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Structure and Stereochemistry of the First Isoflavanone-benzofuranone Biflavonoids

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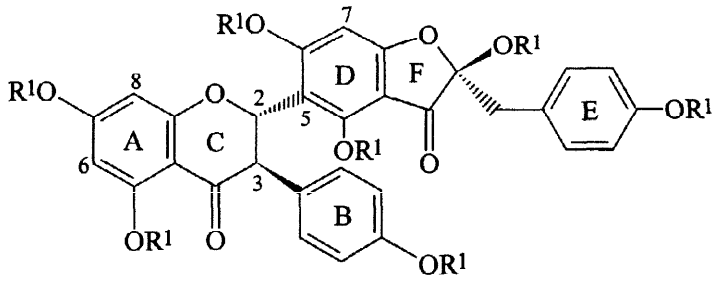
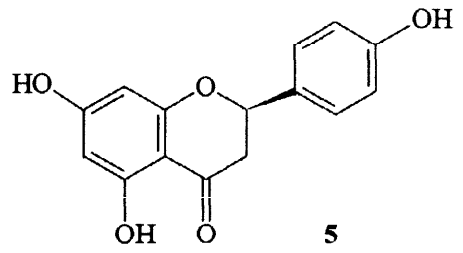
Abstract: The structure and stereochemistry of (2*S*,3*R*)-dihydrogenistein-(2α→5)-(2*R*)-maesopsin and its 2*S* (F-ring) epimer from the heartwood of *Berchemia zeyheri*, representing the first isoflavanone-benzofuranone biflavonoids, were established by ^{1}H NMR and CD data. © 1998 Elsevier Science Ltd. All rights reserved.

Our first reports[1,2] on the 2-benzylbenzofuranoid-type (maesopsin) constituents of the red heartwood of *Berchemia zeyheri* revealed the presence of the first flavanone-benzofuranoid oligomers (*zeyherins*).[3] Definition of the structure and stereochemistry of these were permitted by the collective utilization of chemical degradation, ^{1}H NMR and CD spectrometry in conjunction with computational data.[1,2] Here we report the identification of (2*S*,3*R*)-dihydrogenistein-(2β→5)-(2*R*)-maesopsin **1** and its 2*S*(F)-epimer **3**, representing the first natural isoflavanone-benzofuranoid biflavonoids.

The *aq.* acetone (4:1) extract of the heartwood of *B. zeyheri* was fractionated by repetitive counter-current distribution in H_2O/*sec*-BuOH/*n*-hexane (5:3.5:1.5, 20 transfers) and in H_2O/*sec*-BuOH/*n*-hexane (5:4:1, 103 transfers) followed by column chromatography on Sephadex LH-20 in EtOH. Owing to the complexity of the resulting fractions and having established the absence of natural methoxy groups by



1 R^1=H
2 R^1=Me
3 R^1=H, C-2(F) epimer
4 R^1=Me, C-2(F) epimer



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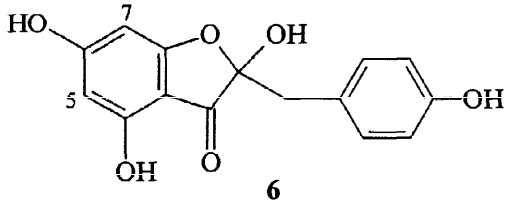

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^{1}H NMR, the polyphenols **1** and **3** were isolated and identified as their permethylaryl ethers **2** and **4**, following methylation with dimethylsulphate under anhydrous conditions, the additional chromatographic step offered by derivatization being a prerequisite for sample purity.

The close structural relationships between the derivatives **2** and **4** and the permethylaryl ethers of the zeyherin epimers[1,2] were evident from the close resemblance of their ^{1}H NMR data (Table), supported by COSY and NOESY data. The spectra of both epimers **2** and **4** exhibit an AM-spinsystem associated with H-2 (δ 5.61, 5.62 for **2** and **4**, resp.) and H-3 (δ 4.66, 4.62 for **2** and **4**, resp.; $J_{2,3\text{-}trans}$ = 10.5 Hz for both **2** and **4**) of the heterocyclic C-rings and the shielded 2(F)-OMe (δ 3.24, 3.19 for **2** and **4**, resp.) and the α-methylene (δ 3.13, 3.05 and 3.19, 3.06 for **2** and **4**, resp., J_{AB} = 14.0 Hz) resonances reminiscent of the benzofuranoid moieties. The B- and E-ring protons, appearing as two AA'BB' spin systems, were common to both derivatives while the A- and D-ring protons resonated respectively as an AB-spin system (J_{AB} = 2.0 Hz for both **2** and **4**) and a residual singlet (δ 5.93, 5.95 for **2** and **4**, resp.). NOE-association of the latter protons with only one methoxy group [6-OMe(D)] define these compounds as 5(D)-linked dimers.

Table: ^{1}H NMR data for the Isoflavanone-benzoofuranoid biflavonoids **2** and **4** [δ (m, J in Hz)].

Ring	H	**2**	**4**
A	6* 8*	5.99 (d,2.0) 5.98 (d,2.0)	6.05 (d,2.0) 6.00 (d,2.0)
B	2/6 3/5	7.32 (d,8.5) 6.84 (d,8.5)	7.38 (d,8.5) 6.82 (d,8.5)
C	2 3	5.61 (d,10.5) 4.66 (d,10.5)	5.62 (d,10.5) 4.62 (d,10.5)
D	7	5.93 (s)	5.95 (s)
E	2/6 3/5	7.01 (d,8.5) 6.65 (d,8.5)	7.15 (d,8.5) 6.62 (d,8.5)
F	-CH_2-	3.13,3.05 (both d, both 10.5)	3.19,3.06 (both d, both 14.0)
	2(F)-OMe	3.24(s)	3.19(s)
	OMe	3.89,3.87,3.86,3.79,3.78,3.73, each s	3.92,3.88(x2),3.82,3.79, 3.71,each s

* May be interchanged.

Long-range COSY- and NOESY-experiments permitted definition of compounds based on a 3-substituted flavanone by association of H-2 and -6(B) with H-2(C), as displayed by the 3α(C) → 7(D)-linked

zeyherins[1,2]. This contrasts notably with the analogues **2** and **4** where coupling of H-2 and -6(B) occurs with H-3(C), indicative of 2α(C) → 5(D)-linked oligomers based on a 2α-substituted isoflavanone moiety.

High-amplitude positive and negative Cotton effects for the n → π* transition in the 350-370 nm region of the CD spectra (Figure) of derivatives **2** and **4**, respectively, are in accord with 2*R*(F) and 2*S*(F) absolute configuration[1,2] for the maesopsin moieties, thus illustrating their epimeric relationship. Isoflavanones display Cotton effects for their n → π* transitions in the same region of their CD curves.[4,5]

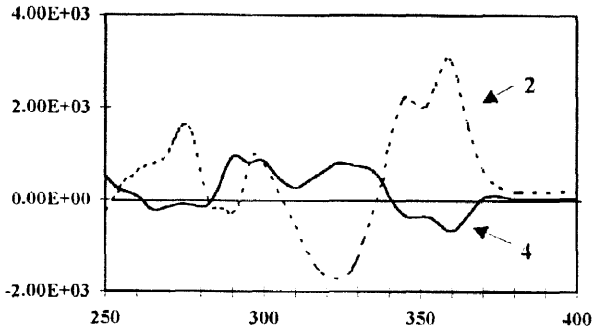

Figure CD spectra of isoflavanone-benzofuranoid biflavonoid derivatives **2** and **4**.

Thus, the positive effect at these wavelengths in the spectrum of **2** is reminiscent of 3*R* configuration, its high amplitude being the result of the cumulative effects of chirality at this centre as well as that at C-2(F). The much reduced negative Cotton effect for derivative **4** similarly reflects 3*R* configuration, the effects due to C-3(C) and C-2(F) now opposing each other. Compounds **2** and **4** additionally exhibit negative and positive Cotton effects in the 310-330 nm regions of their CD spectra. When taken in conjunction with the coupling constants of the protons of the heterocyclic C-ring ($^3J_{2,3}$ = 10.5 Hz) indicating a 2,3-*trans* configuration for both **2** and **4**, the absolute configuration of these novel biflavanoid derivatives may be assigned as 2*R*,3*S*(C): 2*R*(F) for **2** and 2*R*,3*S*(C): 2*S*(F) for **4**.

Biogenetically, the novel biflavonoids **1** and **3** presumably originate *via* 2,3-phenyl migration of the (2*R*) 4',5,7-trihydroxyflavanone **5** (naringerin) which coexists in *B. zeyheri*.[2] Irrespective of the particular mechanism involved, *i.e.* ionic or radical,[6-8] such a migration proceeds in a *suprafacial* mode thus leading to an isoflavanone intermediate with a 3β aryl group and a C-2 electron deficient centre. The less hindered α-face of the electrophilic C-2 centre in such an intermediate is then prone to nucleophilic attack by the phloroglucinol-type D-ring of maesopsin **6**. Since the latter coexists as the racemate in *B. zeyheri*[1,2] the two epimers **5** and **6** originate.

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