Published in final edited form as:
Chem Soc Rev. 2009 November ; 38(11): 3175–3192. doi:10.1039/b816697h.

The Development of Endo-Selective Epoxide-Opening Cascades in Water†

Christopher J. Morten, **Jeffery A. Byers**, **Aaron R. Van Dyke**, **Ivan Vilotijevic**, and **Timothy F. Jamison**
Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, MA 02139, USA

1. Introduction to the Ladder Polyethers

1.1. Biological Importance

Red tides are massive and harmful algal blooms (HABs) that can wreak tremendous environmental destruction. They poison and devastate fish, mammal, bird, and other marine populations, crippling the fishing, tourism, and other industries that depend on their continued health. The scientific community continues to investigate both the long-term and acute causes of red tides and strives to predict when these disasters will strike.[i] Remarkable detective work over the last 30 years by both chemists and biologists has implicated members of the ladder polyether family of natural products as the poisons responsible for the ill effects of many of these red tides.ii Ladder polyether toxins have been identified off the coasts of regions as disparate as Tahiti, Japan, Vietnam, and New Caledonia, and they are a regular threat to the west coast of Florida.iii

In addition to their importance as extraordinarily potent neurotoxins and agents of ecological destruction, ladder polyether natural products have long captivated organic chemists because of their fascinating structures; a few of the dozens of known compounds are shown in Figure 1.[iv] Because the toxicity of the larger members of the ladder polyether family arises from their very high affinity for binding to voltage-gated sodium, potassium, or calcium ion transport channel proteins, some of these natural products have proven useful as probes of protein structure and function, including the brevetoxins (**1** and **4**), the ciguatoxins (e.g., ciguatoxin 3C (**5**)), and gambierol (**2**).[2,4,v]

Although they are believed to share a common polyketide origin,[vi,vii] there is considerable diversity among ladder polyether natural products. Their complexity derives in part from the wide variety of oxacyclic ring sizes encountered, from five- up to nine-membered cyclic ethers. Individual rings may be fused together into ladders in numbers as few as four (as in the compact hemibrevetoxin B (**9**, Figure 1)) or as many as 15 (as in gymnocin B (**10**)). The truly massive maitotoxin (**11**), which represents the single largest nonbiopolymeric structure from nature to be characterized to date (as well as one of the most toxic),[viii] contains some 32 rings in four separate ladders. Across the family of structures, rings are occasionally decorated with methyl or hydroxyl substituents, while larger rings can contain a *cis*-alkene. While most ring junctions are substituted with two hydrogens, many bear a methyl substituent in place of one of the hydrogens (see gymnocin B (**10**)).

Despite the wide geographic dispersion of these poisons, the considerable phylogenetic variety of the dinoflagellates that produce them, and the remarkable size and complexity of these

†Part of the rapid formation of molecular complexity in organic synthesis themed issue.

compounds, they also show a surprising structural uniformity. All ladder polyethers share a conserved C-C-O bond motif that can be traced through the length of the ladder (see ciguatoxin 3C (**5**), Figure 1). Furthermore, the relative stereochemistry of the ladder ring junctions is almost invariably *trans-syn-trans* (see brevetoxin A (**4**), Figure 1), with the sole exception found in maitotoxin.[6,ix]

1.2. Total Synthesis of Ladder Polyethers

Due to their unique and fascinating structures, the ladder polyethers have attracted great attention from the synthetic community.[4,x,xi] The tremendous size and stereochemical complexity of the ladder polyethers have tested the limits of what organic chemistry can achieve. Their synthesis has invariably demanded monumental endeavors; witness the Nicolaou group's landmark total synthesis of brevetoxin B,[xii] which involves more than 100 individual synthetic operations. In the course of these total synthesis efforts, many new and powerful synthetic methodologies have been developed,[xiii] primarily for the construction of six membered-tetrahydropyran, seven memberedoxepane and oxepene, and eight membered-oxocane and oxocene rings, and for the controlled fusion of these rings in the appropriate *trans-syn-trans* geometry. As in all complex molecule synthesis, convergence has been emphasized, and, specifically, the prevailing paradigm has been that the convergent assembly of preformed ring systems is the most efficient route to the ladder polyethers. That is to say, the most common strategy is ring formation via cyclization or annulation steps that construct one or two rings at a time, followed by the piecing together of these ring systems, usually two to five rings at a time.

2. Biosynthesis and Biomimetic Synthesis of Ladder Polyethers

2.1. Nakanishi's Hypothesis and *endo*-Selective Epoxide-Opening Cascades

Despite its proven utility, the aforementioned synthetic strategy is conceptually quite distant from the proposed biosynthesis of the ladder polyethers. On the basis of carbon labeling and feeding experiments, Nakanishi and Shimizu suggested a polyketide origin of the carbon skeleton of these compounds,[6] and later studies from Rein and coworkers have corroborated this hypothesis.7 Still, much remains unknown about their biosynthesis, including major questions like how oxygen is incorporated and how the cyclic ethers are formed. This is not to suggest, of course, that chemists have not speculated on these unsolved problems. With Occam's razor in hand, Nakanishi dissected the unique structural regularity of the ladder polyethers and made an educated guess about the final steps of their biogenesis. His proposal has become known as the Nakanishi hypothesis (although similar prospective biosyntheses were advanced contemporaneously by Shimizuxiv and Nicolaou4›12). The hypothesis remains highly appealing in its elegance and concision despite the rather limited experimental evidence in its favor.

In this hypothesis, the distinctive repeating C-C-O pattern and *trans-syn-trans* ring junction stereochemistry of brevetoxin B are neatly explained by a *domino* or *cascade* reaction of multiple epoxide openings (Scheme 1). If each epoxide opening in such a cascade proceeded stereospecifically, with clean inversion of stereochemistry, then the all-(*R*,*R*)-polyepoxide **13** is the requisite cascade substrate. Remarkably, all eleven rings of brevetoxin B would thus be assembled in this one cascade, with no further manipulation of the cascade product required. Nakanishi proposed that **13** could arise from epoxidation of polyene precursor **12**; in theory, a single (*R*,*R*)-selective epoxidase could catalyze this transformation,[9] setting 20 of the natural product's 23 stereocenters.

2.2. The Nakanishi Hypothesis as Inspiration to Synthetic Chemists

Even as the details of ladder polyether biosynthesis remain very much a mystery, Nakanishi's proposal has been inspirational to synthetic chemists. Cascade reactions in general are outstanding tools for improving the economy and efficiency of synthesis.[xv] Even among cascades, however, the proposed two-step conversion of polyene **13** to brevetoxin B (**1**) scores remarkably highly in terms of key synthetic principles such as step economy[xvi] and atom economy.[xvii]

The *in vitro* emulation of this proposal for the rapid, one-pot assembly of multiple rings would greatly streamline the synthesis of ladder polyethers. Emulation of the penultimate step, the exhaustive stereoselective epoxidation of isolated *E* olefins, can be achieved thanks to the powerful and versatile Shi asymmetric epoxidation.xviii The epoxide-opening cascade remains more elusive. Such a cascade method must achieve very high yields for each ring formed in order to overcome the "arithmetic demon,"[xix] the precipitous decrease in yields inherent to one-pot processes involving many consecutive reactions.

2.3. Methods for *endo*-Regioselective Epoxide Opening

The sticking point is that achieving a good yield of the desired product in even a single epoxide-opening cyclization has historically been quite challenging. Intramolecular epoxide opening by an internal, pendent nucleophile (e.g., an alcohol, as shown in Scheme 2) can proceed via two distinct pathways, to afford regioisomeric products. These two pathways are frequently referred to as *exo* and *endo* processes, in reference to Baldwin's rules for cyclization.[xx,xxi] The climactic cascade of polyepoxide **13** to **1** involves no fewer than ten *endo* epoxide openings. Unfortunately for those seeking to mimic this cascade *in vitro*, pioneering work from Coxon and coworkers[xxii] and a battery of examples sincexxiii have shown that cyclizations of simple epoxy alcohols typically proceed through the spiro transition state to afford the *exo* product.

In simple epoxy alcohol cyclizations – "simple" implying that the epoxides involved are *trans*-disubstituted (as are the majority of epoxides in the proposed biosynthetic intermediates) and therefore electronically relatively unbiased – preferential formation of the smaller-ring *exo* product over the alternative, larger-ring *endo* product has been documented in manifold examples. Under basic, neutral, and acidic conditions, 5-*exo* cyclization generally predominates over 6-*endo*, so as to provide tetrahydrofuran (THF) rather than tetrahydropyran (THP) products.[23] Likewise, 6-*exo* epoxy alcohol cyclization has been shown to proceed in preference to 7-*endo* under acidic promotion, affording THP rather than 7-membered oxepane products.[xxiv]

To overcome this "intrinsic" selectivity, a number of ingenious and highly useful methods have been developed to enforce *endo*-selective epoxide-opening cyclization. Most of these methods rely on electronically biasing the epoxide with a directing group, either by discouraging reactivity through the spiro transition state en route to *exo* opening, as in the work of Mori[xxv] and Murai,[xxvi] or by stabilizing the fused transition state en route to *endo* opening, with key instances from the Nicolaou,xxvii McDonald,xxviii and Morimoto[xxix] groups, as well as a report from our group.[xxx] Scheme 3 provides a few representative examples of these methods. The majority of methods effect cyclization via acidic promotion (either Brønsted or Lewis); cyclizations in basic and neutral media have been studied less extensively.

For epoxides that are not strongly electronically biased, the prevailing wisdom has been that enzymatic control is necessary. A seminal report on protein-promoted *endo* epoxide opening was disclosed by Janda and coworkers,[xxxi] and recent work from Leadlayxxxii and Oikawaxxxiii has clearly shown that the epoxide hydrolase Lsd19 is essential to achieve *endo*-selective epoxide opening in the biosynthesis of lasalocid. It seemed that *directing group*-

free epoxide-opening cascades would not be possible without such enzymatic control, even though epoxide hydrolase enzymes analogous to Lsd19 have yet to be identified in the organisms that produce ladder polyethers.

3. Development of Water-Promoted Directing Group-Free Epoxide-Opening Cascades

3.1. Cascades Promoted by a Disappearing Directing Group

Before we began investigation of directing group-free cascades, our group developed a cascade method for ladder synthesis that was base-promoted and directed by trimethylsilyl (TMS) groups at each epoxide.[30] We found that these TMS groups could act as *disappearing* directing groups, protiodesilylated *in situ* with the aid of cesium fluoride to afford tetrahydropyran (THP) tetrad **26**, a characteristic subunit of ladder polyether natural products (Scheme 4).

While TMS directing groups are notable in that they can be efficiently removed during the cascade, their removal complicated the cascade conditions, and their stereocontrolled introduction made the synthesis of **25** rather challenging. Furthermore, the installation of a disappearing TMS group at a given position precludes the placement of a methyl group at that site, hindering the incorporation of methyl groups at ring junctions. To avoid some of the limitations associated with these directing groups, and to more closely emulate the Nakanishi hypothesis, we therefore sought to explore whether an *endo*-selective cascade might be possible without them.

In retrospect, an early clue towards what would become such a directing group-free method was observed in the course of our studies of TMS direction. Modifying the substrate from linear epoxy alcohol **27** to compound **30**, in which one THP ring has already been formed, resulted in a dramatic increase in *endo* regioselectivity (Scheme 5).xxxiv

3.2. Development of Directing Group-Free *endo*-Selective Epoxide-Opening Cyclizations

Abandoning directing groups reduces the number of possible approaches for control of regioselectivity in intramolecular epoxide-opening cyclization. While strong substrate control via powerful electronic directing groups on the epoxide electrophile would no longer be possible, we hoped that some element of substrate control could still play a role. The approach taken by our group stemmed from a rather simple analysis of the potential factors governing the regioselectivity of epoxide opening in these reactions.

We reasoned that pre-organization of the substrate in an appropriate fashion could encourage, or "*template*," the cyclization towards the *endo* pathway. We will herein use the term "template" to describe a molecular architecture that induces otherwise atypical reactivity and/or selectivity. Our initial working hypothesis was that a molecular template could alter the approach of the alcohol nucleophile to the epoxide electrophile and bias the substrate towards *endo* cyclization. In retrospect, such an effect would explain the unusual reactivity of **30**. Our initial analysis was predicated on a single assumption – that the greater stability of the desired 6,6-fused (*endo*) product **37** as compared to the undesired 6,5-fused (*exo*) product **38** could, with judicious design of the template, be translated into a kinetic selectivity (Scheme 6). We conjectured that the reaction of **36**, in which one THP is already in place and the epoxy alcohol appeared "primed" for cyclization, might go through more product-like transition states. Furthermore, preliminary calculations suggested that the predicted *trans*-bicyclo[4.4.0]decane transition state en route to **37** should be substantially less strained than the *trans*-bicyclo [4.3.0] nonane transition state proposed en route to **38**. Were this difference in developing ring strain reflected in the transition states, then the desired THP product might be favored in this templated system under the appropriate reaction conditions. Later mechanistic studies have

revealed that the basis of THP template effect is considerably more complex than our initial analysis assumed, but this germinal idea has proved quite fruitful nonetheless, as it led to the discovery of a powerful cooperative effect between the THP template and water as solvent (*vide infra*).

To evaluate this hypothesis, we prepared simple THP-templated epoxy alcohol **36**.[xxxv] Cyclization reactions of **36** were monitored under a variety of conditions (Table 1).

Based on our experience with trimethylsilyl-substituted epoxy alcohols **27** and **30**, we initially imagined that relatively forcing conditions would be necessary. Unfortunately, upon cyclization of **36** under the strongly basic conditions (Cs_2CO_3 in MeOH, Table 1, entry 1) that proved ideal for **27** and **30**, the undesired THF product **38** predominated. However, slight preference for the desired larger ring in THP **37** was observed under both Lewis and Brønsted acidic conditions (e.g., Table 1, entries 2 and 3).

Intrigued by this turnover in selectivity upon shifting from basic to acidic promotion, we moved reactions of **36** into aqueous media, wherein buffers allow for careful control of acid and base concentrations. Regioselectivity was examined in potassium phosphate buffers. These experiments revealed an unexpected and exciting trend. While the low *endo*:*exo* regioselectivity in strong aqueous acid and base (i.e., below pH 4 and above pH 10) was consistent with that observed in organic solvents, selectivity increased sharply on moving towards neutrality, with greater than 10:1 selectivity observed at pH 7 (Figure 2). The balance of acid and base found at neutral pH appeared essential, but the buffer clearly was not, as simple deionized water also promoted cyclization with greater than 10:1 *endo*:*exo* regioselectivity (Table 1, entry 4). Evidently, water is the key promoter, not potassium phosphate.

Several lines of evidence clearly indicate that water effects both a rate acceleration and an increase in selectivity in these reactions. In less polar solvents (e.g., CH_2Cl_2 and toluene), cyclization of **36** is slow, and in polar aprotic solvents (e.g., CH_3CN, dimethyl sulfoxide (DMSO), and *N*,*N*′-dimethylformamide (DMF)) some cyclization occurs, but the selectivity is greatly reduced (≤3:1 **37**:**38**). Intriguingly, the only neutral organic solvents that approach the selectivity and rate possible in water are ethylene glycol and methanol (Table 1, entries 5 and 6). Like water, both of these solvents are excellent hydrogen bond donors and acceptors, but conversion in these solvents was lower than that observed in aqueous media. Conversion and regioselectivity were lower still in bulkier alcohols like EtOH and *i*PrOH. Studies in water/THF mixtures showed that both increased *endo*:*exo* selectivity and increased conversion of **36** correlate with increased water content in the reaction medium (Figure 2).

Further evidence for the critical role of the THP template was provided by the recent work of Qu and coworkers,xxxvi who observed that the regioselectivity of epoxide opening in untemplated epoxy alcohol **33** in water (6:1 *exo*:*endo* regioselectivity, Scheme 7) was dramatically different than the 10:1 *endo* regioselectivity observed with the analogous, templated **36**. This attests to a *synergistic* relationship between THP template and water that is necessary to overturn the “intrinsic” *exo* regioselectivity normally observed in epoxide-opening cyclizations.

3.3. Mechanistic Analysis of Water-Promoted *endo*-Selective Epoxide-Opening Cyclization

Our attention was piqued by the power of water, in conjunction with a THP template, to promote *endo* opening. Exploration of the literature revealed that efforts directed towards understanding the reaction mechanism of aqueous intramolecular cyclizations of aliphatic epoxy alcohols have been mostly limited to theoretical studies.xxxvii,xxxviii However, the analogous *inter*molecular variant, epoxide solvolysis, has been studied more extensively.xxxix The most relevant of these studies, with seminal work from Long and Pritchart[xl] and more recent reports

by Pocker and coworkers,[xli] use product distributions, reaction kinetics, and solvent isotope effects to show that epoxide hydrolysis reactions can proceed by any one of three mechanisms depending on pH: an acid-catalyzed mechanism at low pH, a base-catalyzed mechanism at high pH, and a pH-independent or neutral mechanism at intermediate pH. Importantly, unsymmetrically substituted epoxides displayed different regioselectivities depending on reaction conditions. For example, propylene oxide (**41**) in isotopically labeled water undergoes hydrolysis at both sites of the epoxide. The ratio of ^{18}O incorporation at the secondary (**42**) versus the primary (**43**) position varies, with selectivities (**42**:**43**) of 2:1, 1:2, and 1:3 observed for reactions carried out under acidic, neutral, and basic conditions, respectively (Scheme 8).[40]

This pH-dependent regioselectivity was explained by the relatively greater ability of the secondary carbon to stabilize positive charge in the acid-catalyzed mechanism and by the relatively greater steric accessibility of the primary carbon in the base-catalyzed mechanism. In the neutral mechanism, both factors may contribute, leading to intermediate regioselectivity. Intriguingly, Pocker, among others, has suggested that the transition state for epoxide opening in the neutral manifold may have considerable zwitterionic character.[41]

Something similar was observed for the cyclization of epoxy alcohol **36**. Regioselectivities at high and low pH reflect those inherent to acid- and base-catalyzed mechanisms, while regioselectivities observed under neutral conditions apparently reflect selectivities inherent to a pH-independent mechanism (Scheme 9). A striking difference between hydrolysis reactions of propylene oxide and cyclizations of **36**, however, is that the cyclization of **36** under neutral conditions is surprisingly selective despite the fact that **36** is a 1,2-disubstituted epoxide with no obvious electronic or steric bias. Furthermore, as previously stated, the *endo*-selectivity observed under neutral conditions is markedly higher than the regioselectivity normally observed for epoxy alcohol cyclizations.

These observations suggested an interplay between the tetrahydropyran template and neutral water that was not well understood, and they prompted us to undertake a more detailed mechanistic study of epoxy alcohol cyclizations in neutral water.[xlii] A surprising finding during these studies was that the carbocyclic analog (**44**) of the original template reacted to give a nearly equal quantity of *endo* and *exo* cyclization products (Table 2). Furthermore, reaction kinetics revealed cyclization rates for **44** that are an order of magnitude faster than for **36**. A series of experiments determined that both reactions are kinetically controlled and occur in solution rather than on the surface of water or in micelles. Solvent isotope effects for both reactions are consistent with those measured for the pH-independent hydrolysis of epoxides, implicating a neutral mechanism.

Moreover, kinetic experiments carried out in water-rich dimethyl sulfoxide/water mixtures revealed a first-order dependence on the concentration of water for cyclizations of **44**, while cyclizations of **36** displayed evidence for two competing mechanisms that are first and second order in water, respectively. These studies of reaction rate and selectivity in water/DMSO mixtures were broadly consistent with what we had previously observed in water/THF mixtures (Figure 2). We must emphasize here that these experiments do not conclusively identify the *absolute* number of water molecules present around **36** in the transition state but simply indicate the *relative* excess in the number of water molecules required to promote reaction, *in addition to* those water molecules already in place around **36**, to solvate the epoxy alcohol. We surmised that the pathway that is first-order in water for THP **36** is similar to what is observed in cyclohexane **44** and is therefore unselective. To account for the high selectivity in cyclizations of **36**, we concluded that the pathway for **44** that is second order in water must be very selective for the *endo* product **37**.

From these experiments we hypothesized that epoxy alcohol cyclizations in water occur for hydrated conformations that are situated appropriately for reaction (Scheme 10). The presence of the oxygen in the template of **36** likely serves two functions. First, its inductive electron-withdrawing effect electronically biases the epoxy alcohol towards *endo* cyclization both by decreasing the nucleophilicity of the alcohol and by discouraging the development of positive charge at the nearby *exo* site of attack on the epoxide.

Second, the THP oxygen may also facilitate reaction through the putative *endo*-selective pathway that is second order in water, possibly via an intermediate with the tetrahydropyran template in a twist-boat conformation such as **45** (although **45** is depicted in Scheme 10 with three water molecules, it is possible that one of these molecules originates from the solvated ground state). If a conformer like **45** is indeed involved, then the observed synergistic relationship between the THP template and water as solvent could be partially explained by water's ability to encourage the twist boat conformation via hydrogen bonding. Water may also be essential to facilitate proton transfer from the alcohol to the epoxide oxygen during the reaction.

Reaction through conformer **45** significantly alters the trajectory of nucleophilic attack by the epoxy alcohol as compared to the reactive conformer in the first-order pathway, presumably one with the template in a chair conformation (**46**, Scheme 10). This fact is particularly relevant because theoretical studies carried out by Houk[37] and Coxon[38] indicate that the most important factor dictating regioselectivity in epoxy alcohol cyclizations is the angle with which the alcohol approaches the epoxide, with an incidence angle of 100° being optimal. Such a trajectory is ideal because it allows for maximum overlap between the hydroxyl lone pair and the $C–O_{epox}$ σ^* orbital. The critical role of nucleophile trajectory in determining the regioselectivity of epoxide-opening cyclization was also examined empirically by Stork and Cohen in their pioneering report on epoxynitrile cyclizations.[xliii]

Whatever the precise rationale, it is clear from these studies that an oxygen in the template is critical for *endo*-selective cyclization and that the conformational and electronic advantages that such a substitution engenders is amplified by interactions with neutral water molecules. It is important to note that the mechanistic studies carried out by our group were limited to monoepoxides and are, therefore, not necessarily applicable to cascade reactions of multiple epoxides. Nevertheless, we believe that many important factors required for *endo*-selective cyclizations have been identified, and we are currently applying lessons learned from this mechanistic work towards the rational design of more highly regioselective cascade templates.

3.4 Water-Promoted Epoxide-Opening Cascades

Having developed a directing group-free epoxide-opening cyclization, we were excited to explore the extension of this method to cascades of multiple epoxides. For the synthesis of cascade substrates, we again turned to Nakanishi's biogenetic hypothesis for inspiration. Emulating the penultimate step of the Nakanishi hypothesis, we began with an attempted exhaustive and stereoselective epoxidation of a polyene.

We found that bishomopropargylic alcohol **47** and its silyl ether derivative could be converted to skipped diyne **48** and skipped triyne **52** in high yield via alkylation with the appropriate propargylic bromides (Scheme 10).[xliv] Dissolving metal reduction of **48** and **52** afforded unstable skipped polyenes that were immediately subjected to Shi's asymmetric epoxidation method,[18] which capably effected one-pot exhaustive and stereoselective epoxidation to afford diepoxide **50** and triepoxide **53**. Notably, in the conversion of **52** to **53**, three epoxidations are performed in a single step, in 3:1 overall dr (3:1 being the ratio of the desired compound to the sum of all other diastereomers). Of the eight stereogenic centers contained in THP tetrad **54**, six are set in this one operation.

Stirring diepoxy alcohol **50** in deionized water for 24 hours at 70°C afforded THP triad **51** in 60% isolated yield (75% yield when corrected for the purity of **50**). Similarly, THP tetrad **54**, a characteristic structural subunit of the majority of known ladder polyethers, was obtained in 53% isolated yield (71% when corrected for starting material purity) upon the reaction of **53** in water.

These water-promoted transformations are notable for two reasons. First, epoxide opening proceeds with clean inversion, such that the requisite *trans-syn-trans* ladder polyether geometry is generated with complete stereospecificity. Second, after adjustment for the purity of cascade substrates **50** and **53**, the yields per epoxide opening of THP triad **51** and tetrad **54**, 87% and 89%, respectively, are quite good. In fact, the yields of these directing group-free cascades are markedly *better* than those observed in cascades guided by directing groups.[26,28,30] Even with silyl protection and deprotection steps adding to the total count, the assembly of THP tetrad **54** is notably concise; given that alkyne **47** can be synthesized in five steps from 2,3-dihydropyran,[xlv] polyether **54** is only eleven steps from commercially available starting materials.

3.5. Water-Promoted Epoxide-Opening Cascades Accommodate Methyl Substitution

Methyl groups are the only substituents other than hydrogen found at ladder polyether ring junctions. Indeed, at least one methyl-substituted junction is found in every member of this large family of natural products, and approximately one quarter of ring junctions across the whole set of structures are methylated (see Figure 1). For example, brevetoxin B (**1**) bears methyl substituents at five of its ten ring junctions. Methyl substituents also appear in **12** and **13**, Nakanishi's hypothesized polyene and polyepoxide precursors to brevetoxin B. Critically, the methyl groups that adorn the trisubstituted epoxides of **13** are encountered both *distal* (Me_d, Scheme 12) and *proximal* (Me_p) to the internal nucleophile. We herein refer to *distal* epoxides as being methyl-substituted at the *far* side of the epoxide with respect to that pendent nucleophile, at the *endo* site of attack, while *proximal* epoxides bear methyl substituents at the *near* side of the epoxide, on the *exo* site of attack (see inset, Scheme 12).

In Nakanishi's putative cascade of all (*R*,*R*)-polyepoxide **13**, a generic base deprotonates the leftmost carboxylic acid to generate a nucleophilic species. There is some discussion in the literature over whether **13** or all (*S*,*S*)-polyepoxide **55** is more likely a polyepoxide precursor to brevetoxin B; some contend that an activated carboxylate species (as shown in **55**) is more likely to serve as the terminal electrophile of the cascade.[9,12]

Again, the key point is that regardless of which direction the epoxide-opening cascade proceeds, both varieties of epoxide substitution will be encountered in the cascade, as both **13** and **55** contain a mixture of distal and proximal trisubstituted epoxides. Indeed, nearly all ladders bearing more than one methyl group, including the brevetoxins, maitotoxin, gambierol, and gymnocin B, are proposed to arise from similar polyepoxides bearing an “out-of-register” mixture of both distally and proximally substituted epoxides.

This point is quite important, as the methyl group can exert a rather powerful directing effect on the regioselectivity of epoxide opening, particularly under acidic activation – witness the acid-promoted *endo*-selective cascade methods developed by McDonald,[28] as well as methyl-directed *endo* cyclization methods from Morimoto[29] and Floreancig[xlvi] and the highly *exo*-selective methyl-directed epoxide-opening cascade in Corey's total synthesis of glabrescol.xlvii

When we began our work, there were no examples of the *endo*-selective opening of epoxides with methyl or other simple alkyl substituents proximal to the pendent nucleophile (at the *exo* site of attack), except under enzymatic catalysis[33] or in systems with a stronger electronic

directing group at the *endo* site of attack.xlviii Acid-activated *endo*-selective cascades accommodate distal substitution and, to a lesser extent, *trans*-disubstituted epoxides[28,46] but presumably cannot tolerate proximally trisubstituted epoxides. We conjectured that cascades of THP-templated epoxy alcohols promoted by neutral water could prove less sensitive to the electronic perturbation of methyl substitution.

We prepared monoepoxy alcohols **56** and **59**, the trisubstituted analogs of the disubstituted **36**, which respectively bear a methyl group proximal to the pendent hydroxyl nucleophile and a methyl group distal to the internal nucleophile (Table 3).[45] Upon cyclization of these compounds under Brønsted basic, Brønsted acidic, Lewis acidic, and aqueous promotion, we found that only water afforded the desired *endo* product for all three substrates. Furthermore, *endo* selectivity was *highest* for each substrate in neutral water, with 4.9:1 *endo* regioselectivity observed for the challenging proximally trisubstituted **56** and better than 20:1 selectivity achieved with distally trisubstituted **59**. Investigations of these systems in pH buffers indicated that peak *endo* selectivity occurs near neutral pH for both **56** and **59**, as it did for the disubstituted **36**.

The unique ability of water to promote the *endo*-selective opening of all three types of epoxides encountered in the Nakanishi hypothesis (*trans*-disubstituted, proximally methyl-substituted, and distally methyl-substituted) spurred us to attempt the cascade reactions of variously methyl-substituted diepoxy alcohols **62**, **64**, and **66** (Scheme 13). Water again proved successful, enabling the rapid construction of methylated THP triads **63**, **65**, and **67** in modest to good yields. While acidic activation of **64** and **66**, both of which bear distal methyl substituents, also afforded the desired product in both cases (in yields competitive with those obtained in water), only cascades in water provided *any* of THP triad **63** from diepoxide **62**. To the best of our knowledge, the transformation of **62** to **63** represents the first *endo*-selective epoxide-opening cascade to accommodate a proximal methyl substituent.

Recall that yields per epoxide opening in cascades of all-disubstituted polyepoxides **50** and **53** approached 90% (*vide supra*, Scheme 11), consistent with the 10:1 regioselectivity predicted by monoepoxide model system **36**. However, yields per epoxide in reactions of methylated diepoxides **62**, **64**, and **66** were substantially lower than expected, in light of the good regioselectivities observed with trisubstituted monoepoxides **56** and **59**. We submit that suppressing side reactions during cascades becomes more challenging with trisubstituted epoxides. Such epoxides are potentially both more nucleophilic, due to electronic donation by the methyl substituent, and more electrophilic at their tertiary centers in the presence of an acidic activator like the trace of hydronium ion in neutral water. This heightened reactivity could be a vulnerability, making undesired epoxide-on-epoxide activation competitive with the desired cascade pathway initiated by the templated alcohol. We have isolated side products from cascade reactions of **62**, **64**, and **66** that are consistent with epoxide-on-epoxide opening; such products have not been detected in reactions of **50** and **53**.[35] It is also possible that the mechanism of cascade reactions is simply more complex than we currently understand. Cascades require considerably higher temperatures and/or longer reaction times than single-epoxide cyclizations, a property we cannot fully explain but are currently studying.

Another recent example of an *endo*-selective epoxide-opening reaction of trisubstituted epoxides in water was disclosed by Qu and coworkers.[36] They found that diepoxy ketone **68** cyclized in water to afford the *endo* oxepane product **69** as the major product, along with a smaller quantity of the *exo* THF product **70** (Scheme 14). This regioselectivity is remarkably different from the high *exo* regioselectivity of intramolecular epoxide opening normally observed for linear systems in water (see Scheme 7); the difference may arise from a directing effect of the distal methyl substituents on the epoxides of **68**. Distal substitution could stabilize the development of carbocationic character on the *endo* sites of attack in those epoxides, which

may be critical if zwitterionic transition states are indeed involved in neutral water-promoted epoxide opening.

4. Epoxide-Opening Cascades in Total Synthesis

4.1. Seminal Work on *Exo*-Selective Opening

A number of total syntheses involve epoxide-opening cascades, but the vast majority are *exo*-selective.[23] For example, a number of efficient and beautiful epoxide-opening cascades have been applied to syntheses of polyether ionophores and squalene-derived polyethers. Many of these cascades closely mimic the Cane-Celmer-Westley proposal for polyether ionophore biogenesis.[xlix] Key demonstrations of such cascades have been reported by Hoye,[l] Schreiber,[li] Still,[lii] Paterson,[liii] Evans,[liv] and Corey,[47] with their reports among a number of landmark achievements in the development of *exo*-selective epoxide-opening cascades dating back into the 1980s (two canonical examples of such cascades, from Still and Schreiber, are shown in Scheme 15).

4.2. *Endo*-Selective Epoxide-Opening in the Total Synthesis

Given the difficulties associated with forging *endo*-selective epoxide-opening cascades, on the other hand, examples of their application to total synthesis have been scarce until quite recently. Discrete *endo*-cyclization steps have been employed in total synthesis contexts: for example the Nicolaou group made frequent and gainful use of its vinyl epoxide cyclization protocol (Scheme 3) in its historic syntheses of hemibrevetoxin B,[12] brevetoxin B,[12] and brevetoxin A.[lv] Scheme 16 shows characteristic examples of this method being used to form THP rings in high yield en route to brevetoxin B.

Mori and coworkers effectively implemented their own method for *endo*-selective cyclization onto sulfone-substituted epoxides (Scheme 3) in an impressive formal total synthesis of hemibrevetoxin B (Scheme 17).[lvi]

Each of these reactions is a cyclization of a *single* epoxide, however, not a cascade; notably, it was not until 2003 that Holton and coworkers became the first to incorporate an *endo*-selective epoxide opening into a selenonium-induced cascade of cyclizations in their synthesis of hemibrevetoxin B.[lvii]

Extensive application of *endo*-selective epoxide-opening cascades to total synthesis was reported by the McDonald group, who used two hybrid oxa/carbacyclization cascades in a closely biomimetic and remarkably concise synthesis of the enantiomer of the terpenoid abudinol (**87**, Scheme 18).lviii These Lewis acid-promoted cascades, each of which involves the opening of multiple epoxides, build on earlier studies from the McDonald group on the cascade synthesis of fused oxepane systems.[28] An early cascade reaction of diepoxide **84** rapidly assembles tricycle **85** in 50% yield (79% average yield per ring), and the two remaining rings of *ent*-abudinol (**87**) are constructed in short order via a second cascade of diepoxy alkene **86**, in 15% yield (39% average per ring).

Our group recently applied a bromonium-induced, *endo*-selective epoxide-opening cascade (conceptually related to those of Holton and McDonald) to the total synthesis of *ent*-dioxepandehydrothyrsiferol.[lix] While these cascades are not in water and therefore fall outside the scope of this review, they, along with earlier examples of epoxide-opening cyclization applied to the synthesis of natural products, serve as encouragement and as instructive comparisons for our own explorations into the utility of water-promoted epoxide opening in total synthesis.

4.3. An Application of Water-Promoted Epoxide-Opening Cascades towards Total Synthesis

We have thus far discussed how THP rings can effectively template epoxide-opening cascades in water to rapidly construct ladder polyether subunits. Unfortunately, because the THP templates used in all of these studies were bereft of substitution, the triand tetracyclic cascade products thereof could not be easily elaborated into larger natural products. As straightforward product derivatization is an indispensable criterion for any effective method in total synthesis, we consequently sought to replace the undecorated THP template with one more substituted, one where judicious choice of substituents could facilitate rapid elaboration of the cascade product into a natural product.

The substituted template we ultimately chose to investigate is ring *K* of the polyether gymnocin A (**8**).[lx] This highly cytotoxic natural product is one of the largest of the polyethers; at 14 consecutive rings gymnocin A is among the longest continuous ladders yet identified. We envisioned that a cascade of epoxide-openings initiated by the secondary alcohol on ring *K*, a highly functionalized THP (**89**), could construct three additional rings (*HIJ*) of the natural product. The *HIJK* fragment formed (**88**) would possess two sites for functionalization at *each* end of the ladder, making it a potentially synthetically versatile intermediate primed for elaboration into the full natural product (Scheme 19).[lxi]

Our retrosynthetic analysis began with this water-promoted cascade of triepoxy alcohol **89**, a cascade in which ring *K* would template the transformation (Scheme 15). Triepoxy alcohol **89** could, in turn, arise from cross-metathesis[62] of alkene **90** with another epoxy alkene. THP **90** could be liberated on cleavage of the acetal **91**, which could itself be prepared by cyclization of epoxy alcohol **92**. Significantly, the cyclization of **92** would involve a novel benzylidene acetal template (more generically referred to as a 1,3-dioxane template). We anticipated that this template would be “removable”; that is, it could be cleaved after cyclization to reveal handles for further synthetic manipulation.

Having never investigated benzylidene acetals as templates, we began with the synthesis and evaluation of **92** in this context. Inexpensive 2-deoxyribose (**93**) was transformed into epoxy alcohol **92** in 8 steps and 31% overall yield (Scheme 20).

Remarkably, epoxy alcohol **92** did not cyclize in water at ambient temperature, and heating the reaction led to hydrolysis of the acetal (Scheme 21). Clearly, the benzylidene acetal template behaves differently from the THP template. We conjecture that one reason that **92** does not cyclize appreciably in water at room temperature is the reduced nucleophilicity of the alcohol, a presumable result of the presence of a second inductively electron-withdrawing oxygen in the template. Consequently, we needed to identify a new promoter for this new template, and we gratifyingly found that silica gel (SiO_2) and its hydrated sibling, silicic acid (SiO_3H_2), serve as excellent promoters, promoting the cyclization with greater than 9:1 *endo* selectivity to afford the desired 6,6-fused bicycle **91** in good yield. We believe that silica, like water, can serve as both hydrogen bond donor and hydrogen bond acceptor and may thereby facilitate proton transfer during cyclization of the epoxy alcohol. Silica may represent a flexible and valuable scaffold for the design of new cyclization promoters. Other amphoteric oxides similar to silica, such as alumina, zinc oxide, and a wide variety of mixed metal and metalloid oxides, also marry Brønsted acidity and basicity, and achieving a balance between these properties could be essential for promoting opening with even higher regioselectivity.

In order to transform diad **91** into the ring *K* template, installation of an axial methyl group at the 3-position of the THP ring remained. This proved straightforward (Scheme 22), showcasing the synthetic flexibility of the benzylidene acetal and providing (in the form of **90**) the fully functionalized *K* ring of gymnocin A. Cross metathesis[lxii] of **90** with an excess of tetraepoxyalkene **96** and catalyzed by Hoveyda-Grubbs 2nd generation catalystlxiii afforded

97 and completed the assembly of the entire carbon framework of the *HIJK* rings. Such a cross metathesis tactic represents an alternative method for the efficient construction of skipped polyepoxide chains, one complementary to the strategy described earlier of skipped polyyne reduction under dissolving metal conditions and subsequent epoxidation (see Scheme 10). Alkene **97** was epoxidized via one final Shi asymmetric epoxidation,[18] and deprotection of the THP-templated secondary alcohol yielded triepoxy alcohol **89**, ready for cascade studies.

As our studies with cyclohexane-templated epoxy alcohols clearly indicated that template composition can radically affect the regioselectivity of epoxide opening, we could not be certain *a priori* whether ring *K* in **89**, which bears a methoxymethyl substituent at the 2-position as well as a tertiary alcohol and axial methyl group at the 3-position, would template the reaction as well as the undecorated THP template of **53** (Scheme 11). We were therefore pleased to discover that incubation of **89** in H_2O at 60 °C for 5 days followed by acetylation afforded some of the desired THP tetrad **88** (Scheme 23). We were surprised, however, to isolate a larger quantity of compound **98**, in which rings *IJ* had formed but the final epoxide remained intact.

The cascade reaction of **89** was intriguing. It appeared to proceed substantially more slowly than the cascade of analogous triepoxy alcohol **53** in water, wherein complete conversion was observed after 3 days at 70 °C. Moreover, prior to the isolation of **98** we had not observed any epoxide-containing intermediates en route to the final cascade products. The attenuated reactivity of the surviving epoxide of **98** is hypothesized to arise from the presence of the oxygen atom in the neighboring benzyl ether. An inductive electron-withdrawing effect could destabilize the formation of positive charge at the site of epoxide opening, an effect that could be pivotal if epoxide opening proceeds through a transition state with significant zwitterionic character. Deactivation of a given epoxide toward opening is a potentially useful feature that may find application in future cascades. A higher temperature and longer reaction time (80 °C, 9 d) overcame this stalled cascade and, upon acetylation, afforded **88**, the desired *HIJK* fragment of gymnocin A in 35% yield (38% adjusted for the purity of **89**), corresponding to approximately 70% yield per newly formed ring.

Notably, THP tetrad **88** bears four differently substituted pendent hydroxyl groups ready for synthetic elaboration. Its formation from **89** marked the first *endo*-selective cascade from a highly decorated THP template, a template of a form more likely to be encountered in nature than the simpler 2,3-disubstituted tetrahydropyranols we had studied previously. Still, we hesitate to speculate too much on what this result implies for the biosynthesis of gymnocin A (and other ladder polyether natural products). The success of this cascade clearly does not *prove* the Nakanishi hypothesis – one obvious incongruity is that marine dinoflagellates are unlikely to heat up to 90 °C or more for days on end in order to synthesize their secondary metabolites!

5. Conclusion

We have herein recounted the development of *endo*-selective epoxide-opening cascades in water, a method useful for the rapid assembly of fused tetrahydropyran structures found in ladder polyether natural products. Throughout our work we have been guided and inspired by Nakanishi's famous hypothesized biosynthesis of these fascinating and forbidding natural products. While we cannot claim to be rigorously testing the Nakanishi hypothesis, we strive to emulate its concision. Our intellectual journey has in a sense carried us ever more closely towards this biogenetic hypothesis, as we have progressed from trimethylsilyl-directed cascades in organic solvent to directing group-free cascades in water, the biological reaction medium, and finally to a cascade templated by a “real” template, the *K* ring of gymnocin A. Adding to the intrigue is the recent isolation of the tetrahydropyranol brevisamide from *Karenia*

brevis by Wright, Baden, and coworkers,[lxiv] who suggest that the compound might point to the existence of a tetrahydropyran template in nature.

Many outstanding challenges remain. Not least among these are the invention of methods for seven- and eight-membered ring formation via *endo*-selective epoxide opening and the development of new templates and small molecule catalysts to expedite epoxide-opening cascades. We continue our ongoing mission: to seek out new cascade reactions that can reduce the staggering complexity of ladder polyethers to simpler problems.

References

i. Sellner KG, Doucette GJ, Kirkpatrick GJ. J. Ind. Microbiol. Biotechnol 2003;30:383. [PubMed: 12898390]

ii. Yasumoto T, Murata M. Chem. Rev 1993;93:1897.

iii. For an article on the economic and environmental impact of red tides on the Gulf Coast of Florida, see: Schrope M. Nature 2008;452:24. [PubMed: 18322500]

iv. Nicolaou KC, Frederick MO, Aversa RJ. Angew. Chem. Int. Ed 2008;47:7182.

v. For a few examples of the use of ladder polyethers as probes of ion transport channel protein function, see: (a) Baden DG, Bourdelais AJ, Jacocks H, Michelliza S, Naar J. Environ. Health Perspect 2005;113:621. [PubMed: 15866774] . (b) Matile S, Nakanishi K. Angew. Chem. Int. Ed. Engl 1996;35:757.. (c) Ghiaroni V, Sasaki M, Fuwa H, Rossini GP, Scalera G, Yasumoto T, Pietra P, Bigiani A. Toxicol. Sci 2005;85:657. [PubMed: 15689421]

vi. (a) Lee MS, Qin G.-w. Nakanishi K, Zagorski MG. J. Am. Chem. Soc 1989;111:6234. (b) Chou H-N, Shimizu Y. J. Am. Chem. Soc 1987;109:2184.

vii. (a) Snyder RV, Gibbs PDL, Palacios A, Abiy L, Dickey R, Lopez JV, Rein KS. Mar. Biotechnol 2003;5:1. [PubMed: 12925913] (b) Snyder RV, Guerrero MA, Sinigalliano CD, Winshell J, Perez R, Lopez JV, Rein KS. Phytochemistry 2005;66:1767. [PubMed: 16051286]

viii. Murata M, Naoki H, Iwashita T, Matsunaga S, Sasaki M, Yokoyama A, Yasumoto T. J. Am. Chem. Soc 1993;115:2060.

ix. Gallimore AR, Spencer JB. Angew. Chem. Int. Ed 2006;45:4406.

x. Nakata T. Chem. Rev 2005;105:4314. [PubMed: 16351046]

xi. At least three additional total syntheses of ladder polyethers have been reported since the publication of ref. 4. (a) Crimmins MT, Zuccarello JL, Ellis JM, McDougall PJ, Haile PA, Parrish JD, Emmitte KA. Org. Lett 2009;11:489. Brevetoxin A. [PubMed: 19099481] . (b) Hamajima A, Isobe M. Angew. Chem. Int. Ed 2009;48:2941. Ciguatoxin. . (c) Takamura H, Kikuchi S, Nakamura Y, Yamagami Y, Kishi T, Kadota I, Yamamoto Y. Org. Lett 2009;11:2531. Brevenal. [PubMed: 19441795]

xii. Nicolaou KC. Angew. Chem. Int. Ed. Engl 1996;35:589. and references therein.

xiii. Inoue M. Chem. Rev 2005;105:4379. [PubMed: 16351048]

xiv. Shimizu, Y. Natural Toxins: Animal, Plant, and Microbial. Harris, JB., editor. Clarendon; Oxford: 1986. p. 123

xv. Nicolaou KC, Edmonds DJ, Bulger PG. Angew. Chem. Int. Ed 2006;45:7134.

xvi. Wender, PA.; Miller, BL. Organic Synthesis: Theory and Applications. Hudlicky, T., editor. Vol. vol. 2. JAI; Greenwich: 1993. p. 27-66.

xvii. Trost BM. Science 1991;254:1471. [PubMed: 1962206]

xviii. Wang Z-X, Tu Y, Frohn M, Zhang J-R, Shi Y. J. Am. Chem. Soc 1997;119:11224.

xix. Crispino GA, Ho PT, Sharpless KB. Science 1993;259:64. [PubMed: 8418495]

xx. Baldwin JE. J. Chem. Soc. Chem. Commun 1976;18:734.

xxi. Technically, since the breaking C–O bond is outside the newly formed ring in the transition states to both "*endo*" product **15** and "*exo*" product **16**, both processes are formally *exo*. A more rigorous description of **15** and **16** would be "large ring" product and "small ring" product, respectively. Alternatively, **15** may be described as the product arising from a *fused* transition state, while **16**

arises from a *spiro* transition state. However, we will use the "*endo*" and "*exo*" terminology throughout this article, as it is deeply ingrained in the literature and serves as a convenient shorthand.

xxii. Coxon JM, Hartshorn MP, Swallow WH. Aust. J. Chem 1973;26:2521.

xxiii. Vilotijevic I, Jamison TF. Angew. Chem. Int. Ed 2009;48:5250.

xxiv. Iimori T, Still WC, Rheingold AL, Staley DL. J. Am. Chem. Soc 1989;111:3439.

xxv. Mori Y, Furuta H, Takase T, Mitsuoka S, Furukawa H. Tetrahedron Lett 1999;40:8019. and references therein.

xxvi. Tokiwano T, Fujiwara K, Murai A. Chem. Lett 2000:272. and references therein.

xxvii. Nicolaou KC, Prasad CVC, Somers PK, Hwang CK. J. Am. Chem. Soc 1989;111:5330.

xxviii. Valentine JC, McDonald FE. Synlett 2006;12:1816. and references therein.

xxix. Morimoto Y, Nishikawa Y, Ueba C, Tanaka T. Angew. Chem. Int. Ed 2006;45:810.

xxx. (a) Heffron TP, Jamison TF. Org. Lett 2003;5:2339. [PubMed: 12816443] (b) Simpson GL, Heffron TP, Merino E, Jamison TF. J. Am. Chem. Soc 2006;128:1056. [PubMed: 16433504]

xxxi. Janda KD, Shevlin CG, Lerner RA. Science 1993;277:936.

xxxii. Smith L, Hong H, Spencer JB, Leadlay PF. ChemBioChem 2008;9:2967. [PubMed: 19025863]

xxxiii. Shichijo Y, Migita A, Oguri H, Watanabe M, Tokiwano T, Watanabe K, Oikawa H. J. Am. Chem. Soc 2008;130:12230. [PubMed: 18710235]

xxxiv. Heffron, TP. Ph.D. thesis. Massachusetts Institute of Technology; 2005.

xxxv. Vilotijevic I, Jamison TF. Science 2007;317:1189. [PubMed: 17761875]

xxxvi. Wang Z, Cui Y-T, Xu Z-B, Qu J. J. Org. Chem 2008;73:2270. [PubMed: 18288864]

xxxvii. Na J, Houk KN, Shevlin CG, Janda KD, Lerner RA. J. Am. Chem. Soc 1993;115:8453.

xxxviii. Coxon JM, Thorpe AJ. J. Org. Chem 1999;64:5530. [PubMed: 11674617]

xxxix. Whalen, DM. Advances in Physical Organic Chemistry. Richard, JP., editor. Vol. 40. Elsevier; Boston: 2005. p. 247

xl. Long FA, Pritchard JG. J. Am. Chem. Soc 1956;78:2663.

xli. Pocker Y, Ronald BP, Anderson KW. J. Am. Chem. Soc 1988;110:6492. and references therein.

xlii. Byers JA, Jamison TF. J. Am. Chem. Soc 2009;131:6383. [PubMed: 19385615]

xliii. Stork G, Cohen JF. J. Am. Chem. Soc 1974;96:5270.

xliv. Jeffery T, Gueugnot S, Linstrumelle G. Tetrahedron Lett 1992;33:5757.

xlv. Morten CJ, Jamison TF. J. Am. Chem. Soc 2009;131:6687.

xlvi. Wan S, Gunaydin H, Houk KN, Floreancig PE. J. Am. Chem. Soc 2007;129:7915. [PubMed: 17547399]

xlvii. Xiong Z, Corey EJ. J. Am. Chem. Soc 2000;122:9328.

xlviii. Matsukura H, Morimoto M, Koshino H, Nakata T. Tetrahedron Lett 1997;38:5545.

xlix. Cane DE, Celmer WD, Westley JW. J. Am. Chem. Soc 1983;105:3594.

l. (a) Hoye TR, Suhadolnik JC. J. Am. Chem. Soc 1985;107:5312. (b) Hoye TR, Witowski NE. J. Am. Chem. Soc 1992;114:7291. and references therein.

li. Schreiber SL, Sammakia T, Hulin B, Schulte G. J. Am. Chem. Soc 1986;108:2106.

lii. Still WC, Romero AG. J. Am. Chem. Soc 1986;108:2105.

liii. Paterson I, Craw PA. Tetrahedron Lett 1989;30:5799. and references therein.

liv. Evans DA, Ratz AM, Huff BE, Sheppard GS. J. Am. Chem. Soc 1995;117:3448.

lv. Nicolaou KC, Yang Z, Shi G-Q, Gunzer JL, Agrios KA, Gartner P. Nature 1998;392:264. [PubMed: 9521320]

lvi. Mori Y, Yaegashi K, Furukawa H. J. Org. Chem 1998;63:6200. and references therein. [PubMed: 11672250]

lvii. Zakarian A, Batch A, Holton RA. J. Am. Chem. Soc 2003;125:7822. [PubMed: 12822999]

lviii. Tong R, McDonald FE. Angew. Chem. Int. Ed 2008;47:4377.

lix. Tanuwidjaja J, Ng S-S, Jamison TF. J. Am. Chem. Soc 2009;131:12084. [PubMed: 19663441]

lx. For the isolation and initial toxicity studies of gymnocin A, see: (a) Satake M, Shoji M, Oshima Y, Naoki H, Fujita T, Yasumoto T. Tetrahedron Lett 2002;43:5829.. One total synthesis of **3** has been

reported to date: (b) Tsukano C, Sasaki M. J. Am. Chem. Soc 2003;125:14294. and references therein. [PubMed: 14624575]

lxi. Van Dyke AR, Jamison TF. Angew. Chem. Int. Ed 2009;48:4430.

lxii. (a) Blackwell HE, O'Leary DJ, Chatterjee AK, Washenfelder RA, Bussmann DA, Grubbs RH. J. Am. Chem. Soc 2000;122:58. (b) O'Leary DJ, Blackwell HE, Washenfelder RA, Grubbs RH. Tetrahedron Lett 1998;39:7427.

lxiii. Garber SB, Kingsbury JS, Gray BL, Hoveyda AH. J. Am. Chem. Soc 2000;122:8168.

lxiv. Satake M, Bourdelais AJ, Van Wagoner RJ, Baden DG, Wright JLC. Org. Lett 2008;10:3465. [PubMed: 18646771]

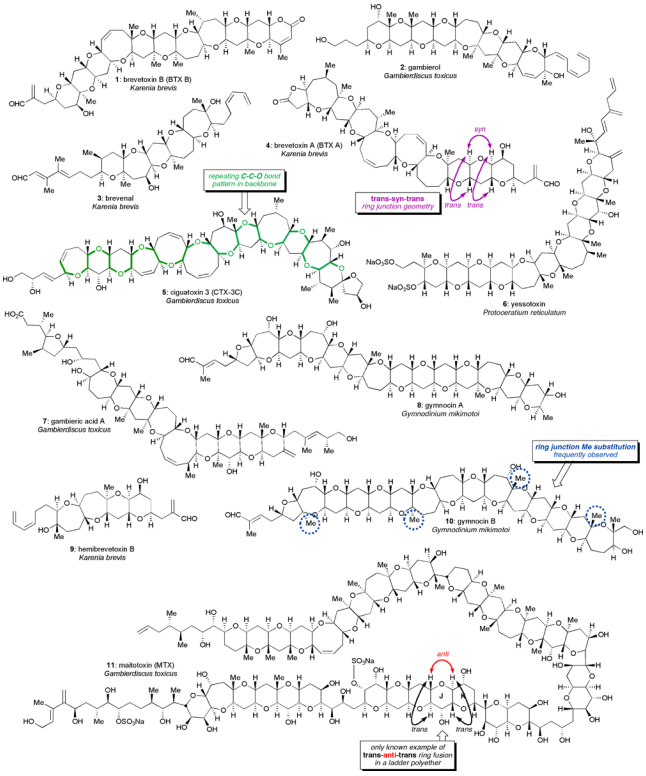


Figure 1.
Representative structures from the ladder polyether family of natural products.

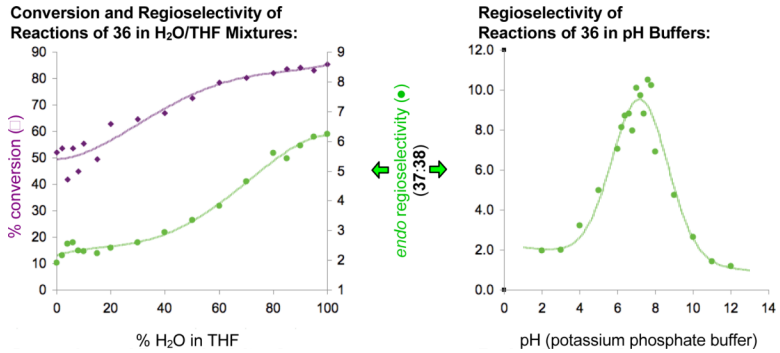
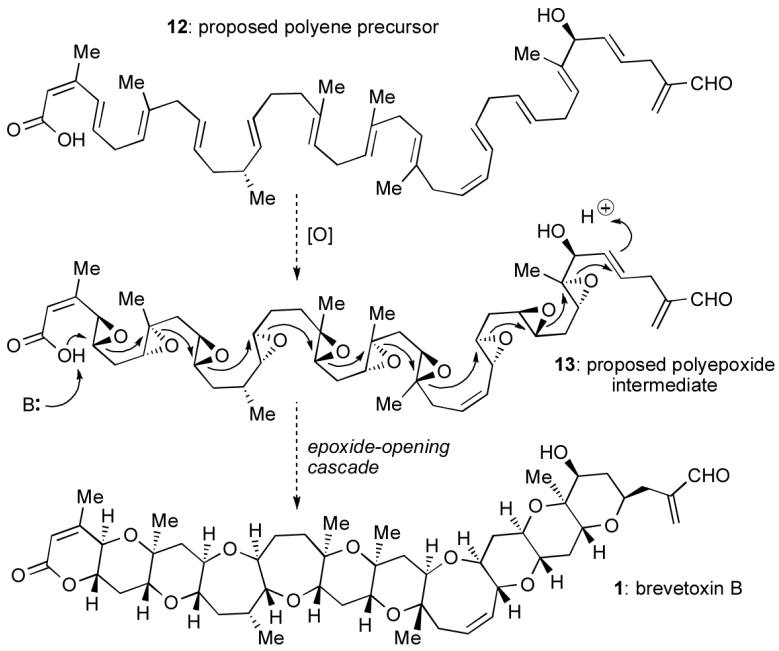
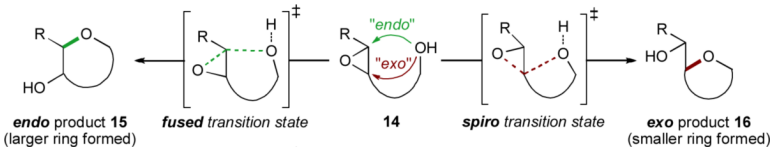


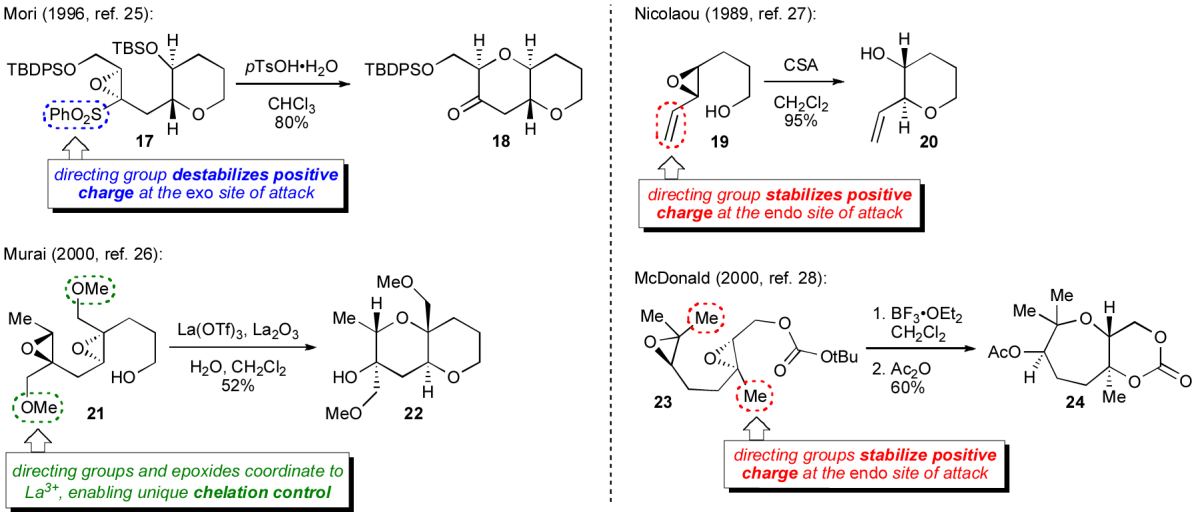
Figure 2.
Regioselectivity of cyclization of **36** in H_2O/THF mixtures and at various pH.



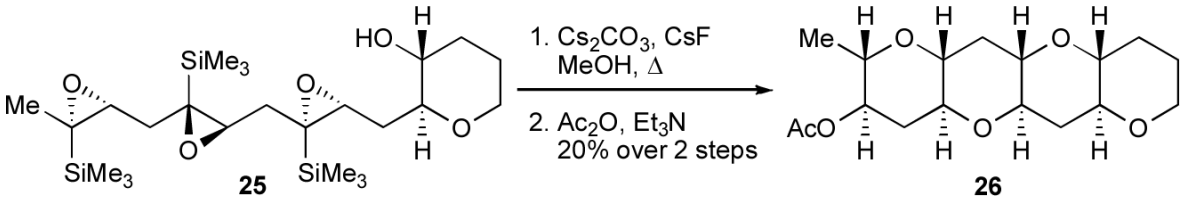
Scheme 1.
Nakanishi's proposed biosynthesis of brevetoxin B.



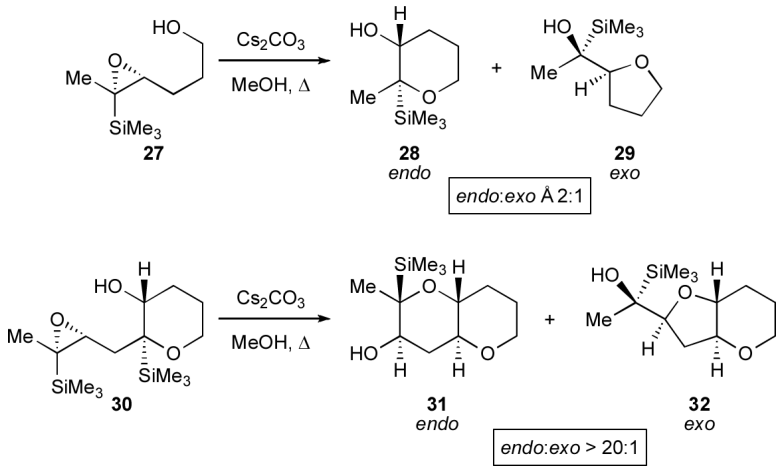
Scheme 2.
Regiochemical possibilities for intramolecular epoxide opening.



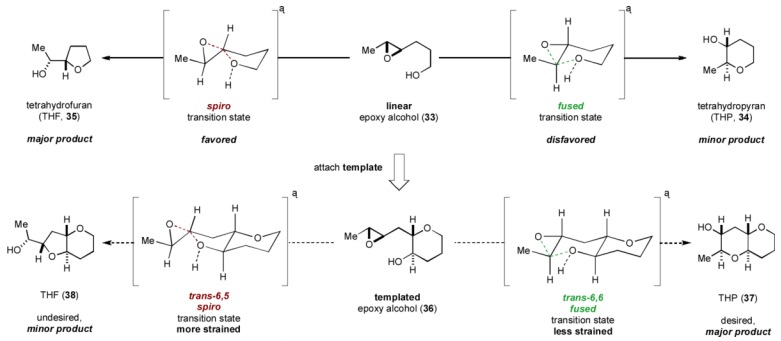
Scheme 3.
Directed *endo*-selective methods for epoxide-opening cyclization.



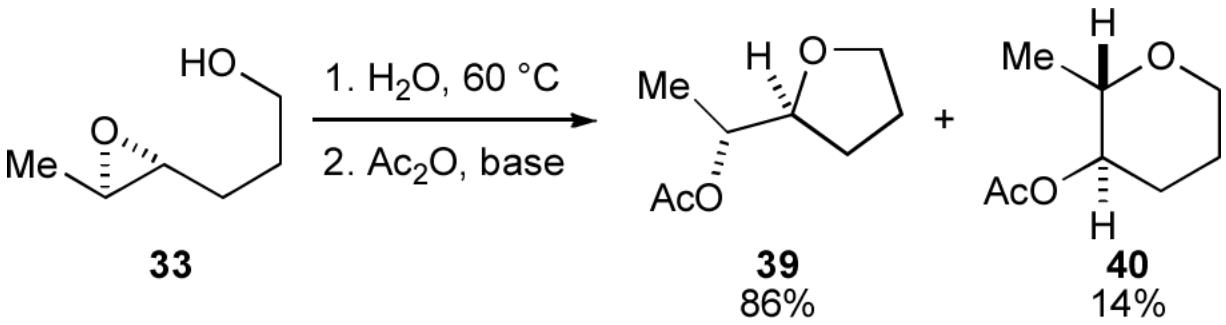
Scheme 4.
Trimethylsilyl-directed epoxide-opening cascade.



Scheme 5.
Early suggestions of a template effect.

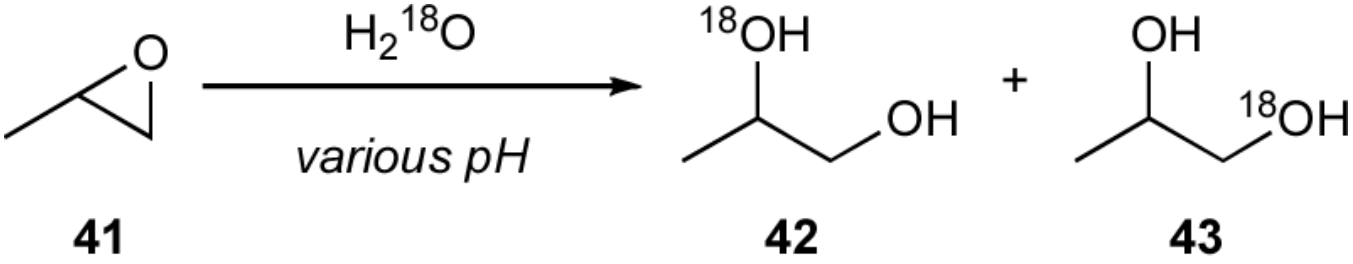


Scheme 6.
Initial analysis and design of a THP template.



33 **39** 86% **40** 14%

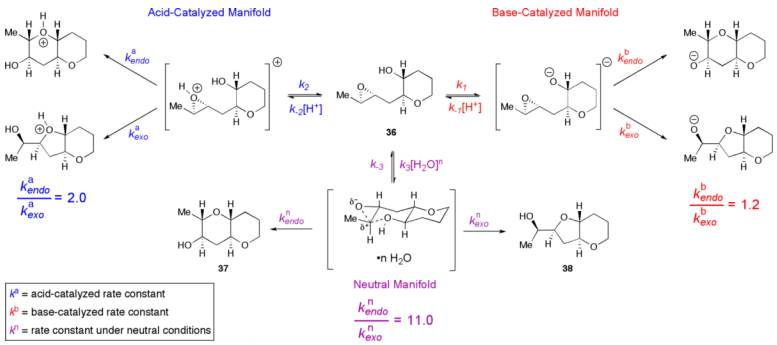
Scheme 7.
Exo-selective cyclization of linear epoxy alcohol **33**.



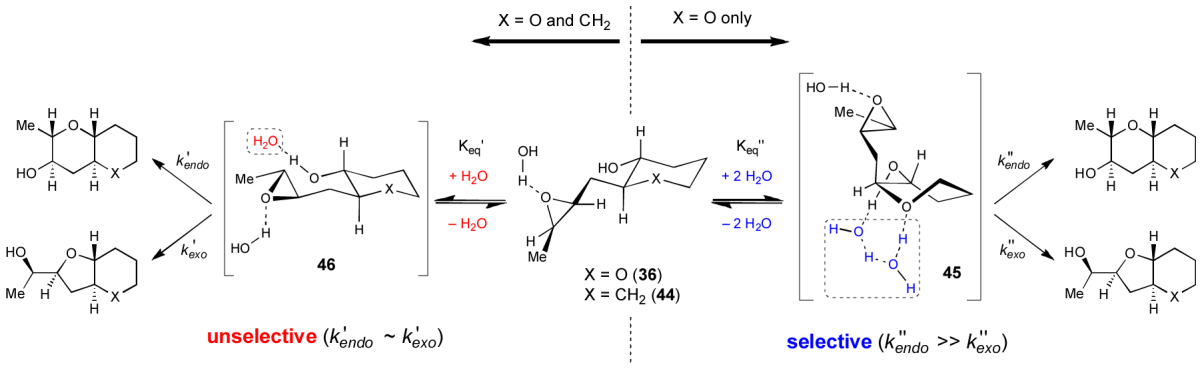
41 **42** **43**

entry	pH	observed rate	42:43
1	0.6	k^{a}_{obs}[**41**][H^{+}]	66:34
2	7.0	k^{n}_{obs}[**41**]	36:64
3	14.0	k^{b}_{obs}[**41**][OH^{-}]	22:78

Scheme 8.
Hydrolysis of propylene oxide under acidic, neutral, and basic conditions.

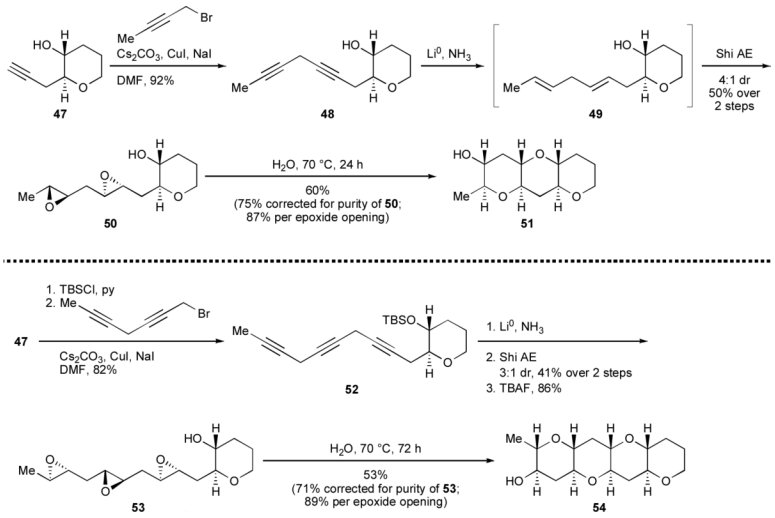


Scheme 9.
Proposed pathways for cyclization of **36** in aqueous solutions at various pH.



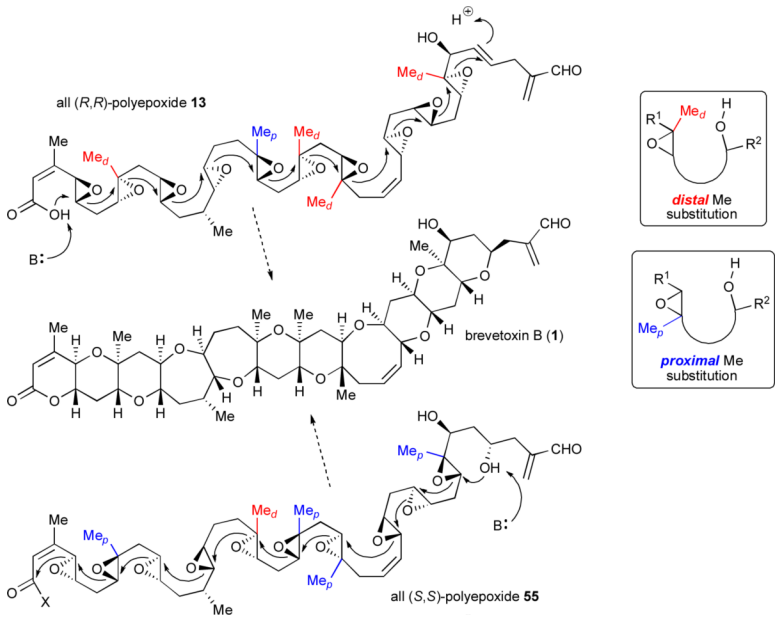
Scheme 10.

Proposed mechanism for the cyclizations of **36** and **44** in neutral water. Proton transfer step(s) are omitted for clarity. The highlighted water molecules indicate the number and not necessarily the identity of water molecules that are kinetically relevant. Other water molecules represent generic waters of solvation.

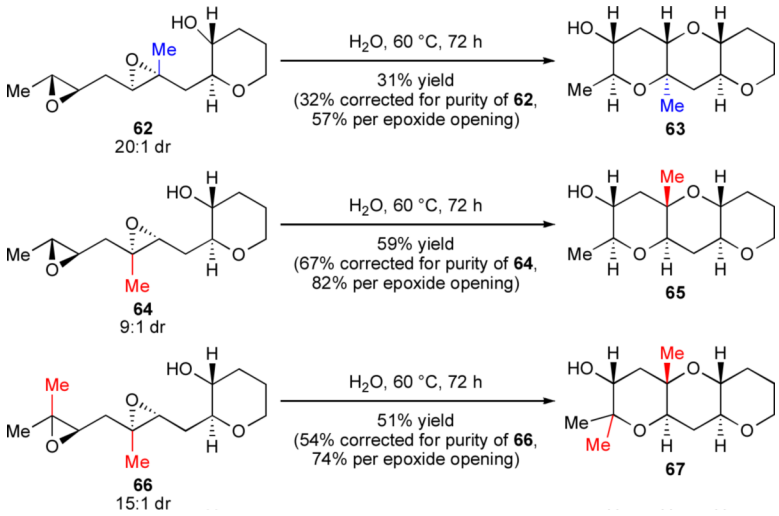


Scheme 11.

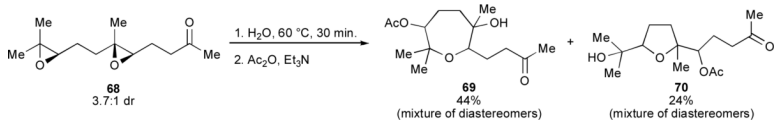
Directing group-free epoxide-opening cascades (Shi AE = Shi asymmetric epoxidation).



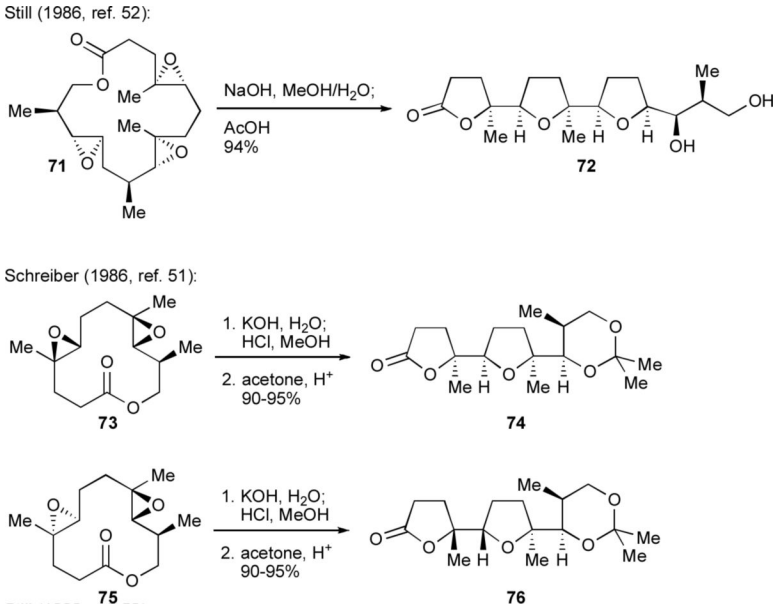
Scheme 12.
Two proposed biosyntheses of brevetoxin B.



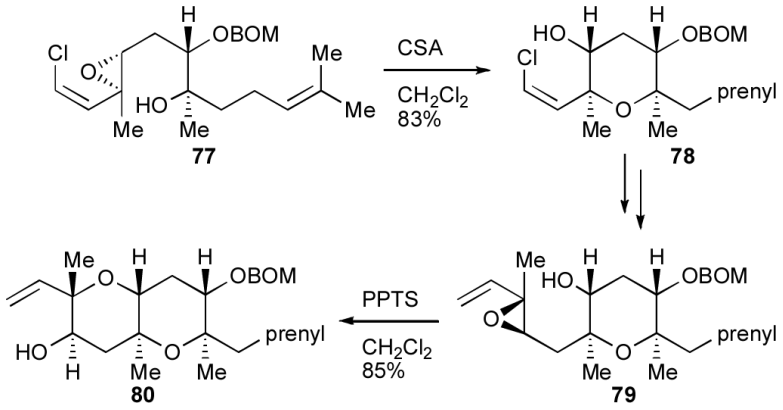
Scheme 13.
Endo-selective cascades of methyl-substituted epoxides.



Scheme 14.
Water-promoted, *endo*-selective epoxide opening in a linear system.

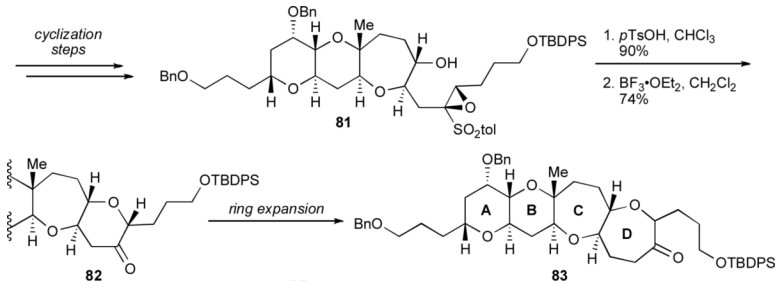


Scheme 15.
Exo-selective cascades applied to the synthesis of subunits of monensin.

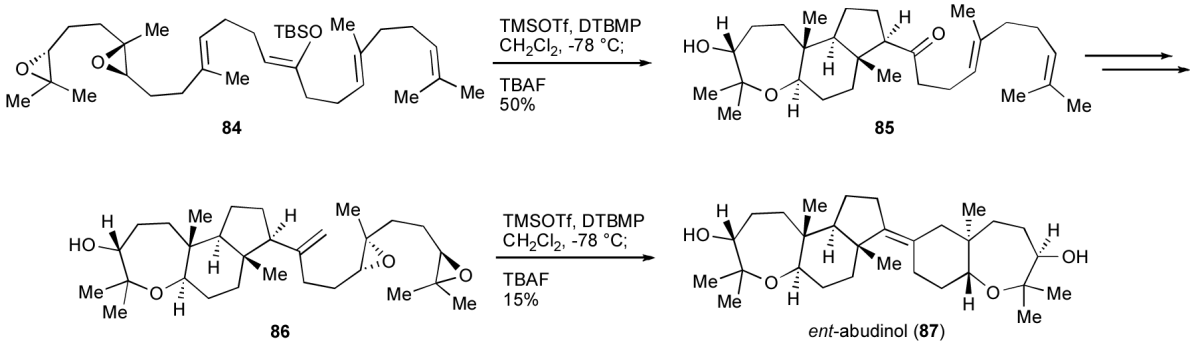


Scheme 16.

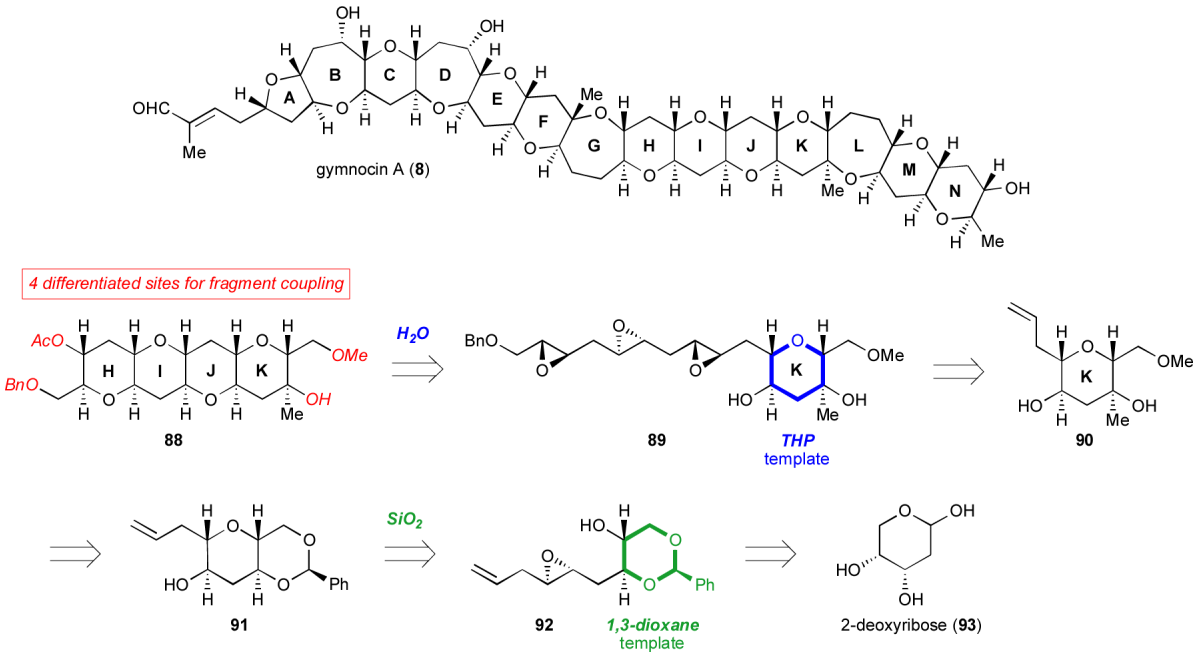
Endo-selective epoxide-opening cyclizations in the synthesis of the FG rings of brevetoxin B.



Scheme 17.
Endo-selective epoxide-opening cyclization in the synthesis of hemibrevetoxin B.

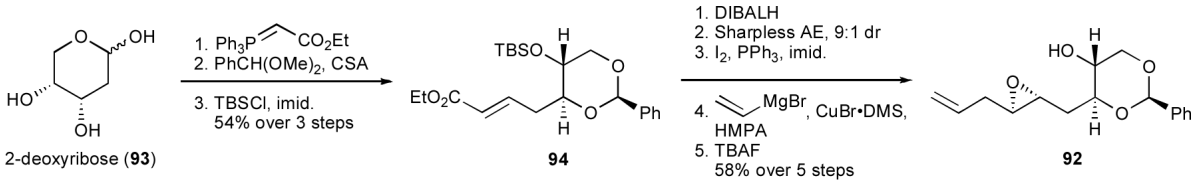


Scheme 18.
Biomimetic synthesis of *ent*-abudinol (DTBMP = 2,6-di-*t*-butyl-4-methylpyridine).

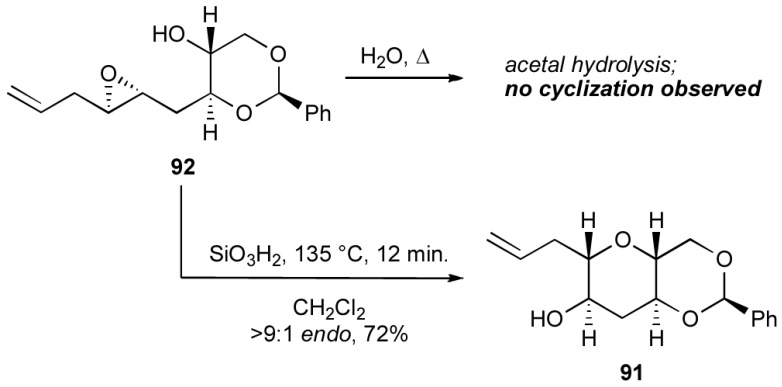


Scheme 19.

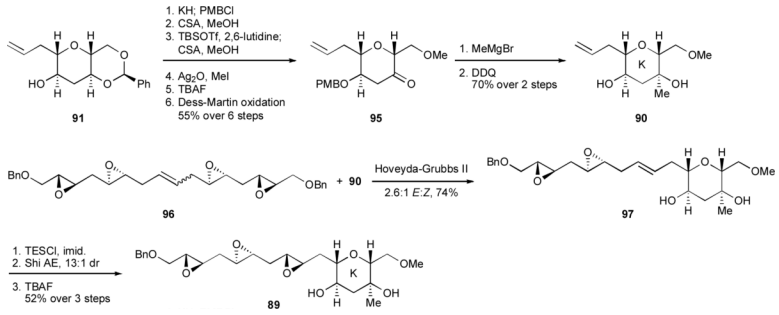
Retrosynthetic analysis of the *HIJK* ring system of gymnocin A.



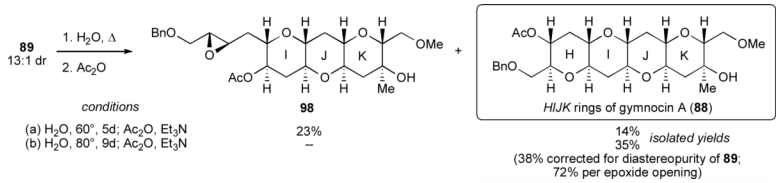
Scheme 20.
Synthesis of epoxy alcohol **92**.



Scheme 21.
Cyclization of 1,3-dioxane-templated epoxy alcohol **92**.



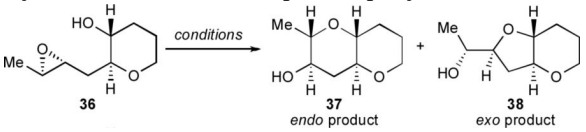
Scheme 22.
Synthesis of the *K* ring of gymnocin A.



Scheme 23.
Cascade synthesis of the *HIJK* rings of gymnocin A.

Table 1

Cyclization studies of templated epoxy alcohol **36**.

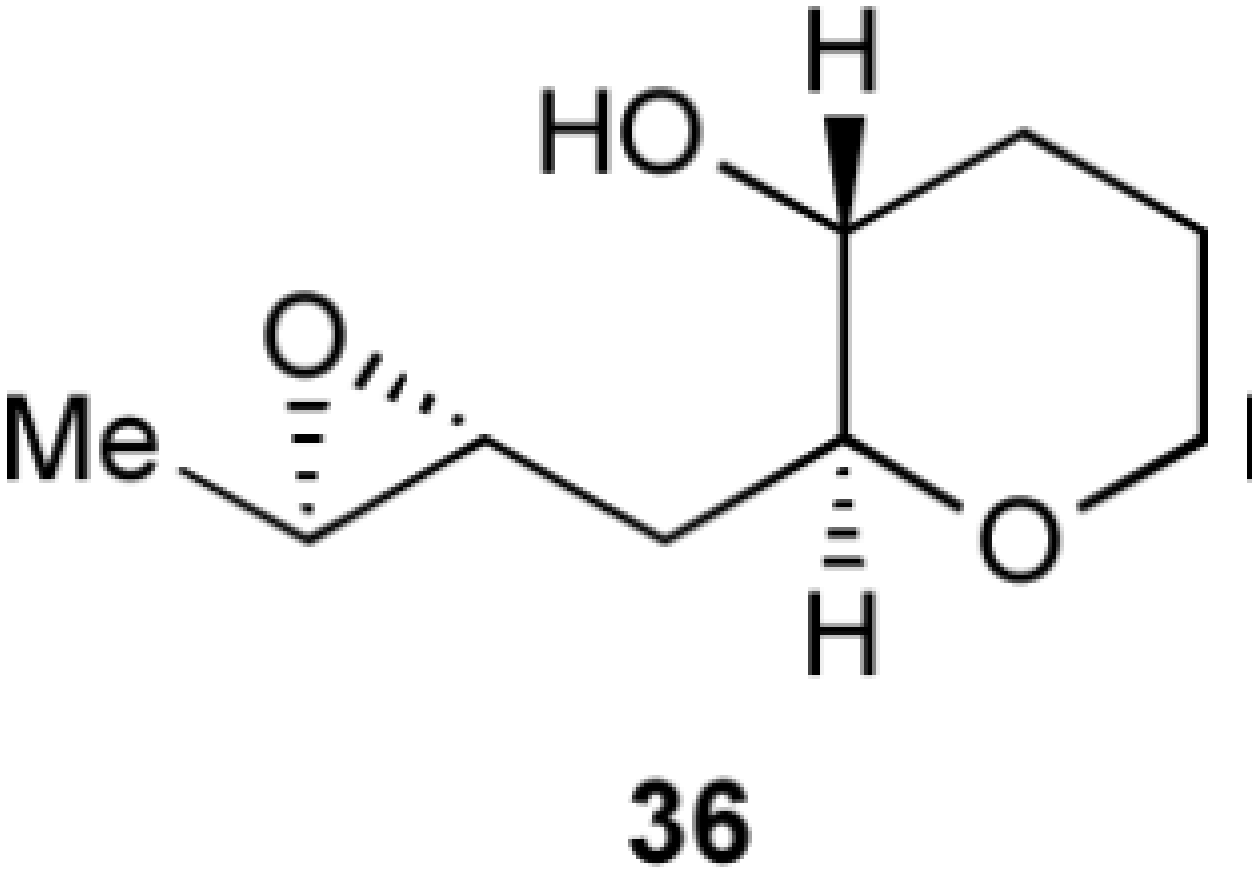


36 **37** *endo* product **38** *exo* product

entry	condition	*product ratio* (37:38)
1	Cs_2CO_3, MeOH	1:2.7
2	BF_3•OEt_2, CH_2Cl_2	1.4:1
3	AcOH, PhMe	1.6:1
4	H_2O (rt or 60 °C)	>10:1
5	ethylene glycol	9:1
6	methanol	8:1

Table 2

Summary of kinetic experiments carried out for the cyclizations of **36** and **44** in water at 45 °C (pH 7, 0.1 M potassium phosphate buffer).



36

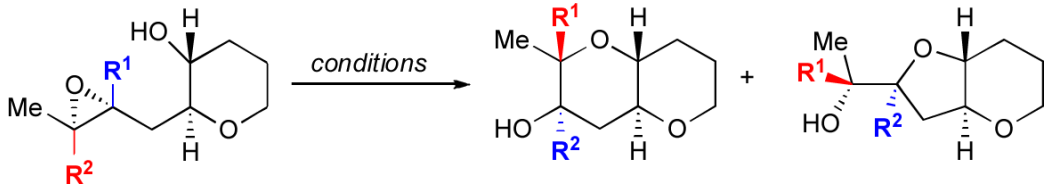
endo:*exo*	11.0
k_{obs} (10^{-4}, S^{-1})	0.47
$t_{1/2}$ (h)	4.11
k_{H2O}/k_{D2O}	1.33
kinetic order in water[a]	1st *and* 2nd [b]

[a] determined in DMSO-d_6/D_2O mixtures.

[b] 70 °C.

Table 3

Effect of Methyl Substitution on the Regioselectivity of Epoxide Opening under Various Conditions.



epoxy alcohol | *endo* product | *endo* product

R^1 = H, R^2 = H:	**36**	**37**	**38**
R^1 = Me, R^2 = H:	**56**	**57**	**58**
R^1 = H, R^2 = Me:	**59**	**60**	**61**

			conditions and regioselectivity (*endo:exo*)			
epoxy alcohol	**R^1**	**R^2**	**Cs_2CO_3, MeOH**	**CSA, CH_2Cl_2**	**BF_3•OEt_2, CH_2Cl_2**	**H_2O**
36	H	H	1 :2.7	1 : 1.2	1.4 : 1	**10 : 1**
56	Me	H	3.0 : 1	1 : 5.2	1 : 11	**4.9 : 1**
59	H	Me	1 : 17	5.8 : 1	>20 : 1	**>20 : 1**