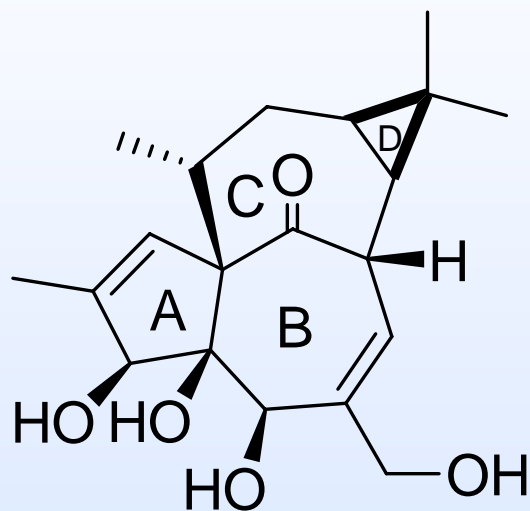
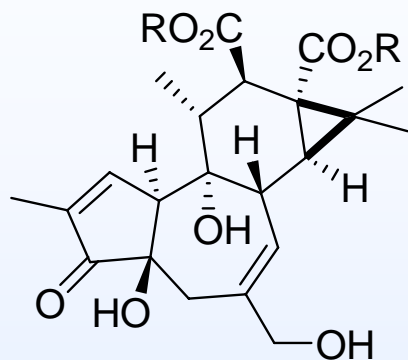


Synthetic Approaches Towards Ingenol

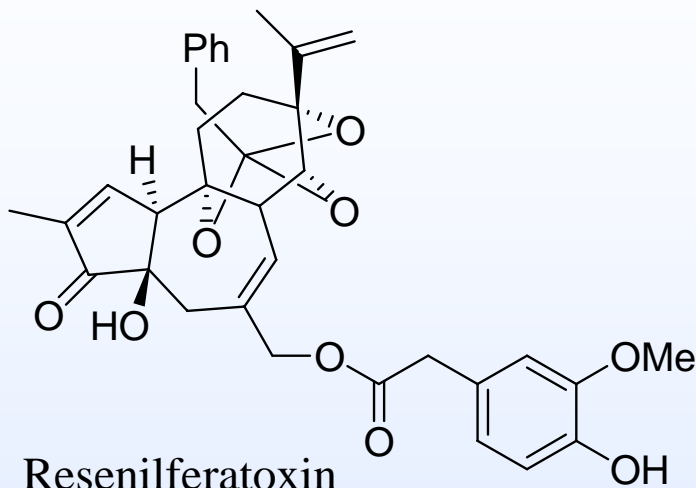


Columbia University
Leighton Group Meeting
Arash Soheili
April 17, 2006

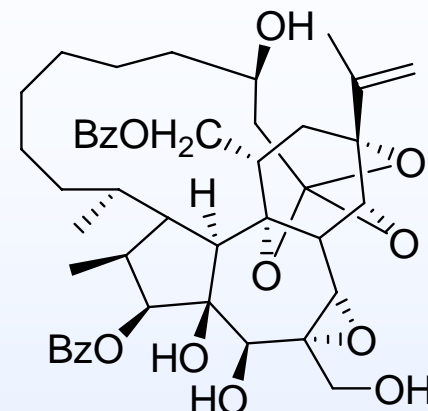
Ingenol and Related Structures



Phorbol Esters



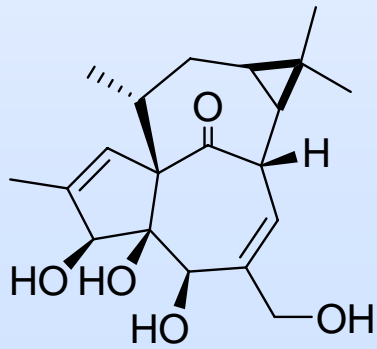
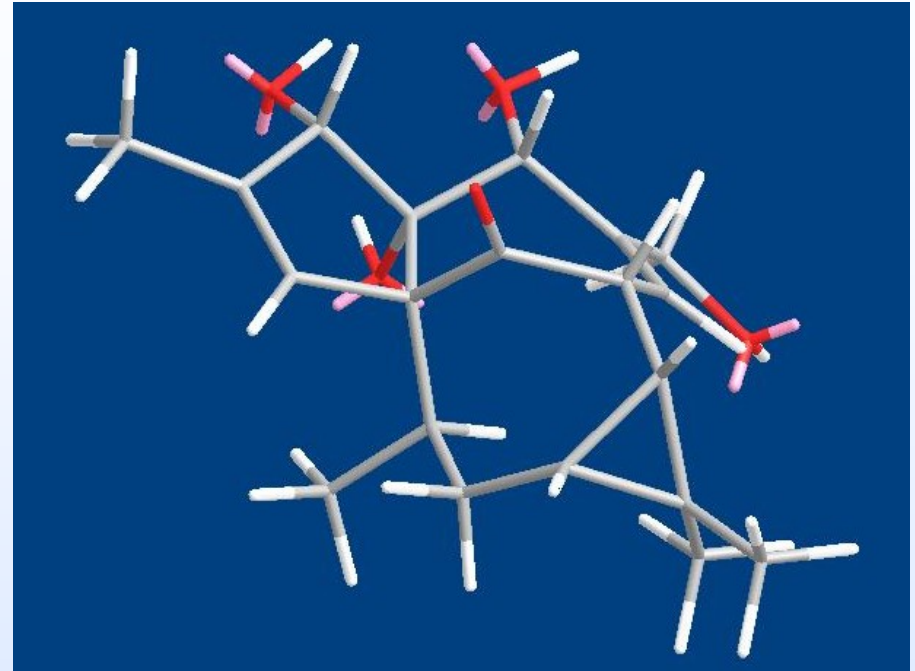
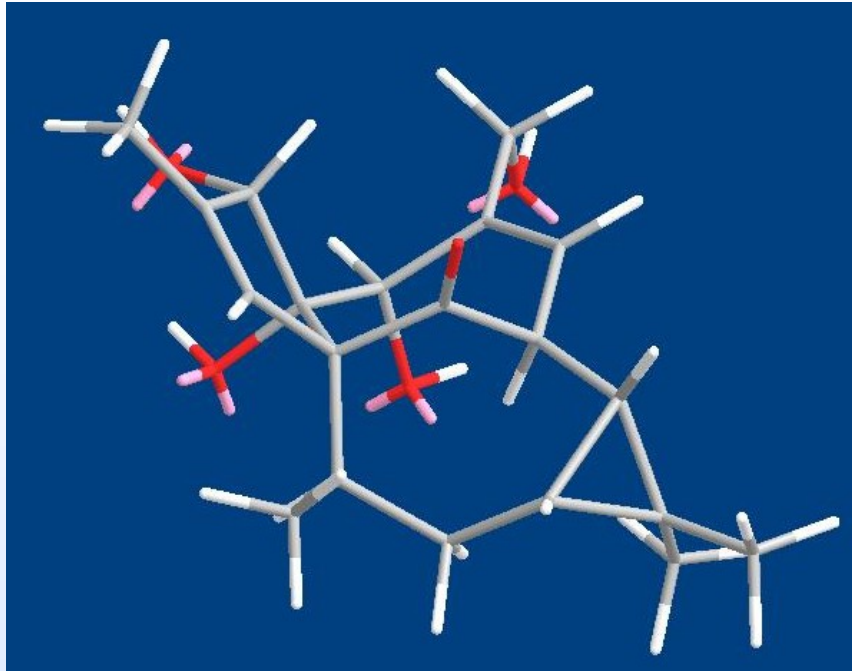
Resenilferatoxin



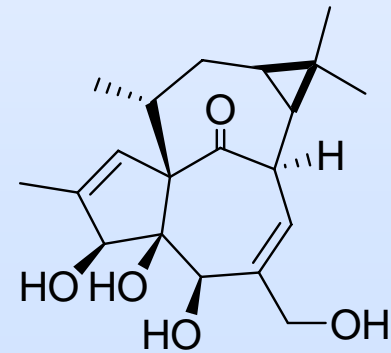
Gnidimacrin

- Isolated from roots of *Euphorbia Ingens* (*Cancer Res.* **1968**, 28, 2338)
- Structure elucidation through x-ray derivative (*Tet. Lett.* **1970**, 4075)
- Highly potent tumor promotor associated with protein kinase C
- Ingenol derivatives have showed anti-tumor and anti-HIV properties
- Member of a diverse structural family

In-Out Stereochemistry

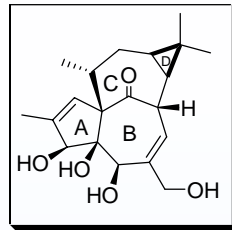


Ingenol - 5.9 kcal/mol



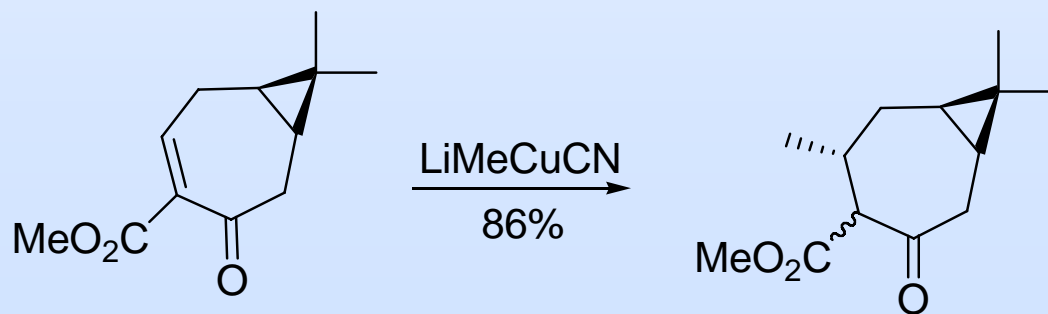
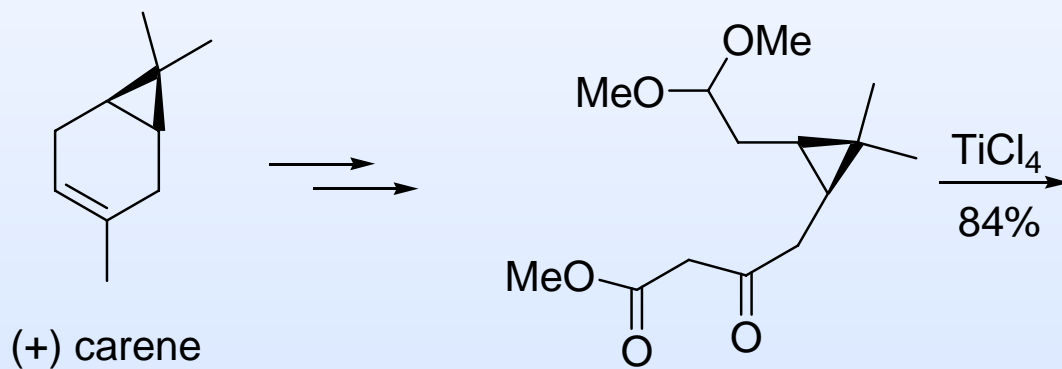
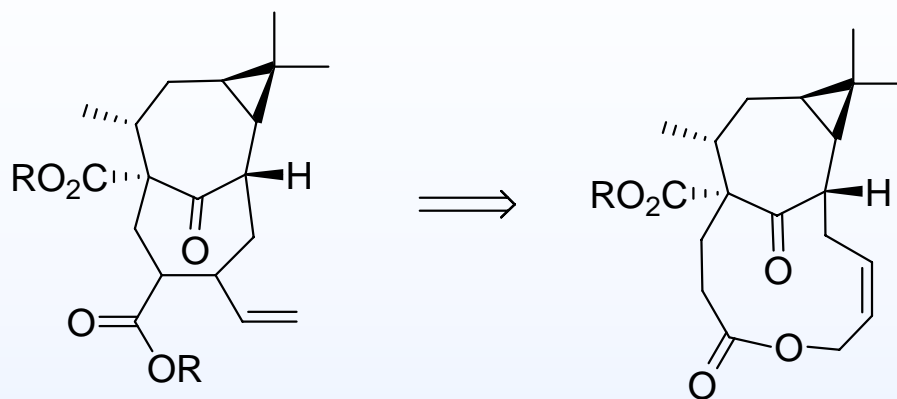
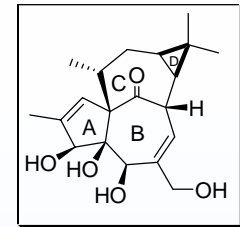
Iso-Ingénol

Outline of Ingenol Approaches

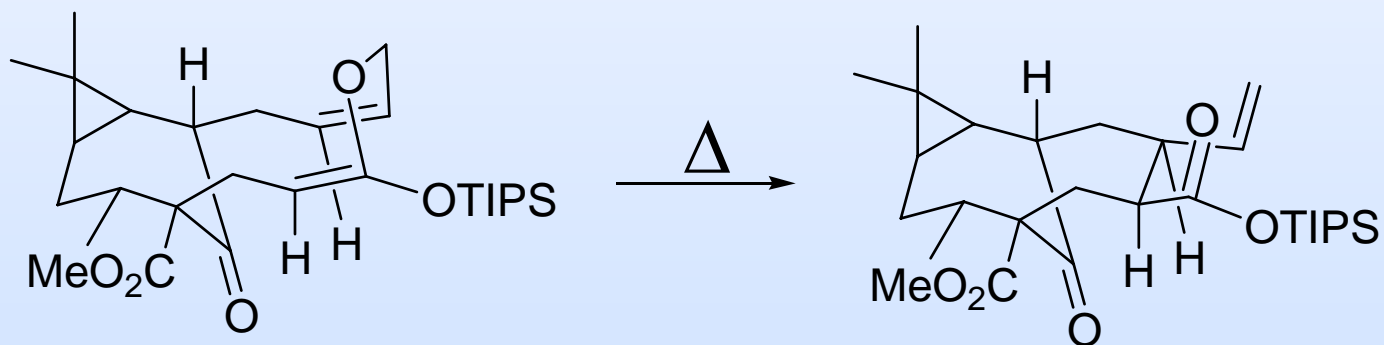
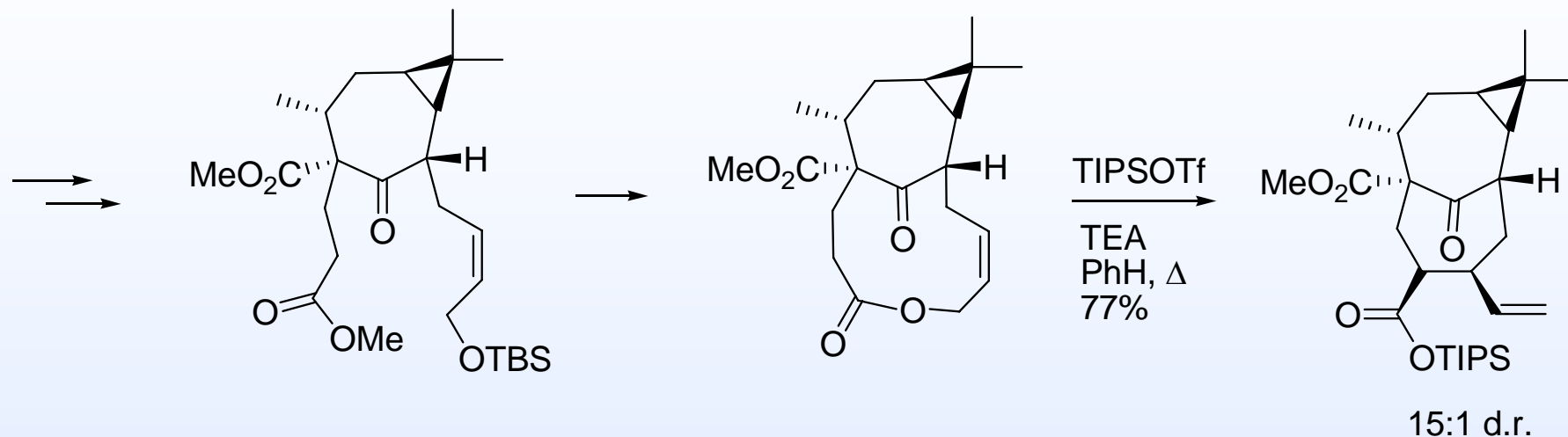
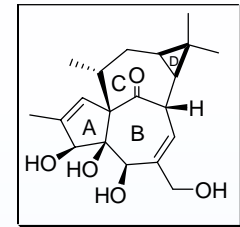


- Funk's Ireland-Claisen rearrangement
- Rigby's 1,5-hydrogen sigmatropic rearrangement
- Wood's total synthesis
- Tanino-Kuwajima's total synthesis
- Winkler's total synthesis

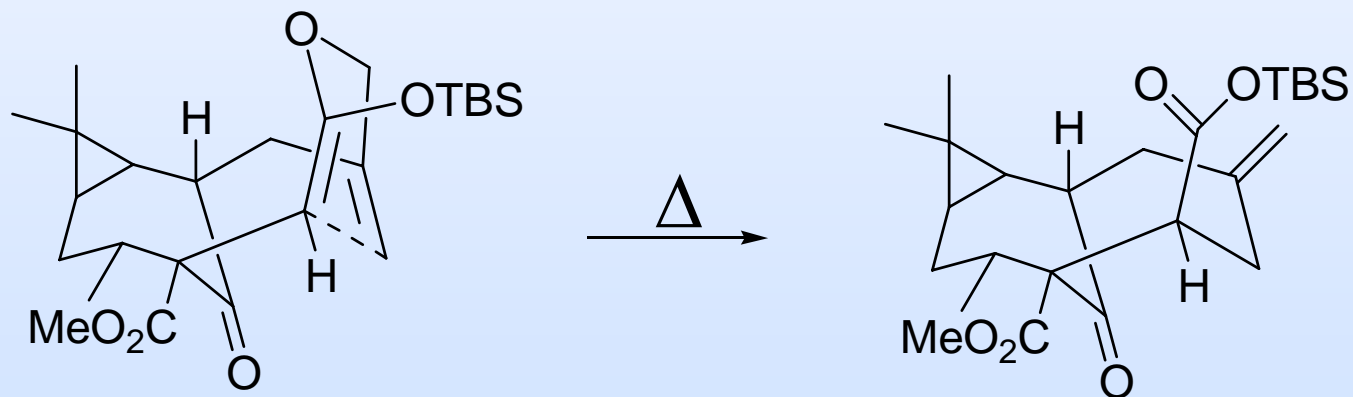
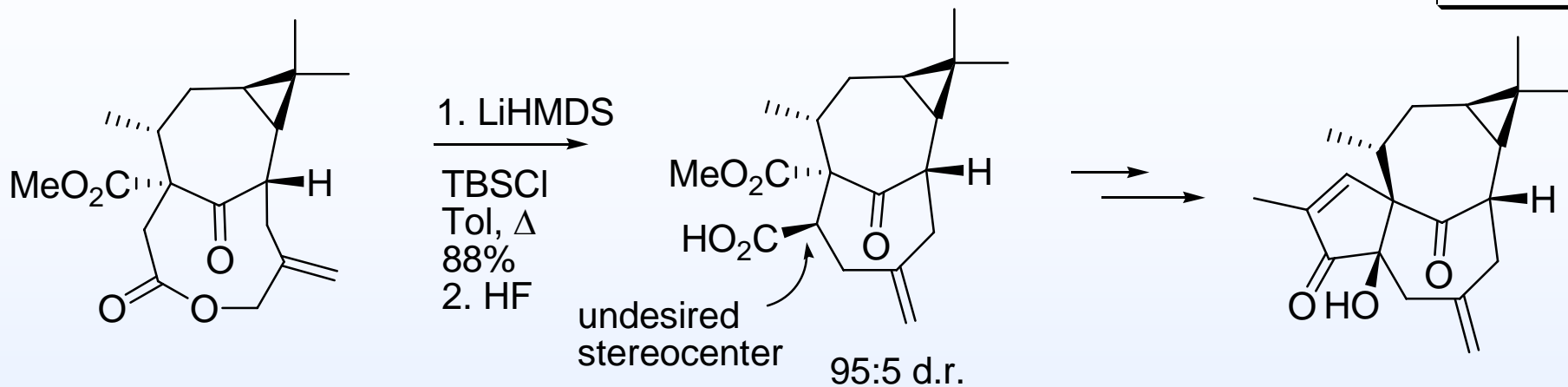
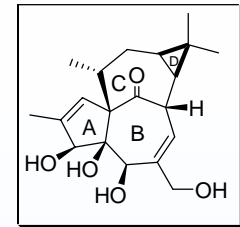
Funk's Ireland-Claisen



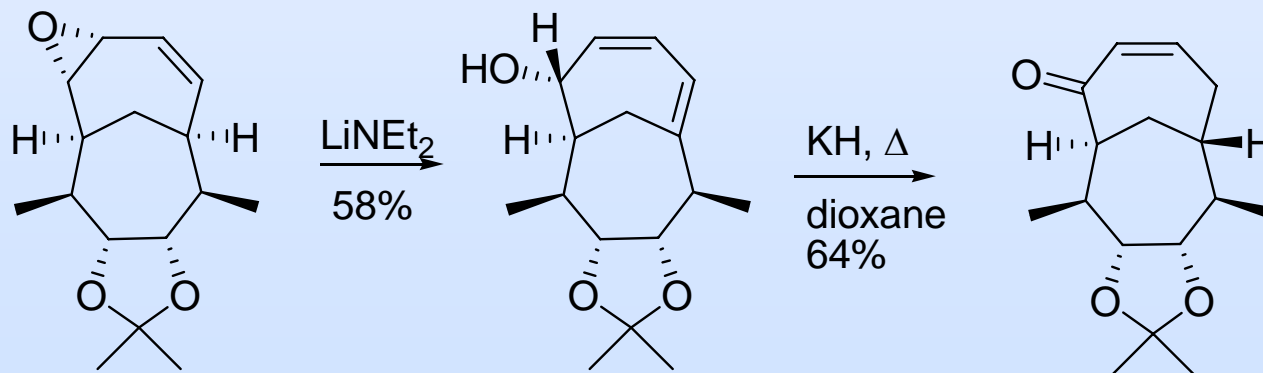
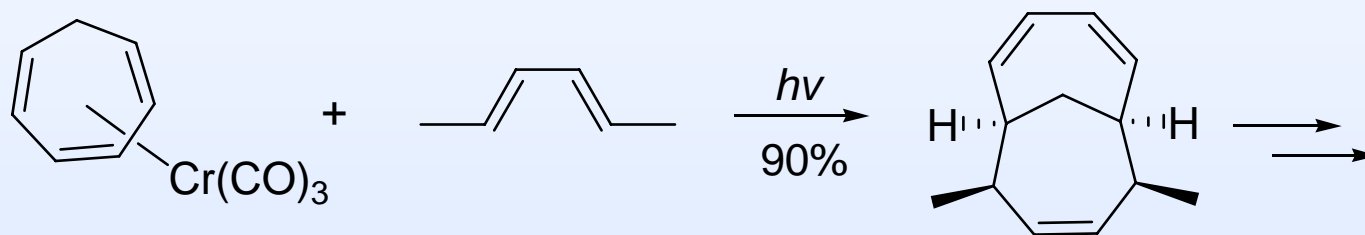
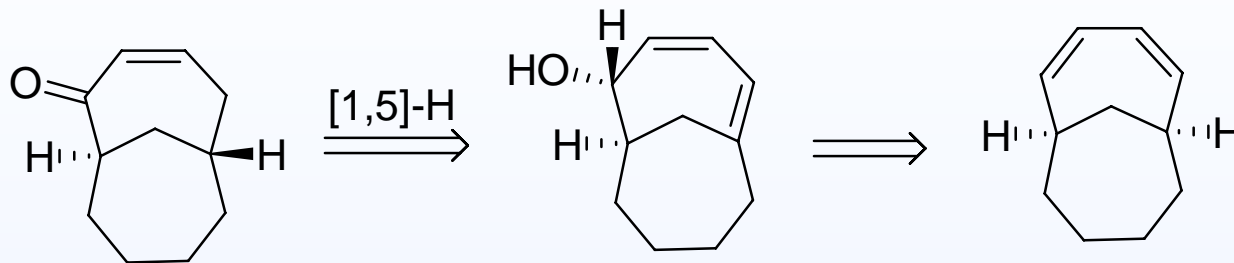
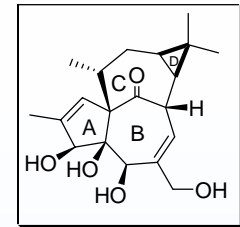
Funk's Ireland-Claisen



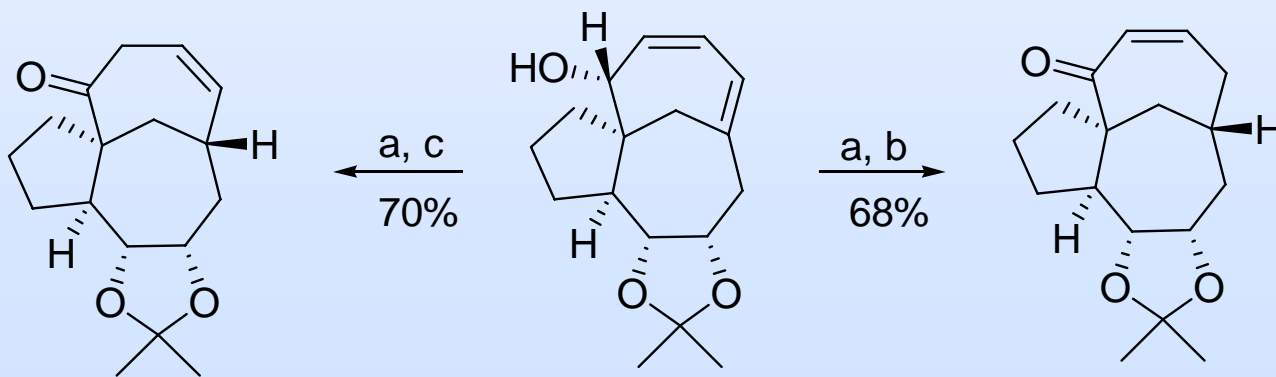
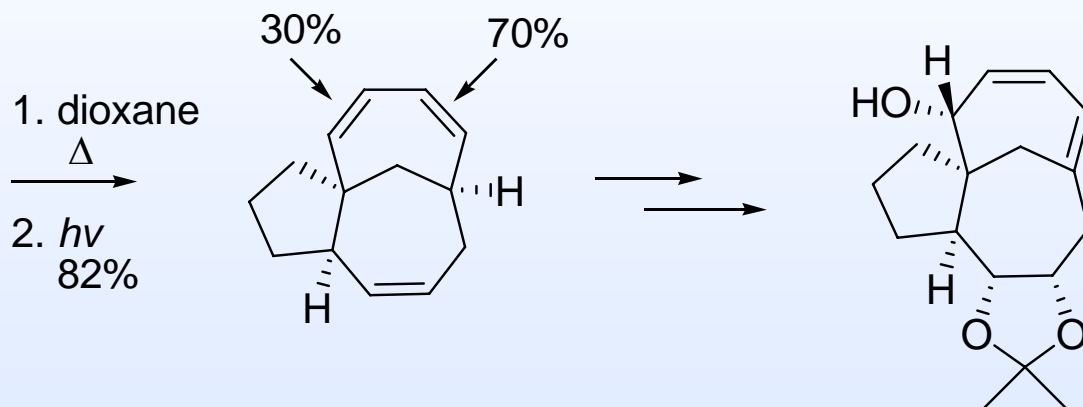
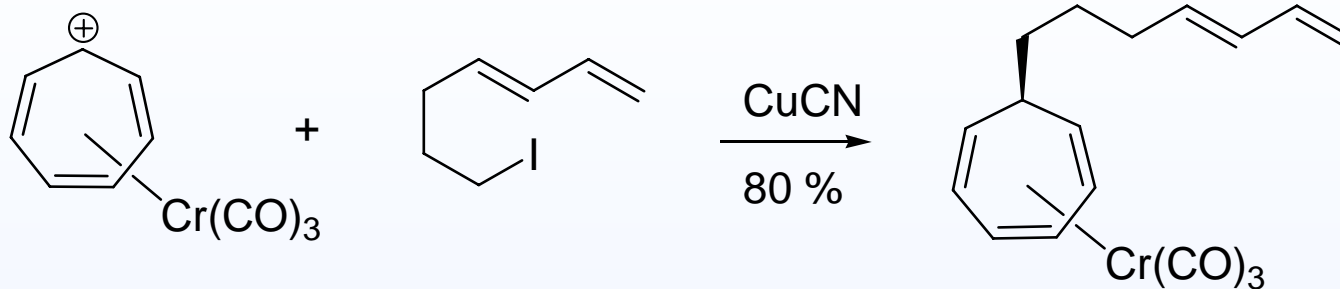
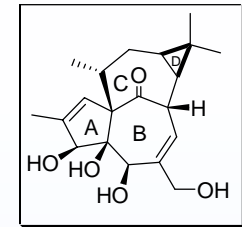
Funk's Ireland-Claisen



Rigby's Approach

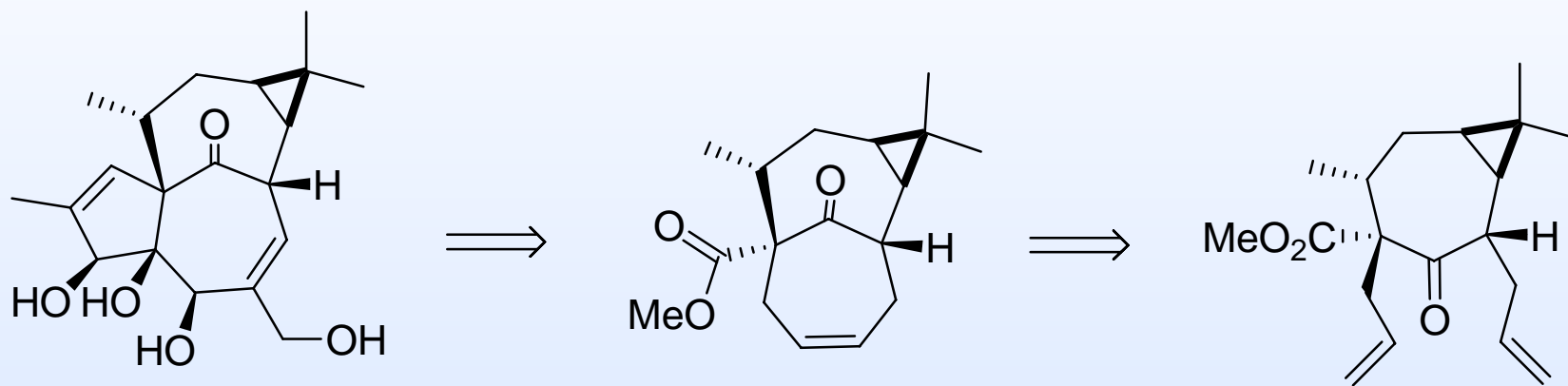
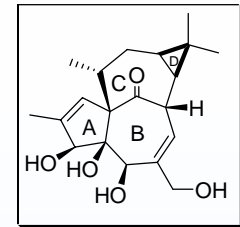


Rigby's Approach

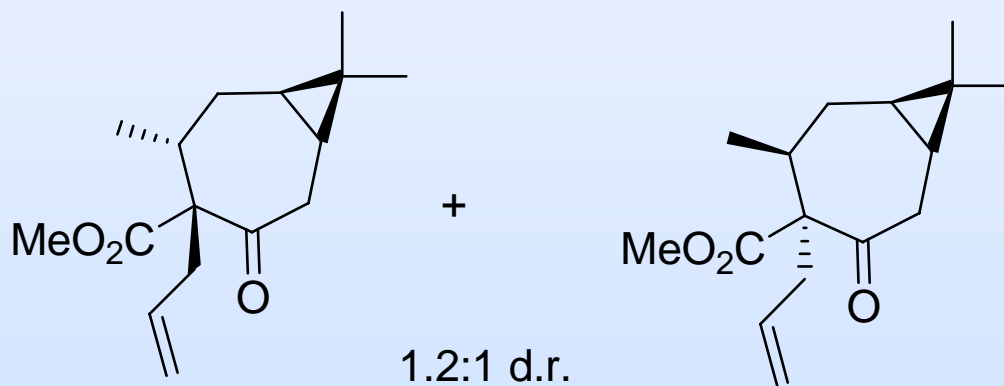
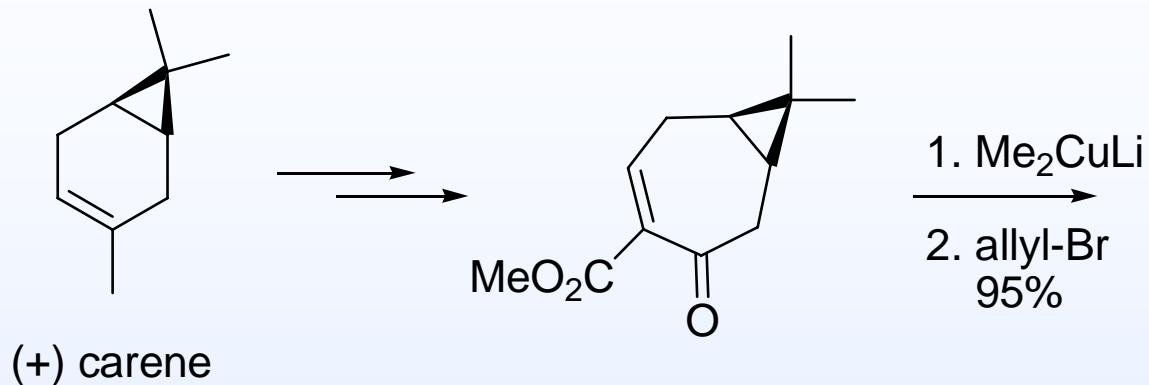
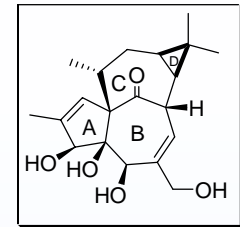


a) KH, 18-cr-6, THF 0°C b) NH₄Cl(aq) c) SiO₂, -78 °C

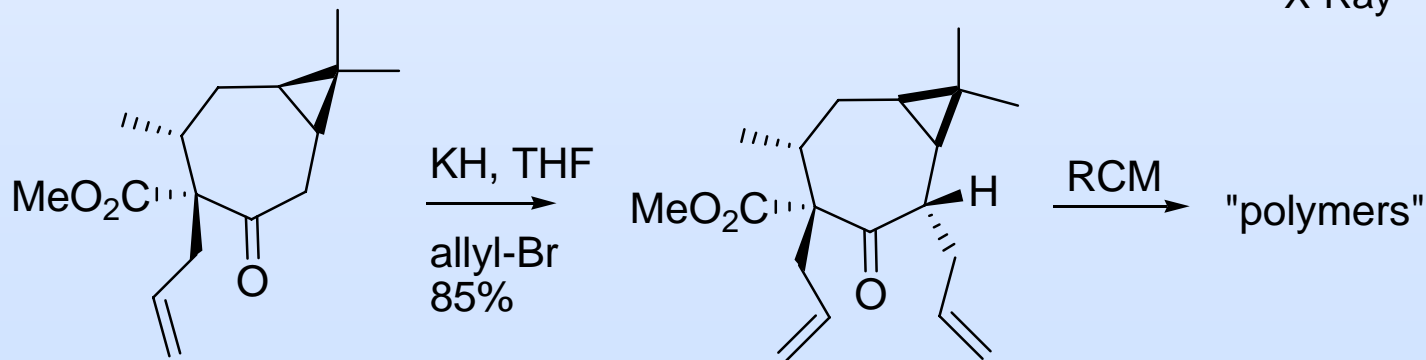
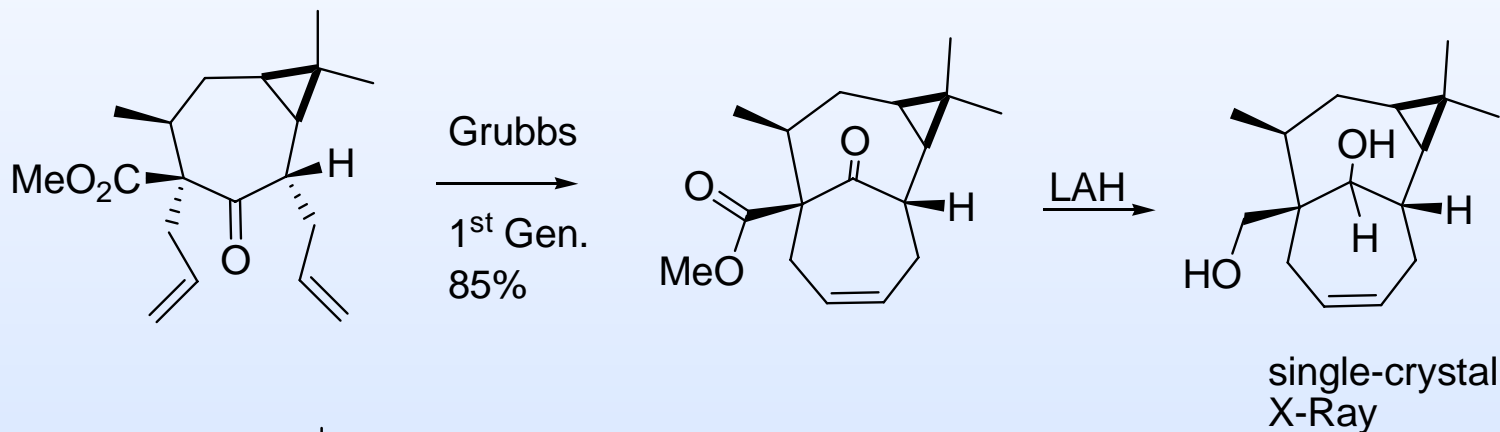
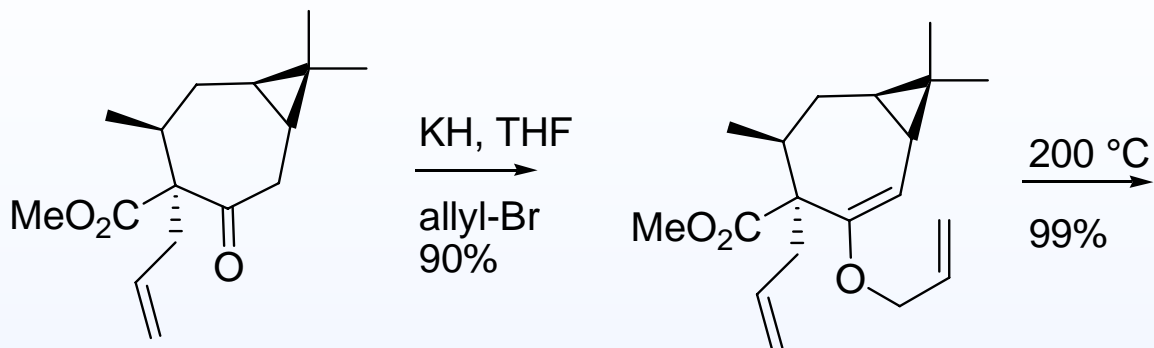
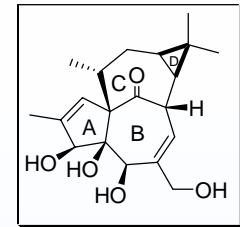
Wood's RCM Approach



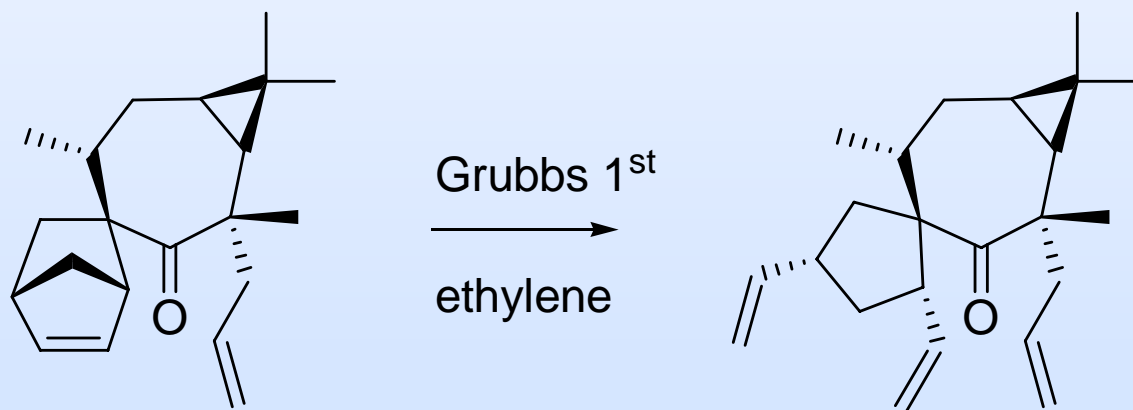
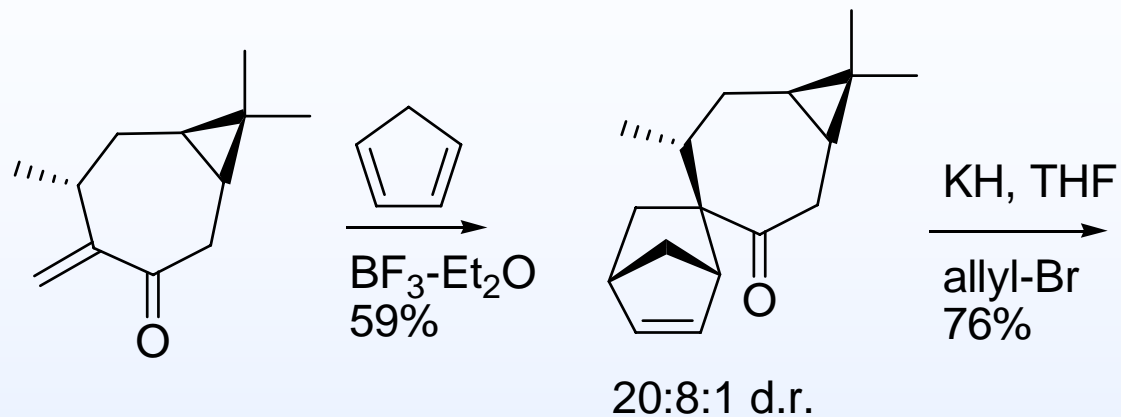
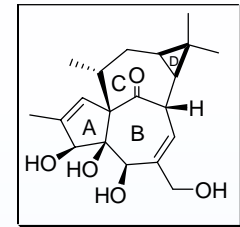
Wood's RCM Approach



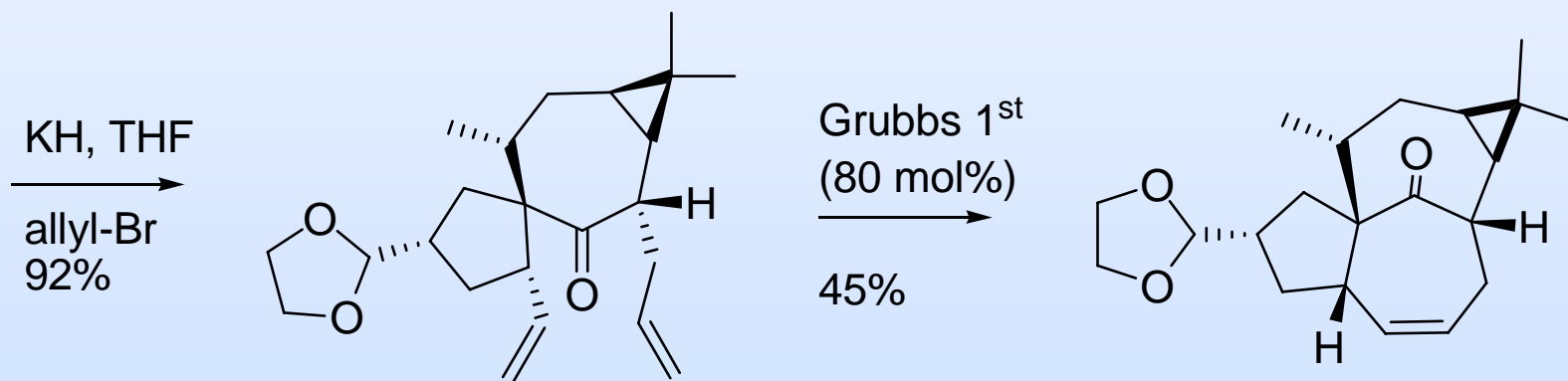
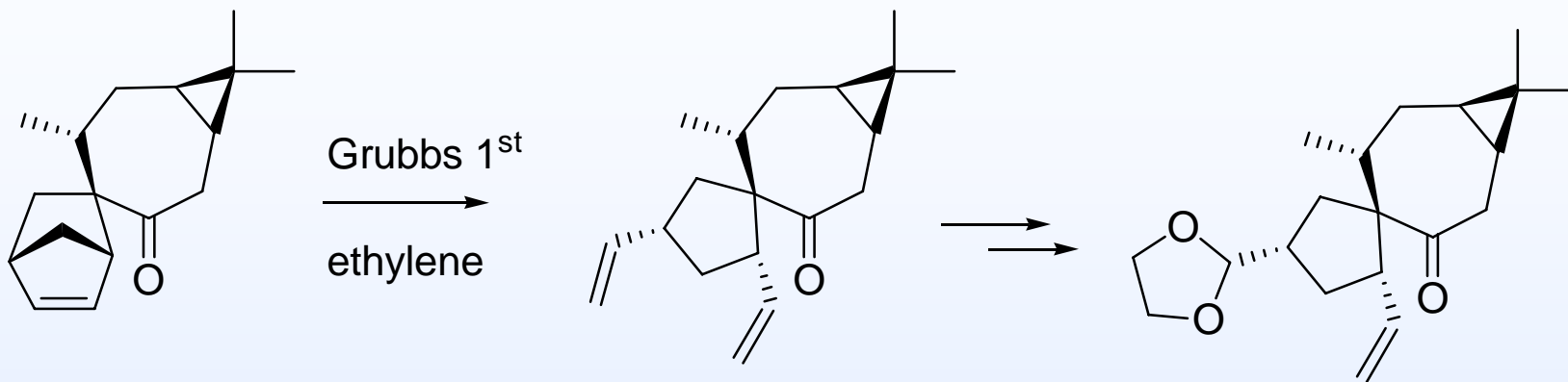
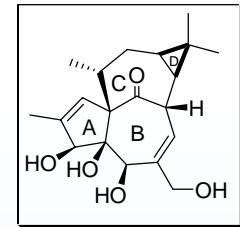
Wood's RCM Approach



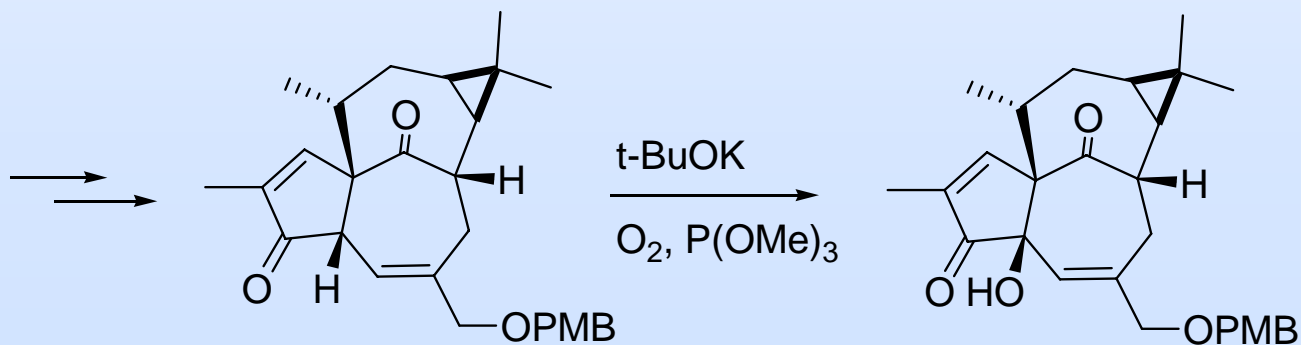
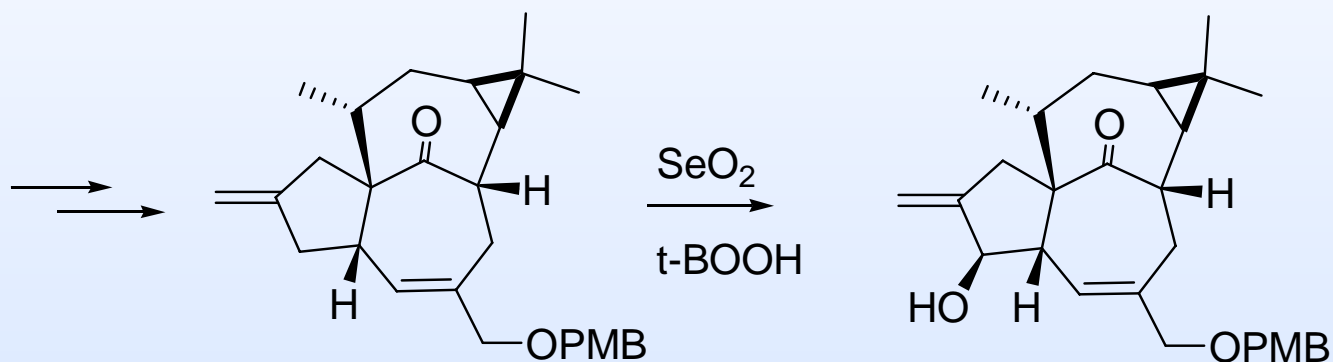
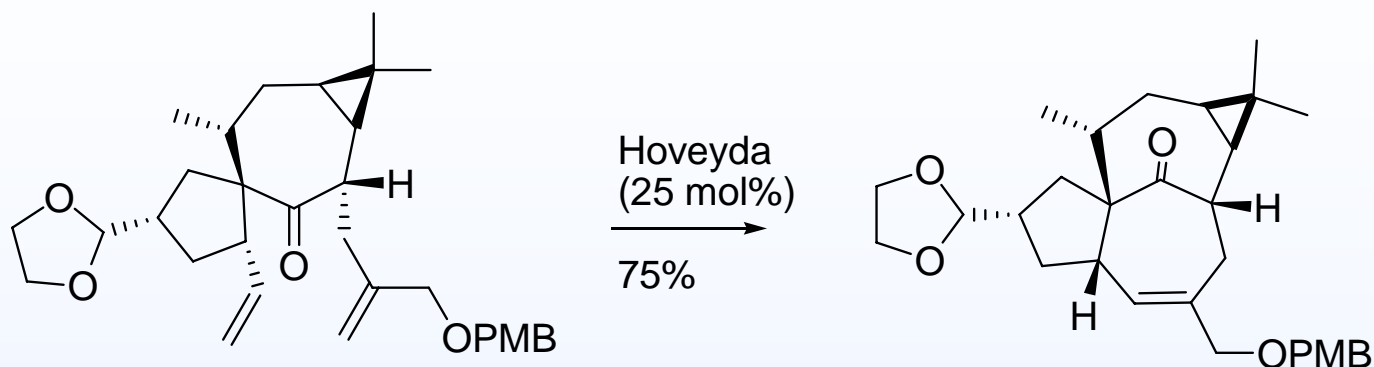
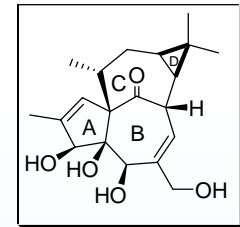
Wood's RCM Approach



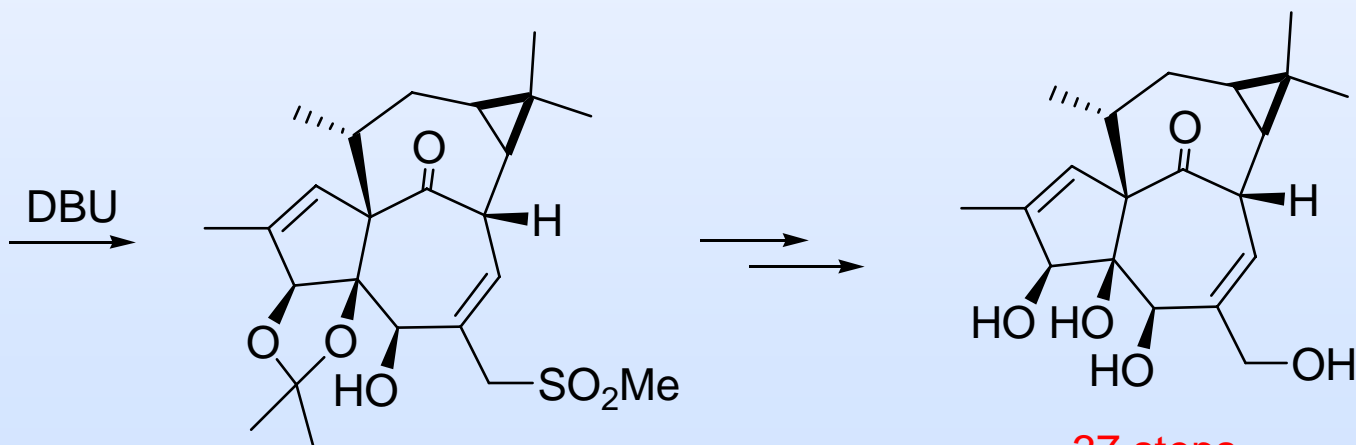
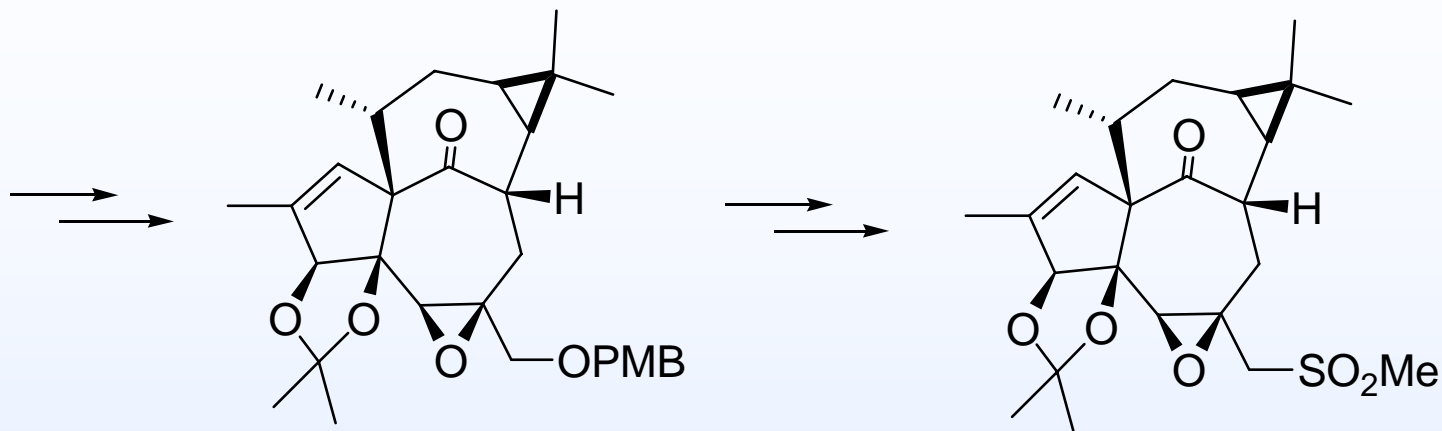
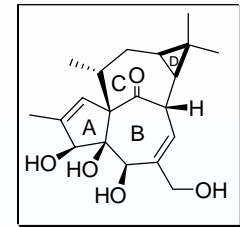
Wood's RCM Approach



Wood's Total Synthesis

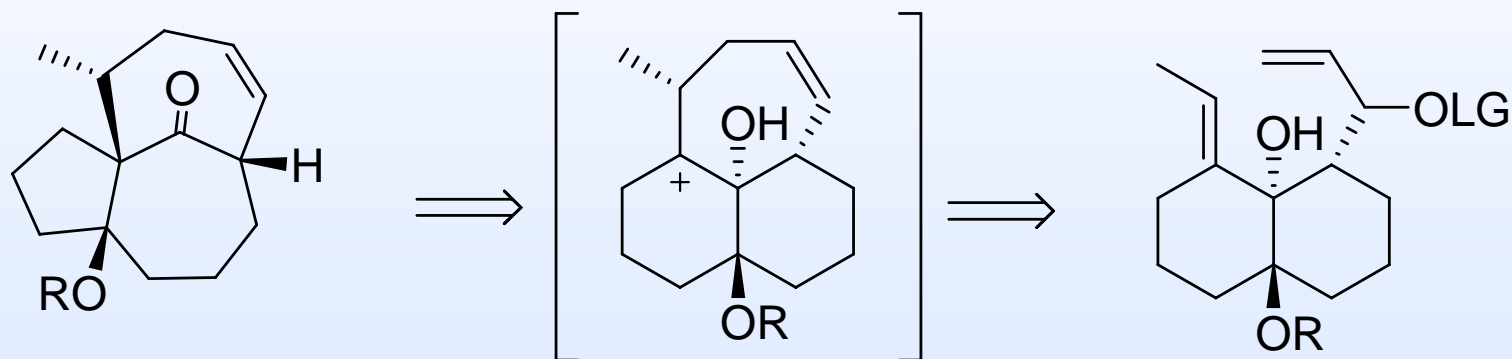
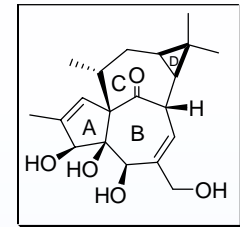


Wood's Total Synthesis

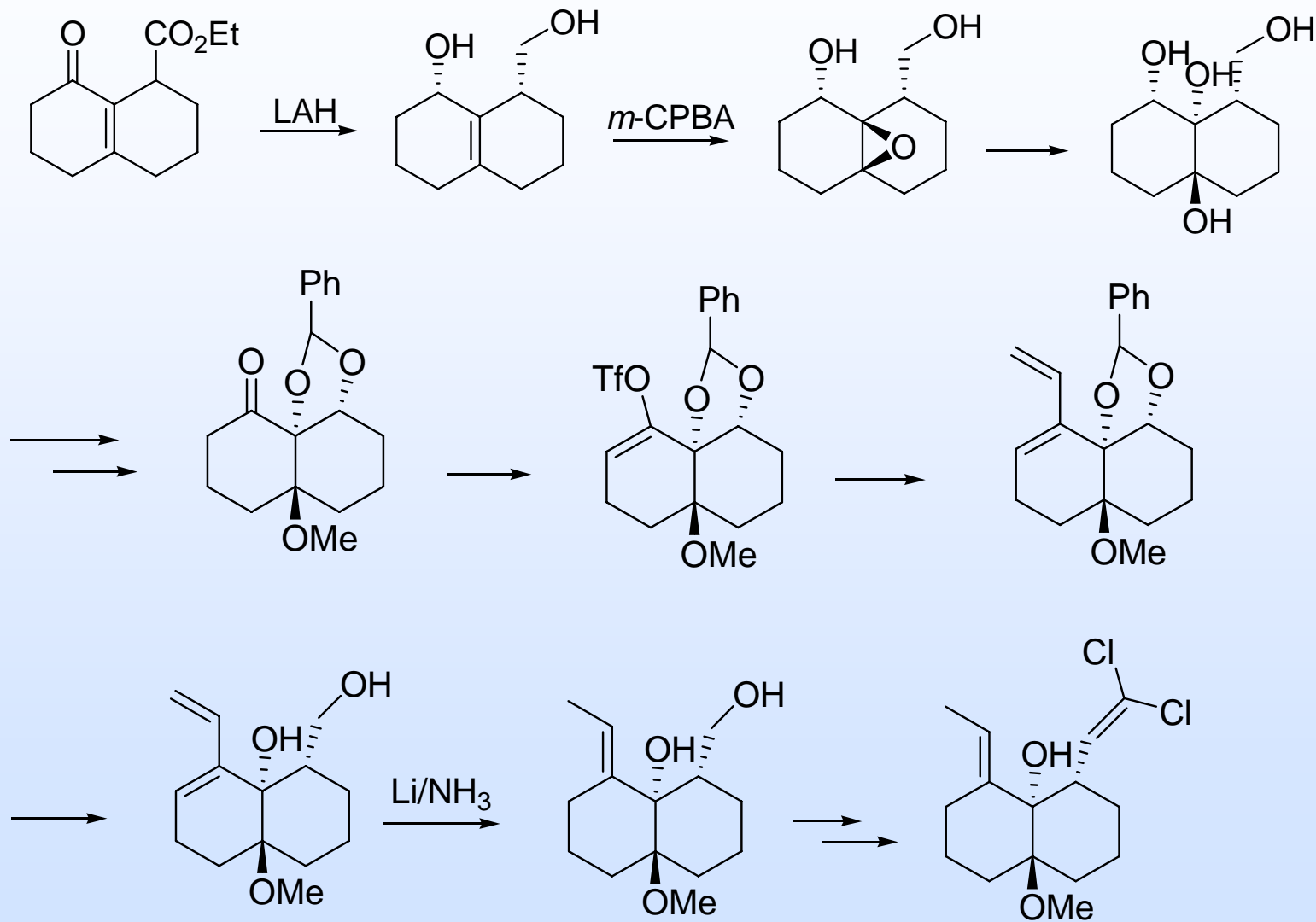
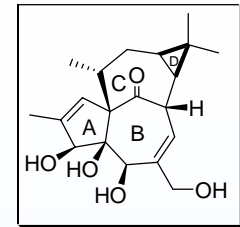


37 steps
0.002% yield

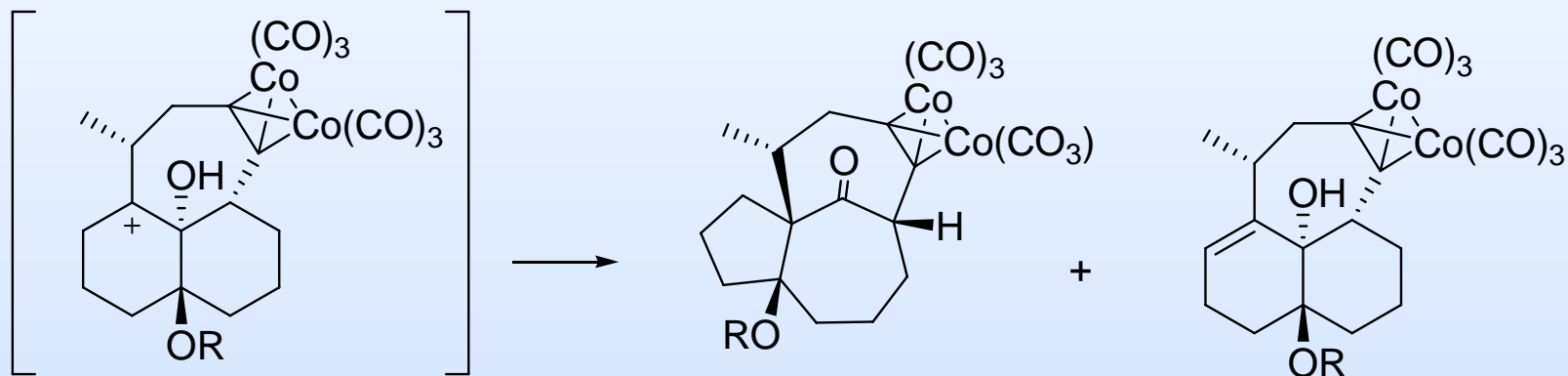
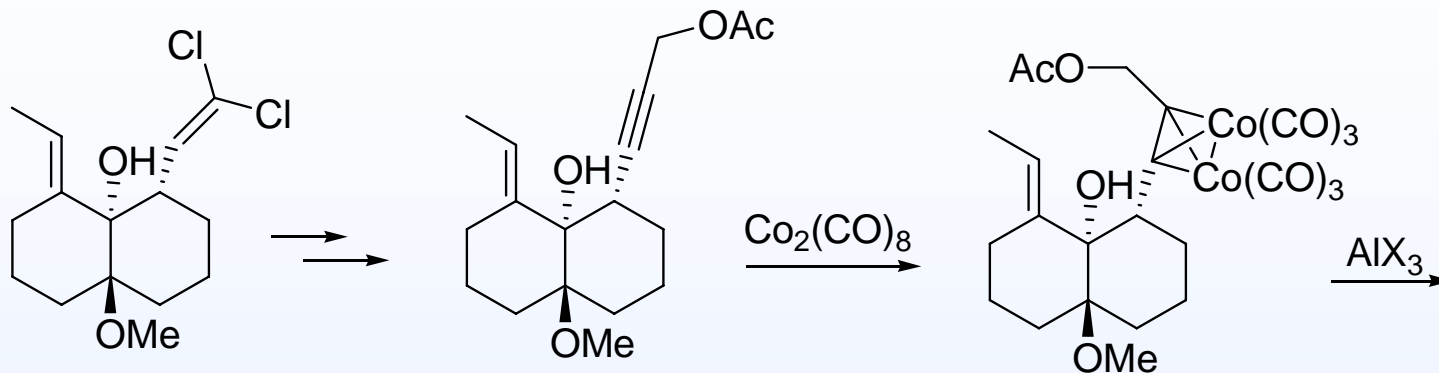
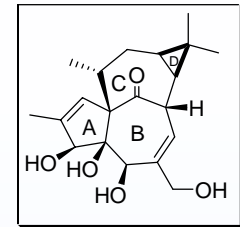
Tanino-Kwajima Approach



Tanino-Kwajima Approach

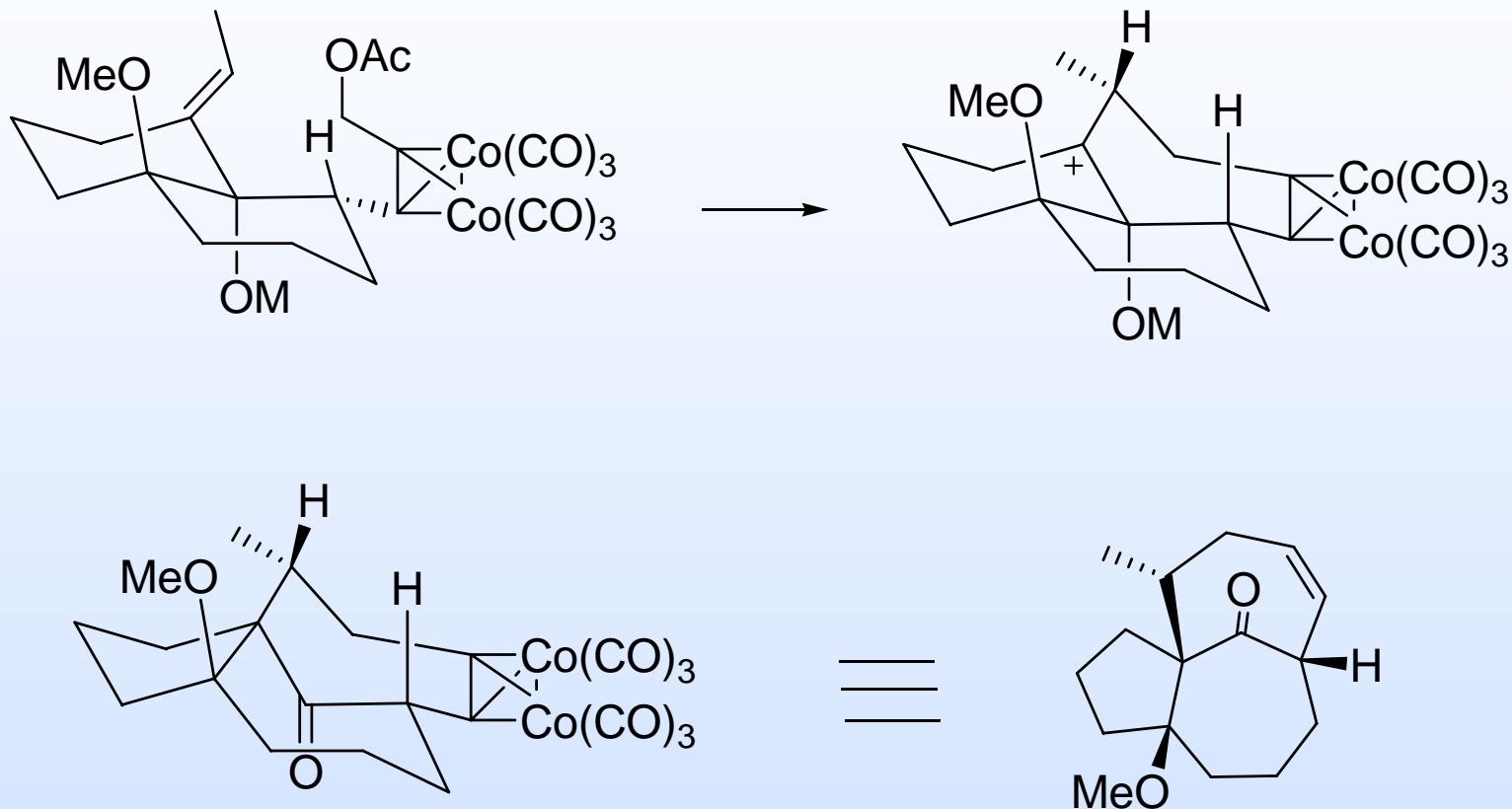
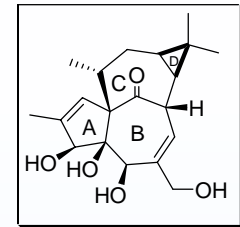


Tanino-Kwajima Approach

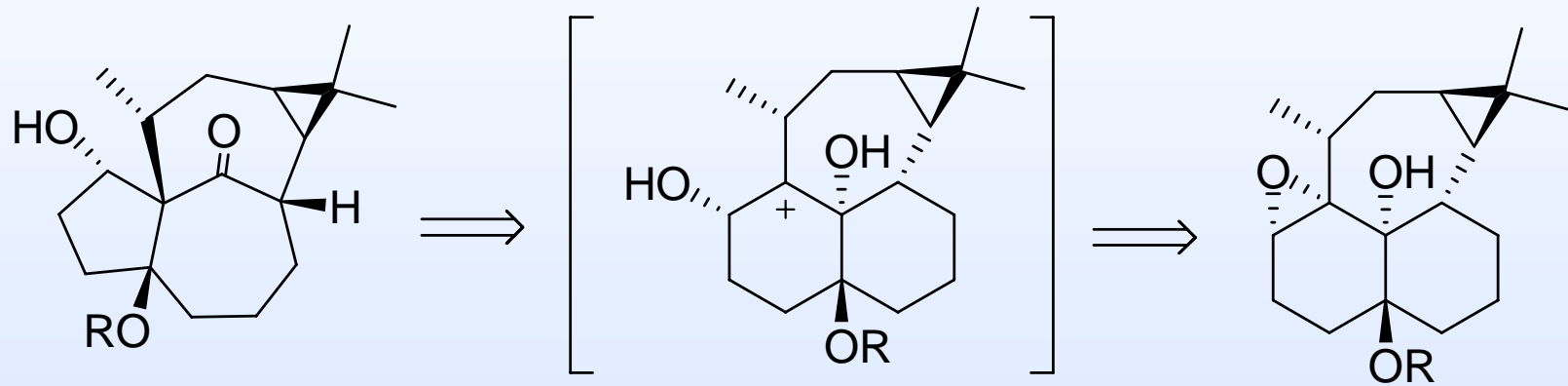
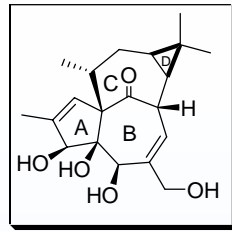


Me_2AlCl	50%	
$\text{Me}_2\text{Al}(\text{OTf})$	69%	13%
$\text{MeAl}(\text{OCOCF}_3)(\text{OAr})$	21%	77%

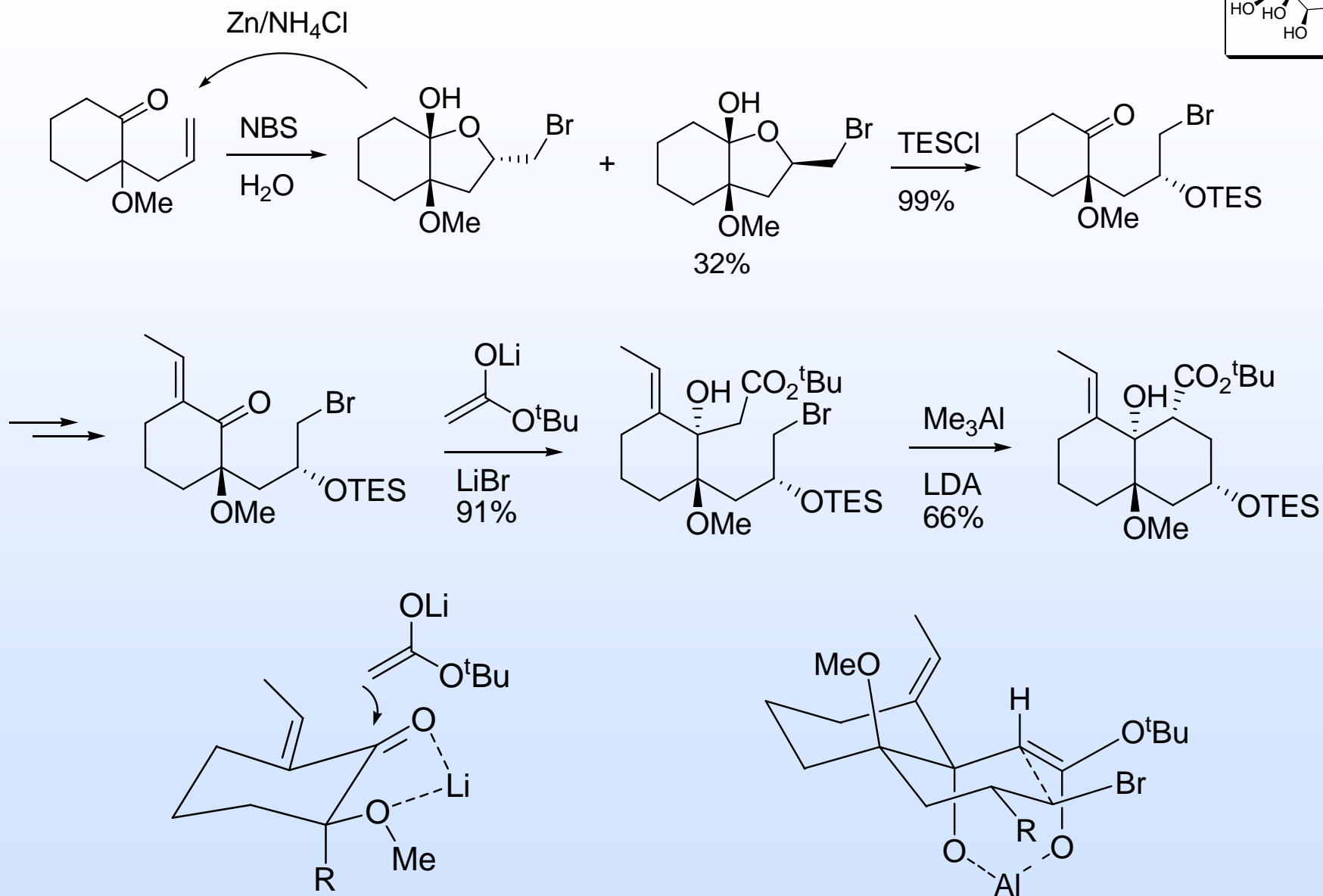
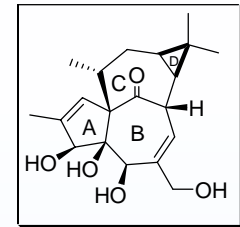
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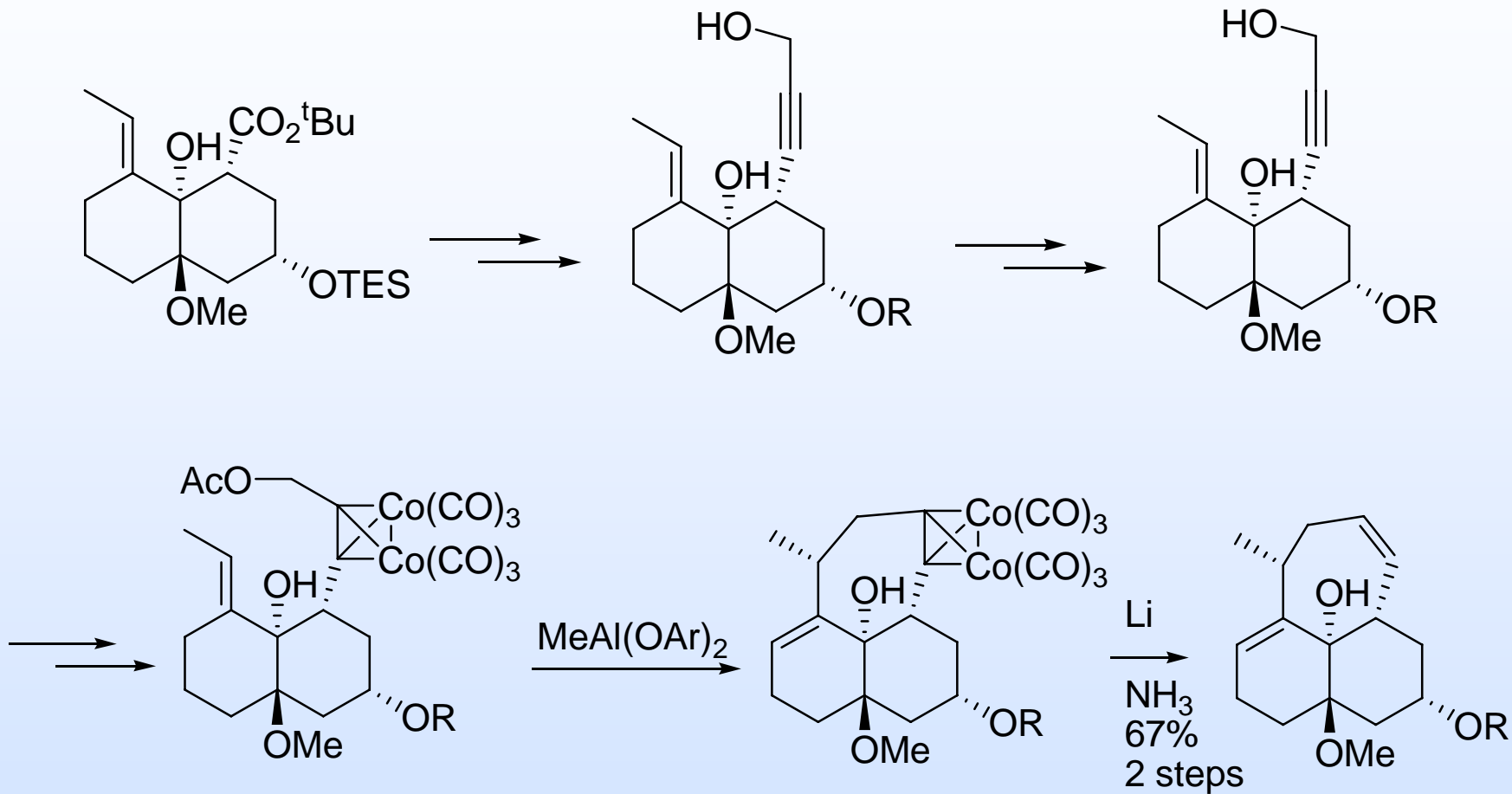
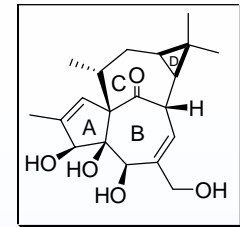
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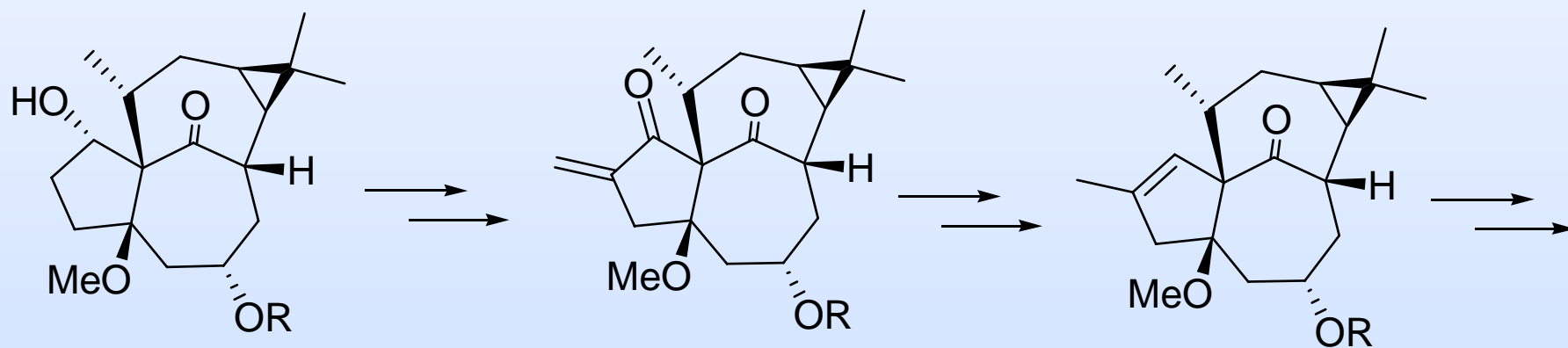
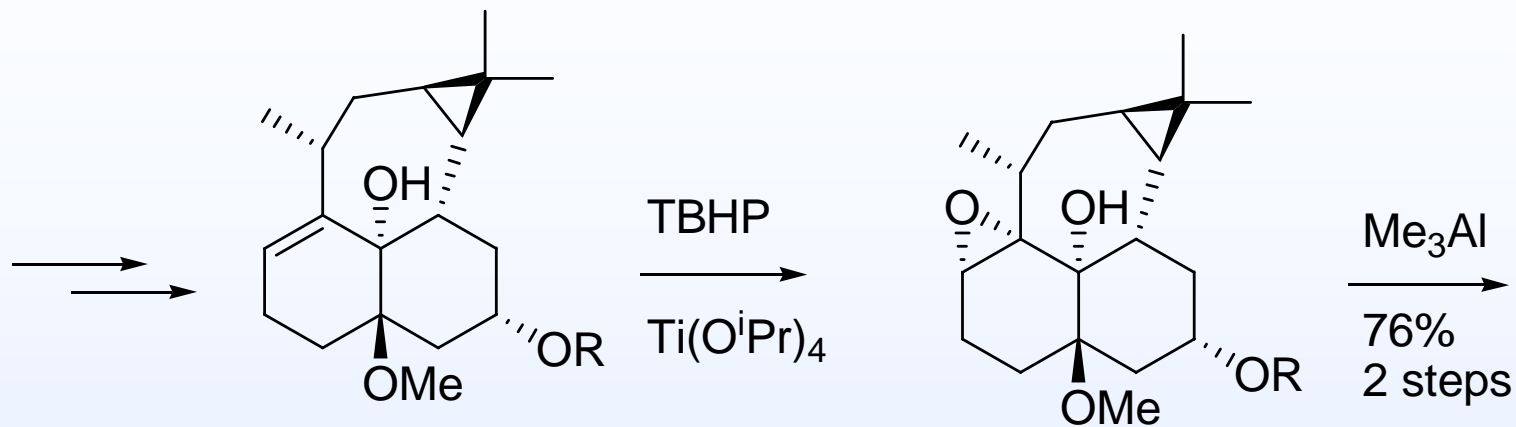
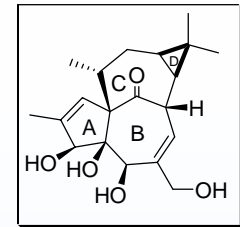
Tanino-Kwajima Synthesis



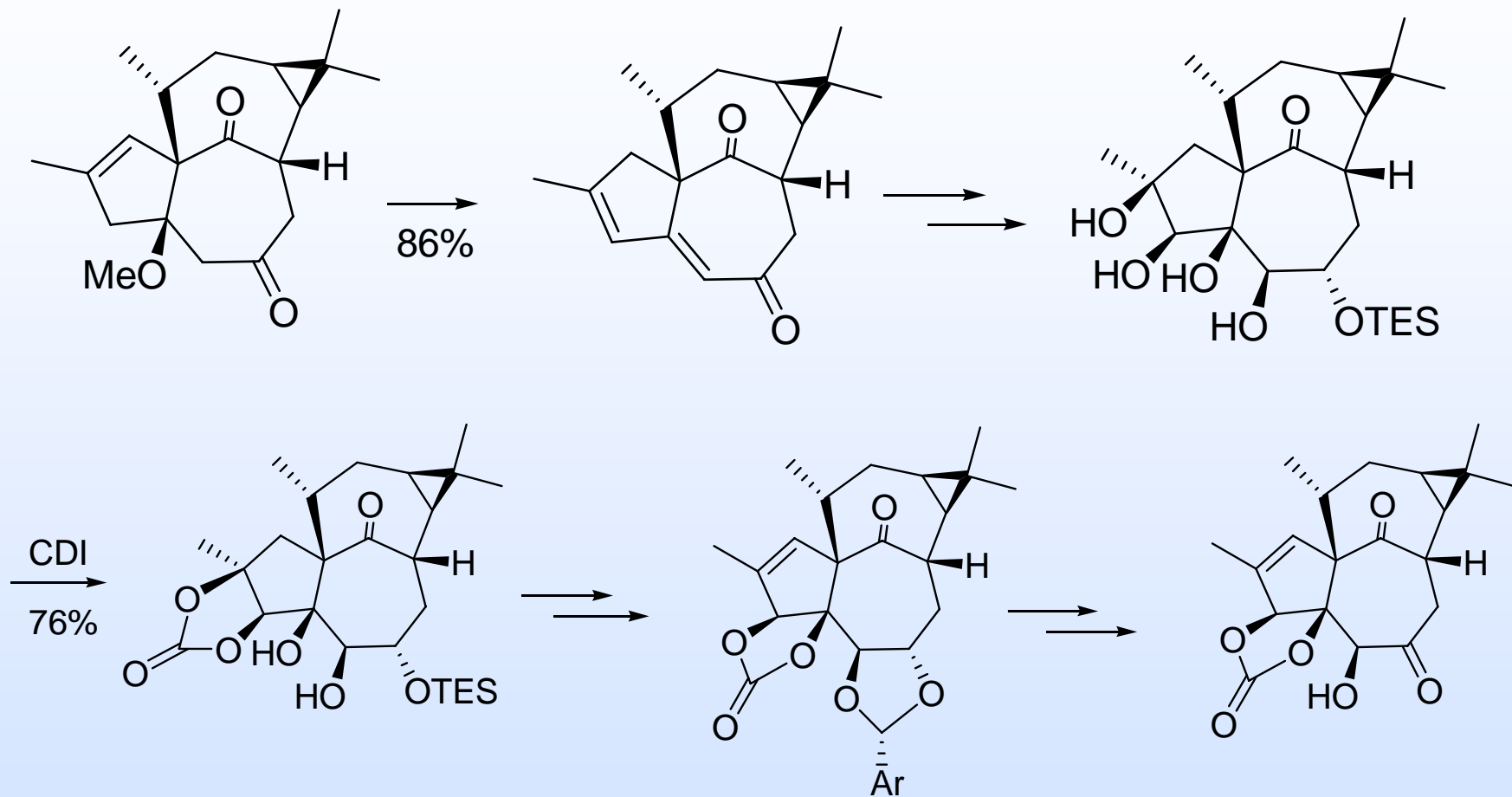
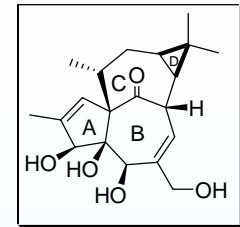
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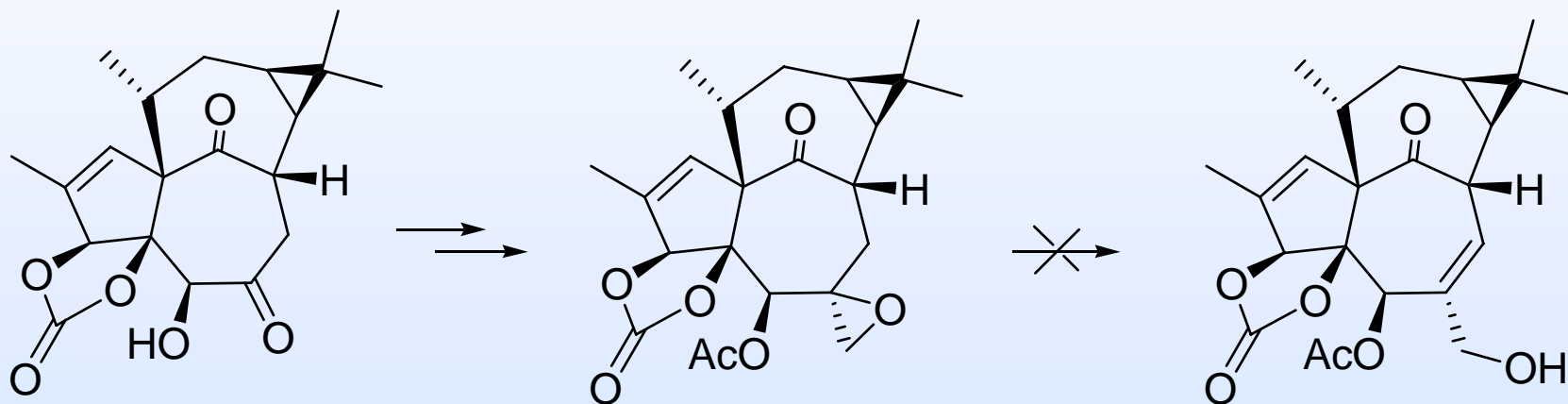
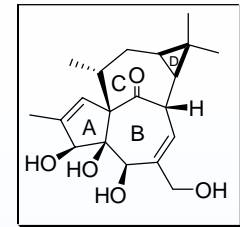
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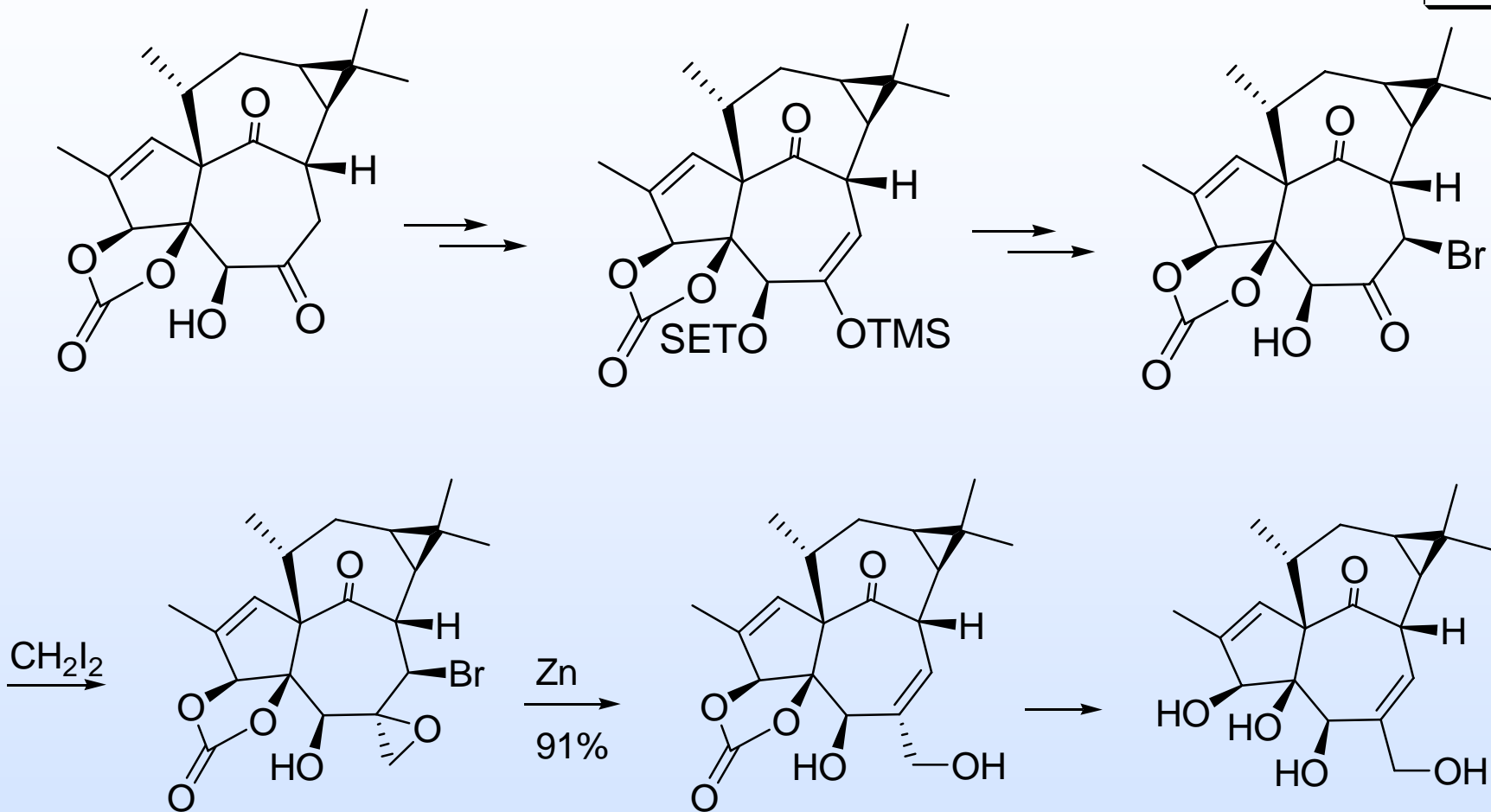
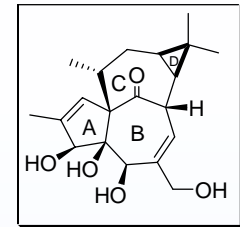
Tanino-Kwajima Synthesis



Tanino-Kwajima Synthesis

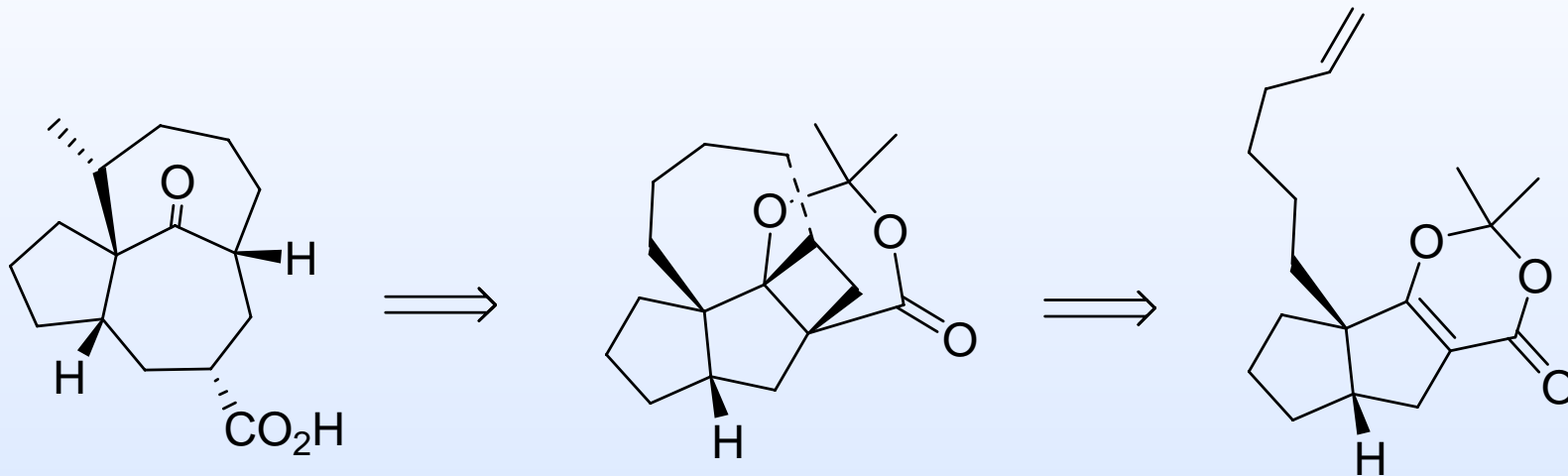
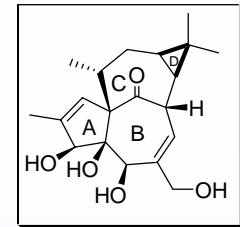


Tanino-Kwajima Synthesis

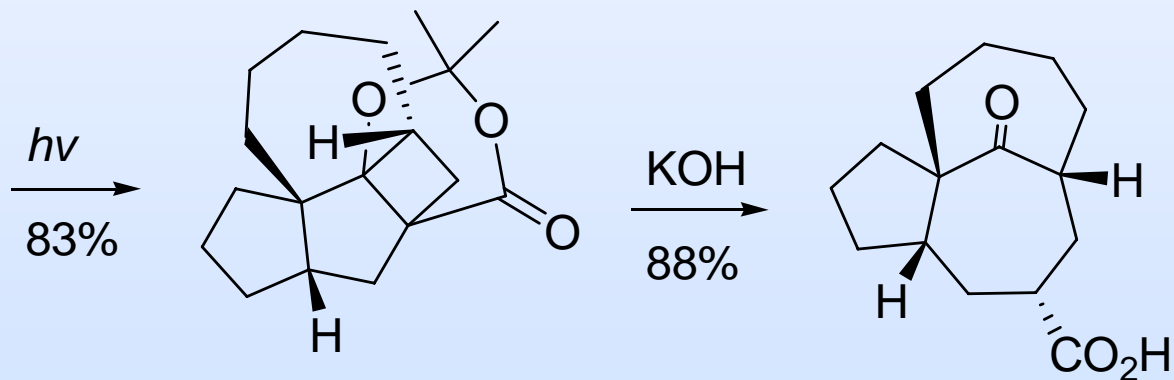
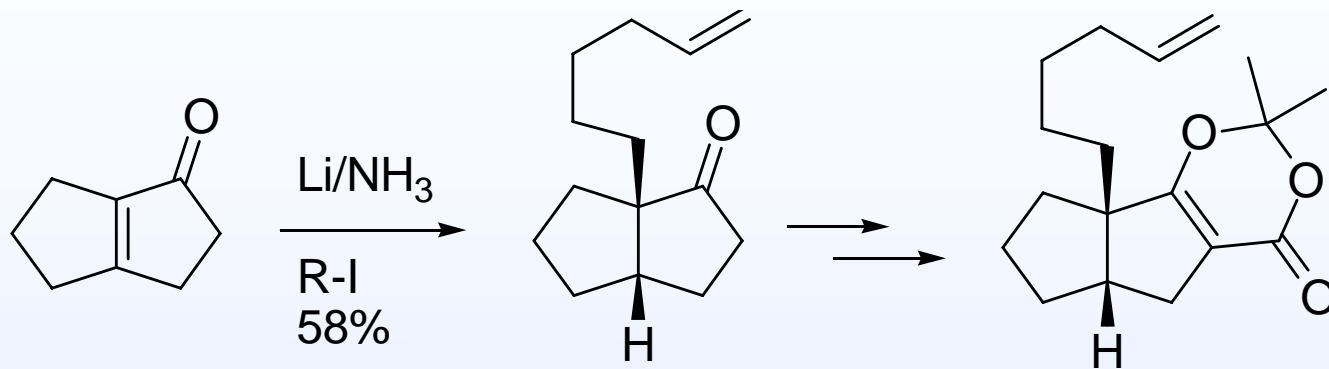
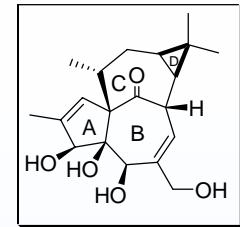


45 steps
0.03% yield

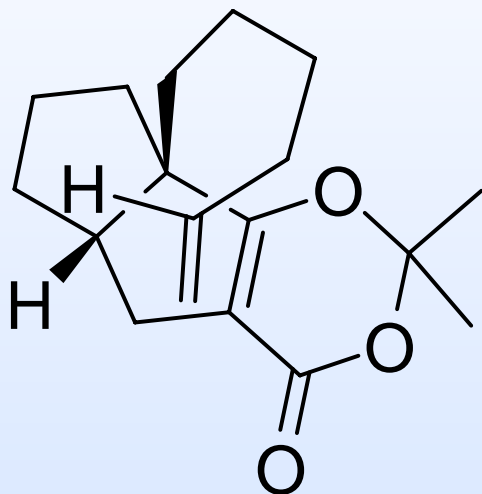
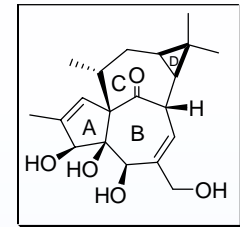
Winkler Approach



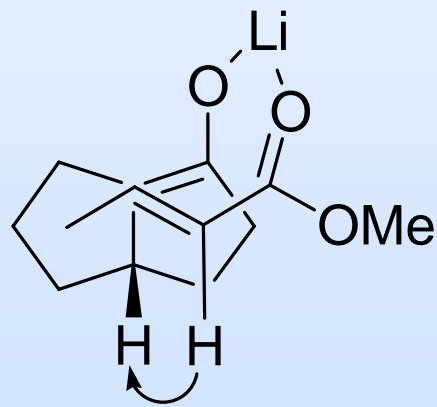
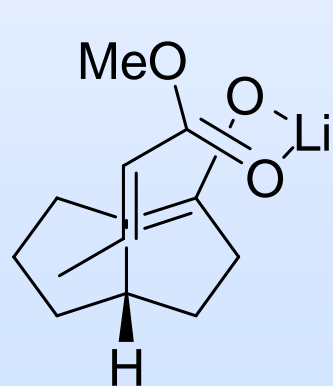
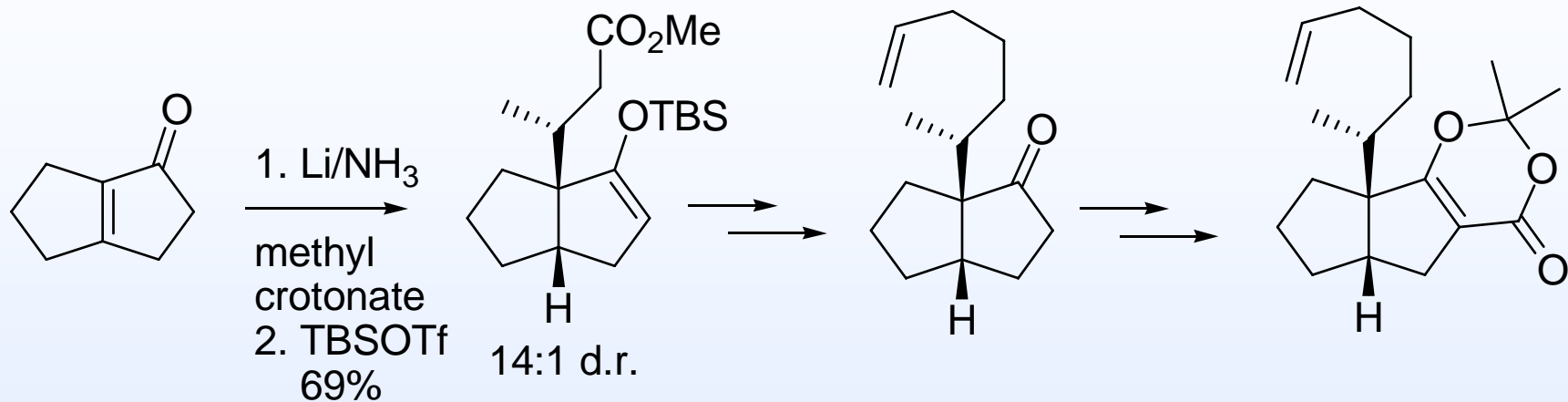
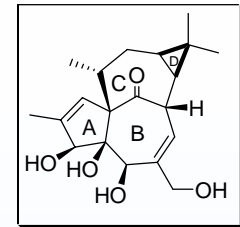
Winkler Approach



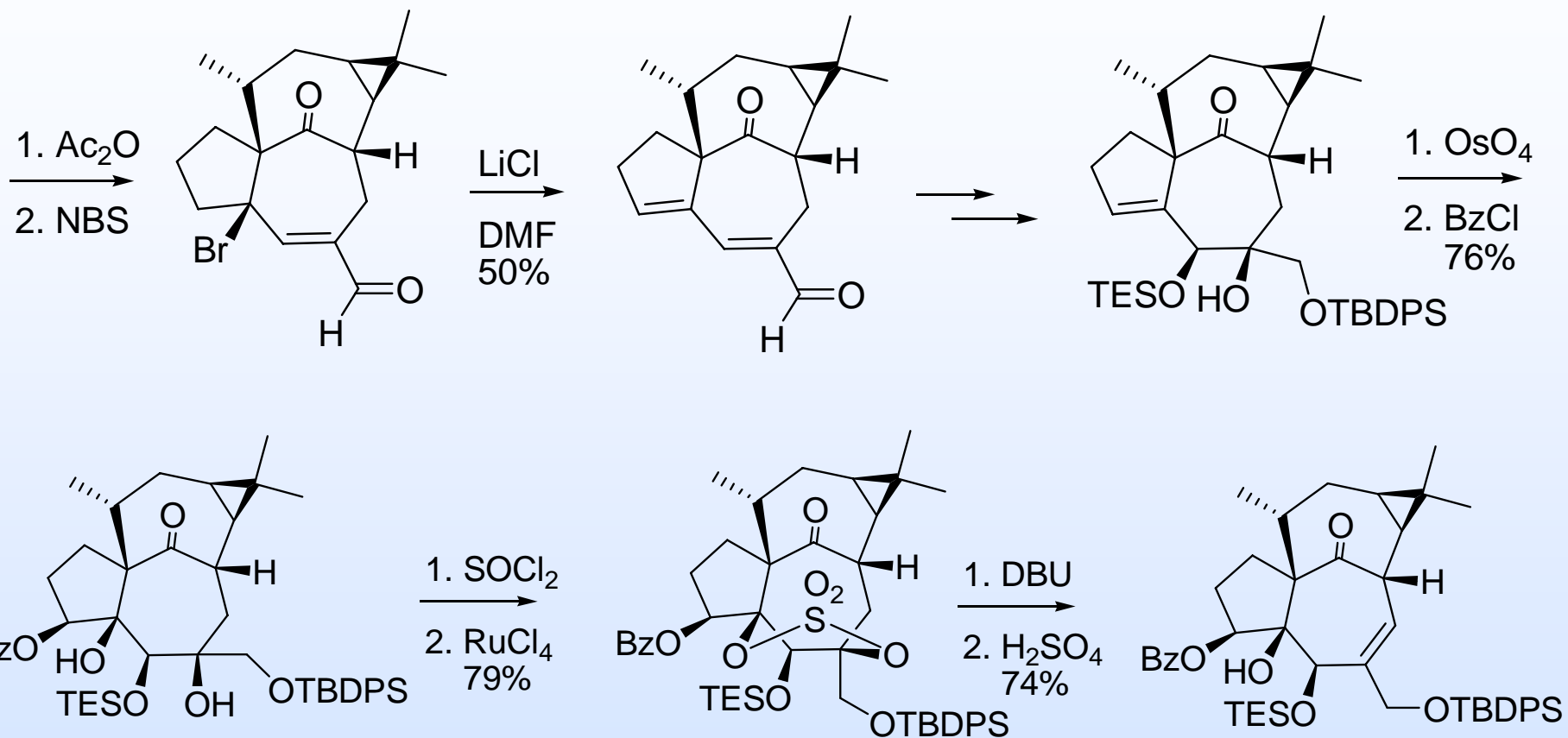
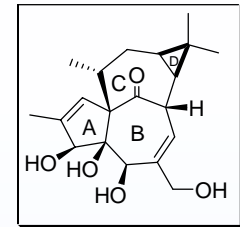
Winkler Approach



Winkler Synthesis



Winkler Synthesis



Winkler Synthesis

