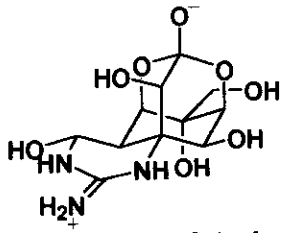
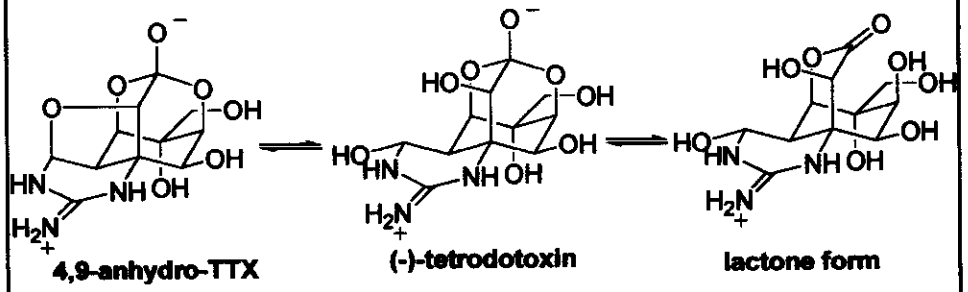
A Stereoselective Synthesis of (-)-Tetrodotoxin

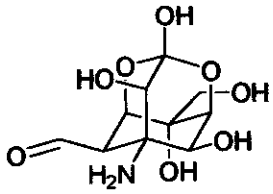


(-)-tetrodotoxin

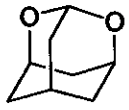
- Tetrodotoxin is found in the livers and ovaries of puffer fish (first isolated in 1909).
- One of the most toxic natural products.
- The structrue was independently determined by three groups (Hirata-Goto, Tsuda, and Woodward) in1964.
- Essential tool in the research area of brain and neuroscience due to its specific inhibition of voltage depended sodium ion-channels.



4,9-anhydro-TTX (-)-tetrodotoxin lactone form

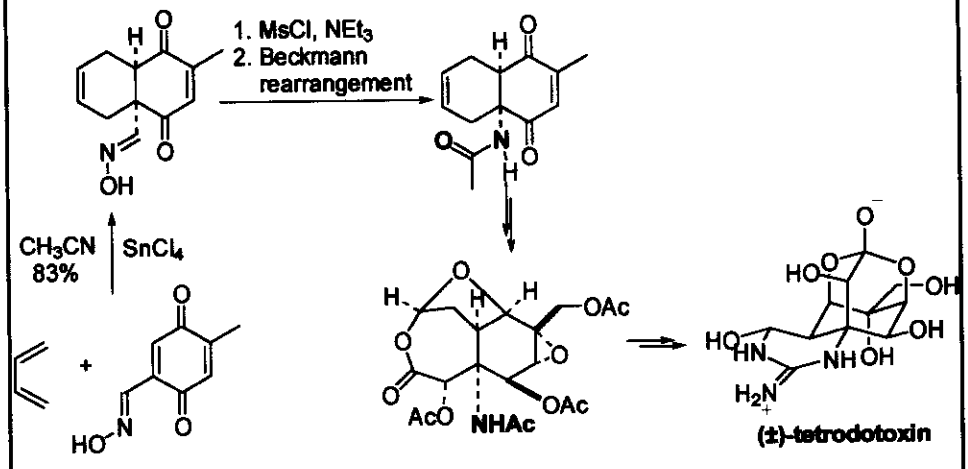


tetrodamine



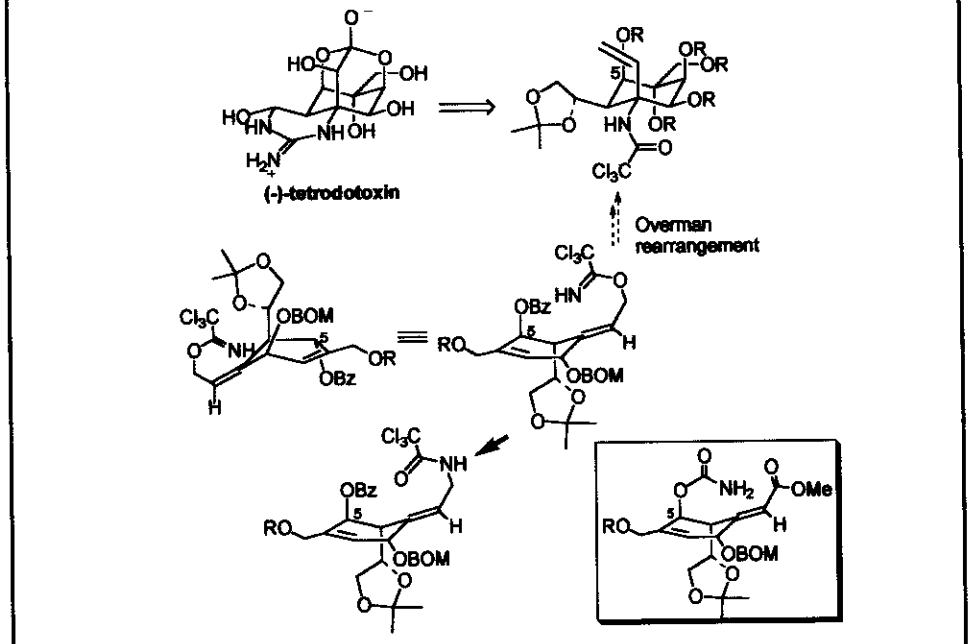
Dioxa-adamantane

First Total Synthesis



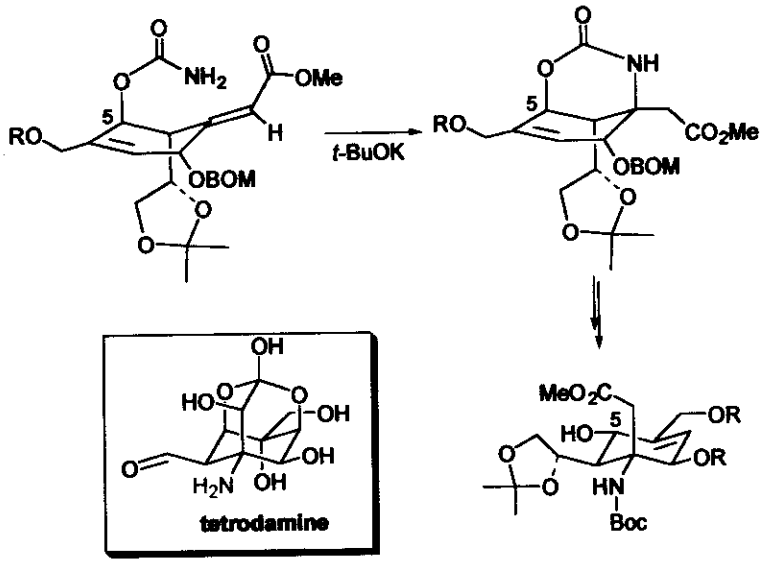
Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am.Chem. Soc.* **1972**, *94*, 9219.

First Asymmetric Total Synthesis of Tetrodotoxin



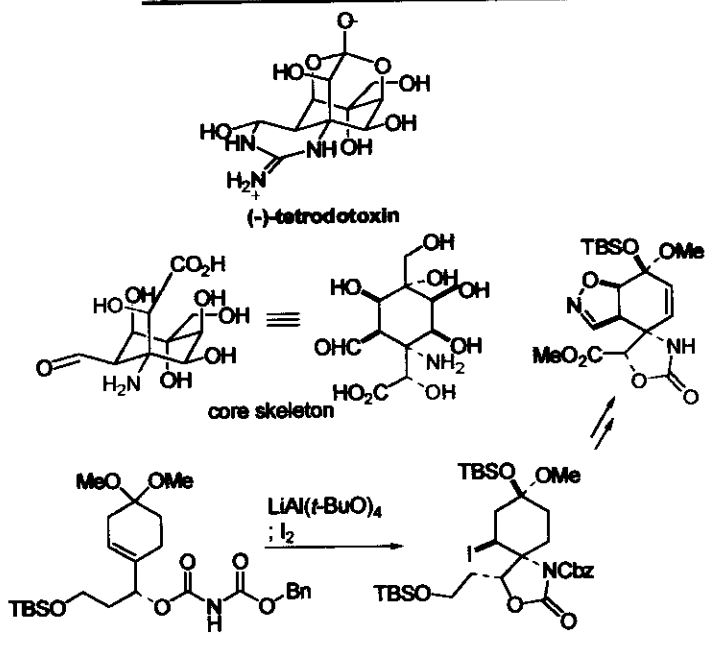
Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798

First Asymmetric Total Synthesis of Tetrodotoxin



Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798

Synthetic Approach to Tetrodotoxin



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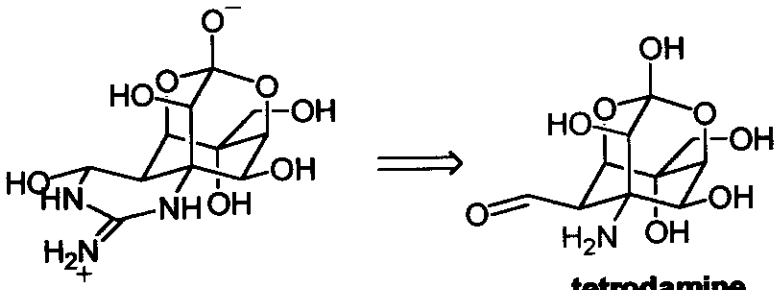
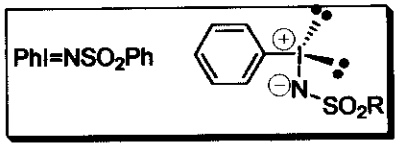
A Stereoselective Synthesis of (-)-Tetrodotoxin



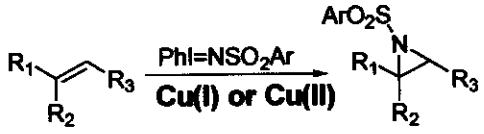
(-)-tetrodotoxin tetrodamine

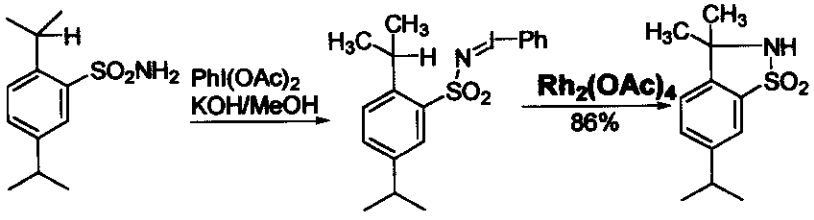
Hinman, A.; J. Du Bois *J. Am. Chem. Soc.* **2003**, *125*, 11510

Iminoiodanes and C-N Bond Formation



[*N*-(Arylsulfonyl)imino]phenyliodane





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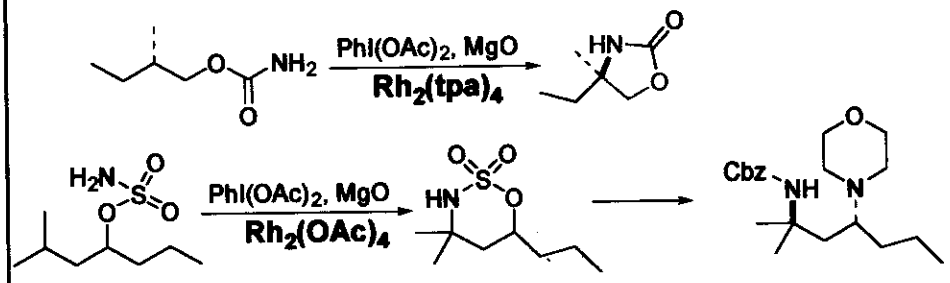
Review: Dauban, P.; Dodd, R. H. *Synlett* **2003**, *11*, 1571

Iminoiodanes and C-N Bond Formation



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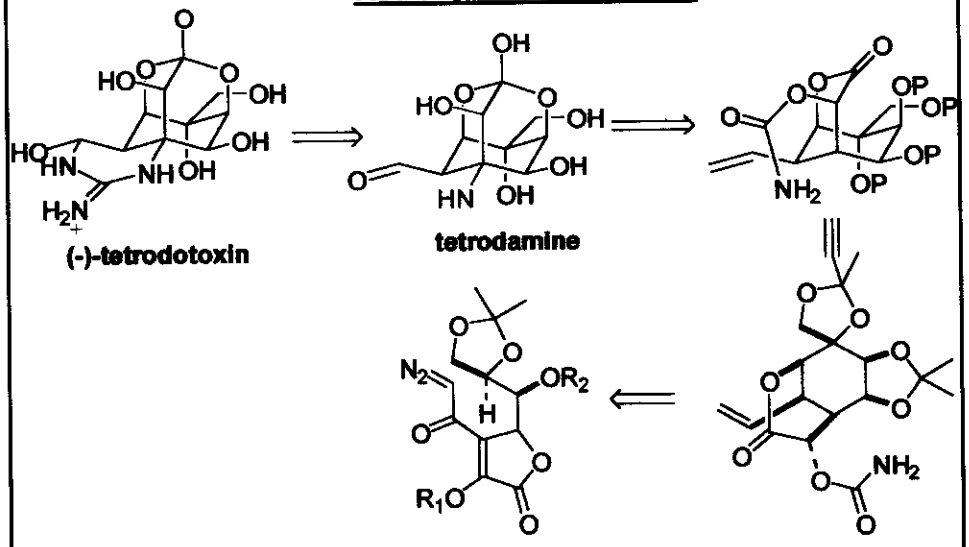
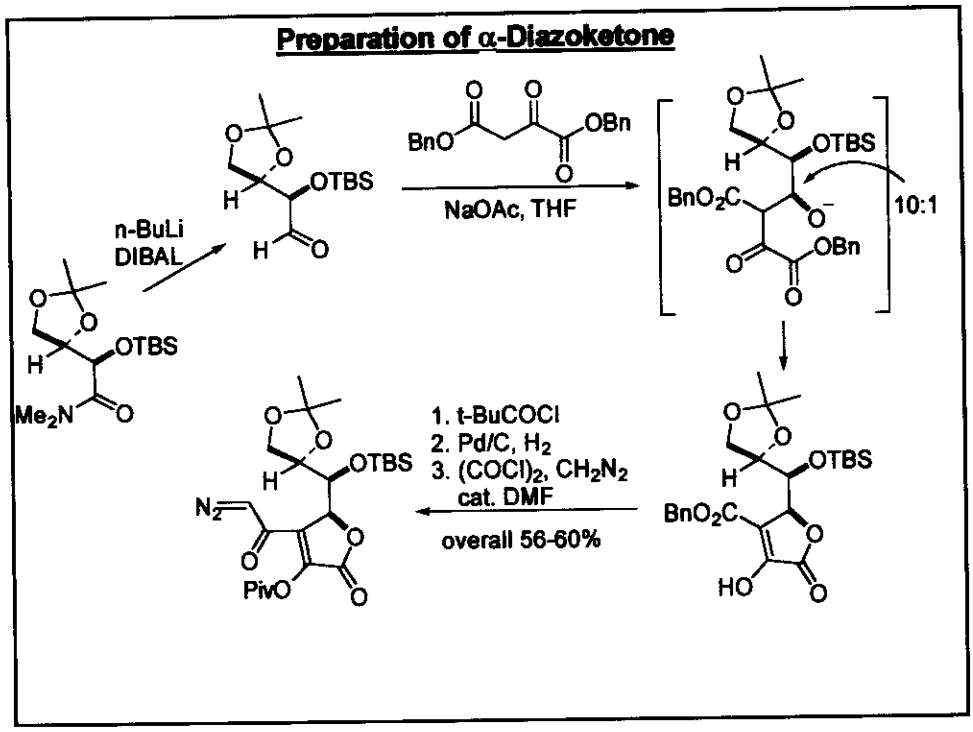
Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 935.

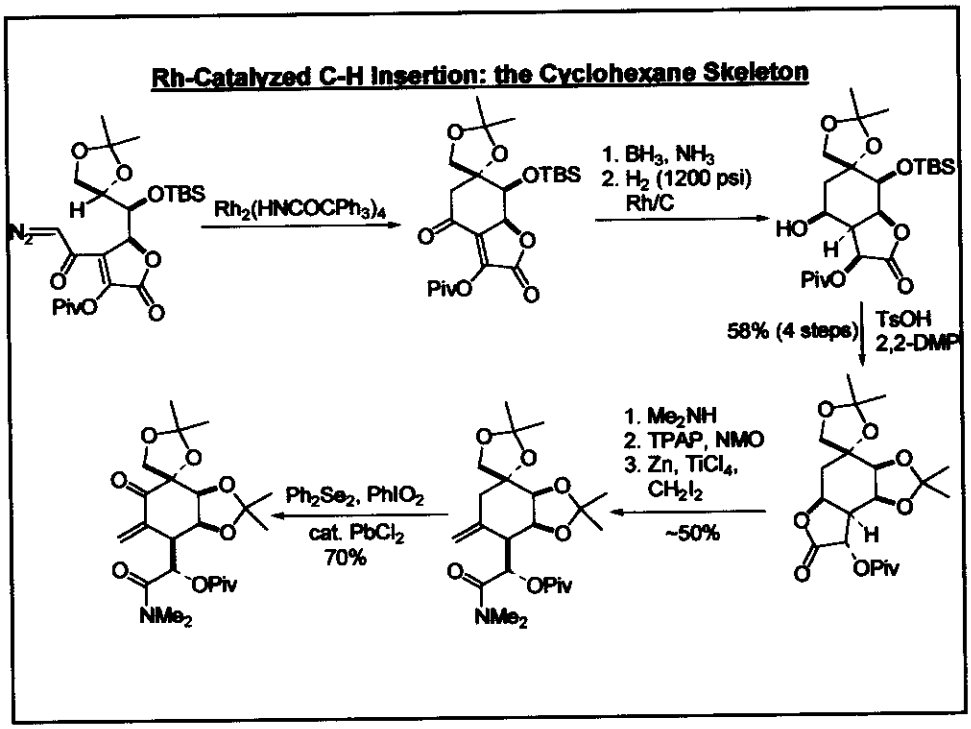
Retrosynthetic Analysis

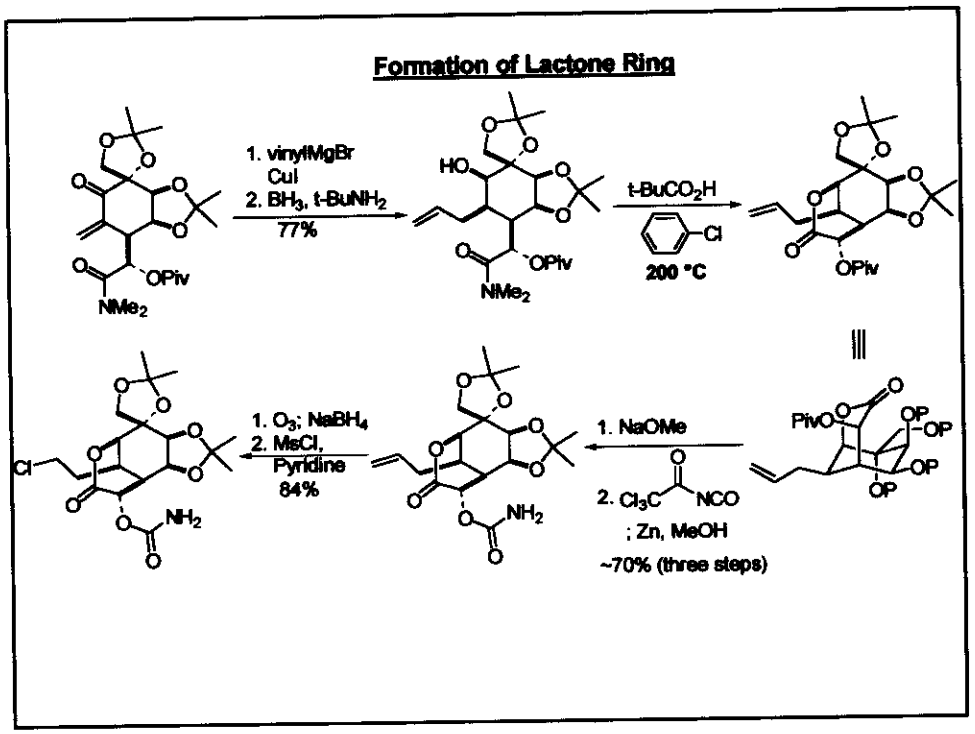


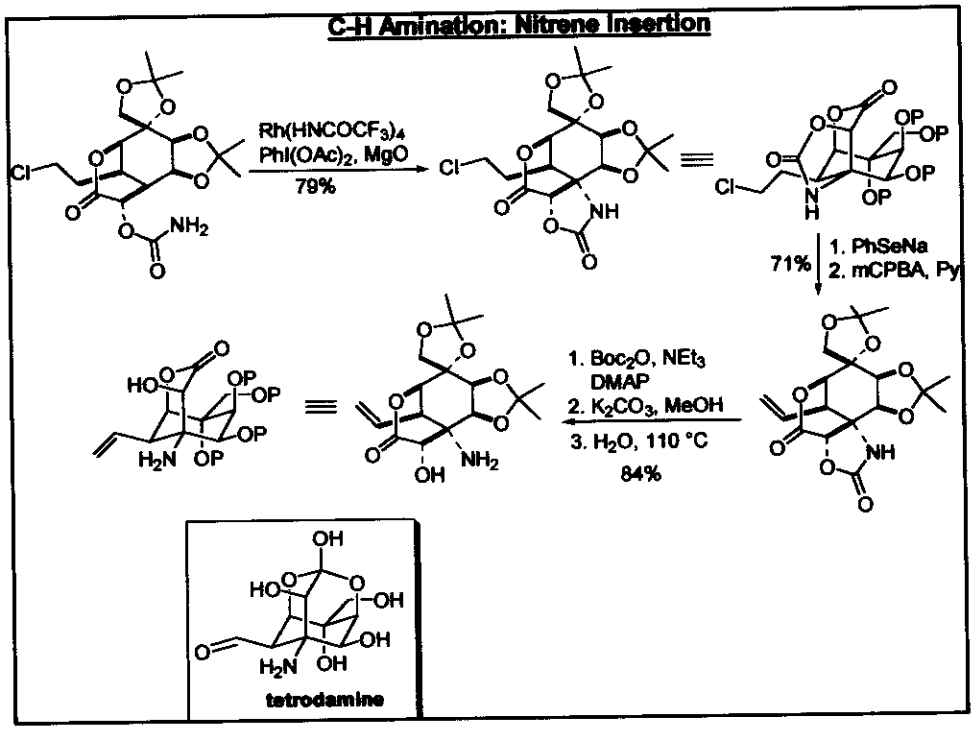
(-)-tetrodotoxin

tetrodamine

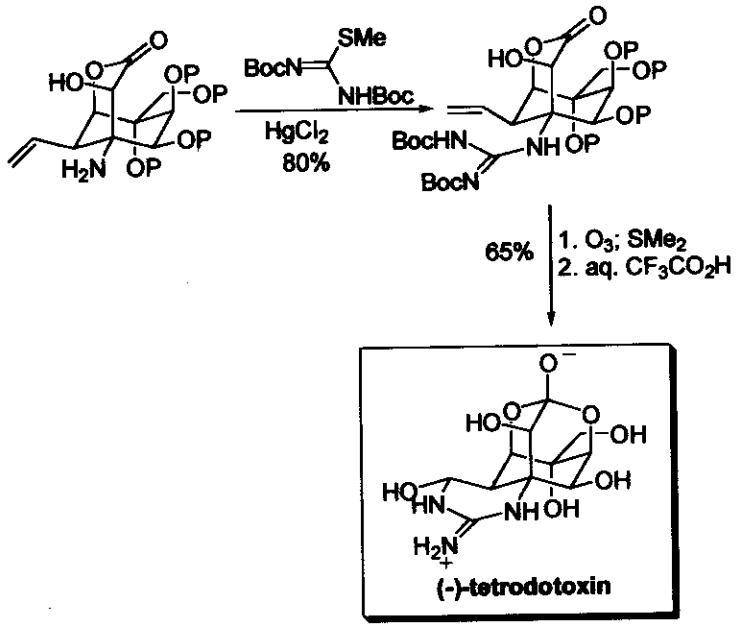

Preparation of α-Diazoketone
n-BuLi
DIBAL
NaOAc, THF
10:1
1. t-BuCOCl
2. Pd/C, H2
3. (COCl)2, CH2N2
cat. DMF
overall 56-60%


Rh-Catalyzed C-H Insertion: the Cyclohexane Skeleton
Rh2(HNCOCPh3)4
1. BH3, NH3
2. H2 (1200 psi)
Rh/C
58% (4 steps)
TsOH
2,2-DMP
1. Me2NH
2. TPAP, NMO
3. Zn, TiCl4,
CH2I2
~50%
Ph2Se2, PhIO2
cat. PbCl2
70%


Formation of Lactone Ring
1. vinylMgBr
CuI
2. BH3, t-BuNH2
77%
t-BuCO2H
Cl
200 °C
1. NaOMe
2. Cl3C NCO
; Zn, MeOH
~70% (three steps)
1. O3; NaBH4
2. MsCl,
Pyridine
84%


C-H Amination: Nitrene Insertion
Rh(HNCOCF3)4
PhI(OAc)2, MgO
79%
71%
1. PhSeNa
2. mCPBA, Py
1. Boc2O, NEt3
DMAP
2. K2CO3, MeOH
3. H2O, 110 °C
84%
tetrodamine

Introduction of Guanidine and Completion of Synthesis



Conclusion

- C-H Functionalization as a useful strategy for complex target molecules
- Demonstration of Rh-catalyzed nitrene insertion as powerful new tool in organic synthesis