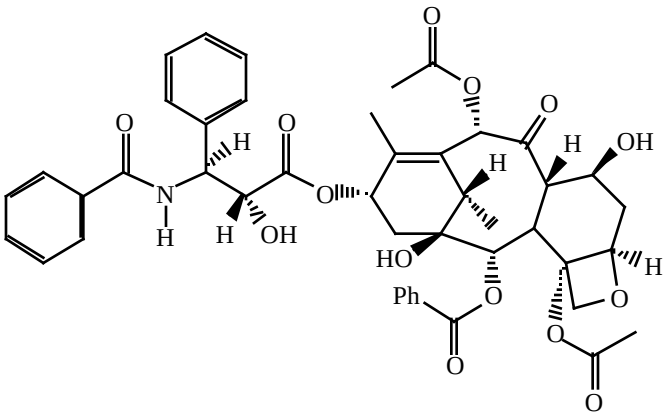
Multi-step Organic Synthesis

Conversion of existing molecules into other useful molecules.

Natural sources: petroleum natural gas natural products Commercial sources Etc.	→ → →	Pharmaceuticals Polymers Gasoline Textiles Etc.

- Little molecules ----> big molecules
- Synthesis of unnatural products
- Modification of existing structures
- Synthesis of rare and useful natural products

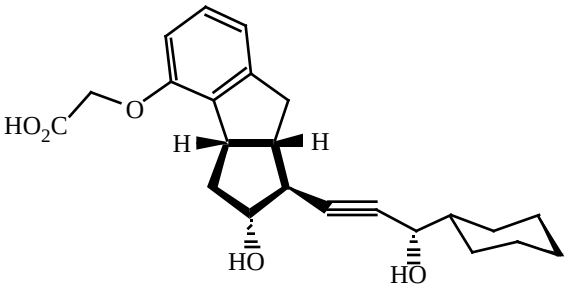
Example: Paclitaxel (taxol): anticancer drug and rare natural product



Example #2: Synthesis of indynaprost from cyclopentadiene

Cyclopentadiene

into



Indynaprost
(Experimental platelet aggregation inhibitor)

Fundamental Synthesis Operations

C-C bond formation

functional group interconversions (FGI):

- oxidation
- reduction
- substitution
- elimination
- addition
- others

skeletal rearrangements

protection/deprotection

Keys to Doing Synthesis Problems

- Use reactions you know (flash cards)

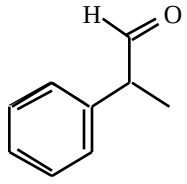
- Keep an eye on the requirements of the problem: Can I solve the problem in one step from where I am?

- Think backwards: **retrosynthesis** (E.J. Corey, Harvard, Nobel Prize in Chemistry, 1990)

  Retrosynthesis (Corey's definition): "a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively materials along a pathway which ultimately leads to a simple or commercially available starting material for chemical synthesis"

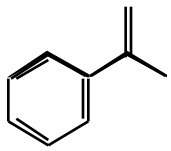
✓ ***Practice*** ✓ ***Practice*** ✓ ***Practice*** ✓ ***Practice***

Sample Problem #1



Target molecule

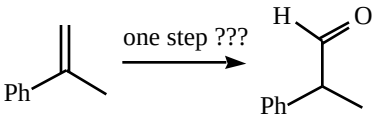
from



Starting material

Hint: Unless otherwise specified, any other reagents can also be used.

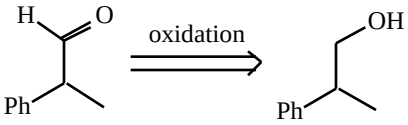
Can the target molecule be made from the starting material in one reaction?



Analysis: No change in carbon count
FGI: alkene → aldehyde

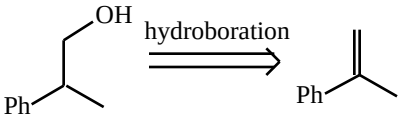
How to make an aldehyde?
- Alkene ozonolysis (alters carbon count)
- Oxidation of a primary alcohol (carbon count unchanged)

Hint: Flash cards may suggest reactions to carry out the desired FGI.

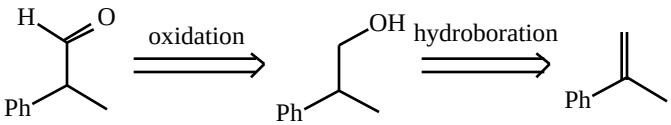


⟹ means: "thinking backwards"
"the molecule on the left could be made from the molecule on the right by the reaction above the arrow"

Can the new target molecule (the alcohol) be made in one step from the starting alkene?

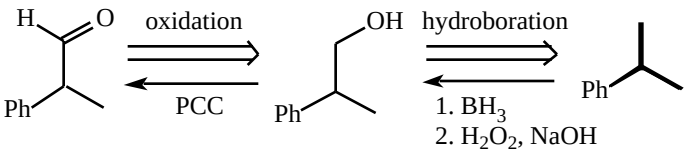


Complete Retrosynthesis:

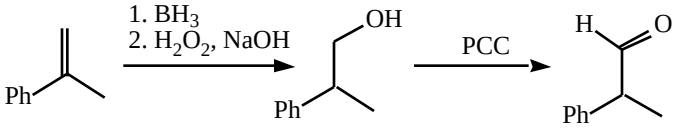


Forward Direction:
· Fill in the reaction details

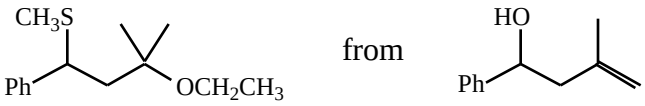
· Carefully check each step: stereochemistry, carbocation rearrangements, etc.



Or:



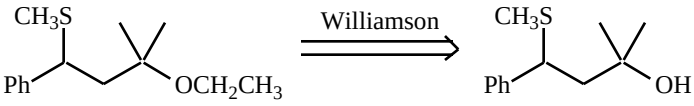
Sample Problem #2



Can the target molecule be made from the starting material in one reaction?

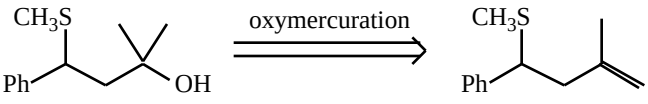
Analysis: Target has three more carbons than starting material, but no new C-C bonds.
FGI: Alcohol → thioether
Alkene → ether

How to make an ether?
- S_N2 with $CH_3CH_2O^-$
- S_N2 with RO^- and CH_3CH_2I
- Alkoxymercuration



Can the target molecule be made from the new starting material in one reaction?

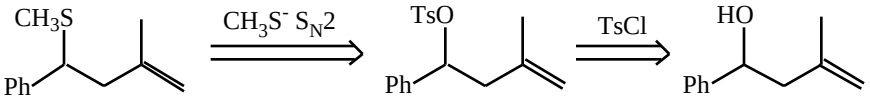
How to make an alcohol?
- S_N2 with HO^-
- Alkene hydration
- Nucleophilic addition to epoxide



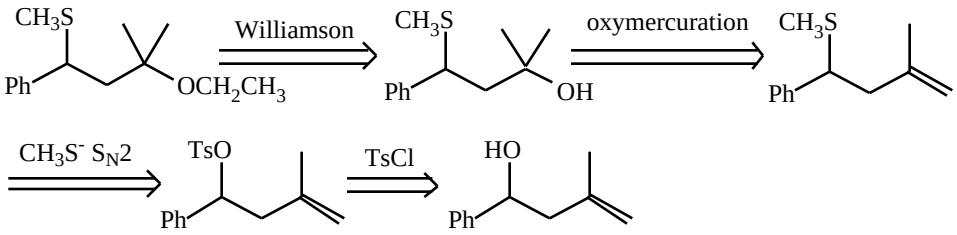
Can the target molecule be made from the new starting material in one reaction?

How to make a thioether?

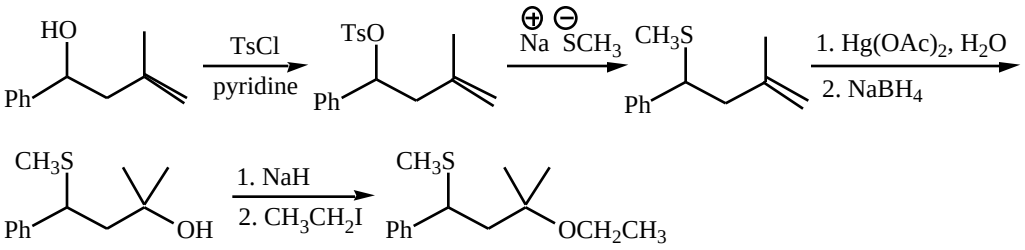
- S_N2 with RS^- (Must first convert OH into LG)



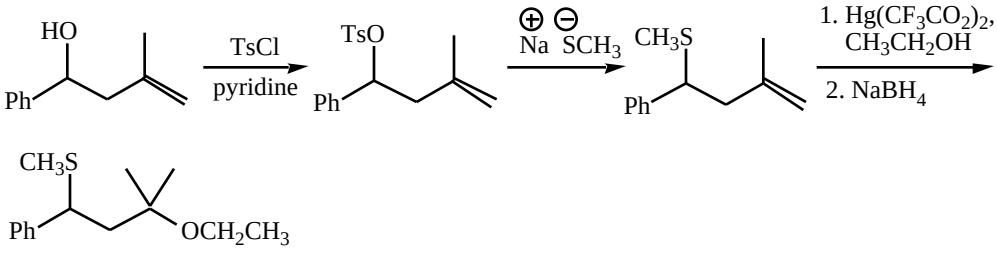
Complete Retrosynthesis



Forward Direction

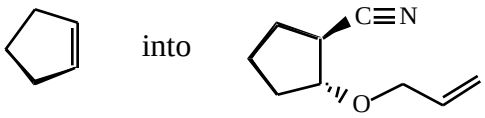


Shorter Forward Direction: Alkoxymercuration achieves the alkene → ether conversion in just one step



Hint: Thorough reaction knowledge increases flexibility and simplifies synthesis problems. Some problems might not be doable without good mastery of reactions!

Sample Problem #3



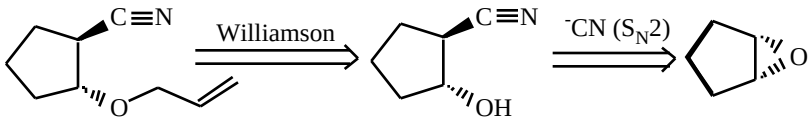
Can the target be made in one step from the given starting material?

Analysis: New C-C bond between ring and nitriles
FGI: Alkene → ether + nitrile + another alkene, with trans stereochemistry

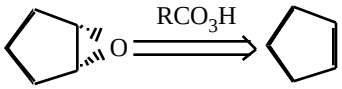
How to make a nitrile?
- S_N2 with ^-CN and alkyl halide, alkyl sulfonate, or epoxide

How to make an ether?
- S_N2 with RO^-
- oxymercuration with ROH
- Williamson ether synthesis

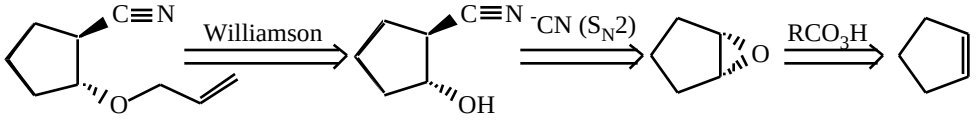
Several routes to consider. Pick one and explore it! The trans relationship of the ether and nitrile groups suggests an epoxide opening.



Can the new target molecule (the epoxide) be made from the original starting material (alkene) in one step?



Complete Retrosynthesis



Forward Direction