

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

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

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

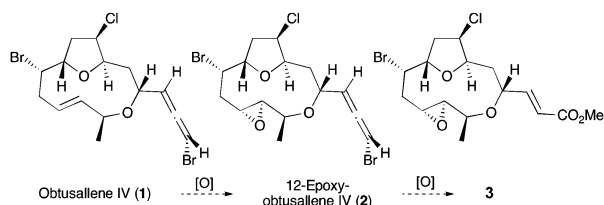
The remarkably wide structural diversity and complexity of halogenated  $\text{C}_{15}$  acetogenin metabolites isolated from marine red algae of *Laurencia* species<sup>1</sup> continue to stimulate innovative efforts in their target synthesis,<sup>2</sup> in the discovery of new synthetic transformations<sup>3</sup> and in advancing biosynthetic hypotheses.<sup>4</sup> A recent re-isolation<sup>5</sup> of obtusallene IV (**1**)<sup>6</sup> from *Laurencia marilzae* provided also 12-epoxyobtusallene IV (**2**) and unnamed  $\alpha,\beta$ -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,<sup>7</sup> and on the basis of their co-isolation, we propose

that bromoallene **2** and  $\alpha,\beta$ -unsaturated carboxylate **3** may also be connected biogenetically by epoxidation.

While the epoxidation of allenes<sup>8,9</sup> and vinyl bromides<sup>10</sup> has been studied, the epoxidation of bromoallenes has not been reported.<sup>11</sup> Herein, we report the hitherto unknown direct conversion of bromoallenes to  $\alpha,\beta$ -unsaturated carboxylic acids via an initial epoxidation event and the presumed intermediacy of a bromoallene oxide. We also show by computational modeling and  $^2\text{H}$ - and  $^{13}\text{C}$ -labeling studies that the latter's spontaneous reorganization to an  $\alpha,\beta$ -unsaturated carboxylic acid under the reaction conditions is consistent with a bromocyclopropanone intermediate in an intersecting allene oxide – Favorskii manifold.

Bromoallene **4**<sup>12</sup> was selected as a suitable substrate for investigating epoxidation and was synthesized by a standard sequence from heptanal (ESI†).<sup>13</sup> Much to our delight, epoxidation of bromoallene **4** using dimethyl dioxirane (DMDO), generated either *in situ*<sup>14</sup> or as a solution (ESI†)<sup>15</sup> (Scheme 1), gave a mixture of *Z* and *E*- $\alpha,\beta$ -unsaturated carboxylic acids **5** directly in low but reproducible yields (note §, ESI†). The low yields can be attributed to decomposition of DMDO<sup>16a</sup> under the reaction conditions to methyl radicals,<sup>16b</sup> and subsequent radical attack on either of the products or starting materials (note ¶, ESI†).

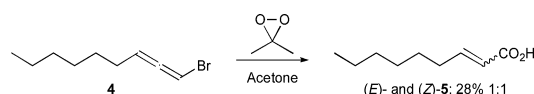
Mechanistically, we invoke the following pathway for the formation of  $\alpha,\beta$ -unsaturated carboxylic acids from DMDO mediated epoxidation of bromoallenes (Fig. 2). Initial epoxidation of the bromoallene would give bromoallene oxides of the type **A** and/or **B** (note ¥, ESI†). Spontaneous epoxide opening<sup>8c</sup> 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  $\alpha,\alpha'$ - and  $\alpha,\alpha'$ -dibromoketones where the resulting bromocyclopropanones **E** are known to collapse after attack by water giving hydrate **F** to  $\alpha,\beta$ -unsaturated carboxylic acids **5** (note \*\*, ESI†).<sup>17,18</sup> 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.

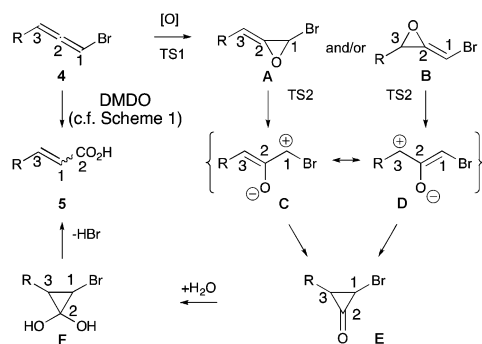
Department of Chemistry, Imperial College London, London, SW7 2AZ, UK.  
E-mail: c.braddock@imperial.ac.uk; Fax: +44 (0)2075945805;  
Tel: +44 (0)2075945772

† 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- $^2\text{H}$ )-**4** and (1- $^{13}\text{C}$ )-**4** and epoxidation thereof leading to *E*- and *Z*-**5**, (*E*-2- $^2\text{H}$ )- and (*Z*-2- $^2\text{H}$ )-**5**, and (*E*-2- $^{13}\text{C}$ )- and (*Z*-2- $^{13}\text{C}$ )-**5**; Copies of  $^1\text{H}$  and  $^{13}\text{C}$  spectra for all compounds showing  $^2\text{H}$  and  $^{13}\text{C}$  isotopic shifts and coupling constants where appropriate; ESI references. See DOI: 10.1039/c3cc46720a



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



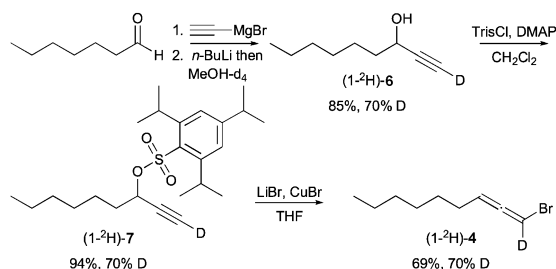


**Fig. 2** Mechanistic rationale for conversion of bromoallenes into  $\alpha,\beta$ -unsaturated carboxylic acids, with the carbon atoms of the functional groups numbered 1–3 showing an interchange of carbon atoms 1 and 2 (see also interactive Fig. 2 in HTML version of this article).

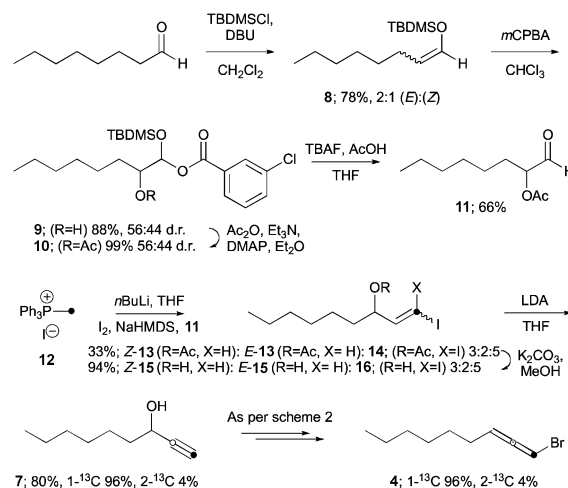
Interestingly, regardless of the initial site of epoxidation, this mechanism predicts that carbon atoms 1 and 2 in bromoallene **4** interchange positions in the  $\alpha,\beta$ -unsaturated carboxylic acid products **5**.

This mechanism can be subjected to scrutiny *via* density functional level ( $\omega$ B97XD/6-311G(d,p)/SCRF = acetone)<sup>19</sup> exploration of the potential energy surface ( $R = H, Me$ , presented as an interactive version of Fig. 2 (ref. 20) *via* a digital data repository<sup>21</sup>). Oxygen transfer from dimethyldioxirane to form both **A** and **B** (TS1) have thermally accessible free energy activation barriers  $\Delta G_{298}^\ddagger$  ( $R = H$ , 26.8 for **A**, 27.3 for **B**;  $R = Me$ , 26.8 for **A**, 24.6 kcal mol<sup>-1</sup> 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.<sup>22</sup> 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**).<sup>23</sup> Calculations having demonstrated the thermal accessibility of the epoxidation-bromocyclopropanone sequence,<sup>2H</sup> and <sup>13</sup>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.<sup>24</sup>

Deuterated bromoallene ( $1\text{-}^2\text{H}$ )-**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 ( $1\text{-}^2\text{H}$ )-**4**.

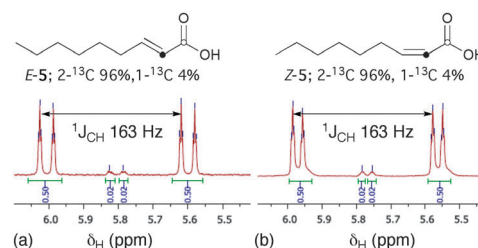


**Scheme 3** Synthesis of <sup>13</sup>C-labeled bromoallene ( $1\text{-}^{13}\text{C}$ )-**4**.

MeOH- $d_4$  to give labeled propargylic alcohol ( $1\text{-}^2\text{H}$ )-**6** (Scheme 2). Subsequent alcohol trisylation<sup>25</sup> gave ( $1\text{-}^2\text{H}$ )-**7**, and  $S_N2'$  displacement of the trisylate with bromide under the action of  $\text{LiCuBr}_2$  (ref. 26) provided bromoallene ( $1\text{-}^2\text{H}$ )-**4** with 70% deuterium incorporation at the 1-position.<sup>†</sup>

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

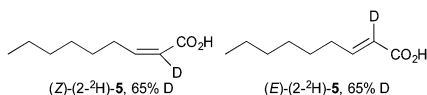
Dehydrohalogenation of *Z*- and *E*-iodides ( $1\text{-}^{13}\text{C}$ )-**15** in the presence of inseparable diiodide ( $1\text{-}^{13}\text{C}$ )-**16** with LDA gave propargylic alcohol ( $1\text{-}^{13}\text{C}$ )-**7** in good overall yield, with the unprecedented observation that LDA converts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



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



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



With (1-<sup>2</sup>H)-4 and (1-<sup>13</sup>C)-4 in hand, epoxidation with DMDO was conducted. For deuterated (1-<sup>2</sup>H)-4, after the reaction was conducted in the usual manner (cf., Scheme 1), *E*-(2-<sup>2</sup>H)-5 and *Z*-(2-<sup>2</sup>H)-5 were isolated each showing 65% deuteration at the  $\alpha$ -position only (note ‡, ¶¶, ESI†). Evidently, this result is consistent with the proposed mechanism (cf., Fig. 2) (note †††, ESI†). More compellingly, epoxidation of bromoallene (1-<sup>13</sup>C)-4 gave (*E*-2-<sup>13</sup>C)-5<sup>33</sup> and (*Z*-2-<sup>13</sup>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-<sup>13</sup>C)-5 and (*Z*-1-<sup>13</sup>C)-5 isotopomers (ESI†). The expected <sup>1</sup>J<sub>CH</sub> coupling constants experienced by the  $\alpha$ -vinyl protons of the major isotopomers are clearly apparent in their <sup>1</sup>H NMR spectra (Fig. 3).

In conclusion we have established that the hitherto unknown direct conversion of bromoallenes to  $\alpha,\beta$ -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  $\alpha,\beta$ -unsaturated carboxylate 3 from bromoallene 2 by epoxidation (note †††, ESI†).

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