

Epoxidation of bromoallenes connects red algae metabolites by an intersecting bromoallene oxide – Favorskii manifold†

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DMDO epoxidation of bromoallenes gives directly α,β -unsaturated carboxylic acids under the reaction conditions. Calculated (ω B97XD/6-311G(d,p)/SCRF = acetone) potential energy surfaces and ^2H - and ^{13}C -labeling experiments are consistent with bromoallene oxide intermediates which spontaneously rearrange via a bromocyclopropanone in an intersecting bromoallene oxide – Favorskii manifold.

The remarkably wide structural diversity and complexity of halogenated C_{15} acetogenin metabolites isolated from marine red algae of *Laurencia* species¹ continue to stimulate innovative efforts in their target synthesis,² in the discovery of new synthetic transformations³ and in advancing biosynthetic hypotheses.⁴ A recent re-isolation⁵ of obtusallene IV (1)⁶ from *Laurencia marilzae* provided also 12-epoxyobtusallene IV (2) and unnamed α,β -unsaturated carboxylate ester (3) with an identical macrocycle to epoxybromoallene 2 (Fig. 1). It seems reasonable to connect *E*-alkene 1 and *trans*-epoxide 2 biogenetically via enzymatic epoxidation,⁷ and on the basis of their co-isolation, we propose

that bromoallene 2 and α,β -unsaturated carboxylate 3 may also be connected biogenetically by epoxidation.

While the epoxidation of allenes^{8,9} and vinyl bromides¹⁰ has been studied, the epoxidation of bromoallenes has not been reported.¹¹ Herein, we report the hitherto unknown direct conversion of bromoallenes to α,β -unsaturated carboxylic acids via an initial epoxidation event and the presumed intermediacy of a bromoallene oxide. We also show by computational modeling and ^2H - and ^{13}C -labeling studies that the latter's spontaneous reorganization to an α,β -unsaturated carboxylic acid under the reaction conditions is consistent with a bromocyclopropanone intermediate in an intersecting allene oxide – Favorskii manifold.

Bromoallene 4¹² was selected as a suitable substrate for investigating epoxidation and was synthesized by a standard sequence from heptanal (ESI†).¹³ Much to our delight, epoxidation of bromoallene 4 using dimethyl dioxirane (DMDO), generated either *in situ*¹⁴ or as a solution (ESI†)¹⁵ (Scheme 1), gave a mixture of *Z* and *E*- α,β -unsaturated carboxylic acids 5 directly in low but reproducible yields (note §, ESI†). The low yields can be attributed to decomposition of DMDO^{16a} under the reaction conditions to methyl radicals,^{16b} and subsequent radical attack on either of the products or starting materials (note ¶, ESI†).

Mechanistically, we invoke the following pathway for the formation of α,β -unsaturated carboxylic acids from DMDO mediated epoxidation of bromoallenes (Fig. 2). Initial epoxidation of the bromoallene would give bromoallene oxides of the type A and/or B (note ¥, ESI†). Spontaneous epoxide opening^{8c} via bromo oxallyl cations C and D (note ††, ESI†) respectively converge on the same bromocyclopropanone E. This intermediate now intersects with the Favorskii rearrangement manifold of α,α' - and α,α' -dibromoketones where the resulting bromocyclopropanones E are known to collapse after attack by water giving hydrate F to α,β -unsaturated carboxylic acids 5 (note **, ESI†).^{17,18} Evidently, there is sufficient water in the dioxirane solution to function as a nucleophile here (note ††, ESI†).

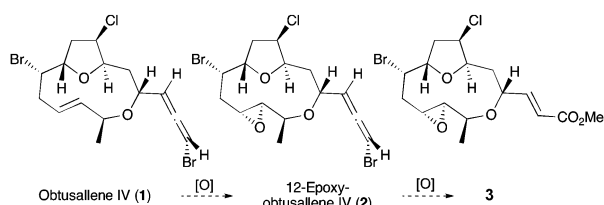
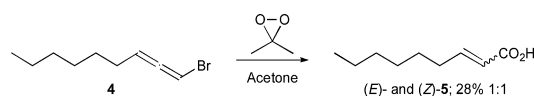


Fig. 1 Metabolites 1–3 from *Laurencia marilzae* and proposed biogenesis via epoxidation events.

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† Electronic supplementary information (ESI) available: Notes §, ¶, ¥, ††, **, ††, §§, ¶¶, ¥¥, †††, ***, †††; general experimental; experimental details and characterising data for compounds leading to bromoallenes 4 (including ESI Scheme S1 for the synthesis of bromoallenes 4), (1- ^2H)-4 and (1- ^{13}C)-4 and epoxidation thereof leading to *E*- and *Z*-5, (*E*-2- ^2H)- and (*Z*-2- ^2H)-5, and (*E*-2- ^{13}C)- and (*Z*-2- ^{13}C)-5; Copies of ^1H and ^{13}C spectra for all compounds showing ^2H and ^{13}C isotopic shifts and coupling constants where appropriate; ESI references. See DOI: 10.1039/c3cc46720a



Scheme 1 Epoxidation of bromoallene 4 using DMDO solution.



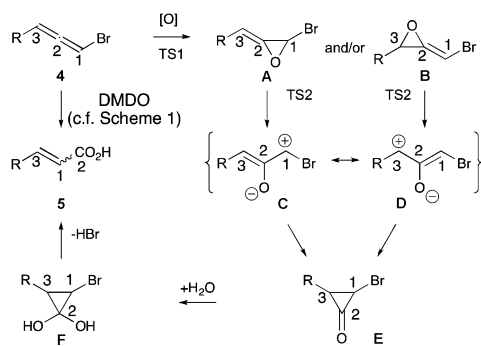
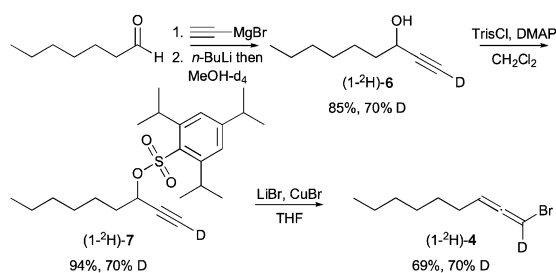


Fig. 2 Mechanistic rationale for conversion of bromoallenes into α,β -unsaturated carboxylic acids, with the carbon atoms of the functional groups numbered 1–3 showing an interchange of carbon atoms 1 and 2 (see also interactive Fig. 2 in HTML version of this article).

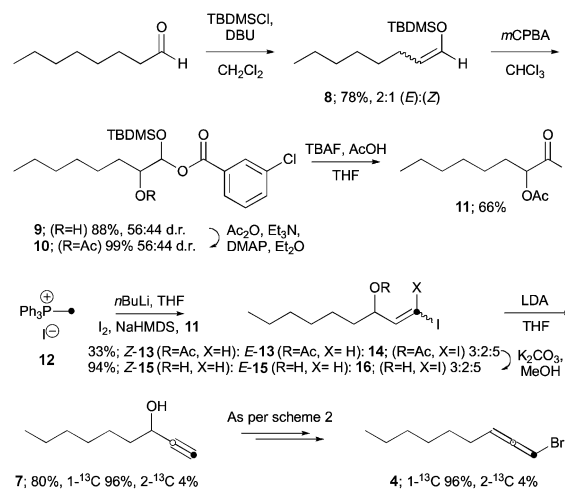
Interestingly, regardless of the initial site of epoxidation, this mechanism predicts that carbon atoms 1 and 2 in bromoallene **4** interchange positions in the α,β -unsaturated carboxylic acid products **5**.

This mechanism can be subjected to scrutiny *via* density functional level (ω B97XD/6-311G(d,p)/SCRF = acetone)¹⁹ exploration of the potential energy surface (R = H, Me, presented as an interactive version of Fig. 2 (ref. 20) *via* a digital data repository²¹). Oxygen transfer from dimethyldioxirane to form both **A** and **B** (TS1) have thermally accessible free energy activation barriers ΔG_{298}^\ddagger (R = H, 26.8 for **A**, 27.3 for **B**; R = Me, 26.8 for **A**, 24.6 kcal mol⁻¹ for **B**), followed by a second, lower energy dyotropic rearrangement (TS2) to give **E**. An intrinsic reaction coordinate (IRC) reveals that TS2 (R = H, Me) represents the concerted transformation of **A** or **B** to **E**, with **C/D** acting as “hidden intermediates” in the process.²² Such hidden intermediates can be potentially transformed to *real* ones by tuning the substituents, and in this instance changing R from H or Me to OMe is predicted to accomplish this by stabilization of **C/D** (see interactive Fig. 2). TS2 itself (R = Me) has some early character of **C/D**; the C–Br bond is calculated to initially contract in length due to a significant stabilising resonance contribution of Br lone pairs, from 1.924/1.896 Å (**A** and **B** respectively) *via* 1.840/1.885 (TS2), 1.856/1.868 (**C/D** acting as hidden intermediates) to 1.921/1.922 Å (**E**).²³ Calculations having demonstrated the thermal accessibility of the epoxidation-bromocyclopropanone sequence,^{2H- and ¹³C-labeling experiments were necessary to verify the overall reorganization (**4** to **A/B** to **E** to **F** to **5**, Fig. 2) of the carbon framework.²⁴}

Deuterated bromoallene (**1**-²H)-**4** was prepared by addition of ethynylmagnesium bromide to heptanal, *in situ* deprotonation of the propargylic alkoxide with *n*-butyllithium and quenching with



Scheme 2 Synthesis of deuterated bromoallene (**1**-²H)-**4**.



Scheme 3 Synthesis of ¹³C-labeled bromoallene (**1**-¹³C)-**4**.

MeOH-*d*₄ to give labeled propargylic alcohol (**1**-²H)-**6** (Scheme 2). Subsequent alcohol trisylation²⁵ gave (**1**-²H)-**7**, and *S_N2'* displacement of the trisylate with bromide under the action of LiCuBr₂ (ref. 26) provided bromoallene (**1**-²H)-**4** with 70% deuterium incorporation at the 1-position.†

¹³C-labeled bromoallene (**1**-¹³C)-**4** was similarly targeted, commencing with silyl enol ether **8** formation²⁷ from octanal (Scheme 3). Oxidation using *m*CPBA gave interrupted Rubottom²⁸ adduct **9**, which could be acetylated to give acetate **10**. Desilylation using buffered TBAF²⁹ revealed protected α -hydroxyaldehyde **11**, which we planned to use in a Wittig reaction with a suitably ¹³C-labeled phosphorous ylid. To the best of our knowledge, there is only a single report³⁰ using methyltriphenylphosphonium iodide to generate the Stork–Wittig reagent³¹ using an *in situ* deprotonation–iodination–deprotonation procedure which we adapted using ¹³C-labeled salt **12** – available from relatively inexpensive 99% atom ¹³C-labeled methyl iodide – to give vinyl iodides *Z*-(¹³C)-**13**, *E*-(¹³C)-**13** and diiodide (¹³C)-**14**.³² Acetate deprotection as a mixture gave the corresponding alcohols *Z*-(¹³C)-**15**, *E*-(¹³C)-**15** and (¹³C)-**16** all with 99% ¹³C at the alkene terminus.†

Dehydrohalogenation of *Z*- and *E*-iodides (¹³C)-**15** in the presence of inseparable diiodide (¹³C)-**16** with LDA gave propargylic alcohol (**1**-¹³C)-**7** in good overall yield, with the unprecedented observation that LDA converts vinyl 1,1-diiodides into terminal alkynes also (note §§, ESI†). Interestingly, 4% of the alkyne product was found to be the 2-¹³C isotopomer (ESI†), implicating a 1,1-elimination reaction pathway for diiodide **16**

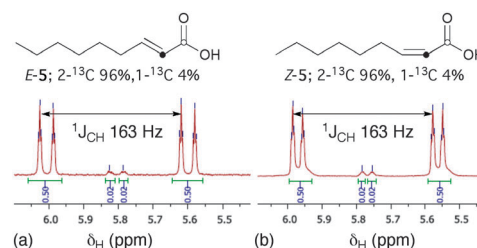
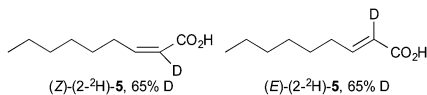


Fig. 3 ¹H NMR spectra of (a) (*E*-2-¹³C)-**5** and (b) (*Z*-2-¹³C)-**5** displaying the expected ¹J_{CH} values for the α -vinyl protons.



and competitive alkyl group migration from a vinylidene intermediate (note ¶¶, ESI†). Alcohol (1-¹³C)-7 was then converted to the desired bromoallene (1-¹³C)-7 (as 4% of its 2-¹³C-isotopomer, ESI†) as previously described (cf., Scheme 2).



With (1-²H)-4 and (1-¹³C)-4 in hand, epoxidation with DMDO was conducted. For deuterated (1-²H)-4, after the reaction was conducted in the usual manner (cf., Scheme 1), *E*-(2-²H)-5 and *Z*-(2-²H)-5 were isolated each showing 65% deuteration at the α -position only (note ‡, ¶¶, ESI†). Evidently, this result is consistent with the proposed mechanism (cf., Fig. 2) (note †††, ESI†). More compellingly, epoxidation of bromoallene (1-¹³C)-4 gave (*E*-2-¹³C)-5³³ and (*Z*-2-¹³C)-5 (28% isolated yield) where carbon atoms 1 and 2 from the bromoallene have entirely interchanged positions, giving also 4% of each of the (*E*-1-¹³C)-5 and (*Z*-1-¹³C)-5 isotopomers (ESI†). The expected ¹J_{CH} coupling constants experienced by the α -vinyl protons of the major isotopomers are clearly apparent in their ¹H NMR spectra (Fig. 3).

In conclusion we have established that the hitherto unknown direct conversion of bromoallenes to α,β -unsaturated carboxylic acids using DMDO is consistent with an initial epoxidation event (note ***, ESI†) followed by a spontaneous reorganization *via* a bromocyclopropanone, a mechanism supported by calculations, in an intersecting bromoallene oxide – Favorskii manifold. These experiments support the proposed biogenesis of α,β -unsaturated carboxylate 3 from bromoallene 2 by epoxidation (note †††, ESI†).

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