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Absolute configurations of endoperoxides determined by vibrational circular dichroism (VCD)

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Abstract—Diastereomeric mixture on the peroxide portion of an endoperoxide acetylmajapolene A (**1**) was efficiently separated by HPLC on a chiral column, submitting to vibrational circular dichroism (VCD) investigation. The ab initio theoretical VCD and IR calculations of **1a** and **1b** were performed by density functional theory (DFT) using the B3PW91/6-31G(d,p) level of theory. Focusing on an isolated characteristic peroxide vibrational band, absolute configurations of **1a** and **1b** were unambiguously determined as (1*R*,4*R*,7*S*,10*S*) and (1*S*,4*S*,7*S*,10*S*), respectively. This is the first VCD application to endoperoxides which exist abundantly in nature.

Numerous acyclic and cyclic peroxides showing, for example, unique cytotoxicity, anti-tumor, and anti-malarial biological activities were isolated from terrestrial organisms as well as marine natural resources.[1] The cyclic peroxides represented as endoperoxides were structurally assumed to be biosynthesized by oxidation with a plausible diene precursor. From the viewpoint of the relationship between structures and their biological activities, stereochemical and total synthetic studies of the peroxides have been widely investigated.[2] Elucidation of absolute configurations on the endoperoxides is still a tedious task. Typically, an endoperoxide has been submitted to a reductive cleavage reaction to produce a diol derivative.[3] The absolute configuration of the resulting secondary alcohol was elucidated by the advanced Mosher's method.[3,4] However, the reaction occasionally produces a tertiary alcohol that depends on a structure of the original endoperoxide. Recently, a new methodology has demonstrated that optical rotation angles could be computed reliably and accurately for a certain peroxide molecule.[5] In this report, we have investigated by applying an emerging vibrational circular dichroism (VCD) technique to the endoperoxides for the first time. When focusing on an isolated characteristic peroxide vibrational band, their absolute configurations were clearly elucidated with the aid of theoretical calculations.

To continue our studies on chemical compositions for the red algal genus *Laurencia*,[6] we focused on a marine peroxide, acetylmajapolene A (**1**) isolated from *Laurencia* as an inseparable diastereomeric mixture in the part of the peroxide. Its deacetyl derivative, majapolene A displayed a modest cytotoxity.[7] Since, a pair of diastereomers have led to reliable discussion concerning stereochemistry on the endoperoxide parts. Also, acetylmajapolene A (**1**), which possesses a relatively large number of atoms for a VCD calculation, would be a challenging target, demonstrating applicability for more simple endoperoxides.

Keywords: Peroxide; Absolute configuration; Vibrational circular dichroism; VCD; DFT calculation.

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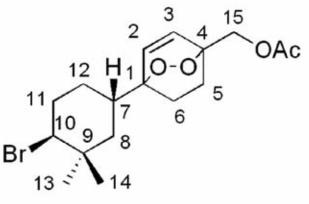
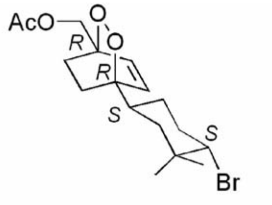
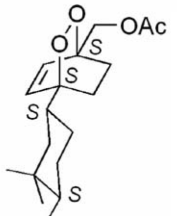


1



1a



1b

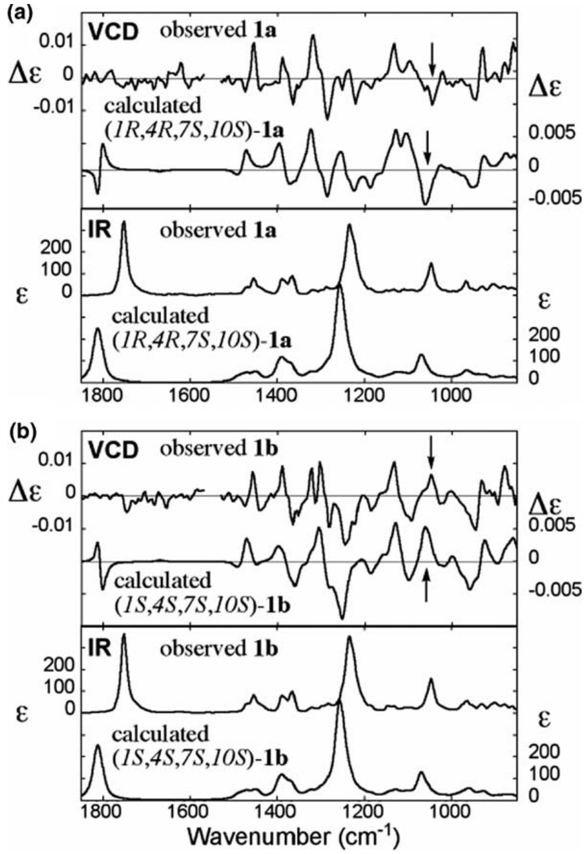


Figure 1. (a) Comparison of IR (lower frame) and VCD (upper frame) spectra observed (CCl$_4$, $c = 0.15$ M, $l = 71$ μm) for **1a** with one calculated for (1*R*,4*R*,7*S*,10*S*)-**1a**. Arrows indicate the characteristic VCD band of the peroxide function. (b) Comparison of IR (lower frame) and VCD (upper frame) spectra observed (CCl$_4$, $c = 0.18$ M, $l = 71$ μm) for **1b** with one calculated for (1*S*,4*S*,7*S*,10*S*)-**1b**.

In fact, a two diastereomeric mixture of **1** would not be separated by normal phase HPLC. However, the chiral HPLC system[8] on a CHIRALPAK® IA column was considerably effective for this diastereomeric mixture as expected ($t_0 = 5.3$, $t_1 = 13.7$, $t_2 = 22.1$ min; $\alpha = 2.0$ at hexane–ethyl acetate = 60:40; **1a**:**1b** = 45:55) to give first eluted **1a** and second eluted **1b**.[9] ^{1}H NMR spectra of two diastereomers were quite similar indicating the impossibility of assignment for their stereochemistries by them. These facts suggested that the bicyclo ring of the endoperoxide rotates relatively around a C1–C7 bond. The peroxide parts behave as enantiomers supporting the results of the HPLC study. IR spectra of both **1a** and **1b** showed one characteristic band (around 1048 cm^{-1}) attributed to the endoperoxide part.[10] In this study, by focusing on this isolated characteristic peroxide vibrational band, VCD studies were examined.

VCD examines differences between vibrational spectra with respect to left vs. right circularly polarized radiation. The absolute configuration is determined nonempirically by comparison between the observed VCD spectra with the simulated VCD spectra.[11] Recently, VCD has advanced instrumentally and theoretically, and now covers organic and bioorganic molecules, such as from simple alcohols,[12a] sulfoxides,[12b] to more complicated carbohydrates,[12c] as well as functional molecules.[12d–f] IR and VCD spectra were measured at 8 cm^{-1} resolution in CCl$_4$ solution using a BaF$_2$ cell. The VCD spectra of **1a** and **1b** were rather similar, except for the characteristic band around 1050 cm^{-1} of the peroxide function (Fig. 1). This indicates that VCD is quite sensitive toward the local chiral environment formed by two independent chiral cyclic moieties.

Using molecular mechanics (MM) with the MMFF94S force field from the CONFLEX program,[13] the 12 low-lying conformers for (1*R*,4*R*,7*S*,10*S*)-**1a**[14] were selected such that the cumulative Boltzmann weighted population sum was over 95%. To obtain accurate energies and IR and VCD spectra, geometrical optimizations and harmonic frequency analyses were performed with density functional theory (DFT) calculations using the B3PW91/6-31G(d,p) level of theory. Twelve low-lying conformers (**1**-(I), **1**-(XII)) survived, however the only differences elucidated were in the rotation angles between C1–C7 and C4–C15 due to the rigid structure of the two rings. Simulated VCD spectra were obtained by convolution with the Lorenzian bandshape function and by averaging with the Boltzmann weighted population of the conformers (Fig. 2). (1*S*,4*S*,7*S*,10*S*)-**1b** was also submitted to the ab initio calculation in a similar manner. The experimental VCD spectra and the population-weighted theoretical VCD spectra for both **1a** and **1b** were found to be in excellent agreement including the peroxide band showing an opposite sign (Fig. 1), except for the carbonyl region.[15] This concludes unambiguously that the absolute configurations of **1a** and **1b** as 1*R*,4*R*,7*S*,10*S* and 1*S*,4*S*,7*S*,10*S*, respectively.

In general, the characteristic IR absorption band of the peroxide is strong in the finger print region and is possibly responsible for its straightforward assignment. In particular, the conformation of the endoperoxides tends to be rigid, which is suitable for this VCD methodology. Thus, this example could be applicable to general endoperoxides without any derivatization. To the best of our knowledge, this is the first VCD application for the peroxide, which exists abundantly in nature.

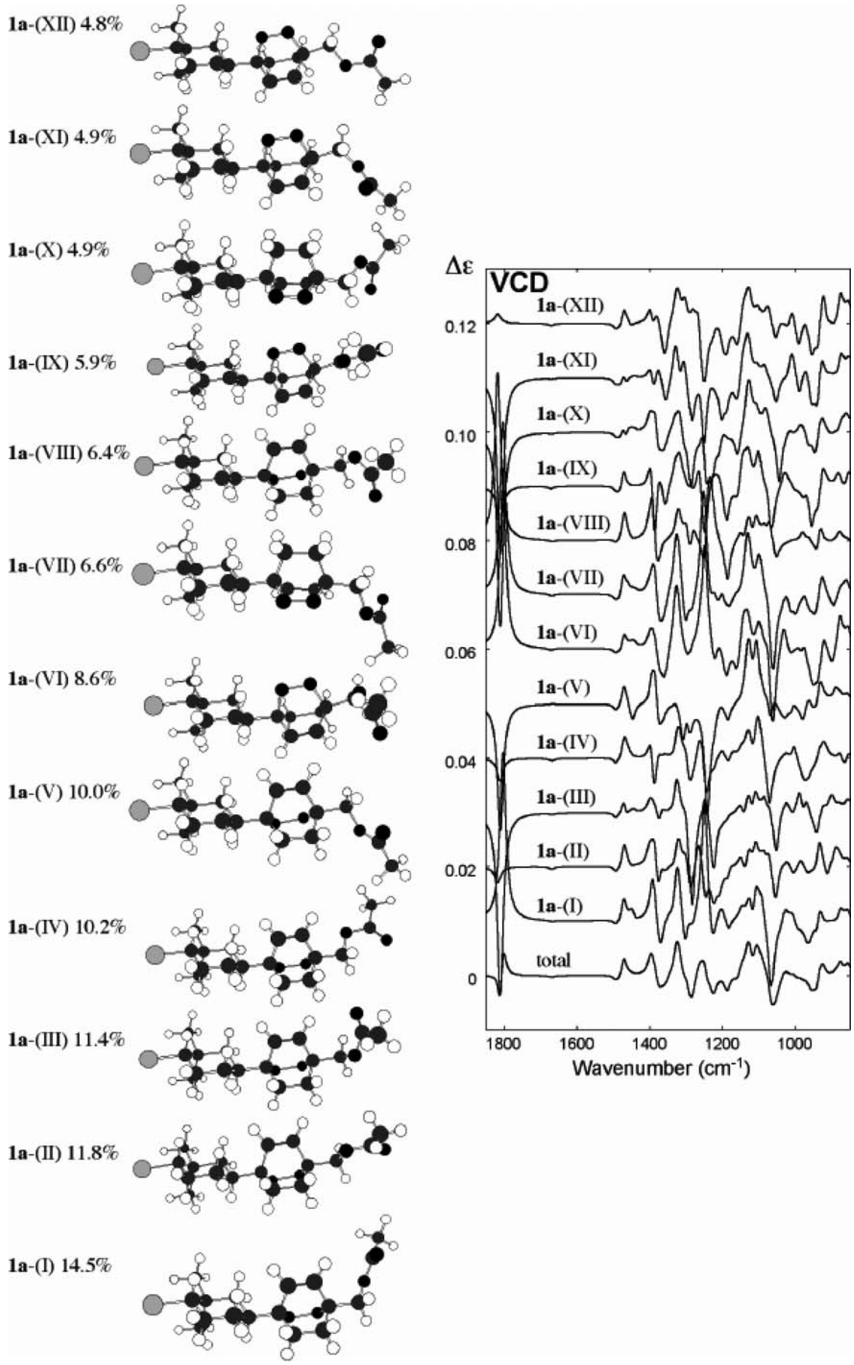


Figure 2. (a) The DFT calculated VCD spectra of (1*R*,4*R*,7*S*,10*S*)-**1a**. Percentage numbers indicate Boltzmann populations at 25 °C renormalized for the 12 conformers. The total spectrum is a Boltzmann population-weighted average of the 12 conformers' spectra. The spectra of conformers **1a**-(I)–**1a**-(XII) are shifted vertically for clarity.

In conclusion, the absolute configurations of endoperoxides **1a** and **1b** separated by the HPLC on the chiral column were elucidated clearly by VCD technique as 1*R*,4*R*,7*S*,10*S* and 1*S*,4*S*,7*S*,10*S*, respectively. This successful VCD study with the complex conformational analysis of **1** suggests that this methodology could be generalized for a peroxide which has less conformer by focusing on the characteristic absorption band. This could also be a superior example of the VCD application for the determination of diastereomeric stereochemistries that can not be distinguished by NMR.

Acknowledgements

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9. *(1R,4R,7S,10S)-(−)-acetylmajapolene A* (**1a**): ^{1}H NMR ($CDCl_3$) δ 6.54 (2H, s, H-2, H-3), 4.33 (1H, d, $J = 12.5$ Hz, H-15a), 4.21 (1H, d, $J = 12.5$ Hz, H-15b), 3.94 (1H, dd, $J = 12.6, 4.2$ Hz, H-10), 2.23 (1H, dddd, $J = 13.3, 3.7, 3.7, 3.4$ Hz, H-11a), 2.14 (1H, ddd, $J = 12.6, 9.3, 3.1$ Hz, H-5a), 2.11 (3H, s, –OAc), 2.05 (1H, ddd, $J = 12.7, 9.3, 3.3$ Hz, H-6a), 2.03 (1H, dddd, $J = 13.2, 13.2, 13.2, 3.9$ Hz, H-11b), 1.93 (1H, dddd, $J = 12.7, 12.7, 3.2, 3.1$ Hz, H-7), 1.84 (1H, ddd, $J = 13.5, 2.9, 2.8$ Hz, H-8a), 1.79 (1H, ddddd, $J = 13.2, 3.3, 3.3, 3.3, 3.3$ Hz, H-12a), 1.52 (1H, ddd, $J = 12.2, 12.2, 3.1$ Hz, H-5b), 1.45 (1H, ddd, $J = 12.2, 12.2, 3.1$ Hz, H-6b), 1.26 (1H, dddd, $J = 13.1, 13.1, 13.1, 3.9$ Hz, H-12b), 1.22 (1H, dd, $J = 13.2, 13.2$ Hz, H-8b), 1.07 (3H, s, H-13), 1.05 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ 170.7 ($\mathit{C}OCH_3$), 133.6 (C-2), 132.5 (C-3), 79.3 (C-1), 75.9 (C-4), 65.1 (C-10), 64.6 (C-15), 40.4 (C-8), 37.2 (C-7), 36.5 (C-9), 33.8 (C-11), 31.7 (C-13), 28.3 (C-12), 25.3 (C-6), 24.9 (C-5), 20.7 ($CO\mathit{C}H_3$), 20.3 (C-14); IR ($CDCl_3$) 2954, 1752, 1237, 1048 cm^{-1}, MS (EI) *m*/*z* 340 ($[M{-}O_2]^+$), HRMS (ESI) *m*/*z* for $C_{17}H_{25}O_4BrNa$ ($[M + Na]^+$), calcd 395.0834, found 395.0831. $[\alpha]_D$ −2.8° ($CHCl_3$, *c* 0.18). *(1S,4S,7S,10S)-(−)-acetylmajapolene A* (**1b**): ^{1}H NMR ($CDCl_3$) δ 6.54 (2H, s, H-2, H-3), 4.33 (1H, d, $J = 12.5$ Hz, H-15a), 4.21 (1H, d, $J = 12.5$ Hz, H-15b), 3.93 (1H, dd, $J = 12.6, 4.3$ Hz, H-10), 2.21 (1H, dddd, $J = 13.4, 3.7, 3.7, 3.4$ Hz, H-11a), 2.13 (1H, ddd, $J = 12.4, 9.1, 2.8$ Hz, H-5a), 2.11 (3H, s, –OAc), 2.06 (1H, ddd, $J = 12.4, 9.3, 2.8$ Hz, H-6a), 2.01 (1H, dddd, $J = 13.1, 13.1, 13.1, 4.0$ Hz, H-11b), 1.94 (1H, dddd, $J = 12.8, 12.7, 3.3, 3.2$ Hz, H-7), 1.86 (1H, ddddd, $J = 13.3, 3.3, 3.3, 3.3, 3.3$ Hz, H-12a), 1.76 (1H, ddd, $J = 13.5, 3.0, 3.0$ Hz, H-8a), 1.51 (1H, ddd, $J = 12.1, 12.1, 2.8$ Hz, H-5b), 1.45 (1H, ddd, $J = 12.0, 12.0, 2.9$ Hz, H-6b), 1.27 (1H, dd, $J = 13.1, 13.1$ Hz, H-8b), 1.24 (1H, dddd, $J = 13.1, 13.1, 13.1, 3.9$ Hz, H-12b), 1.08 (3H, s, H-13), 1.06 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ 170.7 ($\mathit{C}OCH_3$), 133.9 (C-2), 132.4 (C-3), 79.2 (C-1), 75.9 (C-4), 65.1 (C-10), 64.6 (C-15), 40.4 (C-8), 37.3 (C-7), 36.6 (C-9), 33.8 (C-11), 31.8 (C-13), 28.4 (C-12), 25.0(C-5), 25.0 (C-6), 20.7 ($CO\mathit{C}H_3$), 20.4 (C-14); IR ($CDCl_3$) 2954, 1752, 1237, 1049 cm^{-1}, MS (EI) *m*/*z* 340 ($[M{-}O_2]^+$), HRMS (ESI) *m*/*z* for $C_{17}H_{25}O_4BrNa$ ($[M{+}Na]^+$), calcd 395.0834, found 395.0832. $[\alpha]_D$ −19.2° ($CHCl_3$, *c* 0.18).
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14. Absolute configurations at C7 and C10 in **1** were postulated as 7*S*,10*S* from the previous stereochemical study of related metabolites, majapolene B and acetylmajapolene B. Monde, K.; Taniguchi, T.; Miura, N.; Vairappan, C. S.; Suzuki, M. *Chirality* **2006**, *18*, 335–339.
15. Due to inherent weak VCD signals around 1800 cm^{-1} of **1a** and **1b**, clear opposite VCD pattern which was expected by their VCD calculations could not be observed.