Masayuki Inoue

• The University of Tokyo, B.S. in Chemistry (1989-1993)

• The University of Tokyo, Ph.D. in Organic Chemistry (1993-1998)
Research advisor: Professor Kazuo Tachibana

• Sloan-Kettering Institute for Cancer Research (1998-2000)
Research advisor: Professor Samuel J. Danishefsky

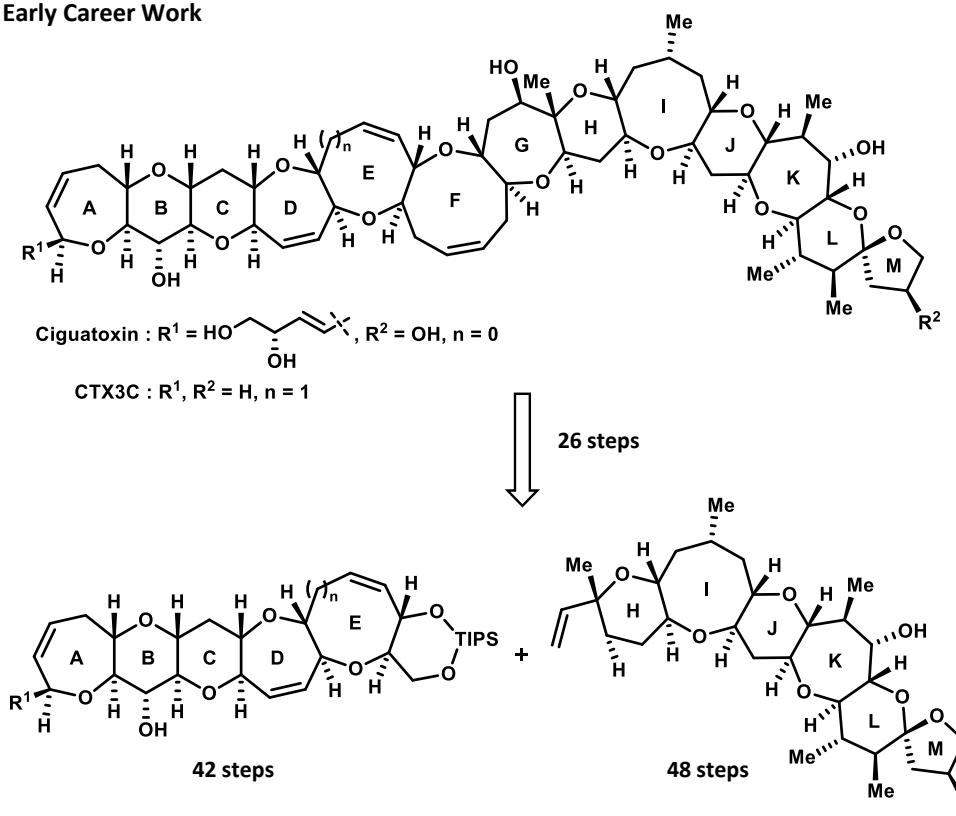
Department of Chemistry, Tohoku University
• Assistant Professor (Lab of Professor Masahiro Hirama) (2000)
• Lecturer (2003)
• Associate Professor (2004)

Current: Professor at The University of Tokyo

• 180+ publications
• >20 completed natural product syntheses

•Awards - Young Scientist's Research Award in Natural Product Chemistry (2001), Chugai Award in Synthetic Organic Chemistry, Japan (2001), Thieme Journal Award 2005, Mukaiyama Award Year 2014, JOC Outstanding Publication of the Year Award Lectureship (2018)

Early Career Work



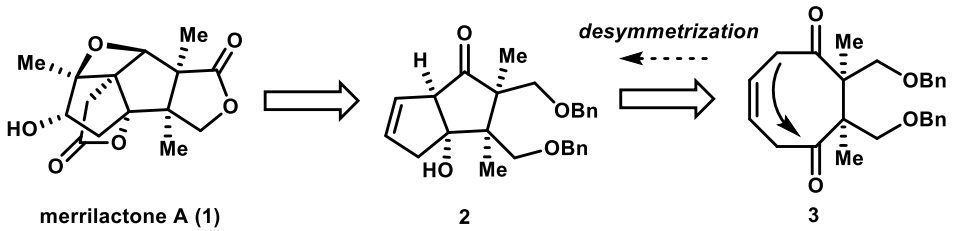
- 116 steps in total
- ~40 publications on ciguatoxin/CTX3C (~20 synthetic studies)

Science **2001**, *294* (5548), 1904–1907
Tetrahedron **2002**, *58* (10), 1835–1851
Tetrahedron **2002**, *58* (32), 6493–6512

Research Interests (non-exhaustive):

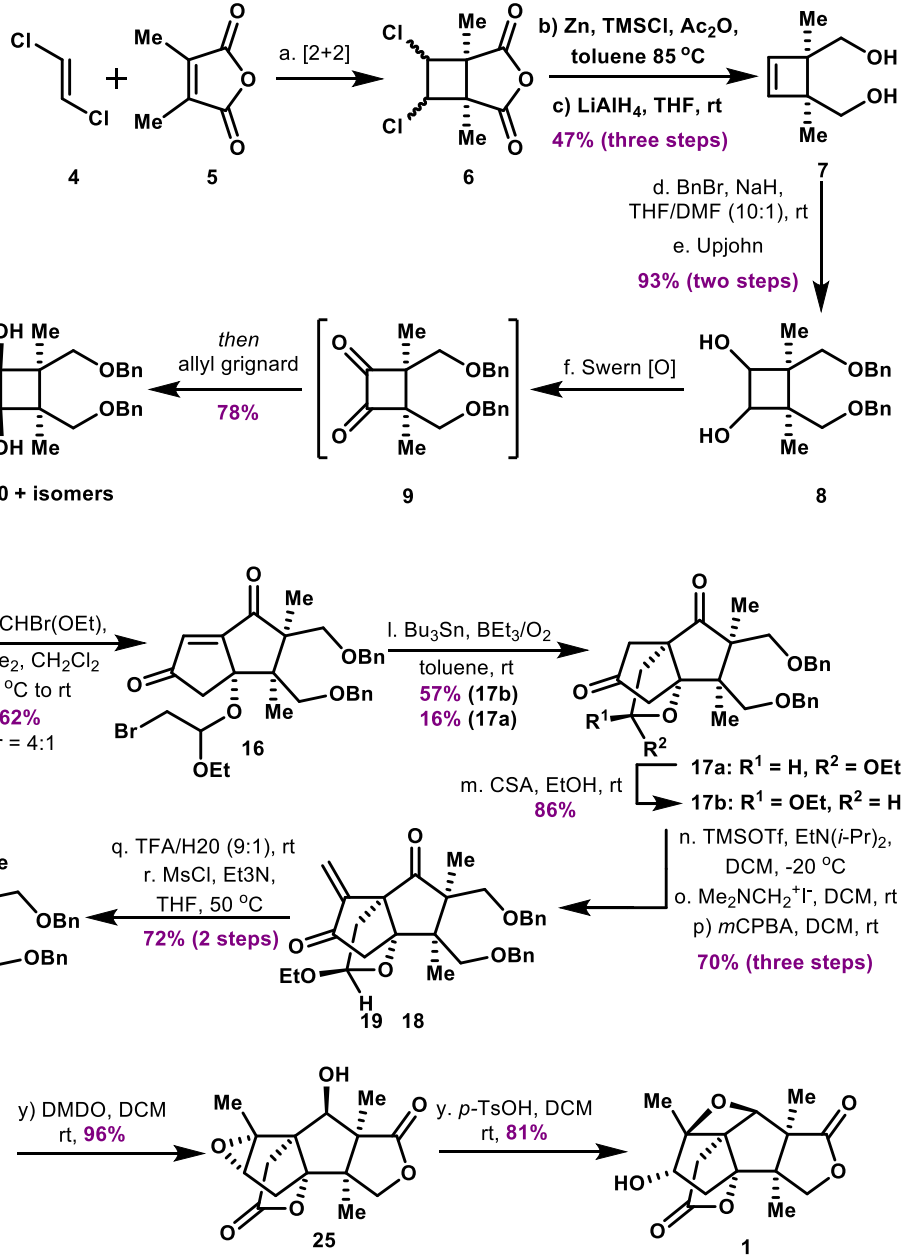
- Synthesis of complex natural products with unresolved bioactivity
- Study of the biological function of prepared natural products
- Development of radical methodologies for use in total synthesis

Retrosynthesis of Merrilactone A

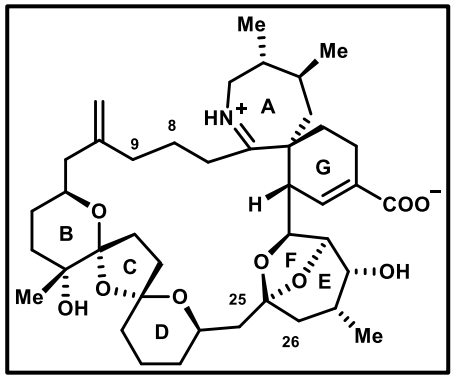


J. Am. Chem. Soc. **2003**, *125* (36), 10772–10773

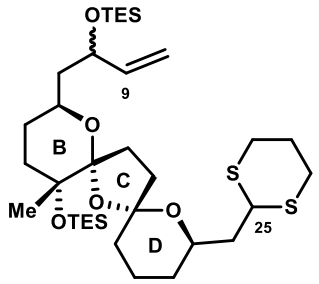
Forward Synthesis of Merrilactone A



Retrosynthesis of (+)-Pinnatoxin A

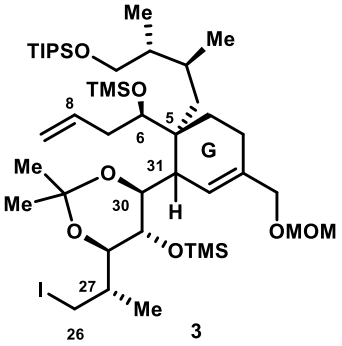


dithiane coupling (C25-26)
RCM (C8-9)



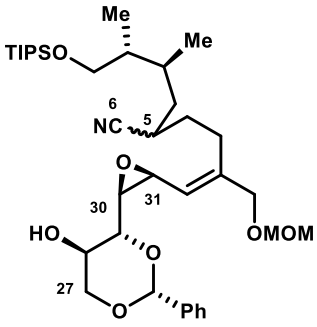
2

+



3

intramolecular alkylation (C5-31)



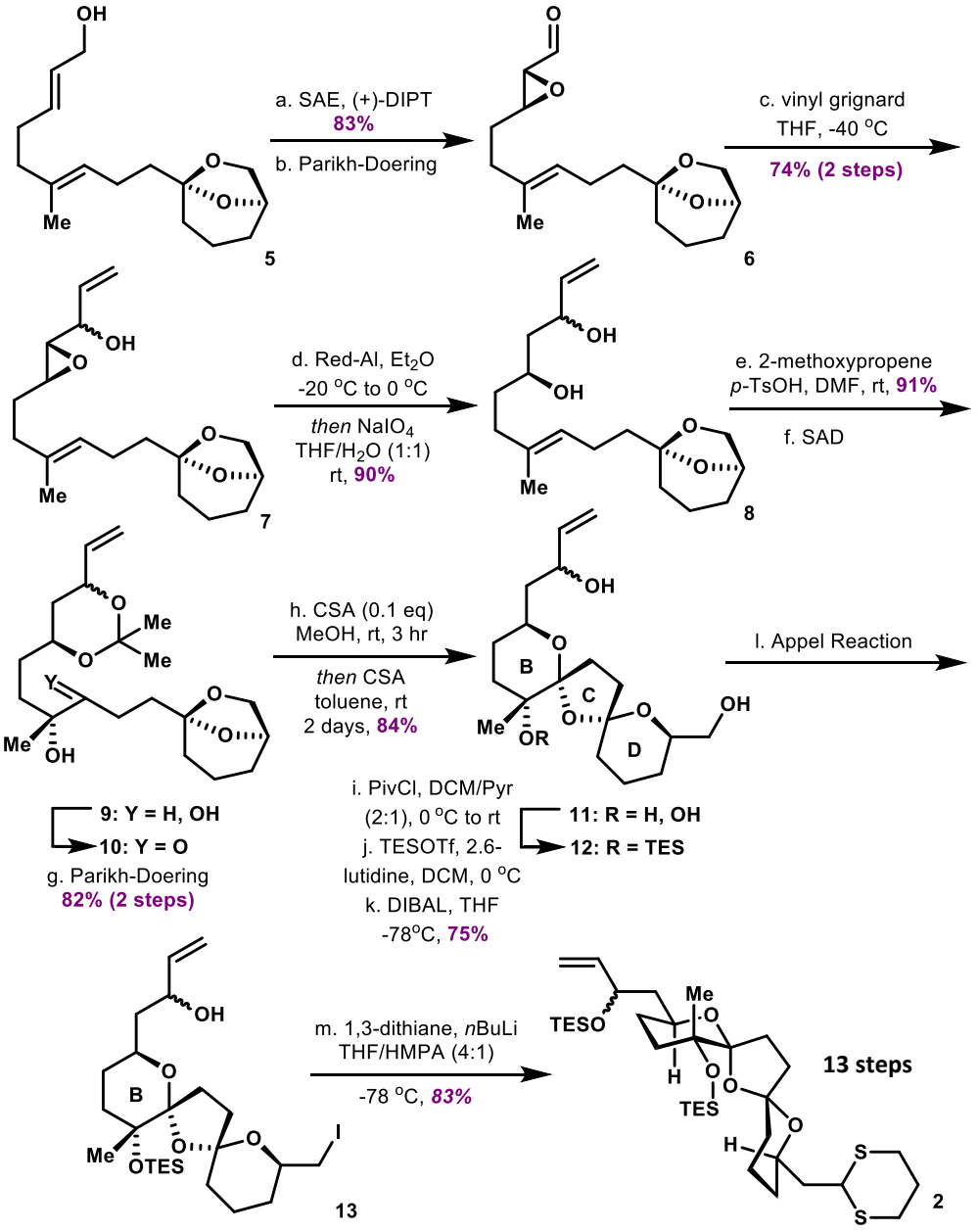
4

ACIE **2004**, *43* (47), 6505–6510

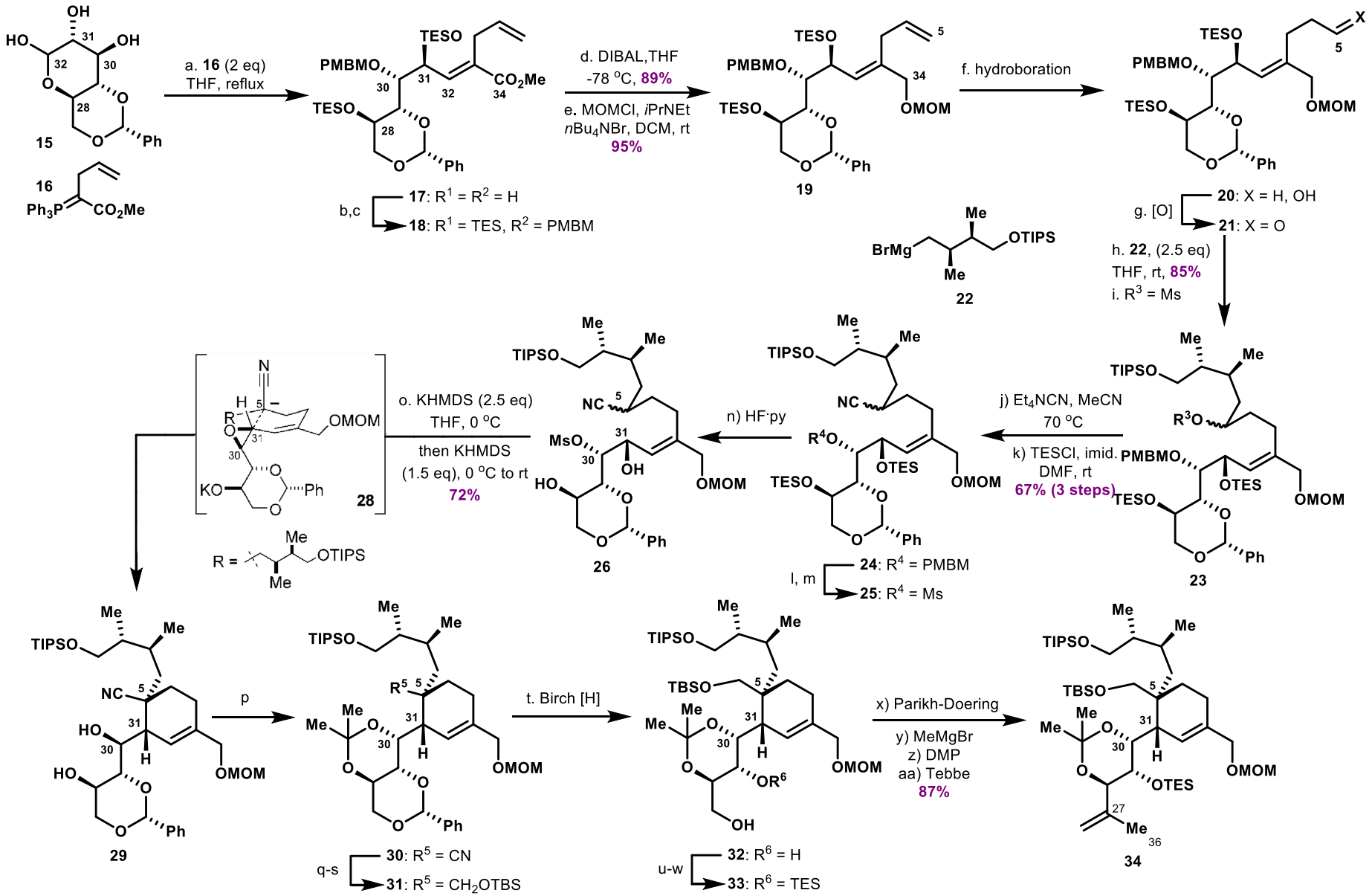
Quick Facts:

- one of the major toxic principles responsible for outbreaks of Pinna shellfish poisonings in China and Japan
- Precise biological activity is unclarified – suspected to be Ca^{2+} ion channel activator
- 70 step synthesis

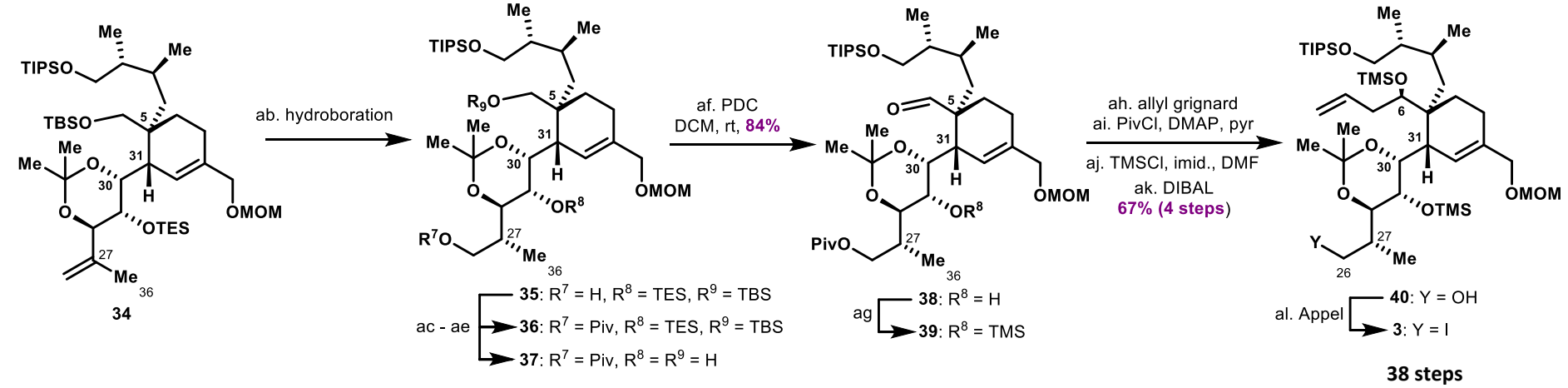
Forward Synthesis of (+)-Pinnatoxin A



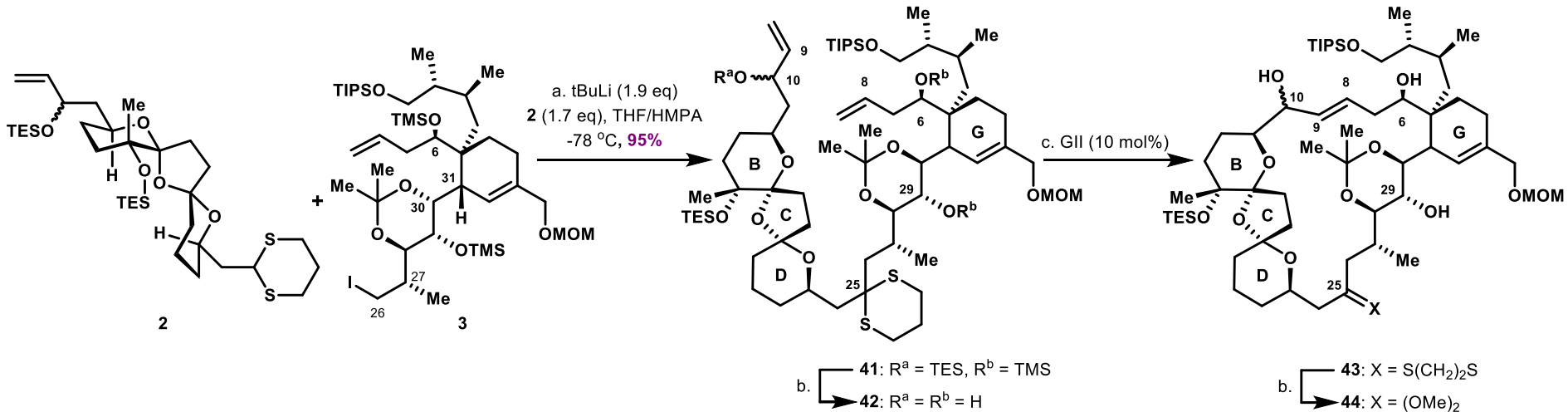
Forward Synthesis of (+)-Pinnatoxin A



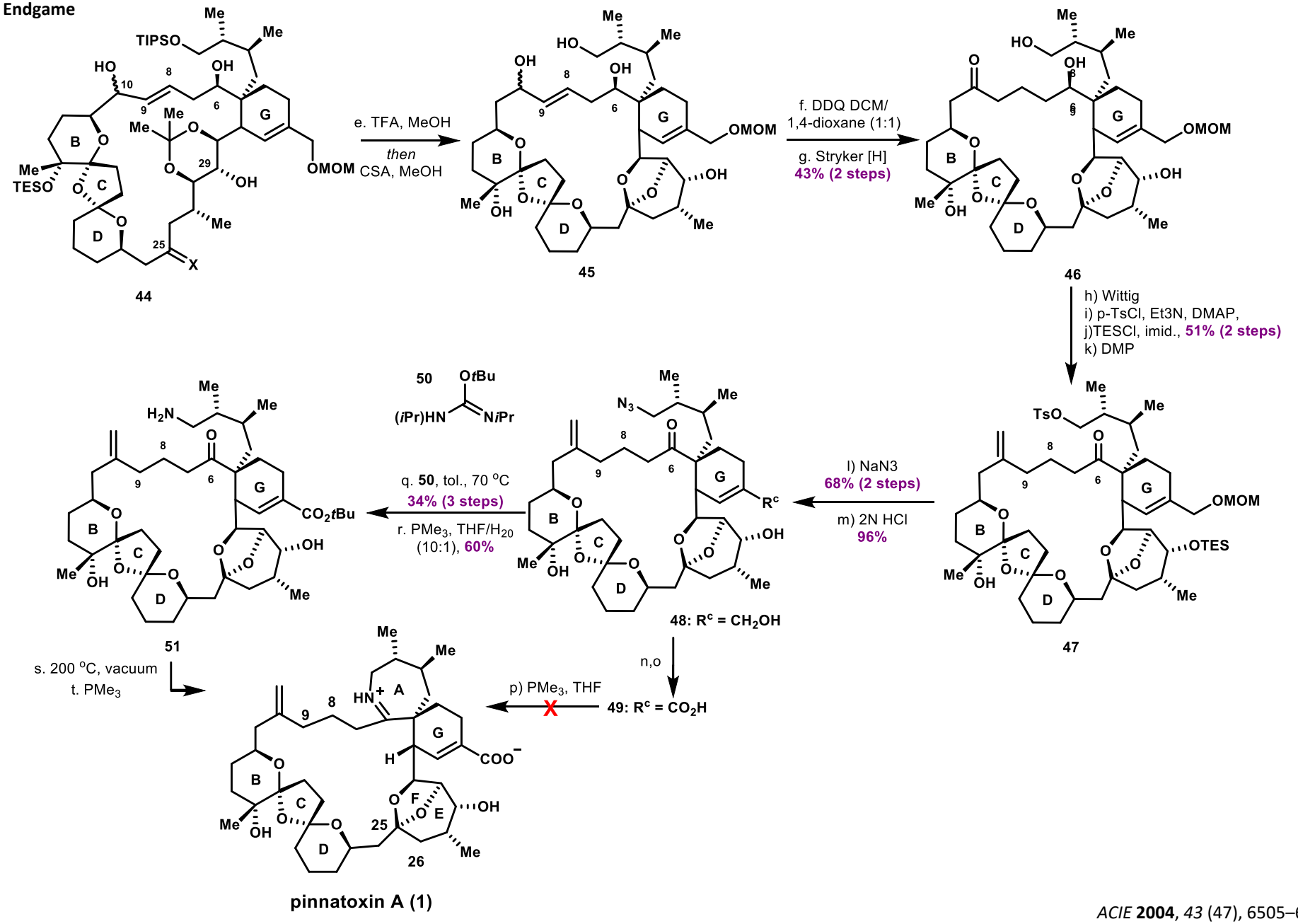
Forward Synthesis of (+)-Pinnatoxin A



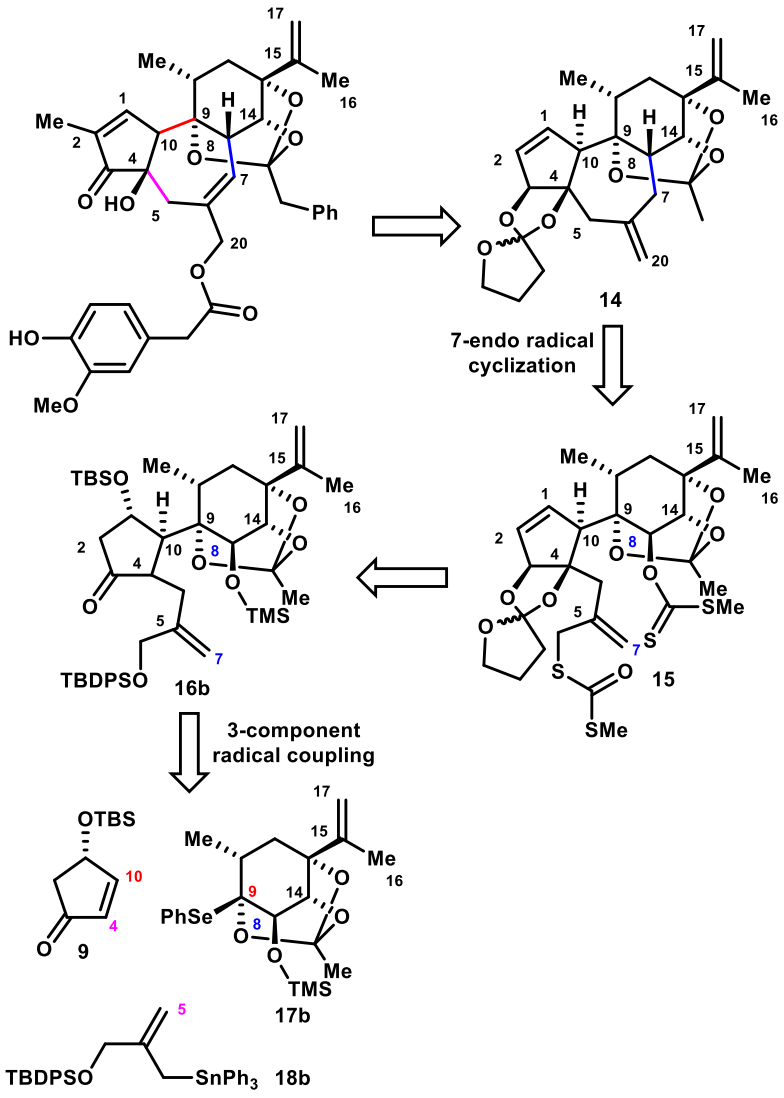
19 Step Endgame



Endgame


44
e. TFA, MeOH
then
CSA, MeOH
45
f. DDQ DCM/
1,4-dioxane (1:1)
g. Stryker [H]
43% (2 steps)
46
h) Wittig
i) p-TsCl, Et3N, DMAP,
j)TESCl, imid., 51% (2 steps)
k) DMP
47
l) NaN3
68% (2 steps)
m) 2N HCl
96%
48: R^c = CH2OH
50
q. 50, tol., 70 °C
34% (3 steps)
r. PMe3, THF/H20
(10:1), 60%
51
s. 200 °C, vacuum
t. PMe3
n,o
49: R^c = CO2H
p) PMe3, THF
26
pinnatoxin A (1)

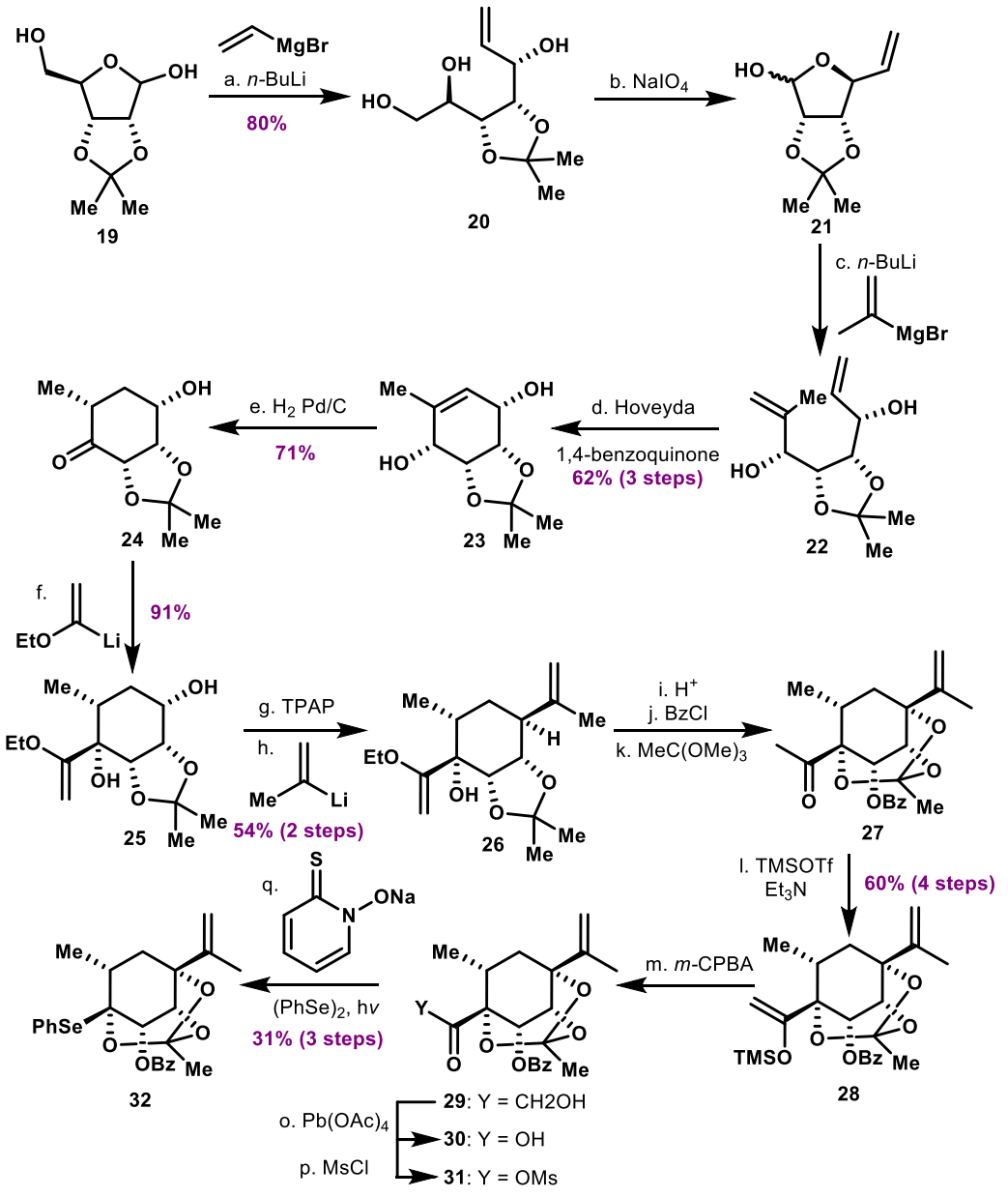
Retrosynthesis of Resiniferatoxin



Quick Facts:

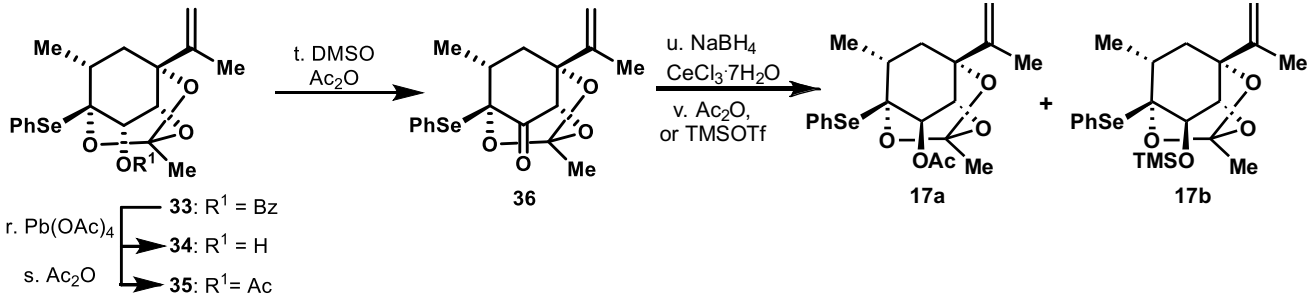
- belongs to daphnane diterpenoid family
- potently activating transient receptor potential vanilloid 1 (TRPV1)

Forward Synthesis of Resiniferatoxin

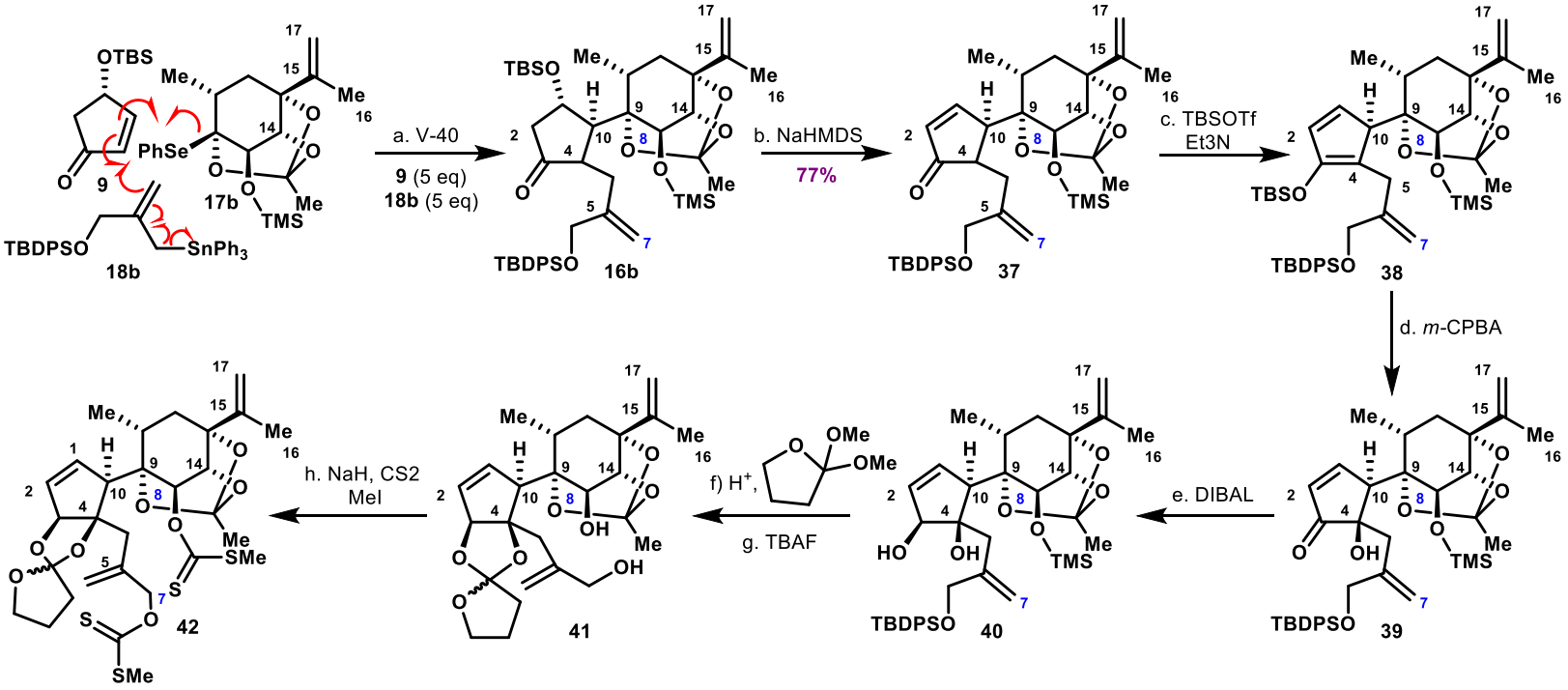


J. Am. Chem. Soc. **2017**, *139* (45), 16420–16429

Forward Synthesis of Resiniferatoxin

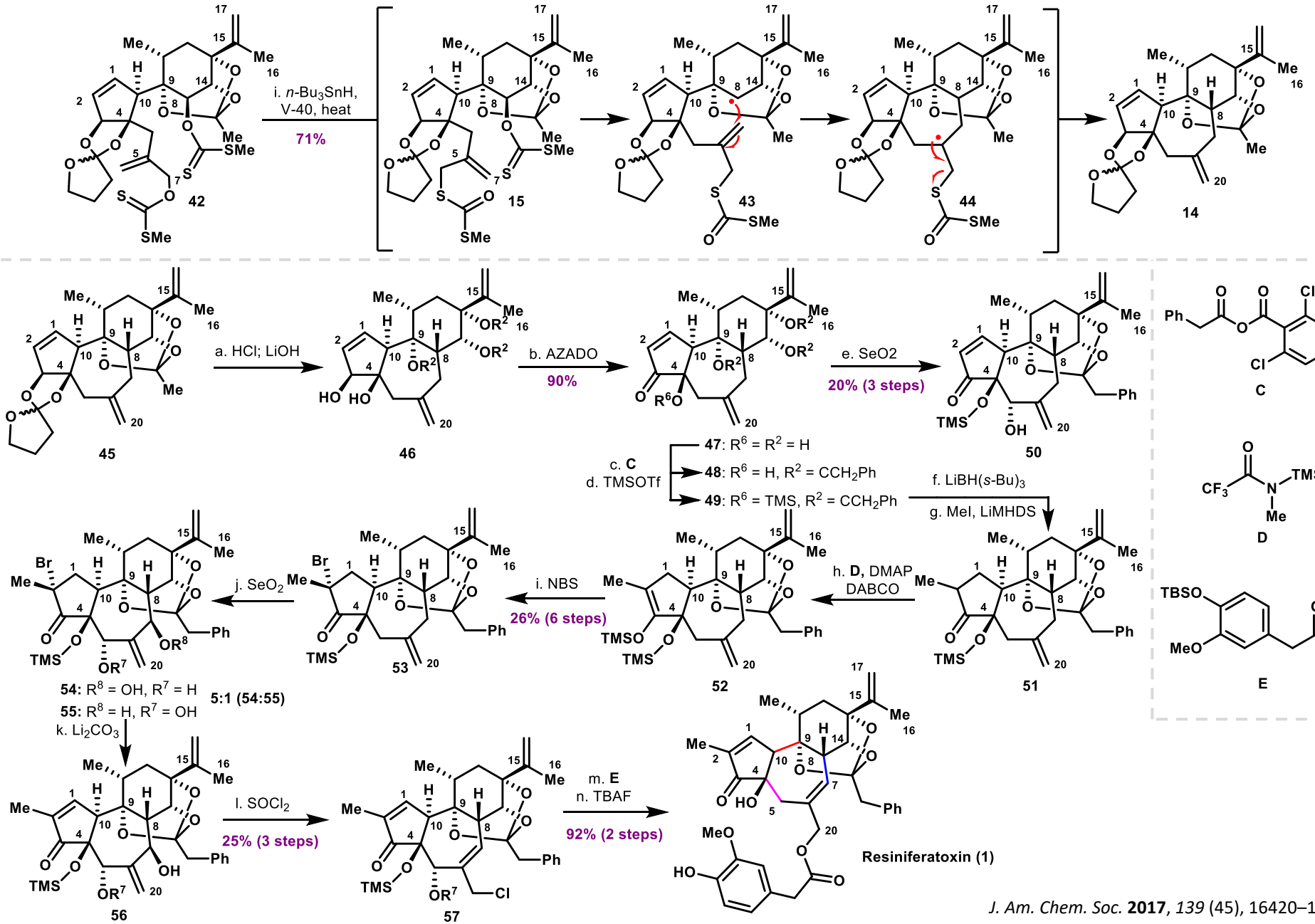


Tricyclic Framework from Two Radical Reactions



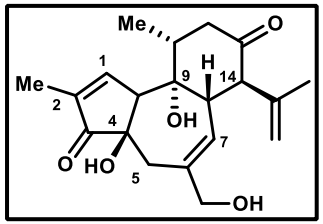
J. Am. Chem. Soc. **2017**, *139* (45), 16420–16429

Tricyclic Framework from Two Radical Reactions

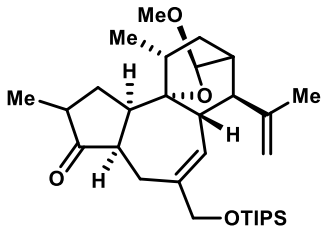


J. Am. Chem. Soc. **2017**, *139* (45), 16420–16429

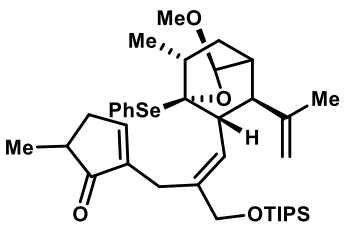
Crotophorbolone



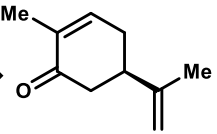
14 steps



$(TMS)_3SiH$
V-40

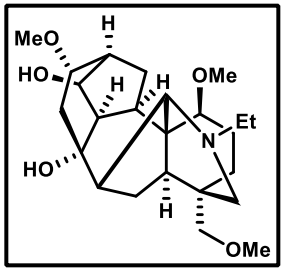


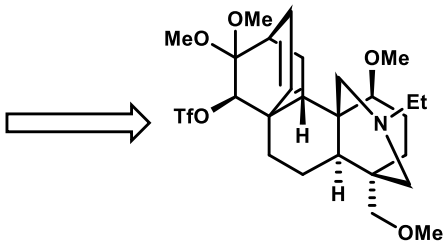
19 steps

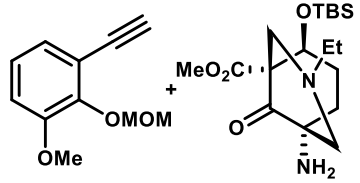


ACIE **2015**, *54* (48), 14457–14461

(±)-Talatisamine

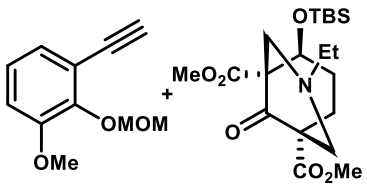






Quick Facts:

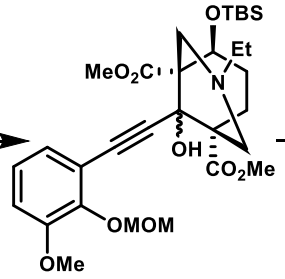
- Diterpenoid alkaloid
- exhibits K^+ channel inhibitory and antiarrhythmic activities



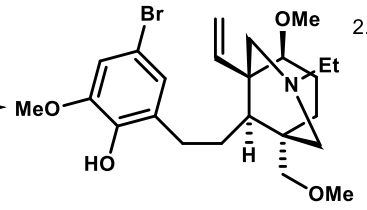
A
2 steps, **70%**

B
7 steps, **19%**

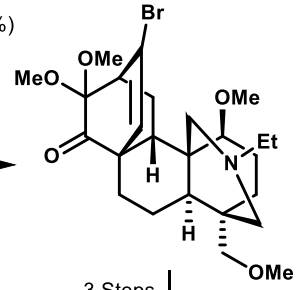
EtMgBr, THF
-78 to 0 °C



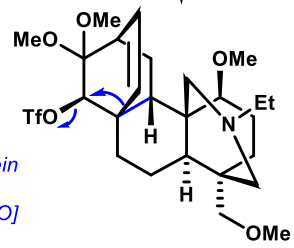
12 Steps



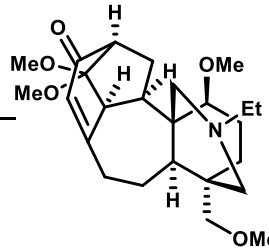
1. HCl, MeOH, methyl red (0.2 mol%)
0 °C, then $PhI(OAc)_2$, 0 °C
2. BHT (0.5 mol%) PhMe, 130 °C
89%, dr = 2.2:1
dearomatization and IMDA



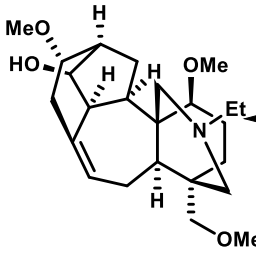
3 Steps
45%



DBU, DMSO
120 °C
83%
Wagner-Meerwein shift
Kornblum-type [O]



7 Steps
27%

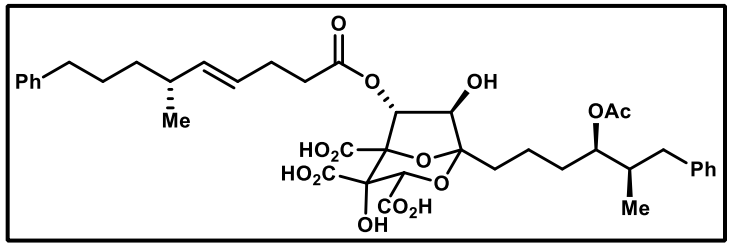


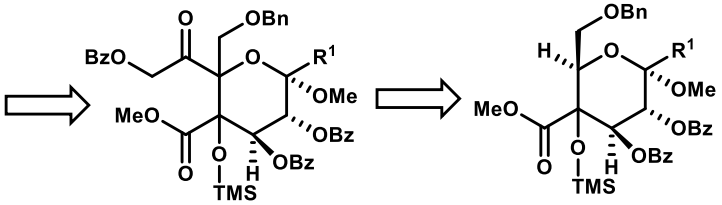
1. $Hg(OAc)_2$, AcOH
60 °C
2. 1,4-dioxane-H_2O
(1:1) 90°C
29%
aza-Prins reaction

(+)-Talatisamine

ACIE **2020**, *59* (1), 479–486

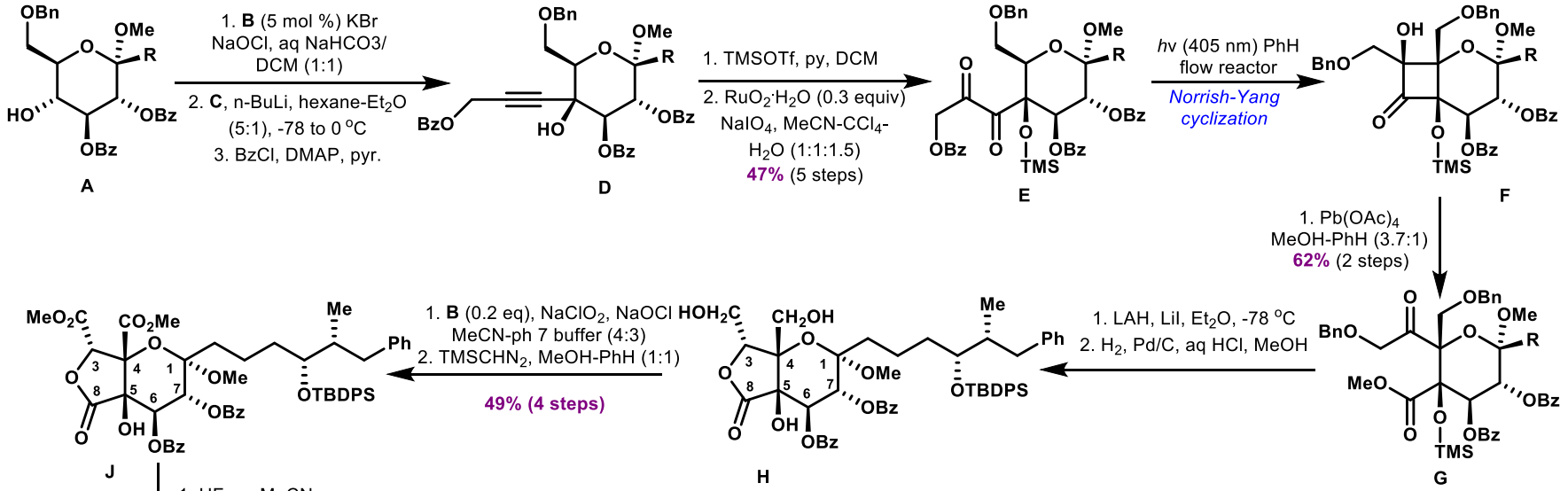
Zaragozic Acid C

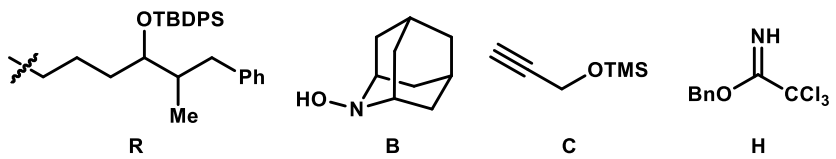




Quick Facts:

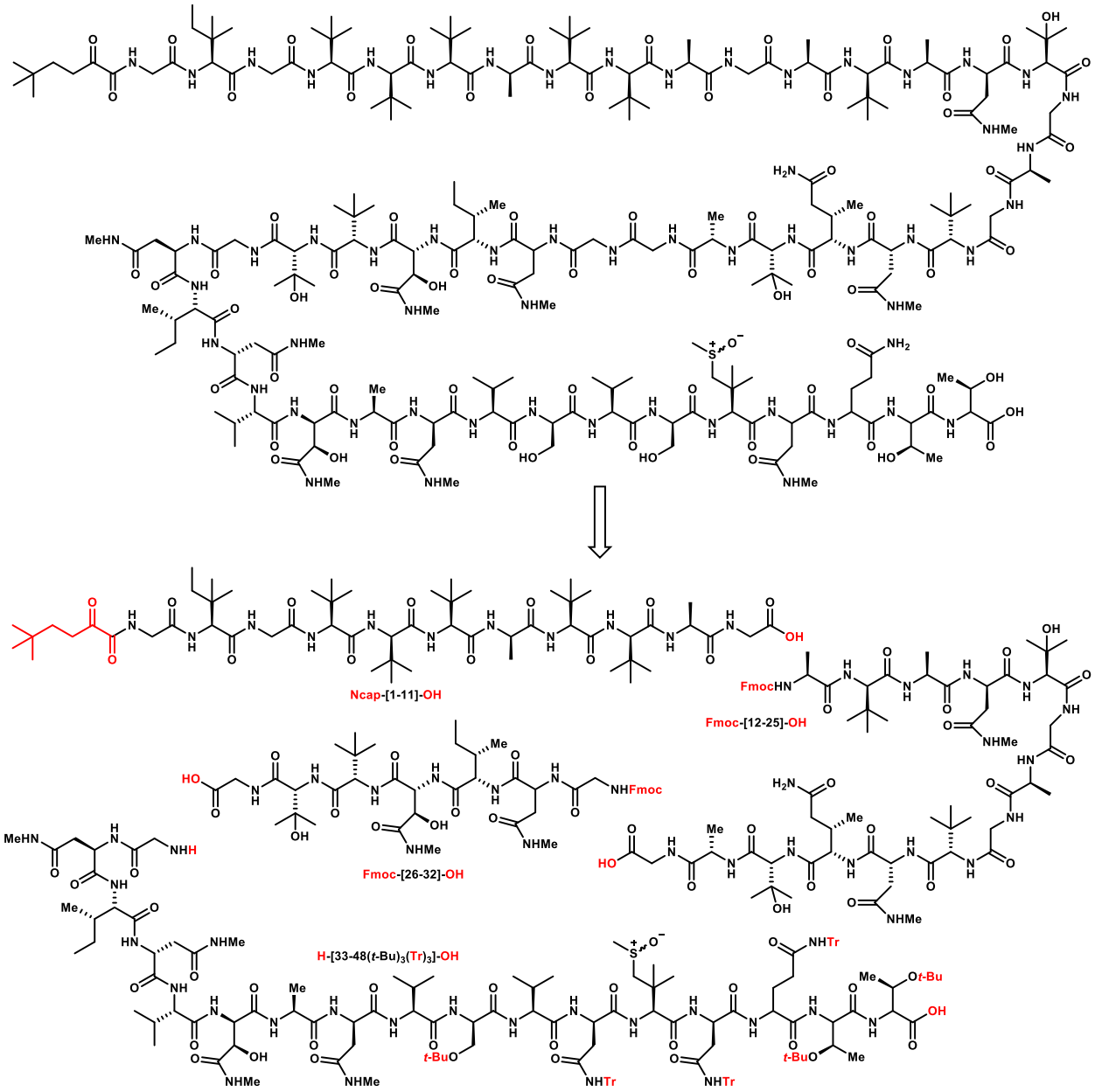
- Member of zaragozic acids and squalestatins natural product families
- potent squalene synthase inhibitor
- Potential as an antitumor agent





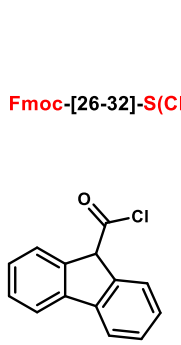
J. Am. Chem. Soc. **2017**, *139* (5), 1814–1817

Polytheonamide



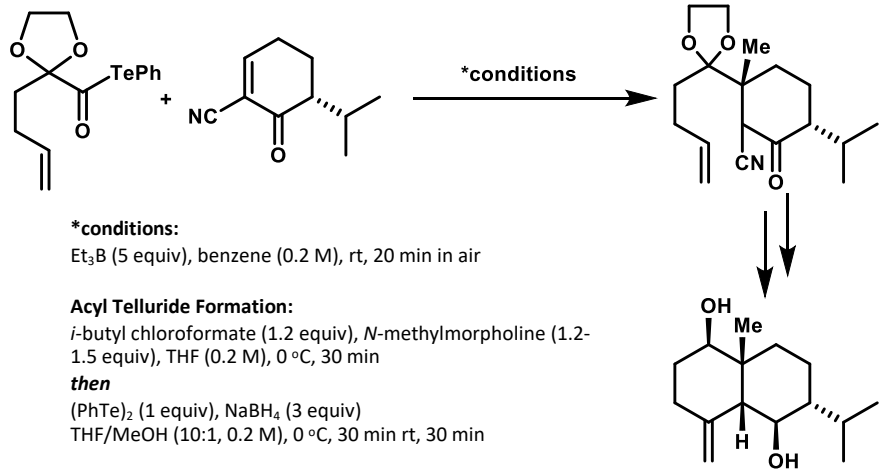
Quick Facts:

- Longest non-ribosomal peptide known (2010)
- 13 of 19 amino acid types are non-proteinogenic
- Possesses properties of ion channel proteins at 1/20th the size – regarded as a minimalist transmembrane channel



Nature Chemistry **2010**, *2* (4), 280–285

Decarbonylative Radical-Radical Coupling



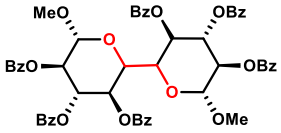
***conditions:**
Et_3B (5 equiv), benzene (0.2 M), rt, 20 min in air

Acyl Telluride Formation:
i-butyl chloroformate (1.2 equiv), *N*-methylmorpholine (1.2-1.5 equiv), THF (0.2 M), 0 °C, 30 min
then
$(PhTe)_2$ (1 equiv), $NaBH_4$ (3 equiv)
THF/MeOH (10:1, 0.2 M), 0 °C, 30 min rt, 30 min

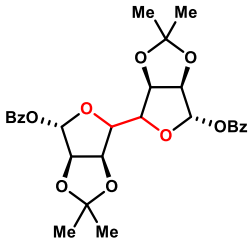
Homocoupling of pentoses and hexoses

- Easy route to highly oxygenated heterocycles

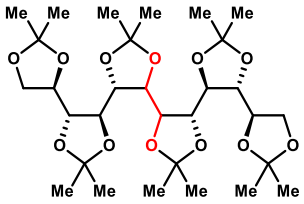
(αα:αβ:ββ)
0:42:58



(αα:αβ:ββ)
0:42:58



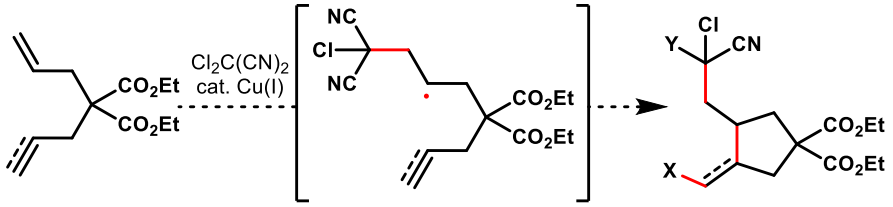
(αα:αβ:ββ)
33:55:10

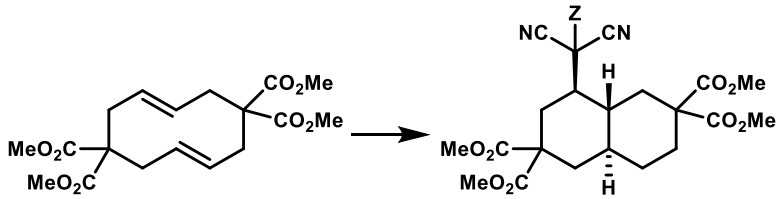


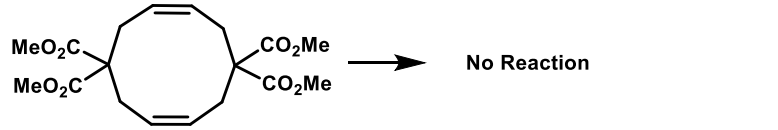
(αα:αβ:ββ)
6:43:51

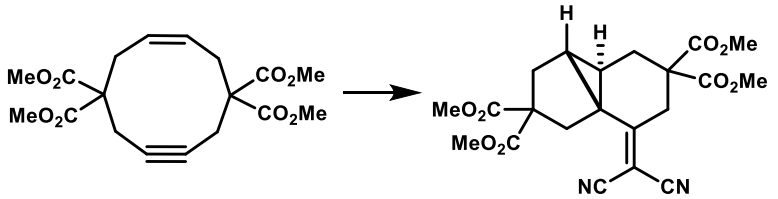
Org. Lett. **2019**, *21* (18), 7619–7623
Nature Chem **2017**, *9* (3), 207–212

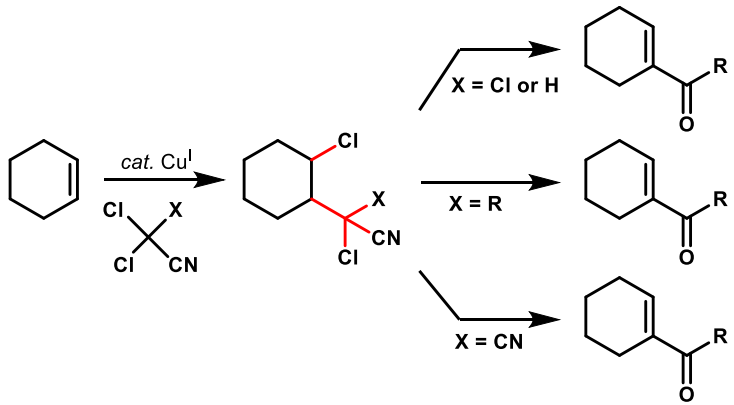
Radical Carbocycle Formation





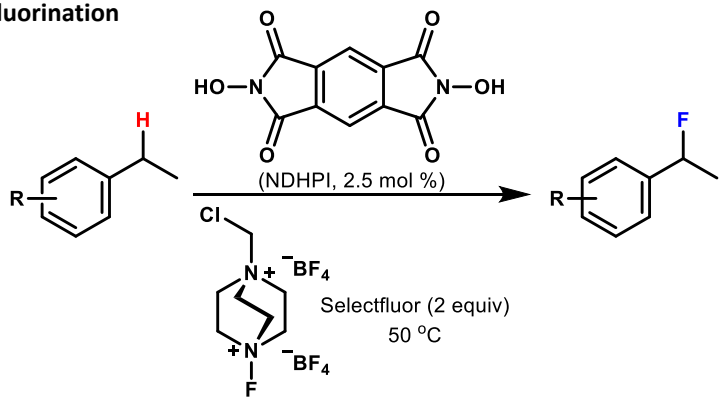




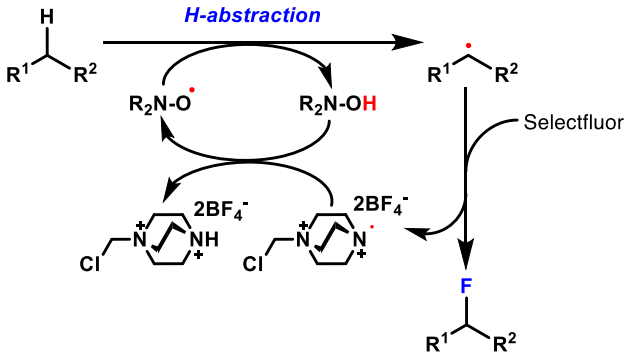


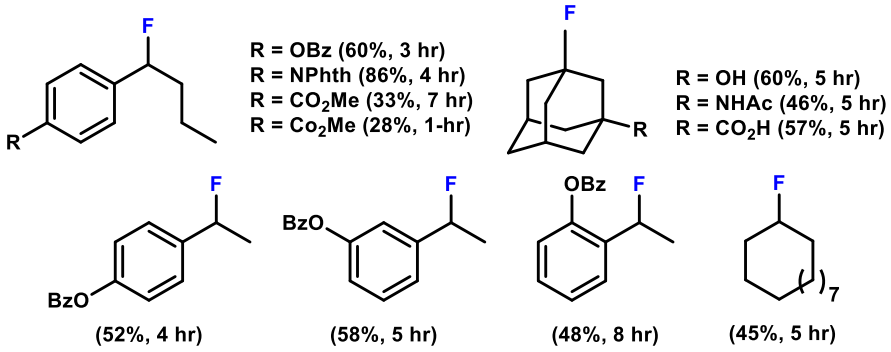
Tetrahedron **2017**, *73* (26), 3596–3605
Tetrahedron **2012**, *68* (26), 5290–5296

sp^3 C-H fluorination



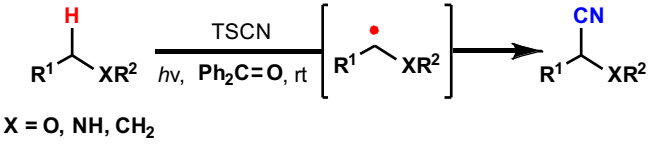
fluorination sp^3 C-H bonds with NHPI as catalytic N-oxyl radical source

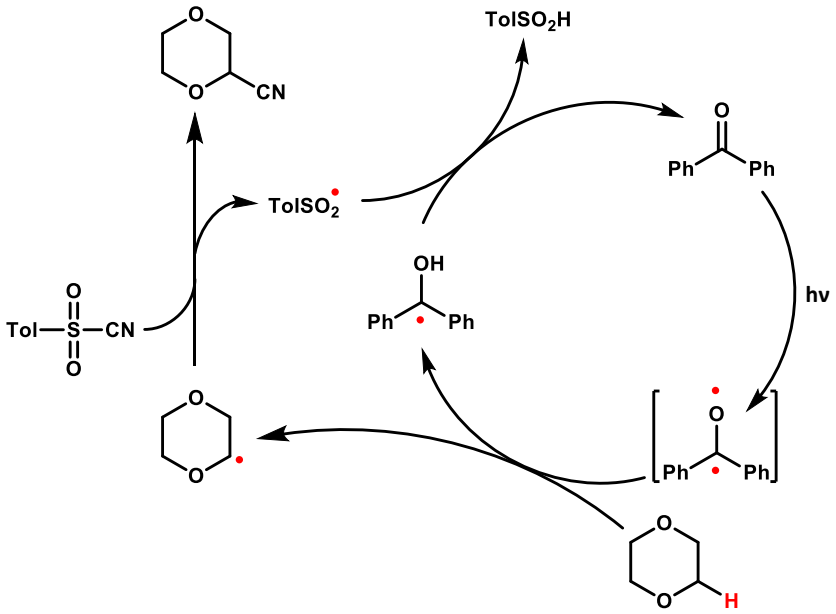


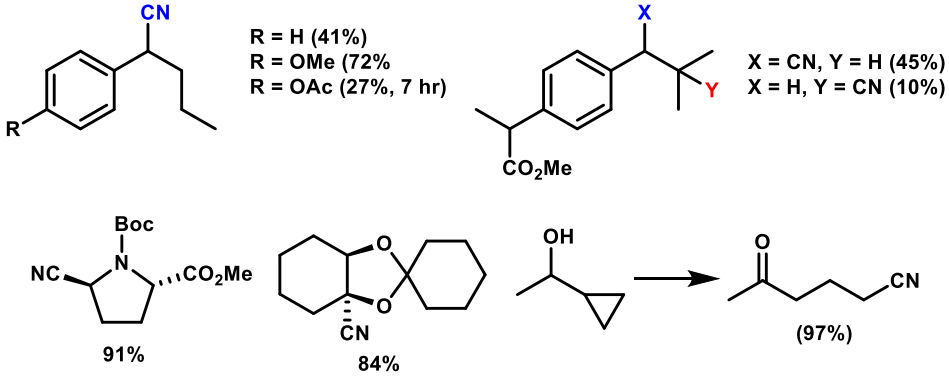


Org. Lett. **2013**, *15* (9), 2160-2163

sp^3 C-H cyanation

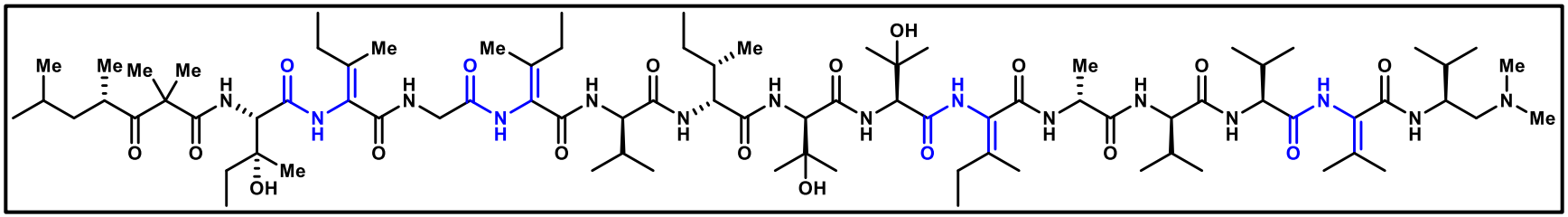


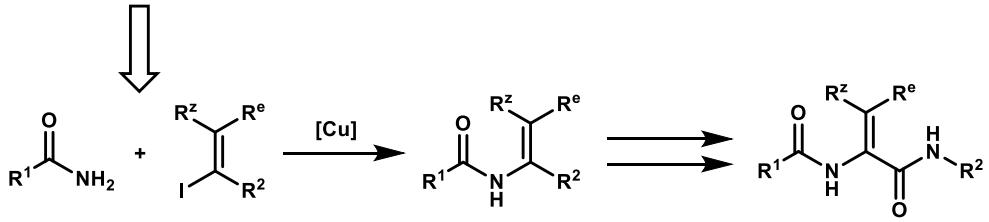




Org. Lett. **2011**, *13* (21), 5928–5931

Yaku'amide A from Enamide Formation



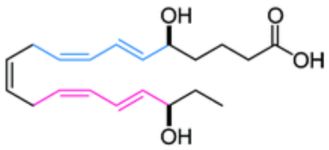


Conditions: CuI (60 mol%)
1 (2 eq), Cs_2CO_3 (1.2 eq)
Dioxane (1M) 70 °C, 24 hr

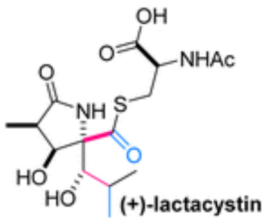
(Structure Revised)

ACIE **2015**, *54* (5), 1537–1541
J. Am. Chem. Soc. **2013**, *135* (14), 5467–5474
J. Am. Chem. Soc. **2015**, *137* (29), 9443–9451

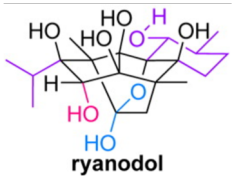
Part of what we missed:



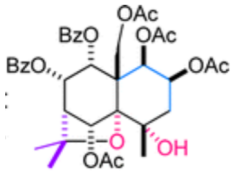
resolvin E2



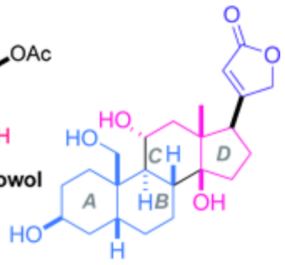
(+)-lactacystin



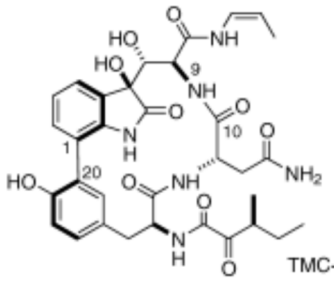
ryanodol



(-)-4-hydroxyzinowol



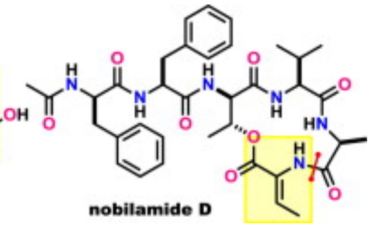
19-hydroxysarmentogenin



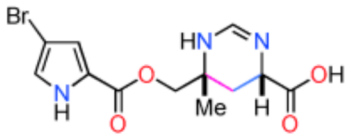
TMC-95A

: traceless Staudinger ligation

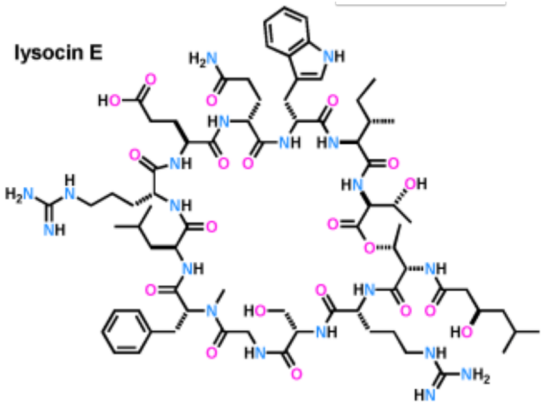
nobilamide B



nobilamide D



manzacidin A



lysocin E