

① Chem 634 - Lecture 1

1) Intro

2) Nucleophilic Substitution Chem  
(part 1 of many)

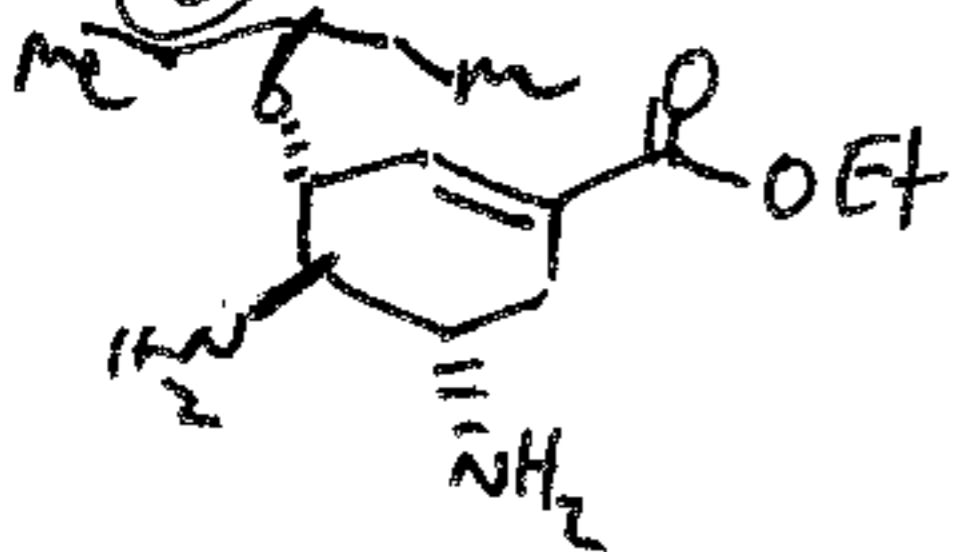
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Why organic synthesis?

- Pharma / Biology
- Electronics
- Biocoujugation - for Proteomics
- Mechanism Questions
- Inorganic Chem - Ligands
- Polymers & materials
- Agrochemicals
- Energy Problems

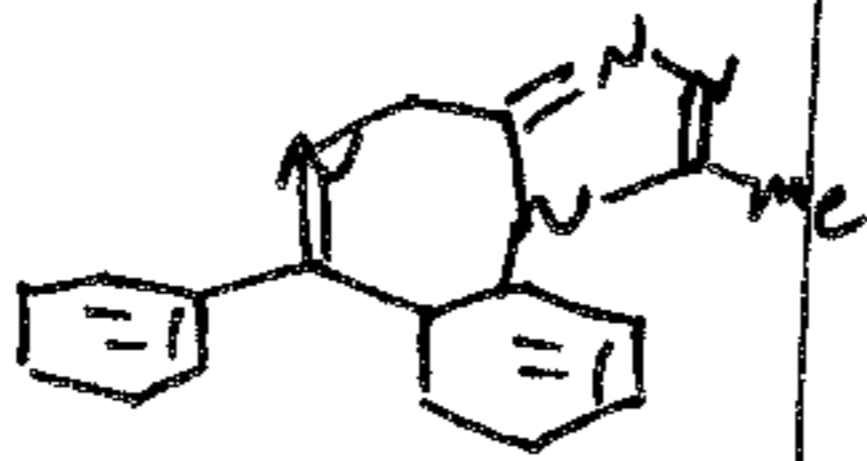
All require complex organic molecules

③ What is a complex molecule?



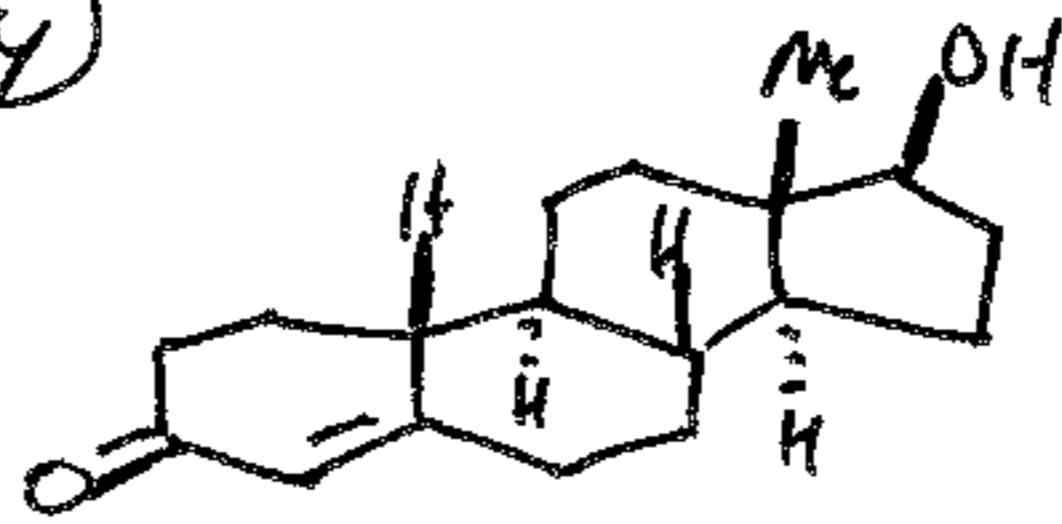
(Tamiflu-Gilead)  
Osetamivir

Unnatural



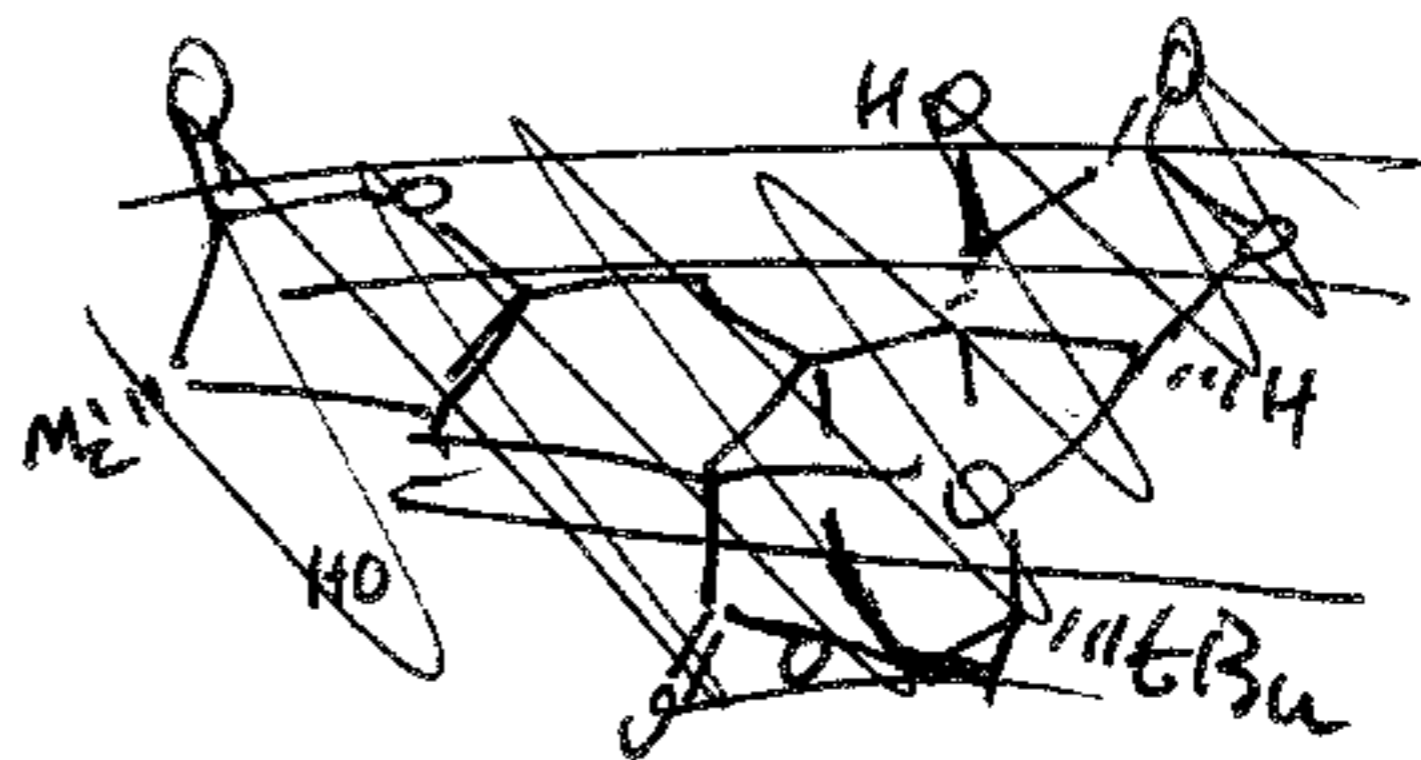
Xanax - Upjohn  
Alprazolam  
(anxiety)

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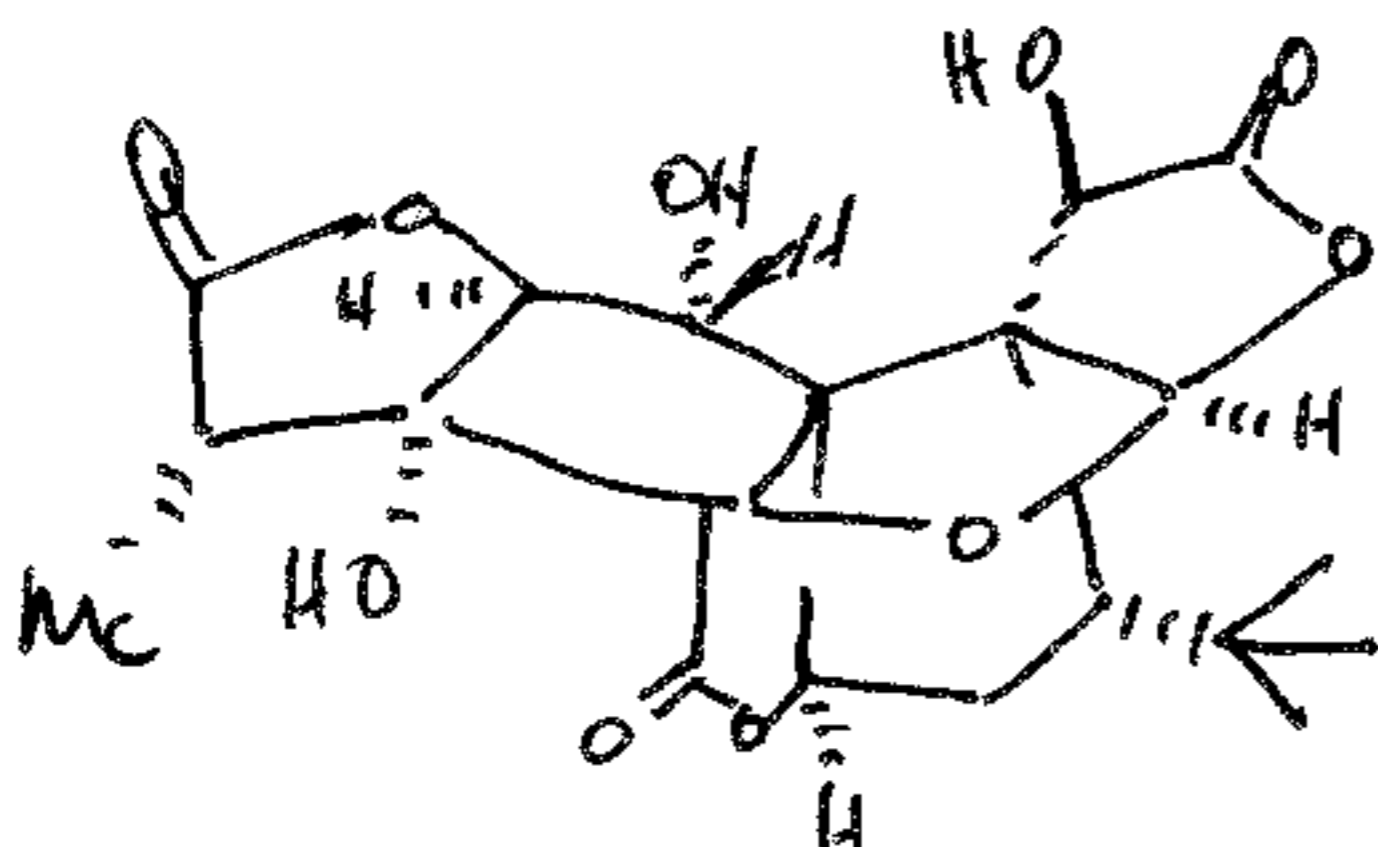


testosterone

Natural



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ginsenoside B

(ES core, 1967, 31 steps)

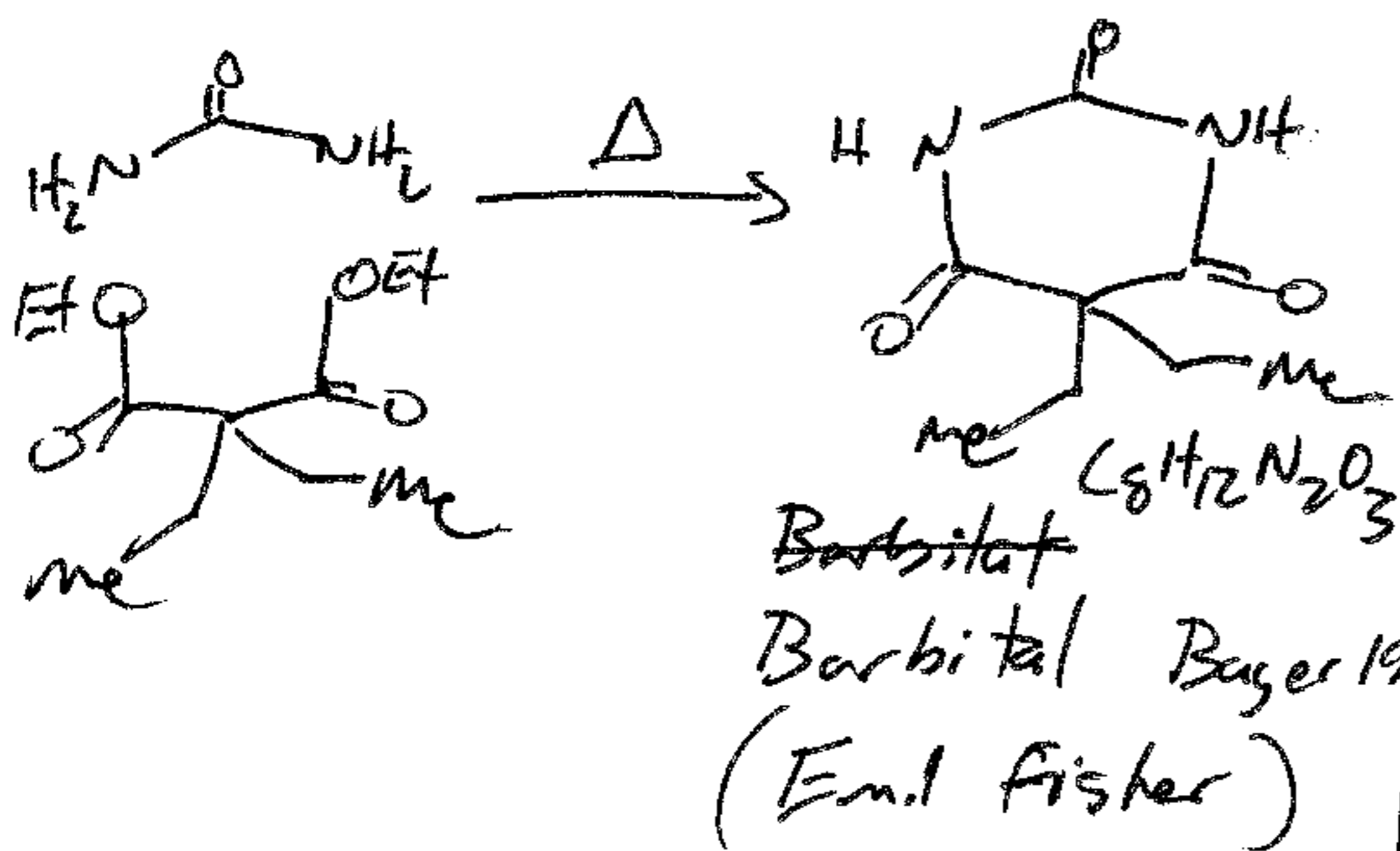
⑥

complexity (core)

size, topology, functional groups  
Atom content, stereochemistry  
functional group density, stability/  
reactivity

①

① Molecule made from molecules:  
example (early drug)



② General considerations  
In Synthetic routes:

1) yield  
consider 3 step sequence  
 $A \rightarrow B \rightarrow C$   
If 90% yield average average  
 $\therefore 73\%$  overall yield  $(0.9)^3$   
( $\frac{1}{4}$ th lost)  
If 70% (more realistic)  
 $\therefore 34\%$  yield ( $\frac{2}{3}$  lost)

③ 2) Length

15 steps at 70%  $\Rightarrow 0.47\%$   
(999/1000 sm lost)

also, In lab:

Each step 2-4 weeks  
(minimum) sometimes years.

Longer if new

④ 3) Convergence

$A \rightarrow B \rightarrow C \rightarrow D \rightarrow E \rightarrow F$   
5 steps @ 70% = 17%

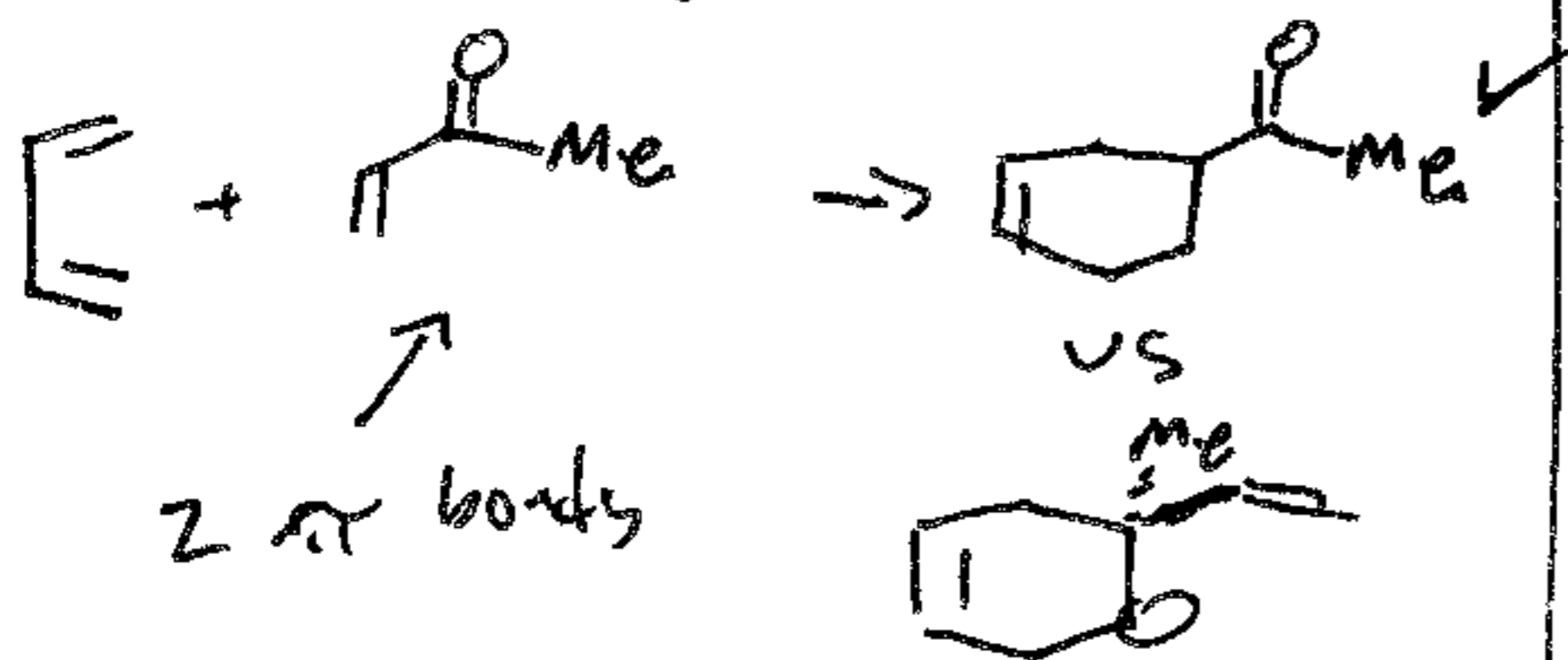
$A \rightarrow B \rightarrow C$   
 $D \rightarrow E \rightarrow G$   
 then  $C + G \rightarrow F$

70% = 34% yield

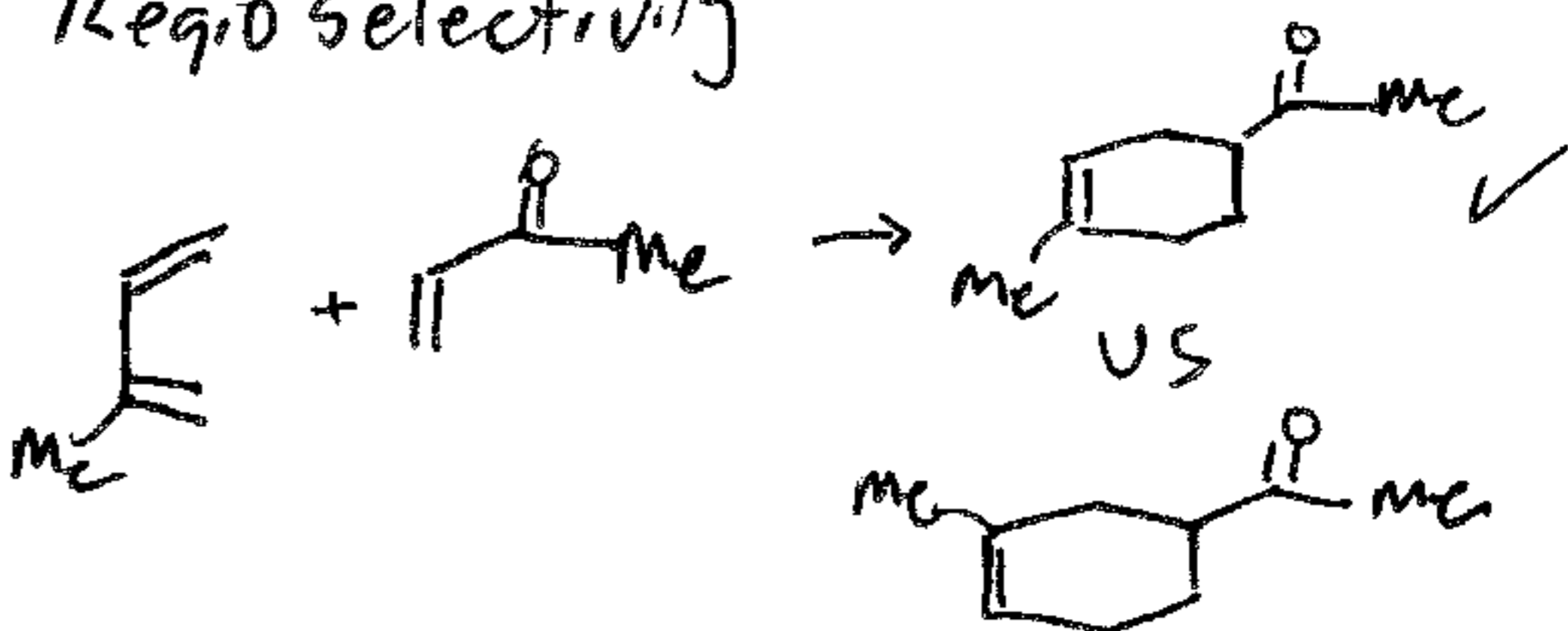
2x material

⑤ 4) Selectivity (many types)

Chemoselectivity (which group)

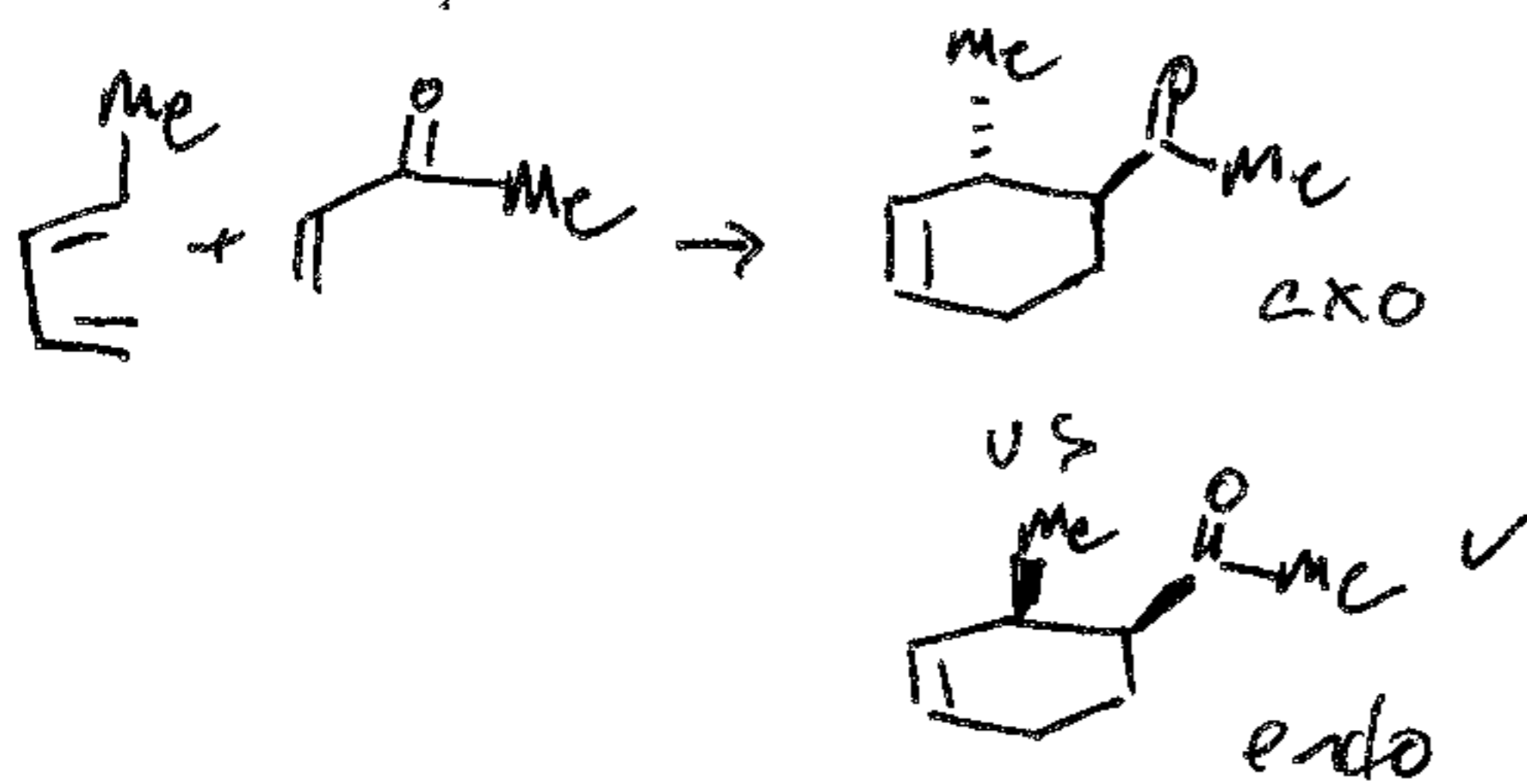


⑥ Regioselectivity

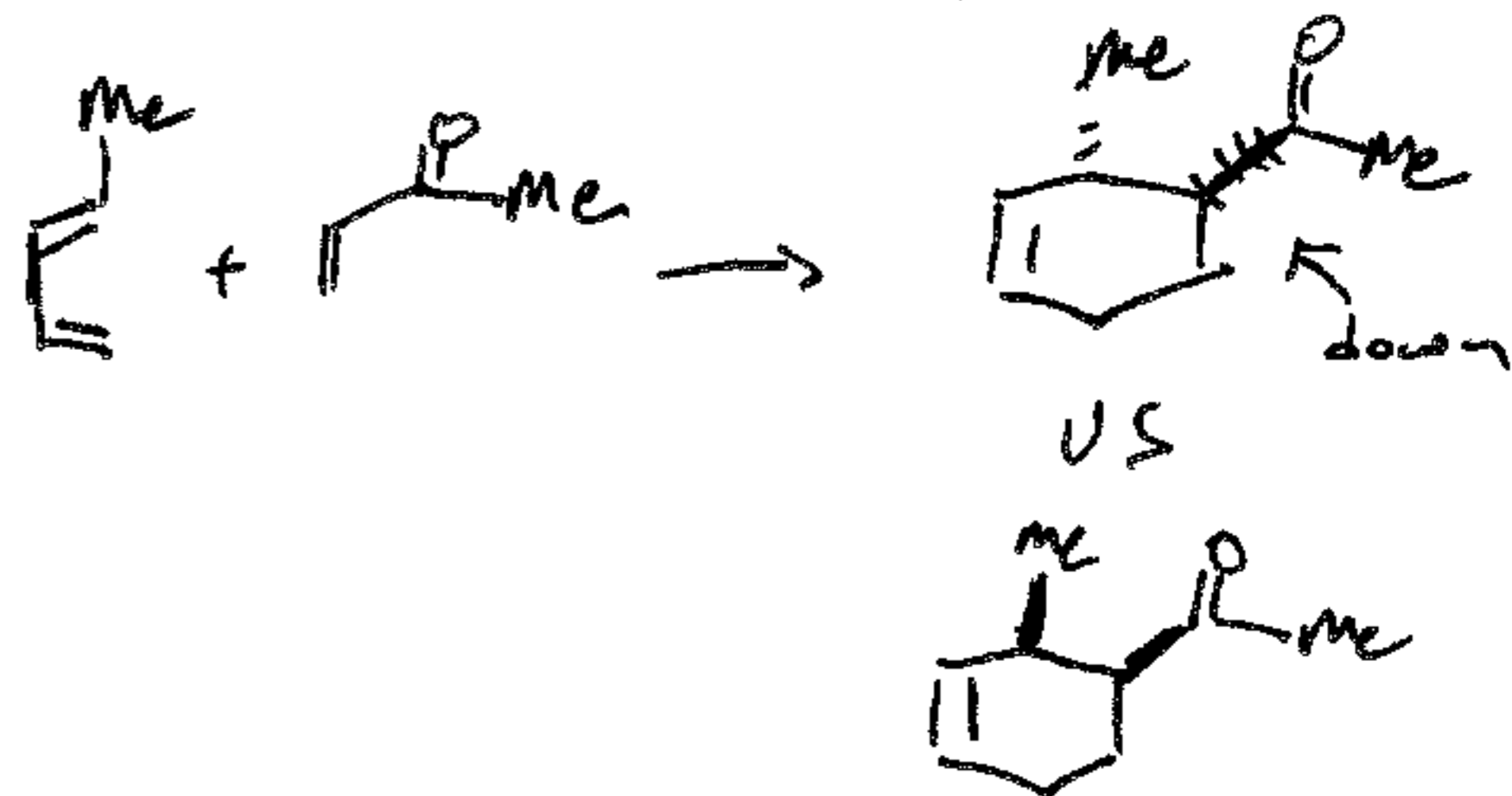


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① Diastereoselectivity (which diastereomer)



② Enantioselectivity (which enantiomer)



③ 5) Precedent

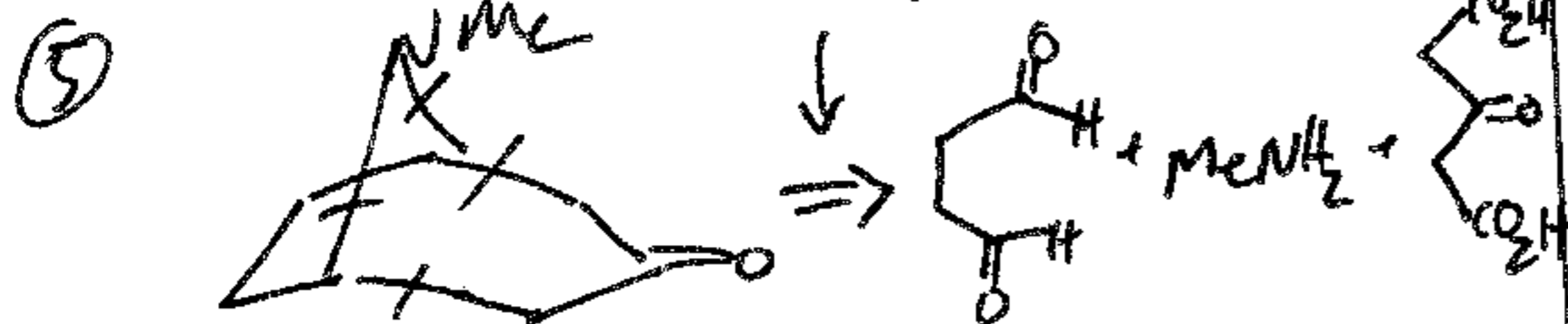
1h in ~~library~~ library = 1 month in lab

Exact vs close

If close: consider F.B.,  
ring size, ~~substituent~~  
substituents

↳ all can effect out

6) Other factors  
waste stream, cost, toxicity, scale



tropinone  
tropinone

~~image~~  
"imaginary hydrolysis"

Robinson JACS, 1917, 111, 762

④

Molecules can be complex,  
requires rational approach  
to prepare them.

Retrosynthetic analysis  
used to plan routes to  
target molecules

Focus Focus Syn II  
but intro here

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EJ Corey

Harvard University  
Nobel Prize 1990

"Retrosynthetic analysis"  
1960's

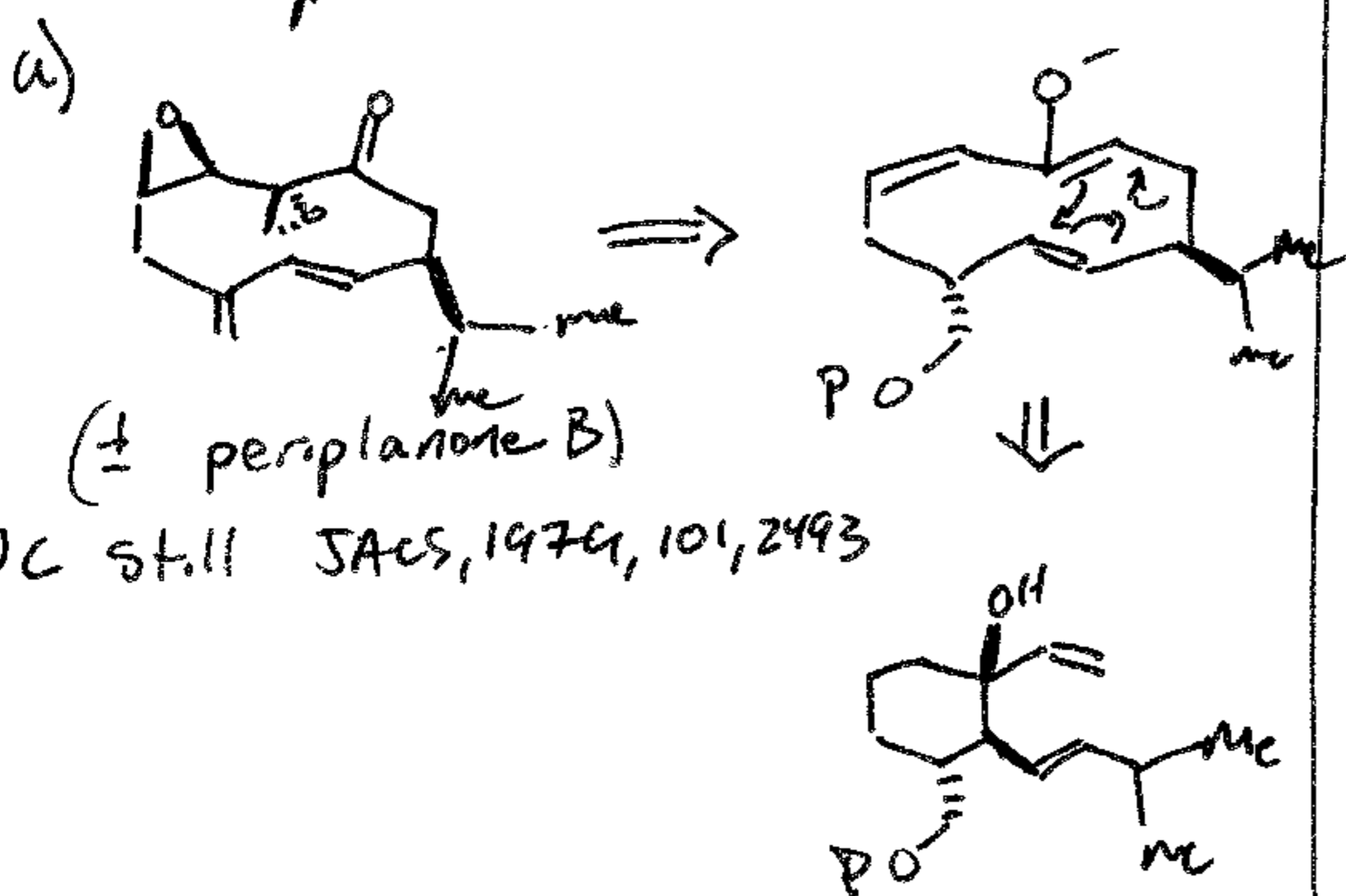
① Retrosynthesis 101

- 1) Maximize convergence
- 2) Minimize steps
  - a) look at multiple routes
  - b) avoid ~~the~~ Functional Group Interconversion & protecting groups when possible

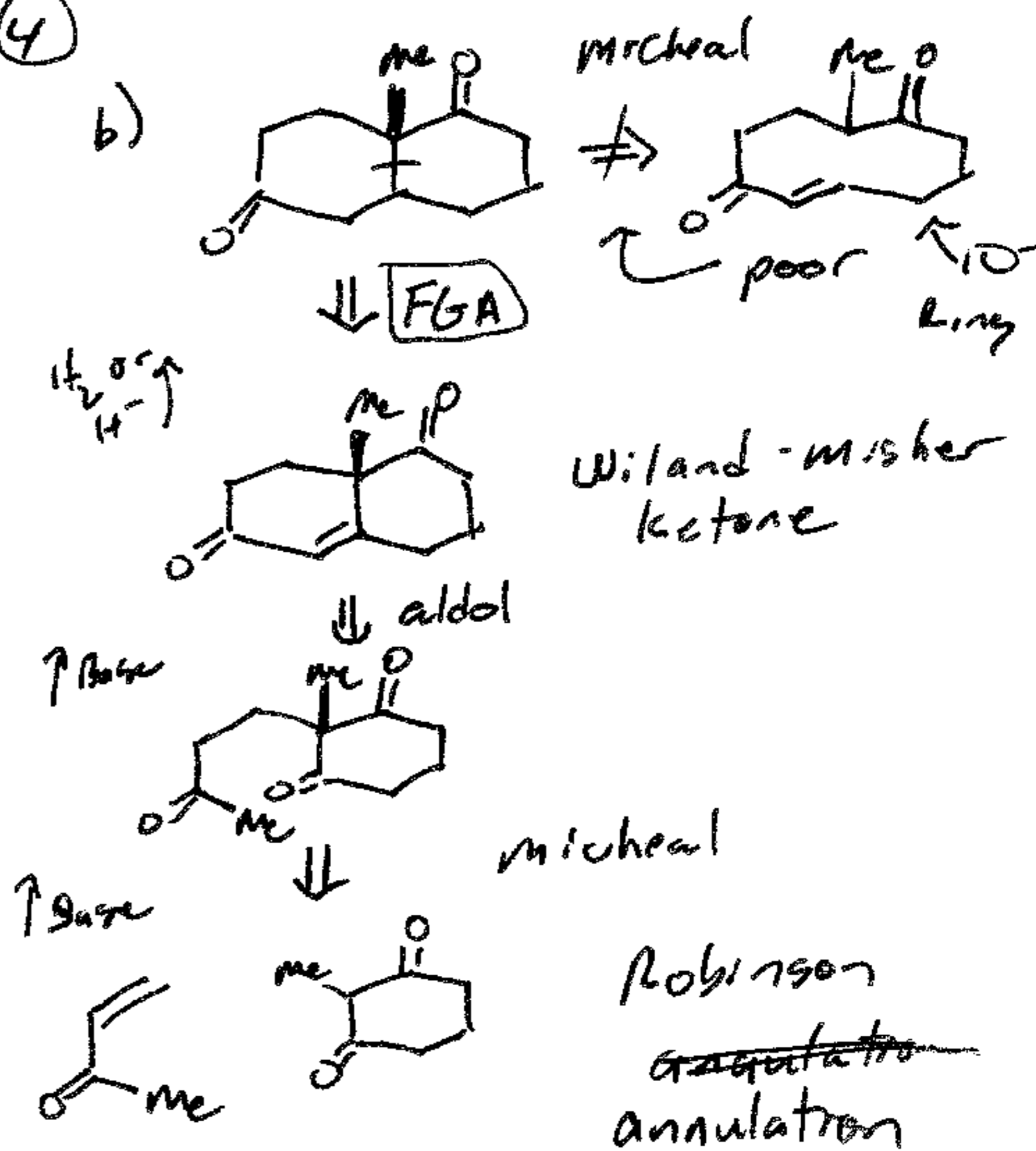
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- 3) Add FG's if they can help
- 4) C-X & C-CX Bonds are usually good disconnections
- 5) Disconnect stereocenters (clear) where possible.

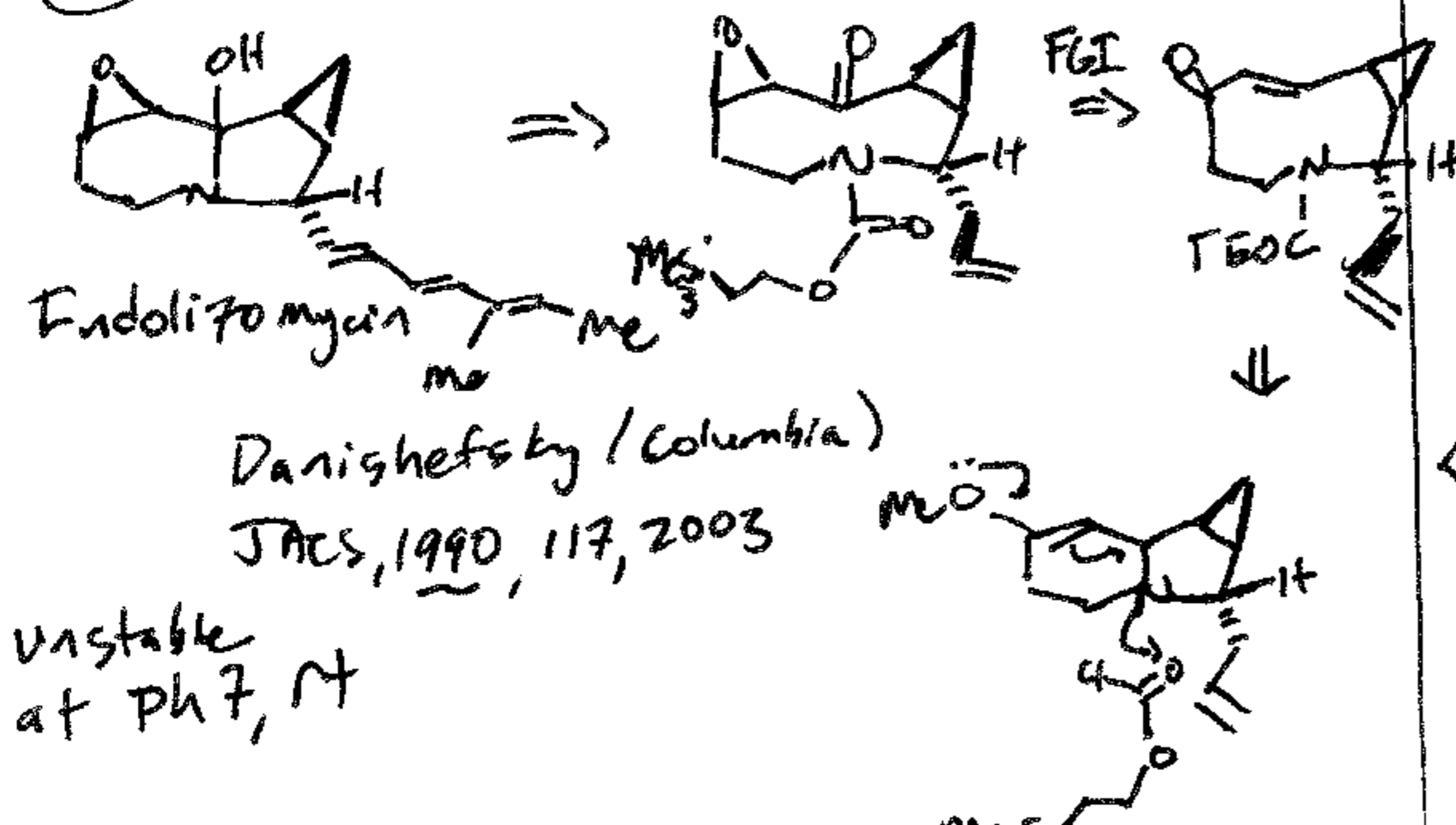
③ ~~6~~ Minimize Med & large Rings (Or have really good plan).



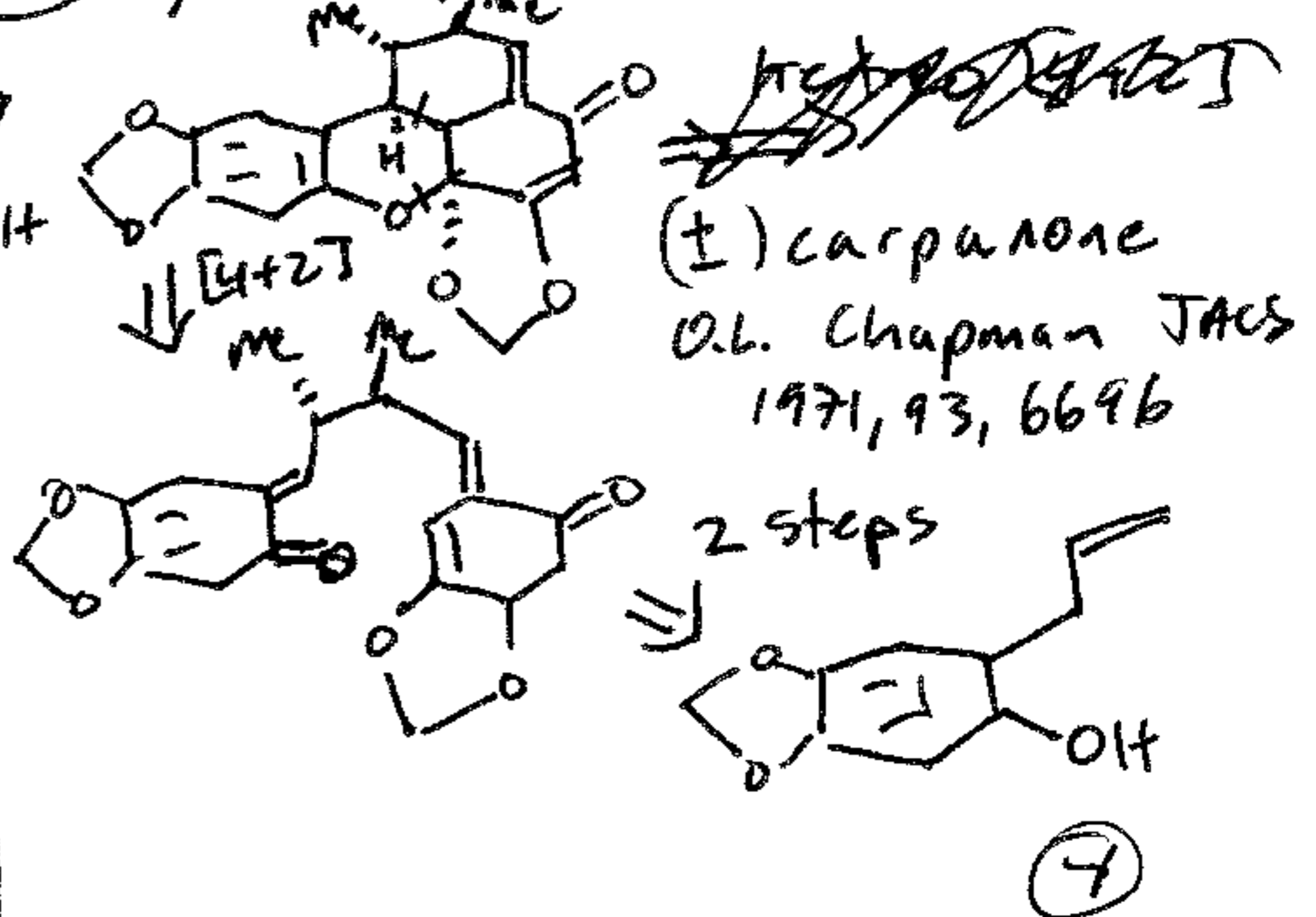
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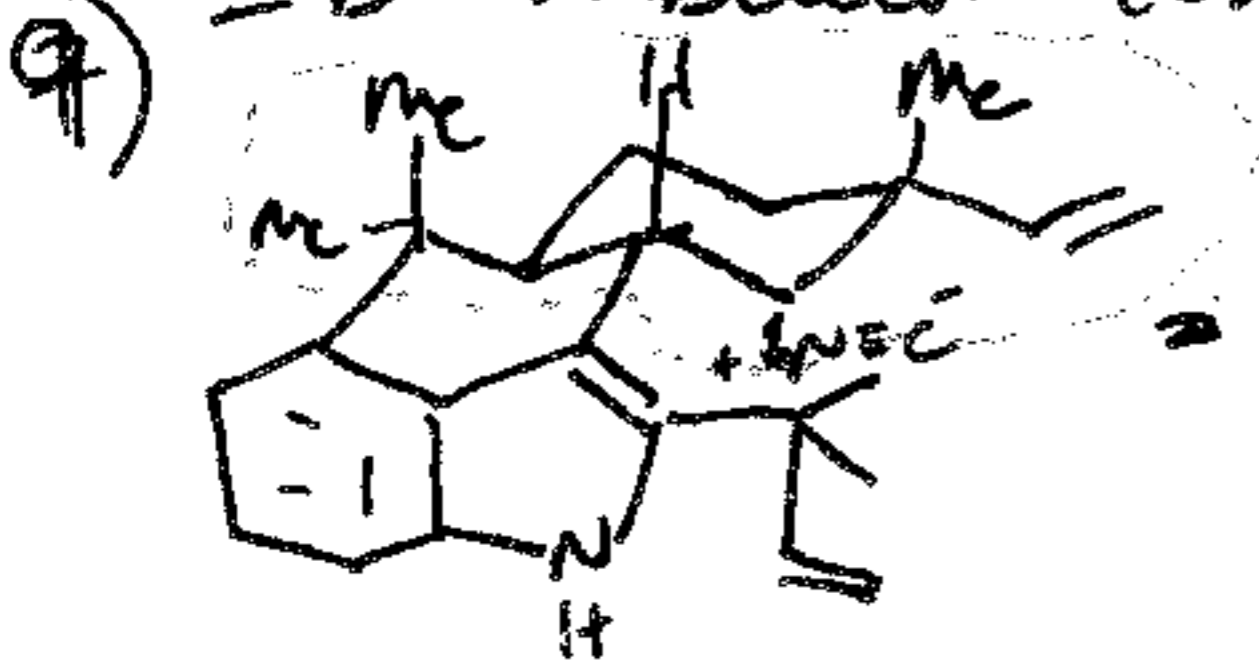
⑤ ~~7~~ Disconnect unstable Groups Early



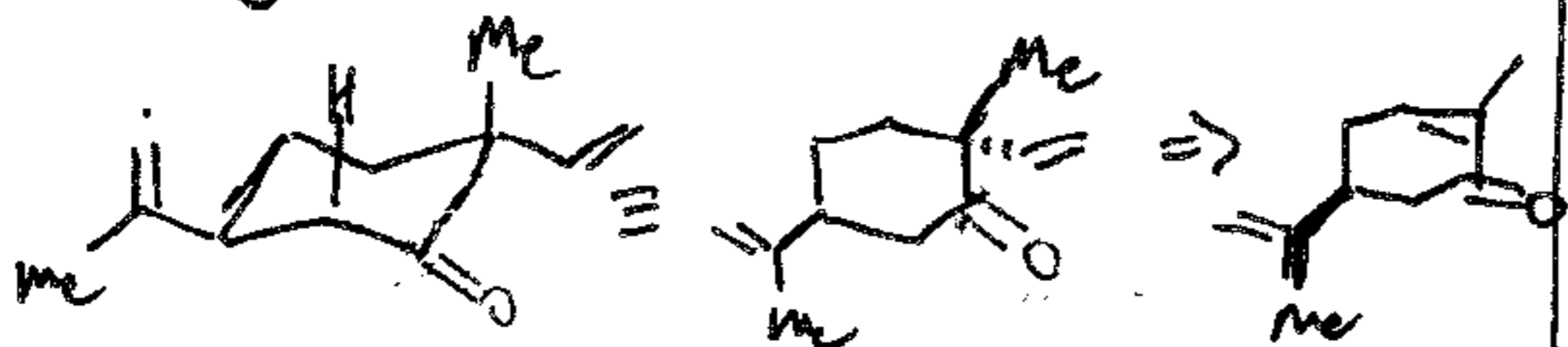
⑥ ~~8~~ Recognize Embedded Symmetry



① ID Embedded "complex" molecules

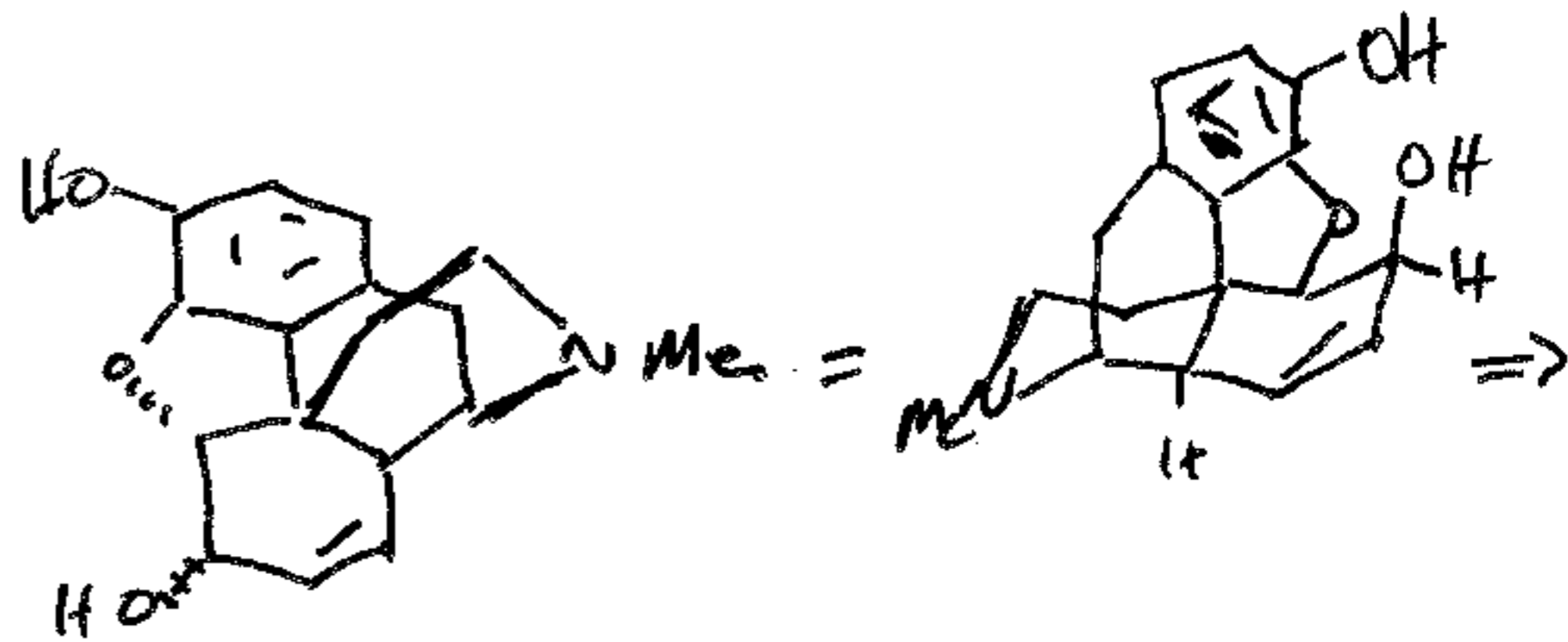


Ambiguine  
Baran,  
Nature, 2007  
446, 404



"Chiral pool" (S)-carvone

② Use topology



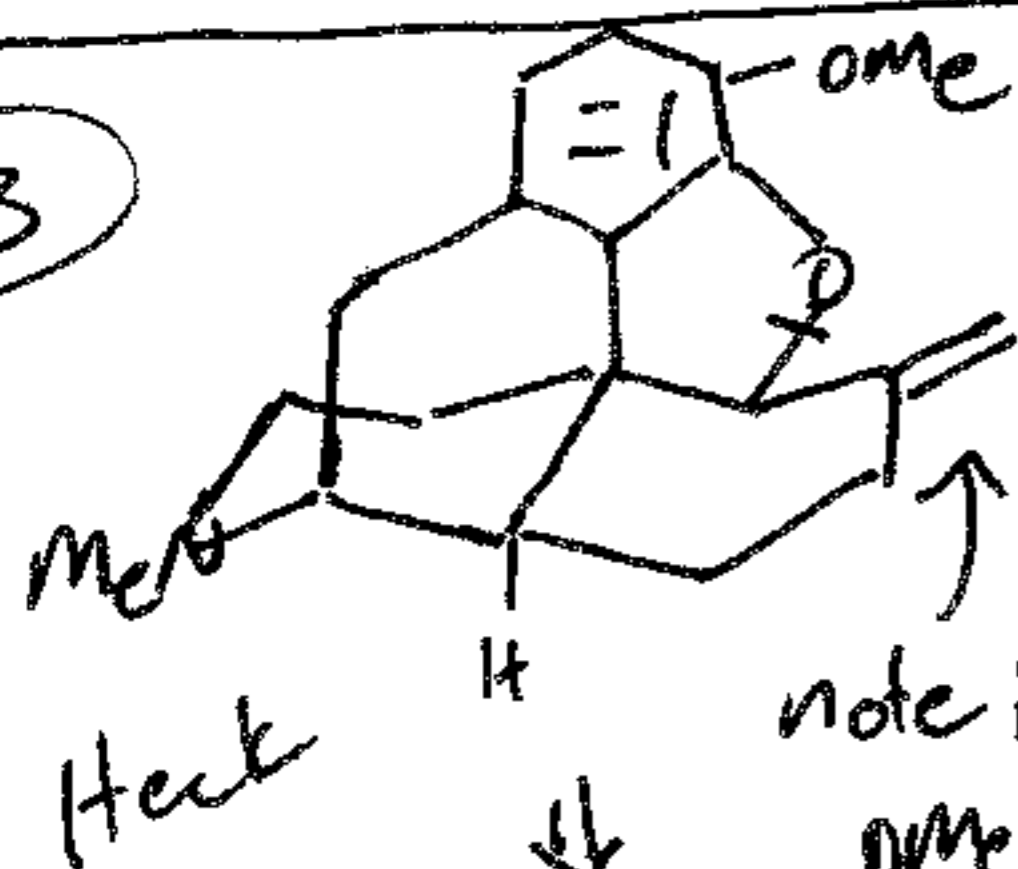
(-) morphine

Overman Pure & Applied Chem

1994, 66, 1423

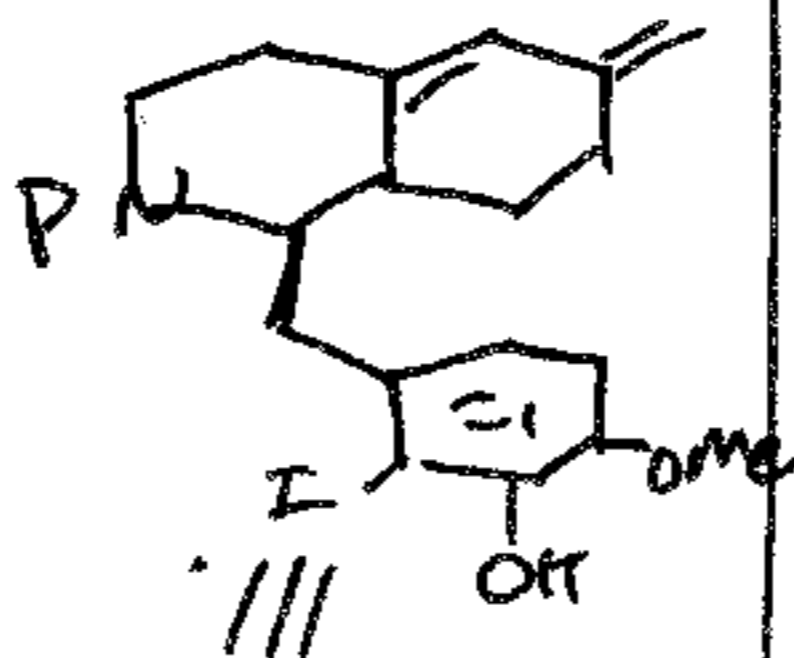
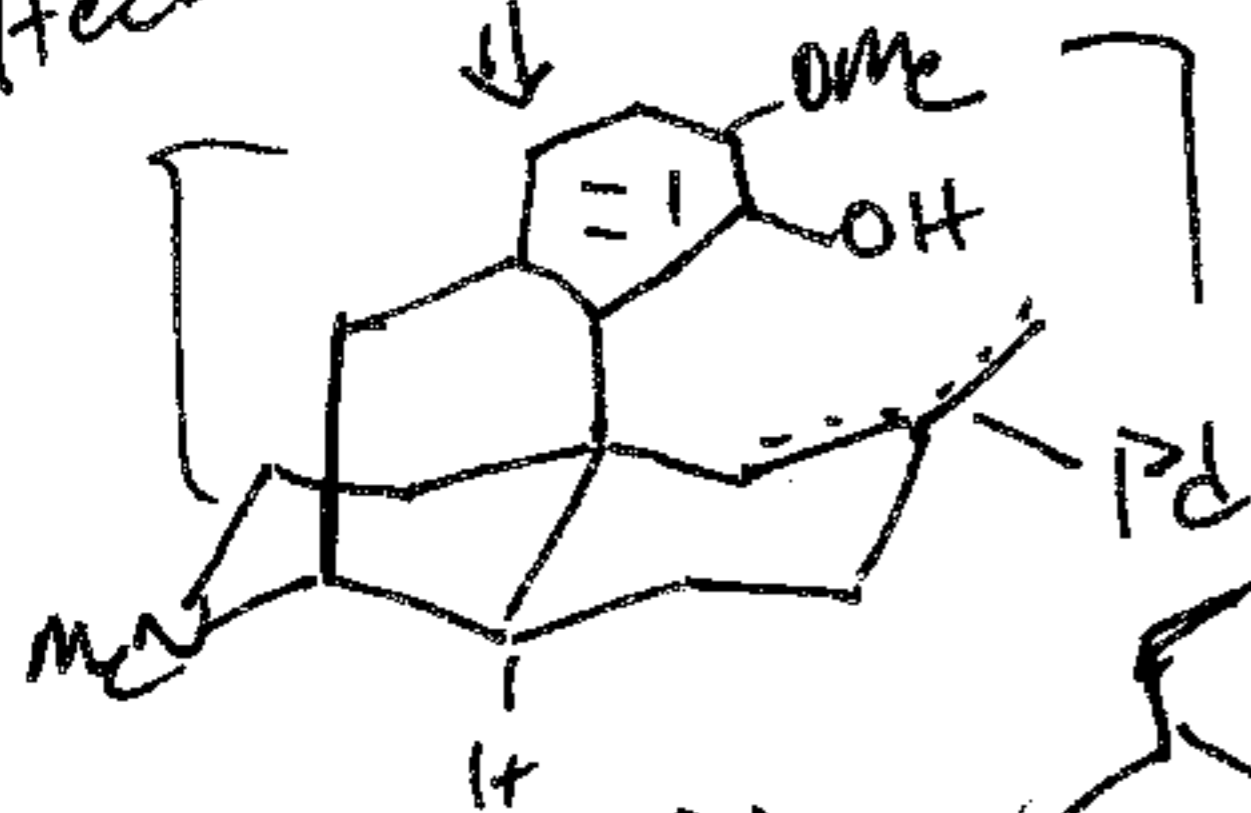
(Build Models)

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Heck

note FGA



$\pi$ -allyl Pd

Tandem Rxn

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⑤

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