Notes

Resolution and Absolute Configuration of Naturally Occurring Auronols

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Received September 26, 2000

Resolution of racemic 2-benzyl-2-hydroxy-1-benzofuran-3(2*H*)-ones (auronols) and CD data of the ensuing enantiomers permit assessment of the absolute configuration at the single stereocenter.

The 2-benzyl-2-hydroxy-1-benzofuran-3(2*H*)-ones (auronols), e.g., maesopsin **1a/1b**, constitute a small but biosynthetically significant group of naturally occurring aurone derivatives.[1,2] The C-2-substituted benzofuranone moiety is a prominent structural unit in a growing number of bi- and triflavonoids[3−8] and also as a separate entity in plants.[9] Owing to their facile equilibration with the α-diketo form **2** of α-hydroxychalcones **3** by virtue of the hemiacetal functionality, e.g., **1a/1b** ⇌ **2** ⇌ **3** (Scheme 1), the auronols are usually obtained as racemates.[2,10] The only exception in this regard is (+)-nigrescin **4**, which was reported some 28 years ago.[11] However, the positive Cotton effect (CE) near 300 nm in the CD spectrum of its tetra-*O*-methyl ether **5** could not, at the time, be interpreted in terms of the absolute configuration at C-2. When the auronols are linked to other chiral biomolecules, e.g., the flavanone- and isoflavanone-benzofuranone biflavonoids[3−7] and the maesopsin glycosides from *Hovenia trichocarea*[10] and *Ceanothus americanus*,[12] the racemates are transformed into diastereoisomers. These should, in principle, be separable and their absolute configurations at C-2 then assessable via chiroptical methods. Results relevant to the resolution and subsequent correlation of circular dichroic data and the absolute configuration of this class of naturally occurring polyphenols are discussed here.

The $O_{(1)}$−$C_{(2)}$ and $C_{(3)}$−$C_{(4)}$ bonds of the C-ring in the diastereoisomeric flavanone-benzofuranone biflavonoid derivatives **6** and **7** are subject to cleavage with sodium cyanoborohydride in trifluoroacetic acid to give the 7-(4-methoxyphenethyl)tetra-*O*-methylmaesopsin enantiomers **8a** and **8b**.[4,5] Their CD spectra (Figure 1) may, in principle, be used to define the absolute configuration at C-2, providing that the preferred conformation of their C-rings is known.[13] Estimation of the latter can be achieved by semiempirical[14](AM1) methods and a global search routine[14] (GMMX), which indicates that in the (2*R*) enantiomer **8a** the oxacyclopentanone ring preferentially 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), as shown in partial structure **9**,

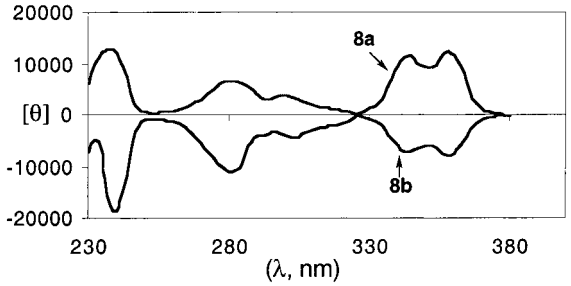
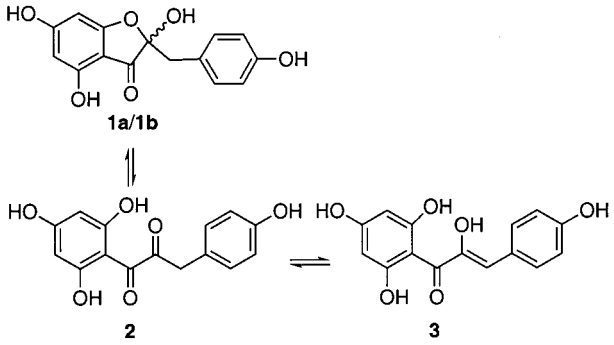
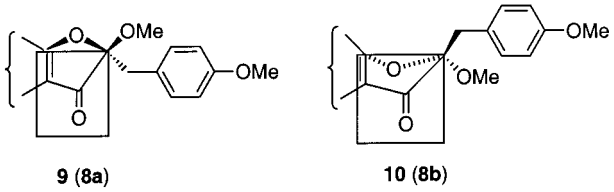


Figure 1. CD spectra of the (2*R*)- and (2*S*)-7-phenethylmaesopsin **8a** and **8b**.

Scheme 1. Facile Conversion of **1a**/**1b** into **2** and **3**



Scheme 2. C-Ring Conformations **9** and **10** of **8a**/**8b**, Respectively



and for the (2*S*)-enantiomer, below the plane in an α-O_1-envelope conformation, as shown in partial structure **10** (Boltzman population, 99.77%) (Scheme 2).[4,5] 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 7-phenethylmaesopsin derivatives **8a** and **8b**, respectively, are then in accord with β-O_1- and α-O_1-envelope conformations for **8a** and **8b**, respectively. By application of Snatzke's chirality rule for cyclopentenones,[13] which

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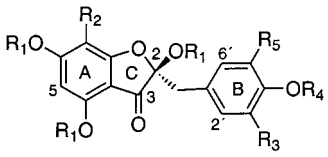
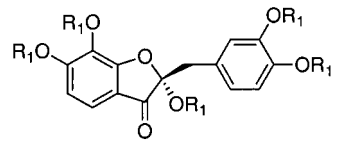
10.1021/np000463i CCC: $20.00
Published on Web 02/01/2001

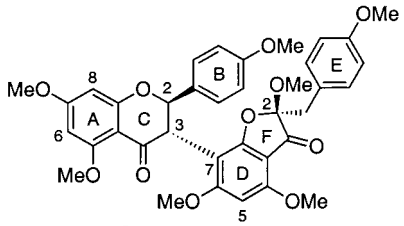


1a $R_1 = R_2 = R_3 = R_4 = R_5 = H$
8a $R_1 = R_4 = Me$, $R_3 = R_5 = H$, R_2 = 4-methoxyphenethyl
11a $R_1 = R_4 = Me$, $R_2 = R_3 = R_5 = H$
12a $R_1 = Ac$, $R_2 = H$, $R_3 = R_5 = OAc$, $R_4 = Me$
13a $R_1 = R_2 = H$, $R_3 = R_5 = OH$, $R_4 = Me$
14a $R_1 = R_4 = Ac$, $R_2 = H$, $R_3 = R_5 = OAc$
15a $R_1 = R_2 = R_4 = H$, $R_3 = R_5 = OH$

1b, 8b, 11b–15b C-2 enantiomers



4 $R_1 = H$
5 $R_1 = Me$



6
7 C-2(F) diastereoisomer

correlates the sign of the Cotton effect with the absolute stereochemistry of the cyclopentenone, compounds **8a** and **8b** possess 2*R* and 2*S* absolute configuration, respectively. The Cotton effects for the $\pi\rightarrow\pi^*$ transition in the 270−310 nm region of the CD spectra of both compounds **8a** and **2b** are opposite those of the $n\rightarrow\pi^*$ transitions, i.e., positive for the 2*S* enantiomer **8b** and negative for the 2*R* enantiomer **8a**.

Resolution of racemic tetra-*O*-methylmaesopsin from *Berchemia zeyheiri* Sond.[15] using a chiralcel OD column (4.5 × 250 mm, 10 μm) at ambient temperature permits access to the two enantiomers **11a** and **11b** in high enantiomeric purity (>99%).[16] The CD spectra (Figure 2) of these enantiomers exhibit Cotton effects for both the $n\rightarrow\pi^*$ (330−365 nm) and $\pi\rightarrow\pi^*$ (300−325 nm) transitions similar to those observed for the 7-(4-methoxyphenethyl) derivatives **8a** and **8b**. Thus, the sequential positive and negative Cotton effects in the 330−365 and 300−325 nm regions, respectively, are reminiscent of 2*R* absolute configuration for enantiomer **11a**. The mirror-image relationship of the CD curve in the same region for enantiomer **11b** accordingly defines its 2*S* absolute stereochemistry (Figure 2).

Under similar conditions the penta-*O*-acetyl derivatives **12a**/**12b** of amaronol B **13a**/**13b** from *Pseudolarix amabilis* L.[2] are efficiently resolved into the two enantiomers **12a** and **12b** (ee ca. 90%). Their CD spectra again show sequential positive and negative Cotton effects for the $n\rightarrow\pi^*$ (325−365 nm) and $\pi\rightarrow\pi^*$ (280−320 nm) transitions, indicating α- and β-orientations of the 2-benzyl- and 2-*O*-acetyl substituents, respectively for enantiomer **12a** and vice versa for enantiomer **12b**, when viewed as indicated. Owing to the change in priority of the 2-*O*-acetyl group

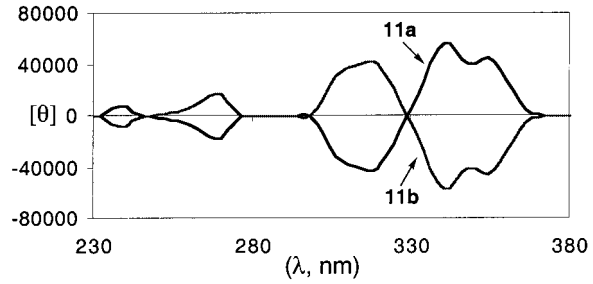


Figure 2. CD spectra of the (2*R*)- and (2*S*)-tetra-*O*-methylmaesopsin **11a** and **11b**.

compared to the 2-hydroxyl and 2-*O*-methyl substituents in terms of the Cahn−Ingold−Prelog convention, the positive Cotton effects in the 325−365 nm region denote 2*S* absolute configuration for **12a**, and the negative Cotton effects in the same region 2*R* absolute stereochemistry for enantiomer **12b**.

The per-*O*-acetyl derivatives **14a**/**14b** of amaronol A **15a**/**15b** from *P. amabilis*[2] could not be resolved under similar conditions. Finally, we revisited the segment of the CD curve of (+)-penta-*O*-methylnigrescin **5** from *Acacia nigrescens* that was published in 1972.[11] Although only the 270−330 nm portion of the spectrum was recorded, the high-amplitude positive Cotton effect of the $\pi\rightarrow\pi^*$ transition in this region presumably indicates 2*S* absolute configuration and hence structure **5** for this nigrescin derivative.

The well-defined CD curves (Figures 1, 2) of the auronol enantiomers **8a**/**8b**, **11a**/**11b**, and **12a**/**12b** should thus contribute significantly toward assessing the absolute configuration of the auronol moiety in natural products comprising this structural unit. Our results additionally indicate that oftentimes insufficient effort is devoted to separate the diastereoisomers of natural products, hence leaving the issues of defining their absolute configurations and preferred conformations, which are essential to eventually comprehending their interaction with other biomolecules, unresolved.

Experimental Section

General Experimental Procedures. HPLC was performed on a Waters Liquid Chromatograph equipped with a Waters 600 Controller and a Waters 486 Tunable Absorbance Detector. A Chiralcel OD (4.6 × 250 mm, 10 μm) stainless steel column [Daicel (Europa) GMBH, Düsseldorf, Germany] was used at ambient temperature, and fractions were collected manually. CD data were recorded in MeOH (ca. 0.1 mg/mL MeOH) on a Jasco-J710 spectrometer; scan parameters: bandwidth (2.0 nm), sensitivity (10 mdeg), response (4 s), scan speed (50 nm/min), step resolution (0.1 nm).

The formation of the 7-phenethylmaesopsin derivatives **8a** and **8b** by degradation of the flavanone-(3→7)-maesopsin derivatives **6** and **7** as well as their conformational data were previously described.[4,5]

Resolution of 11a and 11b. (±)-2,4,4′,6-Tetra-*O*-methylmaesopsin[15] (2 mg) was dissolved in $CHCl_3$ (2 mL) and resolved by means of HPLC (20 injections, 100 μL each) in hexane/EtOH/EtOAc (250/250/0.6, flow rate 6 mL/min) using a chiral column to yield two fractions, 1 (retention time 4 min, 9 s, 0.78 mg) and 2 (retention time 5 min, 4 s, 0.66 mg)

(2*R*)-2,4,4′,6-Tetra-*O*-methylmaesopsin (11a). Fraction 1 comprised the title compound as a white amorphous solid (ee > 99%): ^{1}H NMR data, identical to published data;[15] CD $[\theta]_{354}$ 4.5 × 10^4, $[\theta]_{341}$ 5.7 × 10^4, $[\theta]_{317}$ −4.2 × 10^4, $[\theta]_{268}$ −1.8 × 10^4, and $[\theta]_{238}$ 8.5 × 10^3.

(2*S*)-2,4,4′,6-Tetra-*O*-methylmaesopsin (11b). Fraction 2 comprised the title compound as a white amorphous solid (ee > 99%): ^{1}H NMR data, identical to published data;[15] CD

$[\theta]_{354}$ −3.1 × 10^4, $[\theta]_{341}$ −3.8 × 10^4, $[\theta]_{317}$ 2.9 × 10^4, $[\theta]_{268}$ 1.2 × 10^4, and $[\theta]_{239}$ −5.0 × 10^3.

Resolution of 12a and 12b. (±)-2,3′,4,5′,6-Penta-*O*-acetylamaronol B[2] (2 mg) was similarly resolved in hexane/EtOH/HOAc (350/150/0.6) to give two fractions, 1 (retention time 7 min, 36 s, 0.69 mg) and 2 (retention time 8 min, 36 s, 0.55 mg).

(2*S*)-2,3′,4,5′,6-Penta-*O*-acetylamaronol B (12a). Fraction 1 gave the title compound as a white amorphous solid (ee ca. 90%): ^{1}H NMR data ($CDCl_3$, 300 MHz) δ 6.89 (2H, s, H-2',6'), 6.73, 6.59 (1H each, d, J = 1.8 Hz, H-5, 7), 3.77 (3H, s, 4'-OMe), 3.14, 2.98 (1H each, d, J = 14.3 Hz, H-α), 2.4−2.2 (5 × OAc); CD $[\theta]_{338}$ 1.5 × 10^4, $[\theta]_{306}$ −1.0 × 10^4, $[\theta]_{228}$ 8.3 × 10^2, and $[\theta]_{216}$ −5.7 × 10^3.

(2*R*)-2,3′,4,5′,6-Penta-*O*-acetylamaronol B (12b). Fraction 2 afforded the title compound as a white amorphous solid (ee ca. 90%): ^{1}H NMR data identical to **12a**; CD $[\theta]_{338}$ −1.5 × 10^4, $[\theta]_{306}$ 1.0 × 10^4, $[\theta]_{228}$ −1.2 × 10^3, and $[\theta]_{216}$ 4.8 × 10^3.

Acknowledgment. Financial support by the National Research Foundation, Pretoria, and the "Sentrale Navorsingsfonds" of UOFS is acknowledged. This work was supported in part by the United States Department of Agriculture, Agricultural Research Service Specific Cooperation Agreement No. 58-6408-7-012.

References and Notes

(1) Bohm, B. A. In *The Flavonoids. Advances in Research Since 1980*; Harborne, J. B., Ed.; Chapman & Hall: London, 1988; p 329.
(2) Li, X.-C.; ElSohly, H. N.; Nimrod, A. C.; Clark, A. M. *J. Nat. Prod.* **1999**, *62*, 767−769.
(3) Volsteedt, F. du. R.; Roux, D. G. *Tetrahedron Lett.* **1971**, 1647−1650.
(4) Bekker, R.; Brandt, E. V.; Ferreira, D. *J. Chem. Soc., Chem. Commun.* **1996**, 957−958.
(5) Bekker, R.; Brandt, E. V.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2535−2540.
(6) Bekker, R.; Brandt, E. V.; Ferreira, D. *Tetrahedron Lett.* **1998**, *39*, 6407−6410.
(7) Bekker, R.; Brandt, E. V.; Ferreira, D. *Tetrahedron* **1999**, *55*, 10005−10012.
(8) Bekker, R.; Brandt, E. V.; Ferreira, D. *Tetrahedron* **2000**, *56*, 5297−5302.
(9) Imakura, Y.; Kuwata, T.; Hara, T.; Hayafuji, Y.; Singhu, T.; Kobayashi, S.; Kawazoe, K.; Takaishi, Y.; Hashimoto, T.; Yamashita, S. *Phytochemistry* **1998**, *48*, 1179−1185.
(10) Yoshikawa, K.; Eiko, K.; Mimura, N.; Kondo, Y.; Arihara, S. *J. Nat. Prod.* **1998**, *61*, 786−790.
(11) Fourie, T. G.; Du Preez, I. C.; Roux, D. G. *Phytochemistry* **1972**, *11*, 1763−1770.
(12) Li, X.-C.; Cai, L.; Wu, C. D. *Phytochemistry* **1997**, *46*, 97−102.
(13) Snatzke, G. *Tetrahedron* **1965**, *21*, 413−419; 421−438.
(14) 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.
(15) Bekker, R.; Smit, R. S.; Brandt, E. V.; Ferreira, D. *Phytochemistry* **1996**, *43*, 673−679.
(16) Ee was assessed by injecting the two enantiomers onto the same column, which indicated a single peak in each instance.

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