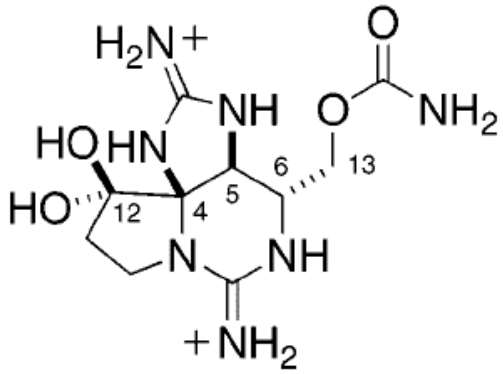
A Synthesis of (+)-Saxitoxin

James J. Fleming and J. Du Bois

J. Am. Chem. Soc., **128** (12), 3926 -3927, 2006



(+)-saxitoxin

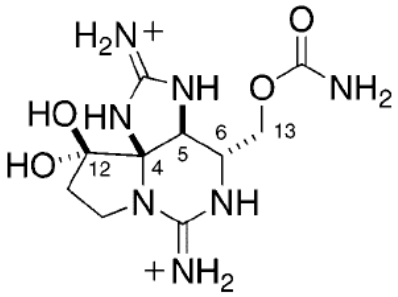
Erikah Englund, Current Lit. (4/06)

Outline:

- Introduction to Saxitoxin
- Biological Activity
- Previous Syntheses
  - Kishi
  - Jacobi
- C-H activation in the Du Bois Group
- Current Paper
- Conclusions

Saxitoxin

- Isolated from:
  - Alaska butter clams, mussels, axenic cultures of *Gonyaulax catanella* and aged scallop extracts during *G. tamarensis* bloom
- Characterization:
  - Structure elucidated by single crystal X-ray diffraction (Schantz, *JACS*, **1975**, *97*, 1238)
- Biological Activity:
  - neurotoxin
  - One of most toxic non-protein poisons (LD_{50} 5-10 µg/kg)
  - Saxitoxin and ricin are only two natural toxins classified as Schedule 1 Chemical Warfare Agents



(+)-saxitoxin

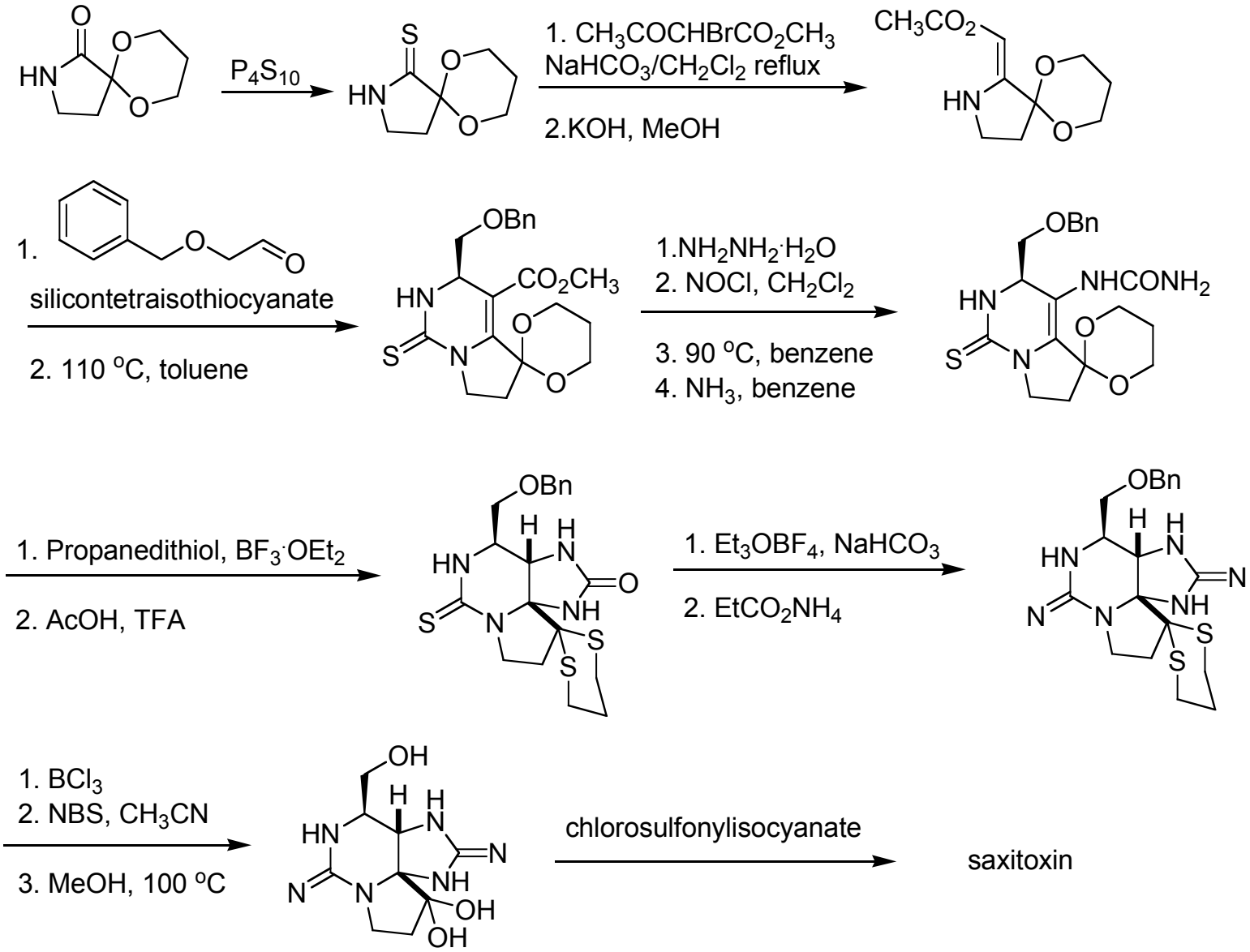
ricin

Biological Activity:

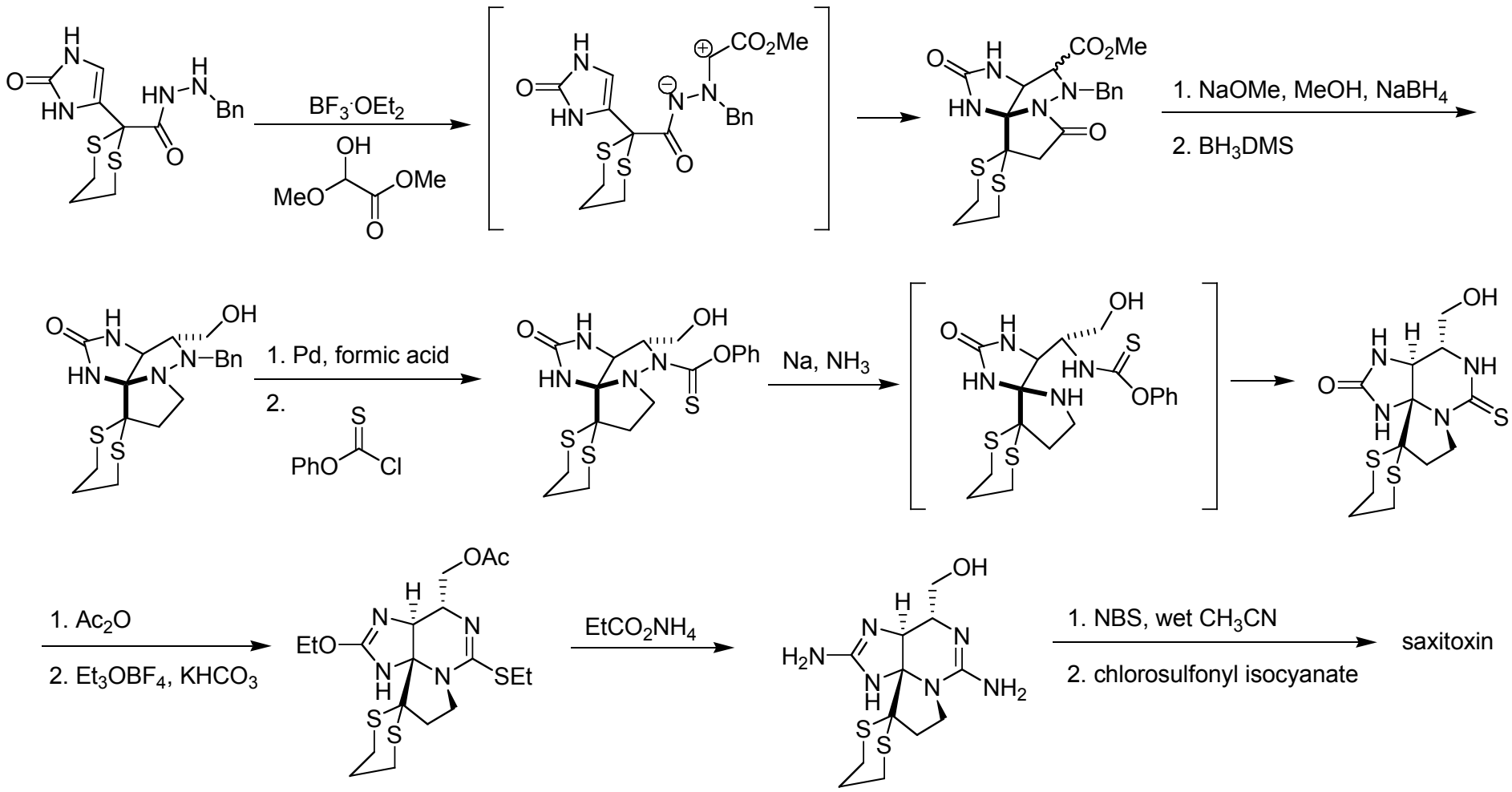
- Paralytic shellfish poisoning (PSP)
  - All 20 compounds responsible for PSP are derivatives of STX
    - Death occurs within 2-12 hours in untreated cases
    - Symptoms include:
      - dizziness, diarrhoea vomiting, disorientation, respiratory distress and eye irritation
- Effects on Na Channels
  - Potent and selective sodium channel blocker
  - No effect on potassium or calcium channels, chloride ion flux or acetylcholine release.
  - Saxitoxin has been used for labelling, characterisation and isolation of various sodium channel components,

University of Sussex at Brighton: http://www.chm.bris.ac.uk/motm/stx/saxi.htm
FDA: http://www.cfsan.fda.gov/~mow/chap37.html

Kishi (*JACS*, **1977**, *99*, 2818)

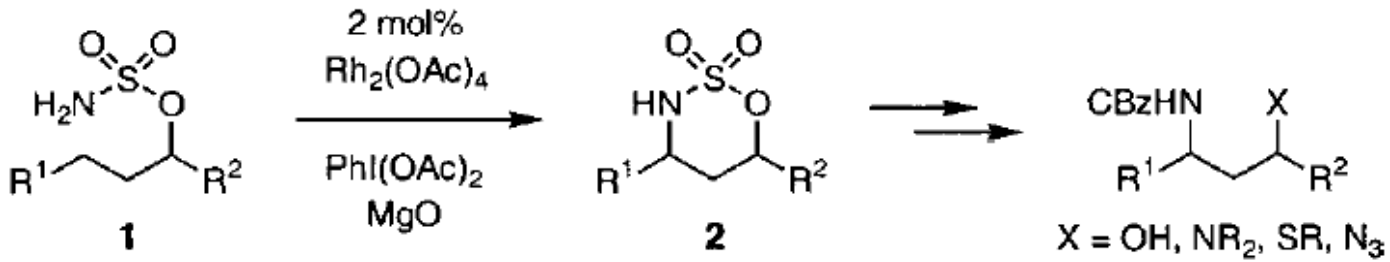


Jacobi (*JACS*, **1984**, *106*, 5594)

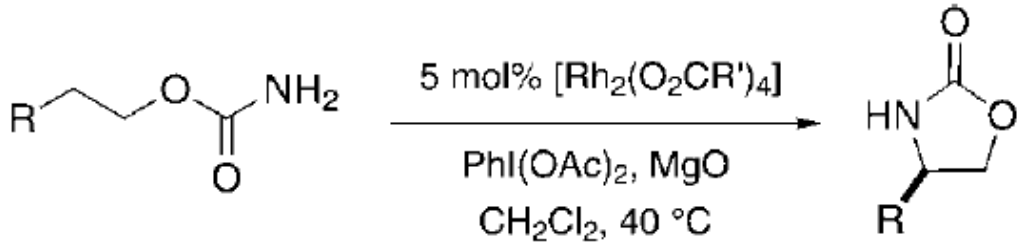


C-H Insertion

- Du Bois, *JACS,* **2001**, *123*, 6935

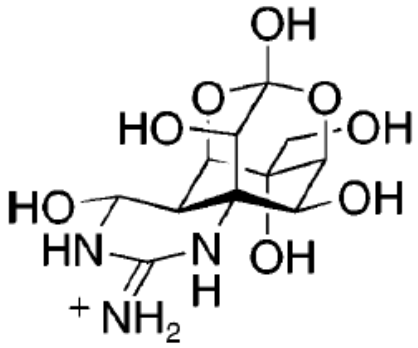


- Du Bois, *Angew.Chem.Int.Ed*, **2001,** *40,* 598

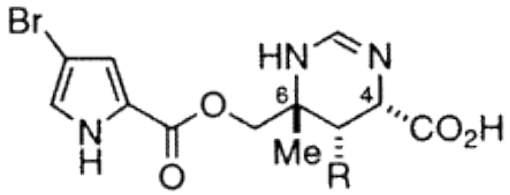


Application of CH Insertion Chemistry

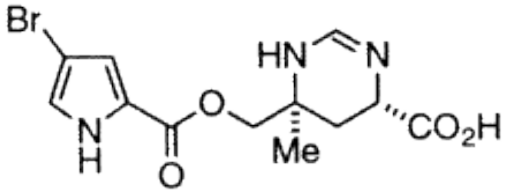
- Tetradotoxin (Du Bois, *J. Am. Chem. Soc., 125,* 11510 -11511, **2003**)



- Manzicidin A and C (Du Bois *J. Am. Chem. Soc.* **2002**; *124*; 12950-12951)

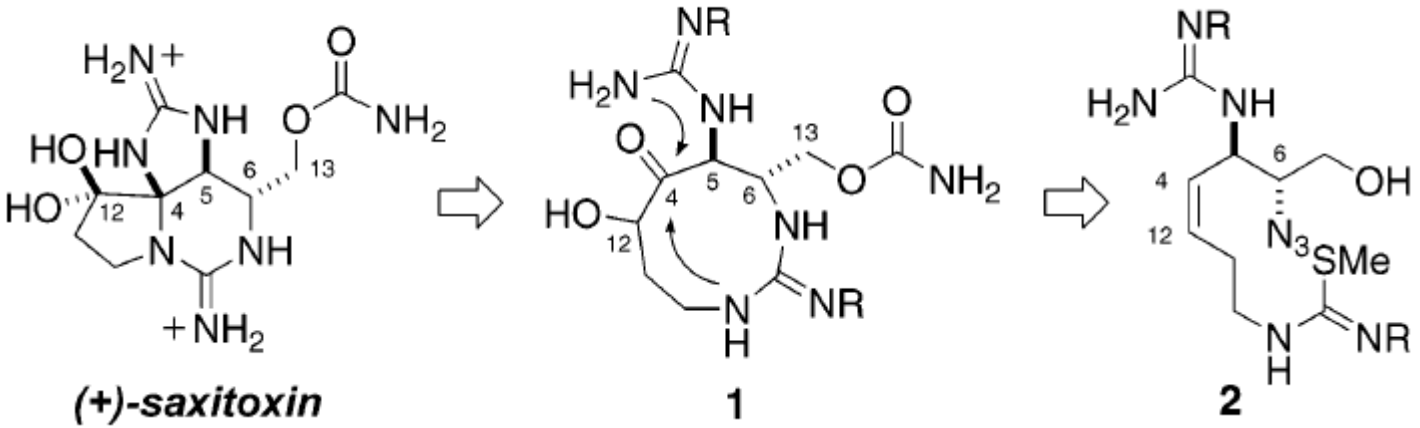


manzacidin A **1a**: R = H
manzacidin B **1b**: R = OH



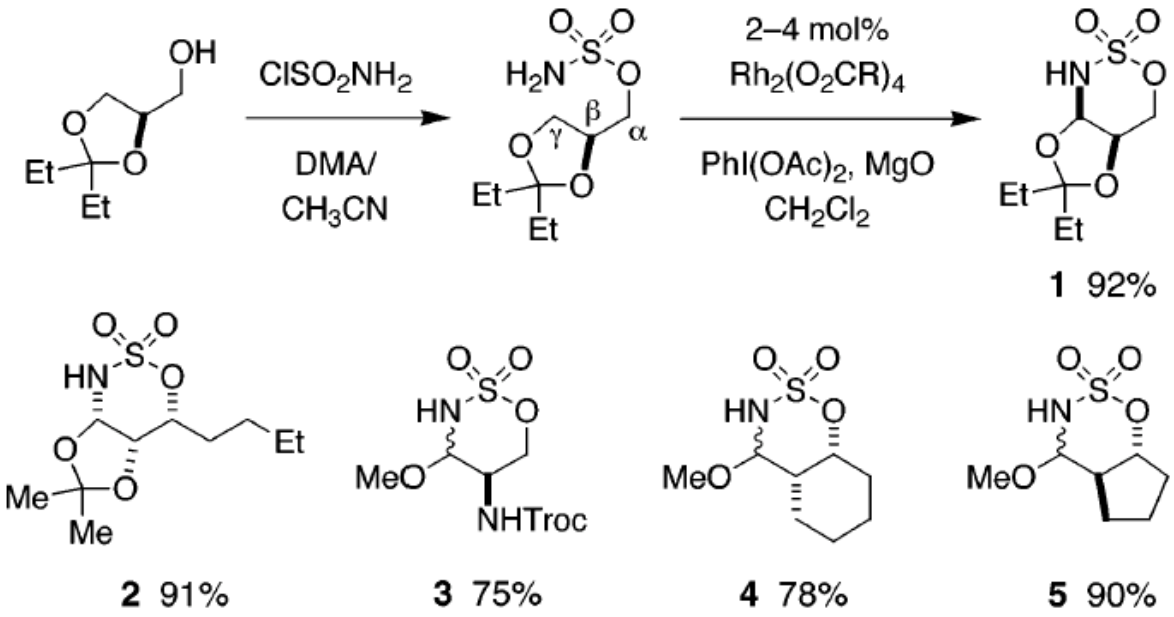
manzacidin C **1c**

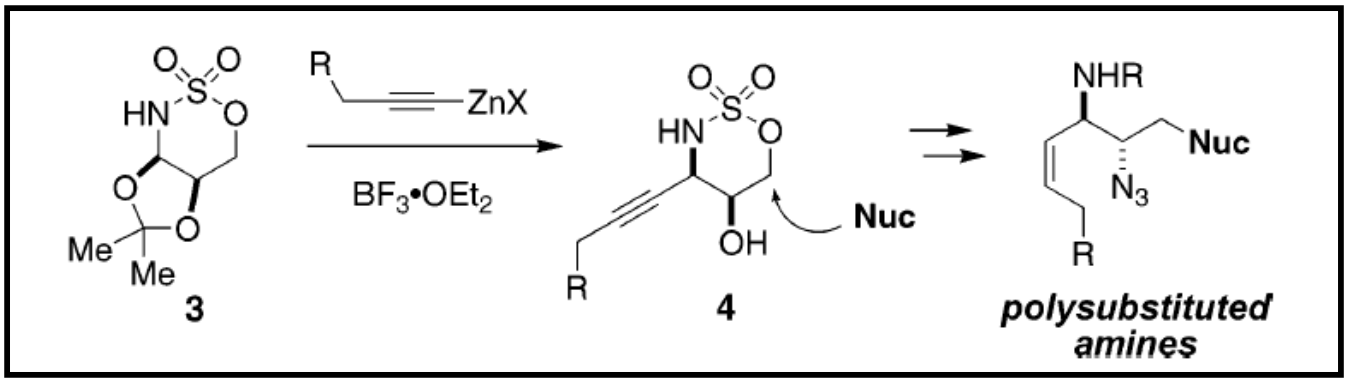
Saxitoxin Retrosynthesis



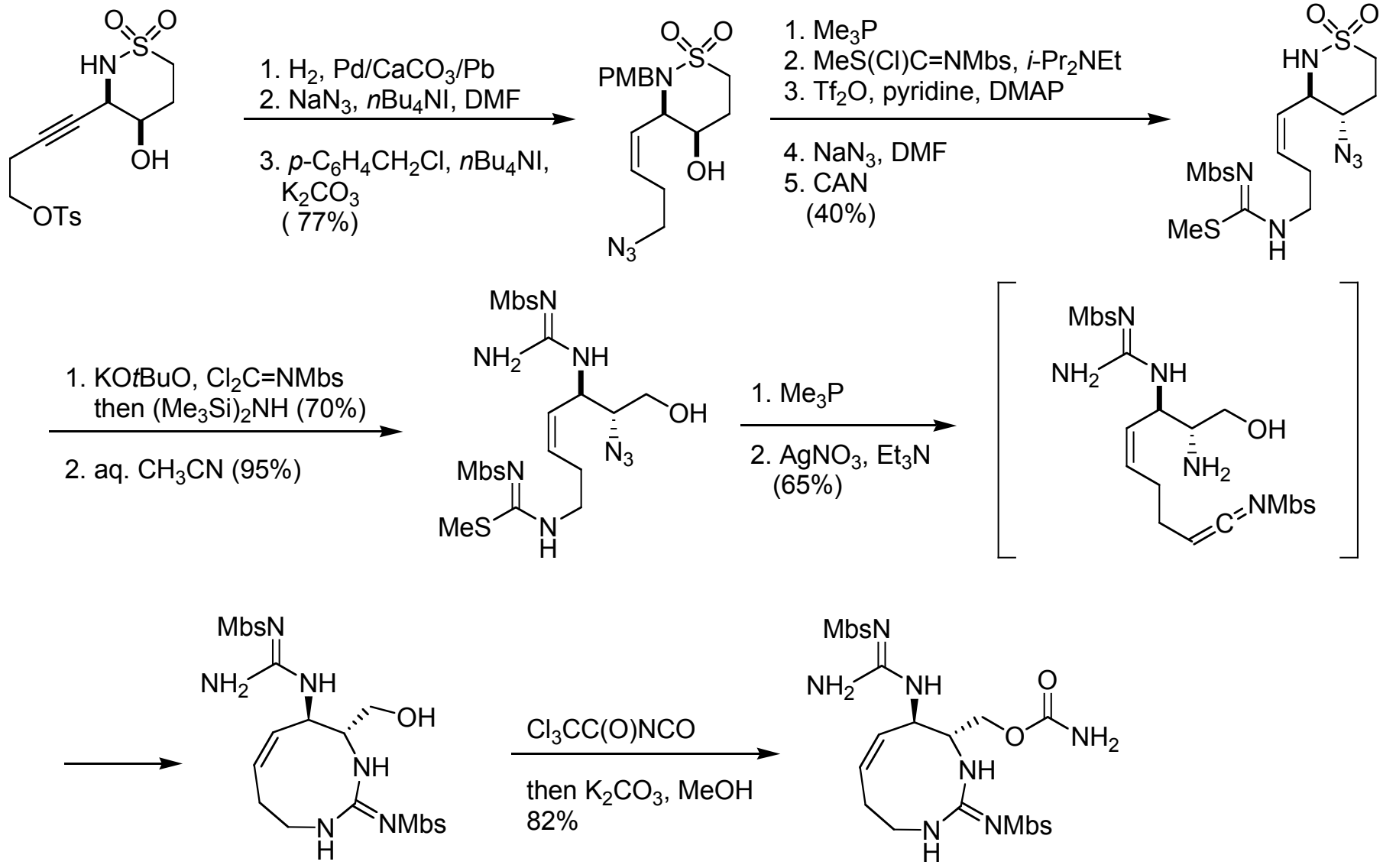
Saxitoxin-1

- Synthesis of Starting Material (Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 2028)



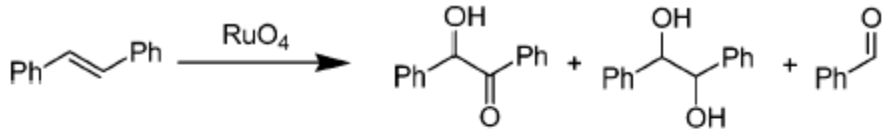


Saxitoxin-2


1. H_2, Pd/$CaCO_3$/Pb
2. NaN_3, nBu_4NI, DMF
3. p-$C_6H_4CH_2Cl$, nBu_4NI, K_2CO_3 (77%)
1. Me_3P
2. MeS(Cl)C=NMbs, i-Pr_2NEt
3. Tf_2O, pyridine, DMAP
4. NaN_3, DMF
5. CAN (40%)
1. KOtBuO, Cl_2C=NMbs then $(Me_3Si)_2NH$ (70%)
2. aq. CH_3CN (95%)
1. Me_3P
2. $AgNO_3$, Et_3N (65%)
$Cl_3CC(O)NCO$
then K_2CO_3, MeOH
82%

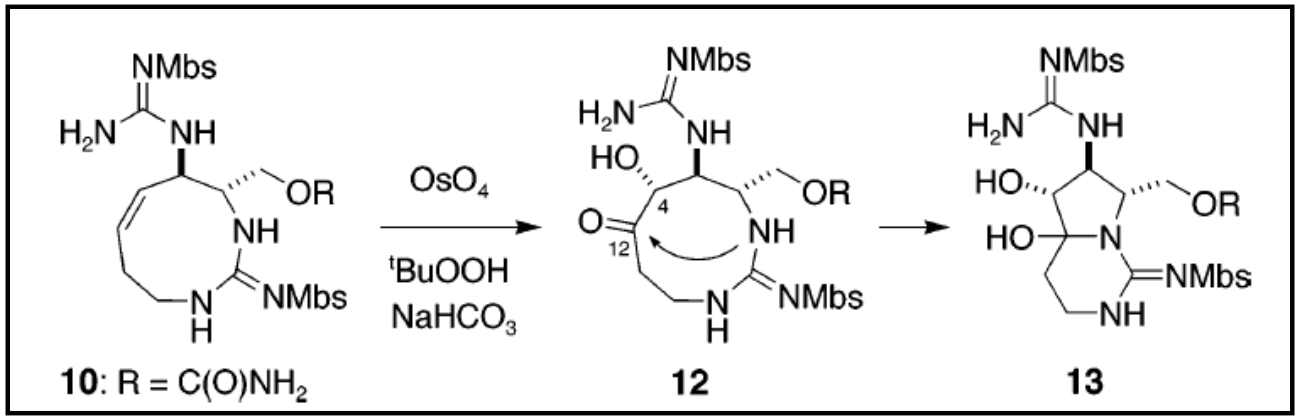
Oxidation

- Plietker, *JOC*, **2004**, *69*, 8287



1 **2** **3** **4**

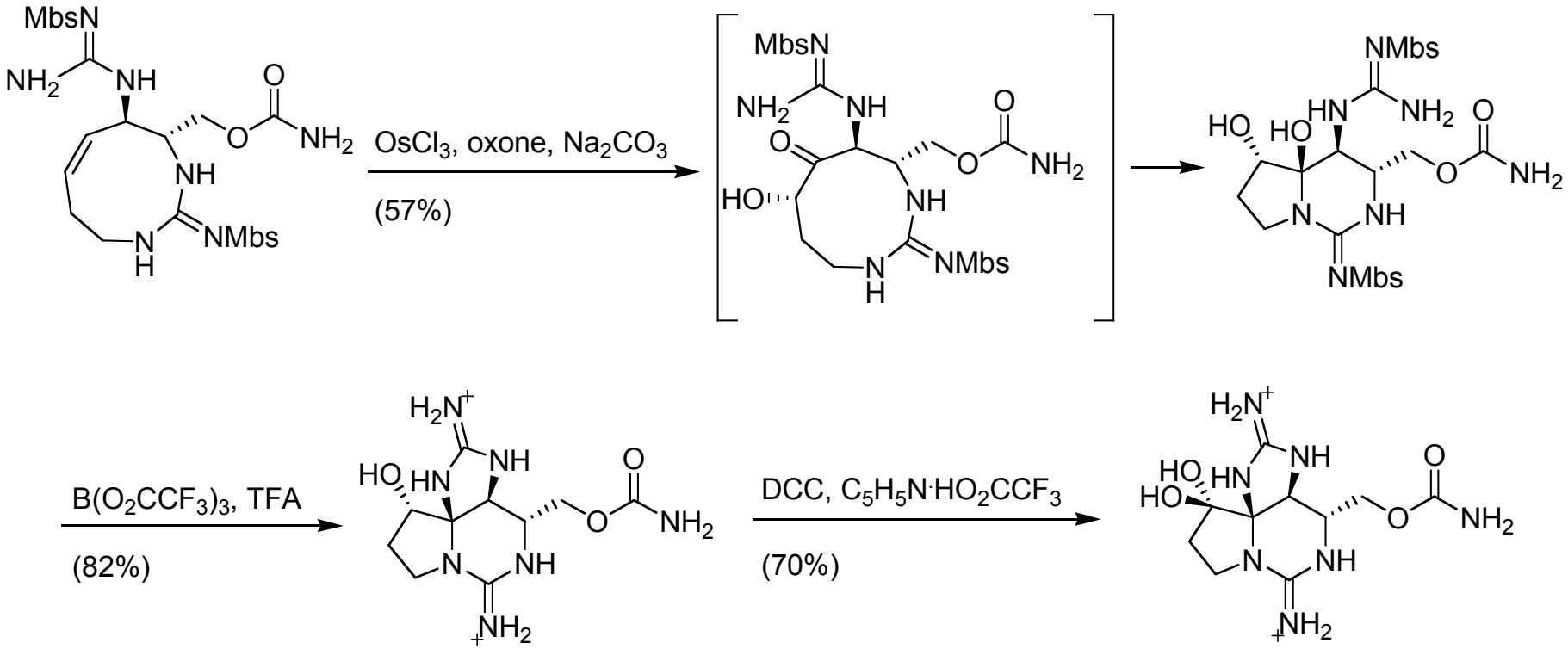
entry	reoxidant[a]	time	conversion[b] (%)	**2/3/4**[c] (%)
1	*t*-BuOOH, Et_4NOH	1 d	30	17:5:78
2	H_2O_2, Et_4NOH	1 d	12	n.d.
3	NaOCl	60 min	60	15:10:75
4	Oxone, $NaHCO_3$[d]	10 min	80	66:23:11



10: R = $C(O)NH_2$ **12** **13**

Undesired ketol (57%) afforded **13** (<5%)

Saxitoxin-3


MbsN
NH2
NH
O
NH2
O
NH
N
H
NMbs
OsCl3, oxone, Na2CO3
(57%)
MbsN
NH2
NH
O
O
NH2
HO
NH
N
H
NMbs
NMbs
HO
HO
HN
NH2
O
O
NH2
N
NH
NMbs
B(O2CCF3)3, TFA
(82%)
H2N+
HO
HN
NH
O
O
NH2
N
NH
+NH2
DCC, C5H5N·HO2CCF3
(70%)
H2N+
HO
HO
HN
NH
O
O
NH2
N
NH
+NH2

Conclusions

- The stereoselective synthesis (+)-saxitoxin was accomplished in 16 steps and 3% overall yield from known starting material
- The efficient synthesis of a 9 membered guanidine containing ring was demonstrated
- Through ketohydroxylation condition optimization, the desired regioisomer could be obtained