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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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 diastero- and constitutional isomeric monocyclic (C$_{15}$H$_{21}$Br$_{2}$O$_{2}$) and bicyclic (C$_{15}$H$_{20}$Br$_{2}$O$_{2}$) 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,ω-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 (3bromoetherifications of straight-chain co-isolated unsaturated C$_{15}$-diols – laurediols (3,6,6R,7R)-7a and (3Z,6S,7S)-7b – to monocyclic medium-ring ethers deacetyl laurencin 1b and prelaureatin 2 respectively, albeit in very low yields (Scheme 1, top). 3 We have recently advanced an alternative biogenesis for the monocyclic (C$_{15}$H$_{21}$Br$_{2}$O$_{2}$) medium-ring ethers from Laurencia species from (6S,7R)-epoxide 8 via an intramolecular bromonium ion assisted epoxide ring-opening (IBIAREO) 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 monoycyclics, 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.

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 (6S*,7R*)-[H$_{6}$]-8, with the aim that this
would undergo an initial IBIAREO reaction via \([\text{H}_6]\)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., \([\text{H}_6]-1\text{b} \rightarrow [\text{H}_6]-3\), Scheme 2) with a second equivalent of an electrophilic bromine source. While we had previously demonstrated successful IBIAREO reactions in water with NBS as the electrophilic bromine source, the attempted IBIAERO reaction with water functioning as the external nucleophile (bottom) failed. 

**Scheme 1** Irie–Murai biogenesis of monocyclic medium-ring ethers from laurediacids \(7\text{a} \) and \(7\text{b}\) (top); alternative biogenesis of deacetyllaurencin \(1\text{b}\) and prelaureatin \(2\) via IBIAERO reaction with water functioning as the external nucleophile (bottom). The other six possible monocyclic ethers of formulae \(\text{C}_{15}\text{H}_{21}\text{BrO}_2\) are not shown.

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 \(\text{C}_4-\text{C}_4\) enyne moiety; (iii) hexahydrobicyclic compounds of formulae \(\text{C}_{13}\text{H}_{26}\text{O}_2\text{Br}_2\) are known in the literature as a consequence of the structural elucidation of the naturally occurring compounds via hydrogenation, providing data for identification of bicyclic products.

Accordingly, epoxide \((6\text{S}^*,7\text{R}^*)-[\text{H}_6]-8\) was synthesised from bromide \(12\), itself prepared from \((E)-2\text{-penten-1-ol}\) 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 \(14\). Epoxydation of triene \(14\) with DMO \(^{18}\) was found to be entirely selective for the \(Z\)-olefins, giving a mixture of mono epoxides \((6\text{S}^*,7\text{R}^*)-[\text{H}_6]-8\) and \(15\) which could be separated by chromatography. \(^{19}\)

With epoxide \((6\text{S}^*,7\text{R}^*)-[\text{H}_6]-8\) 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. 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. \(^{10}\) Much to our delight, by further chromatography of the non-polar components, hexahydrolaureoxanyne \(([\pm]-[\text{H}_6]-3)\) \(^{12a}\) was isolated as a bicyclic medium-ring ether with \(^1\text{H}\) NMR data identical to that previously reported, \(^{12a}\) along with dibromooxepines \(16\). Thus the desired proof-of-principle has been achieved. This also constitutes the first synthetic route to the lauroxanyne bicyclic medium-ring ether scaffold, and the isolated yield of \((\pm)-[\text{H}_6]-3\) (2.5%) from \((6\text{S}^*,7\text{R}^*)-[\text{H}_6]-8\) compares well with the reported enzymatic conversion of deacetyl laurenecin \(1\text{b}\) (obtained from natural laurenecn \(1\text{a}\)) into \(3\) (3%). \(^{12a}\)

**Scheme 2** Proposed proof-of-principle direct cyclisation of \((6\text{S}^*,7\text{R}^*)-[\text{H}_6]-8\) to bicyclic medium ring ethers via IBIAERO reaction and subsequent bromoetherification of the remaining unsaturation.
In conclusion, we have demonstrated the proof-of-principle direct cyclisation of a linear unsaturated C11− precursor into a C15-dibrominated bicyclic medium-ring ether relevant to Laurencia species – where hexahydrolaureoxanyne (±)−[H8]−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 (65,78R)−8 acting as the biogenetic precursor10 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 C12 epoxide suffers from an intra-molecular hydrogen bond from the alcohol functional group reducing its nucelophilicity.

‡ 25% of a bis-epoxide was also observed.

§ Attempted epoxidation of 14 with mCPBA was unselective for the Z-olefins.

∥ 31H−3C and 1H−1H NMR correlation spectroscopy were used to distinguish between epoxides (65,78R)−[H8]−8 and 15.†

†† In an experiment with 1 equivalent of NBS in water, (±)−[H8]−3 was isolated in 1.8% yield after extensive chromatography.

†‡ The ‘polar’ components were expected to contain regioisomeric bromo-hydroxyls and dibromohydrins by reference to our earlier work (ref. 10) and were not further characterised.

‡‡ The medium-ring bicyclic structure of [H8]−3 is also supported by a NOESY cross-peak between H7 and H9 as previously distinguished between epoxides (688)− and (788)− Z14 species – where hexahydrolaureoxanyne (±)−[H8]−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 (65,78R)−8 acting as the biogenetic precursor10 for bromocyclisation to bicyclic medium-ring ethers of Laurencia species via IBIAERO reactions followed by subsequent bromoetherification events.

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