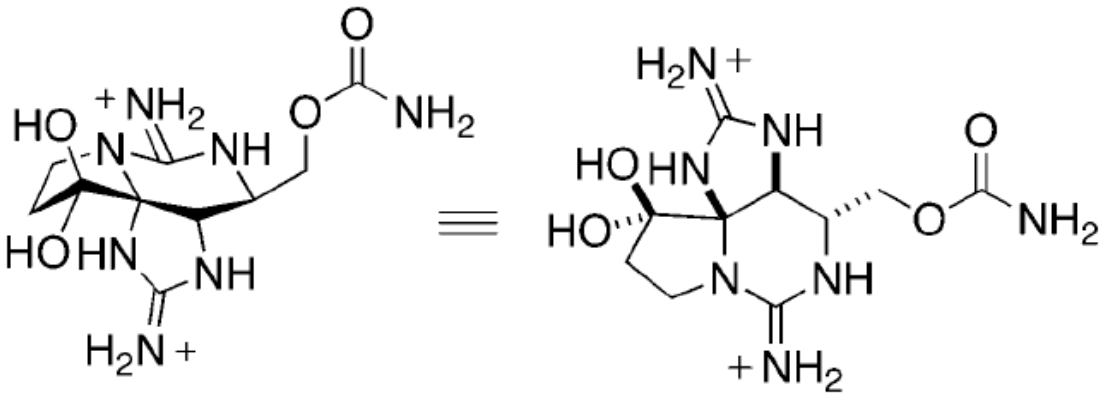
(+)-Saxitoxin : A First and Second Generation Stereoselective Synthesis



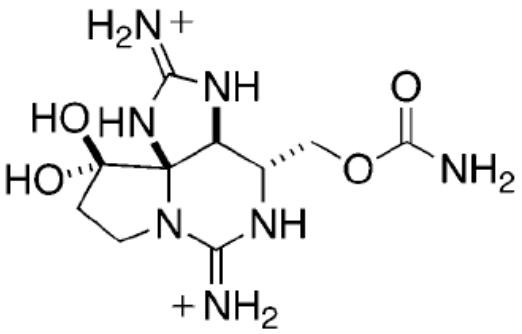
Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, 129, 9964.

Literature Presentation

Zhenjie Lu

Sep 28, 2007

Introduction



➢ Isolation and structure characterization:

First isolated by Schantz in 1957 from Alaskan butter clams *Saxidomus giganteus*. (A shellfish poison associated with red tide)

Structure characterized in 1975 by Schantz/Clardy and Rapoport groups.

➢ Bioactivity:

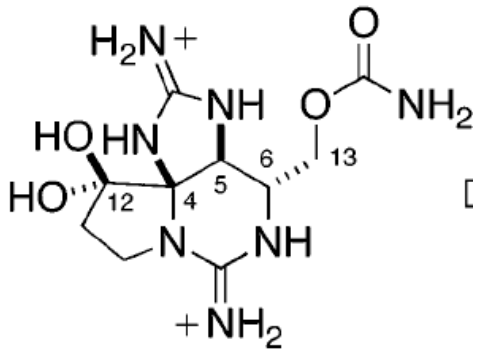
One of the most lethal non-protein poison.

It is a potent and extremely selective sodium channel blocker and is widespread used in the study of various nerve disorders.

It has been indispensible tool in medical research.

1. Schantz, E. J.; Mold, J. D.; Stanger, D. W.; Shavel, J.; Riel, F. J.; Bowden, J. P.; Lynch, J. M.; Wyler, R. S.; Riegel, B.; Sommer, H. *J. Am. Chem. Soc.* **1957**, *79*, 5230.
2. Schantz, E. J.; Ghazarossian, V. E.; Schnoes, H. K.; Strong, F. M.; Springer, J. P.; Pezzanite, J. O.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 1238.
3. Bordner, J.; Thiessen, W.E.; Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, *97*, 6008.

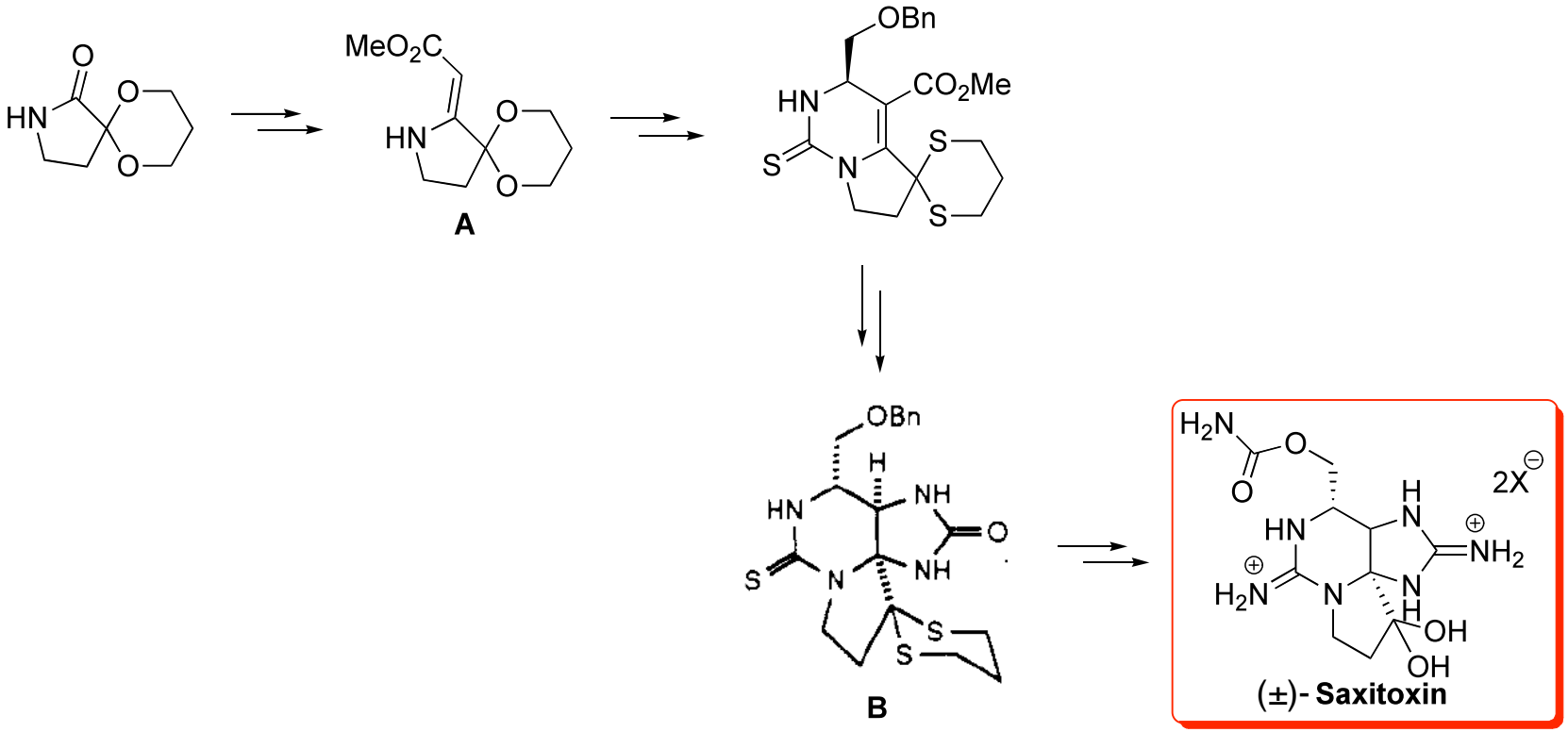
Synthetic Challenges



(+)-Saxitoxin

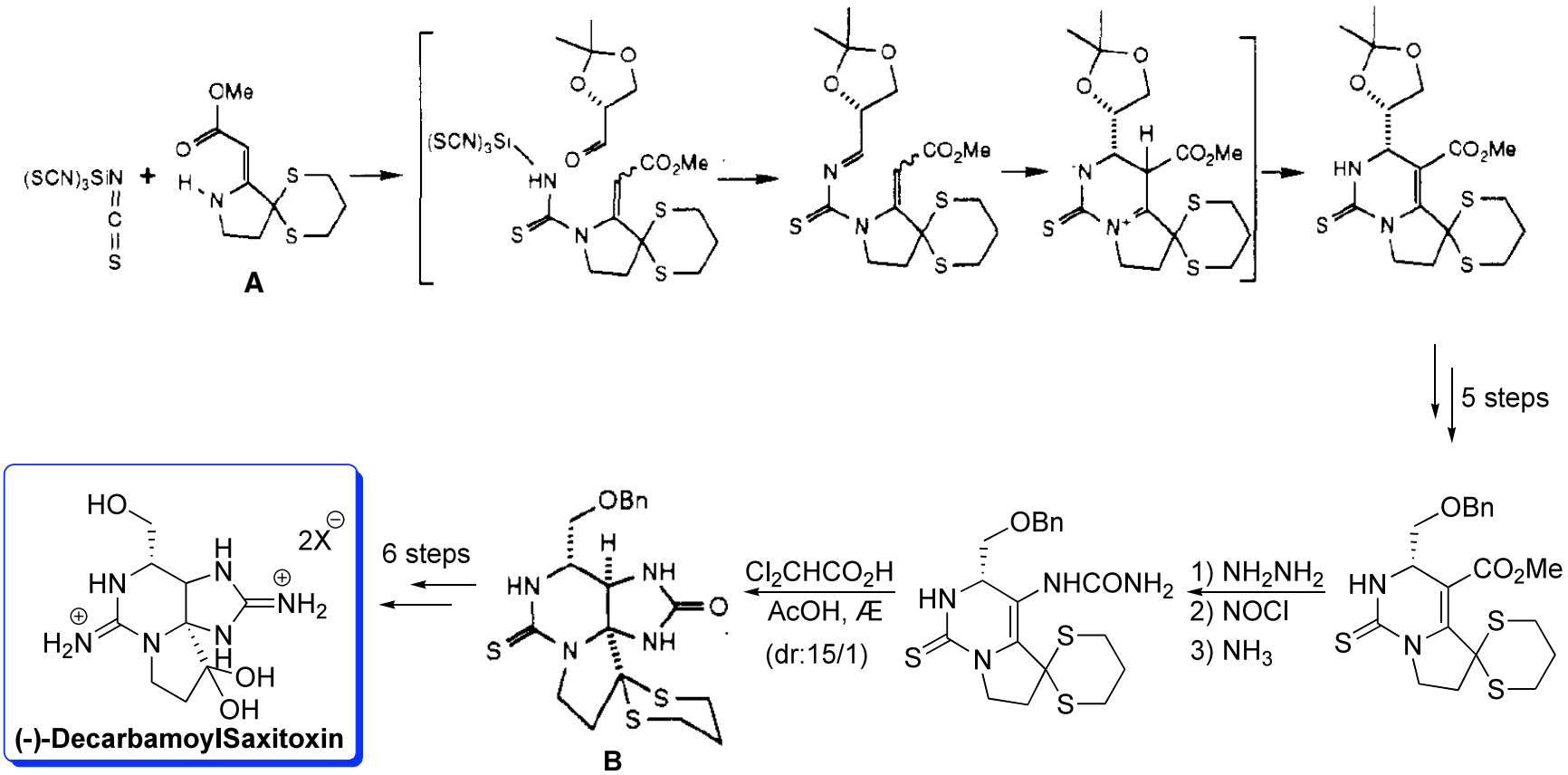
- It is highly functionalized and very susceptible to oxidation.
- Remarkably dense configuration of heteroatoms about the tricyclic core. $C_{10}H_{19}N_7O_4$
- The dicationic nature causes difficulties on handling and purification.
- Synthetic approaches:
  first total synthesis of (±)-saxitoxin : Kishi, Y.; etc. JACS, 1977, 2818.
  (-)-decarbamoylsaxitoxin : Kishi, Y.; etc. JACS, 1992, 7001.
  formal synthesis of (±)-saxitoxin : Jacobi, P, A.; etc. JACS, 1984, 5594.

- The first total synthesis



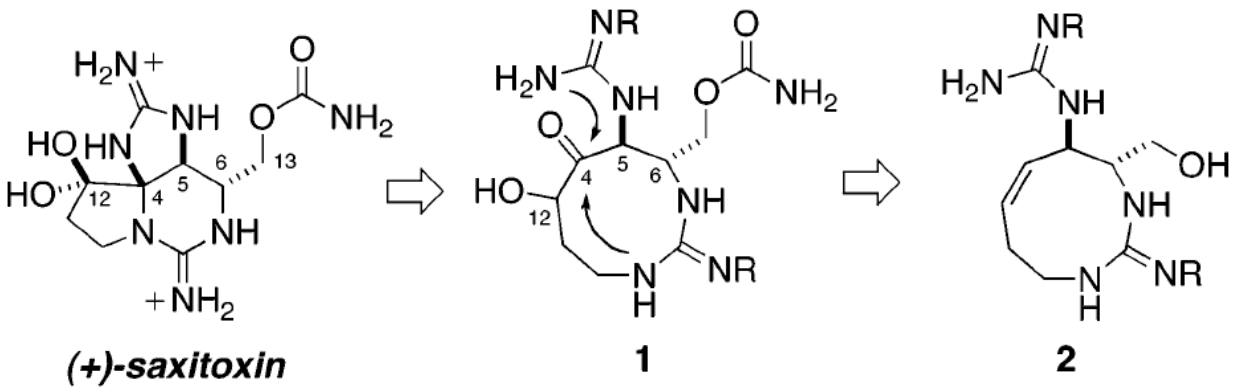
Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc*. **1977**,*99*, 2818.

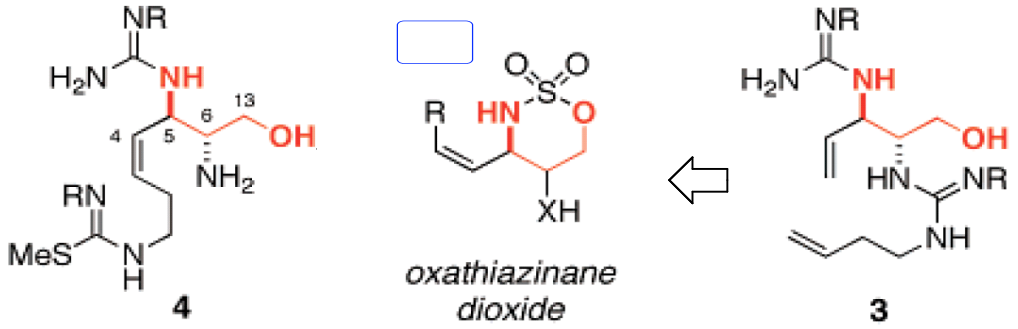
- Enantioselective synthesis of (-)-Decarbamoylsaxitoxin



Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**,*114*, 7001.

Du Bois' Synthetic Plan

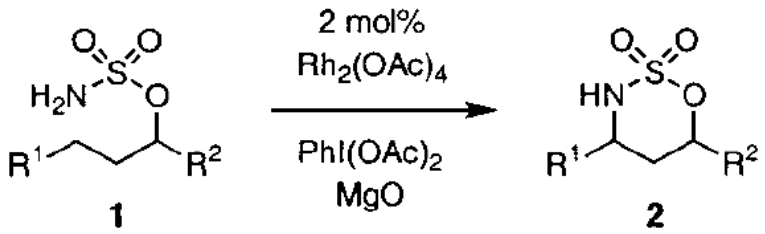




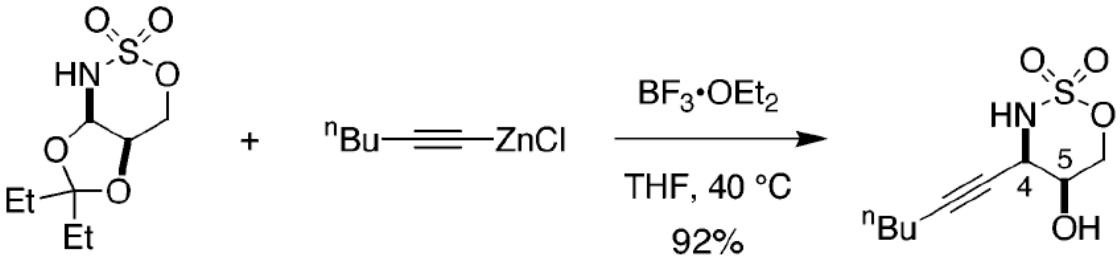
-- In above plan, all three rings of the STX core can bee formed from a nine-membered ring, thus avoid late-stage functional group exchange.
-- Both Kishi and Jacobi assembled the tricyclic core first.

Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc*. **2007**,*125*, 2028.

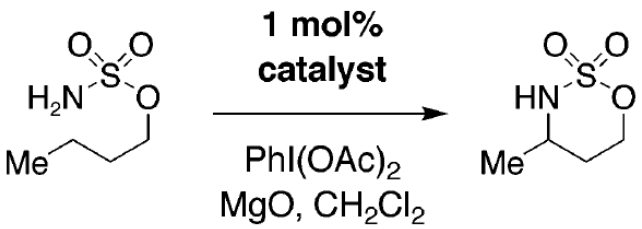
C-H Oxidation Amination



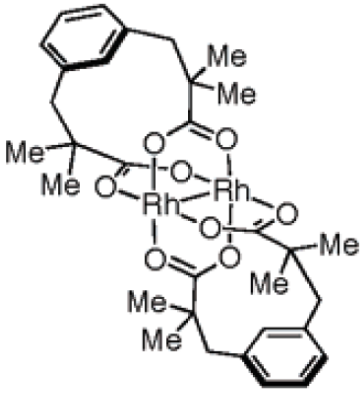
Espino, C. G.; When, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**,*123*, 6935.



Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**,*125*, 2028.



$Rh_2(O_2C^tBu)_4$	15%
$Rh_2(esp)_2$	**90%**

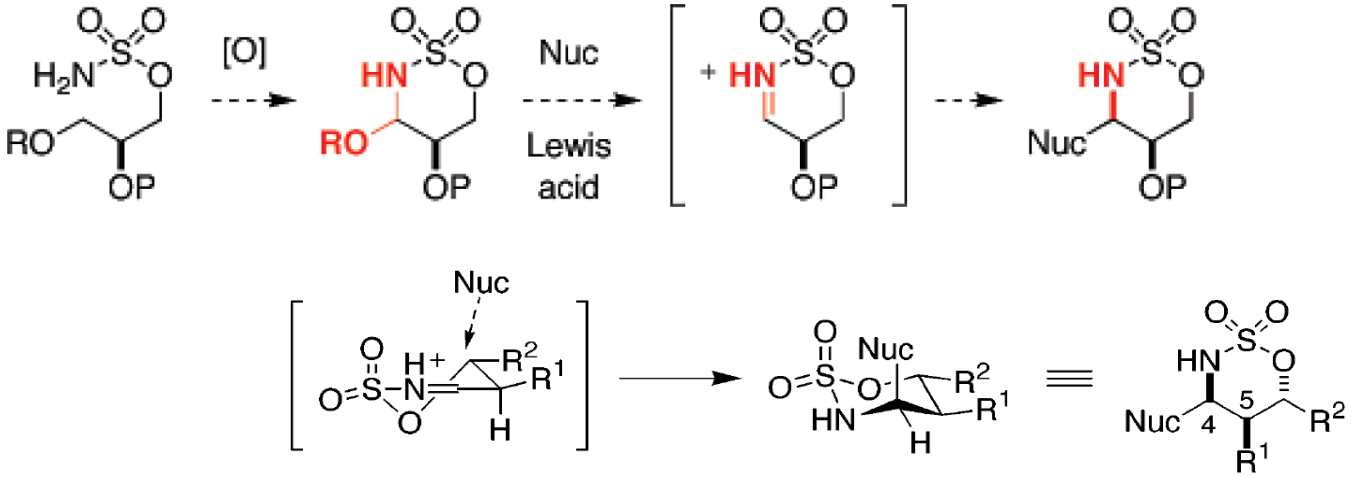


$Rh_2(eps)_2$ was found to be significantly more active and robust…

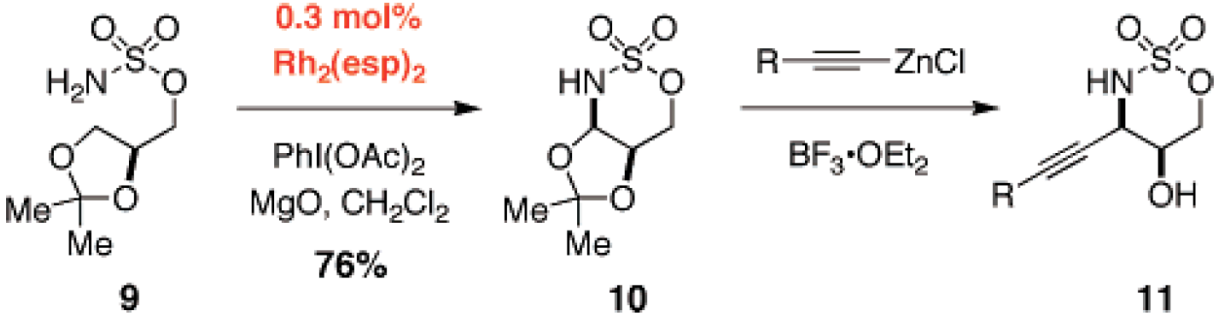
Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**,*124*, 15378.

Background and Model Studies

N,O-acetal strategy for accessing substituted oxathiazinane:

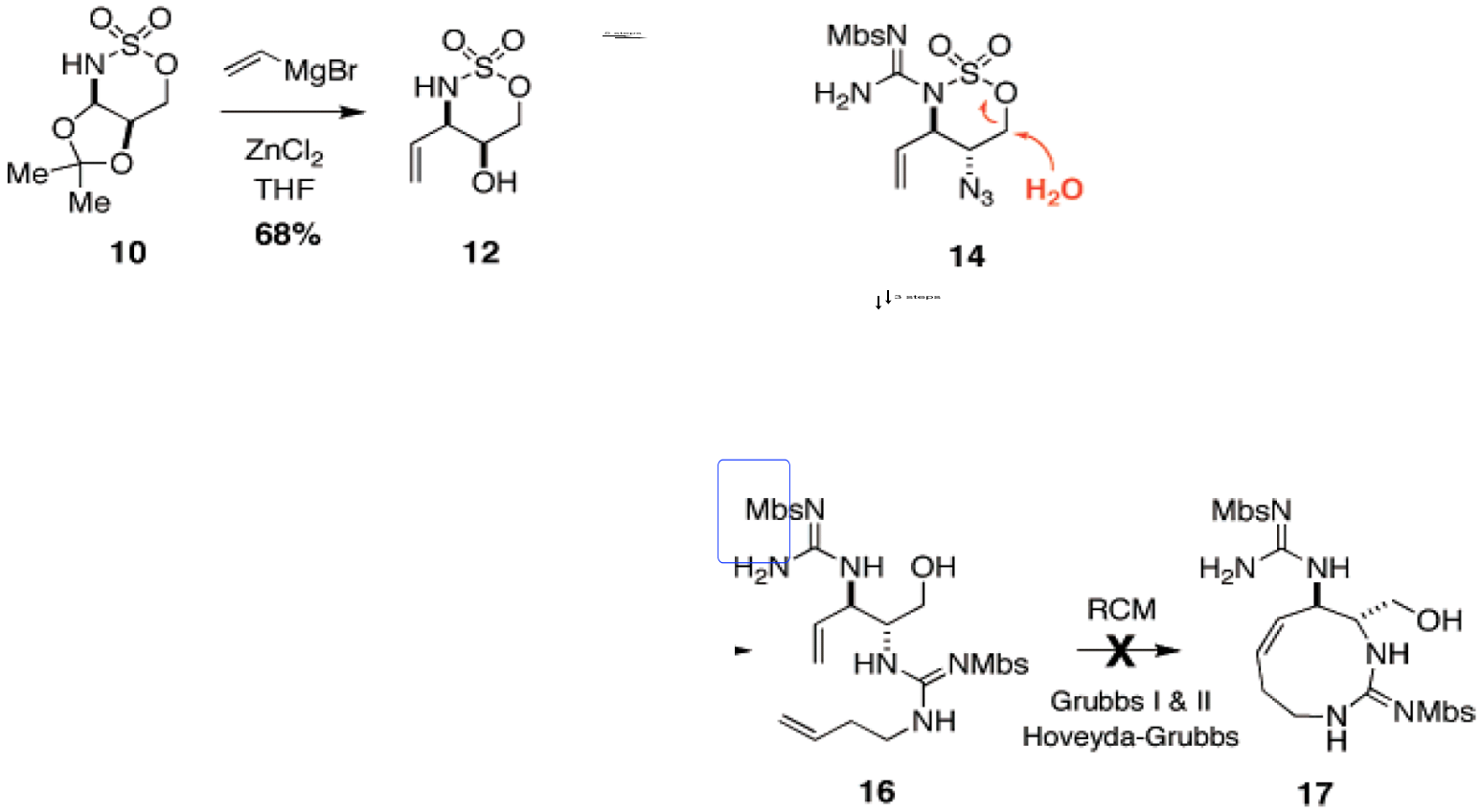


Organozinc addition to *N,O*-acetal **10** affords alkyne-derived oxathiazinane products.:



9 **10** **11**

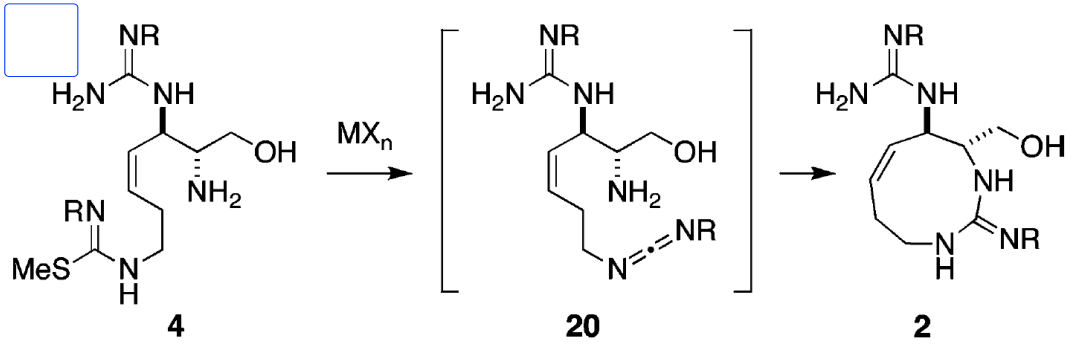
Plan A: Formation of the Nine-Membered Ring Guanidine via RCM



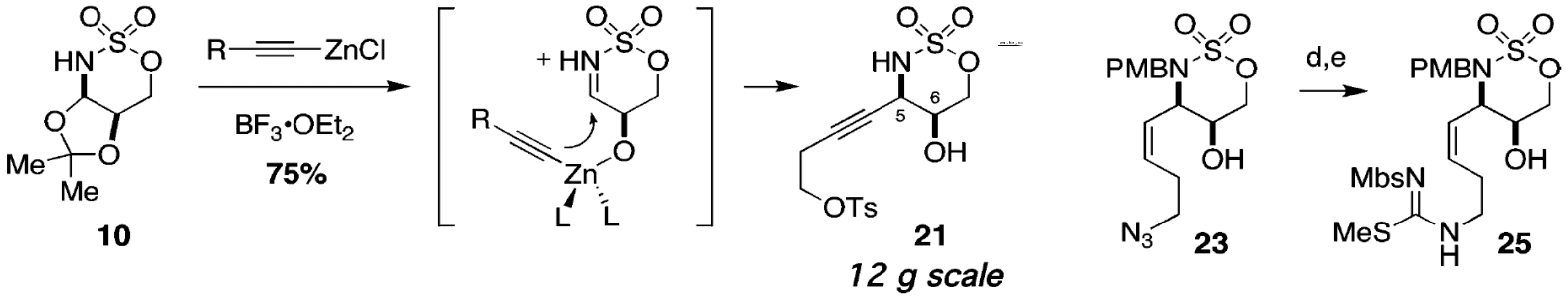
Failure of RCM may be due to the polar nature of two guanidine units and/or aggregation effects by hydrogen bond donor/acceptor groups; low yielding step (8% yield)

Plan B: Formation of Guanidine via Carbodiimide Addition

Another plan: Cyclic guanidine formation via carbodiimide addition

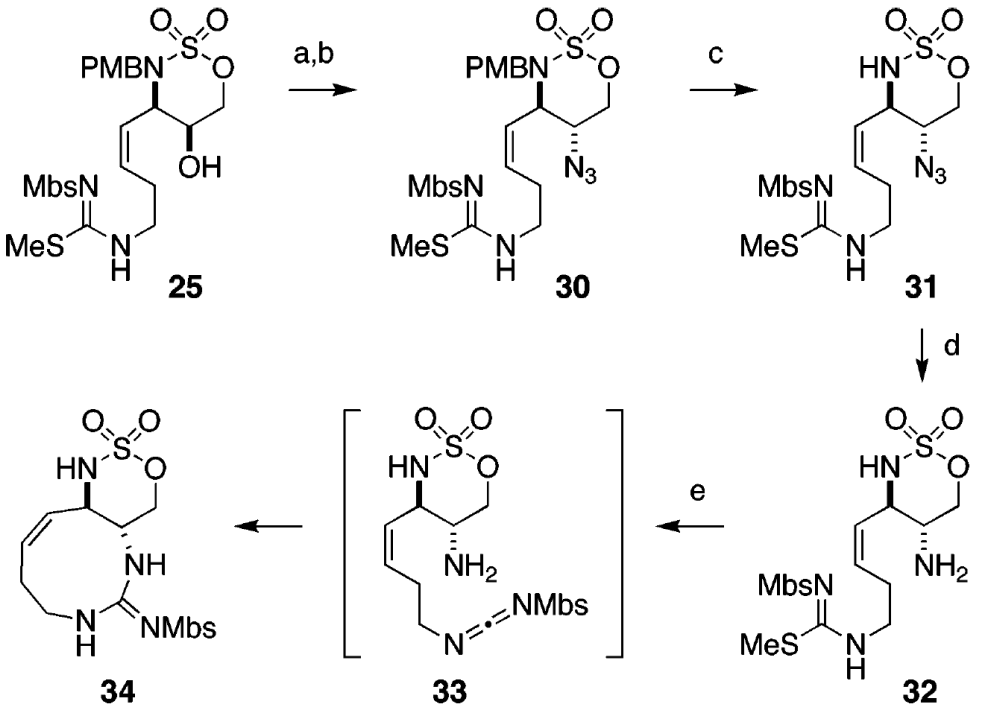


Preparation of Intermediate **25**:



(a) $Pd/CaCO_3/Pb$, quinoline, THF, H_2;
(b) NaN_3, nBu_4NI, DMF, 80% (two steps);
(c) PMBCl, K_2CO_3, nBu_4NI, 80%;
(d) Me_3P, H_2O/THF;
(e) MbsN=C(Cl)SMe **24**, iPr_2NEt, CH_3CN, 70% (two steps).

Plan B: Formation of Guanidine via Carbodiimide Addition

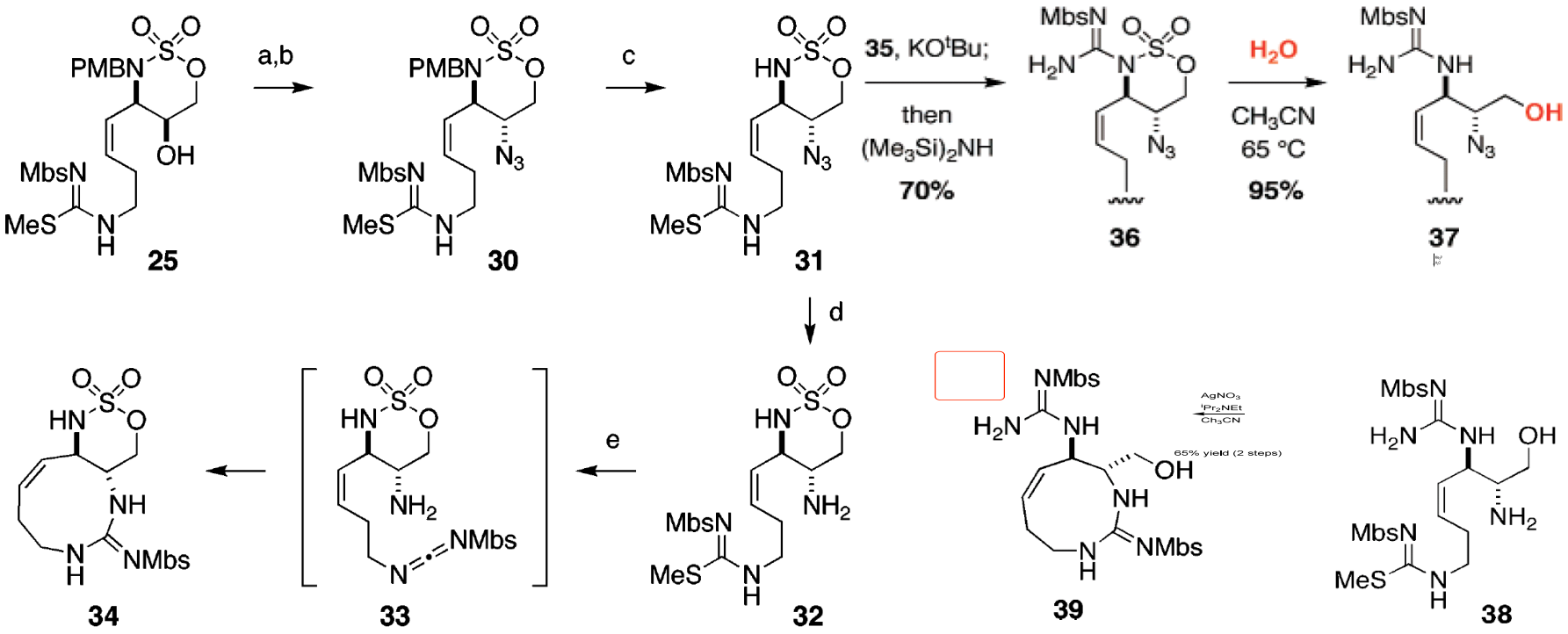


(a) Tf_2O, C_5H_5N, DMAP, CH_2Cl_2, 0 °C; (b) NaN_3, DMF, -15 °C, (70%, two steps);
(c) $(NH_4)_2Ce(NO_3)_6$, tBuOH, CH_2Cl_2, 74%;
(d) $SnCl_2$, THF, MeOH; (e) $AgNO_3$, iPr_2NEt, CH_3CN, 40% (two steps).

34 was too unstable (presumably due to strain-promoted ring opening of the fused oxathiazinane);
Strain in trans-substituted **33** may also be responsible for low yield of cyclization.

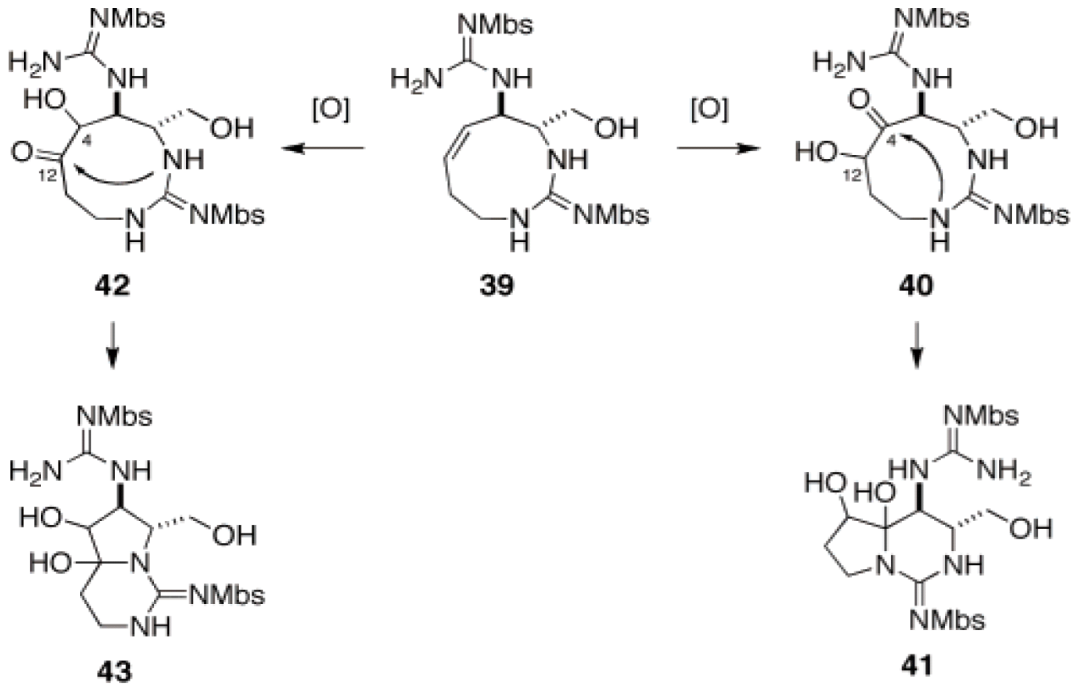
Lesson: Cyclic starting material is problematic.

Plan B: Formation of Guanidine via Carbodiimide Addition



34 is unstable to chromatography and storage;
low yield (40% in 2 steps).

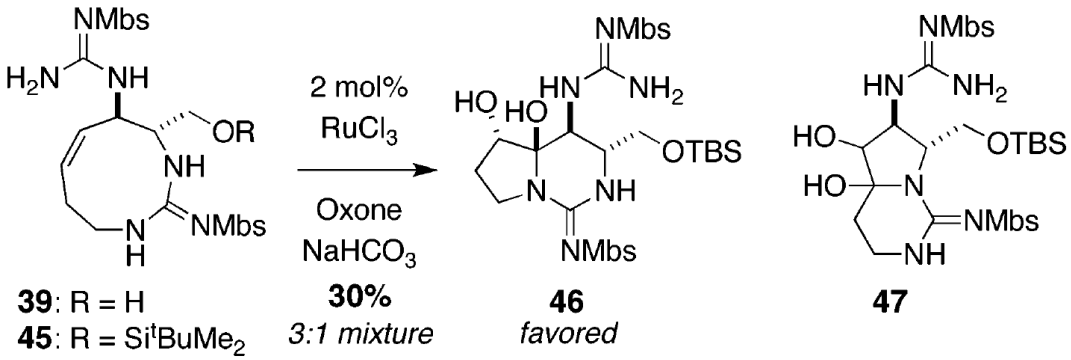
Plan C: Potential Complications with C4, C12-Alkene Oxidation



DFT calculations suggests that desired **41** is thermodynamically (strongly) preferred.

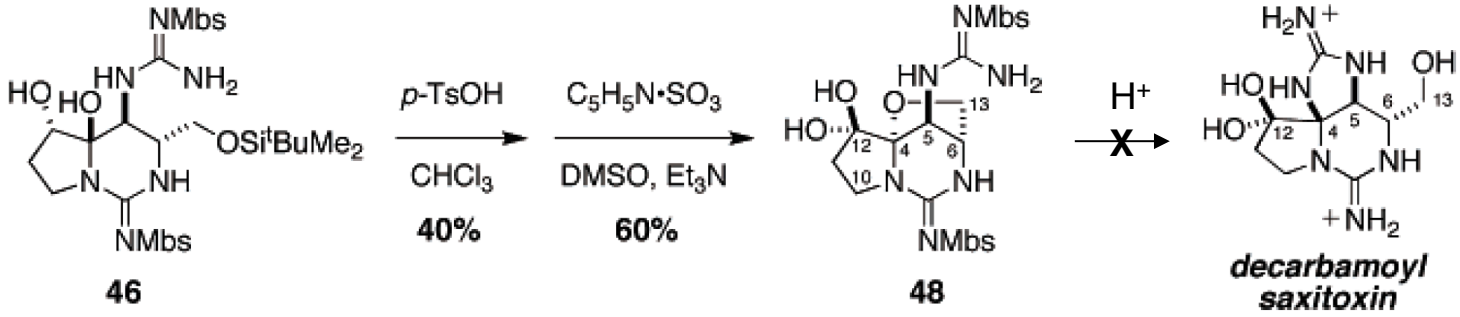
Plan C: Unexpected Formation of N,O-Acetal

However, absence of oxathiazinane ring in **39** results in low selectivity in ring-closing reaction:



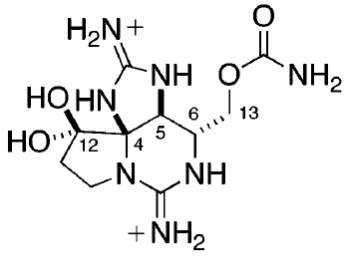
39: R = H
45: R = Si^{t}BuMe$_2$

Attempted formation of tricyclic core gave undesired isomeric structure:

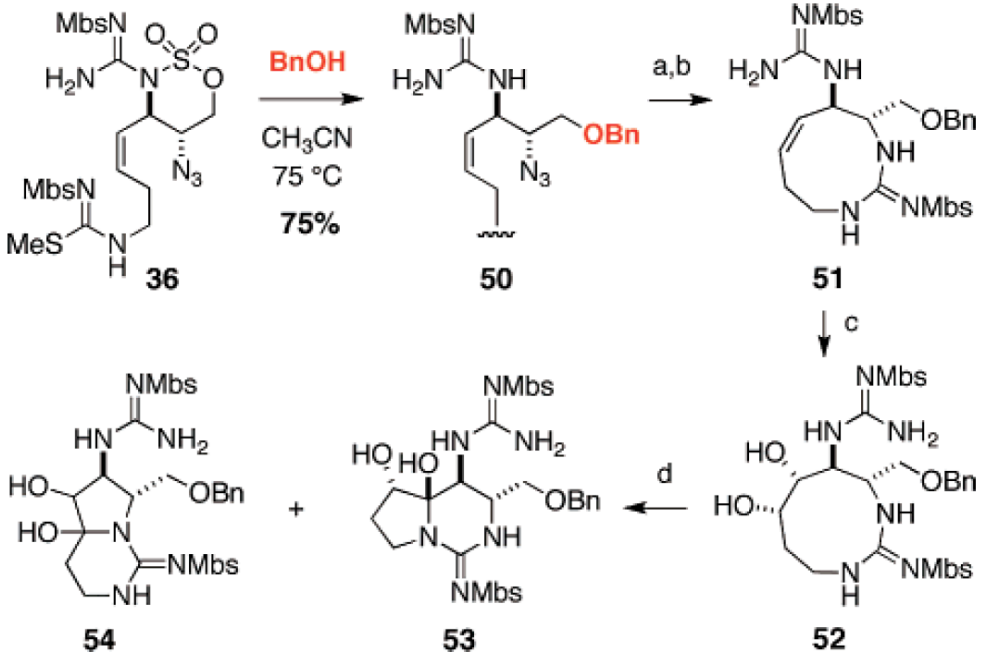


Lesson: Acid-labile hydroxy protecting group resulted in undesired N,O-acetal.

Plan C: Synthesis of *β-dcSTXol*

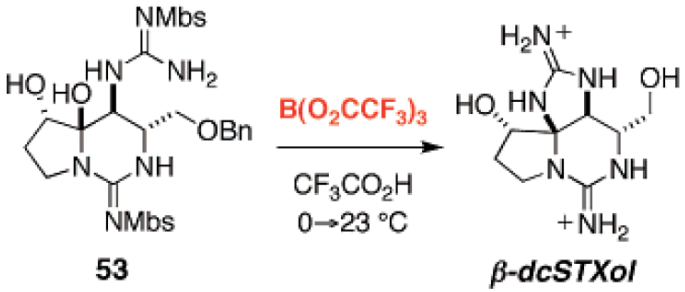


(+)-saxitoxin



(a) Me_3P, H_2O/THF;
(b) $AgNO_3$, iPr_2NEt, CH_3CN, 65% (two steps);
(c) 20 mol % OsO_4, NMO, DABCO, H_2O, tBuOH/acetone, 84%;
(d) DMP, CH_2Cl_2, 85% (50% **53**, 35% **54**).

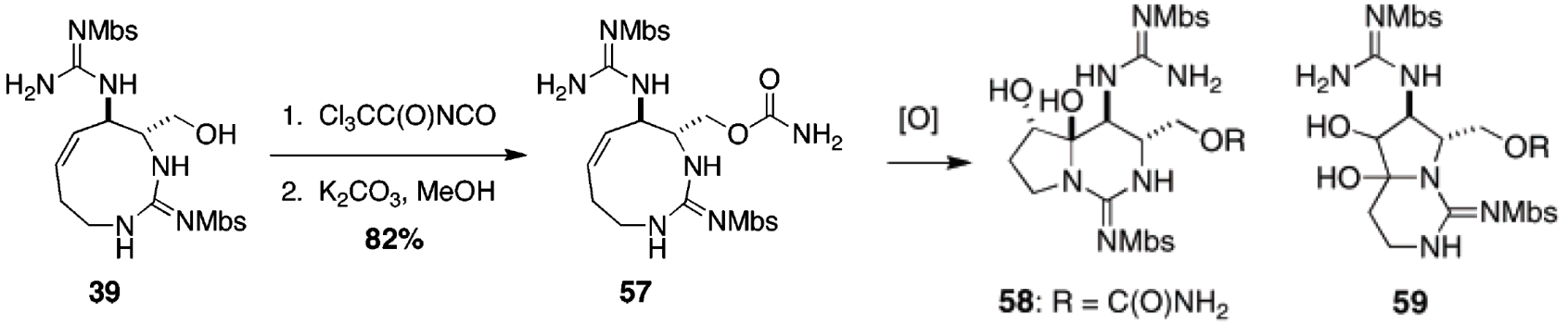
Conversion from **54** to **53** failed.



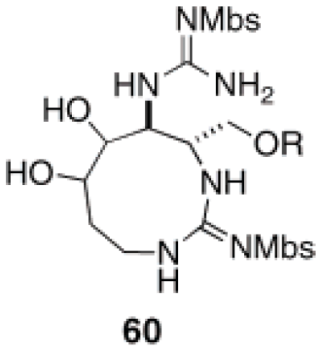
exclusive formation
>80% conversion

Only two more steps…but selective carbamoylation of C13 questionable.

Plan D: Alkene Ketohydroxylation from Acylic Precursor

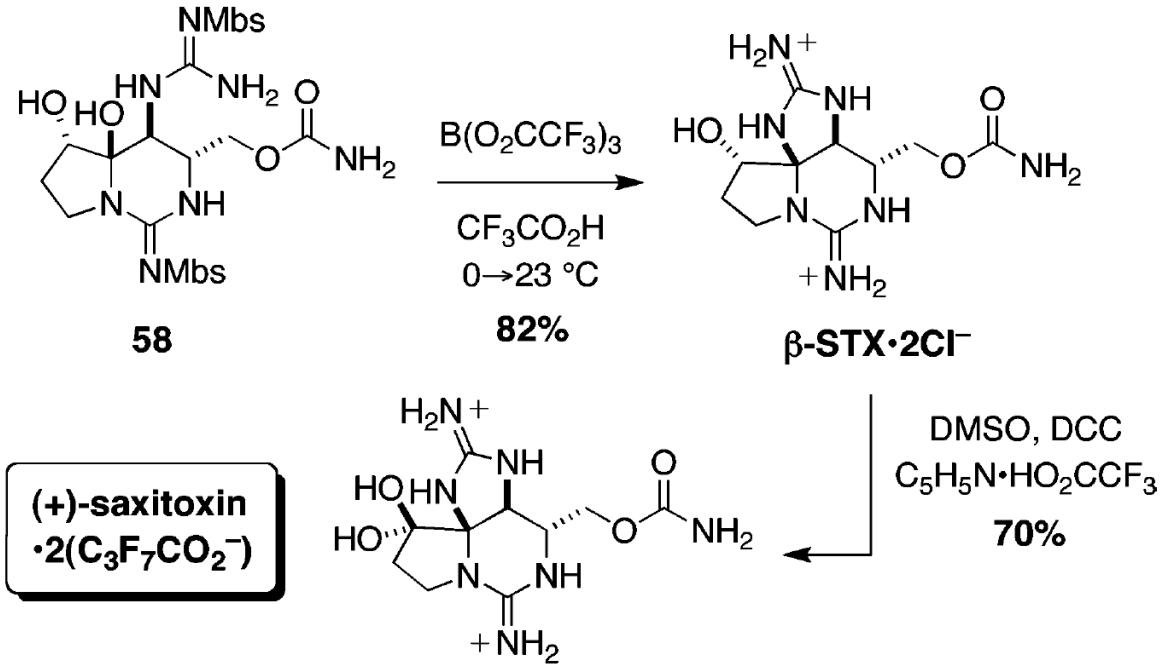


entry	catalyst[a]	oxidant	base	58	59	60[b]	% yield[c]
1	$RuCl_3$	Oxone	$NaHCO_3$	2.3	1	1	35
2	$RuCl_3$	Oxone	$NaHCO_3$	2.3	1	1	40[d]
3	**OsO_4**	**^tBuOOH**	**none**	**1**	**10**	**–**	**70**
4	$OsCl_3$	Oxone	$NaHCO_3$	5	1	2.3	35
5	$OsCl_3$	Oxone	Na_2CO_3	12	1	1	62
6	$RuCl_3$	Oxone	Na_2CO_3	5	1.5	1	33



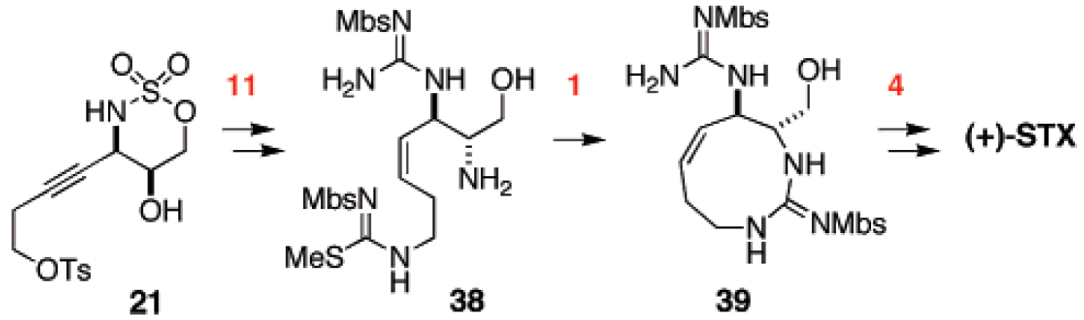
[a] Reactions performed with 2−10 mol % catalyst at 25 °C. [b] Product ratio determined by HPLC analysis. [c] %Yield is combined for **58** and **59**. [d] Reaction performed at 10 °C.

Final Steps of the First Generation



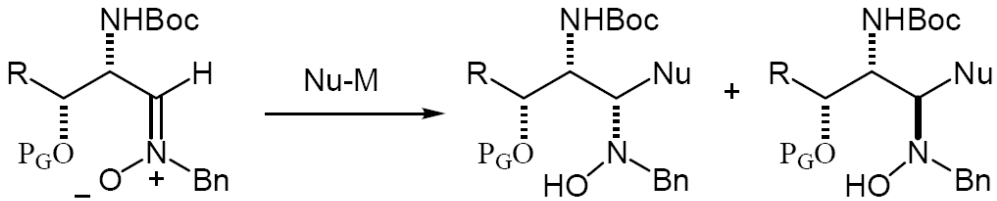
19 steps sequence in 1.3% overall yield

Step-count Analysis of the First Generation



Alkynyl oxathiazinane **21** proved exceptionally versatile, allow various strategy;
Discovery of new class of heterocyclic iminium ion surrogates;
However, preparation of **39** require 15 steps—too long for two stereogenic centers;

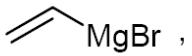
Work of Merino: Nucleophilic addition of organometallic to chiral nitrones: *Synlett* **2000**, 442 (Review)

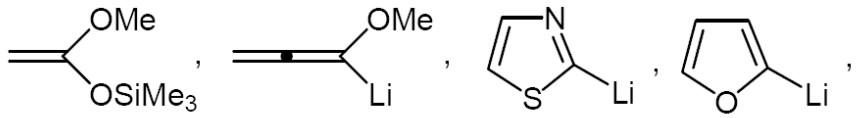


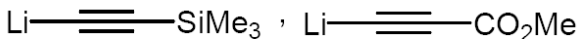
5 R = H
14 R = Me

P_G = $^tBuPh_2Si$

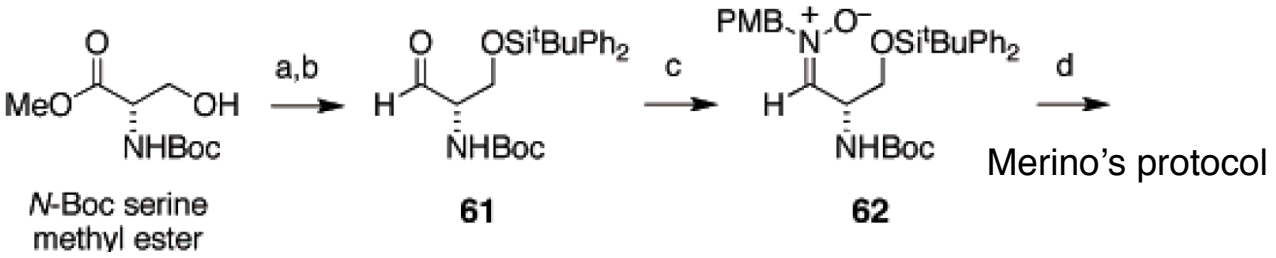
15 R = H ds = 70-92% (*anti*)
16 R = Me ds = 81-88% (*syn*)

Nu-M = MeMgBr, PhMgBr, EtMgBr, Me_3SiCN, 





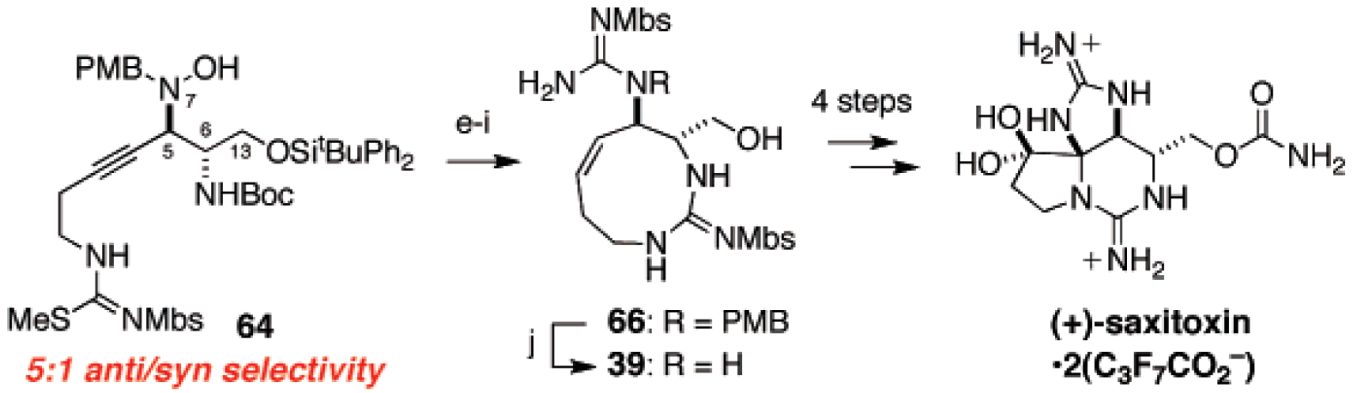
The Second Generation Synthesis of (+)-Saxitoxin (in 14 Steps)



N-Boc serine methyl ester

61

62



64

5:1 anti/syn selectivity

(+)-saxitoxin
·2($C_3F_7CO_2^-$)

(a) $tBuPh_2SiCl$, imidazole, DMF, 95%; (b) iBu_2AlH, CH_2Cl_2, 71%;
(c) PMBNHOH, $MgSO_4$, CH_2Cl_2, 76%;
(d) MbsN=C(SMe)NHCH$_2$CH$_2$C≡CH **63**, iPrMgCl, THF, -78 °C, 78%;
(e) p-TsNHNH$_2$, NaOAc, THF, H_2O, 100 °C, 78%;
(f) Zn, $Cu(OAc)_2$, HOAc, H_2O,70 °C, 81%;
(g) Mbs=C(SMe)NHBoc **65**, $HgCl_2$, Et_3N, CH_2Cl_2, 74%;
(h) HCl, MeOH, 52%;
(i) $AgNO_3$, Et_3N, CH_3CN, 73%;
(j) CF_3CO_2H, 60 °C, 91%.