

## Absolute configuration of naturally occurring glabridin

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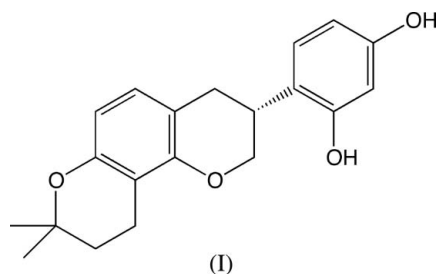
The title compound [systematic name: 4-[(3*R*)-8,8-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-3-yl]benzene-1,3-diol, commonly named glabridin], C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>, is a species-specific biomarker from the roots *Glycyrrhiza glabra* L. (European licorice, Fabaceae). In the present study, this prenylated isoflavan has been purified from an enriched CHCl<sub>3</sub> fraction of the extract of the root, using three steps of medium-pressure liquid chromatography (MPLC) by employing HW-40F, Sephadex LH-20 and LiChroCN as adsorbents. Pure glabridin was crystallized from an MeOH–H<sub>2</sub>O mixture (95:5 *v/v*) to yield colorless crystals containing one molecule per asymmetric unit (*Z'* = 1) in the space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>. Although the crystal structure has been reported before, the determination of the absolute configuration remained uncertain. Stereochemical analysis, including circular dichroism, NMR data and an X-ray diffraction data set with Bijvoet differences, confirms that glabridin, purified from its natural source, is found only in a *C*3 *R* configuration. These results can therefore be used as a reference for the assignment of the configuration and enantiopurity of any isolated or synthetic glabridin sample.

**Keywords:** crystal structure; absolute configuration; glabridin; natural compounds.

### 1. Introduction

Glabridin, (I), is a prenylated isoflavan, which has previously been isolated from the roots of *Glycyrrhiza glabra* (Shibata & Saitoh, 1978; Zhang & Ye, 2009). Interestingly, glabridin is one of the most studied licorice flavonoids, and has been widely considered to be a phytoestrogen with numerous biological activities including antioxidant (Vaya *et al.*, 1997), antibacterial (Fukai *et al.*, 2002), neuroprotective (Cui *et al.*, 2008) and potential antitumorogenic properties (Tsai *et al.*, 2010;

Hsu *et al.*, 2011), as well as antinephritic, antibacterial and skin-whitening activities (Simmler *et al.*, 2013a). The structure of glabridin was first characterized in 1976 (Saitoh *et al.*, 1976) and subsequently more fully investigated by various spectroscopic methods (Kinoshita *et al.*, 1996; Kim *et al.*, 2009). The chemical synthesis was reported in 2007 (Yoo & Nahm, 2007) and the X-ray crystal structure at 293 K was reported last year (Tantishaiyakul *et al.*, 2012). However, the determination of the absolute stereochemistry and enantiopurity of natural glabridin remains uncertain.



### 2. Experimental

#### 2.1. Synthesis and crystallization

The CHCl<sub>3</sub> extract (4.97 g) from *G. glabra* roots was fractionated on an HW-40F column (2.5 × 60 cm) with 100% MeOH elution at a flow rate of 2.5 ml min<sup>-1</sup>, to yield seven fractions. The fourth fraction (1.92 g) was further separated on a Sephadex LH-20 column (1.1 × 9 m) eluted with 100% MeOH at a flow rate of 1 ml min<sup>-1</sup>, to give a glabridin-enriched fraction (234 mg). The final purification step was carried out on a LiChroCN (1.1 × 30 cm) column using an isocratic elution with CHCl<sub>3</sub>–MeOH (95:5 *v/v*). After drying under vacuum, the purified glabridin (10 mg), (I), was dissolved in MeOH–H<sub>2</sub>O (2.5 ml, 95:5 *v/v*) and left in a round-bottomed flask at room temperature for 24 h in order to obtain clear colorless crystals.

The <sup>1</sup>H NMR spectra (600 MHz in DMSO-*d*<sub>6</sub> and in CDCl<sub>3</sub> at 10 mM) were acquired under quantitative conditions and recorded on a Bruker AVANCE 600 MHz spectrometer equipped with a 5 mm TXI cryoprobe. Off-line data processing was performed using the TOPSPIN 3.0.b.8 software package (Bruker BioSpin GmbH), and PERCH NMR software (Laatikainen *et al.*, 1996) was employed for the full spin-system analysis. The NMR and circular dichroism (CD; 230–330 nm, in acetonitrile at 50 μM) data obtained for this secondary metabolite were in accordance with previously published data (Kinoshita *et al.*, 1996; Kim *et al.*, 2009; Yoo & Nahm, 2007). Chiral one-dimensional <sup>1</sup>H NMR was performed by adding a D<sub>2</sub>O solution (20 mM) of a chiral reagent [sodium [(*R*)-1,2-diaminopropane-*N,N,N',N'*-tetraacetato]samarate(III) hydrate; TCI Co. Ltd] to the crystalline sample dissolved in DMSO-*d*<sub>6</sub> (12 mM). Spectra were acquired at 600 MHz. Chiral <sup>1</sup>H NMR data processing was done following a Lorentzian-to-Gaussian modification (LB = –2.5 Hz, GF = 0.06), as reported previously (Jaki *et al.*, 2004). If the sample were to contain two enantiomers, a split in the proton resonance near the chiral

**Table 1**

Experimental details.

Crystal data	
Chemical formula	C <sub>20</sub> H <sub>20</sub> O <sub>4</sub>
<i>M<sub>r</sub></i>	324.36
Crystal system, space group	Orthorhombic, <i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Temperature (K)	92
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.3744 (10), 11.961 (2), 21.041 (3)
<i>V</i> (Å <sup>3</sup> )	1604.3 (4)
<i>Z</i>	4
Radiation type	Cu <i>K</i> α
<i>μ</i> (mm <sup>-1</sup> )	0.76
Crystal size (mm)	0.15 × 0.05 × 0.03
Data collection	
Diffractometer	Bruker Kappa APEXII DUO CCD area-detector diffractometer
Absorption correction	Multi-scan ( <i>SADABS</i> ; Sheldrick, 2004)
<i>T<sub>min</sub></i> , <i>T<sub>max</sub></i>	0.895, 0.978
No. of measured, independent and observed [ <i>I</i> > 2σ( <i>I</i> )] reflections	47918, 2879, 2708
<i>R<sub>int</sub></i>	0.046
(sin θ/λ) <sub>max</sub> (Å <sup>-1</sup> )	0.603
Refinement	
<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )], <i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>S</i>	0.026, 0.061, 1.03
No. of reflections	2879
No. of parameters	277
H-atom treatment	Only H-atom coordinates refined
Δρ <sub>max</sub> , Δρ <sub>min</sub> (e Å <sup>-3</sup> )	0.13, -0.13
Absolute structure	Flack <i>x</i> parameter determined using 1096 quotients [( <i>I</i> <sup>+</sup> ) - ( <i>I</i> <sup>-</sup> )] / [( <i>I</i> <sup>+</sup> ) + ( <i>I</i> <sup>-</sup> )] (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	-0.03 (6)

Computer programs: *APEX2* (Bruker, 2007), *SAINT* (Bruker, 2007), *SHELXS97* (Sheldrick, 2008), *SHELXL2013* (Sheldrick, 2008), *ORTEP-3 for Windows* (Farrugia, 2012) and *pubCIF* (Westrip, 2010).

center would be observed. The signal split should be all the more significant as the proportion of chiral reagent in the NMR sample increases. The chiral NMR method was previously assessed using a racemic sample of liquiritigenin (Part No. 00012290; Chromadex Inc.), from which the recorded CD spectrum (40 μM in acetonitrile) gave a flat line: 25 μl of samarate solution at 20 mM in D<sub>2</sub>O added to 200 μl of a liquiritigenin solution at 10 mM in DMSO-*d*<sub>6</sub> led to splitting of the signals from protons H2 (chiral center) and H3 (adjacent to the chiral center).

Chiral high-performance liquid chromatography (HPLC) was carried out on different types of stationary phases: permethylated B cyclodextrins (Nucleodex β-OH, and α-, β- and γ-PM; Macherey Nagel, GmbH & Co.); sodium magnesium silicate particles and anion exchange with ruthenium (Ceramospher RU-2; Shiseido Co. Ltd); and derivatized cellulose or amylose tris(3,5-dimethylphenylcarbamate) (Chiralpak 1B and 1A, respectively; Chiral Technologies, Inc.). Different elution conditions using various solvent mixtures, such as MeOH-H<sub>2</sub>O, ACN-H<sub>2</sub>O and *n*-hexane-EtOH, and various flow rates from 0.7 to 1 ml min<sup>-1</sup>, were also tested according to the type of stationary phase.

Several crystals were selected and screened, and complete X-ray data sets were collected on the LS-CAT beamline 21-ID-D (APS, Argonne, USA) at 0.7 Å to determine crystal quality. One small colorless crystal was selected for further

data collection. An Ewald sphere of intensity data was collected and averaged to a quadrant in the Bravais lattice (*Pmmm*). The final unit-cell parameters were obtained from refinement using 9904 reflections to a maximum Bragg angle of 68.81°.

## 2.2. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. The space group was identified as *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> based upon systematic absences and intensity statistics, with a final total of 2879 unique observations. The positions of the H atoms were evident in a difference electron-density map, and were then freely refined, with *U*<sub>iso</sub>(H) = 1.5*U*<sub>eq</sub>(parent atom) for hydroxy and methyl H atoms or 1.2*U*<sub>eq</sub>(parent atom) otherwise. The structure has been deposited with the Cambridge Crystallographic Data Centre (deposition No. 918747).

## 3. Results and discussion

After the final step of the medium-pressure liquid chromatography (MPLC) purification process, natural glabridin was crystallized from a mixture of methanol and water to give clear colorless crystals of (I) containing one molecule per asymmetric unit (*Z'* = 1) in the space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (Fig. 1). A comparison of bond lengths obtained for this and the previous determination is given in the *Supplementary materials*. An intermolecular hydrogen bond is observed between atom O1B (O1'' according to the biogenetic labeling) and atom H4A on atom O4A (O4') of an adjacent molecule, with an O—H...O angle of 178 (2)° (Table 2). In addition, it has been reported (Tantishaiyakul *et al.*, 2012) that there is a putative O—H...π interaction between the hydroxy group on atom O2A and C1A–C6A aromatic ring of a neighboring molecule (Table 2).

The one-dimensional <sup>1</sup>H NMR spectra (600 MHz, in DMSO-*d*<sub>6</sub> and CDCl<sub>3</sub>; see *Supplementary materials*) obtained for the present sample of glabridin are in accordance with previously published data (Kinoshita *et al.*, 1996; Kim *et al.*, 2009). The two-dimensional NMR spectra (HSQC and HMBC recorded at 600 MHz in DMSO-*d*<sub>6</sub>) further confirmed the structural assignments. Additionally, the enantiopurity of the crystalline sample has been evaluated by means of chiral HPLC, using different types of stationary phases and elution systems. Under all of these conditions, the glabridin sample eluted only as a single enantiomer. Moreover, chiral <sup>1</sup>H NMR in DMSO-*d*<sub>6</sub> was also performed using a chiral water-soluble reagent (samarate). Even after adding 50% molar concentration of the samarate, no splitting of glabridin <sup>1</sup>H NMR

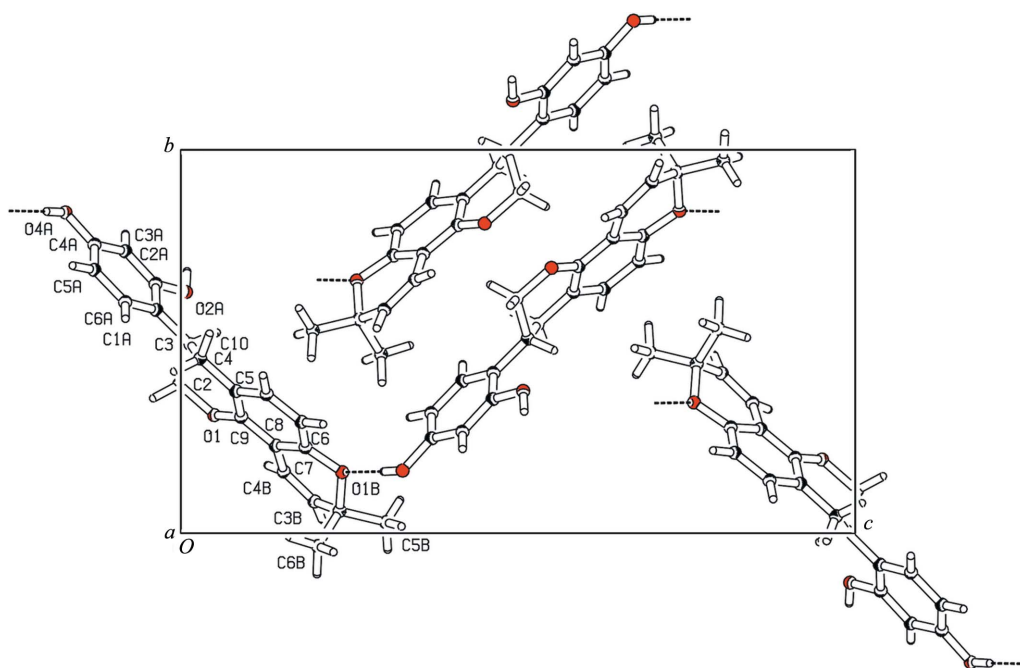
**Table 2**

Hydrogen-bond geometry (Å, °).

*CgA* is the centroid of the C1A–C6A ring.

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O4A—H4A...O1B <sup>i</sup>	0.86 (3)	1.96 (3)	2.8214 (19)	178 (2)
O2A—H2A...CgA <sup>ii</sup>	0.84 (3)	2.46 (2)	3.1505 (16)	139 (2)

Symmetry codes: (i)  $-x + \frac{3}{2}, -y + 1, z - \frac{1}{2}$ ; (ii)  $x + \frac{1}{2}, -y + \frac{3}{2}, -z$ .


**Figure 1**

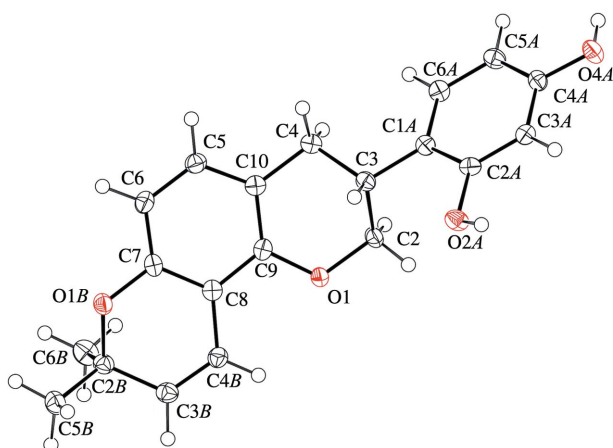
The hydrogen-bonding scheme of glabridin in the unit cell. Dashed lines indicate hydrogen bonds.

signals was observed, suggesting that only one enantiomer was present in the NMR tube. Taken together, these observations suggest that the collected sample was enantiopure.

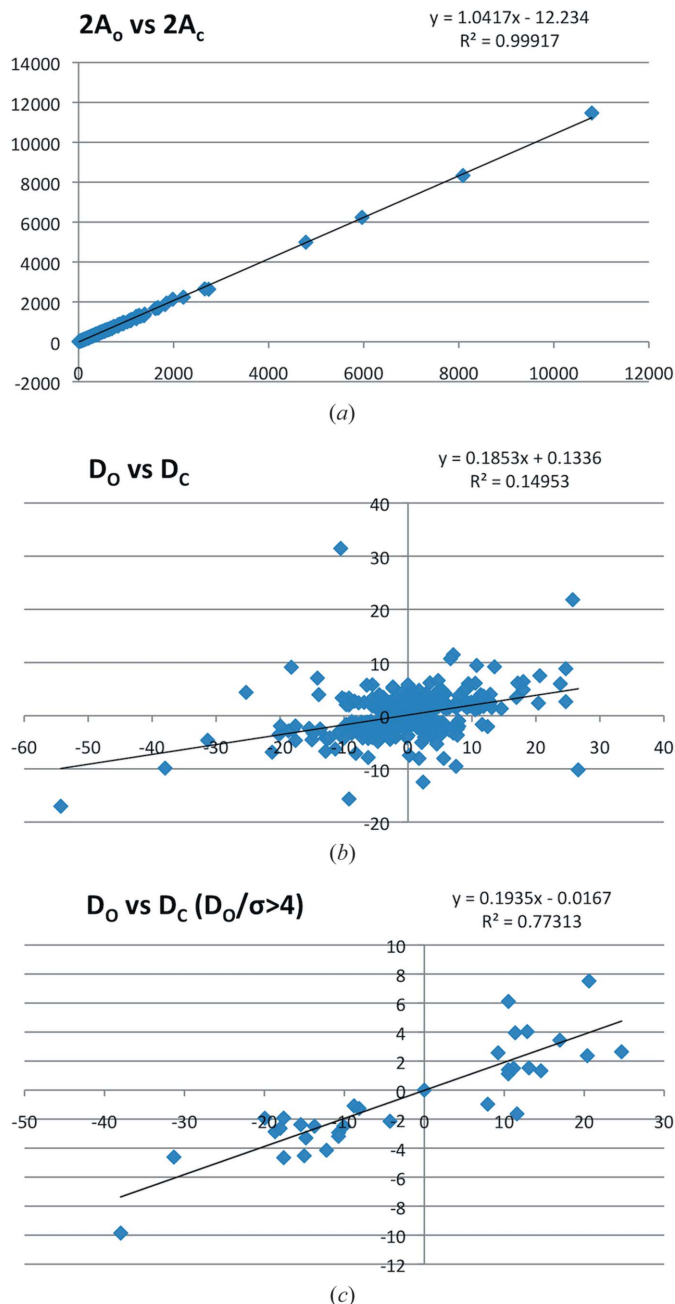
The stereochemistry of glabridin was determined using Cu  $K\alpha$  radiation and by carefully measuring a large number of Bijvoet differences. We assert that the isolated glabridin crystallized as a pure C3 *R* enantiomer (Fig. 2). The Flack parameter (Flack, 1983) refined to  $-0.14$  (19) for the 'hole-in-one' fit, and to  $-0.03$  (6) for the 1096 selected quotients from Parsons' method (Parsons *et al.*, 2013). *PLATON* (Spek, 2009) was also used to analyze the 1096 Bijvoet differences (Hooft *et al.*, 2008) and suggested that the glabridin structure is enantiopure: the probability  $P2$  (true) =  $P3$  (true) = 1.000 with

$P3$ (racemate-twin) =  $5.0 \times 10^{-27}$ ,  $P3$  (false) =  $1.0 \times 10^{-97}$ ,  $G$  = 1.09 (10), and the Hooft parameter  $\gamma$  =  $-0.05$  (5) for the C3 *R* enantiomer. *CRYSTALS* (Betteridge *et al.*, 2003) was also used to refine the structure. It reported a Flack parameter of  $-0.13$  (16), a  $G$  parameter of 1.03 (12) and a Hooft parameter of  $-0.01$  (6).

The determination of absolute structure, and the relative uncertainties in the measurement of the intensities of the Friedel pairs, has been revisited (Flack, 2013; Parsons *et al.*, 2012; Flack *et al.*, 2011). In particular, it has been noted that the average of the observed intensities between Friedel pairs,  $2A_o = |F_o(hkl)|^2 + |F_o(\bar{h}\bar{k}\bar{l})|^2$ , can be in good agreement with the corresponding average of the calculated intensities of the model,  $2A_c = |F_c(hkl)|^2 + |F_c(\bar{h}\bar{k}\bar{l})|^2$ , but the differences between the observed intensities of the Friedel pairs,  $D_o = |F_o(hkl)|^2 - |F_o(\bar{h}\bar{k}\bar{l})|^2$ , can be overwhelmed by random and systematic errors in the measurements when compared with the corresponding differences between the calculated intensities of the model,  $D_c = |F_c(hkl)|^2 - |F_c(\bar{h}\bar{k}\bar{l})|^2$  (Flack, 2013). Ideally, the plots of  $2A_o$  versus  $2A_c$  and of  $D_o$  versus  $D_c$  would each yield linear fits with slopes of 1 and intercepts at zero. From Fig. 3(a), we see that  $2A_o$  is in good agreement with  $2A_c$ , with a slope near 1, but this is clearly not true for Fig. 3(b) with  $D_o$  plotted against  $D_c$ . However, the slope of the linear fit in Fig. 3(b) is near 0.2, suggesting a weak resonant-scattering contribution and the correct absolute structure assignment. Indeed, a plot of  $D_o$  versus  $D_c$  for  $D_o > 4\sigma$  results in a slope near 0.2 with a correlation coefficient of 0.77 (Fig. 3c). Likewise, various assessment factors employing  $A$  and  $D$  can be defined to ascertain the magnitude of the resonant-scattering contributions to the Friedel pair differences:  $R_A = \Sigma|2A_o - 2A_c|/\Sigma|2A_o| = 3.5\%$ ,  $R_D = \Sigma|D_o - D_c|/\Sigma|D_o| = 92.0\%$ ,  $R_{AD} = \Sigma|D_o|/\Sigma|A_o| = 1.5\%$  and  $\langle D_o/\sigma \rangle = (1/n)\Sigma|D_o|/\sigma = 1.9$ . These assessment factors suggest that the resonant-scattering


**Figure 2**

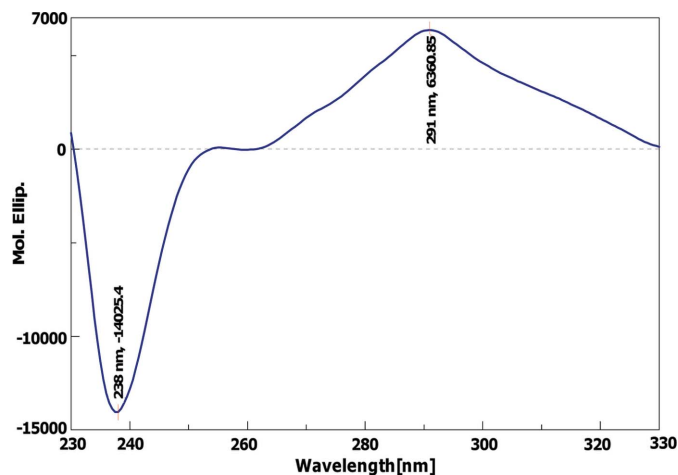
The molecular structure of glabridin, showing the atom-labeling scheme according to the crystallographic coordinates. Displacement ellipsoids are drawn at the 50% probability level. The biogenetic labeling scheme relates to the crystallographic atom labels as follows: 'A' corresponds to primed (') labels and 'B' corresponds to double primed (") labels, e.g. C3A is C3' and C3B is C3''.



**Figure 3**  
 $2A$  and  $D$  plots of (a)  $2A_o$  versus  $2A_c$ , (b)  $D_o$  versus  $D_c$  for all data and (c)  $D_o$  versus  $D_c$  for all Friedel pairs with  $D_o > 4\sigma$ .

contributions to the observed intensities are weak, but still significant enough to assign the absolute structure correctly.

Circular dichroism (CD) of flavonoids can indicate the configuration of a sample regardless of its enantiopurity (Slade *et al.*, 2005). If a sample is defined by an enantiomeric excess, its CD spectrum will only indicate the configuration of the enantiomer present in excess (Simmler *et al.*, 2013b). Given that the enantiopurity and stereochemistry of the present glabridin sample have been determined by means of complementary techniques (chiral HPLC, NMR and X-ray diffraction), the CD spectrum recorded from the crystalline sample (50  $\mu\text{M}$  in acetonitrile) displays the molecular ellipticity



**Figure 4**  
 The CD spectrum of C3 *R* enantiopure glabridin at 50  $\mu\text{M}$  in acetonitrile.

city of an enantiopure glabridin in a C3 *R* configuration (Kim *et al.*, 2009) (Fig. 4).

#### 4. Conclusions

The present description of the crystal structure of glabridin complements existing spectroscopic data, and confirms that glabridin naturally occurs in the C3 *R* configuration. From this stereochemical point of view, it is important to consider that all the biological activities reported for natural glabridin are likely obtained from the *R* enantiomer. Therefore, the reported CD spectrum can be used as a reference for further characterization and elucidation of the enantiopurity of an isolated or synthetic glabridin sample. The results presented herein provide an unequivocal foundation for the structural characterization of this phytochemical and biological marker of European licorice, *G. glabra* L.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN3162). Services for accessing these data are described at the back of the journal.

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## supplementary materials

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### Computing details

Data collection: *APEX2* (Bruker, 2007); cell refinement: *SAINT* (Bruker, 2007); data reduction: *SAINT* (Bruker, 2007); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2013* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012); software used to prepare material for publication: *publCIF* (Westrip, 2010).

### 4-[(3*R*)-8,8-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-3-yl]benzene-1,3-diol

#### Crystal data

C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>

*M<sub>r</sub>* = 324.36

Orthorhombic, *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>

*a* = 6.3744 (10) Å

*b* = 11.961 (2) Å

*c* = 21.041 (3) Å

*V* = 1604.3 (4) Å<sup>3</sup>

*Z* = 4

*F*(000) = 688

*D<sub>x</sub>* = 1.343 Mg m<sup>-3</sup>

Cu *Kα* radiation, λ = 1.54184 Å

Cell parameters from 9904 reflections

θ = 4.2–68.6°

μ = 0.76 mm<sup>-1</sup>

*T* = 92 K

Needle, colourless

0.15 × 0.05 × 0.03 mm

#### Data collection

Bruker Kappa APEXII DUO CCD aea-detector diffractometer

Radiation source: IμS microfocus

φ and ω scans

Absorption correction: multi-scan

(*SADABS*; Sheldrick, 2004)

*T<sub>min</sub>* = 0.895, *T<sub>max</sub>* = 0.978

47918 measured reflections

2879 independent reflections

2708 reflections with *I* > 2σ(*I*)

*R<sub>int</sub>* = 0.046

θ<sub>max</sub> = 68.5°, θ<sub>min</sub> = 4.2°

*h* = -7→7

*k* = 0→14

*l* = 0→24

#### Refinement

Refinement on *F*<sup>2</sup>

Least-squares matrix: full

*R*[*F*<sup>2</sup> > 2σ(*F*<sup>2</sup>)] = 0.026

*wR*(*F*<sup>2</sup>) = 0.061

*S* = 1.03

2879 reflections

277 parameters

0 restraints

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: difference Fourier map

Only H-atom coordinates refined

*w* = 1/[σ<sup>2</sup>(*F<sub>o</sub>*<sup>2</sup>) + (0.0324*P*)<sup>2</sup> + 0.3419*P*]

where *P* = (*F<sub>o</sub>*<sup>2</sup> + 2*F<sub>c</sub>*<sup>2</sup>)/3

(Δ/σ)<sub>max</sub> < 0.001

Δρ<sub>max</sub> = 0.13 e Å<sup>-3</sup>

Δρ<sub>min</sub> = -0.13 e Å<sup>-3</sup>

Absolute structure: Flack *x* parameter

determined using 1096 quotients

[(*I*<sup>+)-(*I*<sup>-</sup>)]/[(*I*<sup>+</sup>)+(*I*<sup>-</sup>)] (Parsons *et al.*, 2013)</sup>

Absolute structure parameter: -0.03 (6)

*Special details*

**Geometry.** All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ( $\text{\AA}^2$ )*

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
C1A	0.5348 (3)	0.41798 (14)	0.46350 (8)	0.0178 (4)
C2A	0.3549 (3)	0.34964 (15)	0.46223 (8)	0.0179 (4)
O2A	0.2046 (2)	0.37100 (11)	0.50754 (6)	0.0235 (3)
H2A	0.119 (4)	0.317 (2)	0.5091 (11)	0.035*
C3A	0.3301 (3)	0.26477 (15)	0.41751 (9)	0.0183 (4)
H3A	0.209 (4)	0.2201 (17)	0.4177 (9)	0.022*
C4A	0.4854 (3)	0.24727 (15)	0.37179 (8)	0.0189 (4)
O4A	0.4515 (2)	0.16339 (11)	0.32871 (6)	0.0243 (3)
H4A	0.550 (4)	0.161 (2)	0.3009 (11)	0.036*
C5A	0.6645 (3)	0.31343 (16)	0.37152 (9)	0.0211 (4)
H5A	0.774 (4)	0.3022 (18)	0.3398 (9)	0.025*
C6A	0.6871 (3)	0.39709 (15)	0.41730 (9)	0.0203 (4)
H6A	0.814 (4)	0.4403 (17)	0.4177 (10)	0.024*
O1	0.4235 (2)	0.69199 (10)	0.54946 (6)	0.0214 (3)
C2	0.4297 (3)	0.61178 (16)	0.49751 (9)	0.0203 (4)
H21	0.487 (4)	0.6480 (17)	0.4591 (10)	0.024*
H22	0.280 (4)	0.5939 (18)	0.4886 (10)	0.024*
C3	0.5547 (3)	0.50714 (15)	0.51435 (8)	0.0182 (4)
H3	0.493 (3)	0.4770 (17)	0.5531 (10)	0.022*
C4	0.7802 (3)	0.54459 (15)	0.52873 (9)	0.0205 (4)
H41	0.865 (3)	0.4797 (19)	0.5424 (10)	0.025*
H42	0.838 (3)	0.5780 (18)	0.4902 (10)	0.025*
C5	0.9300 (3)	0.63739 (16)	0.62720 (9)	0.0217 (4)
H5	1.051 (4)	0.5890 (18)	0.6218 (9)	0.026*
C6	0.9161 (3)	0.70976 (16)	0.67885 (9)	0.0217 (4)
H6	1.029 (4)	0.7158 (18)	0.7106 (9)	0.026*
C7	0.7389 (3)	0.77578 (14)	0.68483 (8)	0.0180 (4)
C8	0.5746 (3)	0.77139 (15)	0.64067 (8)	0.0177 (4)
C9	0.5938 (3)	0.69660 (15)	0.58945 (8)	0.0176 (4)
C10	0.7716 (3)	0.62927 (14)	0.58174 (8)	0.0183 (4)
O1B	0.7192 (2)	0.84092 (10)	0.73914 (6)	0.0208 (3)
C2B	0.5885 (3)	0.94209 (15)	0.73530 (9)	0.0205 (4)
C3B	0.3909 (3)	0.91720 (16)	0.69821 (9)	0.0219 (4)
H3B	0.269 (4)	0.9652 (18)	0.7094 (10)	0.026*
C4B	0.3886 (3)	0.83923 (16)	0.65271 (8)	0.0204 (4)
H4B	0.264 (4)	0.8230 (17)	0.6288 (10)	0.024*
C5B	0.5396 (3)	0.97127 (19)	0.80411 (9)	0.0266 (4)
H51B	0.455 (4)	1.043 (2)	0.8066 (11)	0.040*
H52B	0.672 (4)	0.982 (2)	0.8270 (11)	0.040*
H53B	0.451 (4)	0.914 (2)	0.8248 (11)	0.040*

C6B	0.7177 (4)	1.03343 (17)	0.70313 (10)	0.0289 (5)
H61B	0.756 (4)	1.010 (2)	0.6609 (12)	0.043*
H62B	0.849 (4)	1.049 (2)	0.7261 (12)	0.043*
H63B	0.631 (4)	1.107 (2)	0.7017 (11)	0.043*

*Atomic displacement parameters (Å<sup>2</sup>)*

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
C1A	0.0214 (9)	0.0164 (8)	0.0156 (9)	0.0009 (8)	-0.0006 (8)	0.0026 (7)
C2A	0.0188 (9)	0.0191 (9)	0.0159 (9)	0.0031 (7)	0.0031 (7)	0.0042 (7)
O2A	0.0217 (7)	0.0227 (7)	0.0262 (7)	-0.0035 (6)	0.0081 (6)	-0.0026 (5)
C3A	0.0187 (9)	0.0162 (8)	0.0201 (9)	-0.0009 (7)	-0.0010 (8)	0.0025 (7)
C4A	0.0239 (10)	0.0167 (9)	0.0160 (9)	0.0016 (8)	-0.0021 (7)	0.0007 (7)
O4A	0.0280 (7)	0.0241 (7)	0.0207 (7)	-0.0048 (6)	0.0051 (6)	-0.0061 (5)
C5A	0.0231 (10)	0.0221 (9)	0.0181 (9)	0.0010 (8)	0.0037 (8)	0.0007 (7)
C6A	0.0211 (9)	0.0196 (9)	0.0202 (9)	-0.0021 (8)	0.0015 (8)	0.0015 (7)
O1	0.0215 (7)	0.0226 (7)	0.0201 (6)	0.0047 (6)	-0.0051 (6)	-0.0058 (5)
C2	0.0244 (10)	0.0211 (9)	0.0155 (9)	0.0023 (8)	-0.0016 (8)	-0.0038 (7)
C3	0.0201 (9)	0.0191 (9)	0.0154 (9)	0.0002 (7)	0.0018 (7)	0.0003 (7)
C4	0.0203 (9)	0.0200 (9)	0.0214 (9)	0.0014 (8)	0.0013 (8)	-0.0006 (8)
C5	0.0193 (9)	0.0200 (9)	0.0258 (10)	0.0010 (8)	-0.0008 (8)	0.0000 (8)
C6	0.0207 (9)	0.0226 (10)	0.0219 (10)	-0.0008 (8)	-0.0047 (8)	0.0007 (7)
C7	0.0227 (9)	0.0163 (9)	0.0151 (9)	-0.0044 (7)	-0.0003 (7)	0.0014 (7)
C8	0.0200 (9)	0.0164 (8)	0.0168 (9)	-0.0022 (7)	0.0010 (7)	0.0034 (7)
C9	0.0193 (9)	0.0176 (8)	0.0158 (9)	-0.0030 (7)	-0.0013 (7)	0.0038 (7)
C10	0.0187 (9)	0.0169 (8)	0.0193 (9)	-0.0017 (7)	0.0022 (7)	0.0029 (7)
O1B	0.0244 (7)	0.0198 (6)	0.0182 (6)	0.0014 (5)	-0.0035 (5)	-0.0016 (5)
C2B	0.0227 (9)	0.0182 (9)	0.0206 (9)	0.0022 (8)	-0.0002 (8)	-0.0003 (7)
C3B	0.0234 (10)	0.0216 (10)	0.0209 (10)	0.0032 (8)	0.0008 (8)	0.0014 (8)
C4B	0.0202 (9)	0.0222 (9)	0.0188 (9)	0.0013 (7)	-0.0015 (8)	0.0008 (7)
C5B	0.0269 (11)	0.0312 (11)	0.0217 (10)	-0.0014 (10)	0.0001 (9)	-0.0056 (8)
C6B	0.0348 (12)	0.0217 (10)	0.0302 (11)	-0.0034 (9)	0.0042 (10)	0.0010 (8)

*Geometric parameters (Å, °)*

C1A—C6A	1.396 (3)	C5—C6	1.392 (3)
C1A—C2A	1.408 (2)	C5—C10	1.394 (3)
C1A—C3	1.516 (2)	C5—H5	0.97 (2)
C2A—O2A	1.376 (2)	C6—C7	1.384 (3)
C2A—C3A	1.393 (3)	C6—H6	0.98 (2)
O2A—H2A	0.84 (3)	C7—O1B	1.389 (2)
C3A—C4A	1.396 (3)	C7—C8	1.401 (3)
C3A—H3A	0.94 (2)	C8—C9	1.406 (2)
C4A—O4A	1.369 (2)	C8—C4B	1.459 (3)
C4A—C5A	1.389 (3)	C9—C10	1.400 (3)
O4A—H4A	0.86 (3)	O1B—C2B	1.471 (2)
C5A—C6A	1.396 (3)	C2B—C3B	1.512 (3)
C5A—H5A	0.97 (2)	C2B—C5B	1.521 (3)
C6A—H6A	0.96 (2)	C2B—C6B	1.526 (3)
O1—C9	1.375 (2)	C3B—C4B	1.337 (3)



O1—C2	1.455 (2)	C3B—H3B	1.00 (2)
C2—C3	1.525 (3)	C4B—H4B	0.96 (2)
C2—H21	0.99 (2)	C5B—H51B	1.01 (3)
C2—H22	1.00 (2)	C5B—H52B	0.98 (3)
C3—C4	1.536 (3)	C5B—H53B	0.99 (3)
C3—H3	0.97 (2)	C6B—H61B	0.96 (3)
C4—C10	1.508 (2)	C6B—H62B	0.99 (3)
C4—H41	0.99 (2)	C6B—H63B	1.04 (3)
C4—H42	0.98 (2)		
C6A—C1A—C2A	116.68 (16)	C10—C5—H5	116.9 (12)
C6A—C1A—C3	123.98 (16)	C7—C6—C5	118.54 (17)
C2A—C1A—C3	119.33 (16)	C7—C6—H6	119.5 (12)
O2A—C2A—C3A	121.62 (16)	C5—C6—H6	122.0 (12)
O2A—C2A—C1A	116.49 (15)	C6—C7—O1B	117.95 (15)
C3A—C2A—C1A	121.89 (16)	C6—C7—C8	121.89 (16)
C2A—O2A—H2A	109.7 (16)	O1B—C7—C8	119.96 (16)
C2A—C3A—C4A	119.60 (17)	C7—C8—C9	117.87 (17)
C2A—C3A—H3A	120.3 (12)	C7—C8—C4B	118.12 (16)
C4A—C3A—H3A	120.1 (12)	C9—C8—C4B	123.89 (16)
O4A—C4A—C5A	122.99 (16)	O1—C9—C10	123.05 (16)
O4A—C4A—C3A	117.00 (16)	O1—C9—C8	115.22 (16)
C5A—C4A—C3A	120.01 (16)	C10—C9—C8	121.69 (16)
C4A—O4A—H4A	111.3 (17)	C5—C10—C9	117.82 (16)
C4A—C5A—C6A	119.34 (17)	C5—C10—C4	121.88 (16)
C4A—C5A—H5A	120.7 (13)	C9—C10—C4	120.12 (16)
C6A—C5A—H5A	119.9 (13)	C7—O1B—C2B	117.87 (13)
C5A—C6A—C1A	122.47 (18)	O1B—C2B—C3B	109.77 (14)
C5A—C6A—H6A	118.6 (13)	O1B—C2B—C5B	104.62 (15)
C1A—C6A—H6A	118.9 (13)	C3B—C2B—C5B	111.45 (16)
C9—O1—C2	117.69 (14)	O1B—C2B—C6B	107.92 (16)
O1—C2—C3	112.39 (14)	C3B—C2B—C6B	111.20 (16)
O1—C2—H21	109.6 (12)	C5B—C2B—C6B	111.62 (17)
C3—C2—H21	111.0 (12)	C4B—C3B—C2B	121.07 (17)
O1—C2—H22	104.9 (12)	C4B—C3B—H3B	124.2 (13)
C3—C2—H22	111.6 (12)	C2B—C3B—H3B	114.7 (12)
H21—C2—H22	107.1 (18)	C3B—C4B—C8	120.24 (17)
C1A—C3—C2	111.68 (14)	C3B—C4B—H4B	121.8 (13)
C1A—C3—C4	115.00 (15)	C8—C4B—H4B	117.9 (13)
C2—C3—C4	107.17 (15)	C2B—C5B—H51B	110.6 (13)
C1A—C3—H3	107.3 (12)	C2B—C5B—H52B	108.8 (14)
C2—C3—H3	106.7 (12)	H51B—C5B—H52B	109 (2)
C4—C3—H3	108.7 (12)	C2B—C5B—H53B	112.0 (14)
C10—C4—C3	107.92 (15)	H51B—C5B—H53B	105.2 (19)
C10—C4—H41	109.3 (12)	H52B—C5B—H53B	111 (2)
C3—C4—H41	109.9 (12)	C2B—C6B—H61B	109.9 (16)
C10—C4—H42	110.7 (13)	C2B—C6B—H62B	112.3 (15)
C3—C4—H42	108.1 (12)	H61B—C6B—H62B	107 (2)
H41—C4—H42	110.9 (17)	C2B—C6B—H63B	109.4 (14)

C6—C5—C10	122.20 (18)	H61B—C6B—H63B	111 (2)
C6—C5—H5	120.9 (12)	H62B—C6B—H63B	107 (2)
C6A—C1A—C2A—O2A	-179.56 (15)	C6—C7—C8—C4B	176.53 (17)
C3—C1A—C2A—O2A	1.4 (2)	O1B—C7—C8—C4B	1.8 (2)
C6A—C1A—C2A—C3A	0.5 (2)	C2—O1—C9—C10	0.9 (2)
C3—C1A—C2A—C3A	-178.56 (16)	C2—O1—C9—C8	-176.83 (15)
O2A—C2A—C3A—C4A	179.01 (16)	C7—C8—C9—O1	176.92 (15)
C1A—C2A—C3A—C4A	-1.0 (3)	C4B—C8—C9—O1	1.0 (2)
C2A—C3A—C4A—O4A	-179.39 (16)	C7—C8—C9—C10	-0.9 (2)
C2A—C3A—C4A—C5A	0.8 (3)	C4B—C8—C9—C10	-176.78 (17)
O4A—C4A—C5A—C6A	-179.83 (17)	C6—C5—C10—C9	-0.3 (3)
C3A—C4A—C5A—C6A	0.0 (3)	C6—C5—C10—C4	-175.28 (17)
C4A—C5A—C6A—C1A	-0.6 (3)	O1—C9—C10—C5	-176.79 (16)
C2A—C1A—C6A—C5A	0.3 (3)	C8—C9—C10—C5	0.8 (2)
C3—C1A—C6A—C5A	179.32 (16)	O1—C9—C10—C4	-1.7 (3)
C9—O1—C2—C3	31.4 (2)	C8—C9—C10—C4	175.90 (16)
C6A—C1A—C3—C2	100.6 (2)	C3—C4—C10—C5	146.12 (17)
C2A—C1A—C3—C2	-80.5 (2)	C3—C4—C10—C9	-28.8 (2)
C6A—C1A—C3—C4	-21.8 (2)	C6—C7—O1B—C2B	154.92 (16)
C2A—C1A—C3—C4	157.13 (16)	C8—C7—O1B—C2B	-30.2 (2)
O1—C2—C3—C1A	172.12 (15)	C7—O1B—C2B—C3B	42.0 (2)
O1—C2—C3—C4	-61.09 (19)	C7—O1B—C2B—C5B	161.71 (15)
C1A—C3—C4—C10	-177.75 (14)	C7—O1B—C2B—C6B	-79.32 (19)
C2—C3—C4—C10	57.45 (18)	O1B—C2B—C3B—C4B	-29.3 (2)
C10—C5—C6—C7	-0.2 (3)	C5B—C2B—C3B—C4B	-144.71 (18)
C5—C6—C7—O1B	174.93 (16)	C6B—C2B—C3B—C4B	90.1 (2)
C5—C6—C7—C8	0.1 (3)	C2B—C3B—C4B—C8	3.9 (3)
C6—C7—C8—C9	0.4 (3)	C7—C8—C4B—C3B	11.4 (3)
O1B—C7—C8—C9	-174.32 (15)	C9—C8—C4B—C3B	-172.65 (17)

Hydrogen-bond geometry ( $\text{\AA}$ ,  $^\circ$ )

CgA is the centroid of the C1A—C6A ring.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O4A—H4A $\cdots$ O1B <sup>i</sup>	0.86 (3)	1.96 (3)	2.8214 (19)	178 (2)
O2A—H2A $\cdots$ CgA <sup>ii</sup>	0.84 (3)	2.46 (2)	3.1505 (16)	139 (2)

Symmetry codes: (i)  $-x+3/2, -y+1, z-1/2$ ; (ii)  $x+1/2, -y+3/2, -z$ .

One-dimensional  $^1\text{H}$  NMR data [ $\delta_{\text{H}}$ , ( $m$ ,  $J$  in Hz)] of glabridin in DMSO  $d_6$  and  $\text{CDCl}_3$  (600 MHz)

Protons	DMSO $d_6$	$\text{CDCl}_3$
H-2 (pro-S) a	3.94 ( $t$ , $J_{\text{H-3}} = 10.26$ )	4.01 ( $t$ , $J_{\text{H-3}} = 10.56$ )
H-2 (pro-R) b	4.23 ( $dt$ , $J_{\text{H-4a}} = 2.61$ , $J_{\text{gem}} = -10.20$ )	4.37 ( $dt$ , $J_{\text{H-4a}} = 2.55$ , $J_{\text{gem}} = -10.56$ )
H-3	3.29 ( $m$ )	3.48 ( $m$ )
H-4 (pro-S) a	2.69 ( $ddd$ , $J_{\text{H-2b}} = 1.76$ , $J_{\text{H-3}} = 4.77$ , $J_{\text{H-4b}} = 15.52$ )	2.86 ( $ddd$ , $J_{\text{H-2b}} = 1.57$ , $J_{\text{H-3}} = 4.71$ , $J_{\text{H-4b}} = 15.62$ )
H-4 (pro-R) b	2.89 ( $dd$ , $J_{\text{H-3}} = 11.36$ , $J_{\text{H-4a}} = 15.52$ )	2.97 ( $dd$ , $J_{\text{H-3}} = 10.77$ , $J_{\text{H-4a}} = 15.62$ )
H-5	6.83 ( $d$ , $J_{\text{H-6}} = 8.22$ )	6.82 ( $d$ , $J_{\text{H-6}} = 8.23$ )

H-6	6.29 ( <i>d</i> , $J_{H-5} = 8.22$ )	6.36 ( <i>d</i> , $J_{H-5} = 8.23$ )
H-3A	6.33 ( <i>d</i> , $J_{H-5A} = 2.40$ )	6.33 ( <i>d</i> , $J_{H-5A} = 2.30$ )
H-5A	6.19 ( <i>dd</i> , $J_{H-3A} = 2.40$ , $J_{H-6A} = 8.32$ )	6.38 ( <i>dd</i> , $J_{H-3A} = 2.30$ , $J_{H-6A} = 8.37$ )
H-6A	6.86 ( <i>d</i> , $J_{H-5A} = 8.32$ )	6.95 ( <i>d</i> , $J_{H-5A} = 8.37$ )
2A-OH	9.11 ( <i>s</i> )	
4A-OH	9.39 ( <i>s</i> )	
H-3B	5.65 ( <i>d</i> , $J_{H-4B} = 9.90$ )	5.55 ( <i>d</i> , $J_{H-4B} = 9.90$ )
H-4B	6.54 ( <i>d</i> , $J_{H-3B} = 9.90$ )	6.64 ( <i>d</i> , $J_{H-3B} = 9.90$ )
H <sub>3</sub> -5B	1.33 ( <i>s</i> )	1.40 ( <i>s</i> )
H <sub>3</sub> -6B	1.34 ( <i>s</i> )	1.42 ( <i>s</i> )

Chemical shifts  $\delta$  in p.p.m.. Coupling patterns are given in parentheses ( $J$  in Hz). All assignments were confirmed by gHSQC and qHMBC.

*Results of one-dimensional <sup>1</sup>H NMR full-spin analysis of glabridin in DMSO d<sub>6</sub> ( $\delta_H$ ,  $m$ ,  $J$  in Hz)*

Protons	DMSO <i>d</i> <sub>6</sub>
H-2 (pro-S) a	4.271 ( <i>t</i> , $J_{H-3} = 10.29$ , $J_{gem} = -10.25$ )
H-2 (pro-R) b	4.319 ( <i>dt</i> , $J_{H-3} = 3.49$ , $J_{gem} = -10.25$ , $J_{H-4a} = 2.11$ )
H-3	3.359( <i>dddd</i> , $J_{H-2a} = 10.29$ , $J_{H-2b} = 3.49$ , $J_{H-4a} = 4.85$ , $J_{H-4b} = 11.36$ )
H-4 (pro-S) a	2.703 ( <i>ddd</i> , $J_{H-2b} = 2.11$ , $J_{H-3} = 4.85$ , $J_{H-4b} = 15.59$ )
H-4 (pro-R) b	2.776 ( <i>dd</i> , $J_{H-3} = 11.36$ , $J_{H-4a} = 15.59$ , $J_{H-5} = -0.90$ )
H-5	7.140 ( <i>d</i> , $J_{H-6} = 8.22$ )
H-6	6.487 ( <i>d</i> , $J_{H-5} = 8.22$ )
H-3A	6.356 ( <i>dd</i> , $J_{H-5A} = 2.40$ , $J_{H-6A} = 0.44$ )
H-5A	6.330 ( <i>dd</i> , $J_{H-3A} = 2.40$ , $J_{H-6A} = 8.32$ )
H-6A	7.036 ( <i>dd</i> , $J_{H-3A} = 0.44$ , $J_{H-5A} = 8.32$ )
2A-OH	9.418 ( <i>s</i> )
4A-OH	9.919 ( <i>s</i> )
H-3B	6.337 ( <i>d</i> , $J_{H-4B} = 9.91$ )
H-4B	7.111 ( <i>d</i> , $J_{H-3B} = 9.91$ )
H <sub>3</sub> -5B	1.392 ( <i>s</i> )
H <sub>3</sub> -6B	1.405 ( <i>s</i> )

*Comparison of bond lengths ( $\text{\AA}$ ) for glabridin in this work and with those from Tantishaiyakul et al. (2012)*

Atom 1	Atom 2	This work	Tantishaiyakul et al.
C1A	C6A	1.396 (3)	1.388 (3)
C1A	C2A	1.408 (2)	1.398 (3)
C1A	C3	1.516 (2)	1.506 (3)
C2A	O2A	1.376 (2)	1.369 (3)
C2A	C3A	1.393 (2)	1.383 (3)
C3A	C4A	1.396 (3)	1.380 (3)
C4A	O4A	1.369 (2)	1.361 (3)
C4A	C5A	1.389 (3)	1.377 (3)
C5A	C6A	1.396 (3)	1.384 (3)
O1	C9	1.375 (2)	1.372 (3)
O1	C2	1.455 (2)	1.442 (2)
C2	C3	1.525 (3)	1.516 (3)
C3	C4	1.536 (3)	1.528 (3)
C4	C10	1.508 (2)	1.501 (3)

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C5	C10	1.394 (3)	1.385 (3)
C5	C6	1.392 (3)	1.386 (3)
C6	C7	1.384 (3)	1.370 (3)
C7	O1B	1.389 (2)	1.380 (3)
C7	C8	1.401 (3)	1.389 (3)
C8	C9	1.406 (2)	1.400 (3)
C8	C4B	1.459 (3)	1.449 (3)
C9	C10	1.400 (3)	1.386 (3)
O1B	C2B	1.471 (2)	1.463 (3)
C2B	C3B	1.512 (3)	1.493 (4)
C2B	C5B	1.521 (3)	1.516 (3)
C2B	C6B	1.526 (3)	1.524 (4)
C3B	C4B	1.337 (3)	1.321 (3)
O2A	H2A	0.84 (3)	0.802 (17)
C3A	H3A	0.97 (2)	0.93
O4A	H4A	0.86 (3)	0.820 (17)
C5A	H5A	0.97 (2)	0.93
C6A	H6A	0.96 (2)	0.93
C2	H21	0.99 (2)	0.97
C2	H22	1.00 (2)	0.97
C3	H3	0.97 (2)	0.98
C4	H41	0.99 (2)	0.97
C4	H42	0.98 (2)	0.97
C5	H5	0.97 (2)	0.93
C6	H6	0.98 (2)	0.93
C3B	H3B	1.00 (2)	0.93
C4B	H4B	0.96 (2)	0.93
C5B	H5B1	1.01 (3)	0.96
C5B	H5B2	0.98 (3)	0.96
C5B	H5B3	0.99 (3)	0.96
C6B	H6B1	0.96 (3)	0.96
C6B	H6B2	0.99 (3)	0.96
C6B	H6B3	1.04 (3)	0.96

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