Water Overcomes Methyl Group Directing Effects in Epoxide-Opening Cascades

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Water Overcomes Methyl Group Directing Effects in Epoxide-Opening Cascades

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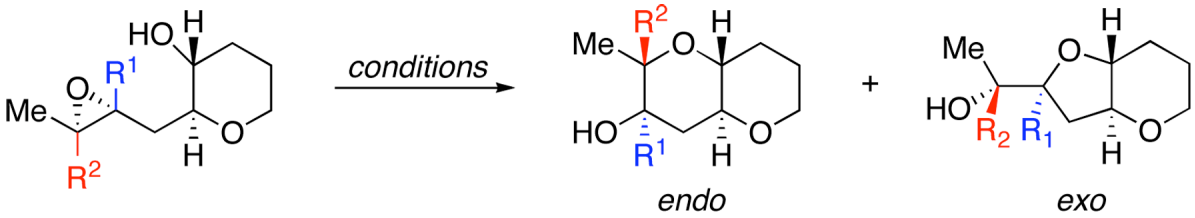
Abstract



R^1	R^2	acid	base	H_2O
H	H	~ 1:1	exo	**endo**
Me	H	exo	endo	**endo**
H	Me	endo	exo	**endo**

Water is an effective promoter of the *endo*-selective opening of trisubstituted epoxides, enabling related cascades leading to a variety of substituted ladder polyether structures. When used in conjunction with a tetrahydropyran-templated nucleophile, water can overcome the powerful electronic directing effect of a methyl substituent at either site of the epoxide, making water a uniquely versatile medium and promoter for epoxide opening.

In 1985 Nakanishi 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).[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, and we herein report that water (as solvent) is also a simple and general solution for cascades involving trisubstituted epoxides. Overcome by this method is the well documented, strong directing effect that methyl (Me) groups have on epoxide ring-opening reactions,[3] and thus enabled is the rapid assembly of multiple patterns of substituted ladder polyether subunits.

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

An angular Me group is the only substituent other than hydrogen (H) 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 catalysis7 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 desired bis-THP product **3b**, with 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 buffer within a pH range of 8 to 10 (Chart 1); intriguingly, this selectivity drops again as pH increases 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•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 (Chart 1) revealed that very high selectivity holds under acidic, neutral, and mildly basic conditions; only at pH >9 does 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 **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 now 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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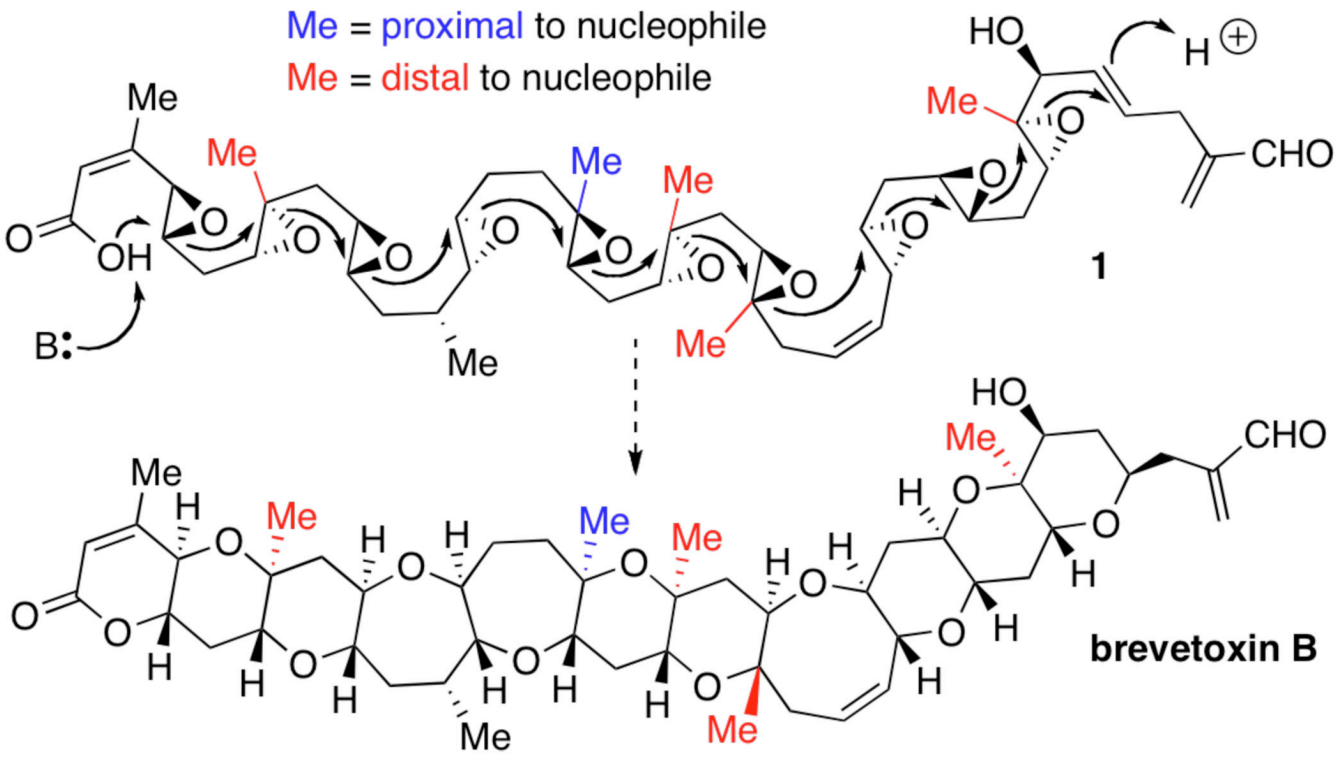
4. Distal and *proximal* Me groups are shown in red and blue, respectively.
5. In cascades to form polyoxepanes, *trans*-disubstituted epoxides can be accommodated to some extent, generally with lower yields; see references [4c] and [4d].
6. *Endo*-selective cyclization with methoxymethyl substitution 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.
7. Smith L, Hong H, Spencer JB, Leadlay PF. ChemBioChem 2008;9:2967. [PubMed: 19025863]
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 Supporting Information.



Scheme 1.
Proposed Biosynthetic Cascade to Brevetoxin B

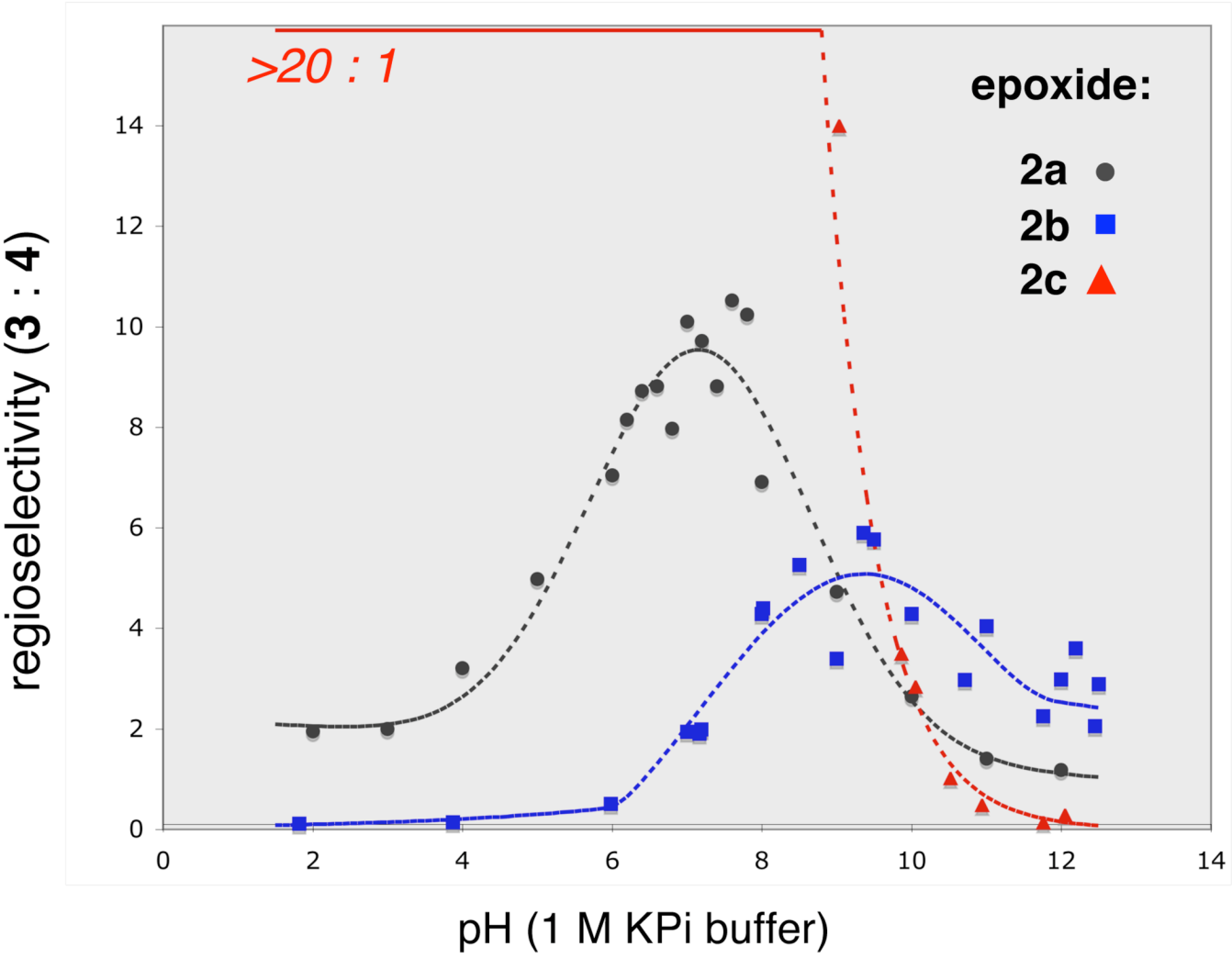
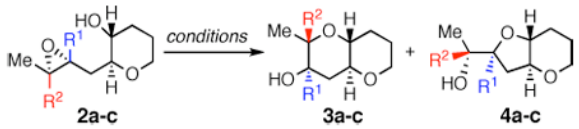


Chart 1.
Dependence of Regioselectivity on pH

Table 1

Dependence of Regioselectivity under Various Epoxide-Opening Conditions



epoxide	R^1	R^2	conditions and regioselectivity (3:4)[a]			
			Cs_2CO_3, MeOH[b]	CSA, CH_2Cl_2[c]	BF_3•OEt_2, CH_2Cl_2[d]	H_2O[e]
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] 30 equiv Cs_2CO_3, rt, 0.02 M.

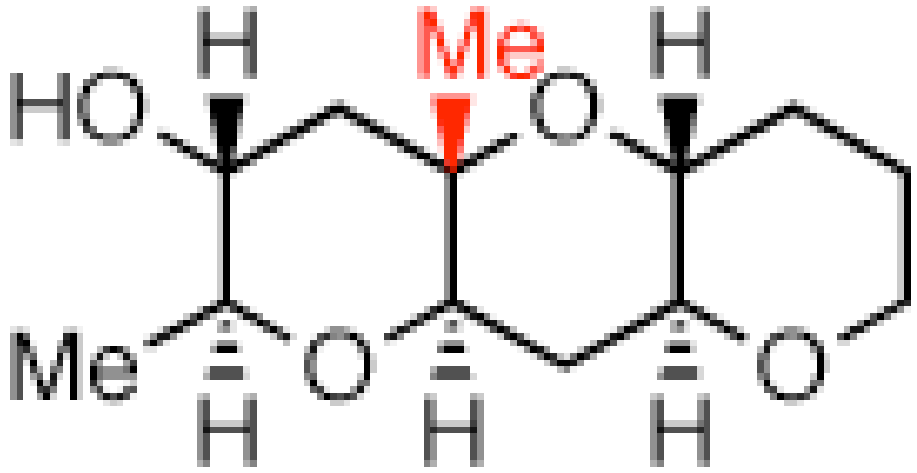
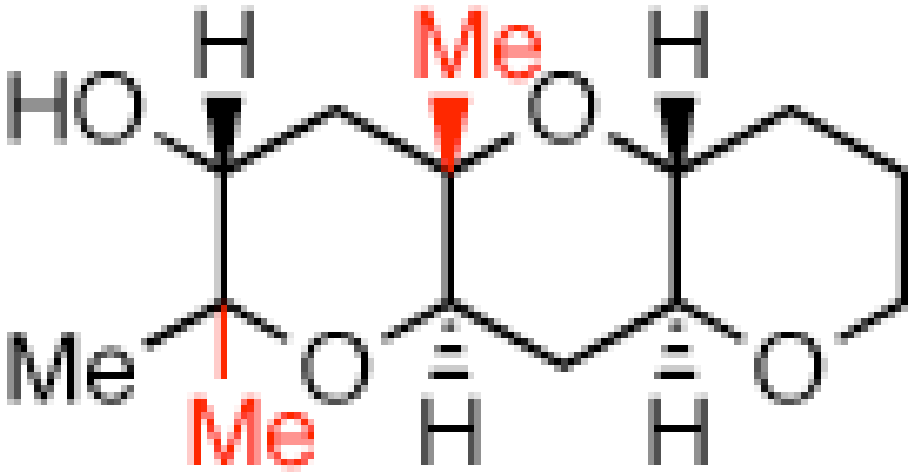
[c] 1 equiv (+/−)-CSA, rt, 0.02 M.

[d] 0.25 equiv BF_3•OEt_2, −78° to rt, 0.02 M.

[e] deionized water, rt, 0.02 M.

[f] Isopropyl ketone side product also isolated, see Supporting Information.

desired product	conditions and isolated yield[a] of desired product:			
	Cs_2CO_3 in MeOH[b]	CSA in CH_2Cl_2[c]	$BF_3{\cdot}OEt_2$ CH_2Cl_2[d]	H_2O[e]
6	0%	trace[f]	trace[f]	74%
8	0%	0%	0%	32%

	desired product	conditions and isolated yield[a] of 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]
10		0%	46%	63%	**67%**
11		0%	43%	61%	**54%**

[a] Corrected for diastereomeric purity of starting material (between 7.5:1 and 20:1 for all cases, see Supporting Information); average of at least two experiments.

[b] 30 equiv Cs_2CO_3, rt, 0.02 M.

[c] 1 equiv (+/−)-CSA, rt, 0.02 M.

[d] 0.25 equiv BF_3•OEt_2, −78° to rt, 0.02 M.

[e] 60°, 0.02 M.

[f] <5% (^{1}H NMR).