



Absolute configuration of eremophilanoids by vibrational circular dichroism

Eleuterio Burgueño-Tapia^a, Pedro Joseph-Nathan^{b,*}

^aDepartamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación de Carpio y Plan de Ayala, Col. Santo Tomás, México D.F., 11340 México

^bDepartamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México D.F., 07000 México

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ABSTRACT

The absolute configurations (AC) of natural occurring 6-hydroxyeuryopsin (**1**), of its acetyl derivative **2**, and of eremophilanolide **8** were confirmed by comparison of the experimental vibrational circular dichroism (VCD) spectra with theoretical curves generated from density functional theory (DFT) calculations. Initial analyses were carried out using a Monte Carlo searching with the MMFF94 molecular mechanics force field. All MMFF94 conformers were further optimized using DFT at the B3LYP/6-31G(d) level of theory, followed by calculations of their vibrational frequencies at the B3LYP/6-31G(d,p); the VCD spectra of **2** and **8** were also calculated at the B3PW91/DGDZVP level of theory. Good agreement between theoretical and experimental VCD curves unambiguously verified the 4S,5R,6S absolute configuration for **1** and **2**, and the 1S,4S,5R,6S,8S,10S configuration for **8**.

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1. Introduction

Eremophilanoids, along with pyrrolizidine alkaloids, are the most common natural products isolated from *Senecio* species (Bohlmann et al., 1997). 6-Hydroxyeuryopsin (**1**), a sesquiterpenoid that belongs to the reduced group of furanoremerophilanoids bearing a free hydroxyl group at C-6, and its acetylated derivative **2**, have shown strong antifeedant activity against the insects *Leptinotarsa decemlineata* and *Myzus persicae* (Burgueño-Tapia et al., 2007). Compound **1** was first prepared from natural 6-angeloyloxyeuryopsin isolated from *Euryopsis empetrifolus* and *Euryopsis othonoids* (Bohlmann and Zdero, 1978), and then isolated as a natural product from *Senecio toluccanus* (Arciniegas et al., 2000) along with the eremophilanolides **3** and **4**. The relative and absolute configuration of the later two molecules was deduced from their NMR spectroscopic data and the electronic circular dichroism curve of the C-3 oxo derivative **5** (Pérez et al., 1991). By contrast, the absolute configuration of **1** was only inferred from the fact that it was considered a probable biogenetic precursor of **3** and **4**. In addition, the C4 stereogenic center of cacalol was deduced from its ozonolysis product, (S)-(+)-2-methylhexanedioic acid (Terabe et al., 1978), and this observation has been extrapolated to related sesquiterpenoids based on biogenetical considerations (Wang et al., 2007).

Recently, a new synthetic route to obtain (\pm)-6-hydroxyeuryopsin (**1**) and some eremophilanolides was developed (Mace et al.,

2006). In order to prove the structure of cyclization product **6**, the TMS ether residue was cleaved and the alcohol esterified with *p*-nitrobenzoyl chloride to afford **7**. An X-ray analysis of **7** showed, however, that the crystal structure was the enantiomer of the natural product. Taking into account all the above considerations, and in particular the strong antifeedant activity of **1** and **2**, we decided to confirm their absolute configurations (AC) using independent methodology.

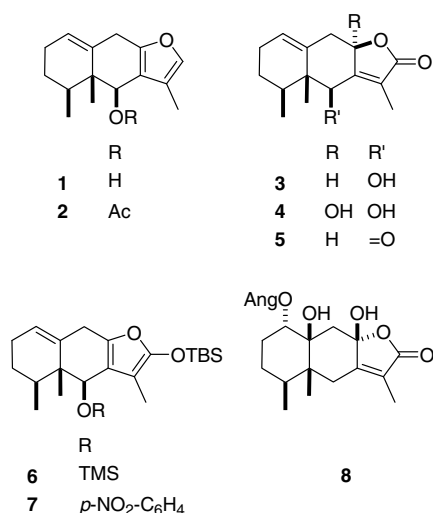
Since the pioneering systematization of chiroptical methods here in Mexico City almost half a century ago (Djerassi, 1960), in particular regarding to optical rotatory dispersion (ORD), which includes optical rotations (OR), and circular dichroism (Crabbé, 1965), now referred to as electronic circular dichroism (ECD), it is well recognized that either of these methods leads to the same absolute configuration of organic molecules. Our own work in the natural products field (Romo et al., 1963, 1964) has been referenced in the latter book and experimental ORD and ECD curves derived from our subsequent studies (Walls et al., 1965, 1966), validating these conclusions, were fully reproduced (Crabbé, 1968). In addition, the recent incorporation of time dependent density functional theory (TDDFT) calculations further enhanced these methodologies, since it is now possible to compare the OR, or the ORD, ECD or VCD curve to the calculated results and thereby to establish the AC of a molecule. This has been exemplified carefully in recent studies using all these methods (Stephens et al., 2007a,b,c), from where it becomes evident that either method works adequately. Furthermore, quite recent examples in the natural products field, utilizing only one of these methodologies were published, as was the case of OR for quinols (Mennucci et al., 2007),

* Corresponding author. Tel.: +52 55 5747 7112; fax: +52 55 5747 7137.

E-mail address: pjoseph@nathan.cinvestav.mx (P. Joseph-Nathan).

or of ECD for a tropane alkaloid (Humam et al., 2008), or of VCD for eudesmanolide sesquiterpene lactones (Krautmann et al., 2007) and for an iridoid (Stephens et al., 2007d).

VCD has some advantages over OR and ECD methods since it affords multiple data for the determination of AC (Cerdeja-García-Rojas et al., 2007), in contrast to OR, and by extension ORD curves, where values at each wavelength have to be calculated one at a time. In VCD, only the electronic ground state of the molecule plays a fundamental role, in contrast to ECD calculations in which the excited states also participate. From the above considerations it follows that VCD is now mature for its straightforward utilization by natural products chemists to determine AC. In addition, it has very recently been stated in the conclusions of an extensive review article by Nafie (2008) on the use of VCD for the determination of structure and absolute configuration of natural products, that “as demonstrated in several published papers, VCD is a more accurate and powerful method compared with all previous spectroscopic approaches to AC determination including ECD and OR”. Thus, in this work, we describe the absolute configuration determination of **1**, **2** and **8** by comparison of the experimental VCD spectra with the respective theoretical curves obtained by calculating the significant conformations using DFT, followed by generation of the weighted-averaged VCD plots.



2. Results and discussion

The theoretical VCD spectrum of (4S,5R,6S)-6-hydroxyeuryopsin (**1**) was obtained following a protocol which started by calculation of the global minimum energy conformation at the MMX level (Gajewski et al., 1990) using the PC model program. The minimum energy MMX structure was used as input data for a Monte Carlo (Chang et al., 1989) search at the MMFF94 (Halgren, 1996a,b,c,d; Halgren and Nachbar, 1996) level from which a total of six conformers with a $\Delta E = 4.54$ kcal mol⁻¹ were obtained in the initial 10 kcal mol⁻¹ range. All conformers were submitted to geometry optimization using DFT (Perdew, 1986) calculations at the B3LYP/6-31G(d,p) level of theory, affording the ΔG values summarized in Table 1.

This initially selected combination of functionals and basis set for our calculations is higher than the B3LYP/6-31G(d) level of theory (Freedman et al., 2003a,b; Furo et al., 2005; Kuppens et al., 2005; Monde et al., 2005; Muñoz et al., 2006). That, in turn, provided in all cases satisfactory balances between invested comput-

Table 1

Calculated relative energies (kcal mol⁻¹) and abundances (%) of the (4S,5R,6S)-6-hydroxyeuryopsin (**1**) and (4S,5R,6S)-6-acetyloxyeuryopsin (**2**) conformers

Configuration	ΔE_{MMFF}^a	% MMFF ^a	ΔE_{DFT}^b	% DFT ^b	ΔG_{OPT}^c	% OPT ^c
1a	0.00	89.95	0.00	53.09	0.00	85.29
1b	1.83	4.13	0.16	40.75	1.30	9.31
1c	4.41	0.05	1.61	3.54	2.40	1.47
1d	1.66	5.43	2.28	1.14	2.34	1.63
1e	3.24	0.40	2.39	0.95	3.05	0.49
1f	4.54	0.04	2.71	0.55	2.29	1.81
2a	0.23	40.22	0.00	83.71	0.00	91.06
2b	0.00	50.77	0.97	16.29	1.35	8.94

^a Calculated using the MMFF94 energies with Spartan'04W software.

^b Calculated using the DFT B3LYP/6-31G(d) energies with Spartan'04W software.

^c Calculated using the optimization DFT B3LYP/6-31G(d,p) energies with Gaussian'03W software.

ing time and spectral similarity of calculated and experimental VCD spectra. The initial matching of theoretical and experimental VCD spectra obtained indicates that the use of the B3LYP/6-31G(d,p) functional and basis set is appropriate for this type of molecule, as was also the case in our study of eudesmanolide sesquiterpene lactones (Krautmann et al., 2007). In fact, in the case of verticillene diterpenoids, we have explored the use of higher computing levels which afforded (Cerdeja-García-Rojas et al., 2007) calculated VCD curves that were essentially similar to those obtained at the B3LYP/6-31G(d,p) level of theory. As shown below, the use of a larger basis set and functional just confirms the goal of the present work, which is the absolute configuration determination of eremophilanolides **1**, **2** and **8**, and is not providing any significant benefit associated to larger elapsed computer times.

After complete DFT B3LYP/6-31G(d,p) optimization (Table 1), essentially two conformations for the C1–C2–C3–C4–C5–C10 ring and three rotamers for the hydroxyl group were observed in the ΔG range of 3.05 kcal mol⁻¹ for **1**. From these six conformers, two account for 94.60% of the total population. In the most stable conformation (**1a**, Fig. 1) the Me-15 group is *quasi*-equatorial with an H3 α –H4 α dihedral angle of 69.2°, while this angle is –56.1° for **1b**. The calculated VCD spectra of these two lower energy conformers of **1**, using the DFT B3LYP/6-31G(d,p) level of theory, were combined in a single weighted plot according to the Boltzmann conformational populations derived from their relative free energy values of the optimized structures (Fig. 2). They showed good agreement with the experimental spectrum, excepting in the region around 1200 cm⁻¹, a situation that was considered attributable to intermolecular hydrogen bonding of the hydroxyl group.

To verify this assumption, the acetylated derivative **2** was studied, for which we compared the experimental and calculated VCD spectra. The Monte Carlo analysis at the MMFF94 level again showed six conformers, but in this case the two most stable ones (Fig. 1) contributed to 99.99% of the conformational population. After DFT optimization, the lowest energy conformation **2a** showed the Me-15 group was *quasi*-axial, with an H3 α –H4 α dihedral angle of –57.2°, which contributed to 91.06%, whereas in **2b** the Me-15 group was *quasi*-equatorial, with an H3 α –H4 α dihedral angle of 65.2°, and contributed 8.94%. Comparison of the experimental and calculated DFT B3LYP/6-31G(d,p) VCD curves of **2** (Fig. 3) were in good agreement, including the 1200 cm⁻¹ spectral region, thereby confirming that in **1** there was intermolecular hydrogen bonding.

In order to explore if there was a significant advantage for the use of VCD calculations based on a larger number of hybrid density functionals and larger basis sets, the calculations for **2** were also performed at the B3PW91/DGDZVP level of theory. For this purpose, the atom coordinates of the B3LYP/6-31G(d,p) optimized conformers were used as input parameters for the new conformational

optimization calculations. As a result, two main conformers, differing by a ΔG value of $1.54 \text{ kcal mol}^{-1}$ were obtained, accounting for a 93.22:6.68 conformational ratio of **2a:2b**, for which VCD calculations were done. The combined weighted plot, according to the Boltzmann conformational populations derived from their relative free energy values, are also shown in Fig. 3, from where it is visually evident that both B3LYP/6-31G(d,p) and B3PW91/DGDZVP calculations led to the same absolute configuration of **2**; therefore, there is no need to invest additional computer time.

Although there are a few statistical comparisons of calculated and experimental VCD data (Stephens et al., 2007a,b,c,d), in most cases visual comparison of spectra has been used (Cichewicz

et al., 2005; Freedman et al., 2003b; Lassen et al., 2005; Monde et al., 2005; Monde et al., 2006; Muñoz et al., 2006) for absolute configuration determination, and even very recently to establish the structure of a natural occurring coumarin in a case where NMR measurements were not of further utility (Min et al., 2007). In any event, we evaluated the statistical methodology developed by Stephens et al. (2007a,b,c,d). For this purpose, since the measured IR and VCD frequencies derive from an anharmonic force field, while calculated frequencies derive from a harmonic force field, the later were scaled using an anharmonicity factor of 0.97. The bands of the calculated IR spectrum were numbered and assigned to the bands in the measured spectrum using described

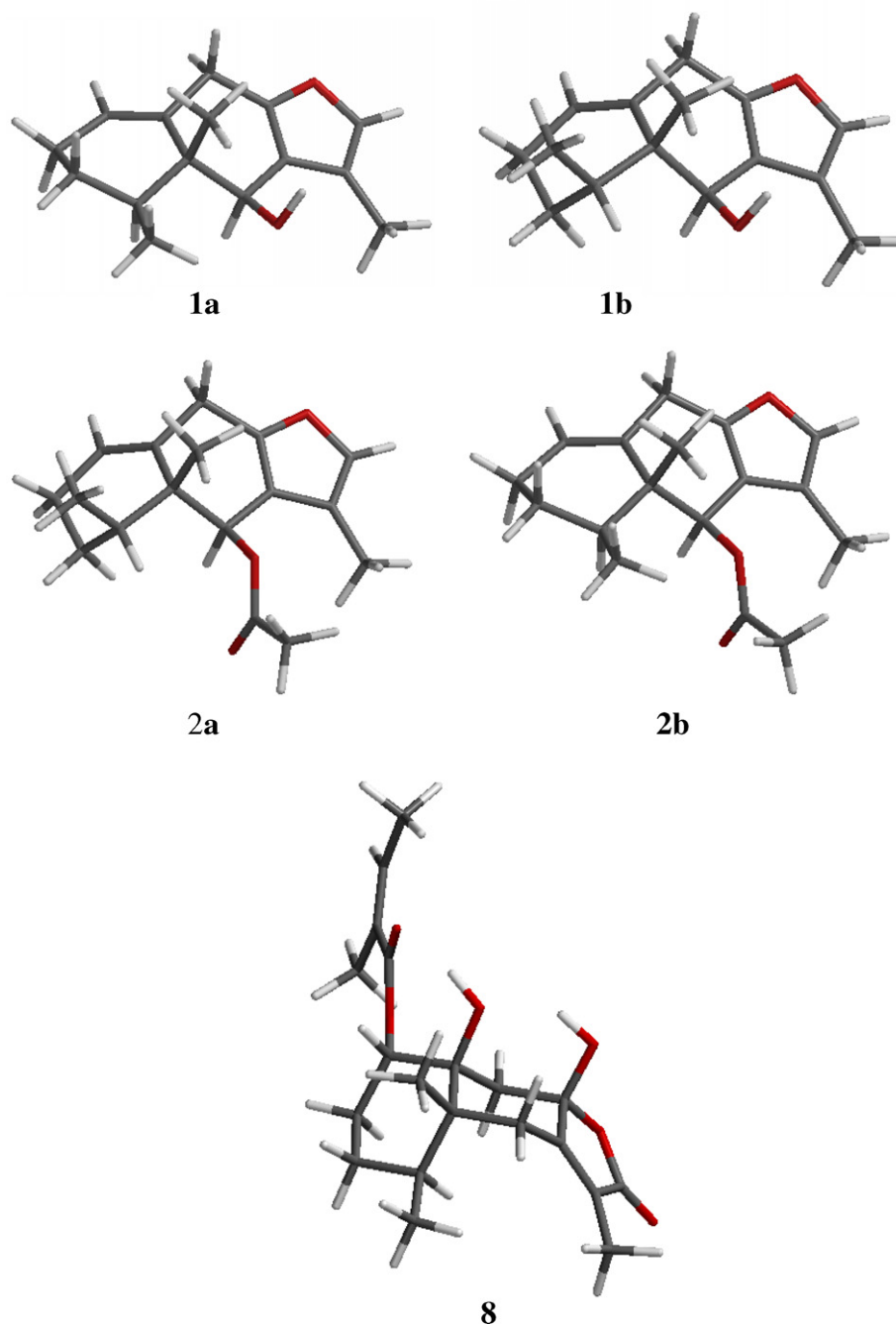


Fig. 1. Minimum energy DFT structures of (4S,5R,6S)-**1**, (4S,5R,6S)-**2**, and (1S,4S,5R,6S,8S,10S)-**8**. For details see Table 1.

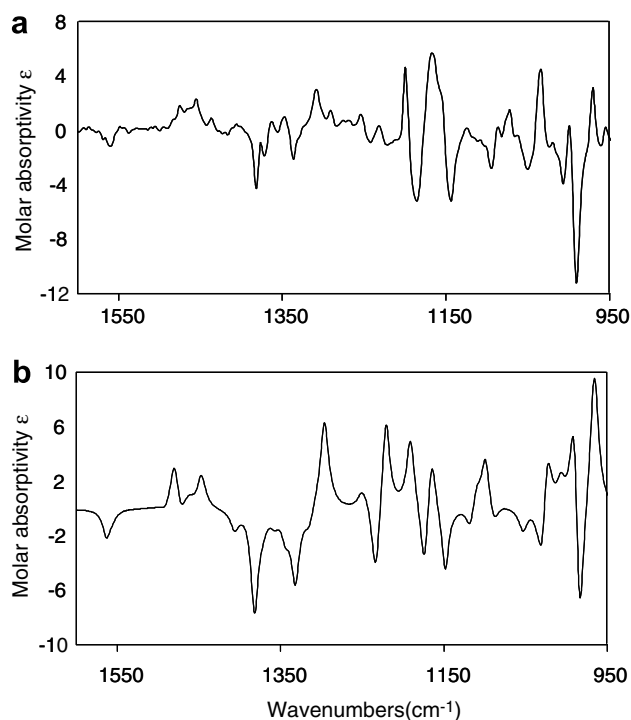


Fig. 2. (a) Experimental and (b) DFT B3LYP/6-31G(d,p) Boltzmann weighted VCD spectra of (4S,5R,6S)-6-hydroxyeuryopsin (**1**).

methodology (Nafie, 2008), and then the same numbers were used for the VCD spectra in which the bands were positive and negative. After rotational strengths were obtained by integration using the Varian resolutions software, plots of measured versus calculated rotational strengths were constructed and the corresponding R^2 coefficients were calculated. Of course a perfect fit is obtained if all points lie along a line of slope +1, thus providing an R^2 coefficient of 1. The corresponding R^2 coefficients for **2** are given in the figure legend of Fig. 3.

The conformational analysis of **8**, isolated from *Psacalium paucicapitatum* (Burgueño-Tapia et al., 2006), was also carried out as in the cases of **1** and **2**. The Monte Carlo search of (1S,4S,5R,6S,8S,10S)-**8** using the MMFF94 force field, followed by DFT B3LYP/6-31G(d,p) optimization indicated that this eremophilanolide exists in a single preferred conformation which seems to be stabilized by two intramolecular hydrogen bonding electronic interactions, one between the hydroxyl groups, and the other one between the hydroxyl group at C10 and the angeloyloxy carbonyl group, as shown in Fig. 1. The VCD calculations for **8** were done as in the case of **2**, at the DFT B3LYP/6-31G(d,p) and at the B3PW91/DGDZVP levels of theory, and the experimental VCD spectrum was compared with those calculated at both used levels of theory in Fig. 4, whose figure legend included the corresponding statistical R^2 values.

2.1. Conclusions

Good agreement between experimental and calculated spectra (Fig. 4) of **8** unambiguously allowed to us assign the 1S,4S,5R,6S,8S,10S absolute configuration to the natural product. Similarly, detailed comparisons of experimental and calculated spectra of **1** (Fig. 2) and **2** (Fig. 3) confirmed the 4S,5R,6S absolute configuration for 6-hydroxyeuryopsin, in agreement with the configuration originally described (Pérez et al., 1991) for the natural product.

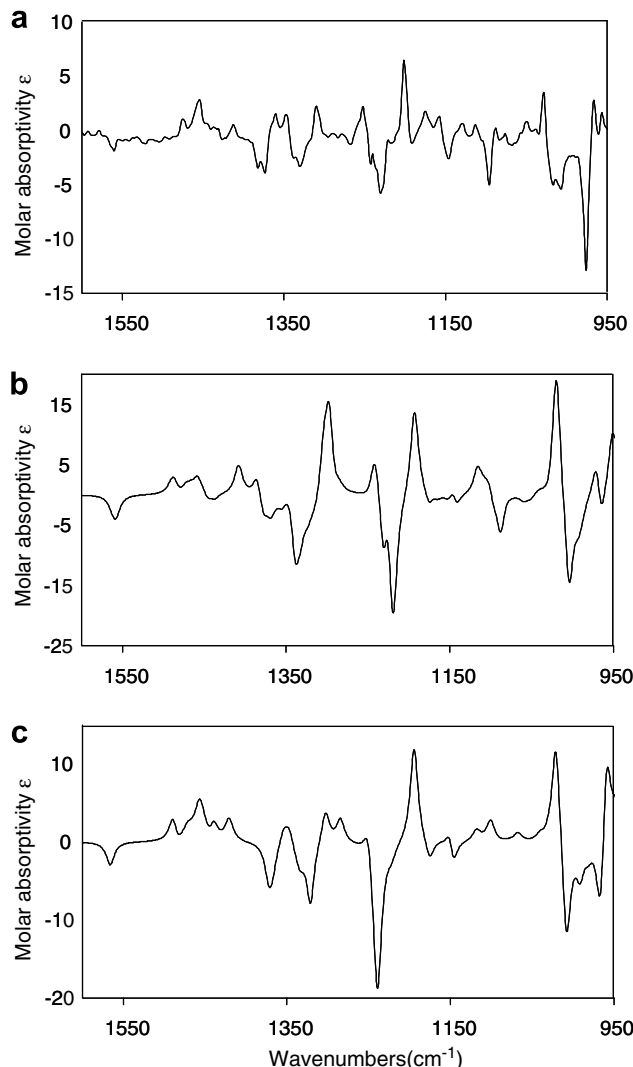


Fig. 3. (a) Experimental, (b) DFT B3LYP/6-31G(d,p), and (c) DFT B3PW91/DGDZVP Boltzmann weighted VCD spectra of (4S,5R,6S)-6-acetyloxyeuryopsin (**2**). The R^2 coefficient for plot 'a' versus plot 'b' is 0.9318, and that for plot 'a' versus plot 'c' is 0.9463.

3. Experimental

3.1. Compounds

Natural product **1**, its acetate **2**, and eremophilanolide **8**, were available from previous studies (Burgueño-Tapia et al., 2004; Burgueño-Tapia et al., 2006). VCD spectra were measured using a dual-PEM ChiralIR FT-VCD spectrophotometer at BioTools Inc. (Jupiter, FL). Samples dissolved in CCl_4 (100 μL) were placed in a BaF_2 cell with a pathlength of 100 μm and data were acquired at a resolution of 4 cm^{-1} . For **1**, 5.0 mg were used and measured during 3 h, for **2**, 5.7 mg were also measured during 3 h, and in the case of **8**, 4.8 mg were measured during 6 h.

3.2. Molecular modeling

Geometry optimizations for (4S,5R,6S)-6-hydroxyeuryopsin (**1**), its acetylated derivative **2**, and the eremophilanolide **8** were carried out using the MMX force field calculations (Gajewski et al., 1990) as implemented in the PCModel program. The E_{MMX} values were used as the convergence criterion, and a further search with the Monte Carlo protocol (Chang et al., 1989) was carried out with

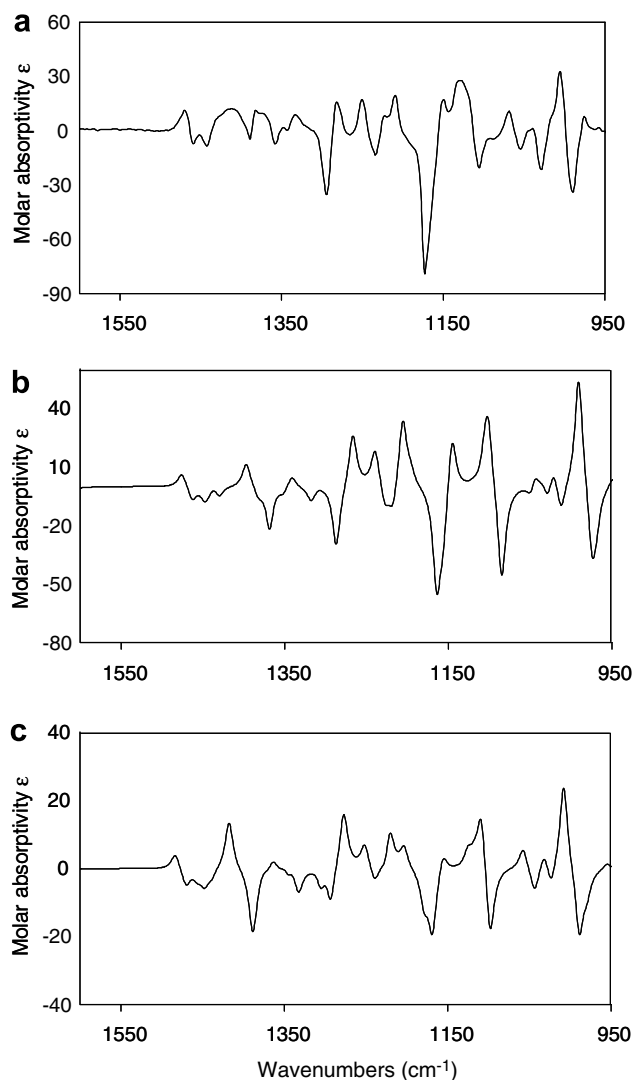


Fig. 4. (a) Experimental, (b) DFT B3LYP/6-31G(d,p), and (c) DFT B3PW91/DGDZVP Boltzmann weighted VCD spectra of (1S,4S,5R,6S,8S,10S)-**8**. The R^2 coefficient for plot 'a' versus plot 'b' is 0.8451, and that for plot 'a' versus plot 'c' is 0.7793.

no restriction. A total of six structures for both **1** and **2**, and only one for **8** were found. All structures were further optimized by DFT (Perdew, 1986) calculations at the B3LYP/6-31G(d,p) level of theory using the Spartan'04W program routines. Vibrational calculations of IR and VCD frequencies for **1**, **2** and **8** at the DFT B3LYP/6-31G(d,p) level of theory were then performed using Gaussian 03W software. No solvent effects were included in the calculations. The DFT B3LYP/6-31G(d,p) calculations required between 20 and 24 h of computational time per conformer for **1** and **2**, and 50 h for **8** using a desktop personal computer with 2 Gb RAM operated at 3 GHz. In the case of the DFT B3PW91/DGDZVP calculations, each conformer of **2** required additional 31 h, while the sole conformer of **8** consumed 49 h on the same desktop computer. The integrated VCD intensities, also referred to as the rotational strengths, were obtained using the Varian resolutions software v. 4.1.0.101. Negative bands were integrated after multiplying the VCD intensities by -1 .

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