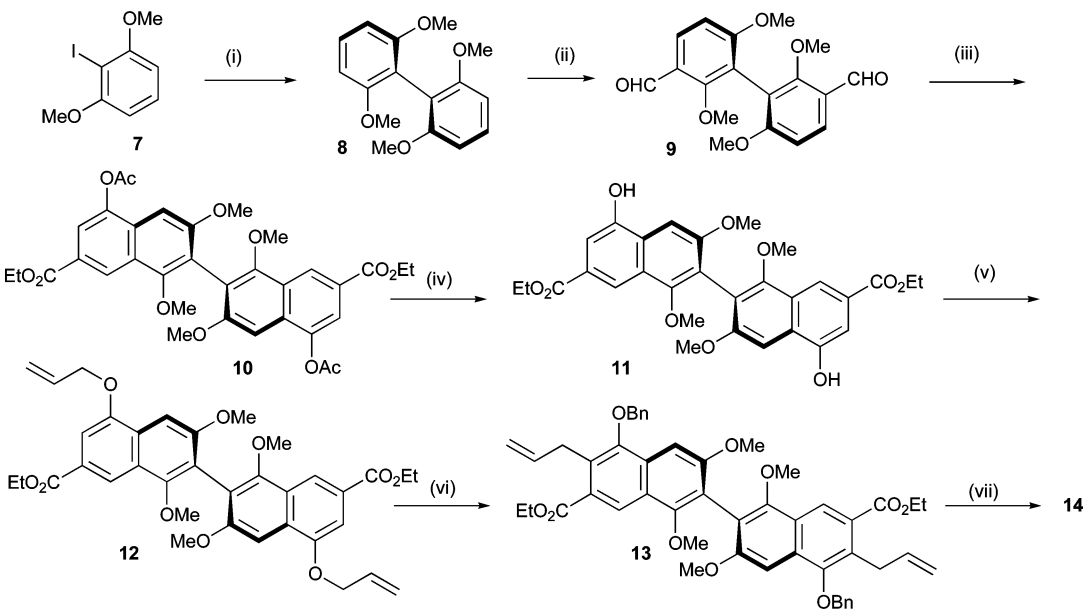
Selective removal of the *O*-acetate of the bis-naphthalene **10** with guanidine gave the desired naphthol **11** in 78% yield without touching the other ester substituent. The naphthol **11** was easily converted into the *O*-allyl bis-naphthalene **12**. Subjecting this compound to microwave[11] conditions for the Claisen rearrangement yielded the required *C*-allyl bis-naphthol, which was *O*-benzylated to afford **13**.

We were now in a position to attempt the use of Wacker-type conditions we have developed for specifically constructing *cis*-1,3-dimethylpyrans.[5] We initially had to convert the ester of the bis-naphthalene **13** into the desired methyl substituted benzyl alcohol **15**. However, what we anticipated to be a trivial reduction of the ester of **13** into the primary benzyl alcohol, proved to be the most problematic step in the entire synthesis! Using a variety of reduction conditions[12] gave mixtures of products resulting from incomplete reduction of both esters. The best yield (42%) was obtained with $LiAlH_4$ as the reagent and using the specific conditions outlined in the Experimental section for the work-up of the reaction. The benzylic alcohol was then oxidized to the aldehyde **14** using PCC (Scheme 1). Attempts to convert **13** into aldehyde **14** directly with DIBAL also met with failure.

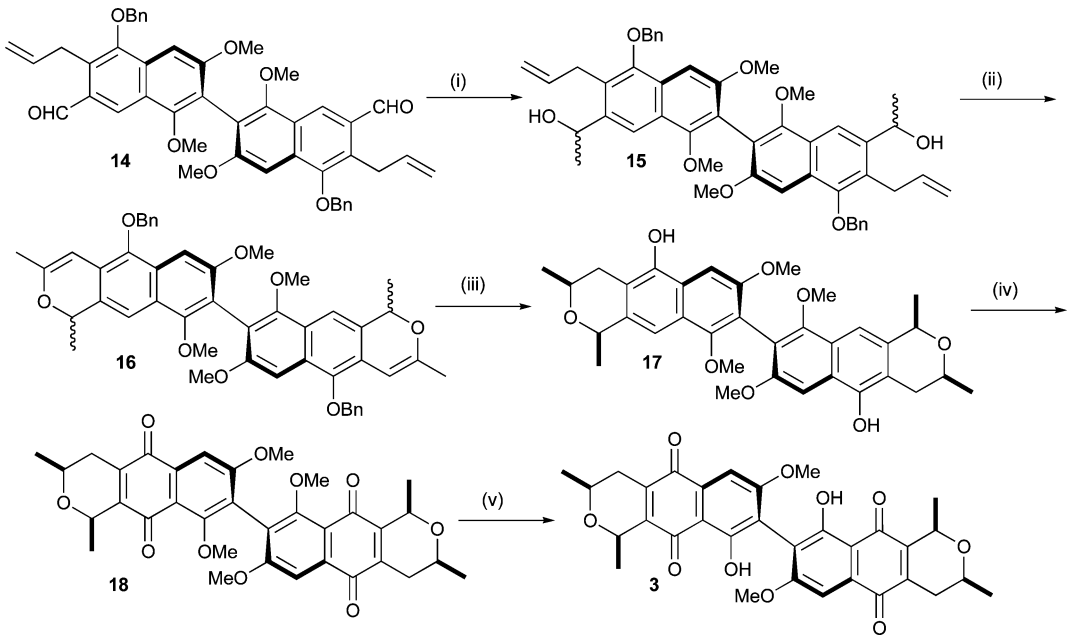
Exposure of aldehyde **14** to MeMgI afforded racemic **15** (Scheme 2). At this point some of the signals in the NMR spectra were doubled as a result of the formation of a mixture of diastereoisomers. For example, one of the methoxy signals now appeared as two singlets at δ 3.63 and 3.62 in the ^{1}H NMR spectrum. Gratifyingly, when **15** was treated with 10% $PdCl_2$ and stoichiometric $CuCl_2$ under an oxygen atmosphere the reaction proceeded in good yield (78%) to afford **16**. Treatment of **16** with 10% Pd/C appeared to exclusively afford the desired *cis*-1,3-dimethylpyran **17** in near quantitative yield. In addition, as planned, the *O*-benzyl protecting group was removed under these conditions.

All that remained in the synthesis was the oxidation of the naphthol into the desired quinone **18** and then the removal of one of the *O*-methyl protecting groups to yield cardinalin 3 **3**. The first step was achieved using salcomine and oxygen to yield **18**. The second step was accomplished using BCl_3 in CH_2Cl_2 at 0 °C to afford the target cardinalin 3 **3**.

The NMR spectral data for **3** were in general agreement with that reported in the literature.[1] As a diastereoisomeric mixture of products was formed, additional peaks for some of the signals in the ^{1}H NMR and ^{13}C NMR spectra were noted. Two doublets were seen at δ 1.58 and 1.57 for the methyl attached to C-1. H-6



Scheme 1 *Reagents and conditions*: (i) (a) 1,3-dimethoxybenzene, *n*-BuLi, THF, 0 °C, 1 h, (b) CuI, **7**, pyridine, reflux, 72 h, 93%; (ii) $MeOCHCl_2$, CH_2Cl_2, $TiCl_4$, 0 °C, 95%; (iii) (a) diethyl succinate, *t*-BuOH, KOBu^t, reflux, 2 h, (b) Ac_2O, NaOAc, 140 °C, 60%; (iv) guanidine·HCl, KOBu^t EtOH–CH_2Cl_2, rt, 1.5 h, 78%; (v) allyl bromide, K_2CO_3, Me_2CO, reflux, 18 h, 84%; (vi) (a) DMF, microwave (200 W), 170 °C, 250 psi, 25 min, 98%, (b) BnCl, KI, K_2CO_3, Me_2CO, 18 h, 90%; (vii) (a) $LiAlH_4$, THF, 0 °C, 18 h, 42%, (b) PCC–Al_2O_3, CH_2Cl_2, rt, 8 h, 90%.



Scheme 2 *Reagents and conditions*: (i) MeMgI–Et_2O–THF, rt, 18 h, 79%; (ii) 10% $PdCl_2$, $CuCl_2{\cdot}H_2O$–DMF, rt, O_2, 18 h, 78%; (iii) 10% Pd/C, H_2, CH_2Cl_2–dioxane, rt, 48 h, *cis*-100%; (iv) 1.1 equiv. salcomine, DMF, O_2, rt, 18 h, 51%; (v) BCl_3, CH_2Cl_2, 15 min, 0 °C, 64%.

also appeared as two singlets, both very close to δ 7.33 (δ 7.331 and 7.329). In the expanded ^{1}H NMR spectrum of **3** a small complex multiplet between δ 3.96–4.04 for H-3 and H-3′ was observed. This is diagnostic for *trans*-1,3-dimethylbenzopyrans[13] and therefore it is believed that a small amount (<5%) of this had also formed. As there were only trace amounts of the possible *trans*-product, its identity could not be confirmed. The melting point of **3** was also different to the value of 213–220 °C described in the literature.[1] We observed darkening of the crystals taking place above 145 °C and melting only took place between 236 and 241 °C.

In conclusion, the first synthesis of racemic cardinalin 3 has been achieved. Presently we are developing methodology for the construction of the 1,3-dimethylbenzopyran system in a stereoselective manner that could be applied to the asymmetric synthesis of cardinalin 3.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded either on a 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 in Köln. The EIMS low resolution spectra were measured on a Finnigan INCOS 50 single quadrupole MS-instrument. The samples were introduced *via* a direct inlet probe and ionized with electrons at 70 eV energy. The samples were dissolved in CH_2Cl_2 to give solutions of 1.0 mg ml^{-1} and aliquots of these analyte solutions were vaporized in respective crucibles. Approximately 1 µg of the dried compound of interest was finally introduced to the ion source, thermally transferred to the gas phase and analyzed by ESMS with unit resolution of the single quadrupole analyzer. The exact mass measurements by electrospray-MS were conducted on a Finnigan MAT 900 MS instrument with EBqQ configuration equipped with an electrospray ion source. The analyte solutions (CH_2Cl_2 1.0 mg ml^{-1}) were diluted with methanol to concentrations of 10^{-4}–10^{-6} mol l^{-1}. The exact mass measurement of the molecular ions (specified on the result form: mostly sodiated molecular ion species $[M + Na]^+$) experiments were conducted by peak matching with adequate internal reference ions (respective polypropyleneglycol PPG reference ions reported on the result forms). The solution of PPG was added to the analyte solution prior to the ESMS measurement (flow rate: 3 µl min^{-1}, electrospray voltage: 3.7 kV, temperature of the heated capillary: 230 °C). The resolution was at least 9000 (resolution: 10% valley definition). The error of the exact ion mass measurements was always smaller than 5 ppm (relative) respectively smaller than 0.002u (absolute). The measurements were repeated 100 times and the respective mean results reported. Microwave reactions were performed in a CEM Discover microwave. 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. Removal or concentration of solvent *in vacuo* implies the evaporation of solvent at 20–25 Torr utilising a rotary evaporator.

2-Iodo-1,3-dimethoxybenzene 7

Into a flame dried RB flask fitted with a dropping funnel was placed dry THF (50 ml), followed by 1,3-dimethoxybenzene (4.74 ml, 5.00 g, 36.2 mmol). The solution was cooled down to 0 °C. Once cooled, the *n*-BuLi (1.4 M in hexane, 28.4 ml, 39.8 mmol) was slowly added using a dropping funnel. The solution was stirred at 0 °C for 1 h. The dropping funnel was

then charged with a solution of I_2 (10.1 g, 39.8 mmol) in THF (70 ml). This solution was then added dropwise to the milky white reaction mixture. The end point of the reaction was observed by the appearance of the light brown halogen colour. The resulting solution was stirred for an additional 1 h at rt. Water was then added to the product mixture and the product extracted with CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was recrystallized from CH_2Cl_2–EtOH to give large white crystals of 2-iodo-1,3-dimethoxybenzene **7** (8.84 g, 93%). Mp = 105–106 °C (CH_2Cl_2–EtOH) (lit.[14] 102–103 °C); IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1587 and 1470 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.26 (1H, t, J = 8.3, H-5), 6.50 (2H, d, J = 8.3, H-4 and H-6) and 3.89 (6H, s, 2 × OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 158.4 (C-1 and C-3), 128.7 (C-5), 112.6 (C-2) 104.5 (C-4 and C-6) and 56.1 (2 × OMe); HRMS: Found M^+, 263.9654. $C_8H_9IO_2$ requires M 263.9647; m/z (EI) 264 (M^+, 100%), 249 (6), 221 (18), 206 (7), 122 (8), 107 (37), 92 (9), 77 (10) and 51 (8).

2,2′,6,6′-Tetramethoxy-1,1′-biphenyl 8

Into a flame dried RB flask fitted with a dropping funnel was placed dry THF (50 ml), followed by 1,3-dimethoxybenzene (3.47 ml, 3.66 g, 26.5 mmol). The solution was cooled down to 0 °C. Once cooled, *n*-butyllithium (1.6 M in hexane, 16.6 ml, 26.5 mmol) was slowly added using the dropping funnel. The solution was stirred at 0 °C for 1 h. Copper(I) iodide (5.05 g, 26.5 mmol), first purified by Soxhlet extraction using THF and then dried overnight in an oven at 110 °C, was added in portions, and the mixture was stirred at rt for another 2 h. The dropping funnel was then charged with a solution of 2-iodo-1,3-dimethoxybenzene **7** (6.36 g, 24.0 mmol) in dry pyridine (50 ml). Once added, the dropping funnel was replaced with a condenser, and the mixture was heated under reflux for 72 h. The product mixture was then poured onto ice and acidified with concentrated aqueous HCl (*ca.* 25 ml). The product was then extracted with CH_2Cl_2 (3 × 80 ml). The organic extracts were then combined, dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The crude product was recrystallized from CH_2Cl_2–EtOH to give 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **8** (6.12 g, 93%). Mp = 175–177 °C (CH_2Cl_2–EtOH) (lit.[15] 174–175 °C); IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1587 and 1451 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.28 (2H, t, J = 8.3, 4- and 4′-H), 6.65 (4H, d, J = 8.3, 3-H, 3′-H, 5-H and 5′-H) and 3.71 (12H, s, 4 × OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 158.4 (2-C, 2′-C, 6-C and 6′-C), 128.7 (4-C and 4′-C), 112.5 (1-C and 1′-C), 104.4 (3-C, 3′-C, 5-C and 5′-C) and 56.1 (4 × OMe); HRMS: Found M^+, 274.1198. $C_{16}H_{18}O_4$ requires M 274.1205; m/z (EI) 274 (M^+, 100%), 243 (7), 228 (11), 155 (5), 151 (52), 115 (18) and 91 (17).

2,2′,6,6′-Tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde 9

Into a two neck RB flask under argon, fitted with a rubber septum, was added 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **8** (0.70 g, 2.55 mmol) in dry CH_2Cl_2 (50 ml). To this solution was added $TiCl_4$ (1.12 ml, 1.93 g, 10.2 mmol) using a syringe. The solution immediately changed to an orange colour. The reaction mixture was then cooled down to −78 °C and dichloromethyl methyl ether (0.64 ml, 0.82 g, 7.1 mmol) was then added. The solution changed to a dark brown colour. Stirring at this temperature was continued for 30 min. The resulting solution was then warmed up to 0 °C over 1 h and stirred at this temperature for an additional 15 min. The product mixture was then poured into a separating funnel containing crushed ice (*ca.* 10 g) and aqueous conc. HCl (*ca.* 8 ml) and shaken vigorously. The pink–purple organic layer was then separated, washed with water (*ca.* 50 ml) and brine (*ca.* 50 ml). It was then dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (40% EtOAc–hexane) to give 2,2′,6,6′-tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde **9** as a white solid (0.80 g, 95%). Mp = 147–149 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1677 (ArC=O), 1586 and 1463 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 10.17 (2H, s, 2 × CHO), 7.91 (2H, d, J = 8.8, 4- and 4′-H), 6.83 (2H, d, J = 8.8, 5- and 5′-H), 3.76 (6H, s, 2 × OMe) and 3.52 (6H, s, 2 × OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 188.8 (2 × CHO), 163.5 (2- and 2′-C), 162.7 (6- and 6′-C), 130.6 (4- and 4′-C), 123.1 (3- and 3′-C), 116.4 (1- and 1′-C), 107.1 (5- and 5′-C), 63.0 (2 × OMe) and 56.1 (2 × OMe); HRMS: Found M^+, 330.1093. $C_{18}H_{18}O_6$ requires M 330.1103; m/z (EI) 330 (M^+, 79%), 299 (100), 283 (16), 255 (28), 239 (66), 219 (17), 179 (28), 155 (10), 142 (9), 115 (10), 91 (5), 69 (19) and 51 (5).

Diethyl 5,5′-diacetoxy-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate 10

In a two neck RB flask, fitted with a condenser, under Ar, dicarbaldehyde **9** (1.53 g, 4.63 mmol) and diethyl succinate (2.31 ml, 2.42 g, 13.9 mmol) were dissolved in dry *tert*-butyl alcohol (20 ml). To this mixture was slowly added KOBu^t (1.56 g, 13.9 mmol). The resulting solution was heated under reflux for 2 h and then allowed to cool down to rt, poured into a separating funnel containing ice and acidified to pH 3 with aqueous conc. HCl. The product was then extracted with EtOAc (3 × 50 ml). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo*. The resultant oil was not purified or characterized, but used immediately in the next step.

Into a two neck RB flask, fitted with a condenser, under Ar, the Stobbe condensation product from above was dissolved in acetic anhydride (80 ml). To this was added anhydrous NaOAc (1.89 g, 23.2 mmol). The mixture was heated at 140 °C for 2 h and then allowed to cool. The acetic anhydride was removed *in vacuo*, water (*ca.* 100 ml) was added, and the product extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (30% EtOAc–hexane) to yield the product **10** as a bright yellow solid (1.78 g, 60% over two steps). Mp = 268–272 °C (with sweating starting at 258 °C); IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1770, 1716, (C=O), 1627 (ArC=C), 1498 and 1459; ^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.77 (2H, s, 8- and 8′-H), 7.87 (2H, s, 6- and 6′-H), 7.01 (2H, s, 4- and 4′-H), 4.43 (4H, q, J = 7.1, 2 × CH_2CH_3), 3.84 (6H, s, 2 × OMe), 3.64 (6H, s, 2 × OMe), 2.51 (6H, s, 2 × OAc) and 1.42 (6H, t, J = 7.1, 2 × CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 169.4 (2 × OAc), 166.2 (2 × CO_2Et), 159.2 (2 × ArC), 156.5 (2 × ArC), 145.7 (2 × ArC), 130.9 (2 × ArC), 125.2 (2 × ArC), 124.7 (2 × ArC), 123.9 (8- and 8′-C), 118.9 (6- and 6′-C), 117.8 (2 × ArC), 94.9 (4- and 4′-C), 61.9 (2 × OMe), 61.1 (2 × CH_2CH_3), 55.8 (2 × OMe), 21.0 (2 × OAc) and 14.4 (2 × CH_2CH_3); HRMS:

Found M+, 634.2038. $C_{34}H_{34}O_{12}$ requires *M* 634.2050; *m/z* (EI) 634 (M+, 2%), 512 (32), 470 (27), 428 (73), 382 (5), 54 (26) and 43 (18).

Diethyl 5,5′-dihydroxy-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate 11

To a solution of guanidine hydrochloride (0.934 g, 9.78 mmol) in dry EtOH (70 ml), stirring at room temperature under Ar was added KOBu′ (1.10 g, 9.78 mmol) and the resulting suspension stirred for 30 min. To this mixture was added the ester **10** (2.8 g, 4.44 mmol) dissolved in CH_2Cl_2 (70 ml) and stirring was continued for 1.5 h. The reaction mixture was then poured into a beaker containing water (100 ml) and acidified to pH 4 with conc. HCl. The solution was then extracted with EtOAc (3 × 100 ml). The organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (40% EtOAc–hexane) to yield a yellow solid **11** (1.89 g, 78%). Mp = 283–288 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3413 (OH) and 1640 (ArC=O); ^{1}H NMR (300 MHz, DMSO): δ_H = 10.51 (2H, s, 2 × OH), 8.15 (2H, br s, 8- and 8′-H), 7.45 (2H, d, *J* = 1.3, 6- and 6′-H), 7.42 (2H, s, 4- and 4′-H), 4.35 (4H, q, *J* = 6.9, 2 × CH_2CH_3). 3.81 (6H, s, 2 × OMe), 3.57 (6H, s, 2 × OMe) and 1.35 (6H, t, *J* = 7.0, 2 × CH_2CH_3); ^{13}C NMR (75 MHz, DMSO) δ_C = 166.0 (2 × CO_2Et), 157.5 (2 × ArC), 155.2 (2 × ArC), 152.7 (2 × ArC), 128.4 (2 × ArC), 125.1 (2 × ArC), 123.4 (2 × ArC), 117.6 (2 × ArC), 115.5 (2 × ArC), 107.4 (2 × ArC), 96.2 (4- and 4′-C), 61.1 (2 × OMe), 60.5 (2 × CH_2CH_3), 55.7 (2 × OMe), 14.2 (2 × CH_2CH_3); HRMS (ESI): Found [M + Na]+, 573.174. $C_{30}H_{30}O_{10}Na$ requires *M* 573.1736; *m/z* (EI) 551 (M+ + 1, 32%), 550 (M+, 100), 505 (13), 504 (18), 275 (30) and 216 (28).

Diethyl 5,5′-bis(allyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate 12

Allyl bromide (0.96 ml, 1.34 g, 11.1 mmol) and K_2CO_3 (1.53 g, 11.1 mmol) were added to a solution of the di-naphthol **11** (2.03 g, 3.69 mmol) in acetone (100 ml), stirring in a RB flask fitted with a condenser. The mixture was stirred under reflux for 18 h. After this time it was then allowed to cool to rt and filtered through Celite. The acetone was then removed *in vacuo* and the light brown oil was purified using silica gel column chromatography (30% EtOAc–hexane) to yield the diallylated product **12** as a light yellow solid (1.95 g, 84%). Mp = 74–78 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1713 (ArC=O), 1622, 1495 and 1461 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.51 (2H, br s, 8- and 8′-H), 7.54 (2H, s, 4- and 4′-H), 7.48 (2H, d, *J* = 1.1, 6- and 6′-H), 6.23 (4H, ddd, *J* = 17.3, 10.5, 5.2, 2 × $CH_2CH{=}CH_2$), 5.57 (2H, dd, *J* = 17.3 and 1.5, *trans*-$CH_2CH{=}CH_2$), 5.38 (2H, dd, *J* = 10.5 and 1.3, 2 × *cis*-$CH_2CH{=}CH_2$), 4.84 (4H, br d, *J* = 5.2, 2 × $CH_2CH{=}CH_2$), 4.50–4.37 (4H, m, 2 × CH_2CH_3), 3.88 (6H, s, 2 × OMe), 3.64 (6H, s, 2 × OMe) and 1.43 (6H, t, *J* = 7.1, 2 × CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 167.1 (2 × CO_2Et), 158.4 (2 × ArC), 156.1 (2 × ArC), 153.5 (2 × ArC), 133.2 (2 × $CH_2CH{=}CH_2$), 129.7 (2 × ArC), 125.3 (2 × ArC), 124.0 (2 × ArC), 118.8 (8- and 8′-C), 117.8 (2 × ArC), 117.6 (2 × $CH_2CH{=}CH_2$), 105.2 (6- and 6′-C), 96.2 (4- and 4′-C), 69.3 (2 × $CH_2CH{=}CH_2$), 61.7 (2 × OMe), 60.9 (2 × CH_2CH_3), 55.9 (2 × OMe) and 14.4 (2 × CH_2CH_3); HRMS (ESI): Found [M + Na]+, 653.236. $C_{36}H_{38}O_{10}Na$ requires *M* 653.2363; *m/z* (EI) 631 (M+ + 1, 22%), 630 (M+, 54), 590 (40), 589 (100), 561 (20), 548 (41), 315 (22) and 295 (26).

Diethyl 6,6′-diallyl-5,5′-dihydroxy-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate

The allylated phenol **12** (1.92 g, 3.04 mmol) was dissolved in DMF (3.0 ml) and the solution transferred to a microwave vessel. The reaction mixture was then subjected to microwave radiation at a temperature of 170 °C and pressure of 250 psi with 200 W of power for a period of 25 min with stirring. The light yellow solution changed to a dark brown colour. This was transferred to a separating funnel and washed with water (100 ml) and the organic product extracted with CH_2Cl_2 (2 × 20 ml). The extracts were dried over anhydrous $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The dark brown viscous oil was purified by column chromatography (40% EtOAc–hexane) to yield a yellow foam (1.89 g, 98%) of diethyl 6,6′-diallyl-5,5′-dihydroxy-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate. Mp = 93–98 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3420 (OH), 1713 (ArC=O) and 1461 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.36 (2H, s, 8 and 8′-H), 7.41 (2H, s, 4 and 4′-H), 6.25–6.07 (2H, m, 2 × $CH_2CH{=}CH_2$), 5.84 (2H, s, 2 × OH), 5.30–5.22 (4H, m, 2 × $CH_2CH{=}CH_2$), 4.45–4.34 (4H, m, 2 × CH_2CH_3), 3.96 (2H, br d, *J* = 5.2, 2 × $CH_2CH{=}CH_2$), 3.86 (6H, s, 2 × OMe), 3.62 (6H, s, 2 × OMe) and 1.41 (6H, t, *J* = 7.1, 2 × CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 168.2 (2 × CO_2Et), 158.4 (2 × ArC), 155.7 (2 × ArC), 150.1 (2 × ArC), 136.4 (2 × $CH_2CH{=}CH_2$), 128.1 (2 × ArC), 126.4 (2 × ArC), 122.6 (2 × ArC), 119.2 (C-8 and C-8′), 118.3 (2 × ArC), 117.4 (2 × ArC), 116.2 (2 × $CH_2CH{=}CH_2$), 95.6 (C-4 and C-4′), 61.6 (2 × CH_2CH_3), 60.9 (2 × OMe), 55.8 (2 × OMe), 31.8 (2 × $CH_2CH{=}CH_2$) and 14.3 (2 × CH_2CH_3); HRMS (ESI): Found [M + Na]+, 653.235. $C_{36}H_{38}O_{10}Na$ requires *M* 653.2363; *m/z* (EI) 631 (M+ + 1, 32%), 630 (M+, 100), 585 (8), 584 (10), 315 (17), 255 (30), 87 (62) and 55 (75).

Diethyl 6,6′-diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate 13

In a two neck RB flask fitted with a condenser was placed a solution of diethyl 6,6′-diallyl-5,5′-dihydroxy-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarboxylate (1.10 g, 1.75 mmol) in acetone (70 ml). To this yellow solution was added benzyl chloride (0.40 ml, 0.46 g, 3.7 mmol), K_2CO_3 (0.51 g, 3.7 mmol) and KI (0.61 g, 3.7 mmol). The mixture was stirred under reflux for 18 h. After cooling to rt, the mixture was filtered through Celite and the filtrate concentrated on a rotary evaporator. The resultant oil was purified by silica gel column chromatography (10% EtOAc–hexane) to give the product **13** as a yellow foam (1.28 g, 90%). Mp = 55–57 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1736 (ArC=O) and 1456 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.52 (2H, s, 8 and 8′-H), 7.60–7.58 (4H, m, 4 × ArH), 7.47–7.34 (8H, m, 6 × ArH and 4 and 4′-H), 6.18–6.03 (2H, m, 2 × $CH_2CH{=}CH_2$), 5.12–4.91 (8H, m, 2 × $CH_2CH{=}CH_2$ and 2 × CH_2Ph), 4.39 (4H, q, *J* = 6.3, 2 × CH_2CH_3), 4.07 (4H, br d, *J* = 5.6, 2 × $CH_2CH{=}CH_2$), 3.72 (6H, s, 2 × OMe), 3.62 (6H, s, 2 × OMe) and 1.41 (6H, t, *J* = 7.1, 2 × CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 168.0 (2 × CO_2Et), 158.8 (2 × ArC), 156.2 (2 × ArC), 152.7 (2 × ArC),

137.9 ($CH_2CH=CH_2$), 137.6 (2 × ArC), 131.7 (2 × ArC), 129.4 (2 × ArC), 128.7 (4 × ArCH), 128.1 (2 × ArCH), 127.6 (4 × ArCH), 127.0 (2 × ArC), 123.0 (2 × ArC), 122.9 (2 × ArC), 117.0 (8 and 8′-C), 115.0 (2 × $CH_2CH=CH_2$), 96.2 (4 and 4′-C), 76.1 (2 × CH_2Ph), 61.7 (2 × CH_2CH_3), 60.9 (2 × OMe), 55.7 (2 × OMe), 31.0 (2 × $CH_2CH=CH_2$) and 14.3 (2 × CH_2CH_3); HRMS (ESI): Found $[M + H]^+$, 811.347. $C_{51}H_{50}O_{10}$ requires *M* 811.3481; *m/z* (EI) 810 (M^+, 3%), 721 (2), 720 (5), 719 (13), 555 (4), 92 (5), 91 (100) and 65 (6).

1,1′-[6,6′-Diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-diyl]dimethanol

The ester **13** (0.70 g, 0.86 mmol) dissolved in dry THF (150 ml) was placed into a flame-dried two neck RB flask under Ar. The solution was cooled to 0 °C by means of an ice bath and once cooled, $LiAlH_4$ (0.13 g, 3.5 mmol) was added portion-wise resulting in effervescence of the solution. The reaction mixture was analyzed by TLC at 1 h intervals for the first few hours and still showed starting material present. It was left to proceed at rt overnight. After 18 h the TLC revealed that the reaction was still not complete. However the reaction mixture was cooled down to 0 °C and water added drop-wise (approx. 10 ml) until the evolution of gas had stopped. The emulsion formed was broken by adding a 10% solution of HCl (aq.) (*ca.* 5 ml). The mixture was transferred to a separating funnel and the product was extracted using EtOAc (2 × 25 ml) and CH_2Cl_2 (2 × 25 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered through Celite and the solvent finally removed *in vacuo*. The crude oil was purified by silica gel column chromatography (50% EtOAc–hexane) to give 1,1′-[6,6′-diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-diyl]dimethanol (0.264 g, 42%); Mp = 86–91 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3417 (OH), 1600, 1496 and 1455 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.96 (2H, s, 8 and 8′-H), 7.60–7.56 (4H, m, 4 × ArH), 7.47–7.30 (6H, m, 6 × ArH), 7.26 (1H, s, 4 and 4′-H), 6.20–6.08 (2H, m, 2 × $CH_2CH=CH_2$), 5.14–4.99 (4H, m, 2 × $CH_2CH=CH_2$), 5.10 (4H, s, 2 × CH_2Ph), 4.84 (4H, s, 2 × CH_2OH), 3.83–3.69 (4H, br m, 2 × $CH_2CH=CH_2$), 3.70 (6H, s, 2 × OMe), 3.61 (6H, s, 2 × OMe) and 1.84 (1H, s, 2 × OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 157.2 (2 × ArC), 155.4 (2 × ArC), 152.6 (2 × ArC), 137.8 (2 × ArC), 137.7 (2 × $CH_2CH=CH_2$), 135.7 (2 × ArC), 129.4 (2 × ArC), 128.6 (4 × ArCH), 128.0 (2 × ArCH), 127.5 (4 × ArCH), 124.0 (2 × ArC), 118.7 (2 × $CH_2CH=CH_2$), 117.0 (2 × ArC), 115.5 (8 and 8′-C), 96.3 (4 and 4′-C), 76.0 (2 × CH_2Ph), 64.1 (2 × CH_2OH), 61.4 (2 × OMe) and 55.6 (2 × OMe) and 30.4 (2 × $CH_2CH=CH_2$); HRMS (ESI): Found $[M + H]^+$, 727.327. $C_{46}H_{47}O_8$ requires *M* 727.3271; *m/z* (EI) 726 (M^+, 2%), 637 (2), 636 (7), 635 (15), 92 (10), 91 (100) and 65 (12).

6,6′-Diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-dicarbaldehyde 14

Pyridinium chlorochromate (0.81 g, 3.7 mmol) was dissolved in MeCN (20 ml) and dried onto neutral alumina (8 g) using a rotary evaporator. This bright orange solid was then added to a solution of 1,1′-[6,6′-diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-diyl]dimethanol (0.68 g, 0.94 mmol) dissolved in CH_2Cl_2 (50 ml). The now dark reaction mixture was allowed to stir at rt for 18 h. This was followed by filtration of the mixture through Celite and concentration of the filtrate on a rotary evaporator. The crude oil was purified by silica gel column chromatography (20% EtOAc–hexane) to yield the aldehyde **14** (0.61 g, 90%). Mp = 67–71 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1691 (C=O), 1614 and 1455 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 10.24 (2H, s, 2 × CHO), 8.47 (2H, s, 8 and 8′-H), 7.60–7.57 (4H, m, 4 × ArH), 7.48–7.39 (6H, m, 6 × ArH), 7.28 (2H, s, 4 and 4′-H), 6.24–6.11 (2H, m, 2 × $CH_2CH=CH_2$), 5.15–4.98 (4H, m, 2 × $CH_2CH=CH_2$), 5.11 (4H, s, 2 × CH_2Ph), 4.12 (4H, br d, *J* = 5.5, 2 × $CH_2CH=CH_2$), 3.73 (6H, s, 2 × OMe) and 3.66 (6H, s, 2 × OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 192.4 (2 × CHO), 159.8 (2 × ArC), 156.8 (2 × ArC), 152.9 (2 × ArC), 137.6 (2 × C), 137.4 (2 × C), 133.1 (2 × C), 131.0 (2 × C), 129.2 (2 × ArCH), 128.7 (4 × ArCH), 128.2 (2 × ArCH), 127.6 (4 × ArCH), 123.3 (2 × C), 117.0 (2 × C), 115.7 (8 and 8′-C), 96.6 (4 and 4′-C), 76.3 (2 × CH_2Ph), 61.9 (2 × OMe), 55.8 (2 × OMe) and 29.7 (2 × $CH_2CH=CH_2$), one carbon not observed; HRMS (ESI): Found $[M + H]^+$, 723.295. $C_{46}H_{43}O_8$ requires *M* 723.2958; *m/z* (EI) 722 (M^+, 2%), 633 (4), 632 (10), 631 (22), 92 (7), 91 (100) and 65 (12).

1,1′-[6,6′-Diallyl-5,5′-bis(benzyloxy)-1,1′,3,3′-tetramethoxy-2,2′-binaphthalene-7,7′-diyl]diethanol 15

Into a flame-dried two neck RB flask fitted with a condenser, under Ar was placed oven dried Mg turnings (0.034 g, 1.4 mmol) and dry Et_2O (10 ml). To this suspension was added MeI (0.082 ml, 0.19 g, 1.3 mmol). The reaction mixture immediately became cloudy. It was slowly stirred to allow the formation of the Grignard reagent. Once most of the Mg metal had reacted, the aldehyde **14** (0.32 g, 0.44 mmol) dissolved in dry THF (10 ml) was added dropwise to the cloudy reaction mixture. The now yellow solution was allowed to stir at rt under Ar for a further 18 h. At this point it had become milky orange in colour. Water (~5 ml) was carefully added to the reaction to quench the excess Grignard reagent. The mixture was then transferred to a separating funnel and the organic product extracted with EtOAc (3 × 50 ml) and CH_2Cl_2 (3 × 50 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$ and filtered through Celite. The solvent was removed *in vacuo* and the yellow oily residue was purified by silica gel column chromatography (30% EtOAc–hexane) to give the secondary alcohol **15** (0.26 g, 79%). Mp = 85–90 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3415 (OH), 1627, 1596, 1496 and 1455 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.14 (2H, s, 8 and 8′-H), 7.60–7.24 (10H, m, 2 × Ph), 7.25 (2H, s, 4 and 4′-H), 6.22–6.09 (2H, m, 2 × $CH_2CH=CH_2$), 5.25 (2H, q, *J* = 6.2, 2 × $CH_3(CH)OH$), 5.12–4.97 (4H, m, 2 × $CH_2CH=CH_2$), 5.10 (4H, s, 2 × CH_2Ph), 3.92–3.79 (2H, m, 2 × $CH_2CH=CH_2$), 3.71 (6H, s, 2 × OMe), 3.62 (6H, s, 2 × OMe), 1.88 (1H, s, 2 × OH) and 1.60 (6H, d, *J* = 6.2, 2 × *Me*(CH)OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 157.1 (2 × ArC), 155.4 (2 × ArC), 152.3 (2 × ArC), 140.6 (2 × ArC), 137.9 (2 × C), 137.8 (2 × C), 137.8 (2 × C), 128.9 (2 × C), 128.6 (4 × ArCH), 128.0 (2 × ArCH), 127.5 (4 × ArCH), 127.1 (2 × C), 124.2 (2 × C), 117.0 (2 × C), 115.5 (8 and 8′-C), 96.1 (4 and 4′-C), 75.9 (2 × CH_2Ph), 66.7 (2 × Me(*C*H)OH), 61.4 (2 × OMe), 55.6 (2 × OMe), 30.2 (2 × $CH_2CH=CH_2$) and 24.5 (2 × *Me*(CH)OH); HRMS (ESI): Found $[M + Na]^+$, 777.340. $C_{48}H_{50}O_8Na$ requires

M 777.3403; *m/z* (EI) 754 (M^+, 1%), 665 (2), 664 (6), 663 (11), 92 (8), 91 (100) and 65 (10).

5,5′-Bis(benzyloxy)-7,7′,9,9′-tetramethoxy-1,1′,3,3′-tetramethyl-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene 16

To a solution of the secondary alcohol **15** (0.06 g, 0.08 mmol) in DMF (5 ml), stirred at rt under O_2 (g) (balloon) in a two neck RB flask, was added $CuCl_2{\cdot}2H_2O$ (0.014 g, 0.08 mmol) and $PdCl_2$ (0.0014 g, 0.0081 mmol, 10 mol%) in water (5 ml). The resultant suspension slowly changed from light yellow to dark orange in colour and was left to stir at rt for 18 h. Work-up of the reaction was accomplished by adding a 10% solution of HCl (aq.) (10 ml) and the mixture was transferred to a separating funnel. The organic product was extracted with EtOAc (3 × 30 ml) and CH_2Cl_2 (30 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The crude yellow residue was purified by silica gel column chromatography (30% EtOAc–hexane) to yield the benzoisochromene **16** (0.048 g, 78%). Mp = 87–90 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1599, 1496 and 1455 (C=C);^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.60–7.57 and 7.46–7.35 (12H, m, overlapping signals 6 and 6′-H and 2 × Ph), 7.21 (2H, s, 10 and 10′-H), 6.05 (2H, s, 4 and 4′-H), 5.36–5.28 (2H, m, 1 and 1′-H), 5.11 (2H, d, *J* = 11.8, 2 × one of C*H*$_2$Ph), 5.06 (2H, d, *J* = 11.8, 2 × one of C*H*$_2$Ph), 3.71 (6H, s, 2 × OMe), 3.56 and 3.54 (6H, 2 × s, 2 × OMe), 2.00 (6H, s, 3 and 3′-Me), 1.70 (6H, d, *J* = 6.5, 1 and 1′-Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 157.1 (2 × C), 155.4 and 154.6 (2 × C), 154.4 (2 × C), 145.7 (2 × C), 137.9 (2 × C), 130.0 (2 × C), 129.5 (2 × C), 128.6 (4 × ArCH), 128.0 (2 × ArCH), 127.9 (2 × ArCH) and 127.8 (4 × ArCH), 123.4 (2 × C), 121.6 and 121.5 (2 × C), 116.1 and 116.0 (2 × C), 113.2 and 113.1 (C-10 and C-10′), 96.1 (C-6 and C-6′), 95.9 and 95.8 (C-4 and C-4′), 75.7 (C-5 and C-5′), 74.3 and 74.3 (C-1 and C-1′), 61.3 and 61.2 (2 × OMe), 55.7 (2 × OMe), 20.5 (1-Me and 1′-Me), 20.0 (3-Me and 3′-Me), some assignments were confirmed using C–H correlation spectra; HRMS (ESI): Found [M + Na]$^+$, 773.309. $C_{48}H_{46}O_8Na$ requires *M* 773.3090; *m/z* (EI) 750 (M^+, 2%), 661 (5), 660 (13), 659 (22), 571 (3), 570 (9), 569 (10), 285 (7), 289 (18), 92 (14), 91 (100) and 65 (19).

7,7′,9,9′-Tetramethoxy-*cis*-1,3-*cis*-1′,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene-5,5′-diol (mixture of diastereomers) 17

To a solution of the benzoisochromene **16** (0.16 g, 0.021 mmol) in a 3 : 1 CH_2Cl_2–dioxane mixture (40 ml), stirred at rt under H_2 (g) (balloon) was added 10% w/w palladium on charcoal (0.016 g) and stirring was continued for 18 h. The reaction mixture was then filtered through Celite, the filtrate concentrated on a rotary evaporator and the resultant yellow oil purified by column chromatography (40% EtOAc–hexane) to give the unprotected benzoisochromane **17** (0.12 g, 100%) as a flaky off white solid. Mp = >300 °C; IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3424 (OH), 1601, 1495 and 1457 (C=C);^{1}H NMR (400 MHz, $CDCl_3$ + drop DMSO): δ_H = 8.54 (2H, br s, 2 × OH), 7.46 (2H, s, 10 and 10′-H), 7.39 and 7.37 (2H, 2 × br s, 6 and 6′-H), 5.00–4.93 (2H, m, 1 and 1′-H), 3.89–3.83 (2H, m, 3 and 3′-H), 3.81, 3.80 and 3.80 (6H, 3 × s, 2 × OMe), 3.58, 3.57, 3.54 and 3.53 (6H, 4 × s, 2 × OMe), 3.04 (2H, dd, *J* = 16.5, and 2.5, 4α and 4α′-H), 2.61 (2H, dd, *J* = 16.5, and 11.3, 4β and 4β′-H), 1.62 (6H, d, *J* = 6.3, 1 and 1′-Me), 1.42 (6H, d, *J* = 6.1, 3 and 3′-Me); ^{13}C NMR (100 MHz, $CDCl_3$ and 4 drops DMSO) δ_C = 155.7 (2 × C), 154.3, 154.2 and 153.1 (2 × C), 147.9 and 147.8 (C-5 and C-5′), 135.5 and 135.4 (2 × C), 124.4 (2 × C), 122.8 and 122.7 (2 × C), 116.6 and 116.7 (2 × C and 10 and 10′-C), 109.0, 108.9 and 108.8 (2 × C), 95.5 (6 and 6′-C), 73.4 and 73.3 (1 and 1′-C), 70.2 (3 and 3′-C), 60.7 and 60.6 (×2) and 60.5 (2 × OMe), 55.5 (2 × OMe), 31.5 (4 and 4′-C), 21.9 (1-Me and 1′-Me), 21.7 (3-Me and 3′-Me); HRMS (ESI): Found [M + Na]$^+$, 597.247. $C_{34}H_{38}O_8Na$ requires *M* 597.2465; *m/z* (EI) 576 (M^+ + 2, 12%), 575 (M^+ + 1, 37), 574 (M^+, 100), 560 (7), 559 (32), 558 (93), 531 (4), 530 (11), 529 (17), 272 (37) and 258 (52).

7,7′,9,9′-Tetramethoxy-*cis*-1,3-*cis*-1′,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene-5,5′,10,10′-tetrone (mixture of diastereomers) 18

To a solution of the benzoisochromane **17** (0.10 g, 0.17 mmol) in DMF (10 ml), stirred at rt under an O_2 atmosphere (balloon) was added the salcomine complex *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II) hydrate (0.062 g, 019 mmol). Stirring was continued at rt for 18 h. The reaction mixture was then poured into a beaker containing ice water (100 ml) and acidified to pH 3 by the dropwise addition of conc. HCl (aq.). This mixture was transferred to a separating funnel and the organic product extracted with CH_2Cl_2 (3 × 50 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered through Celite and the product purified by silica gel column chromatography (40% EtOAc–hexane) to yield the quinone **18** (0.54 g, 51%). Mp = 174–177 °C (darkens above 132 °C); IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1659 and 1573 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (2H, s, 6 and 6′-H), 4.90–4.82 (2H, m, 1 and 1′-H), 3.87 (6H, s, 2 × OMe), 3.64, 3.63, 3.62 and 3.61 (8H, 4 × s and overlapping m, 2 × OMe and 3 and 3′-H), 2.78 (2H, br d, *J* = 18.4, 4α and 4α′-H), 2.22 (2H, ddd, *J* = 18.5, 10.3 and 3.2, 4β and 4β′-H), 1.54 (6H, d, *J* = 6.8, 1 and 1′-Me), 1.38 (6H, d, *J* = 6.0, 3-Me and 3′-Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 183.7 (2 × C=O), 182.7 (2 × C=O), 161.7, 161.6, 161.5 and 161.4 (C-7 and C-7′)[a], 159.7, 159.6, 159.5 and 159.4 (C-9 and C-9′)[a], 148.7 and 148.6 (C-10a and C-10a′), 140.0, 139.9 and 139.8 (C-4a and C-4a′), 135.3 and 135.2 (C-5a and C-5a′), 123.5, 123.4 and 123.3 (C-8 and C-8′), 119.1, 118.9, 118.8 and 118.7 (C-9a and C-9a′), 104.7 (C-6 and C-6′), 70.2 (C-1 and C-1′), 68.7 (C-3 and C-3′), 61.9, 61.8 and 61.7 (2 × OMe), 56.3 (×2) (2 × OMe), 30.0 (C-4 and C-4′), 21.2 (1-Me and 1′-Me), 20.9, 20.8 and 20.7 (3-Me and 3′-Me), assignments with the same superscript may be interchanged; HRMS (ESI): Found [M + Na]$^+$, 625.205. $C_{34}H_{34}O_{10}Na$ requires *M* 625.2050; *m/z* (EI) 604 (M^+ + 2, 12%), 603 (M^+ + 1, 33), 602 (M^+, 100), 544 (13), 543 (34), 497 (7), 469 (9), 286 (18), 279 (25), 264 (27) and 257 (37).

9,9′-Dihydroxy-7,7′-dimethoxy-*cis*-1,3-*cis*-1′,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene-5,5′,10,10′-tetrone (mixture of diastereomers) 3 (cardinalin 3)

In a flame-dried two neck RB flask under Ar, a solution of the dimethoxy quinone **18** (40 mg, 0.066 mmol) in dry CH_2Cl_2 (10 ml) was cooled to 0 °C and to this was added the BCl_3 solution (0.27 ml,

1.0 M in CH_2Cl_2). The reaction mixture immediately changed from a light yellow colour to a dark red colour. Analysis of the reaction mixture by TLC showed a new yellow spot at a slightly higher R_f and the absence of the starting material. The reaction still at 0 °C was quenched with water, transferred to a separating funnel and the organic product extracted with CH_2Cl_2 (3 × 20 ml). The solvent was dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude material was dried over silica and purified by silica gel column chromatography (30% EtOAc–hexane) to yield racemic cardinalin 3 **3** as a yellow powder (24 mg, 64%). Mp = 236–241 °C (darkening of the crystals above 145 °C) (lit.[1] 213–220 °C); IR ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3450 (OH), 1660 and 1636 (C=O); NMR assignments were made by comparison with the literature data. As a mixture of diastereoisomers was obtained assignments with the same chemical shift as the natural product were assigned according to the axial chirality of the natural product (*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 12.352 and 12.349 [2H, s, (*S*)-2 × OH], 12.31 and 12.30 [2H, s, 2 × OH], 7.331 [2H, s, (*S*)-6 and 6′-H], 7.329 [2H, s, 6 and 6′-H], 4.95–4.80 (2H, m, 1 and 1′-H), 3.91 [6H, s, (*S*)-2 × OMe], 3.90 [6H, s, 2 × OMe], 3.67–3.47 (2H, m, 3 and 3′-H), 2.76 (2H, dt, *J* = 18.7 and 2.4, 4α and 4α′-H), 2.26 (2H, ddd, *J* = 18.6, 10.0 and 3.9, 4β and 4β′-H), 1.58 [6H, d, *J* = 6.5, (*S*)-1 and 1′-Me], 1.57 [6H, d, *J* = 6.5, 1 and 1′-Me], 1.37 (6H, d, *J* = 6.1, 3 and 3′-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 187.9 (2 × C=O), 183.2 (2 × C=O), 163.2 (C-7 and C-7′), 161.0, 161.0 and 160.9 (C-9 and C-9′), 146.7 and 146.7 (C-10a and C-10a′), 143.1 and 143.0 (C-4a and C-4a′), 133.2 (C-5a and C-5a′), 114.5 (C-8 and C-8′), 110.2 (C-9a and C-9a′), 102.7 (C-6 and C-6′), 69.8 (C-1 and C-1′), 68.7 (C-3 and C-3′), 56.6 and 56.5 (2 × OMe), 30.6 and 30.6 (C-4 and C-4′), 21.3 (1-Me and 1′-Me) and 21.2 (3-Me and 3′-Me); HRMS (ESI): Found $[M + Na]^+$, 597.174. $C_{32}H_{30}O_{10}Na$ requires *M* 597.1736; *m/z* (EI) 576 (M^+ + 2, 5%), 575 (M^+ + 1, 27), 574 (M^+, 100), 530 (12), 515 (35), 271 (35), 244 (37), 243 (91) and 98 (87).

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References and notes

1 M. Gill, M. S. Buchanan and J. Yu, *J. Chem. Soc., Perkin Trans. 1*, 1997, 919.
2 M. Gill, M. S. Buchanan and J. Yu, *Aust. J. Chem.*, 1997, **50**, 1081.
3 S. R. Jammula, S. B. Pepalla, H. Telikepalli, K. V. J. Rao and R. H. Thomson, *Phytochemistry*, 1991, **30**, 3741.
4 D. W. Cameron, G. I. Feutrill and G. A. Pietersz, *Aust. J. Chem.*, 1982, **35**, 1481.
5 E. M. Mmutlane, J. P. Michael, I. R. Green and C. B. de Koning, *Org. Biomol. Chem.*, 2004, **2**, 2461.
6 L. M. Tewierk, C. Dimitriadis, M. Gill and B. Willems, *Org. Biomol. Chem.*, 2006, **4**, 3311.
7 For a review see: (*a*) M. Vrettou, A. A. Gray, A. R. E. Brewer and A. G. M. Barrett, *Tetrahedron*, 2007, **63**, 1487; (*b*) W.-X. Hong, L.-J. Chen, C.-L. Zhong and Z.-J. Yao, *Org. Lett.*, 2006, **8**, 4919; (*c*) F. M. Hauser and P. J. F. Gauuan, *Org. Lett.*, 1999, **1**, 671; (*d*) D. Drochner, W. Huttel, S. E. Bode, M. Muller, U. Karl, M. Nieger and W. Steglich, *Eur. J. Org. Chem.*, 2007, 1749.
8 J. C. Anderson and D. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2023.
9 J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.
10 H. Gross, A. Rieche and G. Mattey, *Chem. Ber.*, 1963, **96**, 308.
11 C. J. Davis, T E. Hurst, A. M. Jacob and C. J. Moody, *J. Org. Chem.*, 2005, **70**, 4414.
12 For example, $LiBH_4$–MeOH, (*a*) K. Soai and A. Ookawa, *J. Org. Chem.*, 1986, **51**, 4000; (*b*) $NaBH_4$–MeOH, K. Luthman, M. Orbe, T. Waglund and A. Claesson, *J. Org. Chem.*, 1987, **52**, 3777; (*c*) Na–EtOH, S. G. Ford and C. S. Marrel, *Org. Synth.*, 1943, **Coll. Vol. II**, 372–374; (*d*) $LiBH_4$–toluene, H. C. Brown, S. Narasimhan and Y. M. Choi, *J. Org. Chem.*, 1982, **47**, 4708; (*e*) L-Selectride, A. B. Bueno, M. C. Carreño, J. L. G. Ruano, B. Peña, A. Rubio and M. A. Hoyos, *Tetrahedron*, 1994, **50**, 9355.
13 For *trans*-1,3-dimethyl aromatic-fused pyrans the signal for H-3 appears between δ 4.0–4.2, while for the corresponding *cis*-compound the signal for H-3 appears between δ 3.5–3.9.
14 U. Azzena, T. Denurra, G. Melloni and A. M. Piroddi, *J. Org. Chem.*, 1990, **55**, 5386.
15 G. Lindson, O. Wennerstom and R. Isakson, *J. Org. Chem.*, 1987, **52**, 547.

