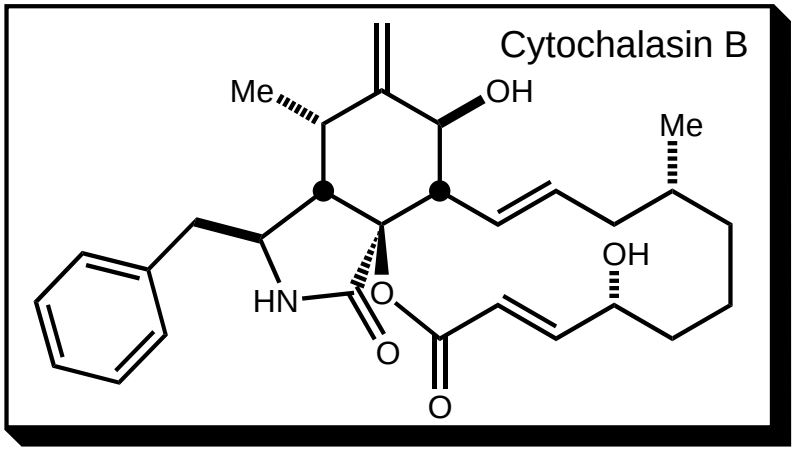
Cytochalasins

Synthesis, Biosynthesis and Methodology

Evans Group Seminar

March 12, 1999

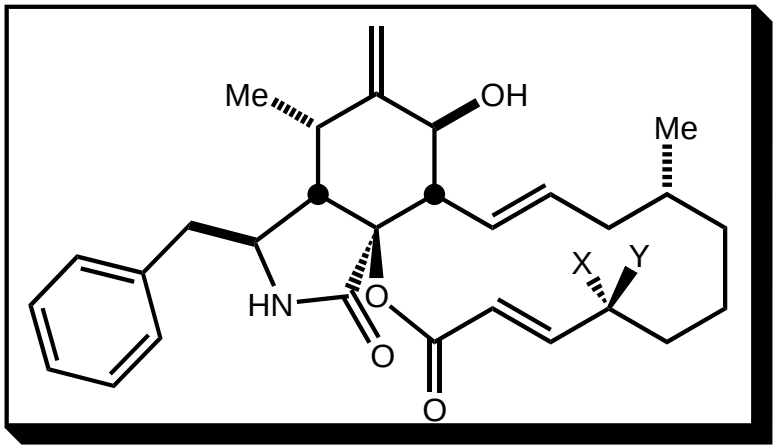
Jason Burch



I. Isolations
II. Biosynthesis
III. Total Syntheses: Cytochalasin B x 2 - Stork
Proxiphomin - Thomas
IV. Methodology: Enolate assisted fragmentation - Fuchs
2,3-dipolar cycloaddition - Vedejs
Reformatsky cyclisation - Vedejs
V. Chaetochalasin

Cytochalasan Isolations

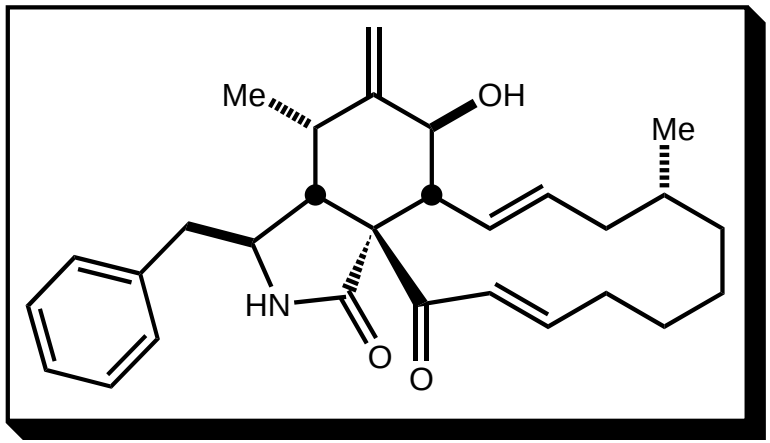
[14]-Cytochalasans



Cytochalasin A (*dehydrophomin*): X,Y = O
Cytochalasin B (*phomin*): X = OH, Y = H

- **Isolation**
  - Tamm *et. al.*, *Experientia*, **1966**, *22,* 750.
    -> isolated from *Phoma*, S 298
  - Aldridge *et. al.*, *Chem. Commun.*, **1967**, 26.
    -> isolated from *Helminthosporium dematioideum*
- **Synthetic Approaches**
  - Stork *et al.*, *JACS*, **1978**, *100*, 7775.
    JACS, **1982**, *105*, 5510
  - Weinreb *et al.*, *JOC*, **1981**, *46*, 5383
- **Biological Activity**
  - inhibit glucose transport
    Bloch, *Biochemistry*, **1973**, *12*, 4799
  - many others
    see Tamm in *Frontiers in Biology*, Tanenbaum, S.W., Ed.; **1976**, *46*, pp. 15

[13]-Cytochalasans

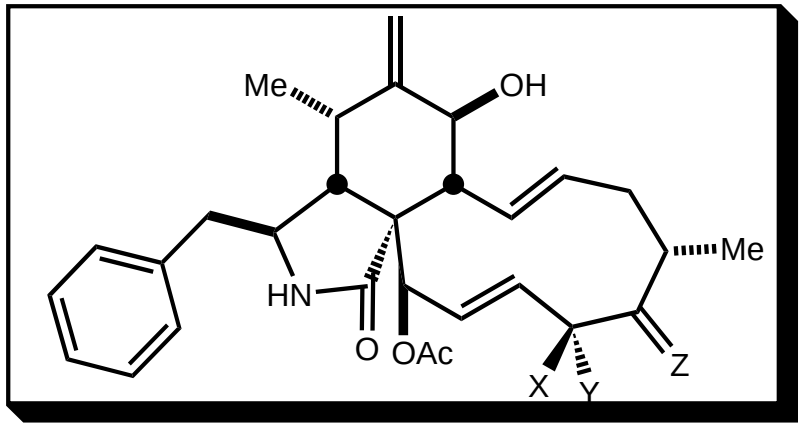


Proxiphomin

- **Isolation**
  - Tamm *et. al.*, *Helv. Chim. Acta*, **1984**, *67*, 1998
- **Synthetic Approach**
  - Thomas *et. al.*, *Chem. Commun*, **1985**, 143

Cytochalasan Isolations

[11]-Cytochalasans



Cytochalasin D: X = Me, Y = H, Z = O
Cytochalasin H: X = H, Y = Me, Z = H,H

•Isolation

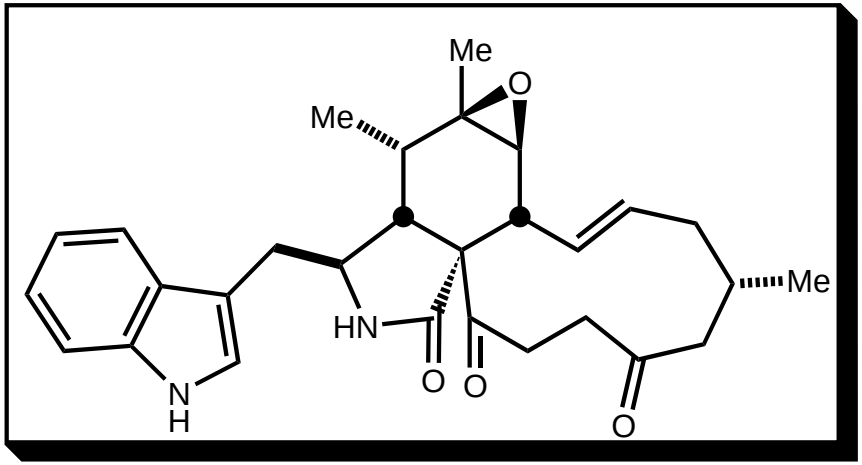
- •Aldridge *et al.*, *J. Chem. Soc. C.*, **1969**, 923.
  -> isolated from *Metarrhizium anisopliae*
- •Minato *et al.*, *J. Antibiotics*, **1968**, *21*, 523.
  -> isolated from *Zygosporium masonii*

•Synthetic Approaches

- •Fuchs *et al.*, *JACS*, **1979**, *101*, 3567
- •Vedejs *et al.*, *JACS*, **1984**, *106*, 4617
  TL, **1988**, *29*, 2291
- •Thomas *et al.*, *JCS Perk. Trans. I.,* **1989**, 507
  JCS Perk. Trans. I., **1989**, 519

• Biological Activity

- • D inhibits protein and RNA synthesis
  Brown *et al*., *J. Cell. Biol.*, **1981**, *88*, 487



Cytochalasin G

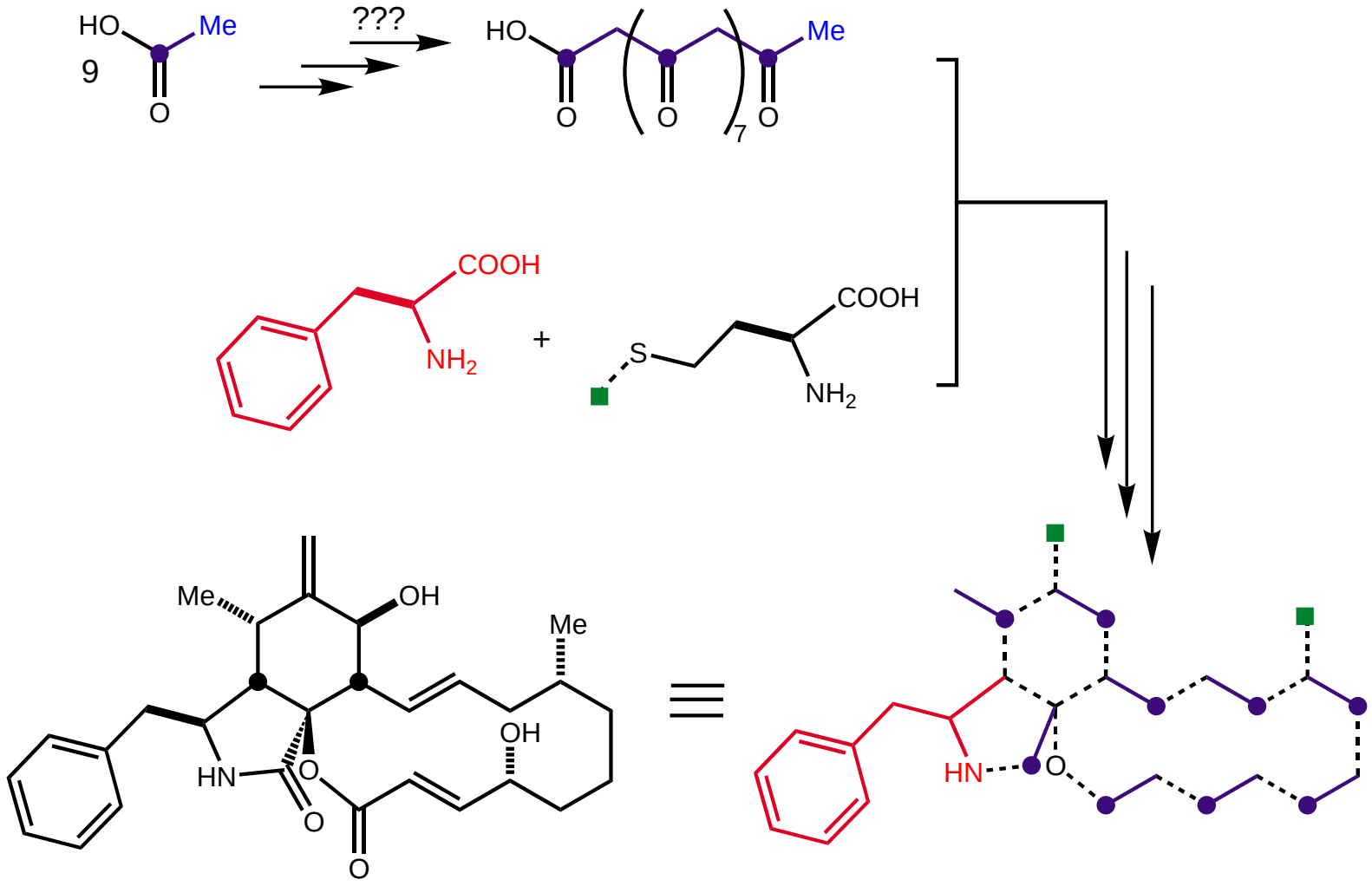
•Isolation

- •Yamada *et al.*, *Chem. Pharm. Bull.*, **1977**, *25*, 29.

•Synthetic Approaches

- •Thomas *et al.*, *JCS Perk. Trans. I.,* **1989**, 525

Biosynthesis of Cytochalasin B



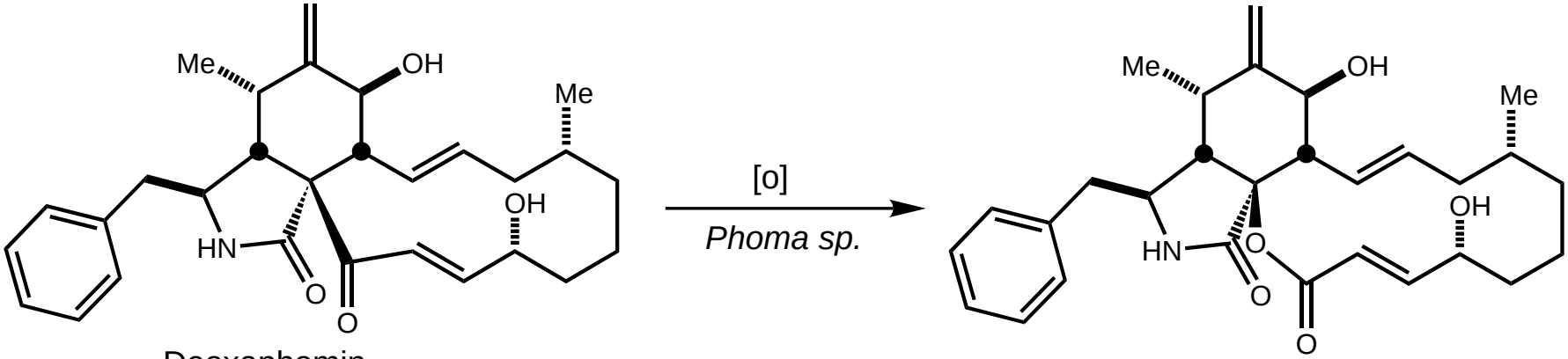
-verified by "feeding" [1-^{13}C]- and [2-^{13}C]-sodium acetate, [4'-^{3}H] phenylalanine and [^{13}C-S-Me]-methionine to *Phoma sp*.

Tamm *et al.*, *Helv. Chim. Acta*, **1974**, *57*, 1785.

Biosynthesis of Cytochalasin B

In vivo Baeyer-Villager Reaction

- illustrated that an enzymatic "Baeyer-Villager"-like oxidation converts deoxaphomin into phomin *in vivo*



Deoxaphomin

Cytochalasin B

•Isolation

Tamm *et al.*, *Helv. Chim. Acta*, **1973**, *56*, 966

Precedents: adrost-4-ene-3,17-dione ⟶ testolactone

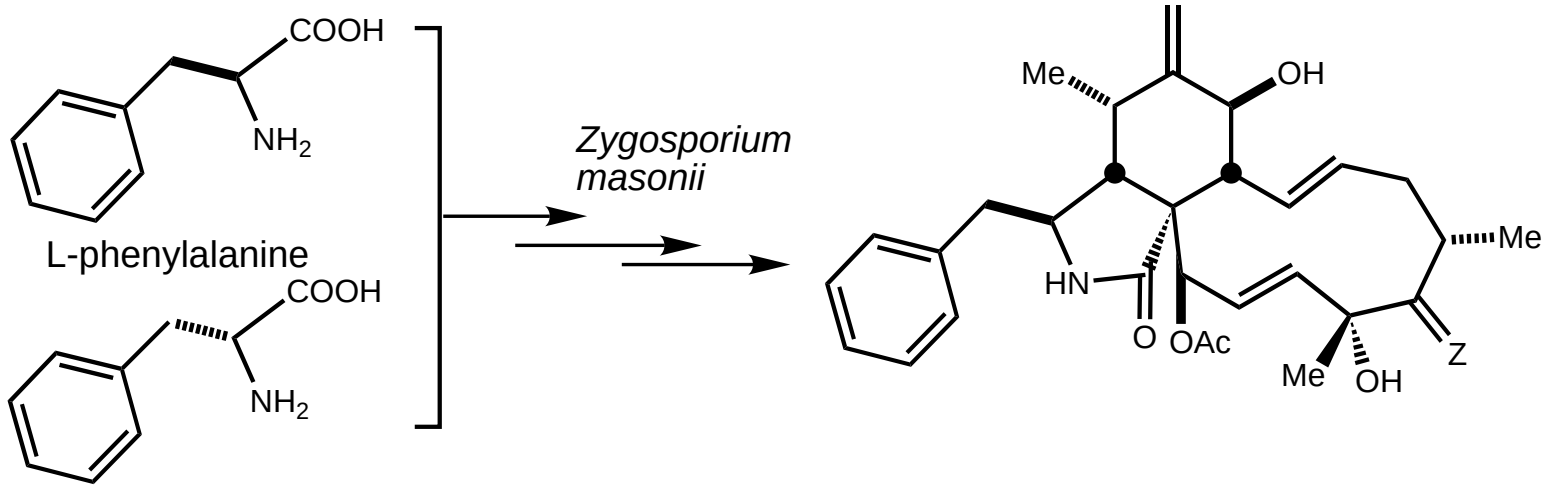
progesterone ⟶ testosterone

Conclusion: deoxaphomin likely a biosynthetic precursor to cytochalasin B

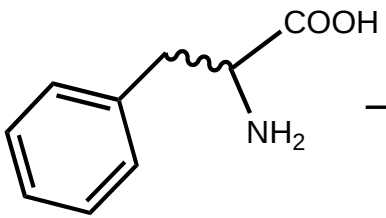
Tamm *et al.*, *Helv. Chim. Acta*, **1975**, *58*, 2501

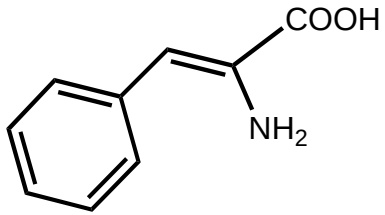
Biosynthesis of Cyctochalasin D

- Either enantiomer of phenylalanine incorporated into natural product

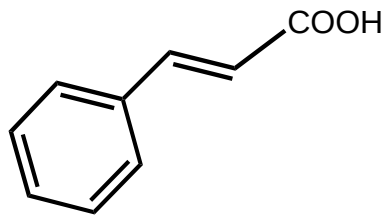


Possibilities:

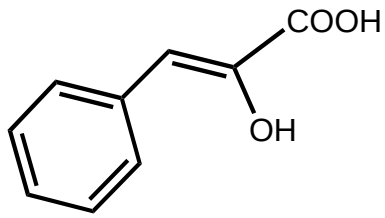




-^{15}N label not seen in natural product



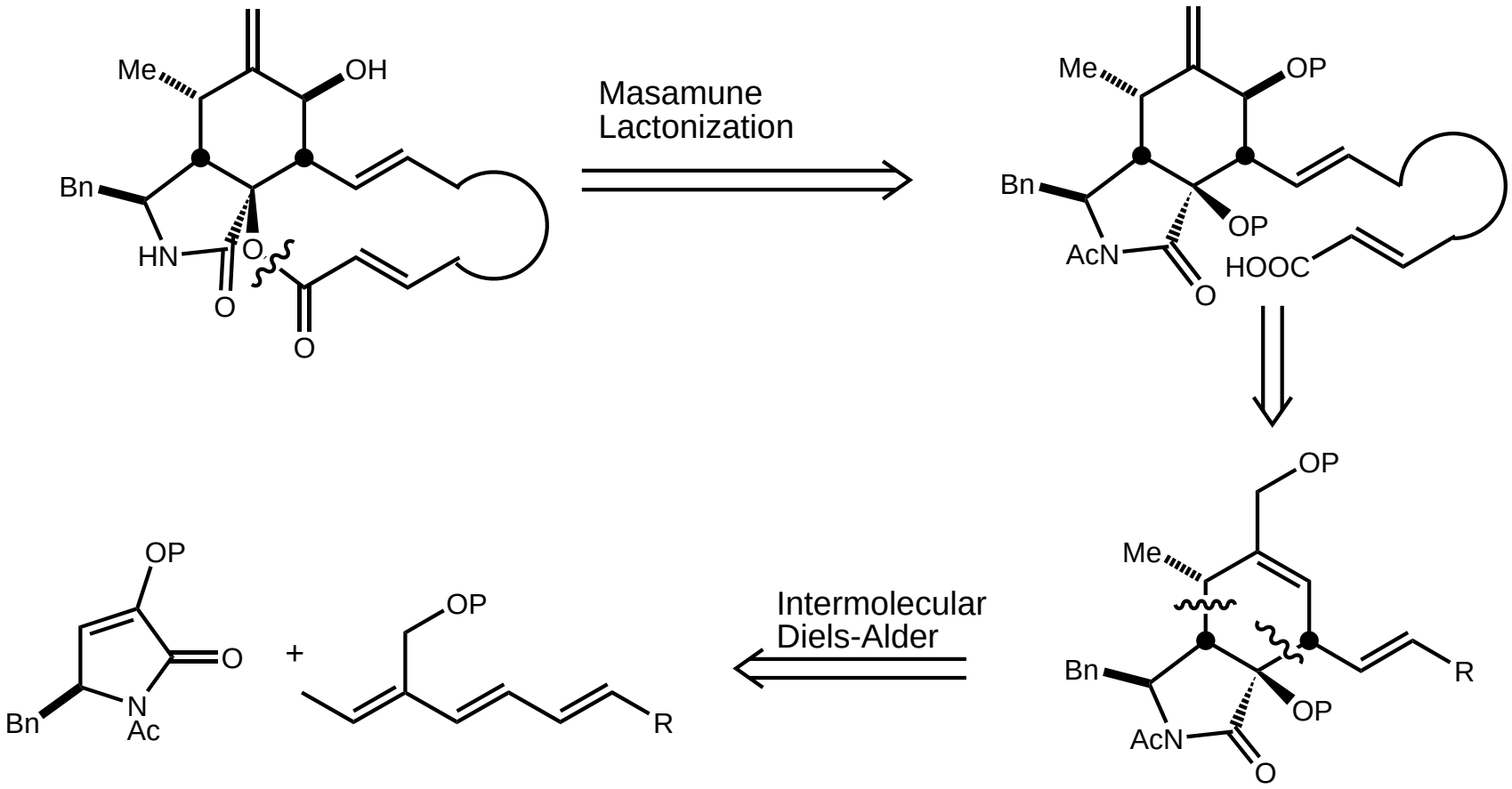
- loss of either β proton for D-phenylalanine
- precedent: phenyl-alanine ammonium lyase



-precedent: many biosyntheses including the penicillins

Tamm *et al.*, *Helv. Chim. Acta*, **1976**, *59*, 558

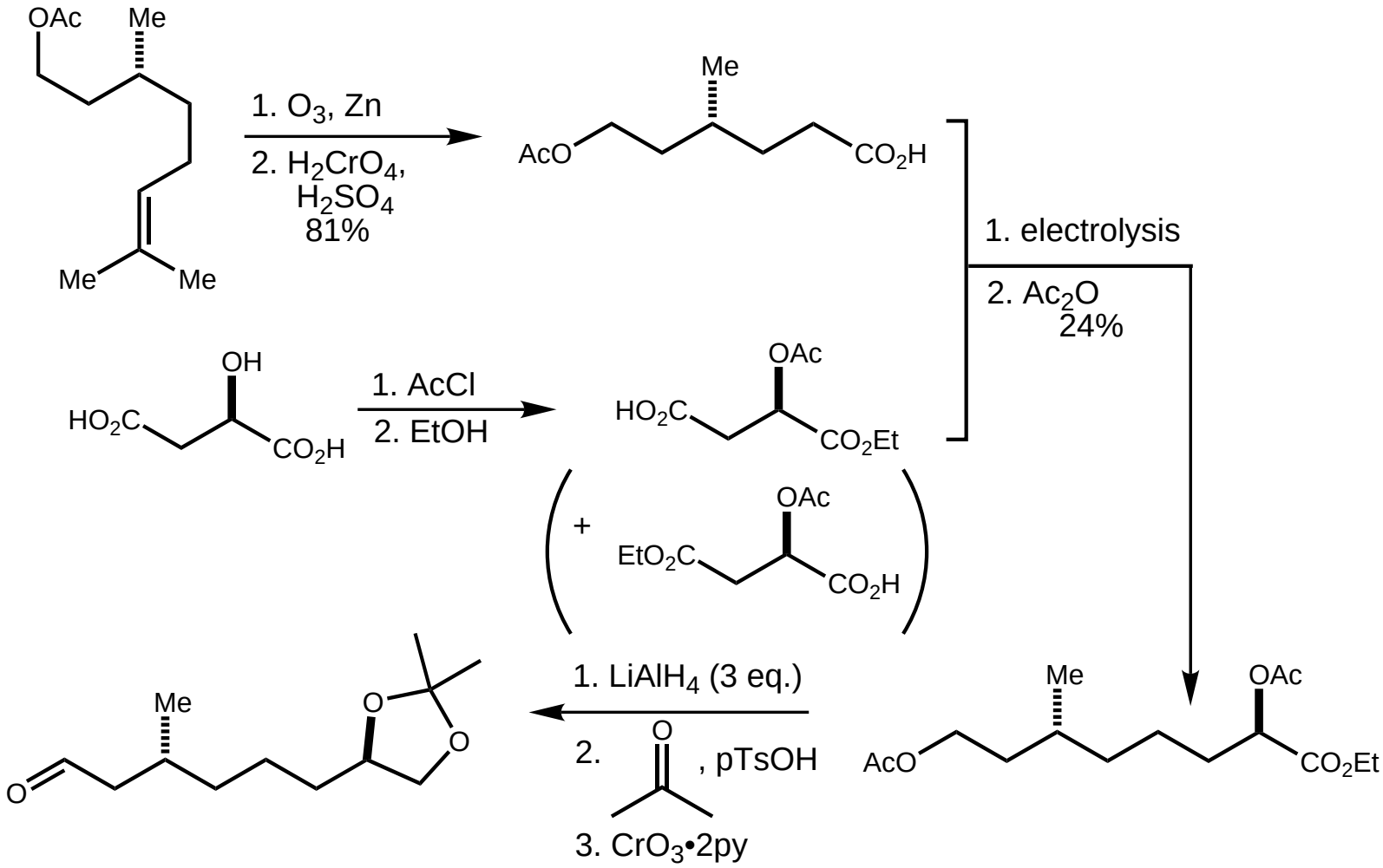
Stork's Original Retrosynthetic Plan



Stork *et al.*, *JACS*, **1978**, *100*, 7775

Synthesis of Cytochalasin B - Stork

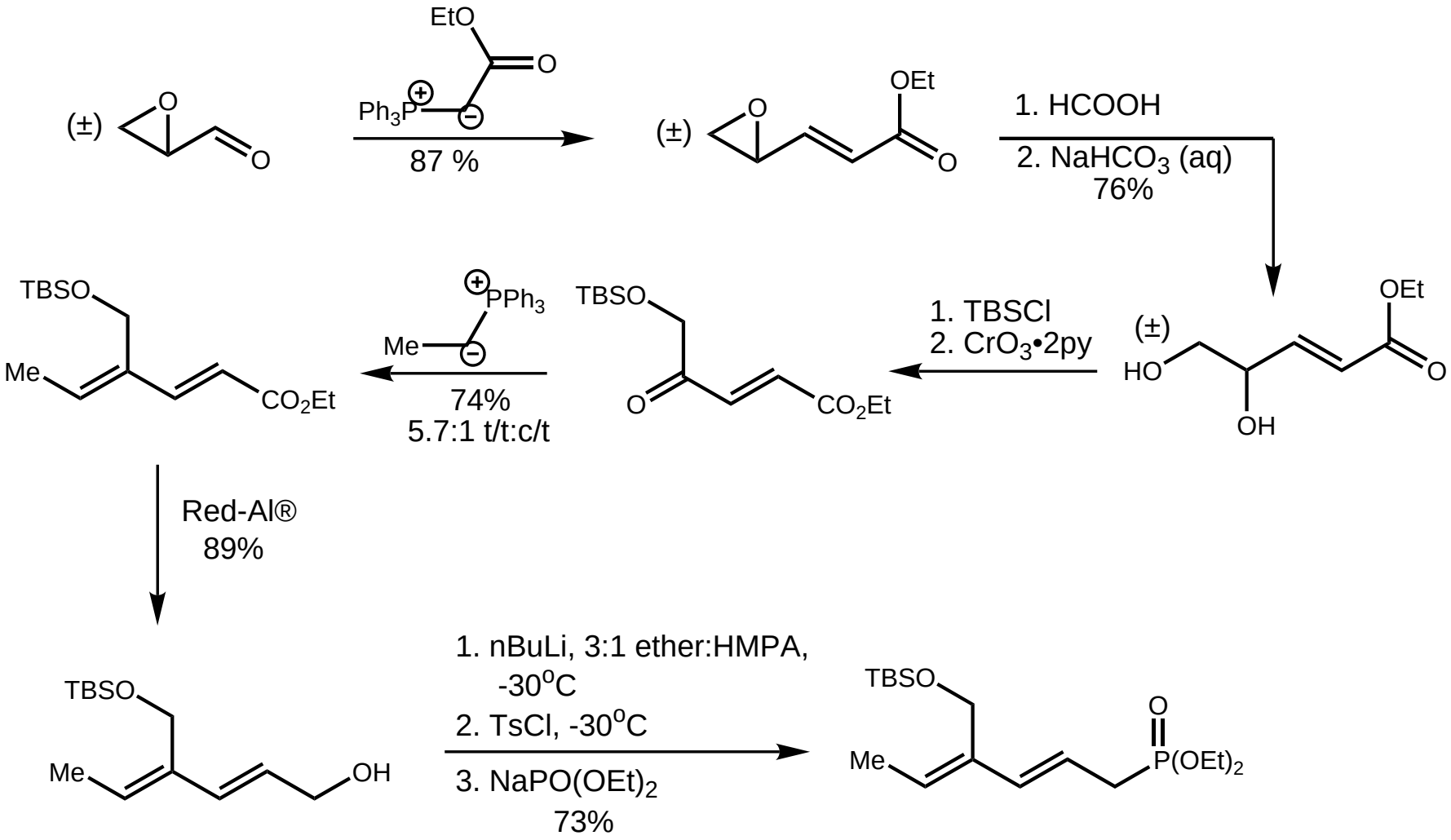
Coupling of Chiral Precursors



Stork *et al.*, *JACS*, **1978**, *100*, 7775
Horn *et al.*, *JCS*, **1954**, 1460
Schäfer, *ACIEE*, **1981**, *20*, 911

Synthesis of Cytochalasin B - Stork

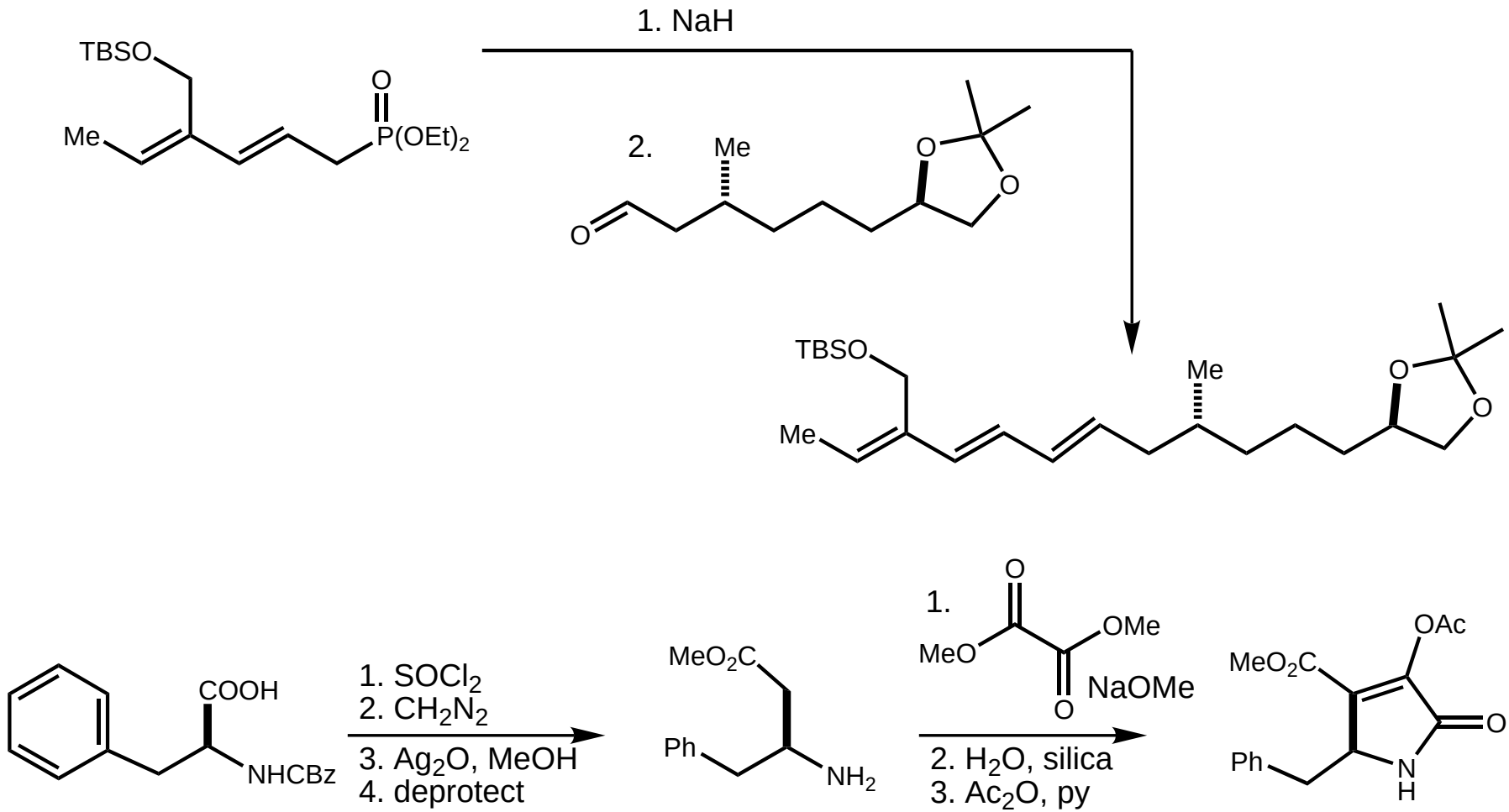
Preparation of Polyene



Stork *et al.*, *JACS*, **1978**, *100*, 7775

Synthesis of Cytochalasin B - Stork

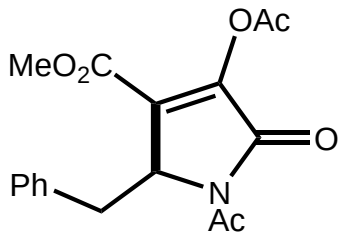
Completion of Polyene; Synthesis of Dienophile



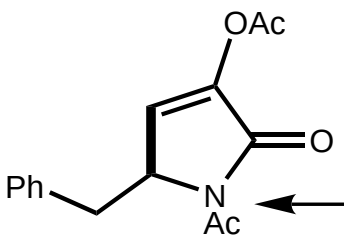
Stork *et al.*, *JACS*, **1978**, *100*, 7775
Crouch *et al.*, *JACS*, **1953**, *75*, 3413

Synthesis of Cytochalasin B - Stork

The Diels-Alder Reaction

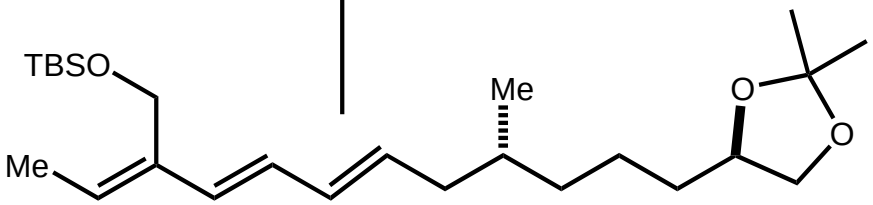


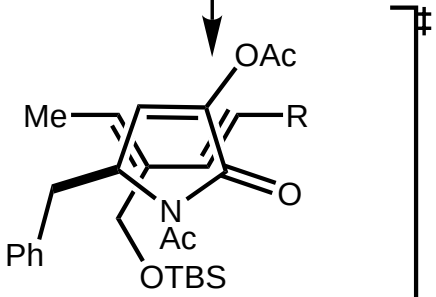
1. DMSO, NaCl, H_2O
2. Ac_2O

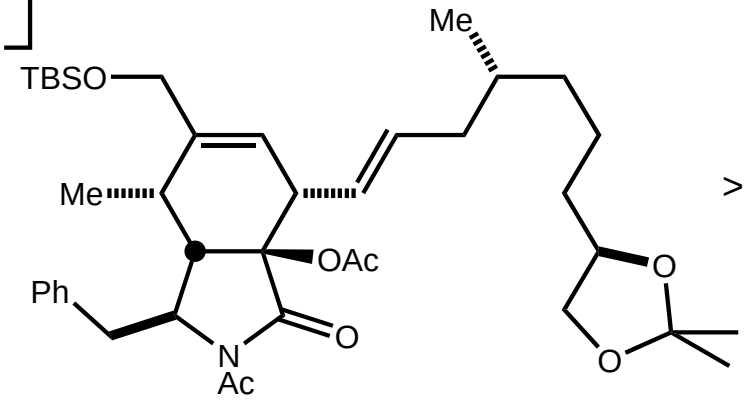


Vedejs showed N-acyl protecting group important

xylene, 170°C, 4 days, ~40%





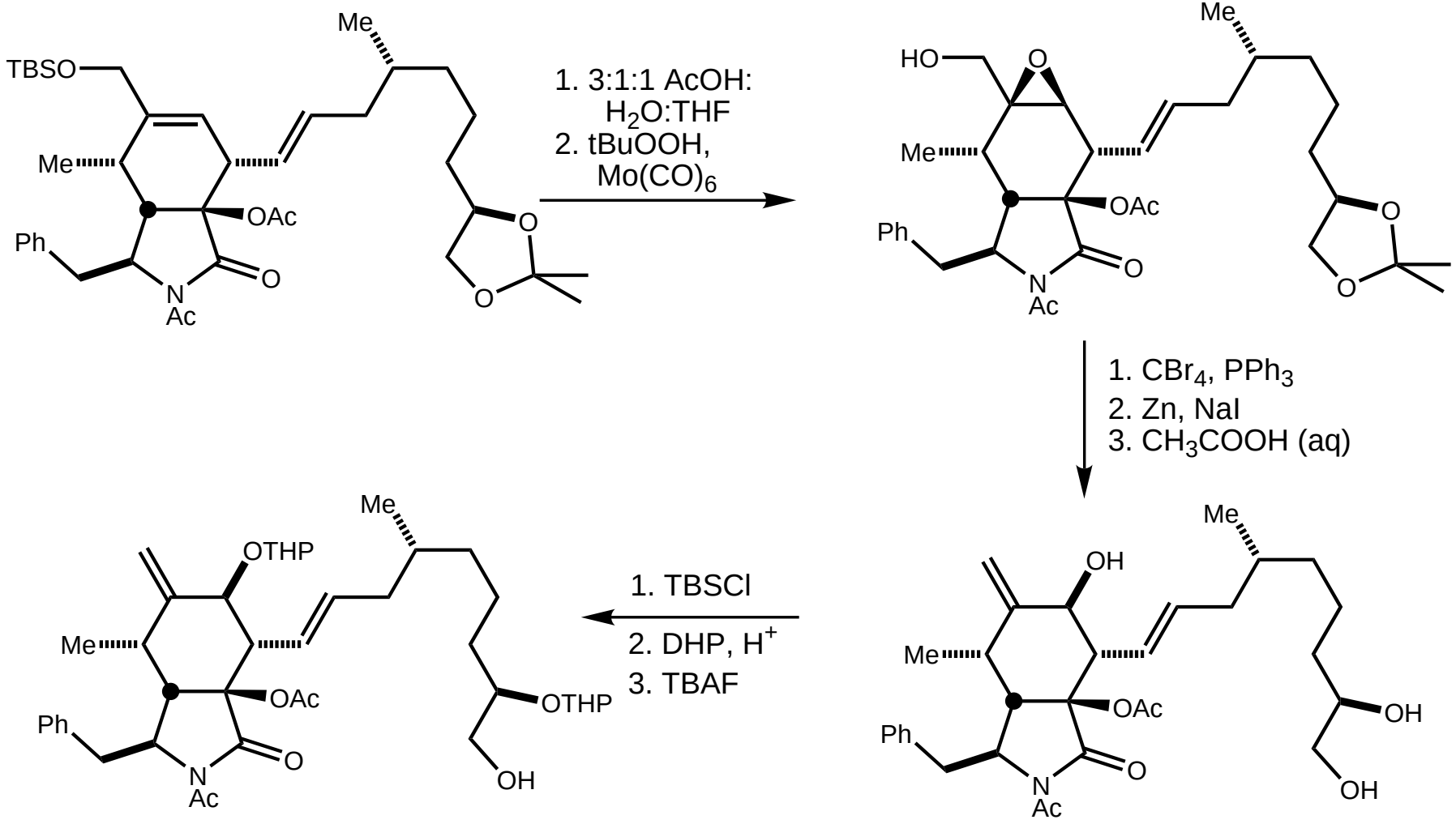


> 4:1 "mixture of diastereomers"

Stork *et al.*, *JACS*, **1978**, *100*, 7775
Vedejs *et al.*, *JOC*, **1978**, *43*, 376

Synthesis of Cytochalasin B - Stork

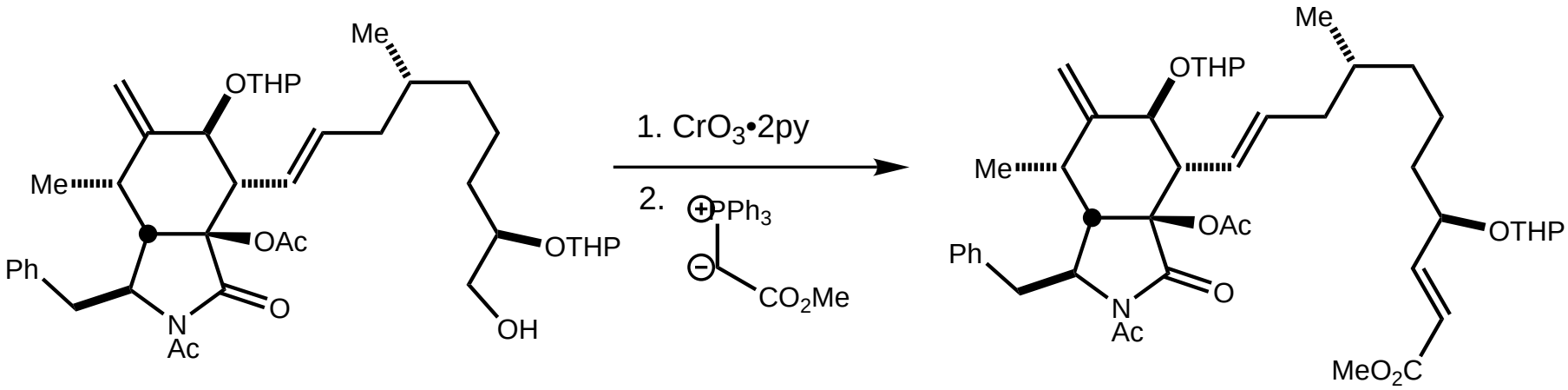
Introduction of Methylene Cyclohexanol Unit



Stork *et al.*, *JACS*, **1978**, *100*, 7775

Synthesis of Cytochalasin B - Stork

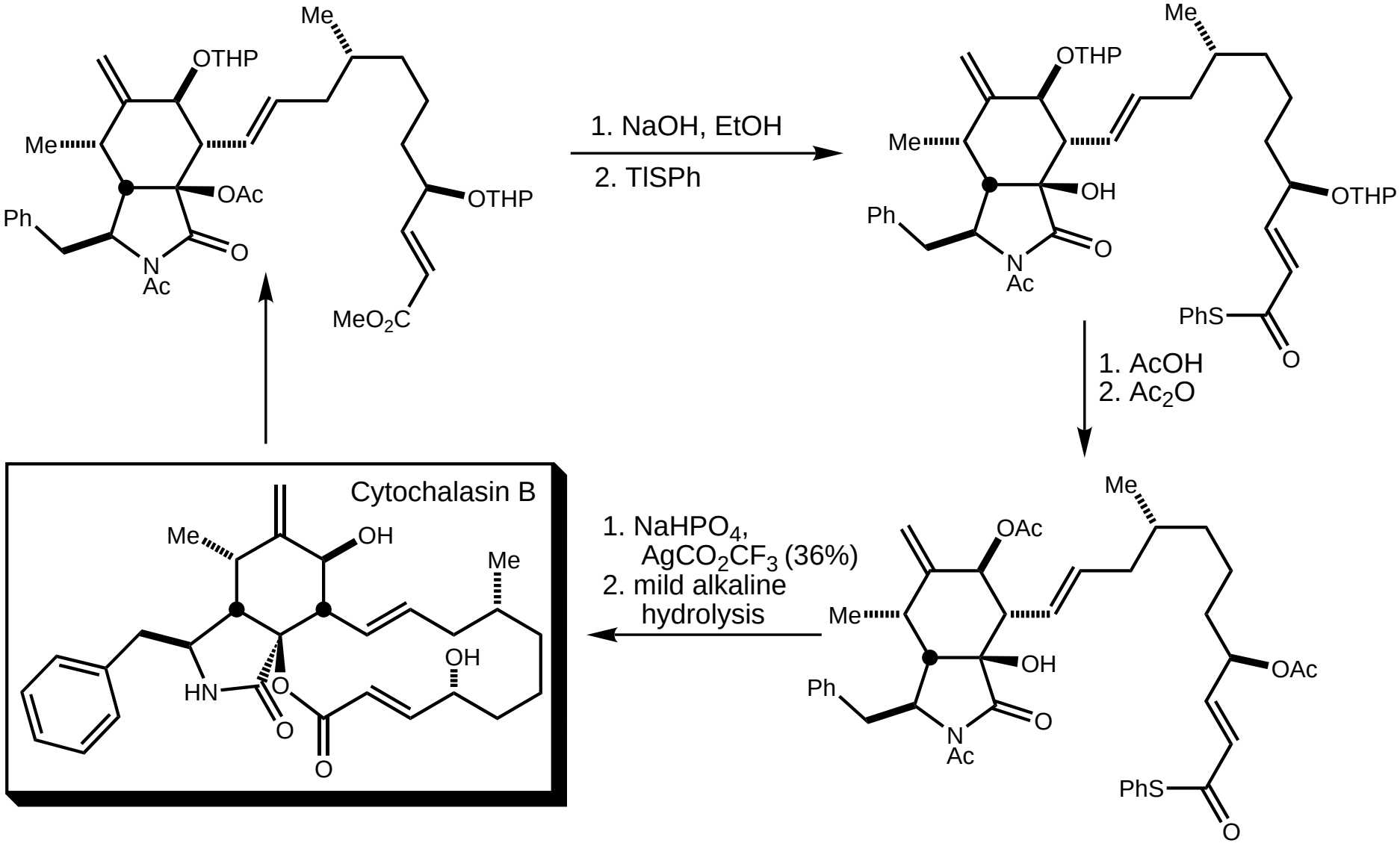
Completion of Formal Synthesis



Stork *et al.*, *JACS*, **1978**, *100*, 7775

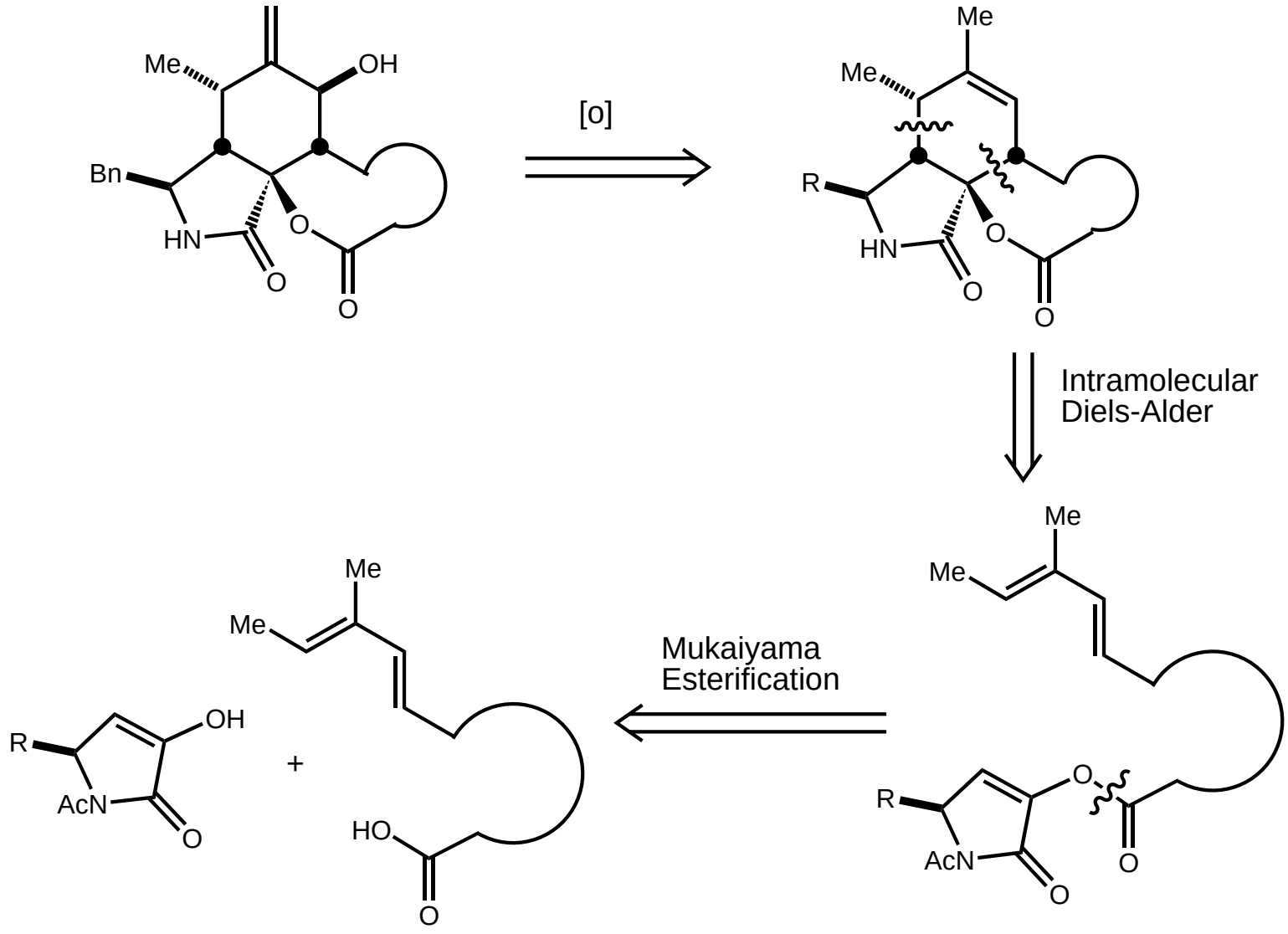
Masamune Lactonization

-Application to the synthesis of Cytochalasin B



Masamune *et al.*, *JACS*, **1977**, *99*, 6756

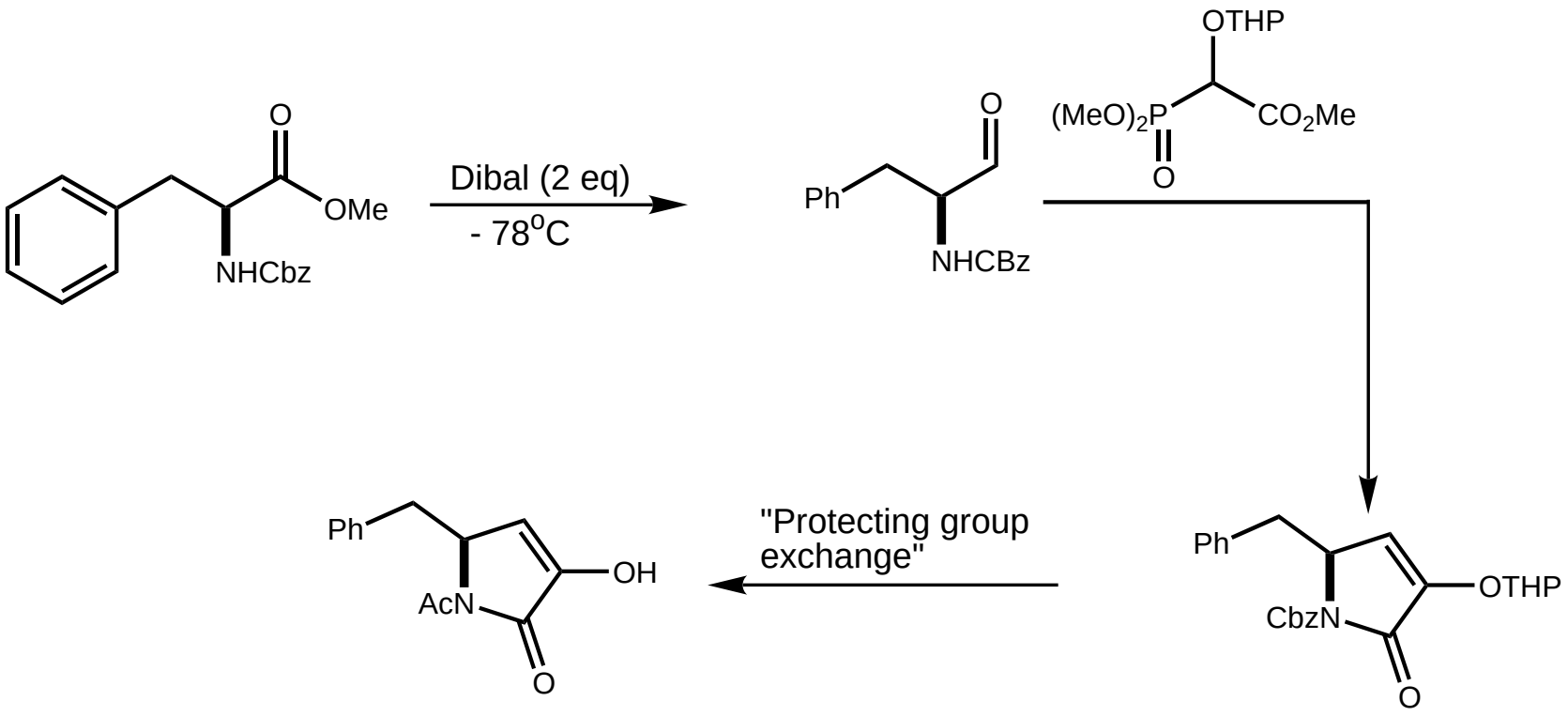
Stork's Revised Retrosynthetic Plan



Stork *et al.*, *JACS*, **1983**, *105*, 5510

Alternate Synthesis of Cytochalasin B - Stork

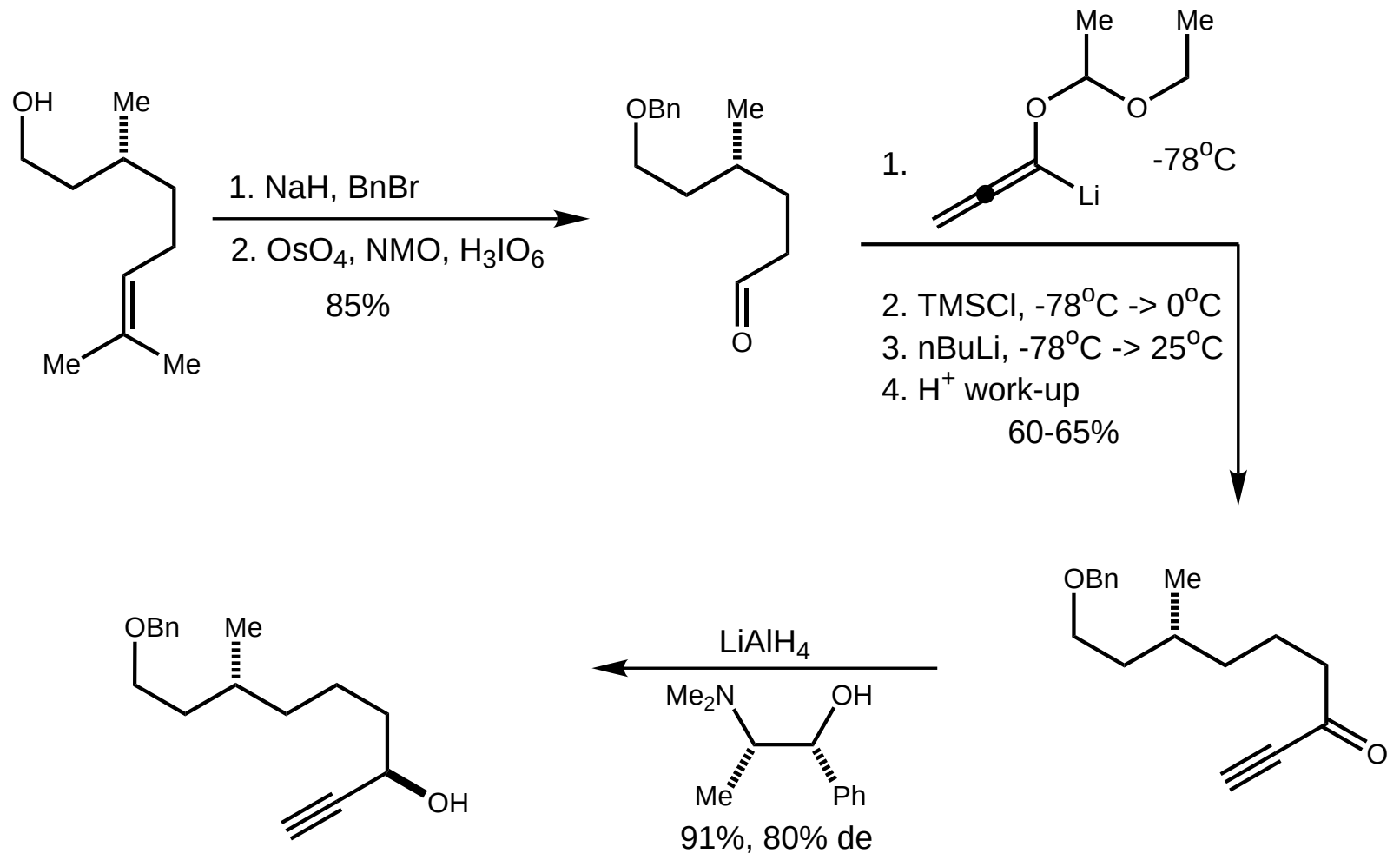
Preparation of Dienophile



Stork *et al*.,*JACS*, **1983**, *105*, 5510
Nakamura, *TL*, **1981**, *22*, 663

Alternate Synthesis of Cytochalasin B - Stork

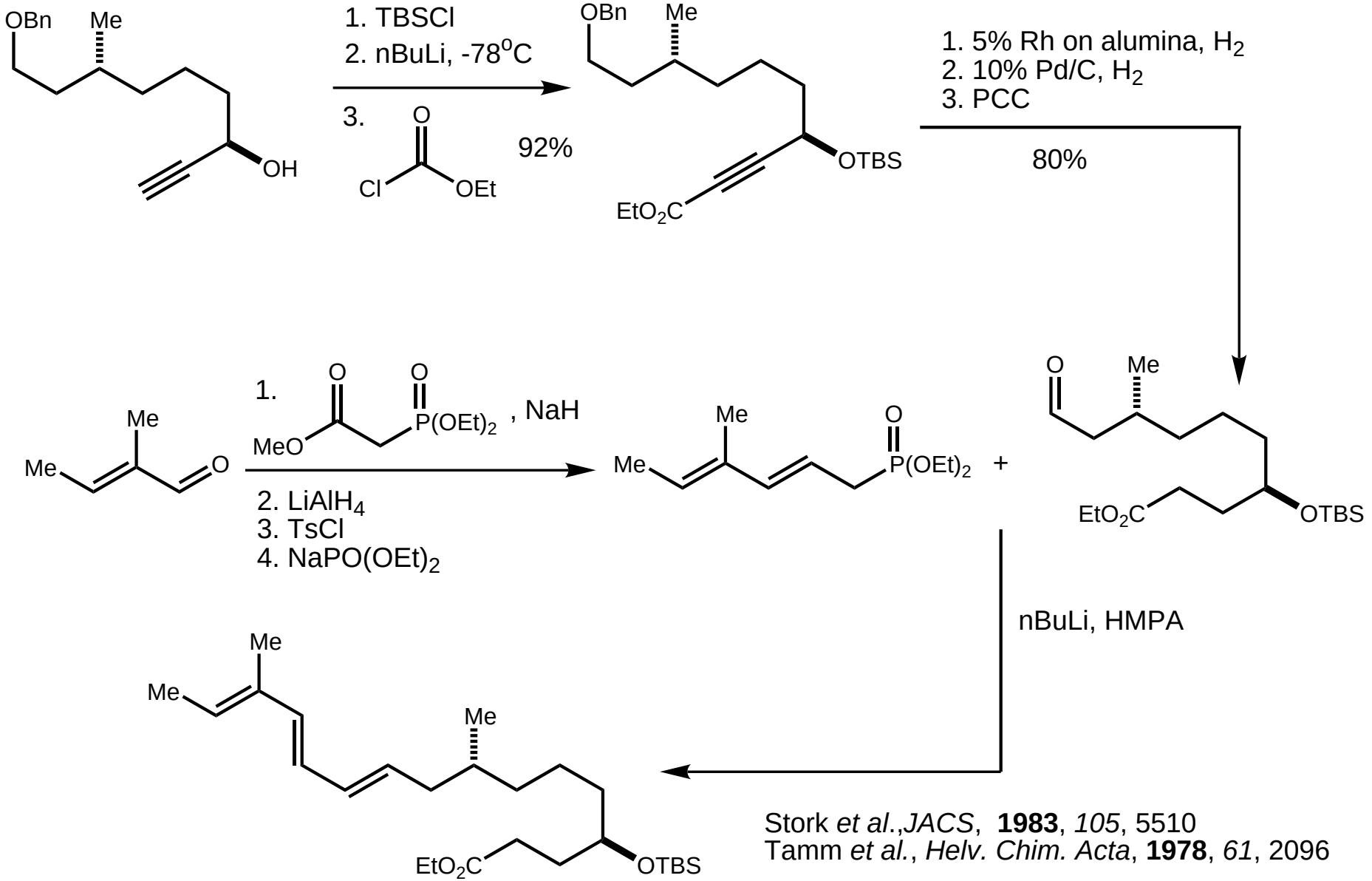
Manipulation of Alkyl Chain



Stork *et al*.,*JACS*, **1983**, *105*, 5510
Vigneron *et al*., *TL*, **1979**, 2683

Alternate Synthesis of Cytochalasin B - Stork

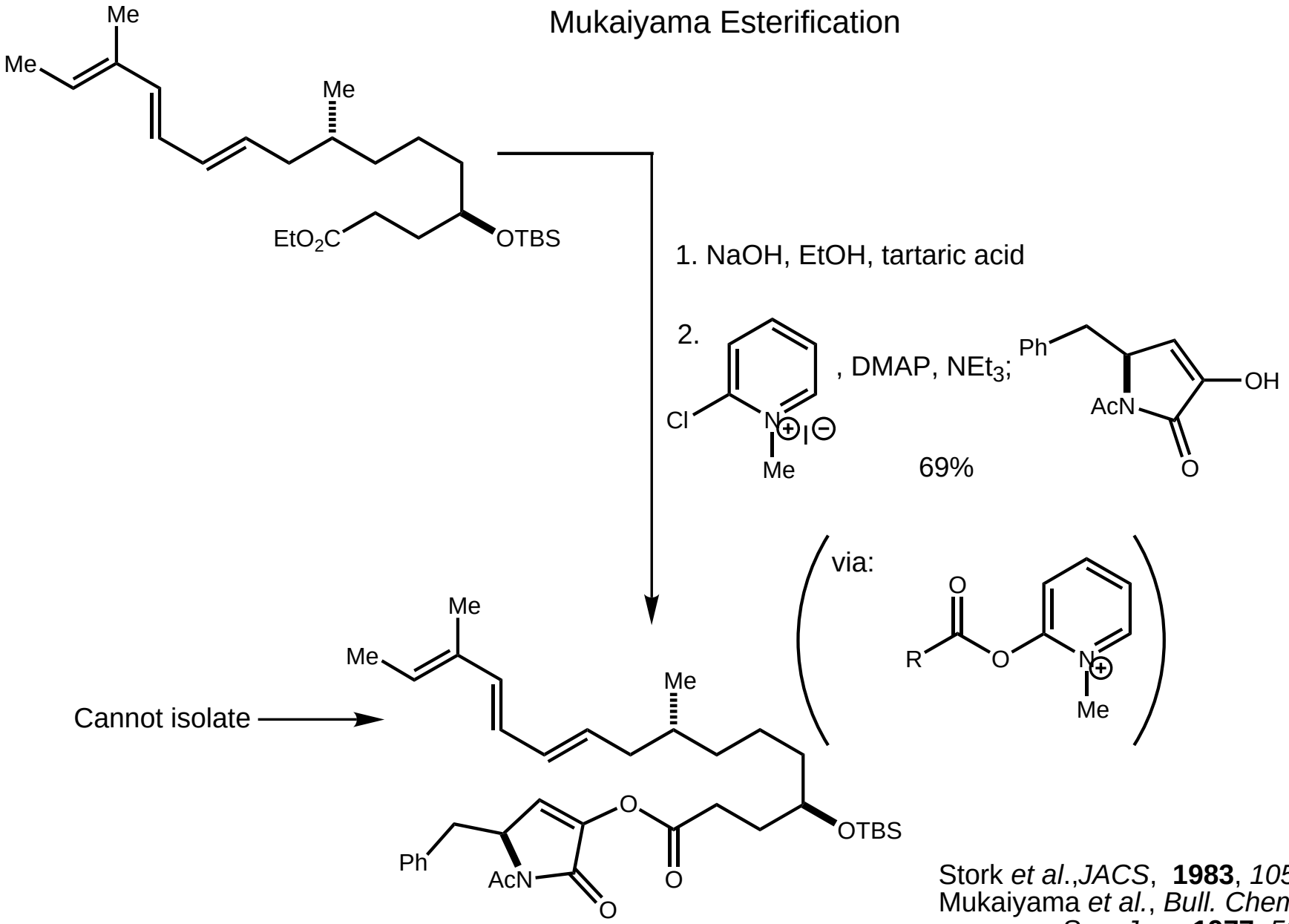
Preparation of Polyene



Stork *et al.*,*JACS*, **1983**, *105*, 5510
Tamm *et al.*, *Helv. Chim. Acta*, **1978**, *61*, 2096

Alternate Synthesis of Cytochalasin B - Stork

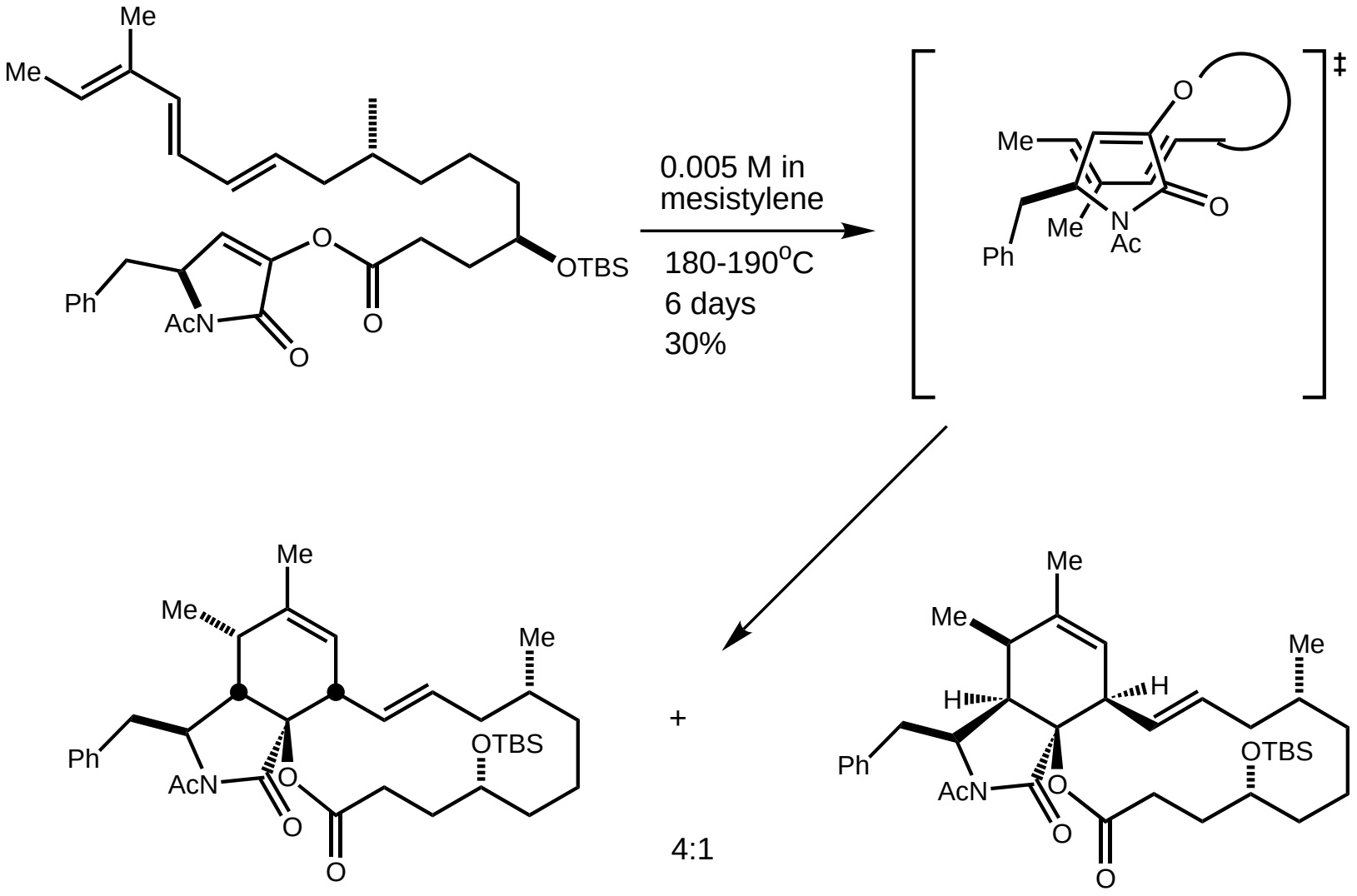
Mukaiyama Esterification



Stork *et al*.,*JACS*, **1983**, *105*, 5510
Mukaiyama *et al.*, *Bull. Chem. Soc. Jpn.,* **1977**, *50*, 1863

Alternate Synthesis of Cytochalasin B - Stork

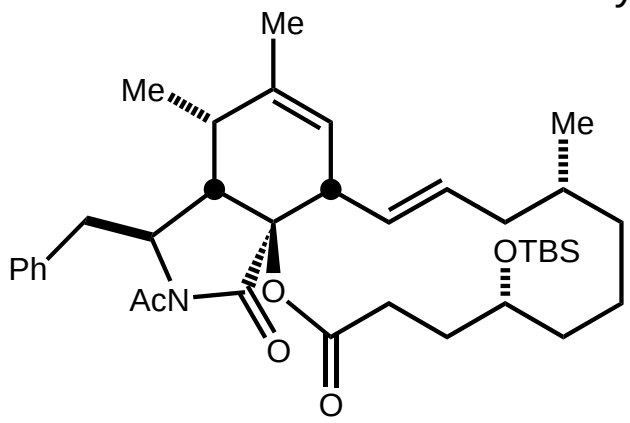
Diels-Alder Reaction



Stork *et al.*,*JACS*, **1983**, *105*, 5510

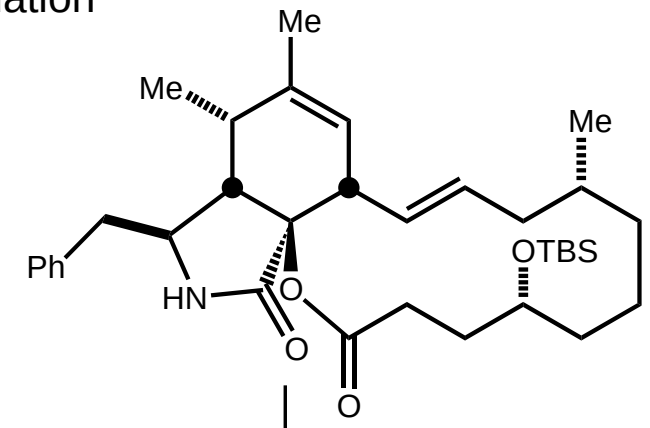
Alternate Synthesis of Cytochalasin B - Stork

Phenylselenation and Epoxidation

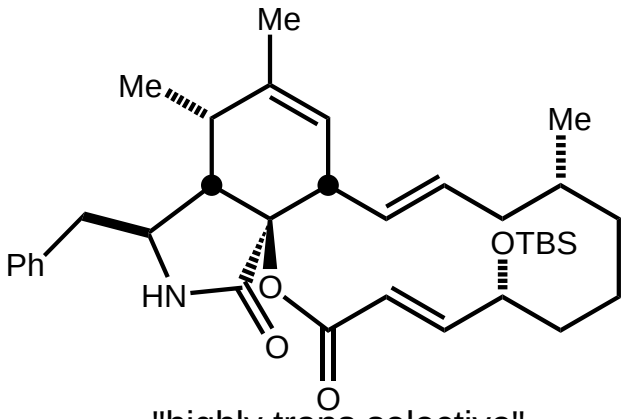


(+diastereomer)

1. K_2CO_3, MeOH
2. Separate

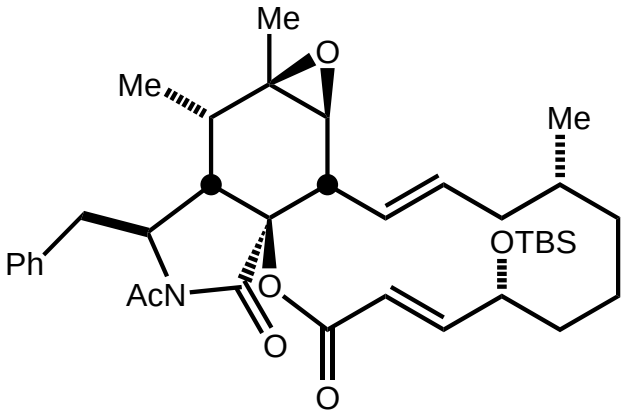


1. LDA (3 eq.), -78^{o}C
2. PhSeCl (3 eq.)
3. H_2O_2, py



"highly trans selective"

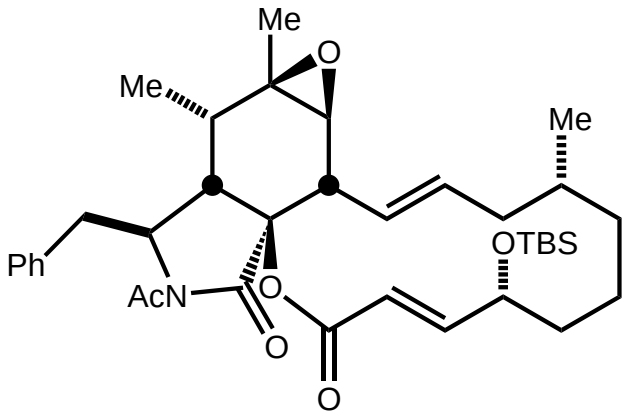
1. Ac_2O, DMAP, NEt_3
2. $^{t}BuOOH$, $Mo(CO)_6$
80%



Stork *et al*.,*JACS*, **1983**, *105*, 5510

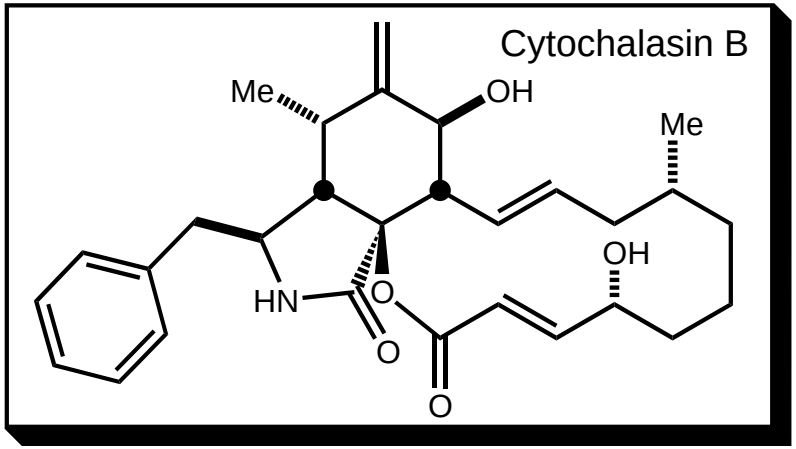
Alternate Synthesis of Cytochalasin B - Stork

Completion of the Synthesis



1. $Al(O^iPr)_3$, xylene, 8h
2. K_2CO_3, MeOH
3. TBAF

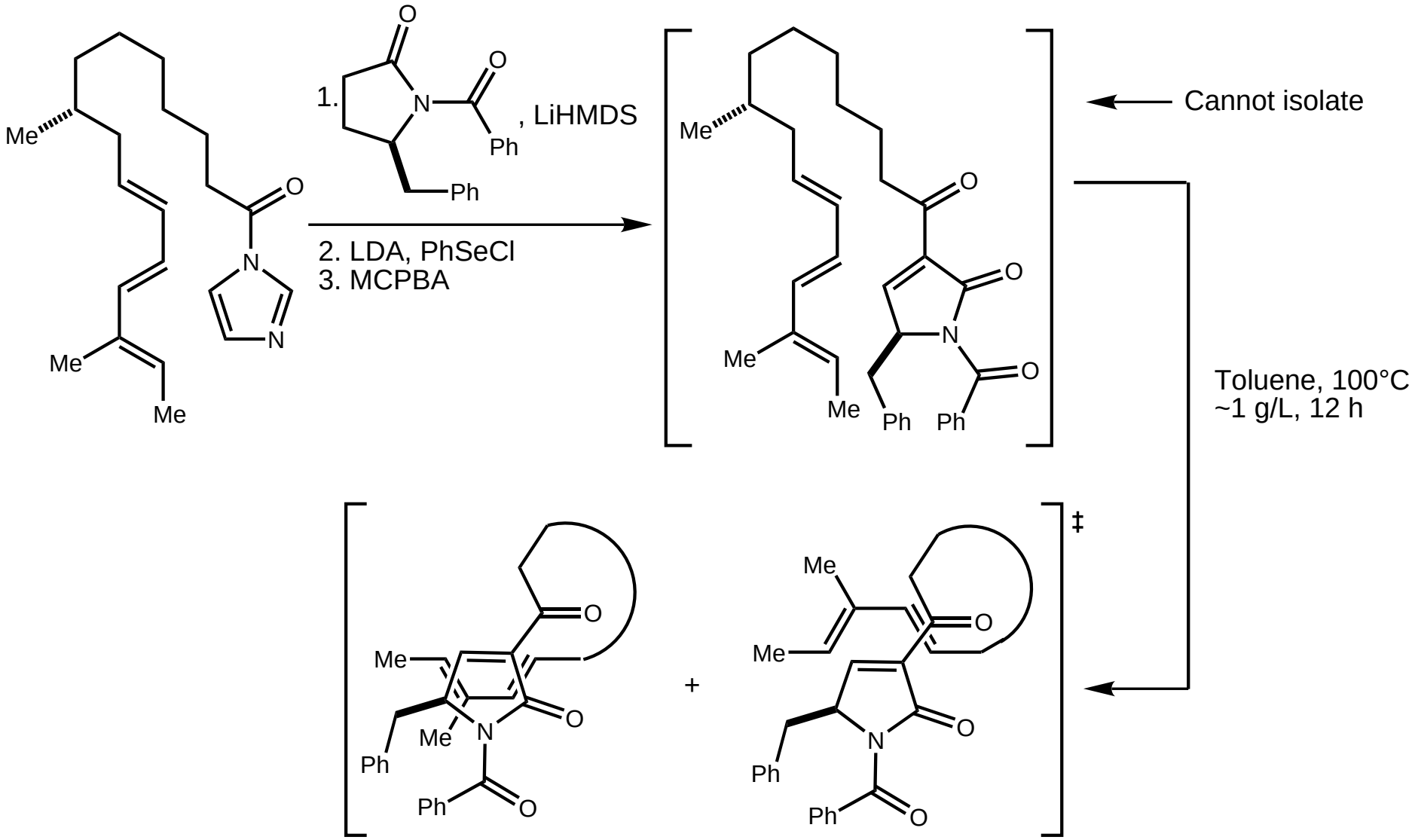
74%



Stork *et al.*,*JACS*, **1983**, *105*, 5510

Synthesis of Proxiphomin - Thomas

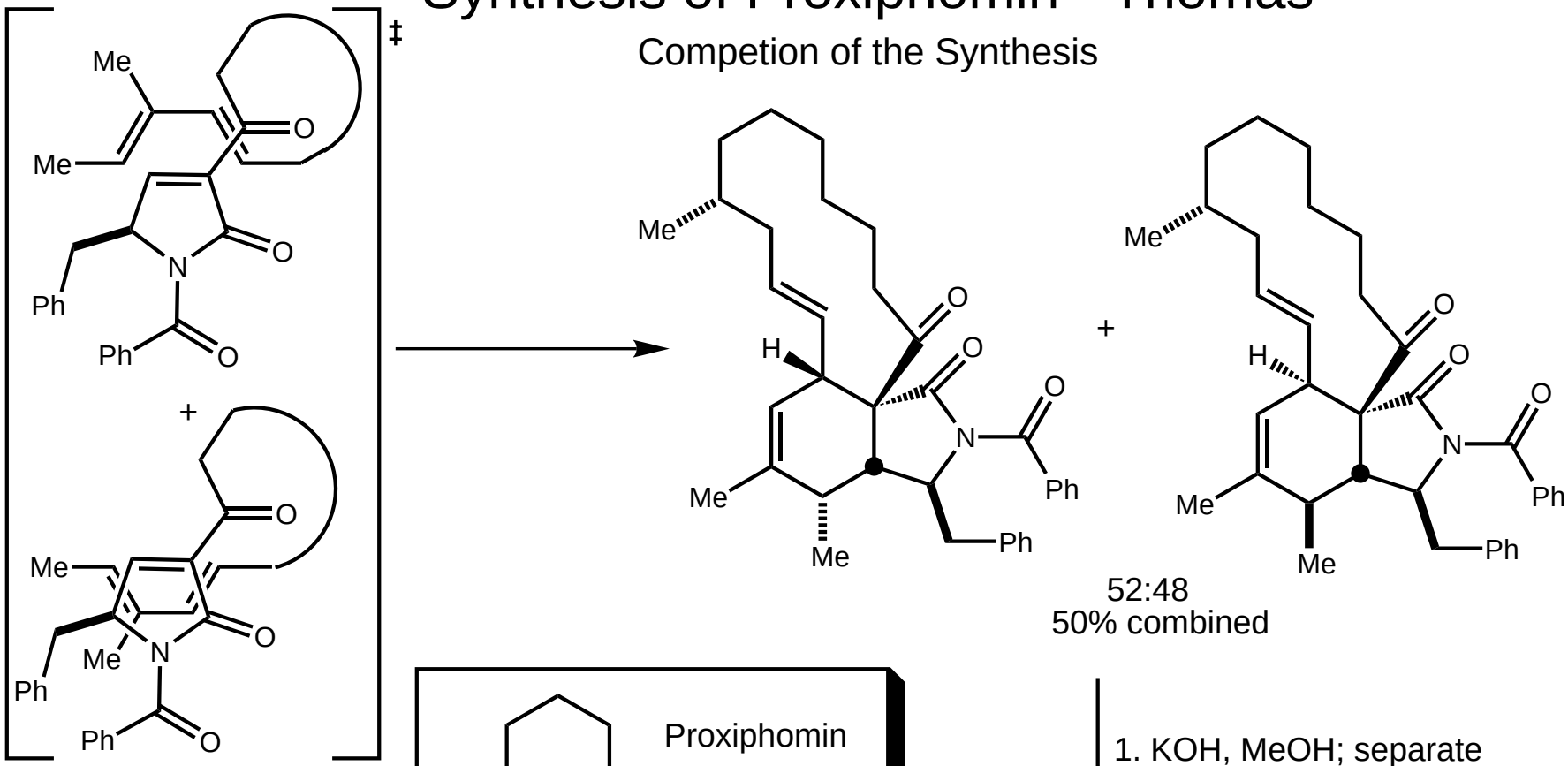
Diel-Alder Reaction



Thomas *et al.*, *Chem. Commun.*, **1985**, 143

Synthesis of Proxiphomin - Thomas

Competion of the Synthesis



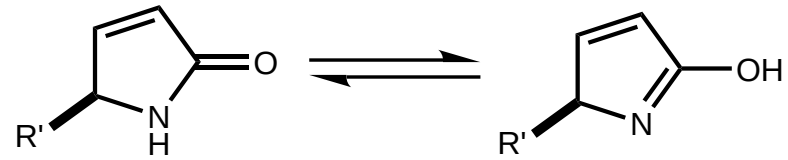
Thomas *et al.*, *Chem. Commun.*, **1985**, 143

Stork and Thomas Syntheses

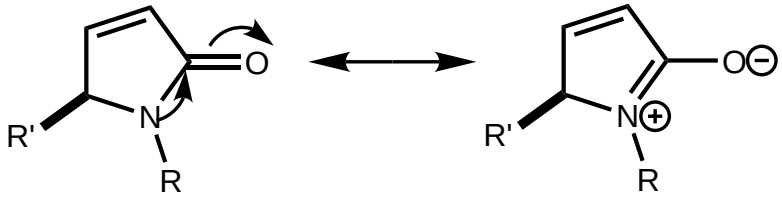
Summary of important points

1. N-Acyl protecting groups are important

   Reasons: prevents tautomerization; destabilises undesirable resonance form



Vedejs *et al.*, *JOC*, **1978**, *43*, 376

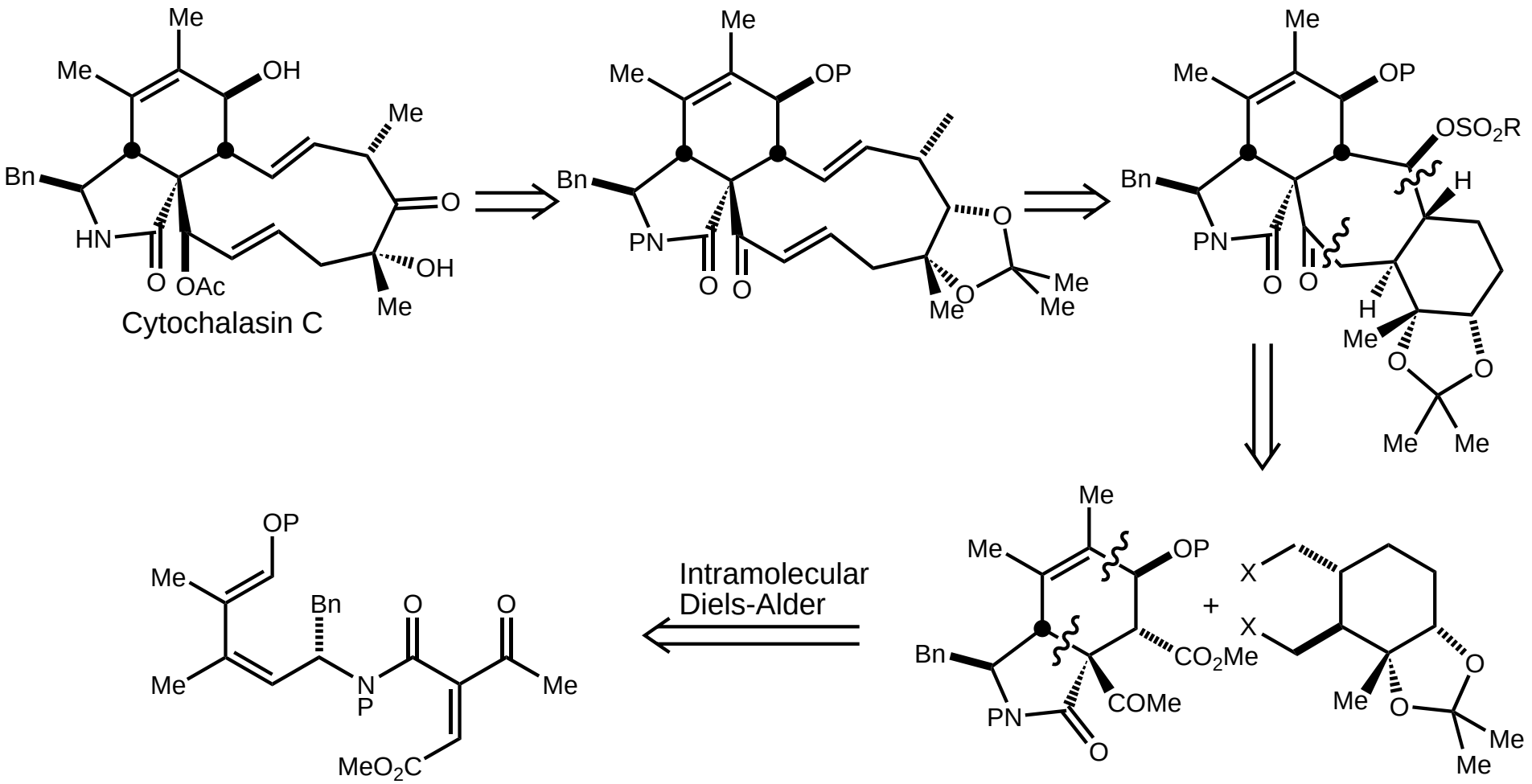


R = alkyl

2. Diactivated dienophiles lead to endo/exo selectivity problems

3. Polyenes polymerize on isolation; leave in solution

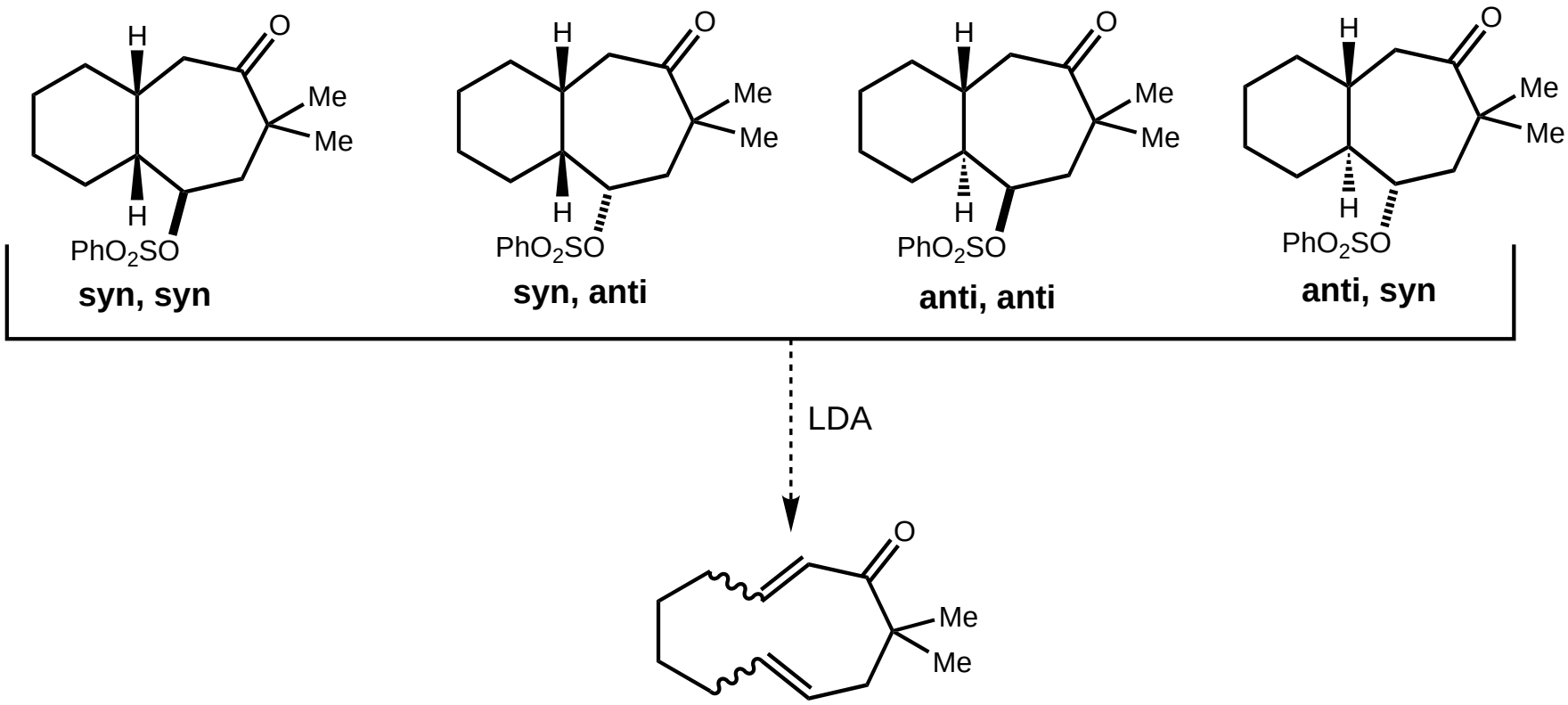
Fuchs' Retrosynthetic Plan



Fuchs *et al.*, *JACS*, **1979**, *101*, 3567
Syn. Comm., **1986**, *16*, 1297

Fuchs' Cyctochalasin D Model Studies

Plan: Form 11-membered cyclic diene using enolate-assisted intraannular 1,4 fragmentation
Method: Test all four possible diastereomers

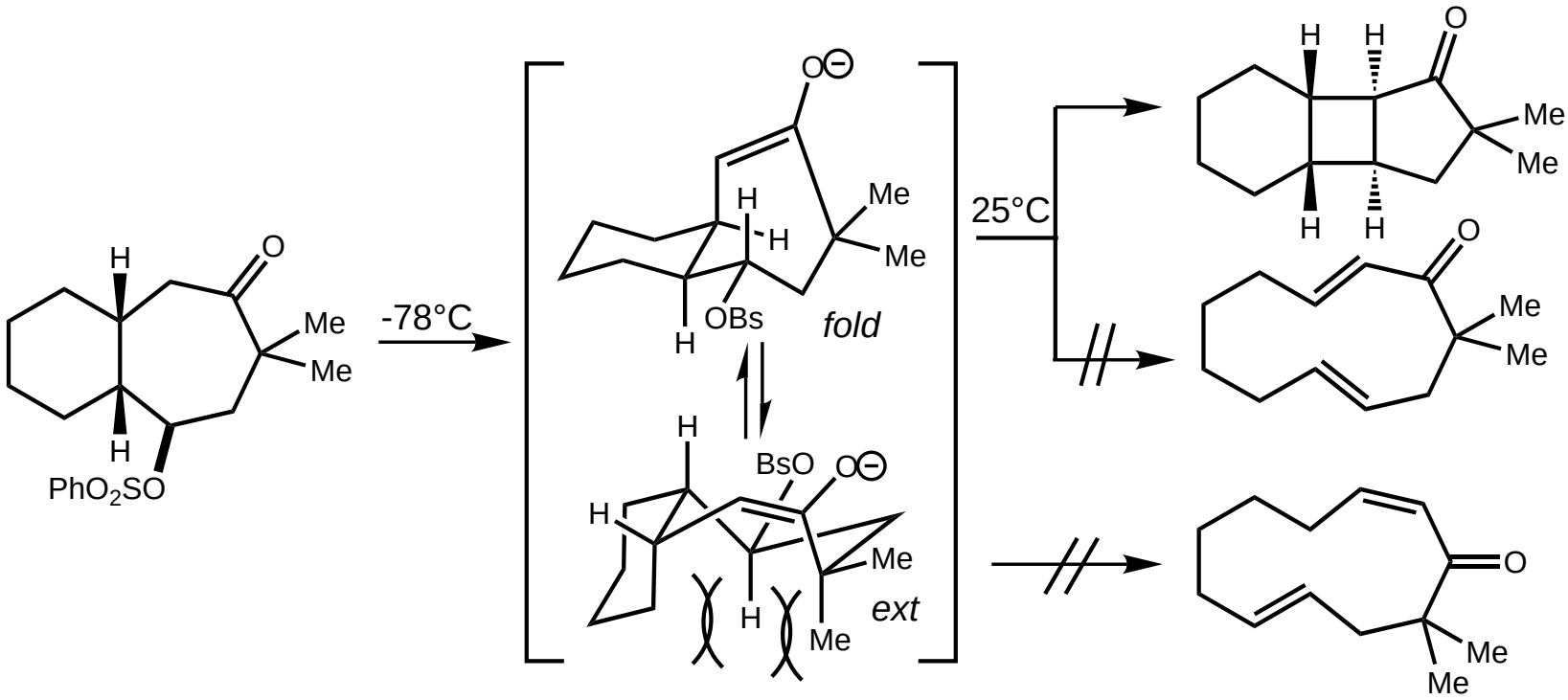


Fuchs *et al.*, *JACS*, **1979**, *101*, 3567

Fuchs' Cyctochalasin D Model Studies

- In all cases, two enolate conformers (*fold* and *ext*) proposed to explain major product formed
- two possible products: ketocyclobutanes (varying stereochem.) by direct diplacement
  11-membered cyclic diene (varying double bond geometry) by fragmentation

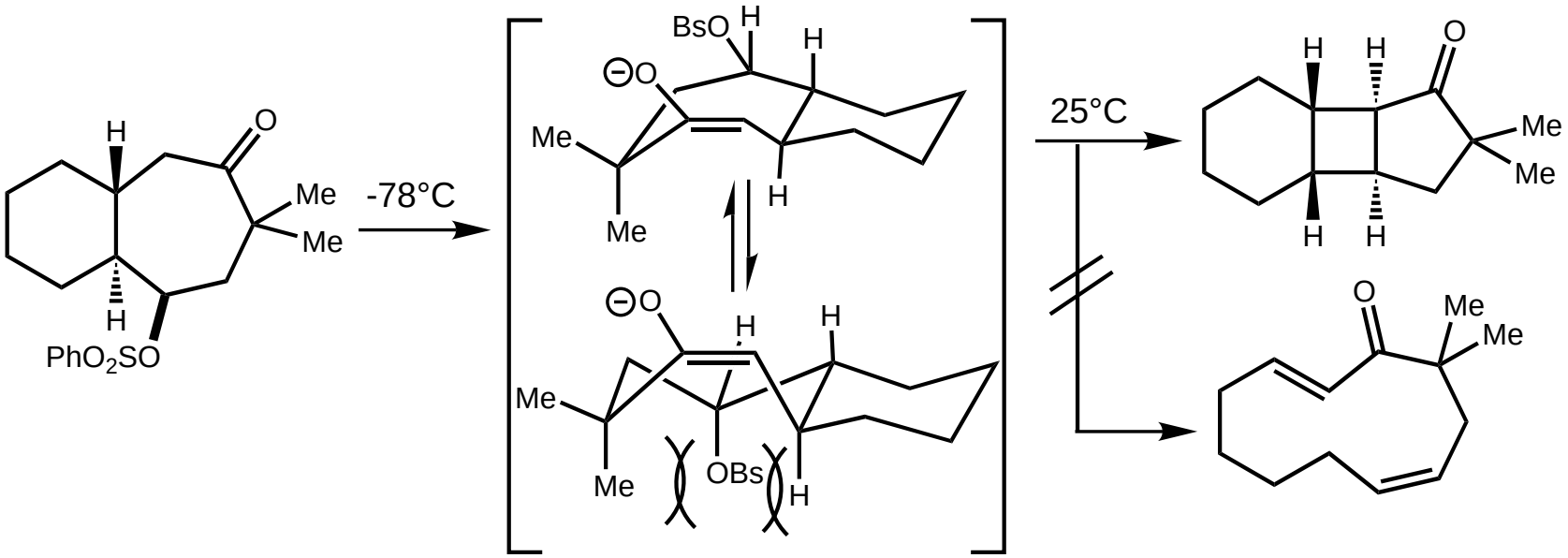
•**syn, syn** isomer: only ketocyclobutane formed via *fold* conformer



Fuchs *et al.*, *JACS*, **1979**, *101*, 3567

Fuchs' Cyctochalasin D Model Studies

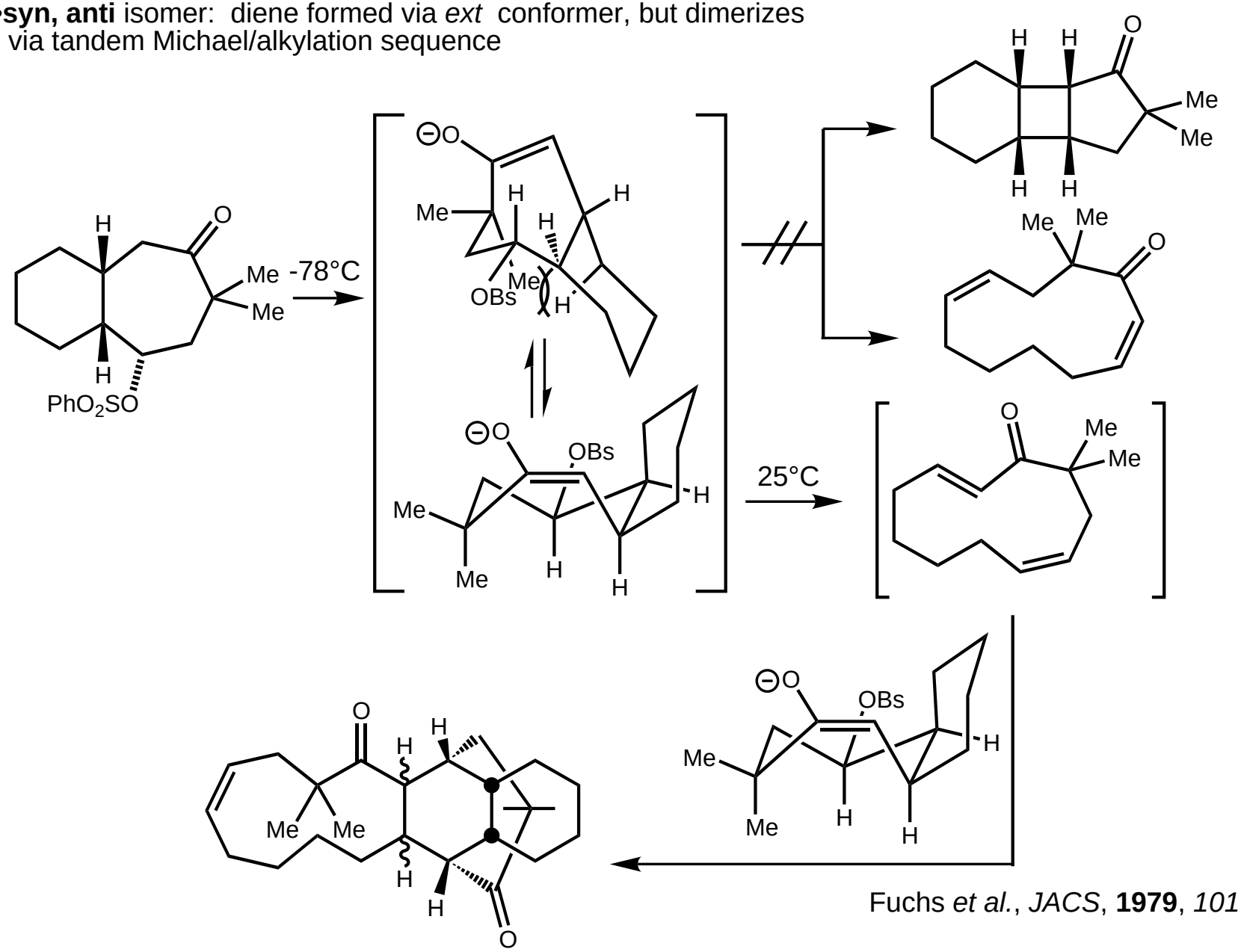
•**anti, anti** isomer: only ketocyclobutane formed via *fold* conformer



Fuchs *et al.*, *JACS*, **1979**, *101*, 3567

Fuchs' Cyctochalasin D Model Studies

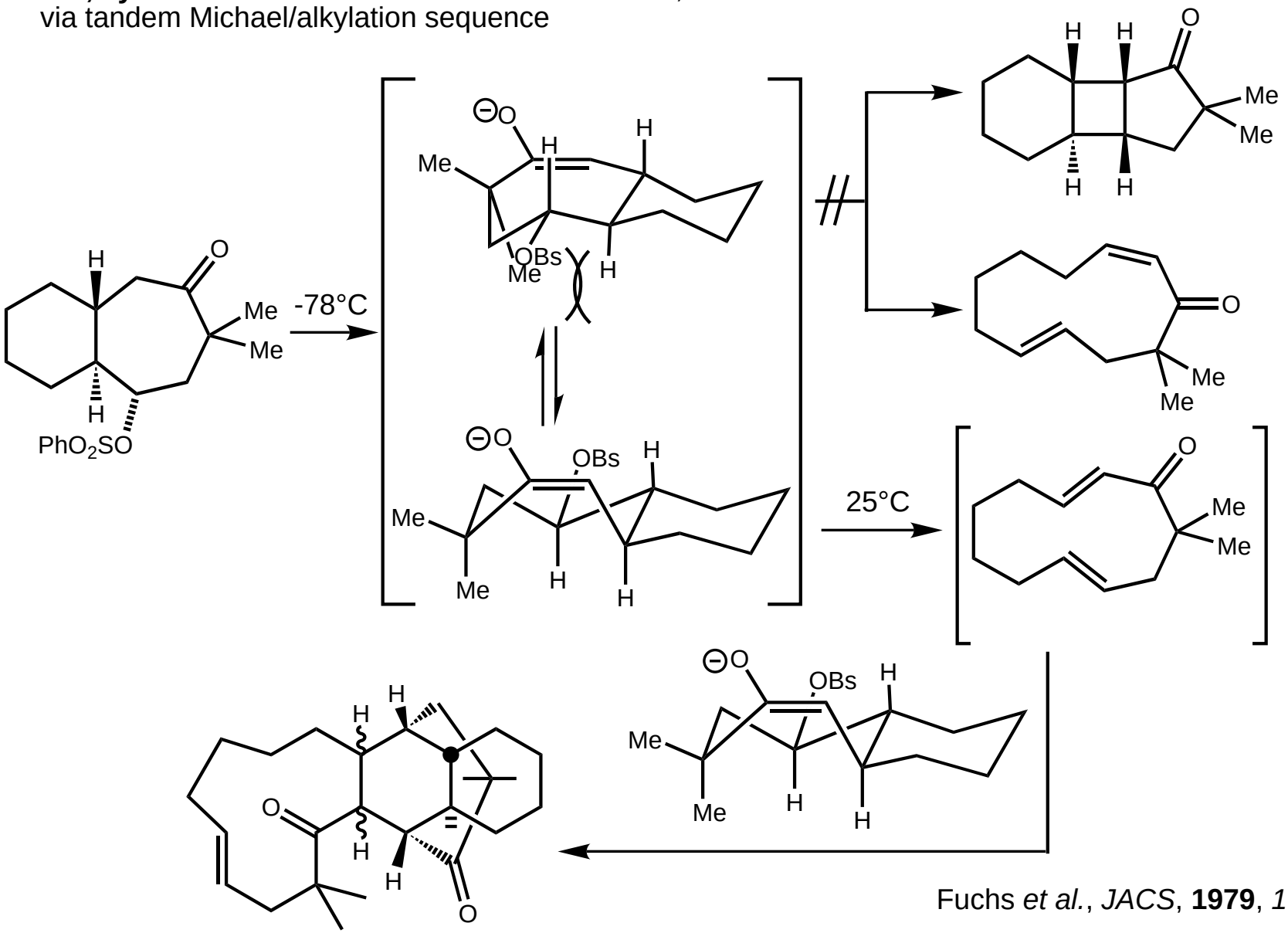
- **syn, anti** isomer: diene formed via *ext* conformer, but dimerizes via tandem Michael/alkylation sequence



Fuchs *et al.*, *JACS*, **1979**, *101*, 3567

Fuchs' Cyctochalasin D Model Studies

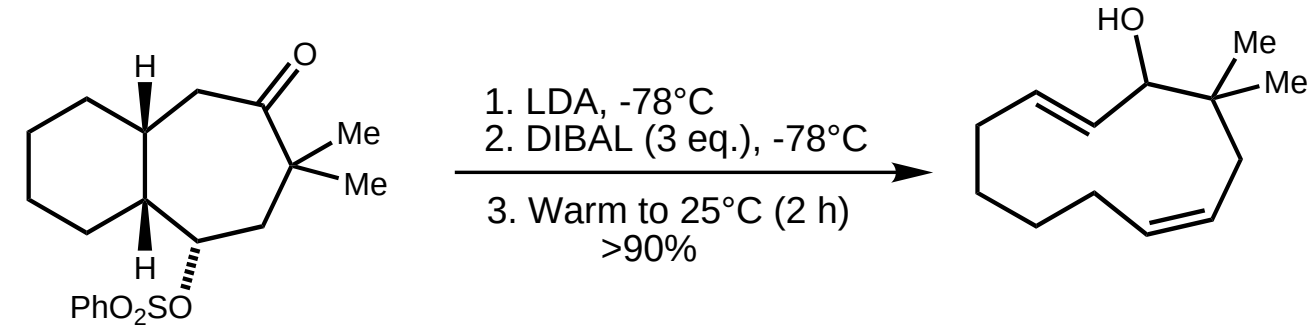
•**anti, syn** isomer: diene formed via *ext* conformer, but dimerizes via tandem Michael/alkylation sequence

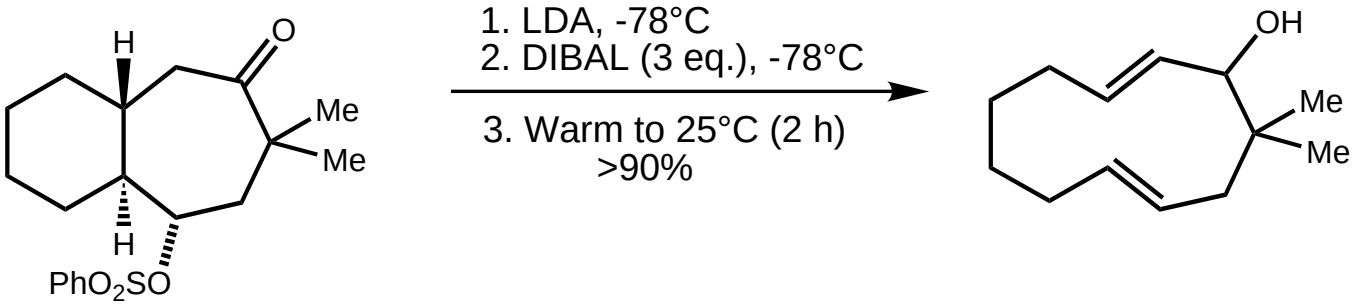


Fuchs *et al.*, *JACS*, **1979**, *101*, 3567

Fuchs' Cyctochalasin D Model Studies

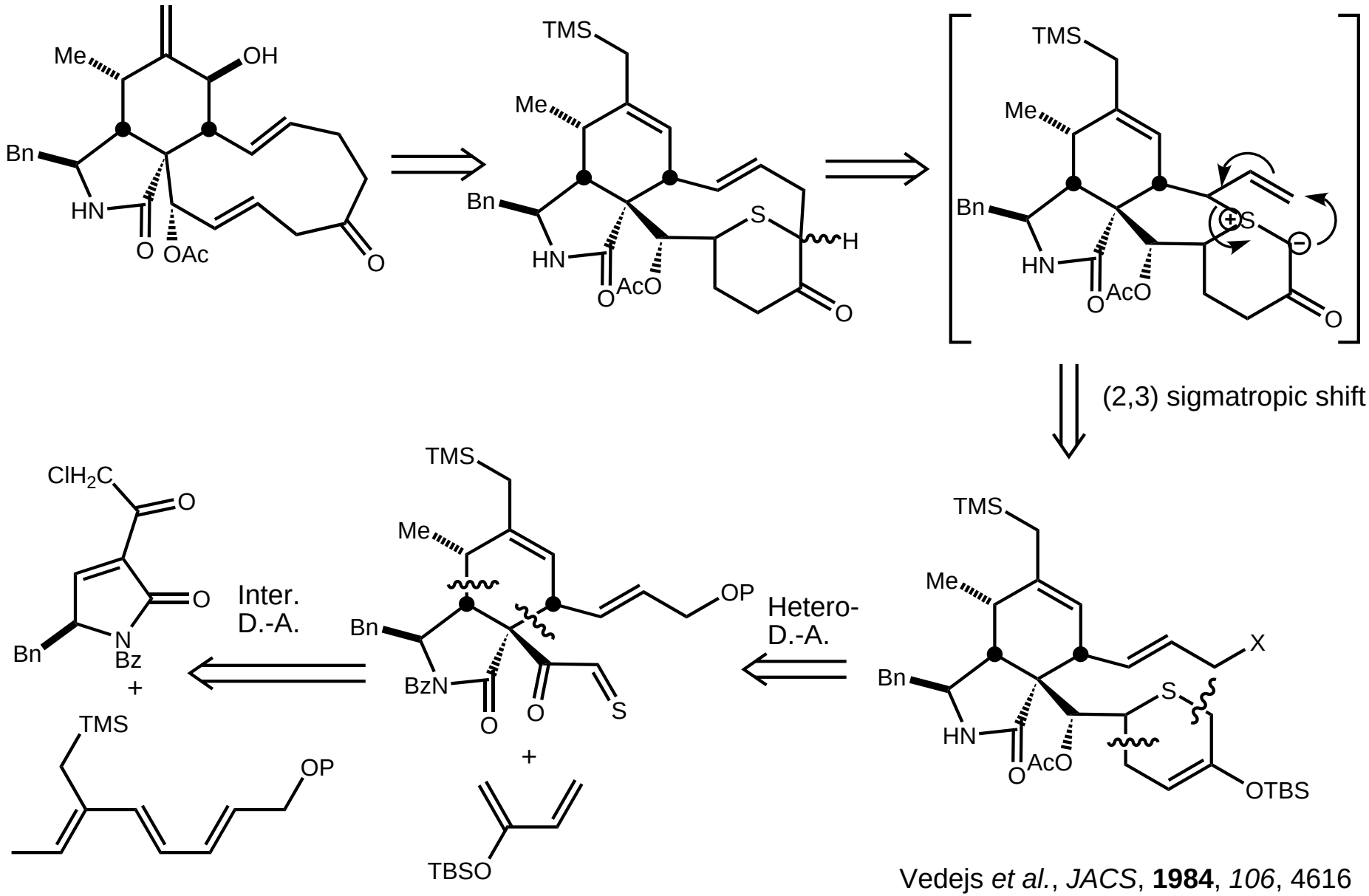
The solution: *in situ* reduction





Fuchs *et al.*, *JACS*, **1979**, *101*, 3567

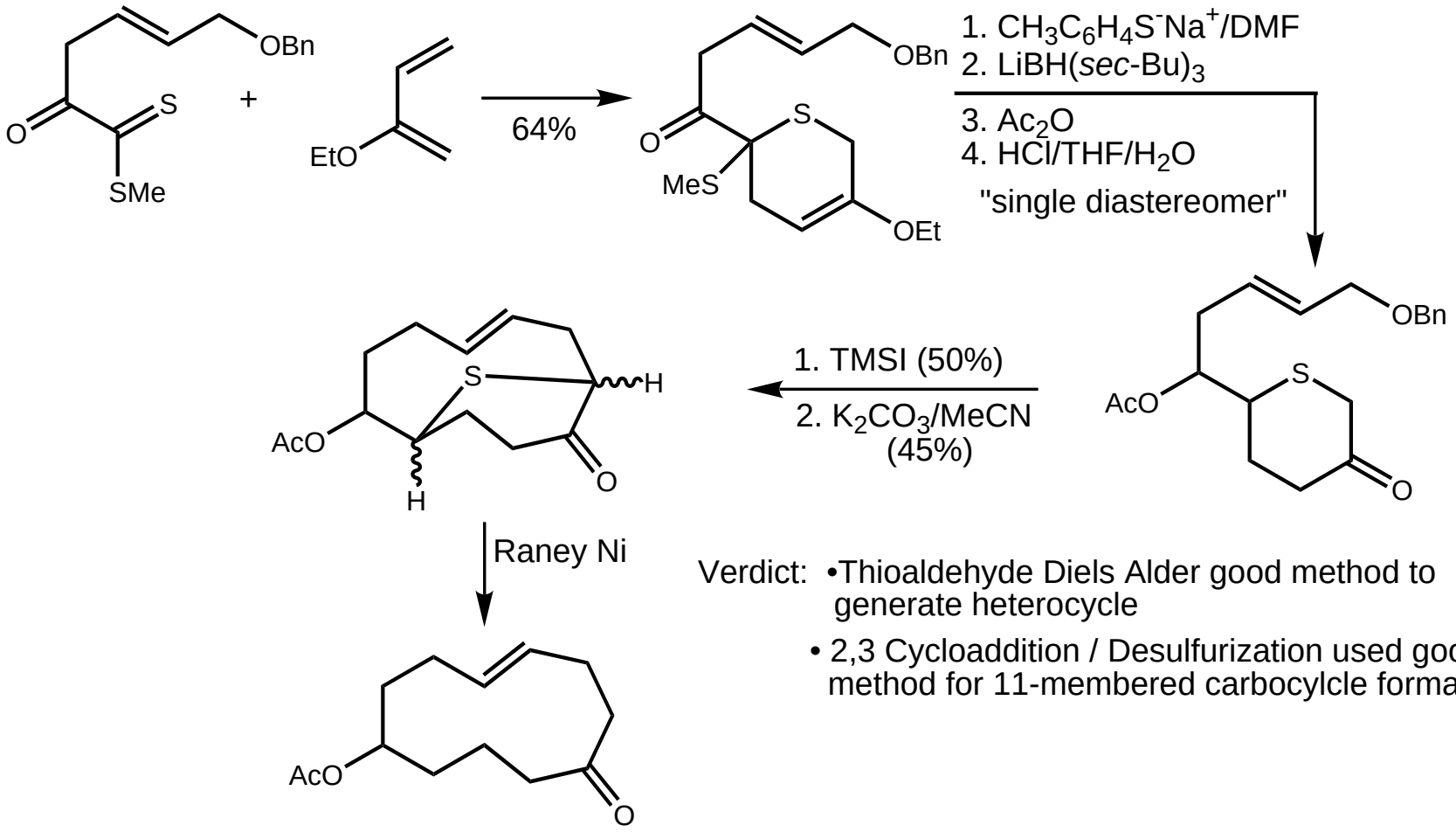
Vedejs' Retrosynthetic Plan



Vedejs *et al.*, *JACS*, **1984**, *106*, 4616

Synthesis of Cytochalasin D Analog I - Vedejs

2,3 Sigmatropic Shift Model Studies



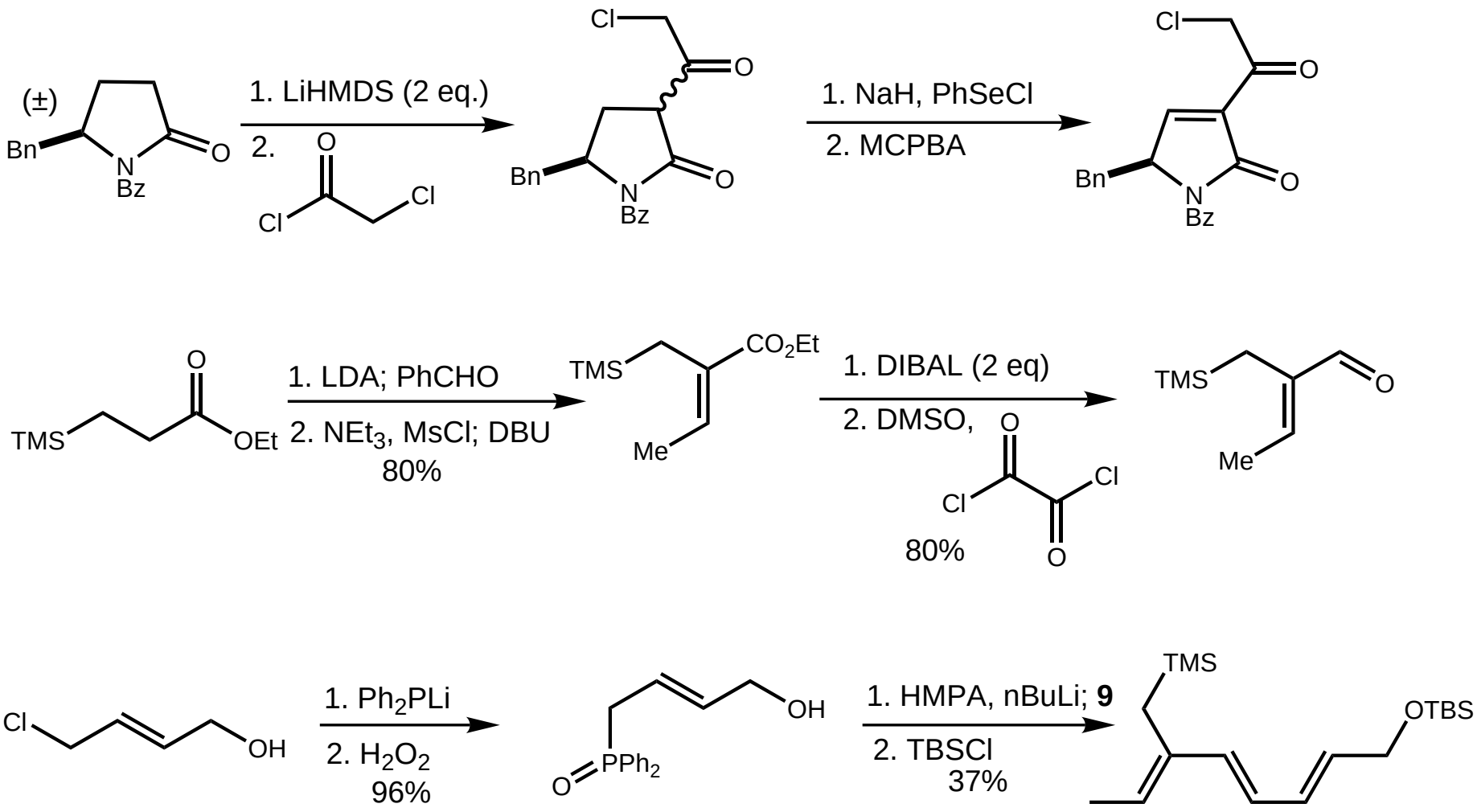
Verdict: •Thioaldehyde Diels Alder good method to generate heterocycle

• 2,3 Cycloaddition / Desulfurization used good method for 11-membered carbocylcle formation

Vedejs *et al.*, *JOC*, **1982**, *47*, 4384

Synthesis of Cytochalasin D Analog I - Vedejs

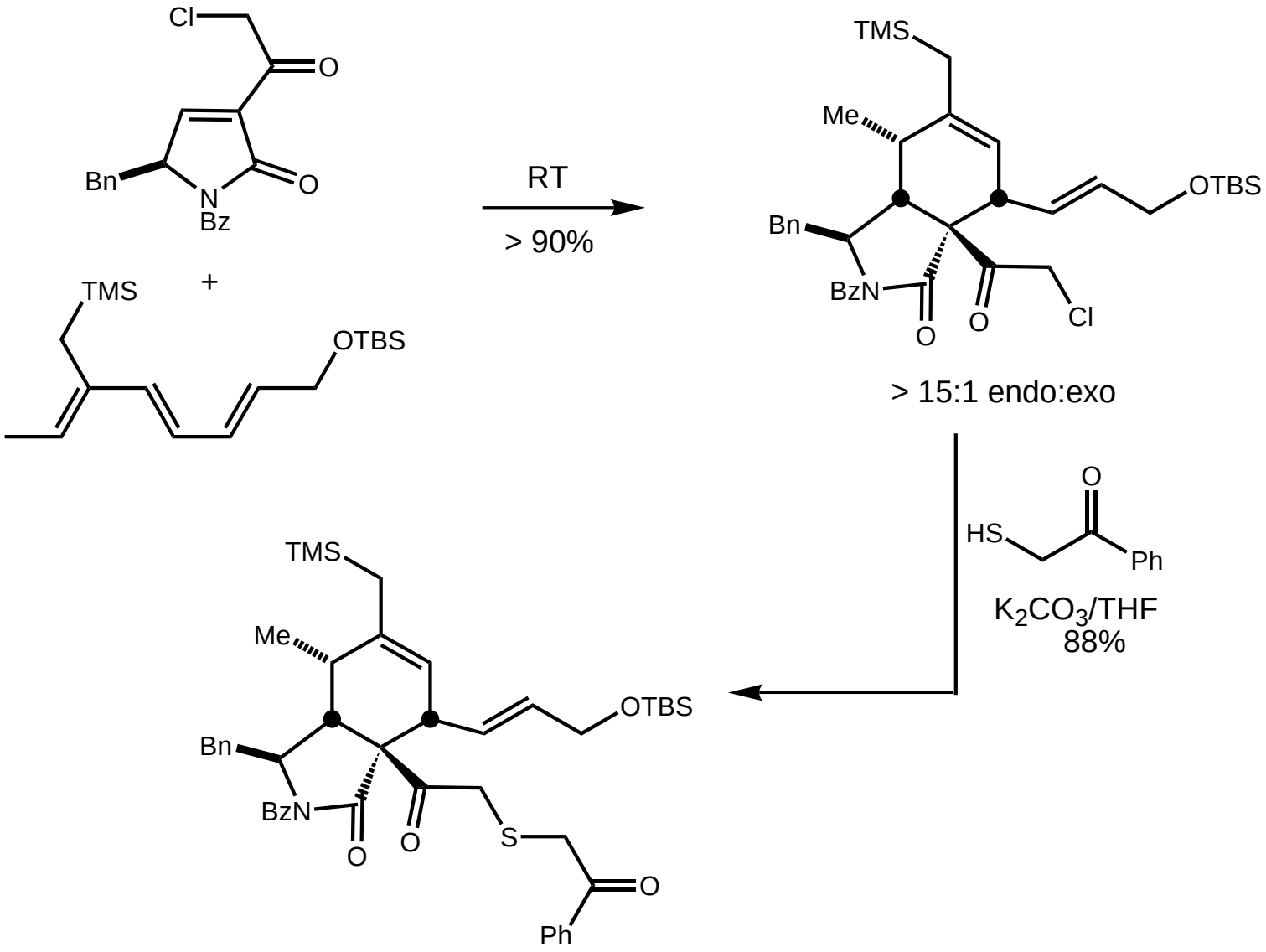
Synthesis of Precursors



Vedejs *et al.*, *JACS*, **1984**, *106*, 4617
JOC, **1982**, *47*, 1534

Synthesis of Cytochalasin D Analog I - Vedejs

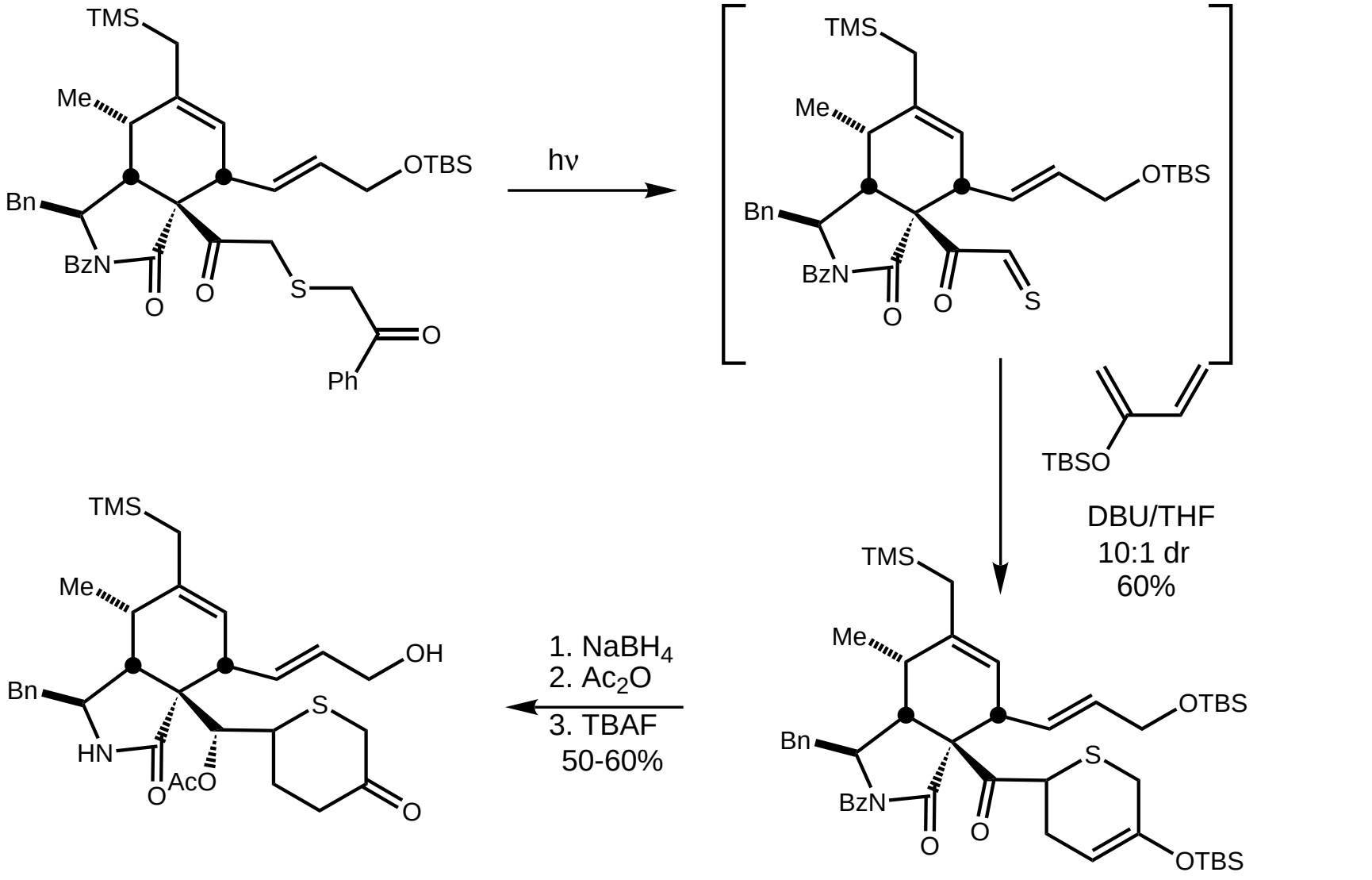
Diels-Alder Reaction



Vedejs *et al.*, *JACS*, **1984**, *106*, 4617
JOC, **1982**, *47*, 1534

Synthesis of Cytochalasin D Analog I - Vedejs

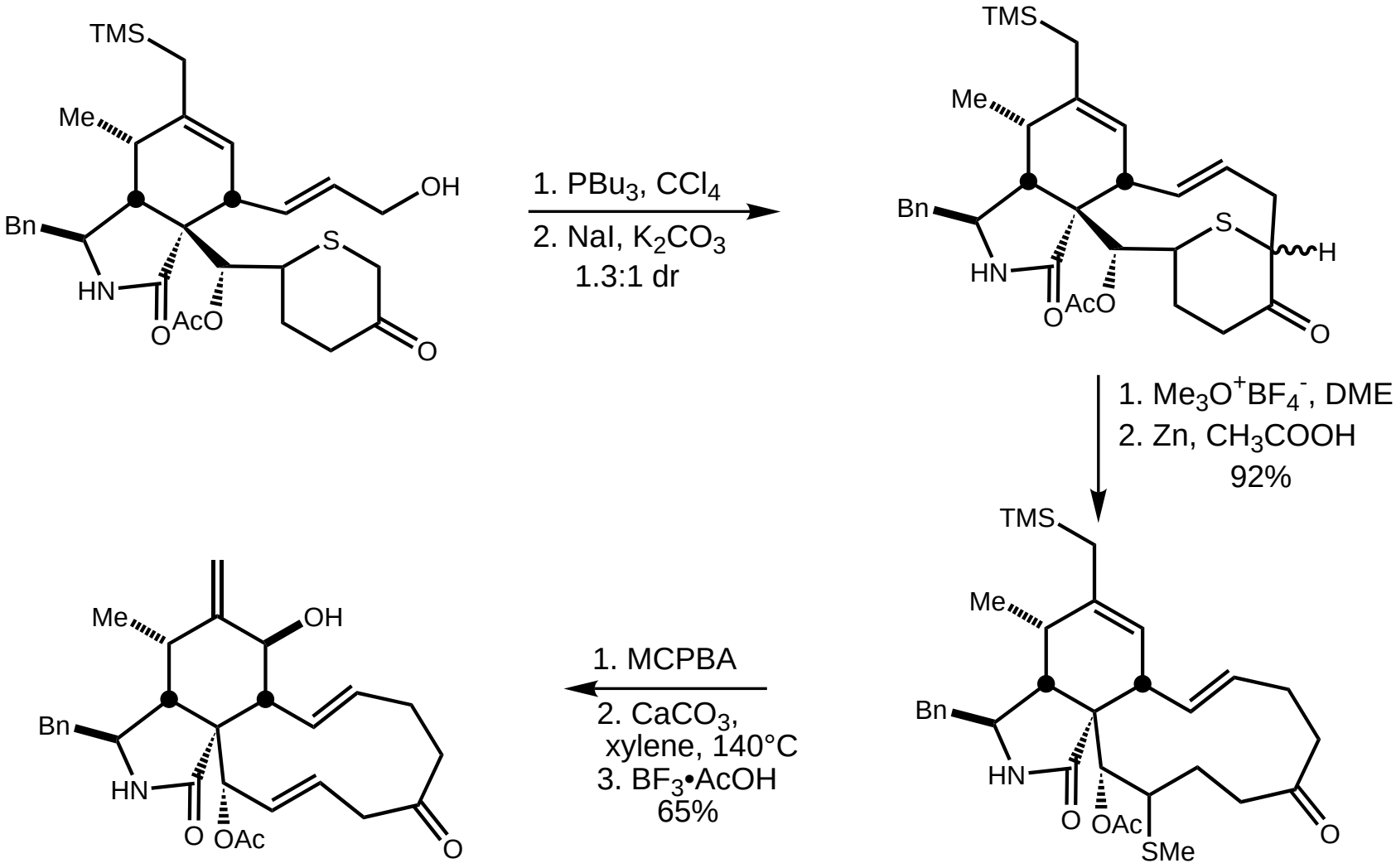
Thioaldehyde Diels-Alder Reaction



Vedejs *et al.*, *JACS*, **1984**, *106*, 4617
JACS, **1982**, *104*, 1445

Synthesis of Cytochalasin D Analog I - Vedejs

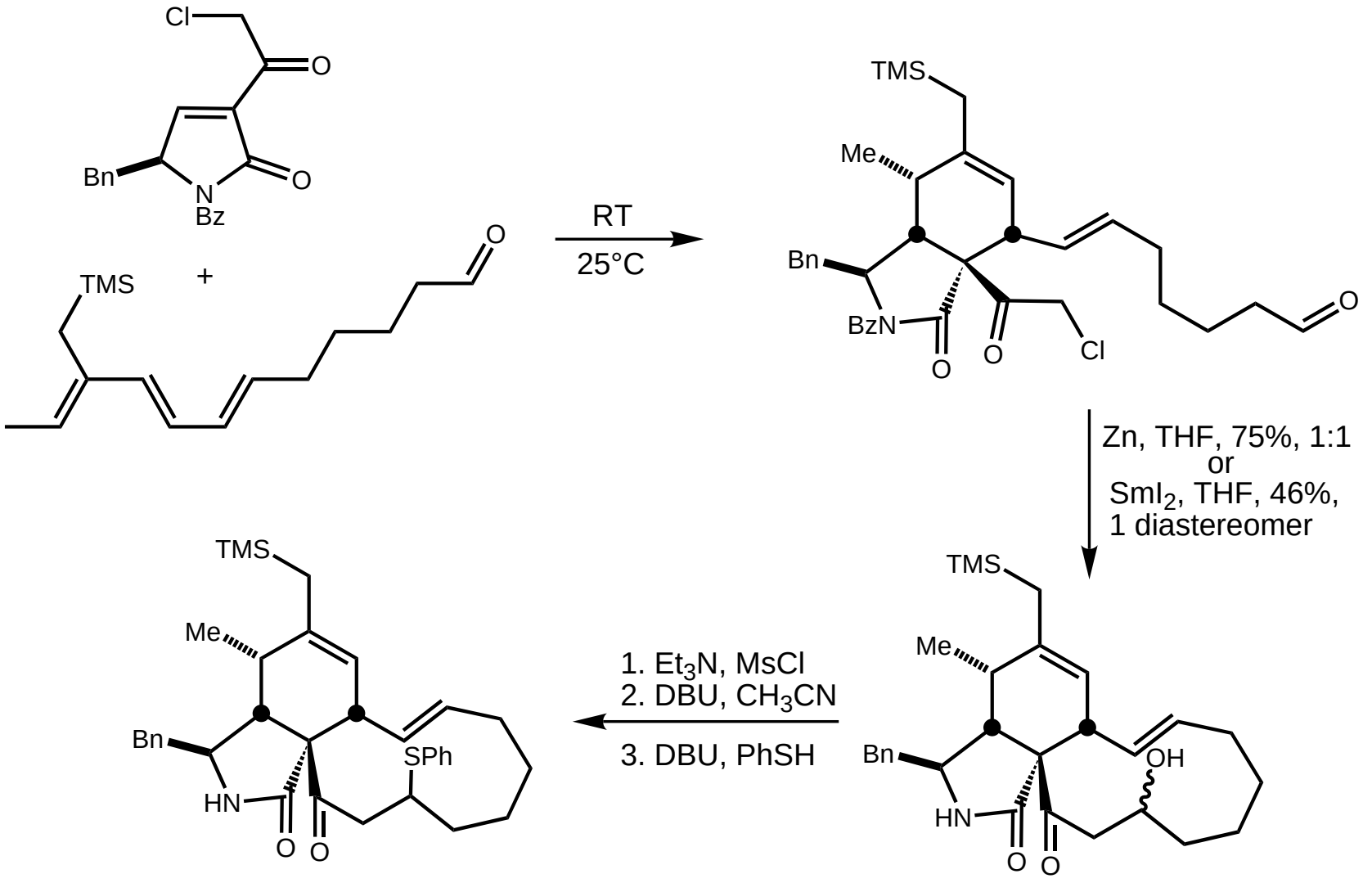
2,3 Sigmatropic Shift and Desulfurization



Vedejs *et al.*, *JACS*, **1984**, *106*, 4617
JOC, **1982**, *47*, 4383

Synthesis of Cytochalasin D Analog II - Vedejs

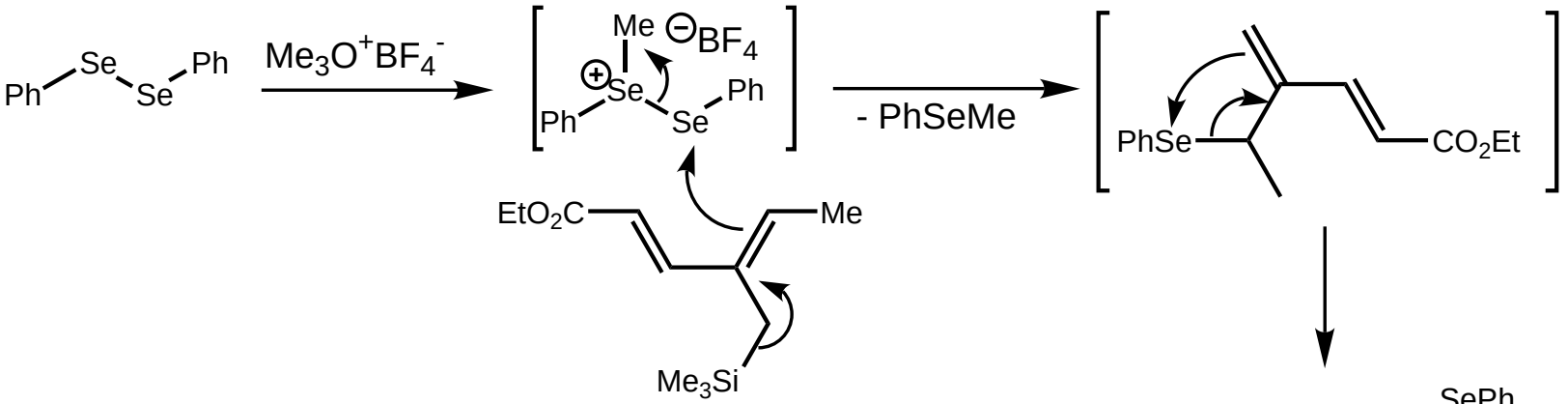
Reformatsky Cyclisation

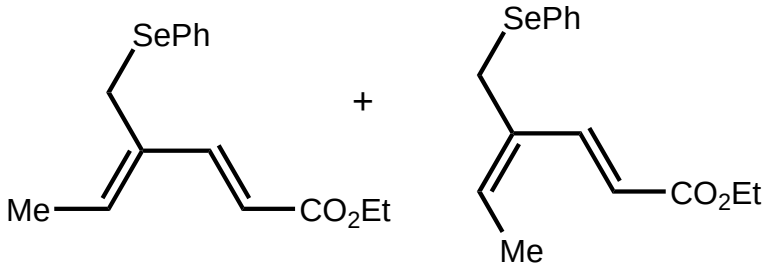


Vedejs *et al.*, *TL*, **1988**, *29*, 2291

Synthesis of Cytochalasin D Analog I - Vedejs

Mild Phenylselenation

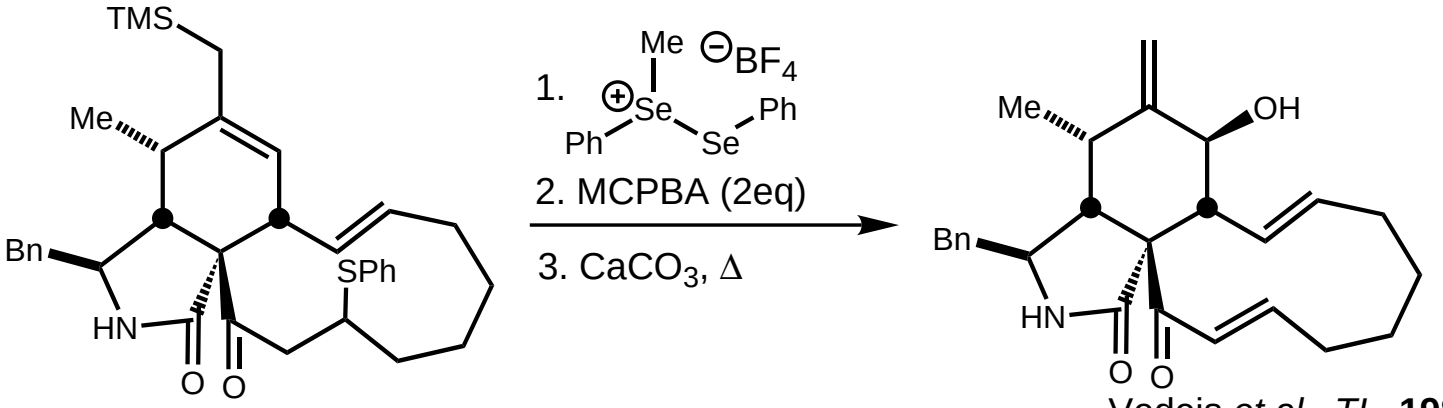




2.8:1

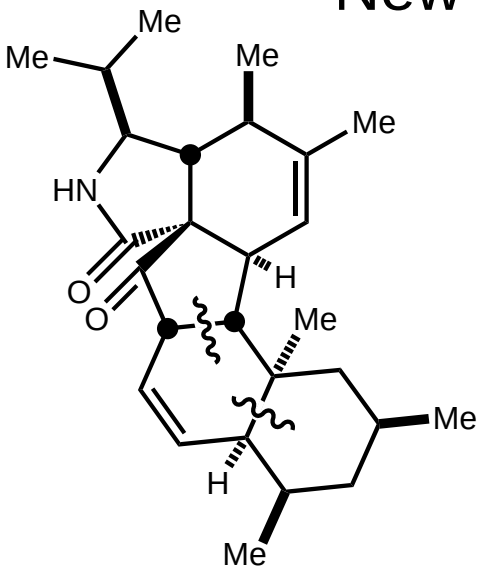
•Products stable to reaction conditions
∴ mixture of E+Z isomers supporst gamma selenation followed by isomerization to most substituted double bond

Use in synthesis:



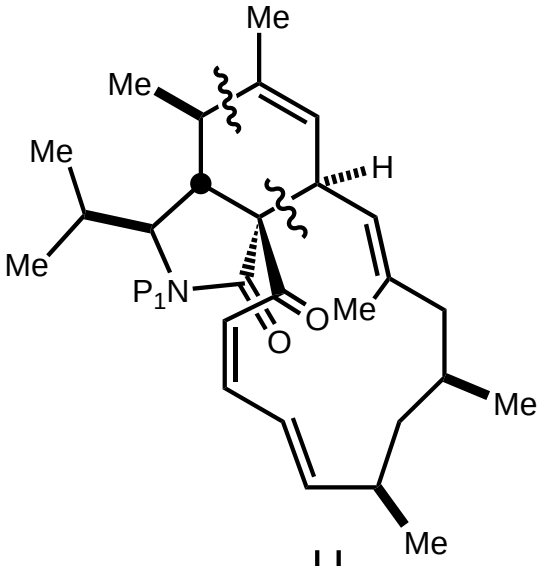
Vedejs *et al.*, *TL*, **1988**, *29*, 2287
TL, **1988**, *29*, 2291

New "Cytochalasans"



Chaetochalasin A

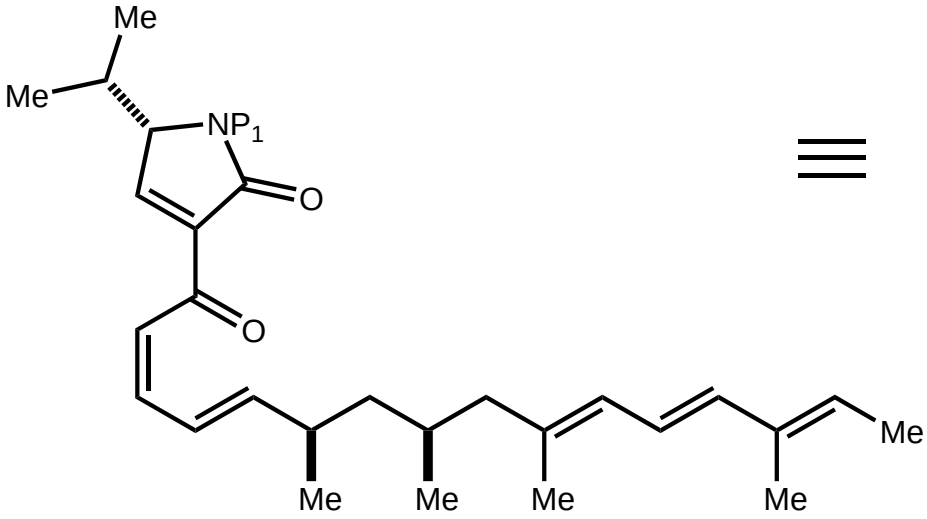
A double Diels-Alder candidate?



Selectivity problems?

- Isolated from *Chaetomium brasiliense*, in extract which showed antifungal and antiinsectan effects

  Gloer *et al.*, *TL*, **1998**, *39*, 7633



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