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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 2 H- and 13 C-labeling experiments are consistent with bromoallene oxide intermediates which spontaneously rearrange *via* a bromocyclopropane in an intersecting bromoallene oxide – Favorskii manifold†

The remarkably wide structural diversity and complexity of halogenated C₁₅ 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 2 H- 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 oxyallyl 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†).

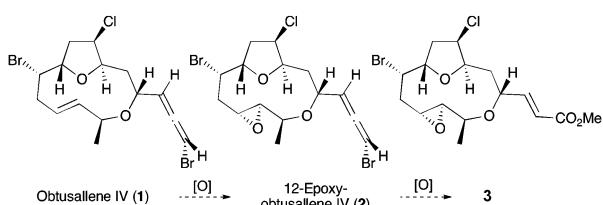


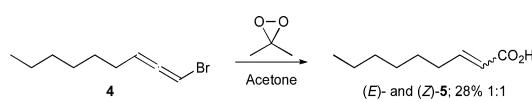
Fig. 1 Metabolites 1–3 from *Laurencia marilzae* and proposed biogenesis *via* epoxidation events.

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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 H)-4 and (¹³ C)-4 and epoxidation thereof leading to *E*- and *Z*-5, (*E*-² H)- and (*Z*-² H)-5, and (*E*-² H -¹³ C)- and (*Z*-² H -¹³ C)-5; Copies of ¹ H and ¹³ C spectra for all compounds showing ² H 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.



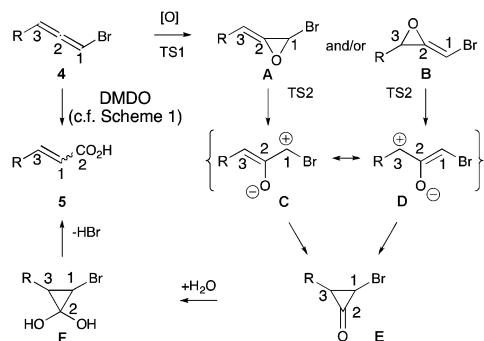
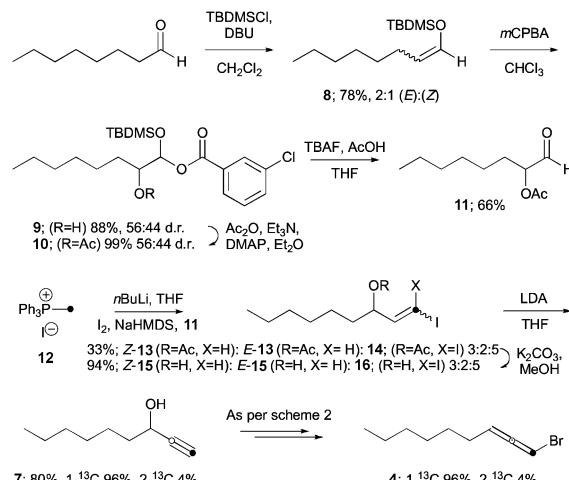


Fig. 2 Mechanistic rationale for conversion of bromoallenes into α,β -unsaturated carboxylic acids, with the carbon atoms of the functional groups numbered 1–3 showing an interchange of carbon atoms 1 and 2 (see also interactive Fig. 2 in HTML version of this article).

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 (¹²H)-4 was prepared by addition of ethynylmagnesium bromide to heptanal, *in situ* deprotonation of the propargylic alkoide with *n*-butyllithium and quenching with

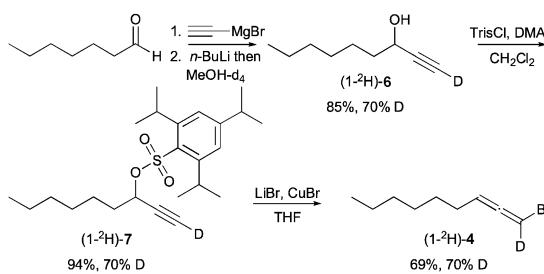


Scheme 3 Synthesis of ¹³C-labeled bromoallene (¹¹³C)-4.

MeOH-d₄ to give labeled propargylic alcohol (¹²H)-6 (Scheme 2). Subsequent alcohol trisylation²⁵ gave (¹²H)-7, and S_N2' displacement of the trisylate with bromide under the action of LiCuBr₂ (ref. 26) provided bromoallene (¹²H)-4 with 70% deuterium incorporation at the 1-position.[†]

¹³C-labeled bromoallene (¹¹³C)-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*(¹¹³C)-13, *E*(¹¹³C)-13 and diiodide (¹¹³C)-14.³² Acetate deprotection as a mixture gave the corresponding alcohols *Z*(¹¹³C)-15, *E*(¹¹³C)-15 and (¹¹³C)-16 all with 99% ¹³C at the alkene terminus.[†]

Dehydrohalogenation of *Z*- and *E*-iodides (¹¹³C)-15 in the presence of inseparable diiodide (¹¹³C)-16 with LDA gave propargylic alcohol (¹¹³C)-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 ²¹³C isotopomer (ESI[†]), implicating a 1,1-elimination reaction pathway for diiodide 16



Scheme 2 Synthesis of deuterated bromoallene (¹²H)-4.

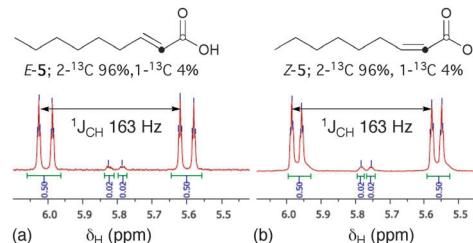
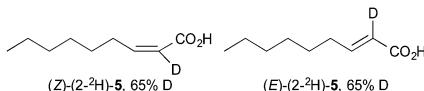


Fig. 3 ¹H NMR spectra of (a) (*E*-2-¹³C)-5 and (b) (*Z*-2-¹³C)-5 displaying the expected $^1J_{CH}$ values for the α -vinyl protons.

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



With (1^{-2}H)-4 and (1^{-13}C)-4 in hand, epoxidation with DMDO was conducted. For deuterated (1^{-2}H)-4, after the reaction was conducted in the usual manner (cf, Scheme 1), E -(2^{-2}H)-5 and Z -(2^{-2}H)-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^{-13}C)-4 gave (E - 2^{-13}C)-5³³ and (Z - 2^{-13}C)-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^{-13}C)-5 and (Z - 1^{-13}C)-5 isotopomers (ESI†). The expected $^1\text{J}_{\text{CH}}$ 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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