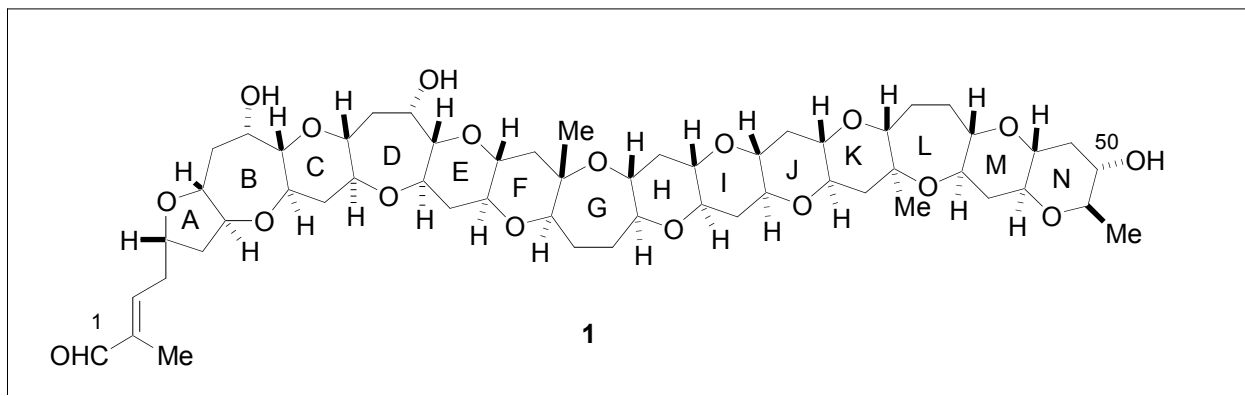


# Total Synthesis of Gymnocin-A

Makoto Sasaki, Chihiro Tsukano, Kazuo Tachibana, Tohoku Univ., Japan



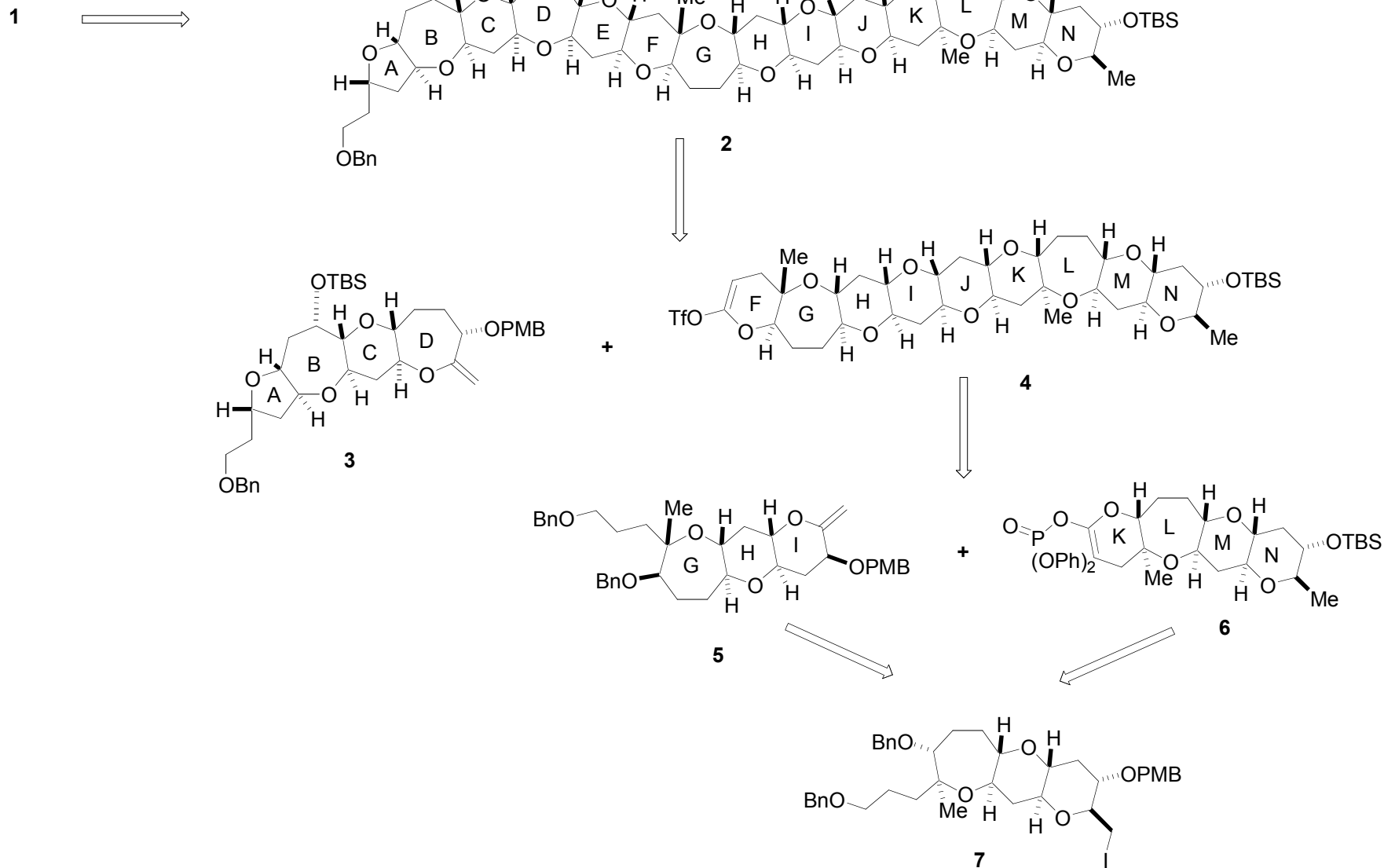
- Isolated by Satake and coworkers in 2001 from red tide dinoflagellate, *Karenia mikimotoi*
- Contains 14 contiguous rings with two repeating 6/6/7/6/6 systems
- Contains largest number of rings of polyethers known to date
- In vitro cytotoxicity against P388 cancer cells
- First total synthesis to date.

References: A-D: *Tet. Lett.* **2003**, 44, 4351.

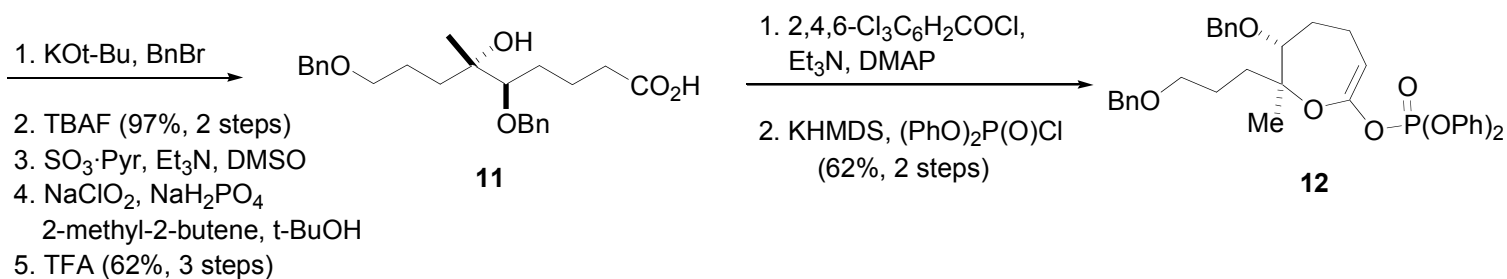
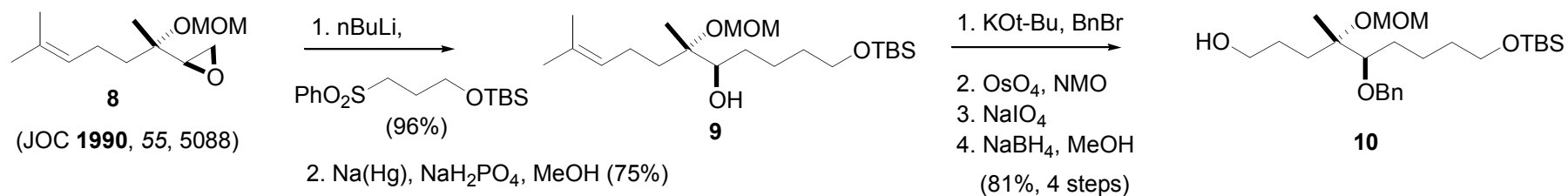
F-N: *Org. Lett.* **2002**, 4, 1747.

completion: *JACS* **2003**, 125, 14294.

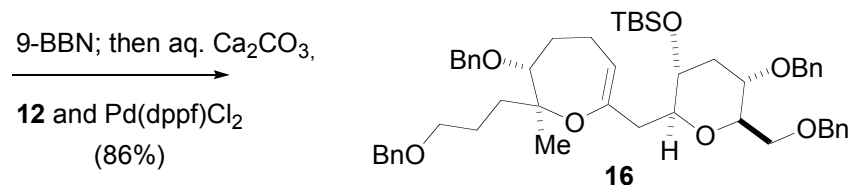
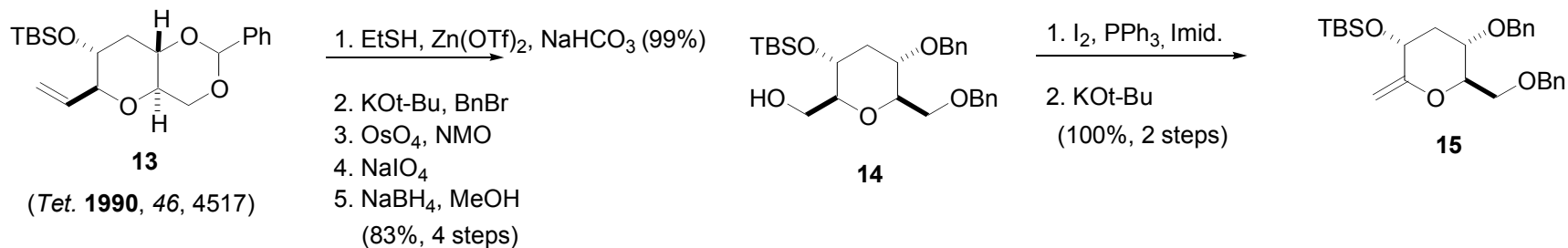
## Retrosynthetic Plan

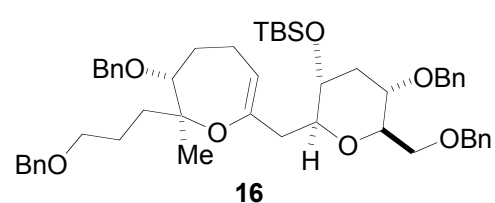


## Synthesis of the common intermediate **7**



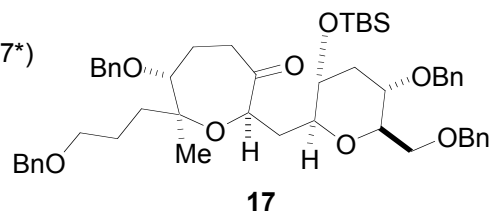
**Q**



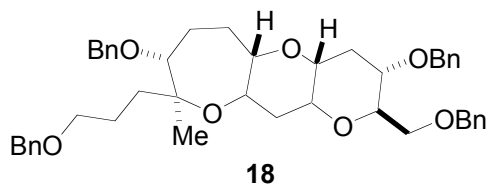


1.  $\text{BH}_3 \cdot \text{THF}$ ;  $\text{NaOH}$ ,  $\text{H}_2\text{O}_2$  (55:37\*)
2. TPAP, NMO (98%)

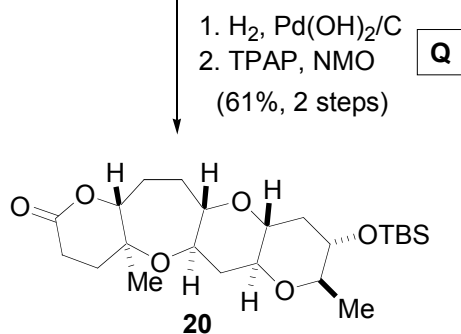
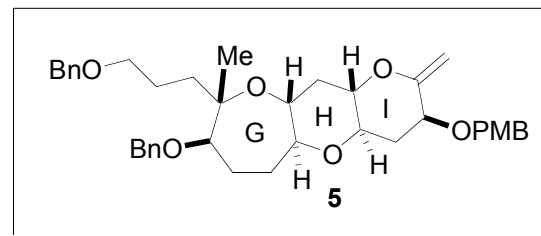
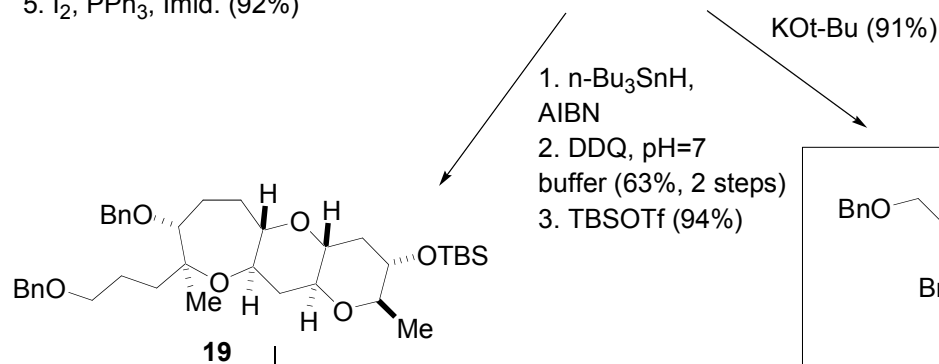
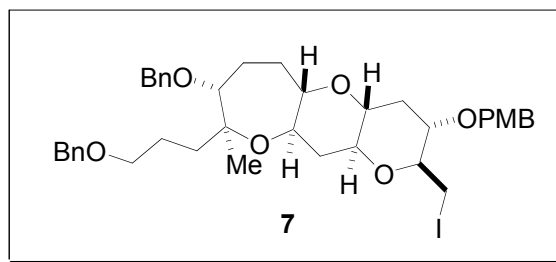
\*55% desired, 37% undesired  
(could be recycled w/ DBU  
after oxidation; 48%)



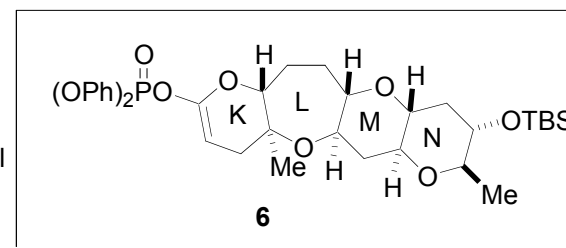
1. p-TsOH, MeOH (84%)
2.  $\text{Et}_3\text{SiH}$ ,  $\text{BF}_3 \cdot \text{OEt}_2$  (quant)



1.  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$
2. p-MeOC<sub>6</sub>H<sub>4</sub>CH(OMe)<sub>2</sub>, PPTS (84%)
3. KOt-Bu, BnBr
4. DIBAL (67%)
5. I<sub>2</sub>, PPh<sub>3</sub>, Imid. (92%)

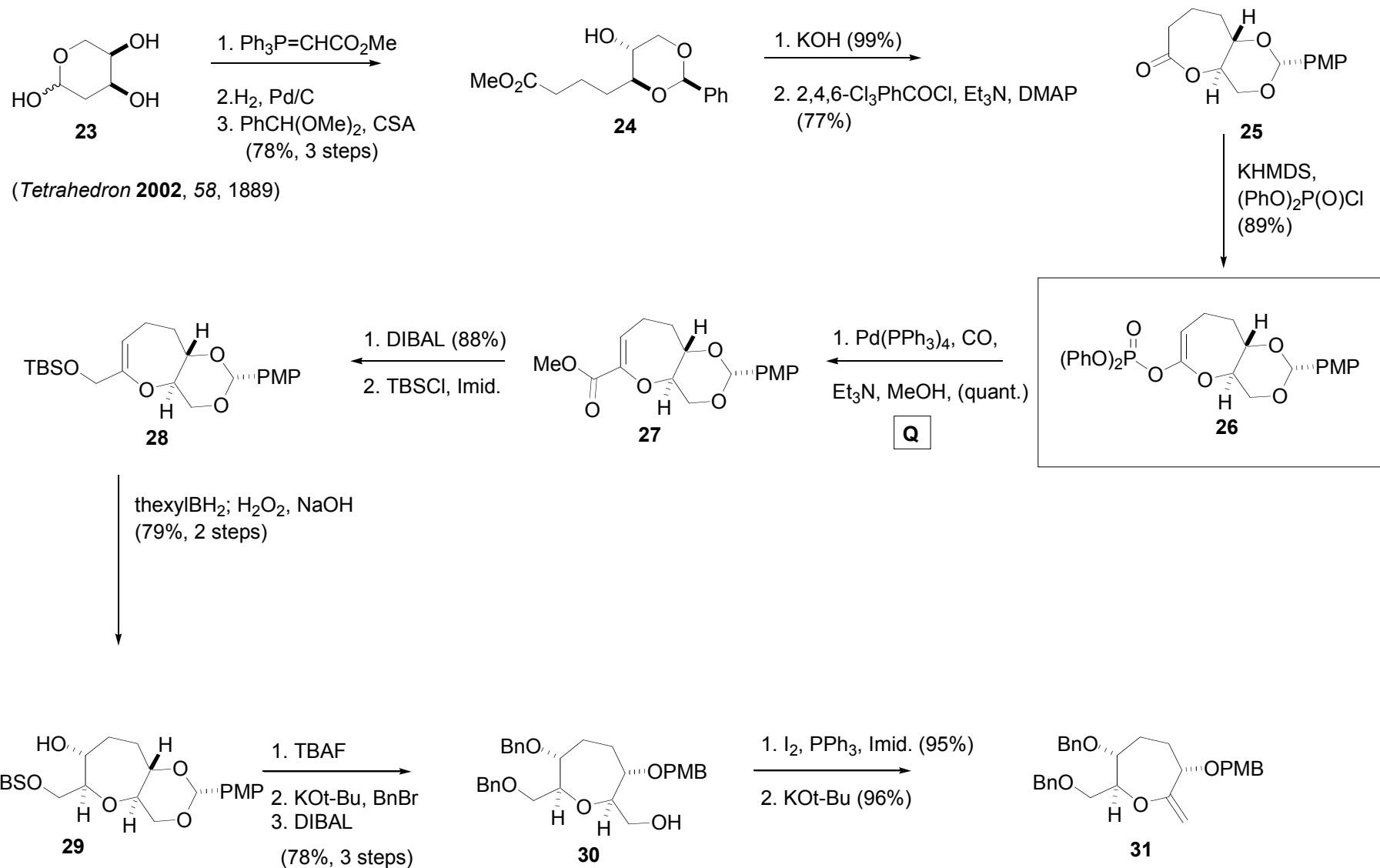


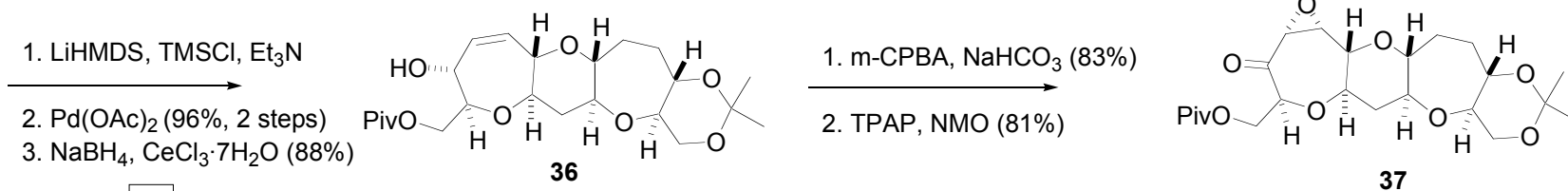
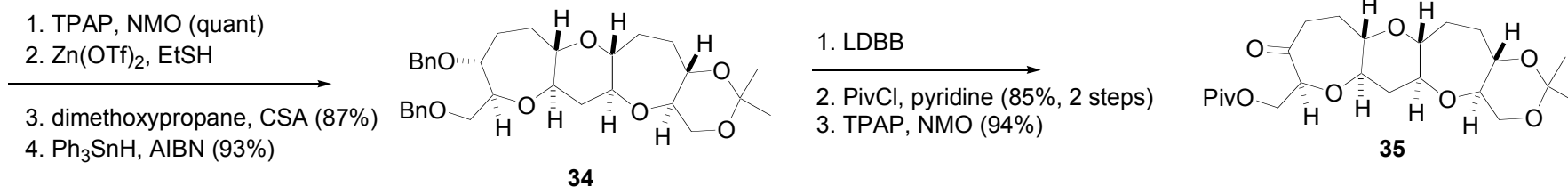
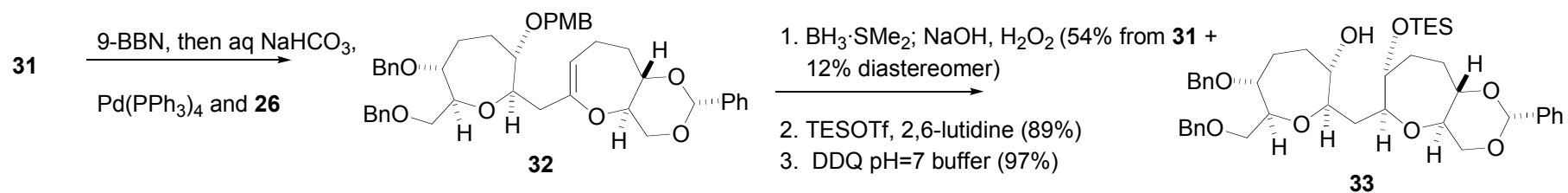
- KHMDS,  
(PhO)<sub>2</sub>P(O)Cl



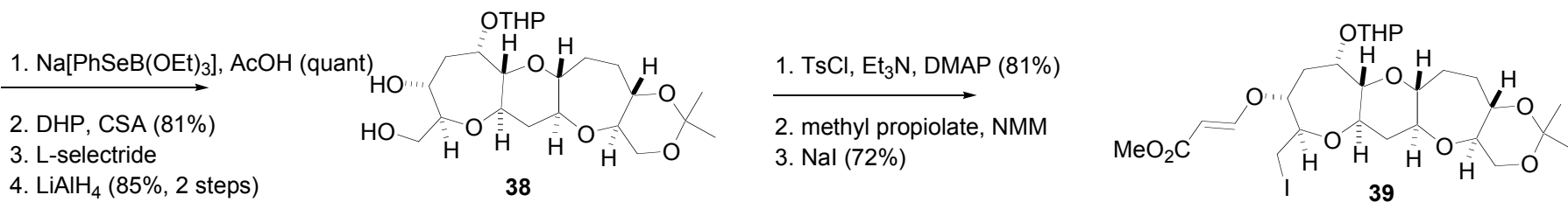


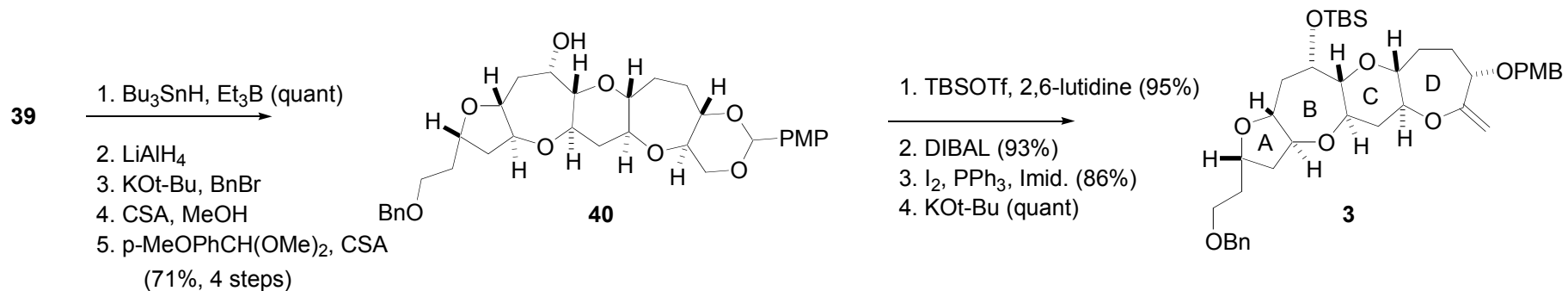
## Synthesis of the A-D fragment



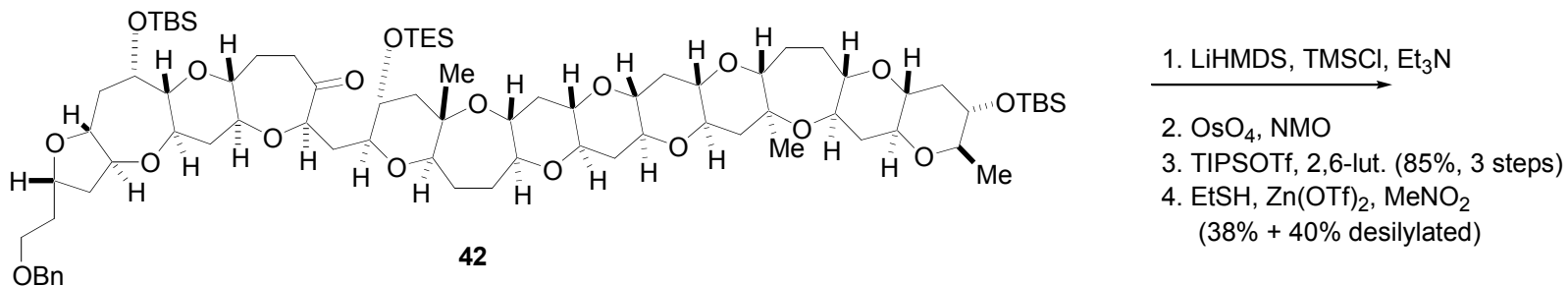
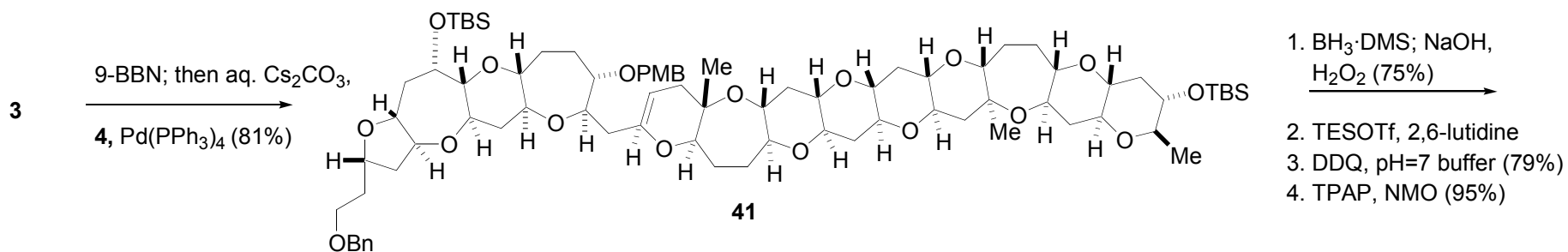


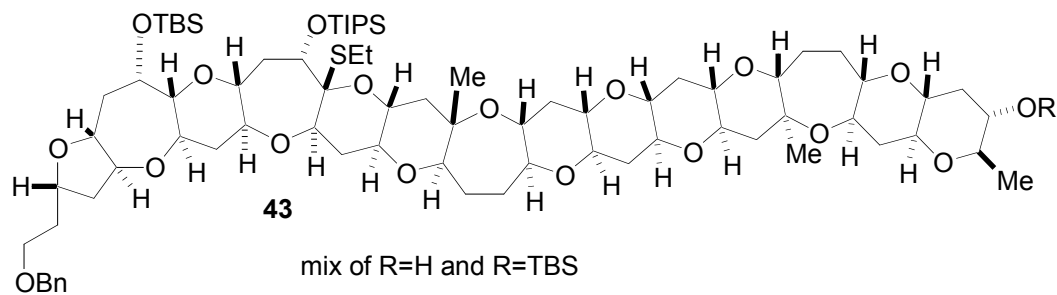
**Q**





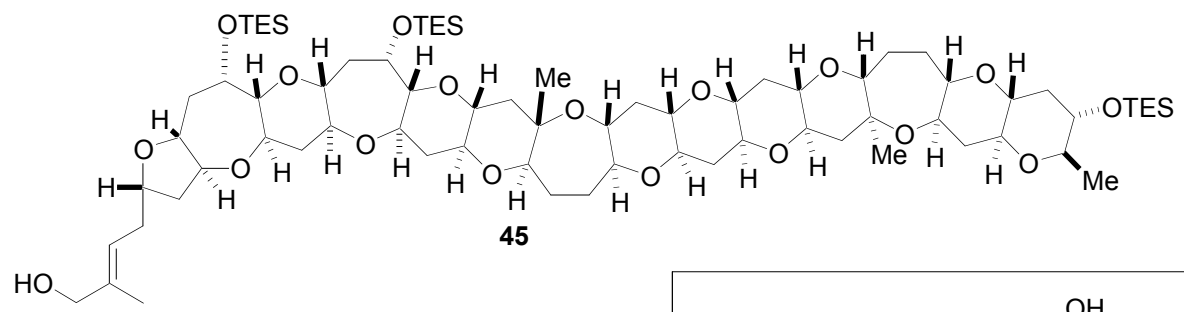
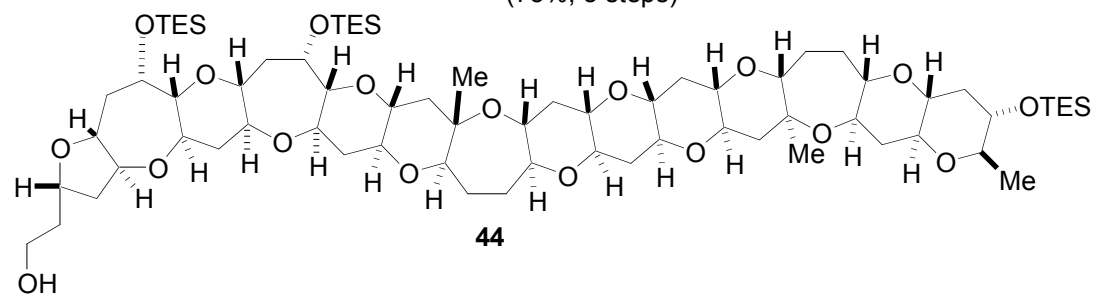
### Coupling of fragments 3 and 4 and completion of gymnocin-A



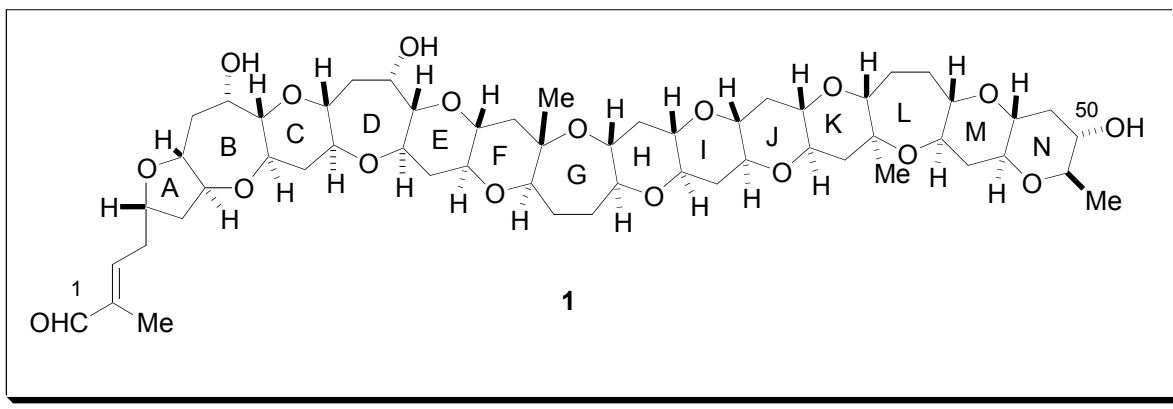


1. TBSOTf (71%)
  2. Ph<sub>3</sub>SnH, AIBN (98%)
  3. TBAF
  4. TESOTf, 2,6-lutidine
  5. LDBB
- (73%, 3 steps)

1. TPAP, NMO
  2. Ph<sub>3</sub>P=C(Me)CO<sub>2</sub>Me
  3. DIBAL
- (66%, 3 steps)



1. TASF\*
  2. MnO<sub>2</sub>
- (91%, 2 steps)



\* TASF = tris(dimethylamino)sulfonium difluoro-trimethylsilicate