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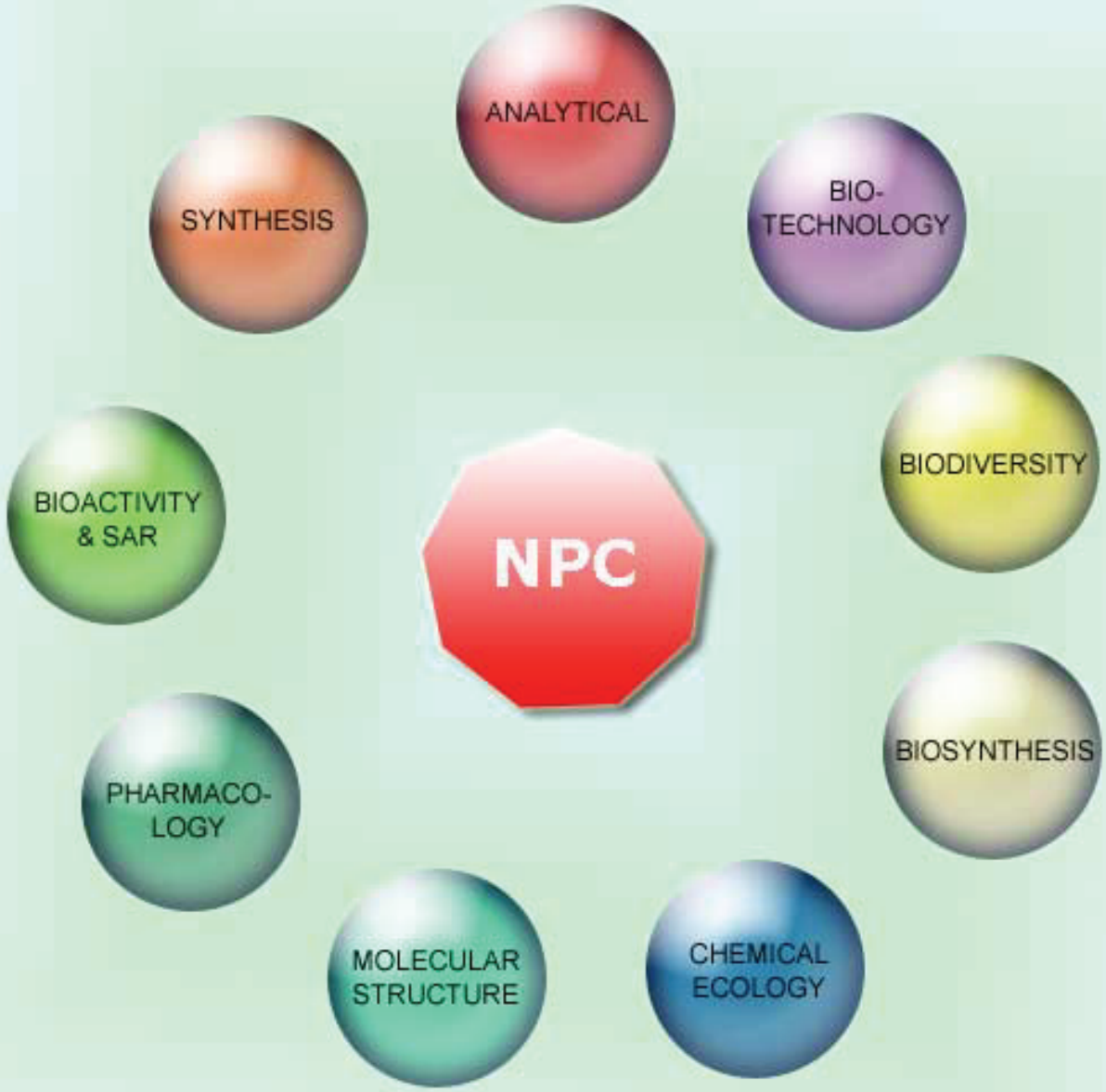

This Issue is Dedicated to
Professor Alejandro F. Barrero
On the Occasion of his 68th Birthday

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Vibrational Circular Dichroism: Recent Advances for the Assignment of the Absolute Configuration of Natural Products

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Vibrational circular dichroism (VCD) emerged during the last decade as a reliable tool for the absolute configuration (AC) determination of organic compounds. The principles, instrumentation, and methodology applied prior to early 2013 were recently reviewed by us. Since VCD is a very dynamic field, the aim of this review is to update VCD advances for the AC assignment of terpenoids, aromatic compounds, alkaloids, and other natural products for the 2013-2014 period, when VCD was applied to the AC assignment of some 70 natural products. In addition, although discovered in 2012, a brief introduction to the VCD exciton coupling approach and its applications in natural products AC assignment is presented.

Keywords: Natural products, Absolute configuration, Vibrational circular dichroism, Vibrational circular dichroism exciton coupling.

Chirality is the property of handedness, which is probably the most intriguing aspect found in Nature, that goes from the shape of galaxies to the shape of millions of molecules. It allows the existence of life since amino acids that constitute proteins have an *S* absolute configuration (AC), and in our organism these proteins interact differently with the two enantiomers of a given molecule. From here it follows that knowing the AC of organic molecules is fundamental to understanding many aspects of life. Of course, secondary metabolites, biosynthesized by living organism, have their own handedness [1,2].

Although the determination of the AC of natural products has been dominated during the 20th century by circular dichroism of electronic transitions, which was simply known as CD, and is currently known as electronic circular dichroism (ECD), the situation changed approximately at entry into the 21th century when circular dichroism of vibrational transitions gained relevance to perform this task [3]. One of the advantages of vibrational circular dichroism (VCD) over ECD is that electronic transitions that can be measured in the ultraviolet and visible regions are limited to the presence of chromophors, while transitions associated with vibrational modes of molecules, which are measured in the infrared region of the electromagnetic spectrum, are present in any chiral natural product regardless of its simplicity or complexity. An additional advantage of VCD over ECD is that the number of vibrations detected in the infrared region is significantly larger than the number of electronic transitions that can be detected for a given molecule, thus providing much more detailed information. A third advantage of VCD over ECD is that conformational details of molecules are more sensitive to vibrational transitions than to electronic transitions.

Of relevance is also to note that most AC determinations made during the 20th century were based on comparisons with model compounds, which in some cases led to the wrong AC assignment, which of course can be established correctly by VCD, as is the case of esquelane derivatives, which are constituents of a commercial fragrance [4]. A similar situation was observed for chromane derivatives, for which the relationship between the stereostructure and their ECD was determined almost exclusively by the empirical chromane helicity rule, although failures of the rule have been detected in some cases [5].

VCD has allowed the re-examination of the AC of some natural products like (−)-brevianamide [6] and (+)-schizandrin [7], and it has eventually aided the re-examination and reassignment of the molecular structure of klaivanolide [8]. The VCD superiority over other spectroscopic methods has allowed the structural analysis of complex molecules, like the atropisomer distribution of bridled chiroporphyrins in solution [9], or the planar configuration of nona- and dodecamethoxycryptophanes [10]. It also has been used to determine the secondary structure of NH-indazoles such as (4*S*,7*R*)-campho[2,3-c]pyrazole [11]. In addition, VCD has been used for reaction monitoring, and to show solvent induced conformational changes in cyclic peptides [12]. VCD spectra of aminoacids (aa_s), peptides and proteins are difficult to obtain under biological conditions, making it necessary to work with highly concentrated samples to reach acceptable signal intensity, although eventually this is not possible due to low solubility and aggregation phenomena. The VCD signal intensity of aa_s and oligopeptides was enhanced by up to 2 orders of magnitude by coupling them to a paramagnetic metal ion [13].

Since VCD acquired relevance in AC assignments [14-17], efforts have been made in generating virtual spectrometers [18,19], and groups with large resources have systematized conformational analyses, VCD calculation curves, and comparison between experimental and calculated spectra [20].

Misassignments would be rare in VCD since the method is mainly based on the comparison of an experimental spectrum with one based on good level quantum chemical calculations. The determination of the experimental spectrum is a task that requires some 5-10 mg of the natural product, and it consumes typically

5-6 h instrument time, and an additional equal time to measure the solvent spectrum, which has to be subtracted from the spectrum containing the sample. In contrast, the quantum chemical calculation is a quite laborious procedure which can consume from many hours to a few weeks, depending on the number of electrons the sample possesses and the number of conformers which have to be considered. Thus, to illustrate this point, a critical example was a phloroglucinol derivative which shows its sole stereogenic center on a chain appending from an aromatic ring, and which required over 600 h to complete calculations when using a desktop computer operating at 3 GHz with 8 Gb RAM [21]. From here it follows that the limiting time, by far, is the calculation time and not the experimental instrument time.

Fortunately, not all are bad regarding quite long calculation times. It was shown a few years ago that exciton coupling, based on the interaction of two IR chromophores, is a convenient and versatile method to determine AC [22]. Similar to the ECD exciton coupling [23,24], vibrational circular dichroism exciton coupling (VCDEC) [25] is based on the though-space interaction of two or more chromophores which yield a pair of VCD signals with opposite signs around the absorption region of the chromophores. The sign of this split VCD signal reflects the AC of the molecule. Thus, when the interacting chromophores are counterclockwise oriented, the long wave number component of the associated exciton couplet can be expected to exhibits a negative Cotton effect, while when they are clockwise oriented, the long wavelength Cotton effect is positive (Figure 1). For this purpose carbonyl groups have been selected because of their well localized stretching vibration mode that gives rise to electronic transition moments whose direction is virtually parallel to the carbonyl bond. In addition, carbonyl groups can be routinely installed in a desired part of the molecule. Thus, for a chiral molecule containing two chromophores, the AC can be determined without the need of time expensive theoretical calculations.

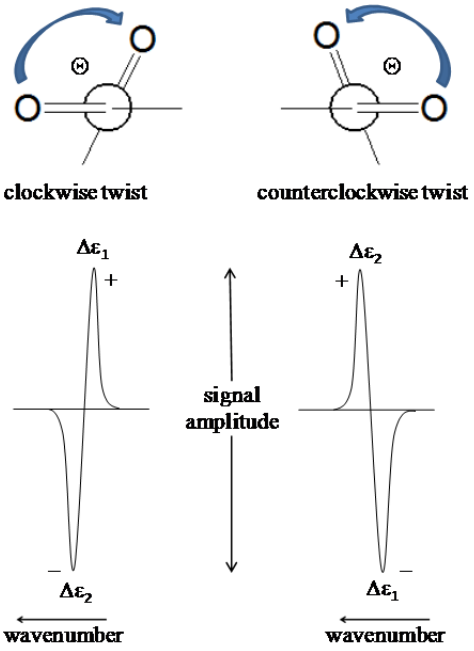


Figure 1: Relative orientation of two carbonyl groups and amplitude of the VCDEC signals.

The VCDEC approach has been tested for AC assignment of a small number of natural compounds including spiroindicumides A and B [26], a 3-substituted isoindolinone [27], berkeleyamide D [28], a germacranolide [29], and a series of angular 3'-acyloxypyranocumarins [25] and 3',4'-diacyloxypyranocumarins [30]. The method has also been used for monitoring the enolization of camphor diketones [31].

In a recent review [14], an introduction to the principles, instrumentation, and theoretical quantum chemistry methods for VCD spectra calculation, along with VCD methodology applied to chiral mono-, sesqui-, di-, mero- and triterpenoids, as well as other natural products prior to mid-2013 was provided. Since VCD is currently a very dynamic field, the aim of this review is to update VCD advances for the AC assignment of terpenoids, aromatic compounds, alkaloids, and other natural products for the 2013-2014 period.

Terpenoids

A few mono- and sesquiterpenes have been studied by VCD in the period covered by this review, and of course the most abundant group of studied terpenes is that comprised of diterpenes. Regarding triterpenes, the only studied molecule, already reviewed [14] is a lupeol derivative.

Monoterpenes

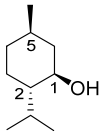
VCD is quite sensitive to slight differences in the conformation of chiral molecules and their local environment. A study about the effect of a hydroxy group was addressed using menthol (**1**) as a representative chiral molecule. Comparison of the VCD spectrum with calculations for various rotational conformations of sustituents revealed that the 1064-1254 cm^{-1} region sensitively reflects conformational changes. The use of a Boltzmann-weighted analysis to account for the various conformers improved the agreement between the calculated and experimental results, although some discrepancies remained. This sensibility shows the potential application for conformational selective analysis of the local environment of the hydroxy group in chiral molecules and its interaction with neighboring solvent molecules [32].

Although over 150 naturally-occurring thymol derivatives containing a stereogenic center are known [33], (+)-(8*S*)-8,9-epoxy-6-hydroxy-10-benzoyloxy-7-oxothymol isobutyrate (**2**), isolated from *Ageratina cylindrica*, is the only compound whose AC has been assigned. After a Monte Carlo protocol at the MMFF level of theory, followed by complete optimization and harmonic vibrational frequencies calculation using DFT with the B3LYP/DGDZVP basic set and functional, IR and VCD Boltzmann-weighted spectra matched modestly (Table 1). B3PW91 and PBEPBE functionals with the same basis set were therefore used. The enantiomer similarity index increased significantly when using B3PW91. Although the similarity index of IR is smaller, the VCD spectrum is better, and the computer time per conformer is almost one half of that when using the PBEPBE functional [34].

Table 1: Confidence level data for the IR and VCD spectra of **2** calculated using DFT at different levels of theory.

Method	anH[a]	S_{IR}[b]	S_E[c]	S_{-E}[d]	ESI[e]	C[f](%)	CPU[g] (min)
B3LYP/DGDZVP	0.972	86.5	66.9	26.0	40.9	79	215
B3PW91/DGDZVP	0.962	92.8	71.6	21.4	20.0	100	266
PBEPBE/DGDZVP	1.002	70.3	72.5	13.4	59.1	100	154

[a]Anharmonicity factor. [b]IR spectra similarity. [c]VCD spectra similarity for the correct enantiomer. [d]VCD spectra similarity for the incorrect enantiomer. [e]Enantiomer similarity index calculated as $S_E - S_{-E}$. [f]Confidence level for the stereochemical assignments. [g]Job CPU average time per conformer when using a node with eight processors at 2.93 GHz and 8 Gb of RAM.



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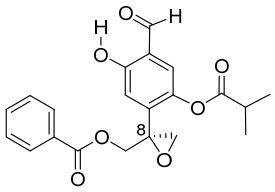

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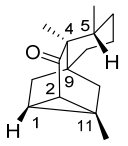
Sesquiterpenes

The AC of (+)-3-ishwarone (**3**), isolated from *Peperomia scandens*, was assigned using three chiroptical methods. Based on the reported C1,C2,C9,C11 relative configuration, experimental and calculated ECD, ORD, and VCD spectra of the four possible diastereomers 1*R*,2*S*,4*S*,5*R*,9*R*,11*R*, 1*R*,2*S*,4*R*,5*R*,9*R*,11*R*, 1*R*,2*S*,4S,5*S*,9*R*,11*R*, and 1*R*,2*S*,4*R*,5*S*,9*R*,11*R* were evaluated. Comparison of ECD data failed to establish undoubtedly the AC of **3**. The electronic dissymmetry factor (EDF) (ratio of CD to absorption spectra) suggested that the AC of **3** may be 1*R*,2*S*,4*S*,5*R*,9*R*,11*R*, although the conclusion needed support. In turn, ORD data suggested the 1*R*,2*S*,4*S*,5*R*,9*R*,11*R* and 1*R*,2*S*,4*S*,5*R*,9*R*,11*R* diastereomers were feasible. Finally, VCD results provided better similarity for the 1*R*,2*S*,4*S*,5*R*,9*R*,11*R* diastereomer [35].

Addition of diazomethane has been used for many years to prove the presence of an exocyclic methylene group in an α,β-unsaturated lactone. The stereochemistry of this addition was confirmed recently using zaluzanin A (**4**) as a model. The AC of **4** was assured by VCD spectroscopy of its diacetyl derivative and confirmed by X-ray diffraction analysis, while the AC of the diazomethane addition product followed after ^{1}H NMR chemical shifts evaluation with respect to **4**, and confirmed by X-ray diffraction analysis, including Flack and Hooft parameters AC determination [36].



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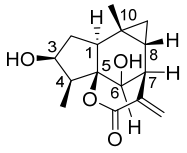

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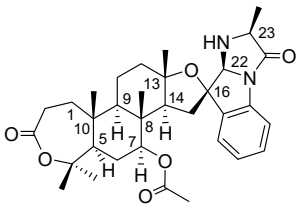
Diterpenes

The four spiro fused diterpene-indole alkaloids **5**-**8** were isolated from *Aspergillus terrus*. The relative configuration followed from ROESY experiments. Consequently, the 5*R*,7*S*,8*R*,9*R*,10*R*,13*S*,4*S*, 16*S*,22*S*,23*S* AC for **5** and **6**, and the 5*R*,7*S*,8*R*,9*R*,10*R*,3*S*,14*S*,16*S*, 22*S* AC for **7** and **8**, was established using a combination of Marfey´s method [37] and by comparisons of the DFT B3LYP/6-31G(d,p) calculated and experimental ECD and VCD spectra [38].

The isoneoamphilectane diterpenes **9**-**11**, strong growth inhibitors of *Mycobacterium tuberculosis*, were isolated from the sponge *Svenzea flava.* Since the 7-formaldehyde group in **11** undergoes *cis*/*trans* isomerization, it was transformed into its amino derivative **12**. After geometry optimization of **12**, frequency, IR, and VCD calculations, followed by comparison with its experimental VCD spectrum, the 3*S*,4*R*,7*S*,8*S*,11*R*,12*S*,13*R* AC was established [39].

From *Acacia schaffneri*, a plant used to alleviate stomach pain and toothache, the macrocyclic dimeric diterpene **13**, containing a C_2 symmetry axis, was isolated. The structure was established by NMR data, with the HMBC correlation of H-7 with C-17' a key to



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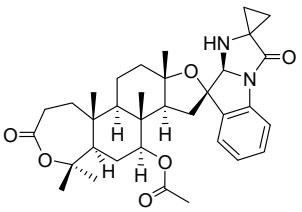
6 Δ^1



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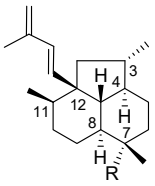
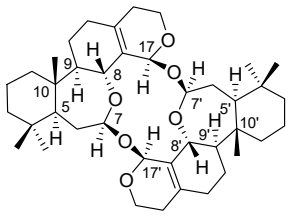
8 Δ^1



	R		R
9	CN	**11**	NHCHO
10	$NHCH_3$	**12**	NH_2



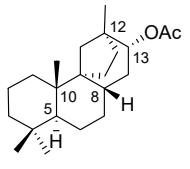
13

assume the dimeric structure. Comparison of its VCD spectrum with that calculated using DFT with the B3LYP/DGDZVP basis set and functional, assigned its preferred conformation and its 5*S*,7*S*,8*R*,9*R*,10*S*,17*S*,5′*S*,7′*S*,8′*R*,9′*R*,10′*S*,17′*S* AC, which was confirmed by evaluation of the Flack and Hooft parameters obtained after single crystal X-ray diffraction analysis [40].

The diterpene content of Chilean *Calceolaria* species up to now comprises 11 abietanes, 6 labdane, 34 pimarane, 11 stemarane, 13 scapadulane, and 6 metabolites having two diterpene units linked as a malonate diester. The AC of these compounds is quite confusing, since abietanes and scopadulanes have been depicted as *normal* diterpenes, while pimaranes, labdanes, and stemaranes have been depicted as *ent* diterpenes. The depicted AC of 13-acetoxyscopadulane (**14**), isolated from several *Calceolaria* species, was established by VCD in combination with DFT calculations, as well as by evaluation of Flack and Hooft single crystal X-ray parameters. It follows that this compound belongs to the normal enantiomeric series of diterpenes, and that at least 11 out of 13 scopadulanes, for which chemical or biogenetical relationships with **14** are established, also belong to the same stereochemical series [41].

Diterpenes **15**-**17** were isolated from *Solidago shortti*, an endangered species. Its relative 3*R**,4*S**,5*R**,7*S**,8*S**,9*S**,10*S** configuration was assigned from NMR data and analysis of coupling constant values using an energy-minimized model and the Tori equation. In turn, the AC was assigned by comparison of the calculated and experimental VCD spectra. The flexibility of the side chain of **15** resulted in a large number of low-energy conformers, giving a poor confidence level for the calculated spectra. ROESY correlations were therefore used to limit the number of possible conformers and to improve the quality of the calculated spectra. Evaluation of the VCD data using the Compare*VOA* software supported the 3*R*,4*S*,5*R*,7*S*,8*S*,9*S*,10*S* AC. Furthermore, the calculated OR ($[\alpha]_D$ +121) compared well with the experimental ($[\alpha]_D$ +76) value and further supports the proposed AC. [42].

A chemical study of the flowers and leaves of *Ageratine jocotepecana* afforded diterpenoids **18**-**20**. After evaluation of the



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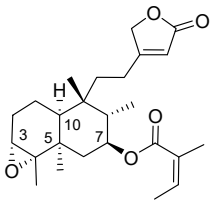

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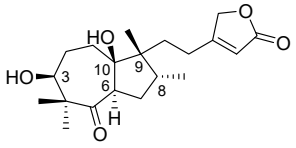

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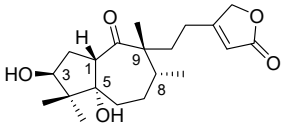

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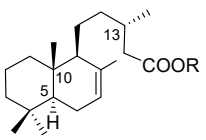
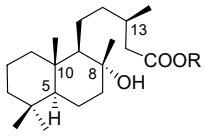
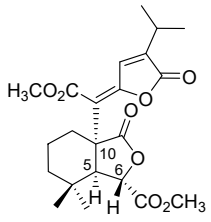
reported controversial arguments for the assignment of the C-13 configuration, the coexistence of 13*R* and 13*S*-labdanes, belonging to the *normal* 5*S*,10*S* diterpene series, in the same species, was unexpected and demonstrated by VCD measurements of **19** and **21** in comparison with the DFT B3LYP/DGDZVP calculated spectra. To gain chemical evidence for the configuration at C-13 in **18** and **20**, these natural products were transformed into their respective 8-en methyl ester derivatives. Interestingly, the ^{13}C NMR chemical shifts of **19** and **21** were very similar, revealing the inability of ^{13}C NMR spectroscopy to distinguish these C-13 epimers [43].



	R
18	H
19	CH_3



	R
20	H
21	CH_3



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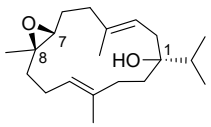


23

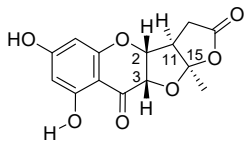
Hyptisolide A (**22**), isolated from *Hyptis crenata* Pohl ex Benth, was the first diterpenoid that had the 7,8;11,12-*bis*-secoabietane skeleton. Its structure and relative stereochemistry were elucidated by HRESIMS, NMR, and X-ray diffraction analyses. The 5*S*,6*S*,10*R* AC of **22** was determined by comparing the experimental VCD spectrum with the calculated spectrum. Although an intense bisignate signal in the stretching carbonyl groups region was observed, no further evaluation was made [44] in terms of VCDEC.

(−)-(1*S*,3*E*,7*R*,8*R*,11*E*)-7,8-Epoxycembrane-3,11-dien-1-ol (**23**), its derived acetate, cembrene A, nephtenol, and cembrenol were isolated from *Burcera multijuga*. The conformational preference of **23** followed from molecular modeling, and its AC from comparison of DFT B3LYP/DGDZVP calculated and experimental VCD curves [45].

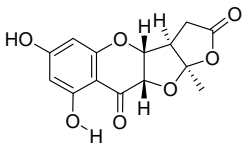
Aromatic compounds

DFT calculations of two conformers of planchol E (**24a** and **24b**) at the DFT B3LYP/6-31+G(d) level of theory showed that the experimental ^{1}H NMR spectra display the features of **24a** without an intramolecular H-bond, while the measured IR spectrum originated from **24b** has an intramolecular H-bond. Calculated ECD and VCD at the same level of theory showed significant differences between **24a** and **24b**, although no comparison with experimental data was made [46].

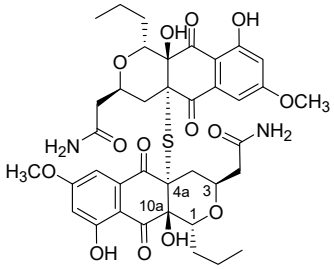
The *S*-bridged dimeric pyronaphtoquinone hypogeamicin A (**25**), along with hypogeamicin B (**26**), and other monomeric precursors were isolated from a cave-derived actinomycete *Nonomuraea specus*. The AC of **26** was assigned using ECD, VCD, and ORD spectra and *ab initio* quantum chemical calculations. The four stereoisomers 1*R*,3*R*,4a*S*,10a*R*, 1*S*,3*R*,4a*S*,10a*R*, 1*R*,3*S*,4a*S*,10a*R*, and 1*S*,3*S*,4a*S*,10a*R* were considered. The similarity between the experimental and calculated spectra was determined via overlap. The consensus of quantum mechanical calculations, suggested the AC of (−)-**26** to be 1*R*,3*S*,4a*S*,10a*R*. On the basis of the likely conservation of the epoxide ring opening stereo- and regiochemistry and stereochemical assignment of **26**, the 1*R*,3*R*,4a*R*,10a*S*,10*R*, 3′*R*,4a′*R*,10a′*S* AC was proposed for **25** [47].



24a



24b



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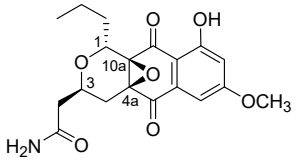

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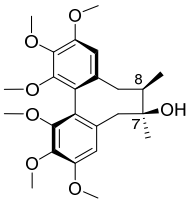
(+)-Schizandrin (**27**) is an antihepatotoxic, anti-HIV, and anti-tumor natural product, whose originally described 7*S*,8*S* AC was reassigned as 7*S*,8*R* after comparison of the DFT B3LYP/6-311+G(d) spectra of 7*S*,8*S* and 7*S*,8*R* diastereoisomers with the experimental spectrum. Both experimental and B3LYP/6-31G(d) calculated VCD spectra for (7*S*,8*S*)-**27** look similar in some regions. The major difference between the predicted and experimental VCD spectra is a strong negative signal near 1400 cm^{-1} in the calculated spectrum, which was assumed to be caused by the use of low level computation sets. Therefore, the B3LYP/6-311+G(d) higher level of theory was used. Unfortunately, the predicted VCD and IR spectra look similar to those obtained at the B3LYP/6-31G(d) level. The B3LYP/6-311+G(d) predicted VCD and IR spectra for (7*S*,8*R*)-**27** look similar to the experimental results. It clearly exhibited that the AC is 7*S*,8*R*. ECD was also used to reach the same conclusion [7].



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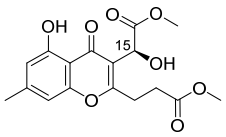

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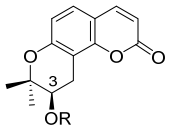
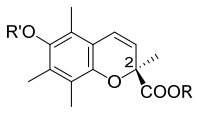


	R
29	H
30	Ang
31	Ac
32	isobutyroyl

	R
33	isovaleroyl
34	senecioyl
35	tigloyl
36	dodecanoyl



	R	R
37	H	H
38	CH_3	Ac

The first racemic total synthesis, chiral resolution, and AC elucidation of oxalicumone C (**28**) was described [48]. After enantiomeric resolution, determination of the AC was achieved by comparison of measured VCD and ECD spectra with those obtained from *ab initio* calculations. The VCD spectrum of **28** does not match well with the calculated one because of intermolecular hydrogen bonding of the two hydroxy groups. Only the 1050–1225 cm^{-1} region showed reasonable agreement. To avoid hydrogen-bonding interactions, the hydroxy groups of both enantiomers were silylated to obtain their respective bis(trimethylsilyl) ethers. In the absence of hydrogen bonding, the experimental and calculated VCD spectra showed good agreement over the measured range (1050–1800 cm^{-1}). Nevertheless, the signals between 1600 and 1800 cm^{-1} in the VCD spectra of **28** and its silylated compound were handled with caution because of birefringence artifacts, and were, therefore, not used to determine the AC. Solvation was treated with the integral equation formalism polarizable continuum model for CH_3CN during the second optimization and subsequent frequency analysis to obtain the vibrational spectra and time-dependent DFT calculations [TD-B3LYP/6-311G(d,p)] for the electronic spectra. Finally, the stereochemistry of the natural product was determined by comparing the optical rotation values from both synthesized enantiomers of **28** {(*S*)-**28** $[\alpha]_D$ = +57.6 (CH_3CN) and (*R*)-**28** $[\alpha]_D$ = –69.7 (CH_3CN)} with the reported data of naturally-occurring **28** {$[\alpha]_D$ = +11.25 ($CHCl_3$)} [48].

A complex mixture of lomatin (**29**) C-3' esters and (–)-*O*-angeloyllomatin (**30**) were isolated from the seeds of *Prionosciadium thapsoides*. A literature search revealed that some lomatin C-3' monoesters have positive specific rotations, while others had negative values. The mixture was hydrolyzed and resulting **29** was re-esterified to afford (–)-*O*-angeloyl- (**30**), (–)-*O*-acetyl- (**31**), (–)-*O*-isobutyroyl- (**32**), (+)-*O*-isovaleroyl- (**33**), (+)-*O*-senecioyl- (**34**), (+)-*O*-tigloyl- (**35**), and (+)-*O*-dodecanoyllomatin (**36**). The AC of all molecules was determined as (*R*) from the strong bisignate VCD couplet in the stretching carbonyl group, and by applying the VCDEC approach. In addition to the observed couplet, DFT calculations at the B3LYP/DGDZVP level allowed identification of some vibrational modes of (*R*)-acetyllomatin, which show good similarity to all other esterified derivatives, thus validating the VCDEC conclusion [25].

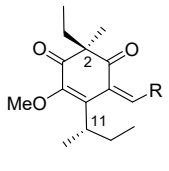
To investigate the scope and limitations of the empirical chromane elicity rule [49], a combination of ECD spectroscopy, especially the temperature dependence, single crystal X-ray diffraction analysis, and DFT calculations were used in a set of ten (*S*)-trolox (**37**) [(*S*)-6-hydroxy-2,3,7,8-tetramethyl]chromanes. VCD was applied to selected diacetyl derivative **38** because this compound does not show hydrogen bonding and, consequently, the interpretation of the VCD spectrum is facilitated. The spectra were calculated using the B3LYP functional and the 6-31G(d), 6-311++G(d,p) and TZVP basis sets. The best fit of the experimental and calculated spectra was obtained for the TZVP basis. The overall agreement of the predicted and experimental VCD spectra independently supported the configurational and conformational assignment of **38** obtained from ECD studies. The results demonstrated that the chromane helicity rule should always be applied cautiously [5].

Alkaloids

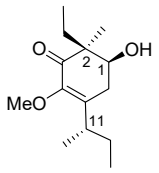
Mycosphacrella sp. fungus, isolated from *Aloe arborescens*, was cultivated in the presence of nicotinamide to afford mycosphines A-D (**39**-**42**). Although the ^{13}C NMR spectrum of **39** resembled that of similin B, the chemical shifts of C-6 differed by 4.3 ppm. The relative configuration of similyn B was determined as 2*S**,11*R** by X-ray crystallography, while that of **39** corresponded to the 2*S**,11*S** configuration, indicating that **39** was either the C-2 or the C-11 epimer of similin B. The AC at C-2 and C-11 followed after applying the VCD method using DFT calculations for the acetyl derivative of **39**. While the AC of **40** and **41** was established using biogenetic considerations, the 1*S*,2*S* AC of **42** was determined by the Mosher method [50]).

The AC of (+)-caripyrin (**43**) was assigned as 2'*R*,3'*R* by VCD in combination with DFT calculations at the B3LYP/6-311G(d,p) level of theory using the integral equation formalism polarizable continuum model IEFPCM for CCl_4 solvation. IR and VCD for the relevant conformers were presented and discussed [51].

(–)-Berkeleyamide D (**44**), described as a matrix metalloproteinase-3 caspase-1 inhibitor, was synthesized as the racemate. After chiral separation of (+)-**44** the AC was determined using the VCDEC approach. The VCD spectrum of (–)-**44** showed a positive-negative couplet, going from lower to higher wave number, indicating a clockwise orientation of the two adjacent carbonyl groups, and thereby assigning the 5*S*,8*R*,9*R* AC for the natural product [28].



	R
39	NH_2
40	$NH(CH_2)_2OH$
41	OH



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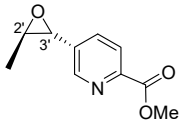

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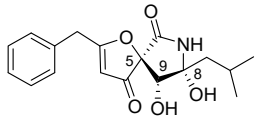

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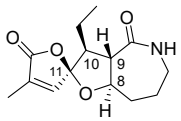
Alkaloids from plants of the genus *Stemona* (family Stemonaceae) typically are characterized by the incorporation of a pyrrolo[1,2-a]azepine core. Stemona lactam S (**45**) and tuberostemospiroline



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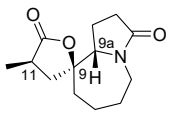

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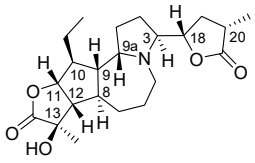

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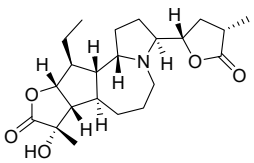
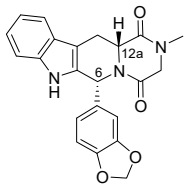


48

(**46**) were isolated from *S. tuberosa* Lour, a plant used in Chinese traditional medicine [52]. Its structure and AC were established by X-ray and VCD spectroscopy. Three optimized conformers with essentially the same conformation, except for the side ethyl group of **45**, and only one conformer for **46**, were observed. After geometrical optimization, IR and VCD data were calculated using the DFT B3PW91/DGDZVP2 level of theory. The calculated VCD spectra of (8*R*,9*S*,10*S*,11*R*)-**45** and (9*S*,9a*S,*11*R*)-**46** were in good agreement with the respective experimental ones. In addition, stemona-amides C-D (**47**-**48**), alkaloids having a novel skeleton, were isolated from the same plant [53]. The relative configuration was established by X-ray crystallography and by NOESY experiments, while the AC for **47** and **48** followed after comparison of the experimental VCD spectra with those calculated for the 3*S*,8*R*,9*R*,9a*S*,10*S*,11*R*,12*S*,13*R*,18*S*,20*S* and 3*S*,8*R*,9*R*,9a*S*, 10*S*,11*R*,12*S*,13*S*,18*S*,20*S* diastereoimers, respectively, using DFT at the B3PW91/DGDZVP2 level of theory.

Tadalafil (**49**), which contains two stereogenic centers, is an approved drug for the treatment of erectile dysfunction, pulmonary arterial hypertension, and benign prostate hyperplasia. It was used to search if VCD allows the determination of the AC without prior knowledge of the relative stereochemistry. Besides VCD, IR and NMR spectra were also used to determine the relative stereochemistry. ECD and ORD spectroscopy, as possible alternative chiral spectroscopic methods to VCD, were used to investigate the complementarily of the three chiroptical techniques. ECD and ORD methods identified the 6*S*,12a*R*/6*R*,12a*S* enantiomeric pair, but for the 6*R*,12a*R*/6*S*,12a*S* pair the AC was uncertain since the lowest-energy conformers have opposite ORD values, and the specific rotation is small. As a result, VCD was clearly the superior discriminatory method for diastereoisomers, and the VCD and NMR combination was optimal [54].

Colchicine (**50**) is the main agent for the treatment of acute cases of gout, and although it was first isolated in 1820 [55] several unknown aspects remain to be explored. DFT studies of geometry, energy, and ^{1}H, ^{13}C, and ^{15}N NMR studies were described. In addition, the assignment of both enantiomers by using a chiral solvating agent, and IR and VCD studies of natural anhydrous (–)-**50**, (–)-**50**·2H$_2$O, anhydrous (±)-**50**, and (±)-**50**·2H$_2$O samples were reported. The two achiral samples do not display chirooptical response in $CHCl_3$ solution, as expected. However, they present a weak chirooptical response in the solid phase, which could be explained by a small enantiomeric excess. After VCD measurement of these four samples, and comparison with the DFT B3LYP/6-311++G(d,p) calculated spectra, natural (–)-colchicine was established as the *P*,7*S* diasteroisomer [56].



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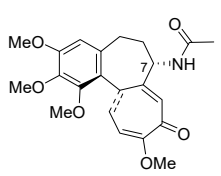

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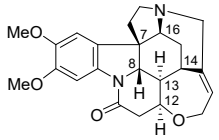

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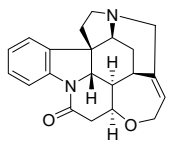

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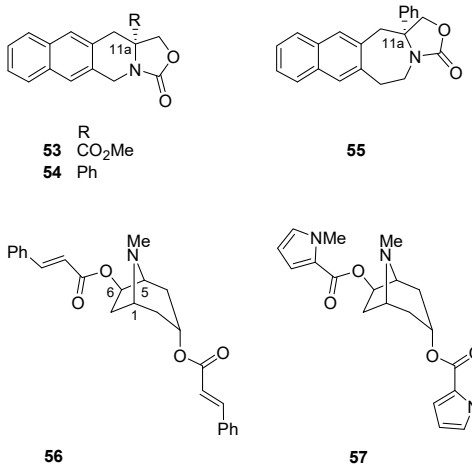
Brucine (**51**) and strychnine (**52**) are found in several species of the *Strychnos* genus. These alkaloids can be absorbed by the human body to produce stimulating central nervous system activity along with other effects. However, several negative effects have been described, indicating that the demarcation line between these activities is very narrow. DFT calculations at the B3LYP/6-311G++(d,p) level of theory were used to study the equilibrium geometry, vibrational spectra, thermodynamics, and non lineal optical (NLO) properties of **51** and **52**. Calculation of the VCD spectra show good agreement with those previously described and indicate that the VCD peaks due to out-of phase stretching modes of aromatic rings and carbonyl stretching modes, in combination with CH stretching modes, are good configuration markers and can be used for AC identification [57].

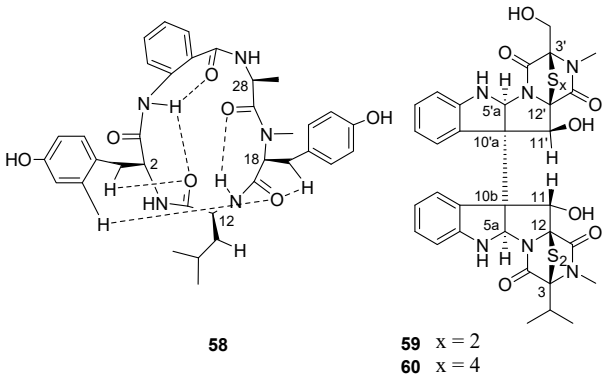
The AC of azaheterocycles **53**-**55**, resulting from the cascade rearrangement of enediynes, were assigned by the joint use of VCD and Cu X-ray diffraction using the Flack and Hooft parameters, thus demonstrating that the rearrangement of enediynes proceeded with retention of configuration. IR and VCD were calculated using DFT with the B3LYP and 6311+G (d,p) functional and basic set. Solvent effects (CH_2Cl_2) were introduced using the polarizable continuum model IEF-PCM combined with SMD [58] quantum mechanical continuum solvation parameters [59].

Diagnostic VCD bands of tropane alkaloids from *Erythroxylaceae* species can be related to the AC without the need to perform DFT calculations. Specifically, the /–/–/+/+ pattern has been observed in the VCD 1100-950 cm^{-1} region of compounds which possess the 3*R*,6*R* AC, while the antipodal /+/+/–/– pattern has been observed in compounds which possess the 3*S*,6*S* AC, independently of the ester identity on each hydroxy group. Racemic samples of **56** and **57** were resolved by chiral HPLC. The first eluate of **57** shows [α] = –36.2 (EtOH), in agreement with that reported for natural catuabine E ([α] = –35.4). For (–)-**56** and (–)-**57**, four main bands with the /–/–/+/+ pattern, going from low to high wave numbers, were observed, while isomers (+)-**56** and (+)-**57** showed the opposite /+/+/–/– pattern. Following this empirical rule, the AC of each isolated enantiomer was established as (–)-(3*R*,6*R*)-**56**, (+)-(3*S*,6*S*)-**56**, (–)-(3*R*,6*R*)-**57**, and (+)-(3*S*,6*S*)-**57** [60].

Cycloaspeptide G (**58**) is a pentapeptide isolated from the fungus *Isaria farinosa*, which displays an excellent cytotoxic effect against HeLa and MCF7 cell lines. Although its AC was determined by spectroscopic techniques, its conformational characteristics were explored using DFT. Four conformers were considered, and after



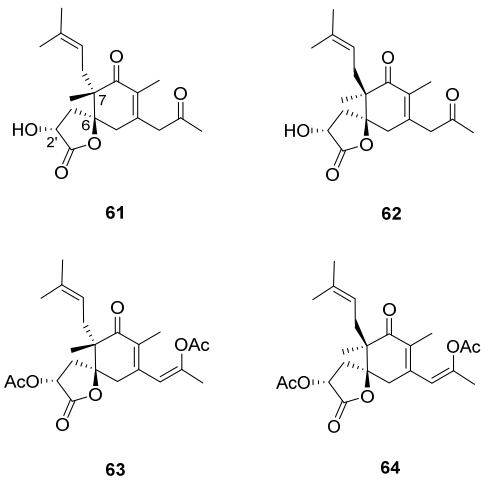
DFT B3LYP/6-31G geometry optimization the low energy conformer was considered to study the ECD and VCD spectra. The computations revealed the B3LYP/6-31G(d) level is preferred over the B3LYP/6-31G level. Some NH, and carbonyl stretching modes, and CH bending modes were assigned and discussed at the DFT B3LYP/6-31G and B3LYP/6-31G(d) levels of theory [61].



The epipolythiodiketopiperazine (ETP) alkaloids are a large family of fungal secondary metabolites with very interesting cytotoxic activities. The isolation, structural determination, AC assignments, and conformational analyses of two ETPs, preussiadins A (**59**) and B (**60**) from *Preussia tyoharum* were described. Assignment of the AC of **59** was initially hindered when all attempts to crystallize the compound and its derivatives failed. Based on the proposed 3*S**,5a*R**,10b*S**,11*S**,12*S**,3′*R**,5′a*S**,10′b*R**,11′*S**,12′*R** AC, quantum chemical computational calculations at the DFT B3LYP/6-31+G(d,p) level were carried out to generate VCD and ECD spectra, as well as a specific rotation value for **59**. In both cases, the calculated VCD and ECD spectra matched well with the experimental data. The calculated specific rotation value of **59** ($[\alpha]_D$ +53) was in agreement with the experimental observations ($[\alpha]_D$ +66). Therefore, the AC of **59** followed as 3*S*,5a*R*,10b*S*,11*S*, 12*S*,3′*R*,5′a*S*,10′b*R*,11′*S*,12′*R*. The proposed structure and AC assignment for **60** was determined by *S*-methylation. This provided three products that were confirmed as being identical to the products of the cleavage/methylation reaction of **59**. Thus **59** and **60** share the same AC [62].

Other natural products

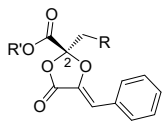
Cultivation of the filamentous fungus *Chaetomium indicem* yield spiroindocumines A (**61**), and B (**62**) as minor constituents. Their AC could not be deduced by Mosher derivatization, and was



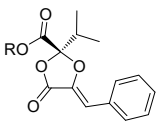
therefore assigned using the VCDEC approach. Although the VCD spectra of **61** and **62**, at a 0.05 M concentration, showed small signals with no significant peaks above 1700 cm^{-1}, in their respective diacetates, **63** and **64**, a strong bisignate VCD signal with a positive-negative couplet, from lower to higher wave number, that suggested a clockwise orientation between the adjacent carbonyl groups at C1' and AcO-2', was observed using a 0.01 M solution, allowing it to be concluded that C2' is *R*, and the entire AC are (2′*R*,6*S*,7*S*)-**61** and (2′*R*,6*S*,7*R*)-**62**. These AC assignments represent the first application of the VCDEC approach to novel natural products [26].

Typically ECD provides dependable data for the AC assignment and is more sensitive than VCD. Comparison of simulated and measured VCD and ECD spectra of natural dioxolanes **65**-**70** from *Guignardia bedwelli*, and semisynthetic derivatives shows the superiority of VCD over ECD for the AC determination of these compounds. After conformation analysis, UV and ECD spectra were obtained as Boltzmann-weighted averages. The calculated ECD spectrum of **65** did not match the experimental data, although the calculated UV spectrum showed a reasonable agreement with the recorded absorption bands. The VCD spectrum of **65** reasonably compared with a B3LYP/6-311G(d,p) calculated spectrum considering $CDCl_3$ solvation. However, rotational strengths at 1251 and 1207 cm^{-1}, along with frequencies of the C=O stretching of the COOH group are not correctly predicted. This was attributed to the known aggregation effect of carboxylic acids in nonpolar solvents, which is difficult to represent *in silico*, while measurements in DMSO-d_6 did not improve this situation. Compound **65** was therefore transformed into its methyl ester, whereby the agreement between the predicted VCD spectrum and the experimental data was much better. A similar situation was observed for **66**, which was also transformed into its methyl ester. The naturally occurring esters **67**–**70** showed highly similar VCD spectra, each with a characteristic triplet consisting of a positive band around 1282 cm^{-1} [ν_{as}(C2–C6–O)] and two negative bands around 1247 cm^{-1} [ν(C4–C5) + ν(C1'–C8)] and 1170 cm^{-1} [ν(C4–C5) + ν(C1'–C8)]. This constant pattern is predicted with high accuracy, excepting the rotational strengths of the lowest-frequency bands in **67** and **68**, which are overestimated by DFT. These results indicate all investigated compounds have the *S* AC [63].

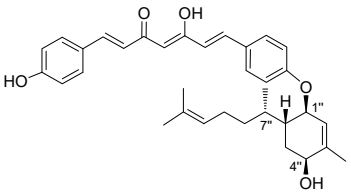
From *Curcuma longa* L., a popular plant of Chinese herbal medicine, fourteen cytotoxic terpene-conjugated curcuminoids J-W were isolated. After relative configuration NMR assignments, the AC was established by ECD and confirmed for terpecurcumin S (**71**) by VCD using the DFT B3LYP/6-31G(d) level of theory [64].



	R	R'
65	Ph	H
66	H	H
67	H	C_2H_4Ph
68	Ph	C_2H_4Ph



	R
69	C_2H_4Ph
70	Me



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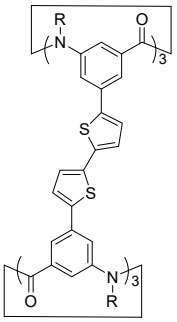
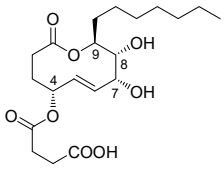


72

The construction of well-arranged π-conjugated chromophores has attracted much attention since the relative orientations and distances of the chromophores are crucial in determining their photophysical properties. The tubular compound **72**, in which three π-conjugated chromophores are connected, was synthesized as a diasteromeric mixture with planar chirality, a pair of enatiomers and a *meso* compound. Each compound was separated by chiral HPLC. The inherent chirality of *m*-calex[3]amide (**72**) induced a predominantly one-handed helicity to the arrangement of π–conjugated chromophores, without the help of a chiral guest or a stereogenic center. The AC of *m*-calex[3]amide, and the preferred helicity of the bithiophene unit were determined by combined experimental and theoretical studies. The ECD and VCD analyses were mutually complementary in adding the interpretation of the chiral structure in the present system; ECD spectroscopy was sensitive to the helicity of the bithiophene chromophores, whereas VCD spectroscopy was sensitive to the planar chirality of *m*-calex[3]amide [65].

The dihydroxylated macrolide **73**, along with ten known compounds were isolated from a solid culture of the endophytic fungus *Pestalotiopsis manguifera*. Structural elucidation and relative configuration followed after spectroscopic data including coupling constant values and NOESY evaluation. The 4*R*,7*R*,8*R*,9*S* AC of **73** was determined by VCD at the DFT B3LYP/6-31G(d) level [66].

Methyl mandelate (**74**) is a relatively small chiral α-hydroxyester which undergoes intra- and intermolecular hydrogen bonding interactions, and possesses a phenyl ring that influences the closeness and orientation of solvent molecules. It was selected to establish a general strategy to account for solvent effects. A comparative VCD study of **74** in methanol, dimethyl sulfoxide, and chloroform, using explicit and implicit solvent models, was performed. The results showed that the simultaneous inclusion of explicitly and implicitly solvent has a significant impact on the appearance of the vibrational absorption and VCD spectra, and is crucial for reliable spectral assignments when solvents are capable of hydrogen-bonding with solutes. When no strong solute solvent hydrogen-bonding interactions exist, like in chloroform, the gas phase monomer model is adequate for spectra interpretation, while inclusion of implicit solvation improves the frequency agreement with the experimental data [67].



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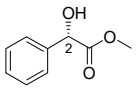
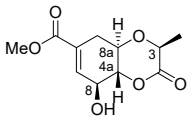
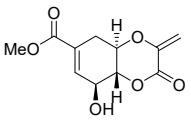


(+)-(*S*)-**74**



75

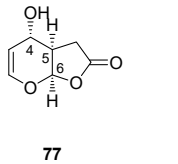


76

Phyllostin (**75**), seytolide (**76**), and oxysporone (**77**) are promising natural herbicides for the weed biocontrol of some *Orabanche* species. Supported by the knowledge of the relative configuration, the combined application of ORD, ECD, and VCD approaches permitted the assignment of the 3*S*,4a*R*,8*S*,8a*R* AC to (−)-**75**. In **76**, theoretical analysis of both electronic and vibrational CD spectra provided consistent results, while ORD was found unsuitable. Therefore, in the case of (−)-**76**, only two of the used chiroptical methods allowed the 4a*R*,8*S*,8a*R* AC assignment. The good agreement between the experimental and calculated ORD and ECD spectra of **77** led to the AC assignment. Taking into account solvent effects, all calculated VCD bands gave a satisfactory agreement with the experimental spectrum. Consequently, all three chiroptical methods support the AC assignment of (+)-**77** as 4*S*,5*R*,6*R*. This study suggests that for flexible molecules, a concerted application of more than one chiroptical methodology should be considered [68].

The configuration complexity of oligostilbenoids increases with their degree of polymerization. Four dimeric stilbene glucosides, two diasteroisomers of (−)-gnemonoside A (**78** and **79**), (−)-gnemonoside C (**80**), and (−)-gnemonoside D (**81**), as well as a mixture of the enantiomers of gnetin C (**82**, **83**) were isolated from the rhizomes of *Gnetum africanum*. ^{1}H and ^{13}C NMR spectra of **78** and **79** were superimposable, and similar to that reported for gnemoside A. VCD spectra of **78** and **79** are not perfectly opposite, revealing that they are not enantiomers, but could be diastereomers. After enzymatic hydrolysis, **78** and **79** gave aglycones (−)-**83** and (+)-**82**, respectively. Their AC was assigned by VCD experiments in combination with calculations and ^{1}H NMR experiments. The VCD data indicated that the 7a*S*,8a*S* enantiomer of gnetin C is slightly predominant in natural gnetin C. Interestingly, all the bands observed in the VCD spectra of **80** and **81** had the same sign as those of compound **78**, but their intensities were slightly lower. The 7a*S*,8a*S* configuration was preserved for the stilbene dimers **78**, **80**, and **81**. [69].

Klaivanolide, originally assumed as **84**, was presented as a promising antileishmanial agent from *Uvaria klaineana*, whose AC determination was made by VCD spectroscopy. The difficulties experienced in the synthesis led to revise and re-assign its structure as the butyrolactone acetylmelodorinol **85**. The calculated VCD spectra of the originally assigned structure for klaivanolide and the revised structure known as acetylmelodorinol are similar. This observation was rationalized by the authors considering that the VCD phenomenon ensues from IR absorption properties of functional groups that are identical in both compounds, and are strongly correlated with their relative arrangement around the stereogenic center, which remains as *S* in both structures [8].



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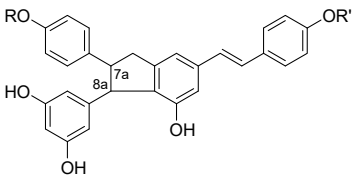
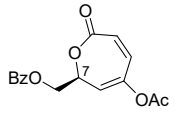
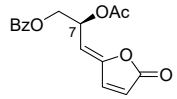


	C7a	C8a	R	R'
78	*S*	*S*	*β*-D-Glc	*β*-D-Glc
79	*R*	*R*	*β*-D-Glc	*β*-D-Glc
80	*S*	*S*	*β*-D-Glc	H
81	*S*	*S*	H	*β*-D-Glc
82	*R*	*R*	H	H
83	*S*	*S*	H	H



84



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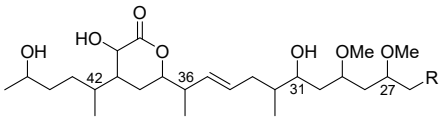

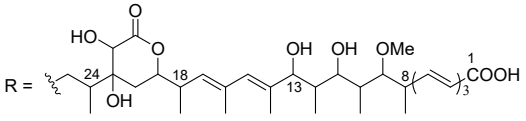

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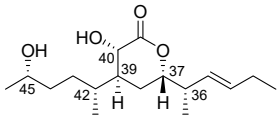

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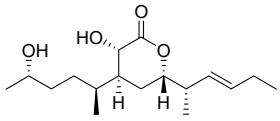

88

Hemicalide (**86**) is a highly bioactive marine natural product for which the relative configuration of the C8–C13 fragment and of the C18–C24 α,β-dihydroxy-δ-lactone subunit have been described. The relative configuration of the C36–C42 subunit was assigned by combining stereocontrolled synthesis with NMR, IR, and VCD analysis. Diastereomeric model compounds corresponding to the C36–C46 subunit were synthesized for ^{1}H and ^{13}C NMR data comparison with those of **86**. An attempt to determine the relative configuration at C42 by a statistical analysis of calculated and measured NMR chemical shifts was made. However, despite the seemingly high probabilities calculated, different conclusions were reached based on the ^{13}C and ^{1}H spectra. To make an unambiguous assignment of the relative configuration, a VCD analysis was performed for **87** and **88**. The AC at C42 in these two key epimeric compounds was particularly challenging for VCD analysis due to the large number of conformations and the presence of six stereocenters. The commonly used 6-31G(d) basis set overestimated the abundance of conformers showing intramolecular H-bonding. The use of the aug-cc-p-VDZ calculation level with a polarizable continuum model gave a more realistic Boltzmann distribution. Although the use of VCD spectroscopy can be sufficient to assign the AC of epimers containing multiple stereocenters, spectra subtraction of the epimers, for the calculations and the experiments, greatly enhanced the power for epimer distinction. The AC determination at C42 in **87** and **88** allowed the assignment of the relative configuration of the C36–C42 subunit [70].

In summary, several reviews [3,14-17], and a just published one [71], show VCD is currently a superior and preferred technique for the AC determination of natural products. It accounts for some 70 additional natural products reviewed herein for less than the last two years period. The easy empirical interpretation of the VCDEC bisignated couplet will certainly attract more users to this methodology since thereby no long and tedious DFT calculations are required.

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