

Circular Dichroic Properties of Flavan-3,4-diols[‡]

Daneel Ferreira,^{*,‡} Jannie P. J. Marais,[‡] Desmond Slade,[‡] and Larry A. Walker^{‡,§}

National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, and Department of Pharmacology, School of Pharmacy, The University of Mississippi, University, Mississippi 38677

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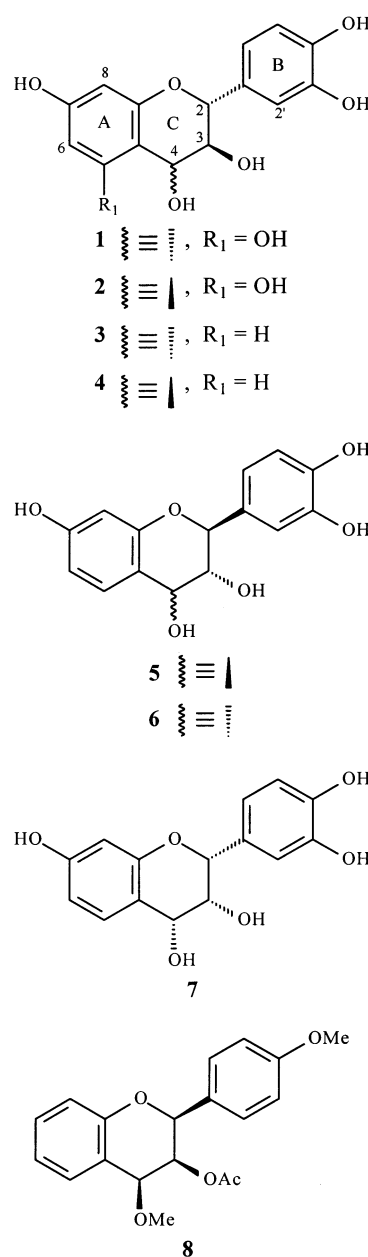
CD data of the eight diastereoisomers of free phenolic and different *O*-derivatized analogues of a series of flavan-3,4-diols permit assignment of the absolute configuration at the stereocenters of the heterocyclic ring.

The circular dichroic (CD) method is a powerful tool for establishing the absolute configuration of mono- and oligomeric flavonoids. It has been utilized to study the absolute stereochemistry of flavanones and dihydroflavonols,^{1–8} flavan-3-ols,^{9–11} flavan-4-ols,^{12–14} 4-arylflavan-3-ols,^{15,16} dimeric proanthocyanidins,^{17,18} various classes of biflavonoids,^{19–24} and auronols.^{22,25} Notably absent from this series of compounds is a systematic CD study of the flavan-3,4-diols, which together with the flavan-3-ols represent the biogenetic precursors to the proanthocyanidins (also known as the “condensed tannins”).²⁶ Results relevant to the correlation of circular dichroic data and the absolute configuration of the eight diastereoisomeric flavan-3,4-diols are discussed herein.

The flavan-3,4-diols with their benzopyran (chroman) ring systems are benzene chromophores with a chiral second sphere, according to Sznatzke's terminology.²⁷ The benzene chromophore is chirally perturbed by the fused stereogenic heterocyclic ring (second sphere) and its substituents (third sphere), thus giving rise to the observed Cotton effects (CEs) in the 270–290 and 220–240 nm regions²⁸ (¹L_b and ¹L_a transitions, respectively). It has been demonstrated²⁹ that for chiral tetralins the sign of the CD band of the A-ring chromophore is determined by the helicity of the nonaromatic ring. For tetralins where the aromatic ring is not substituted and the benzylic carbon does not carry a pseudoaxial substituent, *P*-helicity (see Figure 1) leads to positive CEs within the ¹L_b transition, and *M*-helicity to negative ones. Once the aromatic ring is substituted or a heteroatom is introduced into the saturated ring, the electric transition moment vector³⁰ is no longer projected in the direction of the pseudo *C*₂-axis of these chromophores, which may lead to inversion of the tetralin helicity rule.^{27,31} Such a phenomenon is demonstrated in Figure 2 for (a) an unsubstituted tetralin, (b) a 6-substituted tetralin, and (c) the benzopyran ring system. It should also be realized that the *C*_{2v} symmetry of the tetralin chromophore is absent in the chroman system. The aforementioned inversion of the tetralin helicity rule has indeed been demonstrated for flavans,¹⁴ flavan-3-ols,^{9–11} and flavan-4-ols.^{12–14}

The relative configuration of flavan-3,4-diols is readily assessable from the ³J_{H,H} values of their C-ring three-bond proton coupling constants.³² Small but significant differ-

ences in the coupling constants of 2,3-*cis*-3,4-*trans* and 2,3-*cis*-3,4-*cis* analogues allow assignment of the relative configurations via appropriate NOE experiments. These data in conjunction with CD information may then be utilized to define the absolute configuration at the stereocenters of the heterocyclic ring.



[‡] Dedicated to the late Dr. Monroe E. Wall and to Dr. Mansukh C. Wani of Research Triangle Institute for their pioneering work on bioactive natural products.

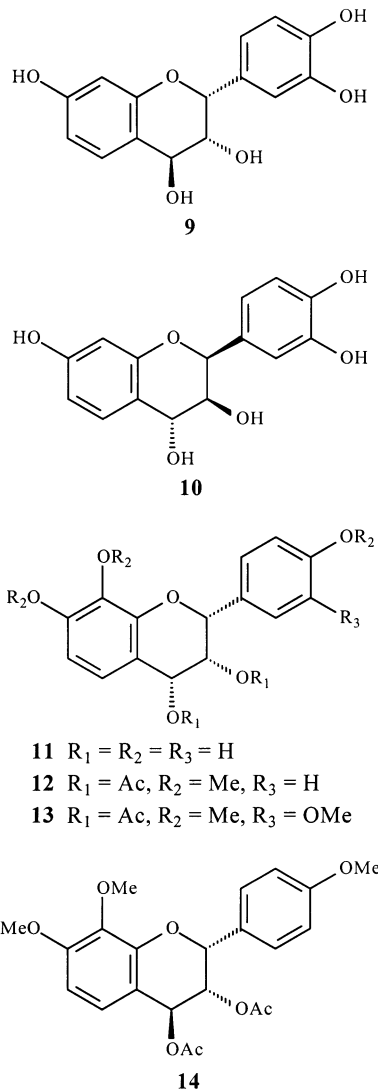
* To whom correspondence should be addressed. Tel: +1-662-915-1572. Fax: +1-662-915-7062. E-mail: dferreir@olemiss.edu.

[‡] National Center for Natural Products Research.

[§] Department of Pharmacology.

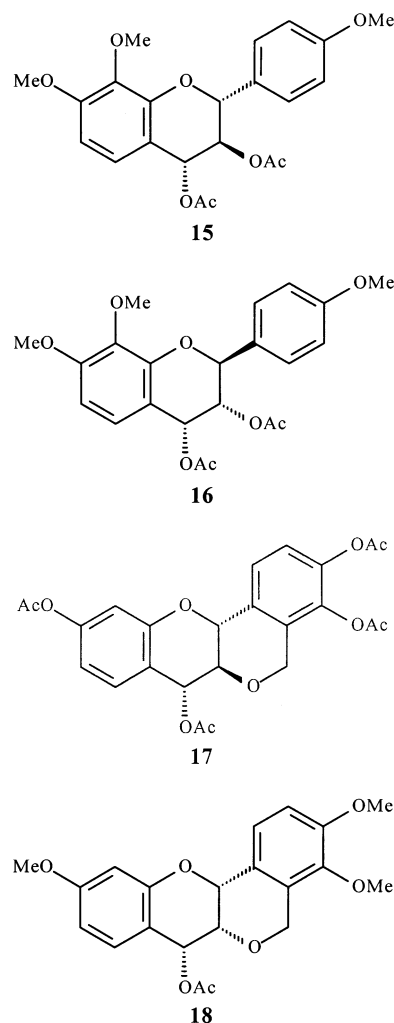
Results and Discussion

The CD data of a variety of flavan-3,4-diols and some of their *O*-alkyl/acetyl derivatives **1**–**18** are collated in Table 1. Representative CD curves for 2,3-*trans*-3,4-*trans* (e.g., **3** and **5**), 2,3-*trans*-3,4-*cis* (e.g., **4** and **6**), 2,3-*cis*-3,4-*cis* (e.g., **7** and **8**), and 2,3-*cis*-3,4-*trans* (e.g., **9** and **10**) enantiomers are depicted in Figures 3–7.



The 1L_b Transition. The 1L_b band of C-ring substituted flavans at ca. 280 nm is usually exploited for configurational assignment since it is less prone to mixing with other transitions or overlapping than the 1L_a band at shorter wavelengths.¹⁴ The sign and a substantial part of the magnitude of the CE within each absorption band are determined by the chiral sphere closest to the A-ring chromophore, i.e., the C-ring of the flavan-3,4-diols. Accordingly, the absolute configuration at C-3 will have a minor influence on the sign of the CE of this transition. Thus, the spectra of the flavan-3,4-diols with their chiral second sphere (C-ring) and the preference of the B-ring for an equatorial orientation should be explicable in terms of the “inversed” helicity rules proposed for the dihydropyran ring system.^{9–14} *P*-helicity of the C-ring with its preferred half-chair/*C*-2 sofa conformation^{32,33} should lead to negative CEs within the 1L_b transition, and *M*-helicity to positive ones. Flavan-3,4-diols with *2R* absolute configuration, e.g.,

catechin-4 α -ol (**1**),³⁴ will display *P*-helicity (Figure 1), and those with *2S* configuration, e.g., *ent*-fisetinidol-4 β -ol (**5**), *M*-helicity.



The data in Table 1 show that flavan-3,4-diols with *2R* absolute configuration, e.g., fisetinidol-4 α -ol (**3**), invariably display negative CEs within the 1L_b transition, irrespective of the orientation of the C-4 substituent (third sphere contributor). This contrasts with observed 1L_b transition CEs for 2,4-*trans*-flavan-4-ols with unsubstituted A-rings where the axial 4-hydroxy group apparently forces the heterocycle into a flat sofa conformation, hence causing the chiral third sphere contribution to overrule the influence of the helicity of the C-ring.^{12,14} All the flavan-3,4-diols with *2S* absolute stereochemistry, e.g., *ent*-fisetinidol-4 β -ol (**5**), give positive CEs within the 1L_b transition. CEs with the same sign are consistently also displayed by derivatized analogues, e.g., a negative CE at 273.1 nm for the (2*R*,3*R*,4*R*)-all-*cis* derivative **12** and a positive CE at 278.8 nm for the (2*S*,3*R*,4*R*)-2,3-*trans*-3,4-*cis* derivative **16**. Mopanol and epimopanol derivatives **17** and **18**³⁵ with their *2R* absolute configurations and conformationally more rigid C-rings similarly also obey the “inversed” helicity rule, hence showing negative CEs at 281 and 286 nm, respectively, for their 1L_b transitions.

A conspicuous feature of the pairs of CD curves of, for example, fisetinidol-4 α -ol/*ent*-fisetinidol-4 β -ol (Figure 3) and fisetinidol-4 β -ol/*ent*-fisetinidol-4 α -ol (Figure 4) is the reduced amplitude of the 1L_b CEs of the former pair. This

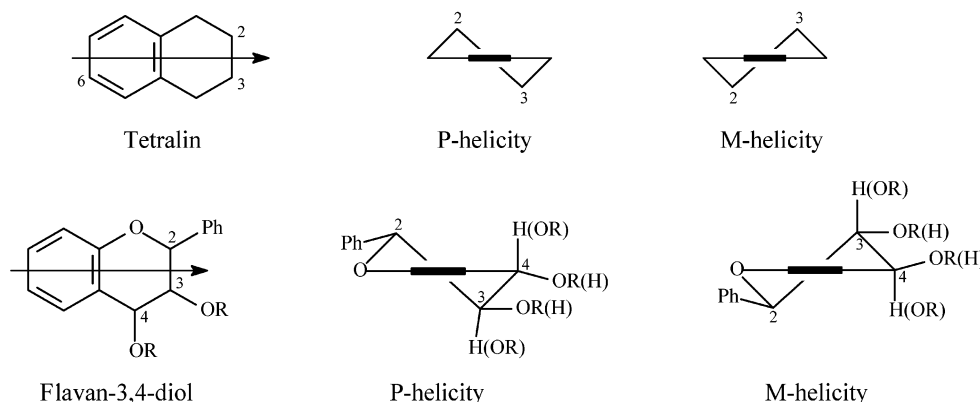


Figure 1. *P*- and *M*-helicity of the tetralin and the chroman ring system of flavan-3,4-diols (projection in the direction of the arrow, wedge represents the plane of the benzenoid A-ring).

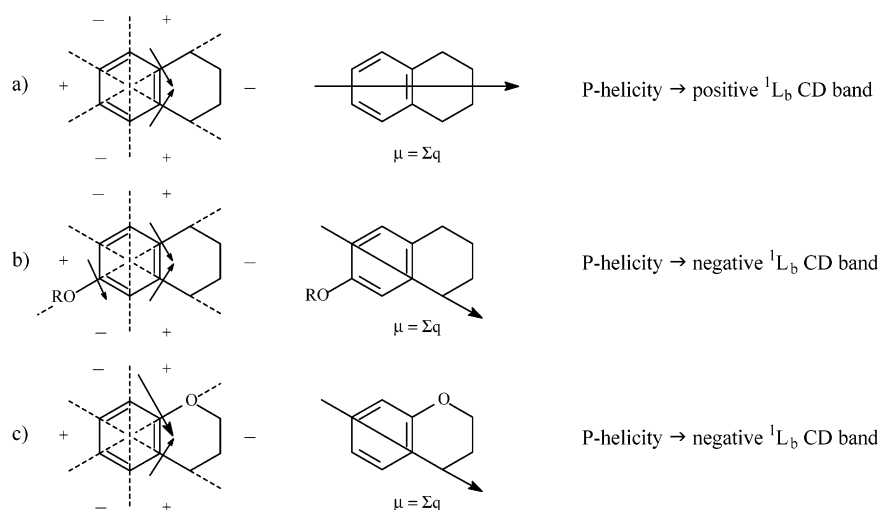


Figure 2. Polarization diagrams of the 1L_b band for (a) unsubstituted tetralin, smaller arrows denote spectroscopic moment vectors (q), and larger ones the electric transition moment vector (μ); (b) 6-substituted tetralins; and (c) unsubstituted chromans.

Table 1. CD Data of Diastereomeric Flavan-3,4-diols and/or *O*-Alkyl/Acetyl Derivatives **1–18**

compound	configuration	1L_b (ca. 280 nm) ($\lambda \times 10^3$)	1L_a (ca. 240 nm) ($\lambda \times 10^3$)
1	2,3- <i>trans</i> -3,4- <i>trans</i> (2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)	292.2 (−4.3)	236.4 (−54.1)
2	2,3- <i>trans</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>)	291.3 (−3.8)	234.4 (−43.7)
3	2,3- <i>trans</i> -3,4- <i>trans</i> (2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)	289.3 (−4.4)	237.4 (−63.4)
4	2,3- <i>trans</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>)	289.3 (−8.0)	240.0 (+8.2)
5	2,3- <i>trans</i> -3,4- <i>trans</i> (2 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)	288.3 (+8.2)	240.5 (+62.6)
6	2,3- <i>trans</i> -3,4- <i>cis</i> (2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)	290.7 (+1.5)	242.2 (−1.4)
7	2,3- <i>cis</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i>)	288.3 (−1.8)	240.1 (−6.0)
8	2,3- <i>cis</i> -3,4- <i>cis</i> (2 <i>S</i> ,3 <i>S</i> ,4 <i>S</i>)	279.1 (+6.25)	237.1 (ca. 0)
9	2,3- <i>cis</i> -3,4- <i>trans</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)	286 (−1.3)	237.4 (−0.7)
10	2,3- <i>cis</i> -3,4- <i>trans</i> (2 <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)	287.1 (+8.7)	241.0 (+5.2)
11	2,3- <i>cis</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i>)	274.2 (−13.5)	240 (−38.1)
12	2,3- <i>cis</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i>)	273.1 (−4.6)	241.9 (−1.4)
13	2,3- <i>cis</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i>)	276.5 (−6.5)	237.3 (−1.0)
14	2,3- <i>cis</i> -3,4- <i>trans</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)	276.6 (−6.6)	242.2 (−8.3)
15	2,3- <i>trans</i> -3,4- <i>trans</i> (2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)	273.5 (−2.7)	239.2 (−6.7)
16	2,3- <i>trans</i> -3,4- <i>cis</i> (2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)	278.8 (+1.2)	237.8 (−8.0)
17	2,3- <i>trans</i> -3,4- <i>trans</i> (2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)	281 (−0.5)	228 (+2.24)
18	2,3- <i>cis</i> -3,4- <i>cis</i> (2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i>)	286 (−1.0)	229 (−13.3)

presumably results from the necessity for a conformational change of all-*trans* analogues **3** and **5** in order to alleviate allylic strain between the equatorial 4-hydroxy group and H-5. Such a conformational itinerary will then include a considerable proportion of an inversed half-chair/C-2 sofa A-conformation³³ exhibiting *M*-helicity as opposed to the *P*-helicity for 2*R*-all-*trans*-flavan-3,4-diols, and vice versa for the 2*S* analogues. An A-conformation with 2,4-*cis*-diaxial substituents may feasibly be stabilized via hydrogen bonding between the 4-hydroxyl and aromatic B-ring. Although a similar observation may be anticipated for the

all-*cis* analogues, e.g., compounds **7** and **11**, its “normal” half-chair/C-2 sofa conformation will be stabilized by hydrogen bonding between the axial 3-hydroxyl group and the *O*-heteroatom of the C-ring.³⁶ Once the 4-hydroxy function is derivatized as in compound **15**, hydrogen bonding and hence stabilization of an A-conformer are eliminated and the amplitude of the 1L_b band CE increases relative to that of the 1L_a transition. We cannot explain the presence of the “additional” Cotton effect at ca. 270 nm in the spectra of the fisetinidol-4 β -ol/*ent*-fisetinidol-4 α -ol enantiomers **4** and **6** (Figure 4).

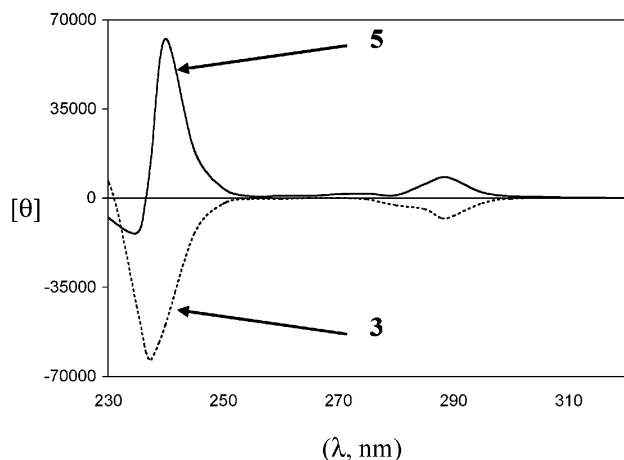


Figure 3. CD curves of 2,3-*trans*-3,4-*trans*-flavan-3,4-diol enantiomers **3** and **5**.

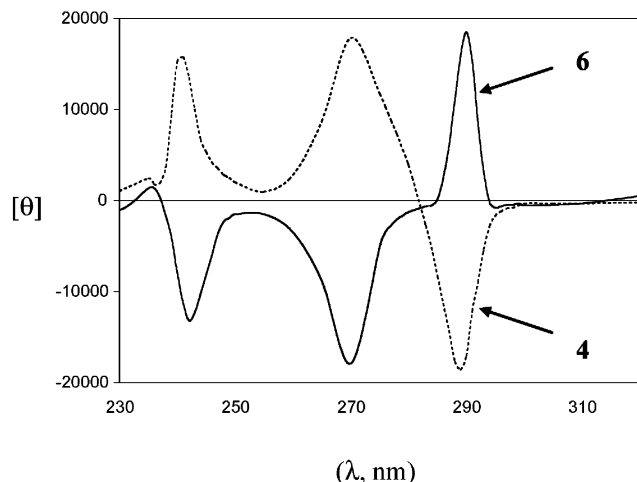


Figure 4. CD curves of 2,3-*trans*-3,4-*cis*-flavan-3,4-diol enantiomers **4** and **6**.

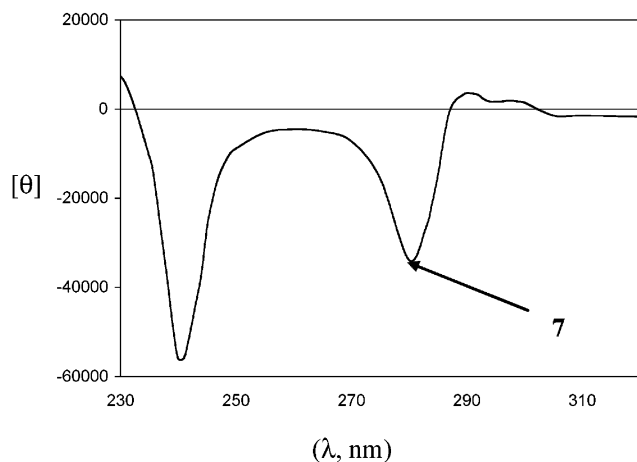


Figure 5. CD curve of (2*R*,3*R*,4*R*)-2,3-*cis*-3,4-*cis*-flavan-3,4-diol (**7**).

The 1L_a Transition. The sign of the CE of the 1L_a transition near 240 nm is the same as that at long wavelength for all the all-*trans*-, all-*cis*-, and 2,3-*cis*-3,4-*trans*-flavan-3,4-diols, e.g., fisetinidol-4 α -ol (**3**), *ent*-epifisetinidol-4 α -ol (**7**), and *ent*-epifisetinidol-4 β -ol (**9**), respectively, but not for the 2,3-*trans*-3,4-*trans*-mopanol derivative **17**. Except for the catechin-4 β -ol **2**, the signs of these CEs seem to be opposite for the 2,3-*trans*-3,4-*cis*-flavan-3,4-diols, e.g., the *ent*-fisetinidol-4 α -ol **6** and the *ent*-oritin derivative **16**, respectively. Screening of the signs of the 1L_a CEs in

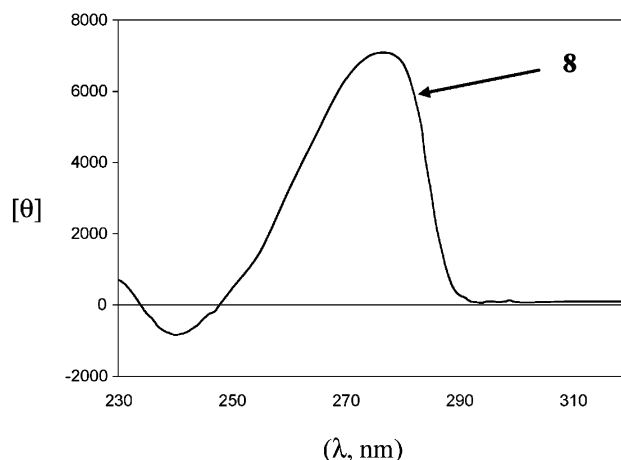


Figure 6. CD curve of (2*S*,3*S*,4*S*)-2,3-*cis*-3,4-*cis*-flavan-3,4-diol (**8**).

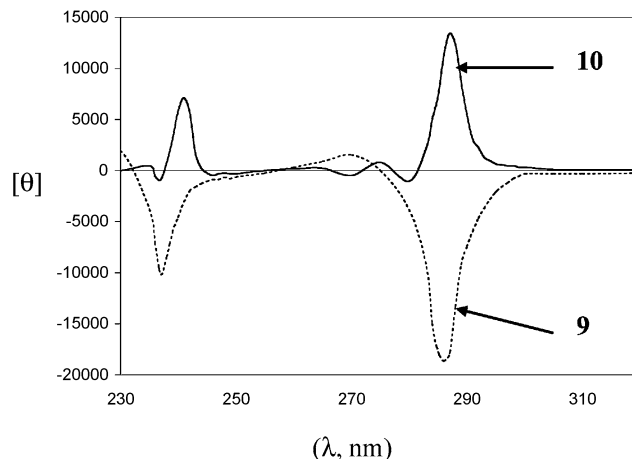


Figure 7. CD curves of 2,3-*cis*-3,4-*trans*-flavan-3,4-diol enantiomers **9** and **10**.

Table 1, however, clearly indicates that these CEs do not consistently obey the De Angelis–Wildman aromatic quadrant rule³⁷ for correlating the 1L_a CE sign with the absolute C-4 configuration as was proposed occasionally for some flavan-3,4-diol derivatives.^{35,38–41} In all these cases, the more reliable CEs of the long-wavelength 1L_b transition were completely ignored.

Comparison of the CD data of epioritin-4 α -ol (**11**) with those of its permethylaryl ether diacetate **12**, and of those of the fisetinidol-4-ols **3** and **4** with those of their corresponding derivatives,³⁸ indicates that the sign and the wavelength of the CEs are not significantly changed by derivatization of the hydroxyl functionalities. It is important to point out that sample concentrations are vitally important for spectral reproducibility. Optimal concentrations have to be established for each individual compound and spectra repeatedly recorded until reproducible data are obtained. Thus, discrepancies in the magnitude of the CEs of enantiomers in Table 1 presumably result from small concentration differences and probably also from the presence of minor impurities.

The CD data in Table 1 and the curves depicted in Figures 3–7 should find useful application for the straightforward and unequivocal establishment of the absolute configuration of flavan-3,4-diols.

Experimental Section

General Experimental Procedures. CD data were recorded in MeOH (ca. 1 mg/10 mL MeOH) on a JASCO J-715 spectrometer, with the following scan parameters: bandwidth

(2.0 nm), sensitivity (10 mdeg), response (4 s), scan speed (50 nm min⁻¹), step resolution (0.1 nm). The flavan-3,4-diols and appropriate derivatives were from our collection of flavonoid-type reference compounds. The purities of these compounds are in excess of 98%, and the methods used to define their absolute configurations may be found in the appropriate references.

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