

Stereochemical Uniformity in Marine Polyether Ladders—Implications for the Biosynthesis and Structure of Maitotoxin**

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The largest known, nonpolymeric natural product, maitotoxin, is a 3422 Da polyketide-derived polycyclic ether isolated from the marine dinoflagellate, *Gambierdiscus toxicus*.^[1] The structure of maitotoxin consists of four extended fused-ring systems termed polyether ladders, A–D (Figure 1). The family of

massive fish kills.^[2] Maitotoxin itself displays the highest toxicity of any non-proteinaceous natural product isolated thus far.^[3]

The biogenesis of the polyether ladders, whilst attracting speculation, has advanced little further than the identification of their polyketide origin.

“monensin”, which is subsequently epoxidized and cyclized in a cascade of S_N2 epoxide openings (Scheme 1). This hypothesis has remained foremost and has received widespread acceptance. $^{18}O_2$ labeling and sequencing of the gene cluster support this model.^[8,9] Crucially, inactivation of the gene thought to be responsible for epoxidation of the double bonds recently led to the isolation of a triene shunt metabolite by our group.^[10] Obviously, this strongly suggests that a triepoxide intermediate precedes monensin. The structures of the marine toxins also suggest that cyclization of a polyepoxide precursor may be a general biosynthetic strategy for the construction of polycyclic ethers. Indeed, both Shimizu and Nakanishi have independently proposed such a model for brevetoxin A—an octaepoxide precursor cyclizes in a cascade of S_N2 epoxide openings, mechanistically similar to that proposed for monensin (Scheme 2).^[11] Indirect evidence for such a mechanism is provided by the $^{18}O_2$ -labeling pattern of okadaic acid, a related marine polyether, suggesting an epoxide intermediate.^[12] Also, the isolation of 27,28-epoxy-brevetoxin-B (the double bond in the 8-membered H ring is epoxidized) may suggest the extraneous over-epoxidation of a polyene precursor.^[13]

Although a polyepoxide intermediate may be feasible en route to the brevetoxin skeleton, a straightforward extrapolation of the Cane–Celmer–Westley cyclization mechanism cannot be considered wholly satisfactory. The most notable concern is the manner in which the polyepoxide must cyclize to

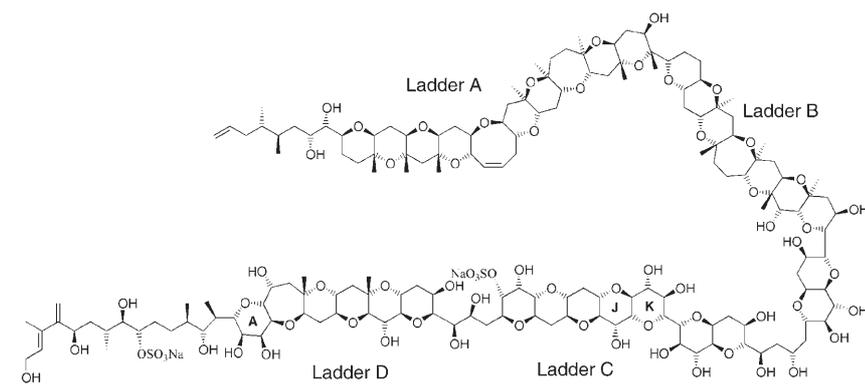


Figure 1. Maitotoxin.

marine polyether ladders (Figure 1 and Figure 2) can be grouped into 14 backbone structures and has gained much notoriety in being responsible for countless cases of human food poisoning and

Although labeling studies have shed some light on the construction of the obligatory polyketide chain precursor,^[4] anything further than this remains speculative. However, the most closely analogous non-marine molecules, the polyether antibiotics, have been helpful in generating biosynthetic models for the more elaborate marine structures. In particular, monensin, a polyether ionophore antibiotic isolated from *Streptomyces cinnamonensis*,^[5] has been studied fairly extensively.^[6] A biosynthetic proposal was first put forward by Cane, Celmer, and Westley.^[7] The Cane–Celmer–Westley model involves a polyketide-derived triene intermediate, “premo-

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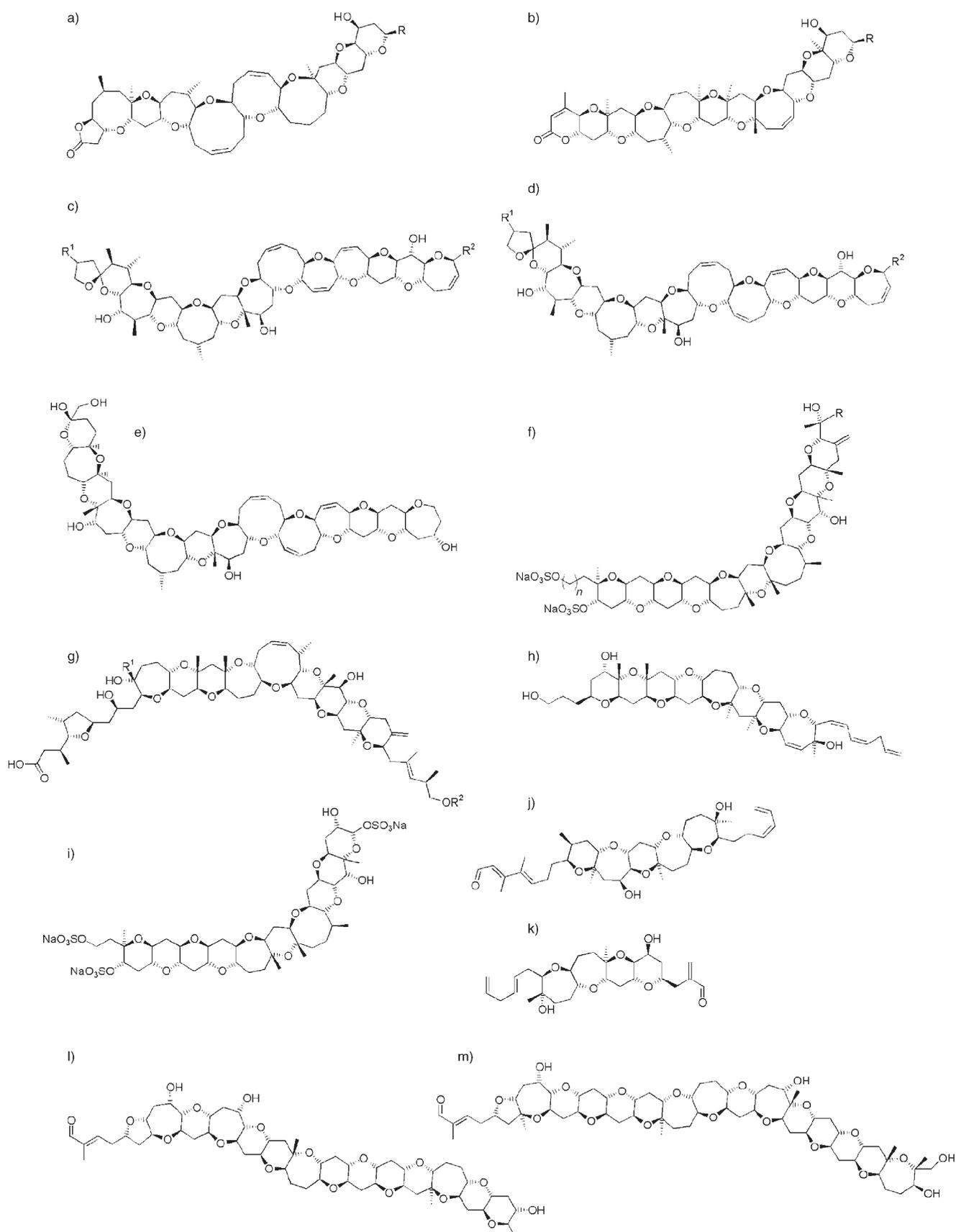
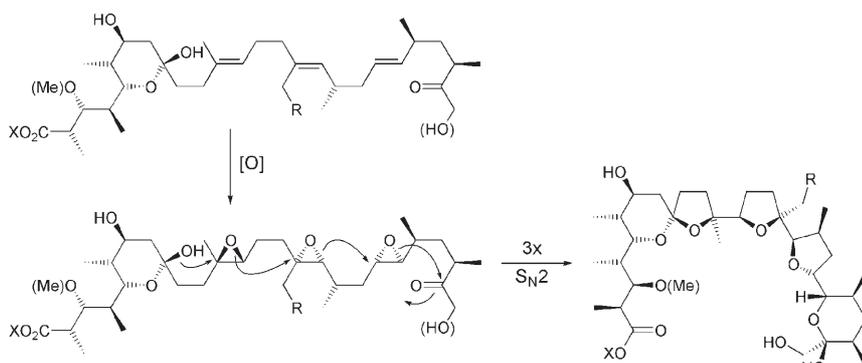
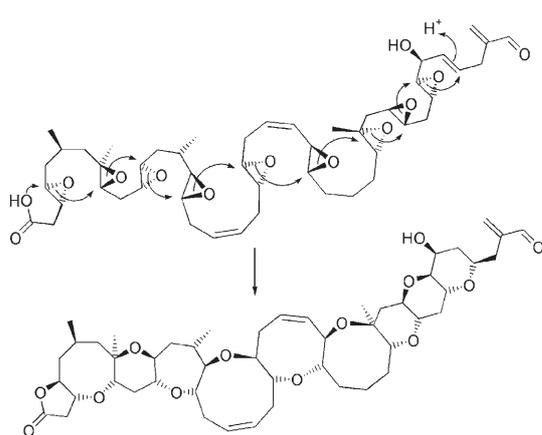


Figure 2. Marine polyether-ladder backbones. a) Brevetoxin type 1, b) Brevetoxin type 2, c) Ciguatoxin type 1, d) Ciguatoxin type 2, e) C-CTX-1, f) Yessotoxin, g) Gambieric Acid, h) Gambierol, i) Adriatoxin, j) Brevenal, k) Hemibrevetoxin B, l) Gymnocin A, m) Gymnocin B.



Scheme 1. Cane–Celmer–Westley model for monensin biosynthesis.



Scheme 2. Shimizu/Nakanishi cascade mechanism for brevetoxin A cyclization.

generate the contiguous fused ether rings characteristic of these toxins. Unlike the monensin triepoxide intermediate, which must cyclize in a series of favored *exo*-tet S_N2 closures, a pre-brevetoxin polyepoxide would entail nine disfavored *endo*-tet closures, each violating Baldwin's rules (Scheme 3)^[14] As of yet, no satisfying and unifying hypothesis has been proposed for all the polyether ladders beyond the idea of a pre-brevetoxin polyepoxide intermediate.

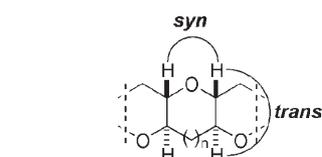
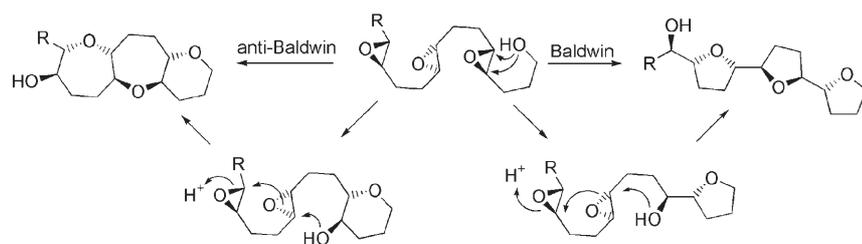


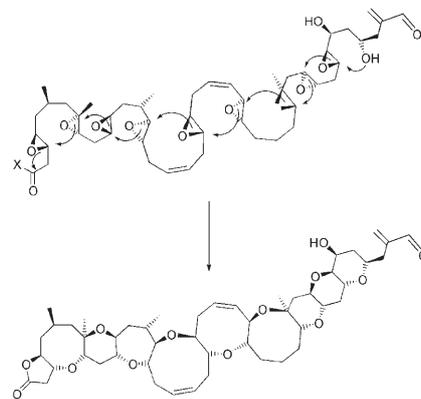
Figure 3. Common structural features of ladder ring junctions.

A characteristic feature of these toxins is the *syn/trans* stereochemistry of the ring junctions (Figure 3). Examination of all known polyether ladders demonstrates that this feature is conserved across the family. This prompted us to carry out the retrosynthetic analyses to their hypothetical polyepoxide precursors. This has revealed, for the first time, that all of the contiguous rings, in any single polyether, can be derived from stereochemically identical, either all (*R,R*) or all (*S,S*), *trans* epoxides. As the mechanism of terminal ring formation is unclear in some cases, this rule can only be generally applied to ring junctions. However, when terminal *trans* epoxide, then our rule is not deviated from. Further, the direction of cyclization is always, to some degree, ambiguous. To illustrate this, Shimizu and Nakanishi show the cyclization from



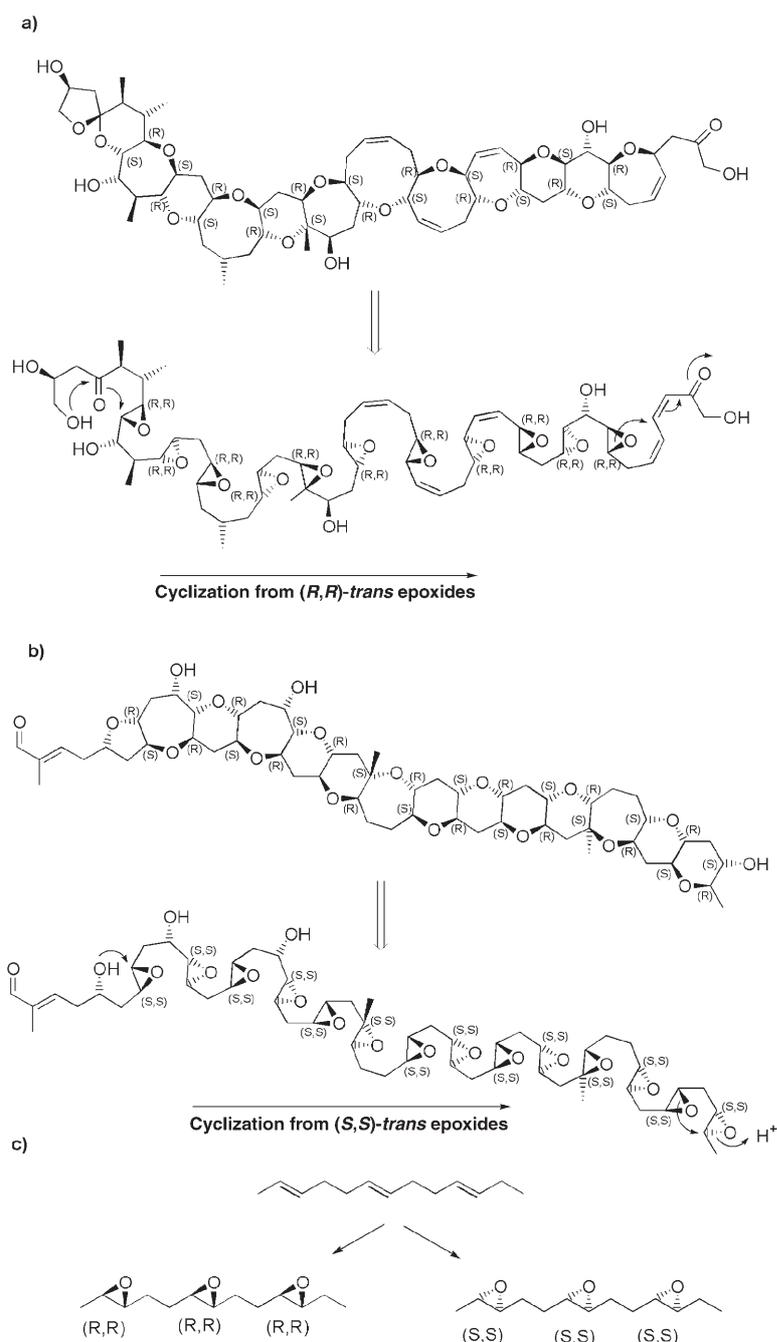
Scheme 3. Epoxide opening showing a Baldwin versus anti-Baldwin pathway.

a series of (*R,R*-*trans*) epoxides that terminates in the protonation of a double bond.^[11] However, by simply invoking a series of (*S,S*-*trans*) epoxides, the cyclization may proceed from the opposite direction, terminating by closure of the lactone ring (probably more likely) and yielding the same structure (Scheme 4). What is important is the



Scheme 4. An alternative to the Shimizu/Nakanishi brevetoxin cyclization mechanism from all (*S,S*-*trans*) epoxides (compare with Scheme 2).

relative stereochemistry of the epoxides and, thus, likewise of the final cyclized structure. This, of course, applies to any of the ladders (a–m) in Figure 2 in which the absolute stereochemistry has not yet been established. It follows that all of the *trans* double bonds in the polyene precursor are epoxidized from the same face and thus a single monooxygenase could be responsible for all of the *trans* epoxides (Scheme 5). The polyene intermediate may contain over twenty double bonds, as would be the case with maitotoxin. Differential epoxidation of these would, obviously, require them to be distinguished by their individual monooxygenase enzymes. Intuitively, this seems unlikely and examination of the ladder structures supports this view. A broadly specific monooxygenase could effect all of the asymmetric epoxidations from one face of the polyene without difficulty. This rule is shown to apply to all the polyether ladders thus far characterized—namely, the brevetoxins and hemibrevetoxin B^[15], the yessotoxins (and the truncated adriatoxin),^[16] the Pacific and Caribbean ciguatoxins,^[17] the gambieric acids and gam-



Scheme 5. Retrosynthetic analyses of a) Ciguatoxin (CTX); b) Gymnocin A; c) Epoxidation patterns. Arrows depicting the epoxide cyclization process have been omitted for clarity. However, see Scheme 2 for a general mechanism.

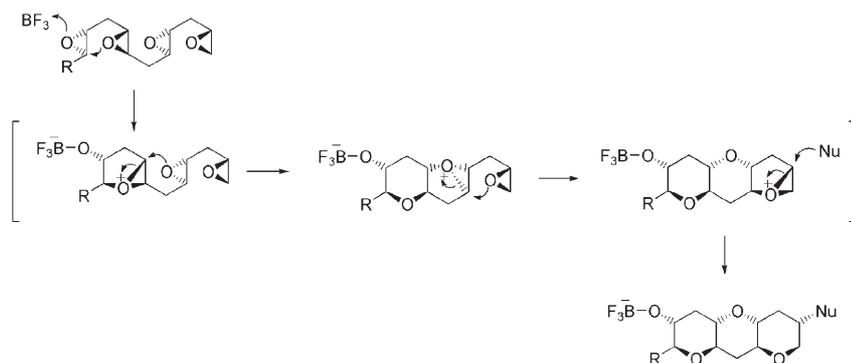
bierol,^[18] the gymnocins^[19] and brevenal^[20] (see the Supporting Information). Interestingly, maitotoxin appears exceptional, but this will be returned to later.

Assuming a polyepoxide precursor to the polyether ladders, the mechanism of cyclization is of fundamental concern. The cyclization of polyepoxide precursors, in the construction of fused polycyclic ethers, has been explored as an approach to total synthesis, as well as

facilitating mechanistic proposals for their biosynthesis. Although synthetic models have shown that formation of polycyclic ethers from polyepoxides is facile, Baldwin's rules are adhered to in simple, acid-catalyzed reactions.^[21] However, there have been three distinct biomimetic approaches taken to effect apparent *endo*-selective epoxide opening in ring closure.^[22] The first method uses successive ring closure of a hydroxy

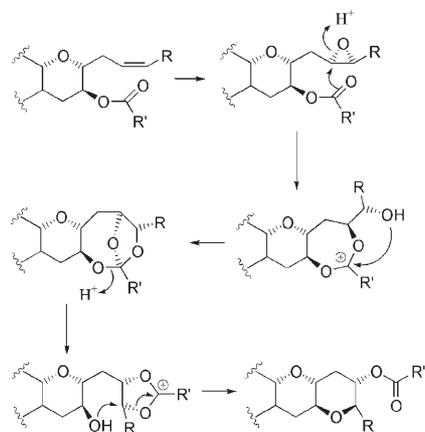
polyepoxide, which is analogous to the Cane–Celmer–Westley mechanism. However, the attack is guided electronically by substituents on the *endo* position of the epoxide. In the early work of Nicolaou, for example, an electron-rich double bond is placed adjacent to the *endo* position and stabilizes the *endo* transition state by electron donation from the π orbital. This has been effective in achieving both 6-*endo* over 5-*exo* selectivity, as well as 7-*endo* over 6-*exo* selectivity, in such epoxide openings.^[23] The putative biosynthetic polyepoxides do not have such directing groups, however, so the selectivity could not occur in this manner. The second method that has been used to obtain *endo* selectivity is a successive ring expansion of a polyepoxide, in which the epoxide acts as a nucleophile (Scheme 6). This methodology typically employs a suitable Lewis acid to activate the terminal epoxide.^[24] The first step in such a reaction is the intramolecular attack by an adjacent epoxide on the activated terminal epoxide to generate a bridged oxonium ion intermediate—the initiation step. The next step is the nucleophilic attack of the second epoxide, either *exo* or *endo*, to open the oxonium ion. Thus, the first ether ring is completed and a second oxonium ion is formed. This forms the electrophilic site for the next epoxide, and so on. The *endo* regioselectivity has been explained by minimization of ring strain in the formation of each oxonium ion. *Endo* attack, although disfavored in terms of Baldwin's rules, generates a less-strained oxonium ion, an effect that appears to dominate.^[25] In theory, the Lewis acid mediated initiation step, or its enzymatic equivalent, could generate the complete polycyclic structure. This could be an elegant biosynthetic strategy and may be considered as a feasible alternative to the Cane–Celmer–Westley extrapolation. However, the synthetic methodology has serious limitations in terms of the number of rings that may be assembled as well as the substituents and ring sizes, perhaps making it less appealing as a general biosynthetic proposal for the polyether ladders.^[26]

The third approach, developed by Giner, involves the rearrangement of an epoxy ester and is a very different mode of cyclization from the other two bio-



Scheme 6. Lewis acid initiated ring-expansion approach to polyether synthesis.

mimetic models (Scheme 7).^[27] Extrapolating this synthetic strategy to the biosynthesis of polyethers would require an all-*cis* polyene precursor, noted as



Scheme 7. Formation of a fused polycyclic ether through an epoxy ester rearrangement.

advantageous in explaining the *cis* bonds in the brevetoxins and ciguatoxins. Although an inventive synthetic approach to obtaining *endo* selectivity, it seems rather overcomplicated for an enzyme-catalyzed reaction.

Perhaps the most straightforward biosynthetic methodology would involve the stepwise closure of each ring by an epoxide hydrolase. The role of the enzyme would simply be to protonate the epoxide and direct the hydroxy nucleophile so as to close the ring in an *endo*-selective manner. Recently, we provided evidence for the involvement of epoxide hydrolases in the cyclization of monensin.^[28] The enzymes have homology to limonene epoxide hydrolase, an enzyme that employs simple acid–base chemistry^[29] and, unlike classical epoxide hydrolases, does not in-

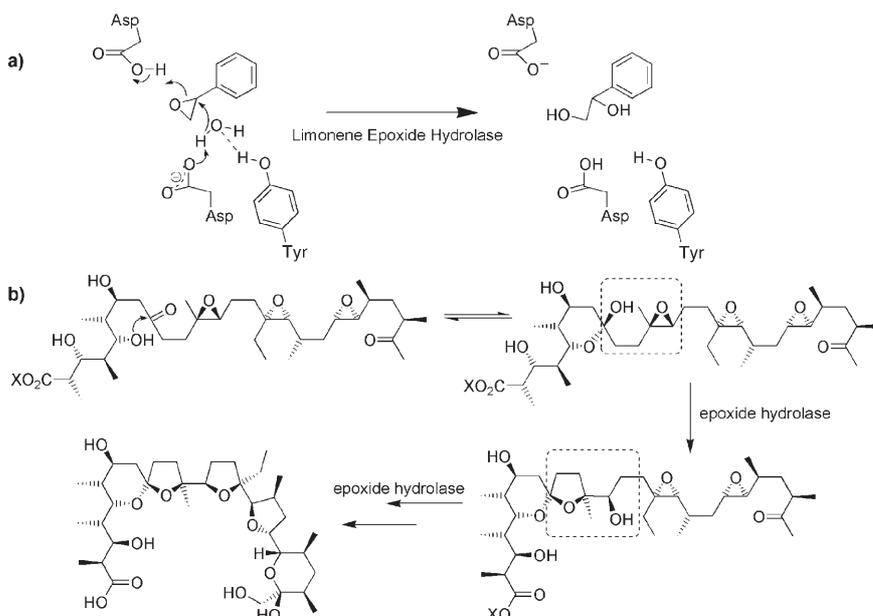
volve an enzyme-bound intermediate (Scheme 8).^[30] Further to this, the uniform stereochemistry of the proposed marine polyepoxides suggests a single epoxide hydrolase could be responsible for all of the ring closures.

Although a stepwise cyclization accomplished by an epoxide hydrolase is a rational model, the inherent reactivity of the hypothetical polyepoxide intermediate may itself be a cause for concern. All of the double bonds of the prerequisite polyene must each be epoxidized and only when this is complete may the process of cyclization begin, so as to effect the smooth conversion of the polyepoxide to a polycyclic ether. An *in trans* epoxidation process, in which each double bond is epoxidized as it is formed on the polyketide synthase, would provide a more closely controlled sequen-

tial model. However, potentially there is also the problem of avoiding nonenzymatic side reactions during the construction of a series of somewhat reactive epoxides. So far, gymnocin B contains the largest number of contiguous rings (15) of any polyether ladder. However, there is no reason to suggest that gymnocin B represents the ceiling level in this respect. Any sequential biosynthetic model would, ideally, be applicable to any hypothetical polyether ladder of any length.

By coupling the epoxidation and cyclization steps more closely, this concern could be circumvented—the epoxidation of the first double bond creates the substrate for the epoxide hydrolase and the first ring is then closed. Epoxidation of the second double bond then presents the epoxide hydrolase with its next substrate. This iterative process continues until the final polycyclic structure is realized. The epoxidase and hydrolase enzymes would thus work in close cooperation, perhaps as a multi-enzyme complex. This bis-enzymatic model avoids constructing a polyepoxide prior to cyclization and may in fact be simplified further.

Janda et al. have utilized a “catalytic antibody” to direct the *endo* cyclization of hydroxy epoxides.^[31] These antibodies are generated by means of a hapten that mimics the *endo* transition state. The suitably programmed antibody



Scheme 8. a) Mechanism of styrene oxide hydrolysis by limonene epoxide hydrolase; b) Putative role of epoxide hydrolases in monensin cyclization.

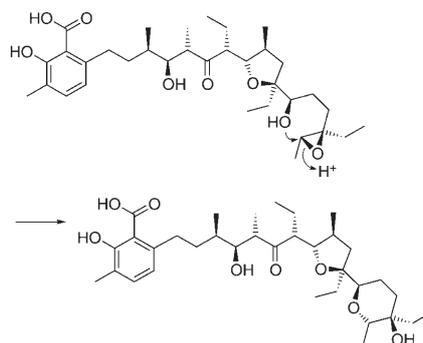
merely intercedes at, or near, the transition state to alter the energy balance in favor of the otherwise disfavored reaction pathway (Scheme 9). It is hypothesized that, through suitably placed charged residues, the antibody simply stabilizes the *endo* transition state relative to the *exo* as the tethered hydroxy group attacks. Applying this to polyether construction, it is feasible that, as the monooxygenase epoxidizes each double bond of the polyene, the bound enzyme acts in such a manner and facilitates *endo* attack of the hydroxy nucleophile. The size of the ring being closed would be largely irrelevant (the nine-membered ring of brevetoxin A may represent a realistic limit in this regard). The role of the enzyme at this stage would be no more than to bind and activate the newly formed epoxide, thus ensuring that the energy of the *endo* transition state is lowered relative to the *exo*. Once the ring is closed, the enzyme dissociates and moves on to the next double bond (Scheme 10). A distinct

hydrolase enzyme that catalyzes ring closure may be superfluous. The oxidation–cyclization may be considered a single step and, overall, a single enzyme converts a simple polyene chain to a more sophisticated polyether ladder.

It is highly significant that neither of these models inherently place any limitation on the number of contiguous rings that may be constructed. Once the polyene precursor is assembled, conversion to the polycyclic structure is relatively straightforward. This could provide an explanation as to how polyether biosynthesis can be effected on such a grand scale, as exemplified by maitotoxin. Considering the remarkable biological activity of this structure, such scaling has clearly been a successful strategy.

Although the genes responsible for the formation of marine polyethers are difficult to obtain, it is noteworthy that the terminal ring of the ionophore, lasalocid A, produced by *Streptomyces lasaliensis*, also appears to be formed from a disfavored, *endo*-tet, epoxide

opening (Scheme 11).^[32] Interestingly, a very small quantity of the *exo*-tet product (<1%) has also been isolated,

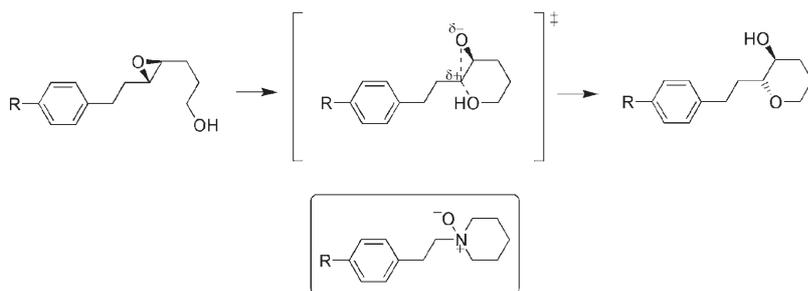


Scheme 11. Proposed formation of lasalocid through an *endo*-tet epoxide opening.

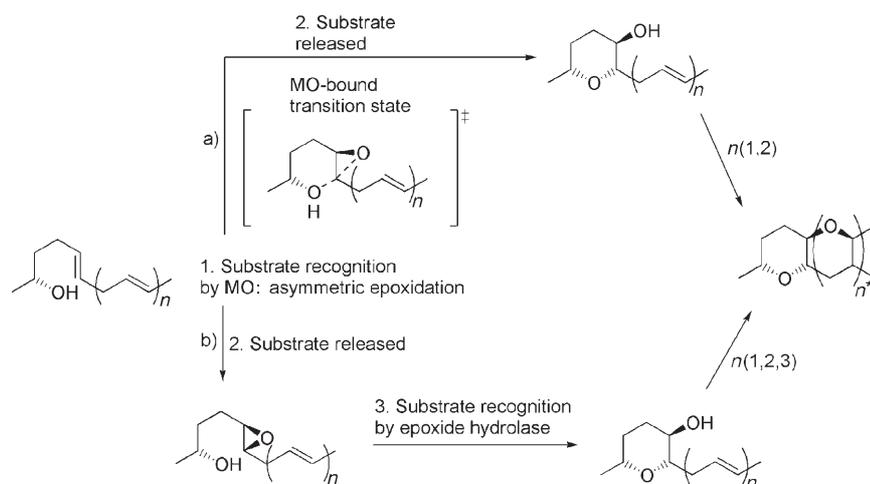
presumably resulting from the chemically favored, nonenzymatic cyclization. Alborixin, salinomycin, and narasin also have such terminal rings.^[33] The gene clusters for lasalocid A and the other three polyethers should be obtainable as the organisms can be cultured, and this could confirm a role of *endo*-directing epoxide hydrolases in polyether biosynthesis.

As mentioned earlier, maitotoxin appears to be exceptional.^[1] The main body of the molecule consists of four separate ladder sections (A–D), as well as a central “hinge” consisting of two identical bicyclic structures. This identity suggests a common mechanism of construction distinct from the ladder sections. Although conforming to our stereochemical model in three of the ladder sections (see the Supporting Information), retrobiosynthetic analysis of ladder C reveals an epoxide with the opposite stereochemistry to the others (Scheme 12). This is striking as it leads to the only example of an exceptional ring junction (the “J–K ring junction”) in any of the known polyether ladders.

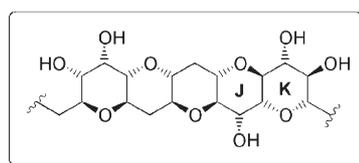
From the 28 *trans* double bonds that must be epoxidized to construct the maitotoxin ladders, the selective discrimination of one double bond appears unrealistic. Without exception, none of the other polyether ladders that are derived from considerably fewer double bonds display any such stereochemical variation. As discussed, a single monooxygenase is likely to be responsible for epoxidation of all the *trans* double



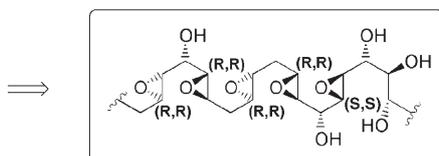
Scheme 9. Antibody-mediated *endo* cyclization. Antibody generated from hapten (boxed) that mimics the *endo* transition state.



Scheme 10. a) Mono-enzymatic route to a fused polyether; b) Bis-enzymatic route. MO = monooxygenase, * = alternating orientation of the oxane ring.



Ladder C



Scheme 12. Retrobiosynthetic analysis of maitotoxin ladder C showing an exceptional (S,S)-*trans* epoxide.

bonds in any single polyether. To arrive at maitotoxin, this enzyme would be required to skip the double bond in question despite having broad enough specificity to recognize all of the others. Differential epoxidation of this double bond would certainly require a separate enzyme. Referring to the complete stereochemical assignment by Satake et al.,^[34] it is striking that this region of the molecule is specifically noted as being highly challenging. In fact, the communication discusses this particular difficulty exclusively. Owing to overlap of signals in the ¹H NOESY NMR spectra, advanced 3D NMR experiments were required to assign the stereochemistry in this area of the molecule. In light of this and the results of our analyses, we propose that this assignment should be re-examined.

In conclusion, until now, mechanistic hypotheses for marine polyether ladder biosynthesis have not been considered in detail. Beyond the original Cane–Celmer–Westley extrapolation, as initially proposed by Shimizu and Nakanishi, only fragments of other models have been proposed or, often, only alluded to. These have been restricted to the brevetoxins. Herein we show that contiguous rings, in any single polyether, can be derived from stereochemically identical *trans* epoxides. This has allowed us to put forward a simple model that can explain the biosynthesis of the ring structure of all the marine polyether ladders thus far characterized. Finally, we propose that the established structure of the largest known non-polymeric

natural product, maitotoxin, may justifiably be questioned.

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