The Absolute Configuration of 1-(3′,4′-Dihydroxycinnamoyl)cyclopentane-2,3-diol from the Amazonian Tree *Chimarrhis turbinata*

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An antioxidant, 1-(3′,4′-dihydroxycinnamoyl)cyclopentane-2,3-diol [or (*E*)-2,3-dihydroxycyclopentyl-3-(3′,4′-dihydroxyphenyl)acrylate (**1**)], and two known *trans*- and *cis*-chlorogenic acid methyl esters were isolated from the ethanolic extract of the leaves of *Chimarrhis turbinata*. The relative configuration of **1** was determined by NMR and by comparison of the circular dichroic spectrum (CD) with those of the enantiomers of synthetic 3′,4′-dimethoxycinnamoyl analogues. The absolute configuration of one of the synthetic enantiomers was determined using the CD exciton chirality method. This established the structure of naturally occurring **1** as (*E*)-2,3-dihydroxycyclopentyl-3-(3′,4′-dihydroxyphenyl)acrylate.

The tree *Chimarrhis turbinata* DC. Prodr. (Rubiaceae), which grows mainly in Central America, tropical South America, and the Caribbean Islands, is prized for its light and resistant wood, which is used in the manufacture of tools. In the Amazonian region, the species is constantly under threat from the indigenous population, who construct paddles from the wood, giving rise to the popular name of "pau-de-remo" for the species.[1] Previous phytochemical studies of *C. turbinata* established the presence of indole alkaloids, including turbinatine, which was identified as a key intermediate in the biosynthesis of corinantheans.[2] Further investigations have led to the isolation of several phenolics with antioxidant properties,[3,4] including the chlorogenic acid derivative 1-(3′,4′-dihydroxycinnamoyl)cyclopentane-2,3-diol (**1**)[5] and *trans*- and *cis*-chlorogenic acid methyl esters (**2** and **3**, respectively). Identification of the known compounds **2** and **3** was based on their spectroscopic data and comparison with literature values. While compound **1** had been reported previously from *Prunus cerasus*, its relative and absolute configurations were not determined.[6]

We here report the structural elucidation and determination of the absolute configuration of **1** by application of the circular dichroic (CD) exciton chirality technique. In this nonempirical microscale method for establishing the conformation and absolute configuration of chiral molecules in solution,[7−11] the hydroxyl groups are converted into corresponding esters with *p*-substituted benzoates or other chromophores.[8] Interactions between the electric transition moments of proximally located chirally disposed chromophores give rise to CD curves that exhibit split Cotton effects or couplets, although the *cisoid* triol structure **1** exhibited a weak but distinct CD spectrum,[6] as presented in Figure 3. To obtain a dichromophoric compound, attempts were made to derivatize **1** directly, but were unsuccessful owing to the instability of the molecule under acidic and basic conditions. The absolute configuration of **1** was thus established from the CD spectra of synthetic enantiomers of 1-(3′,4′-dimethoxycinnamoyl)cyclopentane-2,3-diol (**4**). The absolute configuration of one of these synthetic enantiomers was then determined by the CD exciton chirality method.

Results and Discussion

Compound **1**, 1-(3′,4′-dihydroxycinnamoyl)cyclopentane-2,3-diol, was isolated from an EtOH extract of the leaves of *C. turbinata* as a brown powder; UV (MeOH) λ_{max} (log ϵ) 205 (3.95), 215 (3.94), 243 (3.76), 299 (3.81), 327 (3.90) nm; IR (KBr) ν_{max} 3414 (OH), 1694 (C═O) cm^{-1}; ^1H and ^{13}C NMR data see Table 1; EIMS *m*/*z* 281 (10), $[M + H]^+$ 180 (20), 163 (82).

The molecular formula of **1**, as determined from ESIMS and ^{13}C NMR data, was $C_{14}H_{16}O_6$. Signals at δ 149.5, 147.2, 127.6, 122.9, 115.2, and 116.5 in the ^{13}C NMR of **1** (Table 1) were typical of a 3′,4′-dihydroxylcinnamoyl group, while those at δ 146.8 and 115.3, together with correlations indicated by the gHMBC spectrum between H-7′ and H-8′ with the carbonyl group at 168.7, suggested the presence of a caffeic acid moiety. The signals at δ 72.0 (s), 73.6, and 71.5 were assigned to the hydroxymethine carbons C-1, C-2, and C-3. When the spectroscopic data of **1** were compared with those of chlorogenic acid, the presence of methylene carbon signals at δ 38.2 and 38.9, and the absence of a quaternary carbon around δ 70.0 and a second carbonyl group, suggested that the caffeic acid moiety was not connected to quinic acid but to a cyclopentane-2,3-diol moiety.

The ^1H NMR of **1** (Table 1) revealed two aromatic protons appearing as doublets at δ 7.46 (J = 16.0 Hz, H-7′) and 6.16 (J = 16.0 Hz, H-8′), the coupling constant of which suggested that they were *trans*-oriented. The signals at δ 6.85 (J = 2.0; 8.0 Hz), 6.68 (J = 8.0 Hz), and 6.95 (J = 2.0 Hz) were assigned to the aromatic hydrogens of a 3′,4′-dihydroxylcinnamoyl group and exhibited chemical shifts similar to those of the corresponding protons in chlorogenic acid.[12] The presence of a caffeic acid moiety in **1** was confirmed from peaks at *m*/*z* 180 and 163 in the EIMS. The multiple signals at δ 5.23 (H-1) and 4.07 (H-3) together with the doublet of doublets at δ 3.62 (H-2) were attributed to three hydroxymethine hydrogens, while, on the basis of 1D correlation from the NOESY and COSY spectra, those at δ 1.98, 2.07 (H-4), 2.12 and 1.93 (H-5) could be assigned to the four protons of two methylene groups that completed a pentacyclic system. Individual irradiation of each hydrogen of the ring system permitted the observation of visible spatial correlations between H-1, H-2, and H-5, between H-2, H-1, and H-3, and between H-3, H-2, and H-4. On the basis of these correlations it was established that the oxymethine hydrogens were in the same plane. Moreover, the coupling constants of H-2 (J = 3.0; 3.0 Hz) suggested *cis* coupling between H-2, H-1, and H-7, and from the evidence thus available the relative configuration of **1** could be inferred (Figure 1).

Comparison of the spectroscopic data of **1** with literature values[6] revealed that compound **1** was an enantiomer of the compound previously described as 1-(3′,4′-dihydroxycinnamoyl)cyclopentane-2,3-diol. The absolute configuration of **1** could not be determined in a straightforward manner, since in addition to the flexibility of

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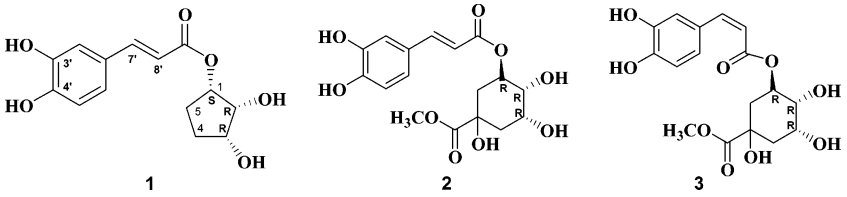


Figure 1. Structures of compounds **1**−**3**.

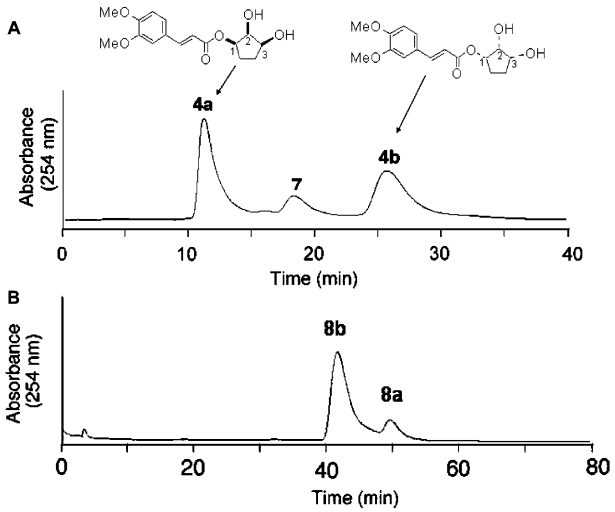


Figure 2. (A) Resolution of enantiomers **4** by Chiralcel OD column. Experimental conditions: eluent hexane/2-propanol (3:1), flow 1.0 mL min^{-1}, $\lambda = 254$ nm. (B) Resolution of enantiomers **8** by Chiralcel OD column. Experimental conditions: eluted with hexane/2-propanol (3:1), flow 1.0 mL min^{-1}, $\lambda = 254$ nm.

the cyclopentane-1,2,3-triol system, the CD of **1** exhibited no conspicuous extreme (Figure 3). Hence application of the CD exciton chirality method[10,11] was carried out.

The racemic analogues **4** were prepared by reacting *syn*-cyclopentane-1,2,3-triol (**5**)[9] with 1-(3′,4′-dimethoxycinnamoyl)-1,2,4-triazole (**6**) (Scheme 1) and resolved by chiral HPLC using a Chiralcel OD column and isocratic elution with hexane/2-propanol (3:1) (Figure 2). As shown in Figure 2, enantiomers **4a** and **4b** and the isomer **7** showed baseline separation under these conditions. When enantiomer **4b** was maintained in solution in the HPLC mobile phase for 12 h, 10% of enantiomer **4a** was generated (80% ee) possibly through two consecutive 1,2-migrations.

The CD spectra of enantiomers **4a** and **4b** were weak but distinct (Figure 3), with that of **4b** being very similar to the spectrum exhibited by the natural product **1**. The absolute configuration of enantiomer **4b** was therefore determined using the CD exciton chirality method.

To restrict the flexibility of the cyclopentane ring as well as to introduce a second chromophore that might couple with the 1-aromatic chromophore, the hydroxyl groups were converted into acetals by reaction with 4-biphenylcarboaldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) (Scheme 2). After stirring the reaction mixture for 10 h, substrate **4b** was completely consumed, giving rise to the racemic *endo* compounds **8** (60% yield) and the corresponding racemic *exo* isomer (15% yield). Interestingly, the 4-biphenyl group [UV (MeOH) λ_{max} ^1L_a band (log ϵ) ca. 260 nm (4.40)] stereoselectively approached **4b** from the concave face to give the *endo* adduct **8b** (60% yield) along with the enantiomeric *endo* adduct **8a** (15% yield), the latter being generated by transfer of 1-ArO to 2-ArO and then to 3-ArO (Scheme 2).

While the enantiomers were readily separated on a Chiralcel OD column (Figure 2), the CD spectra of neither **8a** nor **8b** exhibited clear-cut couplets between the 4-biphenyl and the 3′,4′-dimethoxycinnamoyl groups (Figure 4).

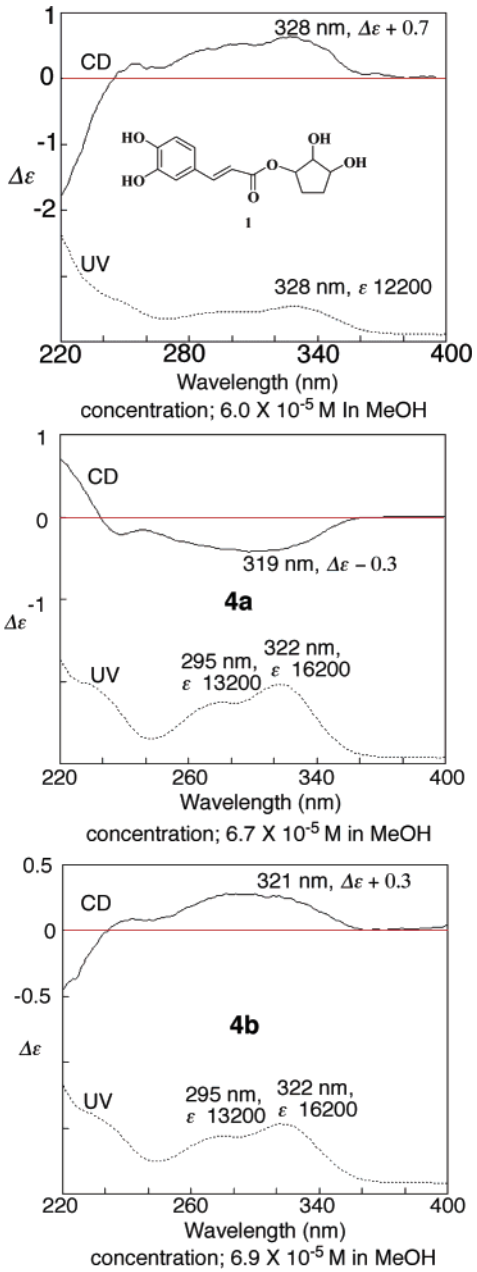


Figure 3. CD spectra of **1** and isomers **4a** and **4b**.

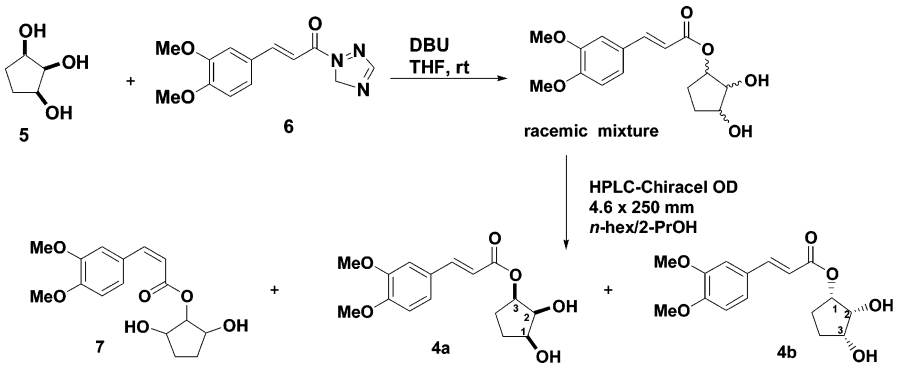
To overcome this problem, the 3,4-dimethoxycinnamoyl group was replaced with a *p*-bromobenzoate group [UV (MeOH) λ_{max} ^1L_a band (log ϵ) ca. 244 nm (4.29)], as outlined in Scheme 3.[11] The 3,4-dimethoxycinnamoyl group was readily removed by NaOMe in MeOH to give acetal **9b**, which was then reacted with *p*-bromobenzoyl chloride to yield the benzoate derivative **10b**. No racemization was observed during this transformation. The CD spectrum of **10b** (Figure 5A) exhibited two weak CD signals at 255 nm ($\Delta\epsilon$ −11.5) and 237 nm ($\Delta\epsilon$ +2.5) arising from exciton coupling. A negative couplet indicates negative helicity between the benzoate and the biphenyl chromophores corresponding to a (1*S*,2*R*,3*R*) configuration. The corresponding enantiomer **10a** gave

Table 1. ^{1}H and ^{13}C NMR Data for **1**[a]

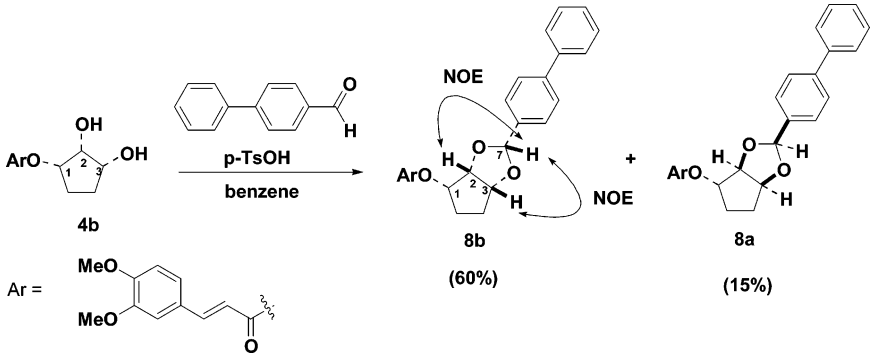
C	δ_C[b]	gHMQC δ_H	gHMBC	COSY	TOCSY	NOESY 1D	literature values[6] δ_C	literature values[6] δ_H, mult., J (Hz)
1′	127.6 s		H-7′; H-8′; H-5′				128.0	
2′	115.2 d	6.95 (J = 2.0 Hz)	H-6′; H-7′	6.95	6.95	7.46; 6.16; 6.68; 6.84	115.1	7.04 d (J = 1.8 Hz)
3′	149.5 s		H-2′; H-5′; H-6′				149.4	
4′	147.2 s		H-6′, H-5′; H-2′				146.8	
5′	116.5 d	6.68 d (J = 8.0 Hz)	H-7′; H-6′	6.85	6.85	6.68; 6.16; 7.46	116.5	6.76 d (J = 8.2 Hz)
6′	122.9 d	6.85 dd (J = 2.0; 8.0 Hz)	H-7′; H-2′; H-5′	6.68	6.68	6.16; 7.46; 6.68; 6.94	122.9	6.93 dd (J = 8.2; 1.8 Hz)
7′	146.8 d	7.46 d (J = 16.0 Hz)	H-6′; H-7′	6.16	6.16	6.16; 6.84; 6.94	146.8	7.58 d (J = 15.9 Hz)
8′	115.3 d	6.16 d (J = 16.0 Hz)	H-2′; H-6′	7.46	7.46	7.46; 6.84; 6.94	115.8	6.30 d (J = 15.9 Hz)
9′	168.7 s		H-7′; H-8′				169.0	
1	72.0 d	5.23 m	H-2	3.62; 2.12; 1.93	4.07; 3.62; 2.12; 1.93	2.12; 2.07; 3.62;	73.0	5.35 m
2	73.6 d	3.62 dd (J = 3.0; 3.0 Hz)		5.23; 4.07	5.23; 4.07; 2.12; 1.93	5.23; 4.07; 2.07; 1.98	74.8	3.64 dd (J = 8.3; 3.1 Hz)
3	71.5 d	4.07 m		2.07; 1.98; 3.62	5.23;3.62; 2.07; 1.98	3.62; 1.98; 2.07	68.3	4.14 m
4	38.2 t	2.07 m−1.98 m		4.07; 2.12	4.07; 2.12		36.7	2.15 m
5	38.9 t	2.12 m−1.93 m		1.93; 5.23	5.23; 3.62; 1.98		41.5	2.15 m; 1.95 m

[a] Spectra measured in CD_3OD at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR: ^{1}H NMR assignments were based on 2D NMR and HMQC correlations. [b] Internal standard TMS, δ_{TMS} = 0.00.

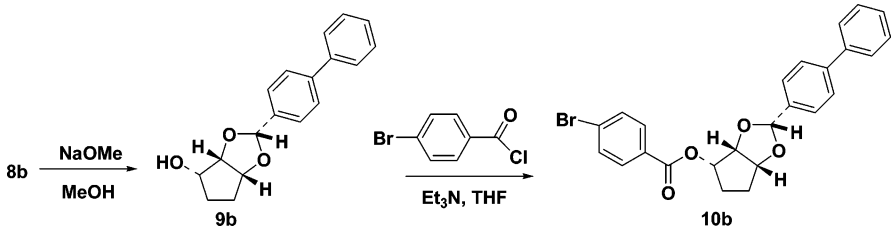
Scheme 1



Scheme 2



Scheme 3



an opposite split CD curve (Figure 5B). Comparison of the CD spectrum of naturally occurring **1** (Figure 3) with those of **10b** and **10a** (Figure 5) established the absolute configuration of **1** as (1*S*,2*R*,3*R*) (Figure 6).

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Nicolet FT-IR model EMACT-40 and a Perkin-Elmer 1600 FTIR spectrophotometer in the range 500−4000 cm^{-1}. ^{1}H NMR, ^{13}C NMR,

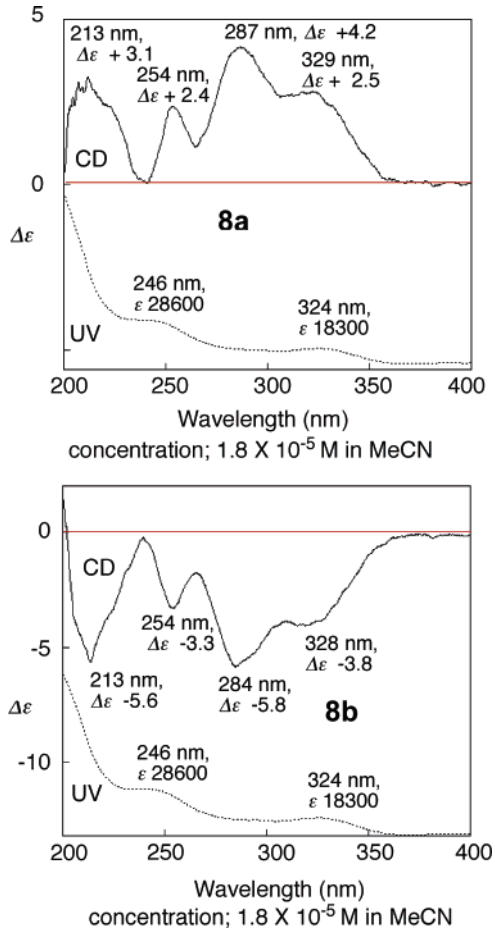


Figure 4. CD spectra of 8a and 8b.

gCOSY, gHMQC, gHMBC, TOCSY, and NOESY spectra were recorded on a Varian Unity 500 spectrometer at 25 °C and referenced to the residual solvent resonances of CD_3OD at δ 3.33 and 49.0, respectively, for ^1H and ^{13}C NMR using TMS as internal standard. EIMS spectra were obtained on a VG Platform Fisons mass spectrometer.

TLC was performed using precoated silica gel 60 PF_{254} plates (Merck): separated components were visualized under UV light and/or by spraying with anisaldehyde-H_2SO_4 reagent followed by heating at 120 °C. Column chromatography was carried out using a Pharmacia Sephadex LH-20 column (88.0 × 2.0 cm i.d.) eluted isocratically with MeOH. HPLC separations were performed on a Varian Prep Star Dynamax model SD-1 equipped with a Supelco C-18 semipreparative column (250 × 10 mm i.d.; 5 μm) or a Phenomenex ODS Luna 10 preparative column (250 × 21.20 mm; 5 μm) protected by a Phenomex ODS Luna 10 precolumn (50 × 10 mm i.d.; 5 μm). Components were detected using a Varian model 320 chromato-integrator connected to a UV detector set at 280 nm.

Synthetic reactions were carried out under an atmosphere of argon in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. UV−visible spectra were measured at 25 °C on a Perkin-Elmer Lambda 40 spectrophotometer, and CD spectra were recorded on a Jasco-810 spectrophotometer. ^1H NMR spectra were determined on a Bruker DPX-300 spectrometer and referenced to the residual proton solvent resonances of CD_3OD at δ 3.30 ppm. Low- and high-resolution FABMS were measured on a JEOL JMS-DX303 HF mass spectrometer using a glycerol matrix and Xe ionizing gas.

HPLC analyses and the preparation and resolution of synthetic compounds were performed using a Shimadzu separation HPLC (Shimadzu, Kyoto, Japan), which consisted of the two LC 10 AD VP pumps, a UV−vis detector (SPD-M10AV VP), and manual sampler equipped with a Dicel Chiralcel OD column (250 × 4.6 mm i.d.; 10 μm): the mobile phase was *n*-hexane/2-propanol at a flow rate of 1 mL/min and detection at 254 nm.

Plant Material. Leaves of *Chimarrhis turbinata* DC. Prodr. were collected in the Reserva do Viro, Belém, PA, Brazil, in February 2000, and identified by Dr. Marina Thereza V. do A. Campos from Botanic Garden Institute. A voucher specimen was deposited in the Herbarium of the Botanic Garden Institute, São Paulo, Brazil, with voucher code Lopes-51.

Extraction and Isolation of Phenolics. Dried and powdered leaves of *C. turbinata* (1.2 kg) were extracted with EtOH to afford 57.12 g of dry residue, which was dissolved in MeOH/H_2O (8:2) and partitioned with *n*-hexane. The aqueous alcoholic fraction was evaporated to roughly MeOH/H_2O (6:4) and then extracted successively with CH_2Cl_2, EtOAc, and *n*-BuOH. The dried EtOAc extract (4.16 g) was dissolved in MeOH (5 mL) and submitted to gel filtration over Sephadex LH-20. A total of 25 fractions of 25 mL each were collected and pooled according to their TLC profiles ($CHCl_3$/MeOH/H_2O, 65:30:5). Fractions A-6/7 and A-8 to A-12 showed antioxidant activities and were further purified by HPLC. Fractions A-8 to A-12 yielded the compounds described elsewhere.[5]

Fraction A-6/7 (599.0 mg) was purified by gel filtration over Sephadex LH-20. Thirty-six fractions of 10 mL each were collected and pooled according to their TLC profiles ($CHCl_3$/MeOH/H_2O, 65:30:5). Fractions 20−30 showed antioxidant activity and were pooled and purified by preparative HPLC (isocratic elution; H_2O/MeCN, 82:12; 12.0 mL/min flow rate) to afford 10 subfractions. Subfraction B-3 (97.2 mg) was purified by preparative HPLC (isocratic elution; H_2O/MeCN, 85:15; 12.0 mL/min flow rate) to yield 18 fractions; fraction 12 (8.8 mg) was identified as compound **1**. Subfraction B-4 (17.2 mg) was purified by semipreparative HPLC (isocratic elution; H_2O/MeCN, 80:20; 10.0 mL/min flow rate) to yield compounds **2** (8.0 mg) and **3** (2.3 mg). The EIMS of **2** and **3** presented pseudomolecular ions at *m*/*z* 369 $[M + H]^+$, 391 $[M + Na]^+$, and 407 $[M + K]^+$ and fragment ions at *m*/*z* 163. The ^1H and ^{13}C NMR spectra of **2** and **3** were identical to the published data for chlorogenic acid methyl ester with *trans* and *cis* relative configurations, respectively.[12]

Synthesis of 1-(3′,4′-Dimethoxycinnamoyl)cyclopentane-2,3-diol (4). To a solution of cyclopentane-1,2,3-triol (**5**; 5.7 mg; 48 μmol) in tetrahydrofuran (THF; 1.5 mL), maintained at room temperature under argon, were added 1-(3′,4′-dimethoxycinnamoyl)-1,2,4-triazole (**6**; 11 mg, 41 μmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 16 mg, 100 μmol), and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by TLC (EtOAc) and by HPLC (isocratic elution; *n*-hexane/2-PrOH, 75:25) to give **4a** (4.4 mg; 30% yield; t_R 11 min) and **4b** (4.4 mg; 30% yield; t_R 26 min) as colorless oils: UV (MeOH) λ_{max} (log ϵ) 322 (4.21), 295 (4.12) nm; ^1H NMR (CD_3OD, 300 MHz) δ 7.67 (1H, d, J = 16 Hz), 7.21−7.16 (2H, m), 6.97 (1H, d, J = 8.3 Hz), 6.45 (1H, d, J = 16 Hz), 5.11−5.09 (1H, m), 4.11−4.08 (1H, m), 4.02 (1H, t, J = 4.6 Hz), 3.86 (6H, s), 2.01−1.82 (4H, m); HRFABMS *m*/*z* 308.1256 (calcd for $C_{16}H_{20}O_6$, 308.1260).

Synthesis of 1-(3′,4′-Dimethoxycinnamoyl)-2,3-[(4′-biphenyl)methylenedioxy]cyclopentane (4′ endo) (8b). To a solution of **4b** (2.0 mg; 6.5 μmol) in benzene (0.3 mL) maintained at room temperature under argon was added 4-biphenylcarboxaldehyde (5.3 mg; 29 μmol) and *p*-TsOH monohydrate (50 μg; 0.5 μmol) and the mixture stirred for 2 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by TLC (*n*-hexane/EtOAc, 2:1) and by HPLC (isocratic elution; *n*-hexane/2-PrOH, 95:5) to give **8b** (1.4 m; 46% yield; t_R 42 min) and **8a** (0.4 mg; 13% yield; t_R 50 min) as colorless oils: UV (MeCN) λ_{max} (log ϵ) 324 (4.26), 246 (4.46) nm; ^1H NMR (CD_3OD, 300 MHz) δ 7.68−7.55 (7H, m), 7.45−7.41 (2H, m), 7.37−7.33 (1H, m), 7.08−7.03 (2H, m), 6.82 (1H, d, J = 8.3 Hz), 6.37 (1H, d, J = 16 Hz), 5.80 (1H, s), 4.97−4.92 (1H, m), 4.79 (1H, t, J = 5.4 Hz), 4.74 (1H, t, J = 5.4 Hz), 3.89 (3H, s), 3.86 (3H, s), 2.21−2.04 (3H, m), 1.69−1.62 (1H, m); HRMS *m*/*z* 472.1885 (calcd for $C_{29}H_{28}O_6$, 472.1886).

Synthesis of 1,2-[(4′-Biphenyl)methylenedioxy]cyclopentane-3-ol (4′ endo) (9b). To a solution of **8b** (1.4 mg; 3.0 μmol) in MeOH/$CHCl_3$ (1:1; 0.2 mL) maintained at room temperature was added 2.5 M NaOMe/MeOH (30 μL), and the mixture was stirred for 6 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by TLC (*n*-hexane/EtOAc, 2:1) to give **9b** (0.80 mg; 95% yield) as a colorless oil: UV (MeCN) λ_{max} (log ϵ) 252 (4.19) nm; ^1H NMR (CD_3OD, 300 MHz) δ 7.62−7.56 (6H, m), 7.45−7.23 (3H, m), 5.81 (1H, s), 4.69 (1H, t, J = 5.5 Hz), 4.50 (1H, t, J = 5.4 Hz), 4.02−3.92 (1H, m), 2.34 (1H, d, J = 10 Hz), 2.07−1.94 (2H, m), 1.88−1.76 (1H, m), 1.59−1.47 (1H, m); HRMS *m*/*z* 283.1333 (calcd for $C_{18}H_{18}O_3$,

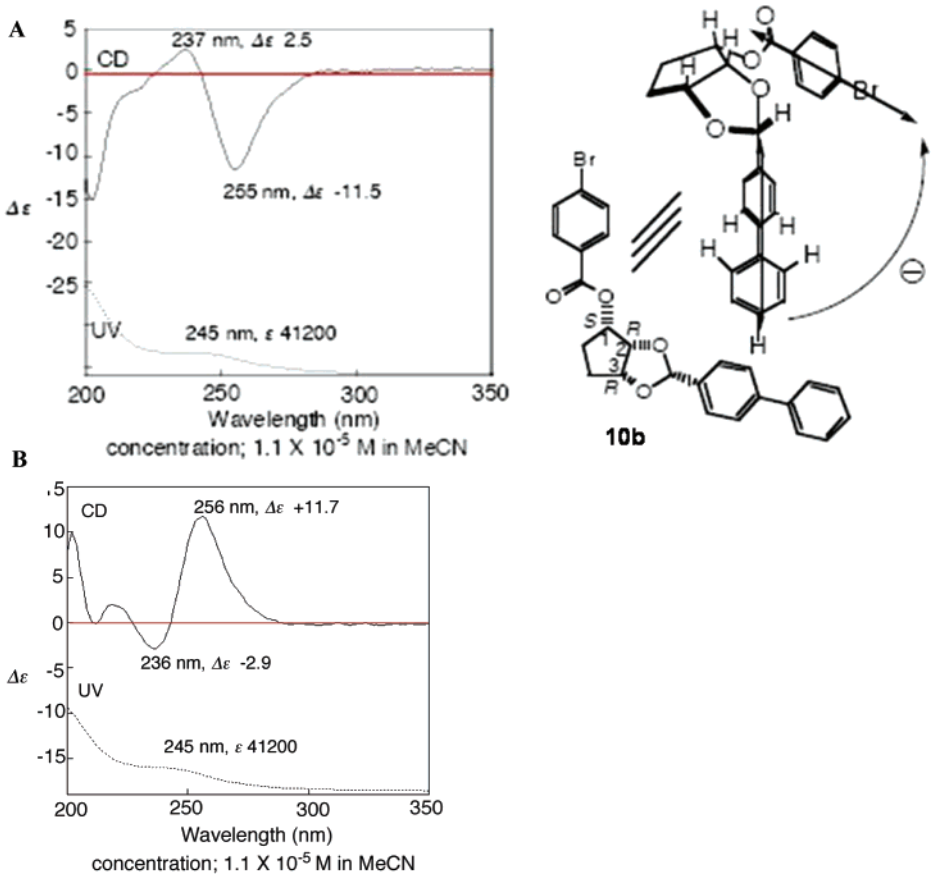


Figure 5. (A) CD spectrum of **10b** and assignment of absolute configuration. (B) CD spectrum of **10a**.

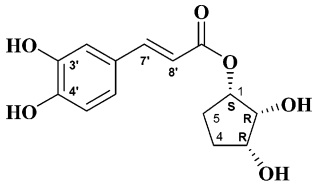


Figure 6. Absolute configuration of compound **1**.

283.1334). The enantiopurity was checked by HPLC (isocratic elution; *n*-hexane/2-PrOH, 85:15; t_R 8 min).

Synthesis of 1-(*p*-Bromobenzoyl)-2,3-[(4′-biphenyl)methylene-dioxy]cyclopentane (4′ endo) (10b). To a solution of **9b** (0.80 mg; 2.8 μmol) in THF (0.1 mL) maintained at room temperature were added *p*-bromobenzoyl chloride (3.0 mg; 14 μmol) and triethylamine (10 μL), and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by TLC (*n*-hexane/EtOAC, 3:1) to give **10b** (0.64 mg; 49%) as a colorless oil: UV (MeCN) λ_{max} (log ϵ) 245 (4.61) nm; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.91−7.88 (2H, m), 7.61−7.31 (11H, m), 5.79 (1H, s), 5.04−4.97 (1H, m), 4.84 (1H, t, J = 5.4 Hz), 4.75 (1H, t, J = 5.4 Hz), 2.32−2.04 (3H, m), 1.73−1.62 (1H, m); HRMS *m*/*z* 463.0550 (calcd for $C_{25}H_{22}{}^{79}BrO_4$, 463.0545). The enantiopurity was checked by HPLC (isocratic elution; *n*-hexane/2-PrOH, 99:1; t_R 27 min).

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