Literature Seminar (Kuramochi A.[D3]; 2007.09.12)

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

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1st Section:

1. Introduction
2. Total Syntheses by other 3 groups
3. Du Bois' Synthesis

2nd Section:

1. C-H Amination
2. 9-Membered Ring Formation

3rd Section:

1. Dead Ends
2. a-Keto Alcohol Formation
3. End Game
4. 2nd Generation Synthesis

(+)-Saxitoxin

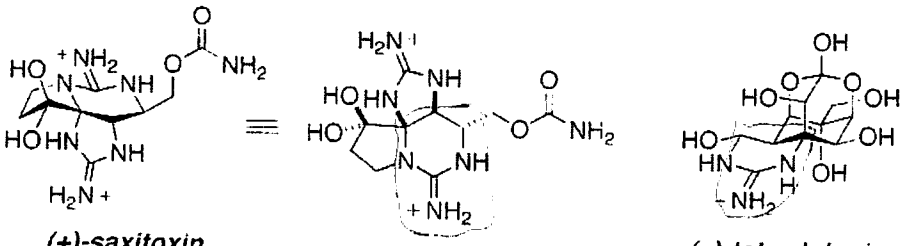


Figure 1. Structurally unique guanidinium toxins act as site 1 selective blockers of voltage-gated Na^+ ion channels.

- **guanidine**-based molecule (like tetrodotoxin)
- $C_{10}H_{19}N_7O_4$ (N+O > C) : highly heteroatomic
- densely fused tricyclic **aminal congifuration**
- dicationic nature (= difficult to handle and purify)

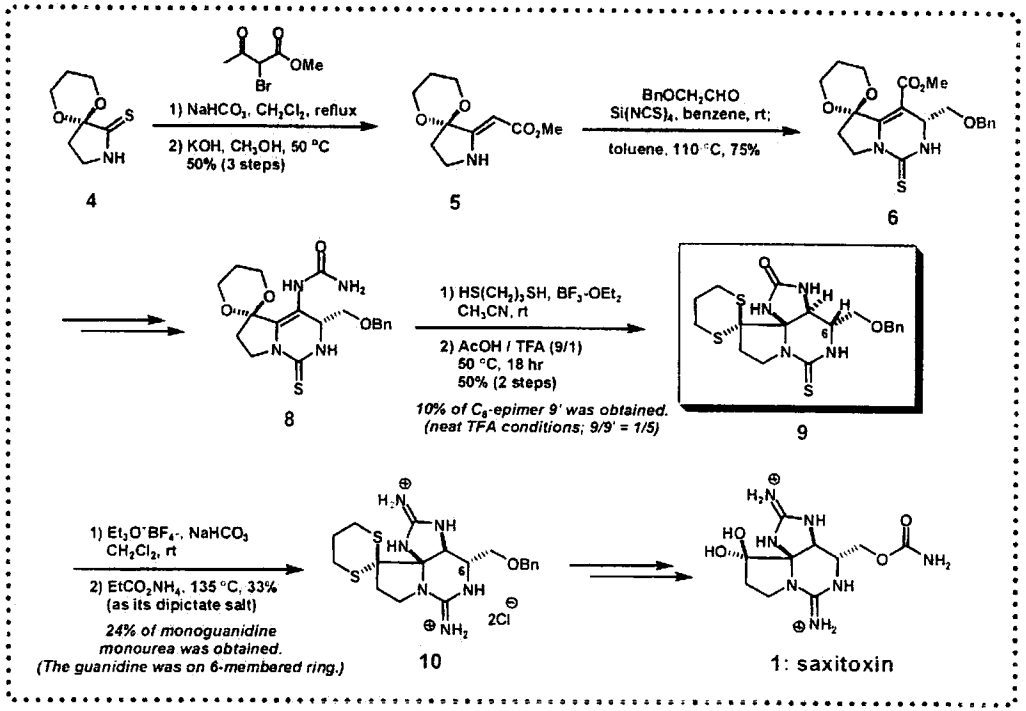
サキシトキシン

出典: フリー百科事典『ウィキペディア(Wikipedia)』

サキシトキシン(Saxitoxin)とは、主にアレクサンドリウム属(Alexandrium catenellaなど)の有毒渦鞭毛藻がつくる毒。その藻類を食べることで、通常は毒を持たない貝類などが毒化することがある。サキシトキシンは、テトロドトキシン同様に神経などのNa+チャネルを阻害し、麻痺や、重度の場合には呼吸困難を引き起こし、最終的には呼吸麻痺で死に至る。
*化学兵器の禁止及び特定物質の規制等に関する法律*で特定物質に指定されており製造、使用、所持などが厳しく規制されている。

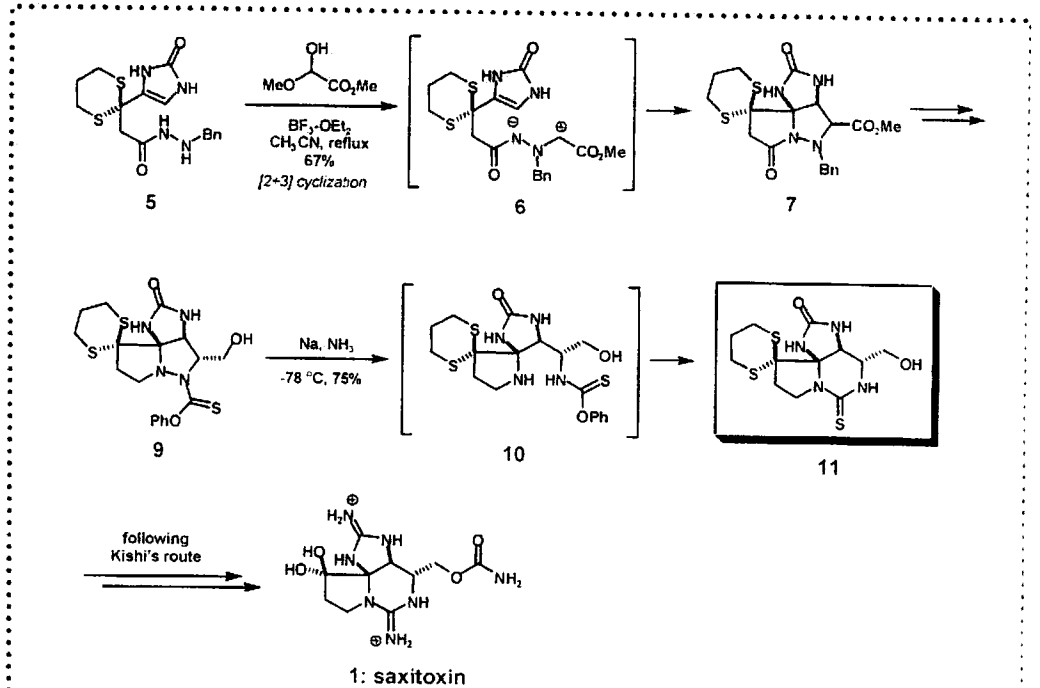
Kishi's Route

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

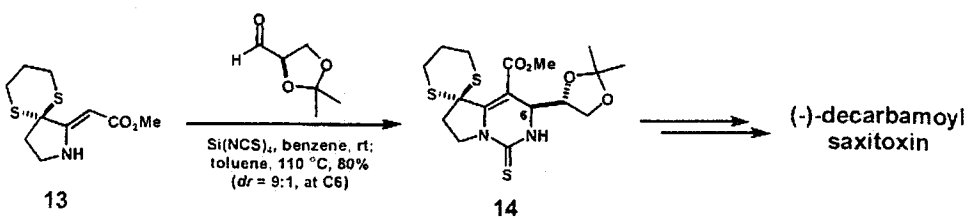


Jacobi's Route

Jacobi, P. A.; Martinelli, M. J.; Polanc, S.
J. Am. Chem. Soc. 1984, *106*, 5594.



*enantioselective synthesis: *JACS* 1992, *114*, 7001.



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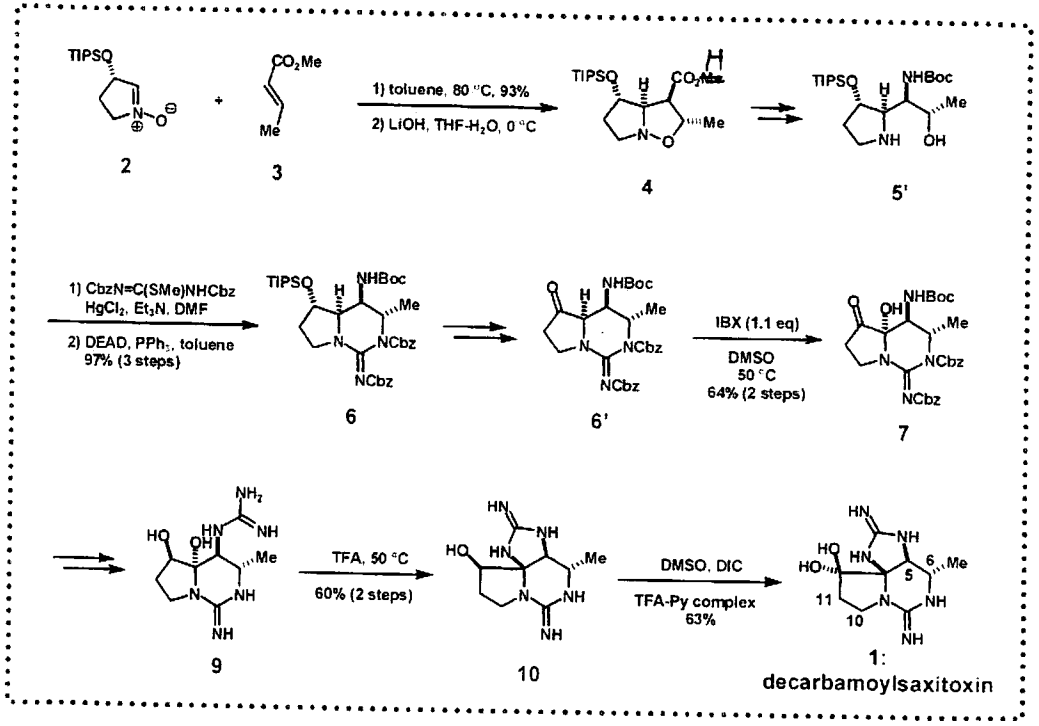
Nagasawa's Route

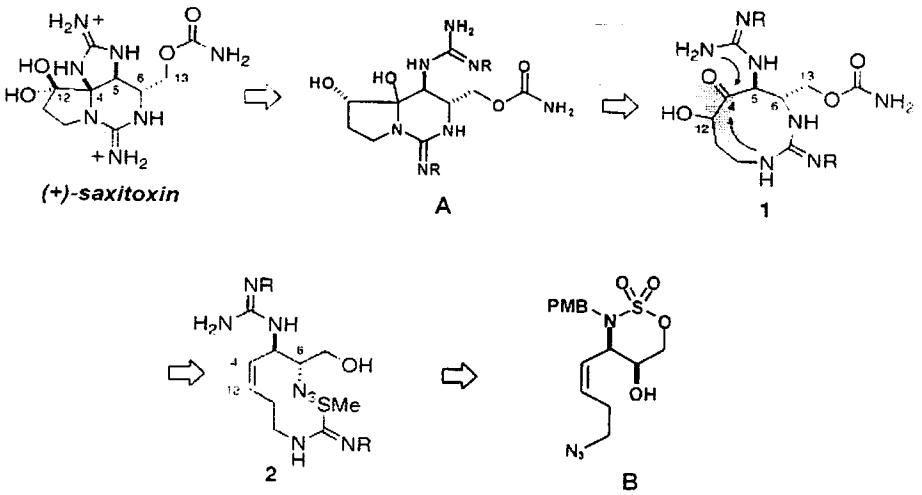
Iwamoto, O.; Koshino, H.; Hashizume, D.; Nagasawa, K.
Angew. Chem., Int. Ed. (will be shown in ASAP)



岩本君とのメールのやり取り

なにはともあれ、一番大変だったのは構造決定ですね。合成が進むにつれてどんどんHが少なくなってしまうので。
特に立体化学は苦戦しました。5位6位側と10位11位側がNOEでは届かないので。
…
あとは脱保護した後の極性ですね。
水溶性化合物ですから有機溶媒には溶けないし、シリカカラムでは出てこないし。

Retrosynthetic Analysis



- **The aminal moiety**, centered at C-4, would be constructed with **cyclodehydration with 9-membered ring** involved both guanidines.
- **A 9-membered ring** would be constructed through the intermediacy of **a reactive carbodiimide**, from a pseudothiourea **(2)**
- **The intact guanidinium groups** would be directly used. (Both Kishi and Jacobi's groups suffered from preparing the guanidines from pseudoureas.)
- Enantioenriched **oxathiazinane (B)** would be set as a starting material

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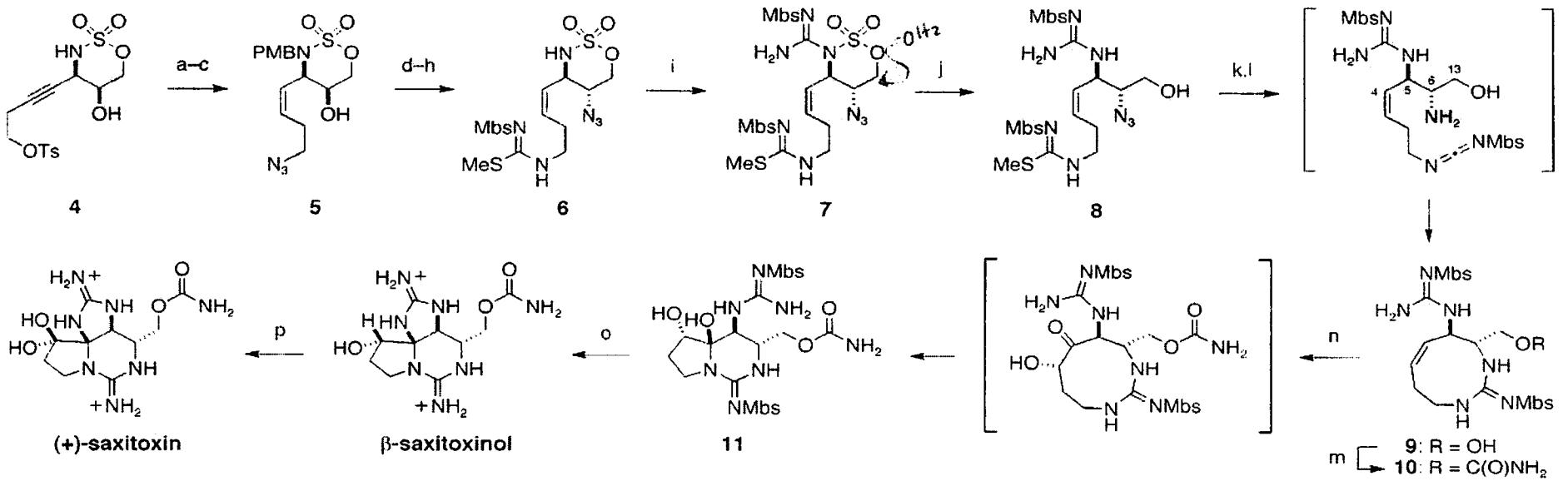
Du Bois's Route

Scheme 1 [a]



[a] Conditions: (a) H_2, $Pd/CaCO_3/Pb$, THF; (b) NaN_3, $^nBu_4NI$, DMF, 90% (2 steps); (c) *p*-$MeOC_6H_4CH_2Cl$, $^nBu_4NI$, K_2CO_3, CH_3CN, 85%; (d) Me_3P, THF/H_2O; (e) $MeS(Cl)C{=}NMbs$, $^iPr_2NEt$, CH_3CN, 72% (2 steps); (f) Tf_2O, C_5H_5N, DMAP, CH_2Cl_2; (g) NaN_3, DMF, −15 °C, 70% (2 steps); (h) $(NH_4)_2Ce(NO_3)_6$, $^tBuOH/CH_2Cl_2$, 74%; (i) KO^{t}Bu, $Cl_2C{=}NMbs$; then $(Me_3Si)_2NH$, 70% (+20% of **6**); (j) aq. CH_3CN, 70 °C, 95%; (k) Me_3P, THF/H_2O; (l) $AgNO_3$, Et_3N, CH_3CN, 65% (2 steps); (m) $Cl_3CC(O)NCO$, THF/CH_3CN, −78 °C; then K_2CO_3, MeOH, 82%; (n) 10 mol % of $OsCl_3$, Oxone, Na_2CO_3, ~~$EtOAc/CH_3CN/H_2O$, 57%~~; (o) $B(O_2CCF_3)_3$, CF_3CO_2H, 82%; (p) DCC, $C_5H_5N{\cdot}HO_2CCF_3$, DMSO, 70%. Mbs = *p*-$MeOC_6H_4SO_2$.

6e⁻ oxidation.

- How was enantioenriched-**4** prepared?
- Why was the oxathiazinane moiety removed at the stage of **7**? (It also played the role of protecting groups of N/O.)
- Is the cyclization (*in situ* carbodiimide formation) a standard? (RCM should be commonly used.)
- Why was a tricky oxidation condition used at **10**? ($OsCl_3$, oxone.)
- Did the guanidine "N" have its sufficient nucleophilicity to form the aminal moiety at **11**?

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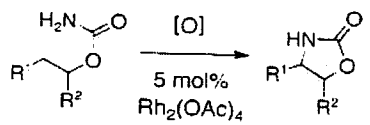
C-H amination

A Rh-Catalyzed C–H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones**

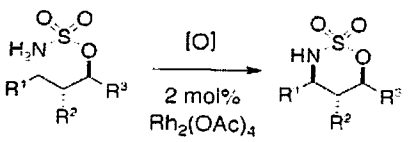
Christine G. Espino and J. Du Bois*



Angew. Chem. Int. Ed. **2001**, *40*, 598

Synthesis of 1,3-Difunctionalized Amine Derivatives through Selective C–H Bond Oxidation

Christine G. Espino, Paul M. Wehn, Jessica Chow, and J. Du Bois*



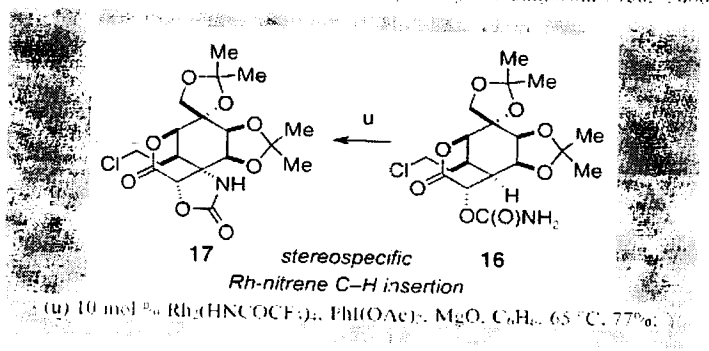
J. Am. Chem. Soc. **2001**, *123*, 6935–6936

J. AM. CHEM. SOC. 2003, *125*, 11510–11511

A Stereoselective Synthesis of (−)-Tetrodotoxin

Andrew Hinman and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080



C-H amination is effective in the late stage of total syntheses.

For more details: Mr. Tanaka's Lit. Seminar (2007.02.07)

Designed Ligand: $Rh_2(esp)_2$

J. AM. CHEM. SOC. 2004, *126*, 15378–15379

Expanding the Scope of C–H Amination through Catalyst Design

Christine G. Espino, Kristin Williams Fiori, Mihyong Kim, and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

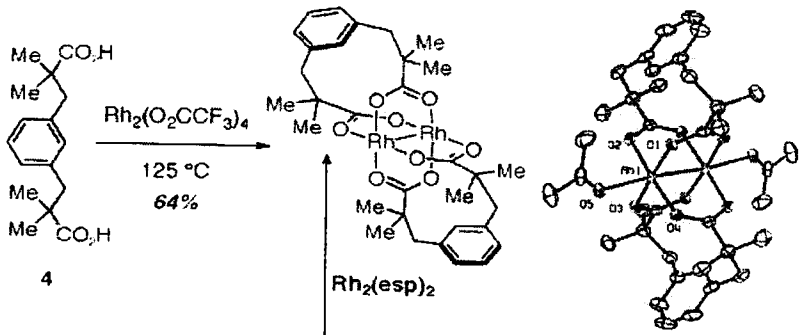


Figure 2. Preparation and X-ray analysis of $[Rh_2(esp)_2 \cdot (acetone)_2]$.

Joining of two carboxylate ligands → **stable complex (= high reactive)**

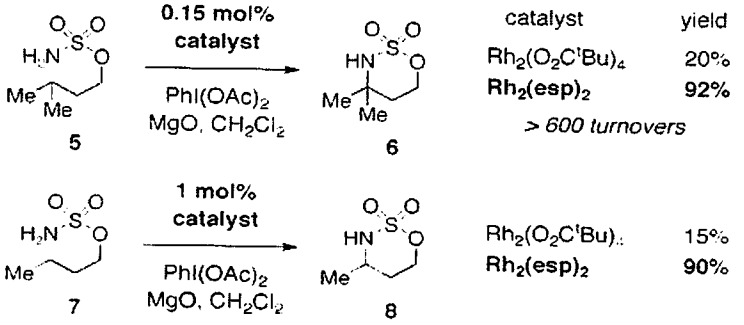


Figure 3. Comparative data of $Rh_2(esp)_2$ and $Rh_2(O_2C^tBu)_4$ as catalysts for intramolecular C–H amination with sulfamates.

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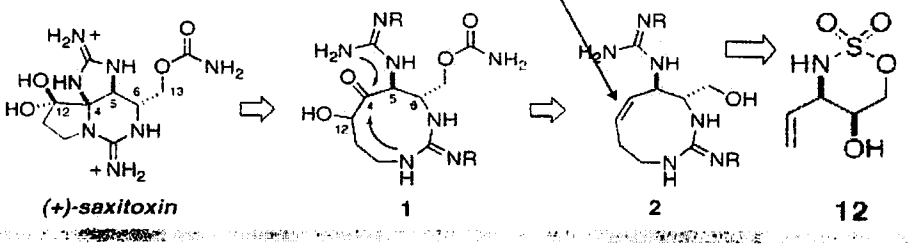
Preparation of Oxathiazine

Alkene is a good surrogate of the ketol unit.



For 1:

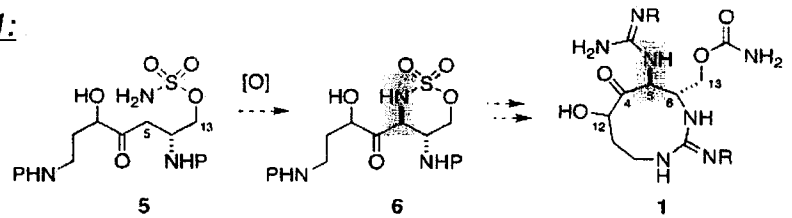


Figure 4. Possible strategy for employing C−H amination.

In general, amination reactions at carbon centers proximal to electron-withdrawing groups are difficult.

For 2:

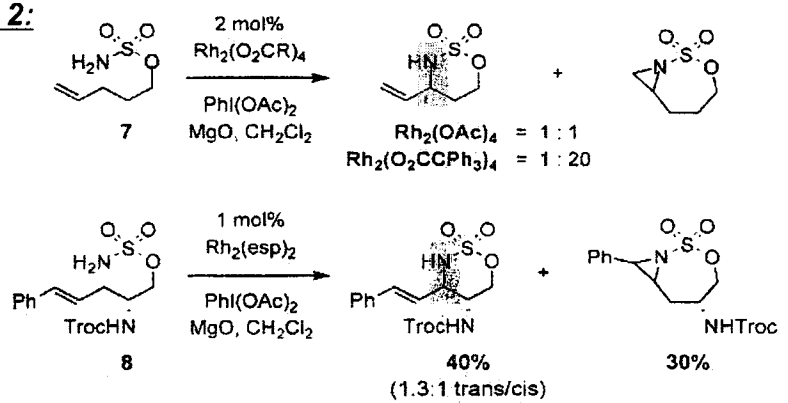


Figure 5. Exploring reaction chemoselectivity with sulfamate ester model systems.

Alkene aziridinations competed against C-H aminations.

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Published on Web 01/29/2003

J. AM. CHEM. SOC. 2003, *125*, 2028−2029

Novel Iminium Ion Equivalents Prepared through C−H Oxidation for the Stereocontrolled Synthesis of Functionalized Propargylic Amine Derivatives

James J. Fleming, Kristin Williams Fiori and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

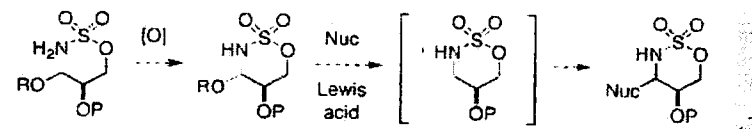
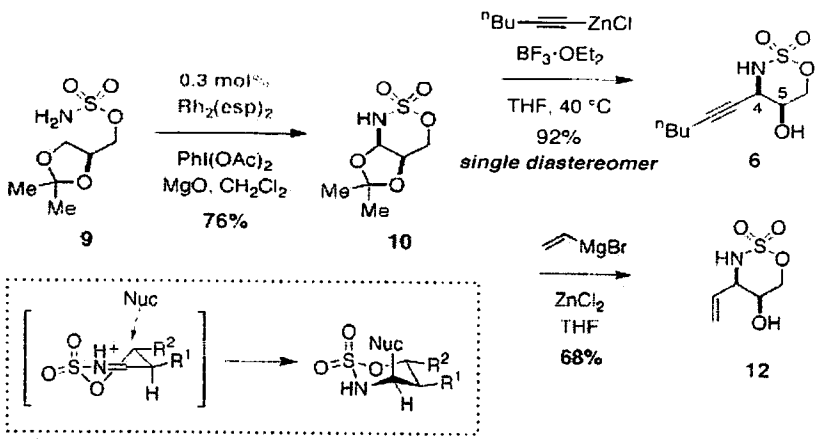


Figure 6. *N,O*-Acetal strategy for accessing substituted oxathiazinane heterocycles.



For other nucleophiles:

N,O-Acetals

Rh-Catalyzed Amination of Ethereal C$^{\alpha}$−H Bonds: A Versatile Strategy for the Synthesis of Complex Amines**

*Kristin Williams Fiori, James J. Fleming, and Justin Du Bois**

Angew. Chem. Int. Ed. 2004, *43*, 4349−4352

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RCM Failed for The Cyclization

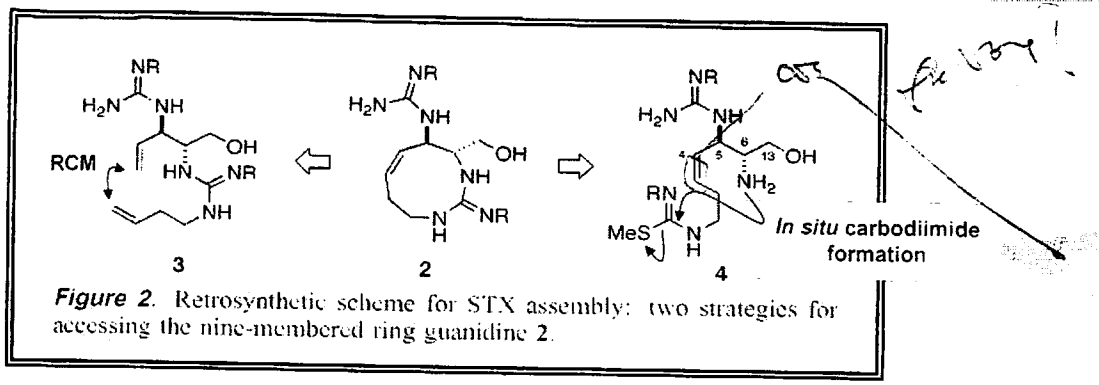


Figure 2. Retrosynthetic scheme for STX assembly: two strategies for accessing the nine-membered ring guanidine **2**.

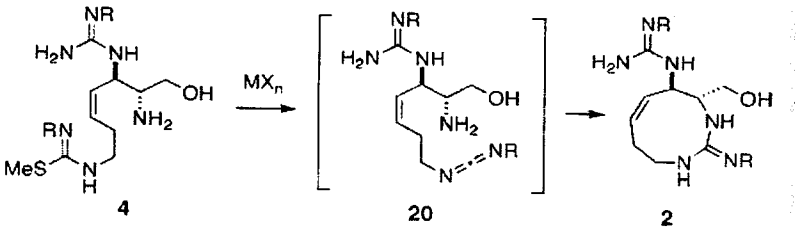
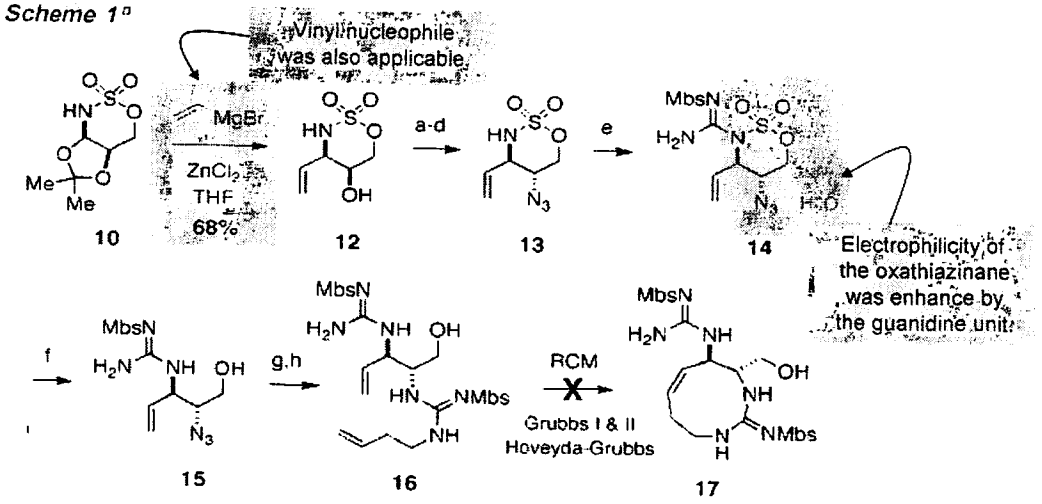


Figure 9. Cyclic guanidine formation via carbodiimide addition.

Scheme 1[a]



[a] Reagents and conditions: (a) PMBCl, K_2CO_3, $^nBu_4NI$, 71%; (b) Tf_2O, C_5H_5N; (c) NaN_3, DMF, −15 °C, 8% (two steps); (d) $(NH_4)_2Ce(NO_3)_6$, ^tBuOH, 55 °C, 92%; (e) NaO^{t}Bu, MbsN=CCl_2, CH_2Cl_2; then $(Me_3Si)_2NH$, 63%; (f) H_2O, CH_3CN, 65 °C, 70%; (g) Me_3P, H_2O/THF; (h) MbsN=C(SMe)NHCH$_2$CH$_2$CH=CH_2, $AgNO_3$, 80% (two steps).

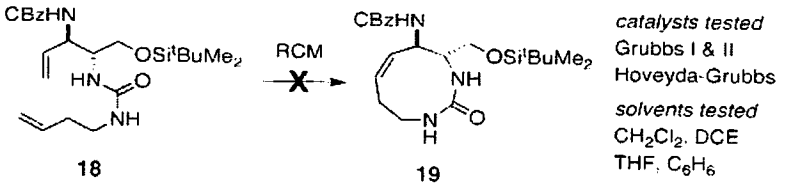


Figure 8. Urea analog also fails to provide nine-membered ring through metathesis reaction.

RCM should be fruitless for the following reasons:

- The polar nature in **16** such as guanidine units
- Aggregation effects caused by the large number of hydrogen donors/acceptors (such as **18**)

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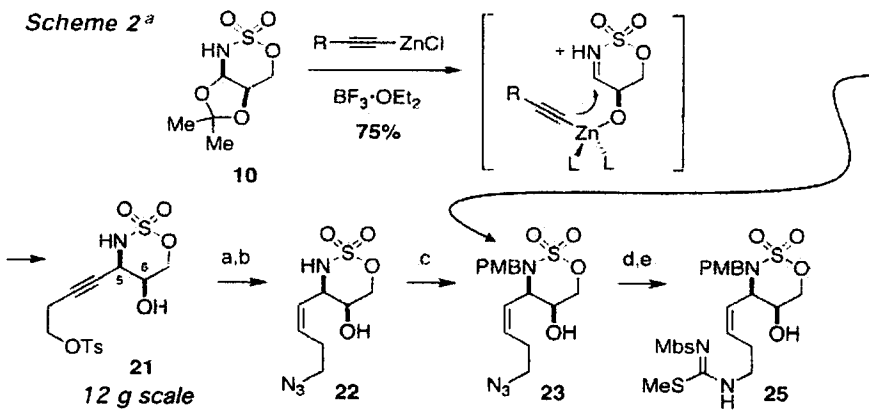
9-Membered Ring Formation

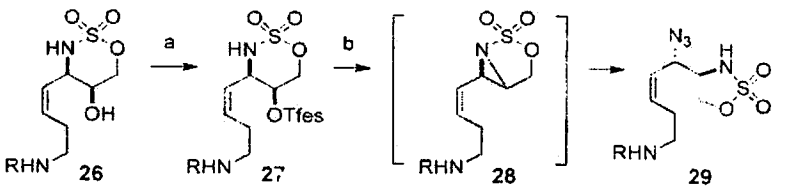
Scheme 2[a]



[a] Reagents and conditions: (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).

The reason for the use of a temporal PMB group.

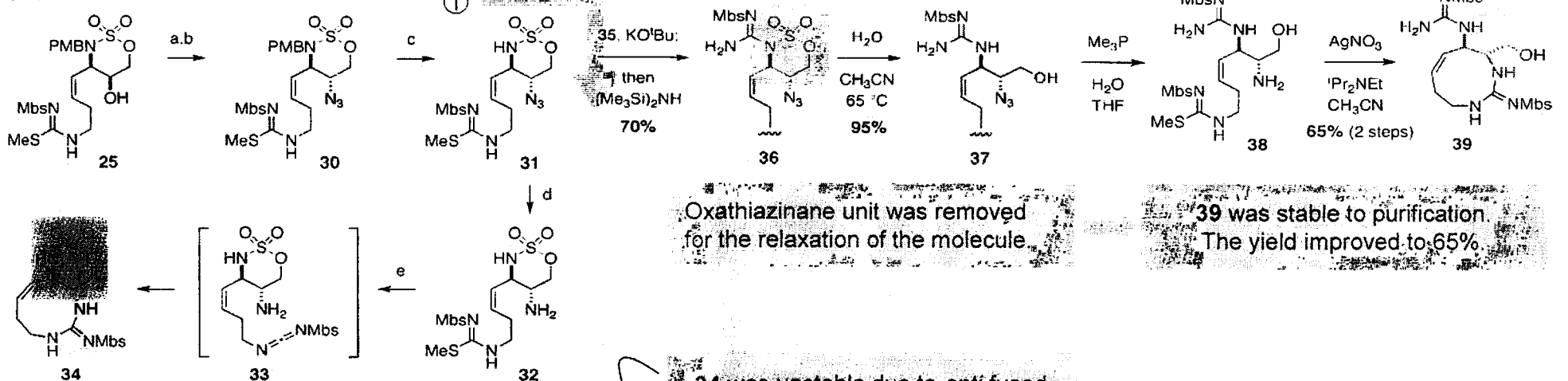
Scheme 3. An Unexpected Ring Contraction [a]



[a] Reagents and conditions: (a) $CF_3CH_2SO_2Cl$, C_5H_5N, DMAP, CH_2Cl_2, 0 °C, 89%; (b) NaN_3, DMF, 0 °C, 70%; R = MbsN=C(SMe).

順路 ② ①

Scheme 4[a]



[a] Reagents and conditions: (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; (two steps).

Oxathiazinane unit was removed for the relaxation of the molecule.

39 was stable to purification. The yield improved to 65%.

34 was unstable due to *anti*-fused oxathiazinane unit, thus the yield was not satisfactory.

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Dead End 1: *N,O*-acetal

Ru-oxidation (6 electrons) afforded desired **46**, although in low yield.
(For detailed conditions of the oxidation: see the next page.)

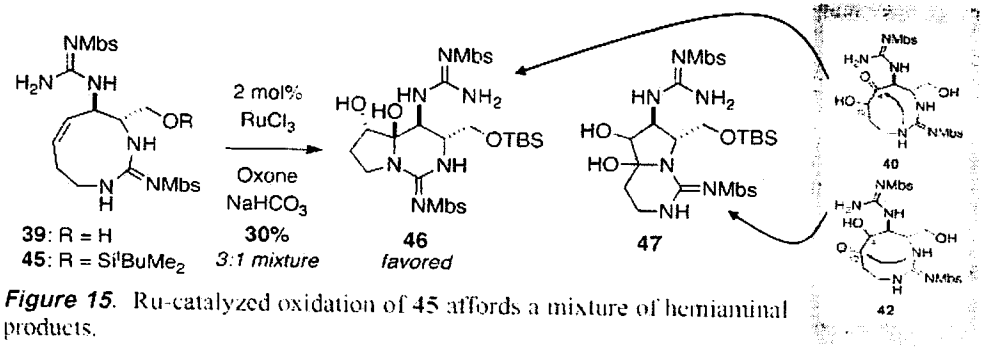
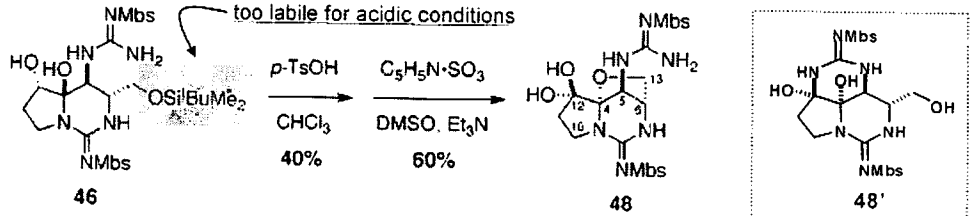


Figure 15. Ru-catalyzed oxidation of **45** affords a mixture of hemiaminal products.



Suggested by
岩本君(D1)
@長澤研

Figure 16. An attempt to form the tricyclic core of STX gives an undesired isomeric structure.

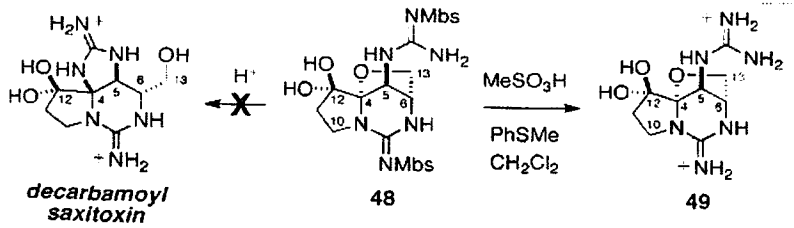


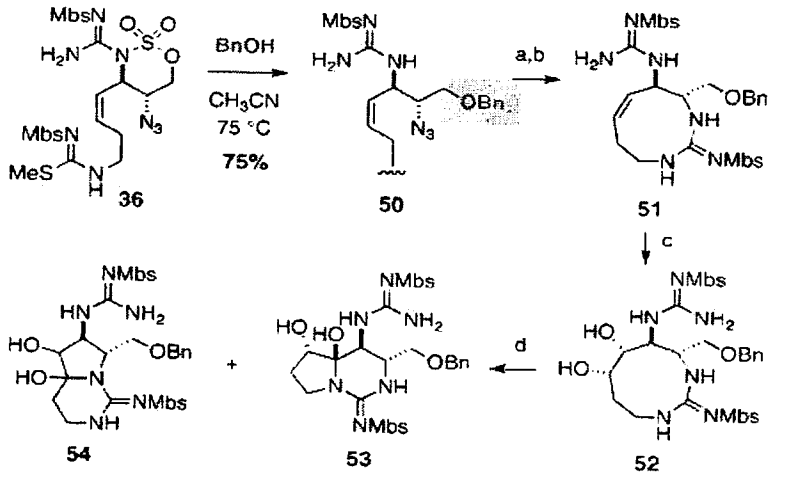
Figure 17. Acid treatment of **48** does not afford decarbamoyl STX.

N,O-acetal **49** should be a dead end.

Acid-stable protecting groups would be used instead of TBS group.

Dead End 2: β-dcSTXol

Scheme 5[a]



[a] Reagents and conditions: (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**).

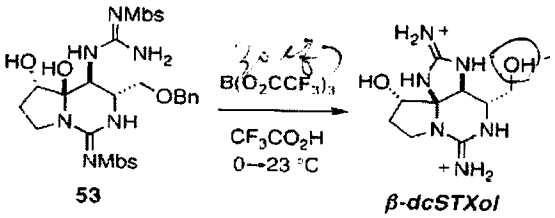
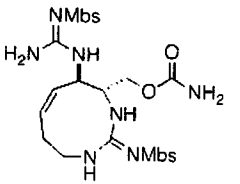


Figure 19. Guanidine deprotection affords decarbamoyl β-saxitoxinol.

As a consequence of our inability to manipulate β-dcSTXol, an alternative end-game strategy was devised.

Carbamoylation should be performed at an early stage.



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α-Keto Alcohol Formation

Selectivity in the formation of a C4, C12-hydroxy ketone **40** is essential, as the regioisomeric structure **42** has the potential for transannular collapse to give an undesired **43**.

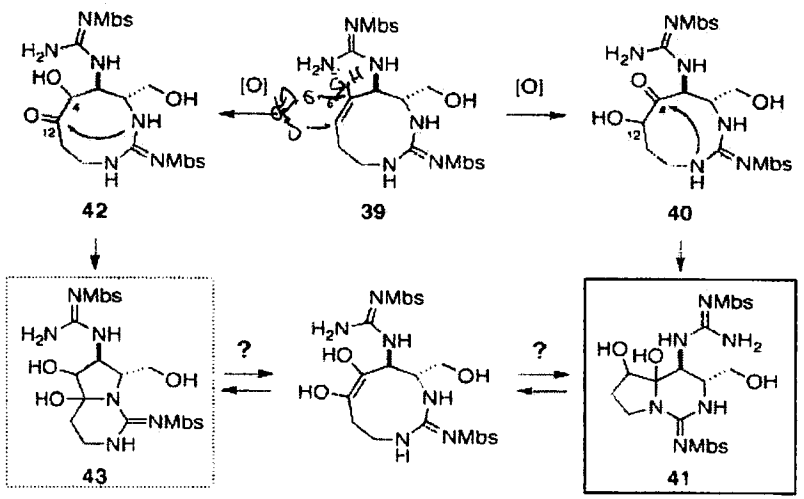
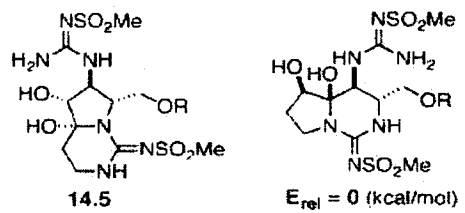
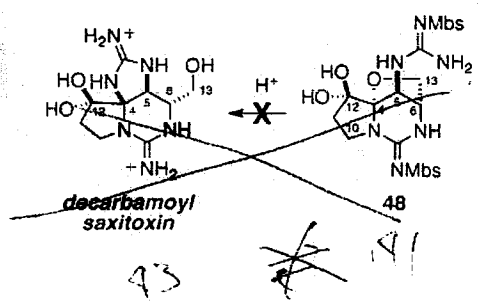


Figure 13. Potential complications associated with C4,C12-alkene oxidation.



DFT calculations suggested the possibility to afford the sole product **41** after the equilibration.

Unfortunately, the isomerization didn't occur.



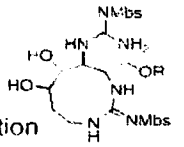
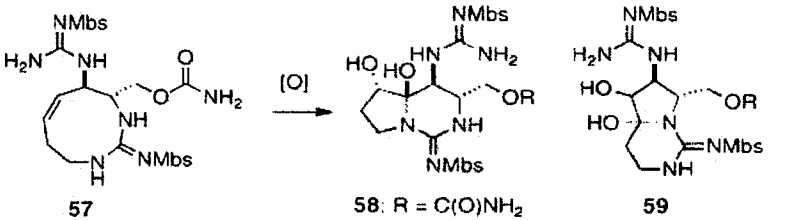


Table 1. Reaction Conditions Influence Alkene Ketohydroxylation



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.

The low yield (entries 1-2) was likely due to **C-C bond cleavage**.

Os **Os-catalyzed dihydroxylation using H_2O_2 or TBHP** gives varying amounts of the **vicinal keto-alcohol** as a side product. (For a mechanistic study: *J. Org. Chem.* **1994**, *59*, 1375.)

*For the use of $OsCl_3$:

CHEMISTRY LETTERS, pp. 1767-1770, 1993.

Osmium-Catalyzed Oxidative Transformation of Alkenes to α-Ketols with Peracetic Acid

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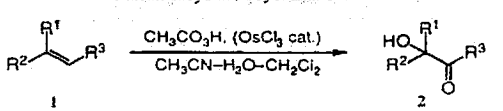

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End Game

Critical is the choice of the stage where the carbamate is installed

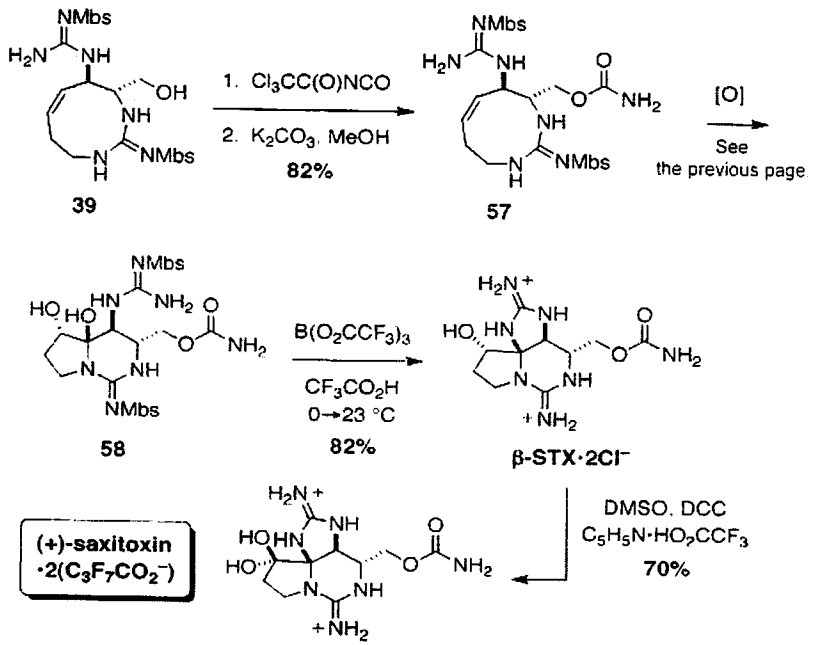
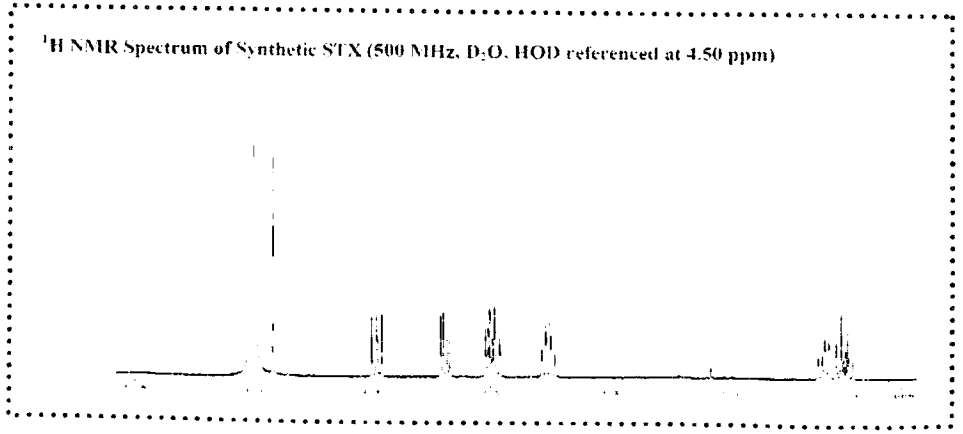


Figure 20. Completed first-generation synthesis of the desired target.

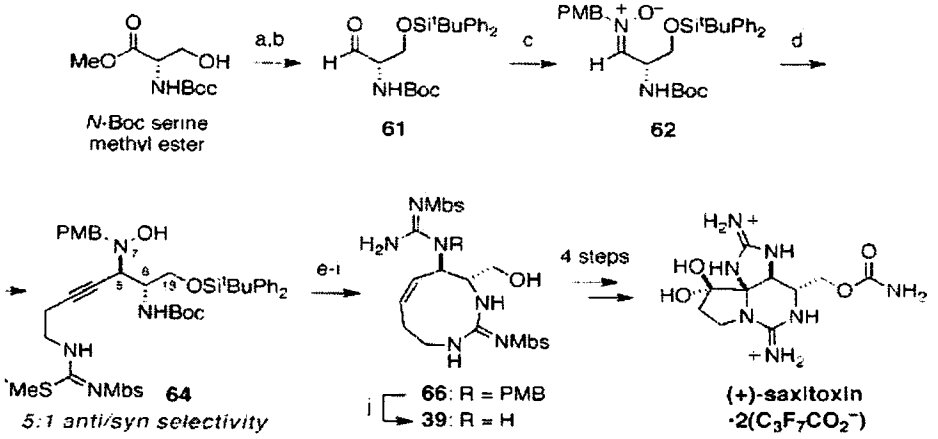


2nd Generation Synthesis

1st generation synthesis:

Preparation of a 9-membered ring = 15 steps

2nd generation synthesis: *starting from an amino acid!*



[a] Reagents and conditions: (a) ^{t}BuPh$_2$SiCl, imidazole, DMF, 95%; (b) ^{i}Bu$_2$AlH, CH_2Cl_2, 71%; (c) PMBNHOH, $MgSO_4$, CH_2Cl_2, 76%; (d) MbsN=C(SMe)NHCH$_2$CH$_2$C≡CH **63**, ^{i}PrMgCl, THF, −78 °C, 78%; (e) p-TsNHNH$_2$, NaOAc, THF, H$_2$O, 100 °C, 78%; (f) Zn, Cu(OAc)$_2$, HOAc, H$_2$O, 70 °C, 81%; (g) MbsN=C(SMe)NHBoc **65**, HgCl$_2$, Et$_3$N, CH$_3$CN, 74%; (h) HCl, MeOH, 52%; (i) AgNO$_3$, Et$_3$N, CH$_3$CN, 73%; (j) CF$_3$CO$_2$H, 60 °C, 91%.

Scheme 6. (+)-Saxitoxin in 14 Steps from *N*-Boc-L-Serine Methyl Ester[a]

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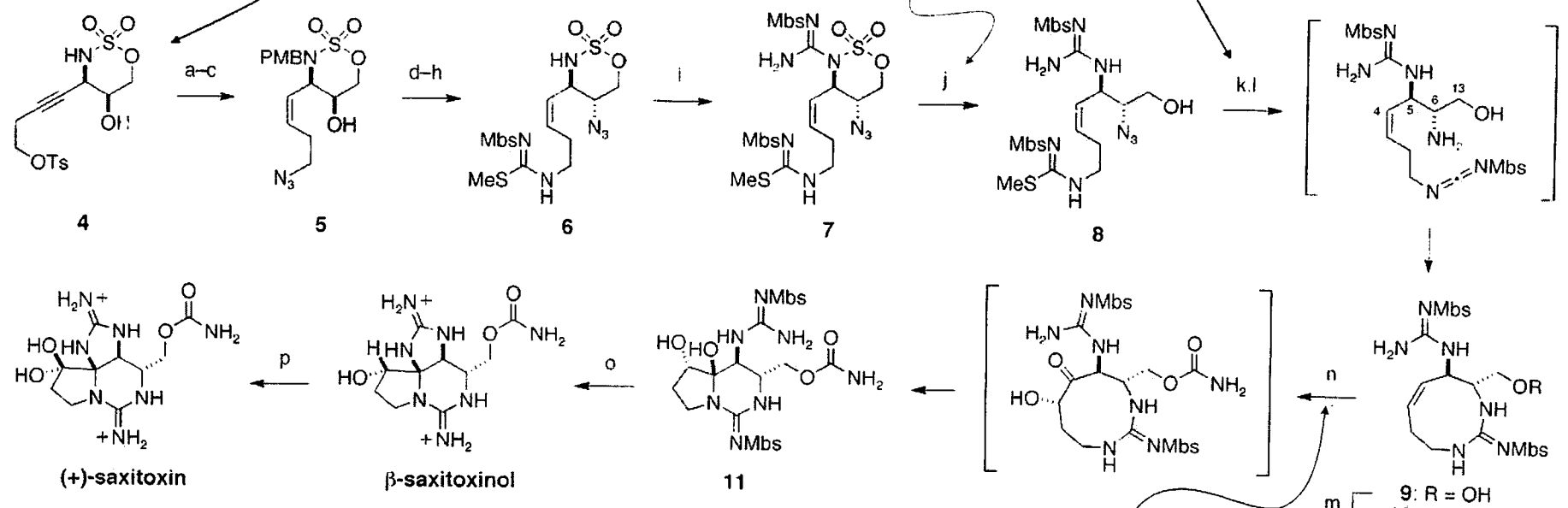
Summary

4 was easily prepared by C-H amindation developed by Du Bois.

For the stability of **8**, the oxathiazinene ring should be removed before the key cyclization.

RCM didn't work in the system of saxitoxins probably due to the high polarity.

Scheme 1 [a]



[a] Conditions: (a) H_2, Pd/$CaCO_3$/Pb, THF; (b) NaN_3, $^nBu_4NI$, DMF, 90% (2 steps); (c) *p*-$MeOC_6H_4CH_2Cl$, $^nBu_4NI$, K_2CO_3, CH_3CN, 85%; (d) Me_3P, THF/H_2O; (e) MeS(Cl)C=NMbs, $^iPr_2NEt$, CH_3CN, 72% (2 steps); (f) Tf_2O, C_5H_5N, DMAP, CH_2Cl_2; (g) NaN_3, DMF, −15 °C, 70% (2 steps); (h) $(NH_4)_2Ce(NO_3)_6$, $^tBuOH/CH_2Cl_2$, 74%; (i) KO^{t}Bu, Cl_2C=NMbs; then $(Me_3Si)_2NH$, 70% (+20% of **6**); (j) aq. CH_3CN, 70 °C, 95%; (k) Me_3P, THF/H_2O; (l) $AgNO_3$, Et_3N, CH_3CN, 65% (2 steps); (m) $Cl_3CC(O)NCO$, THF/CH_3CN, −78 °C; then K_2CO_3, MeOH, 82%; (n) 10 mol % of $OsCl_3$, Oxone, Na_2CO_3, $EtOAc/CH_3CN/H_2O$, 57%; (o) $B(O_2CCF_3)_3$, CF_3CO_2H, 82%; (p) DCC, $C_5H_5N{\cdot}HO_2CCF_3$, DMSO, 70%. Mbs = *p*-$MeOC_6H_4SO_2$.

The tricky oxidative conditions was choiced for the reason that Os was a mild oxidant and the proper regioselectivity was obtained.

Carbamoylation must be introduced at this stage where the molecule was soluble in organic solvents.

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