History and Biology of Tetrodotoxin

1909, Tahara: **Crude toxin** (ca. 0.2–4 % pure) from globefish ovaries, and named it 'tetrodotoxin'

1950, Yokoo: **Crystalline form TTX** from the liver and ovaries of Sphoeroides rubripes.

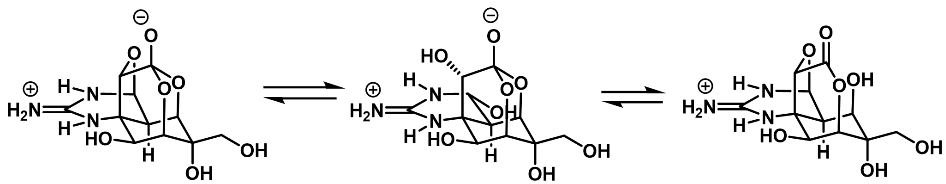
1964, Woodward, Tsuda, Goto, and Mosher: **3D structure confirmed**

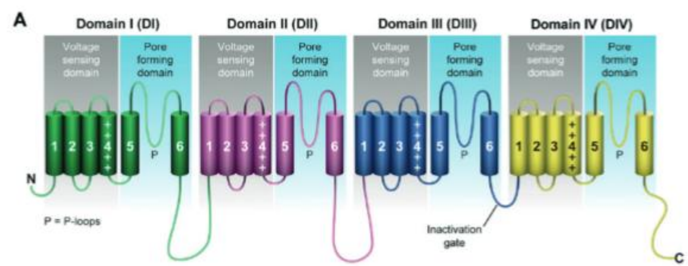
1972, Kishi: Total synthesis of **(±)-TTX**

2003, Isobe, Du Bois Asymmetric synthesis of **(-)-TTX**

2008, Sato
2017, Fukuyama
2020, Yokoshima
2022, Trauner
2023, Qi

TTX's interconversion in water





TTX's bioactivity:
Block voltage gated sodium channels(VGSC)
impede neuronal communication

Table 1: Mammalian isoforms of Na_v α-subunits.

Isoform	TTX IC_{50} [nM]	Primary localization	Disease link[a]
TTX-sensitive			
$Na_v1.1$	5.9[28,29]	CNS,[b] Heart	Epilepsy 癫痫
$Na_v1.2$	7.8[30,31]	CNS	Epilepsy
$Na_v1.3$	2.0[31,32]	Embryonic CNS	Nerve injury
$Na_v1.4$	4.5[31,33]	Skeletal muscle	Myotonias 肌无力
$Na_v1.6$	3.8[31,34]	DRG,[c] CNS	CNS disorders
$Na_v1.7$	5.5[31,35]	DRG	Pain sensation
TTX-resistant			
$Na_v1.5$	1970[28,31]	Heart, CNS	Cardiac arrhythmias
$Na_v1.8$	1330[31,36]	DRG	Pain sensation
$Na_v1.9$	59600[37,38]	DRG	Pain sensation

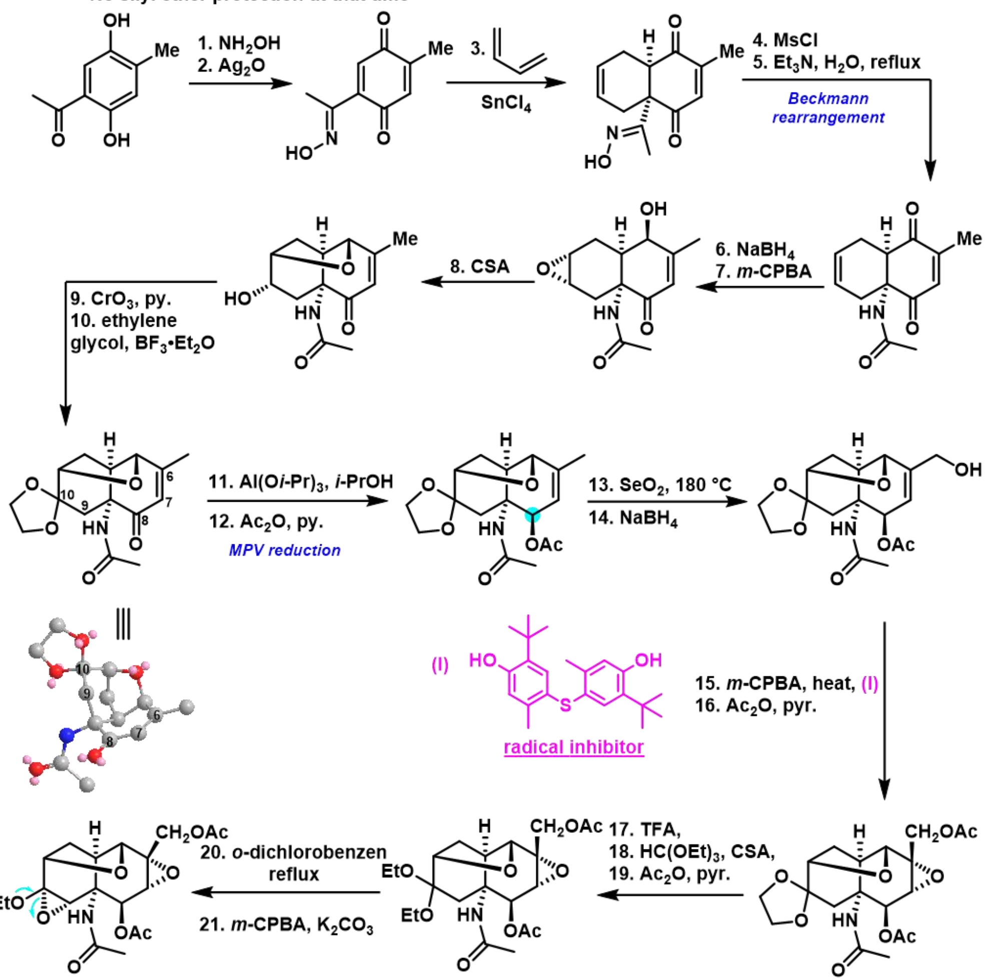
[a] This list represents only a partial list of associated disease states.
[b] CNS: Central nervous system. [c] DRG: Dorsal root ganglion.

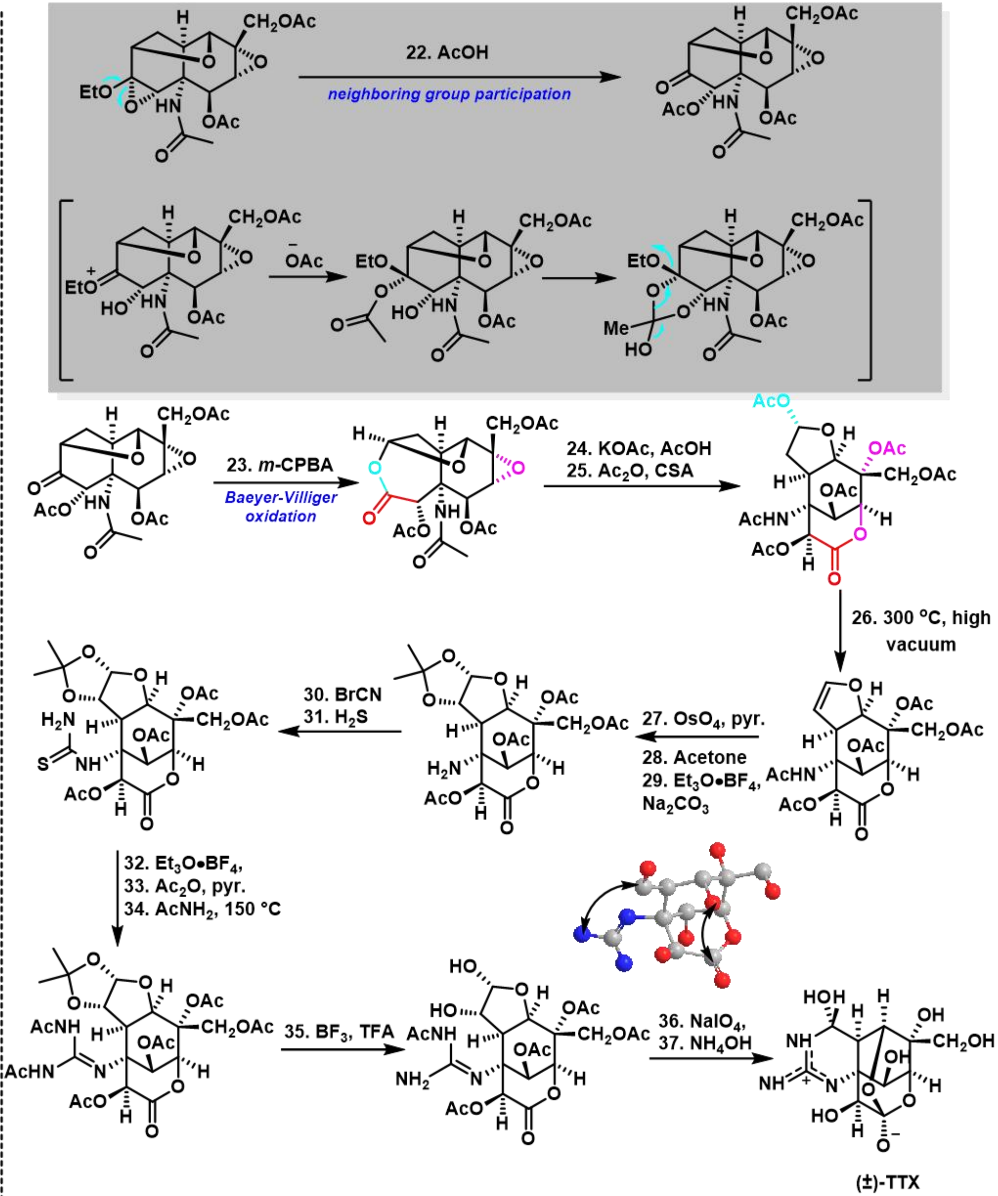
TTX's potential application in clinic:
1. Anesthetic (No cardiovascularside effects, synergistic effect)
2. Cancer (combate cancer, release acute pain)
3. Drug addiction (alleviatean acute heroin withdrawal effect)

1. Kishi's work, 1972

Tetrahedron Lett., **59**, 5127-5132 (1970)
J. Am. Chem. Soc., **94**, 9219-9221 (1972)

- Masterpiece of synthetic chemistry
- All regio- and stereoselective manipulations are substrate-controlled
- No silyl ether protection at that time

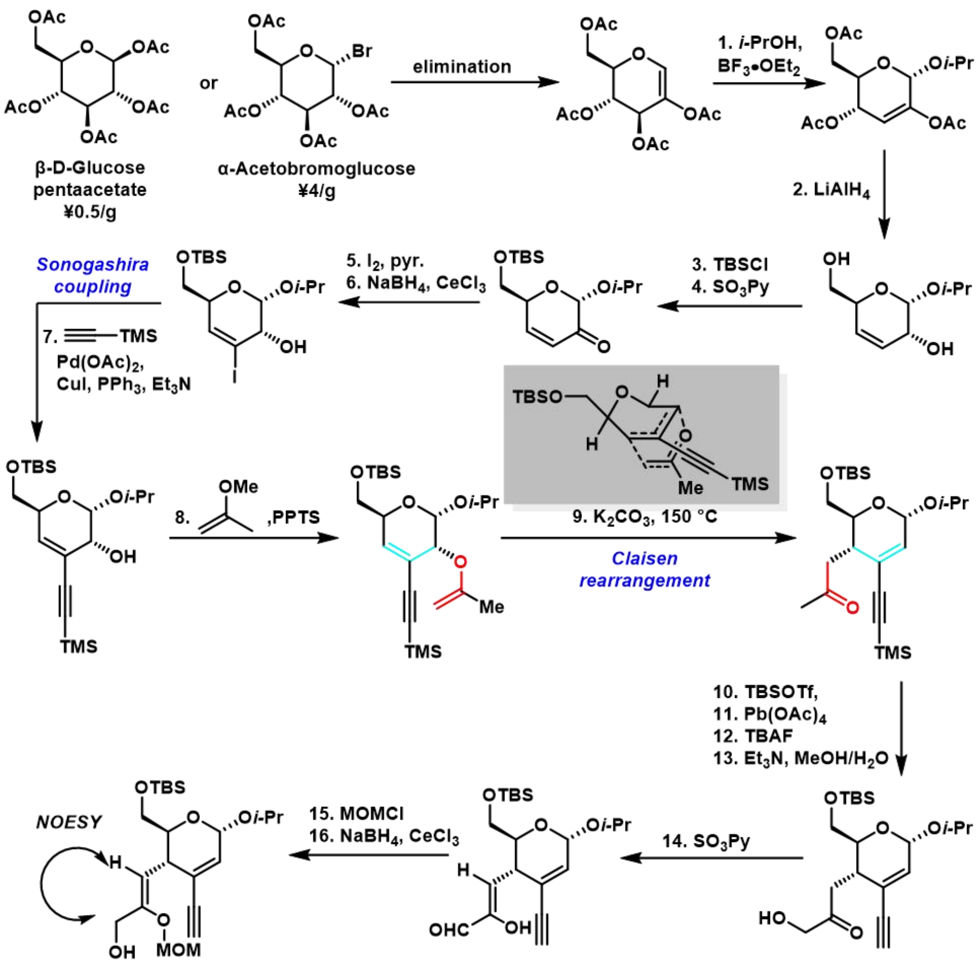


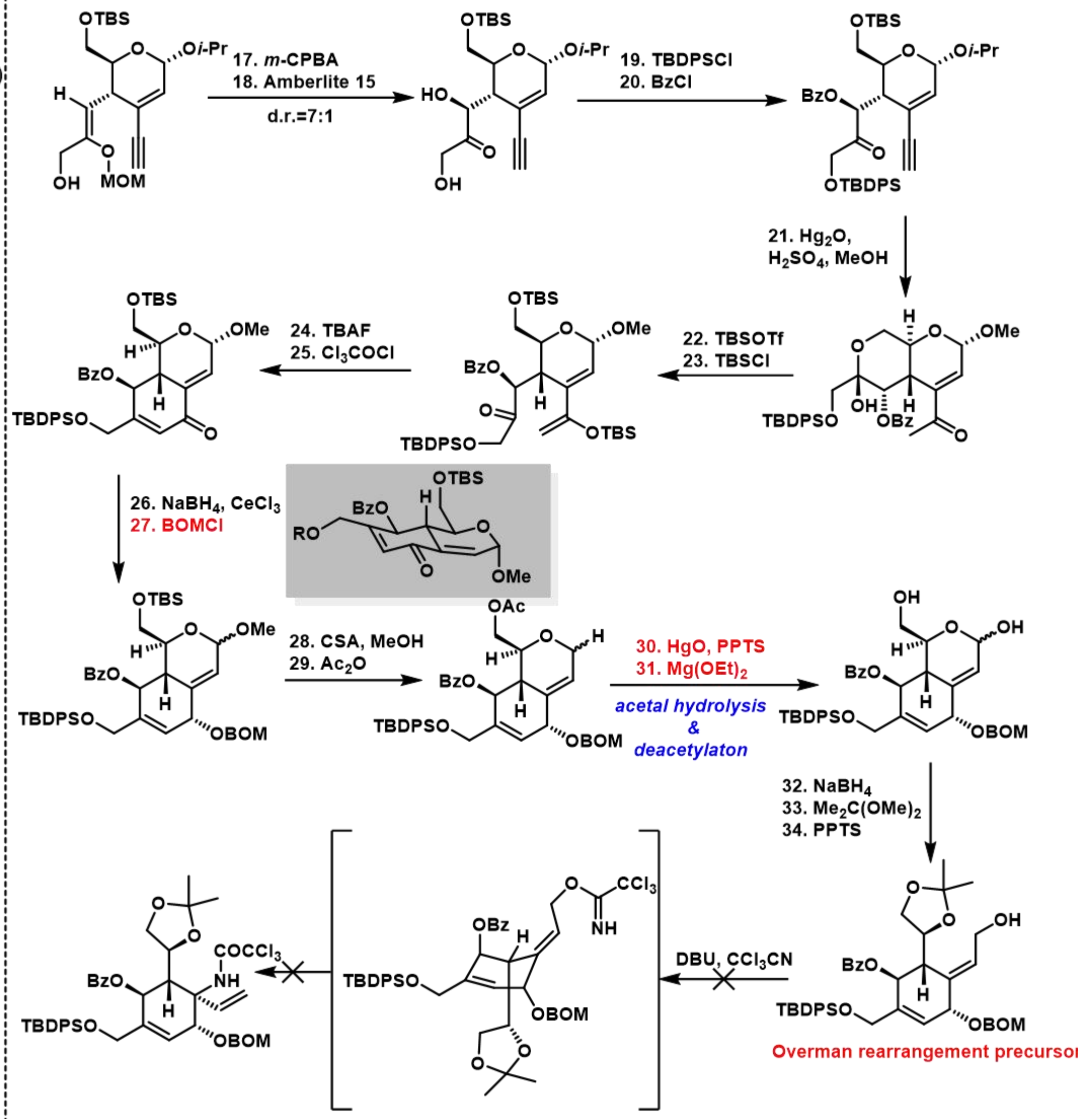


2. Isobe's work, first generation, 2003

J. Am. Chem. Soc. 125, 8798–8805 (2003)
Angew. Chem. Int. Ed. 43, 4782–4785 (2004)
Chem. Asian J. 1, 125–135 (2006)

- more than 72 steps in total, 39 steps of 2nd gen.
- use suger as a chiral unit
- Overmann rearrangement to form tertiary amine





Tetrodotoxin Synthesis

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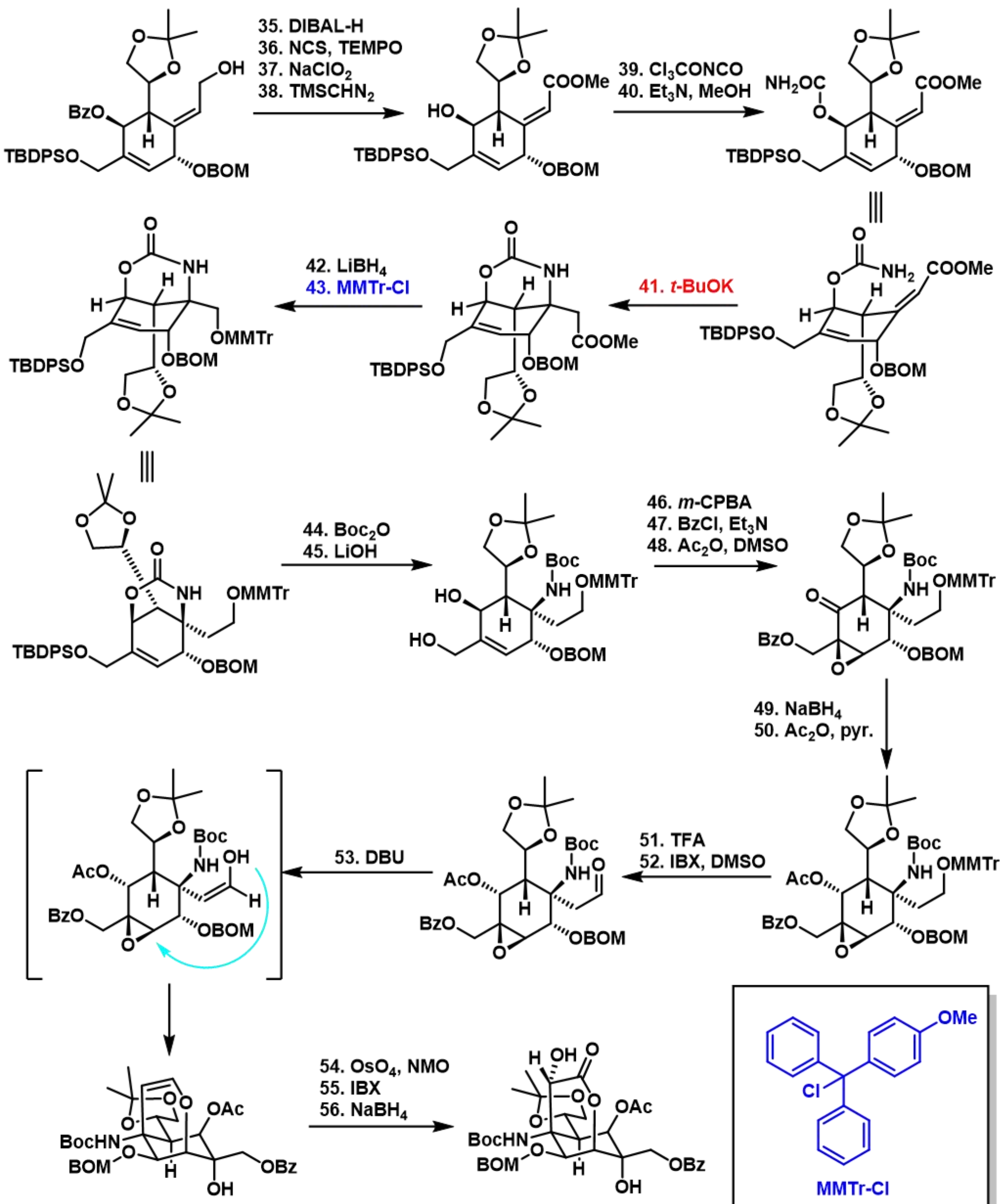
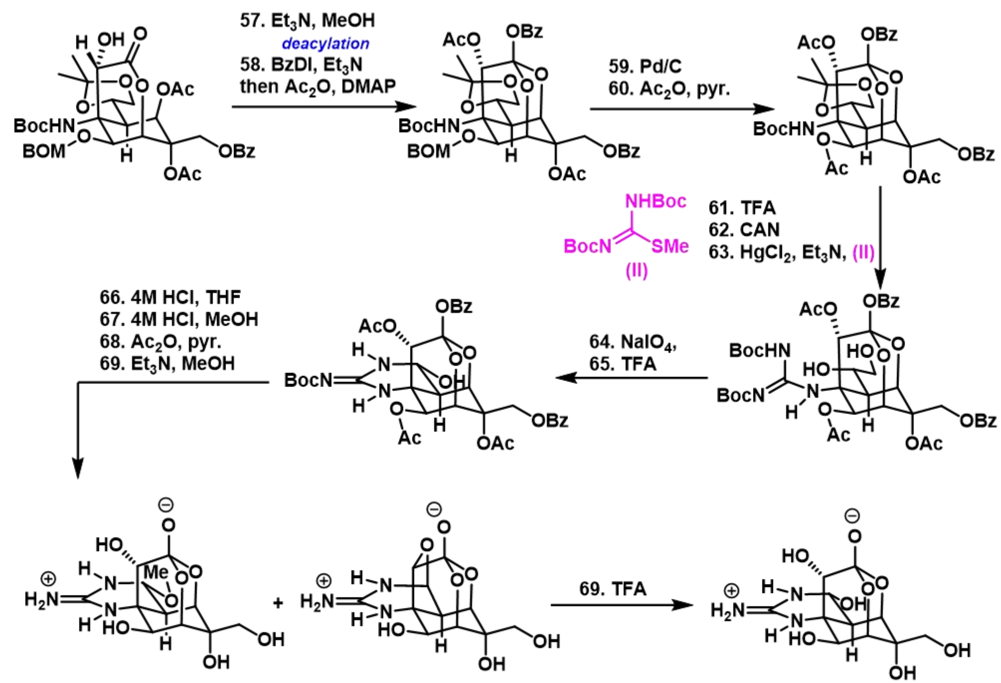
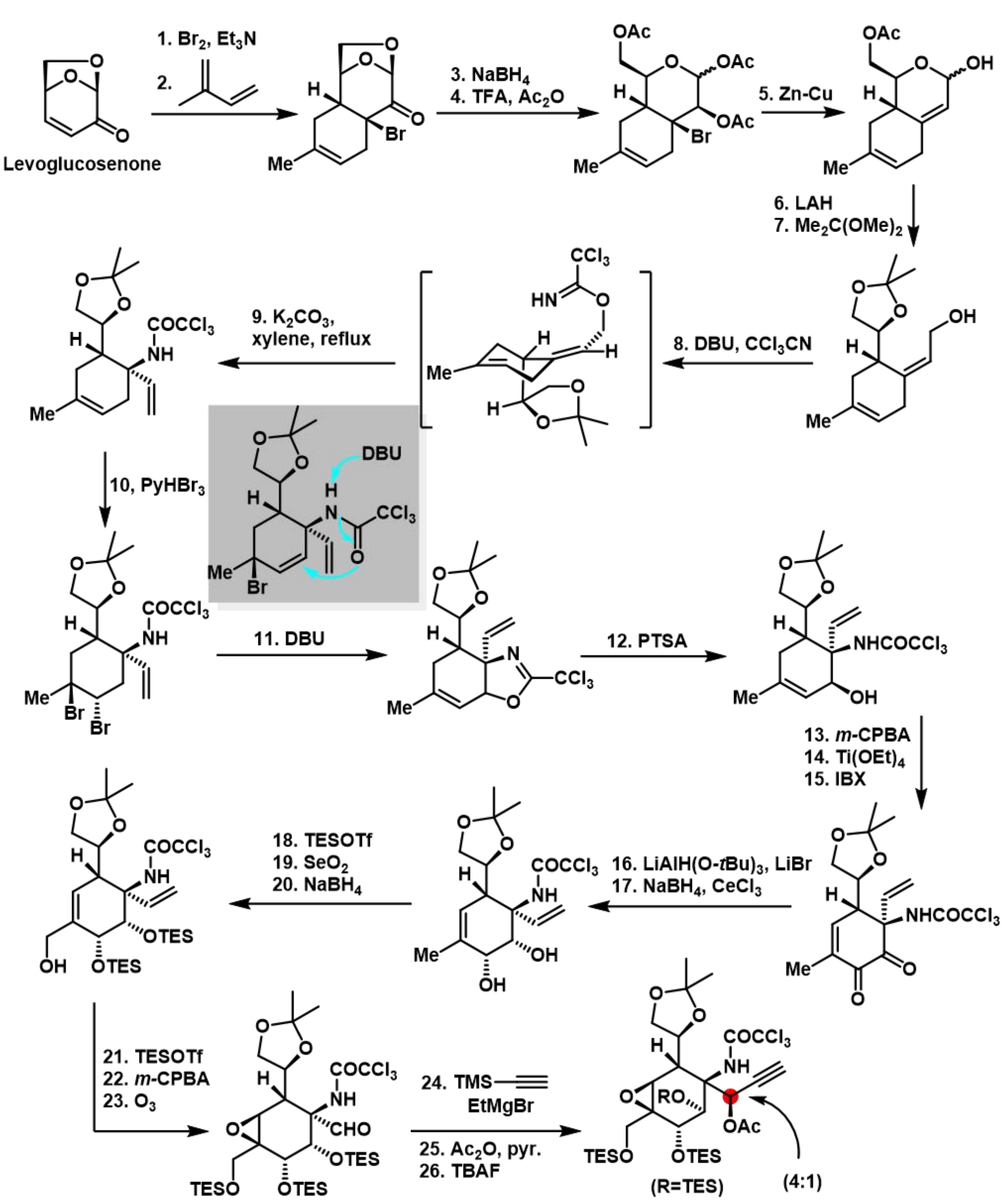
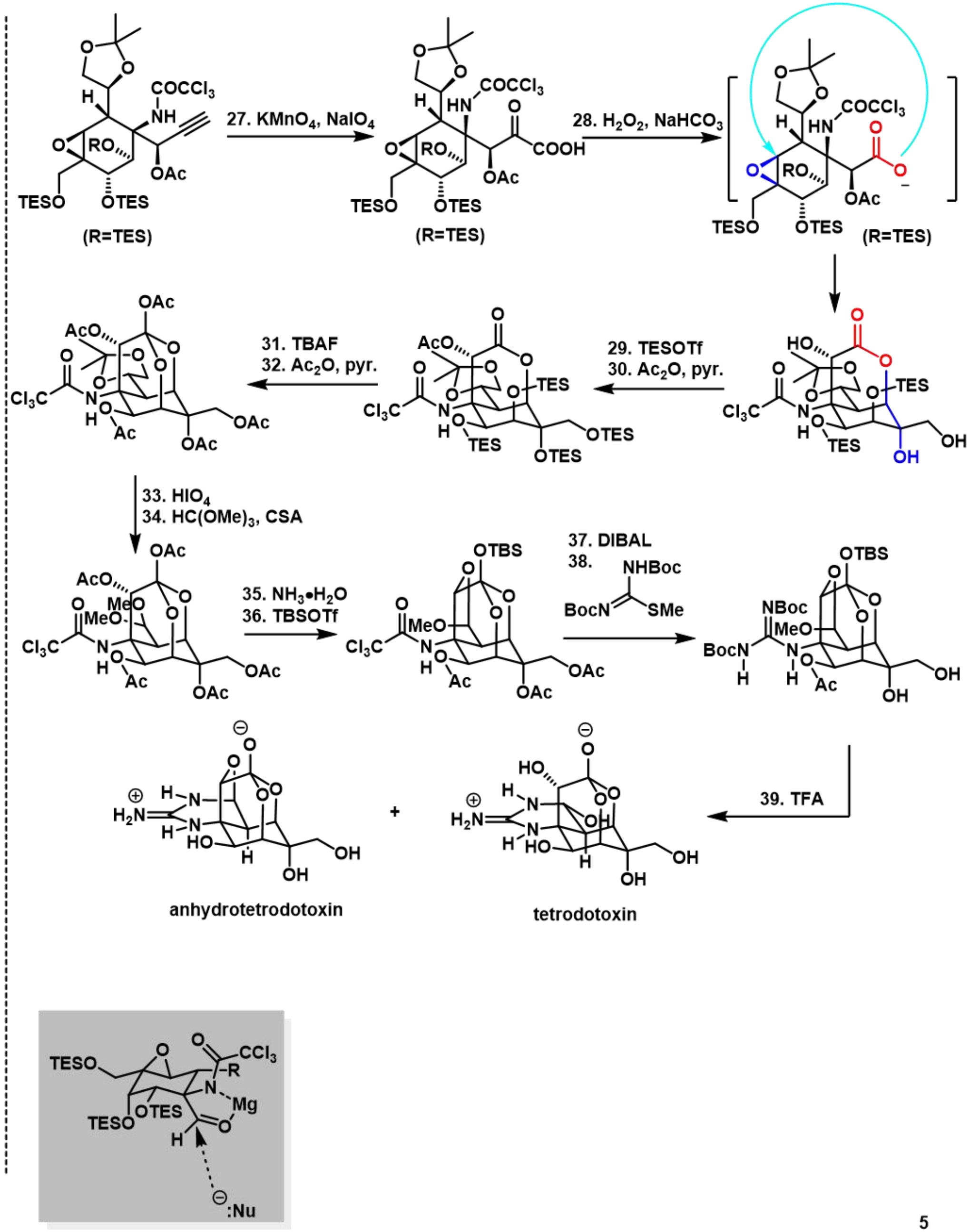
12/09/2023





2. Isobe's work, second generation, 2004

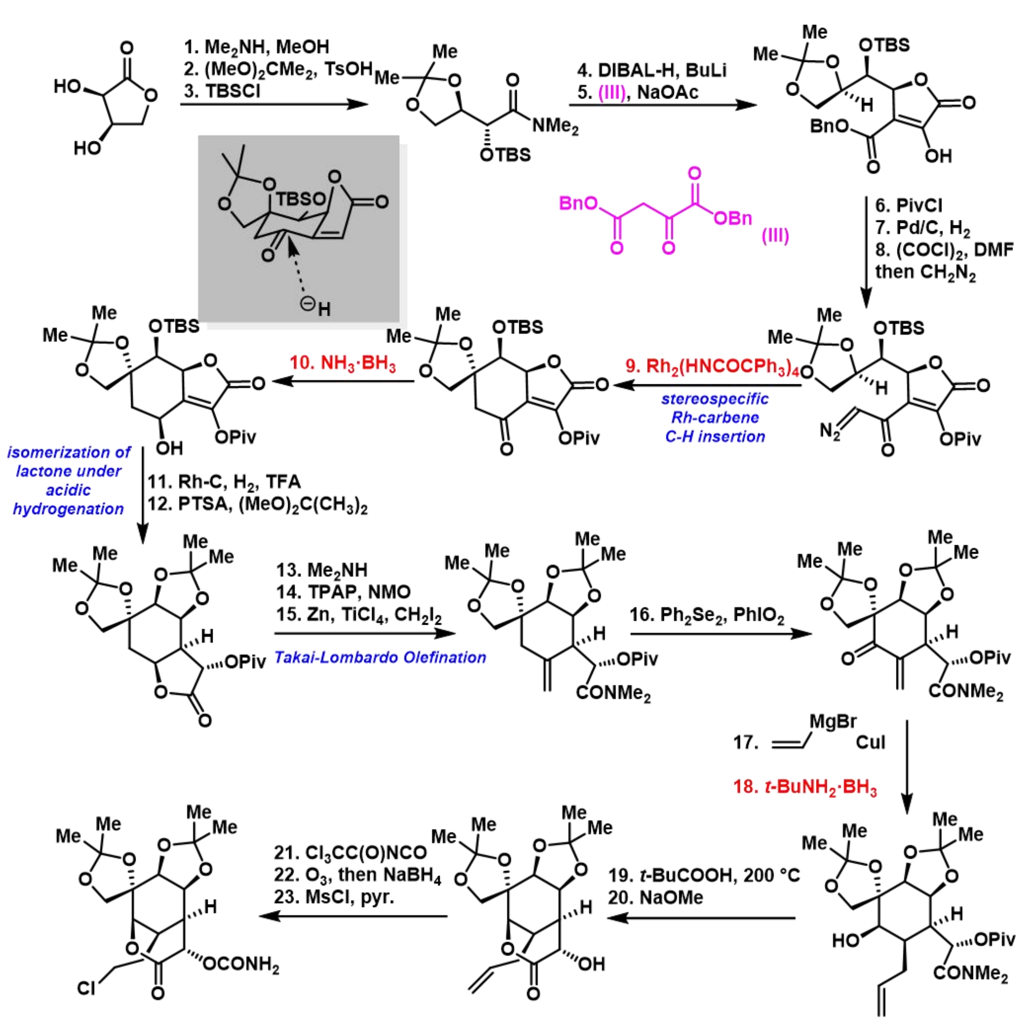


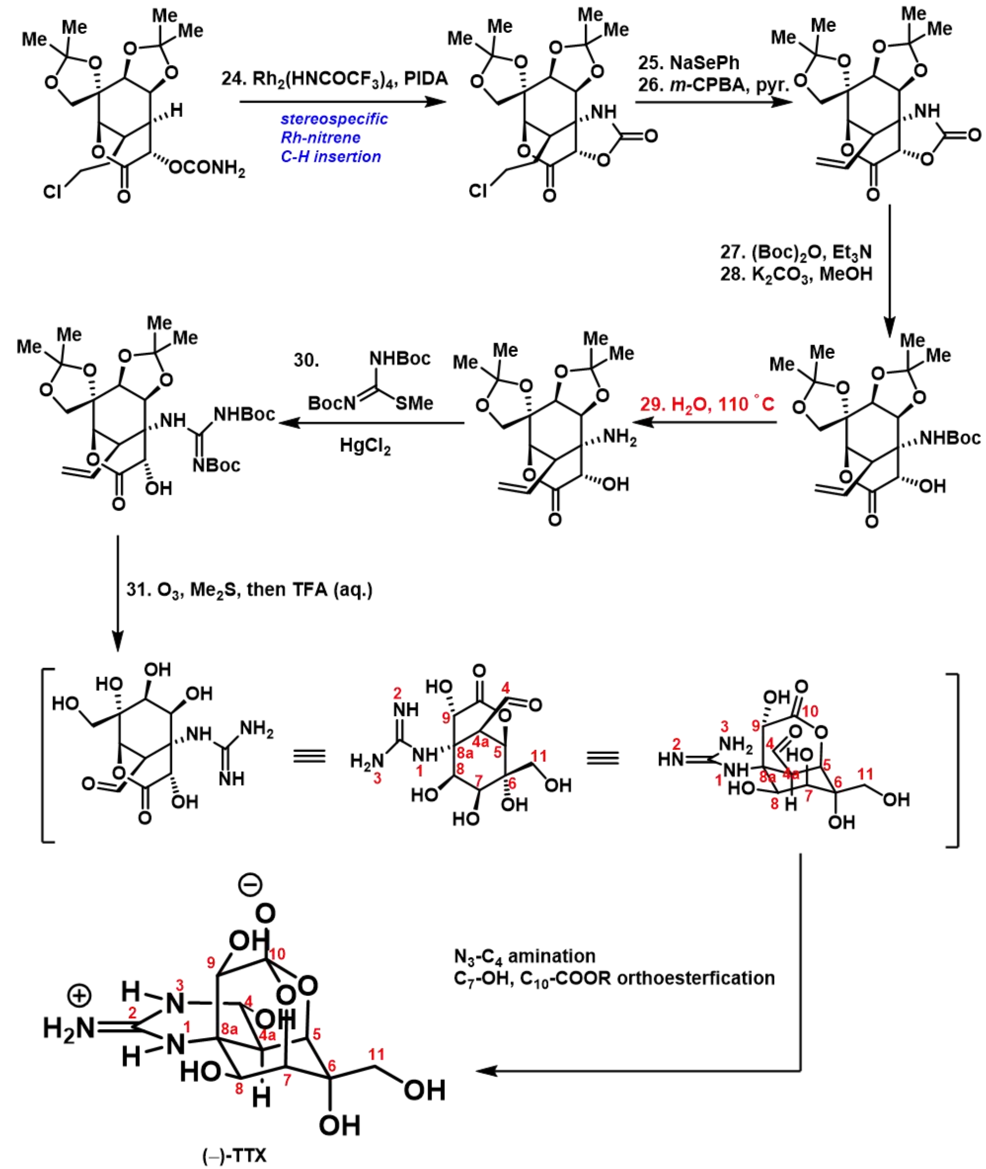


3. Du Bois's work, 2003

J. Am. Chem. Soc. 125, 11510 -11511 (2003)

- Rhodium-catalyzed C-H bond activation
- Three rings in one step at final stage





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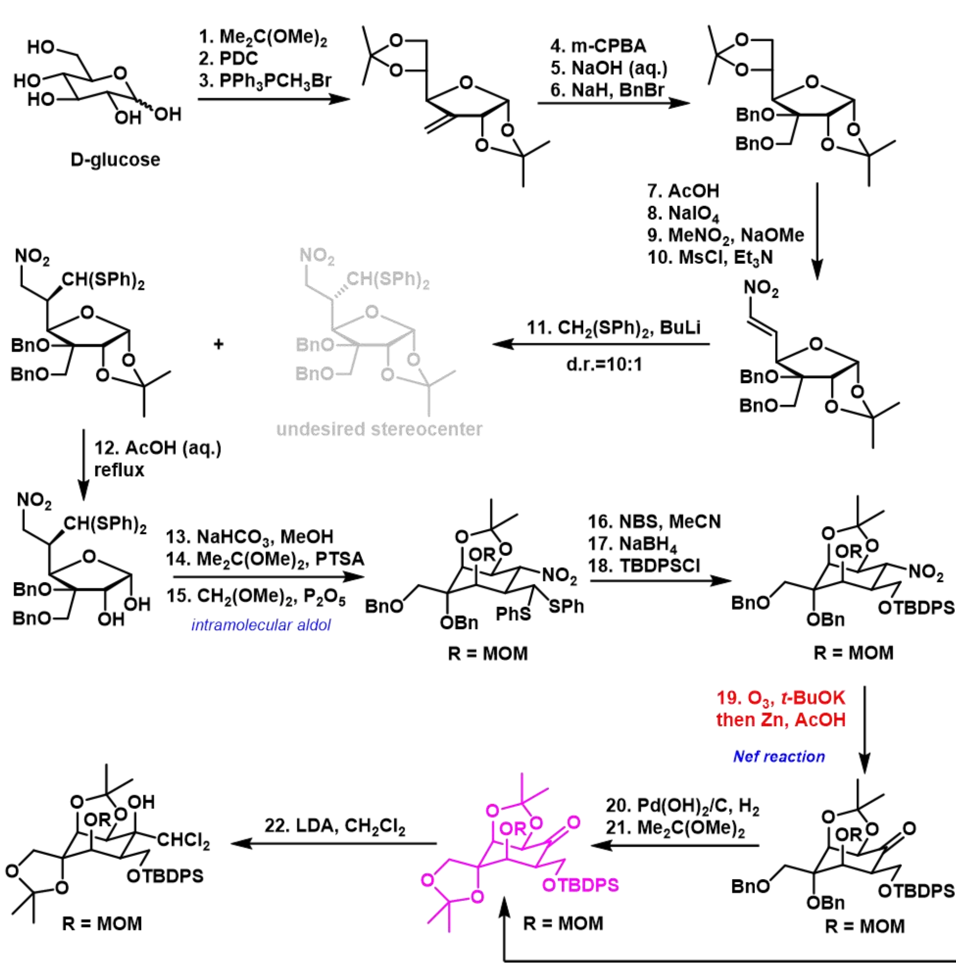
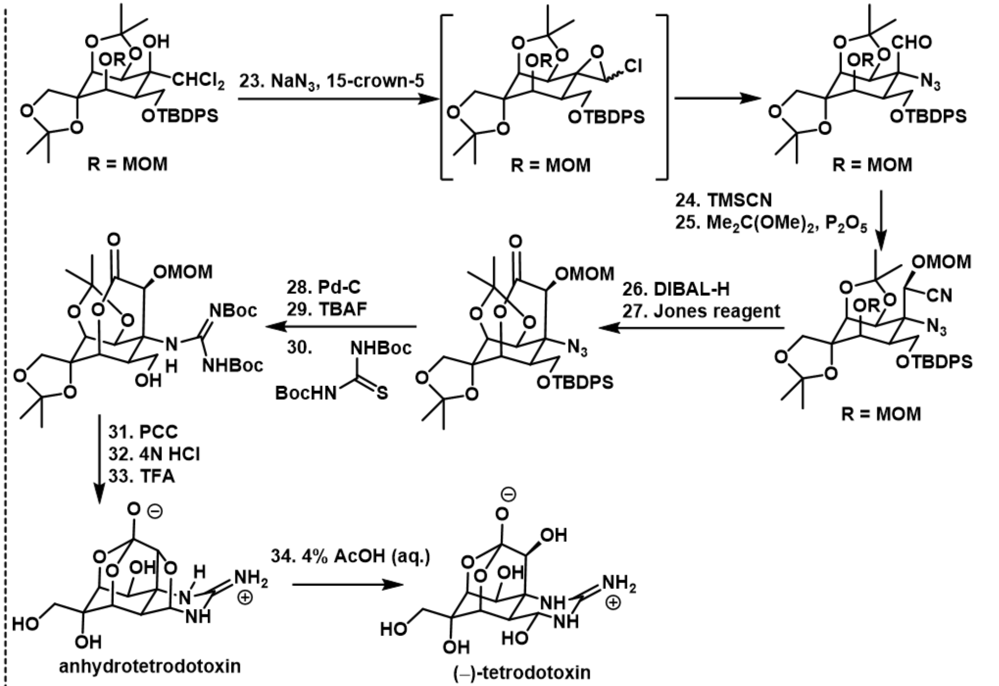
4. Sato's work, 2008

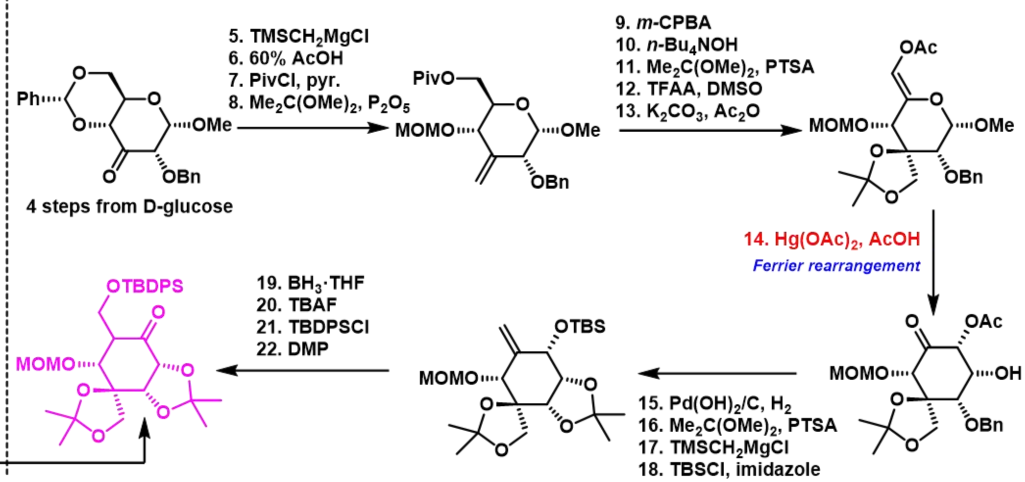
J. Org. Chem. 73, 1234 -1242 (2008)
Bull. Chem. Soc. Jpn, 83, 279-287(2010)

- D-glucose as chiral source
- 15 steps to form the cyclohexane ring
- Epoxide opening with azide and form tertiary amine





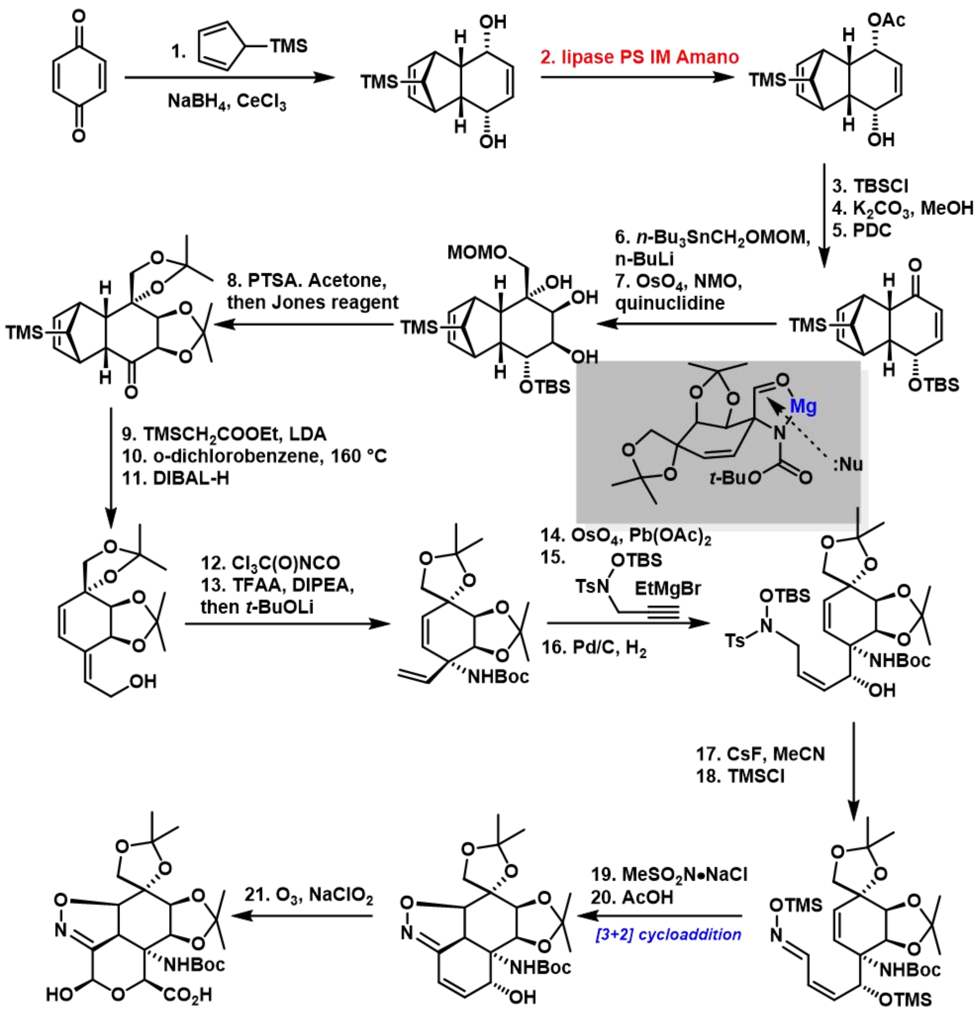
Second generation_formal synthesis

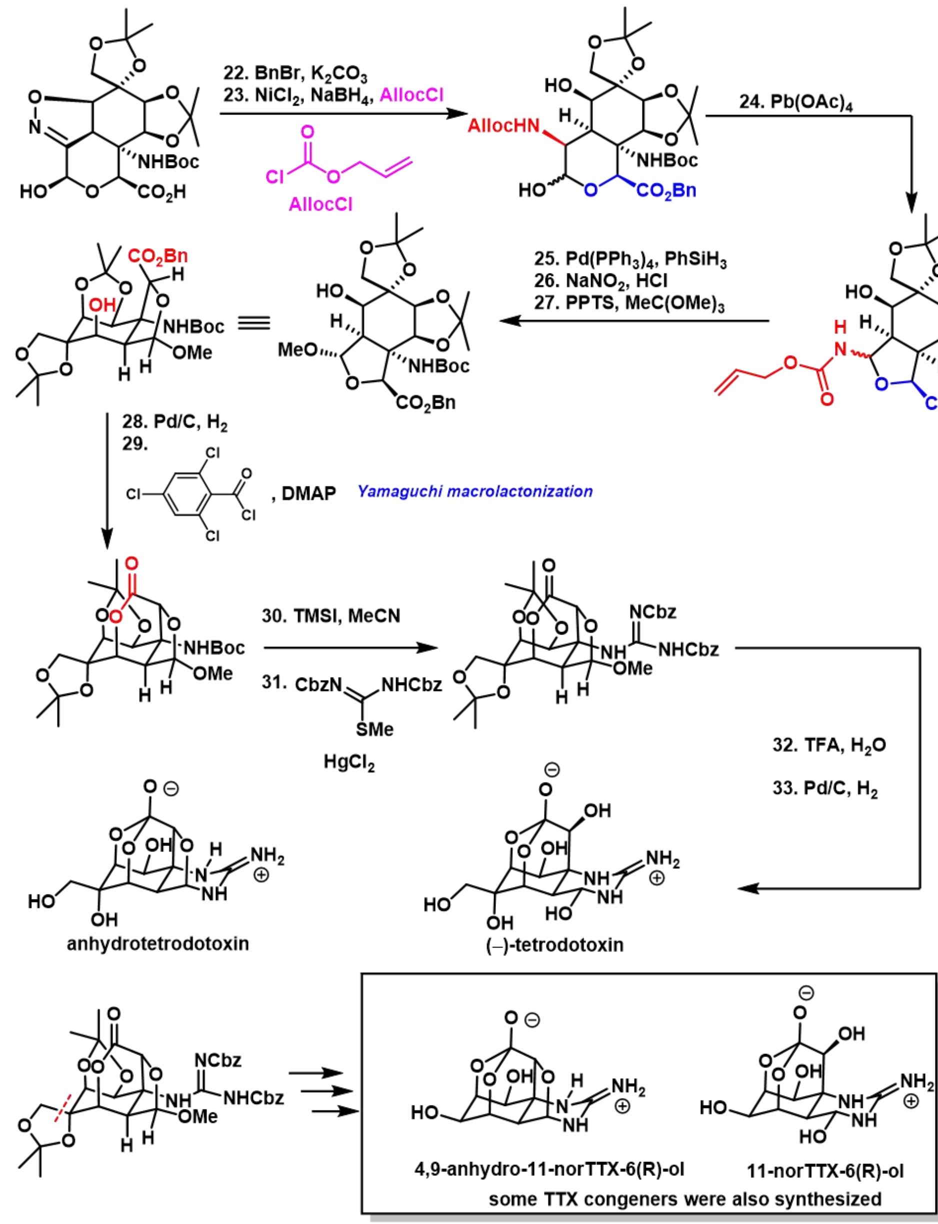


5. Fukuyama's work, 2017

Angew. Chem. Int. ed. 56, 1549 -1552 (2017)

- enzymatic deasymmetration
- overmann rearrangement to form tertiary amine
- Yamaguchi macrolactonization

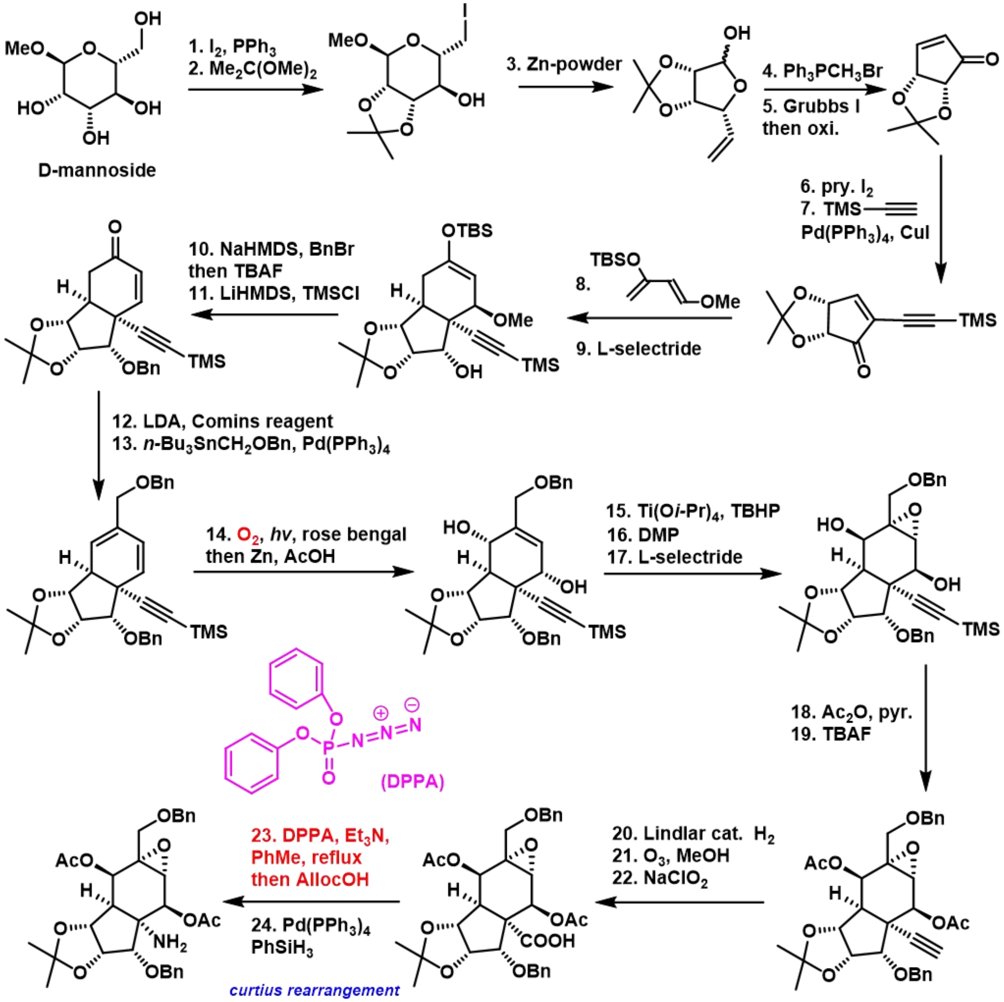


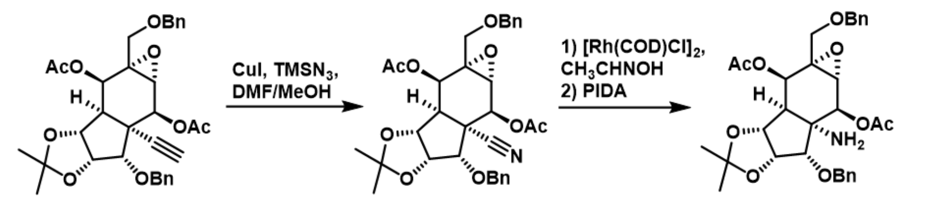


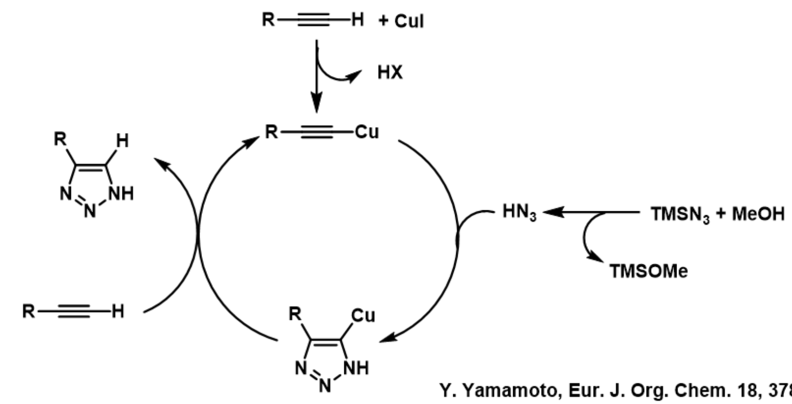
6. Yokoshima's work, 2020

Angew. Chem. Int. ed. 59, 6253 -6257 (2020)

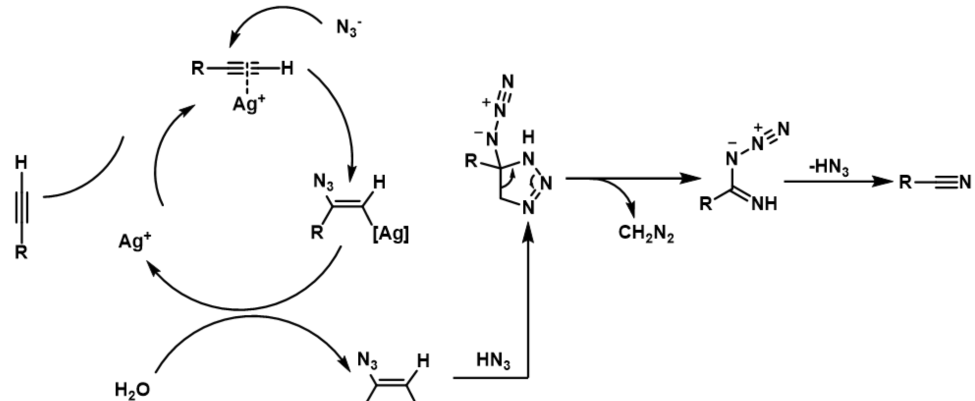
- Diels-Alder reaction with O_2
- Curtius rearrangement to form tertiary amine
- Rhodium catlyzed turning alkyne into cyanide







Y. Yamamoto, Eur. J. Org. Chem. 18, 3789-3791, 2004



N. Jiao, Angew. Chem. Int. Ed. 52, 6677-6680, 2013

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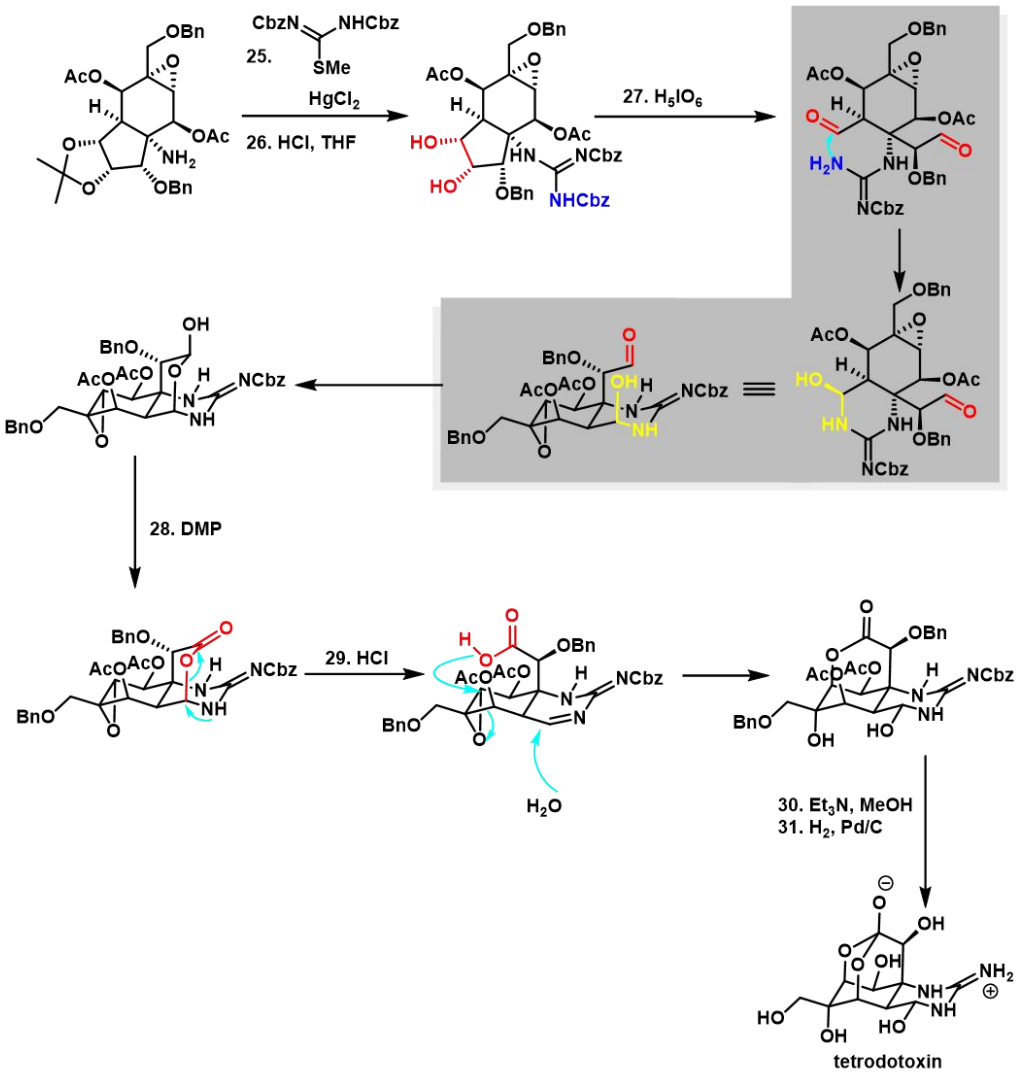
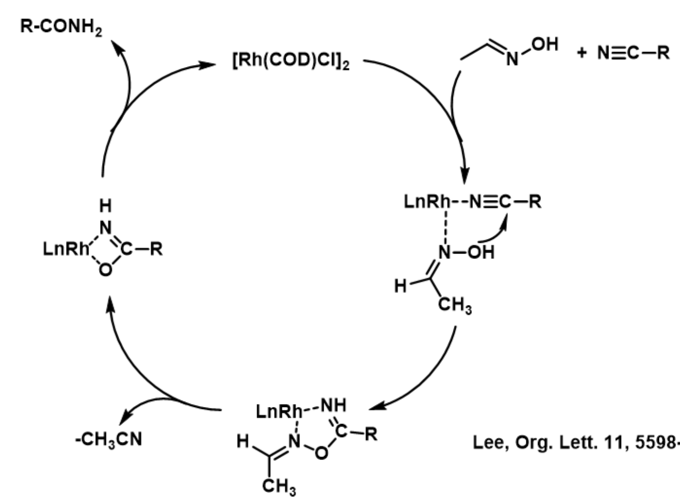


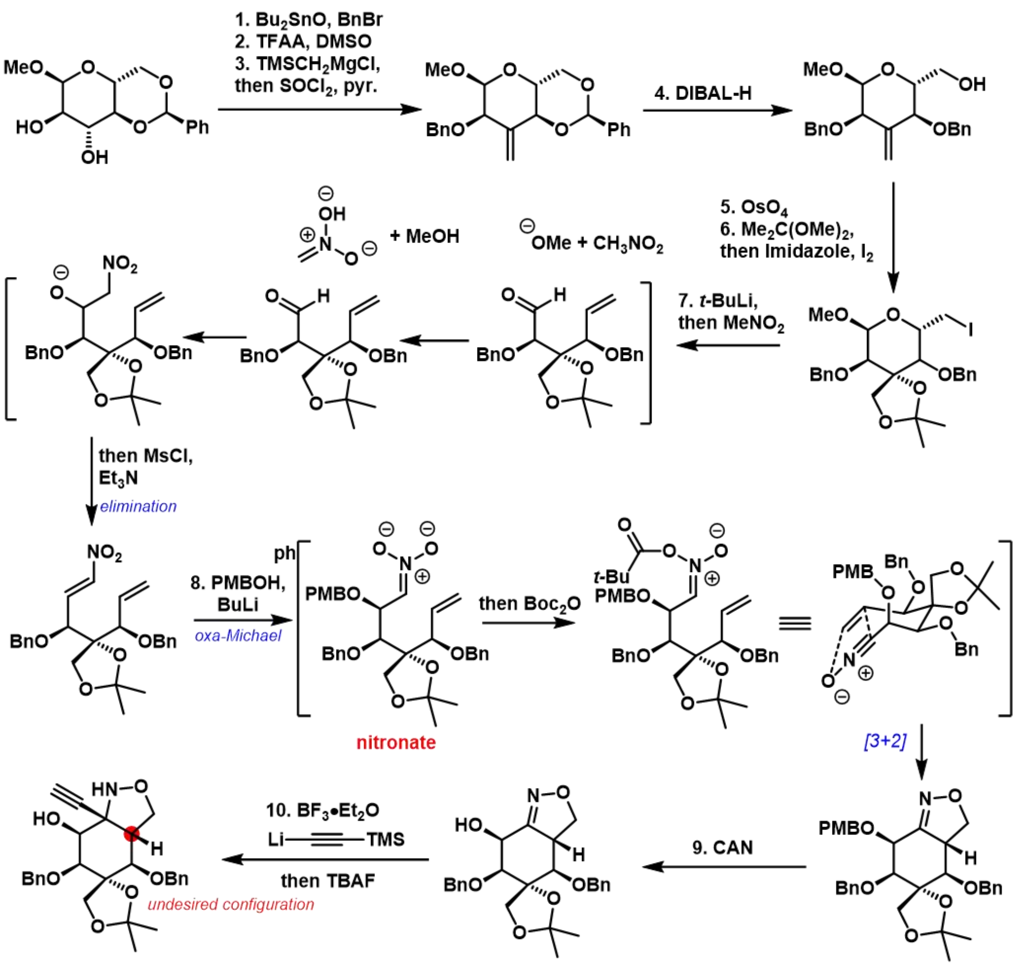


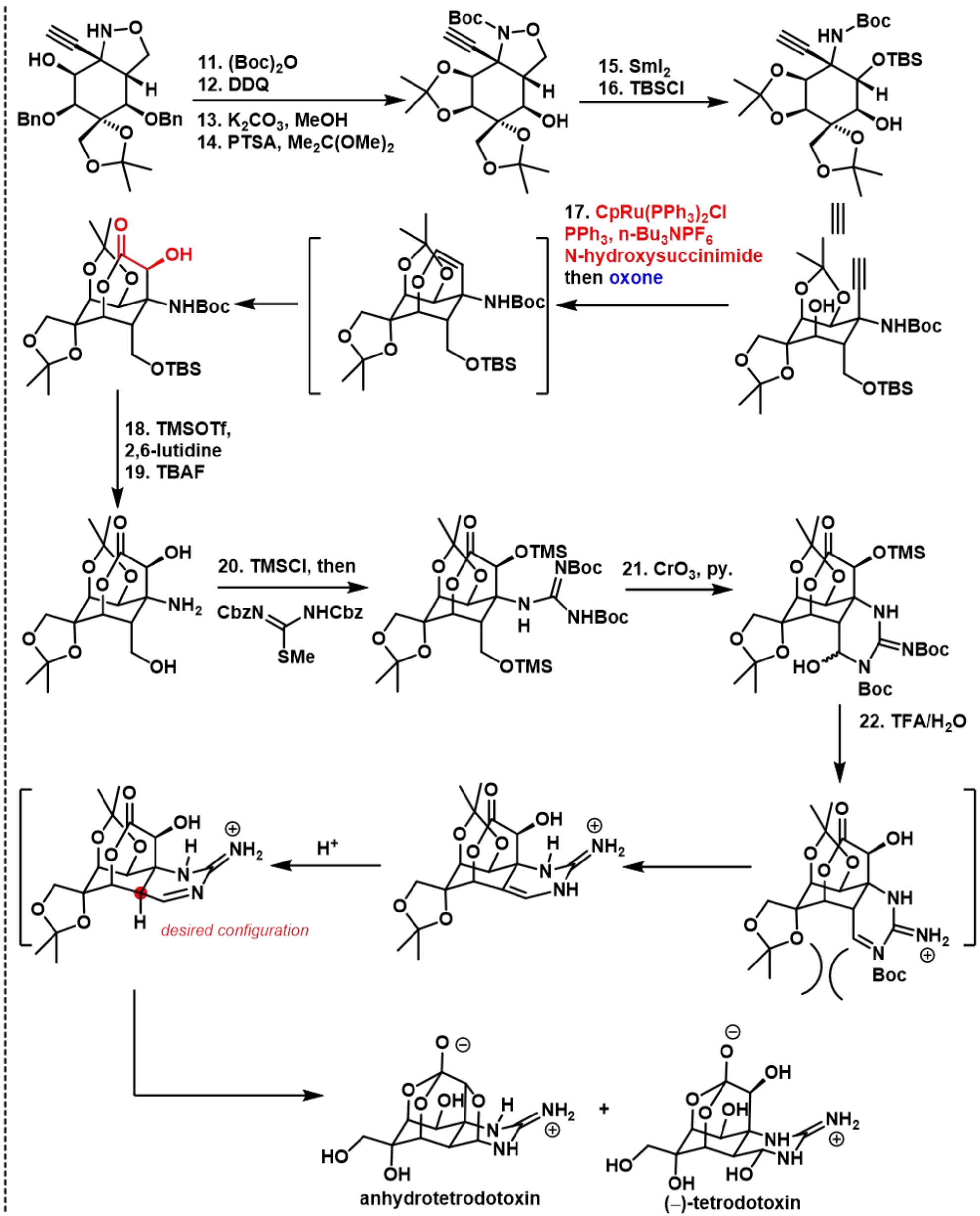
Lee, Org. Lett. 11, 5598-5601, 2009

7. Trauner's work, 2022

Science, 377, 411-415, 2022

- one pot [3+2] cascade reaction to introduce tertiary amine precursor
- ruthenium double-catlyzed cycloisomerization and ketohydroxylation
- 11% overall yield in 22 steps





8. Qi's work, 2023

10.26434/chemrxiv-2023-76wll

- chiral auxiliary assisted Diels-Alder reaction
- SmI_2-mediated epoxide opening
- three rings construction in the last step