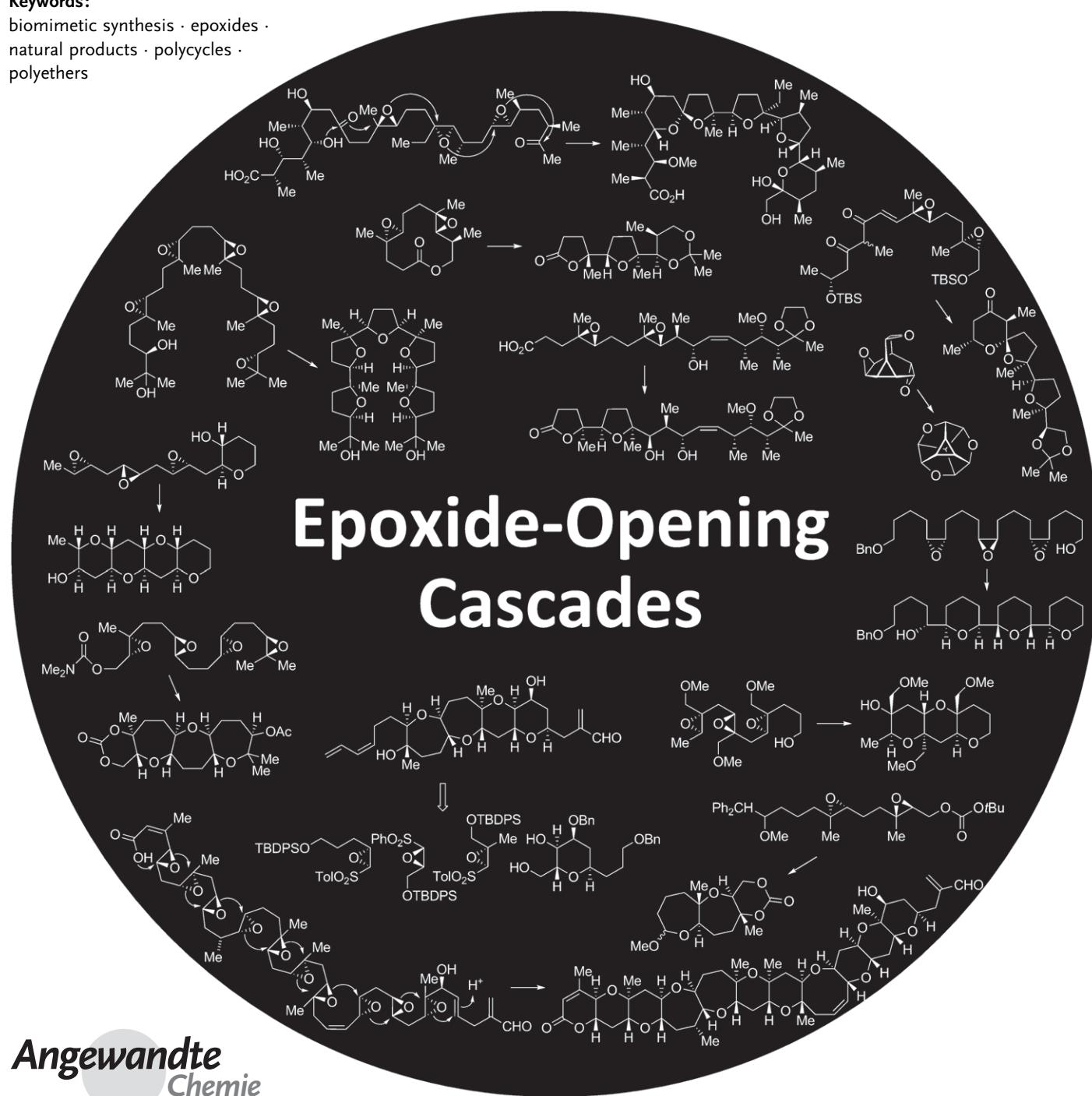# Epoxide-Opening Cascades in the Synthesis of Polycyclic Polyether Natural Products

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Epoxide-Opening Cascades

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*T*he group of polycyclic polyether natural products is of special interest owing to the fascinating structure and biological effects displayed by its members. The latter includes potentially therapeutic antibiotic, antifungal, and anticancer properties, and extreme lethality. The polycyclic structural features of this class of compounds can, in some cases, be traced to their biosynthetic origin, but in others that are less well understood, only to proposed biosynthetic pathways that feature dramatic, yet speculative, epoxide-opening cascades. In this review we summarize how such epoxide-opening cascade reactions have been used in the synthesis of polycyclic polyethers and related natural products.

From the Contents

1. Introduction

Almost all families of oxygen-containing natural products that are found in all kingdoms of life have members that feature ether functionality in their structure. A subgroup of natural products characterized by the regular occurrence of multiple C−O−C motifs is designated the polyether family, which can be broadly divided into linear and polycyclic polyethers. The latter group is of special interest owing to its fascinating structural diversity and the interesting biological activity of its members, which ranges from antibiotic, antifungal, and anticancer properties to extreme toxicity. The structural features and biosynthetic origin of these molecules can be used as a foundation for their classification. The majority of polycyclic polyethers are of polyketide or terpene origin. Depending on their structural features, which can generally be traced back to the biosynthetic pathways for the synthesis of these molecules, polycyclic polyethers can be divided into two groups. The first group includes molecules with multiple fused cyclic ethers and are postulated to be formed in nature by an *all-endo* cascade of epoxide openings. The other group consists of molecules that are produced by an *all-exo* biosynthetic cascade of epoxide-opening reactions, and normally feature multiple rings that are interconnected by a carbon–carbon bond.

For purposes of this review, polycyclic polyethers will be classified in three major groups: polyether ionophores,[1] squalene-derived polyethers,[2] and the ladder polyethers.[3] Each of these families of natural products will be discussed in the context of epoxide-opening cascade reactions. Such reactions are postulated to be involved in the biosynthesis of these natural products and could ultimately be utilized as a method to rapidly construct polyether frameworks in the synthesis of the members of these families.[4] Other related groups of naturally occurring substances, such as annonaceous acetogenins from plants and diverse marine polycyclic polyethers, are also discussed in context of their similarities to polyether ionophores and ladder polyethers.

2. Synthetic Considerations: Baldwin's Rules

Baldwin's rules are a three-criteria classification of ring-closing reactions: namely, the size of the formed ring, the position of the bond that is broken relative to the smallest formed ring, and the geometry of the electrophile.[5] If the position of the bond broken during the ring-closing reaction is exocyclic, that is, outside of the formed ring, then the reaction is classified as *exo*; if the broken bond is within the smallest formed ring, the reaction is classified as *endo* (Figure 1). In Baldwin's classification, reactions involving sp^3-hybridized electrophiles are described as *tet* owing to the tetragonal geometry of the electrophile, sp^2-hybridized electrophiles are trigonal, or *trig,* and sp electrophiles are digonal, or *dig*. With such classification in mind, Baldwin formulated a simple set of guidelines to predict the relative feasibility of different ring-closing reactions.[5] Although empirical, Baldwin's rules also followed a number of studies based on stereoelectronic considerations (for example, the Bürgi–Dunitz trajectory).[5–7] Therefore, the favored ring-closing reactions are those in

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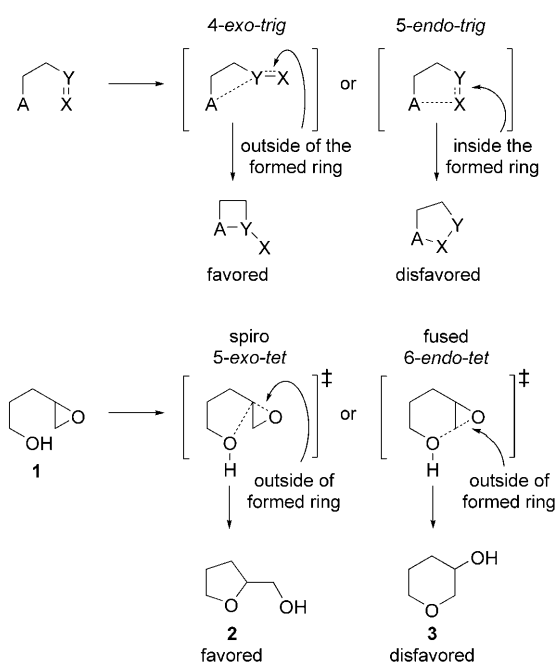
Figure 1. Baldwin's rules as they relate to intramolecular epoxide-opening reactions (Baldwin, 1976).[5]

which the length and nature of the linking chain enable the terminal atoms to achieve the proper geometries for the reaction. The disfavored ring closings, on the other hand, would require severe distortions of bond angles and bond distances. For instance, 4-*exo-trig* reactions are predicted to be favored over 5-*endo-trig* ring-closing reactions (Figure 1).

With a few exceptions, intramolecular epoxide-opening reactions favor the smaller heterocycle (e.g., tetrahydrofuran **2**, likely arising from a *spiro* transition state, Figure 1), not the larger one (tetrahydropyran **3**, from a fused transition state).[8] Baldwin's rules would classify the fused and spiro transition states as *endo* and *exo*, respectively. However, because the epoxide C—O bond that breaks is outside the newly formed ring in both cases, each may also be considered to be an *exo* process under the same construct (Figure 1). Thus, to avoid potential confusion, the distinct terms "fused" and "spiro" are preferred.[9] Although Baldwin's rules were not specifically formulated for epoxide-opening reactions, intramolecular epoxide openings tend to follow the rules that lie between those for tetrahedral and trigonal systems, and generally favor the *exo* processes, which proceed via a spiro transition state.[5]

2.1. Methods That Overcome Inherent Selectivity in Intramolecular Epoxide Opening

The development of efficient methods for enantioselective epoxidation, such as the Sharpless asymmetric epoxidation of allylic and homoallylic alcohols,[10–12] Jacobsen epoxidation,[13–16] and the Shi epoxidation of unactivated alkenes[17–20] have made epoxides attractive intermediates in asymmetric synthesis.[21] These methods enable efficient syntheses of many of the polyepoxides that will be discussed herein, thus motivating explorations in the field of epoxide-opening cascades.

To fully utilize epoxides as versatile intermediates in synthesis, effective ways to control the regioselectivity in epoxide-opening reactions are necessary. As noted by Baldwin,[5] the *exo* mode of cyclization is typically preferred; therefore, methods to facilitate *endo* cyclization have constituted a particularly active area of research.

Most of the approaches to promote the desired outcome of intramolecular epoxide openings use directing groups covalently attached to the epoxides. These directing groups either stabilize (relative to an H atom) the desired transition states, enabling regioselective nucleophilic attack, or make the undesired cyclization route less energetically favorable by changing the electronic properties of the epoxide. Currently available methods for *endo*-cyclization of epoxides rely on effects of alkenyl,[22–26] alkynyl,[27–30] alkyl,[31–33] and silyl[34–36] substituents that stabilize the partial positive charge within the desired, fused transition state in the Lewis or Brønsted acid-catalyzed reactions (Scheme 1). The directing groups that promote *endo* cyclization by destabilization of the undesired spiro transition state include sulfones[37–39] and methoxymethyl substituents in combination with a lanthanoid Lewis acid[40–42] (Scheme 2).

Catalytic antibodies[43–46] and transition-metal complexes[47,48] can also be particularly effective in promoting *endo* cyclization by lowering the energies of fused transition states in certain cases.

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Ivan Vilotijevic was born in Uzice, Serbia. He received his bachelor's degree in chemistry from the University of Belgrade. During his undergraduate studies, he worked with Prof. Leo A. Paquette at The Ohio State University and Prof. David Y. Gin at University of Illinois, Urbana-Champaign. He is currently carrying out PhD research at the Massachusetts Institute of Technology, under the guidance of Prof. Timothy F. Jamison, where he is working on development of cascade approaches to ladder polyether natural products.
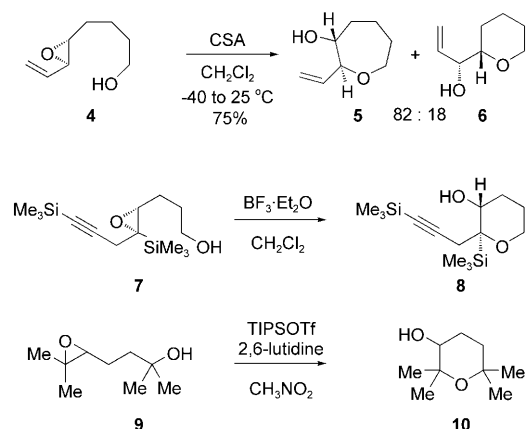
Scheme 1. *Endo* cyclizations via fused transition states stabilized by directing groups.[24,33,36] CSA = camphosulfonic acid, Tf = trifluorosulfonyl, TIPS = triisopropylsilyl.
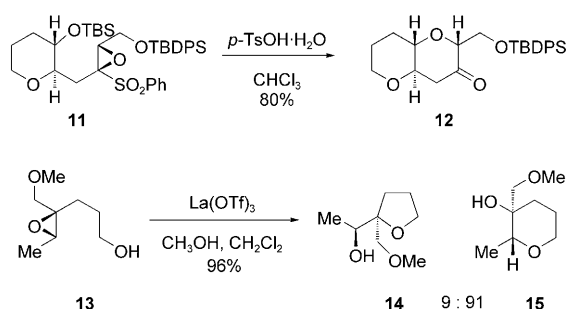
Scheme 2. *Endo* cyclizations enabled by deactivation of the *exo* pathway.[37,40] Ts = toluenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

3. Polyether Ionophores

The polyether ionophores are lipophilic carboxylic acids that contain multiple five- and six-membered cyclic ethers organized either as spiroketals or as linked bicyclic ethers (Figure 2). The first members of this family, X-206, nigericin, and lasalocid (**18**), were isolated in 1951, but owing to their toxicity did not initially draw much attention.[49,50] It was not until 1967, when an X-ray structure of monensin A (**16**) was disclosed[51] and the cation binding abilities of these molecules were first examined,[52] that this family of natural products was thrust back into the spotlight. Subsequent discoveries of their ability to control coccidiosis,[53] a devastating poultry disease, and their action as growth promoters in ruminant animals[54] (both of which capitalize upon the antibiotic activity of these structures) inspired a number of research groups to pursue the isolation of novel members of this family, study their biosynthesis, and put effort into their total synthesis. The biological function of polyether ionophores is directly related to their ability to selectively bind metal cations via coordination with multiple oxygen atoms and, owing to their lipophilic nature, transport them through biological membranes.[52] By doing so, polyether ionophores disturb the delicate dynamic equilibria of cations across the cell membrane and thus disrupt regular cell function,[55] resulting in

diverse effects, which include antibiotic, antimalarial, antiobesity, and insecticide activity.

Since the isolation of the first polyether ionophores in early 1950s, well over a hundred members of this family have been isolated and characterized.[1,56–59] Although most of these compounds are produced by the *Streptomyces* genus, polyether ionophores have also been isolated from other actinomycetes.[4] A surge of interest in polyether ionophores generated a large body of data on their biosynthesis during the 1970s.[60–69] Feeding studies on multiple organisms that produce polyether ionophores revealed their polyketide origin. Studies on the origin of oxygen atoms in this class of natural products established that not all of them are derived from the corresponding carboxylates in acetate, propionate, and butyrate building units, but rather also from molecular oxygen from the growth medium.[65,68] This observation implied the involvement of monooxygenase enzymes in the biosynthetic routes to these natural products. Accumulated experimental data and earlier speculation by Westley[62] led the groups of Cane, Celmer, and Westley to propose a unified stereochemical model of polyether antibiotic structure and biogenesis in 1983.[70]

According to the Cane–Celmer–Westley hypothesis, in the biosynthesis of monensin A, an *all-E* polyene precursor (**26**; Figure 3), produced in a classic type I polyketide synthase fashion from five acetates, seven propionates, and one butyrate unit, is oxidized to the corresponding polyepoxide (**27**; Figure 3). Nucleophilic addition of the C5 hydroxy group in **27** to the C9 ketone forms a hemiketal that triggers a cascade of *all-exo* epoxide-opening events leading to the formation of monensin A. Cane, Celmer, and Westley further extended this proposal to the biosynthesis of all polyether ionophores known at the time and described the requisite polyene precursors and pathways to each of these.

The work on the biosynthesis of numerous polyether molecules that followed the original Cane–Celmer–Westley proposal has largely supported this hypothesis.[71–83] However, the failure of the producing organism to incorporate synthetic *all-E* premonensin triene **26** into the biosynthetic pathway and convert it into monensin A encouraged Townsend and Basak to propose an alternate biosynthetic route.[84,85] According to this hypothesis, monensin A may be produced from an *all-Z* triene precursor (an *all-Z* isomer of **26**) through a series of oxidative cyclizations proceeding via a [2+2] mechanism that involves the action of an iron-containing monooxygenase (Figure 4). Synthetic studies by Townsend himself[84] and work on model systems closely related to the proposed *all-Z* premonensin triene by McDonald[86,87] provided further support for this hypothesis. The issue of stereochemistry of the alkenes in the monensin A precursor was also raised by Leadlay et al. Speculating that the cascade of epoxide opening may be initiated by activation of the methyl ketone electrophile, Leadlay proposed that a *Z,Z,E*-alkene would be required en route to monensin A.[88]

In 2001, Leadlay et al. described their efforts in sequencing the monensin biosynthetic gene cluster.[88] Their success ultimately led to significant advancement in understanding the biosynthetic pathways of polyether ionophores. In their analysis of the polyketide gene cluster containing twelve
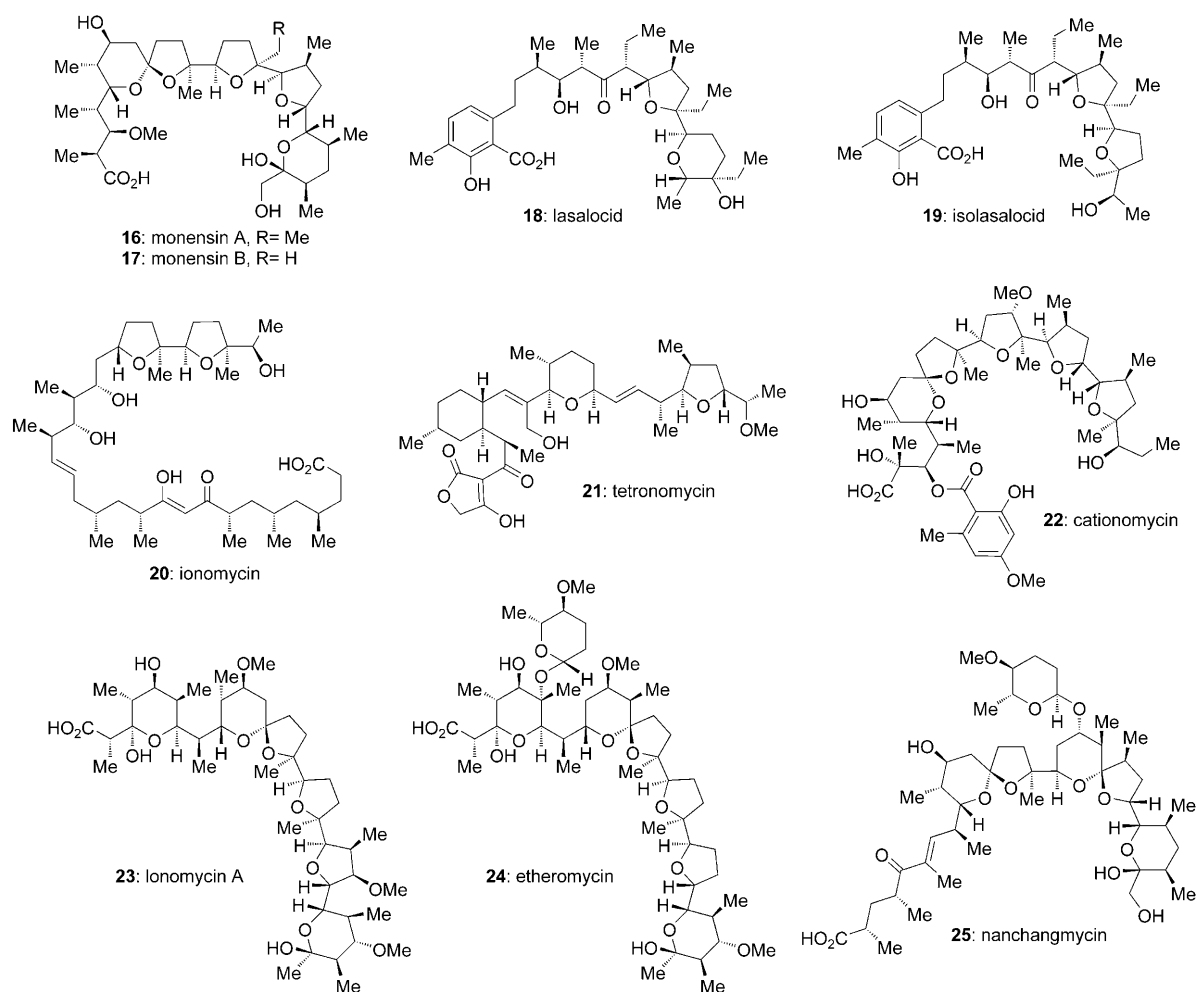
Figure 2. Structures of representative polyether ionophores.

modules responsible for the incorporation of the twelve acyl units of monensin A, Leadlay and co-workers identified the genes *monBI*, *monBII*, and *monCI*, which are atypical for polyketide synthase gene clusters.[89] Although it was speculated that products of *monBI* and *monBII* may both act as isomerase enzymes, thus supporting Leadlay's modification of the Cane–Celmer–Westley hypothesis involving a *Z,Z,E*-triene, studies on the Δ*monCI* mutant suggested otherwise. Deletion of *monCI* from the producing organism led to accumulation of *all-E* premonensin triene (**26**; Figure 3), suggesting that a single oxidase enzyme, the product of *monCI*, is involved in the production of triepoxide **27**.[90] Disruption of *monBI* and *monBII* genes led to the production of partially cyclized intermediates that all proved to be chemically competent, leading to monensin A upon treatment with an acid.[91] Studies on the biosynthesis of nanchangmycin,[92–95] salinomycin,[96] nigericin,[97] and tetronomycin[98,99] shortly followed the pioneering studies on monensin A and provided strong support for the original proposal by Cane, Celmer, and Westley.
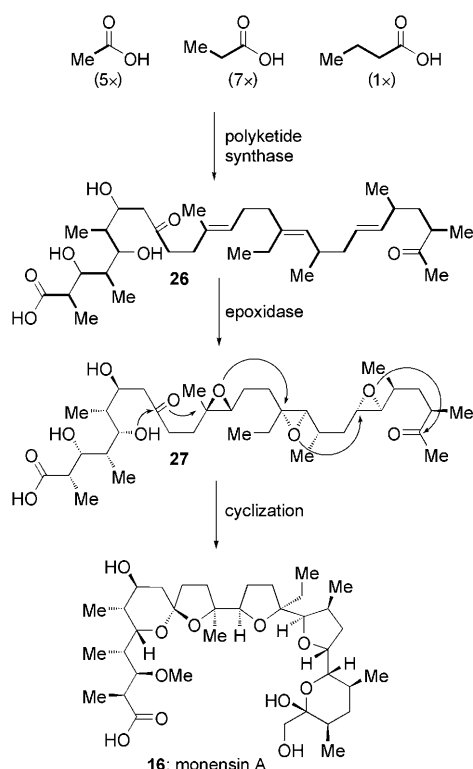
A recent report by Oikawa et al. provided the final, direct evidence for the involvement of an enzyme-catalyzed cascade of epoxide-opening reactions in the biosynthesis of lasalocid

(**18**; Figure 2).[100] Analysis of lasalocid biosynthetic genes revealed significant homology of *lsd19* to the putative epoxide hydrolase genes *monBI* and *monBII*. The *lsd19* gene was successfully cloned and expressed in *Escherichia coli* to afford Lsd19 in nearly pure form. This enzyme was then utilized in the efficient transformation of synthetic prelasalocid diepoxide **35** to lasalocid in vitro (Figure 5).[101] Further in vivo studies by Leadlay and colleagues focused on the production of lasalocid and isolasalocid in the producing organism and a mutant lacking *lsd19*.[102] These studies clearly demonstrated that the presence of Lsd19 changes the stereochemical course of polyether ring formation, thereby channeling the polyepoxide intermediate to lasalocid as the major product. When Lsd19 is not present, the formation of the second ring proceeds exclusively by the kinetically favored pathway to form isolasalocid, thus demonstrating that Lsd19 is responsible for the final stage of the biosynthesis of lasalocid.
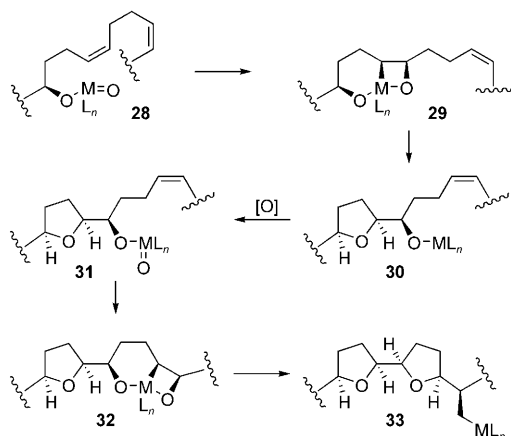
3.1. Polyethers Derived From Squalene

In recent years, a number of polycyclic polyethers derived from squalene and having structures reminiscent of polyether

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Figure 3. Cane–Celmer–Westley hypothesis; a model of monensin A biogenesis.[70]

Figure 4. Townsend–McDonald hypothesis; a model of polyether biogenesis by a metal-mediated oxidative cyclization.[84, 86]

ionophores have been isolated from diverse sources, including marine sponges, red algae, and tropical plants.[2] Discoveries in the biosynthesis of steroids from squalene oxide[103] revealed an exciting continuation in proposed biosynthetic pathways to polycyclic polyether triterpenes, such as teurilene and glabrescol (**36** and **37**; Figure 6). That these oxasqualenoids could be efficiently derived from squalene polyepoxide precursors was recognized soon after similar proposals were put forward for polyether ionophores and ladder polyethers.[2, 104, 105] Over the years a number of marine natural
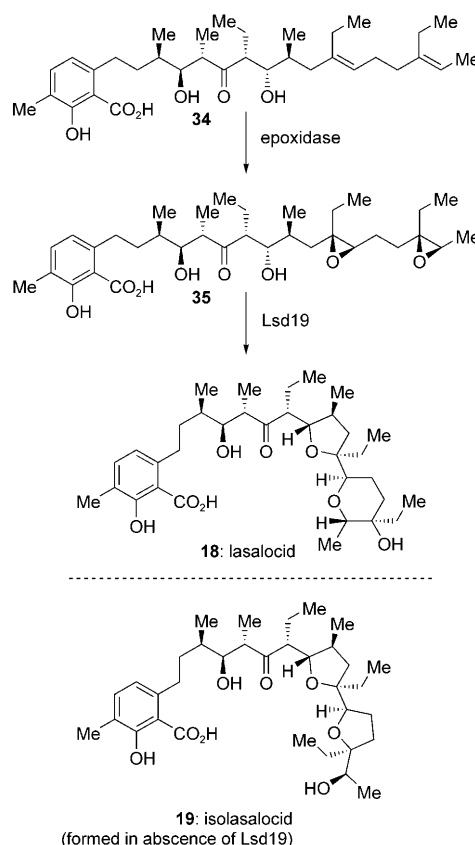
Figure 5. The role of Lsd19 in final stages of the lasalocid biosynthesis.[100, 102]

product structures consistent with this proposal have been isolated that contribute to the credibility of the hypothesis (Figure 6).

4. Ladder Polyethers

The group of ladder polyether natural products consists of molecules featuring anywhere from 4 to 32 five- to nine-membered cyclic ethers, fused to each other in a *trans-syn-trans* arrangement. This creates a repeating C–C–O sequence that stretches throughout the polycyclic core of these molecules (Figure 7). The first member of this family to be isolated, brevetoxin B (**45**), was reported by Nakanishi and Clardy in 1981[106] and was followed by numerous others, including maitotoxin (**55**),[107–111] the largest nonpolymeric molecule isolated from natural sources to date. The minimal availability combined with the unprecedented size of ladder polyethers have inspired heroic endeavors in the isolation and structural characterization of these molecules, and have pushed the limits of the analytical methods used in these pursuits, such as chromatography, mass spectrometry, NMR spectroscopy, and X-ray diffraction. The structural challenges associated with synthesizing these molecules have stimulated development of many novel synthetic methodologies.[112–115]

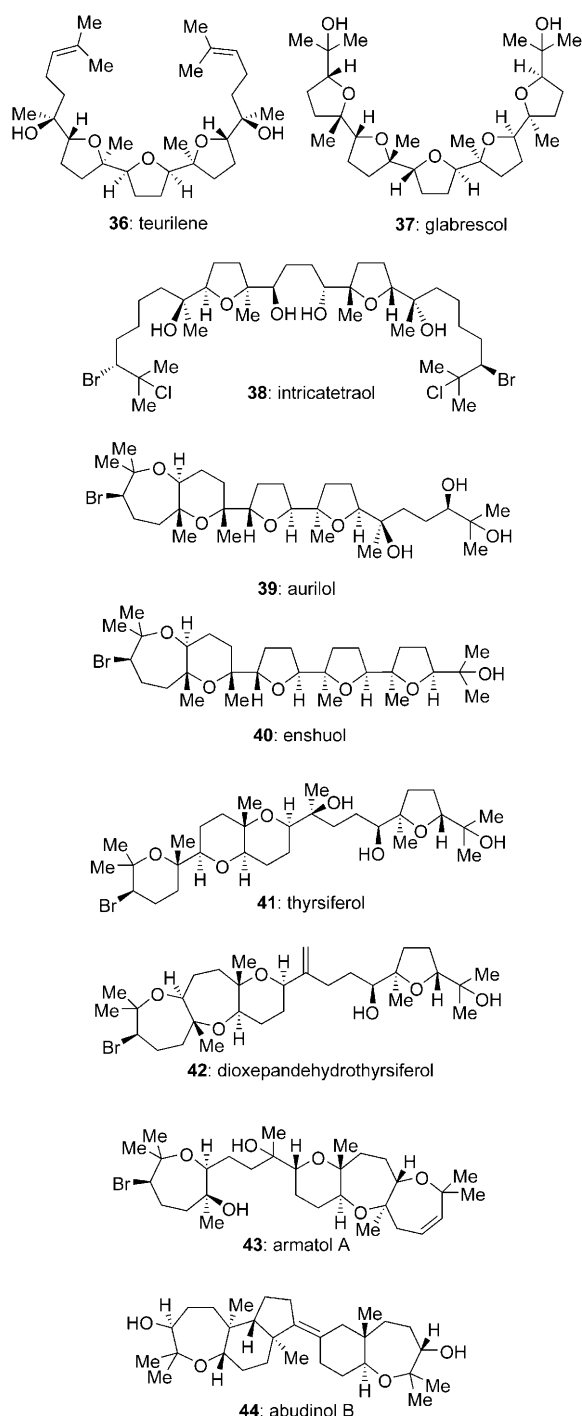Ladder polyethers are notorious for their association with harmful algal blooms, which are commonly referred to as red

Figure 6. Structures of representative oxasqualenoids.

tides.[116] A rapid increase in concentration of dinoflagellate algae, for example the brevetoxin-producing *Karenia brevis*, leads to the increased production of red tide toxins, of which some are members of ladder polyether family. The effects of red tide are devastating killings of fish and marine mammals. However, some marine species not affected by red tide accumulate, and occasionally further elaborate the toxins,[117] thus transferring them up the food chain, which ultimately resulting in human poisoning by ingestion of shellfish exposed to a red tide.[118] Although several proposals are under

investigation, the definitive ecological causes of red tides are still unknown.[119–122]

Despite their uniform structure, ladder polyethers exhibit various biological activities that range from extreme toxicity[123–127] to beneficial anticancer[128–130] and antifungal[131] properties. Recently, a member of this family, brevenal (**47**; Figure 7), has been shown to protect the fish from neurotoxic effects of brevetoxins,[132,133] and has also been identified as a potential therapeutic agent for cystic fibrosis.[134] Although their mode of action is not well understood on the molecular level, it is known that brevetoxins and ciguatoxins bind and disrupt voltage-sensitive sodium channels.[135–140] Glycophorin A has been identified as the molecular target of yessotoxins. Binding of yessotoxin (**50**; Figure 7) to the transmembrane domain of glycophorin A causes the dissociation of this oligomeric protein into monomeric units.[141] Although the target of maitotoxin has not yet been identified, it is known that it causes an influx of calcium ions into cells, which in turn causes uncontrolled secretion of neurotransmitters and other messenger molecules, ultimately causing severe muscle contractions.[123,142–150]

Soon after structure of brevetoxin B was reported, Nakanishi[151] and Shimizu[152] hypothesized that the structural and stereochemical similarities among ladder polyethers are a direct consequence of their biosynthetic origin. Such similarity was proposed to arise through the transformation of a polyepoxide into a ladder polyether via a series or cascade of epoxide-opening events (Figure 8). The oxygen and two carbon atoms of each epoxide ring constitute the C–C–O backbone, and with the proviso that all of the ring openings proceed with inversion of configuration at each epoxide derived from an *E* alkene, the *trans-syn* topography is explained by this mechanism. Noteworthy is the fact that all alkenes in a hypothetical polyene precursor would require identical stereoselectivity of epoxidation to produce either an *all-S,S* or *all-R,R* polyepoxide, suggesting that a single promiscuous oxidase could be sufficient.[153] Despite its intellectual appeal, the hypothesis relies upon a ring-opening process that is generally regarded to be disfavored. As discussed earlier, according to the Baldwin's rules,[5] epoxide-opening reactions of this type typically favor the smaller heterocycle, for example THF over THP; in the case of the proposed precursor to brevetoxin B, the cascade would have to overcome ten separate disfavored epoxide openings.

In an effort to shed some light on the validity of Nakanishi's hypothesis, labeling studies were carried out for brevetoxins A and B.[152,154,155] However, as these studies only provided insight into their polyketide origin, which was also supported by genetic studies,[156–159] and did not illuminate any subsequent epoxidation or cyclization steps, the proposal remains speculative. Some remote evidence in support of this hypothesis can be taken from biosynthetic studies on a related natural product, okadaic acid.[160,161] Labeling studies with $^{18}O_2$ revealed that the oxygen atom incorporated at the fused THP diad of okadaic acid is derived from molecular oxygen, suggesting the involvement of an epoxide intermediate in the formation of this ladder-polyether-like motif.

Despite the lack of strong experimental support in its favor, Nakanishi's hypothesis is nonetheless in the forefront
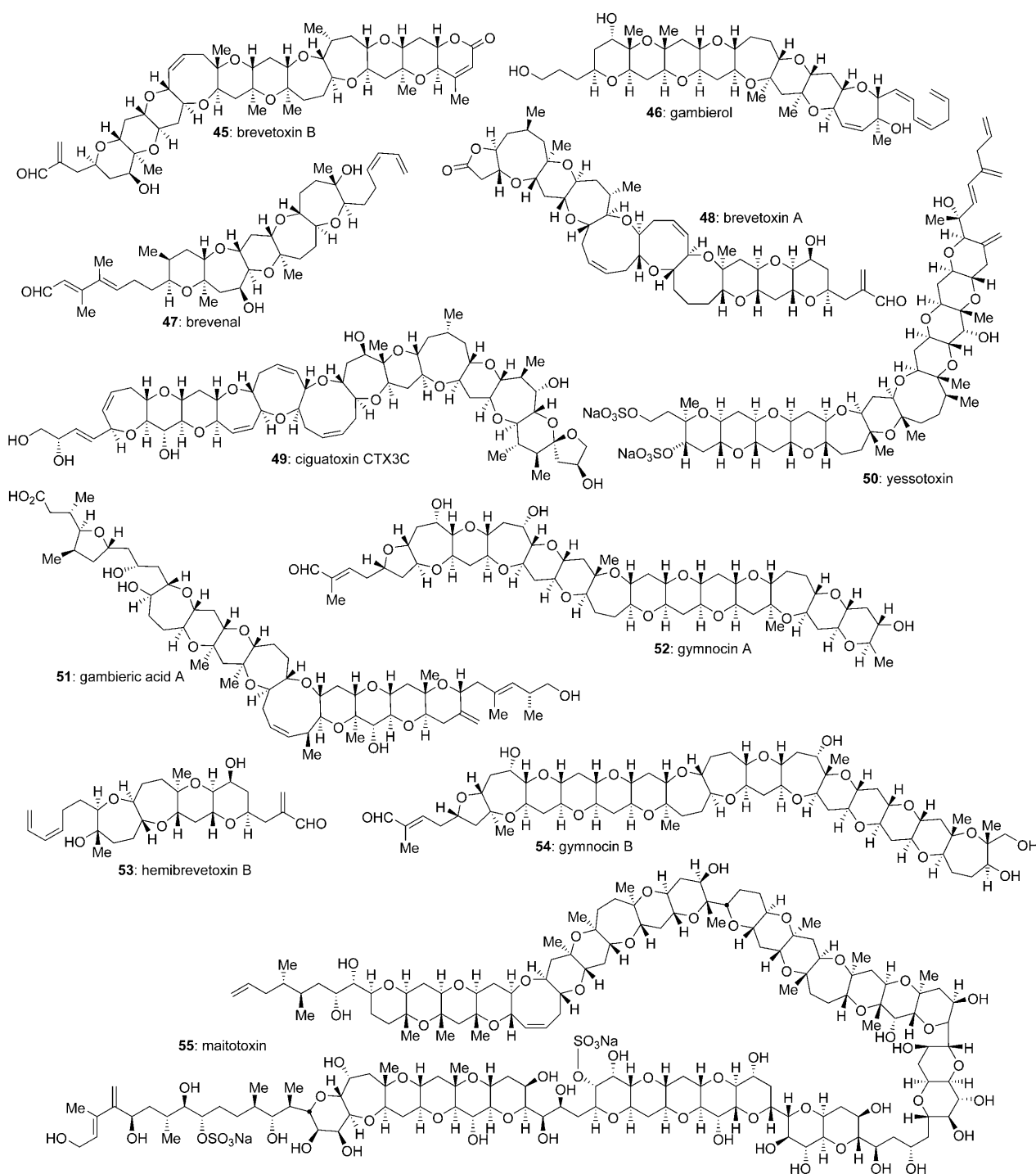
Figure 7. Structures of representative members of ladder polyethers.

of the collective mind of the scientific community. It is interesting to note that the stereochemical uniformity inferred from the polyene to polyepoxide to ladder polyether pathway has served as the basis for speculative structural reassignment of two members of the ladder polyethers: the relatively small brevenal and the largest known natural product, maitotoxin. Total synthesis of the proposed structure of brevenal by Sasaki revealed that the originally proposed configuration required revision.[162] Upon closer inspection of

spectroscopic data and analysis of the proposed biosynthetic precursor, the irregularity in the stereochemistry of one epoxide in the prebrevenal polyepoxide led to the reassignment of stereochemistry in the ring derived from the hypothesized precursor so as to bring that structure into the full agreement with Nakanishi's proposal.[163] This structural reassignment of brevenal was confirmed by total synthesis of both the original and revised structure.[162,163] As for maitotoxin, a single exception to the rule of stereochemical
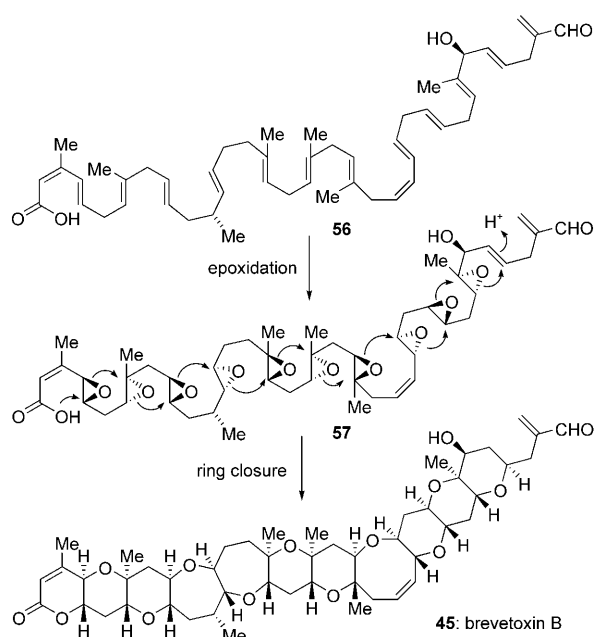
Figure 8. Nakanishi's hypothesis; a model of brevetoxin B biosynthesis.[151]

uniformity in the linear polyepoxide precursor placed the original structure under scrutiny. It was proposed that the JK ring junction of maitotoxin should be revised so that it adheres to the rule of a single epoxide configuration throughout the entire polyepoxide precursor to the natural product.[153] Synthetic work by Nicolaou, however, provided support for the originally proposed structure and thus against the revision.[164, 165]

In addition to Nakanishi's proposal, Giner and Mullins suggested that ladder polyethers may be derived from an *all-Z* polyene precursor.[166, 167] They hypothesized that an epoxy ester intermediate may undergo cyclization with the carbonyl group of the ester as nucleophile, leading to the formation of an orthoester intermediate **60** (Figure 9). Upon collapse of the orthoester, attack of the alcohol nucleophile on what used to be the second electrophilic site of the starting *cis* epoxide then produces the ring of a ladder polyether and regenerates an ester for the next ring-closing reaction. As yet, this hypothesis has not been tested experimentally. The Townsend–McDonald hypothesis for polyether ionophores can be
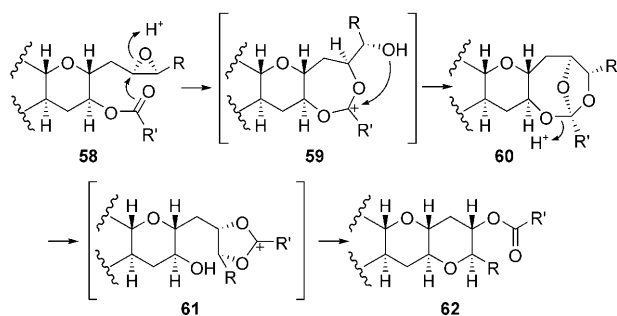

Figure 9. Biosynthesis of ladder polyethers via the epoxy ester pathway (Giner, 2003).[166]

extended to incorporate a similar *all-Z* polyene precursor to ladder polyethers.

5. Epoxide-Opening Cascades in the Synthesis of Topologically Interesting Molecules

The first epoxide-opening cascades were disclosed in the early 1950s.[168] These early reports typically involved the rearrangement of 1,5-diepoxides that, under appropriate conditions, react with an external nucleophile to undergo a cascade of epoxide openings. Depending on the reaction conditions, these cascades may involve direct epoxide opening or formation of epoxonium ion intermediates, which in either case produce tetrahydrofuran products in agreement with Baldwin's rules.[5] This strategy was later extended into a general method for the synthesis of substituted tetrahydrofuran rings, and it is often used in preparation of biologically relevant molecules, such as nucleosides, and natural and unnatural monosaccharides.[169–178]
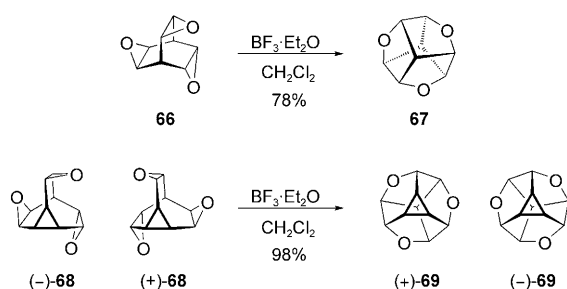
Other early reports on epoxide-opening cascades were focused on rearrangements of topologically interesting molecules. In their pursuit of a postulated [2σ+2σ+2σ] to [2σ+2σ+2σ] sigmatropic rearrangement, the groups of Simmons[179, 180] and Paquette[181, 182] independently reported the transformation of triepoxide **64** to hexaquinane **65** under acidic conditions (Scheme 3). Studies on the two diastereo-
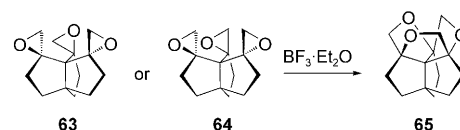
Scheme 3. Synthesis of the first topologically non-planar molecule **65** via an epoxide-opening cascade (Simmons and Paquette, 1981, 1984).[179–182]

meric triepoxides **63** and **64**[181] and labeling studies[179] demonstrated that this transformation proceeds via a cascade of epoxide-opening reactions to form the first topologically nonplanar molecule **65**. The desired sigmatropic rearrangement was not observed. The proposed mechanism involves breaking a carbon–oxygen bond in the Lewis acid-activated epoxide to form a tertiary carbocation, which is then trapped by the oxygen nucleophile from the neighboring epoxide.

In similar studies, de Meijere et al. reported the synthesis of achiral triepoxide **66**, which is derived from barrelene, and the cascade cyclization of this molecule to the corresponding, chiral D_3-trioxatrishomocubane **67** (Scheme 4).[183] In 2005, the groups of de Meijere, Howard, Okamoto, and Schreiner revisited studies on barrelene triepoxide and extended their studies to analogues derived from bullvalene.[184] Bullvalene triepoxide (**68**) is itself chiral, and can rearrange stereoselectively to the C_3-symmetric oligocycle **69** with propeller chirality (Scheme 4). Opening of the three C−O bonds in the epoxide moieties adjacent to the skeletal cyclopropane ring in (+)-**68** would afford (−)-**69**. In contrast, opening at the

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Scheme 4. Rearrangement of barrelene and bullvalene triepoxides to the corresponding D_3- and C_3-symmetric oligocycles (de Meijere, 1985, 2005).[183,184]

C—O bond in the β position would give the enantiomer (+)-69. Theoretical considerations and computational and experimental studies enabled de Meijere and co-workers to determine that this cascade indeed proceeds in the former fashion, forming exclusively (−)-69 starting from (+)-68. This can only occur by ring-opening of all three C—O bonds of the starting epoxides at the α position, which is in turn in agreement with the well-known stabilizing effect of cyclopropyl substituents on an adjacent positive charge.

Transannular epoxide-opening cascades on conformationally flexible substrates have also been studied. During their exploration of functionalized tris-(σ)π-homobenzenes, Prinzbach et al. discovered reactions of triepoxides derived from (Z,Z,Z)-1,4,7-cyclononatriene and their analogues of the type **71** (Figure 10a), including transannular epoxide-opening
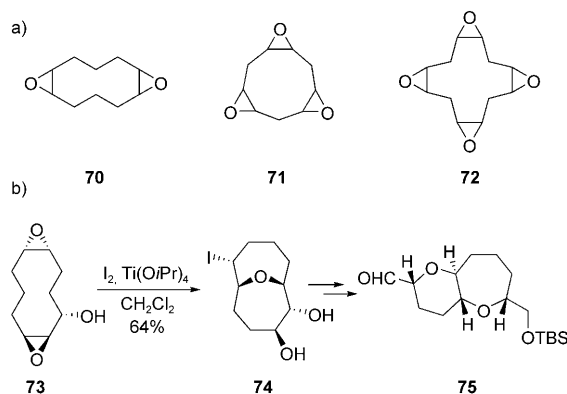

Figure 10. a) Macrocyclic polyepoxide frameworks for transannular epoxide-opening cascade reactions (Prinzbach, 1996, Parrain, 2003, Martin, 1988).[185–187] b) Transannular epoxide-opening cascade reaction in the synthesis of fused polyether fragments (Martin, 1994).[188]

reactions.[185] Similarly, the synthesis and reactions of tetraepoxides **72** derived from (Z,Z,Z,Z)-1,4,7,10-cyclododecatetraene were reported by Parrain et al.[186] Also of note are the transannular epoxide-opening reactions of diepoxides derived from nine- and ten-membered cyclic dienes that were studied by Martin et al. and utilized in the synthesis of ladder polyether fragments (Figure 10b).[187,188]

6. Epoxide-Opening Cascades in the Synthesis of Polyether Ionophores

The Cane–Celmer–Westley proposal[70] for the biosynthesis of polyether ionophores by a sequential epoxide-opening cascade quickly sparked great interest in the synthetic community, as the emulation of such biosynthetic pathway could provide a rapid, straightforward approach to a number of natural products in this family. Especially encouraging was the agreement of the proposed cascade reactions with empirical guidelines[5] for regioselectivity in epoxide-opening reactions.

Dolle and Nicolaou successfully induced an epoxide-opening cascade on diepoxide **76** to construct the THF-containing central backbone of aurodox (Scheme 5)[189] in a strategy reminiscent of the previously described methods for
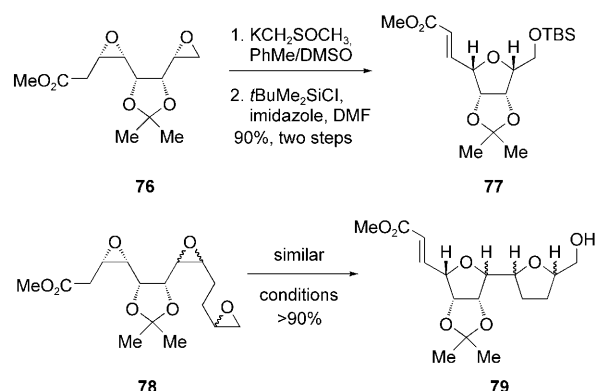

Scheme 5. Construction of the central backbone of aurodox and related epoxide-opening cascade leading to 2,5-linked bistetrahydrofuran **79** (Nicolaou, 1985).[189]

the construction of substituted THF motifs. Seeing the opportunity to extend this methodology to the synthesis of polyether antibiotics, these authors also examined a similar cascade on triepoxide substrate **78** and reported their initial results in a side note. Although more extensive reports on these studies are not available, this represents the first epoxide-opening cascade that affords the 2,5-linked bistetrahydrofuran motif present in a large number of polyether ionophores.

Further work was done by the Hoye group in efforts towards the total synthesis of uvaricin, in which they reported studies on triepoxides **80**, **81**, and **82**.[190,191] Their strategy involves freeing an alcohol nucleophile by ester hydrolysis followed by a base-promoted Payne rearrangement. This procedure unveils a secondary alcohol as a new nucleophile that triggers a cascade of two consecutive epoxide-opening reactions to afford 2,5-linked bistetrahydrofuran products **83**, **84**, and **85** (Scheme 6). To distinguish between the pathway which operates via Payne rearrangement and other possible pathways involving epoxide opening by water, Hoye and Jenkins conducted experiments on a diastereomeric mixture of diepoxides **86** and **87** in ¹⁸O-labeled water (Scheme 7).[192] In these experiments, ¹⁸O was incorporated only in the primary alcohols of **88** and **89**, which is consistent with the
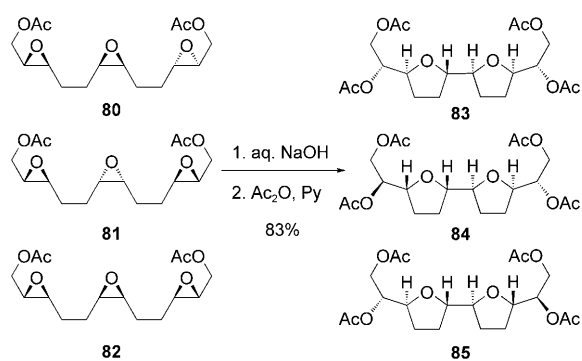
Scheme 6. Epoxide-opening cascades leading to formation of adjacent bistetrahydrofurans (Hoye, 1985).[190, 191] Py = pyridine.
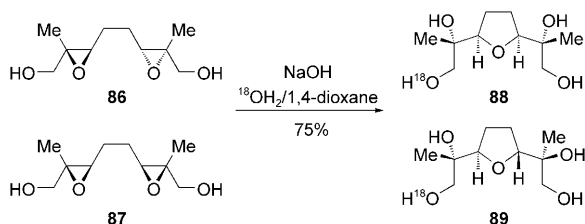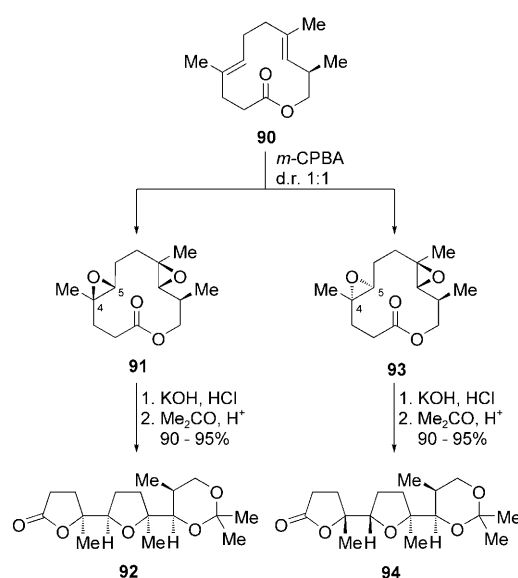

Scheme 7. Studies supporting the Payne rearrangement mechanism in epoxide-opening cascades (Hoye, 1987).[192]

Scheme 8. Preparation of diepoxides **91** and **93** and cascade transformation to corresponding 2,5-linked bistetrahydrofurans (Schreiber, 1986).[195] m-CPBA = meta-chloroperbenzoic acid.

proposed Payne rearrangement pathway. Although successful in forming the desired bistetrahydrofurans via what appears to be stereospecific epoxide opening, these cascades were burdened by racemization (the enantioenriched starting material led to racemic product) owing to initiation at both ends of the symmetric triepoxide substrates. To address this problem, Hoye and co-workers developed a protecting-group strategy for the desymmetrization of related diepoxides that takes advantage of the different rates of hydrolysis of different ester protecting groups compared to the rate of epoxide-opening cascade: certain esters were found to hydrolyze at a rate slower than epoxide opening, which allowed for cleanly unidirectional cascades.[193]

The first specific emulations of the alkene-epoxidation/epoxide-opening cascade sequence from the proposed biosynthetic pathway to polyether ionophores came from the groups of Still[194] and Schreiber.[195] Taking advantage of the powerful stereocontrol effects of allylic chiral centers on epoxidations of macrocyclic alkenes by peroxyacids described by Vedejs et al.,[196] Schreiber synthesized two diastereomers of diepoxides derived from a cyclic diene **90** (Scheme 8). The diepoxides **91** and **93** formed in this process were then studied as substrates for a one-pot sequence of ester hydrolysis followed by an epoxide-opening cascade, leading to 2,5-linked bistetrahydrofurans. Both bistetrahydrofuran product **92** (corresponding to the C9–C18 fragment of monensin B) and diastereomeric **94** were isolated after acetonide formation in remarkable yields, irrespective of the stereochemistry of the C4–C5 epoxide in the starting diepoxides.[195]

In a parallel report, Still and Romero described the preparation of a tricycle closely related to the C9–C23 fragment of monensin B.[194] They used the resident chirality

at C18 and C22 of **95** (carbon numbering as in premonensin B) to effectively direct stereocontrol in the epoxidation reaction (Scheme 9). Triepoxide **96**, isolated in 59% yield (74% corrected for purity of **95**), was then taken through a
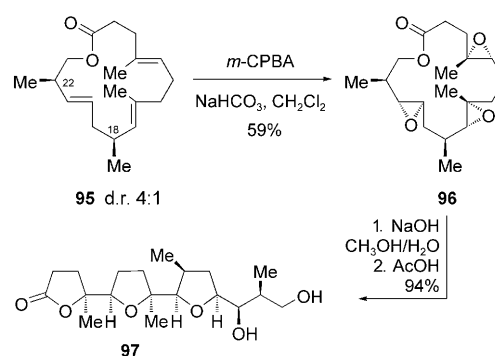
Scheme 9. Preparation of triepoxide **96** and an epoxide-opening cascade leading to tricyclic product **97** (Still, 1986).[194]

one-pot ester hydrolysis and acid-catalyzed epoxide-opening cascade to afford **97**, a diastereomer of the C9–C23 fragment of monensin B. Emulation of the proposed biosynthetic pathway leading from polyene to polyether via polyepoxide afforded **97**, which contains three 2,5-linked tetrahydrofurans, in a highly efficient manner. More significantly, it provided solid support for feasibility of such a proposal.

Shortly after the pioneering work by Still and Schreiber, Paterson and co-workers reported their initial studies on epoxide-opening cascades that afford fragments of polyether ionophores.[197] Instead of relying on the directing properties of alkyl substituents in allylic positions of unsaturated macrocycles like Still and Schreiber, efforts were made to assure the

stereoselectivity of epoxidation of an acyclic substrate by Sharpless asymmetric epoxidation. Under acidic conditions, diepoxyesters **98** and **100** were converted into the corresponding bistetrahydrofurans **99** and **101** in good yields (Scheme 10).
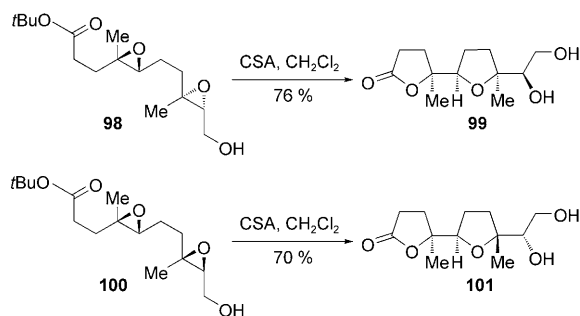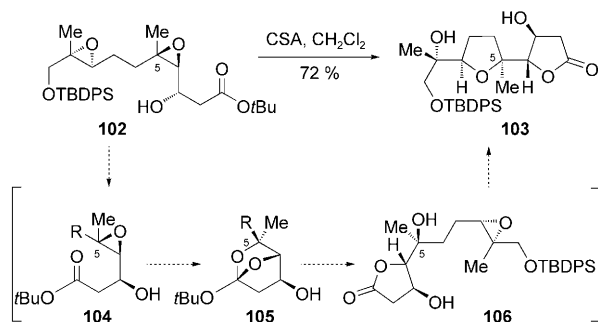

Scheme 10. Epoxide-opening cascades reported by Paterson (1987).[197]

It is worth noting that the stereochemical outcome of cascades similar to those reported by Paterson may be compromised in cases where an electronic preference for 6-*endo* cyclization exists. As noted by Jaud and co-workers, inversion of stereochemistry at C5 of **102** can be observed in acid-catalyzed cyclizations.[198] The authors propose that initial cyclization via a 6-*endo* pathway operates to produce an orthoester intermediate **105** with inverted configuration at C5 (Scheme 11). Subsequent elimination of 2-methylpropene results in the formation of a final five-membered lactone and liberates a tertiary alcohol, which serves as nucleophile for further epoxide opening.


Scheme 11. Stereochemical outcome of cascades with an electronic preference for 6-*endo* cyclization (Jaud, 1999).[198]

The epoxide-opening cascades described so far have typically relied on acid or base catalysis. In these regimes, a cascade can be initiated by either activation of an alcohol nucleophile by deprotonation or by epoxide activation with Brønsted or Lewis acids. Although nucleophile activation allows good control over the direction of the cascade, it is limited to polyepoxide substrates with protic nucleophiles, such as alcohols. On the other hand, activation of the epoxide with acid typically suffers from unselective activation of any or all of the epoxides in the polyepoxide substrate. The cascade can thus proceed in both directions, with varying

points of initiation, which is a problem that becomes increasingly pronounced as more epoxides are added to the chain. Acid-catalyzed cascades are therefore typically limited to di- or triepoxides.

Several research groups have offered alternative means of initiation in epoxide-opening cascades that address some of these issues in activation using acid and base. Perhaps inspired by the cleavage of the thioester linkage between the polyepoxide substrate and the acyl-carrying protein in the proposed biosynthesis of polyether ionophores, a number of cascades have been initiated by the release of a carboxylic acid nucleophile from an ester through the action of esterase enzymes under mild conditions. Robinson and co-workers subjected esters **107** and **110** to pig-liver esterase in aqueous phosphate buffers at slightly basic pH (Scheme 12).[199]
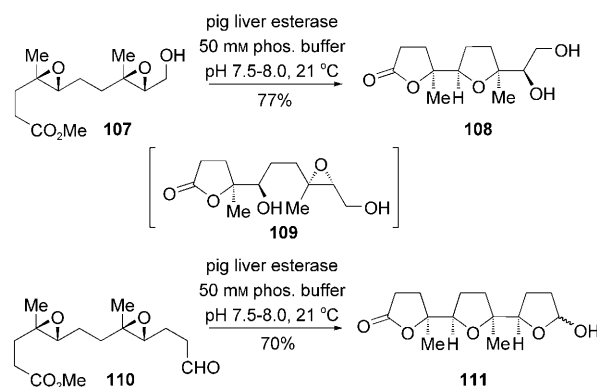
Scheme 12. Epoxide-opening cascades initiated by pig liver esterase (Robinson, 1987).[199]

Efficient cascades afforded **108** and **111** in good yields after prolonged exposure. These cascades appeared to proceed in a stepwise fashion, as the intermediate **109** could be detected. The observation of intermediate **109** is consistent with the hypothesis that the anionic carboxylate of hydrolyzed **107** initiates the cascade and is a more effective nucleophile than is a secondary alcohol in the second stage leading from **109** to **108**.

The concept of the selective generation of a reactive epoxonium intermediate on one side of a polyepoxide substrate was introduced by Murai et al. in their work toward the synthesis of ladder-type polyethers (see the discussion in Section 8.2, Scheme 38).[200] By introducing the same concept for the control of cascade direction to the arena of polyether ionophores, Floreancig and co-workers demonstrated that mesolytic carbon–carbon bond cleavage in the benzylic position of the radical cations of homobenzylic ethers, such as **112**–**115**, form oxonium ions that react with pendent epoxides to form epoxonium ions, which can then undergo further cyclization.[201,202] They have shown that both *cis*- and *trans*-substituted epoxides **112** and **113** are competent in these reactions with preservation of stereochemical information during the cascade (Scheme 13). With examples in which mono and diepoxides with a pendent acetal nucleophile are efficiently transformed to bistetrahydrofuran products **116**–**119**, Floreancig and co-workers have demonstrated that
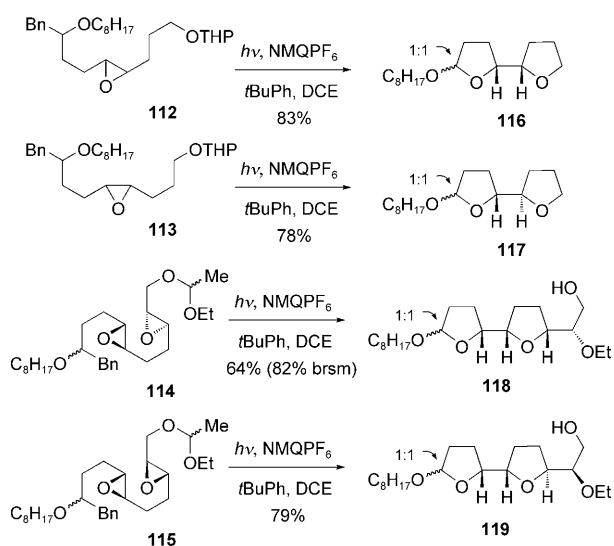
Scheme 13. Initiation of cascade cyclizations via single electron oxidation of homobenzylic ethers (Floreancig, 2002, 2005).[201,202] NMQ = *N*-methylquinolinium, DCE = 1,2-dichloroethane; brsm: based on recovered starting material.

single-electron oxidation is another effective method for the initiation of a heterogenerative cascade cyclization.

Starting with bromomethylepoxides (**120**; Figure 11), the Marshall group successfully initiated epoxide-opening cascades through the transient formation of allylic alkoxy zinc
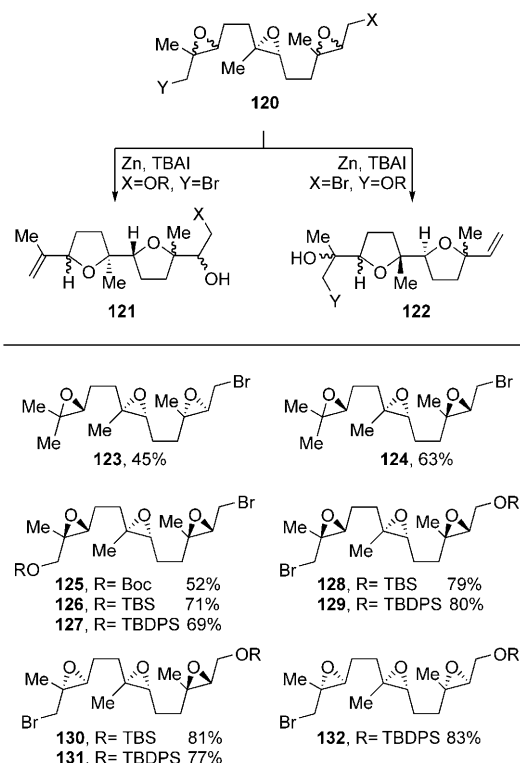
Figure 11. The synthesis of bistetrahydrofurans by epoxide-opening cascades of triepoxyfarnesyl bromides (Marshall, 2008).[203,205] Boc = butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, TBA = tetrabutylammonium.

species.[203–205] These reactions are reminiscent of Nicolaou's initial reports, but avoid the basic conditions used in early cascades, replacing them with the milder treatment of starting material with metallic zinc in alcoholic solvents. The utility of this approach is clearly demonstrated by the preparation of a large number of bistetrahydrofuran products derived from diastereomeric triepoxyfarnesyl bromides (Figure 11).

A report on the initiation of epoxide-opening reactions in water at elevated temperatures was reported in 2008 by Qu and co-workers (Scheme 14).[206] It is interesting to note that these conditions preferentially afford the larger-ring oxepane **134** over the tetrahydrofuran **135** that is typically obtained in both acid- and base-catalyzed cyclizations of 1,4-diepoxides as described earlier in this section. This selectivity may result from the electronic properties of the trisubstituted epoxides involved in this cascade cyclization.
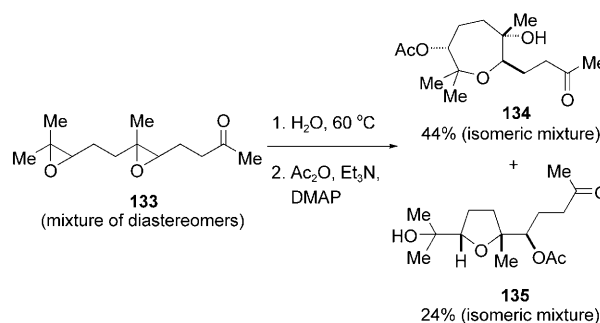

Scheme 14. Epoxide-opening cascade on geraniol-derived diepoxides in hot water (Qu, 2008).[206] DMAP = 4-dimethylaminopyridine.

6.1. Epoxide-Opening Cascades in the Synthesis of Polyether Ionophores

The epoxide-opening cascade reactions described herein have been inspired by the Cane–Celmer–Westley biosynthetic proposal for polyether natural products. Their development was typically driven by the search for chemical evidence in favor of this biosynthetic pathway. Equally important for synthetic community is that these reactions were developed with specific targets in mind, and, similarly to the cyclization of squalene oxide in the synthesis of steroids, they represent a classic example of the rapid generation of chemical complexity from relatively simple starting materials. Although inspired by nature and developed for the synthesis of natural products, epoxide-opening cascades were successfully used in preparation of artificial ionophores even before the biosynthetic proposal was put forth.[207] These early reports that involve polymeric materials with ionophoric properties, while intriguing, are not covered herein owing to lack of structural data.

A notable example of the use of *exo*-selective cascade reactions in the synthesis of materials with interesting cation-binding properties is the synthesis of diastereomeric oligotetrahydrofuran motifs **139** and **140** by Koert et al. (Scheme 15).[208] It is worth noting that Koert departs from the usual polyene to polyepoxide pathway and development
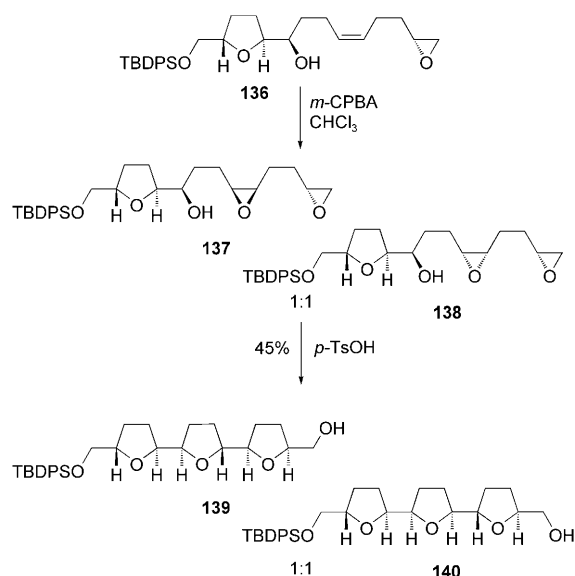
Scheme 15. Synthesis of tricyclic ionophores **139** and **140** from a cascade of epoxide openings (Koert, 1994).[208]

of the convergent syntheses of polyepoxides that rely on addition of enantiopure epoxyorganolithium reagents to α-alkoxy aldehydes.

Still and co-workers have shown that acid-catalyzed epoxide-opening cascades can be extended from 1,5-diepoxides to 1,6-diepoxides to produce 2,6-linked oligotetrahydropyran fragments.[209] With the goal of producing novel ionophoric materials, the Still group synthesized podands containing three and four 2,6-linked THP rings (**143** and **146**; Scheme 16), and demonstrated that such structures ably bind cations of various metals.
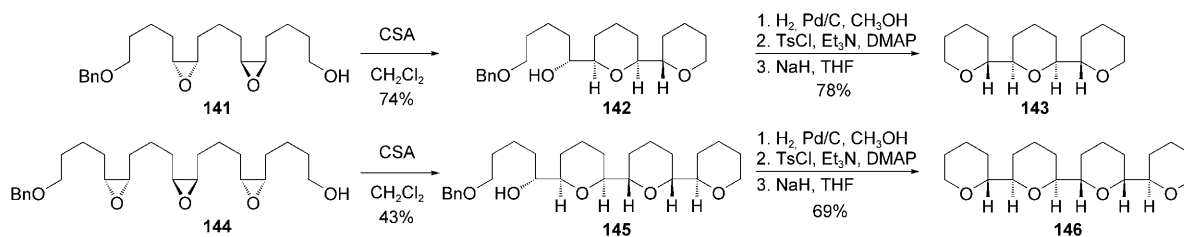
A number of research groups were successful in extending these reactions to the total synthesis of polyether ionophores or fragments thereof. Notable contributions came from the Paterson group in their investigations towards etheromycin (**24**; Scheme 17). In their first-generation approach, Paterson and co-workers extended studies on model diepoxides **98** and **100** (Scheme 10) to mixtures of more complex diastereomeric triepoxides **148** and **149**. These two compounds, which both feature a *tert*-butyl ester as the trapping nucleophile, underwent an acid-promoted cascade reaction to afford the CDE ring system of etheromycin **150** and its diastereomer **151** in good yield.

In their second-generation approach, the Paterson group planned a more elaborate polyepoxide cyclization that would
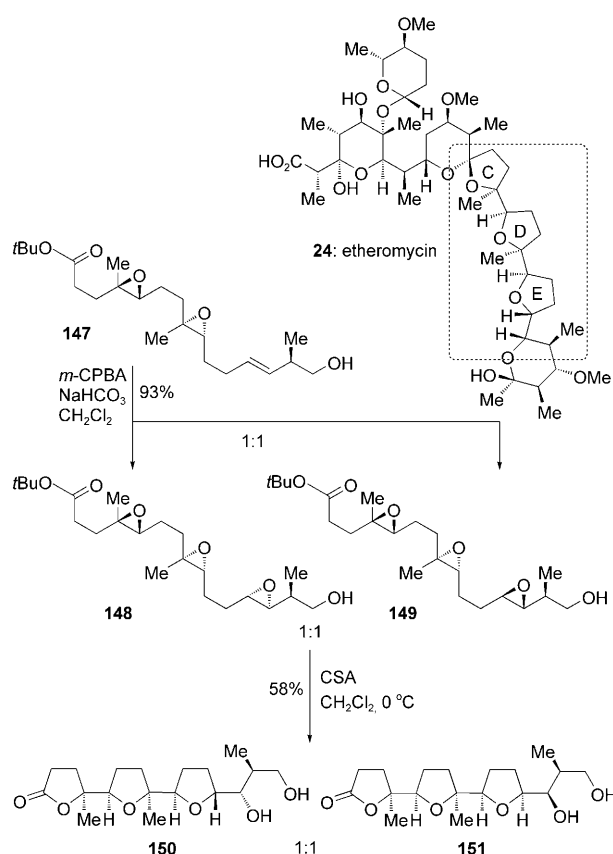
Scheme 17. First-generation cascade approach to etheromycin (Paterson, 1987).[197]

allow the formation of the BC spiroacetal subunit of etheromycin during the cascade.[210] Exposure of diepoxide **152** to acidic conditions triggered deprotection of the secondary alcohol, forming the hemiketal. The hemiketal nucleophile initiates the cascade of epoxide openings, resulting in formation of **153** (Scheme 18a). As etheromycin features oxidation at C4 of the tetrahydropyran ring in the BC spiroacetal, Paterson and co-workers attempted to incorporate the appropriate substitution pattern in the starting diepoxide. Rapid elimination of the secondary alcohol to form a trisubstituted alkene in **155** was observed (Scheme 18b); however, further optimization led to successful incorporation of appropriate oxidation pattern of etheromycin. When diketone **156** was used instead of β-hydroxyketone **154**, the desired BCD fragment of etheromycin (**157**; Scheme 18c) was efficiently produced in a single step.[211]

Scheme 16. Synthesis of oligotetrahydropyran ionophores **143** and **146** (Still, 1989).[209]

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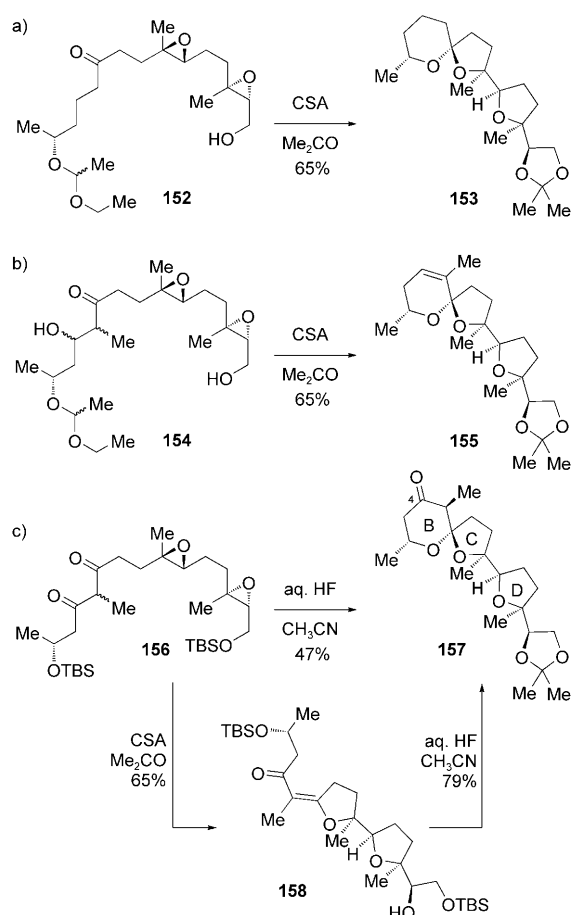
Scheme 18. Second- (a) and third-generation (b,c) cascade approach to etheromycin (Paterson, 1988, 1989).[210,211]

In their efforts to construct the CDE fragment **23** of lonomycin A (Scheme 19), Evans et al. elegantly incorporated an epoxide-opening cascade to construct the bistetrahydrofuran CD ring system **161** by way of macrocyclic diepoxide **159**.[212] Upon lactone hydrolysis, a cascade of epoxide openings afforded **161** in a straightforward manner. The E ring of lonomycin A was then constructed in a fashion that mimics the next step of the proposed biosynthetic cascade to produce tricycle **162** (Scheme 19). The authors noted that a cascade starting from triepoxide **163** would, in principle, be more direct route to the lonomycin A backbone; however, a stereocontrolled synthesis of such substrate would have been considerably more complex.

The latest example of an epoxide-opening cascade in the synthesis of polyether ionophores is the synthesis of the C17–C32 fragment of ionomycin (**20**; Scheme 20) by Marshall and Mikowski. Expanding on their zinc-initiated epoxide-opening cascades of terminal iodomethylepoxides,[205,213] they constructed a bistetrahydrofuran motif **166** of ionomycin and transformed this fragment to **167**, a fully elaborated C17–C32 fragment of ionomycin.[204]
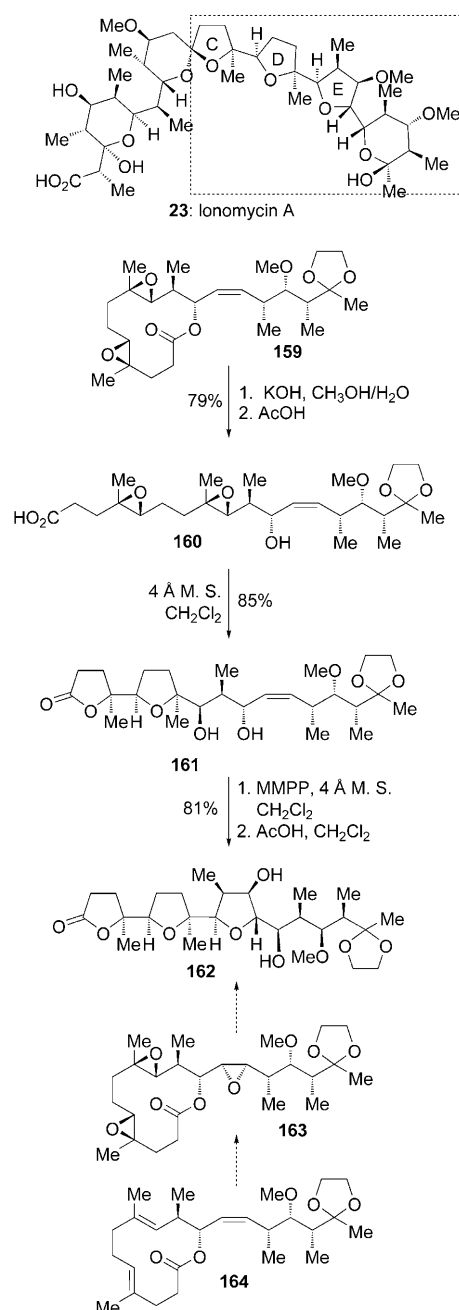
Scheme 19. Synthesis of the CDE ring system of lonomycin A (Evans, 1995).[212] MMPP = magnesium monoperoxyphthalate.

7. Epoxide-Opening Cascades in the Synthesis of Squalene-Derived Polyethers

As discussed in Section 6, the Hoye group examined diepoxides that are reminiscent of those required for the cascade synthesis of the central tetrahydrofuran ring of teurilene (**36**; Scheme 21). In the same vein, Franck and Lindel reported a similar cascade in their studies towards the synthesis of the same natural product.[214] Truncated diepoxide intermediate **168** was treated with a Brønsted acid, efficiently converting it into a diester **169** that features the
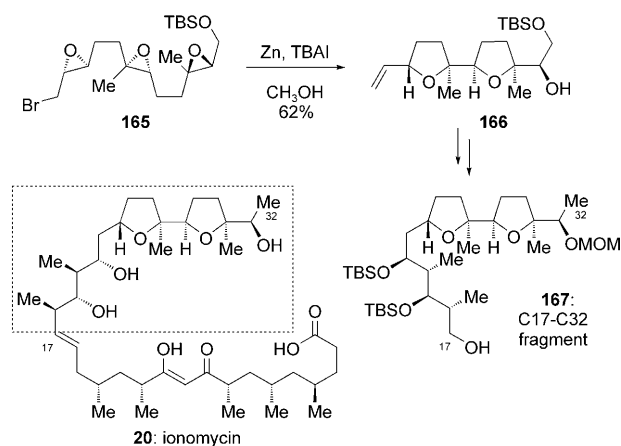
Scheme 20. Synthesis of the C17–C32 fragment of ionomycin (Marshall, 2006).[204]
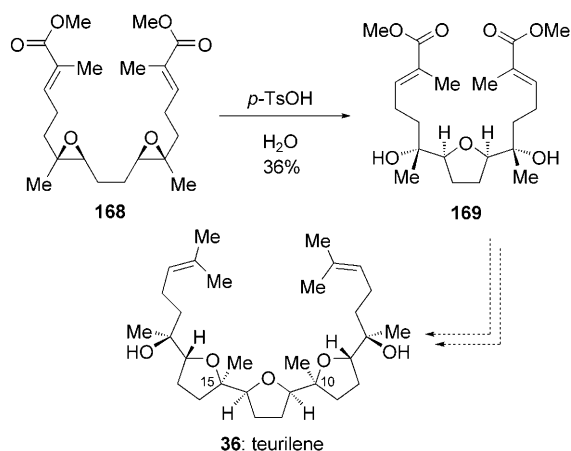
Scheme 21. Synthesis of teurilene core by an epoxide-opening cascade (Lindel, 1995).[214]

C10–C15 fragment of teurilene. The necessary alkenes and tertiary alcohols are in place for an epoxidation/epoxide-opening sequence to the tricyclic core of teurilene (Scheme 21).

In their pioneering studies towards the total synthesis of glabrescol,[215] Corey and Xiong reported a rapid synthesis of proposed structure of glabrescol (**37**; Figure 6) from the corresponding pentaepoxide **170** in a single step under acidic conditions, only to find that this material (Scheme 22) had physical and spectroscopic properties that were different from

Scheme 22. Synthesis of the proposed structure of glabrescol and C_s-symmetric diastereomers (Corey, 2000).[215]

natural glabrescol. The authors also prepared three other diastereomers of pentaepoxide **170**, all of which cyclized to corresponding C_s-symmetric pentacyclic polyethers under the same conditions described for **170**. However, none of the produced polyethers were identical to natural glabrescol.
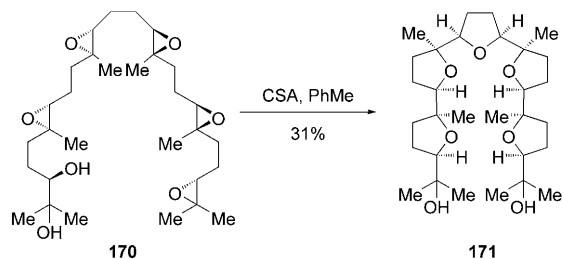
The correct structure of glabrescol was disclosed in a subsequent report by Morimoto.[216] Relying on hydroxy-directed [VO(acac)$_2$]-catalyzed oxidative cyclizations of bish-omoallylic alcohols, a strategy used by Shirahama in syntheses of thyrsiferol, venustatriol, and teurilene,[217–221] Morimoto was able to produce a number of structures diatereomeric to the proposed structure of glabrescol and demonstrate that natural glabrescol is in fact a C_2-symmetric molecule.

Corey and Xiong also investigated the possibility that glabrescol is a C_2-symmetric molecule, and confirmed this revised structure of glabrescol through total synthesis.[222] Corey's synthesis of the revised structure of glabrescol relies on a bidirectional double cyclization of a tetraol tetraepoxide **172** (Scheme 23). The choice of acidic reaction conditions is
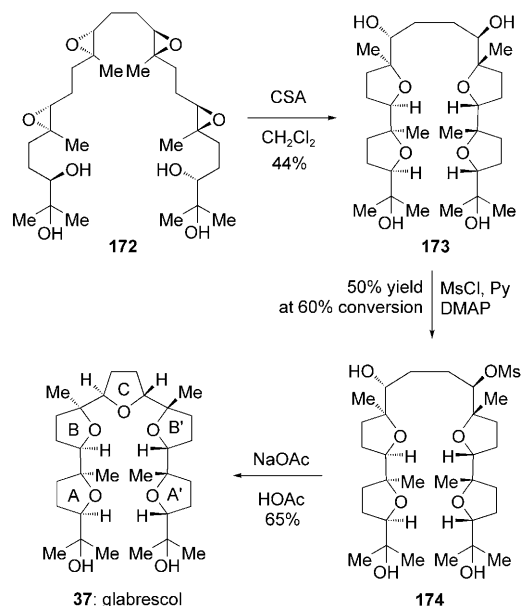
Scheme 23. Bidirectional double cyclization of a tetraol tetraepoxide **172** to form glabrescol (Corey, 2000).[222] Ms = methanesulfonyl.

crucial in this case, so as to ensure that cyclization to form the AB and A′B′ rings of glabrescol via the epoxide opening at more substituted positions is faster than the rate of cyclization to form the C ring via *exo*-opening at the less substituted position of the epoxide. As such, bidirectional formation of AB and A′B′ proceeds in good yield, rather than a unidirectional cascade that would form ABCB′ tetracycle.

A large body of work on the synthesis of squalene-derived polyethers by epoxide opening, in both cascade and iterative fashions, has been reported by Morimoto. For example, in the synthesis of aurilol, epoxide-opening reactions were used extensively (**39**; Scheme 24). In the course of this linear synthetic sequence, Morimoto and co-workers use a base-promoted epoxide-opening cascade on diepoxide **175**[223,224] to construct the C ring of aurilol. After transformation to
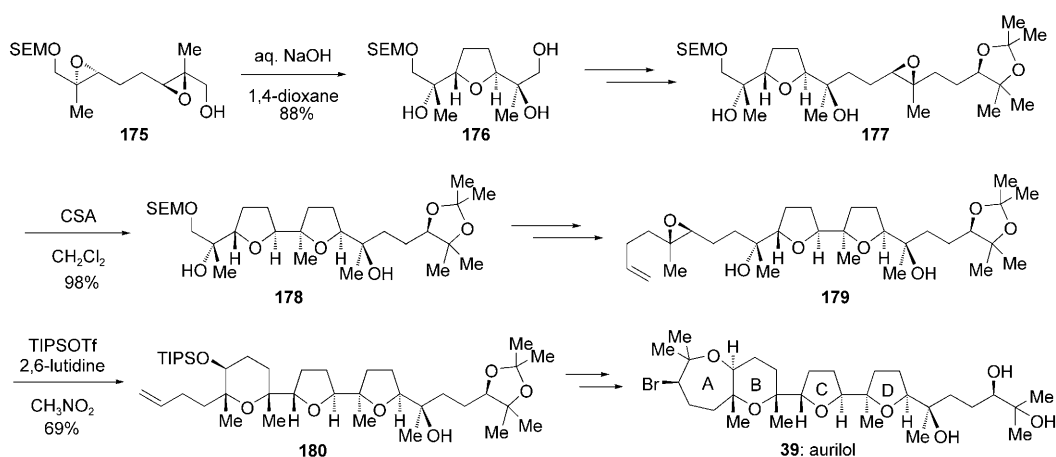
Scheme 24. Total synthesis of aurilol (Morimoto, 2005).[224] SEM = 2-(trimethylsilyl)ethoxymethyl.

epoxyalcohol **177**, Brønsted acid-catalyzed epoxide opening afforded the D ring of the natural product. Finally, reagent-controlled, silyl triflate-catalyzed opening of the trisubstituted epoxide **179** with a tertiary alcohol nucleophile via 6-*endo* cyclization[225] efficiently formed **180**, which contains the B ring of aurilol. Elaboration of this intermediate led to the first total synthesis of aurilol and determination of its absolute configuration (Scheme 24).

Morimoto later adapted the aurilol strategy to the synthesis of the related natural product enshuol (**40**; Scheme 25).[226] Structural analysis of aurilol and enshuol revealed a single difference between the natural products: whereas enshuol contains a fifth ring, tetrahydrofuran E, aurilol features a diol, which may originate from epoxide

opening by water during biosynthesis. Accordingly, Morimoto used a cascade of epoxide openings on epoxyalcohol **181** to construct both the D and E rings of enshuol in a single step (Scheme 25).

Morimoto et al. took advantage of the C_2-symmetric nature of intricatetraol (**38**; Scheme 26) and reduced the
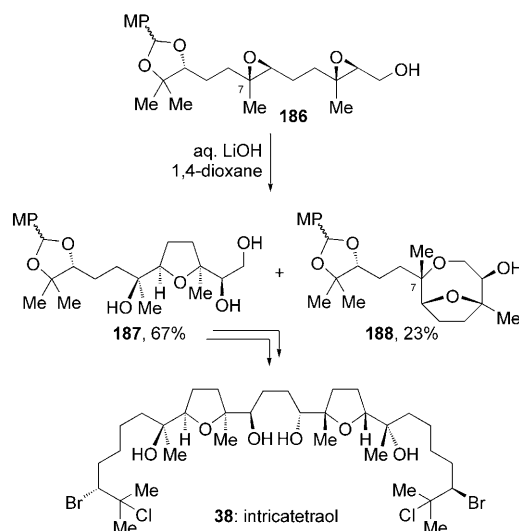
Scheme 26. Synthesis of C_s-symmetric intricatetraol by an epoxide-opening cascade followed by dimerization (Morimoto, 2007).[227]

synthetic challenge to the synthesis of the appropriately functionalized half of the natural product. Subsequent dimerization produced the natural product.[227] Epoxide-opening cascades are the central theme in the synthesis of the requisite monomer (Scheme 26). Diepoxide **186** rearranges to the functionalized tetrahydrofuran **187** under basic conditions. It is interesting that a single bicyclic side product **188** was produced in this reaction, possibly via the initial Payne rearrangement followed by 5-*exo* epoxide opening; however, instead of an opening of the terminal epoxide by base that produces **187**, the terminal epoxide would be opened by the tertiary alkoxide at C7. The configuration of

Scheme 25. Total synthesis of enshuol (Morimoto, 2007).[226]

the newly formed THF ring appears to place the two reactive species in a *cis* relationship, thus encouraging this side reaction.

Notable work on the squalene-derived polyether abudinol (**44**; Figure 6) was reported recently by McDonald and co-workers.[228,229] Because of their conceptual similarities to the synthesis of ladder polyether natural products, these studies will be discussed in the following section.

8. Epoxide-Opening Cascades in the Synthesis of Ladder Polyethers

Epoxide-opening cascades were initially, and nearly exclusively, explored in the context of the synthesis of polyether ionophores and other natural products that could arise from *exo* opening of epoxides. This is not surprising considering the breadth of data supporting Baldwin's rules, which suggest that smaller rings are kinetically favored in intramolecular epoxide-opening reactions. Successful *endo*-selective cascades for preparation of ladder polyether-like fragments would thus require circumventing this inherent selectivity for smaller rings in epoxide-opening reactions.

8.1. Iterative Approaches

As discussed in Section 2.1, most methods for regioselective *endo* epoxide opening rely on the effects of directing groups directly attached to the epoxide. These directing groups are not usually present in the target ladder polyethers; the fact that they are incorporated in products of such epoxide-opening reactions therefore presents a major challenge for their successful utilization in total synthesis of ladder polyethers because of the need for their removal or extensive synthetic elaboration. If such reactions are extended to a cascade of epoxide openings, multiple directing groups would be incorporated at the ring junctions of the final product, thus creating the need for selective elaboration of each of the groups into H or Me groups, which are the exclusive substituents found at the ring junctions of ladder polyethers. As they are good directors of regioselectivity, methyl groups would appear to be the exception; however, they are typically present at only a few ring junctions in each ladder polyether and are rarely distributed in a uniform substitution pattern.

Despite the problems associated with the use of directing groups in cascades of epoxide-opening reactions, they have been of tremendous value in iterative approaches to ladder polyether synthesis. Such approaches depend on the type of the directing group used in the epoxide-opening reaction and require an efficient removal of this group after each iteration. If all these requirements are met, a sequence of *endo* cyclization, removal of the directing group, and homologation to a new epoxide bearing the appropriate directing group for the next cyclization results in the formation of one cyclic ether per iteration.

The Nicolaou group was the first to explore and report a successful iterative approach to ladder polyethers based on
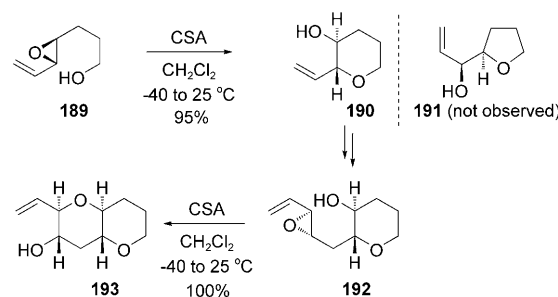
Scheme 27. Iterative approach to the synthesis of oligotetrahydropyran fragments by a 6-*endo* cyclization of alkenyl epoxides (Nicolaou, 1989).[23]

endo-selective epoxide opening (Scheme 27).[23] The epoxyalcohol **189** bearing an alkenyl directing group undergoes Brønsted acid-catalyzed cyclization with excellent *endo*-selectivity, which is due to the ability of alkenyl substituent to stabilize partial positive charge in the transition state for the desired cyclization. Upon elaboration of the tetrahydropyran **190** to epoxyalcohol **192**, another acid-catalyzed opening of alkenyl epoxide afforded diad **193** with excellent efficiency.

Mori et al. reported a complementary approach to ladder polyethers that relies on *endo*-selective opening of epoxysulfones (Scheme 28).[37] Exposure of epoxysulfone **195** to Brønsted acid leads to 6-*endo* cyclization and subsequent loss of phenylsulfonate to yield ketone **196**. A sequence involving alkylation of the sulfone-stabilized *cis*-oxyranyl anion completes the homologation process to **197**, which contains an epoxide with the appropriate directing group for the next iteration. Repeating this procedure three times leads
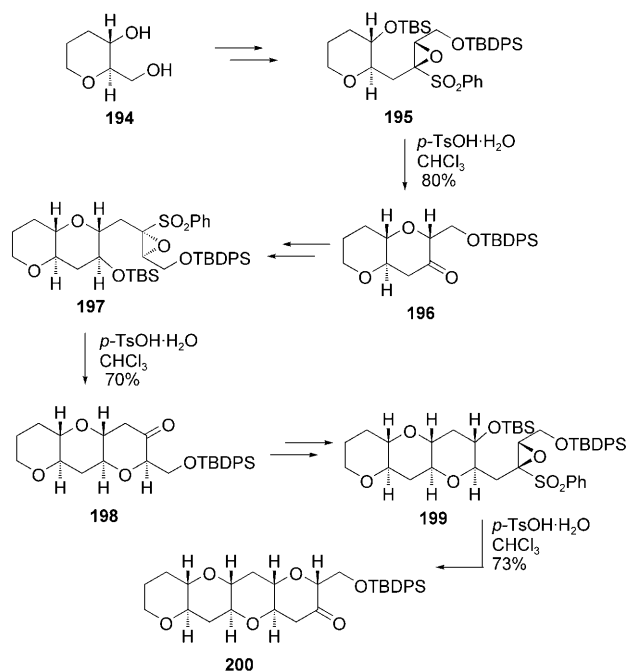
Scheme 28. Iterative approach to the oligotetrahydropyran fragment synthesis by a 6-*endo* cyclization of epoxysulfones (Mori, 1996).[37]

to formation of tetracycle **200**. Mori and co-workers have also developed methods for larger oxygen heterocycles[230] and ring-junction substitution patterns (Me and H)[39, 231] present in ladder polyether natural products.

The structural effects of a silyl group attached directly to an epoxide have been studied in detail by Hudrlik[232–234] and Paquette,[235] and the electronic properties of these substituents have been exploited in epoxide-opening reactions of epoxysilanes. For example, Heffron and Jamison developed an iterative approach to the synthesis of *trans*-fused oligotetrahydropyran fragments in this fashion (Scheme 29).[36] In contrast to epoxysulfones, in which the sulfone deactivates the

undesired site of epoxide opening, silyl groups stabilize positive charge in the transition state leading to 6-*endo* epoxide opening. After cyclization, removal of the directing group can be achieved cleanly with TBAF. To enable homologation to the epoxysilane for next iteration, Jamison and co-workers developed a protocol for the synthesis of skipped enynes by phosphine-promoted coupling reactions of propargylcopper reagents with alkenyl iodides.[236] A Shi epoxidation[237] of the intermediate vinyl silane completes the cycle, and the utility of this approach was demonstrated by synthesis of THP triad **207** (Scheme 29).

8.2. Epoxide-Opening Cascades Leading to Fused Polyether Systems

Early work in this area by the Murai group led to the development of methods for the *endo*-selective lanthanide-promoted opening of epoxides bearing methoxymethyl groups.[40] Murai and co-workers prepared polyepoxides **208**, **213**, and **217**, which incorporate a methoxymethyl directing group at each epoxide.[238] Under conditions described for substrates containing one epoxide, diepoxide **208** was converted into a THP diad **209** with methoxymethyl groups present at the ring junctions (Scheme 30). The side products isolated in this reaction suggest a pathway that proceeds in a stepwise fashion from the primary alcohol nucleophile, initially forming intermediate **211**, and then affords **209** and **210**. The authors also reported that the diastereomeric diepoxide **213** does not afford the corresponding THP diad (diastereomer of **209**). It is postulated that intermediate **215** does not react further owing to strain in the requisite boat-like transition state that would lead to 6-*endo* opening and also to steric repulsion between the two methoxymethyl substituents (Scheme 30). Murai has also demonstrated that cascades directed by methoxymethyl groups in combination with an
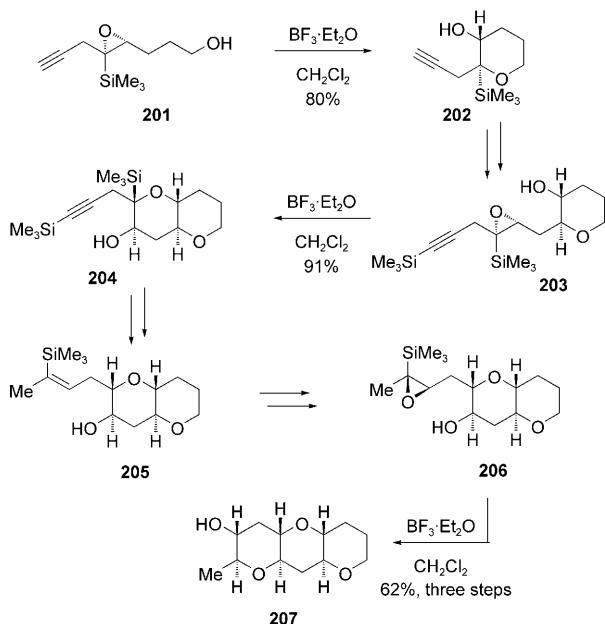
Scheme 29. Iterative approach to the oligotetrahydropyran fragment synthesis via 6-*endo* cyclization of epoxysilanes (Jamison, 2003).[36]
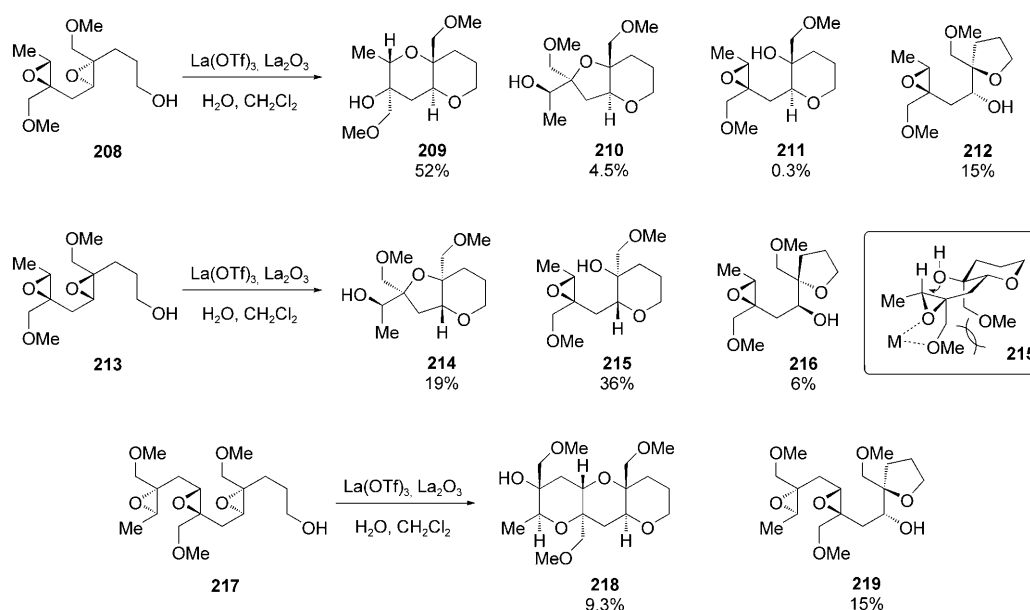
Scheme 30. Epoxide-opening cascades directed by the methoxymethyl group (Murai, 2000).[238]

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appropriate chelating Lewis acid can be extended to larger ladder-polyether-type fragments, such as triad **218**, albeit in low yield.

McDonald and co-workers reported the first cascade reactions that include formation of an oxepane ring and *trans*-fused bisoxepane motifs via an *endo*-selective epoxide opening.[31,239] They also examined a range of terminating nucleophiles, such as ketones, esters, carbonates, and acetals, demonstrating that *endo* regioselectivity in these Lewis acid-promoted polyepoxide cyclizations depends to some extent on the type of terminating nucleophile (Scheme 31).
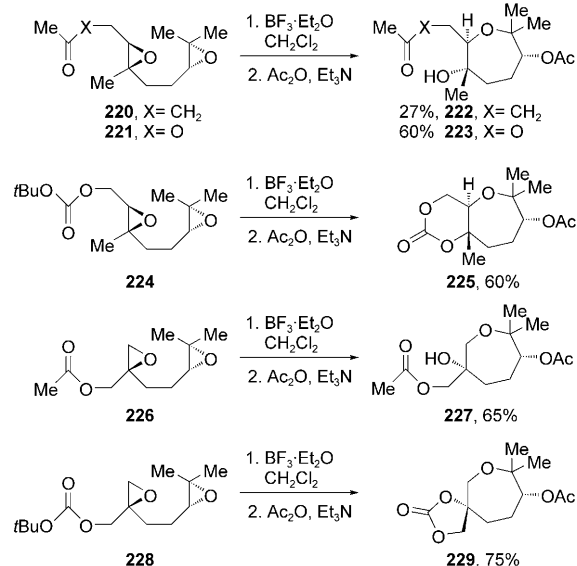

Scheme 31. Lewis acid-catalyzed cascades that form oxepanes from 1,5-diepoxides (McDonald, 2000, 2002).[31,239]

McDonald et al. extended this approach to polyepoxides for the synthesis of polyoxepane systems **230–233**.[31,239] The efficiency of these reactions tends to drop as the number of epoxides in the polyepoxide precursor increases (Scheme 32). A possible reason for a non-linear decrease of yield in cascades that involve more than two epoxides may be unselective activation of any and all of the epoxides in the starting materials (see Section 6). If selective activation of only the epoxide that is distal to the terminating nucleophile could be achieved, cascades would presumably proceed only in one direction, and higher yields should be observed. With this in mind, the McDonald group prepared substrates **238** and **239** that feature a vinyl and a methyl substituent instead of the two geminal methyl substituents on the terminal epoxides in the polyepoxide chain of **230–233** (Scheme 33).[240] Based on work on alkenyl epoxides by the Nicolaou group,[22–24] it was expected that the stabilization provided by the vinyl substituent would not only improve selectivity in epoxide-opening reactions, but also lead to selective activation of the alkenyl epoxide over the interior epoxides under finely tuned conditions. Optimization revealed Gd(OTf)₃ and Yb(OTf)₃ to be the most efficient Lewis acids. Indeed, desired oxepane ring-containing products **240** and **241** were produced
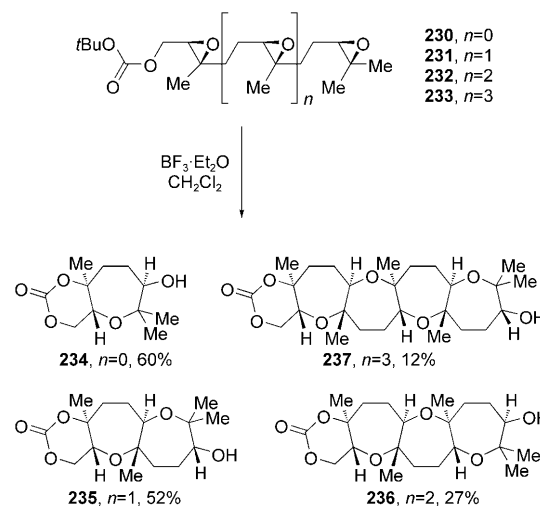
Scheme 32. Methyl-directed epoxide-opening cascades forming polyoxepane systems (McDonald, 2000, 2002).[31,239]
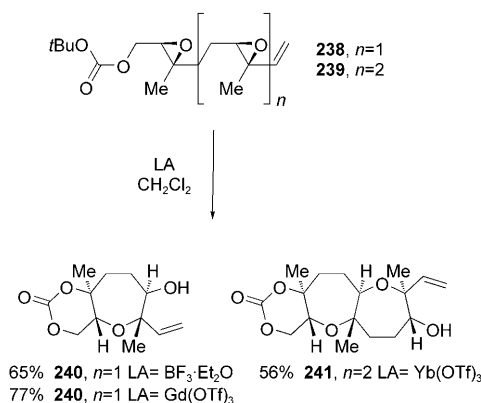
Scheme 33. Lewis acid (LA)-promoted cyclizations of polyepoxide substrates with terminal alkenyl epoxides (McDonald, 2004).[240]

in higher yield than in the corresponding reactions of substrates **230** and **231** that lack vinyl substituents.

The synthetic utility of these impressive cascades is however limited by the requirement for an alkyl directing group on each epoxide, resulting in the incorporation of the directing groups at every ring junction of the final cascade product. Were these cascades to be used in the synthesis of naturally occurring molecules, they would have to accommodate polyepoxides without directing groups (disubstituted epoxides) and allow a variety of substitution patterns that would install methyl groups only at the desired positions of the final products. The McDonald group has offered two approaches to address these concerns. The first is based on the directing effects of silyl groups described by Paquette and Hudrlik and elaborated by Jamison. Silyl groups exhibit similar directing effects to those of alkyl groups, but they can generally also be removed after the cascade. McDonald showed that epoxide-opening cascades that use both alkyl and silyl direction are possible by Lewis acid promotion.[241] For

example, **242** and **243** were converted into the corresponding cyclization product **244** with efficiencies comparable to those of cascades with only methyl-substituted epoxides (Scheme 34).

242, R=O*t*Bu   40% **244**
243, R=Me₂N   45% **244**

245, R=O*t*Bu   30% **247**
246, R=Me₂N   35% **247**

248, R=O*t*Bu
249, R=Me₂N

20% **250**
25% **250**
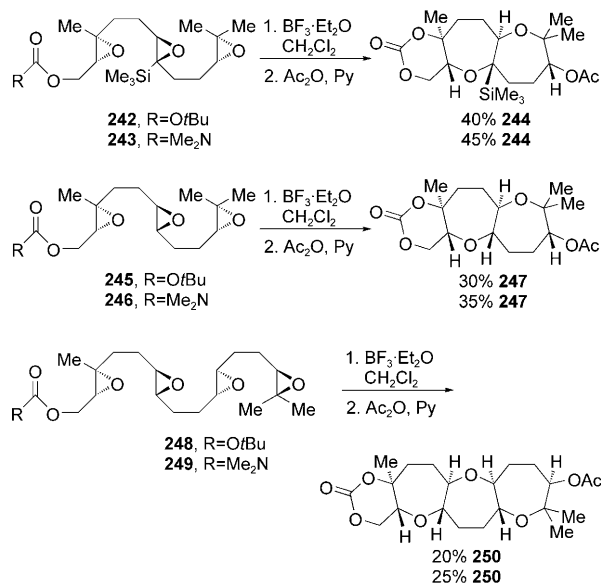
Scheme 34. Synthesis of polyoxepane systems from substrates with divergent directing groups and without directing groups at internal epoxides (McDonald, 2005).[241]

The McDonald group also investigated cascades that would incorporate disubstituted epoxides with no directing groups present, as in **245** and **246** (Scheme 34).[241] The difference between the electronic properties of disubstituted and trisubstituted epoxides may work in favor of the desired cascade through preferential activation of the epoxide distal to the terminating nucleophile, in a fashion similar to cascades on alkenyl epoxides **238** and **239**. Cascades of both triepoxide **246** and tetraepoxide **249** proceed under standard Lewis acid activation to form the desired tricyclic **247** and tetracyclic polyether **250** (Scheme 34). It was proposed that once the first epoxonium ion is formed at the distal end, the transition states leading to *endo* and *exo* opening of the disubstituted epoxonium ion differ in energy, with a higher degree of ring strain associated with the bicyclo[3.1.0] intermediate than for the bicyclo[4.1.0] intermediate formed as the product of *endo* opening. The authors also noted that a directing group is required on the epoxide proximal to the trapping nucleophile, as there is minimal strain associated with either 5- or 6-membered carbonates formed at the end of the cascade if carbonate or carbamate nucleophiles are used. A directing group is therefore necessary to ensure *endo* regioselectivity in the opening of this last epoxide.

In addition to their studies on the use of epoxide-opening cascades in the construction of oxepanes, the McDonald group has also explored cascades for the synthesis of tetrahydropyrans in similar fashion. As in the case of oxepanes, the effects of the terminating nucleophile on epoxide-opening cascades of 1,4-diepoxides **251**–**255** were

first examined.[32] Depending on the nucleophile, these reactions can proceed with either retention or inversion of configuration at the ring junction (Table 1). It is apparent that stronger nucleophiles at elevated temperatures tend to favor the inversion of stereochemistry in the opening of internal epoxide, thus setting a *trans* geometry at the ring junction of **256**. In contrast, less nucleophilic carbonates favor the production of diastereomeric product **257**, corresponding to retention of configuration.

Table 1: Effects of the terminating nucleophile on distribution of products and the stereochemical outcome in cascade reactions of 1,4-diepoxides (McDonald, 2003).[32]

251, R = *t*BuO
252, R = PhNH
253, R = Me₂N
254, R = (CH₂)₄N
255, R = O(CH₂CH₂)₂N

256   **257**   **258**

Entry	Substrate[a]	T [°C]	Time [min]	Yield of isolated products [%]		
				256	257	258
1	251	−40	10	< 4	56	12
2	251	+40	2		65	4
3	251[b]	−40	10		42	10
4	252	−40	10[c]		70	
5	253	−40	10[c]	35	10	
6	253	+20	2[c]	55	21	
7	254	−40	10[c]	32	8.5	
8	255	−40	10[c]	34	13	

[a] Concentration was 0.05 M of substrate in CH₂Cl₂ unless otherwise stated. [b] Concentration: 0.5 M. [c] The reaction mixture was subsequently stirred with aq NaHCO₃ for 2 h to hydrolyze iminium ions.

These observations may be explained by the mechanism outlined in the Scheme 35, in which the terminating nucleophile intercepts a cationic intermediate at different points in the continuum between the extremes of epoxonium ion and tertiary alkyl carbocation. McDonald et al. proposed that *cis*-fused products arise from fast nucleophilic addition to the tertiary carbocation, whereas *trans*-fused products are favored with a stronger nucleophile, which intercepts a tight ion pair intermediate structurally related to the epoxonium ion.[32]

The McDonald group extended these findings to epoxide-opening cascades of triepoxides **265** and **266**, which carry directing groups on each of the epoxides. When activated by a Lewis acid at an appropriate temperature, triepoxide **265** (with the carbamate terminating nucleophile) is transformed into the ladder polyether-like tricycle **267** in 31% yield. Unlike its carbamate analogue, triepoxide **266** (with a carbonate nucleophile) surprisingly failed to afford any of the desired products and, instead, gave **268** at low temperatures (Scheme 36). The fused THF/THP product **268** is presumably produced through isomerization of the initially formed bicyclo[3.1.0]epoxonium intermediate, which leads to
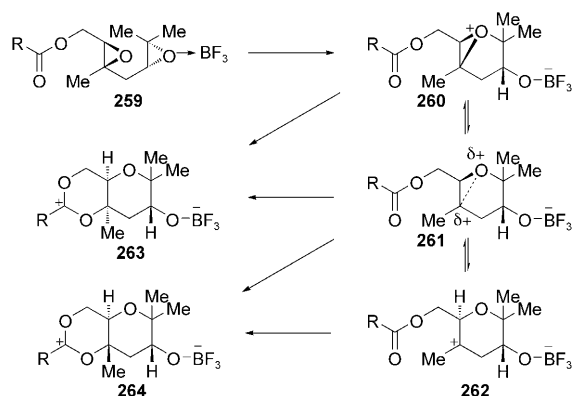
Scheme 35. Mechanistic rationale for the stereochemical outcome of epoxide-opening cascades as function of the type of terminating nucleophile (McDonald, 2003).[32]
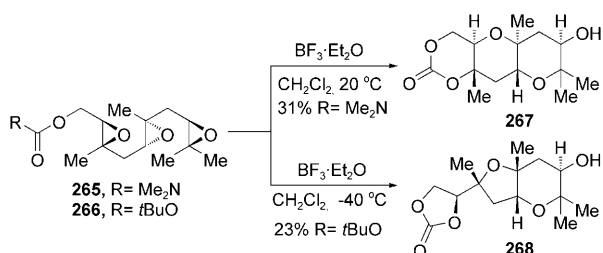
Scheme 36. Effects of the terminating nucleophile on the outcome of a methyl-directed cascade leading to polytetrahydropyran systems (McDonald, 2003).[32]

Scheme 37. Effects of different Lewis acids on cascades of **269** and **272** (McDonald, 2007).[242]

cis geometry at the ring junction, followed by 5-*exo* cyclization in the last epoxonium opening event of the cascade. Therefore, the choice of the terminal nucleophile not only dictates whether cyclization will proceed with retention or inversion, but in the case of 1,4,7-triepoxides, it determines the regioselectivity of the cyclization of the epoxide proximal to the carbonyl nucleophile.[32]
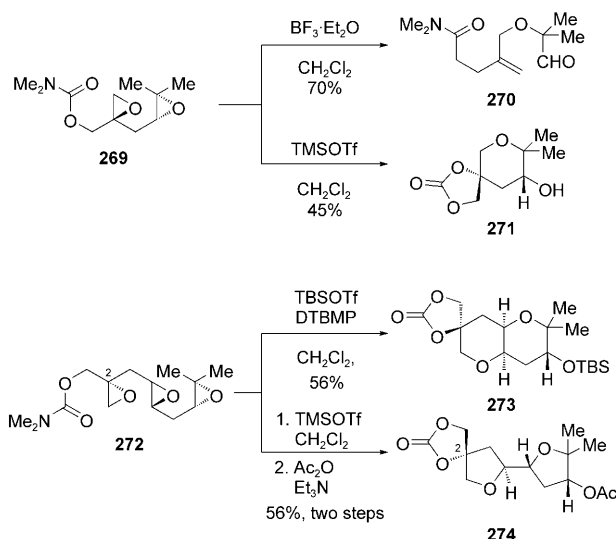
Finally, the McDonald group investigated the dependence of the cascade outcome on the type of Lewis acid for 1,4-diepoxide substrates (Scheme 37).[242] Their studies on a THP precursor, diepoxide **269**, which is homologous to diepoxide **228** used in the production of oxepane rings (Scheme 31), showed that the desired cascade reaction does not proceed when BF$_3$·Et$_2$O was used. Instead, the product of carbon–carbon bond cleavage (**270**; Scheme 37) was isolated in high yield. However, when trimethylsilyl triflate was used, the desired tetrahydropyran **271** was obtained as the sole isolable product. Interestingly, the reactivity patterns of triflates proved to be more complex than initial results suggested. When trimethylsilyl triflate was used with triepoxide **272**, the product of an *all-exo* epoxide-opening cascade (**274**; Scheme 37) was isolated. Notably, the stereochemistry at C2 was preserved in this cascade, suggesting that epoxide opening occurs with retention (or double inversion) at this site. In contrast, when *tert*-butyldimethylsilyl triflate was used, a fused THP diad (**273**), which differs from the desired product, was isolated. Structural analysis of this material revealed *syn*

geometry of the ring fusion, suggesting that opening of the epoxonium intermediate proceeds with retention of configuration. Although the reasons for these apparent differences are unclear, it was proposed that the weakly nucleophilic triflate anion may compete with the epoxide oxygen in the opening of the epoxonium intermediate, leading to double inversion and net retention of configuration at C5.

A conceptually different way of promoting epoxide-opening cascades to ladder polyethers was investigated by Murai and co-workers. They envisioned that activation of an epoxy bromide with a silver salt would selectively generate an epoxonium ion at one end of the polyepoxide chain.[200] This epoxonium ion would then serve as an electrophile for the nucleophilic attack by the neighboring epoxide, thereby forming a new ring and a new epoxonium intermediate and thus propagating the cascade. The direction of the cascade in these reactions is therefore controlled by the position of the halide, and the need for selective activation of only one of many epoxides in polyepoxide substrates is avoided. These studies by Murai were the first studies directed toward epoxide-opening cascades in the synthesis of ladder-like polyether products.

Murai and co-workers focused their attention on *trans*-disubstituted epoxide substrates without directing groups, and showed that opening of the epoxonium ion derived from bromo epoxide **275** with an external nucleophile preferentially forms tetrahydropyran **276** over tetrahydrofuran **277** (Scheme 38a) However, when more than one epoxide is present in the starting material, the reactions proved to be more capricious, and diverse products from a number of different pathways were formed. External nucleophiles present in the reaction mixture, such as water, competed with the epoxide oxygen in opening the epoxonium ion. If such nucleophilic species are not present and the reaction was activated with AgOTf, the triflate anion competes with the epoxide, thus producing yet another electrophilic species that, over time, undergoes another displacement reaction to give

a)

278
THF/H$_2$O (5:1), 1 h (24% recovered 278)
THF/H$_2$O (5:1), 4 h
CH$_2$Cl$_2$ 0.5 h

279
39%

280
31%

281
11%
47%

282
THF/H$_2$O (5:1), 1 h (12% recovered 282)
THF/H$_2$O (5:1), 4 h
CH$_2$Cl$_2$ 0.5 h

283
29%

284
41%

285
46%

b)

286   287   288   289
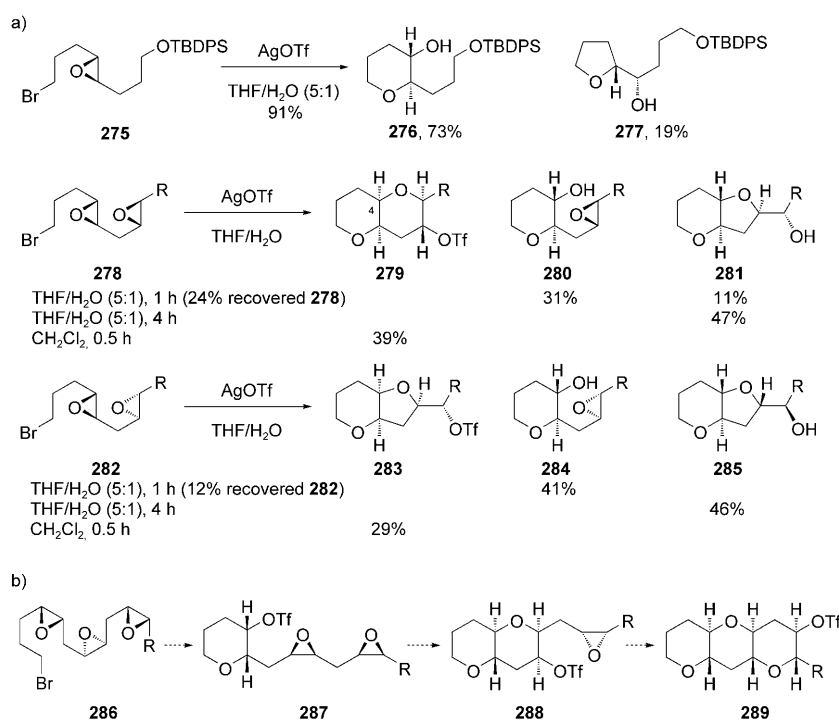
Scheme 38. a) Cascades of epoxy halides and polyepoxy halides selectively activated with silver salts. b) Proposed cascade of an *all-cis* polyepoxide, initiated by silver(I) and propagated by the weakly nucleophilic triflate anion, involving double inversion of configuration at each site of nucleophilic attack (Murai, 1997).[200]

the *cis* geometry at the ring junction via double inversion at the C4 position of 279 and 283 (Scheme 38a). If such a trend were to hold in the case of a polyepoxide, then an *all-cis* polyepoxide could lead to formation of the *trans-syn-trans* fragments of ladder polyethers.[200] In this scenario, the initial epoxonium ion would be opened by a triflate anion that would, in turn, be displaced by the neighboring epoxide to generate the new epoxonium, thus propagating the cascade (Scheme 38b).

An extension of those studies were reported by Heffron and Jamison.[243] The triepoxide analogue of 275 (290; Scheme 39) was treated with silver triflate to initiate the cascade. As in cascades of 278 and 282, the presence of an external water nucleophile led to opening of the epoxonium intermediate rather than propagation of the cascade. The intermediate 291 formed by this sequence can react further to generate 292 through a 5-*exo* epoxide opening. All attempts
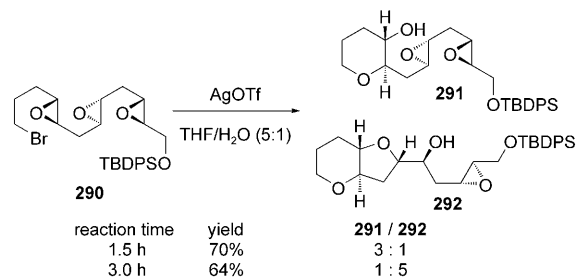
to eliminate nucleophilic additives and anions in reactions of 290 and carry out a cascade similar to the one proposed by Murai under anhydrous conditions with AgOTf, AgPF$_6$, or AgSbF$_6$ were unsuccessful.[243]

As described in section 6 on polyether ionophores, Floreancig and co-workers have demonstrated that mesolytic cleavage of the benzylic carbon–carbon bond in the radical cations of homobenzylic ethers, such as 112–115 (Scheme 13), forms oxonium ions, which react with pendent epoxides to form epoxonium ions capable of undergoing further nucleophilic attack. This strategy is conceptually similar to reactions of halo epoxides reported by Murai[200] and Jamison.[243] After their initial success in the synthesis of bistetrahydrofuran fragments of polyether ionophores, the Floreancig group, in collaboration with Houk and co-workers, published their experimental and computational studies on the structure–reactivity relationships for intramolecular additions to bicyclic epoxonium ions.[244] They observed that ring size has a significant impact on these processes, with *endo*-cyclizations being preferred for bicyclo-[4.1.0] epoxonium ions bearing an alkyl directing group, and *exo*-cyclizations being preferred for bicyclo[3.1.0] epoxonium ions despite the presence of a directing group (Scheme 40). The authors propose that these effects can be attributed to the ability of the larger ring to accommodate a looser transition state with significant S$_N$1 character, thereby promoting the *endo* process regardless of solvent polarity. As they had clearly demonstrated that the epoxonium ion structure is a significant determinant of regioselectivity under these kinetic cyclization conditions, Floreancig and co-workers then designed a number of extended substrates that undergo cascade cyclizations that form fused tricyclic systems under the oxidative conditions described earlier (Scheme 40).

As described above, the Jamison group has successfully utilized the directing effects of trimethylsilyl groups to develop an iterative approach to the synthesis of oligotetrahydropyran fragments. However, when a cascade reaction under similar Lewis acid conditions was attempted on diepoxide 306 with suitably positioned directing groups, the only isolable product was bistetrahydrofuran 307.[245]

Thorough evaluation of reaction conditions revealed that the outcome of this reaction was very different when a Brønsted base in alcoholic solvents was used (Scheme 41). Under these conditions diepoxide 306 undergoes a cascade to produce THP diad 308. Surprisingly, the trimethylsilyl directing group was absent from the ring junction in the product.

Further modifications to the design of polyepoxide substrates and reaction conditions resulted in the development of epoxide-opening cascades directed by "disappearing"

reaction time	yield	291 / 292
1.5 h	70%	3 : 1
3.0 h	64%	1 : 5

Scheme 39. Cascades of polyepoxy halides activated with silver salts (Jamison, 2006).[243]
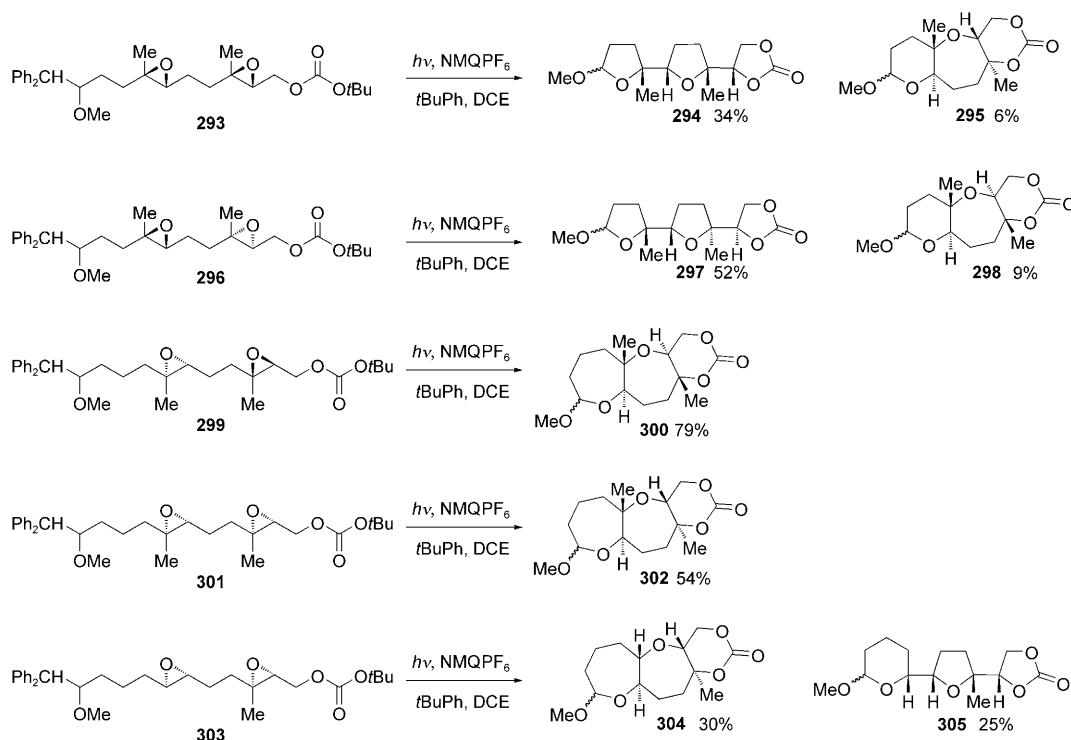
Scheme 40. Epoxide-opening cascades initiated by oxidative cleavage of homobenzylic ethers (Floreancig, 2007).[244]
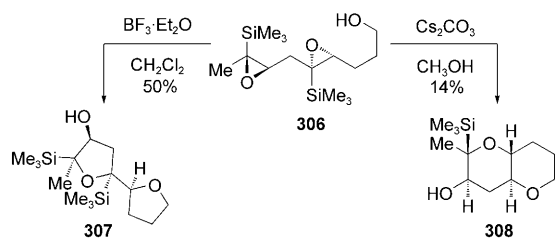
Scheme 41. Silyl-directed cascade cyclizations of epoxysilanes (Jamison, 2006).[245]

Scheme 42. Epoxide-opening cascades with a disappearing silyl group (Jamison, 2006).[245]

silyl groups (Scheme 42).[245] These modifications include the construction of one THP ring prior to the cascade and the addition of CsF. The authors suggest that the cascades proceed as a sequence of silyl-directed epoxide opening followed by protiodesilylation, which most likely occurs via a homo-Brook rearrangement pathway. After each Brook rearrangement, removal of silyl group by fluoride reveals the alcohol nucleophile for the next stage of the cascade reaction.

Although disappearing directing groups address problems related to the removal of substituents not present in the natural targets, these reactions developed by Jamison et al. suffer from the inability to incorporate the methyl substituents found occasionally at the ring junctions. Thus, a cascade reaction free of directing groups and capable of incorporating the various types of substitution present in ladder-type polyethers is required. The Jamison group reasoned that in epoxyalcohol **318** (Scheme 43), where one THP is already in place, issues that might normally favor the undesired *exo*-

transition state would be minimized and, instead, enthalpic contributions to the energies of the competing transition states would change.[246] *Trans*-bicyclo[4.4.0]decane derivatives are typically less strained than their *trans*-bicyclo-[4.3.0]nonane counterparts, and were this difference in developing ring strain reflected in the transition states, the desired tetrahydropyran product might be favored in this templated system under appropriate conditions.

In investigating this hypothesis, Vilotijevic and Jamison discovered that regioselectivity of epoxide opening in epoxyalcohol **318** is dependent on the pH of the aqueous medium
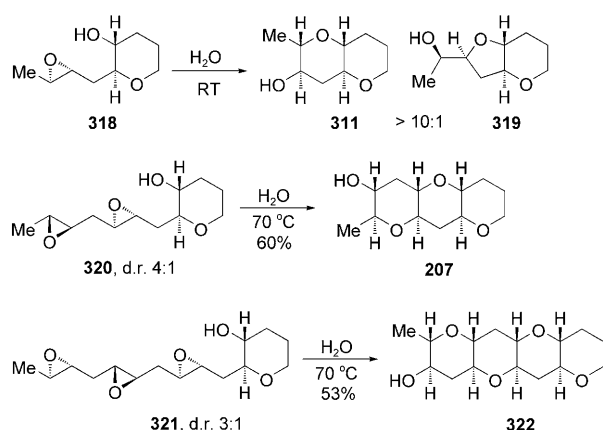
Scheme 43. Epoxide-opening cascades promoted by water (Jamison, 2007).[246]

used to promote the cyclization.[246] The selectivity for the desired THP product **311** increases substantially as the pH of the reaction environment approaches neutrality (Figure 12). Templated cascades promoted by water were then examined
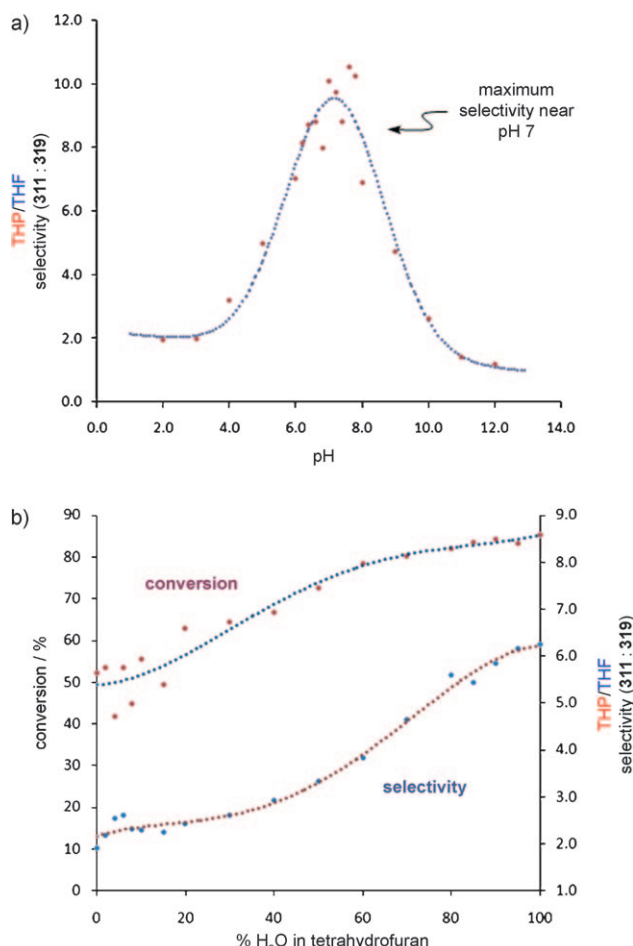
Figure 12. a) Dependence of selectivity in epoxyalcohol cyclizations on the pH of the reaction medium. b) The effect of water on conversion and selectivity of epoxyalcohol cyclizations in THF/water mixtures (Jamison, 2007).[246]

with diepoxide **320** and triepoxide **321**, which lack directing groups. Both cascades proceed with good yield in water at elevated temperatures, affording THP triad **207** and tetrad **322**; these subunits are found in more than half of the known ladder polyether natural products.

Vilotijevic and Jamison proposed that a synergistic effect of the template and catalysis by water is responsible for the high *endo* selectivity in these reactions. A model was proposed that involves a network of hydrogen-bonded water molecules interacting simultaneously with both the epoxide electrophile and the alcohol nucleophile. Such a network could bring the desired site of nucleophilic attack closer to the secondary alcohol on the THP template. Experiments that demonstrate that water is responsible for both an increase in selectivity and in the rate of cyclization are in agreement with this proposal (Figure 12). These models are currently under investigation.

8.3. Epoxide-Opening Cascades in the Synthesis of Ladder Polyethers

The epoxide-opening reactions used in the synthesis of ladder polyethers are generally based on the *endo*-selective opening of alkenyl epoxides developed by Nicolaou to form tetrahydropyran rings. This method has been used by the groups of Nicolaou, Yamamoto, Nakata, Mori, and Sasaki in syntheses of hemibrevetoxin,[247–253] brevetoxin B,[254–267] brevetoxin A,[268–274] gambierol,[275–284] and brevenal.[162,163] Although this method can be implemented in a straightforward manner in a number of syntheses, it is not amenable to cascades, that is, to more than one epoxide. Nevertheless, it has been used by Nicolaou in the iterative synthesis of the FG fragment of brevetoxin B (Scheme 44).[247] Nicolaou's approach includes an acid-catalyzed opening of the alkenyl epoxide to form both F and G rings of brevetoxin B. Epoxyalcohol **323** was efficiently transformed to a corresponding tetrahydropyran **324**. Upon elaboration of **324** to **325**, another Brønsted acid-catalyzed epoxide opening affords **326**, which contains the F and G rings of brevetoxin B.

Other iterative approaches have found use in the synthesis of both ladder polyether natural products and their fragments. Mori and co-workers reported a total synthesis of hemibrevetoxin B (**53**; Figure 13) that relies solely on their
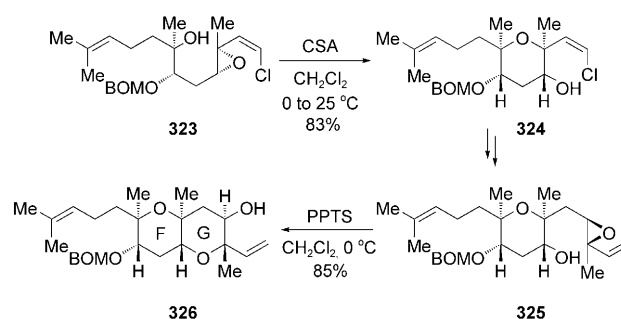
Scheme 44. Iterative synthesis of the FG fragment of brevetoxin B (Nicolaou).[254] BOM = benzyloxymethyl, PPTS = pyridinium *p*-toluene-sulfonate.
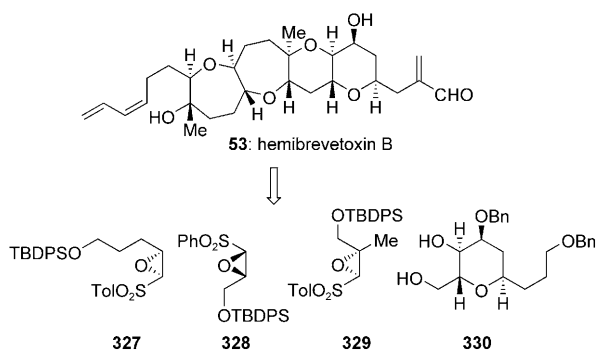
Figure 13. Retrosynthetic analysis of the iterative synthesis of hemi-brevetoxin B (Mori, 1998).[253]

iterative strategy for construction of *trans*-fused tetrahydropyran rings. In combination with methods that allow ring expansion of tetrahydropyran to oxepane systems,[230] hemibrevetoxin B was prepared in an iterative fashion using *endo*-selective intramolecular opening of epoxysulfones (Figure 13).

The Mori group was also successful in the preparation of the ABCDEF ring system of yessotoxins and adriatoxins (**331**; Figure 14). Especially appealing is the fact that the same epoxysulfone **328** could be used for the construction of four of the six rings. To introduce methyl substituents at the ring junction efficiently, Mori has developed two strategies.[39,231] The first requires elaboration of a 3-ketooxepane to a corresponding 3-methylidene compound, followed by epoxidation and reduction of the epoxide with lithium triethylborohydride. The other method is the inherently more convergent incorporation of a methyl substituent into the epoxysulfone **329**.

An interesting cascade was utilized by Holton and co-workers in the total synthesis of hemibrevetoxin B.[286] Although only one epoxide is involved in this reaction, two cyclic ethers of the natural product are nevertheless produced in a single operation. Computational studies by Houk et al.[44,46] suggesting that alkyl-group-directed 6-*endo* cyclization normally requires a loose, S_N1-like transition state prompted Holton to carry out the cascade in a strongly polar solvent, namely hexafluoroisopropanol. In a fashion conceptually complementary to work by Murai,[200] Jamison,[243] and Floreancig,[244] appropriate activation of the

alkene in **335** was achieved with *N*-(phenylseleno)phthalimide, and the cascade leading to formation of the 7,6-fused CB ring system of hemibrevetoxin B proceeded in high yield (Scheme 45).
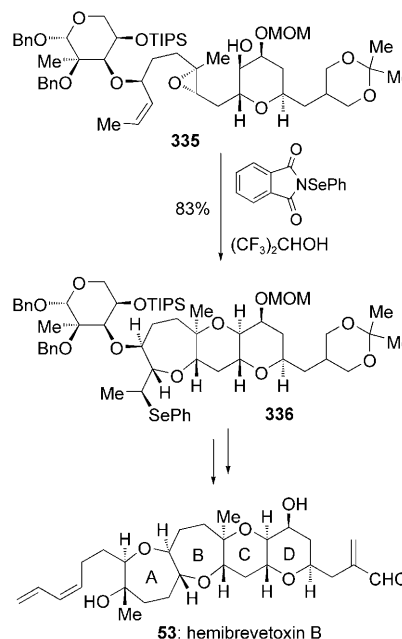
Scheme 45. Application of a cascade involving epoxide in the synthesis of hemibrevetoxin B (Holton, 2003).[286]

Elegant work on *ent*-abudinol B and the related terpenes *ent*-durgamone and *ent*-nakorone was recently reported by McDonald.[228,229] Although these molecules are squalene-derived polyether natural products, we discuss this work here because of the conceptual similarities to McDonald's synthesis of ladder polyether fragments. In their first-generation approach to *ent*-abudinol, McDonald and co-workers devised a convergent synthetic scheme that involves late-stage coupling of fragments derived from *ent*-durgamone and *ent*-nakorone (Scheme 46).[229] In the synthesis of subunit **339**, a cascade of epoxide openings on diepoxide **337** was employed. Using *tert*-butyldimethylsilyl triflate as a Lewis acid, two *endo*-selective cyclizations directed by methyl substituents, with an enolsilane as trapping nucleophile, leads to formation of bicyclic compound **338**, which can be further elaborated to
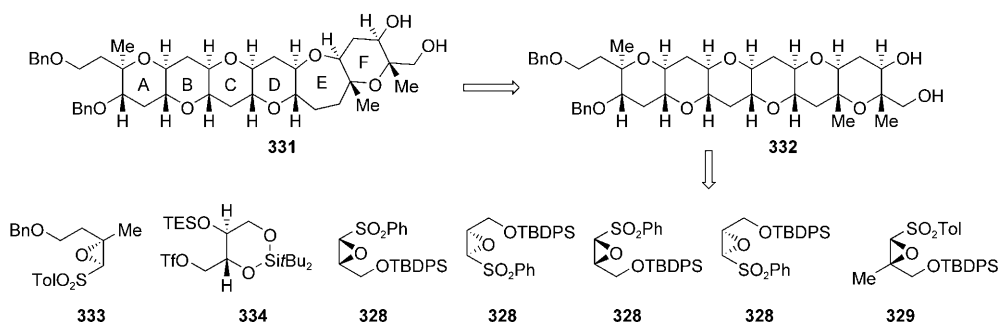
Figure 14. Conceptual retrosynthesis of the ABCDEF ring fragment of yessotoxin and adriatoxin (Mori, 2003).[285] TES = triethylsilyl.
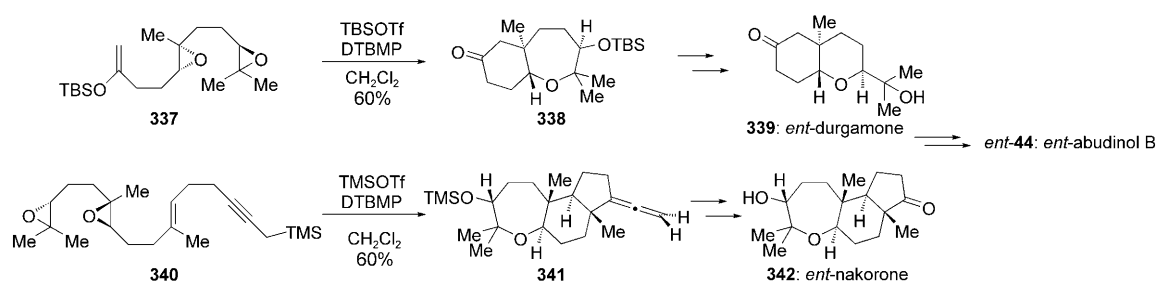
Scheme 46. Convergent synthesis of *ent*-abudinol via hybrid oxa/carbacyclization (McDonald, 2007).[229] DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

ent-durgamone (**339**). An analogous strategy was utilized in the synthesis of the more complex *ent*-nakorone. Along with epoxide openings, a hybrid cascade of oxacyclizations and carbacyclizations was designed. Diepoxide **340**, which carries a terminating propargyl silane nucleophile, underwent efficient trimethylsilyl triflate-promoted cyclization, resulting in tricyclic allene **341**. Further elaboration of these fragments into their corresponding vinyl triflates and subsequent modified Suzuki–Miyaura coupling produced *ent*-abudinol B.

A second-generation approach was based on the proposed biosynthetic pathway to *ent*-abudinol,[2, 104, 105] which involves a hybrid cascade of epoxide openings and carbacyclizations.[228] In a fashion similar to the first-generation approach, diepoxide **343** was treated with trimethylsilyl triflate to produce **344**, which contains the tricyclic fragment of *ent*-abudinol (Scheme 47). A two-step elaboration of the cascade product **344**, using Wittig methylenation and Shi epoxidation, resulted in the formation of diepoxide **345**, thus setting the stage for a cascade reminiscent of that used for *ent*-durgamone. Diepoxide **345**, which carries a terminal alkene instead of an enol ether as trapping nucleophile, was subjected to the same conditions as in the reaction of **340** to **341** to produce *ent*-abudinol, along with several isomeric products resulting from pathways enabled by the relatively low nucleophilicity of the terminating alkene. Despite the linear nature of this route to *ent*-abudinol, structural complexity is generated quickly, and this rapid synthesis demonstrates all of the advantages of cascade approaches to the synthesis of polyethers and related molecules.

Cascade cyclizations that involve epoxides have found use in many syntheses of natural products outside the polyether families discussed herein.[287] For instance, a hybrid biomimetic oxa/carbacyclization of **346** provides a rapid entry to the hexahydroxanthene core of the schweinfurthin natural products (Scheme 48).[288, 289]

It is also important to note that epoxide-opening cascades are in no way limited to syntheses of products that are postulated to be generated in a similar fashion in nature. Combination with various non-oxygen nucleophiles or electrophiles other than epoxides themselves can lead to efficient methods for synthesis of a wide variety of structural motifs present in diverse natural products. An elegant example of this strategy is the *endo*-selective epoxide-opening cascade used in the synthesis of wortmannin (via **351**) by Shibasaki et al. (Scheme 49).[290]
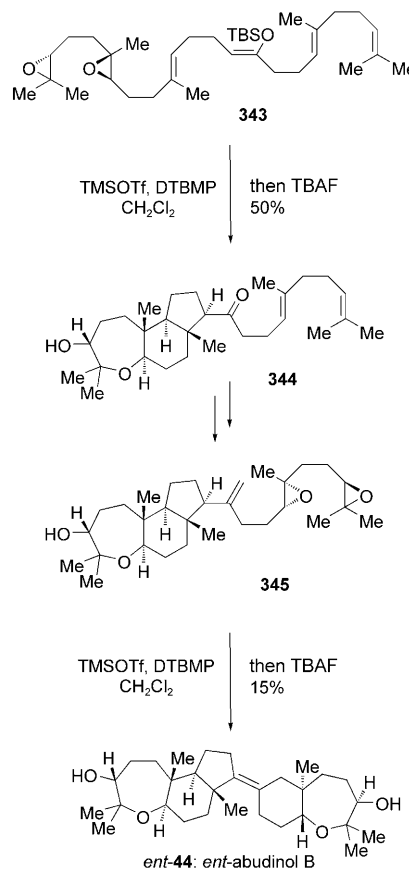
Scheme 47. Biomimetic synthesis of *ent*-abudinol (McDonald, 2008).[228]
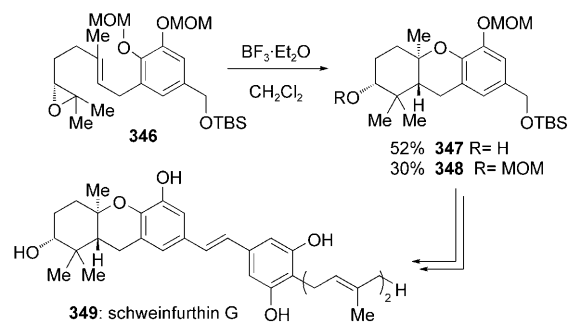
Scheme 48. Application of a hybrid epoxide-opening cascade in the synthesis of the hexahydroxanthene core of schweinfurthin (Wiemer, 2008).[288, 289]
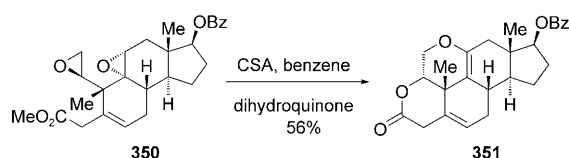
Scheme 49. Application of a hybrid epoxide-opening cascade in the synthesis of wortmannin (Shibasaki, 1996).[290]

9. Summary and Outlook

Epoxide-opening cascades leading to 2,5-linked oligotetrahydrofurans are almost always highly regioselective for the smaller rings, and proceed in agreement with Baldwin's rules. Although regioselectivity in these reactions is not a major challenge, further development is necessary to accommodate more diverse substrates and better address problems in total synthesis. Development of mild conditions for better functional group compatibility and methods for selective activation of specific epoxides are imperative, especially in cascades that involve three or more epoxides in the starting materials.

Epoxide-opening cascades leading to the formation of fused polyethers are burdened by empirical rules of regioselectivity that generally regard *endo*-selective, intramolecular epoxide-opening reactions to be disfavored. Despite the body of work toward epoxide-opening cascades that produce large fragments of ladder polyethers in a single synthetic operation, this goal remains elusive. For a cascade to be successful, it must be sufficiently flexible to accommodate all of the challenges posed by the target molecules, thus making the design of such reactions all the more difficult. For example, the only currently available cascade reaction without directing groups would have to accommodate a number of modifications and still maintain efficiency. Such methodology would have to be extended to the construction of larger cyclic ethers. Furthermore, methyl substitution on the epoxides would have to be tolerated in these reactions, thus overcoming the directing effects of alkyl substituents. Moreover, along with secondary alcohol nucleophiles, tertiary alcohols would also have to be accommodated in the cascade. Cyclizations must not be affected by alkyl substitution or oxidation of the carbon backbone in polyepoxide substrate. Finally, and most importantly, the cascade products would need to be amenable to rapid elaboration and assembly into large fragments and, ultimately, entire natural products. We anticipate that such challenges will continue to stimulate research in the development of even more powerful synthetic methods.[291]

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[291] After submission of this Review, we have reported studies of the mechanisms of the water-promoted epoxide-opening reactions,[291a] investigations of water-promoted cascades involving epoxides of diverse substitution patterns,[291b] and the development of novel templates of cascades that are amenable to the target-oriented synthesis of ladder polyethers:[291c] a) J. A. Byers, T. F. Jamison, *J. Am. Chem. Soc.* **2009**, *131*, 6383–6385; b) C. J. Morten, T. F. Jamison, *J. Am. Chem. Soc.* **2009**, *131*, 6678–6679; c) A. R. Van Dyke, T. F. Jamison, *Angew. Chem.* **2009**, *121*, 4494–4496; *Angew. Chem. Int. Ed.* **2009**, *48*, 4430–4432.