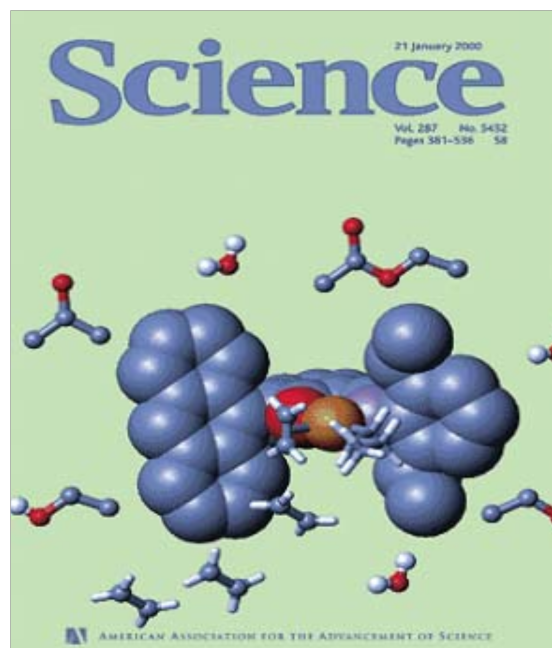
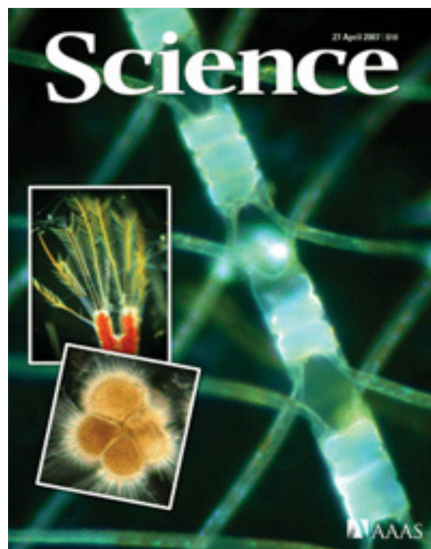


# Syntheses Published in *Science* from 2001-2010 and Why They Made It In



MacMillan Group Meeting  
12-08-2010  
Chris Jamison

# What Makes a Synthesis Paper Important?

## The Synthesis

New Reaction Methodology

New Application of Old Chemistry  
to Make a Complex Motif  
in a Novel Way

## The Molecule

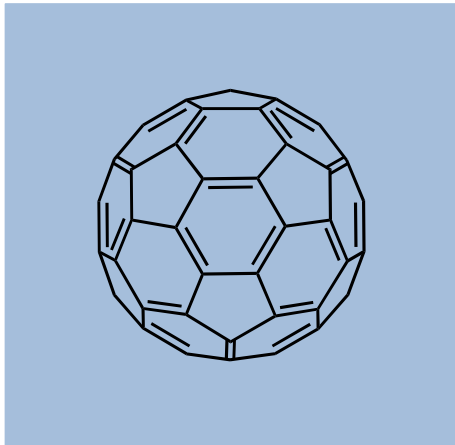
Important Material or  
Pharmacological Properties

Structurally Profound

## Both

The Synthesis Can Actually Produce  
an Important Molecule on Large Scale

# Buckminsterfullerene



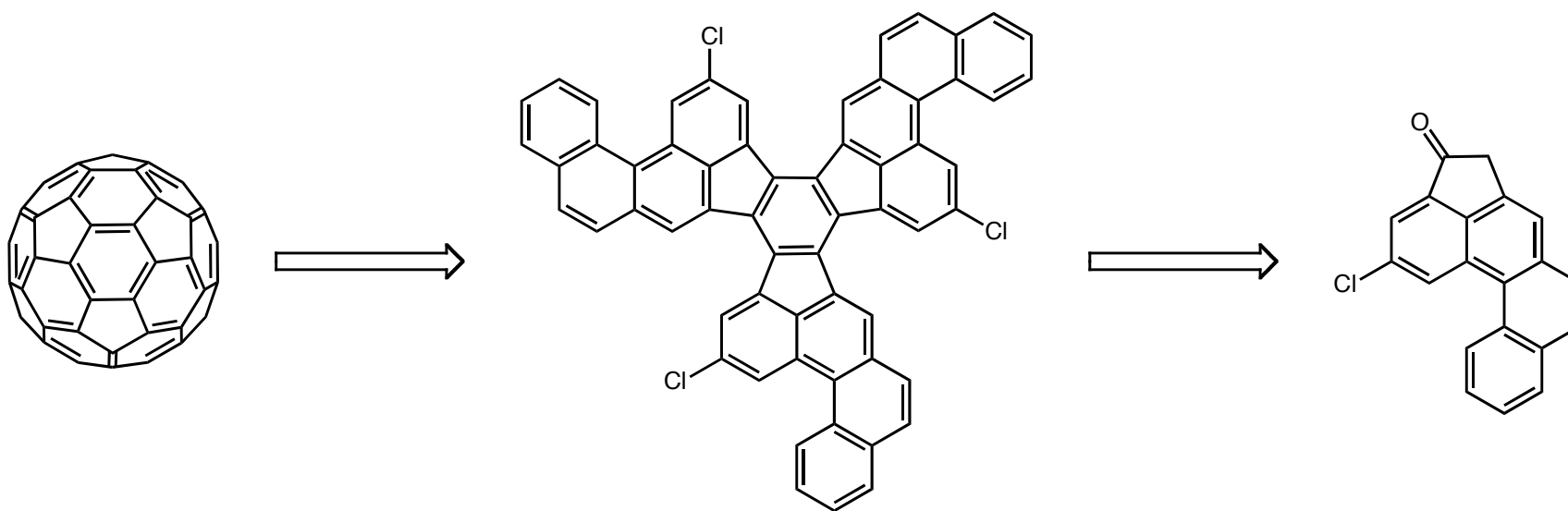
First observed in 1985 via laser vaporization of graphite,<sup>2</sup> which led to the 1996 Nobel Prize in Chemistry

Isolated and fully characterized in 1990 via resistive heating of graphite electrodes<sup>3</sup>

Global annual industrial production by such empirical synthetic methods exceeds 40 metric tons<sup>4</sup>

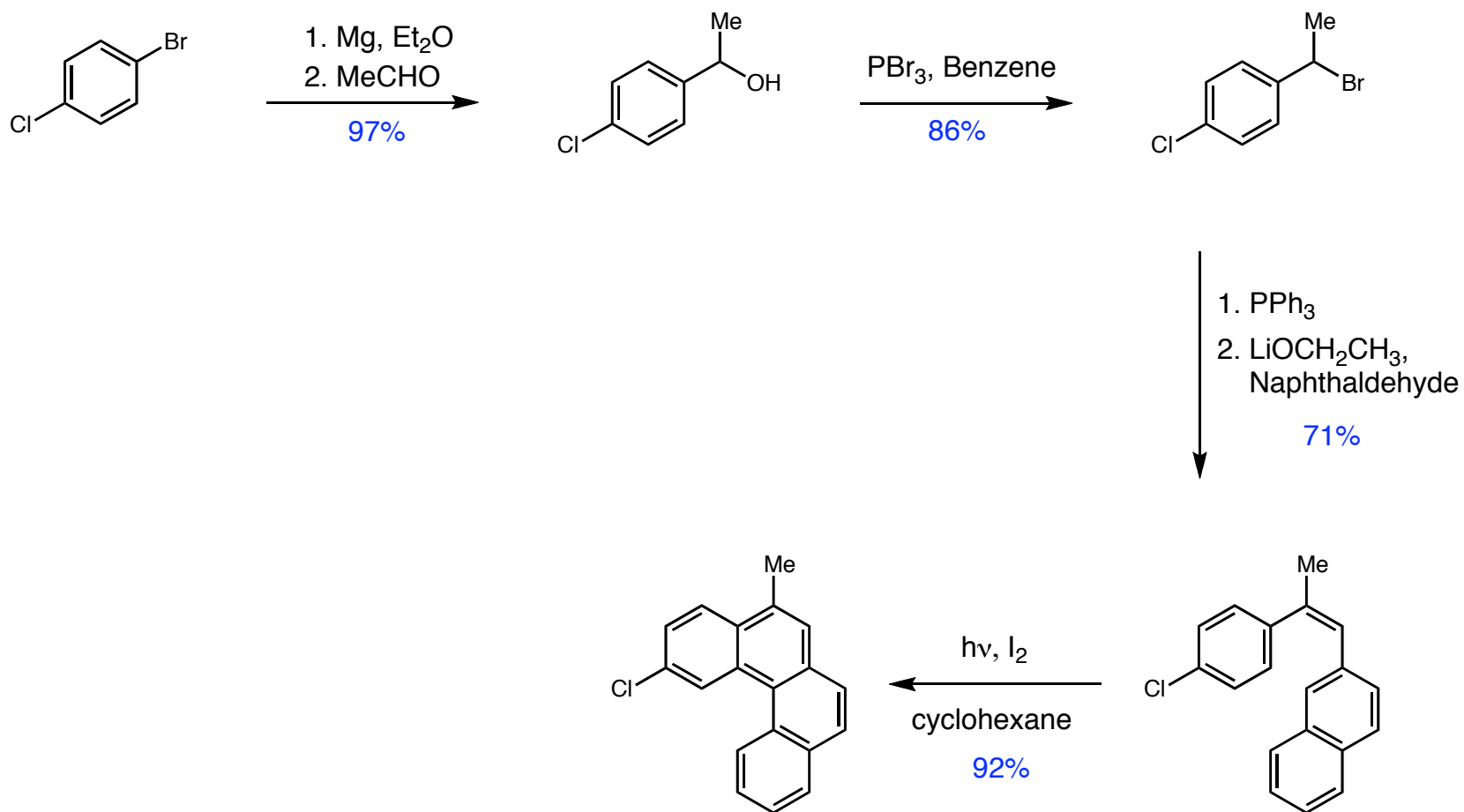
1. Scott, L. *et al. Science*, **2002**, 295, 1500 – 5003
2. Kroto, H. *et al. Nature*, **1985**, 318, 162-163
3. Kratschmer, W. *et al. Nature*, **1990**, 347, 354-358
4. Scott, L. *Angew. Chem. Int. Ed.* **2004**, 43, 4994

## Buckminsterfullerene Retrosynthetic Analysis

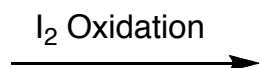
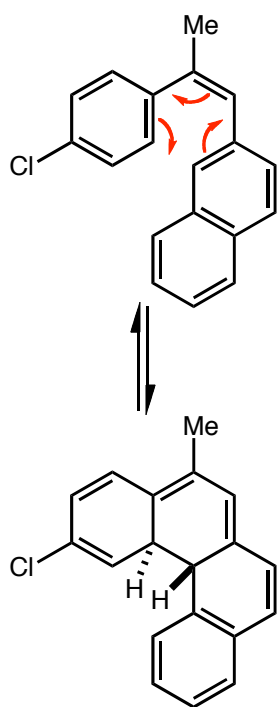
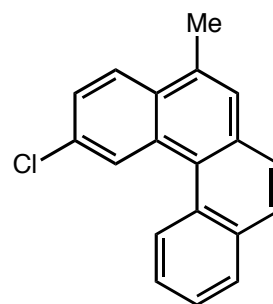
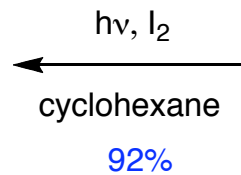
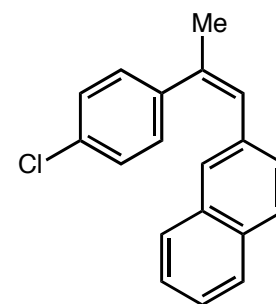
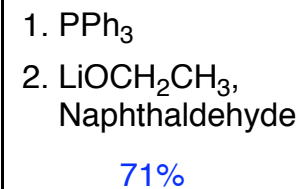
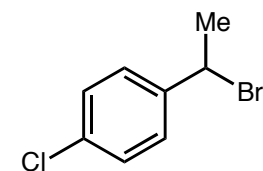
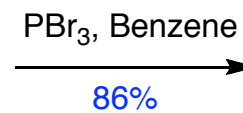
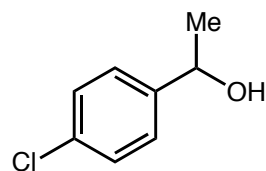
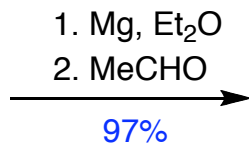
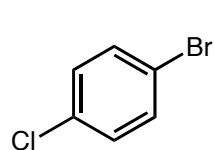




## Synthesis of the Chlorinated Monomer

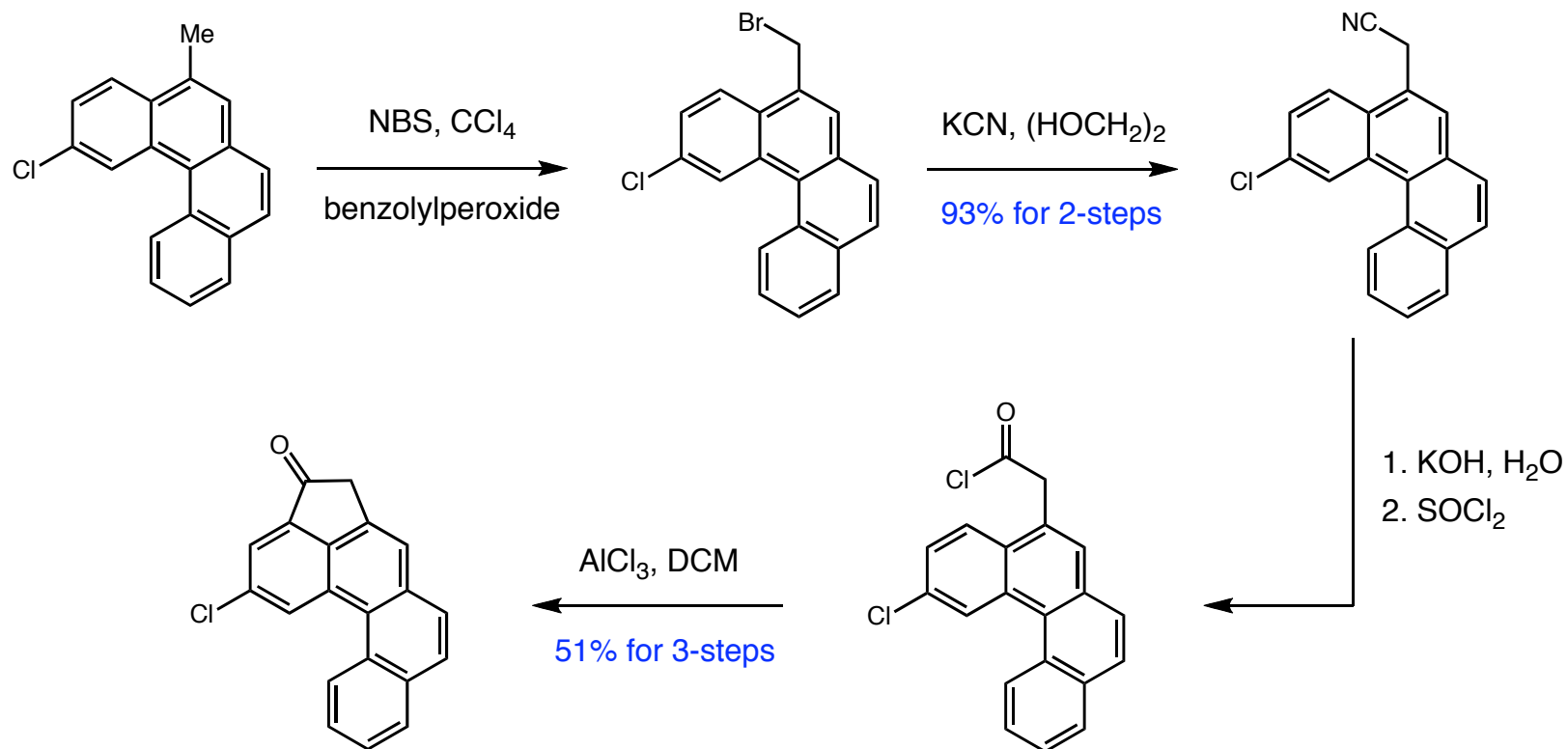


## Synthesis of the Chlorinated Monomer

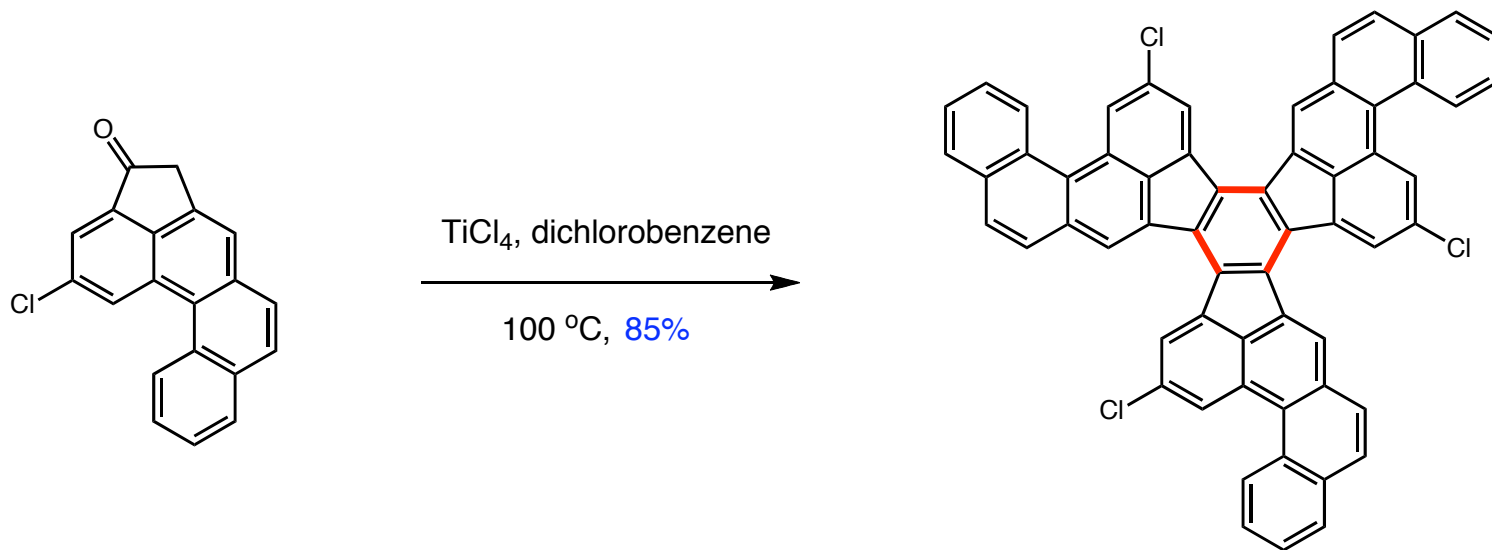


**STILBENE PHOTOCYCLIZATION**  
6π photochemical electrocyclization

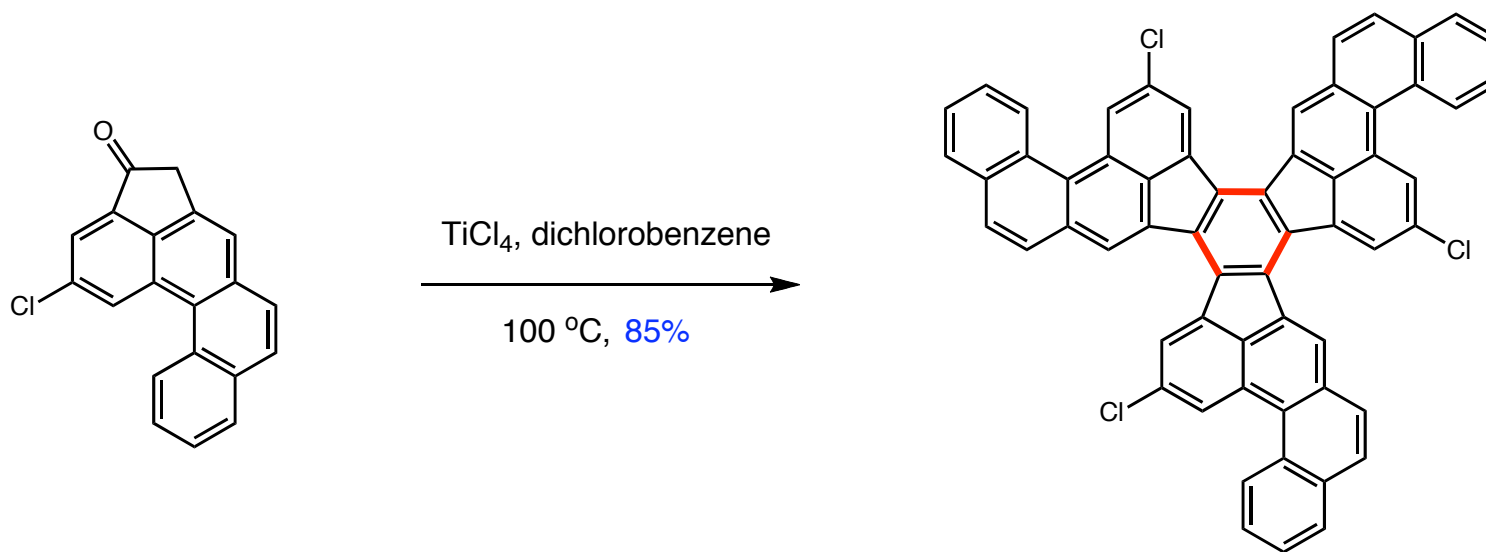
## Synthesis of the Chlorinated Monomer



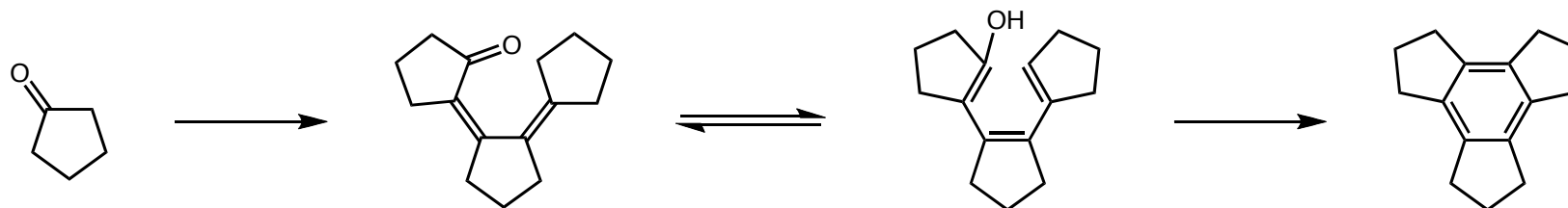
## Syntheses of the Trimer by Aldol Cyclotrimerization



## Syntheses of the Trimer by Aldol Cyclotrimerization

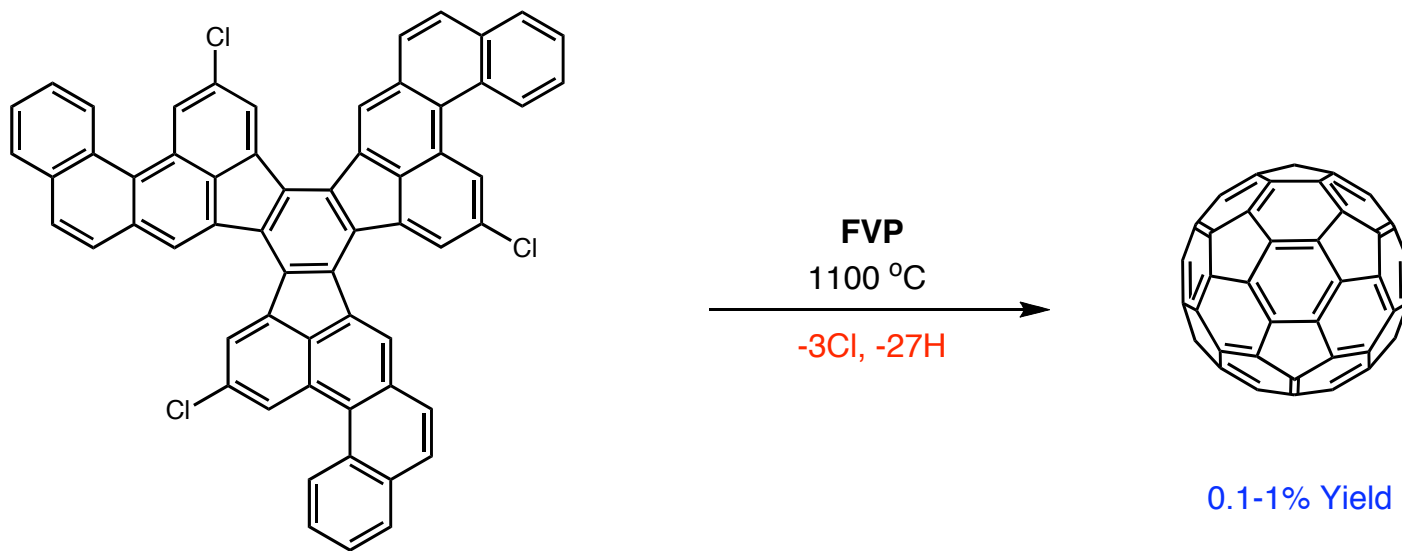


### The Aldol Cyclotrimerization Reaction<sup>1</sup>

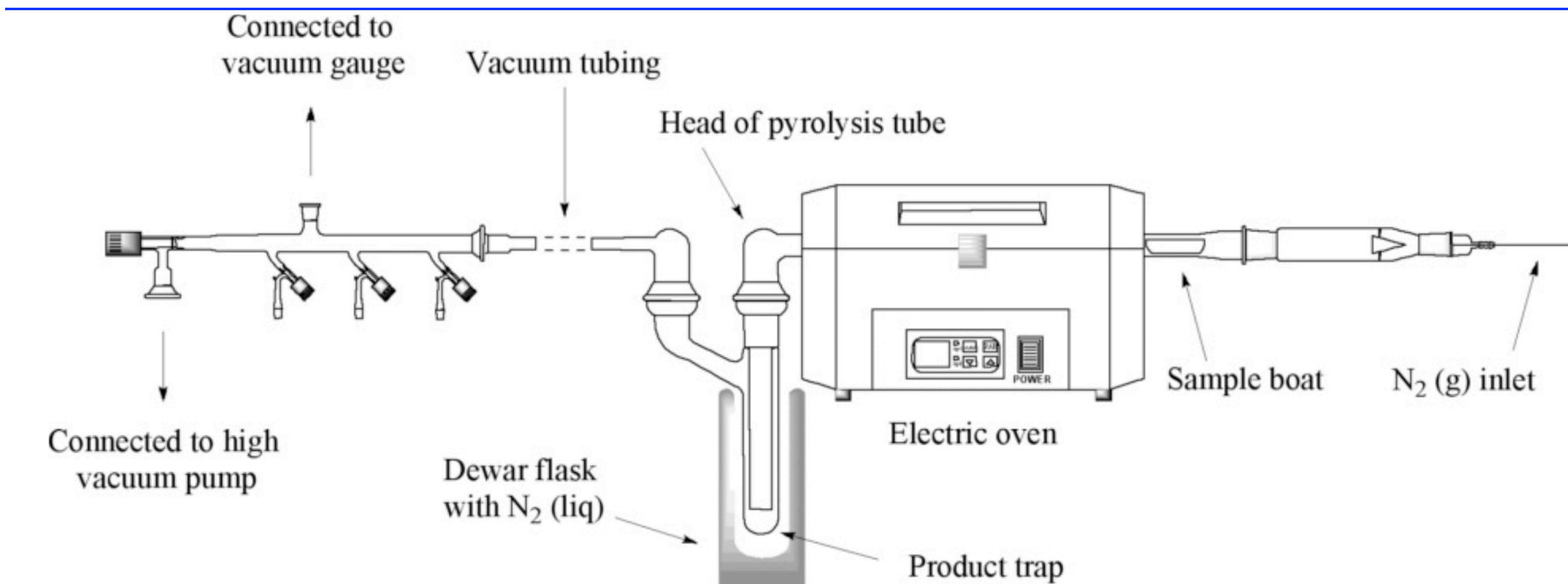


1. Amick, A.; Scott, L. *J. Org. Chem.* **2007**, 72, 3412

## "Stitching Together" the Fullerene by Flash Vacuum Pyrolysis



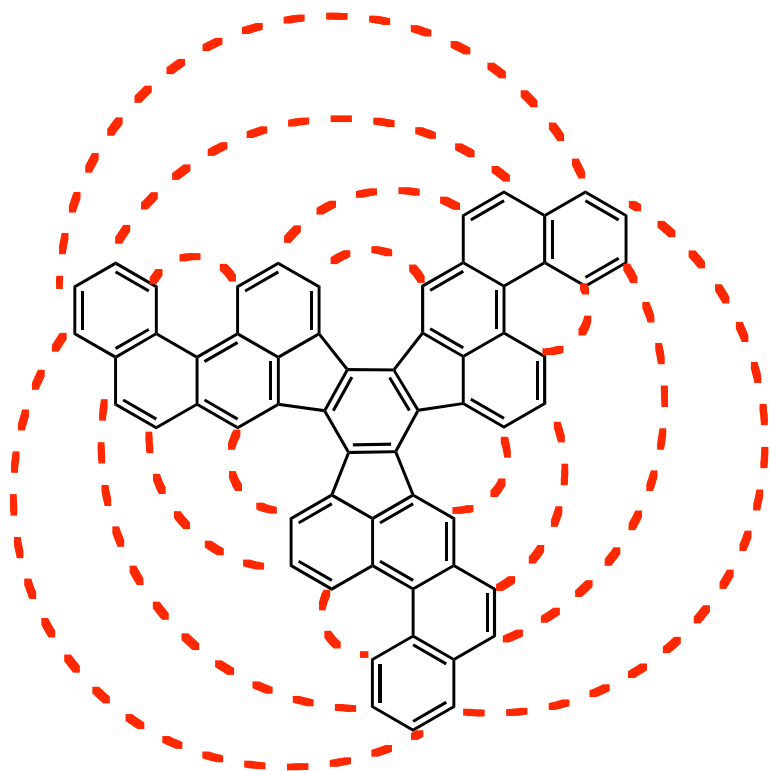
## Flash Vacuum Pyrolysis



Gas phase reaction minimizes bimolecular pathways

High temperature accentuates the entropic contribution to  $\Delta G_{\text{rxn}}$

## Buckminsterfullerene



15 new C-C bonds

>60% yield per bond formation

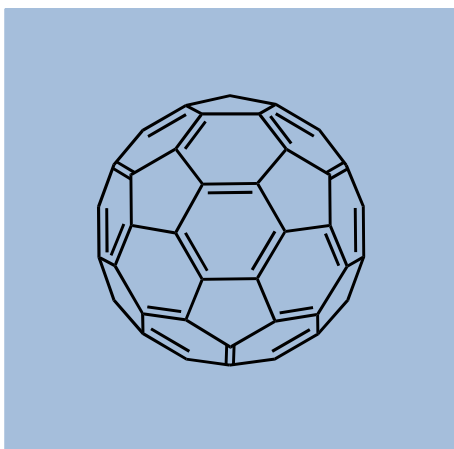
16 new rings formed

~600 kcal/mol strain introduced<sup>1</sup>

1. Scott, L. *Angew. Chem. Int. Ed.* **2004**, 43, 4994 – 5007



## Why is this a Science Paper?



Not a preparatively useful way to make C60

No new chemical reactivity demonstrated

Buckminsterfullerene is a celebrity molecule at the height of its popularity during the disclosure of this synthesis

This demonstrates the feasibility of **rationally** synthesizing large fullerenes, which lays the groundwork for constructing novel fullerenes with superior material properties.

# Buckminsterfullerene

## The Synthesis

New Reaction Methodology

New Application of Old Chemistry  
to Make a Complex Motif  
in a Novel Way

## The Molecule

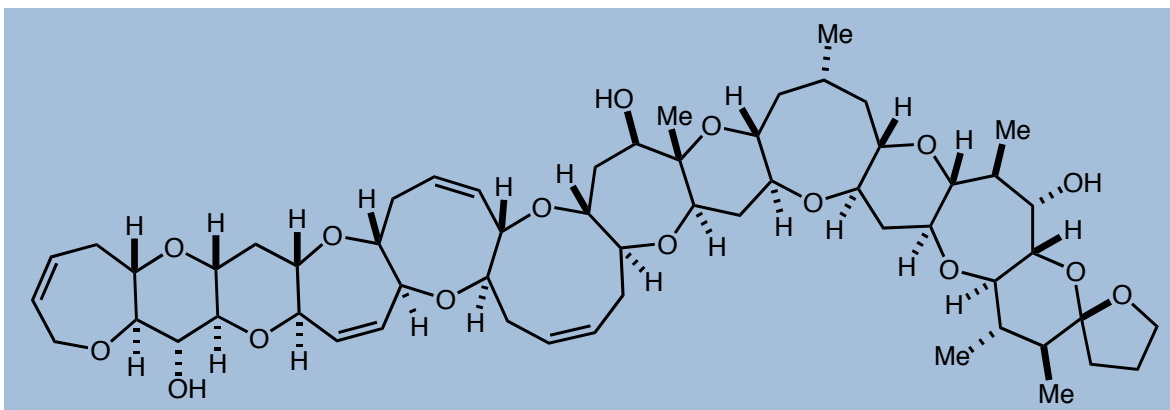
Important Material or  
Pharmacological Properties

Structurally Profound

## Both

The Synthesis Can Actually Produce  
an Important Molecule on Large Scale

## Ciguatoxin CTX3C



Structure elucidated in 1989 using sample from the marine dinoflagellate *Gambierdiscus toxicus*<sup>2</sup>

A ladderlike polyether with 30 stereocenters

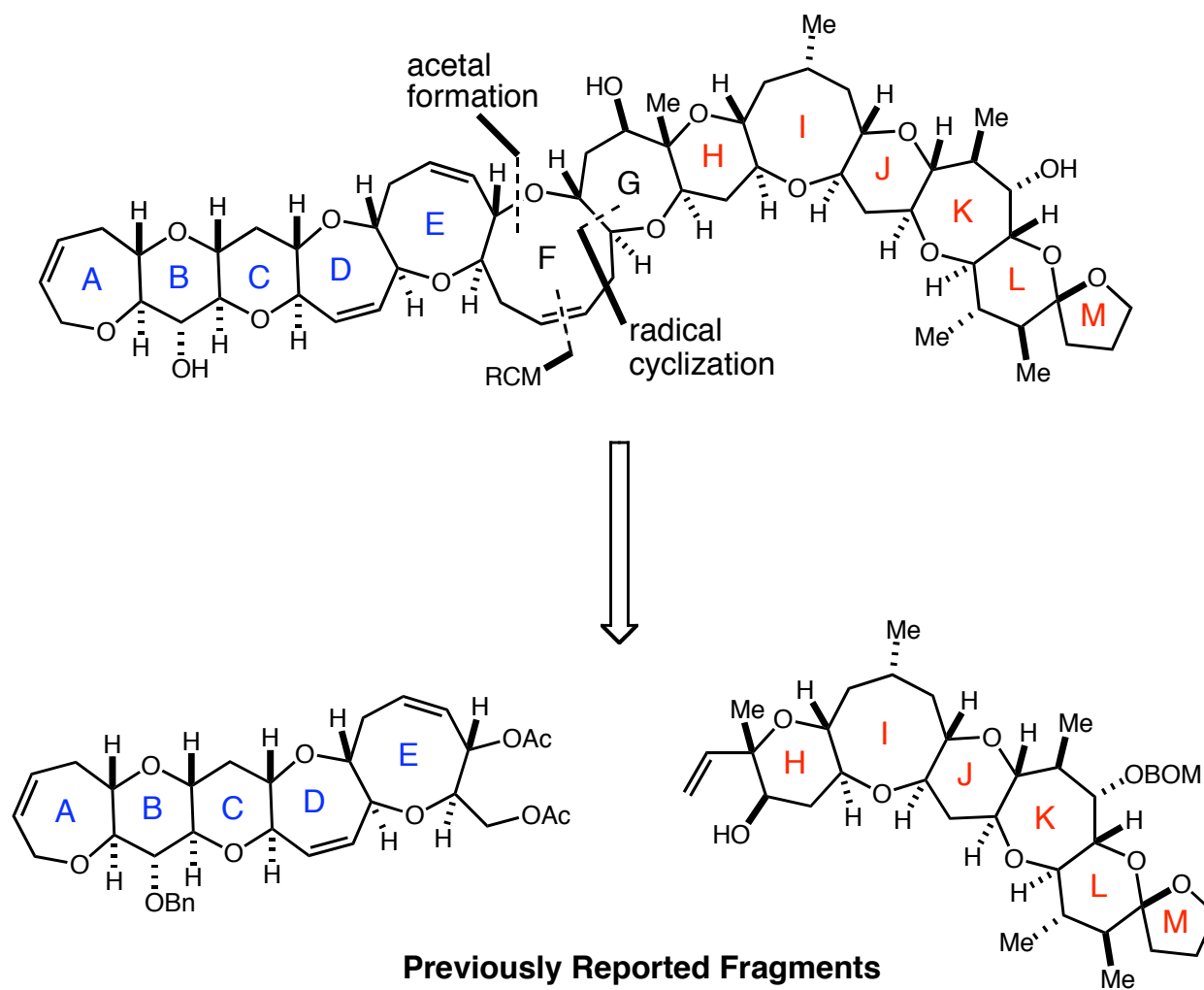
LD<sub>50</sub> = 0.25 μg/kg in mice. Compare to brevetoxins > 100 μg/kg.

20,000 people suffer annually from ciguatera from eating contaminated seafood

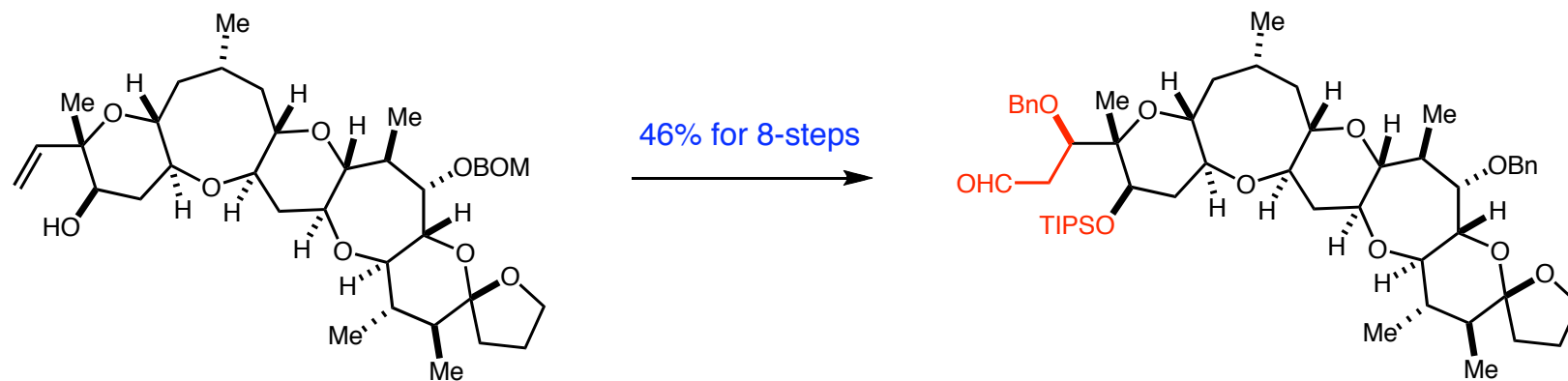
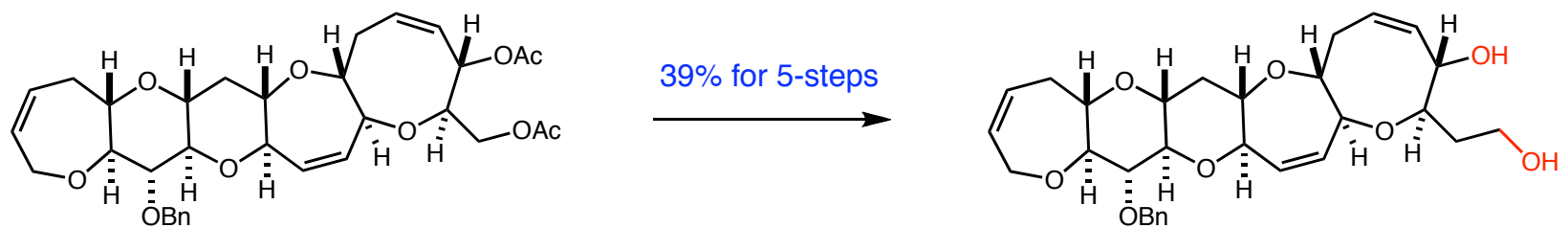
Low natural availability has hampered preparation of anti-ciguatoxin antibodies for detecting ciguatoxin contamination in fisheries

1. Hirama, M. *et al. Science*, **2001**, 294, 1904-1907
2. Murata, M. *et al. J. Am. Chem. Soc.*, **1989**, 111, 8929

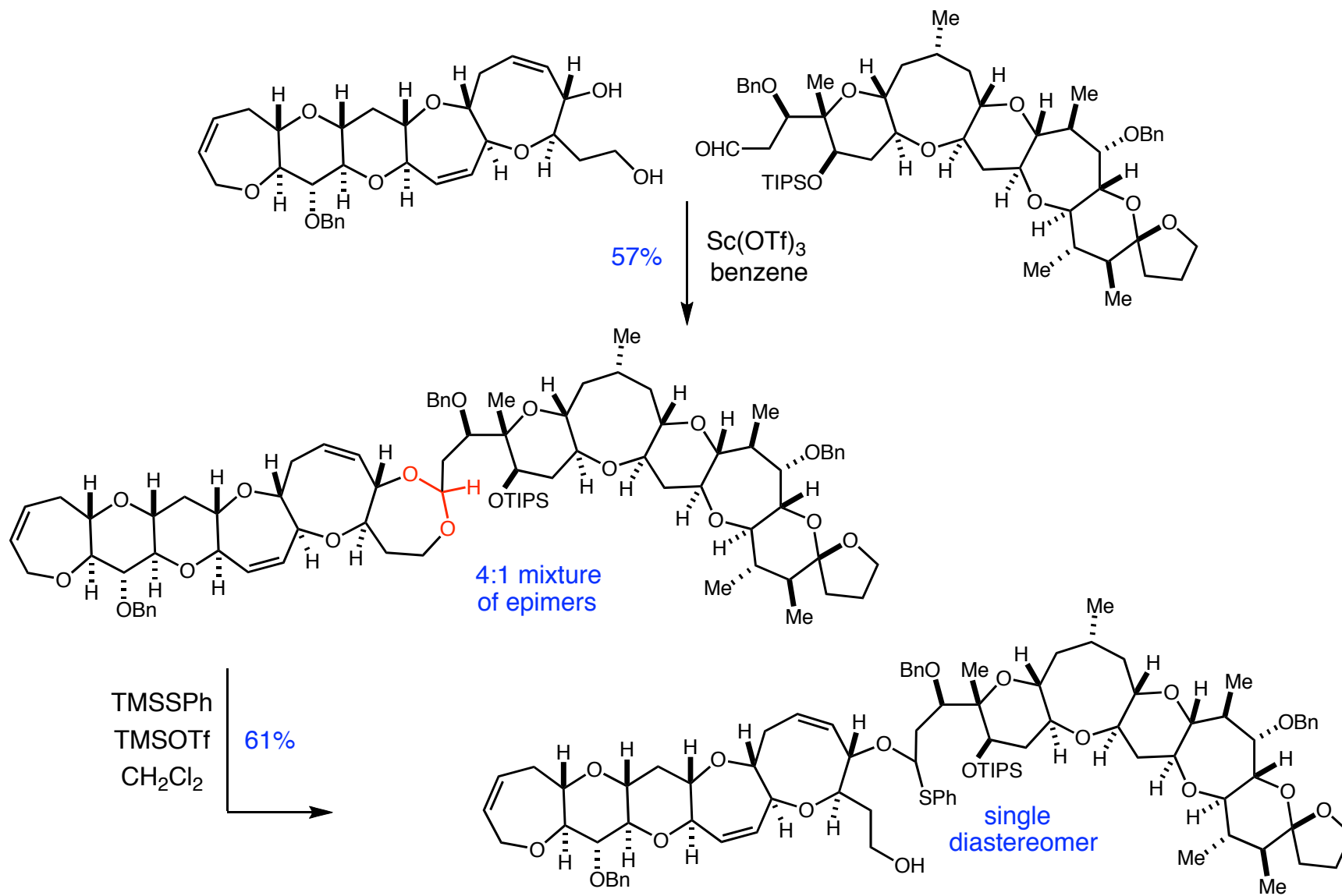
# Ciguatoxin CTX3C Retrosynthetic Analysis



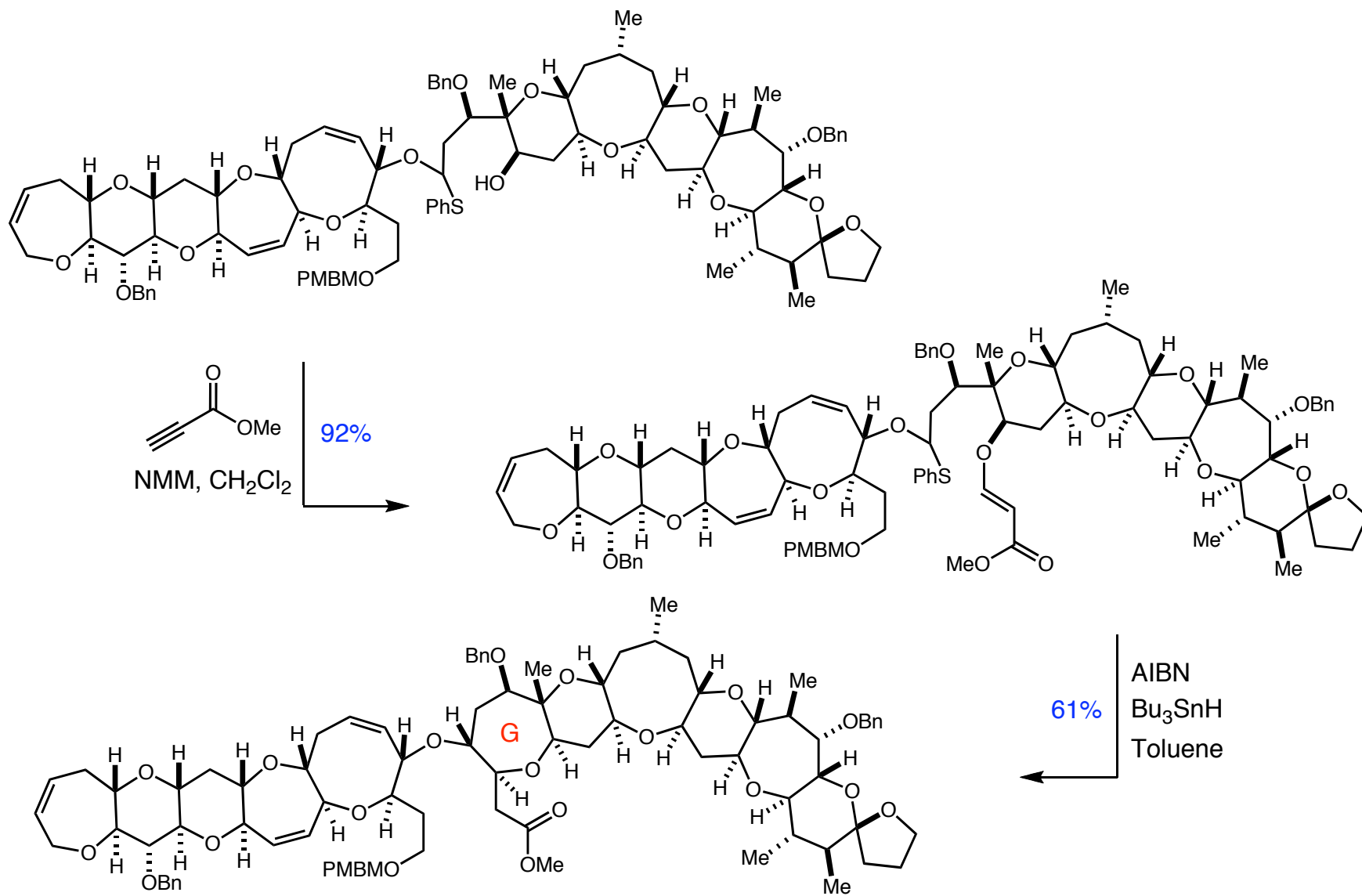
## Preparing the Fragments for Coupling



## Coupling the Fragments by Acetal Formation



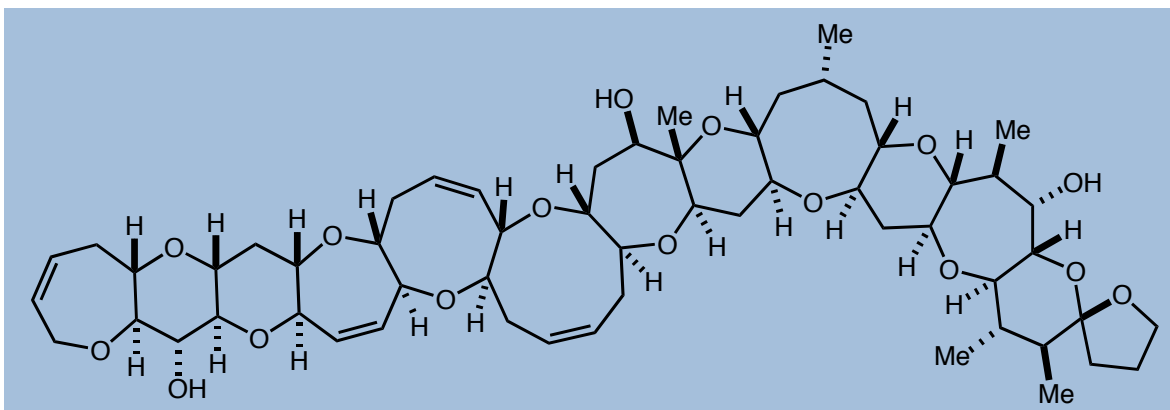
## Closing the 7-Membered G Ring by Radical Cyclization







## Why is This a Science Paper?



No new chemistry, but the RCM was impressive for its time

First synthesis of an incredibly complex natural product

Material furnished from the study to be used for the preparation of anti-ciguatera antibodies

# Ciguatoxin CTX3C

## The Synthesis

New Reaction Methodology

New Application of Old Chemistry  
to Make a Complex Motif  
in a Novel Way

## The Molecule

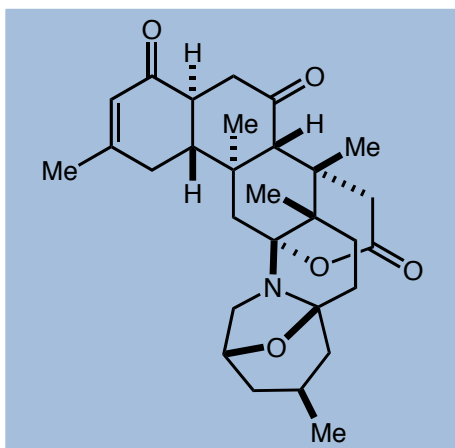
Important Material or  
Pharmacological Properties

Structurally Profound

## Both

The Synthesis Can Actually Produce  
an Important Molecule on Large Scale

## Norzoanthamine

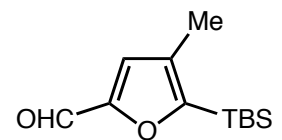
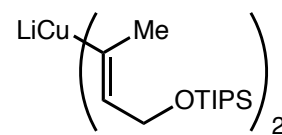
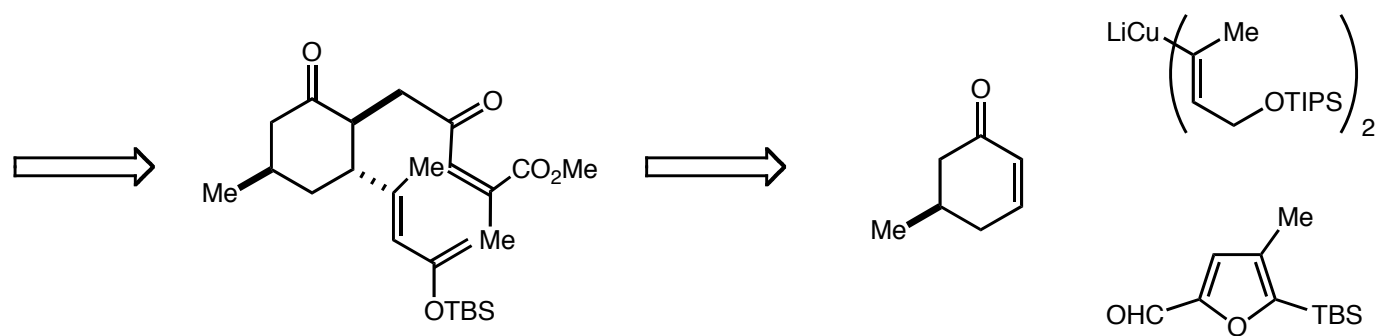
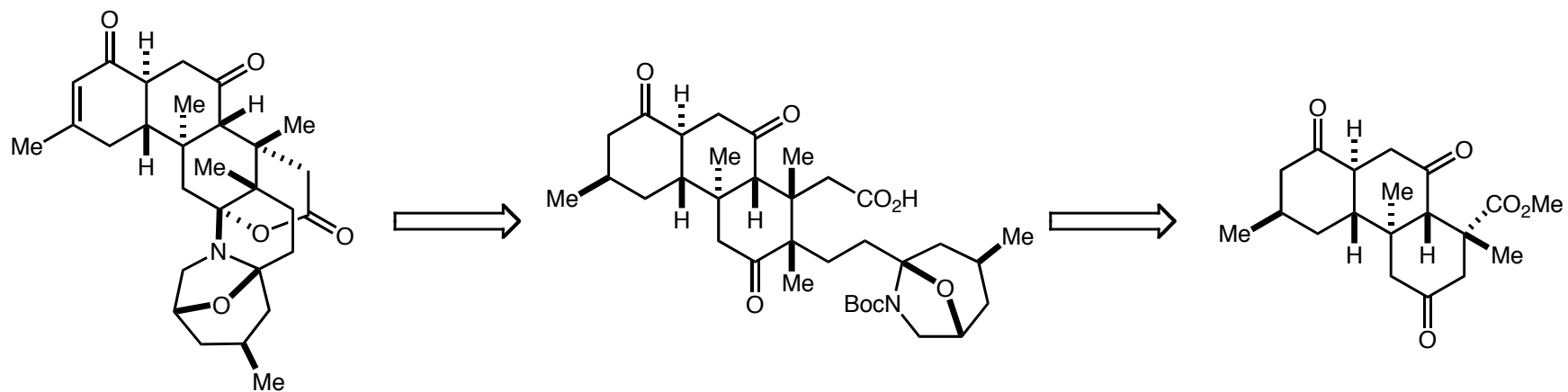


First isolated in 1995 from the zoanthids of the genus *Zoanthus*

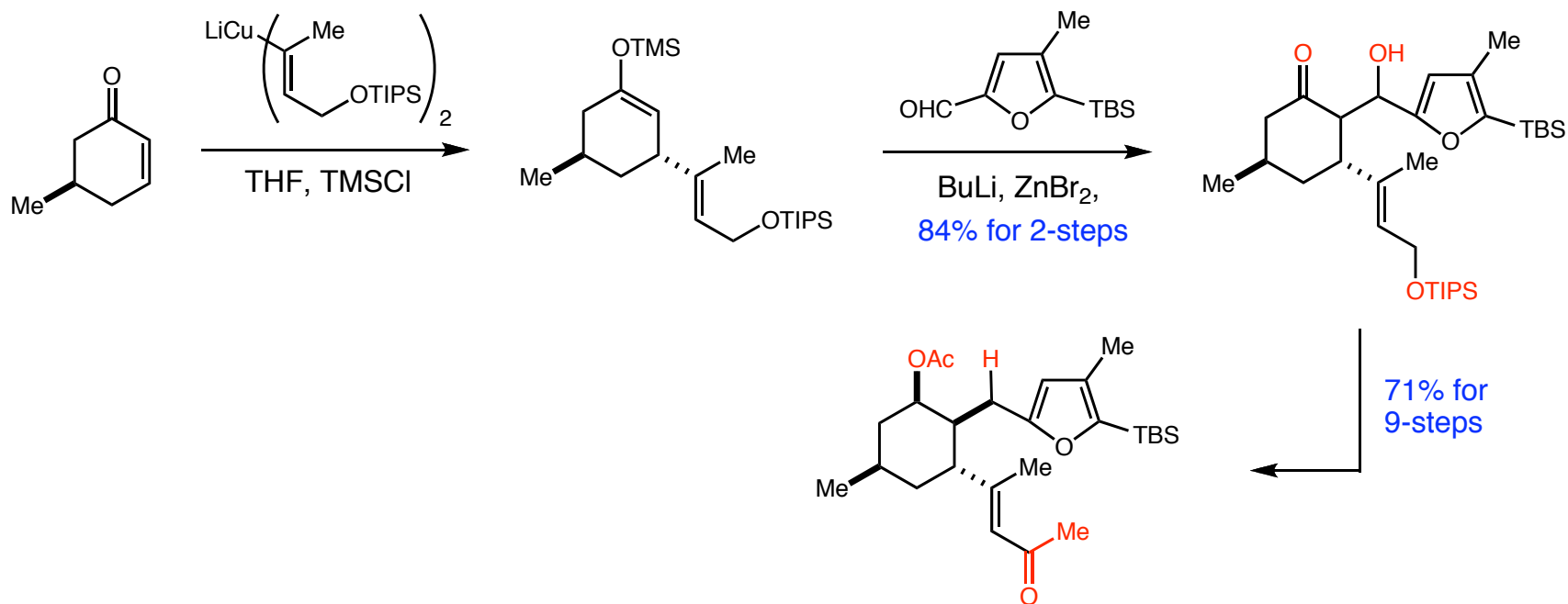
Inhibits the growth of P-388 murine leukemia cell lines and also demonstrates promising anti-osteoporotic activity in mice

Novel and stereochemically dense structure attracted attention from the synthetic community

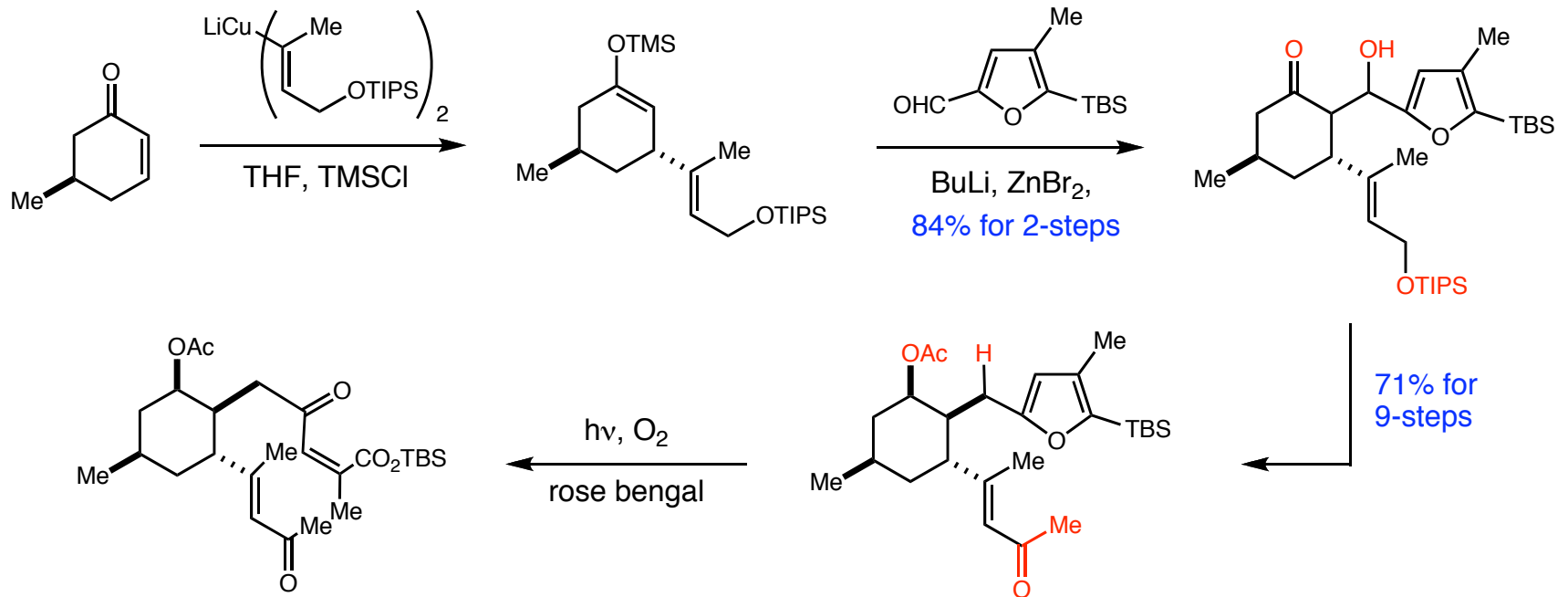
## Norzoanthamine Retrosynthetic Analysis



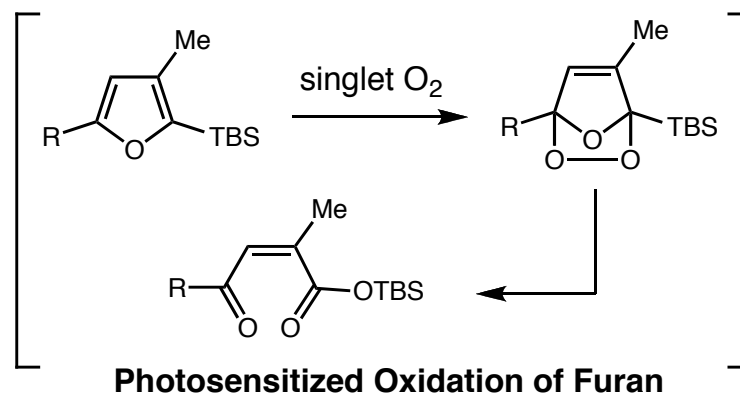
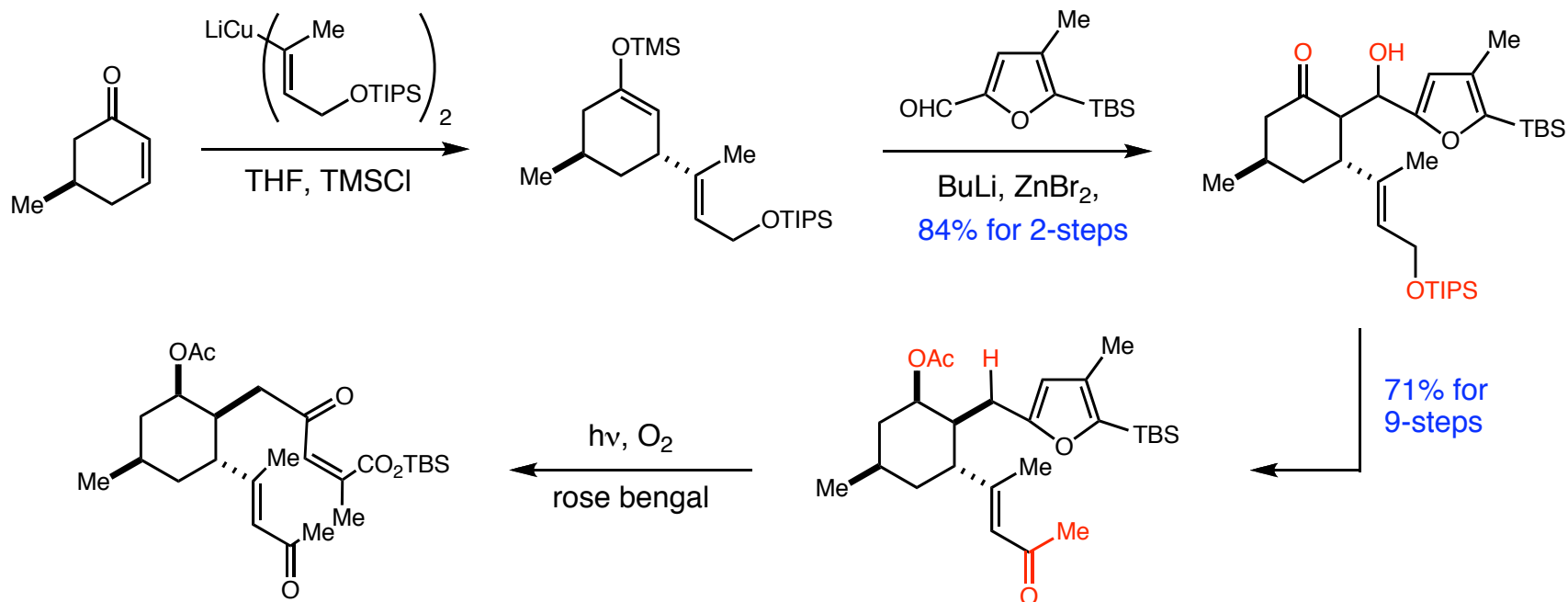
## Synthesis of the Diels-Alder Precursor



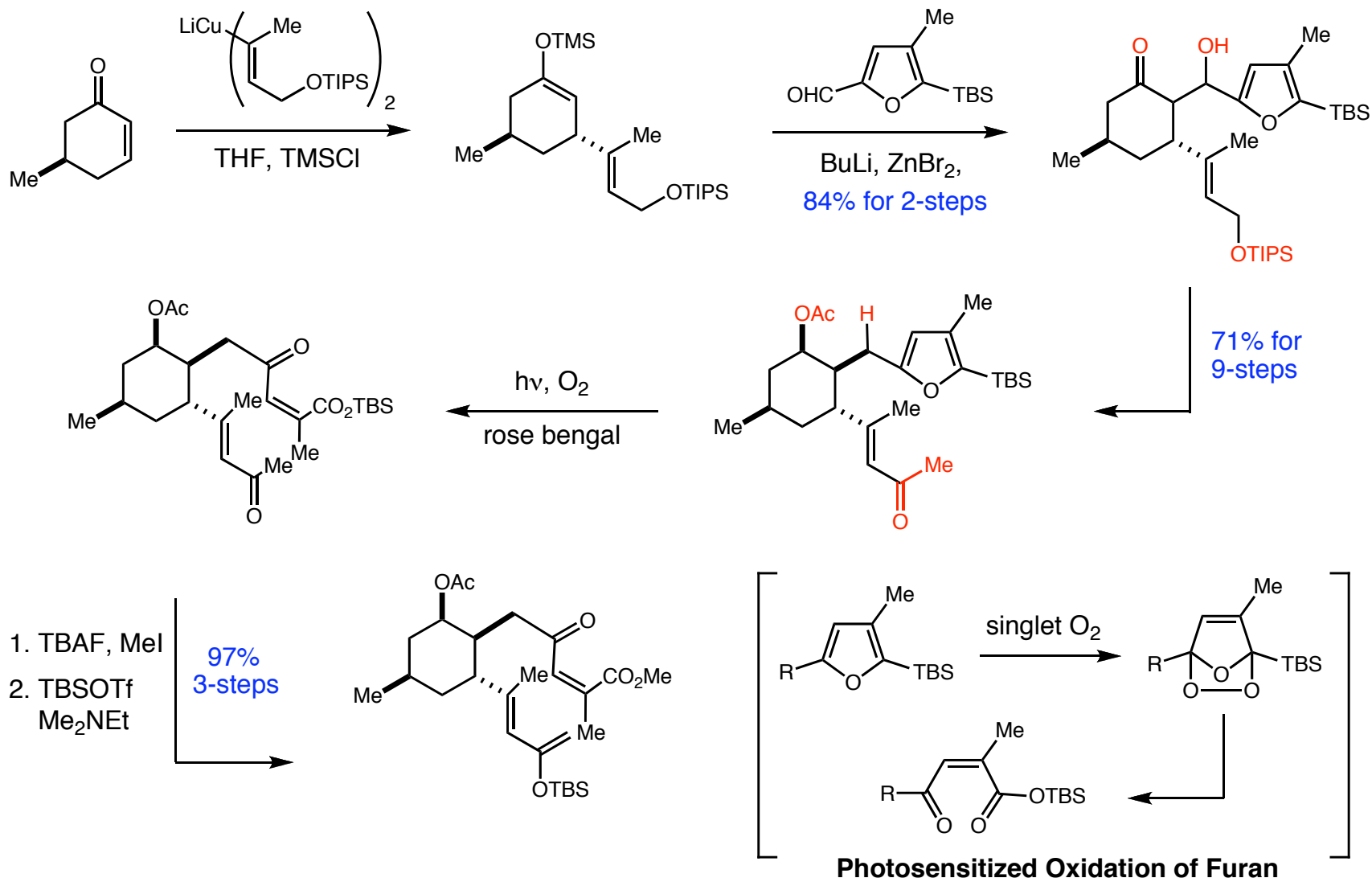
## Synthesis of the Diels-Alder Precursor



## Synthesis of the Diels-Alder Precursor

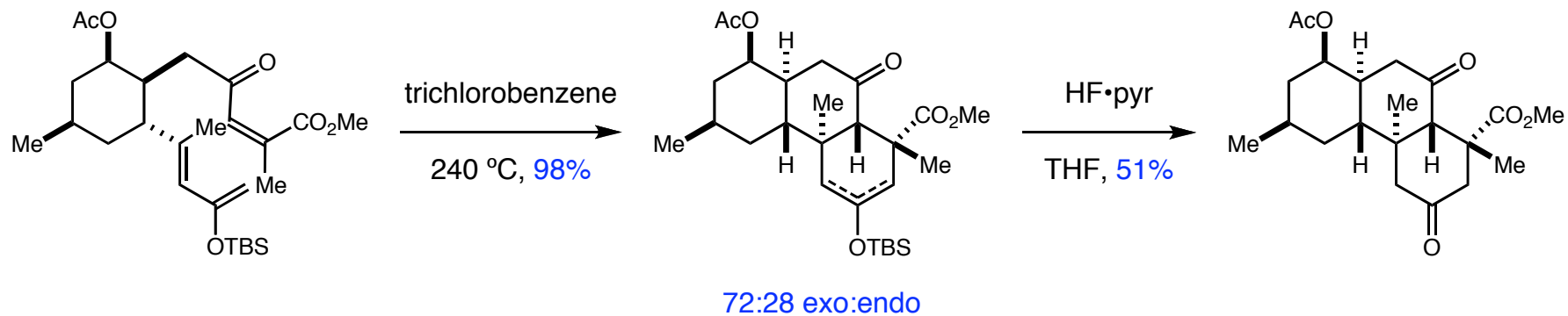


## Synthesis of the Diels-Alder Precursor

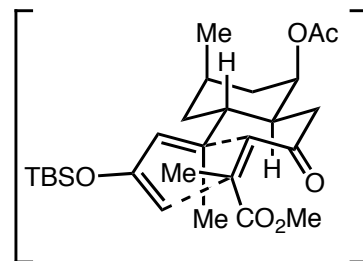




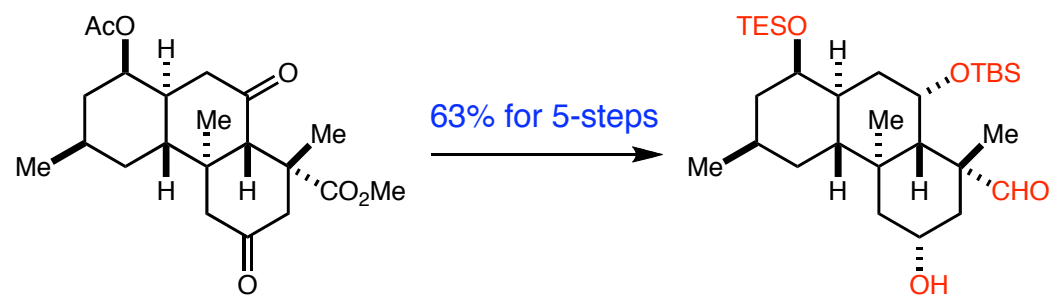
## Key Intramolecular exo-Diels-Alder



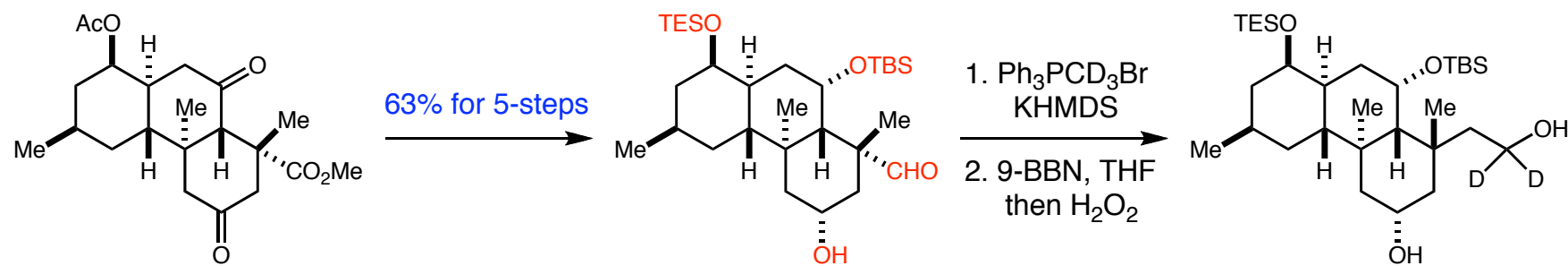
Exo-transition  
state



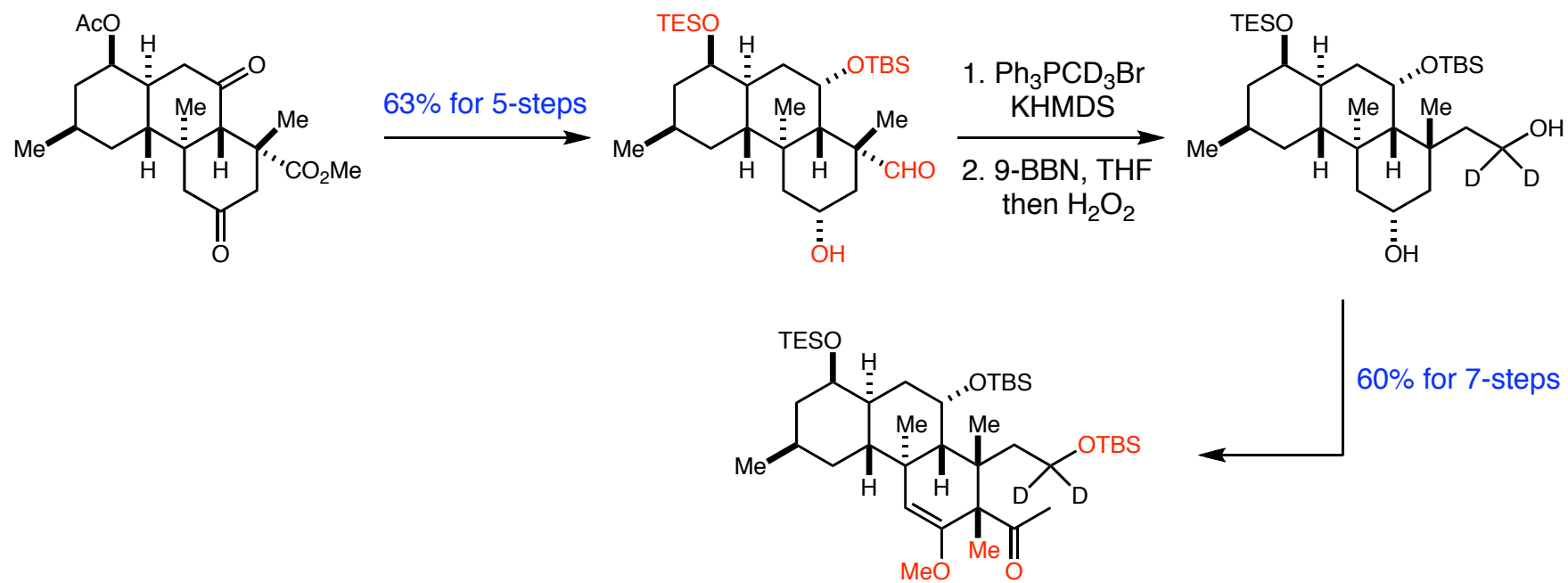
## Synthesis of the Alkyne Segment



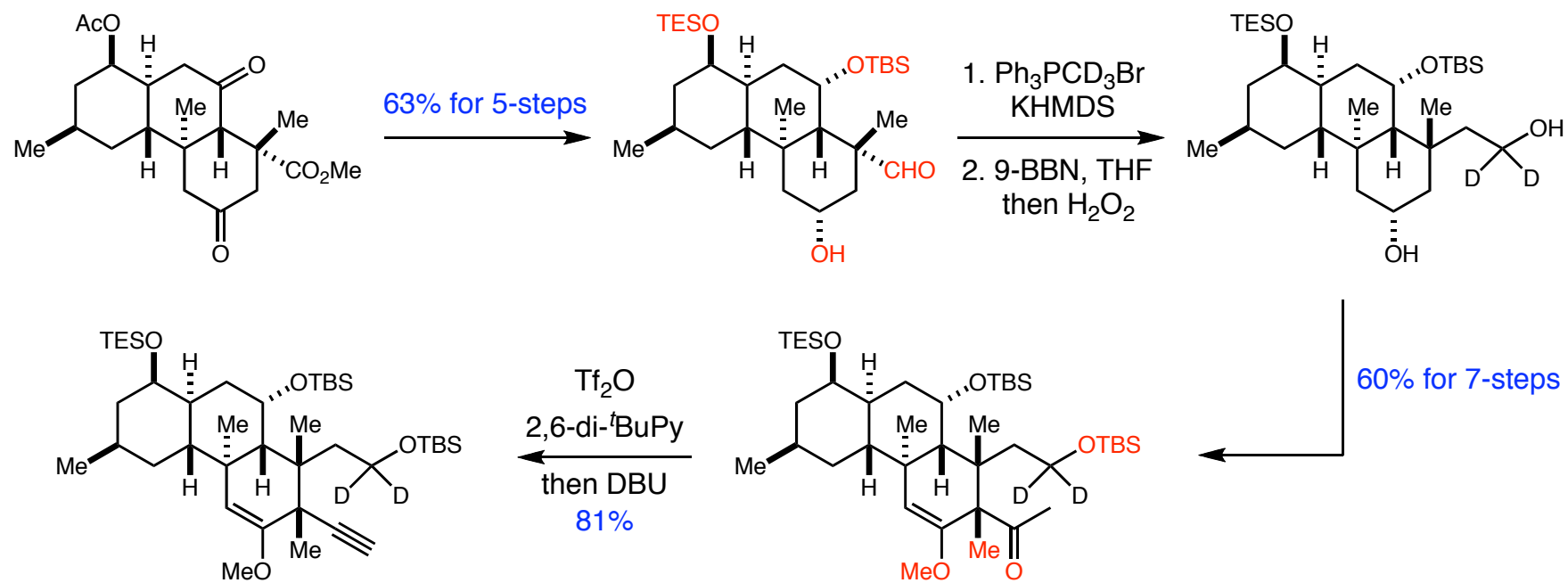
## Synthesis of the Alkyne Segment



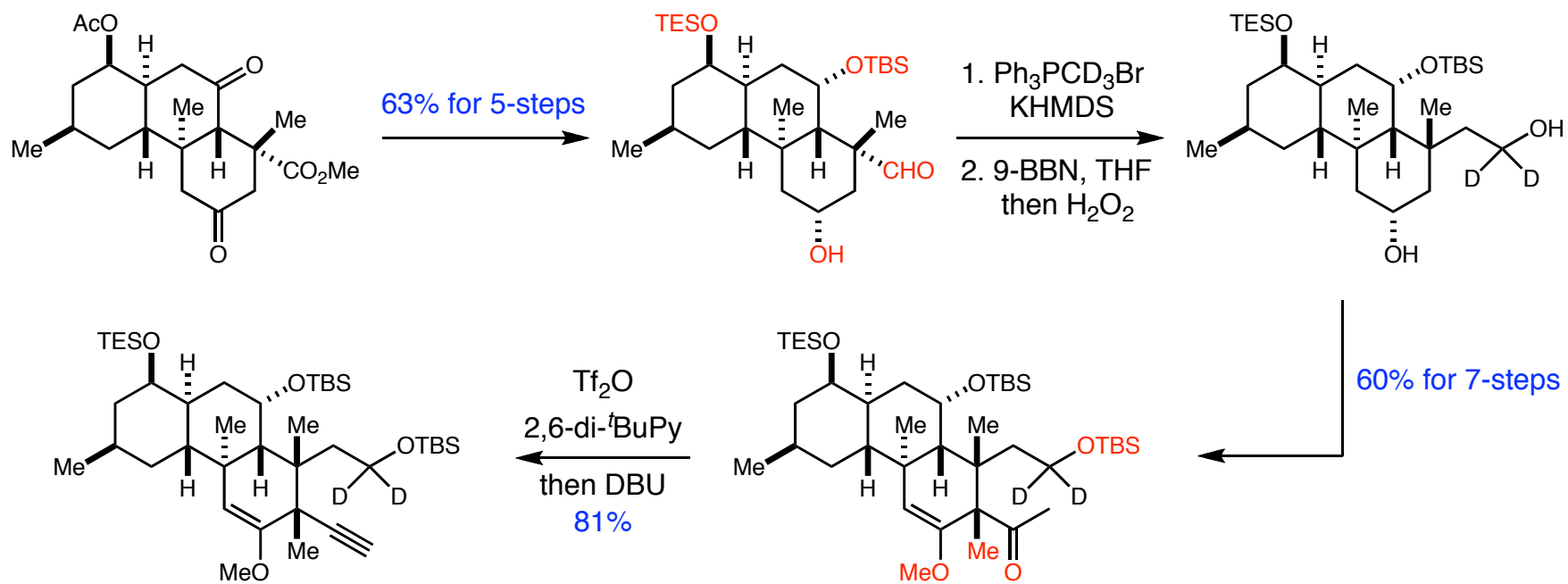
## Synthesis of the Alkyne Segment



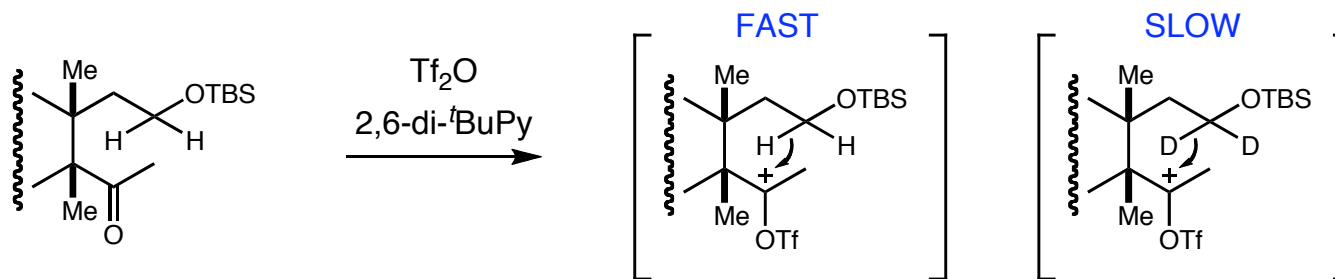
## Synthesis of the Alkyne Segment



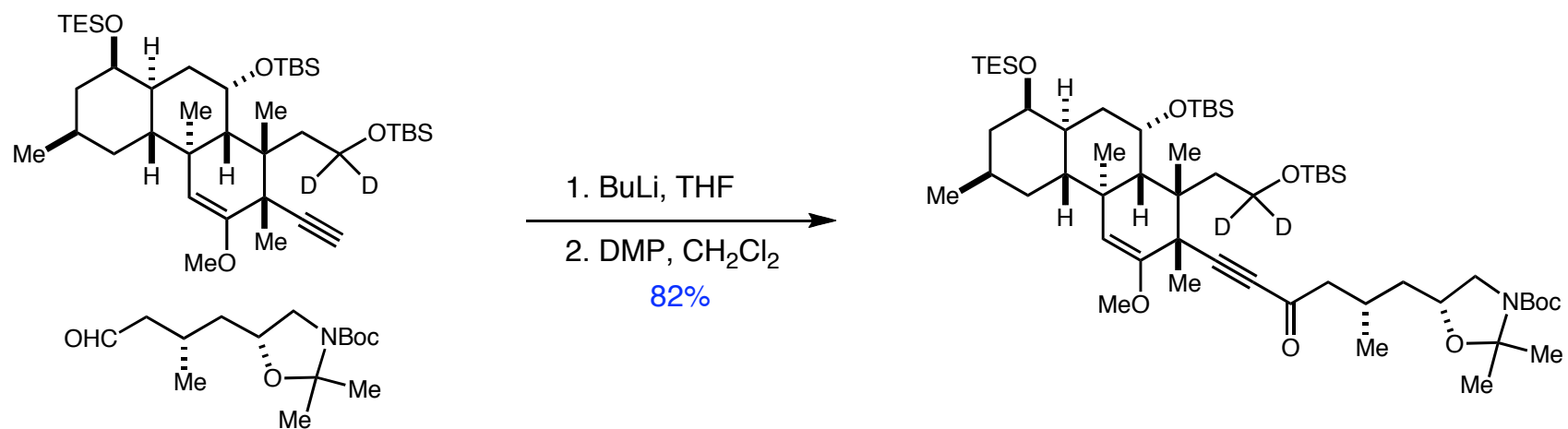
## Synthesis of the Alkyne Segment



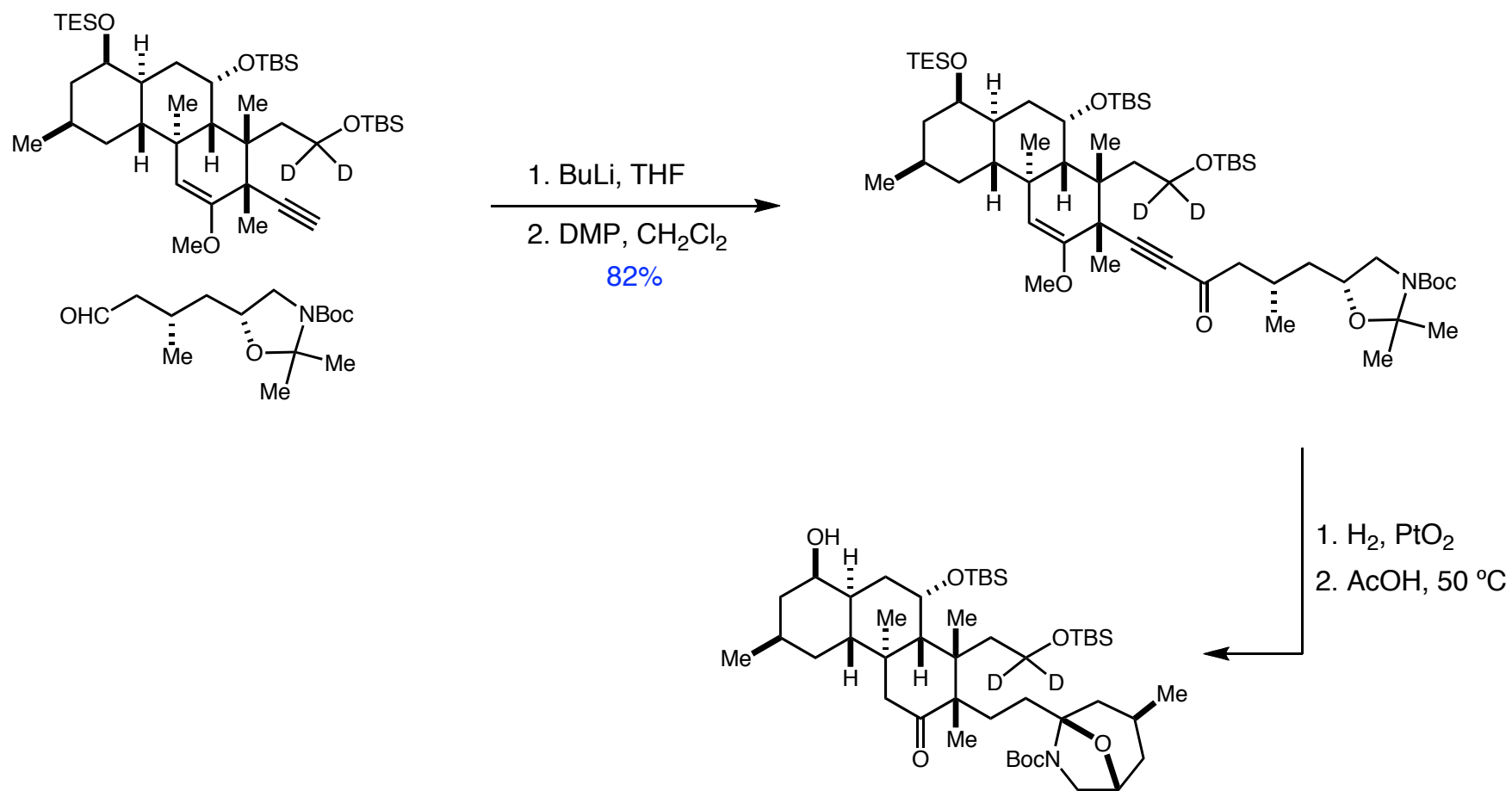
### Kinetic Isotope Effect Exploited to Prevent 1,5-hydride Shift



## Forming the Aminoacetal and Removing the Deuterium

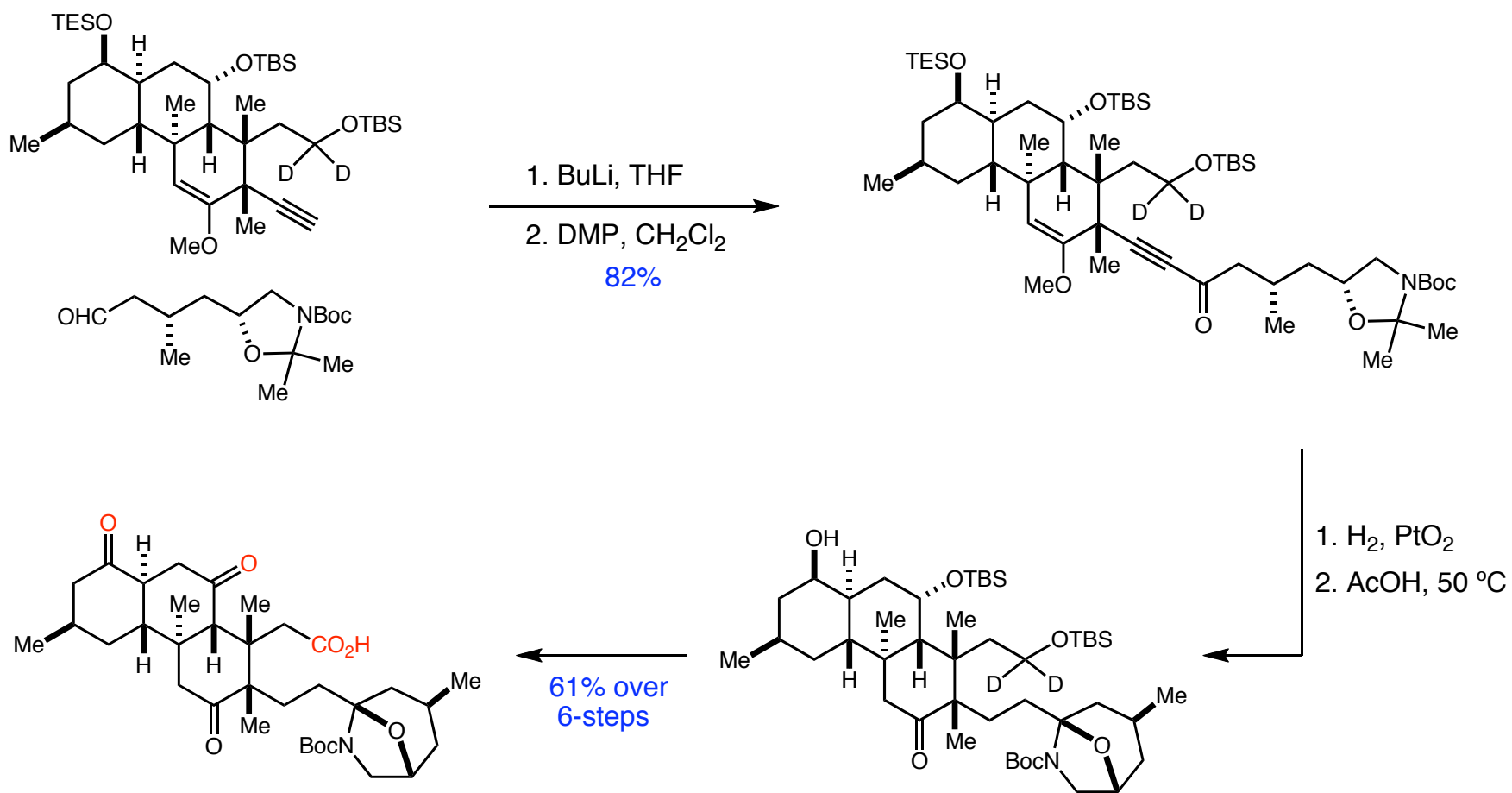


## Forming the Aminoacetal and Removing the Deuterium



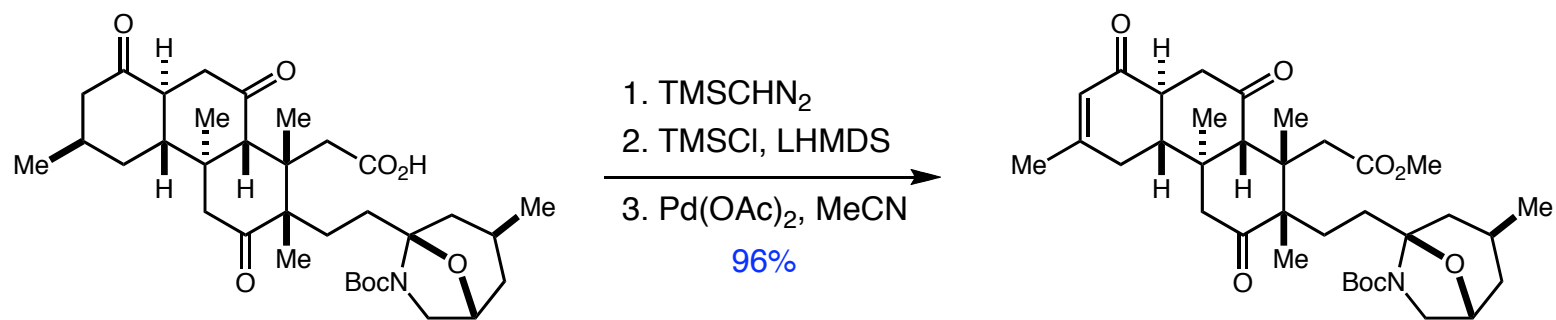


## Forming the Aminoacetal and Removing the Deuterium

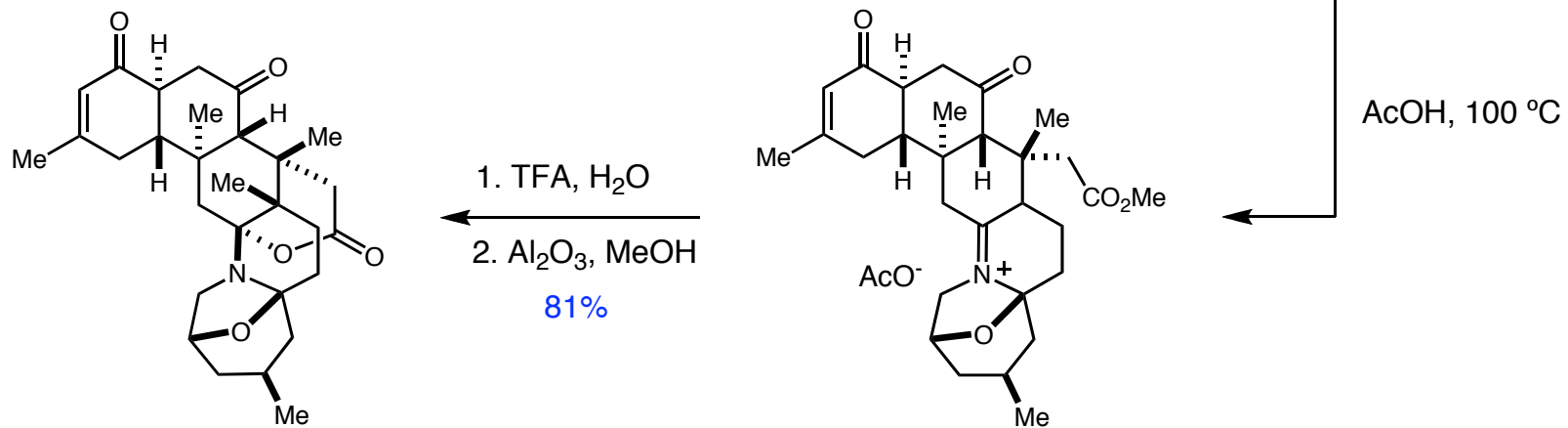
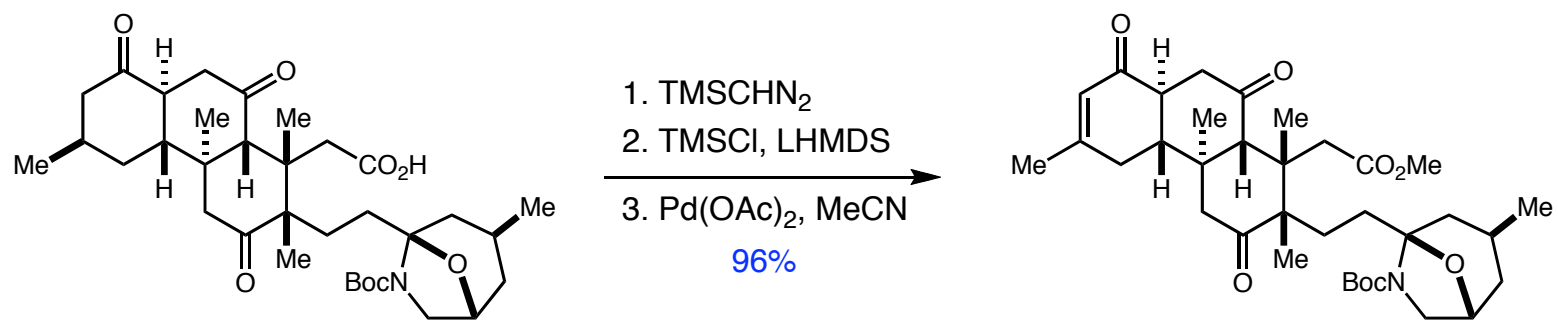


Deuterium Burned-Out

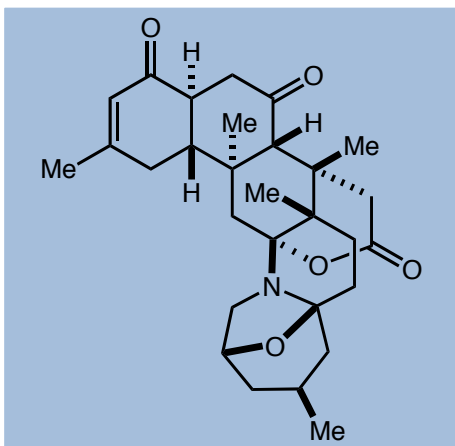
## End Game



## End Game



## Why is This a Science Paper?



First synthesis of Norzoanthamine

Extremely high yielding despite non-convergent synthesis:  
3.5% overall yield from a 41 step synthesis (92% per step)

Clever exploitation of kinetic isotope effect

A key exo-selective diels-alder sets the core

# Norzoanthamine

## The Synthesis

New Reaction Methodology

New Application of Old Chemistry  
to Make a Complex Motif  
in a Novel Way

## The Molecule

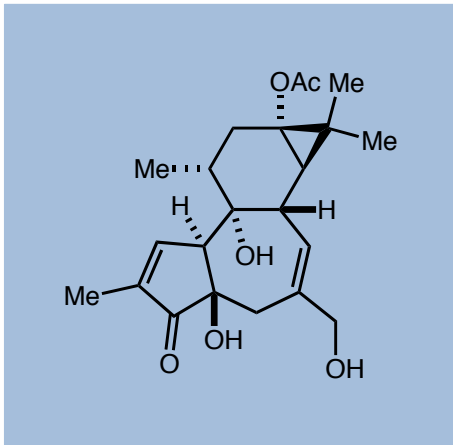
Important Material or  
Pharmacological Properties

Structurally Profound

## Both

The Synthesis Can Actually Produce  
an Important Molecule on Large Scale

## Prostratin



First isolated from *Pimelea prostrata* in 1976 in limited quantities

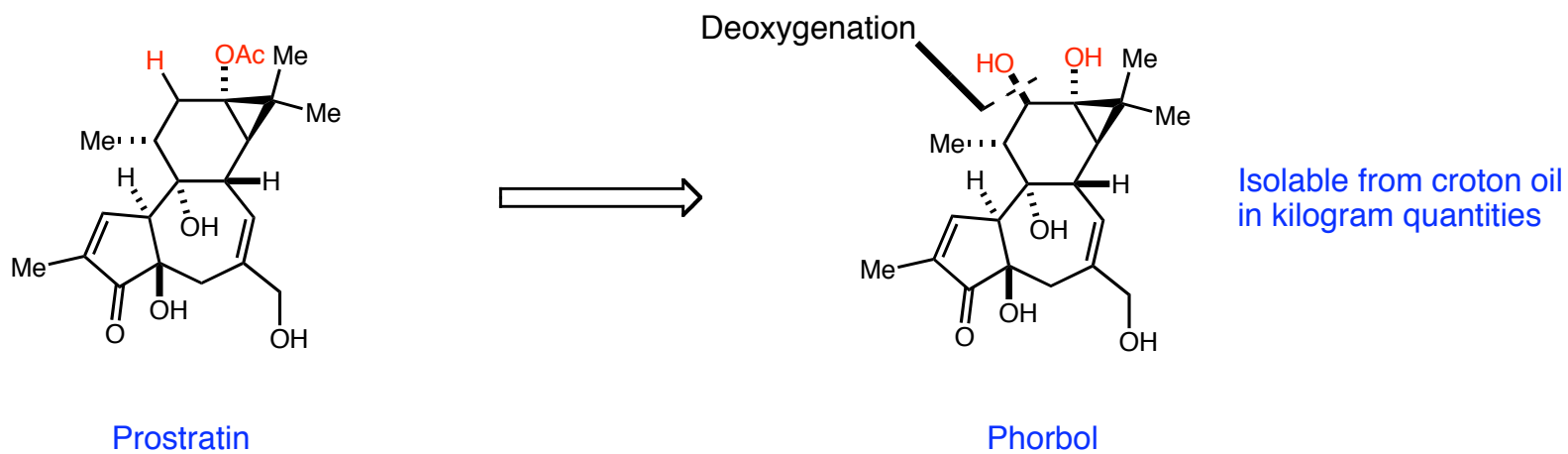
Protein kinase C activator capable of activating viral reservoirs in latently HIV infected CD4 T-cells

A combination therapy of prostratin and antiretroviral drugs offers a **potential cure to HIV-AIDS** by "flushing out" viral reservoirs

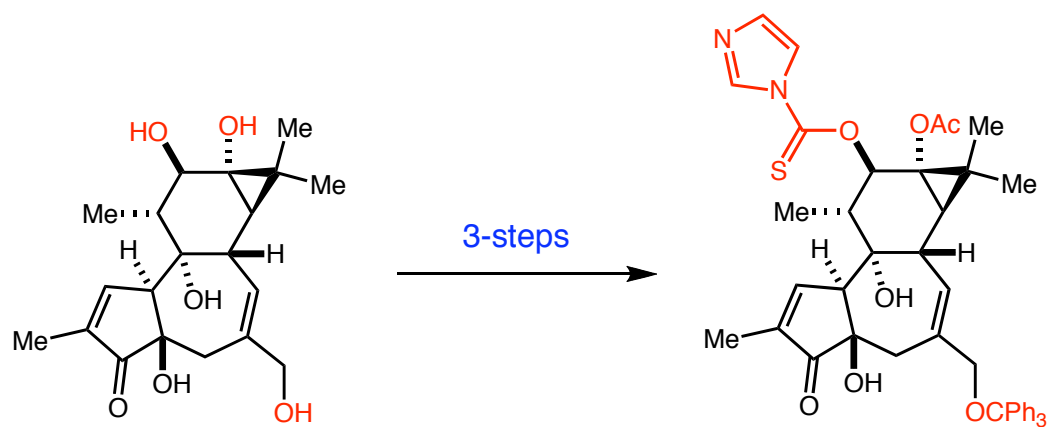
Currently poised to enter phase I clinical trials conducted by the AIDS ReSearch Alliance using material furnished by this route

Wender, P.; Kee, J.; Warrington, J. *Science*, **2008**, 320, 649-652

## The Semi-Synthesis of Prostratin from Phorbol

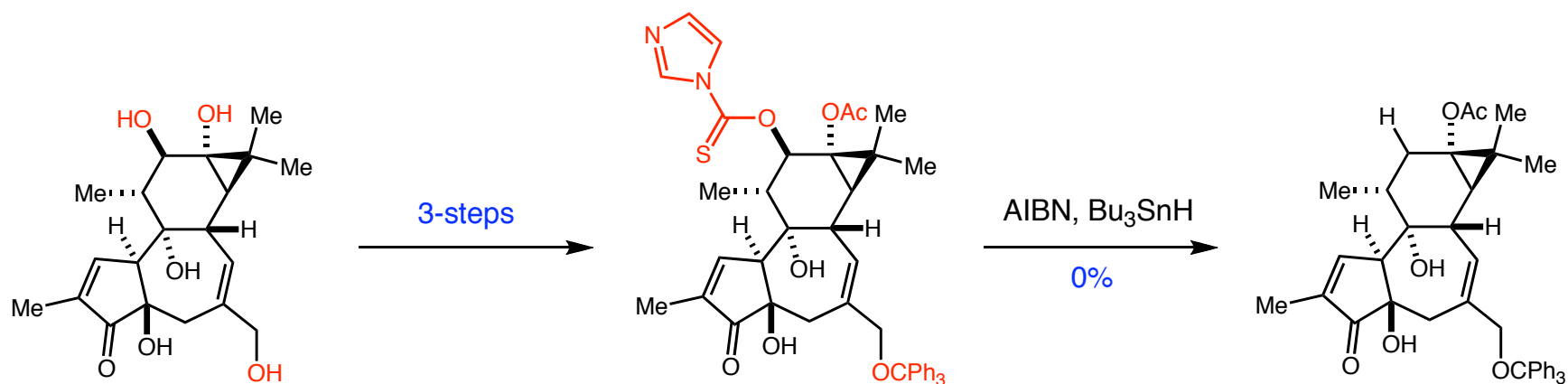


## Cyclopropane Complicates Radical Deoxygenation Strategy

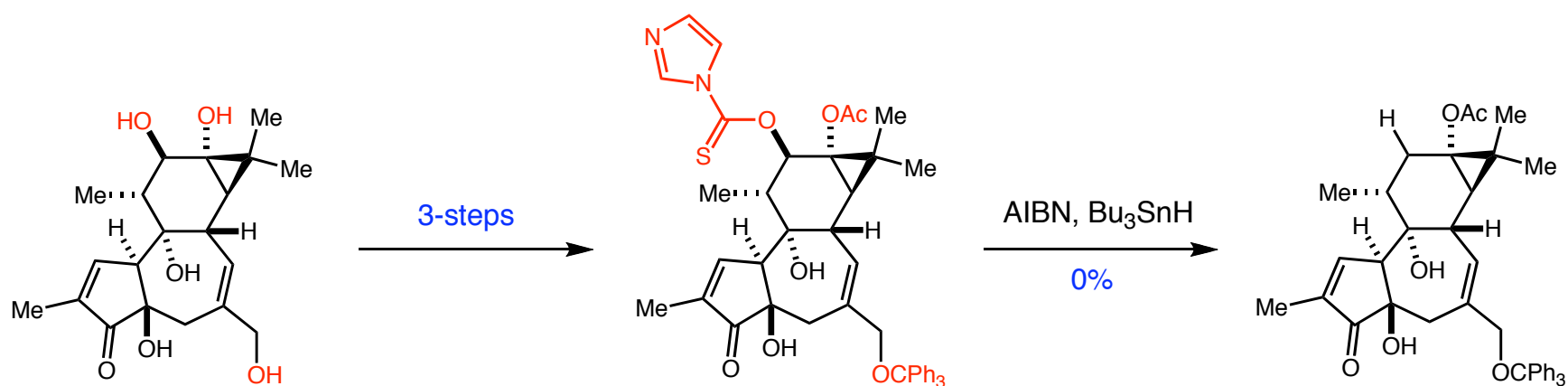




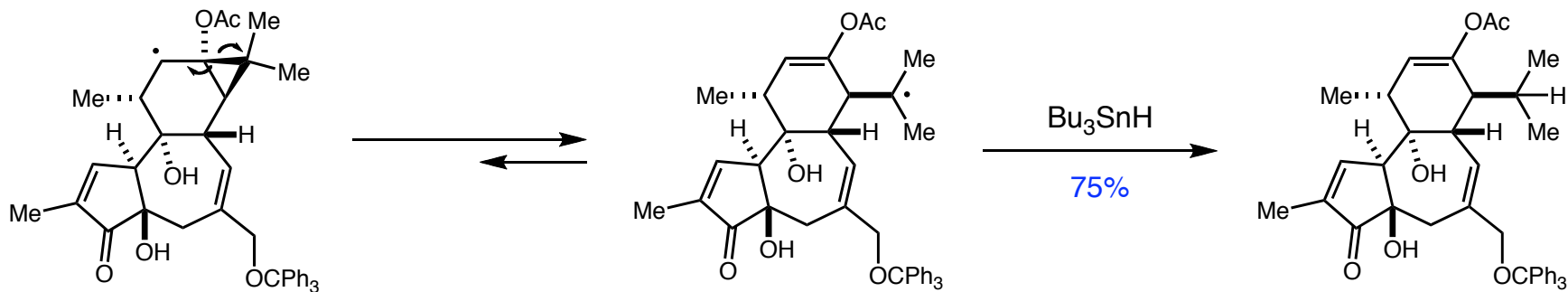
## Cyclopropane Complicates Radical Deoxygenation Strategy



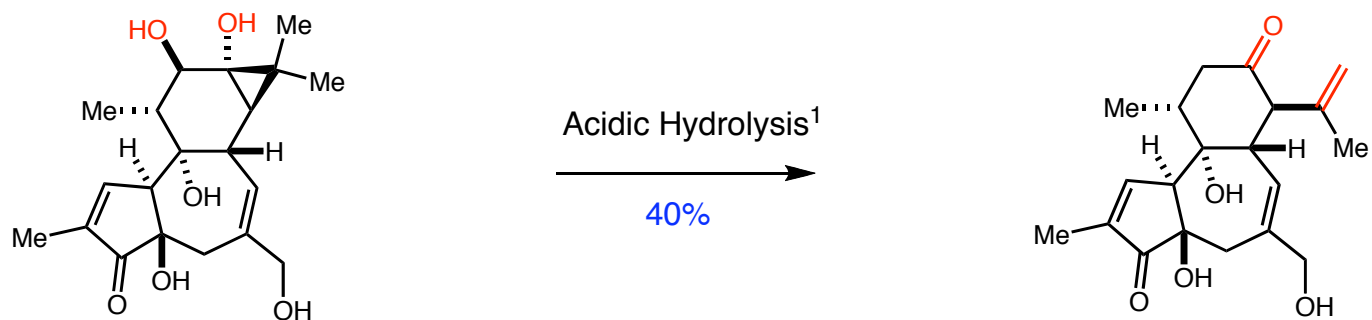
## Cyclopropane Complicates Radical Deoxygenation Strategy



## Intramolecular Ring Cleavage Outcompetes Intermolecular H Delivery

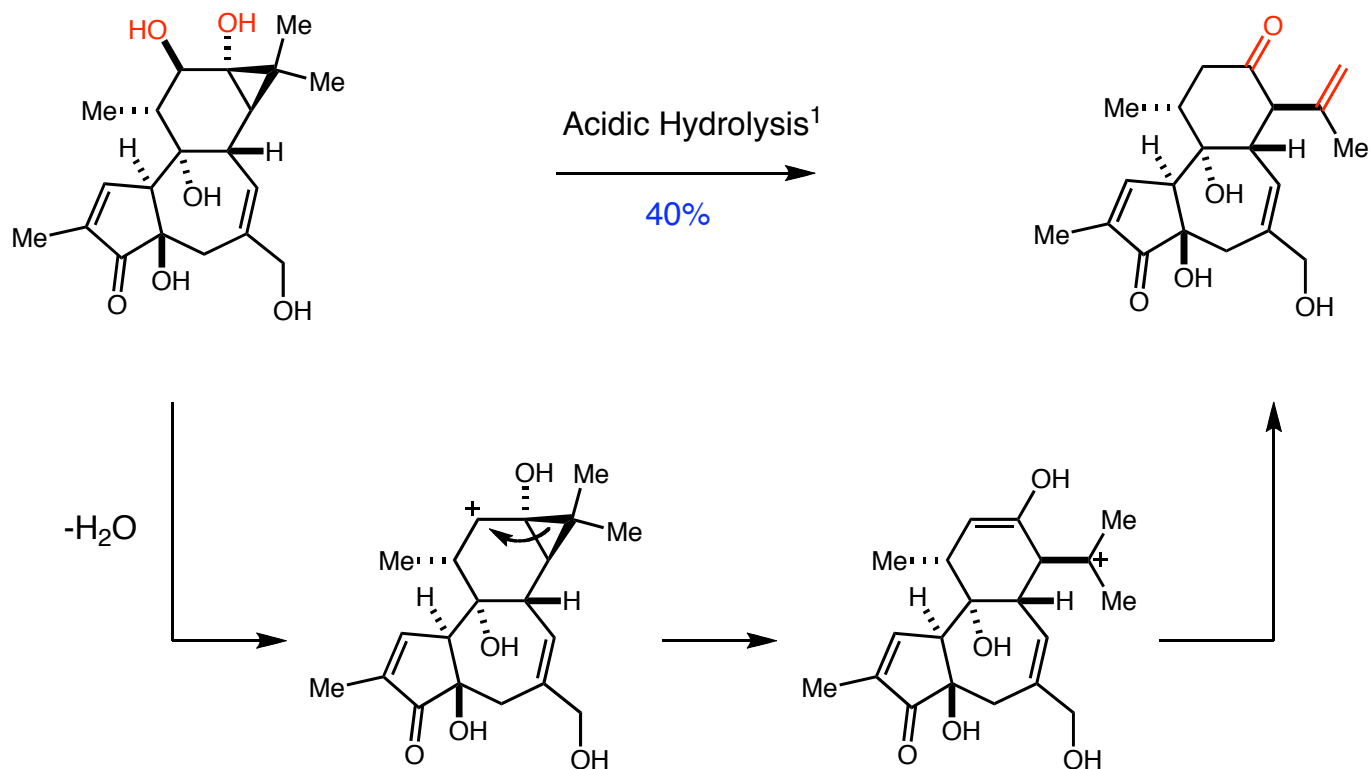


## Deoxygenation by Hydrolysis Leaves Handles to Reform Cyclopropane



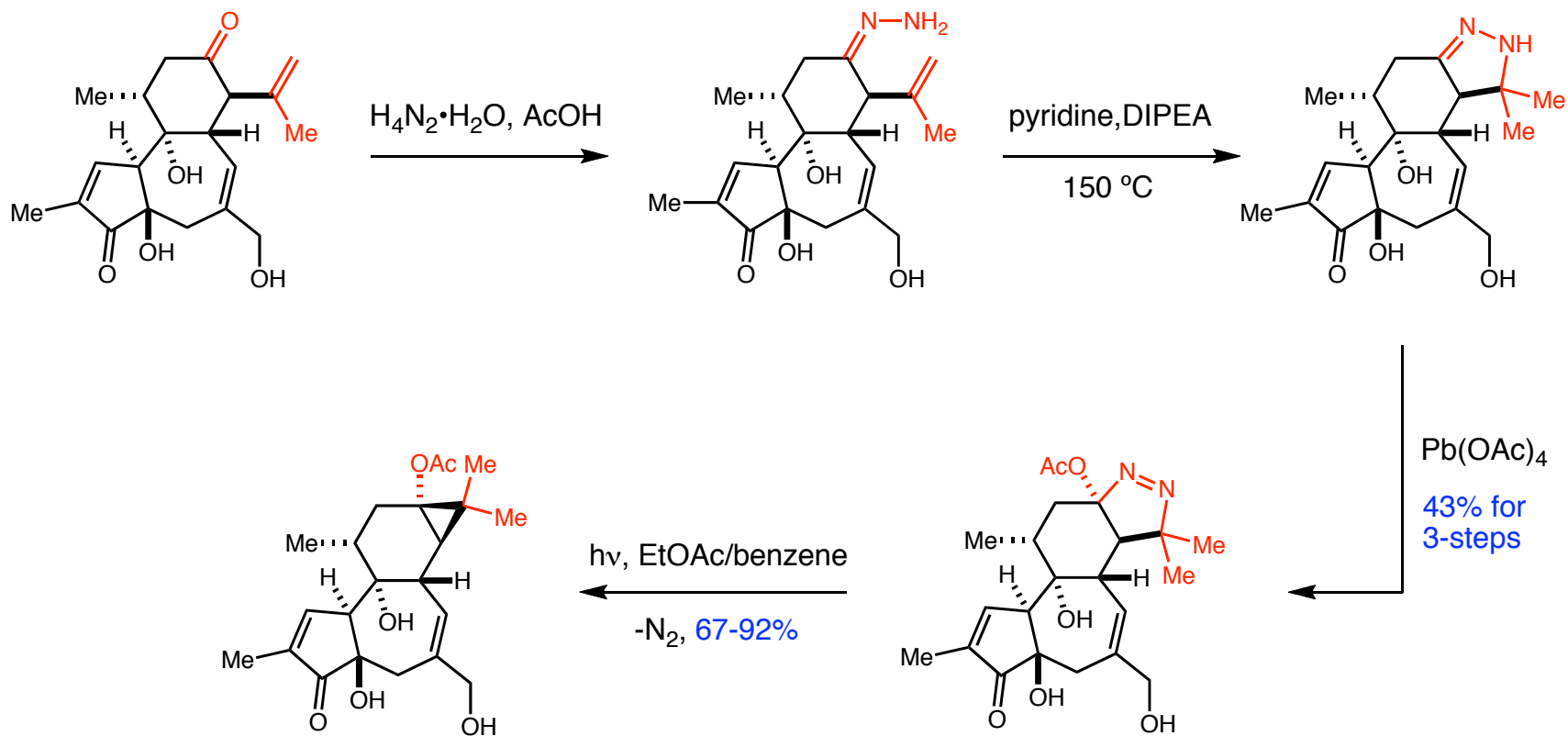
1. Thielmann, H.; Hecker, E. *Liebigs Ann. Chem.* **1969**, 728, 158

## Deoxygenation by Hydrolysis Leaves Handles to Reform Cyclopropane

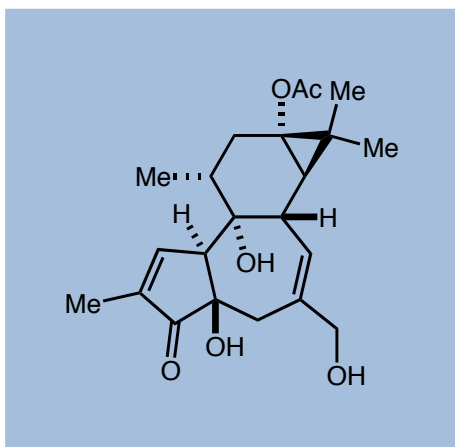


1. Thielmann, H.; Hecker, E. *Liebigs Ann. Chem.* **1969**, 728, 158

## Cyclopropane Reestablished in 4-steps



## Why is This a Science Paper?



No new chemical reactivity demonstrated, but the synthetic strategy is concise and non-obvious

The route is amenable to preparing various ether derivatives during the pyrazoline oxidation step

Preparatively useful way to make a very important substance

# Prostratin

## The Synthesis

New Reaction Methodology

New Application of Old Chemistry  
to Make a Complex Motif  
in a Novel Way

## The Molecule

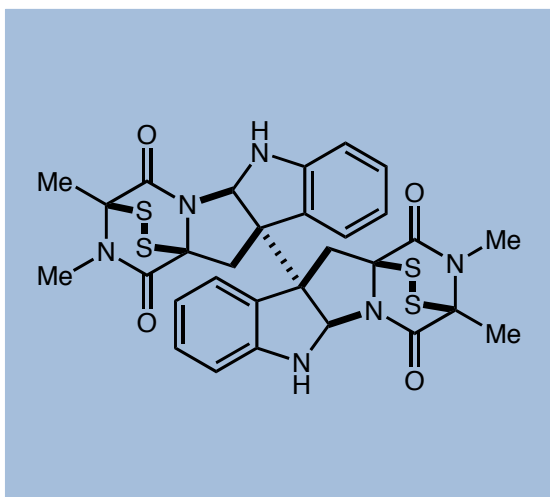
Important Material or  
Pharmacological Properties

Structurally Profound

## Both

The Synthesis Can Actually Produce  
an Important Molecule on Large Scale

## (+)-11,11'-Dideoxyverticillin A



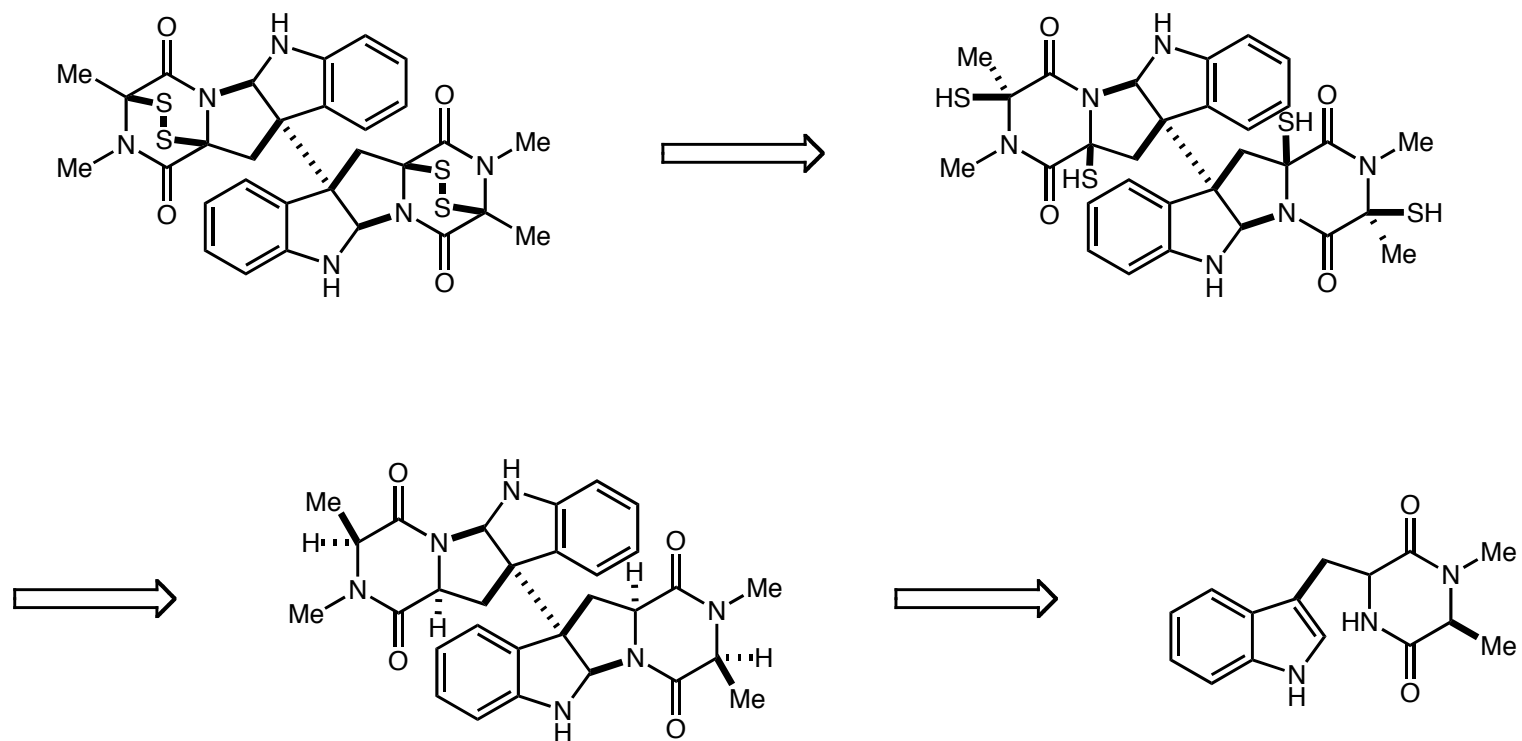
Cytotoxic alkaloid isolated from marine *Penicillium* first reported in 1970

Inhibits tyrosin kinase activity of the epidermal growth factor receptor, and displays antiangiogenic activity

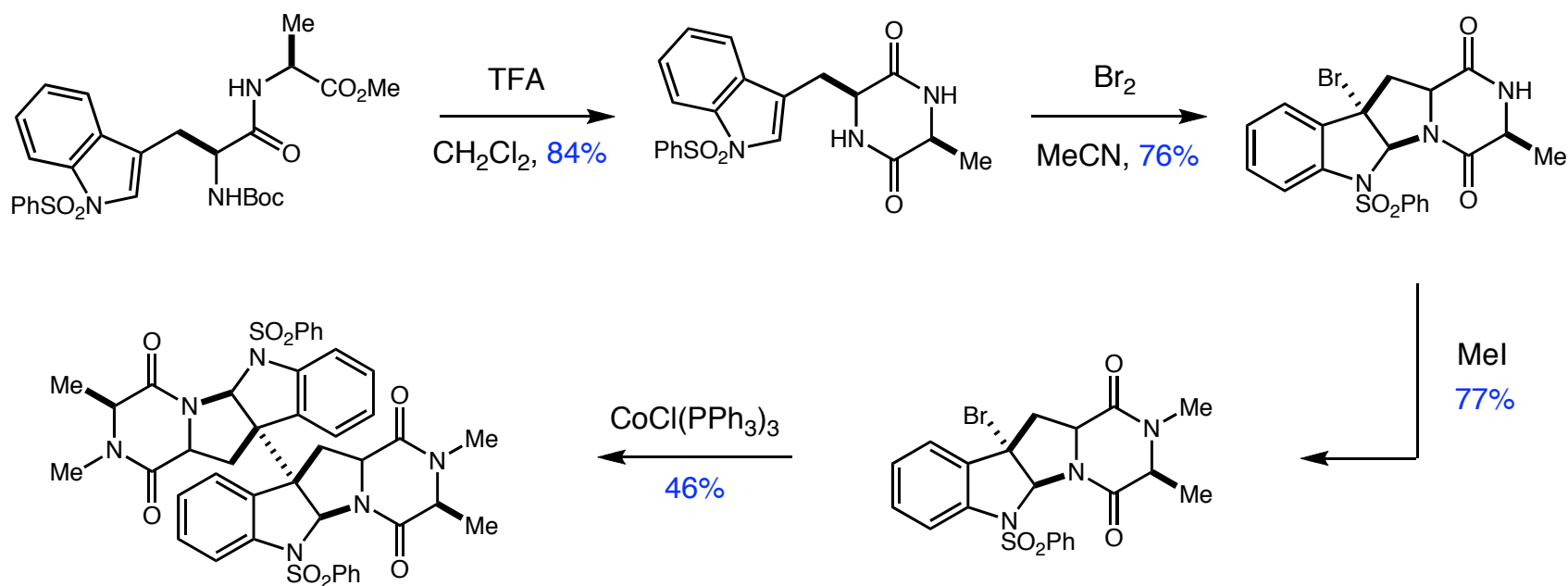
Densely functionalization with acid-, base-, and redox sensitive groups hampered synthesis of epidithioketopiperazine alkaloids



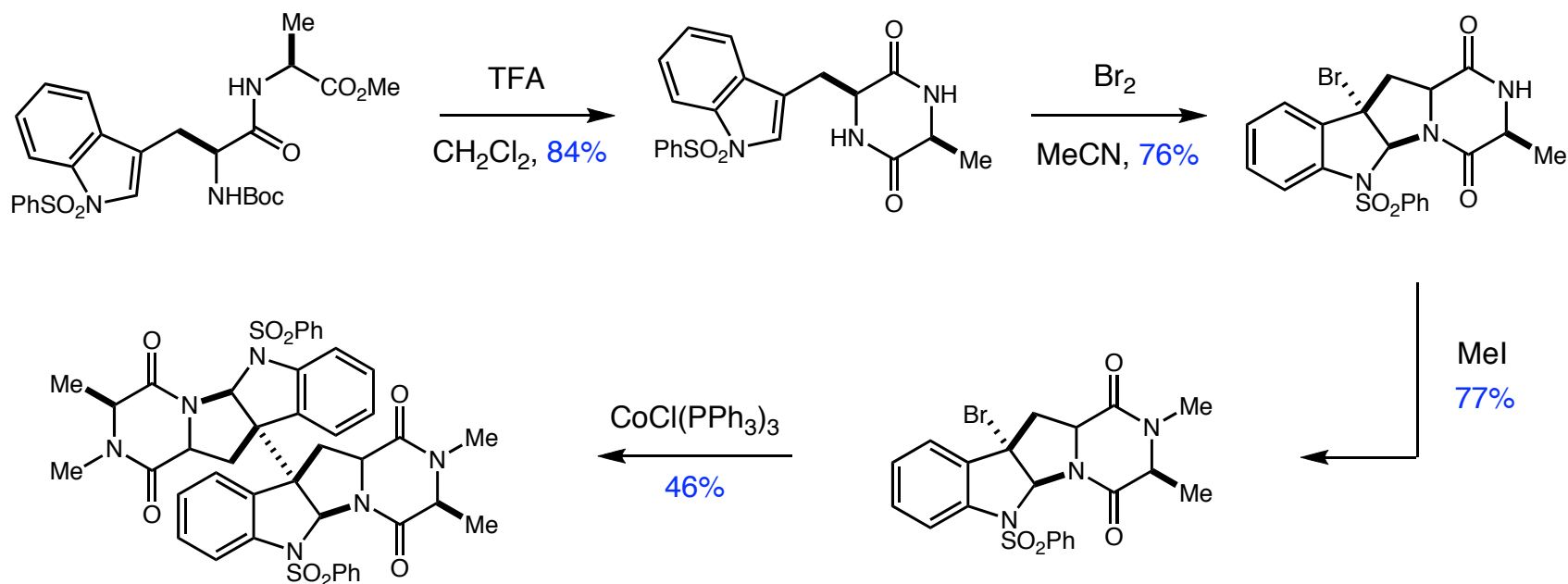
## (+)-11, 11'-Dideoxyverticillin A Retrosynthetic Analysis



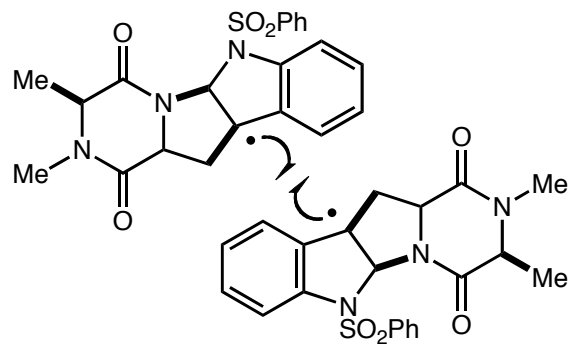
## Synthesis of the Dimer Framework by Intermolecular Radical Coupling



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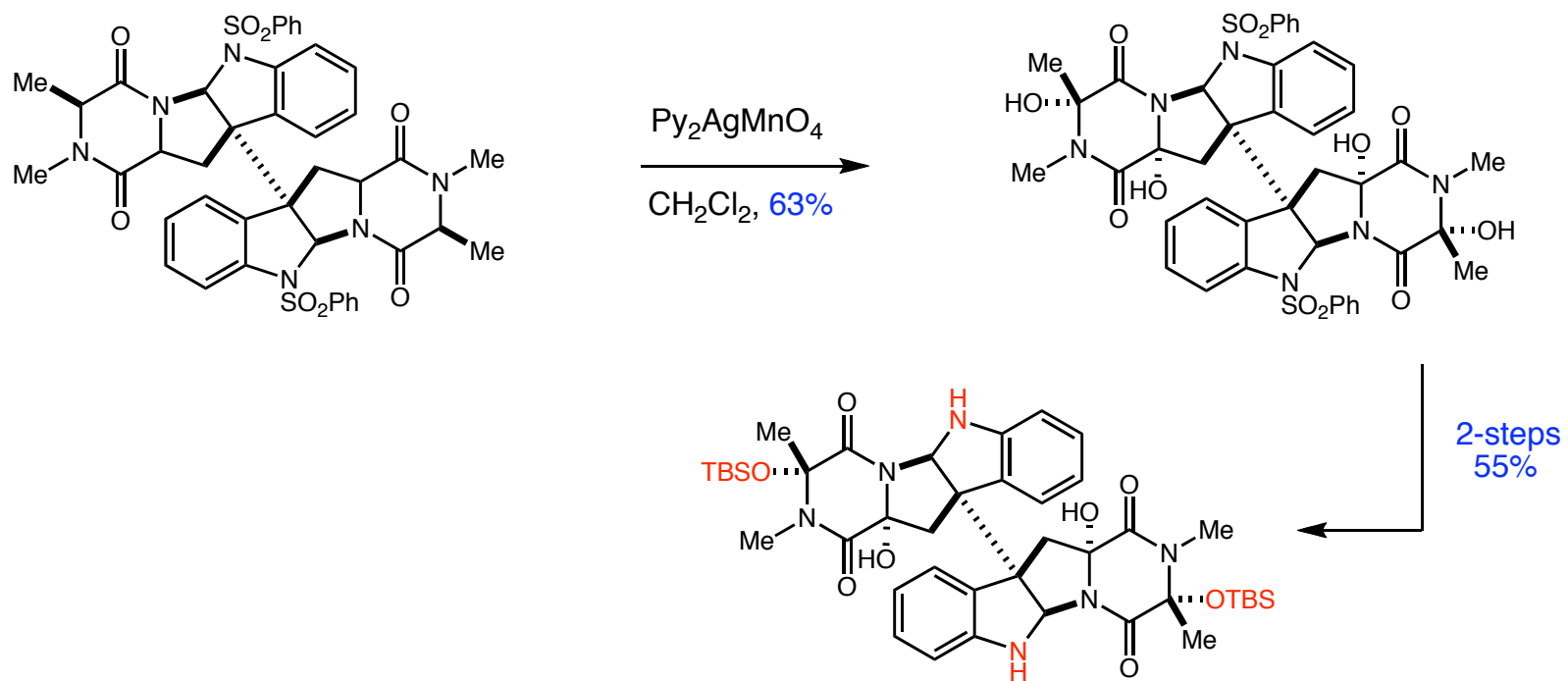


### Intermolecular Radical Coupling

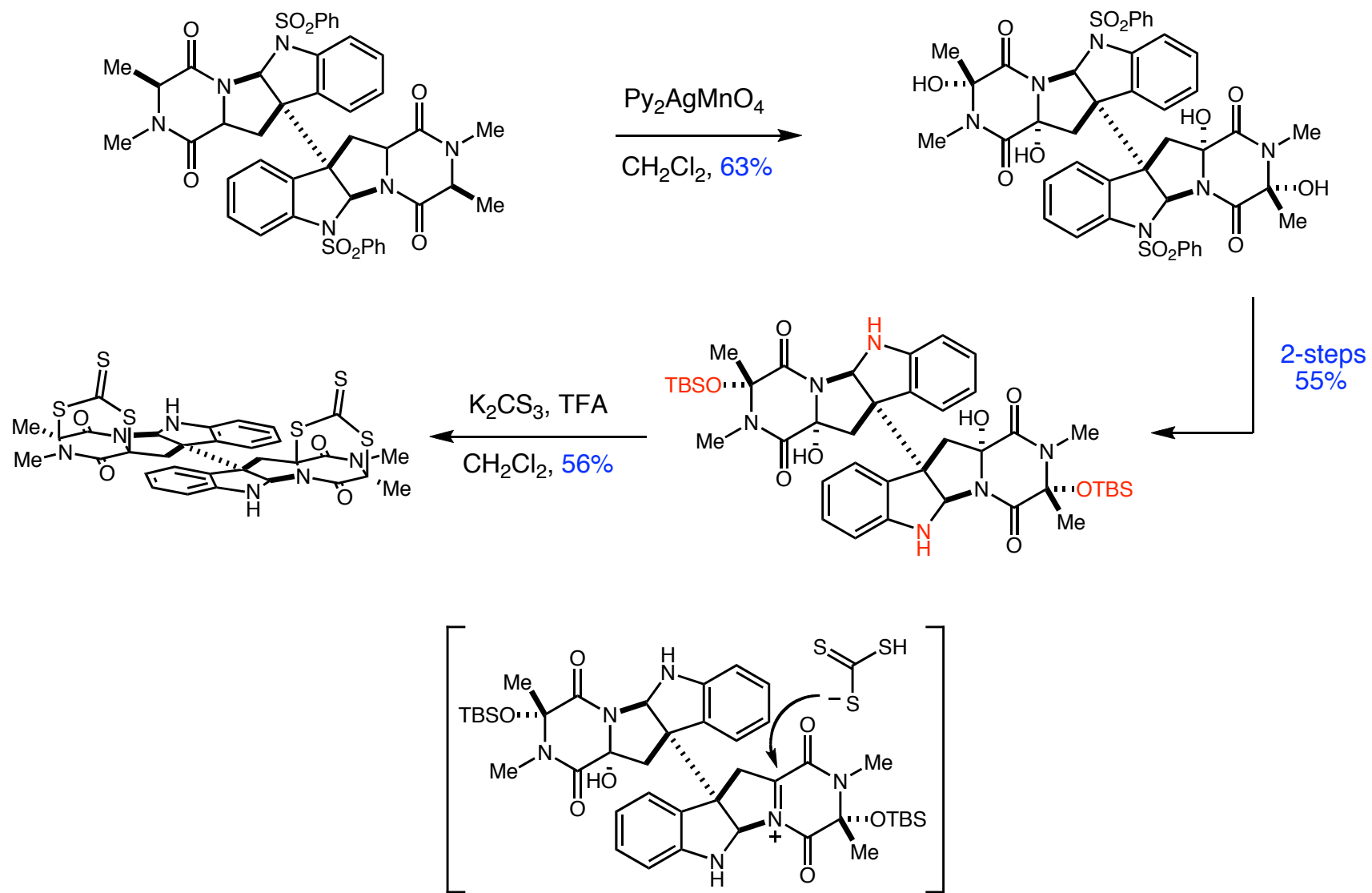




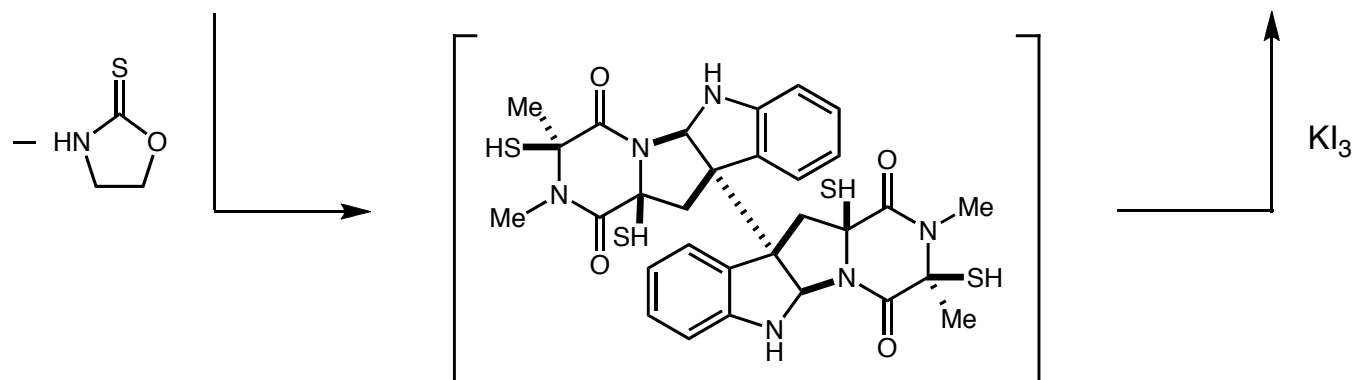
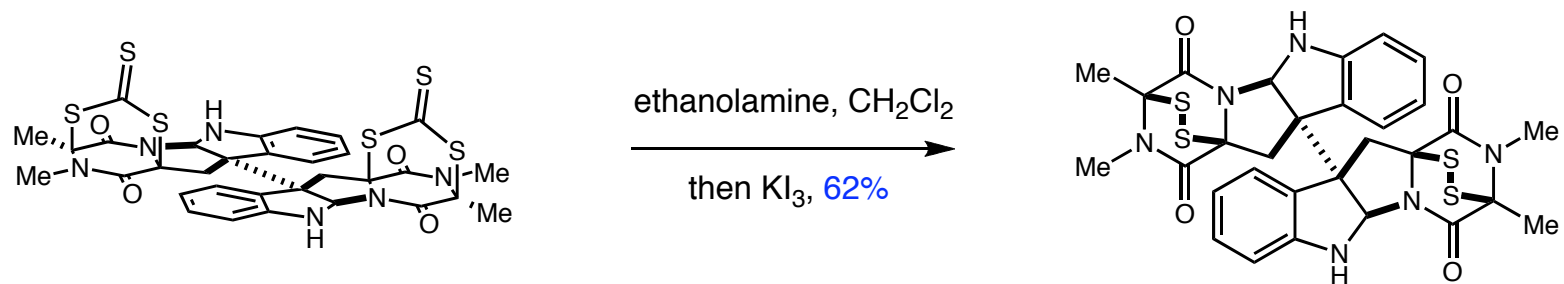
## Tetrahydroxylation and Tetrathiolation



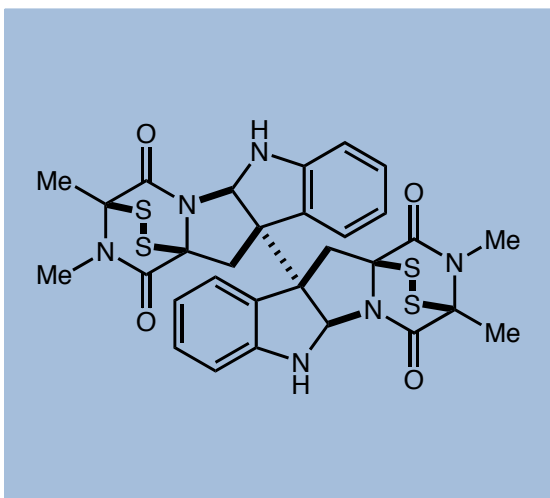
## Tetrahydroxylation and Tetrathiolation



## Oxidation to Form the Disulfides



## Why is This a Science Paper?



First synthesis of a dimeric epidithioketopiperazine alkaloid

Clever manipulation of sensitive, advanced-stage intermediates to generate the disulfide

Strategy should be amenable to synthesizing related compounds for further biological studies



# 11,11'-Dideoxyverticillin A

## The Synthesis

New Reaction Methodology

New Application of Old Chemistry  
to Make a Complex Motif  
in a Novel Way

## The Molecule

Important Material or  
Pharmacological Properties

Structurally Profound

## Both

The Synthesis Can Actually Produce  
an Important Molecule on Large Scale

## Final Thought

### The Synthesis

New Reaction Methodology

**This is the only bullet point that was never colored red in this talk. Why is that?**