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ARTICLE

Scope and Limitations of Absolute Configuration Determination of Allenic Natural Products Using C=C=C Stretching VCD Signal

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Allene functional group in natural products isolated so far exists as a non-racemic form, but its axial chirality is difficult to elucidate. Allenes exhibit a characteristic antisymmetric C=C=C stretching mode at around 1950 cm^{-1}, whose VCD properties have not been studied in detail. This work, for the first time, applied VCD spectroscopy to allenic natural products as well as allenic molecules with other asymmetric centers with focusing on the antisymmetric C=C=C stretching mode. This vibrational mode yielded a negligibly weak VCD signal for several molecules but, in the presence of electron-withdrawing and/or conjugating substituents, generated a stronger one. Its sign was found to be influenced by the nature of substituents. These findings should deepen the understanding of the VCD properties of allene functional group and should be useful for future studies of chiral allenes.

Introduction

Allene (C=C=C) functional group is an important structural motif in natural product chemistry, drug development, and organic synthesis.[1] Allenes found in natural products so far are known to exist as a non-racemic form.[1a] The absolute configuration (AC) of newly isolated chiral allenes has been assigned using Lowe-Brewster's rule, an empirical rule based on optical rotation.[2] However, substituents on allene may largely influence optical rotation value and thus this rule shows limited applicability to complex allenic molecules. In fact, exceptions to this rule is reported by some of the authors.[3] Electronic circular dichroism (ECD) signals originating from allene π-π^* transition (usually observed in a region shorter than 250 nm) has been shown indicative of its AC,[4] but the ECD spectrum of allenes with UV-active chiral substituents has to be interpreted with great care. Although chemical correlation[5] and total synthesis[6] have elucidated the AC of chiral allenes, other methods are to be explored.

Allenes exhibit a characteristic antisymmetric C=C=C stretching (ν_{as} C=C=C) IR signal at ca. 1950 cm^{-1}. Considering the sensitivity of vibrational circular dichroism (VCD) spectroscopy to molecular stereostructure,[7] observation of a ν_{as} C=C=C VCD signal seems promising for the AC determination of allenic natural products. While several VCD studies on synthetic allenes,[8] including those dedicated solely for theoretical calculations without measured spectra,[8c, 8d] are reported, none reported allenic natural products and allenes with other asymmetric centers. Moreover, to our knowledge, only two works presented the measured spectra of allenes in the 1950 cm^{-1} region, with 1-haloallenes being mainly focused.[8b, 8h] Thus, properties of the ν_{as} C=C=C VCD signal have largely been unknown.

Infrared absorptions in the 2300-1900 cm^{-1} region are well isolated from most of the other vibrational signals and have been used for characterization of molecules with alkyne, nitrile, isonitrile, azido, carbodiimide, and allene functional groups.[9] Our previous VCD studies in this region revealed that antisymmetric stretching of carbodiimide (N=C=N) exhibits an intense VCD signal whose sign depends on its axial chirality (ε 880, $\Delta\varepsilon$ -0.16 at 2099 cm^{-1}).[10] Recently, we also found that VCD signals originating from OCD_3 vibrations in the 2300-1900 cm^{-1} region reflect the AC of an asymmetric center in the vicinity of OCD_3 group with little influence from other chiral centers.[11] Because no previous VCD studies dealt with allenic molecules containing more than one chiral center, influence from other chiral centers to a VCD signal of ν_{as} C=C=C is not known. Here, through VCD studies on allenic natural products and several synthetic model allenes, we discuss the scope and limitations of the use of a ν_{as} C=C=C VCD signal for AC determination of allene.

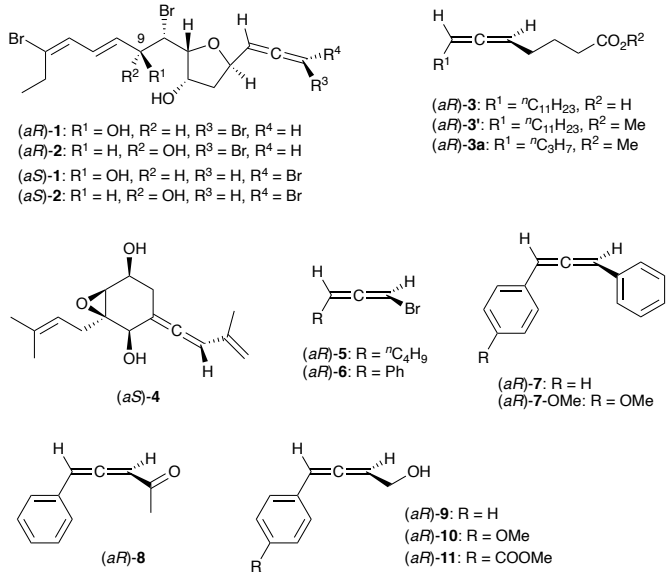
Results and discussion

Allenic natural products are classified into a few subclasses such as bromoallenes, linear allenes, and others.[1a] To examine the capability of VCD spectroscopic approach to allenic molecules,

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we studied a bromoallene (*aR*)-**1** (omaezallene),[3] a linear allene (*aR*)-**3** (laballeic acid),[12] and one of other allenes (*aS*)-**4** (iso-A82775C).[13] Additionally, several synthetic simple allenes **5**-**11** were studied to understand the properties of ν_{as} C=C=C VCD signals (Scheme 1). All the studied allenes were synthesized with high enantiomeric excess (>90%ee, see ESI).



Scheme 1 Structures of axially chiral allenes studied in this work. Omaezallene ((*aR*)-**1**), labelleic acid ((*aR*)-**3**), and iso-A82775C ((*aS*)-**4**) are naturally occurring ones.

First, we studied the VCD spectra of naturally occurring bromoallenes (*aR*)-**1** and its synthetic unnatural C-9 epimer, (*aR*)-**2**.[3] Despite their identical structures except for the AC of C-9, the epimeric pair showed readily distinguishable VCD patterns (Fig. 1). As for the ν_{as} C=C=C vibration, both (*aR*)-**1** and (*aR*)-**2** showed a characteristic IR signal at 1960 cm^{-1} with very small intensity (ε ca. 10). However, the corresponding VCD signals were also negligibly weak.

We performed theoretical calculations of the VCD spectra of (*aR*)-**1** and (*aR*)-**2**. Theoretical VCD spectra shown in Fig. 1 were calculated at the DFT/B3LYP/6-311G(d,p) level of theory (see ESI for the detailed computational procedure). The VCD spectra of (*aR*)-**1** and (*aR*)-**2** showed a moderate agreement with the observed ones in the overall frequency region, which supported the accuracy of the calculations. See Table S1 for the results of quantitative comparison.[14] These theoretical spectra also showed small intensities for ν_{as} C=C=C VCD signals. Closer examination of the theoretical VCD spectra found that each predicted conformer of (*aR*)-**1** and (*aR*)-**2** (16 and 12 conformers, respectively) exhibited very small ν_{as} C=C=C VCD signals (Fig. S1). This suggested that the small VCD intensity of **1** and **2** is due to an intrinsic nature of the ν_{as} C=C=C mode and not due to the cancellation of strong positive and negative VCD signals by each conformer. The dipole strength *D* and the rotational strength *R* of the ν_{as} C=C=C mode of the most stable conformers are listed in Table 1. See Fig. S2 for the calculated VCD spectra of (*aR*)-**1** and (*aR*)-**2** using different theoretical conditions.

Negligibly weak ν_{as} C=C=C VCD signals of (*aR*)-**1** and (*aR*)-**2** do not exclude a possibility that the allenic diastereomers (*aS*)-**1** and (*aS*)-**2** show completely different ν_{as} C=C=C VCD signatures indicative of their allenic AC. To examine this possibility, we calculated the VCD spectra of (*aS*)-**1** and (*aS*)-**2** as shown in Fig. 1. The predicted ν_{as} C=C=C signals of (*aS*)-**1** and (*aS*)-**2** were found as weak as those of (*aR*)-**1** and (*aR*)-**2**. Furthermore, both (*aR*)-**1** and (*aS*)-**1** showed a positive VCD signal with similar intensities (Table 1). These results suggest that the sign of a ν_{as} C=C=C VCD signal is not independent from the substituents of allene group. Thus, we concluded that, in the case of **1** and **2**, ν_{as} C=C=C VCD signal alone does not lead to the elucidation of the allenic AC. While the nature of ν_{as} C=C=C mode is the focus of this work, note that the allenic AC of **1** and **2** could be determined by comparison of the observed and calculated spectra below 1900 cm^{-1}, as supported by higher quantitative similarity scores for (*aR*)-**1** and (*aR*)-**2** (Table S1).

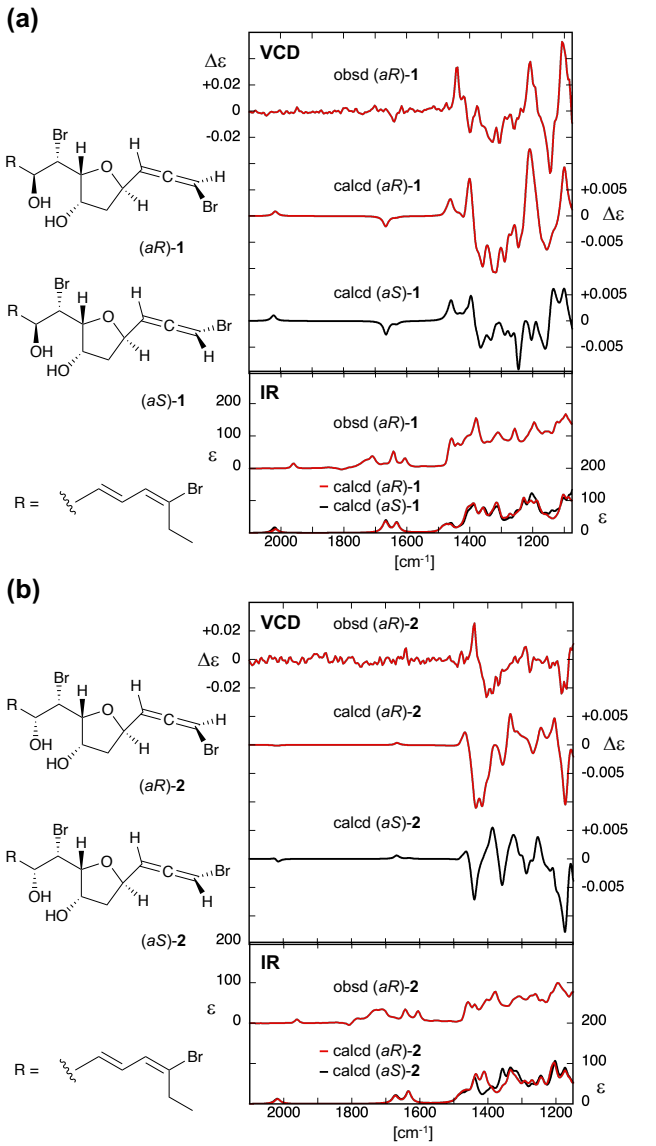


Fig. 1 Observed and calculated VCD/IR spectra of (a) **1** and (b) **2**. Measurement conditions: 0.25 M (for (*aR*)-**1**) or 0.15 M (for (*aR*)-**2**) in $CDCl_3$; *l* 85 μm. Calculation conditions: DFT/B3LYP/6-311G(d,p). Scaling factor: 0.985.

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The properties of ν_{as} C=C=C VCD signal of other types of allenic natural products were investigated through VCD studies on (*aR*)-**3'** and (*aS*)-**4**. Linear allene (*aR*)-**3'** did not show any discernible ν_{as} C=C=C signal at 1961 cm^{-1} (ε 12, $\Delta\varepsilon$ weaker than 1.5×10^{-4}) (Table 1 and Fig. S3a), whereas alkenyl allene (*aS*)-**4** showed a more than 50 times stronger VCD signal with similarly small IR band at 1956 cm^{-1} (ε 32, $\Delta\varepsilon$ $+9 \times 10^{-3}$) (Figure 2).

Theoretical calculations of these molecules were not straightforward due to the high degrees of conformational freedom[15] and hydrogen bonding properties. We calculated a truncated model (*aR*)-**3a** to obtain insight into the ν_{as} C=C=C VCD signal of (*aR*)-**3'**. The analysis of the ν_{as} C=C=C mode of the most stable conformer of (*aR*)-**3a** found its *D* and *R* to be as small as those of **1** and **2** (Table 1). As for (*aS*)-**4**, its entire structure was calculated despite its severely hydrogen bonding properties. Its theoretical VCD spectrum calculated at DFT/B3LYP/6-311G(d,p) indeed showed a strong negative signal at around 1300 cm^{-1} that did not match to the experimental spectrum. This band arises from OH deformation vibrations predicted for a single molecular state. Nevertheless, the calculated spectrum well reproduced the observed ν_{as} C=C=C positive signal (Figure 2 and Table 1), which should be useful for its AC determination.

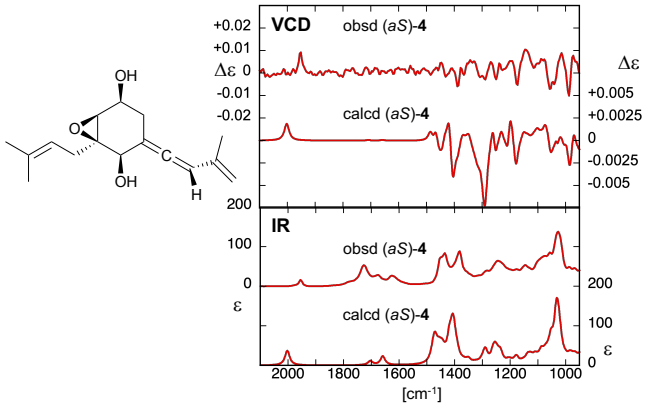


Fig. 2 Observed and calculated VCD/IR spectra of **4**. Measurement conditions: 0.35 M in $CDCl_3$; *l* 85 µm. Calculation conditions: DFT/B3LYP/6-311G(d,p). Scaling factor: 0.985.

The results so far found that the ν_{as} C=C=C signals of **1**, **2**, and **3'** are negligibly weak. Meanwhile, the ν_{as} C=C=C VCD signals of allenes attached only to hydrogen and carbon atoms, as in (*aR*)-**3'** and (*aS*)-**4**, could be more than 50 times different in their intensity. To obtain more insight into the relationship between the ν_{as} C=C=C VCD intensity and allene substituents, we studied synthetic 1,3-disubstituted allenes **5**-**11**.

Studies on these synthetic allenes started with the measurement of alkylbromoallenes (*aR*)-**5**. As shown in Fig. 3a and Table 1, (*aR*)-**5** exhibited a negative ν_{as} C=C=C VCD signal ($\Delta\varepsilon$ -2×10^{-3}). Its weak intensity was comparable to that of naturally occurring alkylbromoallene (*aR*)-**1**. The sign of ν_{as} C=C=C VCD signal of (*aR*)-**5** was opposite to that of (*aR*)-**1** despite the same *aR* chirality, which supports our notion that its sign is affected by the substituents. Meanwhile, comparison of (*aR*)-**3'** and (*aR*)-**5** suggested that replacement of an alkyl group to a Br group leads to more than 10 times signal amplification. Substitution of an alkyl group to a phenyl group, *e.g.*, from (*aR*)-**5** to phenylbromoallene (*aR*)-**6**,[16] resulted in ca. 10 times signal enhancement ($\Delta\varepsilon$ -1.9×10^{-2}) (Fig. 3b and Table 1). The intensity of ν_{as} C=C=C VCD signal of 1,3-diphenylallene (*aR*)-**7**[8b] is also high but is slightly smaller than that of (*aR*)-**6** (Fig. 3c and Table 1).

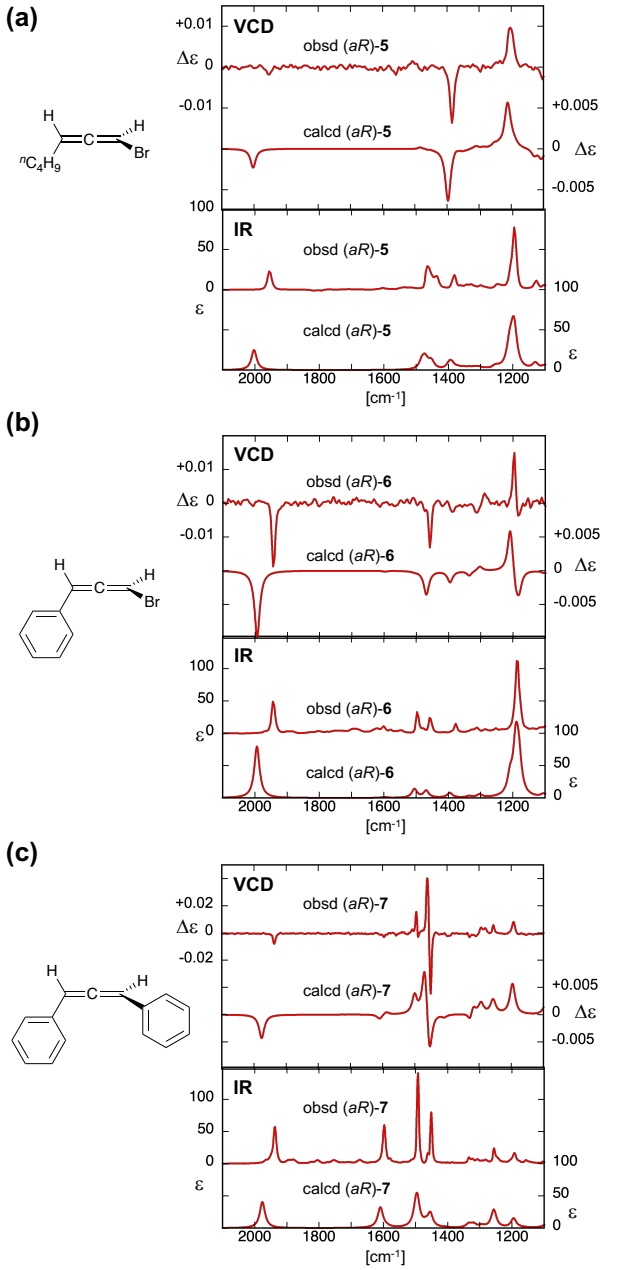


Fig. 3 Observed and calculated VCD/IR spectra of (a) **5**, (b) **6**, and (c) **7**. Measurement conditions: 0.4 M in $CDCl_3$; *l* 85 µm. Calculation conditions: DFT/B3LYP/6-311G(d,p). Scaling factors: 0.98.

Phenyl and Br groups exert induction and conjugation effects that alter the nature of a C=C=C bond and thereby its vibrations. While both groups are electron-withdrawing compared to alkyl group, Br shows higher electronegativity than phenyl does.[17] Conjugation by Br group is less effective than that by phenyl group due to the poor overlap of the 2p orbital

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of carbon and 4p orbital of bromine. Extent of conjugation seems to be reflected in the frequency shift: compared to the observed wavenumber ν of (*aR*)-**5** (1956 cm^{-1}), the shift of (*aR*)-**6** (1944 cm^{-1}) is smaller than that of (*aR*)-**7** (1937 cm^{-1}). Qualitative trend of their frequency shifts and VCD intensities is reproduced by theoretical calculations (Fig. 3 and Table 1).

Table 1 Observed wavenumber ν, IR intensity (ε), and VCD intensity ($\Delta\varepsilon$) and the calculated wavenumber ν (unscaled), dipole strength *D*, and rotational strength *R* of the ν_{as} C=C=C mode of each allene. Calculated results are of the most stable conformer with respective Boltzmann population (*P*) of each molecule predicted using DFT/B3LYP/6-311++G(d,p).

	Observed			Calculated			
	ν [cm^{-1}]	ε	$\Delta\varepsilon$	ν [cm^{-1}]	D [10^{-40} esu^2 cm^2]	R [10^{-44} esu^2 cm^2]	P
(*aR*)-**1**	1960	15	+2 × 10^{-3}	2048	15.0	+6.3	19.1%
(*aS*)-**1**	-	-	-	2052	28.5	+5.7	29.4%
(*aR*)-**2**	1960	10	N.D. [a]	2046	13.7	-3.3	22.1%
(*aS*)-**2**	-	-	-	2048	15.0	-4.8	39.0%
(*aR*)-**3′**	1961	12	N.D. [b]	2053 [c]	57.0 [c]	-5.3 [c]	5.7% [c]
(*aS*)-**4**	1956	32	+9 × 10^{-3}	2036	30.8	+2.8 [b]	41.5% [d]
(*aR*)-**5**	1956	23	-2 × 10^{-3}	2044	34.4	-8.3	25.7%
(*aR*)-**6**	1944	49	-1.9 × 10^{-2}	2024	113	-34.9	100%
(*aR*)-**7**	1937	58	-8 × 10^{-3}	2016	58.2	-15.4	100%
(*aR*)-**8**	1936	108	-6 × 10^{-3}	2013	189	-35.4	100%
(*aR*)-**9**	1950	48	-1.5 × 10^{-3}	2031	102	-19.8	39.5%
(*aR*)-**10**	1949	20	N.D. [e]	2030	64.1	-13.9	17.1%
(*aR*)-**11**	1950	46	-2 × 10^{-3}	2029	166	-28.8	18.2%
(*aR*)-**7**-OMe	1936	32	-3 × 10^{-3}	2015	30.8	-5.8	54.7%

[a] Weaker than 2 × 10^{-4}. [b] Weaker than 1.5 × 10^{-4}. [c] Results of (*aR*)-**3a**. [d] Predicted values for the second most stable conformer of (*aS*)-**4** were ν 2032 cm^{-1}, *D* 81.4 × 10^{-40} esu^2 cm^2, and *R* +16.2 × 10^{-44} esu^2 cm^2 (*P* 19.7%). [e] Weaker than 5 × 10^{-4}.

Both induction and conjugation effects may change the intensity of ν_{as} C=C=C VCD signals. In line with this assumption, the VCD intensity of (*aR*)-**8**, an allenic methyl ketone whose structural motif is seen in grasshopper ketone and its glycosides,[1a] was similar ($\Delta\varepsilon$ -6 × 10^{-3} at 1936 cm^{-1}) to that of (*aR*)-**7** (Table 1 and Fig. S3b). To dissect factors enhancing ν_{as} C=C=C VCD signal, we designed allenes possessing a *para*-substituted phenyl group with different induction properties. Our attempted synthesis of phenylbromoallenes with an electron-donating *p*-OMe group and an electron-withdrawing *p*-COOMe group was not successful because of their chemical instability. Instead, *aR* enantiomers of **9**-**11** were synthesized using a $CuBr_2$-catalyzed enantioselective reaction reported by Ma and coworkers.[12b] The enantiomeric purities of these allenes were confirmed to be higher than 90%ee by their conversion to MTPA esters and the following ^{1}H NMR measurement (see ESI). Table 1 and Fig. S4 show the experimental VCD and IR results of **9**-**11**. These allenes showed IR signals at virtually the same frequency (1950 cm^{-1}), which is indicative of the negligible differences in their conjugation influences on the allene functional group. Analysis of their ν_{as} C=C=C VCD signals revealed that their intensity is enhanced by electron-withdrawing groups and attenuated by electron-donating groups ($\Delta\varepsilon$ -1.5 × 10^{-3} for (*aR*)-**9**, not detected for (*aR*)-**10**, and -2 × 10^{-3} for (*aR*)-**11**). Influence of induction effects was also examined by preparing (*aR*)-**7**-OMe, which possesses electron-donating *p*-OMe group. The signal frequencies of (*aR*)-**7**-OMe and (*aR*)-**7** were almost the same, but (*aR*)-**7**-OMe showed a much weaker VCD signal compared to that of (*aR*)-**7** (Table 1 and Fig. S3c). Thus, we suggest that allenes with electron-withdrawing substituents show a ν_{as} C=C=C VCD signal that is sufficiently strong to observe.

Influence by conjugation effects alone was difficult to accurately evaluate within this set of allenes because conjugating substituents could also exert induction effects. Nevertheless, VCD comparisons between **5** (alkyl-substituted) and **6** (phenyl-substituted) and between **8** (acetyl-substituted) and **9** (hydroxymethyl-substituted) indicated that allenes attached to an sp^2 carbon show a stronger ν_{as} C=C=C VCD signal. Thus, we tentatively suggest that conjugation effect also enhances ν_{as} C=C=C VCD intensity. In an attempt to explore other factors affecting ν_{as} C=C=C VCD signal, the VCD spectrum of (*aR*)-**7** was measured using DMSO-d_6 solvent instead of $CDCl_3$ (Fig. S5). We found its ν_{as} C=C=C VCD intensity virtually unchanged and concluded that interactions between allene and solvent molecules do not play a major role. We also confirmed that the angles made by the electric and magnetic dipole transition moments are somewhat similar (84.6° to 102.5°) for all the studied allenes (Table S2). While there may be other factors to be considered, we propose that allenes with electron-withdrawing and conjugating substituents show an intense ν_{as} C=C=C VCD signal.

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Conclusions

VCD spectroscopy has been used for the structural determination of various natural products,[7] but it has not been applied to allenic natural products. Detailed VCD properties of C=C=C functional group have not been studied either. In this work, through studies on several natural products and synthetic molecules, we showed that ν_{as} C=C=C VCD signal is often very weak but is enhanced by an electron-withdrawing substituent. Presence of multiple electron-withdrawing substituents led to further signal amplification. Furthermore, this work indicated that allenes connected to an sp^2 carbon show a stronger signal. On the other hand, this work also found that ν_{as} C=C=C VCD signal is readily affected by substituents. The sign of the VCD signal may be changed in the presence of other asymmetric centers. Thus, care must be taken for interpretation of the VCD spectrum of allenic molecules with multiple asymmetric centers, and, for such molecules, use of multiple analytical methods such as ECD spectroscopy[4] is recommended. The studied set of allenes is not comprehensive and mostly focused on 1,3-disubstituted allenes partially because of difficulties in preparation of allenic molecules. Nevertheless, a simple relationship between the ν_{as} C=C=C VCD intensity and the nature of the substituents revealed here should be useful for future studies of chiral allenes.

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