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Water Overcomes Methyl Group Directing Effects in Epoxide-Opening Cascades

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In 1985, Nakanishi[1] advanced a concise and appealing proposal for the biosynthesis of the ladder polyether family of natural products, a synthesis that culminates in a cascade of regio- and stereoselective epoxide openings (Scheme 1). Our group recently reported an emulation of the Nakanishi hypothesis wherein water serves as the superior promoter of endo-selective epoxide-opening cascades.[2] This earlier account was limited to cascades of trans-disubstituted epoxides, but herein we report that water (as the solvent) is also a simple and general solution for cascades involving trisubstituted epoxides. This method overcomes the well-documented strong directing effect that methyl (Me) groups have on epoxide ring-opening reactions[3] and thus enables the rapid assembly of multiple patterns of substituted ladder polyether subunits.

An angular Me group is the only substituent other than hydrogen observed at ladder polyether ring junctions, and every structure in this large family of natural products possesses at least one Me group. Nature has conceived two variations of this substitution, requiring two chemically quite different kinds of *E*-trisubstituted epoxides in the corresponding polyepoxide precursors. For example, in the hypothesized precursor **1** to brevetoxin B (Scheme 1), Me groups are observed both *distal* and *proximal*[4] to the internal nucleophile; the putative cascade must tolerate both possibilities. In fact, nearly all ladders bearing more than one Me group, including the brevetoxins, maitotoxin, gambierol, and gymnocin B, are proposed to arise from similar polyepoxides bearing an "out-of-register" mixture of both distally and proximally substituted epoxides.

The crux of the problem is that the Me group is generally a strong director of epoxide-opening regioselectivity, particularly under acid catalysis. Valuable methods for endo-selective opening, epitomized by those developed by the McDonald group,[3a−c] take advantage of this directing effect,[3] but these necessarily accommodate only *distal* Me substitution. Moreover, distal Me substitution at every epoxide is generally vital for high regioselectivity and yield.[5] The endo-selective opening of epoxides with a Me or other simple alkyl group[6] *proximal* to the pendent nucleophile has *not* been documented, except under enzyme catalysis[7] or when a stronger directing group at the distal site of the epoxide was used.[8] We conjectured that tetrahydropyran (THP)-templated, water-promoted cascades might prove relatively insensitive to the electronic effects and afford a general solution to the problem of Me substitution, particularly for the challenging case of proximal Me substitution noted above.

We accordingly began our investigation with proximally Me-substituted monoepoxide **2b** (Table 1). Unsurprisingly, both Brønsted (CSA) and Lewis (BF_3) acids were highly exo-selective, affording the undesired **4b**. Conversely, Brønsted base activation by Cs_2CO_3 provided the desired bis-THP product **3b**, with the moderate endo selectivity apparently arising from the alkoxide's preference for the less sterically hindered site of attack. Most striking was water, which effected cyclization with nearly 5:1 selectivity for **3b** over **4b**. Furthermore, the selectivity of cyclizations of **2b** improved to almost 6:1 endo/exo in potassium phosphate

Scheme 1. Proposed Biosynthetic Cascade to Brevetoxin B

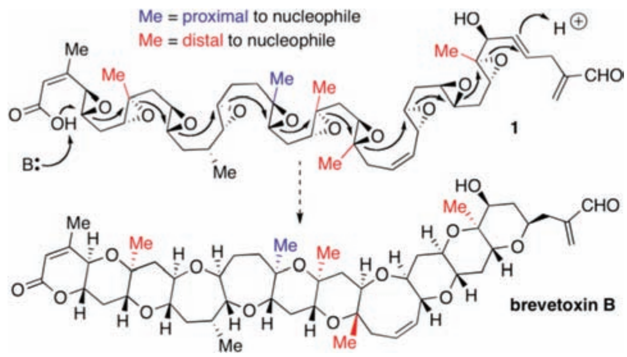
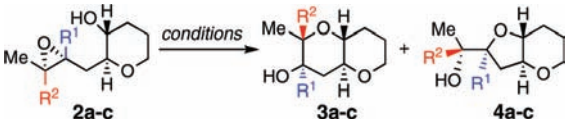


Table 1. Dependence of Regioselectivity under Various Epoxide-Opening Conditions



epoxide	R^1	R^2	Cs_2CO_3, MeOH[b]	CSA, CH_2Cl_2[c]	BF_3•OEt_2, CH_2Cl_2[d]	H_2O[e]
			conditions and regioselectivity (3:4)[a]			
2a	H	H	1 : 2.7	1 : 1.2	1.4 : 1	**10 : 1**
2b	Me	H	3.0 : 1	1 : 5.2	1 : 11	**4.9 : 1**
2c	H	Me	1 : 17	5.8 : 1[f]	>20 : 1[f]	**>20 : 1**

[a] Ratios determined by ^{1}H NMR spectroscopy. [b] Cs_2CO_3 (30 equiv), rt, 0.02 M. [c] (±)-CSA (1 equiv), rt, 0.02 M. [d] $BF_3 \cdot OEt_2$ (0.25 equiv), −78° to rt, 0.02 M. [e] Deionized water, rt, 0.02 M. [f] An isopropyl ketone side product was also isolated (see the Supporting Information).

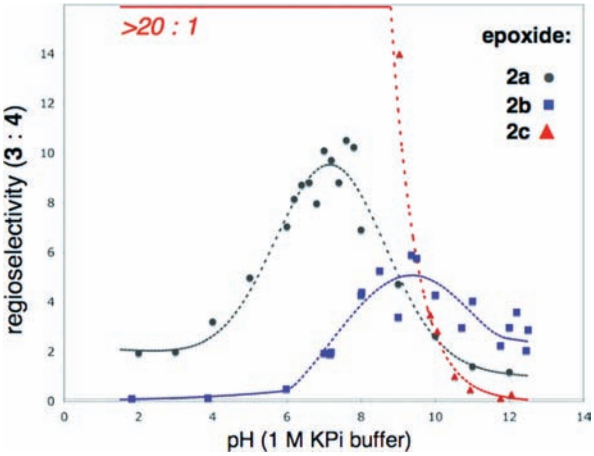


Figure 1. Dependence of Regioselectivity on pH.

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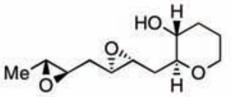
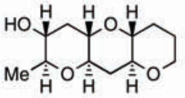
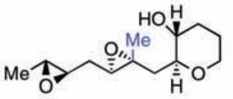
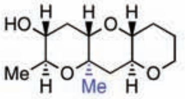
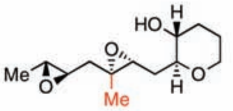
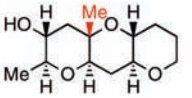
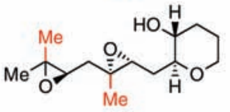
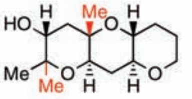
Table 2. Cascades of Methyl-Substituted Diepoxytetrahydropyranols under Various Epoxide-Opening Conditions

		conditions and isolated yield[a] of desired product:			
substrate	desired product	Cs_2CO_3 in MeOH[b]	CSA in CH_2Cl_2[c]	BF_3•OEt_2 CH_2Cl_2[d]	H_2O[e]
 **5**	 **6**	0%	trace[f]	trace[f]	**74%**
 **7**	 **8**	0%	0%	0%	**32%**
 **9**	 **10**	0%	46%	63%	**67%**
 **11**	 **12**	0%	43%	61%	**54%**

[a] Corrected for diastereomeric purity of the starting material (between 7.5:1 and 20:1 in all cases; see the Supporting Information); values are averages of at least two experiments. [b] Cs_2CO_3 (30 equiv), rt, 0.02 M. [c] (±)-CSA (1 equiv), rt, 0.02 M. [d] $BF_3 \cdot OEt_2$ (0.25 equiv), −78° to rt, 0.02 M. [e] At 60°, 0.02 M. [f] Less than 5% (^{1}H NMR).

buffer at pH 8−10 (Figure 1); intriguingly, this selectivity decreased again as the pH increased past 10.

Epoxides with distal Me substituents have been shown to open with high endo regioselectivity with a variety of acidic promoters.[3a−e] Indeed, exposure of epoxy alcohol **2c** to both $BF_3 \cdot OEt_2$ and CSA induced selective cyclization to bis-THP **3c**, but considerable amounts (up to 20%) of isomerization of **2c** to an isopropyl ketone side product were also observed under these conditions. A cleaner reaction was achieved in deionized water, which smoothly transformed **2c** to **3c** with >20:1 endo/exo selectivity and no trace of the ketone byproduct. A pH screen (Figure 1) revealed that very high selectivity holds under acidic, neutral, and mildly basic conditions; only for pH >9 does the selectivity drop below 10:1.

Optimistic that cascades of substituted epoxides should be possible in aqueous media, we prepared diepoxy alcohol **7** (Table 2) bearing a proximal Me group. Stirring of **7** in warm water produced the desired tris-THP triad **8** in 32% yield.[9] To the best of our knowledge, this transformation represents the first endo-selective epoxide-opening cascade to accommodate a proximal Me substituent. Cascades with base or acid in organic solvent supplied no trace of **8**.

A distal Me group was incorporated into diepoxide **9**, and water again proved amenable, affording triad **10** in 67% yield. A somewhat lower 54% yield of triad **12** was obtained in the aqueous reaction of diepoxide **11**, in which both epoxides bear distal Me substituents. In promoting cascades of **9** and **11,** CSA and BF_3 were competitive with water, with water slightly better than BF_3 in reactions of **9** and the reverse observed in reactions of **11**.

Reactions of **5**,[2] the parent system containing two trans-disubstituted epoxides, revealed that only water provides a significant quantity (74%) of the desired triad **6**. Thus, water-promoted cyclizations provide a uniquely versatile strategy for the construction of *all three* epoxide substitution patterns found in the Nakanishi hypothesis and clearly proceed by a mechanism fundamentally different from those operating under simple acid or simple base catalysis.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Distal and proximal Me groups are shown in red and blue, respectively.
(5) In cascades to form polyoxepanes, trans-disubstituted epoxides can be accommodated to some extent, generally with lower yields (see refs 3c and 3d).
(6) Endo-selective cyclization with methoxymethyl substitution on the epoxide proximal to the pendent nucleophile was reported by Murai and coworkers. See: (a) Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8063. (b) Fujiwara, K.; Mishima, H.; Amano, A.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1998**, *39*, 393.
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(8) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.
(9) A 6,5-fused side product arising from exo opening was also collected in 39% yield (see the Supporting Information).

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