Ladder polyether - what's next?

Yusuke Sasano

<Outline>

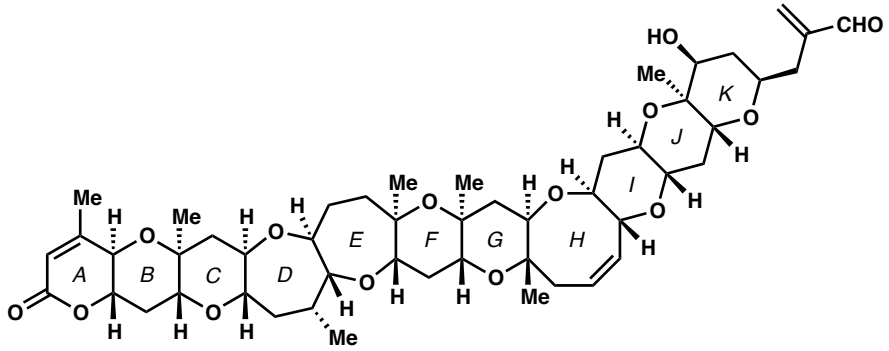
1. Introduction
   (General Information about Ladder Polyethers)
2. Landmark Total Synthesis
   2-1. First Total Synthesis of CTX3C (Hirama et al.)
   (2-2. First Total Synthesis of Gambierol (Sasaki et al.) see: *Nat. Prod. Rep.* **2008**, *25*, 401)
3. Recent Updates on Strategies
   3-1. Use of Co Complexes in Total Synthesis of Ciguatoxin (Isobe et al.)
   3-2. HWE/cyclodehydration/reductive etherification Convergent Coupling Strategy in Total Synthesis of Brevetoxin A (Crimmins et al.)
4. Next Targets: Maitotoxin, Yessotoxin, and Adriatoxin
   4-1. Structure and Summary of Synthetic Studies
   4-2. Most Recent Update on Synthetic Study of Maitotoxin
5. Next Strategy: Epoxide-Opening Cascades

1. Introduction

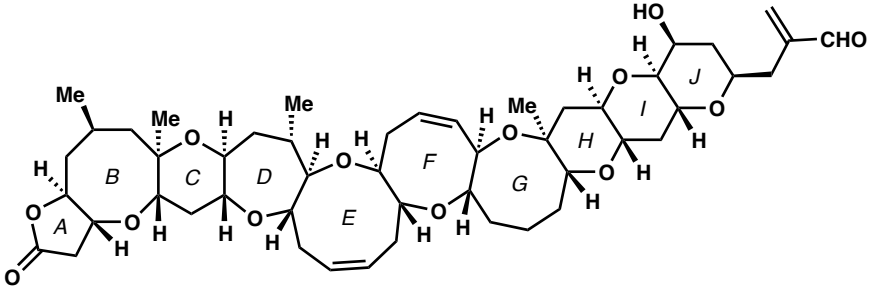
See: reviews, Nicolaou, et al. *ACIE* **2008**, *47*, 7182; Inoue *Chem. Rev.* **2005**, *105*, 4379; Nakata *Chem. Rev.* **2005**, *105*, 4314.

- First isolation and structural elucidation: brevetoxin B by Nakanishi et al. in 1981
- Representative members: see figures
- Structural feature:
  extensive *trans*-fused polycyclic ether framework, consisting of five to nine-membered cyclic ethers
- Biological activities: diverse and potent activities (despite the common structural motif)
  e.g. brevetoxins and ciguatoxins = neurotoxicity by binding voltage-sensitive sodium channels (VSSC)
  gambieric acids = antifungal activity with only moderate toxicity against mammals
- Total synthesis: all examples shown in figures (except hemibrevetoxin, the most simple one)
  Recent updates (after 2008):
  Crimmins, M. T. et al. *OL* **2009**, *11*, 489 (brevetoxin A)
  Isobe, M. et al. *ACIE* **2009**, *48*, 2941 (ciguatoxin)
  Kadota, I. et al. *OL* **2009**, *11*, 2531 (brevenal)
  Mori, Y. et al. *OL* **2009**, *11*, 4382 (gambierol)
  Rainier, J. D. et al. *JACS* **2011**, *133*, 3208 (brevenal)
  Sasaki, M., Fuwa, H. et al. *JACS* **2012**, *134*, 11984 (gambieric acid A)

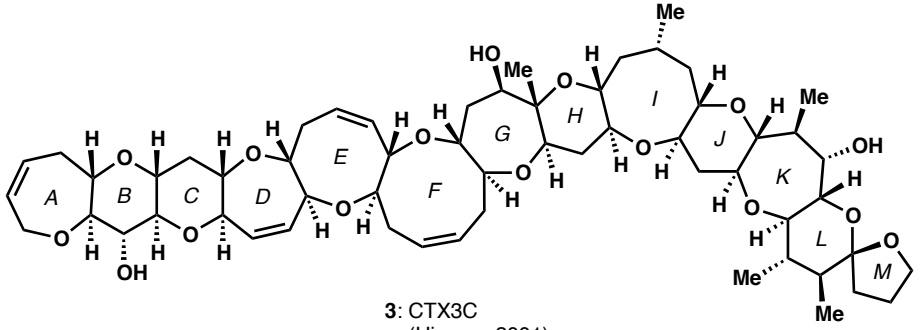
Structures of Ladder Polyether (Repoted Total Synthesis)



1: brevetoxin B
(Nicolaou, 1995)
(Nakata, 2004)
(Kadota, 2005)



2: brevetoxin A
(Nicolaou, 1998)
(Crimmins, 2009)



3: CTX3C
(Hirama, 2001)

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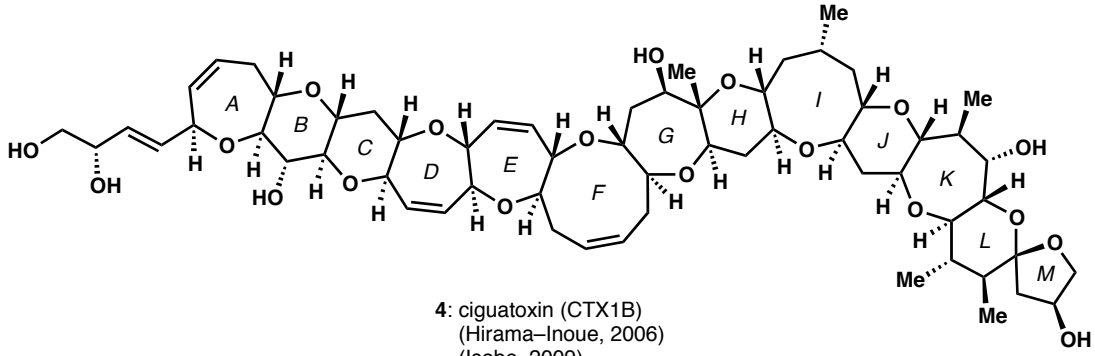
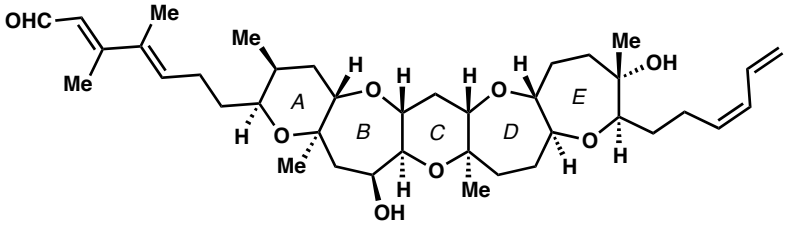
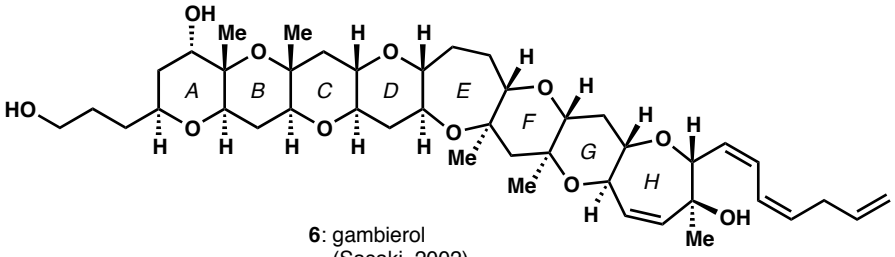


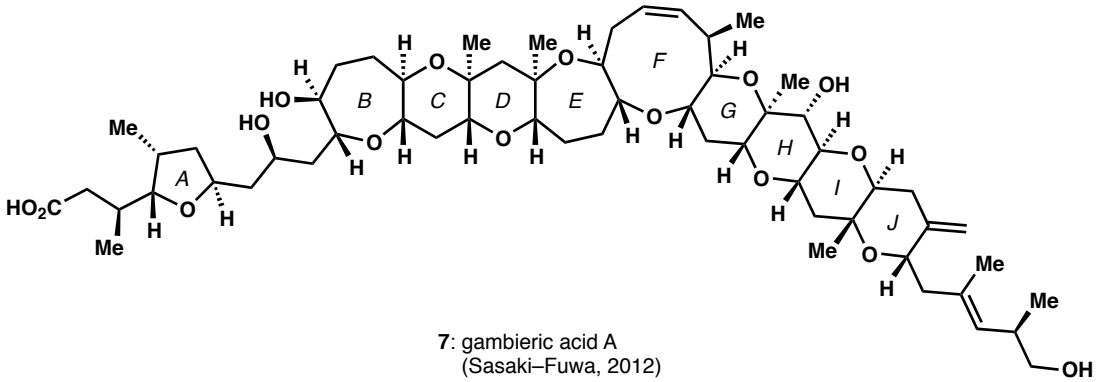
4: ciguatoxin (CTX1B)
(Hirama–Inoue, 2006)
(Isobe, 2009)



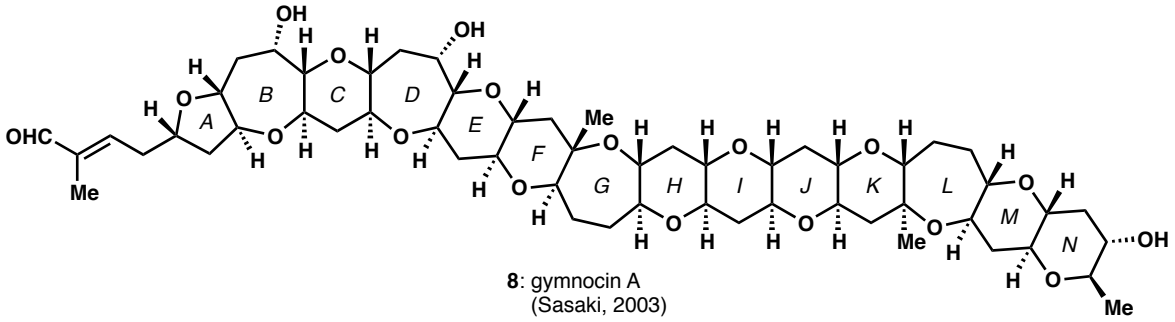
5: brevenal
(Sasaki, 2006)
(Kadota, 2009)
(Rainier, 2011)



6: gambierol
(Sasaki, 2002)
(Yamamoto–Kadota, 2003)
(Rainier, 2005)
(Mori, 2009)



7: gambieric acid A
(Sasaki–Fuwa, 2012)



8: gymnocin A
(Sasaki, 2003)

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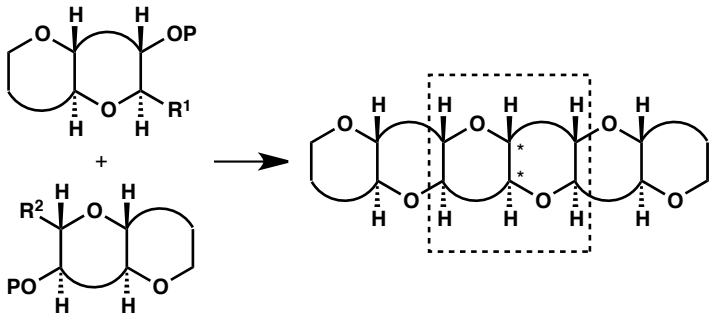
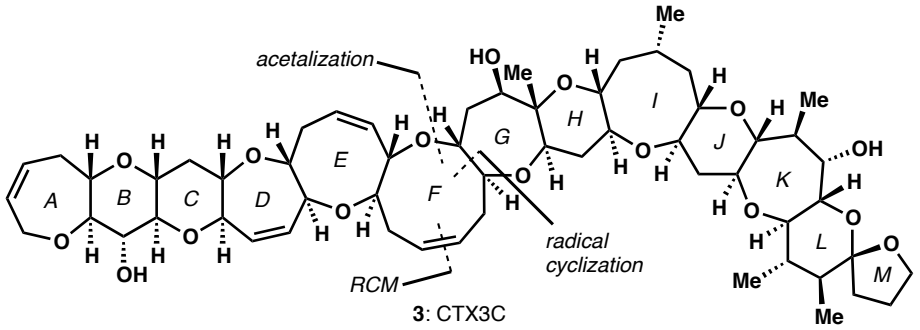
2. Landmark Total Synthesis

2-1. First Total Synthesis of CTX3C (Hirama et al.)

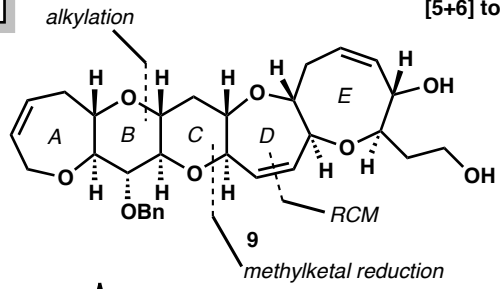
Ref. *Science* **2001**, *294*, 1904; *J. Synth. Org. Chem., Jpn.* **2003**, *61*, 562 (Account)

Key: **[X+2+X] approach** for convergent synthesis



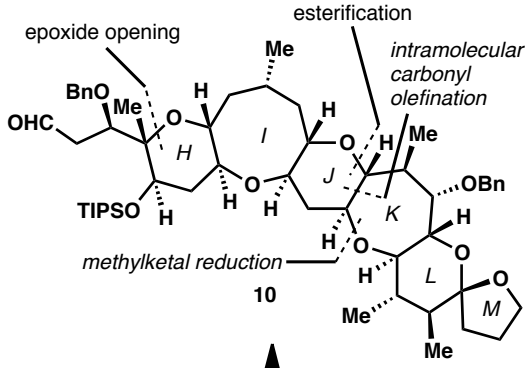


3: CTX3C



9

[5+6] to [13]



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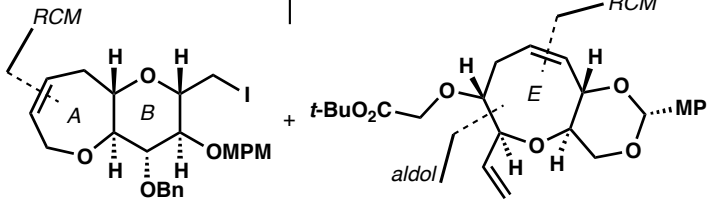
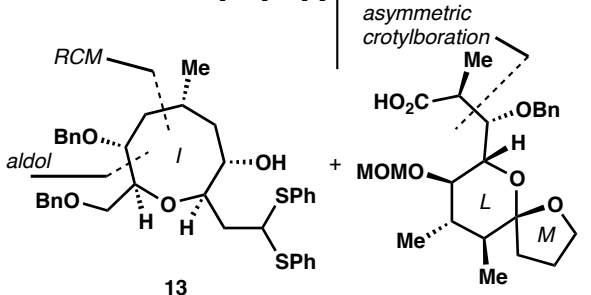
[2+1] to [5]

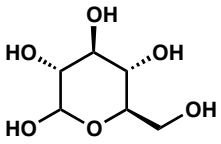


11 **12**

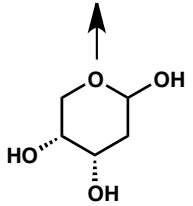
[1+2] to [5]



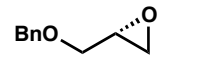
13 **14**



D-glucose (**15**)



D-2-deoxyribose (**16**)



(*S*)-*O*-benzylglycidol (**17**)

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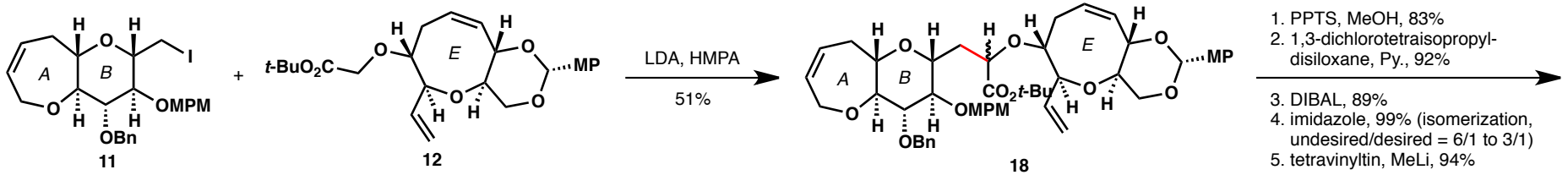
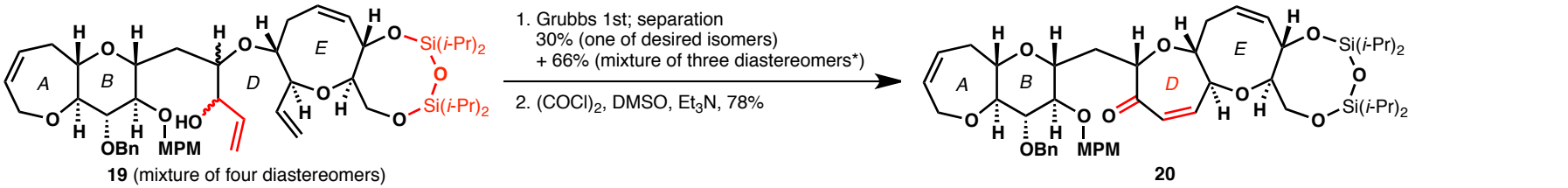
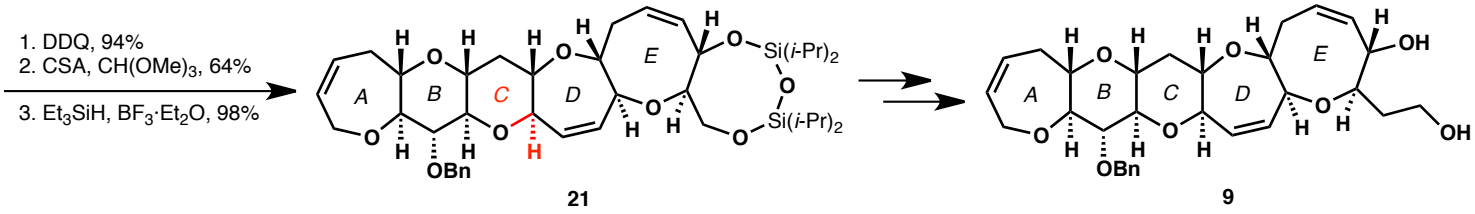
<Synthesis of 9>







Ladder polyether - what's next?

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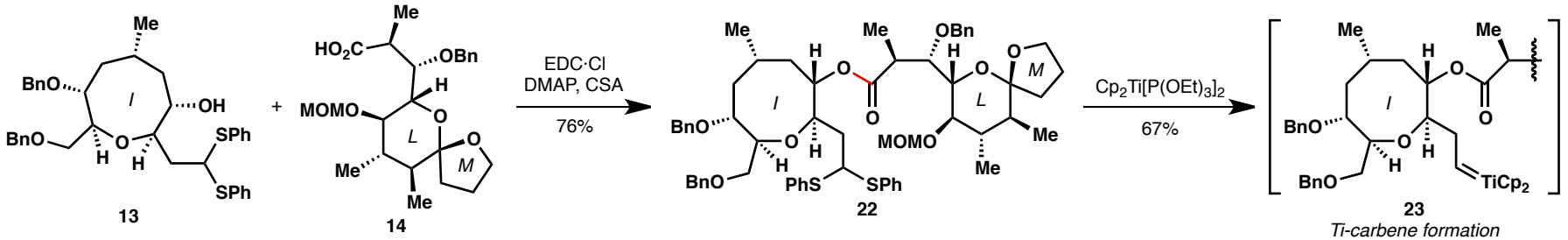
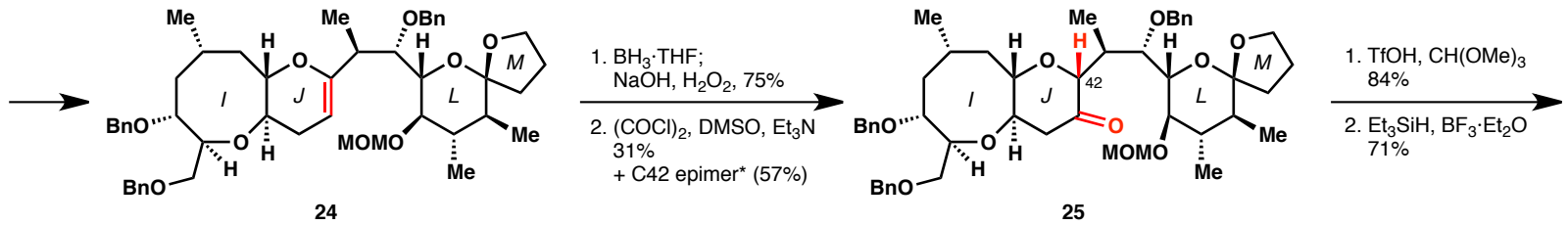
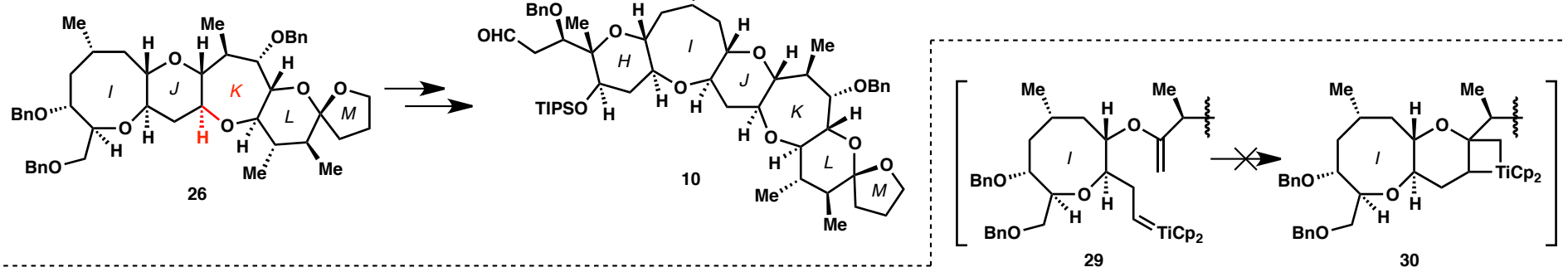
<Synthesis of 10>

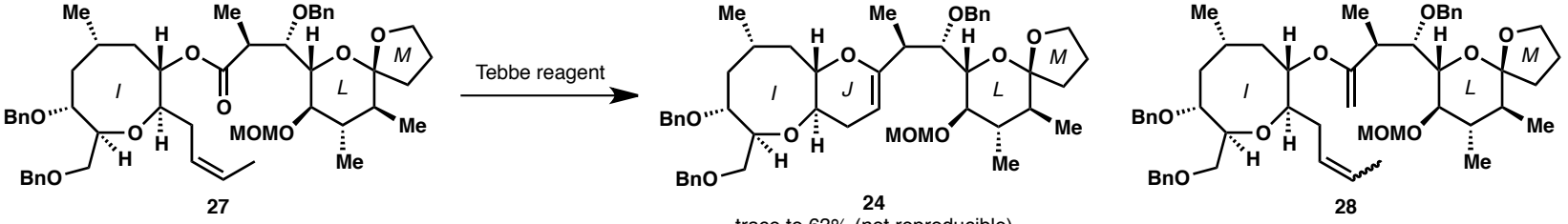




(*C42 epimer was conveted to **25** by treatment with DBU)



(Unsuccessful results)



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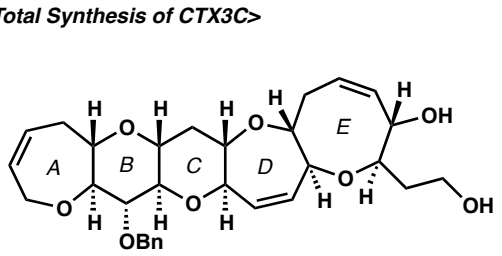
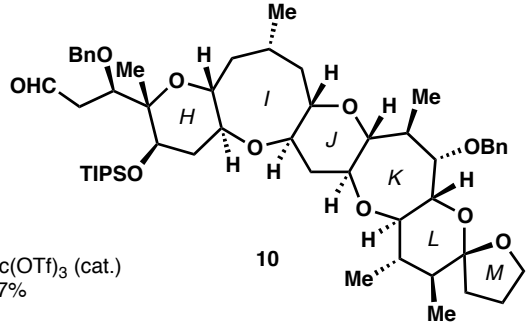
<Total Synthesis of CTX3C>



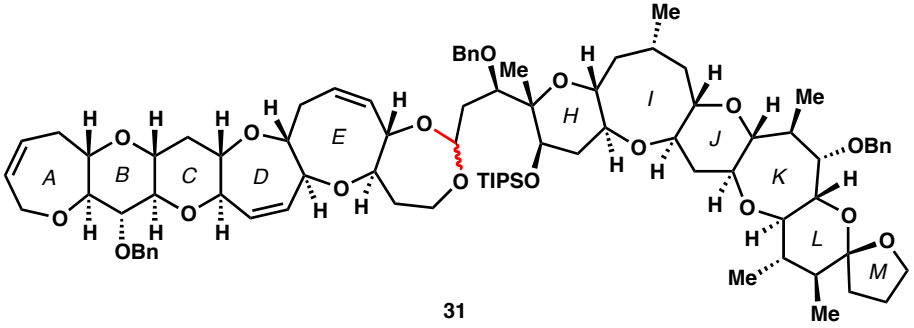
9

+



10

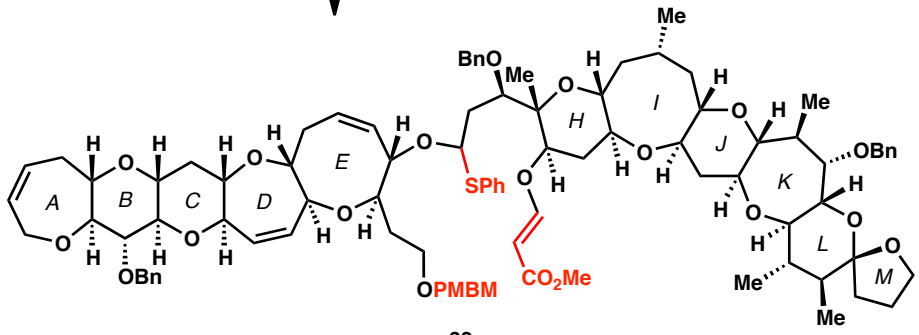
$Sc(OTf)_3$ (cat.)
57%



31

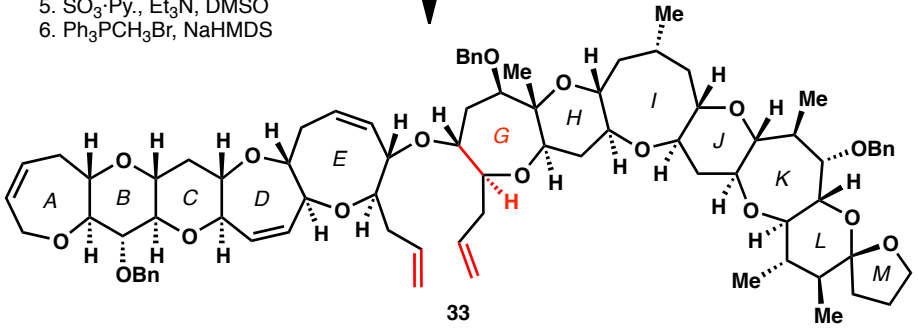
1. TMSSPh, TMSOTf; K_2CO_3, MeOH, 61%
2. PMBMCl, *i*-Pr_2NEt, 70%
3. TBAF, 92%
4. methyl propiolate, NMM, 92%

(PMBM = *p*-methoxybenzyloxymethyl)



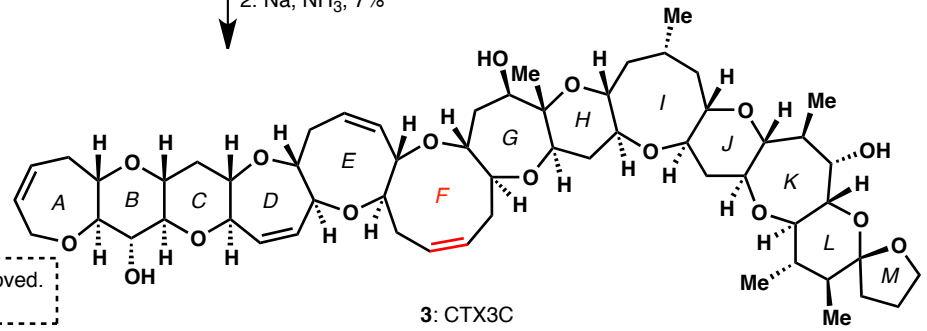
32

1. Bu_3SnH, AIBN
2. DIBAL
3. Ph_3PCH_3Br, NaHMDS, 61% (3 steps)
4. TMSBr, 93%
5. SO_3·Py., Et_3N, DMSO
6. Ph_3PCH_3Br, NaHMDS



33

1. Grubbs 1st, 60% (3 steps)
2. Na, NH_3, 7%*



3: CTX3C

*When NAP was used instead of Bn, yield of the deprotection was improved. (DDQ, 63%)

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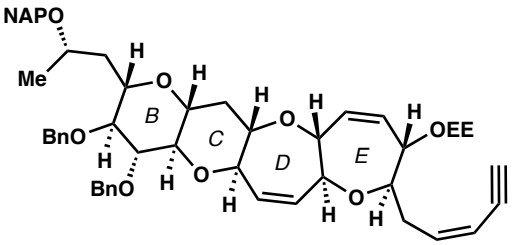
3. Recent Updates on Strategies

3-1. Use of Co Complexes in Total Synthesis of Ciguatoxin (Isobe et al.)

Ref. *ACIE* **2009**, *48*, 2941; *Nat. Prod. Rep.* **2010**, *27*, 1204 (Account)

<Construction of F and G Riings>



34

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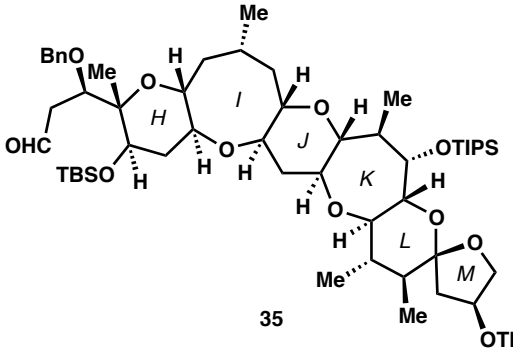
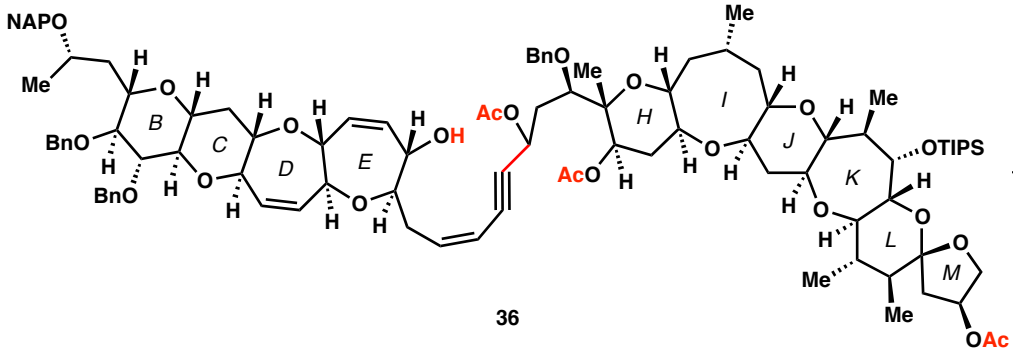


35

coupling

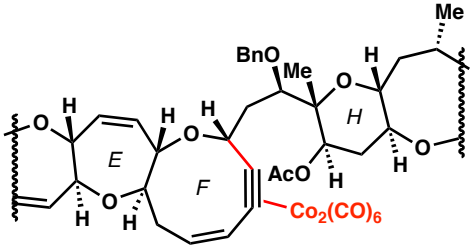
1. *n*-BuLi
2. TBAF, 54% (2 steps)
3. Ac_2O, Py. DMAP
4. Amberlyst 15, MeOH
   77% (2 steps)



36

1. $[Co_2(CO)_8]$
2. $TsOH{\cdot}H_2O$
   72% (2 steps)

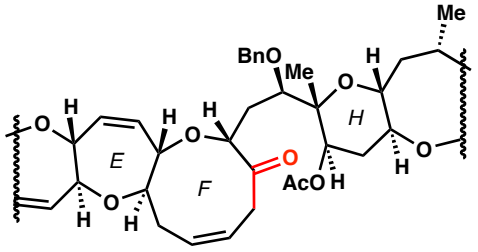
Nicholas reaction



37

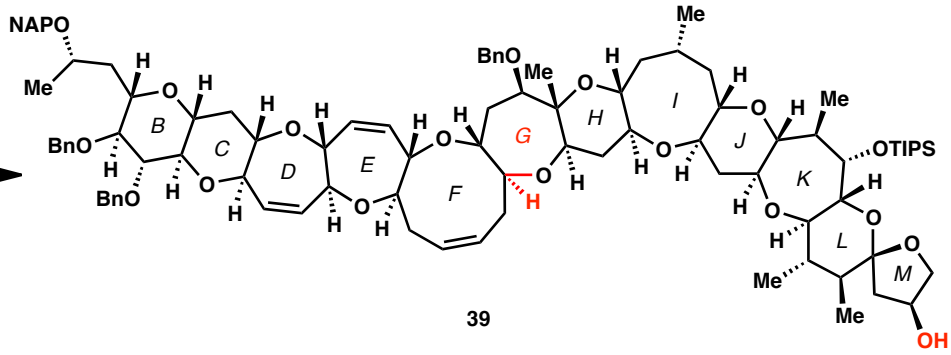
Ph_2P PPh_2
dppm
under N_2;
then air
48%

oxidative decomplexation



38

1. K_2CO_3, MeOH
2. $HC(OMe)_3$, CSA
   ca. 80% (2 steps)
3. $BF_3{\cdot}Et_2O$, Et_3SiH
   60%



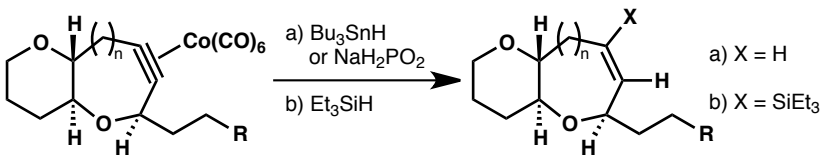
39

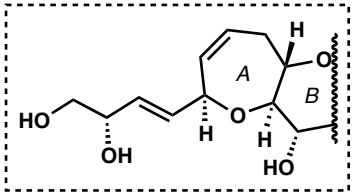
construction
of A ring

4: ciguatoxin
(CTX1B)

Point

- A, D, E, I, and K rings were also constructed by using Nicholas reaction.
- After Nicholas reaction, cobalt complexes can be transformed under reductive decomplexation conditions into ether *cis* olefins or vinylsilanes.





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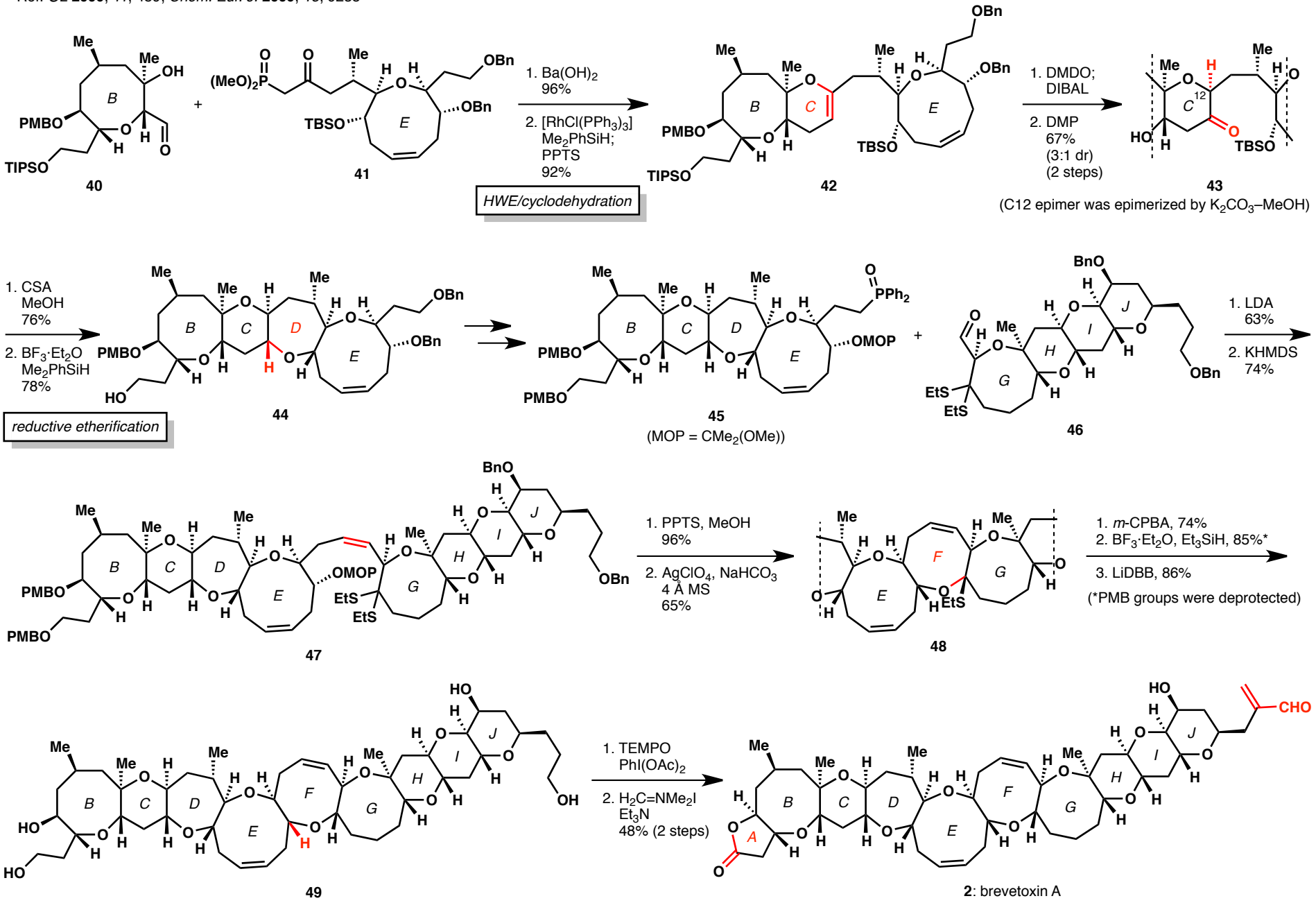
3-2. HWE/cyclodehydration/reductive etherification Convergent Coupling Strategy in Total Synthesis of Brevetoxin A (Crimmins et al.)

Ref. *OL* **2009**, *11*, 489; *Chem. Eur. J.* **2009**, *15*, 9235



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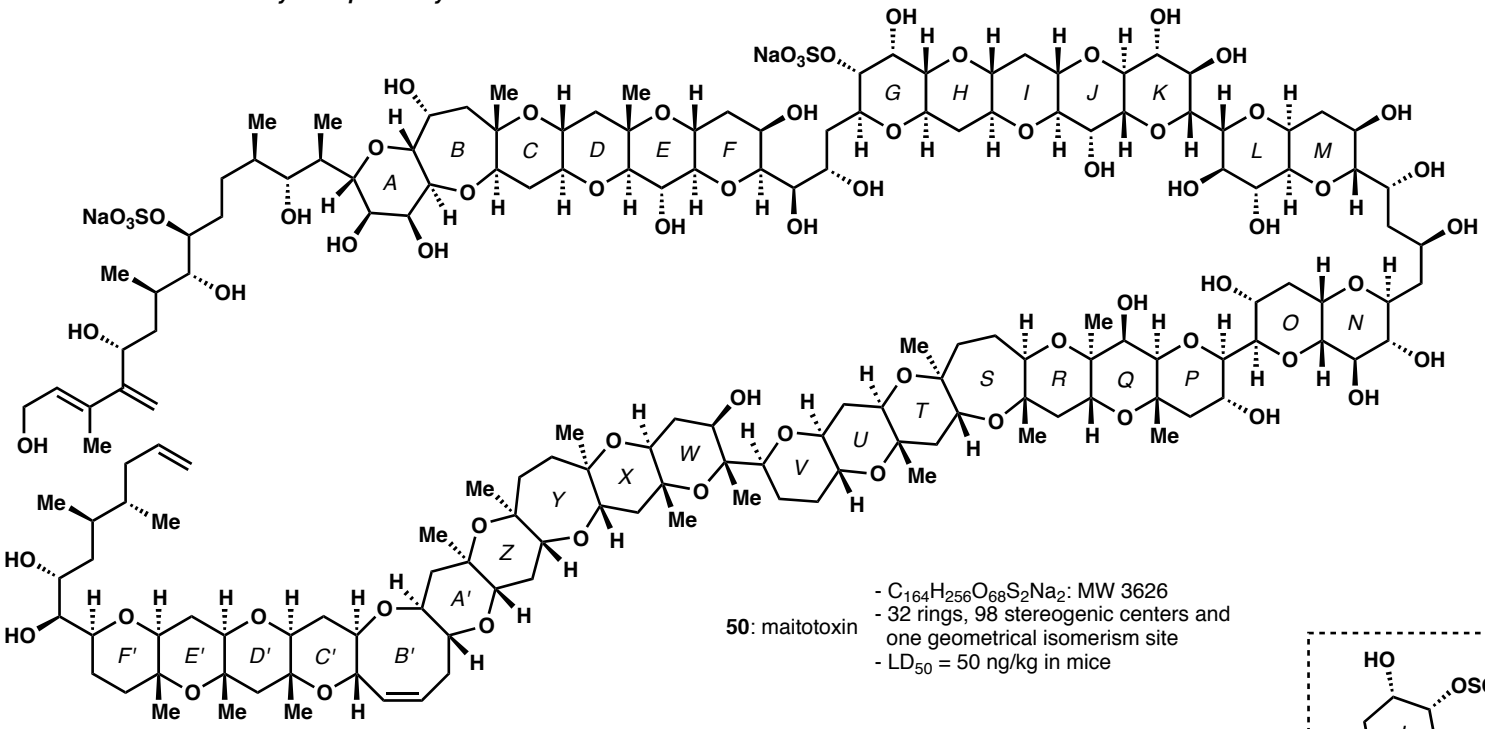
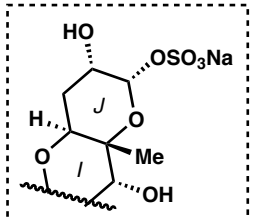
4. Next Targets: Maitotoxin, Yessotoxin, and Adriatoxin

4-1. Structure and Summary of Reported Synthetic Studies



50: maitotoxin

- $C_{164}H_{256}O_{68}S_2Na_2$: MW 3626
- 32 rings, 98 stereogenic centers and one geometrical isomerism site
- LD_{50} = 50 ng/kg in mice



52: adriatoxin

51: yessotoxin

<Synthetic studies of maitotoxin (after 2008)>

Nicolaou, et al.
- **GHIJKLMNO** (2008)
- **ABCDEFG** (2010)
- **QRSTU** (2010)
- **C'D'E'F'** (2011)
- **WXYZA'** (2011)
- **QRSTUVWXYZA'** (2014)

Nakata, et al.
- **GHI** (2008)
- **C'D'E'F'** (2008)
- **WXYZA'** (2008)
- **BCDE** (2008)

Oishi, et al.
- **WXYZA'** (2008)
- **QRS** (2014)
- **C'D'E'F'** (2014)

<Synthetic studies of yessotoxin>

Oishi, et al.
- **FGHI** (2005)
- **ABC** and **IJ** (2006)
- **CDEF** (2006)
- **JK** (2007)
- **ABCDEFGHIJ** (2008)
- **FGHIJ** (2010)

Mori, et al.
- **BCDE** (2002)
- **ABCDEF** (2003)

Kadota, et al.
- **ABCDEF** (2003)
- **FGHI** (2006)
- **IJK** (2006)

Others
- **ABCDEF** (Nakata, et al. 2002)
- **AB** (Hirai, et al. 2014)

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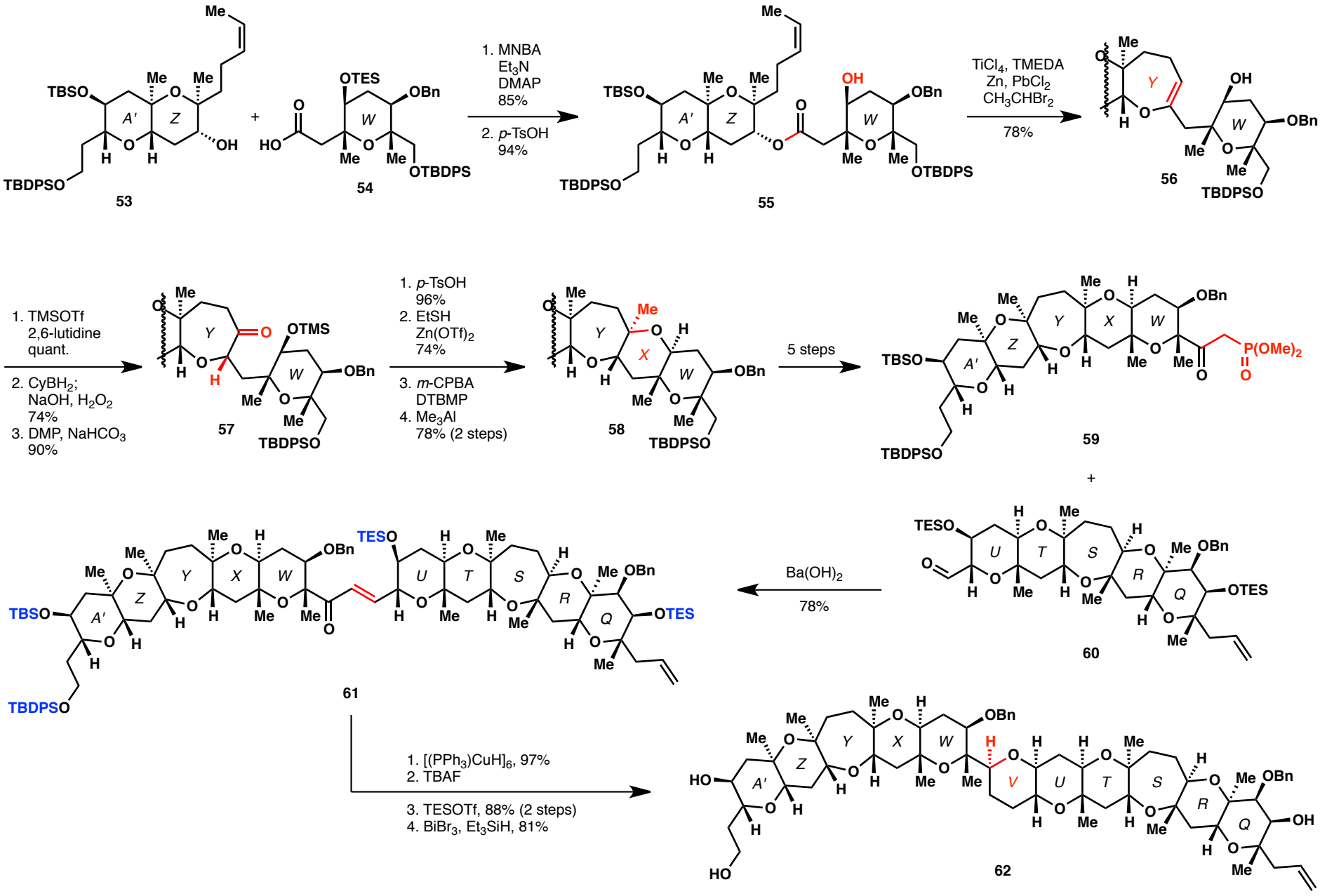
4-2. Most Recent Update on Synthetic Study of Maitotoxin

Synthesis of QRSTUWXYZA' Domain (Nicolaou, K. C. et al. *JACS* **2014**, *136*, 16444)



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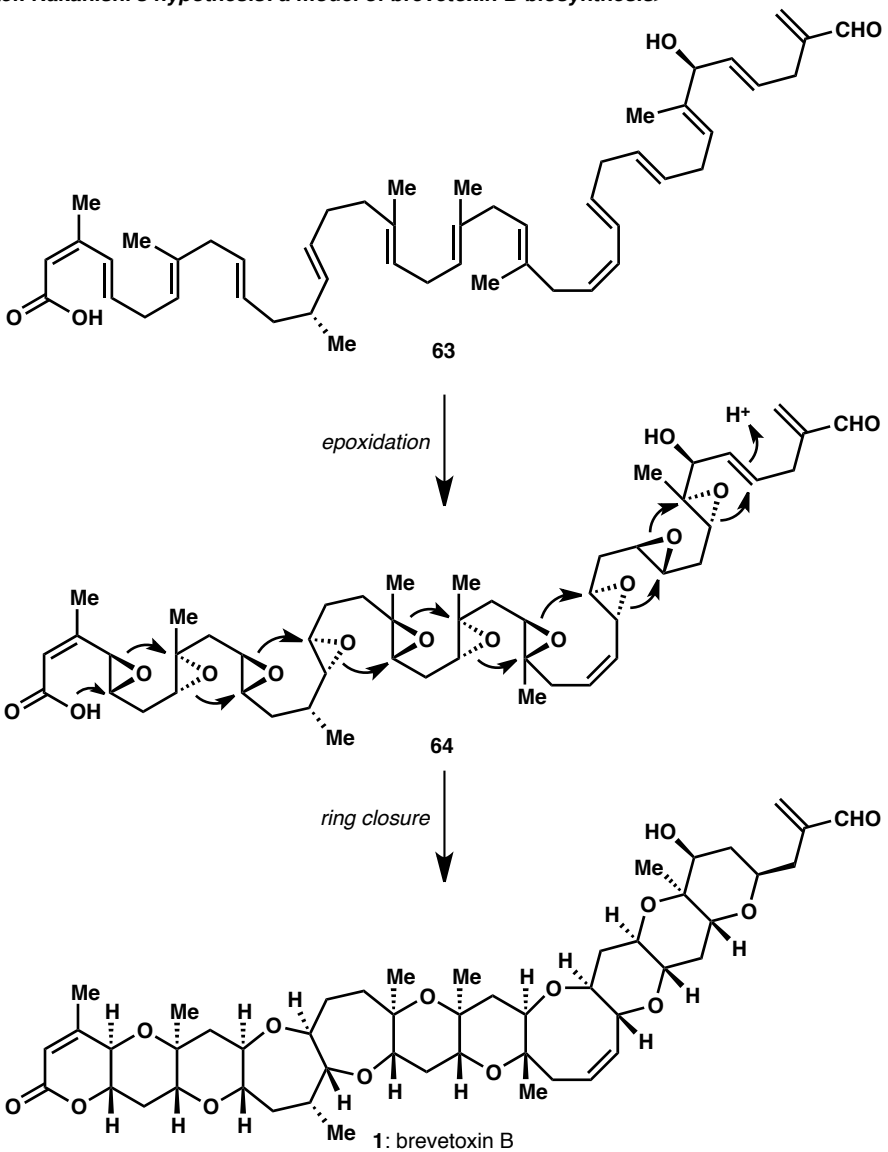
5. Next Strategy: Epoxide-Opening Cascades

Ref. (review): Vilotijevic and Jamison *ACIE* **2009**, *48*, 5250;
Nicolaou, et al. *ACIE* **2008**, *47*, 7182

<cf. Nakanishi's hypothesis: a model of brevetoxin B biosynthesis>

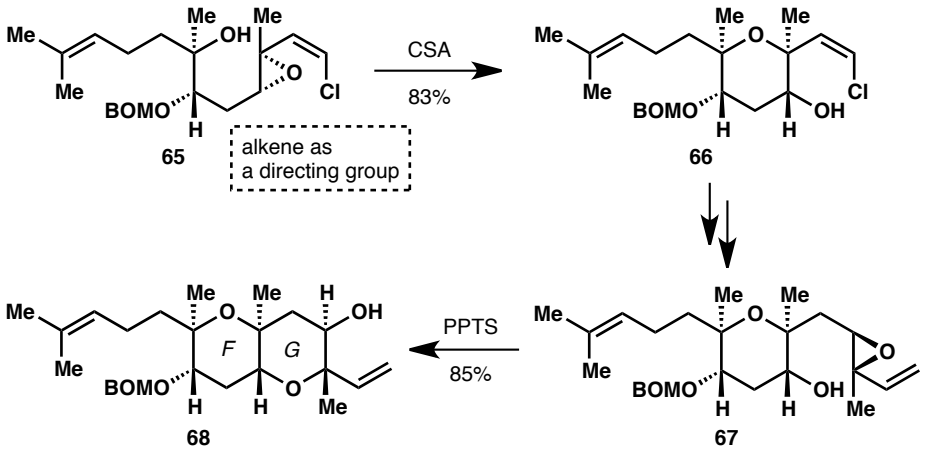


<What is challenge??>

"This strategy was not considered feasible in the laboratory, since some of the S_N2-type reactions required for its implementation contravented the Baldwin rules of ring closure, and because of the lack of suitable methods to construct the precursor polyepoxide. "
(Nicolaou, 2008)

<Stepwise approaches to single ether rings>

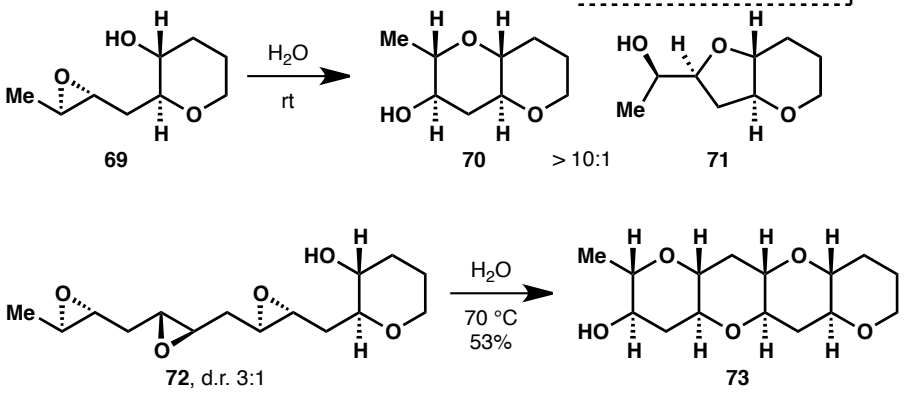
cf. Iterative synthesis of FG fragment of brevetoxin B
(Nicolaou, K.C . et al. *JACS* **1989**, *111*, 6676.



<Cascade Reactions>

cf. Epoxide-opening cascades, promoted by water
(Jamison, T. F. et al. *Science* **2007**, *317*, 1189)

trans-bicyclo[4.3.0]nonane
= more strained



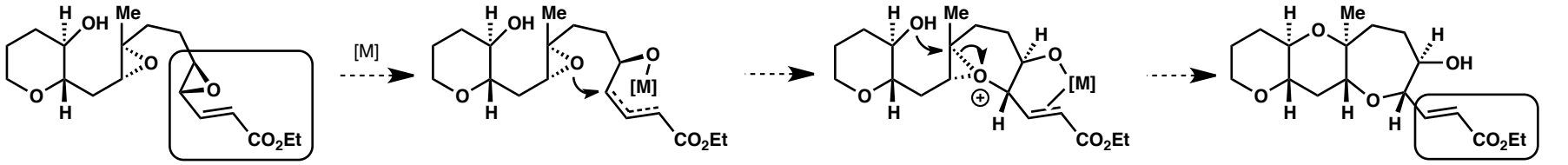
Ladder polyether - what's next?

Yusuke Sasano

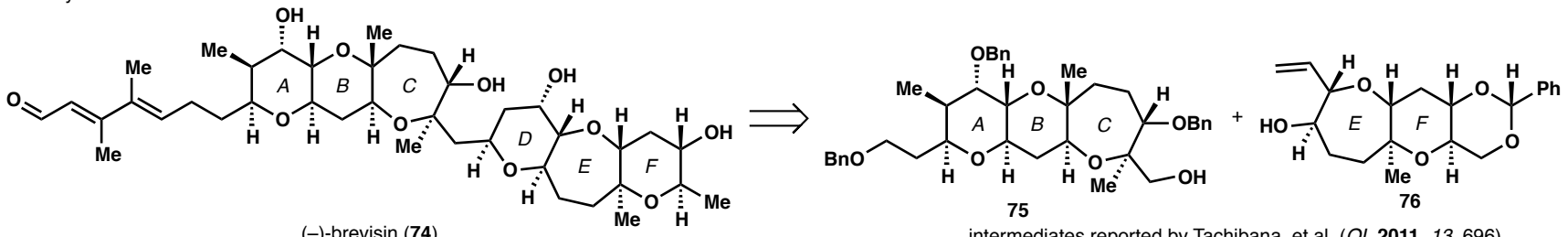
<Application to Synthesis of a Polyether>

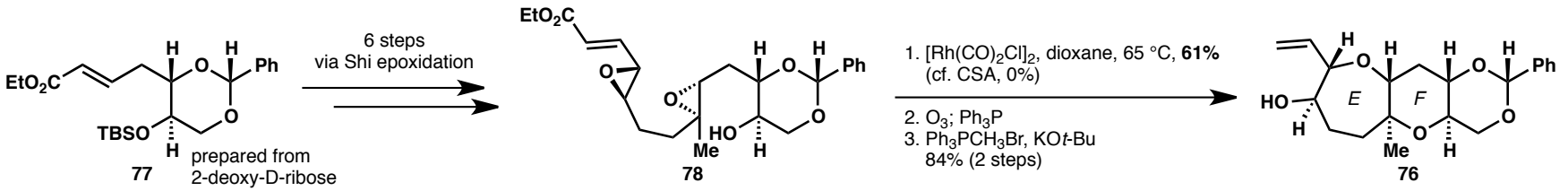
"Rhodium-Catalyzed *Endo*-Selective Epoxide-Opening Cascades: Formal Synthesis of (–)-Brevisin" Jamison, T. F. et al. *JACS* ASAP (DOI: 10.1021/jacs.5b03570)

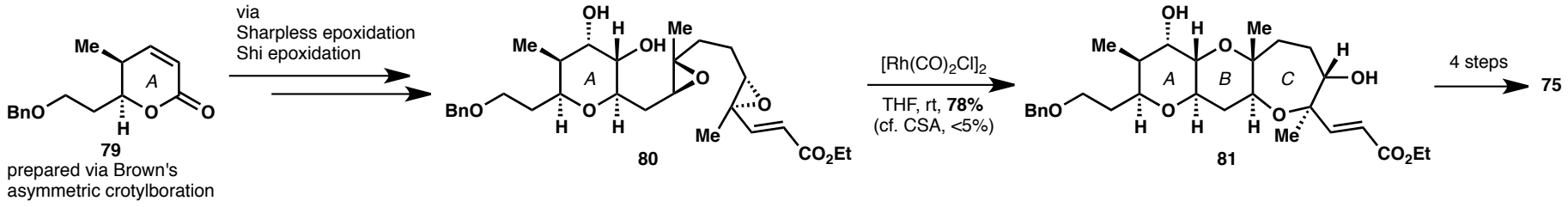
- Reaction Design



- Retrosynthesis







see also: "Hydroxyl-Substituted Ladder Polyethers via Selective Tandem Epoxidation/Cyclization Sequence" Jamison, T. F. et al. *OL* **2015**, *17*, 774.
(Synthesis of *HIJ* ring fragment of yessotoxin)