北京大学
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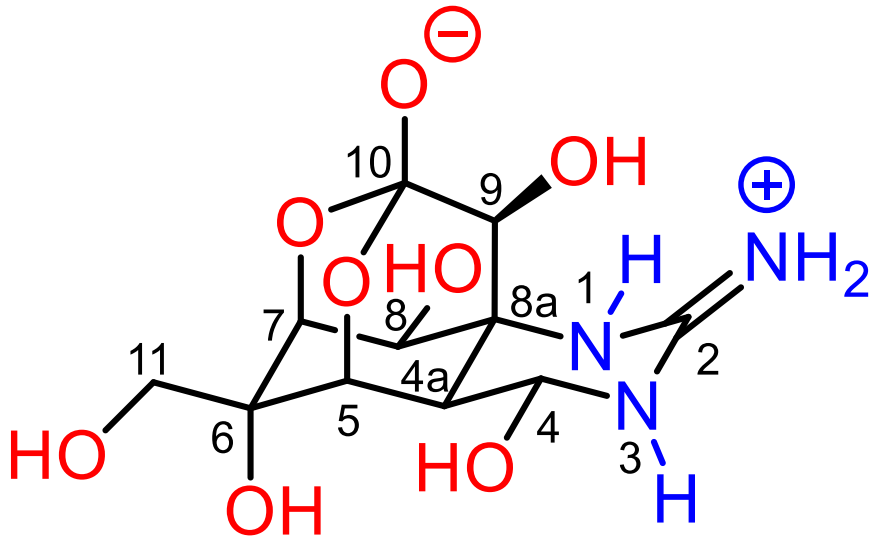
Total Synthesis of Tetrodotoxin

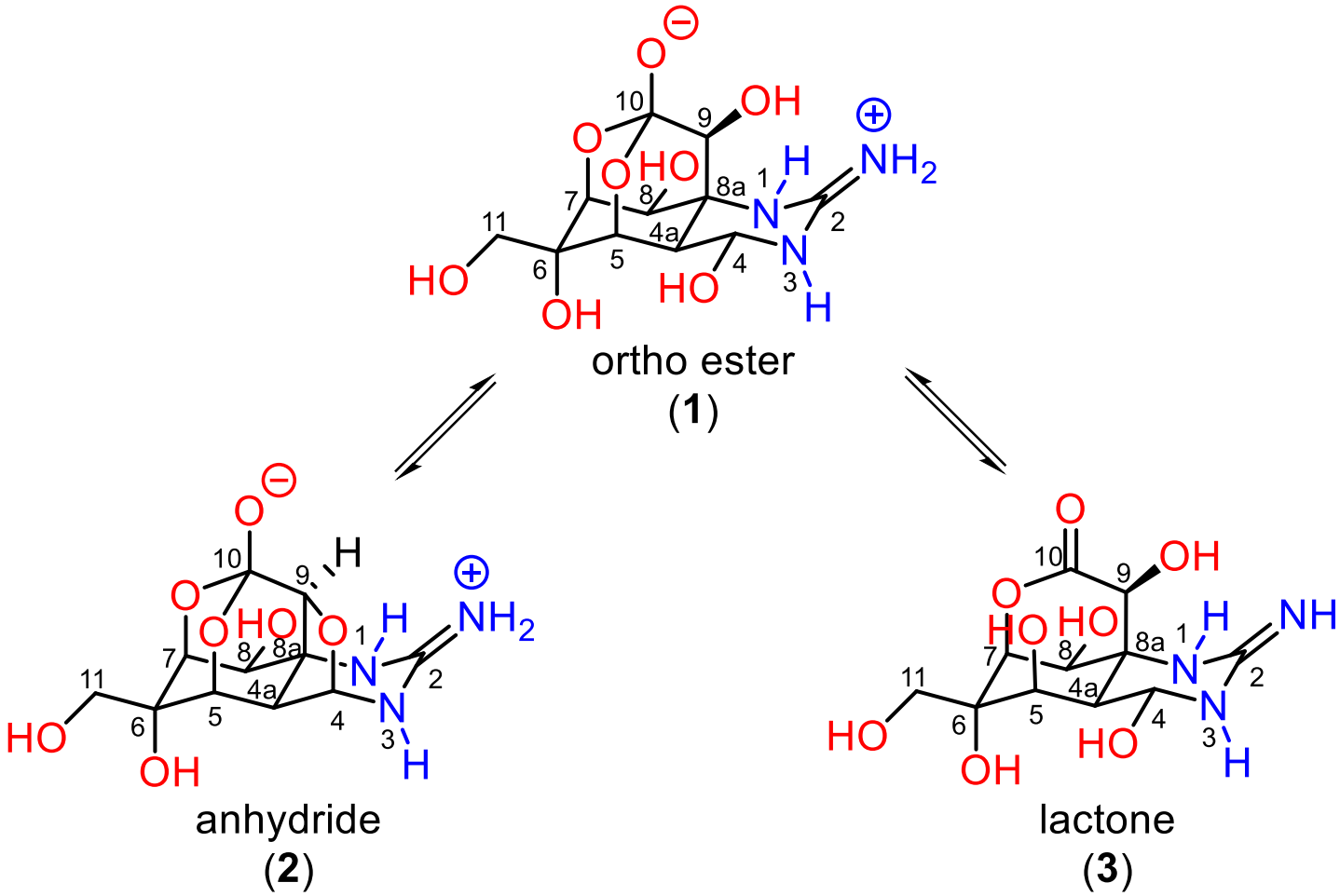


Tetrodotoxin
TTX

Shumi Jia

2022.09.22

研究背景



Chemical Formula: $C_{11}H_{17}N_3O_8$

Exact Mass: 319.10156

研究历史

公元前140年：
《神农本草经》记载了河豚鱼的毒性

在汉朝时期（公元前202年–220年）人们意识到毒性主要集中在河豚鱼的肝脏

在隋朝时期（581年–618年）准确的记载了毒性集中在河豚鱼的肝脏、卵和卵巢中

1596年：
《本草纲目》中详细描述了河豚鱼
同时，河豚已经成为日本和中东的一道美食

17世纪初：
欧洲首次出现了河豚中毒事件

1909年，**Y. Tahara**从成功提取出河豚毒素的粗品（ 纯度：0.2 – 4 % ）
命名为“**tetrodotoxin**”

1950年，**A. Yokoo, K. Tsuda**和**M. Kawamura**成功分离出河豚毒素晶体
1964年，**R. B. Woodward, K. Tsuda, T. Goto**和**H. S. Mosher**不约而同的阐明了河豚毒素结构

Mariia Makarova, et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 18338 – 18387.

全合成研究

Yoshito Kishi
Harvard
1972

Tohru Fukuyama
University of Tokyo
2017

Satoshi Yokoshima
Nagoya University
2020

Minoru Isobe
National Tsing Hua University
2003, 2004

Justin Du Bois
Stanford
2003

Ken-ichi Sato
Kanagawa University
2005, 2008, 2010

Dirk Trauner
New York University
2022

Minoru Isobe
Nagoya University
National Tsing Hua University

Education:

1967.03 B.S. Dept. of Agricultural Chemistry, **Nagoya University**

1969.03 M.S. Dept. of Agricultural Chemistry, **Nagoya University**

1973.05 PhD. Dept. of Agricultural Chemistry, **Nagoya University**

Professional:

1970.01	Assistant Professor	**Nagoya University**
1973.08 ~ 1975.06	Postdoctoral fellow	**Columbia University**
1975.08-1991.06	Assosiate Professor	**Nagoya University**
1991.06-2008.04	Professor	**Nagoya University**
2008 ~	Professor	**National Tsing Hua University**

Awards and Honors:

2007.03	Honorary Director	**Shanghai Institute of Materia Medica, CAS**
2007.08	Appreciation of Service for Outstanding Contributions to the Advancement of Worldwide Chemistry, IUPAC	
2008.04	Honorary Professor	**Nagoya University**
2008.04	Purple Ribbon Medal	
2014	Chair Professor	**National Sun Yat-Sen University**
2015	Visiting Professor	**The Chinese University of Hong Kong**

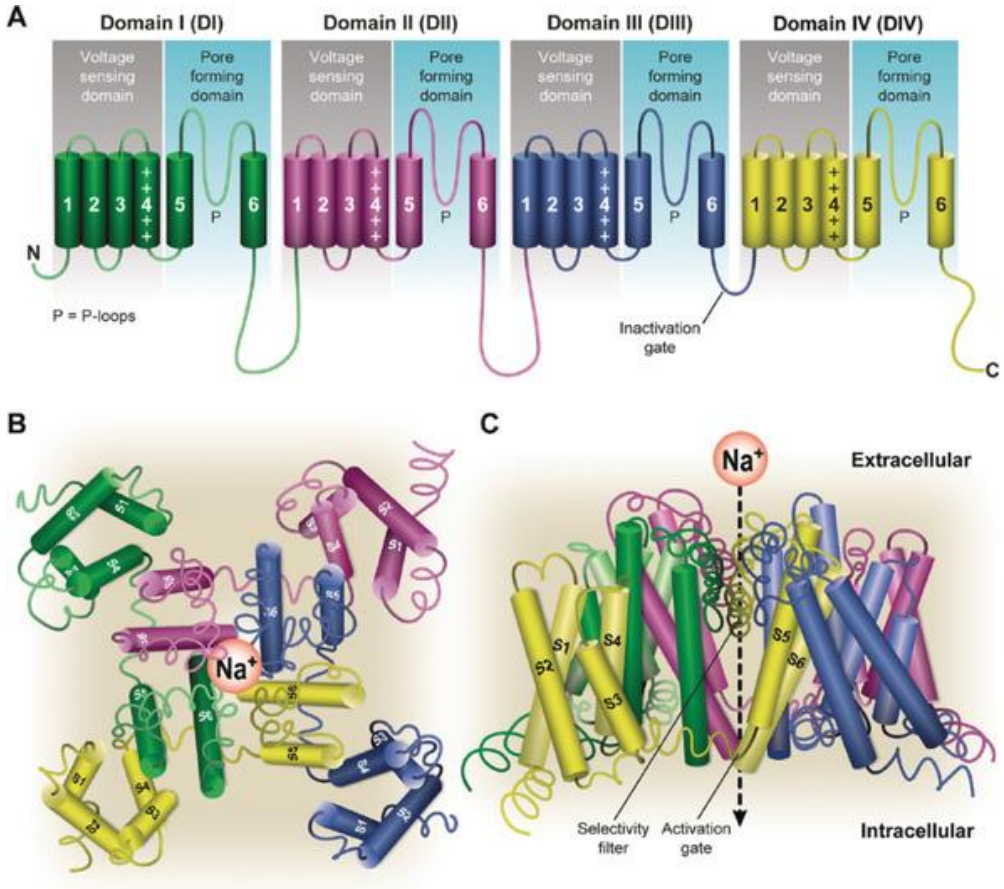
生物作用机制与潜在应用

- **TTX的毒性来源于其阻断钠离子通道（VGSC）。**
- **TTX会对许多重要器官基本功能(如呼吸) 抑制。**

  TTX的人体致死剂量为 1.33 μg/kg。
- **羟基和胍基的存在对其与VGSC结合是至关重要的。**
- **TTX具有局部麻醉的潜在应用。**
- **TTX与肿瘤的治疗：**

1、TTX对非兴奋细胞VGSC的相互作用和阻断，导致癌细胞代谢失调和细胞死亡。2、缓解病人疼痛。

- **TTX在阿片类药物成瘾治疗中的应用。**

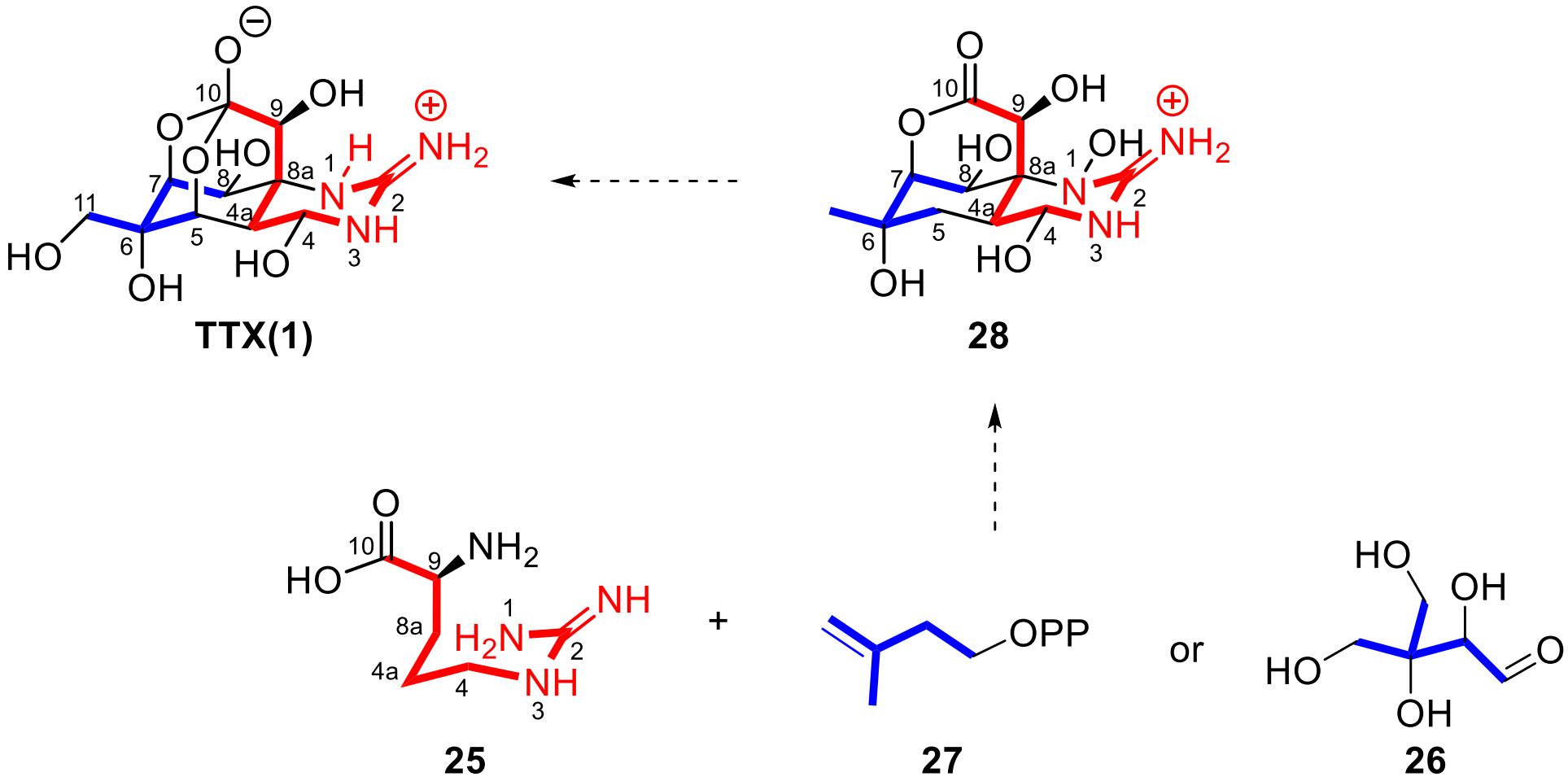


The structure of voltage gated sodium channels (VGSC).

$Na_V1.1$	$Na_V1.2$	$Na_V1.3$	$Na_V1.4$	$Na_V1.5$	$Na_V1.6$	$Na_V1.7$
4.1±0.2 nM	14±2 nM	5.3±0.6 nM	7.6±2.6 nM	1.0±0.1 μM	2.3±0.0 nM	36±7 nM

M. de Lera Ruiz, R. L. Kraus, *J. Med. Chem.* **2015**, *58*, 093 – 7118.

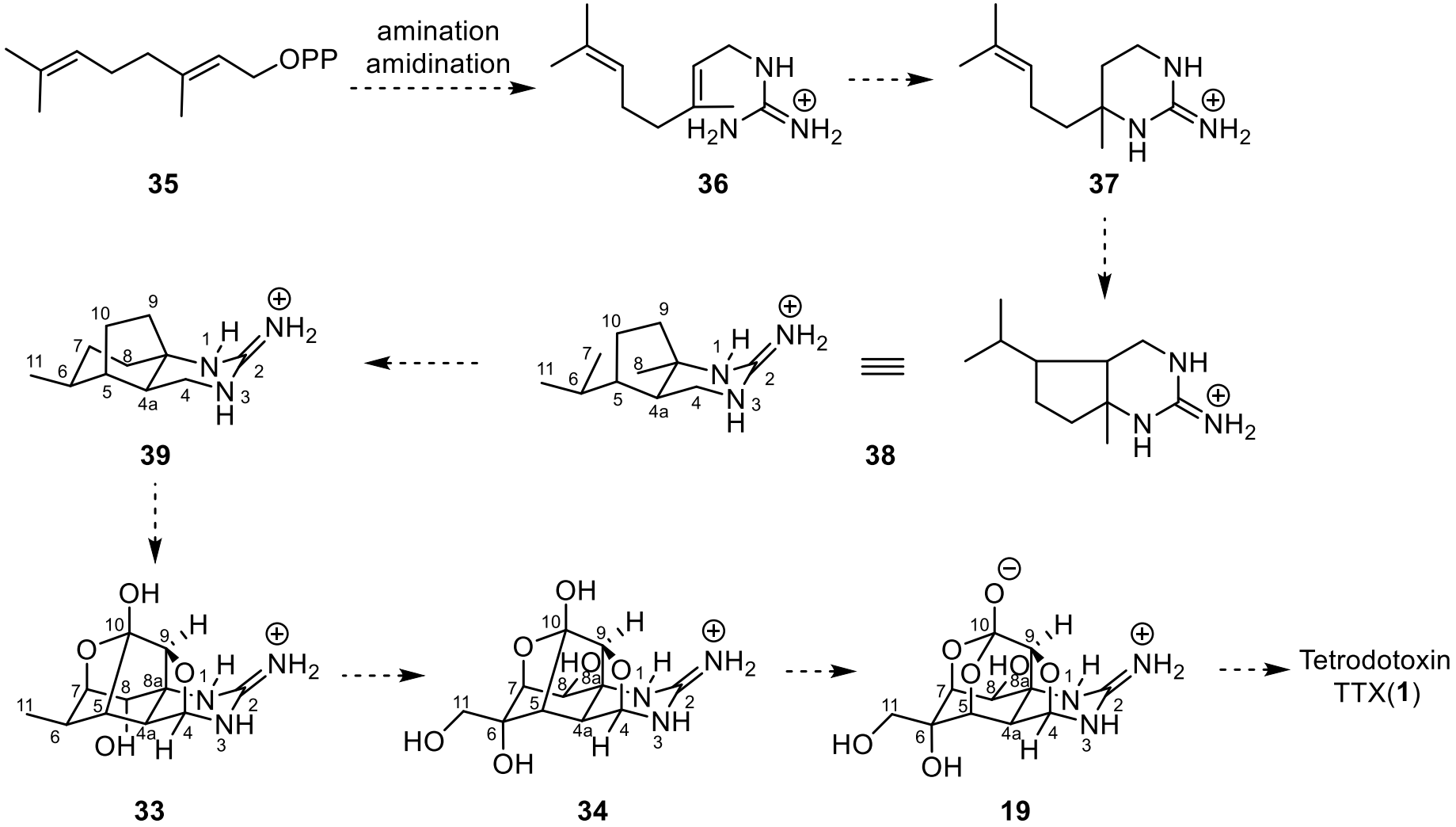
TTX生源途径猜想



Shimizu‘s biogenetic speculations on the origin of TTX

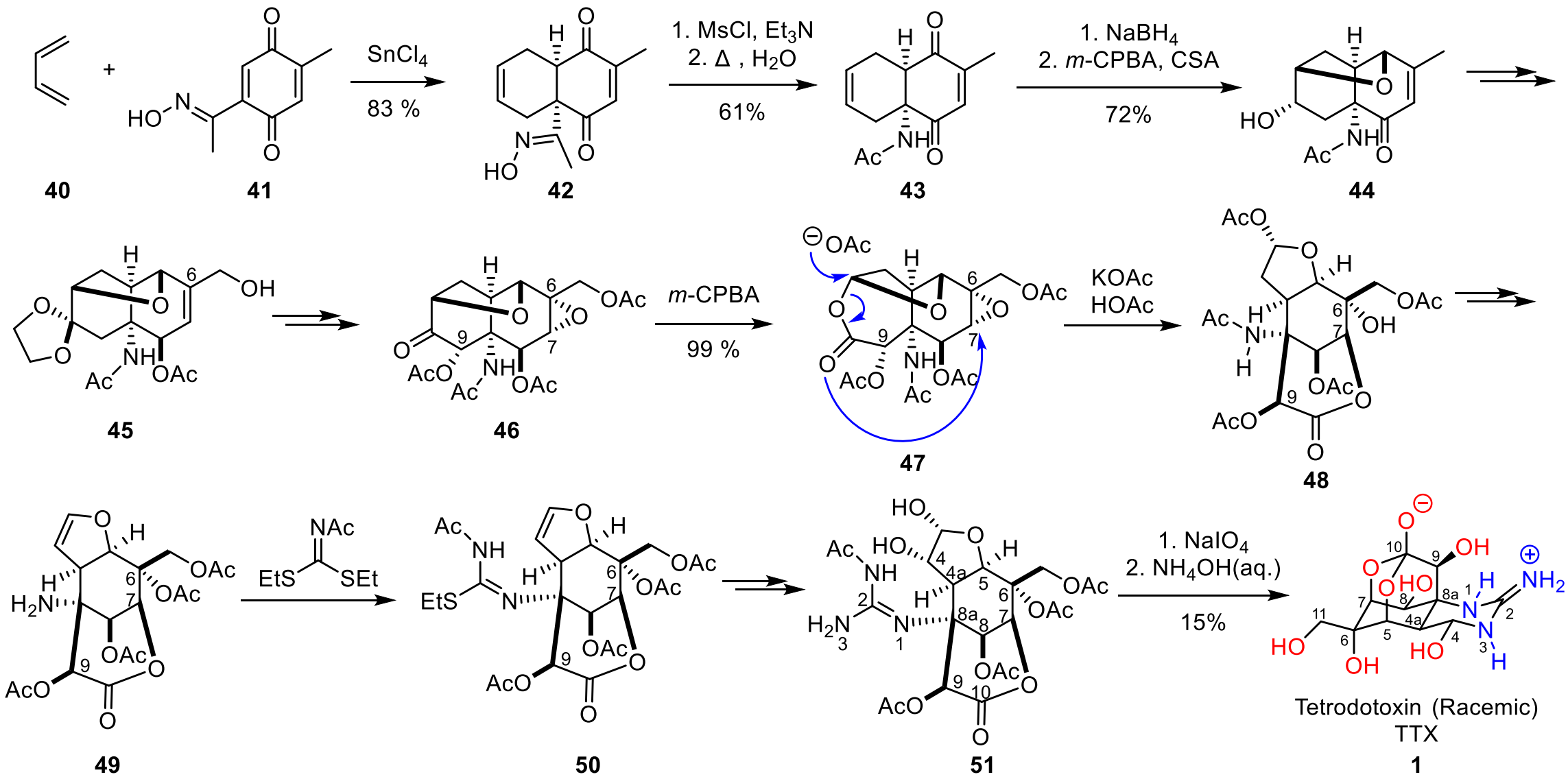
Y. Kotaki, Y. Shimizu, *J. Am. Chem. Soc.* **1993**, *115*, 827 – 830.

TTX生源途径猜想



Possible biogenetic scenario of TTX biosynthesis from geranyl pyrophosphate

Y. Kudo, Y. Yamashita, D. Mebs, et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 14546 – 14549; *Angew. Chem.* **2014**, *126*, 14774 – 14777.

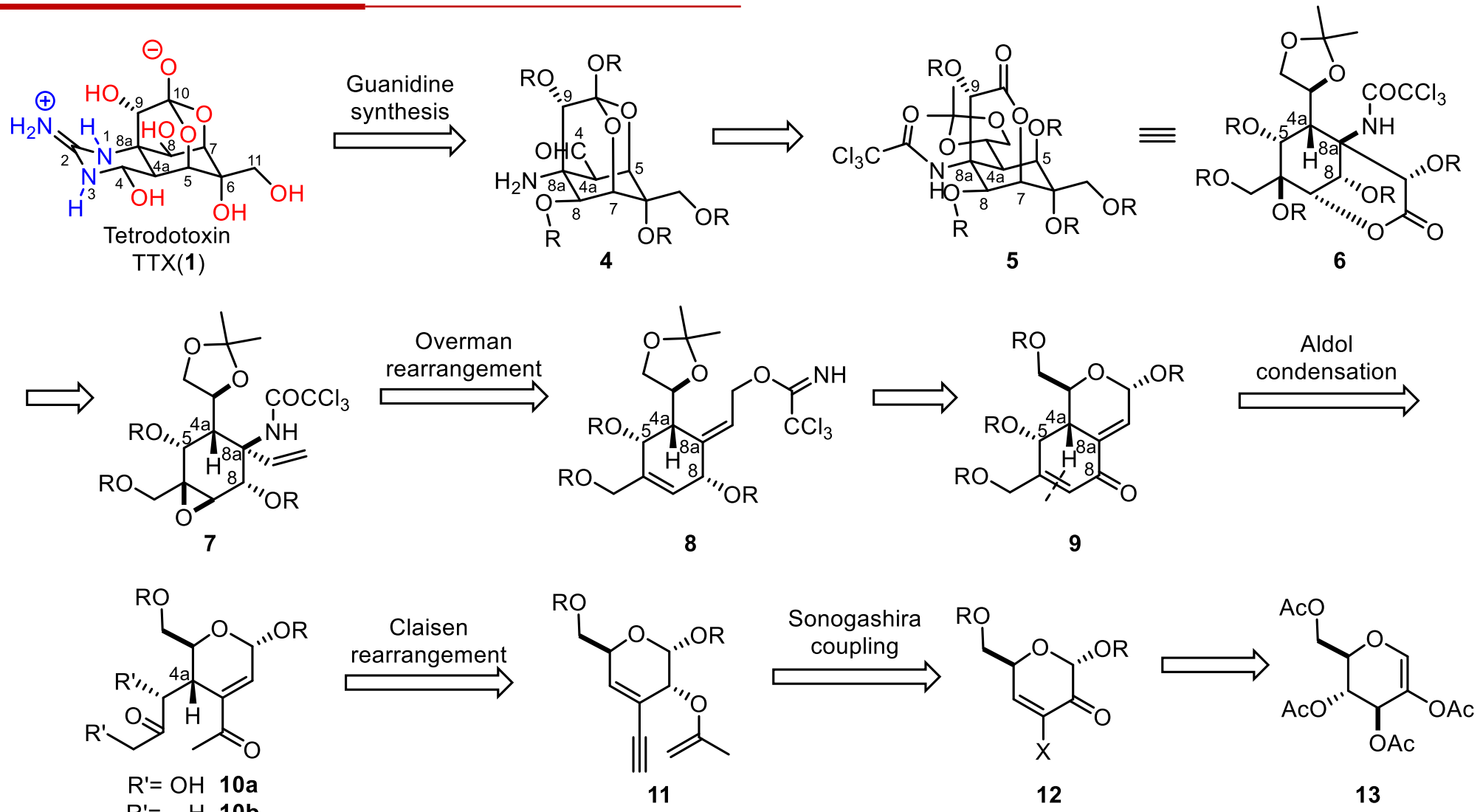


The First Total Synthesis by **Kishi**: a Milestone in TTX Research (**32 steps**)

Y. Kishi, M. Aratani, T. Fukuyama, et al. *J. Am. Chem. Soc.* **1972**, *94*, 9217 – 9219;

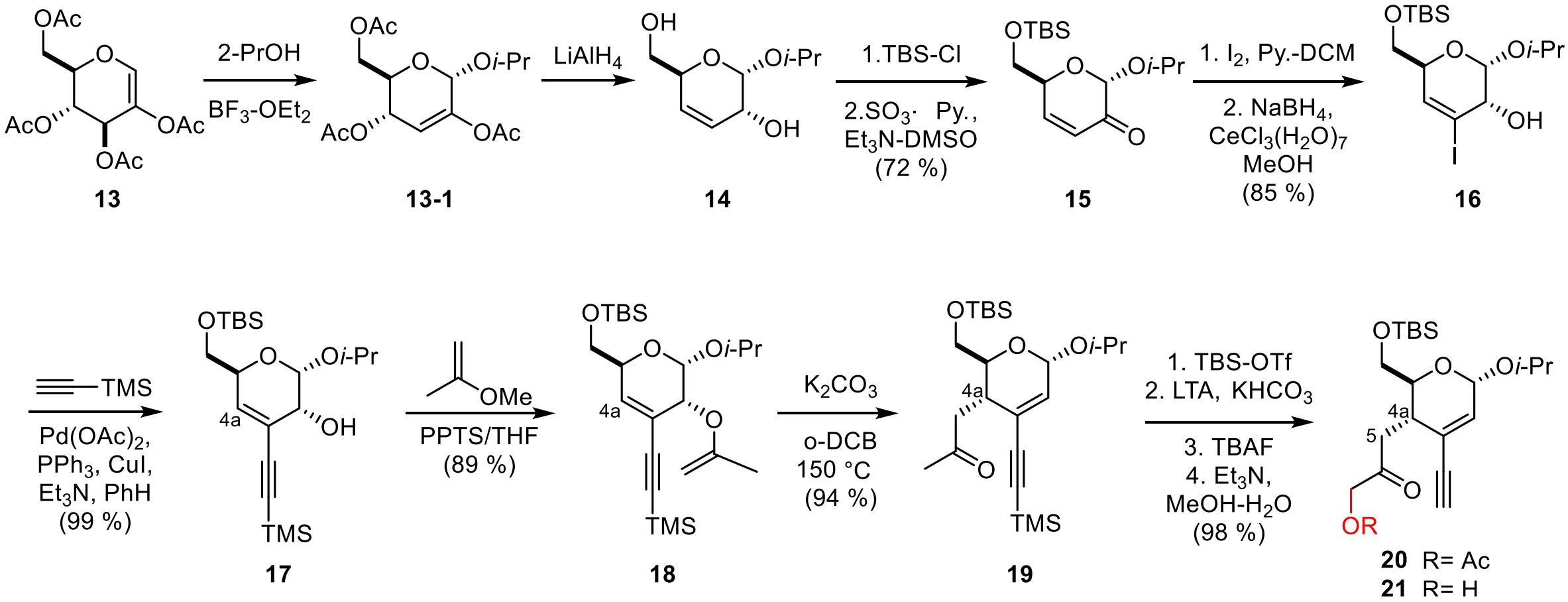
Y. Kishi, T. Fukuyama, M. Aratani, et al. *J. Am. Chem. Soc.* **1972**, *94*, 9219 – 9221.

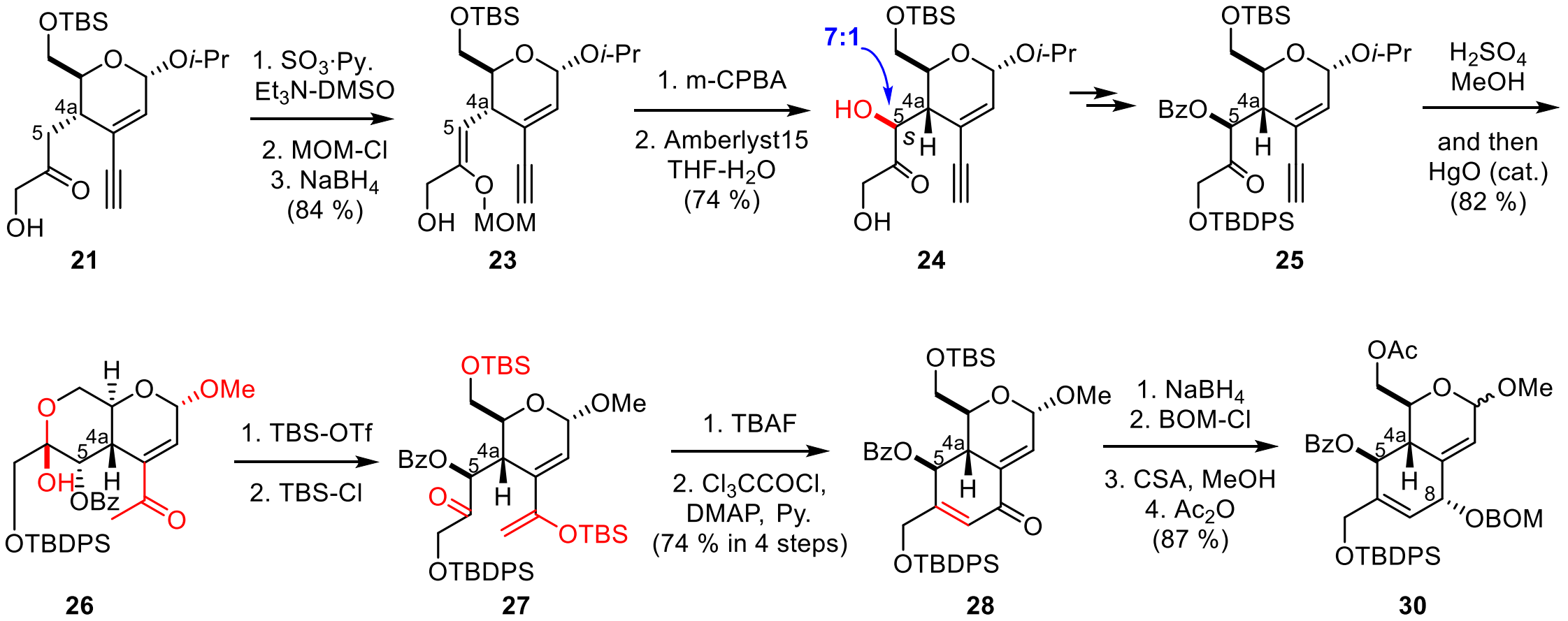
逆合成分析–Isobe

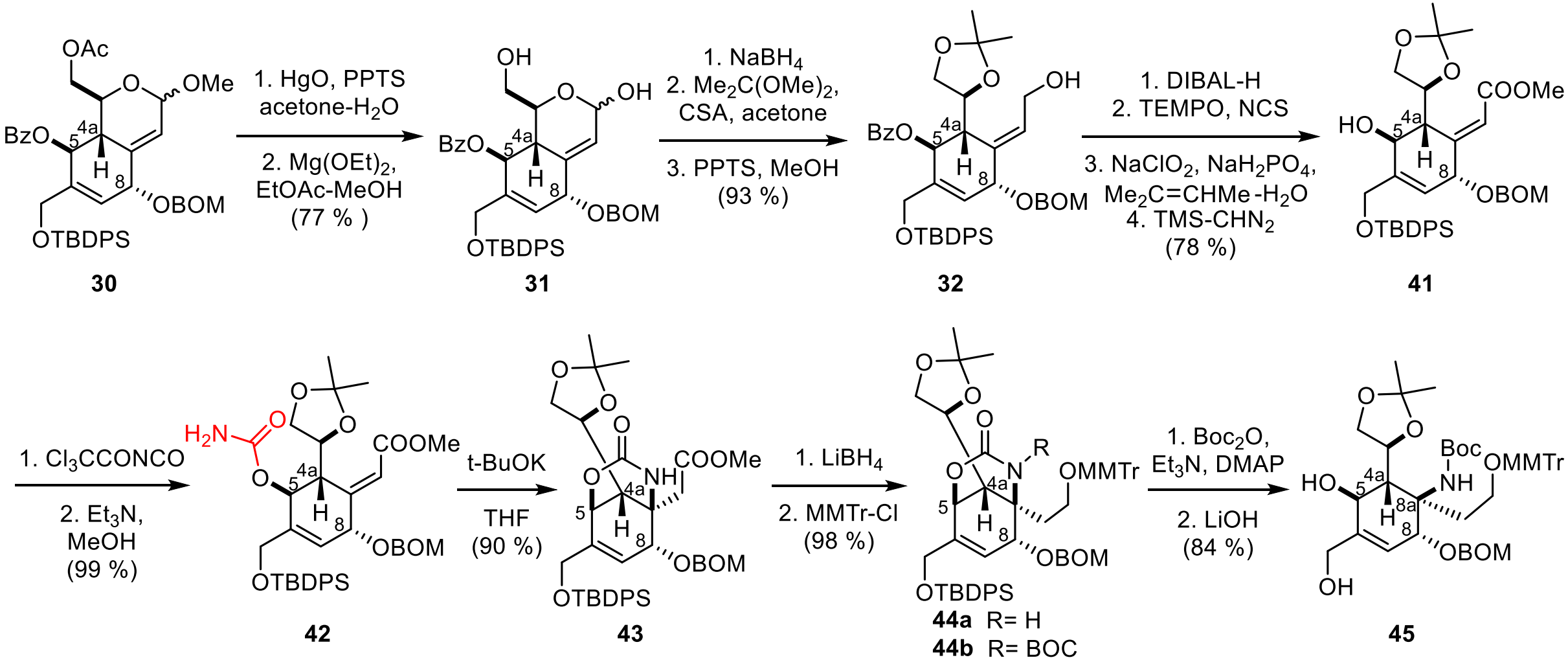


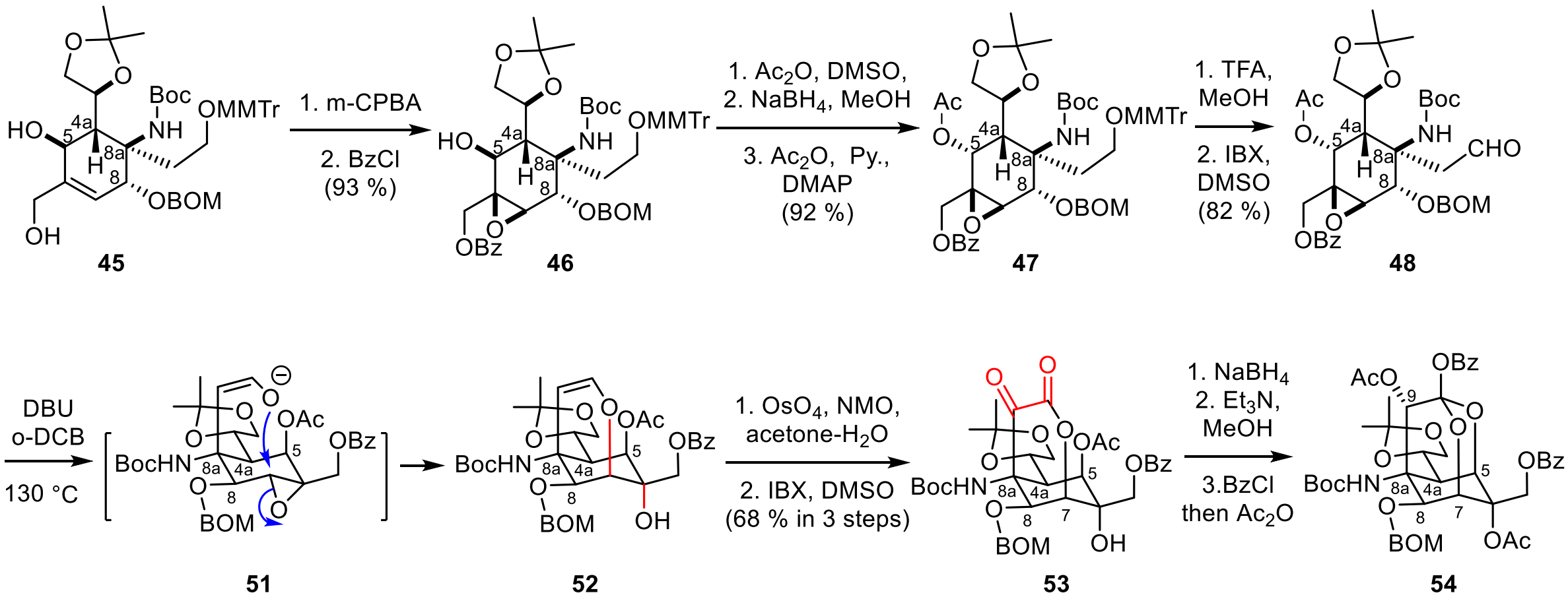
The First Asymmetric Total Synthesis by **Isobe** (no less than **72 steps**)

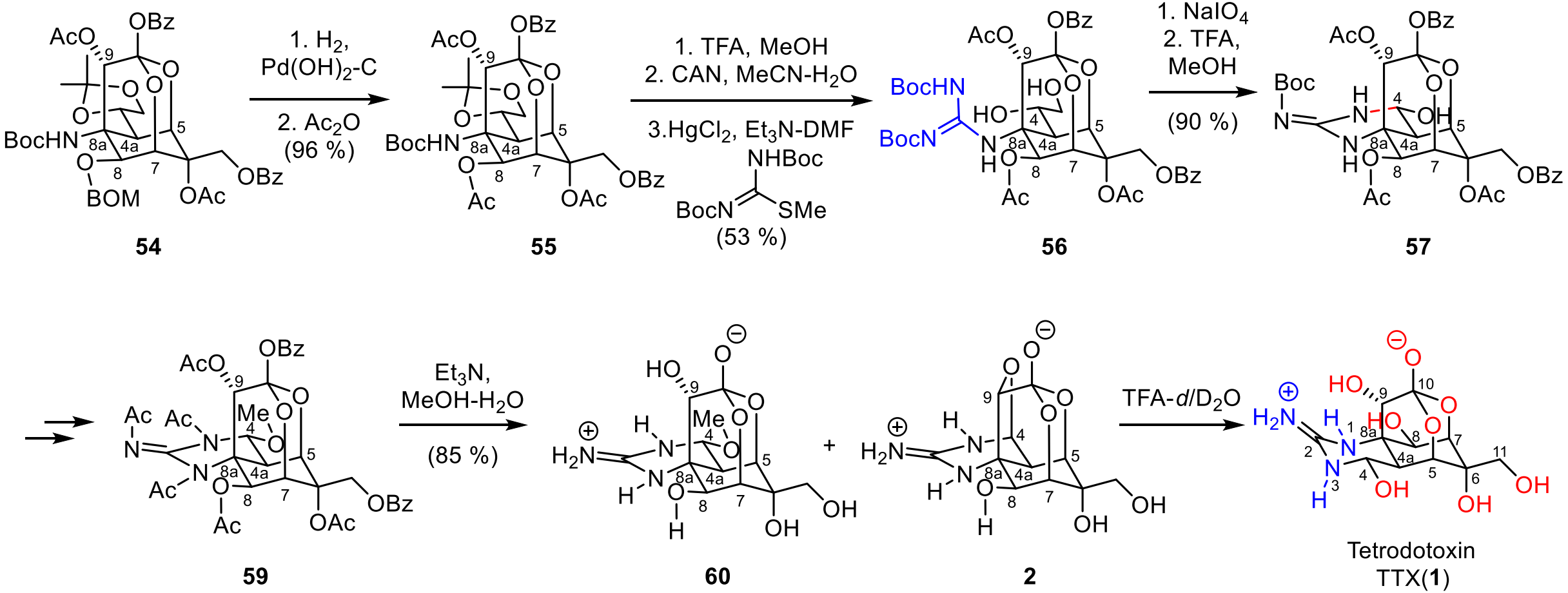
N. Ohyabu, T. Nishikawa, M. Isobe, *J. Am. Chem. Soc.* **2003**, *125*, 8798 – 8805.


OAc
AcO
OAc
OAc
13
2-PrOH
BF3-OEt2
OAc
AcO
OAc
O
Oi-Pr
13-1
LiAlH4
OH
OH
O
Oi-Pr
14
1.TBS-Cl
2.SO3· Py.,
Et3N-DMSO
(72 %)
OTBS
O
Oi-Pr
O
15
1. I2, Py.-DCM
2. NaBH4,
CeCl3(H2O)7
MeOH
(85 %)
OTBS
O
Oi-Pr
OH
I
16
TMS
Pd(OAc)2,
PPh3, CuI,
Et3N, PhH
(99 %)
OTBS
O
Oi-Pr
4a
OH
TMS
17
OMe
PPTS/THF
(89 %)
OTBS
O
Oi-Pr
4a
O
TMS
18
K2CO3
o-DCB
150 °C
(94 %)
OTBS
O
Oi-Pr
4a
O
TMS
19
1. TBS-OTf
2. LTA, KHCO3
3. TBAF
4. Et3N,
MeOH-H2O
(98 %)
OTBS
O
Oi-Pr
4a
5
O
OR
20 R= Ac
21 R= H

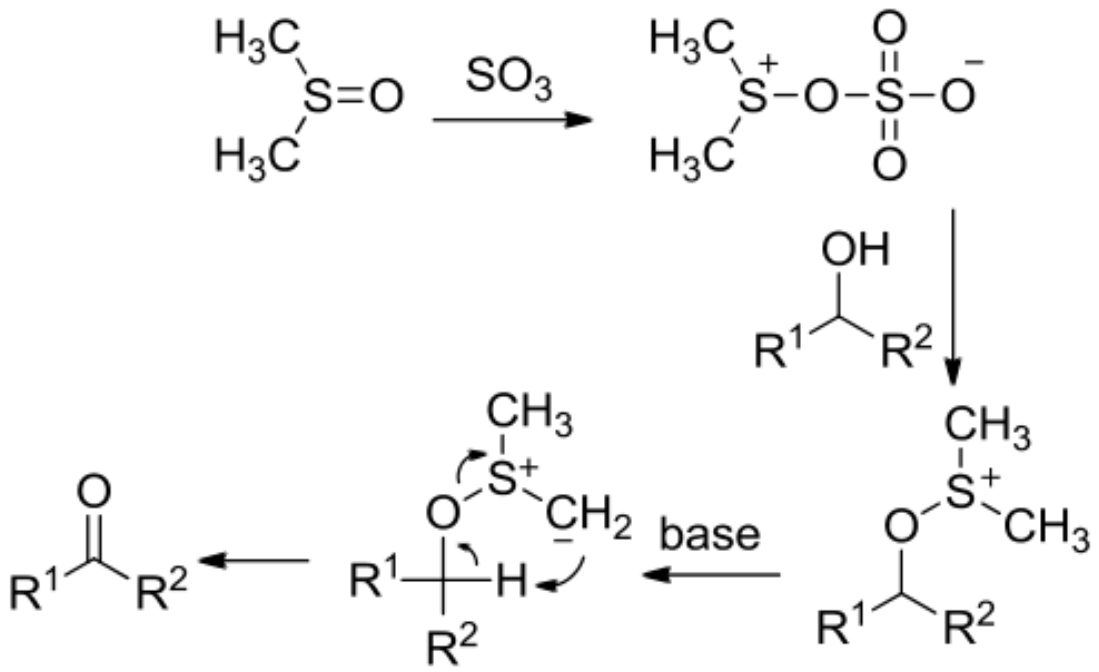

OTBS
Oi-Pr
4a
5
O
OH
21
1. SO3·Py.
Et3N-DMSO
2. MOM-Cl
3. NaBH4
(84 %)
OTBS
Oi-Pr
4a
5
O
OH
MOM
23
1. m-CPBA
2. Amberlyst15
THF-H2O
(74 %)
7:1
OTBS
Oi-Pr
HO
5
4a
S
H
O
OH
24
OTBS
Oi-Pr
BzO
5
4a
H
O
OTBDPS
25
H2SO4
MeOH
and then
HgO (cat.)
(82 %)
H
O
OMe
4a
5
OH
H
OBz
O
OTBDPS
26
1. TBS-OTf
2. TBS-Cl
OTBS
OMe
BzO
5
4a
H
O
OTBS
OTBDPS
27
1. TBAF
2. Cl3CCOCl,
DMAP, Py.
(74 % in 4 steps)
OTBS
OMe
BzO
5
4a
H
O
OTBDPS
28
1. NaBH4
2. BOM-Cl
3. CSA, MeOH
4. Ac2O
(87 %)
OAc
O
OMe
BzO
5
4a
H
8
OBOM
OTBDPS
30


OAc
OMe
BzO
4a
5
H
8
OBOM
OTBDPS
30
1. HgO, PPTS
acetone-H2O
2. Mg(OEt)2,
EtOAc-MeOH
(77 %)
OH
OH
31
1. NaBH4
2. Me2C(OMe)2,
CSA, acetone
3. PPTS, MeOH
(93 %)
32
1. DIBAL-H
2. TEMPO, NCS
3. NaClO2, NaH2PO4,
Me2C=CHMe -H2O
4. TMS-CHN2
(78 %)
COOMe
HO
41
1. Cl3CCONCO
2. Et3N,
MeOH
(99 %)
H2N
42
t-BuOK
THF
(90 %)
NH
43
1. LiBH4
2. MMTr-Cl
(98 %)
R
N
OMMTr
44a R= H
44b R= BOC
1. Boc2O,
Et3N, DMAP
2. LiOH
(84 %)
Boc
8a
45


1. m-CPBA
2. BzCl
(93 %)
1. Ac2O, DMSO,
2. NaBH4, MeOH
3. Ac2O, Py.,
DMAP
(92 %)
1. TFA,
MeOH
2. IBX,
DMSO
(82 %)
45
46
47
48
DBU
o-DCB
130 °C
1. OsO4, NMO,
acetone-H2O
2. IBX, DMSO
(68 % in 3 steps)
1. NaBH4
2. Et3N,
MeOH
3.BzCl
then Ac2O
51
52
53
54

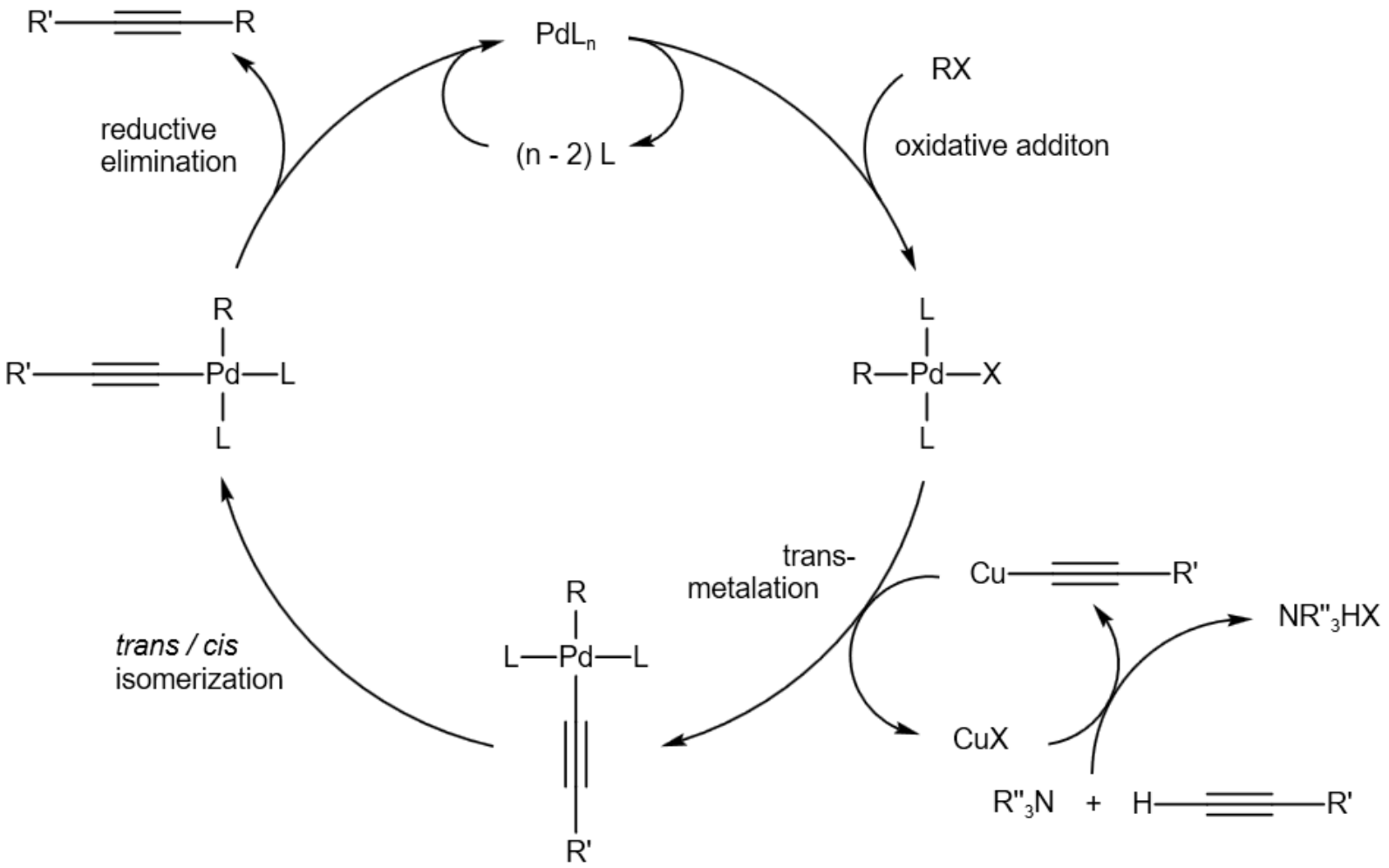

1. H_2, $Pd(OH)_2$-C
2. Ac_2O (96 %)
1. TFA, MeOH
2. CAN, MeCN-H_2O
3.$HgCl_2$, Et_3N-DMF
(53 %)
1. $NaIO_4$
2. TFA, MeOH
(90 %)
Et_3N, MeOH-H_2O
(85 %)
TFA-*d*/D_2O
54
55
56
57
59
60
2
Tetrodotoxin
TTX(1)

Parikh-Doering 氧化



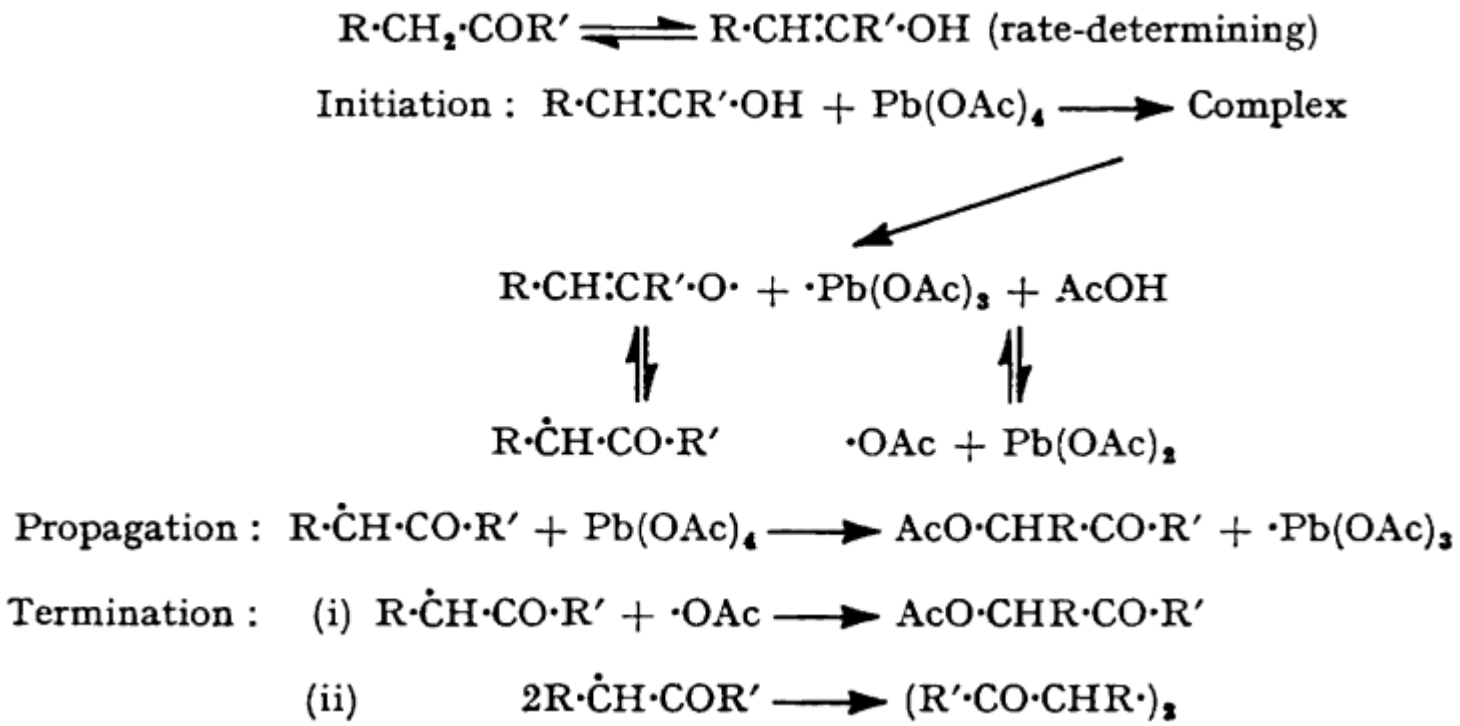
Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

Sonogashira 偶联



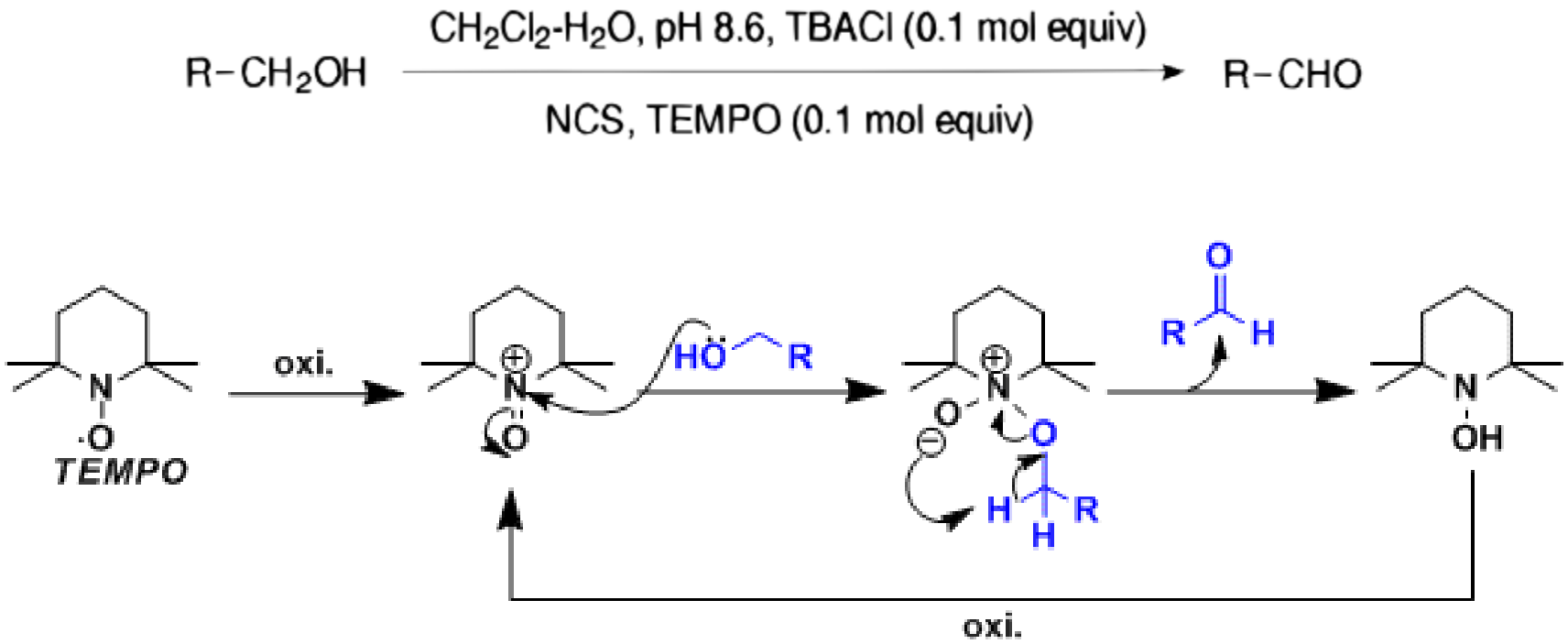
Sonogashira, K.; Tohda, Y.; Hagiwara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

LTA氧化



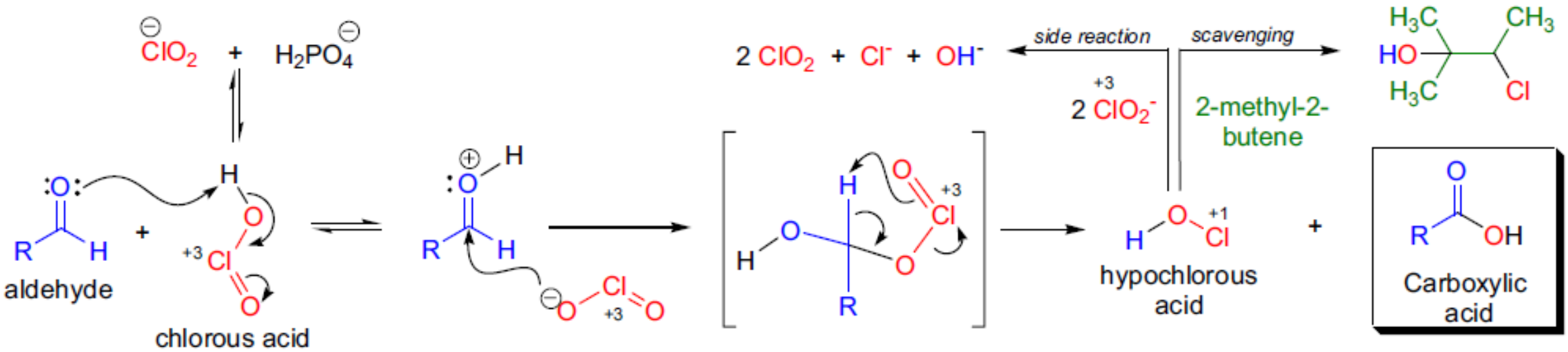
G. W. K. Cavill, D. H. Solomon, *J. Chem. Soc.* **1955**, 4426-4429.

TEMPO氧化



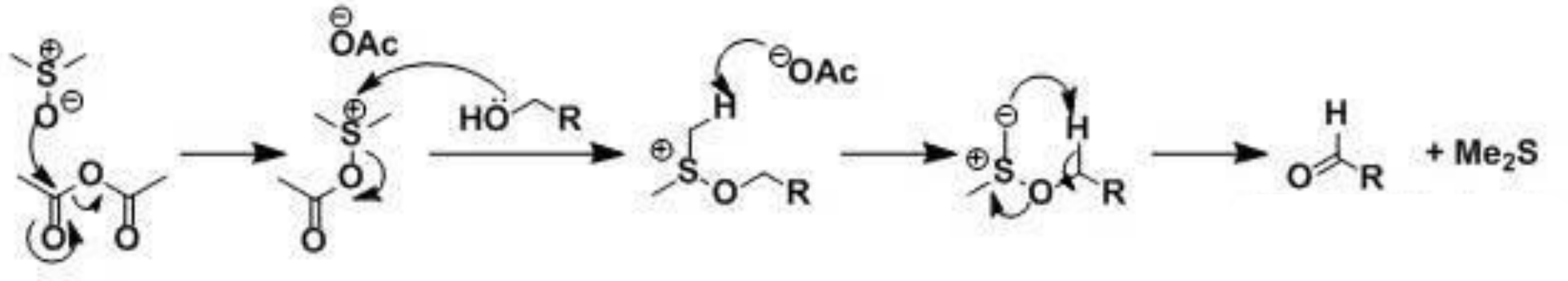
Einhorn, J.; Einhorn, C.; Ratajczak, F., et al. *J. Org. Chem.* **1996**, *61*, 7452-7454.

Pinnick氧化



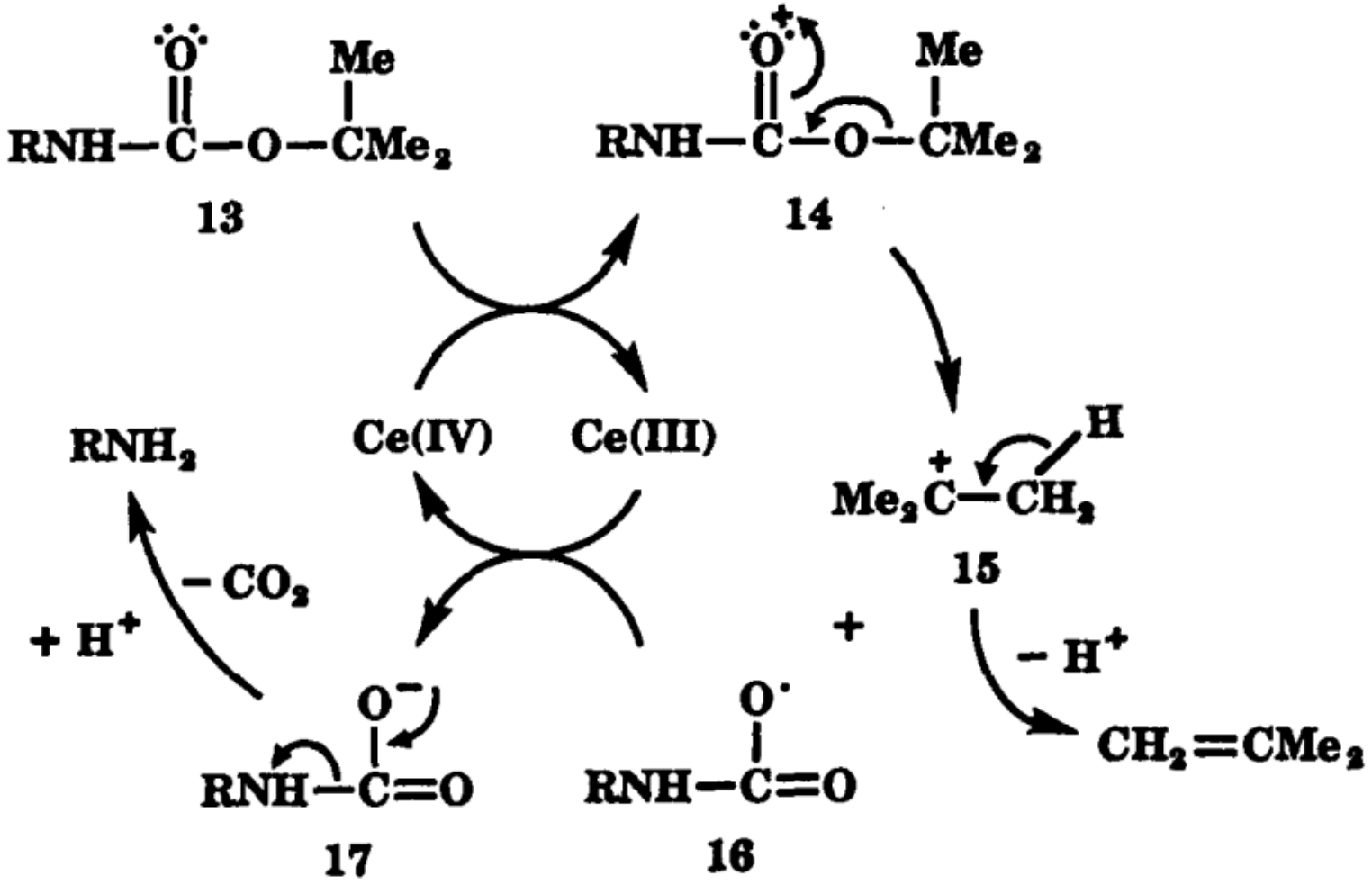
Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.

Albright–Goldman氧化



Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214-4216.

CAN脱Boc保护基



J. R. Hwu, M. L. Jain, et al. *Tetrahedron Letters*, **1996**, *37*, 2035-2038.

Peking University

谢谢观看

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