Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7809

www.rsc.org/obc

PAPER

The synthesis of the pyranonaphthoquinones dehydroherbarin and anhydrofusarubin using Wacker oxidation methodology as a key step and other unexpected oxidation reactions with ceric ammonium nitrate and salcomine†‡

Adushan Pillay, Amanda L. Rousseau, Manuel A. Fernandes§ and Charles B. de Koning*

Received 12th June 2012, Accepted 10th August 2012
DOI: 10.1039/c2ob26126j

The synthesis of two closely related pyranonaphthoquinones, dehydroherbarin and anhydrofusarubin, is described. The construction of the naphthalene nuclei was achieved using the Stobbe condensation reaction using 2,4-dimethoxybenzaldehyde and 2,4,5-trimethoxybenzaldehyde as their respective starting materials. Two key steps *en route* include a PIFA-mediated addition of a methoxy substituent onto the naphthalene skeleton and a Wacker oxidation reaction to construct the benzo[*g*]isochromene nucleus. Two interesting oxidation reactions of the intermediate isochromene enol ether of 7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5-ol were observed. Treatment of the substrate with salcomine resulted in the formation of (3-formyl-4-hydroxy-6,8-dimethoxynaphthalene-2-yl)methyl acetate, while treatment of the same substrate with CAN resulted in the formation of racemic (3*R*,4*R*)-3-hydroxy-7,9-dimethoxy-3-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-benzo[*g*]isochromen-4-yl nitrate.

Introduction

The quinone dehydroherbarin **1** has been isolated from the dematiaceous fungus *Torula herbarum*[1] that is often found on the dry leaves and twigs of *Felia microphylla*. In addition, it has been found in the endolichenic fungal strain, *Corynesspora* sp. BA-10763, which occurs in the cavern beard lichen *Usnea cavernosa*.[2] Dehydroherbarin **1** has been shown to exhibit antimicrobial and antiamoebic activity, as well as cause significant inhibition of both metastatic prostate and breast cancers (PC-3M and MDA-MB-231 respectively).[1,2] The related quinone, anhydrofusarubin **2**, has been known for decades, and was recently isolated from the sea-fan-derived fungus *Fusarium* spp PSU-F135.[3] There has been renewed interest in this quinone owing to the excellent cytotoxic activity against oral human carcinoma cells (KB) and human breast cancer cells (MCF-7). The reported activity was better than the anticancer standards, ellipticine and doxorubicin respectively (Scheme 1).[3]

The synthesis of dehydroherbarin **1** has been accomplished by both the De Kimpe and Brimble groups.[4,5] De Kimpe *et al.* utilized the quinone **4** as a key intermediate which, on exposure to Et_3N, gave dehydroherbarin **1** *via* what is believed to be the quinone methide **5**. More recently, the Brimble group took advantage of Staunton–Weinreb annulation methodology to assemble the advanced intermediate **6** from **7** and the Michael acceptor **8**, albeit in poor yield (Scheme 1).

The synthesis of anhydrofusarubin **2** has not been documented, but it has been noted that anhydrofusarubin undergoes hydration to afford the related quinone fusarubin **3**, if left standing in the atmosphere.[6]

As part of our programme on the synthesis of pyranonaphthoquinones[7] and, in particular, on the use of Wacker oxidation methodology for their synthesis,[8] we wished to extend this methodology to the synthesis of both dehydorherbarin and anhydrofusarubin. In this paper we describe the synthesis of dehydroherbarin and anhydrofusarubin, as well as present some unprecedented oxidation reactions mediated by ceric ammonium nitrate and salcomine *en route*.

Results and discussion

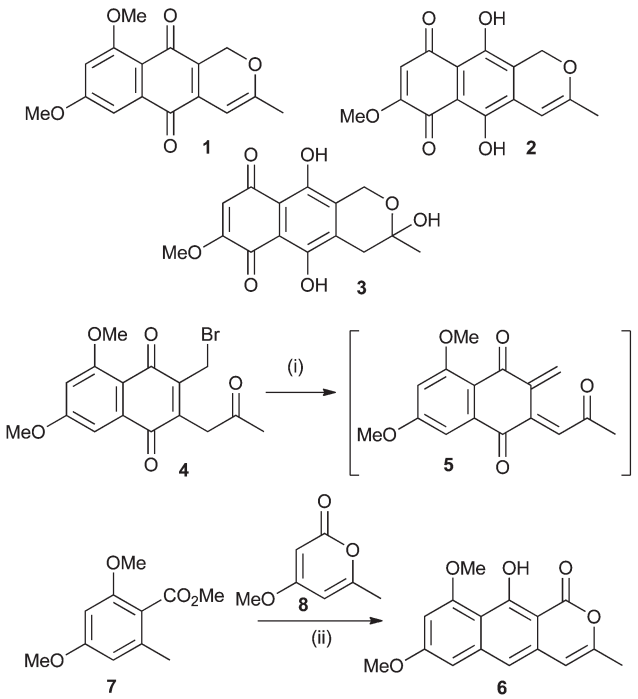
The Stobbe condensation is well documented[9] as a key step for the construction of naphthalene nuclei (Fig. 1).

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits 2050, Johannesburg, South Africa. E-mail: Charles.deKoning@wits.ac.za; Fax: +27 11 7176749; Tel: +27 11 7176724

† Dedicated to my friends and colleagues, Robin Giles and Ivan Green, who inspired me to research quinone chemistry.

‡ Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra are provided. CCDC 885420, 885421 and 885422. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26126j

§ For correspondence regarding crystallography, Manuel.Fernandes@wits.ac.za



Scheme 1 (i) Et_3N, toluene, 84%; (ii) LDA, THF, −78 °C, 27%.

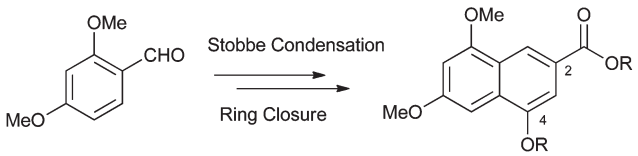


Fig. 1 Stobbe condensation reaction for the assembly of naphthalenes.

The limitation with this methodology is that substituents are introduced only at position 2 and 4 on the newly constructed ring of the naphthalene product. However, we believed that we would be able to construct the appropriately substituted naphthoquinone moiety of dehydroherbarin using this methodology, provided that we could introduce the requisite extra oxygen substituent on the naphthalene at a later stage. Precedent for this type of transformation has been reported for the synthesis of dehydorherbarin,[5] where a naphthol is oxidized using salcomine to the corresponding quinone (Fig. 2).

Hence, starting from 2,4-dimethoxybenzaldehyde, the tetrasubtituted naphthalene **9** was formed in reasonable yield by reaction with diethylsuccinate in the presence of NaOEt, followed by treatment with NaOAc in acetic anhydride.[7] In our first attempt at the synthesis of dehydroherbarin (Scheme 2), potassium hydroxide hydrolysis of naphthalene **9** followed by exposure to allylbromide and potassium carbonate yielded **10**. A thermally induced Claisen rearrangement on **10** followed by protection of the naphthol **11** with TBDMSCl furnished **12**. This was then followed by reduction of the ester **12** to afford the benzylic alcohol **13**. We were now in a position to attempt the Wacker oxidation to form the isochromene ring. The desired product **14** was formed in an acceptable yield of 52%. Removal of the silicon protecting group of **14** with TBAF afforded the required

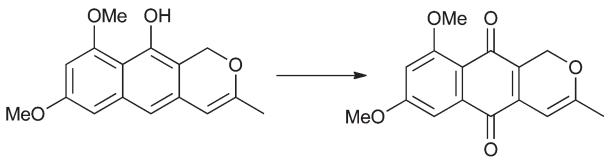
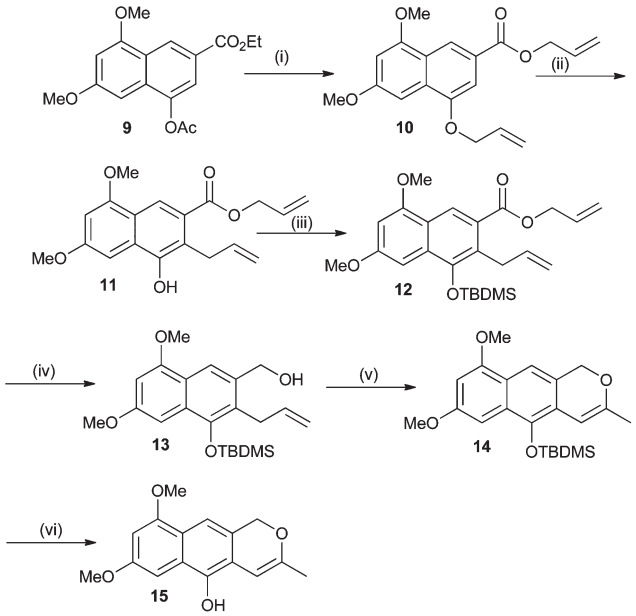


Fig. 2 Oxidation of naphthol to naphthoquinone.



Scheme 2 *Reagents and conditions*: (i) (a) KOH, MeOH/H_2O, rt, 6 h, (b) aq HCl, (c) K_2CO_3, allyl bromide, Me_2CO, reflux, 18 h, 83% over 2 steps, (ii) 170 °C, 18 h, 87%, (iii) TBDMSCl, imidazole, DMAP (cat.), DCM, rt, 24 h, 93%, (iv) LAH, THF, 5 °C, 2 h, 96%, (v) cat $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF/H_2O, O_2(g), rt, 24 h, 52%, (vi) TBAF, THF, rt, 18 h, 73%.

naphthol **15** in good yield. Now all that was required was oxidation of **15** to the target quinone, dehydroherbarin **1**.

As salcomine has been successfully utilised in the oxidation of the regioisomeric naphthol, 7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromen-10-ol (Fig. 2)[5] we assumed that this would be a trivial reaction. However, exposure of **15** to salcomine [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)] only resulted in the isolation of the dicarbonyl **16**, formed as a result of the oxidation of the enol ether of **15**. The identity of the product **16** was confirmed by X-ray crystallography (Fig. 3 and Scheme 3).[10]

Frustrated by this result, we tested the use of ceric ammonium nitrate in the oxidation reaction. Although ceric ammonium nitrate oxidation of **15** resulted in the formation of the desired quinone, the enol ether had also undergone an addition reaction resulting in the formation of the hemiacetal **17**. In this case, a nitrate had formally added to the other side of the double bond of the enol ether. An X-ray crystallography study clearly identified the product with a *trans*-relationship between the nitrate and hydroxyl substituents (Fig. 4).[11] Precedent for this type of reaction has been found in the work of Nair *et al.*[12] Based on this study, we propose that the Ce(IV) reagent is reduced by the enol ether of **15**, providing a radical cation (Fig. 4) to which

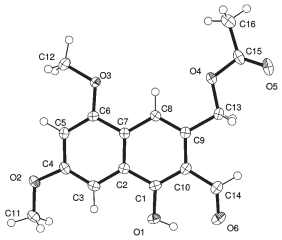
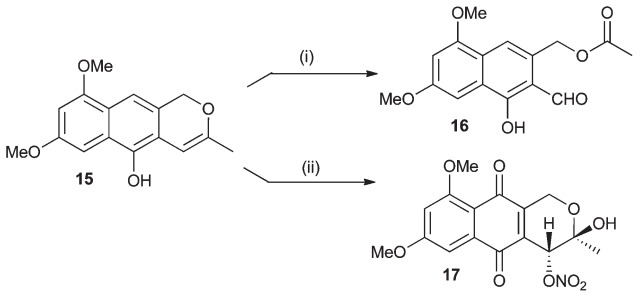


Fig. 3 ORTEP diagram of (3-formyl-4-hydroxy-6,8-dimethoxy-naphthalene-2-yl)methyl acetate **16**.



Scheme 3 *Reagents and conditions*: (i) salcomine, CH_3CN, O_2(g) atm, rt, 24 h, 30%, (ii) CAN, H_2O/CH_3CN, rt, 30 min, 54%.

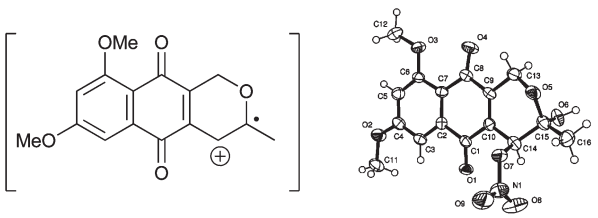
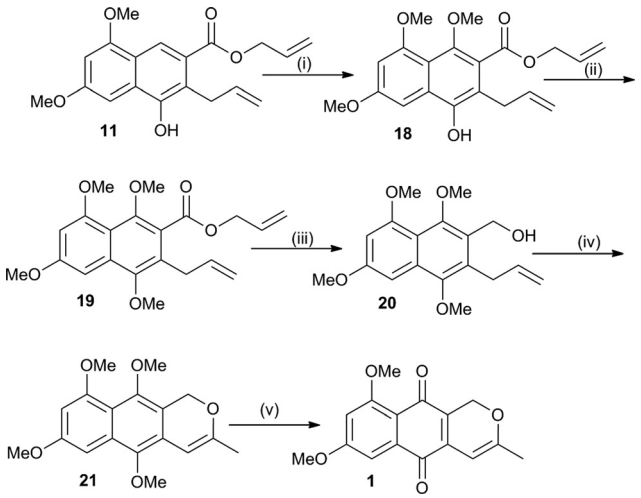


Fig. 4 Intermediate radical cation and ORTEP diagram of quinone **17**.

both a nitrate anion and a hydroxyl substituent are able to add to afford **17**.

At this point we believed that the best way forward would be to assemble the correctly substituted naphthalene nucleus at an earlier stage of the synthesis of dehydroherbarin. Methodology for the introduction of a methoxy substituent on an aromatic ring bearing a *para* hydroxyl group using PIFA has recently been reported by Kozlowski and co-workers.[13] We decided to attempt the introduction of the extra oxygen on our naphthalene system using this methodology, prior to formation of the isochromene ring.

Hence, exposure of **11** to PIFA in the presence of methanol, followed by aromatization with sodium ethoxide, gave the desired naphthol **18** containing an extra methoxy substituent (Scheme 4). Protection of the naphthol as a methyl ether afforded the naphthalene **19**. Reduction of the allyl ester of **19** furnished the desired benzyl alcohol **20** on which to attempt our Wacker mediated ring closure reaction. Exposure of **20** to catalytic palladium(II) chloride and copper(II) chloride in the presence of oxygen afforded the desired isochromene **21**. Finally, oxidation of **21** with PIFA afforded the desired product, dehydroherbarin **1**, although in a disappointing yield of 25%.



Scheme 4 *Reagents and conditions*: (i) (a) PIFA, MeOH, rt, 15 min, (b) NaOEt, EtOH, rt, 15 min, 57% over 2 steps, (ii) K_2CO_3, Me_2SO_4, Me_2CO, reflux, 18 h, 92%, (iv) LAH, Et_2O, rt, 2 h, 83%, (iv) cat $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF/H_2O, O_2(g), rt, 2 h, 63%, (v) (a) PIFA, H_2O/CH_3CN, rt, 2 h, 25%.

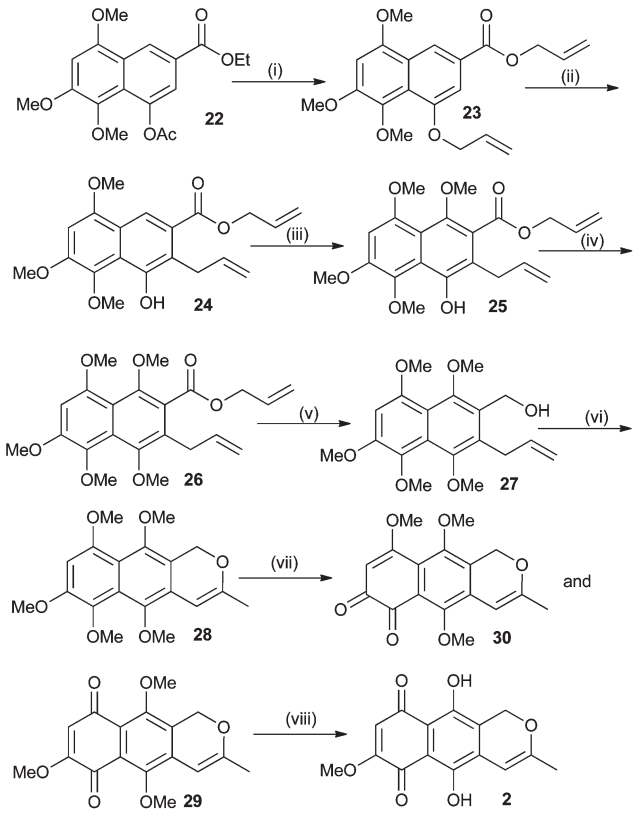
Armed with this newly developed methodology for the synthesis of dehydroherbarin, an obvious extension was to utilise this methodology for the synthesis of anhydrofusarubin **2** containing a penta-oxygenated naphthalene nucleus.

Starting from 2,4,5-trimethoxybenzaldehyde, naphthalene **22** was prepared using the Stobbe reaction followed by acetic anhydride mediated ring closure.[7] Using the same methodology as described for the synthesis of dehydroherbarin, benzylic alcohol **27** was prepared from naphthalene **22** by the uneventful sequence of synthetic transformations shown in Scheme 5. We were now in a position to attempt the Wacker-mediated ring closure reaction on **27** to form the isochromene ring of anhydrofusarubin. Exposure of **27** to oxygen, catalytic $PdCl_2$ and $CuCl_2$ resulted in the formation of the desired isochromene **28**. Treatment of **28** with AgO resulted in the formation of both *para*- **29** and *ortho*-quinones **30** in yields of 63% and 27% respectively. The identity of **29** was established with the aid of X-ray crystallography (Fig. 5).[14] Treatment of **29** with BCl_3 at −78 °C resulted in the formation of anhydrofusarubin **2** in a yield of 65%. Both the ^1H and ^{13}C NMR spectral data agreed with that published.[15]

Finally, using this methodology a 10-deoxy derivative of anhydrofusarubin **31** was easy to prepare as shown in Scheme 6. Naphthol **24** was converted to the ester **32** which was reduced to alcohol **33**. Again using our Wacker reaction conditions on **33** furnished the desired product **31**.

Conclusions

In summary, we have been able to synthesize two closely related pyranonaphthoquinones, dehydroherbarin **1** and anhydrofusarubin **2**. Dehydroherbarin was synthesized in 10 steps from 2,4-dimethoxybenzaldehyde in an overall yield of 4% while anhydrofusarubin was made from 2,4,5-trimethoxybenzaldehyde in 11 steps in an overall yield of 5%. Stobbe methodology was



Scheme 5 *Reagents and conditions*: (i) (a) KOH, MeOH/H_2O, rt, 6 h, (b) aq HCl, (c) K_2CO_3, allyl bromide, Me_2CO, reflux, 18 h, 84% over 2 steps, (ii) 170 °C, 18 h, 88%, (iii) (a) PIFA, MeOH, rt, 10 min, (b) NaOEt, EtOH, rt, 15 min, 54% over 2 steps, (iv) K_2CO_3, Me_2SO_4, Me_2CO, reflux, 18 h, 81%; (v) LAH, THF, 5 °C, 2 h, (vi) cat $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF/H_2O, O_2(g), rt, 24 h, 49%, over 2 steps. (vii) (a) AgO, 6 M HNO_3, dioxane, **29**, 63%, **30**, 27%; (viii) BCl_3, CH_2Cl_2, −78 °C, 65%.

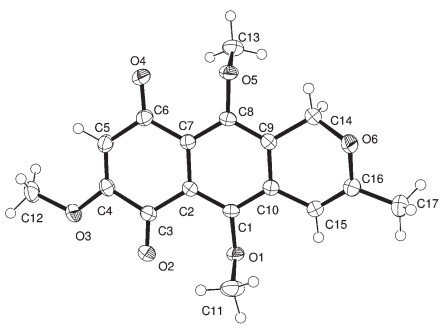
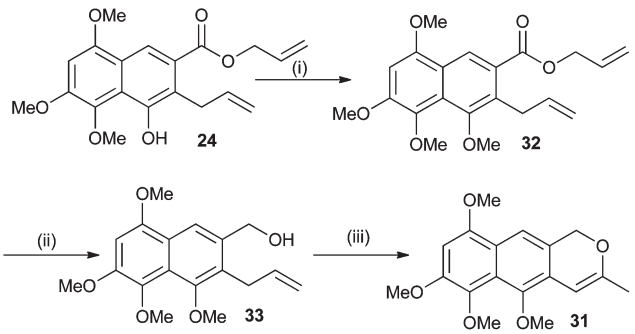


Fig. 5 ORTEP diagram of quinone **29**.

used to assemble the core naphthalene nuclei of both natural products, then a PIFA-mediated addition of methanol to the two respective naphthols, allowed for the introduction of a methoxy substituent onto each naphthalene nucleus. This provided the correct naphthalene substitution pattern of the target quinones. Once the appropriate functionalities had been introduced, a Wacker-mediated reaction allowed for the construction of the isochromene ring.



Scheme 6 *Reagents and conditions*: (i) K_2CO_3, Me_2SO_4, Me_2CO, reflux, 18 h, 90%; (ii) LAH, THF, rt, 2 h, 86%, (iii) cat $PdCl_2$, $CuCl_2{\cdot}2H_2O$, DMF/H_2O, O_2(g) atm, rt, 24 h, 64%.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer, a Bruker AVANCE 400 spectrometer or a Bruker AVANCE III 500 spectrometer. All spectra were recorded in $CDCl_3$, or d_6-acetone. All chemical shift values are reported in parts per million referenced against TMS which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in Hertz (Hz). For most NMR spectra a range of 2-D experiments were done to allow for a more complete assignment of ^{13}C NMR spectra. All mass spectroscopy data were collected on a Waters Micromass LCT TOF Mass Spectrometer. The sample was dissolved in MeOH to a concentration of 2 ng μl^{-1} and introduced by direct infusion. The ionization mode was electrospray positive with a capillary voltage of 2500 V and a desolvation temperature of 250 °C using N_2 gas at 250 L h^{-1}. Infrared spectra were recorded on a Bruker Tensor 27 standard system spectrometer. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel column chromatography with various EtOAc and hexane mixtures as the mobile phase. TLC was performed on aluminum-backed Macherey-Nagel Alugram Sil G/UV254 plates precoated with 0.25 mm silica gel 60. *In vacuo* refers to refers to the solvent evaporated under reduced pressure utilizing a rotary evaporator.

Ethyl 4-acetoxy-6,8-dimethoxy-2-naphthoate 9

To a solution of 2,4-dimethoxybenzaldehyde (4.00 g, 24.1 mmol) and diethyl succinate (5.45 g, 31.3 mmol) in dry THF (50 ml), at 0 °C, was added NaOEt (3.28 g, 48.1 mmol). The reaction mixture was refluxed for 2 h, cooled to rt and then acidified to pH 3 with aqueous HCl [33% (v/v)]. The product therefore precipitated and was extracted with EtOAc (2 × 50 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue and anhydrous NaOAc (2.57 g, 31.3 mmol) were dissolved in acetic anhydride (50 ml) and refluxed for 3 h. The solvent was removed *in vacuo* and the resulting residue was dissolved in EtOAc (60 ml). Aqueous $NaHCO_3$ was slowly added to the EtOAc layer until all the traces of acetic anhydride were removed. The organic layer was then separated, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The

residue was purified by column chromatography (30% EtOAc–hexane) to afford ethyl 4-acetoxy-6,8-dimethoxy-2-naphthoate **9** (8.69 g, 82%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.79 (1H, d, *J* 1.1, H-1), 7.81 (1H, d, *J* 1.1, H-3), 6.66 (1H, d, *J* 1.9, H-5), 6.51 (1H, d, *J* 1.9, H-7), 4.42 (2H, q, *J* 7.1, OCH_2CH_3), 3.98 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.46 (CH_3CO_2), 1.42 (3H, t, *J* 7.1, OCH_2CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 169.3 (CH_3CO_2), 166.3 ($ArCO_2Et$), 161.0, 157.9, 145.4 (C-4), 133.2 (C-4a), 124.4 (C-2), 123.4 (C-1), 122.2 (C-8a) 119.1 (C-3), 98.6 (C-5), 91.7 (C-7) 61.0 (OCH_2CH_3), 55.8 (OCH_3), 55.4 (OCH_3), 20.9 (CH_3CO_2), 14.4 (OCH_2CH_3).[7]

Allyl 4-(allyloxy)-6,8-dimethoxy-2-naphthoate 10

Ethyl 4-acetoxy-6,8-dimethoxy-2-naphthoate **9** (10.0 g, 31.4 mmol) was dissolved in MeOH (100 ml) followed by the drop-wise addition of an aqueous KOH solution (8.81 g, 157 mmol, 200 ml H_2O). The dark-orange reaction was stirred was 6 h at rt, before the MeOH was removed *in vacuo*. The aqueous solution was then carefully acidified to pH 4.0 with aqueous HCl (30%), and then extracted with EtOAc (3 × 150 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude, off-white solid was then dissolved in acetone (150 ml), and allyl bromide (9.41 g, 78.5 mmol), anhydrous K_2CO_3 (10.8 g, 78.5 mmol) were added to the reaction mixture which was then refluxed for 18 h under a N_2(g) atmosphere. The mixture was then allowed to cool to rt, filtered through a bed of celite, and the solvent was removed *in vacuo*. The light-yellow residue was then purified *via* column chromatography (10% EtOAc–hexane) to yield allyl 4-(allyloxy)-6,8-dimethoxy-2-naphthoate **10** as a yellow amorphous solid (8.56 g, 83%). **Mp.** = 64–65 °C; **IR** ν_{max} (cm^{-1}) = 1647 (C═O), 1600 (C═C), 1429, 1285, 1217, 1146; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 8.53 (1H s, H-1), 7.41 (1H, d, *J* 1.3, H-3), 7.13 (1H, d, *J* 2.0, H-5), 6.51 (1H, d, *J* 2.2, H-7), 6.26–6.01 (2H, m, $COOCH_2CH$═CH_2 and OCH_2CH═CH_2), 5.57–5.39 (2H, m, $COOCH_2CH$═CH_2), 5.38–5.25 (2H, m, OCH_2CH═CH_2), 4.87 (2H, dt, *J* 5.6, 1.3, $COOCH_2CH$═CH_2), 4.75 (2H, d, *J* 5.2, OCH_2CH═CH_2), 3.95 (3H, s, OCH_3), 3.93 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C = 167.0 (C═O), 160.4, 157.8, 153.3, 133.3 (OCH_2CH═CH_2), 132.8 ($COOCH_2CH$═CH_2), 130.2 (C-2), 124.4 (C-4a), 121.8 (C-8a), 118.4 (C-1) 118.2 (OCH_2CH═CH_2), 117.8 ($COOCH_2CH$═CH_2), 105.9 (C-3), 98.8 (C-4), 92.9 (C-6), 69.4 (OCH_2CH═CH_2) 65.7 ($COOCH_2CH$═CH_2), 55.8 (OCH_3), 55.6 (OCH_3); **HR-TOF-MS**: *m*/*z* found 329.1389 $[M + H]^+$ (calculated for $C_{19}H_{21}O_5$, 329.1389).

Allyl 3-allyl-4-hydroxy-6,8-dimethoxy-2-naphthoate 11

Allyl 4-(allyloxy)-6,8-dimethoxy-2-naphthoate **10** (7.20 g, 21.9 mmol) was loaded neat into in a round-bottom flask (100 ml) equipped with a reflux condenser and a magnetic stirrer bar. The reaction vessel was then heated to 180 °C for 18 h under a N_2(g) atmosphere. The dark viscous residue was allowed to cool to rt and was then purified using column chromatography (20% EtOAc–hexane) to yield allyl 3-allyl-4-hydroxy-6,8-dimethoxy-2-naphthoate **11** as a yellow amorphous solid (6.48 g, 90%). **Mp**. = 90–91 °C; **IR** ν_{max} (cm^{-1}) = 3539 (OH), 1673 (C═O), 1580 (C═C), 1461, 1291, 1249, 1158; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.43 (1H, s, H-1), 7.04 (1H, d, *J* 1.8, H-5), 6.48 (1H, d, *J* 2.2, H-7), 6.20–6.01 (2H, m, $COOCH_2CH$═CH_2 and $ArCH_2CH$═CH_2), 5.82 (1H, s, OH), 5.44 (1H, ddd, *J* 17.2, 3.0, 1.5, one of $COOCH_2CH$═CH_2), 5.37–5.25 (1H, m, one of $COOCH_2CH$═CH_2), 5.18 (2H, ddd, *J* 5.1, 3.9, 1.7, $ArCH_2CH$═CH_2), 4.88–4.80 (2H, m, $COOCH_2CH$═CH_2), 3.97–3.88 (2H, m, $ArCH_2CH$═CH_2, under OCH_3) 3.94 (3H, s, OCH_3), 3.91 (OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 167.8 (C═O), 160.1, 157.3, 149.7, 136.5 ($COOCH_2CH$═CH_2), 132.5 ($ArCH_2CH$═CH_2), 128.5 (C-8a), 125.1 (C-4a), 120.3 (C-3), 119.2 (C-2), 118.9 (C-1), 118.3 ($COOCH_2CH$═CH_2), 116.1 ($ArCH_2CH$═CH_2), 98.3 (C-5), 92.1 (C-7), 65.7 ($COOCH_2CH$═CH_2), 55.7 (OCH_3), 55.5 (OCH_3), 31.7 ($ArCH_2CH$═CH_2); **HR-TOF-MS**: *m*/*z* found 329.1376 $[M + H]^+$ (calculated for $C_{19}H_{21}O_5$, 329.1389).

Allyl 3-allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxy-2-naphthoate 12

Allyl 3-allyl-4-hydroxy-6,8-dimethoxy-2-naphthoate **11** (7.20 g, 21.9 mmol), *tert*-butyldimethylsilyl chloride (4.96 g, 32.9 mmol), imidazole (2.23 g, 32.9 mmol) and dimethylaminopyridine (0.400 g) were dissolved in CH_2Cl_2 (150 ml) and stirred at rt for 24 h under a N_2(g) atmosphere. The mixture was then washed with H_2O (2 × 100 ml), dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc–hexane) to afford allyl 3-allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxy-2-naphthoate **12** (9.01 g, 93%) as a clear oil. **IR** ν_{max} (cm^{-1}) = 1767 (C═O), 1589 (C═C), 1468, 1317, 1251, 1188; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.44 (1H, s, H-1), 6.96 (1H, d, *J* 1.9, H-5), 6.47 (1H, d, *J* 2.1, H-7), 6.08 (1H, ddd, *J* 16.1, 10.9, 5.7, $COOCH_2CH$═CH_2), 5.93 (1H, ddt, *J* 16.3, 10.4, 5.9, $ArCH_2CH$═CH_2), 5.43 (1H, dd, *J* 17.2, 1.5, one of $COOCH_2CH$═CH_2), 5.29 (1H, dd, *J* 10.4, 1.2, one of $COOCH_2CH$═CH_2), 4.99–4.86 (2H, m, $ArCH_2CH$═CH_2), 4.82 (2H, d, *J* 5.7, $COOCH_2CH$═CH_2), 3.99–3.93 (2H, m, $ArCH_2CH$═CH_2, under OCH_3), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 1.13 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.23 (6H, s, $OSi(CH_3)_2C(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 168.0 (C═O), 159.6, 157.4, 148.3, 137.5 ($ArCH_2CH$═CH_2), 132.7 ($COOCH_2CH$═CH_2), 131.6, 126.4, 126.2, 120.4, 119.9, 118.1 ($COOCH_2CH$═CH_2), 114.9 ($ArCH_2CH$═CH_2), 97.9 (C-5), 94.2 (C-7), 65.6 ($COOCH_2CH$═CH_2), 55.7 (OCH_3), 55.4 (OCH_3), 31.2 ($ArCH_2CH$═CH_2), 26.2 ($OSi(CH_3)_2C(CH_3)_3$), 18.8 ($OSi(CH_3)_2C(CH_3)_3$), −2.9 ($OSi(CH_3)_2C(CH_3)_3$); **HR-TOF-MS**: *m*/*z* found 443.2248 $[M + H]^+$ (calculated for $C_{25}H_{35}O_5Si$, 443.2254).

(3-Allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxynaphthalen2-yl)methanol 13

Allyl 3-allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxy-2-naphthoate **12** (7.90 g, 18.4 mmol) was dissolved dry THF (100 ml) and cooled to 0 °C in an ice bath. Lithium aluminium hydride (2.09 g, 55.1 mmol) was added slowly over 15 min. The

reaction mixture was then stirred vigorously for 2 h at rt under a N_2 atmosphere. The solution was then cooled to 0 °C in an ice bath and cold H_2O (1.5 ml) was added drop-wise until the fizzing stopped. Aqueous NaOH (1.5 ml, 15% m/v) and H_2O (4.5 ml) were then added and the resulting mixture was stirred for 3 h at rt. EtOAc (100 ml) was then added and the organic layer was extracted, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc–hexane) of the residue afforded (3-allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxynaphthalen2-yl)methanol **13** as a clear oil (6.86 g, 96%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 7.90 (1H, s, H-1), 6.97 (1H, d, *J* 1.9, H-5), 6.46 (1H, d, *J* 2.2, H-7), 5.96 (1H, dq, *J* 10.3, 5.7, $ArCH_2CH{=}CH_2$), 4.98 (1H, dd, *J* 10.2, 1.7, one of $ArCH_2CH{=}CH_2$), 4.91 (1H, dd, *J* 17.2, 1.7, one of $ArCH_2CH{=}CH_2$), 4.77 (2H, s, $ArCH_2$), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.66 (2H, br d, *J* 5.7, $ArCH_2CH{=}CH_2$), 2.60 (1H, brs, OH), 1.14 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.25 (6H, s, $OSi(CH_3)_2C(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 157.6, 156.6, 148.1, 137.1, 135.5, 129.0, 125.0, 121.4, 115.4, 115.0, 97.3, 94.1, 64.0, 55.4, 55.2, 30.7, 26.1, 18.8, −2.8.[16]

tert-Butyl(7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5-yloxy)dimethylsilane 14

Compound **13** (1.27 g, 3.27 mmol) was dissolved in a DMF–H_2O mixture (1 : 1 v/v, 40 ml). $PdCl_2$ (0.0589 g, 0.327 mmol) and $CuCl_2{\cdot}2H_2O$ (0.558 g, 3.27 mmol) were added to the solution which was stirred vigorously for 24 h at rt under an O_2(g) atmosphere. The reaction was filtered, and EtOAc (2 × 40 ml) was added. The organic layers were combined, washed with H_2O (3 × 20 ml), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (15% EtOAc–hexane) of the residue afforded the product **14** as a clear oil (0.657 g, 52%). **IR** ν_{max} (cm^{-1}) = 1504, 1450, 1367, 1257, 1154; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 7.50 (1H, s, H-10), 6.95 (1H, d, *J* 2.0, H-6), 6.41 (1H, d, *J* 2.2, H-8), 5.99 (1H, s, H-4), 5.14 (2H, d, *J* 0.8, H-1), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 2.01 (3H, d, *J* 0.5, CH_3), 1.17 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.21 (6H, s, $OSi(CH_3)_2C(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 157.7, 156.6 (C-3), 154.6, 141.8, 129.8 (C-9a), 125.1 (C-10a), 120.9 (C-5a), 119.9 (C-4a), 110.7 (C-10), 97.9 (C-4), 96.9 (C-8), 94.0 (C-6), 69.3 (C-1), 55.6 (OCH_3), 55.3 (OCH_3), 26.2 ($OSi(CH_3)_2C(CH_3)_3$), 20.1 (CH_3), 18.8 ($OSi(CH_3)_2C(CH_3)_3$), −3.1 ($OSi(CH_3)_2C(CH_3)_3$); **HR-TOF-MS**: *m*/*z* found 387.1984 $[M + H]^+$ (calculated for $C_{22}H_{31}O_4Si$, 387.1992).

7,9-Dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5-ol 15

Tert-butyl(7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5-yloxy)dimethylsilane **14** (0.456 g, 1.16 mmol) was dissolved in dry THF (3 ml) and was treated with *tert*-butylammonium fluoride (0.609 g, 2.33 mmol) and stirred for 18 h at rt under a N_2(g) atmosphere. H_2O (10 ml) and EtOAc (15 ml) were added and the upper organic layer was extracted, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc–hexane) to afford 7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5-ol **15** (0.256 g, 73%) as a white crystalline solid. **Mp**. = 156–157 °C; **IR** ν_{max} (cm^{-1}) = 3348 (OH), 1508, 1435, 1290, 1204, 1185; **^{1}H NMR** (500 MHz, acetone) δ_H = 7.91 (1H, br s, OH), 7.34 (1H, s, H-10), 7.11 (1H, d, *J* 2.1, H-6), 6.44 (1H, d, *J* 2.1, H-8), 6.15 (1H, s, H-4), 5.07 (2H, d, *J* 0.8, H-1), 3.91 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 1.91 (3H, d, *J* 0.6, CH_3); **^{13}C NMR** (125 MHz, acetone) δ_C = 158.9, 157.5, 155.3 (C-3), 143.7, 127.8 (C-9a), 125.8 (C-4a), 121.5 (C-5a), 116.1 (C-10a), 109.6 (C-10), 97.7 (C-8), 96.9 (C-4), 93.5 (C-6), 69.7 (C-1), 55.9 (OCH_3), 55.5 (OCH_3), 20.0 (CH_3); **HR-TOF-MS**: *m*/*z* found 273.1118 $[M + H]^+$ (calculated for $C_{16}H_{17}O_4$, 273.1127).

(3-Formyl-4-hydroxy-6,8-dimethoxynaphthalene-2-yl)methyl acetate 16

7,9-Dimethoxy-3-methyl-1*H*-benzo[g]isochromene-5-ol **15** (0.200 g, 0.764 mmol) and salcomine complex *N*,*N*′-bis(salicylidene)-ethylenediaminocobalt(II) hydrate (0.148 g, 0.44 mmol) were dissolved in CH_3CN (30 ml) and stirred for 3 h at rt under an O_2(g) atmosphere. The reaction was then filtered through celite and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (30% EtOAc–hexane) to afford (3-formyl-4-hydroxy-6,8-dimethoxynaphthalene-2-yl) methyl acetate **16** (0.070 g, 30%) as an orange solid. **Mp.** = 118–119 °C; **IR** ν_{max} (cm^{-1}) = 3455 (OH), 1737 (C═O), 1620 (C═O), 1578 (C═C), 1433, 1282, 1208, 1160; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 13.48 (1H, br s, OH), 10.26 (1H, s, CHO), 7.64 (1H, s, H-1), 7.27 (1H, d, *J* 2.1, H-5), 6.67 (1H, d, *J* 2.2, H-7), 5.44 (2H, s, $ArCH_2O$), 3.96 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 2.10 (3H, s, $OCOCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 195.4 (C═O), 170.6 (C═O), 162.6, 159.4, 156.6, 128.5, 127.1, 124.6, 116.0, 113.1, 102.5, 94.6, 64.3 ($ArCH_2O$), 55.9 (OCH_3), 55.8 (OCH_3), 21.1 (CH_3); **HR-TOF-MS**: *m*/*z* found 305.1027 $[M + H]^+$ (calculated for $C_{16}H_{17}O_6$, 305.1025).

(3*R*,4*R*)-3-Hydroxy-7,9-dimethoxy-3-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-benzo[*g*]isochromen-4-yl nitrate 17

7,9-Dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5-ol **15** (0.308 g, 1.01 mmol) was dissolved in CH_3CN–H_2O mixture (2 : 1 v/v ratio, 75 ml), and CAN (2.41 g, 4.40 mmol) in H_2O (25 ml) was added drop-wise. The reaction was then stirred for 1 h at rt followed by the addition of H_2O (100 ml) and EtOAc (100 ml). The organic layer was extracted, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc–hexane) to afford the product **17** (0.201 g, 54%) as an orange solid. **Mp**. = 105–106 °C; **IR** ν_{max} (cm^{-1}) = 3427 (OH), 1728 (C═O), 1658 (C═O), 1591, 1457, 1269, 1203; **^{1}H NMR** (300 MHz, acetone-d_6) δ_H = 7.17 (1H, d, *J* 2.4, H-6), 6.93 (1H, d, *J* 2.4, H-8), 5.95 (1H, s, H-4), 4.62–4.56 (2H, m, H-1), 3.97 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 2.87 (1H, br s, OH), 1.52 (3H, s, CH_3); **^{13}C NMR** (75 MHz, acetone-d_6) δ_C = 183.3 (C═O), 180.6 (C═O), 166.0, 163.4, 149.0 (C-4a), 136.1 (C-5a), 131.6 (C-10a), 114.6 (C-9a), 105.0 (C-6)*, 104.8 (C-8)*, 95.9 (C-3), 73.3 (C-4), 58.6 (C-1), 56.8 (OCH_3), 56.6 (OCH_3), 24.1 (CH_3). *assignments may be interchanged.

Allyl 3-allyl-4-hydroxy-1,6,8-trimethoxy-2-naphthoate 18

Allyl 3-allyl-4-hydroxy-6,8-dimethoxy-2-naphthoate **11** (2.00 g, 6.10 mmol) was dissolved in MeOH (80 ml) in a round-bottom flask (100 ml). PIFA (3.41 g, 7.93 mmol) was added and the reaction was stirred for 15 min at rt. Aqueous $NaHCO_3$ was added until fizzing stopped and the MeOH was removed *in vacuo* to leave only an aqueous medium. The H_2O layer was extracted with EtOAc (2 × 50 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then treated with an ethanolic solution of NaOEt (10.9 ml, 33.5 mmol) with vigorous stirring for 20 min at rt. The reaction was then quenched with the addition of saturated aqueous NH_4Cl (10 ml). EtOAc (30 ml) was added and the resulting upper organic layer was removed, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (10% EtOAc–hexane) of the residue afforded **18** as a brown oil (1.21 g, 60%). **Mp**. = 58–59 °C; **IR** ν_{max} (cm^{-1}) = 3257 (OH), 1738 (C=O), 1601 (C=C), 1441, 1274, 1229, 1189; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 7.08 (1H, br s, H-5), 6.52 (1H, br s, H-7), 6.10–5.90 (2H, m, $COOCH_2CH$=CH_2 and $ArCH_2CH$=CH_2), 5.57 (1H, s, OH), 5.41 (1H, ddd, *J* 17.2, 2.9, 1.4, one of $COOCH_2CH$=CH_2), 5.33–5.14 (3H, m, one of $COOCH_2CH$=CH_2 and $ArCH_2$-CH=CH_2), 4.89–4.79 (2H, m, $COOCH_2CH$=CH_2), 3.94 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.43 (2H, br d, *J* 6.1, $ArCH_2CH$=CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 168.2 (C=O), 158.7, 157.4, 147.6, 145.3, 135.3 (COO-CH_2CH=CH_2 and C-4a, overlapped), 131.9 ($ArCH_2CH$=CH_2), 129.5 (C-3), 124.3 (C-8a), 118.8 ($COOCH_2CH$=CH_2), 116.8 ($ArCH_2CH$=CH_2), 116.7 (C-2), 114.9, 99.4 (C-7), 92.9 (C-5), 66.0 ($COOCH_2CH$=CH_2), 63.9 (OCH_3), 55.9 (OCH_3), 55.2 (OCH_3), 32.6 ($ArCH_2CH$=CH_2); **HR-TOF-MS-ES**: *m*/*z* found 381.1314 $[M + Na]^+$ (calculated for $C_{20}H_{22}O_6Na$, 381.1314).

Allyl 3-allyl-1,4,6,8-tetramethoxy-2-naphthoate 19

Allyl 3-allyl-4-hydroxy-1,6,8-trimethoxy-2-naphthoate **18** (0.513 g, 1.40 mmol), anhydrous K_2CO_3 (0.289 g, 2.10 mmol) and Me_2SO_4 (0.264 g, 2.10 mmol) were dissolved in acetone (30 ml). The mixture was then refluxed for 18 h, cooled to rt, filtered, and the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (50 ml) and was successively washed with aqueous NH_3 (25%, 50 ml) and H_2O (50 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (10% EtOAc–hexane) of the residue afforded **19** as a yellow solid (0.466 g, 89%). **Mp**. = 60–61 °C; **IR** ν_{max} (cm^{-1}) = 1718 (C=O), 1581 (C=C), 1450, 1299, 1214, 1191; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H = 6.97 (1H, s, H-5), 6.52 (1H, s, H-7), 6.07–5.90 (2H, m, $COOCH_2CH$=CH_2 and $ArCH_2CH$=CH_2), 5.41 (1H, d, *J* 17.2, one of $COOCH_2CH$=CH_2), 5.26 (1H, d, *J* 10.4, one of $COOCH_2CH$=CH_2), 5.04 (2H, t, *J* 14.0, $ArCH_2CH$=CH_2), 4.80 (2H, dd, *J* 6.0, 0.8, $COOCH_2CH$=CH_2), 3.93 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.84 (3H, s, OCH_3) 3.82 (3H, s, OCH_3), 3.55 (2H, d, *J* 6.2, $ArCH_2CH$=CH_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C = 167.7 (C=O), 159.4, 157.9, 150.6, 149.2, 136.2 ($COOCH_2CH$=CH_2), 132.7 (C-4a), 132.1 ($ArCH_2CH$=CH_2), 126.6 (C-3), 124.7 (C-8a), 118.8 ($COOCH_2CH$=CH_2), 115.9 ($ArCH_2CH$=CH_2), 115.3 (C-2), 99.3 (C-5), 93.2 (C-7), 65.9 ($COOCH_2CH$=CH_2), 63.9 (OCH_3), 61.5 (OCH_3), 56.1 (OCH_3), 55.3 (OCH_3), 31.7 ($ArCH_2CH$=CH_2); **HR-TOF-MS-ES**: *m*/*z* found 395.1466 $[M + Na]^+$ (calculated for $C_{21}H_{24}O_6Na$, 395.1471).

(3-Allyl-1,4,6,8-tetramethoxynaphthalen-2-yl)methanol 20

Allyl 3-allyl-1,4,6,8-tetramethoxy-2-naphthoate **19** (6.30 g, 16.9 mmol) was dissolved dry Et_2O (100 ml) and cooled to 0 °C in an ice bath. Lithium aluminium hydride (1.29 g, 33.8 mmol) was added slowly over 5 min. The reaction mixture was then stirred vigorously for 2 h at rt under a N_2(g) atmosphere. The solution was then cooled to 0 °C in an ice bath and cold H_2O was added drop-wise until the fizzing ceased. EtOAc (100 ml) was added and the solution was washed with HCl (aq) (2 M, 30 ml). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (40% EtOAc–hexane) of the residue afforded **20** as a white crystalline solid (4.50 g, 84%). **Mp**. = 122–123 °C; **IR** ν_{max} (cm^{-1}) = 3481 (OH), 1580 (C=C), 1447, 1262, 1204, 1114; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 6.97 (1H, d, *J* 2.3, H-5), 6.52 (1H, d, *J* 2.3, H-7), 6.19–5.98 (1H, m, $ArCH_2CH$=CH_2), 5.05 (1H, dd, *J* 10.2, 1.7, one of $ArCH_2$-CH=CH_2), 4.90 (1H, dd, *J* 17.2, 1.8, one of $ArCH_2CH$=CH_2), 4.78 (2H, s, $ArCH_2$), 3.96 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.70 (2H, dt, *J* 5.3, 1.7, $ArCH_2CH$=CH_2), 2.55 (1H, br s, OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 158.7, 157.6, 152.2, 149.5, 137.9 ($ArCH_2CH$=CH_2), 131.9 (C-4a), 129.1 (C-3), 128.1 (C-2), 115.6 (C-8a), 115.4 ($ArCH_2CH$=CH_2), 99.0 (C-5), 93.2 (C-7), 63.3 (OCH_3), 61.6 (OCH_3), 57.5 ($ArCH_2$), 56.1 (OCH_3), 55.3 (OCH_3), 30.7 ($ArCH_2CH$=CH_2); **HR-TOF-MS-ES**: *m*/*z* found 341.1367 $[M + Na]^+$ (calculated for $C_{18}H_{22}O_5Na$, 341.1365).

5,7,9,10-Tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromene 21

(3-Allyl-1,4,6,8-tetramethoxynaphthalen-2-yl)methanol **20** (4.00 g, 12.6 mmol) was dissolved in a DMF–H_2O mixture (1 : 1 v/v, 100 ml). $PdCl_2$ (0.223 g, 1.26 mmol) and $CuCl_2 \cdot 2H_2O$ (2.14 g, 12.6 mmol) were added to the solution and O_2(g) was bubbled through the solution which was stirred vigorously for 2 h at rt. The reaction was filtered, and EtOAc (2 × 50 ml) was added. The organic layers were combined, washed with H_2O (3 × 20 ml), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (eluant 15% EtOAc–hexane) of the residue afforded **21** as a white crystalline solid (2.62 g, 66%). **Mp**. = 134–135 °C; **IR** ν_{max} (cm^{-1}) = 1601 (C=C), 1501, 1444, 1256, 1217, 1155; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 6.96 (1H, d, *J* 2.3, H-6), 6.46 (1H, d, *J* 2.2, H-8), 5.95 (1H, s, H-4), 5.28 (2H, s, H-1), 3.94 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.02 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C = 158.5, 157.7, 156.1 (C-3), 147.5, 143.0, 131.9 (C-5a), 122.3 (C-4a), 116.9 (C-10a), 114.9 (C-9a), 98.3 (C-6), 95.6 (C-4), 93.1 (C-8), 64.0 (C-1), 62.2 (OCH_3), 61.2 (OCH_3), 56.0 (OCH_3), 55.3 (OCH_3), 20.1 (CH_3); **HR-TOF-MS-ES**: *m*/*z* found 339.1209 $[M + Na]^+$ (calculated for $C_{18}H_{20}O_5Na$, 339.1208).

7,9-Dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5,10-dione 1

5,7,9,10-Tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromene **21** (0.200 g, 0.632 mmol) was dissolved in a CH_3CN–H_2O mixture (1 : 1 v/v, 8 ml), followed by the addition of PIFA (0.408 g, 0.948 mmol). The reaction was stirred for 2 h at rt, before being quenched by aqueous $NaHCO_3$ (15 ml). EtOAc was added (2 × 30 ml), and the organic layers were separated, combined, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography (30% EtOAc–hexane) to afford 7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-5,10-dione **1** (0.045 g, 25%) as a dark-red amorphous solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H = 7.21 (1H, d, *J* 2.4, H-6), 6.68 (1H, d, *J* 2.4, H-8), 5.81 (1H, s, H-4), 5.09 (2H, s, H-1), 3.93 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 1.98 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 182.4 (C=O), 181.0 (C=O), 164.3, 163.4, 161.6 (C-3), 135.7 (C-4a), 135.5 (C-5a), 124.9 (C-10a), 114.7 (C-9a), 104.4 (C-8) 103.7 (C-6), 93.9 (C-4), 63.5 (C-1), 56.5 (OCH_3), 56.0 (OCH_3), 20.2 (CH_3).[4]

Ethyl 4-acetoxy-5,6,8-trimethoxy-2-naphthoate 22

To a solution of 2,4,5-trimethoxybenzaldehyde (4.00 g, 24.1 mmol) and diethyl succinate (5.45 g, 31.29 mmol) in dry THF (50 ml), at 0 °C, was added NaOEt (3.28 g, 48.1 mmol). The reaction mixture was refluxed for 2 h, cooled to rt and then acidified to pH 3 with aqueous HCl [33% (v/v)]. The product precipitated and was extracted with EtOAc (2 × 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue, anhydrous NaOAc (2.57 g, 31.3 mmol) were dissolved in acetic anhydride (50 ml) and refluxed for 3 h. The solvent was removed *in vacuo* and the resulting residue was dissolved in EtOAc (60 ml). Aqueous $NaHCO_3$ was slowly added to the EtOAc layer until no effervesce was visible and all the traces of acetic acid were eliminated. The organic layer was then separated, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc–hexane) to afford ethyl 4-acetoxy-6,8-dimethoxy-2-naphthoate **22** (8.69 g, 82%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.83 (1H, d, *J* 1.6, H-1), 7.68 (1H, d, *J* 1.6, H-3), 6.67 (1H, s, H-7), 4.39 (2H, q, *J* 7.1, OCH_2CH_3), 3.98 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.38 (CH_3CO_2), 1.42 (3H, t, *J* 7.1, OCH_2CH_3).[7]

Allyl 4-(allyloxy)-5,6,8-trimethoxy-2-naphthoate 23

Ethyl 4-acetoxy-5,6,8-trimethoxy-2-naphthoate **22** (5.40 g, 15.5 mmol) was dissolved in MeOH (80 ml) followed by the drop-wise addition of aqueous KOH (4.35 g, 77.5 mmol, 150 ml H_2O). The dark-orange reaction was stirred was 6 h at rt, before the MeOH was removed *in vacuo*. The aqueous solution was then carefully acidified to pH 4.0 with aqueous HCl (30%), and then extracted with EtOAc (3 × 100 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude, off-white solid was then dissolved in Me_2CO (100 ml). Allyl bromide (4.69 g, 38.8 mmol), anhydrous K_2CO_3 (5.36 g, 38.8 mmol) was then added to the solution which was refluxed for 18 h under a N_2(g) atmosphere. The mixture was then allowed to cool to rt, filtered through a bed of celite, and the solvent was removed *in vacuo*. The light-yellow residue was then purified using column chromatography (10% EtOAc–hexane) to yield allyl 4-(allyloxy)-5,6,8-trimethoxy-2-naphthoate **23** as a yellow solid (4.67 g, 84%). **Mp.** = 70–71 °C; **IR** ν_{max} (cm^{-1}) = 1712 (C=O), 1505, 1465, 1258, 1201, 1180; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.57 (1H, d, *J* 1.2, H-1), 7.41 (1H, d, *J* 1.0, H-3), 6.66 (1H, s, H-7), 6.28–5.97 (2H, m, $COOCH_2CH$=CH_2 and OCH_2CH=CH_2), 5.57 (1H, dd, *J* 17.2, 1.4, one of $COOCH_2$-CH=CH_2), 5.41 (1H, dd, *J* 17.2, 1.3, one of $COOCH_2CH$=CH_2), 5.30 (2H, dd, *J* 15.1, 5.7, OCH_2CH=CH_2), 4.84 (2H, d, *J* 5.6, $COOCH_2CH$=CH_2), 4.69 (2H, d, *J* 5.1, OCH_2CH=CH_2), 3.97 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.80 (3H, s, OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 166.5 (C=O), 154.6, 153.5, 152.3, 137.7, 133.2 (OCH_2CH=CH_2), 132.6 ($COOCH_2CH$=CH_2), 124.5 (C-2), 124.2 (C-4a), 122.1 (C-8a), 118.8 (C-1), 118.1 (OCH_2CH=CH_2), 117.5 ($COOCH_2CH$=CH_2), 107.7 (C-3), 96.0 (C-7), 70.4 (OCH_2CH=CH_2) 65.6 ($COOCH_2CH$=CH_2), 62.0 (OCH_3), 55.1 (OCH_3), 55.9 (OCH_3); **HR-TOF-MS**: *m/z* found 359.1499 $[M + H]^+$ (calculated for $C_{20}H_{23}O_6$, 359.1495).

Allyl 3-allyl-4-hydroxy-5,6,8-trimethoxy-2-naphthoate 24

Allyl 4-(allyloxy)-5,6,8-trimethoxy-2-naphthoate **23** (3.10 g, 8.65 mmol) was loaded neat into in a round-bottom flask (50 ml) equipped with a reflux condenser and a magnetic stirrer bar. The reaction vessel was then heated to 190 °C for 18 h under a N_2(g) atmosphere. The dark viscous residue was allowed to cool to rt and was then purified by column chromatography (20% EtOAc–hexane) to yield allyl 3-allyl-4-hydroxy-5,6,8-trimethoxy-2-naphthoate **24** as a yellow amorphous solid (2.73 g, 88%). **Mp.** = 68–69 °C; **IR** ν_{max} (cm^{-1}) = 3280 (OH), 1738 (C=O), 1604 (C=C), 1365, 1229, 1208, 1182; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 10.07 (1H, br s, OH), 8.25 (1H, s, H-1), 6.55 (1H, s, H-7), 6.15–5.99 (2H, m, $COOCH_2CH$=CH_2 and $ArCH_2CH$=CH_2 overlapped), 5.41 (1H, dd, *J* 17.2, 1.5, one of $COOCH_2CH$=CH_2), 5.27 (1H, dd, *J* 10.4, 1.3, one of $COOCH_2CH$=CH_2), 5.06–4.97 (2H, m, $ArCH_2CH$=CH_2), 4.86–4.77 (2H, m, $COOCH_2CH$=CH_2), 3.98 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.88 (2H, br d, *J* 5.9, $ArCH_2CH$=CH_2); (75 MHz, $CDCl_3$) δ_C = 167.7 (C=O), 153.9, 151.1, 149.3, 137.4 ($COOCH_2CH$=CH_2), 135.9, 132.6 ($ArCH_2CH$=CH_2), 127.4 (C-3) 121.1 (C-4a), 120.0 (C-8a), 119.6 (C-2), 118.2 ($COOCH_2CH$=CH_2), 116.7 (C-1), 114.4 ($ArCH_2CH$=CH_2), 94.8 (C-7), 65.6 ($COOCH_2CH$=CH_2), 62.3 (OCH_3), 57.0 (OCH_3), 55.8 (OCH_3), 30.1 ($ArCH_2CH$=CH_2); **HR-TOF-MS-ES**: *m/z* found 381.1307 $[M + Na]^+$ (calculated for $C_{20}H_{22}O_6Na$, 381.1314).

Allyl 3-allyl-4-hydroxy-1,5,6,8-tetramethoxy-2-naphthoate 25

Allyl 3-allyl-4-hydroxy-5,6,8-trimethoxy-2-naphthoate **24** (8.00 g, 22.3 mmol) was dissolved in MeOH (120 ml) in a round-bottom flask (250 ml). PIFA (12.5 g, 29.0 mmol) was added and the reaction was stirred for 10 min at rt. Aqueous $NaHCO_3$ was added until fizzing stopped and the MeOH was removed *in vacuo* to leave only an aqueous medium. The H_2O layer was extracted with

EtOAc (2 × 100 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then treated with an ethanolic solution of NaOEt (36.1 ml, 111.5 mmol) with vigorous stirring for 20 min at rt. The reaction was then quenched with the addition of saturated aqueous NH_4Cl (50 ml). EtOAc (100 ml) was added and the resulting upper organic layer was removed, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (15% EtOAc–hexane) of the residue afforded **25** as an orange amorphous solid (4.70 g, 54%). **IR** ν_{max} (cm^{-1}) = 3215 (OH), 1724 (C═O), 1609 (C═C), 1580 (C═C), 1287, 1260, 1152; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 10.18 (1H, br s, OH), 6.59 (1H, s, H-7), 6.07–5.89 (2H, m, $COOCH_2CH$═CH_2 and $ArCH_2CH$═CH_2), 5.44–5.33 (1H, m, one of $COOCH_2CH$═CH_2), 5.24 (1H, dd, *J* 10.4, 1.3, one of $COOCH_2CH$═CH_2), 5.08–4.93 (2H, m, $ArCH_2CH$═CH_2), 4.83–4.77 (2H, m, $COOCH_2CH$═CH_2), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.42 (2H, br d, *J* 6.3 $ArCH_2CH$═CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 167.8 (C═O), 154.0, 148.3, 147.1, 145.7, 136.5 (C-4a), 135.9 ($ArCH_2CH$═CH_2), 132.1 ($COOCH_2CH$═CH_2), 126.3 (C-3), 120.2 (C-8a), 118.8 ($COOCH_2CH$═CH_2), 118.0 (C-2), 115.23 ($ArCH_2CH$═CH_2), 115.19, 96.8 (C-7), 65.9 ($COOCH_2CH$═CH_2), 63.9 (OCH_3), 62.3 (OCH_3), 56.8 (OCH_3), 56.7 (OCH_3), 31.5 ($ArCH_2CH$═CH_2); **HR-TOF-MS-ES**: *m*/*z* found 411.1417 $[M + Na]^+$ (calculated for $C_{21}H_{24}O_7Na$, 411.1420).

Allyl 3-allyl-1,4,5,6,8-pentamethoxy-2-naphthoate 26

Allyl 3-allyl-4-hydroxy-1,5,6,8-tetramethoxy-2-naphthoate **25** (3.80 g, 10.09 mmol), anhydrous K_2CO_3 (2.09 g, 15.1 mmol) and Me_2SO_4 (1.91 g, 15.1 mmol) were dissolved in acetone (60 ml). The mixture was then refluxed for 18 h, cooled to rt, filtered, and the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (80 ml) and was successively washed with aqueous NH_3 (25%, 80 ml) and H_2O (80 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (15% EtOAc–hexane) of the residue afforded **26** as a yellow oil (3.30 g, 81%). **IR** ν_{max} (cm^{-1}) = 1738 (C═O), 1603 (C═C), 1438, 1364, 1216, 1045; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 6.69 (1H, s, H-7), 6.07–5.86 (2H, m, $COOCH_2CH$═CH_2 and $ArCH_2CH$═CH_2), 5.38 (1H, dd, *J* 17.2, 1.5 one of $COOCH_2CH$═CH_2), 5.23 (1H, dd, *J* 10.4, 1.2, $COOCH_2CH$═CH_2), 5.07–4.93 (2H, m, $ArCH_2CH$═CH_2), 4.82–4.73 (2H, m, $COOCH_2CH$═CH_2), 3.95 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.53 (2H, br d, *J* 6.2, $ArCH_2CH$═CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 167.7 (C═O), 153.8, 151.1, 150.2, 149.2, 136.7 (C-4a), 136.6 ($ArCH_2CH$═CH_2), 132.1 ($COOCH_2CH$═CH_2), 127.7 (C-8a), 126.5 (C-2)*, 125.3 (C-3)*, 119.0 ($COOCH_2CH$═CH_2), 116.0 ($ArCH_2CH$═CH_2), 115.9, 97.1 (C-7), 66.1 ($COOCH_2CH$═CH_2), 63.9 (OCH_3), 62.8 (OCH_3), 62.1 (OCH_3), 56.9 (OCH_3), 56.8 (OCH_3), 31.6 ($ArCH_2CH$═CH_2); *assignments may be interchanged; **HR-TOF-MS-ES**: *m*/*z* found 425.1573 $[M + Na]^+$ (calculated for $C_{22}H_{26}O_7Na$, 425.1576).

5,6,7,9,10-Pentamethoxy-3-methyl-1*H*-benzo[*g*]isochromene 28

Allyl 3-allyl-1,4,5,6,8-pentamethoxy-2-naphthoate (3.30 g, 8.20 mmol) was dissolved dry Et_2O (100 ml) and cooled to 0 °C in an ice bath. Lithium aluminium hydride (0.622 g, 16.4 mmol) was added slowly over 5 min. The reaction mixture was then stirred vigorously for 2 h at 40 °C under a N_2(g) atmosphere. The solution was then cooled to 0 °C in an ice bath and cold H_2O was added drop-wise until the fizzing stopped. EtOAc (100 ml) was added and the solution was washed with aqueous HCl (2 M, 20 ml). The organic layer was then dried over anhydrous $MgSO_4$, filtered through a short pad of silica, and concentrated under reduced pressure to yield a yellow residue of what was presumed to be (3-allyl-1,4,5,6,8-pentamethoxy-2-naphthalen-2-yl)methanol **27**. This residue was dissolved in a DMF–H_2O mixture (1 : 1 v/v, 70 ml). $PdCl_2$ (0.145 g, 0.820 mmol) and $CuCl_2{\cdot}2H_2O$ (1.40 g, 8.20 mmol) were added to the solution and O_2(g) was bubbled through the solution which was stirred vigorously for 2 h at rt. The reaction was filtered, and EtOAc (2 × 50 ml) was added. The organic layers were combined, washed with H_2O (3 × 50 ml), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (10% EtOAc–hexane) of the residue afforded **28** as a white crystalline solid (1.40 g, 49% over two steps). Mp. = 122–123 °C; **IR** ν_{max} (cm^{-1}) = 1654 (C═C), 1597 (C═C), 1339, 1178, 1134; (500 MHz, $CDCl_3$) δ_H = 6.64 (1H, s, H-8), 6.03 (1H, s, H-4), 5.26 (2H, s, H-1), 3.99 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.00 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C = 156.9 (C-3), 153.3, 150.0, 147.3, 142.6, 136.8, 125.8 (C-5a), 122.6 (C-10a), 117.6 (C-4a), 115.7 (C-9a), 96.1 (C-8), 95.6 (C-4), 63.8 (C-1), 62.3 (OCH_3), 62.2 (OCH_3), 62.0 (OCH_3), 56.9 (OCH_3), 56.5 (OCH_3), 20.1 (CH_3); **HR-TOF-MS-ES**: *m*/*z* found 369.1312 $[M + Na]^+$ (calculated for $C_{19}H_{22}O_6Na$, 369.1314).

5,7,10-Trimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-6,9-dione 29 and 5,9,10-trimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-6,7-dione 30

5,6,7,9,10-Pentamethoxy-3-methyl-1*H*-benzo[*g*]isochromene (0.400 g, 1.15 mmol) was dissolved in 1,4-dioxane (30 ml) at RT. AgO (5.77 mmol, 0.715 g) was then added to the stirred solution, followed by the drop-wise addition of HNO_3 (6 M, 6.4 ml) to the solution which was the stirred for a further 5 min. CH_2Cl_2 (50 ml) and H_2O (50 ml) were added and the lower organic layer was extracted, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc–hexane) of the residue afforded **29**[14] as an orange amorphous solid (0.230 g, 63%). **Mp**. = 205–206 °C. **IR** ν_{max} (cm^{-1}) = 1782 (C═O), 1755 (C═O), 1705 (C═C), 1440, 1407; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H = 5.98 (1H, s, H-8), 5.96 (1H, s, H-4), 5.22 (2H, s, H-1), 3.84 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3), 2.00 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C = 183.7 (C═O), 179.3 (C═O), 159.8 (C-3), 159.0, 151.8, 149.8, 134.6 (C-10a), 128.2 (C-4a), 124.3 (C-5a), 122.0 (C-9a), 110.2 (C-8), 95.2 (C-4), 63.5 (C-1), 61.8 (OCH_3), 61.6 (OCH_3), 56.3 (OCH_3), 20.0 (CH_3); **HR-TOF-MS-ES**: *m*/*z* found 317.1022 $[M + H]^+$ (calculated for

$C_{17}H_{17}O_6$, 317.1025). Further elution (50% EtOAc–hexane) led to the isolation of **30** as a dark red solid (0.100 g, 27%). **Mp**. = 205–206 °C; **IR** ν_{max} (cm^{-1}) = 1794 (C═O), 1758 (C═O), 1698 (C═C), 1465, 1401; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H = 5.91 (1H, s, H-4), 5.88 (1H, s, H-8), 5.17 (2H, s, H-1), 3.99 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 2.00 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C = 179.8 (C═O), 179.4 (C═O), 170.7, 159.4 (C-3), 152.6, 150.4, 132.8 (C-10a), 129.0 (C-4a), 123.6 (C-5a), 121.2 (C-9a), 101.9 (C-8), 95.0 (C-4), 63.5 (C-1), 62.4 (OCH_3), 61.8 (OCH_3), 57.0 (OCH_3), 20.0 (CH_3); **HR-TOF-MS-ES**: *m/z* found 317.1027 $[M + H]^+$ (calculated for $C_{17}H_{17}O_6$, 317.1025).

Anhydrofusarubin 2

5,7,10-Trimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-6,9-dione (0.200 g, 1.15 mmol) was dissolved in dry CH_2Cl_2 (50 ml) and cooled to −78 °C under a N_2(g) atmosphere. BCl_3 (1.58 ml, 1.58 mmol) was added drop-wise to the solution which was stirred for a further 40 min at −78 °C, and then allowed to warm to rt. The reaction was then carefully quenched with a few drops of cold H_2O and then CH_2Cl_2 (50 ml) and H_2O (100 ml) were added. The lower organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc–hexane) of the residue afforded **2** as a crystalline purple solid (0.130 g, 65%). **Mp**. = 195–196 °C (199–202 °C);[18] **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H = 13.04 (1H, s, OH), 12.65 (1H, s, OH), 6.17 (1H, s, H-8), 5.99 (1H, s, H-4), 5.22 (2H, s, H-1), 3.92 (3H, s, OCH_3), 2.02 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C = 183.0 (C═O), 177.9 (C═O), 161.7 (C-3), 160.1, 158.1, 158.0, 133.2 (C-4a), 122.9 (C-10a), 111.1 (C-5a), 110.1 (C-8), 108.1 (C-9a), 94.9 (C-4), 63.1 (C-1), 56.8 (OCH_3), 20.2 (CH_3); **HR-TOF-MS-ES**: *m/z* found 288.0633 $[M]^+$ (calculated for $C_{15}H_{12}O_6$, 288.0634).

Allyl 3-allyl-4,5,6,8-tetramethoxy-2-naphthoate 32

Allyl 3-allyl-4-hydroxy-5,6,8-trimethoxy-2-naphthoate **24** (2.60 g, 7.25 mmol), anhydrous K_2CO_3 (1.50 g, 10.9 mmol) and Me_2SO_4 (1.37 g, 10.9 mmol) were dissolved in acetone (50 ml) in a round-bottom flask (100 ml). The solution was then refluxed for 12 h under a N_2(g) atmosphere. The mixture was then allowed to cool to rt, filtered through a bed of celite, and the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (50 ml) and was successively washed with aqueous NH_3 (25%, 3 × 20 ml), HCl (0.5 M, 2 × 20 ml) and H_2O (50 ml). The EtOAc layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (10% EtOAc–hexane) of the residue afforded allyl 3-allyl-4,5,6,8-tetramethoxy-2-naphthoate **32** (2.43 g, 90%) as an off-white solid. **Mp**. = 66–67 °C; **IR** ν_{max} (cm^{-1}) = 1740 (C═O), 1602 (C═C), 1358, 1442, 1225, 1137; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.52 (1H, s, H-1), 6.65 (1H, s, H-7), 6.13–5.95 (2H, m, $COOCH_2CH$═CH_2 and $ArCH_2CH$═CH_2 overlapped), 5.39 (1H, ddd, *J* 17.2, 3.0, 1.5, one of $COOCH_2CH$═CH_2), 5.26 (1H, dd, *J* 10.4, 1.3, $COOCH_2CH$═CH_2), 4.98–4.91 (2H, m, $ArCH_2CH$═CH_2), 4.79 (2H, dt, *J* 5.6, 1.3, $COOCH_2CH$═CH_2), 3.98 (3H, s, OCH_3), 3.96 (5H, br s, OCH_3 and $ArCH_2CH$═CH_2 overlapped), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 167.4 (C═O), 156.6, 153.1, 152.2, 138.2 ($COOCH_2CH$═CH_2), 135.8, 132.4 ($ArCH_2$-CH═CH_2), 130.4 (C-3) 126.3 (C-4a), 125.4 (C-8a), 122.2 (C-1), 120.7 (C-2) 118.2 ($COOCH_2CH$═CH_2), 114.7 ($ArCH_2CH$═CH_2), 94.8 (C-7), 65.5 ($COOCH_2CH$═CH_2), 62.7 (OCH_3), 62.0 (OCH_3), 56.9 (OCH_3), 55.8 (OCH_3), 30.1 ($ArCH_2CH$═CH_2); **HR-TOF-MS-ES:** *m/z* found 395.1465 $[M + Na]^+$ (calculated for $C_{21}H_{24}O_6Na$, 395.1471).

(3-Allyl-4,5,6,8-tetramethoxynaphthalen-2-yl)methanol 33

Allyl 3-allyl-4,5,6,8-tetramethoxy-2-naphthoate **32** (1.80 g, 4.83 mmol) was dissolved dry Et_2O (50 ml) and cooled to 0 °C in an ice bath. Lithium aluminium hydride (0.367 g, 9.67 mmol) was added slowly over 5 min. The reaction mixture was then stirred vigorously for 2 h at rt under a nitrogen atmosphere. The solution was then cooled to 0 °C in an ice bath and cold H_2O was added drop-wise until the fizzing stopped. EtOAc (50 ml) was added and the solution was washed with aqueous HCl (2 M, 10 ml). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (40% EtOAc–hexane) of the residue afforded (3-allyl-4,5,6,8-tetramethoxynaphthalen-2-yl)methanol **33** as a white crystalline solid (1.32 g, 86%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 8.02 (1H, s, H-1), 6.64 (1H, s, H-7), 6.07 (1H, tdd, *J* 15.7, 10.5, 5.5, $ArCH_2CH$═CH_2), 5.05–4.94 (1H, m, one of $ArCH_2CH$═CH_2), 4.94–4.81 (1H, m, one of $ArCH_2CH$═CH_2), 4.76 (2H, s, $ArCH_2OH$), 3.98 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.71–3.61 (2H, m, $ArCH_2CH$═CH_2), 2.33 (1H, br s, OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 152.9, 152.6, 150.0, 138.0 ($ArCH_2CH$═CH_2), 136.2 (C-4a), 135.8, 129.3 (C-3), 123.2 (C-2), 122.0 (C-8a), 117.5 (C-1), 115.1 ($ArCH_2CH$═CH_2), 95.0 (C-7), 63.6 ($ArCH_2OH$), 62.8 (OCH_3), 62.0 (OCH_3), 57.1 (OCH_3), 55.8 (OCH_3), 29.8 ($ArCH_2CH$═CH_2).[17]

5,6,7,9-Tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromene 31

(3-Allyl-4,5,6,8-tetramethoxynaphthalen-2-yl)methanol **32** (1.40 g, 4.40 mmol) was dissolved in a DMF–H_2O mixture (1 : 1 v/v, 20 ml). $PdCl_2$ (0.0780 g, 0.440 mmol) and $CuCl_2{\cdot}2H_2O$ (0.750 g, 4.40 mmol) were added to the solution and O_2(g) was bubbled through the solution which was stirred vigorously for 2 h at rt. The reaction was filtered, and EtOAc (2 × 30 ml) was added. The organic layers were combined, washed with H_2O (3 × 20 ml), separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (15% EtOAc–hexane) of the residue afforded **31** as a white crystalline solid (0.890 g, 64%). Mp. = 101–102 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H = 7.61 (1H, s, H-10), 6.57 (1H, s, H-8), 6.18–6.03 (1H, m, H-4), 5.12 (2H, s, H-1), 3.97 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 2.00 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 156.1 (C-3), 152.6, 149.9, 146.1, 136.6, 125.5 (C-4a), 123.9 (C-10a), 123.4 (C-9a), 121.4 (C-5a), 113.0 (C-10), 96.0 (C-4), 94.3 (C-8), 68.7 (C-1), 62.3 (OCH_3), 62.0 (OCH_3), 55.8

(OCH_3), 55.7 (OCH_3), 20.1 (CH_3); **HR-TOF-MS-ES:** *m/z* found 339.1207 $[M + Na]^+$ (calculated for $C_{18}H_{20}O_5Na$, 339.1209).

Acknowledgements

This work was supported by SABINA (Southern African Biochemistry and Informatics for Natural Products Network), the National Research Foundation (NRF, GUN 2053652 and IRDP of the NRF (South Africa) for financial support provided by the Research Niche Areas programme), Pretoria, and the University of the Witwatersrand (Science Faculty Research Council). We also gratefully acknowledge the NRF scarce skills programme for generous funding to MMJ. Mr R Mampa (University of the Witwatersrand) and Ms C. Janse Van Rensburg (University of Kwa-Zulu Natal, Pietermaritzburg) are thanked for providing the NMR and HRMS MS spectroscopy services, respectively. Mr J. Sumani (University of the Witwatersrand) is thanked for purification of some compounds.

Notes and references

1 M. V. Kadkol, K. S. Gopalkrishnan and N. Narasimhachari, *J. Antibiot.*, 1971, **24**, 245–248.
2 P. A. Paranagama, E. M. K. Wijeratne, A. M. Burns, M. T. Marron, M. K. Gunatilaka, A. E. Arnold and A. A. L. Gunatilaka, *J. Nat. Prod.*, 2007, **70**, 1700–1705.
3 K. Trisuwan, N. Khamthong, V. Rukachaisirikul, S. Phongpaichit, S. Preedanon and J. Sakayaroj, *J. Nat. Prod.*, 2010, **73**, 1507–1511.
4 B. Kesteleyn and N. De Kimpe, *J. Org. Chem.*, 2000, **65**, 640–644.
5 D. Wadsworth, J. Sperry and M. A. Brimble, *Synthesis*, 2010, 2604–2608.
6 W. S. Chilton, *J. Org. Chem.*, 1968, **33**, 4299–4300.
7 See for example: (*a*) C. B. de Koning, R. G. F. Giles and I. R. Green, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2743–2748; (*b*) C. B. de Koning, J. P. Michael and W. A. L. van Otterlo, *J. Chem. Soc., Perkin Trans. 1*, 2000, 799–811; (*c*) C. B. de Koning, I. R. Green, J. P. Michael and J. R. Oliveira, *Tetrahedron*, 2001, **57**, 9623–9634; (*d*) E. M. Mmutlane, J. P. Michael, I. R. Green and C. B. de Koning, *Org. Biomol. Chem.*, 2004, **2**, 2461–2470.
8 (*a*) S. Govender, E. M. Mmutlane, W. A. L. van Otterlo and C. B. de Koning, *Org. Biomol. Chem.*, 2007, **5**, 2433–2440; (*b*) For a recent review on these types of Wacker oxidations see: J. Muzart, *Tetrahedron*, 2005, **61**, 5955–6008.
9 W. S. Johnson and G. H. Daub, "The stobbe condensation", in *Organic Reactions*, John Wiley & Sons, Inc., 1951, vol. 6, pp. 1–73.
10 The three data sets were collected using ω-scans on a APEX II CCD area detector diffractometer. The crystals for compound **16** and **17** were prepared by dissolving the samples in CH_2Cl_2 in a vial. These vials were put into bigger vials filled with hexane and the whole system was sealed. Cotton wool was used to keep the inner and outer vials apart. Crystal data for **16**: CCDC 885420, $C_{16}H_{16}O_6$: M_r 304.29 g mol^{-1}; crystal dimensions (mm) 0.42 × 0.25 × 0.22; crystal system, monoclinic; space group, *C*2/*m*; unit cell dimensions and volume, a = 19.2003(6) Å, b = 6.7203(2) Å, c = 11.0340(4) Å, α = 90°, β = 99.379(2)°, γ = 90°, V = 1404.70(8) $Å^3$, no. of formula units in the unit cell Z = 4; calculated density r_{calcd} 1.439 Mg m^{-3}; linear absorption coefficient, m 0.111 mm^{-1}; radiation and wavelength, MoKα = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 8613 and 1842; R_{int} = 0.0473; $R[I > 2.0\sigma(I)]$ = 0.0473, wR = 0.1176, GoF = 1.069, refined on F; residual electron density, 0.247 and −0.363 $eÅ^{-3}$.
11 Crystal data for **17**: CCDC 885421, $C_{16}H_{15}NO_9$: M_r 365.29 g mol^{-1}; crystal dimensions (mm) 0.32 × 0.06 × 0.03; crystal system, monoclinic; space group, $P2_1/c$; unit cell dimensions and volume, a = 13.913(4) Å, b = 13.475(4) Å, c = 8.404(3) Å, α = 90°, β = 94.246(9)°, γ = 90°, V = 1571.2(9) $Å^3$, no. of formula units in the unit cell Z = 4; calculated density r_{calcd}, 1.544 Mg m^{-3}; linear absorption coefficient, m 0.129 mm^{-1}; radiation and wavelength, MoKα = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 7954 and 2722; R_{int} = 0.1022; $R[I > 2.0\sigma(I)]$ = 0.0497, wR = 0.0821, GoF = 0.874, refined on F; residual electron density, 0.184 and −0.196 $eÅ^{-3}$.
12 V. Nair, T. D. Suja and K. Mohanan, *Synthesis*, 2006, 2531–2534.
13 (*a*) A. N. Lowell, M. W. Fennie and M. C. Kozlowski, *J. Org. Chem.*, 2008, **73**, 1911–1918; (*b*) For the initial research in this area on the introduction of an hydroxyl substituent onto an aromatic ring, see for example, the review: T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka and Y. Kita, *Tetrahedron*, 2009, **65**, 10797–10815. In our research limited success wasmet in trying to introduce a hydroxyl substituent onto an aromatic ring with PIFA.
14 The crystals for compound **29** was prepared by dissolving the sample in CH_2Cl_2 in a vial and left overnight: Crystal data for **29**: CCDC 885422, $C_{17}H_{16}O_6$: M_r 316.30 g mol^{-1}; crystal dimensions (mm) 0.41 × 0.40 × 0.06; crystal system, triclinic; space group, $P\bar{1}$; unit cell dimensions and volume, a = 8.4652(2) Å, b = 9.6050(2) Å, c = 9.6340(2) Å, α = 111.5360(10)°, β = 90.649(2)°, γ = 98.224(2)°, V = 719.41(3) $Å^3$, no. of formula units in the unit cell Z = 2; calculated density r_{calcd}, 1.460 Mg m^{-3}; linear absorption coefficient, m 0.111 mm^{-1}; radiation and wavelength, MoKα = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 17 177 and 3470; R_{int} = 0.0442; $R[I > 2.0\sigma(I)]$ = 0.0421, wR = 0.1150, GoF = 1.017, refined on F; residual electron density, 0.346 and −0.222 $e.Å^{-3}$.
15 I. Kurobane, L. C. Vining, A. G. McInnes and J. A. Walter, *Can. J. Chem.*, 1980, **58**, 1380–1385.
16 G. A. Kraus and H. Ogutu, *Tetrahedron*, 2002, **58**, 7391–7395.
17 C. B. de Koning, S. S. Manzini, J. P. Michael, E. M. Mmutlane, T. R. Tshabidi and W. A. L. van Otterlo, *Tetrahedron*, 2005, **61**, 555–564.
18 C.-L. Shao, W.-C. Wang, D.-S. Deng, Z. G. She, Y.-C. Gu and Y.-C. Lin, *Chin. J. Struct. Chem.*, 2008, **27**, 824–828.