Recent advances in the use of vibrational chiroptical spectroscopic methods for stereochemical characterization of natural products

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ARTICLE TYPE

Recent advances in the use of vibrational chiroptical spectroscopic methods for stereochemical characterization of natural products

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This review covers conformational and configurational assignments in natural product molecules using chiroptical spectroscopy reported over the last 15 years. Special attention is given to vibrational optical activity methods associated with quantum mechanical calculations. **Covering: 2000 to 2014**

Introduction

Chirality is omnipresent in nature manifesting itself in all material objects ranging from fundamental particles to galaxies.[1] When it comes to natural product chemistry, molecular chirality, that is, the chiral three-dimensional arrangement of atoms in a given molecule, is of paramount importance to the understanding of biosynthesis, functions and biological activities.[2] However, characterizing such arrangements in the absolute sense is not a trivial task. Enantiomers share, in an achiral environment, basically the same physical and chemical properties that make them indistinguishable in many aspects. One way of getting around this problem is to take advantage of the diastereomeric discrimination provided by chiroptical methods.[3]

Although the term "chiroptical" (Chiral + Optical) may not be readily recognizable to all natural product chemists, this concept is commonly present in their everyday lives. Optical rotation (OR, polarimetry), one of the oldest chiroptical methods available, is widely used in teaching, analytic, synthetic and natural product laboratories, mainly to determine enantiomeric purity.[4] Other examples of chiroptical methods include optical rotatory dispersion (ORD), electronic circular dichroism (ECD), and vibrational optical activity (VOA) methods, represented by vibrational circular dichroism (VCD) and Raman optical activity (ROA). The latter two will be the focus of the present review article.

All chiroptical methods arise from the differential interaction of a chiral non-racemic molecule with left- and right-circularly polarized light beams,[5] which are chiral entities with one being the mirror image of the other. OR and ORD (variation of OR with wavelength) are based on different indices of refraction for left- and right-circularly polarized light in a chiral (optically active) medium, known as circular birefringence. As light traverses a chiral medium, the circularly polarized electromagnetic field components slow to a different extent and the plane of polarization is rotated with respect to the original case. Circular dichroism methods originate from the differential absorption by a chiral molecule of left- versus right-circularly polarized radiation during an electronic (ECD) or vibrational transition (VCD). ROA, on the other hand, results from a small difference in the intensity of vibrational Raman scattering from chiral molecules when using right- and left-circularly polarized incident light (ICP-ROA). It can be equivalently measured as the difference in intensity of a small circularly polarized component in the scattered light by using incident light of fixed nonelliptical polarization (SCP-ROA).

OR, ORD, ECD, VCD, and ROA, which are all inherently sensitive to chirality, are nondestructive methods that can be measured directly in solution, without the need of crystallization or the use of chiral auxiliaries. Additionally, due to their sensitivity to molecular conformations, not only is absolute stereochemistry determination feasible but also conformational analysis in solution. Nevertheless, the interpretation of chiroptical data in order to obtain molecular structure information is not straightforward. Although the so-called ECD "exciton chirality" method (ECM)[6] has been successfully used for many years to determine the absolute configuration of suitable molecules, only recently, due to the development of reliable *ab initio* calculations for predicting theoretical spectra, the use of chiroptical methods for configurational analysis of chiral molecules faced a renaissance.[7]

This renewed interest in chiroptical spectroscopy methods involved not only VOA techniques. The development of the accurate theoretical calculations mentioned above also greatly expanded the applicability of OR/ORD and ECD for structural characterization of natural products, with a great number of reports published every year. Interestingly, these calculations have recently revealed the first apparent exception of ECM for a simple biaryl system.[8] Although not the focus of this review article, excellent references on the use of OR/ORD and ECD techniques for synthetic and natural organic molecules can be found here.[5,9-27]

Compared to the other chiroptical methods, VCD and ROA present some advantages, since they can be measured for virtually any molecule without the requirement of either UV-Vis chromophores for ECD, derivatizations, or simulations of excited-state wavefunctions. In addition, as these two spectroscopic methods represent global molecular properties, all degrees of freedom (3N-6, where N is the number of atoms) of a

molecule can be investigated, at least in theory. Nevertheless, at the same time, it becomes more difficult to extract stereochemical information from VOA spectra, which increases the dependence on the accuracy of the calculations. VCD and ROA also require larger amounts of sample (~ 0.01-0.1M) and longer acquisition times (~ 1-12 h) than do OR/ORD and ECD.

Despite the advantages described above, an early review article on chiroptical methods published by Allenmark in 2000,[28] presented only a single example on the use of VCD for natural products (the Scolytidae insect pheromone frontalin). Fortunately, this scenario has been changing rapidly and a number of review articles and book chapters have already been published dealing with the use of VOA to natural product chemistry, although focused mainly on VCD.[5,25,29-36]

The present review will report approximately 190 molecules whose stereochemical properties have been studied using VOA methods, including VCD and ROA, over the last fifteen years. We hope this comprehensive review will demonstrate the evolution of the applications of VOA to natural product chemistry, and help spread the word about the potential of these methods to solve stereochemical problems of chiral natural molecules.

VOA techniques

VCD and ROA were first measured in the early-to-mid-1970s,[37-39] and, ever since then, VOA has undergone tremendous evolution that culminated in the availability of user-friendly commercial instrumentation[40] and software packages[41] for reliable spectral measurement and quantum mechanical calculations of theoretical spectra. The determination of the absolute configuration and conformations of chiral small molecules using VOA consists of comparing the sign and intensity of the measured VOA spectrum with the corresponding density functional theory (DFT) calculated VOA spectrum of a chosen configuration. It is important to mention that the choice of the arbitrary configuration is based on the relative configuration determined using NMR or X-ray crystallography. If the major bands of the measured and calculated VOA spectra agree in relative magnitude and sign, then the AC chosen for the calculation is the same as that of the sample measured. If the relative magnitudes agree, but the signs are opposite, then the AC of the sample is the opposite of that chosen for the calculation.[29]

As the timescale of a vibrational transition is shorter than a ps (10^{-12} s), the boundary for conformational rearrangements in flexible molecules is reasonably low at room temperature.[21] Consequently, VOA experimental spectra are composed of the linear superpositions of the spectra of individual conformers, weighted by the corresponding conformational populations.[42] This fact makes it extremely important to carry out a thorough conformational search,[43] followed by geometry optimization, before calculating the chiroptical property of interest using DFT methods. Overlooking any significantly populated conformer may result in inaccurate VOA theoretical spectra and therefore poor agreement between experimental and calculated data.

The level of agreement between experimental and calculated VOA spectra may be determined visually, which is considered to be the least reliable method, since it is prone to user bias, or by using recently developed statistical methods. The first one consists of extracting dipole and rotational strengths from experimental data and plotting it against the calculated values. This method offers the possibility of calculating statistical measures, such as the correlation coefficient R^2.[30] A second method called SimIR/VCD[44] uses computationally optimized frequency scaling and shifting to match calculated and observed spectra. A third method is the confidence level algorithm[45] that provides a direct quantitative comparison of the experimental spectrum with the calculated spectra for both enantiomers as a measure of the degree of agreement and hence level of confidence. The most recent method is based on the similarity of dissymmetry factor spectra placing emphasis on robust regions both in the experimental and calculated spectra.[46]

Recently, there have also been some attempts to interpret VCD data without the aid of theoretical calculations, which resulted in the development of the exciton chirality method for VCD.[47] Briefly, this methodology is based on the coupling of two infrared chromophores (e.g. carbonyl groups) that yields a strong VCD couplet whose sign reflects the absolute configuration of the molecule.

However, it is important to emphasize that, even when DFT calculations are employed to generate theoretical spectra, the assignment of absolute configurations may be inaccurate. This may be caused by errors in the equilibrium geometries and conformational populations as mentioned before, by density functional and/or basis set errors, and finally by solvent effects. Density functional and basis set errors are expected to develop in any quantum mechanical calculation because it is based on approximations of atomic wave functions, the accuracy of such predictions being sensitive to the choice of the functional (either pure or hybrid), and directly proportional to the size of the basis set used. Solvent effects may be considered one of the most important sources of deviations between experimental and calculated data. In liquid phase, solute – solvent interactions play an important role in the conformer geometry and population of flexible molecules, mainly if experimental data in polar (H-bond forming) solvents need to be reproduced. In the case of rigid molecules, solvent polarization effects may be the principal cause of deviations. Thus, the inclusion of either the polarizable continuum model (PCM) or the conductor-like screening model (COSMO),[48] as opposed to gas phase calculations, is preferred. Nevertheless, in some cases, the use of explicit solvation may be necessary for a reliable simulation.[49]

Regarding conformational studies of biomacromolecules, the interpretation of VOA spectra has been predominantly based on empirical analysis (structure-spectra correlations).[50,51] In this case, the comparison of similar spectral patterns of molecules of known structure with those of samples of unknown conformation is used to assign the structural features of the latter. This practice allows for the identification of marker bands that are diagnostic of particular structural motifs. Such empirical correlation may be supported by statistical methods, such as principal components analysis.[52] Further discussions on VOA theory, instrumentation, measurements and calculations are beyond the scope of this review article and one can find valuable information in the extensive literature available.[53-66]

In the following sections we will present examples of the application of VCD and ROA for stereochemical characterization

of representative natural products. These examples will be organized chronologically in different classes and subclasses of secondary metabolites, such as terpenes, alkaloids, lignans, meroterpenes, coumarins and flavonoids, miscellaneous, peptides and carbohydrates, regardless of the sources from which they were isolated.

VOA and Natural Products

Terpenes

Historically, chiral terpenes, especially monoterpenes, have been used to test VOA devices because of their availability in suitable enantiomeric purity and their high-quality vibrational spectra in the mid-IR region.[67] Indeed, neat α-pinene enantiomers remain the most widely used standards to verify calibration of VCD and ROA instruments. Examples of experimental and calculated VCD and ROA for α-pinene are presented in Figure 1.

Additionally, a number of technological advancements in the VOA field were achieved using monoterpenes. Just to cite a few examples, (+)-(1*R*)-α-pinene (**1**), (−)-(1*S*)-camphor (**2**) and (−)-(1*S*)-*endo*-borneol (**3**) were used in the first application of Fourier transform VCD (FT-VCD) to follow changes in the percent enantiomeric excess (% EE) of chiral molecules in time (real-time monitoring).[68] Compound **2** and (+)-(1*S*)-fenchone (**4**) were used in experimental and theoretical studies of near-infrared VCD.[69] Other monoterpenes whose VCD spectra were investigated in both mid-IR and near-IR regions include (+)-(*R*)-limonene (**5**), (−)-(*R*)-carvone (**6**) and its antipode (**7**), (+)-(*R*)-pulegone (**8**), (−)-(1*S*)-β-pinene (**9**), and both enantiomers of menthol (**10** and **11**).[70-72] The enantiomers of camphor were also employed to investigate in detail the phenomenon of induced solvent chirality as probed by VCD.[73] The *S* enantiomer of compound **1** along with compound **5** were used in the first mid-IR observation of vibrational optical rotatory dispersion.[74] Regarding ROA, compound **1** was used in the first simultaneous acquisition of all four forms of circular polarization ROA.[75] Finally, chiral limonenes were used in the development of the femtosecond characterization of VOA of chiral molecules.[76]

Based on what was described above, an increasing number of papers have been published describing the use of VCD and/or ROA to determine conformations and the absolute configuration of terpene molecules.

The first example is the VCD determination of the absolute configuration of bisabolene-type sesquiterpenes isolated from the marine sponge *Didiscus aceratus*.[77] The atropisomeric dimers (+)-dicurcuphenol B (**12**) and (+)-dicurcuphenol C (**13**) had their axial chirality assigned as *P* and *M*, respectively, while the absolute configurations at C-7 and C-7′ were determined as *S* by comparing experimental and B3LYP/6-31G(d) calculated data. This was the first application of VCD to the stereochemical analysis of marine natural products. The derivatization of (+)-(1*R*)-*endo*-borneol (**14**) to form derivatives **15-18** was used to demonstrate that conformational rigidification of chiral molecules facilitates the determination of their absolute configuration using VCD.[78] The absolute configuration of the guaianolide 7,10-epoxy-1,5-guaia-3,11-dien-8,12-olide isolated (**19**) from the leaves of *Hedyosmum arborescens* was determined as 1*R*,5*R*,7*S*,8*S*,10*R* by comparison of experimental and calculated VCD data at the B3LYP/6-31+G(d,p) level.[79] The brominated sesquiterpenes (−)-majapolene B (**20**) and (−)-acetylmajapolene B (**21**) isolated from the red algal genus *Laurencia* had their absolute configuration determined as 7*S*,10*S* using VCD and DFT calculations at the B3PW91/6-31G(d,p) level.[80] Similarly, a diastereomeric mixture on the peroxide portion of the brominated sesquiterpene acetylmajapolene A was separated and the absolute configuration of the diastereomers (−)-**22** and (−)-**23**, which were basically indistinguishable, was assigned as 1*R*,4*R*,7*S*,10*S* and 1*S*,4*S*,7*S*,10*S*, respectively.[81] Another example include the cytotoxic sesquiterpene quadrone (**24**) isolated from *Aspergillus terreus*.[82] The absolute configuration of (−)-**24** was determined as 1*R*,2*R*,5*S*,8*R*,11*R* by using a combination of OR, ECD, and VCD. Comparison of experimental VCD with the B3PW91/TZ2P calculated spectrum was considered to provide the most reliable assignment, which was in accordance with previous results obtained via total synthesis. The reinvestigation of the absolute configuration of the iridoids plumericin (**25**) and isoplumericin (**26**) using the same combination of chiroptical methods and calculations presented above also confirmed the previous assignments of (+)-**25** and (+)-**26** as 1*R*,5*S*,8*S*,9*S*,10*S*.[83] In addition, the highly cytotoxic iridoid (−)-prismatomerin (**27**), isolated from *Primatomeris tetrandra*, had its absolute configuration assigned as 1*R*,5*S*,8*S*,9*S*,10*S* using VCD and DFT calculations (B3PW91/TZ2P) of its acetate derivative in order to avoid aggregation. [84,85] Interestingly, the signs of the OR of **25** and **27** are opposite despite their identical absolute configuration, that points out the risks of relying on the comparison of OR values for assigning absolute configurations. Experimental and theoretical [B3LYP/6-31G(d,p)] VCD studies of a new eudesmanolide-type sesquiterpene (**28**) isolated from *Mikania campanulata* led to the assignment of its absolute configuration as (+)-(1*S*,4*S*,5*S*,6*S*,7*S*,10*R*).[86] Good agreement between experimental VCD and the spectra calculated at the B3LYP/6-31G(d,p) and B3LYP/DGDZVP levels confirmed the absolute configuration of the diterpene (+)-verticilla-3*E*,7*E*-dien-12-ol (**29**), isolated from *Bursera suntui*, as 1*S*,11*S*,12*S*.[87] The eremophilanoids 6-hydroxyeuryopsin (**30**), isolated from *Senecio toluccanus*, and compound **31** isolated from *Psacalium paucicapitatum* had their absolute configuration determined as 4*S*,5*R*,6*S* and 1*S*,4*S*,5*R*,8*S*,10*S*, respectively, by VCD and DFT calculations. VCD measurements were also carried out for the acetylated derivative of **30** in order to avoid intermolecular hydrogen bonding of the hydroxyl group and thus improve the agreement with calculated data (B3PW91/DGDZVP).[88] Salvileucalin B (**32**), presenting an unprecedented rearranged neoclerodane skeleton, was isolated from *Salvia leucantha* along with salvileucalin A (**33**). Their relative configurations were determined by X-ray crystallographic analysis and their absolute configurations (as shown in Figure 3) were assigned using VCD and DFT [B3LYP/6-31G(d)] calculations.[89] The africanane sesquiterpene (+)-**34** isolated from *Lippia integrifolia* had its absolute configuration assigned as 4*R*,9*R*,10*R* using VCD and DFT calculations at the B3LYP/6-31G(d), B3LYP/DGDZVP, and B3PW91/DGDZVP2 levels. The lippifoliane sesquiterpene **35**, isolated from the same species, had its absolute configuration confirmed as 4*R*,9*S*,10*R* using the same VCD protocol.[90]

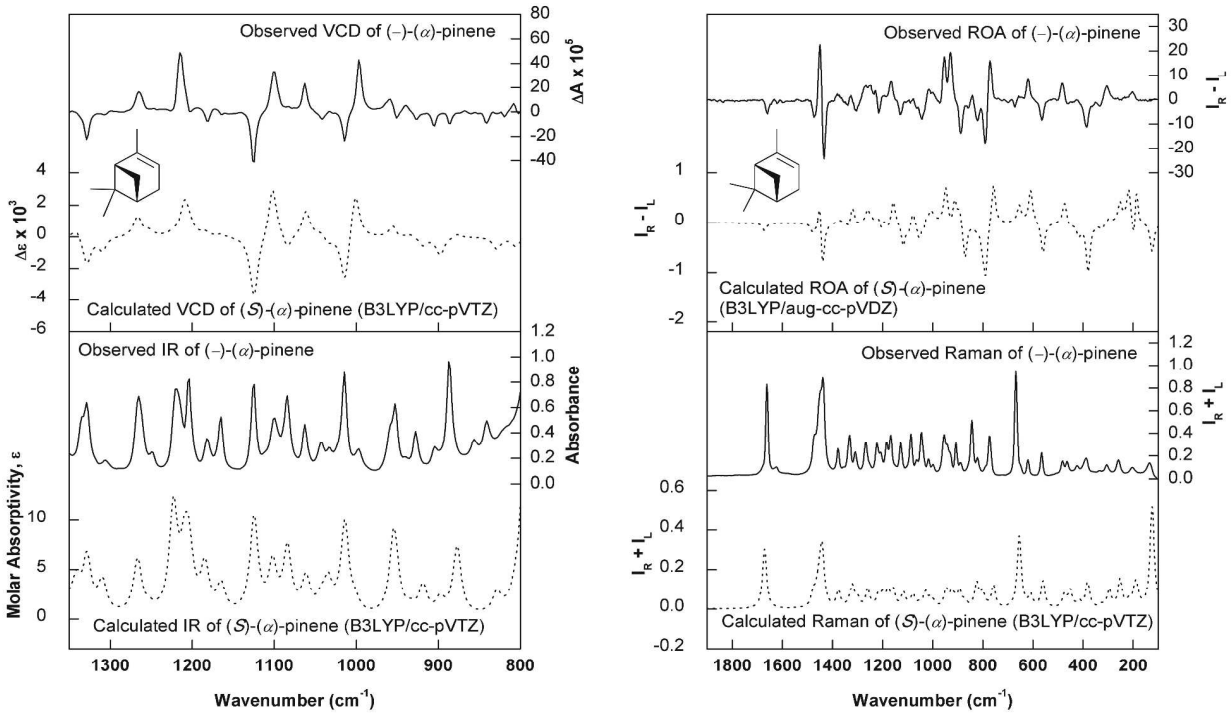

Figure 1. (Left) Comparison of observed IR and VCD spectra of (−)-(α)-pinene with those calculated for (*S*)-(α)-pinene using DFT methods; (Right) Comparison of observed Raman and SCP-ROA spectra of (−)-(α)-pinene with those calculated for (*S*)-(α)-pinene using DFT methods. These comparisons unambiguously establish the absolute configuration of (−)-(α)-pinene as *S*.

The following example deals with stereochemical studies on (+)-(*E*)-junionone (**36**), a monoterpene isolated from *Juniperus communis*. This is one of the few examples of the use of ROA spectroscopy to assign the absolute configuration of natural products.[91] The naturally occurring (+)-(*E*)-**36** was assigned as *R*. The absolute configuration of another monoterpene molecule, (+)-pulegone (**8**), was confirmed as *R* by comparison of experimental and calculated [B3LYP/6-311+G(d,p)] VCD spectra.[92] This work points out the importance of taking solvent effects into account in the calculations by using a continuum model. A thorough conformational analysis of the baccatin III ring (**37**) of paclitaxel using experimental and calculated VCD provided further insights on the conformational changes induced in paclitaxel upon binding with β-tubulin.[93] Conformational flexibility of (*S*)-(−)-perillaldehyde (**38**), a secondary metabolite and atmospheric pollutant, was also investigated using experimental and theoretical VCD.[94] The diterpene (+)-aframodial (**39**), isolated from *Aframonum latifolium*, and its diastereomers were subjected to a theoretical VCD study that demonstrated this VOA technique to be very sensitive not only to the local stereochemistry of each chiral center, but also to the helicity of the entire molecules.[95]

Even though chiroptical methods are ideally used to tell apart enantiomers, the absolute configuration of the pacifenol derivative (−)-(**40**) was determined using VCD measurements and calculations for both diastereomers possible at C-8. This approach clearly indicated that compound **40** possesses the 2*R*,5*R*,5a*R*,8*R*,9a*S* configuration.[96] Phytochemical studies in *Stevia monardifolia* afforded the new compound 7β-angeloyloxy-8α-isovaleroyloxylongipin-2-en-1-one. Its absolute configuration was assigned as 4*S*,5*S*,7*S*,8*S*,10*R*,11*R* by VCD measurements in comparison to calculations at the B3LYP/DGDZVP level.[97] The enantiomers of 3-oxo-1,8-cineole were synthesized and their absolute configurations were determined as (−)-(1*S*,4*S*)-**41** and consequently (+)-(1*R*,4*R*) using VCD and DFT calculations (B3LYP/DGDZVP).[98] The conformational landscapes of compounds **5**,[67] **7**,[99] and (−)-(*S*)-limonene oxide (**42**),[100] a secondary metabolite and atmospheric pollutant, were probed by VCD and quantum chemical calculations. These works also reveal that IR, Raman, and VCD are helpful complementary techniques for characterizing flexible systems. Another monoterpene whose absolute configuration was assigned using VCD and DFT calculations is (−)-myrtenal (**43**). Compound **43** was assigned as 1*R* and the authors indicated B3LYP/DGDZVP calculations as providing a superior balance between computer cost and VCD spectral accuracy.[101] The same level of theory described above was used in VCD spectral calculations to confirm the absolute configuration of the longipinene derivative 7,9-diacetyloxylongipin-2-en-1-one (**44**) as 4*R*,5*S*,7*R*,9*R*,10*R*,11*R*.[102] The structure of the sesquiterpene (−)-*epi*-presilphiperfolan-1-ol isolated from *Anemia tomentosa* was reassigned to (−)-9-*epi*-presilphiperfolan-1-ol (**45**) and its absolute configuration was established as 1*S*,4*S*,7*R*,8*R*,9*S* using VCD spectroscopy and DFT (B3LYP/DGDZVP) calculations.[103] The structure and absolute configuration of ginkgolide B (**45**) were characterized directly in solution using experimental and calculated [B3LYP/6-31G(d)] VCD.[104] Differences between

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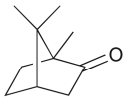

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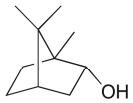

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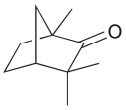

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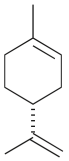

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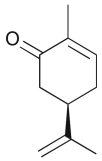

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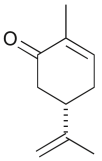

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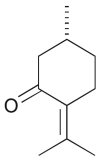

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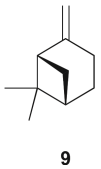

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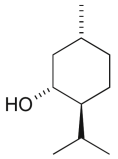

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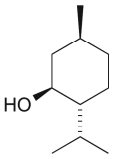

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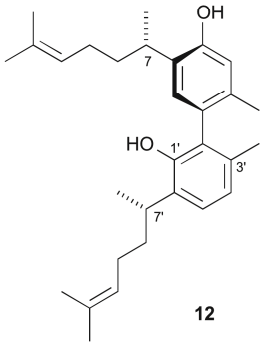

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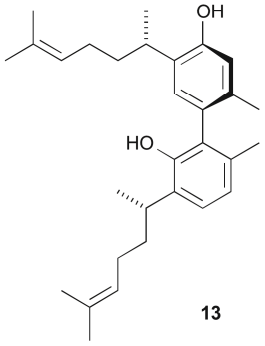

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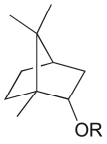
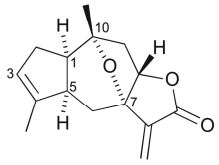


14 R = H
15 R = CH_3
16 R = $COCH_3$
17 R = $C(CH_3)_3$
18 R= $Si(CH_3)_3$



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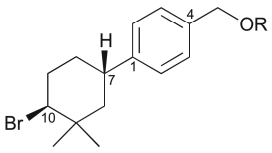
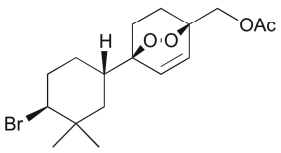


20 R = H
21 R = Ac



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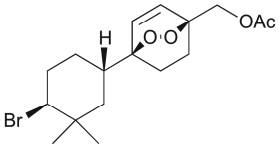

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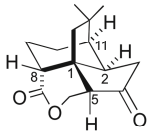

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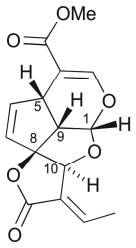

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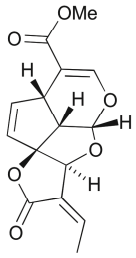

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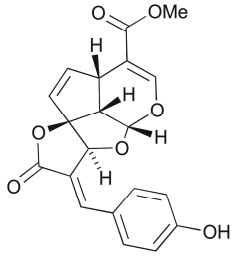

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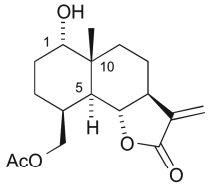

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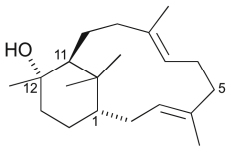

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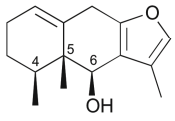

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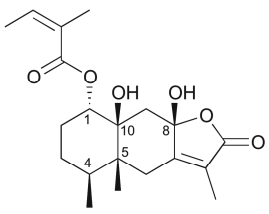

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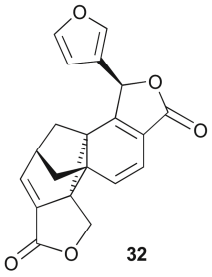

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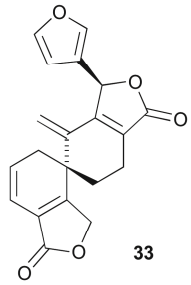

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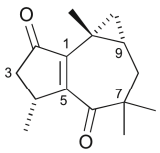

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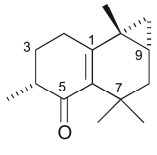

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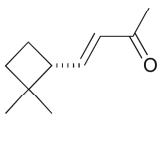

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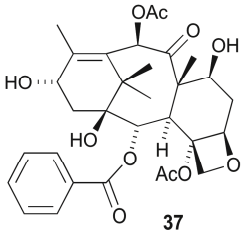

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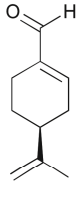

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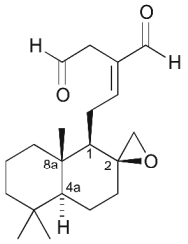
measured and calculated IR and VCD spectra for **46** were rationalized in terms of interactions with solvent as well as intermolecular interactions. Theoretical calculations were also performed for ginkgolides A (**47**), C (**48**), J (**49**) and M (**50**). The absolute configurations of two groups of diterpenes belonging to opposite enantiomeric series, isolated from *Chromolaena pulchella*, were determined as (5*S*,8*R*,9*S*,10*R*)-(−)-hautriwaic acid lactone (**51**) and (5*S*,8*R*,9*R*,10*S*)-(+)-isoabienol (**52**) using VCD and DFT (B3LYP/DGDZVP) calculations.[105] These results supported the biogenetic proposal to diterpenes in the studied species. The new serrulatane-type diterpene (−)-leubethanol (**53**), isolated from *Leucophyllum frutescensi,* had its absolute configuration determined as 1*R*,4*S*,11*S* after comparison of experimental VCD with B3LYP/DGDZVP calculations for both C-11 diastereomers of **53**.[106] The absolute configuration of *seco*-oxacassane diterpenes was determined for the first time by comparing the experimental VCD of the conformationally restricted derivative **54** with B3PW91/DGDZVP2 calculated spectra.[107] Compound (−)-**54** was assigned as 5*S*,8*R*,9*R*,10*S*. The chiral recognition of the tricyclic sesquiterpenes (+)-6*R*-cedrol (**55**) and (−)-6*S*-isocedrol (**56**) was successfully achieved using VCD spectrosocopy. Calculations of the anisotropy factor (*g*) provided the regions of maximum VCD effect for each epimer.[108] Conformational analysis of the sesquiterpene benzoquinones (*R*)-perezone (**57**) and (*R*)-dihydroperezone (**58**) using VCD and DFT (B3LYP/DGDZVP) calculations suggested analogous conformations for both molecules and confronted previous reports on the presence of weak π-π interactions between the alkyl chain double-bond and the quinone ring in **57**.[109] The relative stereochemistry at C-13 and the absolute configuration of the *ent*-labdane salvic acid (**59**), isolated from *Eupatorium salvia*, was determined as 13*R* using VCD and DFT (B3LYP/DGDZVP) calculations of an *O*-methyl ether methyl ester derivative.[110] The absolute configuration of (+)-(*R*)-**5** and its antipode, as well as that of (+)-(*E*)-α□□□□□□□□□1 (**60**) were determined using ROA spectrosocopy.[111] The lupane triterpenoid epoxylupenone (**61**), prepared from lupeol, had its 20-(*S*) absolute configuration determined by comparison of observed and calculated (B3LYP/DGDZVP) spectra.[112] Once again, VCD analysis was able to distinguish between two possible epimers of a natural product.

The revised structure of (+)-rosmaridiphenol (**62**), an antioxidant isolated from *Rosmarinus officinalis*, had its absolute configuration determined as 5*S*,10*R* using VCD and DFT calculations of its diacetate derivative.[113] The absolute configuration of the unusual diepoxyguaianolide (−)-**63**, isolated from *Stevia tomentosa*, was determined as 1*S*,3*S*,4*S*,5*R*,7*R*,8*R*,11*S* by VCD in combination with DFT (B3LYP/DGDZVP) calculations.[114] This assignment was supported by X-ray crystallography. The cassane diterpenes (−)-6-acetoxyvoucapane (**64**), (−)-hydroxyvoucapane (**65**), and (+)-6-oxovoucapane (**66**), isolated from *Caesalpinia platyloba*, had their absolute configurations assigned as (5*S*,6*R*,8*S*,9*S*,10*R*,14*R*)-**64**, (5*S*,6*R*,8*S*,9*S*,10*R*,14*R*)-**65** and (5*S*,8*S*,9*S*,10*R*,14*R*)-**66** using VCD and DFT (B3LYP/DGDZVP) calculations.[115] Preferred conformations and the absolute configuration of the unprecedented macrocyclic dimeric diterpene (−)-schaffnerine (**67**), isolated from *Acacia schaffneri*, were determined using VCD and DFT (B3LYP/DGDZVP) calculations.[116] This molecule was assigned as 5*S*,7*S*,8*R*,9*R*,10*S*,17*S*,5′*S*,7′*S*,8′*R*,9′*R*,10′*S*,17′*S*. The absolute configuration of the rare isoneoamphilectane carbon skeleton, present in marine diterpenes isolated from the sponge *Svenzea flava*, was determined using VCD and DFT [B3LYP/6-31G(d)] calculations.[117] Semisynthetic derivative (+)-**68** was assigned as 3*S*,4*R*,7*S*,8*S*,11*R*,12*S*,13*R*. VCD spectroscopy in combination with DFT calculations (B3PW91/DGDZVP) was able to reliably discriminate four diastereomeric cedrol-related tricyclic sesquitepenes: cedranol (**69**), neoisocedranol (**70**), neocedranol (**71**), and isocedranol (**72**).[118] The absolute configurations of their acetate derivatives were determined as (3*R*,3a*R*,5*R*,6*R*,7*S*,8a*S*)-(−)-**69**, (3*R*,3a*R*,5*R*,6*S*,7*S*,8a*S*)-(−)-**70**, (3*R*,3a*R*,5*S*,6*R*,7*S*,8a*S*)-(−)-**71**, and (3*R*,3a*R*,5*S*,6*S*,7*S*,8a*S*)-(+)-**72**. The presence of 13*R* and 13*S* labdane diterpenes coexisting in *Ageratina jocotepecana* was demonstrated using VCD and DFT (B3LYP/DGDZVP) calculations.[119] A VCD study on (−)-**73** and (+)-**74** established their absolute configurations as 5*S*,9*S*,10*S*,13*S* and 5*S*,8*R*,9*R*,10*S*,13*R*, respectively. The absolute configuration of the diterpene (+)-shortolide A (**75**), isolated from the endangered species *Solidago shortii*, was determined as 3*R*,4*S*,5*R*,7*S*,8*S*,9*S*,10*S* using VCD and DFT [B3LYP/6-311+G(2d,p)] calculations, as the crystal structure obtained for **75** did not allow for such assignment.[120] The rare sesquiterpene (+)-3-ishwarone (**76**), isolated from *Peperomia scandens*, had its absolute configuration determined by a combination of chiroptical methods and theoretical predictions for different diastereomers.[121] The best results were obtained using VCD and vibrational dissymmetric factor spectra that led to the assignment of **76** as 1*R*,2*S*,4*S*,5*R*,9*R*,11*R*. The diterpenoid demalonyl thyrsiflorin A acetate (**77**), isolated from *Calceolaria* species, was determined as belonging to the *normal* enantiomeric series of diterpenes by VCD and DFT (B3LYP/DGDZVP) calculations. This result, which was supported by single crystal X-ray diffraction, was used to assign the stereochemistry of related molecules.[122] Finally, the diastereoselectivity of diazomethane addition to the conjugated double bond of unsaturated sesquiterpene lactones was explored using zaluzanin A, for which the absolute configuration was secured using VCD spectroscopy.[123]

Alkaloids

The second class of secondary metabolites with most reports on the use of VOA for stereochemical characterization is alkaloids. The alkaloid (6*R*,7*S*,9*S*,11*S*)-(−)-spateine (**78**) was used in the first *ab initio* VCD calculation for a molecule containing a closed-shell transition metal. The same molecule was also used to report a new VCD enhancement mechanism in open-shell Co(II) and Ni(II) complexes.[124] The solution-state conformation of (−)-cinchonidine (**79**), used as a chiral modifier, was studied using VCD and theoretical calculations [B3LYP/6-31G(d)].[125] The same work also reported the investigation of induced VCD activity in achiral trifluoroacetic acid upon interaction with **79** and (+)-cinchonine (**80**). The absolute configuration at C-21 bearing an epoxide ring on citranidin A (**81**), a pentacyclic indolinone alkaloid isolated from *Penicillium citrinum*, was assigned as *S* by comparison of the observed VCD spectrum with



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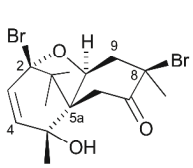

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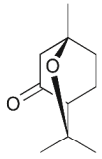

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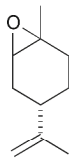

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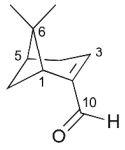

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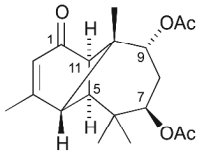

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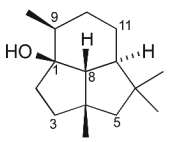

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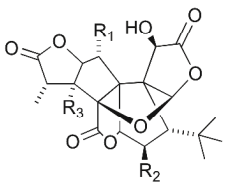
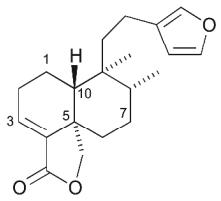


46 R_1 = OH, R_2 = H, R_3 = OH
47 R_1 = H, R_2 = H, R_3 = OH
48 R_1 = OH, R_2 = OH, R_3 = OH
49 R_1 = H, R_2 = OH, R_3 = OH
50 R_1 = OH, R_2 = OH, R_3 = H



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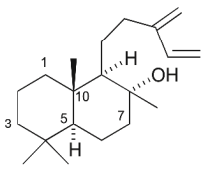

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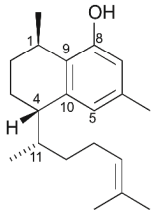

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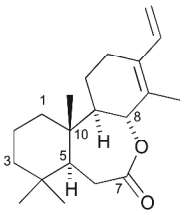

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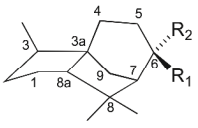
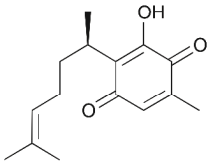


55 R_1 = OH, R_2 = Me
56 R_1 = Me, R_2 = OH



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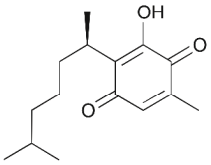

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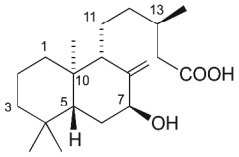

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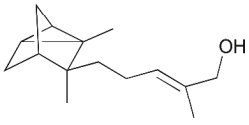

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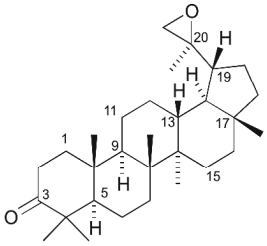

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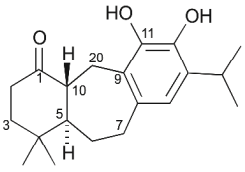

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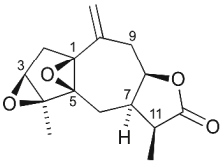

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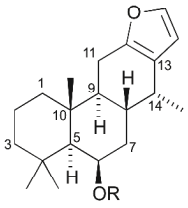

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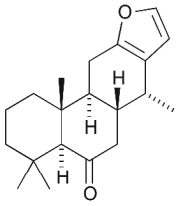

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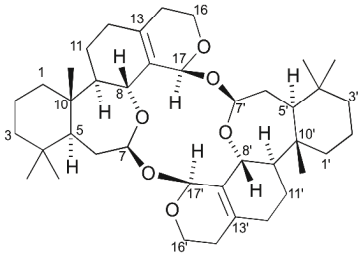

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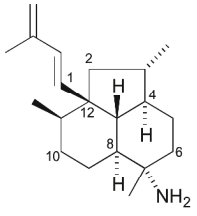

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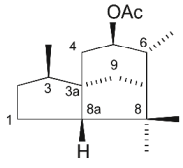

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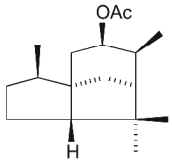

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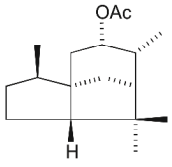

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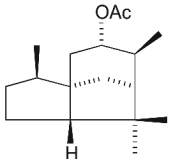

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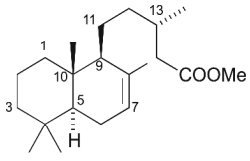

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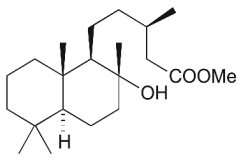
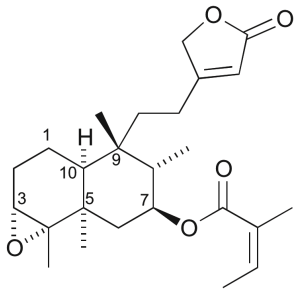


74

those of model compounds.[126] The absolute stereochemistry of the pentacyclic core was assigned using NMR and ECD. Two natural diastereoisomers of 6*β*-hydroxyhyoscyamine (+)-**82** and (−)-**83** had their absolute configurations assigned as 3*R*,6*R*,2′*S* and 3*S*,6*S*,2′*S*, respectively, using VCD and DFT [B3LYP/6-31G(d)] calculations.[127] It was also possible to observe that the lowest-energy conformers in both cases showed the N-Me group in the *syn* orientation. The absolute configuration of (+)-schizozygine (**84**), isolated from *Schizozygia caffaeoides*, was determined as 2*R*,7*S*,20*S*,21*S* using a concerted application of DFT calculations of VCD, ECD and OR.[128] The related alkaloids (+)-schizogaline (**85**), (−)-schizogamine (**86**), and 6,7-dehydro-19*β*-hydroxychizozygine (**87**), isolated from the same species, had their absolute configurations defined by that of **84** assuming a common biosynthetic pathway. A second example of concerted application of chiroptical methods to assign absolute configuration on natural products included the alkaloids isochizagaline (**88**) and isochizogamine (**89**). The naturally occurring (−)-**88** and (−)-**89** were determined definitively to be 2*R*,7*R*,20*S*,21*S*.[129] In the case of actinophyllic acid, isolated from *Alstonia actinophylla*, VCD could not be used for stereochemical analysis since this compound had limited solubility in noncoordinating solvents such as CCl_4 and $CDCl_3$. The measurement using DMSO-d_6, a strongly coordinating solvent exhibited discrepancies with calculated data. Therefore, ECD was recorded in methanol and the molecule was assigned as 15*R*,16*S*,19*S*,20*S*,21*R*.[130] The unexpected montanine-type alkaloid (**90**), obtained as a rearrangement product of haemanthanine-type alkaloids in the presence of halogenating agents, had its absolute configuration assigned as 2*S*,3*S*,4a*S*,11*S* using VCD and DFT (B3PW91/DGDZVP) calculations.[131] The absolute configuration of the tropane alkaloids 6*β*-hydroxy-3*α*-senecioyloxytropane (**91**), 3*α*-hydroxy-6*β*-tigloyloxytropane (**92**), 3*α*-hydroxy-6*β*-senecioyloxytropane (**93**), and 3*α*-hydroxy-6*β*-angeloyloxytropane (**94**), isolated from *Schizanthus* species, was determined as 1*R*,3*R*,5*S*,6*R*. VCD and DFT (B3LYP/DGDZVP) calculations were compared for a pure sample of **91**, as well as for a 69:31 mixture of **92** and **93**, and for a 7:3 mixture of **91** and **94**.[132] The semisynthetic (−)-3*α*,6*β*-acetoxytropane (**95**), prepared from **83**, had its absolute configuration determined as 3*S*,6*S* by comparison of experimental and calculated (B3LYP/DGDZVP) VCD spectra.[133] The orientation of the N-Me group was found to be predominantly equatorial. The absolute configuration of the highly flexible marine antibiotic (+)-synoxazolidinone A (**96**), isolated from *Synoicum pulmonaria*, was assigned as 6*Z*,10*S*,11*R* using ECD, VCD and ROA spectroscopies in combination with theoretical calculations for the eight possible stereoisomers of **96**.[134] ROA allowed for a reliable determination of the configuration at the double bond, while VCD was necessary to resolve the chlorine-substituted stereogenic center. VCD was also used to assign the absolute configuration of a derivative of **96**, **97** with three stereogenic centers as 6*Z*,10*S*,11*R*. VOA methods were found to be more reliable than ECD.[134] Both enantiomers of 3*α*,6*β*-dibenzoyloxytropane were prepared from optically active 6*β*-hydroxyhyoscyamines and their absolute configurations were determined as (+)-(3*S*,6*S*)-**98**, and consequently (−)-(3*R*,6*R*), using VCD spectroscopy. The experimental spectra showed



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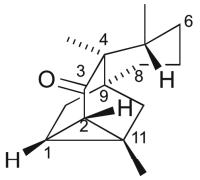

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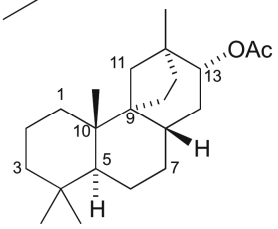

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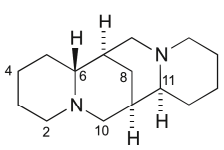
bands characteristic of these configurations observed in previously studied tropanediol derivatives.[135] The absolute configuration of the dextrorotatory aspidospermatan-type indoline alkaloid (**99**), isolated from *Geissospermum reticulatum*, was determined as 2*R*,7*R*,15*R*,17*S*,19*S* by VCD spectrosocopy and DFT (B3LYP/DGDZVP) calculations.[136] This assignment facilitated the deduction of the absolute stereochemistry of structurally related alkaloids isolated from this plant. The fungal secondary metabolite (+)-caripyrin (**100**), first described from *Caripia montagnei*, had its absolute configuration determined as *R*,*R* using VCD and DFT [B3LYP/6-311G(d,p)] calculations.[137] Finally, the absolute configuration of (−)-cataubine E (**101**), isolated from *Erythroxylum hypericifolium*, was established as 3*R*,6*R* by correlation with a synthetic sample, whose configuration was secured using VCD.[138]

Lignans

The first compound of this class investigated using VCD and DFT calculations was the norlignan (+)-nyasol (**101**), reported from *Asparagus africans*. Compound **102**, which is among the most flexible small organic molecules studied by VCD spectroscopy, was assigned as *S* after comparison of observed VCD, both in solution and KBr pellets, with calculated (B3LYP/aug-cc-pVDZ) data.[139] This result enabled the establishment of the absolute configuration of (−)-hinokiresinol (**103**) also as *S*. The absolute configurations of podophyllotoxin related lignans isolated from *Bursera fagaroides* were determined using VCD. Initially, the absolute configuration of (−)-podophyllotoxin (**104**) and (−)-deoxypodophyllotoxin (**105**) was assigned as 7*R*,7′*R*,8*R*,8′*R* and 7′*R*,8*R*,8′*R*, respectively, by comparison of experimental VCD and B3LYP/DGDZVP predicted spectra. Then, VCD measurements of (−)-morelensin (**106**), (−)-yatein (**107**), and (−)-5′-desmethoxyyatein (**108**) led to their assignments as (7′*R*,8*R*,8′*R*)-**106**, (8*R*,8′*R*)-**107**, and (8*R*,8′*R*)-**108**.[140] The absolute configuration and solution-state conformers of three peperomin-type secolignans isolated from *Peperomia blanda* were unambiguously determined by using VCD spectroscopy associated with DFT calculations.[141]



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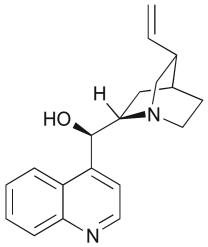

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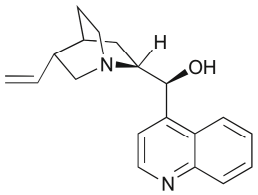

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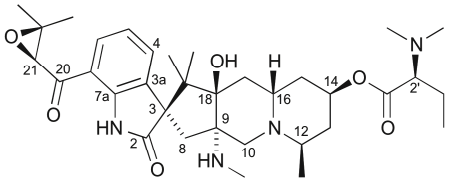

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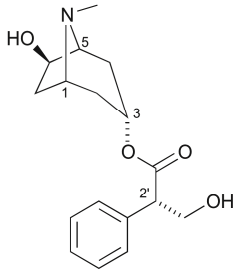

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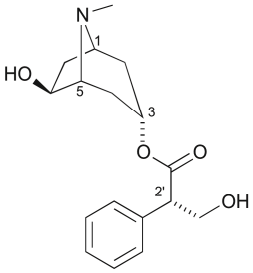

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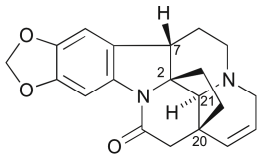

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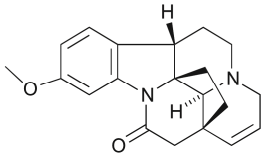

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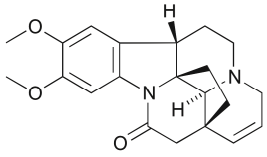

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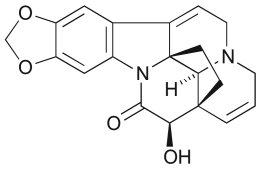

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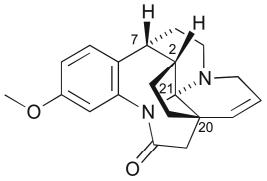

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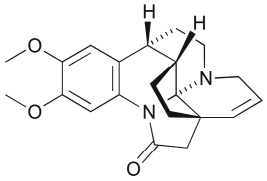

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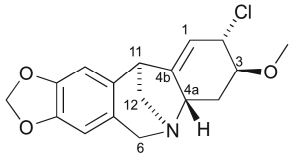

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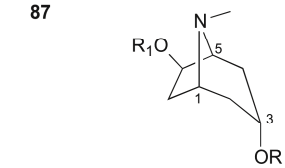
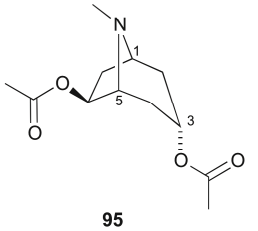


91 R = R$_1$ = H

92 R = H R$_1$ =

93 R = H R$_1$ =

94 R = H R$_1$ =



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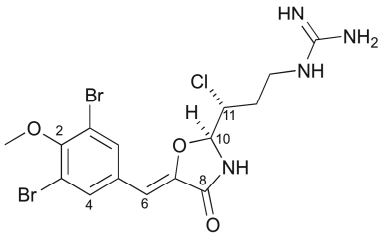

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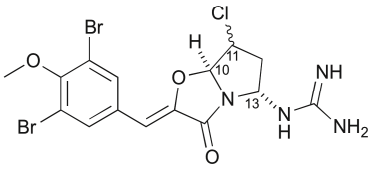

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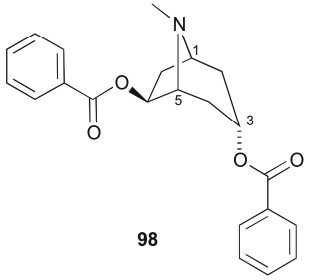

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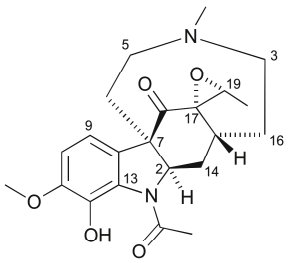

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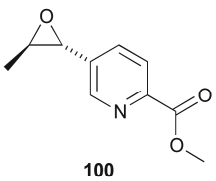

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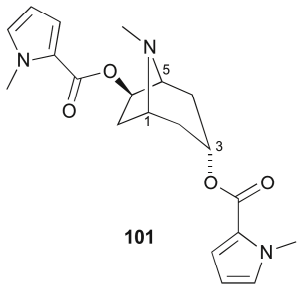
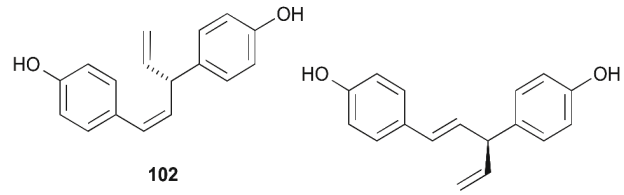


101

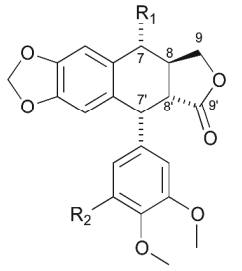
Compound (–)-**109** was confirmed as 2*R*,3*S*, the same configuration assigned previously using ECD spectroscopy.[142] Peperomin B (**110**) was assigned as (+)-(2*S*,3*S*,5*S*)-**110** by comparing observed and calculated [B3LYP/6-31G(d)] data. The novel compound (–)-**111** was determined as 2*R*,3*S*,5*S* with the aid of calculations at the B3PW91/TZVP level. ECD was not able to distinguish possible C-5 epimers for **110** and **111**.[141] Several dimeric stilbene glucosides were isolated from *Gnetum africanum* and had their absolute configurations assigned using VCD and DFT [B3PW91/6-31G(d,p)] calculations.[143] The two diastereomers of (–)-gnemonoside A were assigned as (7a*R*,8a*R*)- and (7a*S*,8a*S*)-**112**. Compounds (–)-gnemonoside C (**113**) and (–)-gnemonoside D (**114**) were assigned as 7a*S*,8a*S*. The two enantiomers of gnetin C, obtained from the aglycones of **112** and its diastereomer, were assigned as (–)-(7a*S*,8a*S*)-**115** and (+)-(7a*R*,8a*R*). Finally, the bioactive compound (+)-schizandrin (**116**), isolated from *Schisandra sphenanthera*, had its absolute configuration reassigned using VCD and DFT [B3LYP/6-311+G(d)] calculations for two the diastereomers possible.[144] The configuration of (+)-**116** was unambiguously established as 7*S*,8*R* and not 7*S*,8*S* as previously reported.

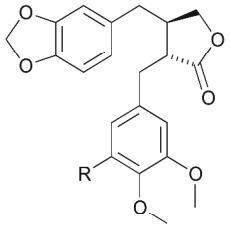
Meroterpenes

Meroterpenes are another class of secondary metabolites commonly studied using VOA spectroscopic methods. Novofumigatonin (**117**), a new orthoester meroterpenoid isolated from *Aspergillus novofumigatus* had its relative stereogeometry established by NMR and X-ray analysis. However the determination of its absolute configuration (as depicted below), was only possible by using VCD and DFT [B3LYP/6-31G(d,p)] calculations.[145] The absolute configuration of (–)-stypotriol (**118**) isolated from *Stypodium zonale* was determined as 3*S*,5*R*,8*R*,9*R*,10*S*,13*S*,14*S* using VCD and B3LYP/DGDZVP predicted spectra for the triacetate derivative. This derivative was considered the largest natural product molecule studied by VCD at that time.[146] Recently, larger molecules have been successfully studied using this technique, and an example has been published (see compound **67**). The meroditerpenoid isoepitaondiol (**119**), isolated from *Stypopodium flabelliforme*, had its structure reassigned based on NMR and X-ray diffraction data. The absolute configuration of the revised structure (as depicted below) was determined using VCD and DFT (B3LYP/DGDZVP) calculations for the diacetate derivative.[147] The absolute configuration of two prenylated chromanes from *Peperomia obtusifolia*, (+)-peperobtusin A (**120**) and (+)-**121**, was reassigned as *R* using VCD and DFT [B3LYP/6-31G(d)] calculations.[148] The previous erroneous assignments were based on the ECD helicity rule for the chromane chromophore,[149] which was shown to be invalid for the title molecules after theoretical calculations of ECD spectra. Sargaol acetate (**122**), a chromene substituted with a large unsaturated carbon chain isolated from *Stypopodium flabelliforme*, had its absolute configuration determined as (+)-(*R*) using VCD and DFT (B3LYP/DGDZVP) calculations.[150] The absolute configuration of a dextrorotatory benzodihydrofuran (**123**) isolated from *Cyperus teneriffae* was determined as *S* by comparison of observed and B3LYP/DGDZVP calculated data.[151] The prenylated chromene gaudichaudianinc acid (**124**), the major metabolite from *Piper gaudichaudianum*, was isolated as a



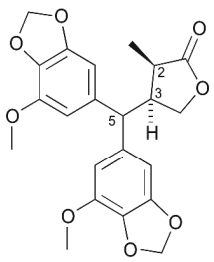
102 **103**

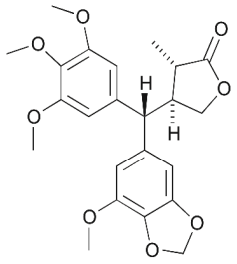




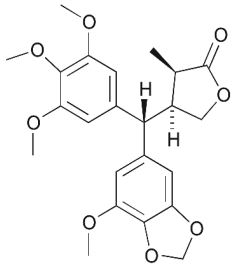
104 R_1 = OH; R_2 = OMe
105 R_1 = H; R_2 = OMe
106 R_1 = H; R_2 = H

107 R = OMe
108 R = H





109 **110**



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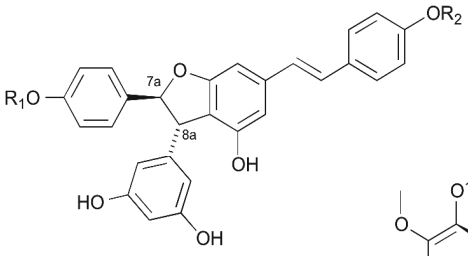
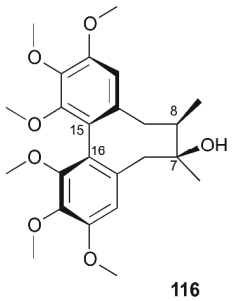


112 R_1 = β-D-Glc; R_2 = β-D-Glc
113 R_1 = β-D-Glc; R_2 = H
114 R_1 = H; R_2 = β-D-Glc
115 R_1 = H; R_2 = H



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racemic mixture and the absolute configuration of its enantiomers was determined as (−)-(*R*)-**124** and consequently (+)-(*S*), by means of a combination of ECD and VCD spectroscopy using DFT calculations.[152] Six novel monoterpene chromane esters were isolated from *Peperomia obtusifolia* and their absolute configurations, which could not be assessed using any standard classical technique, were determined using VCD and DFT [B3LYP/6-31G(d)] calculations. The molecules (−)-**125**, (+)-**126**, (−)-**127**, and (+)-**128**, were elucidated as both enantiomers of **121** esterified with the enantiomers of **3**, while compounds (−)-**129** and (+)-**130** were characterized as both enantiomers of **121** esterified with (+)-(1*R*)-*endo*-fenchol. Arithmetical operations of experimental and calculated spectra led to the identification of VCD spectral signatures for the monoterpene and the chromane moieties.[153] The structure of filifolinol acetate (**131**) was reassigned using NMR and single crystal X-ray analysis, and its absolute configuration was determined as 2*S*,9*S*,12*R* using VCD and DFT (B3LYP/DGDZVP) calculations.[154] The absolute configuration of the algal meroditerpenoids (−)-taondiol diacetate (**132**) and (+)-epitaondiol diacetate (**133**) was determined by VCD and DFT calculations (B3LYP/DGDZVP and B3LYP/DGDZVP2, respectively). Compound **132** was assigned as 2*S*,3*S*,6*R*,7*R*,10*R*,11*R*,14*S* while **133** was determined as 2*S*,3*S*,6*S*,7*S*,10*R*,11*R*,14*S*.[155] A new diasteromeric mixture (**134**) containing the enantiomers of **129** and **130** was isolated from *Peperomia obtusifolia*.[156] VCD analysis, which was carried out without the aid of DFT calculations, allowed the assignment of the putative compounds as a racemic mixture of the chiral chromane **121** esterified with the monoterpene (1*S*,2*S*,4*R*)-fenchol. Zonaquinone acetate (**135**), isolated from *Stypopodium zonale*, had its absolute stereochemistry assessed by VCD measurements and DFT (B3LYP/DGDZVP) calculations. Compound (+)-**135** was confidently assigned as 2*R*,3*R*,6*R*,7*R*,10*R*,11*R*,14*S*.[157] Finally, the absolute configurations of spiroindicumides A (**136**) and B (**137**), isolated from *Chaetomium indicum*, were determined as 2′*R*,6*S*,7*S* and 2′*R*,6*S*,7*R*, respectively, by the VCD exciton chirality method using only ca. 0.3 mg of each sample.[158]

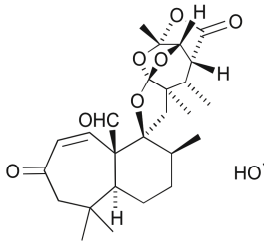
Coumarins and Flavonoids

Despite their wide occurrence in nature, there is only one example of the use of VOA for stereochemical characterization of a coumarin and one of a flavonoid. The dihydrofuranocoumarin (+)-alternamin (**138**), isolated from *Murraya alternans*, had its structure and absolute configurations determined as (*S*)-5,8-dimethoxymarmesin using VCD and DFT (B3PW91/6-311++G(d,p) calculations.[159] The flavanone naringenin (**139**) had its configurational and conformational properties assessed by VCD and DFT (B3PW91/TZ2P) calculations. The *R* configuration was assigned to the enantiomer exhibiting (+) optical rotation. Once again VOA was found to be superior to ECD in monitoring conformational changes in chiral molecules.[160]

Miscellaneous

VOA methods have also been successfully applied to determine the solution-state conformation and absolute configuration of compounds exhibiting mixed biosynthetic origins. The first example is the polyphenolic binaphthyl dialdehyde gossypol (**140**), which presents axial chirality. The excellent agreement between experimental VCD and intensity calculations carried out at DFT [B3LYP/6-31G(d)] level established the absolute configuration of (−)-**139** as *M*.[161] A series of phytoalexins have also been studied using VCD spectrosocopy. The absolute configuration of the naturally occurring (−)-dioxibrassinin (**141**) and (−)-3-cyanomethyl-3-hydroxyoxindole (**142**), first isolated from *Pseudomonas cichorii* inoculated cabbage (*Brassica oleracea*), was determined as *S* by VCD and DFT [B3LYP/6-31G(d,p)] calculations performed for semisynthetic samples.[162] The other cruciferous phytoalexins (+)-1-methoxyspirobrassinin (**143**) and (−)-methoxyspirobrassinol methyl ether (**144**) had their absolute configurations determined as *R* and 2*R*,3*R*, respectively, by comparison of observed VCD and B3LYP/6-31G(d,p) calculated spectra.[163] These assignments were also supported by ECD analysis. The absolute configuration of (−)-brassicanal C (**145**), which was also isolated from cabbage inoculated with *P. cichorii*, was determined as *S* by using a combination of OR, ECD, VCD along with DFT predicted spectra.[164]

Many chromones and furanones have also been investigated using VOA methods. The dihydrofurochromones (+)-**146**, (+)-**147** had their absolute configuration assigned as *S* by chemical correlation with (+)-5-*O*-methylvisamminol (**148**), whose absolute stereochemistry was established as *S* by VCD spectroscopy and DFT (B3LYP/DGDZVP) calculations.[165] The new visamminol derivative (+)-4′-angeloylvisamminol (**149**), isolated from *Arracacia tolucensis*, had its structure and absolute configuration determined using VCD and DFT (B3LYP/DGDZVP) calculations. Compound (+)-**149** was assigned as *S*.[166] The absolute configuration of the new metabolite (+)-microsphaeropsone A (**150**), isolated from *Microsphaeropsis* species, was safely determined as 1*R*,2*R* by comparison of ECD and VCD spectra with theoretical calculations of both properties.[167] The natural product (+)-oxalicumone C (**151**) was synthesized and had its absolute configuration determined as *S* using a combination of experimental and calculated ECD and VCD data. In order to improve the agreement between experimental and B3LYP/6-311G(d,p) calculated VCD, the two hydroxyl groups of **151** were silylated to avoid hydrogen-bonding interactions.[168] The odorous 2-substituted-3(2*H*)-furanones (+)-**152** and (+)-**153** had their absolute configurations determined for the first time as *R* by using VCD in combination with B3PW91/6-31G(d,p) calculated spectra. VCD measurements on the corresponding alcohol molecule were hampered by its immediate racemization in CCl_4, $CDCl_3$, and CD_2Cl_2.[169] The absolute configuration of two tautomers of homofuraneol (+)-**154** and (+)-**155**, with unique keto-enol structures, was determined as *R* by direct measurement of the VCD spectra of their methyl ether derivatives compared with B3PW91/6-31(d,p) calculations.[170] The chiral furanones (−)-sotolon (**156**) and (+)-maple furanone (**157**) had their absolute configurations assigned as *R* by comparing VCD experimental spectra with B3PW91/6-31G(d,p) calculated ones. Interestingly, these two compounds present opposite signs of optical rotation, despite their striking structural similarity and identical absolute configuration.[171] Klaivanolide (**158**), an antiparasitic compound



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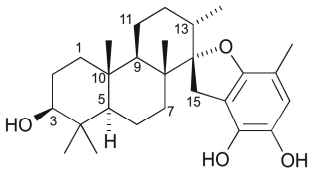

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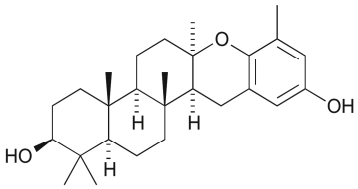

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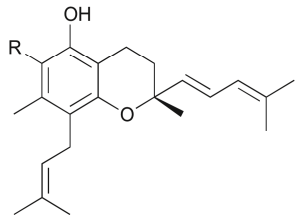

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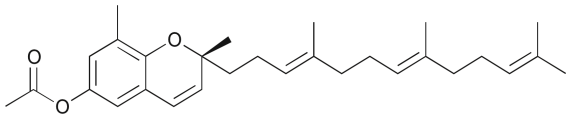

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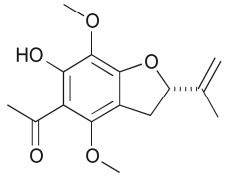

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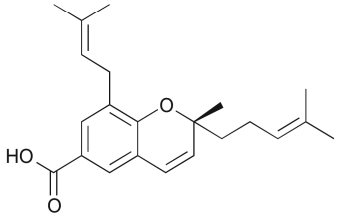

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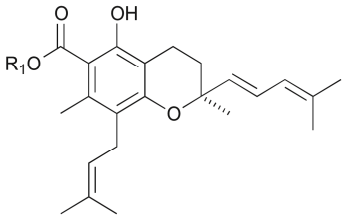

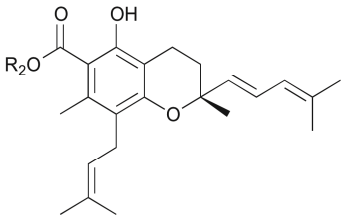

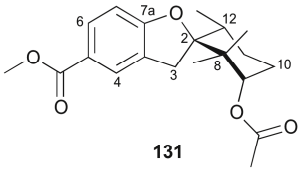

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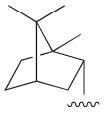

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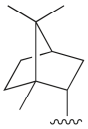
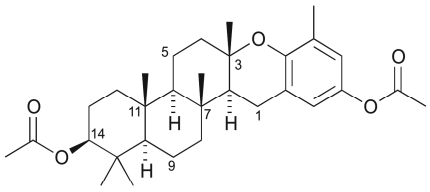


ii

iii

125 R_1 = i
126 R_2 = i
127 R_1 = ii
128 R_2 = ii
129 R_1 = iii
130 R_2 = iii



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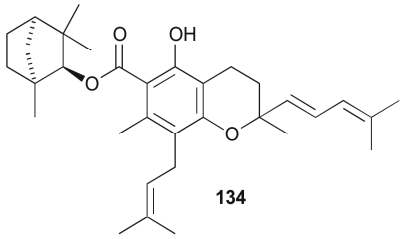

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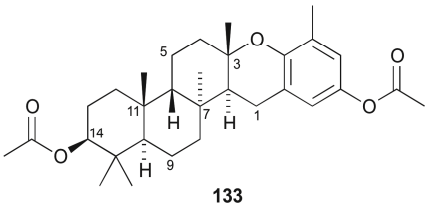

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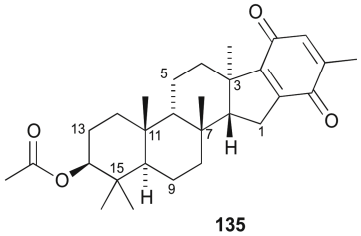

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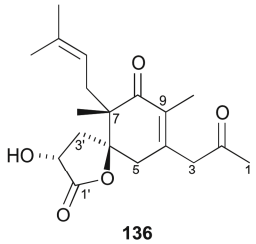

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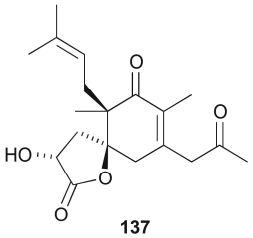
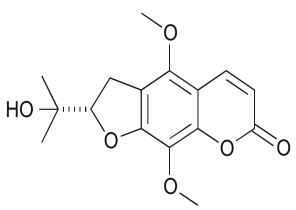


137

isolated from *Uvaria klaineana*, was originally assigned as a seven-membered lactone whose absolute configuration was determined as (+)-(*S*) using VCD and DFT (B3LYP/TZ2P).[172] However, the attempt to synthesize **158** led to the complete reinterpretation of its originally assigned structure. Klaivanolide is actually the known molecule acetylmelodorinol (**159**). VCD calculations [B3LYP/6-31G(d)] on the reassigned structure confirmed the absolute configuration at C7 as *S*.[173] The absolute configuration of (+)-cephalochromin (**160**), a homodimeric naphthpyranone containing both axial and central chirality was determined as a*S*,2*R*,2′*R* using a combination of OR, ECD, and VCD in conjunction with the corresponding quantum chemical predictions at the B3LYP/6-311G(d) level. VCD was found to be the only method capable of determining simultaneously the configuration of both chirality elements.[174] Comparison of theoretical (B3PW91/TZ2P) and experimental VCD spectra of a synthetic sample of the obscure mealybug sex pheromone (+)-**161** allowed the determination of the absolute configuration of the insect's pheromone as 1*S*,2*S*,3*R*.[175] The absolute configuration of the fungal metabolite hexylitaconic acid (**162**), a structurally unique methylenesuccinic acid, was determined as (−)-(*R*)/(+)-(*S*) using VCD and DFT [B3LYP/6-311++G(d,p)] calculations for methyl ester and lactone derivatives.[176] Aeroplysinin-1 (**163**), an antiangiogenic drug extracted from *Aplysina cavernicola*, had its conformational properties in aqueous solution and absolute configuration determined using ROA and DFT (B3LYP/aug-cc-pVDZ) calculations. The calculations were performed for the four stereoisomers possible, which resulted in the assignment of **163** as 1*S*,6*R*.[177] VCD in the solid state was also investigated showing a nice example of the complementarity of both techniques in different conditions. The great importance of including solvent effects in quantum chemical calculations of OR, ECD and VCD was demonstrated using (+)-(2*S*,3*S*)-garcinia acid dimethyl ester (**164**).[178] (+)-Crassipin C (**165**), a new terpenylated acylphoroglucinol isolated from *Elaphoglossum crassipes*, had its absolute configuration at C-4 determined as *R* by ECD, VCD, and theoretical calculations. However, comparison of experimental and calculated VCD at the B3LYP/6-31G(d) level could not confidently establish the absolute configuration at C-2′.[179] The formation of aggregates and/or solute-solvent complexes in chiral natural products occurring as carboxylic acids makes the use of chiroptical methods more challenging. In order to avoid aggregations, the use of the corresponding sodium salts or acid anhydrides was proposed. The effects of this approach on VCD, ECD and OR properties were evaluated using the acid form of **164** and (+)-(2*S*,3*R*)-hibiscus acid (**166**).[180] The uncommon compound (−)-preussidone (**167**), obtained from *Preussia typharum*, had its absolute configuration unambiguously assigned as *R* using quantum chemical ECD and VCD calculations.[181] The absolute configurations of (−)-phyllostin (**168**), (−)-scytolide (**169**), isolated from *Phyllosticta cirsii*, and (+)-oxysporone (**170**), isolated from *Diplodia africana*, were determined by computational analysis of their ORD, ECD, and VCD spectra. Compound (−)-**168** was assigned as 3*S*,4a*R*,8*S*,8a*R* using the three chiroptical methods, while (−)-**169** was assigned as 4a*R*,8*S*,8a*R* using ECD and VCD. Satisfactory agreement between experimental and calculated VCD for (+)-**170**, assigned as 4*S*,5*R*,6*R*, was only obtained after taking into account solvent



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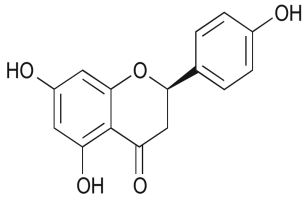
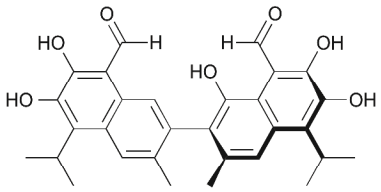


139

effects.[182] A series of dioxolanone-type secondary metabolites from *Guignardia bidwelli* had their absolute configurations assigned using VCD and ECD spectroscopies. VCD was considered to be superior to ECD for the determination of absolute configurations of these compounds exhibiting central chirality.[183] Pheguignardic acid (**171**), alaguignardic acid (**172**), guignardianone A (**173**), guignardianone B (**174**), guignardianone C (**175**), and guignardianone D (**176**) were assigned as *S* by comparison of experimental VCD and B3LYP/6-311G(d,p) predicted spectra. As for **171** and **172**, methyl ester derivatives were prepared in order to improve the agreement with theoretical data. Teraspiridoles A (**177**) and B (**178**), formed from the merger of a diterpene and modified indole scaffold, were isolated from *Aspergillus terreus* and had their absolute configurations assigned as (+)-(5*R*,7*S*,8*R*,9*R*,10*R*,13*S*,14*S*,16*S*,22*S*,23*S*)-**177** and (+)-(5*R*,7*S*,8*R*,9*R*,10*R*,13*S*,14*S*,16*S*,22*S*)-**178** by using a combination of ECD and VCD experiments and calculations [B3LYP/6-31+G(d,p)].[184] The absolute configuration of the thymol derivative (+)-**179**, isolated from *Ageratina cylindrical*, was established as *S* using X-ray analysis as well as VCD in combination with DFT calculations. In this case, the functional PBEPBE was found to provide a better agreement between experimental and calculated data at a lower computational cost.[185]

Naphtoquinones have also been investigated using VOA methods. The rare derivatives of dehydroiso-α-lapachone (−)-**180** and (−)-**181**, isolated from *Heterophragma adenophyllum*, had their relative and absolute configurations reassigned using NMR Mosher's method, X-ray analysis, and VCD combined with DFT [B3LYP/6-311++G(d,p)] calculations. The relative orientation of the isopropenyl and OH groups of **180** and **181** was revised to *trans* and the absolute configuration at C-3 was assigned as *S*.[186] The absolute configuration of a new S-bridged pyranonaphytoquinone dimer, isolated from *Nonomuraea specus*, was determined by comparing experimental and calculated OR, ECD, and VCD for the monomeric congener hypogeamicin B (**182**). Compound (−)-**182** was assigned as 1*R*,3*S*,4a*S*,10a*R*. Accordingly, on the basis of the likely conservation of epoxide ring opening stereo- and regiochemistry, the dimer was proposed to have 1*R*,3*R*,4a*R*,10a*S*,10*R*,3′*R*,4a′*R*,10a′*S*.[187]

Finally, the relative configuration of a key subunit of hemicalide, isolated from *Hemimycale* sp., was established by combining stereocontrolled synthesis of model substrates, with NMR and VCD spectroscopy. The C-36-C46 unity (**183**) of hemicalide had its configuration determined as 36*S**,37*S**,39*S**,40*S**,42*R**,45*R**. The absolute configuration at C-42 of the synthetic models was secured by VCD and DFT (B3LYP/aug-cc-pVDZ) calculations.[188]



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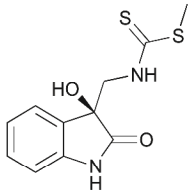

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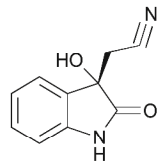

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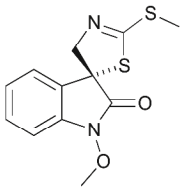

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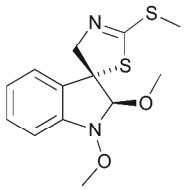

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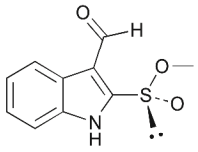

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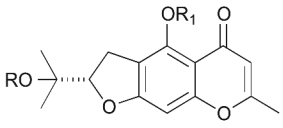
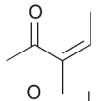
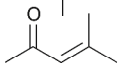


146 R =  ; R_1 = Me

147 R =  ; R_1 = Me

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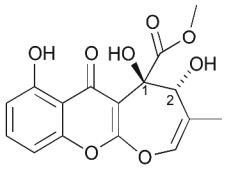

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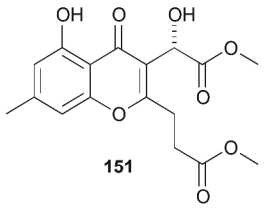

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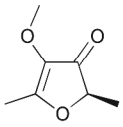

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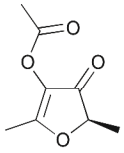

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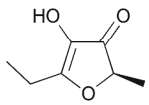

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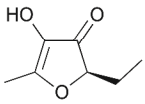

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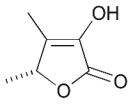

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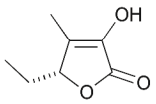

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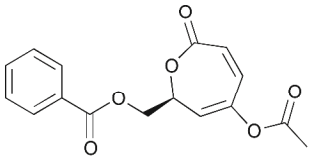

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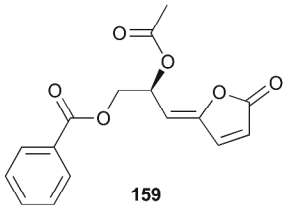

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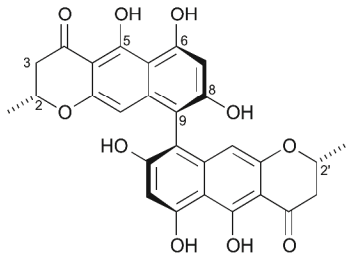

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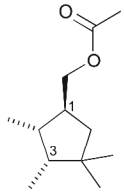

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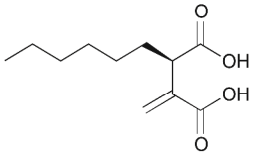

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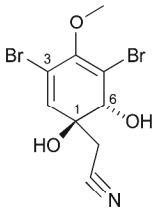

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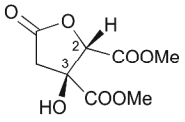

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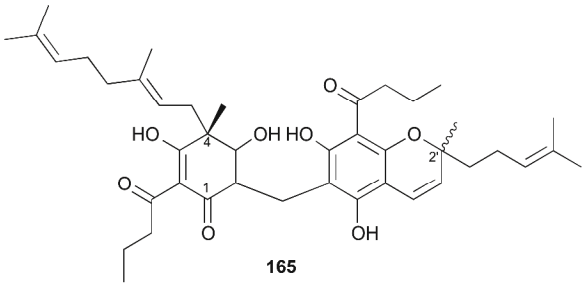

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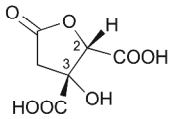

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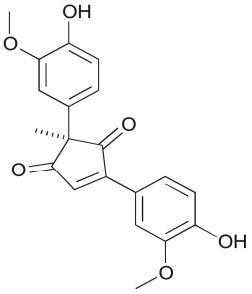

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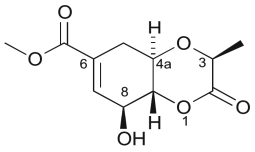

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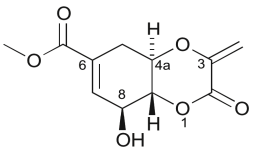

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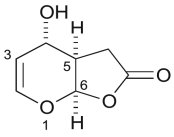

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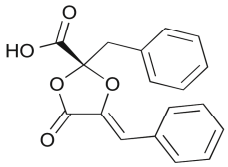

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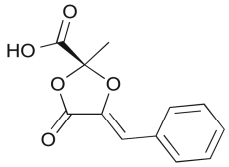

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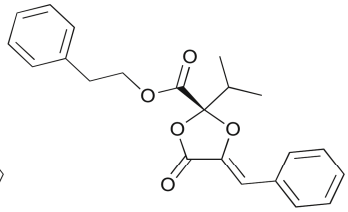

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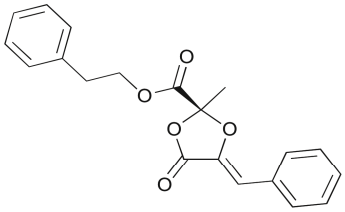

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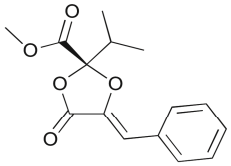

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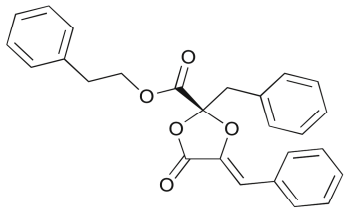

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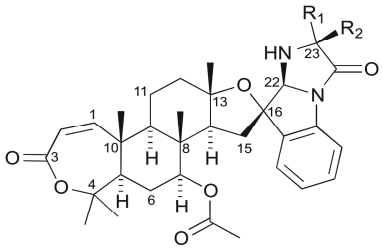
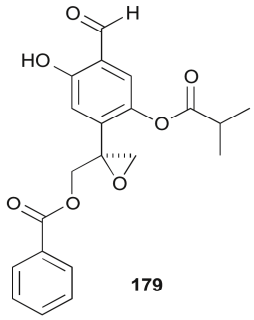


177 R_1 = H; R_2 = CH_3
178 R_1R_2 = CH_2CH_2



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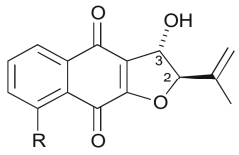
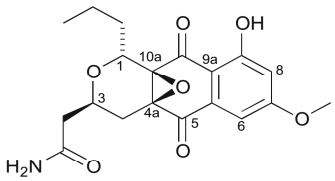


180 R = H
181 R = OH



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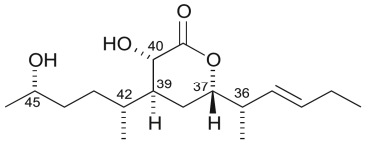


183

Peptides and Carbohydrates

Peptides and carbohydrates comprise important and varied classes of biomolecules for which the use of VCD and ROA are well established. Although not the focus of this review article a few examples on the use of VOA for stereochemical characterization of peptides will be presented. Cyclosporins A (**184**), C (**185**), D (**186**), G (**187**), and H (**188**) had their conformational preferences in $CDCl_3$, as well as that of their magnesium complexes in CD_3CN, investigated using VCD spectrosocopy. DFT calculations at B3PW91/6-31G(d) level were used for fragments of **184** and **188** obtained from crystal structure.[189] The conformations of valinomycin (**189**) in different solvents and the influence of various cations were investigated using VCD spectrosocopy and B3LYP/6-31G(d) calculations. Compound **189** was found to adopt a bracelet-type structure in inert solvents, while a propeller-type structure was suggested in polar solvents.[190] The structure of the potassium complex of **189** in solution was also investigated using ROA and theoretical calculations. It was found that the most populated conformer does not exhibit C_3 symmetry, and is different from that present in the crystal and the NMR-derived strucuture.[191] Pexyganan, a 22 amino acid peptide analogous to the magainin peptides present in the skin of the African clawed frog, had its conformational preferences in solution probed by VCD and ECD spectroscopies. This peptide appears to adopt an α-helical conformation in TFE, a sheet-stabilized β-turn structure in methanol, a random coil with β-turn structure in D_2O, and a solvated β-turn structure in DMSO.[192] The desulfurization of the 3,6-epidithio-diketopiperazine metabolite chaetocin (**190**), isolated from

Chaetomiun virescens, was demonstrated to take place with retention of configuration by the analysis of the desulfurized product using ECD and VCD.[193] This work was the base for the establishment of a universal mechanism for the desulfurization of this class of compounds.[194] Furthermore, a combination of chiroptical spectroscopic methods was successfully applied to two new dimeric epipolythiodiketopiperazines, preussiadins A (**191**) and B (**192**), obtained from the mycelia of a *Preussia typharum* isolate. These compounds had their absolute configurations determined using OR, ECD, and VCD,[195] and compound **191** was assigned as 3*S*,5a*R*,10b*S*,11*S*,12*S*,3′*R*,5a′*S*,10b′*R*,11′*S*,12′*R* by comparison of its experimental and calculated [B3LYP/6-31+G(d,p)] chiroptical data. Following this assignment, the absolute configuration of **192** was also confirmed to be identical to that of **191** by chemical correlation.

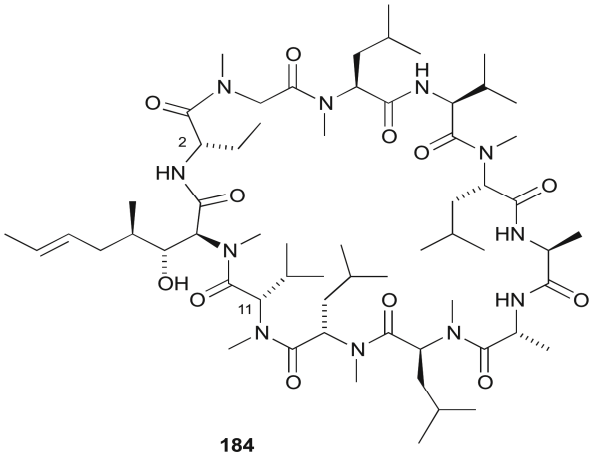
Regarding carbohydrates, VOA, especially VCD, has been extensively used to assign the configuration at the anomeric carbons in monosaccharides as well as the stereochemistry of the glycosidic bonds in disaccharides. Suitable references can be found here.[196-205]

Conclusions

Back in 2000,[28] Allenmark stated: "This (VCD) is likely to become of great importance for the structural elucidation of natural products in the future". Almost fifteen years later, we can confirm herein that VOA methods have indeed become robust and reliable alternatives for the stereochemical characterization of natural product molecules, especially in conditions not accessible to other methods. Nevertheless, a careful look at the data presented here reveals that almost 50% of all literature reports on VOA for conformational and configurational analysis of natural products come from two main research groups, that is, Pedro Joseph-Nathan's group in Mexico and that of Kenji Monde in Japan. Given the large number of researchers focused on natural products all over the world, and the growing need for accurate methods to characterize the molecular structure of natural compounds, we believe that VOA has a great potential to and should become a more routinely used tool in this field worldwide. Another interesting fact is how much the use of ROA spectroscopy still lags behind that of VCD. Out of all the examples given here, only 6 involved ROA. However, as more spectrometers become installed and more natural product research groups learn about the advantages of using ROA spectroscopy, this scenario is likely to change in the near future.

Acknowledgements

We thank São Paulo Research Foundation (FAPESP) grant #2014/50304-9, 2013/07600-3 and 2011/22339-4. We also thank Dr. Andrea N. L. Batista for her invaluable help with the literature search.



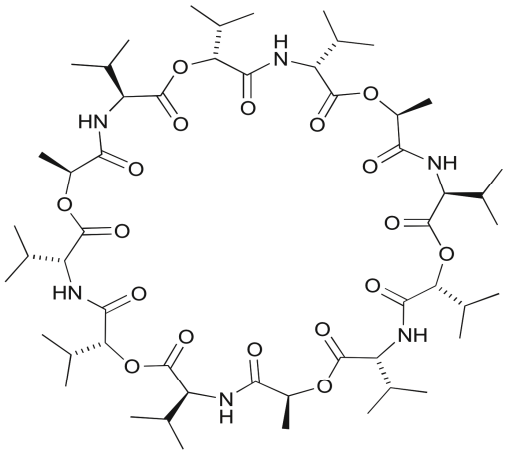
184

185 2 = *L*-Thr - $CH(OH)CH_3$

186 2 = *L*-Val - $CH(CH_3)_2$

187 2 = *L*-NorVal - $CH_2CH_2CH_3$

188 11 = *D*-MeVal - $CH(CH_3)_2$



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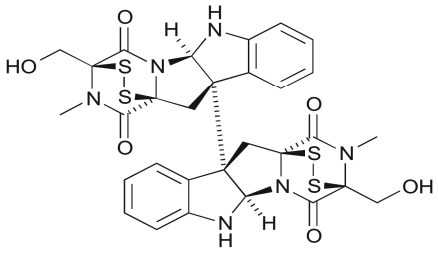

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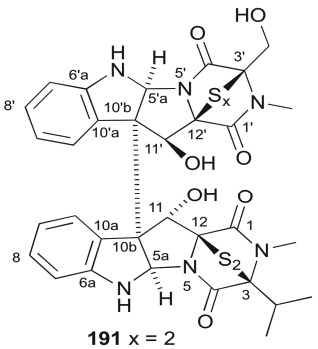

191 x = 2

192 x = 4

Notes and references

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1 V. Davankov, *Chirality*, 2006, **18**, 459-461.
2 J. M. Finefield, D. H. Sherman, M. Kreitman and R. M. Williams, *Angew. Chem. Int. Ed.*, 2012, **51**, 4802-4836.
3 N. Berova, L. Di Bari and G. Pescitelli, *Chem. Soc. Rev.*, 2007, **36**, 914-931.
4 P. L. Polavarapu, *Chirality*, 2002, **14**, 768-781.
5 J. M. Batista Jr., in *Stereoselective synthesis of drugs and natural products*, ed. V. Andrushko and N. Andrushko, John Wiley and Sons, New York, 2013, pp. 1571-1599.
6 N. Harada, K. Nakanishi and N. Berova, in *Comprehensive chiroptical spectroscopy: applications in stereochemical analysis of synthetic compounds, natural products, and biomolecules*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 115-166.
7 P. L. Polavarapu, *Chem. Rec.*, 2007, **7**, 125-136.
8 T. Bruhn, G. Pescitelli, S. Jurinovich, A. Schaumlöffel, F. Witterauf, J. Ahrens, M. Bröring and G. Bringmann, *Angew. Chem. Int. Ed.*, 2014, **53**, 14592-14595.
9 E. Giorgio, R. G. Viglione, R. Zanasi and C. Rosini, *J. Am. Chem. Soc.*, 2004, **126**,12968-12976.
10 P. J. Stephens, D. M. Mccann, J. R. Chesseman and M. J. Frisch, *Chirality*, 2005, **17**, S52-S64.
11 D. Slade, D. Ferreira and J. P. J. Marais, *Phytochemistry*, 2005, **66**, 2177-2215.
12 G. Bringmann, T. A. M. Gulder, M. Reichert and T. Gulder, *Chirality*, 2008, **20**, 628-642.
13 G. Bringmann, T. Bruhn, K. Maksimenka and Y. Hemberger, *Eur. J. Org. Chem.*, 2009, 2717-2727.
14 G. Pescitelli, T. Kurtán, U. Flörke and K. Krohn, *Chirality*, 2009, **21**, E181-E201.
15 A. G. Petrovic, A. Navarro-Vázquez and J. L. Alonso-Gómez, *Curr. Org. Chem.*, 2010, **14**, 1612-1628.
16 X.-C. Li, D. Ferreira and Y. Ding, *Curr. Org. Chem.*, 2010, **14**, 1678-1697.
17 T. F. Molinski, *Curr. Opin. Biotechnol.*, 2010, **21**, 819-826.
18 N. Berova, G. A. Ellestad and N. Harada, in *Comprehensive natural products II: modern methods in natural products chemistry*, ed. L. Mander and H.-W. Liu, Elsevier, Oxford, 2010, pp. 91-146.
19 J. Autschbach, L. Nitsch-Velasquez and M. Rudolph, *Top. Curr. Chem.*, 2011, **298**, 1-98.
20 S.-D. Zhao, L. Shen, D.-Q. Luo and H.-J. Zhu, *Curr. Org. Chem.*, 2011, **15**, 1843-1862
21 G. Pescitelli, L. Di Bari and N. Berova, *Chem. Soc. Rev.*, 2011, **40**, 4603-4625.
22 C. Bertucci and D. Tedesco, *J. Chromatogr. A*, 2012, **1269**, 69-81.
23 G. Pescitelli, T. Kurtán and K. Krohn, in *Comprehensive chiroptical spectroscopy: applications in stereochemical analysis of synthetic compounds, natural products, and biomolecules*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 217-249.
24 T. F. Molinski and B. I. Morinaka, *Tetrahedron*, 2012, **68**, 9307-9343.
25 L.-Y. Kong and P. Wang, *Chin. J. Nat. Med.*, 2013, **11**, 193-198.
26 A. Goel, A. Kumar and A. Raghuvanshi, *Chem. Rev.*, 2013, **113**, 1614-1640.
27 A. E. Nugroho and H. Morita, *J. Nat. Med.*, 2014, **68**, 1-10.
28 S. Allenmark, *Nat. Prod. Rep.*, 2000, **17**, 145-155.
29 L. A. Nafie, *Nat. Prod. Commun.*, 2008, **3**, 451-446.
30 P. J. Stephens, F. J. Devlin and J.-J. Pan, *Chirality*, 2008, **20**, 643-663.
31 P. J. Stephens and F. J. Devlin, in *Encyclopedia of spectroscopy and spectrometry*, ed. J. C. Lindon, G. E. Tranter and D. W. Koppenaal, Academic Press, London, 2010, pp. 2916-2937.
32 Y. He, B. Wang, R. K. Dukor and L. A. Nafie, *Appl. Spectrosc.*, 2011, **65**, 699-723.
33 P. L. Polavarapu, in *Comprehensive chiroptical spectroscopy: applications in stereochemical analysis of synthetic compounds, natural products, and biomolecules*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 147-177.
34 P. J. Stephens, F. J. Devlin and J. R. Cheeseman, *VCD spectroscopy for organic chemists*, CRC Press, Boca Raton, 2012.
35 J. M. Batista Jr. and V. S. Bolzani, in *Studies in natural products chemistry*, ed. A.-u. Rahman, Elsevier, Oxford, 2014, pp. 383-417.
36 P. Joseph-Nathan and B. Gordillo-Román, in *Progress in the chemistry of organic natural products*, ed. A. D. Kinghorn, H. Falk and J. Kobayashi, Springer International Publishing, 2015, pp. 311-452.
37 L. D. Barron, A. D. Bogaard and A. D. Buckingham, *J. Am. Chem. Soc.*, 1973, **95**, 603-605.
38 G. Holzwarth, E. C. Hsu, H. S. Mosher, T. R. Faulkner and A. Moscowitz, *J. Am. Chem. Soc.*, 1974, **96**, 251-252.
39 L. A. Nafie, J. C. Cheng and P. J. Stephens, *J. Am. Chem. Soc.*, 1975, **97**, 3842-3843.
40 Bruker, Corp., Jasco, Inc., and BioTools, Inc. offer either VCD accessories or stand-alone instrumentation. BioTools, Inc. is to date the only company offering ROA spectrometers.
41 The main software packages available for DFT calculations of VOA spectra are: Gaussian, Dalton, and CADPAC. References for these three packages, respectively, are given below.
(a) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision D.01*, Gaussian, Inc., Wallingford CT, 2013; (b) K. Aidas, C. Angeli, K. L. Bak, V. Bakken, R. Bast, L. Boman, O. Christiansen, R. Cimiraglia, S. Coriani, P. Dahle, E. K. Dalskov, U. Ekström, T. Enevoldsen, J. J. Eriksen, P. Ettenhuber, B. Fernández, L. Ferrighi, H. Fliegl, L. Frediani, K. Hald, A. Halkier, C. Hättig, H. Heiberg, T. Helgaker, A. C. Hennum, H. Hettema, E. Hjertenæs, S. Høst, I.-M. Høyvik, M. F. Iozzi, B. Jansik, H. J. Aa. Jensen, D. Jonsson, P. Jørgensen, J. Kauczor, S. Kirpekar, T. Kjærgaard, W. Klopper, S. Knecht, R. Kobayashi, H. Koch, J. Kongsted, A. Krapp, K. Kristensen, A. Ligabue, O. B. Lutnæs, J. I. Melo, K. V. Mikkelsen, R. H. Myhre, C. Neiss, C. B. Nielsen, P. Norman, J. Olsen, J. M. H. Olsen, A. Osted, M. J. Packer, F. Pawlowski, T. B. Pedersen, P. F. Provasi, S. Reine, Z. Rinkevicius, T. A. Ruden, K. Ruud, V. Rybkin, P. Salek, C. C. M. Samson, A. Sánchez de Merás, T. Saue, S. P. A. Sauer, B. Schimmelpfennig, K. Sneskov, A. H. Steindal, K. O. Sylvester-Hvid, P. R. Taylor, A. M. Teale, E. I. Tellgren, D. P. Tew, A. J. Thorvaldsen, L. Thøgersen, O. Vahtras, M. A. Watson, D. J. D. Wilson, M. Ziolkowski, and H. Ågren, *WIREs Comput. Mol. Sci.*, 2014, **4**, 269-284; (c) R. D. Amos, I. L. Alberts, J. S. Andrews, S. M. Colwell, N. C. Handy, D. Jayatilaka, P. J. Knowles, R. Kobayashi, K. E. Laidig, G. Laming, A. M. Lee, P. E. Maslen, C. W. Murray, J. E. Rice, E. D. Simandiras, A. J. Stone, M.-

D. Su and D. J. Tozer, *CADPAC: the Cambridge Analytic Derivatives Package*, Cambridge 1995.

42 P. J. Stephens, in *Computational medicinal chemistry for drug discovery*, ed. P. Bultinck, H. De Winter, W. Langenaeker and J. P. Tollenaere, Marcel Dekker, New York, 2004, pp. 699-726.

43 Conformational searches at molecular mechanics, molecular dynamics, or semi-empirical levels may be performed with, but not restricted to, the following software packges: (a) *Spartan'14*, Wavefunction, Inc. Irvine, CA; (b) *HyperChem 8*, Hypercube, Gainesville, FL; (c) *CONFLEX 7B*, Conflex Corp., Tokyo.

44 J. Shen, C. Zhu, S. Reiling and R. Vaz, *Spectrochim. Acta A*, 2010, **76**, 418-422.

45 E. Debie, E. De Gussen, R. K. Dukor, W. Herrebout, L. A. Nafie and P. Bultinck, *ChemPhysChem*, 2011, **12**, 1542-1549.

46 C. L. Covington and P. L. Polavarapu, *J. Phys. Chem. A*, 2013, **117**, 3377-3386.

47 T. Taniguchi and K. Monde, *J. Am. Chem. Soc.* 2012, **134**, 3695-3698.

48 J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999-3094.

49 J. R. Cheeseman, M. S. Shaik, P. L. A. Popelier and E. W. Blanch, *J. Am. Chem. Soc.*, 2011, **133**, 4991-4997.

50 T. A. Keiderling and A. Lakhani, in *Comprehensive chiroptical spectroscopy: applications in stereochemical analysis of synthetic compounds, natural products, and biomolecules*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 707-758.

51 L. D. Barron, in *Comprehensive chiroptical spectroscopy: applications in stereochemical analysis of synthetic compounds, natural products, and biomolecules*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 759-793.

52 E. W. Blanch, L. Hecht, C. D. Syme, V. Volpetti, G. P. Lomonossof, K. Nielsen and L. D. Barron, *J. Gen. Virol.*, 2002, **83**, 2593-2600.

53 T. B. Freedman, X. Cao, R. K. Dukor and L. A. Nafie, *Chirality*, 2003, **15**, 743-758.

54 L. D. Barron, *Molecular light scattering and optical activity*, Cambridge University Press, Cambridge, 2004.

55 T. D. Crawford, *Theor. Chem. Account.*, 2006, **115**, 227-245.

56 J. Autschbach, *Chirality*, 2009, **21**, E116-E152.

57 K. Ruud and A. J. Thorvaldsen, *Chirality*, 2009, **21**, E54-E67.

58 M. Pecul, *Chirality*, 2009, **21**, E98-E104.

59 S. Abbate, E. Castiglioni, F. Gangemi, R. Gangemi and G. Longhi, *Chirality*, 2009, **21**, E242-E252.

60 J. Sadlej, J. C. Dobrowolski and J. E. Rode, *Chem. Soc. Rev.*, 2010, **39**, 1478-1488.

61 L. D. Barron, *Chem. Phys. Lett.*, 2010, **492**, 199-213.

62 L. A. Nafie, *Vibrational optical activity: principles and applications*, John Wiley and Sons, West Sussex, 2011.

63 B. Mennucci, C. Cappelli, R. Cammi and J. Tomasi, *Chirality*, 2011, **23**, 717-729.

64 S. Yamamoto, *Anal. Bional. Chem.*, 2012, **403**, 2203-2212.

65 L. A. Nafie, in *Comprehensive chiroptical spectroscopy: instrumentation, methodologies, and theoretical simulations*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 387-420.

66 K. Ruud, in *Comprehensive chiroptical spectroscopy: instrumentation, methodologies, and theoretical simulations*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Wood, John Wiley and Sons, New Jersey, 2012, pp. 699-727.

67 F. Partal Ureña, J. R. A. Moreno and J. J. López González, *Tetrahedron: Asymmetry*, 2009, **20**, 89-97.

68 C. Guo, R. D. Shah, R. K. Dukor, X. Cao, T. B. Freedman and L. A. Nafie, *Anal. Chem.*, 2004, **76**, 6956-6966.

69 G. Longhi, R. Gengeni, F. Lebon, E. Castiglioni, S. Abbate, V. M. Pultz and D. A. Lightner, *J. Phys. Chem. A*, 2004, **108**, 5338-5352.

70 V. Andrushchenko, J. L. McCann, J. H. van de Sande, and W. Wieser, *Vib. Spectrosc.*, 2000, **22**, 101-109.

71 C. Guo, R. D. Shah, R. K. Dukor, T. B. Freedman, X. Cao and L. A. Nafie, *Vib. Spectrosc.*, 2006, **42**, 254-272.

72 G. G. Hoffmann, *J. Mol. Struct.*, 2003, **661-662**, 525-539.

73 E. Debie, L. Jasper, P. Bultinck, W. Herrebout and B. Van Der Veken, *Chem. Phys. Lett.*, 2008, **450**, 426-430.

74 R. A. Lombardi and L. A. Nafie, *Chirality*, 2009, **21**, E277-E286.

75 H. Li and L. A. Nafie, *J. Raman Spectrosc.*, 2012, **43**, 89-94.

76 H. Rhee, Y.-G. June, J.-S. Lee, K.-K. Lee, J.-H. Ha, Z. H. Kim, S.-J. Jeon and M. Cho, *Nature*, 2009, **458**, 310-313.

77 R. H. Cichewicz, L. J. Clifford, P. R. Lassen, X. Cao, T. B. Freedman, L. A. Nafie, J. D. Deschamps, V. A. Kenyon, J. R. Flanary, T. R. Holman and P. Crews, *Bioorg. Med. Chem.*, 2005, **13**, 5600-5612.

78 F. J. Devlin, P. J. Stephens and P. Besse, *J. Org. Chem.*, 2005, **70**, 2980-2993.

79 S. Bercion, T. Buffeteau, L. Lespade and M.-A. C. deK. Martin, *J. Mol. Struct.*, 2006, **791**, 186-192.

80 K. Monde, T. Taniguchi, N. Miura, C. S. Vairappan and M. Suzuki, *Chirality*, 2006, **18**, 335-339.

81 K. Monde, T. Taniguchi, N. Miura, C. S. Vairappan and M. Suzuki, *Tetrahedron Lett.*, 2006, **47**, 4389-4392.

82 P. J. Stephens, D. M. McCann, F. J. Devlin and A. B. Smith, *J. Nat. Prod.*, 2006, **69**, 1055-1064.

83 P. J. Stephens, J.-J. Pan, F. J. Devlin, K. Krohn and T. Kurtán, *J. Org. Chem.*, 2007, **72**, 3521-3536.

84 P. J. Stephens, J.-J. Pan, F. J. Devlin and K. Krohn, *J. Org. Chem.*, 2007, **72**, 7641-7649.

85 K. Krohn, D. Gehle, S. K. Dey, N. Nahar, M. Mosihuzzaman, N. Sultana, M. H. Sohrab, P. J. Stephens, J.-J. Pan and F. Sasse, *J. Nat. Prod.*, 2007, **70**, 1339-1343.

86 M. Krautmann, E. C. de Riscala, E. Burgueño-Tapia, Y. Mora-Pérez, C. A. N. Catalán and P. Joseph-Nathan, *J. Nat. Prod.*, 2007, **70**, 1173-1179.

87 C. M. Cerda-García-Rojas, H. A. García-Gutiérrez, J. D. Hernández-Hernández, L. U. Román-Marín and P. Joseph-Nathan, *J. Nat. Prod.*, 2007, **70**, 1167-1172.

88 E. Burgueño-Tapia and P. Joseph-Nathan, *Phytochemistry*, 2008, **69**, 2251-2256.

89 Y. Aoyagi, A. Yamazaki, C. Nakatsugawa, H. Fukaya, K. Takeya, S. Kawauchi and H. Izumi, *Org. Lett.*, 2008, **10**, 4429-4432.

90 C. M. Cerda-García-Rojas, C. A. N. Catalán, A. C. Muro and P. Joseph-Nathan, *J. Nat. Prod.*, 2008, **71**, 967-971.

91 M. A. Lovchik, G. Fráter, A. Goeke and W. Hug, *Chem. Biodiv.*, 2008, **5**, 126-139.

92 E. Debie, P. Bultinck, W. Herrebout and B. van der Veken, *Phys. Chem. Chem. Phys.*, 2008, **10**, 3498-3508.

93 H. Izumi, A. Ogata, L. A. Nafie and R. K. Dukor, *J. Org. Chem.*, 2008, **73**, 2367-2372.

94 F. P. Ureña, J. R. A. Moreno and J. J. L. González, *J. Phys. Chem. A*, 2008, **112**, 7887-7893.

95 K. J. Jalkanen, J. D. Gale, P. R. Lassen, L. Hemmingsen, A. Rodarte, I. M. Degtyarenko, R. M. Nieminen, S. B. Christensen, M. Knapp-Mohammady and S. Suhai, *Theor. Chem. Account.*, 2008, **119**, 177-190.

96 M. A. Muñoz, C. Chamy, A. Carrasco, J. Rovirosa, A. S. Martín and P. Joseph-Nathan, *Chirality*, 2009, **21**, E208-E214.

97 R. E. Rojas-Pérez, E. Cedillo-Portugal, P. Joseph-Nathan and E. Burgueño-Tapia, *Nat. Prod. Commun.*, 2009, **4**, 757-762.

98 M. H. Loandos, M. B. Villecco, E. Burgueño-Tapia, P. Joseph-Nathan and C. A. N. Catalán, *Nat. Prod. Commun.*, 2009, **4**, 1537-1545.

99 J. R. A. Moreno, F. P. Ureña and J. J. L. González, *Vibr. Spectrosc.*, 2009, **51**, 318-325.

100 J. R. A. Moreno, F. P. Ureña and J. J. L. González, *Phys. Chem. Chem. Phys.*, 2009, **11**, 2459-2467.

101 E. Burgueño-Tapia, G. Zepeda and P. Joseph-Nathan, *Phytochemistry,* 2010, **71**, 1158-1161.

102 C. M. Cerda-García-Rojas, E. Burgueño-Tapia, L. U. Román-Marín, J. D. Hernández-Hernández, T. Agulló-Ortuño, A. González-Coloma and P. Joseph-Nathan, *Planta Med.*, 2010, **76**, 297-302.

103 P. Joseph-Nathan, S. G. Leitão, S. C. Pinto, G. G. Leitão, H. R. Bizzo, F. L. P. Costa, M. B. Amorin, N. Martinez, E. Dellacassa, A. Hernández-Barragán and N. Pérez-Hernandez, *Tetrahedron Lett.*, 2010, **51**, 1963-1965.

104 N. H. Andersen, N. J. Christensen, P. R. Lassen, T. B. Freedman, L. A. Nafie, K. Strømgaard and L. Hemmingsen, *Chirality*, 2010, **22**, 217-223.

105 M. A. Gómez-Hurtado, J. M. Torres-Valencia, J. Manríquez-Torres, R. E. del Río, V. Motilva, S. García-Mauriño, J. Ávila, E. Talero, C. M. Cerda-García-Rojas and P. Joseph-Nathan, *Phytochemistry*, 2011, **72**, 409-414.

106 G. M. Molina-Salinas, V. M. Rivas-Galindo, S. Said-Fernández, D. C. Lankin, M. A. Muñoz, P. Joseph-Nathan, G. F. Pauli and N. Walsman, *J. Nat. Prod.*, 2011, **74**, 1842-1850.

107 J. Manríquez-Torres, J. M. Torres-Valencia, M. A. Gómez-Hurtado, V. Motilva, S. García-Mauriño, J. Ávila, E. Talero, M. Cerda-García-Rojas and P. Joseph-Nathan, *J. Nat. Prod.*, 2011, **74**, 1946-1951.

108 B. Gordillo-Román, J. Camacho-Ruiz, M. A. Bucio and P. Joseph-Nathan, *Chirality*, 2012, **24**, 147-154.

109 E. Burgueño-Tapia, C. M. Cerda-García-Rojas and P. Joseph-Nathan, *Phytochemistry*, 2012, **74**, 190-195.

110 M. A. Muñoz, A. Urzúa, J. Echeverría, M. A. Bucio, A. Hernández-Barragán and P. Joseph-Nathan, *Phytochemistry*, 2012, **80**, 109-114.

111 A. Sakamoto, N. Ohya, T. Hasegawa, H. Izumi, N. Tokita and Y. Hamada, *Nat. Prod. Commun.*, 2012, **7**, 419-421.

112 F. Gutiérrez-Nicolás, B. Gordillo-Román, J. C. Oberti, A. Estévez-Braun, A. G. Ravelo and P. Joseph-Nathan, *J. Nat. Prod.*, 2012, **75**, 669-676.

113 M. A. Muñoz, N. Perez-Hernandez, M. W. Pertino, G. Schmeda-Hirschmann and P. Joseph-Nathan, *J. Nat. Prod.*, 2012, **75**, 779-783.

114 A. Valdez-Calderón, J. M. Torres-Valencia, J. J. Manríquez-Torres, R. Velázquez-Jiménez, L. U. Román-Marín, J. D. Hernández-Hernández, C. M. Cerda-Gracía-Rojas and P. Joseph-Nathan, *Tetrahedron Lett.*, 2013, **54**, 3286-3289.

115 M. A. Gómez-Hurtado, F. E. Álvarez-Esquivel, G. Rodríguez-García, M. M. Martínez-Pacheco, R. M. Espinoza-Madrigal, T. Pamatz-Bolaños, J. L. Salvador-Henández, H. A. García-Gutiérrez, C. M. Cerda-García-Rojas, P. Joseph-Nathan and R. E. del Río, *Phytochemistry*, 2013, **96**, 397-403.

116 J. J. Maríquez-Torres, J. M. Torres-Valencia, R. Velázquez-Jiménez, A. Valdez-Calderón, J. G. Alvarado-Rodríguez, C. M. Cerda-García-Rojas and P. Joseph-Nathan, *Org. Lett.*, 2013, **15**, 4658-4661.

117 E. Avilés, A. D. Rodríguez and J. Vicente, *J. Org. Chem.*, 2013, **78**, 11294-11301.

118 B. Gordillo-Román, J. Camacho-Ruiz, M. A. Bucio and P. Joseph-Nathan, *Chirality*, 2013, **25**, 939-951.

119 E. García-Sánchez, C. B. Ramírez-López, A. Talavera-Alemán, A. León-Henández, R. E. Martínez-Muñoz, M. M. Martínez-Pacheco, M. A. Gómez-Hurtado, C. M. Cerda-García-Rojas, P. Joseph-Nathan and R. E. del Río, *J. Nat. Prod.*, 2014, **77**, 1005-1012.

120 R. B. Williams, L. Du, V. L. Norman, M. G. Goering, M. O'Neil-Johnson, S. Woodbury, M. A. Albrecht, D. R. Powell, R. H. Cichewicz, G. R. Eldridge and C. M. Starks, *J. Nat. Prod.*, 2014, **77**, 1438-1444.

121 F. M. S. Junior, C. L. Covington, M. B. de Amorin, L. S. M. Velozo, M. A. C. Kaplan and P. L. Polavarapu, *J. Nat. Prod.*, 2014, **77**, 1881-1886.

122 M. A. Muñoz, C. Chamy, M. A. Bucio, A. Hernández-Barragán and P. Joseph-Nathan, *Tetrahedron lett.*, 2014, **55**, 4274-4277.

123 A. Ortiz-León, J. M. Torres-Valencia, J. J. Manríquez-Torres, J. G. Alvarado-Rodríguez, U. Hernández-Balderas, C. M. Cerda-García-Rojas and P. Joseph-Nathan, *Nat. Prod. Commun.*, 2014, **9**, 753-756.

124 Y. He, X. Cao, L. A. Nafie and T. B. Freedman, *J. Am. Chem. Soc.*, 2001, **123**, 11320-11321.

125 T. Bürgi, A. Vargas and A. Baiker, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1596-1601.

126 T. Mugishima, M. Tsuda, Y. Kasai, H. Ishiyama, E. Fukushi, J. Kawabata, M. Watanabe, K. Akao and J. Kobayashi, *J. Org. Chem.*, 2005, **70**, 9430-9435.

127 M. A. Muñoz, O. Muñoz and P. Joseph-Nathan, *J. Nat. Prod.*, 2006, **69**, 1335-1340.

128 P. J. Stephens, J.-J. Pan, F. J. Devlin, M. Urbanová and J. Hájíček, *J. Org. Chem.*, 2007, **72**, 2508-2524.

129 P. J. Stephens, J.-J. Pan, F. J. Devlin, M. Urbanová, O. Julínek and J. Hájíček, *Chirality*, 2008, **20**, 454-470.

130 T. Taniguchi, C. L. Martin, K. Monde, K. Nakanishi, N. Berova and L. E. Overman, *J. Nat. Prod.*, 2009, **72**, 430-432.

131 J. C. Cedrón, A. Estévez-Braun, A. G. Ravelo, D. Gutiérrez, N. Flores, M. A. Bucio, N. Pérez-Henández and P. Joseph-Nathan, *Org. Lett.*, 2009, **11**,1491-1494.

132 M. Reina, E. Burgueño-Tapia, M. A. Bucio and P. Joseph-Nathan, *Phytochemistry*, 2010, **71**, 810-815.

133 M. A. Muñoz, O. Muñoz and P. Joseph-Nathan, *Chirality*, 2010, **22**, 234-241.

134 K. H. Hopmann, J. Šebestík, J. Novotná, W. Stensen, M. Urbanová, J. Svenson, J. S. Svendsen, P. Bouř and K. Ruud, *J. Org. Chem.*, 2012, **77**, 858-869.

135 M. A. Muñoz, M. Martínez and P. Joseph-Nathan, *Phytochemistry Lett.*, 2012, **5**, 450-454.

136 B. Gordillo-Román, M. Reina, L. Ruiz-Mesia, W. Ruiz-Mesia and P. Joseph-Nathan, *Tetrahedron Lett.*, 2013, **54**, 1693-1696.

137 L. Andernach and T. Opatz, *Eur. J. Org. Chem.*, 2014, 4780-4784.

138 M. A. Muñoz, S. Arriagada and P. Joseph-Nathan, *Nat. Prod. Commun.*, 2014, **9**, 27-30.

139 P. R. Lassen, D. M. Skytte, L. Hemmingsen, S. F. Nielsen, T. B. Freedman, L. A. Nafie and S. B. Christensen, *J. Nat. Prod.*, 2005, **68**, 1603-1609.

140 R. Velásquez-Jiménez, J. M. Torres-Valencia, C. M. Cerda-García-Rojas, J. D. Hernández-Hernández, L. U. Román-Marín, J. J. Manríquez-Torres, M. A. Gómez-Hurtado, A. Valdez-Calderón, V. Motilva, S. García-Mauriño, E. Talero, J. Ávila and P. Joseph-Nathan, *Phytochemistry*, 2011, **72**, 2237-2243.

141 L. G. Felippe, J. M. Batista Jr., D. C. Baldoqui, I. R. Nascimento, M. J. Kato, Y. He, L. A. Nafie and M. Furlan, *Org. Biomol. Chem.*, 2012, **10**, 4208-4214.

142 L. G. Felippe, J. M. Batista Jr., D. C. Baldoqui, I. R. Nascimento, M. J. Kato, V. S. Bolzani and M. Furlan, *Phytochemistry Lett.*, 2011, **4**, 245-249.

143 T. Buffeteau, D. Cavagnat, J. Bisson, A. Marchal, G. D. Kapche, I. Battistini, G. Da Costa, A. Badoc, J.-P. Monti, J.-M. Mérillon and P. Waffo-Téguo, *J. Nat. Prod.*, 2014, **77**, 1981-1985.

144 P. He, X. Wang, X. Guo, Y. Ji, C. Zhou, S. Shen, D. Hu, X. Yang, D. Luo, R. K. Dukor and H. Zhu, *Tetrahedron Lett.*, 2014, **55**, 2965-2968.

145 C. Rank, R. K. Phipps, P. Harris, P. Fristrup, T. O. Larsen and C. H. Gotfredsen, *Org. Lett.*, 2008, **10**, 401-404.

146 M. A. Muñoz, C. Areche, A. San-Martín, J. Rovirosa and P. Joseph-Nathan, *Nat. Prod. Commun.*, 2009, **4**, 1037-1040.

147 C. Areche, A. San-Martín, J. Rovirosa, M. A. Muñoz, A. Hernández-Barragán, M. Bucio and P. Joseph-Nathan, *J. Nat. Prod.*, 2010, **73**, 79-82.

148 J. M. Batista Jr., A. N. L. Batista, D. Rinaldo, W. Vilegas, Q. B. Cass, V. S. Bolzani, M. J. Kato, S. N. López, M. Furlan and L. A. Nafie, *Tetrahedron: Asymmetry*, 2010, **21**, 2402-2407.

149 J. M. Batista Jr., S. N. López, J. S. Mota, K. L. Vanzolini, Q. B. Cass, D. Rinaldo, W. Vilegas, V. S. Bolzani, M. J. Kato, and M. Furlan, *Chirality*, 2009, **21**, 799-801.

150 M. A. Muñoz, C. Areche, J. Rovirosa, A. San-Martín and P. Joseph-Nathan, *Heterocycles*, 2010, **81**, 625-635.

151 A. Amesty, E. Burgueño-Tapia, P. Joseph-Nathan, A. G. Ravelo and A. Estévez-Braun, *J. Nat. Prod.*, 2011, **74**, 1061-1065.

152 J. M. Batista Jr., A. N. L. Batista, D. Rinaldo, W. Vilegas, D. L. Ambrósio, R. M. B. Cicarelli, V. S. Bolzani, M. J. Kato, L. A. Nafie, S. N. López and M. Furlan, *J. Nat. Prod.*, 2011, **74**, 1154-1160.

153 J. M. Batista Jr., A. N. L. Batista, J. S. Mota, Q. B. Cass, M. J. Kato, V. S. Bolzani, T. B. Freedman, S. N. López, M. Furlan and L. A. Nafie, *J. Org. Chem.*, 2011, **76**, 2603-2612.

154 M. A. Muñoz, A. Urzua, J. Echeverria, B. Modak and P. Joseph-Nathan, *Nat. Prod. Commun.*, 2011, **6**, 759-762.

155 M. A. Muñoz, C. Areche, J. Rovirosa, A. San-Martín, B. Gordillo-Román and P. Joseph-Nathan, *Heterocycles*, 2012, **85**, 1961-1973.

156 J. M. Batista Jr., A. N. L. Batista, M. J. Kato, V. S. Bolzani, S. N. López, L. A. Nafie and M. Furlan, *Tetrahedron Lett.*, 2012, **53**, 6051-6054.

157 N. Penicooke, K. Walford, S. Badal, R. Delgoda, L. A. D. Williams, P. Joseph-Nathan, B. Gordillo-Román and W. Gallimore, *Phytochemistry*, 2013, **87**, 96-101.

158 T. Asai, T. Taniguchi, T. Yamamoto, K. Monde and Y. Oshima, *Org. Lett.*, 2013, **15**, 4320-4323.

159 H. M. Min, M. Aye, T. Taniguchi, N. Miura, K. Monde, K. Ohzawa, T. Nikai, M. Niwa and Y. Takaya, *Tetrahedron Lett.*, 2007, **48**, 6155-6158.

160 S. Abbate, L. F. Burgi, E. Castiglioni, F. Lebon, G. Longhi, E. Toscano and S. Caccamese, *Chirality*, 2009, **21**, 436-441.

161 T. B. Freedman, X. Cao, R. V. Oliveira, Q. B. Cass and L. A. Nafie, *Chirality*, 2003, **15**, 196-200.

162 K. Monde, T. Taniguchi, N. Miura, S.-I. Nishimura, N. Harada, R. K. Dukor and L. A. Nafie, *Tetrahedron Lett.*, 2003, **44**, 6017-6020.

163 K. Monde, T. Taniguchi, N. Miura, P. Kutschy, Z. Čurillová, M. Pilátová and J. Mojžiš, *Bioorg. Med. Chem.*, 2005, **13**, 5206-5212.

164 T. Taniguchi, K. Monde, K. Nakanishi and N. Berova, *Org. Biomol. Chem.*, 2008, **6**, 4399-4405.

165 J. M. Torres-Valencia, O. E. Chávez-Ríos, C. M. Cerda-García-Rojas, E. Burgueño-Tapia and P. Joseph-Nathan, *J. Nat. Prod.*, 2008, **71**, 1956-1960.

166 E. Burgueño-Tapia, C. Ordaz-Pichardo, A. I. Buendía-Trujillo, F. J. Chargoy-Antonio and P. Joseph-Nathan, *Phytochemistry Lett.*, 2012, **5**, 804-808.

167 K. Krohn, S. F. Kouam, G. M. Kuigoua, H. Hussain, S. Cludius-Brandt, U. Flörke, T. Kurtán, G. Pescitelli, L. Di Bari, S. Draeger and B. Schulz, *Chem. Eur. J.*, 2009, **15**, 12121-12132.

168 C. Wink, L. Andernach, T. Opatz and S. R. Waldvogel, *Eur. J. Org. Chem.*, 2014, 7788-7792.

169 M. Emura, Y. Yaguchi, A. Kakahashi, D. Sugimoto, N. Miura and K. Monde, *J. Agric. Food Chem.*, 2009, **57**, 9909-9915.

170 K. Monde, A. Nakahashi, N. Miura, Y. Yaguchi, D. Sugimoto and M. Emura, *Chirality*, 2009, **21**, E110-E115.

171 A. Nakahashi, Y. Yaguchi, N. Miura, M. Emura and K. Monde, *J. Nat. Prod.*, 2011, **74**, 707-711.

172 F. J. Devlin, P. J. Stephens and B. Figadère, *Chirality*, 2009, **21**, E48-E53.

173 L. Ferrié, S. Ferhi, G. Bernadat and B. Figadère, *Eur. J. Org. Chem.*, 2014, 6183-6189.

174 P. L. Polavarapu, N. Jeirath, T. Kurtán, G. Pescitelli and K. Krohn, *Chirality*, 2009, **21**, E202-E207.

175 B. Figadère, F. D. Devlin, J. G. Millar and P. J. Stephens, *Chem. Commun.*, 2008, 1106-1108.

176 A. Nakahashi, N. Miura, K. Monde and S. Tsukamoto, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3027-3030.

177 B. Nieto-Ortega, J. Casado, E. W. Blanch, J. T. L. Navarrete, A. R. Quesada and F. J. Ramírez, *J. Phys. Chem. A*, 2011, **115**, 2752-2755.

178 P. L. Polavarapu, G. Scalmani, E. K. Hawkins, C. Rizzo, N. Jeirath, I. Ibnusaud, D. Habel, D. S. Nair and S. Haleema, *J. Nat. Prod.*, 2011, **74**, 321-328.

179 C. Socolsky, S. M. K. Rates, A. C. Stein, Y. Asakawa and A. Bardón, *J. Nat. Prod.*, 2012, **75**, 1007-1017.

180 P. L. Polavarapu, E. A. Donahue, K. C. Hammer, V. Raghavan, G. Shanmugam, I. Ibnusaud, D. S. Nair, C. Gopinath and D. Habel, *J. Nat. Prod.*, 2012, **75,** 1441-1450.

181 L. Du, J. B. King, B. H. Morrow, J. K. Shen, A. N. Miller and R. H. Cichewicz, *J. Nat. Prod.,* 2012, **75**, 1819-1823.

182 G. Mazzeo, E. Santoro, A. Andolfi, A. Cimmino, P. Troselj, A. G. Petrovic, S. Superchi, A. Evidente and N. Berova, *J. Nat. Prod.*, 2013, **76**, 588-599.

183 L. Andernach, L. P. Sandjo, J. C. Liermann, I. Buckel, E. Thines and T. Opatz, *Eur. J. Org. Chem.*, 2013, 5946-5951.

184 S. Cai, L. Du, A. L. Gerea, J. B. King, J. You and R. B. Cichewicz, *Org. Lett.*, 2013, **15**, 4186-4189.

185 C. Bustos-Brito, M. Sánchez-Castellanos, B. Esquivel, J. S. Calderón, F. Calzada, L. Yepez-Mulia, A. Hernández-Barragán, P. Joseph-Nathan, G. Cuevas and L. Quijano, *J. Nat. Prod.,* 2014, **77**, 358-363.

186 P. Khandelwal, P. Singh, T. Taniguchi, K. Monde, K. Johmoto, H. Uekusa, H. Masubuti and Y. Fujimoto, *Phytochemistry Lett.*, 2014, **10**, 224-229.

187 D. K. Derewacz, C. R. McNees, G. Scalmani, C. L. Covington, G. Shanmugam, L. J. Marnett, P. L. Polavarapu and B. O. Bachmann, *J. Nat. Prod.*, 2014, **77**, 1759-1763.

188 E. De Gussem, W. Herrebout, S. Specklin, C. Meyer, J. Cossy and P. Bultinck, *Chem. Eur. J.*, 2014, **20**, 17385-17394.

189 L. A. Bodack, T. B. Freedman, B. B. Chowdhry and L. A. Nafie, *Biopolimers*, 2004, **73**, 163-177.

190 F. Wang, C. Zhao and P. L. Polavarapu, *Biopolymers*, 2004, **75**, 85-93.

191 S. Yamamoto, M. Straka, H. Watarai and P. Bouř, *Phys. Chem. Chem. Phys.*, 2010, **12**, 11021-11032.

192 G. Shanmugam, P. L. Polavarapu, D. Gopinath and R. Jayakumar, *Biopolymers (Peptide Science)*, 2005, **80**, 636-642.

193 F. Cherblanc, Y.-P. Lo, E. De Gussem, L. Alcazar-Fuoli, E. Bignell, Y. He, N. Chapman-Rothe, P. Bultinck, W. A. Herrebout, R. Brown, H. S. Rzepa and M. J. Fuchter, *Chem. Eur. J.*, 2011, **17**, 11868-11875.

194 F. Cherblanc, Y.-P. Lo, W. A. Herrebout, P. Bultinck, H. S. Rzepa and M. J. Fuchter, *J. Org. Chem.*, 2013, **78**, 11646-11655.

195 L. Du, A. J. Robles, J. B. King, S. L. Mooberry and R. H. Cichewicz, *J. Nat. Prod.*, 2014, **77**, 1459-1466.

196 P. K. Bose and P. L. Polavarapu, *Carbohydr. Res.*, 1999, **322**, 135-141.

197 K. Monde, T. Taniguchi, N. Miura and S.-I. Nishimura, *J. Am. Chem. Soc.*, 2004, **126**, 9496-9497.

198 A. G. Petrovic, P. K. Bose and P. L. Polavarapu, *Carbohydr. Res.*, 2004, **339**, 2713-2720.

199 T. Taniguchi, K. Monde, N. Miura and S.-I. Nishimura, *Tetrahedron Lett.*, 2004, **45**, 8451-8453.

200 N. A. Macleod, C. Johannessen, L. Hecht, L. D. Barron and J. P. Simons, Int. J. Mass Spectrom., 2006, **253**, 193-200.

201 N. Miura, T. Taniguchi, K. Monde and S.-I. Nishimura, *Chem. Phys. Lett.*, 2006, **419**, 326-332.

202 A. Nakahashi, T. Taniguchi, N. Miura and K. Monde, *Org. Lett.*, 2007, **9**, 4741-4744.

203 T. Taniguchi and K. Monde, *Chem. Asian J.*, 2007, **2**, 1258-1266.

204 T. Taniguchi and K. Monde, *Org. Biomol. Chem.*, 2007, **5**, 1104-1110.

205 T. Taniguchi, I. Tone and K. Monde, *Chirality*, 2008, **20**, 446-453.