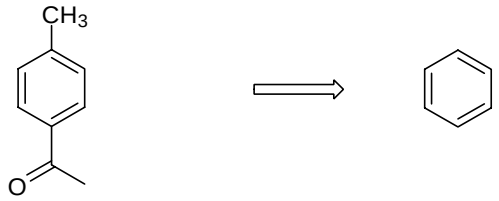
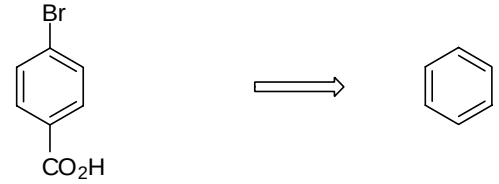
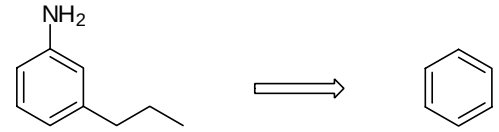
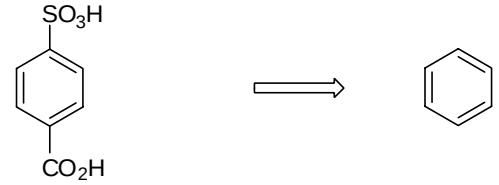
Chemistry 3720 Benzene Synthesis Problems

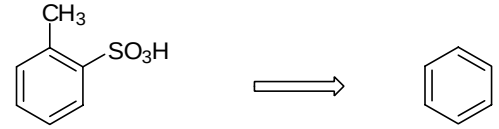
Provide an efficient synthesis of each of the following substituted benzenes from benzene itself. Use any of the reagents seen in Chemistry 3719/3720 so far and pay careful attention to the order of steps. Assume that mixtures may be separated.

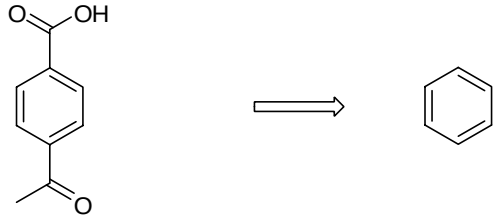










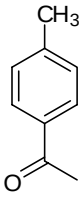


Chemistry 3720 Benzene Synthesis Problems - Key

Provide an efficient synthesis of each of the following substituted benzenes from benzene itself. Use any of the reagents seen in Chemistry 3719/3720 so far and pay careful attention to the order of steps. Assume that mixtures may be separated.

1. CH_3Cl, $AlCl_3$

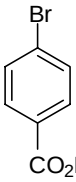
2. CH_3COCl, $AlCl_3$



Put CH_3 on first then send next group o/p major and separate the isomers

1. Br_2, Fe

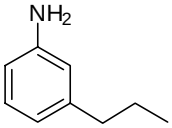
2. CH_3Cl, $AlCl_3$
(separate from *o*-isomer)
3. $KMnO_4$



Br and CH_3 both o/p directors but CH_3 is activating - probably a cleaner reaction (fewer over-substituted products if Br goes on first - have to oxidize last as -CO_2H is a meta director

1. CH_3CH_2COCl, $AlCl_3$

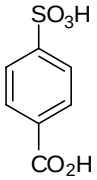
2. HNO_3, H_2SO_4
3. Sn, HCl
4. Zn, HCl



Putting NO_2 or the acyl group on first would send the next group to the meta position (either would do) and then reduction would give the desired product

1. CH_3Cl, $AlCl_3$

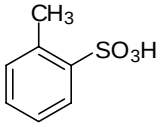
2. SO_3, H_2SO_4
(separate from *o*-isomer)
3. $KMnO_4$



Put CH_3 on first (o/p director) then bring in SO_3H group (m director) - oxidize CH_3 to CO_2H (m director)

1. CH_3Cl, $AlCl_3$

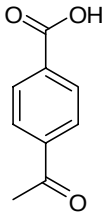
2. SO_3, H_2SO_4



Introduce CH_3 first (o/p director), separate isomers, then bring in SO_3H group (m director)

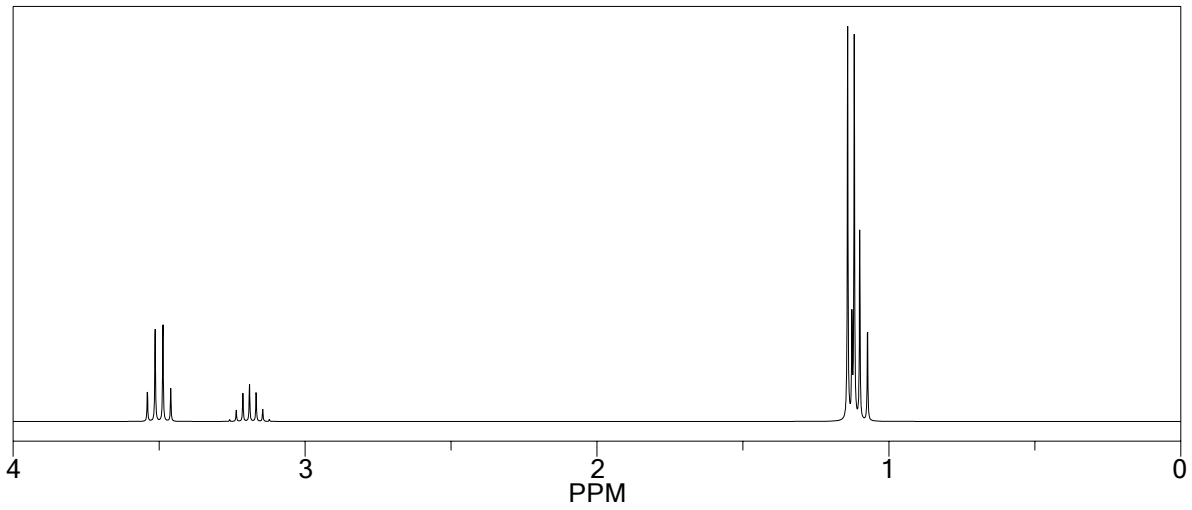
1. CH_3Cl, $AlCl_3$

2. CH_3COCl, $AlCl_3$
(separate from *o*-director)
3. $KMnO_4$

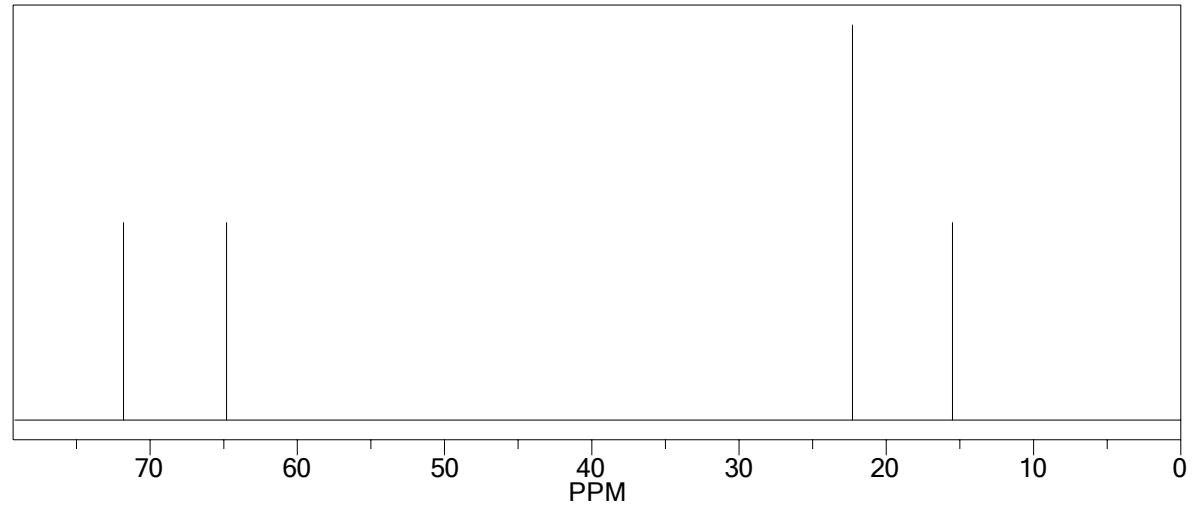


Put CH_3 on first (o/p director) then bring in acyl group (m director) - separate from o-isomer - then oxidise the CH_3 group to CO_2H

1. (10 pts) An unknown organic compound has the molecular formula $C_5H_{12}O$, in the mass spectrum, M+ = 88.09. Given the following ^1H and ^{13}C data, give the structure of the unknown and assign all of the ^1H and ^{13}C signals.

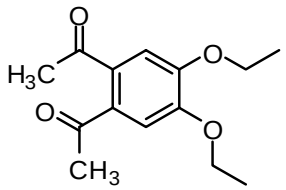


^1H NMR (ppm) 1.14 (t, 3H, *J* = 7.2 Hz), 1.09 (d, 6H, *J* = 7.0 Hz), 3.19 (septet, 1H, *J* = 7.0 Hz), 3.50 (q, 2H, *J* = 7.2 Hz)



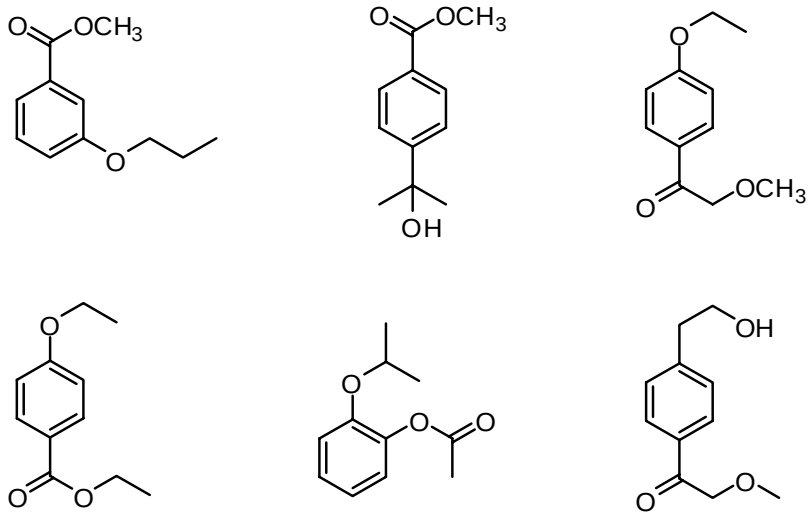
^{13}C NMR (ppm) 15.5, 22.3 (double), 64.8, 71.8

2. (10 pts) Draw the approximate ^{13}C NMR spectrum of the following molecule. Include approximate chemical shifts and indicate which signal corresponds to which carbon(s) in the molecule.



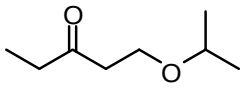
3. (10 pts) A chemist produces a new compound with the following spectral characteristics and considers the new material to be one of the possibilities shown below. Which structure is correct and why? Include a complete assignment of all of the spectral data in your answer.

^{1}H NMR (ppm)	1.32 (t, 3H, *J* = 7.0 Hz), 3.30 (s, 3H,), 4.09 (q, 2H, *J* = 7.0 Hz), 4.63 (s, 2H), 7.10 (m, 2H), 7.83 (m, 2H)
^{13}C NMR (ppm)	14.8, 57.2, 64.6, 81.2, 126.1, 129.4 (double), 129.7 (double), 163.8, 198.3
IR (cm^{-1})	1740, 810

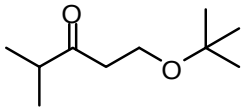


4. (10 pts) Draw the expected ^{1}H and ^{13}C NMR spectra of the following molecules. Include chemical shifts and line shapes (singlet, doublet, etc.) in the ^{1}H spectra and intensities in the ^{13}C spectra. Also indicate which signal corresponds to which proton(s) and carbon(s).

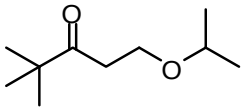
a.



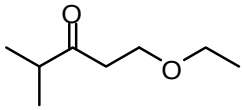
b.



c.



d.



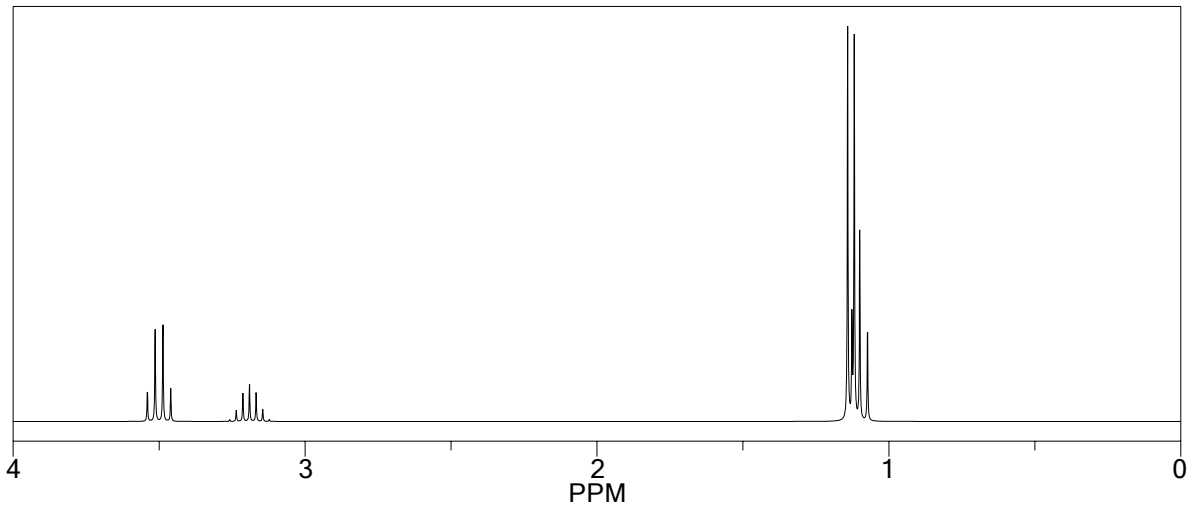
5. (10 pts) An unknown organic compound has the molecular formula $C_{11}H_{14}O_2$. Given the following spectral data, provide a structure for the unknown that agrees with the data, and then assign the data.

^{1}H NMR (ppm)	2.50 (s, 3H), 2.75 (t, 2H, *J* = 7.2 Hz), 3.30 (s, 3H), 2.52 (t, 2H, *J* = 7.2 Hz), 7.37-7.76 (m, 4H)
^{13}C NMR (ppm)	26.6, 35.3, 59.3, 73.0, 126.0, 127.7, 128.5, 132.1, 1391, 139.2, 197.0
Mass spectrum (m/z)	178.10 (M+)
Infra Red (cm^{-1})	1730, 760, 690

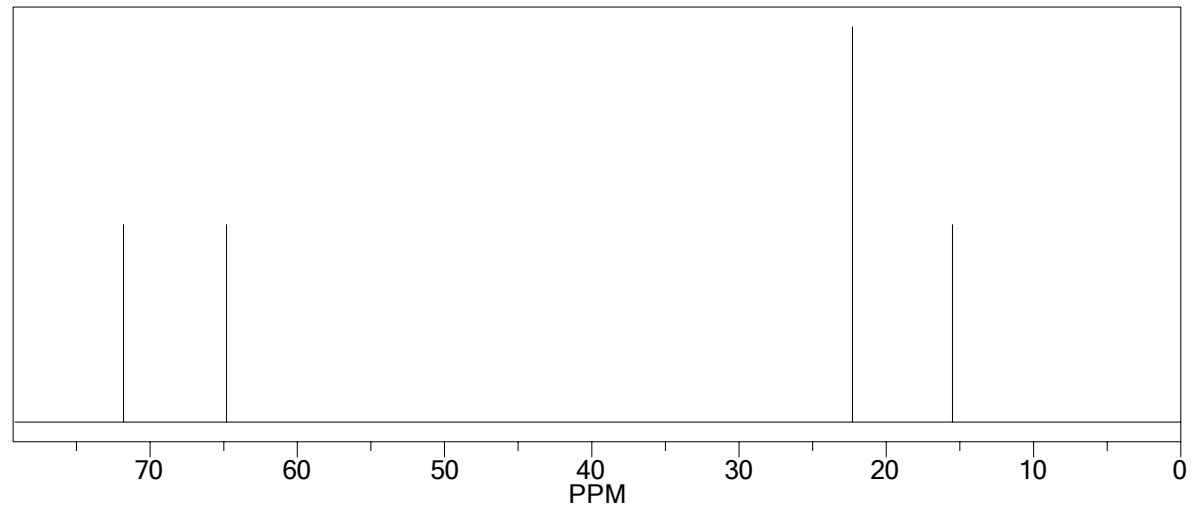
6. (10 pts) An unknown organic compound has the molecular formula $C_{12}H_{16}O_2$ and, in the mass spectrum, M+ = 192.12. Given the following ^{1}H and ^{13}C data, give the structure of the unknown and then assign all of the ^{1}H signals.

^{1}H NMR (ppm)	1.20 (d, 6H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.1 Hz), 2.87 (septet, 1H, *J* = 7.0 Hz), 4.30 (q, 2H, *J* = 7.1 Hz), 7.41 (d, 2H), 7.97 (d, 2H)
^{13}C NMR (ppm)	14.1, 23.3 (double), 33.2, 60.9, 126.0 (double), 127.3, 129.6 (double), 155.7, 165.9

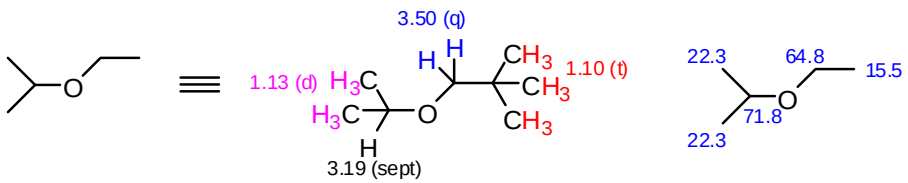
1. (10 pts) An unknown organic compound has the molecular formula $C_5H_{12}O$, in the mass spectrum, M+ = 88.09. Given the following ^1H and ^{13}C data, give the structure of the unknown and assign all of the ^1H and ^{13}C signals.



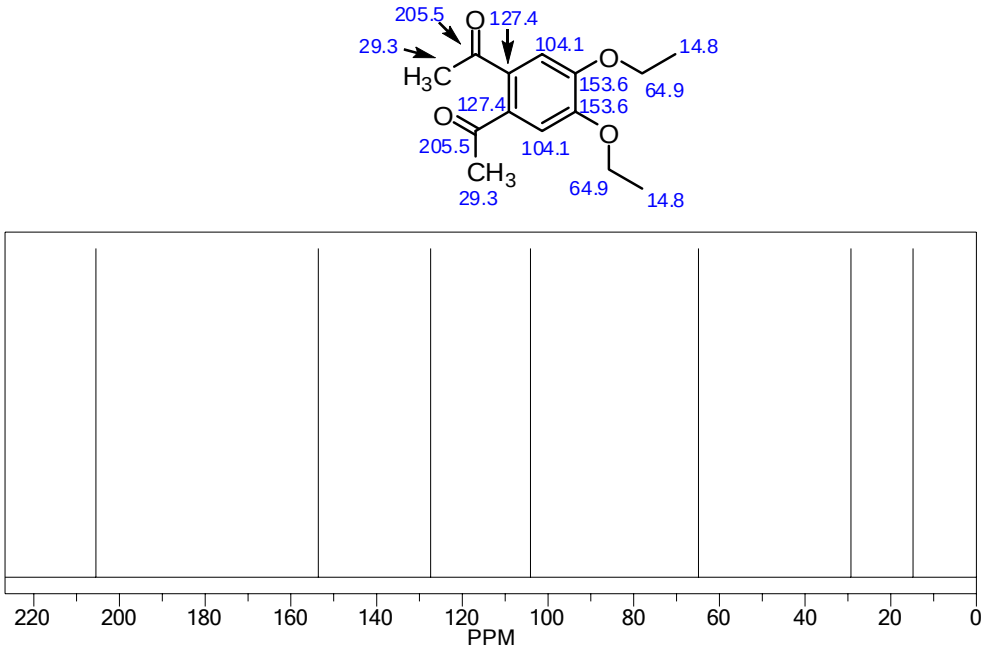
^1H NMR (ppm) 1.14 (t, 3H, *J* = 7.2 Hz), 1.09 (d, 6H, *J* = 7.0 Hz), 3.19 (septet, 1H, *J* = 7.0 Hz), 3.50 (q, 2H, *J* = 7.2 Hz)



^{13}C NMR (ppm) 15.5, 22.3 (double), 64.8, 71.8

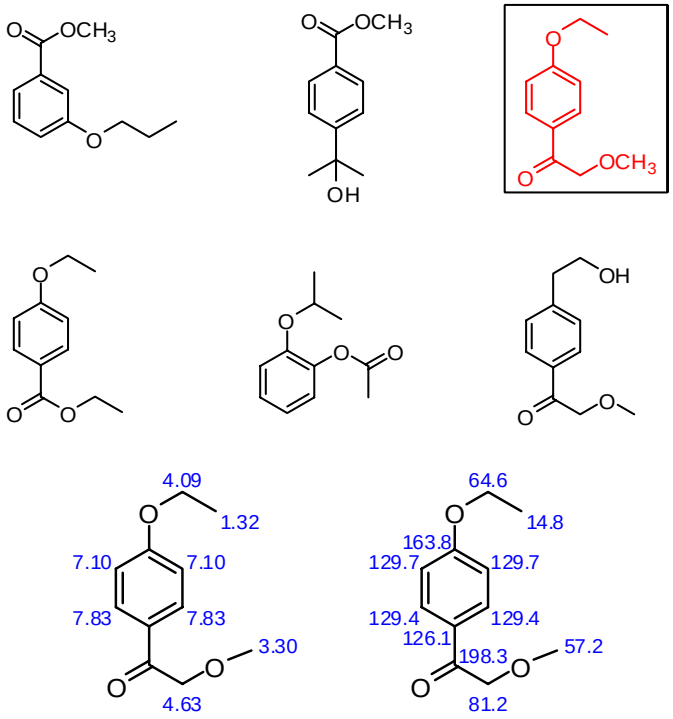


2. (10 pts) Draw the approximate ^{13}C NMR spectrum of the following molecule. Include approximate chemical shifts and indicate which signal corresponds to which carbon(s) in the molecule.



3. (10 pts) A chemist produces a new compound with the following spectral characteristics and considers the new material to be one of the possibilities shown below. Which structure is correct and why? Include a complete assignment of all of the spectral data in your answer.

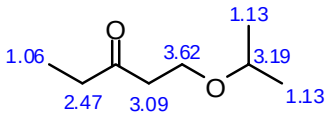
^{1}H NMR (ppm)	1.43 (t, 3H, J = 7.0 Hz), 3.47 (s, 3H,), 4.11 (q, 2H, J = 7.0 Hz), 4.76 (s, 2H), 7.17 (m, 2H), 7.83 (m, 2H)
^{13}C NMR (ppm)	14.8, 57.2, 64.6, 81.2, 126.1, 129.4 (double), 129.7 (double), 163.8, 198.3
IR (cm^{-1})	1740, 810

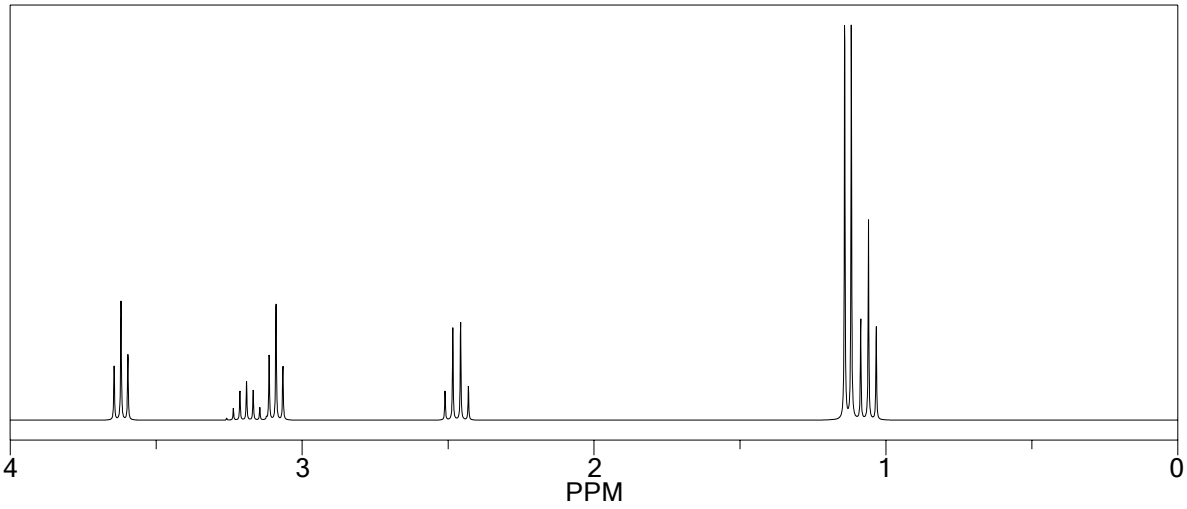


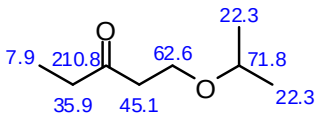
IR: 1740 = C=O, 810 = *para* disubstitution

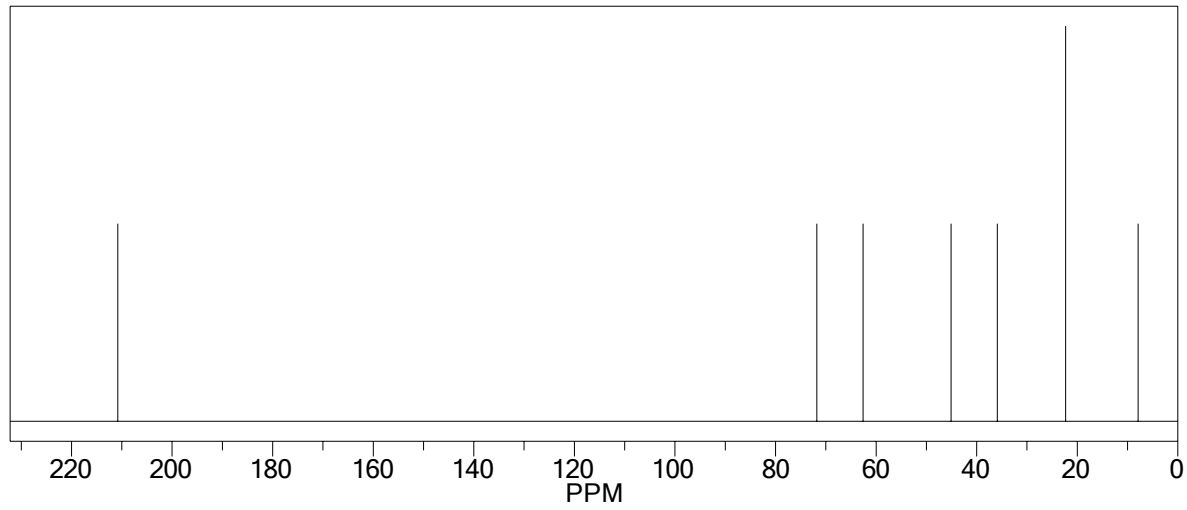
4. (10 pts) Draw the expected ^{1}H and ^{13}C NMR spectra of the following molecules. Include chemical shifts and line shapes (singlet, doublet, etc.) in the ^{1}H spectra and intensities in the ^{13}C spectra. Also indicate which signal corresponds to which proton(s) and carbon(s).

a.

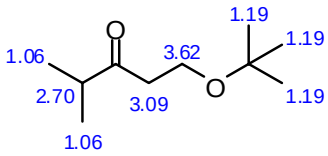


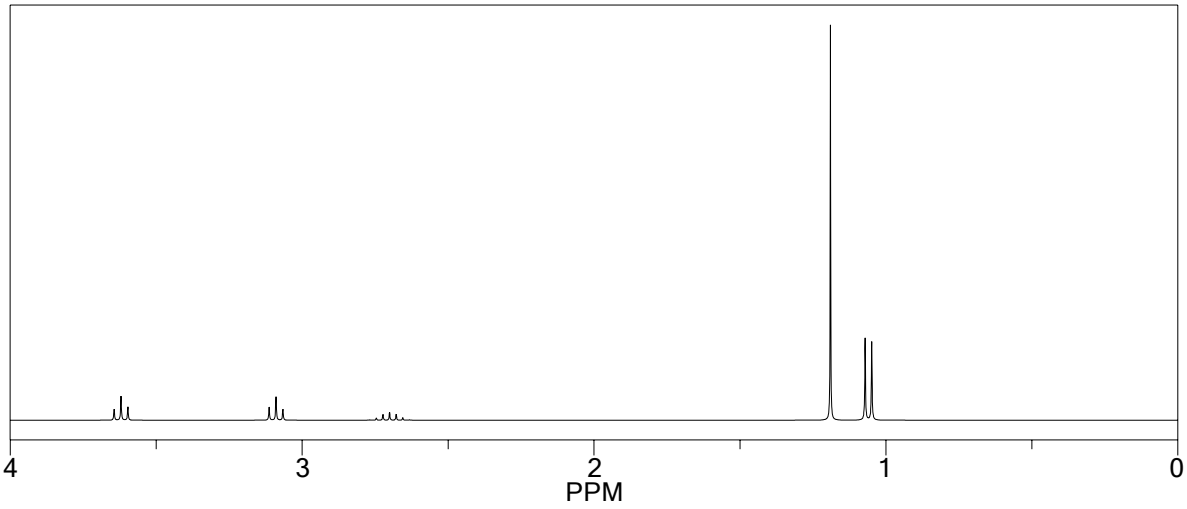


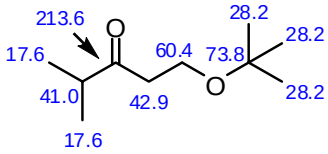


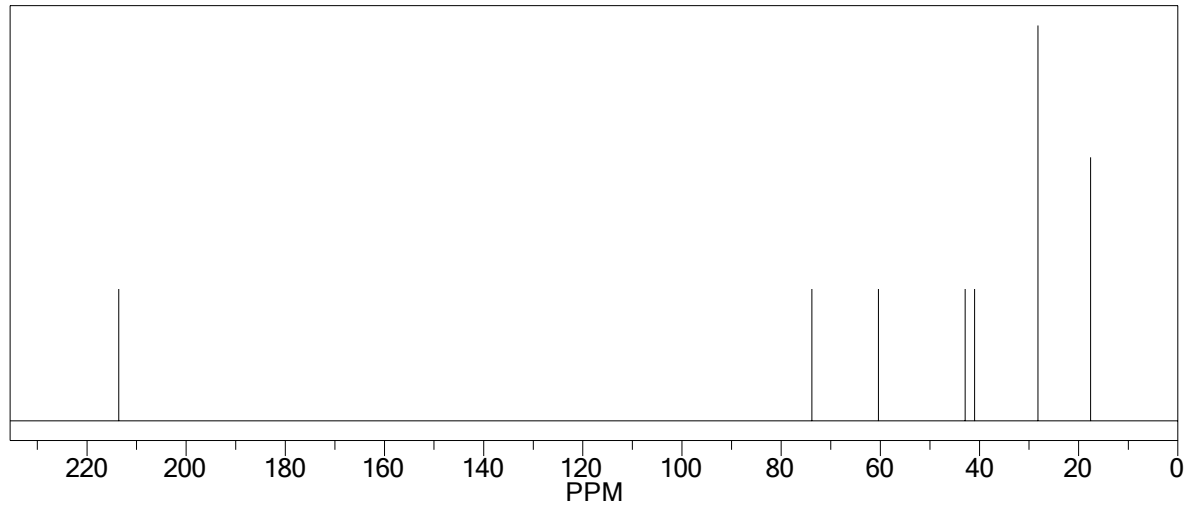


b.

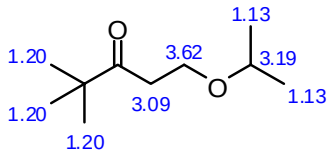

1.19
1.19
1.06
3.62
O
2.70
3.09
1.19
1.06

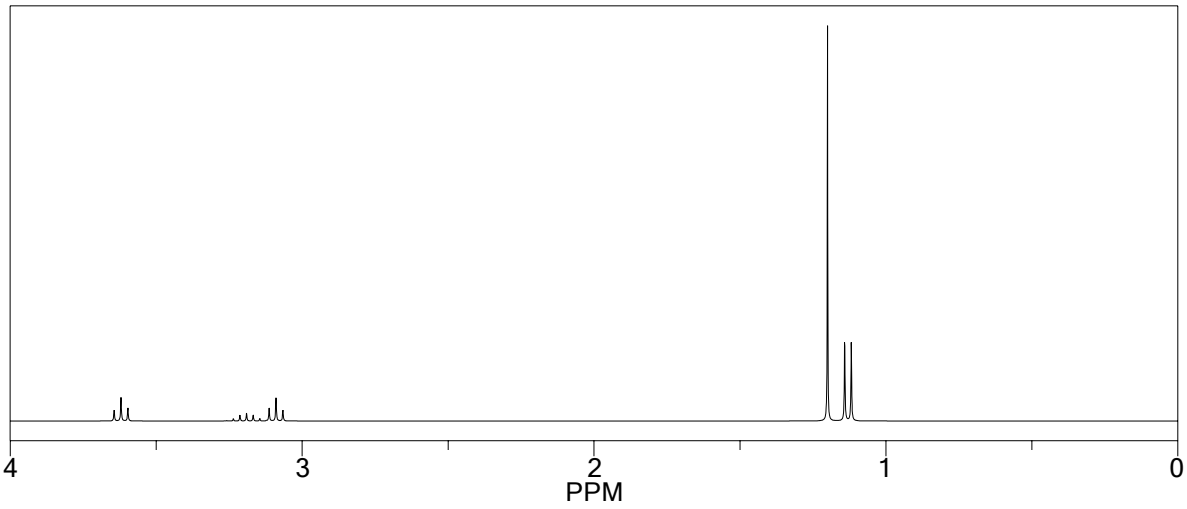

4
3
2
1
0
PPM

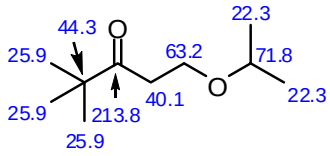

213.6
28.2
O
17.6
60.4
73.8
28.2
O
41.0
42.9
28.2
17.6

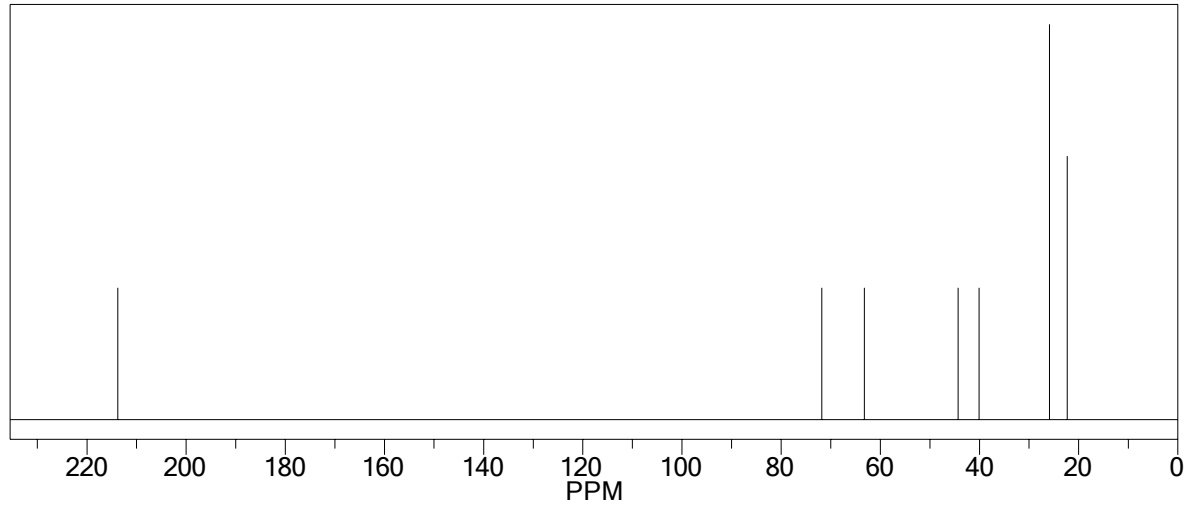

220
200
180
160
140
120
100
80
60
40
20
0
PPM

c.

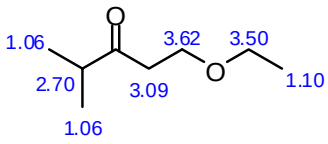

1.13
O
1.20
3.62
3.19
O
1.13
3.09
1.20
1.20

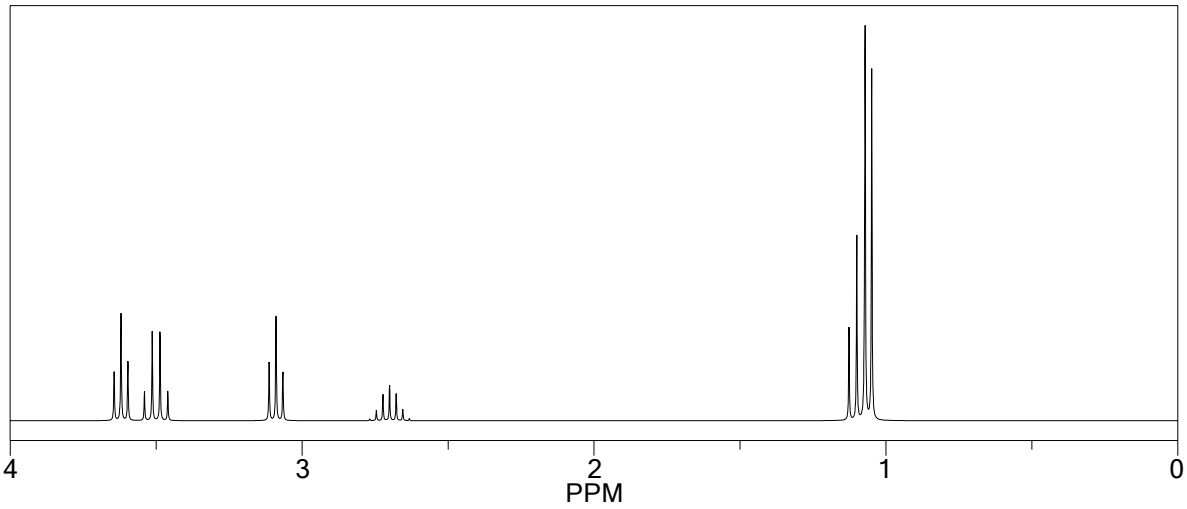

4
3
2
1
0
PPM

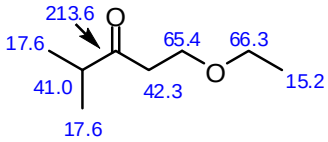

22.3
44.3
O
25.9
63.2
71.8
O
40.1
22.3
25.9
213.8
25.9

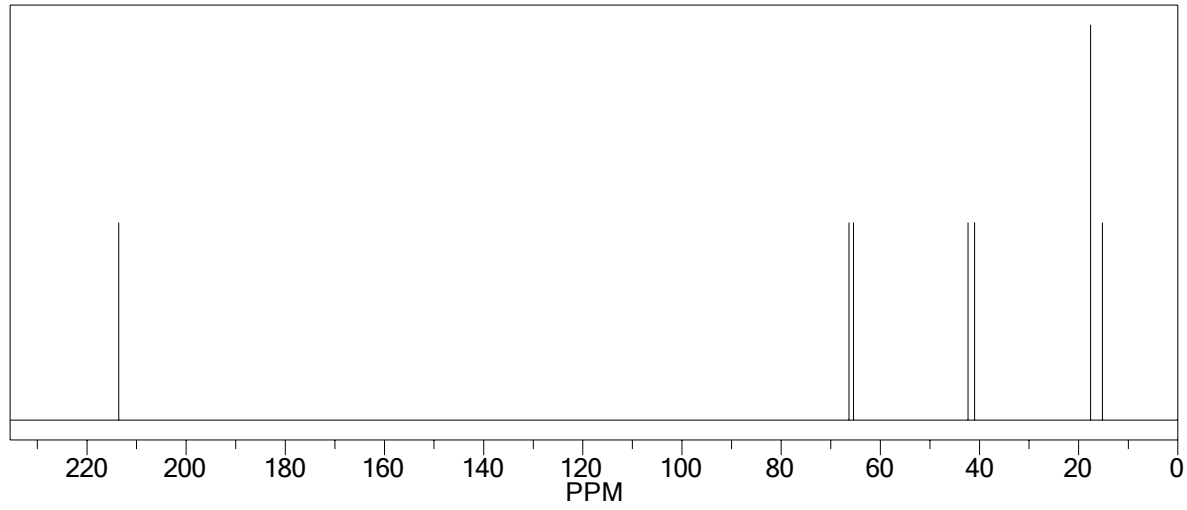

220
200
180
160
140
120
100
80
60
40
20
0
PPM

d.


1.06
2.70
1.06
3.09
3.62
3.50
1.10
O
O


4
3
2
1
0
PPM

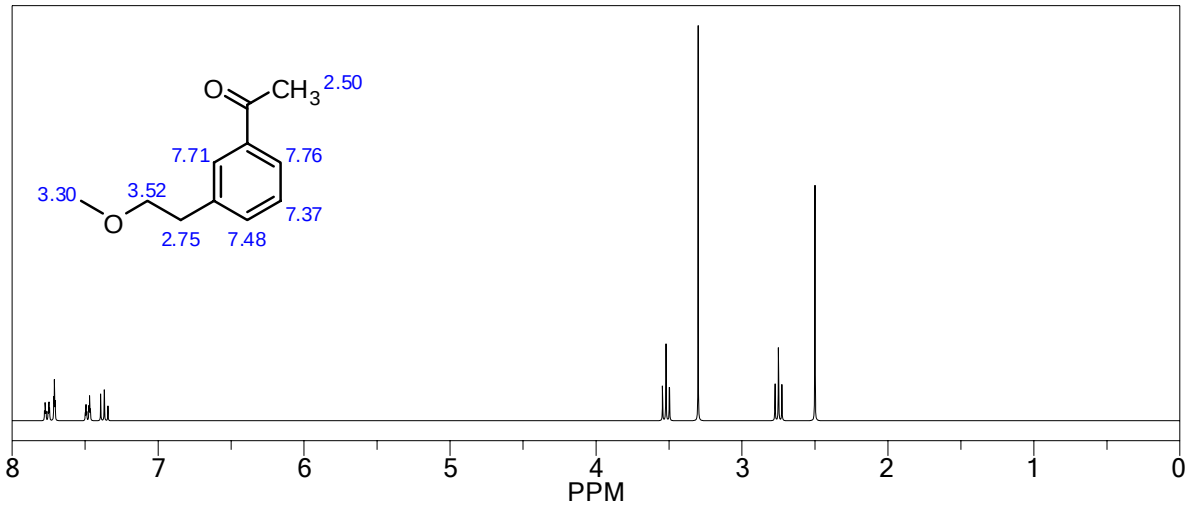

213.6
17.6
41.0
17.6
42.3
65.4
66.3
15.2
O
O


220
200
180
160
140
120
100
80
60
40
20
0
PPM

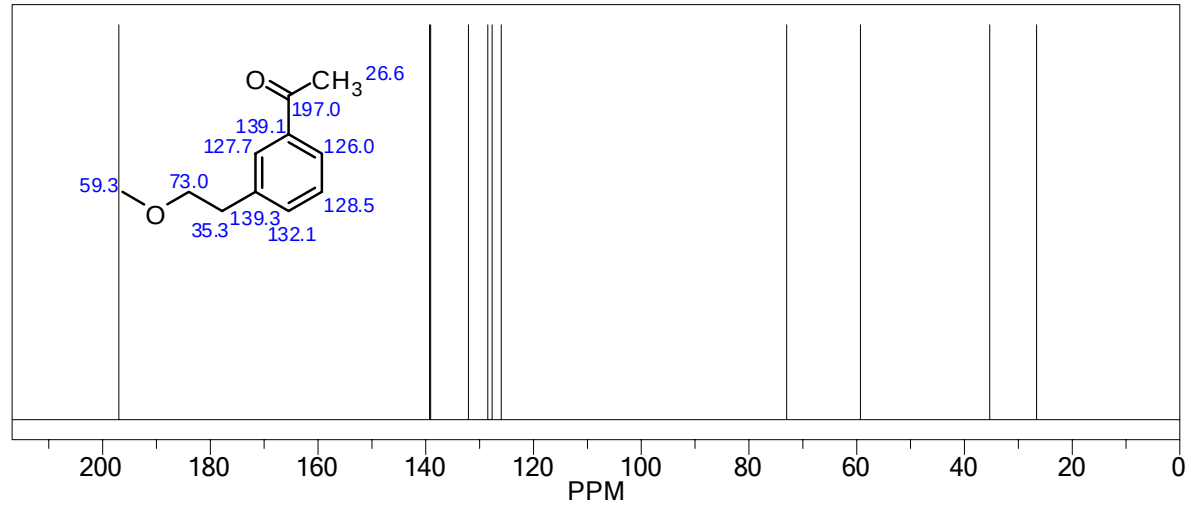
5. (10 pts) An unknown organic compound has the molecular formula $C_{11}H_{14}O_2$. Given the following spectral data, provide a structure for the unknown that agrees with the data, and then assign the data.

^{1}H NMR (ppm)	2.50 (s, 3H), 2.75 (t, 2H, *J* = 7.2 Hz), 3.30 (s, 3H), 2.52 (t, 2H, *J* = 7.2 Hz), 7.37-7.76 (m, 4H)
^{13}C NMR (ppm)	26.6, 35.3, 59.3, 73.0, 126.0, 127.7, 128.5, 132.1, 1391, 139.2, 197.0
Mass spectrum (m/z)	178.10 (M+)
Infra Red (cm^{-1})	1730, 760, 690

^{1}H NMR data



^{13}C NMR data



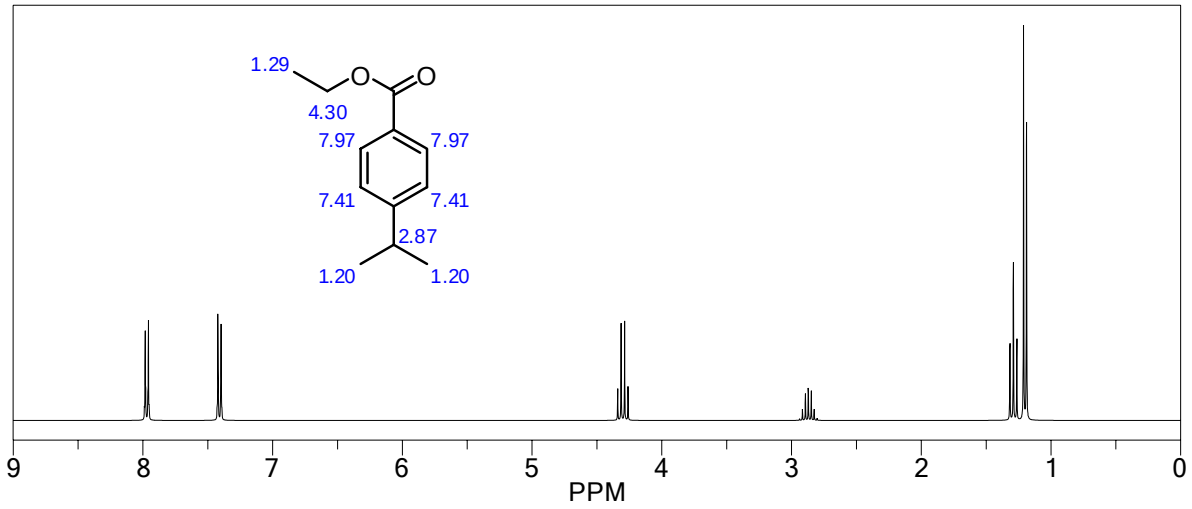
(m/z) 178.10 (M+): this means that $C_{11}H_{14}O_2$ is the actual formula of the unknown

Infra Red (cm^{-1}): 1730 corresponds to C=O; 760, 690 correspond to *meta* substitution

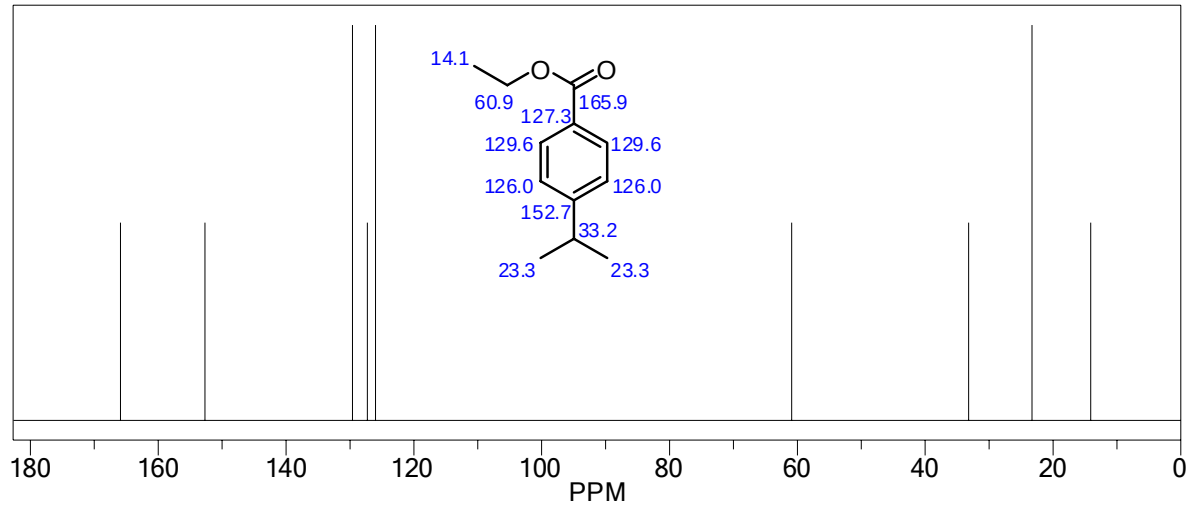
6. (10 pts) An unknown organic compound has the molecular formula $C_{12}H_{16}O_2$ and, in the mass spectrum, M+ = 192.12. Given the following ^{1}H and ^{13}C data, give the structure of the unknown and then assign all of the ^{1}H signals.

^{1}H NMR (ppm)	1.20 (d, 6H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.1 Hz), 2.87 (septet, 1H, *J* = 7.0 Hz), 4.30 (q, 2H, *J* = 7.1 Hz), 7.41 (d, 2H), 7.97 (d, 2H)
^{13}C NMR (ppm)	14.1, 23.3 (double), 33.2, 60.9, 126.0 (double), 127.3, 129.6 (double), 155.7, 165.9

^{1}H NMR data



^{13}C NMR data

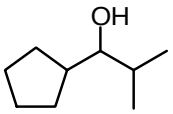


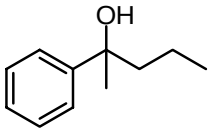
M+ = 192.12 means that $C_{12}H_{16}O_2$ is the actual formula of the compound

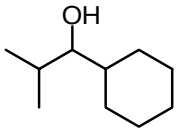
Chemistry 3720 **Ch. 14-15 Synthesis Problems**

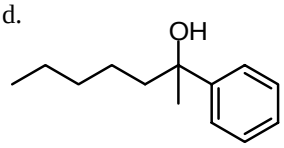
These problems are typical of those that will be on the upcoming exams in 3720.

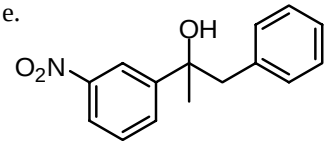
1. From Chapters 12-14: Show retrosynthetic analyses for each of the following molecules that go back only to the starting materials given below. Then, using any chemistry seen in 3719 and 3720 so far, give an efficient synthesis of each molecule showing the products formed in each step. Assume that you have access to any of the usual reagents such as Br_2, $AlCl_3$, Fe, HBr, HNO_3, H_2SO_4, etc.

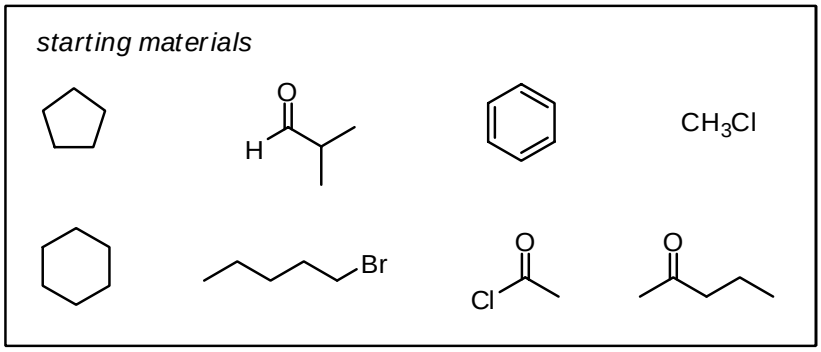
a. 

b. 

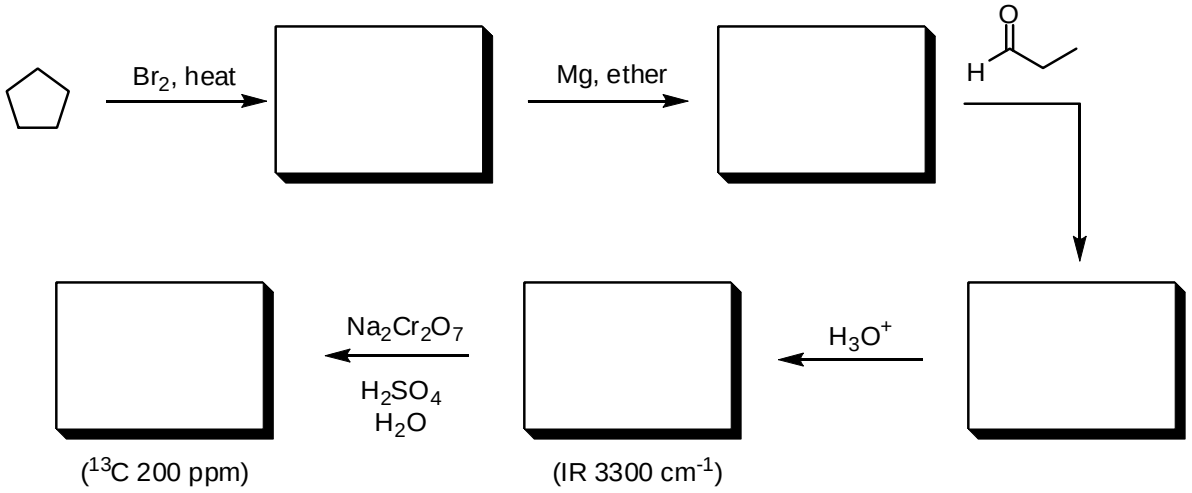
c. 

d. 

e. 



2. From 14 and 15: Give structures of the products from each step within the following "roadmap" and match the spectral data to the product.



3. From 12-15: Give structures of the products from each step in the following reaction sequences.

a.

1. Br_2, heat
2. 2 Li, ether
3. CH_3CHO

→

4. H_3O^+
5. HBr

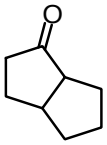
b.

1. CH_3COCl, $AlCl_3$
2. $LiAlH_4$, ether
3. H_3O^+

→

4. NaH, ether
5. CH_3CH_2Br

c.



1. $NaBH_4$, CH_3OH
2. HBr
3. 2 Li, ether

→

4. CH_3CH_2CHO
5. H_3O^+

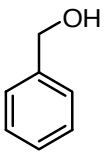
d.

1. H_2SO_4, H_2O
2. $Na_2Cr_2O_7$, H_2SO_4
3. PhMgBr, ether

→

4. H_3O^+
5. NaH, ether
6. $CH_3CH_2CH_2Br$

e.



1. PDC, CH_2Cl_2
2. CH_3Li, ether
3. H_3O^+

→

4. $Na_2Cr_2O_7$, H_2SO_4
5. PhMgBr, ether
6. H_3O^+

f.

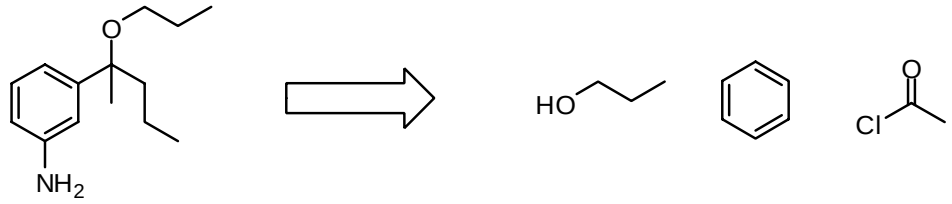
1. CH_3COCl, $AlCl_3$
2. HNO_3, H_2SO_4
3. $NaBH_4$, CH_3OH

→

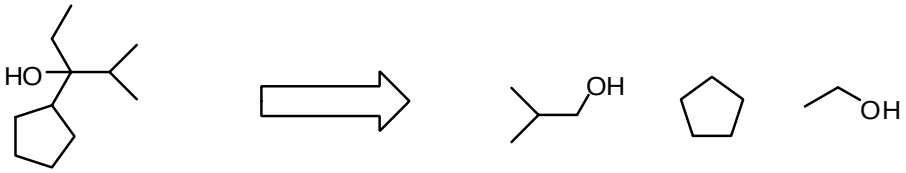
4. NaH, ether
5. $CH_3CH_2CH_2Br$

4. From 1-15: Design syntheses of the following molecules using any of the chemistry seen so far in 3719 and 3720 and using only the sources of carbon shown below. Again, assume that you have access to all of the common inorganic reagents (Br_2, $AlCl_3$, Fe, HBr, etc.).

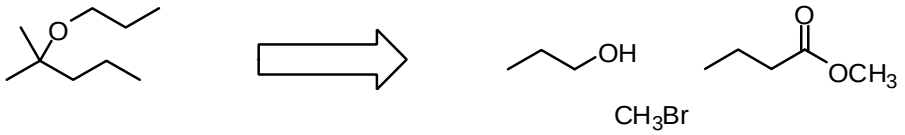
a.



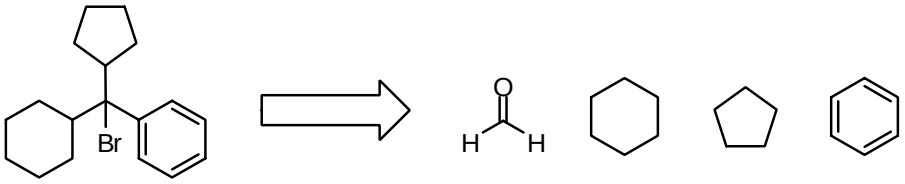
b.



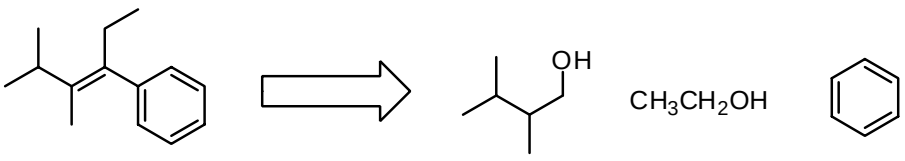
c.



d.



e.



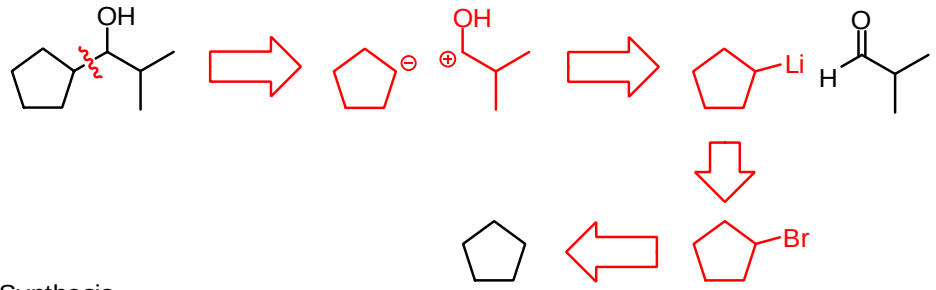
Chemistry 3720 **Ch. 14-15 Synthesis Problems - Key**

These problems are typical of those that will be on the upcoming exams in 3720.

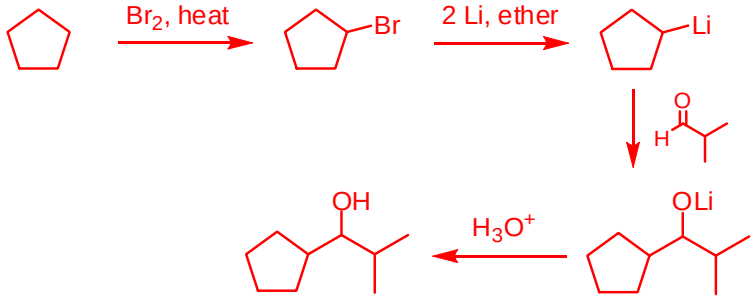
1. From Chapters 12-14: Show retrosynthetic analyses for each of the following molecules that go back only to the starting materials given below. Then, using any chemistry seen in 3719 and 3720 so far, give an efficient synthesis of each molecule showing the products formed in each step. Assume that you have access to any of the usual reagents such as Br_2, $AlCl_3$, Fe, HBr, HNO_3, H_2SO_4, etc.

a.

Retrosynthesis

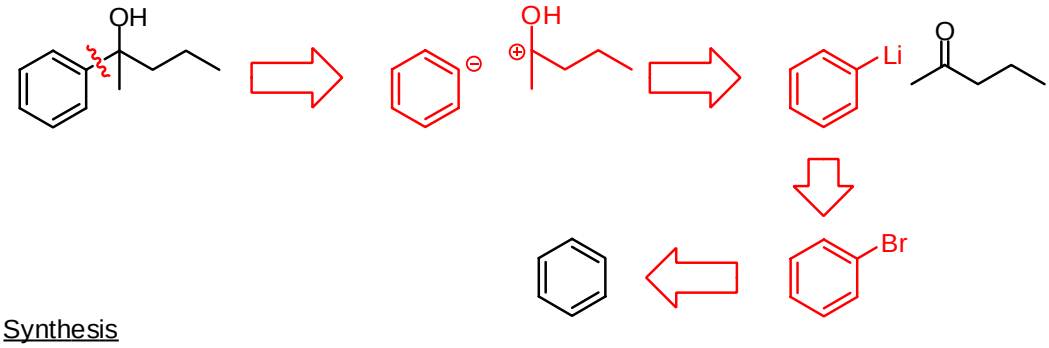


Synthesis

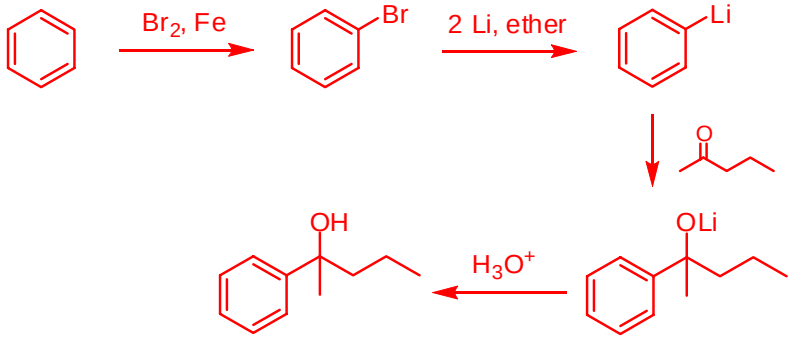


b

Retrosynthesis

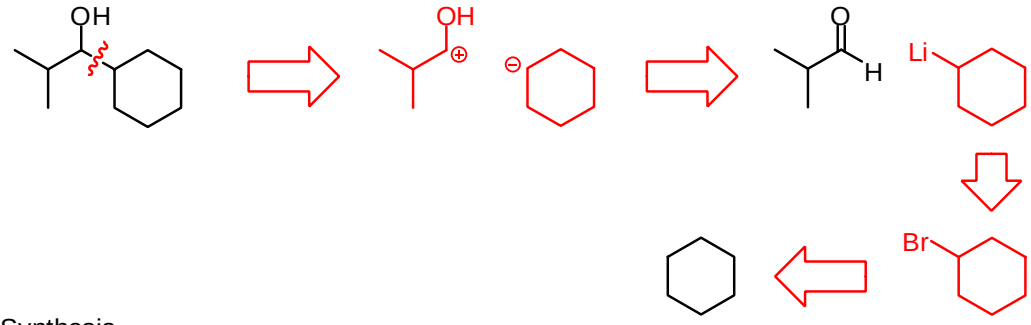


Synthesis

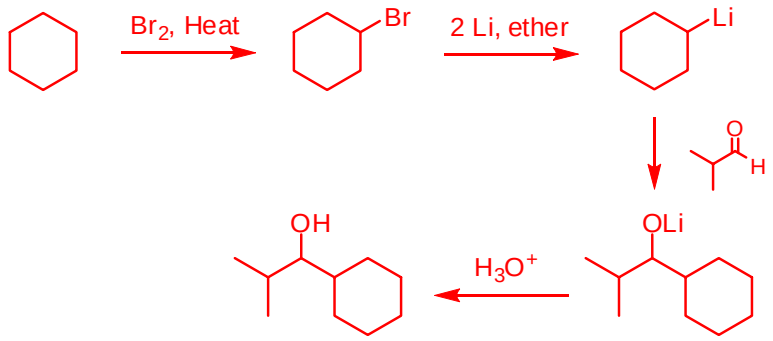


c.

Retrosynthesis

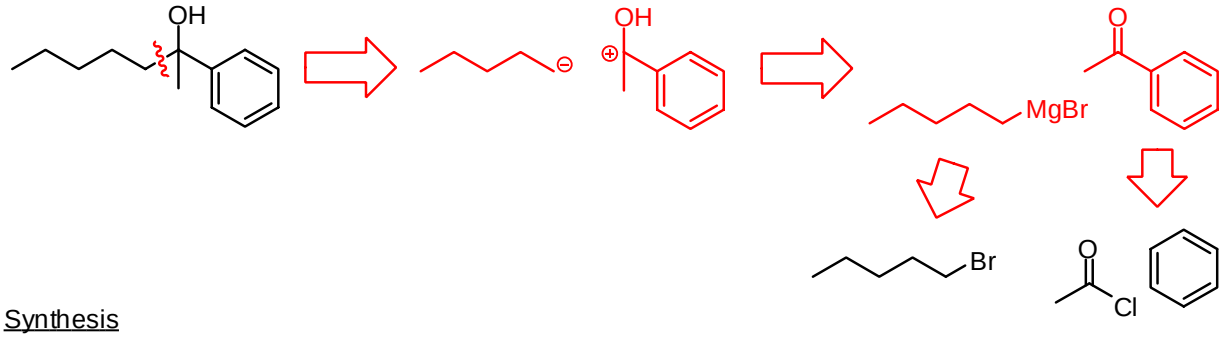


Synthesis

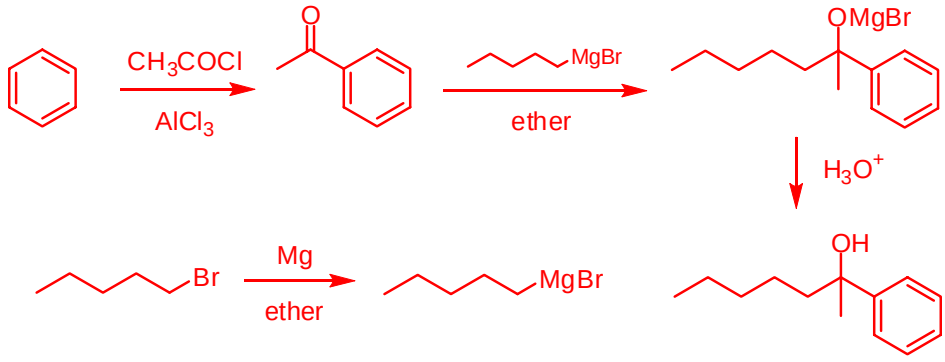


d.

Retrosynthesis

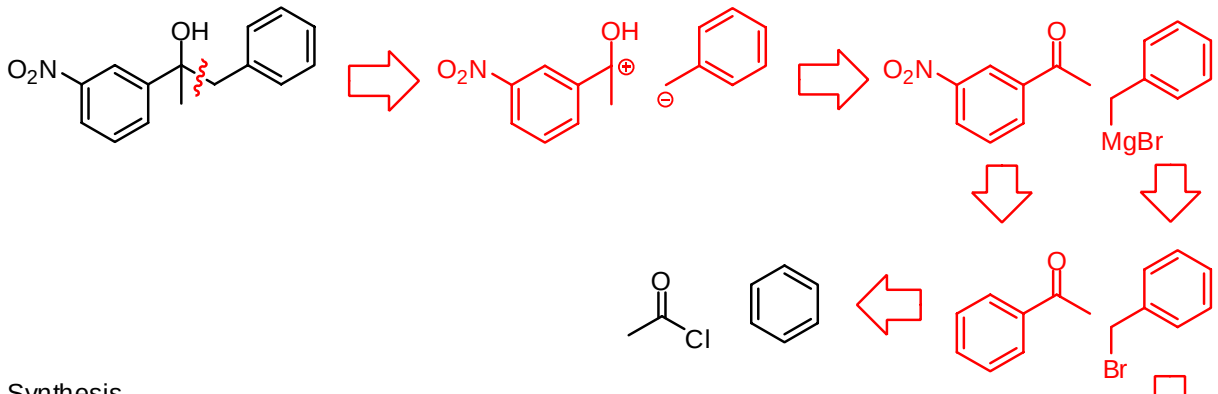


Synthesis

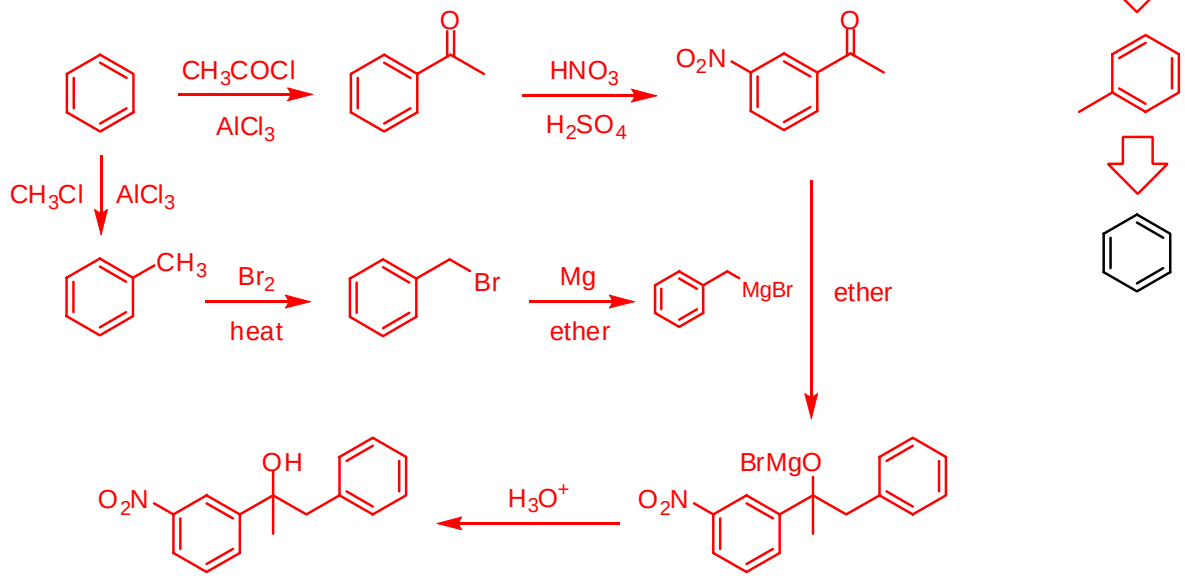


e.

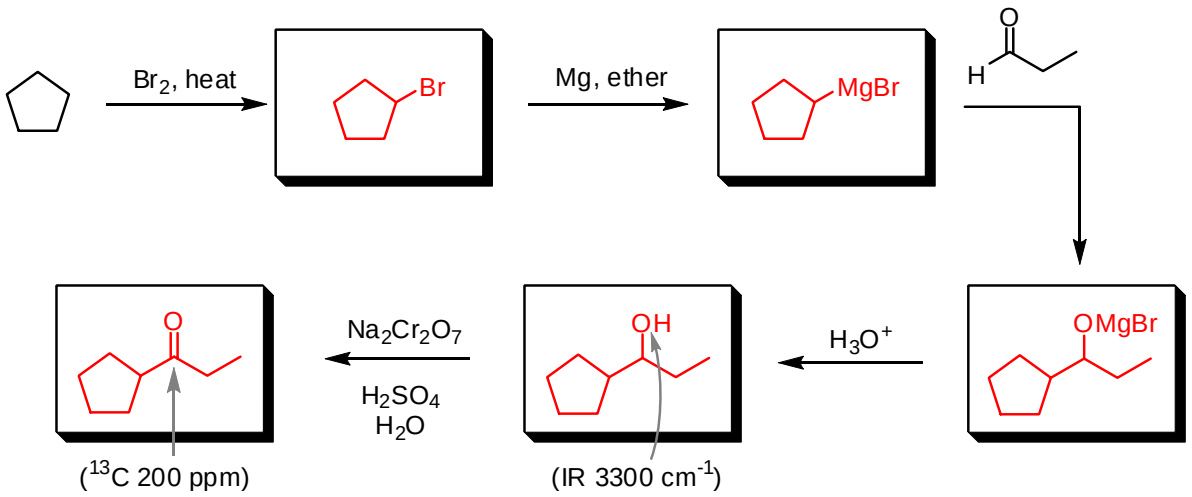
Retrosynthesis



Synthesis

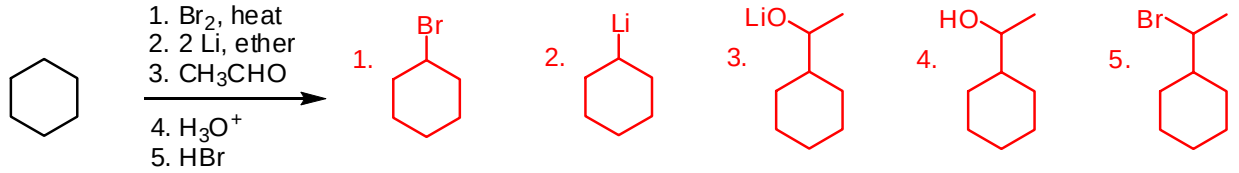


2. From 14 and 15: Give structures of the products from each step within the following "roadmap" and match the spectral data to the product.

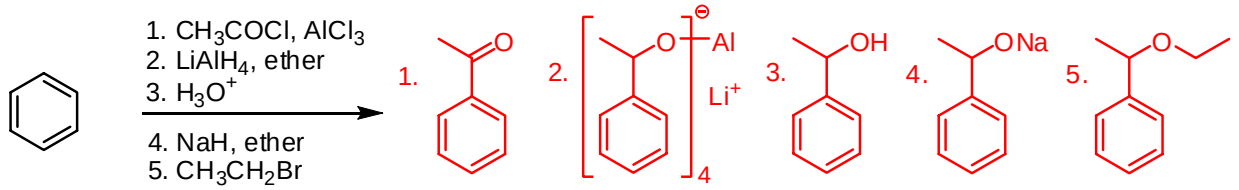


3. From 12-15: Give structures of the products from each step in the following reaction sequences.

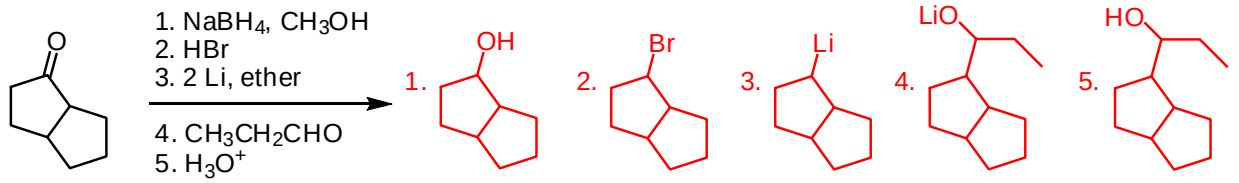
a.



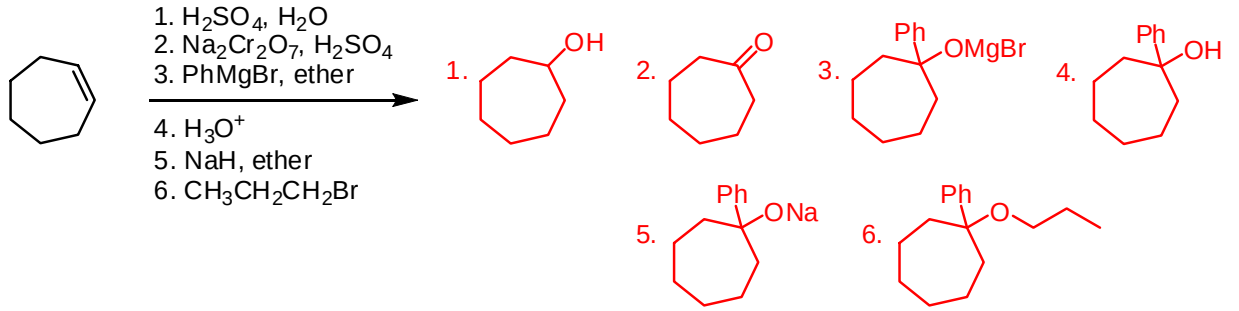
b.



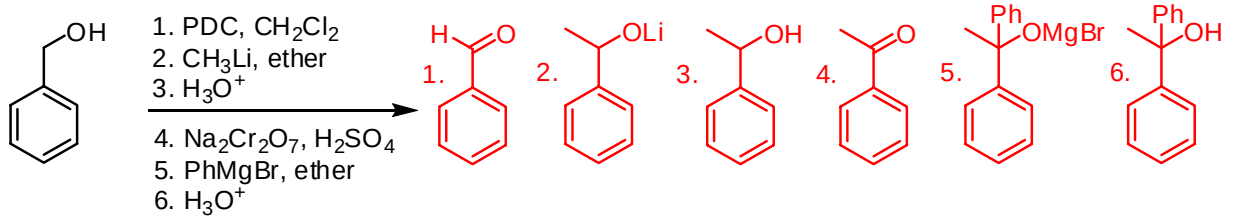
c.



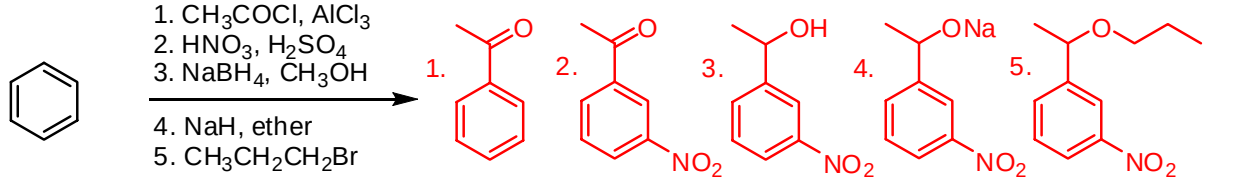
d.



e.



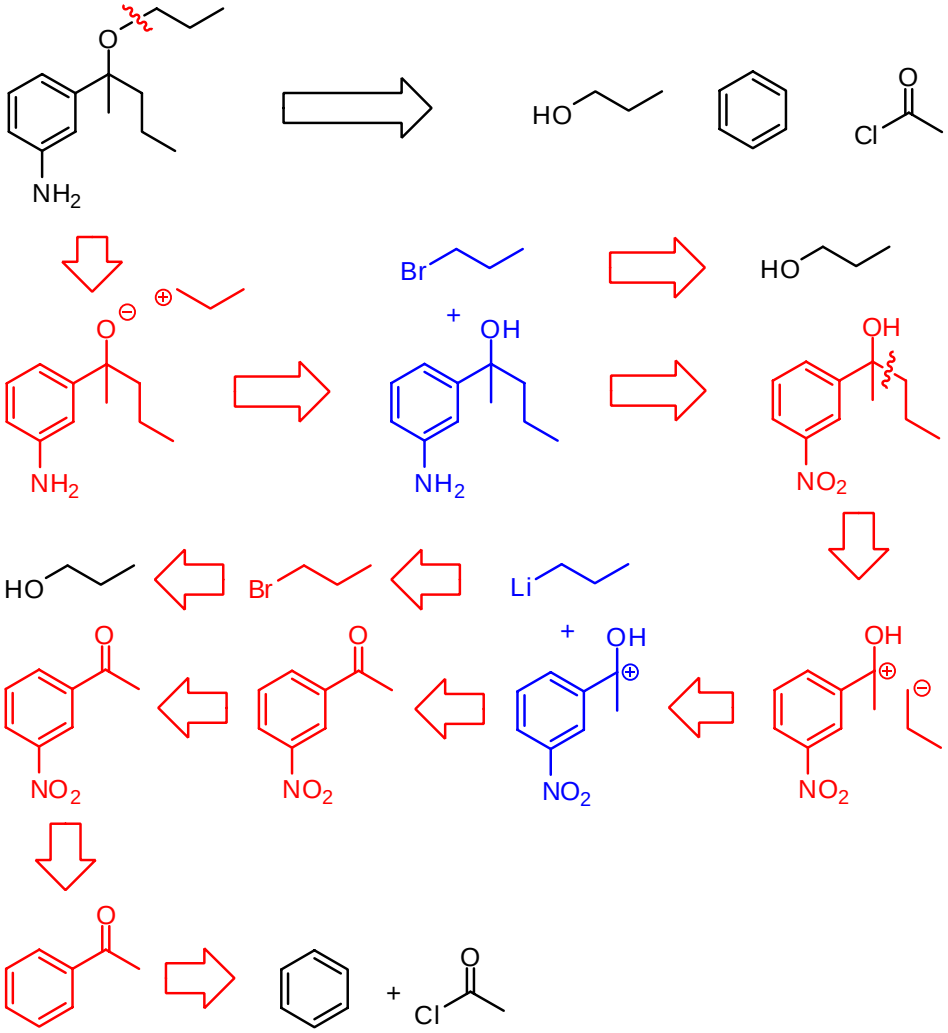
f.



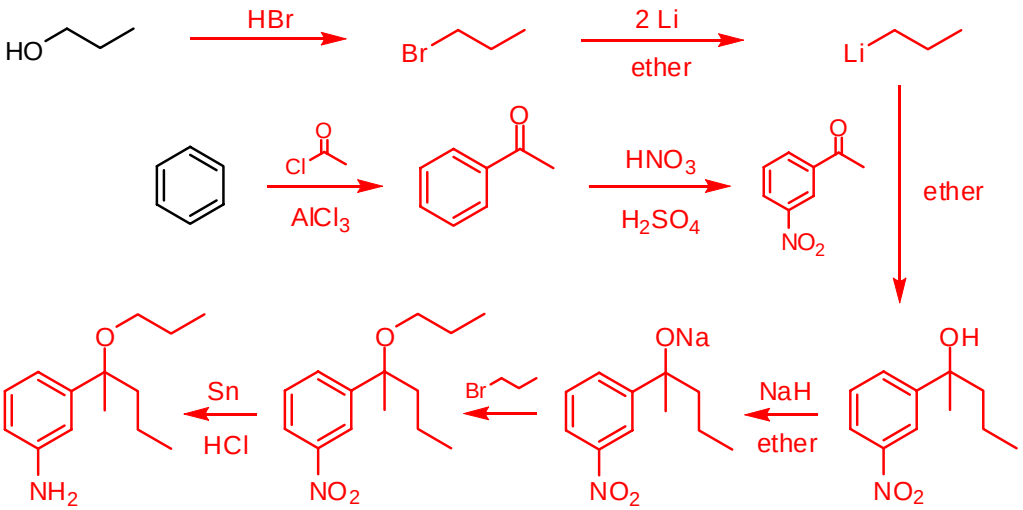
4. From 1-15: Design syntheses of the following molecules using any of the chemistry seen so far in 3719 and 3720 and using only the sources of carbon shown below. Again, assume that you have access to all of the common inorganic reagents (Br_2, $AlCl_3$, Fe, HBr, etc.).

a.

Design (Retrosynthesis)

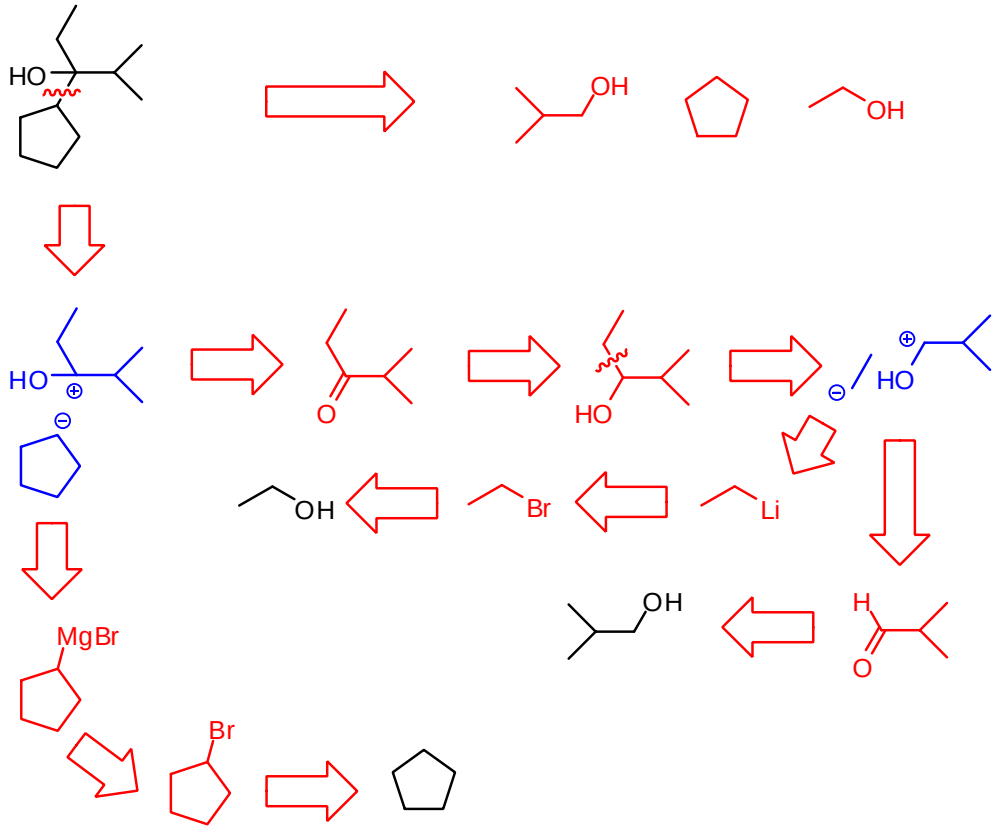


Construction (Synthesis)

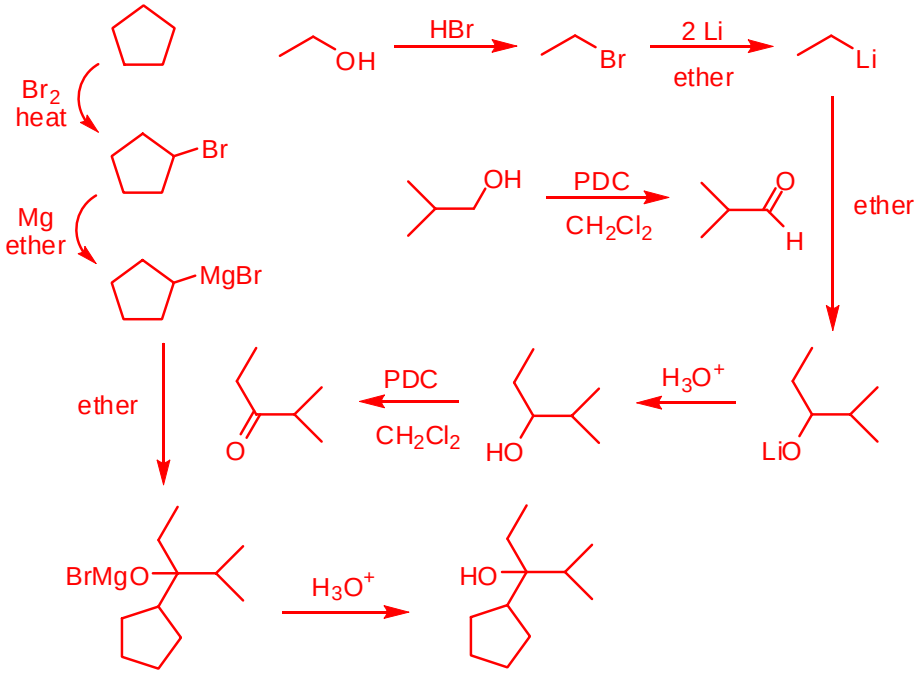


b.

Design (Retrosynthesis)

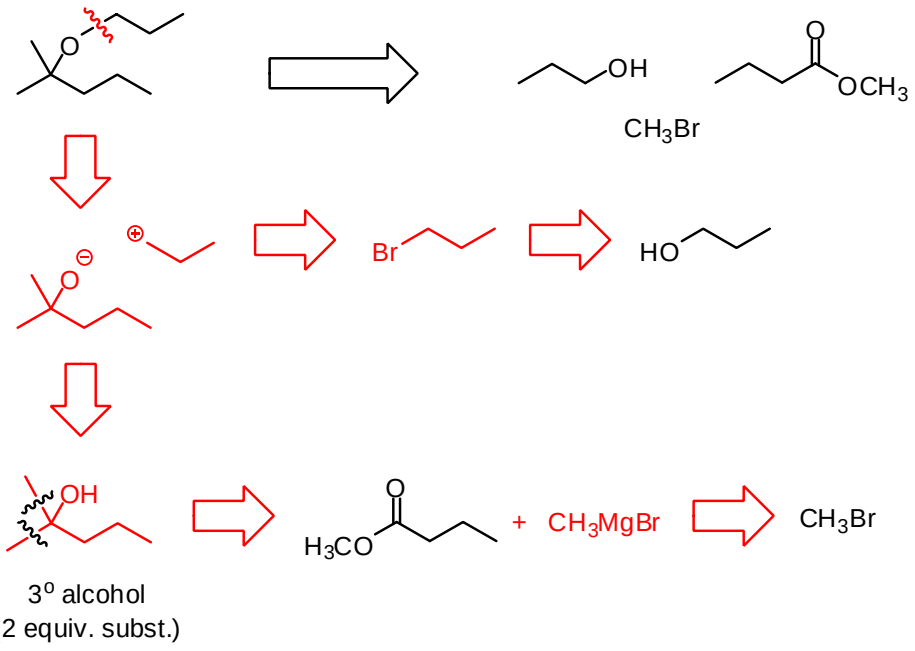


Construction (Synthesis)



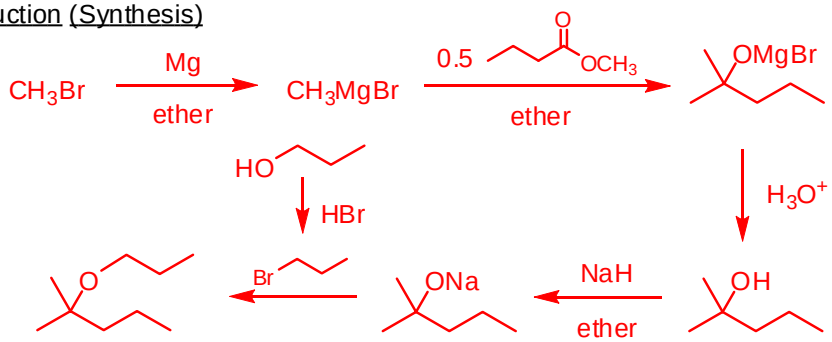
c.

Design (Retrosynthesis)



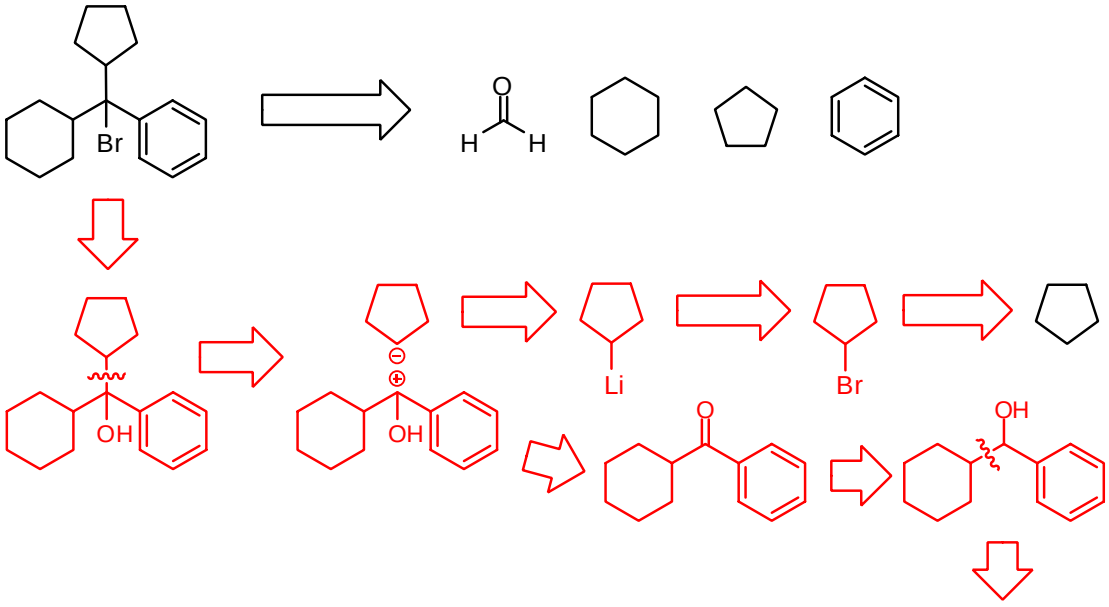
3° alcohol
(2 equiv. subst.)

Construction (Synthesis)

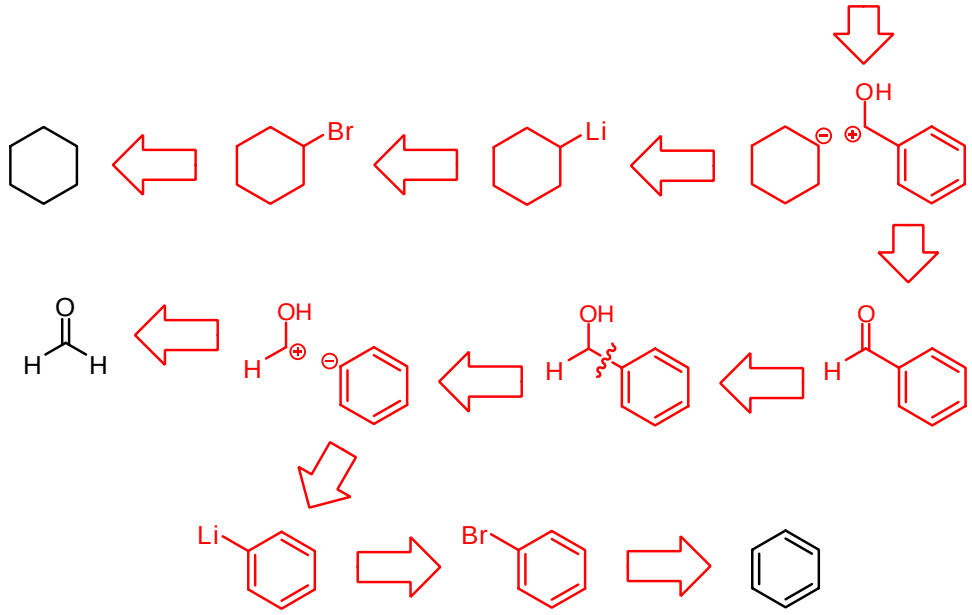


d.

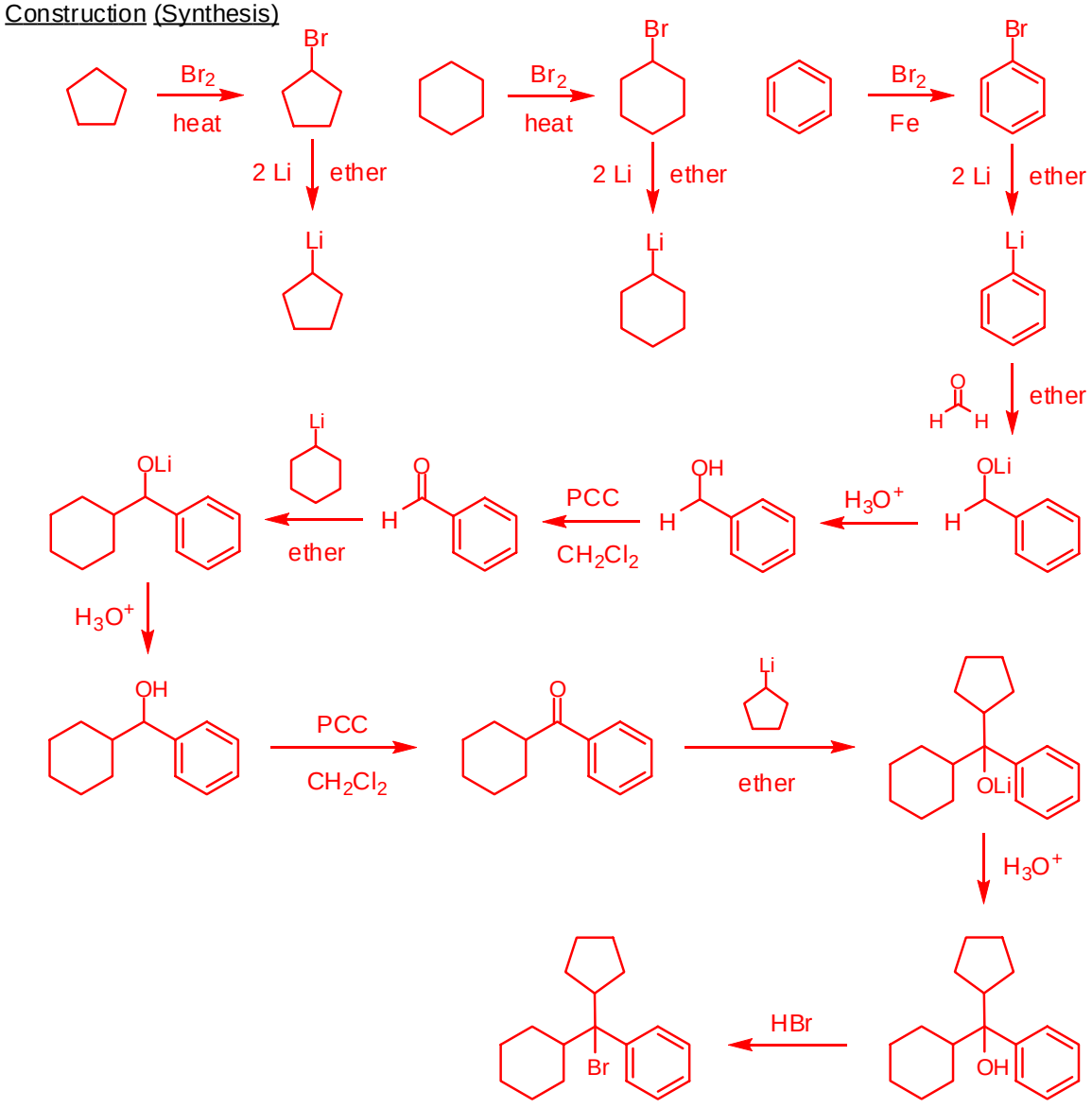
Design (Retrosynthesis - several ways to do this one)



d. (cont'd.)

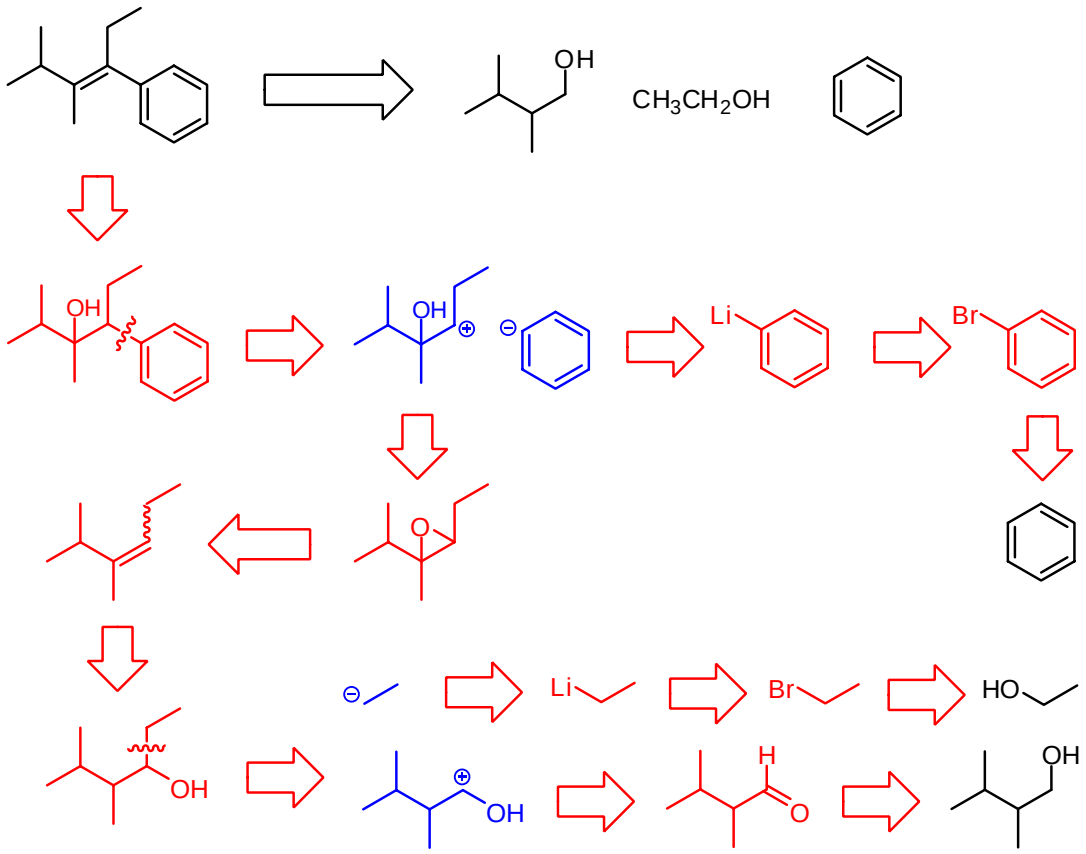


Construction (Synthesis)

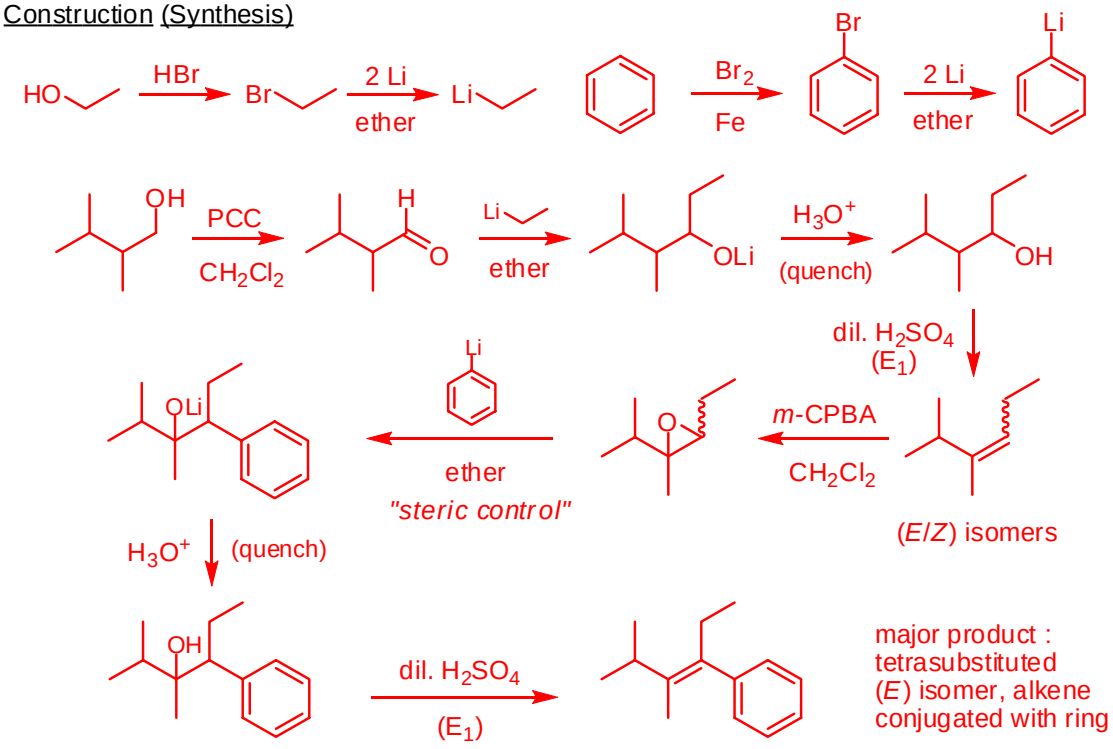


e.

Design (Retrosynthesis)



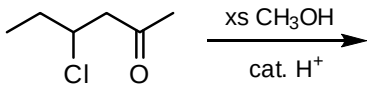
Construction (Synthesis)

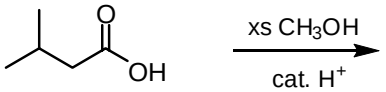


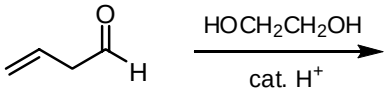
Chemistry 3720 **Ch. 14-17 Synthesis Problems**

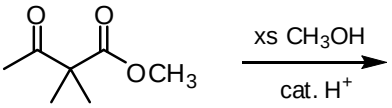
These problems are typical of those that will be on the next exams in 3720. You should be comfortable with each reaction in the forward direction, how to think about each reaction in a retrosynthetic manner, and then be able to complete multi-step syntheses.

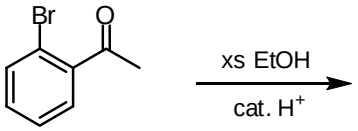
1. Give the major organic product(s) from each of the following reaction sequences and then a detailed mechanism for each reaction. Be careful with any regiochemical issues.

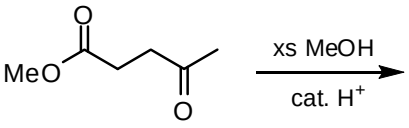
a. 

b. 

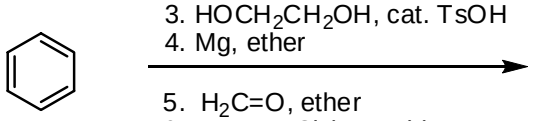
c. 

d 

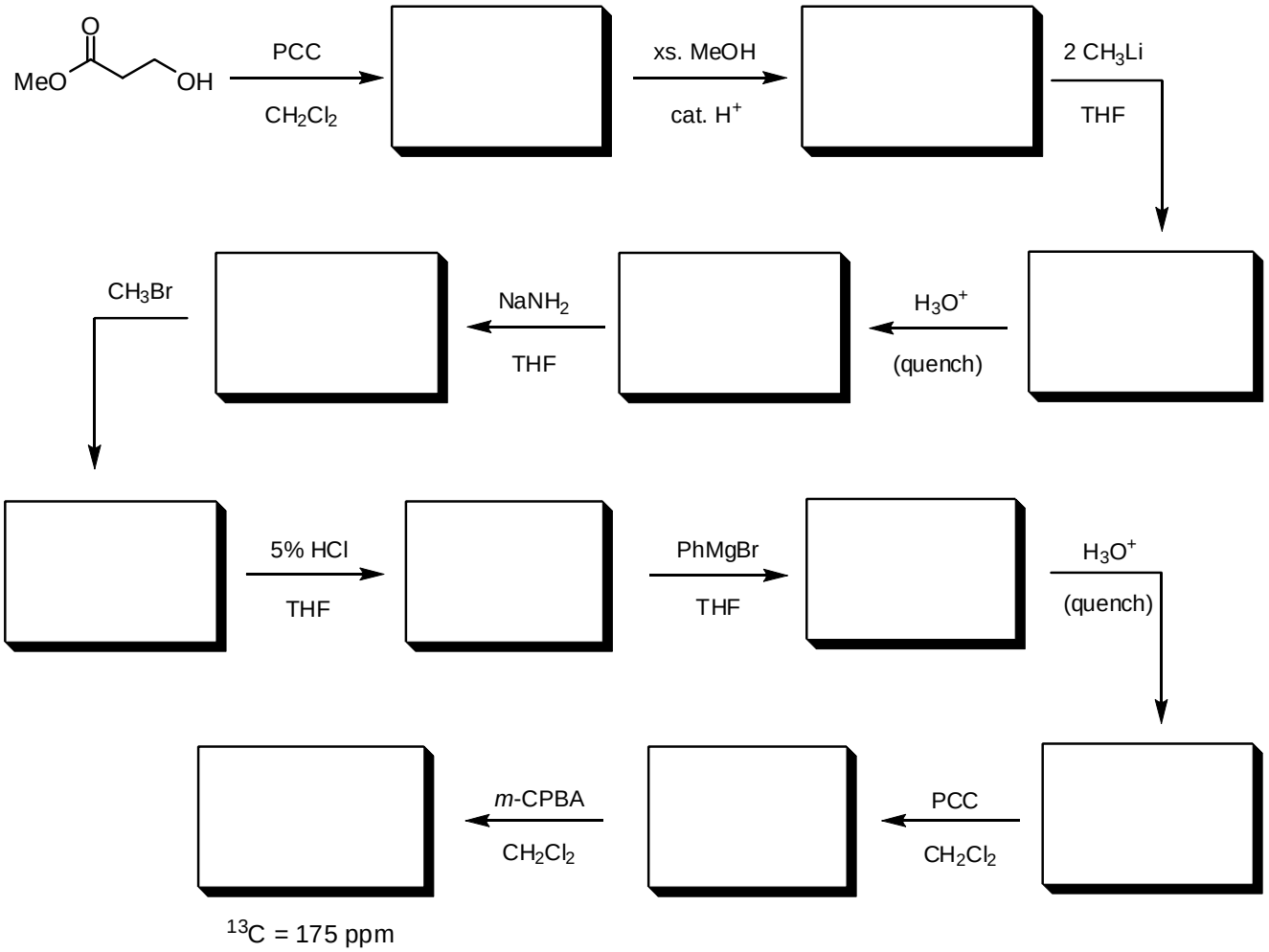
e. 

f. 

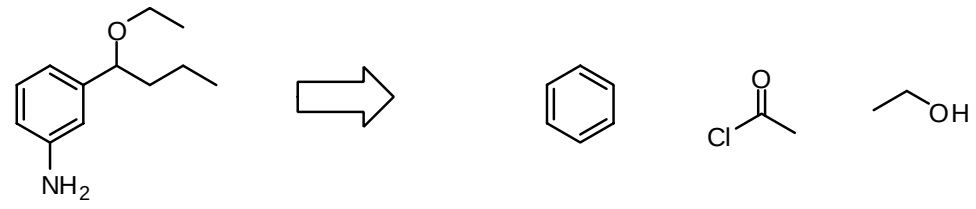
2. Give the major organic product(s) from each step of the following synthetic scheme.

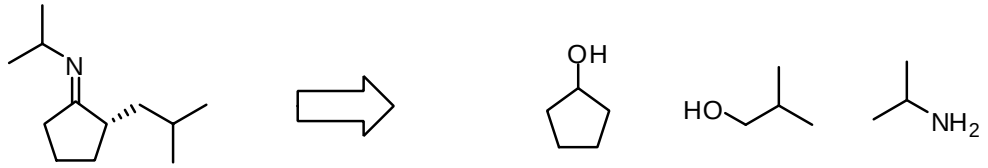


3. In the boxes provided, give the products from each step in the following "road-map" scheme.



4. Give retrosynthetic analyses for the following molecules that go back to the given starting materials, and then provide the synthesis in the forward direction. Assume you have access to the usual other reagents (HBr, HNO_3, $NaBH_4$, etc.) in the lab.

a. 

b. 

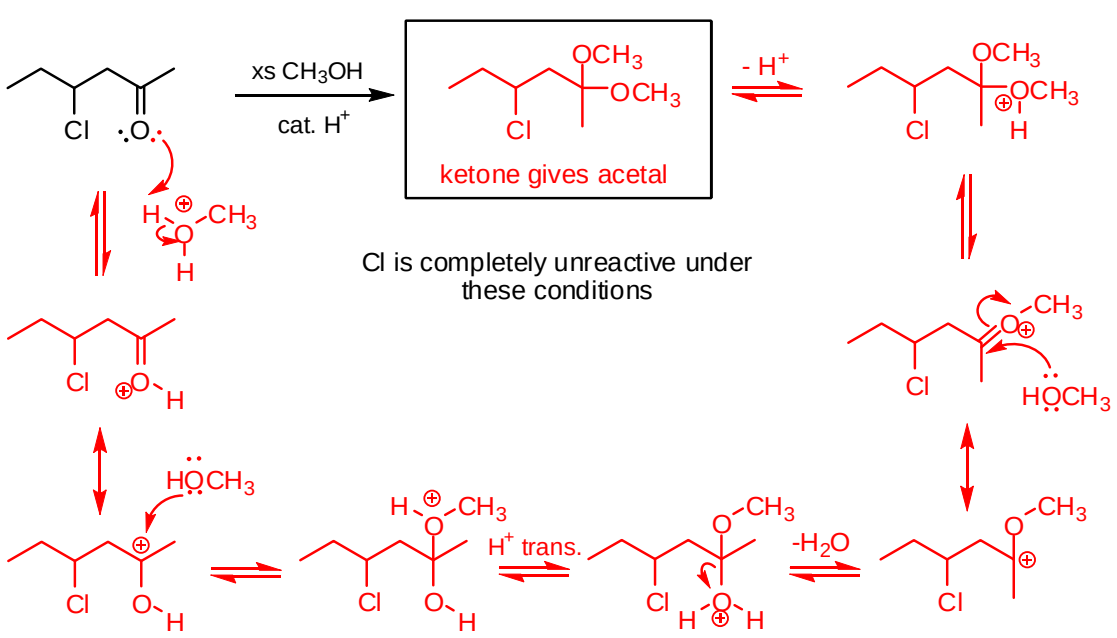
c. 

Chemistry 3720 **Ch. 14-17 Synthesis Problems Key**

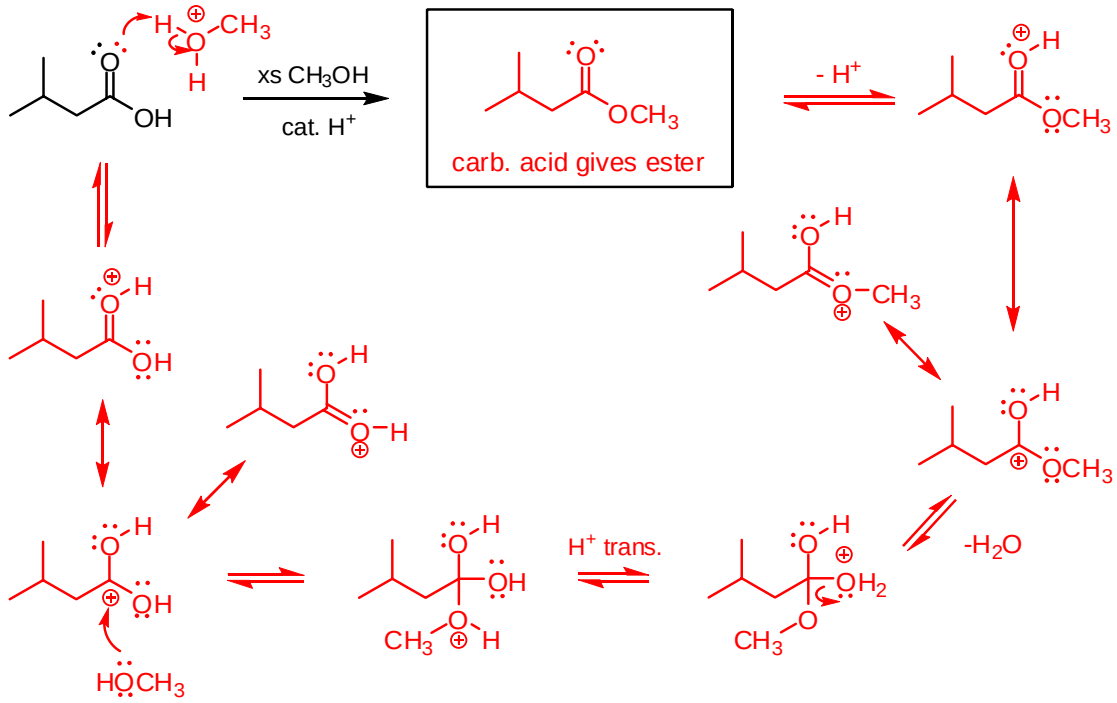
These problems are typical of those that will be on the next exams in 3720. You should be comfortable with each reaction in the forward direction, how to think about each reaction in a retrosynthetic manner, and then be able to complete multi-step syntheses.

1. Give the major organic product(s) for each of the following sets of reaction conditions and then a detailed mechanism for each reaction. Be careful with any regiochemical issues.

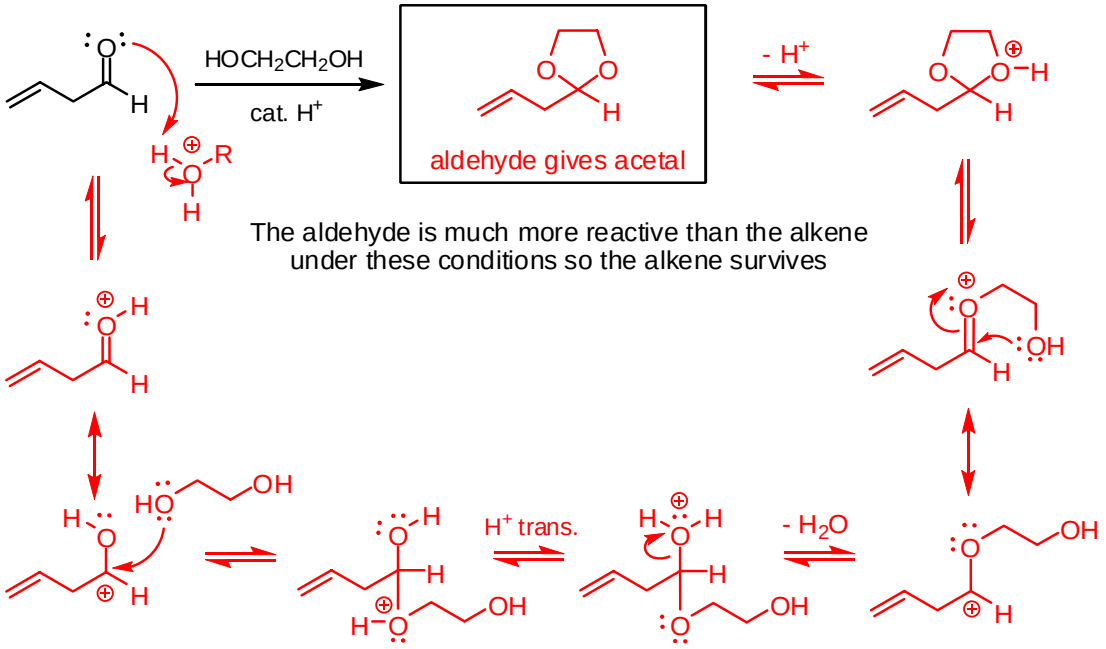
a.



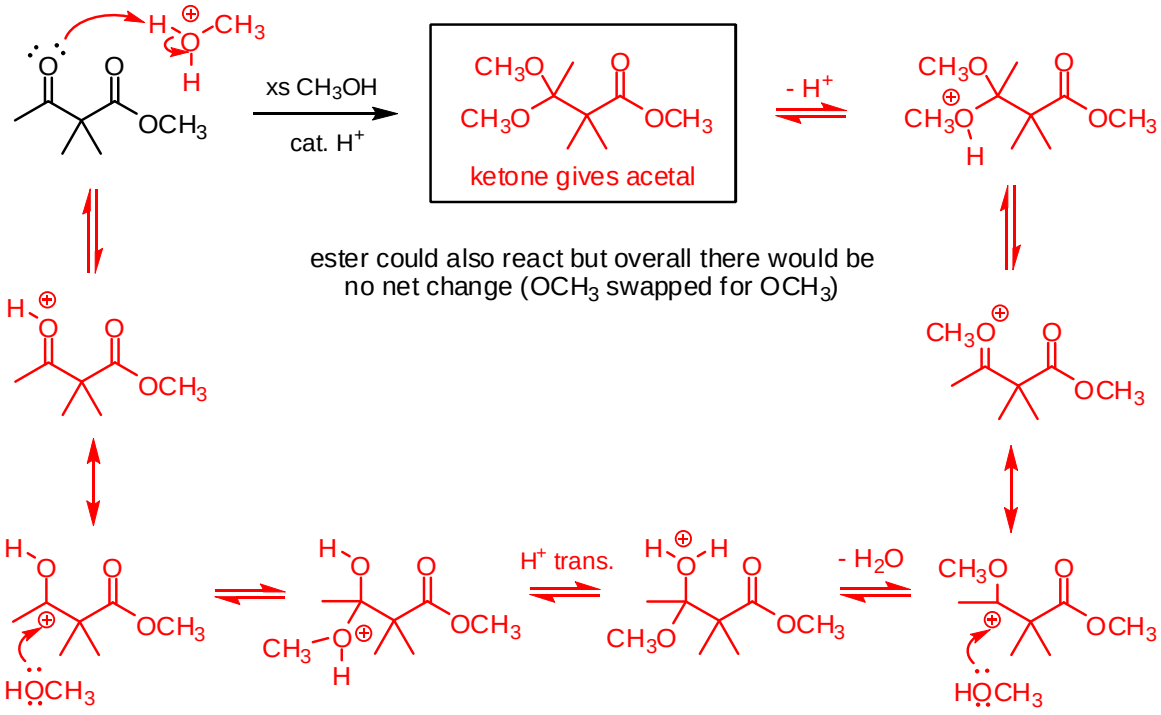
b.



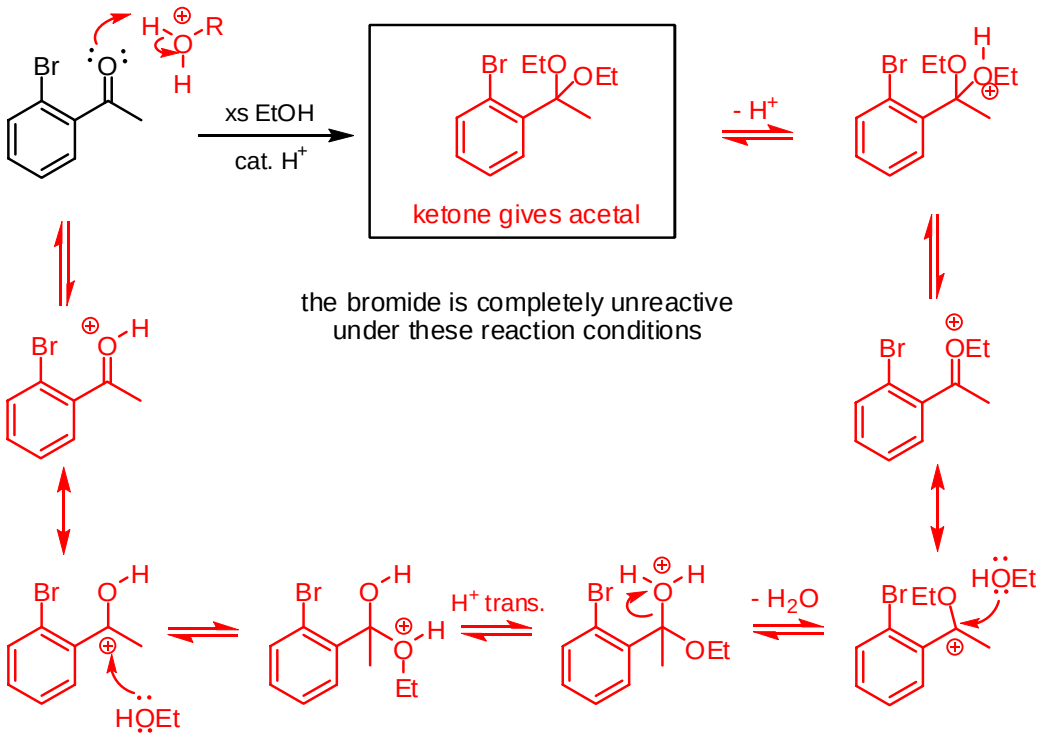
c.


HOCH2CH2OH
cat. H+
aldehyde gives acetal
- H+
The aldehyde is much more reactive than the alkene under these conditions so the alkene survives
H+ trans.
- H2O

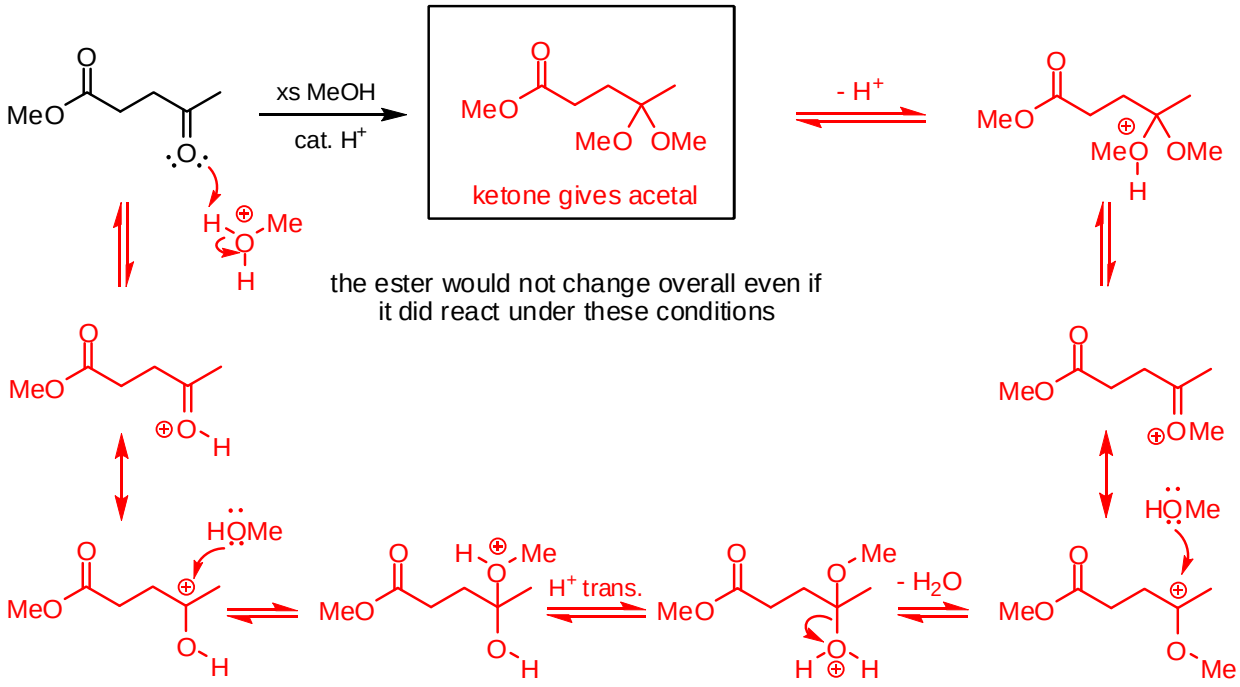
d.


xs CH3OH
cat. H+
ketone gives acetal
- H+
ester could also react but overall there would be no net change (OCH3 swapped for OCH3)
H+ trans.
- H2O

e.


xs EtOH
cat. H+
ketone gives acetal
- H+
the bromide is completely unreactive
under these reaction conditions
H+ trans.
- H2O

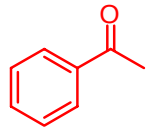
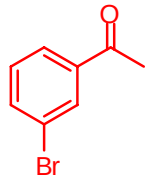
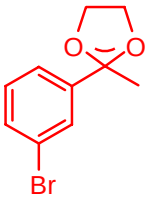
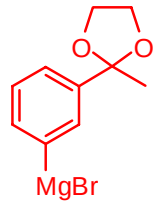
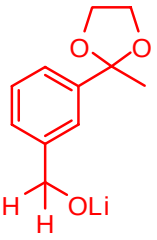
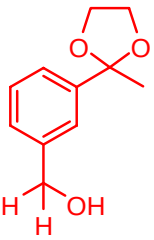
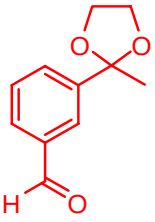
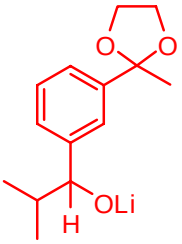
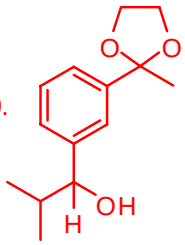
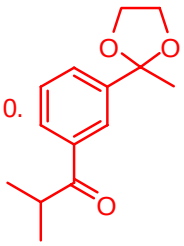
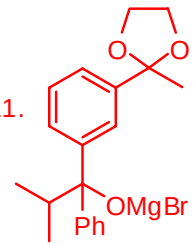
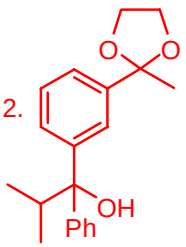
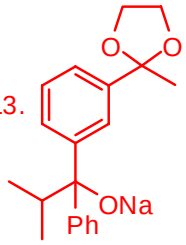
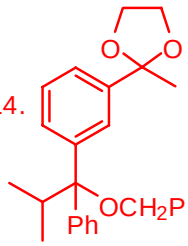
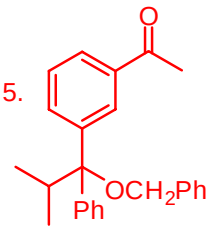
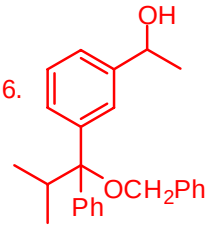
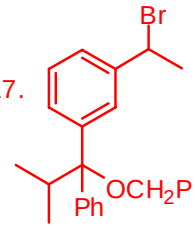
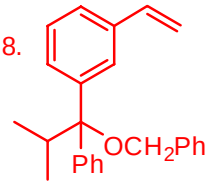
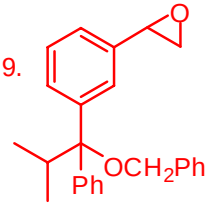
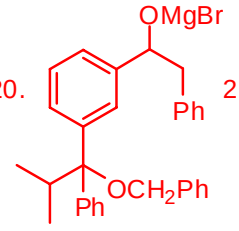
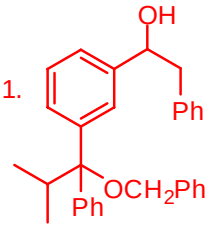
f.


xs MeOH
cat. H+
ketone gives acetal
- H+
the ester would not change overall even if
it did react under these conditions
H+ trans.
- H2O

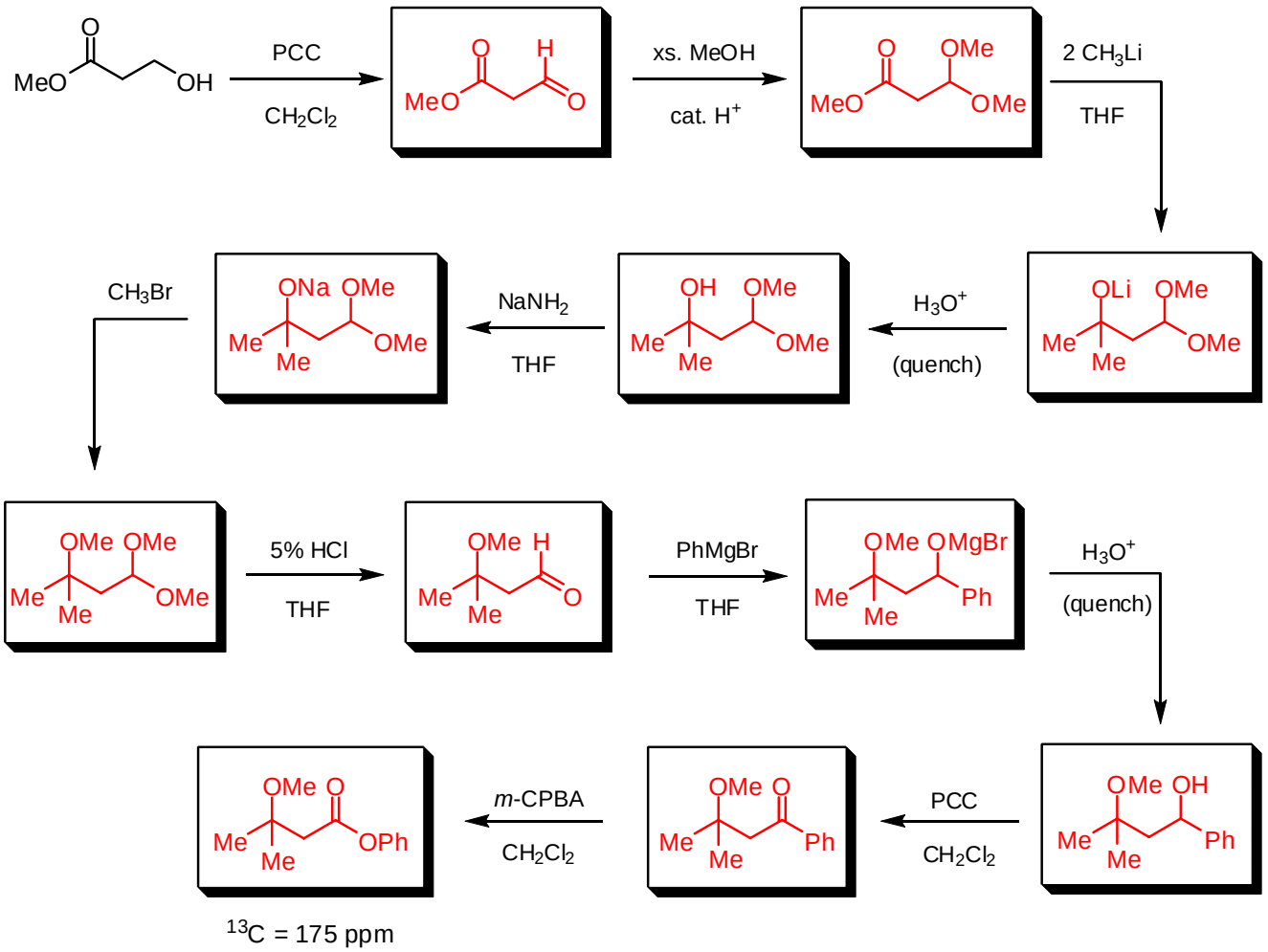
2. Give the major organic product(s) from each step of the following synthetic scheme.

1. CH_3COCl, $AlCl_3$
2. Br_2, Fe
3. $HOCH_2CH_2OH$, cat. TsOH
4. Mg, ether

5. $H_2C{=}O$, ether
6. aq. NH_4Cl (quench)
7. PCC, CH_2Cl_2
8. $(CH_3)_2CHLi$, THF
9. aq. NH_4Cl (quench)
10. PDC, CH_2Cl_2
11. PhMgBr, THF
12. aq. NH_4Cl (quench)
13. NaH, ether
14. $PhCH_2Br$, ether
15. 5% HCl, 3 h, RT
16. $NaBH_4$, CH_3OH
17. HBr
18. $NaOCH_3$, CH_3OH
19. *m*-CPBA, CH_2Cl_2
20. PhMgBr, ether
21. aq. NH_4Cl (quench)

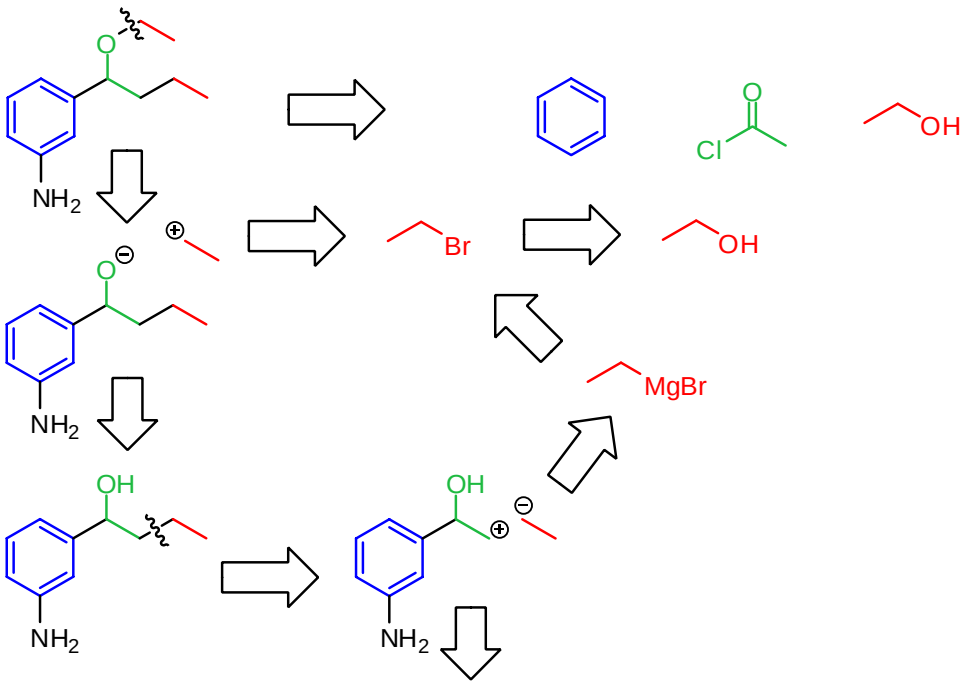
1. 
2. 
3. 
4. 
5. 
6. 
7. 
8. 
9. 
10. 
11. 
12. 
13. 
14. 
15. 
16. 
17. 
18. 
19. 
20. 
21. 

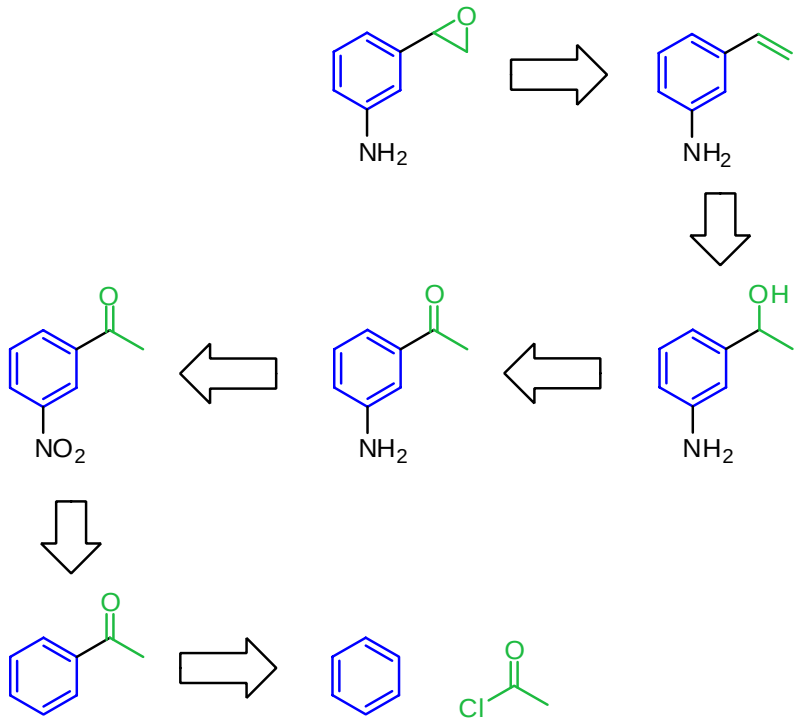
3. In the boxes provided, give the products from each step in the following "road-map" scheme.



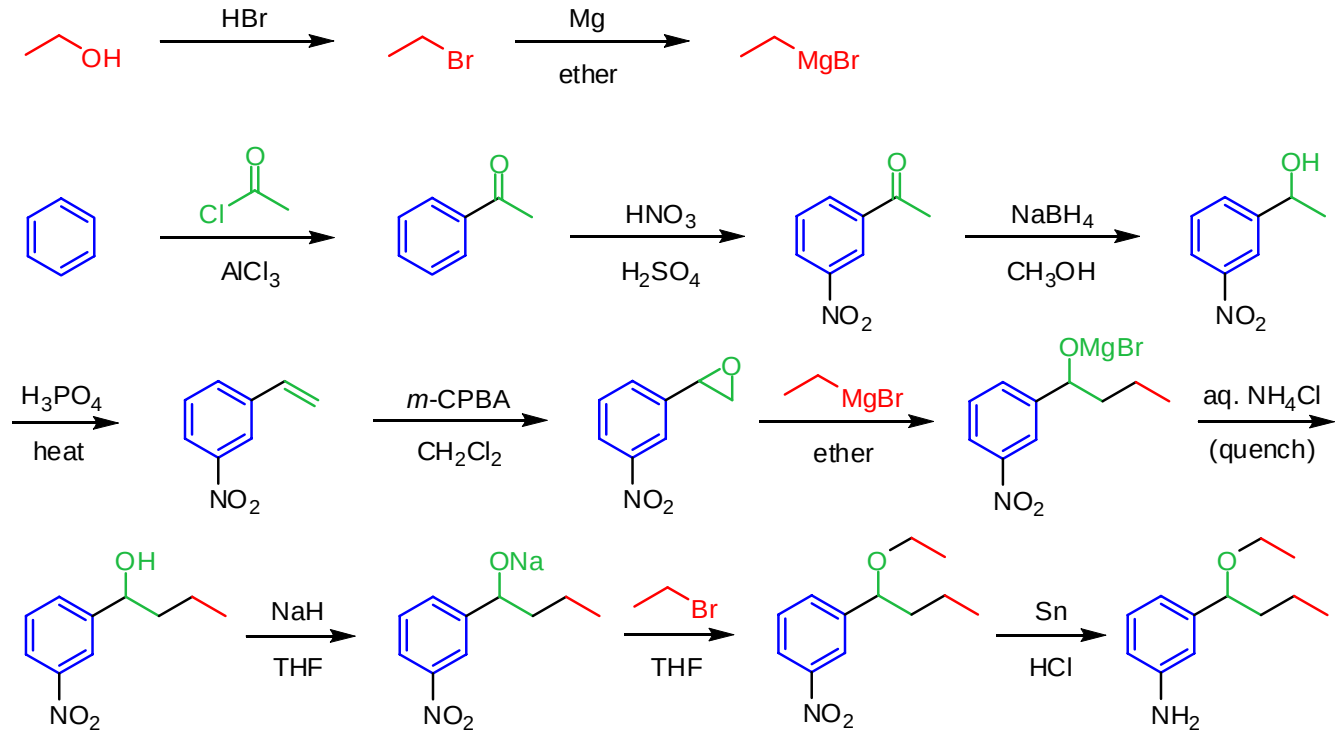
4. Give retrosynthetic analyses for the following molecules that go back to the given starting materials, and then provide the synthesis in the forward direction. Assume you have access to the usual other reagents (HBr, HNO_3, $NaBH_4$, etc.) in the lab.

a.

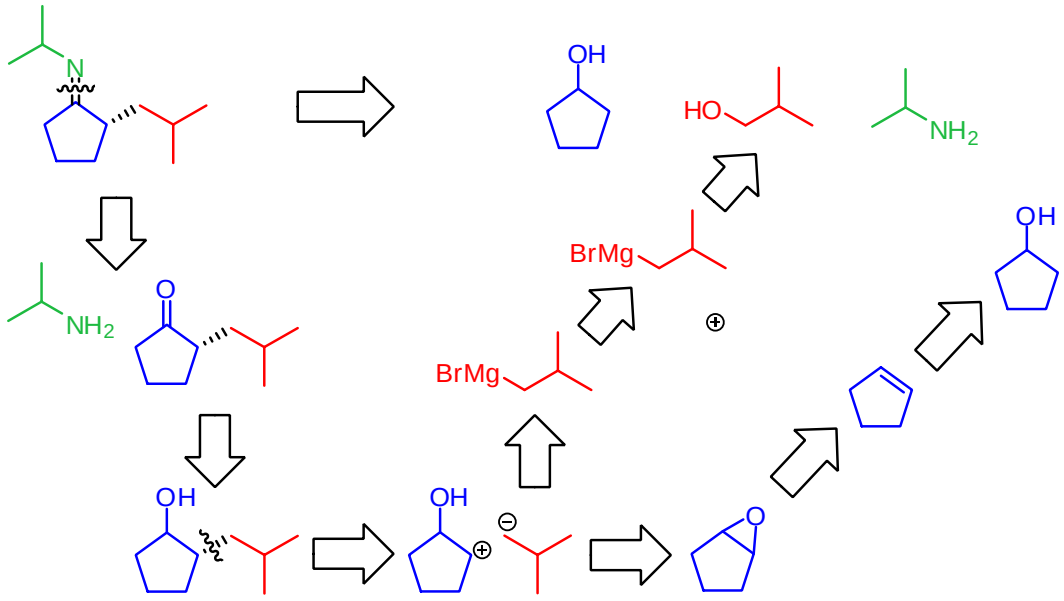




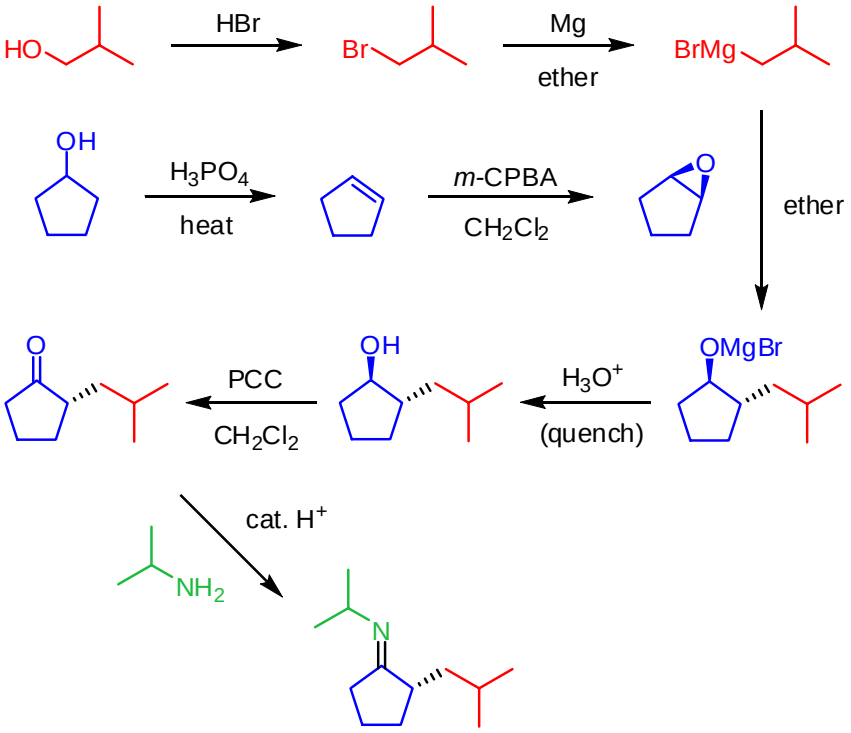
Synthesis


HBr
Mg
ether
HNO3
H2SO4
NaBH4
CH3OH
AlCl3
H3PO4
heat
m-CPBA
CH2Cl2
MgBr
ether
aq. NH4Cl
(quench)
NaH
THF
Br
THF
Sn
HCl

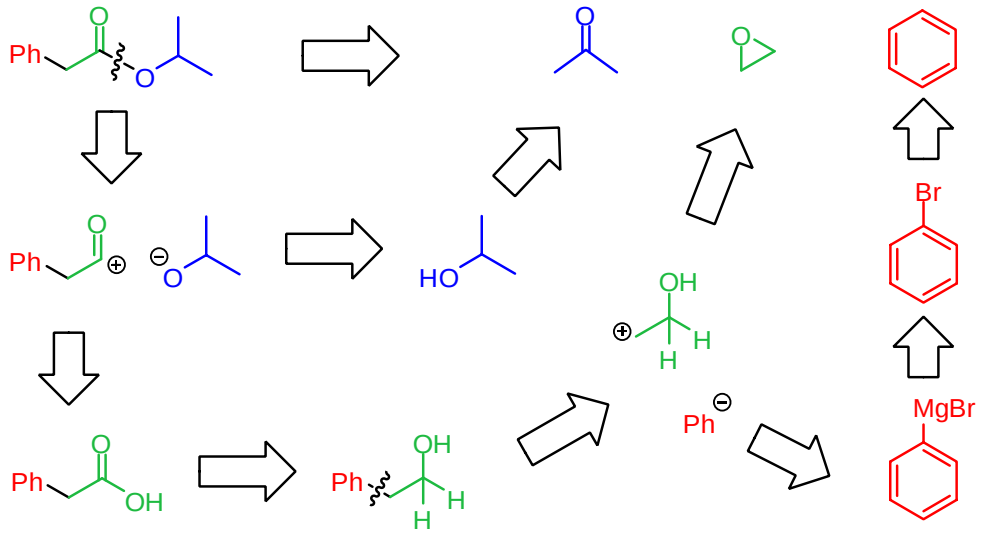
b.


N
NH2
O
OH
HO
NH2
BrMg
BrMg
OH
OH
OH
O

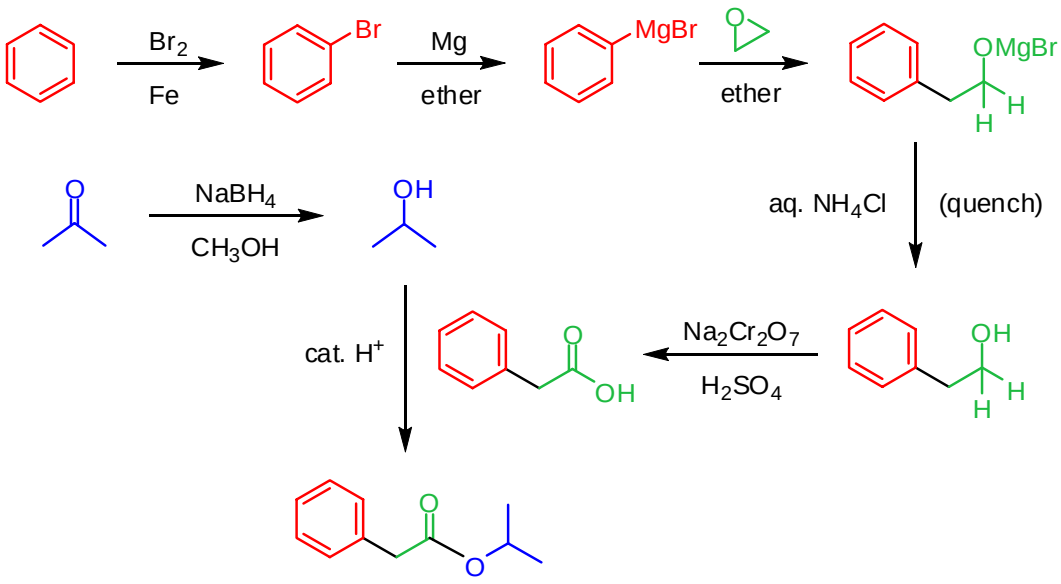
Synthesis


HO
HBr
Br
Mg
ether
BrMg
OH
H3PO4
heat
m-CPBA
CH2Cl2
O
ether
O
PCC
CH2Cl2
OH
H3O+
(quench)
OMgBr
cat. H+
NH2
N

c.


Ph
O
O
HO
OH
H
H
Br
MgBr
Ph
Ph
OH
OH
H
H

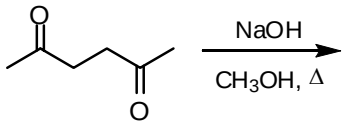
Synthesis

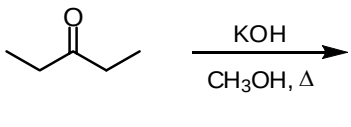

Br2
Fe
Br
Mg
ether
MgBr
ether
OMgBr
H
H
aq. NH4Cl
(quench)
NaBH4
CH3OH
OH
cat. H+
O
OH
Na2Cr2O7
H2SO4
OH
H
H
O
O

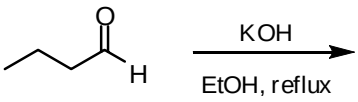
Chemistry 3720 **Ch. 17-20 Synthesis Problems**

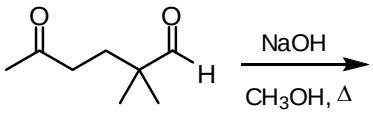
These problems are from various parts of 3719 and 3720 and deal with the two main synthetic issues studied; C-C bond formation and manipulation of functional groups. We'll have covered all of the required chemistry from Chapter 18 by the end of next week.

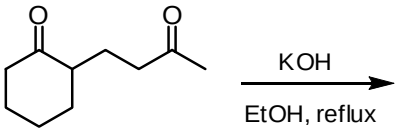
1. Give the major organic product(s) from each of the following aldol reactions as well as a detailed mechanism for each case. Be careful with any regiochemical issues.

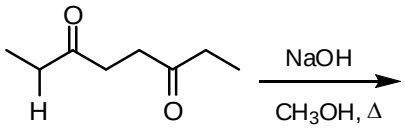
a. 

b. 

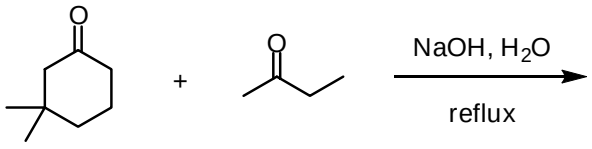
c. 

d. 

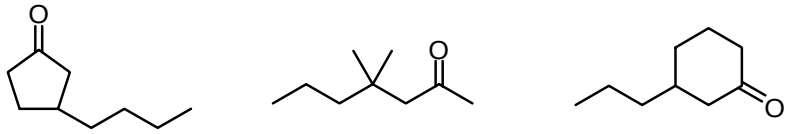
e. 

f. 

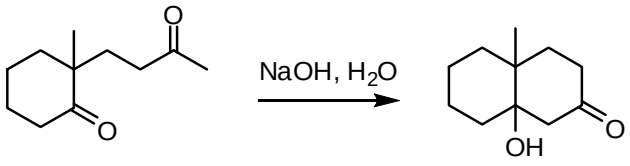
2. Draw all of the possible ***aldol condensation*** products formed under the following conditions.



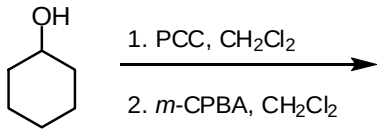
3. Provide the reagents required to make each of the following compounds *via* 1,4-addition chemistry.

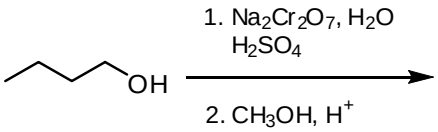


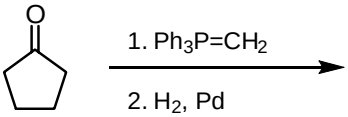
4. In the following Robinson annulation, 3 aldol products are possible; draw them and then explain why only the one shown below is formed. Give a complete mechanism for the reaction including important resonance structures.

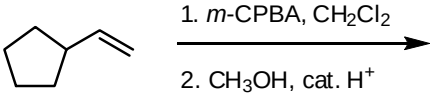


5. Give the major products from each step of the following reaction sequences.

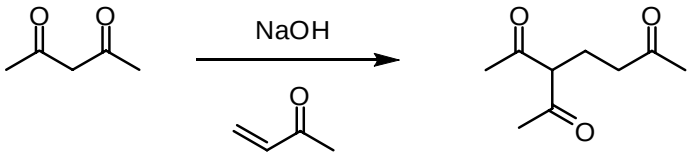
a. 

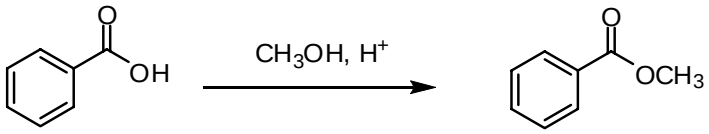
b. 

c. 

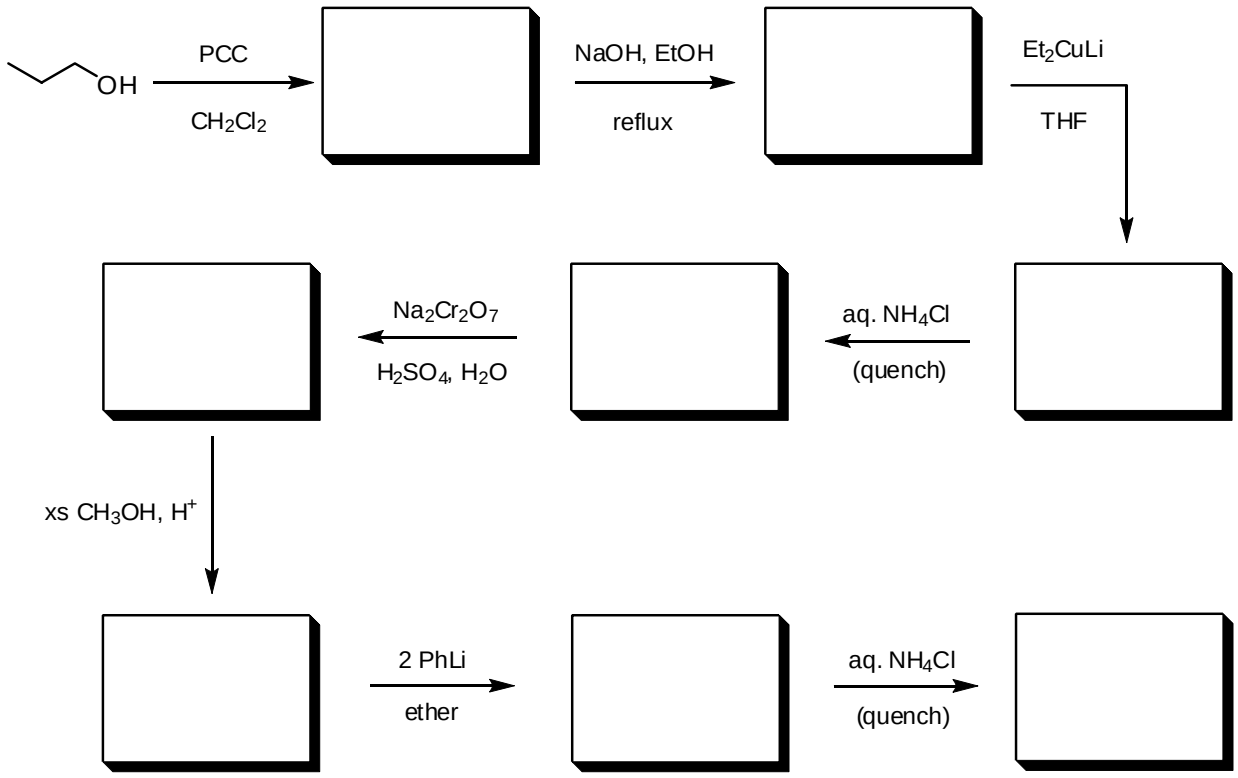
d. 

6. Provide complete mechanisms for the following conversions. Include all resonance structures for any intermediates that may be formed.

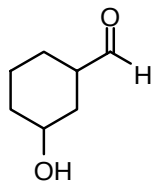




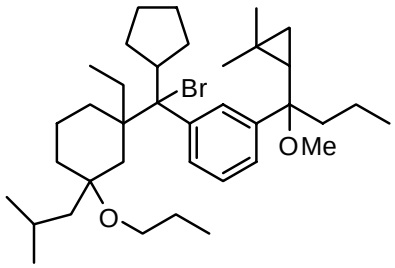
7. Give structures for each of the products in the following "roadmap."



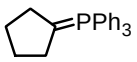
8. The polyether compound *chauncydermolide G* (shown below) was recently isolated by Triplet Pharmaceuticals Inc. and found to have promising antibiotic properties. In order to prove the structure unequivocally, a total synthesis beginning with the shown starting material was carried out. Give structures for each of the products in the synthetic sequence.



1. NaH, THF
2. $PhCH_2Br$
3. PhLi, THF
4. aq. NH_4Cl (quench)
5. PCC, CH_2Cl_2
6. xs CH_3OH, cat. H^+
7. H_2, Pt
8. PDC, CH_2Cl_2
9. $(CH_3)_2CHCH_2MgBr$, ether
10. aq. NH_4Cl (quench)
11. NaH, THF
12. $CH_3CH_2CH_2Br$



chauncydermolide G

13. 5% HCl, 3 h, RT
14. Br_2, Fe
15. $(CH_2OH)_2$, cat. H^+
16. 2 Li, THF
17. $H_2C{=}O$
18. aq. NH_4Cl (quench)
19. PCC, CH_2Cl_2
20. $Ph_3P{=}CH_2$, ether
21. *m*-CPBA, CH_2Cl_2
22. $(CH_3)_2CHMgBr$, ether
23. aq. NH_4Cl (quench)
24. PCC, CH_2Cl_2
25. Br_2, H_2O, THF
26. $NaOCH_3$, CH_3OH
27. $CH_3CH_2CH_2MgBr$, ether
28. aq. NH_4Cl (quench)
29. NaH, THF
30. CH_3Br
31. CH_2I_2, Zn, THF
32. 5% HCl, 3 h, RT
33. LDA, THF, -78 °C
34. CH_3CH_2Br
35. 

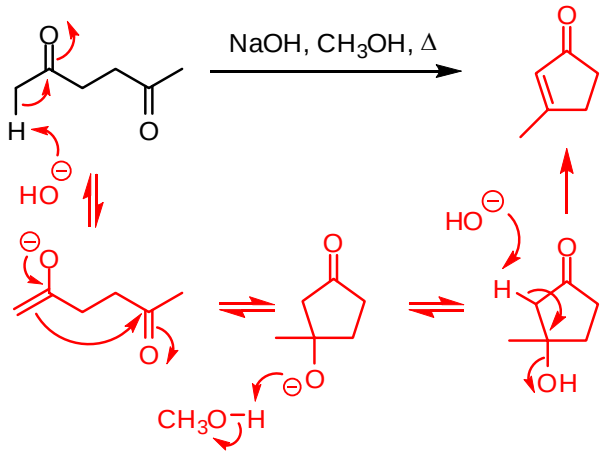
, THF
36. dil. H_2SO_4
37. HBr

Chemistry 3720 **Ch. 17-20 Synthesis Problems – Key**

These problems are from various parts of 3719 and 3720 and deal with the two main synthetic issues studied; C-C bond formation and manipulation of functional groups.

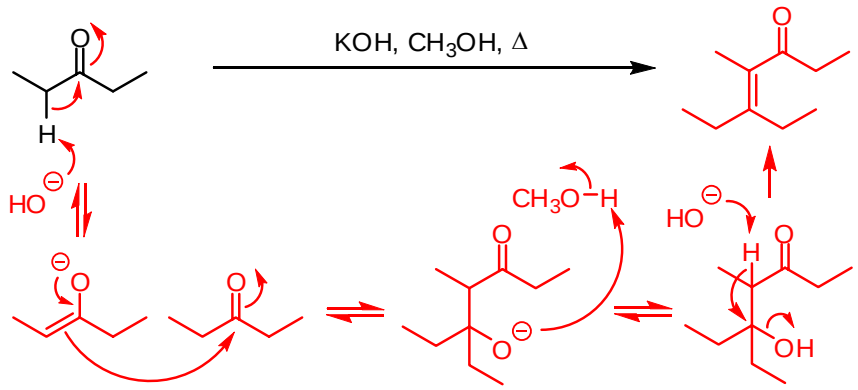
1. Give the major organic product(s) from each of the following aldol reactions as well as a detailed mechanism for each case. Be careful with any regiochemical issues.

a.



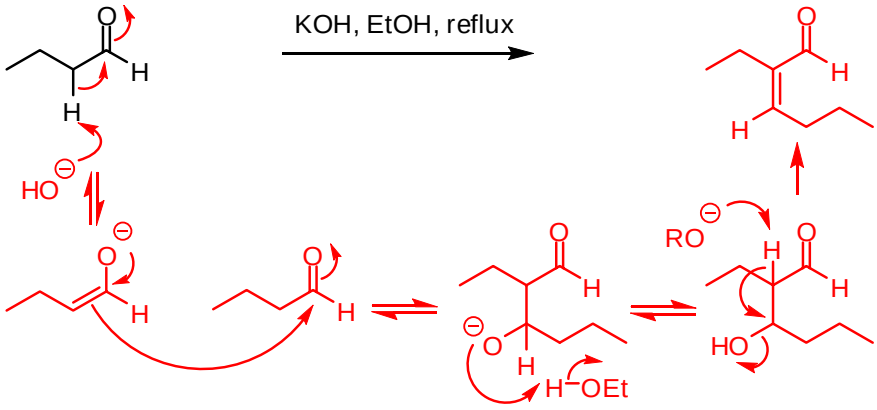
Intramolecular aldol is much faster than the intermolecular reaction, therefore a cycle is formed. Refluxing the mixture promotes loss of H_2O in the final step and formation of the α,β-unsaturated product. There are two types of α-H but loss of the other type would lead to an unstable 3-membered ring.

b.



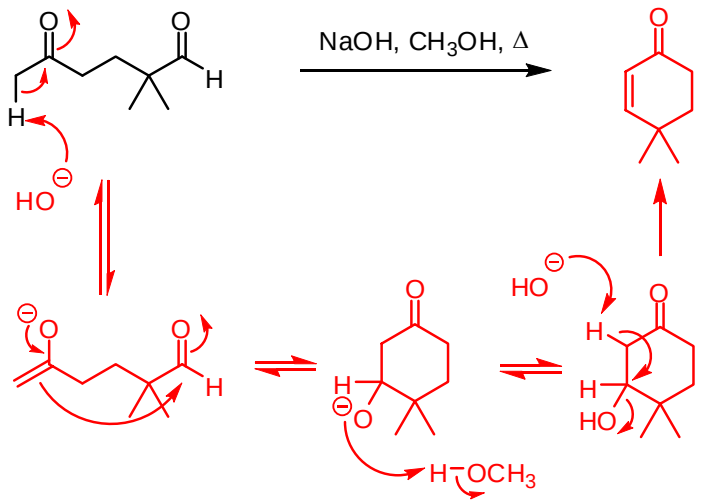
Intermolecular aldol reaction is the only possibility here since there isn't a second carbonyl in the substrate. The use of KOH as base ensures that both some enolate and some of the starting ketone are present. Running these reactions at higher temp usually results in loss of H_2O, especially when conjugation is possible.

c.



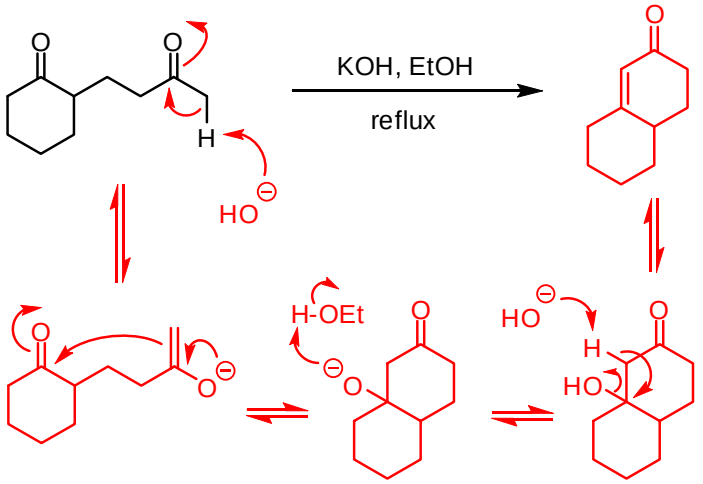
Again, ***intermolecular*** aldol reaction is the only possibility here since there isn't a second carbonyl in the substrate. The use of KOH as base ensures that both some enolate and some of the starting aldehyde are present. Carrying out these reactions at higher temp usually results in elimination of H_2O to form α,β-unsaturated product.

d.



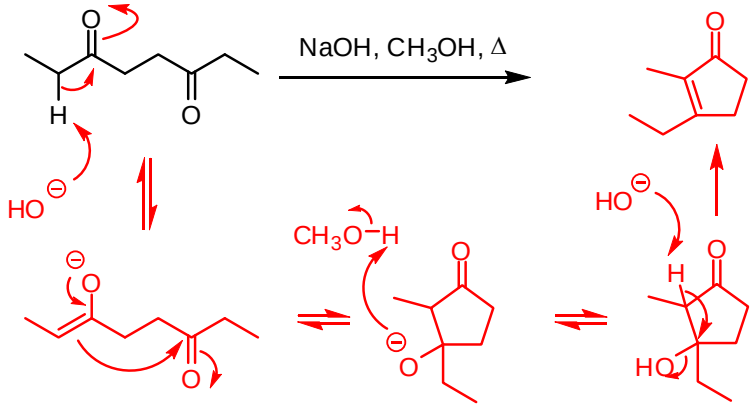
The ***intramolecular*** aldol is much faster than intermolecular reaction, therefore a cycle is formed. There are two types of α-H in the starting material, however only one cyclization leads to a stable ring. Refluxing (boiling) the mixture promotes loss of H_2O in the final step.

e.



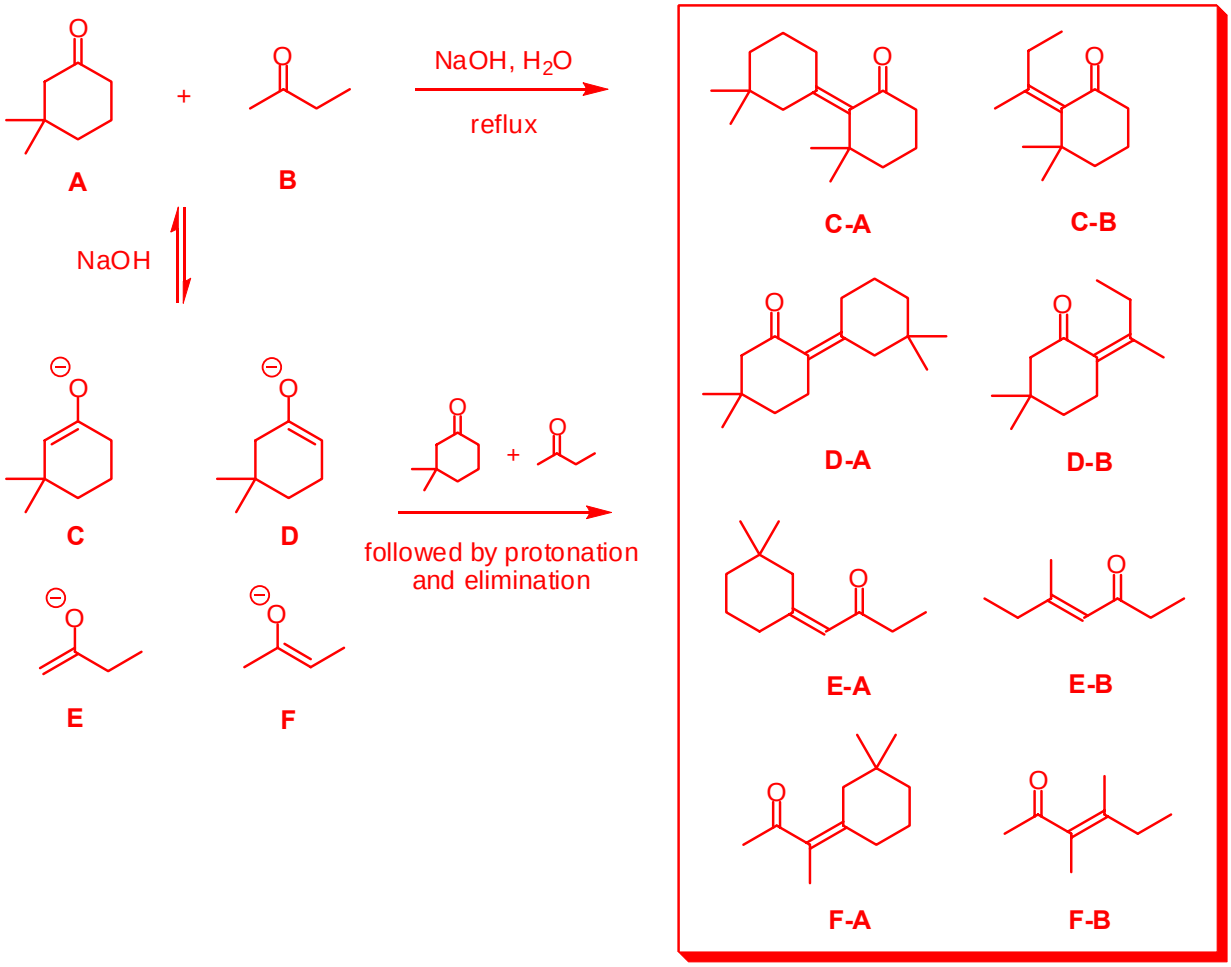
The ***intramolecular*** aldol much faster than the intermolecular reaction, therefore a cycle is formed. There are several types of α-H in the starting material; so several cyclization paths may be possible. The reaction is reversible and will yield the most stable product, the one shown. Refluxing the mixture promotes loss of H_2O in the final step.

f.

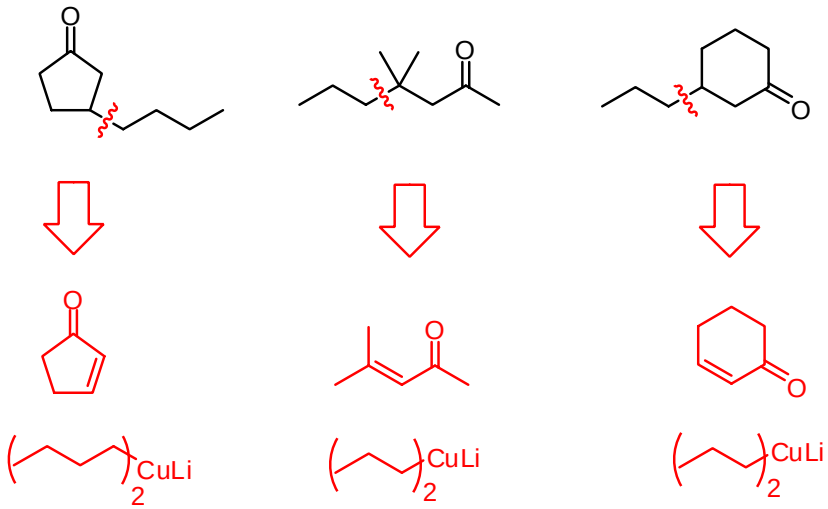


The ***intramolecular*** aldol much faster than the intermolecular reaction, therefore a cycle is formed. Two types of α-H but only one pathway leads to a stable product, in this case a five-membered ring. Refluxing the mixture promotes loss of H_2O in the final step.

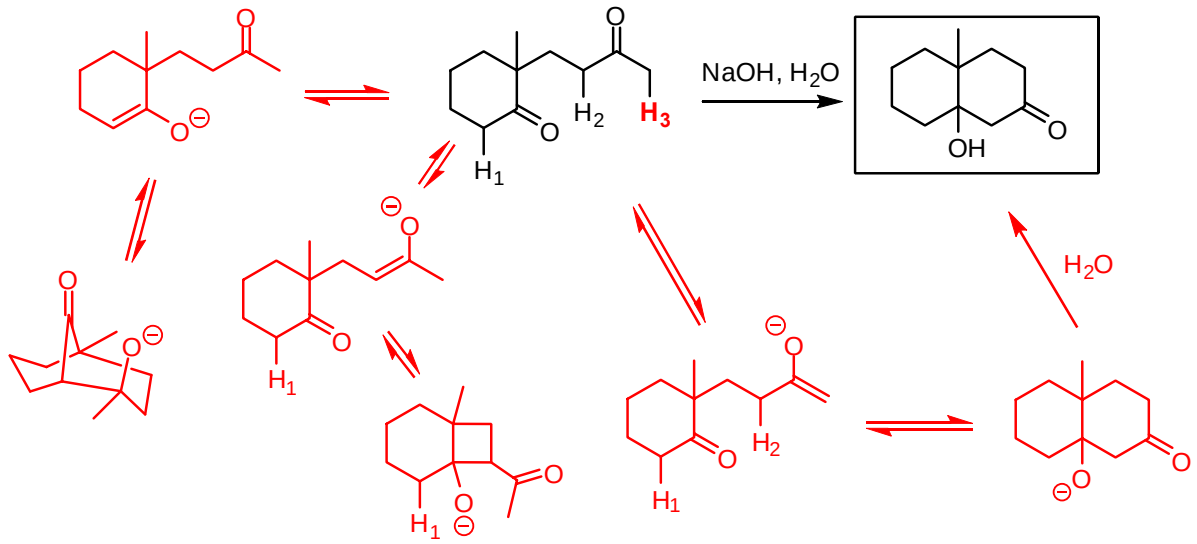
2. Draw all of the possible ***aldol condensation*** products possible in the following reaction.



3. Provide the reagents required to make each of the following compounds *via* 1,4-addition chemistry.

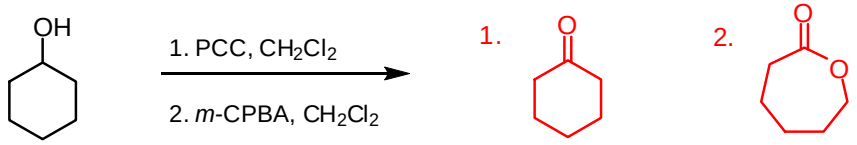


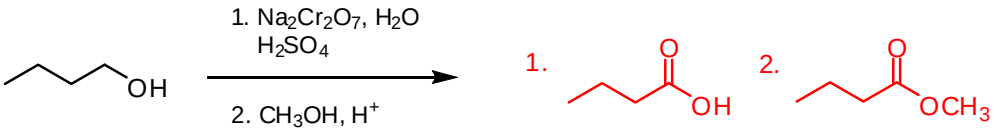
4. In the following Robinson annulation, 3 aldol products are possible; explain why only one is formed.

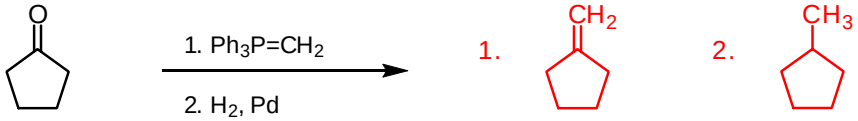


Since there are 3 different types of α-H there are 3 different enolates possible here. The outcome of the reaction is governed by thermodynamics (i.e. stability) since the steps are reversible, therefore the most stable product will result. The enolate formed by removal of H_1 would generate a bicylic system (somewhat strained), the one formed by removal of H_2 would only afford a 4-membered ring (quite strained), whereas the enolate generated by removal of H_3 would give the favourable 6-membered ring shown above.

5. Give the major products from each step of the following reaction sequences.

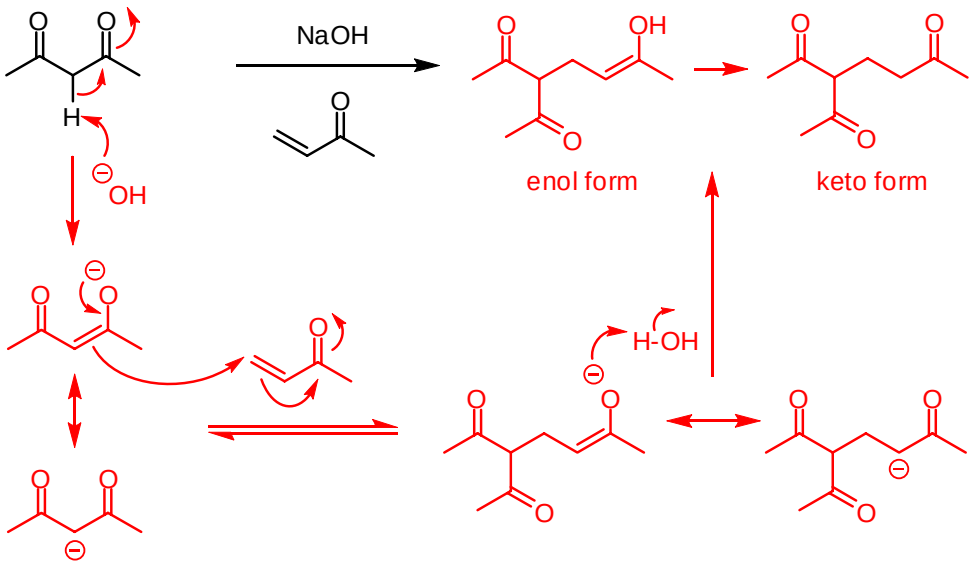
a. 

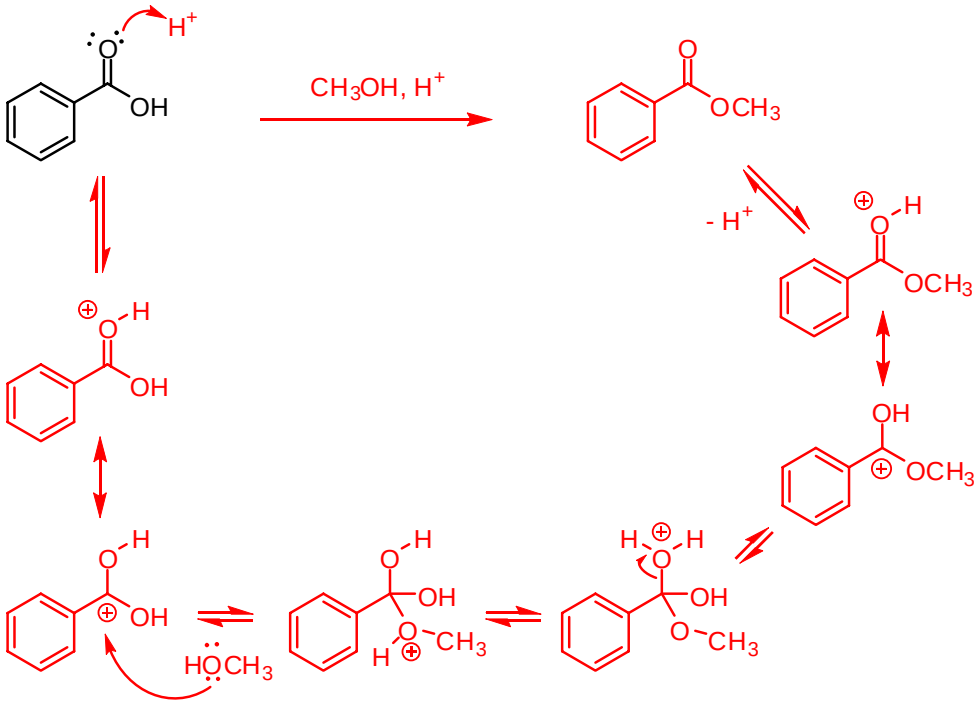
b. 

c. 

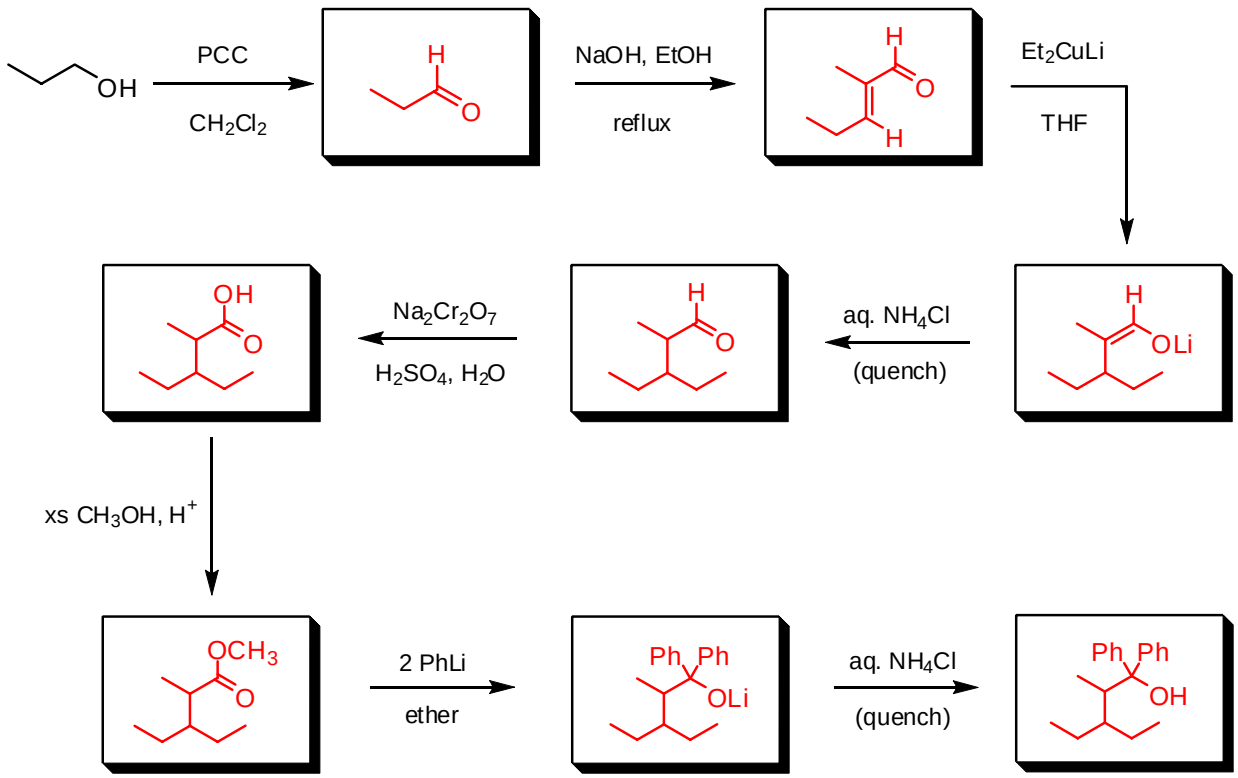
d. 

6. Provide complete mechanisms for the following conversions. Include all resonance structures for any intermediates that may be formed.

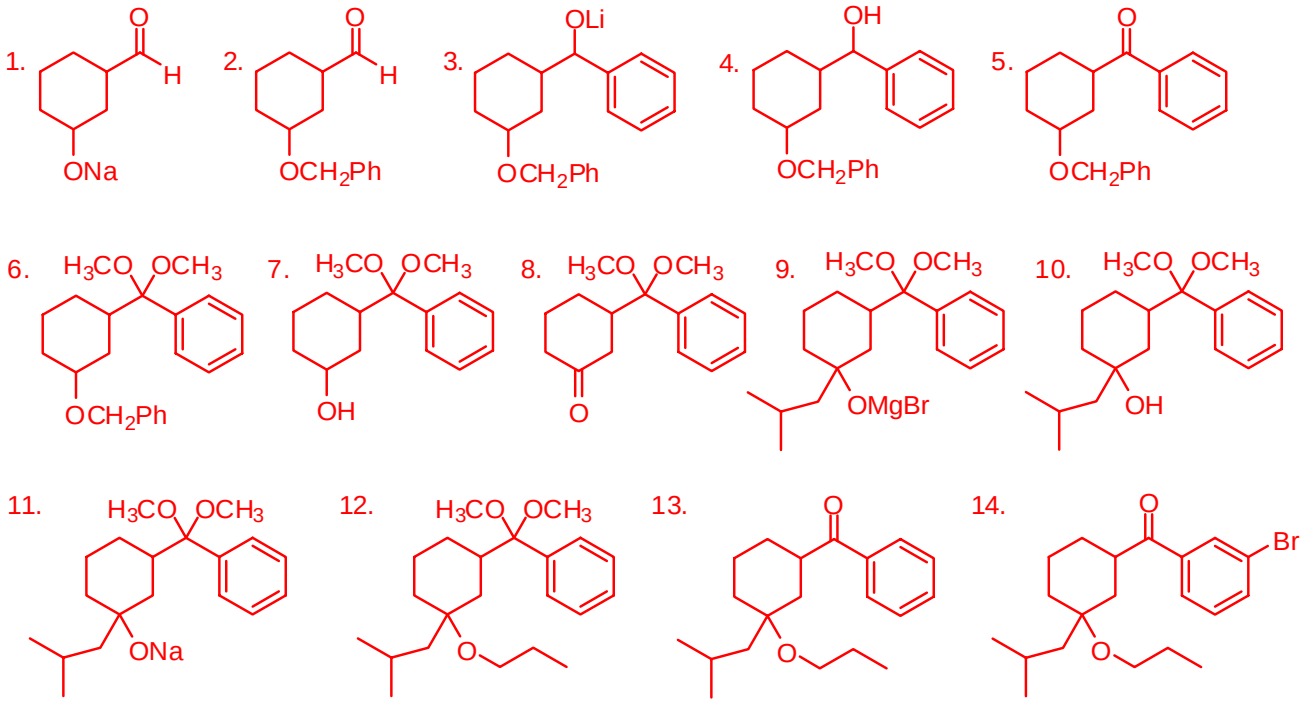




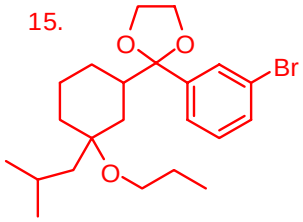
7. Give structures for each of the products in the following “roadmap.”



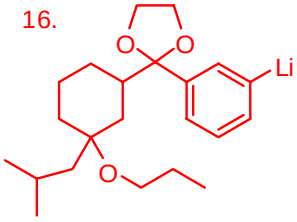
8. The polyether compound *chauncydermolide G* (shown below) was recently isolated by Triplet Pharmaceuticals Inc. and found to have promising antibiotic properties. In order to prove the structure unequivocally, a total synthesis beginning with the shown starting material was carried out. Give structures for each of the products in the synthetic sequence.



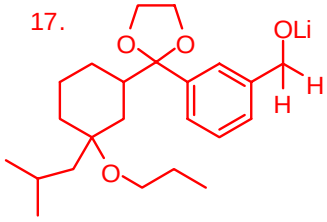
15.



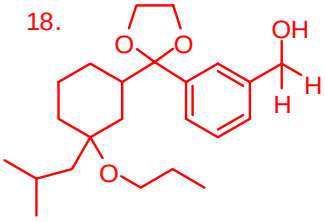
16.



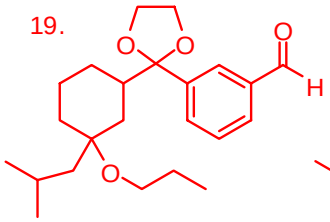
17.



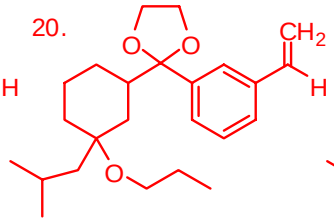
18.



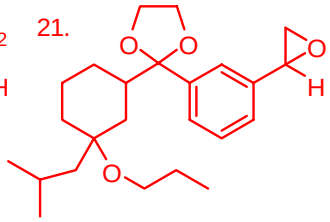
19.



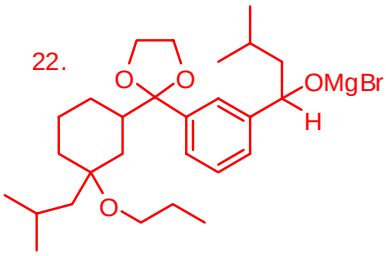
20.



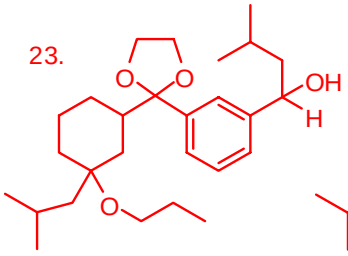
21.



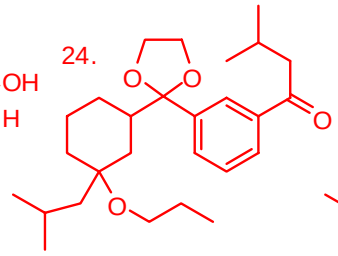
22.



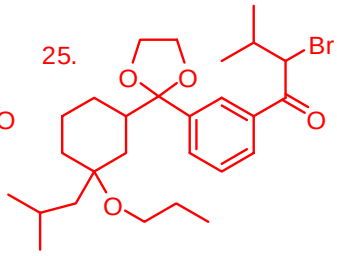
23.



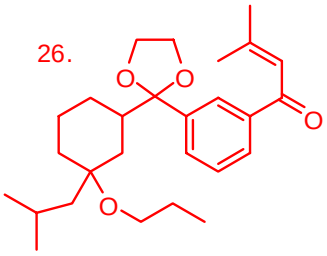
24.



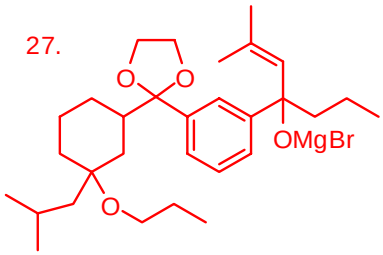
25.



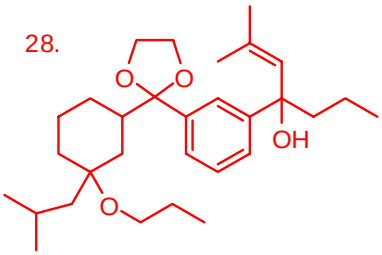
26.



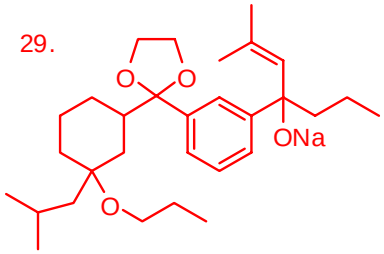
27.



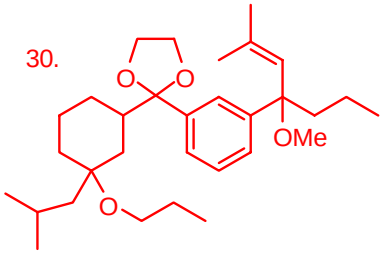
28.



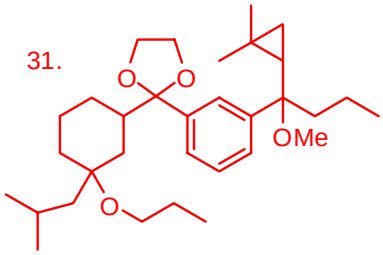
29.



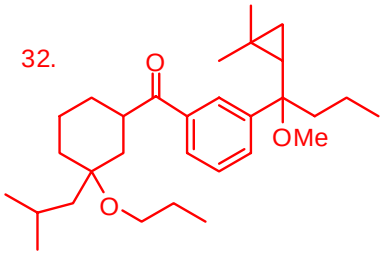
30.



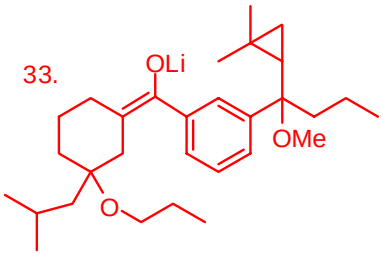
31.



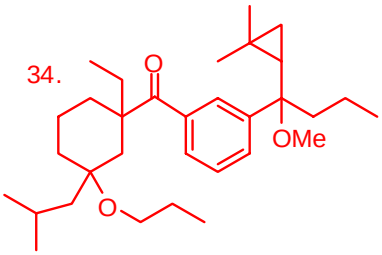
32.



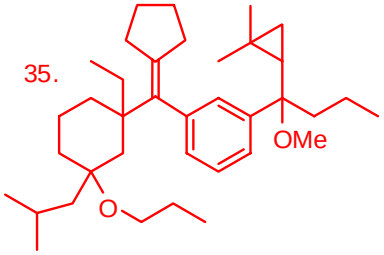
33.



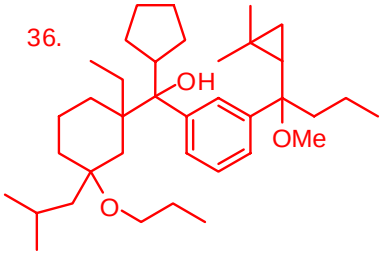
34.



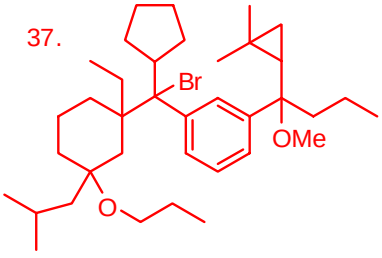
35.



36.



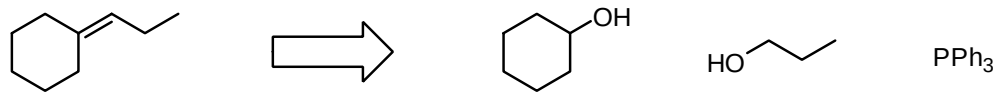
37.



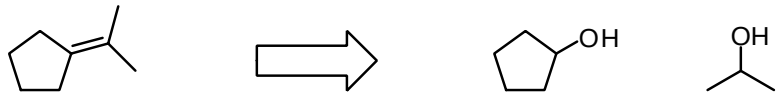
Chemistry 3720 **Further Synthesis Problems 1**

1. Give retrosynthetic analyses for the following molecules that go back to the given starting materials, and then provide the synthesis in the forward direction. Assume you have access to the usual other reagents (HBr, HNO_3, $NaBH_4$, etc.) in the lab.

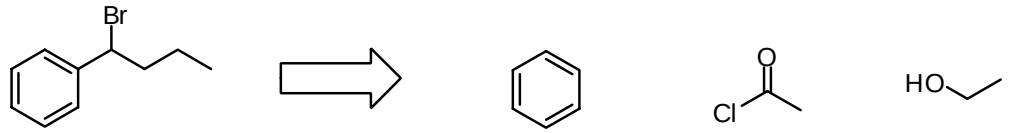
a.



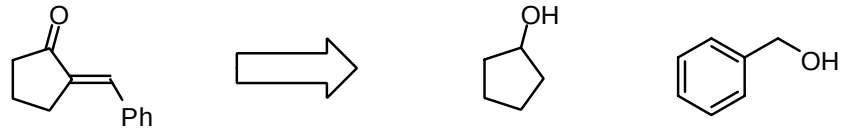
b.



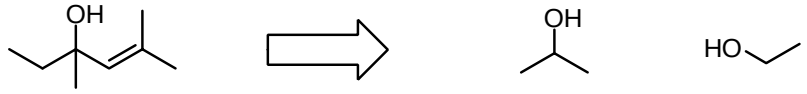
c.



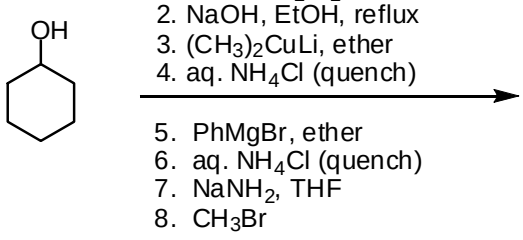
d.



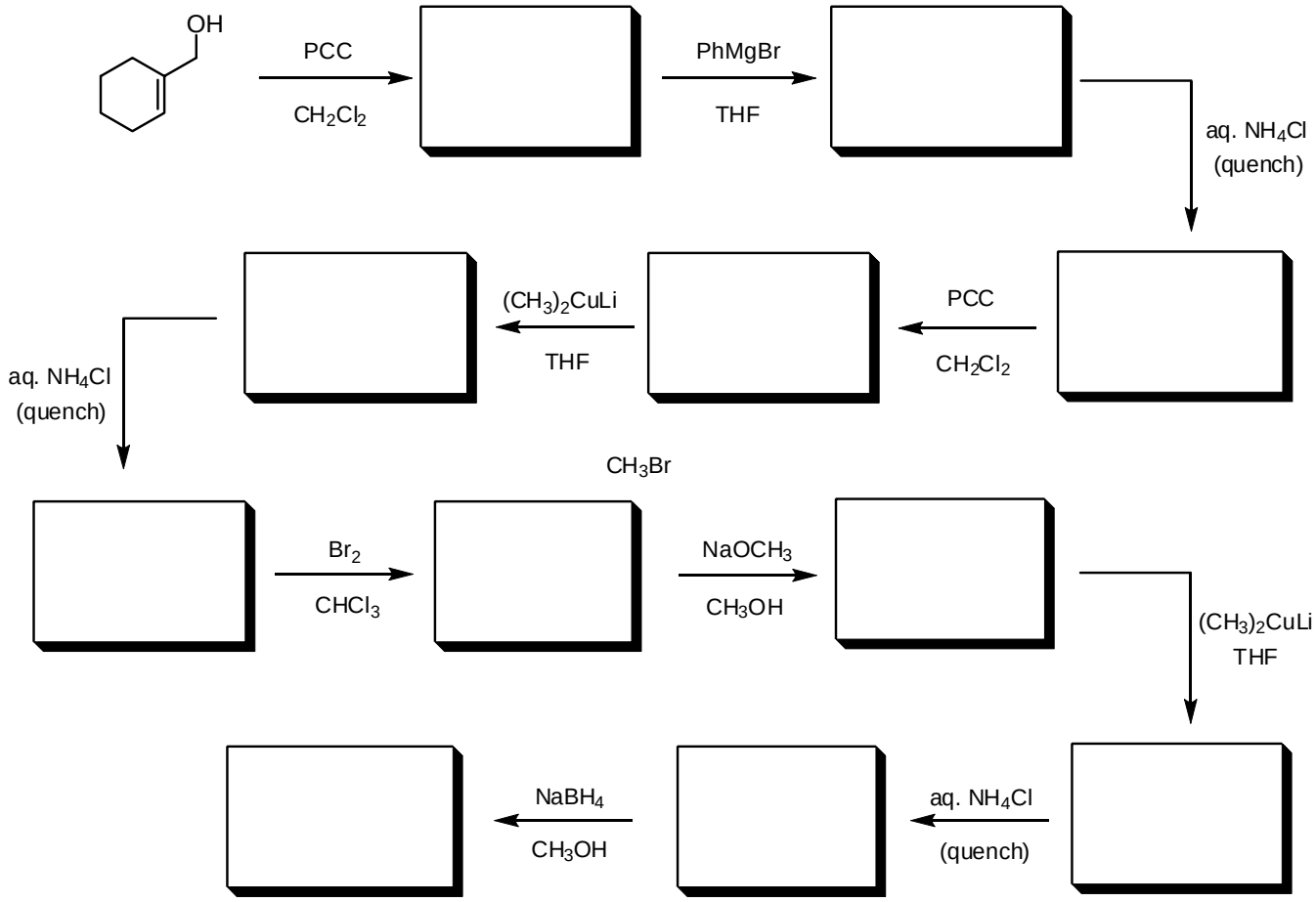
e.



2. Give the major organic product(s) from each step of the following synthetic scheme.

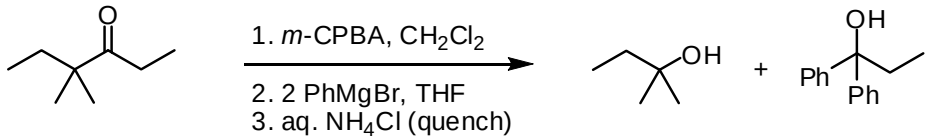


3. In the boxes provided, give the products from each step in the following "road-map" scheme.

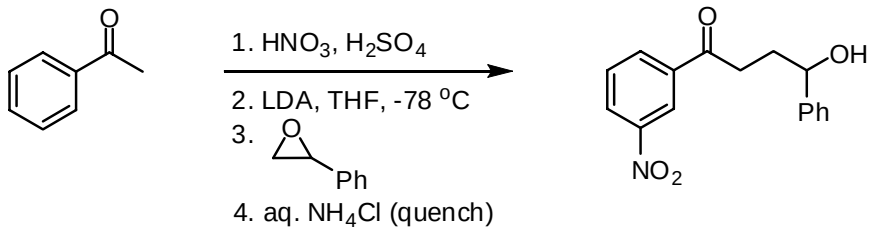


4. Give complete mechanisms, including any important resonance structures for intermediates where applicable, that explain the bond-making and bond-breaking events in the following conversions.

a.



b.

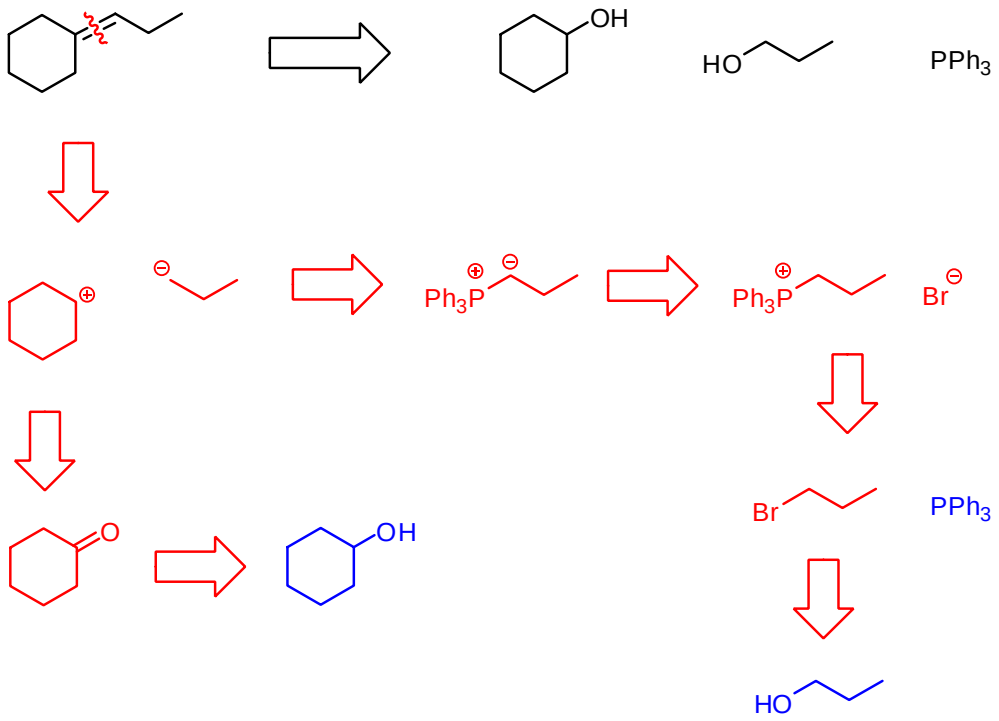


Chemistry 3720 **Further Synthesis Problems 1 - Key**

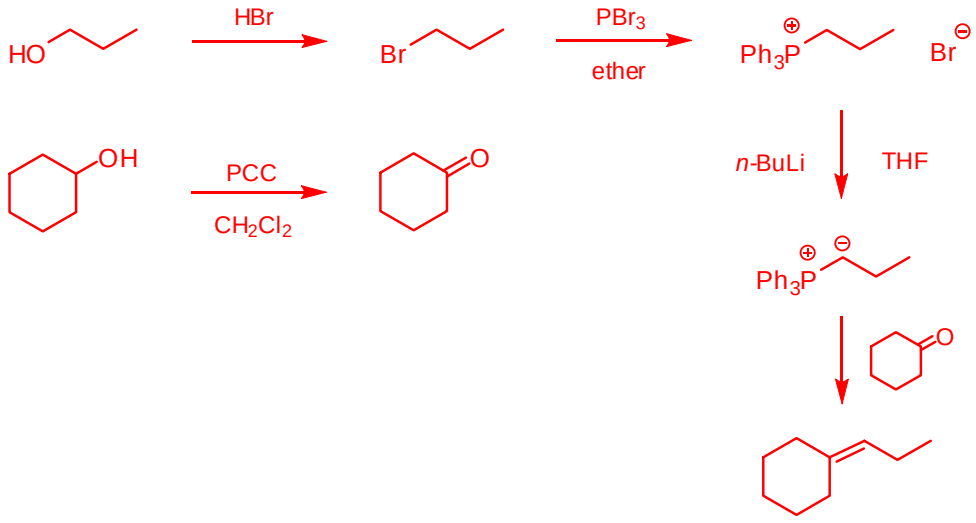
1. Give retrosynthetic analyses for the following molecules that go back to the given starting materials, and then provide the synthesis in the forward direction. Assume you have access to the usual other reagents (HBr, HNO_3, $NaBH_4$, etc.) in the lab.

a.

Retrosynthesis

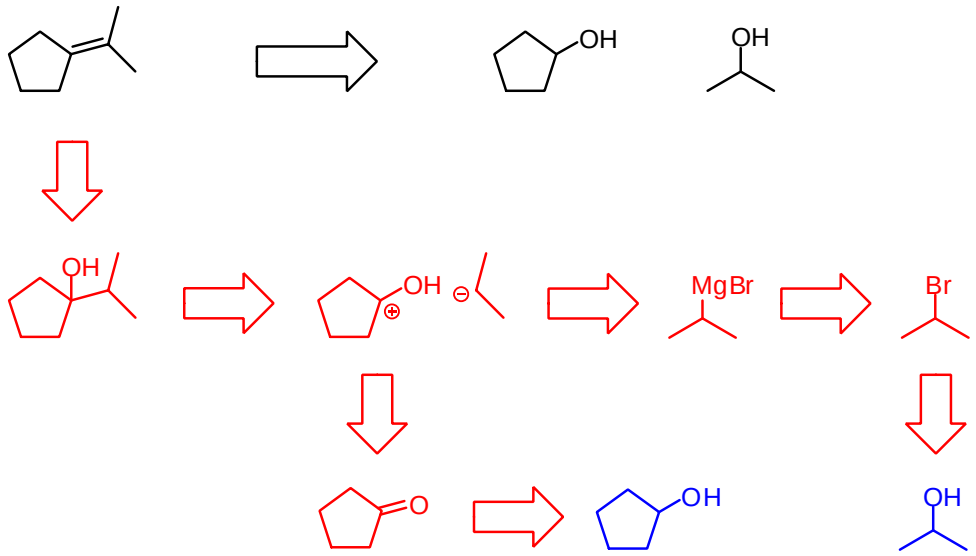


Synthesis

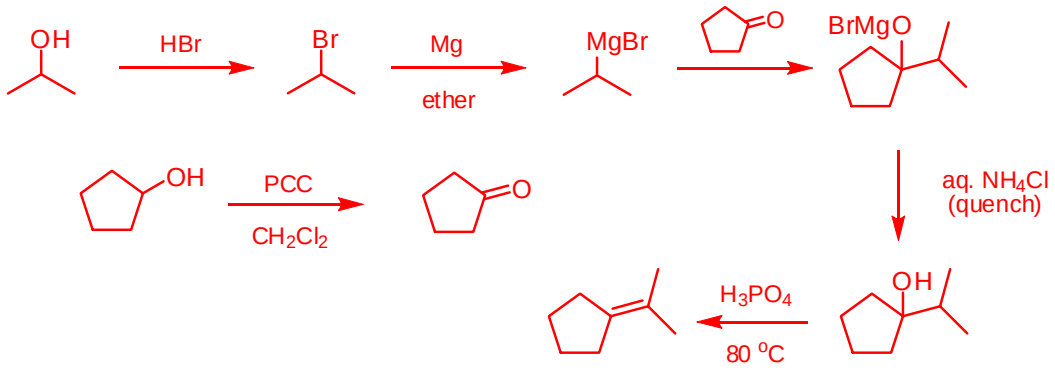


It would also be possible to use organometallic chemistry in this synthesis (e.g. turn one piece into a Grignard reagent and then add to a ketone, followed by acid-catalyzed elimination), however that might not give you this alkene as the major isomer in the elimination step. The Wittig route puts the double bond in the right place without any complications.

b. **Retrosynthesis**

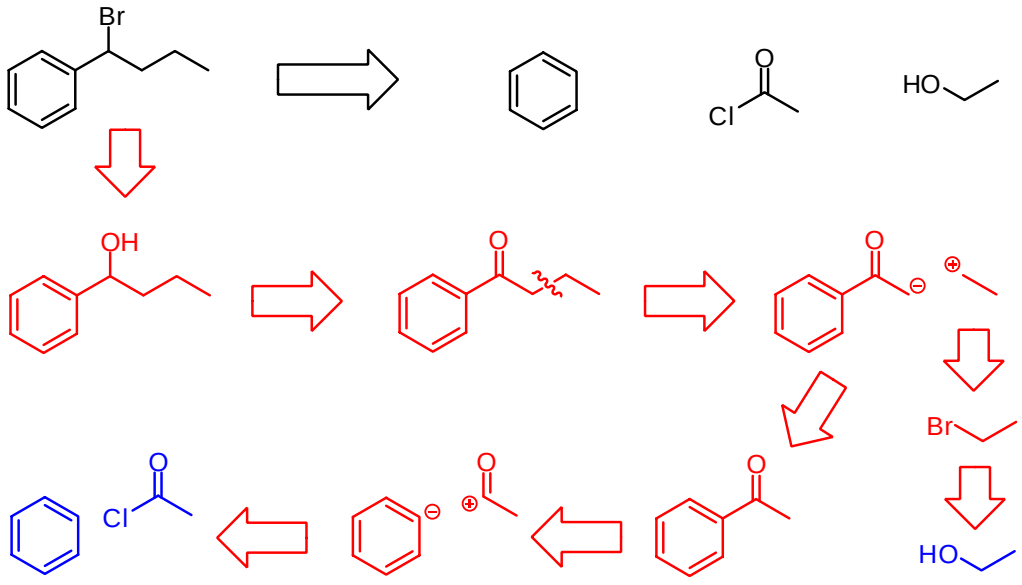


Synthesis

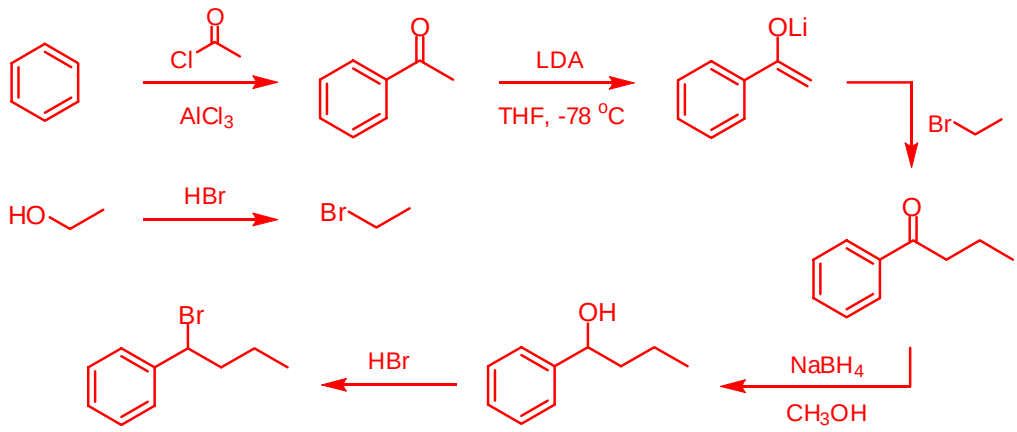


One could also make the Grignard reagent from the cyclopentanol and the ketone from the isopropanol or even use Wittig chemistry here. Since the product is the most highly substituted alkene anyway, both methods work.

c. **Retrosynthesis**

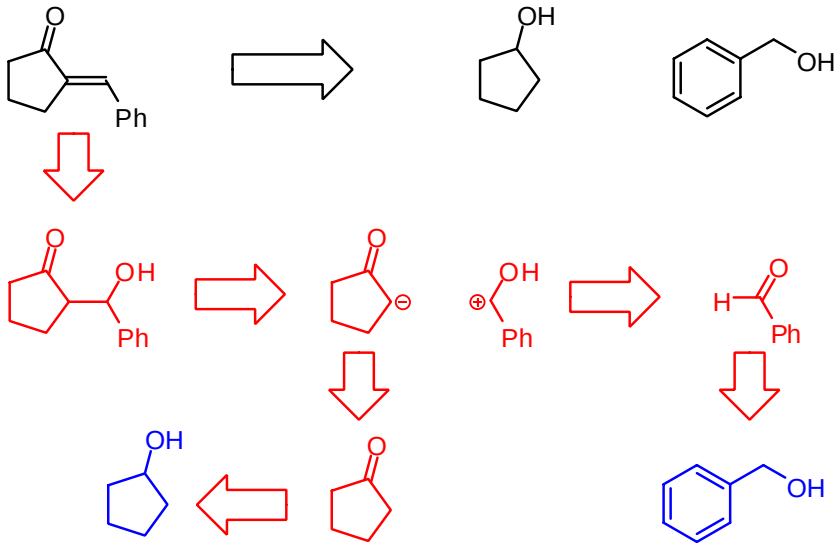


Synthesis

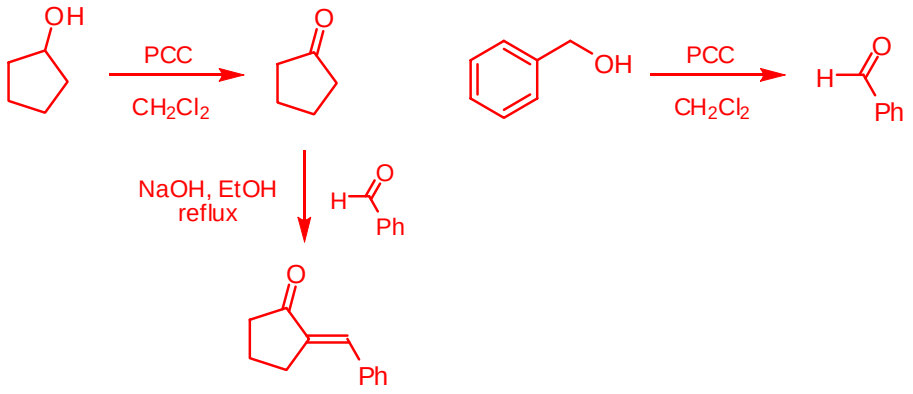


The limitation here is the starting materials that are given; the 2-carbon alcohol limits what type of chemistry can be applied and the only logical way really is to recognize that the ***alpha***-carbon of the ketone may be deprotonated to form the nucleophilic enolate.

d. **Retrosynthesis**



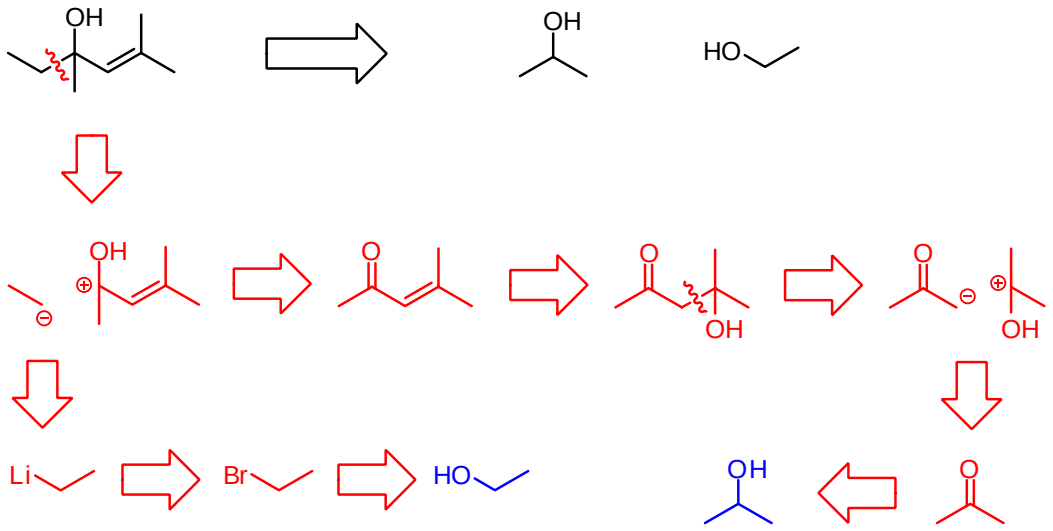
Synthesis



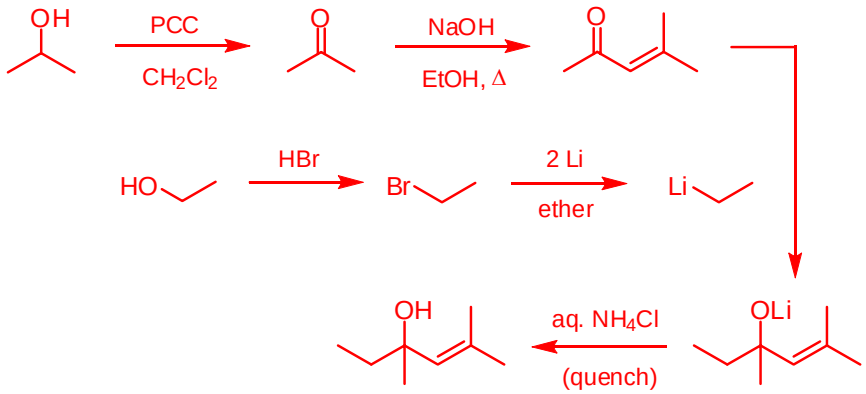
Logical to use crossed-aldol here since the alkene is ***alpha*** to the ketone carbonyl. Heating ensures elimination.

e.

Retrosynthesis

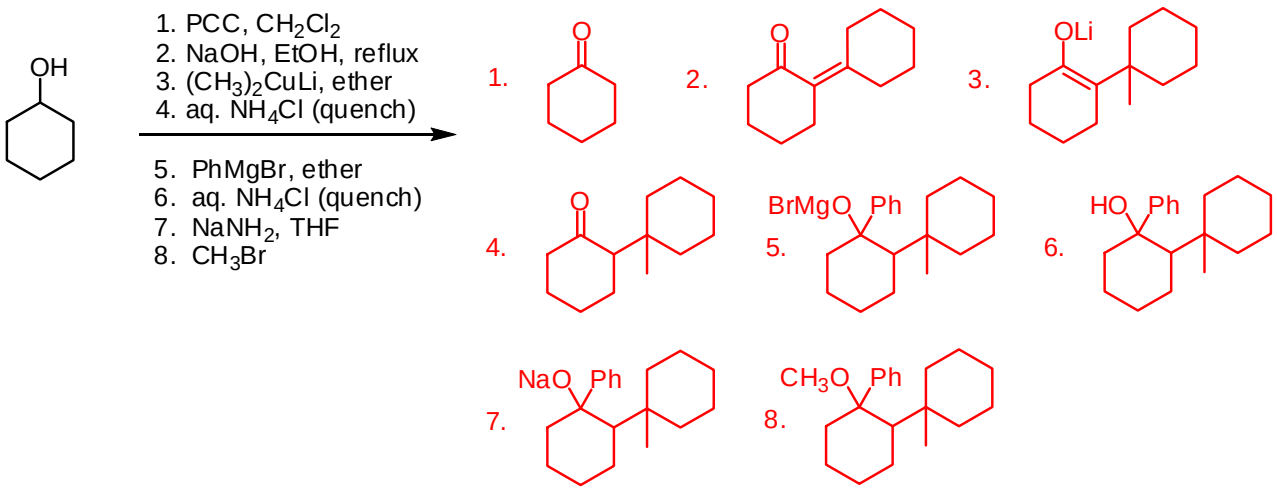


Synthesis

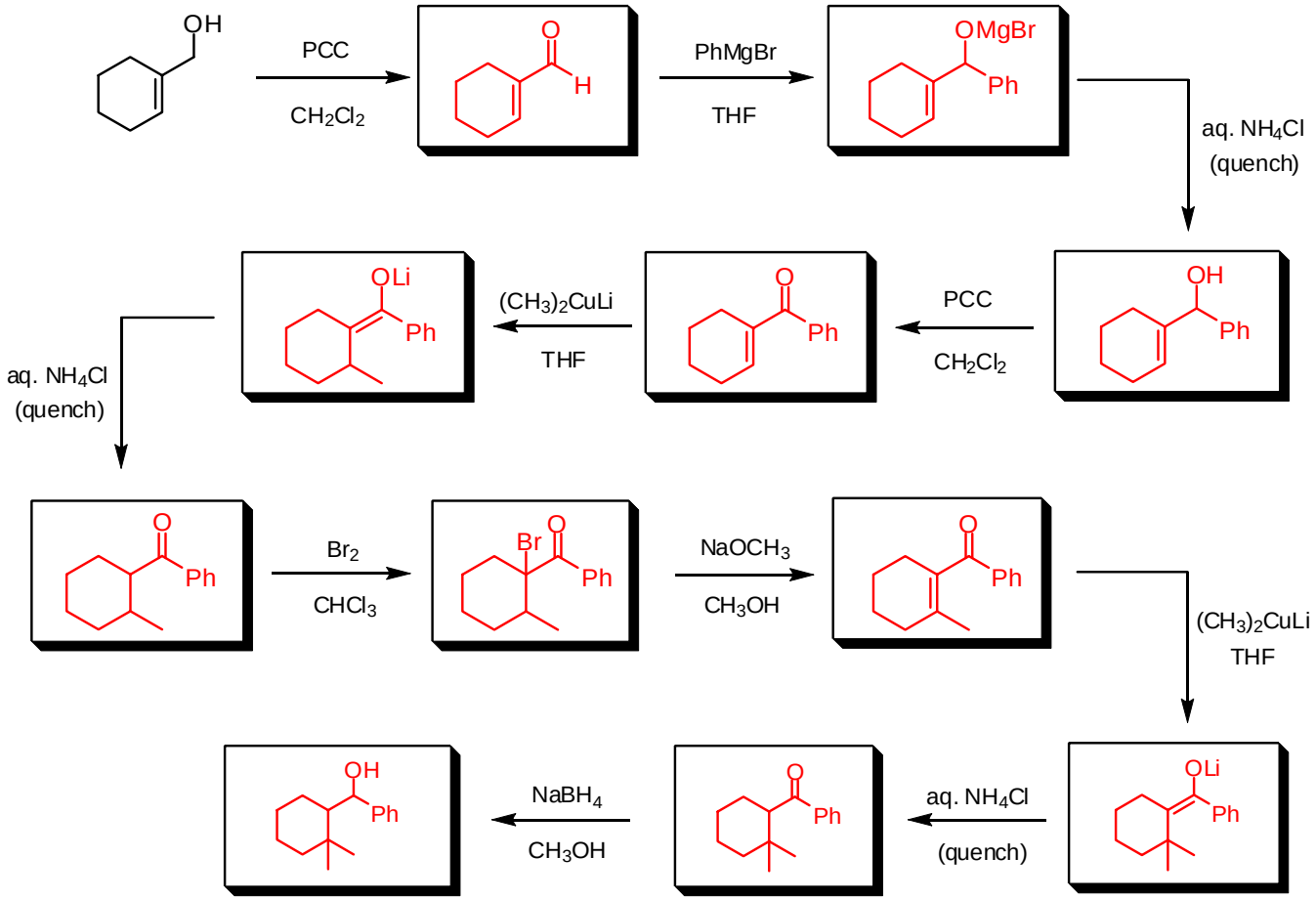


Given the two alcohols here the logical first disconnection is the ethyl group, which reveals a 6-carbon fragment that is then accessible by a simple intermolecular aldol reaction. Heating the aldol step ensures that elimination occurs to give the required α,β-unsaturated product.

2. Give the major organic product(s) from each step of the following synthetic scheme.

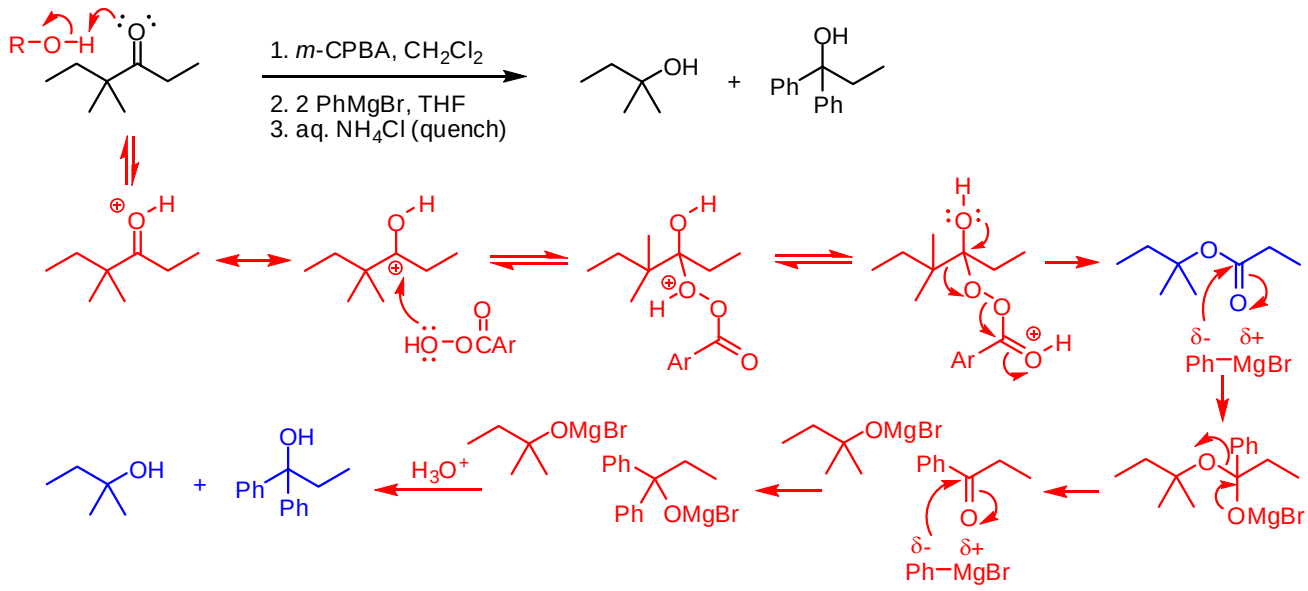


3. In the boxes provided, give the products from each step in the following “road-map” scheme.

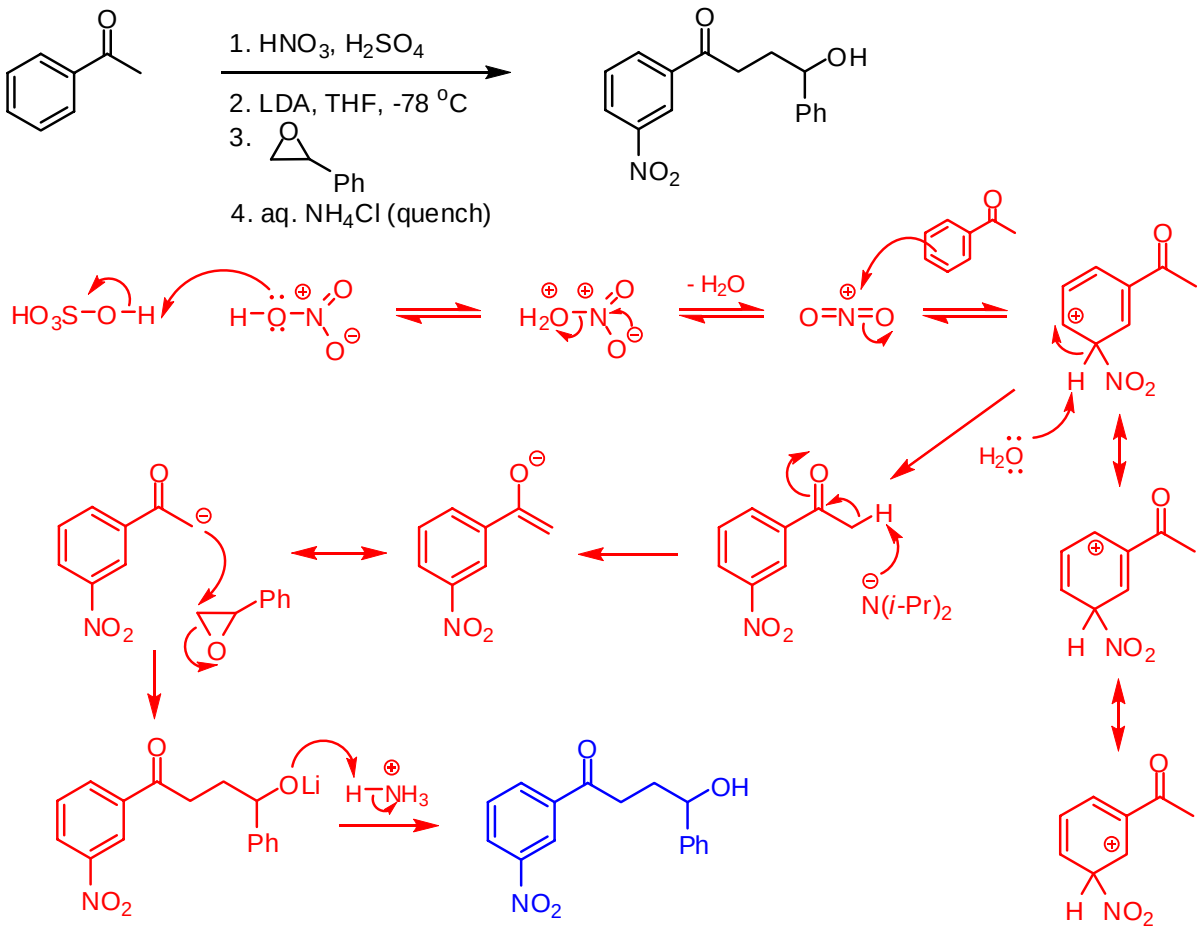


4. Give complete mechanisms, including any important resonance structures for intermediates where applicable, that explain the bond-making and bond-breaking events in the following conversions.

a.



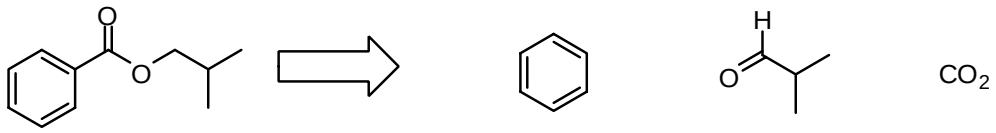
b.


1. HNO3, H2SO4
2. LDA, THF, -78 °C
3.
Ph
4. aq. NH4Cl (quench)
OH
Ph
NO2
- H2O
HO3S–O–H
H2O
H
NO2
N(i-Pr)2
OLi
NH3

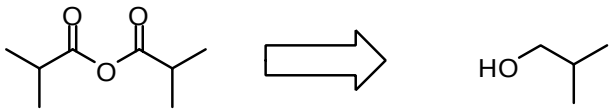
Chemistry 3720 **Further Synthesis Problems 2**

1. Give retrosynthetic analyses for the following molecules that go back to the given starting materials, and then provide the synthesis in the forward direction. Assume you have access to the usual other reagents (HBr, HNO_3, $NaBH_4$, etc.) in the lab.

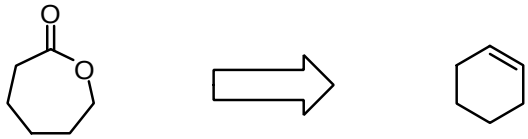
a.



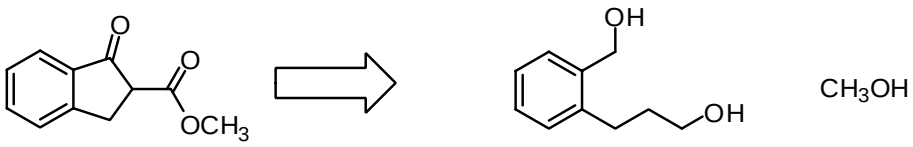
b.



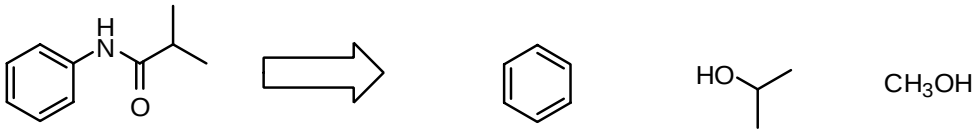
c.



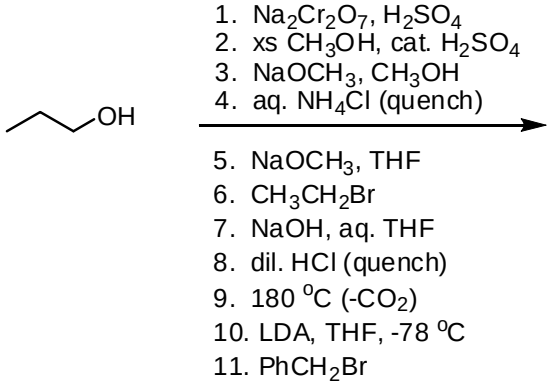
d.



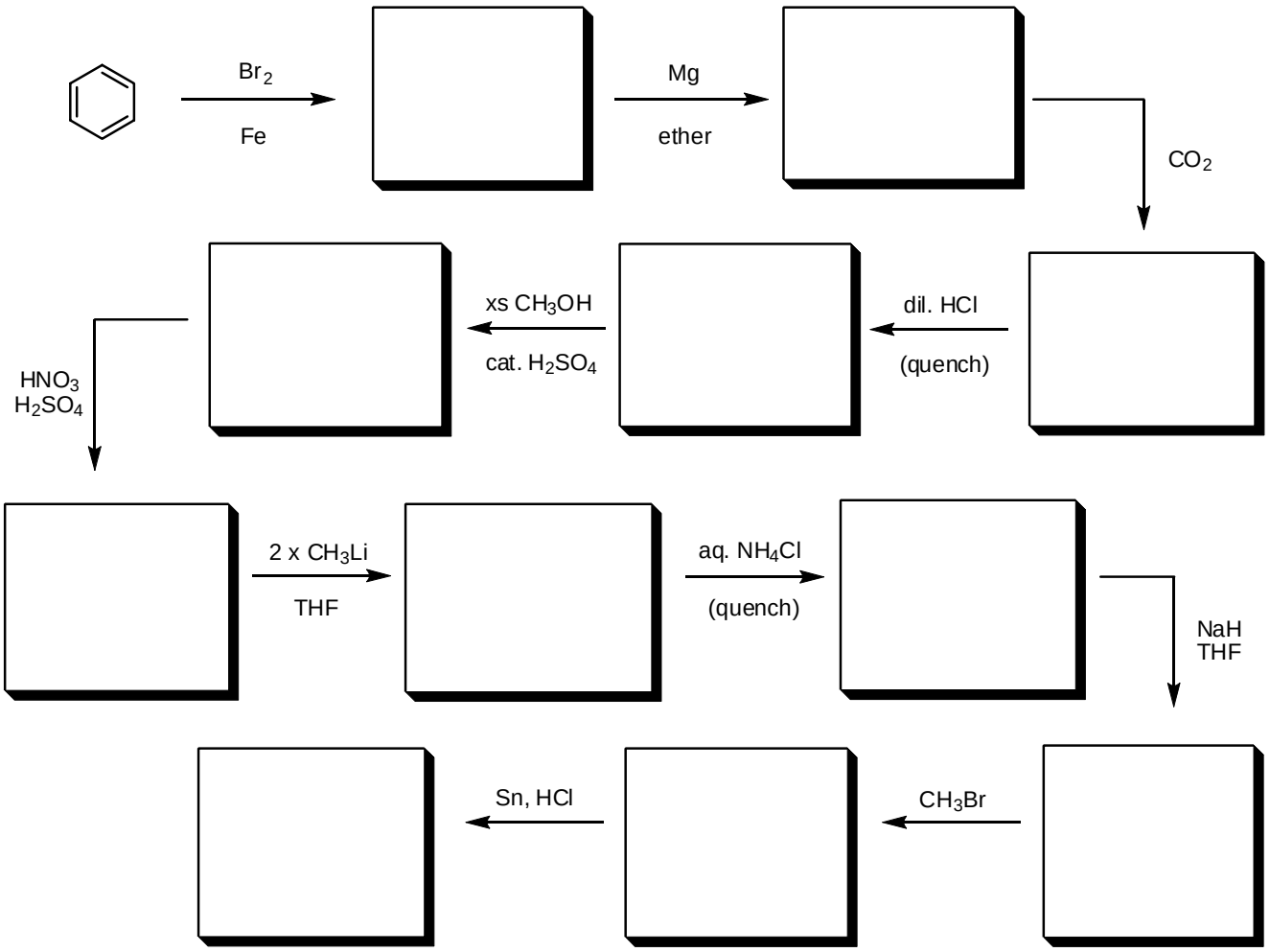
e.



2. Give the major organic product(s) from each step of the following synthetic sequence.

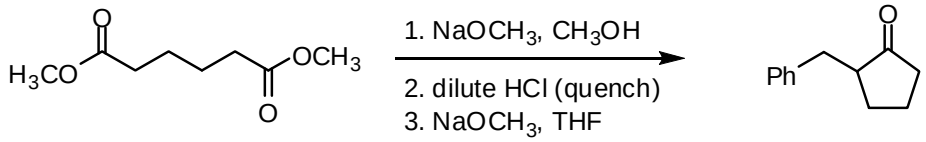


3. In the boxes provided, give the products from each step in the following "road-map" scheme. Predict the ^{1}H NMR spectra of each of the organic products from each step.



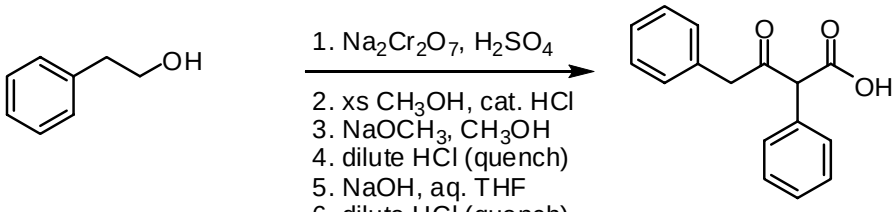
4. Give complete mechanisms, including any important resonance structures for intermediates where applicable, that explain the bond-making and bond-breaking events, in each step of the following conversions.

a.



1. $NaOCH_3$, CH_3OH
2. dilute HCl (quench)
3. $NaOCH_3$, THF
4. $PhCH_2Br$
5. NaOH, aq. THF
6. dilute HCl (quench)
7. 180 ^oC ($-CO_2$)

b.



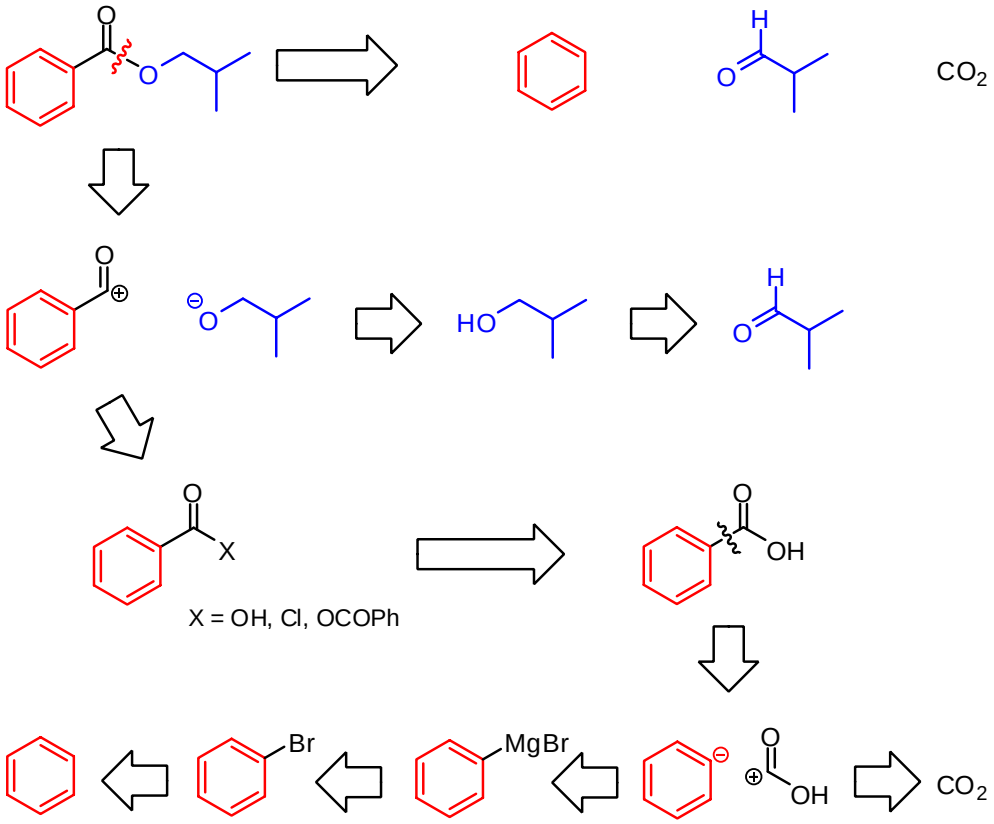
1. $Na_2Cr_2O_7$, H_2SO_4
2. xs CH_3OH, cat. HCl
3. $NaOCH_3$, CH_3OH
4. dilute HCl (quench)
5. NaOH, aq. THF
6. dilute HCl (quench)

Chemistry 3720 **Further Synthesis Problems 2 Key**

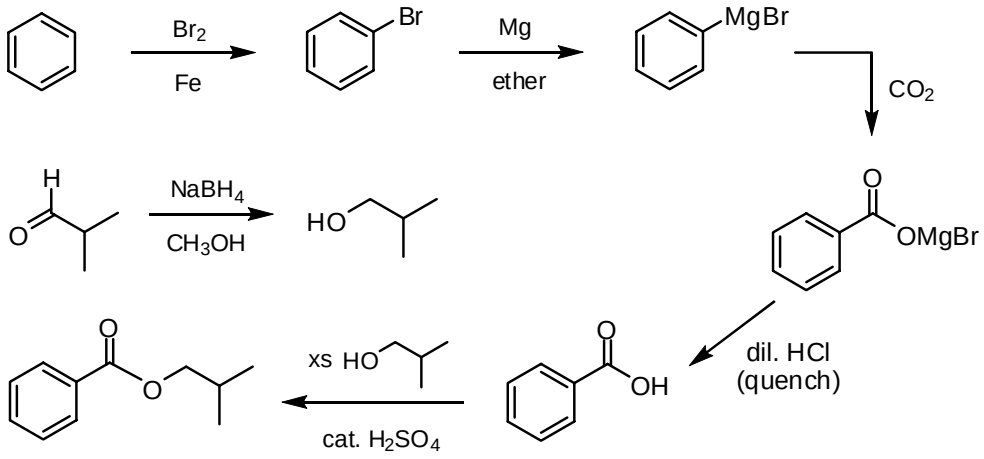
1. Give retrosynthetic analyses for the following molecules that go back to the given starting materials, and then provide the synthesis in the forward direction. Assume you have access to the usual other reagents (HBr, HNO_3, $NaBH_4$, etc.) in the lab.

a.

Retrosynthesis



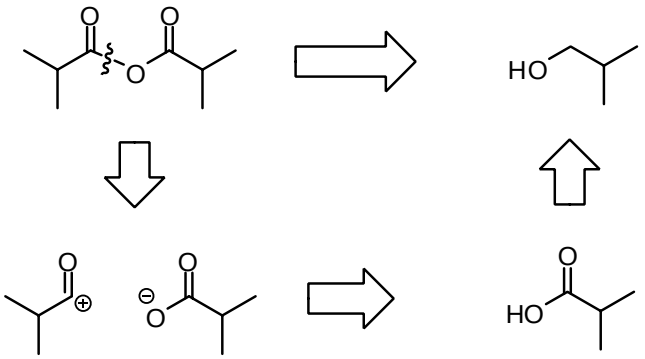
Synthesis



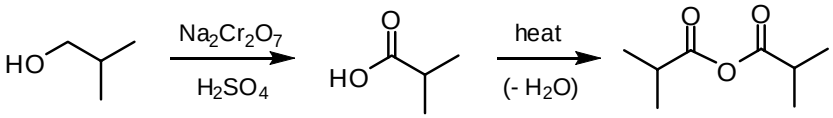
If the alcohol is inexpensive and readily available then the Fischer esterification works well, however if the alcohol is expensive, it is better to convert the carboxylic acid to the acid chloride (X = Cl) using $SOCl_2$/pyridine or the anhydride (X = OCOPh) by heating and removing H_2O. Both of these reactive carboxylic acid derivatives require 1 equivalent of alcohol to give the ester (with pyridine as a base).

b.

Retrosynthesis



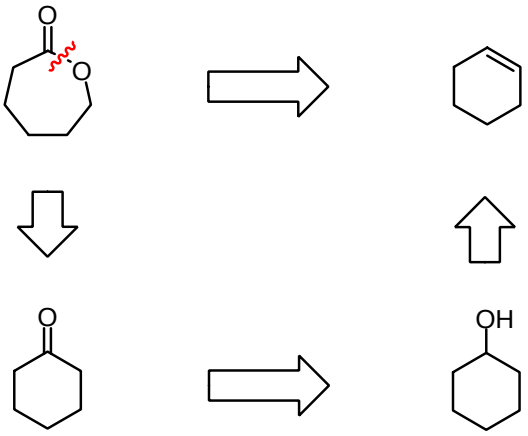
Synthesis



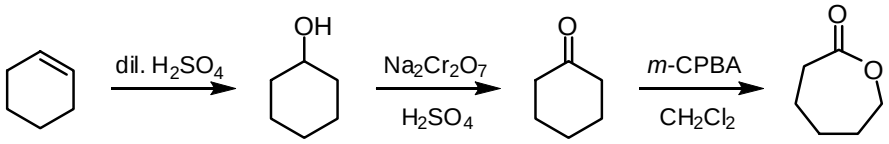
The most straightforward way to make an anhydride from a volatile (i.e. easily distillable) carboxylic acid is to heat it up with a small amount of a mineral acid and remove the water that is formed. You could also form the acid chloride from a portion of the carboxylic acid (using $SOCl_2$/pyridine) and then react that with more of the remaining carboxylic acid.

c.

Retrosynthesis



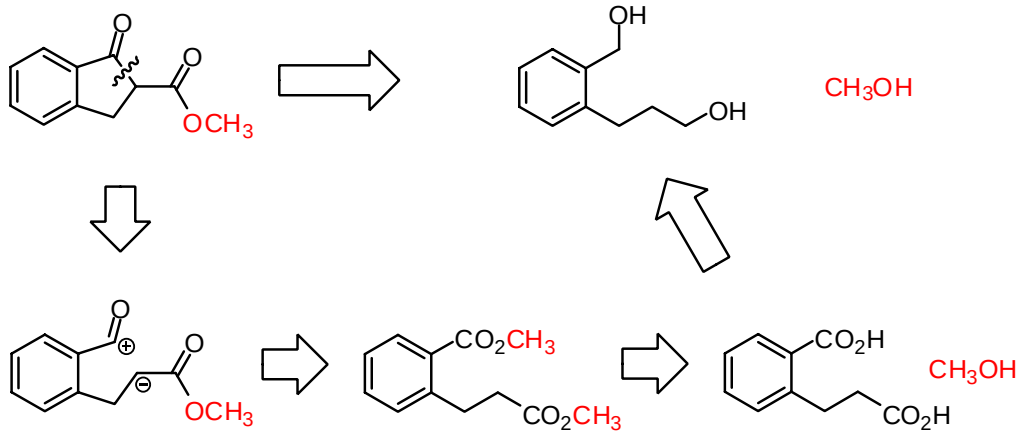
Synthesis



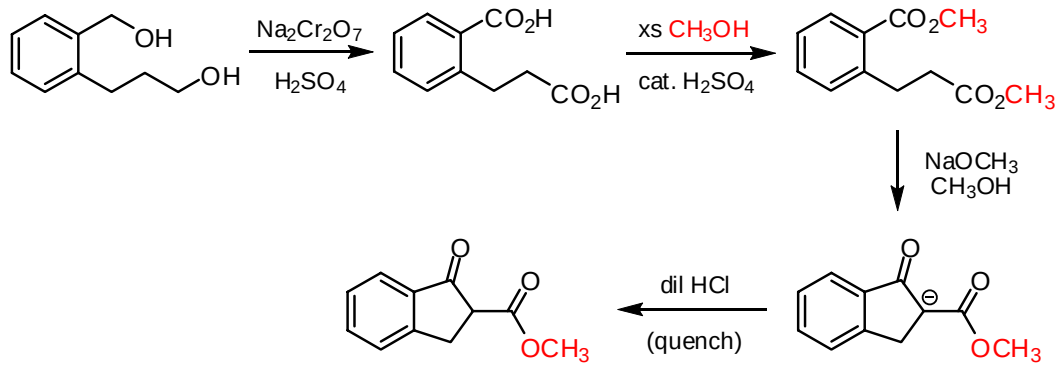
All of the required carbon atoms for the product are found in the given starting material, which needs to be manipulated to introduce oxygen. The system has to be oxidized to produce the lactone (cyclic ester) so the Baeyer-Villager oxidation is appropriate.

d.

Retrosynthesis

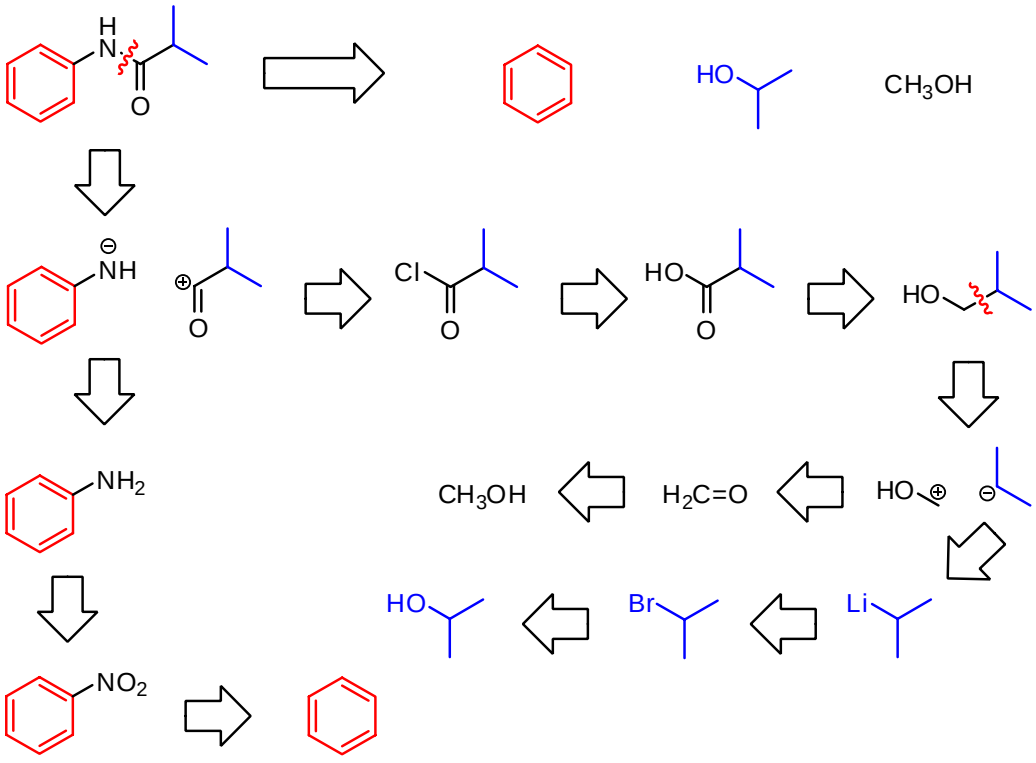


Synthesis

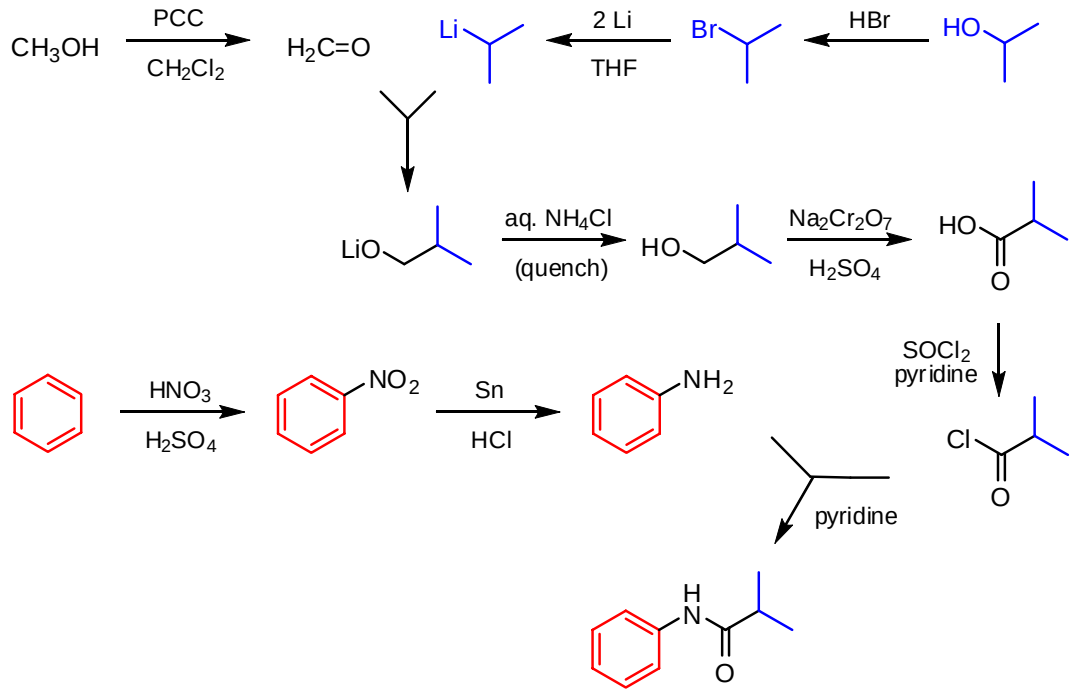


e.

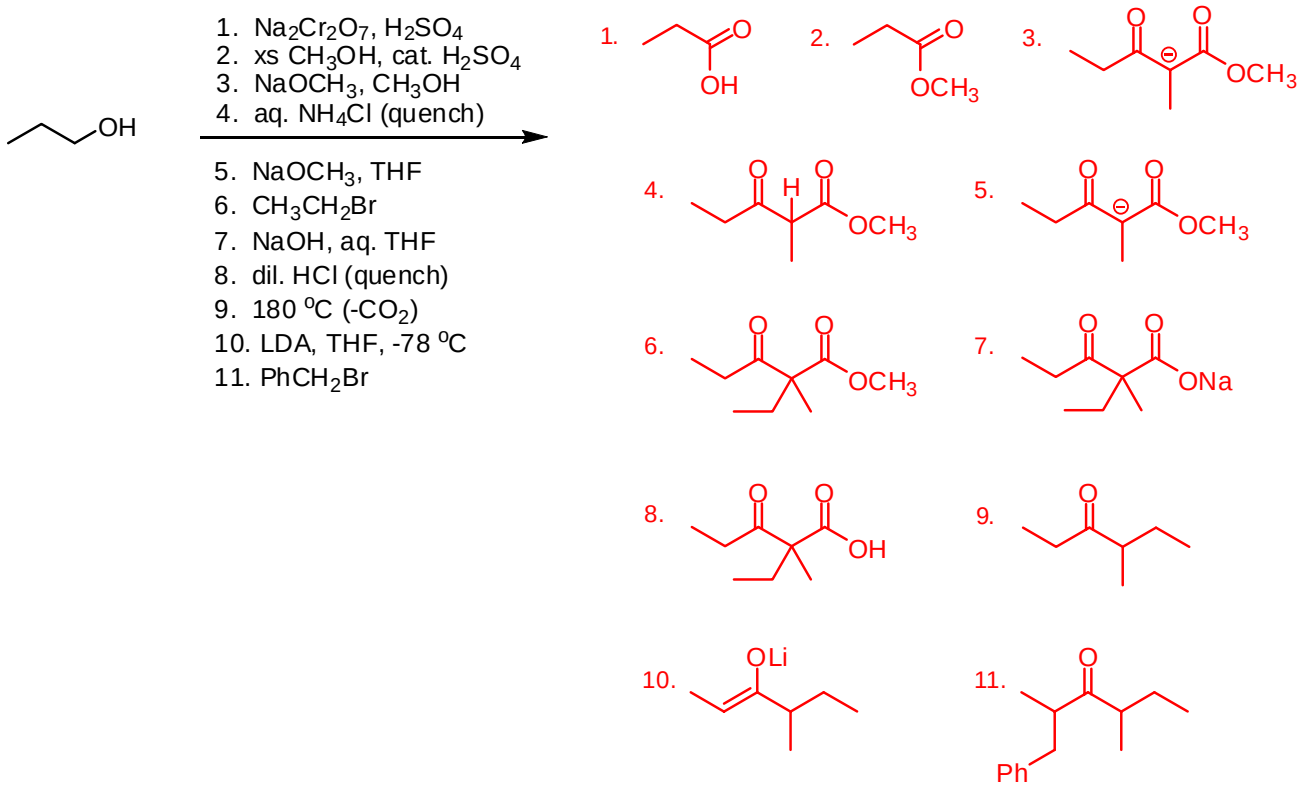
Retrosynthesis



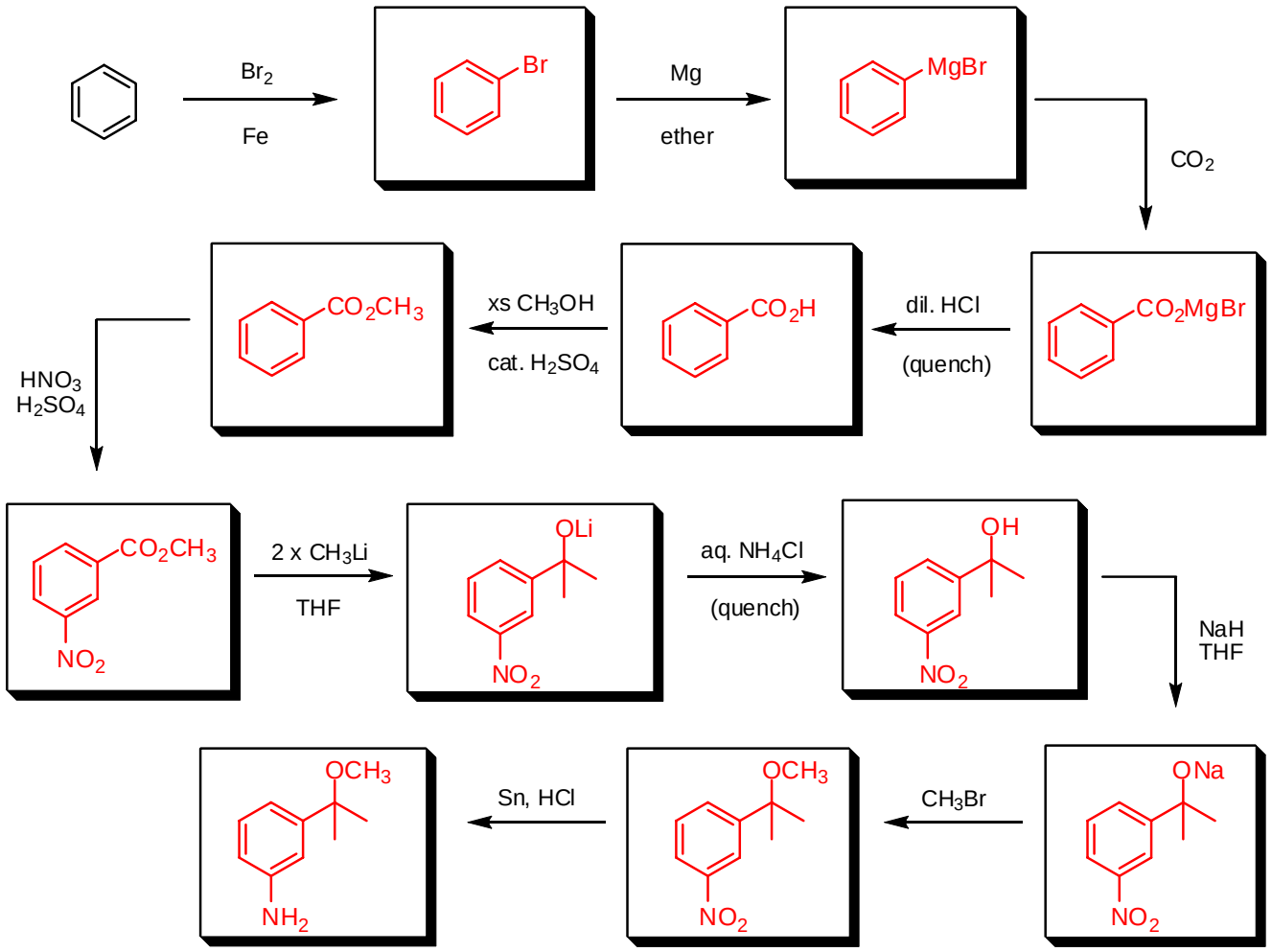
Synthesis

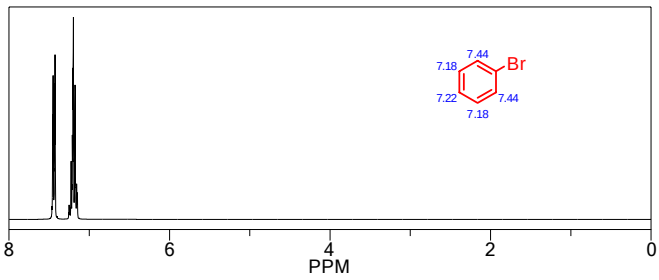


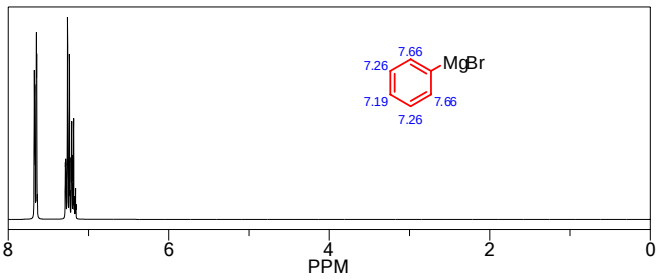
2. Give the major organic product(s) from each step of the following synthetic sequence.

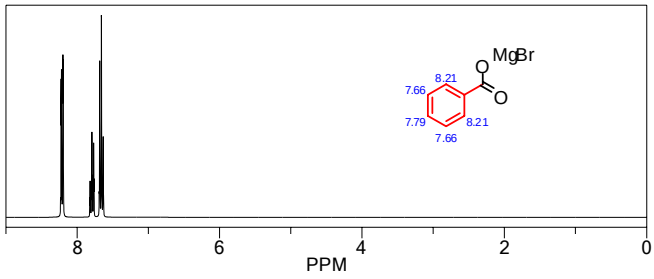


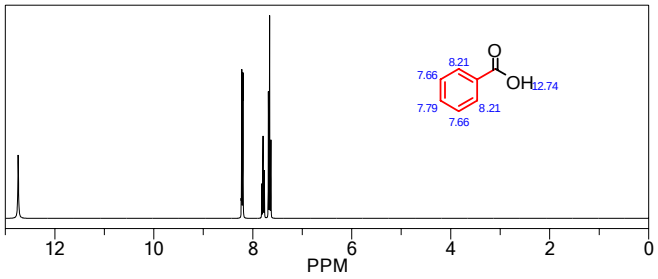
3. In the boxes provided, give the products from each step in the following "road-map" scheme. Predict the ^{1}H NMR spectra of each of the organic products from each step.

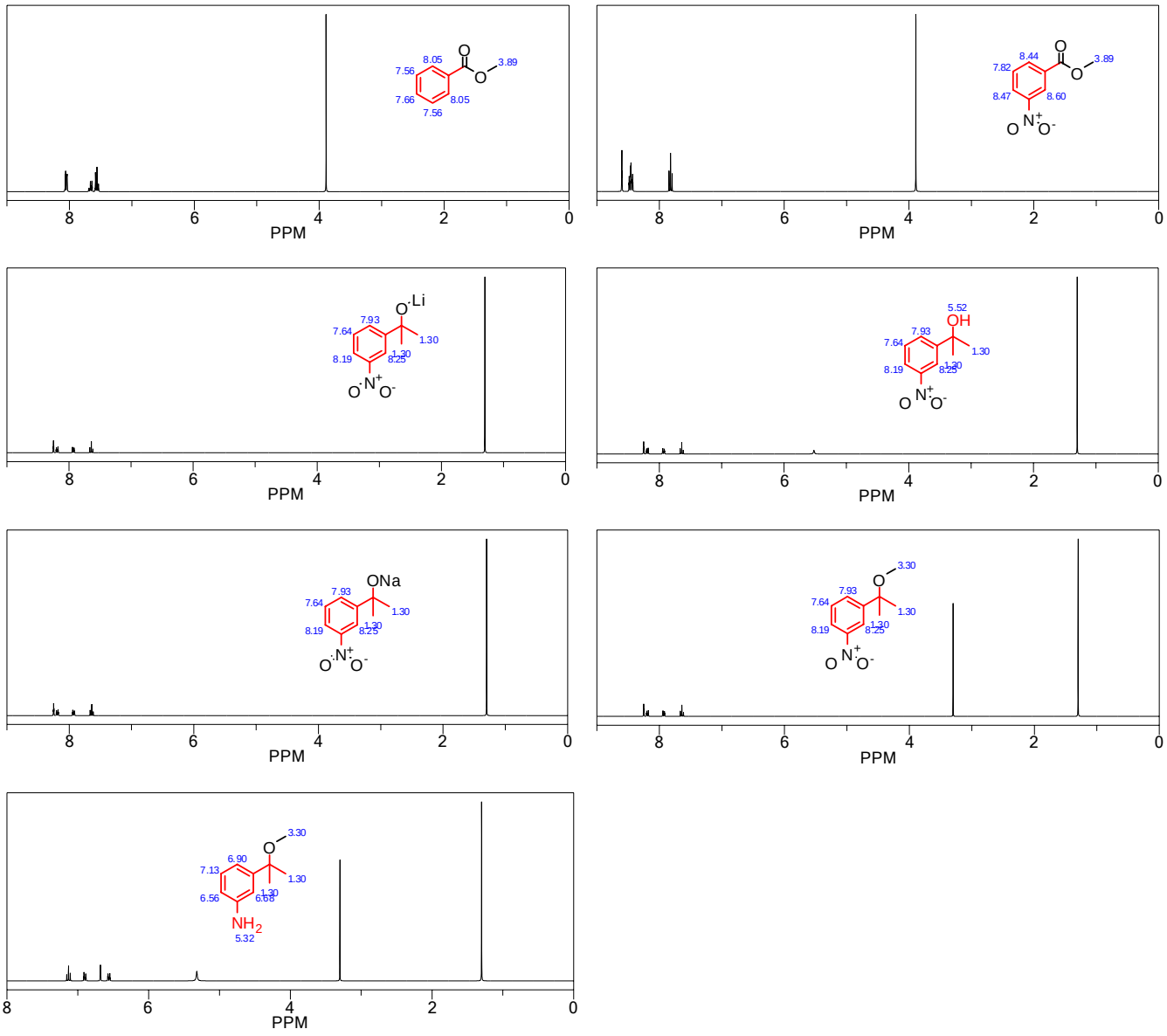






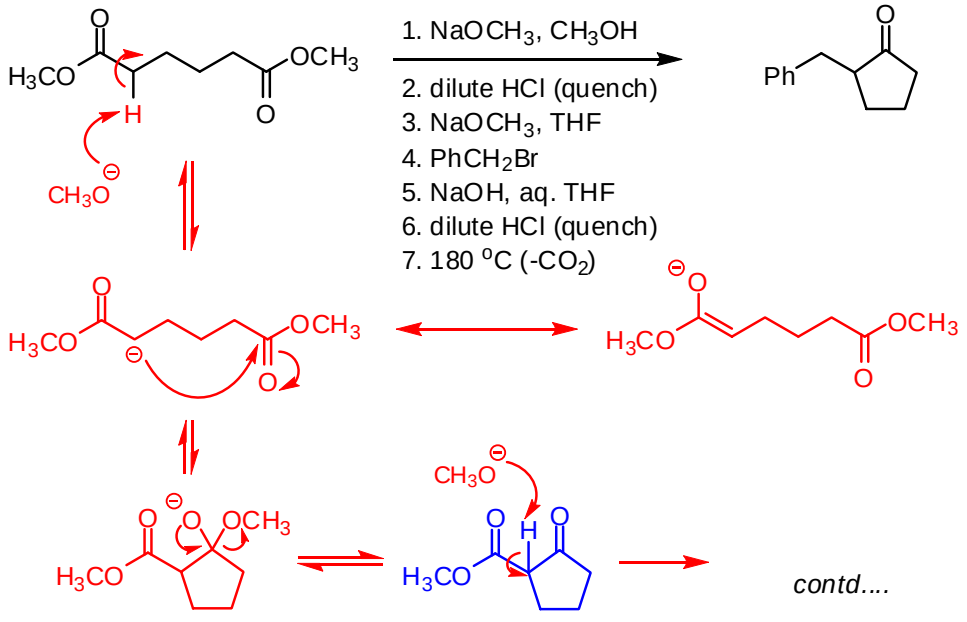


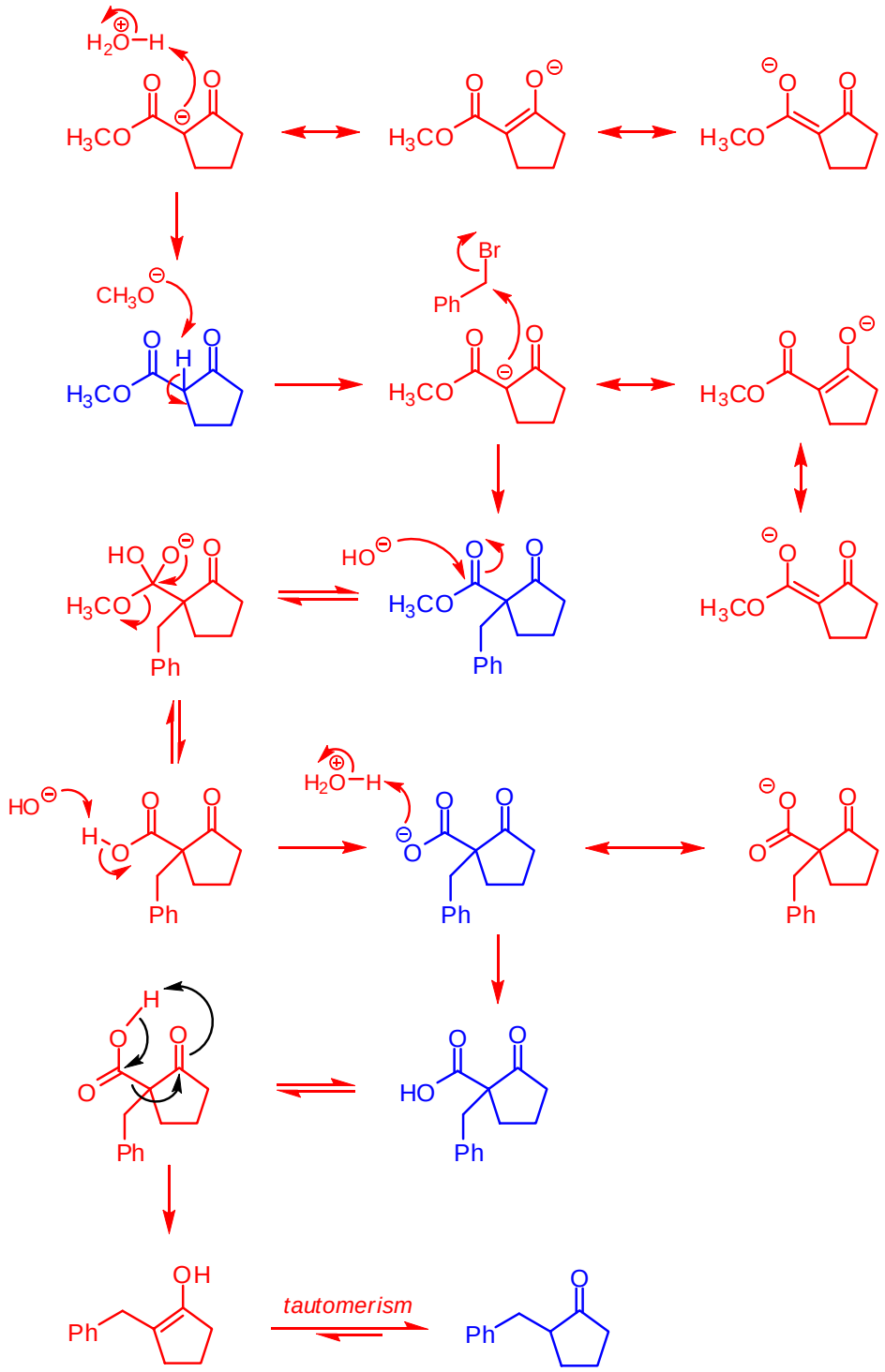




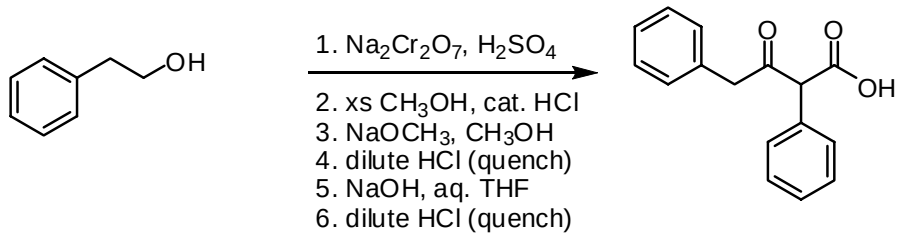
4. Give complete mechanisms, including any important resonance structures for intermediates where applicable, that explain the bond-making and bond-breaking events in the following conversions.

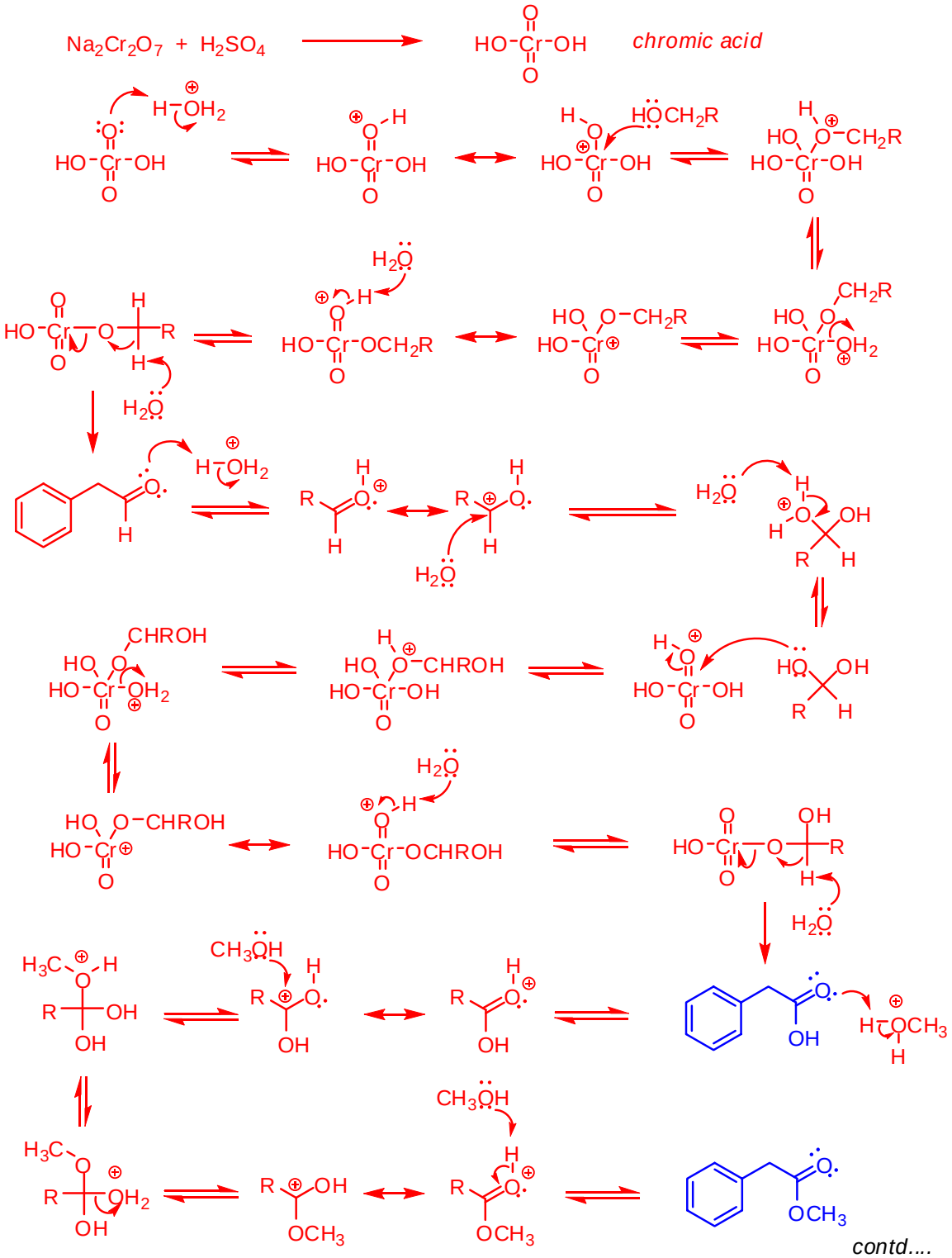
a.

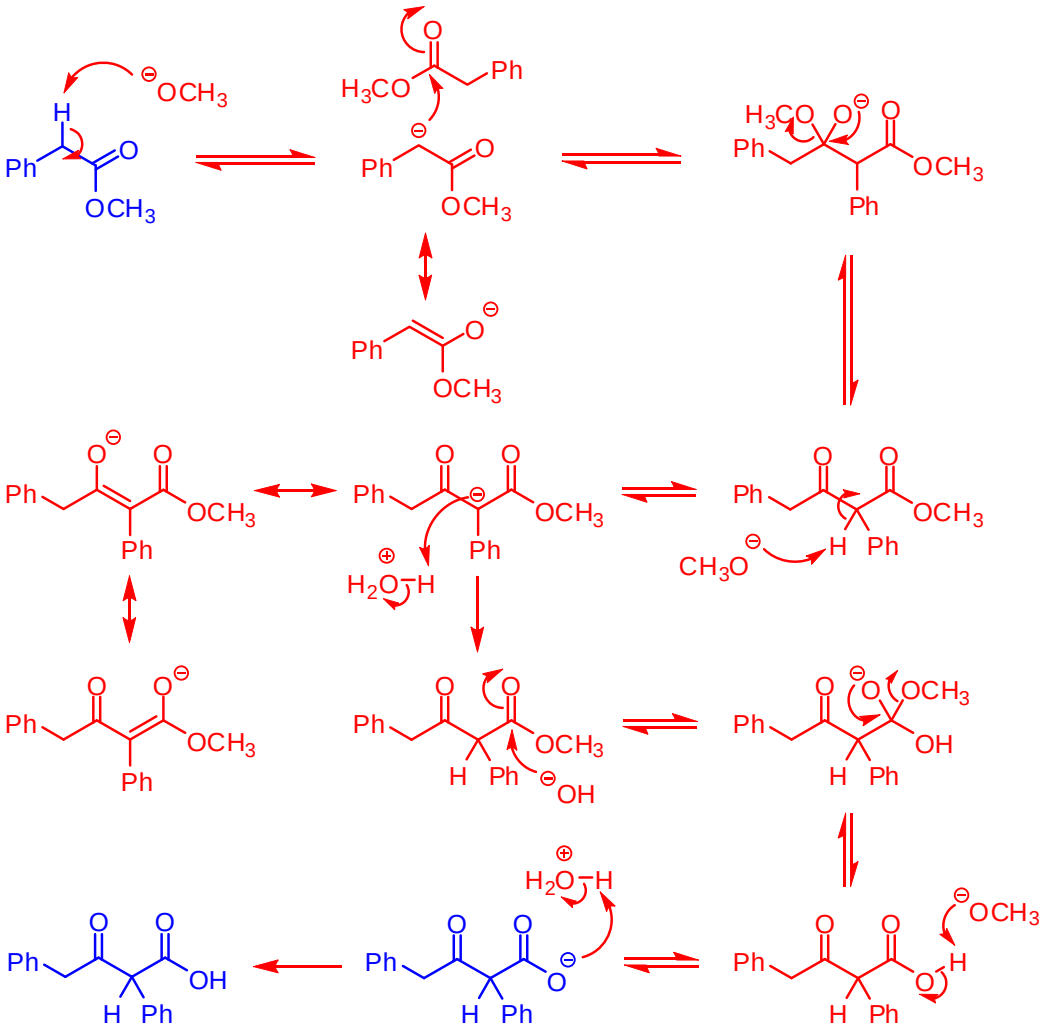



tautomerism

b.


1. $Na_2Cr_2O_7$, H_2SO_4
2. xs CH_3OH, cat. HCl
3. $NaOCH_3$, CH_3OH
4. dilute HCl (quench)
5. NaOH, aq. THF
6. dilute HCl (quench)


chromic acid
contd....


OCH3
H
Ph
O
OCH3
H3CO
Ph
O
Ph
OCH3
H3CO
O
O
Ph
OCH3
Ph
O
Ph
OCH3
O
O
Ph
OCH3
Ph
O
O
Ph
OCH3
Ph
H2O
H
CH3O
H
Ph
O
O
Ph
OCH3
Ph
O
O
Ph
OCH3
H
Ph
OH
O
O
OCH3
Ph
OH
H
Ph
H2O
H
O
O
Ph
OH
H
Ph
O
O
Ph
O
H
H
Ph
O
O
OCH3
Ph
O
H
Ph