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 diastereoisomeric and constitutional isomeric monocyclic (C_{15}H_{22}BrO_{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 a,x-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 naturally occurring Laurencia species from recently advanced an alternative biogenesis for the monocyclic (C_{15}H_{21}BrO_{2}) medium-ring ethers from Laurencia species. 10,11 The concurrent formation of 7-, 8- and 9-ring ethers corresponding to the external nucleophile (Scheme 1, top), 3–5 has been postulated for both monocycle bromocyclisation events had been postulated for both monocycle and bicyclic formation, prior to our 2012 report 10 and Snyder's recent elegant work: 6bc A non-enzymatic bromonium-ion induced cyclication process to directly form medium-ring ether cores relevant to Laurencia species has 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 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: 6bc A non-enzymatic bromonium-ion induced cyclication process to directly form medium-ring ether cores relevant to Laurencia species has 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.

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would undergo an initial IBIAREO reaction via [H₆]-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., [H₆]-1b → [H₆]-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 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 C₃-C₄ enyne moiety; (iii) hexahydrobicyclic compounds of formulae C₁₅H₂₆O₂Br₂ are known in the literature as a consequence of the structural elucidation of the naturally occurring compounds (Scheme 3).

Accordingly, epoxide (6S*,7R*)-[H₆]-8 was synthesised from bromide 12, itself prepared from (E)-2-penten-1-ol (9) via a known sequence with minor modifications. Subsequent copper-mediated coupling with hept-1-yn to give novel enediyne 13 (Scheme 3). caf 1/2, Chemoselective and stereoselective hydrogenation of triene afforded (E,Z,Z)-doubly skipped triene 14. Epoxidation of triene 14 with DMDO was found to be entirely selective for the Z-olefins, giving a mixture of mono epoxides (6S*,7R*)-[H₆]-8 and 15 which could be separated by chromatography.

With epoxide (6S*,7R*)-[H₆]-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 dibromotetrahydrofuran are expected to be formed by competing processes. According to the experimental results, a complex mixture was obtained that constituted the first synthetic route to the laureoxanyne bicyclic framework, and the isolated yield of (E,Z,Z)–2-penten-1-ol (3%) from (6S*,7R*)-[H₆]-8 compared well with the reported enzymatic conversion of deacetyl laurencin 1b (obtained from natural laurencin 1a) into 3 (3%) and 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 C₃-C₄ enyne moiety; (iii) hexahydrobicyclic compounds of formulae C₁₅H₂₆O₂Br₂ 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.

**Scheme 1** Irie–Murai biogenesis of monocyclic medium-ring ethers from laurendiol 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 C₁₅H₂₁BrO₂ are not shown.

**Scheme 2** Proposed proof-of-principle direct cyclisation of (6S*,7R*)-[H₆]-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 C15-precursor into a C15-dibrominated bicyclic medium-ring ether relevant to Laurencia species – where hexahydrolaureoxanyne (±)-[H6]-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 (65,7R)-8 acting as the biogenetic precursor to bromocyclisation to bicyclic medium-ring ethers of Laurencia species via IBIAREO reactions followed by subsequent bromoetherification events.

We thank the Dinu Patriciu Foundation for funding (to D.-T. S.).

Notes and references

† We speculate that the truncated C12 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 mCPBA was unselctive for the Z-olefins.
∥ || [H-1]C-[H-1]H NMR correlation spectroscopy were used to distinguish between epoxides (65,7R)-[H6]-8 and 15.‡
** In an experiment with 1 equivalent of NBS in water, (±)[H6]-3 was isolated in 1.8% yield after extensive chromatography.
†† The ‘polar’ components were expected to contain regiosomeric bromohydins and dibromohydins by reference to our earlier work (ref. 10) and were not further characterised.
‡‡ The medium-ring bicyclic structure of [H6]-3 is also supported by a characteristic NOESY cross-peak between H7 and H9 as previously reported (as nOe) for 3 (cf. Scheme 2).

Scheme 4  Proof-of-principle direct double cyclisation of (6S,7R)-[H6]-8 into (±)-[H6]-3 via IBIAREO 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 C15-precursor into a C15-dibrominated bicyclic medium-ring ether relevant to Laurencia species – where hexahydrolauroxyanone (±)[H6]-3 has an identical bicyclic medium ring ether framework to lauroxyanone 3 – by two successive bromination events in the same pot. These studies are also consistent with epoxide (65,7R)-8 acting as the biogenetic precursor to bromocyclisation to bicyclic medium-ring ethers of Laurencia species via IBIAREO reactions followed by subsequent bromoetherification events.

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