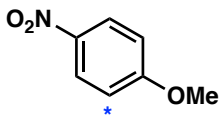
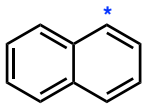
Problem Set 5 Answer Key
Chem 2211

1. a. Identify the most likely site of electrophilic aromatic substitution (EAS) on the following molecules. Explain your reasoning.

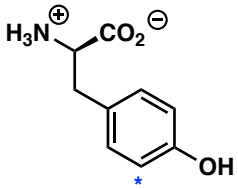


nitro = m director
OMe = o,p director

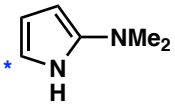


naphthalene

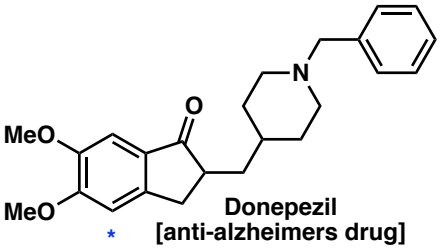
resultant cation (after attack) has more resonance



tyrosine
OH = o,p director



resultant carbocation is stabilized by lone pairson both nitrogens

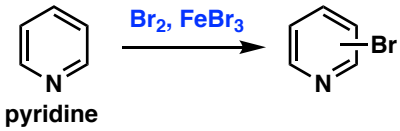


Donepezil
[anti-alzheimers drug]

OMe = o,p director
ketone = m director
CH_2 = o,p director

b. Pyridine is typically very unreactive in electrophilic aromatic substitution reactions because is is quite electron poor. However, adding substitutents to the ring can make it more reactive. For scenario 1, give and rationalize the major site of bromination on pyridine. Then, in scenario 2, annotate a group for **X** that would make the arene more reactive (i.e. more e^- rich), and then provide reagents, a mechanism, and the structure of the major product of the depicted transformation.

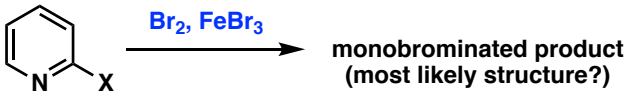
scenario 1:



pyridine

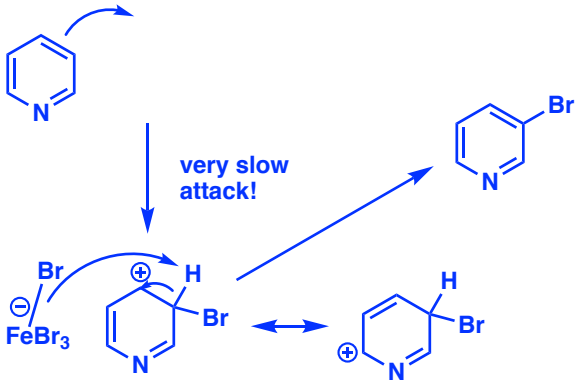
very slow reaction!
pyridine not e^- rich!

scenario 2:

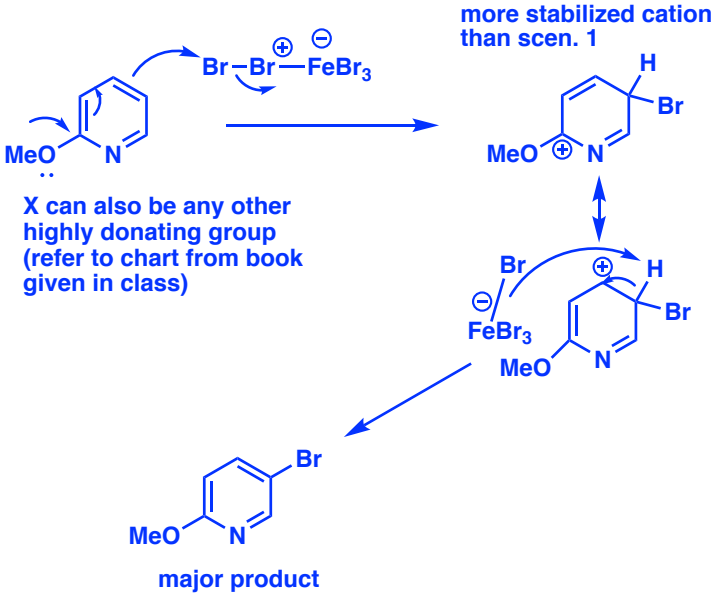


substituted pyridine
how can X make this e^- rich?

monobrominated product
(most likely structure?)



bromination at other positions produces resonance structures with positive charge on N (very unfavorable!)

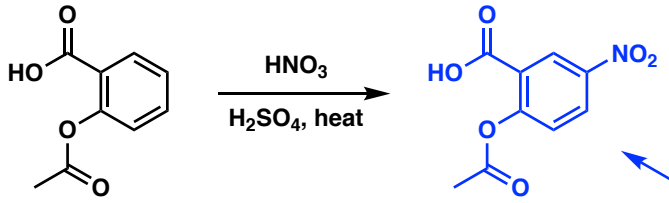


X can also be any other highly donating group (refer to chart from book given in class)

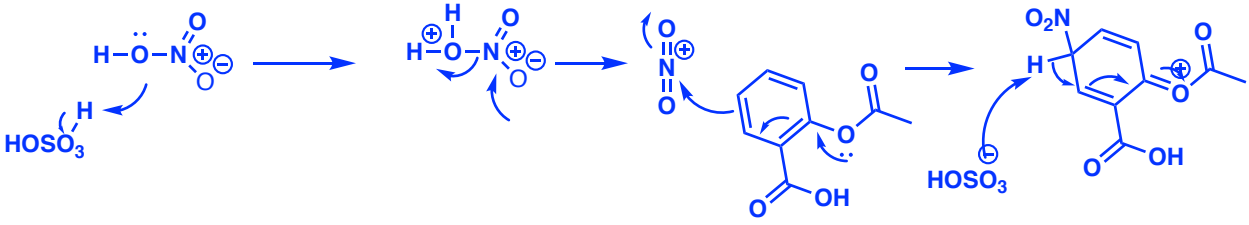
more stabilized cation than scen. 1

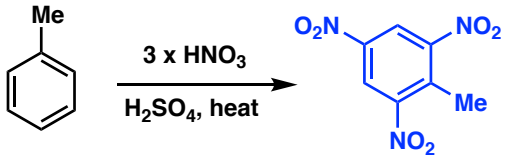
major product

2. a. The introduction of nitrogen to an aromatic system is important in the diversification of aromatic compounds. Provide the most likely product in the following transformations and draw a mechanism for each.

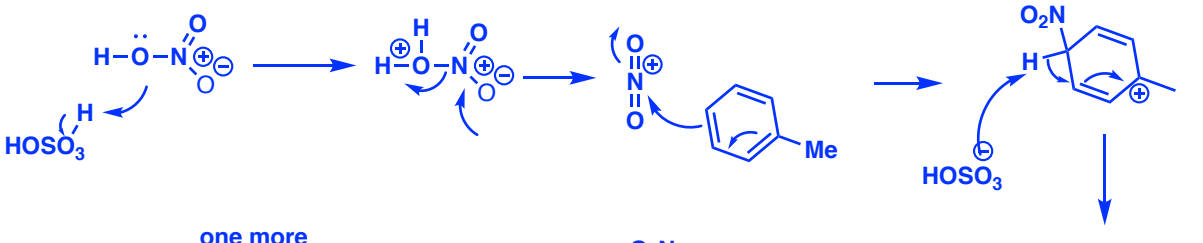


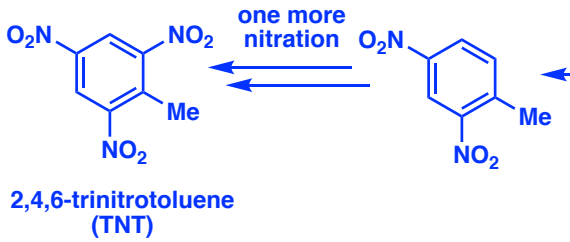
acetylsalicylic acid
(aspirin)





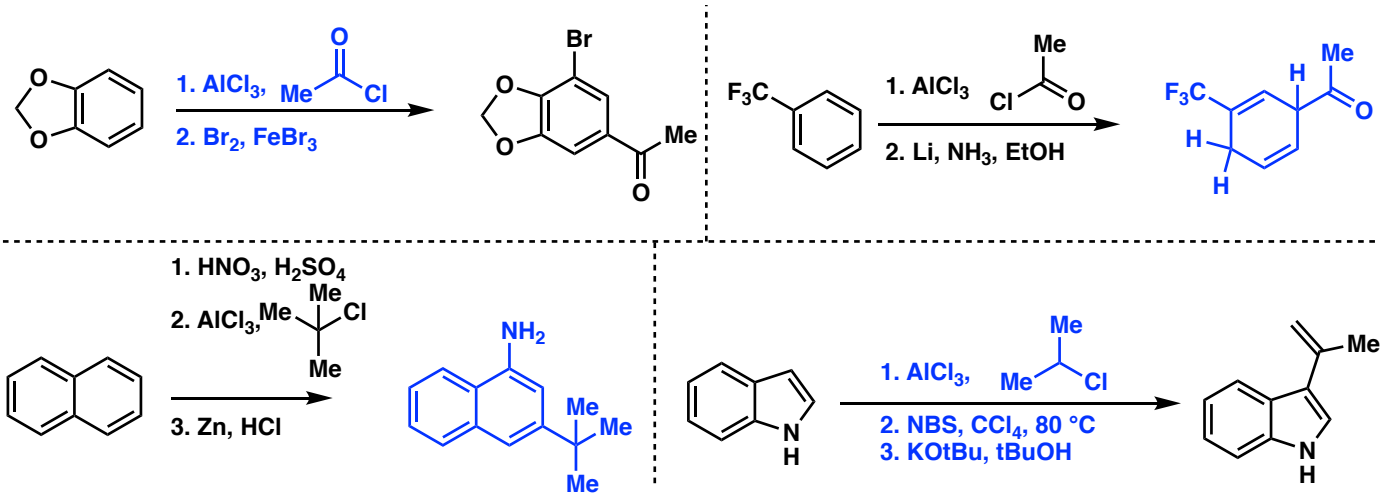
2,4,6-trinitrotoluene
(TNT)



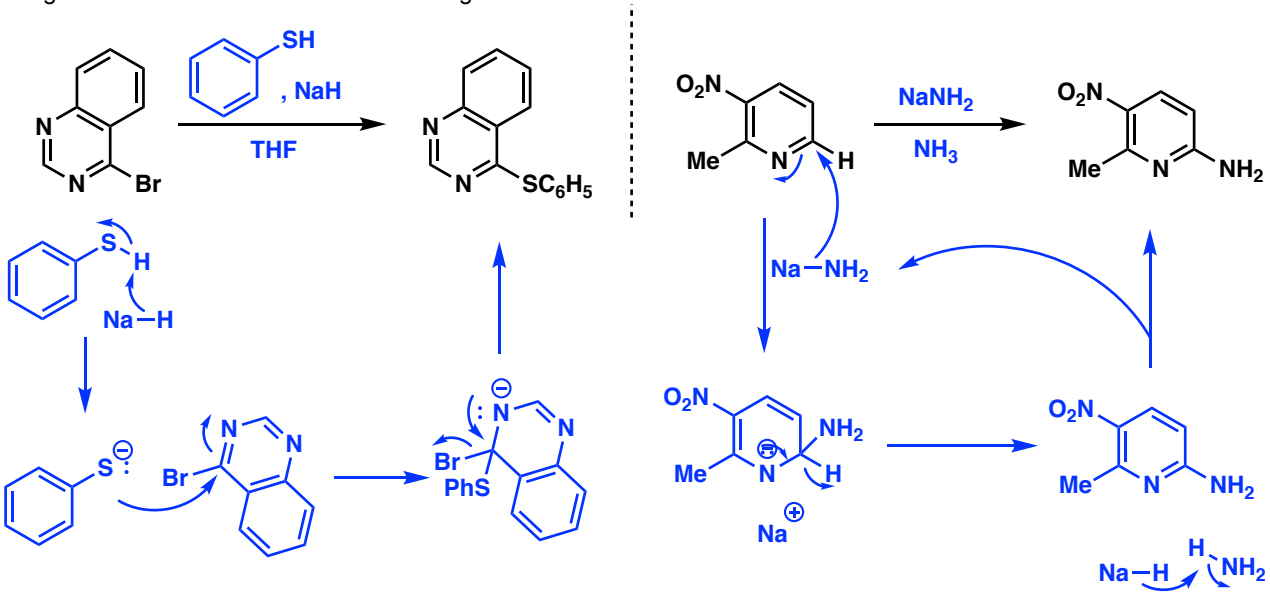


2,4,6-trinitrotoluene
(TNT)

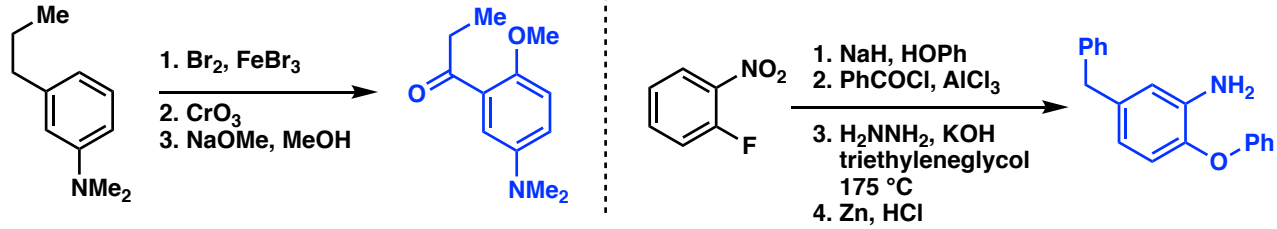
b. Complete the following with either the appropriate reagents or the most likely product. Although not necessary, it is highly recommended to draw out the mechanism for each elementary transformation for practice.



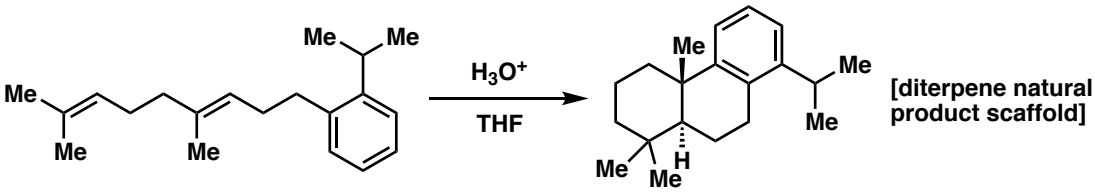
3. a. Nucleophilic aromatic substitution (NAS) is an important way that chemists strategically synthesize molecules. Provide reagents and a mechanism for the following transformations.



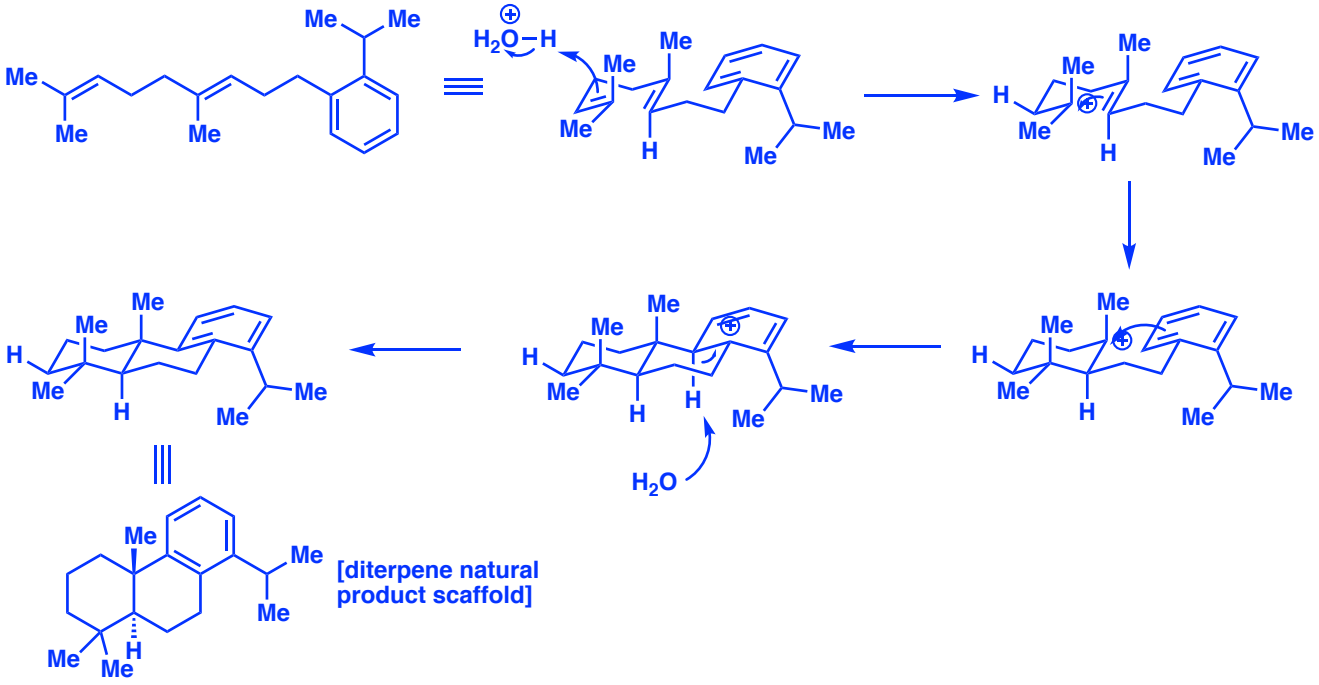
b. Somtimes utilizing NAS and EAS together can provide diverse products. Provide the most likely product in the following synthetic sequences:



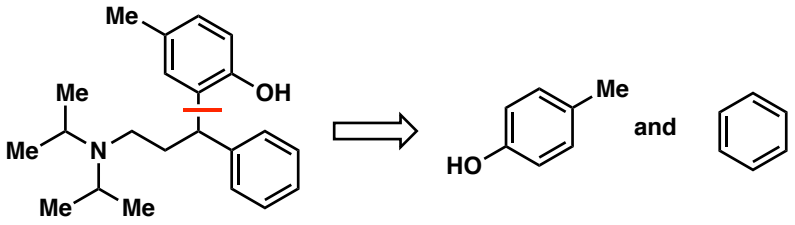
4. Oftentimes, organisms will synthesize natural products for the purpose of cell signaling, cellular structure, and/or defense against parasites/pathogens. In this vein, EAS plays an important role in many chemists' approaches to their synthesis. Using your intuition about arene and alkene reactivity, provide a mechanism for the following transformation. Also, provide a 3D structural justification for the stereochemical outcome.



(Hint: number the carbons in the starting material and product to help you!)



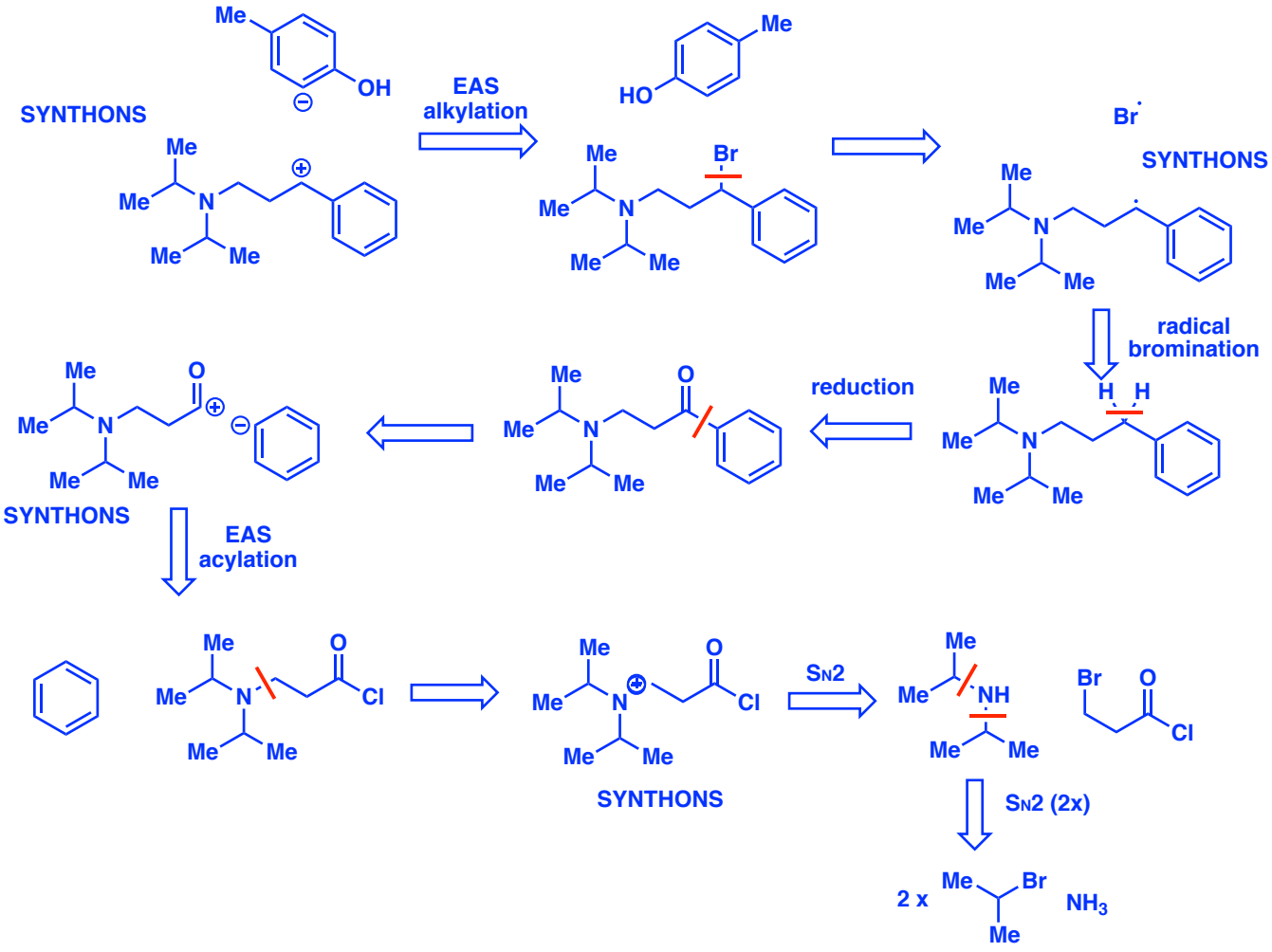
5. Provide a retrosynthetic analysis including synthons, transforms, and synthetic equivalents for the following two target molecules from the given starting materials. Then, provide a forward synthesis based off of your retrosynthesis.

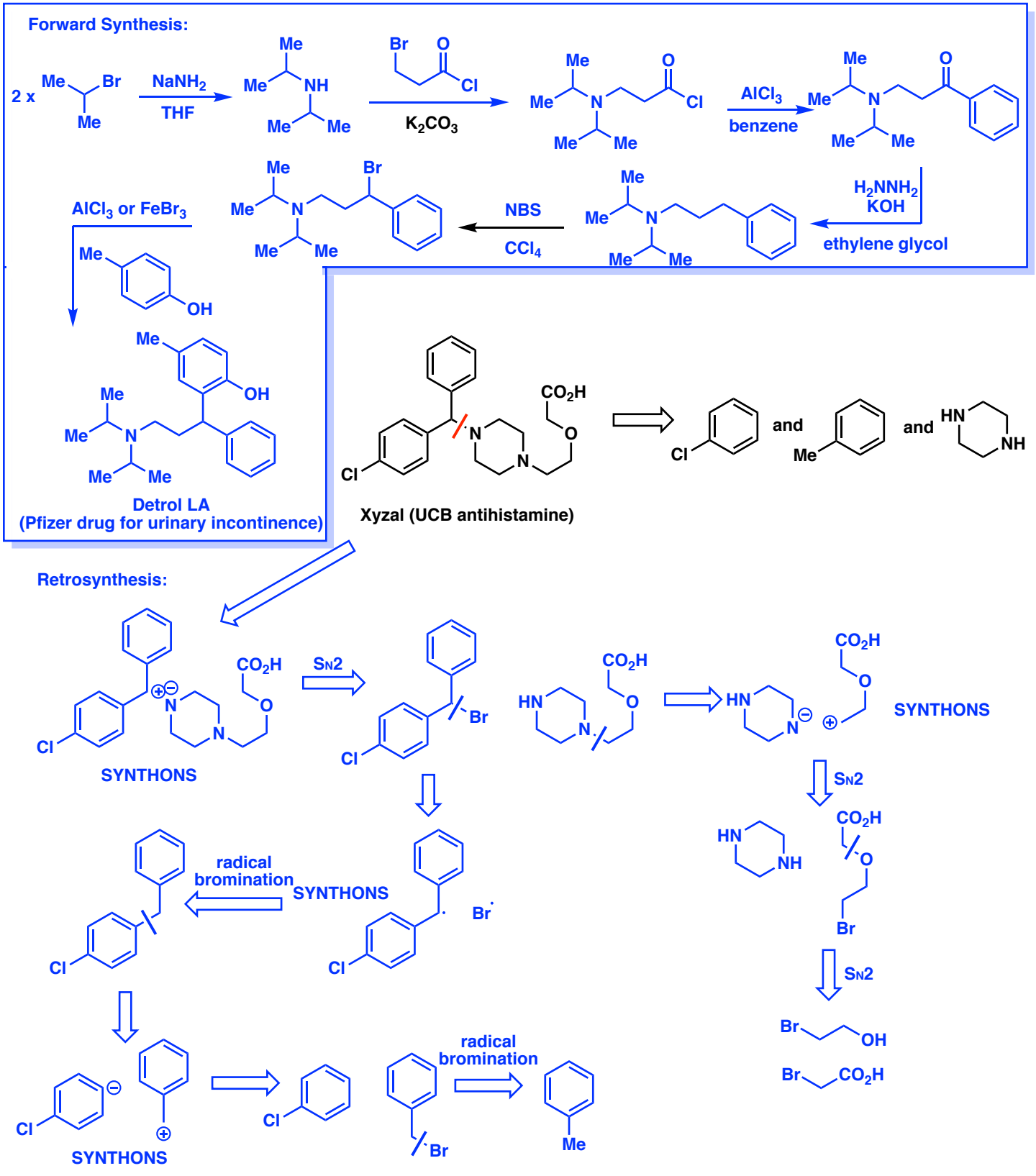


Detrol LA
(Pfizer drug for urinary incontinence)

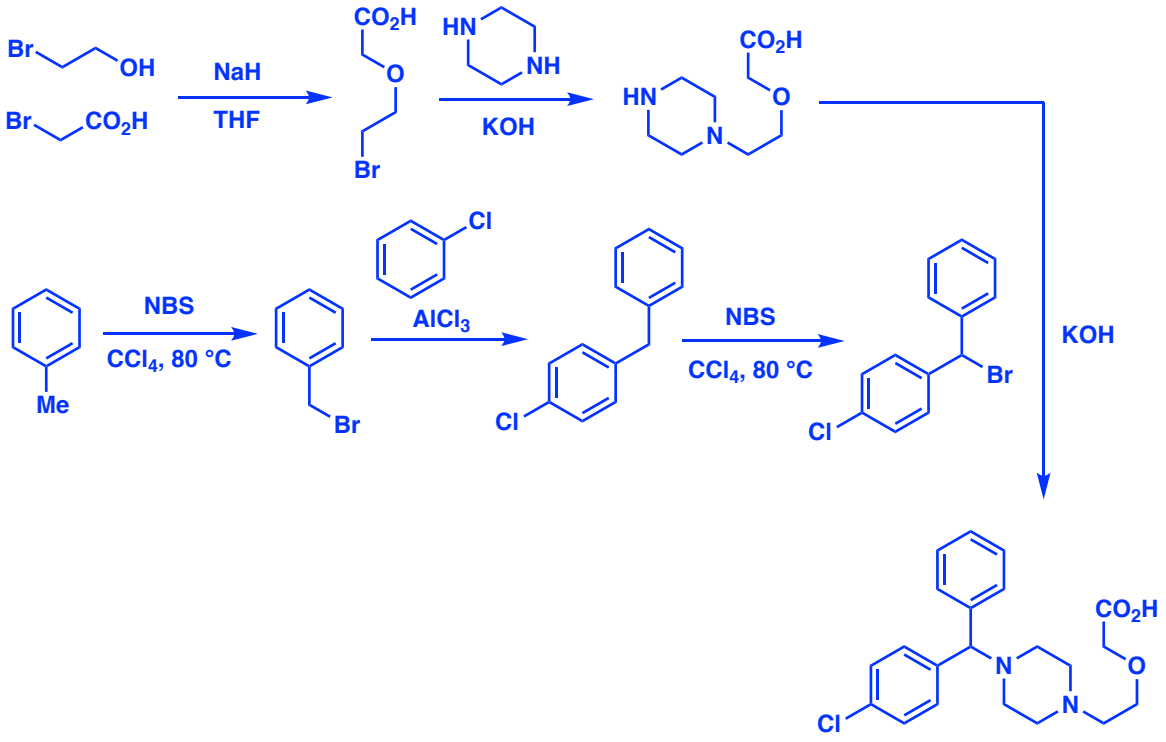
Note: your synthesis should include the given starting materials and any other molecules of 3 carbons or fewer.

Retrosynthesis:




Forward Synthesis:
2 x
NaNH2
THF
K2CO3
AlCl3
benzene
H2NNH2
KOH
ethylene glycol
NBS
CCl4
AlCl3 or FeBr3
Detrol LA
(Pfizer drug for urinary incontinence)
Xyzal (UCB antihistamine)
and
and
Retrosynthesis:
SN2
SYNTHONS
radical
bromination
SYNTHONS
SN2
SYNTHONS
radical
bromination
SN2

Forward Synthesis:



Xyzal (UCB antihistamine)