

# Diastereoisomeric Assignment in a Pacifenol Derivative Using Vibrational Circular Dichroism

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**ABSTRACT** The configuration of a chiral center in semisynthetic (–)-(2*R*,5*R*,5*aR*,8*ç*,9*aS*)-2,8-dibromo-2,5,9,9*a*-tetrahydro-5-hydroxy-5,8,10,10-tetramethyl-6*H*-2,5*a*-methano-1-benzoxepin-7(8*H*)-one (**3** or **4**), prepared in two steps from (–)-(2*R*,5*R*,5*aR*,7*S*,8*S*,9*aS*)-2,7-dibromo-8-chloro-2,5,7,8,9,9*a*-hexahydro-5,8,10,10-tetramethyl-6*H*-2,5*a*-methano-1-benzoxepin-5-ol, known as pacifenol **1**, has been determined using vibrational circular dichroism (VCD) measurements. The vibrational spectra (IR and VCD) of diastereoisomers **3** and **4** were calculated using density functional theory (DFT) at the B3LYP/DGDZVP level of theory for the two conformers that in each case account for the total energetic distribution found in the first 10 kcal/mol range. The DFT conformational optimization of the 8*R* diastereoisomer **3** indicates the cyclohexanone exists almost exclusively in a boat conformation with a β-equatorial bromine atom and an α-axial methyl group at the chiral center alpha to the carbonyl group, while for the 8*S* diastereoisomer **4** a 5:1 conformational distribution in favor of a chair conformation with an α-axial bromine atom and a β-equatorial methyl group is calculated, suggesting due to well-known chair versus boat relative stabilities that the plausible diastereoisomer would be the 8*S* molecule. A comparison of the IR spectrum of the reaction product with the calculated spectra of **3** and **4** provided no means for the diastereoisomeric assignment, while from comparison of the VCD spectra it became immediately evident that the rearranged molecule possesses the 8*R* absolute configuration as shown in **3**, in concordance with a single crystal X-ray diffraction study that could be refined to an *R*-factor of 2.9%. *Chirality* 21:E208–E214, 2009. © 2009 Wiley-Liss, Inc.

**KEY WORDS:** VCD; diastereoisomeric assignment; relative configuration; pacifenol; chamigrene

## INTRODUCTION

Pacifenol **1** is the first sesquiterpene of marine origin containing chlorine and bromine atoms that was originally isolated from the red alga *Laurencia pacifica*<sup>1</sup> and has afterwards been isolated from many species of the genus *Laurencia*.<sup>2–6</sup> The structure and absolute configuration of **1** followed<sup>1</sup> from a very early single crystal X-ray analysis, performed using precession and Weissenberg cameras, which was later repeated to find a more accurate molecular representation.<sup>7</sup> Detailed <sup>1</sup>H- and <sup>13</sup>C NMR studies<sup>8</sup> of chamigrenes, which include pacifenol **1**, are reported and several biological evaluations of these compounds are well-documented in the literature.<sup>9–11</sup> The closely related dibrominated chamigrene **2**, found as a constituent<sup>12</sup> of *Laurencia nipponica*, could be prepared in quantitative yields after treatment of **1** with sodium hydride.<sup>13</sup> In turn compound **2** is the first vinyl bromide chamigrene metabolite of marine origin. When diene **2** was reacted<sup>14,15</sup> with *m*-chloroperbenzoic acid it was cleanly transformed into a

single alpha-bromoketone (**3** or **4**, Scheme 1) in which only one carbon–carbon double bond was oxidized and the vinylic bromine atom underwent an unprecedented 1,2-bromine atom shift. Although the chirality of the newly formed stereogenic center, containing the migrated bromine atom, is not trivial to be ascertained mainly due to the lack of suitable NMR correlations, fortunately the reaction product provided solid material that could be evaluated by a single crystal X-ray diffraction study. This study allowed data refinement<sup>14</sup> to a modest *R*-factor of 6%, no hydrogen atoms were depicted, and the results were not

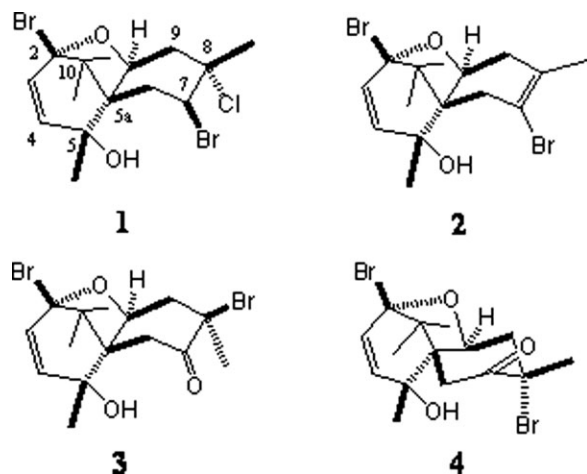
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**Scheme 1.** Chemical structures of pacifenol **1**, the dibrominated chamigrene **2**, and diastereoisomeric cyclohexanones **3** and **4**.

deposited at the Cambridge Crystallographic Data Centre. These limitations are amended in the present work during which the crystal structure was determined again and could nicely be refined to an *R*-factor of 2.9%.

Inspection of molecular structures **3** and **4** reveals that their distinction seems to be an ideal case to explore the potential of vibrational circular dichroism (VCD) for a diastereoisomeric assignment since the molecule under study has a rigid scaffold with very limited conformational freedom, only one of five stereogenic centers requires assignment and this unknown center contains a heavy bromine atom.

VCD in combination with quantum mechanics calculations has proven to be very useful in the task to ascertain the absolute configuration of natural products<sup>16,17</sup> and to our knowledge no application for a typical diastereoisomeric assignment, in which epimers at a specific chiral center are involved, is described, although we reported a VCD study<sup>18</sup> to distinguish diastereoisomers owing to the presence of a common chiral ester residue in molecules which in the absence of such ester residue would be enantiomers. Other chiroptical methods, like direct comparison of optical rotatory dispersion<sup>19</sup> (ORD) or classical circular dichroism<sup>19</sup> (CD) curves have in the present case disadvantages as compared to VCD. Although these methods are adequately recognized for cyclohexanones, due to the well established octant rule, in the present case its direct application is not easy due to the lack of comparison models since the six-member ring adopts a boat conformation.

In continuation of our studies of natural products<sup>20</sup> and their derivatives<sup>21</sup> using VCD, we herein present a detailed theoretical study of diastereoisomers **3** and **4** that allows the absolute configuration assignment of one newly formed chiral center using a combination of VCD spectroscopy, molecular mechanics and density functional theory (DFT) calculations at the B3LYP/DGDZVP level of theory. Our results will be of value for future configurational assignments of hemisynthetic derivatives obtained from syntons of known absolute configuration when the per-

formed reaction yields either one or both possible diastereoisomers at a newly generated chiral center.

## EXPERIMENTAL

### General Experimental Procedures

IR and VCD measurements were performed on a BioTools-BOMEM Chiral/R FT-VCD spectrophotometer equipped with a single photoelastic modulator. A sample of 8.5 mg of **3** was dissolved in 150  $\mu$ L of 100% atom-D  $\text{CDCl}_3$ , placed in a  $\text{BaF}_2$  cell with a pathlength of 100  $\mu\text{m}$  and data were acquired at a resolution of 4  $\text{cm}^{-1}$  during 10 h. The sample was available from the original study,<sup>14</sup> which describes its preparation by treatment of **2** with *m*-chloroperbenzoic acid. Compound **3** was purified by fast chromatography through a gravity silica gel column using chloroform to afford prisms mp 168–169°C (Ref. 14 mp 169°C). Its identity and purity was verified by <sup>1</sup>H NMR measurement at 300 MHz on a Varian Mercury spectrometer using a 99.8% atom-D  $\text{CDCl}_3$  solution containing TMS as the internal standard immediately before VCD measurement.

### Computational Methods

Conformational searches were started using a Monte Carlo guided protocol considering an initial energy cutoff of 10 kcal/mol above the global minimum value. The searches were conducted independently for **3** and **4**, and the conformations **3a-c** and **4a-c** found for each diastereoisomer were then submitted to geometry reoptimizations using the DFT B3LYP hybrid functional and the DGDZVP basis set. It followed that conformers **3b** and **4c** vanished in favor of conformers **3a** and **4b**, respectively, during this geometry reoptimization, and therefore only two conformers for each diastereoisomer account for the total conformational distribution. These four molecular arrangements were subjected to vibrational calculations using the same hybrid functional and basis set. The use of this B3LYP/DGDZVP combination of basis set and functional has shown to require less computing time than the 6-31G(d) basis set while producing very similar results, as is evident in figures of recently published work.<sup>20-22</sup> This situation, seems to be associated with the fact that DGauss basis sets, such as DGDZVP, are optimized for DFT methods. Computer time could turn crucial when larger molecules are studied, as was the recent case of stypotriol triacetate,<sup>23</sup> a  $\text{C}_{33}\text{H}_{46}\text{O}_7$  molecule with 300 electrons which required almost 1100 hours of computer time using the B3LYP/DGDZVP level of theory.

Conformational searches were made using the Spartan'04 software package,<sup>24</sup> while geometry reoptimizations and vibrational spectra were calculated using the Gaussian 03W software package.<sup>25</sup> Typical calculations required between 30 and 35 hours of computational time per conformer when using a desktop personal computer (PC) with 2 Gb RAM operated at 3 GHz. Tabulated theoretical vibrational frequencies, rotational strengths and dipole strengths were obtained from the calculations using GaussView software. Since the measured IR and VCD

frequencies derive from an anharmonic force field and the calculated frequencies derive from a harmonic force field, the intense bands of the calculated IR spectrum and those of the experimental spectrum were compared to obtain an anharmonicity factor of 0.97 which then allowed scaling the calculated VCD frequencies. Experimental vibration frequencies, rotational strengths and dipole strengths were converted to molecular absorptivities ( $M^{-1} \text{ cm}^{-1}$ ). They were obtained from experimental IR and VCD spectra by Lorentzian fitting with half-widths of  $6 \text{ cm}^{-1}$  using the PeakFit software.<sup>26</sup> To compare calculated and experimental data, the bands of the theoretical IR spectrum were numbered and assigned to the bands in the measured IR spectrum using described methodology.<sup>17</sup> Construction of a plot of calculated versus measured frequencies gave an  $R^2$  correlation coefficient of 0.9266 in good agreement with published cases.<sup>27</sup> We have also used these plots to compare experimental and calculated  $^1\text{H}$  NMR coupling constants during a VCD study of verticillanes.<sup>28</sup> The calculated frequencies are 1–5% higher than experimental values, pointing to the use of an anharmonicity factor of 0.97, after which the bands differ between –2% and +2%. The same assignment was used for the VCD spectra in which the bands were positive and negative. After rotational strengths were obtained, they were successfully compared to the experimental VCD spectrum, fully substantiating the stereochemistry of **3**.

### Single Crystal X-Ray Analysis of **3**

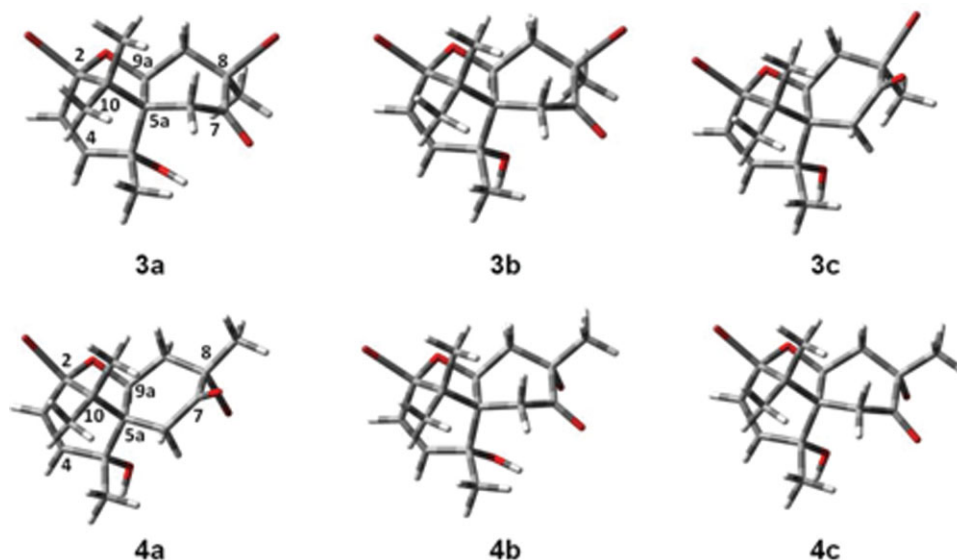
Slow evaporation of an acetonitrile solution gave crystals suitable for X-ray analysis. A prism measuring  $0.38 \times 0.06 \times 0.04 \text{ mm}$  was mounted on a Bruker-Nonius CAD4 diffractometer. The crystal was orthorhombic, space group  $P2_12_12_1$ , with cell dimensions  $a = 6.557(2) \text{ \AA}$ ,  $b = 12.307(1) \text{ \AA}$ ,  $c = 19.318(2) \text{ \AA}$ ,  $V = 1589.9(5) \text{ \AA}^3$ ,  $\rho_{\text{calcd}} = 1.739 \text{ g/cm}^3$  for  $Z = 4$ ,  $\text{C}_{15}\text{H}_{20}\text{O}_3\text{Br}_2$ ,  $M_w = 408.13$ , and  $F(000) = 816 \text{ e}$ . Unit cell refinements were done using the CAD4 Express v 2.0 software package provided by the diffractometer manufacturer. A total of 1256 reflections were collected using Cu  $K\alpha$  radiation ( $\lambda = 1.54184 \text{ \AA}$ ) within a  $\theta$  range of  $4.48\text{--}59.93^\circ$  for  $0 \leq h \leq 7$ ,  $0 \leq k \leq 13$ ,  $0 \leq l \leq 21$ . The data were corrected for background, Lorentz polarization, and absorption ( $\mu = 6.639 \text{ mm}^{-1}$ ), while crystal decay was negligible. The structure was solved by direct methods using the Sir2004 program.<sup>29</sup> For the structural refinement, the nonhydrogen atoms were treated anisotropically, and the hydrogen atoms were refined isotropically. The unique reflections were 1188, the observed reflections were 1126, and final discrepancy indices, refining 198 parameters, were  $R_F = 2.9\%$  and  $R_W = 7.5\%$ . The final difference Fourier map was essentially featureless, the highest residual peak and hole having densities of 0.246 and  $-0.348 \text{ e/\AA}^3$ .

## RESULTS AND DISCUSSION

The molecular scaffold of the tricyclic oxidation product (**3** or **4**) obtained from **2** imposes several restrictions to conformational freedom due to the spiro nature of the two six-membered rings and the *cis*-fused tetrahydrofuran and cyclohexanone. Construction of Büchi solid Dreiding models reveals that only two conformational arrangements of the cyclohexanone are feasible. One of them is a chair-like arrangement in which the equatorial H6 $\beta$  atom and the carbonyl group are coplanar, and the other is a boat-like conformation in which the carbonyl group and the equatorial H6 $\alpha$  atom become coplanar. In both cases the methyl group and bromine atom substituents at C8 hold their special arrangement since only C6 and C7 are twisted during a chair to boat interconversion. A third molecular arrangement in which C8 and C9 of the chair conformation are twisted to afford the cyclohexanone in boat shape is completely ruled out due to severe steric interaction between one of the methyl groups of the gem-dimethyl group and either the bromine atom or the methyl group substituents located at C8. From these considerations one could assume, due to the very well established conformational preference of cyclohexanones to undertake chair conformations rather than boat conformations,<sup>30</sup> that diastereoisomer **4** would be the reaction product of **2** with *m*-chloroperbenzoic acid.

The conformational distributions of **3** and **4** were asserted using Monte Carlo-MMFF94 conformational searches followed by geometry optimization at the B3LYP/DGDZVP level of theory (Fig. 1 and Table 1). In both molecules the MMFF94 calculations showed three low energy conformations dependent on two conformational features that were the hydroxyl group orientation and the chair-boat disposition of the  $\alpha$ -brominated cyclohexanone. In the case of **3** the molecular mechanics calculations predicted two conformations with the cyclohexanone in a boat disposition and different hydroxyl group orientations, one intersecting the C5a-C5-Me bond angle with a C5a-C5-O–H dihedral angle of  $88.9^\circ$ , and oriented towards the carbonyl oxygen atom (global minimum **3a**), and the other intersecting the C4-C5-Me bond angle with a C5a-C5-O–H dihedral angle of  $177.0^\circ$  (**3b**), being 0.11 kcal/mol more energetic than the first conformer. These two molecular arrangements were followed by a third conformer (**3c**) with an energy 2.75 kcal/mol above the global minimum, and arranged in a chair cyclohexanone disposition with the hydroxyl group orientation identical to that found in **3b**. For isomer **4**, also three equivalent conformations were found using the same search methodology, but with differences in their relative stability order. The global minimum **4a** showed the same chair cyclohexanone conformational characteristics as conformer **3c** with an energy difference of 0.65 kcal/mol above the global minimum **3a**, while **4b** being 1.07 kcal/mol above **4a** showed to be conformationally equivalent to **3a**, and **4c** showed to be equivalent to **3b**, as observed in Figure 1. Further geometry optimizations followed by vibrational calculations gave Gibbs free energy values that permitted a more accurate assessment of the conformational

Crystallographic data are deposited with the Cambridge Crystallographic Data Centre under CCDC deposition number 736634. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.



**Fig. 1.** Atom arrangements for the three more stable conformers of diastereoisomers **3** and **4**. Conformers **3a**, **3c**, **4a**, and **4b** were optimized at the B3LYP/DGDZVP level of theory while conformers **3b** and **4c** are only optimized at the MMFF94 level of theory since they vanished in favor of **3a** and **4b**, respectively, during the DFT geometry optimization process. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

distributions. In both isomers conformations with the boat cyclohexanone disposition **3b** and **4c** changed their hydroxyl group orientations during the geometry optimization procedure towards the carbonyl oxygen atom, becoming **3a** and **4b**, respectively, and thus showing that conformations **3b** and **4c** are no longer local minima on the DFT potential energy surface. In addition, the relative order of stability of both distributions obtained from the DFT calculations remained unchanged as compared to the MMX calculations, predicting **3a** to be 3.62 kcal/mol more stable than **3c**, and **4a** to be 0.99 kcal/mol more stable than **4b**. This conformational preference of isomer **3** for the boat disposition can be explained based on an energetically favorable “anti” disposition of the equatorial bromine atom towards the carbonyl group ( $\text{O}=\text{C}-\text{C}8-\text{Br}$  dihedral angle of  $-82.9^\circ$ ), which also leads to energy stabilization produced by the hydrogen bonding interaction between the hydroxyl group and the carbonyl oxygen atom of the cyclohexanone ring showing an  $\text{OH}-\text{O}=\text{C}$  interatomic distance of 2.5 Å. In contrast the hydrogen bond interaction in the boat configuration of **4b**, in which the bromine atom is axial, leads to a more energetic “syn” orientation of the bromine atom towards the carbonyl oxygen with an  $\text{O}=\text{C}-\text{C}8-\text{Br}$  dihedral angle of  $49.9^\circ$ , explaining the preference of **4** to the chair conformation that avoids this unstable disposition. Table 1 illustrates the conformational behavior on going from MMFF94 to DFT calculations.

Further comments to the molecular behavior are related to the presence of the hydroxyl and carbonyl functionalities, since some alcohols can associate in solution, as we have shown<sup>27</sup> for a secondary nonintramolecularly bonded alcohol which provides good agreement of observed and calculated spectra only after acetylation. In contrast, for

tertiary alcohols, due to steric hindrance, good spectral fits are easily obtained<sup>28</sup> without derivatization. In the current case we are dealing with a tertiary alcohol which in addition is intramolecularly hydrogen-bonded to a carbonyl group and therefore no significant intermolecular association of the hydroxyl group might be expected.

The vibrational calculations performed for the obtained conformations, along with their conformational distributions, permitted to generate Boltzmann weighted plots of calculated IR and VCD spectra of diastereoisomers **3** and **4**, as shown in Figures 2 and 3, respectively. Since the main objective of the present study is to evaluate the possibility and limitations to differentiate epimers like **3** and **4** in the infrared region of the electromagnetic spectrum, the

**TABLE 1.** Calculated relative energies (kcal/mol), relative free energies and abundances (%) of the three more stable conformers of **3** and **4** using Monte Carlo search and geometry optimization calculations at the MMFF94 and B3LYP/DGDZVP levels of theory. Conformers are ordered according to their relative abundance

| Conf.     | $\Delta E_{\text{MMFF94}}^a$ | $\%_{\text{MMFF94}}$ | $\Delta G_{\text{OPT}}^a$ | $\%_{\text{OPT}}^b$ |
|-----------|------------------------------|----------------------|---------------------------|---------------------|
| <b>3a</b> | 0.00                         | 54.4                 | 0.00                      | 99.8                |
| <b>3b</b> | 0.11                         | 45.1                 | –                         | –                   |
| <b>3c</b> | 2.75                         | 0.5                  | 3.62                      | 0.2                 |
| <b>4a</b> | 0.00                         | 75.6                 | 0.00                      | 84.1                |
| <b>4b</b> | 1.07                         | 12.4                 | 0.99                      | 15.9                |
| <b>4c</b> | 1.09                         | 12.1                 | –                         | –                   |

<sup>a</sup>Relative to the lowest energy conformer in the molecular mechanics force field ( $E_{\text{MMFF}}\mathbf{3a} = 68.42$  kcal/mol,  $E_{\text{MMFF}}\mathbf{4a} = 69.07$  kcal/mol) and DFT ( $\Delta G_{\text{OPT}}\mathbf{3a} = -3737732.12$  kcal/mol,  $\Delta G_{\text{OPT}}\mathbf{4a} = -3737730.76$  kcal/mol) levels of theory.

<sup>b</sup>Calculated using the optimized free energies of the relevant conformers.

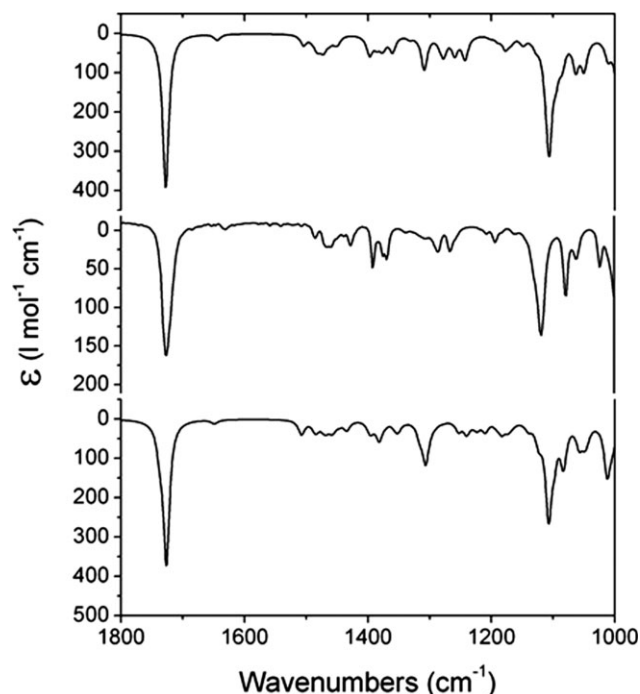


Fig. 2. Comparison of the experimental IR spectrum (center) of the oxidation product, obtained by treatment of **2** with *m*-chloroperbenzoic acid, to the calculated IR spectra of putative oxidation products **3** (top) and **4** (bottom).

calculated results need to be compared to find differences that can later be helpful in the configurational assignment of the reaction product. In the case of the IR spectra the changes in intensity and frequency are rather small and no band in particular stands out as useful for the differentiation purpose. The IR spectral presentation shown in Figure 2 is in full agreement with published cases<sup>18,31</sup> and allows a visual comparison in a similar way as organic chemists are used to seeing spectra, although in the present case we are dealing with absorption plots. Accordingly, a comparison between the theoretical IR spectra of both possible diastereoisomers and the observed IR spectrum of the reaction product showed a good agreement in both cases (Fig. 2), precluding any stereochemical assignment by these means. Nevertheless the opposite scenario is observed for the weighted VCD spectra of **3** and **4**, in which several differences between them are evident at first glance (Fig. 3). Among them are the negative carbonyl band at  $1728\text{ cm}^{-1}$ , the most intense positive band located at  $1360\text{ cm}^{-1}$ , the positive band at  $1168\text{ cm}^{-1}$  and the negative band at  $1112\text{ cm}^{-1}$  in the VCD spectra of **3**, which are not observed or differ considerably in sign and intensity in the calculated VCD spectrum of **4**. As expected, these bands allow unambiguous assignment of the absolute stereochemistry of the C8 chiral center of the synthetic sample as the one depicted for **3**, since the corresponding experimental spectrum shows the presence of the negative band at  $1724\text{ cm}^{-1}$ , the positive band at  $1370\text{ cm}^{-1}$ , the positive band at  $1180\text{ cm}^{-1}$  and the negative band at  $1129\text{ cm}^{-1}$ , along with an overall spectral similar-

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ity when compared with the corresponding calculated VCD spectrum. In the present case it is also of relevance to note that due to the previously discussed intramolecular hydrogen-bonded hydroxyl group, the well studied carbonyl absorption artefacts<sup>32</sup> seem to be significantly decreased making the sign and VCD band intensity more reliable as can be seen in the spectral comparison shown in Figure 3.

Complementary evidence to establish stereostructure **3** for the oxidation product of **2** with *m*-chloroperbenzoic acid follows from a comparison<sup>33</sup> of experimental rotational strengths of the reaction product with those of both possible diastereoisomers (**3** and **4**). The plots included in Figure 4 show an overall agreement only in the case of **3**.

To compare the calculated molecular shape with experimental data, we turned our attention to the originally published<sup>14</sup> solid state structure of **3**. Since this structure was refined only to a modest *R*-factor of 6.0%, no hydrogen atoms were depicted, and the corresponding data are not deposited at the Cambridge Crystallographic Data Centre, we decided to repeat these measurements. The pertinent crystal data, data collection, structure determination and refinement procedures are detailed in the "Experimental" section and a representation of the final refined molecular model is given in Figure 5. The solid state structure is in excellent agreement with the conformation calculated by DFT as evidenced by the data summarized in Table 2. The solid state structure of pacifenol **1** also shows<sup>1,7</sup> the cyclohexane in a boat conformation.

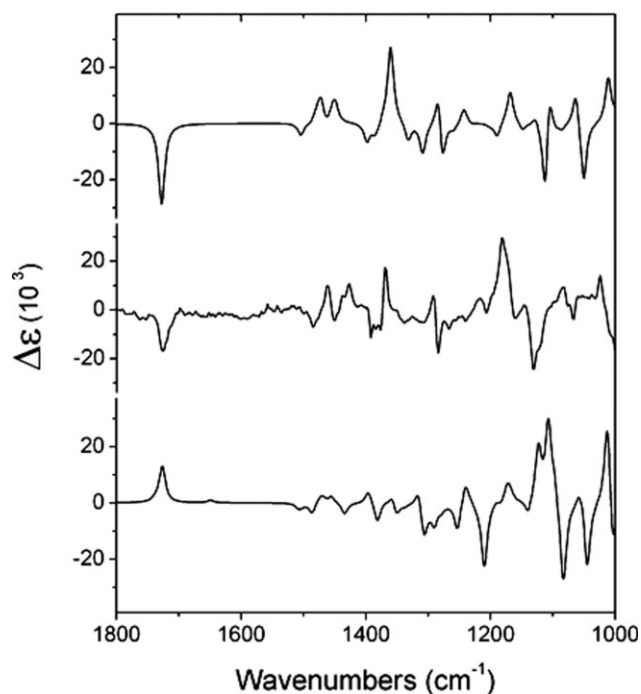


Fig. 3. Comparison of the experimental VCD spectrum (center) of the oxidation product, obtained by treatment of **2** with *m*-chloroperbenzoic acid, to the calculated VCD spectra of putative oxidation products **3** (top) and **4** (bottom).

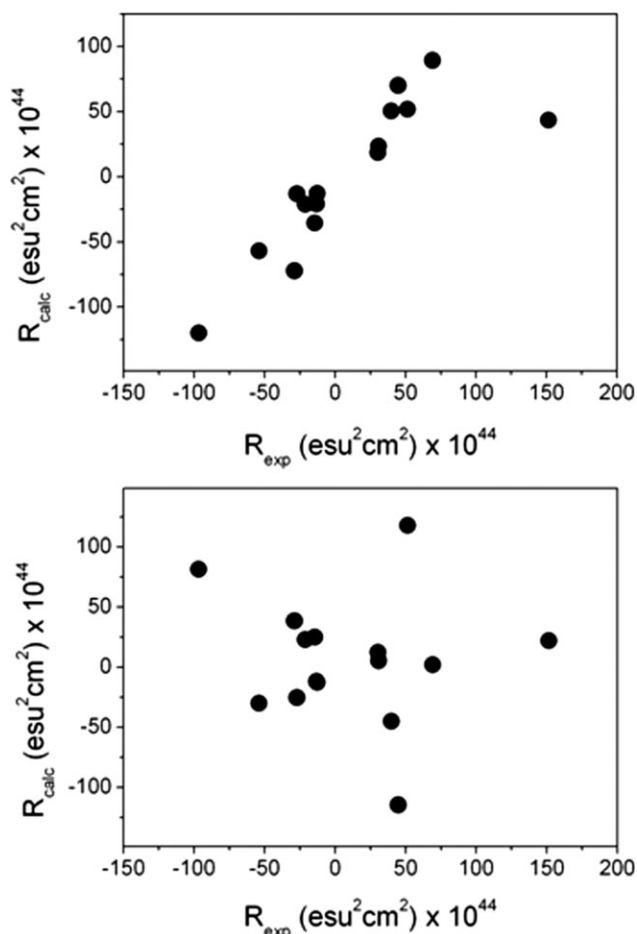


Fig. 4. Comparison of the experimental rotational strengths of the oxidation product of **2** with those calculated for structures **3** (top) and **4** (bottom).

### CONCLUSIONS

The conformational distributions of both possible diastereoisomers (**3** or **4**) generated by reaction of pacifenol derivative **2** with *m*-chloroperbenzoic acid where asserted using Monte Carlo-MMFF94 conformational searches and geometry optimization at the B3LYP/DGDZVP level of theory. Comparing **3** and **4** revealed the presence of three similar conformations on the molecular mechanics poten-

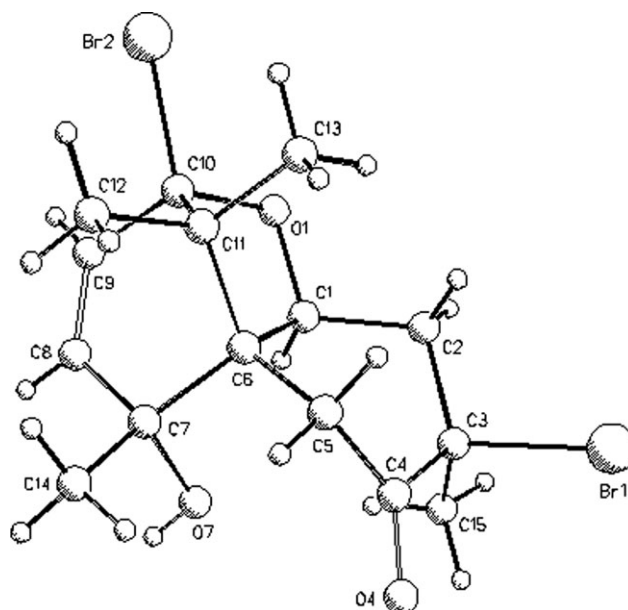


Fig. 5. Perspective view of the X-ray crystal structure of **3**. Atom numbering differs from systematic numbering.

tial energy surface, but with differences in their stability order. Subsequent geometry optimization calculations at the B3LYP/DGDZVP level of theory showed the presence of only two conformers in each case, and that these conformations are mainly determined by a hydrogen bond interaction between the hydroxyl group and the carbonyl oxygen atom of the cyclohexanone and by the syn or anti orientations of the bromine atom towards the carbonyl oxygen atom. These two conformational features caused the preference of the cyclohexanone in **3** and **4** for boat and chair conformations, respectively.

Furthermore, these conformational distributions, together with the calculation of vibrational frequencies and intensities, allowed obtaining weighed theoretical plots for IR and VCD spectra, which in turn permitted the configurational assignment for the reaction product of the oxidation reaction of **2** as the one depicted for **3**. In the case of the calculated IR intensities and frequencies, these showed only small differences between isomers which avoided the use of these spectra in the task of diastereois-

TABLE 2. Comparison of endocyclic calculated (in the gas phase) and measured (solid state single crystal X-ray diffraction) dihedral angles for compound **3**

| Tetrahydrofuran |       |       | Cyclohexene   |       |       | Cyclohexanone |       |       |
|-----------------|-------|-------|---------------|-------|-------|---------------|-------|-------|
| Dihedral        | X-ray | DFT   | Dihedral      | X-ray | DFT   | Dihedral      | X-ray | DFT   |
| C2-C10-C5a-C9a  | 38.5  | 38.0  | C2-C3-C4-C5   | 0.8   | 0.6   | C5a-C6-C7-C8  | 55.0  | 61.4  |
| C10-C5a-C9a-O   | -13.7 | -14.1 | C3-C4-C5-C5a  | -7.8  | -6.3  | C6-C7-C8-C9   | -7.4  | -15.4 |
| C5a-C9a-O-C2    | -19.0 | -19.2 | C4-C5-C5a-C10 | 47.8  | 46.9  | C7-C8-C9-C9a  | -47.4 | -42.6 |
| C9a-O-C2-C10    | 47.4  | 46.8  | C5-C5a-C10-C2 | -75.6 | -74.7 | C8-C9-C9a-C5a | 59.1  | 59.4  |
| O-C2-C10-C5a    | -53.8 | -52.8 | C5a-C10-C2-C3 | 66.5  | 66.3  | C9-C9a-C5a-C6 | -13.0 | -14.2 |
|                 |       |       | C10-C2-C3-C4  | -35.2 | -35.4 | C9a-C5a-C6-C7 | -42.8 | -43.7 |

meric differentiation. In contrast, the theoretical VCD weighed plots showed several differences between diastereoisomers, such as the negative carbonyl band at  $1728\text{ cm}^{-1}$ , the positive band at  $1360\text{ cm}^{-1}$ , the positive band at  $1168\text{ cm}^{-1}$  and the negative band at  $1112\text{ cm}^{-1}$  present in the theoretical VCD spectra of **3** that are absent in the spectrum of **4**. These results allowed obtaining unambiguous stereochemical conclusions by comparison with the experimental VCD spectrum of the reaction product that showed these bands and overall VCD spectral similarity. In addition, the conformation of **3** in the solid state, as deduced from single crystal X-ray measurements, is also in good agreement with that calculated by DFT as evidenced by dihedral angles comparison of the cyclohexanone.

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