Absolute configuration of flavanone–benzofuranone-type biflavonoids and 2-benzyl-2-hydroxybenzofuranones

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The O-1–C-2 and C-3–C-4 bonds in the flavanone–benzofuranone-type biflavonoids 1 and 3 are subject to cleavage with sodium cyanoboranuide in trifluoroacetic acid at 0 °C. Conformational information available from computational data in conjunction with ^{1}H NMR and CD spectroscopic observations of the biflavonoids and their degradation products have permitted assignment of absolute configuration to three biflavonoids and the 2-benzyl-2-hydroxy-1-benzofuran-3(2*H*)-one group of natural products.

Introduction

Although the biflavonoids represent a major group of phenolic natural products,[1] the assessment of the absolute configuration of analogues possessing stereocentres other than those originating from atropisomerism of the interflavonoid bond, has hitherto met with no success. This also precluded stereochemical assignment of zeyherin,[2] the first and thus far sole entry with a benzofuranoid constituent unit, which was isolated some 25 years ago from the heartwood of 'red ivory' (*Berchemia zeyheri* Sond.).[3] The collective utilization of chemical degradation and ^{1}H NMR and CD spectroscopic and computational data has now permitted estimation of the absolute stereochemistry of two zeyherin epimers, and for the first time also of two 2-benzyl-2-hydroxy-1-benzofuran-3(2*H*)-one enantiomers, a small but biosynthetically significant group of aurone derivatives.[4]

Results and discussion

The zeyherin epimers **1** and **3**, and the closely related analogue **5** with an α,2′,4,4′,6′-pentahydroxychalcone constituent unit, coexist in the red heartwood of *B. zeyheri* with the predominant benzofuranone, (±)-maesopsin [2,4,6-trihydroxy-2-(*p*-hydroxybenzyl)benzofuran-3(2*H*)-one] **7**[2,5] (7% of the total extract), (2*R*)-4′,5,7-trihydroxyflavanone **9** (naringenin),[4] the α,2′,4,4′,6′-pentahydroxychalcone **11**,[5] 2′,4,4′,6′-tetrahydroxychalcone **13**,[4] and a variety of monomeric[6] and oligomeric flavonoids.† Owing to the complexity of the mixture the polyphenols were identified as their permethylaryl ethers, *e.g.* **2**, following methylation of suitable fractions with dimethyl sulfate under anhydrous conditions.

A conspicuous feature of the ^{1}H NMR spectra (Table 1) of the zeyherin hepta-*O*-methyl ethers **2** and **4**, notably free of the effects of dynamic rotational isomerism about the interflavonoid bond, is the presence of the elements of a tetra-*O*-methylmaesopsin unit substituted at C-5 or -7 (A-ring) (residual singlet at δ 5.87 and 5.79 for **2** and **4** respectively) and a C-3 substituted tri-*O*-methylnaringenin moiety [doublets for H-2 and -3(C) at δ 5.82, 4.65 and δ 5.60, 4.43 for **2** and **4** respectively] with 2,3-*trans* relative configuration ($J_{2,3}$ 12.0 Hz). The C-7(D) bonding position to the maesopsin unit in both derivatives **2** and **4** was confirmed by the NOE association of 5-H(D) (δ 5.87, 5.79 for **2** and **4** respectively) with the two D-ring *O*-methyl resonances (δ 3.80, 3.86 and δ 3.69, 3.82 for **2** and **4** respectively). Differentiation between the very similar four-spin systems of the B- and E-rings was effected *via* COSY spectra using the benzylic methylene and 2-H(C) resonances as reference signals.

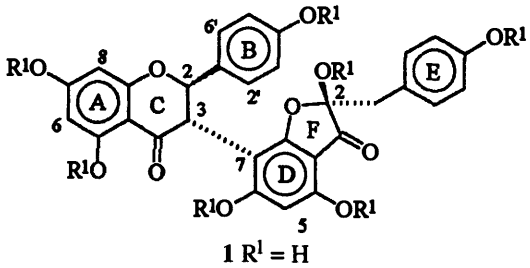
The above structural assignments correlated with the EI mass spectral fragmentation data of derivatives **2** and **4**. Apart from the molecular ion M^+, *m/z* 656 (15.1 and 6.2% for **2** and **4** respectively), prominent peaks occurred at *m/z* 535 (42.2, 29.5%), 476 (100, 100%), 355 (75.2, 88.4%), 313 (10.6, 10.1%), 312 (29.1, 28.6%), 181 (21.0, 11.7%) and 121 (75.6, 63.0%). The latter fragment reflects the loss of a 4-methoxybenzyl radical involving the E-ring hence affording the *m/z* 535 ion while the base peak (*m/z* 476) results from the equivalent of retro-Diels–Alder (RDA) fragmentation of the naringenin ABC-unit.

The ^{1}H NMR spectrum (Table 1) of the octa-*O*-methyl ether derivative **6** of the natural product **5**, the first biflavonoid with an α-hydroxychalcone constituent unit, exhibits the typical effects of dynamic rotational isomerism about the interflavonoid bond at ambient temperature. At elevated temperature (70 °C) the data are reminiscent of an α,2′,4,4′,6′-pentamethoxychalcone unit (vinylic H, δ 6.25) coupled *via* C-3′(A) (residual H-5′ singlet, δ 6.18) to C-3 of a tri-*O*-methylnaringenin moiety (doublets for H-2 and -3, δ 5.85, 4.58) with 2,3-*trans* relative configuration ($J_{2,3}$ 12.0 Hz). Differentiation of the spin systems of the B- and E-rings was again effected by a COSY spectrum using the H-2(C) and vinylic proton resonances as reference signals. Appropriate NOE associations between the A- and D-ring protons and *O*-methyl signals permitted differentiation of H-6 and -8(A) and of H-5(D) and the vinylic β-proton. The conspicuous absence of an NOE association of the latter proton and the enolic *O*-methyl resonance (δ 3.76) confirmed the *Z*-configuration‡ of the chalcone double bond. The mass spectrum confirmed the molecular formula, $C_{38}H_{38}O_{11}$ (M^+, *m/z* 670, 43.3%), and is dominated by an RDA fragmentation involving the C-ring thus leading to the base peak, *m/z* 490, and the A-ring fragment, *m/z* 181 (52%). The structure of the novel biflavonoid **5** thus closely resembles that of the flavanone–chalcone dimer that was obtained from *Brackenridgea zanguebarica*.[7]

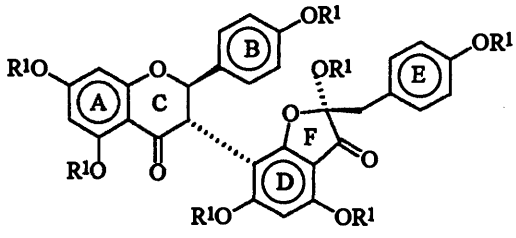
Owing to the complexity imposed by the three stereocentres, the well defined CD spectra (Fig. 1) did not permit stereochemical assignment to either of the zeyherin derivatives **2** or **4**. In the absence of direct stereochemical levers we opted for an approach of chemical degradation in order to reduce the number of stereocentres. Whereas the interflavonoid bond in epimers **2** and **4** is stable towards acid-catalysed thiolytic cleavage,[8,9] treatment of these compounds with sodium cyanoboranuide $[Na(CN)BH_3]$[10] (12 molar excess) in

† To be described elsewhere.

‡ In (*E*)-2′-hydroxy-α,4,4′,6′-tetramethoxychalcone such an association is prominent—D. Ferreira and E. V. Brandt, unpublished results.



1 R^1 = H
2 R^1 = Me



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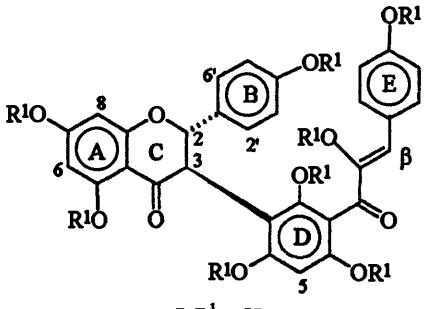

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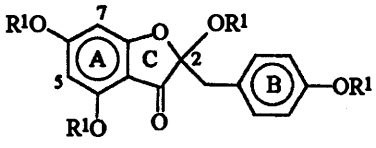
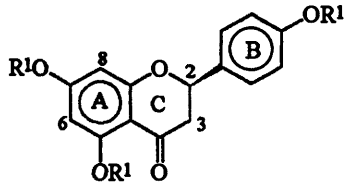
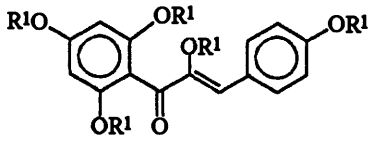


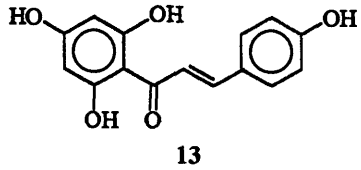
7 R^1 = H
8 R^1 = Me



9 R^1 = H
10 R^1 = Me



11 R^1 = H
12 R^1 = Me



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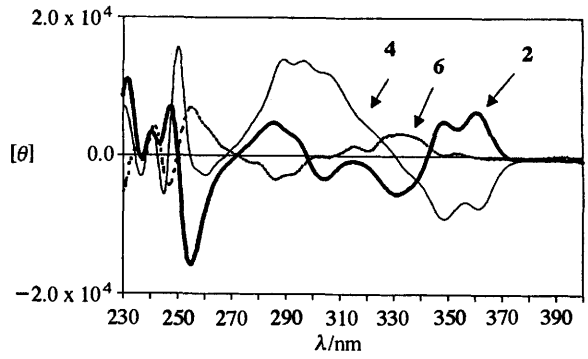


Fig. 1 CD curves of the biflavanoid derivatives **2**, **4** and **6**

trifluoroacetic acid (TFA) for 2 h at 0 °C under nitrogen[11] led to the formation of the 7-(4-methoxyphenethyl)tetra-*O*-methylmaesopsin enantiomers **14** and **16** (Scheme 1). The genesis of the latter two compounds requires the breaking of both the O-1–C-2 and C-3–C-4 bonds of the C-rings of the zeyherin epimers **2** and **4**. The initial step presumably involves reductive cleavage of the O-1–C-2 bond *via* the protonated species **17**/**18** hence leading to the formation of the 2,3-diarylpropiophenones **19**/**20** which are subsequently reduced to the 1,2,3-triarylpropanes **21**/**22**.[12,13] Protonation of the electron-rich phloroglucinol-type A-ring presumably imparts lability to the equivalent of the C-3–C-4 bond which then breaks under the influence of the electron-releasing D-ring in intermediates **23**/**24**. Aromatization of the A-ring fragment **25** *via* [1,3]-sigmatropic rearrangement results in the formation of 2-hydroxy-4,6-dimethoxytoluene§ while reduction of the *o*-quinomethane type intermediates **26**/**27** affords the 7-(4-methoxyphenethyl)-tetra-*O*-methylmaesopsin enantiomers **14** and **16**. This mechanism was confirmed by utilizing sodium cyanotrideuterioboranuide [$Na(CN)CD_3$] under the same conditions for reduction of the zeyherin epimer **2** which resulted in the formation of the dideuteriomaesopsin analogue **15**. The ^1H NMR data of the latter compound are collated in Table 1.

The CD spectra (Fig. 2) of the maesopsin enantiomers **14** and **16** may in principle be used to define the absolute configuration at C-2 providing that the preferred conformations of their benzofuranone moieties are known. Estimation of the latter by semi-empirical methods[14] (AM1) indicates that the oxacyclopentenone ring preferentially adopts a β-O-1-envelope conformation **28** with the heteroatom projecting above the plane (dihedral angle C*O*–C-3–C-2–O-1 = −178.8°) of the enone ring system in the 2*R* enantiomer **14** and for the 2*S* enantiomer **16** an α-O-1-envelope conformation **29** with the heteroatom projecting below the plane (dihedral angle C*O*–C-3–C-2–O-1 = 179.5°) of the enone ring system. To account, however, for the dependence of the CD-curves on the total ensemble of conformers significantly populated at ambient temperature rather than a single preferred conformer, a global search routine[14] (GMMX 1.0) was employed to explore the potential energy surface (PES) of both enantiomers **14** and **16**. The results (Table 2) conformed to those of the initial calculations, indicating conformers (Boltzmann population, 99.72%) with a β-O-1-envelope conformation **28** for the 2*R* enantiomer **14** and conformers (Boltzmann population, 99.77%) with an α-O-1-envelope conformation **29** for the 2*S* enantiomer **16** within 3 kcal mol^{-1} energy window of the minimum.¶

Thus, the observed positive and negative Cotton effects for the n ⟶ π* transition in the 330–365 nm region of the CD

§ Not isolated.
¶ 1 cal = 4.184 J.

Table 1 ^{1}H NMR peaks (δ_H) of the biflavonoid derivatives **2**, **4** and **6**, the 7-phenethylmaesopsin enantiomers **14**/**16** and maesopsin **8** at 300 MHz (25 °C) in $CDCl_3$. Splitting patterns and *J* values (Hz) are given in parentheses

Ring	H	**2**	**4**	**6**	**14**/**15**[a]/**16**	**8**
A	6/5	6.11 (d, 2.0)	6.13 (d, 2.0)	6.13 (d, 2.0)	—	5.88 (d, 2.0)
	8/7	6.14 (d, 2.0)	6.16 (d, 2.0)	6.16 (d, 2.0)	—	6.05 (d, 2.0)
B	2/6	7.27 (d, 8.5)	7.07 (d, 8.5)	7.26 (d, 8.5)	7.07 (d, 8.5)	7.13 (d, 9.0)
	3/5	6.76 (d, 8.5)	6.69 (d, 8.5)	6.76 (d, 8.5)	6.79 (d, 8.5)	6.70 (d, 9.0)
C	2	5.82 (d, 12.0)	5.60 (d, 12.0)	5.85 (d, 12.0)	2.81–2.73 (m, 3-CH_2)	3.14, 3.02 (each d, 13.5, -CH_2-)
	3	4.65 (d, 12.0)	4.43 (d, 12.0)	4.58 (d, 12.0)	2.71–2.63 (m, 2-CH_2) 2.75 (d, 8.0, 3-H)[a] 2.69 (d, 8.0, 2-H)[a]	
D	5	5.87 (s)	5.79 (s)	6.18 (s)	5.87 (s)	
	7	—	—	—	—	
E	2/6	7.12 (d, 8.5)	7.04 (d, 8.0)	7.57 (d, 8.5)	7.13 (d, 8.5)	
	3/5	6.65 (d, 8.5)	6.67 (d, 8.0)	6.85 (d, 8.5)	6.69 (d, 8.5)	
F	-CH_2-	2.99 (d, 13.5) 2.76 (d, 13.5)	2.98 (d, 13.5) 3.05 (d, 13.5)	6.25 (s, β-H) —	3.15 (d, 13.0) 3.07 (d, 13.0)	
	OMe	3.11 (2-F), 3.71 (4-E), 3.72 (4-B), 3.80 (5-A), 3.80, 3.86 (4/6-D), 3.89 (7-A), each s	2.99 (2-F), 3.69 (4-B), 3.69, 3.82 (4/6-D), 3.79 (4-E), 3.84 (5-A), 3.86 (7-A), each s	3.69, 3.73 (4/6-D), 3.68 (4-B), 3.82 (4-E), 3.87 (7-A), 3.81 (5-A), 3.67 (α), 3.57 (2-D), each s	3.18 (2-F), 3.69 (4-E), 3.76 (4-B), 3.79, 3.88 (4/6-D), each s	3.24 (2-C), 3.71 (4-B), 3.82, 3.84 (4/6-A), each s

[a] Peaks for the dideuterio analogue **15**.

Table 2 GMMX search results

Structure	Total conformers[a]	Unique conformers[b]	Final ensemble[c]	Dihedral angle[d]/°	E_{min}[e]/kcal mol^{-1}
14	7464	2993	1961	−168 to −179	52.09
16	6547	2616	1582	168 to 179	52.04
30	8989	2804	613[f]	100 to 110	77.70
31	3183	1098	331[f]	50 to 60	76.02

[a] Total number of conformers considered during search. [b] Number of unique conformers (carbon skeleton only) within 3 kcal mol^{-1} of the most stable conformer. [c] Final ensemble of conformers (hydrogens attached) within 3 kcal mol^{-1} of the most stable conformer. [d] Dihedral C*O*–C-3–C-2–O-1 for **14** and **16**; dihedral C-2(C)–C-3(C)–C-7(D)–C-6(D) for **30** and **31**. [e] E_{min} of the most stable conformer in the final ensemble. [f] Resulting conformers further refined by four additional cycles.

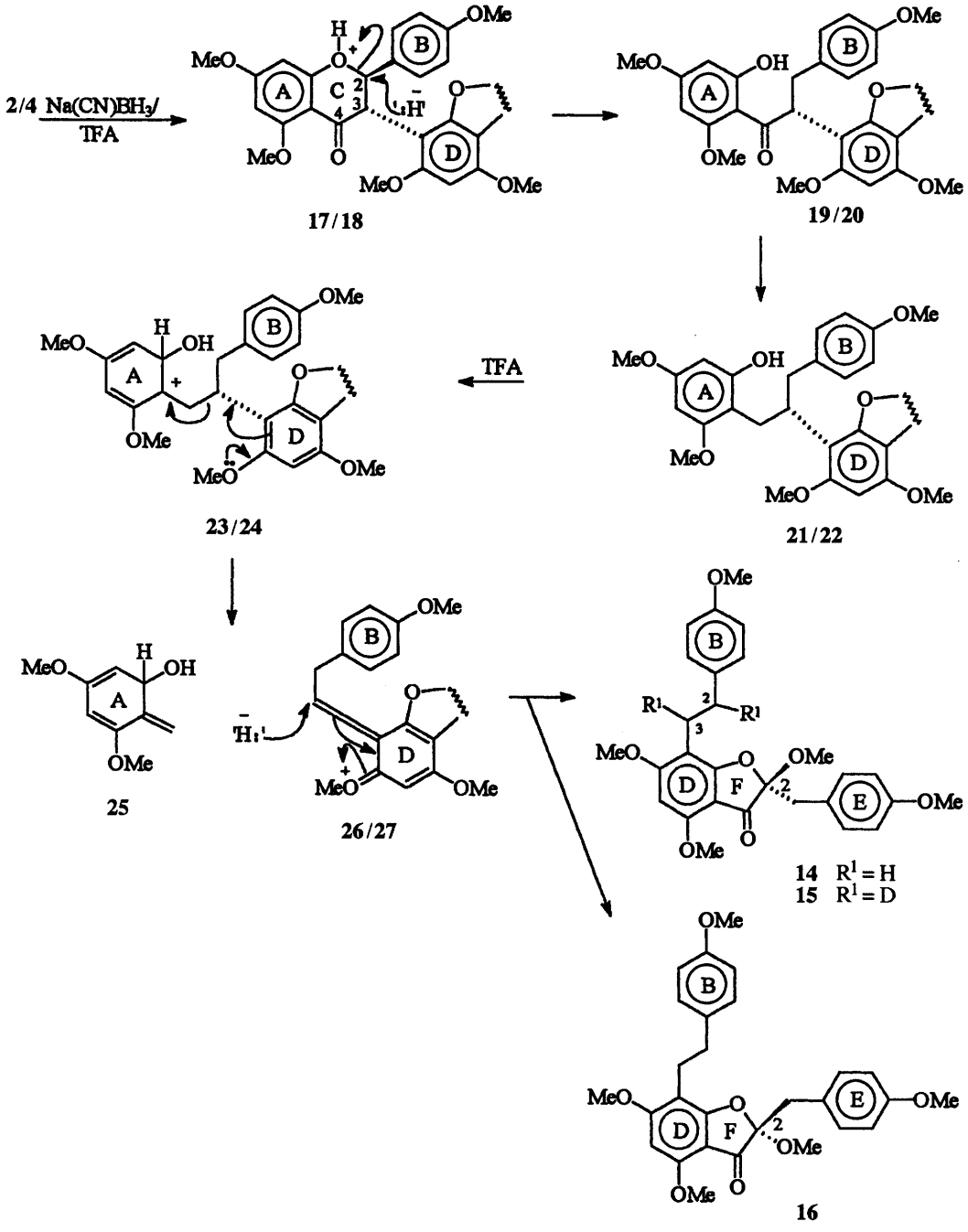
spectra of the derivatives of the maesopsin analogues **14** and **16**, are then in accord with β-O-1- and α-O-1-envelope conformations for **14** and **16** respectively, and 2*R* absolute configuration for compound **14** and 2*S* for **16** by application of Snatzke's chirality rule for cyclopentenones.[15] The CD curves (Fig. 2) for derivatives **14** and **16** should additionally also permit the unambiguous assessment of the absolute stereochemistry of the 2-benzyl-2-hydroxybenzofuranone group of naturally occurring flavonoids.

The CD data of the maesopsin-type enantiomers **14** and **16** subsequently also permitted tentative assignment of 2*R* (C-ring) configuration to both the zeyherin epimers **2** and **4** *via* high-amplitude positive Cotton effects ($[\theta]_{274.3}$ +4.8 × 10^3 and $[\theta]_{278.3}$ +1.4 × 10^4 respectively) for the π ⟶ π* transitions in their CD spectra.[16] A global conformational search routine (GMMX 1.0)[14] was used to estimate the dihedral angle [C-2(C)–C-3(C)–C-7(D)–C-6(D)] about the C-3(C)–C-7(D) bond for conformers of zeyherins **30** and **31** significantly populated within 3 kcal mol^{-1} of the minimum energy (Table 2). The results indicated preferred *E*-conformers (C-ring) for both **30** and **31** with interflavonoid dihedral angles of 100–110° (Boltzmann population, 99.98%) and 50–60° (Boltzmann population, 99.90%) respectively.

When taken in conjunction with the observed NOE association (0.7%) of 2-OMe(F) (δ 3.11) with 2-H(C) (δ 5.82) permitted in conformer **30** of derivative **2** with the (2*R*)-benzofuranoid constituent unit and its conspicuous absence in the diastereomer **4** with 2*S*(F) configuration, these data unequivocally confirmed the 2*R*(C) absolute configuration of the zeyherins **1** and **3**. The 3*S*(C) configuration of both these natural products is then evident from the ^{1}H NMR coupling constants ($^3J_{2,3}$ 12.0 Hz) establishing 2,3-*trans* (C) relative configuration for derivatives **2** and **4**. Although the same basic skeleton of the zeyherin epimers **1** and **3** was proposed for zeyherin by Volsteedt and Roux,[2] the 60 MHz ^{1}H NMR data of their compound differ conspicuously from the 300 MHz data of the permethylaryl ethers **2** and **4**. This may suggest that their compound could have been a different diastereomer.

The CD data (Experimental section) of the octamethyl ether **6** of the flavanone-(3,3′)-α-hydroxychalcone biflavonoid **5** resemble those of dihydrokaempferol[(2*R*,3*R*)-2,3-*trans*-3,4′,5,7-tetrahydroxyflavanone)]. Thus, the high-amplitude positive Cotton effect ($[\theta]_{326.1}$ + 3.2 × 10^3) for the n ⟶ π* transition and the negative Cotton effect ($[\theta]_{275}$ −3.6 × 10^3) for the π ⟶ π* transition, in conjunction with ^{1}H NMR data indicating the 2,3-*trans* relative configuration of the C-ring, are reminiscent of 2*S*,3*R* absolute stereochemistry[16] for the biflavonoid derivative **6**. Owing to the fact that the absolute stereochemistry of biflavonoids **1**, **3** and **5** is now established, we choose to name these compounds according to the proposals of Hemingway *et al.*[17] for the proanthocyanidins, *e.g.* **1** is (2*R*,3*S*)-naringenin-(3α,7)-(2*R*)-maesopsin (see also Experimental section).

The biosynthetic significance of the enantiomeric relationship of the C-ring stereocentres of zeyherins **1** and **3** compared to those of the flavanone-α-hydroxychalcone **5**, as well as the enantiomerism of the maesopsin constituent units of the zeyherins in contrast to the racemic nature of the parent maesopsin **7** in *B. zeyheri* is not clear. It appears reasonable to propose that a quinomethane radical **32** originating by oxidation of 2′,4,4′,6′-tetrahydroxychalcone[18] **13** effects electrophilic substitution[19] on the phloroglucinol-type ring of either maesopsin **7**, presumably a specific enantiomer, or the α-hydroxychalcone **11**. The facile interconversion,[20] 2-benzyl-2-



Scheme 1 Degradation of the zeyherin epimers **2** and **4** with $Na(CN)BH_3$ in TFA. Symbols for the rings as in **2** and **4** and numbering 2 and 3 for the 'ethyl' carbons are retained for **14** and **16**

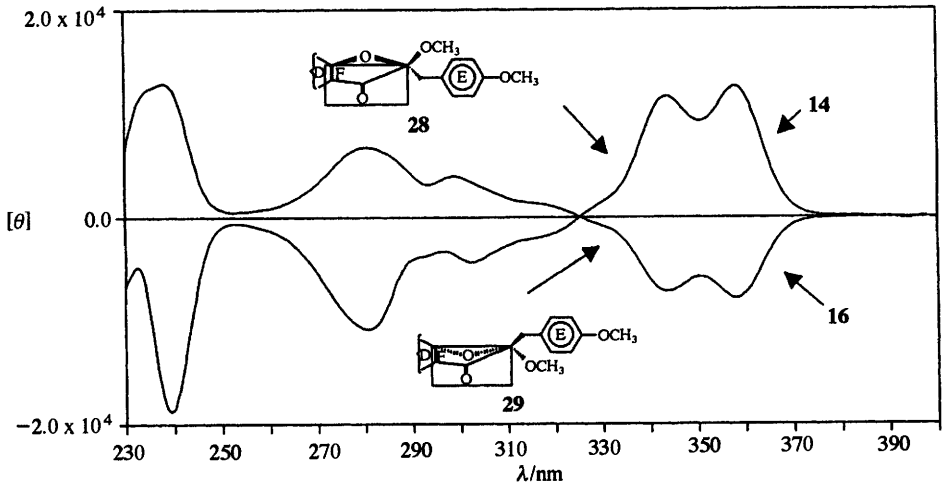
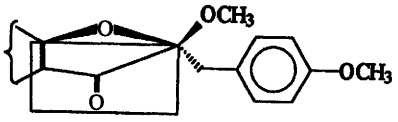


Fig. 2 CD spectra of maesopsin enantiomers **14** and **16**



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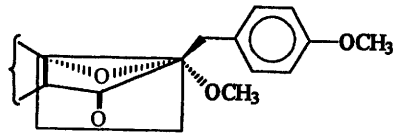

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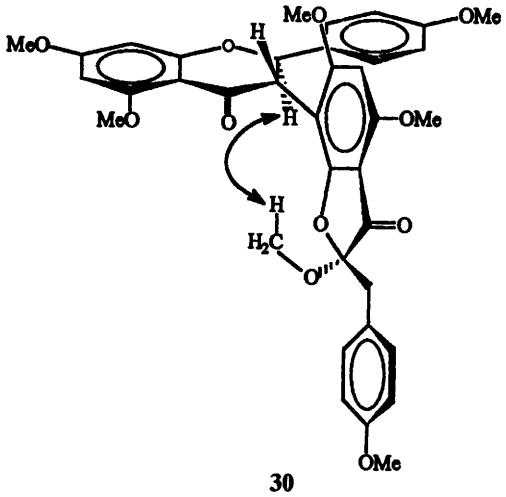

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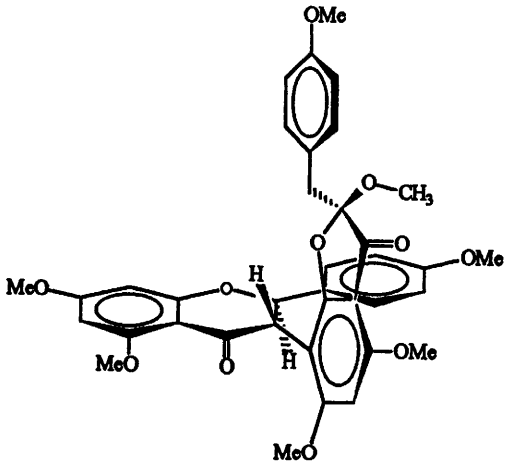

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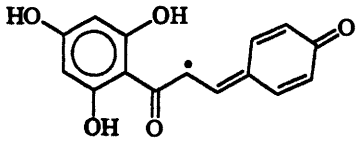

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hydroxybenzofuranone $\rightleftharpoons$ α-hydroxychalcone and flavanone $\rightleftharpoons$ chalcone may feature prominently during the ageing process thus explaining the array of enantiomerism depicted above. The former interconversion also precludes an unambiguous claim of the flavanone-α-hydroxychalcone being a natural product since such a conversion may feasibly be induced by the process of *in vitro* methylation. We have evidence of the occurrence of additional diastereomers and regioisomers, involving C-5(A) of the maesopsin moiety as the bonding position, of the zeyherins in the red ivory. These will be described elsewhere.

The results described here demonstrate that the absolute configuration of at least some of the biflavonoids possessing stereocentres is indeed assessable when chemical degradation and appropriate physical data are used collectively. It additionally led to the generation of CD data facilitating the determination of the absolute configuration of the 2-benzyl-2-hydroxybenzofuranones for the first time.

Experimental

^{1}H NMR Spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with Me_4Si as internal standard. *J* Values are given in Hz. Mass spectra were obtained with a Kratos MS-80 instrument and CD data in MeOH on a JASCO J-710 spectropolarimeter. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and the plates were sprayed with H_2SO_4–HCHO (40:1, v/v) after development. Preparative plates (PLC), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Separations on Sephadex LH-20 were in EtOH at a flow rate of *ca.* 0.5 cm^3 min^{-1} (30 min fractions). Flash column chromatography (FCC) was carried out in a glass column (5 cm diameter) charged with Merck Kieselgel 60 (230–400 mesh) at a flow rate of 3 cm^3 min^{-1} (30 cm^3 fractions) under N_2 pressure. Methylations were performed with dimethyl sulfate in dry acetone containing anhydrous K_2CO_3 at reflux temperature. Water-soluble phenolics were freeze-dried with a Virtis Freeze mobile 12 SL. Evaporations were carried out under reduced pressure at *ca.* 40 °C in a rotary evaporator.

Calculations

All calculations were performed on a SUN SPARCstation 10 running SunOs Release 4.1.3. The global search routine, GMMX version 1.0,[14] based on the MMX force field of PC-MODEL,[14] was used to explore conformational space. Input was prepared with PC-MODEL's graphical user interface treating aromatic carbons as type 40 and the search run *via* the statistical option, alternating between internal (bonds) and external (cartesian) coordinates. The hydrogen bond function was activated and a relative permittivity (ε = 1.5) employed. Searches were allowed to run until the default cut-off criteria were reached and the Boltzmann populations calculated at 25 °C for the final ensemble of conformers within 3 kcal mol^{-1} of the minimum energy. Semi-empirical calculations were performed by MOPAC 93[14] using the AM1 Hamiltonian with gradient minimization and GNORM = 0.1. Criteria for terminating optimizations were increased by a factor 10 (PRECISE).

The extraction of the heartwood of *B. zeyheri* with aqueous acetone (8:2, v/v) and fractionation of the extract by means of countercurrent distribution and column chromatography using Sephadex LH-20 in ethanol leading to fractions 7–8.9.1 to 7–8.9.25 were fully described in ref. 6 and need not be repeated. This reference also contains the procedures involving the derivatization and characterization of maesopsin **7**, naringenin **9** and the chalcones **11** and **13**.

Methylation of fraction 7–8.9.15 (600 mg) and subsequent FCC in hexane–benzene–acetone–methanol (40:40:15:5, v/v) afforded three fractions 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). Fraction 7–8.9.15.1 was further purified (see ref. 6) to give the naringenin derivative **10**. Fraction 7–8.9.15.2 was further resolved by PLC in benzene–ethyl methyl ketone (8:2, v/v) into two bands at R_f 0.21 (40.5 mg) and R_f 0.11 (10 mg). The latter band comprised of 3,4′,5,7-tetra-*O*-methylkaempferol (see ref.

6) as a yellow amorphous solid. The R_f 0.21 band gave (2S,3R)-4′,5,7-*tri*-O-*methylnaringenin*-(3β,3′)-α,2′,4,4′,6′-*pentamethoxychalcone* **6** as a light yellow amorphous solid (Found: M^+, 670.2417. $C_{38}H_{38}O_{11}$ requires *M*, 670.2414); δ_H see Table 1; *m/z* 670 (M^+, 34.3%), 638 (15.2), 490 (100), 327 (31.8), 195 (87.9) and 181 (52); CD (Fig. 1) $[\theta]_{348.7}$ 3.3×10^2, $[\theta]_{344}$ 4.4×10^1, $[\theta]_{326.1}$ 3.2×10^3, $[\theta]_{312.8}$ 6.5×10^2, $[\theta]_{307.6}$ 1.3×10^3, $[\theta]_{299.8}$ 1.5×10^0, $[\theta]_{275}$ -3.6×10^3 and $[\theta]_{259.3}$ -1.5×10^0.

Fraction 7–8.9.15.3 (183.4 mg) was further resolved by PLC in chloroform–acetone (95:5, v/v, × 4) into two bands at R_f 0.80 (26.7 mg) and 0.74 (19.7 mg). The R_f 0.80 band comprised (2R,3S)-4′,5,7-*tri*-O-*methylnaringenin*-(3α,7)-(2R)-2,4,4′,6-*tetra*-O-*methylmaesopsin* **2** as a yellowish amorphous solid (Found: C, 67.6; H, 5.6; M^+, 656.2257. $C_{37}H_{36}O_{11}$ requires C, 67.7; H, 5.5%; *M*, 656.2258); δ_H see Table 1; *m/z* 656 (M^+, 15.1%), 535 (42.2), 476 (100), 355 (75.2), 327 (5.0), 313 (10.6), 312 (29.1), 195 (28.8), 181 (21.0) and 121 (75.6); CD (Fig. 1) $[\theta]_{369.2}$ 5.3×10^0, $[\theta]_{357.5}$ 6.4×10^3, $[\theta]_{349.6}$ 4.0×10^3, $[\theta]_{344}$ 5.0×10^3, $[\theta]_{377}$ 4.4×10^1, $[\theta]_{324.1}$ -5.7×10^3, $[\theta]_{306.3}$ -8.3×10^2, $[\theta]_{294.7}$ -3.4×10^3, $[\theta]_{287.5}$ 3.6×10^1 and $[\theta]_{274.3}$ 4.8×10^3. The R_f 0.74 band afforded (2R,3S)-4′,5,7-*tri*-O-*methylnaringenin*-(3α,7)-(2S)-2,4,4′,6-*tetra*-O-*methylmaesopsin* **4** as a yellowish amorphous solid (Found: C, 67.7; H, 5.4; M^+, 656.2258. $C_{37}H_{36}O_{11}$ requires C, 67.7; H, 5.5%; *M*, 656.2258); δ_H see Table 1, *m/z* 656 (M^+, 6.2%), 535 (29.5), 476 (100), 355 (88.4), 327 (5.3), 313 (10.1), 312 (28.6), 195 (26.9), 181 (11.7) and 121 (63); CD (Fig. 1) $[\theta]_{372.5}$ -8.2×10^2, $[\theta]_{357.4}$ -7.7×10^3, $[\theta]_{351.9}$ -6.8×10^3, $[\theta]_{343.5}$ -9.3×10^3, $[\theta]_{323.5}$ 2.3×10^1, $[\theta]_{294.1}$ 1.2×10^4, $[\theta]_{286.3}$ 1.4×10^4, $[\theta]_{282.3}$ 1.3×10^4 and $[\theta]_{278.3}$ 1.4×10^4.

Reductive cleavage of zeyherins 2 and 4

The zeyherin derivative **2** (15 mg) was dissolved in trifluoroacetic acid (TFA) (1.5 cm^3) under nitrogen at 0 °C. $Na(CN)BH_3$ (16.9 mg) was added in portions over a period of 30 min at this temperature and the mixture was stirred for an additional 90 min. The reaction was quenched by the careful addition of water and the pH of the mixture was adjusted to *ca.* 6.9 (Merck special indicator, pH 4.0–7.0) with 2% aq. $NaHCO_3$. The mixture was extracted with ethyl acetate (3 × 5 cm^3), the combined solvent was dried over Na_2SO_4 and evaporated to dryness. Separation by PLC in benzene–acetone (9:1, v/v) afforded (2R)-7-[2-(4-*methoxyphenyl*)*ethyl*]-2,4,4′,6-*tetra*-O-*methylmaesopsin* **14** as a white amorphous solid (R_f 0.56, 1.64 mg, 15%) (Found: M^+, 478.1984. $C_{28}H_{30}O_7$ requires *M*, 478.1991); δ_H see Table 1; *m/z* 478 (M^+, 2.7%), 447 (3.0), 357 (100), 193 (89.3) and 121 (48); CD (Fig. 2) $[\theta]_{374}$ 3.2×10^2, $[\theta]_{358}$ 1.3×10^4, $[\theta]_{350.5}$ 9.3×10^3, $[\theta]_{343.5}$ 1.2×10^4, $[\theta]_{325.2}$ 4.7×10^0, $[\theta]_{302.3}$ -4.4×10^3 and $[\theta]_{280.5}$ -1.1×10^4. Identical treatment of the zeyherin derivative **4** (15 mg) gave (2S)-7-[2-(4-*methoxyphenyl*)*ethyl*]-2,4,4′,6-*tetra*-O-*methylmaesopsin* **16** (2.2 mg, 20%) (Found: M^+, 478.1987. $C_{28}H_{30}O_7$ requires *M*, 478.1991); δ_H see Table 1; CD (Fig. 2) $[\theta]_{375}$ -1.5×10^2, $[\theta]_{358.1}$ -7.9×10^3, $[\theta]_{350.5}$ -5.8×10^3, $[\theta]_{343.6}$ -7.3×10^3, $[\theta]_{325.3}$ 2.2×10^0, $[\theta]_{298.7}$ 4.0×10^3, $[\theta]_{293.3}$ 3.2×10^3 and $[\theta]_{280.1}$ 6.8×10^3. Similar treatment of zeyherin derivative **2** (15 mg) with $Na(CN)BD_3$ (16.5 mg) in TFA (1.5 cm^3) afforded the dideuterio 7-phenethylmaesopsin derivative **15** (1.1 mg, 10%); δ_H see Table 1.

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