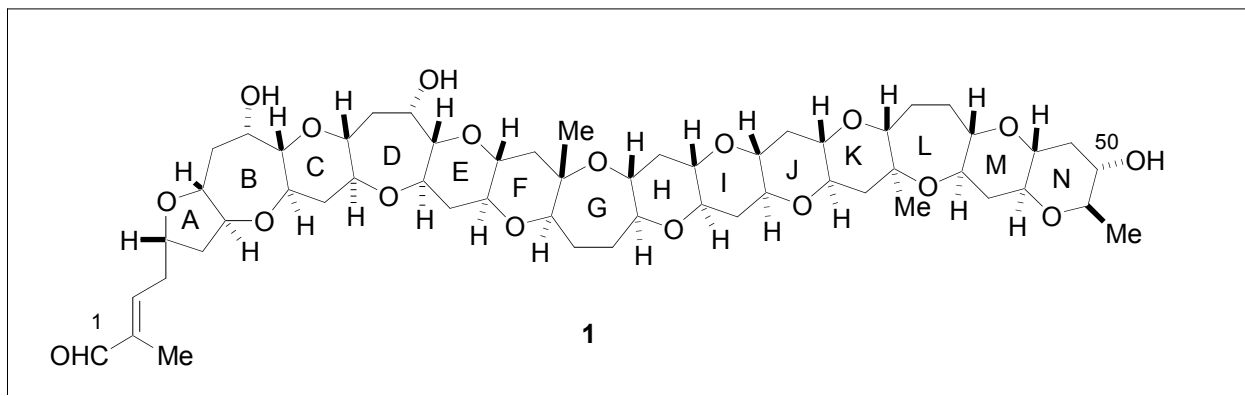


Total Synthesis of Gymnocin-A

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



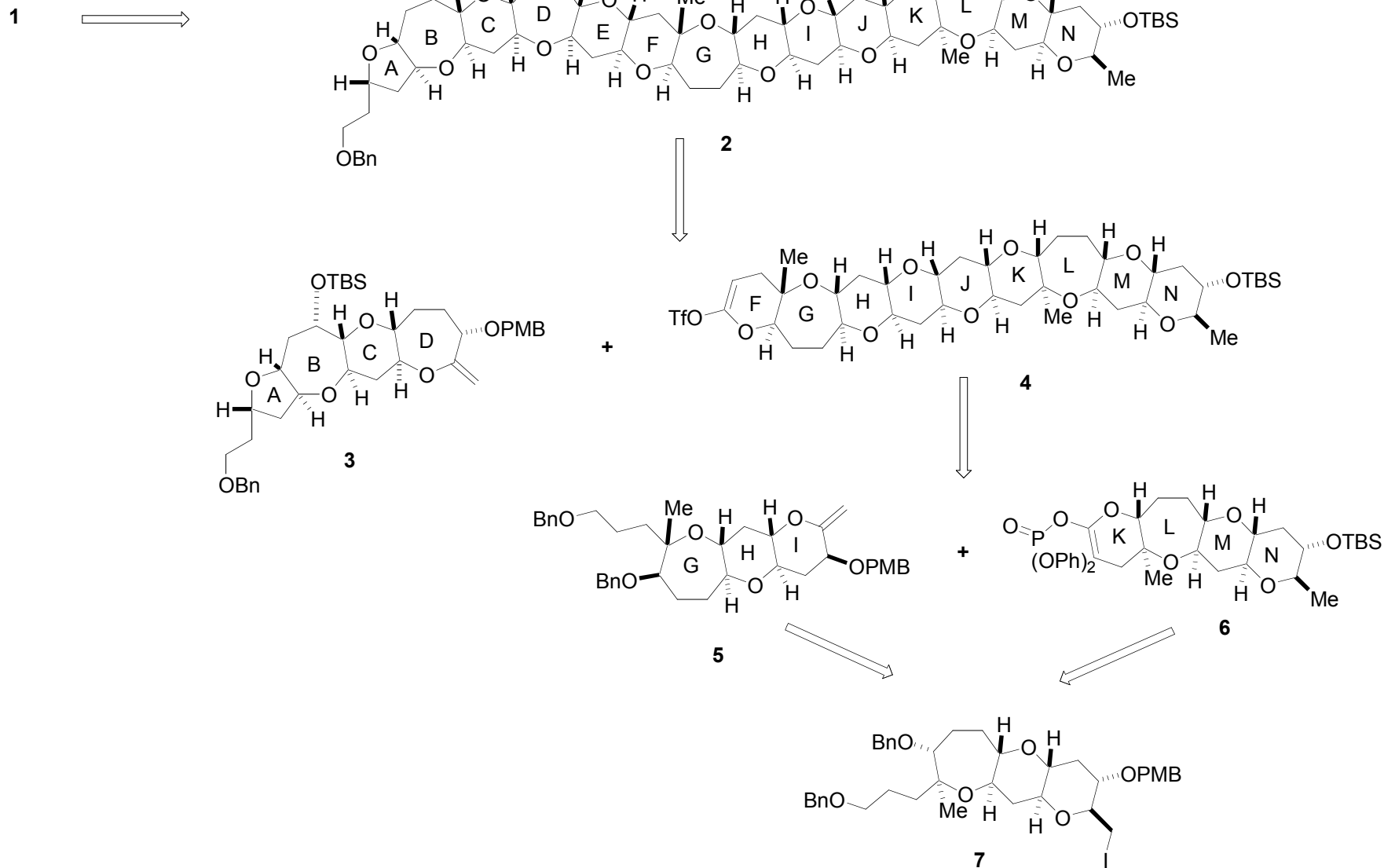
- Isolated by Satake and coworkers in 2001 from red tide dinoflagellate, *Karenia mikimotoi*
- Contains 14 contiguous rings with two repeating 6/6/7/6/6 systems
- Contains largest number of rings of polyethers known to date
- In vitro cytotoxicity against P388 cancer cells
- First total synthesis to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

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

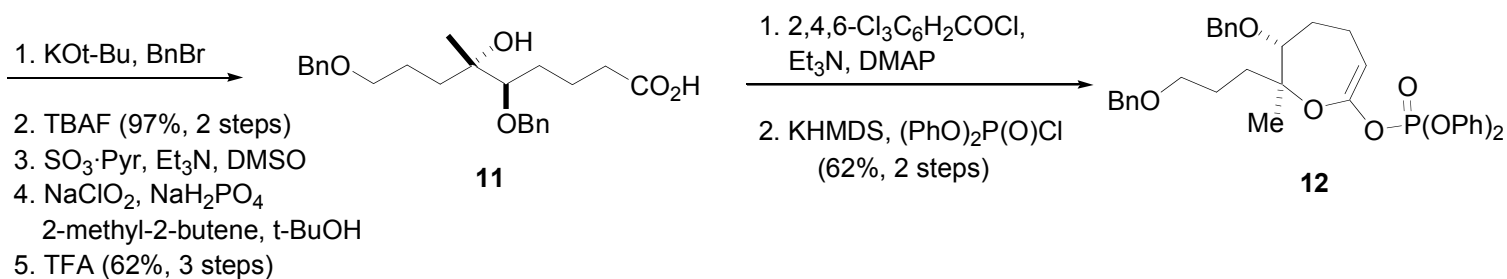
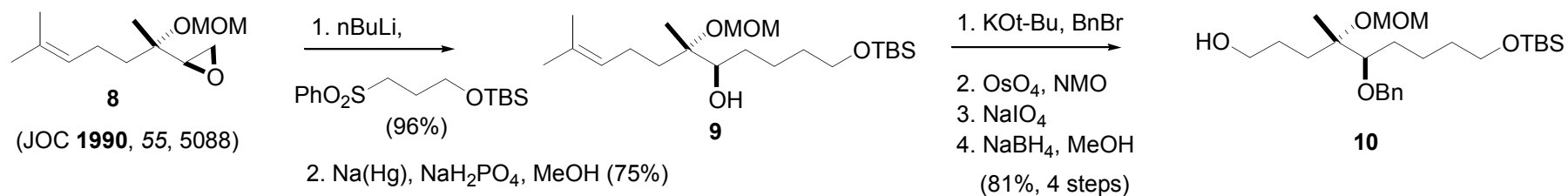
F-N: *Org. Lett.* **2002**, 4, 1747.

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

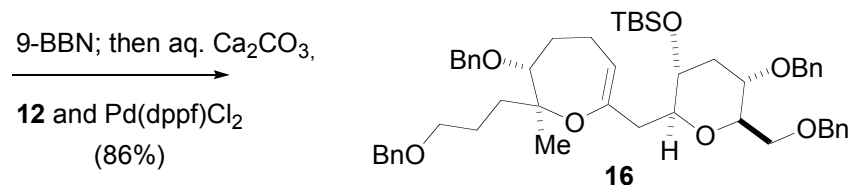
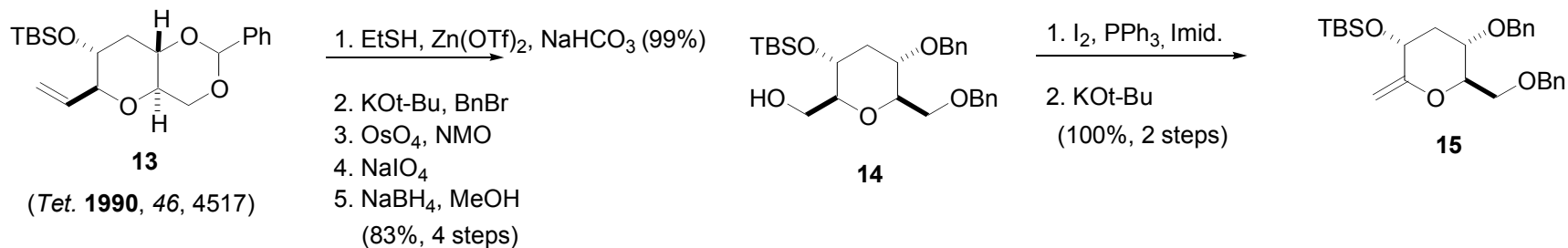
Retrosynthetic Plan

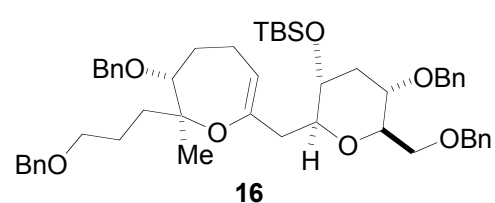


Synthesis of the common intermediate **7**



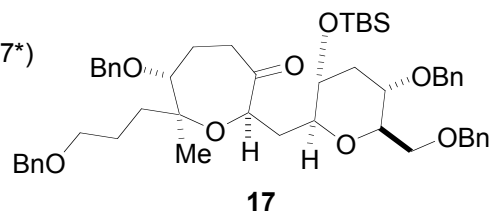
Q



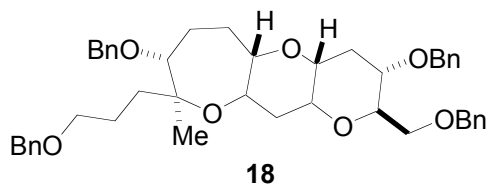


1. $\text{BH}_3 \cdot \text{THF}$; NaOH , H_2O_2 (55:37*)
2. TPAP, NMO (98%)

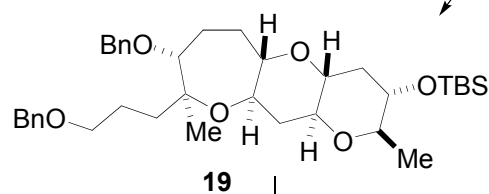
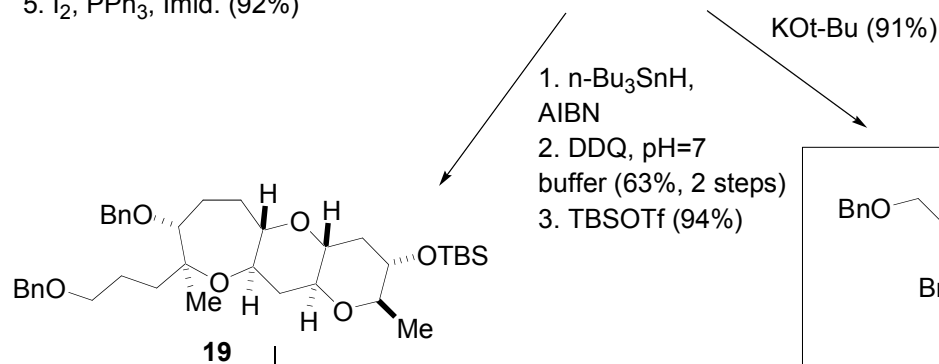
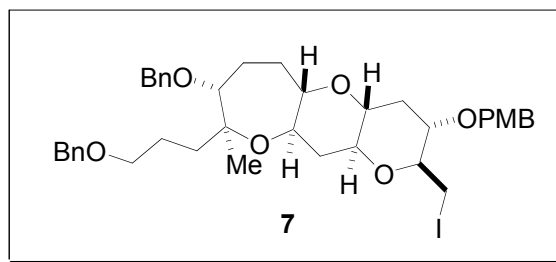
*55% desired, 37% undesired
(could be recycled w/ DBU
after oxidation; 48%)



1. p-TsOH, MeOH (84%)
2. Et_3SiH , $\text{BF}_3 \cdot \text{OEt}_2$ (quant)

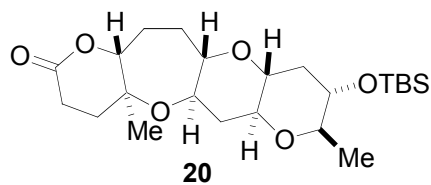


1. H_2 , $\text{Pd}(\text{OH})_2/\text{C}$
2. p-MeOC₆H₄CH(OMe)₂, PPTS (84%)
3. KOt-Bu, BnBr
4. DIBAL (67%)
5. I₂, PPh₃, Imid. (92%)

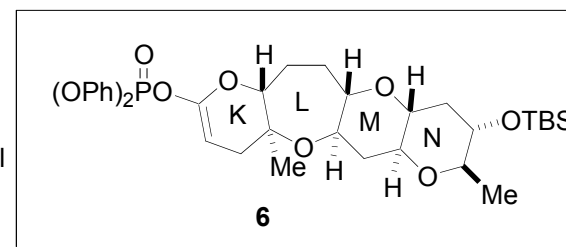


1. H_2 , $\text{Pd}(\text{OH})_2/\text{C}$
 2. TPAP, NMO
- (61%, 2 steps)

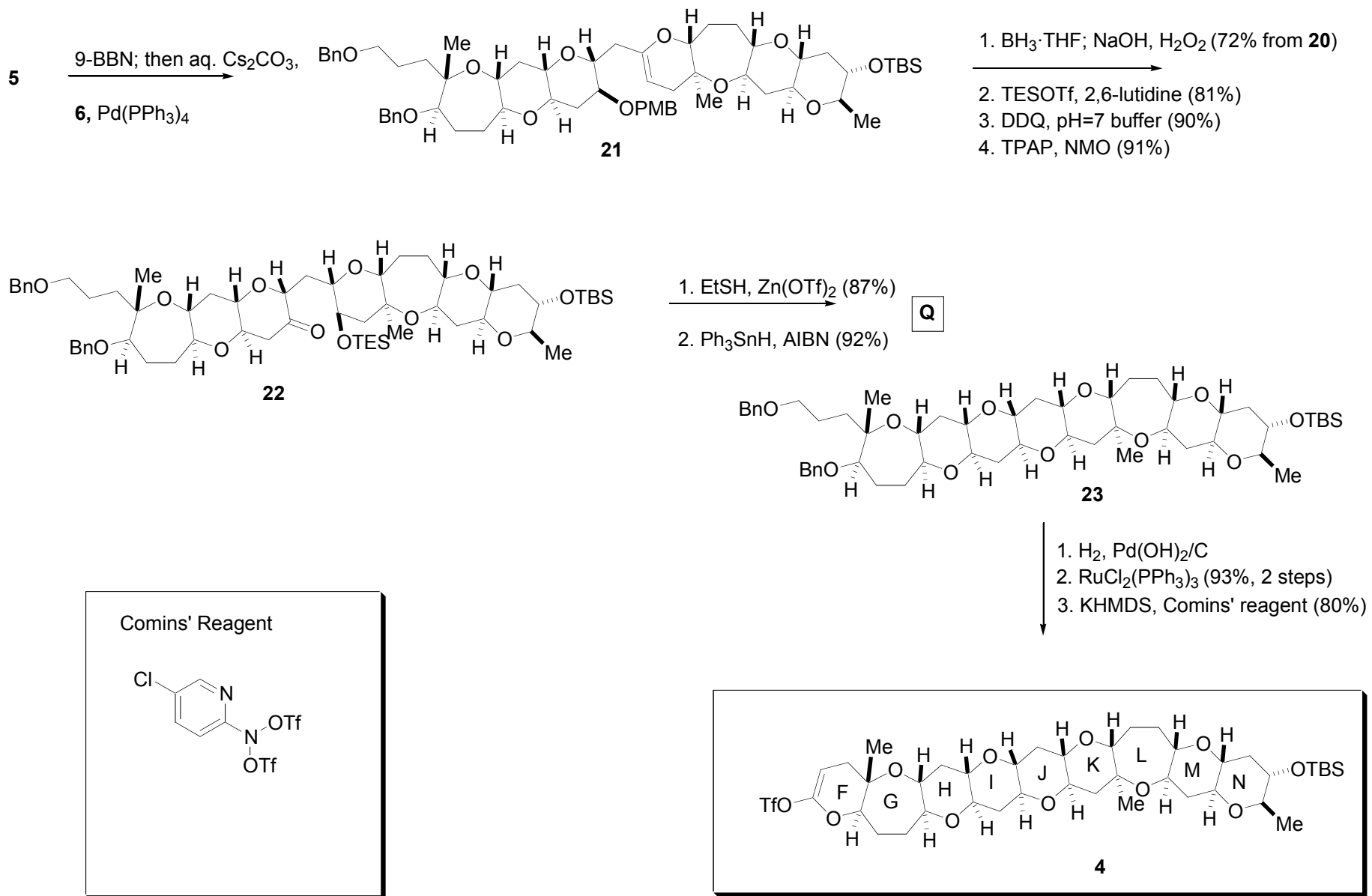
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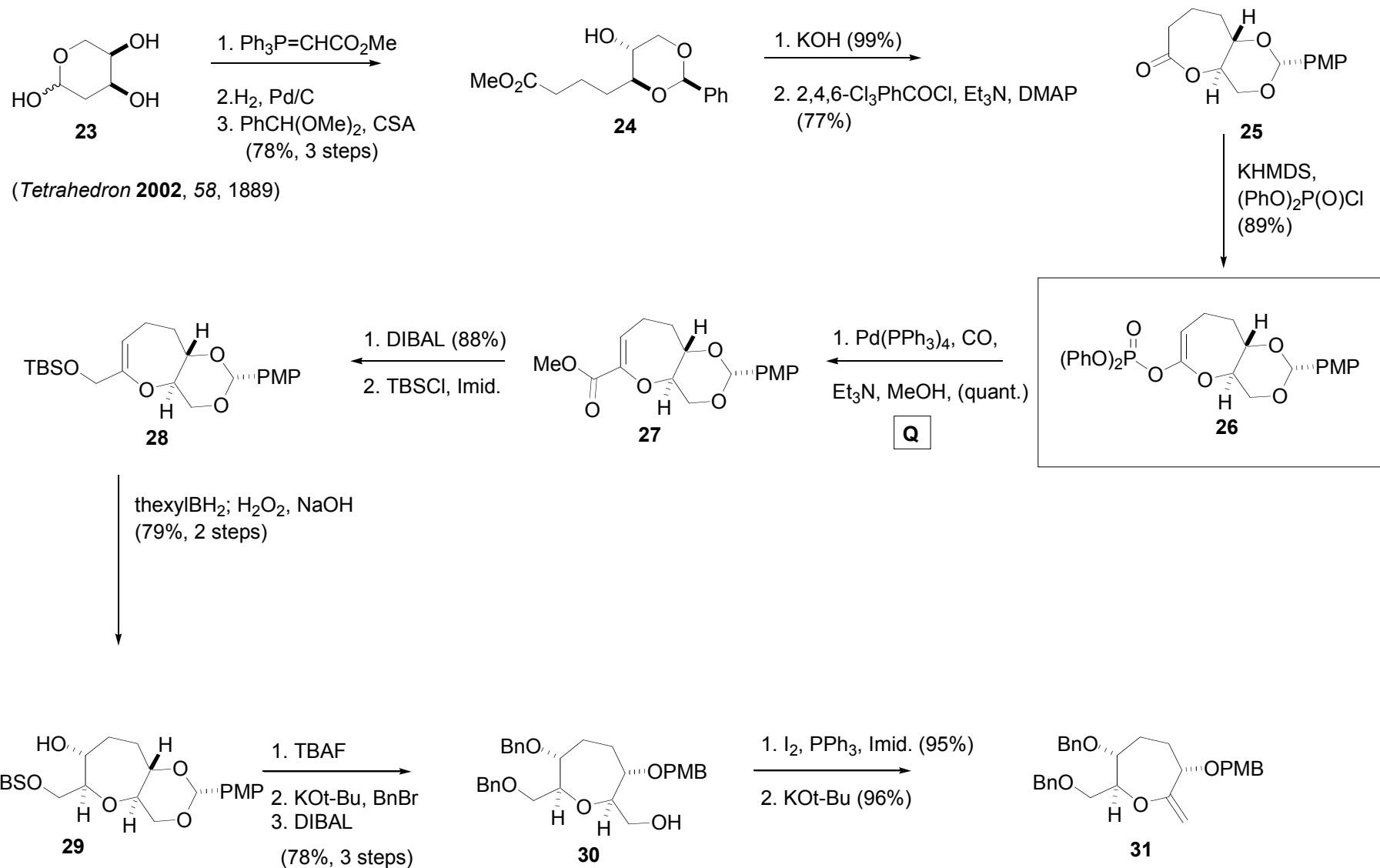
- KHMDS,
(PhO)₂P(O)Cl

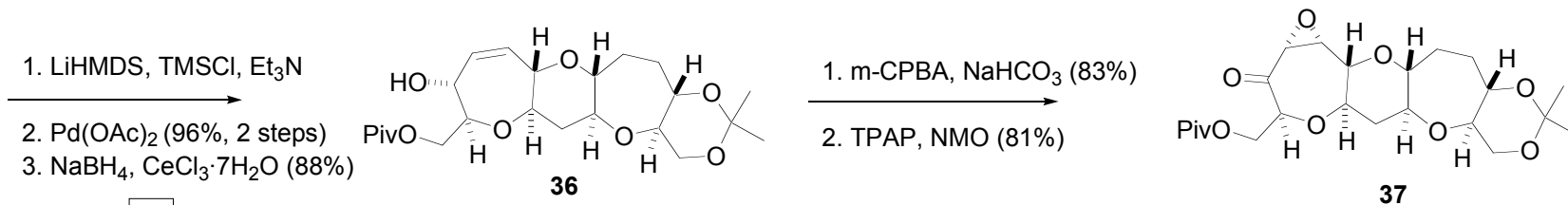
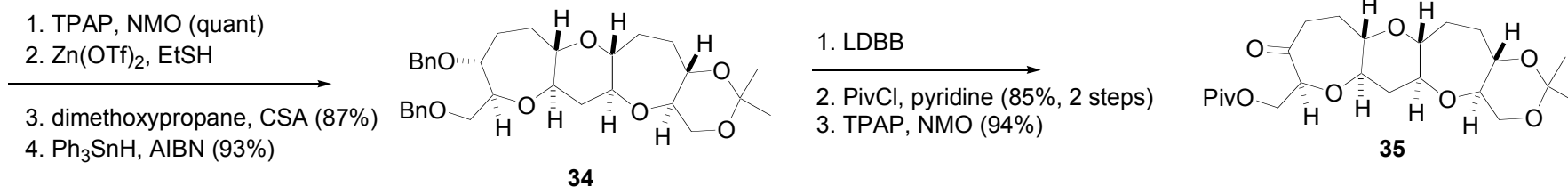
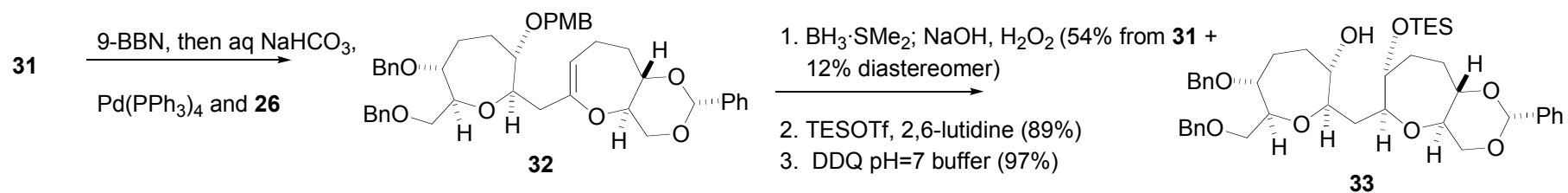


Completion of the F-N fragment

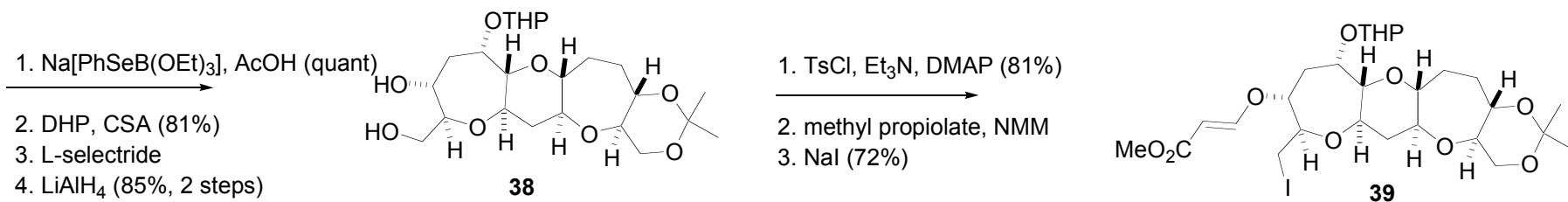


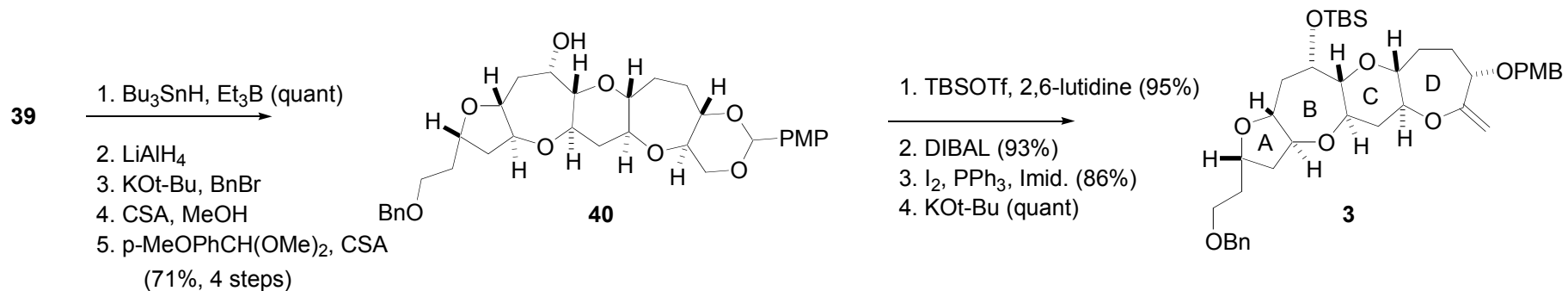
Synthesis of the A-D fragment



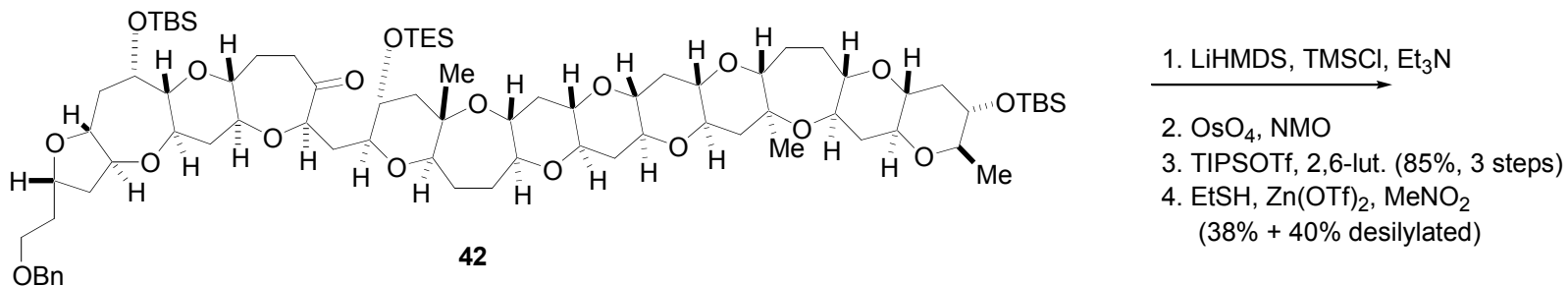
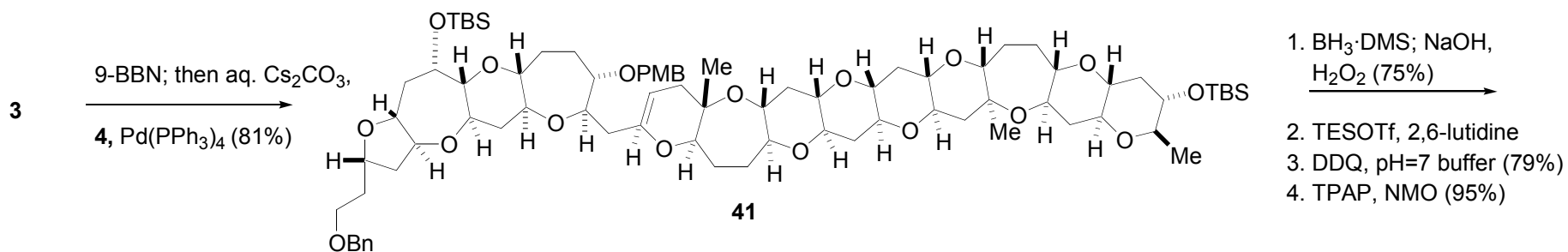


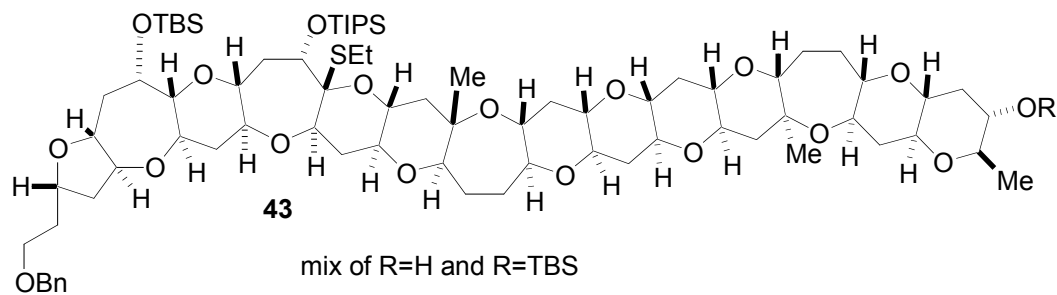
Q





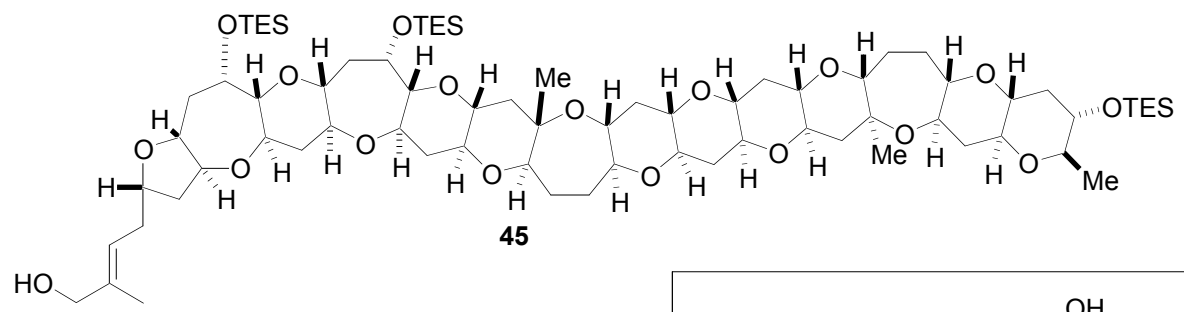
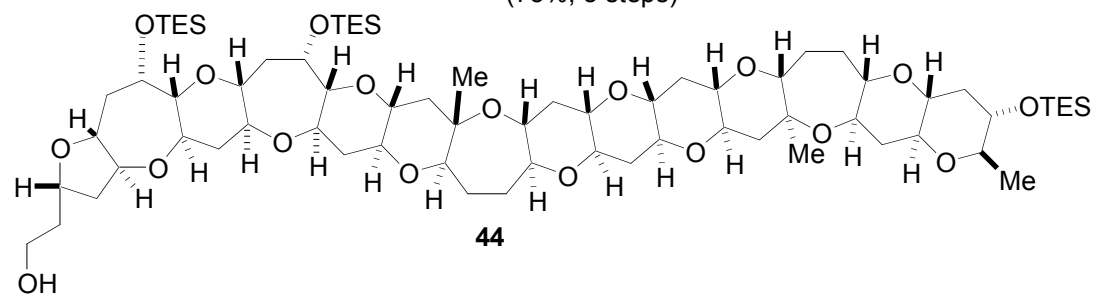
Coupling of fragments 3 and 4 and completion of gymnocin-A



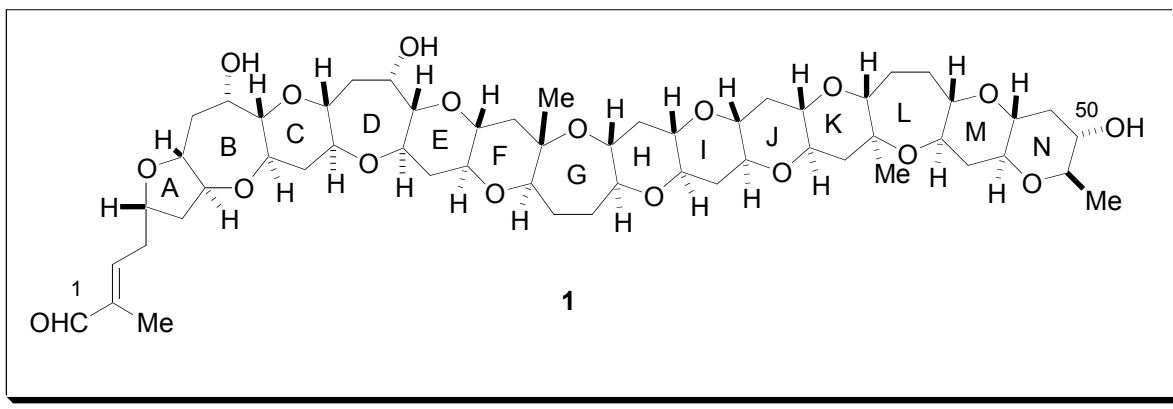


1. TBSOTf (71%)
 2. Ph₃SnH, AIBN (98%)
 3. TBAF
 4. TESOTf, 2,6-lutidine
 5. LDBB
- (73%, 3 steps)

1. TPAP, NMO
 2. Ph₃P=C(Me)CO₂Me
 3. DIBAL
- (66%, 3 steps)



1. TASF*
 2. MnO₂
- (91%, 2 steps)



* TASF = tris(dimethylamino)sulfonium difluoro-trimethylsilicate