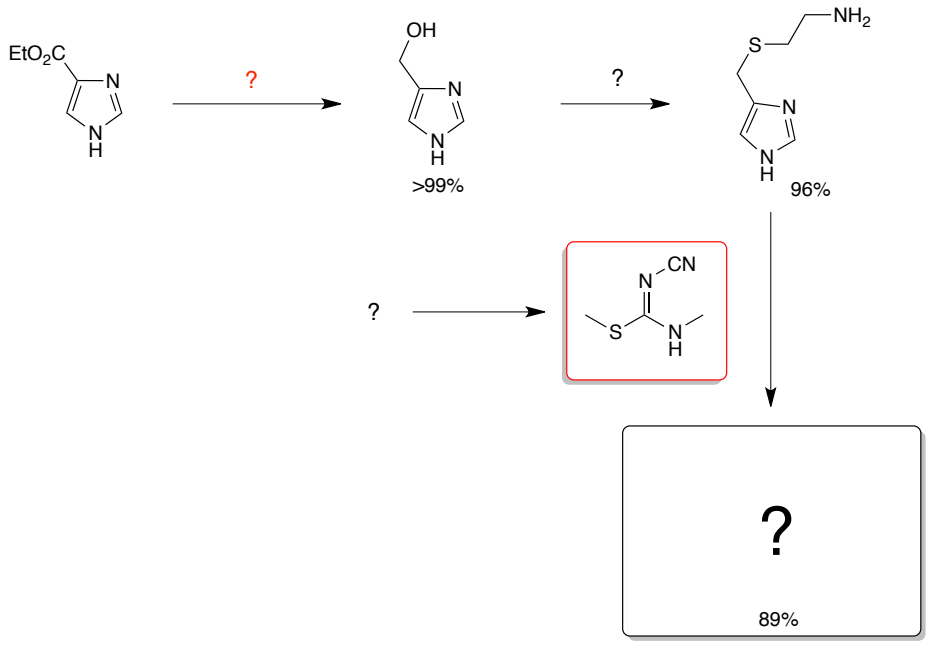
Scalable synthesis of pharmaceutically active compounds

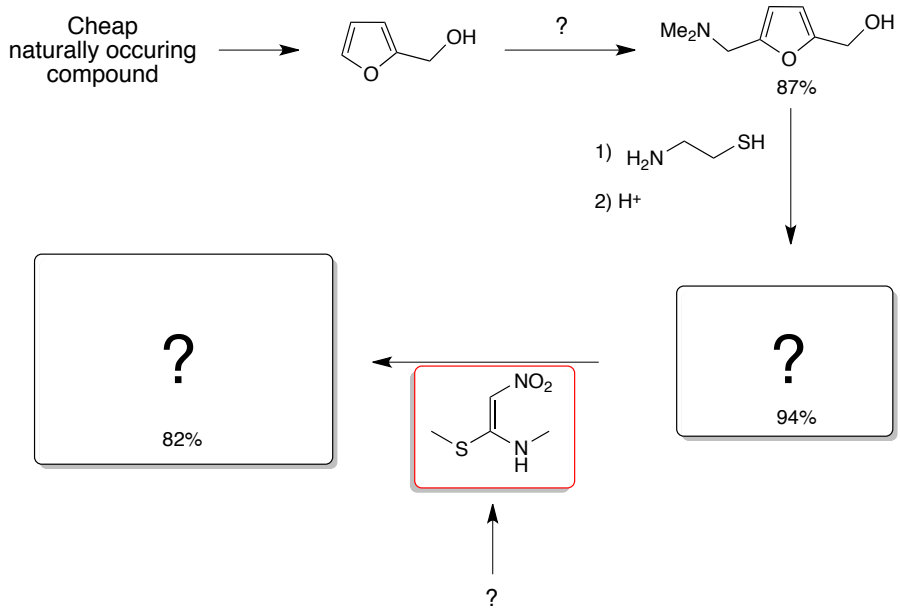
The following syntheses are used for the production scale synthesis of pharmaceutically active compounds. These compounds are produced in over 1000 tonnes each year. To achieve economically viable production of these API's each synthetic step must be high yielding, require minimum purification and use cheap, available and safe reagents.

Please identify the reagents/products of each synthetic step and discuss the scalability of each synthesis by considering the above, the use of reagents in **red** should be discussed and safer/more economical processes should be identified. **Note**: the commercial names and use of each compound have been deliberately omitted.

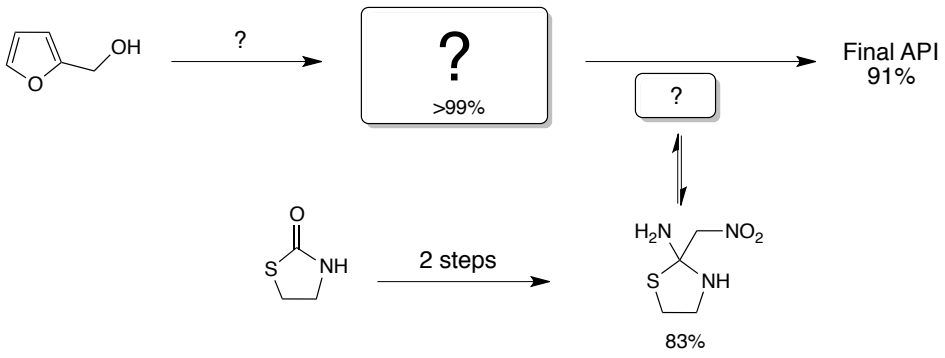
1)



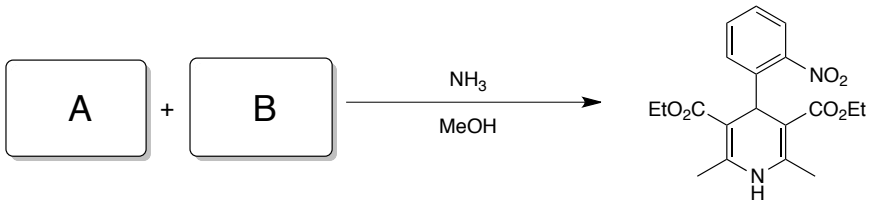
2)



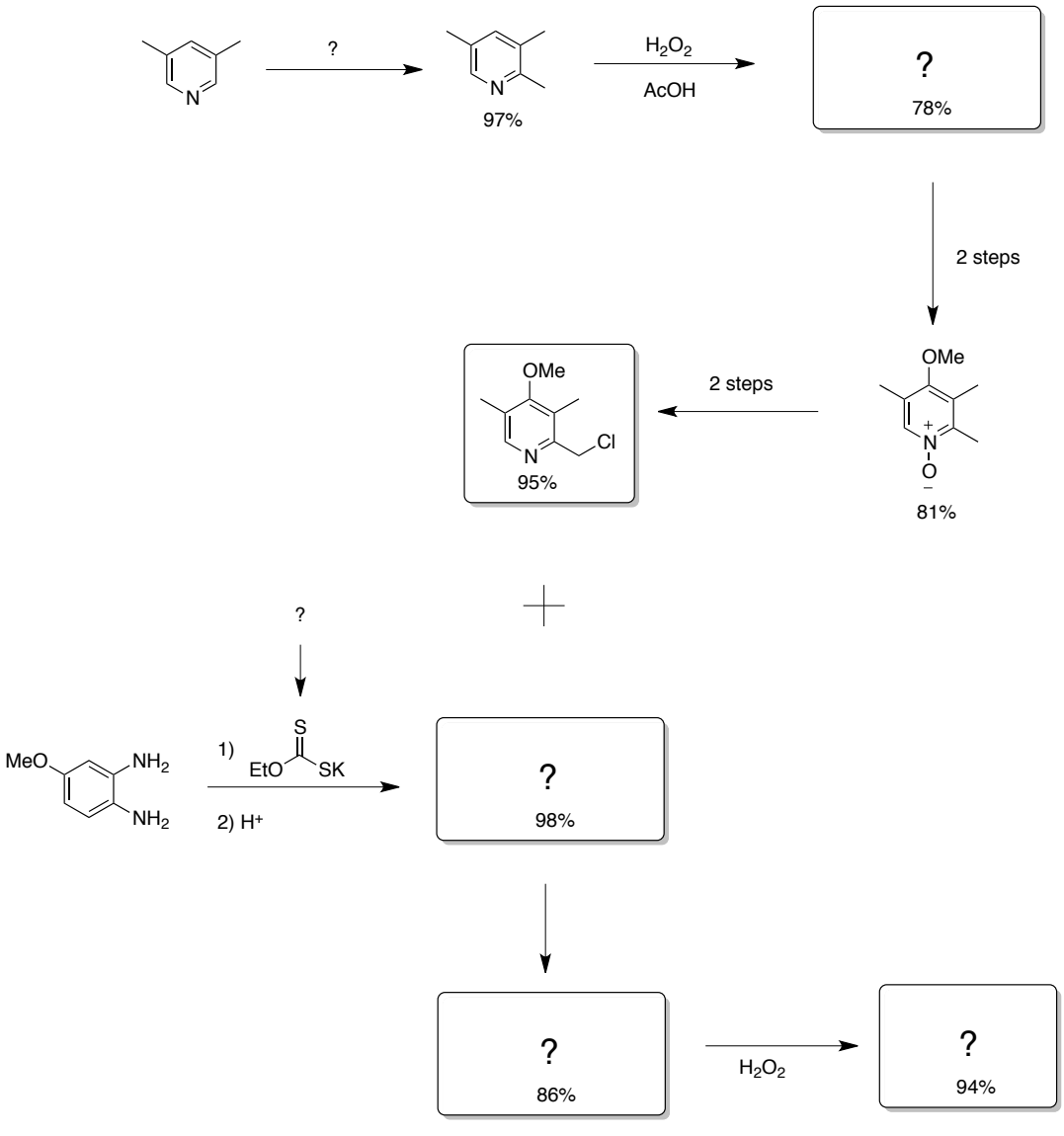
A second generation synthesis of this compounds avoids the use of the final reagent and shortens the overall synthesis, it is outlined below.



3) The first generation synthesis of the following compound was initially conducted in one pot. What starting materials would you use to do this? The second generation moved to a two step process, why do you think this was the case and what order would you carry out the two steps and why?



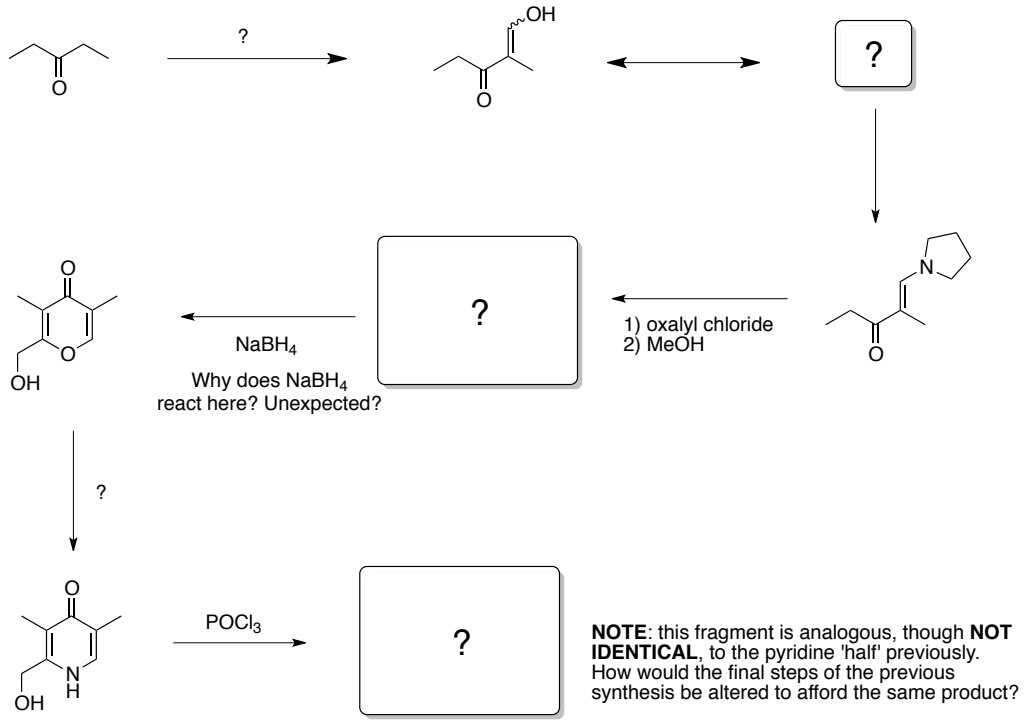
4)



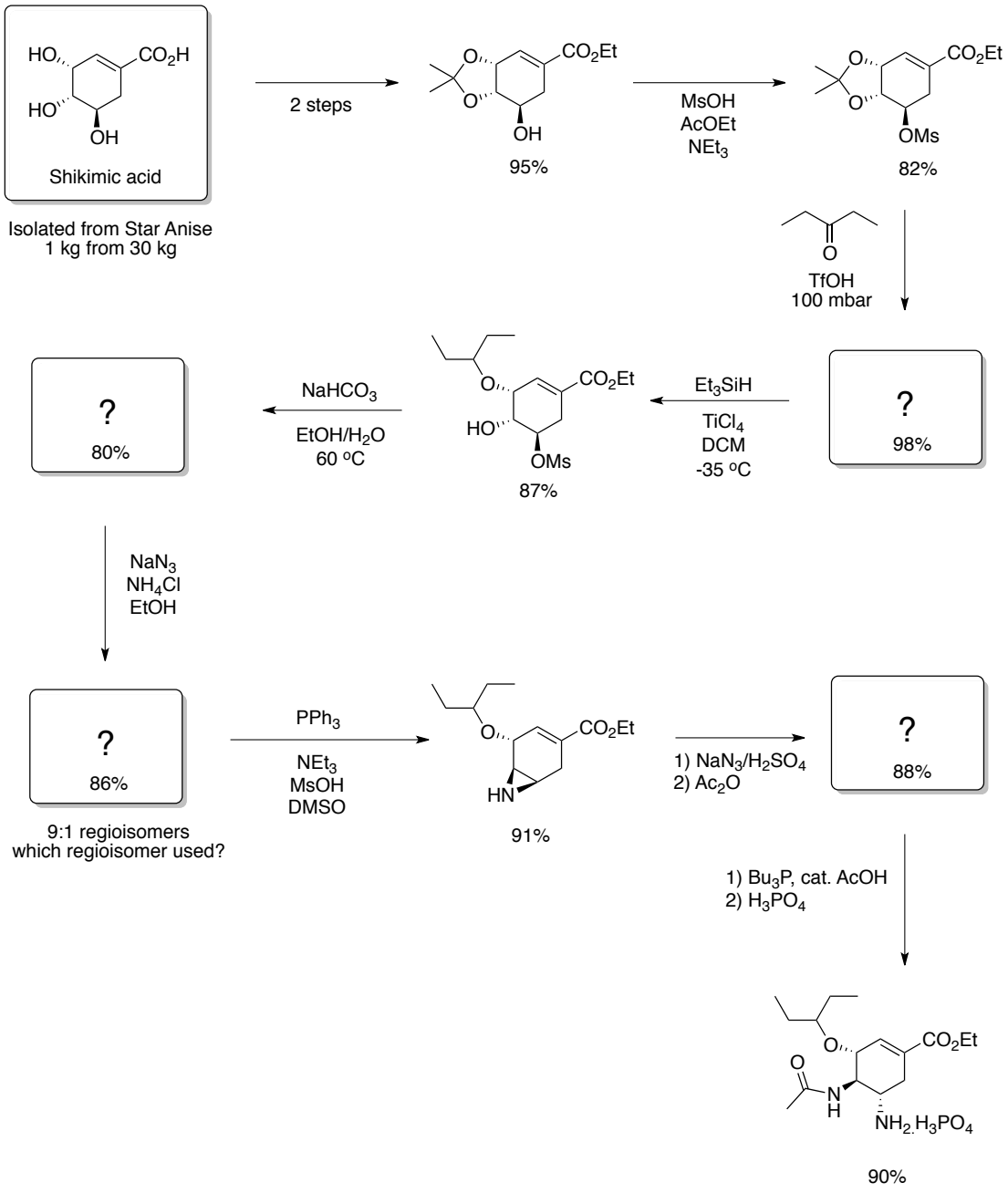
The final API is chiral, it is resolved by through the use of diastereoisomers (which can be separated *via* chromatography, or depending upon the substituents introduced through the use of chiral salts).

How would you create diastereoisomers of this final compound to allow separation of the enantiomers and then remove the functionality introduced to obtain chirally pure API?

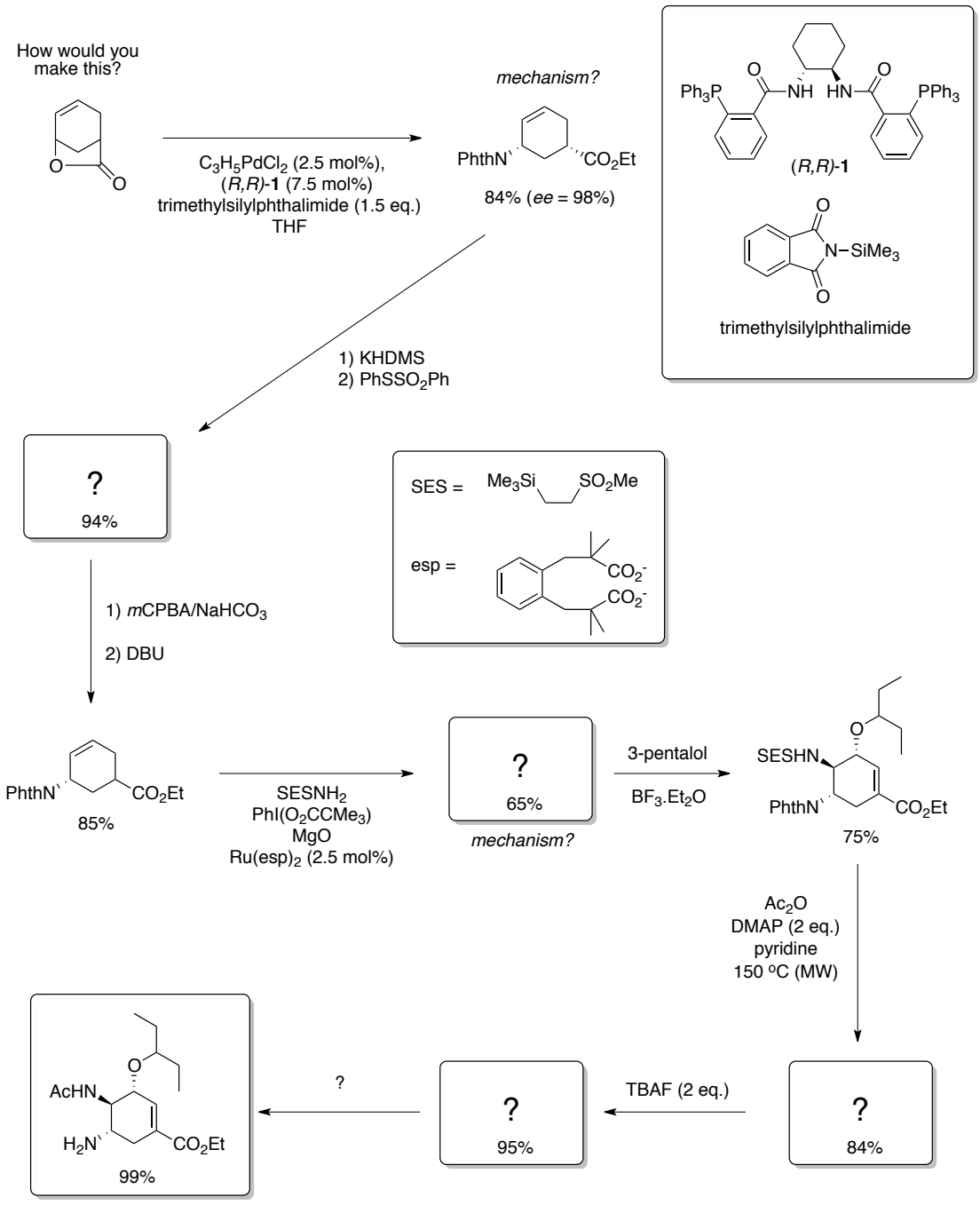
A production scale problem with the above synthesis is use of *N*-oxides in synthesis of the 'pyridine' half of the molecule, *N*-oxides are highly hygroscopic which leads to poor reproducibility of their purity and use in subsequent steps. How would you avoid the use of *N*-oxides for the synthesis of the pyridine half of the molecule? Some 'hints' for one option are outlined below.



5) The following compound has received much publicity recently due to large government stockpiles of the drug and new clinical trial data indicating that it is not as active as previously claimed…. Its initial synthesis was conducted by Gilead before IP was purchased by Hoffman-La Roche. Below is an outline of the Roche process chemistry route, which is currently used in production. Although this synthetic route is used for production are there any features of this route that you would identify as costly/hazardous/inefficient?



Although industrial synthesis of this compound uses shikimic acid as a chiral starting material, isolation of this product is costly and supply is reliant upon the star anise. Barry Trost published the first enantioselective synthesis of this compound. Do you think this synthesis is scaleable?


How would you make this?
$C_3H_5PdCl_2$ (2.5 mol%),
(*R,R*)-**1** (7.5 mol%)
trimethylsilylphthalimide (1.5 eq.)
THF
mechanism?
PhthN
CO_2Et
84% (*ee* = 98%)
Ph_3P
NH HN
PPh_3
(*R,R*)-**1**
$N-SiMe_3$
trimethylsilylphthalimide
1) KHDMS
2) $PhSSO_2Ph$
?
94%
SES = Me_3Si SO_2Me
esp =
CO_2^-
CO_2^-
1) *m*CPBA/$NaHCO_3$
2) DBU
PhthN
CO_2Et
85%
$SESNH_2$
$PhI(O_2CCMe_3)$
MgO
$Ru(esp)_2$ (2.5 mol%)
?
65%
mechanism?
3-pentalol
$BF_3.Et_2O$
SESHN
PhthN
CO_2Et
75%
Ac_2O
DMAP (2 eq.)
pyridine
150 °C (MW)
?
84%
TBAF (2 eq.)
?
95%
?
AcHN
H_2N
CO_2Et
99%