ChemPubSoc Europe

DOI: 10.1002/ejoc.201801595

EurJOC European Journal of Organic Chemistry

Full Paper

Wacker Oxidation

The synthesis of 9-*O*-Methylpaepalantine and Dehydroxanthomegnin: Related Isocoumarin-Containing Natural Products

Jimmy E. Y. Sumani,[a] Kennedy J. Ngwira,[a] Andreas Lemmerer,[a] and Charles B. de Koning*[a]

Abstract: The first synthesis of two related isocoumarin-containing natural products, 9-*O*-methylpaepalantine and dehydroxanthomegnin is described. Commencing with 2,4-dimethoxybenzaldehyde and utilizing the Stobbe reaction as a key step resulted in the formation of the required naphthalene containing compound, ethyl 4-acetoxy-3-allyl-6,8-dimethoxynaphthalene-2-carboxylate. *O*-Allylation of 4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate followed by a Claisen rearrangement afforded the naphthol, ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate. Introduction of a methoxy substituent onto the 1-position of the naphthalene nucleus utilizing a PIFA-mediated method afforded, after *O*-methylation, ethyl 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylate. Reduction of the ester was followed by oxidation to the aromatic acid, utilizing firstly a PCC oxidation and then a Pinnick oxidation to afford 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylic acid. Wacker oxidation of the aromatic acid resulted in the formation of 5,7,9,10-tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one, which was then converted into 9-*O*-methylpaepalantine by treatment with boron trichloride. Utilizing similar synthetic methodology dehydroxanthomegnin was synthesized in thirteen steps commencing from 2,4,5-trimethoxybenzaldehyde in an overall yield of 1.3 %.

Introduction

Anhydrofusarubin lactone **1** and the related quinone containing naphthopyranone 5-methoxy-3,4-dehydrosemixanthomegnin **2** (also referred to as 5-methoxy-3,4-dehydroxanthomegnin or dehydroxanthomegnin) belong to a growing class of quinone containing compounds (Figure 1).[1] Anhydrofusarubin lactone **1**[2] is found in several fungi such as *Nectria haematococca* and *Fusarium solani*, while 5-methoxy-3,4-dehydrosemixanthomegnin **2**[3] has been isolated from *Paepalanthus latipes* Silveira, Eriocaulaceae, often found in Brazil. A related compound, paepalantine **3** and its dimer **4** have been isolated from a related Eriocaulaceae species *Paepalanthus bromelioides*,[4] as well as *Paepalanthus vellozioides*.[5]

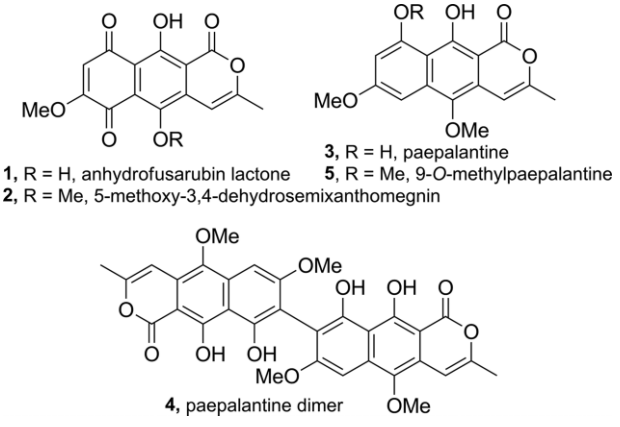


Figure 1. Naturally occurring isocoumarins.

This class of isocoumarin-containing compounds shows a wide range of biological activities. For example, 5-methoxy-3,4-dehydrosemixanthomegnin **2** shows cytotoxicity against murine mammary tumor cells (LM2, CI_{50} 74.6 μM) and lung adenocarcinoma cells (LPO7, CI_{50} 6.2 μM)[6] while paepalantine **3** shows antimicrobial activity against bacteria including *Bacillus cereus* (MIC 7.5 μg mL^{-1}), *Staphylococcus aureus* (MIC 7.5 μg mL^{-1}) and *Staphylococcus epidermidis* (MIC 15 mg mL^{-1}).[7] In addition, both of these isocoumarins show promising activity against the *Helicobacter pylori* bacterium, which is one of the main causes of chronic gastritis, peptic ulcers and possibly gastric cancer.[8,9] As a result of our interest in the synthesis of isochromanes[10] we envisaged that the synthesis of the isocoumarins, 5-methoxy-3,4-dehydrosemixanthomegnin **2** and paepalantine **3** could be accomplished in our laboratories.

In this paper we describe the first synthesis of 5-methoxy-3,4-dehydrosemixanthomegnin **2** and 9-*O*-methylpaepalantine **5**, a methoxy derivative of paepalantine **3**. A key step in the synthesis of both of these isocoumarins is a Wacker-mediated ring closure of the aromatic carboxylic acids **6** and **7** bearing an allyl substituent to afford the isocoumarins **8** and **9** respectively (Figure 2).

[a] *Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits 2050, Johannesburg, South Africa*
E-mail: Charles.deKoning@wits.ac.za

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201801595.

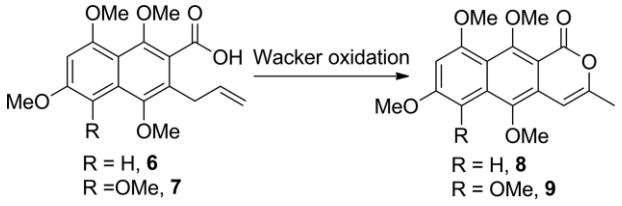
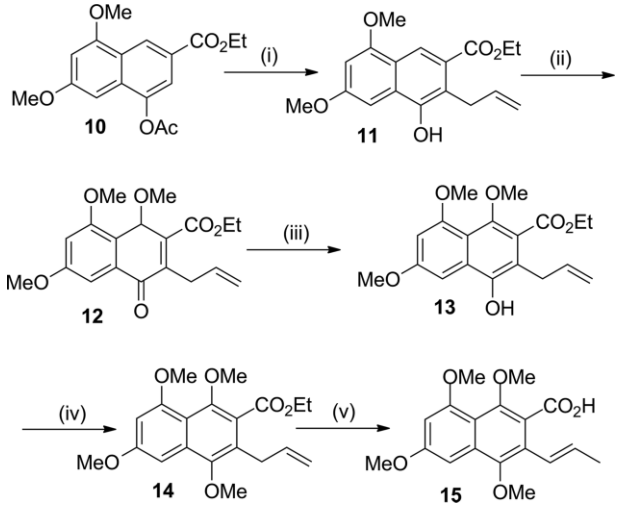


Figure 2. Wacker-mediated oxidations for the synthesis of isocoumarins **8** and **9**.

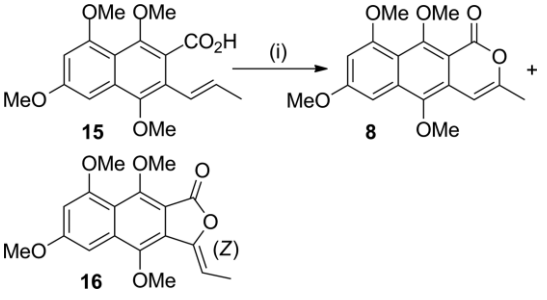
Results and Discussion

As a starting point for the synthesis of 9-*O*-methylpaepalantine **5**, the preparation of the naphthalene containing acid **6** was needed. As described in the literature[10a] commencing with 2,4-dimethoxybenzaldehyde, treatment with diethyl succinate and potassium *tert*-butoxide in the Stobbe condensation reaction, followed by an aromatic ring forming procedure afforded naphthalene **10**. As previously described, selective removal of the acetate of **10**, followed by *O*-allylation and a Claisen rearrangement afforded the naphthol **11** as shown in Scheme 1. Following protocols developed in our laboratories[10c] the extra aromatic methoxy substituent was introduced onto the naphthalene nucleus by treatment of **11** with phenyliodine(III) bis(trifluoroacetate (PIFA) in methanol to afford the intermediate **12**. In contrast to our previous work re-aromatization was best accomplished by treatment of **12** with potassium *tert*-butoxide in ethanol to afford **13** in a 60 % yield. Protection of the naphthol **13** as the methyl ether afforded **14**. The stage was now set to convert the ester of **14** into the corresponding aromatic acid **6**. Although a stubbornly slow reaction, treatment of **14** with potassium hydroxide in an aqueous alcohol solution at reflux was the best method for achieving this conversion (55 % yield). Unfortunately, at the same time isomerization of the allyl substituent occurred resulting in the styrene **15** (Scheme 1).



Scheme 1. *Reagents and conditions:* (i) (a) 1 % KOH, EtOH/H_2O, r.t., 3 h; (b) *32 %* aq. HCl, 88 %; (c) K_2CO_3, allyl bromide, Me_2CO, reflux, 24 h, 87 %; (d) heat, 180 °C, N_2(g) atm, 24 h, 69 %; (ii) PIFA, MeOH, r.t., 15 min; (iii) *t*BuOK, EtOH, r.t., 20 min, 60 %; (iv) K_2CO_3, Me_2SO_4, Me_2CO, reflux, 24 h, 89 %; (v) (a) NaOH/KOH, MeOH/H_2O, reflux, 84 h; (b) *32 %* aq. HCl, 55 %.

We were now in a position to test one of the key steps of the synthesis, the Wacker mediated ring closure. Exposure of naphthalene **15** to catalytic palladium in the presence of a copper(II) source afforded the desired isocoumarin **8** in 47 % yield (Scheme 2). Disappointingly, a second product produced in a significant yield was the five membered analogue **16** (21 %). The structure of both compounds **8** and **16** was determined by X-ray crystallography (Figure 3).[11] All other hydrolysis methods for the conversion of **14** into the desired allyl-containing compound **6** were unsuccessful.[12] Hence alternative methodology had to be sought.



Scheme 2. *Reagents and conditions*: (i) cat. $PdCl_2$, $CuCl_2$•$2H_2O$, DMF/H_2O, O_2(g) atm, r.t., 24 h, **8** 47 %, **16** 21 %.

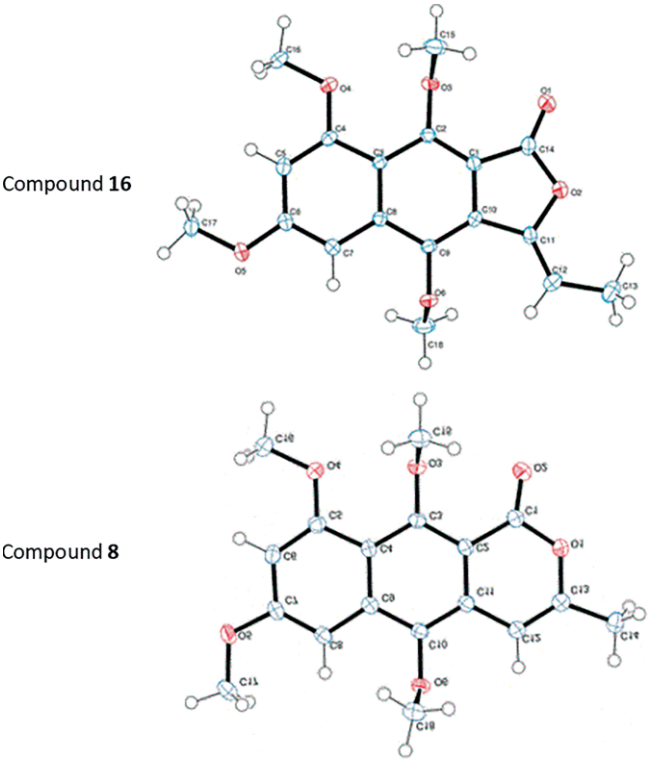
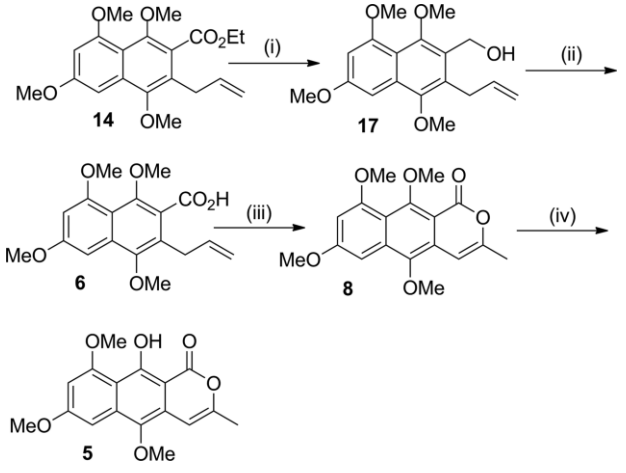


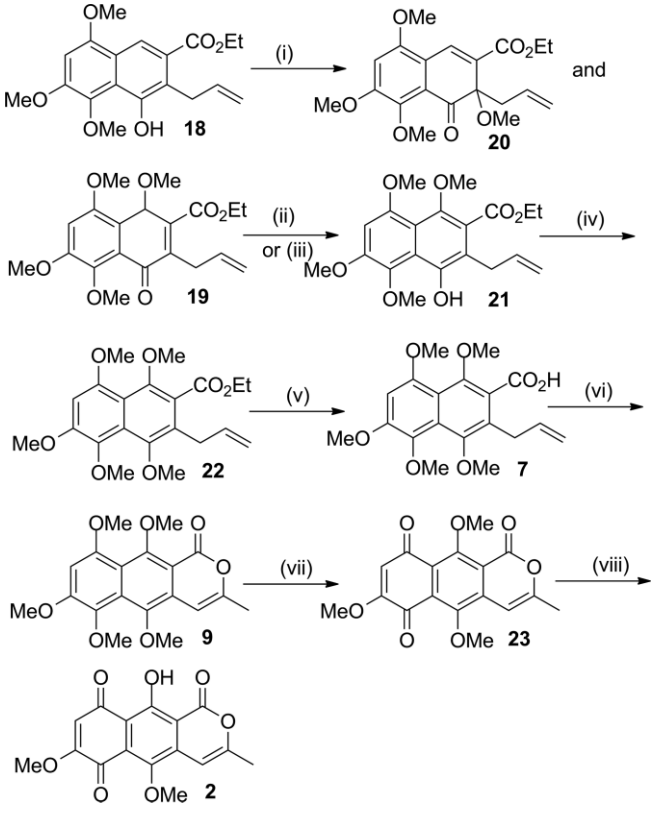
Figure 3. ORTEP diagrams of compounds **16** and **8** (displacement ellipsoids at 50 % probability).

Reduction of the ester group of **14** with lithium aluminium hydride afforded the primary alcohol **17**. Oxidation of **17** to the intermediate aldehyde was followed by a Pinnick oxidation to afford the desired aromatic acid **6** containing the required allyl

substituent (Scheme 3). Subjecting **6** to Wacker oxidation conditions gratifyingly only yielded the desired isocoumarin **8** in good yield. Treatment of **8** with boron trichloride afforded 9-*O*-methylpaepalantine **5** in a reasonable yield. However, none of the methods[13] we attempted resulted in the cleavage of the final *O*-methyl substituent to furnish paepalantine.



Scheme 3. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C, 4 h; (ii) (a) PCC, silica, CH_2Cl_2, N_2(g) atm, 4 h; (b) NaH_2PO_4, $NaClO_2$, H_2O, *t*BuOH, 2-methyl-2-butene, 6 h, 60 % over three steps (including the reduction step); (iii) (a) cat. $PdCl_2$, $CuCl_2$·$2H_2O$, DMF/H_2O, O_2(g) atm, r.t., 24 h, 70 %; (iv) BCl_3, CH_2Cl_2, N_2(g) atm, –78 °C → r.t., 65 %.



Scheme 4. *Reagents and conditions*: (i) PIFA, MeOH, r.t., 15 min; (ii) NaOEt, EtOH, r.t., 20 min 10 % **20**, 52 % **21**; or (iii) *t*BuOK, EtOH, r.t., 20 min., 60 % (over two steps from **18**); (iv) K_2CO_3, Me_2SO_4, Me_2CO, reflux, 24 h, 83 %; (v) (a) $LiAlH_4$, THF, 0 °C, 4 h; (b) PCC, silica gel, 4 h, N_2(g) atm; (c) NaH_2PO_4, $NaClO_2$, H_2O, *t*BuOH, 2-methyl-2-butene, 6 h, 66 % (over 3 steps); (vi) cat. $PdCl_2$, $CuCl_2$·$2H_2O$, DMF/H_2O, O_2(g) atm, r.t., 24 h, 72 %; (vii) AgO, 55 % aq. HNO_3, 1,4-dioxane, r.t., 75 %; (viii) 2 mol. equiv. BCl_3, CH_2Cl_2, N_2(g) atm, –78 °C → r.t., 20 %.

As the synthesis of 9-*O*-methylpaepalantine **5** had been successful we wished to apply the same methodology to the synthesis of 5-methoxy-3,4-dehydrosemixanthomegnin **2**. Using the same synthetic methodology naphthol **18** could easily be prepared in 34 % yield over five steps from 2,4,5-trimethoxybenzaldehyde.[14] Treatment of **18** with PIFA in methanol followed by sodium ethoxide in ethanol resulted in the formation of the desired product **21** (*via* **19** as shown in Scheme 4). However, a small amount of a product identified as **20**, (Figure 4a)[15] where methanol had added *ortho* to the naphthol substituent of **18** was also isolated. The best way to accomplish this transformation (**18** → **21**) was by subjecting **18** to PIFA in methanol and then potassium *tert*-butoxide in ethanol which afforded **21** in a 60 % yield. The naphthol of **21** was easily converted into naphthalene ether **22** (Figure 4b).[16] Again, conversion of the ester of **22** into the acid **7** was accomplished by reduction, followed by oxidation with PCC and further Pinnick oxidation to furnish **7**. Wacker oxidation of **7** resulted in the formation of the desired isocoumarin **9** (Figure 4c) in a yield of 72 %.[17] Oxidation of **9** with silver(II) oxide resulted in the formation of the quinone **23**. Finally, treatment of **23** with boron trichloride at low temperature gave the final product, 5-methoxy-3,4-de-

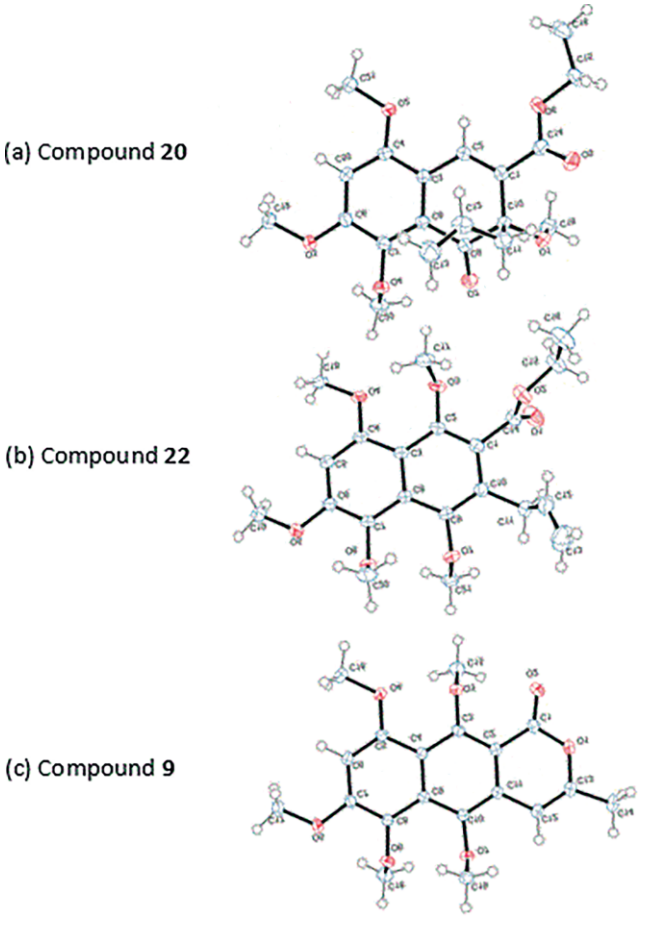


Figure 4. a-c: ORTEP diagrams of compounds **20**, **22** and **9** (displacement ellipsoids at 50 % probability).

hydrosemixanthomegnin **2** in a poor yield of 20 %. We suspect this was as a result of our purification method by using silica gel chromatography.

Conclusion

In summary, the synthesis of two related isocoumarin containing natural products has been accomplished. 9-*O*-methylpaepalantine **5** was synthesized in twelve steps from 2,4-dimethoxybenzaldehyde in an overall yield of 6.2 %. Commencing with 2,4,5-trimethoxybenzaldehyde the synthesis of 5-methoxy-3,4-dehydrosemixanthomegnin **2** was accomplished in thirteen steps in an overall yield of 1.3 %. In each of these syntheses, one of the key steps was a Wacker-mediated oxidation to convert the aromatic carboxylic acids **6** and **7**, bearing an *ortho*-allyl substituent, to afford in good yields the isocoumarins **8** and **9** respectively.

Experimental Section

Solvents utilized for chromatographic techniques (ethyl acetate and *n*-hexane) were distilled prior to use by means of conventional distillation processes. The solvents employed in reactions were first dried with the suitable drying agent, followed by distillation under an inert atmosphere (argon or nitrogen gas). Acetonitrile and dichloromethane were distilled from calcium hydride, whereas tetrahydrofuran was distilled from sodium with benzophenone as an indicator. Toluene was distilled from sodium. All the required chemicals or reagents were obtained from FLUKA, SIGMA ALDRICH or MERCK and were used without further purification.

Normal chromatography was performed with silica gel 60 (Macherey-Nagel, particle size 0.063–0.200 mm) adsorbent, with both isocratic and gradient eluent systems being employed. Thin layer chromatography (TLC) of the compounds was executed on Macherey-Nagel Alugram Silica G/UV254 plates pre-coated with 0.25 mm silica gel 60. The TLC plates were viewed under UV light (254 nm and 366 nm).

Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker AVANCE 300 MHz or a Bruker AVANCE III 500 MHz spectrometer. All chemical shift values are reported in parts per million referenced against tetramethylsilane which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in Hertz (Hz).

X-ray Crystallography: All five data sets were collected using ω-scans on a Bruker D8 Venture diffractometer with a PHOTON detector.

The infrared spectra were recorded on a Bruker Tensor 27 standard system spectrometer. Measurements were made by loading the sample directly onto a diamond cell. The measurements are reported on the wavenumber scale (cm^{-1}).

Melting points were determined on a Reichert hot-stage microscope and remain uncorrected. All crystalline compounds were recrystallized from the appropriate solvents prior to melting point determination. Microwave reactions were conducted in a CEM Discover microwave.

High-resolution mass spectra were obtained with a Waters-LCT-Premier mass spectrometer. The sample was dissolved in methanol to a concentration of 2 ng/μL 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 nitrogen gas at 250 L/hr.

Ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate **11**[10a]

Ethyl 4-(allyloxy)-6,8-dimethoxynaphthalene-2-carboxylate [10a] (4.00 g, 12.6 mmol) was loaded neat in a 100 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. The flask was then heated to 180 °C in a silicone oil bath for 24 h under a N_2(g) atmosphere. After 24 h, the dark viscous residue was cooled to r.t., dissolved in acetone and adsorbed on silica gel. Purification of the crude product on silica gel column chromatography (20 % EtOAc/hexane) yielded ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate **11** as a yellow amorphous solid (2.75 g, 69 %). R_f = 0.41 (20 % EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ_H 8.37 (1H, s, H-1), 7.04 (1H, s, H-5), 6.50 (1H, s, H-7), 6.25–6.04 (1H, m, $ArCH_2CH{=}CH_2$), 5.65 (1H, s, ArOH), 5.23 (1H, dd, *J* = 3.8, 1.6, one of $ArCH_2CH{=}CH_2$), 5.18 (1H, dd, *J* = 3.5, 1.6, one of $ArCH_2CH{=}CH_2$), 4.38 (2H, q, *J* = 7.1, $ArCO_2CH_2CH_3$), 3.97 (3H, s, $ArOCH_3$), 3.94 (3H, s, $ArOCH_3$), 3.92 (2H, d, *J* = 6.0, $ArCH_2CH{=}CH_2$), 1.42 (3H, t, *J* = 7.1, $ArCOOCH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ_C 168.3 ($ArCO_2CH_2CH_3$), 160.1 (C-6), 157.2 (C-8), 149.7 (C-4), 136.4 ($ArCH_2CH{=}CH_2$), 128.4 (C-4a), 125.6 (C-2), 120.3 (C-8a), 118.8 (C-3), 118.5 ($ArCH_2CH{=}CH_2$), 116.2 (C-1), 98.8 (C-7), 92.3 (C-5), 60.8 ($ArCO_2CH_2CH_3$), 55.6 ($ArOCH_3$), 55.4 ($ArOCH_3$), 31.8 ($ArCH_2CH{=}CH_2$), 14.4 ($ArCO_2CH_2CH_3$).

Ethyl 3-allyl-4-hydroxy-1,6,8-trimethoxynaphthalene-2-carboxylate **13**[18]

To a solution of ethyl 3-allyl-4-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate **11** (3.50 g, 11.1 mmol) in absolute MeOH (80 mL), was added solid phenyliodine(III) bis(trifluoroacetate (PIFA) (5.12 g, 11.9 mmol) and the reaction mixture was stirred for 15 min at r.t. After the 15 min had elapsed, saturated aqueous $NaHCO_3$ was added to the reaction mixture portion-wise until effervescence stopped and MeOH was removed in vacuo. The aqueous layer was then extracted with EtOAc (3 × 100 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, filtered through a celite pad and concentrated under reduced pressure. The residue was dissolved in EtOH in a clean 250 mL round-bottomed flask to which *t*BuOK (3.32 g, 29.6 mmol) was added and the resultant reaction mixture was vigorously stirred for 20 min at r.t. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the resultant mixture was concentrated under reduced pressure. The aqueous medium was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite pad and the solvents evaporated in vacuo. Purification of the residue by column chromatography (20 % EtOAc/hexane) on silica gel afforded ethyl 3-allyl-4-hydroxy-1,6,8-trimethoxynaphthalene-2-carboxylate **13** as a pale-orange semi-solid (2.31 g, 60 %). R_f = 0.37 (20 % EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 7.08 (1H, s, H-5), 6.53 (1H, s, H-7), 6.19–5.89 (1H, m, $ArCH_2CH{=}CH_2$), 5.56 (1H, s, ArOH), 5.25 (2H, d, *J* = 16.9, $ArCH_2CH{=}CH_2$), 4.40 (2H, q, *J* = 7.1, $ArCO_2CH_2CH_3$), 3.87 (9H, two br d, 3 overlapping $ArOCH_3$), 3.43 (2H, br s, $ArCH_2CH{=}CH_2$), 1.38 (3H, t, *J* = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 168.5 ($ArCO_2CH_2CH_3$), 158.8 (C-6), 157.5 (C-8), 147.5 (C-1), 145.5 (C-4), 135.4 ($ArCH_2CH{=}CH_2$), 129.4 (C-4a), 124.7 (C-3), 117.2 ($ArCH_2CH{=}CH_2$), 116.3 (C-8a), 115.2 (C-2), 99.5 (C-7), 92.8 (C-5), 61.3 ($ArCO_2CH_2CH_3$), 58.4 ($ArOCH_3$), 56.0 ($ArOCH_3$), 55.3 ($ArOCH_3$), 32.9 ($ArCH_2CH{=}CH_2$), 14.3 ($ArCO_2CH_2CH_3$).

Ethyl 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylate **14**

A mixture of ethyl 3-allyl-4-hydroxy-1,6,8-trimethoxynaphthalene-2-carboxylate **13** (2.30 g, 6.64 mmol), anhydrous K_2CO_3 (1.17 g,

8.50 mmol) and Me_2SO_4 (0.804 mL, 8.50 mmol) in acetone (100 mL) was heated under reflux for 24 h under a N_2(g) atmosphere. The reaction mixture was then cooled to r.t., filtered through a celite pad and the solvent removed in vacuo. The resultant residue was dissolved in EtOAc (100 mL) and successively washed with 25 % (v/v) aqueous NH_3 (2 × 50 mL). The EtOAc layer was then acidified to pH 4 with 32 % (v/v) aqueous HCl and the acidic solution was washed with deionised H_2O until the aqueous layer was neutral. The organic layer was dried with anhydrous $MgSO_4$, filtered through a bed of celite and concentrated in vacuo. Purification of the residue by silica gel column chromatography (10 % EtOAc/hexane) yielded ethyl 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylate **14** as a light-yellow solid (2.13 g, 89 %). **R_f** = 0.41 (20 % EtOAc/hexane); Mp 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 6.98 (1H, d, *J* = 2.2, H-5), 6.53 (1H, d, *J* = 2.2, H-7), 5.98 (1H, ddt, *J* = 16.4, 10.1, 6.2, $ArCH_2CH{=}CH_2$), 5.07 (2H, dd, *J* = 3.7, 1.7, $ArCH_2CH{=}CH_2$), 4.39 (2H, q, *J* = 7.1, $ArCO_2CH_2CH_3$), 3.94 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), 3.85 (6H, br s, two overlapping $ArOCH_3$), 3.57 (2H, d, *J* = 6.2, $ArCH_2CH{=}CH_2$), 1.38 (3H, t, *J* = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 168.0 ($ArCO_2CH_2CH_3$), 159.3 (C-6), 157.9 (C-8), 150.4 (C-1 or C-4), 149.3 (C-1 or C-4), 136.3 ($ArCH_2CH{=}CH_2$), 132.7 (C-4a), 126.6 (C-3), 125.1 (C-8a), 115.9 ($ArCH_2CH{=}CH_2$), 115.3 (C-2), 99.2 (C-7), 93.2 (C-5), 63.8 ($ArCO_2CH_2CH_3$), 61.6 ($ArOCH_3$), 61.1 ($ArOCH_3$), 56.1 ($ArOCH_3$), 55.3 ($ArOCH_3$), 31.8 ($ArCH_2CH{=}CH_2$), 14.3 ($ArCO_2CH_2CH_3$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{20}H_{25}O_6$ 361.1646 found $[M + H]^+$ 361.1649.

1,4,6,8-Tetramethoxy-3-((*E*)-prop-1-enyl)naphthalene-2-carboxylic acid **15**

To a solution of ethyl 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylate **14** (2.10 g, 5.83 mmol) in MeOH (100 mL) was added an aqueous solution of NaOH (0.933 g, 23.32 mmol) in H_2O (50 mL) and the resultant reaction mixture was heated under reflux for 36 h. To this reaction mixture, an aqueous solution of KOH (1.59 g, 28.3 mmol) in H_2O (50 mL) was added portion-wise and the resultant mixture was again heated under reflux for 48 h (monitored by TLC). The mixture was then cooled to r.t. and the solvent was concentrated under reduced pressure. The remaining aqueous medium was carefully acidified to pH 4.0 with 32 % (v/v) aqueous HCl and extracted with EtOAc (3 × 150 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered through a celite bed and concentrated in vacuo. The residue was purified by column chromatography (20 % EtOAc/hexane). The isolated product was then dissolved in hot solution of 20 % EtOAc/hexane and allowed to slowly crystallize yielding 1,4,6,8-tetramethoxy-3-((*E*)-prop-1-enyl)naphthalene-2-carboxylic acid **15** as white crystals (1.07 g, 55 %). R_f = 0.26 (40 % EtOAc/hexane). Mp 138–140 °C; IR ν_{max} (cm^{-1}) 3680 (O-H), 1681 (C=O), 1545 (C=C); ^{1}H NMR (300 MHz, MeOD) δ_H 7.05 (1H, d, *J* = 2.3, H-5), 6.63 (1H, d, *J* = 2.2, H-7), 6.57 (1H, dq, *J* = 16.1, 1.5, $ArCH{=}CHCH_3$), 6.41 (1H, dq, *J* = 16.1, 6.3, $ArCH{=}CHCH_3$), 3.96 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 3.79 (3H, s, $ArOCH_3$), 1.93 (3H, dd, *J* = 6.4, 1.4, $ArCH{=}CHCH_3$); ^{13}C NMR (75 MHz, MeOD) δ_C 170.7 ($ArCO_2H$), 159.6 (C-6), 157.6 (C-8), 149.1 (C-1 or C-4), 148.8 (C-1 or C-4), 132.4 ($ArCH{=}CHCH_3$), 131.5 (C-4a), 124.5 ($ArCH{=}CHCH_3$), 124.3 (C-2), 123.7 (C-3), 114.8 (C-8a), 99.2 (C-7), 92.9 (C-5), 62.7 ($ArOCH_3$), 59.5 ($ArOCH_3$), 55.1 ($ArOCH_3$), 54.4 ($ArOCH_3$), 18.2 ($ArCH{=}CHCH_3$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{18}H_{21}O_6$: 333.1333, found $[M + H]^+$ 333.1336.

5,7,9,10-Tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **8** and (*Z*)-3-ethylidene-4,6,8,9-tetramethoxynaphtho[2,3-*c*]furan-1(3*H*)-one **16**

1,4,6,8-Tetramethoxy-3-((*E*)-prop-1-enyl)naphthalene-2-carboxylic acid **15** (1.00 g, 3.01 mmol) and $CuCl_2{\cdot}2H_2O$ (0.597 g, 3.50 mmol) were dissolved in DMF/H_2O mixture (2:1, v/v, 100 mL) in a 2-neck round-bottomed flask to which $PdCl_2$ (53.4 mg, 0.301 mmol) was added under the atmosphere of O_2(g). The reaction mixture was vigorously stirred for 24 h at r.t. after which it was filtered through a thick celite bed which was washed slowly with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL) and dried with anhydrous $MgSO_4$, filtered through a pad of celite and the solvent was removed in vacuo. Purification of the crude residue by column chromatography (EtOAc/CH_2Cl_2/hexane, 2:1:7) on silica gel afforded two compounds. The first compound was 5,7,9,10-tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **8**,obtained as a light-yellow solid (0.467 g, 47 %). R_f = 0.38 (EtOAc/CH_2Cl_2/hexane, 3:1:6); Mp 154–156 °C; IR ν_{max}(cm^{-1}) 1689 (C=O), 1603 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 6.98 (1H, d, *J* = 2.3, H-6), 6.51 (1H, d, *J* = 2.3, H-8), 6.48 (1H, s, H-4), 3.99 (3H, s, $ArOCH_3$), 3.97 (3H, s, $ArOCH_3$), 3.96 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), 2.27 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 161.4 (C-7), 160.0 (C-1), 159.4 (C-9), 159.3 (C-10), 153.4 (C-3), 143.7 (C-5), 135.5 (C-5a), 126.6 (C-4a), 116.4 (C-9a), 108.6 (C-10a), 99.4 (C-8), 97.3 (C-6), 92.2 (C-4), 62.9 ($ArOCH_3$), 61.6 ($ArOCH_3$), 56.4 ($ArOCH_3$), 55.5 ($ArOCH_3$), 19.8 (CH_3); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{18}H_{19}O_6$: 331.1176, found $[M + H]^+$ 331.1181. The second compound was (*Z*)-3-ethylidene-4,6,8,9-tetramethoxynaphtho[2,3-*c*]furan-1(3*H*)-one **16**,obtained as a yellow crystalline solid (0.209 g, 21 %): R_f = 0.40 (EtOAc/CH_2Cl_2/hexane, 3:1:6); Mp 154–156 °C); IR ν_{max}(cm^{-1}) 1762 (C=O), 1679 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 7.02 (1H, d, *J* = 2.3, H-5), 6.56 (1H, d, *J* = 2.2, H-7), 5.92 (1H, q, *J* = 7.3, $ArC{=}CHCH_3$), 4.06 (3H, s, $ArOCH_3$), 3.98 (3H, s, $ArOCH_3$), 3.97 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 2.04 (3H, d, *J* = 7.3, $ArC{=}CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 164.8 (C-1), 161.3 (C-6), 160.1 (C-8), 155.4 (C-9), 144.5 (C-3), 143.8 (C-4), 137.0 (C-4a), 125.4 (C-3a), 117.5 (C-8a), 111.2 (C-9a), 106.8 ($ArC{=}CHCH_3$), 99.9 (C-7), 93.1 (C-5), 63.4 ($ArOCH_3$), 59.9 ($ArOCH_3$), 56.3 ($ArOCH_3$), 55.5 ($ArOCH_3$), 11.7 ($ArC{=}CHCH_3$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{18}H_{19}O_6$: 331.1176, found $[M + H]^+$ 331.1174.

Allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylic acid **6**

To a solution of ethyl 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylate **14** (4.20 g, 10.76 mmol) in dry THF (200 mL), cooled to 0 °C in an ice bath, $LiAlH_4$ (0.569 g, 15.0 mmol) was added portion-wise over a period of 10 min. The reaction mixture was warmed to r.t. and stirred for a further 4 h under an N_2(g) atmosphere. The mixture was again cooled to 0 °C in an ice bath and cold H_2O was added dropwise until effervescence stopped. A 32 % (v/v) aqueous HCl (10 mL) was then added and the resultant mixture was filtered through a thick celite bed and the THF was removed in vacuo. The aqueous medium was extracted with EtOAc (3 × 100 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, filtered through a celite bed and concentrated under reduced pressure. The thick brown residue was carried forward without further purification apart from noting the difference in R_f value compared to the starting material. The presumed alcohol intermediate **17** was dissolved in CH_2Cl_2 (200 mL) and silica gel (2.00 g) was added followed by PCC (4.31 g, 20.0 mmol) in two portions. The reaction mixture was stirred under N_2(g) atmosphere for 4 h as monitored by TLC. After the starting material was completely consumed, the reaction mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo. The resultant viscous brown oil was taken to the next step without further purification. The crude intermediate was dissolved in 2-methyl-2-butene (113 mL) to which H_2O (150 mL), *t*BuOH (150 mL), $NaClO_2$ (5.43 g, 60.0 mmol) and NaH_2PO_4 (7.20 g, 60.0 mmol) were added. The biphasic mixture was stirred rapidly for 6 h after which the layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL). The combined

organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography. The isolated product was recrystallized from a hot solution (20 % EtOAc/hexane) to afford allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylic acid **6** as white crystals (2.34 g, 60 %). R_f = 0.26 (40 % EtOAc/hexane); Mp 138–140 °C; IR ν_{max} (cm^{-1}) 3680 (O-H), 1681 (C=O), 1545 (C=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 10.82 (1H, s, $ArCO_2H$), 7.00 (1H, d, J = 2.3, H-5), 6.55 (1H, d, J = 2.3, H-7), 6.01 (1H, ddt, J = 16.3, 10.1, 6.2, $ArCH_2CH{=}CH_2$), 5.12 (2H, dd, J = 2.8, 1.7, $ArCH_2CH{=}CH_2$), 3.97 (3H, s, $ArOCH_3$), 3.94 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 3.69 (2H, d, J = 6.2, $ArCH_2CH{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 172.3 ($ArCO_2H$), 159.7 (C-6), 158.0 (C-8), 150.9 (C-4), 149.5 (C-1), 136.3 ($ArCH_2CH{=}CH_2$), 133.1 (C-2), 126.9 (C-4a), 123.5 (C-3), 116.1 ($ArCH_2CH{=}CH_2$), 115.2 (C-8a), 99.5 (C-7), 93.4 (C-5), 64.1 ($ArOCH_3$), 61.6 ($ArOCH_3$), 56.1 ($ArOCH_3$), 55.4 ($ArOCH_3$), 31.6 ($ArCH_2CH{=}CH_2$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{18}H_{21}O_6$: 333.1333, found $[M + H]^+$ 333.1332.

5,7,9,10-Tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **8**

In a 2-neck round-bottomed flask equipped with a magnetic stirring bar and charged with 3-allyl-1,4,6,8-tetramethoxynaphthalene-2-carboxylic acid **6** (2.00 g, 6.02 mmol) and $CuCl_2{\cdot}2H_2O$ (1.53 g, 9.00 mmol) in DMF/H_2O mixture (2:1 v/v, 100 mL), was added $PdCl_2$ (0.107 g, 0.602 mmol) under an atmosphere of O_2(g) and the mixture was stirred vigorously for 24 h at r.t. The reaction mixture was then filtered through a thick celite pad and the pad was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried with anhydrous $MgSO_4$, filtered and the solvent was removed in vacuo. The residue was adsorbed onto silica gel and purification was accomplished using flash silica gel column chromatography (EtOAc/hexane/CH_2Cl_2, 2:1:7) to afford 5,7,9,10-tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **8** as a cream crystalline solid (1.39 g, 70 %). The ^1H NMR and ^{13}C NMR spectra were the same as those outlined previously.

9-*O*-Methylpaepalantine **5**

5,7,9,10-Tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **8** (0.400 g, 1.21 mmol) was dissolved in a freshly distilled CH_2Cl_2 (100 mL) in a 2-neck round-bottomed flask fitted with a rubber septum and cooled to –78 °C under an N_2(g) atmosphere. BCl_3 (2.40 mL, 2.40 mmol) was slowly added to the solution via a syringe and the reaction mixture was stirred for a further 40 min at –78 °C. The mixture was then warmed to r.t. and stirred at this temperature for 2 h. After the 2 h had elapsed, the mixture was again cooled to –78 °C and BCl_3 (2.40 mL, 2.40 mmol) was slowly added to the solution for the second time using a syringe. The reaction mixture was stirred for a further 40 min at –78 °C. Thereafter, it was warmed to r.t. and stirred at this temperature for 2 h. The reaction was then carefully quenched with ice cold H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite bed and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (20 % EtOAc/hexane) afforded 9-*O*-methylpaepalantine **5** as a yellow amorphous solid (0.249 g, 65 %). R_f = 0.43 (3:2:5 EtOAc/hexane/CH_2Cl_2); Mp 197–199 °C; IR ν_{max} (cm^{-1}) 3580 (O-H), 1701 (C=O), 1620 (C=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 12.79 (1H, s, H-10), 6.86 (1H, d, J = 2.0, H-6), 6.44 (1H, s, H-4), 6.40 (1H, d, J = 2.0, H-8), 3.96 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 2.24 (3H, s, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 160.0 (C-1), 161.4 (C-7), 159.4 (C-9), 159.3 (C-10), 153.4 (C-3), 143.7 (C-5), 135.5 (C-5a), 126.6 (C-4a), 116.4 (C-9a), 108.6 (C-10a), 99.4 (C-8), 97.3 (C-6), 92.2 (C-4), 62.9 ($ArOCH_3$), 61.6 ($ArOCH_3$), 56.4 ($ArOCH_3$), 19.8 (C-3′); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{17}H_{17}O_6$: 317.1020 found $[M + H]^+$ 317.1021.

Ethyl 4-(allyloxy)-5,6,8-trimethoxynaphthalene-2-carboxylate[14]

To a solution of ethyl 4-hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylate[17] (3.80 g, 12.4 mmol) in acetone (100 mL) was added anhydrous K_2CO_3 (2.07 g, 15.0 mmol) followed by allyl bromide (1.81 g, 15.0 mmol). The reaction mixture was heated under reflux for 24 h under a N_2(g) atmosphere. After this time had elapsed, the reaction mixture was cooled to r.t., filtered through a celite pad and the solvent evaporated in vacuo. The residue was purified by silica gel column chromatography (10 % EtOAc/hexane) yielding ethyl 4-(allyloxy)-5,6,8-trimethoxynaphthalene-2-carboxylate as a yellow amorphous solid (3.82 g, 89 %). R_f = 0.56 (20 % EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 8.56 (1H, d, J = 1.5, H-1), 7.43 (1H, d, J = 1.4, H-3), 6.67 (1H, s, H-7), 6.20 (1H, ddt, J = 17.1, 10.4, 5.1, $ArOCH_2CH{=}CH_2$), 5.60 (1H, dd, J = 17.2, 1.6, one of $ArOCH_2CH{=}CH_2$), 5.33 (1H, dd, J = 10.5, 1.4, one of $ArOCH_2CH{=}CH_2$), 4.71 (2H, d, J = 5.1, $ArOCH_2CH{=}CH_2$), 4.41 (2H, q, J = 7.1, $ArCO_2CH_2CH_3$), 3.98 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 1.43 (3H, t, J = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 167.1 ($ArCO_2CH_2CH_3$), 153.4 (C-8), 149.3 (C-4), 136.4 (C-6), 126.6 ($ArOCH_2CH{=}CH_2$), 124.4 (C-5), 121.9 (C-2), 120.5 (C-8a), 116.5 (C-4a), 110.4 (C-1), 107.3 ($ArOCH_2CH{=}CH_2$), 105.0 (C-3), 99.6 (C-7), 63.9 ($ArOCH_2CH{=}CH_2$), 61.4 ($ArCO_2CH_2CH_3$), 56.1 ($ArOCH_3$), 55.3 ($ArOCH_3$), 52.1 ($ArOCH_3$), 14.3 ($ArCO_2CH_2CH_3$).

Ethyl 3-allyl-4-hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylate **18**[14]

Ethyl 4-(allyloxy)-5,6,8-trimethoxynaphthalene-2-carboxylate (4.00 g, 11.5 mmol) was loaded neat into a 100 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. The flask was heated to 180 °C in silicone oil bath for 24 h under a N_2(g) atmosphere. The dark viscous residue was cooled to 35 °C, dissolved in acetone (20 mL) and adsorbed on silica gel. Purification by silica gel column chromatography (10 % EtOAc/hexane) yielded ethyl 3-allyl-4-hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylate **18** as a yellow amorphous solid (2.83 g, 71 %). R_f = 0.42 (20 % EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 10.09 (1H, s, ArOH), 8.19 (1H, s, H-1), 6.48 (1H, s, H-7), 6.10 (1H, ddt, J = 16.1, 10.1, 6.0, $ArCH_2CH{=}CH_2$), 5.04 (2H, dt, J = 15.9, 1.9, $ArCH_2CH{=}CH_2$), 4.37 (2H, q, J = 7.1, $ArCO_2CH_2CH_3$), 3.98 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.91–3.84 (5H, m, one of the OCH_3 and $ArCH_2CH{=}CH_2$), 1.41 (3H, t, J = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 168.1 ($ArCO_2CH_2CH_3$), 153.7 (C-8), 151.0 (C-4), 149.1 (C-6), 137.4 ($ArCH_2CH{=}CH_2$), 135.7 (C-5), 127.7 (C-2), 120.9 (C-8a), 119.9 (C-4a), 119.4 ($ArCH_2CH{=}CH_2$), 116.4 (C-3), 114.4 (C-1), 94.7 (C-7), 62.1 ($ArCO_2CH_2CH_3$), 60.8 ($ArOCH_3$), 56.8 ($ArOCH_3$), 55.7 ($ArOCH_3$), 30.1 ($ArCH_2CH{=}CH_2$), 14.4 ($ArCO_2CH_2CH_3$).

Ethyl 3-allyl-4-hydroxy-1,5,6,8-tetramethoxynaphthalene-2-carboxylate **21** and ethyl 3-allyl-3,4-dihydro-3,5,6,8-tetramethoxy-4-oxonaphthalene-2-carboxylate **20**

To a solution of ethyl 3-allyl-4-hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylate **18** (3.00 g, 8.66 mmol) in absolute MeOH (80 mL) in a 250 mL round-bottomed flask, PIFA (3.96 g, 9.20 mmol) was added in one portion and the reaction mixture was stirred for 15 min at r.t. Saturated aqueous $NaHCO_3$ (50 mL) was added portion-wise until effervescence stopped and the MeOH was removed in vacuo to leave an aqueous medium. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite pad and concentrated under reduced pressure. The residue was then treated with a 21 % (w/v) ethanolic solution of NaOEt (11.0 mL, 34.0 mmol)

with vigorous stirring for 20 min at r.t. Saturated aqueous NH_4Cl (50 mL) was added to the reaction and the resultant mixture was evaporated at reduced pressure to leave the aqueous medium which was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite pad and concentrated in vacuo. Purification of the residue by silica gel column chromatography (20 % EtOAc/hexane) afforded two compounds. The first compound was ethyl 3-allyl-4-hydroxy-1,5,6,8-tetramethoxynaphthalene-2-carboxylate **21** which was obtained as an orange amorphous solid (1.70 g, 52 %). Compound **21** was characterised by ^1H NMR and ^{13}C NMR spectroscopy, as described in the next experimental procedure.

The second product was ethyl 3-allyl-3,4-dihydro-3,5,6,8-tetramethoxy-4-oxonaphthalene-2-carboxylate **20** which was obtained as yellow crystals (0.326 g, 10 %). R_f = 0.40 (20 % EtOAc/hexane); IR ν_{max}(cm^{-1}) 1708 (C=O), 1698 (C=C), 1625 (C=C); Mp 63–65 °C; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 8.09 (1H, s, H-1), 6.70 (1H, s, H-7), 5.59 (1H, ddt, *J* = 17.4, 10.1, 7.4, $ArCH_2CH{=}CH_2$), 5.06–4.85 (2H, m, $ArCH_2CH{=}CH_2$), 4.46–4.24 (2H, m, $ArCO_2CH_2CH_3$), 3.94 (3H, s, $ArOCH_3$), 3.93 (3H, s, $ArOCH_3$), 3.84 (3H, s, $ArOCH_3$), 3.15 (3H, s, OCH_3 attached to C-3), 3.00–2.79 (2H, m, $ArCH_2CH{=}CH_2$), 1.37 (3H, t, *J* = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 198.3 (C-4), 165.5 ($ArCO_2CH_2CH_3$), 156.2 (C-6), 153.3 (C-8), 143.1 (C-5), 132.4 (C-1), 131.3 ($ArCH_2CH{=}CH_2$), 129.1 (C-2), 125.5 (C-4a), 118.9 ($ArCH_2CH{=}CH_2$), 116.0 (C-8a), 101.4 (C-7), 84.9 (C-3), 61.6 ($ArOCH_3$, attached to C-5), 60.8 ($ArCO_2CH_2CH_3$), 56.4 ($ArOCH_3$), 56.3 ($ArOCH_3$), 53.7 (OCH_3 attached to C-3), 43.3 ($ArCH_2CH{=}CH_2$), 14.4 ($ArCO_2CH_2CH_3$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{20}H_{25}O_7$: 377.1595, found $[M + H]^+$ 377.1591.

Ethyl 3-allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylate **22**

To a solution of ethyl 3-allyl-4-hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylate **18** (4.50 g, 13.0 mmol) in absolute MeOH (100 mL) in a 250 mL round-bottomed flask, PIFA (5.81 g, 13.5 mmol) was added and the reaction was stirred for 15 min at r.t. A saturated aqueous $NaHCO_3$ solution was added to the mixture until effervescence stopped and MeOH was removed in vacuo to leave an aqueous medium. This medium was then extracted with EtOAc (3 × 100 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite pad and concentrated under reduced pressure. The residue was then dissolved in ethanol (200 mL) and *t*BuOK (3.41 g, 30.4 mmol) was added with vigorous stirring for 20 min at r.t. The reaction was quenched by saturated aqueous solution NH_4Cl (50 mL) and the resultant mixture was evaporated under reduced pressure to leave an aqueous medium. This medium was extracted with EtOAc (3 × 100 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite pad and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (15 % EtOAc/hexane) delivered ethyl 3-allyl-4-hydroxy-1,5,6,8-tetramethoxynaphthalene-2-carboxylate **21** as an orange amorphous solid (2.94 g, 60 %). R_f = 0.46 (25 % EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 10.20 (1H, s, ArOH), 6.64 (1H, s, H-7), 6.01 (1H, ddt, *J* = 16.4, 10.0, 6.3, $ArCH_2CH{=}CH_2$), 5.16–4.96 (2H, m, $ArCH_2CH{=}CH_2$), 4.40 (2H, q, *J* = 7.1, $ArCO_2CH_2CH_3$), 3.98 (3H, s, $ArOCH_3$), 3.96 (3H, s, $ArOCH_3$), 3.96 (3H, s, $ArOCH_3$), 3.79 (3H, s, $ArOCH_3$), 3.46 (2H, dt, *J* = 6.3, 1.4, $ArCH_2CH{=}CH_2$), 1.39 (3H, t, *J* = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 168.07 ($ArCO_2CH_2CH_3$), 154.0 (C-8), 148.2 (C-1), 147.1 (C-6), 145.5 (C-4), 136.5 ($ArCH_2CH{=}CH_2$), 135.9 (Ar-C), 126.7 (Ar-C), 120.1 (Ar-C), 118.0 (Ar-C), 115.2 (Ar-C), 115.2 (Ar-C), 96.8 (C-7), 63.8 ($ArCO_2CH_2CH_3$), 62.3 ($ArOCH_3$), 61.1 ($ArOCH_3$), 56.9 ($ArOCH_3$), 56.7 ($ArOCH_3$), 31.5 ($ArCH_2CH{=}CH_2$), 14.3 ($ArCO_2CH_2CH_3$). Dimethylsulfate (1.06 mL, 11.2 mmol) was added to a solution of the intermediate, ethyl 3-allyl-4-hydroxy-1,5,6,8-tetramethoxynaphthalene-2-carboxylate **21** (2.80 g, 7.44 mmol) and anhydrous K_2CO_3 (1.55 g, 11.2 mmol) in acetone (100 mL) in a 250 mL round-bottomed flask. The mixture was then heated under reflux for 24 h after which it was cooled to r.t., filtered through a bed of celite and the solvent was removed in vacuo. The residue was dissolved in EtOAc (100 mL) and successively washed with 25 % (v/v) aqueous NH_3 (2 × 100 mL) after which it was acidified to pH 4 using 32 % (v/v) aqueous HCl. The organic layers were then washed with H_2O until the aqueous layer was neutral. It was then dried with anhydrous $MgSO_4$, filtered through a bed of celite and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (10 % EtOAc/hexane) yielded ethyl 3-allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylate **22** as a yellow oil (2.41 g, 83 %). R_f = 0.53 (20 % EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 6.73 (1H, s, H-7), 5.98 (1H, ddt, *J* = 16.4, 10.1, 6.2, $ArCH_2CH{=}CH_2$), 5.13–4.98 (2H, m, $ArCH_2CH{=}CH_2$), 4.39 (2H, q, *J* = 7.1, $ArCO_2CH_2CH_3$), 4.01 (3H, s, $ArOCH_3$), 3.98 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 3.78 (3H, s, $ArOCH_3$), 3.77 (3H, s, $ArOCH_3$), 3.57 (2H, dt, *J* = 6.2, 1.5, $ArCH_2CH{=}CH_2$), 1.39 (3H, t, *J* = 7.1, $ArCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 168.0 ($ArCO_2CH_2CH_3$), 153.7 (C-8), 150.9 (C-1), 145.0 (C-6), 149.2 (C-4), 136.7 ($ArCH_2CH{=}CH_2$), 136.6 (Ar-C), 127.6 (Ar-C), 126.4 (Ar-C), 125.7 (Ar-C), 116.0 (Ar-C), 115.7 (Ar-C), 97.1 (C-7), 63.8 ($ArCO_2CH_2CH_3$), 62.7 ($ArOCH_3$), 62.1 ($ArOCH_3$), 61.2 ($ArOCH_3$), 56.9 ($ArOCH_3$), 56.8 ($ArOCH_3$), 31.6 ($ArCH_2CH{=}CH_2$), 14.2 ($ArCO_2CH_2CH_3$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{21}H_{27}O_7$: 391.1751, found $[M + H]^+$ 391.1750.

3-Allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylic acid **7**

To a solution of ethyl 3-allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylate **22** (2.10 g, 5.38 mmol) in dry THF (100 mL) cooled to 0 °C in an ice bath, $LiAlH_4$ (0.486 g, 12.8 mmol) was added portion-wise over a period of 5 min. The reaction mixture was warmed to r.t. and stirred for a further 4 h under a N_2(g) atmosphere. After this time had elapsed, the mixture was cooled to 0 °C for a second time and cold H_2O was added portion-wise until the effervescence stopped. The resultant mixture was filtered through a thick celite bed and the THF was removed in vacuo. The aqueous medium was extracted with EtOAc (3 × 100 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered through a bed of celite and concentrated under reduced pressure. Purification of the residue on silica gel column chromatography yielded 3-allyl-1,4,5,6,8-pentamethoxynaphthalen-2-yl)methanol (3.09 g, 80 %). R_f = 0.42 (30 % EtOAc/hexane); Mp 122–123 °C; IR ν_{max}(cm^{-1}) 3481 (O-H), 1580 (C=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 6.73 (1H, s, H-7), 6.14 (1H, ddt, *J* = 17.1, 10.5, 5.4, $ArCH_2CH{=}CH_2$), 5.06 (1H, ddd, *J* = 17.1, 10.2, 1.7, one of $ArCH_2CH{=}CH_2$), 4.95 (1H, ddd, *J* = 15.4, 3.4, 1.6, one of $ArCH_2CH{=}CH_2$), 4.81 (2H, s, $ArCH_2OH$), 4.01 (3H, s, $ArOCH_3$), 4.00 (3H, s, $ArOCH_3$), 3.84 (3H, s, $ArOCH_3$), 3.79 (3H, s, $ArOCH_3$), 3.78–3.72 (5H, m, $ArOCH_3$, and $ArCH_2CH{=}CH_2$), 2.46 (1H, br s, $ArCH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 153.3 (C-8), 151.9 (C-10), 150.3 (C-4), 149.3 (C-6), 138.3 (Ar-C), 136.7 ($ArCH_2CH{=}CH_2$), 130.3 (Ar-C), 128.6 (Ar-C), 125.8 (Ar-C), 116.4 ($ArCH_2CH{=}CH_2$), 115.3 (Ar-C), 97.1 (C-7), 63.2 ($ArOCH_3$), 62.6 ($ArOCH_3$), 62.0 ($ArOCH_3$), 57.4 ($ArCH_2OH$), 56.9 ($ArOCH_3$), 56.8 ($ArOCH_3$), 30.4 ($ArCH_2CH{=}CH_2$). To a solution of majority of the 3-allyl-1,4,5,6,8-pentamethoxynaphthalen-2-yl)methanol (3.00 g, 8.61 mmol) in CH_2Cl_2 (150 mL), flash silica gel (1.50 g) and PCC (3.64 g, 16.9 mmol) were added portion-wise and the reaction mixture was stirred under N_2(g) atmosphere for 4 h. After the starting material was completely consumed (monitored by TLC), the reaction mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo. The resultant viscous oil was taken to the next step without further purification apart from noting the difference in R_f value to the starting material.

The crude intermediate was dissolved in 2-methyl-2-butene (113 mL) in a 500 mL round-bottomed flask to which H_2O (187 mL), *t*BuOH (169 mL), $NaClO_2$ (2.71 g, 30.0 mmol) and NaH_2PO_4 (3.60 g, 30.0 mmol) were added. The biphasic mixture was stirred rapidly for 6 h after which the layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered through a celite bed and concentrated in vacuo. The residue was purified by silica gel column chromatography (30 % EtOAc/hexane) and the isolated product was re-crystallized from a hot 20 % EtOAc/hexane solution affording 3-allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylic acid **7** as white crystals (2.06 g, 66 %). R_f = 0.21 (50 % EtOAc/hexane); Mp 140–142 °C; IR ν_{max} (cm^{-1}) 3680 (O-H), 1692 (C=O), 1637 (C=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 10.80 (1H, s, $ArCO_2H$), 6.76 (1H, s, H-7), 6.04 (1H, ddt, *J* = 16.3, 10.1, 6.2, $ArCH_2CH{=}CH_2$), 5.14 (1H, dd, *J* = 13.8, 1.7, one of $ArCH_2CH{=}CH_2$), 5.10 (1H, dd, *J* = 13.8, 1.6, one of $ArCH_2CH{=}CH_2$), 4.02 (3H, s, $ArOCH_3$), 4.00 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.70 (2H, d, *J* = 6.2, $ArCH_2CH{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 172.4 ($ArCO_2H$), 153.8 (C-8), 151.3 (C-10), 150.3 (Ar-C), 149.3 (Ar-C), 136.6 ($ArCH_2CH{=}CH_2$), 127.6 (Ar-C), 126.6 (Ar-C), 124.3 (Ar-C), 116.0 ($ArCH_2CH{=}CH_2$), 115.8 (Ar-C), 97.3 (H-7), 63.9 ($ArOCH_3$), 62.7 ($ArOCH_3$), 62.0 ($ArOCH_3$), 56.9 ($ArOCH_3$), 56.8 ($ArOCH_3$), 31.4 ($ArCH_2CH{=}CH_2$); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{19}H_{23}O_7$: 363.1438, found $[M + H]^+$ 363.1434.

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

To a 250 mL 2-neck round-bottomed flask equipped with a magnetic stirring bar and charged with 3-allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylic acid **7** (2.00 g, 5.52 mmol) in DMF/H_2O (150 mL, v/v, 2:1) was added $CuCl_2{\cdot}2H_2O$ (1.77 g, 10.4 mmol). The reaction mixture was vigorously stirred under a blanket of O_2(g). After 10 min of stirring, $PdCl_2$ (97.9 mg, 0.552 mmol) was added to the reaction mixture and it was further stirred vigorously for 24 h at r.t. The reaction mixture was then filtered through a thick celite bed and the pad was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried with anhydrous $MgSO_4$, filtered and the solvent was removed in vacuo. The residue was adsorbed on silica and purification by silica gel column chromatography (EtOAc/CH_2Cl_2/hexane, 3:1:6) afforded 5,6,7,9,10-pentamethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **9** as a cream crystalline solid (1.43 g, 72 %). R_f = 0.43 (EtOAc/CH_2Cl_2/hexane, 4:2:4). Mp 160–162 °C; IR ν_{max} (cm^{-1}) 1741 (C=O), 1605 (C=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 6.73 (1H, s, H-8), 6.57 (1H, s, H-4), 4.04 (3H, s, $ArOCH_3$), 4.02 (3H, s, $ArOCH_3$), 3.95 (3H, s, $ArOCH_3$), 3.83 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 2.26 (3H, s, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ_C 159.4 (C-1), 156.3 (C-3), 156.2 (Ar-C), 153.2 (Ar-C), 152.9 (Ar-C), 143.6 (Ar-C), 135.8 (Ar-C), 129.0 (C-6a), 127.5 (C-10a), 116.7 (C-4a), 108.9 (C-9a), 97.4 (C-4), 96.9 (C-8), 63.0 ($ArOCH_3$), 62.8 ($ArOCH_3$), 62.0 ($ArOCH_3$), 57.3 ($ArOCH_3$), 56.5 ($ArOCH_3$), 19.8 (C-3′); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{19}H_{21}O_7$: 361.1282, found $[M + H]^+$ 361.1287.

5,7,10-Trimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-1,6,9-trione **23**

AgO (1.18 g, 9.50 mmol) was added to the stirred solution of 5,6,7,9,10-pentamethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **9** (1.60 g, 4.44 mmol) in 1,4-dioxane (40 mL). The reaction mixture was stirred for 10 min at r.t. after which 55 % (v/v) aqueous HNO_3 was added dropwise until all the AgO dissolved. The resultant solution was stirred for a further 5 min which was followed by addition of CH_2Cl_2 (50 mL) and H_2O (50 mL). The lower organic layer was separated, and the aqueous solution was further extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite bed and concentrated under reduced pressure. Purification of the residue on silica gel column chromatography (EtOAc/hexane/CH_2Cl_2) afforded 5,7,10-trimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-1,6,9-trione **23** as an orange amorphous solid (1.10 g, 75 %). R_f = 0.40 (EtOAc/CH_2Cl_2/hexane, 4:2:4); Mp 220–222 °C; IR ν_{max}(cm^{-1}) 1788 (C=O), 1762 (C=O), 1712 (C=C), 1693 (C=C), 1606 (C=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ_H 6.66 (1H, s, H-8), 6.12 (1H, s, H-4), 4.02 (3H, s, $ArOCH_3$), 3.93 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 2.34 (3H, s, H-3′); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ_C 182.4 (C=O), 178.9 (C=O), 159.3 (Ar-C), 159.1 (Ar-C), 159.0 (Ar-C), 157.4 (Ar-C), 151.0 (Ar-C), 141.2 (Ar-C), 127.7 (Ar-C), 123.4 (Ar-C), 119.4 (Ar-C), 111.6 (C-4), 97.8 (C-8), 63.0 ($ArOCH_3$), 62.8 ($ArOCH_3$), 56.5 ($ArOCH_3$), 20.2 (CH_3); HRMS (*m/z*), calculated for $[M + H]^+$ $C_{17}H_{15}O_7$: 331.0812, found $[M + H]^+$ 331.0814.

5-Methoxy-3,4-dehydrosemixanthomegnin **2**[19]

5,7,10-Trimethoxy-3-methyl-1*H*-benzo[*g*]isochromene-1,6,9-trione **23** (0.334 g, 1.01 mmol) was dissolved in a freshly distilled CH_2Cl_2 (50 mL) in a 150 mL 2-neck round-bottomed flask fitted with a rubber septum. The reaction flask was cooled to –78 °C under a blanket of N_2(g) atmosphere and BCl_3 (2.02 mL, 2.02 mmol) was slowly added to the solution using a syringe. The reaction mixture was stirred for a further 40 min at –78 °C and was then warmed to r.t. The mixture was stirred at this temperature for 2 h after which it was carefully quenched with cold H_2O (100 mL) and the lower layer was separated. The aqueous medium was further extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered through a celite bed and concentrated under reduced pressure. The residue was purified on deactivated silica gel column chromatography (20 % EtOAc/hexane) affording 10-hydroxy-5,7,9-trimethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one **2** as a dirty-red solid (51.1 mg, 20 %). R_f = 0.49 (EtOAc/CH_2Cl_2/hexane, 3:2:5); Mp 139–140 °C (140–142 °C);[19] ^1H NMR (500 MHz, $CDCl_3$) δ_H 14.57 (1H, s, OH attached to C-10), 6.67 (1H, s, H-8), 6.16 (1H, s, H-4), 3.94 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 2.37 (3H, s, C-3′); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ_C 189.3 (C-9), 177.9 (C-6), 161.4 (C-1), 161.0 (C-10), 160.7 (C-7), 157.7 (C-3), 148.0 (C-5), 143.5 (C-5a), 125.1 (C-4a), 113.0 (C-10a), 111.2 (C-9a), 109.3 (C-8), 98.3 (C-4), 62.3 ($ArOCH_3$), 56.9 ($ArOCH_3$), 20.4 (CH_3). The spectroscopic data are in general agreement with that reported by Raddi and co-workers (see supplementary information).[19]

CCDC 1867674 (for **8**), 1867675 (for **16**), 1867676 (for **20**), 1867677 (for **22**) and 1867678 (for **9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgments

This work was supported by SABINA (Southern African Biochemistry and Informatics for Natural Products Network), the National Research Foundation Pretoria, South Africa, and the University of the Witwatersrand (Science Faculty Research Council).

Keywords: Synthetic methods · Oxidation · Aromatic compounds · Oxygen heterocycles · Isocoumarins

[1] C. D. Donner, *Nat. Prod. Rep.* **2015**, *32*, 578–604.
[2] a) D. Parisot, M. Devys, J.-P. Férézou, M. Barbier, *Phytochemistry* **1983**, *22*, 1301–1303; b) J. H. Tatum, R. A. Baker, R. E. Berry, *Phytochemistry* **1989**, *28*, 283–284.

[3] R. R. Kitagawa, M. S. Raddi, L. C. dos Santos, W. Vilegas, *Chem. Pharm. Bull.* **2004**, *52*, 1487–1488.

[4] K. F. Devienne, M. S. Raddi, E. A. Varanda, W. Vilegas, *Z. Naturforsch. C* **2002**, *57*, 85–88.

[5] E. A. Varanda, M. S. G. Raddi, F. de Luz Dias, M. C. P. Araújo, S. C. Gibran, C. S. Takahashi, W. Vilegas, *Teratogenesis, Carcinogenesis, and Mutagenesis* **1997**, *17*, 85–95.

[6] R. R. Kitagawa, W. Vilegas, I. Z. Carlos, M. S. Raddi, *Rev. Bras. Farmacogn.* **2011**, *21*, 1084–1088.

[7] W. Vilegas, N. F. Roque, A. Salatino, A. M. Giesbrecht, S. Davino, *Phytochemistry* **1990**, *29*, 2299–2301.

[8] R. R. Kitagawa, C. Bonacorsi, L. M. da Fonseca, W. Vilegas, M. S. Raddi, *Rev. Bras, Farmacogn. Bras. Farmacogn.* **2012**, *22*, 53–59.

[9] J. P. Damasceno, R. P. Rodrigues, R. de C. R. Gonçalves, R. R. Kitagawa, *Molecules* **2017**, *22*, 786.

[10] a) E. M. Mmutlane, I. R. Green, J. P. Michael, C. B. de Koning, *Org. Biomol. Chem.* **2004**, *2*, 2461–2470; b) S. Govender, E. M. Mmutlane, W. A. L. van Otterlo, C. B. de Koning, *Org. Biomol. Chem.* **2007**, *5*, 2433–2440; c) A. Pillay, A. L. Rousseau, M. A. Fernandes, C. B. de Koning, *Org. Biomol. Chem.* **2012**, *10*, 7809–7819.

[11] Crystal data for **8**, CCDC 1867674 $C_{18}H_{18}O_6$: M, 330.32 g mol^{-1}; crystal dimensions (mm^3) 0.700 × 0.600 × 0.500; crystal system, Triclinic; space group, $P\bar{1}$; unit cell dimensions and volume, a=7.3600(3) Å, b=9.3270(4) Å, c=12.3290(5) Å, α= 106.474(2)°, β= 106.037(2)°, γ=94.670(2)°, V= 768.21(6) Å^3, no. of formula units in the unit cell Z=2; calculated density r_{calcd} 1.428 Mg/m^3; linear absorption coefficient, m 0.108 mm^{-1}; radiation and wavelength, MoK_α=0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 15256 and 3709; R_{int}=0.0266; R [$I > 2.0\sigma(I)$] = R_1=0.0418, wR_2=0.1111, GoF= 1.041, refined on F; residual electron density, 0.271 and –0.343 e Å^{-3}; Crystal data for **16**, CCDC 1867675 $C_{18}H_{18}O_6$: M, 330.32 g mol^{-1}; crystal dimensions (mm^3) 0.470 × 0.160 × 0.050; crystal system, Monoclinic; space group, $P2_1/n$; unit cell dimensions and volume, a=7.0616(2) Å, b= 18.1308(6) Å, c=11.9516(4) Å, α= 90°, β= 91.4520(10)°, γ=90°, V= 1529.70(8) Å^3, no. of formula units in the unit cell Z=4; calculated density r_{calcd} 1.434 Mg/m^3; linear absorption coefficient, m 0.108 mm^{-1}; radiation and wavelength, MoK_α=0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 40839 and 3687; R_{int}=0.0360; R [$I > 2.0\sigma(I)$] = R_1=0.0533, wR_2=0.1369, GoF= 1.054, refined on F; residual electron density, 0.713 and –0.297 e Å^{-3}.

[12] Numerous acid and base mediated methods were attempted. This included the use of sodium, lithium and potassium hydroxide, as well as concentrated hydrochloric and sulfuric acid. In addition, exposure of the related allyl ester, allyl-3-allyl-1,4,6,8-teratmethoxy2-naphthoate[10c] to catalytic $Pd(OAc)_2$, PPh_3 and morpholine yielded the same isomerized carboxylic acid, 1,4,6,8-tetramethoxy-3-((*E*)-prop-1-enyl)naphthalene-2-carboxylic acid **15** in 56 % yield.

[13] The use of a number of Lewis acids including BBr_3 did not facilitate the removal of the methyl of **9** OMe substituent of compound **5** to afford paepalantine.

[14] C. B. de Koning, S. S. Manzini, J. P. Michael, E. M. Mmutlane, T. R. Tshabidi, W. A. L. van Otterlo, *Tetrahedron* **2005**, *61*, 555–564.

[15] Crystal data for **20**, CCDC 1867676 $C_{20}H_{24}O_7$: M, 376.39 g mol^{-1}; crystal dimensions (mm^3) 0.540 × 0.370 × 0.220; crystal system, Monoclinic; space group, $P2_1/n$; unit cell dimensions and volume, a = 7.4837(7) Å, b = 9.9832(8) Å, c = 25.142(2) Å, α= 90°, β= 98.200(2)°, γ = 90°, V = 1859.2(3) Å^3, no. of formula units in the unit cell Z = 4; calculated density r_{calcd} 1.345 Mg/m^3; linear absorption coefficient, m 0.102 mm^{-1}; radiation and wavelength, MoK_α = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 20025 and 3493; R_{int} = 0.0239; R [$I > 2.0\sigma(I)$] = R_1 = 0.0352, wR_2 = 0.1032, GoF = 1.199, refined on F; residual electron density, 0.402 and –0.526 e Å^{-3}.

[16] Crystal data for **22**, CCDC 1867677 $C_{21}H_{26}O_7$: M, 390.42 g mol^{-1}; crystal dimensions (mm^3) 0.570 × 0.300 × 0.180; crystal system, Triclinic; space group, $P\bar{1}$; unit cell dimensions and volume, a = 7.9910(4) Å, b = 9.4841(4) Å, c = 13.7738(6) Å, α= 88.342(2)°, β= 75.427(2)°, γ = 76.988(2)°, V = 76.988(2) Å^3, no. of formula units in the unit cell Z = 2; calculated density r_{calcd} 1.318 Mg/m^3; linear absorption coefficient, m 0.099 mm^{-1}; radiation and wavelength, MoK_α = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 18604 and 4756; R_{int} = 0.0229; R [$I > 2.0\sigma(I)$] = R_1 = 0.0399, wR_2 = 0.1107, GoF = 1.053, refined on F; residual electron density, 0.333 and –0.273 e Å^{-3}.

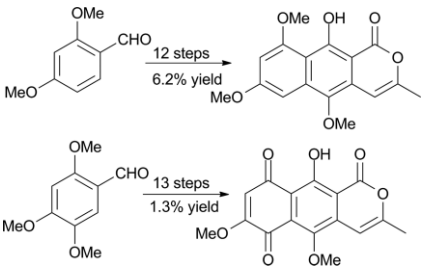
[17] Crystal data for **9**, CCDC 1867678 $C_{19}H_{20}O_7$: M, 360.35 g mol^{-1}; crystal dimensions (mm^3) 0.640 × 0.340 × 0.170; crystal system, triclinic; space group, $P\bar{1}$; unit cell dimensions and volume, a = 7.2651(3) Å, b = 9.5241(3) Å, c = 13.0014(5) Å, α= 79.4850(10)°, β= 91.4520(10)°, γ = 79.6200(10)°, V = 844.28(6) Å^3, no. of formula units in the unit cell Z = 2; calculated density r_{calcd} 1.417 Mg/m^3; linear absorption coefficient, m 0.109 mm^{-1}; radiation and wavelength, MoK_α = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 22542 and 4075; R_{int} = 0.0227; R [$I > 2.0\sigma(I)$] = R_1 = 0.0394, wR_2 = 0.1087, GoF = 1.034, refined on F; residual electron density, 0.334 and –0.254 e Å^{-3}.

[18] G. A. Kraus, H. Ogutu, *Tetrahedron* **2002**, *58*, 7391–7395.

[19] see ref.[3].

Received: October 26, 2018

Wacker Oxidation



A key step in the total synthesis of two aromatic isocoumarin-containing products, 9-*O*-methylpaepalantine and 5-methoxy-3,4-dehydrosemixanthomegnin is a Wacker-mediated ring closure. For example, expoure of 3-allyl-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylic acid to catalytic $PdCl_2$, $CuCl_2$ and O_2 afforded 5,7,9,10-tetramethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one in 72 % yield.

DOI: 10.1002/ejoc.201801595