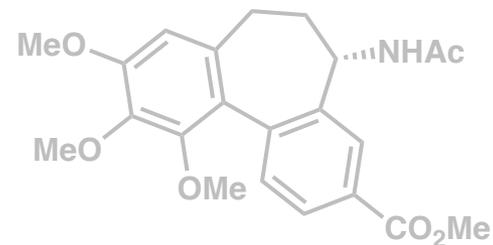
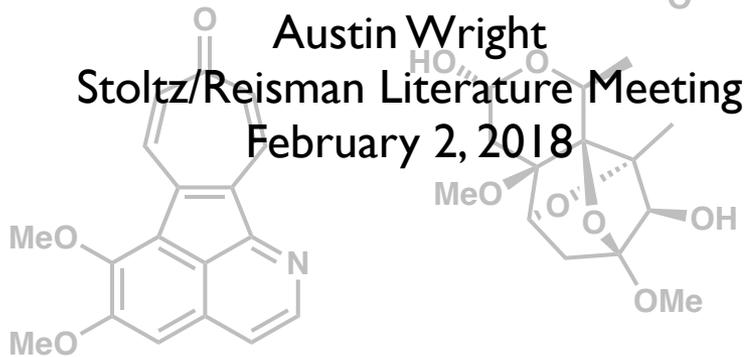
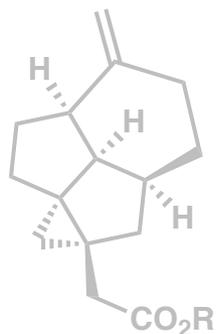
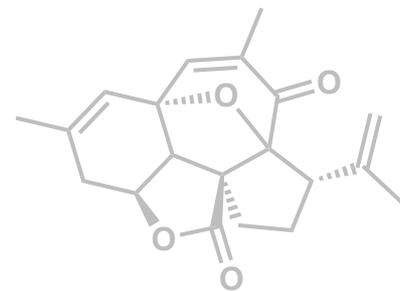
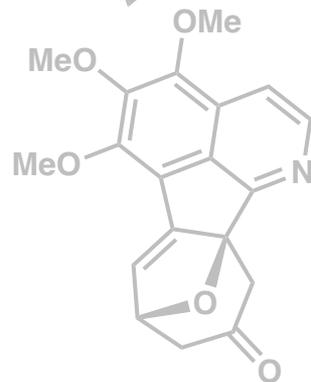
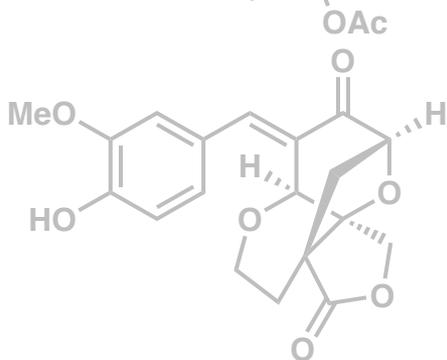
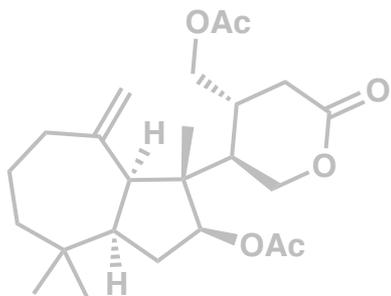
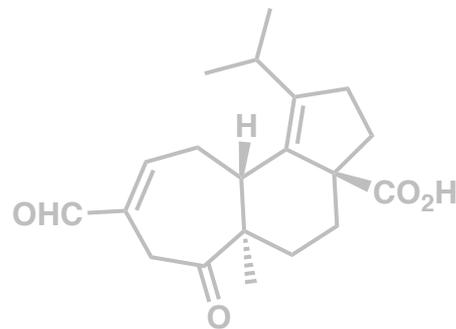
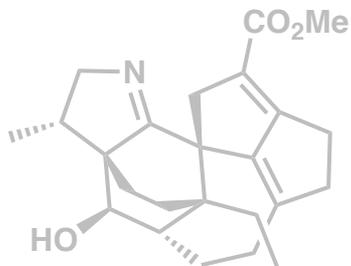
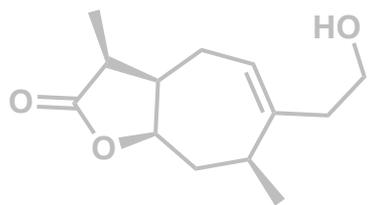
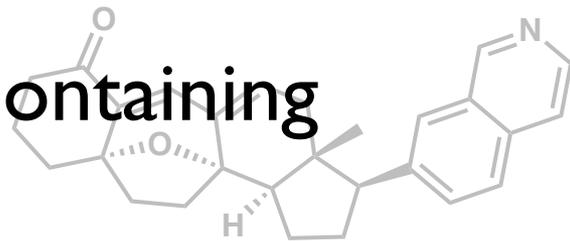
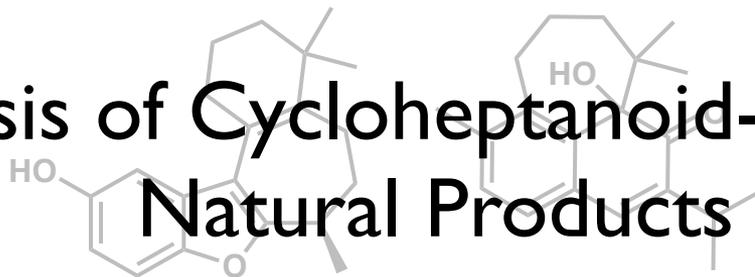
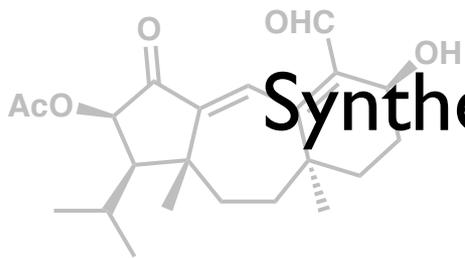


Synthesis of Cycloheptanoid-containing Natural Products



Austin Wright
Stoltz/Reisman Literature Meeting
February 2, 2018

Outline for the Talk

- Challenges of Making Seven-membered Rings
- Methods for the Synthesis of Cycloheptanoid Natural Products

“Classical” Methods

- Aldol chemistry, Friedel–Crafts, Oxidative Cyclization, Prins-Pinacol

Cross Coupling

- Heck, Pauson–Khand

Pericyclic Reactions

- Cycloadditions, Cyclopropane Rearrangements, Group Transfer

Radical Cyclization

Ring-Closing-Metathesis

- Ene–Ene, Ene–Yne

Ring Expansions

- One-carbon, Two-carbon

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Challenges of Making Seven-membered Rings

Thermodynamic

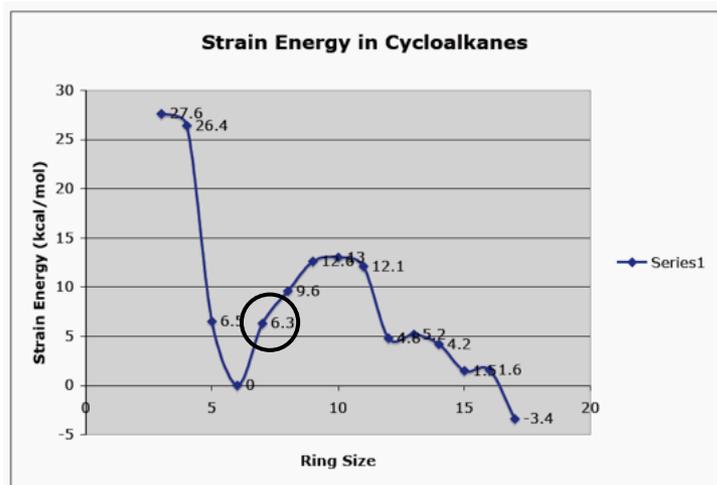
Ring Strain:

- Baeyer (bond angles distorted from ideal) = small rings
- Pitzer (torsional strain) = medium rings (7-13 carbons)
- Transannular strain = medium rings

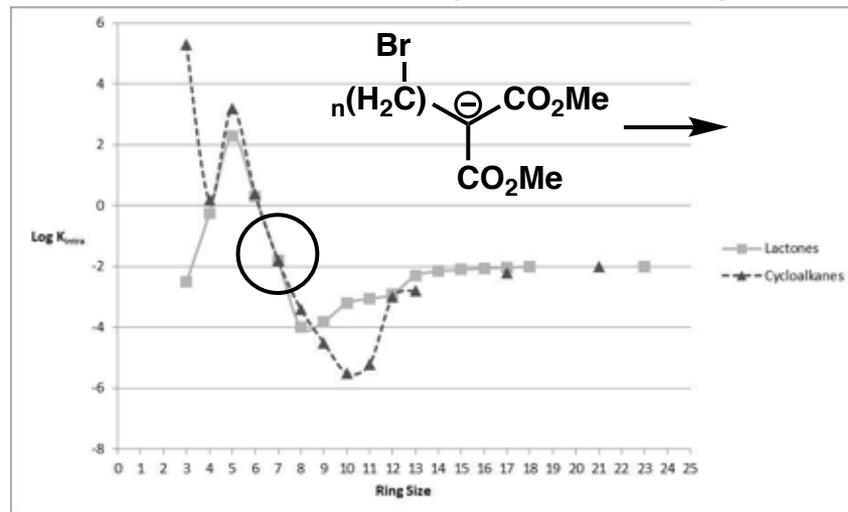
Kinetic

- Intramolecular cyclization becomes competitive with intermolecular

Strain Energy vs. Ring Size



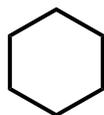
Rates of Intramolecular Cyclization vs. Ring Size



Challenges of Making Seven-membered Rings

Strategic

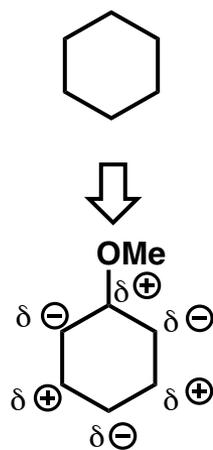
- Lapworth model of polarity



Challenges of Making Seven-membered Rings

Strategic

- Lapworth model of polarity



“consonant” polarity

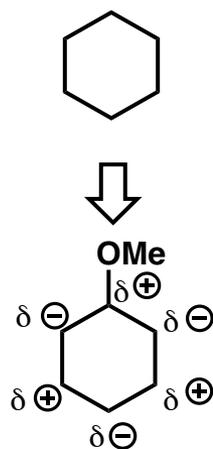


obvious polar synthons

Challenges of Making Seven-membered Rings

Strategic

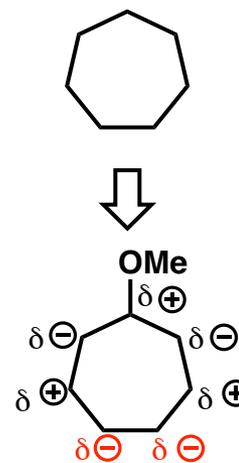
- Lapworth model of polarity



“consonant” polarity



obvious polar synthons



“dissonant” polarity



less obvious polar synthons

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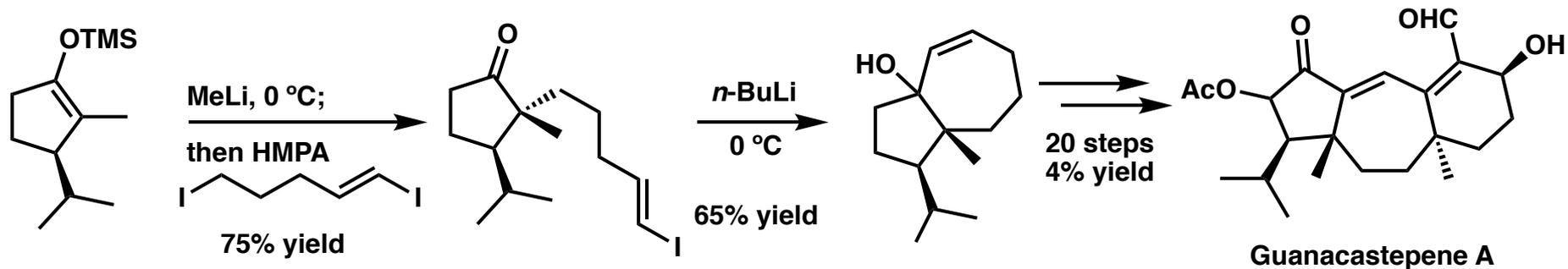
- Ene–Ene, Ene–Yne

Ring Expansions

- One-carbon, Two-carbon

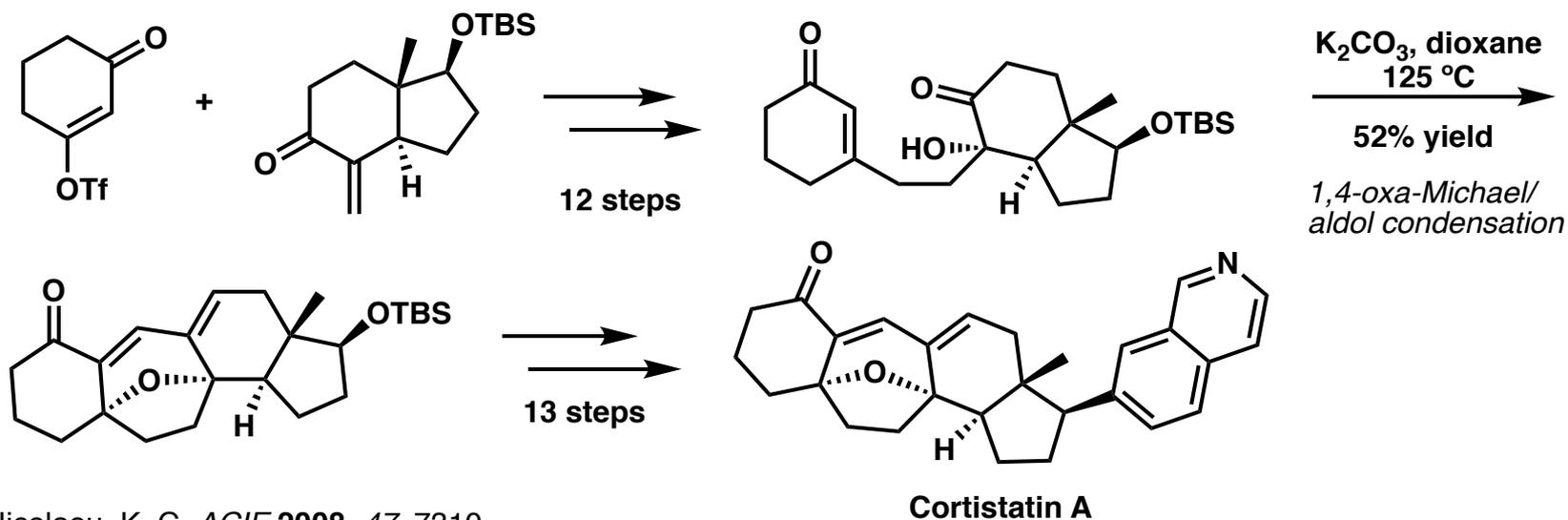
Aldol-type Chemistry

Danishefsky's Synthesis of Guanacastepene A



Danishefsky, S. J. *JOC* **2005**, *70*, 10619.

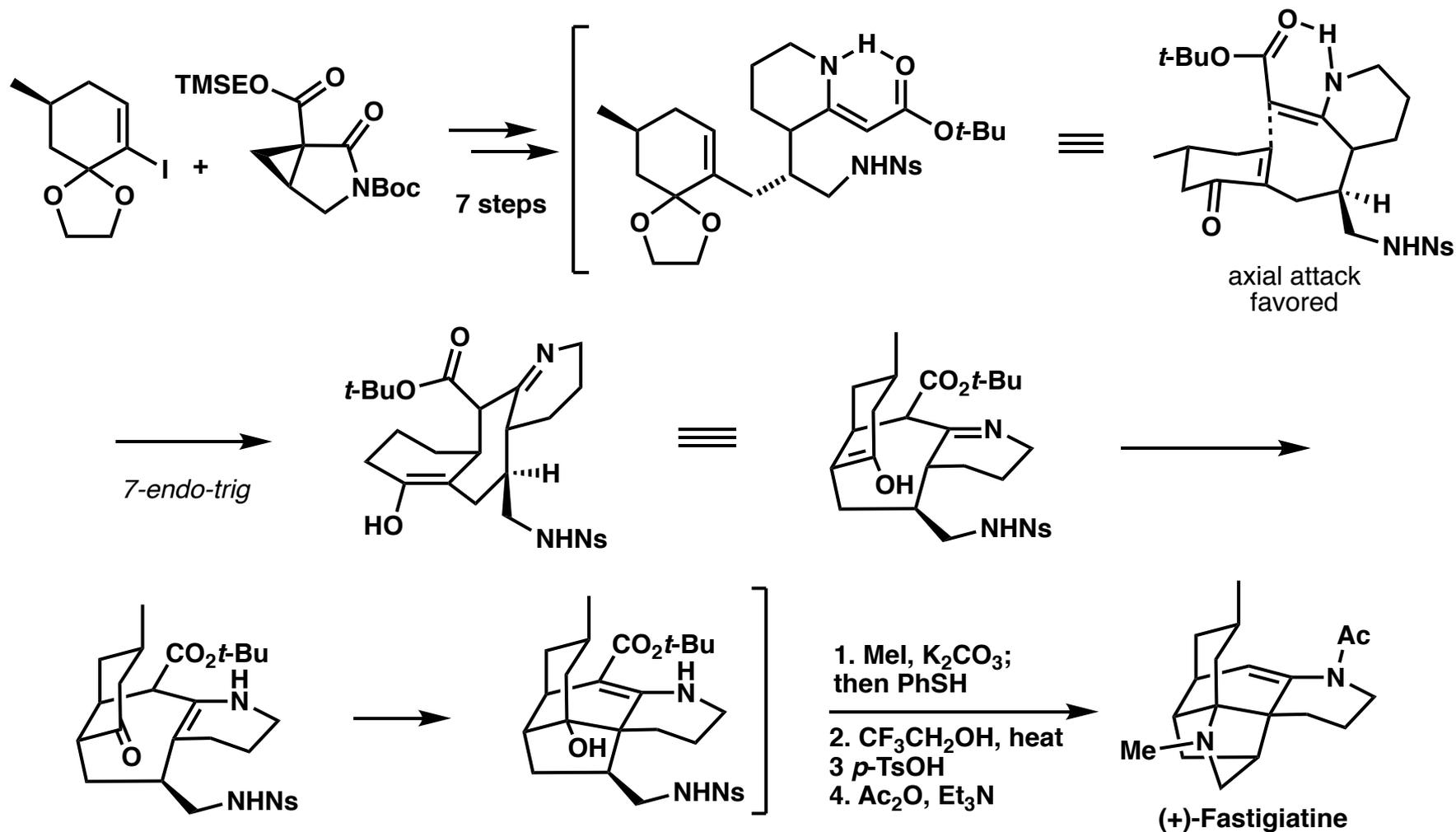
Nicolaou's Total Synthesis of Cortistatin A



Nicolaou, K. C. *ACIE* **2008**, *47*, 7310.

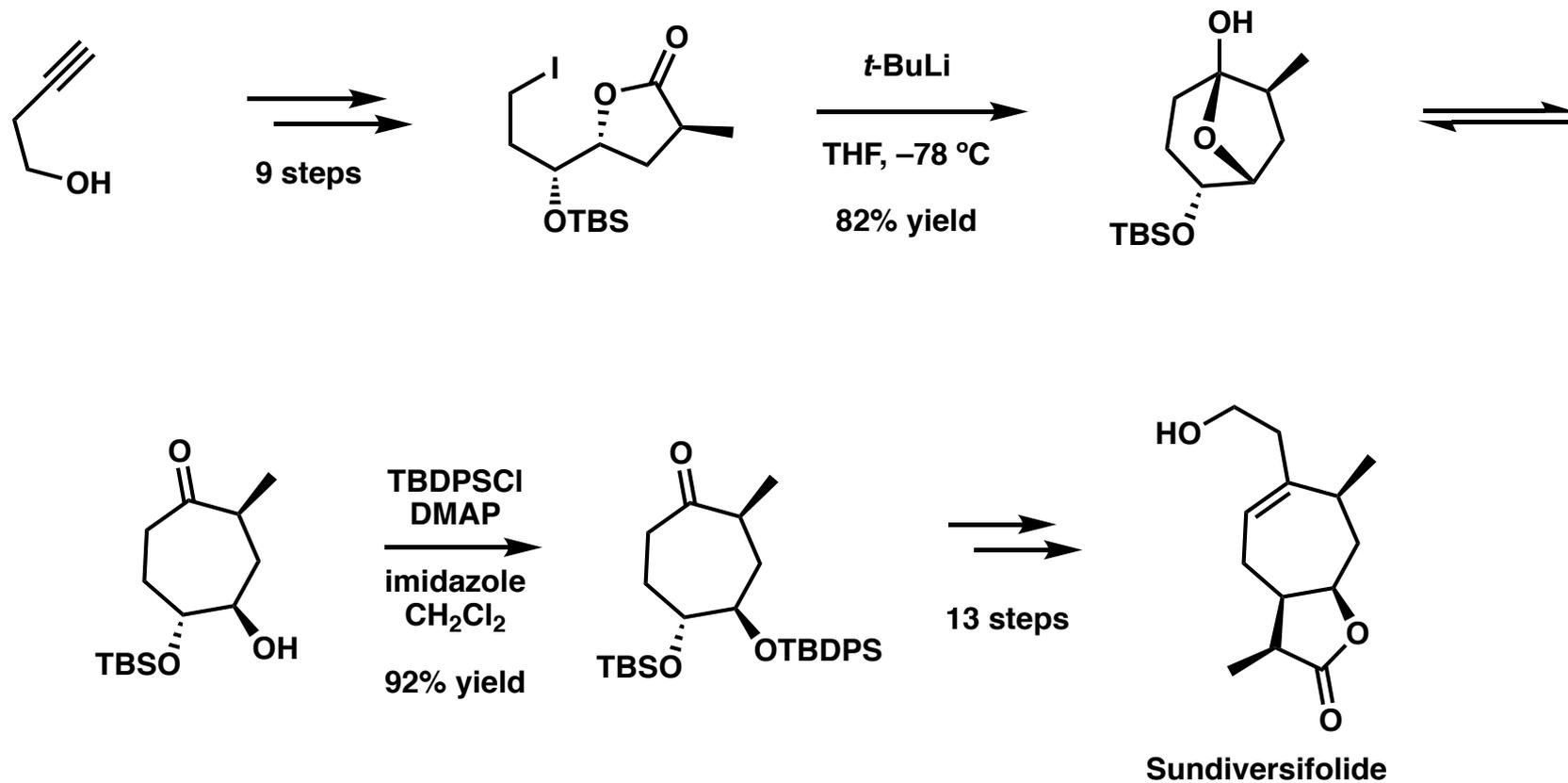
Aldol-type Chemistry

Shair's Synthesis of (+)-Fastigiatine



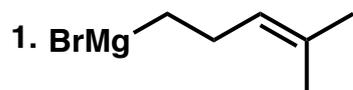
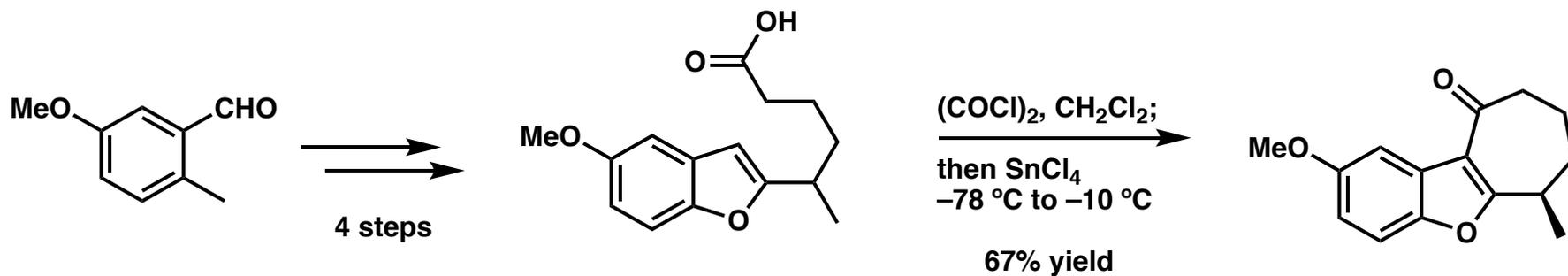
Aldol-type Chemistry

Shindo's Synthesis of the Xanthanolides



Friedel–Crafts Chemistry

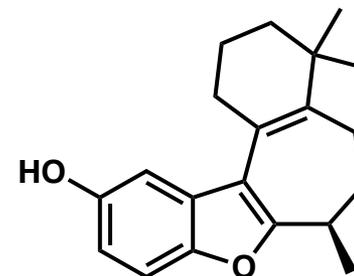
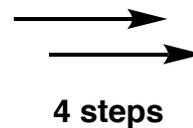
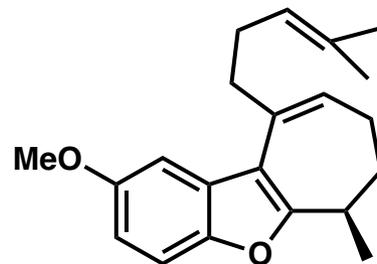
Danishefsky's Synthesis of racemic Frondosin B



CeCl₃, THF
-78 °C



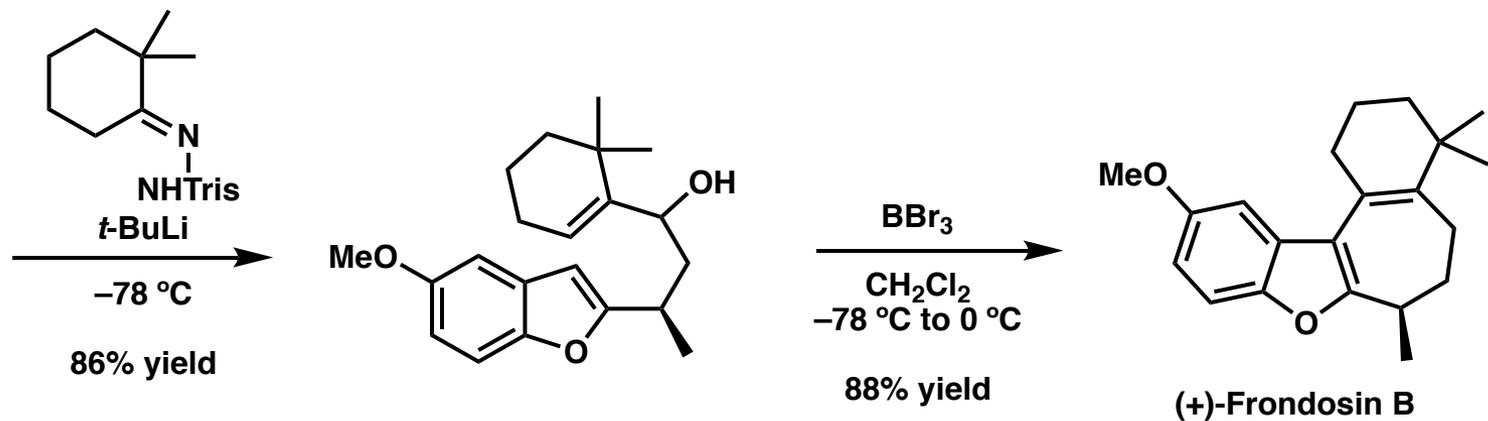
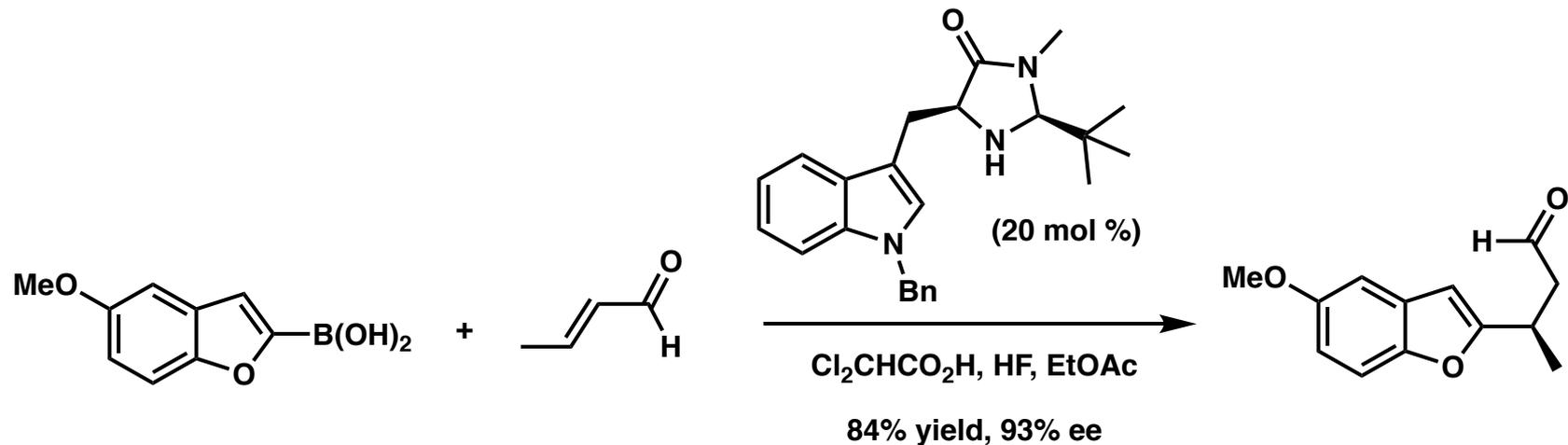
93% yield
over 2 steps



Frondosin B

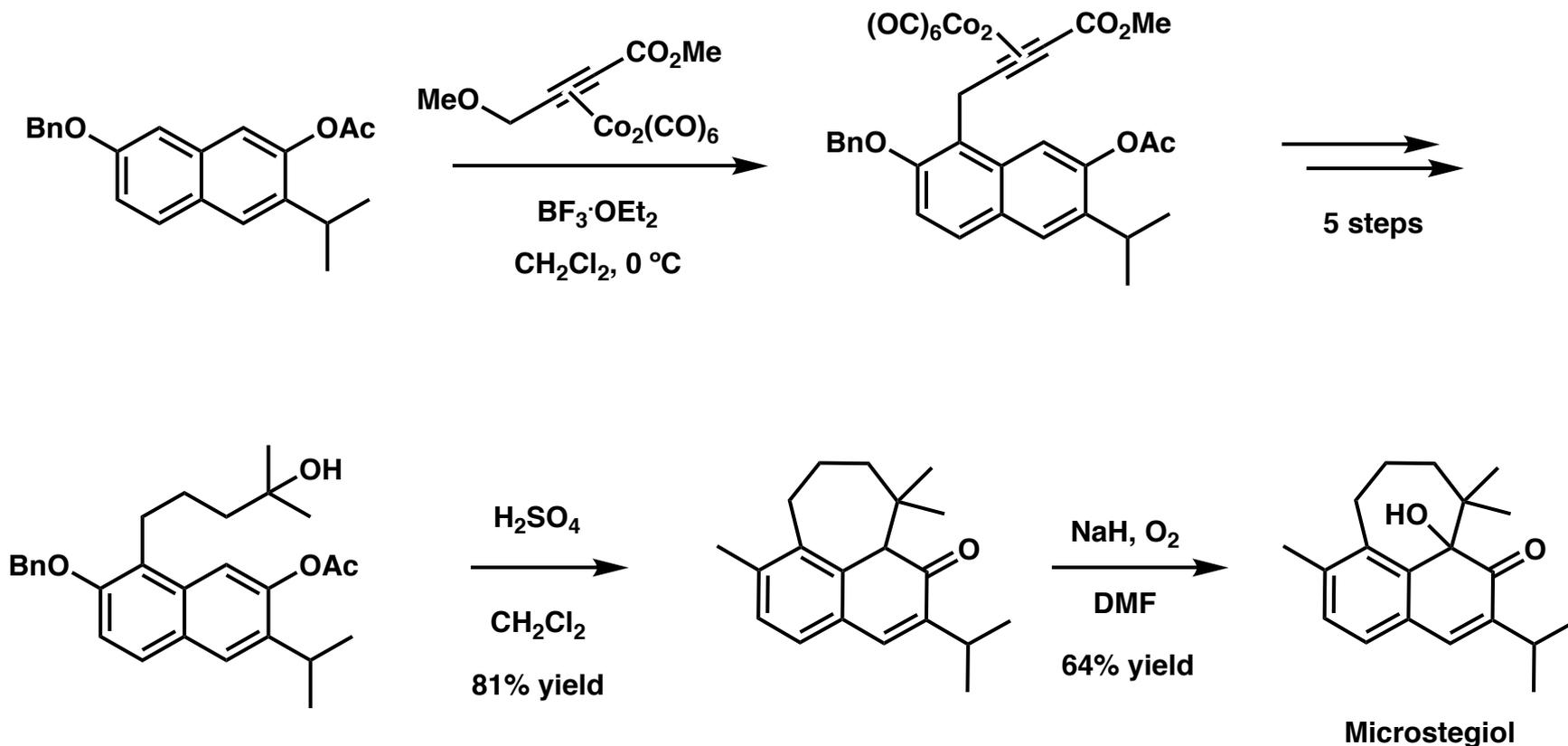
Friedel–Crafts Chemistry

MacMillan's Synthesis of (+)-Fronodosin B



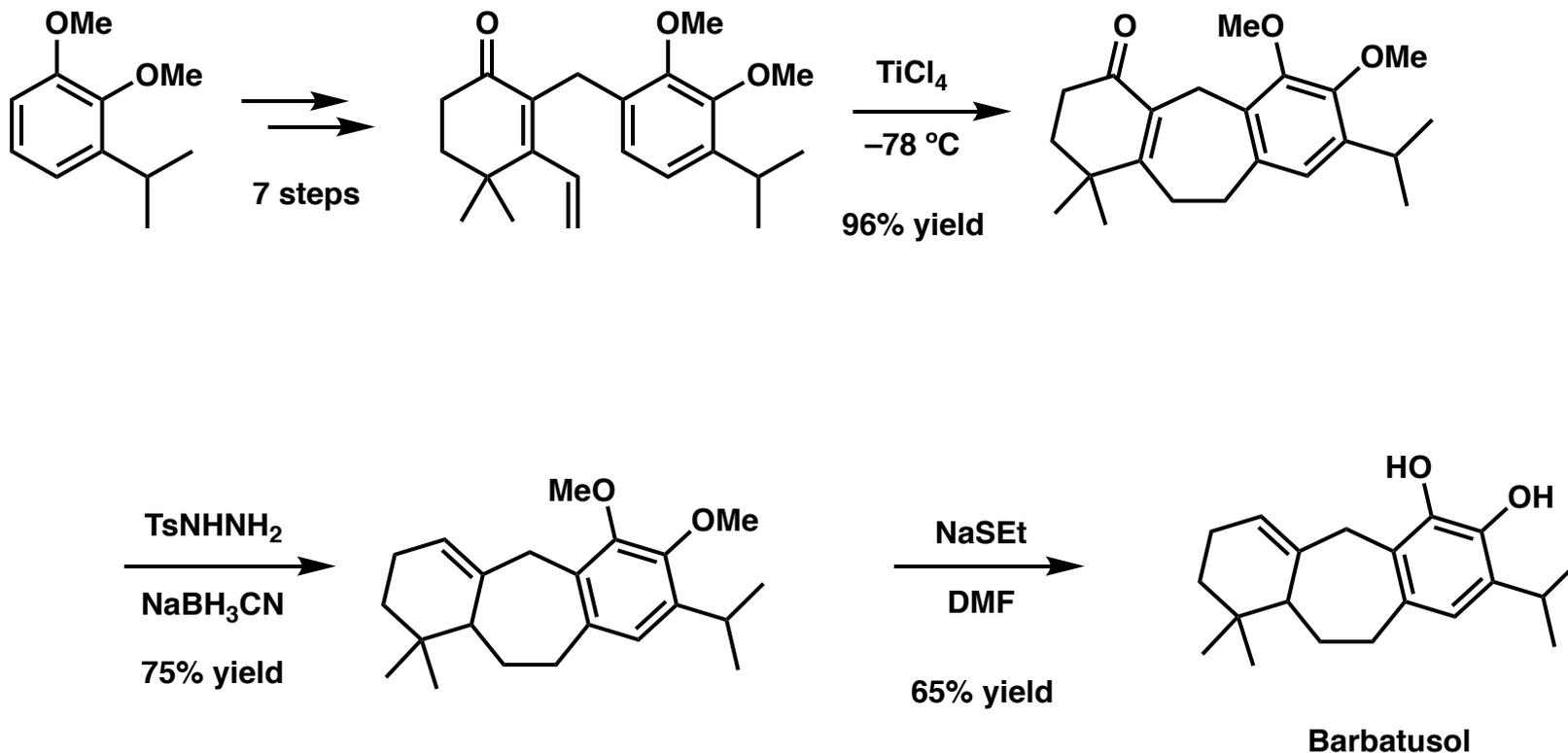
Friedel–Crafts Chemistry

Green's Racemic Synthesis of Microstegiol



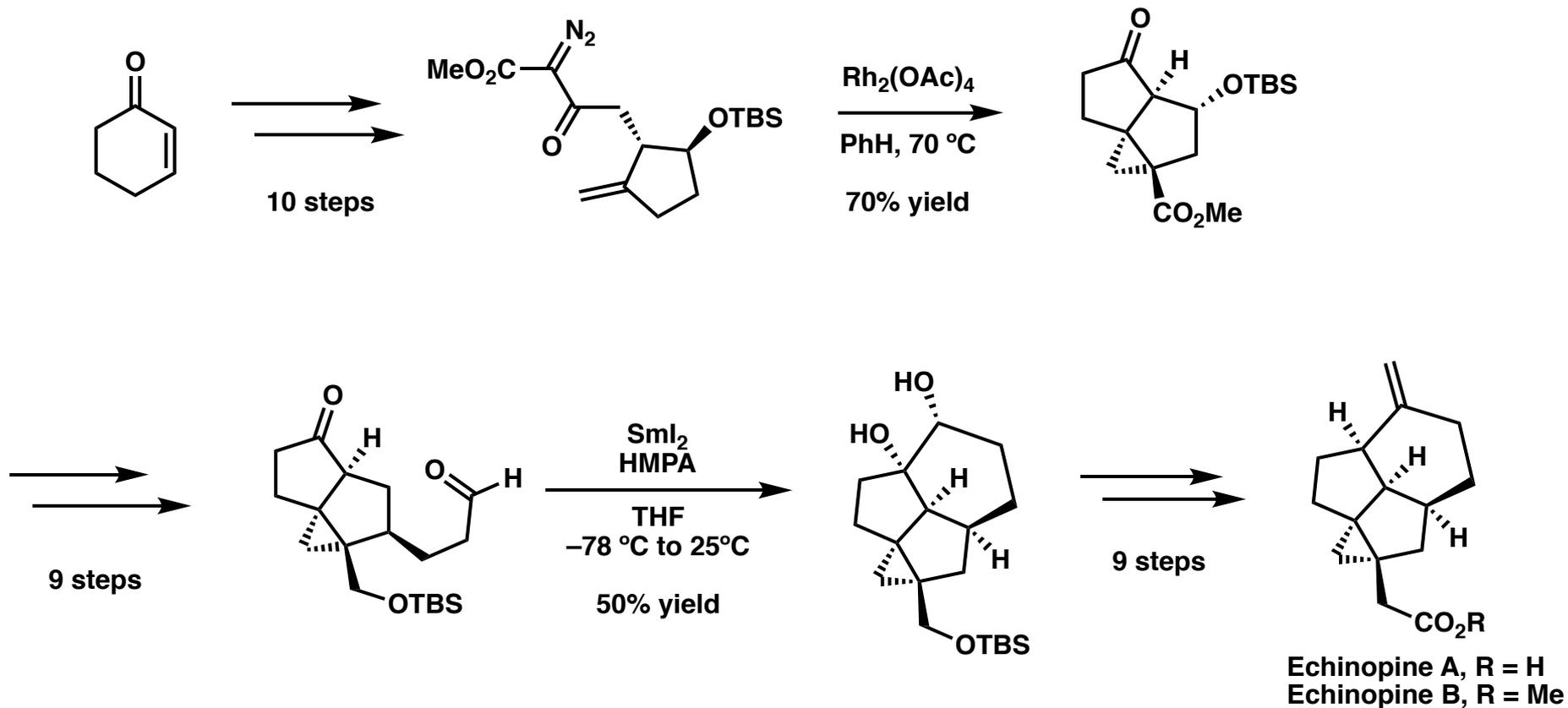
Oxidative Cyclization

Majetich's racemic Synthesis of Barbatusol



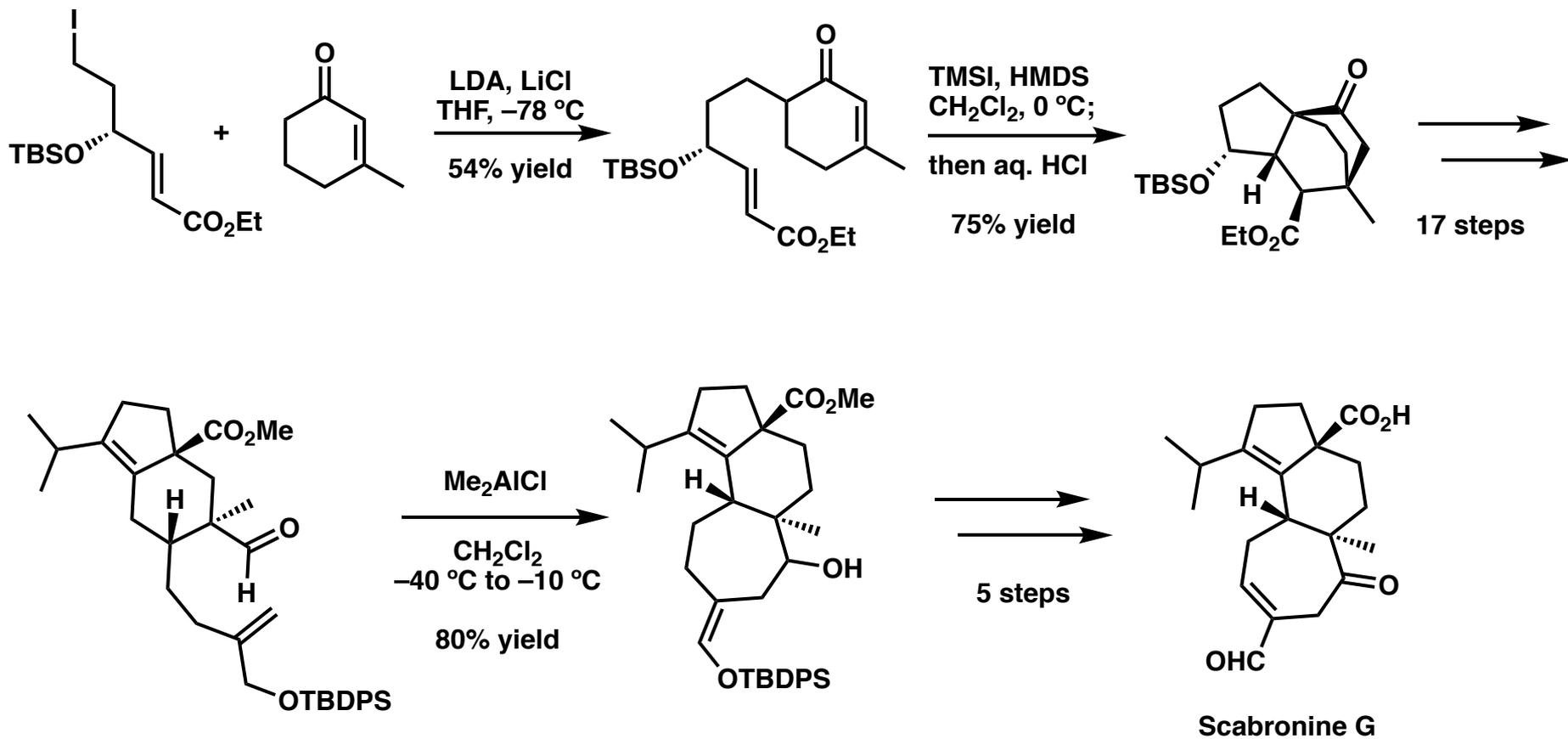
Pinacol Coupling

Nicolaou's Syntheses of Echinopines A and B



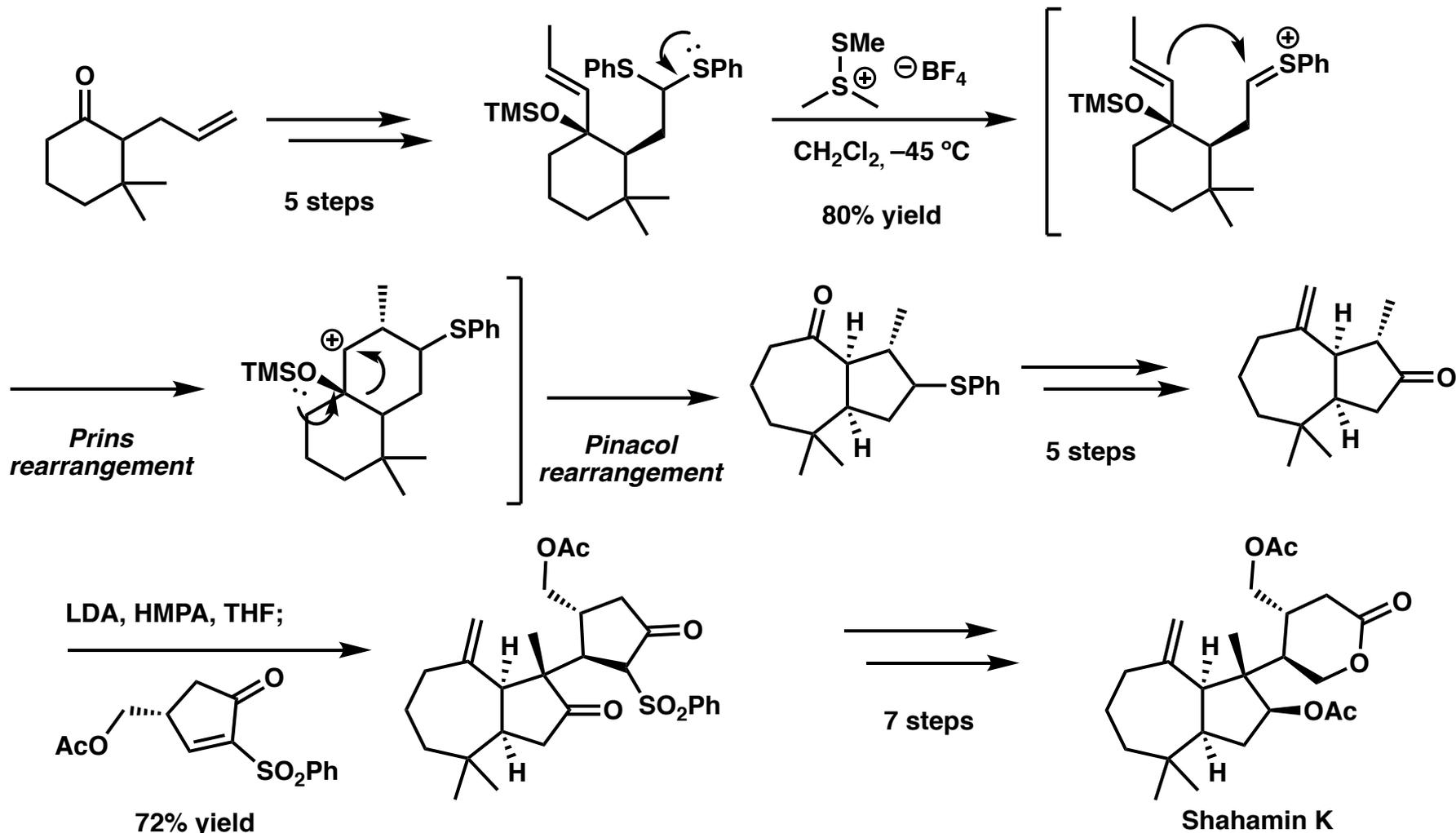
Prins Cyclization

Iwabuchi's Synthesis of Scabronine G



Pinacol Rearrangement

Overman's Enantioselective Synthesis of Shahamin K



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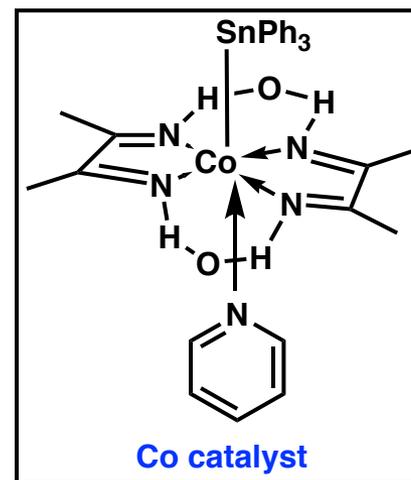
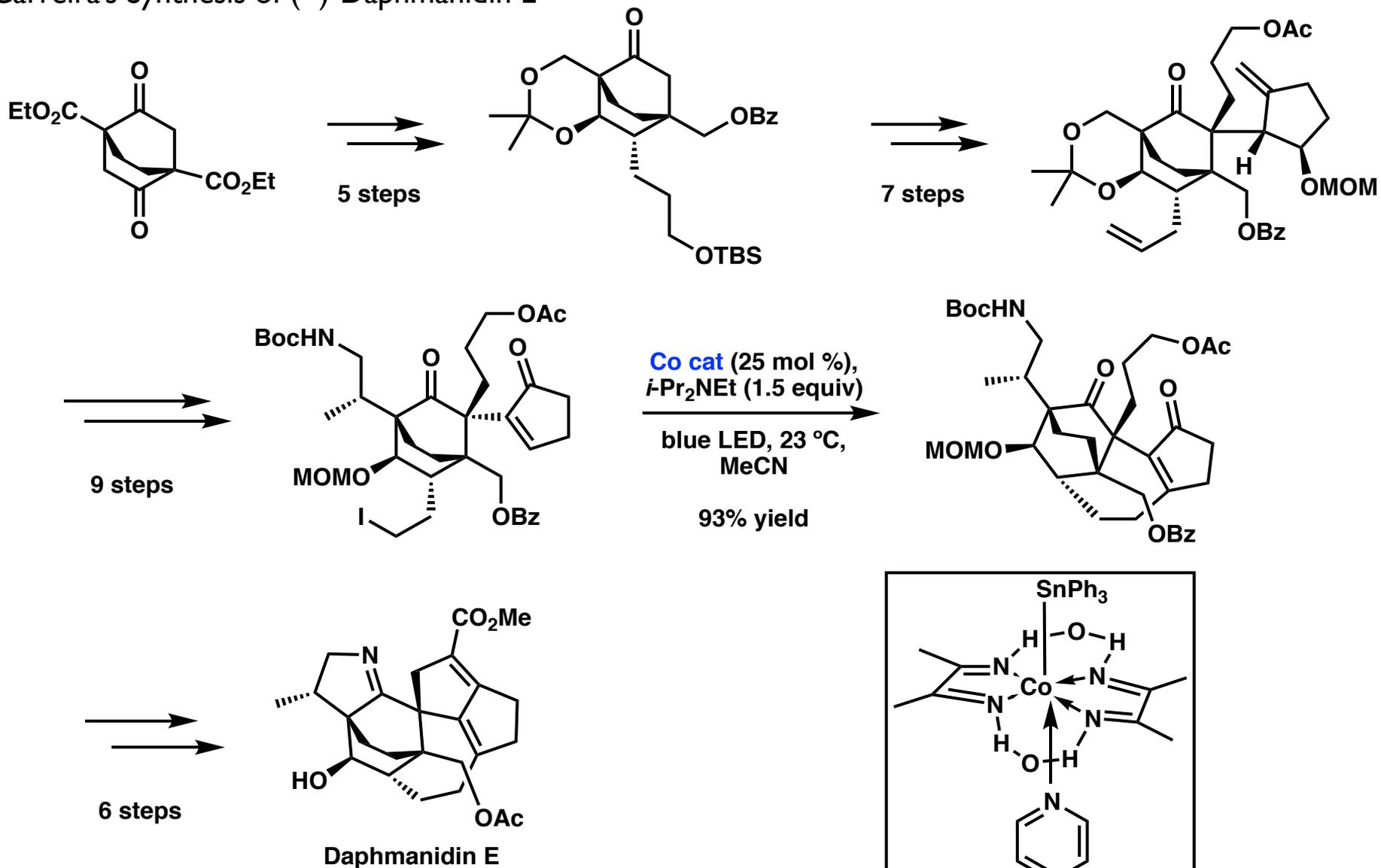
- Ene–Ene, Ene–Yne

Ring Expansions

- One-carbon, Two-carbon

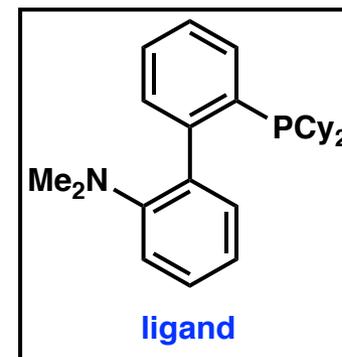
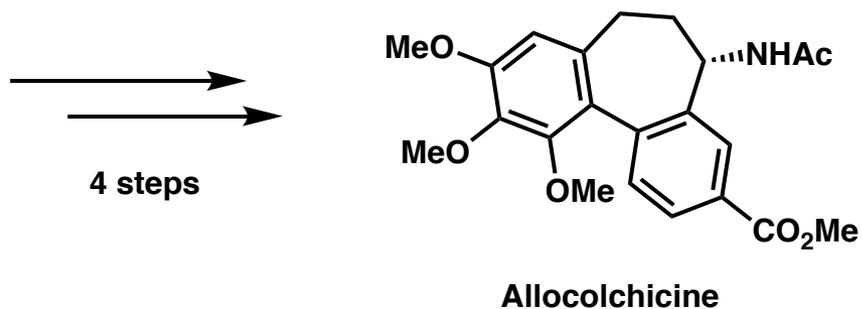
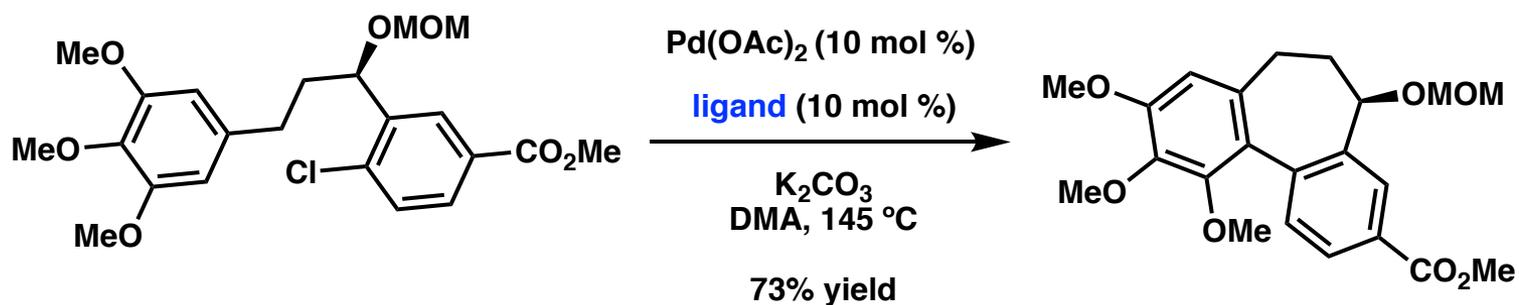
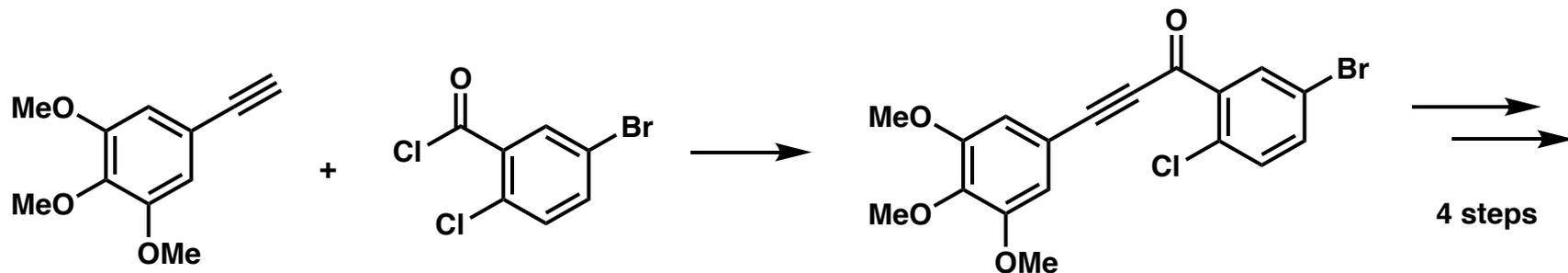
Heck Coupling

Carreira's Synthesis of (+)-Daphmanidin E



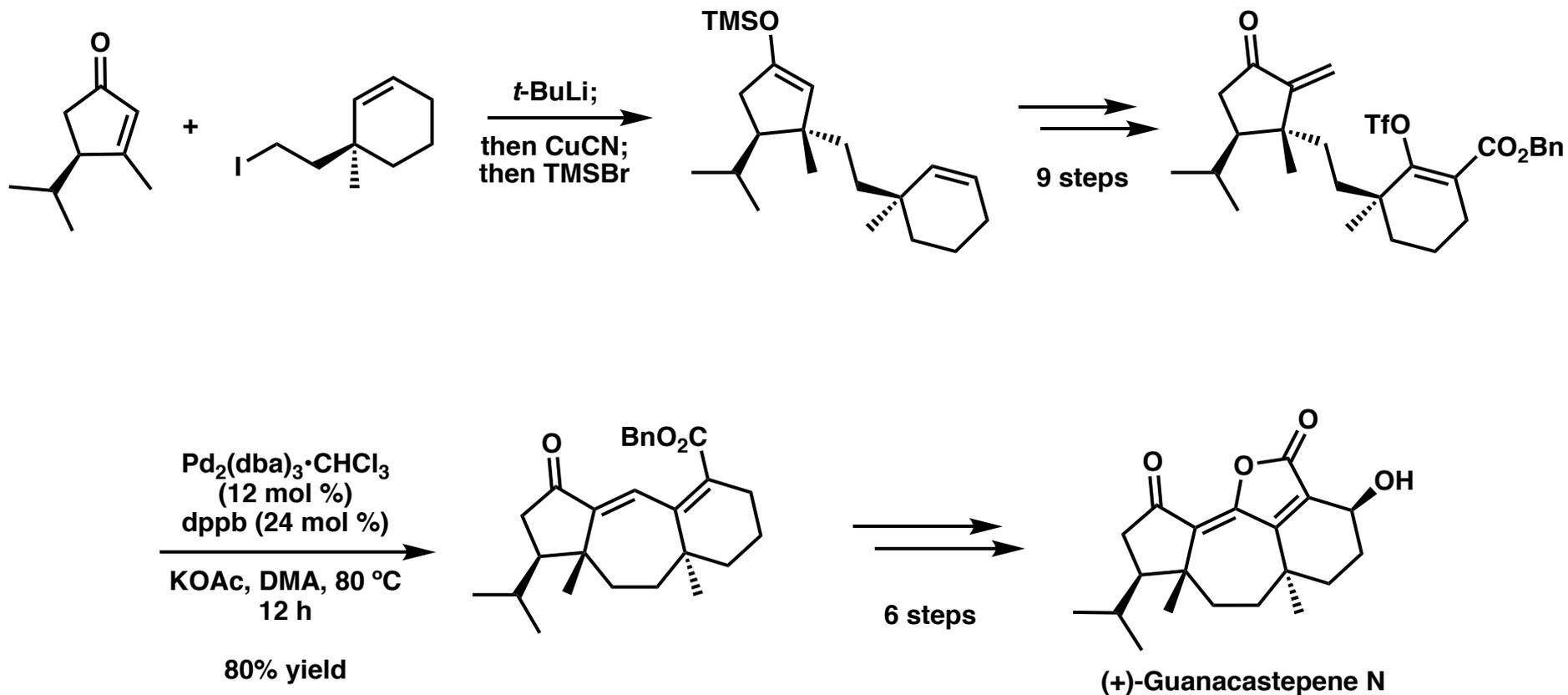
Heck Coupling

Fagnou's Formal Synthesis of Allocolchicine



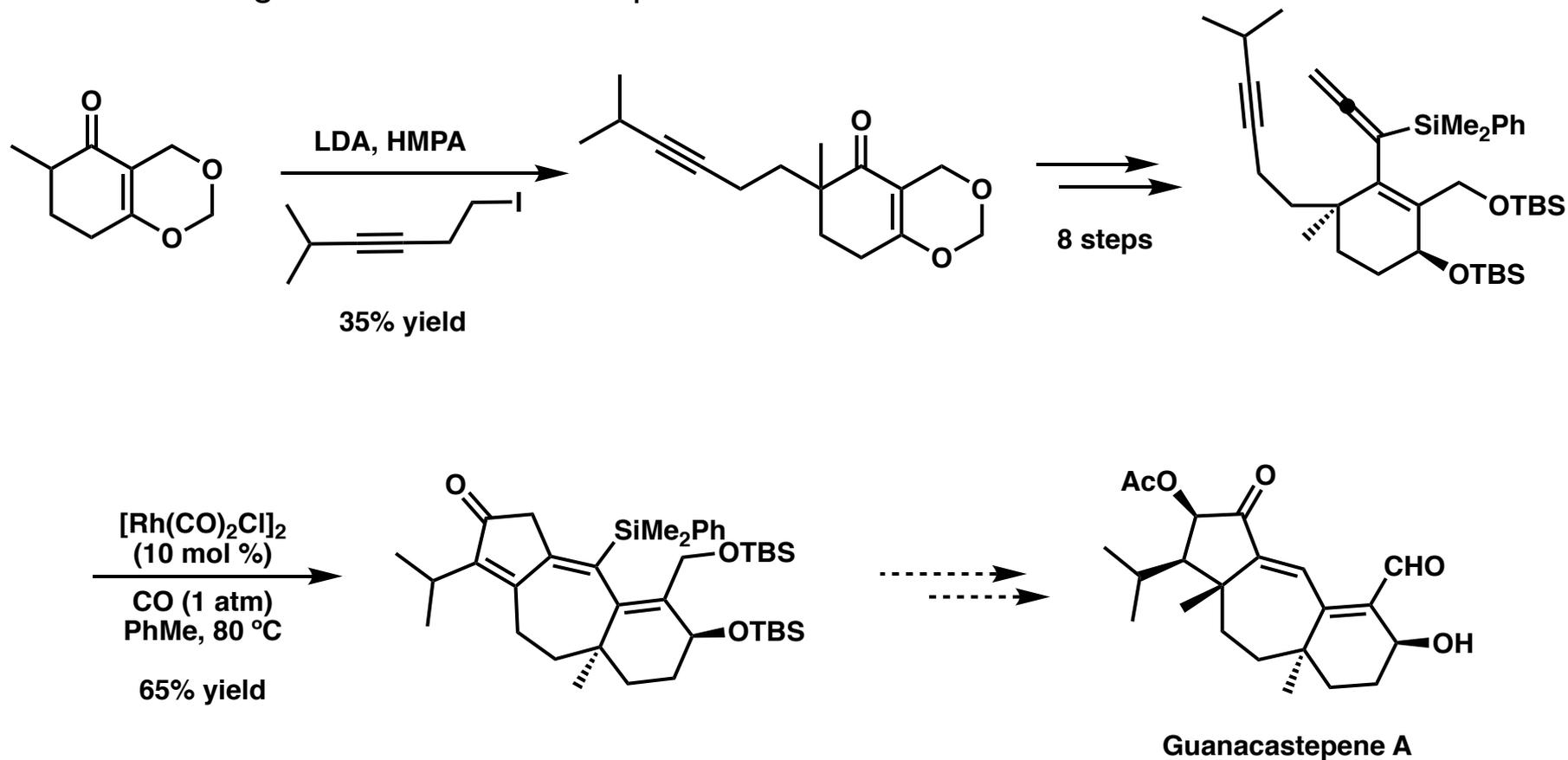
Heck Coupling

Overman's Synthesis of Guanacastepene N



Pauson–Khand Cyclization

Brummond's Progress Toward Guanacastepene A



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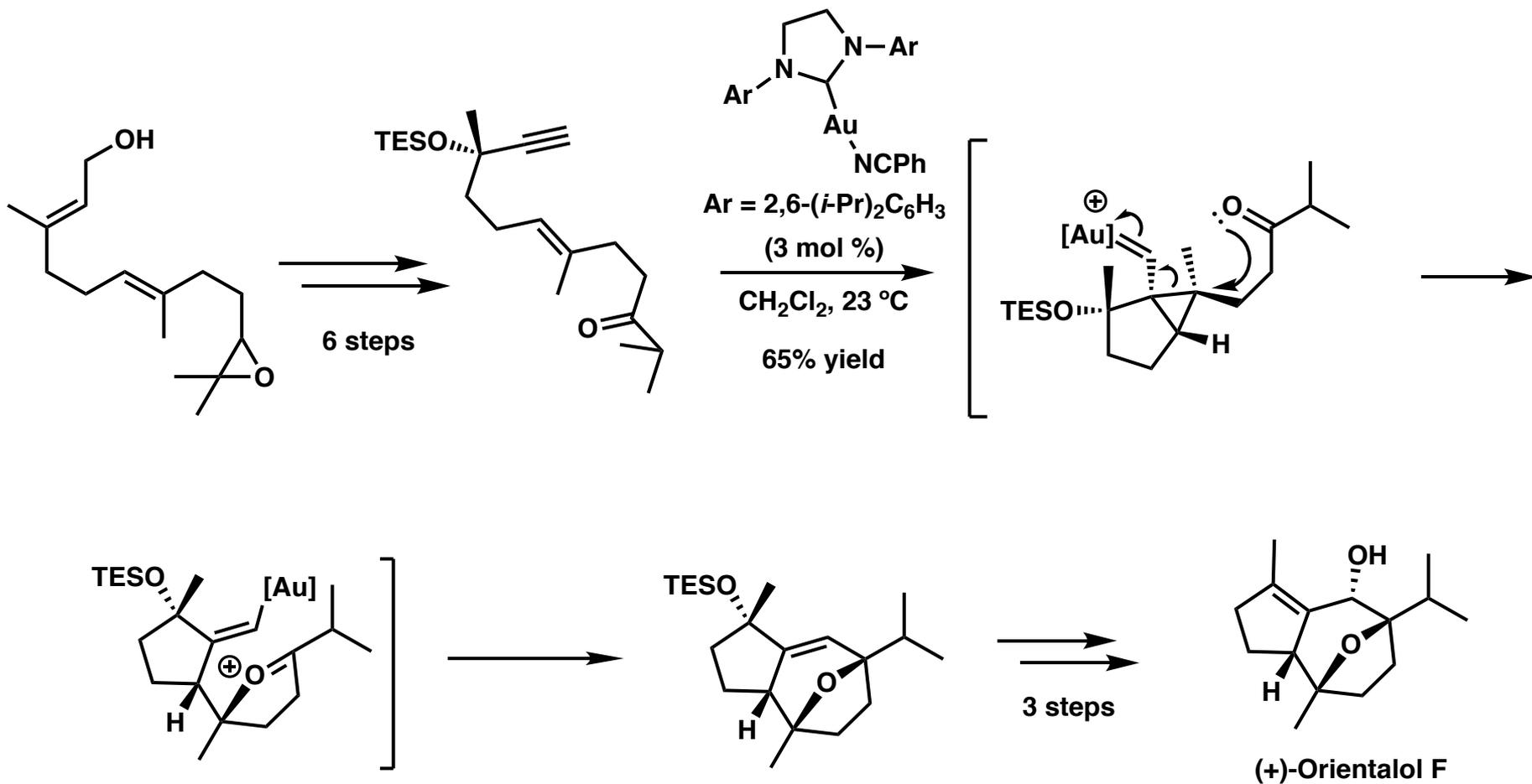
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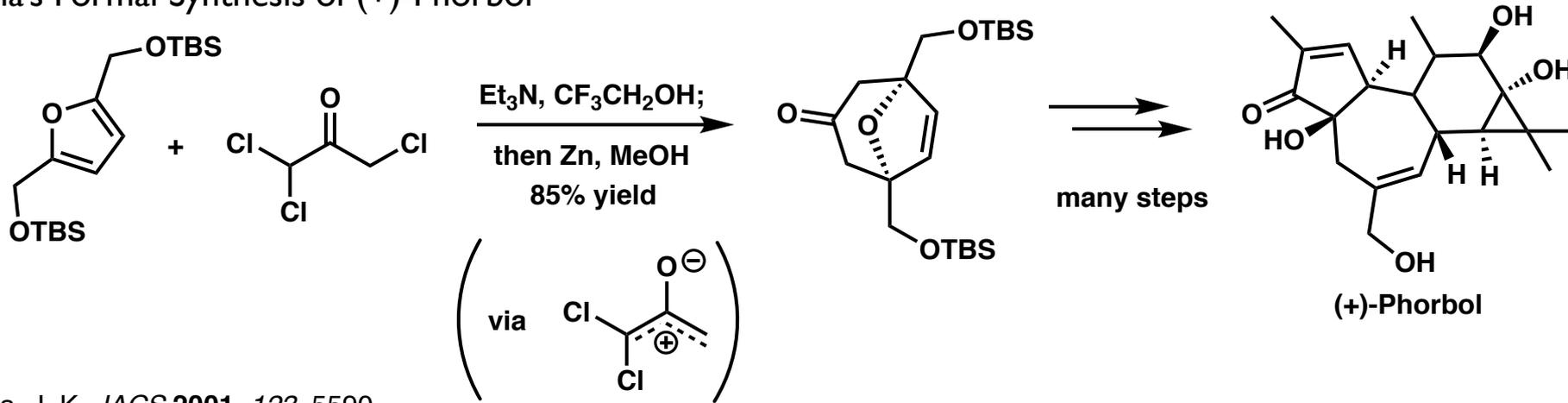
[2+2+2] Cycloaddition

Echavarren's Synthesis of (+)-Orientalol F



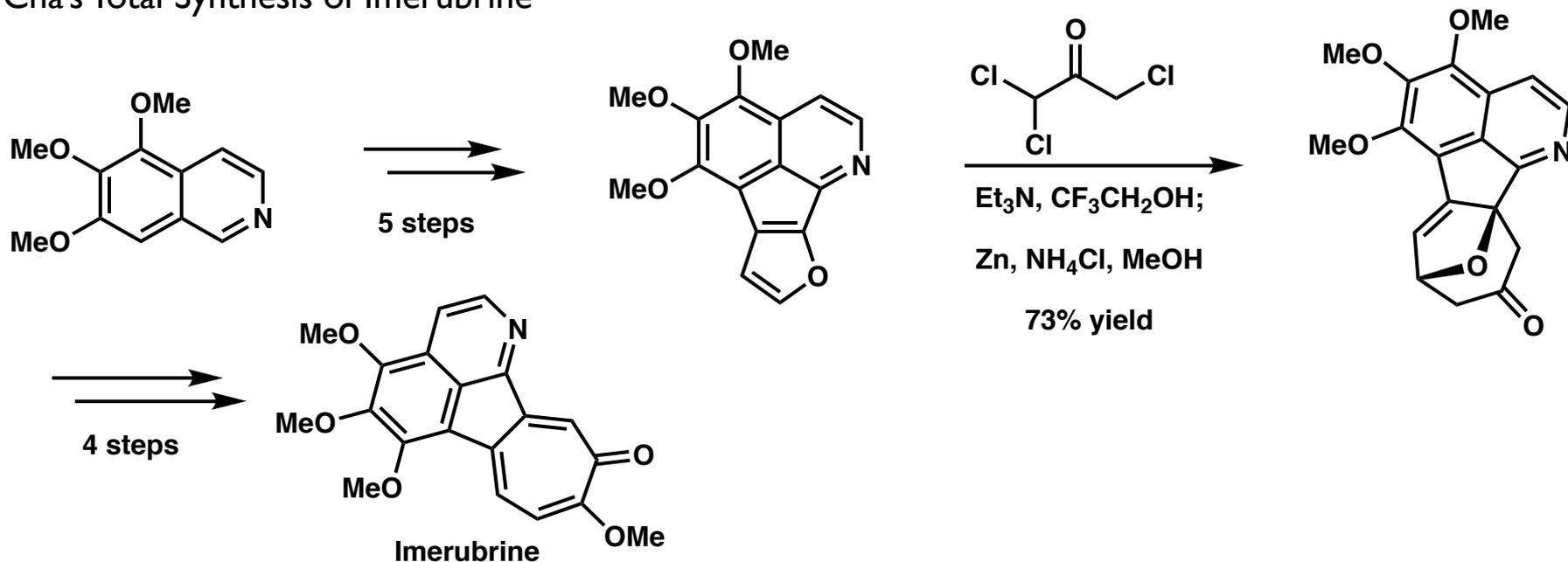
[4+3] Cycloaddition

Cha's Formal Synthesis of (+)-Phorbol



Cha, J. K. *JACS* **2001**, *123*, 5590.

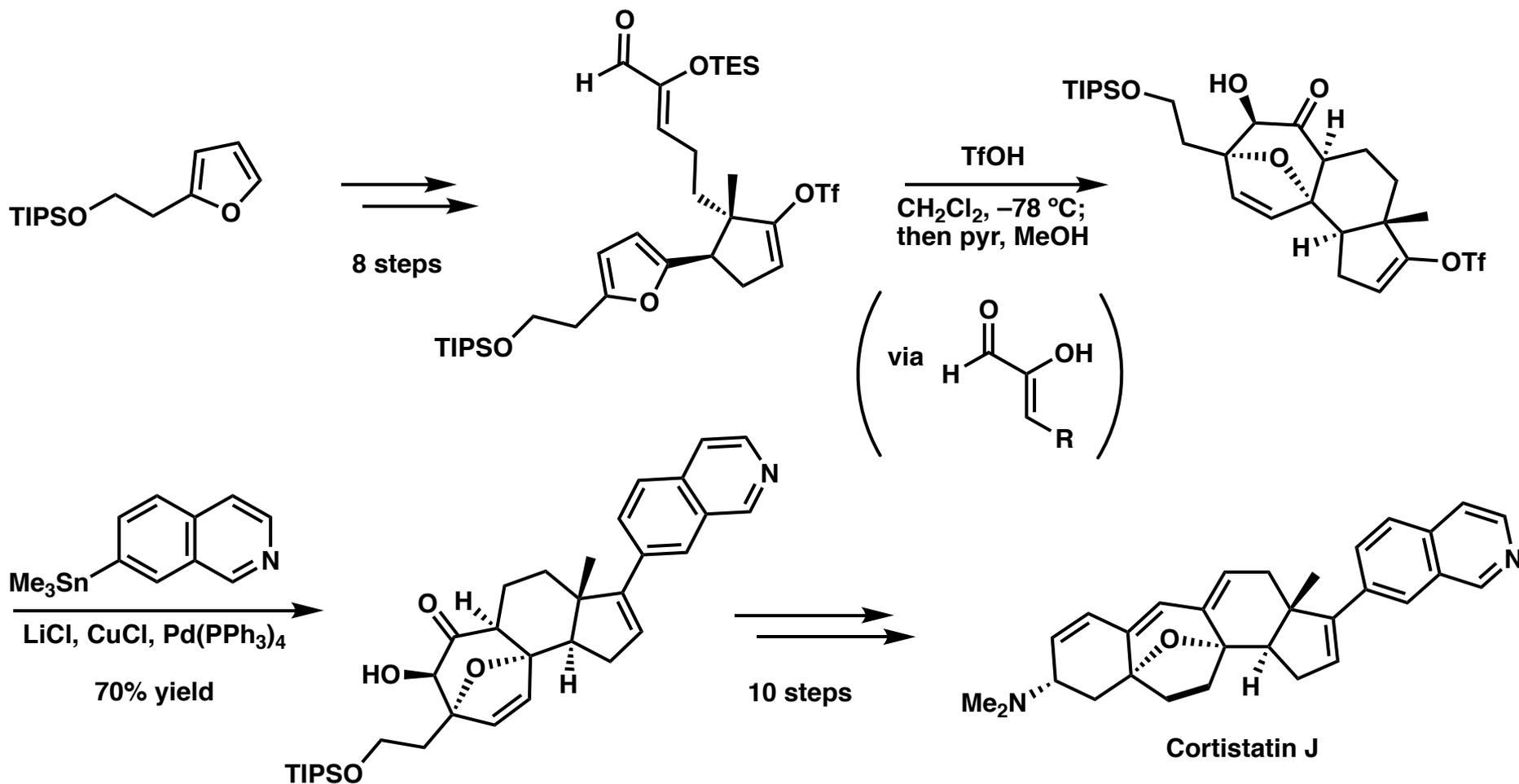
Cha's Total Synthesis of Imerubrine



Cha, J. K. *JACS* **2001**, *123*, 3243.

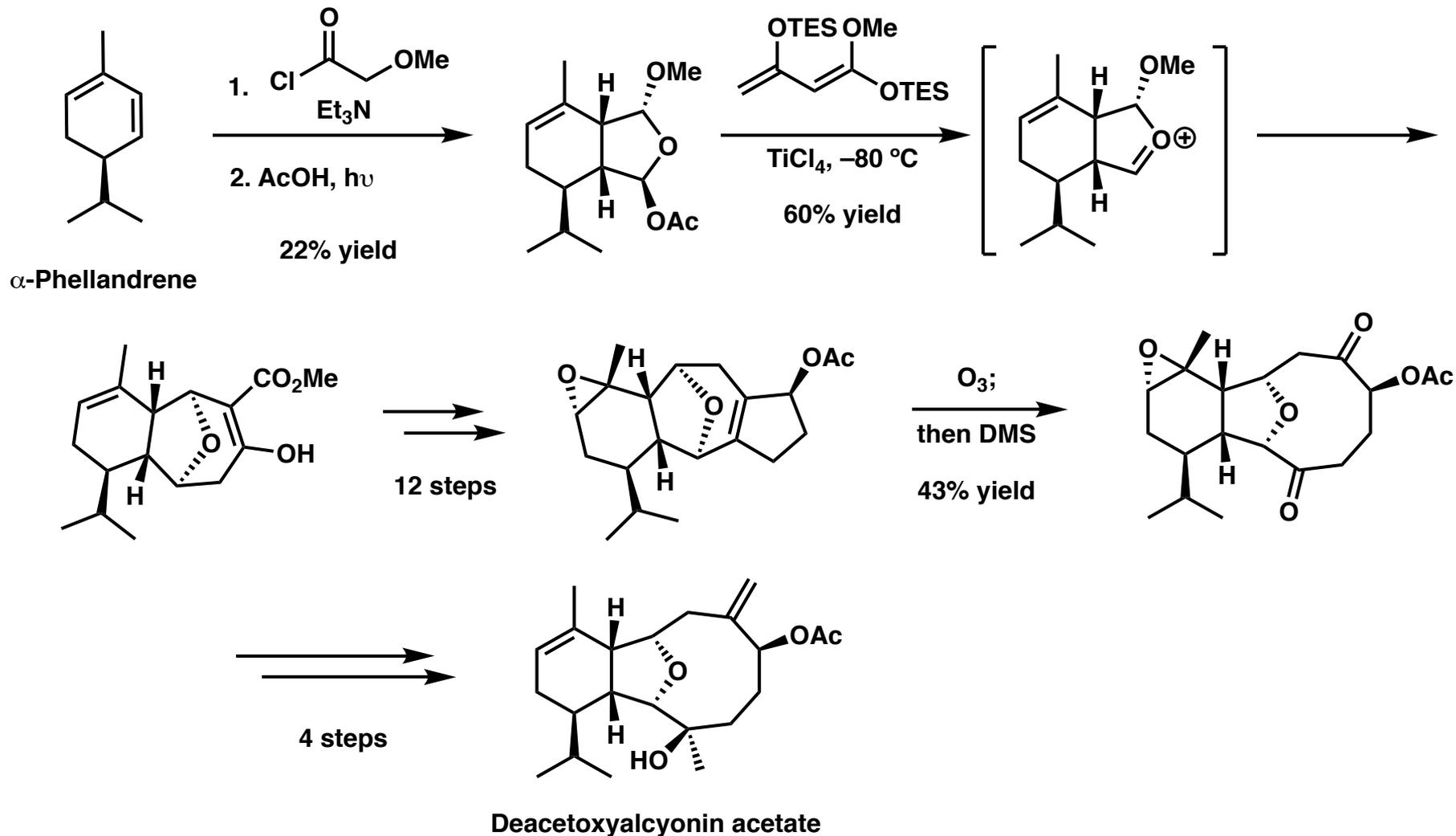
[4+3] Cycloaddition

Funk's Racemic Synthesis of Cortistatin J



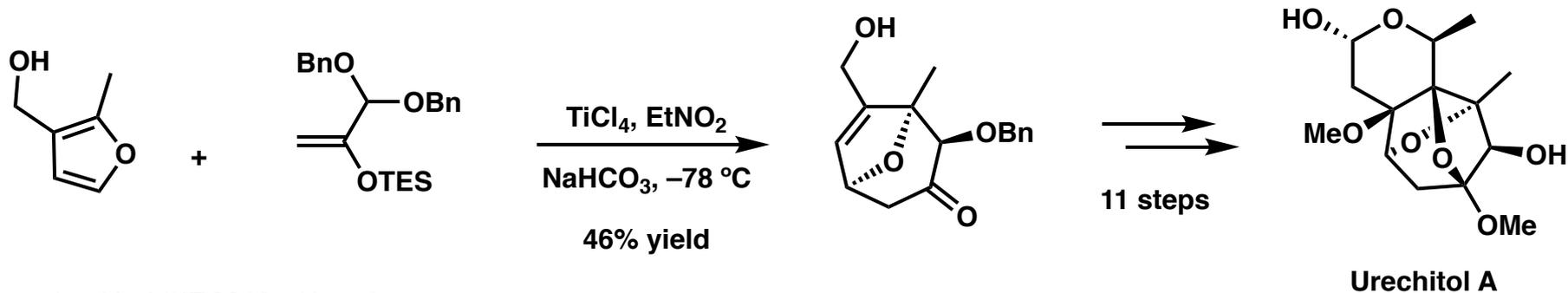
[4+3] Cycloaddition

Molander's Asymmetric Synthesis of Deacetoxyalcyonin Acetate



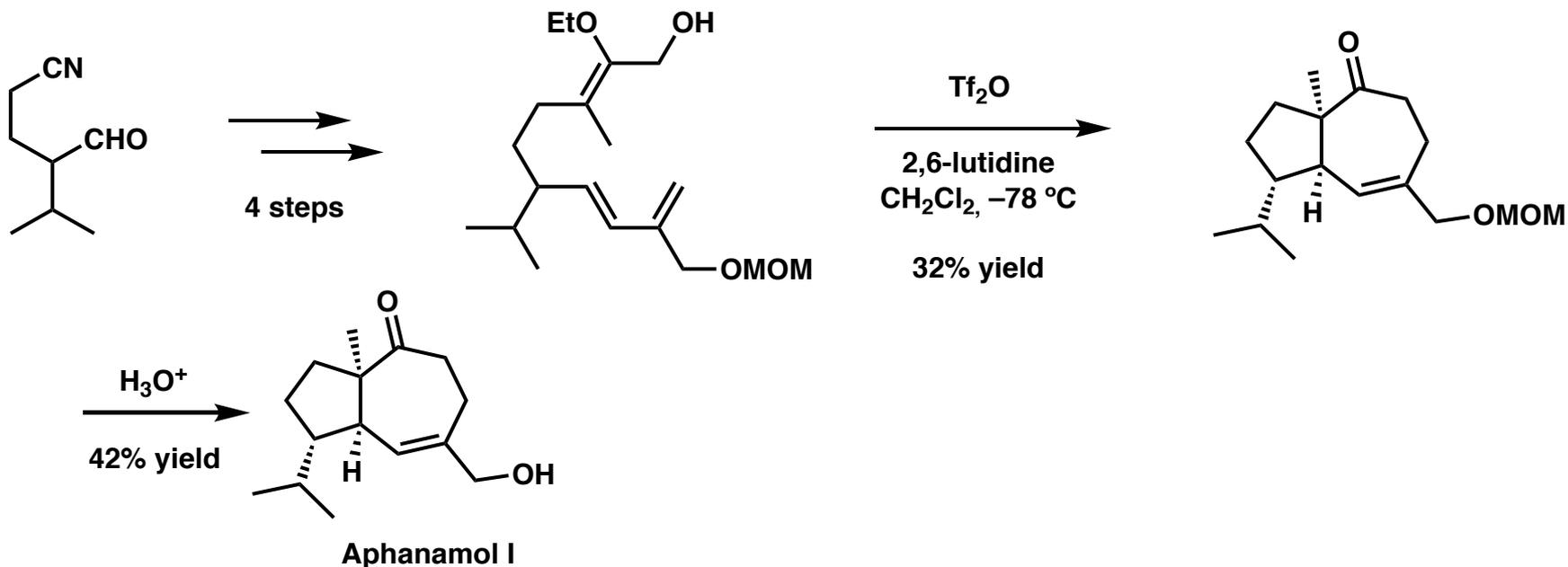
[4+3] Cycloaddition

Watanabe's Racemic Synthesis of Urechitol A



Watanabe, H. *ACIE* 2010, 49, 5527.

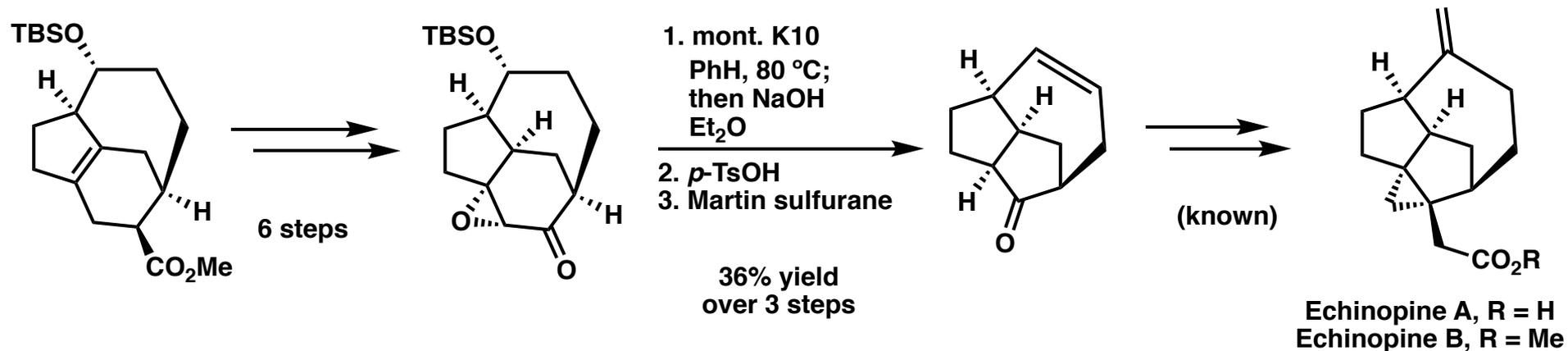
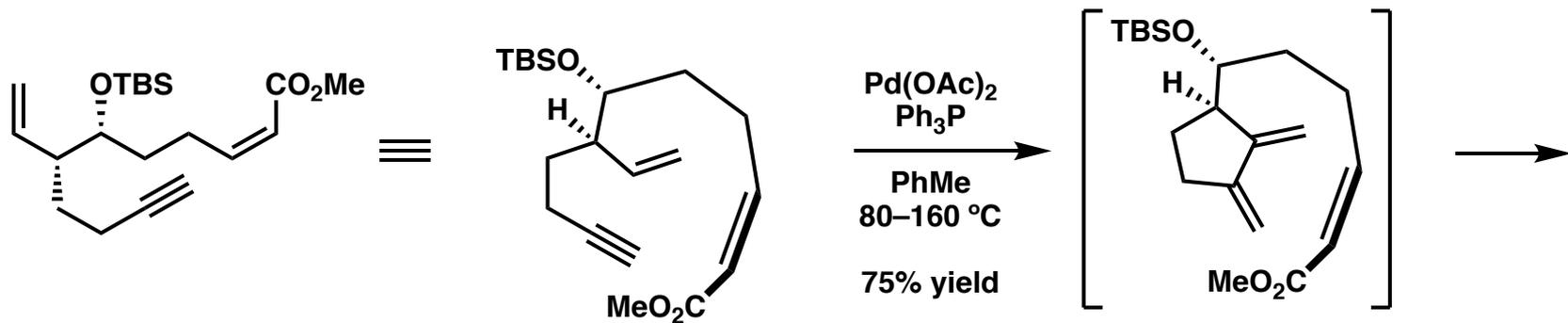
Harmata's Racemic Synthesis of Aphanamol I



Harmata, M. *Tetrahedron Lett.* 1997, 38, 7985.

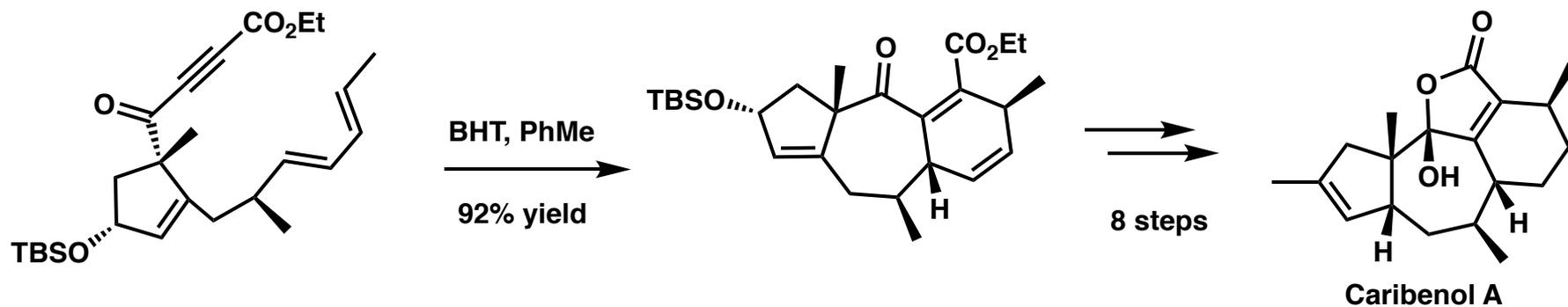
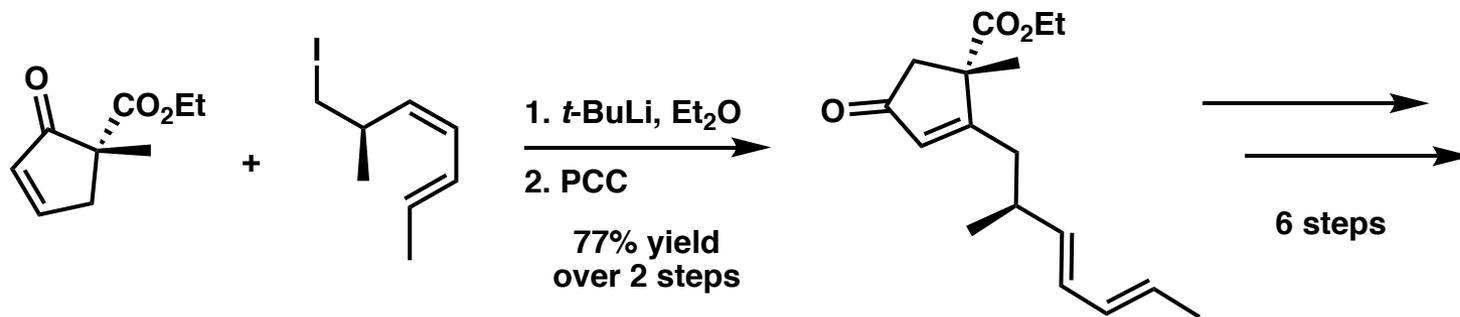
Diels–Alder

Chen's Formal Synthesis of Echinopine A



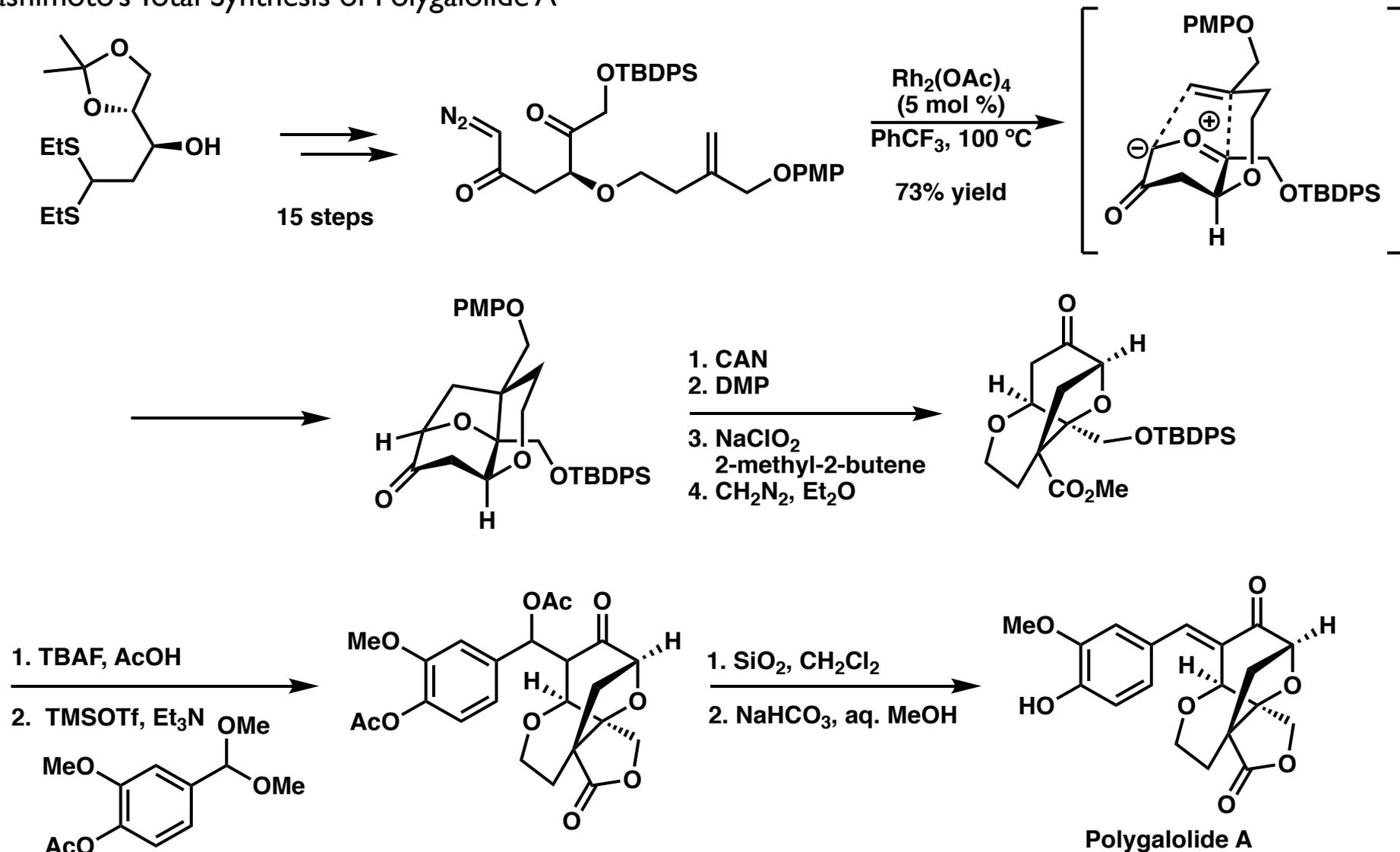
Diels–Alder

Yang's Total Synthesis of Caribenol A



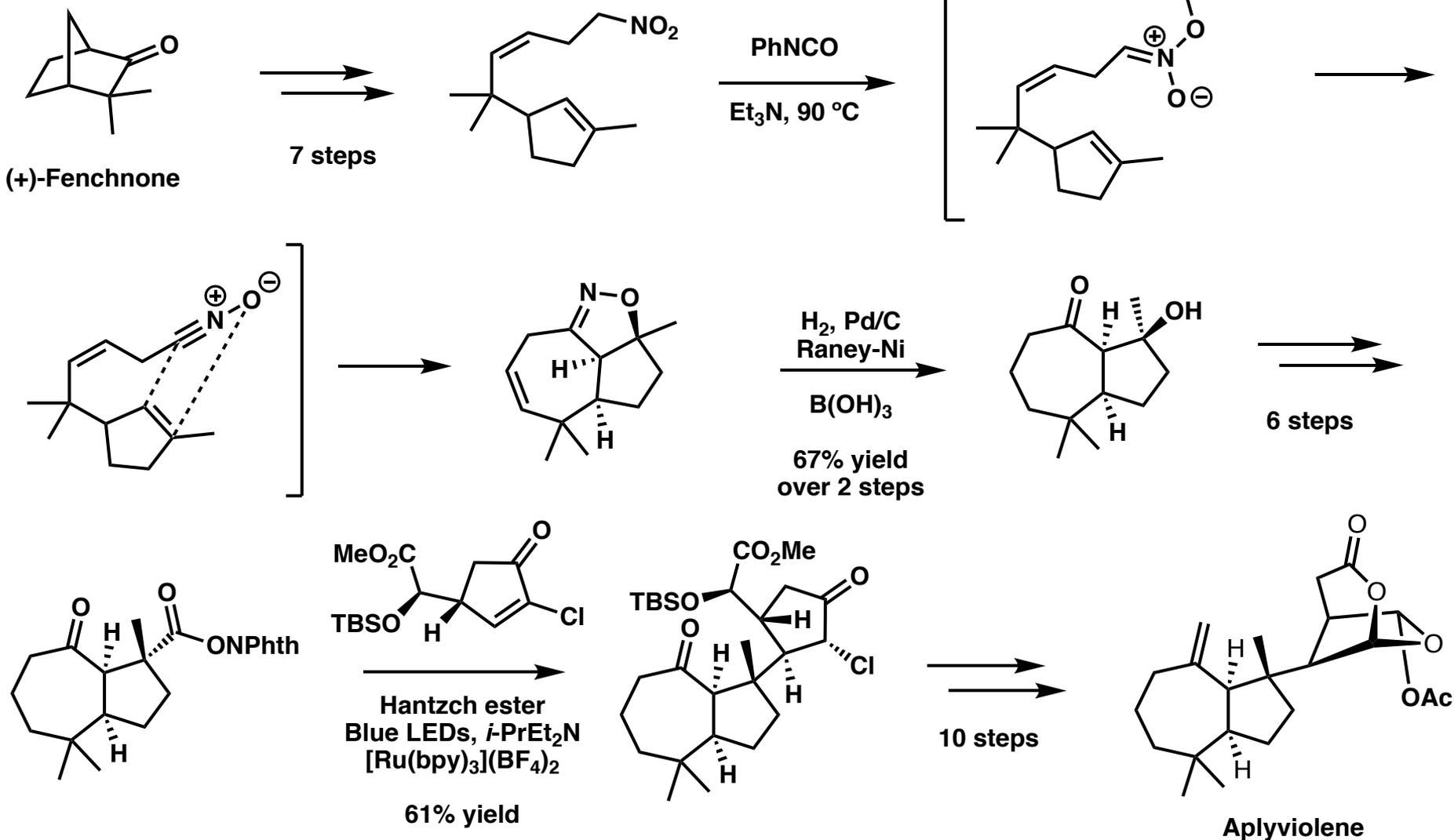
[3+2] Cycloaddition

Hashimoto's Total Synthesis of Polygalolide A



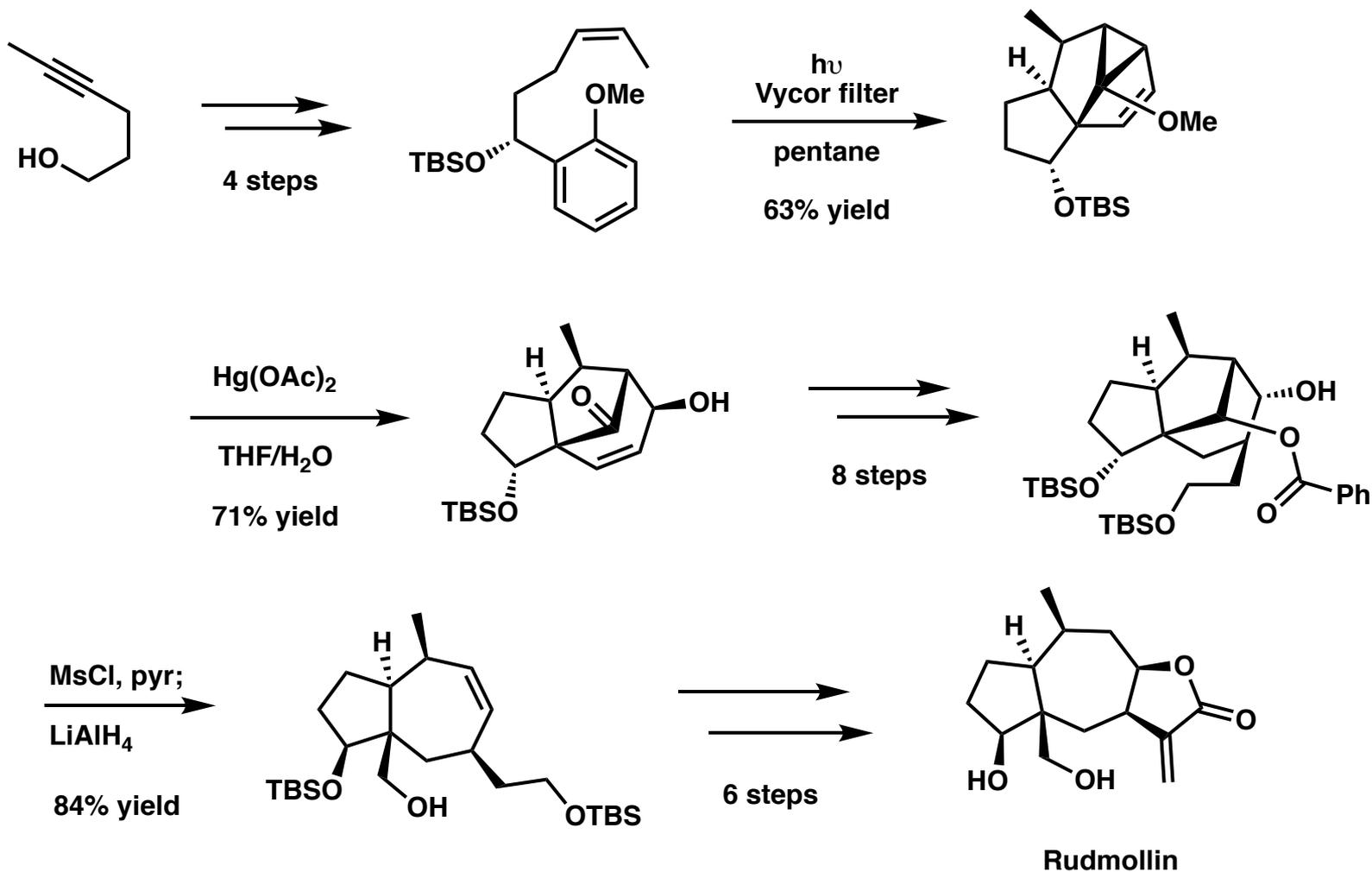
[3+2] Cycloaddition

Overman's Racemic Synthesis of Aplyviolene



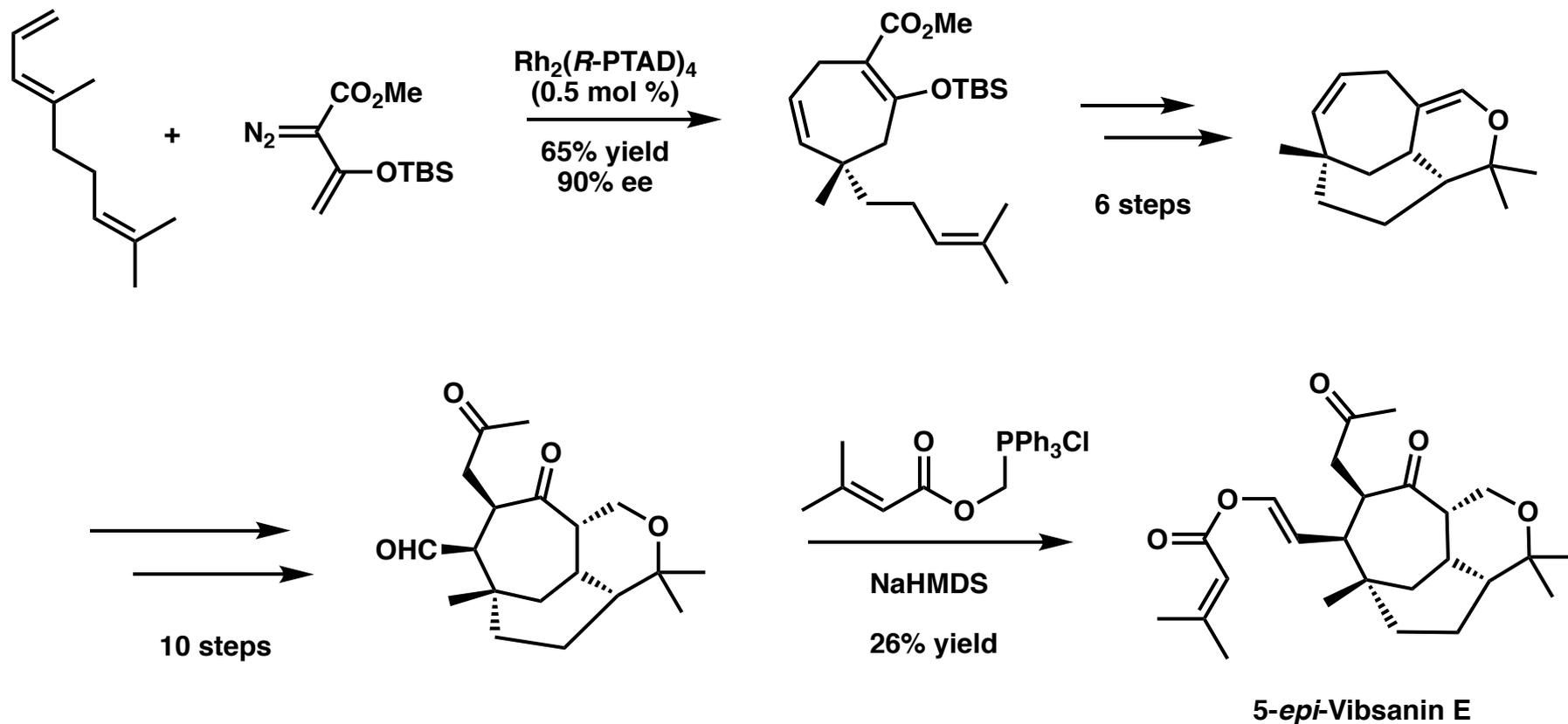
meta-Photocycloaddition

Wender's Racemic Synthesis of Rudmollin



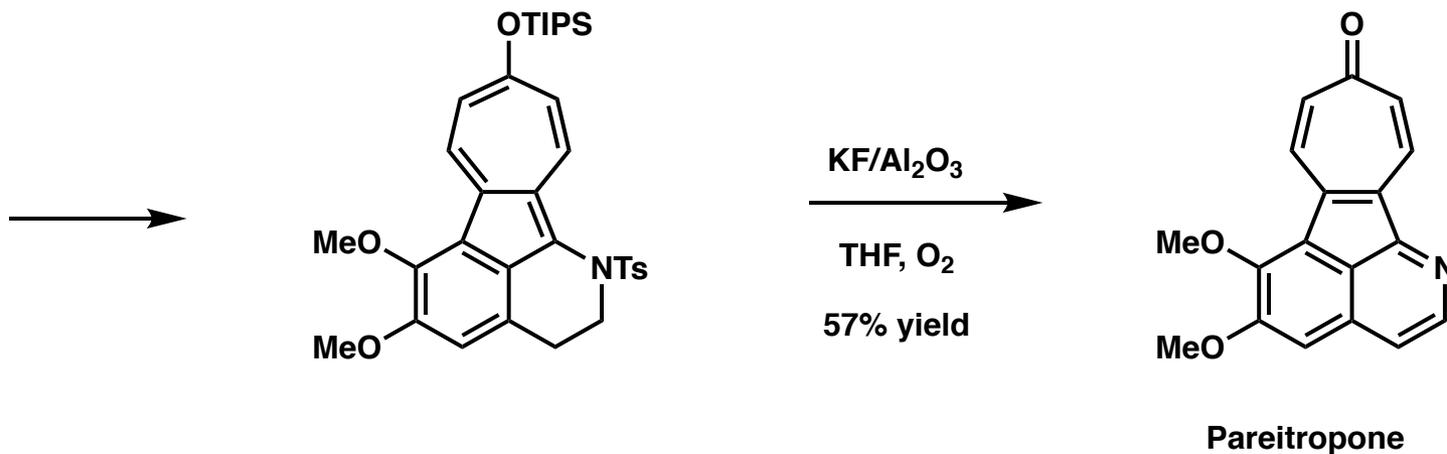
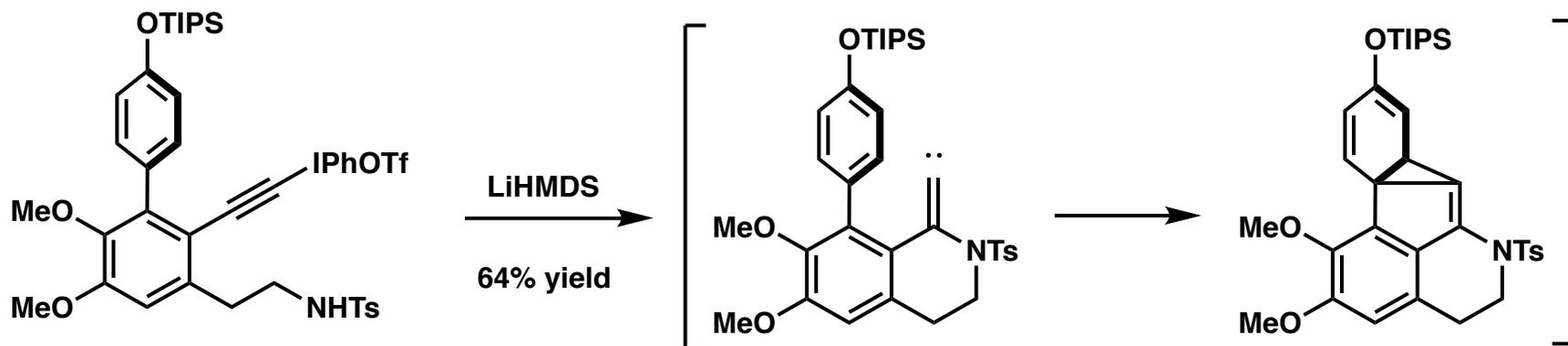
Cyclopropane Rearrangements

Davies' Synthesis of 5-*epi*-Vibsanin E



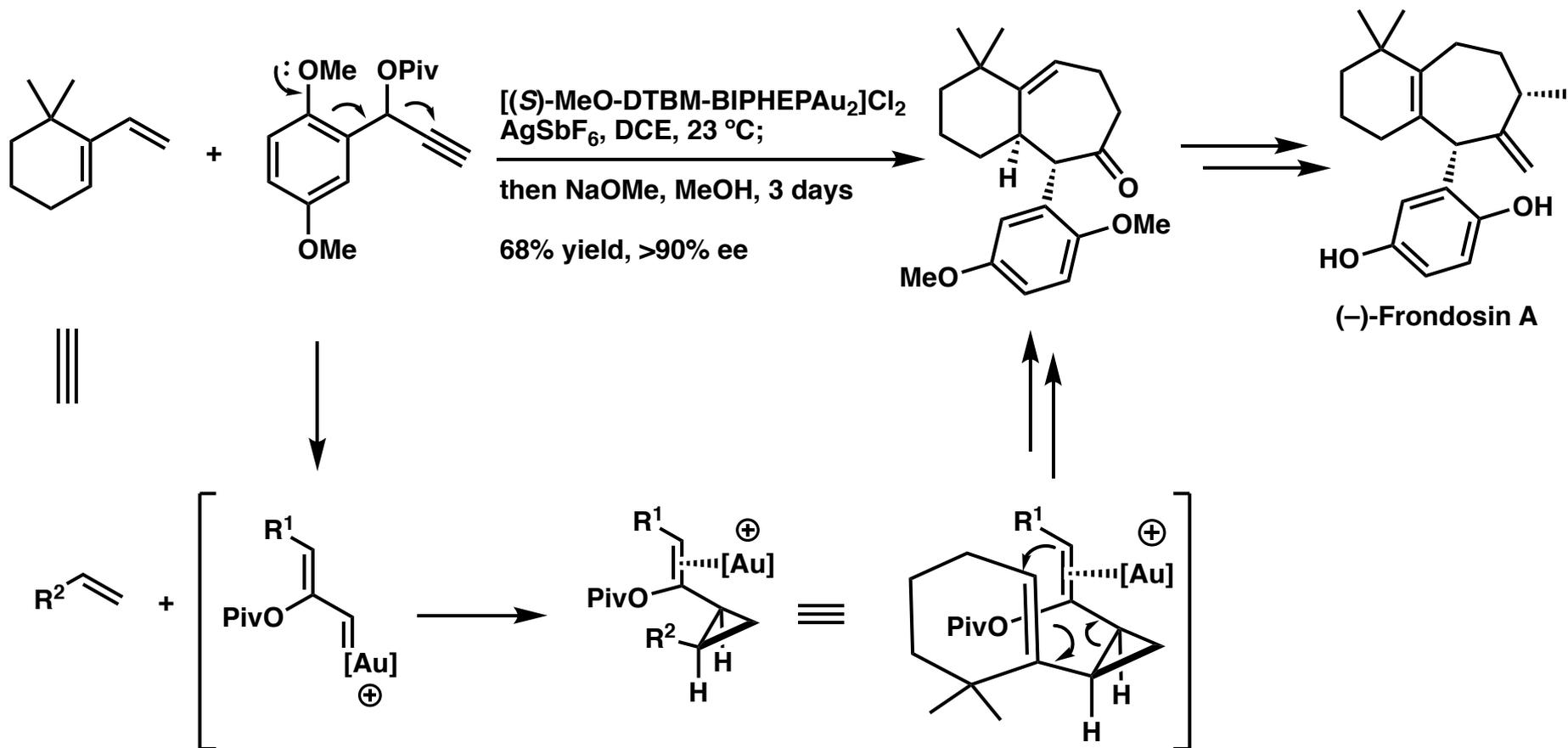
Cyclopropane Rearrangements

Feldman's Synthesis of Pareitropone



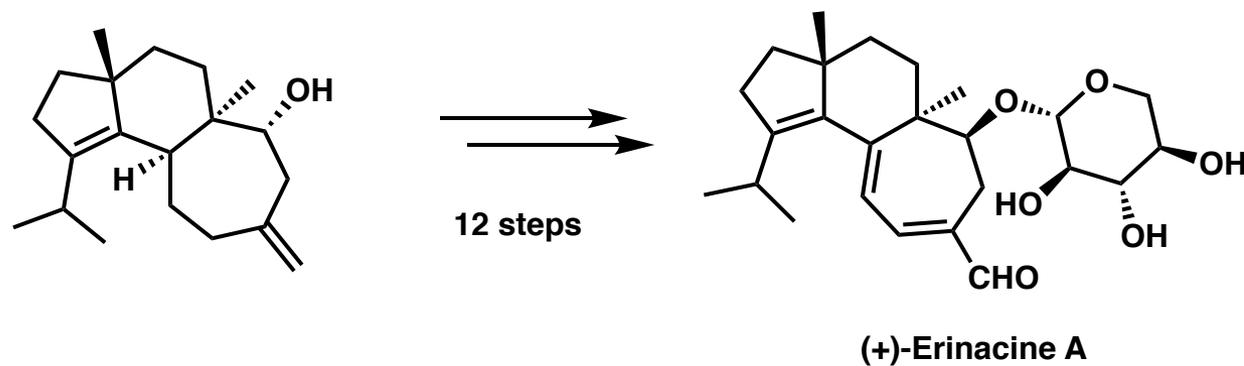
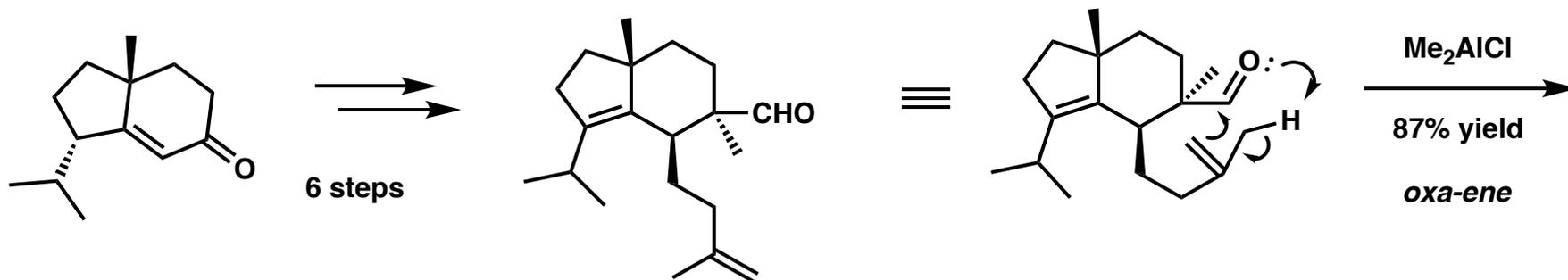
Cyclopropane Rearrangements

Nevado's Formal Synthesis of Frondosins A and B



Group Transfer

Snider's Syntheses of (+)-Erinacine A



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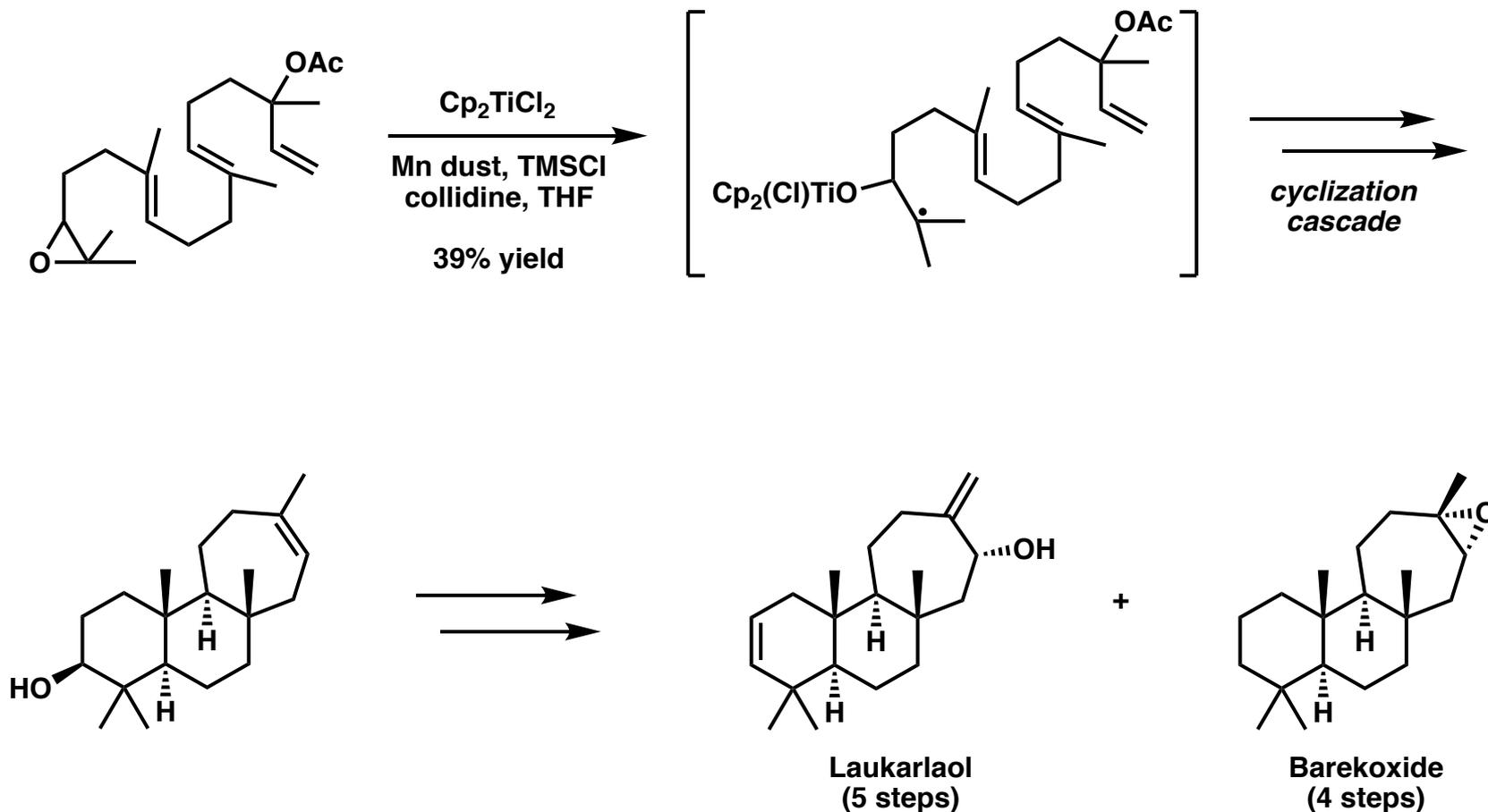
- Ene–Ene, Ene–Yne

Ring Expansions

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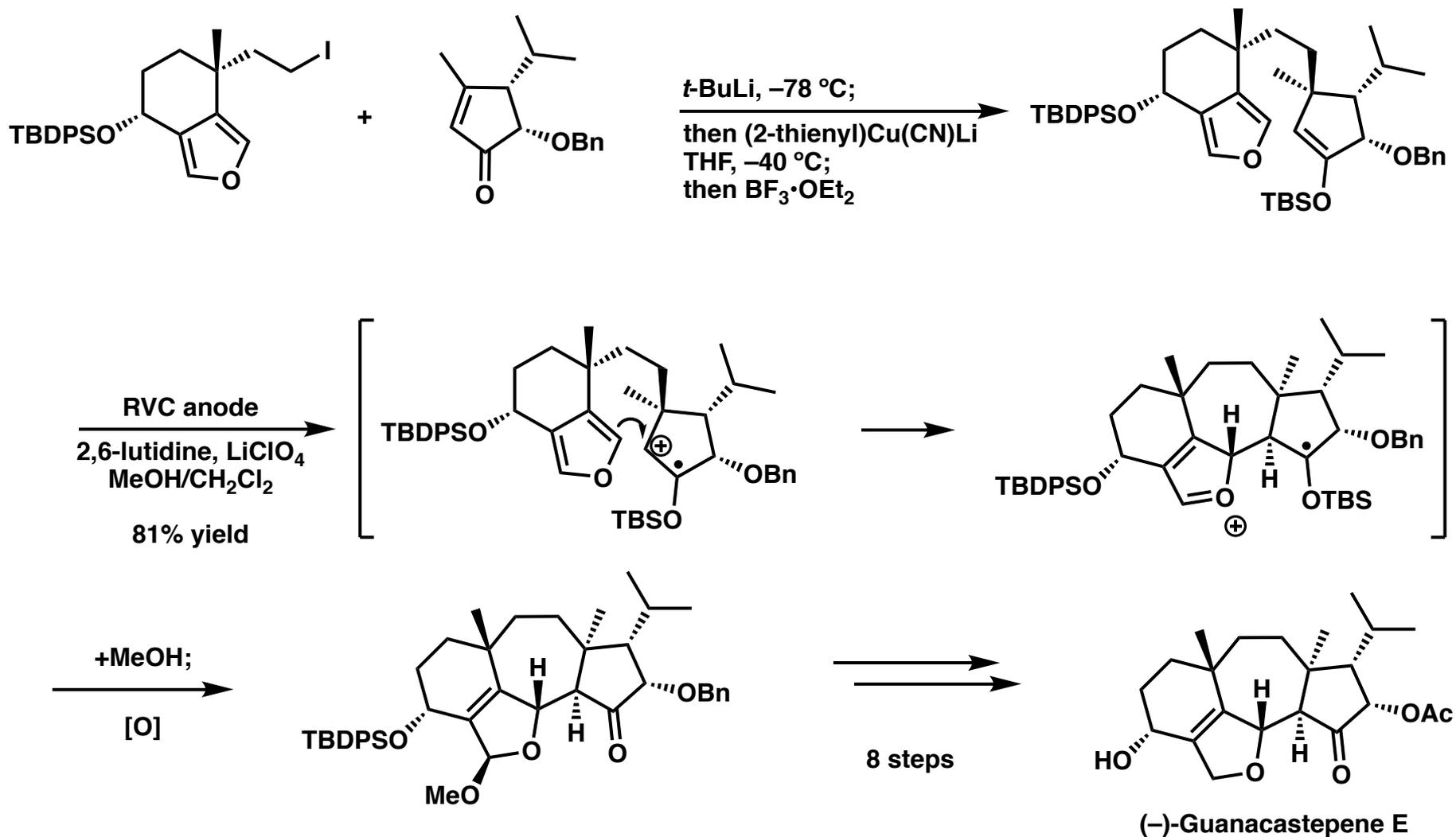
Radical Cyclization

Oltra's Total Syntheses of Laukarlaol and Barekoxide



Radical Cyclization

Trauner's Total Synthesis of (-)-Guanacastepene E



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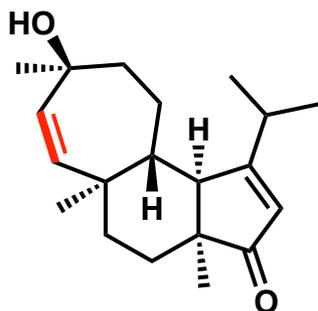
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Ring Expansions

- One-carbon, Two-carbon

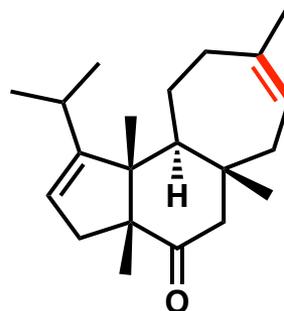
Ring-closing Metathesis

Ene-Ene Metathesis: Selected Examples



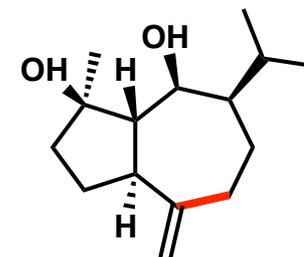
(+)-Cyanthiwigin U

Phillips *JACS* **2005**, 5334



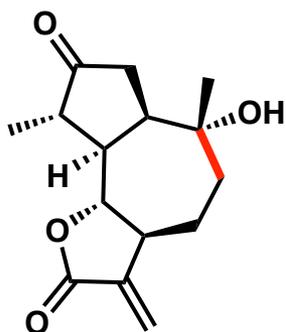
(-)-Cyanthiwigin F

Stoltz *Nature* **2008**, 1228



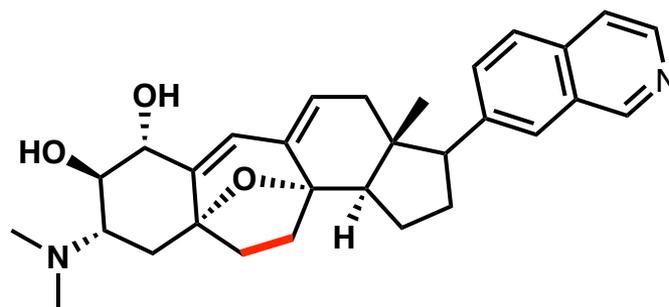
Teucladiol

Vanderwal *JACS* **2009**, 15090



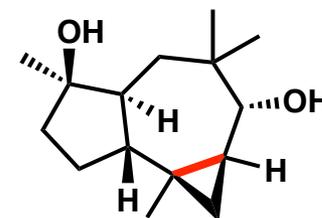
(+)-Chinensiolide B

Hall *JACS* **2010**, 1486



Coristatin A

Myers *Nat. Chem.* **2010**, 886

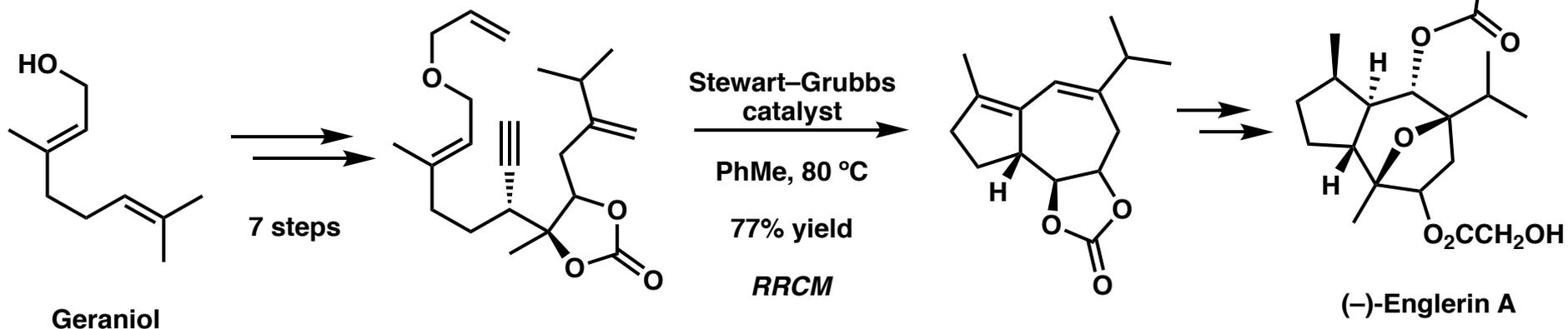


(+)-Omphadiol

Romo *ACIE* **2011**, 7537

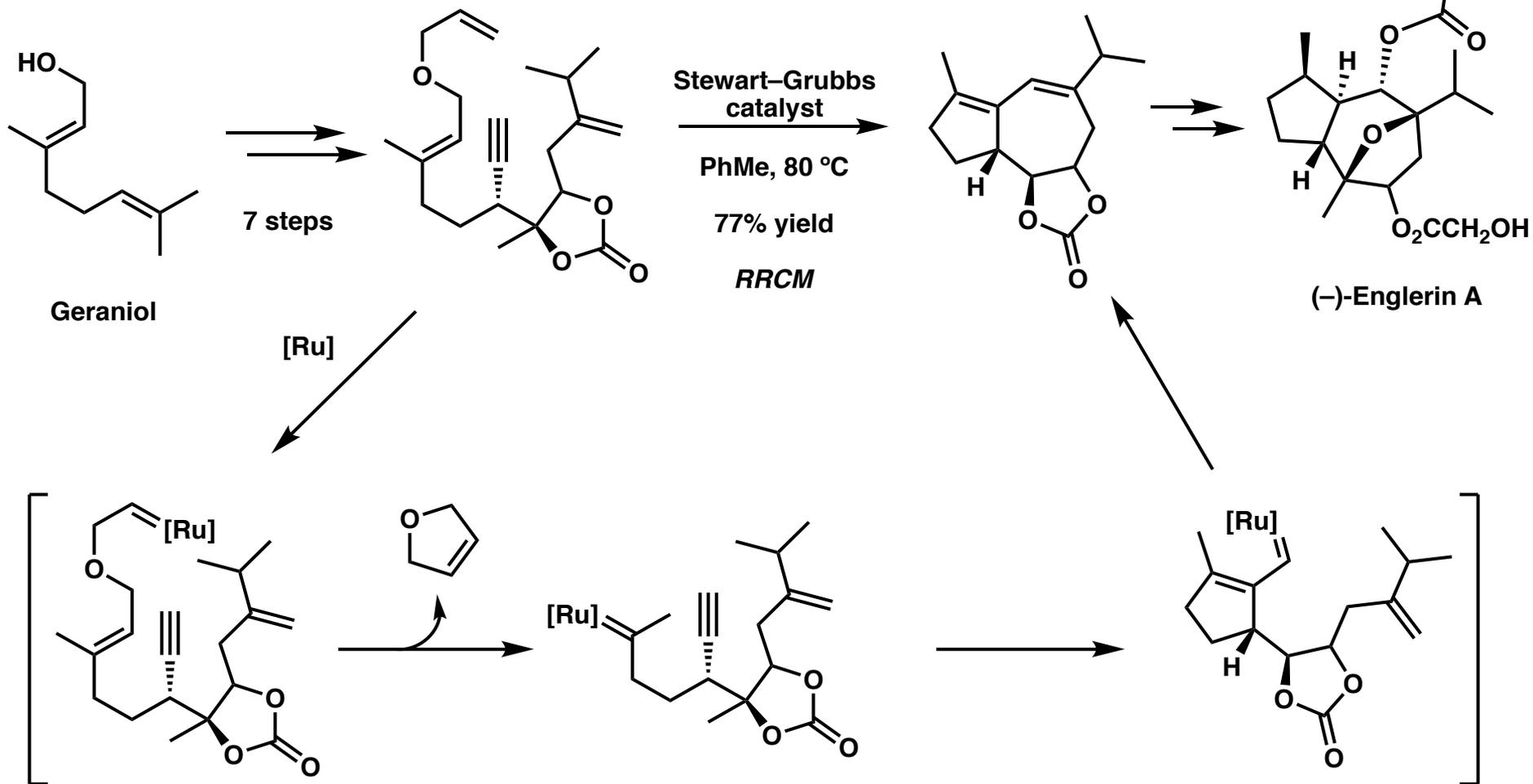
Ring-closing Metathesis

Ene–Yne Metathesis: Parker's Formal Synthesis of (–)-Englerin A



Ring-closing Metathesis

Ene-Yne Metathesis: Parker's Formal Synthesis of (-)-Englerin A



Outline for the Talk

- Challenges of Making Seven-membered Rings
- Methods for the Synthesis of Cycloheptanoid Natural Products

“Classical” Methods

- Aldol chemistry, Friedel–Crafts, Oxidative Cyclization, Prins-Pinacol

Cross Coupling

- Heck, Pauson–Khand

Pericyclic Reactions

- Cycloadditions, Cyclopropane Rearrangements, Group Transfer

Radical Cyclization

Ring-Closing-Metathesis

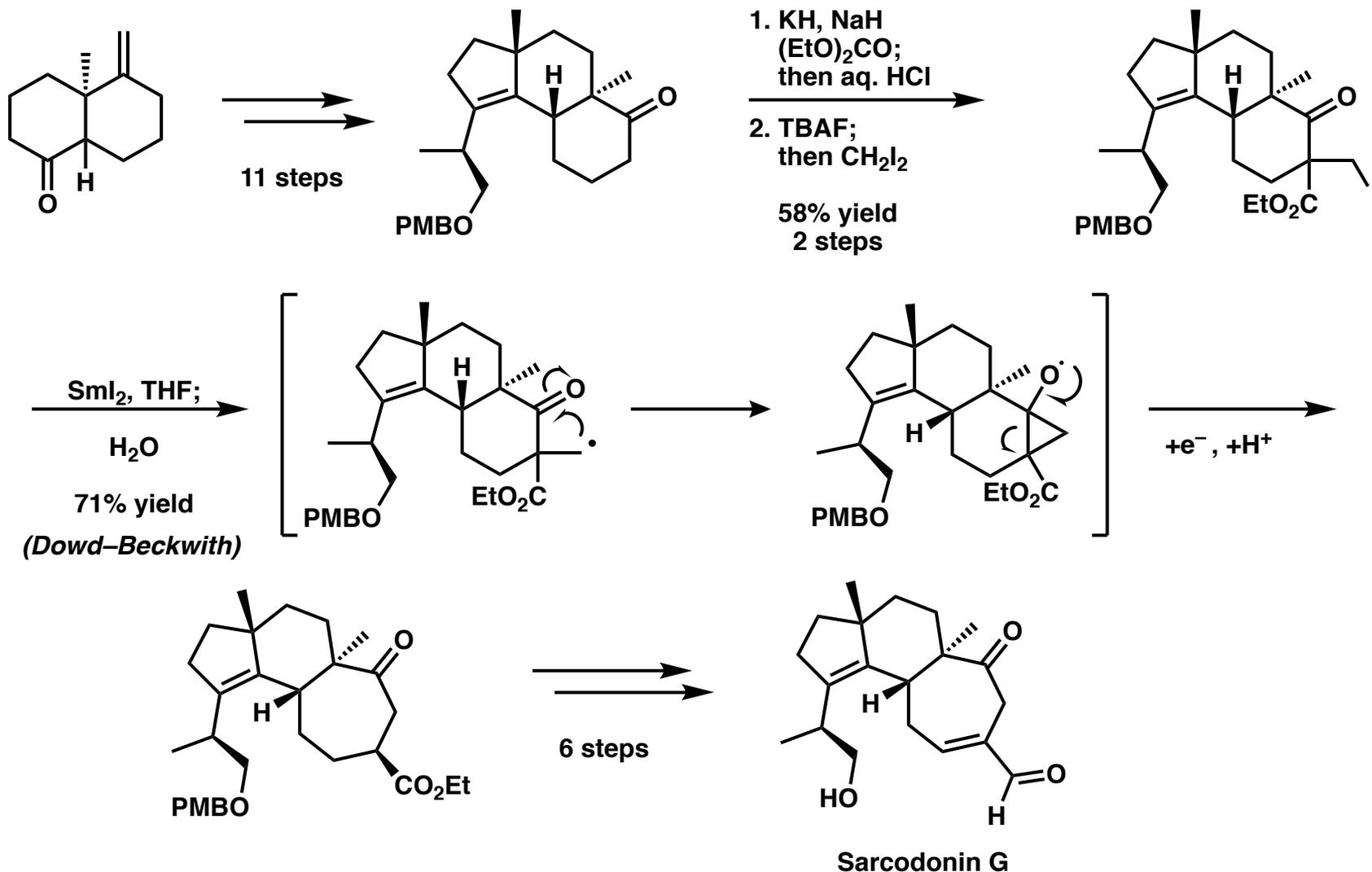
- Ene–Ene, Ene–Yne

Ring Expansions

- One-carbon, Two-carbon

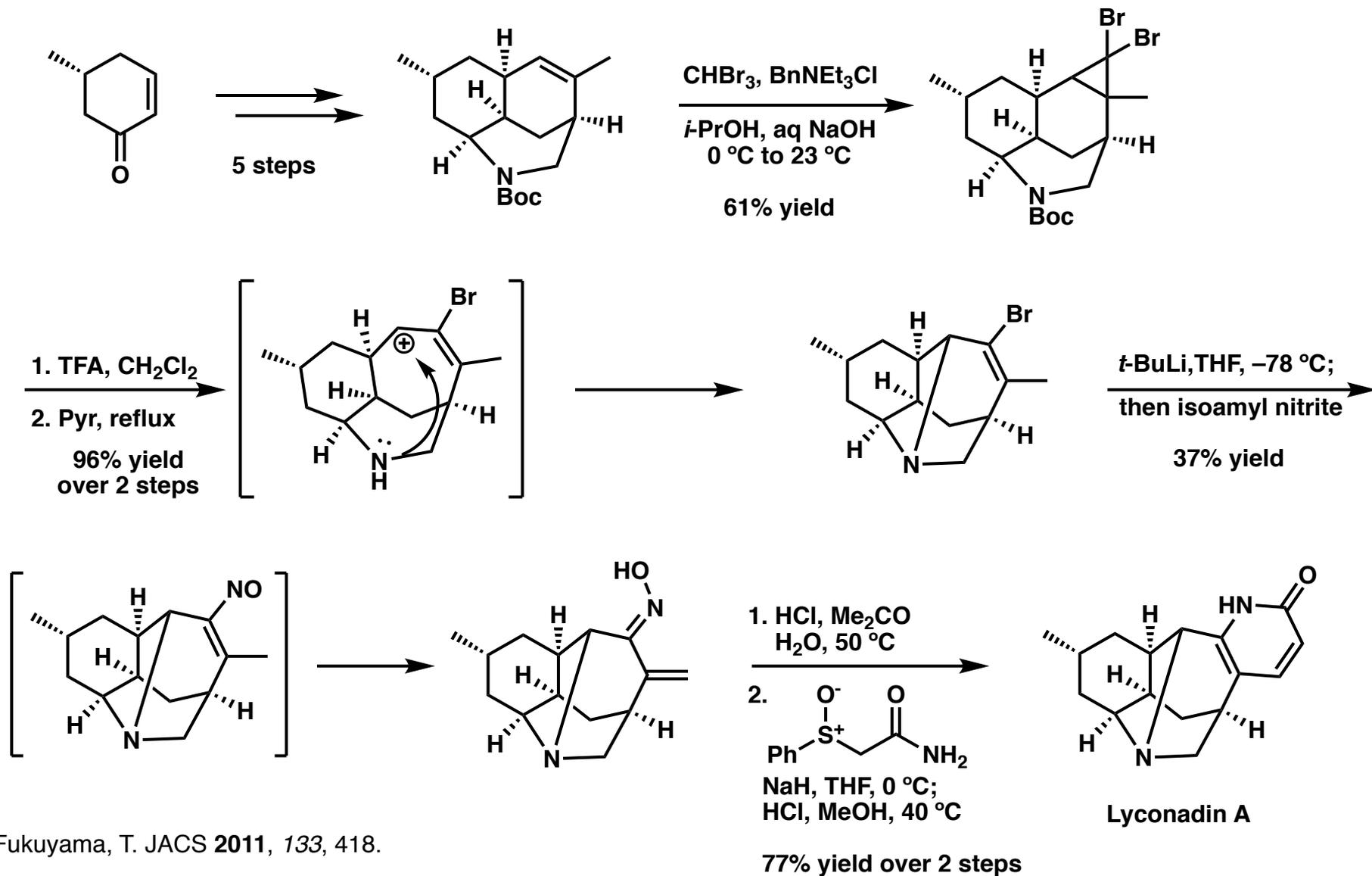
Dowd–Beckwith

Piers' Synthesis of racemic Sarcodonin G



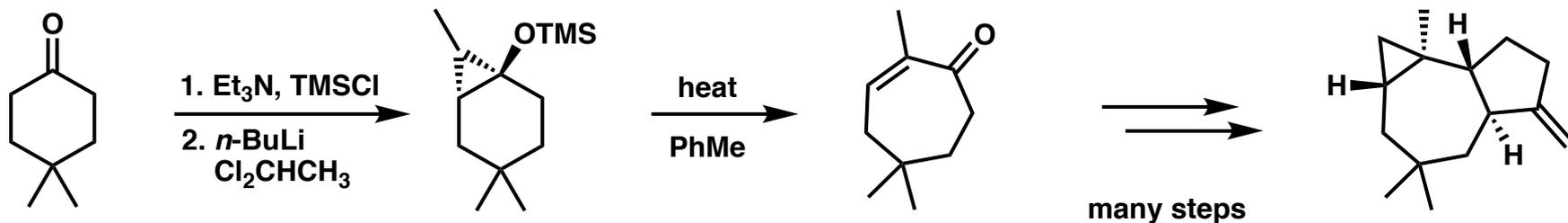
Nozaki Ring Expansion

Fukuyama's Total Synthesis of (+)-Lyconadin A



Nozaki Ring Expansion

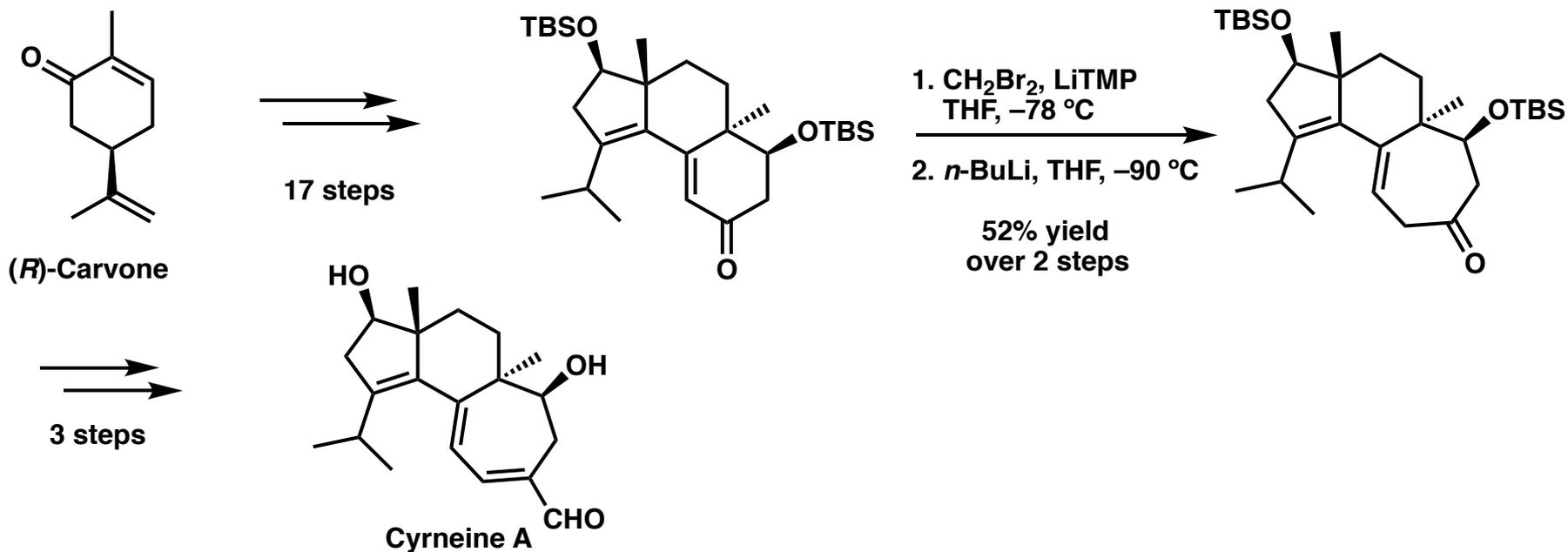
Paquette's Racemic Total Synthesis of Africanol



Paquette, L. A. *JACS* **1987**, *109*, 3025.

Africanol

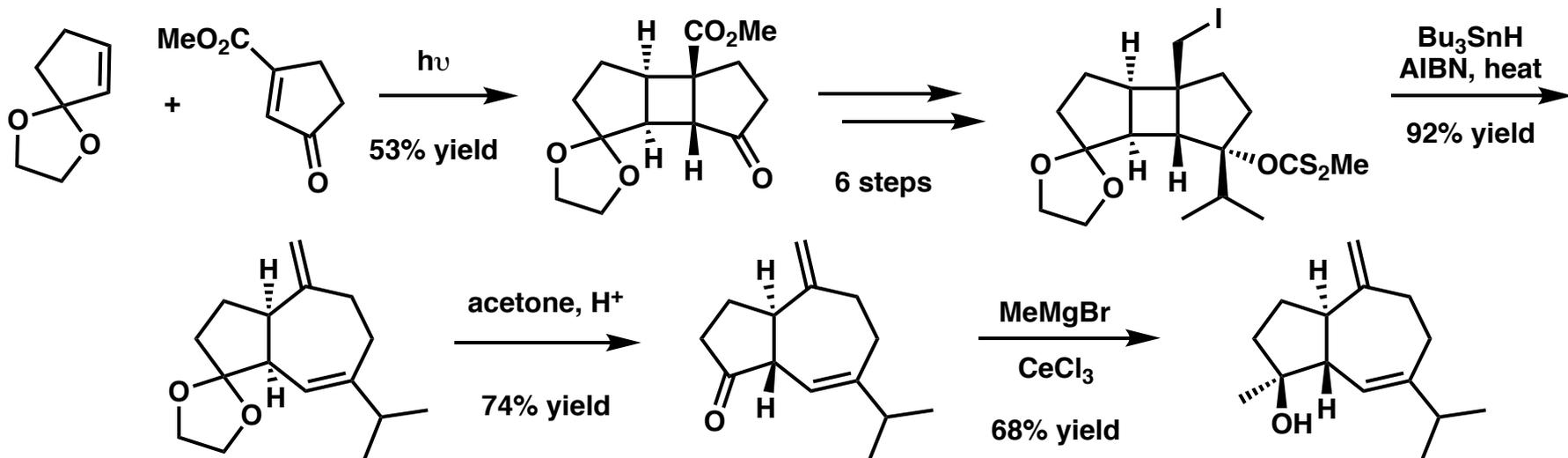
Gademann's Total Synthesis of Cyrneine A



Gademann, K. *ACIE* **2012**, *51*, 4071.

Two-carbon Ring Expansion

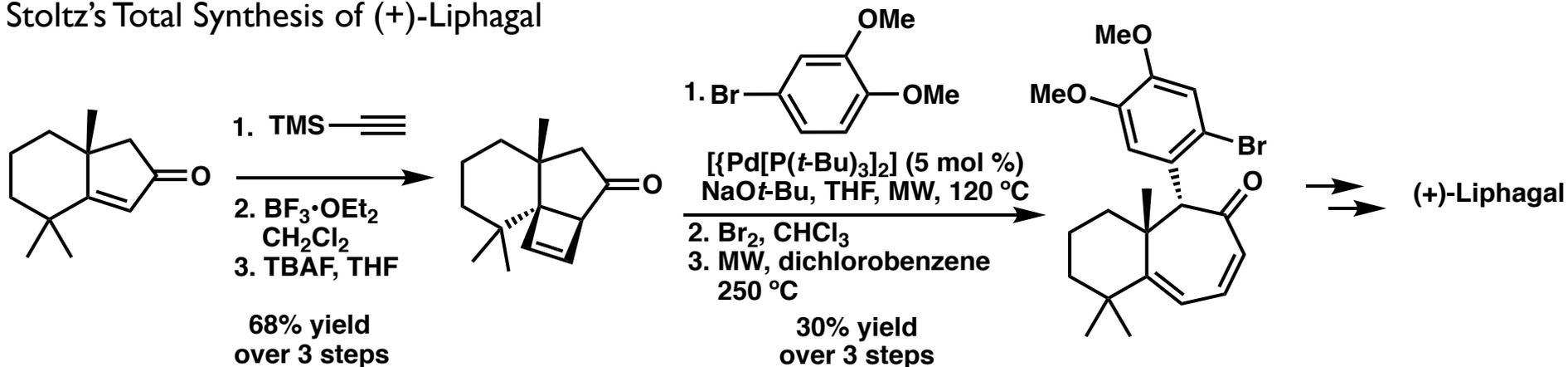
Lange's Synthesis of Alismol



Lange, G. L. *JOC* **1999**, *64*, 6738.

Alismol

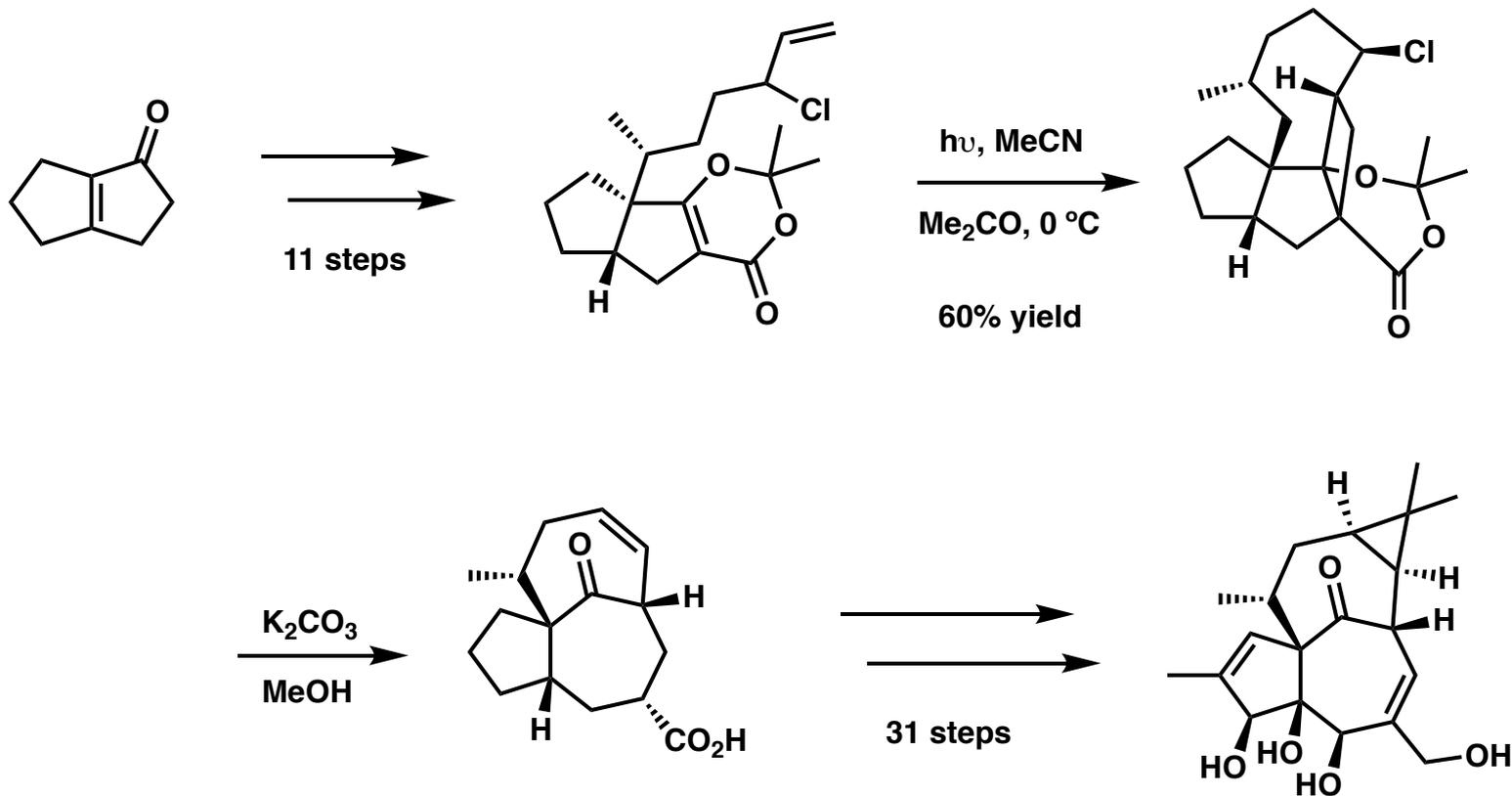
Stoltz's Total Synthesis of (+)-Liphagal



Stoltz, B. M. *ACIE* **2011**, *50*, 6814.

Two-carbon Ring Expansion

Winkler's Racemic Synthesis of Ingenol



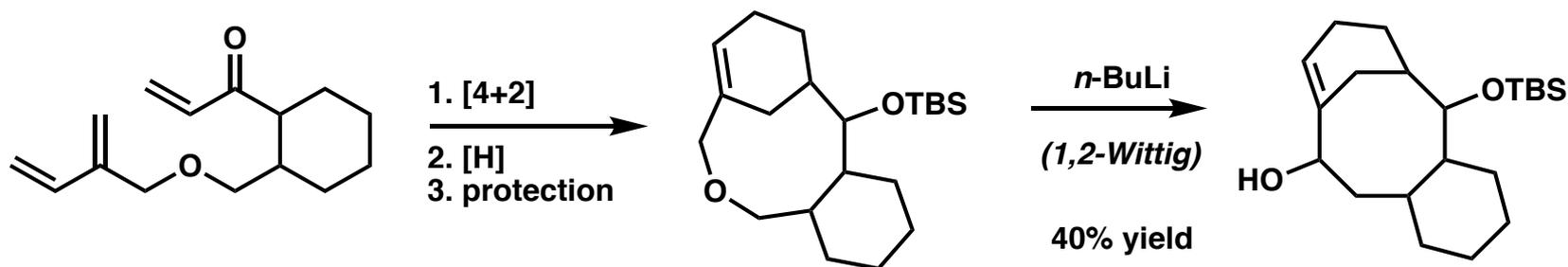
Summary and Outlook

Most Common Approaches to Synthesize Seven-membered Carbocycles

- RCM
- Cycloadditions using discrete or latent 1,3-dipole functionality
- Ring expansions

Prospective Strategies

- Nozaki–Hiyami–Kishi reaction
- McMurry Coupling
- Ring Contractions: Wittig rearrangement, Rämberg–Backlund olefination, etc.



Helpful Resources

- Enders, D. et al. *Synthesis* **2013**, 45, 845.
- Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, 56, 4317.
- de Oliveira, K. T. et al. *J. Stud. Nat. Prod. Chem.* **2014**, 42, 421.