# Chiral sulfinates studied by optical rotation, ECD and VCD: the absolute configuration of a cruciferous phytoalexin brassicanal C

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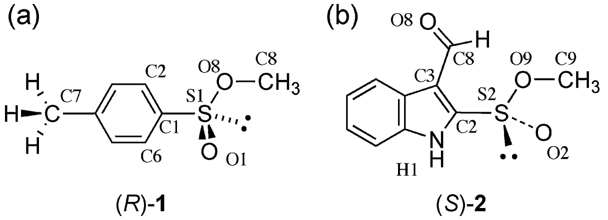
The optical rotation, electronic circular dichroism (ECD) and vibrational circular dichroism (VCD) of chiral sulfinates have been studied experimentally, and analysed by density functional theory calculation, aiming at establishing a reliable and convenient methodology to determine their absolute configuration. Through the study on a model chiral sulfinate with known absolute configuration, (*R*)-(+)-methyl *p*-toluenesulfinate ((*R*)-(+)-**1**), each technique was found to be reliable in assigning chirality of sulfinates. We then applied these methods to a synthetically prepared cruciferous phytoalexin, brassicanal C ((−)-**2**), and unambiguously determined its absolute configuration as *S*. The advantages and disadvantages of each spectroscopy on sulfinates are also discussed.

## Introduction

Chiral sulfinates have been extensively used as the primary source for enantiopure sulfur compounds such as sulfoxides and sulfinamides, which are of considerable importance as bioactive compounds and synthetic intermediates[1] (Scheme 1a). A number of methods have been developed for the formation of chiral sulfinates, including diastereoselective synthesis using chiral auxiliaries such as (*S*)-menthol (Andersen's sulfinate)[2] and diacetone D-glucose,[3] and enantioselective reactions using chiral catalysts.[4] In contrast, determination of absolute configuration of sulfinates have relied on only a few approaches, including chemical conversion to a known sulfoxide using organometallic reagents[5] and X-ray crystallography based on an internal reference.[6] The reliability of the former method is limited since the assumption of the configurational inversion at the chiral sulfur atom was found not to be valid in certain cases.[7] Furthermore, conversion to a known sulfoxide itself becomes demanding when the sulfinic compound has a complicated structure or reactive functional groups. The latter technique has no ambiguity, but it is not applicable to sulfinates without an internal reference. Therefore a versatile methodology to determine sulfinic absolute configuration is in demand in the realm of chiral sulfur compounds.



**Scheme 1** (a) The structure of a representative chiral sulfinate, (*R*)-(+)-methyl *p*-toluenesulfinate ((*R*)-(+)-**1**); (b) The structure of a sulfinic cruciferous phytoalexin, (*S*)-(−)-brassicanal C ((*S*)-(−)-**2**).

In our continuous stereochemical research on natural products, we have studied absolute configurations of several sulfur-containing cruciferous phytoalexins by using chiroptical techniques.[8] Phytoalexins are antimicrobial secondary metabolites produced *de novo* in response to various stresses such as pathogenic invasion and UV light. Since the plant family cruciferae includes a large number of dietary important crops (cabbage, turnip, rapeseed, broccoli, cauliflower, mustard, wasabi, *etc.*), the constituent phytoalexins are intimately related to human health.[9] Stereochemical studies of these phytoalexins are beneficial in understanding the relationship between chirality and biological activities such as antimicrobial[8a,9a] and antitumor activities.[8c,10] Moreover, some natural cruciferous phytoalexins have been isolated with incomplete enantiomeric purities,[8a,c,11] and therefore the analysis of their chiral properties is also informative to elucidate their complicated biosynthetic pathway.[8,9] A cruciferous phytoalexin brassicanal C (**2**, Scheme 1b) was first isolated from cabbage (*Brassica oleracea* var. *capitata*) inoculated with *Pseudomonas cichorii* in 1991 as an optically active sulfinic natural product.[12] Pedras *et al.* recently isolated **2** from cauliflower (*Brassica oleraceae* var. *botrytis*) irradiated with UV light and confirmed its sulfinic structure by synthesis of racemic (±)-**2**.[13] However, the absolute configuration of the naturally occurring (−)-**2** has not yet been assigned due to the lack of an effective method.

Recently, advances in density functional theory (DFT) calculation of optical activities, such as optical rotation, electronic circular dichroism (ECD) and vibrational circular dichroism (VCD), have opened the way for nonempirical determination of absolute configuration of a broad range of chiral molecules.[14] Among them, VCD spectroscopy is the most reliable and informative due to the number of well-isolated signals and the higher accuracy of the calculation of vibrational transitions; however, the requirement of milligram-level sample and the rarity of VCD instruments have restricted the accessibility of this technique. On the other hand, optical rotation and ECD spectroscopies are more commonly used owing to their higher sensitivity and accessibility, although

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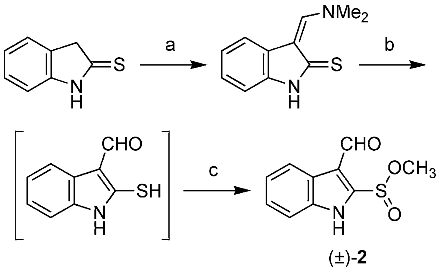
assignments rely on a small number of signals. Although optical rotation, ECD and VCD have recently been used for nonempirical determinations of chirality of sulfoxides and sulfinamides,[15] their application to sulfinates has been limited to a few empirical approaches based on optical rotatory dispersion[2a,5a] and ECD,[7,16] while there is no nonempirical stereochemical study on them. In the present study, we have conducted optical rotation, ECD and VCD measurements of the sulfinates shown in Scheme 1 and their theoretical calculation using DFT, aimed at establishing a convenient and reliable method to assign sulfinic absolute configurations. There is no previous DFT studies on optical activities of sulfinates, and therefore we first applied these three techniques to a sulfinic compound of known chirality, (*R*)-(+)-methyl *p*-toluenesulfinate ((*R*)-(+)-**1**),[17] in order to examine the reliability of each method and to compare their possible scopes and limitations to sulfinates. The results on **1** demonstrated that each method can accurately assign the absolute configuration of sulfinates. Lastly, we applied these techniques to the sulfinic natural product (–)-**2** and determined its absolute configuration as *S*.

## Results and discussion

### Preparation of (*R*)-(+)-1 and (–)-2

Racemic (±)-**1** was prepared by following a reported method using *p*-tolyldisulfide and NBS with an excess amount of methanol.[18] Racemic (±)-**2** was prepared by using a procedure similar to the synthesis reported by Pedras *et al.*[13] as shown in Scheme 2. Reaction of indoline-2-thione[19] and the Vilsmeier reagent prepared from phosphoryl chloride and DMF afforded 3-(*N*,*N*-dimethylamino)methyleneindoline-2-thione[19] (85%). The dimethylamino compound was then transformed to the aldehyde compound by treatment with aqueous hydrochloric acid. The resulting crude compound was oxidized by $I_2$ in methanol solution, yielding (±)-**2** (15% in 2 steps). The NMR data was identical to that previously reported.[12]

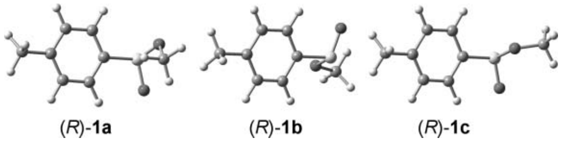


**Scheme 2** Synthesis of (±)-**2**. *Reagents and conditions:* (a) $POCl_3$, DMF, reflux, 85%; (b) HCl aq, EtOH, rt; (c) NBS, MeOH, pyridine, 0 °C, 15% in 2 steps.

The enantiomers of **1** and **2** were separated by using chiral HPLC on a CHIRALCEL® OD column (1 cm $\phi \times 25$ cm) at hexane : EtOAc = 99:1 and 80:20, respectively. The elution time and the separation factors $\alpha$ are as follows ($t_0 = 3.4$ min was used to calculate $\alpha$): For **1**, $t(+) = 15.6$ min, $t(-) = 16.5$ min, $\alpha = 1.07$; For **2**, $t(-) = 16.8$ min, $t(+) = 20.0$ min, $\alpha = 1.24$. Both enantiomers of **1** were purified by repeating chiral HPLC of partially enantioenriched fractions. Each enantiomer of **1** and **2** was confirmed to have >98%ee by chiral HPLC. The first-eluted enantiomer of **1** was found to exhibit positive optical rotation ((+)-**1**, $[\alpha]_D$ +184° (c 0.2; EtOH); lit.[17] $[\alpha]_D$ +220° (c 3.23; EtOH)), while the first-eluted enantiomer of **2** was identified as the levorotatory enantiomer ((–)-**2**, $[\alpha]_D$ –231° (c 0.2; MeOH); lit.[12] $[\alpha]_D$ –13.3 (c 1.04; MeOH)). Interestingly, brassicanal C isolated earlier was levorotatory, but with a much smaller $[\alpha]_D$ value than the optically pure (–)-**2**, indicating poor stereoselectivity in its biosynthesis, as observed in other cruciferous phytoalexins.[8a,c,11]

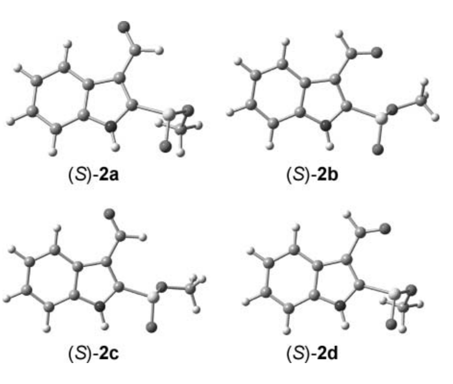
### Conformational analysis of (*R*)-1 and (*S*)-2

Prior to the calculation of chiroptical properties of **1** and **2**, conformational searches were carried out to define their stable conformers. The set of 18 initial conformations of (*R*)-**1** was generated by combination of incremental 60° rotation of the dihedral angle C2C1S1O8 (–120°, –60°, 0°, 60°, 120°, 180 °) and incremental 120° rotation of the dihedral angle C1S1O8C8 (–60°, 60°, 180 °). For (*S*)-**2**, the 36 starting structures were created by rotating the bond C3–C8 by 180° in addition to the rotation of the C2–S2 bond (60 ° each) and the S2–O9 bond (120 ° each). Each geometry was optimized by using the DFT/B3LYP/6–31G(d) level of theory, where some of the initial conformations were converged to the same conformer. Further optimization at the DFT/B3LYP/6–311+G(2df,2p) level of theory led to the three and four stable conformers for **1** and **2**, respectively, within 2 kcal/mol from the most stable one (Fig. 1 and 2). In the stable conformations of **1**, the S1=O1 bond and the phenyl ring are almost coplanar (the tilt angle is less than 3°, data not shown), where the conformers are stabilized by $\pi$ conjugation. On the other hand, the S2=O2 bond of **2** directs toward the neighboring N1–H1 group to avoid the steric repulsion with the C8 aldehyde group, and probably to obtain an extra stabilization from intermolecular hydrogen bonding between O2 and H1. Table 1 and 2 show a few representative dihedral angles, the relative energies and the



(*R*)-**1a** (*R*)-**1b** (*R*)-**1c**

**Fig. 1** B3LYP/6–311+G(2df,2p) optimized structures for three stable conformers of (*R*)-**1**.



(*S*)-**2a** (*S*)-**2b**

(*S*)-**2c** (*S*)-**2d**

**Fig. 2** B3LYP/6–311+G(2df,2p) optimized structures for four stable conformers of (*S*)-**2**.

**Table 1** Three stable conformers of (*R*)-**1** optimized without considering a solvent effect,[a] and their calculated $[\alpha]_{\mathrm{D}}$[b] and observed $[\alpha]_{\mathrm{D}}$ of (+)-**1**

| | ΔE (kcal/mol)[a] | Boltzmann population | Dihedral angles[a] | | calcd $[\alpha]_{\mathrm{D}}$[b] |
|---|---|---|---|---|---|
| | | | C2C1S1O8 | C1S1O8C8 | |
| (*R*)-**1a** | 0.000 | 65.4% | 65.52° | 65.66° | +364.6° |
| (*R*)-**1b** | 0.784 | 17.4% | −112.49° | −174.80° | +352.7° |
| (*R*)-**1c** | 0.790 | 17.2% | 70.81° | −174.75° | +347.5° |
| | | averaged $[\alpha]_{\mathrm{D}}$ | | | +360° |
| | | observed $[\alpha]_{\mathrm{D}}$ (c = 0.2 [g/(100mL)]) | | $CHCl_3$ | +185° |
| | | | | MeCN | +177° |
| | | | | EtOH | +184° |

[a] Optimized at the DFT/B3LYP/6–311+G(2df,2p), [b] Calculated at the TDDFT/B3LYP/aug-cc-pVDZ.

**Table 2** Four stable conformers of (*S*)-**2** optimized without considering a solvent effect,[a] and their calculated $[\alpha]_{\mathrm{D}}$[b] and observed $[\alpha]_{\mathrm{D}}$ of (−)-**2**

| | ΔE (kcal/mol)[a] | Boltzmann population | Dihedral angles[a] | | | calcd $[\alpha]_{\mathrm{D}}$[b] |
|---|---|---|---|---|---|---|
| | | | O8C8C3C2 | C3C2S2O9 | C2S2O9C9 | |
| (*S*)-**2a** | 0.000 | 60.3% | 179.08° | −68.53° | −61.57° | −500.1° |
| (*S*)-**2b** | 0.644 | 20.3% | 0.67° | −76.04° | −146.24° | −264.6° |
| (*S*)-**2c** | 0.956 | 12.0% | 179.40° | −76.13° | −173.19° | −368.1° |
| (*S*)-**2d** | 1.247 | 7.4% | 0.48° | −74.54° | −61.39° | −589.4° |
| | | | averaged $[\alpha]_{\mathrm{D}}$ | | | −443° |
| | | | observed $[\alpha]_{\mathrm{D}}$ (c = 0.2 [g/(100mL)], MeOH) | | | −231° |

[a] Optimized at the DFT/B3LYP/6–311+G(2df,2p), [b] Calculated at the TDDFT/B3LYP/aug-cc-pVDZ.

Boltzmann populations of these conformers. Theoretical optical rotation, ECD and VCD of (*R*)-**1** and (*S*)-**2** were calculated for each stable conformer, and then these data were averaged based on their Boltzmann population to obtain the final spectra.

## Chiroptical Spectra of (*R*)-(+)-1

The $[\alpha]_{\mathrm{D}}$ of (+)-**1** was measured in chloroform, acetonitrile and ethanol, resulting in almost same values around +180° (Table 1). Although optical rotatory power is known to be influenced by solvents,[20] seemingly such an effect on the optical rotation of (+)-**1** is negligible. As is the case for (+)-**1**, chiral sulfinates have been reported to exhibit large $[\alpha]_{\mathrm{D}}$ values.[21] Therefore, this series of compounds represents a favorable case where, according to recent studies, absolute configuration can be assigned by time-dependent DFT calculation of optical rotation at the sodium-D line.[14,22] As Stephens *et al.* pointed out, molecules with $[\alpha]_{\mathrm{D}} < 100°$ should be treated with caution since calculations may predict $[\alpha]_{\mathrm{D}}$ values of incorrect sign.[22] The calculation of the optical rotation of (*R*)-**1** was carried out at the TDDFT/B3LYP/aug-cc-pVDZ level, leading to almost same values for the three conformers irrespective of the rotations of the C1–S1 bond and the S1–O8 bond (Table 1). However, the averaged theoretical $[\alpha]_{\mathrm{D}}$ value of (*R*)-**1** (+360°) is twice larger than the observed ones (*ca.* +180°). This discrepancy could be due to errors in the functional or the basis set, or due to vibrational effects, which are not taken into account in these calculations. Interestingly, twice larger predicted optical rotations have also been seen for a chiral sulfoxide compound in a previous report[15g] and for (−)-**2** in this study (*vide infra*). Most importantly, the calculated value of (*R*)-**1** is accurately predicted to have the positive sign, demonstrating the reliability of the assignment based on optical rotation.

The ECD and UV spectra of (+)-**1** were recorded in acetonitrile as shown in Fig. 3. The observed ECD spectrum exhibits the first positive Cotton effect at 249 nm and the negative band at 215 nm. The theoretical ECD spectrum of (*R*)-**1** was calculated using the TDDFT/B3LYP/aug-cc-pVDZ level, where all three conformers show closely compatible first positive Cotton bands at the longer wavelength region, while different patterns are seen in the shorter wavelength region: (*R*)-**1a** has a slightly positive signal, but (*R*)-**1b** and (*R*)-**1c** have negative bands. The averaged theoretical spectrum therefore exhibits a first positive band and then a weak negative band as shown in Fig. 3. Although the comparison between the observed ECD spectrum and the predicted one finds slight differences in the wavelength of the positive band and the relative intensities of the negative band, the overall spectral pattern in the experimental data is well reproduced in the theoretical one, thus supporting the previously assigned *R*-configuration. The similarity seen between the observed and calculated UV spectra supports the reliability of the calculations. Furthermore, a better agreement of ECD curves has been achieved by considering the influence of the solvent on the stability of these conformers. The energy calculations of the three conformers in acetonitrile solvent conducted at the 6–311+G(2df,2p) basis set using the polarizable continuum model found an increase in the Boltzmann populations of (*R*)-**1b** and (*R*)-**1c** (Table 3). Consequently, the ECD spectrum based on the populations in acetonitrile (Fig. 3b), which exhibit a clearer negative band in the region of 245–205 nm, provides

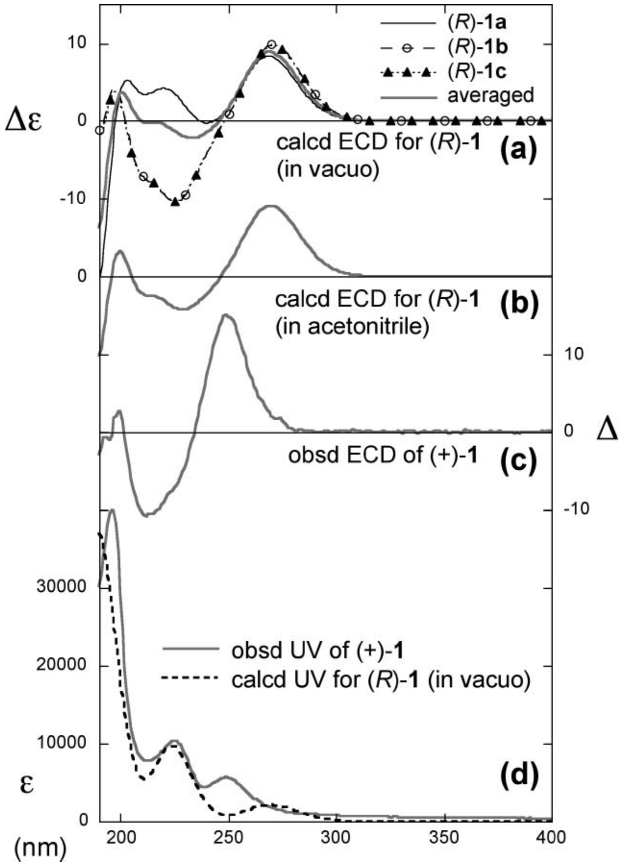


**Fig. 3** (a) The calculated ECD spectra at the TDDFT/B3LYP/aug-cc-pVDZ for (*R*)-**1** in vacuo. (b) The averaged calculated ECD spectrum based on the Boltzmann populations in acetonitrile solution as shown in Table 3. (c) The observed ECD of (+)-**1**. (d) The observed and averaged calculated UV spectra. The UV spectrum calculated in acetonitrile is omitted since it is indistinguishable from that calculated in vacuo. ECD and UV of (+)-**1** (acetonitrile, 0.3 mM) $\lambda_{ext}$ ($\Delta\varepsilon$): 199 (+2.8), 212 (–10.8), 249 (+15.1); $\lambda_{max}$ ($\varepsilon$): 196 (40100), 225 (10400), 249 (5700).

**Table 3** Relative energies and Boltzmann populations of three stable conformers of (*R*)-**1** calculated by using PCM in acetonitrile[a]

| | ΔE (kcal/mol)[a] | Boltzmann population |
|---|---|---|
| (*R*)-**1a** | 0.000 | 46.1% |
| (*R*)-**1b** | 0.315 | 27.0% |
| (*R*)-**1c** | 0.319 | 26.9% |

[a] Calculated using the DFT/B3LYP/6-311+G(2df,2p).

a closer similarity with the experimental, thus confirming the *R* configuration.

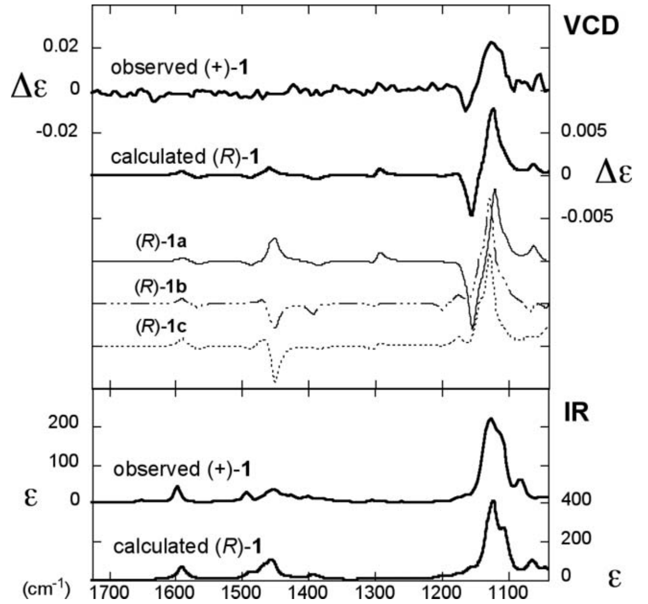


**Fig. 4** Comparison of VCD and IR spectra of observed (+)-**1** in $CDCl_3$ (0.2 M) and the calculated (*R*)-**1** using the DFT/B3LYP/6–311+G(2df,2p).

The VCD and IR spectra of (+)-**1** were measured as a $CDCl_3$ solution, and compared with the theoretical ones calculated for (*R*)-**1** at the DFT/B3LYP/6–311+G(2df,2p) level of theory (Fig. 4). The observed IR spectrum shows good agreement with the calculated in their frequencies and relative intensities, including the intense IR absorption band due to S1=O1 stretching vibration at around 1125 $cm^{-1}$. Similarly, both the experimental and theoretical VCD spectra are almost featureless above 1200 $cm^{-1}$, while they show a characteristic positive couplet, *i.e.*, a positive band at *ca.* 1125 $cm^{-1}$ and a negative band at *ca.* 1160 $cm^{-1}$ originating from S1=O1 stretching and C7 methyl deformation, respectively. The agreement seen between experimental and theoretical VCD bands leads to the *R* assignment. This study represents the first example of the application of VCD spectroscopy to a sulfinate, and provides unambiguous determination of its absolute configuration. It is noteworthy that characteristic VCD signals arising from S=O stretch have been observed in previous studies of sulfoxides and sulfinamides.[15b–j] The stretching of sulfinic S=O, which occurs at the chiral center itself, can be considered to give rise to strong VCD absorption that can be the most informative in the analysis of absolute configuration of sulfinates.

In the study of (+)-**1**, each chiroptical technique reliably predicted the *R* configuration in accordance with the previous assignment by Mikolajczyk and Drabowicz.[17] This is the first example of nonempirical determination of sulfinic absolute configuration. Supported by the finding that optical rotation, ECD and VCD techniques can accurately assign sulfinic chirality, we then applied these methods to the natural product (–)-**2** to determine its absolute configuration.

### Determination of absolute configuration of (–)-2

Calculations of optical activities were carried out for the four stable conformers of (*S*)-**2** (Fig. 2) without consideration of the solvent effects. Compound **2** is rather hydrophilic due to the C8 carbonyl and N1 amino groups, and hence it has limited solubility in apolar solvents. Although aprotic solvents are commonly used for comparison of observed data and theoretical calculation, the experimental $[\alpha]_D$ and ECD measured in methanol and acetonitrile, respectively, showed good agreement with the calculated data as discussed below.

First, the observed $[\alpha]_D$ value in methanol was compared with the calculated shown in Table 2. The TDDFT/B3LYP/aug-cc-pVDZ calculation predicted various optical rotations for each conformer, but all exhibit negative values with large intensities regardless of the rotations of the C3–C8 bond and the S2–O9 bond. The averaged theoretical $[\alpha]_D$ of (*S*)-**2** (−443°) is about twice larger than the experimental one (−231°), as observed in the case of **1**. Both results show large negative values, thus clearly suggesting the absolute configuration of (−)-**2** be *S*. It is noteworthy that the predicted magnitude of the rotation of **2** is greater than that of **1**, as observed experimentally.

To verify the predicted *S*-configuration, ECD spectroscopy was then applied to **2** (Fig. 5). Both the experimental ECD spectrum obtained in acetonitrile and the averaged theoretical spectrum using the TDDFT/B3LYP/aug-cc-pVDZ level show a negative broad band at around 320 nm and a sharp intense peak at around 215 nm. Although the observed small negative couplet at around 250 nm becomes flat in the calculated data because they are compensated by each other (data not shown), the overall agreement between the two spectra unambiguously leads to the assignment as *S*.

Finally, the assignment of the *S*-configuration is further confirmed by VCD spectroscopy (Fig. 6). The IR and VCD measurements were conducted for $CDCl_3$ but at a lower concentration (0.05 M) due to the hydrophilicity of **2**. As a result, the observed spectrum shows a relatively low S/N ratio especially in the region above 1500 cm$^{-1}$, and therefore this region was omitted to avoid any misinterpretation. The theoretical IR and VCD spectra were calculated at the DFT/B3LYP/6–311+G(2df,2p) level and then compared with the experimental ones. The observed IR spectrum shows moderate agreement with the predicted; however, the former exhibits somewhat broader bands than the latter. Considering the molecular property of **2**, the band broadness may indicate that part of the molecule has intermolecular interactions in $CDCl_3$ such as hydrogen bonding between the C8 carbonyl of one molecule and the N1 amino group of another. Nevertheless, the experimental VCD feature reasonably agrees with the theoretical as shown in Fig. 6, where several putative assignments of each observed band

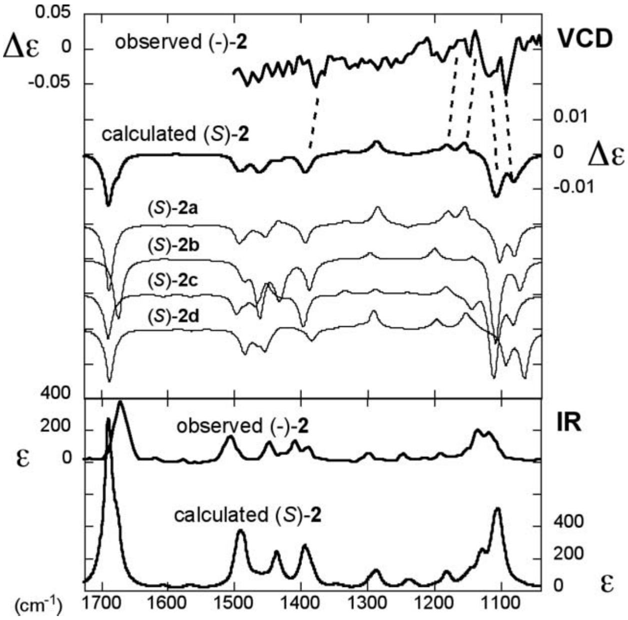


**Fig. 6** Comparison of VCD and IR spectra of observed (−)-**2** in $CDCl_3$ (0.05 M) and the calculated (*S*)-**2** using the DFT/B3LYP/6–311+G(2df,2p). Some of the putative band assignments are shown by dotted lines.

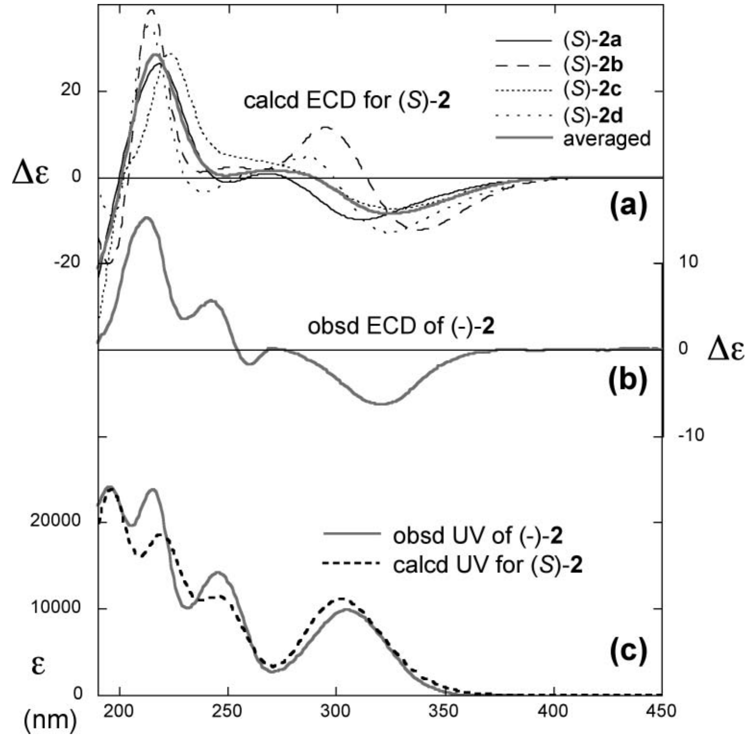


**Fig. 5** (a) The calculated ECD spectra at the TDDFT/B3LYP/aug-cc-pVDZ for (*S*)-**2** in vacuo. (b) The observed ECD of (−)-**2**. (c) The observed and averaged calculated UV spectra. ECD and UV of (−)-**2** (acetonitrile, 0.3 mM). $\lambda_{ext}$ ($\Delta\varepsilon$): 212 (+15.3), 242 (+5.7), 260 (−6.3), 321 (−6.3); $\lambda_{max}$ ($\varepsilon$): 196 (24000), 215 (23800), 245 (14200), 305 (9800).

are depicted. Specifically, the negative feature in the S=O stretching region (*ca.* 1110 cm$^{-1}$) is significant in both the observed and calculated spectra. These VCD results suggest the *S*-configuration of (−)-**2** in consistency with the conclusions deduced from optical rotation and ECD.

## Conclusions

We have applied the theoretical calculation of optical rotation, ECD and VCD spectroscopies to chiral sulfinates for the first time. Comparison of each observed and calculated data of chiral model sulfinate **1** accurately predicted (+)-**1** as *R* in accordance with the previous assignment. Furthermore, the cruciferous phytoalexin (−)-**2** has been unambiguously assigned as *S*. Determination of chirality of sulfinates by chiroptical spectroscopies is a reliable and convenient alternative to conventional methods that require derivatization or crystallization.

Using only a single method could lead to satisfactory assignments for the sulfinates studied here; however, each method has its own advantages and disadvantages in terms of their sensitivity, reliability, restriction of measurement conditions, *etc*. We have shown that the absolute configurations of sulfinates, which typically exhibit large $[\alpha]_D$ values, can conveniently be determined by calculations of optical rotation. However, caution must be taken for this approach in order to avoid erroneous assignments in case the calculated and experimental $[\alpha]_D$ fall into "the zone of indeterminacy" reported in ref 22. In such cases optical rotations at several wavelengths (*i.e.* optical rotatory dispersion)[23] or other methods such as ECD and VCD must be examined. On the other hand, ECD and VCD spectroscopies can be more effective tools when the compound has other chiral moieties. In particular, VCD spectroscopy is advantageous for this purpose because of a large number of well-isolated vibrational transitions[24] including the S=O stretching vibration that strongly reflects sulfinic chirality. The assignment by these methods becomes more reliable by considering solvent effects,[25] as exemplified in the ECD study of **1**. If properly used, each method alone could assign absolute configuration with satisfactory accuracy, and furthermore the use of more than one technique will lead to further reliable conclusions.

## Experimental section

### Preparation of (*R*)-(+)-1 and (−)-2

$^1$H (400 MHz) NMR spectra were recorded on a Bruker Avance spectrometer. FAB MS was performed on a JEOL HX110 spectrometer. Enantioseparation of (±)-**1** and (±)-**2** was conducted on a CHIRALCEL® OD column (1 cm ϕ × 25 cm) using a Shimadzu LC-6A liquid chromatograph instrument equipped with a Shimadzu SPD-6AV UV-Vis spectrometric detector.

Preparation of (±)-**2** used a procedure similar to that reported by Pedras *et al.*[13] Phosphoryl chloride (400 μL) was added dropwisely to DMF (2 mL) with stirring at rt under $N_2$. After 2 h, a solution of indoline-2-thione[19] (300 mg, 2.01 mmol) in DMF (1.5 mL) was added dropwisely to the mixture. The reaction mixture was stirred for 4 h at rt, then poured into 2 mL of wet ice, then added to 10 mL of sat $NaHCO_3$ aq, and stirred overnight. The mixture was poured into water and extracted with EtOAc. The combined extract was washed with brine, then dried over $Na_2SO_4$, filtered and concentrated. The residue was subjected to silica-gel column chromatography (hexane:EtOAc = 30:70 to 0:100) to afford 3-(*N*,*N*-Dimethylamino)methyleneindoline-2-thione[19] (356 mg, 85%).

A solution of 50 mg (0.24 mmol) of the above dimethylamino compound in 8 mL of EtOH was added to 10 mL of 0.5 M HCl aq and stirred for 2 h at rt. The reaction mixture was poured into water and extracted with EtOAc. The combined extract was washed with water, brine, then dried over $Na_2SO_4$, filtered and concentrated. Without further purification, the crude 2-sulfanylindole-3-carboxaldehyde was dissolved in 3 mL of MeOH and 200 mL of pyridine, and then NBS (85 mg, 0.48 mmol) was portionwisely added to the solution at 0 °C. After stirring for 1 h, the mixture was diluted with $CHCl_3$ and washed with water and brine. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The residue was subjected to silica-gel column chromatography (hexane:EtOAc = 85:15 to 80:20) to afford (±)-**2** (7 mg, 15% in 2 steps). Brassicanal C ((±)-**2**): $^1$H NMR (400 MHz, $CDCl_3$): δ 10.34 (1H, s), 9.83 (1H, br s), 8.28 (1H, d, *J* = 7.8 Hz), 7.55 (1H, d, *J* = 8.2 Hz), 7.45 (1H, ddd, *J* = 1.2, 7.6, 7.6 Hz), 7.40 (1H, ddd, *J* = 1.2, 7.5, 7.5 Hz), 3.69 (3H, s); HRMS (FAB) *m*/*z* for $C_{10}H_{10}NO_3S$ ($M^+$), calcd 224.0381, found 224.0384.

### Measurement of optical activities

Optical rotations were measured on a Perkin-Elmer 343 polarimeter at the sodium-D line using a 1-cm optical cell. ECD spectra were recorded on a JASCO J-810 spectrometer with a 1-mm quartz cell. IR and VCD spectra were obtained on a Bomem/BioTools Chiral*ir* spectrometer equipped with a second elastic modulator using a 72-μm $BaF_2$ cell. Data were corrected by solvent data obtained at the same experimental conditions. In each technique, the pairs of enantiomers showed results with the opposite sign.

## Calculations

Geometry optimizations and optical activity calculations were performed with Gaussian 03.[26] The 18 and 36 initial geometries of (*R*)-1 and (*S*)-2, respectively, were first optimized by using DFT/B3LYP/6–31G(d) level of theory, and then resultant stable conformers within 5 kcal/mol from the most stable one were further optimized at the DFT/B3LYP/6–311+G(2df,2p) level. The conformers within 2 kcal/mol from the most stable one were taken into account for optical rotation, ECD and VCD calculations. For the ECD study of (+)-**1**, the energy calculations of the three conformers of (*R*)-1 were conducted at the DFT/B3LYP/6–311+G(2df,2p) level using PCM in acetonitrile (ε = 36.64) as implemented in Gaussian 03. Theoretical optical rotations were calculated using the DFT/B3LYP/aug-cc-pVDZ level at the 589.3 nm. Computation of ECD and UV spectra were carried out using the DFT/B3LYP/6–311+G(2df,2p) level of theory. The ECD spectra were simulated from the first 40 singlet → singlet electronic transitions using Gaussian band shapes and 0.30 eV standard deviation. IR and VCD spectra were calculated at the DFT/B3LYP/6–311+G(2df,2p) level, and simulated with Lorentzian lineshapes of 8 cm$^{-1}$ width. The calculated frequencies ν were scaled with the equation of $(1.04 \times 10^{-5})\nu^2 + 9.894\nu$. Final data were obtained based on the Boltzmann population average of each data.

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