Compilation of [mostly original] Organic Olympiad Problems

This problem compilation consists of several different kinds of organic problems rated by difficulty and style. Everything was redrawn by me.

Additionally at the end, I have provided some original samples of ‘removed reagent problems’ which have become increasingly popular in recent years of USNCO camp.

Special thanks to Alec Zhu and Andrew Feng for helping to check, translate, and write some of these problems.

Problems Part 1

I tried to roughly rate problems by difficulty by the 2020 camp standard as I vaguely remembered it.

A: Virtually impossible in a competition setting. (Tetracycline, Russian Camp)
B: Basically the hardest possible problems that could be reasonable for study camp.
C: Extreme cleverness required, difficult-impossible for 80-90% of campers (2015 ICHO #6)
D: Very nontrivial, significant problem solving required (2016 IChO #7, second half)
E: Tricky but doable given enough time or trial & error
F: Some more intermediate reagents (2016 ICHO #6, harder UKCHOs)

Problems will be titled according to their numbering in this list followed by their difficulty rating (ex: 1.C)

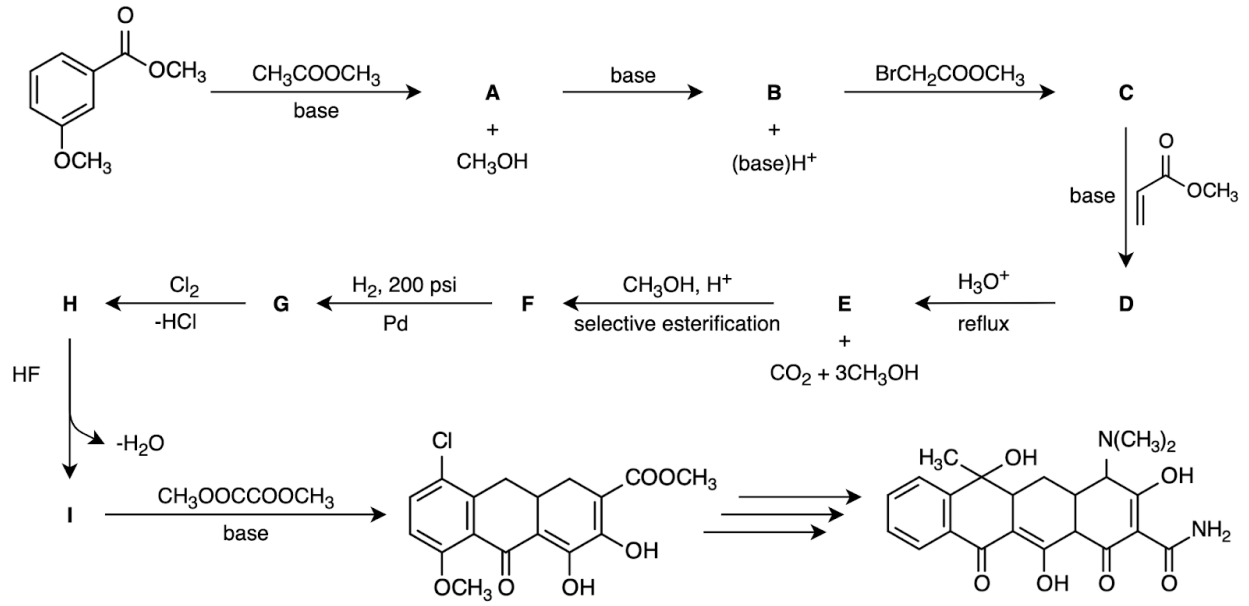
Additionally we define the term “New Age”. Problems that are “New Age” typically have relatively advanced reagents that are nevertheless quite famous within organic chemistry. They can usually be solved without knowing what every single reaction already does, however they very strongly favor already knowing what the reactions do. The term comes from the tendency of modern USA IChO team members to have a near encyclopedic memory of common named reactions which has led to trivialization of even the most challenging organic schemes.

Problems that are deemed particularly beneficial for the New Age approach have been marked with an N after their problem name (ex: 22.BN). We would still recommend trying these questions even if you don't have the aforementioned wide knowledge of reactions because not knowing every reaction is basically an inevitability in competition, and something which you really should practice for!

On some questions I’ve left added hints that are highlighted in black in case you don't want to see them. For example:
HINT: [redacted]
If you want to view the hint, simply highlight the text and the highlighting will make it viewable (or you can copy paste it without formatting into a word doc etc).

Problem 1.D (2012 IChO Prep #26)

Tetracycline is a broad spectrum antibiotic that is active against penicillin-resistant Gram-positive bacterial organisms. The first synthesis of a tetracycline was reported by R. B. Woodward (Harvard University) and the Pfizer Pharmaceutical Company in 1962. Three of the four rings were synthesized by the following steps.



Hints:

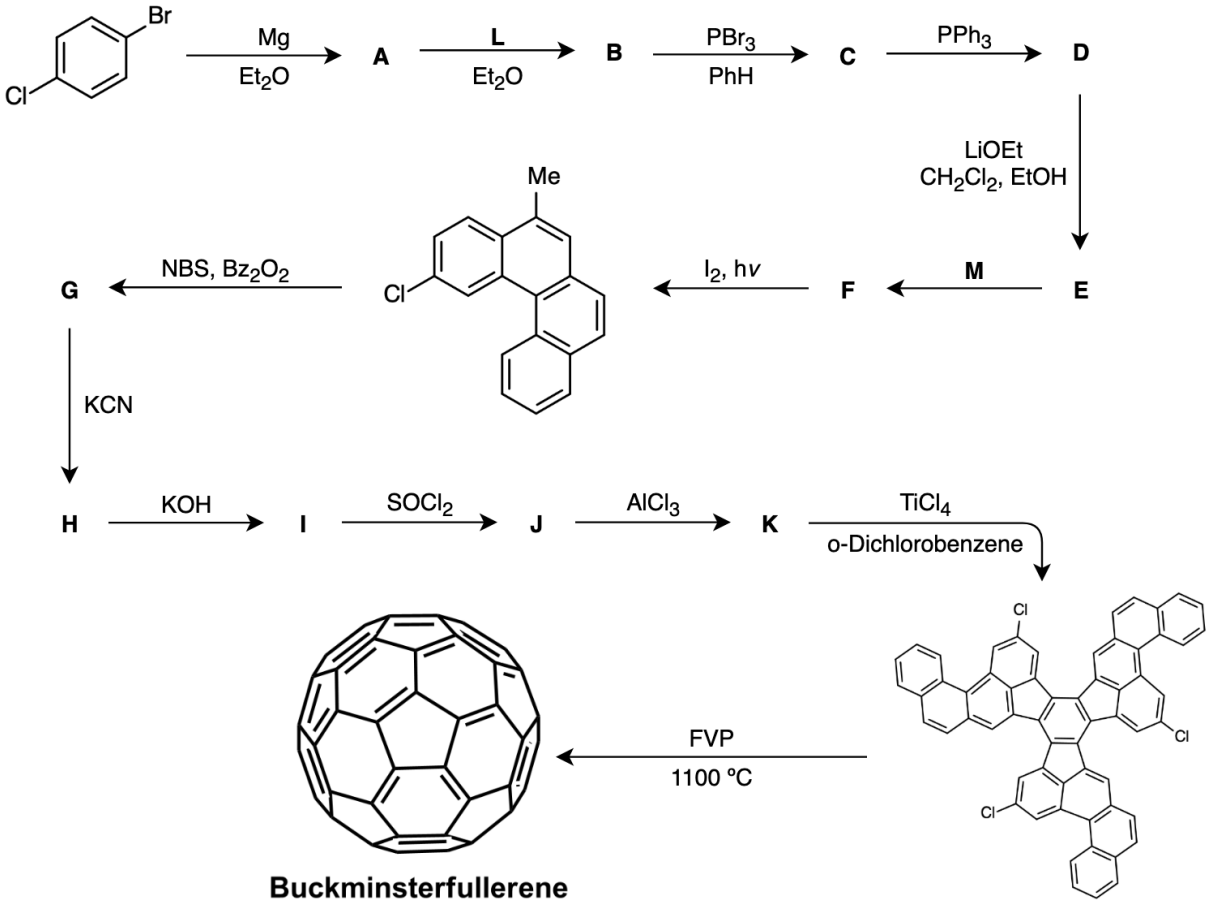
(1) the conversion of **E** to **F** involves only one methanol reactant;

(2) compounds **A**, **B**, **C**, **D**, and **E** have proton NMR spectra with two hydrogen signals above 7.8 ; these absorptions are not present in compounds **G**, **H**, and **I**.

HINT: [redacted]

Problem 10.D,F

Buckminsterfullerene was synthesized in 2002 according to the following scheme

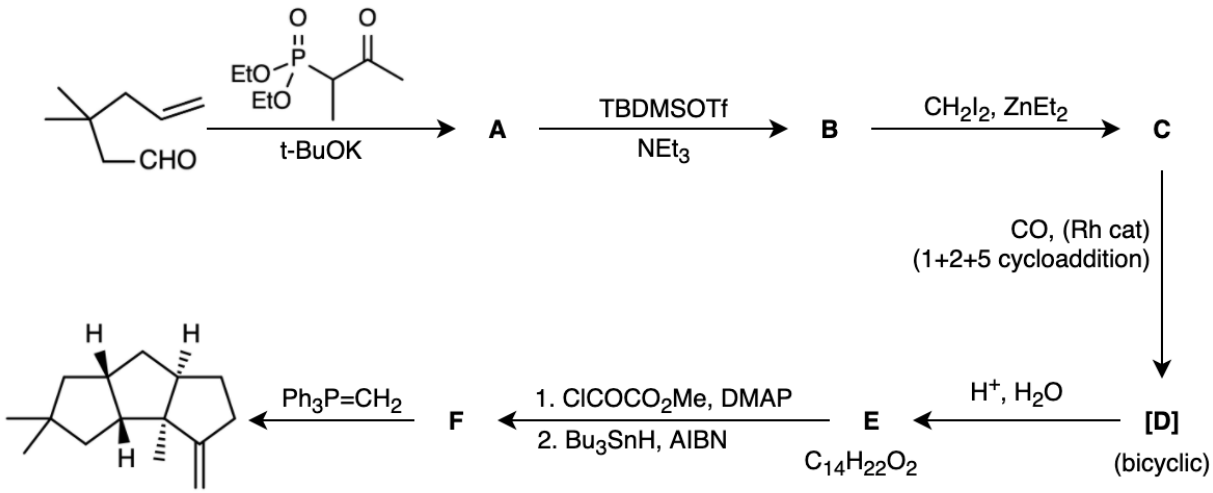


L and **M** are reactants which you must propose.

1. Draw the structures of intermediates **A** - **K** and propose reagents for **L** and **M**.

Problem 12.C-D

Hirsutene was synthesized in 2008 by Lei Jiao, Changxia Yuan, and Zhi-Xiang Yu as follows:



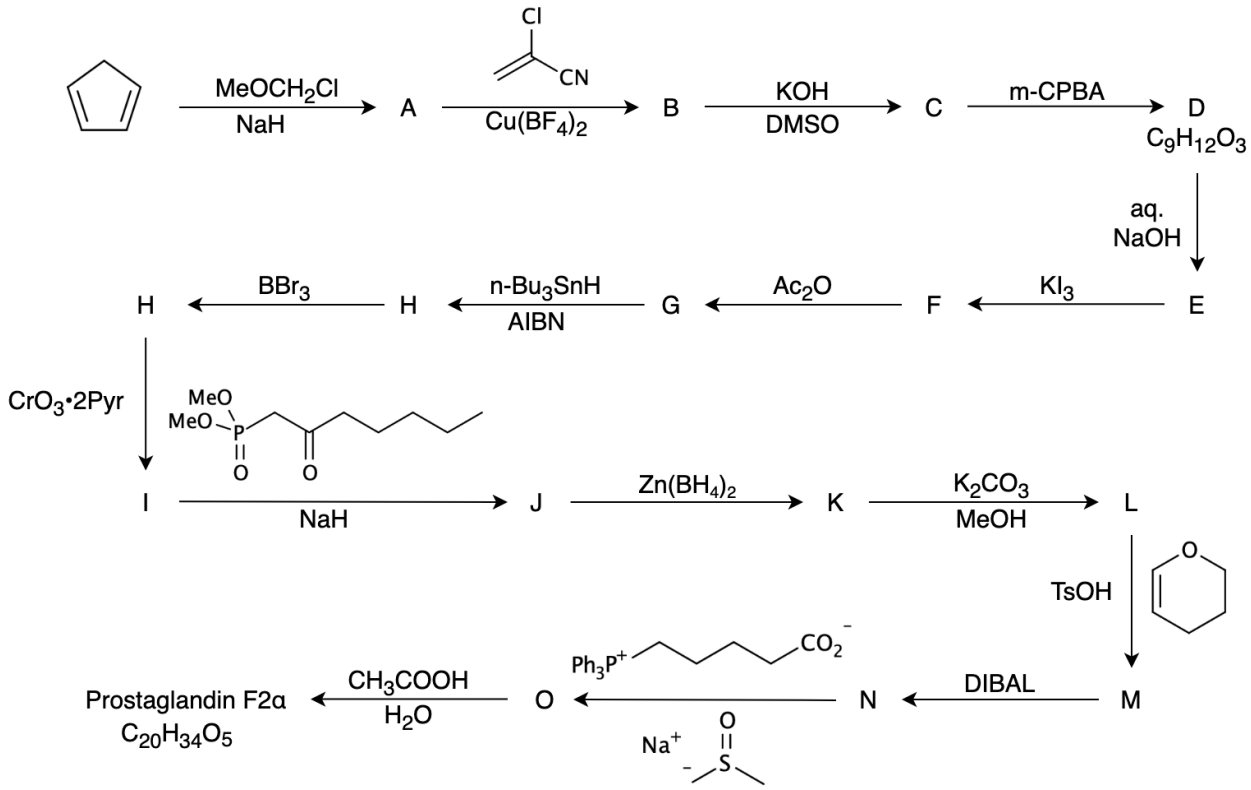
Hints:

1. There are 3 possible locations at which the step from **B**→**C** can react. Only one of these positions ends up reacting
2. **E** and **F** have the same number of rings

1. Draw the structures of intermediates **A**-**F**.

Problem 13.C-DN

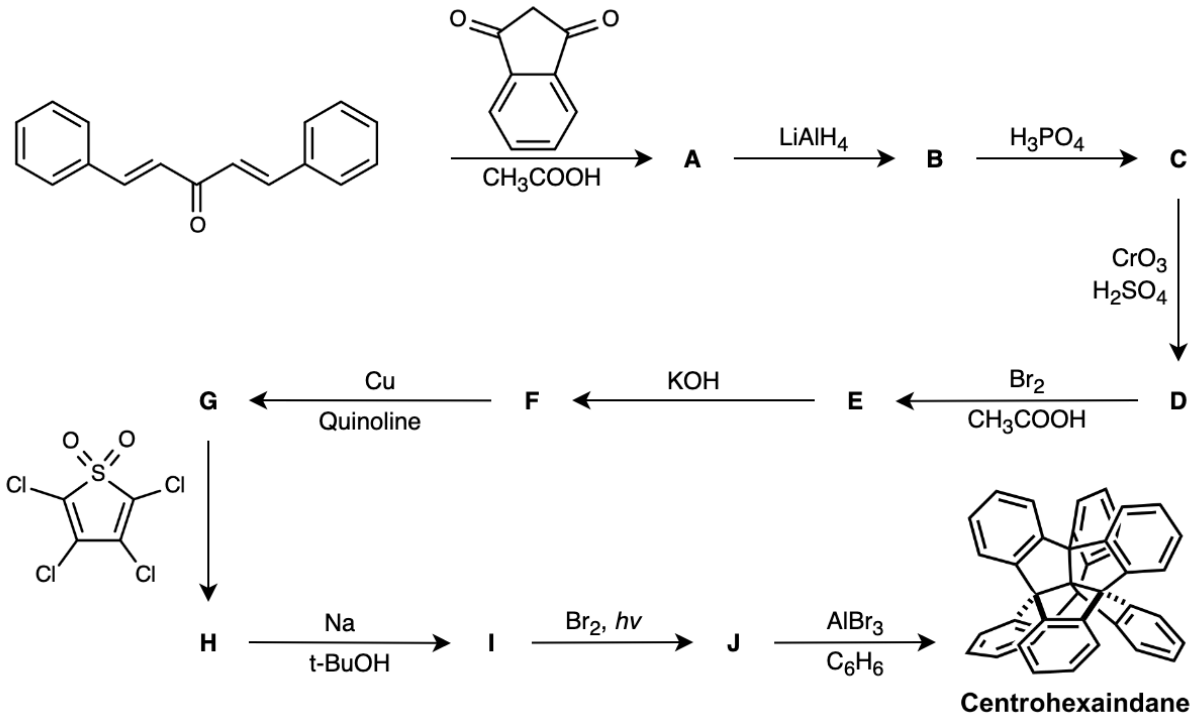
E.J. Corey synthesized Prostaglandin F2α in 1969 according to the following scheme



1. Decipher the structure of intermediates **A**-**O** and draw the structure of Prostaglandin F2α.

Problem 14.C

Centrohexaindane was first synthesized by Dietmar Kuck in 1988 according to the following scheme.



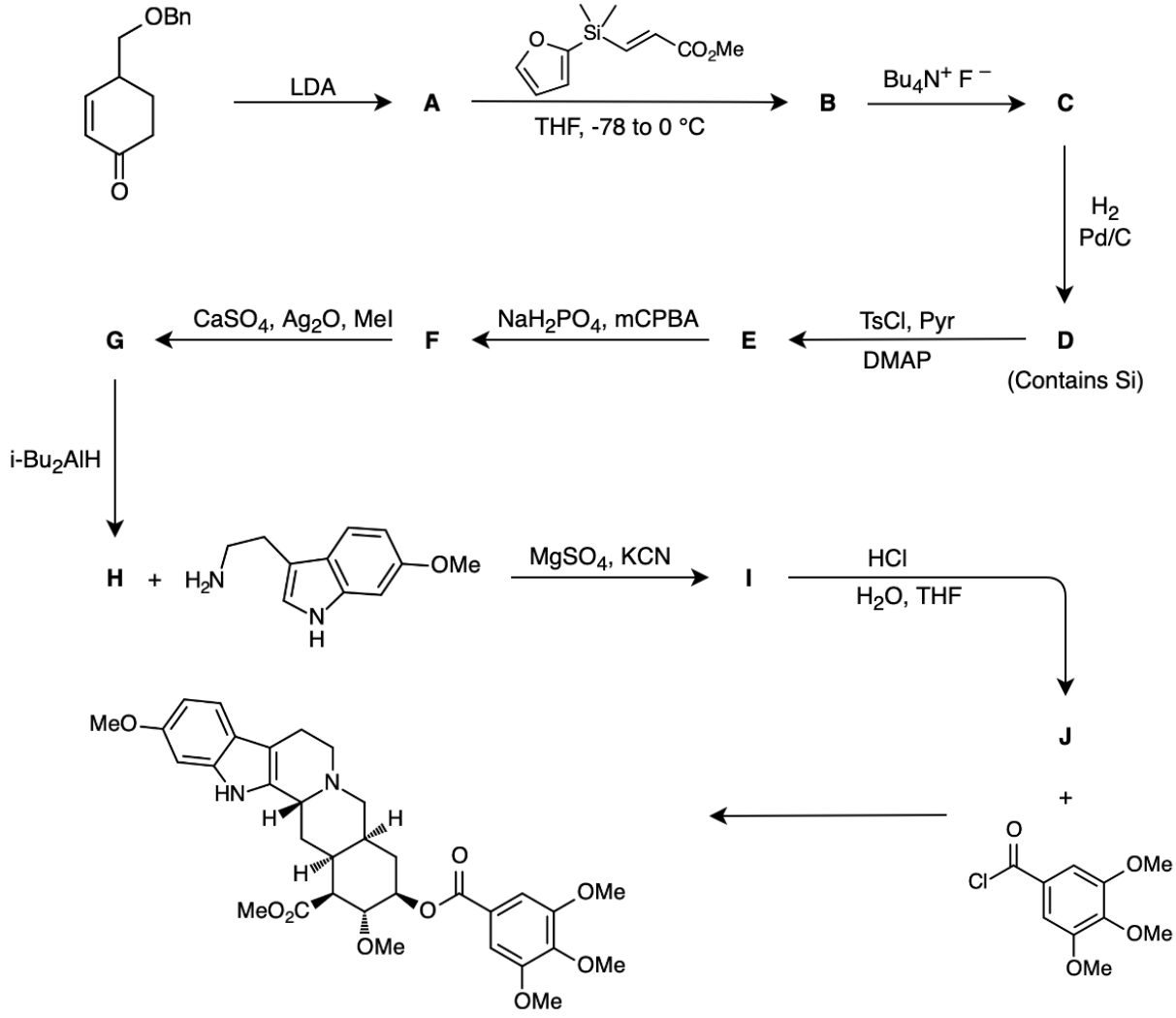
Hints:

- E→F is an example of the Favorskii reaction
- F→G releases CO_2

Draw structures of intermediates **A**-**J**.

Problem 15.C-D

Reserpine is an interesting compound which was synthesized by Stork in 1989. The total synthesis (shown below) uses a pericyclic reaction to build the carbon skeleton



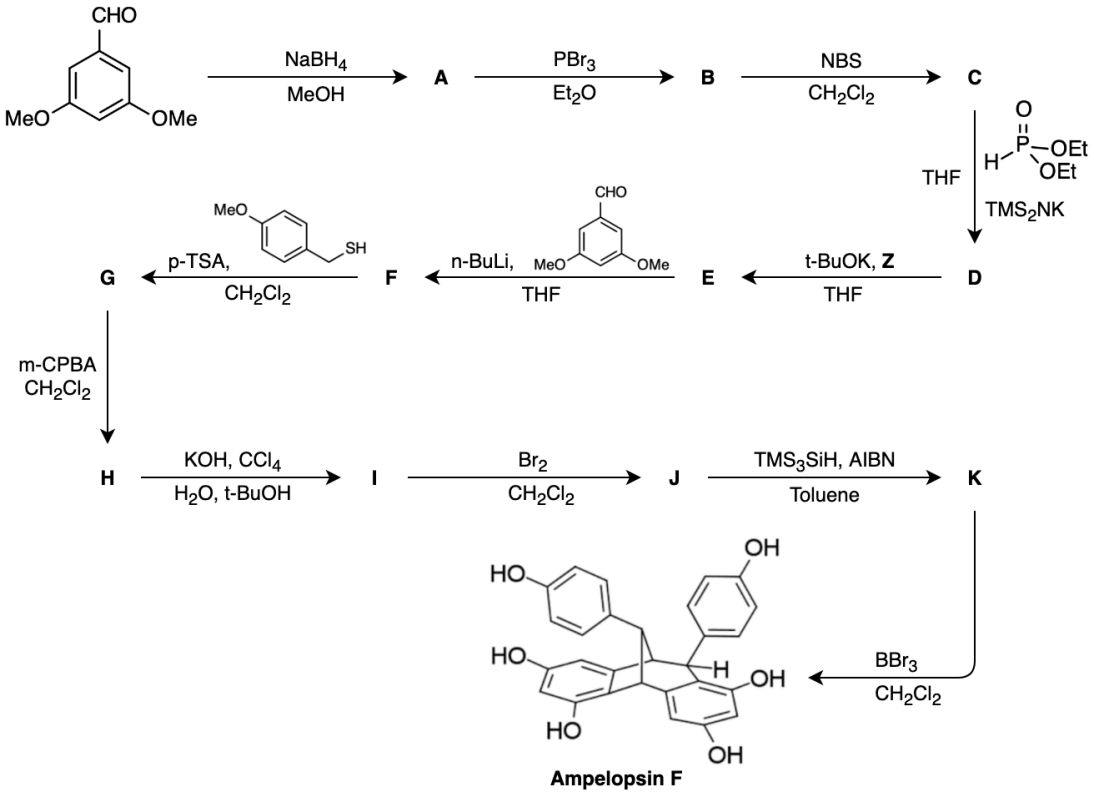
Hints:

- **B** is tetracyclic
- **E** → **F** involves two named oxidation reactions occurring in the same step.
- Optional Hint: [redacted]

Draw the structures of **A** - **J**.

Problem 16.C (CODS-CT Team Round Part 2 #4)
Reagent **Z** is an organic compound with molecular formula $C_8H_8O_2$. ^{13}C NMR suggests that there are 6 different ^{13}C NMR environments. Additionally, **Z** reacts completely with 1 equivalent of $LiAlH_4$ and can also react with some amount of CrO_3 in H_2SO_4. The product of the reaction of **Z** with BBr_3 can be further reacted with more CrO_3 in H_2SO_4 (more than the stoichiometric equivalent for direct oxidation of **Z** detailed above).

Following is a synthetic scheme to create an interesting organic molecule. It employs reagent **Z**:

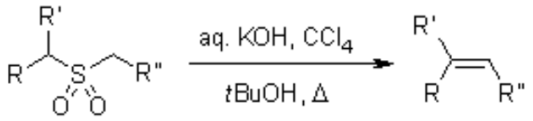


Ampelopsin F

1. Give structures for reagent **Z** and all unknowns in the scheme above.

Hints:

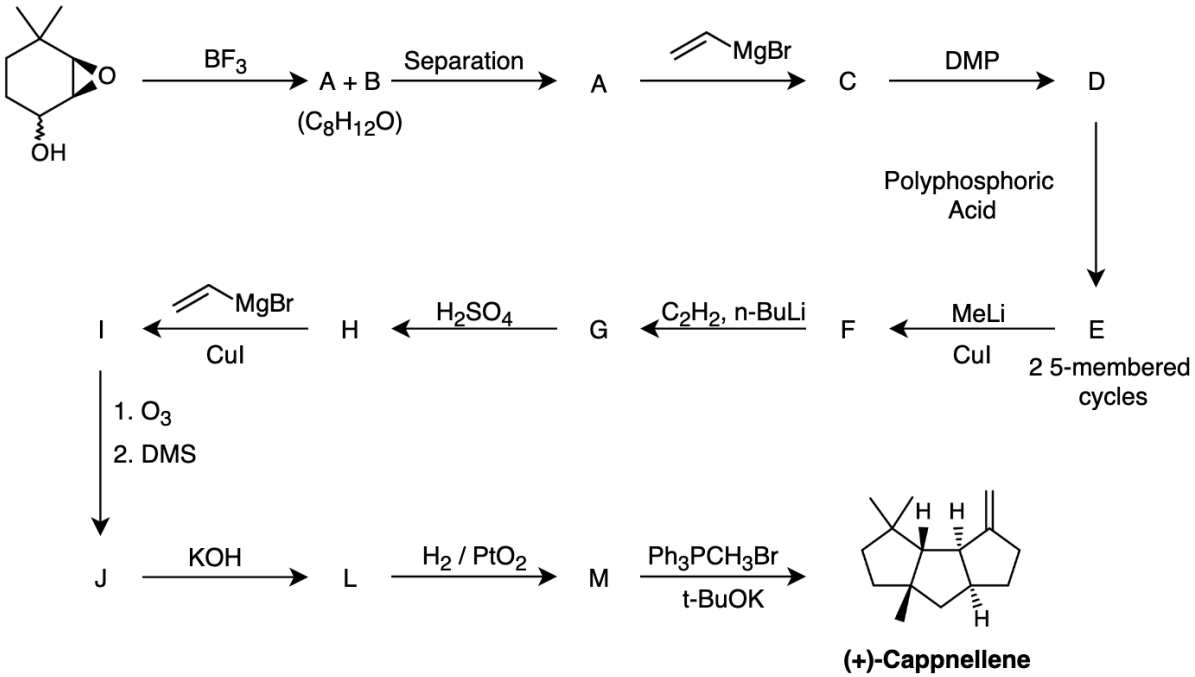
- Compound **C** is tetra-substituted.
- The transformation from **F** to **G** is a cyclization which produces a 5 membered ring.
- The transformation from **H** to **I** is known as the "Ramberg-Backlund reaction."



- The transformation from **I** to **J** is a cyclization.

Problem 17.C

Consider the following synthesis of (+)-Capnellene

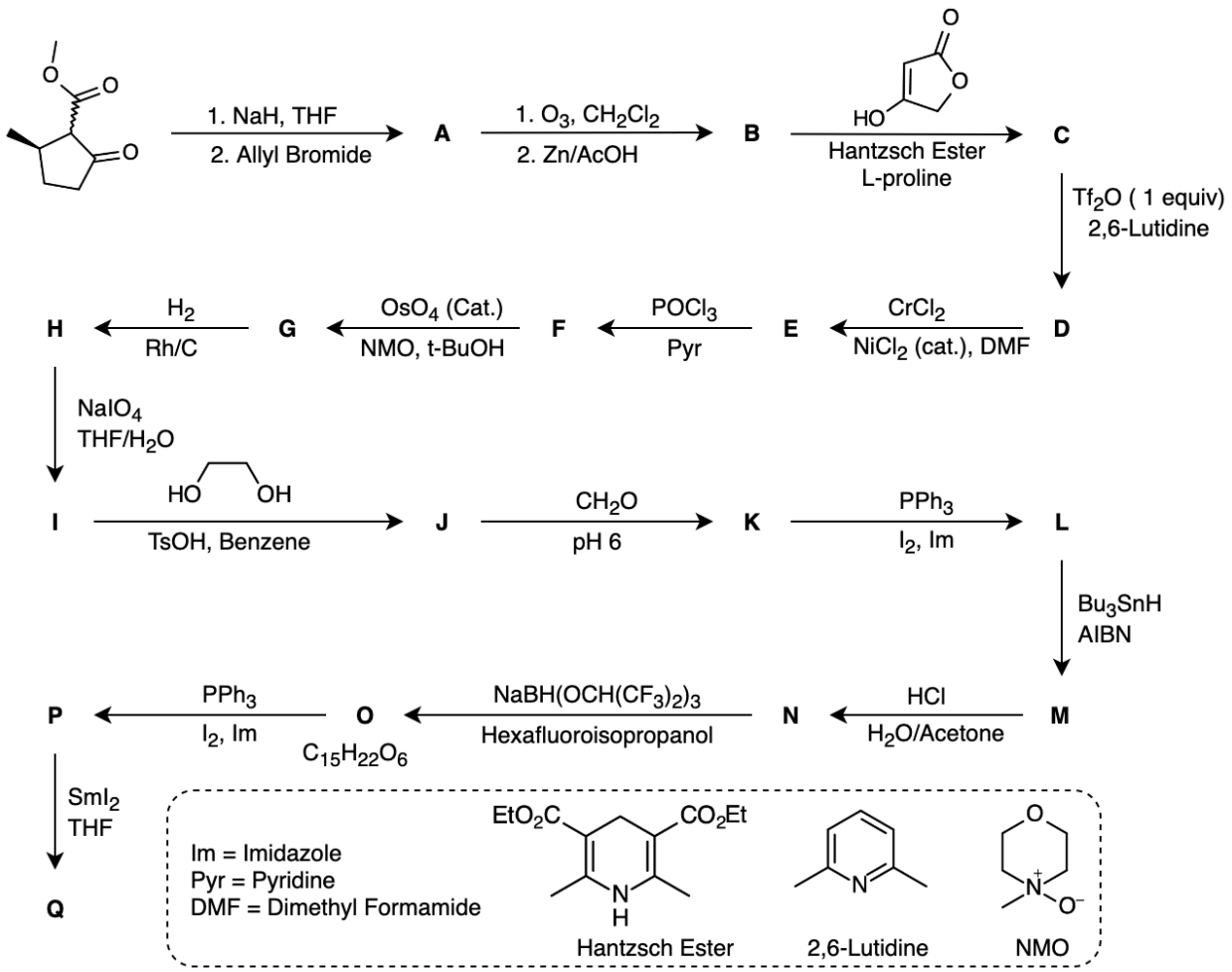


A and **B** are isomers of $C_8H_{12}O$. The **A** isomer is separated and used in the synthesis, while **B** is discarded. Notably, **A** is the more sterically hindered isomer between **A** and **B**.

Draw the structures of **A**-**M**.

Problem 20.B-CN (2019 Russia Winter Camp #1)

Shown below is the total synthesis of one fragment of a terpenoid, carried out in 2006 by a group of Swiss scientists.



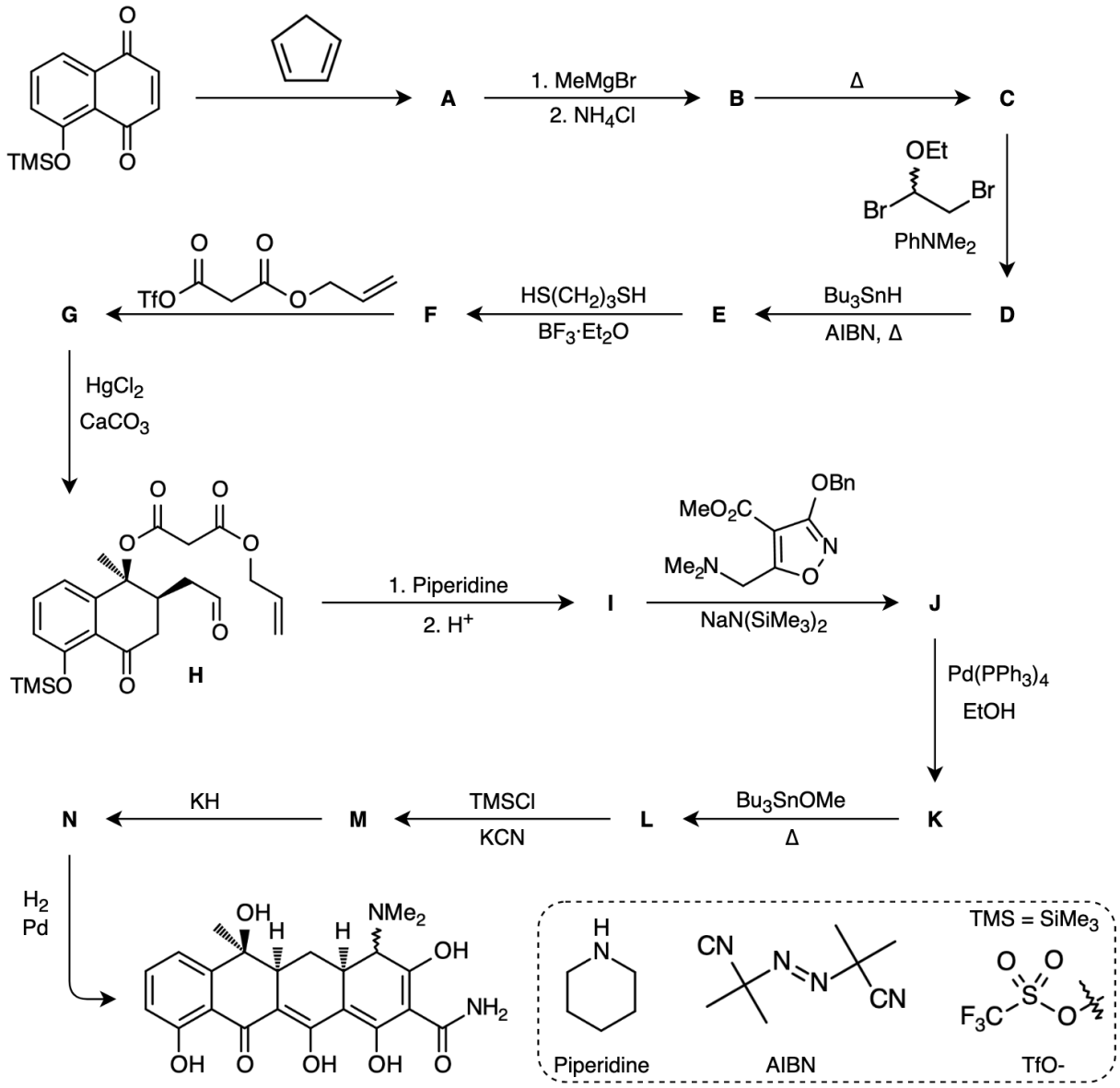
1. Draw the structures of **A** – **Q**, if it is known that the Hantszch ester in the third step reduces the Knoevenagel condensation product.

2. In the **N**→**O** step, a rather specific reducing agent is used. Why can't more common borohydride reducing agents (i.e. $NaBH_4$, $NaBH_3CN$, $NaBH(OAc)_3$) be used instead?

3. Propose a mechanism for **D**→**E**.

Problem 21.B (2017 Russia Winter Camp #5, simplified)

Tetracycline was synthesized by Stork et al. in 1996 according to the following scheme



E is tricyclic

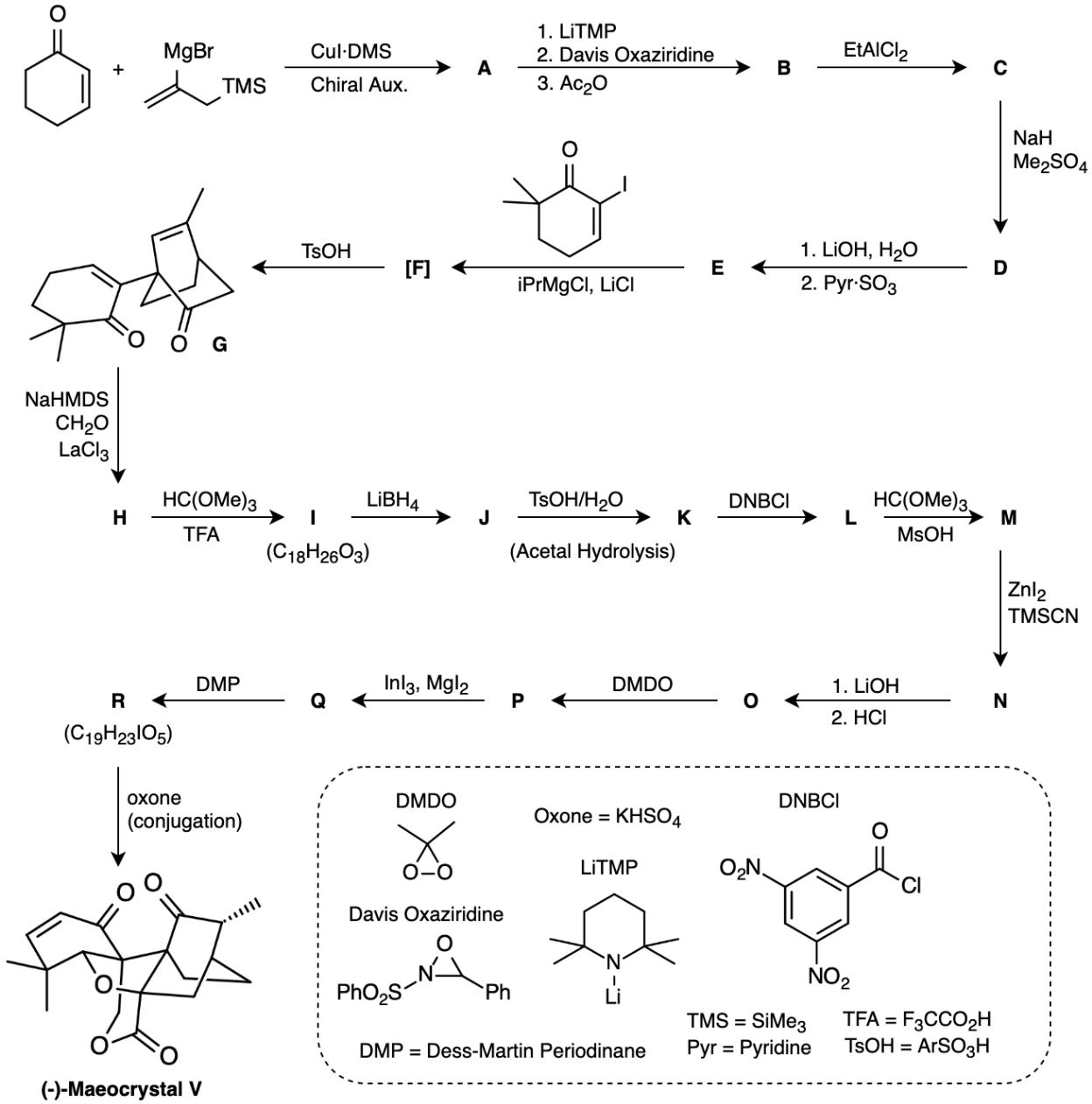
J→**K** are allyl deprotection conditions

1. Draw structures for **A**-**G** and **I**-**N**
2. Propose a mechanism for **J**→**K**

Problem 22.A-BN (2020 CODS-CT Shortlist)

Preface: *This problem is extremely difficult. Attempt at your own risk.*

Consider the following legendary synthesis of (-)-Maoecrystal V pioneered by the even more legendary Phil Baran (Note: necessary hints are present on the next page)



Hints:

- **C** is bicyclic
- The intermediate in the transformation from **G** → **H** is a diene if you squint hard enough.
    - **H** is non-conjugated.
- Although **I** and **M** are both substituted tetrahydrofurans, only 1 C-H bond exists in the THF moiety of **M**, whereas 2 C-H bonds exist in the THF moiety of **I**
- **P** is heptacyclic.
- The carbon with the iodine in **Q** also has a hydrogen attached.

1. Draw the structures of **A**-**R**.

Problems Part 2

The problems in the previous section were standard organic schemes of varying difficulties. However in recent years, a variant of the traditional scheme has become more popular: the so called “removed reagent” schemes. In these schemes, a large number of the reagents in a traditional synthesis scheme problem have been removed, and must now be deciphered along with the structure of the corresponding intermediates.

Naively, it may seem that such problems are impossible, and have no reasonable approach. In fact, I thought as much the first time I saw a problem of this style (for example: #10 in Problems Part 1 was the precursor to this style of problems - the penultimate step of the solution is to propose your own reagent for synthesis of the buckyball). However, they are actually reasonable, but almost always very challenging, problems.

The key to approaching these problems is to apply retrosynthesis and problem solving to come up with a likely approach that fits with whatever few reagents you are given. It is possible that there is more than one valid answer, however a well written problem of this style (note that neither of these qualities is guaranteed for a camp test problem) will typically only have one reasonable approach if you look hard enough. Also, these syntheses can usually be done without extremely complicated named reactions, using only “basic” (relatively speaking) reagents one would pick up from cursorily reading Clayden.

The general ranking scheme for the difficulty rating these problems was the same, however note that the added element of removing reagents makes accurately ranking the difficulty of the problems very tricky. Take the difficulties with a grain of salt.

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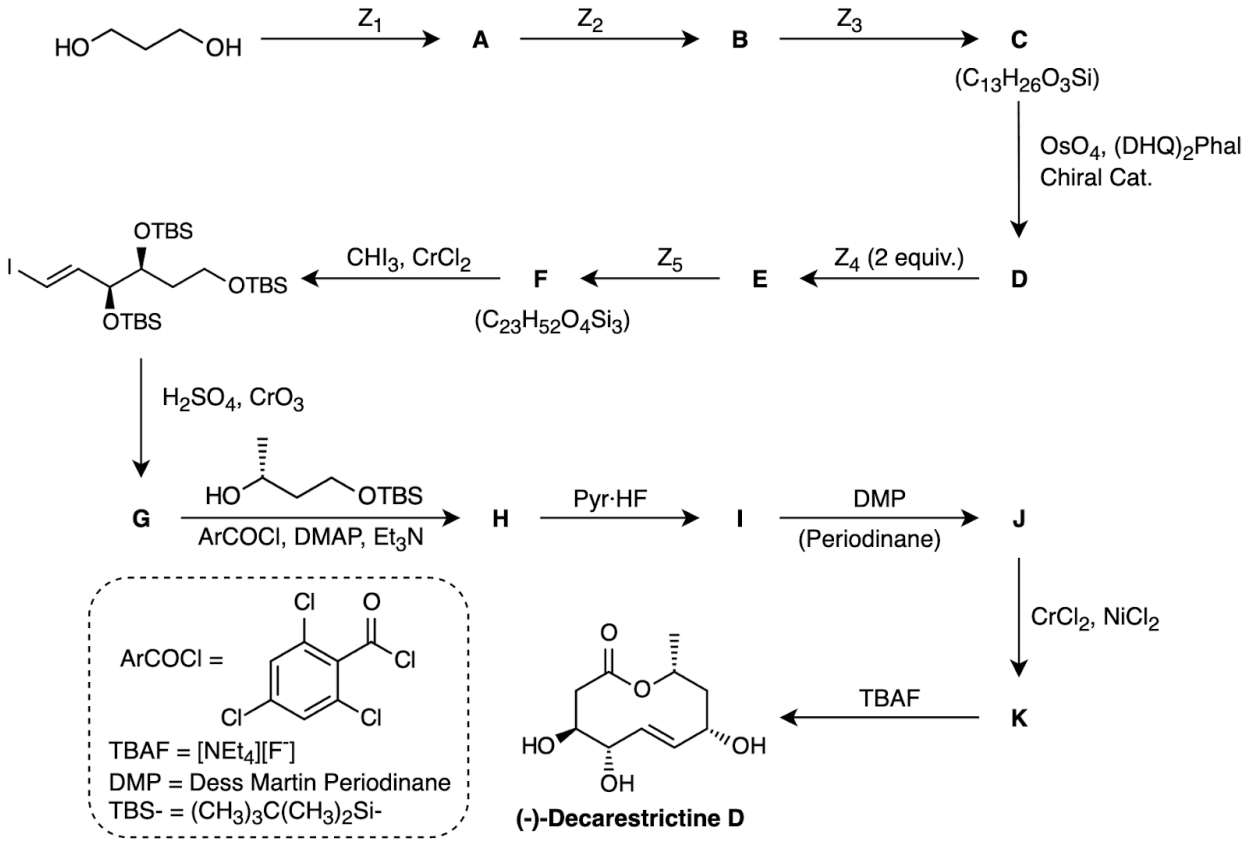
Problem 1.C-DN

Consider the following synthesis of (-)-Decarestrictine D

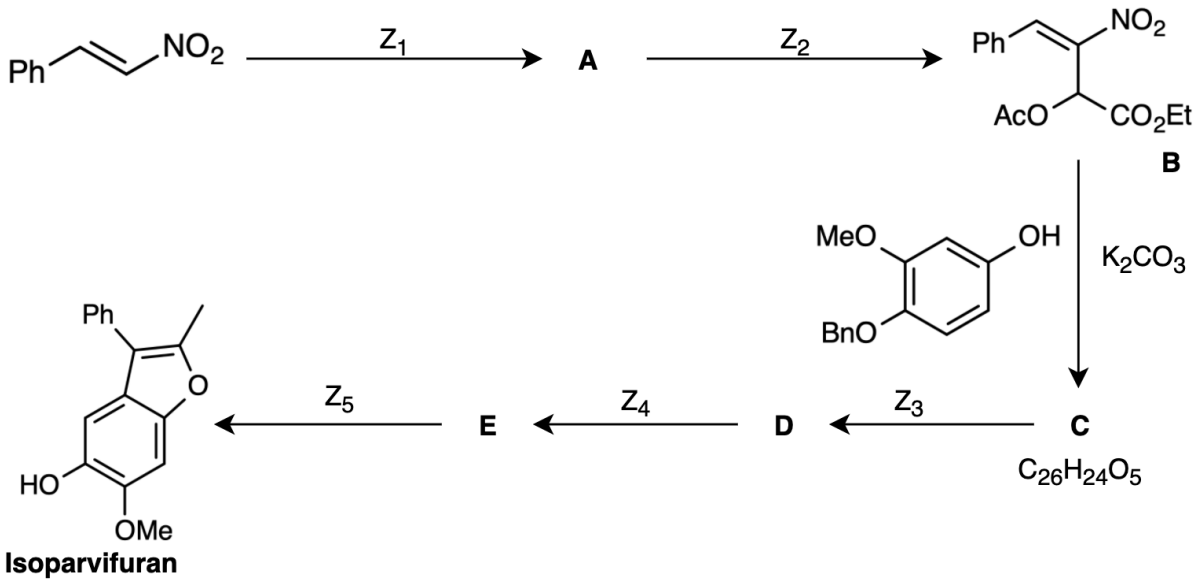


Z_1 - Z_5 are reagents/reaction conditions which you must propose.

1. Propose a suitable set of reagents Z_1 - Z_5 and the corresponding structures of **A**-**K**. More than one answer may be possible. You do not need to state solvents for Z_1 - Z_5.

Problem 2.C-D (Original by Andrew Feng)

Consider the following synthesis of Isoparvifuran



1. Propose a suitable set of reagents Z_1 - Z_5 and the corresponding structures of **A**,**C-E**. More than one answer may be possible. You do not need to state solvents for Z_1 - Z_5.