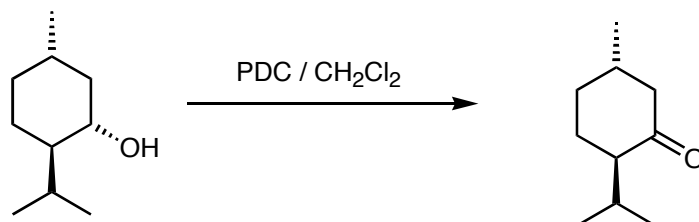


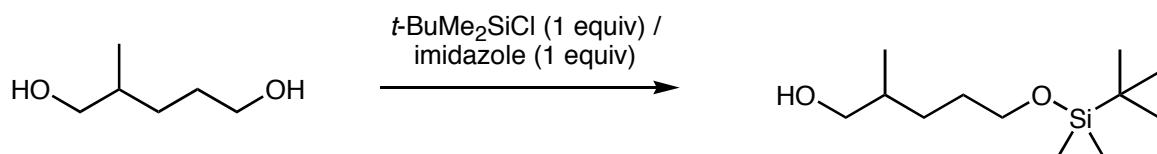
ANSWER GUIDE
APRIL/MAY 2006 EXAMINATIONS
CHEMISTRY 249H

1.

(a)

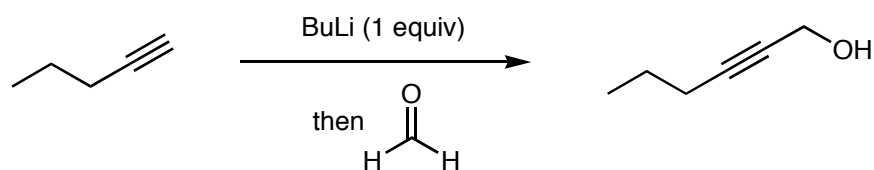


(b)

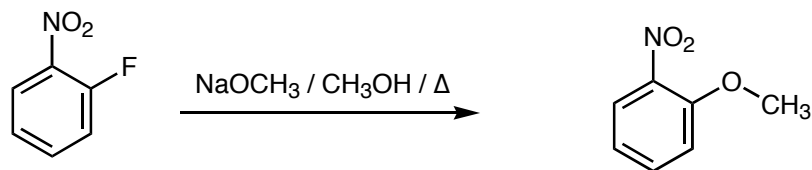


TBDMS protection of the less
sterically hindered alcohol

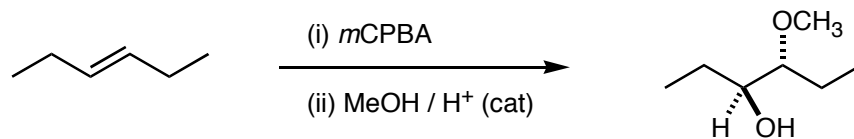
(c)



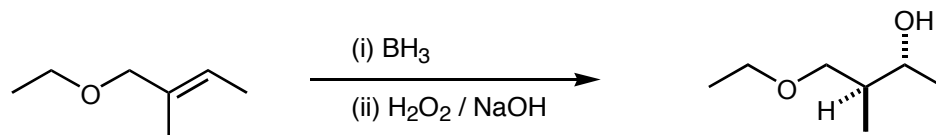
(d)



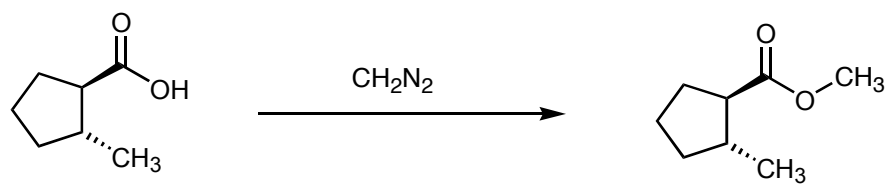
(e)



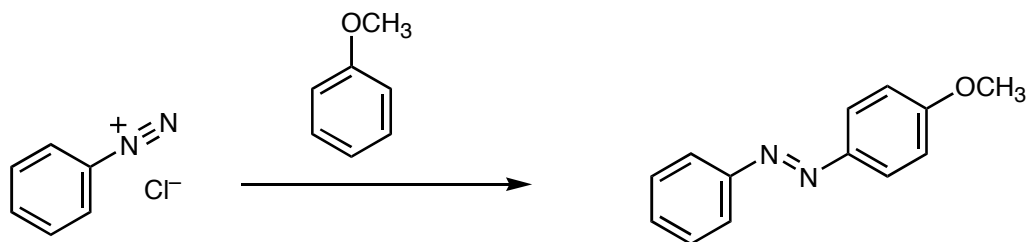
(f)



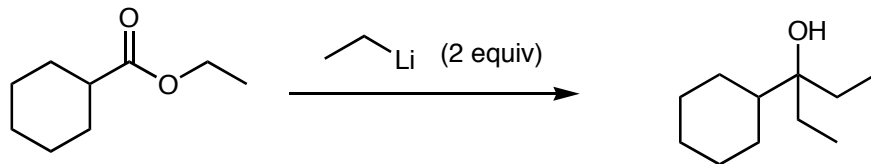
(g)



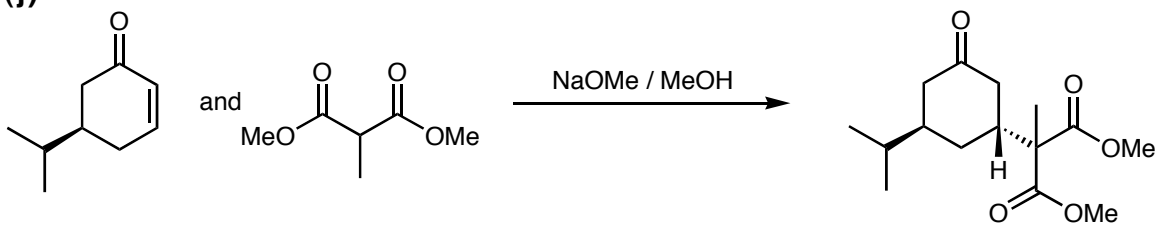
(h)



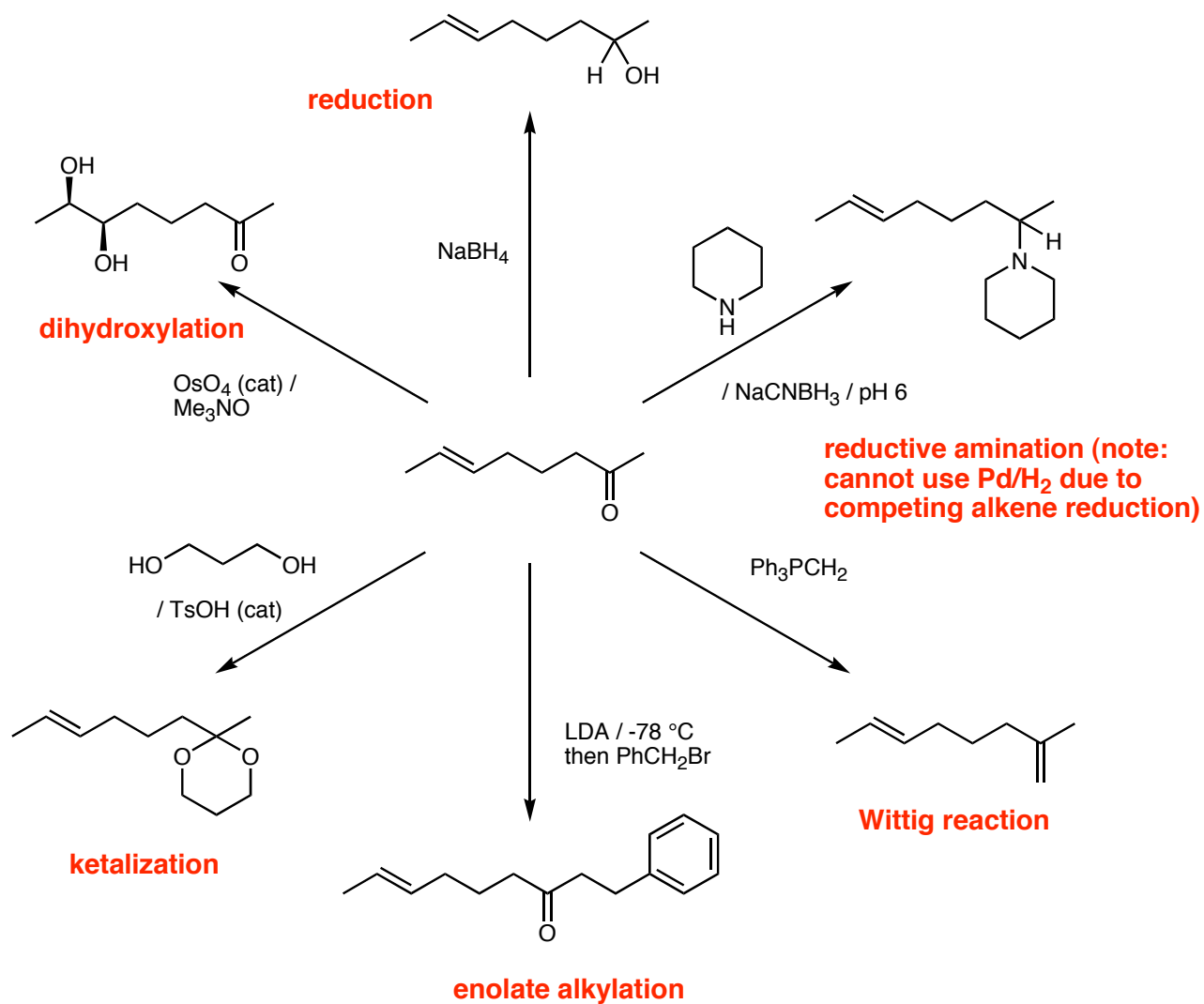
(i)



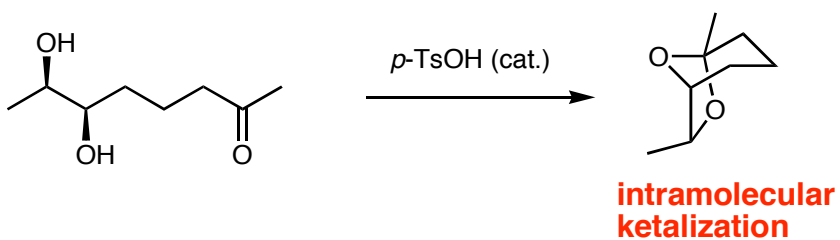
(j)



2. (a).

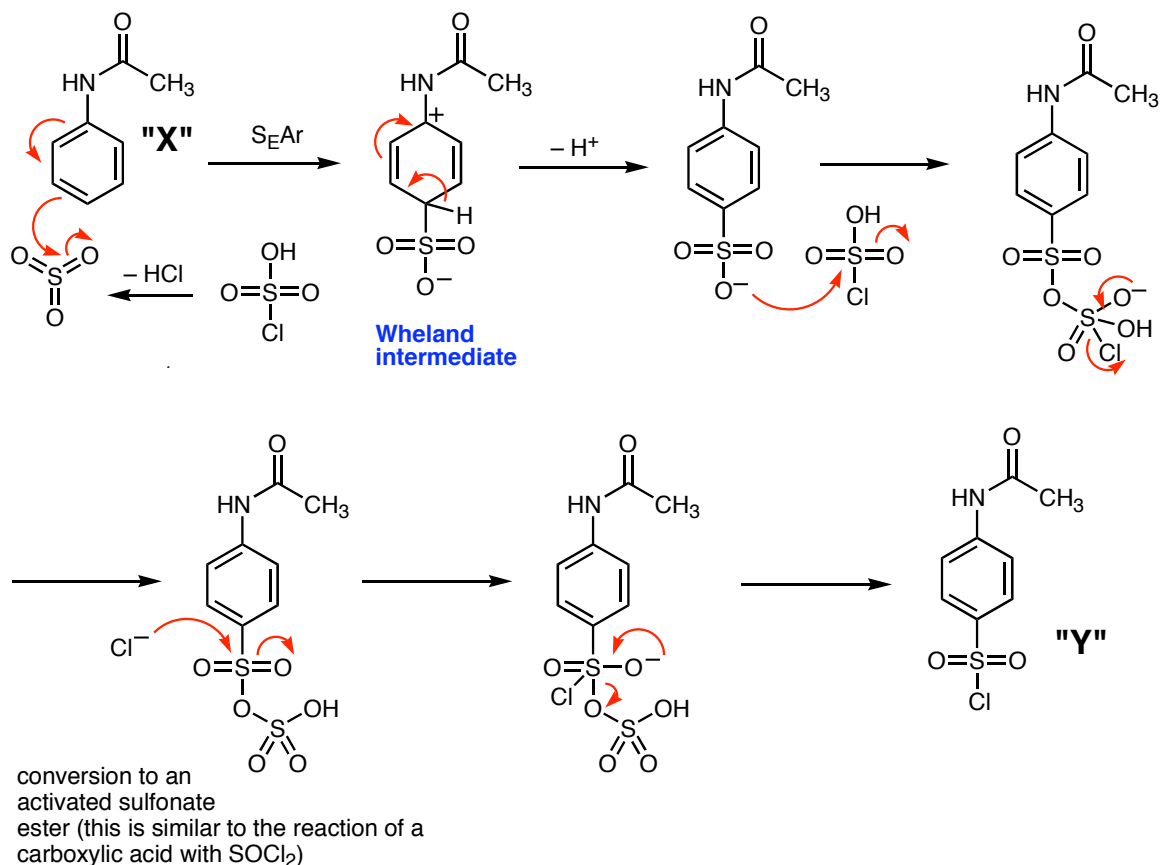


(b)



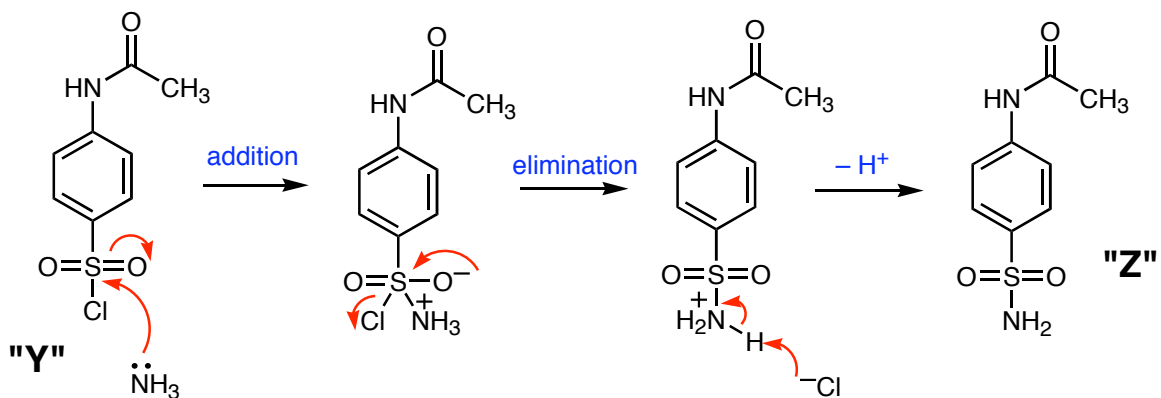
3.

(a) There are various possible mechanisms. Here electrophilic aromatic substitution is followed by activation of the sulfonic acid/sulfonate to an activated sulfonate ester which is attacked by chloride anion.

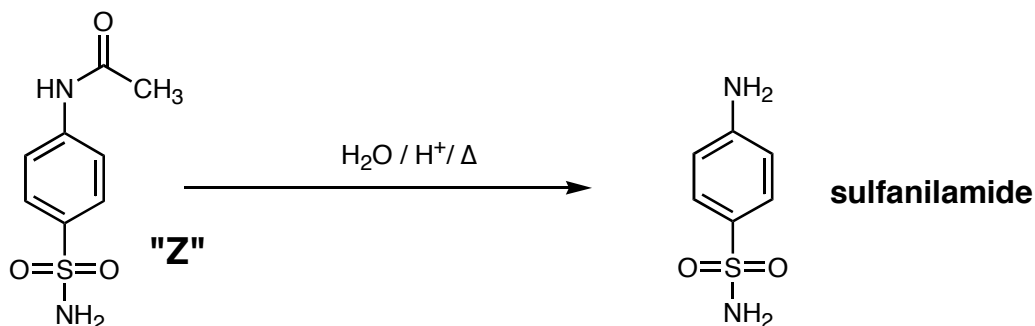


(b) The reaction of ("X" to "Y") gives the para substituted product because the NHCOMe group is electron donating an ortho/para directing group. Steric effects favour the para product over the ortho product.

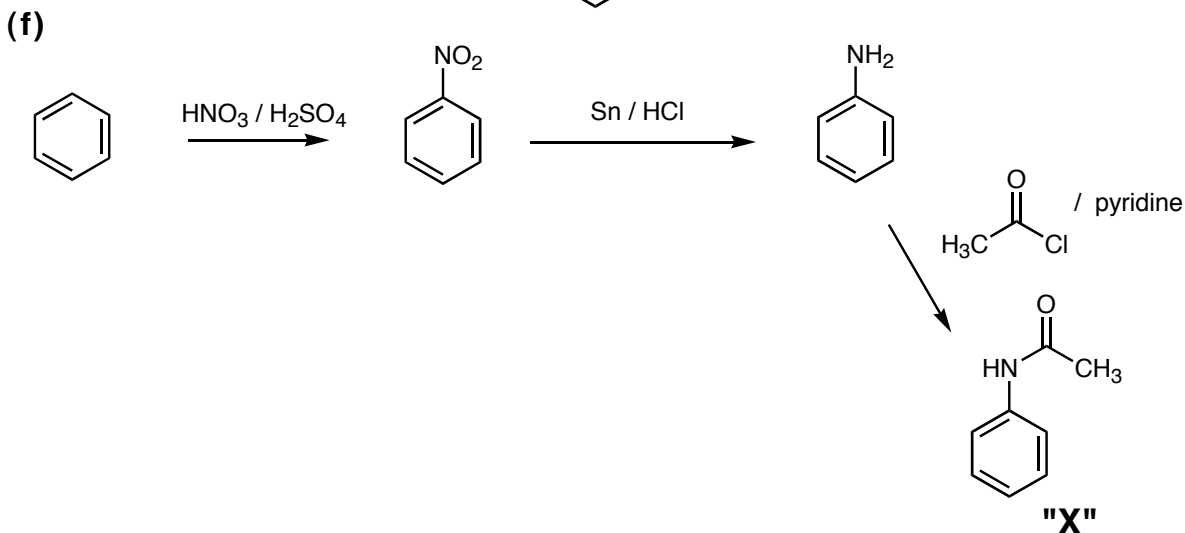
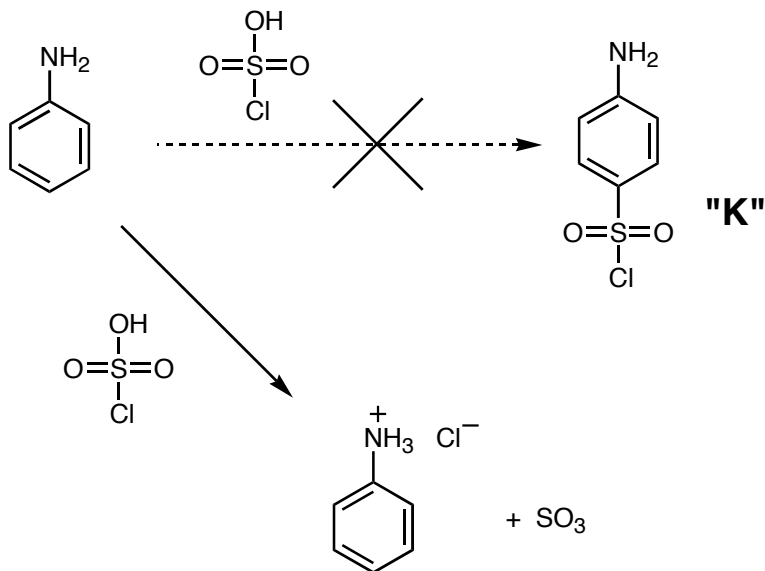
(c) This mechanism is analogous to the reaction of an amine to an acyl chloride. The initial addition step gives a pentavalent sulfur intermediate which has trigonal bipyramidal geometry.



(d) See notes for the full mechanism of amide hydrolysis to an amine under acidic conditions.

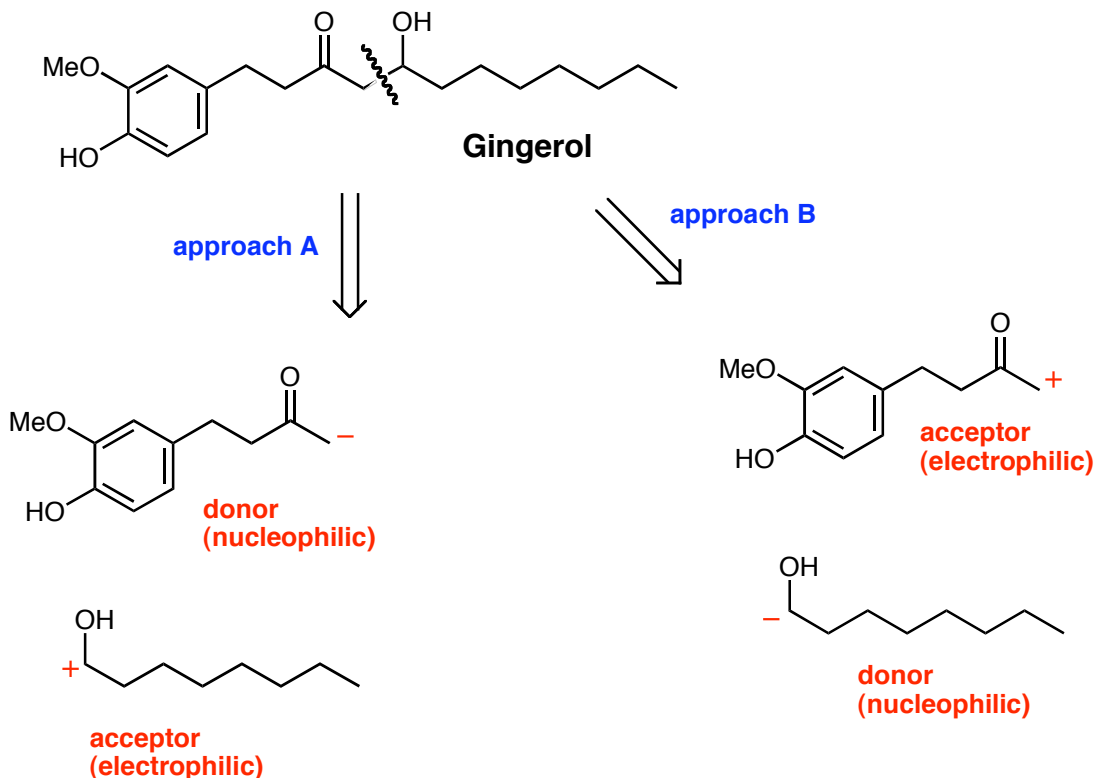


(e) A major problem here is that the aniline will remove a proton from HOSO_2Cl and be converted into the unreactive salt. This is why the aniline nitrogen must first be converted into an amide, with the acetyl group acting as a protecting group for the otherwise basic nitrogen.

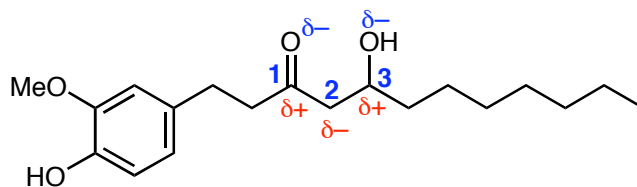


4.

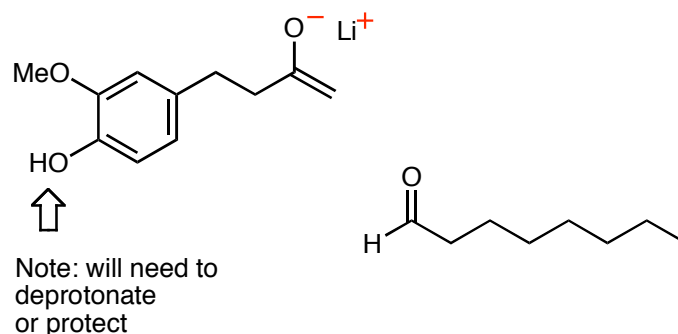
(a) Draw BOTH pairs of synthons that relate to this disconnection.



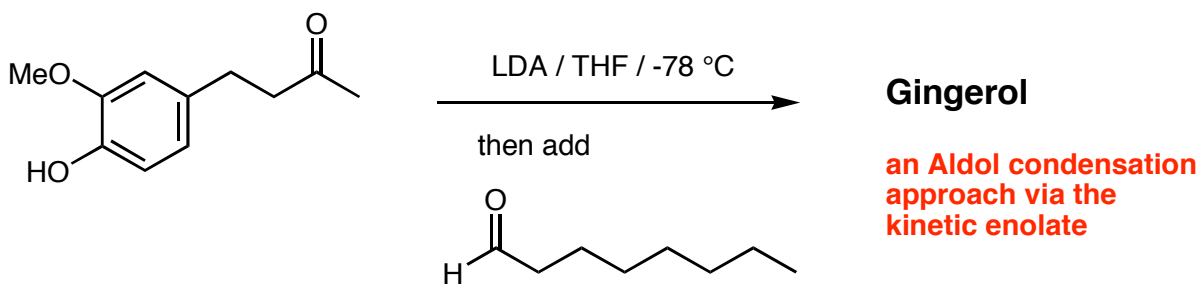
(b) The more natural disconnection is **Approach A**. This can be determined by consideration of the position of the electronegative oxygen atoms – they have a 1,3-functional relationship. They polarize the neighbouring carbons (positions 1 and 3) to be $\delta+$. Ideally in a chain one can use alternating positive and negative charges to show the “natural” disconnections, thus placing the carbon number 2 to be the nucleophile (i.e., $\delta-$) and carbon number 3 to be the electrophile (i.e., $\delta+$).



The species that correspond to these synthons are the enolate anions (derived from deprotonation of the ketone) and the aldehyde:



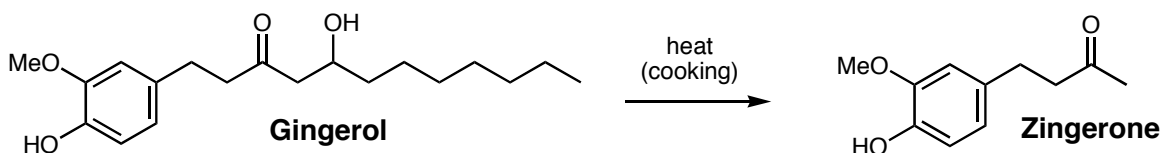
At first sight this approach looks reasonable:



this should be Ok, except for the presence of the acidic phenol OH group, which is more acidic than the α -protons of the ketone. Using 1 equiv of LDA would only deprotonate the phenol OH, and no gingerol would be obtained! It should however be possible to use 2 equivalents of the LDA to deprotonate both groups. Alternatively, you can protect the OH first, as for example as silyl ether. Thus, the synthesis would be, (i) protection of the phenol OH as a TBDMS ether (using TBDMSCl / imidazole), (ii) the Aldol condensation (as above), and then (iii) deprotection to the product (i.e., with TBAF / THF / water).

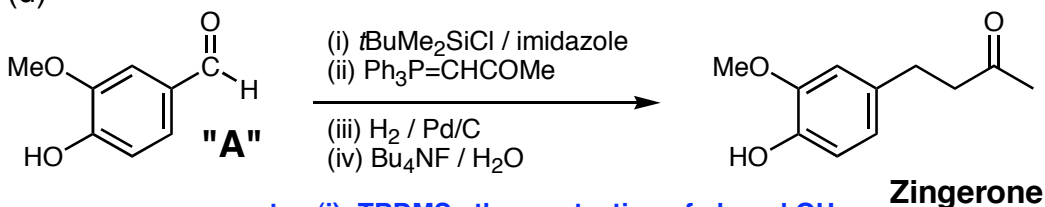
(Note: a disconnection between C-1 and C-2 would lead again to two approaches, but in this case the better approach is the Umpolung approach – i.e., lithiated dithiane as the C-1 nucleophile and an epoxide as the C-2 electrophile).

(c) Cooking fresh ginger transforms *gingerol* into *zingerone*.

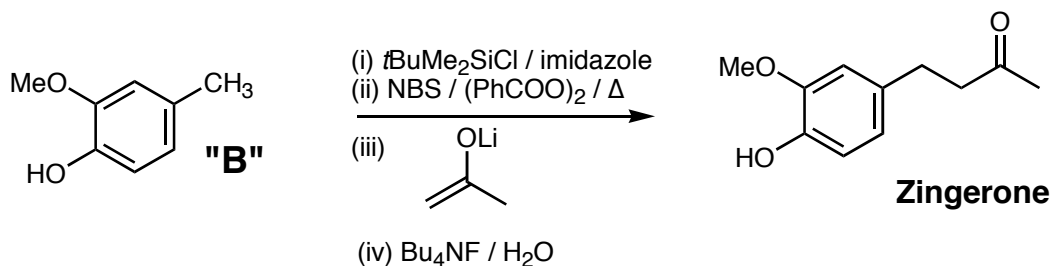


This reaction proceeds via the retro-Aldol reaction. i.e., the reverse of the Aldol condensation. The retro Aldol is favored at very high temperature (the reaction is an equilibrium) since entropy effects start to dominate enthalpy (i.e., bond energies).

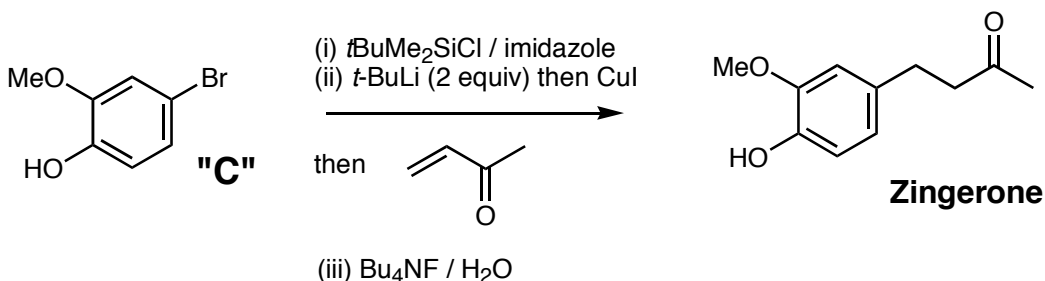
(d)



step (i): TBDMS ether protection of phenol OH
 step (ii): Wittig reaction
 step (iii): alkene reduction
 step (iv): deprotection of TBDMS group

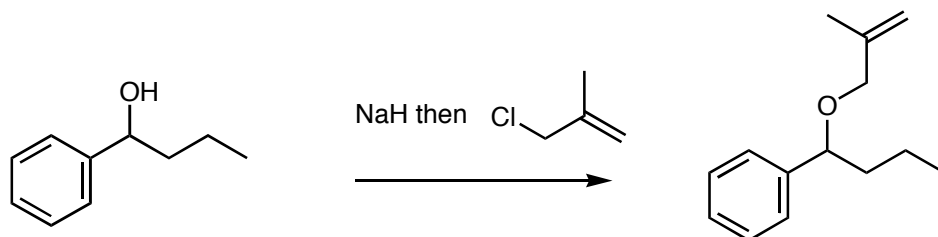
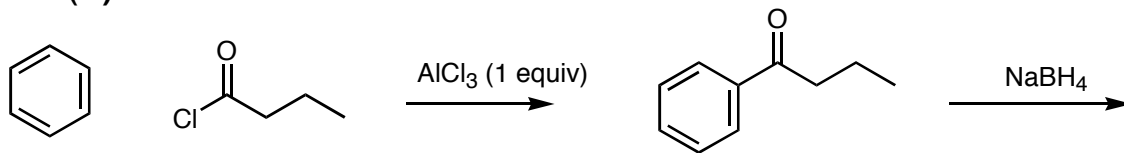


step (i): TBDMS ether protection of phenol OH
 step (ii): benzylic bromination (free-radical conditions)
 step (iii): enolate alkylation
 step (iv): deprotection of TBDMS group

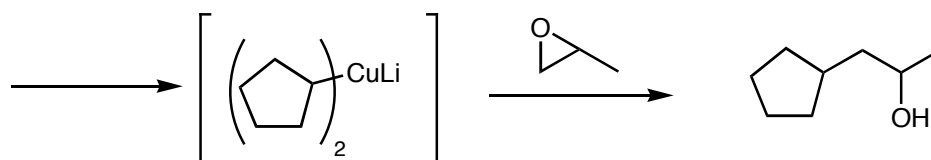
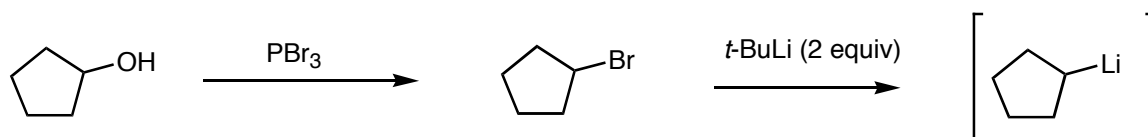
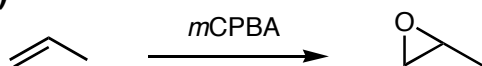


step (i): TBDMS ether protection of phenol OH
 step (ii): Lithium-halogen exchange (to make ArLi), then cuprate formation, and then conjugate addition
 step (iii): deprotection of TBDMS group

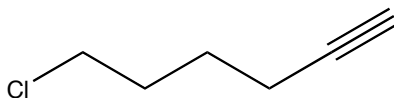
5. (a)



(b)



6. (a) COMPOUND A:



(b) COMPOUND B:

