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A Unifying Mechanism for the Rearrangement of Vinyl Allene Oxide Geometric Isomers to Cyclopentenones†

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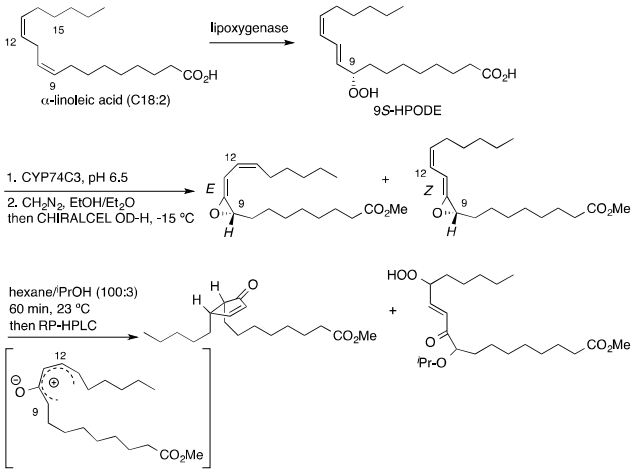
A new mechanism for the rearrangement of vinyl allene oxide geometric isomers to stereodefined cyclopentenones is proposed based on DFT computations. This mechanism comprises two steps, first the ring opening of the oxirane to give a vinylcyclopropanone, and then a [1,3]-C sigmatropic rearrangement. Depending primarily upon the allene oxide double bond geometry the stepwise pathway is either competitive (for *E* allene oxides) or favored (for *Z* allene oxides) relative to the already described S_N2-like concerted pathway. All bond-forming reactions take place through helically chiral transition states, which allows the stereochemical information of the substrates to be transferred to that of the products, in particular in the case of (enantiopure) *Z* allene oxides. In addition to revealing one more of the fascinating mechanisms with memory of chirality, the results deepen our understanding of the important jasmonate and clavulone biosynthetic pathways that occur in plants and corals.

Introduction

Cyclopentenone fatty acids like the 12-oxo-10,15-phytodienoic acid (12-oxo-PDA) in plants[1] and preclavulone A in soft corals[2] are the precursors of phytohormones jasmonates and (presumably) the bioactive clavulones, respectively. Their biosynthetic origin was the subject of some ambiguous hypotheses prior to the detection of the real precursors, short-lived allene oxide fatty acids.[3] The formation of vinyl allene oxides occurs via the dehydration of fatty acid hydroperoxides by allene oxide synthase (AOS).[3a,b] Most AOSs belong to the CYP74A subfamily (CYP74 family) of cytochromes P450.[4] Allene oxides undergo spontaneous hydrolysis[3a] or cyclization[5] to racemic cyclopent-2-en-1-ones. Cyclization also occurs enzymatically under the control of allene oxide cyclase (AOC), an enzyme found widespread in plants.[6]

Natural vinyl allene oxides were first isolated from the incubations of fatty acid hydroperoxides with flax AOS (CYP74A1)[3b] and coral *Plexaura homomalla* AOS[3c]; then their methyl esters were purified by HPLC at -15 ºC and their structures were confirmed by low temperature NMR spectroscopy, but no *Z*/*E* assignment of the double bond at the oxirane was made.[3b,c] The *E* geometry was later assigned to this double bond based on nuclear Overhauser effect (NOE) experiments using purified allene oxide (as its methyl ester derivative) prepared with flax AOS, as well as theoretical prediction of NMR spectra.[7]

Unlike CYP74A enzymes, the CYP74C AOSs, which have been characterized in young potato seedlings,[8] potato (StAOS3, CYP74C10)[9] and tomato (LeAOS3),[10] produce a notable amount of cyclopentenone from linoleate hydroperoxides via the allene oxide.[11] Interestingly, it has recently been shown that the allene oxide produced by LeAOS3 is composed of the two *E* and *Z* geometric isomers.[12] Furthermore, the *Z*-vinyl allene oxide, not the *E* counterpart, spontaneously produced a *cis*-cyclopentenone upon standing at ambient temperature in hexane. A stepwise mechanism involving ring opening of the *Z*-vinyl allene oxide to the oxidopentadienyl zwitterion intermediate (Scheme 1, in brackets) followed by its $4\pi e^-$-electrocyclic (conrotatory) ring closure[13] was proposed to account for the overall skeletal transformation.[12] This proposal, however, does not explain the partial transfer of chirality experimentally observed when the isolated *Z*-vinyl allene oxide from 9*S*-HPODE derivatized as methyl ester was allowed to stand in hexane-^{i}PrOH HPLC solvent (Scheme 1).[12] Since the oxidopentadienyl zwitterion is planar, no transfer of stereochemical information from the enantiopure 9*S*-HPODE would be possible in the absence of enzyme, as both enantiomorphic conrotations available to this formal iso-Nazarov reaction[14] would be equally probable.



Scheme 1. Formation of the vinyl allene oxide geometric isomers derived from 9*S*-HPODE by the action of CYP74C3 AOS and their reactivity in solution.[12]

All these puzzling observations prompted us to computationally address the mechanistic pathways for the rearrangement of a *Z*-vinyl allene oxide model system to the corresponding cyclopent-2-en-1-one as well as the *E* isomer, which was revisited to allow comparison with our previous work.[15] In agreement with the seminal studies by Hess and coworkers using (U)B3LYP DFT calculations at the 6-31G*

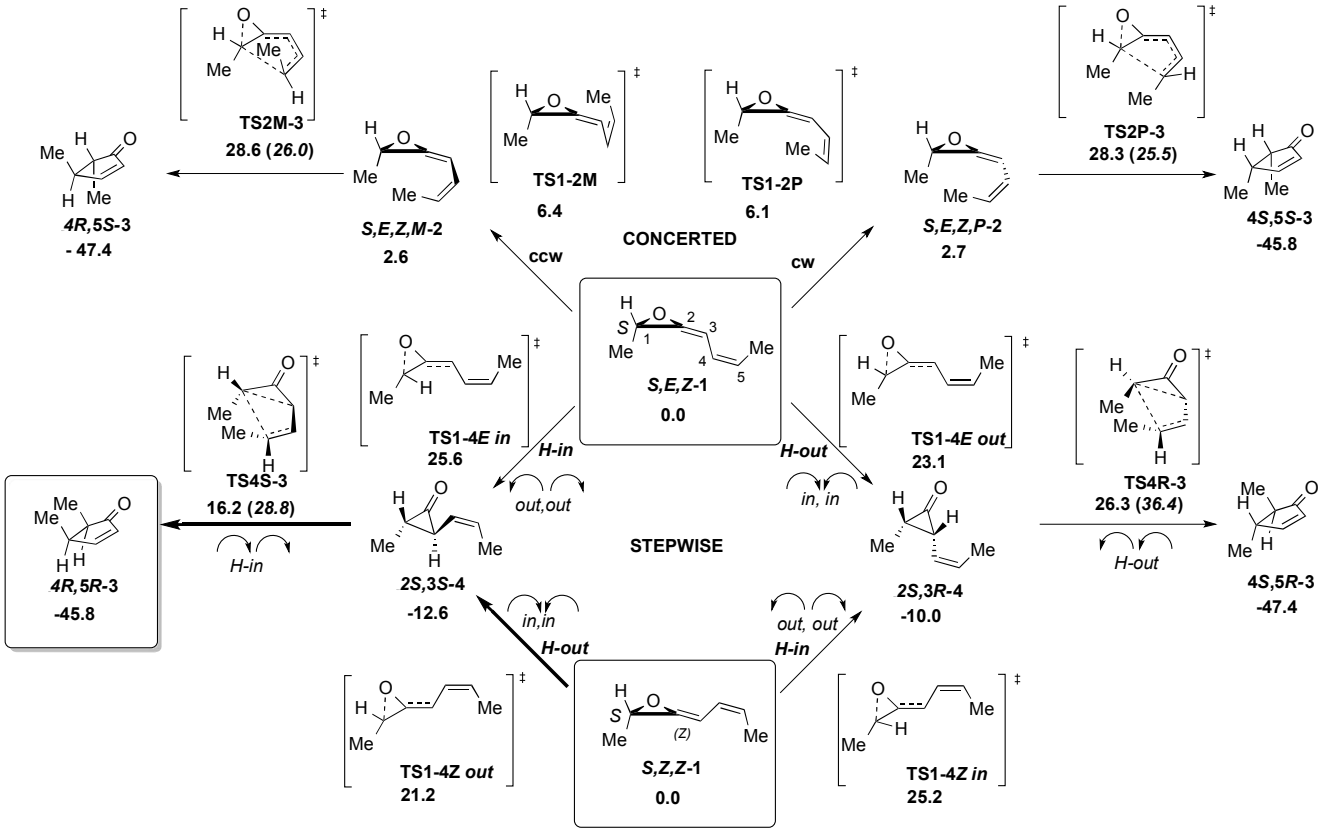
level,[16] we have shown at the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) level that two alternative mechanisms, termed concerted and stepwise, can enter into competition in the rearrangement of parent unsubstituted vinyl allene oxide and also of substituted (*Z*)-prop-1-en-1-yl allene oxide. Whereas in the parent system the concerted S_N2-like ring closure/ring opening reaction of the *s-cis* conformer of the reactant was computed to be preferred over the alternative ring-opening to oxidopentadienyl zwitterion followed by conrotatory electrocyclic ring closure sequence, the latter became more favorable upon increasing the steric interactions of the substituents at the termini. The stepwise pathway was characterized as having biradical/zwitterionic nature.[15] In the present work, we will take into account dispersion effects using the ω-B97XD functional[17] in order to evaluate the role of these interactions on the nature of the species involved in the process.

Methods

All calculations were carried out with the Gaussian 09 suite of programs.[18] Each geometry was optimized at the ω-B97XD/6-31++G(d,p) level.[19] Minima and transition states were individually characterized by the analysis of the number of negative frequencies. Zero-point vibration energies (ZPVE) and thermal corrections (at 298 K, 1 atm) to the energy have been estimated using the computed frequencies applying the free particle, harmonic oscillator and rigid rotor approximations at the high temperature limit in a canonical ensemble. Single-point energy calculations were carried out on the optimized structures taking into account the solvation effects by the Polarizable Continuum Model (PCM)[20] using the UAKS radii for the atoms immersed in water solvent. Furthermore, the basis set was augmented to triple-ζ, thus ω-B97XD/6-311++G(3df,2p), in order to obtain more accurate energy values.[21] The mass-weighted intrinsic reaction coordinate (IRC)[22] was followed from every transition structure (TS) to connect minima and the corresponding TS. Representations were created with CYLview[23a] and ChemCraft.[23b]

Results and discussion

Substituted vinyl allene oxides can have up to three stereogenic units: the C_{sp3} chiral center at one terminus and the double bonds of both the allene oxide and the alkenyl group in conjugation. Thus, we computed the pathways for the rearrangement of model system (*S,E*)-2-[(*Z*)-but-2-en-1-ylidene]-3-methyloxirane and its isomer (*S,Z*)-2-[(*Z*)-but-2-en-1-ylidene]-3-methyloxirane, denoted hereafter as *S,E,Z*-**1** and *S,Z,Z*-**1**, which differ in the geometry of the allene oxide and have in common the *S* configuration presumably obtained from 9*S*-HPODE and the *Z* geometry of the conjugated olefin. Similarly to previous studies,[15,16] we were able to characterize two possible reaction paths, denoted as concerted (**1** → **2** → **3**) and stepwise (**1** → **4** → **3**) in Scheme 2, to 4,5-dimethylcyclopent-2-en-1-one **3**.



Scheme 2. Concerted and stepwise pathways for the rearrangement of vinyl allene oxides *S,E,Z*-**1** and *S,Z,Z*-**1** computed at the ω-B97XD/6-311++G(3df,2p)(PCM,H_2O)// ω-B97XD/6-31++G(d,p) level. Total and relative energies (in parenthesis) are given in kcal/mol. Starting from the *S* enantiomers of **1**, the *R*/*S* configuration at C5 of cyclopentenone **3** is determined by the occurrence of the stepwise (5*R*) or concerted (5*S*) mechanisms, whereas the *R*/*S* configuration at C4 of **3** is dictated by the helicity of the s-*cis* reactant **2** or the transition state **TS4-3**, with *P* giving 4*S* and *M* producing 4*R*. Starting from the *R* enantiomers of **1**, the stereochemical outcome is the opposite (results not shown).

The concerted pathway, which is only feasible for the *E* isomer of the allene oxide, can be visualized as a backside attack of the olefin onto the C_{sp3} terminus of the opening oxirane and shows features of an S_N2 displacement.[16,24] The parent all-carbon system has been previously characterized as an *antara,antara* $[1,5]_{CH2}$ sigmatropic rearrangement.[16b] To reach the proper geometry, the reactant requires a prior conformational change from the s-*trans* to the s-*cis* conformer, the latter denoted as **2**. This change can take place following clockwise (cw) and counterclokwise (ccw) movements through **TS1-2P** and **TS1-2M**, respectively, and generate an additional stereogenic element indicated with the *P* and *M* descriptors of helicity. Both the change of conformation to the two diastereomeric helical structures *S,E,Z,P*-**2** and *S,E,Z,M*-**2** (activation energies of about 6.0 kcal/mol) and their ensuing rearrangement via **TS2P-3** and **TS2M-3** (activation energies of about 28.5 kcal/mol) are virtually isoenergetic. These sequences lead to diastereomers of the product, namely *cis*-4*S*,5*S*-**3** or *trans*-4*R*,5*S*-**3** starting from the *P* or *M* helical conformations. **TS2P-3** and **TS2M-3** preserve some features of the precursor helicity as shown by the ca. 40º dihedral angle of the alkene relative to the plane of the opening oxirane (Table 1). The ring closure proceeds through an apparent conrotatory motion of the termini, which are placed 2.83 Å and 2.61 Å apart, respectively, in the transition structures (Table 1). Nucleus independent chemical shifts (NICS) values for these TSs are close to -12 ppm, thus indicating aromatic character (see S.I.).[25,16b]

	d_{C1-C2} (Å)	d_{C2-C3} (Å)	d_{C1-C3} (Å)	d_{C3-C4} (Å)	d_{C4-C5} (Å)	d_{C5-C1} (Å)	d_{C1-O1} (Å)	d_{C2-O1} (Å)	$\theta_{C1-C2-C3-C4}$ (degrees)	$\theta_{C2-C3-C4-c5}$ (degrees)
2*S*,3*R*-4	1.47	1.48	1.59	1.49	1.34			1.20	107.4	53.1
2*S*,3*S*-4	1.46	1.48	1.58	1.48	1.34			1.20	-107.5	-148.6
4*R*,5*R*-3	1.53	1.48		1.34	1.51	**1.55**		1.21	-6.9	-1.6
4*R*,5*S*-3	1.53	1.48		1.34	1.51	**1.54**		1.21	5.8	0.1
4*S*,5*R*-3	1.53	1.48		1.34	1.51	**1.54**		1.21	-5.8	-0.1
4*S*,5*S*-3	1.53	1.48		1.34	1.51	**1.55**		1.21	6.9	1.6
***S,E,Z*-1**	1.44	1.33		1.46	1.34		1.48	1.35	-3.0	179.7
***S,E,Z,M*-2**	1.43	1.33		1.47	1.34		1.48	1.35	-8.1	-33.1
***S,E,Z,P*-2**	1.44	1.33		1.47	1.34		1.47	1.35	5.7	33.2
***S,Z,Z*-1**	1.43	1.33		1.46	1.34		1.48	1.35	176.7	-179.3
TS1-2*M*	1.44	1.32		1.49	1.34		1.48	1.36	-0.8	-99.9
TS1-2*P*	1.44	1.32		1.49	1.34		1.48	1.35	-4.9	101.7
TS1-4*E*_in	1.44	1.39	**2.52**	1.44	1.35		2.15	1.28	9.1	176.7
TS1-4*E*_out	1.44	1.37	**2.51**	1.44	1.35		2.10	1.28	-4.7	179.7
TS1-4*Z*_in	1.43	1.37	**2.51**	1.44	1.35		2.08	1.28	174.2	178.3
TS1-4*Z*_out	1.43	1.39	**2.51**	1.44	1.35		2.09	1.28	-175.2	-177.8
TS2*M*-3	1.45	1.37	2.48	1.43	1.37	**2.61**	2.05	1.27	-5.5	**-39.2**
TS2*P*-3	1.45	1.37	2.49	1.44	1.36	**2.83**	2.07	1.28	4.0	**44.1**
TS4*R*-3	1.44	1.45	2.42	1.39	1.39	**2.83**	2.35	1.25	50.9	22.5
TS4*S*-3	1.44	1.45	2.37	1.40	1.38	**2.85**	2.37	1.25	-43.2	-23.1

Table 1. Relevant geometric parameters, bond distances (in Å) and dihedral angles (in degrees), corresponding to the structures shown on Scheme 2 (numbering of atoms is indicated in structure *S,E,Z*-1) computed at the ω-B97XD/6-311++G(3df,2p)(PCM,H_2O)//ω-B97XD/6-31++G(d,p) level.

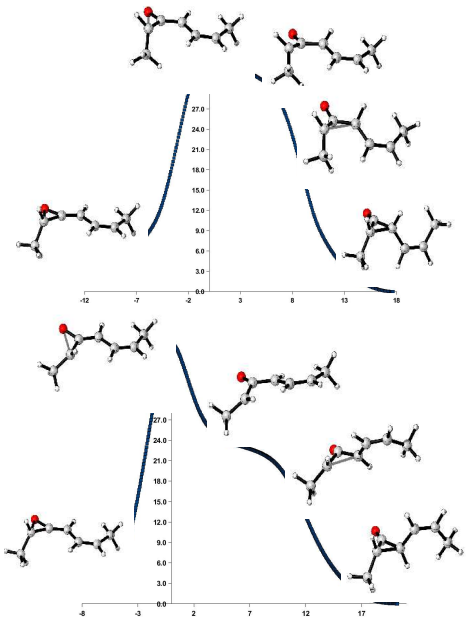
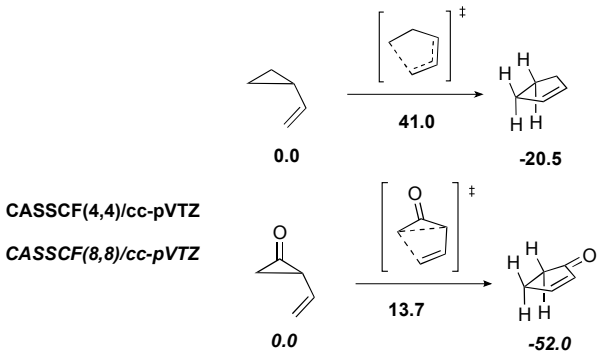


Figure 1. Representation of the IRC for the stepwise rearrangement of vinyl allene oxide S,*E,Z*-**1** to diastereomeric cyclopropanones **4** through transition structures **TS1-4E out** (top) and **TS1-4E in** (bottom) computed at the ω-B97XD/6-31++G(d,p) level. Electronic energies are given in kcal/mol.

The stepwise alternative starts with the opening of the oxirane and concomitant rotation of the terminal C_{sp3} atom. Depending upon the direction of twist, the C2-H can be placed either outside towards the oxygen atom or inside towards the diene, and these alternatives are labeled as H-out and H-in, respectively, in Scheme 2. In contrast to previous studies,[15,16] the intermediate formed is not an oxidopentadienyl zwitterion but a vinylcyclopropanone **4**. The formation of this intermediate is possible because the termini of the allene oxide that undergo first an apparent conrotatory motion move in a disrotatory manner before the HC-C(O)-C-C=C fragment reaches a planar structure. **TS1-4E in** evolves by *out,out* disrotation and leads to *trans*-2*S*,3*S*-**4** whereas **TS1-4E out** follows opposite disrotatory *in,in* motions and affords *cis*-2*S*,3*R*-**4** (see Figure 1).

Hess *et al*. characterized an oxyallyl zwitterion as intermediate in the rearrangement of parent unsubstituted allene oxide to cyclopropanone at the UB3LYP/6-31G* and CASSCF(4,4)/6-31G* levels.[26] The parent oxyallyl was proposed to have a diradical character based on negative ion photoelectron microscopy measurements and computational studies, which also predicted a barrierless ring closure to cyclopropanone.[27] However, we could not attribute radical character to the TSs leading to the vinylcyclopropanone **4** [at the (U)MP2/cc-pVDZ and (U)ω-B97XD/6-31++G(d,p) levels)], and we determined that the wavefunction of these species is stable in all the stationary points characterized along the potential energy surface for the rearrangement of vinyl allene oxide. It appears that the presence of the additional substituents drives the conversion of the vinyl allene oxide to the cyclopentenone via the vinylcyclopropanone through closed-shell structures.

Vinyl cyclopropanone **4** evolves to cyclopentenone **3** (for previous reports on this rearrangement, see[28]) through **TS4-3**, which is another helically chiral structure. The rearrangement of cyclopropanone **4** occurs torquoselectively,[29] since *trans*-2*S*,3*S*-**4** generates *cis*-4*R*,5*R*-**3**, whereas *cis*-2*S*,3*R*-**4** affords the diastereomeric product *trans*-4*S*,5*R*-**3**. This process is the *oxo* variant of the classical [1,3]-C sigmatropic rearrangement.[30] [1,3]-C Sigmatropic shifts are known to give preferentially the *si* (suprafacial inversion) product with inversion of the C_{sp3} atom and at least for the parent system they proceed through diradical intermediates.[31] In general, vinylcyclopropane—cyclopentene rearrangements have activation energies above 45 kcal/mol.[31] For the parent system a value of 42.5 kcal/mol has been calculated at the CASSCF(4,4)/6-31G* level of theory,[32] and we have computed a value of 41.0 kcal/mol (Scheme 3) using CASSCF(4,4)/cc-pVTZ. Incorporation of the carbonyl group lowers considerably the energy of activation for the process. We have computed for this sigmatropic shift activation energies of 13.7 kcal/mol using CASSCF(8,8)/cc-pVTZ (Scheme 3) but 29.9 kcal/mol at the ω-B97XD/6-31++G(d,p) level (cf. with substituents, 28.8 kcal/mol for **TS4S-3** and 36.4 kcal/mol for **TS4R-3** at the ω-B97XD/6-311++G(3df,2p) level). Also the presence of the oxygen likely modifies the nature of the intermediate species. We checked that the wavefunction of these species is stable in all the stationary points characterized along the potential energy surface for the rearrangement. As a variant of the classical $4\pi e^-$ electrocyclic process, the reaction proceeds by a conrotatory motions of the termini (placed 2.83 Å apart) of the *M* or *P* helices, denoted as H-in and H-out, respectively, for **TS4S-3** and **TS4R-3** (Scheme 2). Nucleus independent chemical shifts (NICS) values for these TSs vary between -8 and -11 ppm, thus indicating aromatic character (see S.I.).[25]



Scheme 3. Energy values (in kcal/mol) for the parent rearrangements: vinylcyclopropane to cyclopentene and vinylcyclopropanone to cyclopentenone.

Comparison of the activation energy values shown in Scheme 2 for the rearrangement of the *E* vinyl allene oxide *S,E,Z*-**1** suggests that the stepwise is the preferred mechanism, being the values for the concerted alternative (regardless of the diastereomer of **3** formed) from 3 to 5 kcal/mol higher. For the stepwise rearrangement of *S,E,Z*-**1**, the ring opening with H-in motion requires a higher energy (25.6 kcal/mol) than the H-out counterpart (23.1 kcal/mol). Conversely, the rearrangement of *trans*-**4** to *cis*-**3** is favored (28.8 kcal/mol) over that of the diastereomer *cis*-**4** (36.4 kcal/mol) to the *trans*-**3** cyclopentenone. The significant difference in activation energies for the

diastereomers regarding the second step could be related to the steric effects and to the degree of transition state development, with **TS4R-3** from *cis*-**4** being more retarded (C-C bond cleavage of 2.42 Å) than **TS4S-3** from *trans*-**4** (C-C bond cleavage of 2.37 Å). Orbital analysis indicates that the HOMO of **TS4S-3** has certain π-like symmetry, and the formation of the σ-bond of the cyclopentenone benefits from assistance of the backbone π-like orbital residing in almost the same plane as the breaking cyclopropanone σ-bond. In **TS4R-3** this π-like-symmetry is broken since the orbitals associated to σ-bond breaking and σ-bond formation are extended in almost perpendicular regions, with weaker electron donation and TS destabilization (Figure 2).

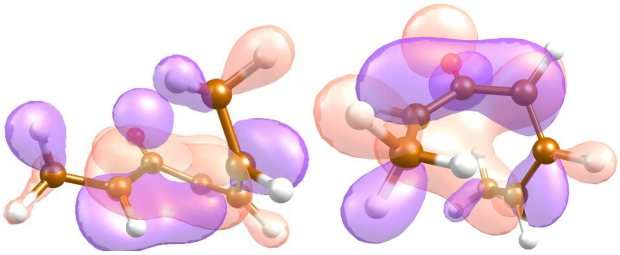


Figure 2. Representation of the HOMO orbitals for **TS4S-3** (left) and **TS4R-3** (right). An animated gif movie can be found as S.I.

Of note the products of the concerted manifold are the enantiomers of those generated in the stepwise alternative: H-out and ccw gives the *trans*-**3** enantiomers and H-in and cw generates the *cis*-**3** enantiomers. The rate-determining steps for oxirane opening/ring closure for H-in and *out,out* disrotation en route to *cis*-4*R*,5*R*-**3** and the vinylcyclopropanone-cyclopentenone rearrangement to *trans*-4*S*,5*R*-**3** for H-out and *in,in* motion differ by only 0.7 kcal/mol (25.6 kcal/mol and 26.3 kcal/mol, respectively). The relatively small difference in activation energies among these alternatives suggest that the transfer of stereochemical information might be compromised in the real setting, and that mixtures of cyclopentenones **4** could be obtained from the rearrangement of vinyl allene oxides represented by *S,E,Z*-**1**.

Due to geometric constraints the rearrangement of vinyl allene oxide *S,Z,Z*-**1** with Z geometries can only occur stepwise. Interestingly, when the oxirane ring of *S,Z,Z*-**1** opens by H-out movement through **TS1-4Z out**, located 21.2 kcal/mol above the reactant, it collapses by an apparent disrotatory movement (*in,in*) to cyclopropanone *trans*-**4** of 2*S*,3*S* absolute configuration. This is the same product that results from the opposite movement (*out,out*) of the termini in **TS1-4E in** starting from diastereomer *S,E,Z*-**1** discussed above (25.6 kcal/mol). Conversely, the evolution of *S,Z,Z*-**1** through **TS1-4Z in** (25.2 kcal/mol) by *out,out* disrotatory movement produces cyclopropanone *cis*-2*S*,3*R*-**4**, the same enantiomer obtained from the *S,E,Z*-**1** geometric isomer of the reactant (23.1 kcal/mol) through **TS1-4E out** and *in,in* disrotation. Thus, the formation of the vinylcyclopropanone **4** is stereoconvergent if both rotations (ring opening and subsequent closure) of the termini of vinyl allene oxide geometric isomers take place in opposite directions. This stereochemical feature is general in this system: a change in one of the stereochemical elements of the allene oxide (chirality center, double bond or helicity of the s-*cis* conformer) causes the inversion of a chiral center of the vinylcyclopropanone, whereas two changes lead to the same enantiomer by double inversion, as indicated in Scheme 2.

Evaluation of the energy landscape shown in Scheme 2 indicates that the H-out direction of oxirane ring opening requires lower energy than the H-in counterpart, and that of *S,Z,Z*-**1** is the more favorable. Therefore, the *Z* vinyl allene oxide is predicted to rearrange to **3** at a greater rate than the corresponding *E* isomer, which is in agreement with the experimental results.[12] Moreover, vinyl allene oxide *S,Z,Z*-**1** is converted into the enantiomer *cis*-4*R*,5*R*-**3** of the cyclopentenone through the intermediacy of cyclopropanone diastereomer *trans*-2*S*,3*S*-**4** (see Figure 3 for the reaction profile). Since the difference in activation energies with respect to the alternative pathway leading to diastereomer *trans*-4*S*,5*R*-**3** amounts to 5.1 kcal/mol, a complete transfer of chirality should be possible in the rearrangement of the *Z* vinyl allene oxide under proper conditions. Chirality transfer processes have been documented in the oxidation of enantiopure vinyl allenes and ensuing rearrangement of the intermediates to the cyclopentenones, although the geometries of the vinyl allene oxides were not characterized.[33] Moreover, Brash and coworkers detected partial chirality transfer (er of 61:39 and 53:47 in the two measurements; no assignment of absolute configuration was carried out) when the *Z* vinyl allene oxide from 9*S*-HPODE was derivatized as methyl ester and allowed to stand in the HPLC solvent.[8]

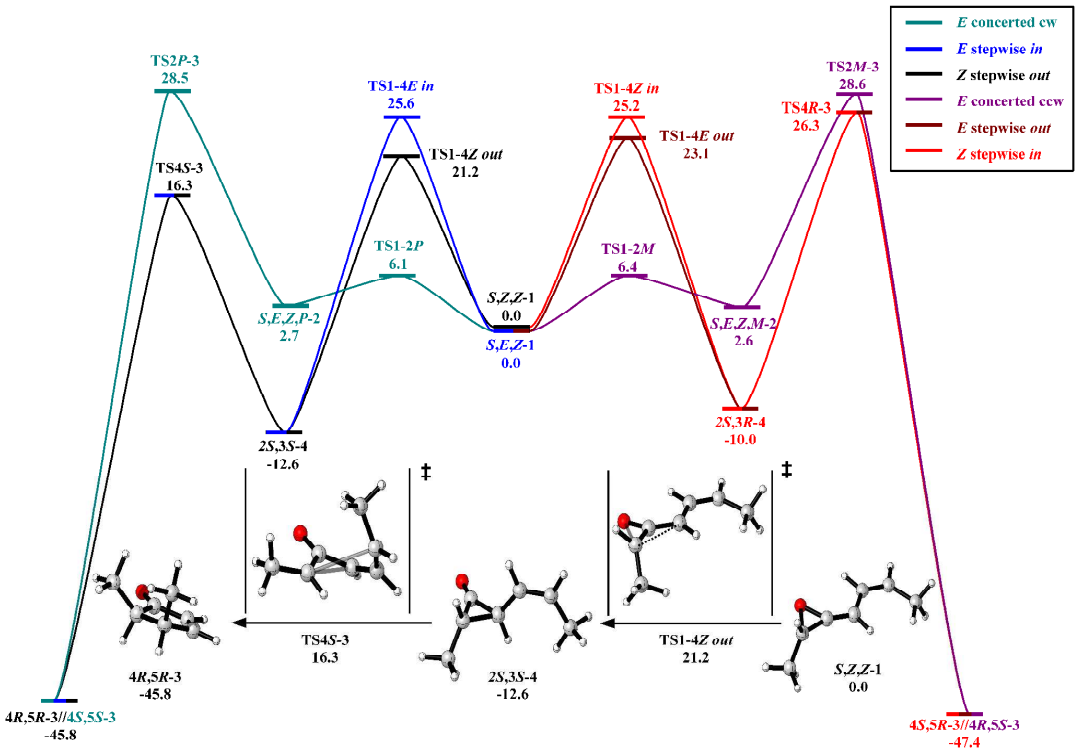
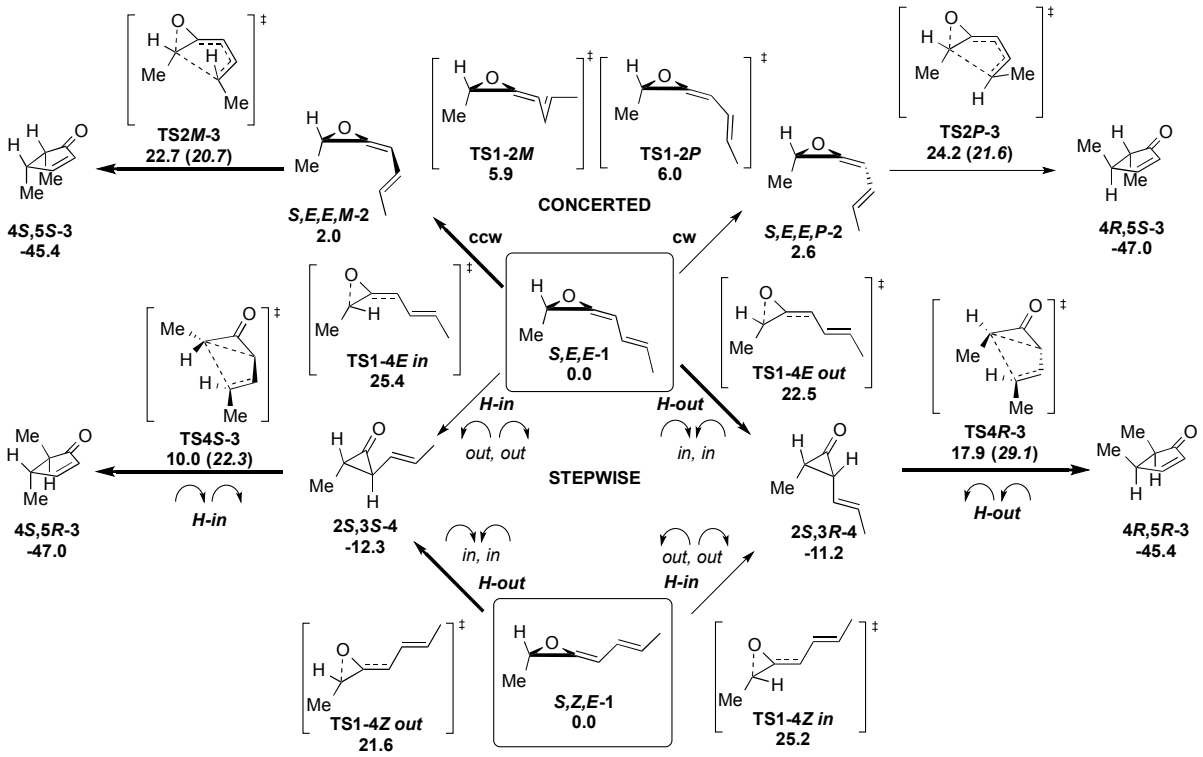


Figure 3. Reaction profile for the rearrangement of (*S,E*)- and (*S,Z*)-2-[(*Z*)-but-2-en-1-ylidene]-3-methyloxirane, *S,E,Z*-**1** and *S,Z,Z*-**1**, respectively. Drawings correspond to the species along the most favored stepwise pathway of *S,Z,Z*-**1**. Energy values (kcal/mol) have been computed at the ω-B97XD/6-311++G(3df,2p)(PCM,H_2O)//ω-B97XD/6-31++G(d,p) level of theory.

To probe that this mechanism is indeed general, we have computed the mechanistic manifold for the geometric isomers of the reactant at the conjugated double bond, namely *S,E,E*-**1** and *S,Z,E*-**1**. Scheme 4 shows a similar scenario comprising concerted and stepwise alternatives for the rearrangement of these geometric isomers. The change in the double bond stereogenic unit is reflected in the inverted configuration at the cyclopentenone C4 chiral center when the reactant evolves following motions similar to those described for *S,E,Z*-**1** and *S,Z,Z*-**1** respectively (Scheme 2). Somehow anticipated, the lowering of the activation energies (between 4 and 6 kcal/mol) relative to those of the terminal *Z* isomers indicates the reduced steric interactions in the transition states of the concerted pathway. This effect is also noted in the vinylcyclopropanone-to-cyclopentenone rearrangement of the stepwise alternative. For *S,E,E*-**1** the two most favored branches of the concerted and stepwise alternatives are almost isoenergetic (22.7 and 22.5 kcal/mol, respectively) and lead to enantiomers of the *cis*-**3** product. Thus, the translation of the absolute configuration of the enantiopure reactant *S,E,E*-**1** to the product is unlikely based on these computations. A similar analysis of the energy values for the stepwise mechanistic options of the *S,Z,E*-**1** isomer points to a process with high stereochemical fidelity since this enantiomer would most likely generate *trans*-4*S*,5*R*-**3** (Scheme 4).

Conclusion

The rearrangement of vinyl allene oxide geometric isomers[3c,12] to cyclopentenones,[28b] of relevance for the important jasmonate and clavulone biosynthetic pathways, has been computationally revisited. A stepwise process, with formation of a vinylcyclopropanone intermediate, has been characterized at the ω-B97XD/6-311++G(3df,2p)(PCM,H_2O) level of theory and found to be the preferred pathway for most of the diastereoisomeric vinyl allene oxides. Thus, the *S* enantiomer of *Z* geometry, *S,Z,Z*-**1**, rearranges with high stereochemical fidelity to the *cis*-cyclopentenone **3** of 4*R*,5*R* absolute configuration. This transfer of chirality follows a path involving a rate-determining (21.2 kcal/mol) oxirane ring opening with H-out motion and *in,in* disrotation to the *trans*-vinylcyclopropanone 2*S*,3*S*-**4** followed by a [1,3]-C sigmatropic shift. For the geometric isomer *S,E,Z*-**1** the stepwise mechanism enters into competition with the concerted alternative. In this complex scenario mixtures of the four diastereomers could be experimentally expected. On the other hand, the *cis*-cyclopentenone is also predicted to form starting from the *E* isomer of the vinyl allene oxide *S,E,E*-**1**, but it would be most likely isolated as a racemate given the similar activation energies computed for the stepwise and concerted mechanism leading to 4*R*,5*R*-**3** and 4*S*,5*S*-**3**, respectively. The rearrangement of vinyl allene oxides with the *S,Z,E*-**1** configuration would produce the *trans*-cyclopentenone **3** of 4*S*,5*R* absolute configuration following motions with the same handedness as those of *S,Z,Z*-**1**.



Scheme 4. Reaction profile for the rearrangement of (*S,E*)- and (*S,Z*)-2-[(*Z*)-but-2-en-1-ylidene]-3-methyloxirane, *S,E,Z*-**1** and *S,Z,Z*-**1**, respectively. Drawings correspond to the species along the most favored stepwise pathway of *S,Z,Z*-**1**. Energy values (kcal/mol) have been computed at the ω-B97XD/6-311++G(3df,2p)(PCM,H_2O)//ω-B97XD/6-31++G(d,p) level of theory.

This unifying mechanism is consistent with the following experimental observations related to vinyl allene oxides derived from unsaturated fatty acid hydroperoxides: 1) the cyclopentenone is formed more rapidly from the isolated *Z* vinyl allene oxide than from the *E* isomer, as shown;[12] 2) *cis*-cyclopentenones are the primary products (except for systems having the yet undescribed *S,Z,E*-**1** configuration) under conditions that prevent epimerization at C5;[12] 3) the rearrangement of enantiopure vinyl allene oxides of *S,Z,Z* (like the one from γ-linolenic acid 9-hydroperoxides)[12] and *S,Z,E* configurations could take place with memory of chirality and afford enantioenriched products; this effect is unlikely for vinyl allene oxides with *S,E,E* configuration (in the experimental setting, also for those with *S,E,Z* configuration) due to the small energy difference between the stepwise and concerted options;[3b,c] 4) Favorskii-type by-products derived from the cyclopropanone intermediate could be formed; these secondary products have been indeed isolated upon incubation of α- and γ-linolenic acid 13- and 9-hydroperoxides (respectively) with AOSs.[34]

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† Electronic Supplementary Information (ESI) available: ESI contains the representation of the NICS, gif movies and the Cartesian coordinates for all the species described in the text. See DOI:

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