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Evidence That Epoxide-Opening Cascades Promoted by Water Are Stepwise and Become Faster and More Selective After the First Cyclization

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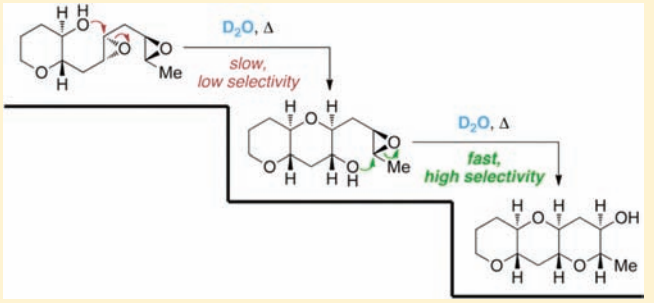
Supporting Information

ABSTRACT: A detailed kinetic study of the endo-selective epoxide-opening cascade reaction of a diepoxy alcohol in neutral water was undertaken using ^{1}H NMR spectroscopy. The observation of monoepoxide intermediates resulting from initial endo and exo cyclization indicated that the cascade proceeds via a stepwise mechanism rather than through a concerted one. Independent synthesis and cyclization of these monoepoxide intermediates demonstrated that they are chemically and kinetically competent intermediates in the cascade. Analysis of each step of the reaction revealed that both the rate and regioselectivity of cyclization improve as the cascade reaction proceeds. In the second step, cyclization of an epoxy alcohol substrate templated by a fused diad of two tetrahydropyran rings proceeds with exceptionally high regioselectivity (endo:exo = 19:1), the highest we have measured in the opening of a simple trans-disubstituted epoxide. The origins of these observations are discussed.



INTRODUCTION

Cascade reactions combine consecutive elementary reactions into a single operation and are an increasingly important province of synthetic organic chemistry.[1] Also known as domino reactions, their potential advantages include step economy, atom economy, and attendant reduced waste generation. Cascades of cyclization reactions are an interesting subset, as these have been implicated in the biosynthesis of diverse families of complex polycyclic natural products.[2−5]

Lanosterol and the other steroids are perhaps the best-known group of natural products of this type. Their biosynthesis involves a dramatic cascade of several cyclization reactions, as was predicted by the celebrated "Stork−Eschenmoser hypothesis".[2] Many decades of remarkable investigation unraveled the details of the conversion of squalene to lanosterol, revealing the extent to which enzymatic control is required, as well as the incompletely concerted and asynchronous character of the cascade.[3] In addition to its profound fundamental interest, mechanistic understanding of these polyene cyclization cascades contributed to the design and optimization of spectacular biomimetic cascade syntheses,[3b] including examples from the groups of W. S. Johnson,[6] E. E. van Tamelen,[7] and E. J. Corey.[8]

Similarly dramatic cascades of cyclization reactions have also been proposed in the biosynthesis of multiple families of polyether natural products, including the polyether ionophores, the terpenoid polyethers, and the ladder polyethers.[4] We are particularly interested in the terpenoid and ladder varieties, the latter of which continue to intrigue the scientific community due to their exceptional toxicity and intricate structures.[5] The details of their biosynthesis remain a mystery, but a particularly compelling hypothesis advanced contemporaneously by Nakanishi,[9] Nicolaou,[10] and Shimizu[11] proposes that the distinctive fused cyclic ethers of the natural products could be formed via a cascade of epoxide-opening cyclizations.[4a] This proposal demands that every cyclization proceed regioselectively with nucleophilic attack at the more remote side of each epoxide (commonly referred to as endo cyclization).

Many questions regarding ladder polyether biosynthesis remain. Little is known beyond the polyketide origin of the carbon skeleton, and there exists no concrete evidence for polyepoxide substrates as biosynthetic precursors to these secondary metabolites.[4a] In their original proposals, Nakanishi and Shimizu left ambiguous some aspects of their hypothesized cascades. One such unanswered biosynthetic question was a central one: whether concomitant formation of many cyclic ether rings is concerted or instead occurs by a stepwise process.

In the intervening 25 years, several groups, including those of Nicolaou,[10,12] Murai,[13] McDonald,[14] and Floreancig,[15] as well as our own,[16] have developed methods to assemble fused tetrahydropyran and oxepane polycycles, subunits of ladder polyethers,

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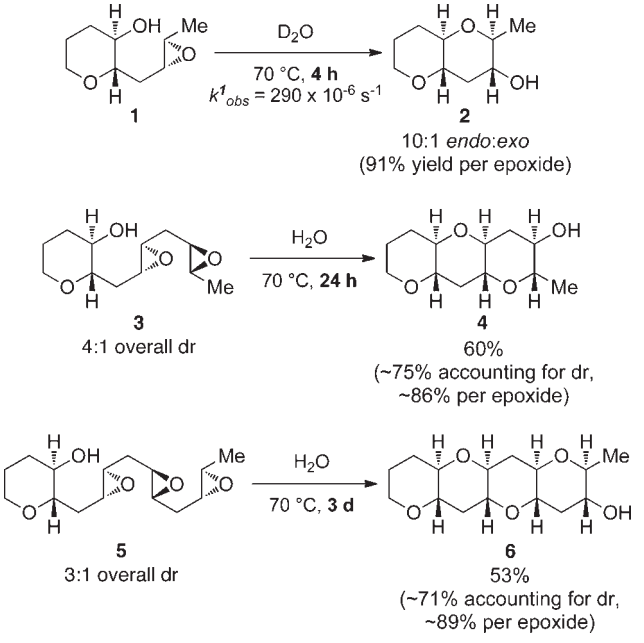
using epoxide-opening cyclizations.[17] The cited reports from Murai, McDonald, and Floreancig describe cascade reactions of multiple endo-selective epoxide-openings, reactions that emulate the biosynthetic proposal. All of these processes are electrophile-driven and involve high-energy epoxonium intermediates.[18] McDonald and Floreancig both suggest synchronous concerted mechanisms for such cascades, a hypothesis that has been supported computationally in the latter case by a collaborative investigation with Houk.[15]

Despite extensive theoretical analysis of cascade reactions, empirical confirmation of cascade mechanisms has historically been difficult. They may involve multiple short-lived intermediates, and the desired products are often obtained as part of a more complex mixture of species. Perhaps due to these associated technical challenges, there are, to the best of our knowledge, no detailed mechanistic studies of epoxide-opening cascade reactions of either the exo- or the endo-selective variety. Even in the extensive literature surrounding polyene and squalene oxide-type cascades, there are relatively few studies that answer the question of a stepwise versus a concerted cascade reaction mechanism.[19]

Recently, we described highly regioselective epoxide-opening cascades that emulate the proposed biosynthesis of the ladder polyethers. These cyclizations are templated by a preformed tetrahydropyran (THP) ring and are promoted by neutral water (Scheme 1).[20] In preliminary mechanistic investigations, we demonstrated that oxygenation of the template was critical to achieve this unusual selectivity and proposed that hydrogen bonding with exogenous water molecules facilitates reaction through a selective pathway.[21] Importantly, the kinetic studies we undertook during our mechanistic investigations were possible because the cyclization reactions are void of any side products that would complicate the kinetic scheme and convolute the NMR spectra used to follow the reaction. We hypothesized that remarkably clean epoxide-opening reactions in water might offer an opportunity to undertake a rare quantitative study of a cascade reaction involving multiple epoxide-opening events and thereby provide valuable insight into the role of neutral water in these unusual reactions. We report herein a kinetic study of such a cascade, that of diepoxy alcohol **3**. We submit that these studies constitute compelling evidence for a stepwise nucleophilic cascade initiated by the templated alcohol. Such cascades are therefore fundamentally distinct from the synchronous processes that have been proposed for cascades involving strongly electrophilic epoxonium intermediates.[14,15]

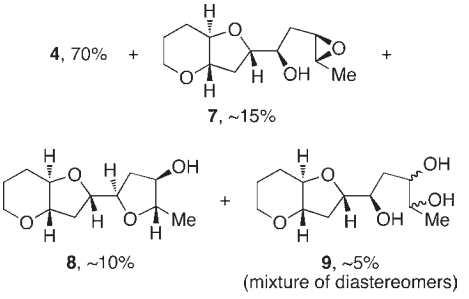
Scheme 1. Regioselective Epoxide-Opening Cyclizations Promoted by Water[20a,21]



RESULTS AND DISCUSSION

Our attention was initially piqued by the observation that cascade reactions of multiple epoxide openings are many times slower than cyclizations of single epoxides, requiring much longer reaction times to proceed to completion (e.g., **3** and **5**, Scheme 1).[20a] Moreover, careful investigation of product mixtures from diepoxide **3** revealed that the major side product was epoxy alcohol **7**, the result of exo cyclization of **3** (Chart 1). Indeed, full analysis indicated that **7** and the products of its further reaction, **8** and **9**, totaled approximately 30% of the reaction mixture. These observations suggested a low regioselectivity of approximately 2:1 in the first epoxide-opening cyclization, which contradicted our initial supposition that regioselectivity is similar in each ring-forming event.[20a] The nearly constant yield per epoxide opening that formed the basis of our original supposition is, in fact, an arithmetic coincidence.

Chart 1. Products of the Reaction of 3 in Water at 60 °C (3 d)



To gain further insight, we elected to follow the reaction of diepoxide **3** in situ by ^{1}H NMR spectroscopy (D_2O, 70 °C, buffered to pD 7 with potassium phosphate). As in our previous study of monoepoxide **1**, we were pleased to find that the signals corresponding to the methyl substituents of the relevant species in the reaction were distinct and diagnostic (Figure 1). We were able to assign the resonances of starting diepoxide **3** (1.310 ppm), desired THP triad **4** (1.240 ppm), exo side product **7** (1.306 ppm), its 5-*endo* cyclization product, 6,5,5-tricycle **8** (1.186 ppm), and its hydrolysis products **9** (1.140 and 1.141 ppm). Early in the reaction ($t \leq 6$ h), one other major resonance was plainly visible, labeled as **10**. We hypothesized that species **10** might be a THP diad, the intermediate in a two-step cascade of cyclizations from diepoxide **3** to triad **4**.

The assignments of intermediates and major products, including diad **10**, were unambiguously confirmed with authentic samples independently synthesized and characterized by ^{1}H NMR spectroscopy (see the Supporting Information for the preparation and properties of compounds **7**, **8**, **9**, **10**, and **11**). These results implied that formation of **4** could proceed in a stepwise fashion, but it remained to be shown that THP diad **10**

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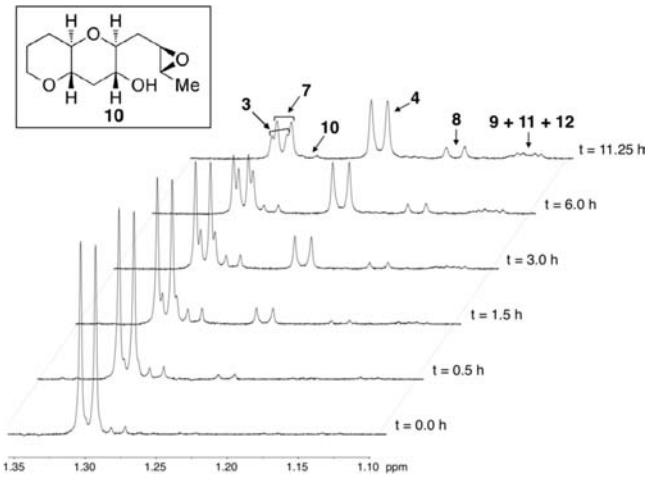

Figure 1. Upfield region of ^{1}H NMR spectra from reaction of **3** in D_2O at 70 °C and pD 7.0 (0.1 M KP_i buffer). For the identities of **11** and **12**, see Scheme 2.

represents a chemically and kinetically competent intermediate. The proposed stepwise mechanism was further corroborated with a full kinetic analysis of the cascade reaction of **3**.

The concentrations of **4**, **8**, and **10** could be determined directly from integration of the ^{1}H NMR peaks corresponding to their methyl groups (Figure 1). Although the doublets corresponding to diepoxide **3** and exo intermediate **7** overlapped, the concentrations of **3** and **7** could be deduced simply by allocating the combined integration in proportion to their relative peak heights. A cluster of peaks was observed around 1.15 ppm, including those corresponding to diastereomeric triols **9**. These overlapping resonances proved more difficult to dissect. One of the components of this cluster was revealed to be undesired 6,6,5-fused tricycle **11** after independent preparation and characterization of the compound (see Scheme 2). Another component, designated **12**, could not be isolated cleanly and is tentatively assigned as a mixture of diastereomeric, highly polar pentaols arising from exhaustive hydrolysis of the epoxides of **3** (Scheme 2). Because of the complexity of the overlapping peaks, as well their low combined integration (less than 10% of total concentration, even after three half-lives), we were unable to apportion [**9**], [**11**], and [**12**] according to peak height, as was possible with [**3**] and [**7**].

We were therefore obliged to determine [**11**] via an alternative method, gas chromatography. Samples of **3** that had been followed by ^{1}H NMR spectroscopy through three half-lives were then exhaustively heated to 70 °C for 5 days so that the reaction mixture contained <1% of epoxide intermediates **7** and **10**. At this point, the ratio of [**4**]:[**11**] was determined to be 15:1 by GC.[22] With the assumption that **4** and **11** are both derived from **10** and that selectivity (k_6^{10}:k_5^{10}) for their formation is constant at 15:1,[23] [**11**] could be then be estimated from [**4**].

A representative graph of the concentrations of all species as a function of time thus obtained is shown in Figure 2. As expected, consumption of diepoxide **3** displayed pseudo first order kinetics. Consistent with the assignment of **7** and **10** as reactive intermediates, their concentrations initially increased and then decreased over time. Interestingly, intermediate **10** was much shorter-lived than **7**, which remained a major species in solution even after 12 h at 70 °C. In conjunction with the formation and then consumption of **10**, we observed a significant induction period for the appearance of product **4**, which is consistent with its formation from **10** and a hallmark of a stepwise reaction mechanism.[24] Finally, it is noteworthy that the overall concentration of starting material, intermediates, and products remained constant to within 3% over the course of the reaction, as compared to a DMSO internal standard. This detail indicates that all species were fully dissolved and is consistent with our earlier studies of epoxide-opening cyclization promoted by water,[21] which demonstrated that the reaction occurs in solution rather than on the surface of water or in micelles.

Having hypothesized a two-step mechanism from diepoxide **3** to THP triad **4** via monoepoxide **10**, we first determined rate constants for the elementary steps of the reaction sequence using direct nonlinear regression analysis.[24] Extraction of the rate constants for the consumption of **3** and **10** using this method was possible from concentration versus time data, and the results fit fairly well with the independently measured rate constant for the cyclization of intermediate **10** (vide infra, Table 1). However, analogous kinetic analysis of the formation of side product **8** via the presumed intermediate **7** in a parallel stepwise cascade reaction that begins with exo cyclization of diepoxide **3** proved inconsistent with kinetic measurements carried out for cyclizations of independently prepared monoepoxide **7**. Particularly troubling was the relative distribution of products **8** and **9**, which was different in cyclizations of the isolated monoepoxide **7** as compared to the cascade cyclization of **3** (vide infra).[25]

Because of the sophisticated kinetic profile of the reaction, we turned to simulation of the experimental data with COPASI ("COmplex PAthways SImulator", an open-source software program for modeling chemical kinetics; see the Supporting Information for details of the computation).[26] The results from the optimized simulation appear as solid lines in Figure 2, and the associated rate constants are reported in Scheme 2 and Table 1. To reiterate, the curves shown are not simply the best statistical fit using nonlinear regression analysis but rather the results predicted from the rate laws that were derived from computer simulation.

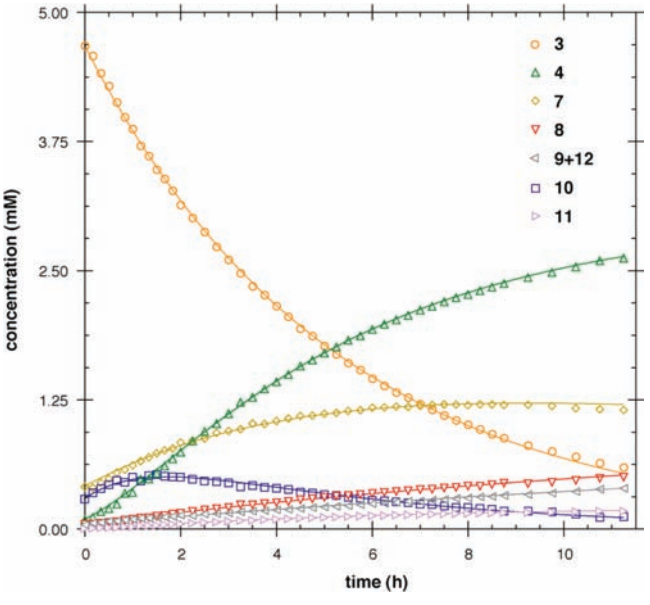

Figure 2. Concentrations of observable species over time in the cascade reaction of **3** in D_2O at 70 °C and pD 7.0. Symbols mark experimental data, and solid lines represent the results of the rate equations derived from simulation, as presented in the mechanism in Scheme 2.

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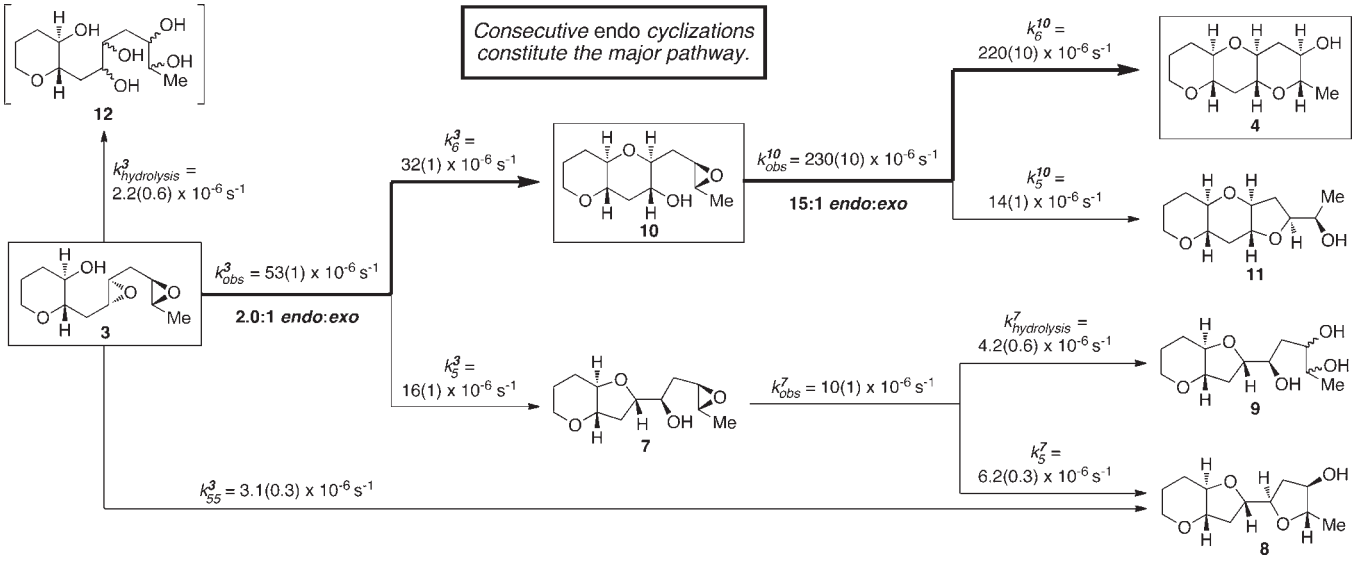
Scheme 2. Proposed Mechanism of the Water-Promoted Epoxide-Opening Cascade Reaction of 3 (D_2O, pD 7, 70 °C)[a]



[a] Rate constants reported are the average results for simulation of experimental data for three independent experiments. The average error over the three experiments is shown in parentheses.

Table 1. Comparison of Rate Constants Determined from the Cascade Reaction of 3 and from Reactions of Isolated 7 and 10[a]

		as determined from isolated reaction of **10**	as determined from isolated reaction of **7**	as determined from direct regression analysis of cascade reaction of **3**	as determined from simulation of cascade reaction of **3**
k^3 ($s^{-1} \times 10^{-6}$)	k^3_{obs}	–	–	52 (2)	53 (1)
	k^3_6:k^3_5	–	–	1.6	2.0
	k^3_{55}	–	–	–	3.1 (0.3)
	$k^3_{hydrolysis}$	–	–	–	2.2 (0.6)
k^{10} ($s^{-1} \times 10^{-6}$)	k^{10}_{obs}	270 (30)	–	183 (3)	230 (10)
	k^{10}_6:k^{10}_5	19	–	15	15
k^7 ($s^{-1} \times 10^{-6}$)	k^7_{obs}	–	11.5 (0.1)	19.2 (0.4)	10 (1)
	k^7_5:$k^7_{hydrolysis}$	–	0.56	1.3	1.5

[a] Values shown in parentheses are the average absolute error for three independent measurements. All experiments were conducted in D_2O at 70 °C and pD 7.0.

Optimization of the simulation to achieve good agreement with experimental data ultimately took several iterations, as is discussed in the following paragraphs. Nevertheless, an immediately striking feature of the results of both regression analysis and simulation was the low rate and regioselectivity of the first cyclization of diepoxide **3**. Simulation indicates that diepoxide **3** reacts at approximately 1/5 the rate of the monoepoxide model system **1** ($k^3_{obs} = 53 \times 10^{-6}$ s^{-1} vs $k^1_{obs} = 290 \times 10^{-6}$ s^{-1})[21] and cyclizes with significantly lower endo selectivity (k^3_6:k^3_5 = 2.0:1 vs k^1_6:k^1_5 = 11:1). In contrast, the rate of cyclization of THP diad **10** is similar to that of **1** ($k^{10}_{obs} = 230 \times 10^{-6}$ s^{-1}), and the cyclization occurs with somewhat higher endo selectivity (k^{10}_6:k^{10}_5 = 15:1). Notably, both 5-*exo* cyclization reactions occur at similar, slow rates (k^3_5 and $k^{10}_5 < 20 \times 10^{-6}$ s^{-1}). The 6-*endo* cyclization of **3** is somewhat faster ($k^3_6 = 32 \times 10^{-6}$ s^{-1}), and 6-*endo* cyclization of **10** ($k^{10}_6 = 220 \times 10^{-6}$ s^{-1}) is much faster still, thus explaining the observations that the concentration of intermediate **10** never exceeded 10% of the total reaction mixture and that **4** is the major product of the reaction (Figure 2).

To corroborate that THP diad **10** is a kinetically competent intermediate, the kinetics of the cyclization of independently synthesized **10** were measured. Consistent with our mechanistic hypothesis, the disappearance of **10** proceeded with clean pseudo first order kinetics to produce **4** as the major product. Only a trace of 6,6,5-fused triad **11** was observed as the sole side product of the reaction. Importantly, both reaction rate (k^{10}_{obs} = 270×10^{-6} s^{-1}) and regioselectivity (k^{10}_6:k^{10}_5 = 19:1) were closely comparable to those determined from simulation of the cascade reaction of diepoxide **3** (Table 1), thereby definitively demonstrating that monoepoxide **10** is a competent intermediate en route to THP triad **4**.

Similar experiments with independently prepared exo intermediate **7** revealed a somewhat more complex situation. Consistent with its long lifetime in the cascade reaction mixture, epoxy alcohol **7** reacted much more slowly than **10** ($k^7_{obs} = 11.5 \times 10^{-6}$ s^{-1}). As expected, **7** was converted to 6,5,5-triad **8** and hydrolysis products **9**, a mixture of diastereomers.[27] However, a critical discrepancy between this reaction and the cascade

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reaction was revealed: the ratio of **8** to **9** proved to be lower in the reaction of isolated **7** than in the cascade reaction of diepoxide **3** ([**8**]:[**9**] = 0.56:1 in the reaction of isolated **7** vs [**8**]:[**9** + **12**] ≈ 1.5:1 in the reaction of **3**). This observation suggested the existence of a competing mechanism for the formation of 6,5,5-tricycle **8** during the cascade reaction of diepoxide **3**, one that directly converts **3** to **8**. Support for this additional pathway came from simulation of the cascade reaction of **3**, which generated poor correlations between simulated and experimental data for [**7**] and especially [**8**] when a direct pathway from **3** to **8** was excluded from the model (Figure 3). With the inclusion of a simulated rate constant for a direct pathway from **3** to **8** ($k^3_{55} = 3.1 \times 10^{-6}$ s^{-1}), good correlation was achieved. We estimate that about 6% of diepoxide **3** is lost to the direct pathway from **3** to **8**. We surmise that this exo-selective cascade pathway is acid-promoted (possibly by trace hydronium present at pD 7) and therefore likely occurs in a synchronous fashion.[15]

A final refinement to the simulation was the inclusion of $k^3_{\text{hydrolysis}}$, a direct hydrolysis pathway from **3** to the presumed pentaols **12** (Scheme 2). The addition of this last pathway made a minor but still significant improvement to the agreement between simulation and experimental data, affording a good fit for each species (Figure 2). Rate constants for each step of the cascade, as determined from this optimized simulation, are presented in Scheme 2 and Table 1. We posit that it is the presence of the small but nonnegligible $k^3_{\text{hydrolysis}}$ and k^3_{55} that account for the imperfect agreement between the experimental data and the rates determined from direct analytical regression, which assumes parallel two-step processes void of any competing one-step side reaction pathways. Computer simulation, however, does not require this assumption.

To summarize our kinetic findings, the water-promoted endo-selective epoxide-opening cascade of **3** occurs via a stepwise mechanism. The first step proceeds with low rate and regioselectivity, while the second is a faster and exceptionally selective cyclization templated by a THP diad. Any direct, concerted mechanism from **3** to THP triad **4** is negligible. In fact, attempts to include this pathway in the COPASI simulation point to an upper limit of just 2×10^{-7} s^{-1}, which would represent much less than 1% of the reaction of **3**.

Continuing efforts are aimed toward understanding why selectivity and rate differ in the two steps of the cascade reaction. The cyclization of **3**, which is much slower and less regioselective than the cyclization of either **1** or **10**, is especially peculiar. We hypothesize that the origins of this difference could be both enthalpic and entropic in nature. An enthalpic explanation would invoke some epoxonium character in the transition state to endo cyclization. If during cyclization of **3** there is some development of positive charge on the epoxide being opened, then the inductive electron-withdrawing effect of the adjoining second epoxide could destabilize the incipient positive charge at the endo site of attack, thereby eroding regioselectivity. While this explanation conveniently rationalizes the improved regioselectivity of the second step, where a neighboring inductive electron-withdrawing group is absent, our current mechanistic understanding of the cyclization of **1** suggests that entropic rather than enthalpic factors dictate selectivity.[21] Consistent with an entropically controlled reaction is the observation that regioselectivity is relatively insensitive to temperature.[20a,21] Therefore, entropic factors, including differences in the ground-state and transition-state conformations of **3** as compared to **1** or differences in solvent reordering for the two reactions, may be more important

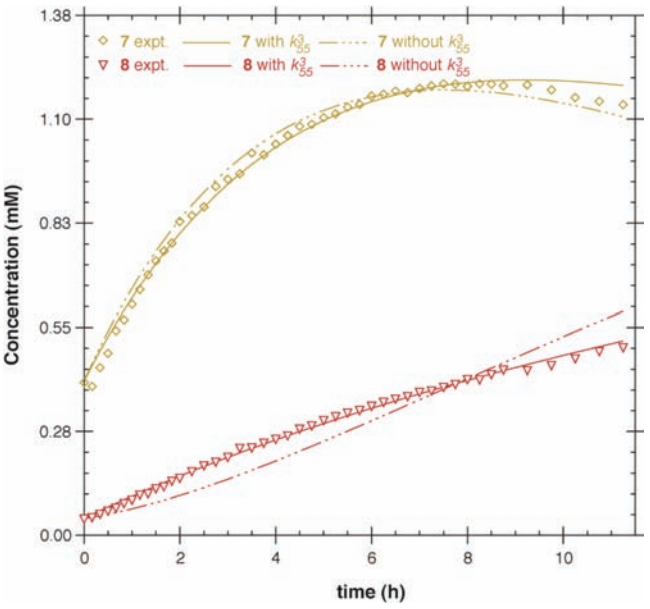

Figure 3. Comparison of simulated data to experimental data in the reaction of diepoxide **3**, showing fit between the two with and without k^3_{55}, a direct pathway from **3** to **8**, included in the simulation. Symbols mark experimental data, and lines show simulated curves.

than any electron-withdrawing effect. The presence of the second epoxide, a substituent significantly longer and bulkier than a simple methyl group, may make organizing **3** into the compressed orientation required for endo cyclization more difficult than **1**, requiring a $\Delta S^{\ddagger}$ that is larger and more negative. Beyond its bulk, the second epoxide of **3** also brings an additional Lewis basic hydrogen bond acceptor into the system, which could perturb the network of water molecules solvating the ground state and reactive conformers of **3**. Any or all of these factors can alter the trajectory of nucleophilic approach to the epoxide, a factor that computational studies have shown to be most important in dictating regioselectivity in epoxy alcohol cyclizations.[28]

While the first cyclization step of **3** is rather poor, the water-promoted cyclization of THP diad-templated epoxy alcohol **10** is remarkably efficient. Although cyclizations of **10** and **1** exhibit similarly low regioselectivities in basic and acidic water,[20a] cyclizations of **10** in neutral water at room temperature displayed substantially higher endo selectivity (greater than 20:1, the limit of detection) than the analogous reactions of **1** (Figure 4). Apparently, the combination of THP diad **10** and neutral water engenders a more powerful template effect than the single THP ring of **1**. Here again, we propose that the essential distinction is conformational, arising from the greater rigidity and increased number of hydrogen bond acceptors inherent to the 1,6-dioxadecalin template of **10**.

■ CONCLUSIONS

The study of the reaction of diepoxy alcohol **3** to THP triad **4** presented above provides experimental evidence that endo-selective epoxide-opening cascade reactions promoted by water proceed by a stepwise mechanism rather than through a concerted process. NMR analysis provides quantitative rate information for both steps of the major pathway as well as for unproductive side reaction pathways. Independent preparation

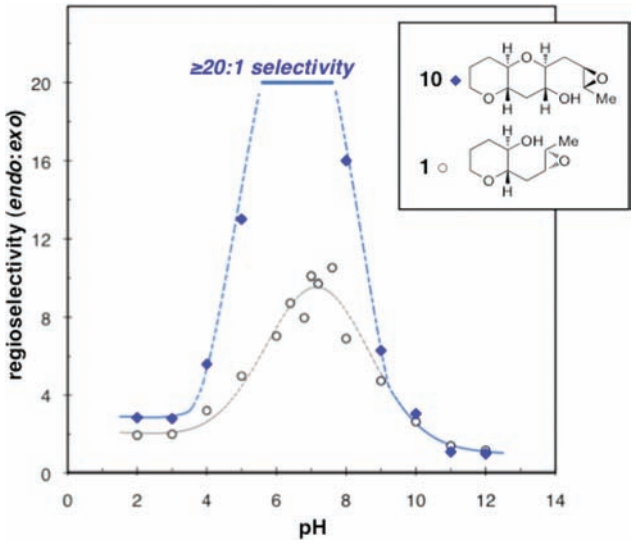

Figure 4. Dependence of regioselectivity on pH for cyclizations of **1**[20a] and **10** (room temperature, 0.1 or 1.0 M KP_i buffer).

and characterization of epoxy alcohol **10** confirm its intermediacy in the cascade reaction and reveal that its THP diad is a more powerful template than a single THP ring. In fact, the regioselectivity of the water-promoted cyclization of **10** (19:1 at 70 °C) is the highest we have ever observed in the cyclization of a trans-disubstituted epoxide that does not contain any strongly directing substituent.

Importantly, this study does not support any significant contribution from a concerted pathway from **3** to **4**. The stepwise mechanism of this nucleophilic endo-selective epoxide-opening cascade promoted by water therefore appears to be fundamentally different from the synchronous mechanism proposed for cascade reactions involving electrophilic epoxonium openings.[14,15] We believe that this difference is further evidence that neutral water is acting as something other than a simple mild Brønsted acid. Rather, water is more likely to serve as a bifunctional promoter, one that activates both the hydroxyl and the epoxide reactive partners through an extensive hydrogen bond network.

We surmise that longer cascades (three or more epoxides) in water (e.g., **5** to **6**, Scheme 1) also proceed via similar stepwise mechanisms. While we hesitate to speculate about any connection between these experiments and the proposed biogenesis of the ladder polyethers,[4a] it is interesting to consider that the first step in the cascade reaction of **3** is the most challenging; it proceeds with low rate and poor regioselectivity. If the appendage of more fused rings to the template makes subsequent cyclization steps faster and more selective, then epoxide-opening cyclizations promoted by neutral water may be more plausibly invoked as components of the biosynthesis of the ladder polyethers. However, as we have yet to demonstrate that any trend of increasing regioselectivity extends to cascades of more than two epoxides, this proposal remains an untested hypothesis.

Nevertheless, knowledge of the stepwise mechanism of water-promoted epoxide-opening cascades will be useful in the application and optimization of such cascades in target-directed synthesis. In particular, the recognition that the more rigid THP diad template of **10** is especially effective may point to a strategy for the formation of medium rings via endo-selective epoxide-opening cyclization, which remains a significant outstanding challenge. Furthermore, it is our hope that deeper understanding of the fundamentals of epoxide activation by neutral water will facilitate the development of new and selective epoxide-opening transformations.

■ ASSOCIATED CONTENT

Supporting Information. Kinetic data and analysis, experimental procedures, and characterization data of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For reviews, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.(b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(2) (a) Bloch, K.; Rittenberg, D. *J. Biol. Chem.* **1945**, *159*, 45. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (c) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (d) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191.

(3) For recent perspectives on polyene cyclization cascades in the biosynthesis of lanosterol and the naming of the "Stork−Eschenmoser hypothesis", see: (a) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (c) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812.

(4) For an overview of the biosynthesis of polyketide-derived polyether ionophores and ladder polyethers, see: (a) Gallimore, A. R. *Nat. Prod. Rep.* **2009**, *26*, 266. For selected examples of epoxide-opening cascades proposed in the biosynthesis of terpenoid polyethers, see: (b) Sakemi, S.; Higa, T. *Tetrahedron Lett.* **1986**, *27*, 4287. (c) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088. (d) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, *24*, 1043.

(5) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *38*, 7141.

(6) (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (c) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi.

(7) (a) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111. (b) van Tamelen, E. E. *Acc. Chem. Res.* **1974**, *8*, 152.

(8) (a) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149. (b) Corey, E. J.; Lin, S. A. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (c) Shenvi, R. A.; Corey, E. J. *Org. Lett.* **2010**, *12*, 3548 and references therein.

(9) Nakanishi acknowledges Prof. Robert Thomas as having first suggested this biogenetic hypothesis via a private communication; see: (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234.

(10) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588.

(11) Shimizu, Y. In *Natural Toxins: Animal, Plant, and Microbial*; Harris, J. B., Ed.; Clarendon: Oxford, 1986; p 123.

(12) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(13) (a) Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8063. (b) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett 2000*, 335.

(14) (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. (c) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

(15) Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.

(16) (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (b) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (c) Heffron, T. P.; Simpson, G. L.; Merino, E.; Jamison, T. F. *J. Org. Chem.* **2010**, *75*, 2681.

(17) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250.

(18) Our group has reported endo-selective epoxide-opening cascades directed by a disappearing trimethylsilyl directing group and promoted by basic methanol and CsF. The mechanism of these cascades is most likely stepwise; please see ref 16.

(19) For pioneering mechanistic analyses of these cyclization cascades, including determination of reaction rates in ref 19d, see: (a) Bartlett, P. A.; Brauman, J. I.; Johnson, W. S.; Volkmann, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 7502. (b) van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 950. (c) Corey, E. J.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Li, D.; Song, X. *J. Am. Chem. Soc.* **1997**, *119*, 1277. (d) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526.

(20) (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (b) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. (c) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

(21) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383.

(22) GC analysis of incomplete reaction mixtures led to thermally induced cyclization of remaining epoxide **3** and intermediates **7** and **10** in the GC inlet, thus leading to innaccurate measurements of selectivity.

(23) Our previous investigations indicate that epoxy alcohol cyclizations promoted by water are under kinetic control and that endo:exo regioselectivity does not change throughout the reaction; please see ref 21.

(24) Connors, K. A. *Chemical Kinetics*; VCH: New York, 1990.

(25) For a more detailed discussion of the difficulties associated with calculating rate constants for the reactions of **3**, **10**, and especially **7** directly from concentration versus time data, please see the Supporting Information.

(26) COPASI (Complex Pathway Simulator) 4.5: Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. *Bioinformatics* **2006**, *22*, 3067.

(27) Other unidentified products were also observed during the cyclization of isolated **7**, which account for nearly 30% of the consumption of **7** and explain the difference between k^3_{obs} and $(k^7_{hydrolysis} + k^7_5)$. The same unknown compounds were observed in trace amounts in the cascade reaction of **3**, where they constitute only about 1% of total concentration after three half-lives. These species were ignored in the kinetic analysis.

(28) (a) Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453. (b) Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530.