

Vibrational Circular Dichroism (VCD), VCD Exciton Coupling, and X-ray Determination of the Absolute Configuration of an α,β -Unsaturated Germacranolide

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ABSTRACT The absolute configuration of **1** was deduced by vibrational circular dichroism together with the evaluation of the Flack and Hooft X-ray parameters. Vibrational circular dichroism exciton coupling, using the carbonyl group signals, confirmed the absolute configuration of **2**. In addition, sodium borohydride reduction of the 11,13-double bond of 6-*epi*-desacetyl-laurenobiolide (**1**) yields an almost equimolecular mixture of C11 epimers, while reduction of the same double bond of 6-*epi*-laurenobiolide (**2**) provided almost exclusively the (11*S*) diastereoisomer **4**. *Chirality* 27:247–252, 2015. © 2015 Wiley Periodicals, Inc.

KEY WORDS: vibrational circular dichroism; exciton coupling; X-ray; 6-*epi*-desacetyl-laurenobiolide; diastereoselective reduction

6-*epi*-Desacetyl-laurenobiolide (**1**) was isolated from *Montanoa grandiflora* three decades ago¹ and more recently from *Laurus nobilis*.² The X-ray analysis of this molecule demonstrated that the 10-membered ring has the unusual boat–boat [₁₅D⁵,₁D¹⁴] conformation with two intra-annular *trans* double bonds in parallel arrangement.¹ The study of conformational properties by nuclear magnetic resonance (NMR) showed that **1** exists, in solution at room temperature, as a mixture of the [₁₅D⁵,₁D¹⁴] and [₁₅D⁵,₁D¹⁴] conformers,³ while evaluation of the potential energy surface indicated the presence of six different conformers, instead of the four conformational forms previously described for germacranolides.^{3,4} Thus, it seems desirable to obtain its absolute configuration (AC), which was previously assumed.¹

Comparison of vibrational circular dichroism calculated and experimental spectra has allowed the determination of the AC of a great number of natural products,⁵ and has even been shown to be a sensitive technique for determining the AC of a single stereogenic center in the presence of several of them.^{6–8} In addition, it was recently shown that the interaction of two IR chromophores, like carbonyl groups within a molecule, yields a strong VCD couplet whose two signs reflect the absolute configuration of the studied compound,⁹ having the great advantage of determining the AC of chiral molecules without the need of calculating the dipole transition moments and rotational strengths, and in addition, the experiment time and sample amount can be reduced significantly since a sharp bisignate VCD couplet can be seen.

In this work we report the AC determination of 6-*epi*-desacetyl-laurenobiolide (**1**) by comparison of experimental and calculated VCD spectra and by X-ray diffraction. In addition, 6-*epi*-laurenobiolide (**2**) and its reduced diastereomers **3** and **4** (Fig. 1) were studied by VCD and by the VCD exciton coupling technique.

MATERIALS AND METHODS

General

The melting point was determined on a Fisher-Jhons apparatus and is uncorrected. 1D and 2D NMR experiments were performed on a Varian

Mercury 300 spectrometer (Palo Alto, CA). Chemical shifts were referred to tetramethylsilane (TMS). IR and VCD spectra were obtained on a BioTools Dual PEM ChiralIR FT-VCD spectrophotometer. Electron impact mass spectrometry (EIMS) was determined on a Varian Saturn 2000 mass spectrometer. High-resolution EIMS (HR-EIMS) was measured on an Agilent (Palo Alto, CA) liquid chromatography-time of flight (LC-TOF) instrument at the UCR Mass Spectrometry Facility, University of California, Riverside. Optical rotations were measured on a Perkin-Elmer (Boston, MA) 341 polarimeter.

VCD Analysis

For the 1550 to 950 cm^{−1} measurements samples of 6.0 mg of **1**, 5.5 mg of **2**, 6.1 mg of **3**, and 5.5 mg of **4** were used, while for the VCD exciton coupling study samples of 4.5, 4.8, and 4.5 mg of **2–4**, respectively, were used. In all cases the samples were dissolved in 150 μ L of 100% atom-D CDCl₃ and placed in a BaF₂ cell with a pathlength of 0.1 mm, data were acquired with a resolution of 4 cm^{−1} for 6 h, and the baseline correction was done by subtracting the spectrum of the solvent acquired under the same conditions.

X-Ray Diffraction Analysis of **1** and **4**

The data for **1** were collected on a Bruker-Nonius CAD4 diffractometer in the ω -2 θ scan mode. Unit cell refinements using 25 machine-centered reflections were done using the CAD4 Express v2.0 software. Data of **4** were acquired on an Agilent Xcalibur Atlas Gemini diffractometer in the ω scan mode. Both crystals were measured using Cu K α radiation (λ = 1.54184 Å) at 293(2) K. Unit cell refinements were made with the CrysAlisPro, Agilent Technologies, v. 1.171.34.49 software. The

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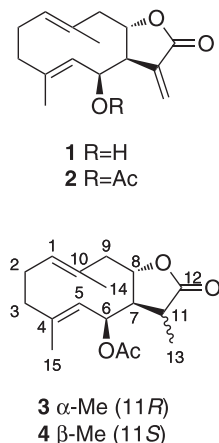


Fig. 1. Formulas of 6-*epi*-desacetyl-laurenobiolide (**1**), 6-*epi*-laurenobiolide (**2**) and 6-*epi*-11,13-dihydrolaurenobiolides **3** and **4**.

structures were solved by direct methods using the SHELXS-97 and SIR2004 programs included in the WinGX v1.70.01 crystallographic software package. For the structural refinement, the nonhydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the CCDC, deposit@ccdc.cam.ac.uk.

6-Epi-11,13-Dihydrolaurenobiolide Diastereoisomers **3** and **4**.

A. A solution of 50 mg of **1** in 5 mL of anhydrous MeOH was cooled to 5 °C, then 25 mg of NaBH₄ was added and stirred for 1 h. The mixture was diluted with water (3 mL), acidified with a 5% HCl solution, and extracted with AcOEt (3 × 50 mL). The combined organic phases were washed with water (3 × 30 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated to give a yellowish oily mixture. A solution of 42 mg of this mixture was treated with pyridine-acetic anhydride. The crude reaction product was chromatographed on SiO₂ 60 (230–400 mesh), eluting with hexanes:EtOAc. In the fractions eluted with hexanes:EtOAc (7:3) a mixture of compounds **3** and **4** was obtained. This mixture was rechromatographed eluting with hexanes:EtOAc 4:1 and 7:3. The earlier fractions gave 12 mg of **3**, followed by a mixture **3** and **4**, and finally 10 mg of **4** were obtained.

B. A solution of 100 mg of **2** in 5 mL of anhydrous MeOH was cooled to 5 °C, 77 mg of NaBH₄ was added, and the reaction mixture was stirred at the same temperature for 1 h. The solvent was evaporated with a stream of N₂ and, after the slow addition of 3 mL of water, the mixture was acidified with a 5% HCl solution and extracted with EtOAc (3 × 50 mL). The organic layer was washed with water (3 × 30 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated to give a yellowish oily liquid which crystallized from EtOAc-hexanes to give 41 mg of diastereomer **4**. The mother liquors were chromatographed over SiO₂ 60 (230–400 mesh) eluting with hexanes:EtOAc (7:3). In the early fractions 1.2 mg of **3** (1%) were obtained, and in the subsequent fractions 31 mg of **4** were recovered, giving a total of 72 mg (71%).

(11*R*)-6-epi-11,13-Dihydrolaurenobiolide (3). Colorless oil. [α]₅₈₉ + 54.1, [α]₅₇₈ + 56.1, [α]₅₄₆ + 62.3, [α]₄₃₆ + 97.8, [α]₃₆₅ + 135.9, (*c* 0.61, CHCl₃). IR (CDCl₃) ν_{\max} 1759, 1738, 1240 cm⁻¹. ¹H and ¹³C NMR (CDCl₃); see Table 1. EIMS *m/z* (int. rel.): 233 [M - OAc]⁺ (100), 232 (92), 205 (97), 204 (86), 150 (37), 133 (34). HR-EIMS *m/z* 293.1748 (calculated for C₁₇H₂₄O₄ + H, 293.1747).

(11*S*)-6-epi-11,13-Dihydrolaurenobiolide (4). Colorless crystals (AcOEt-hexanes). Mp. 143–145 °C. [α]₅₈₉ + 38.4, [α]₅₇₈ + 39.8, [α]₅₄₆ + 44.4, [α]₄₃₆ + 66.4, [α]₃₆₅ + 83.9, (*c* 0.55, CHCl₃). IR (CDCl₃) ν_{\max} 1765, 1742, 1242 cm⁻¹. ¹H and ¹³C NMR (CDCl₃); see Table 1. EIMS *m/z* (int. rel.): 233 [M - OAc]⁺ (61), 232 (80), 205 (51), 204 (100), 150 (42), 133 (64). HR-EIMS *m/z* 293.1745 (calculated for C₁₇H₂₄O₄ + H, 293.1747).

Computational Methods

Conformational searches for **2**, **3**, and **4** were carried out using the molecular mechanics force field incorporated in the Spartan'04 software package. The conformers within the first 10 kcal/mol were submitted to single-point energy calculations at the B3LYP/6-31G(d,p) level. For the structures within 5 kcal/mol above the lowest-energy conformer, a geometry optimization was carried out with the same functional and the DGDZVP basis employing the Gaussian 09W program. For all molecules, including **1**, the optimized geometries were the inputs to calculate the vibrational frequencies, dipole transition moment, and rotational strengths. These data were used to compute the IR and VCD spectra considering a sum of Lorentzian bands with half-widths of 6 cm⁻¹ from the conformers shown in Table 2. Calculated and experimental spectra were compared using the CompareVOA software. All Gaussian calculations were carried out in a server node with 8 processors at 2.93 GHz and 8 GB of RAM.

TABLE 1. ¹H and ¹³C NMR data for the 6-*epi*-11,13-dihydrolaurenobiolide diastereomers **3** and **4** in CDCl₃

Position	δ_{C}	δ_{H} (<i>J</i> in Hz)	HMBC	δ_{C}	δ_{H} (<i>J</i> in Hz)	HMBC
3				4		
1	132.1	4.97		130.9	5.01	
2	24.1	2.16, 2.39 m		24.6	2.18, 2.38 m	
3	36.6	2.17, 2.56 m	2, 4, 5, 15	38.8	2.16 m	4, 5, 15
4	136.3			136.9		
5	125.5	4.75 d(7.8)	3, 15	128.9	4.97	
6	69.5	5.56 d(7.2)	4, 5, 8, 16	69.8	5.43 d(6.7)	4, 8
7	53.8	1.97 m	9, 11, 13	44.8	2.31 m	
8	76.6	4.57 m		79.8	4.71 m	
9	48.4	2.06, 2.74 d(11.0)	7, 8, 10	39.1	1.73, 2.90 m	
10	126.1		14	127.5		
11	36.8	2.51 m	6, 7, 12, 13	34.3	2.79 m	
12	178.3			178.8		
13	16.1	1.34 d (7.0)	7, 11, 12	9.2	1.19 d (7.3)	7, 11, 12
14	17.4	1.62 s	1, 9, 10	21.0	1.69 s	1, 9, 10
15	16.5	1.56 s	3, 4, 5	16.8	1.56 s	3, 4, 5
COCH ₃	170.4			170.2		
COCH ₃	21.0	2.09 s	16	21.1	2.04 s	16

TABLE 2. Relative energies and conformational population of 1–4

Conformer	ΔE_{MMFF}^b	%MMFF ^c	ΔE_{SP}^d	%SP ^e	ΔE_{OPT}^f	%OPT ^g	$\Delta G_{\text{B3LYP}}^h$	%B3LYP ⁱ
1a ^a	—	—	—	—	0.00	60.7	0.00	57.2
1b ^a	—	—	—	—	0.30	36.4	0.19	41.6
1c ^a	—	—	—	—	1.95	2.3	2.27	1.2
2a	0.67	24.0	0.00	66.7	0.00	59.8	0.00	85.8
2b	0.00	74.4	0.42	32.9	0.24	39.9	1.07	14.1
2c	2.32	1.4	3.95	0.1	3.17	0.2	3.79	0.1
3a	0.47	27.0	0.00	77.6	0.00	83.0	0.00	81.8
3b	0.00	48.8	0.77	20.9	1.06	13.9	0.98	15.5
3c	1.86	2.1	2.98	0.5	2.51	1.2	2.01	2.7
4a	2.24	2.3	0.61	26.1	0.44	32.3	0.00	53.0
4b	0.00	97.6	0.00	73.8	0.00	67.6	0.07	46.8
4c	3.92	0.1	4.53	0.1	3.87	0.1	3.42	0.2

^aFor **1** the conformational search started for the six described conformers.³^bMolecular mechanics energy relative to 48.97, 28.29, and 29.42 kcal/mol for **2**–**4**, respectively.^cMolecular mechanics population in percent considering six conformers for **2**, 12 conformers for **3**, and 10 conformers for **4**.^dSingle-point relative energy; the lowest energy values for **2**–**4** were –603629.6, –604447.2, and –604445.4 kcal/mol, respectively.^eConformational population calculated with four conformers for **2**, five conformers for **3**, and three conformers for **4**.^fEnergy of the optimized structures; data are relative to –507871.8 kcal/mol for **1**, –603684.1 kcal/mol for **2**, –604451.7 kcal/mol for **3**, and –604449 kcal/mol for **4**.^gConformational population in percent considering six conformers for **1**, four conformers for **2** and **3**, and three conformers for **4**.^hFree energy relative to –507696.2 kcal/mol for **1**, –603489.6 kcal/mol for **2**, –604242.5 kcal/mol for **3**, and –604238.9 kcal/mol for **4**.ⁱDFT population calculated from ΔG values considering three conformers for each compound.

RESULTS AND DISCUSSION

The AC of **1** was first obtained by VCD. The six reported conformers³ were optimized at the B3LYP/DGDZVP level of theory. Structures with energy 3 kcal/mol above the most stable conformer were discarded, leaving and showing that at this level of theory the [₁₅D⁵,₁D¹⁴], [₁₅D⁵,₁D¹⁴], and [₁₅D₅,₁D₁₄] conformers are the more stable. Dipole transition moments and rotational strengths were calculated for the three conformers and the final spectrum was obtained assuming a Boltzmann weighted distribution. Comparison of

experimental and calculated spectra in the 1550–950 cm^{–1} region (Fig. 2), using the CompareVOA software,¹⁰ revealed IR and VCD spectra similarity. The pertinent numerical comparison¹¹ data are given in Table 3 and allow establishing the depicted (6S,7S,8S) AC of **1**.

A single crystal of **1** was mounted on an X-ray diffractometer equipped with Cu K α monochromatic radiation to collect the complete sphere of data. The molecular structure was solved by direct methods and refined to a discrepancy index of 4.4%. The data were also used to calculate the Flack parameter,¹² which for the enantiomer shown in Figure 3 was $x = -0.2(3)$, and the Hooft parameter,¹³ which was $y = 0.11(12)$. For the inverted structure, these parameters were $x = 1.1(3)$ and $y = 0.89(12)$, respectively, from which follows the correct enantiomer as the one depicted in Figure 3, in agreement with the VCD results. The crystal data are summarized in Table 4.

After discerning the AC of **1** by VCD comparison and X-ray, we prepared 6-*epi*-laurenobiolide (**2**) to contrast the similarity indices of the acetylated derivative with the corresponding hydroxy compound, since the hydroxy group containing

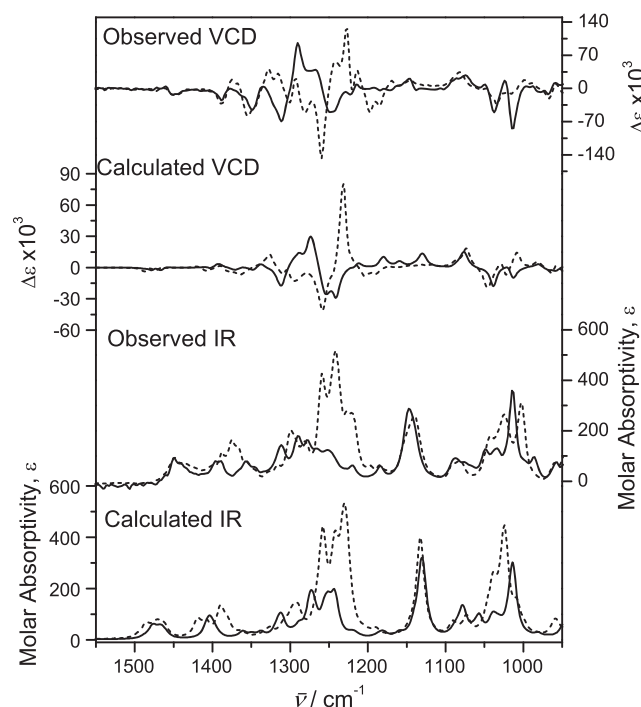


Fig. 2. Vibrational spectra of **1** (solid) and **2** (dashed); calculations were done at the B3LYP/DGDZVP level of theory.

TABLE 3. Confidence level data for the IR and VCD spectra of 1–4, and cross-comparisons

Molecule	anH ^a	S_{IR}^b	S_{E}^c	S_{E}^d	ESI ^e	C ^f
1	0.976	87.4	79.6	8.1	71.5	100
2	0.982	94.4	87.5	9.1	78.4	100
3	0.980	93.4	70.1	13.2	56.9	100
4	0.977	90.8	84.9	13.8	71.1	100
4E vs. 3C ^g	0.982	93.6	31.5	56.4	–24.9	45
3E vs. 4C ^h	1.000	71.8	26.9	46.8	–19.9	32

^aAnharmonicity factor.^bIR spectral similarity.^cVCD spectral similarity for the correct enantiomer.^dVCD spectral similarity for the incorrect enantiomer.^eEnantiomer similarity index, calculated as $S_{\text{E}}-S_{\text{E}}$.^fConfidence (%) for the stereochemical assignments.^gExperimental **4** vs. calculated **3** spectra comparison.^hExperimental **3** vs. calculated **4** spectra comparison.

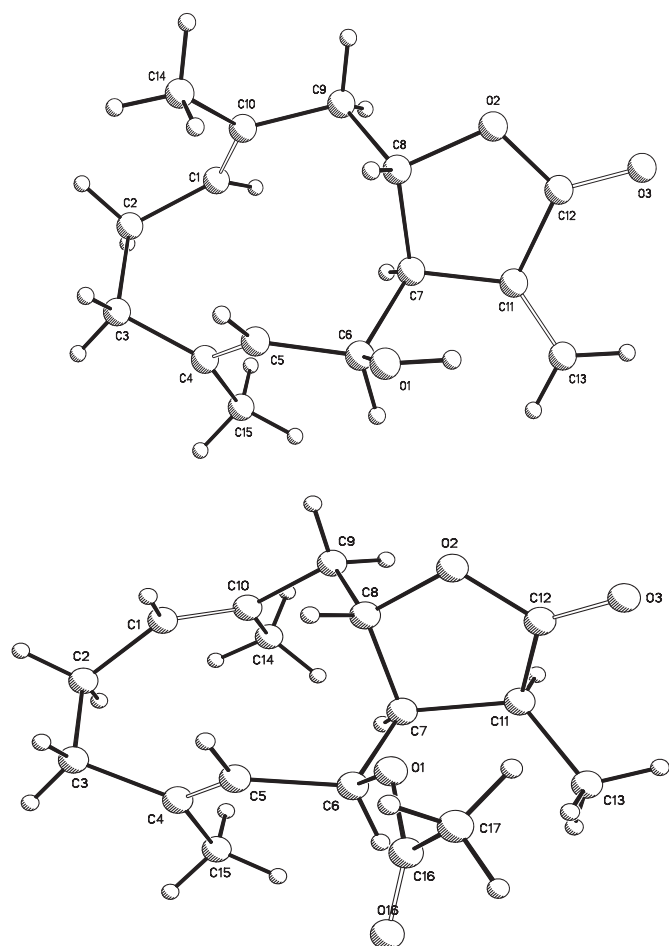


Fig. 3. X-ray crystal structures of 6-*epi*-desacetyl-laurenobiolide (**1**, top) and (11*S*)-6-*epi*-11,13-dihydro-laurenobiolide (**4**, bottom).

molecules has a tendency to associate intermolecularly in solution, whereby poorer agreements of experimental and calculated spectra are observed.¹⁴ In addition, acetate **2** also provided the opportunity to verify the AC using the VCD exciton coupling method.

The six conformers generated by the MMX conformational search of **2** were submitted to single-point calculation at the B3LYP/6-31G(d,p) level of theory providing four structures within a 5 kcal/mol energy gap. Geometry optimization at the B3LYP/DGDZVP level resulted in two conformers with a 0.24 kcal/mol relative energy. These two optimized geometries with $\Delta G = 1.07$ kcal/mol represented 99.9% of the conformational population, for which the Boltzmann-weighted IR and VCD spectra were obtained. Figure 2 shows the spectra after using the CompareVOA software, for which the numerical data are summarized in Table 3. The results for **2** were consistent with the AC obtained for 6-*epi*-desacetyl-laurenobiolide (**1**). The similarity indices (Table 3) confirm a better agreement between calculated and experimental spectra for acetate **2** as compared to **1**.

The two carbonyl groups within **2** enable the molecule as a convenient candidate for a VCD exciton coupling study.^{9,15–18} Its IR spectrum (Fig. 4) shows the stretching absorption bands for the carbonyl acetate at 1740 cm^{-1} , and for the lactone C=O group at 1757 cm^{-1} , while the VCD spectrum exhibits a bisignate couplet with amplitude $A = -0.056\text{ M}^{-1}\text{ cm}^{-1}$ (Table 5), calculated as $\Delta\epsilon_1 - \Delta\epsilon_2$. Figure 4 also displays the conformers weighted arrangement of the dipole transition moments of

TABLE 4. X-ray parameters of 6-*epi*-desacetyl-laurenobiolide (**1**) and (11*S*)-6-*epi*-11,13-dihydro-laurenobiolide (**4**)

Parameter	1	4
Formula	$\text{C}_{15}\text{H}_{20}\text{O}_3$	$\text{C}_{17}\text{H}_{24}\text{O}_4$
<i>M</i>	248.31	292.36
Crystal system	Orthorhombic	Triclinic
Space Group	P2 ₁ 2 ₁ 1	P1
<i>a</i> (Å)	6.157(2)	7.9880(2)
<i>b</i> (Å)	20.057(3)	11.5240(3)
<i>c</i> (Å)	21.991(6)	14.1880(4)
α (deg)	90	101.695(2)
β (deg)	90	90.411(2)
δ (deg)	90	104.218(2)
<i>V</i> (Å ³)	2715.7	1237.53(6)
<i>Z</i> , <i>Z'</i>	4, 2	1, 3
ρ (mg/mm ³)	1.22	1.18
μ (Cu <i>K</i> α , mm ⁻¹)	0.670	0.669
<i>F</i> (000)	1072	474
Theta range for data collection	2.98 to 60.00	3.19 to 77.55
Reflections for cell refinement	25	14583
Total reflections	8462	48923
Unique reflections (<i>R</i> _{int} 0.01%)	3968	9845
Observed reflections	3262	8769
Final <i>R</i> ₁ index [<i>I</i> > 2 σ (<i>I</i>)] (%)	4.4	4.1
Final <i>wR</i> ₂ index [<i>I</i> > 2 σ (<i>I</i>)] (%)	10.12	11.38
Goodness-of-fit on <i>F</i> ²	1.072	1.040
Largest difference peak and hole (e.Å ⁻³)	0.145 and -0.153	0.167 and -0.142
Flack parameter <i>x</i>	-0.2(3)	0.04(14)
Hooft parameter <i>y</i>	0.11(12)	0.02(5)
Flack parameter for inverted structure <i>x</i>	1.1(3)	0.92(14)
Hooft parameter for inverted structure <i>y</i>	0.89(12)	0.98(5)
CCDC deposition number	1039476	1039477

6-*epi*-laurenobiolide (**2**), where the dihedral angle (θ) defined by the two C=O groups is -90.5 (deg), and the interchromophoric distance (*R*), calculated from the mid-points of the two C=O bonds of the carbonyl groups, is 5.1 Å . The obtained parameters gave a negative exciton in agreement with the couplet observed in the VCD experimental spectrum. These data support the 6*S*,7*S*,8*S* absolute configuration of 6-*epi*-laurenobiolide (**2**).

Since conformers of molecule **2** with syn (**2a**, Table 2) and anti orientation of the carbonyl group with respect to the hydrogen atom at C6 have a relative energy of 8.01 kcal/mol at the MM level, we discarded conformer anti, and we assume restricted conformation, allowing the application of the VCD exciton coupling method.

In addition, the VCD spectrum of laurenobiolide, the C6 epimer of **2**, was computed. The parameters obtained for its most stable conformer were $\theta = 81.1$ deg, $R = 5.66\text{ Å}$ and $A = 0.128$. This information may be employed to discriminate between laurenobiolide and 6-*epi*-laurenobiolide derivatives since the VCD exciton couplets have opposite sign.

Once the AC of **1** and **2** was secured, we turned our attention to know the stereochemistry of the originally described¹ dihydro derivatives. For this purpose, compounds **3** and **4** were prepared by two alternatives. First, NaBH₄ reduction of 6-*epi*-desacetyl-laurenobiolide (**1**) was done followed by acetylation, whereby almost equimolar amounts of **3** and **4** were obtained. In the second route 6-*epi*-laurenobiolide (**2**) was treated with NaBH₄, providing almost exclusively **4**.

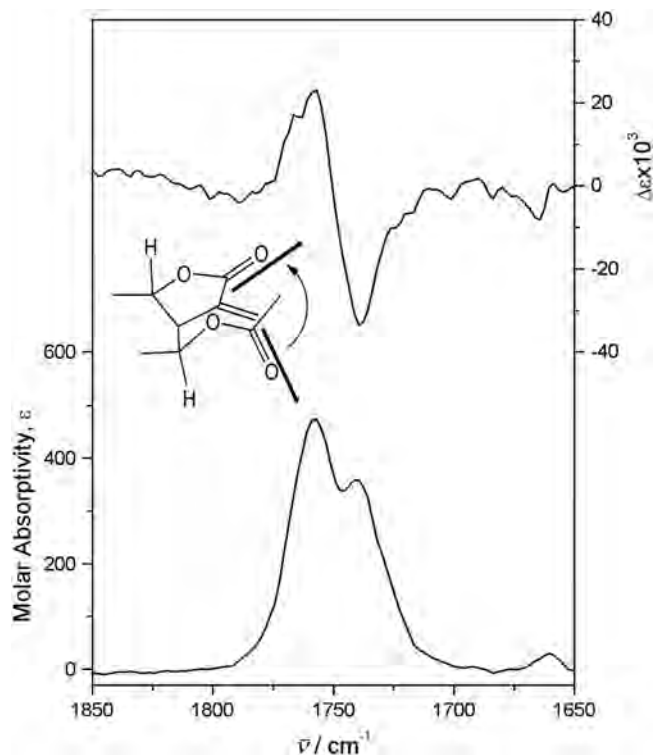


Fig. 4. Carbonyl region of the VCD (top) and IR (bottom) spectra of 6-*epi*-laurenobiolide (**2**). The electric transition moments depicted parallel to the C=O bonds show a negative twist consistent with the negative amplitude (*A*) of the VCD experimental couplet.

Figure 5 displays the optimized geometry of the most stable conformer of **2**, which shows that the steric hindrance of the acetate group hinders the addition of the hydrogen atoms from the top-side of the molecule. Table 1 displays the NMR data of 6-*epi*-11,13-dihydrolaurenobiolide diastereoisomers **3** and **4**. Assignment of the AC of the new stereogenic center was carried out by VCD. Monte Carlo conformational search provided 15 conformers for **3**, and 16 structures for **4**, in the first 10 kcal/mol. DFT single-point energy calculation at the B3LYP/6-31G(d,p) level affording five structures for **3**, and three for **4**, in a 5 kcal/mol range. The geometry of these molecular structures was optimized at the B3LYP/DGDZVP level of theory, leaving four structures for **3** and three structures for **4**, which were submitted to frequency and free energy calculation at the same level of theory. The ΔG calculated values were used to generate a Boltzmann distribution; the conformers shown in Table 2 account for 97.2% and 99.8% of the total population for **3** and **4**, respectively. The dipole and rotational strengths calculated for these geometries were used to generate the IR and VCD spectra, which were obtained by weighting the individual spectra according to the Boltzmann distribution. Figure 6 displays the IR and

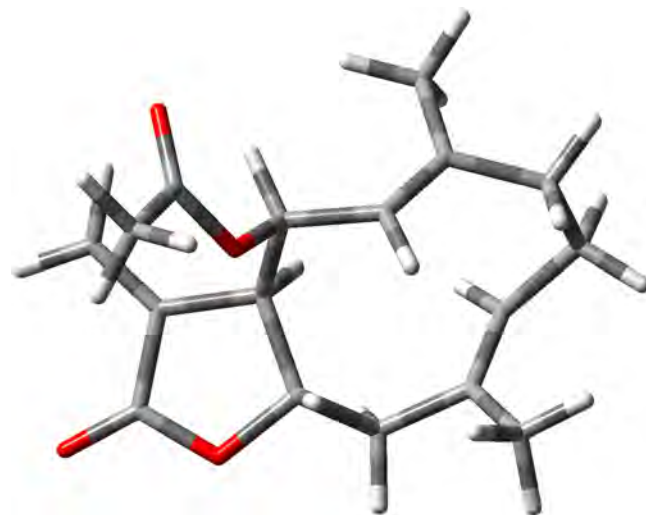


Fig. 5. Low-energy conformer of 6-*epi*-laurenobiolide (**2**) at the B3LYP/DGDZVP level of theory, showing the steric hindrance at the upper face of the molecule.

VCD spectra of dihydroderivatives **3** and **4**, respectively. Cross-comparison of the calculated and experimental spectra, using the CompareVOA software, is shown in Table 3. Although the VCD similarity indices, S_E , were not as high as the S_{IR} values, they are adequate to assign the (11*R*) for **3**, and (11*S*) for **4**, AC with 100% confidence.

A single crystal of **4** was diffracted using X-rays and the molecular structure was solved by direct methods and refined to a discrepancy index of 4.1%. The Flack parameter for the enantiomer shown in Figure 3 was $x = -0.04(14)$, and the Hooft parameter was $y = 0.02(5)$, while for the inverted structure these parameters were $x = 0.92(14)$ and $y = 0.98(5)$, respectively, which again confirms the correct enantiomer is the one depicted in Figure 3, in agreement with the VCD results.

Figure 7 shows the VCD exciton coupling signals for the stretching carbonyl region of **3** and **4**, where a negative couplet is observed in each case. Of course, the VCD exciton coupling methodology cannot distinguish the C11 epimers, since the twist of the dipole moment vectors in the carbonyl groups does not change from **3** to **4**.

CONCLUSION

The absolute configuration of 6-*epi*-desacetyl-laurenobiolide was obtained by the traditional VCD comparison method and by X-ray analysis. VCD exciton chirality was applied to 6-*epi*-laurenobiolide to confirm the absolute configuration of the corresponding hydroxy compound. Sodium borohydride reduction of compound **2** provided mainly the (11*S*)-6-*epi*-11,13-dihydrolaurenobiolide, since the steric hindrance of the acetate group promotes the specific addition of the hydrogen atoms. The stereochemistry of C11 in the reduced

TABLE 5. VCD exciton couplets for **2–4**

Compound	<i>c</i> (mol/L)	$\Delta\epsilon_1$ ($\bar{\nu}$) ^a	$\Delta\epsilon_2$ ($\bar{\nu}$) ^a	<i>A</i> ^a	θ ^b	<i>R</i> (Å) ^b
2	0.109	−0.033(1740)	0.023(1757)	−0.056	−90.5	5.1
3	0.109	−0.040(1741)	0.051(1761)	−0.091	−94.8	5.6
4	0.103	−0.063(1737)	0.032(1760)	−0.095	−113.1	5.2

^a $\Delta\epsilon_i$ and *A* in $M^{-1} cm^{-1}$ and $\bar{\nu}$ in cm^{-1} .

^bCalculated by weighting the angle θ and the distance *R* of each conformer according to the Boltzmann populations given in Table 2.

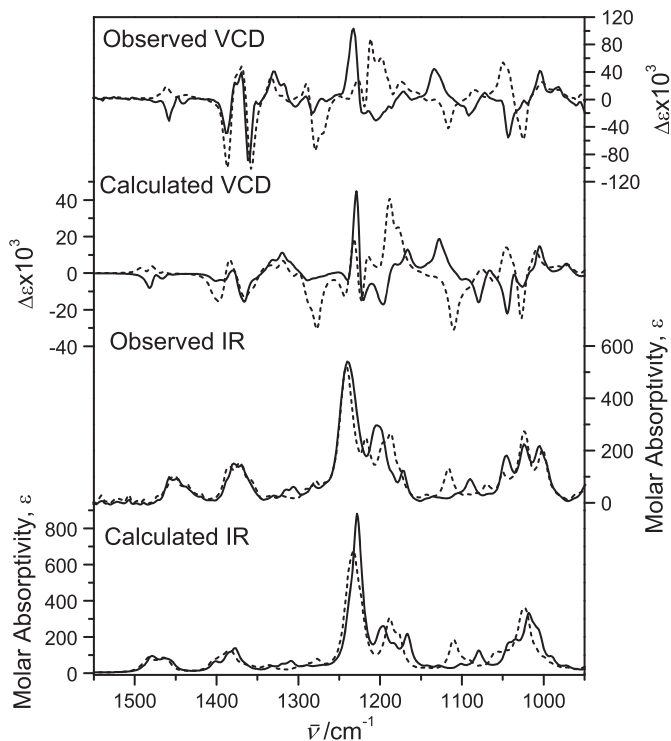


Fig. 6. Vibrational spectra of (11*R*)-**3** (solid) and (11*S*)-6-*epi*-11,13-dihydrolaurenobilide (**4**, dashed); calculations were done at the B3LYP/DGDZVP level of theory.

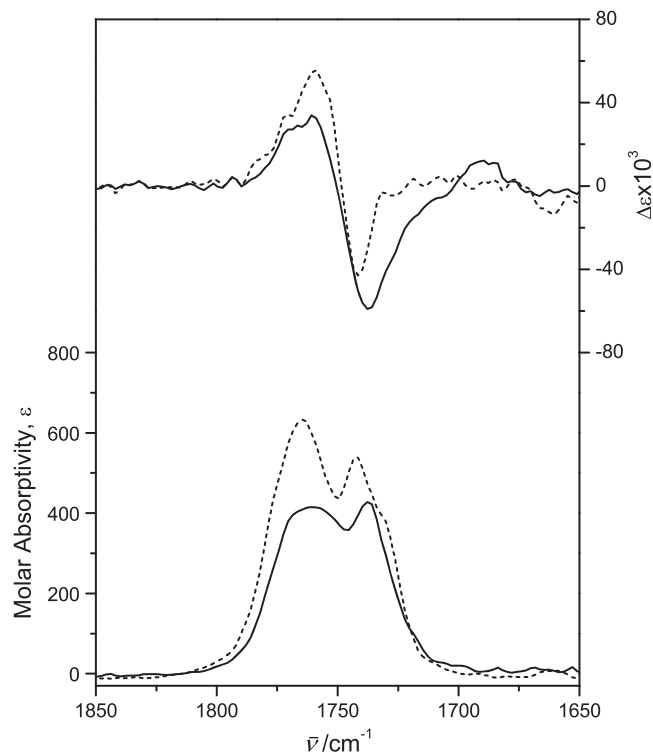


Fig. 7. VCD exciton coupling (top) and IR (bottom) signals of (11*R*)-6-*epi*-11,13-dihydrolaurenobilide (**3**, solid) and (11*S*)-6-*epi*-11,13-dihydrolaurenobilide (**4**, dashed).

compounds was not determined with VCD exciton coupling due the twist of the dipole vectors of the C=O bonds does not change in the epimers **3** and **4**.

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