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Science **317**, 1189 (2007);
DOI: 10.1126/science.1146421

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Epoxide-Opening Cascades Promoted by Water

Ivan Vilotijevic and Timothy F. Jamison*

Selectivity rules in organic chemistry have been inferred largely from nonaqueous environments. In contrast, enzymes operate in water, and the chemical effect of the medium change remains only partially understood. Structural characterization of the "ladder" polyether marine natural products raised a puzzle that persisted for 20 years: Although the stereochemistry of adjacent tetrahydropyran (THP) cycles would seem to arise from a biosynthetic cascade of epoxide-opening reactions, experience in organic solvents argued consistently that such a pathway would be kinetically disfavored. We report that neutral water acts as an optimal promoter for the requisite ring-opening selectivity, once a single templating THP is appended to a chain of epoxides. This strategy offers a high-yielding route to the naturally occurring ladder core and highlights the likely importance of aqueous-medium effects in underpinning certain noteworthy enzymatic selectivities.

Brevetoxin B (Fig. 1, **1**), yessotoxin (**2**), the ciguatoxins, and related ladder polyether natural products are the active constituents of many harmful algal blooms, marine phenomena also known collectively as the red tide. Since the isolation and structural elucidation of **1** by Nakanishi and Clardy in 1981 (*1*), the distinctive molecular architecture and extreme lethality to marine life of these toxins continue to stimulate the development of methods for their chemical synthesis (*2*–*4*) and research into their mode of action (*5*).

How these molecules are assembled by the dinoflagellates that produce them has also been an active area of investigation (*6*–*8*) and, to be sure, speculation. Although they are among the most complex secondary metabolites ever characterized, all ladder polyethers possess a structural pattern and stereochemical regularity that confer upon them a certain degree of simplicity. A backbone of repeating oxygen–carbon–carbon (O–C–C) units extends from one end of the polyether network to the other [e.g., gymnocin B (**3**); Fig. 2A, red bonds and O atoms], regardless of the size of the intervening rings and of any functional groups present on the rings. The "ladder" topography is the consequence of consistently trans stereochemistry across the carbon-carbon bonds of the ring junctions, coupled with the relative syn configuration of adjacent junctions.

The Nakanishi cascade hypothesis. More than 20 years ago, Nakanishi put forth a hypothesis that accounts for these structural and stereochemical similarities—the transformation of a polyepoxide (e.g., **4**) into a ladder polyether via a series or "cascade" of epoxide-opening events (Fig. 2A). (*9*) The oxygen and two carbon atoms of each epoxide constitute the O–C–C backbone, and with the proviso that all of the ring openings proceed with inversion of configuration, the trans-syn topography is explained by this mechanism. That there is little evidence to support this two-decade-old hypothesis has not deterred efforts to emulate such cascades.

Despite its intellectual appeal, however, the hypothesis relies upon a ring-opening process generally regarded to be disfavored (Fig. 2B). With few exceptions, epoxide-opening reactions of this type favor the smaller heterocycle [e.g., a tetrahydrofuran (THF) likely arising from a spiro transition state], not the larger one [a tetrahydropyran (THP), from fused transition state] (*10*–*12*). Most of the approaches to promote the desired outcome use "directing groups" that must be covalently attached to the epoxides. (*13*) In contrast, catalytic antibodies (*14*) and transition-metal complexes (*15*, *16*) can be particularly effective in certain cases involving a single epoxide-opening event. To date, however, all existing THP-selective cascades that open more than one epoxide have required a directing group at every epoxide (*17*–*19*). These directing groups either are not found in the natural products or for other reasons clearly cannot be the natural solution. Therefore, though amenable to the synthesis of certain polyether ring systems, these methods do not provide evidence in support of or against the Nakanishi hypothesis.

Thus, if epoxide-opening reactions are used in ladder polyether biosynthesis, then how is this preference for the smaller ring overcome? Enzymatic control is a logical supposition, but there is as yet no evidence for such an intervention. With the joint aims of addressing this question and accelerating the synthesis of ladder polyethers, we have focused our recent efforts in this area on "directing-group-free," THP-selective cascades (*20*). Our approach stems from an analysis of the potential factors governing the regioselectivity of epoxide opening in these reactions and uses a template to modulate them in the desired manner.

We reasoned that in **5**, where one THP is already in place, entropic issues that might normally favor the undesired spiro transition state would be minimized and instead enthalpic contributions to the energies of the competing transition states would play a more important role (Fig. 2C). *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, then the desired THP product (**6**) might be favored in this templated system under the appropriate reaction conditions.

Water as a reaction promoter. To test these hypotheses, we prepared **5** and exposed it to a wide range of combinations of acids, bases, solvents, and other additives (*21*). Bases tended to favor the THF product **7**, whereas acids exhibited a slight preference for the desired THP product (**6**). Combinations of acids and bases (Lewis or Brønsted) also favored **7**. To better understand the requirements for activation of the nucleophile and the electrophile, we examined the pH dependence of THP-to-THF selectivity [various buffers (e.g., phosphate, tris, His) and ionic strengths]. These experiments revealed a clear and provocative trend (Fig. 2D): In all cases, the selectivity for the desired THP product increases substantially as the pH of the reaction

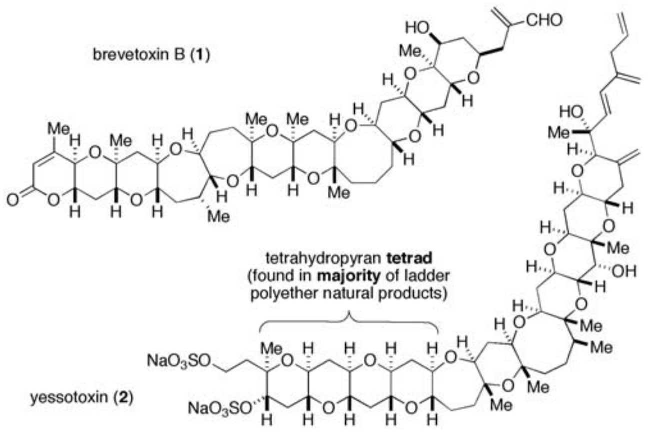

Fig. 1. Representative ladder polyether natural products. Me, methyl.

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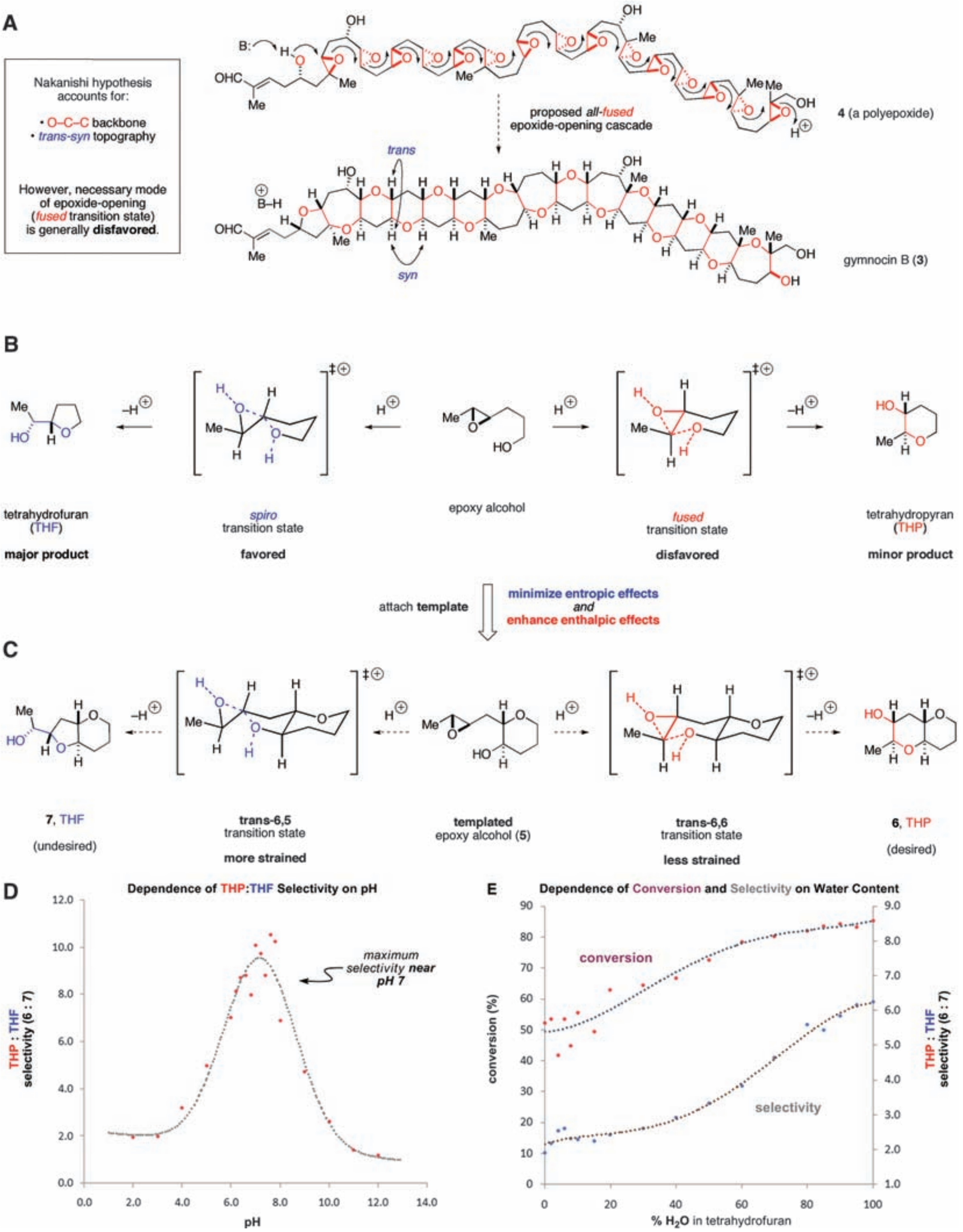
Fig. 2. (**A**) Structural and stereochemical patterns explained by the Nakanishi hypothesis of ladder polyether biosynthesis. (**B**) The two transition states (fused and spiro) and corresponding products for cyclization of an exemplary epoxy alcohol via epoxide opening. (**C**) Templated epoxide-opening cyclizations. (**D**) Dependence of THP:THF (**6**:**7**) selectivity on pH in cyclization of **5**. (**E**) Enhancement of conversion of **5** and of THP:THF selectivity by H_2O.



environment approaches neutrality, even exceeding 10:1 THP:THF selectivity near pH 7.

Several lines of evidence clearly implicate water in both the acceleration and increase in selectivity in these reactions. In less polar solvents (e.g., CH_2Cl_2 and toluene), low conversion of **5** is observed, and in polar aprotic solvents [e.g., CH_3CN, dimethyl sulfoxide, and *N*,*N*′-dimethylformamide (DMF)], although higher conversion to **6** and **7** occurs, the selectivity is greatly reduced (≤3:1 **6**:**7**). Furthermore, both increased THP:THF selectivity and increased conversion of **5** correlate with increased water content in the reaction milieu (Fig. 2E). Finally, deionized H_2O, in which both the ionic strength and percentage of impurities are near zero, provides the highest selectivity (>11:1 THP:THF). The only other promoters that we have found that approach the selectivity and rate exhibited by water are ethylene glycol (9:1) and methanol (8:1), which along with water can both provide and accept hydrogen bonds.

Water-promoted cascades. Having developed a THP-selective epoxide-opening method, we turned our attention to the possibility of using this approach in epoxide-opening cascades. However, we were well aware from our own work and from case studies reported by others that many highly selective epoxide ring-opening methods summarily fail when extended to cascades (*20*).

The synthesis of the epoxides is shown in Fig. 3A and emulates another aspect of Nakanishi's hypothesis, polyepoxidation of a polyene. Alkyne **8a** was extended to diyne **9a** and triyne **10a** in high yield by alkylation with the appropriate propargyl bromide (**11** and **12**, respectively). Alkyne **8b**, in which the hydroxyl group is protected as a silyl ether, was converted to alkynes **9b** and **10b** in the same manner and similar yield. Dissolving metal reduction (Li/NH_3) of **9a** provided a skipped diene (**13**) that was unstable enough to prohibit prolonged storage. The corresponding triene (not shown) from **10b** was even less robust, requiring hydroxyl protection before reduction.

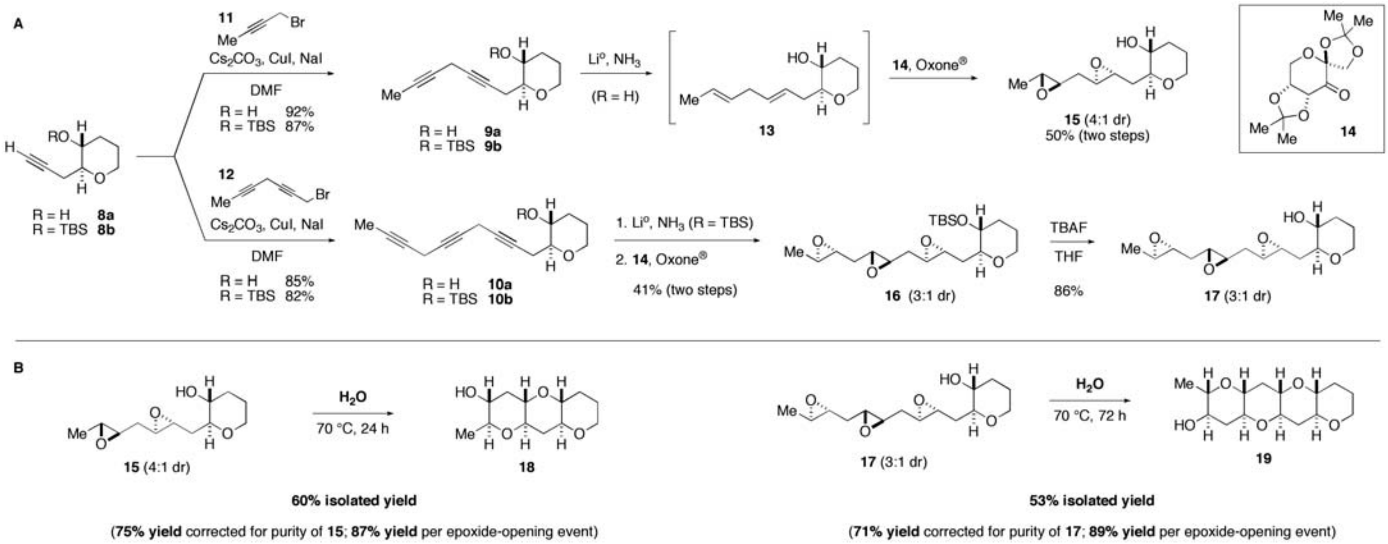


Fig. 3. (**A**) Synthesis of polyepoxides. (**B**) Epoxide-opening cascades promoted by H_2O. dr, diastereomeric ratio; DMF, dimethylformamide; TBS, *tert*-butyldimethylsilyl.

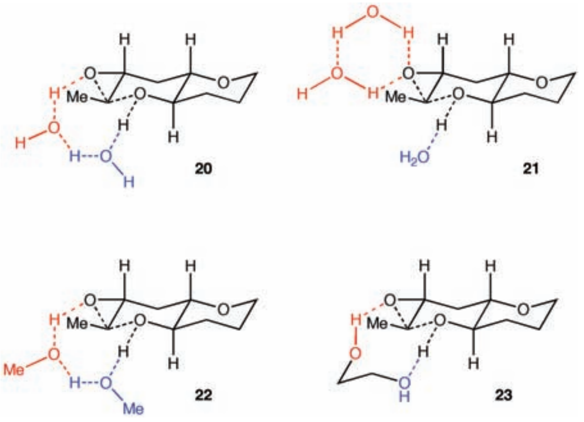


Fig. 4. Models of epoxide-opening reactions promoted by water (**20** and **21**), methanol (**22**), and ethylene glycol (**23**).

An epoxidation method developed by Shi that hinges upon fructose-derived ketone **14** and Oxone converted the diene and triene to the corresponding polyepoxides (**15** and **16**) (*22*). The moderate stereoselectivity appears to be due to the alkene proximal to the hydroxyl group; more remote alkenes do not suffer from this mismatched double diastereoselection. Diepoxide **15** and triepoxide **17** [after removal of the *tert*-butyldimethylsilyl (TBS) protective group] were obtained in 50% and 35% overall yield, respectively, from the diyne (**9a**) and triyne (**10b**).

The suboptimal stereochemical purity of **15** and **17** turned out to be of little concern (Fig. 3B). Heating **15** in deionized water for 24 hours at 70°C afforded a THP triad (**18**) in 60% isolated yield (75% yield when corrected for the purity of **15**). Similarly, a THP tetrad (**19**) representative of that found in more than half of the known ladder polyethers (Fig. 1) was obtained in 53% isolated yield (71% when corrected for the purity of **17**).

These THP-selective, epoxide-opening cascades are far higher-yielding than those that rely upon covalently attached directing groups. The per-epoxide yields of 87% (for **18**) and 89% (for **19**) are in line with the ~10:1 selectivity seen with monoepoxide **5** and do not change as a function of the number of epoxides or the number of THP rings preceding a given epoxide. In addition to validating the "template-by-a-THP" concept, this invariance would seem to support a mechanism for the cascade involving attack of an activated epoxide by the hydroxyl group attached to the preceding THP ring (right-to-left, as drawn in Fig. 3). The alternative mechanism (activated epoxide attacked by the next epoxide) has the opposite directionality (left to right) and is often invoked, even though it involves a highly strained epoxonium intermediate (*17*, *20*, *23*).

The effect of temperature on the reaction rate is substantial, but its impact on selectivity is minimal, consistent with the template concept of minimization of entropic contributions to the competing transition states. For example, about 1 month (28 days) was required for complete consumption of **17** at room temperature in pH 7.6 phosphate buffer (1.0 M), but polyether triad was nonetheless afforded in identical isolated yield (60%).

Mechanism and implications. Just as the development of all-THF epoxide-opening cascades (*24*, *25*) is taken as support of the Cane-Celmer-Westley hypothesis of monensin biosynthesis (*26*), we believe that the all-THP cascades herein represent long-sought evidence in favor of Nakanishi's hypothesis of ladder polyether biosynthesis (or at least the feasibility thereof) for several reasons: They are high yielding and highly THP-selective (yield per epoxide > 85% in all cases), require no directing groups on any of the epoxides, and are most effectively promoted by H_2O.

The template may be functioning as a surrogate for conformational constraints imposed by an enzyme active site, and because water is the superior promoter of the all-THP cascades, it is reasonable to propose that such cascades would be promoted by hydrogen-bond activation of the epoxide in the natural systems (*27*). Monensin and related polyethers are produced via epoxide ring-opening reactions promoted by epoxide hydrolases (EHs), and on the basis of sequence homology to other EHs, the epoxide appears to be activated by hydrogen bonds donated by two conserved tyrosine residues (*28*). Far less is known about brevetoxin and other ladder polyether toxins in this regard, but it is possible that dinoflagellates possess a similar set of polyketide synthase enzymes (*8*), though with epoxide hydrolases that are selective for the larger ring.

Water is one of the most heavily studied molecules, and its colligative structure and catalytic properties are still a subject of intense investigation (*29*–*31*). Thus, the means by which it affects selectivity in these cascades and organic reactions in general (*32*–*36*) is not without uncertainty. Moreover, although the reactions appear to be homogeneous, we cannot rule out surface effects or the formation of micelles that influence the conformation and reactivity of the epoxy alcohols (**5**, **15**, and **17**). Nevertheless, as shown in Fig. 4 (**20**), activation of the nucleophile (OH group) and electrophile (epoxide) may be achieved by two water molecules (red and blue H_2O, respectively) in a cooperative network of hydrogen bonds that would account for not only the enhanced regioselectivity in water (relative to other solvents), but also the marginal effects of temperature on selectivity. Another possibility (**21**) is analogous to the dual-H-bond mode of activation (red H_2O) in epoxide hydrolases, but because activation of the electrophile is disconnected from that of the nucleophile, this model less easily explains the selectivity.

More complex hybrids that unite the attributes of these two models can also be posited, but at this stage we favor **20** for several reasons. Its relative simplicity (i.e., lower molecularity) constitutes a more easily testable structural hypothesis, and the results observed with methanol and ethylene glycol are also adequately explained, in the forms of **22** and **23**, respectively. Furthermore, as illustrated in **23**, ethylene glycol represents an attractive starting point for the development of small molecules that activate the nucleophile and electrophile in such a way as to effect cyclizations and cascades of even higher selectivity and efficiency. In the meantime, templated, water-promoted, THP-selective epoxide-opening cascades provide a straightforward means for efficient and rapid assembly of ladder polyethers, enabling investigations directed toward understanding the mode of action of these extraordinary natural products.

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Supporting Online Material

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Materials and Methods
Schemes S1 to S5
Table S1
References

13 June 2007; accepted 18 July 2007
10.1126/science.1146421

REPORTS

Alfvén Waves in the Solar Corona

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Alfvén waves, transverse incompressible magnetic oscillations, have been proposed as a possible mechanism to heat the Sun's corona to millions of degrees by transporting convective energy from the photosphere into the diffuse corona. We report the detection of Alfvén waves in intensity, line-of-sight velocity, and linear polarization images of the solar corona taken using the FeXIII 1074.7-nanometer coronal emission line with the Coronal Multi-Channel Polarimeter (CoMP) instrument at the National Solar Observatory, New Mexico. Ubiquitous upward propagating waves were seen, with phase speeds of 1 to 4 megameters per second and trajectories consistent with the direction of the magnetic field inferred from the linear polarization measurements. An estimate of the energy carried by the waves that we spatially resolved indicates that they are too weak to heat the solar corona; however, unresolved Alfvén waves may carry sufficient energy.

Alfvén (*1*) first postulated the existence of oscillations of magnetized plasma in 1942. Of the three possible magnetohydrodynamic (MHD) wave modes, the slow and fast magnetoacoustic (MA) modes are compressible and susceptible to damping. The third so-called Alfvén mode is an incompressible transverse oscillation that propagates along field lines with magnetic tension as the restoring force. Following Alfvén's initial work, researchers soon realized that Alfvén waves could transport energy from the turbulent solar photosphere into the solar corona (*2*, *3*) and might explain one of the most important puzzles in solar physics: Why does the temperature of the solar atmosphere rise from 5000 to 2 million degrees Kelvin from the photosphere outward to the corona?

Over the past decade, the variety of wave phenomena observed in the solar corona has increased enormously. Transverse displacement

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