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Determination of the Absolute Configurations of Pharmacological Natural Products via Density Functional Theory Calculations of Vibrational Circular Dichroism: The New Cytotoxic Iridoid Prismatomerin

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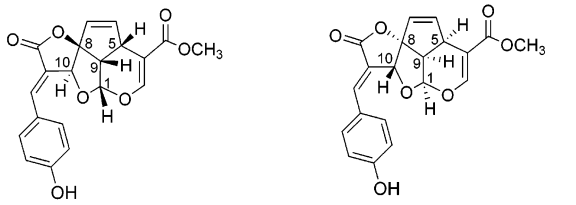
THE ABSOLUTE CONFIGURATION OF THE CYTOTOXIC IRIDOID NATURAL PRODUCT PRISMATOMERIN, **3**, IS

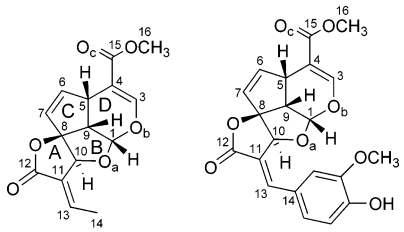


(-)-(1R,5S,8S,9S,10S)-**3** OR (-)-(1S,5R,8R,9R,10R)-**3** ?

A new highly cytotoxic iridoid has very recently been isolated from *Prismatomeris tetrandra* and shown to have the structure **3**, similar to that of the iridoid oruwacin, **2**. We report the determination of the absolute configuration (AC) of the new iridoid, prismatomerin, using vibrational circular dichroism (VCD) spectroscopy. The VCD spectrum of the acetate derivative of **3**, **4**, is analyzed using the Stephens theory of VCD and density functional theory (DFT). The AC of the naturally occurring **3** is shown to be 1*R*,5*S*,8*S*,9*S*,10*S*, identical to that of the naturally occurring iridoid plumericin, **1**, also determined using VCD spectroscopy. The $[\alpha]_D$ values of the natural products **3** and **1** are negative and positive, respectively. Since the ACs of **3** and **1** are identical, it follows that the AC of **3** cannot be correctly determined by empirical comparison of the signs of the $[\alpha]_D$ values of **3** and **1**.

Introduction

More than 200 iridoids have to date been found to occur in nature.[1] Examples of iridoid natural products are plumericin, **1**, and oruwacin, **2**:



(1*R*,5*S*,8*S*,9*S*,10*S*)-**1** (1*R*,5*S*,8*S*,9*S*,10*S*)-**2**

Plumericin was first isolated from the roots of the plant *Plumeria multiflora* by Little and Johnstone in 1951[2] and was shown to be optically active, with $[\alpha]_D = +204$ ($CHCl_3$), and

(1) (a) Bianco, A. The Chemistry of Iridoids. In *Studies in Natural Products Chemistry: Structure and Chemistry, Part A*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1990; Vol. 7, pp 439−497. (b) Bianco, A. *Pure Appl. Chem.* **1994**, *66*, 2335−2338. (c) AlHazimi, H. M. G.; Alkhathlan, H. Z. *J. Chem. Soc. Pakistan* **1996**, *18*, 336−357. (d) Franzyk, H. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: Berlin, 2000; pp 1−114.

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TABLE 1. Relative Energies,[a] Relative Free Energies,[a] and Key Dihedral Angles[b] of the Conformations of (1*R*,5*S*,8*S*,9*S*,10*S*)-1

	MMFF94				B3LYP/6-31G*					
conformer	ΔE	D1	D2	D3	ΔE	ΔG	P^c (%)	D1	D2	D3
A	0.00	177.33	−25.16	−22.63	0.00	0.00	59.26	171.92	−22.13	−20.52
B	0.49	−1.34	−25.19	−22.73	0.35	0.39	30.67	−5.73	−22.12	−20.62
C	1.07	−160.88	18.86	28.72	0.94	1.22	7.55	−173.14	23.12	27.22
D	1.80	20.66	17.60	27.60	1.55	1.87	2.52	6.85	22.54	26.53

[a] ΔE and ΔG in kcal/mol. [b] D1: dihedral angle C3C4C15O_c. D2: dihedral angle C8C9C1O_a. D3: dihedral angle C5C9C1O_b. Dihedral angles in degrees. [c] Derived from the ΔG values at $T = 298.15$ K.

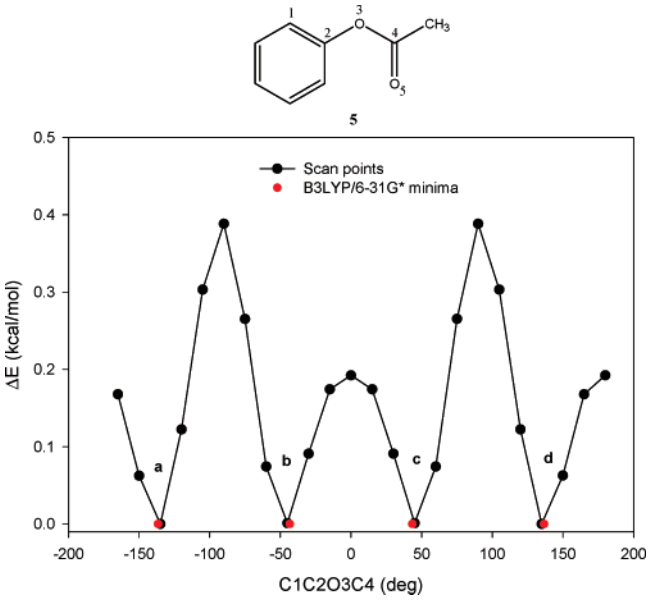

FIGURE 1. B3LYP/6-31G* PES scan of **5**. The dihedral angle C1C2O3C4 was varied in 15° intervals.

to exhibit antifungal and antibacterial activity. In 1960−1961, Albers-Schönberg and Schmid[3] isolated plumericin from the roots of *Plumeria rubra* var. *alba* and, on the basis of chemical and spectroscopic studies, assigned its structure as (1*R*,5*S*,8*S*,9*S*,-10*S*)-**1**. Subsequently, total synthesis of racemic **1** was reported by Trost and co-workers,[4] and the X-ray crystal structure was reported by Elsässer et al.;[5] both studies supported the structure assigned by Albers-Schönberg and Schmid, but neither confirmed nor disproved the absolute configuration (AC) assigned. However, analysis of the electronic circular dichroism (ECD) of plumericin by Elsässer et al.[5] led to the conclusion that the AC of plumericin is the opposite to that assigned by Albers-Schönberg and Schmid, (1*S*,5*R*,8*R*,9*R*,10*R*)-(+). This surprising result led us, very recently, to redetermine the AC of plumericin by comparison of density functional theory (DFT) calculations of its vibrational circular dichroism (VCD), ECD, and optical rotation (OR) to its experimental VCD, ECD, and OR.[6] Both the VCD and the OR of plumericin led to the unambiguous conclusion that its AC is in fact (1*R*,5*S*,8*S*,9*S*,10*S*)-(+), the AC initially assigned by Albers-Schönberg and Schmid.

TABLE 2. Relative Energies and Key Dihedral Angles of the Conformations of 5 at the B3LYP/6-31G* Level

conformer	ΔE^a	C1C2O3C4	C2O3C4O5
a	0.00	−136.63	−0.34
b	0.00	−47.54	0.41
c	0.00	47.32	−0.40
d	0.00	136.65	0.35

[a] In kcal/mol.

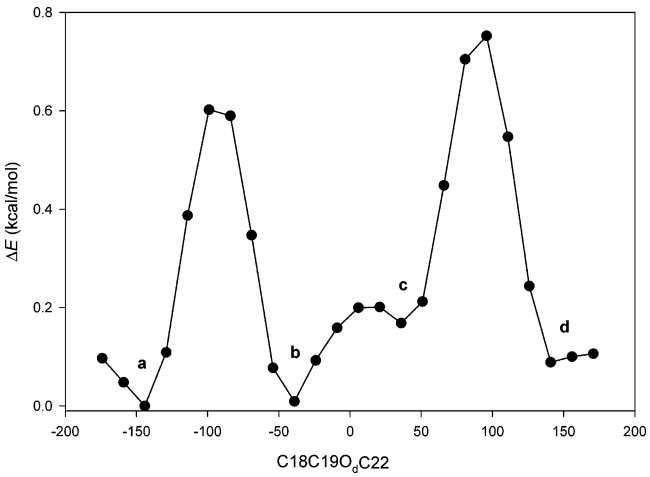

FIGURE 2. B3LYP/6-31G* PES scan of conformation **A** of (1*R*,5*S*,8*S*,9*S*,10*S*)-**4**. The dihedral angle C18C19O$_d$C22 was varied in 15° intervals.

The iridoid oruwacin was first isolated by Adesogan from the plant *Morinda lucida*[7] and the structure **2** assigned on the basis of chemical and spectroscopic studies. The similarity of the $[\alpha]_D$ of oruwacin, +193 ($CHCl_3$), to that of plumericin led Adesogan to propose that the AC of **2** is the same as that of **1**. Subsequently, oruwacin was shown to be biologically active, specifically molluscicidal.[8]

Very recently, a new iridoid, named prismatomerin, has been isolated from the plant *Prismatomeris tetrandra* (Roxb) K. Schum, belonging to the family Rubiaceae.[9] The leaves of *P. tetrandra* have been used in traditional folk medicine for the treatment of several ailments, including stomachaches and

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(7) Adesogan, E. K. *Phytochemistry* **1979**, *18*, 175−176.
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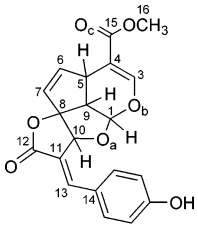
TABLE 3. Relative Energies,[a] Relative Free Energies,[a] Key Distances,[b] and Key Dihedral Angles[b] of the Conformations of (1*R*,5*S*,8*S*,9*S*,10*S*)-4

	B3LYP/6-31G*			B3LYP/TZ2P			B3PW91/TZ2P			B3LYP/6-31G*						
conformer	ΔE	ΔG	P^c (%)	ΔE	ΔG	P^c (%)	ΔE	ΔG	P^c (%)	R1	R2	D1	D2	D3	D4	D5
Aa	0.00	0.00	18.38	0.02	0.00	21.57	0.03	0.03	20.24	10.09	9.28	171.90	−21.96	−20.48	−144.11	21.01
Ab	0.01	0.10	15.50	0.00	0.05	19.88	0.00	0.00	21.27	8.30	7.18	171.93	−22.24	−20.75	−41.94	20.83
Ac	0.17	0.05	16.98	0.18	0.18	16.02	0.18	0.22	14.68	8.07	7.57	171.46	−22.59	−21.18	39.73	20.46
Ad	0.09	0.12	14.89	0.13	0.10	18.25	0.13	0.09	18.18	9.93	9.60	171.60	−22.35	−20.90	146.27	20.55
Ba	0.35	0.50	7.91	0.66	0.74	6.15	0.62	0.72	6.25	10.08	9.28	−5.79	−22.33	−20.95	−144.65	20.89
Bb	0.40	0.67	5.93	0.69	0.88	4.88	0.64	0.80	5.48	8.31	7.20	−5.92	−22.44	−21.06	−42.48	20.55
Bc	0.55	0.67	5.91	0.83	0.92	4.54	0.79	0.94	4.36	8.09	7.60	−5.58	−22.67	−21.31	40.80	20.60
Bd	0.41	0.48	8.12	0.75	0.81	5.51	0.71	0.77	5.83	9.95	9.61	−5.66	−22.56	−21.22	146.76	20.50
Ca	1.49	1.64	1.16	1.95	2.04	0.69	1.87	1.96	0.78	9.33	9.96	−172.59	23.43	27.10	−145.51	14.34
Cb	1.51	1.49	1.48	1.94	1.77	1.08	1.86	1.76	1.08	8.23	8.20	−172.62	23.41	27.05	−41.66	13.85
Cc	1.62	1.66	1.11	2.05	1.94	0.81	1.97	1.84	0.95	7.51	7.58	−172.96	23.47	27.19	40.81	13.58
Cd	1.52	1.63	1.18	1.99	2.10	0.62	1.90	1.87	0.90	8.71	9.47	−172.90	23.49	27.16	145.06	13.52
Da	2.07	2.26	0.40							9.30	9.94	7.82	23.23	26.77	−145.90	13.73
Db	2.13	2.23	0.43							8.22	8.20	7.50	23.06	26.56	−42.44	13.59
Dc	2.26	2.50	0.27							7.49	7.57	7.46	22.99	26.56	41.41	13.34
Dd	2.11	2.35	0.35							8.71	9.47	7.46	23.15	26.70	146.02	13.04

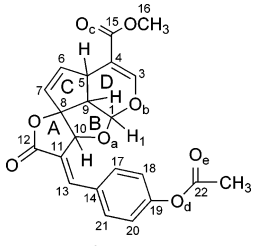
[a] ΔE and ΔG in kcal/mol. [b] Distances in Å: R1 = O_e−H1; R2 = O_e−O_b. Dihedral angles in degrees: D1 = C3C4C15O_c; D2 = C8C9C1O_a; D3 = C5C9C1O_b; D4 = C18C19O_dC22; D5 = C11C13C14C17. [c] Derived from the ΔG values at T = 298.15 K.

wounds. The biological activity of prismatomerin has been investigated and remarkable antitumor activity observed.[9] Spectroscopic analysis of prismatomerin, especially 2D NMR studies, showed its structure to be **3**, similar to that of oruwacin, **2**. In addition, the relative configuration of **3** was shown to be identical to that of plumericin, **1**.



3

The specific rotation, $[\alpha]_D$, of **3** is −136 (EtOH),[9] opposite in sign to that of **1** and **2**, suggesting that the AC of **3** might be the opposite of the ACs of **1** and **2**. However, this conclusion is not definitive, since the assignment of ACs on the basis of comparison of the signs of specific rotations of chemically related molecules is not 100% reliable. Accordingly, we have determined the AC of **3** using VCD spectroscopy. Since, at the concentrations typically used in the measurement of experimental VCD spectra, molecules with OH groups exhibit intermolecular aggregation, we have studied the VCD of the acetate derivative of **3**, **4**, to minimize intermolecular aggregation.



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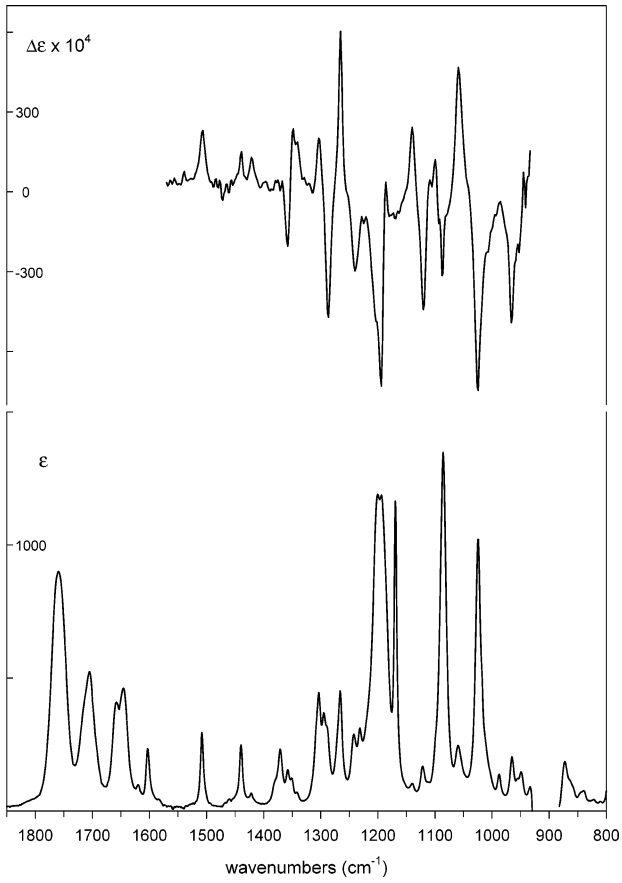

FIGURE 3. Experimental IR and VCD spectra of a 0.03 M $CDCl_3$ solution of (−)-**4**; path length 239 μm.

We here report the determination of the AC of **4** by comparison of DFT calculations of the VCD spectra of its two enantiomers to the experimental VCD spectrum. Since the AC of **4** is the same as that of **3**, the AC of **3** is simultaneously determined.

Methods

Prismatomerin, **3**, was isolated from *P. tetrandra* leaves and bark and converted to the acetate derivative, **4**, as described previously.[9]

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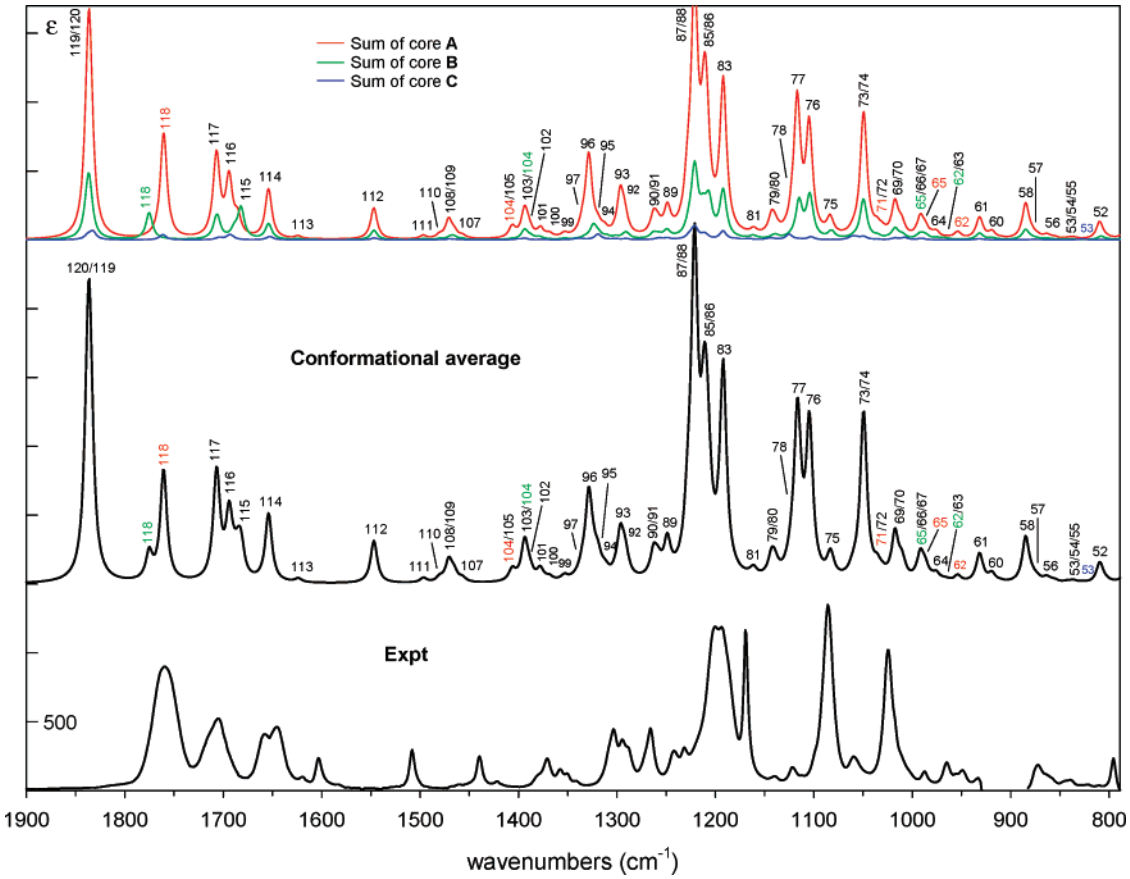

FIGURE 4. Comparison of experimental and B3PW91/TZ2P IR spectra of **4**. The top spectra are the sums of the population-weighted spectra of the conformations with the same core conformation. The middle spectrum is the fully conformationally averaged IR spectrum. Lorentzian bandwidths, $\gamma = 4.0$ cm^{-1}. The red, green, and blue numbers indicate bands from conformations **Aa**−**d**, **Ba**−**d**, and **Ca**−**d**, respectively; the black numbers indicate bands from conformations **Aa**−**d** and **Ba**−**d**.

The specific rotations of **3** and **4** are −136 (*c* 0.01, EtOH) and −98.3 (*c* 0.6, $CHCl_3$), respectively.[9]

The IR and VCD spectra of a 0.03 M solution of **4** in $CDCl_3$ were measured using a Thermo-Nicolet Nexus 670 IR spectrometer and a Bomem/BioTools ChiralIR VCD spectrometer, at resolutions of 1 and 4 cm^{-1}, respectively, and a cell with KBr windows and path length 239 μm.

All DFT calculations of the conformational structures, energies and free energies of **4** and the harmonic vibrational frequencies, dipole strengths and rotational strengths of the conformations of **4** were carried out using GAUSSIAN 03.[10]

Harmonic vibrational rotational strengths were calculated using the Stephens equation[11] and GIAO basis sets[12] (which guarantee origin-independent rotational strengths). IR and VCD spectra were obtained from vibrational frequencies, dipole strengths, and rotational strengths using Lorentzian bandshapes.[13]

Results

Conformational Analysis. The conformational analysis of plumericin, **1**, was carried out initially using Monte Carlo searching together with the MMFF94 molecular mechanics force field, via the SPARTAN 02 program.[6] Four conformations, **A**, **B**, **C**, and **D**, with energies within a 10 kcal/mol window, resulted. The relative energies and key dihedral angles of the four conformations are given in Table 1. Subsequently, the four MMFF94 conformations were optimized using DFT at the B3LYP/6-31G* level, giving the relative energies and dihedral angles in Table 1. Calculation of the harmonic vibrational frequencies of the DFT conformations confirmed their stability and led to the relative free energies in Table 1. Using Boltzmann statistics, the relative free energies permit the prediction of the room-temperature populations, given in Table 1.

The principal variations in the structures of conformations **A**−**D** of **1** are associated with rings B and D and the methoxycarbonyl substituent of ring D. In conformations **1A** and **1C**, the methoxycarbonyl group is oriented with the C═O group in the s-trans conformation with respect to the C3═C4 group, while **1B** and **1D** have the s-cis conformation. In conformations **1A** and **1B**, rings B and D have the same conformations, while in conformations **1C** and **1D** the O atoms of these rings are oppositely puckered. In all conformations **1A**−**1D**, the methyl group and the carbonyl O of the methoxycarbonyl sustituent of ring D are cis.

In prismatomerin acetate, **4**, the C14 methyl group of plumericin is replaced by a phenyl acetate group. In order to define the number, relative energies and structures of the conformations of phenyl acetate, **5**, we have carried out a 1D

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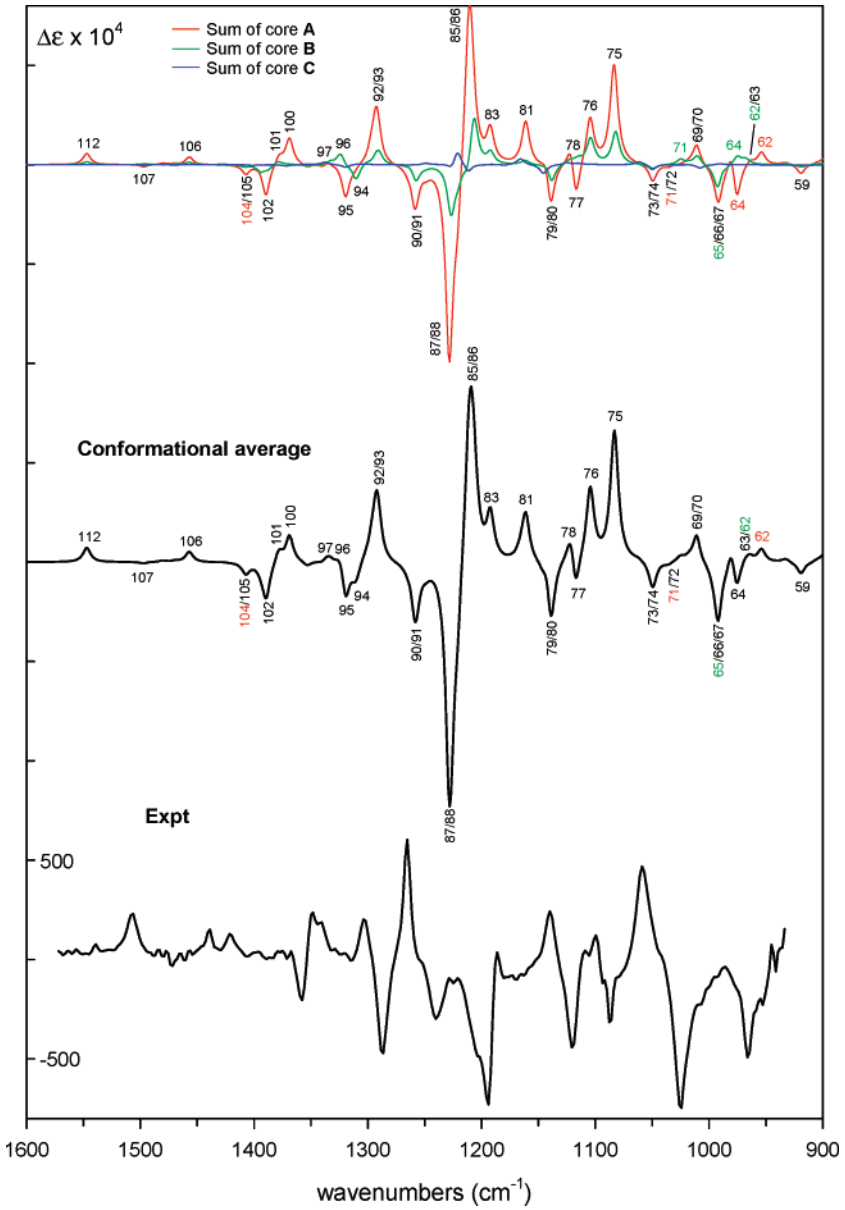


FIGURE 5. Comparison of experimental and B3PW91/TZ2P VCD spectra of **4**. The experimental spectrum is for (−)-**4**. The calculated spectra are for (1*R*,5*S*,8*S*,9*S*,10*S*)-**4**. The top spectra are the sums of the population-weighted spectra of the conformations with the same core conformation. The middle spectrum is the fully conformationally averaged VCD spectrum. Lorentzian bandwidths, $\gamma = 4.0$ cm^{-1}. The red and green numbers indicate bands from conformations **Aa**−**d** and **Ba**−**d**, respectively; the black numbers indicate bands from conformations **Aa**−**d** and **Ba**−**d**.

potential energy surface (PES) scan as a function of the dihedral angle C1C2O3C4, using DFT, at the B3LYP/6-31G* level. (The C4═O5 and C2O3 bonds are cis; the trans orientation is much higher in energy.) The results, shown in Figure 1, demonstrate the existence of four conformations **a**−**d**. Optimization of the structures of these conformations leads to the relative energies and C1C2O3C4 dihedral angles given in Table 2. All four conformations are of equal energy. Surprisingly, conjugation of the acetate and phenyl moieties does not lead to coplanar conformations.

It can be anticipated from the conformational analysis of **1** and **5** that prismatomerin acetate, **4**, will exhibit 16 conformations, each having one of the four conformations **A**−**D** of **1** and one of the four conformations **a**−**d** of **5**. In order to evaluate this expectation, we have replaced the C14 methyl group of conformation **A** of **1** by a phenyl acetate group and carried out a 1D B3LYP/6-31G* PES scan as a function of the C18C19O$_d$-C22 dihedral angle, with the results shown in Figure 2. While quantitatively different from the PES scan of **5**, four conformations, **a**−**d**, are again predicted. Optimization of these four conformations of **4** and harmonic frequency calculations lead to the relative energies, relative free energies, and key dihedral angles given in Table 3. The relative energies and free energies vary by <0.2 kcal/mol. The dihedral angles given in Table 3 are very similar to those of conformation **A** of **1** and conformations **a**−**d** of **5** in Tables 1 and 2.

Combining the four phenyl acetate conformations **a**−**d** of conformations **Aa**, **Ab**, **Ac**, and **Ad** of **4** with the conformations **B**, **C**, and **D** of **1** then leads to 12 additional conformations of **4**, with the relative energies, relative free energies, and key dihedral angles given in Table 3. As anticipated, the dihedral angles of these conformations of **4** are very similar to those of

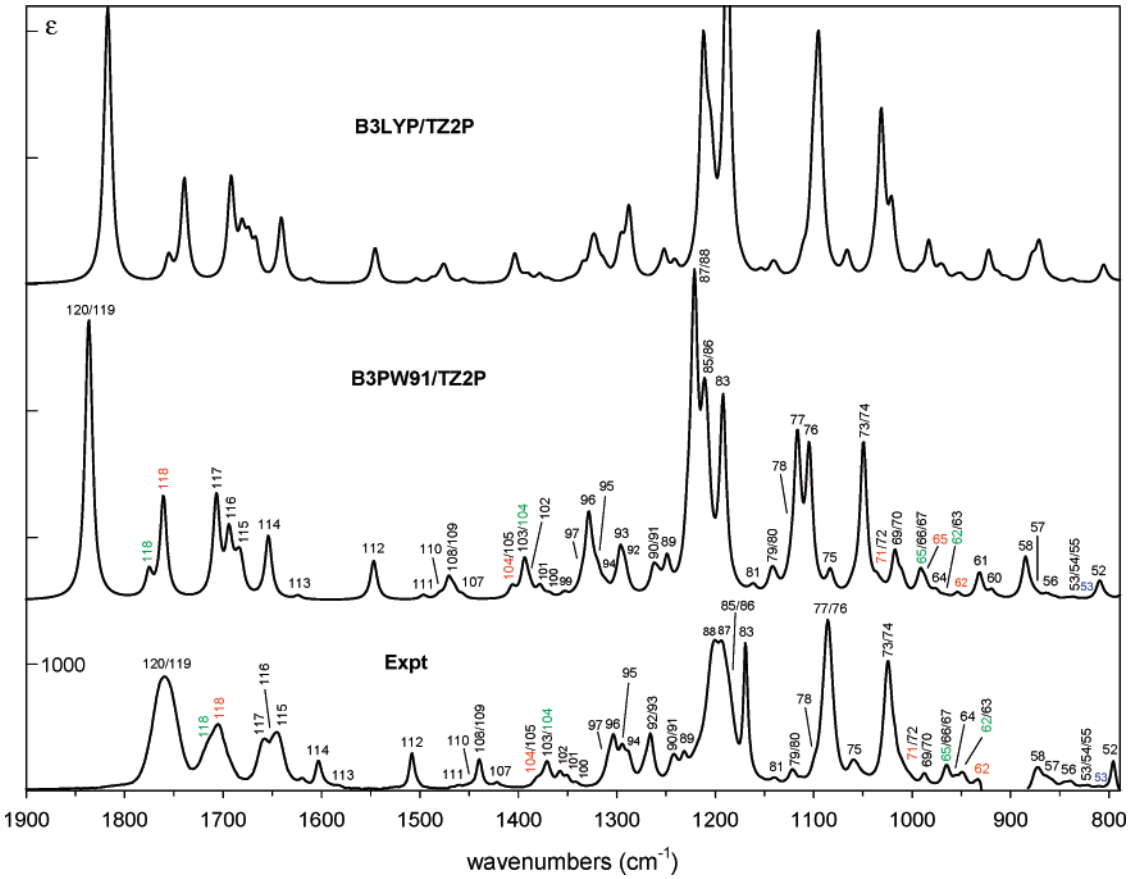


FIGURE 6. Comparison of experimental and calculated IR spectra of **4**. The calculated spectra are conformationally averaged and simulated using Lorentzian bandshapes ($\gamma = 4.0$ cm^{-1}). The red, green, and blue numbers indicate bands from conformations **Aa**−**d**, **Ba**−**d**, and **Ca**−**d** respectively; the black numbers indicate bands from conformations **Aa**−**d** and **Ba**−**d**.

the corresponding conformations of **1** and **5**. The predicted populations of the conformations **Da**, **Db**, **Dc**, and **Dd** are all <1%, leading to the conclusion that these conformations should not contribute significantly to the experimental IR and VCD spectra of **4**.

The 12 conformations having the plumericin conformations **A**, **B**, and **C** have been reoptimized at the B3LYP/TZ2P and B3PW91/TZ2P levels and their harmonic frequencies calculated; the relative energies, relative free energies, and room-temperature populations obtained are given in Table 3.

IR and VCD Spectra. The mid-IR IR and VCD spectra of a 0.03 M solution of **4** in $CDCl_3$ over the range 800−1850 cm^{-1} are shown in Figure 3.

The harmonic frequencies, dipole strengths, and rotational strengths of the 12 conformations of (1*R*,5*S*,8*S*,9*S*,10*S*)-**4**, **Aa-d**, **Ba-d**, and **Ca-d**, have been calculated using DFT at the B3LYP/TZ2P and B3PW91/TZ2P levels, with the results given in Table 1 of the Supporting Information. The IR and VCD spectra obtained thence, using Lorentzian bandshapes, are shown in Figures 1−4 of the Supporting Information. In the case of the IR spectra, over the range 1900−800 cm^{-1} the spectra vary with the conformations **A**, **B**, and **C** but are insensitive to the conformations **a**−**d**. In contrast, for conformations **A**, **B**, and **C** the VCD spectra are sensitive to the conformations **a**−**d**, especially in the regions ∼1200 and ∼1800 cm^{-1}.

The sums of the population-weighted B3PW91/TZ2P IR and VCD spectra of the conformations **Aa-d**, **Ba-d**, and **Ca-d** are shown in Figures 4 and 5, together with the conformationally averaged IR and VCD spectra of all 12 conformations and the experimental IR and VCD spectra. The fully conformationally averaged spectra are dominated by the contributions of the conformations **Aa-d** and **Ba-d**. In Figures 6 and 7, the conformationally averaged B3PW91/TZ2P and B3LYP/TZ2P IR and VCD spectra are compared to the experimental IR and VCD spectra. The B3PW91 spectra are in better agreement with experiment than the B3LYP spectra. Accordingly, the assignments of the experimental spectra are based on the B3PW91/TZ2P calculated spectra, as detailed in Table 1 of the Supporting Information and Figures 6 and 7.

The qualitative agreement of the calculated VCD spectrum for (1*R*,5*S*,8*S*,9*S*,10*S*)-**4** and the experimental VCD spectrum of (−)-**4** leads to the conclusion that the AC of **4** is (1*R*,5*S*,8*S*,9*S*,-10*S*)-(−). Further support for this conclusion is provided by the comparison of the calculated VCD spectra of the two enantiomers of **4** to the experimental VCD spectrum of (−)-**4**, shown in Figure 8.

To further support the assignment of the AC of **4**, we have quantitatively compared the predicted B3PW91/TZ2P conformationally averaged rotational strengths of the two enantiomers of **4** to the experimental rotational strengths of (−)-**4**, obtained by Lorentzian fitting of the experimental VCD spectrum, with the results given in Table 1 of the Supporting Information, as shown in Figure 9. With the exception of the rotational strengths of modes 73/74 and 85/86, the rotational strengths calculated for (1*R*,5*S*,8*S*,9*S*,10*S*)-**4** are in very good quantitative agreement with the experimental rotational strengths, while the rotational

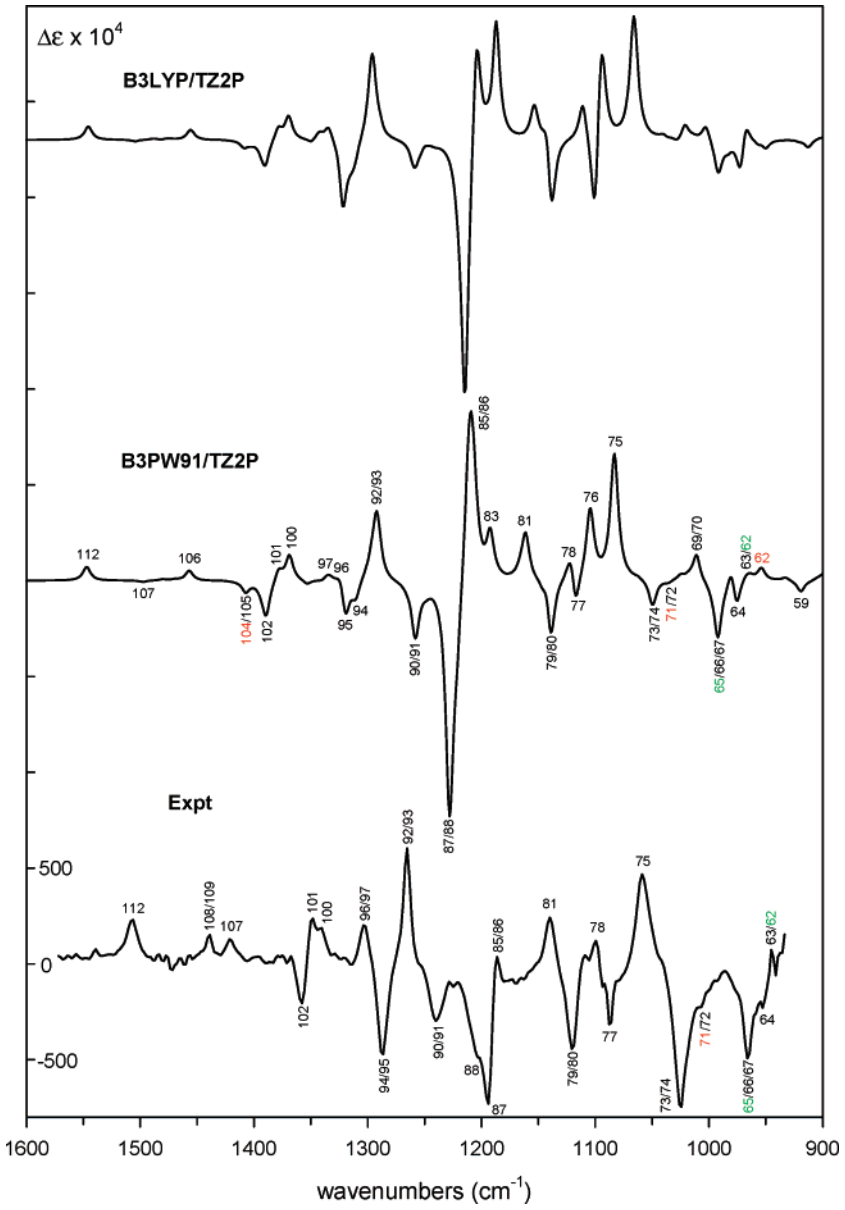
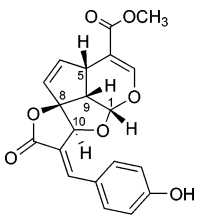


FIGURE 7. Comparison of experimental and calculated VCD spectra of **4**. The experimental spectrum is for (−)-**4**. The calculated spectra are for (1*R*,5*S*,8*S*,9*S*,10*S*)-**4** and are conformationally averaged and simulated using Lorentzian bandshapes (γ = 4.0 cm^{-1}). The red and green numbers indicate bands from conformations **Aa**−**d** and **Ba**−**d**, respectively; the black numbers indicate bands from conformations **Aa**−**d** and **Ba**−**d**.

strengths calculated for (1*S*,5*R*,8*R*,9*R*,10*R*)-**4** are in extremely poor agreement, confirming unambiguously the assignment of the AC of **4** as (1*R*,5*S*,8*S*,9*S*,10*S*)-(−).

(−)-**4** is obtained by acetylation of the OH group of the naturally occurring (-)-**3**. The AC of (-)-**3** is therefore identical to that of (-)-**4**. We have therefore determined the AC of the natural product, prismatomerin, to be (1*R*,5*S*,8*S*,9*S*,10*S*)-(−):



(1*R*,5*S*,8*S*,9*S*,10*S*)-**3**

Discussion

The sign of the specific rotation, $[\alpha]_D$, of the new iridoid, prismatomerin, **3**, is negative, opposite to the positive sign of the $[\alpha]_D$ of plumericin, **1**. The assumption that the substitution of the methyl group of **1**, attached to the C11−C13 double bond, by the *p*-phenol group of **3** should not change the sign of the specific rotation would lead to the conclusion that the AC of **3** is opposite to that of **1**. In order to test this empirical prediction, we have determined the AC of **3** using its VCD spectrum. As documented for many chiral organic molecules,[14−16] the comparison of state-of-the-art DFT calculations of the VCD spectra of the two enantiomers of a chiral molecule, using the Stephens

(14) Stephens, P. J.; McCann, D. M.; Devlin, F. J.; Smith, A. B., III. *J. Nat. Prod.* **2006**, *69*, 1055−1064.

(15) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Urbanová, M.; Hájíček, J. *J. Org. Chem.* **2007**, *72*, 2508−2524.

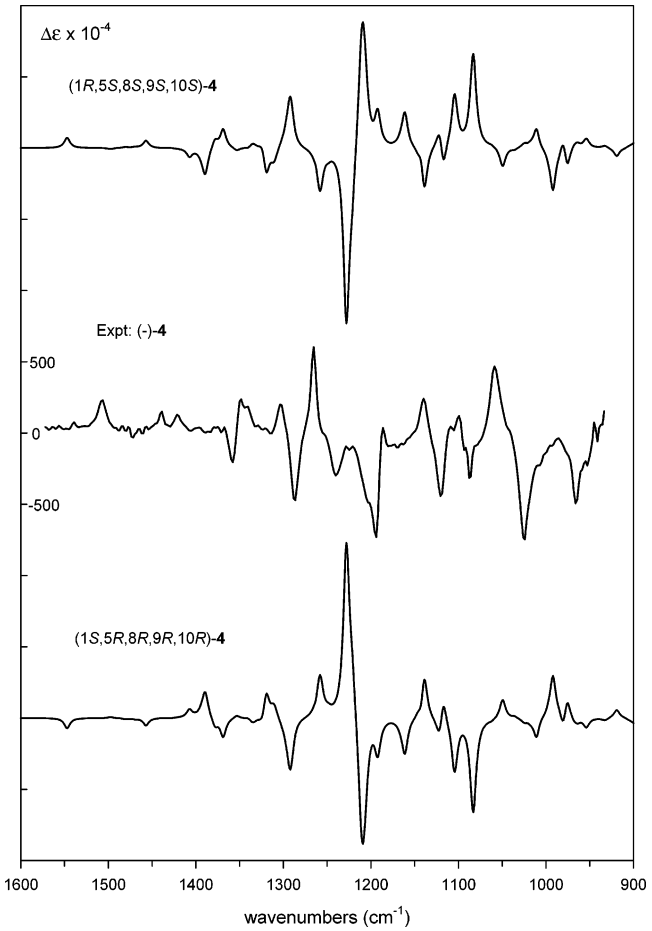


FIGURE 8. Comparison of the experimental VCD spectrum of (−)-**4** and the B3PW91/TZ2P VCD spectra of the two enantiomers of **4**.

theory of VCD,[11] to the experimental VCD spectrum enables the AC of the molecule to be unambiguously determined.

Recently, the utility of VCD spectroscopy in determining the ACs of natural product molecules has been documented by studies of the cytotoxic sesquiterpene, quadrone,[14] the schizozygane alkaloid, schizozygine,[15] and the iridoids plumericin and isoplumericin.[6]

In the case of plumericin, **1**, the AC was unambiguously determined to be (1*R*,5*S*,8*S*,9*S*,10*S*)-(+). The subsequent isolation of prismatomerin, **3**, provided another opportunity to demonstrate the utility of VCD spectroscopy in determining the ACs of iridoids. As shown in this paper, naturally occurring prismatomerin unambiguously possesses the same AC as naturally occurring plumericin. The prediction from their $[\alpha]_D$ values turns out to be wrong. Consequently, we recommend that the prediction of the AC of a natural product by comparison of its $[\alpha]_D$ to that of a related natural product should no longer be carried out by natural products chemists and that VCD spectroscopy should be utilized instead.

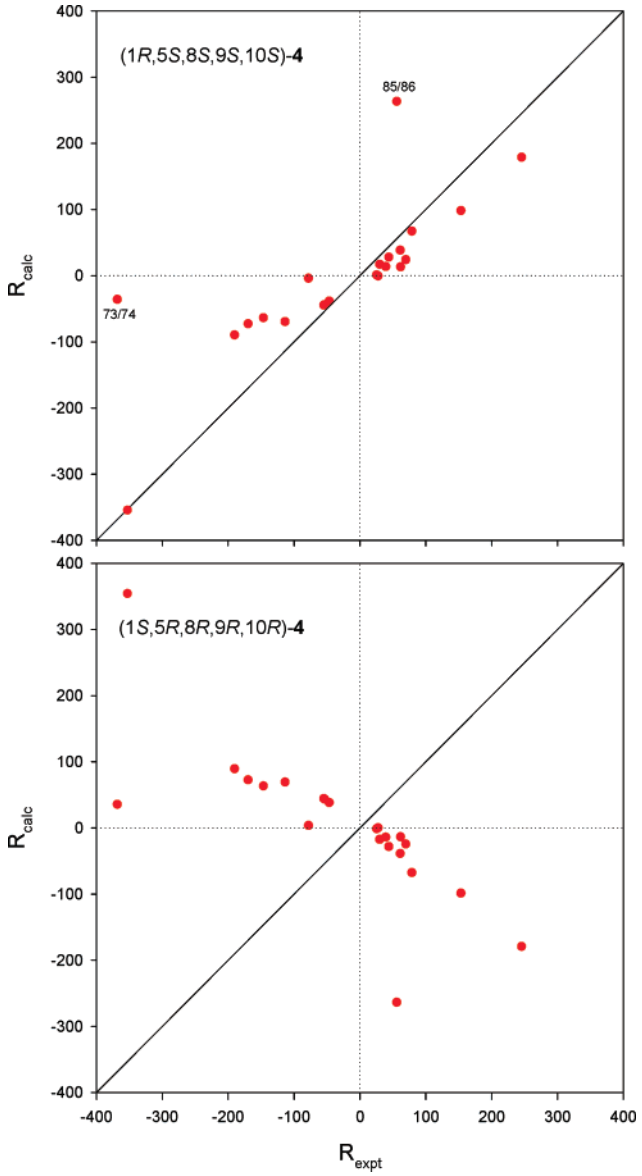


FIGURE 9. Comparison of B3PW91/TZ2P calculated and experimental rotational strengths of **4**. Experimental rotational strengths are for (−)-**4**. Calculated rotational strengths are for (1*R*,5*S*,8*S*,9*S*,10*S*)-**4** (top) and (1*S*,5*R*,8*R*,9*R*,10*R*)-**4** (bottom). Calculated rotational strengths are population-weighted averages. The solid line is of +1 slope. Rotational strengths are in 10^{-44} esu^2 cm^2. The numbers indicate the fundamentals of the points.

(16) See, for example: (a) Ashvar, C. S.; Stephens, P. J.; Eggimann, T.; Wieser, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1107−1110. (b) Aamouche, A.; Devlin, F. J.; Stephens, P. J. *Chem. Commun.* **1999**, 361−362. (c) Stephens, P. J.; Devlin, F. J. *Chirality* **2000**, *12*, 172−179. (d) Aamouche, A.; Devlin, F. J.; Stephens, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 2346−2354. (e) Aamouche, A.; Devlin, F. J.; Stephens, P. J.; Drabowicz, J.; Bujnicki, B.; Mikolajczyk, M. *Chem. Eur. J.* **2000**, *6*, 4479−4486. (f) Stephens, P. J.; Aamouche, A.; Devlin, F. J.; Superchi, S.; Donnoli, M. I.; Rosini, C. *J. Org. Chem.* **2001**, *66*, 3671−3677. (g) Devlin, F. J.; Stephens, P. J.; Scafato, P.; Superchi, S.; Rosini, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1551−1558. (h) Stephens, P. J.; Devlin, F. J.; Aamouche, A. In *Chirality: Physical Chemistry*; Hicks, J. M., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 2002; Vol. 810, Chapter 2, pp 18−33. (i) Devlin, F. J.; Stephens, P. J.; Scafato, P.; Superchi, S.; Rosini, C. *Chirality* **2002**, *14*, 400−406. (j) Devlin, F. J.; Stephens, P. J.; Oesterle, C.; Wiberg, K. B.; Cheeseman, J. R.; Frisch, M. J. *J. Org. Chem.* **2002**, *67*, 8090−8096. (k) Stephens, P. J. In *Computational Medicinal Chemistry for Drug Discovery*; Bultinck, P., de Winter, H., Langenaecker, W., Tollenaere, J., Eds.; Dekker: New York, 2003; Chapter 26, pp 699−725. (l) Cere, V.; Peri, F.; Pollicino, S.; Ricci, A.; Devlin, F. J.; Stephens, P. J.; Gasparrini, F.; Rompietti, R.; Villani, C. *J. Org. Chem.* **2005**, *70*, 664−669. (m) Stephens, P. J.; McCann, D. M.; Devlin, F. J.; Flood, T. C.; Butkus, E.; Stoncius, S.; Cheeseman, J. R. *J. Org. Chem.* **2005**, *70*, 3903−3913. (n) Devlin, F. J.; Stephens, P. J.; Besse, P. *Tetrahedron: Asymmetry* **2005**, *16*, 1557−1566. (o) Devlin, F. J.; Stephens, P. J.; Bortolini, O. *Tetrahedron: Asymmetry* **2005**, *16*, 2653−2663. (p) Carosati, E.; Cruciani, G.; Chiarini, A.; Budriesi, R.; Ioan, P.; Spisani, R.; Spinelli, D.; Cosimelli, B.; Fusi, F.; Frosini, M.; Matucci, R.; Gasparrini, F.; Ciogli, A.; Stephens, P. J.; Devlin, F. J. *J. Med. Chem.* **2006**, *49*, 5206−5216.

The AC of prismatomerin is now definitively established. The result leads to the conclusion that the biosynthetic pathways leading to plumericin in plants of the genera *Plumeria*, *Allamanda*, *Nerium*, *Himatanthus*, and *Duroia* are stereochemically identical to the biosynthetic pathway leading to prismatomerin in *P. tetrandra*.

In addition, establishment of the AC of prismatomerin now permits the stereochemistry of its biological activity to be investigated.

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Supporting Information Available: Experimental and calculated frequencies, dipole strengths, and rotational strengths of **4**; calculated IR and VCD spectra of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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