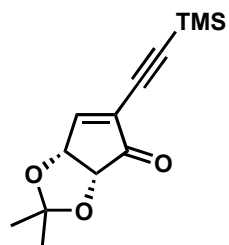


Total Synthesis of Tetrodotoxin



1) Danishefsky's diene,
PhMe, 40°C

A

2) L-Selectride, THF, -78°C
3) NaHMDS, BnBr, DMF, r.t.,
then TBAF, 0°C to r.t.

B

4) LHMDS (2.5 eq), TMSCl (2.5 eq),
THF, -78°C, then 1M HCl, 0°C
5) LDA, Comins reagent,
THF, -78°C

C

6) **1**, Pd(PPh₃)₄, LiCl,
THF, reflux

D

7) O₂, hv, rose bengal,
EtOH, 0°C
then Zn, AcOH

E

8) Ti(OⁱPr)₄, TBHP,
DCM, -20°C

F

9) DMP (2 eq), DCM, r. t.
10) L-Selectride (2 eq),
THF, -78°C

G

11) Ac₂O, py, DMAP,
DMF
12) TBAF, THF, 0°C to r.t.

H

13a) Lindlar cat., H₂, MeOH,
then O₃, MeOH, -78°C, then PPh₃
14a) NaClO₂, NaH₂PO₄,
2-methyl-2-butene, *t*BuOH/H₂O
15a) DPPA, Et₃N, PhMe, reflux,
then allyl alcohol, DMAP, 95°C
16a) Pd(PPh₃)₄, PhSiH₃, DCM

J

17) **3**, HgCl₂, Et₃N,
DCM, r.t.
18) HCl, THF/H₂O, 45°C

K

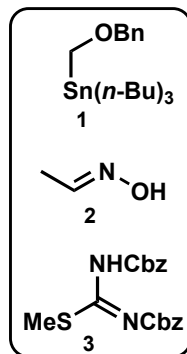
19) H₅IO₆, THF, r.t.

L

13b) CuI (5 eq), TMSN₃ (10 eq),
DMF/MeOH, 100°C

I

14b) **2**, [Rh(COD)Cl]₂,
PhMe, reflux
15b) PIDA,
MeCN/H₂O, 65°C



20) DMP, DCM, r. t.
21) HCl,
THF/H₂O, 35°C

M

