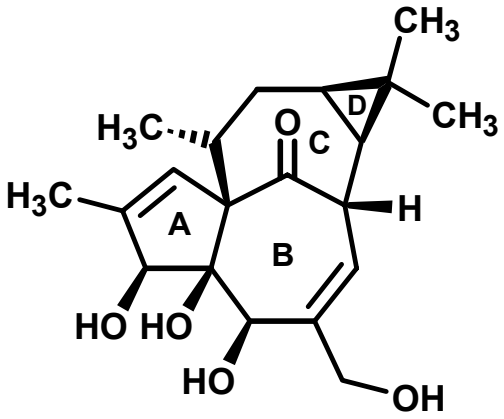
Total Synthesis of Ingenol
A Literature Review

Christoph Zapf

Supergroup Meeting

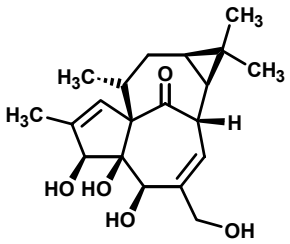
Princeton University
2/26/2004

Ingenol – A highly oxygenated diterpene



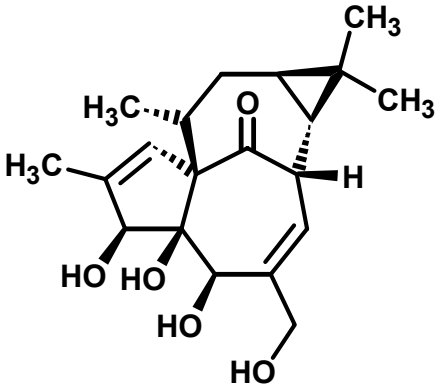
Ingenol

- Isolation from roots of *Euphorbia ingens* reported in 1968 by Hecker.
- X-ray structure analysis was reported in 1970.
- Ingenol and its derivatives show interesting biological properties such as tumor-promoting, anti-HIV and anti-leukemia activities.
- Much research is directed toward synthesis and biological evaluation of Ingenol analogs and derivatives.
- Two racemic total syntheses are reported to date by Winkler (2002) and Tanino, Kuwajima (2003).



Synthetic Challenges

- ***Trans* Intrabridgehead Stereochemistry**



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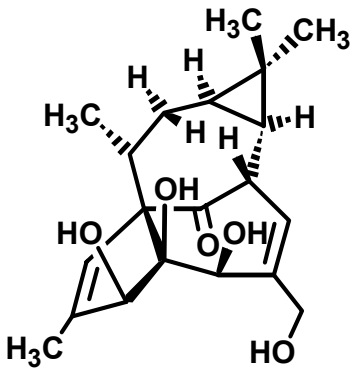
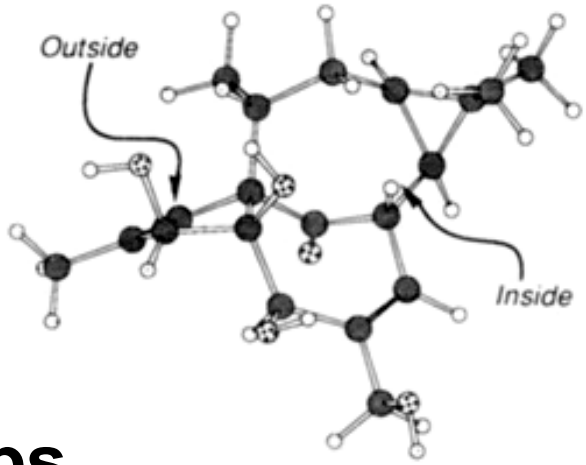
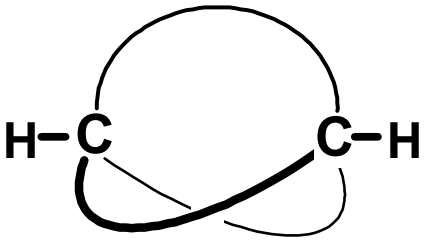


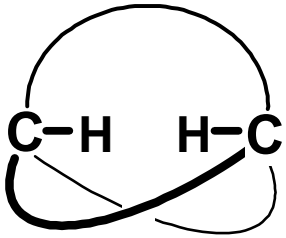


- **Installation of Hydroxyl Groups**
- **Stereochemistry at C-11**

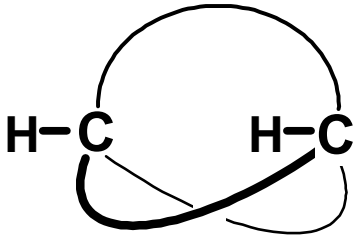
In/Out Isomerism



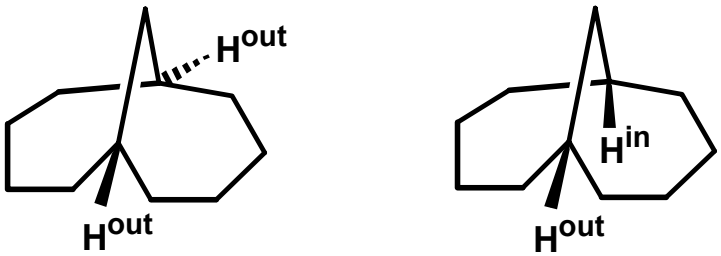
out-out



in-in



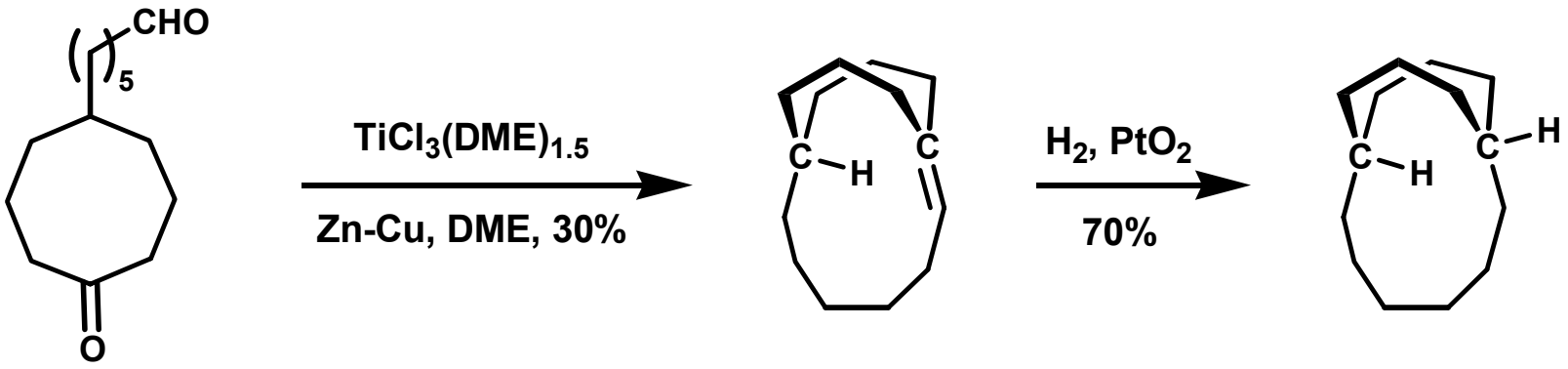
out-in

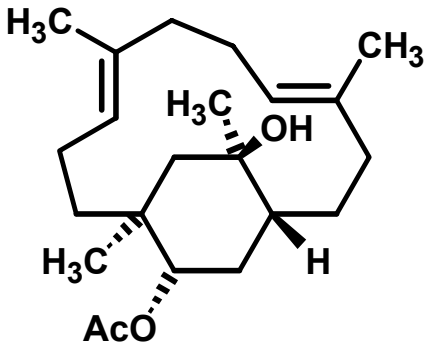


Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097-2111.

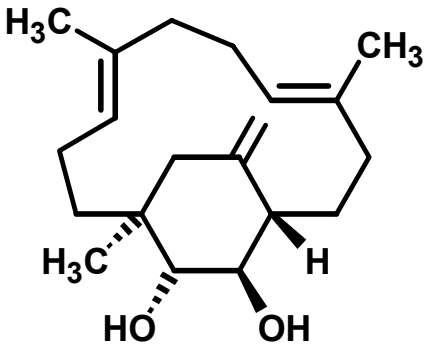
Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298-3300.

Examples for *In/Out* Isomerism





3α-Acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene



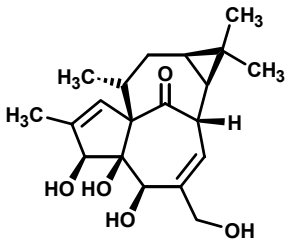
Secotrinerviten-2β,3α-diol

McMurry, J. E.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 10167-10173.
Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097-2111.

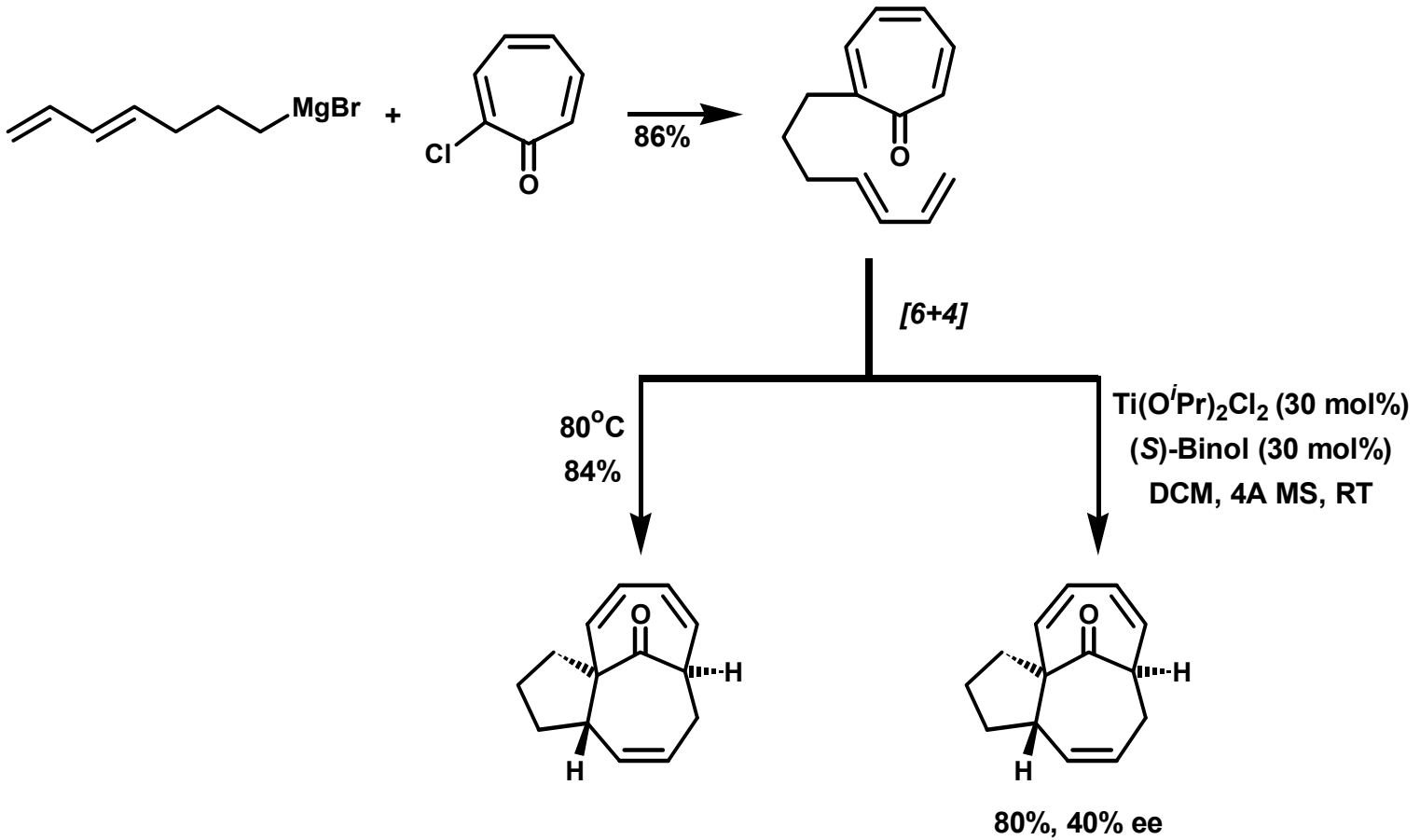
Key Players in the Ingenol Field

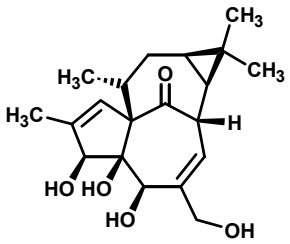
- **Rigby** (1,5-H Sigmatropic Rearrangement)
- **Funk** (Ireland-Claisen Rearrangement)
- **Wood** and **Kigoshi** (Ring Closing Metathesis)

- **Winkler** (De Mayo Photocycloaddition)
- **Tanino, Kuwajima** (Pinacol Rearrangement)



Rigby's Approach





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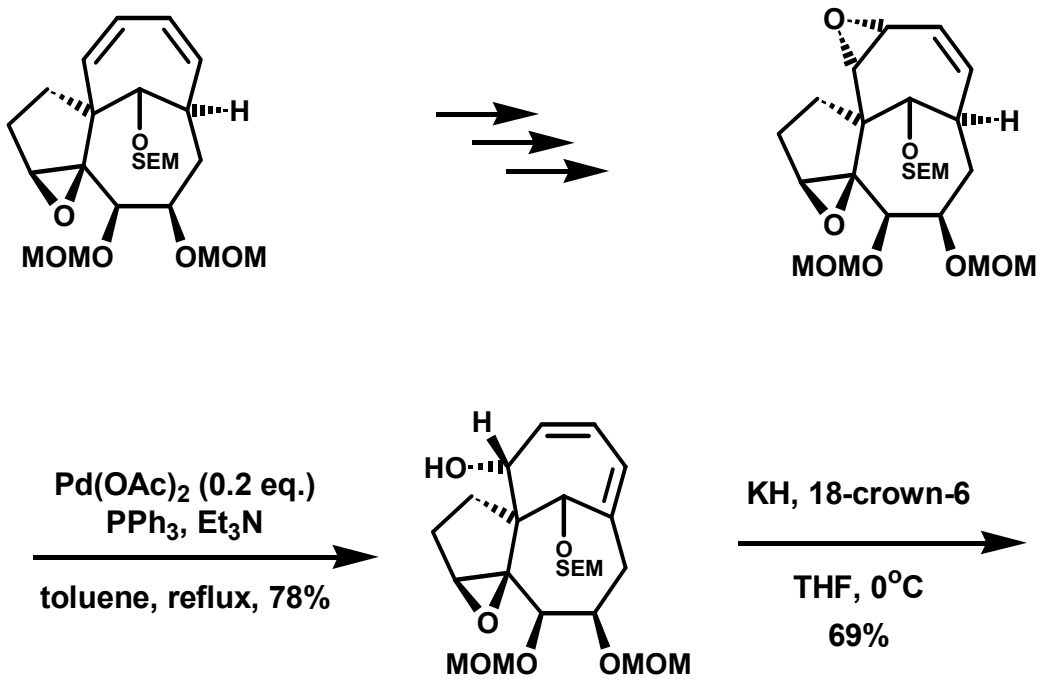
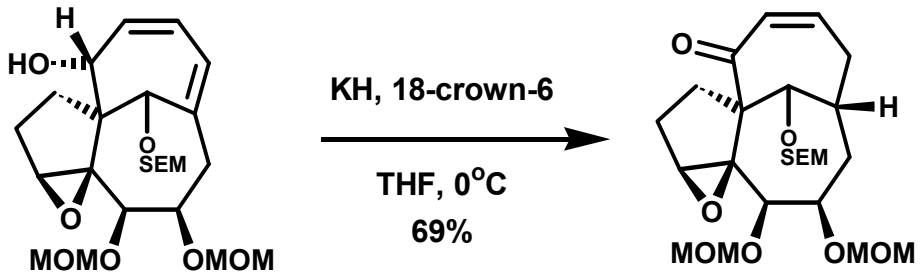
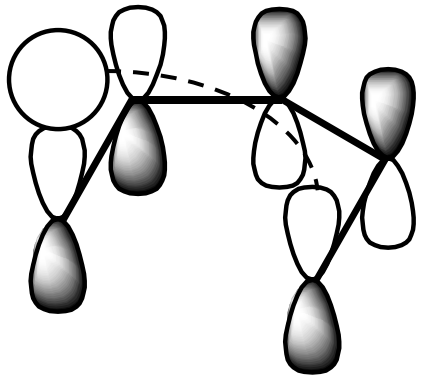
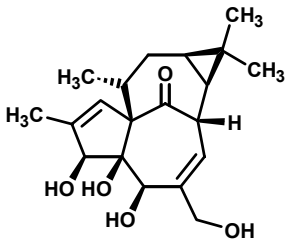


The 1,5-H Sigmatropic Rearrangement





Fleming, I. *Frontier Orbitals and Chemical Reactions*; VCH: Weinheim, 1990.



Funk's Approach

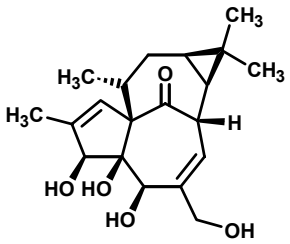
(+)-Carene

1. O_3, Me_2S
2. $CeCl_3$, $HCO(Me)_3$
3. KH, $CO(COMe)_2$
35%

1. $TiCl_4$
2. LiMeCuCN
72%

1. LDA,
2. NaH,
63%

1. HF
2. KOH
3. DCC, DMAP
49%



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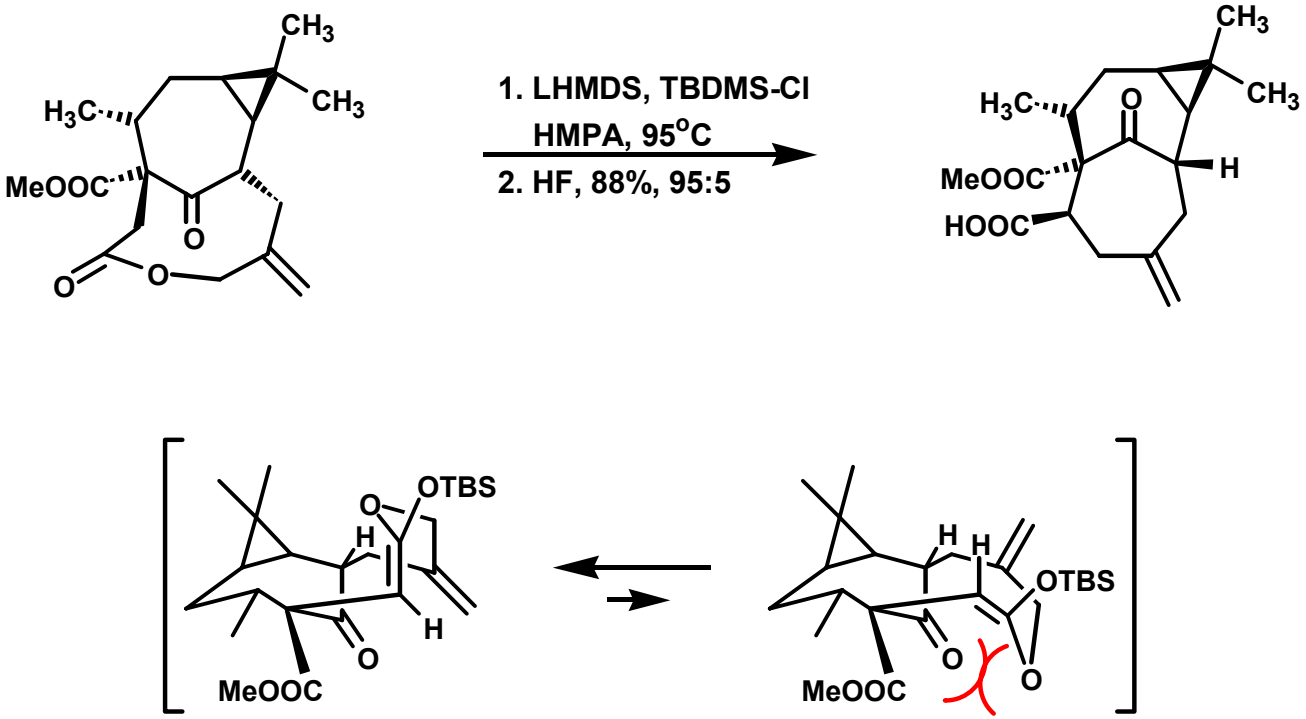

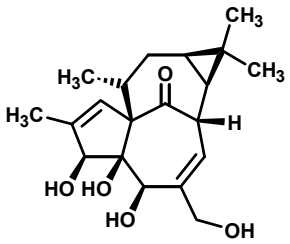

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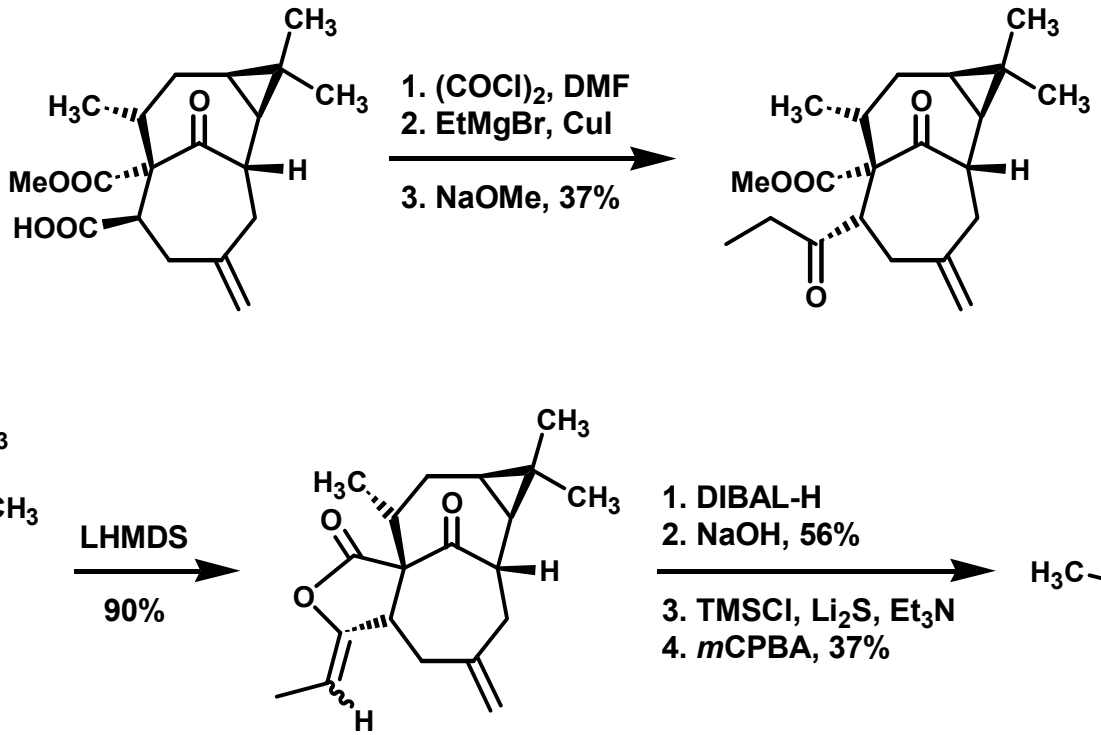
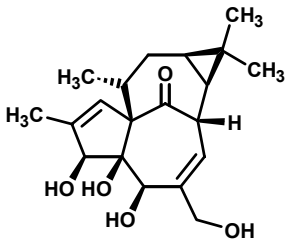
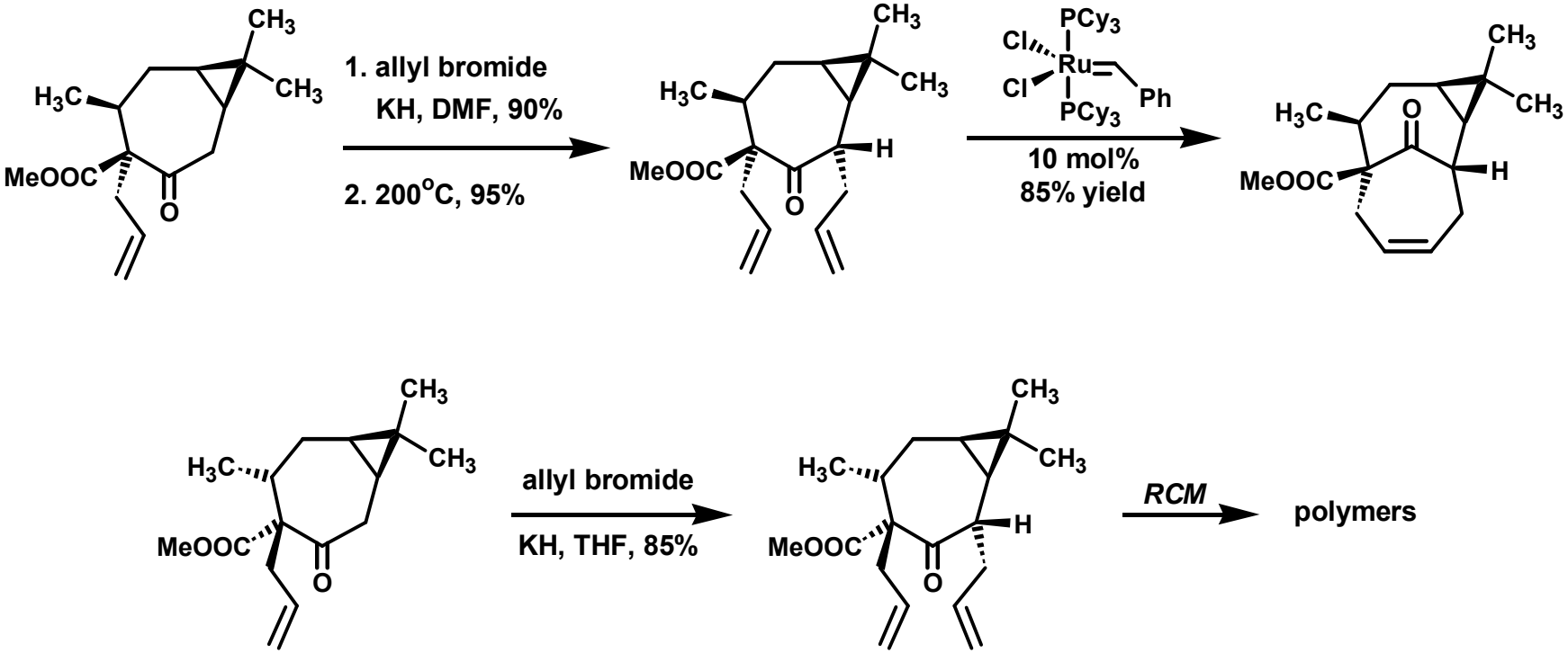
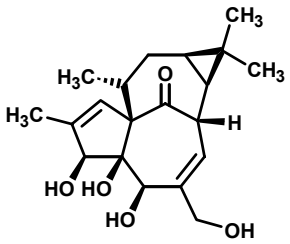




Wood's Approach





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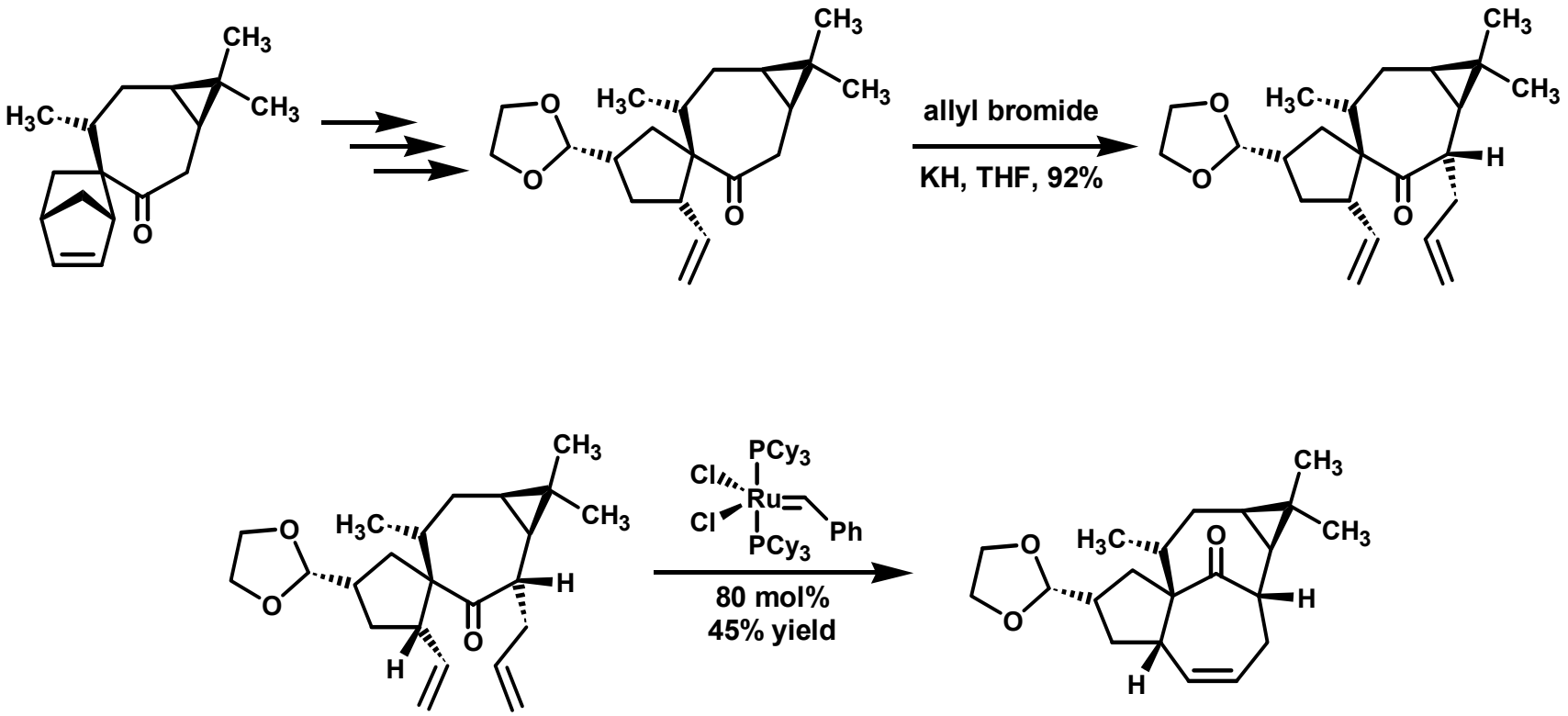
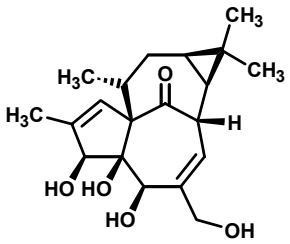
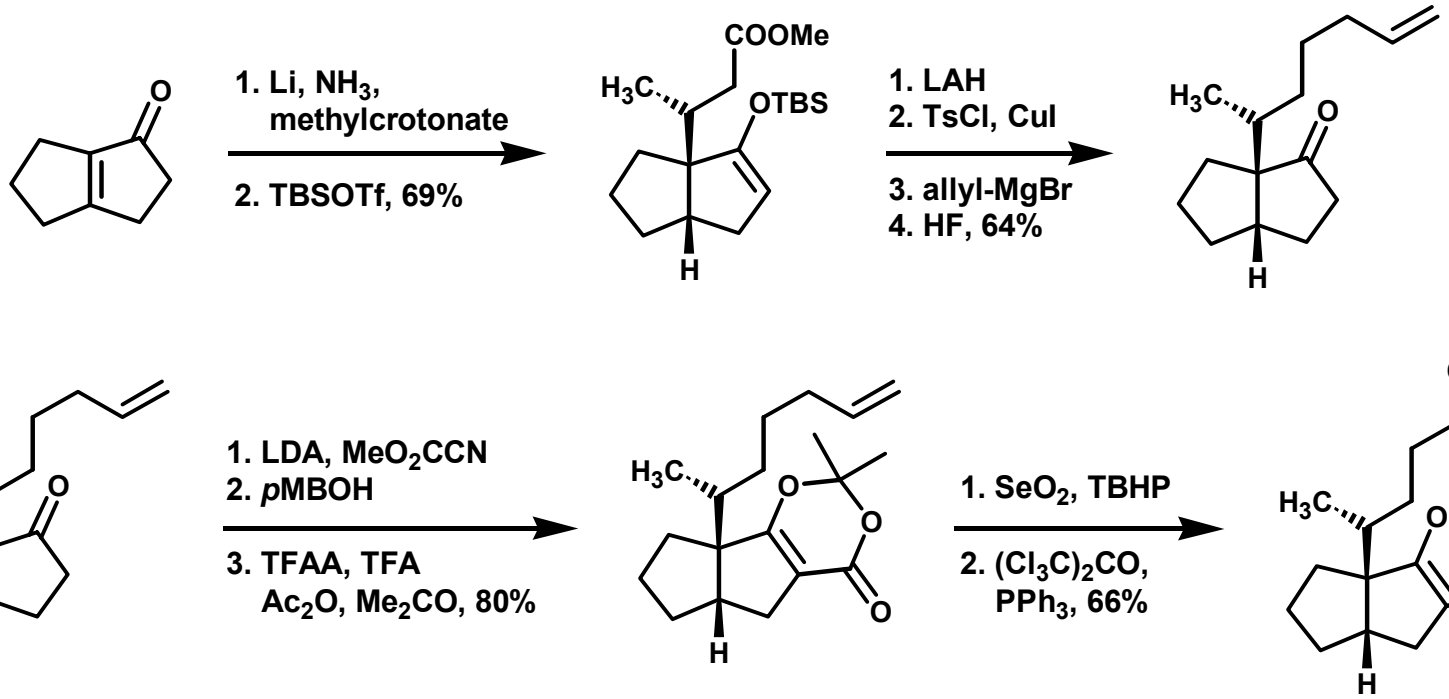
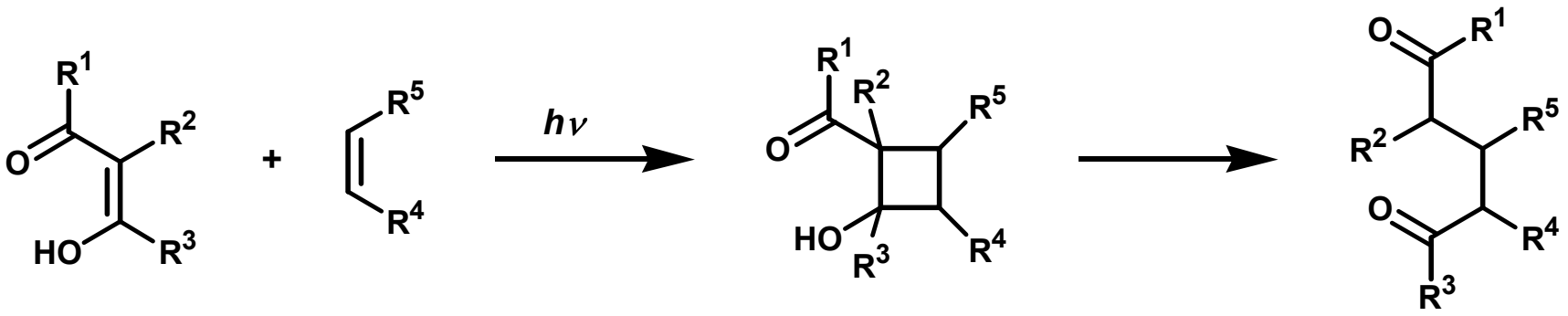




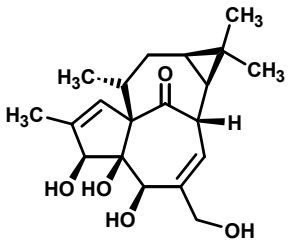
Winkler's Total Synthesis



De Mayo Reaction



De Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41-47.



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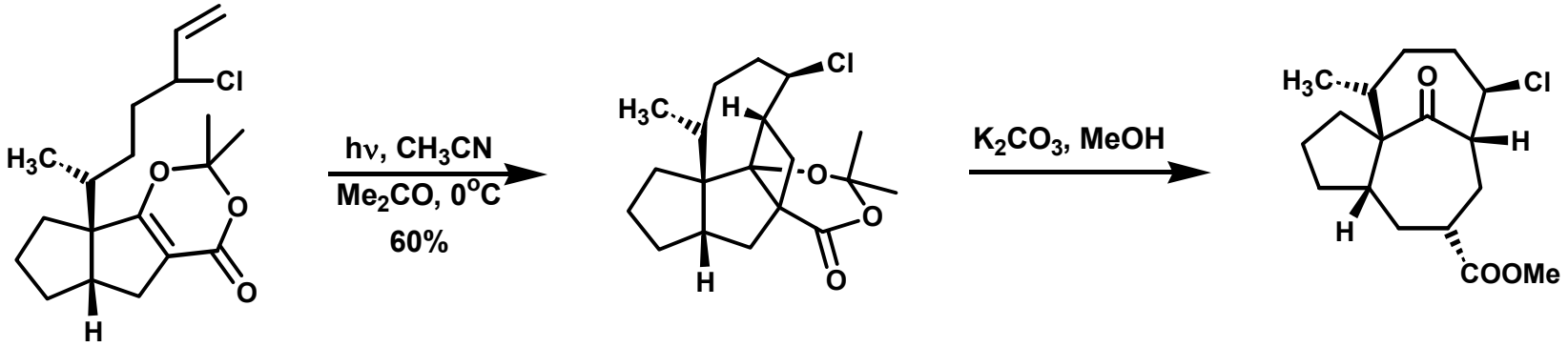

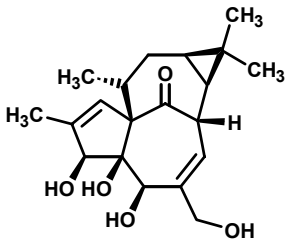

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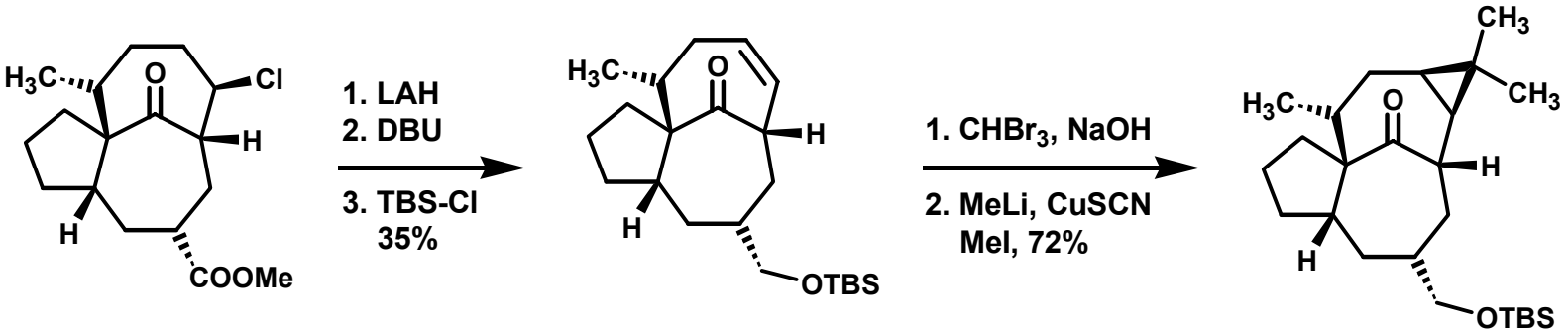

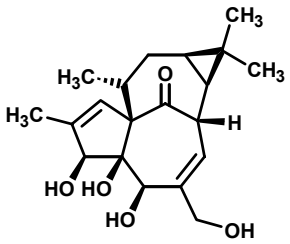

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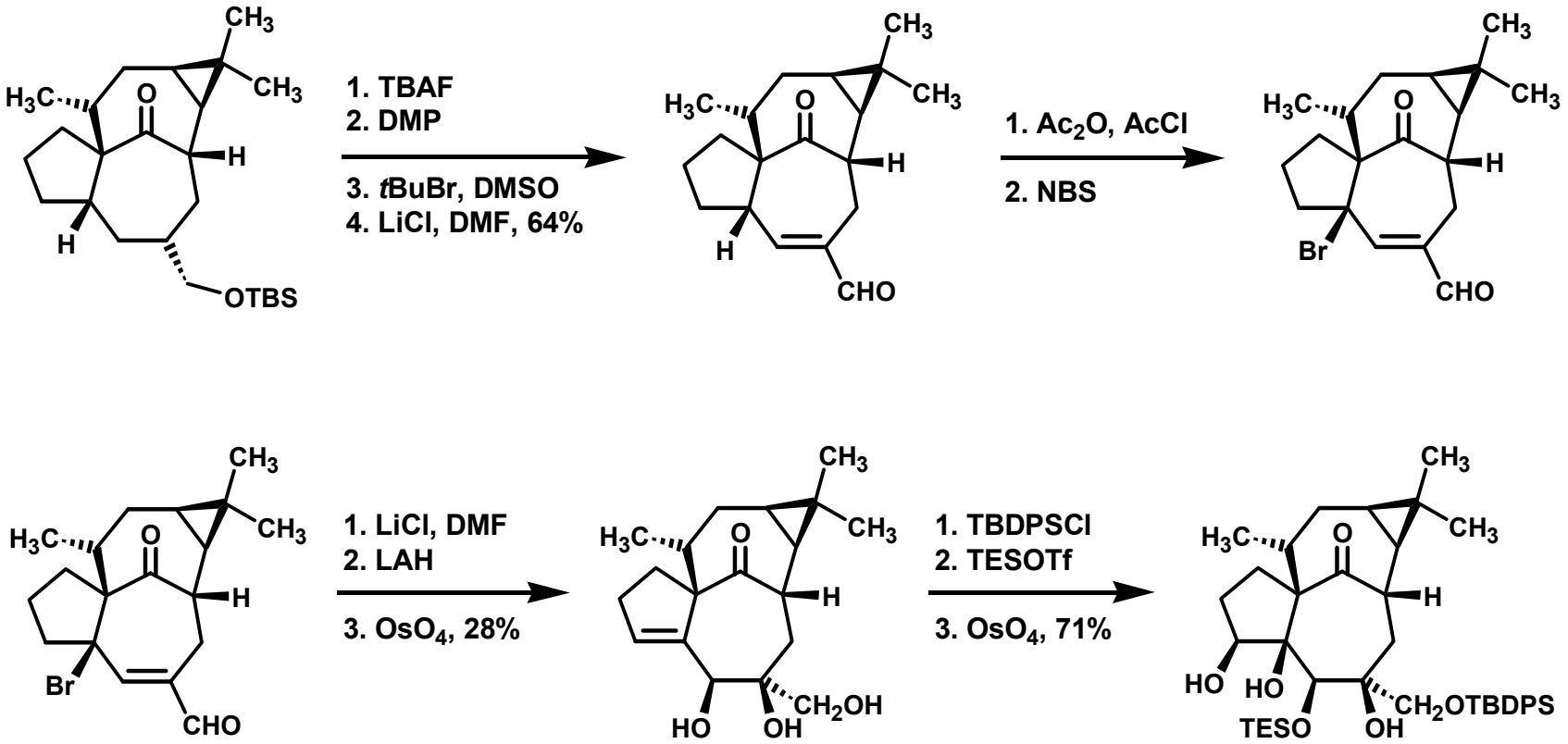

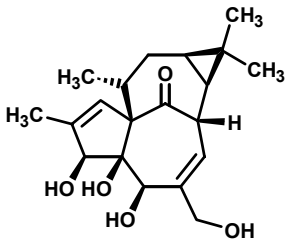

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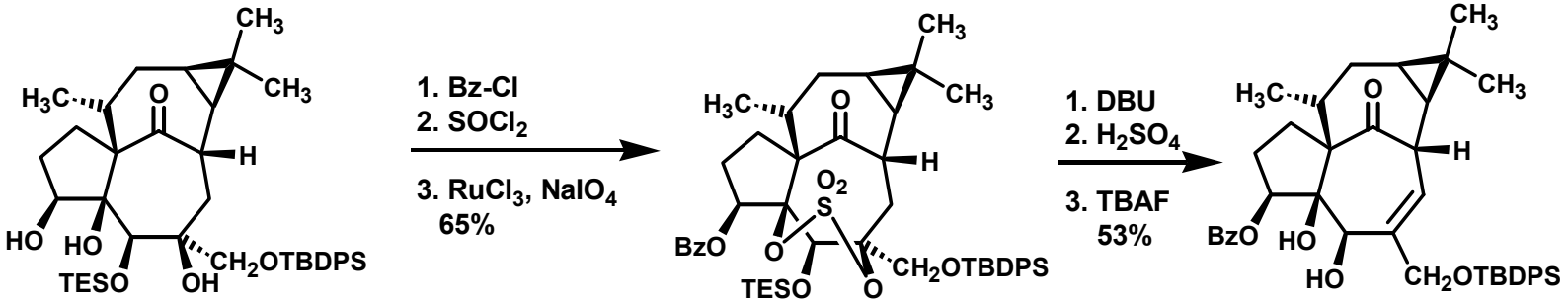
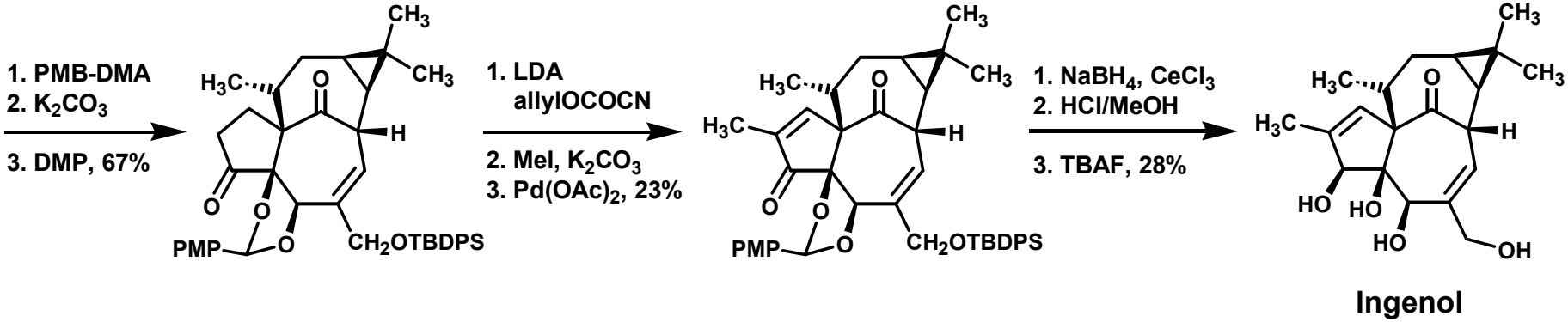
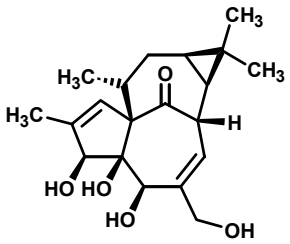


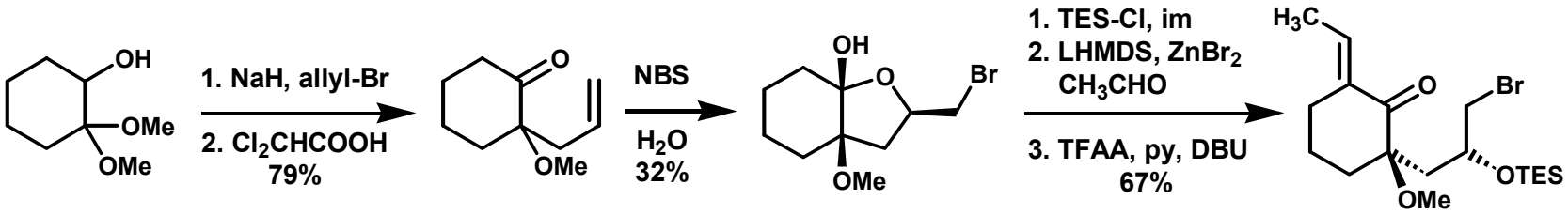


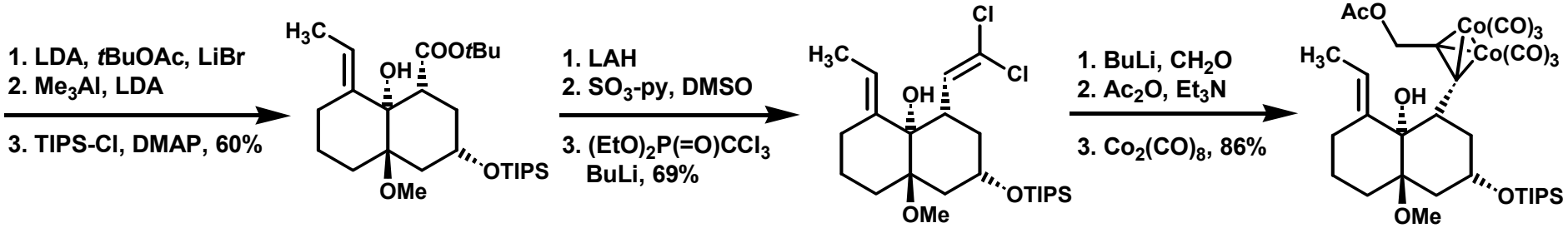
Ingenol

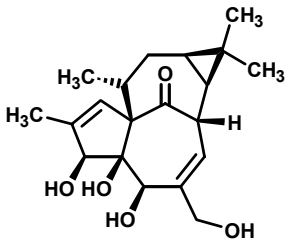
43 STEPS, average 80% yield per step



Tanino-Kuwajima Total Synthesis







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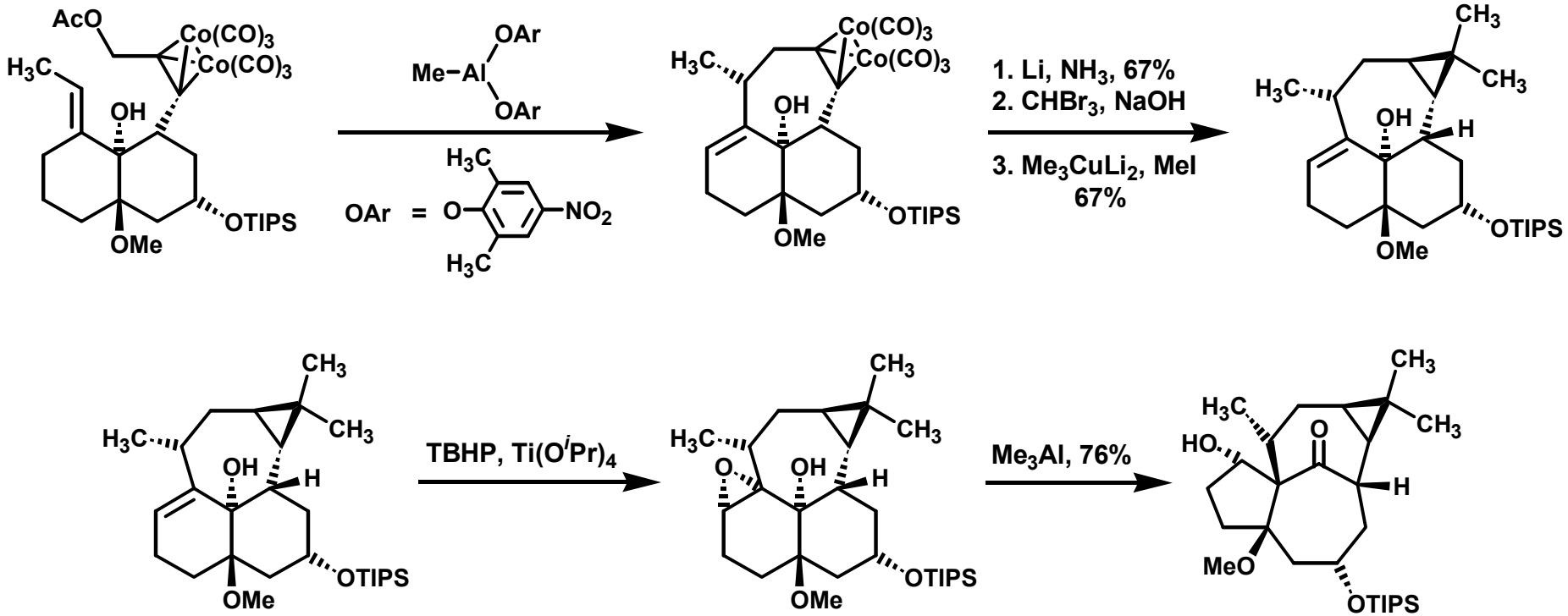
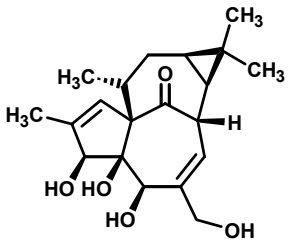
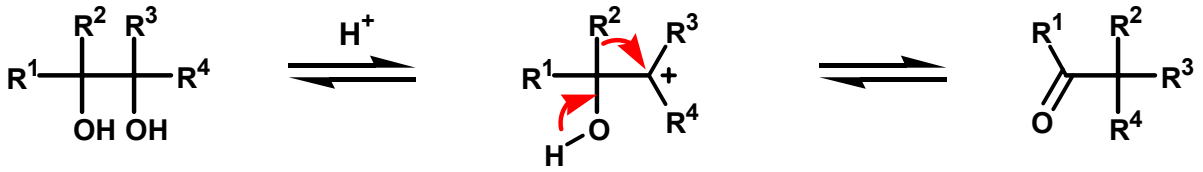
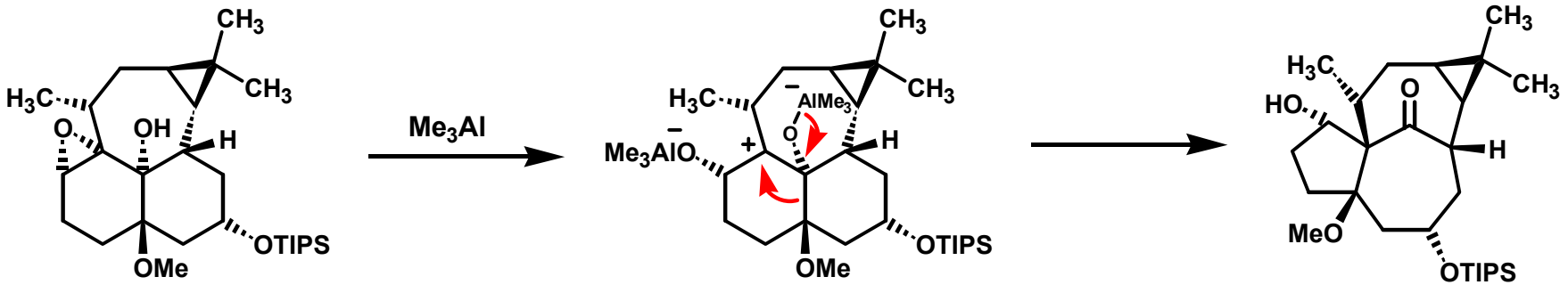


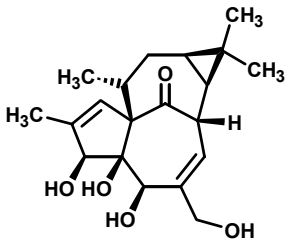


Tanino-Kuwajima Total Synthesis

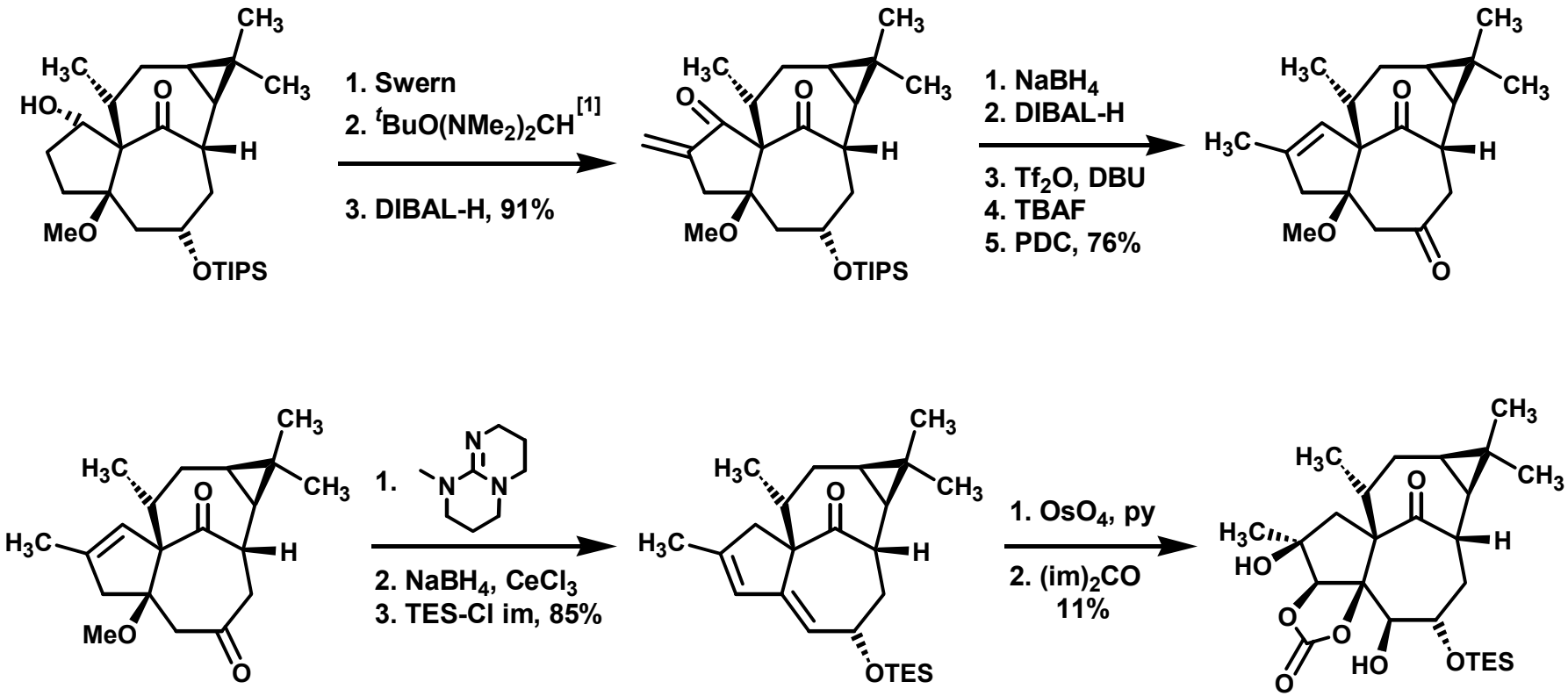
Pinacol Rearrangement



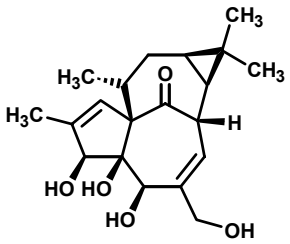




Tanino-Kuwajima Total Synthesis



[1] Trost, B. M.; Preckel, M. *J. Am. Chem. Soc.* **1973**, *95*, 7862-7864.



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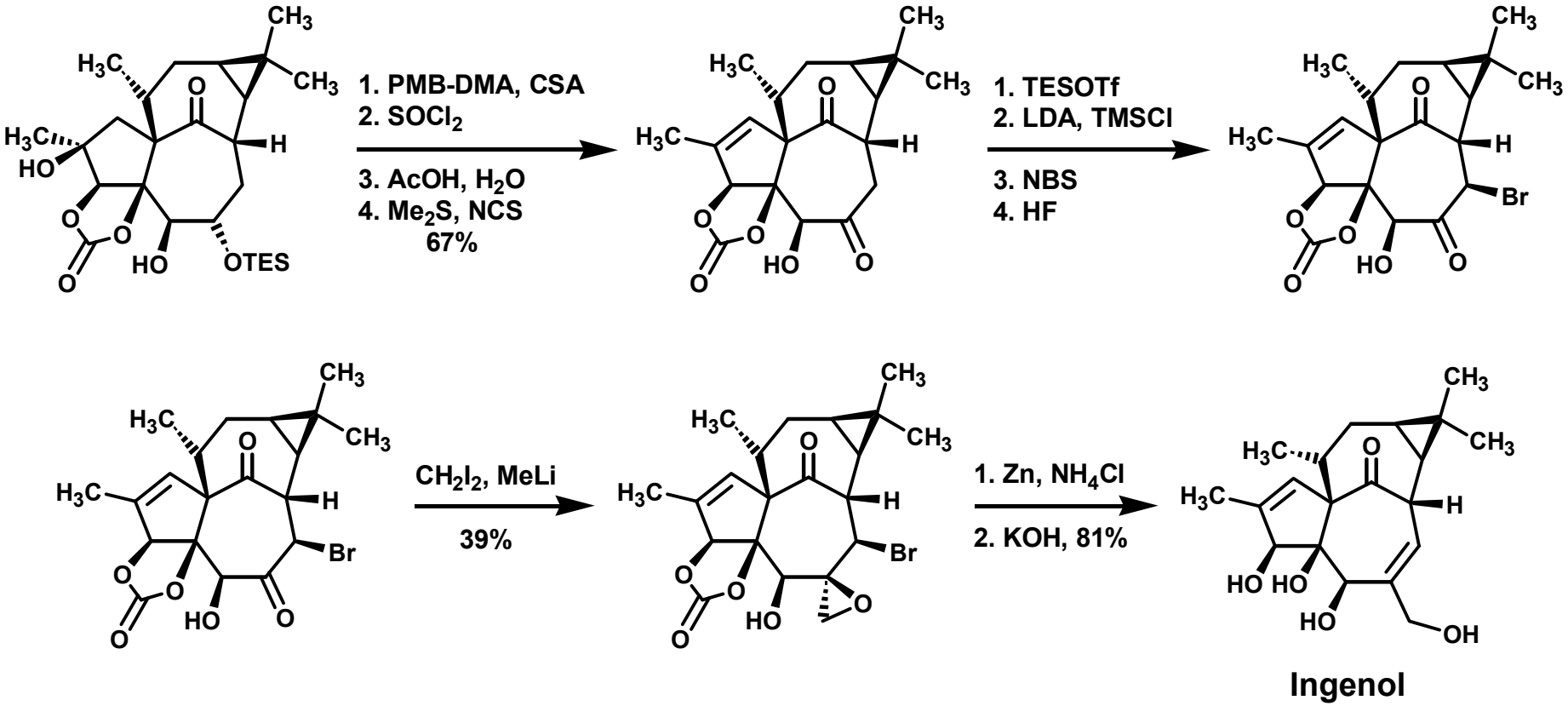

45 STEPS, ca. 0.1% yield overall

Literature

- Ingenol – Isolation and Characterization

  Hecker, E. *Cancer Res.* **1968**, *28*, 2338.

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- In/Out Isomerism

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- Ingenol Syntheses

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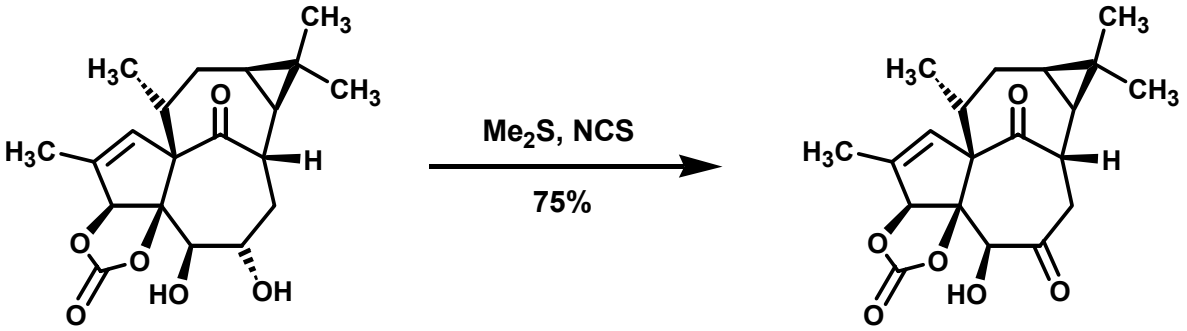

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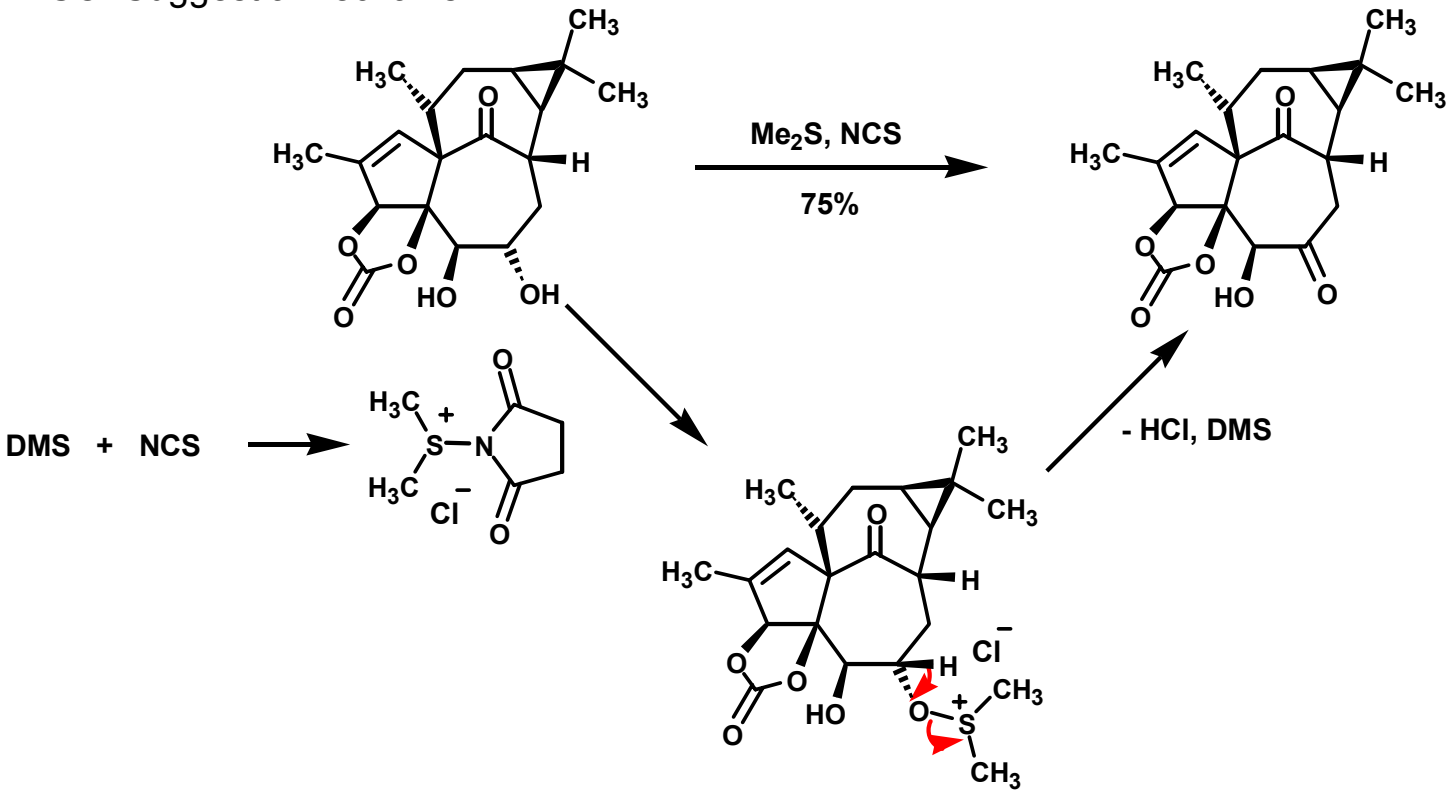

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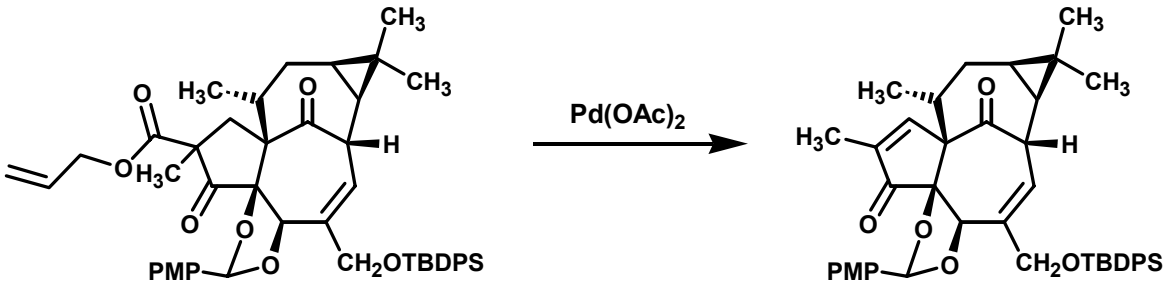

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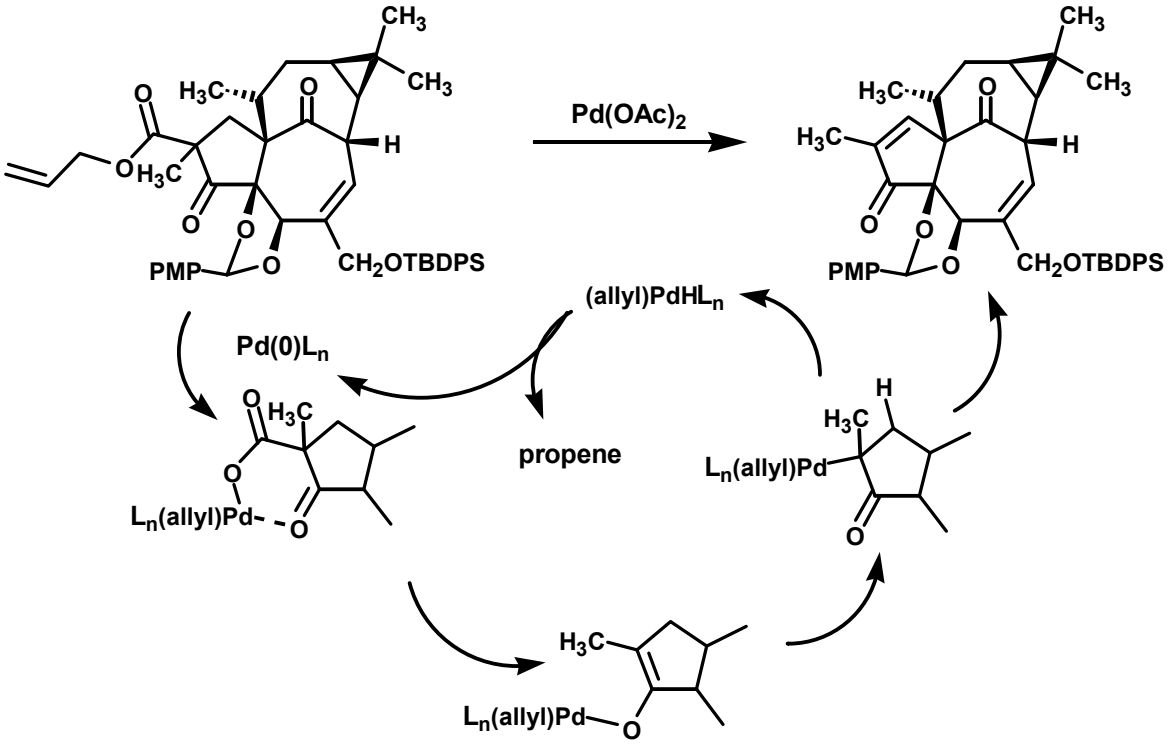

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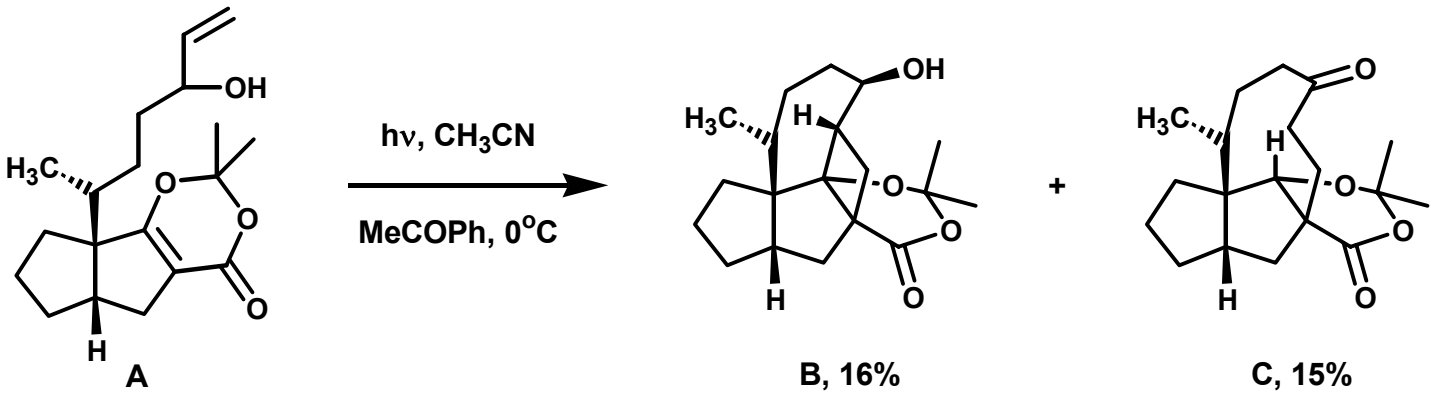

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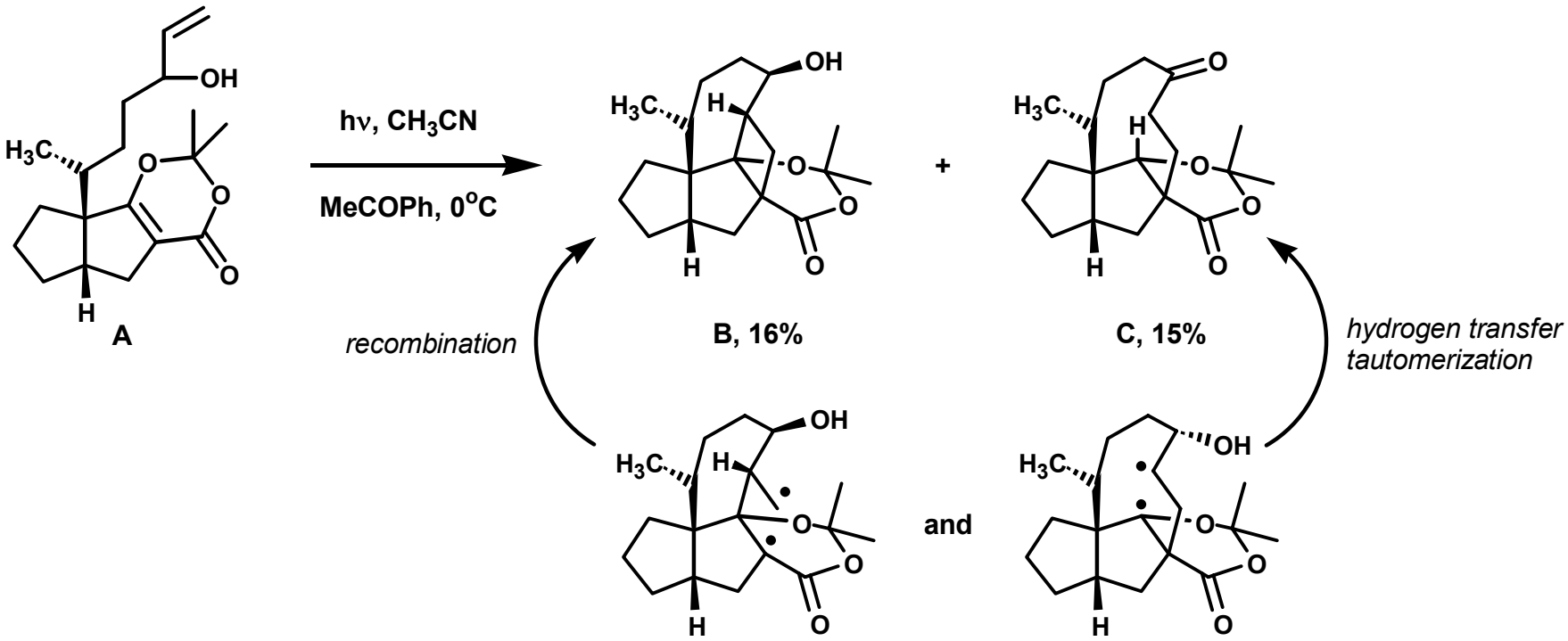

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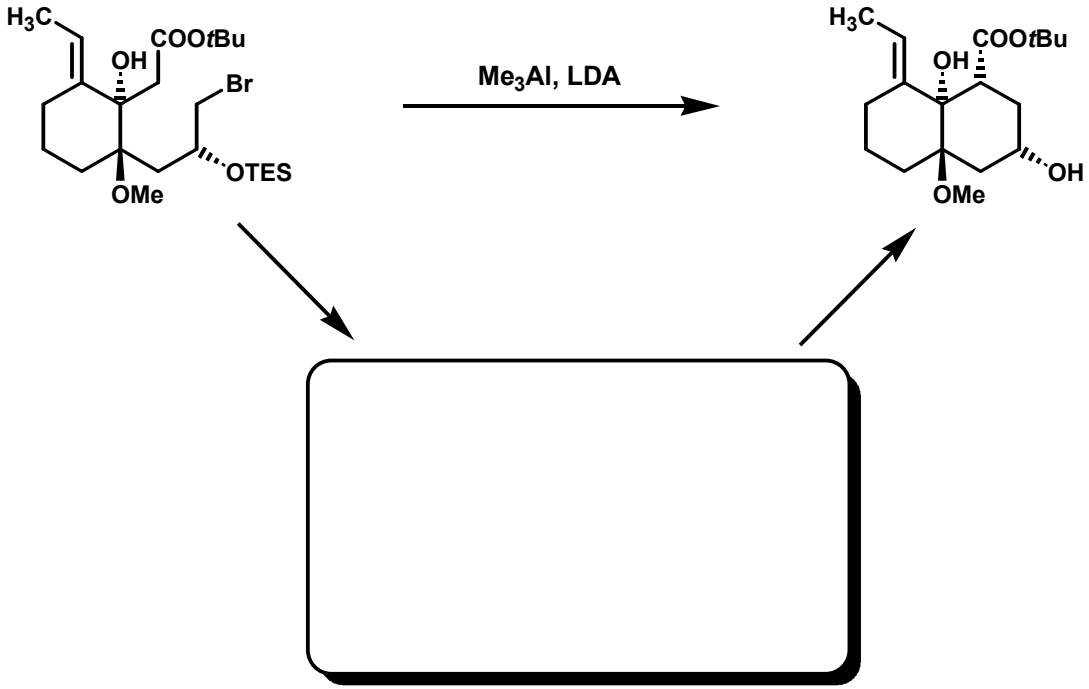

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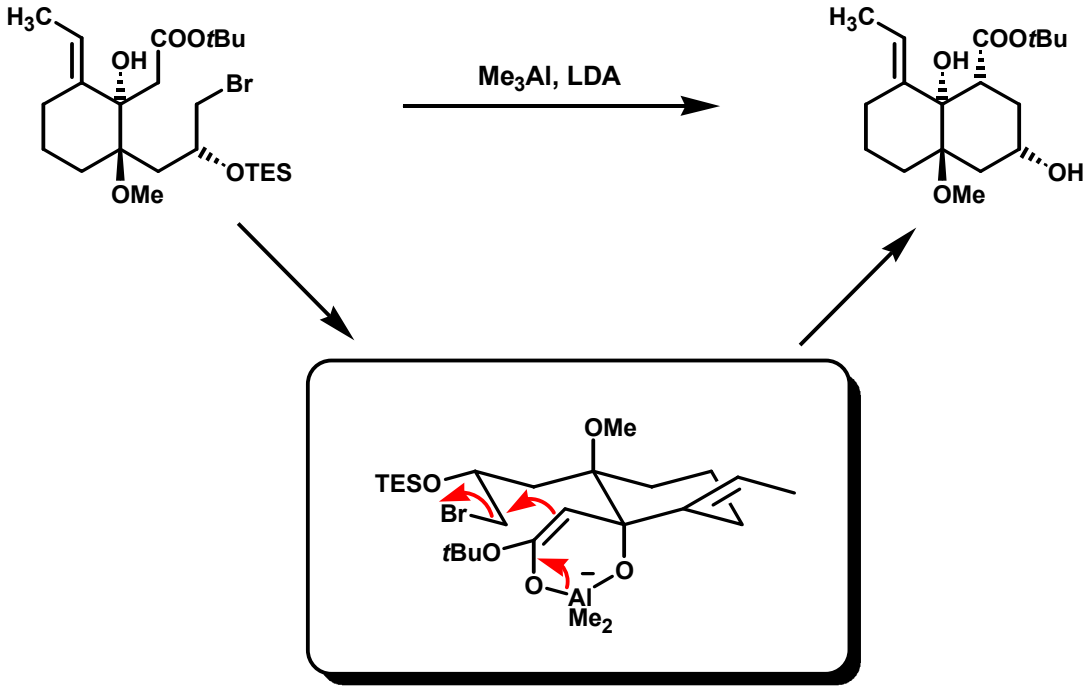

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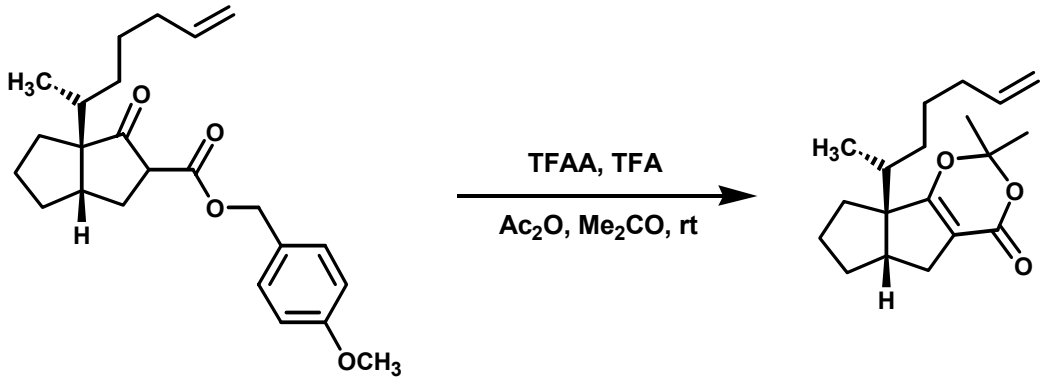

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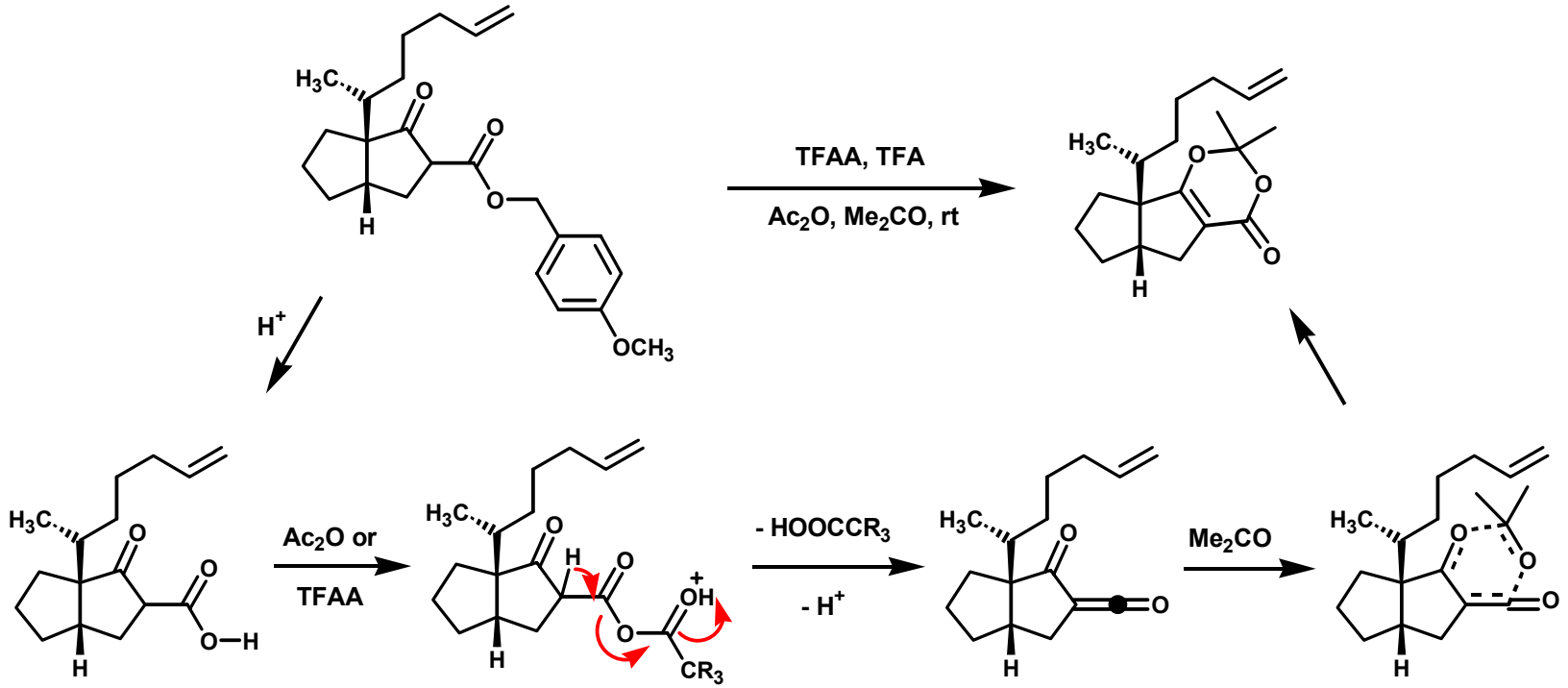

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