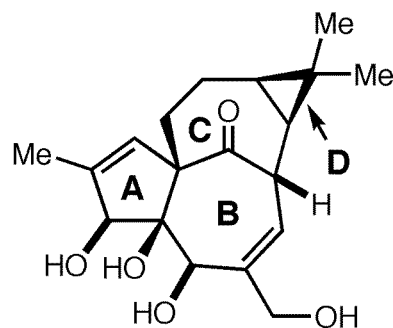


Synthetic Approaches to Ingenol

George Borg
Evans Group Seminar
Friday, December 3, 2004

Overview



- i) Structural features
- ii) Early approaches to the skeleton
- iii) Total syntheses
 - Winkler- racemic
 - Tanino and Kuwajima- racemic
 - Kigoshi- asymmetric (formal)
 - Wood- asymmetric

Isolated from roots of *Euphorbia ingens* (E. Hecker, *Cancer Res.* **1968**, *28*, 2338).
Structural elucidation: X-ray of derivative (E. Hecker, *Tetrahedron Lett.* **1970**, 4075).

Ingenol esters abundant in genus *Euphorbiaceae*, used in traditional medicines to treat a variety of ailments, including tumors, migraines, parasitic infections, venereal diseases, gingivitis, and as purgatives.

Ingenol derivatives have been reported to inhibit HIV-1 replication.

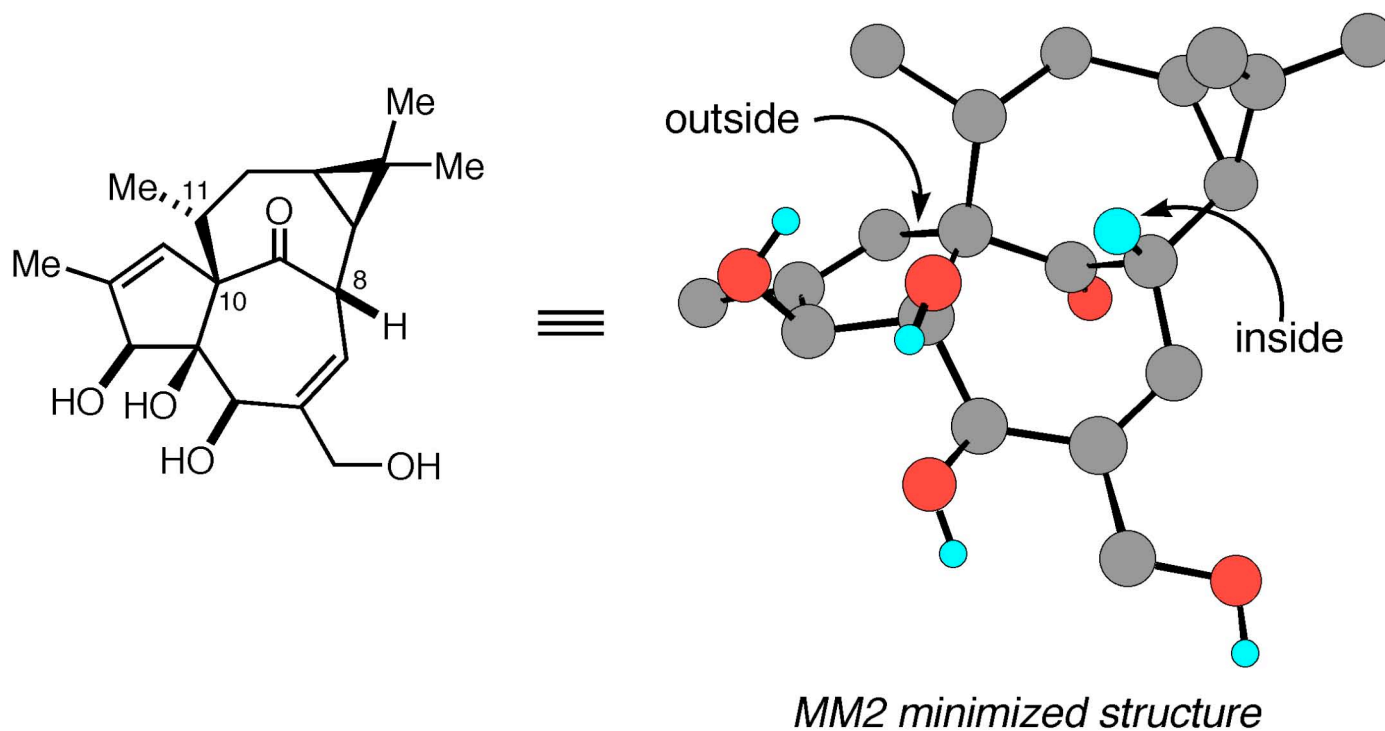
Ingenol derivatives have displayed both tumor-promoting and anti-tumor-promoting properties.

Leading references:

- Winkler, *Chem. Soc. Rev.* **1997**, *26*, 387.
- Winkler, *J. Am. Chem. Soc.* **2002**, *124*, 9726.
- Tanino, Kuwajima, *J. Am. Chem. Soc.* **2003**, *125*, 1498.
- Wood, *JACS ASAP* November 24, 2004.

Synthetic Challenges

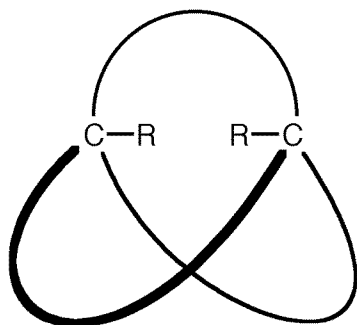
- **Trans intrabridgehead stereochemistry**



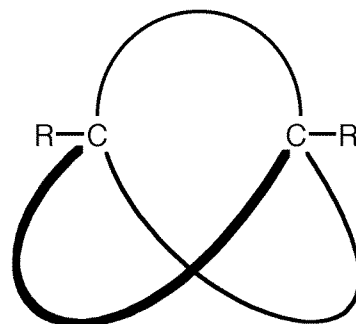
- **Installation of the hydroxyl groups**
- **Stereochemistry at C₁₁**

In-Out Isomerism

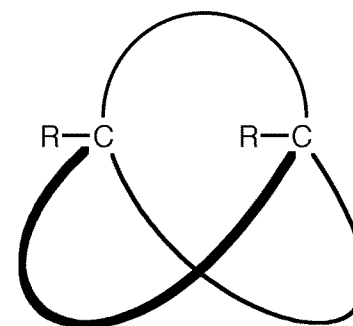
- Bridged bicyclic systems can exist as three different stereoisomers:



in – in



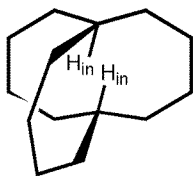
out – out



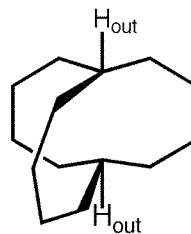
in – out

- The in-in isomer is usually the most unstable
- The energy difference between the in-out and the out-out isomers varies depending on the system:

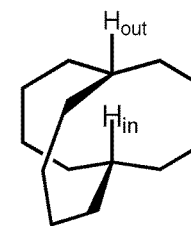
bicyclo[4.4.4]tetradecane



15.47



12.21



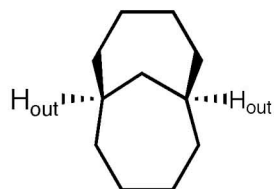
0

ΔE :
(kcal/mol)

MM2 calculated steric energies of lowest energy conformations

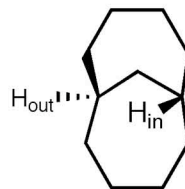
In – Out Isomerism: Ingenol

• Bicyclo[4.4.1]undecane:

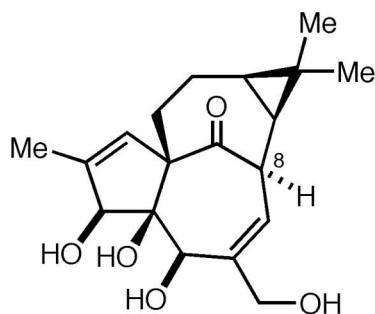


$\Delta E:$
(kcal/mol)

0



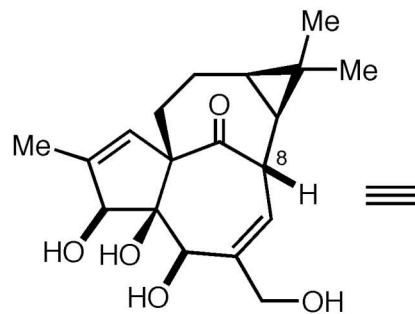
6.3



isoingenol (out-out)

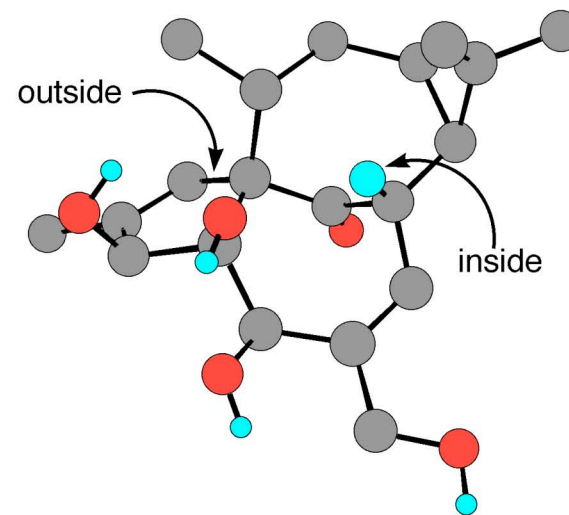
$\Delta E:$
(kcal/mol)

0



ingenol (in-out)

5.9

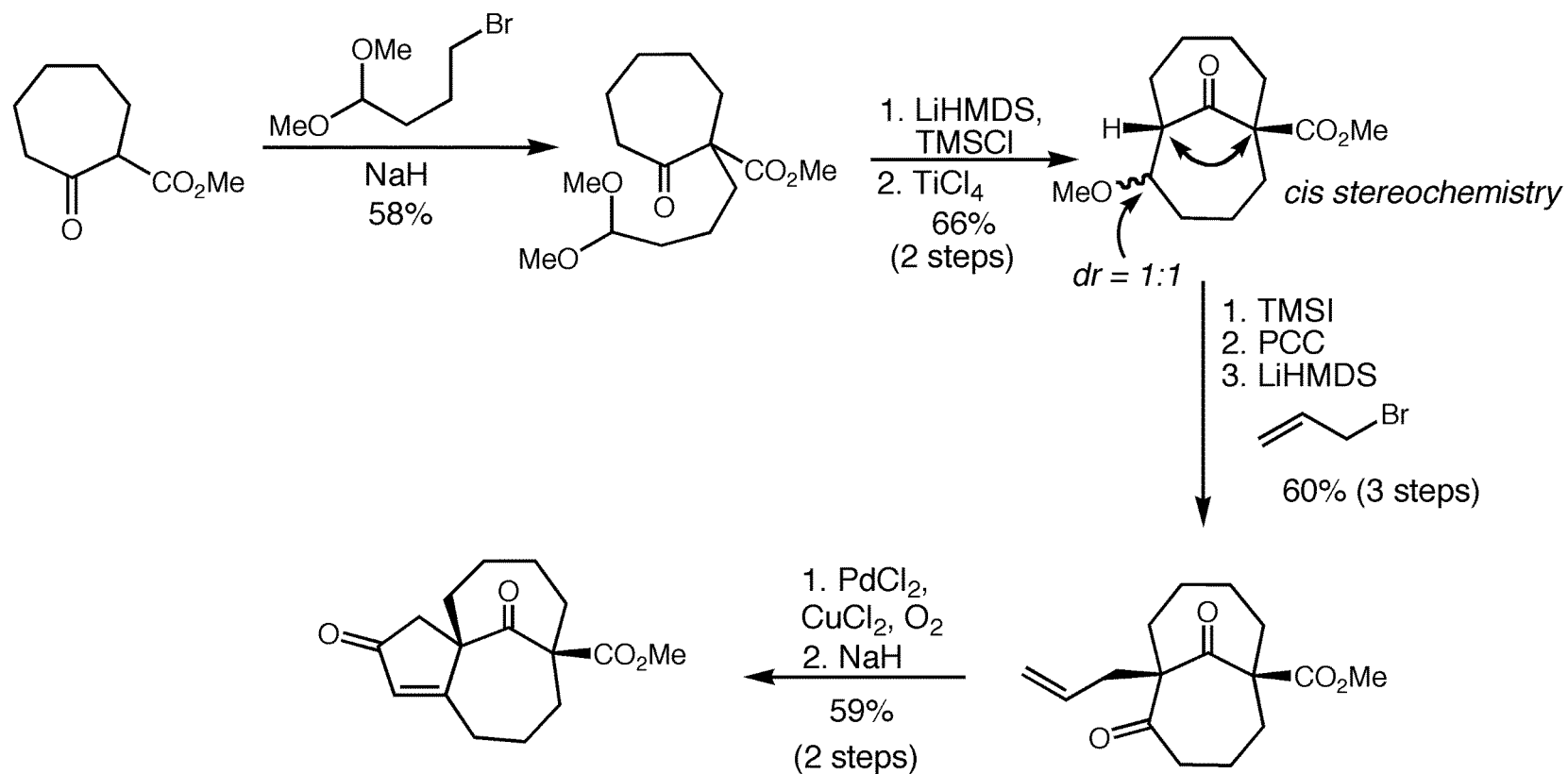


MM2 minimized structure

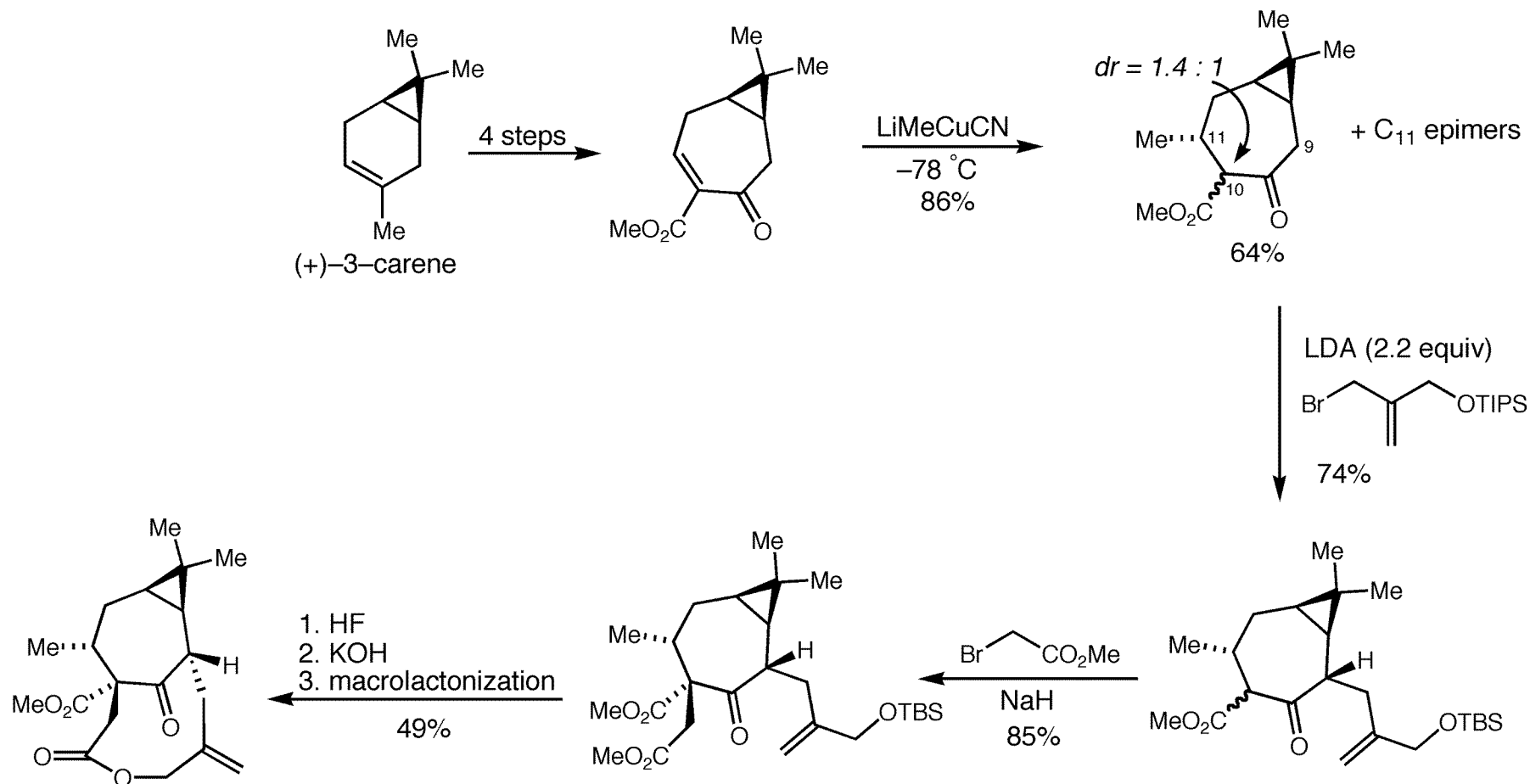
Funk *et al.* *J. Am. Chem. Soc.* **1988**, *110*, 3298.

- Ingenol is probably the higher-energy isomer.
- The in-out stereochemistry is essential for biological activity.

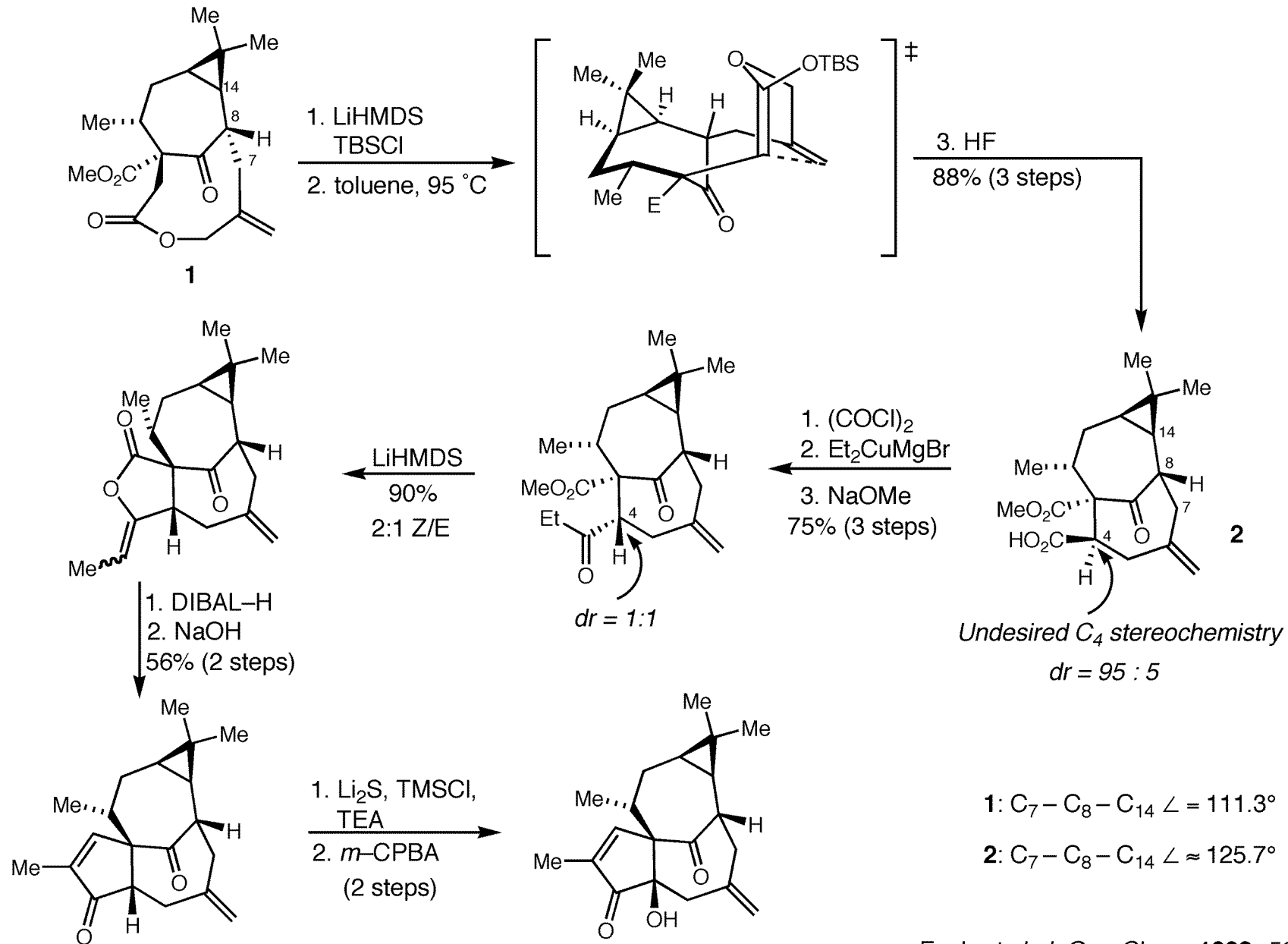
Mehta: A Double-Alkylation Approach to the B Ring



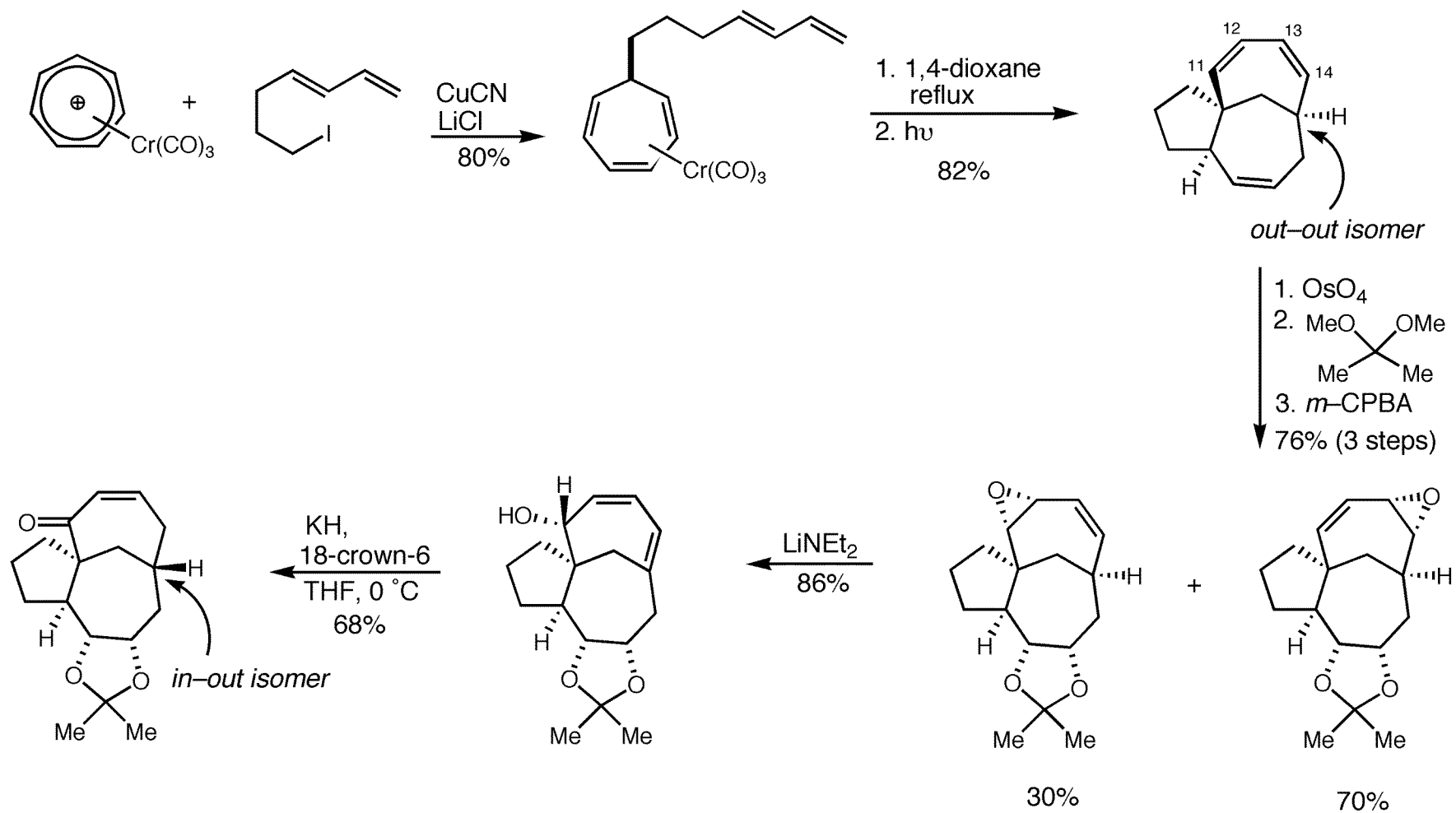
Funk: Relaying the D-Ring Stereochemistry



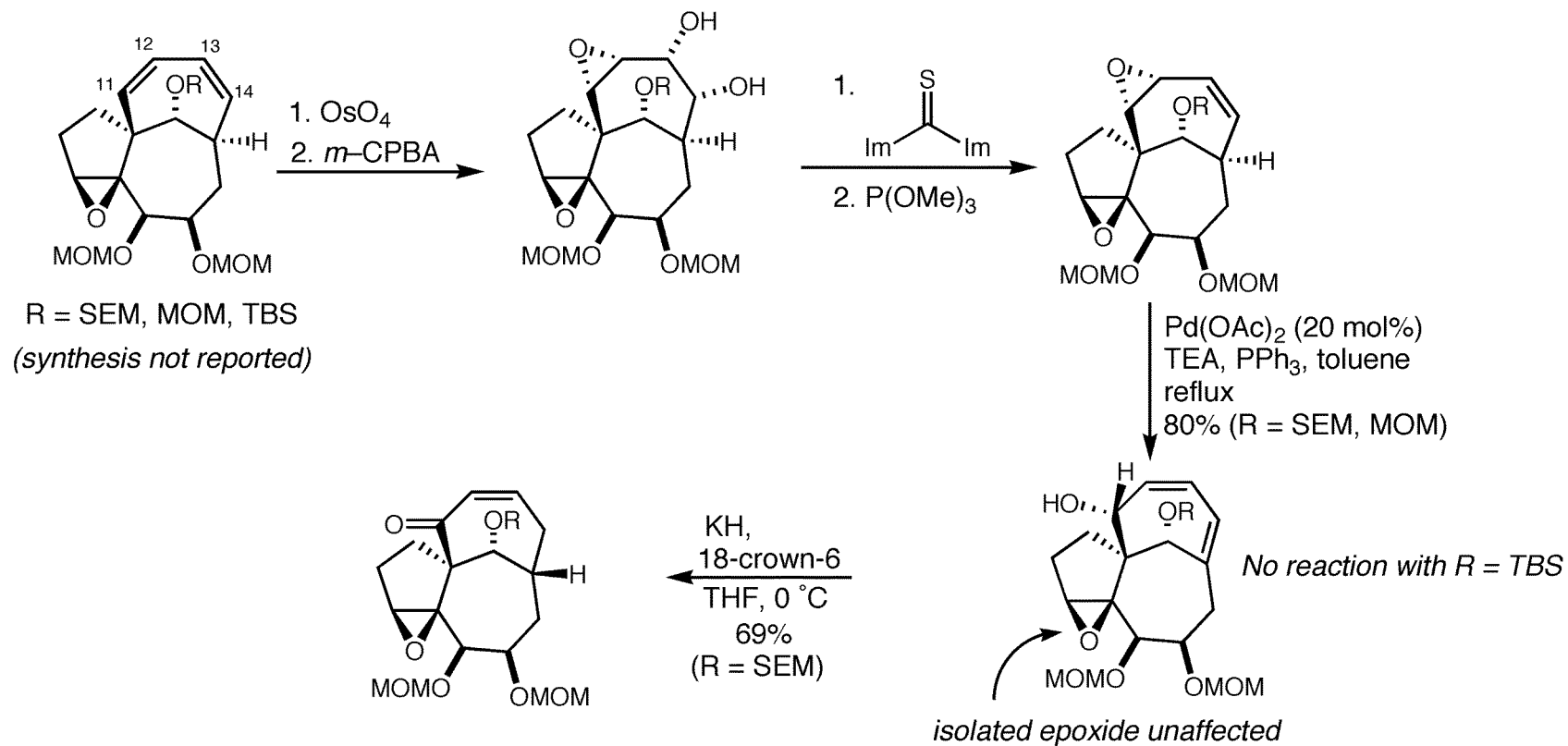
Funk: A Macrocyclic Ireland–Claisen Rearrangement



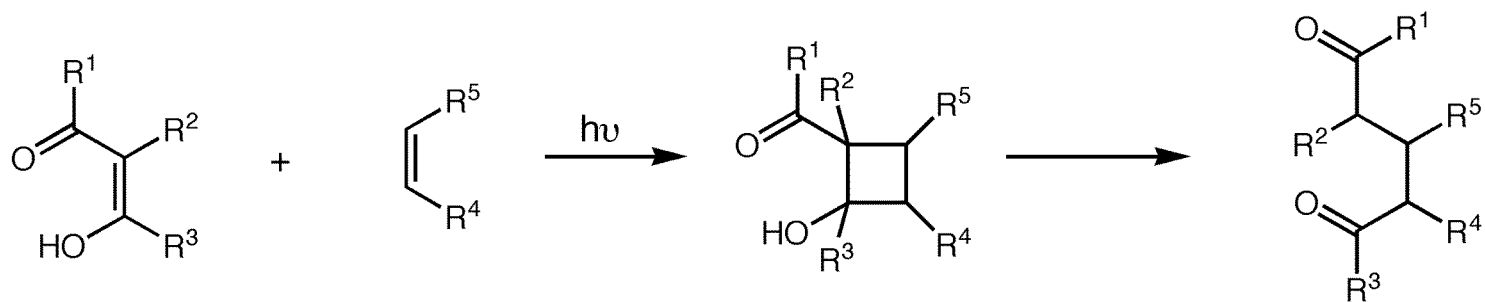
Rigby: A [1,5]-H Shift to Set the In-Out Stereochemistry



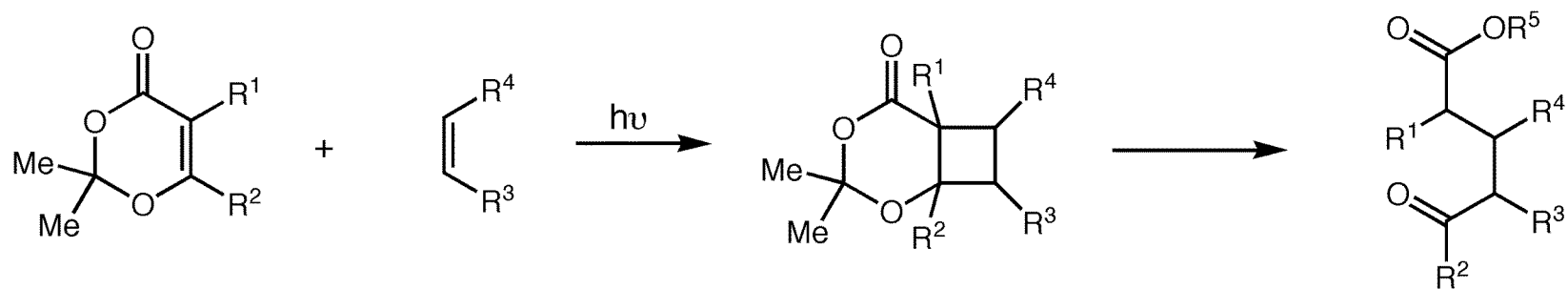
Rigby: A [1,5]-H Shift to Set the In-Out Stereochemistry



Winkler: The de Mayo Reaction

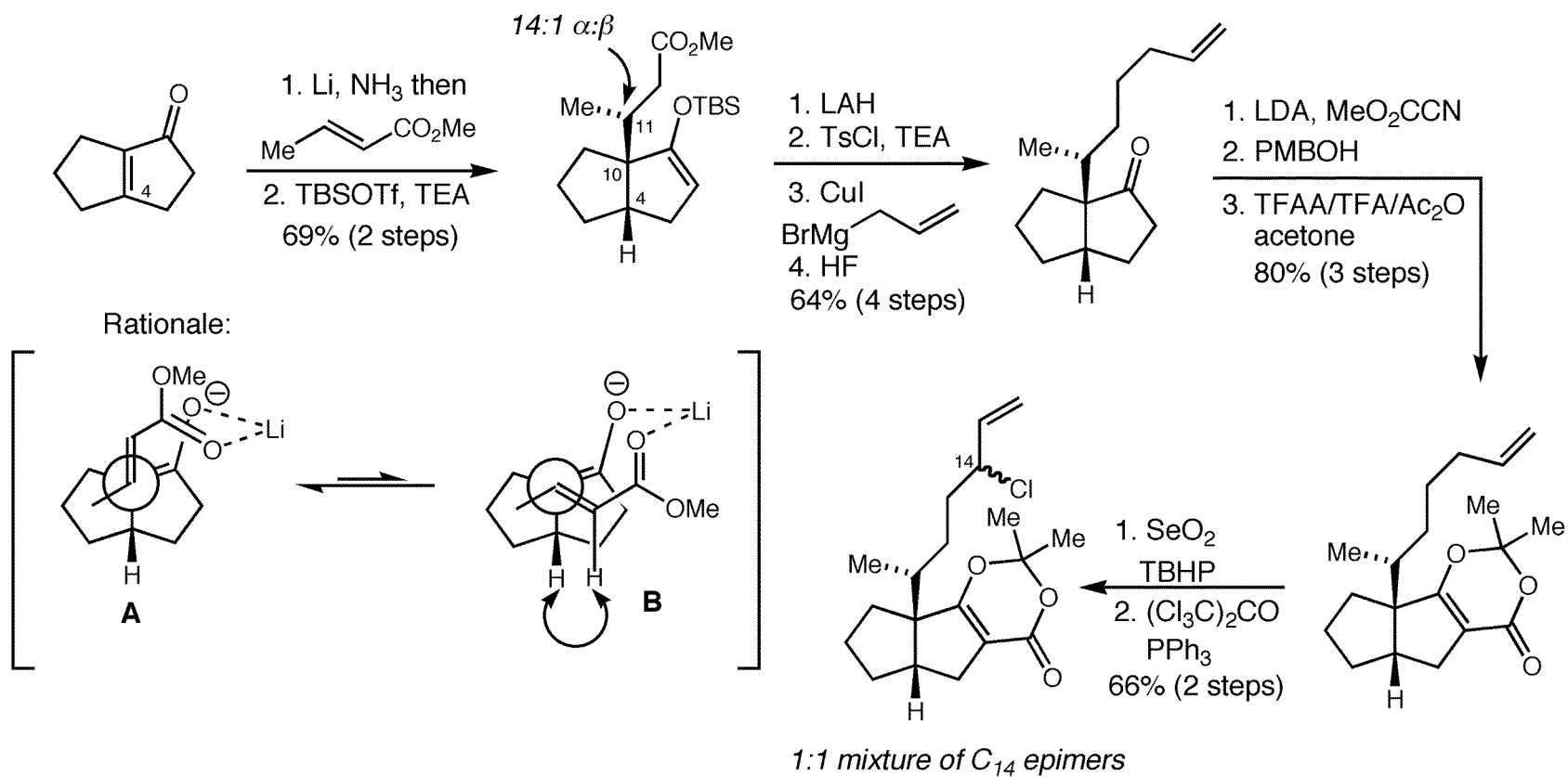


de Mayo, *Acc. Chem. Res.* **1971**, 4, 41

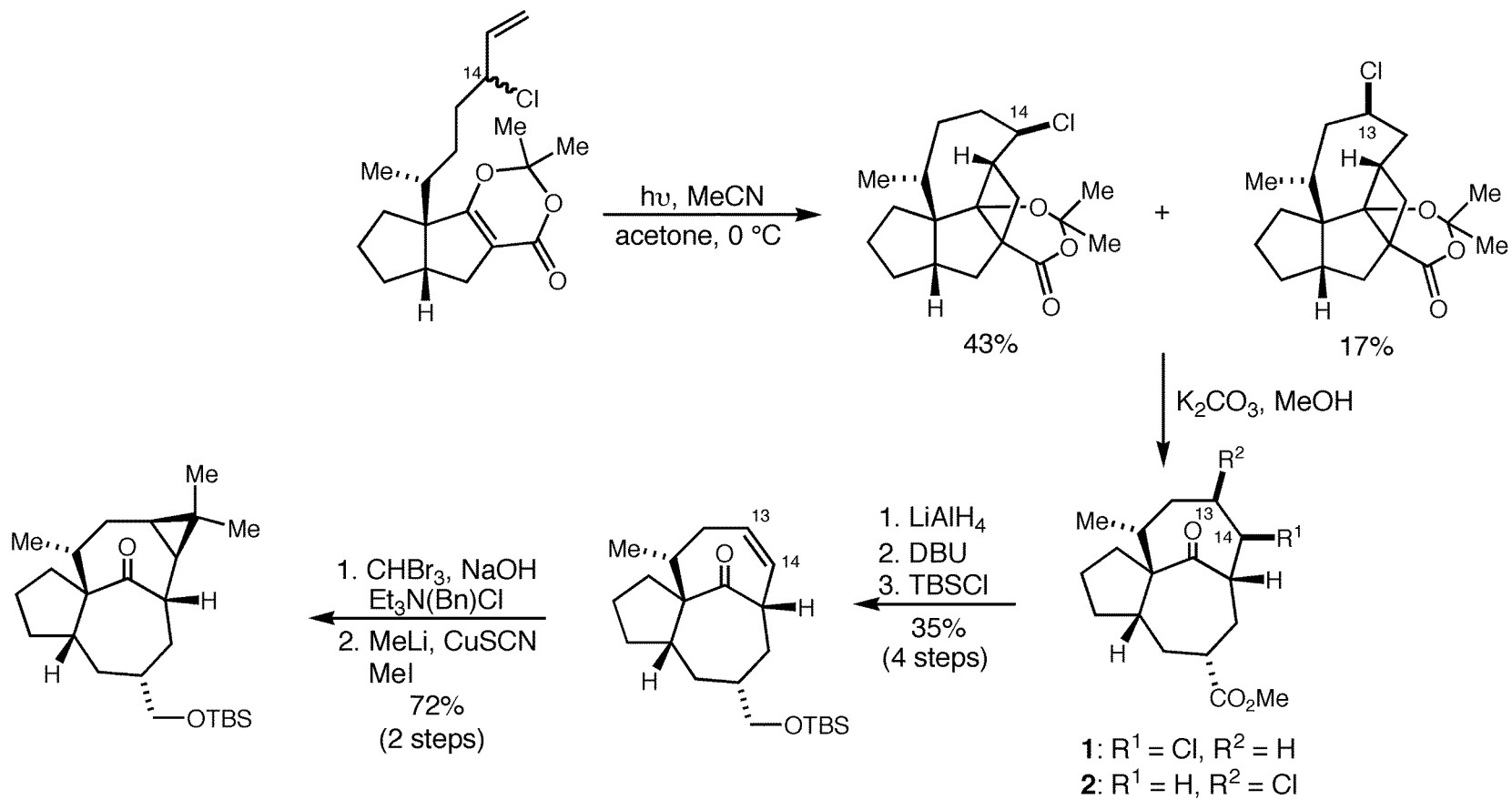


Baldwin *et al.* *J. Am. Chem. Soc.* **1980**, 102, 3634

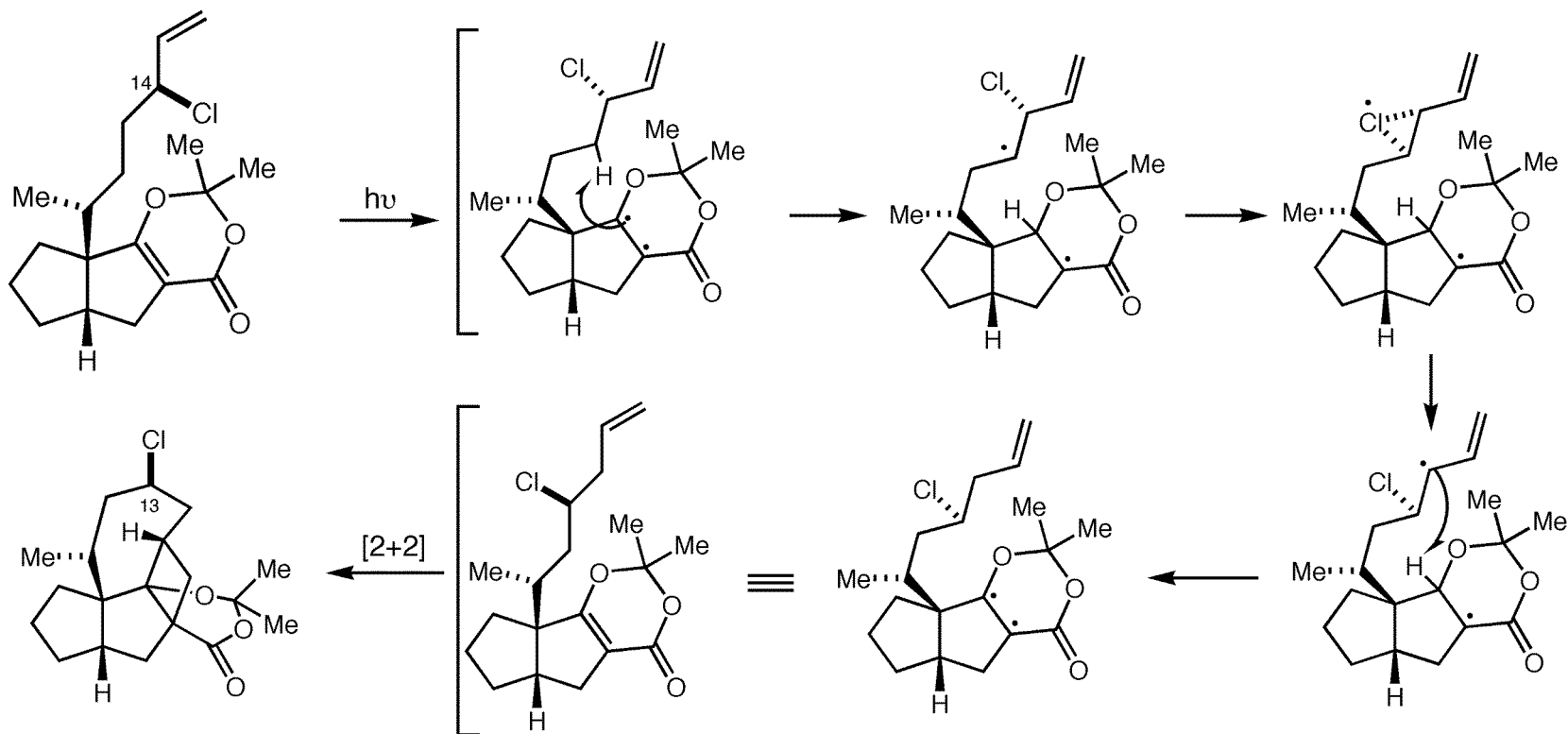
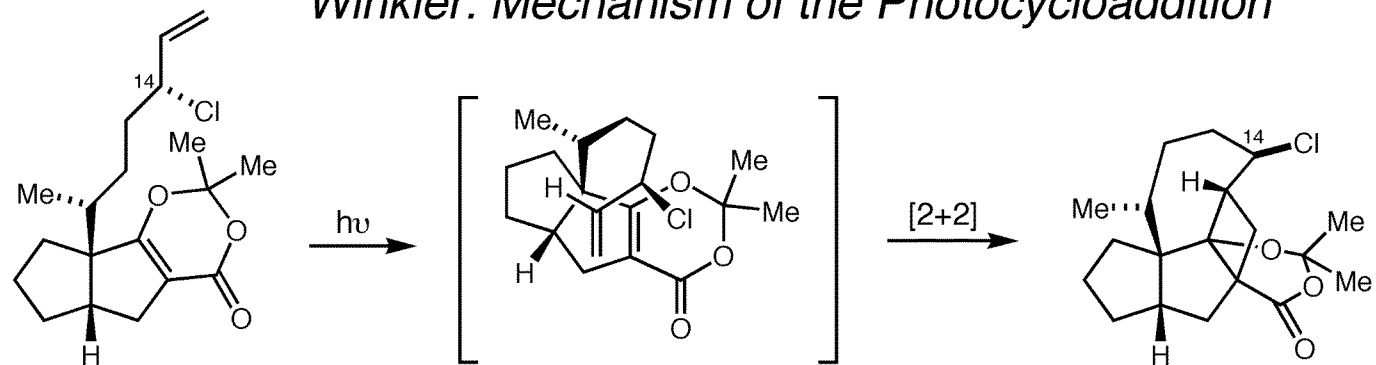
Winkler: A Tandem Conjugate Reduction/Michael Addition



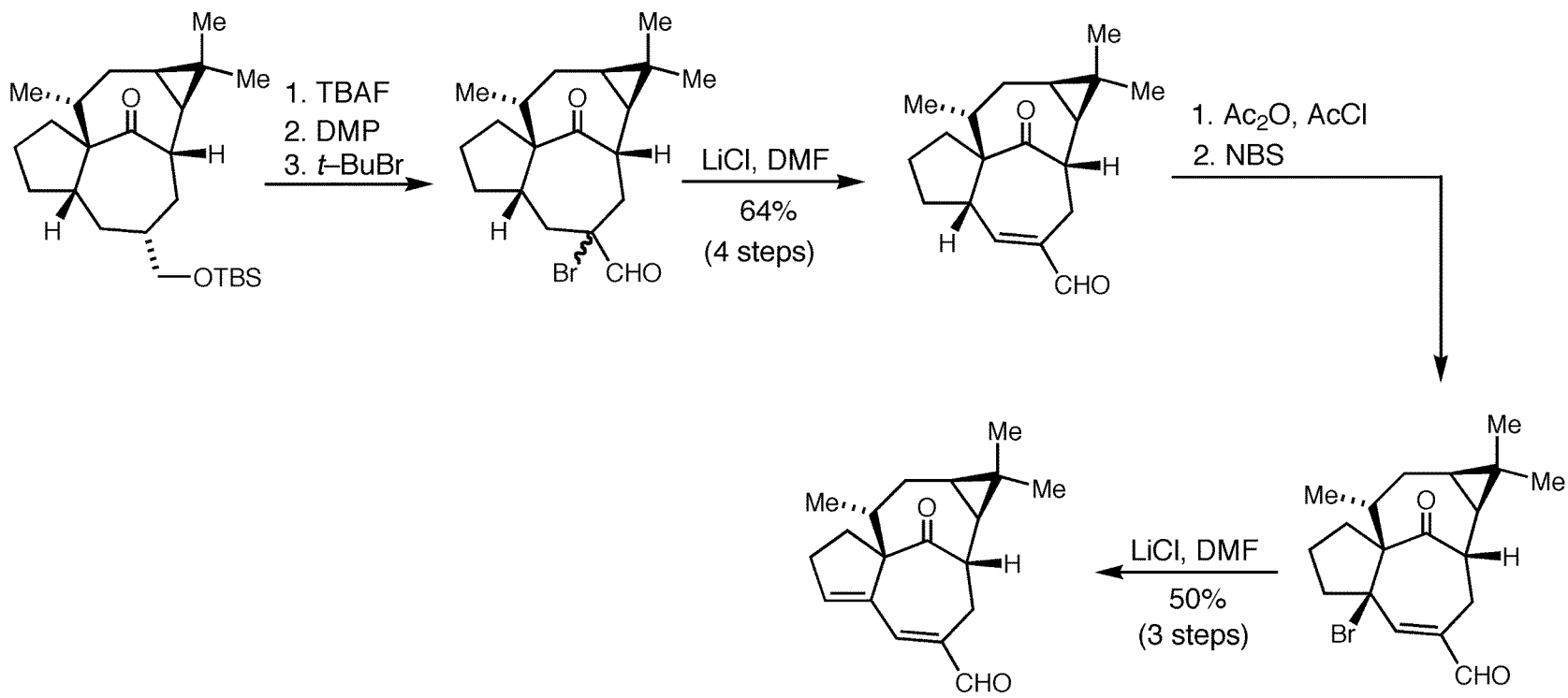
Winkler: A de Mayo Reaction to Set the BC Core



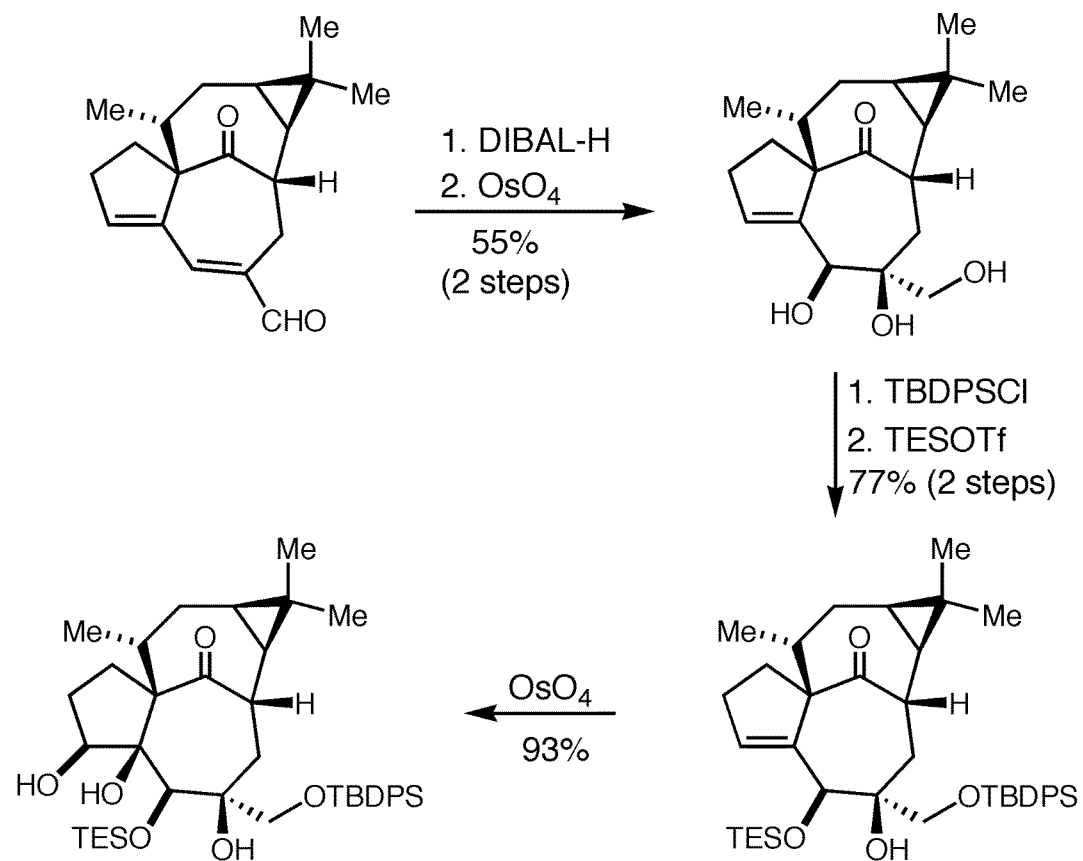
Winkler: Mechanism of the Photocycloaddition



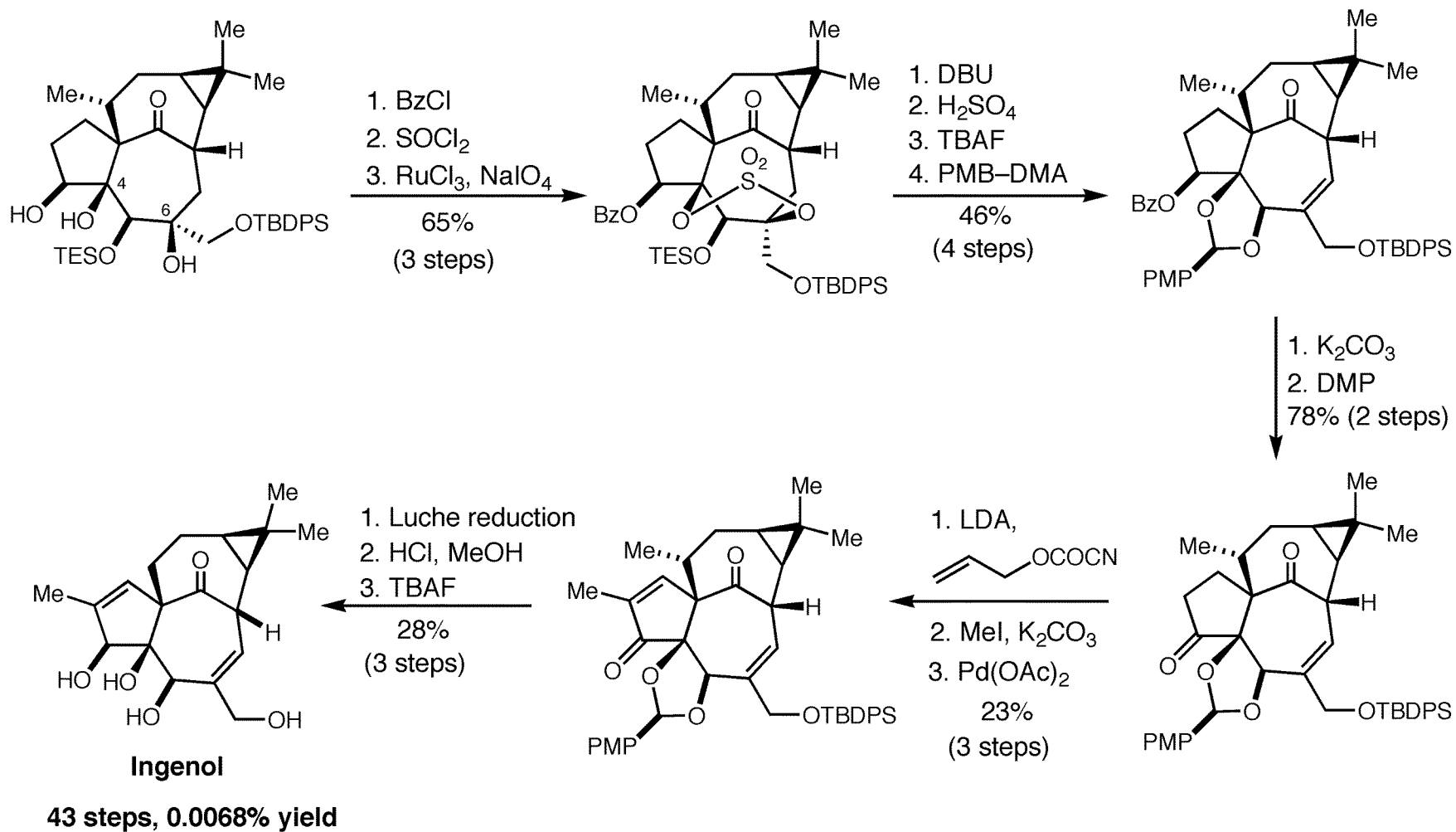
Winkler: Functionalization of the A and B Rings



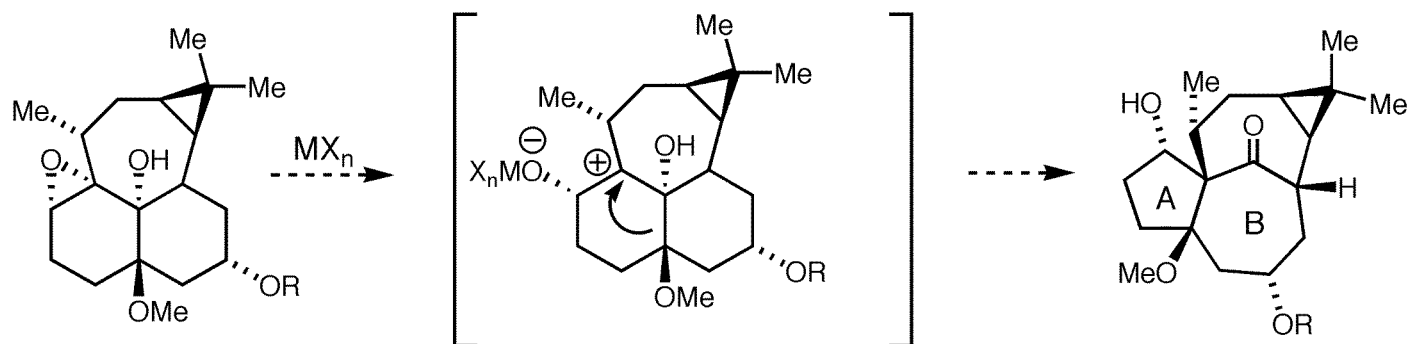
Winkler: Introduction of the Triol



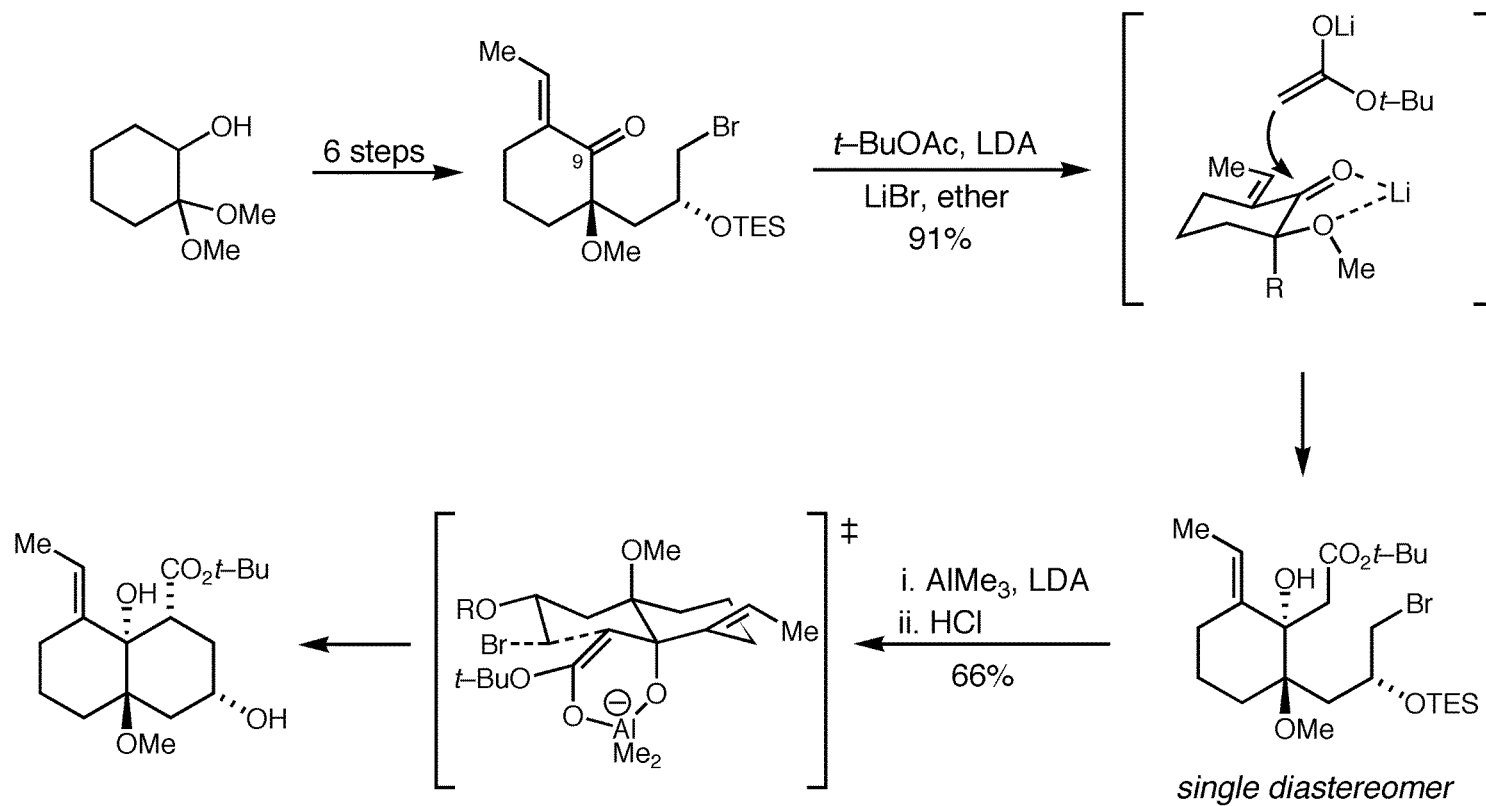
Winkler: Endgame



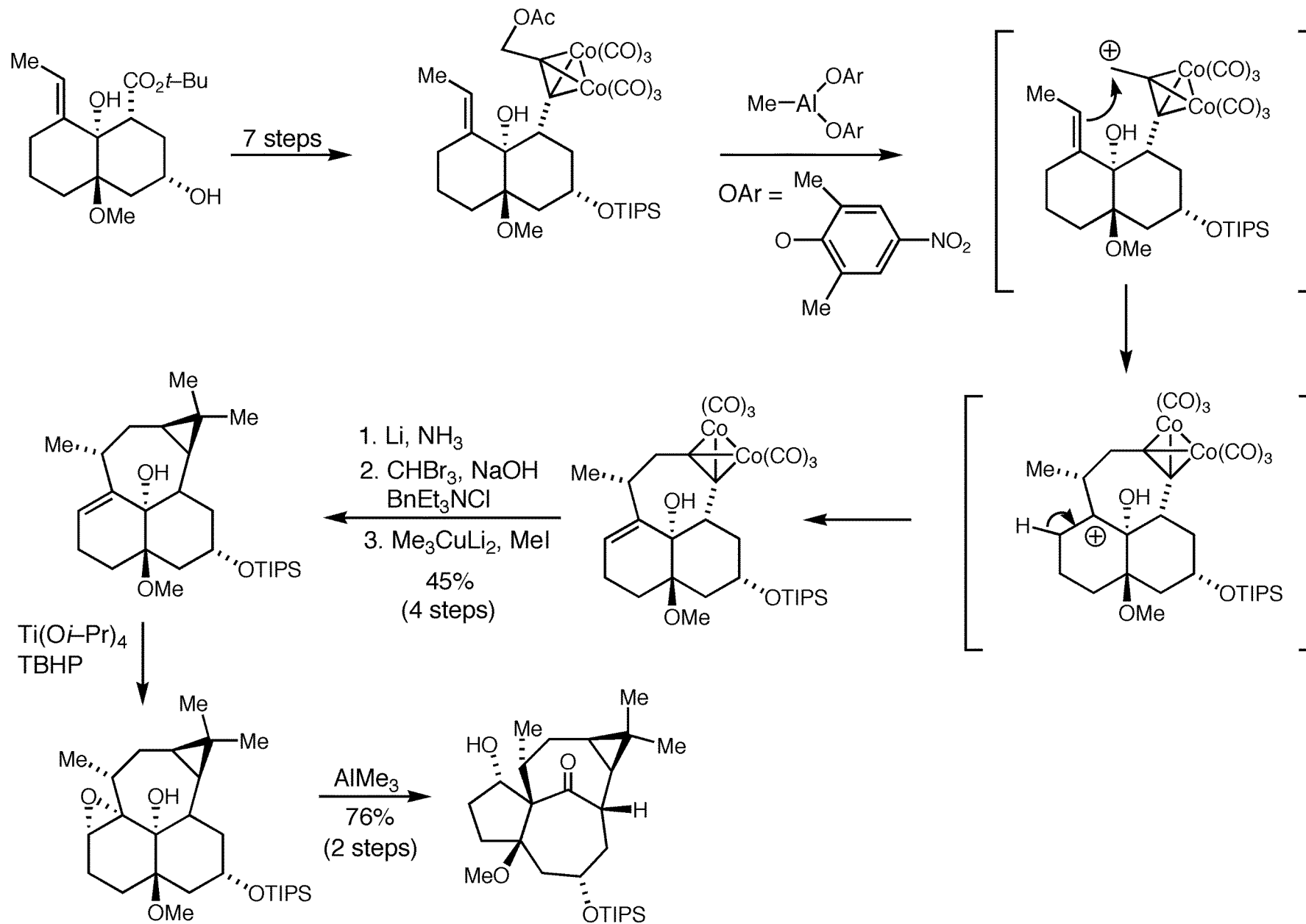
Tanino and Kuwajima: A Pinacol Rearrangement



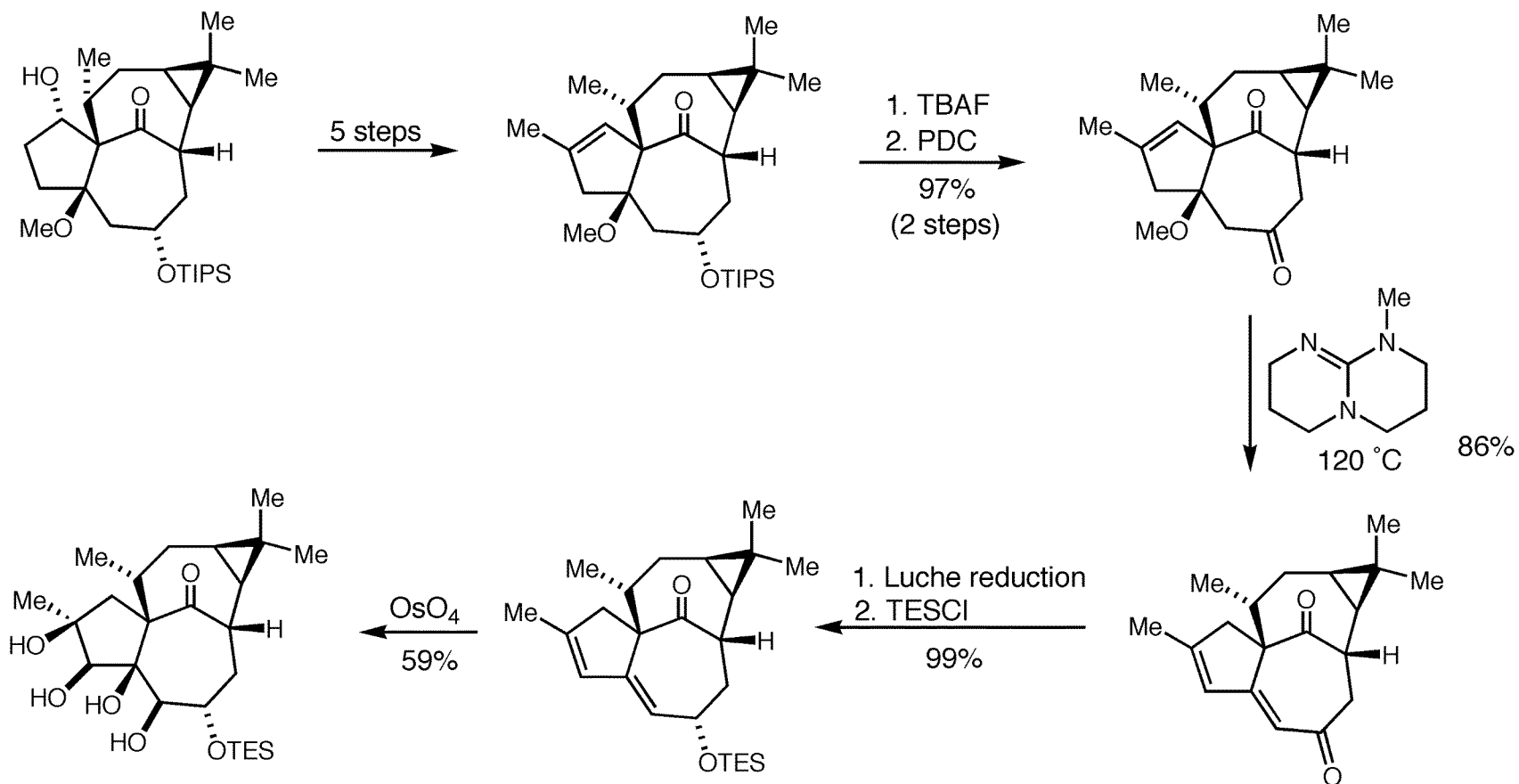
Tanino and Kuwajima: Synthesis of the Trans Decalin System



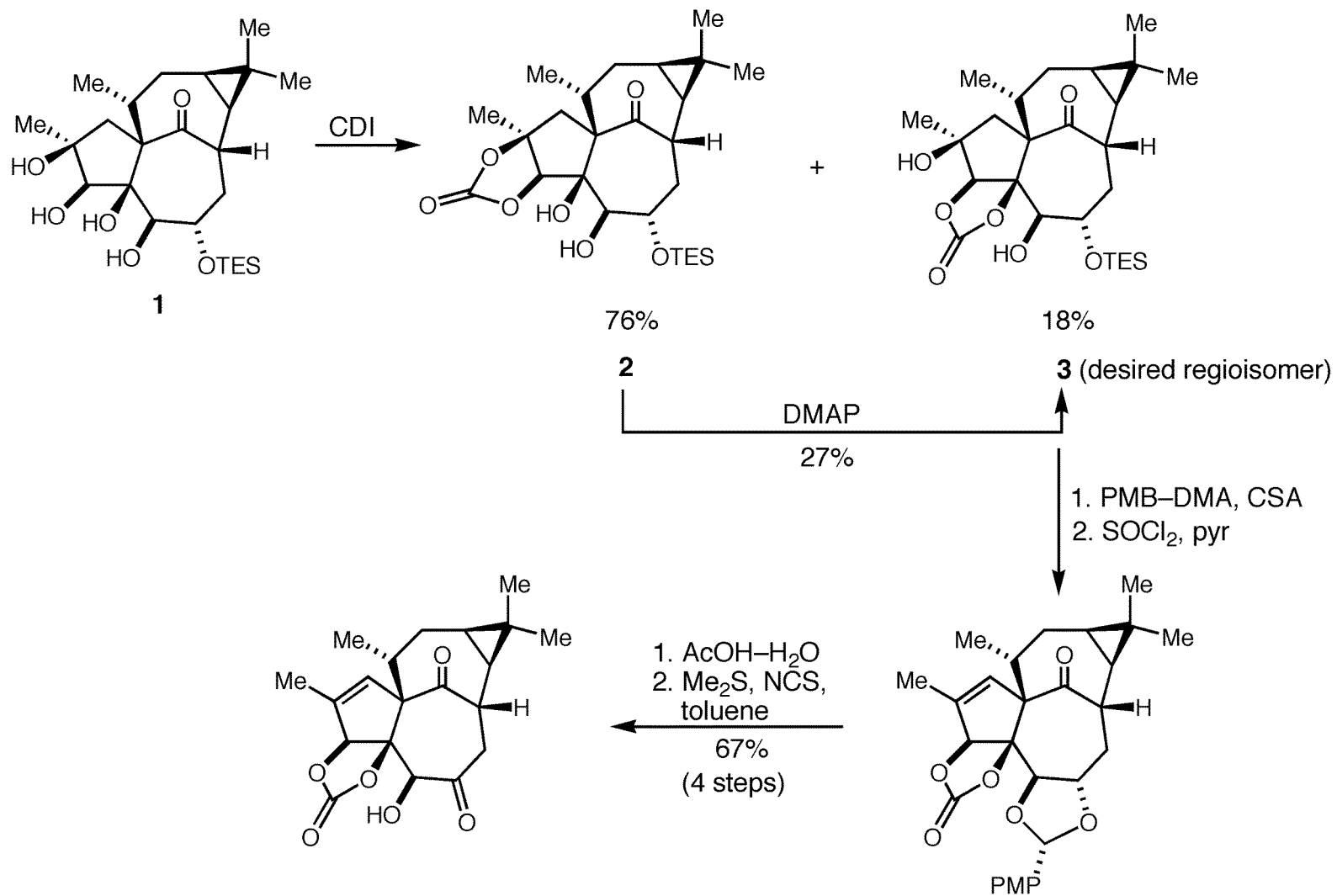
Tanino and Kuwajima: A Pinacol Rearrangement



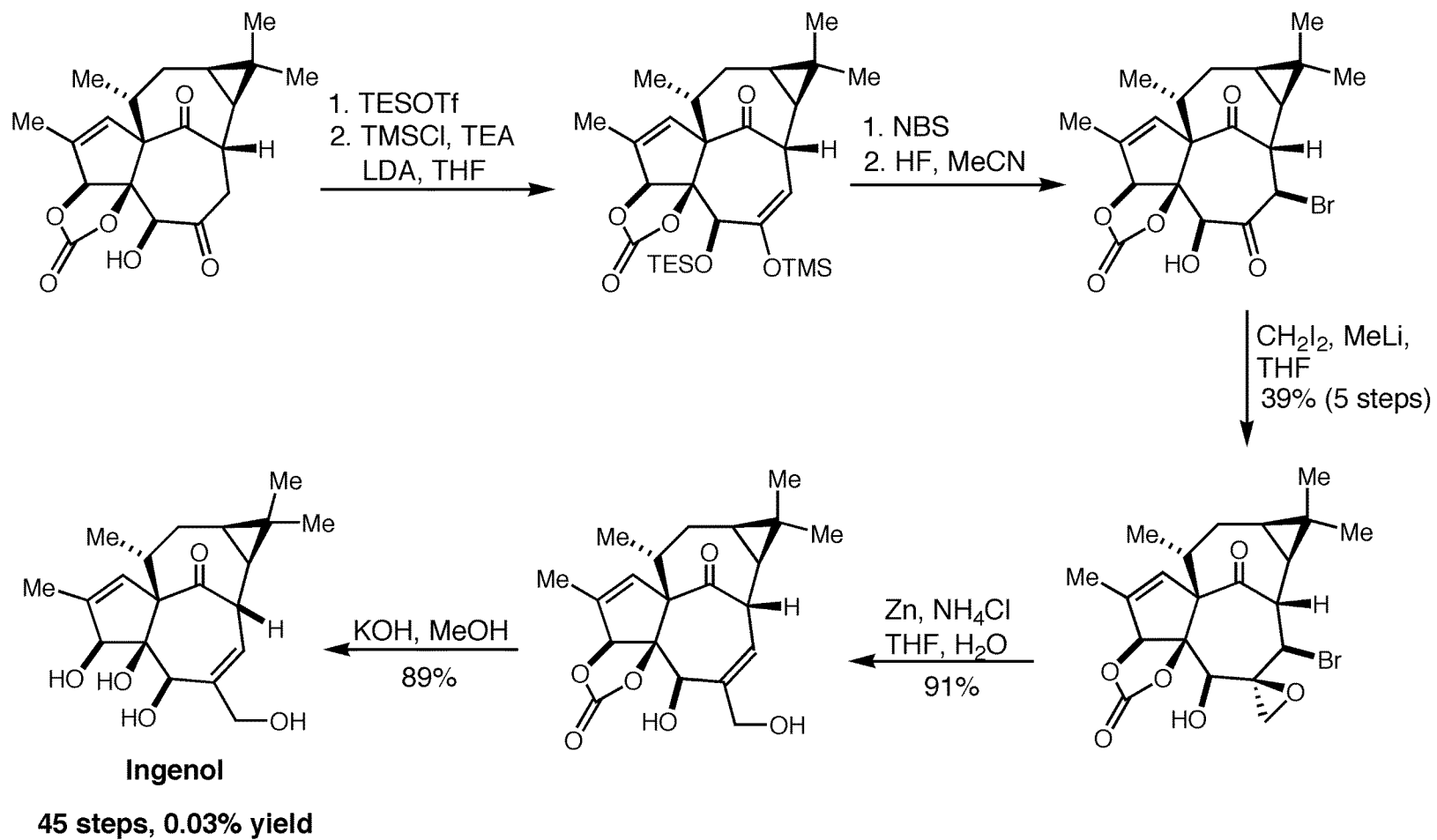
Tanino and Kuwajima: Functionalization of the A and B rings



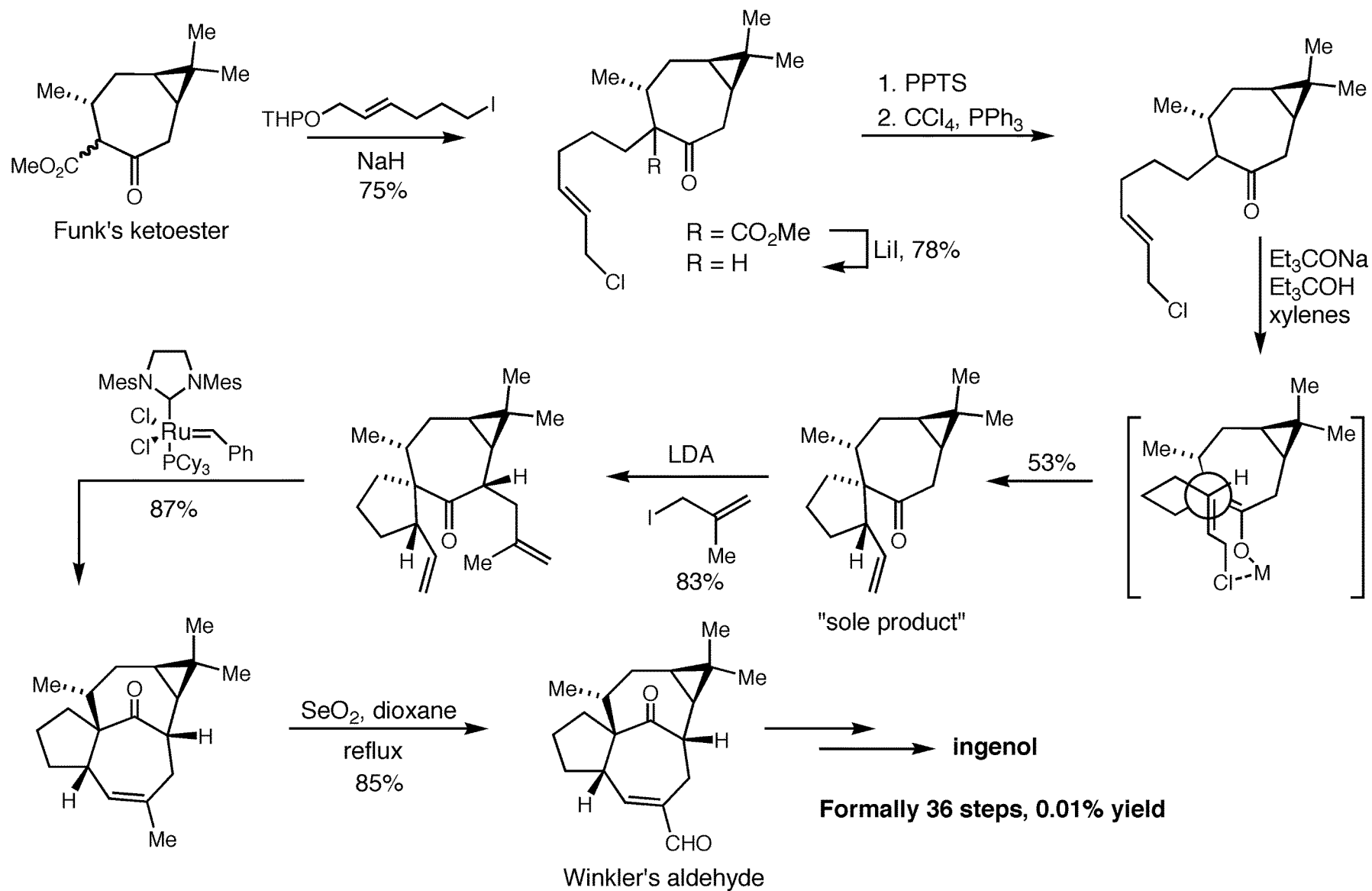
Tanino and Kuwajima: Functionalization of the A and B rings



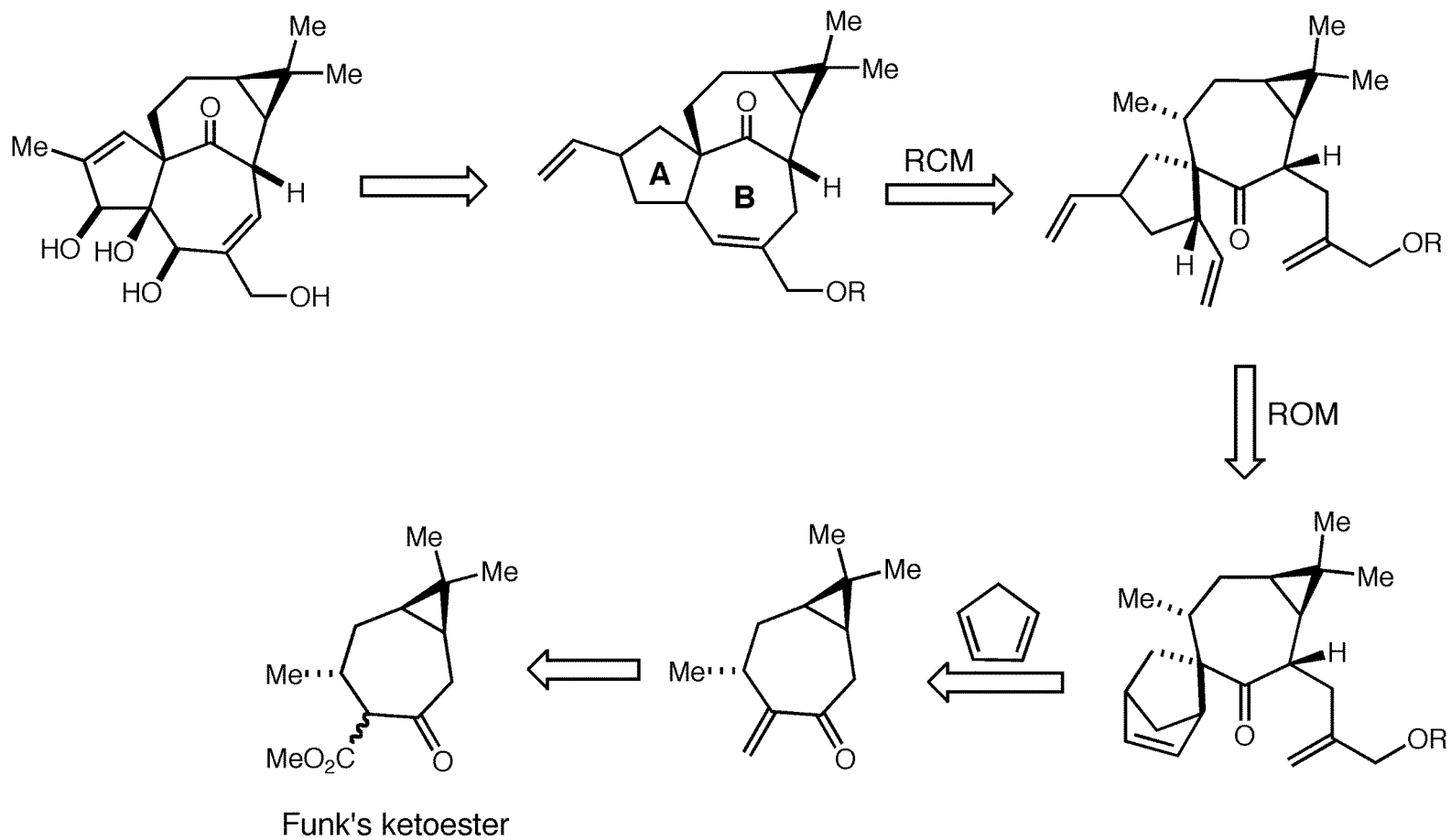
Tanino and Kuwajima: Endgame



Kigoshi: Formal Synthesis of Optically Active Ingenol



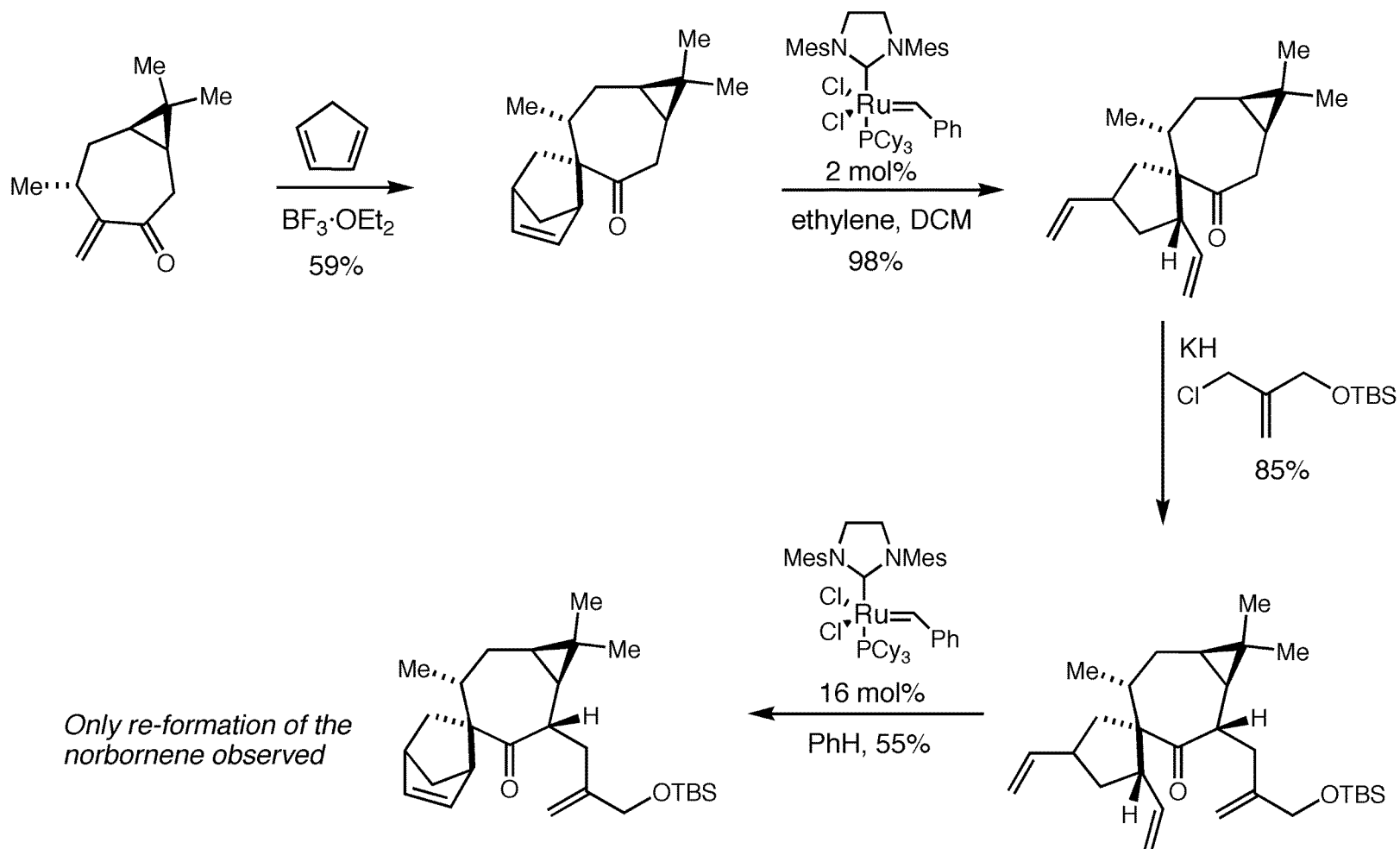
Wood: Another RCM Approach to the B-ring



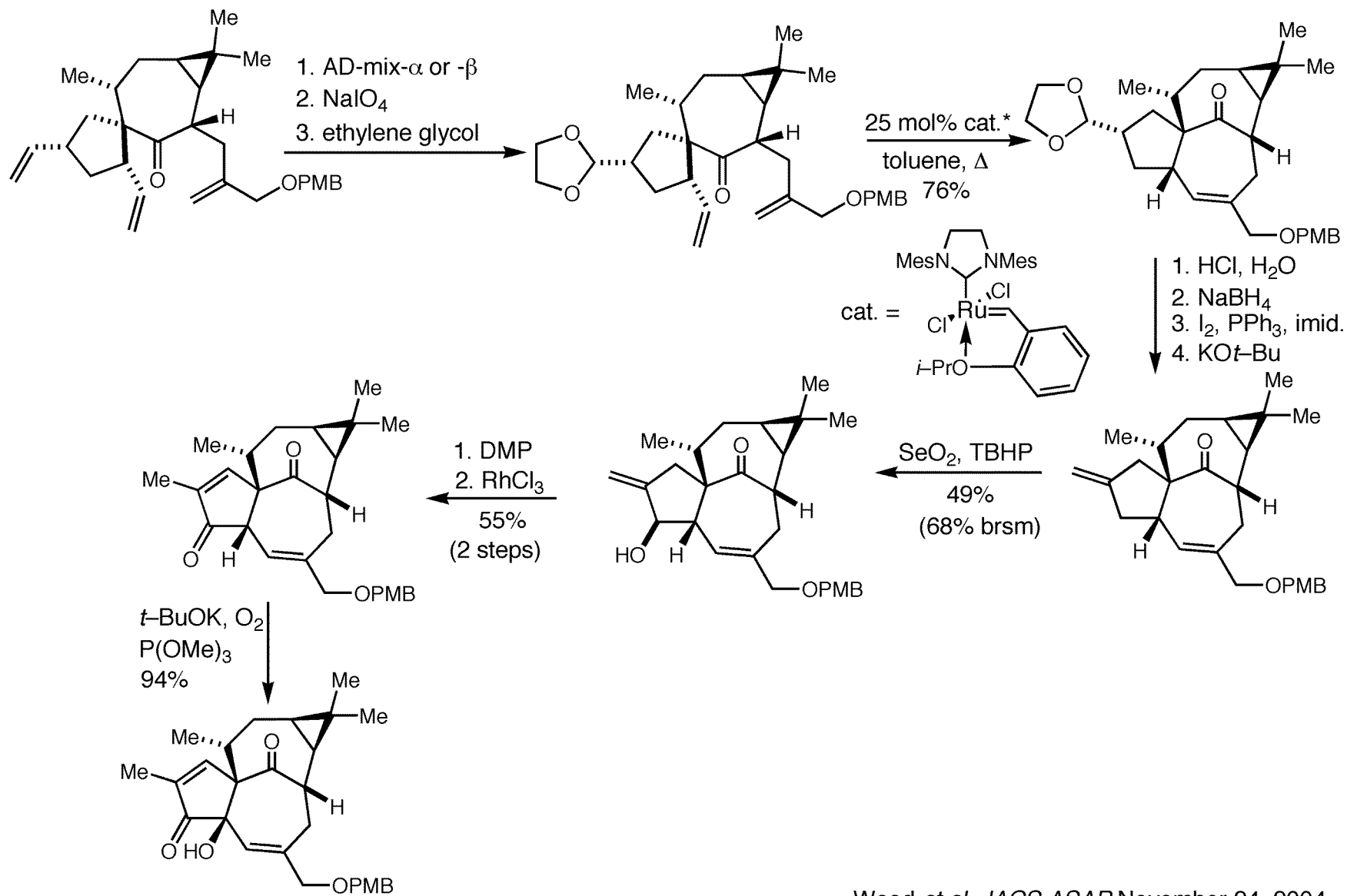
Wood *et al.* *Org. Lett.* **2001**, *3*, 1563.

Wood *et al.* *JACS* ASAP November 24, 2004.

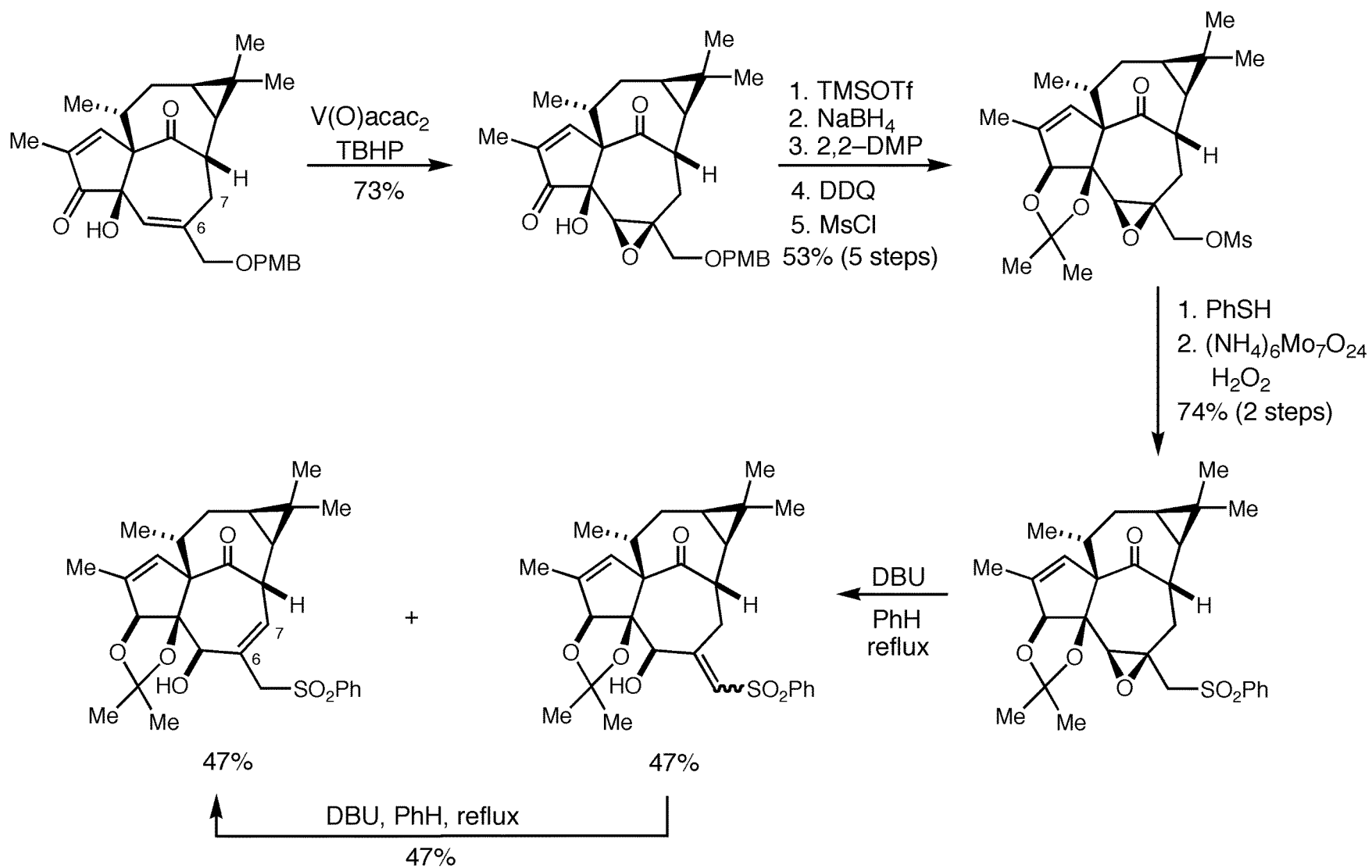
Wood: Wrong RCM



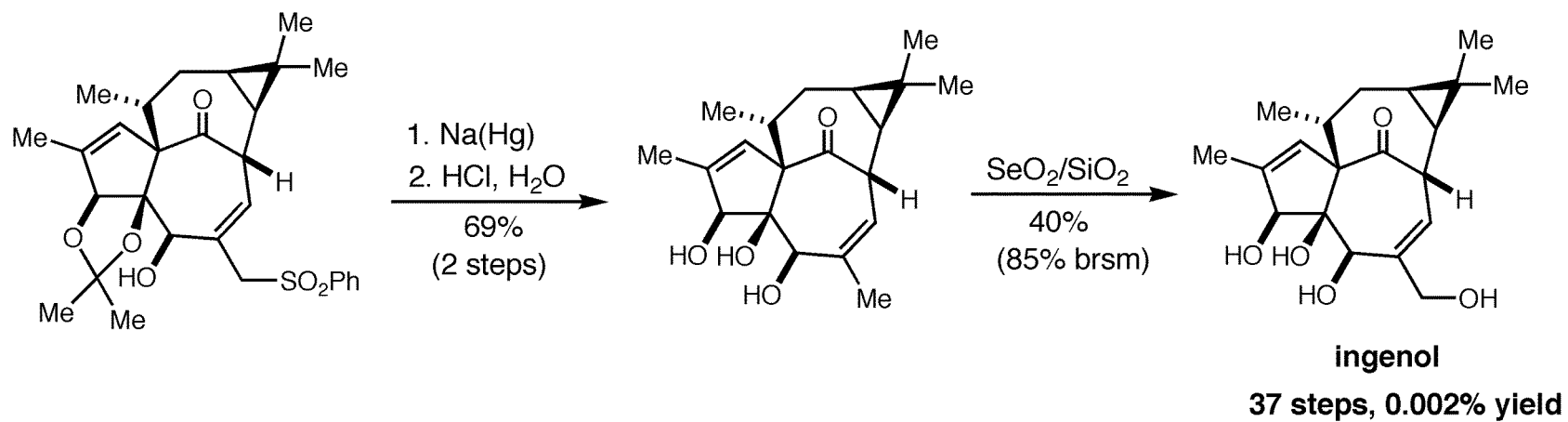
Wood: Recovery and Functionalization of the A and B rings



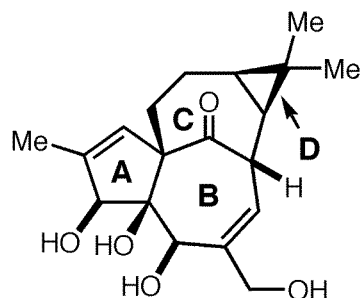
Wood: Installation of the $\Delta^{6,7}$ Double Bond



Wood: Endgame



Summary



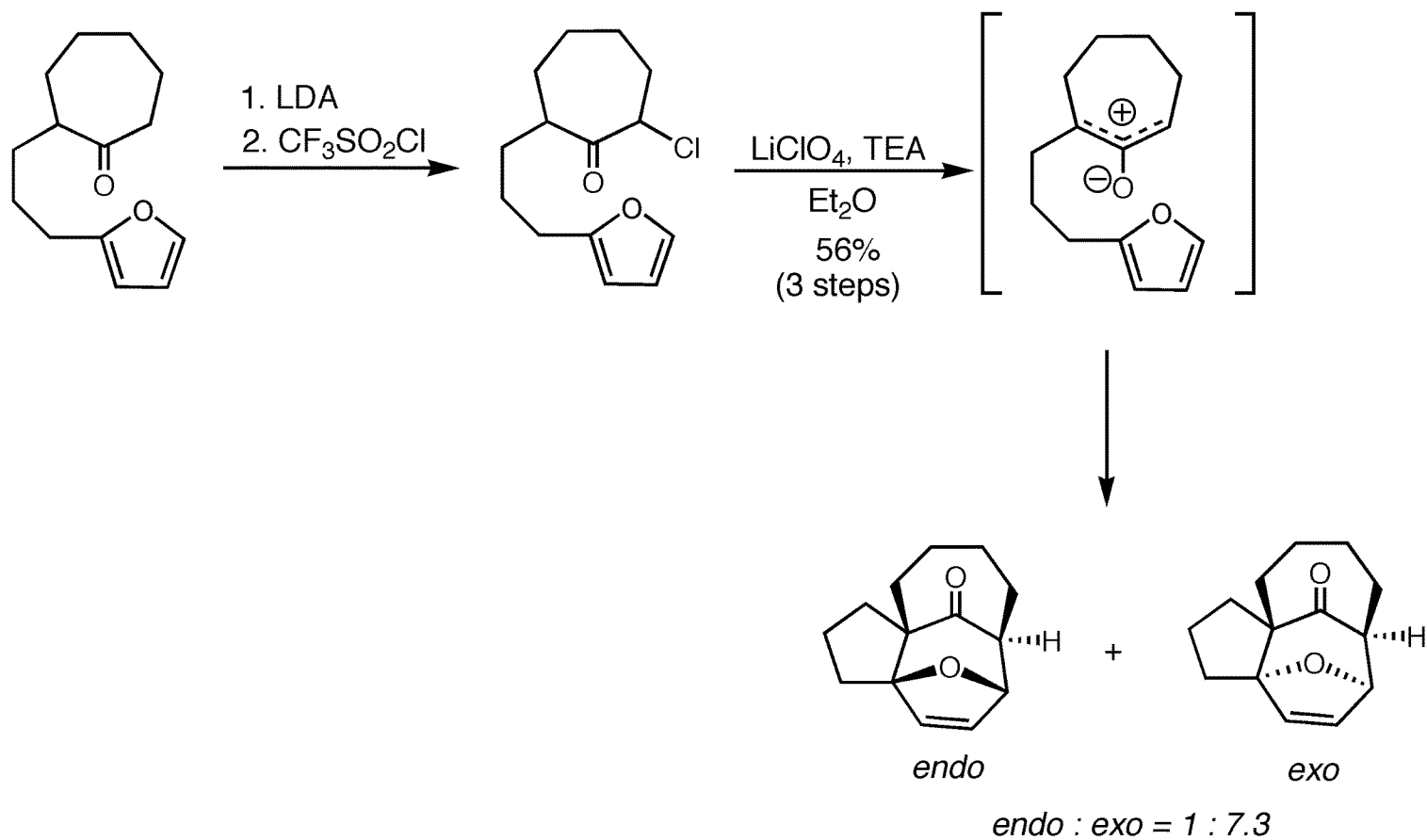
key steps

Skeleton components

Paquette	photoinduced rearrangement	A-B-C	
Mehta	aldol cyclization	A-B-C	
Funk	Ireland-Claisen	A-B-C	
Rigby	[6+4] cycloaddition [1,5]-H Shift	A-B-C	
Winkler	de Mayo reaction	racemic total synthesis	43 steps, 0.007% y
Tanino-Kuwajima	pinacol rearrangement	racemic total synthesis	45 steps, 0.03% y
Kigoshi	RCM	asymmetric formal synthesis	36 steps, 0.01% y*
Wood	RCM	asymmetric total synthesis	37 steps, 0.002% y

*overall yield of ingenol based on cited route

Harmata: A [4+3] Cycloaddition Approach to the AB Ring System



- Both products possess *cis* intrabridgehead stereochemistry (isoingenol).