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1. Introduction

- 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)
Ladder polyether - what's next?

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)
2. Landmark Total Synthesis

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

Key: [X+2+X] approach for convergent synthesis
Ladder polyether - what's next?

1. PPTS, MeOH, 83%
2. 1,3-dichlorotetraisopropyl-disiloxane, Py, 92%
3. DIBAL, 89%
4. imidazole, 99% (isomerization, undesired/desired = 6/1 to 3/1)
5. tetravinyltin, MeLi, 94%

* Mixture of three diastereomers were subjected to Swern oxidation and then isomerization (DBU).
Ladder polyether - what's next?

<Synthesis of 10>

1. BH$_3$·THF; NaOH, H$_2$O$_2$, 75%
2. (COCl)$_2$, DMSO, Et$_3$N 31% + C42 epimer* (57%)

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

(Trace to 63% (not reproducible))
<Total Synthesis of CTX3C>

1. Bu₃SnH, AIBN
2. DIBAL
3. Ph₃PCH₂Br, NaHMDS, 61% (3 steps)
4. TMSBr, 93%
5. SO₃Py, Et₃N, DMSO
6. Ph₃PCH₂Br, NaHMDS

1. Grubbs 1st, 60% (3 steps)
2. Na, NH₃, 7%*

*When NAP was used instead of Bn, yield of the deprotection was improved (DDQ, 63%)
3. Recent Updates on Strategies

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


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


(C12 epimer was epimerized by K₂CO₃–MeOH)
4. Next Targets: Maitotoxin, Yessotoxin, and Adriatoxin

4-1. Structure and Summary of Reported Synthetic Studies

- **Maitotoxin**: C_{164}H_{256}O_{68}S_{2}Na_{2}; MW 3626
- 32 rings, 98 stereogenic centers and one geometrical isomerism site
- LD_{50} = 50 ng/kg in mice

**Synthetic studies of maitotoxin (after 2008)**

Nicolaou, et al.
GHIJKLMNO (2008)
ABCDEFG (2010)
QRSTU (2010)
C'D'E'F' (2011)
Oishi, et al.
FGHIJ (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)
ABCFGH (2008)
FGHI (2010)
Mori, et al.
BCDE (2002)
ABCFD (2003)
Kadota, et al.
ABCFD (2003)
FGHI (2006)
IJ (2006)
Others
ABCFD (Nakata, et al. 2002)
AB (Hirai, et al. 2014)
4-2. Most Recent Update on Synthetic Study of Maitotoxin

1. MNBA Et₃N DMAP 85%
2. p-TsOH 94%

1. p-TsOH 96%
2. EtSH Zn(O Tf)₂ 74%
3. m-CPBA DTBMP 4. Me₃Al 78% (2 steps)

1. TMSOTf 2,6-lutidine quant.
2. CyBH₂; NaOH, H₂O₂ 74%
3. DMP, NaHCO₃ 90%
5. Next Strategy: Epoxide-Opening Cascades

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

"This strategy was not considered feasible in the laboratory, since some of the $S_n2$-type reactions required for its implementation contravened 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>*

*<Cascade Reactions>*

*<What is challenge??>*

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<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

alkenyl epoxide for site- and endo-selective cascade reaction

- Retrosynthesis

(−)-brevisin (74)

intermediates reported by Tachibana, et al. (OL 2011, 13, 696)

6 steps via Shi epoxidation

prepared from 2-deoxy-D-ribose

prepared via Brown's asymmetric crotylboration

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)