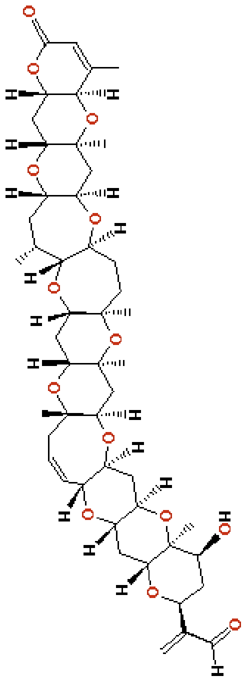


The Effects of Hydrogen Bonding with H_2O on 4,5-epoxyhexan-1-ol Cyclization

Stephanie J. Hirst
July 4, 2008

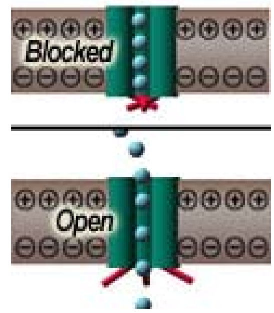
Overview

- Introduction
- Regioselectivity: How to obtain THP
- Organic chemistry in water
- Epoxide openings promoted by water
- Modeling protonated 4,5-epoxyhexan-1-ol cyclization with and without H_2O
- Conclusions

;kj;alkdjf;iaejf;oiajefpoiejafoihdgadsfjadf

Introduction: Brevetoxins

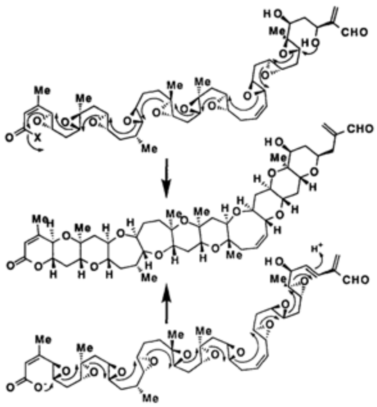
- Ladder-like polyethers synthesized by *Gymnodinium breve*
- Responsible for massive fish kills in the Gulf of Mexico
- Can cause Neurotoxic Shellfish Poisoning (NSP)
- Activate Na^+ channels in nerve cells, causing an influx of Na^+



Voltage-gated ion channel

a) Shimizu, Y. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. I, Chapter 1.;
b) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904-

Nakanishi’s Hypothesis

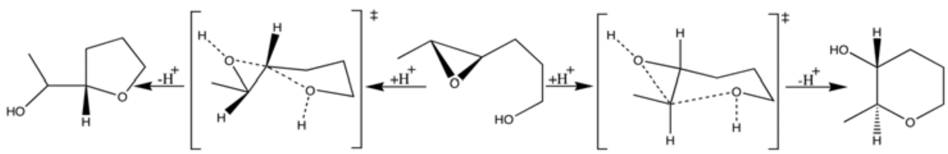


- Nakanishi hypothesized that an epoxide-opening cascade leads to the formation of Brevetoxin B.
- Assumes inversion of configuration at every nucleophilic attack
- Supports formation of polyether with regular *trans-syn* stereochemistry

Nakanishi, K. *Toxicon* **1985**, *23*, 473-479.

Regioselectivity: Baldwin's Rules

- Nakanishi's epoxide-cascade hypothesis requires repeated formation of the tetrahydropyran (THP) over the tetrahydrofuran (THF).
- Baldwin's rules: THF formation generally favored over THP formation
- Dependant on stereochemical requirements of the TS



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Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1978**, *1976*, 734-736.

How to Obtain THP

- Directing groups
  - Nicolau, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc*. **1989**, *111*, 5330-5334.
  - Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339-2342.
- Antibody catalysis
  - Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490-493.
- Lewis acid catalysis
  - Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521-2526.
  - Coxon, J. M.; Thorpe, A. J. *J. Org. Chem*. **1999**, *64*, 5530-5541.
  - Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett*. **1995**, 36, 8063-8066.

Directing Groups

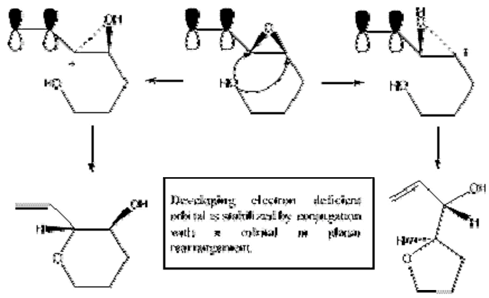
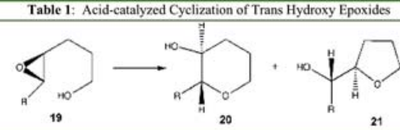
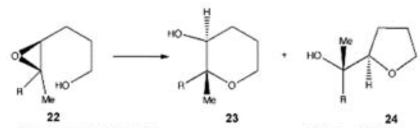


Table 1: Acid-catalyzed Cyclization of Trans Hydroxy Epoxides

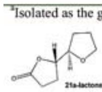


Entry	Substrate	Conditions	Products (ratio)	% Yield
1	**19a**:R= $CH_2CH_2CO_2Me$	0.1 equiv. CSA CH_2Cl_2, -40 to 25°C	20a:21a (0:100)[a]	94
2	**19b**:R= E-CH=$CHCO_2Me$	"	20b:21b (60:40)	96
3	**19c**:R= CH=CH_2	"	20c:21c (100:0)	95
4	**19d**:R= CH=CBr_2	"	20d:21d (100:0)	90



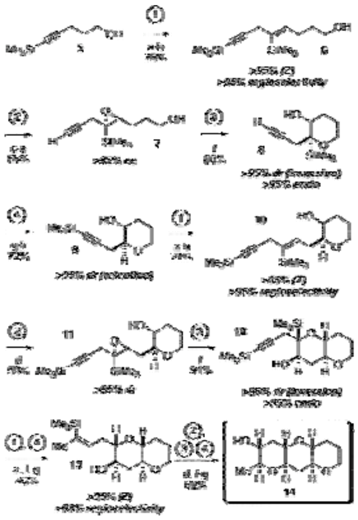
Entry	Substrate	Conditions	Products (ratio)	% Yield
5	**22a**:R= E-CH=$CHCO_2Me$	"	23a:24a (66:34)	92
6	**22b**:R= CH=CH_2	"	23b:24b (100:0)	96

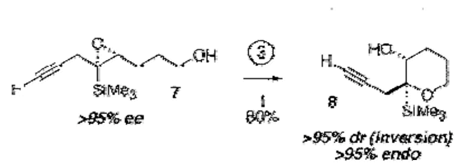
[a]Isolated as the gamma–lactone (**21a-lactone**)



Nicolau, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330-5334.

Directing Groups: Me_3Si

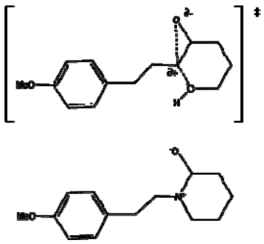


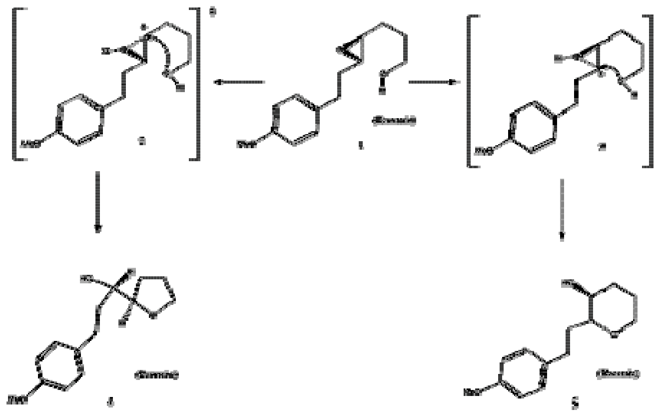


In $Et_2O\text{-}BF_3$, CH_2Cl_2

Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339-2342.

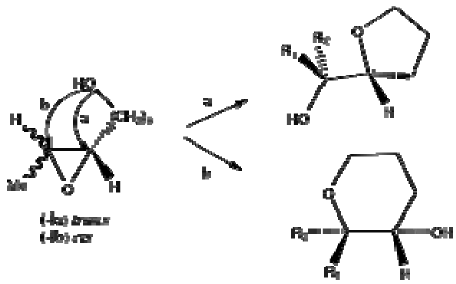
Antibody Catalysis





Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490-493.

Lewis Acid Catalysis: BF_3



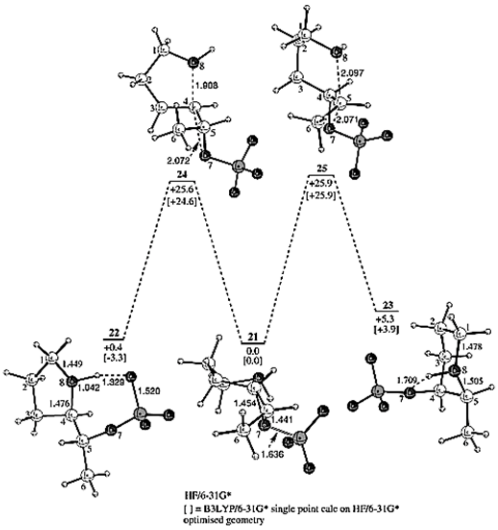
	R_1	R_2	
(5a)	Me	H	(1SR,2'RS)
(5b)	H	Me	(1RS,2'RS)

	R_1	R_2
(6a)	Me	H
(6b)	H	Me

Reaction of **4a** with BF_3-Et_2O in ether gave **5a** (84%) and **6a** (16%). Reaction of **4b** yielded **5b** in 97%.

Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521-2526.

Lewis Acid Catalysis: BF_3 Continued

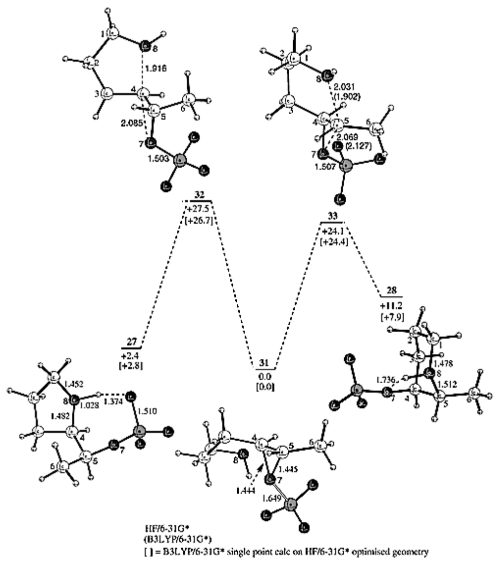


PES for the cyclization of *cis*-4,5-epoxyhexan-1-ol complexed with BF_3

The six-membered TS **25** is 1.3 kcal mol^{-1} higher in energy than **24**.

Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530-5541.

Lewis Acid Catalysis: BF_3 Continued

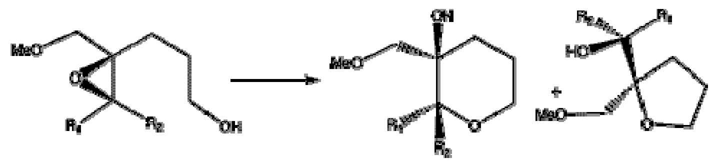


PES for the cyclization of *trans*-4,5-epoxyhexan-1-ol complexed with BF_3

The six-membered TS **33** is 2.3 kcal mol^{-1} *lower* in energy than **32**.

Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530-5541.

Lewis Acid Catalysis: $La(OTf)_3$



1a: R_1=H, R_2=Me
1b: R_1=Me, R_2=H

2a: R_1=H, R_2=Me
2b: R_1=Me, R_2=H

3a: R_1=H, R_2=Me
3b: R_2=Me, R_2=H

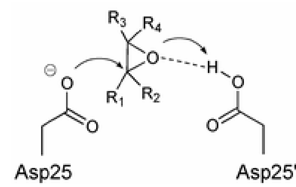
1	Conditions					Cyclic ethers		
	Lewis acid (eq)	H_2O/eq	**Solv.**	**Temp./°C**	**Time**	**Yield/%**		**Ratio**[a)]
1a	$La(OTf)_3$ (1.1)	2.2	CH_2Cl_2	20	2 days	68	**2a : 3a**	82:18
1a	$La(OTf)_3$ (1.1)	3.3	CH_2Cl_2	20	2 days	74	**2a : 3a**	82:18
1b	$La(OTf)_3$ (1.1)	2.2	CH_2Cl_2	20	2 days	96	**2b : 3b**	90:10

[a]Estimated by 400 MHz ^{1}H-NMR

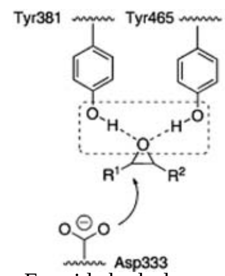
Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett*. **1995**, *36*, 8063-8066.

Organic Chemistry in Water

- Advantages:
  - Abundant, cheap, safe
- Facilitated by:
  - Hydrophobic effect
  - Hydrogen bonding
- The biological solvent
  - HIV-I protease
  - Epoxide hydrolases



Epoxide inhibitor in HIV-I protease active site



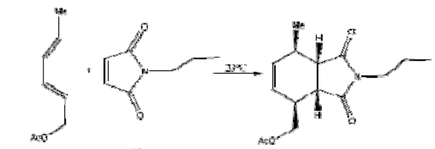
Epoxide hydrolase active site

a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.; b) Prabu-Jeyabalan, M.; Nalivaika, E.; Schiffer, C. A. *J. Mol. Biol*. **2000**, *301*, 1207-1220.; c) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc*. **1985**, *107*, 1082-1083.

Organic Chemistry in Water

- Diels-Alder cycloadditions
  - Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 5275-5279.
- Claisen rearrangements
  - Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219-225.

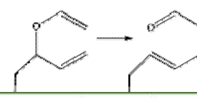
Organic Reactions Promoted in Water



Solvent	Conc. [M]	Time to completion [h]	Yield [%]
Toluene	1	144	79
CH_3CN	1	>144	43[a]
MeOH	1	48	82
Neat	3.69[b]	10	82
H_2O	**3.69[b]**	**8**	**81**

[a] Yield after chromatographic purification. Other yields are of crude products, which were >95% pure by ^{1}H NMR spectroscopy. [b] Calculated from the measured density of a 1:1 mixture of 9 and 10.

Relative Rate Constants for a Claisen Rearrangement of a Soluble Allyl Vinyl Ether Derivative in Various Solvents[a]

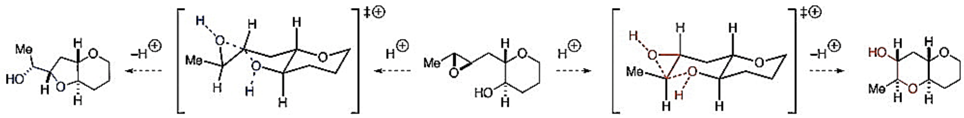


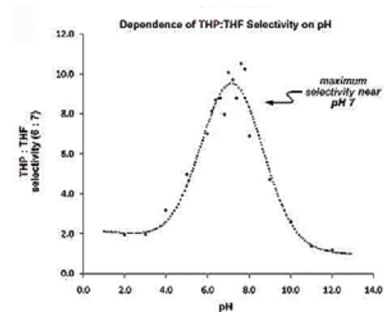
Solvent	k_w (R = Na)	k_{rel} (R = CH_3)	CED[b]	α' [c]
water	214		0.9270	0.2582
1,2,2-trifluoromethanol	31	56	0.2314	0.2902
Methanol	9.4	8.6	0.3461	0.1958
Ethanol		6.1	0.2736	0.1789
Isopropyl alcohol		5.0	0.2250	0.1424
Dimethyl sulfoxide		3.2	0.2850	0.0685
Acetonitrile		3.1	0.2326	0.0662
Acetone		2.1	0.1530	0.0356
Benzene		2.0	0.1414	0.0089
cyclohexane		1.0	0.1134	0.0000

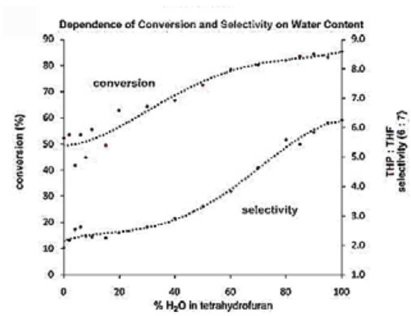
[a] Brandes, E. B.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515 . [b] Cohesive energy density of solvent in units of cm -3 mol-1 calculated by dividing the heat of vaporization of the solvent by the molar volume and by RT(Brower, K. R. *J. Am. Chem. Soc.* **1961**, *83*, 4370). [c] Transfer free energies of chloride ion with the Kirkwood-Onsager dielectric contribution (ε-1)/(2ε+1), and CED contribution subtracted and then divided by 100(RT). This represents the hydrogen bond donor ability in bulk solvents.

a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2005**, *44*, 5275-5279.; b) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219-225.

Epoxide Openings Promoted by Water

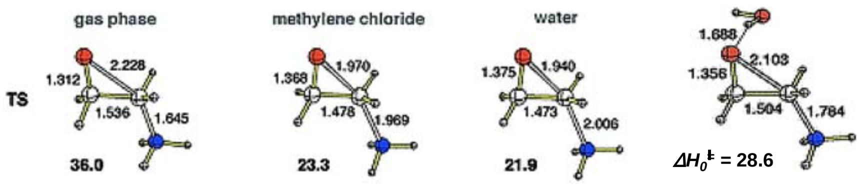






Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189-1192.

Epoxide Openings Promoted by Water Cont.



From experiment, it appeared that epoxide opening reactions were accelerated in water with a highly electron-deficient thiourea catalyst.

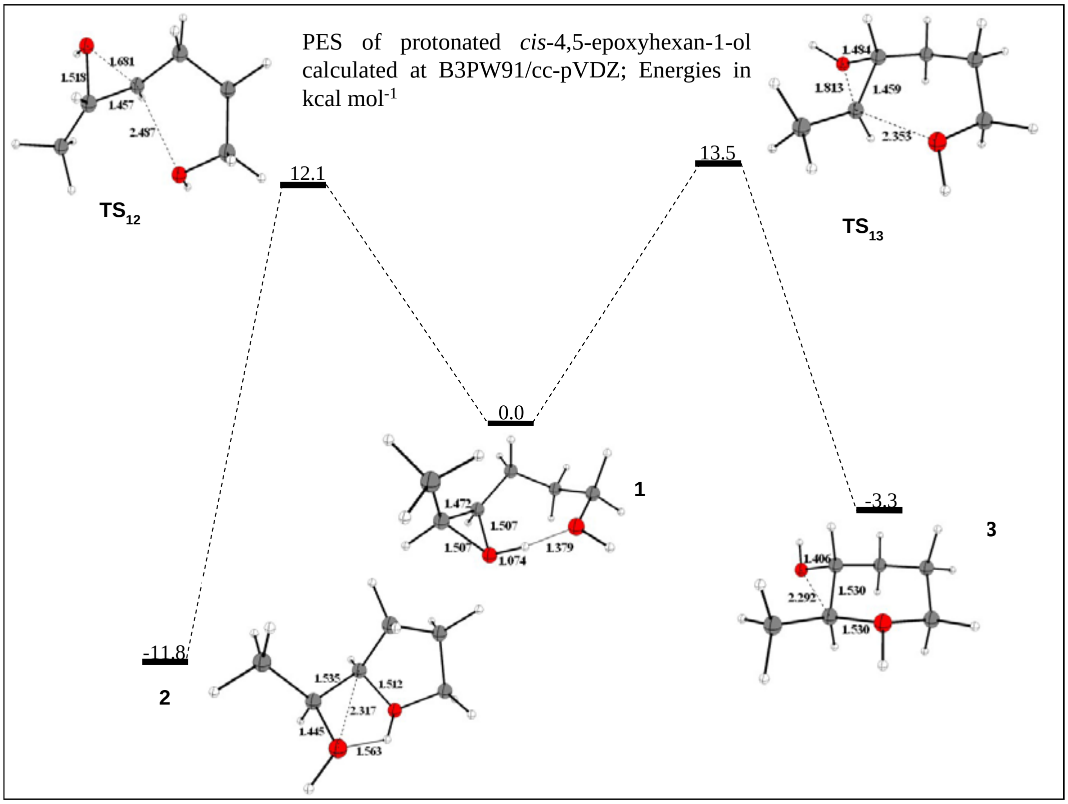
Computed structures and energies evidenced that TS stabilized by hydrogen bonding, which is enhanced in water.

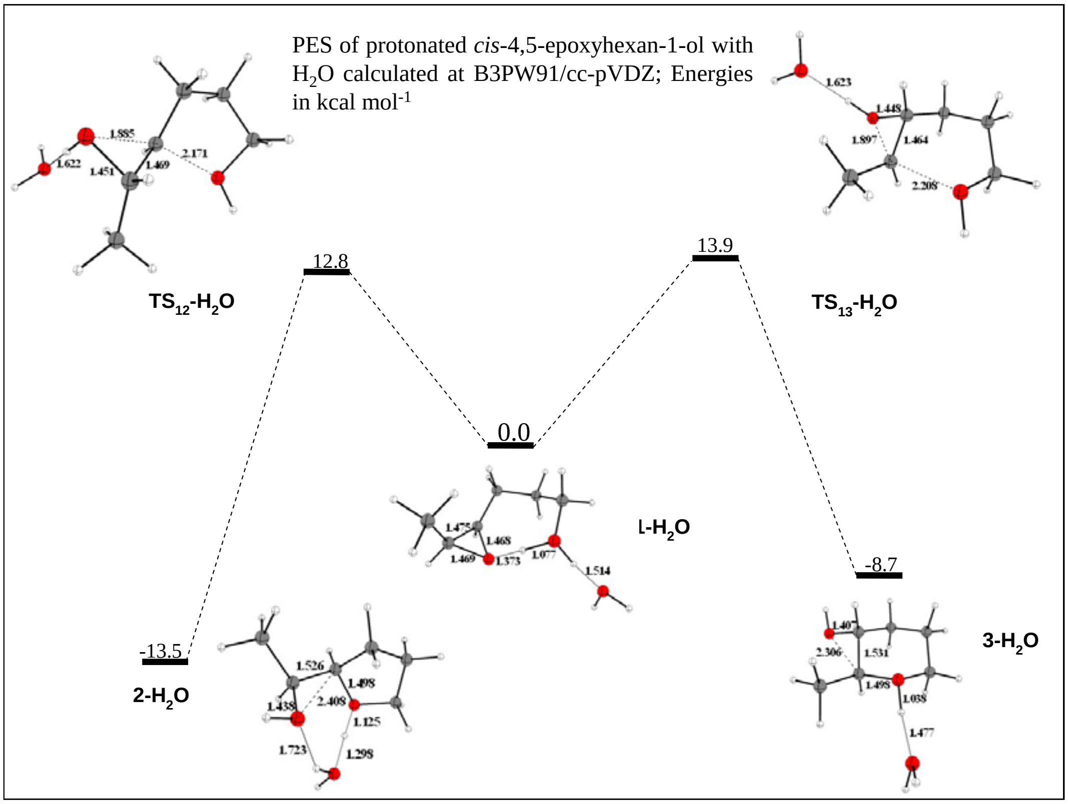
E_a lower for TS-H_2O but not as low as the E_a of TS in bulk water.

Kleiner, C. M.; Schreiner, P. R. *J. Chem. Commun*. **2006**, *41*, 4315-

Protonated 4,5-epoxyhexan-1-ol Cyclization

- Based on findings from previous works, the cycliztion of protonated 4,5-epoxyhexan-1-ol with and without an individual water molecule was modeled using DFT methods.
- PES's for rearrangement of both *cis* and *trans* forms constructed
- Low-energy conformations of reaction minima first determined by searches at AM1 level.
- Minima and TS's further optimized and single points calculated at B3PW91/cc-pVDZ
- All calculations were conducted in the gas phase.

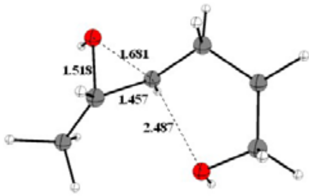

PES of protonated cis-4,5-epoxyhexan-1-ol calculated at B3PW91/cc-pVDZ; Energies in kcal mol-1
TS12
12.1
13.5
TS13
0.0
1
-3.3
3
-11.8
2
1.681
1.518
1.457
2.487
1.484
1.813
1.459
2.353
1.472
1.507
1.507
1.074
1.379
1.406
2.292
1.530
1.530
1.535
1.512
2.317
1.445
1.563



PES of protonated *cis*-4,5-epoxyhexan-1-ol with H_2O calculated at B3PW91/cc-pVDZ; Energies in kcal mol^{-1}
TS_{12}-H_2O
1.885
1.622
1.451
1.469
2.171
12.8
13.9
TS_{13}-H_2O
1.623
1.448
1.897
1.464
2.208
0.0
1-H_2O
1.475
1.468
1.469
1.373
1.077
1.514
-13.5
2-H_2O
1.526
1.498
1.438
2.408
1.125
1.723
1.298
-8.7
3-H_2O
1.407
2.306
1.531
1.498
1.038
1.477

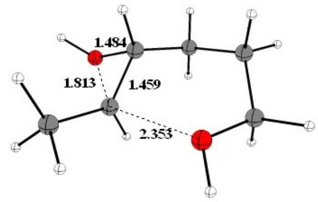
cis-4,5-Epoxyhexan-1-ol Cyclization Transition States

TS_{12}



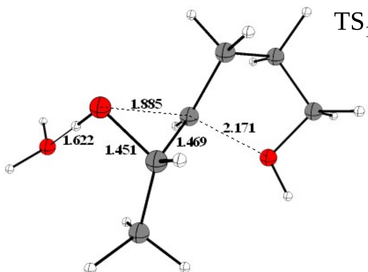
E_a = 12.1 kcal mol^{-1}

TS_{13}



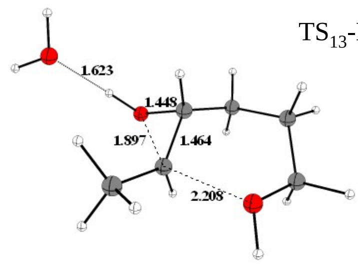
E_a = 13.5 kcal mol^{-1}

TS_{12}-H_2O

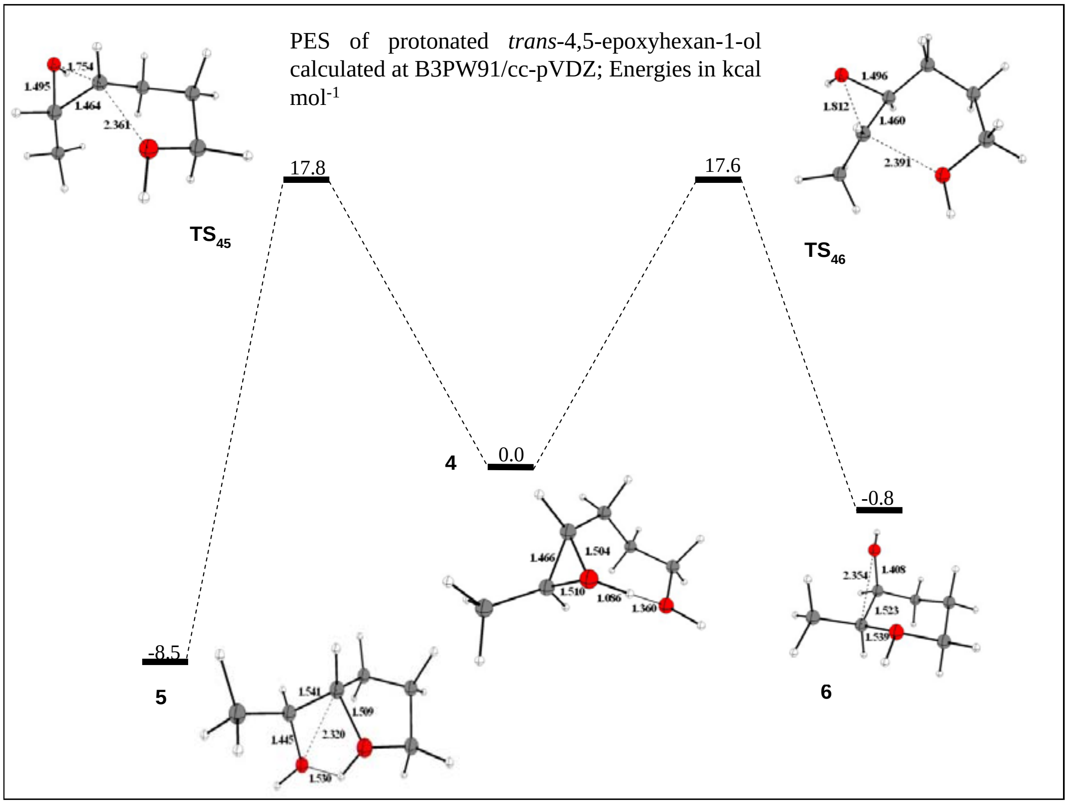


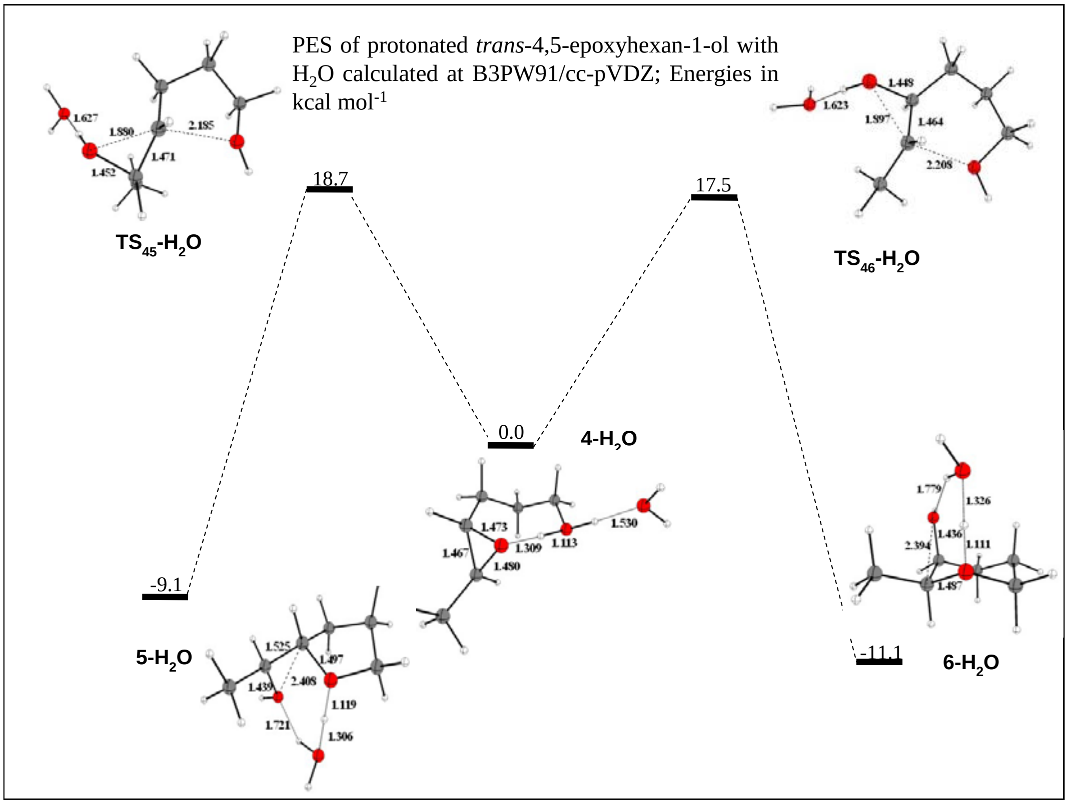
E_a = 12.8 kcal mol^{-1}

TS_{13}-H_2O

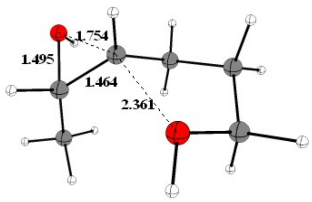


E_a = 13.9 kcal mol^{-1}


PES of protonated trans-4,5-epoxyhexan-1-ol calculated at B3PW91/cc-pVDZ; Energies in kcal mol-1
TS45
17.8
17.6
TS46
4
0.0
-0.8
-8.5
5
6
1.754
1.495
1.464
2.361
1.496
1.812
1.460
2.391
1.466
1.504
1.510
1.066
1.360
2.354
1.408
1.523
1.539
1.541
1.509
1.445
2.320
1.530

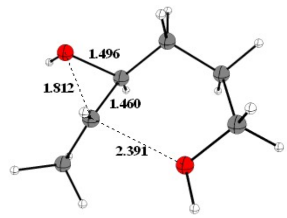

PES of protonated *trans*-4,5-epoxyhexan-1-ol with H_2O calculated at B3PW91/cc-pVDZ; Energies in kcal mol^{-1}
TS_{45}-H_2O
18.7
17.5
TS_{46}-H_2O
0.0
4-H_2O
-9.1
5-H_2O
-11.1
6-H_2O

trans-4,5-Epoxyhexan-1-ol Cyclization Transition States



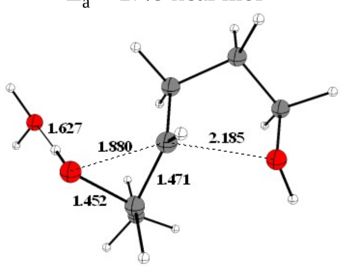
TS_{45}

E_a = 17.8 kcal mol^{-1}



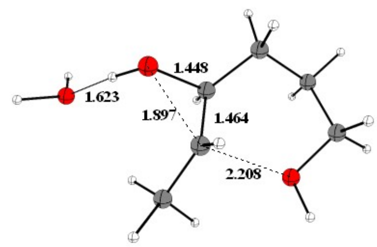
TS_{46}

E_a = 17.6 kcal mol^{-1}



TS_{45}-H_2O

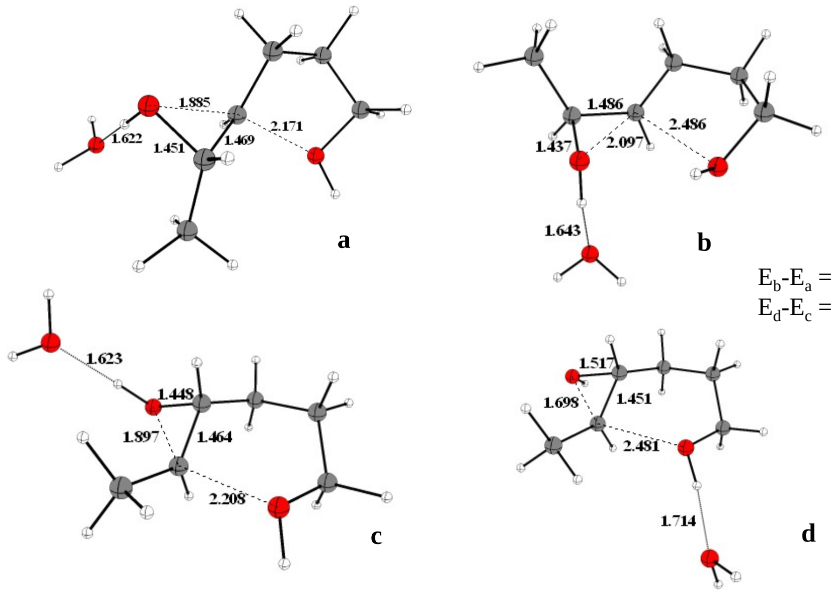
E_a = 18.7 kcal mol^{-1}



TS_{46}-H_2O

E_a = 17.5 kcal mol^{-1}

Positional Preference of H_2O



E_b-E_a = 10.8 kcal mol^{-1}
E_d-E_c = 5.3 kcal mol^{-1}

Conclusions

- Nakanishi's hypothesis for the biosynthesis of brevetoxins contrasts with Baldwin's Rules.
- THP ring selectivity has been accomplished in a number of ways, including the use of directing groups and Lewis acid and antibody catalysts.
- According to experiment, epoxide openings also appear to be promoted by water.
- Theoretically, the presence of a water molecule facilitates THP formation via hydrogen-bond stabilization of the transition state.

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