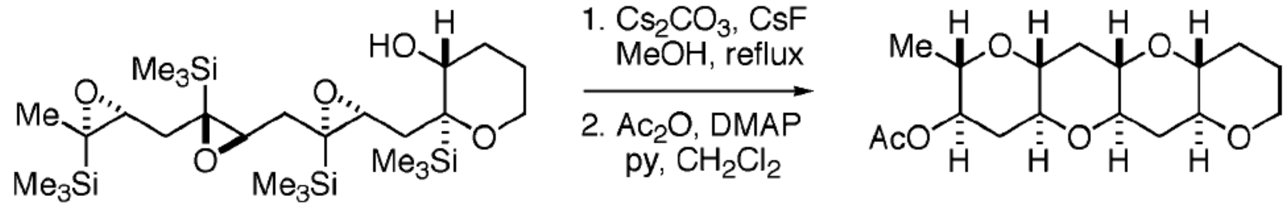
Ladder Polyether Synthesis via Epoxide-Opening Cascades Using a Disappearing Directing Group



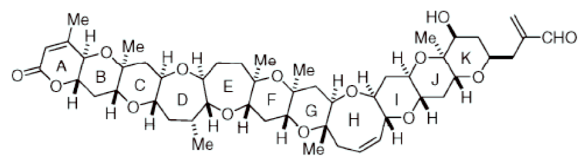
Graham L. Simpson, Timothy P. Heffron, Estibaliz Merino,
and Timothy F. Jamison

J. AM. CHEM. SOC. **2006**, *128*, 1056

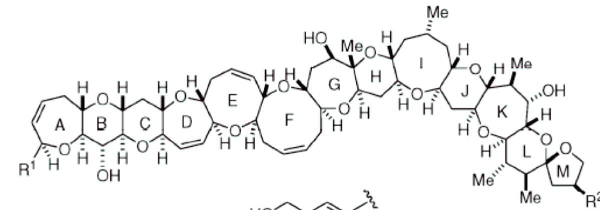
Current Literature
Chenbo Wang @ Wipf Group
March 4, 2006

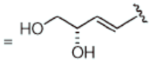
Red Tide And Ladder Polyethers

- Red tide
  - Vast blooms of unicellular algae
  - Associated with the production of ladder ethers
- Ladder ethers
  - Nerotoxins
  - *Trans*-fused polycyclic ethers

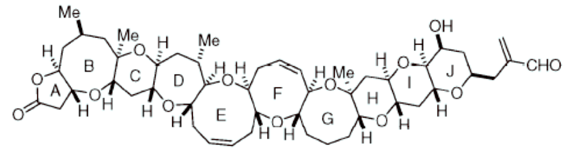


Brevetoxin-B (**1**)

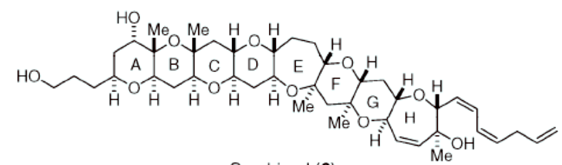


Ciguatoxin (**4**): R^1 =  , R^2 = OH

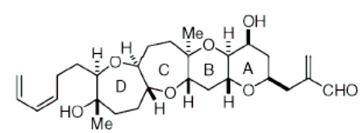
CTX3C (**5**): $R^1 = R^2 = H$



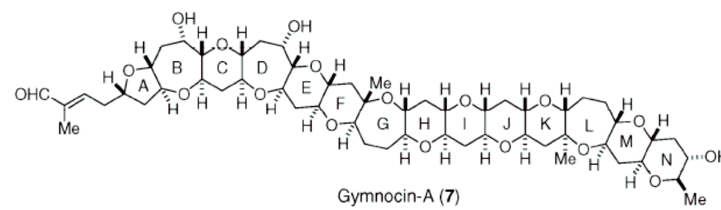
Brevetoxin-A (**2**)



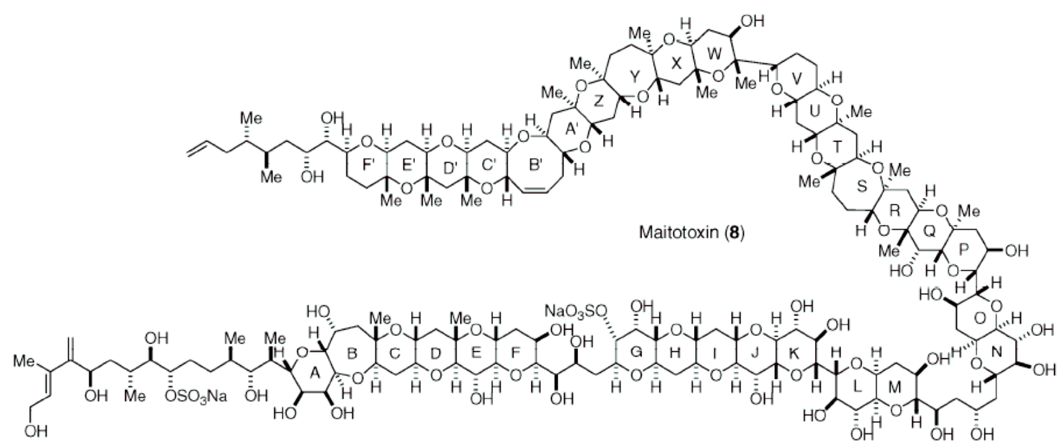
Gambierol (**6**)



Hemibrevetoxin-B (**3**)



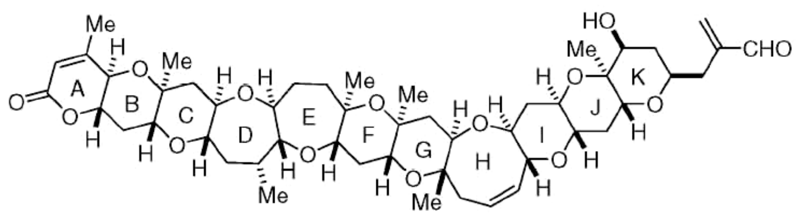
Gymnocin-A (**7**)



Maitotoxin (**8**)

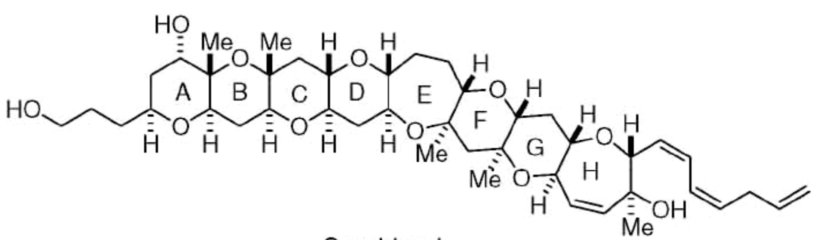
Nakada, T *Chem. Rev.* **2005,** *105,* 4314

Iterative Synthesis of Ladder Polyethers



Brevetoxin-B

123 steps (83 linear steps)

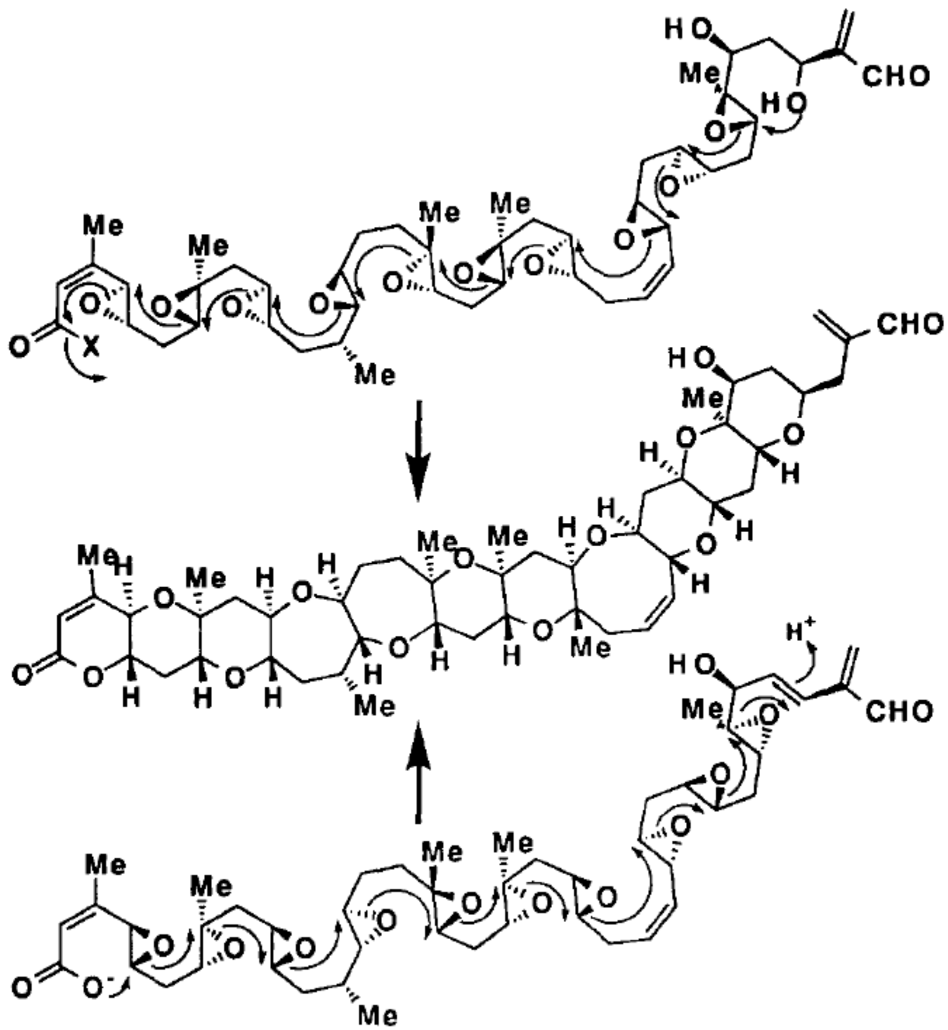


Gambierol

102 steps (66 linear steps)

Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFredds, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodrakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227.
Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.

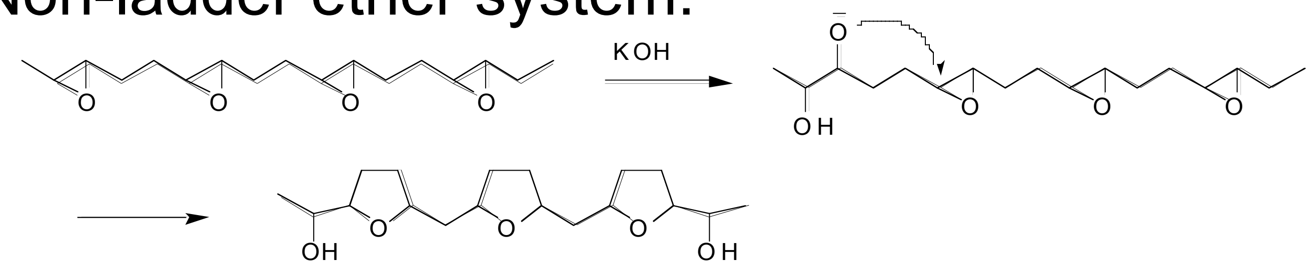
Proposed Biomimetic Synthesis Pathways of Ladder Polyethers



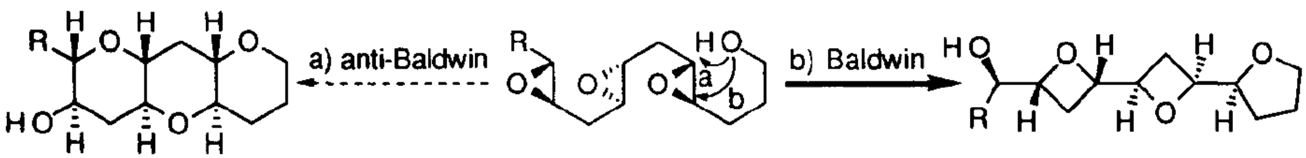
Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron* **1997**, *53*, 12425.

Epoxide-opening Cascades

Non-ladder ether system:



Ladder ether system: Endo *vs.* Exo

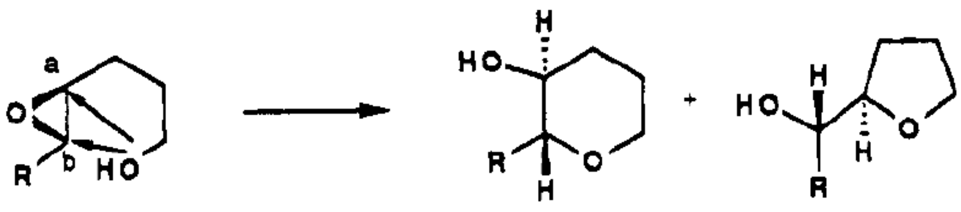


1 2

Scbultz, W. J.; EtterAlphonsus, M. C.; Pock, V.; Smith, S. *J. Am. Chem. Soc.* **1980**, *102*,7981
Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron* **1997**, *53*, 12425.

Directed *Endo*-Attack

Table I. Acid-Catalyzed Cyclization of Trans Hydroxy Epoxides



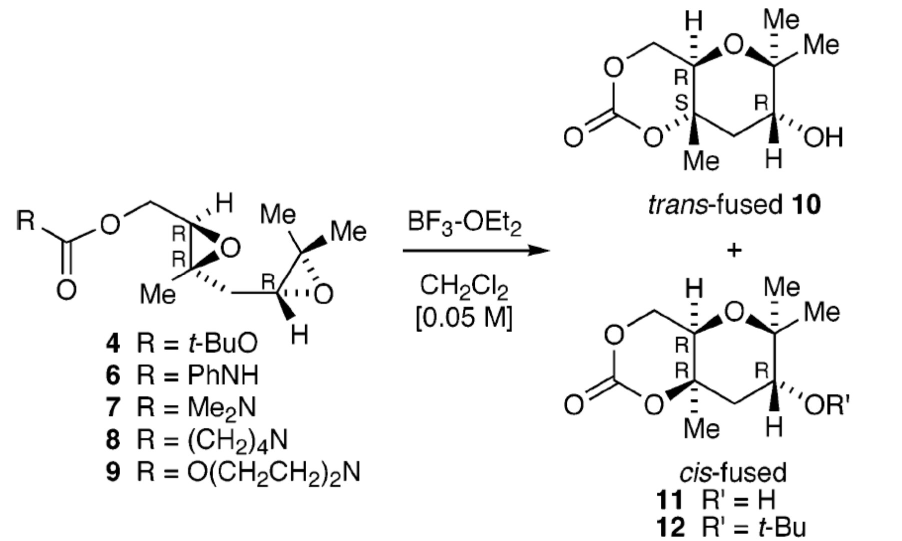
19 20 21

a: 6-*endo* 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)	96
3	**19c**:R=CH=CH_2	"	**20c**:**21c**(100:0)	95
4	**19d**:R=CH=CBr_2	"	**20d**:**21d**(100:0)	90

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

Directed *Endo*-Attack (cont.)



entry	substrate[a]	T (°C)	time (min)	products (isolated yield)
1	**4**	−40	10	**10** (<4%), **11** (56%), **12** (12%)
2	**4**	+40	2	**11** (65%), **12** (4%)
3	**4** (0.5 M)	−40	10	**11** (42%), **12** (10%)
4	**6**	−40	10[b]	**11** (70%)
5	**7**	−40	10[b]	**10** (35%), **11** (10%)
6	**7**	+20	2[b]	**10** (55%), **11** (21%)
7	**8**	−40	10[b]	**10** (32%), **11** (8.5%)
8	**9**	−40	10[b]	**10** (34%), **11** (13%)

[a] Concentration was 0.05 M of substrate in CH_2Cl_2, unless otherwise stated. [b] The reaction mixture was subsequently stirred with aq $NaHCO_3$ for 2 h to hydrolyze iminium ions.

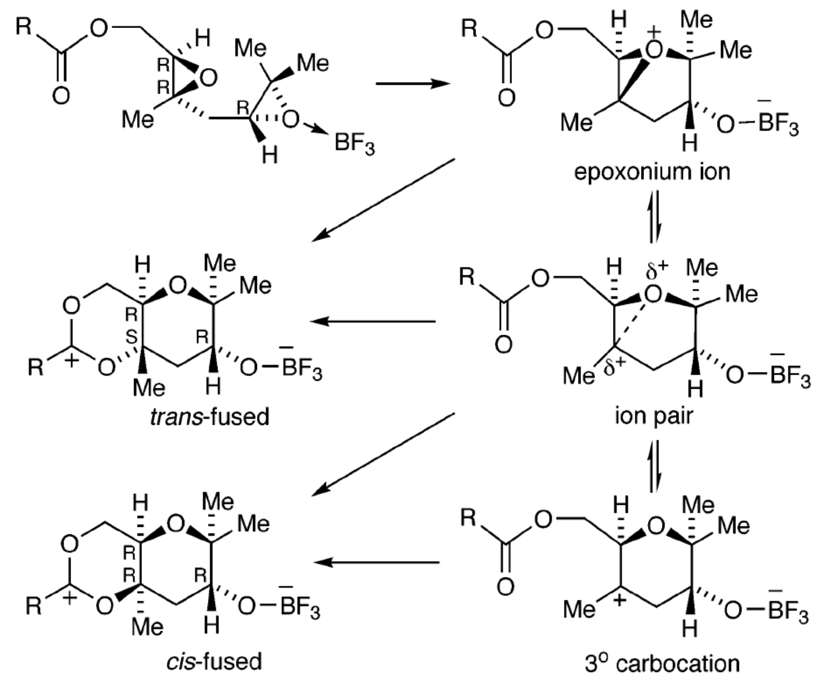
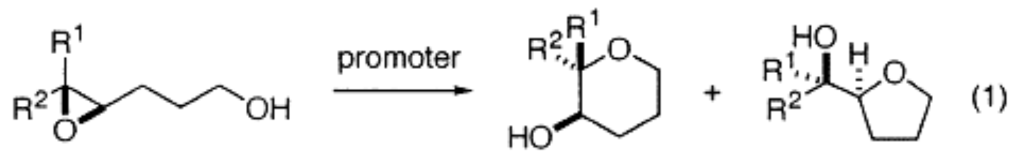


Figure 2. Possible mechanism for oxacyclization process.

Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*,

Si Directed *Endo*-Attack

Table 1. Directing Group Effects in Hydroxyepoxide Cyclizations (Eq 1)



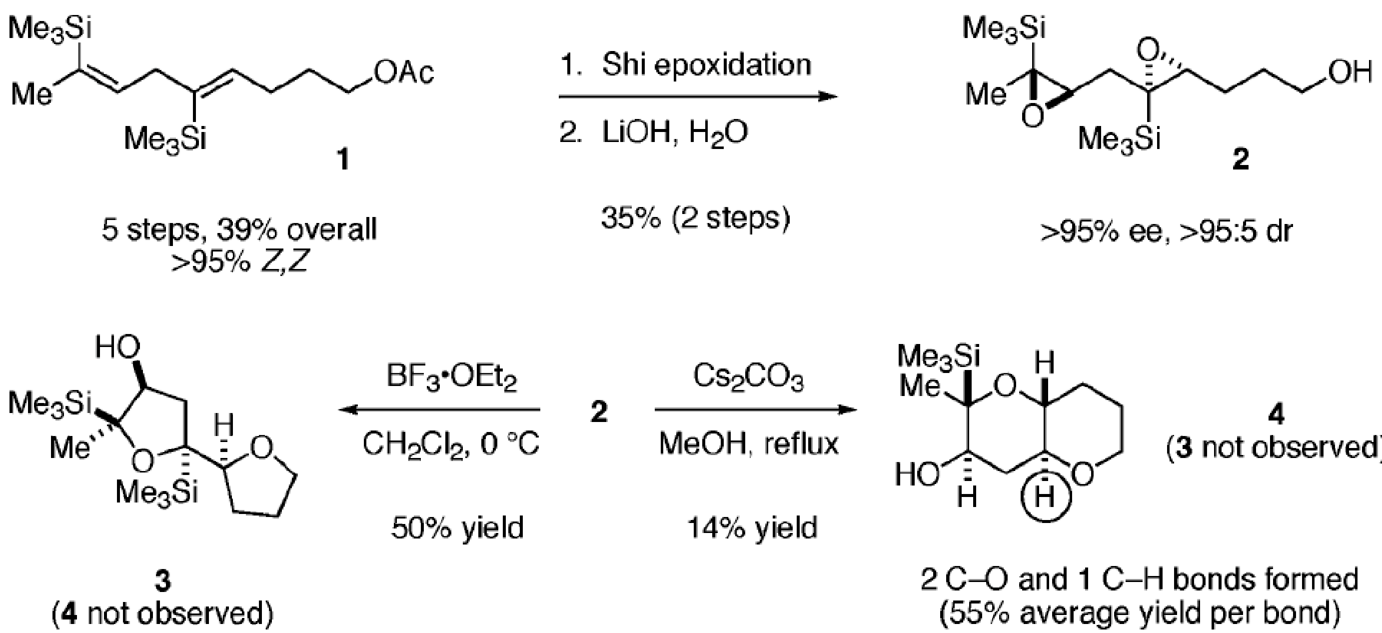
entry	epoxide	R^1	R^2	promoter	**2:3**
1[a]	**1a**	H	Me	$Et_2O{\cdot}BF_3$	14:86
2[a]	**1b**	Me	H	$Et_2O{\cdot}BF_3$	≤3:97
3[b]	**1c**	H	$CH{=}CH_2$	(+)-CSA	>98:2
4[b]	**1d**	$CH{=}CH_2$	H	(+)-CSA	44:56
5[c]	**1e**	$SiMe_3$	Me	$Et_2O{\cdot}BF_3$	>95:5
6[c,d]	**1f**	Me	$SiMe_3$	$Et_2O{\cdot}BF_3$	see text

[a] See Coxon, ref 4. [b] See Nicolaou, refs 10a,b. [c] See Supporting Information. [d] Major product: $HO(CH_2)_4C(O)CH_3$.

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

Si Directed Epoxide-Opening Cascade

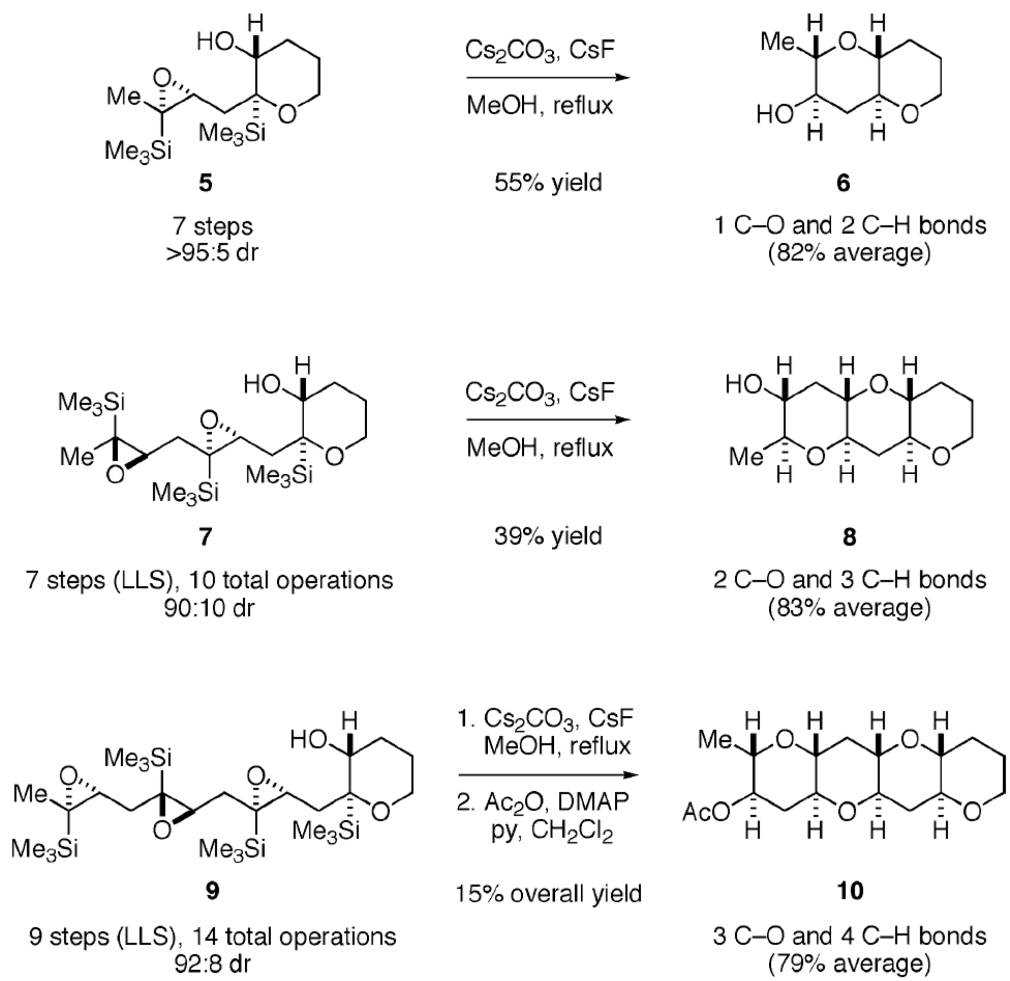
Scheme 1



Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. AM. CHEM. SOC.* **2006**, *128*, 1056

Si Directed Epoxide-Opening Cascade With Preformed THP

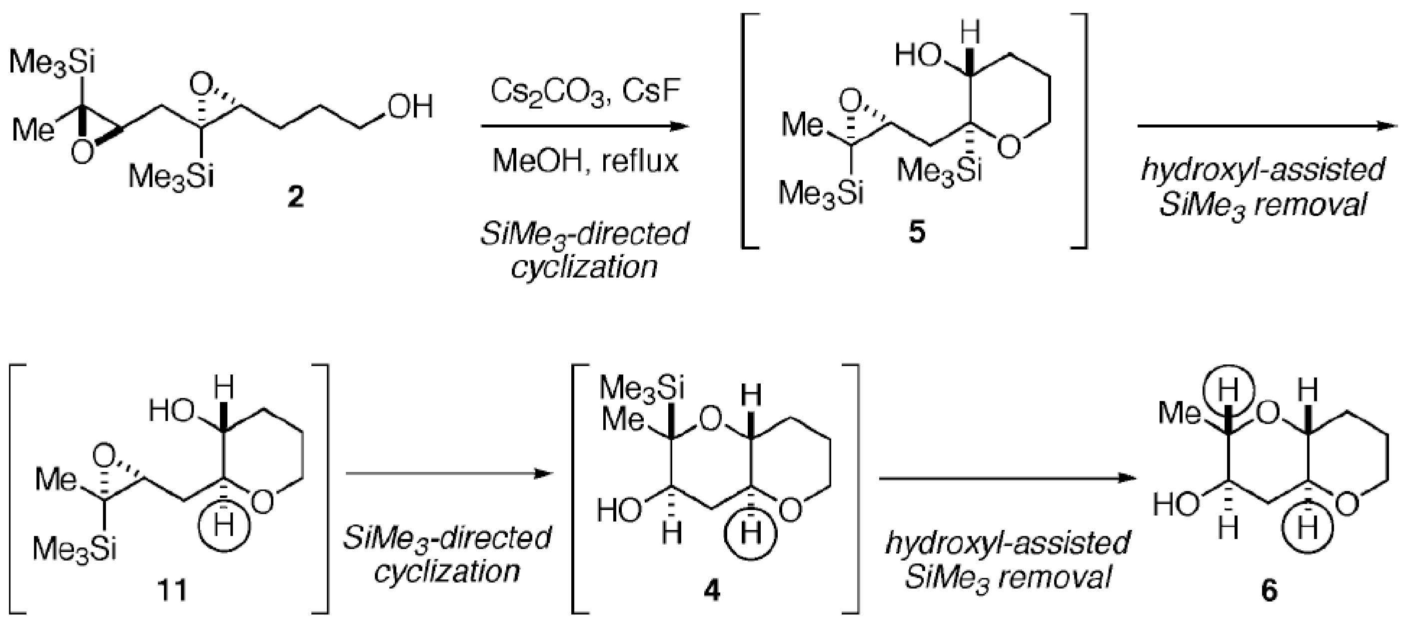
Scheme 2



Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. AM. CHEM. SOC.* **2006**, *128*, 1056

Proposed Mechanism

Scheme 3



Conclusion

- Conclusion:
  - A cascade of epoxide-opening together with *in situ* removal of the directing groups was achieved.
- Future Work:
  - Longer cascade
  - Other ring sizes
  - Ladder ethers with methyl group at the ring conjunction