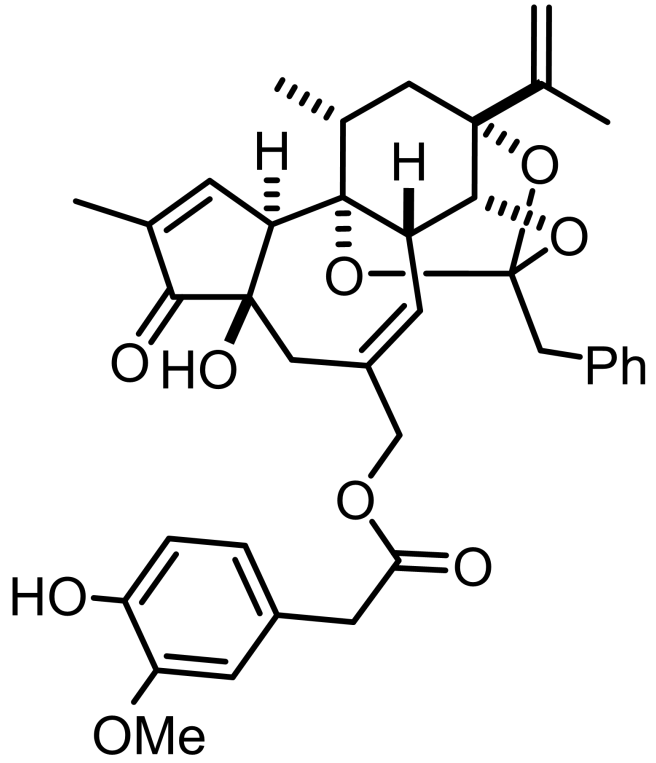
Total Synthesis of Resiniferatoxin



resiniferatoxin

J. Am. Chem. Soc. **2017**, *139*, 16420-16429
Org. Lett. **2022**, *24*, 929-933

Hongpeng Lin
2026.05.14

Introduction of Resiniferatoxin

Euphorbia resinifera

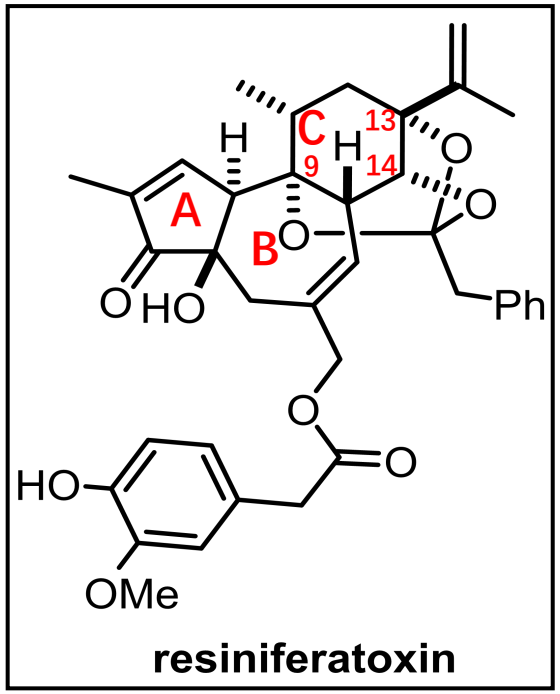
Isolation： from the latex of ***Euphorbia resinifera*** by Hecker et al. in 1975.

Synthesis：

1997, Wender, 44 steps
2017, Masayuki Inoue, 41 steps
2021, Masayuki Inoue, 20 steps, unified
2022, Masayuki Inoue, 27 steps, formal
2022, Maimone , 15 steps
2025, Tuoping Luo, 20 steps, (+)-resiniferatoxin

Structure：

a trans-fused 5/7/6-tricyclic structure (ABC-ring)
a C9,13,14-orthoester motif
a C13-isopropenyl group on the C-ring



resiniferatoxin

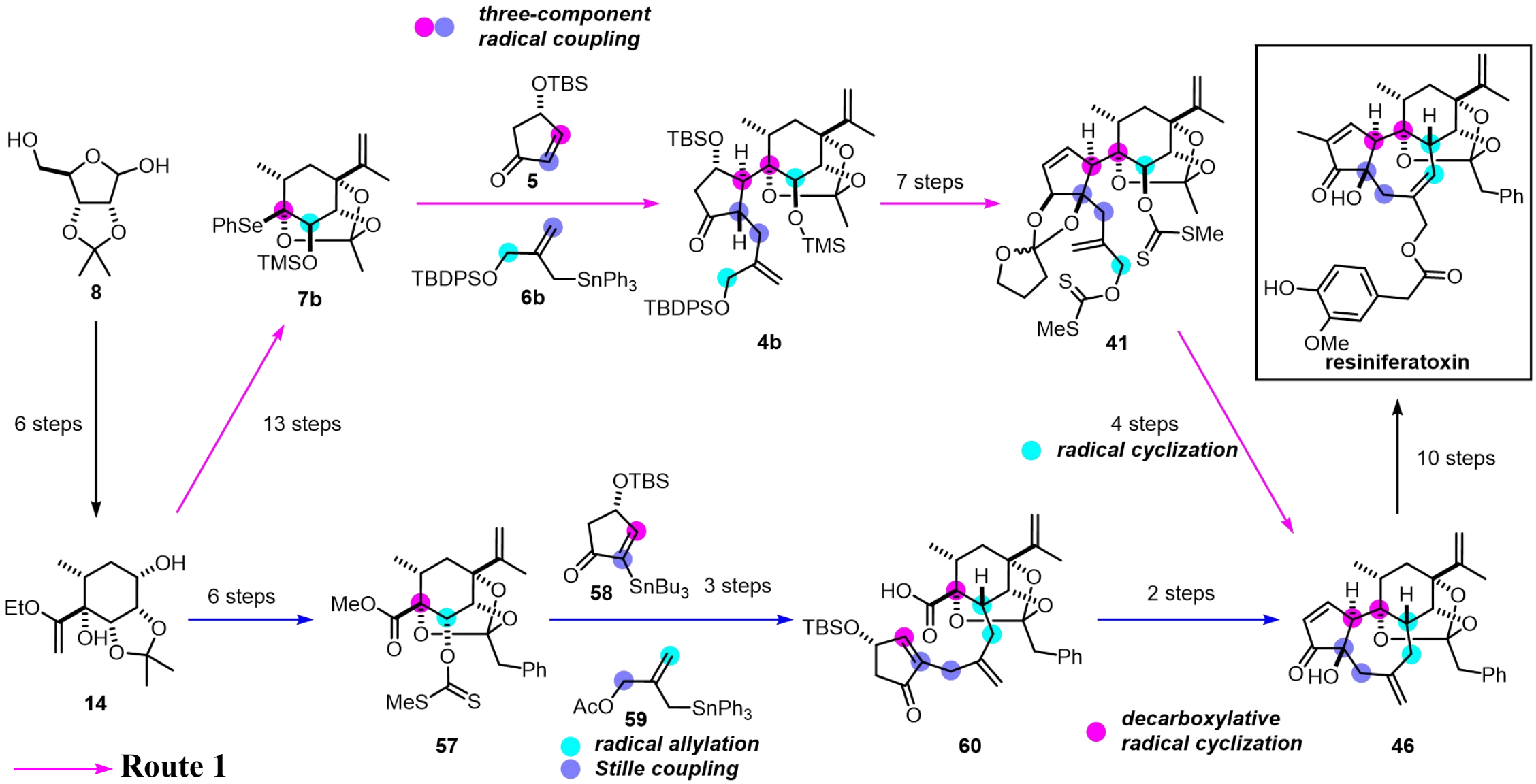
Activity：

potently activating TRPV1
(Which is expected to act as an analgesic agent for pain induced by chronic inflammation, neuropathy, and cancer.)

Tetrahedron Lett. **1975**, *16*, 1595-1598
J. Am. Chem. Soc. **1997**, *119*, 12976–12977
J. Am. Chem. Soc. **2017**, *139*, 16420-16429
J. Am. Chem. Soc. **2021**, *143*, 12387-12396

Org. Lett. **2022**, *24*, 929-933
J. Am. Chem. Soc. **2022**, *144*, 16332-16337
J. Am. Chem. Soc. **2025**, *147*, 42164−42169

Masayuki Inoue's group



Org. Lett. **2022**, *24*, 929-933

Introduction of Prof. Thomas Maimone

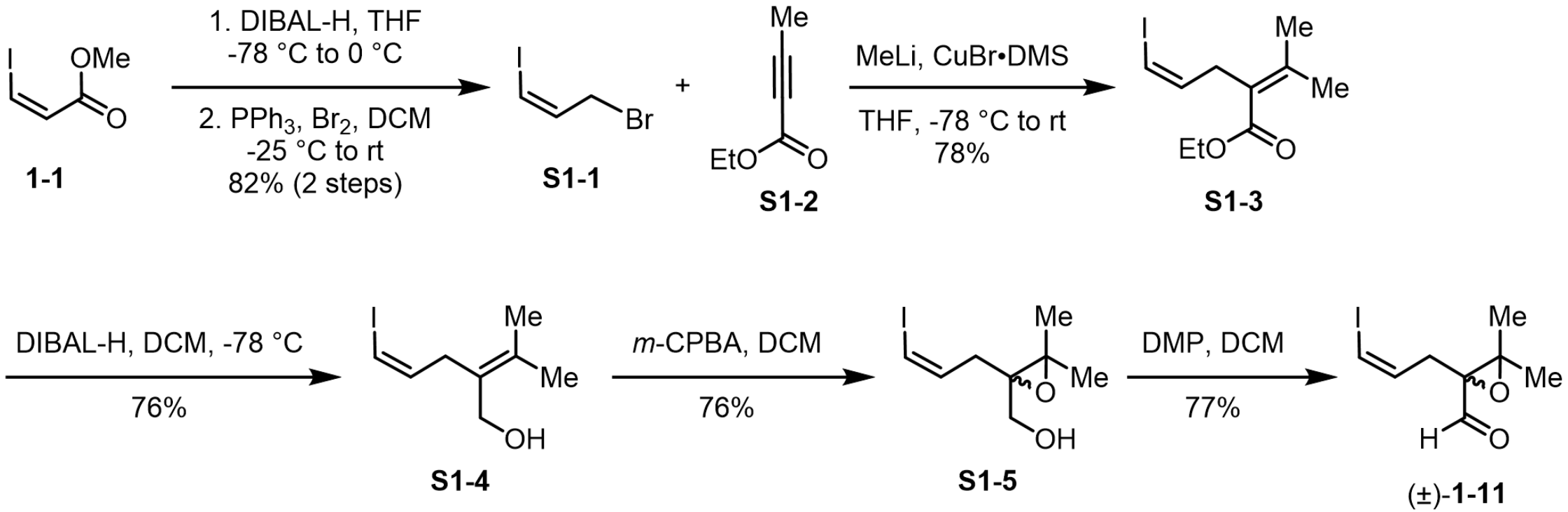
- B.S. University of California, Berkeley **(2004)**
- Ph.D. The Scripps Research Institute, CA **(2009)**

  (mentor: Phil S. Baran)
- NIH Postdoctoral Fellow, Massachusetts

  Institute of Technology **(2009-2012)**

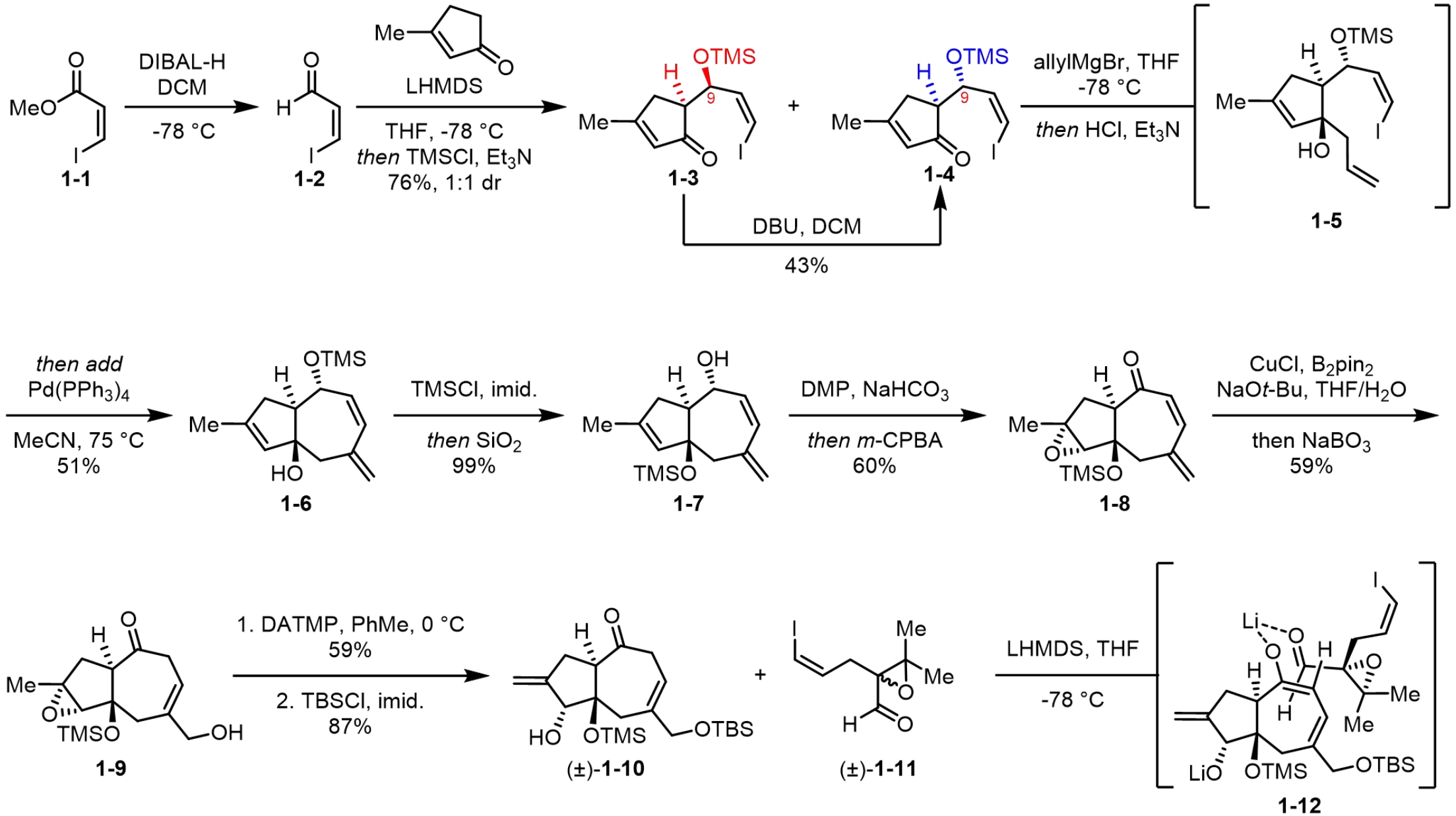
  (mentor: Steve Buchwald)

Total Synthesis of Resiniferatoxin

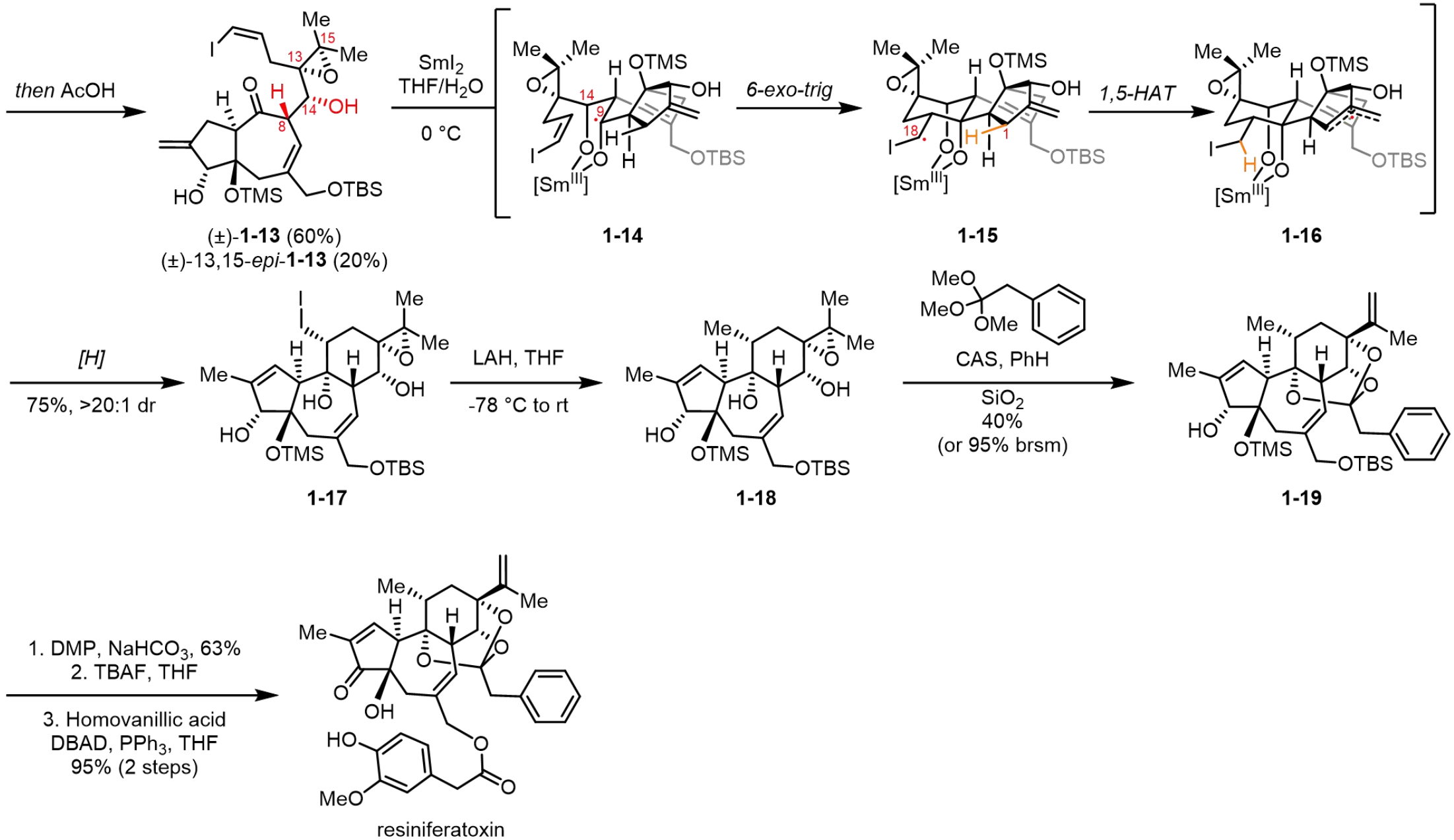


J. Am. Chem. Soc. **2022**, *144*, 16332-16337

Total Synthesis of Resiniferatoxin



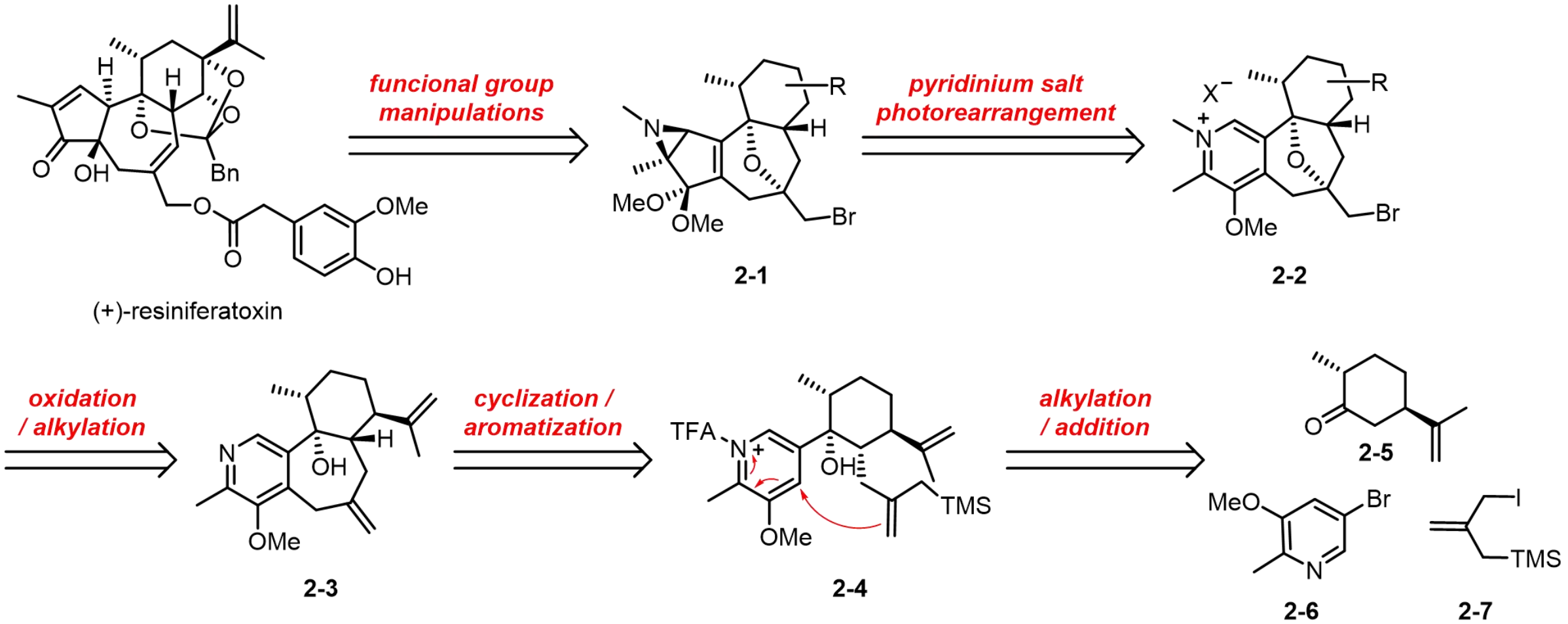
Total Synthesis of Resiniferatoxin



Introduction of Prof.

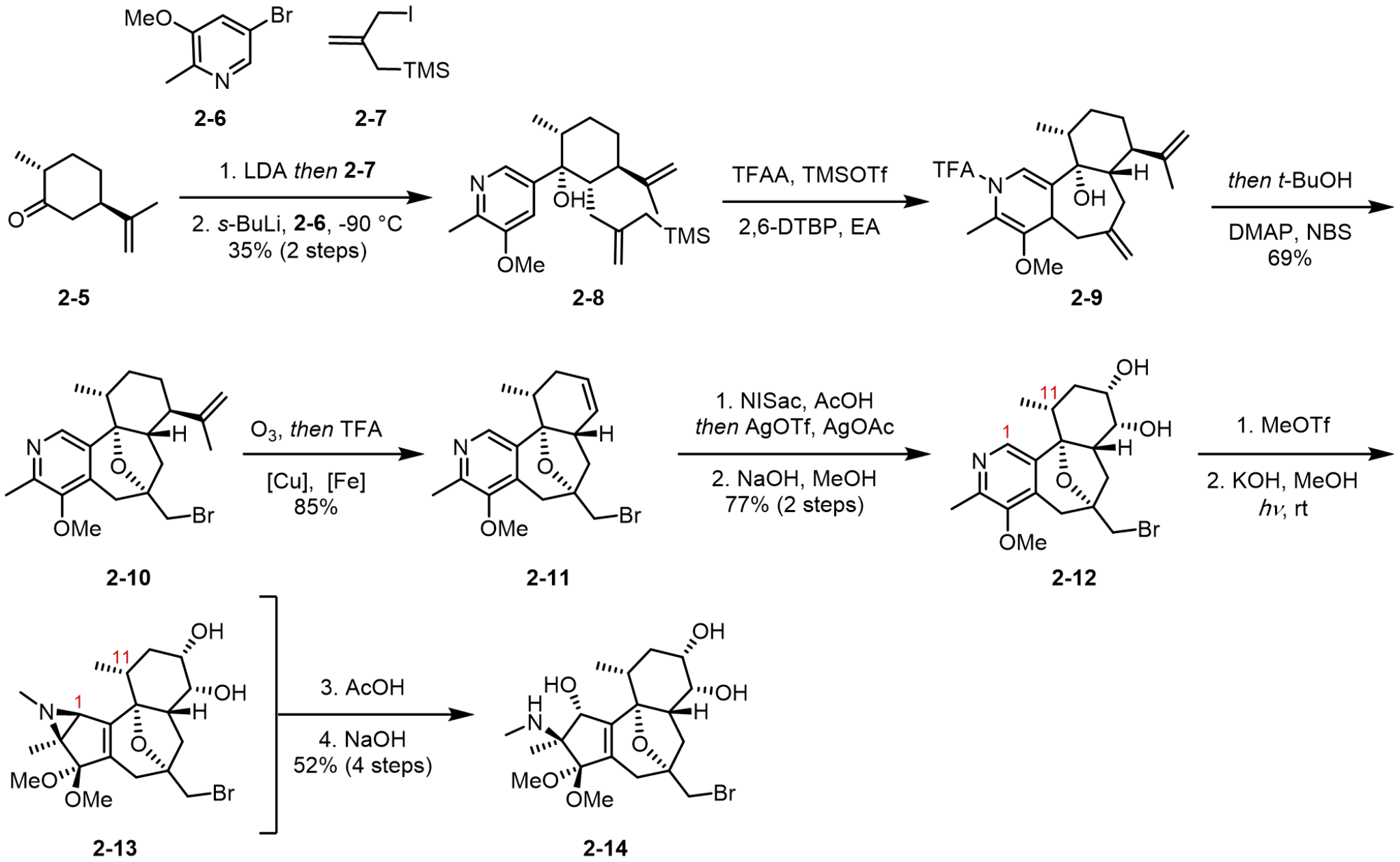
2013-now	Professor, College of Chemistry and Molecular Engineering Principle Investigator, Center for Life Sciences Peking University
2011-2013	Postdoctoral Fellow, H3 Biomedicine Inc., Research advisor: Dr. John Yuan Wang
2005-2011	Ph.D. in Chemistry, Department of Chemistry and Chemical Biology, Harvard University; Chemical Biology Program, Broad Institute, Research advisor: Professor Stuart L. Schreiber
2001-2005	B.S. in Chemistry, College of Chemistry and Molecular Engineering, Peking University, Research advisor: Professor Zhen Yang

Retrosynthetic Analysis



J. Am. Chem. Soc. **2025**, *147*, 42164-42169

Total Synthesis of Resiniferatoxin



Total Synthesis of Resiniferatoxin

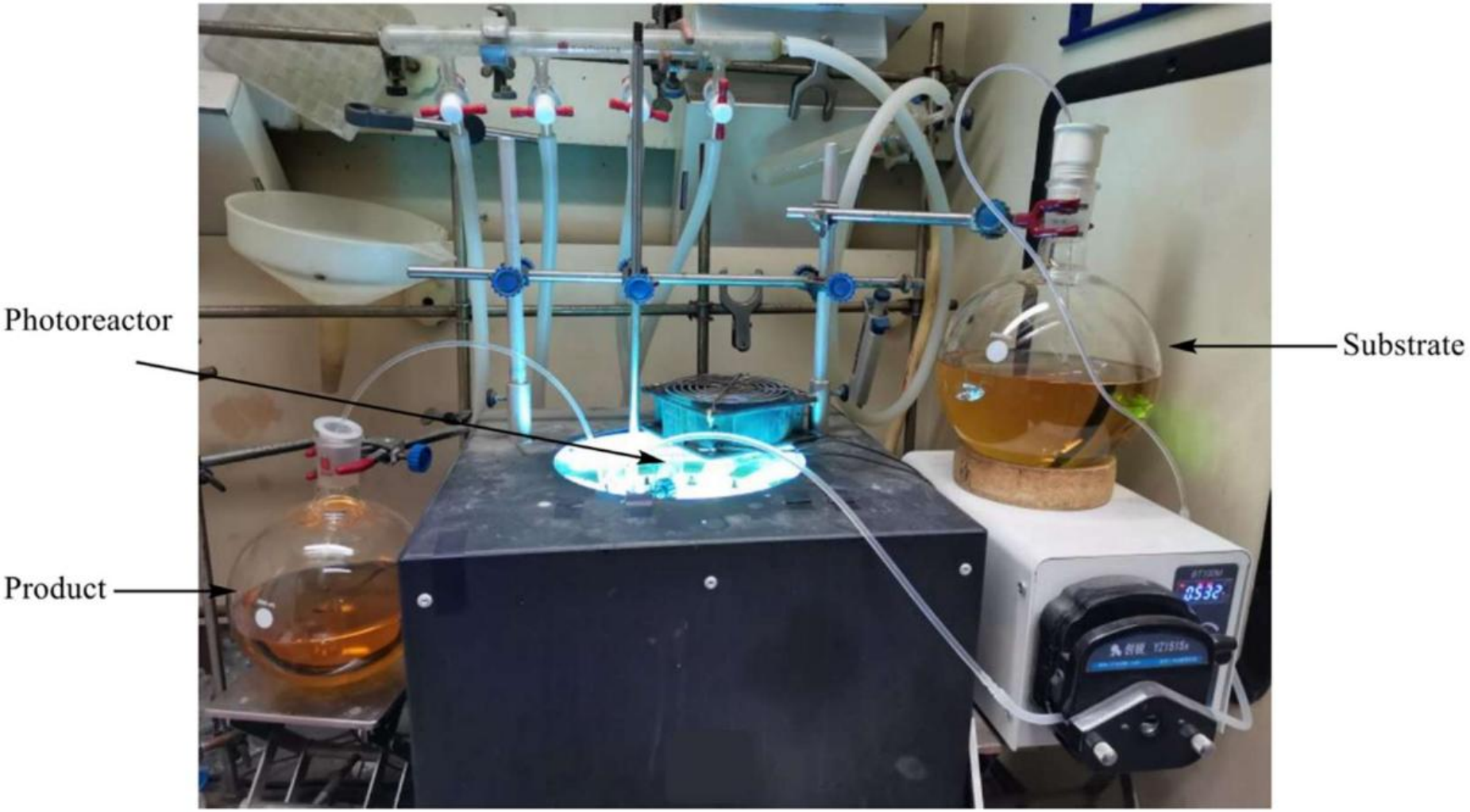


Figure S4. Reaction setup of the photochemical reactors and the flow apparatus

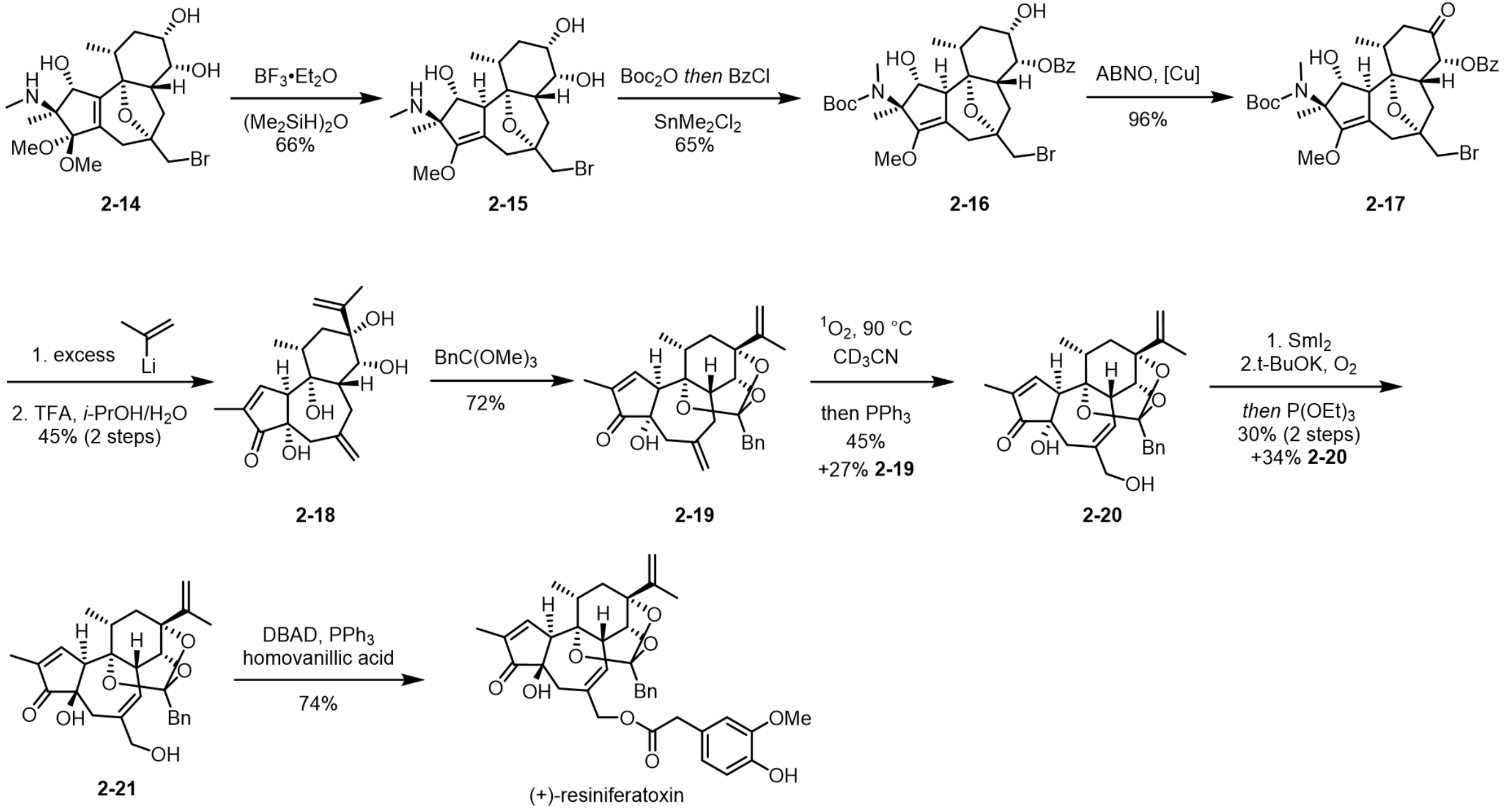
Total Synthesis of Resiniferatoxin

The simple flow apparatus

Inside the photochemical reactor

Figure S5 The flow apparatus and inside the photochemical reactor

Total Synthesis of Resiniferatoxin



Mechanism

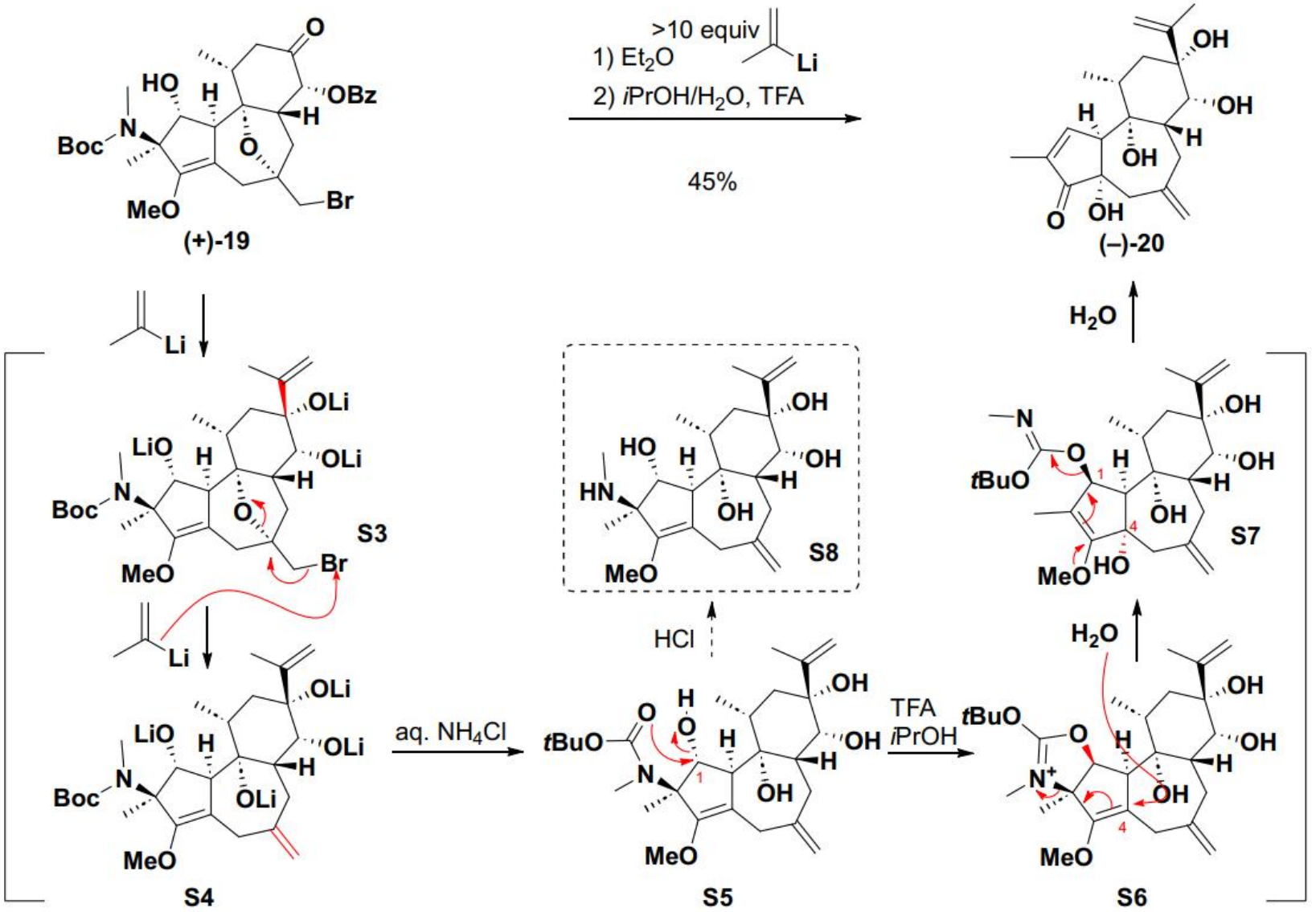
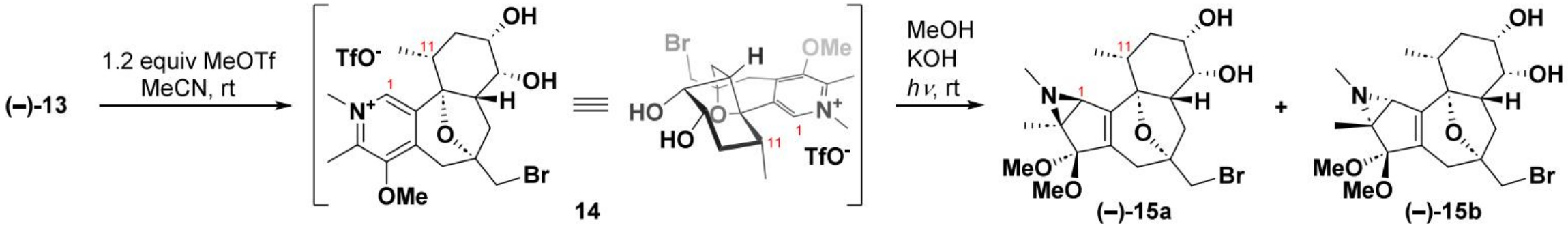


Figure S3. Proposed mechanism of the transformation from **(+)-19** to **(–)-20**

Total Synthesis of Resiniferatoxin

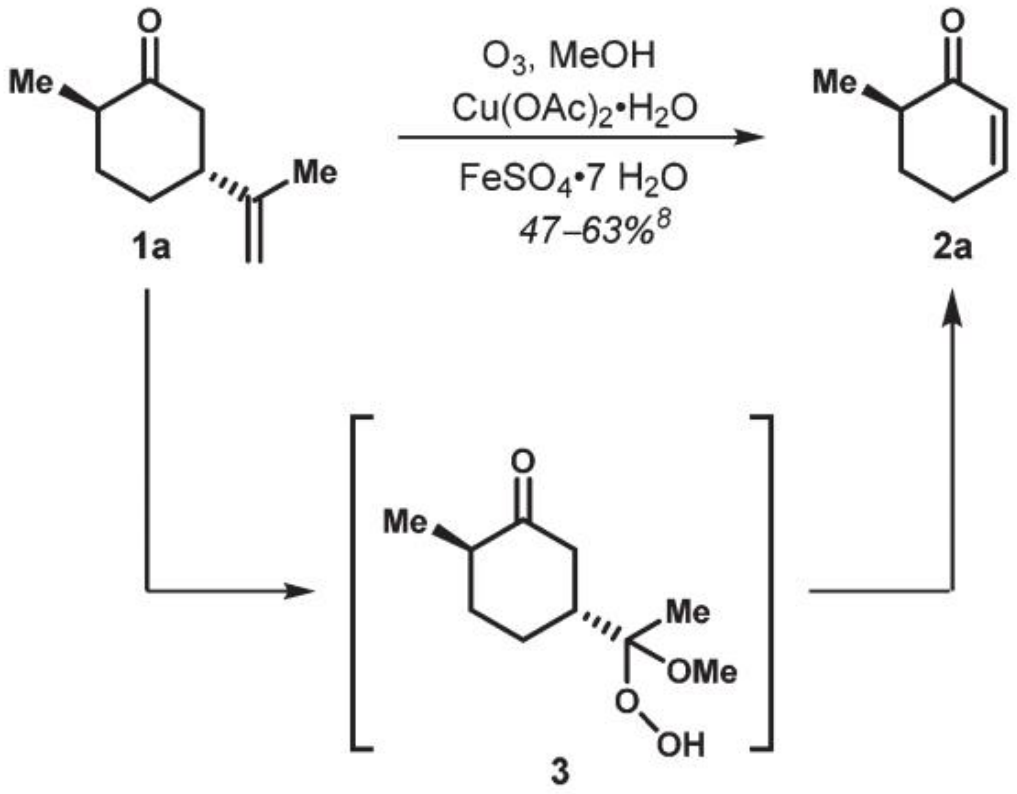
Table 1. Optimization of the Pyridinium Salt Photorearrangement[a]



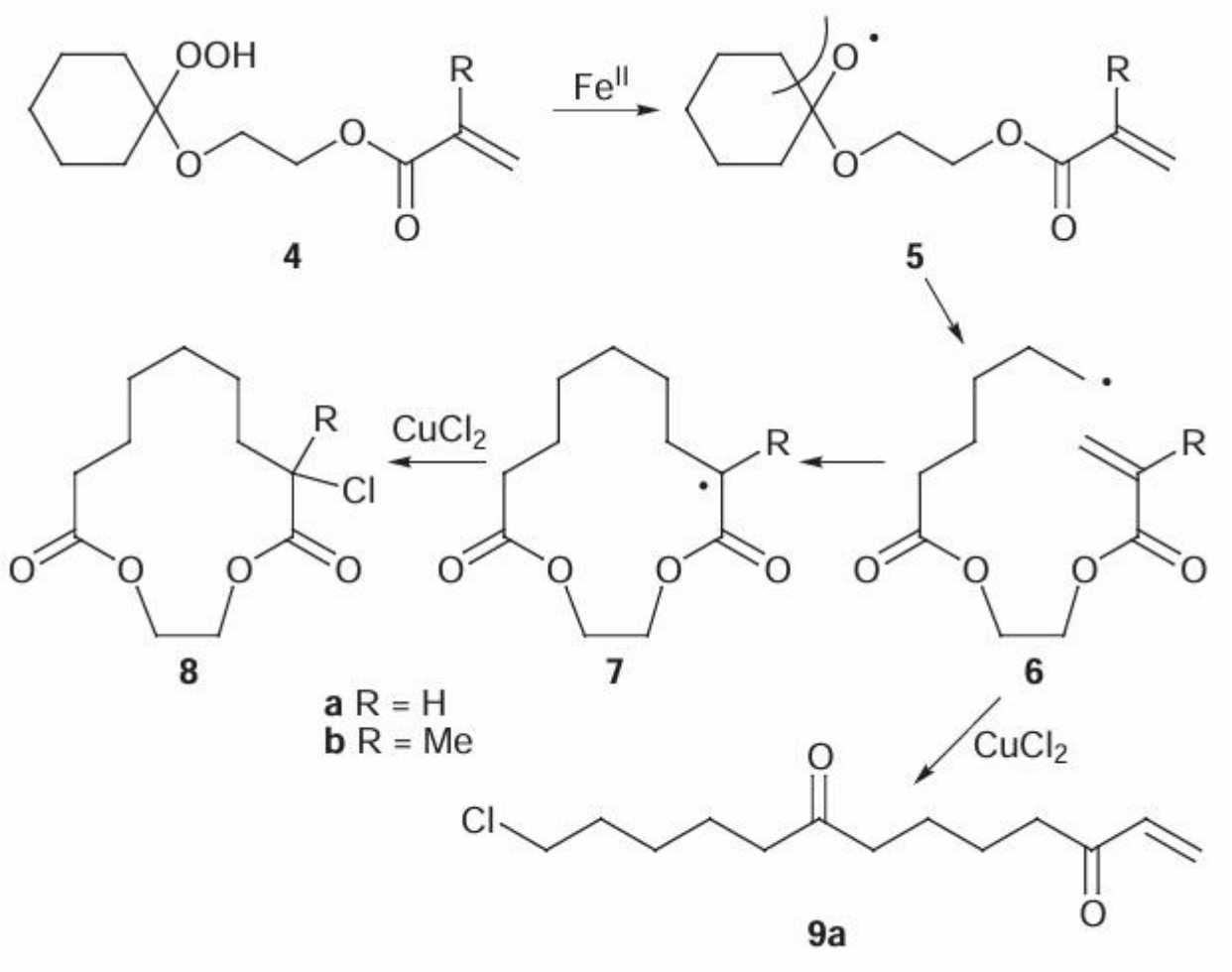
entry	wavelength (nm)	concn (mM)	equiv of KOH	time	yield, %[b] 15a	15b
1	300	24	2.25	4 h	54	11
2	300	12	2.25	2 h	53	11
3	300	6	4.5	1 h	52	12
4	254	6	4.5	10 min	47	12
5	254	12	2.25	20 min	47	11
6	254 (pyrex tube)	12	2.25	2 h	trace[c]	

[a]Reaction performed on 0.06 mmol scale and set up in the 10 mL quartz test tubes. [b]NMR yield determined using 1,3,5-trimethoxybenzene as the internal standard. [c]Low conversion.

Mechanism



Org. Biomol. Chem., **2016**,*14*, 6197-6200

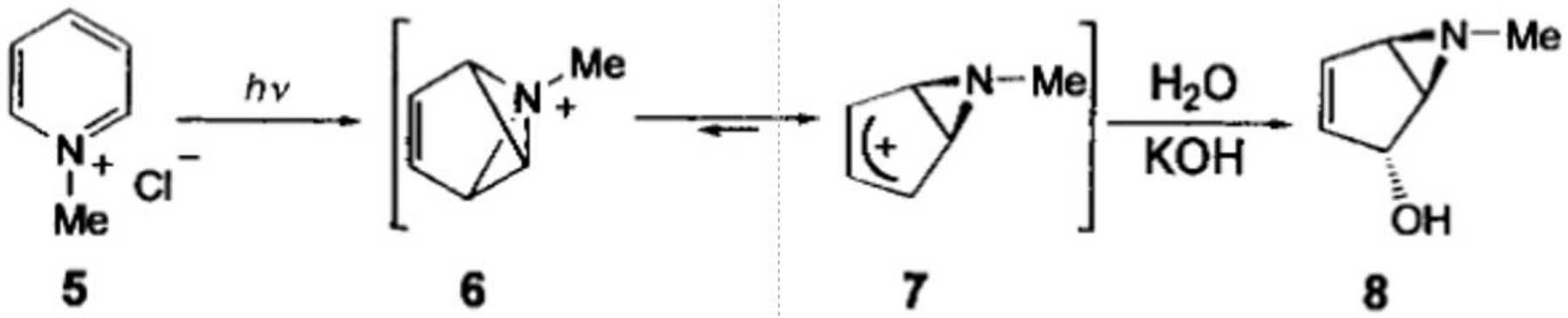


Scheme 2

Chem. Commun., **1998**, 1173-1174

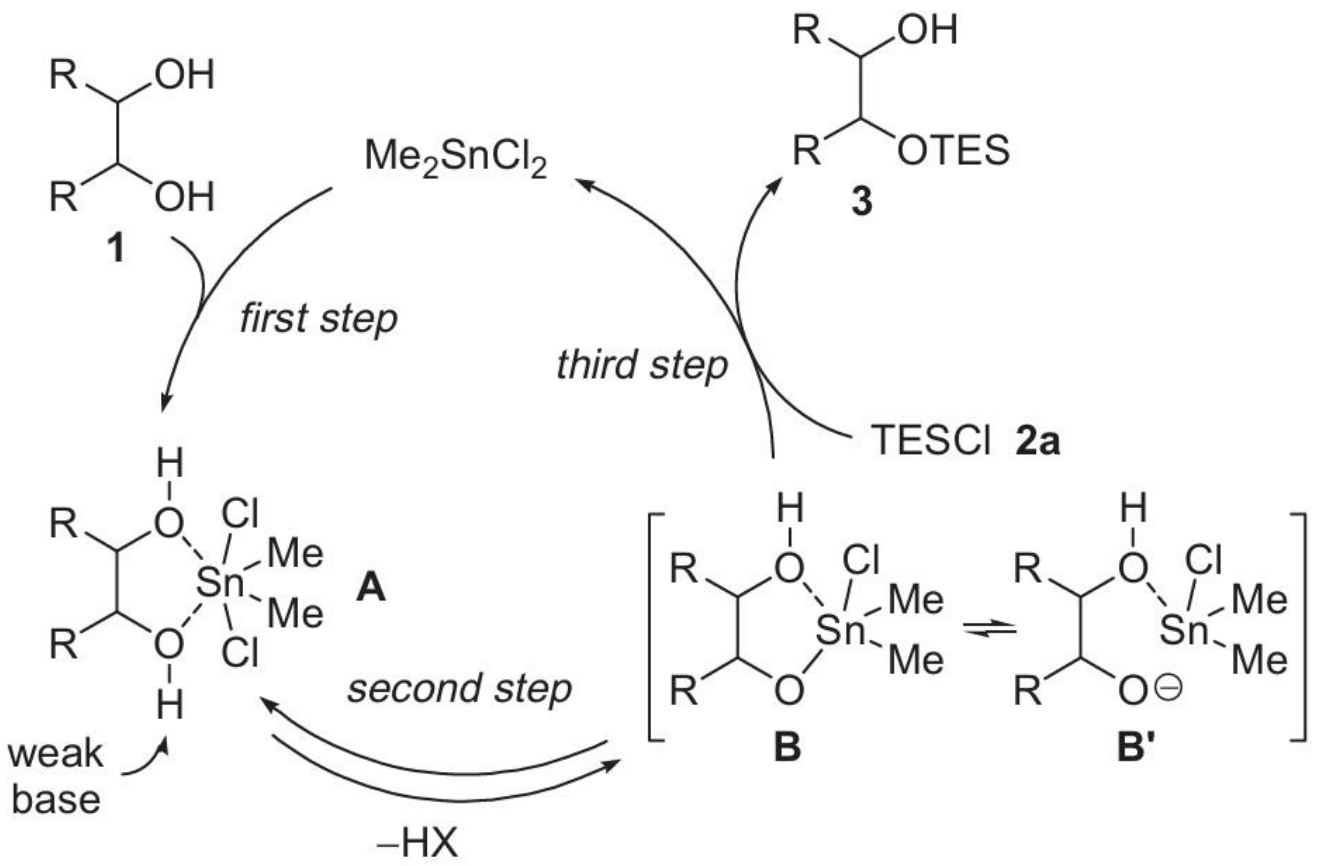
Mechanism

Scheme 1



Helve. Chim. Acta, **1998**, *81,* 1095-1104.

Mechanism



Scheme 1. Working hypothesis for chemoselective monosilylation catalyzed by Me_2SnCl_2.

Tetrahedron Lett. **2011**, *52*, 6646-6648