The absolute configuration of biflavonoids and 2-benzyl-2-hydroxybenzofuranones

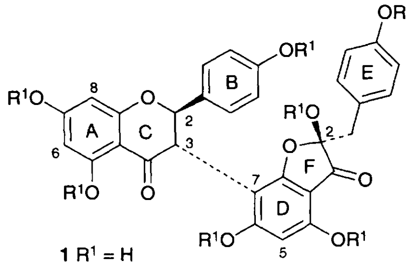
Riaan Bekker, E. Vincent Brandt* and Daneel Ferreira*

Department of Chemistry, University of the Orange Free State, PO Box 339, Bloemfontein, 9300 South Africa

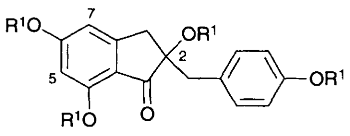
Reductive cleavage of the C-ring of the zeyherin epimers 2 and 4 with sodium cyanoboranuide [Na(CN)BH$_3$] permits the first assessment of the absolute configuration of biflavonoids and 2-benzyl-2-hydroxybenzofuranones.

Although the biflavonoids represent a major group of phenolic natural products,[1] the absolute configuration of those analogues possessing stereocentres† has hitherto not been addressed. Such a deficiency also precluded stereochemical assignment to zeyherin, the first and thus far sole entry with a benzofuranoid constituent unit, which was identified 25 years ago.[2] We now disclose results which permit assessment of absolute configuration of two zeyherin epimers and for the first time also of a 2-benzyl-2-hydroxybenzo[1]furan-3(2*H*)-one, a small but biosynthetically significant group of aurone derivatives.[3]

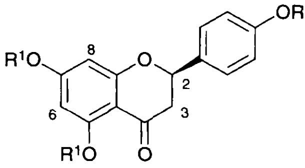
The zeyherin epimers **1** and **3**, identified as permethylaryl ethers **2** and **4** after methylation with dimethyl sulfate, co-exist in the red heartwood of *Berchemia zeyheri* Sond. with the predominant maesopsin **5**,[2,4] (2*R*)-4′,5,7-trihydroxyflavanone **7** and a variety of monomeric and oligomeric flavonoids.[5] A conspicuous feature of the ^{1}H NMR spectra of the zeyherin hepta-*O*-methyl ethers **2** and **4** is the presence of the elements of a tetra-*O*-methylmaesopsin unit **6** substituted at C-5 or -7 (A-ring) (residual singlet at δ 5.87 and 5.79 for **2** and **4** resp.) and a C-3 substituted tri-*O*-methylnaringenin moiety **8** [doublets for H-2 and -3(C) at δ 5.82, 4.65 and δ 5.60, 4.43 ($J_{2,3}$ 12.0 Hz)]. The C-7(A) bonding position to the maesopsin unit in both the zeyherin derivatives **2** and **4** is confirmed by the NOE association of 5-H(D) (δ 5.87, 5.97 for **2** and **4** resp.) with the two D-ring *O*-methyl resonances (δ 3.80, 3.86 and δ 3.69, 3.82 for **2** and **4** resp.). The remaining spin systems correspond to those of the zeyherin derivative **2**.[2]



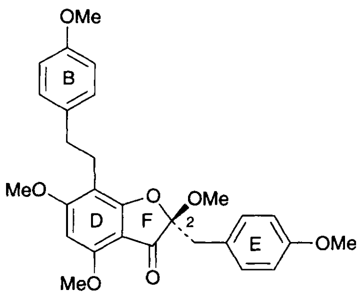
1 R^1 = H
2 R^1 = Me
3 R^1 = H, C-2(F) epimer
4 R^1 = Me, C-2(F) epimer



5 R^1 = H
6 R^1 = Me



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



9
10 C-2(F) enantiomer

Owing to the complexity imposed by the three stereocentres the well defined CD spectra did not permit stereochemical assignment to either of the zeyherin derivatives **2** or **4**. Attempts at cleaving the interflavonoid bond in epimers **2** and **4** using sodium cyanoboranuide[6] (12 molar excess) in TFA for 2 h at 0 °C under nitrogen[7] led to the formation of the tetra-*O*-methyl-7-(4-methoxyphenethyl)maesopsin enantiomers (**9**: 15% yield) and (**10**: 20%) respectively. This novel cleavage presumably involves the sequential reduction of the O(1)–C(2) bond, the carbonyl group and eventually the equivalent of the C(3)–C(4) bond of the C-ring under the prevailing acidic conditions. The CD spectra (Fig. 1) of these enantiomers may in principle be used to define the absolute configuration at C-2(F) providing that the preferred conformations of their benzofuranone moieties are known.[8] Estimation of the latter by semi-empirical (AM1)[9] methods and a global search routine (GMMX)[9] indicates that the oxacyclopentenone ring adopts an O$_1$-envelope conformation (Boltzman population, 99.72%) with the heteroatom projecting above the plane of the enone ring system (β-O$_1$-envelope **11**) in the (2*R*)-enantiomer **9** and for the (2*S*)-enantiomer below the plane in an α-O$_1$-envelope conformation (**12**) (Boltzman population, 99.77%). Thus, the observed positive and negative Cotton effects for the n → π* transition in the 330–365 nm region of the CD spectra of the maesopsin derivatives **9** and **10** respectively are then in accord with β-O$_1$- and α-O$_1$-envelope conformations for **9** and **10** respectively, and 2*R* absolute configuration for compound **9** and 2*S* for **10** by application of Snatzke's chirality rule for cyclopenten- ones.[8] The CD curves of these derivatives should permit assessment of the absolute configuration of the 2-benzyl-2-hydroxybenzofuranone group of flavonoids.

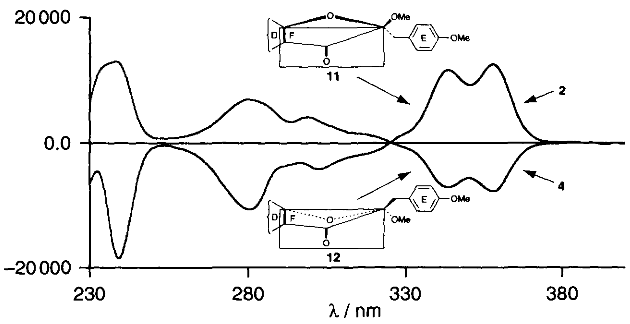


Fig. 1 CD spectra of maesopsin enantiomers **9** and **10**

The CD data of the maesopsin enantiomers **9** and **10** subsequently permitted tentative assignment of 2*R* (C-ring) configuration to both the zeyherin epimers **2** and **4** *via* high-amplitude positive Cotton effects $\{[\theta]_{274.3} + 4.8 \times 10^3$ and $[\theta]_{278.3} + 1.4 \times 10^4$ resp.$\}$ for the $\pi \rightarrow \pi^*$ transitions in their CD spectra.[10] Estimation of interflavonoid bond dihedral angles [C-2(C)–C-3(C)–C-7(D)–C-6(D)] of conformers within a 3.0 kcal mol^{-1}‡ window, defined by a GMMX global search routine,[9] indicated values of 100–110° and 50–60° for the preferred (*E*)-conformers (C-ring) of zeyherins **2** and **4** respectively. When taken in conjunction with the observed NOE association (0.7%) of 2-OMe(F) (δ 3.18) with 2-H(C) in derivative **2** with the (2*R*)-benzofuranoid constituent unit and its conspicuous absence in epimer **4** with 2*S*(F) configuration, this 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 (*vide supra*) confirming 2,3-*trans*(C) relative configuration for derivatives **2** and **4**.

The results described here demonstrate that the absolute configuration of biflavonoids possessing stereocentres is indeed assessable when chemical degradation and appropriate physical data are used collectively.

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Footnotes

† Excluding chirality due to atropisomerism.

‡ 1 cal = 4.184 J.

References

1 H. Geiger, in *The Flavonoids. Advances in Research Since 1986*, ed. J. B. Harborne, Chapman & Hall, London, 1994, 96 and references cited therein.
2 F. du Volsteedt and D. G. Roux, *Tetrahedron Lett.*, 1971, 1647.
3 B. A. Bohm, in *The Flavonoids. Advances in Research Since 1980*, ed. J. B. Harborne, Chapman & Hall, London, 1988, 329.
4 F. du R. Volsteedt, G. J. H. Rall and D. G. Roux, *Tetrahedron Lett.*, 1973, 1001.
5 R. Bekker, R. S. Smit, E. V. Brandt and D. Ferreira, *Photochemistry*, 1996, in the press.
6 C. F. Lane, *Synthesis*, 1975, 135 and references cited therein.
7 P. J. Steynberg, J. P. Steynberg, B. C. B. Bezuidenhoudt and D. Ferreira, *J. Chem. Soc., Chem. Commun.*, 1994, 31; *J. Chem. Soc., Perkin Trans 1*, 1995, 3005.
8 G. Snatzke, *Tetrahedron*, 1965, **21**, 413, 421.
9 GMMX, Version 1.0; PCMODEL, Version 3.0, Serena Software, PO Box 3076, Bloomington, IN 474-3076. MOPAC 93.00, J. J. P. Stewart, Fujitsu Ltd., Tokyo, Japan.
10 W. Gaffield, *Tetrahedron*, 1970, **26**, 4093.

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