

# Medicinal Chemistry: An Overview

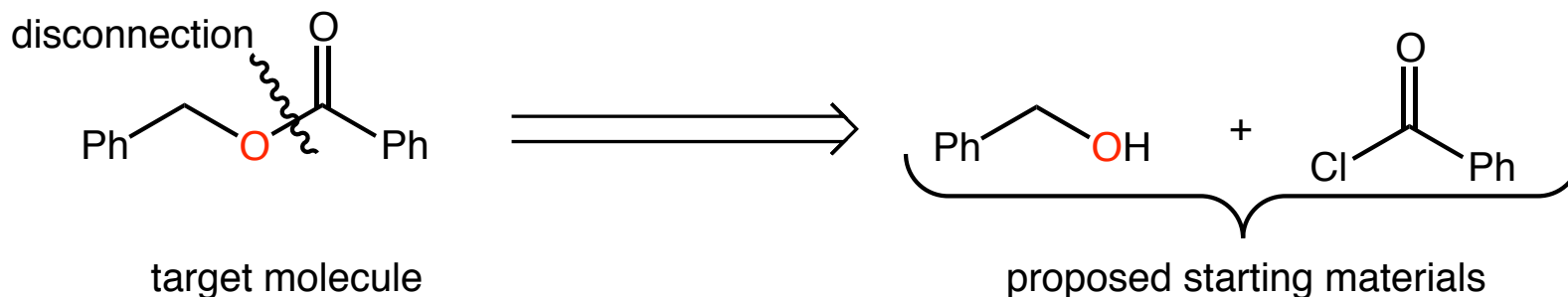
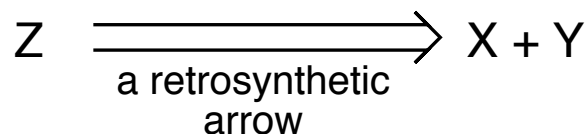
## Course Outline

Lecture	Date	Topic
1	2015/12/17	General Aspects of Medicinal Chemistry
2	2016/01/07	General Biochemistry
3	2016/01/21	Principles of Chemical Synthesis
4	2016/02/04	Chemical Synthesis of Small and Complex Molecules
5	2016/02/18	Chemical Synthesis of Peptides
6	2016/04/07	Strategies for Discovery of Lead Compounds
7	2016/04/14	Structure Activity Relationship
8	2016/04/21	Spatial Organization, Receptor Mapping and Molecular Modeling
9	2016/04/28	Pharmacokinetic Properties
10	2016/05/12	Legal and Economic Aspects of Drug Development

# Retrosynthesis

*Retrosynthesis* is the process of working backwards from the target compound to readily available starting materials.

The art of planning the synthesis of a target molecule is called *retrosynthetic analysis*.



Should the bond disconnections correspond to known reliable reactions?

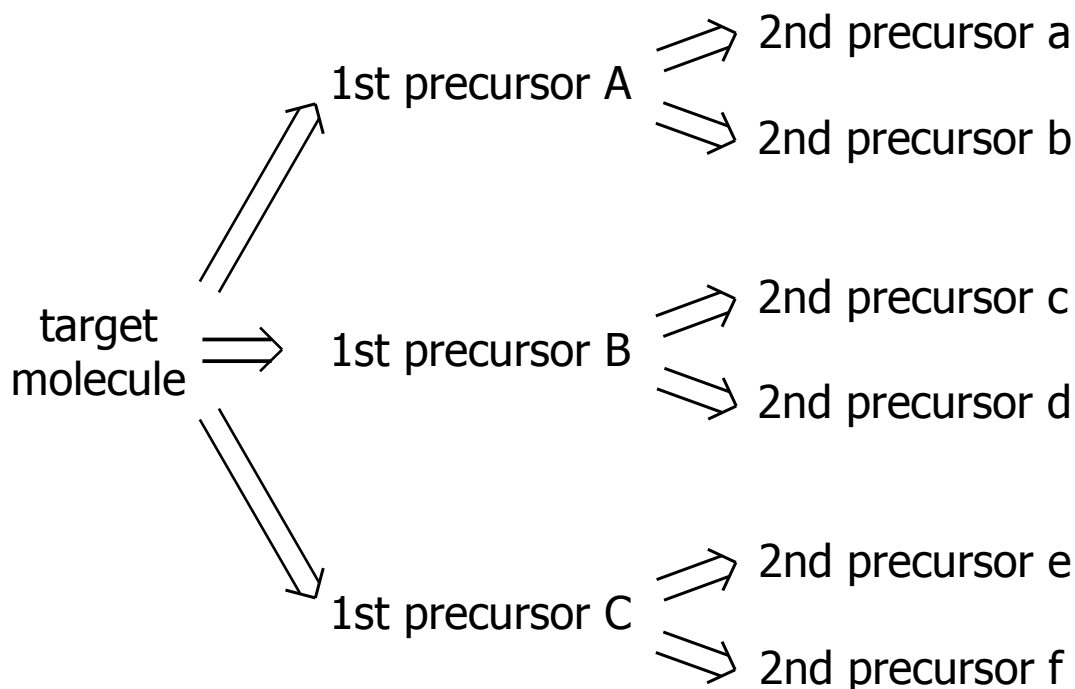
Disconnect next to the heteroatom for molecules joined together by an heteroatom

Disconnect reactive groups first.

Propose other disconnections.

# Retrosynthetic Analysis

- ❖ When doing retrosynthetic analysis, it is necessary to generate as many possible precursors, hence different synthetic routes, as possible.



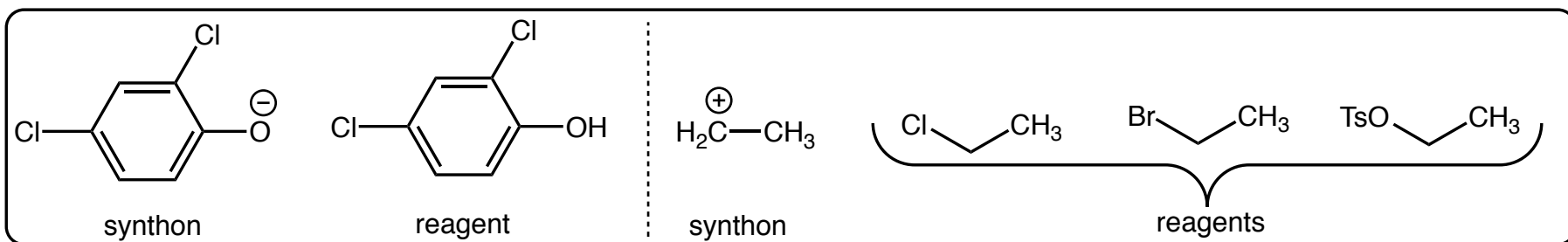
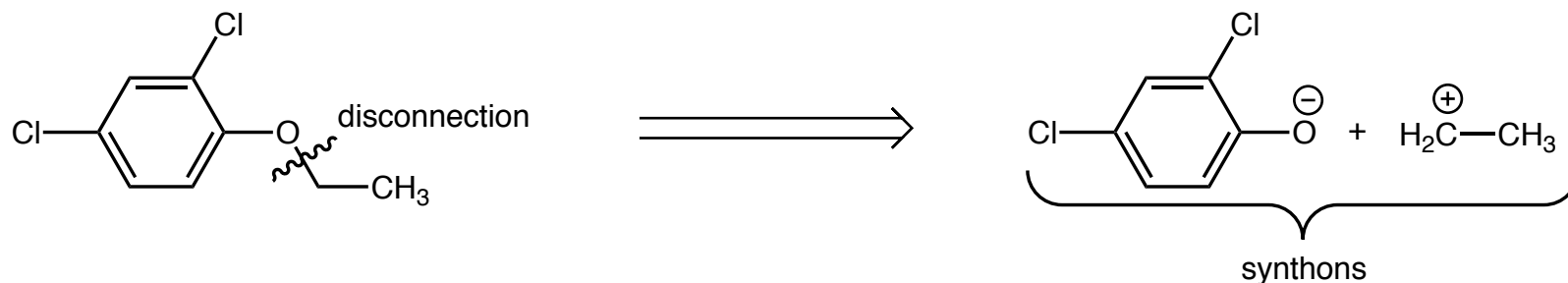
Elias James Corey  
Nobel Prize in Chemistry (1990)  
*"for his development of the theory and methodology of organic synthesis".*

# Synthons & Reagents

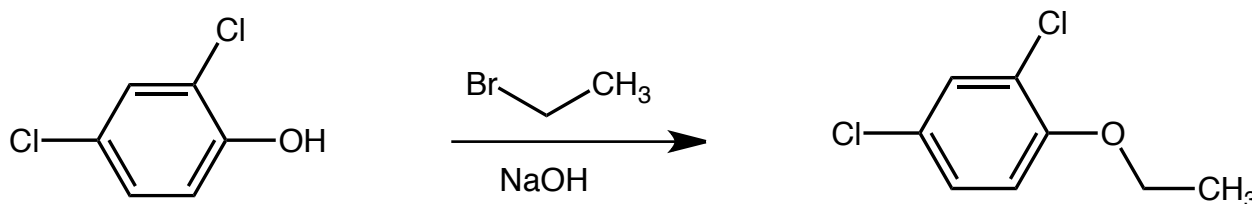
A synthon is an idealized fragment resulting from a disconnection while a reagent is a real chemical compound used in the synthesis.

Synthons need to be replaced by reagents in the proposed synthesis.

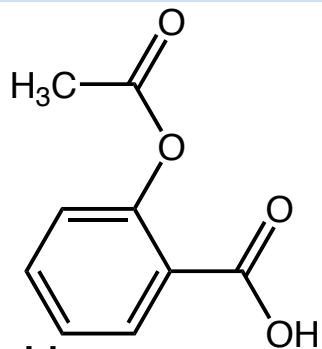
## Retrosynthesis



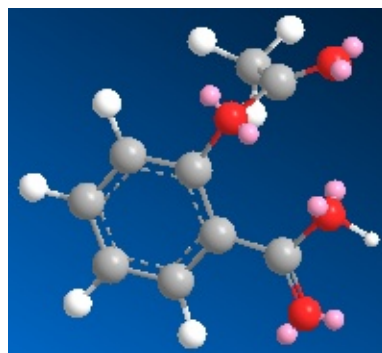
## Synthesis



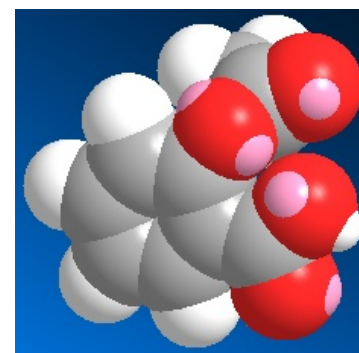
# Acetylsalicylic Acid (Aspirin)



**Aspirin**  
(pain reliever; anticlotting agent)

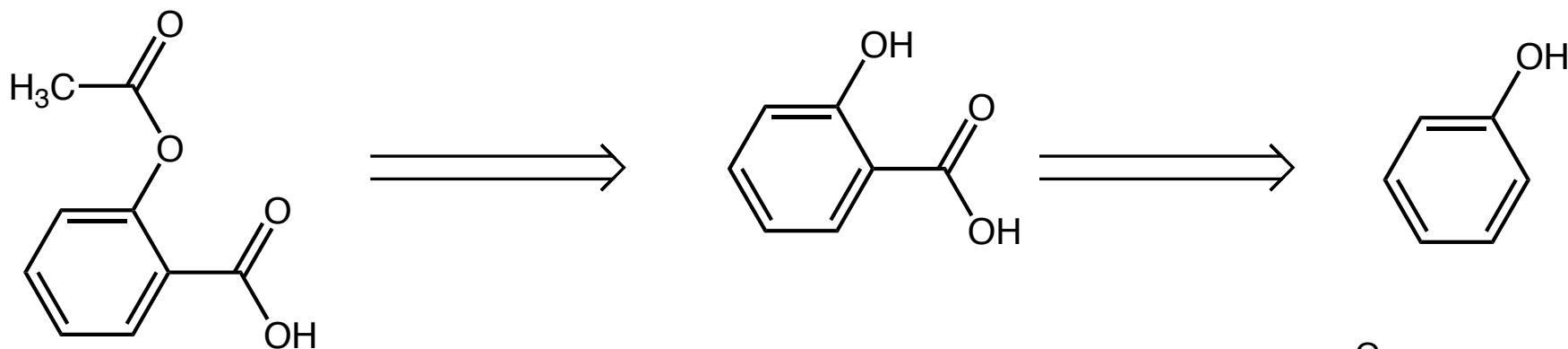


Ball-and-Stick Model

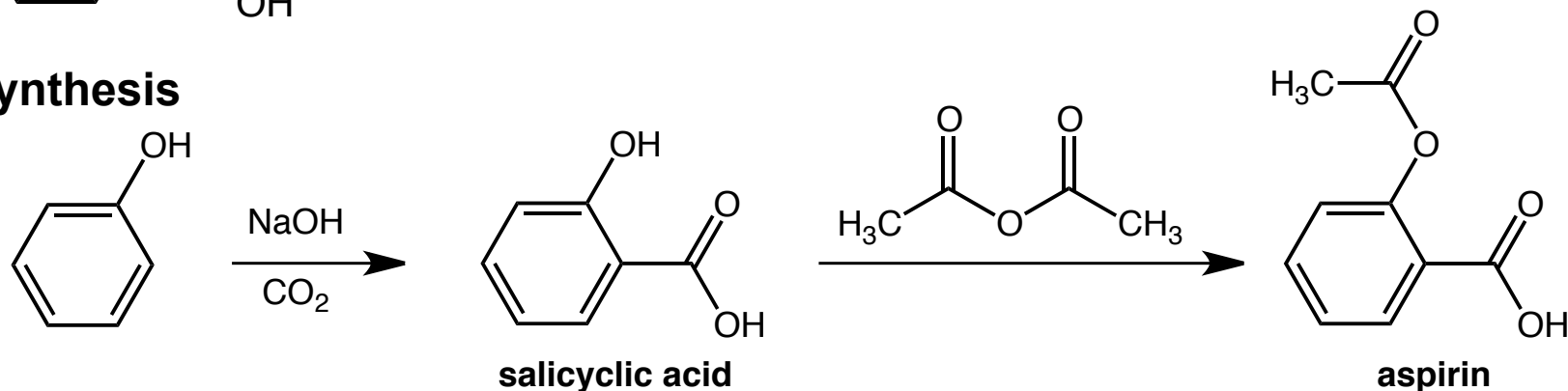


Space-filling Model

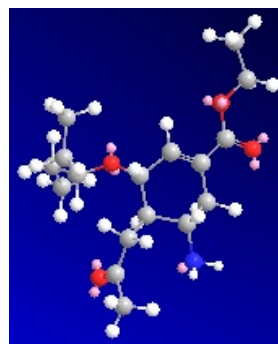
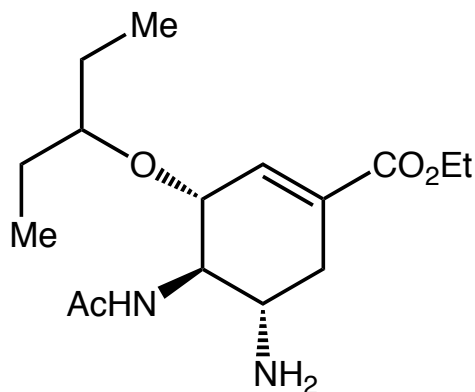
## Retrosynthesis



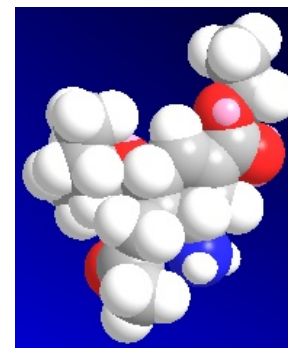
## Synthesis



# Oseltamivir (Tamiflu)



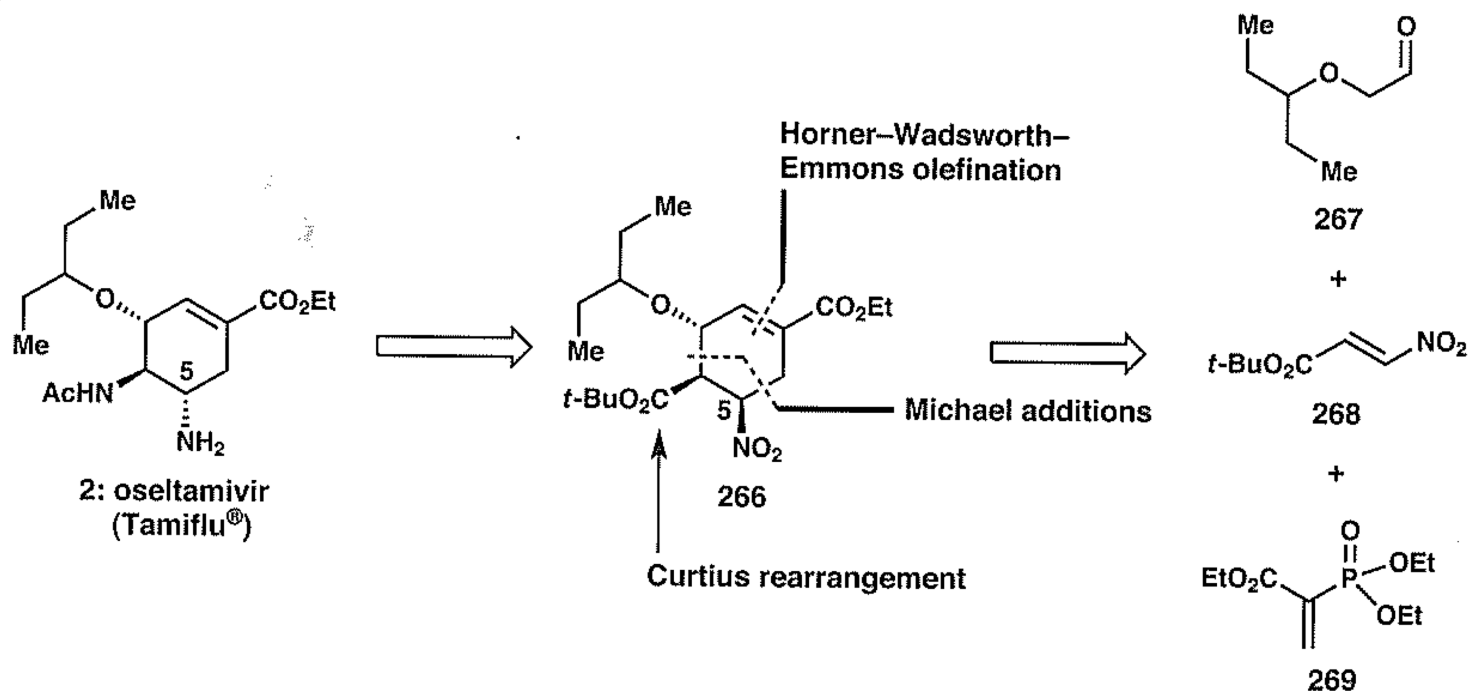
Ball-and-Stick Model



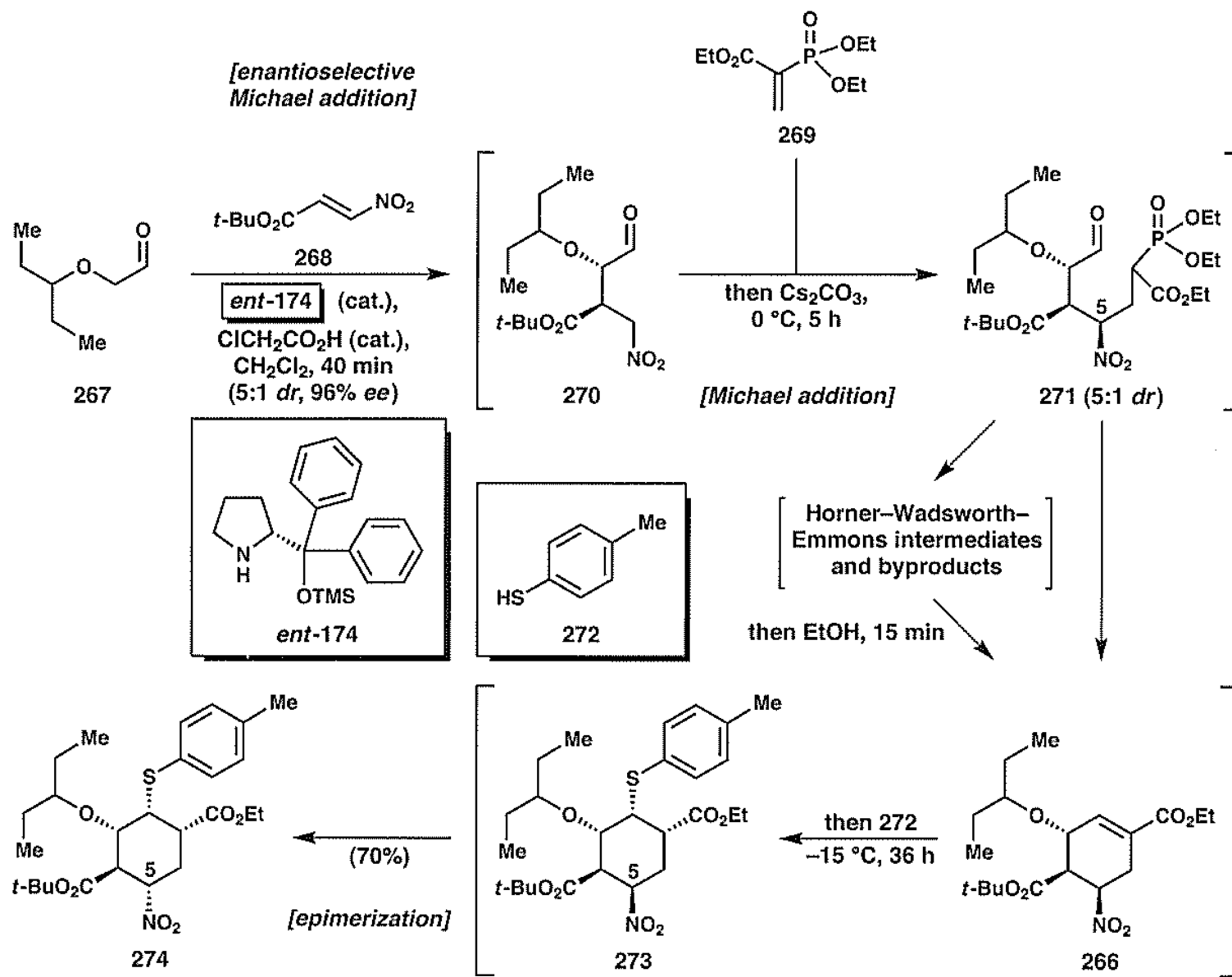
Space-filling Model

Oseltamivir is a neuraminidase inhibitor used for the treatment of influenza A and B viral infections.

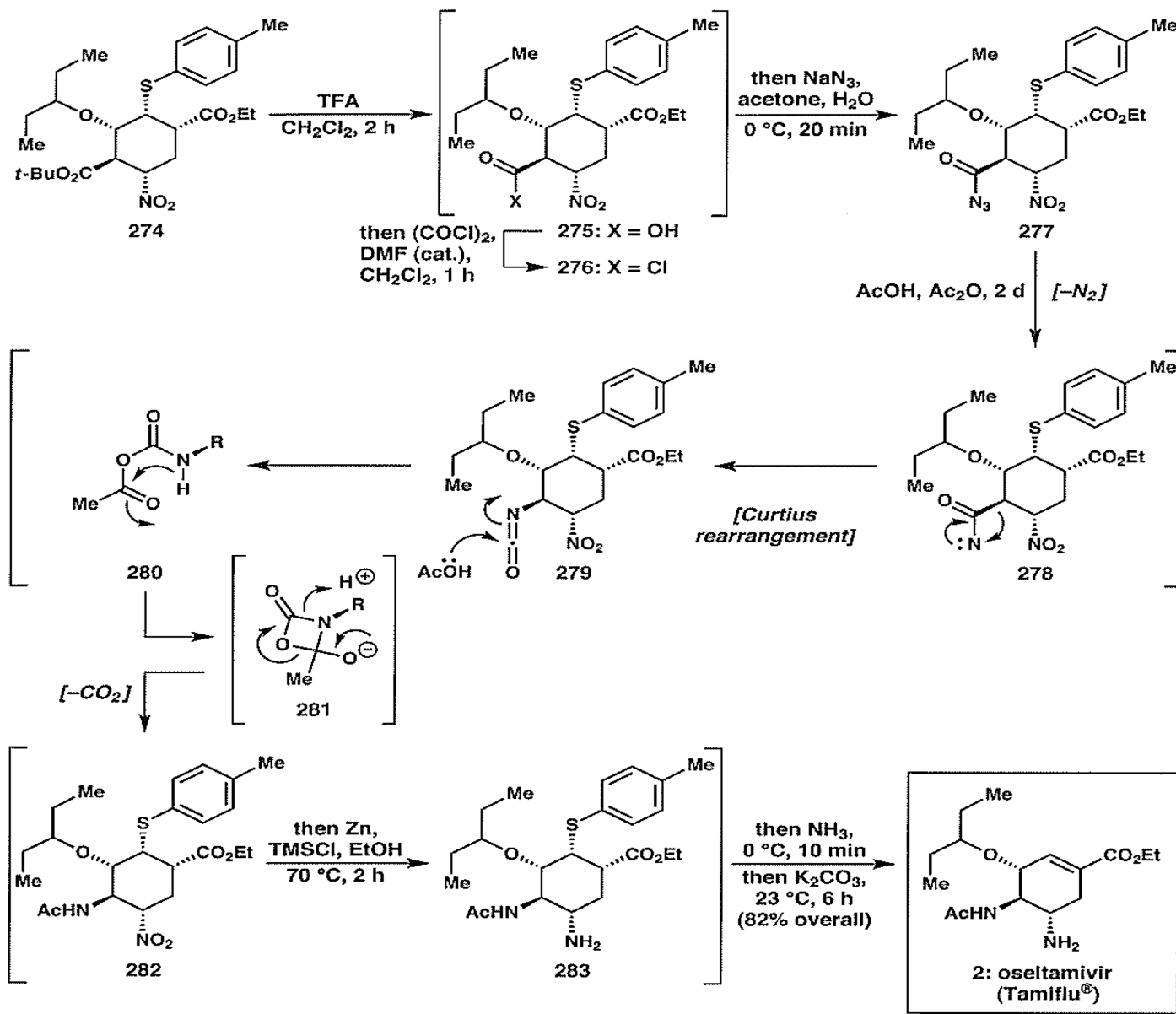
## Retrosynthesis



# Synthesis of Intermediate 274

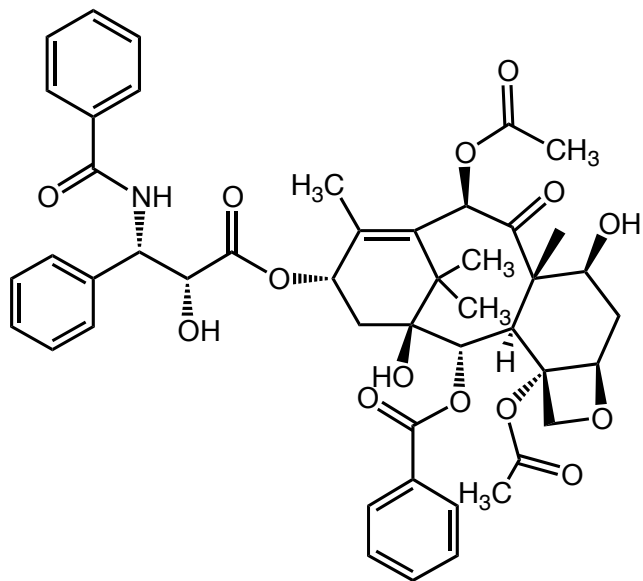


# Synthesis of Oseltamivir





# Paclitaxel (Taxol)



Isolated from Pacific Yew tree

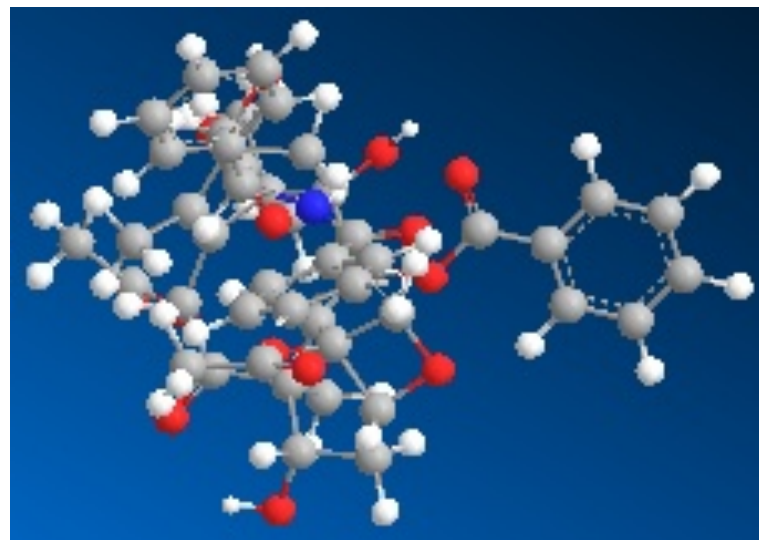
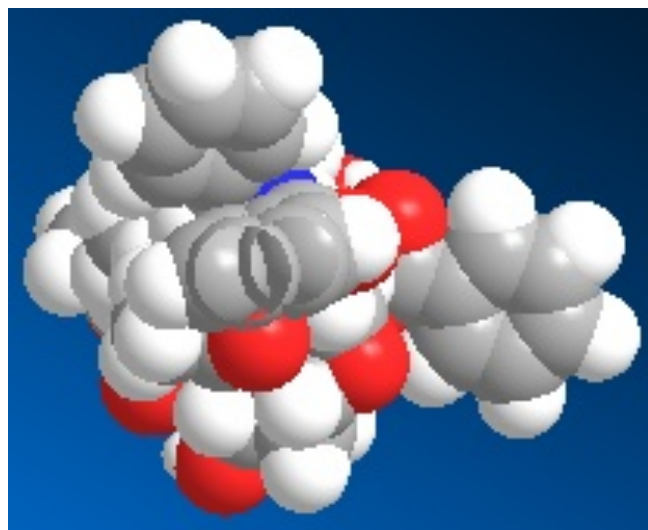
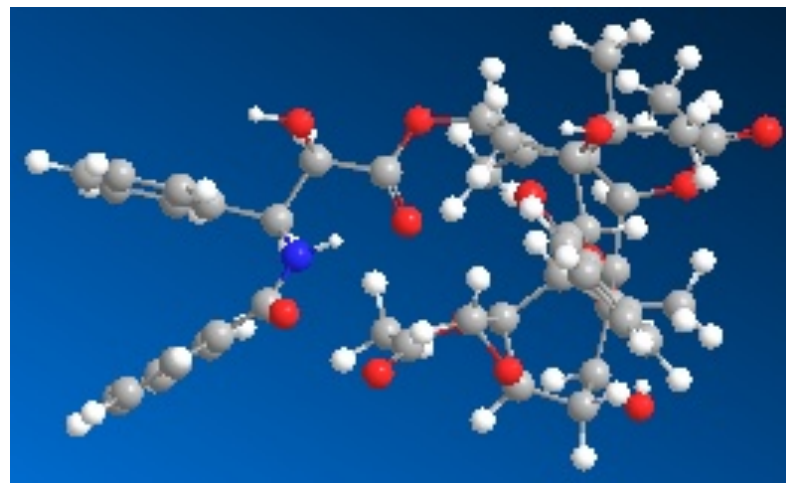
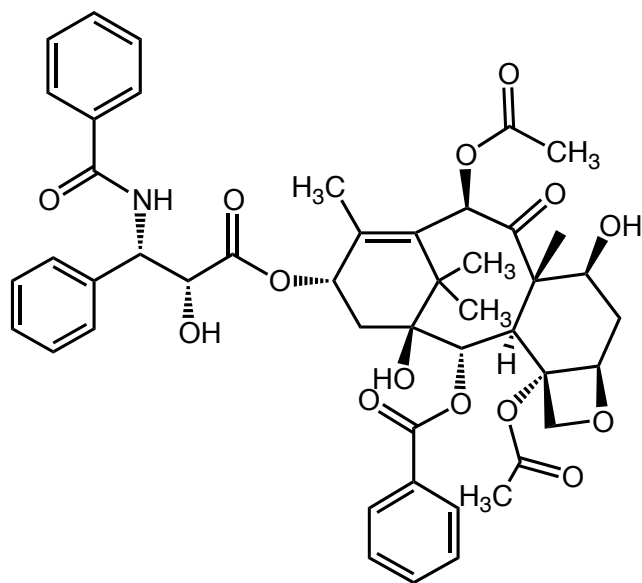


Approved by the U.S. Food & Drug Administration in 1992 for treatment of several types of cancer, including breast cancer, lung cancer, and melanoma.

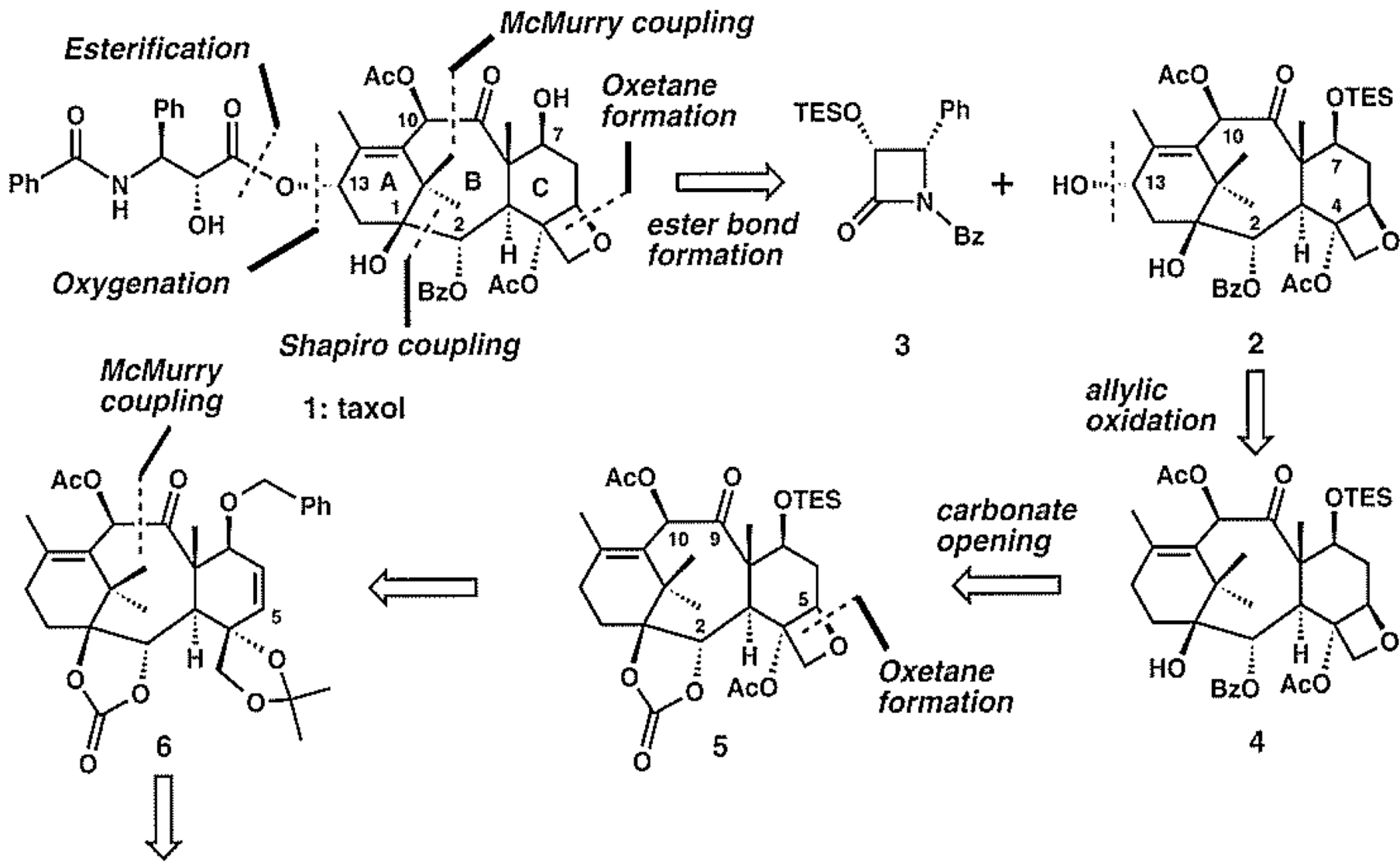
An estimation: a 100-year old yew tree must be sacrificed in order to obtain 300 mg of Taxol, just enough for one single dose for a cancer patient.

Obviously, synthetic organic chemistry methods that would lead to the synthesis of Taxol would be extremely useful.

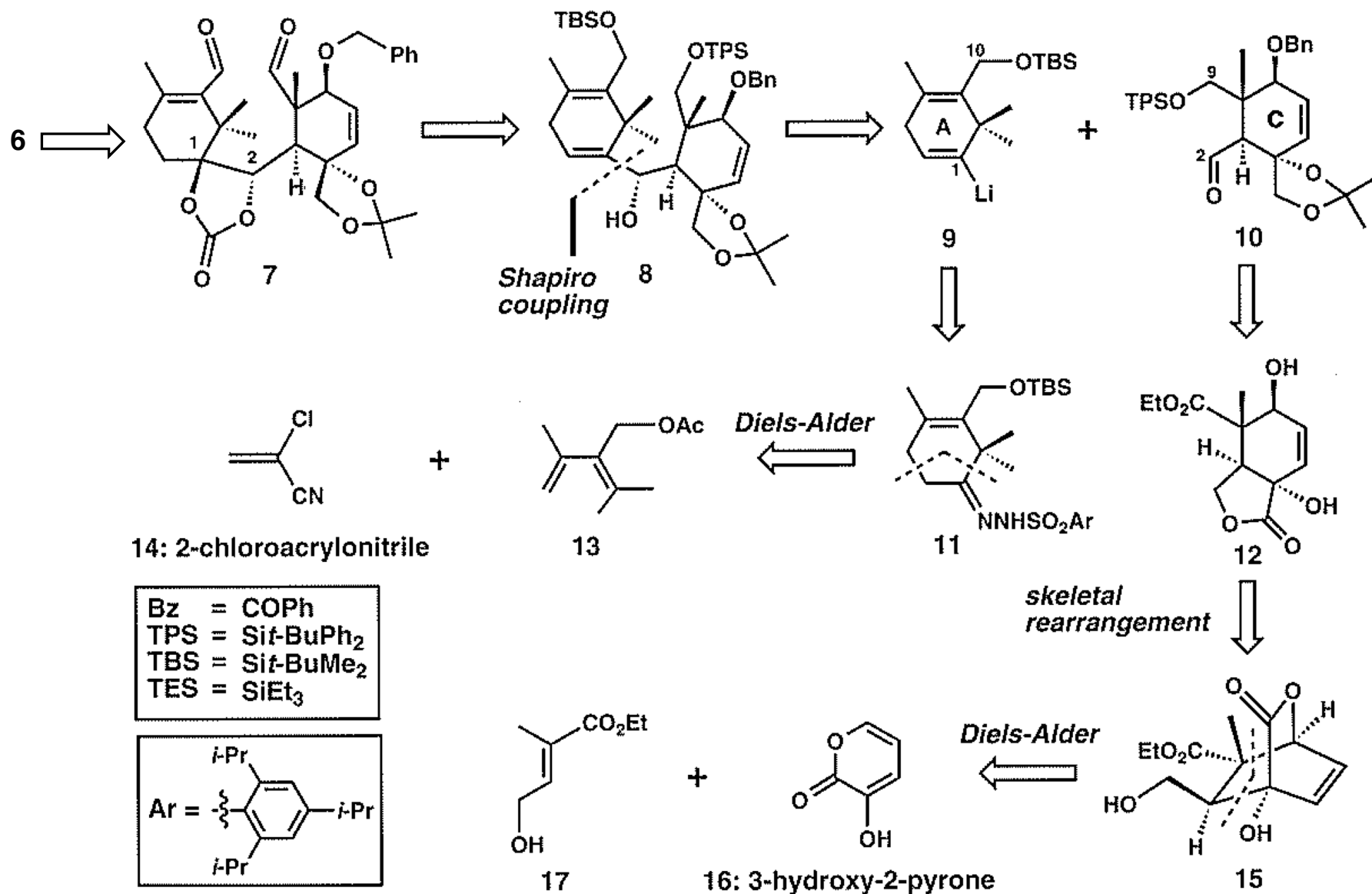
# Paclitaxel (Taxol)



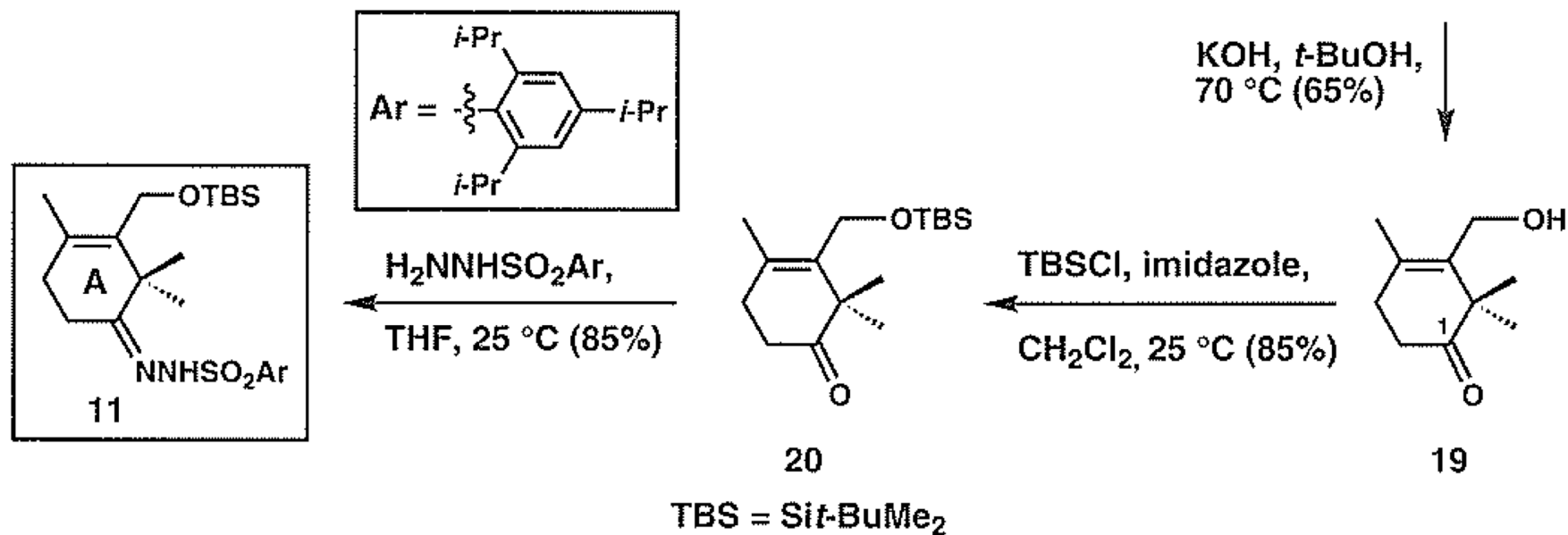
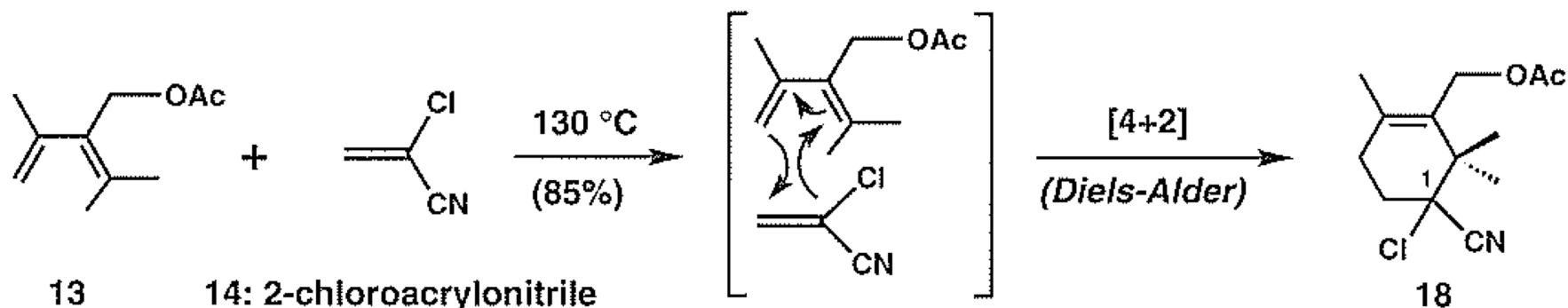
# Retrosynthesis of Taxol (1)



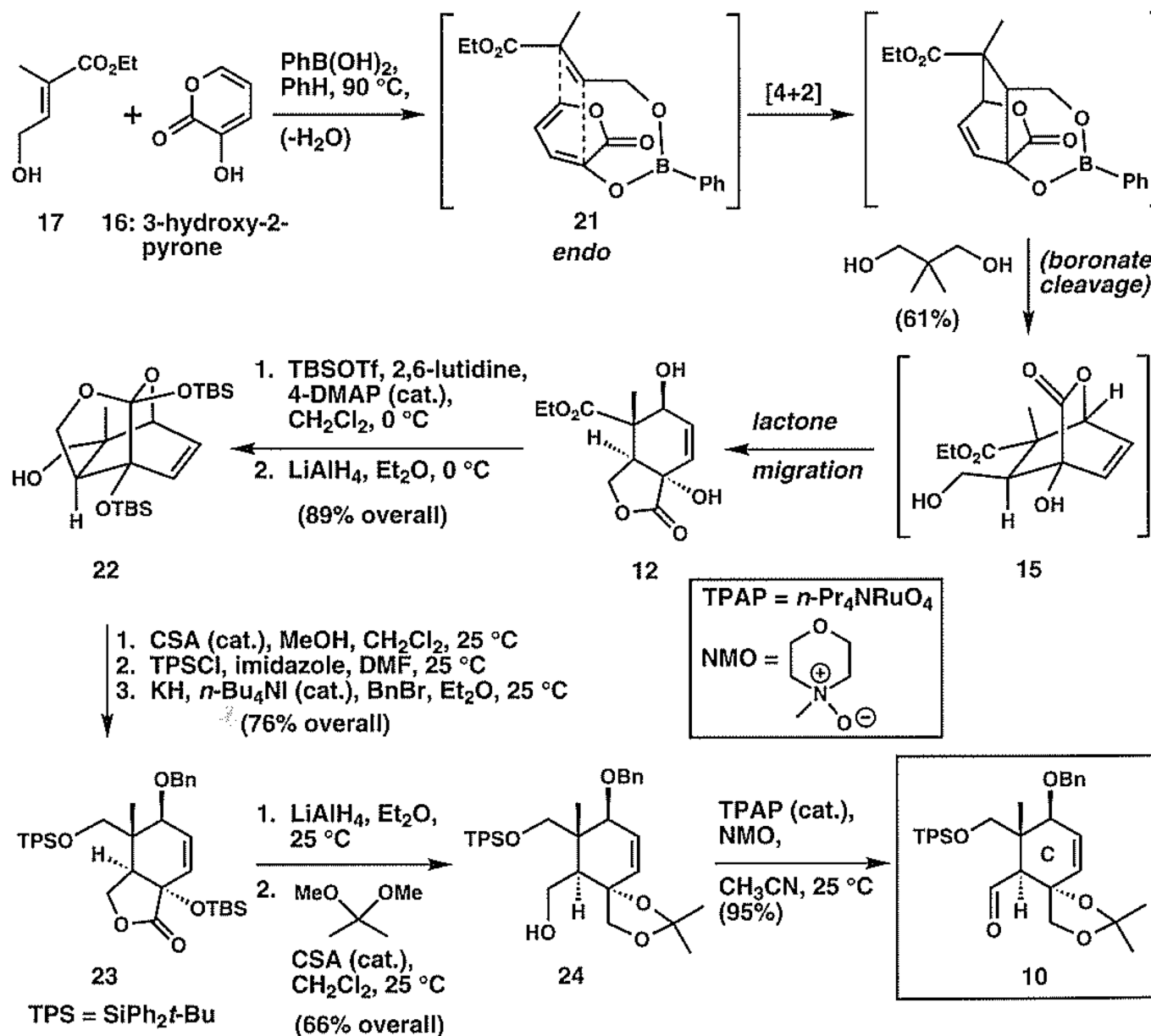
# Retrosynthesis of Taxol (2)



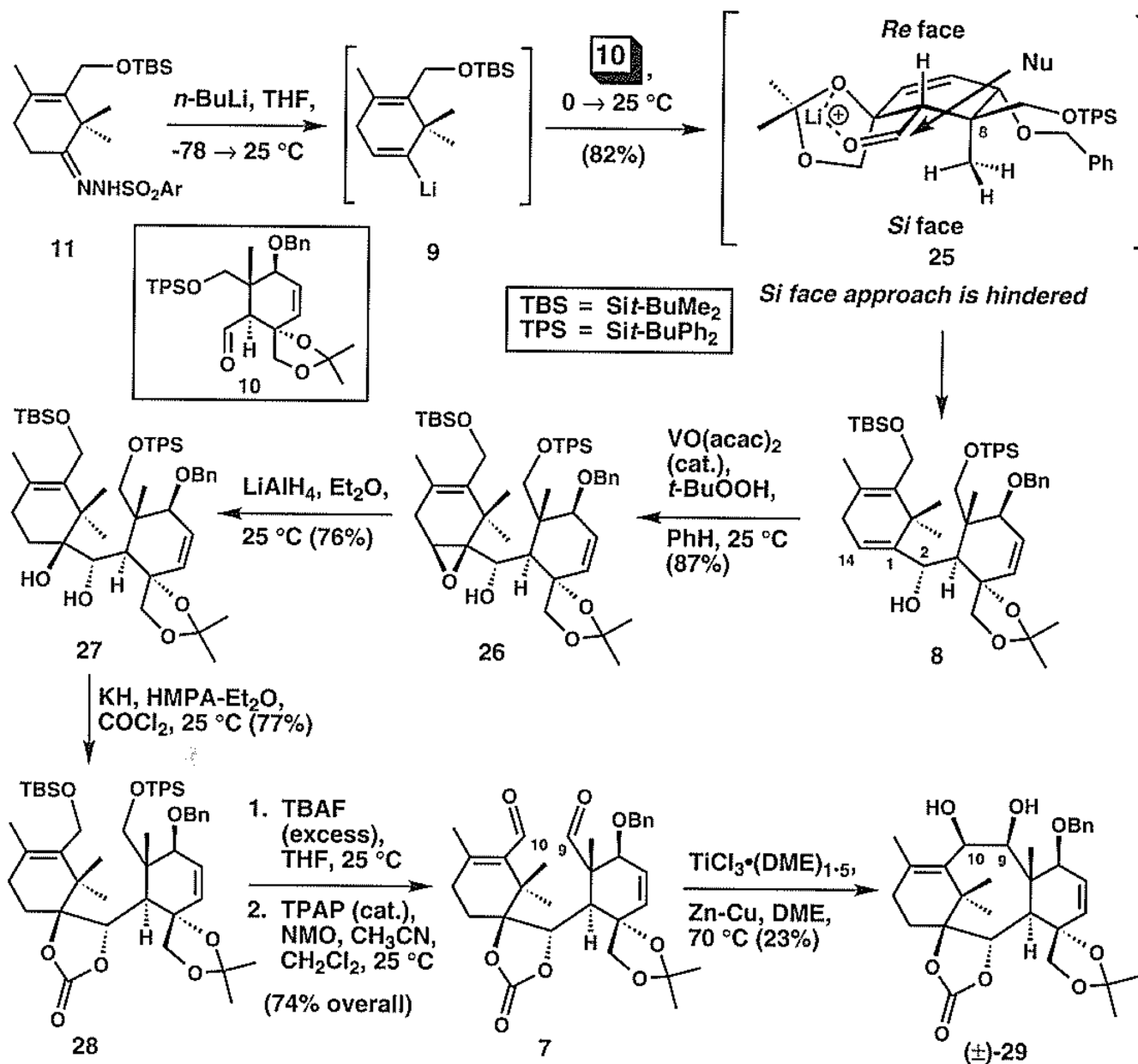
# Synthesis of Hydrazone 11



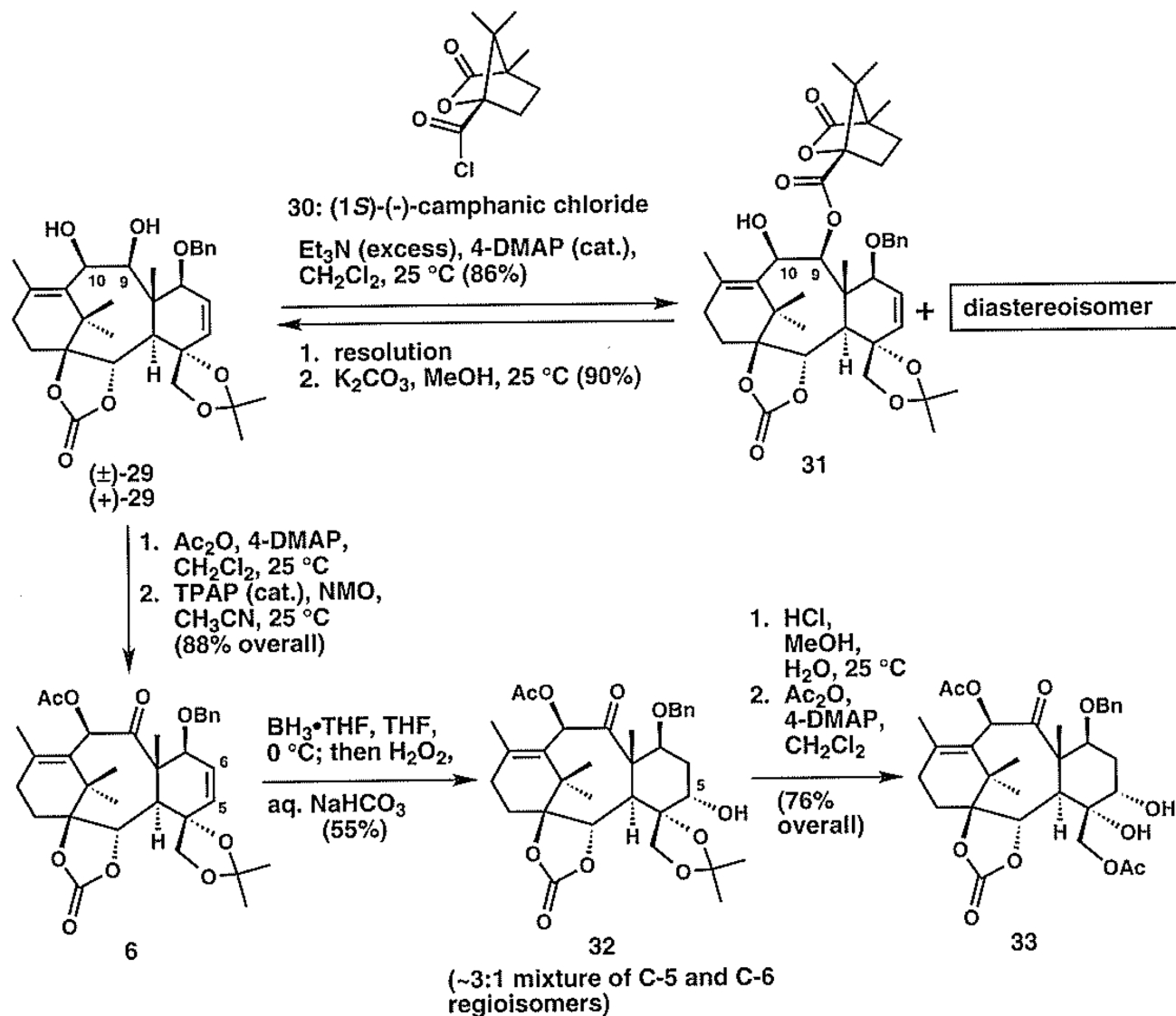
# Synthesis of Aldehyde 10



# Racemic Synthesis of Intermediate 29

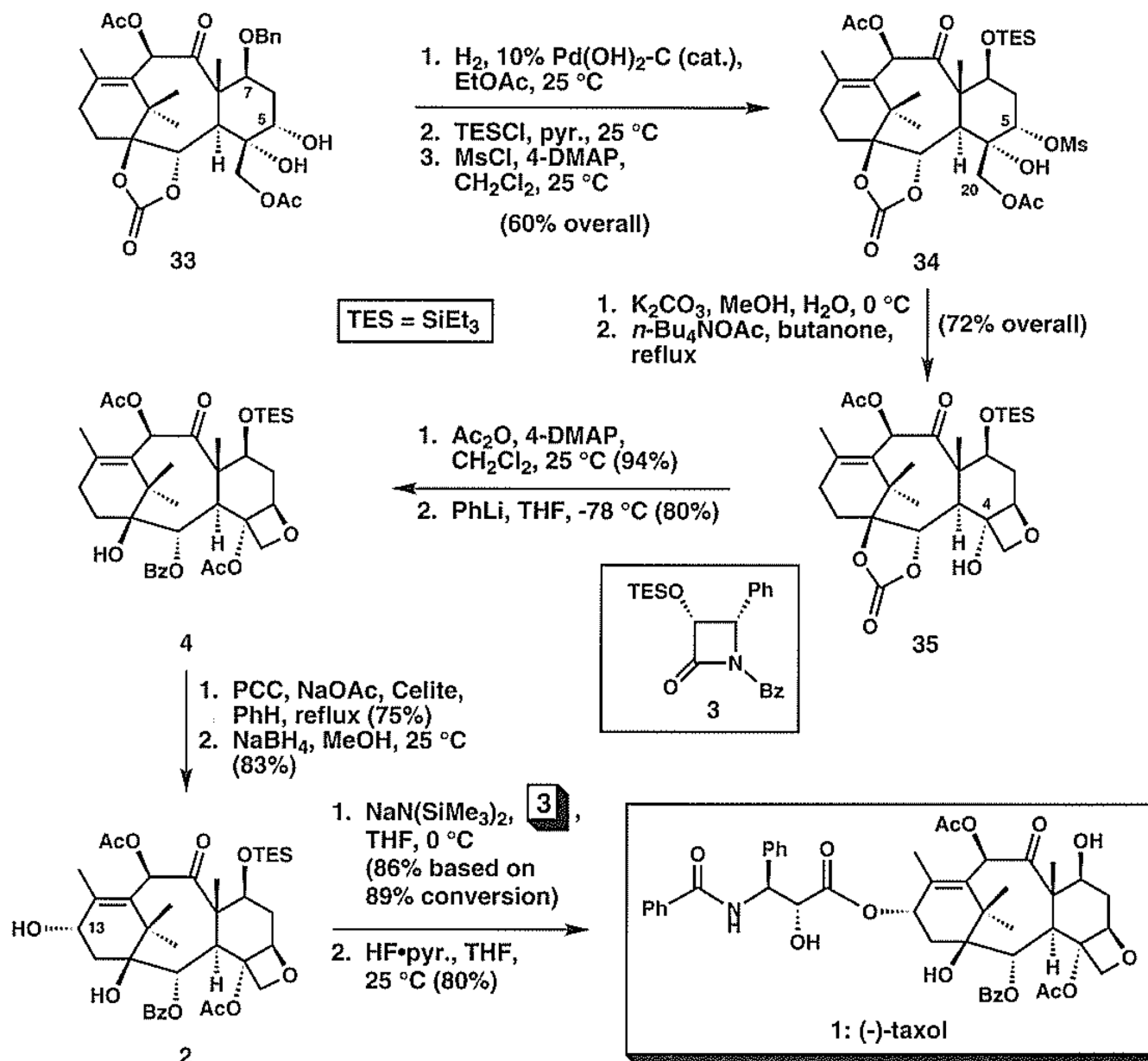


# Resolution of Intermediate 29 & Synthesis of Intermediate 33





# Synthesis of Taxol



# Summary

The chemical syntheses of small and complex molecules are governed by similar principles.

An extraordinary level of creativity is required for success in the chemical synthesis of a complex molecule.

The synthesis of molecules is not a *matured* discipline.

**Next Lecture, 2016/02/18**

Chemical Synthesis of Peptides