

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

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

Cite this: *Chem. Commun.*, 2013, **49**, 11176

Received 3rd September 2013,
Accepted 7th October 2013

DOI: 10.1039/c3cc46720a

www.rsc.org/chemcomm

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 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†).

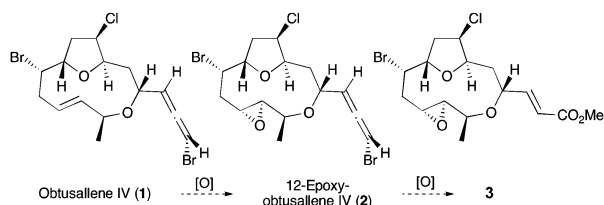
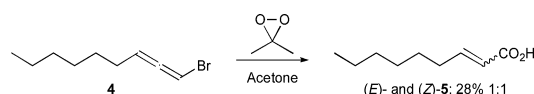


Fig. 1 Metabolites 1–3 from *Laurencia marilzae* and proposed biogenesis via epoxidation events.

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- ^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.



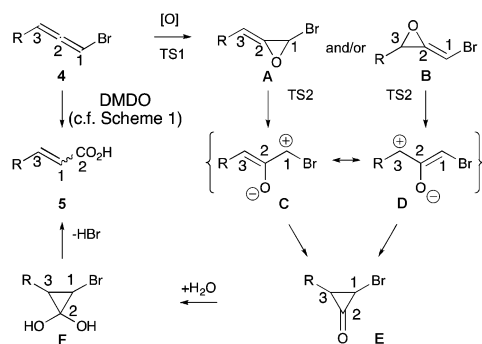
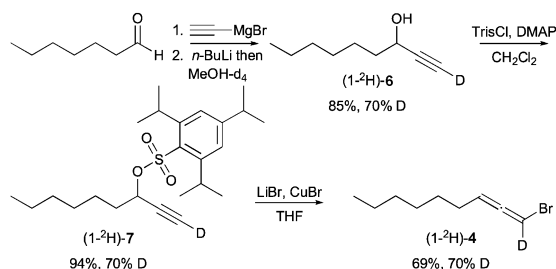


Fig. 2 Mechanistic rationale for conversion of bromoallenes into α,β -unsaturated carboxylic acids, with the carbon atoms of the functional groups numbered 1–3 showing an interchange of carbon atoms 1 and 2 (see also interactive Fig. 2 in HTML version of this article).

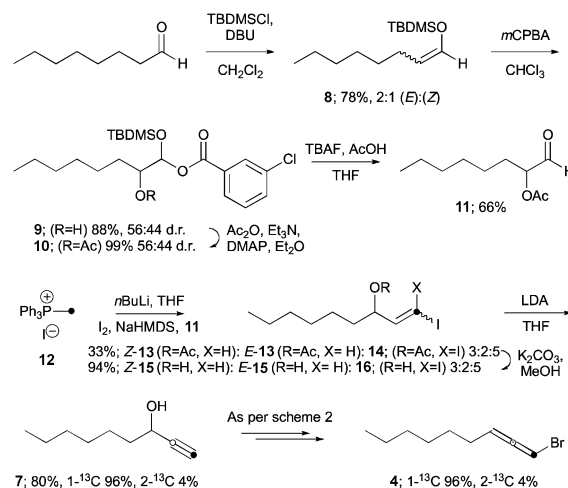
Interestingly, regardless of the initial site of epoxidation, this mechanism predicts that carbon atoms 1 and 2 in bromoallene **4** interchange positions in the α,β -unsaturated carboxylic acid products **5**.

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 ($1\text{-}^2\text{H}$)-**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 ¹³C-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 trisylation²⁵ gave ($1\text{-}^2\text{H}$)-**7**, and S_N2' displacement of the trisylate with bromide under the action of LiCuBr_2 (ref. 26) provided bromoallene ($1\text{-}^2\text{H}$)-**4** with 70% deuterium incorporation at the 1-position.[†]

¹³C-labeled bromoallene ($1\text{-}^{13}\text{C}$)-**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*-($1\text{-}^{13}\text{C}$)-**13**, *E*-($1\text{-}^{13}\text{C}$)-**13** and diiodide ($1\text{-}^{13}\text{C}$)-**14**.³² 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% ¹³C at the alkene terminus.[†]

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[†]). Interestingly, 4% of the alkyne product was found to be the $2\text{-}^{13}\text{C}$ isotopomer (ESI[†]), implicating a 1,1-elimination reaction pathway for diiodide **16**

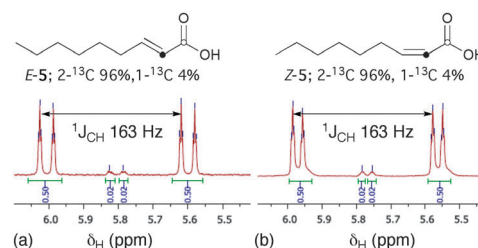
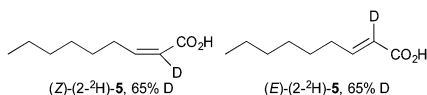


Fig. 3 ¹H NMR spectra of (a) (*E*- $2\text{-}^{13}\text{C}$)-**5** and (b) (*Z*- $2\text{-}^{13}\text{C}$)-**5** displaying the expected $1J_{\text{CH}}$ values for the α -vinyl protons.



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†).

We thank the EPSRC for DTG funding (to J. C.).

Notes and references

- (a) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, *Nat. Prod. Rep.*, 2013, **30**, 237–323 and earlier reviews in this series; (b) B.-G. Wang, J. B. Gloer, N.-Y. Ji and J.-C. Zhao, *Chem. Rev.*, 2013, **113**, 3632–3685.
- For a comprehensive review of the synthesis of medium ring ethers from *Laurencia* sp., see: (a) K. Fujiwara, *Top. Heterocycl. Chem.*, 2006, **5**, 97–148; (b) For recent leading examples see: B. S. Dyson, J. W. Burton, T.-i. Sohn, B. Kim, H. Bae and D. Kim, *J. Am. Chem. Soc.*, 2012, **134**, 11781–11790; (c) M. J. Kim, T.-i. Sohn, D. Kim and R. S. Paton, *J. Am. Chem. Soc.*, 2012, **134**, 20178–20188 and references cited therein.
- For recent representative examples see: (a) S. Keshipeddy, I. Martínez, B. F. Castillo II, M. D. Morton and A. R. Howell, *J. Org. Chem.*, 2012, **77**, 7883–7890; (b) S. A. Snyder, A. P. Brucks, D. S. Treidler and I. Moga, *J. Am. Chem. Soc.*, 2012, **134**, 17714–17721; (c) S. A. Snyder, D. S. Treidler, A. P. Brucks and W. Sattler, *J. Am. Chem. Soc.*, 2011, **133**, 15898–15901; (d) N. Ortega, V. S. Martin and T. Martin, *J. Org. Chem.*, 2010, **75**, 6660–6672 and references cited therein.
- For a review see: (a) A. Murai, in *Comprehensive Natural Products Chemistry*, ed. D. H. R. Barton, O. Meth-Cohn and K. Nakinishi, Elsevier, Oxford, 1999, vol. 1, pp. 303–324. For representative examples see: (b) K. J. Bonney and D. C. Braddock, *J. Org. Chem.*, 2012, **77**, 9574–9584; (c) A. Gutiérrez-Cepeda, J. J. Fernández, M. Norte and M. L. Souto, *Org. Lett.*, 2011, **13**, 2690–2693; (d) D. C. Braddock, D. S. Millan, Y. Perez-Fuertes, R. H. Pouwer, R. N. Sheppard, S. Solanki and A. J. P. White, *J. Org. Chem.*, 2009, **74**, 1835–1841; (e) D. C. Braddock, *Org. Lett.*, 2006, **8**, 6055–6058 and references cited therein.
- A. Gutiérrez-Cepeda, J. J. Fernández, L. V. Gil, M. López-Rodríguez, M. Norte and M. L. Souto, *J. Nat. Prod.*, 2011, **74**, 441–448.
- (a) G. Guella, G. Chiasera, I. Mancini, A. Öztunç and F. Pietra, *Chem.-Eur. J.*, 1997, **3**, 1223–1231; (b) M. L. Ciavatta, M. Gavagnin, R. Puliti, G. Cimino, E. Martínez, J. Ortea and C. A. Mattia, *Tetrahedron*, 1997, **53**, 17343–17350.
- For reviews on enzymatic epoxidation of alkenes see: (a) M. Sono, M. P. Roach, E. D. Coulter and J. H. Dawson, *Chem. Rev.*, 1996, **96**, 2841–2887; (b) P. R. Ortiz de Montellano and J. J. De Voss, *Nat. Prod. Rep.*, 2002, **19**, 477–493.
- For reviews see: (a) G. L'abbé, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 276–289; (b) W. Smadja, *Chem. Rev.*, 1983, **83**, 263–320; (c) T. H. Chan and B. S. Ong, *Tetrahedron*, 1980, **36**, 2269–2289.
- For the first isolated allene oxide and its thermal rearrangement to a cyclopropanone see: R. L. Camp and F. D. Greene, *J. Am. Chem. Soc.*, 1968, **90**, 7349.
- For an early report on their synthesis and reactivity of 2-bromooxiranes see: (a) A. Hassner and P. Catsoulacos, *J. Org. Chem.*, 1967, **32**, 549–553; For a representative naturally occurring 2-bromooxirane see: (b) K. Watanabe, M. Sekine and K. Iguchi, *J. Nat. Prod.*, 2003, **66**, 1434–1440.
- There is a single report of a bromoallene oxide functionality: ethyl 2-bromo-3-(diphenylmethylene) oxirane-2-carboxylate was reported in a study of ketenes and aliphatic diazo compounds: H. Staudinger and T. Reber, *Helv. Chim. Acta*, 1921, **4**, 3–23.
- P. C. Ravikumar, L. Yao and F. F. Fleming, *J. Org. Chem.*, 2009, **74**, 7294–7299.
- See for example: D. C. Braddock, R. Bhuvu, Y. Pérez-Fuertes, R. Pouwer, C. A. Roberts, A. Ruggiero, E. S. E. Stokes and A. J. P. White, *Chem. Commun.*, 2008, 1419–1421 and references cited therein.
- J. K. Crandall, D. J. Batal, F. Lin, T. Reix, G. S. Nadol and R. A. Ng, *Tetrahedron*, 1992, **48**, 1427–1448 and references therein.
- (a) R. W. Murray and M. Singh, *Org. Synth.*, 1997, **74**, 91. For the use of cyclic ketones as dioxirane precursors see: (b) R. W. Murray, M. Singh and R. Jeyaraman, *J. Am. Chem. Soc.*, 1992, **114**, 1346–1351.
- For leading examples see: (a) M. Singh and R. W. Murray, *J. Org. Chem.*, 1992, **57**, 4263–4270; (b) N. N. Kabal'nova, D. V. Kazakov, N. M. Shishlov and V. V. Shereshevets, *Russ. Chem. Bull.*, 1996, **45**, 1481–1483.
- For a review of the Favorskii reaction see: J. Mann, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and G. Pattenden, Pergamon Press, Oxford, 1991, vol. 3, ch. 3.7, pp. 839–859.
- In a previous isolation from red algae *Bonnemaisonia*, both 1,1,3-tribromo-2-ketones and their proposed Favorskii products – *E*- and *Z*-3-bromo-2-alkenoic acids – were co-isolates: O. J. McConnell and W. Fenical, *Phytochemistry*, 1980, **19**, 233–247.
- J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **6615**–6620.
- D. C. Braddock, J. Clarke and H. S. Rzepa, *Figshare*, 2013, DOI: 10.6084/m9.figshare.785756 and the further digital repository links therein.
- J. Downing, P. Murray-Rust, A. P. Tonge, P. Morgan, H. S. Rzepa, F. Cotterill, N. Day and M. J. Harvey, *J. Chem. Inf. Model.*, 2008, **48**, 1571–1581. See also <http://www.force11.org/AmsterdamManifesto> for the Amsterdam Manifesto on data citation principles.
- D. Cremer and E. Kraka, *Acc. Chem. Res.*, 2010, **43**, 591–601; H. S. Rzepa and C. Wentrup, *J. Org. Chem.*, 2013, **78**, 7565–7574.
- Similar non-linear behavior of a bond is found in the related dyotropic rearrangement of dibromoethanes; D. C. Braddock, D. Roy, D. Lenoir, E. Moore, H. S. Rzepa, J. I.-C. Wu and P. von R. Schleyer, *Chem. Commun.*, 2012, **48**, 8943–8945.
- For pioneering labeling work to elucidate the mechanism of the Favorskii rearrangement and to implicate a symmetrical intermediate, viz., a cyclopropanone see: R. B. Loftfield, *J. Am. Chem. Soc.*, 1951, **73**, 4707–4714.
- T. A. Grese, K. D. Hutchinson and L. E. Overman, *J. Org. Chem.*, 1993, **58**, 2468–2477.
- C. J. Elsevier, P. Vermeer, A. Gedanken and W. Runge, *J. Org. Chem.*, 1985, **50**, 364–367.
- Y. Taniguchi, J. Inanaga and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3229–3230.
- A. Hassner, R. H. Reuss and H. W. Pinnick, *J. Org. Chem.*, 1975, **40**, 3427–3429.
- For a representative example see: J. S. Debenham, R. Rodebaugh and B. Fraser-Reid, *J. Org. Chem.*, 1997, **62**, 4591–4600.
- W. Zhu, M. Jiménez, W.-H. Jung, D. P. Camarco, R. Balachandran, A. Vogt, B. W. Day and D. P. Curran, *J. Am. Chem. Soc.*, 2010, **132**, 9175–9187.
- G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, 2173–2174.
- For the unwanted formation of a vinyl 1,1-diiodide in a Stork-Wittig reaction using [Ph₃PCH₂][I] see: P. Li, J. Li, F. Arikian, W. Ahlbrecht, M. Dieckmann and D. Menche, *J. Org. Chem.*, 2010, **75**, 2429–2444.
- D. C. Braddock, J. Clarke and H. S. Rzepa, *Figshare*, 2013, DOI: 10.6084/m9.figshare.785753 viz. ref. 20 and 21 for explanation.

