Asymmetric synthesis of batrachotoxin: Enantiomeric toxins show functional divergence against Na_Vs

Reporter: Xiang Gao
Checker: Zhong Yan
Date: 2016/12/19

Logan, M. M.; Toma, T.; Thomas-Tran, R.; Du Bois, J**.**
Science **2016***, 354,* 865*.*

CV of Justin Du Bois

Stanford University

- Developing tools for chemical synthesis and exploits such inventions to facilitate access to architecturally complex natural products;
- Contemporaneous efforts to explore the mechanism of C–H amination and to evolve new catalytic systems for C–C, C–N, and C–O bond formation.

Education:

- **B.S.** University of California, Berkeley, 1992 ;
- **Ph.D.** California Institute of Technology (Prof. Erick Carreira), 1992-1997.

Research experience:

- **Postdoctoral Fellow**

Massachusetts Institute of Technology (Prof. Stephen Lippard), 1997-1999;

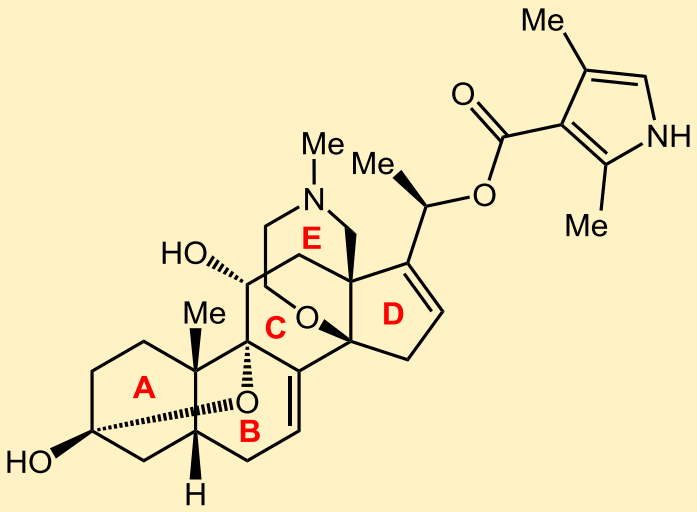
- **Independent Research**

Department of Chemical & Systems Biology, Stanford University, (1999-now).

Contents

- ✓ **Introduction**
- ✓ **Formal synthesis of (+/-)-Batrachotoxin**
- ✓ **Asymmetric synthesis of (-)-Batrachotoxin**
- ✓ **Summary**

Introduction



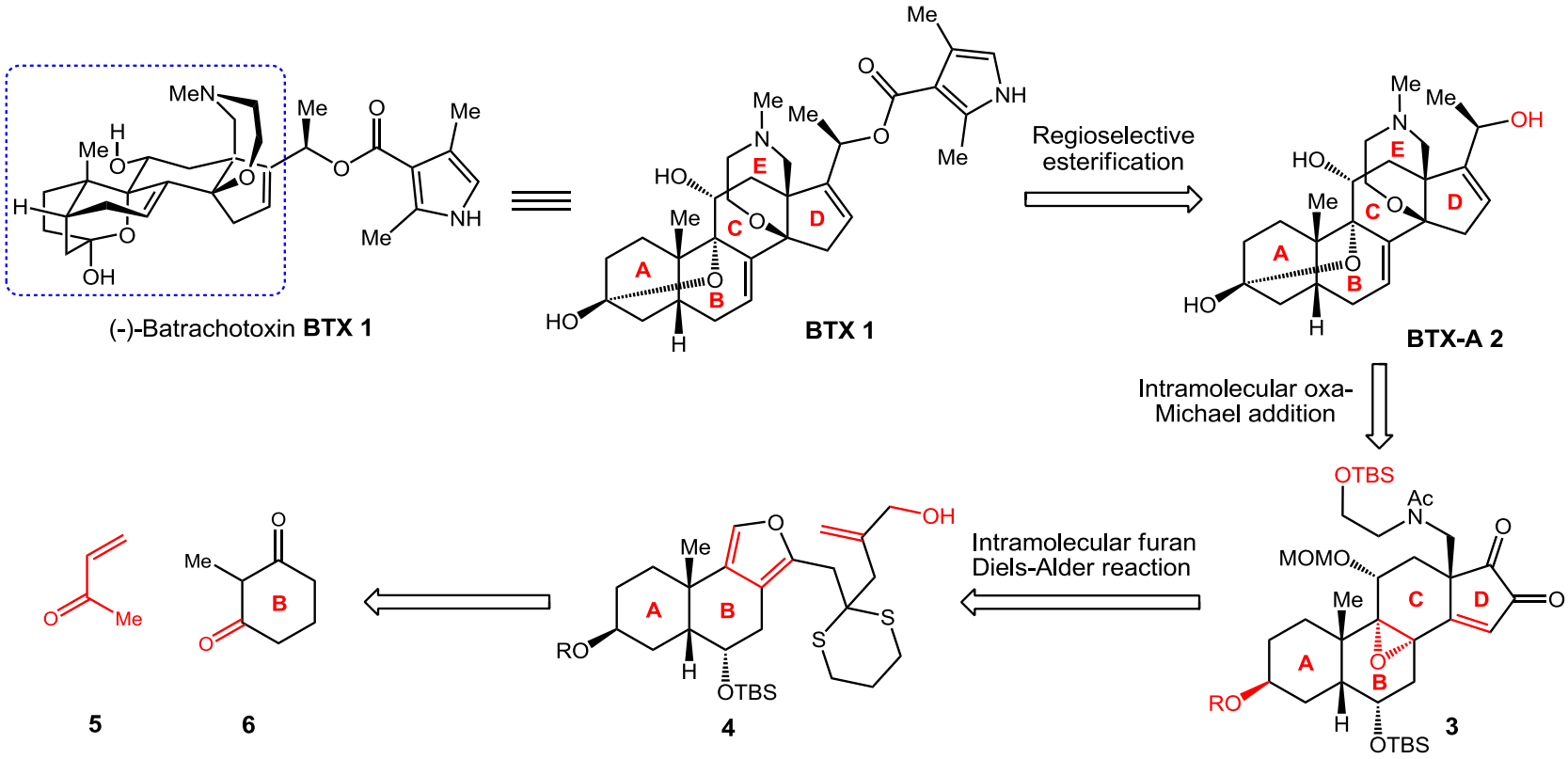
Batrachotoxin (**1**)

Poison dart frog

- An extremely potent cardiotoxic and neurotoxic steroidal alkaloid found in certain species of frogs (poison dart frog), melyrid beetles, and birds;
- Neurotoxin, irreversibly binds to the Na^+ channels to keep it open, LD_{50} in mice: 2 ug/kg, in comparison, LD_{50} (NaCN) in mice: 6.3 mg/kg;
- Structural features: a pentacyclic core skeleton, an intramolecular hemi-ketal, a seven membered oxazapane ring.

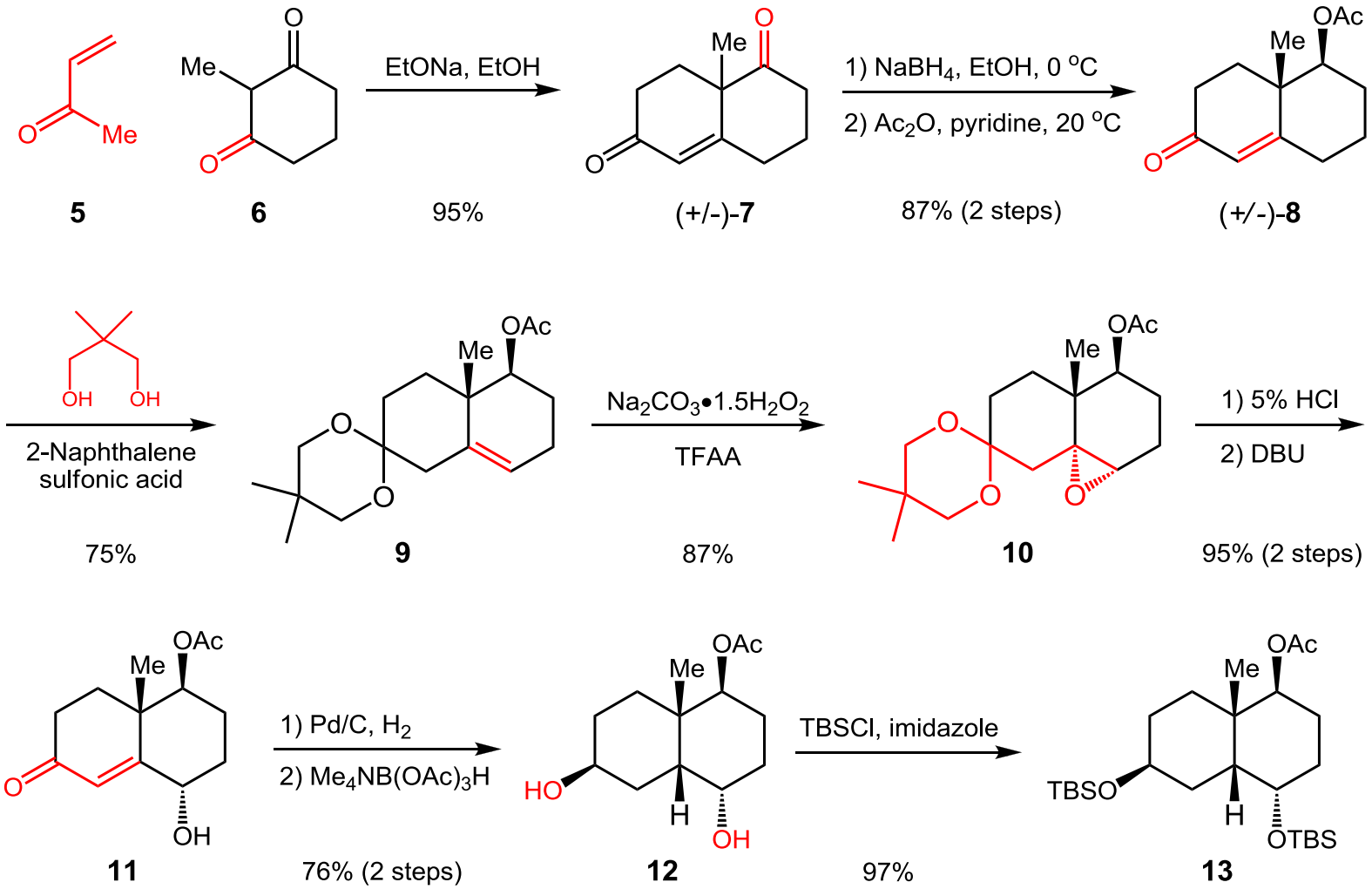
Formal synthesis of (+/-)-Batrachotoxin

Retrosynthetic Analysis

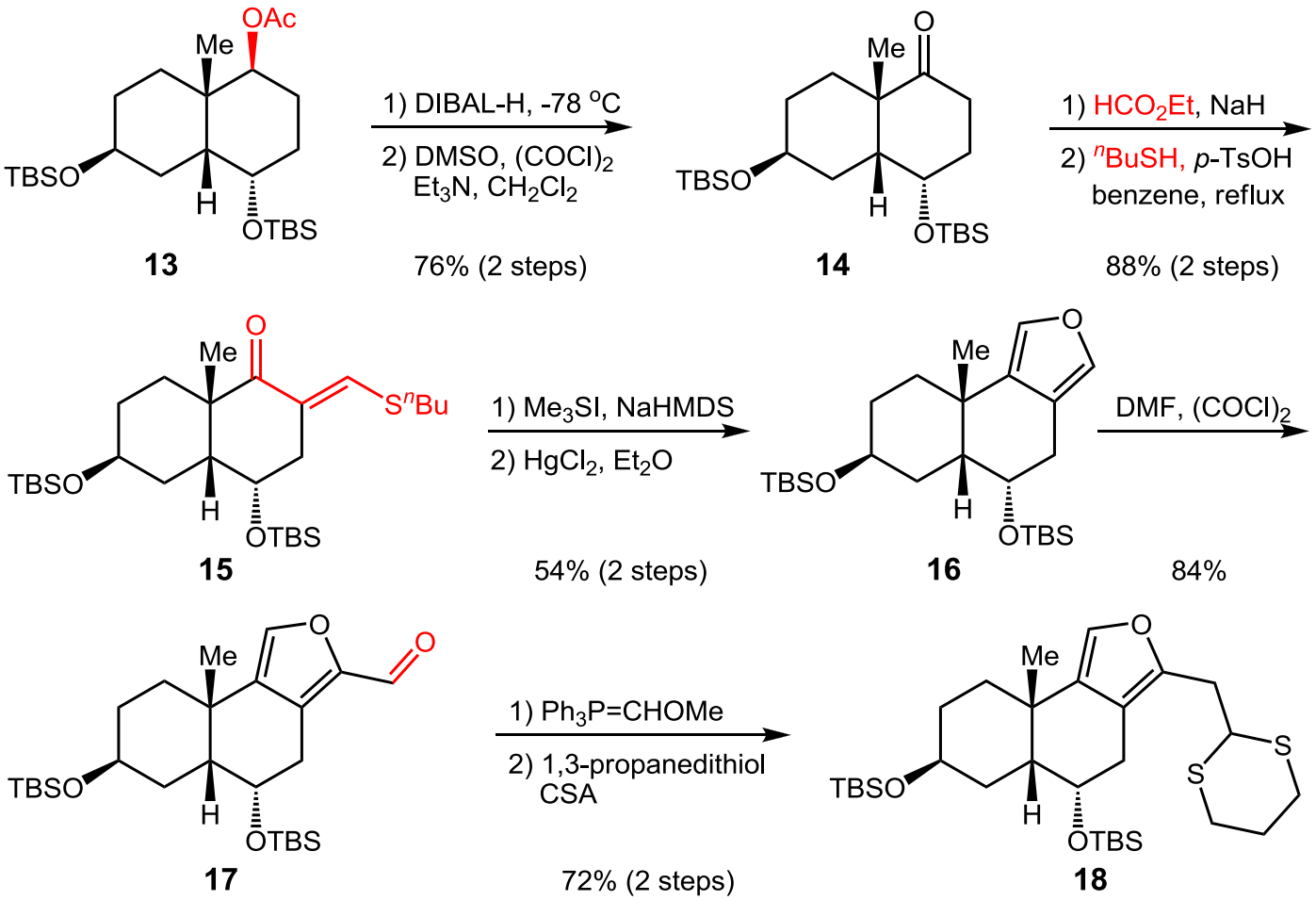


Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627.

Synthesis (+/-)-cis-Decalone 13

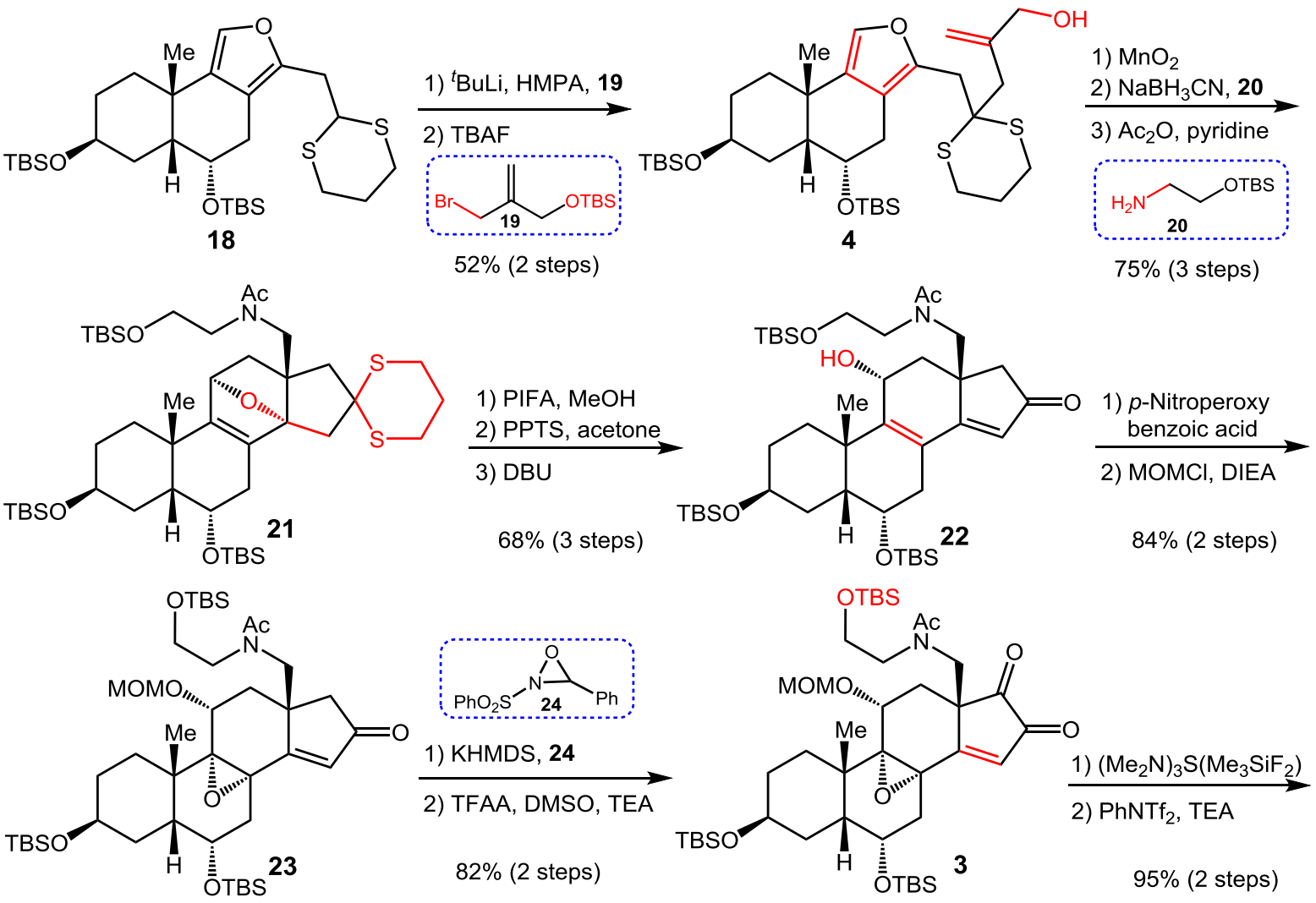


Synthesis of furan substrate 18

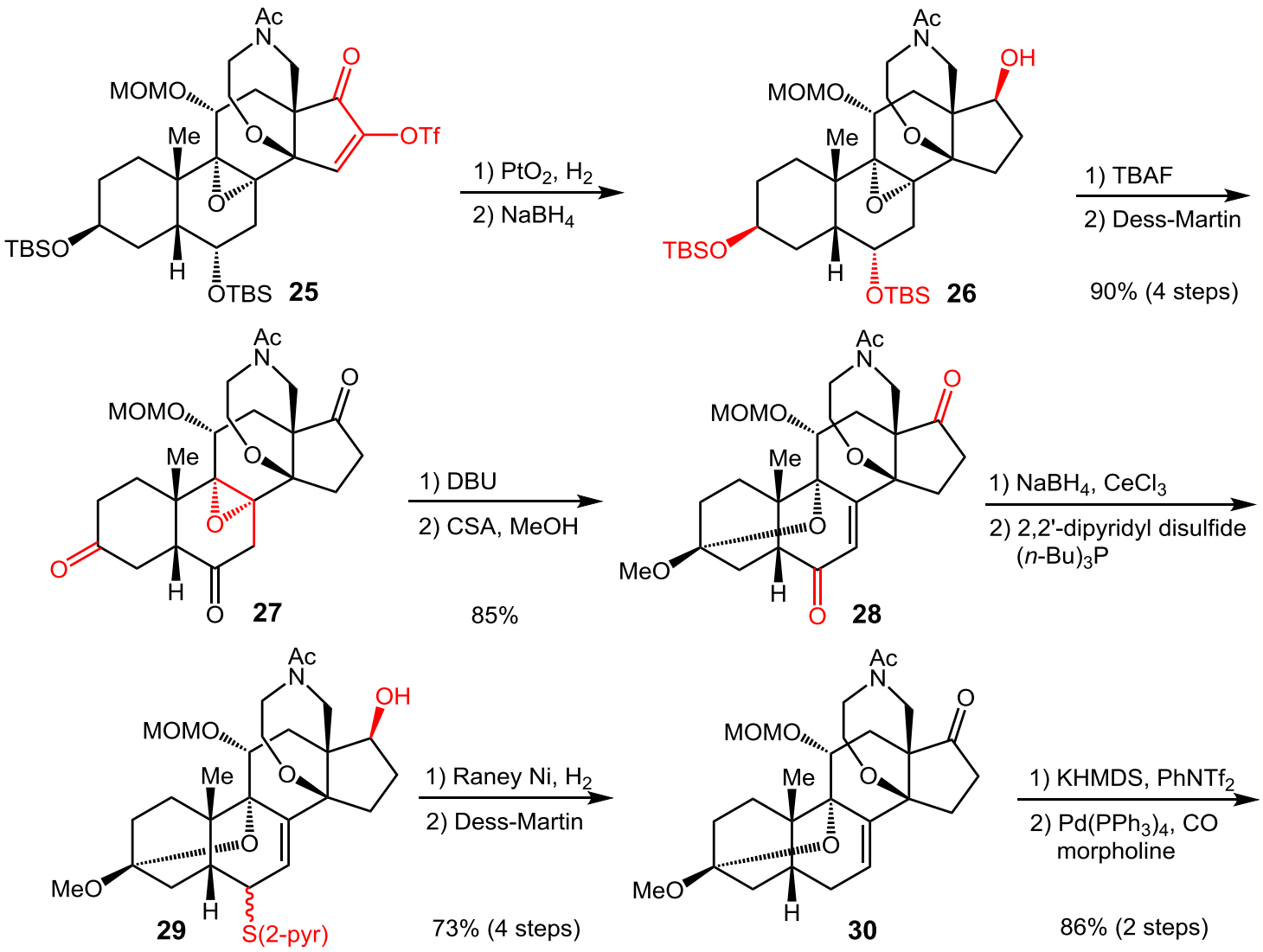


Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250.

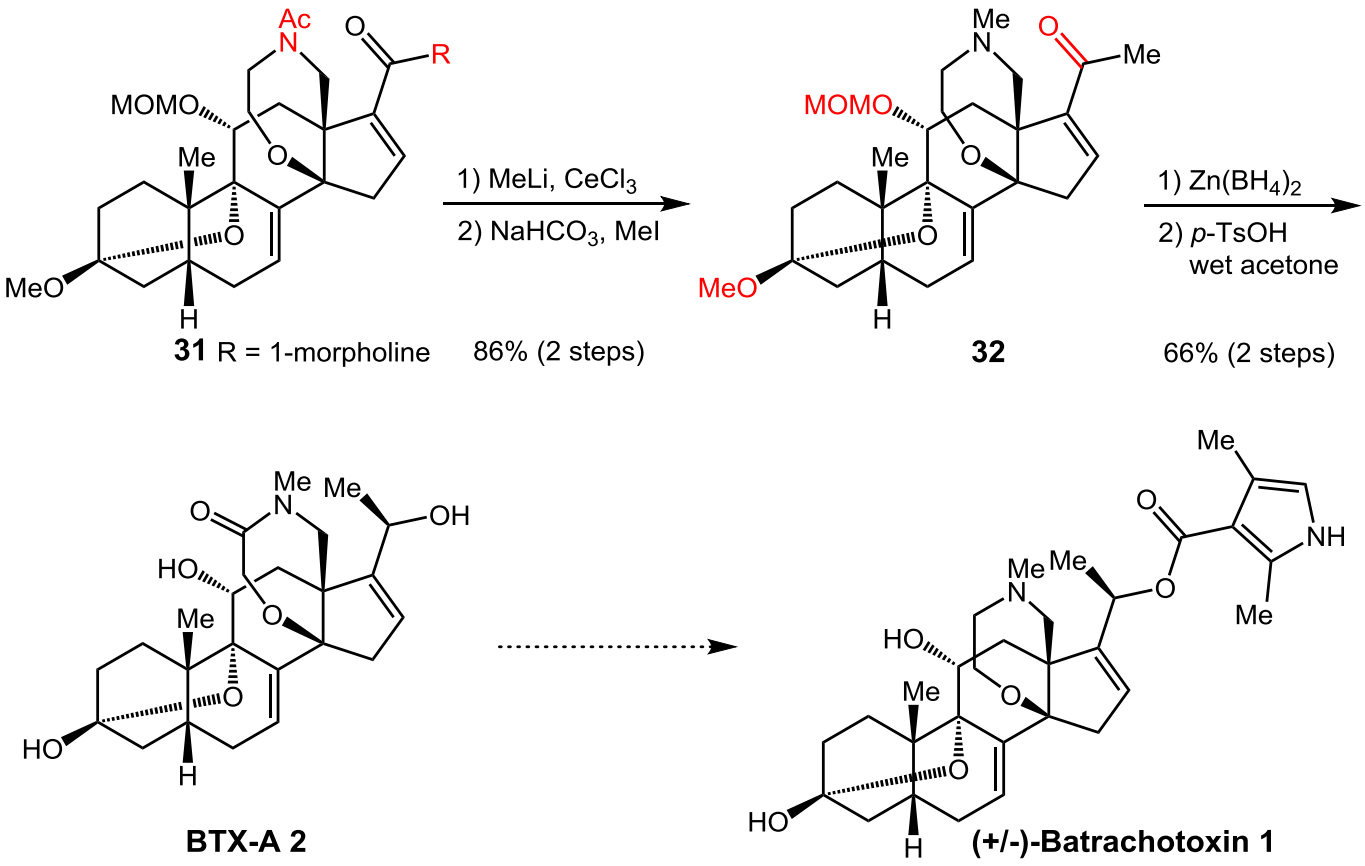
Synthesis of building block 3



Synthesis of building block 30



Synthesis of (+/-)-Batrachotoxin 1



31 R = 1-morpholine

86% (2 steps)

32

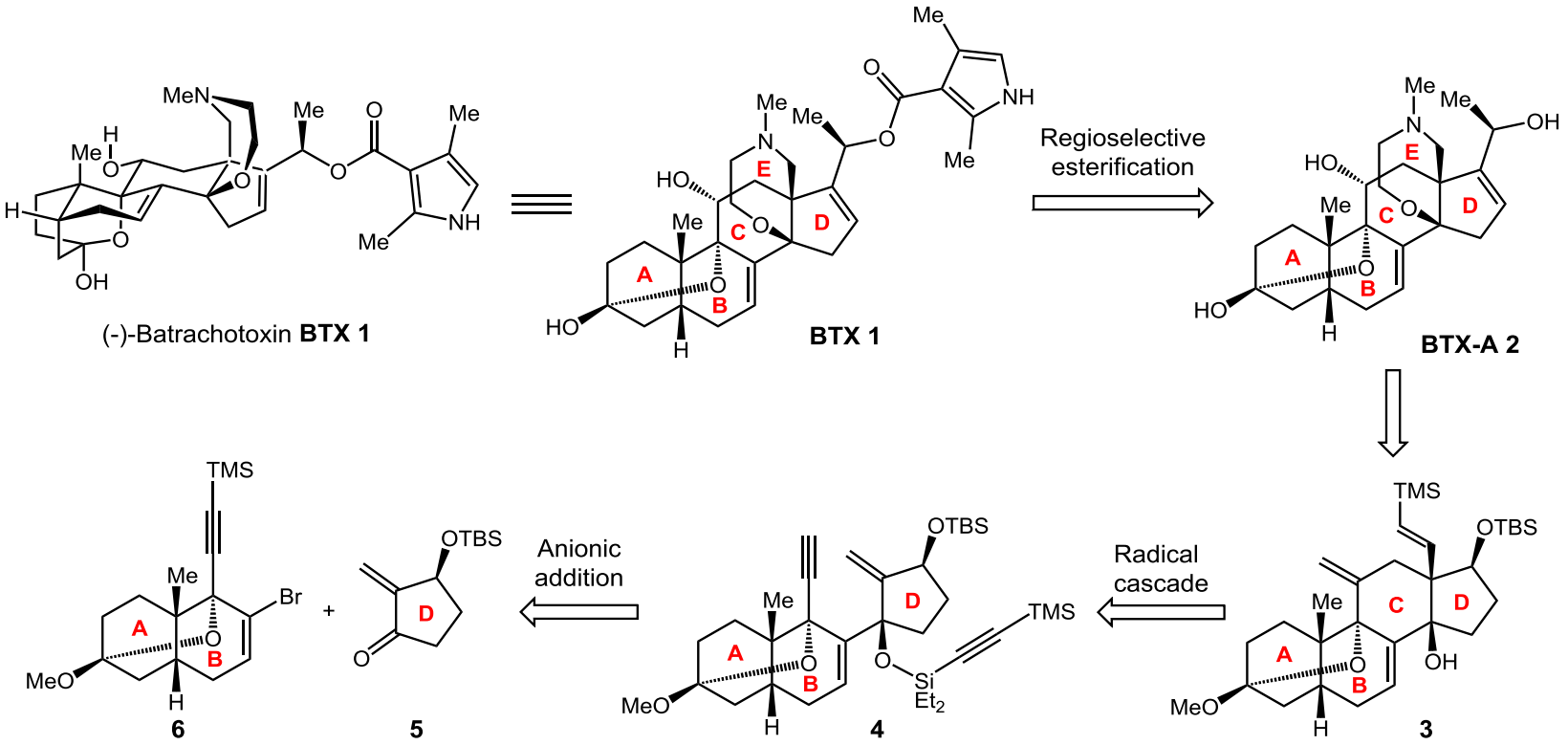
66% (2 steps)

BTX-A 2

(+/-)-Batrachotoxin 1

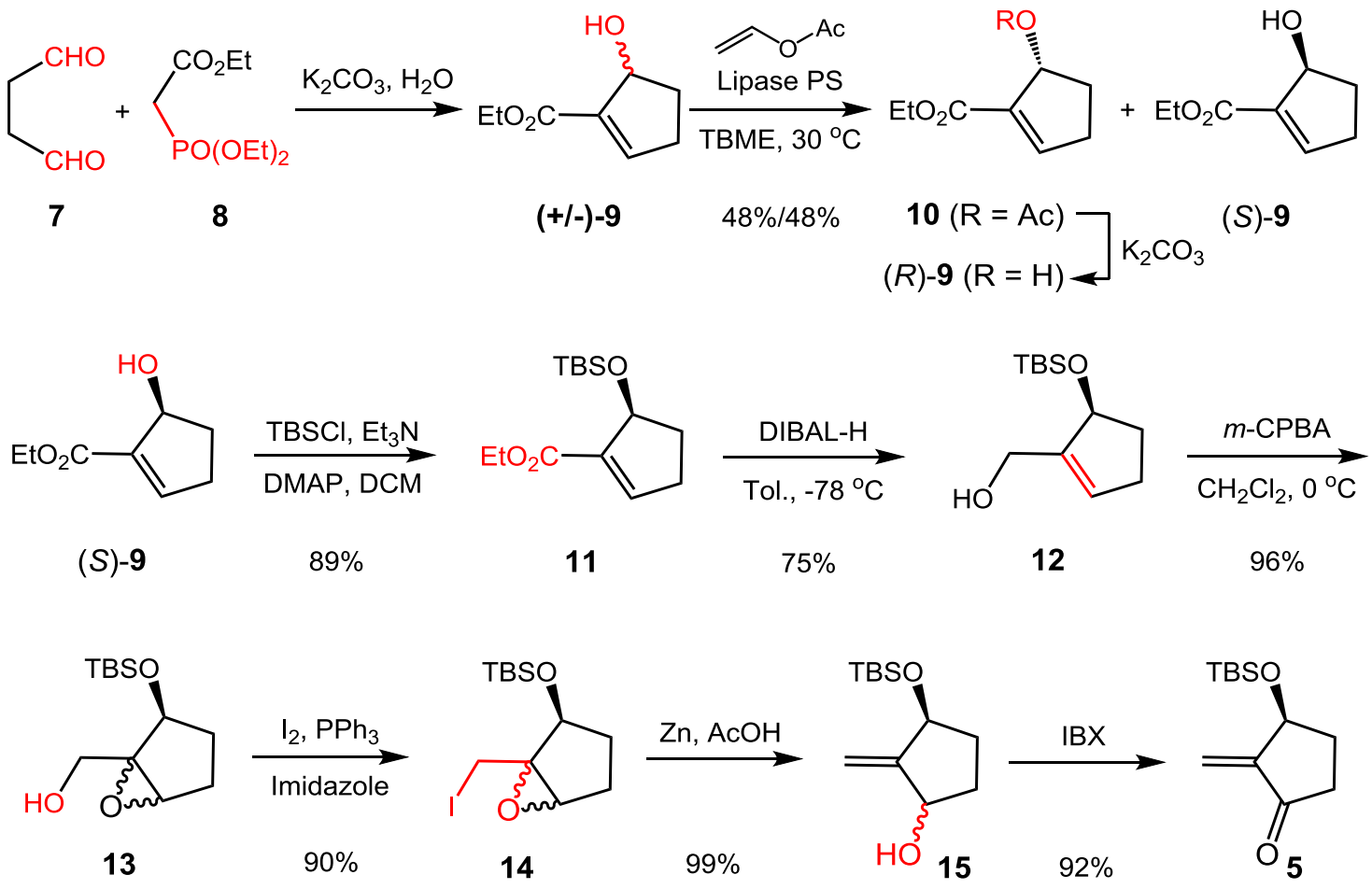
Asymmetric synthesis of (-)-Batrachotoxin

Retrosynthetic Analysis of (-)-Batrachotoxin 1

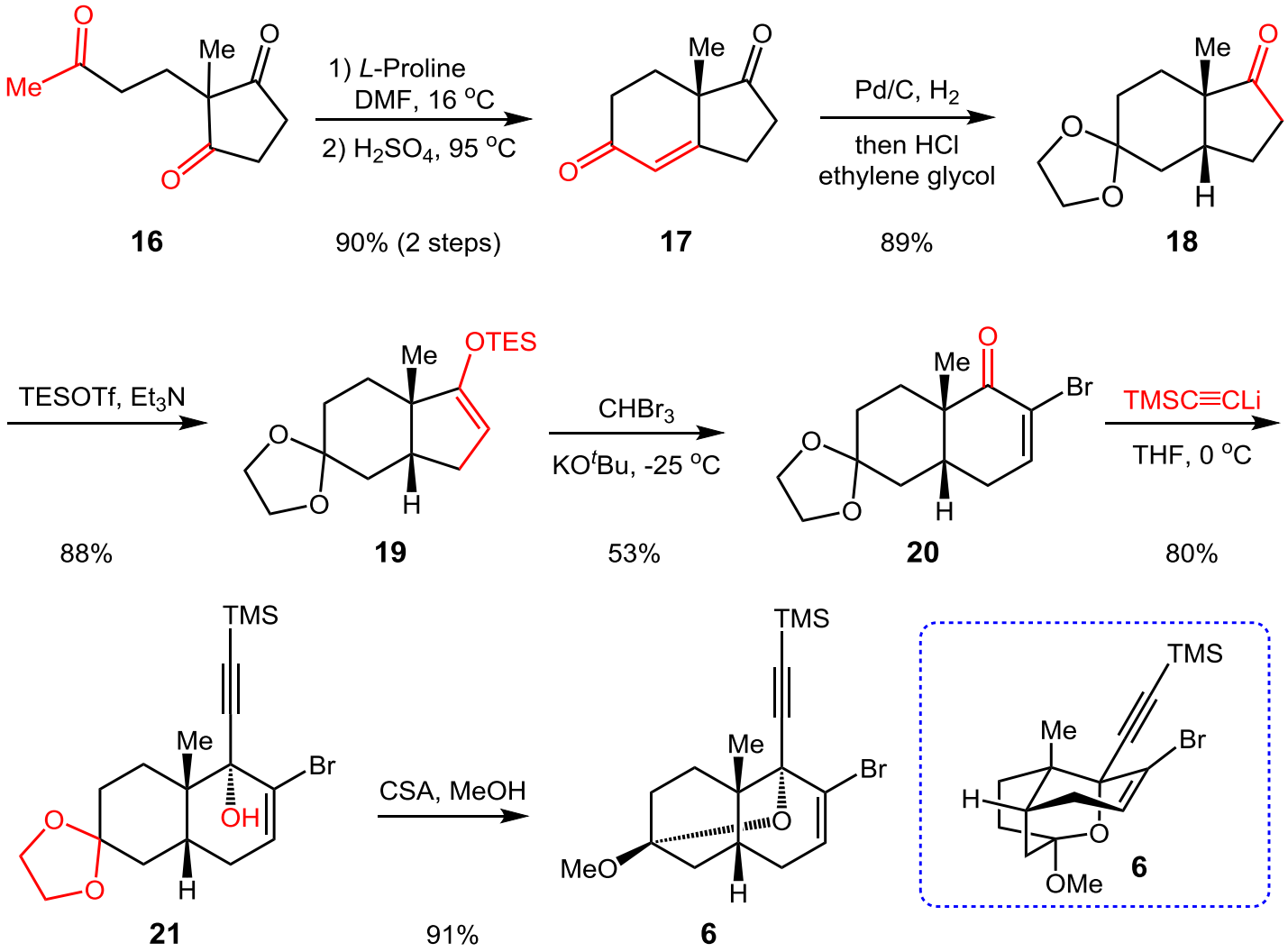


Logan, M. M.; Toma, T.; Thomas-Tran, R.; Du Bois, J. *Science* **2016**, *354*, 865.

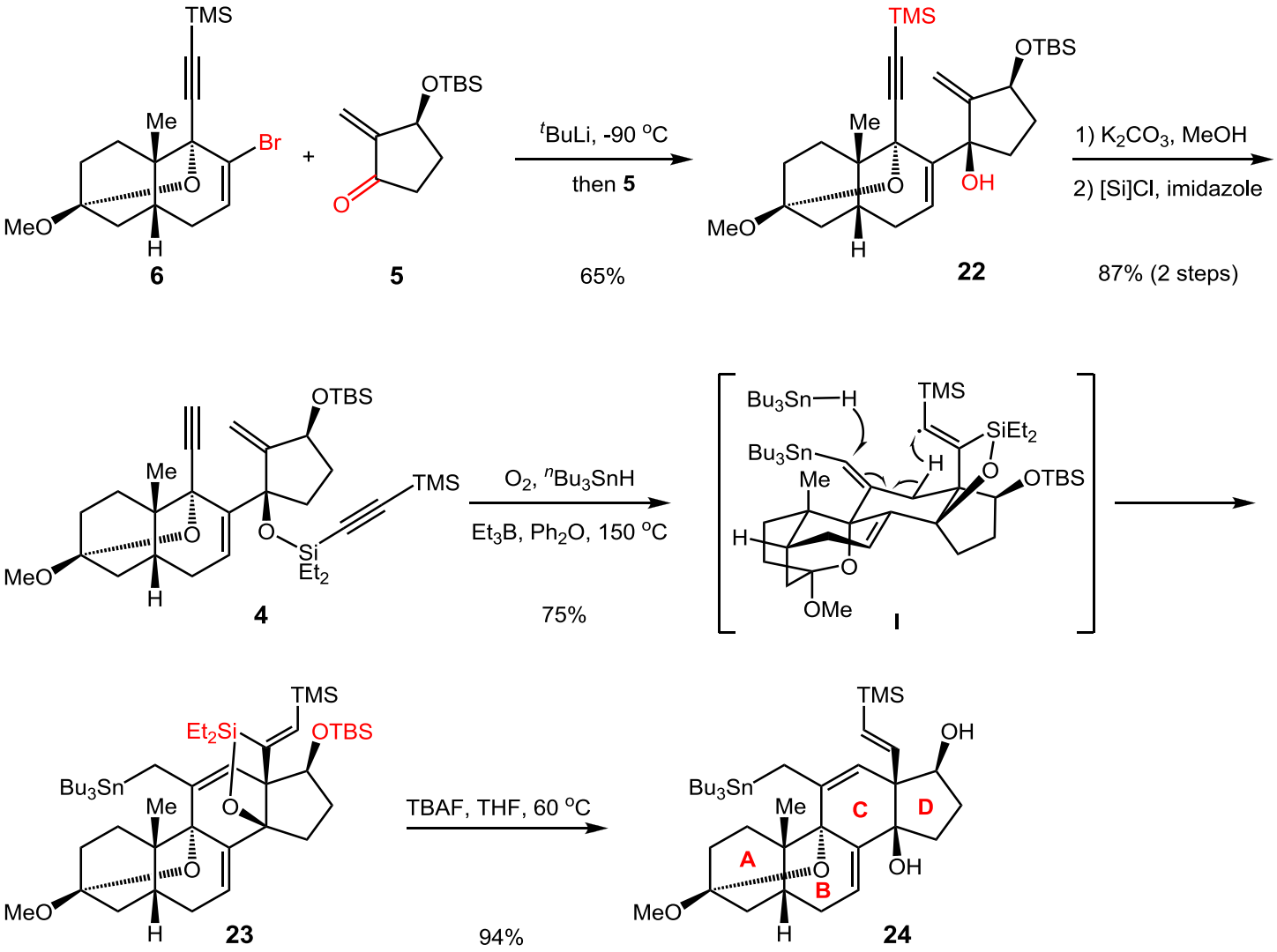
Synthesis of building block 5



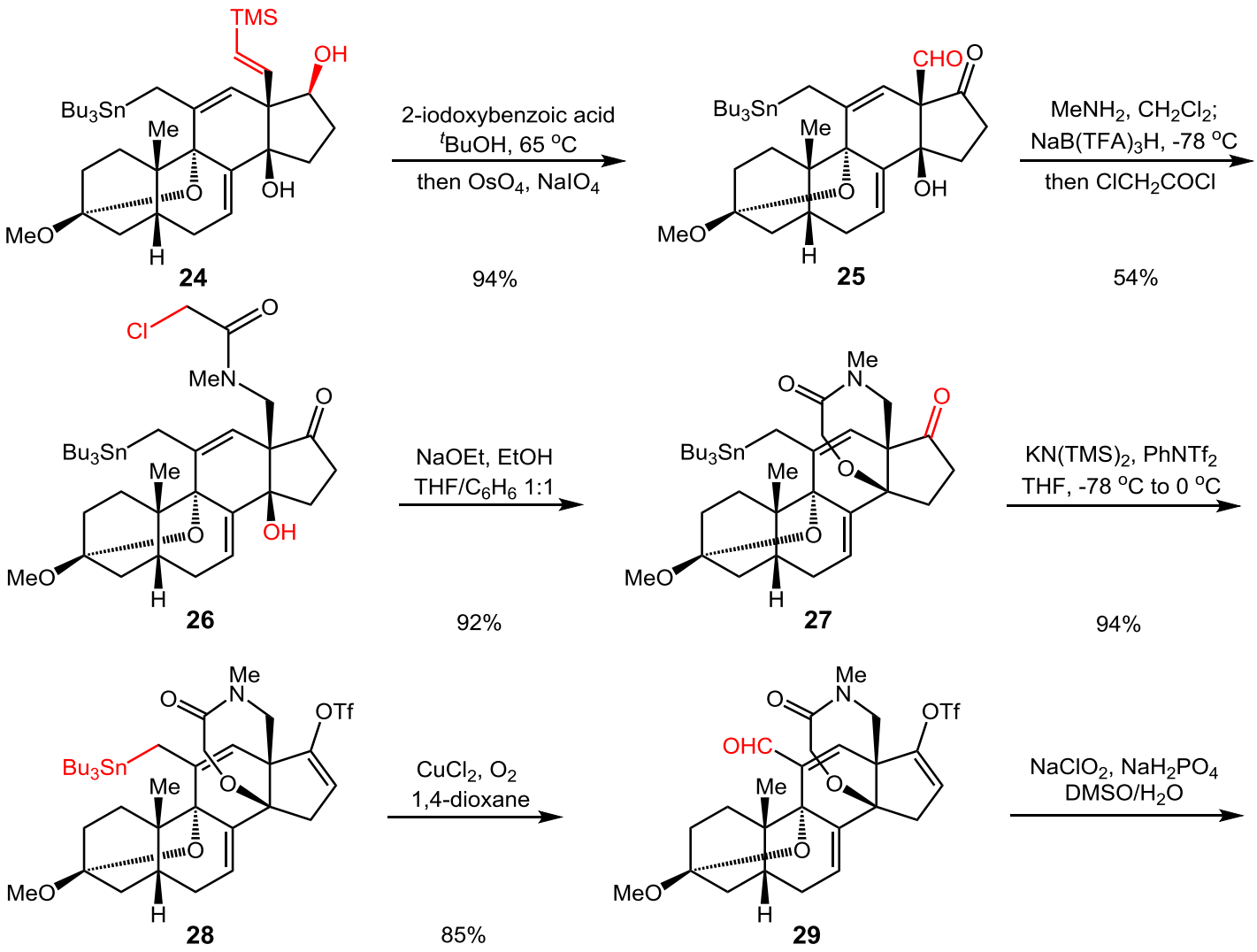
Synthesis of building block 6



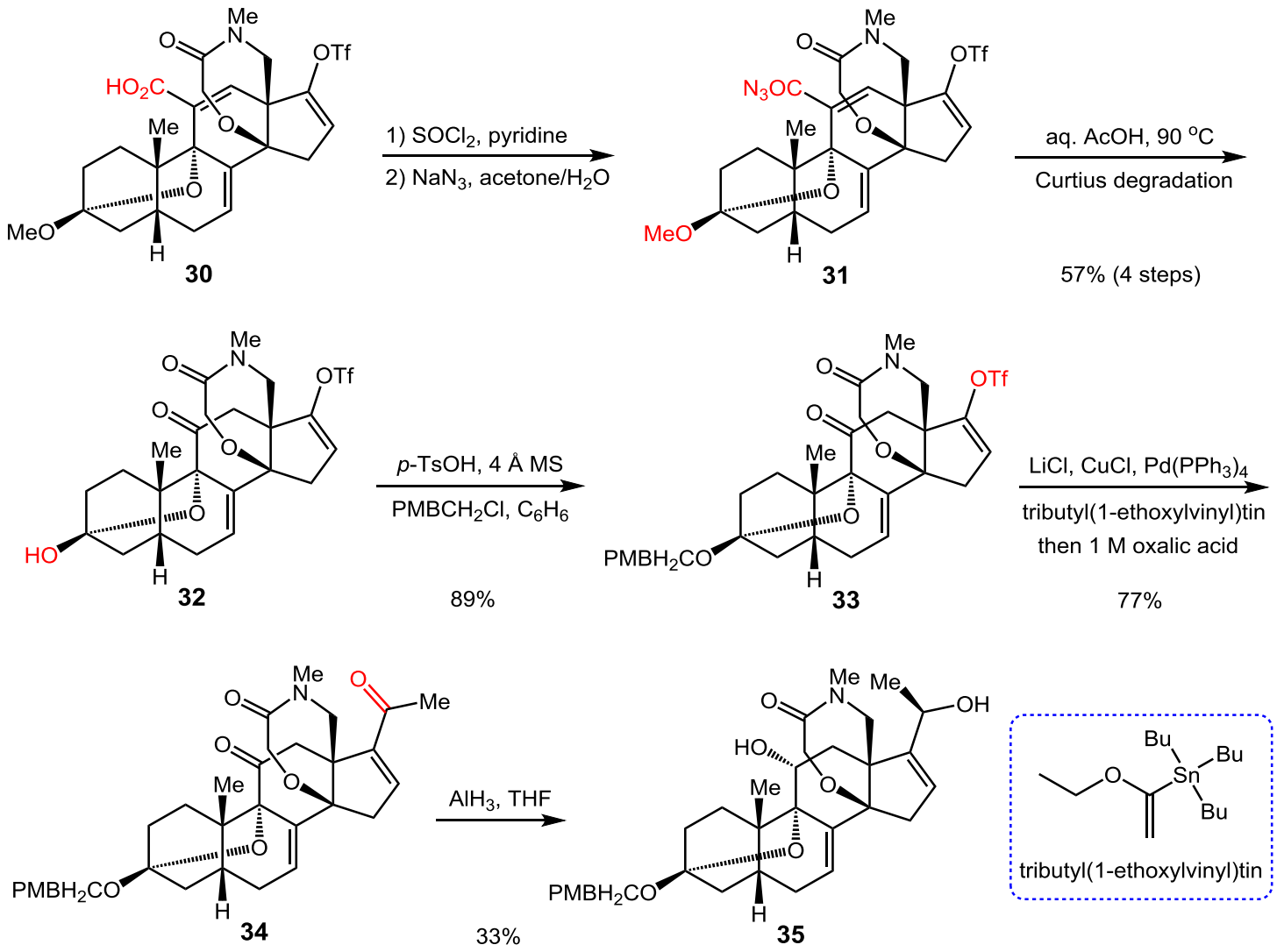
Construction of C ring *via* radical cascade



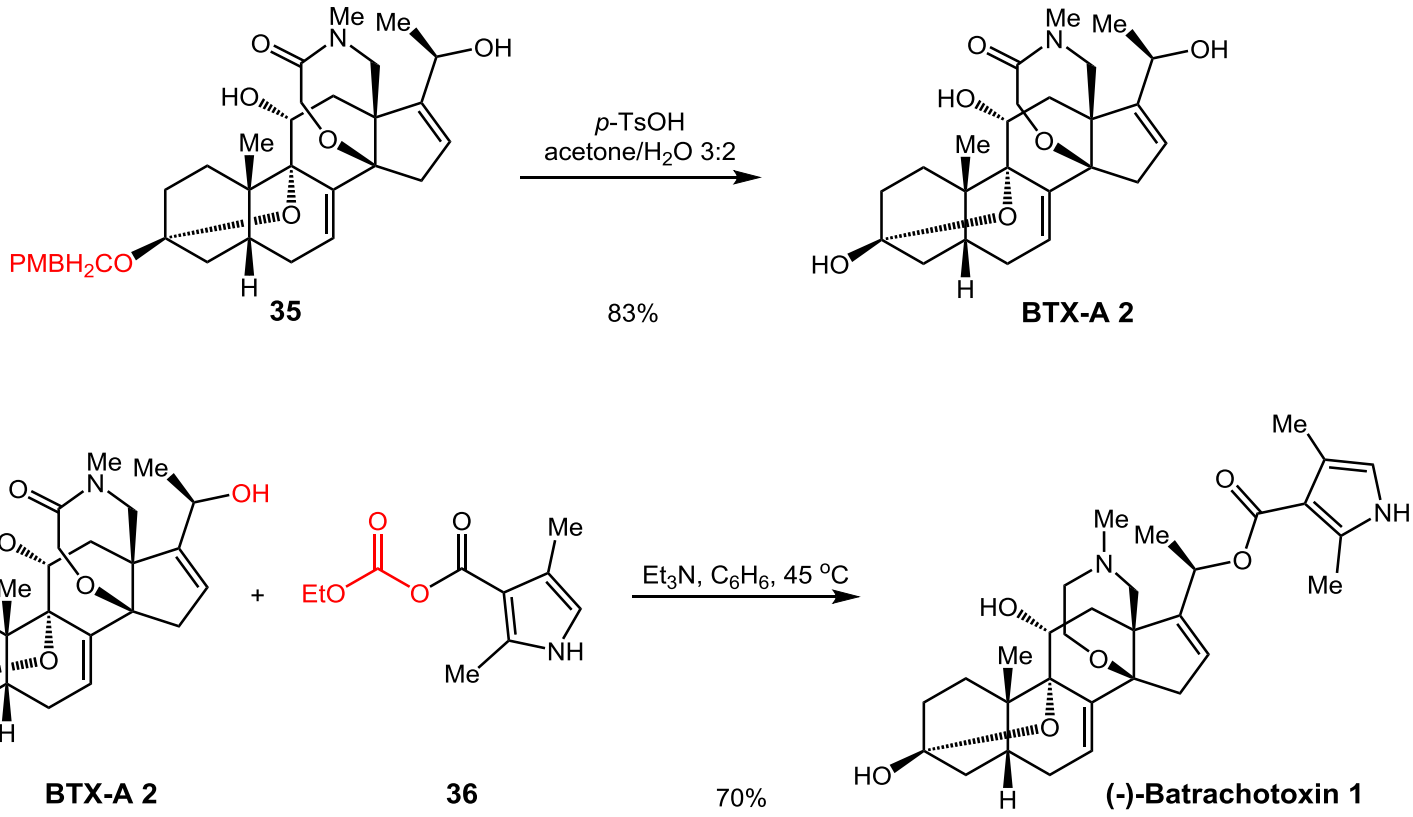
Construction of building block 29



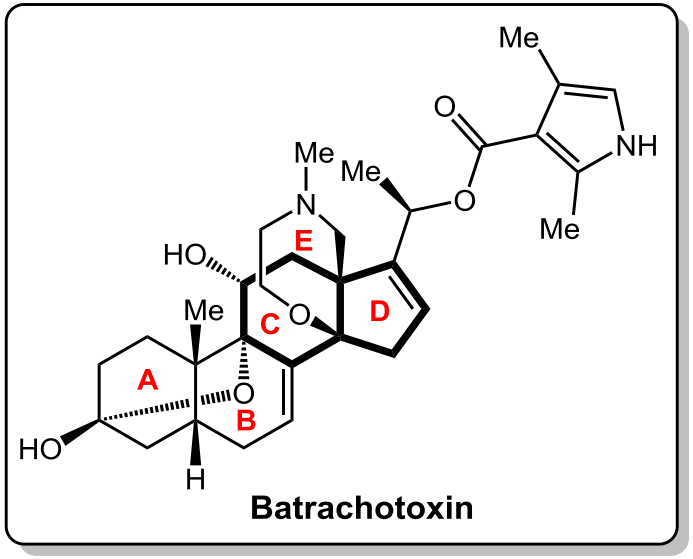
Construction of building block 35



Completion of synthesis of Batrachotoxin



Summary



Batrachotoxin

Kishi's work

[I] Racemic formal synthesis, 40 steps

[II] [4+2] Cycloaddition for constructing C&D rings

[III] Intramolecular oxa-Michael addition for E ring

Du Bois's work

[I] Asymmetric total synthesis, 26 steps

[II] Radical cascade for constructing C&D rings

[III] Intramolecular S_N2 reaction for E ring

The phenotypic effects of acute poisons found among the rich pharmacopeia of terrestrial and marine life have been documented from antiquity. Isolation and characterization of toxic compounds have made available important chemical reagents for studying complex biochemical circuits. Studies of this type have revealed a large number of peptide and small molecule agents that target voltage-gated sodium ion channels (Na_Vs), an obligatory class of membrane proteins for bioelectrical signaling. Among the collection of known Na_V modulators are three structurally related agents, (−)-batrachotoxin, veratridine, and aconitine, sterically large, lipophilic amine derivatives believed to share a common binding locus in the inner pore region of Na_V.

The influence of these toxins on ion gating, however, differs distinctly. On one extreme, (−)-BTX, the primary toxic constituent of Colombian poison dart frogs, is a full Na_V agonist, causing the channel to open more readily at hyperpolarized membrane potentials and blocking fast inactivation. Conversely, the activities of veratridine and aconitine are best described as partial agonism and inhibition of channel function, respectively. Despite recent insights from structural biology into the three-dimensional architecture of prokaryotic Na_V, a molecular understanding of the influence of the site toxins on ion conduction and ion gating kinetics is lacking.

Toxin structure-activity studies, in combination with protein mutagenesis experiments, can address questions related to the dynamical nature of channel function and may guide the rational design of small-molecule modulators of Na_V activity. The potency of (–)-BTX, its storied history as the archetypal small-molecule site probe, and its unparalleled effects on channel gating render it an optimal “lead” compound for such investigations.