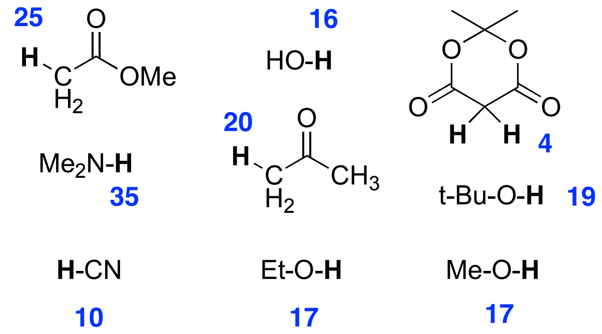
CHEM 330

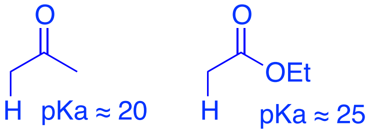
Problem set 2

1. Indicate the approximate pKa of the hydrogen in boldface in the following compounds

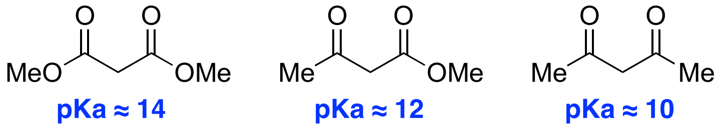


2. Consider the triad of 1,3-dicarbonyl structures shown below. Arrange these molecules in order of increasing Bronsted acidity of the active methylene and briefly - but clearly - account for your prediction.

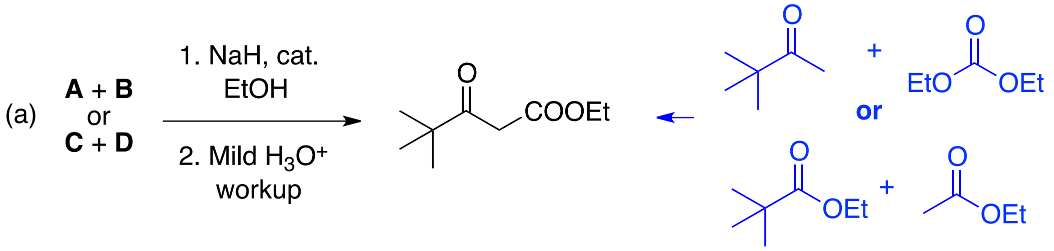
a keto carbonyl induces greater acidity at the α-C–H position than an ester carbonyl:



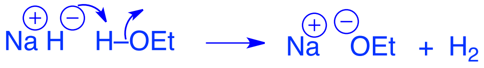
therefore, $CH_3CO{-}CH_2{-}COCH_3$ (2 keto C=O's activating the CH_2) must be more acidic than $CH_3CO{-}CH_2{-}COOCH_3$ (1 ketone + 1 ester C=O), and the latter must be more acidic than $CH_3OOC{-}CH_2{-}COOCH_3$ (2 ester C=O's). In fact:

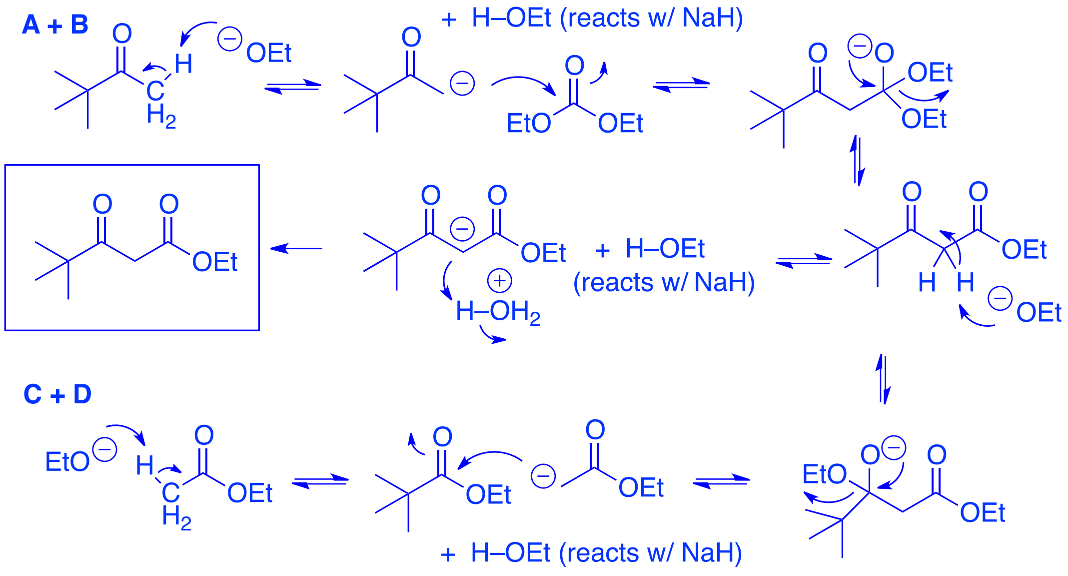


3. Identify the structure of substances **A- H** in the following reactions, and write a detailed electronic mechanism for each transformation:

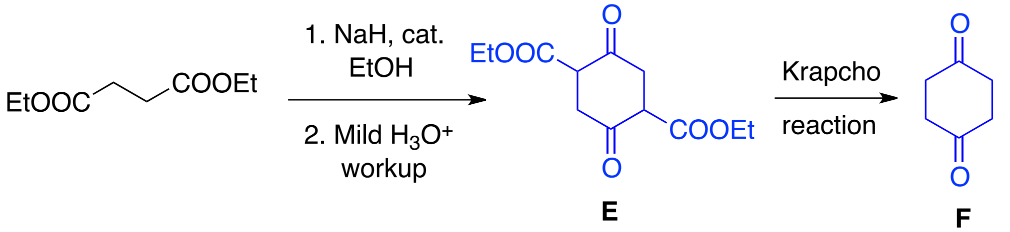


mechanisms:





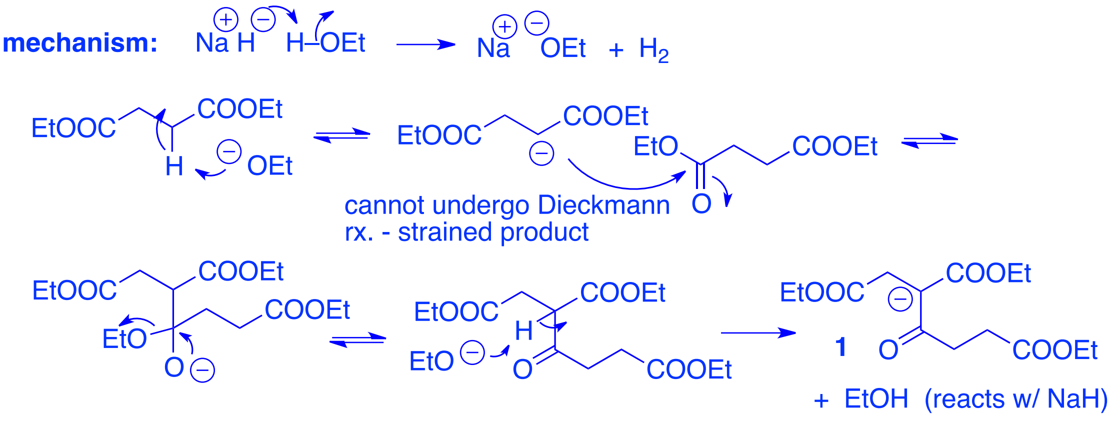
(b)



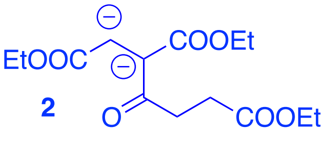
E
$C_{12}H_{16}O_6$

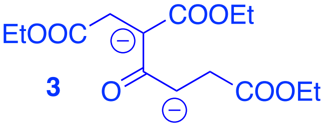
F
$C_6H_8O_2$

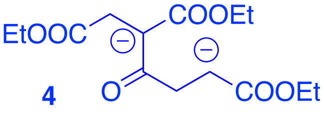
mechanism:



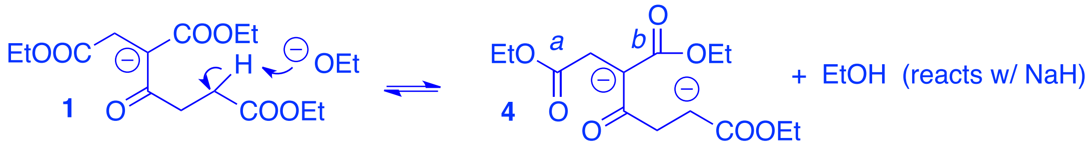
now: the protonated form of compound **1** above has formula $C_{14}H_{22}O_7$. To undergo further reaction leading to a product of formula $C_{12}H_{16}O_6$, **1** must lose a molecule of ethanol. This can only happen through a second Claisen-Dieckmann reaction, which in turn requires **1** to undergo further deprotonation to a dianionic species. Three isomeric dianions, structures **2**-**4** below, could possibly form upon deprotonation of **1:**


2

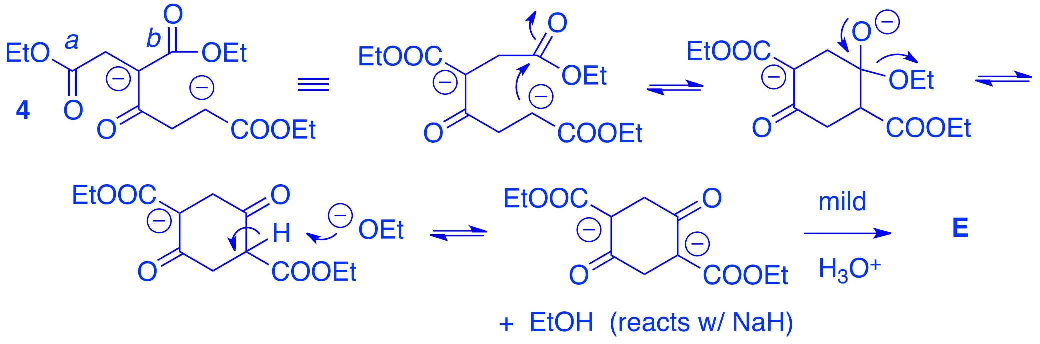

3


4

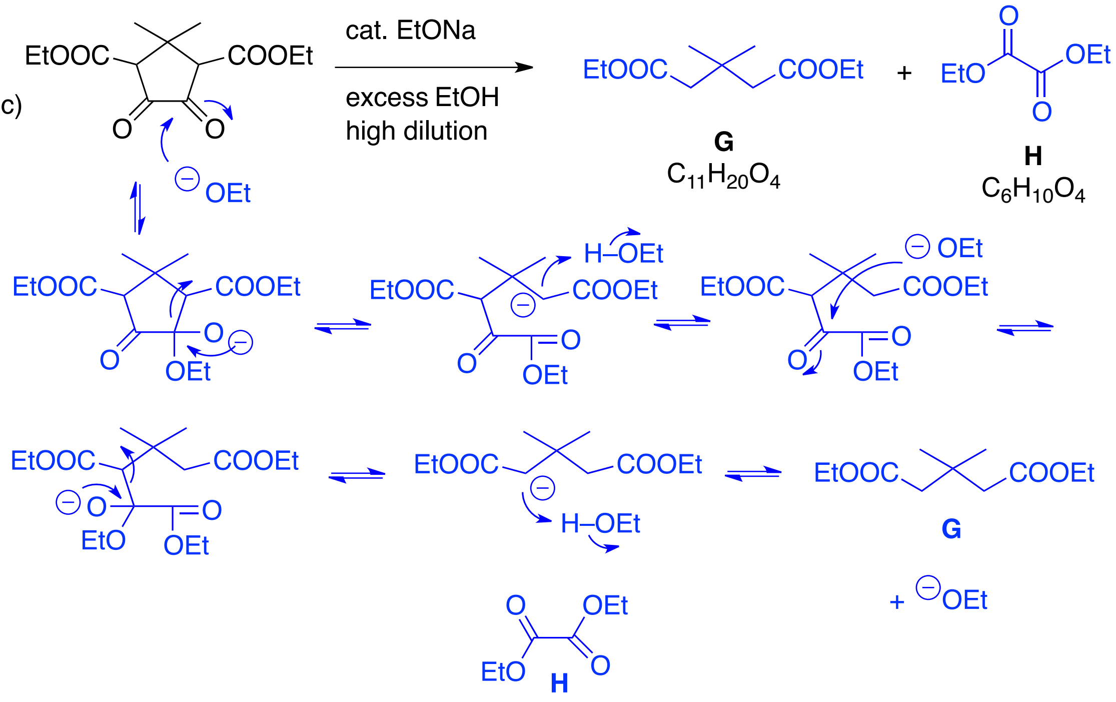
Compound **4** must surely be the least energetic one among the three, because the negative charges are as far apart as possible. Then, subsequent Claisen-Dieckmann steps are likely to evolve from **4**:



The non-stabilized ester enolate in structure **4** can participate in Dieckmann reaction by adding nucleophilically to carbonyl group *a* or to carbonyl group *b*. Addition to *b* is disfavored because that carbonyl participates in resonance stabilization of the ketoester enolate, and so it is significantly less electrophilic than *a*. But then:

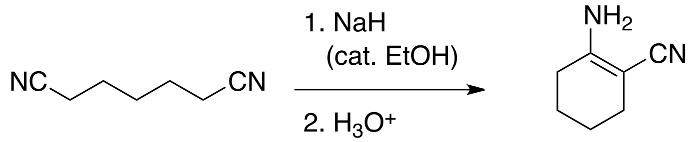


(c)



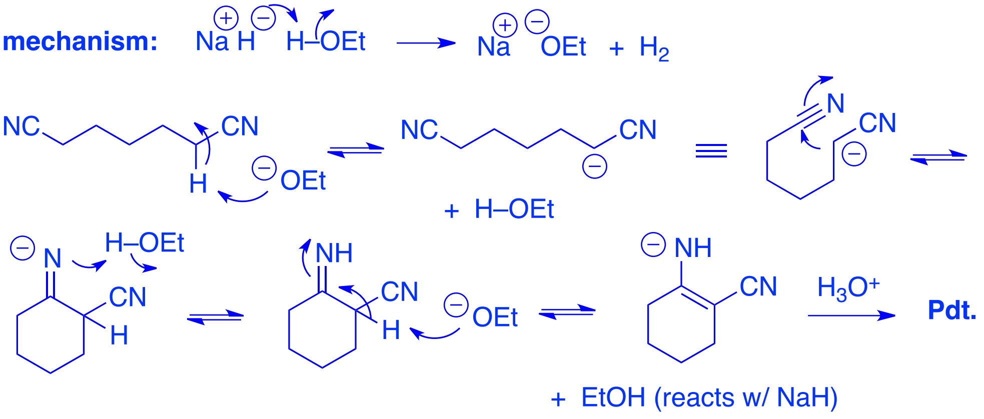
4. Write a detailed mechanism for the following known reactions.

a

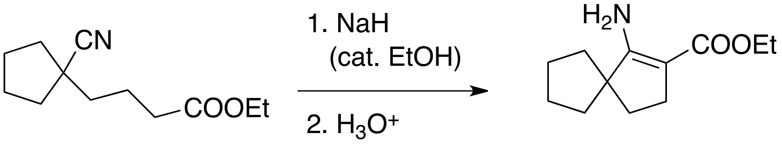


(a Thorpe reaction)

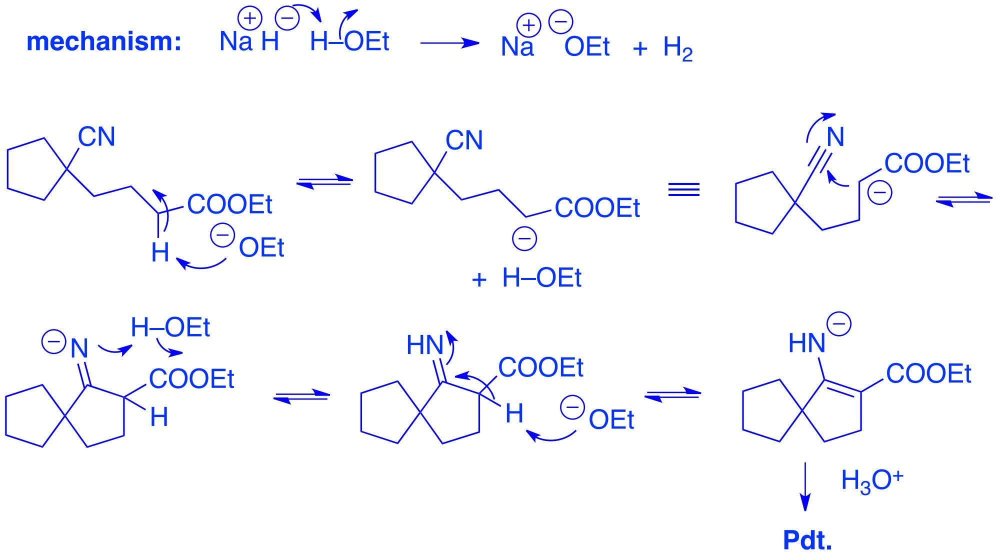
mechanism:



b



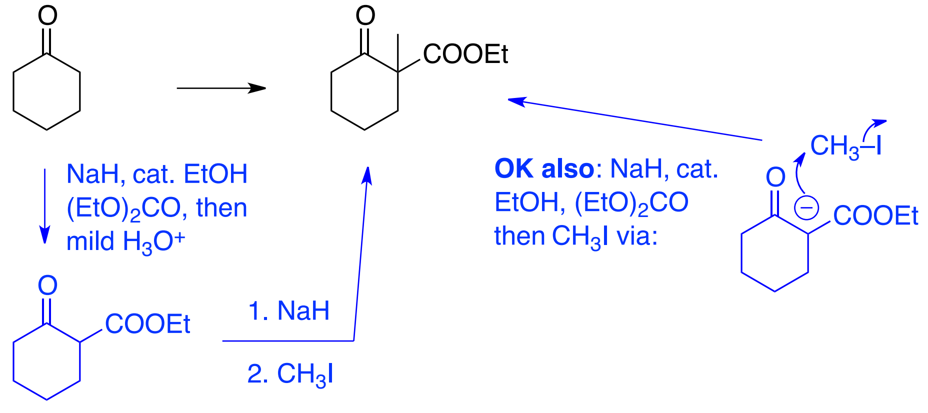
mechanism:



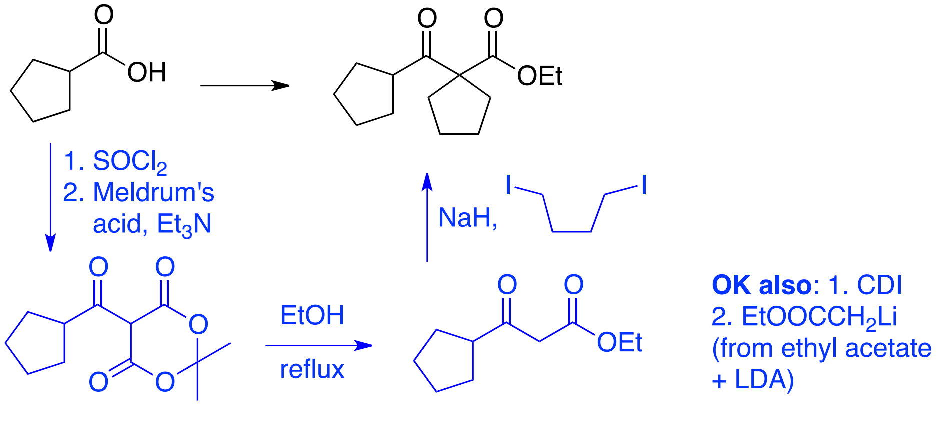
The above exercises underscore the similarity between the ester and the nitrile functionality.

5. Propose a method to accomplish the transformations shown below. In each case, a multistep sequence (= not just one reaction, but several) may be required. Assume the availability of all reagents needed to convert the starting material into the product (e.g, bases, alkyl halides, etc.). Present your answer as a flowchart.

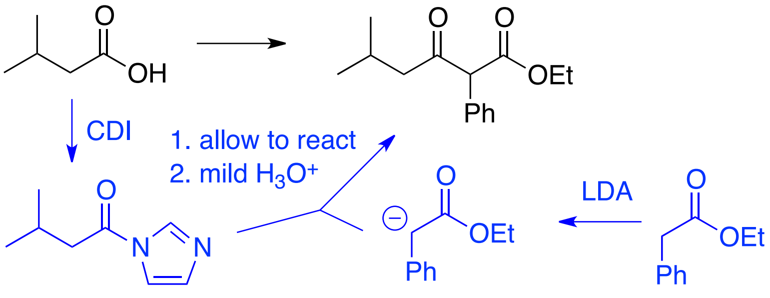
a.



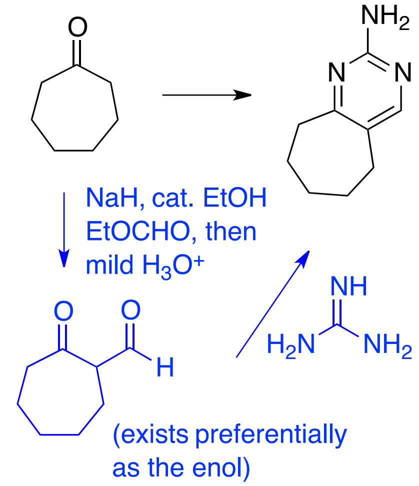
b.



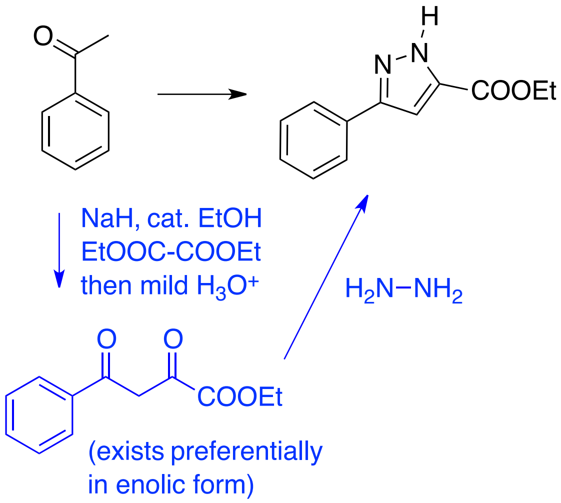
c.



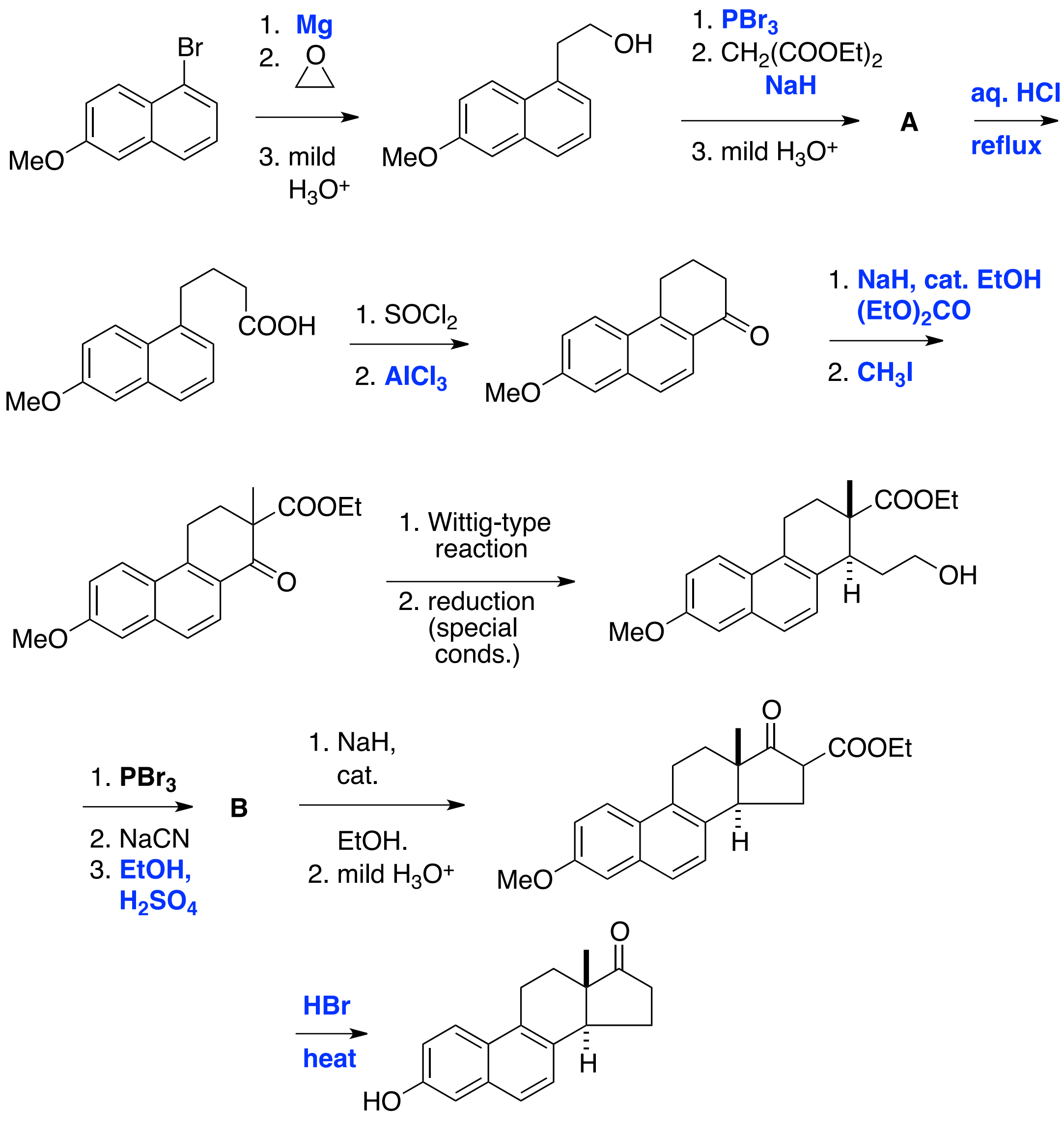
d.



e.



4. The sequence below is inspired by a landmark synthesis of the steroid hormone, equilenin, by Bachmann *et al.* (*J. Am. Chem. Soc.* **1939**, *61*, 974). Provide all missing reagents / intermediates / conditions required to effect the various transformations.


Br
MeO
1. Mg
2. O
3. mild H3O+
OH
MeO
1. PBr3
2. CH2(COOEt)2 NaH
3. mild H3O+
A
aq. HCl
reflux
COOH
MeO
1. SOCl2
2. AlCl3
O
MeO
1. NaH, cat. EtOH (EtO)2CO
2. CH3I
COOEt
O
MeO
1. Wittig-type reaction
2. reduction (special conds.)
COOEt
OH
H
MeO
1. PBr3
2. NaCN
3. EtOH, H2SO4
B
1. NaH, cat. EtOH.
2. mild H3O+
O
COOEt
H
MeO
HBr
heat
O
H
HO

equilenin