Epoxide-Opening Cascades Promoted by Water

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Science, **2007**, *317*, 1189.

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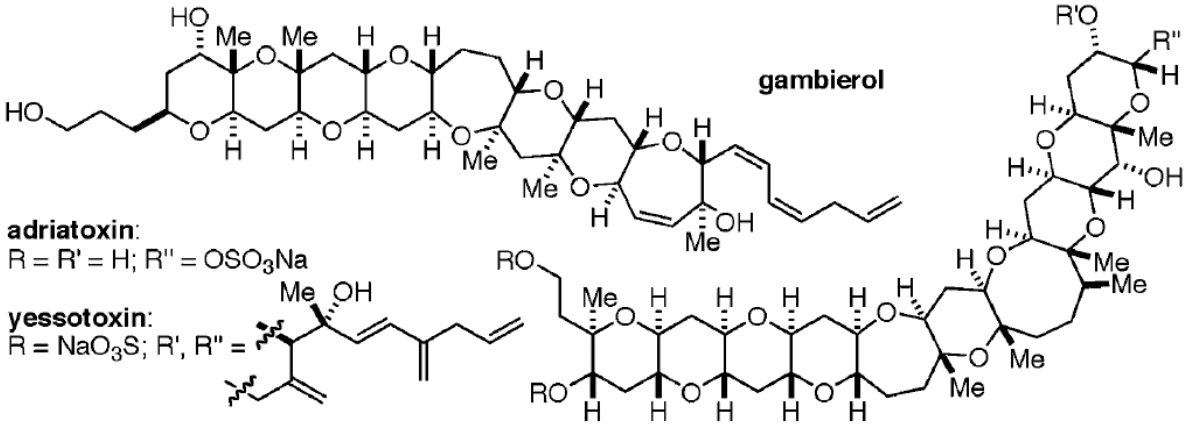
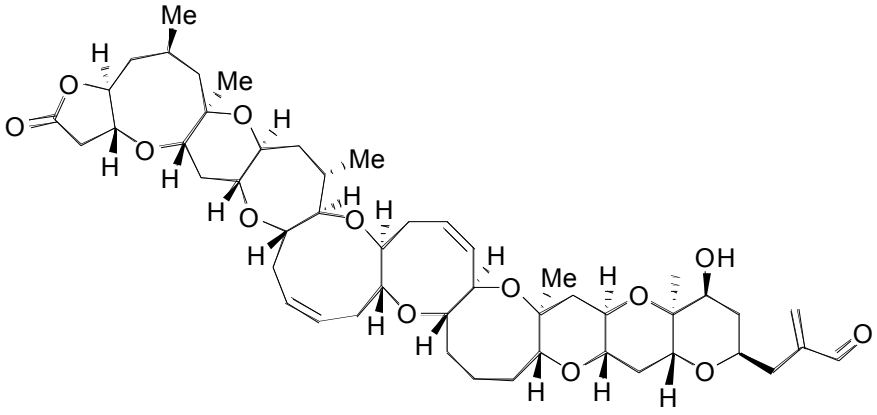
Wipf group current literature meeting

9-15-07

“Ladder” polyether natural products





brevetoxin A

-Potent neurotoxins

-Act by opening a sodium channels

-Toxic for marine organisms (kill fish in ng concentrations)

-Accumulate in shellfish and can poison human consumers

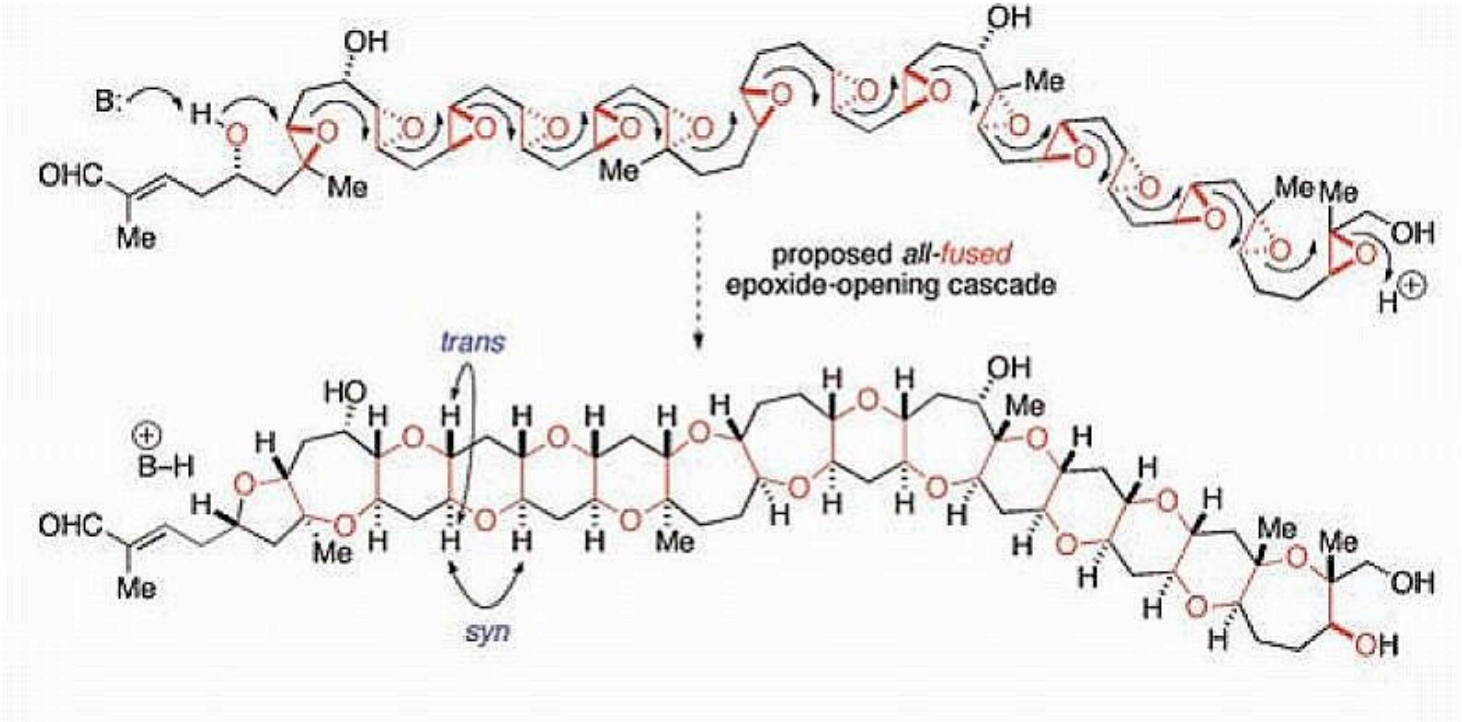
-Synthetically challenging

-Speculative biosynthesis

Nakanishi cascade hypothesis

-Structural pattern and stereochemical regularity imply certain degree of simplicity (repeating O-C-C units, trans stereochemistry across C-C bonds of ring junction)

-Nakanishi: Transformation of polyepoxide into a ladder polyether via cascade of epoxide-opening events



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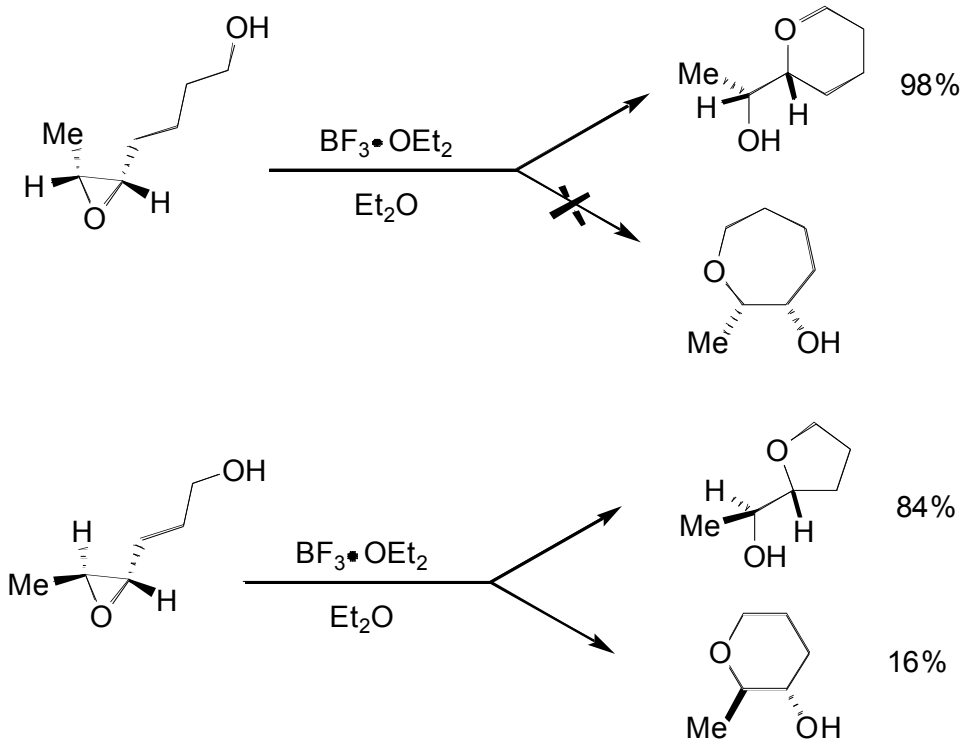
Epoxide opening: Baldwin rules

-Epoxide opening reactions of this type generally favor smaller heterocycle, arising from spiro transition state, over heterocycle arising from fused transition state.

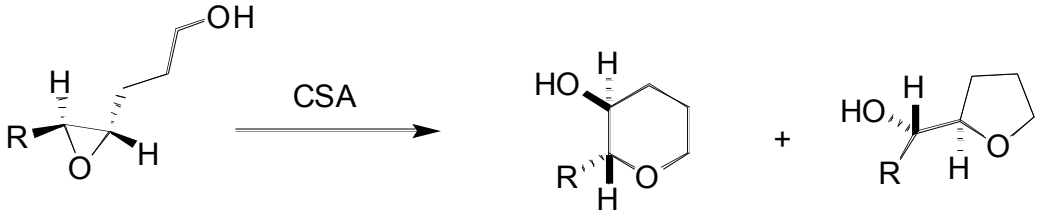


Aus. J. Chem. **1973**, *26*, 2521.

Epoxide opening: endo vs. exo cyclization

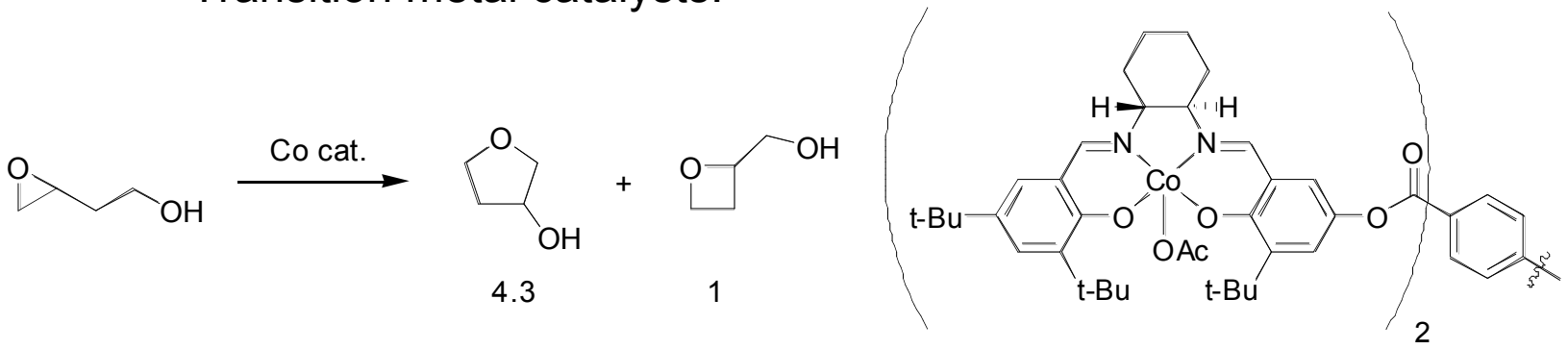
-To obtain desired, but disfavored, “fused” products:

-Directing groups:



R = -$CH_2CH_2CO_2Me$	0	100
-CH_2=CH_2	100	0
TMS (BF_3 OEt_2 as promoter)	95	5

-Transition metal catalysts:



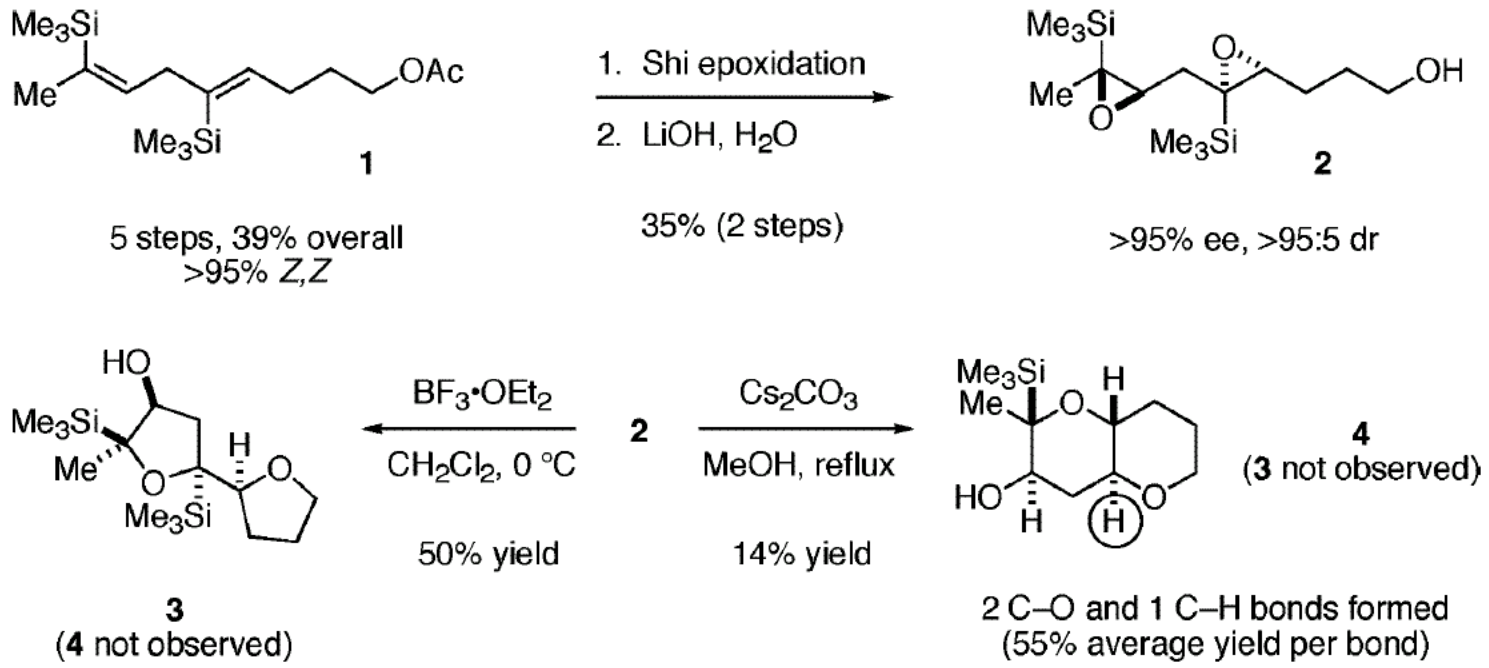
4.3 1 2

Org. Lett, **2003**, *5*, 2339. *JACS* **1989**, *111,* 5330. *ACIE* **1999**, *38*, 2012.

Jamison's previous work: TMS as directing group

-Lewis acid catalyzed reaction leads to THF product, while base catalyzed reaction leads to desired THP product

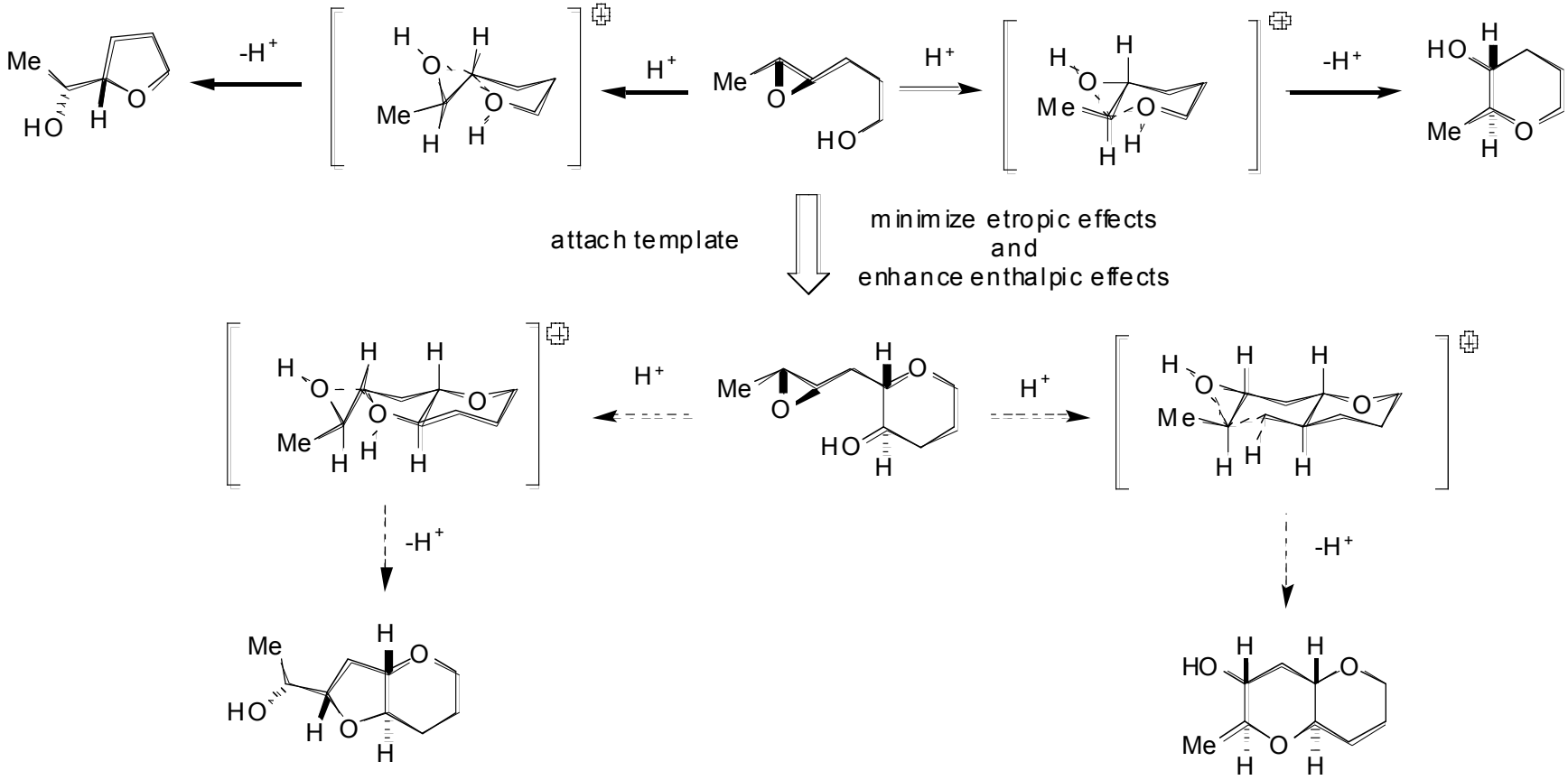
-The loss of one TMS group change the course of investigation towards "disappearing" directing group



Org. Lett, **2003**, *5*, 2339.

Jamison's previous work: template promoted reaction

-*Trans*-bicyclo[4.4.0] decanes are typically less strained than *trans*-bicyclo[4.3.0]nonanes



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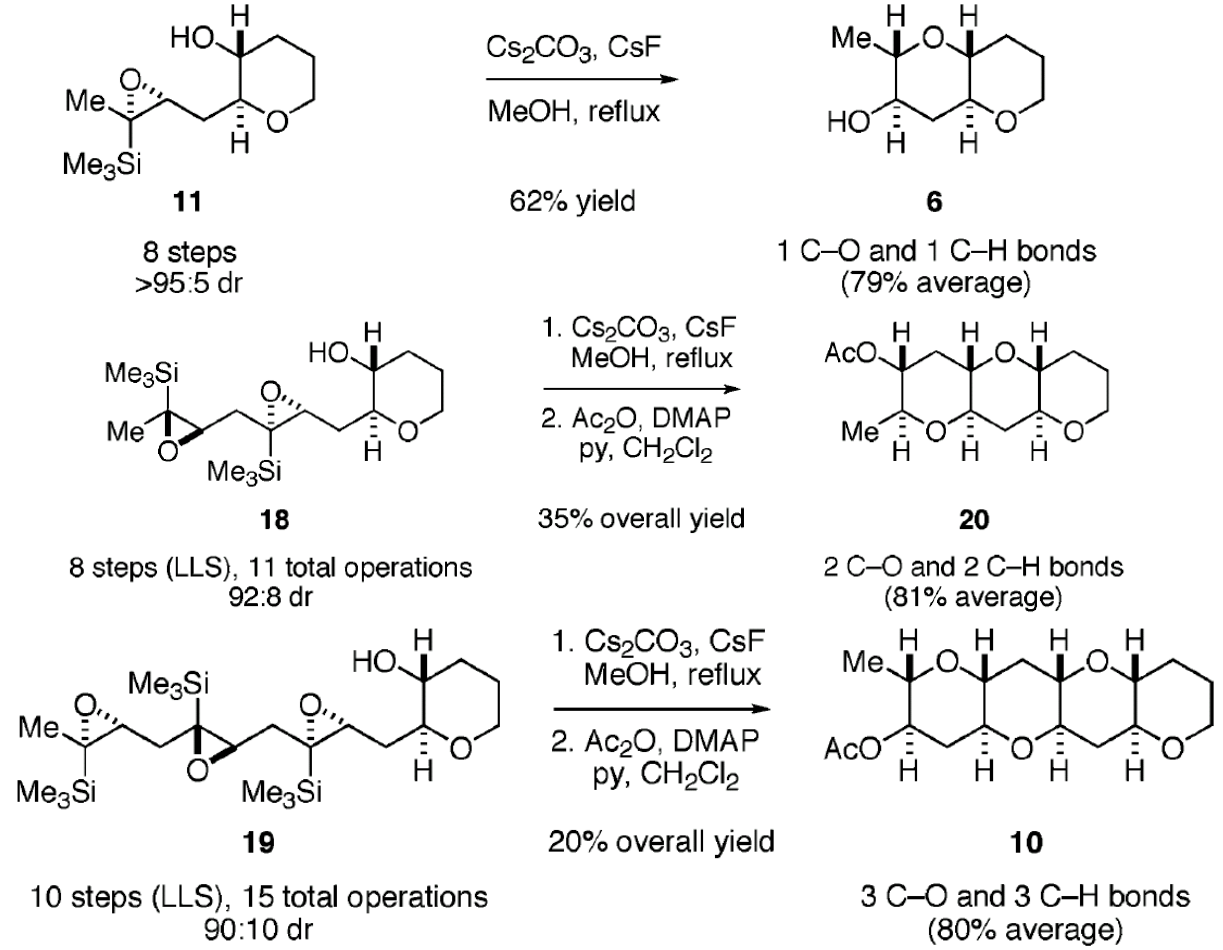
Jamison's previous work: disappearing directing group

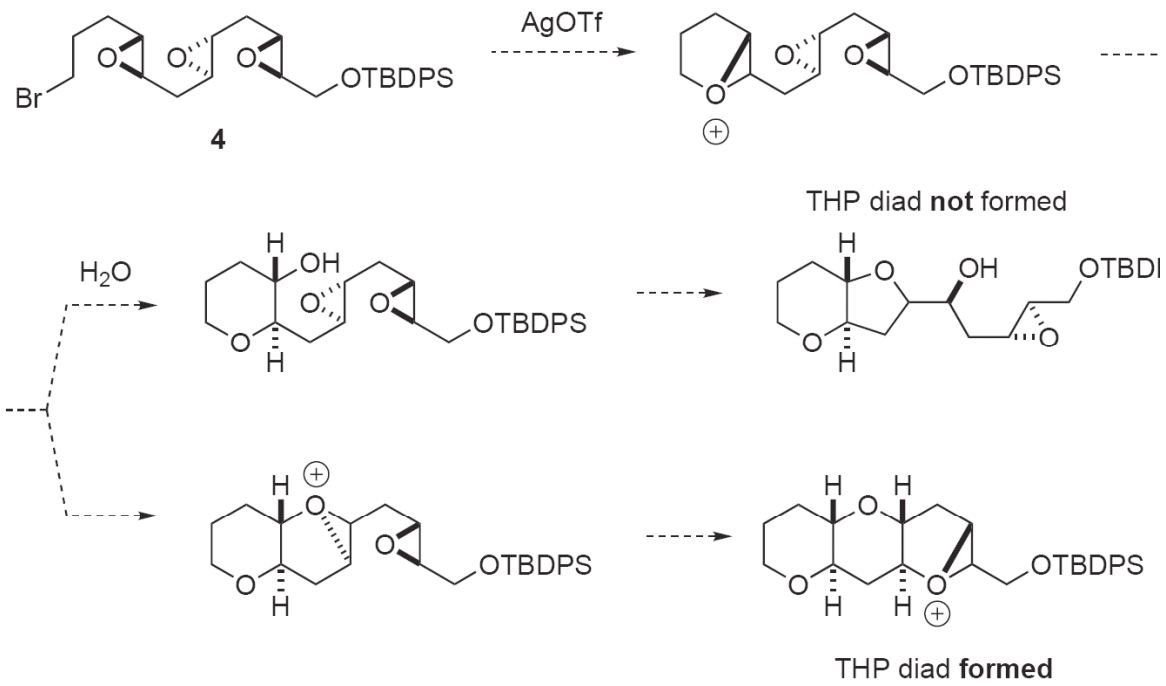
-*Trans*-bicyclo[4.4.0] decanes are typically less strained than *trans*-bicyclo[4.3.0]nonanes



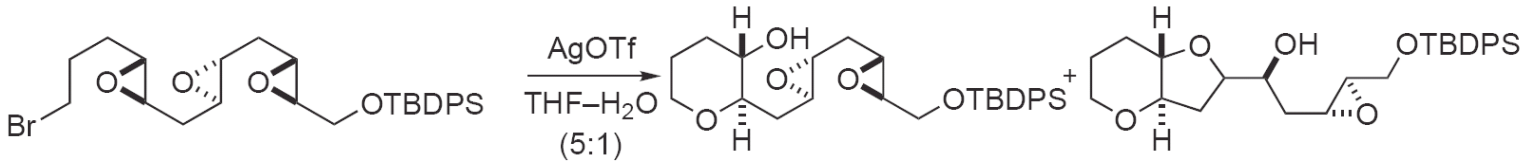
JACS **2006**, *128*, 1056.

Jamison's previous work: directing-group-free epoxide-opening cascades

Jamison's plan

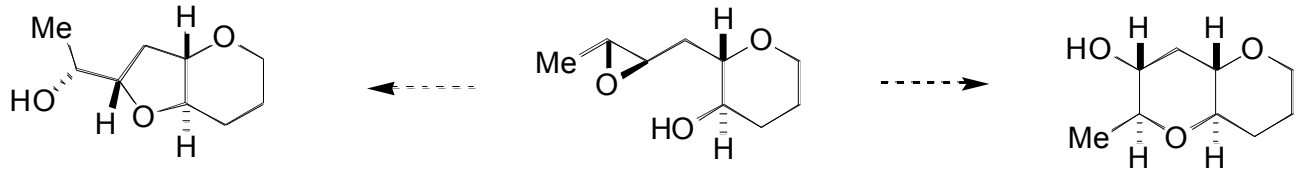


However:



Synlett, **2006**, 2329.

Organic solvents failed-water succeeded



-Wide range of solvents, acids and bases were tested

- Maximum THP:THF selectivity (10:1) obtained at pH near 7, which implied that water might be a suitable solvent for the reaction

-In less polar solvents (CH_2Cl_2, toluene) low conversion is observed and in polar aprotic solvents selectivity is reduced (≤3:1)

-Deionized water as a solvent provides the highest selectivity (11:1)

-Only other acceptable promoters are ethylene glycol (9:1) and methanol (8:1)

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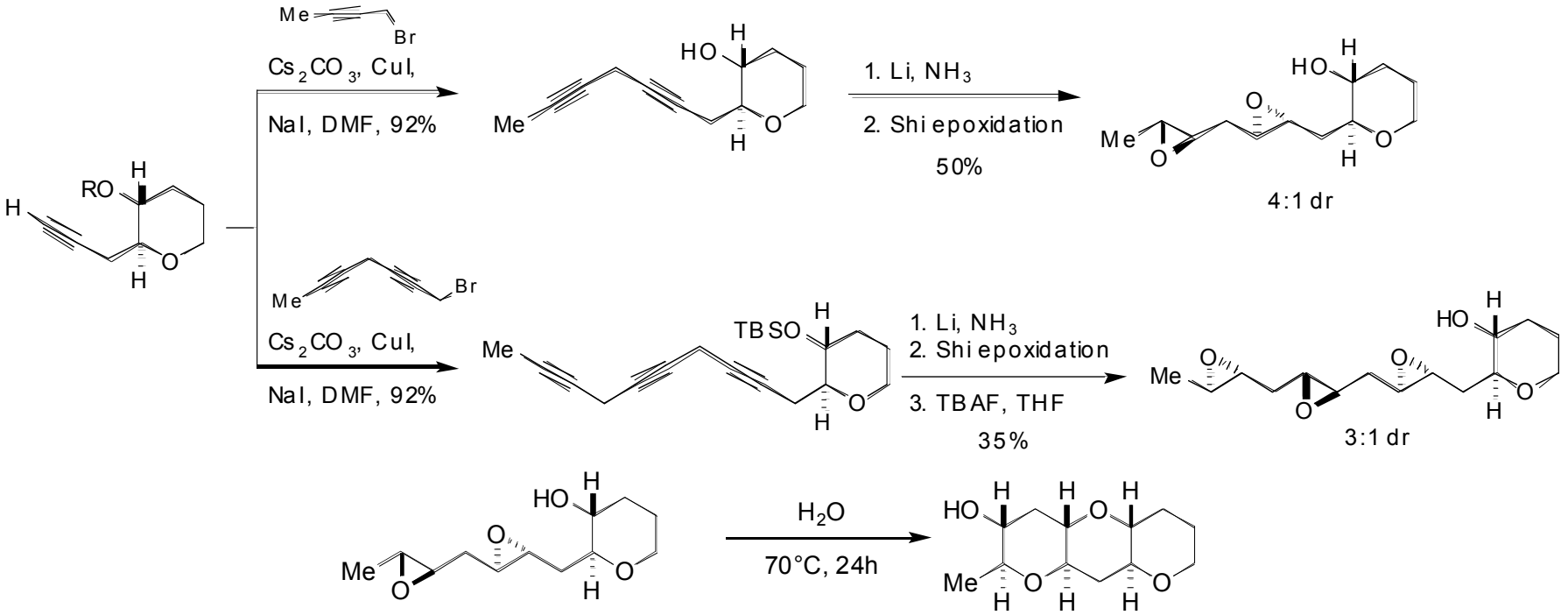
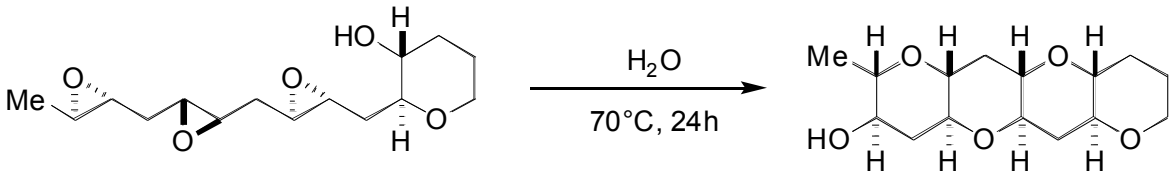
Epoxide-opening cascades



60% isolated yield (87% yield per epoxide opening)



53% isolated yield (89% yield per epoxide opening)

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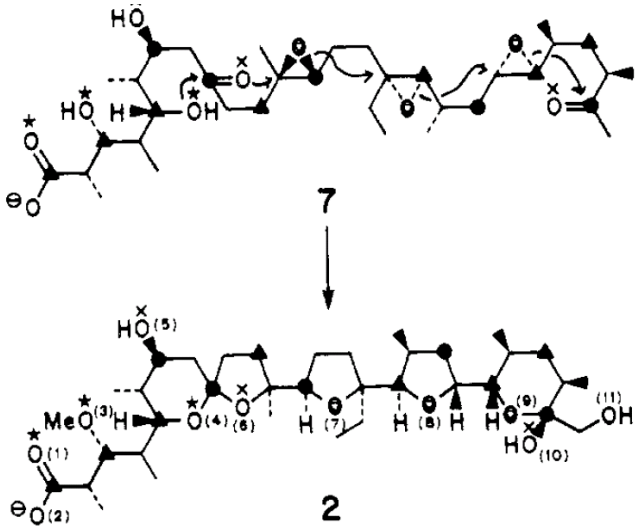
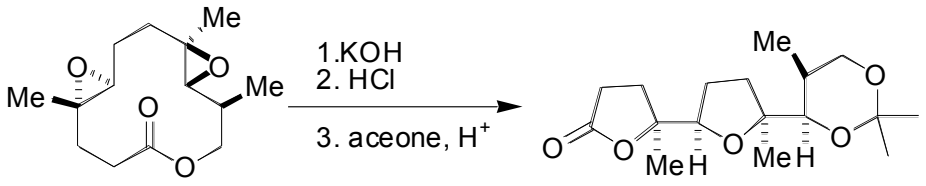
Proof for Nakanishi hypothesis

- Development of all-THF epoxide-opening cascades was taken as a support for Cane-Celmer-Westley hypothesis for biosynthesis of monensin



Proposed biosynthesis

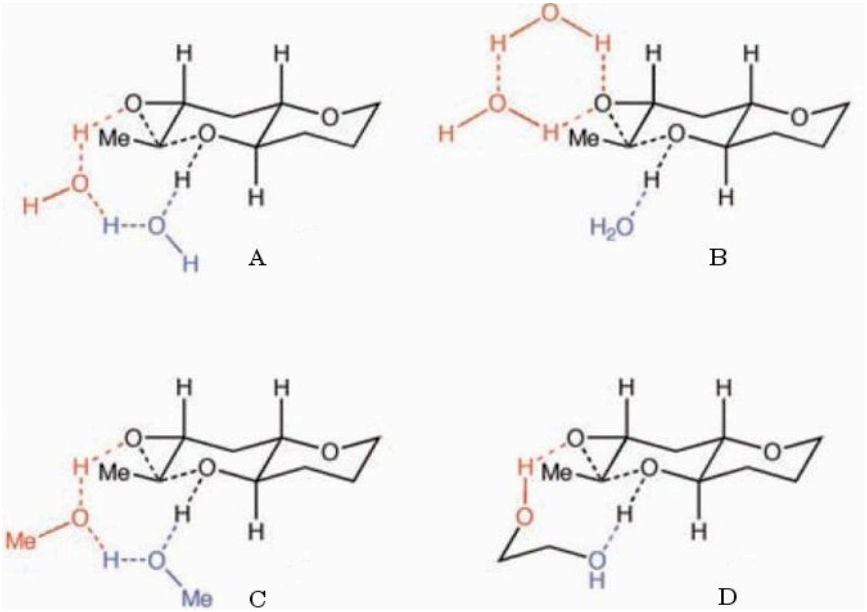


Schreiber's synthesis

- All-THP cascade shown in this paper can be taken as a support for Nakanishi hypothesis for ladder polyether biosynthesis.
- Template THP ring can be used as a surrogate for conformation constraints in enzyme active site
- Water as a promoter may imply hydrogen bond activation in the enzyme surroundings

Science, **2007**, *317*, 1189. *JACS* **1983**, *105*, 3594.

The role of water: assumptions



-Activation of an epoxide and HO-group can be achieved in two ways (A and B).

-Model A accounts for the regioselectivity

- Model B is analogous to epoxide hydrolases TS (monensin biosynthesis)

Authors favor model A due to:

- relative simplicity
- results obtained with methanol and ethylene glycol (C and D)

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Conclusion

- “Templated, water-promoted, THP-selective epoxide-opening cascades provide a straightforward means for efficient and rapid assembly of ladder polyethers.”

- This work is a support for Nakanishi hypothesis for biosynthesis of ladder polyether natural products.