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Proof-of-principle direct double cyclisation of a linear C_{15}-precursor to a dibrominated bicyclic medium-ring ether relevant to *Laurencia* species†

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Bicyclic dibrominated C_{15} medium-ring ether hexahydrolaureoxanyne was produced directly from an acyclic model C_{15}-epoxide when treated with NBS with water as the solvent.

Since the original isolation of Laurencin (**1a**) in 1965,[1] marine red algae of *Laurencia* species have provided a wide variety of C_{15}-acetogenic halogenated diastereo- and constitutional isomeric monocyclic ($C_{15}H_{21}BrO_2$) and bicyclic ($C_{15}H_{20}Br_2O_2$) medium-ring ethers that are oxygenated at both C-6 and C-7 (Fig. 1).[2] Both the monocyclic and bicyclic metabolites have received considerable synthetic attention, with numerous necessarily different strategies used to forge the 7-, 8-, or 9-membered medium-ring, control the *cis* or *trans* α,α′-ether stereochemistry, install the requisite halogen(s), and – in the case of the bicyclic ethers – to fashion the second ring.[3–5] Various recent studies have also been directed at the further understanding of their biogenesis,[6] where the early pioneering work of Murai[7] demonstrated enzymatic bromoetherifications of straight-chain co-isolated unsaturated C_{15}-diols – laurediols (3*E*,6*R*,7*R*)-**7a** and (3*Z*,6*S*,7*S*)-**7b**[8] – to monocyclic medium-ring ethers deacetyl laurencin **1b** and prelaureatin **2** respectively, albeit in very low yields (Scheme 1, top).[9] We have recently advanced an alternative biogenesis for the monocyclic ($C_{15}H_{21}BrO_2$) medium-ring ethers from *Laurencia* species from (6*S*,7*R*)-epoxide **8** *via* an intramolecular bromonium ion assisted epoxide ring-opening (IBIAERO) reaction with water functioning as the external nucleophile (Scheme 1, bottom, **8**→**B**→**O**/**O′**→**1b**/**2**), and experimentally corroborated this with a model epoxide for the concurrent formation of 7-, 8- and 9-ring ethers corresponding to the halogenated medium-ring ethers of known metabolites from Laurencia species.[10,11] The *bicyclic* metabolites are generally considered to originate by further bromoetherification of the residual unsaturation of the monocyclic compounds – the *Z*-configured medium-ring alkene or the pendant enyne – using the free alcohol of the original monocyclic compound located either at C-6 or C-7 as the nucleophile (Scheme 1, top).[7] Several laboratory demonstrations of these later transformations have been successful, either as enzymatic-mediated bromoetherifications of naturally occurring monocycles,[12] or as part of the synthetic strategy in a total synthesis of the bicyclic natural products.[13] Interestingly, although bromocyclisation events had been postulated for both monocycle and bicycle formation, prior to our 2012 report[10] and Snyder's recent elegant work,[6b,c] a non-enzymatic bromonium-ion induced cyclisation process to directly form medium-ring ether cores relevant to *Laurencia* species had not been reported. Moreover, to the best of our knowledge, there has been no report of a C_{15}-dibrominated bicyclic medium-ring ether relevant to *Laurencia* species being formed directly from a linear unsaturated C_{15}-precursor by two successive bromination events in the same pot. Herein we report on a successful strategy to effect such a transformation.

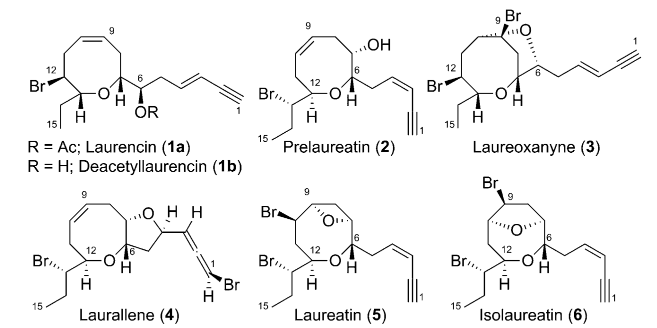

Fig. 1 Representative monocyclic and bicyclic halogenated medium-ring ethers of formulae $C_{15}H_{21}BrO_2$ (**1b**, **2**) and $C_{15}H_{20}Br_2O_2$ (**3–6**) from *Laurencia* species that are oxygenated at C-6 and C-7. Laurencin **1a** is related as the acetate of **1b**.

To investigate the proof-of-principle demonstration of a direct double cyclisation of a C_{15} unsaturated linear precursor to a bicyclic medium-ring ether relevant to *Laurencia* species we targeted hexahydroepoxide (6*S**,7*R**)-[H_6]-**8**, with the aim that this

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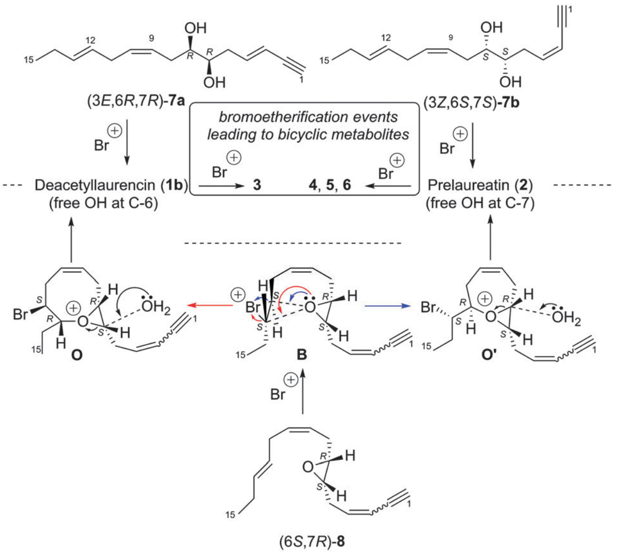
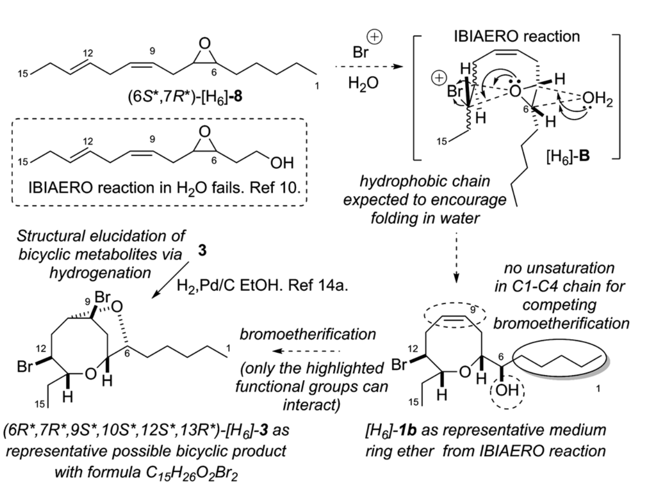
† Electronic supplementary information (ESI) available: Experimental procedures, characterising data and ^1H and ^{13}C NMR spectra for all compounds; a comparison of ^1H NMR data for (±)-[H_6]-**3** with the literature data. See DOI: 10.1039/c4cc06402j

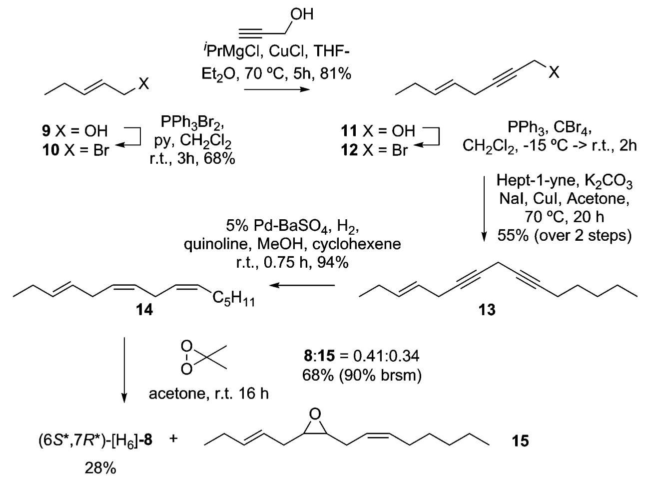


Scheme 1 Irie–Murai biogenesis of monocyclic medium-ring ethers from laurediols **7a** and **7b** (top); alternative biogenesis of deacetyllaurencin **1b** and prelaureatin **2** *via* IBIAERO reaction with water functioning as the external nucleophile (bottom). The other six possible monocyclic ethers of formulae $C_{15}H_{21}BrO_2$ are not shown.

would undergo an initial IBIAERO reaction *via* [H$_6$]-**B** where water functions as both the solvent and the nucleophile (Scheme 2). The use of water in this manner thus guarantees a free hydroxyl group for any subsequent bromoetherification reaction (*e.g.*, [H$_6$]-**1b**→[H$_6$]-**3**, Scheme 2) with a second equivalent of an electrophilic bromine source. While we had previously demonstrated successful IBIAERO reactions in water with NBS as the electrophilic bromine source,[11] the attempted IBIAERO reaction of a model epoxide as a truncated C_{12} alcohol (inset, Scheme 2) under the same conditions had failed.[10]‡ We considered that hexahydroepoxide [H$_6$]-**8** offered distinct benefits compared to this earlier model and also to epoxide **8** for the proposed experiment: (i) the hydrophilic hexahydro chain may encourage



Scheme 2 Proposed proof-of-principle direct cyclisation of (6*S**,7*R**)-[H$_6$]-**8** to bicyclic medium ring ethers *via* IBIAERO reaction and subsequent bromoetherification of the remaining unsaturation.

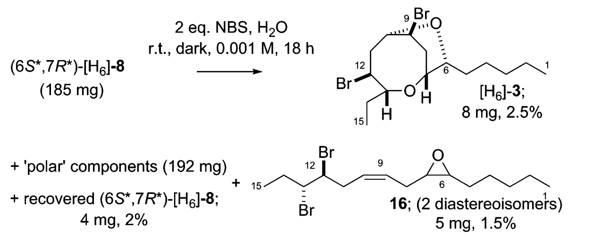


Scheme 3 Synthesis of (6*S**,7*R**)-[H$_6$]-**8**.

folding of the substrate in water thus inherently facilitating the IBIAREO reaction; (ii) post-IBIAERO reaction, the only region of unsaturation will be located in the medium ring and – compared with the hypothetical use of the putative biosynthetic precursor itself, epoxide **8** – there can be no complicating bromoetherifications to form bromoallene adducts by cyclisation onto any C_1–C_4 enyne moiety; (iii) hexahydrobicyclic compounds of formulae $C_{15}H_{26}O_2Br_2$ are known in the literature as a consequence of the structural elucidation of the naturally occurring compounds *via* hydrogenation,[14] providing data for identification of bicyclic products.

Accordingly, epoxide (6*S**,7*R**)-[H$_6$]-**8** was synthesised from bromide **12**, itself prepared from (*E*)-2-penten-1-ol (**9**) *via* a known sequence[10,15] with minor modifications. Subsequent copper-mediated coupling[16] with hept-1-yne gave novel enediyne **13** (Scheme 3).† Chemoselective and stereoselective hydrogenation[17] afforded (*E*,*Z*,*Z*)-doubly skipped triene **14.** Epoxidation of triene **14** with DMDO[18] was found to be entirely selective for the *Z*-olefins,[19] giving a mixture of mono epoxides (6*S**,7*R**)-[H$_6$]-**8** and **15** which could be separated by chromatography.§¶‖

With epoxide (6*S**,7*R**)-[H$_6$]-**8** in hand, it was treated with two equivalents of NBS – a water stable reagent – under high dilution conditions in water (Scheme 4).** Here, various dibromination adducts, bromohydrin regioisomers, and dibromotetrahydrofurans are expected to be formed by competing processes.[10] In the event, as expected, a complex mixture was obtained that was subjected to extensive chromatography, where 'non-polar' components could be separated away from 'polar' components.†† Much to our delight, by further chromatography of the non-polar components, hexahydrolaureoxanyne [(±)-[H$_6$]-**3**][12a] was isolated as a bicyclic medium-ring ether with ^{1}H NMR data identical to that previously reported,†‡‡ along with dibromoepoxides **16.** Thus the desired proof-of-principle has been achieved. This also constitutes the first synthetic route to the laureoxanyne bicyclic medium-ring ether scaffold, and the isolated yield of (±)-[H$_6$]-**3** (2.5%) from (6*S**,7*R**)-[H$_6$]-**8** compares well with the reported enzymatic conversion of deacetyl laurencin **1b** (obtained from natural laurencin **1a**) into **3** (3%).[12a]



Scheme 4 Proof-of-principle direct double cyclisation of (6*S**,7*R**)-[H_6]-**8** into (±)-[H_6]-**3** *via* IBIAERO reaction and subsequent bromoetherification of the remaining unsaturation (*cf.*, Scheme 2).

In conclusion, we have demonstrated the proof-of-principle direct cyclisation of a linear unsaturated C_{15}-precursor into a C_{15}-dibrominated bicyclic medium-ring ether relevant to *Laurencia* species – where hexahydrolaureoxanyne (±)-[H_6]-**3** has an identical bicyclic medium ring ether framework to laureoxanyne **3** – by two successive bromination events in the same pot. These studies are also consistent with epoxide (6*S*,7*R*)-**8** acting as the biogenetic precursor[10] for bromocyclisation to bicyclic medium-ring ethers of *Laurencia* species *via* IBIAERO reactions followed by subsequent bromoetherification events.

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Notes and references

‡ We speculate that the truncated C_{12} epoxide suffers from an intramolecular hydrogen bond from the alcohol functional group reducing its nucleophilicity.
§ 25% of a bis-epoxide was also observed.
¶ Attempted epoxidation of **14** with *m*CPBA was unselective for the *Z*-olefins.
‖ ^1H-^{13}C and ^1H-^1H NMR correlation spectroscopy were used to distinguish between epoxides (6*S**,7*R**)-[H_6]-**8** and **15**.†
** In an experiment with 1 equivalent of NBS in water, (±)-[H_6]-**3** was isolated in 1.8% yield after extensive chromatography.
†† The 'polar' components were expected to contain regioisomeric bromohydrins and dibromohydrins by reference to our earlier work (ref. 10) and were not further characterised.
‡‡ The medium-ring bicyclic structure of [H_6]-**3** is also supported by a characteristic NOESY cross-peak between H_7 and H_9 as previously reported (as an nOe) for **3** (ref. 12*a*).†

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