# Heterocyclic Chemistry – Midterm

## May 5, 2007


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## Department of Chemistry
## The Scripps Research Institute


**Name: _____**

**Last 4 digits of your Social Security #: _____**

**This is an "open-notes" exam designed to last 2 hours that you have 4 hours to complete**
**Definition of "open-notes"**: Only handwritten notes (from lectures and any other source), no copies allowed. Lecture summaries are the only handouts permitted during the test.

**Please present ONLY your FINAL answers on these sheets**

**Question 1 _____ (20 points)**

**Question 2 _____ (30 points)**

**Question 3 _____ (20 points)**

**Question 4 _____ (30 points)**

**Question 5 _____ (75 points)**

**Question 6 _____ (15 points)**

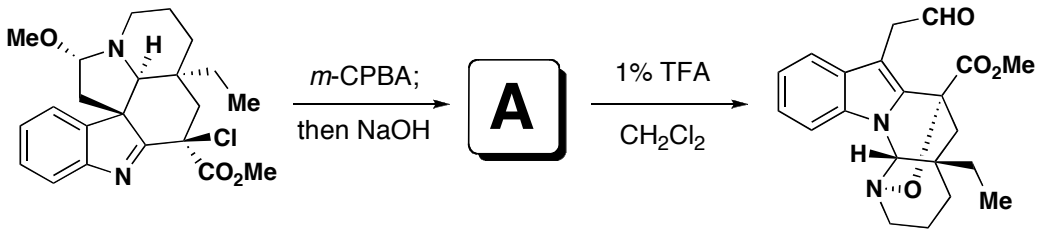
**Question 7 _____ (10 points)**

**Question 8 _____ (75 points)**

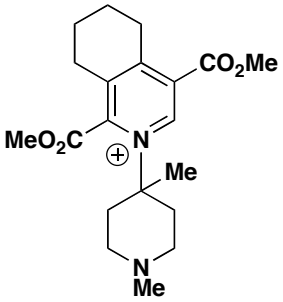
**Question 9 _____ (75 points)**

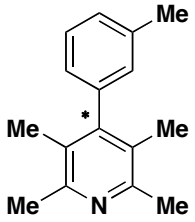
**Total: _____ (out of 350 points)**

**Question 1 (20 points).** An interesting rearrangement was observed when working with the *aspidosperma* alkaloids. Please provide a structure for intermediate A and a mechanism for its formation. Also provide a mechanism for the formation of the observed product when **A** is treated with TFA.

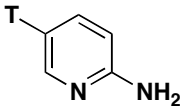


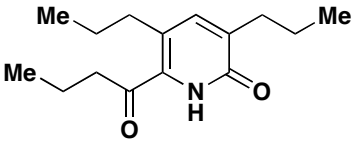
**Question 2 (30 points).** Please propose routes to the following pyridine ring systems.

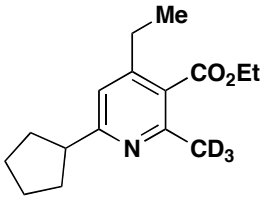


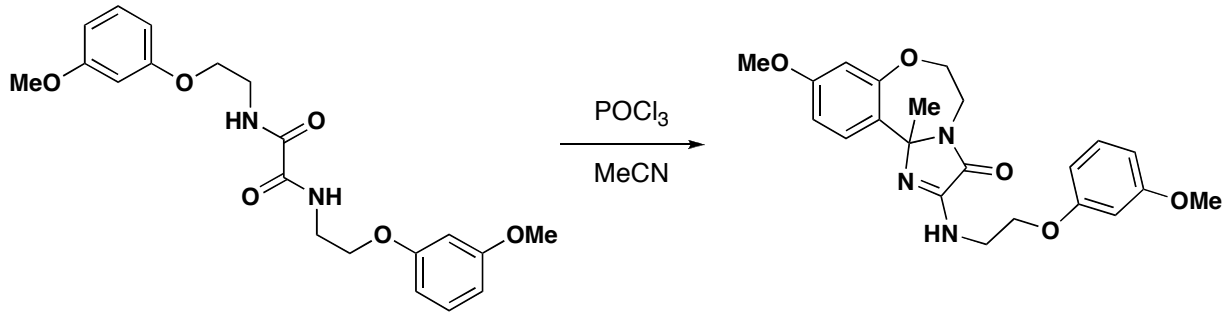

* = $^{14}$C label



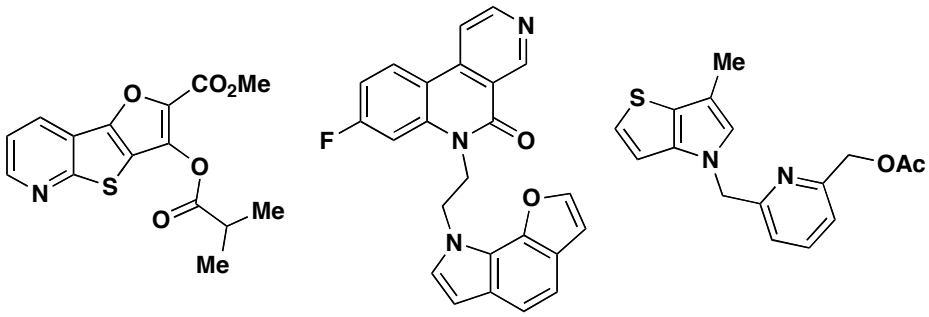



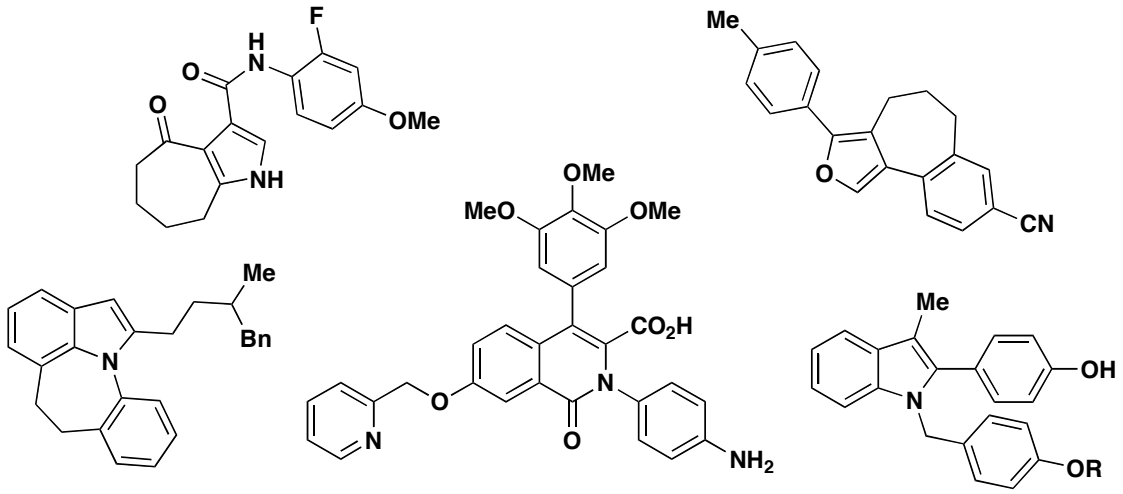
**Question 3 (20 points).** Part 1: Please provide a mechanism to account for this transformation. Part 2: What was the intended product of this reaction and the mechanism for its formation?



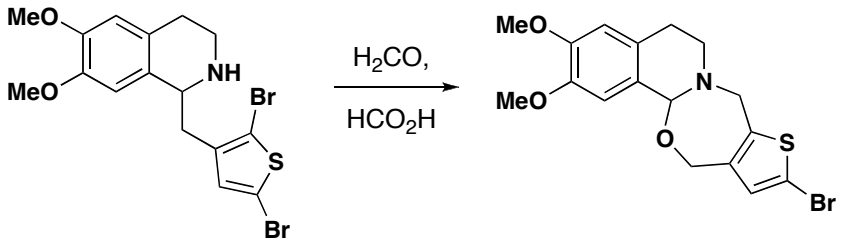
**Question 4 (30 points).** Because you have made it this far in the class, you have been hired as consultant for a small biotech called Heteryx. Since they are a small biotech, they cannot afford to use transition metals, fancy catalysts, or even protecting groups. For full credit and a paycheck, you must advise them on methodology to create the following exotic heterocycles:



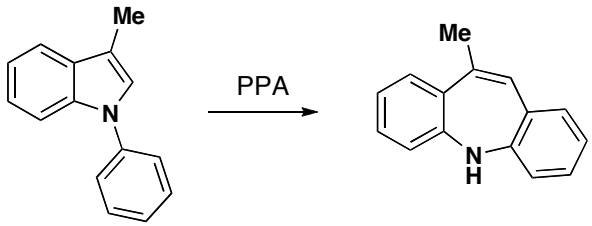
**Question 5 (75 points):** Please provide efficient syntheses of the following medicinal agents. For full credit, avoid protecting groups and cross coupling chemistry.



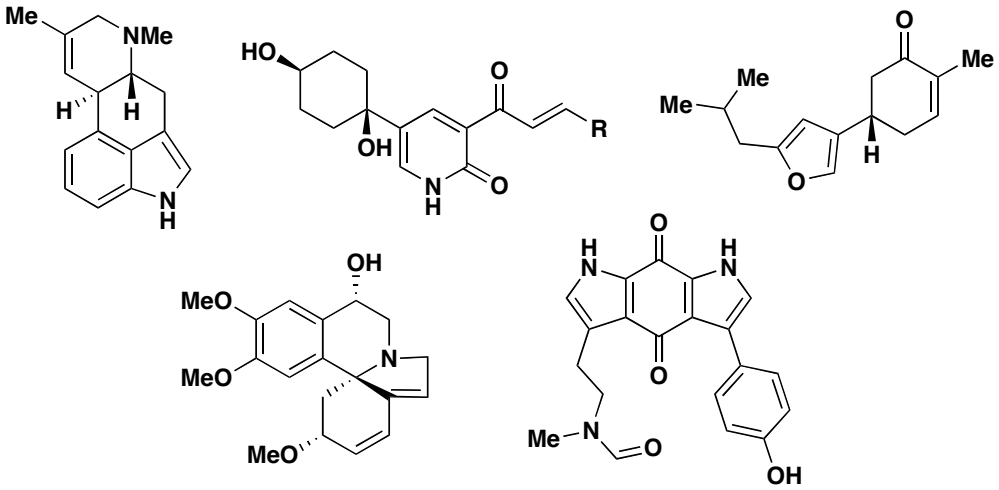
**Question 6 (15 points).** Please provide a mechanism that accounts for the product formed when the tetrahydroisoquinoline below is treated with formaldehyde in acid.



**Question 7 (10 points).** Please provide a reasonable mechanism that accounts for the following conversion of an indole into a dibenzoazepine.



**Question 8 (75 points):** Please provide efficient syntheses of the following natural products, avoiding the use of palladium cross-couplings, protecting groups, and superfluous oxidation state manipulations.



**Question 9 (75 points).** Please deduce the structures of the following heterocycles.

**A.** ($C_{11}H_{12}N_2O$) Obtained by reacting cyanoacetamide with 2-acetylcyclohexanone.

**B.** ($C_{10}H_{13}NO_2$) Obtained by reacting ethyl-3-aminocrotonate with ethyl-2-acetyl-3-ethoxyacrylate.

**C.** ($C_8H_{10}FNO$) Obtained when 3-fluoropyridine is treated with LDA then quenched with acetone.

**D.** ($C_8H_9NO$) Obtained by reacting the sodium salt of acetylacetaldehyde with ammonia.

**E.** ($C_{12}H_{11}NO_2$) Obtained by reacting aniline with methyl acetoacetate then DMF and $POCl_3$.

**F.** ($C_{16}H_{16}ClNO_4$) Obtained by treating 1,3-dichloroisoquinoline with sodium diethyl malonate.

**G.** ($C_{11}H_{15}NO_3$) Obtained by reacting ethyl acetylacetate with $HNO_2$, which is further reacted with zinc metal and 2,4-pentanedione in acetic acid.

**H.** ($C_8H_8O_6S$) Obtained by reacting diethyl oxalate with elemental sulfur, sodium methoxide, and sodium hydroxide, then treating this intermediate with dimethylsulfate.

**I.** ($C_{11}H_9NO$) Obtained by treating pyrrole with *N,N*-dimethylbenzamide and $POCl_3$.

**J.** ($C_6H_8O$) Obtained by reacting propionaldehyde sequentially with allyl magnesium bromide, *m*CPBA, $CrO_3$/pyridine, then $BF_3$.

**K.** ($C_{10}H_{10}N_2O_2$) Obtained by reacting 2-methyl-3-nitropyridine with diethyl oxalate and sodium ethoxide, then hydrogen and Pd/C.

**L.** ($C_{18}H_{19}NO$) Obtained by reacting 3-methylindole with 2-hydroxy-3,5-dimethylbenzyl chloride.

**M.** ($C_{10}H_8N_2$) Obtained by reacting 2,3-dinitro-1,4-dimethylbenzene with DMFDMA then hydrogen and Pd/C.

**N.** ($C_9H_7NO_3$) Obtained by heating 4-fluoronitrobenzene with acetone oxime and HCl.

**O.** (C11H9N) Obtained by treating 2-formylindole with vinyltriphenylphosphonium bromide and sodium hydride.