Development and Implications of Epoxide-Opening Cascades

February 8, 2008

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Overview

- Introduction to Brevetoxins and the Nakanishi Hypothesis
- Baldwin's Rules for Ring Closure
- Ring Selectivity in Epoxide Openings
- Epoxide Openings facilitated by Water
- Organocatalysis of Epoxide Openings
- Conclusions

Brevetoxins and Red Tide

- Neurotoxins produced by red tide dinoflagellates
- Red tides affect marine ecosystems all over the world, including areas near Scandinavia, Japan, the Caribbean, and the South Pacific.
- Can result in large fish kills, NSP and respiratory irritation in humans

Red tide off the coast of Florida. *The Charlotte Sun Herald*-Paul Schmidt; Florida Marine Research Institute

(a) Asai, S. *et al. J. Allergy Clin. Immunol.* **1982**, *69*, 418-428. (b) Catterall, W. A. *et al*. *Toxicon* **1985**, *23*, 497-504. (c) Wu, C. H. *et al. Toxicon* **1985**, *23*, 481-487. (d) United States Center for Disease Control: http://www.cdc.gov/hab/redtide/#cdc

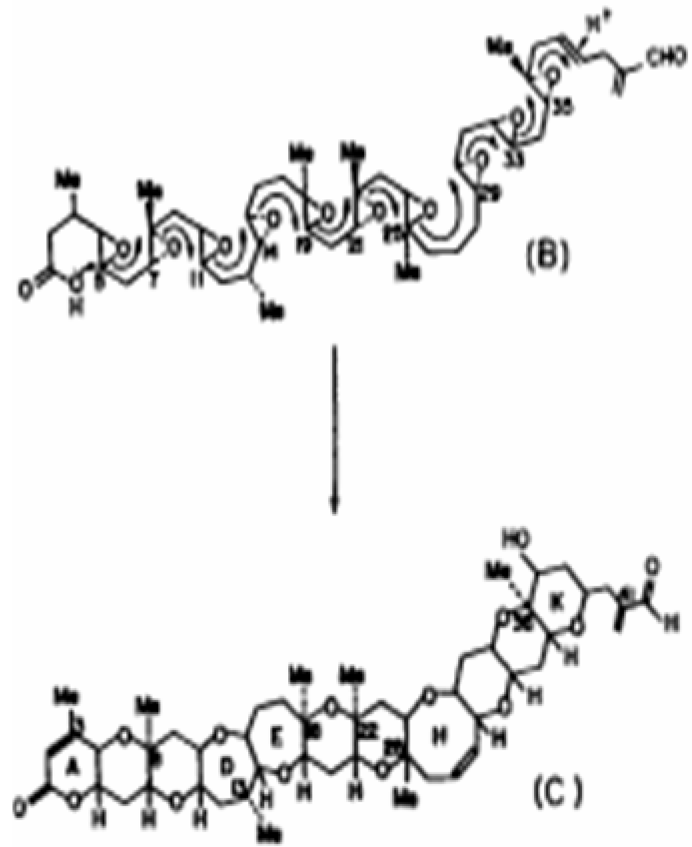
Gymnodinium breve and Problems in the Gulf of Mexico

Red tide bloom of river origin spreading over the waters of the Gulf of Mexico

Dead fish resulting from the red tide in Florida

Nakanishi Hypothesis

- Nakanishi hypothesized that an epoxide-opening cascade (B) leads to the formation of Brevetoxin B (C).



(a) Lin, Y.-Y. *et al. J. Am. Chem. Soc.* **1981**, *103*, 6773-6775. (b) Nakanishi, K. *Toxicon* **1985**, *23*, 473-479. (c) Vilotijevic, I. *et al*. *Science* **2007**, *317*, 1189-1192

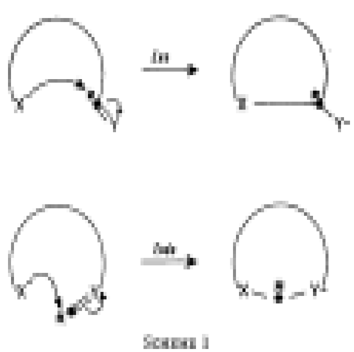
Nakanishi Hypothesis vs. Baldwin's Rules

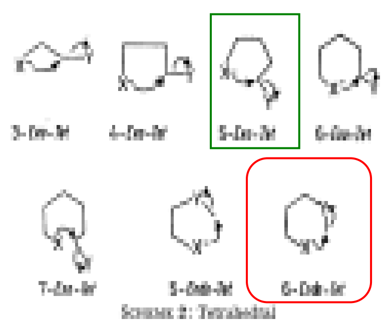
- Nakanishi's hypothesis accounts for stereochemical regularity of ladder polyethers.
- Such epoxide-opening cascades occur in contrast to Baldwin's rules for ring closure.
- Tetrahydrofuran (THF) formation is generally favored over that of tetrahydropyran (THP).

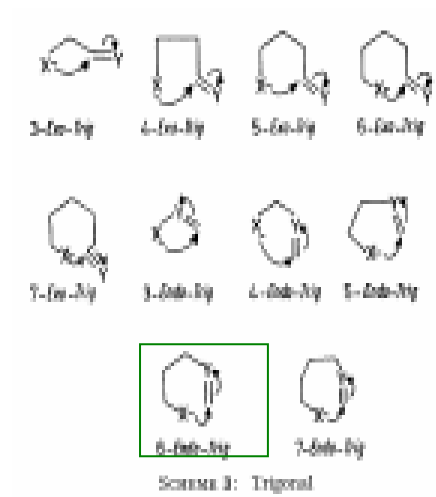
(a) Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734-736. (b) Hayashi, N. *et al. Tetrahedron* **1997**, *53*, 12425-12468. (c) Coxon, J. M. *et al. J. Org. Chem.* **1999**, *64,* 5530-5541. (d) Tokiwana, T. *et al. Synlett.* **2000**, *3*, 335-338.

Baldwin's Rules for Ring Closure

- **Tetrahedral Systems:**
  - 3 to 7-*Exo-Tet* are all favored process.
  - 5 to 6-*Endo-Tet* are disfavored.
- **Trigonal Systems**:
  - 3 to 7-*Exo-Trig* are all favored processes
  - 3 to 5-*Endo-Trig* are all disfavored; 6 to 7-*Endo-Trig* are favored







Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734-736.

Baldwin's Rules (cont.)

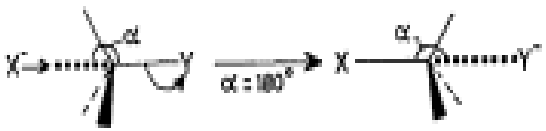


FIGURE 1: Tet.

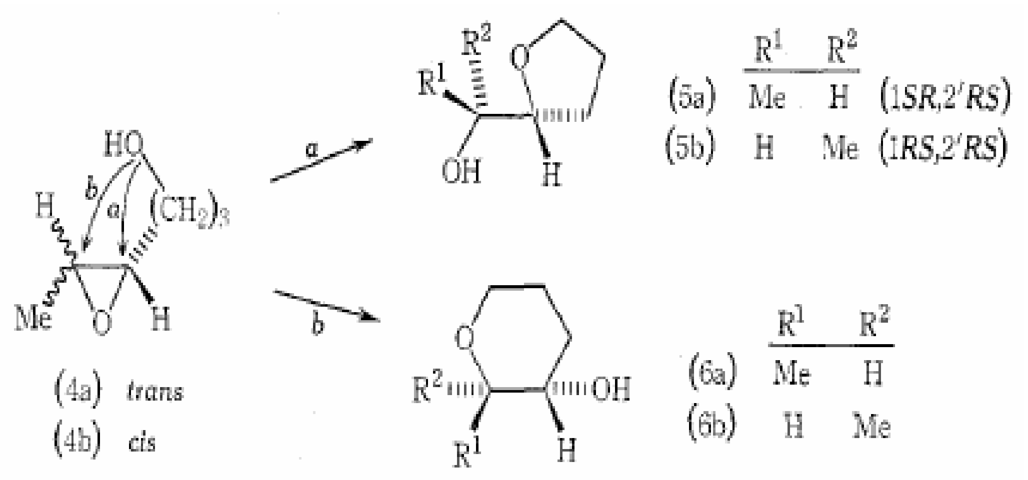
FIGURE 2: Trig.

- Stereochemical requirements of TS
- Ability to acquire proper geometry dictates favorability
- Epoxides lie somewhere between tetrahedral and trigonal systems.

Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734-736.

Rearrangement of 4,5-epoxyhexan-1-ol

- Reaction of *trans*-4,5-epoxyhexan-1-ol with BF_3 etherate in ether yielded a mixture of THF and THP.
- Reaction of the *cis* isomer under the same conditions produced the THF in 97% yield.



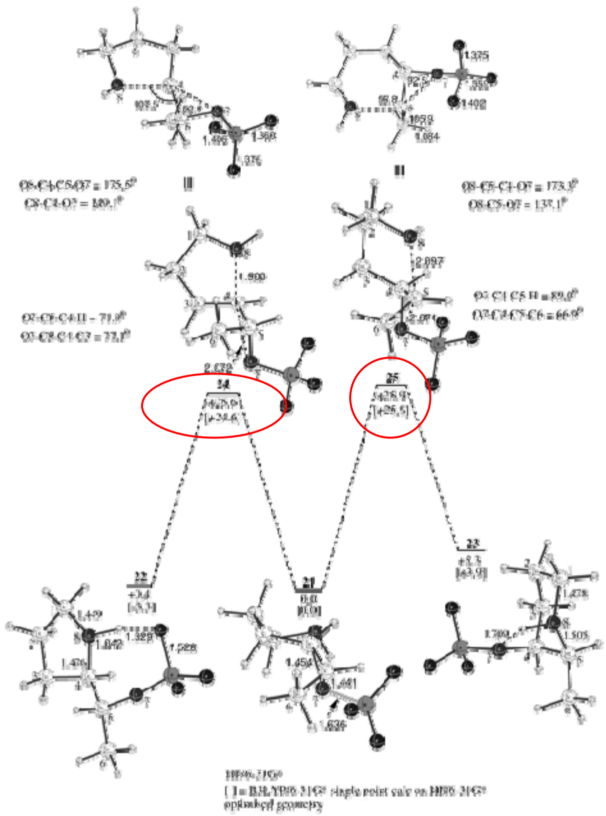
Coxon, J. M. *et al. Aust. J. Chem.* **1973**, *26*, 2521-2526.

H^+ and BF_3-Catalyzed *trans*- and *cis*-4,5-epoxyhexan-1-ol Rearrangement

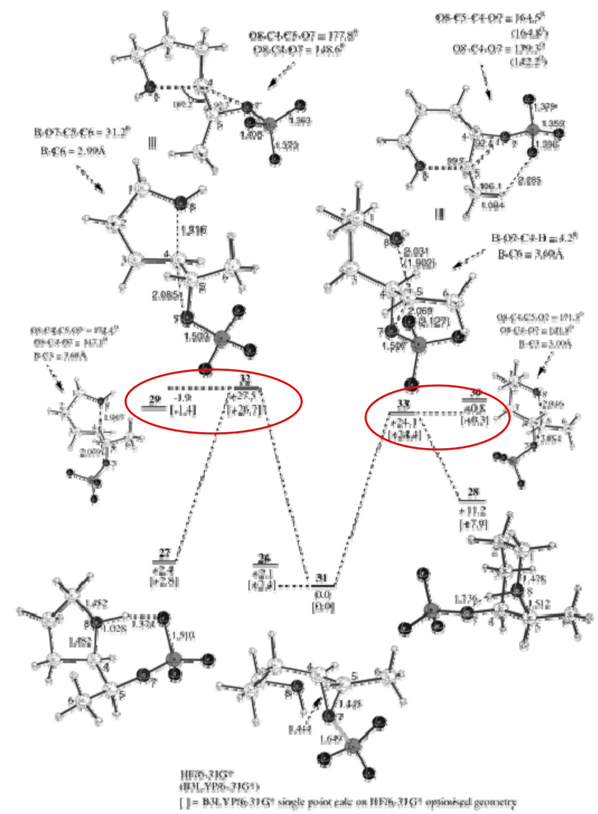
- *T*he rearrangement of *cis*- and *trans*-4,5-epoxyhexan-1-ol with H^+ and BF_3 was studied using *ab initio* methods.
- ***Protonated epoxides***: Pathway involving 5-membered TS favored in both cases
- ***BF_3-coordinated epoxides***: Pathway involving 5-membered TS favored only for rearrangement of *cis* epoxide
- TS of BF_3-catalyzed rearrangement occurs farther along reaction pathway

Coxon, J. M. *et al*. *J. Org. Chem*. **1999**, *64*, 5530-5541

H^+ and BF_3-Catalyzed *trans*- and *cis*-4,5-epoxyhexan-1-ol Rearrangement (cont.)



PES of BF_3-catalyzed rearrangement of *cis*-4,5-epoxyhexan-1-ol



PES of BF_3-catalyzed rearrangement of *trans*-4,5-epoxyhexan-1-ol

Coxon, J. M. *et al*. *J. Org. Chem.* **1999**, *64*, 5530-5541

Achieving Ring Selectivity

- **Use of antibody catalysts**
  - Janda, K. D. *et al. Science* **1993**, *259*, 490-493.

- **Use of other directing groups**
  - Nicolaou, K. C. *et al. J. Am. Chem. Soc.* **1989**, *111*, 5330-5334.
  - Simpson, G. L. *et al. J. Am. Chem. Soc.* **2006**, *128*, 1056-1057.

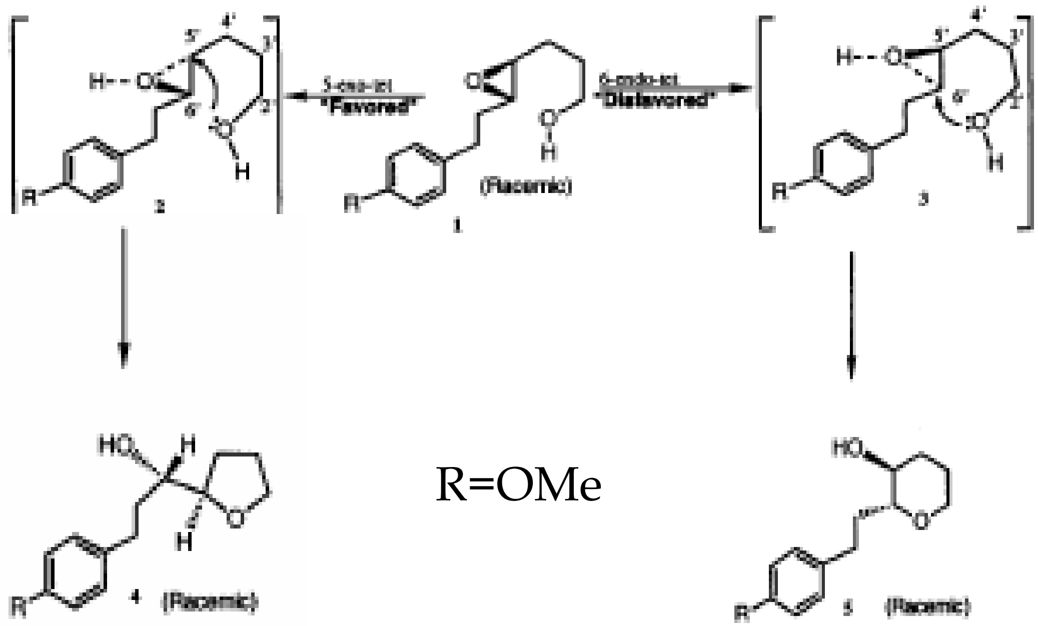
- **Lewis acid-catalyzed epoxide openings**
  - Wu, M. H. *et al. Angew. Chem. Int. Ed.* **1999**, *38*, 2012-2014.
  - Tokiwano, T. *et al. Synlett* **2000**, *3*, 335-338.

Antibody Catalysis

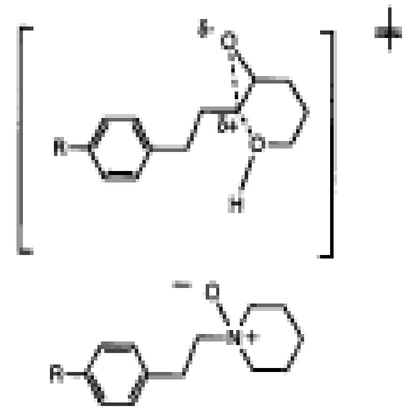
- Antibodies that act like enzymes
- Entropically-disfavored reactions reversed by contribution of antibody binding energy
- Intercedes at or near transition state and alters energy balance in favor of 6-*Endo* geometry formation
- However promising, obtaining an effective antibody catalyst is often complicated.

(a) Tramontano, A. *et al.* *Science* **1986**, *234*, 1566-1570. (b) Pollack, S. J. *et al.* *Science* **1986**, *234*, 1570-1573. (c) Jacobs, J. W. *Biotechnology* **1991**, *9*, 258-262.

Antibody Catalysis (cont.)



R=OMe



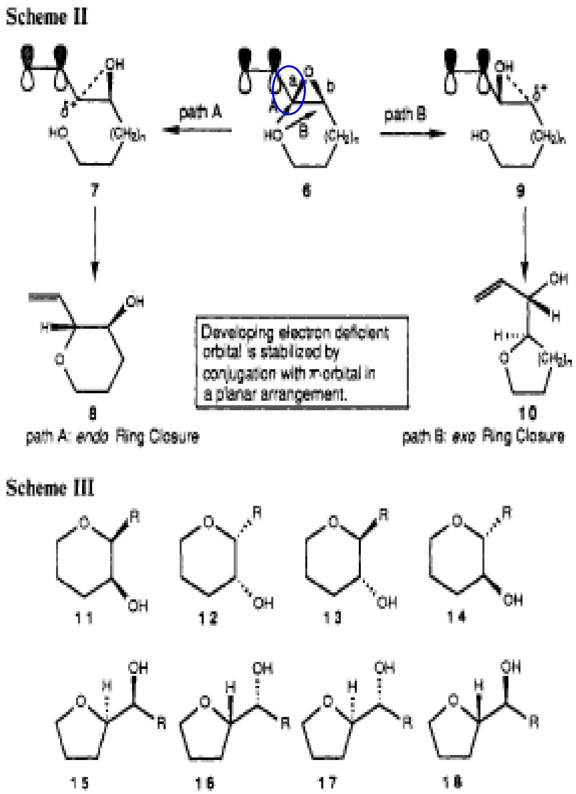
Hapten

In the absence of antibody, only **4** was formed. However, 2 of the 26 antibodies tested were regioselective for formation of **5**.

Janda, K. D. *et al*. *Science* **1993**, *259*, 490-493.

Directing Groups

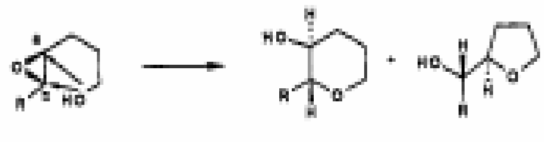
- Several directing groups were placed adjacent to the epoxide and trends in THP formation observed.
- Directing groups place a π-orbital adjacent to C^a.



Nicolaou, K. C. *et al*. *J. Am. Chem. Soc.* **1989**, *111*, 5330-5334.

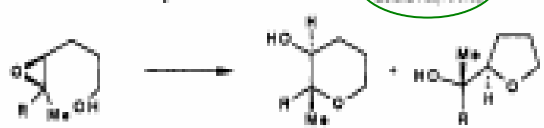
Directing Groups (cont.)

Table I. Acid-Catalyzed Cyclization of Trans Hydroxy Epoxides



19 → 20 (a: 6-endo) + 21 (b: 5-exo)

Entry	Substrate	Conditions	Products(Ratio)	yield(%)
1	19a:R=$CH_2CH_2CO_2Me$	0.1 equiv CSA CH_2Cl_2, -40 to 25 °C	20a:21a (0:100)[a]	94
2	19b:R=E-CH=$CHCO_2Me$	"	20b:21b(60:40)	98
3	19c:R=CH=CH_2	"	20c:21c(100:0)	95
4	19d:R=CH=CBr_2	"	20d:21d(100:0)	90



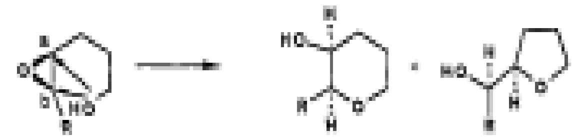
22 → 23 + 24

Entry	Substrate	Conditions	Products(Ratio)	yield(%)
5	22a:R=E-CH=$CHCO_2Me$	"	23a:24a(66:34)	92
6	22b:R=CH=CH_2	"	23b:24b(100:0)	96

[a] Isolated as the γ-lactone (21a-lactone)

21a-lactone

Table II. Acid-Catalyzed Cyclization of Cis Hydroxy Epoxides.



25 → 26 (a: 6-endo) + 27 (b: 5-exo)

Entry	Substrate	Conditions	Products(Ratio)	Yield(%)
1	25a:R=E-CH=$CHCO_2Me$	0.1 equiv CSA CH_2Cl_2, -40 to 25 °C	26a:27a (0:100)	98
2	25b R=CH=CH_2	"	26b:27b(44:56)	95
3	25c R=E-CH=CHCl	"	26c:27c(76:24)	94
4	25d:R=Z-CH=CHCl	"	26d:27d(33:67)	90
5	25e R= CH=CBr	"	26e:27e(0:100)	87

Nicolaou, K. C. *et al. J. Am. Chem. Soc.* **1989**, *111*, 5330-5334

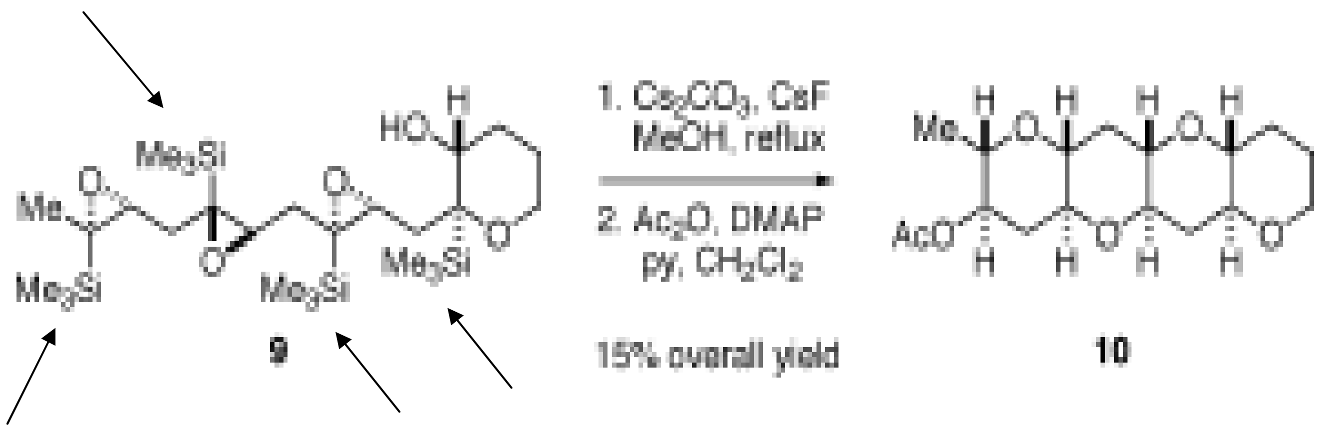
Directing Groups (cont.)

- Favorable THP formation from *trans* hydroxy epoxides when an adjacent π-orbital present
- Favorable THF formation from *cis* hydroxy epoxides in all but one case
- Possibly due to steric interactions and inability of systems to adapt planar geometry required for transition state stabilization

Nicolaou, K. C. *et al. J. Am. Chem. Soc.* **1989**, *111*, 5330-5334

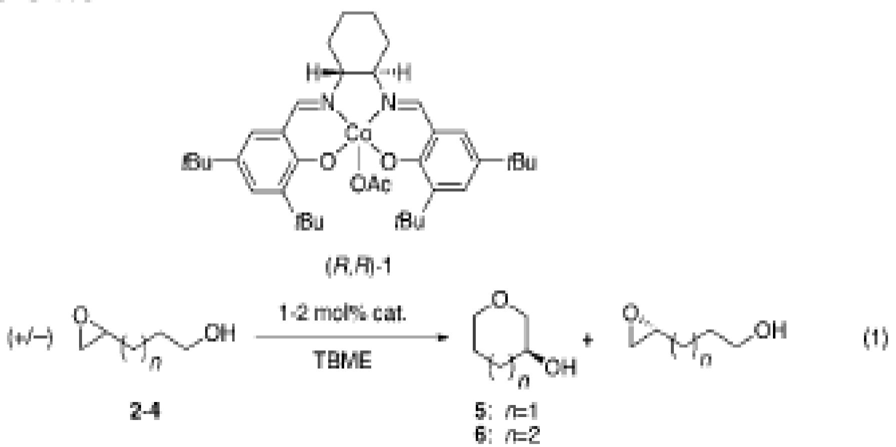
A "Disappearing" Directing Group

- Normally, directing groups must be removed after cyclization.
- Me_3Si directing groups "disappear" during epoxide-opening cascades.
- Reaction takes place under very different conditions



Simpson, G. L. *et al*. *J. Am. Chem. Soc.* **2006**, *128*, 1056-1057.

Lewis Acid Catalysis: $[Co^{III}(salen)]$ Complex



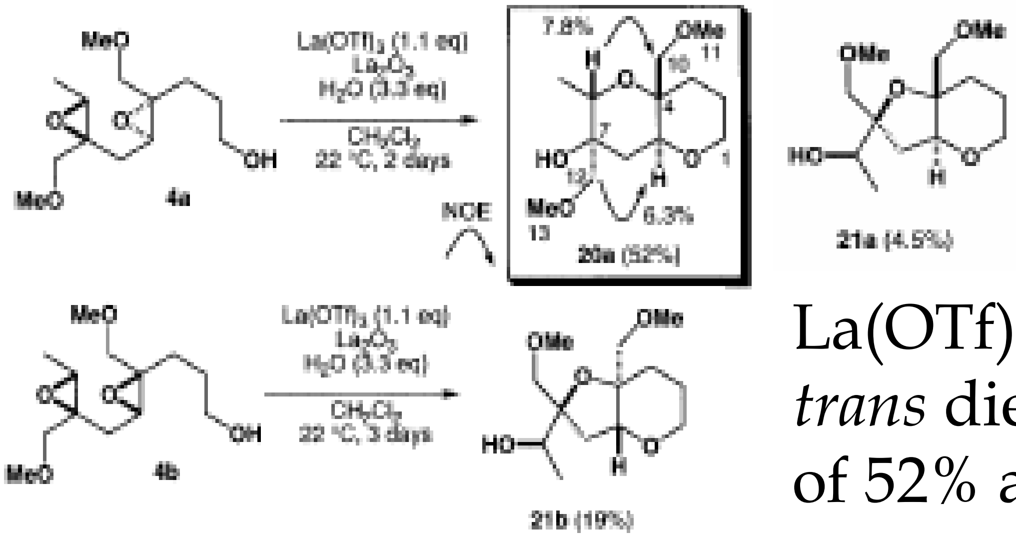
Epoxide	T [°C]	t [h]	ee (product)[a] [%]	Yield[b] [%]	ee (epoxide)[c] [%]	Yield[b] [%]
2 (n = 1)	0	1	95	46 (41)	93	50
3 (n = 2)	0	7	94	47 (39)	98	50
4 (n = 3)	23	48	n.r.[d]	n.r.	n.r.	n.r.

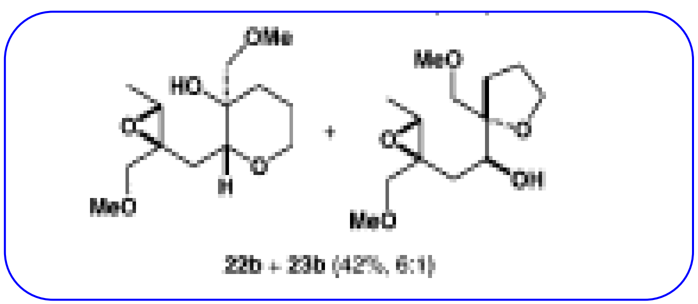
[a] Determined by chiral HPLC (Chiracel AD) of the benzoate esters. [b] GC yields. The yields of the isolated benzoate esters of 5 and 6 are given in parenthesis. [c] The

- Complex **1** catalyzed the *Endo* epoxide opening.
- Only obtained a 41% yield of the THP

Wu, M. H. *et al*. *Angew. Chem. Int. Ed.* **1999**, *38*, 2012-2014.

Lewis Acid Catalysis: La(OTf)$_3$



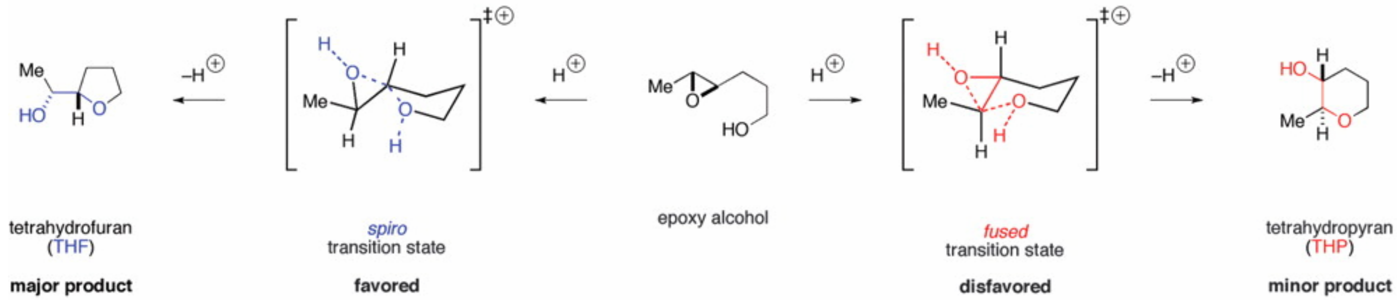


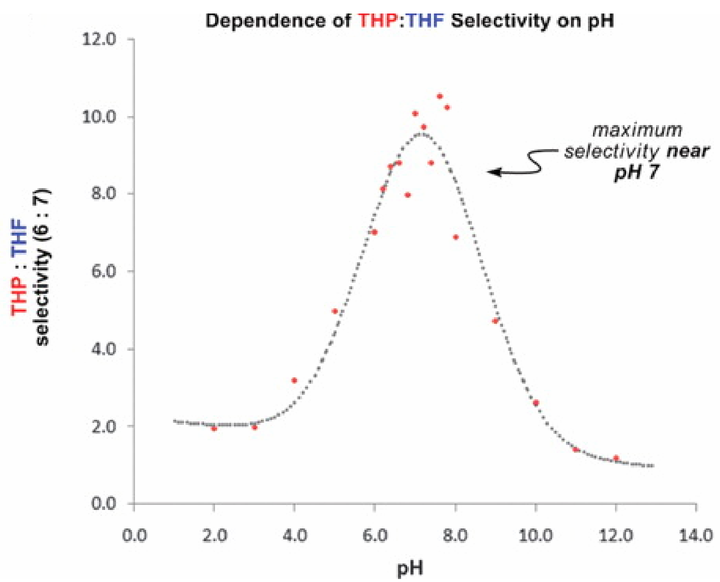
La(OTf)$_3$-catalyzed reaction of the *trans* diepoxide resulted in yields of 52% and 4.5% of *trans*-fused pertetrahydropyran and *trans*-fused pertetrahydrofuran, respectively.

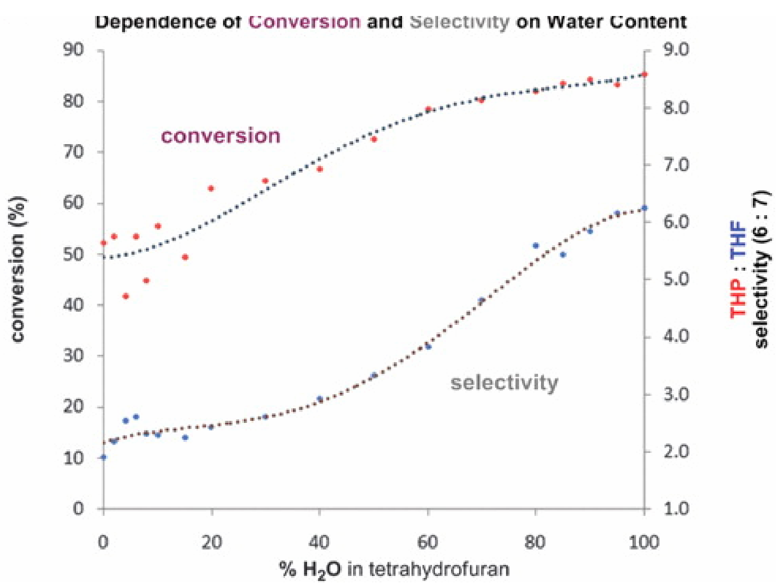
The reaction of the *cis* diepoxide produced no pertetrahydropyran.

Tokiwano, T. *et al*. *Synlett* **2000**, *3*, 335-338.

Stereoselective Epoxide Openings in Water



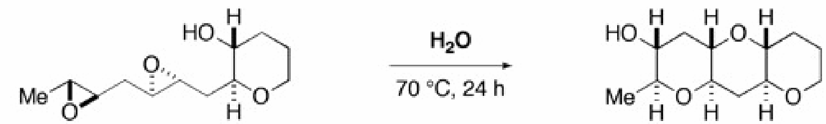




Vilotijevic, I. *et al*. *Science* **2007**, *317*, 1189-1192.

Epoxide-Opening Cascades Promoted by Water

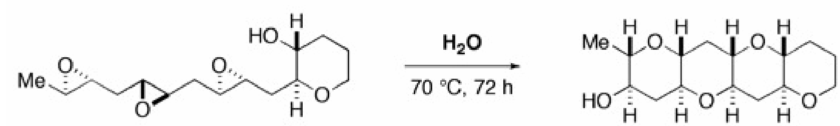
- Polycyclic THP product obtained in high yields
- Results support mechanism in which previously-formed hydroxyl group acts as nucleophile
- Reaction rate is temperature-dependent; product formation is not.



15 (4:1 dr) → **18**

60% isolated yield

(**75% yield** corrected for purity of **15**; **87% yield** per epoxide-opening event)



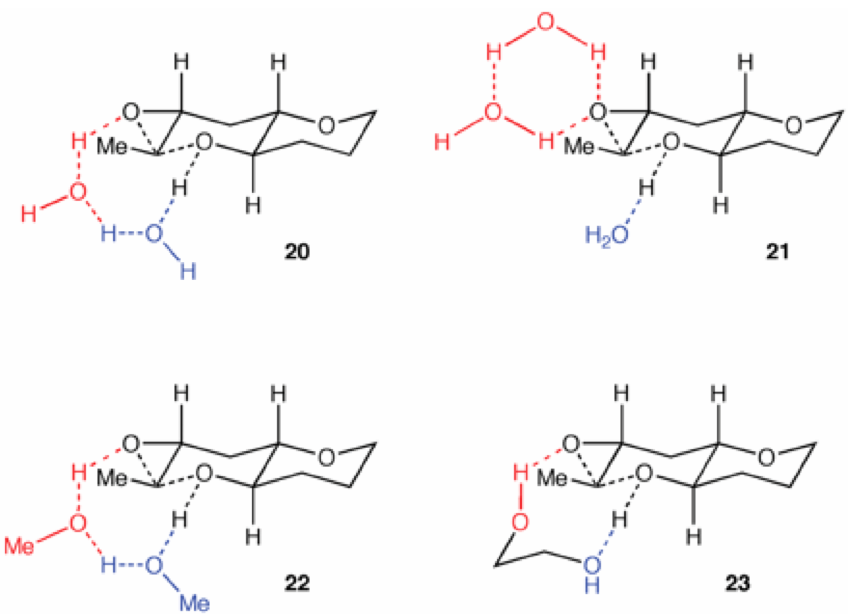
17 (3:1 dr) → **19**

53% isolated yield

(**71% yield** corrected for purity of **17**; **89% yield** per epoxide-opening event)

Vilotijevic, I. *et al*. *Science* **2007**, *317*, 1189-1192.

Epoxide-Opening Cascades Promoted by Water (cont.)

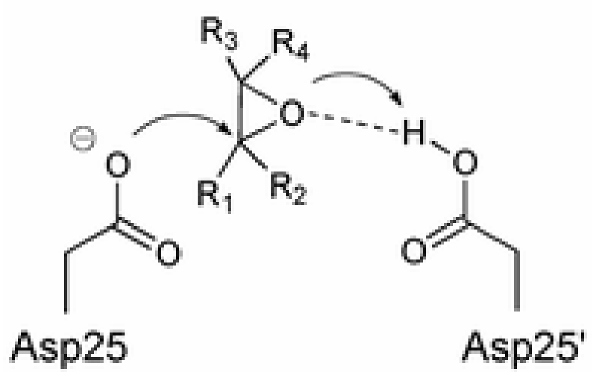


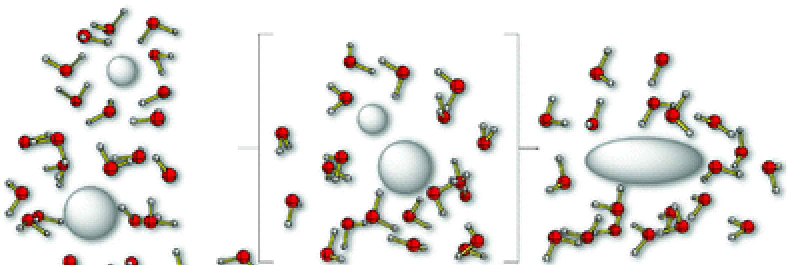
- Mechanism proposed may be similar to biosynthetic pathway
  - Reaction efficiency highest at or near physiological pH
- Could be promoted by hydrogen-bond activation of epoxide and/or nucleophile (~OH)

Vilotijevic, I. *et al*. *Science* **2007**, *317*, 1189-1192.

Organic Chemistry in Water

- **Not unprecedented**
  - Acceleration of Diels-Alder reactions and Claisen rearrangements
- **Advantages**
  - Abundant, safe, and cheap
  - Ease of product isolation
  - Nature's solvent
- **But how?**
  - Hydrophobic effect
  - Activation/stablization





(a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159-164. (b) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219-225. (c) Kolb, H. C. *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021. (d) Narayan, S. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279. (e) Li, C.-J. *et al. J. Chem. Soc. Rev.* **2006**, *35*, 68-82. (f) Kleiner, C. M. *Chem. Commun.* **2006**, 41, 4315-4317. (g) Vilotijevic, I. et al. Science 2007, 317, 1189-1192. (h) Kóňa, J. *Org. Biomol. Chem.* **2008**, *6*, 359-365.

Organocatalysis of Epoxide Openings

The presence of the organocatalyst **1** had a profound effect on percent yield of all epoxide-opening reactions conducted.

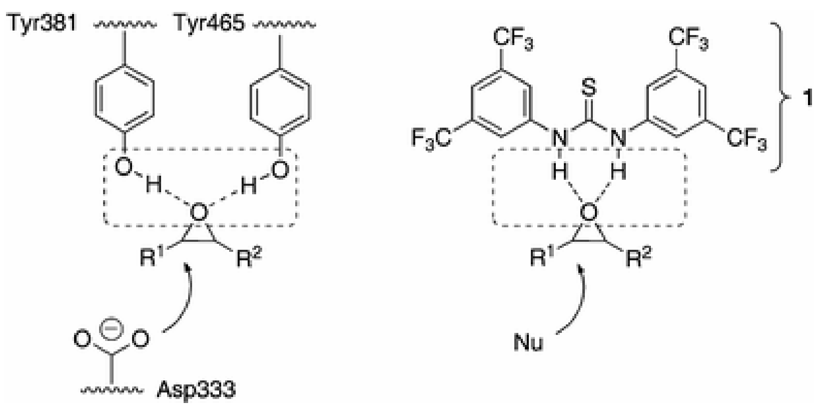
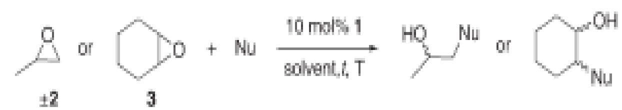


Table 1 Organocatalytic nucleophilic ring opening of oxiranes in water: reactions of ±2 run at rt; of 3 at 40 °C. Nu = nucleophile

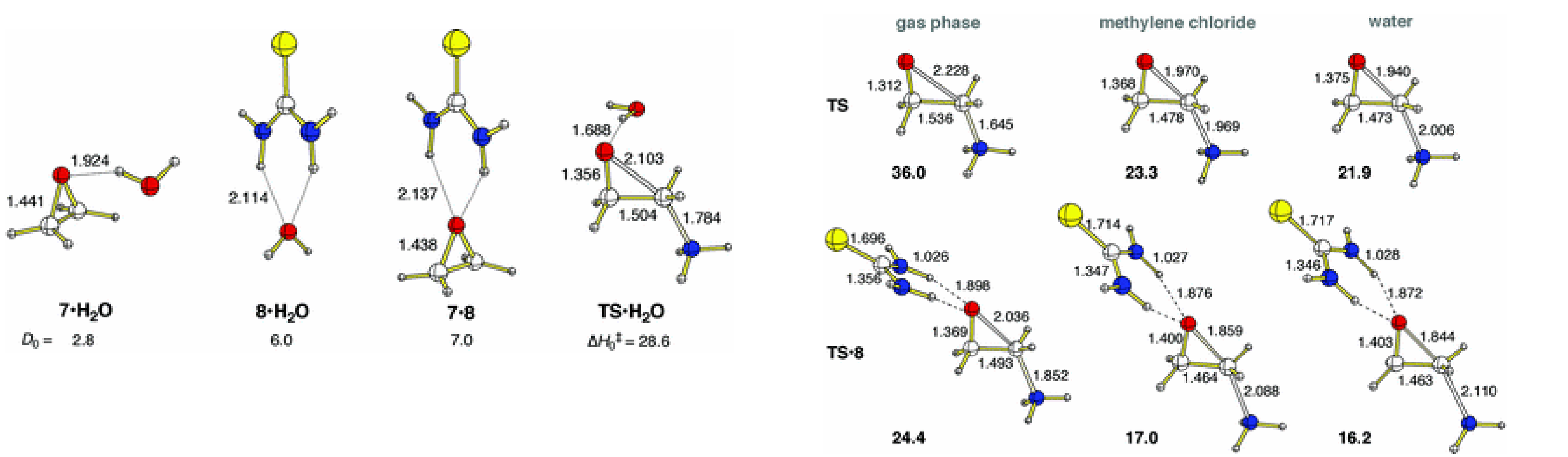


		Yield (%)			
Oxirane	Nu	DCM no cat.	DCM cat.	H_2O no cat.	H_2O cat.
±2	*t*-$BuNH_2$	<0.5	37	29	94
±2	*n*-Bu_2NH	17	70	73	90
±2	*n*-Pr_2NH	36	48	30	91
±2	*i*-Pr_2NH	<1	47	30	64
±2	$(C_3H_5)_2NH$	63	85	78	87
±2	Morpholine	52	62	25	83
±2	Piperidine	45	57	83	87
±2	Pyrrolidine	63	85	82	90
3	*n*-$BuNH_2$	9	27	89	95
3	*t*-$BuNH_2$	<0.5	14	59	68
3	*i*-Pr_2NH	<1	10	11	62
3	$(C_3H_5)_2NH$	4	11	54	60
3	Morpholine	24	37	84	85
3	Piperidine	15	47	72	94
3	Pyrrolidine	63	70	75	97

Kleiner, C. M. *et al*. *Chem. Commun*. **2006**, *41*, 4315-4317.

Organocatalysis of Epoxide Openings (cont.)

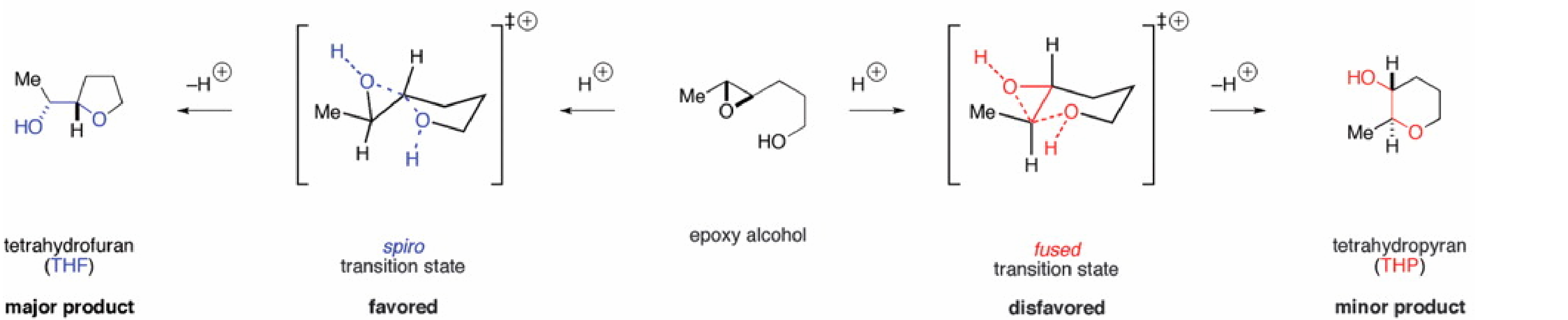
- DFT studies of the opening of ethylene oxide by NH_3 showed that a) increasing solvation power and b) the organocatalyst lower the energy of the transition state.

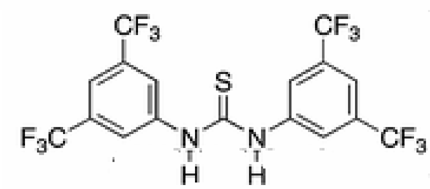


Kleiner, C. M. *et al*. *Chem. Commun*. **2006**, *41*, 4315-4317.

What Next?

- How would the presence of this organocatalyst affect the cyclization of 4,5-epoxyhexan-1-ol?
- Can it effectively catalyze epoxide-opening cascades?





(a) Kleiner, C. M. *Chem. Commun.* **2006**, *41*, 4315-4317. (b) Vilotijevik, I. *et al. Science* **2007**, *317*, 1189-1192.

Conclusions

- The Nakanishi hypothesis for brevetoxin biosynthesis does not agree with Baldwin's rules for ring closure.
- However, several methods (most involving Lewis or Bronsted acids) have overcome these apparent entropic barriers.
- These methods do not mimic biological processes and are sometimes complex and/or inconvenient.
- Epoxide-opening cascades are enhanced in water and perhaps by an organocatalyst. This information can be useful in synthetic and biochemistry.

Acknowledgements

- Prof. Dr. Peter R. Schreiner and AG Prof. Schreiner
- U.S. Department of State and U.S.-German Fulbright Commission

Thank You!