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BENZOFURANOIDS WITH CARBON FRAMEWORKS REMINISCENT OF PRODUCTS OF BENZYLIC ACID REARRANGEMENT

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Key Word Index—*Berchemia zeyheri*; Rhamnaceae; benzofuranoids; benzylic acid rearrangement; 'complex flavonoids'; heartwood; red ivory.

Abstract—The heartwood of *Berchemia zeyheri* yielded 4,6-dihydroxy-3-(4-hydroxybenzyl)-3-methylbenzo[*b*]-furan-2(3*H*)-one and the 5- and 7-[2-(4-coumaroyl)]maesopsins, benzofuranoid-type flavonoids with molecular backbones reminiscent of products of benzylic acid rearrangement. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Despite the simple *in vitro* benzylic acid rearrangement of 2-benzyl-2-hydroxybenzo[*b*]furan-3(2*H*)-ones (e.g. maesopsin, **1**), and dihydroflavonols (e.g. aromadendrin, **4**), to 3-benzyl-3-hydroxybenzo[*b*]furan-2(3*H*)-ones (**6**), presumably via an α-diketone intermediate (**5**) [1–4], flavonoids exhibiting the carbon framework of compound (**6**) have not yet been encountered from natural sources. Reinvestigation of the polyphenols in the heartwood of *Berchemia zeyheri* (red ivory) [5], with its exceptionally high concentration of maesopsin [6, 7], has now yielded benzofuranoids with molecular frameworks resembling those of the benzylic acid rearrangement product (**6**) or its carboxylic acid precursor prior to lactonization.

RESULTS AND DISCUSSION

The aqueous acetone extract of the heartwood of *B. zeyheri* yielded (±)-maesopsin (**1**) [2] (7% of total extract), the chalcones α-2′,4,4′,6′-pentahydroxychalcone [7] and 2′,4,4′,6′-tetrahydroxychalcone [8], the flavanone 2*R*-naringenin [9] (4′,5,7-trihydroxyflavanone), the dihydroflavonol (+)-aromadendrin (**4**) [10] [(2*R*,3*R*)-2,3-*trans*-4′,5,7-trihydroxydihydroflavonol], the flavonol kaempferol [11] (4′,5,7-trihydroxyflavonol), the aurone (*Z*)-4,4′,6-trihydroxyaurone [2, 12, 13], 2′,4,4′,6′-tetrahydroxydihydrochalcone [14] and 3′,4,5′-trihydroxydihydrostilbene [15]. These compounds are accompanied by a complex series of oligomeric benzofuranoids of the zeyherin type [6], the (±)-4,6-dihydroxy-3-(4-hydroxybenzyl)-3-methylbenzo-[*b*]furan-2(3*H*)-one (**7**) and the racemic 5- and 7-[2-(4-coumaroyl)]maesopsins (**9**) and (**11**). These compounds were identified as the permethylaryl ethers (**8**), (**10**) and (**12**), the additional chromatographic step offered by derivatization being a prerequisite for sample purity.

The spin systems in the ^{1}H NMR spectrum (Table 1) of the 3-benzyl-3-methylbenzo[*b*]furan-2(3*H*)-one tri-*O*-methyl ether (**8**) closely resemble those of tetra-*O*-methylmaesopsin (**2**), except for replacement of a methoxyl resonance (δ 3.24) in the maesopsin derivative with a methyl singlet (δ 1.60) in the benzofuranoid derivative **8**. The 4,4′,6-tri-oxygenation pattern was confirmed by relevant NOE associations between aromatic protons and *O*-methyl hydrogens. When taken in conjunction with the observed four-bond coupling between the methyl and methylene protons that was evident from a COSY spectrum of compound (**8**), the chemical shift (δ 180.4) of the carbonyl resonance in the ^{13}C NMR spectrum of derivative **8** compared with δ 193.5 for the carbonyl carbon in the spectrum of the maesopsin derivative **2** strongly indicated a γ-lactone functionality and, hence, the 3-benzyl-3-methylbenzo-[*b*]furan-2(3*H*)-one molecular framework for the novel natural product **7**. This structure was subsequently confirmed via synthesis (see below). Owing to the identification of the 4,4′,6-dimethoxy-5-methylaurone, which is presumably an artefact of C-methylation of the 'enol' functionality of the A-ring of 4,4′,6-trihydroxyaurone with dimethyl sulphate (see Experimental), it may be argued that the natural product derivative (**8**) similarly represents an *in vitro* compound originating by the action of dimethyl sulphate on an enolizable precursor of type **22** (see below). We could, however, find no evidence for the existence of such a compound in the fraction from which the natural product derivative **8** was obtained.

Several phenylpropanoid-substituted flavonoids with a $C_6C_3C_6$–C_3C_6 skeleton, dubbed 'complex flavonoids', were recently isolated and some of their struc-

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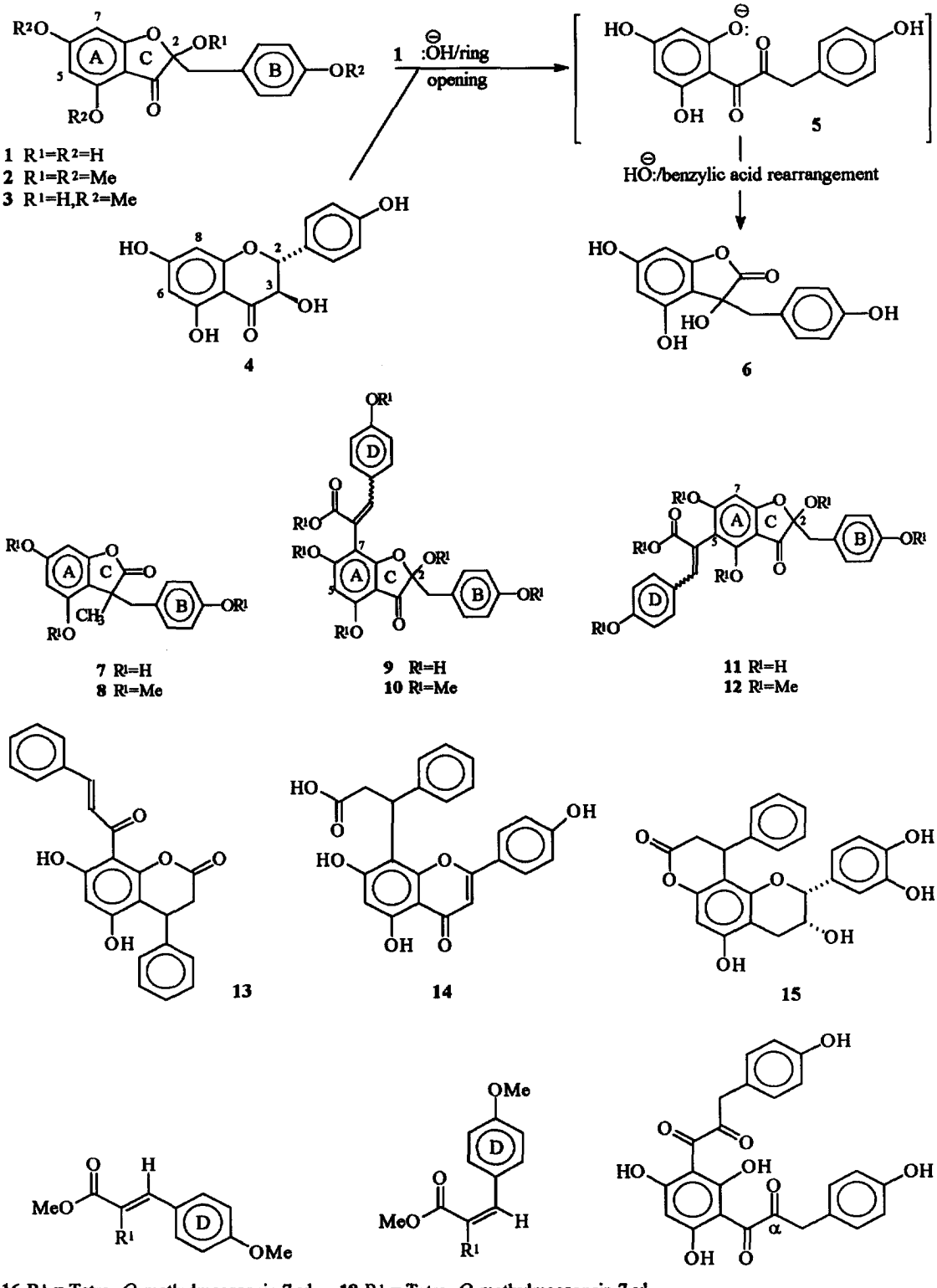


tures have been established by X-ray analysis or synthesis [16–25]. These compounds may be regarded as flavonoids that are condensed with neoflavonoids via a common phloroglucinol moiety, e.g. the 8-cinnamoyl-dihydroneoflavone (**13**), the 8-(3-dihydrocinnamoyl)flavone (**14**) and the dihydroneoflavone-epicatechin (**15**). The 5- and 7-[2-(4-coumaroyl)]-maesopsins **9** and **11** from *B. zeyheri* complement this group of

Table 1. ^{1}H NMR of tetra-*O*-methylmaesopsin (**2**) and permethylaryl ethers, **8**, **16**, **18**, **17**, **19** and **22** in $CDCl_3$ at 300 MHz

Ring	H	**2**	**8**	**16, 18**	**17, 19**	**22**
A	5	5.88 (*d*, 2.0)	6.19 (*d*, 2.0)	5.97, 5.99 (*s*)	–	6.19 (*d*, 2.0)
	7	6.05 (*d*, 2.0)	6.05 (*d*, 2.0)	—	6.20, 6.24 (*s*)	6.10 (*d*, 2.0)
B	2/6	7.13 (*d*, 8.0)	6.77 (*d*, 8.0)	6.74, 7.02 (*d*, 9.0)	7.15, 7.16 (*d*, 9.0)	6.89 (*d*, 8.5)
	3/5	6.70 (*d*, 8.0)	6.58 (*d*, 8.0)	6.42, 6.65 (*d*, 9.0)	6.72, 6.74 (*d*, 9.0)	6.64 (*d*, 8.5)
C	3	–	1.60 (*s*), 3-Me			3.98 (*dd*, 4.0, 5.0)
D	2/6	–	–	7.03, 7.10 (*d*, 9.0)	6.84, 7.06 (*d*, 9.0)	–
	3/5	–	–	6.70, 6.65 (*d*, 9.0)	6.68, 6.67 (*d*, 9.0)	–
	$-CH_2-$	3.14 (*d*, 15.0) 3.02 (*d*, 15.0)	3.26 (*d*, 12.5) 3.06 (*d*, 12.5)	3.02, 3.04 (*d*, 14.0) 2.86, 2.96 (*d*, 14.0)	3.24, 3.18 (*d*, 14.0) 3.16, 3.15 (*d*, 14.0)	3.35 (*dd*, 5.0, 13.0) 3.26 (*dd*, 4.0, 13.0)
	=CH–	–	–	7.90, 7.91 (*s*)	7.75, 7.82 (*s*)	–
	OMe	3.84, 3.82, 3.71, 3.24, each *s*	3.89 (4-A), 3.72 (6-A), 3.68 (4-B), each *s*	3.96, 3.94 (A), 3.76, 3.71 (D), 3.73, 3.79 (CO_2Me), 3.66, 3.80 (A), 3.61, 3.69 (B), 3.20, 2.70 (C), each *s*	3.64, 3.69 (6-A), 3.81, 3.80 (4-D), 3.31, 3.30 (2-C), 3.70 [4-B (**17** and **19**), 4-A (**17**)], 3.71 [CO_2Me (**17**)], 3.74, 3.73 (4-A) and [CO_2Me (**19**)]	3.87, 3.73, 3.69, each *s*

Splitting patterns and *J*-values (Hz) are given in parentheses.

natural products, representing the first phenylpropanoid-substituted flavonoids based on a benzofuranoid constituent unit.

The spin systems of a mono-substituted tetra-*O*-methylmaesopsin moiety are discernible in the ^{1}H NMR spectra of the permethylaryl ethers (**10**) and (**12**). The spectra also exhibits an aromatic AA'BB'-system, two *O*-methyl resonances and a deshielded singlet (δ 7.90 and δ 7.75 for compounds **10** and **12**, respectively] in the aromatic region, which is reminiscent of the β-proton of an α,β-unsaturated ester functionality. These singlets display both four-bond coupling in a COSY spectrum and H-H correlation in a NOESY spectrum with H-2 and H-6 of the aforementioned AA'BB' spin systems. When taken in conjunction with the presence of an aromatic one-proton singlet [δ 5.97 and δ 6.20 for compounds **10** and **12**, respectively] exhibiting NOE association with, respectively, two *O*-methyl resonances (δ 3.96 and δ 3.66, both 1.4%) and a single *O*-methyl group (δ 3.64, 2.2%), and a $[M]^+$ at *m/z* 534 in the mass spectra, the above data collectively indicate a (±)-tetra-*O*-methylmaesopsin moiety substituted, respectively, at C-7 and C-5 to the α-carbon of a methyl(4-*O*-methylcoumaroyl) unit and, hence, structures **10** and **12** for the derivatives of the novel natural products **9** and **11**.

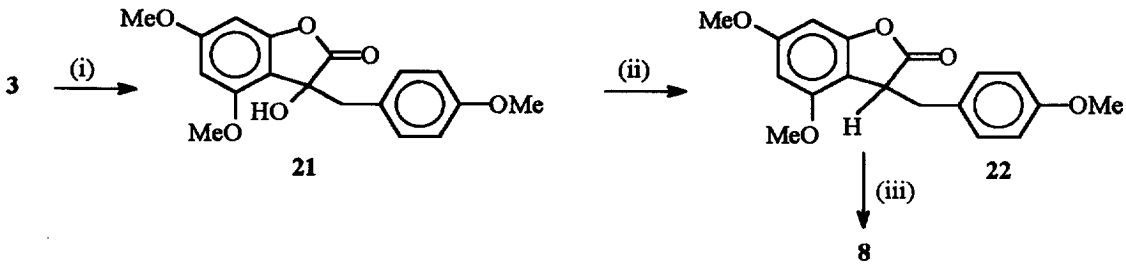
A conspicuous feature of the ^{1}H NMR spectra (Table 1) of the methyl ether derivatives **10** and **12** is the duplicated set of resonances indicating *ca* 55:45 and 71:29 mixture of compounds, respectively. The constituent substances are readily separable by preparative TLC but in solution rapidly revert back into the original mixture. Such an observation strongly indicates a simple equilibration of the *E* and *Z* isomers **16** and **17**, and **18** and **19**, of the α,β-enoate moiety. The NOE association between the vinylic proton at (δ 7.90 and δ 7.75) and the *O*-methyl protons (δ 3.73 and δ 3.71) of the ester functionality in the major isomers (**16**) and (**17**), respectively, and the conspicuous absence of similar association of the vinylic proton (δ 7.91 and δ 7.82) and the *O*-methyl ester protons (δ 3.79 for **18**) in the minor isomers **18** and **19** not only facilitated differentiation between the *E* and *Z* isomers **16** and **18**, and **17** and **19**, but also allowed the allocation of the different sets of resonances (Table 1) to the specific geometric isomers.

The mode of coupling of the maesopsin unit to the α-position of a 4-coumaroyl unit is atypical for this class of naturally occurring flavonoids. Although such a direct coupling to the α-position cannot be ruled out, the disubstituted phloroglucinol analogue (**20**) resulting from condensation of phloroglucinol (polyketide pathway) and two moles of 4-hydroxyphenylpyruvic acid [26] (shikimic acid route), may plausibly serve as the precursor for the natural products **9** and **11**. Selective α-cyclization involving a phloroglucinol ring hydroxyl group and one of the α-diketo moieties would then lead to the 2-benzyl-2-hydroxybenzofuranoid unit, while the equivalent of a benzylic acid rearrangement of the remaining α-diketo functionality, and subsequent dehydration, may explain the genesis of the α-substituted 4-hydroxycoumaroyl unit in the novel natural products **9** and **11**.

Finally, the structure of the novel 3-benzyl-3-methylbenzofuranoid, **7**, was confirmed unequivocally by synthesis (Scheme 1). 4,4',6-Tri-*O*-methylmaesopsin (**3**), available from photolysis [27] of the tetra-*O*-methyl ether (**2**), was transformed into the 3-benzyl-3-hydroxybenzo[*b*]furan-2(3*H*)-one (**21**) with 4% KOH solution [27] in 32% yield. Hydrogenolysis with 5% Pd/C catalyst in dichloromethane yielded 4,6-dimethoxy-3-(4-methoxybenzyl)benzo[*b*]furan-2(3*H*)-one (**22**) (89%) (^{1}H NMR data, Table 1), which was deprotonated with lithium diisopropylamide (LDA) and methylated with methyl iodide, according to the procedure of Grieco [28], to give the natural product derivative, **8**, in 76% yield. The 3-benzyl-3-methylbenzo[*b*]furan-2(3*H*)-one (**7**) presumably originates along similar lines biosynthetically, *S*-adenosylmethionine being the likely source of the electrophilic methyl fragment.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with TMS as int. standard. MS and accurate mass estimations were obtained using a double focusing instrument. CD data was obtained in MeOH. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF_{254}) and sprayed with H_2SO_4–HCHO (40:1)



Scheme 1. Synthesis of benzofuranoid (**8**). Reagents and conditions: (i) 4% KOH at 90° then 1.5 M H_2SO_4; (ii) H_2, Pd/C in CH_2Cl_2; (iii) lithium diisopropylamine in THF at −78° then MeI and hexamethylphosphoric triamide.

after development. Prep. TLC plates (Kieselgel PF_{254}, 1.0 mm) were air-dried and used without prior activation. Sepns on Sephadex LH-20 were on various column sizes and at differing flow rates (specified in each instance). Flash CC was carried out in a glass column (5 cm dia.) charged with Merck Kieselgel 60 (230–400 mesh) at a flow rate of 30 ml min^{-1} under N_2 pressure. Methylations were performed with Me_2SO_4 in dry Me_2CO containing anhydrous K_2CO_3 at reflux temp. Water-soluble phenolics were freeze-dried. Evapns were done under red. pres. at *ca* 40° in a rotary evaporator.

Isolation of phenolic metabolites. Drillings (3.49 kg) from the heartwood of *B. zeyheri* sond. were extracted with hexane (2 × 22 l; 2 × 24 hr) at room temp. in order to remove fats and waxes. Drillings were then air-dried and extracted with Me_2CO–H_2O (4:1, 5 × 15.0 l; 5 × 48 hr) at 22°. Extracts were combined, the Me_2CO evapd at 40° and the aq. soln freeze-dried to give a red amorphous powder (377 g, 10.8% of mass of drillings). This (6 × 40 g) was partitioned between *sec.*-BuOH–H_2O–hexane (5:3.5:1.5) in a 20-tube, 100 mL upper-phase, Craig countercurrent assembly. Following qualitative TLC (benzene–Me_2CO–MeOH, 7:2:1) and 2D PC [Whatman No. 1 (28 × 46 cm) sheets in H_2O-satd. *sec.*-BuOH and in 2% HOAc] analysis, the frs were combined as follows: 1 (tubes 1–2, 13.4 g), 2 (3–4, 4.5 g), 3 (5–7, 5.0 g), 4 (8–10, 7.1 g), 5 (11–12, 10.9 g), 6 (13–16, 42.5 g), 7 (17–19, 38.6 g) and 8 (20, 12.9 g). Subsequent CC of a portion (18.8 g) of fr. 1 on Sephadex LH-20 (5 × 150 cm column, flow rate of 0.5 ml min^{-1}) in EtOH gave the following 11 frs: 1.1 (tubes 1–53, 0.63 g), 1.2 (54–57, 0.04 g), 1.3 (58–80, 1.17 g), 1.4 (81–114, 1.85 g), 1.5 (115–123, 1.01 g), 1.6 (124–156, 0.49 g), 1.7 (157–201, 1.59 g), 1.8 (202–223, 1.09 g), 1.9 (224–240, 0.32 g), 1.10 (241–314, 0.44 g) and 1.11 (315–324, 0.58 g). Fr. 1.1 was purified by prep. TLC in benzene–Me_2CO–MeOH (7:2:1) to give (±)-maesopsin (**1**) as an amorphous powder (80 mg, R_f 0.45), $[\alpha]^{20} = 0°$, δ_H (acetone-d_6) 7.03 [*d*, J = 9.0 Hz, H-2,6(B)], 6.63 [*d*, J = 9.0 Hz, H-3,5(B)], 5.86 [*d*, J = 2.0 Hz, H-7(A)], 5.82 (*d*, J = 2.0 Hz, H-5(A)] and 3.10 (*s*, α-CH_2). Similar treatment of fr. 1.2 yielded an additional sample (10 mg) of (±)-maesopsin (**1**). Methylation of fr. 1.3 (1.17 g) followed by prep. TLC in benzene–Me_2CO (9:1) yielded four main bands, 1.3.1 (R_f 0.65, 5.2 mg), 1.3.2 (R_f 0.37, 17.6 mg), 1.3.3 (R_f 0.26, 13.2 mg) and 1.3.4 (R_f 0.48, 31.2 mg). Band 1.3.3 comprised (±)-4,4′,6-tri-*O*-methylmaesopsin [27] (**3**) and band 1.3.4 of (±)-2,4,4′,6-tetra-*O*-methylmaesopsin (**2**), δ_H (Table 1). Band 1.3.2 gave a mixt. of *E* and *Z*-7-(methyl-4-methoxycinnamoyl)-2,4,4′,6-tetra-*O*-methylmaesopsin (**16** and **18**) as a yellow amorphous powder (Found: $[M]^+$, 534.1890. $C_{30}H_{30}O_9$ requires 534.1888); δ_H (Table 1); MS (rel. int.) *m/z* 534 ($[M]^+$, 20.4), 413 (100), 354 (0.9), 339 (6.7), 312 (6.2), 121 (19.7), 59 (1.2). Band 1.3.1 yielded a mixt. of *E* and *Z*-5-(methyl-4-methoxycinnamoyl)-2,4,4′,6-tetra-*O*-methylmaesopsin (**17** and **19**) as a yellow amorphous powder (found: $[M]^+$ 534.1891. $C_{30}H_{30}O_9$ requires 534.1888); δ_H (Table 1). The remaining frs 1.4–1.11 will be described elsewhere.

Frs 7 (38.6 g) and 8 (12.9 g) from the 20-tube Craig assembly were combined and subjected to countercurrent distribution on a Quickfit Model 20 machine [25 cm^3 top and bottom phases; H_2O–*sec.*-BuOH–hexane (5:4:1)]. Following 103 transfers of top phase, the frs were combined as follows: 7–8.1 (tubes 1–11, 0.05 g), 7–8.2 (12–24, 0.08 g), 7–8.3 (25–37, 0.12 g), 7–8.4 (38–47, 0.16 g), 7–8.5 (48–57, 1.32 g), 7–8.6 (58–70, 14.5 g), 7–8.7 (71–83, 6.0 g), 7–8.8 (84–93, 5.4 g) and 7–8.9 (94–103, 14.5 g). Fr. 7–8.9 (14.5 g) was subjected to CC on Sephadex LH-20 (4 × 150 cm column, flow rate 30 ml hr^{-1}) in EtOH to give the following frs: 7–8.9.1 (tubes 1–51, 0.004 g), 7–8.9.2 (52–80, 0.029 g), 7–8.9.3 (81–84, 0.016 g), 7–8.9.4 (85–93, 0.053 g), 7–8.9.5 (94–104, 0.079 g), 7–8.9.6 (105–122, 0.039 g), 7–8.9.7 (123–144, 0.017 g), 7–8.9.8 (145–159, 0.024 g), 7–8.9.9 (160–172, 0.038 g), 7–8.9.10 (173–181, 0.027 g), 7–8.9.11 (182–191, 0.036 g), 7–8.9.12 (192–196, 0.043 g), 7–8.9.13 (197–205, 0.310 g), 7–8.9.14 (206–213, 0.471 g), 7–8.9.15 (214–230, 2.566 g), 7–8.9.16 (231–236, 0.797 g), 7–8.9.17 (237–249, 1.450 g), 7–8.9.18 (250–280, 1.713 g), 7–8.9.19 (281–302, 0.402 g), 7–8.9.20 (303–317, 0.146 g), 7–8.9.21 (318–329, 0.129 g), 7–8.9.22 (330–343, 0.209 g), 7–8.9.23 (344–390, 1.108 g), 7–8.9.24 (391–408, 0.464 g) and 7–8.9.25 (409–485, 0.956 g). Frs 7–8.9.1–7–8.9.11 still comprised complex mixts and were not investigated further.

Fr. 7–8.9.12 (35.5 mg) was methylated and the mixt. resolved by prep. TLC in $CHCl_3$–benzene–Me_2CO (10:9:1) to give 3′,4,5′-trimethoxystilbene [15] as a colourless amorphous solid (4.2 mg, R_f 0.71). Methylation of fr. 7–8.9.13 (260 mg) followed by flash CC in hexane–EtMeCO (4:1) yielded three frs, 7–8.9.13.1 (tubes 1–16, 63 mg), 7–8.9.13.2 (17–22, 27 mg) and 7–8.9.13.3 (23–45, 88 mg). Fr. 7–8.9.13.1 was further resolved by prep. TLC in benzene (×3) to give two bands at R_f 0.52 (2.8 mg) and R_f 0.22 (1.2 mg). The former band was comprised of (±)-4,6-dimethoxy-3-(4-methoxybenzyl)-3-methylbenzo[*b*]furan-2(3*H*)-one (**8**), which was obtained as an amorphous solid (Found: $[M]^+$ 328.1303. $C_{19}H_{20}O_5$ requires 328.1311), δ_H (Table 1); MS (rel. int): *m/z* 328 ($[M]^+$, 1.2), 207 (66.5) and 121 (100). The R_f 0.22 band gave 4,4′,6-trimethoxy-5-methylaurone as a yellow amorphous solid (This compound is most likely an artefact originating from C-methylation of the A-ring of 4,4′,6-trihydroxy-aurone with Me_2SO_4). (Found: $[M]^+$ 326.1145. $C_{19}H_{18}O_5$ requires 326.1154), δ_H ($CDCl_3$) 7.82 [*d*, J = 8.5 Hz, H-2,6(B)], 6.94 [*d*, J = 8.5 Hz, H-3,5(B)], 6.72 (*s*, H-α), 6.50 [*s*, H-7(A)], 4.14 [*s*, 4-OMe(A)], 3.92 [*s*, 6-OMe(A)] 3.85 [*s*, 4-OMe(B)] and 2.05 [*s*, 5-Me(A)]. Fr. 7–8.9.13.2 (27 mg) comprised 2′,4,4′,6-tetramethoxydihydrochalcone (**14**) as an amorphous solid. Fr. 7–8.9.13.3 (88 mg) was purified by prep. TLC in benzene–EtOAc–Me_2CO (7:2:1) to give 4,4′,6-trimethoxyaurone [12] as a

yellow amorphous solid (44.2 mg, R_f 0.43). Methylation of fr 7–8.9.14 (200 mg) and subsequent flash CC in hexane–EtMeCO (4:1) yielded two frs 7–8.9.14.1 (68.5 mg) and 7–8.9.14.2 (78.9 mg). Purification by prep. TLC in toluene–EtMeCO (9:1, ×3) of the former fr. yielded 2′,4,4′,6′-tetramethoxychalcone [8] as a yellow amorphous solid (R_f 0.51, 4.3 mg). Fr. 7–8.9.14.2 was purified by prep. TLC in toluene–Me_2CO (9:1) to give (2*R*,3*R*)-4′,5,7-tri-*O*-methylaromadendrin [10] as a light-yellow amorphous solid, CD $[\theta]_{323}$ 1.4×10^1, $[\theta]_{308}$ 4.4×10^2, $[\theta]_{297}$ 1.3×10^3, $[\theta]_{294}$ 1.2×10^3, $[\theta]_{291}$ 1.3×10^3, $[\theta]_{287.2} - 4.9$, $[\theta]_{283.30} - 1.7 \times 10^3$, $[\theta]_{279.3} - 1.2 \times 10^3$, $[\theta]_{275.9} - 1.5 \times 10^3$. Methylation of fr. 7 – 8.9.15 (600 mg) and subsequent flash CC in hexane–benzene–Me_2CO-MeOH (8:8:3:1) yielded three frs 7–8.9.15.1 (tubes 1–18, 219.5 mg), 7–8.9.15.2 (19–28, 111.6 mg) and 7–8.9.15.3 (36–51, 183.4 mg). Fr. 7–8.9.15.1 was purified by successive prep. TLC in benzene–Me_2CO (9:1, R_f 0.27, 38.3 mg) and benzene–EtMeCO [4:1, (×2)] to give (2*R*)-4′,5,7-tri-*O*-methylnaringenin [9] as a light-yellow amorphous solid (R_f 0.47, 9.5 mg), CD $[\theta]_{375.7}$ 1.2, $[\theta]_{359.5}$ 1.4×10^3, $[\theta]_{347.6}$ 6.1×10^2, $[\theta]_{340.6} - 5.1$, $[\theta]_{325.3} - 1.7 \times 10^3$, $[\theta]_{310.4}$ 7.4×10^0, $[\theta]_{301.1}$ 7.3×10^2, $[\theta]_{294.8}$ 3.1×10^2, $[\theta]_{285.2}$ 5.1×10^3, $[\theta]_{275.3} - 3.0 \times 10^2$, $[\theta]_{268}$ 3.3×10^3. Fr. 7–8.9.15.2 was further resolved by prep. TLC in benzene–EtMeCO (4:1) into two bands at R_f 0.21 (40.5 mg) and R_f 0.11 (10.0 mg). The latter comprised 3,4′,5,7-tetra-*O*-methylkaempferol [11] as a yellow amorphous solid. The R_f 0.21 band and also the 7–8.9.15.3 fr. (183.4 mg) comprised oligomeric benzofuranoids which will be described elsewhere. Frs obtained that are not further investigated here will be discussed in future publications.

Synthesis of (±)-4,6-*dimethoxy*-3-(4-*methoxybenzyl*)-3-*methylbenzo*[b]*furan*-2(3H)-*one* (**8**). 4,4′,6-*Tri-O*-methylmaesopsin (**3**) (130 mg) was dissolved in 4% KOH (30 ml) and the mixt. heated at 90° for 1 hr. The mixt. was cooled to 0°, acidified with 1.5 M H_2SO_4 and extracted with Et_2O (3 × 50 ml). The combined Et_2O extracts were dried (Na_2SO_4), the Et_2O evapd and the mixt. sepd by prep. TLC in benzene–Me_2CO (9:1) to give 3-hydroxy-4,6-dimethoxy-3-(4-methoxy-benzyl)-benzo[*b*]furan-2(3*H*)-one (**21**) [27] as a light-yellow amorphous solid (R_f 0.39, 42.2 mg). This was dissolved in CH_2Cl_2 (16 ml) containing 5% Pd/C catalyst (50 mg) and the mixt. hydrogenated for 9 hr at 1 atmosphere of H_2 pres. The catalyst was filtered through Celite, the solvent evapd and the mixt. was resolved by prep. TLC in benzene–Me_2CO (9:1) to give 4,6-dimethoxy-3-(4-methoxybenzyl)benzo[*b*]furan-2(3*H*)-one (**22**) as a light-yellow amorphous solid (R_f 0.69, 35.7 mg) (found: $[M]^+$, 314.1146. $C_{18}H_{18}O_5$ requires 314.1154); δ_H (Table 1). This compound (14.7 mg, 0.047 mmol) in THF (3 ml) was added to lithium diisopropylamide (0.0564 mmol) in THF (3 ml), the mixt. stirred at −78° for 20 min and a soln of MeI (0.0035 ml) and hexamethylphosphoric triamide (0.008 ml) in THF (1 ml) added. The temp. was raised to −40°, the mixt. stirred at this temp. for 1 hr and then the reaction was quenched with 10% HCl. Et_2O (20 ml) was added, which was washed with satd NaCl soln, H_2O (3 × 10 ml) and eventually evapd to dryness. Prep. TLC separation in benzene–Me_2CO (9:1) yielded (±)-4,6-dimethoxy-3-(4-methoxybenzyl)-3-methylbenzo[*b*]furan-2(3*H*)-one (**8**) (R_f 0.74, 11.7 mg) with ^1H NMR and MS data identical to those of the same derivative of the natural product (**7**).

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