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OPTICALLY ACTIVE AROMATIC CHROMOPHORES—VIII

STUDIES IN THE ISOFLAVONOID AND ROTENOID SERIES[1,2]

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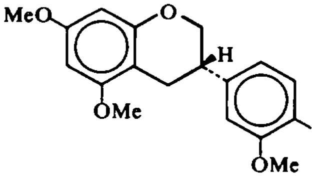
Abstract—(−)-Equol dimethyl ether (7,4′-dimethoxyisoflavan) is shown from ORD and CD data to have the 3S-configuration instead of the *R*-configuration previously assigned from the plain dispersion curves at longer wavelength. The CD spectra of (−)-dihydrodesoxyrotenone and (−)-dihydrodesoxydeguelin are closely similar and their positive Cotton effects at longer wavelength are opposite in sign to the long wavelength Cotton effects of 3*S*-(−)-5,7,3′,4′-tetramethoxyisoflavan and 3*S*-(−)-equol dimethyl ether. The CD curves of *S*-(+)-1-(1,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propane and of *S*-(+)-(2,4,6-trimethoxyphenyl)-2-(3,4-dimethoxyphenyl)propane are virtually identical, and this confirms the identity in configuration of the two propanes previously inferred from the sign of rotation at the sodium D-line, and provides a correlation of the absolute configurations of (+)-catechin, the related isoflavans, and (−)-angolensin.

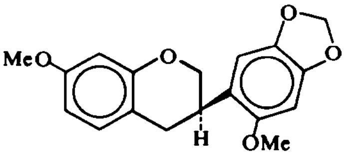
RECENT studies have provided experimental evidence linking the biosynthesis of isoflavonoids and rotenoids.[3] We have carried out ORD and CD measurements in the UV absorption region of selected members of these series and some related compounds in order to obtain stereochemical information. In so doing we have discovered that (−)-equol possesses the opposite configuration to that assigned previously.[4]

RESULTS AND DISCUSSION

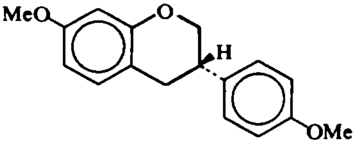
S-(−)-5,7,3′,4′-Tetramethoxyisoflavan, (−)-**1**, and *R*-(−)-dihydropterocarpin dimethyl ether, (−)-**2**, of established absolute configuration[4b, 5] were chosen as suitable reference compounds and their ORD and CD spectra investigated from 600 to ca. 220 nm. The ORD and CD results from these reference compounds were compared with the corresponding data obtained in the present work for (−)-equol dimethyl ether, (−)-**3**,[6] the simplest known naturally-occurring isoflavan.



(−)-**1**



(−)-**2**



(−)-**3**

The ORD data for (−)-**1** in chloroform, in acetone, and in a 50:50 (v/v) mixture of these solvents are shown in Fig. 1. The opposite signs of the plain dispersion curves in chloroform and in acetone and the intermediate values in the mixed solvent indicate the importance of solvational effects upon the observed optical activity in the isoflavonoid series. Such effects have been noted in other systems[7] and interpreted in terms of solvational or conformational equilibria changes or a combination of the two.

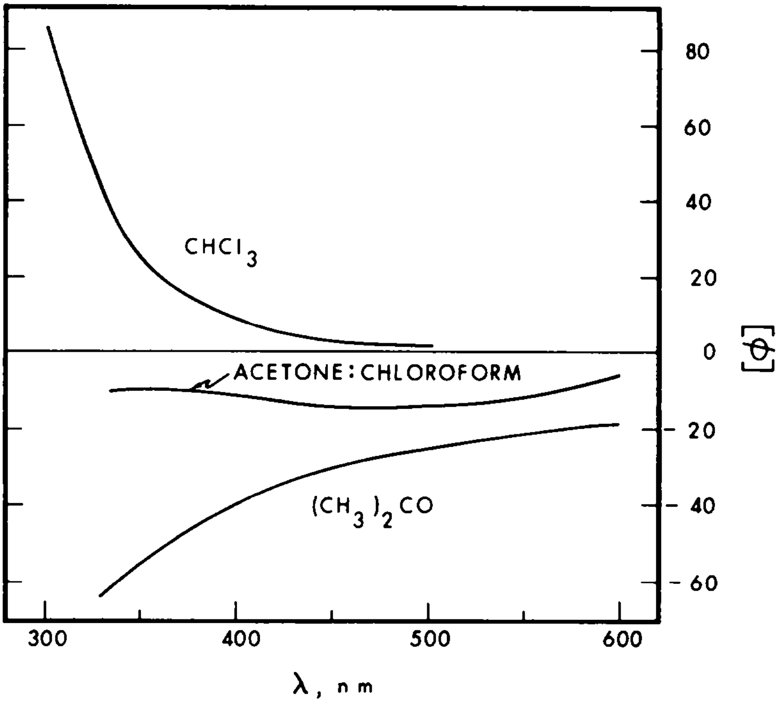


FIG. 1 ORD of S-(−)-5,7,3′,4′-Tetramethoxyisoflavan, (−)-**1**, in chloroform, in acetone, and in a mixture (50:50 v/v) of these two solvents.

It is clear from Fig. 1 that, in the isoflavonoid series, all comparisons of Cotton effects of various members of the series must be referred to the same solvent system. We have chosen methanol as a suitable solvent and the remainder of the work reported here was carried out in methanol at 27°. Although S-**1** possesses a negative D-line rotation in acetone and also in benzene[4b] and will be referred to as (−)-**1**, the same compound would presumably be dextrorotatory in chloroform solution (a limited amount of material together with a very small rotation prevented us from carrying out measurements above 500-nm; see Fig. 1).

The ORD curves of (−)-**1**, (−)-**2** and (−)-**3** from the visible region to about 300 nm are shown in Fig. 2. As is the case in chloroform solution, (−)-**1** exhibits dextrorotation in the visible region in methanol as solvent.

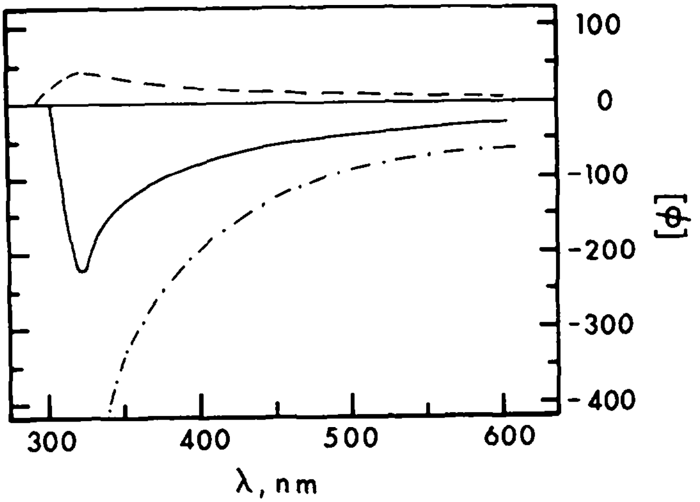


FIG. 2 ORD of S-(−)-5,7,3′,4′-Tetramethoxyisoflavan, (−)-1, ----; R-(−)-dihydropterocarpin dimethyl ether, (−)-2, ——; and S-(−)-equol dimethyl ether, (−)-3, -·-·-; in methanol solution.

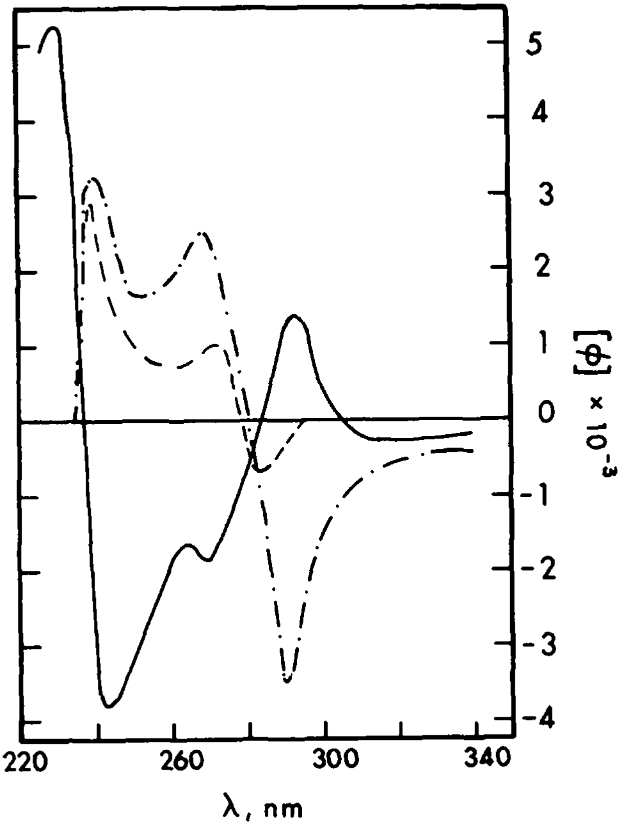


FIG. 3 ORD of S-(−)-5,7,3′,4′-Tetramethoxyisoflavan, (−)-1, – – – –; R-(−)-dihydropterocarpin dimethyl ether, (−)-2, ——; and S-(−)-equol dimethyl ether, (−)-3, -·-·-; in methanol solution.

Above ca. 325 nm the plain curves are similar to those previously reported.[4] It was on the basis of the plain dispersion curves that (–)-**2** and (–)-**3** were inferred to have the opposite configuration to (–)-1.[4] However, the ORD data of the respective compounds in the Cotton effect region, the region of electronic absorption, Figure 3, leads to a different conclusion. It is the sign of a Cotton effect which more accurately reflects absolute configuration, rather than the sign of a plain dispersion curve.[8]

Examination of Fig. 3 indicates the Cotton effects of (–)-**1** and (–)-**3** to be of the same sign while the Cotton effect curve of (–)-**2** is quasi-enantiomeric. That the curves are not exactly identical and enantiomeric, respectively, is due to the differences in substitution patterns for the three compounds.

The situation is made even clearer in the CD spectra, Fig. 4. For all three isoflavans, Cotton effects due to at least two different electronic transitions, one near 290 nm and the other near 230 nm, may be observed in the CD spectra. The fact that the Cotton effects are of the same sign for (–)-**1** and (–)-**3** indicates that these compounds are configurationally identical and allows us to assign the *S*-configuration to (–)-equol dimethyl ether, (–)-**3**, and thereby to (–)-equol.*

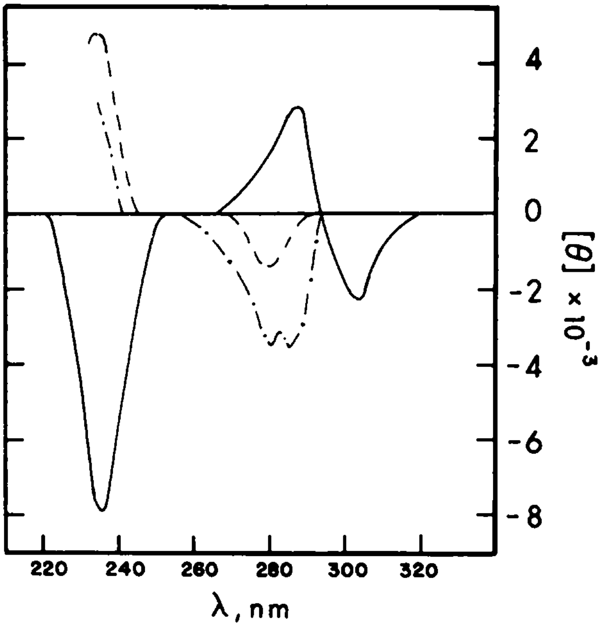


FIG. 4 CD spectra of *S*-(–)-5,7,3′,4′-Tetramethoxyisoflavan, (–)-**1**, ----; *R*-(–)-dihydropterocarpin dimethyl ether, (–)-**2**, ——; and *S*-(–)-equol dimethyl ether, (–)-**3**, –·–·–; in methanol solution.

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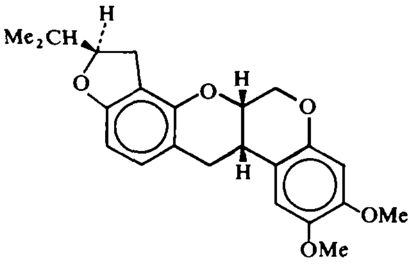
* Shortly after this work was presented at the American Chemical Society National Meeting[1] we learned that Professor W. D. Ollis and co-workers had come to similar conclusions about the configuration of (–)-equol from ORD and CD measurements (private communication to J.W. C.-L.).

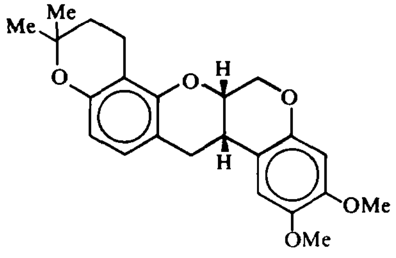
Conversion of a ring OH to a OMe group is known not to affect the sign of the Cotton effect.[9] Examination of the CD spectrum of (−)-dihydropterocarpin, (−)-**2**, indicates that while the short-wavelength Cotton effect is of opposite sign to that found for (−)-**1** and (−)-**3**, a double humped curve is found at longer wavelength with the maxima[10] separated by ca. 15 nm. The substitution pattern in (−)-**2** is considerably different from that of the other two isoflavans in that the methylenedioxy group forms a strained 5-membered heterocyclic ring. The long wavelength negative Cotton effect in (−)-**2** is assigned to a transition of this ring by analogy with the known bathochromic shift and increased transition intensity observed for a methylenedioxy ring compared with a 1,2-dimethoxy grouping.[11]

The two negative maxima[10] near 280 nm in the CD spectrum of (−)-**3** correspond to vibrational structure found in the isotropic absorption spectrum of (−)-**3**. The corresponding maxima in the CD spectrum of (−)-**1** were not resolved due to the weak dichroism of this band.

The naturally occurring rotenoids have been shown to possess the 6a*S*,12a*S*-configuration.[12] The CD spectra of two members of this series, 6a*S*,12a*S*,5′*R*-(−)-dihydrodesoxyrotenone, (−)-**4**, and 6a*S*,12a*S*-(−)-dihydrodesoxydeguelin, (−)-**5**, were examined in order to observe whether any correlations existed with the isoflavonoids of the *S*-configuration.



(−)-**4**



(−)-**5**

The UV and CD spectra of (−)-**4** in methanol solution are shown in Fig. 5.* It is interesting that the long wavelength positive Cotton effect near 295 nm is of opposite sign to the long wavelength Cotton effects of the *S*-isoflavans (−)-**1** and (−)-**3**. The shorter wavelength CD spectrum of (−)-**4** exhibits several overlapping Cotton effects of opposite sign, a complexity not unexpected in a molecule containing two different aromatic chromophores. The strong negative band near 211 nm accounts for the negative sign of the dispersion curve in the visible region. Except for the smaller magnitude of the dichroism, the CD data for (−)-**5** are very similar to (−)-**4** and are given in the Experimental.

* Because of the relative weakness of the long wavelength Cotton effects, the CD curve (*which is continuous*) was divided into two parts: the right-hand ordinate refers to the longer wavelength Cotton effects and the left-hand ordinate refers to the bands below ca. 240 nm. The log ε scale refers to the isotropic absorption spectrum.

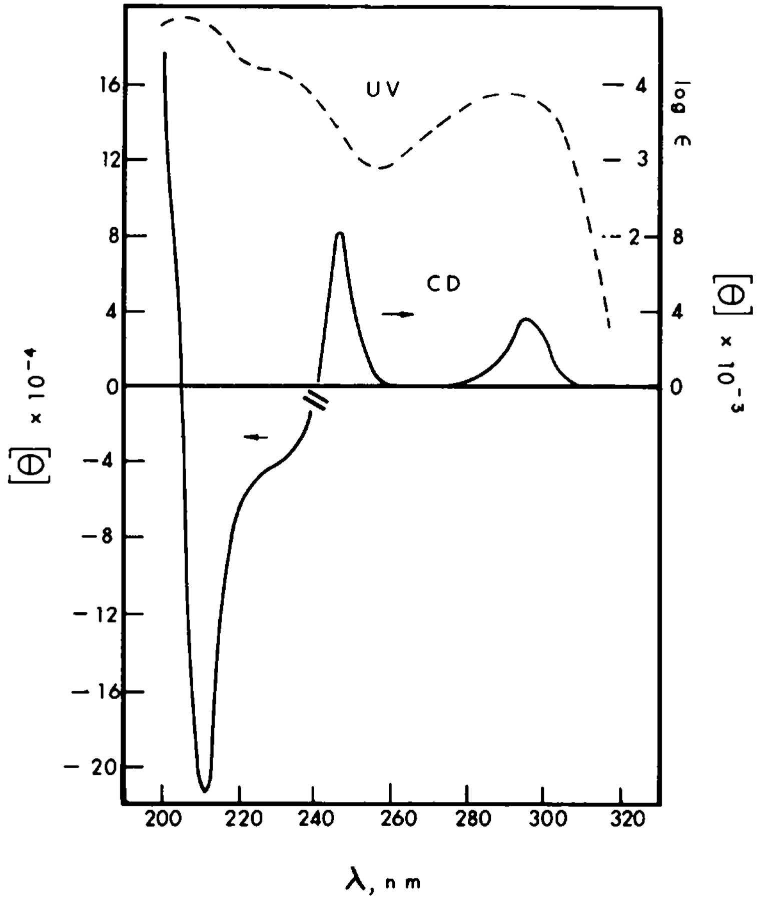
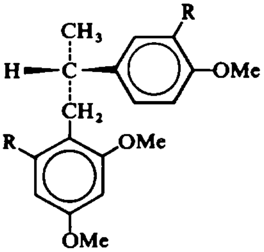


FIG. 5 UV and CD spectra of 6a*S*, 12a*S*, 5′*R*-(−)-dihydrodesoxyrotenone, (−)-4, in methanol solution. The CD data for (−)-5 are very similar to those for (−)-4 (Experimental). See footnote on p. 5523 for explanation of the ordinate scales.

The stereochemistry of the catechins has been related to that of (−)-angolensin[13] by conversion of the latter into *S*-(+)-1-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-propane, (+)-6, an analogue of the 1,2-diarylpropane *S*-(+)-7, obtained by a series



(+)-6 R = H

(+)-7 R = OMe

of stereospecific reactions from (+)-catechin tetramethyl ether via (+)-*cis*-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan.[14] The UV and CD spectra of (+)-6 in methanol solution are shown in Fig. 6.* Both the UV and CD spectra of (+)-7 are virtually identical with that of (+)-6, indicating negligible electronic and steric effects arising from the introduction of the two OMe substituents in (+)-7. In addition, CD data for both compounds in heptane solution are given in the Experimental. The identity of the CD spectra of (+)-6 and (+)-7 confirms the previous assignment of configurations based on D-line measurements[14] and correlates the stereochemistry of the catechins with that of (−)-angolensin.

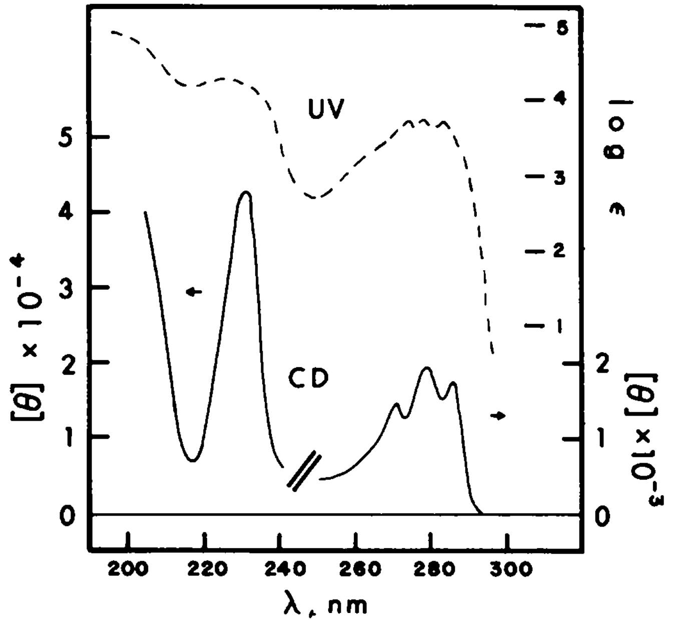


FIG. 6 UV and CD spectra of *S*-(+)-1-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propane, (+)-6, in methanol solution. See footnote on p. 5523 for explanation of the ordinate scales. The UV and CD data for (+)-6 (shown) and (+)-7 are virtually identical.

EXPERIMENTAL

ORD and CD measurements were made using a JASCO Model ORD/UV/CD-5 instrument operating at a sample compartment temp of 27°. The instrument is equipped with double fused-silica monochromators and uses a 450 watt high press Xenon arc source. The entire optical path is under constant flush using the boil-off from liquid N_2. The instrument is operated with a variable slitwidth programmed to maintain a constant dynode voltage. The sensitivity in the CD mode is 1×10^{-5} differential absorbance units per millimeter of chart paper.

We found that our results in the spectral region below 240 nm were dependent upon the output intensity of the Xenon arc source. After approximately 200 lamp-hr the intensity had decreased enough so that much higher noise levels were apparent. Consequently, lamps were replaced after 175 hr.

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* See footnote * on page 5523.

Measurements were made in calibrated fused silica cells with a path length appropriate to keep the maximum absorbance less than 2·5 even though experiments using a potassium dichromate filter indicated valid instrument reproducibility at an absorbance of 3·3.

The JASCO CD instrument records the difference in absorbance for left and right circularly polarized radiation as a function of wavelength. This difference is then converted to the corresponding difference in molar absorptivity, $(\varepsilon_l - \varepsilon_r)$, and finally to molecular ellipticity, $[\theta]$.[15]

$$[\theta] = 2{\cdot}303\left(\frac{4500}{\pi}\right)(\varepsilon_l - \varepsilon_r)\ \text{deg cm}^2/\text{decimole}$$

Isotropic absorption spectra were run on the JASCO and on a Cary Model 14 spectrophotometer. Agreement between the two instruments was ±4% with the Cary reading consistently lower absorbances. The Bouger–Lambert–Beer law was checked and the deviations from this law for circularly dichroic molecules recently pointed out[16] were found to be within the experimental error (< 1%).

S-(−)-*5,7,3′,4′-Tetramethoxyisoflavan*, (−)-**1**, m.p. 127–128°

ORD in CHCl$_3$ (*c*, 0·795). $[\phi]_{500}$ +2·0°, $[\phi]_{450}$ +3·2°, $[\phi]_{400}$ +9·1°; $[\phi]_{350}$ +23°, $[\phi]_{315}$ +65°, $[\phi]_{300}$ +85°.

ORD in acetone (*c*, 0·644). $[\phi]_{589}$ −19°, $[\phi]_{550}$ −21°, $[\phi]_{500}$ −24°, $[\phi]_{450}$ −29°, $[\phi]_{400}$ −39°, $[\phi]_{350}$ −55°, $[\phi]_{330}$ −64°.

ORD in chloroform–acetone (50:50 V/V, *c*, 0·956). $[\phi]_{589}$ −6·9, $[\phi]_{550}$ −11°, $[\phi]_{500}$ −14°, $[\phi]_{450}$ −14°, $[\phi]_{400}$ −11°, $[\phi]_{340}$ −10°.

ORD in methanol (*c*, 0·120). $[\phi]_{589}$ +6·1°, $[\phi]_{550}$ +6·6°, $[\phi]_{500}$ +11°, $[\phi]_{450}$ +15°, $[\phi]_{400}$ +19°, $[\phi]_{350}$ +34°, $[\phi]_{320}$ +39° (peak), $[\phi]_{295}$ 0, $[\phi]_{283}$ −660° (trough), $[\phi]_{270}$ 0, $[\phi]_{272}$ +1000° (peak), $[\phi]_{260}$ +750°, $[\phi]_{240}$ +2900° (peak).

CD in methanol, 4·79 × 10^{-4}M. $[\theta]_{290}$ 0, $[\theta]_{280}$ −1400 (max), $[\theta]_{236}$ +4600 (max).

R-(−)-*Dihydropterocarpin dimethyl ether*, (−)-**2**, m.p. 108–109°

ORD in methanol (*c*, 0·105). $[\phi]_{589}$ −29°, $[\phi]_{550}$ −36°, $[\phi]_{500}$ −45°, $[\phi]_{450}$ −60°, $[\phi]_{400}$ −83°, $[\phi]_{340}$ −150°, $[\phi]_{322}$ −230° (trough), $[\phi]_{305}$ 0°, $[\phi]_{293}$ +1400 (peak), $[\phi]_{285}$ 0°, $[\phi]_{270}$ −1850° (trough), $[\phi]_{264}$ −1600° (peak), $[\phi]_{243}$ −3800° (trough), $[\phi]_{237}$ 0°, $[\phi]_{230}$ +5200° (peak).

CD in methanol, 1·1 × 10^{-3}M. $[\theta]_{320}$ 0, $[\theta]_{304}$ −2300 (max), $[\theta]_{288}$ +2800 (max), $[\theta]_{236}$ −8000 (max).

S-(−)-*Equol dimethyl ether*, (−)-**3**, m.p. 88–89°

ORD in Methanol (*c*, 0·180). $[\phi]_{589}$ −61°, $[\phi]_{550}$ −72°, $[\phi]_{500}$ −91°, $[\phi]_{450}$ −130°, $[\phi]_{400}$ −190°, $[\phi]_{290}$ −3500° (trough), $[\phi]_{281}$ 0°, $[\phi]_{269}$ +2500 (peak), $[\phi]_{240}$ +3200° (peak), $[\phi]_{235}$ 0°.

CD in methanol 2·4 × 10^{-3}M. $[\theta]_{293}$ 0, $[\theta]_{285}$ −3500 (max), $[\theta]_{280}$ −3500 (max), $[\theta]_{236}$ +2500.

6aS, 12aS, 5′R-(−)-*Dihydrodesoxyrotenone*, (−)-**4**, m.p. 170–172°

CD in methanol, 5·8 × 10^{-3}M. $[\theta]_{310}$ 0, $[\theta]_{294}$ +3600 (max), $[\theta]_{246}$ +8300 (max), $[\theta]_{235}$ −36,000, $[\theta]_{212}$ −215,000 (max), $[\theta]_{205}$ 0, $[\theta]_{200}$ +186,000.

6aS, 12aS-(−)-*Dihydrodesoxydeguelin*, (−)-**5**, m.p. 120–120·5°

CD in methanol, 8·7 × 10^{-3}M. $[\theta]_{310}$ 0, $[\theta]_{294}$ +2200 (max), $[\theta]_{246}$ +4300 (max), $[\theta]_{235}$ −28,000, $[\theta]_{212}$ −160,000 (max), $[\theta]_{205}$ 0.

S-(+)-1-(2,4-*Dimethoxyphenyl*)-2-(4-*methoxyphenyl*)*propane*, (+)-**6**, m.p. 36–37·5°.

CD in methanol, 2·1 × 10^{-4}M. $[\theta]_{290}$ 0, $[\theta]_{286}$ +1700 (max), $[\theta]_{278}$ +1900 (max), $[\theta]_{271}$ +1300 (max), $[\theta]_{231}$ +43,000 (max), $[\theta]_{206}$ +40,000.

CD in heptane, 2·4 × 10^{-4}M. $[\theta]_{292}$ 0, $[\theta]_{280}$ +1500 (max), $[\theta]_{266}$ +700 (max), $[\theta]_{231}$ +43,000 (max), $[\theta]_{216}$ +5500.

S-(+)-2-(3,4-*Dimethoxyphenyl*)-1-(2,4,6-*trimethoxyphenyl*)*propane*, (+)-**7**, m.p. 110–111°

CD in methanol, 1·7 × 10^{-4}M. $[\theta]_{292}$ 0, $[\theta]_{284}$ +2000 (max), $[\theta]_{273}$ +2700 (max), $[\theta]_{269}$ +2300 (max), $[\theta]_{238}$ +31,000 (max), $[\theta]_{220}$ +20,000, $[\theta]_{212}$ +36,000.

CD in heptane, 1·8 × 10^{-4}M. $[\theta]_{293}$ 0, $[\theta]_{281}$ +2300 (max), $[\theta]_{275}$ +3300 (max), $[\theta]_{238}$ +28,000 (max), $[\theta]_{210}$ +57,000.

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