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

D. Christopher Braddock,* James Clarke and Henry S. Rzepa

DMDO epoxidation of bromoallenes gives directly α,β-unsaturated carboxylic acids under the reaction conditions. Calculated (ωB97XD/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 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* species[1] continue to stimulate innovative efforts in their target synthesis,[2] in the discovery of new synthetic transformations[3] and in advancing biosynthetic hypotheses.[4] A recent re-isolation[5] 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.

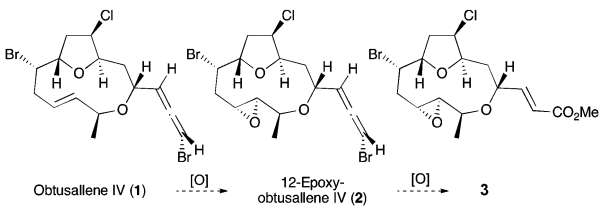
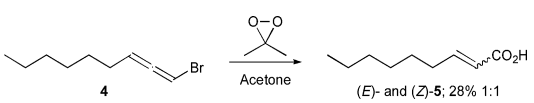


Fig. 1 Metabolites **1–3** from *Laurencia marilzae* and proposed biogenesis *via* epoxidation events.

While the epoxidation of allenes[8,9] and vinyl bromides[10] 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 **4**[12] 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†).



Scheme 1 Epoxidation of bromoallene **4** using DMDO solution.

Department of Chemistry, Imperial College London, London, SW7 2AZ, UK.
E-mail: c.braddock@imperial.ac.uk; Fax: +44 (0)2075945805;
Tel: +44 (0)2075945772

† 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-^{2}H)-**4** and (1-^{13}C-**4**) and epoxidation thereof leading to *E*- and *Z*-**5**, (*E*-2-^{2}H)- and (*Z*-2-^{2}H)-**5**, and (*E*-2-^{13}C)- and (*Z*-2-^{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

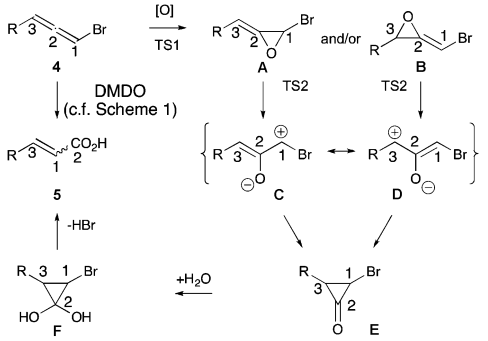
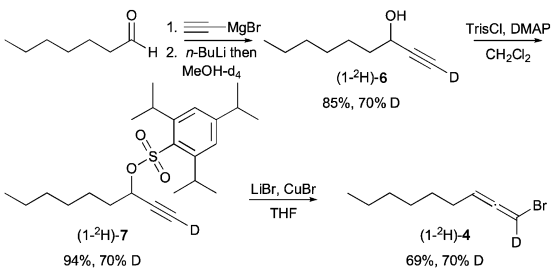


Fig. 2 Mechanistic rationale for conversion of bromoallenes into α,β-unsaturated carboxylic acids, with the carbon atoms of the functional groups numbered 1–3 showing an interchange of carbon atoms 1 and 2 (see also interactive Fig. 2 in HTML version of this article).

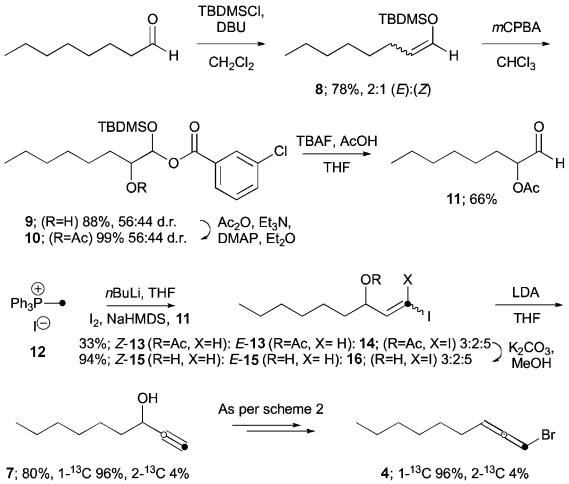
Interestingly, regardless of the initial site of epoxidation, this mechanism predicts that carbon atoms 1 and 2 in bromoallene **4** interchange positions in the α,β-unsaturated carboxylic acid products **5**.

This mechanism can be subjected to scrutiny *via* density functional level (ωB97XD/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 repository[21]). Oxygen transfer from dimethyldioxirane to form both **A** and **B** (TS1) have thermally accessible free energy activation barriers $\Delta G^{\dagger}_{298}$ (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, ^{2}H- and ^{13}C-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-^{2}H)-**4** was prepared by addition of ethynylmagnesium bromide to heptanal, *in situ* deprotonation of the propargylic alkoxide with *n*-butyllithium and quenching with MeOH-d_4 to give labeled propargylic alcohol (1-^{2}H)-**6** (Scheme 2). Subsequent alcohol trisylation[25] gave (1-^{2}H)-**7**, and S_N2' displacement of the trisylate with bromide under the action of $LiCuBr_2$ (ref. 26) provided bromoallene (1-^{2}H)-**4** with 70% deuterium incorporation at the 1-position.†



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



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

^{13}C-labeled bromoallene (1-^{13}C)-**4** was similarly targeted, commencing with silyl enol ether **8** formation[27] from octanal (Scheme 3). Oxidation using *m*CPBA gave interrupted Rubottom[28] adduct **9**, which could be acetylated to give acetate **10**. Desilylation using buffered TBAF[29] revealed protected α-hydroxyaldehyde **11**, which we planned to use in a Wittig reaction with a suitably ^{13}C-labeled phosphorous ylid. To the best of our knowledge, there is only a single report[30] using methyltriphenylphosphonium iodide to generate the Stork–Wittig reagent[31] using an *in situ* deprotonation–iodination–deprotonation procedure which we adapted using ^{13}C-labeled salt **12** – available from relatively inexpensive 99% atom ^{13}C-labeled methyl iodide – to give vinyl iodides *Z*-(1-^{13}C)-**13**, *E*-(1-^{13}C)-**13** and diiodide (1-^{13}C)-**14**.[32] Acetate deprotection as a mixture gave the corresponding alcohols *Z*-(1-^{13}C)-**15**, *E*-(1-^{13}C)-**15** and (1-^{13}C)-**16** all with 99% ^{13}C at the alkene terminus.†

Dehydrohalogenation of *Z*- and *E*-iodides (1-^{13}C)-**15** in the presence of inseparable diiodide (1-^{13}C)-**16** with LDA gave propargylic alcohol (1-^{13}C)-**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-^{13}C isotopomer (ESI†), implicating a 1,1-elimination reaction pathway for diiodide **16**

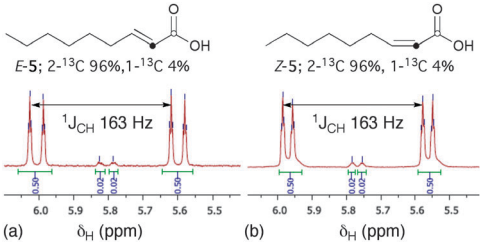
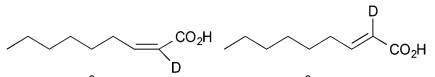


Fig. 3 ^{1}H NMR spectra of (a) (*E*-2-^{13}C)-**5** and (b) (*Z*-2-^{13}C)-**5** displaying the expected $^{1}J_{CH}$ values for the α-vinyl protons.

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)-**5**[33] 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 $^{1}J_{CH}$ coupling constants experienced by the α-vinyl protons of the major isotopomers are clearly apparent in their ^{1}H 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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