

# Heterocyclic Chemistry Final Examination

June 9<sup>th</sup>, 2009

Professor Baran  
Department of Chemistry  
The Scripps Research Institute

Name: \_\_\_\_\_

Last 4 digits of your Social Security #: \_\_\_\_\_

This is a 2-hour test that you have 4 hours to complete

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

Question 1 \_\_\_\_\_ < (40 points)

Question 2 \_\_\_\_\_ < (30 points)

Question 3 \_\_\_\_\_ < (30 points)

Question 4 \_\_\_\_\_ < (20 points)

Question 5 \_\_\_\_\_ < (40 points)

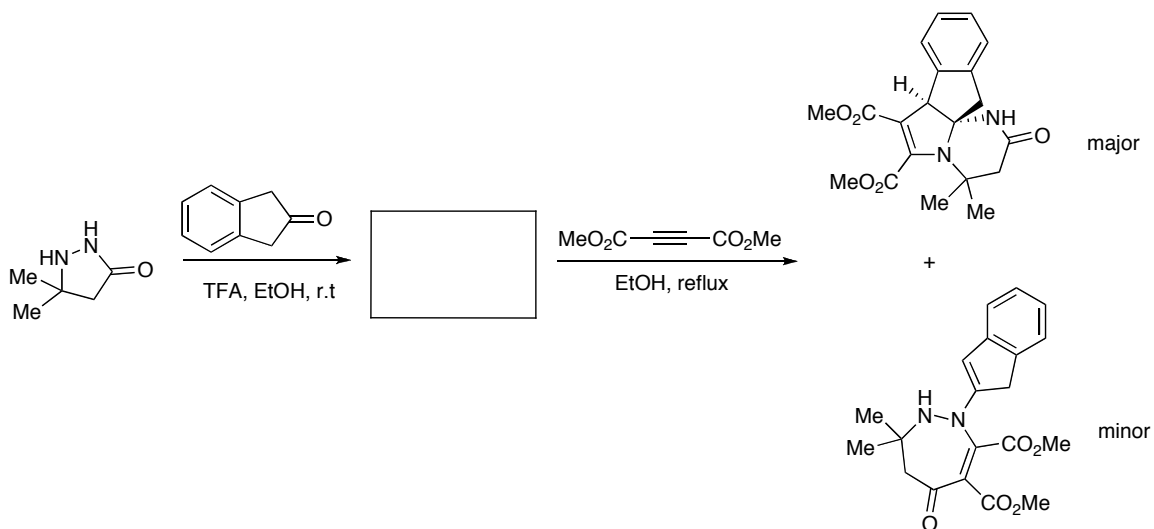
Question 6 \_\_\_\_\_ < (160 points)

Bonus Question \_\_\_\_\_ < (20 points)

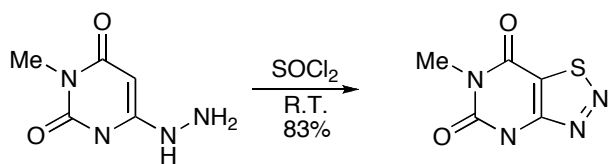
Total \_\_\_\_\_ < (320 points)

**Question # 1 (40 points): Please provide the intermediate where indicated and reasonable mechanisms for the following transformations.**

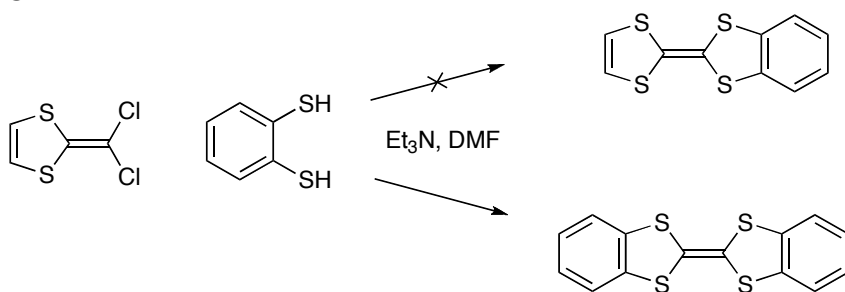
**A.**



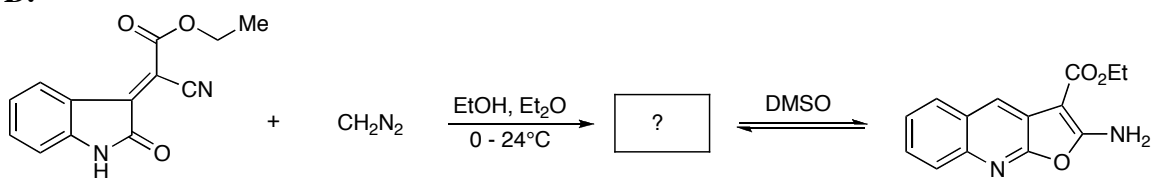
**B.**



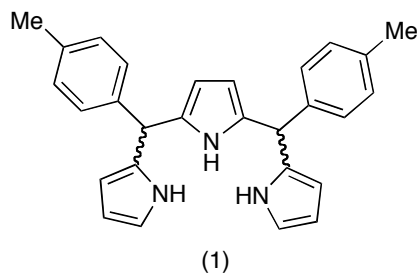
C.

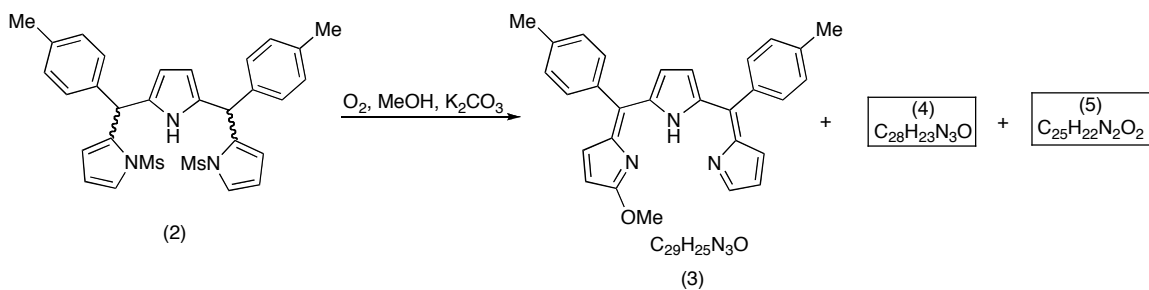


D.



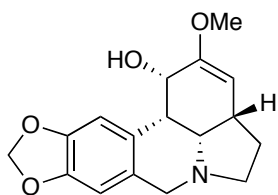
**Question # 2 (30 points):** Tripyrranes are popular building blocks in the construction of various porphyrinoids. They are used in the synthesis of porphyrins, hexaphyrins, rubeprins and chlorins. It is known that they are difficult to synthesize. What do you think could be the potential problems for the synthesis of (1)? Please provide a rational synthesis of (1) avoiding those “potential problems”.



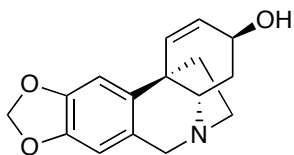


Upon treatment of (2) with  $K_2CO_3/MeOH/O_2$ , three dyes are formed. Both (3) and (4) are red-violet in solution, while (5) was observed as a strong yellow nonpolar band during chromatography. Based on the information furnished here and what you have learned from the class, please provide the structures of (4) and (5).

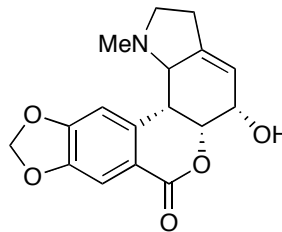
**Question # 3 (30 points):** Amaryllidaceae alkaloids Amarbellsine (1), Vittatine (2) and Hippeastrine (3) were isolated from *A. belladonna L* (an ornamental plant in Egypt). Please propose a biogenetic hypothesis for the formation of (1), (2) and (3).



Amarbellsine (1)



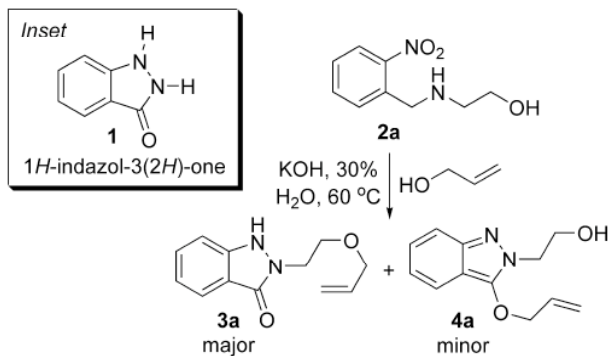
Vittatine (2)



Hippeastrine (3)

**Question # 4 (20 points):** 1*H*-Indazol-3(2*H*)-ones (1) are known to exhibit a wide range of biologically and pharmaceutically relevant properties and are reported to exhibit analgesic, antitumor, anticancer and anti-inflammatory activities. In order to synthesize (1), Kurth and co-workers discovered the following interesting transformation (Scheme 1). Please provide the mechanism based on the results shown below. (Org. Lett. ASAP)

**Scheme 1.** Formation of 1*H*-Indazolone **3a** along with 2*H*-Indazole **4a**



It may be helpful to consult the following (Table 1, Table 2 and Figure 2) as you devise a mechanism.

**Table 1.** Formation of 2,3-Dihydrooxazolo[3,2-*b*]indazoles

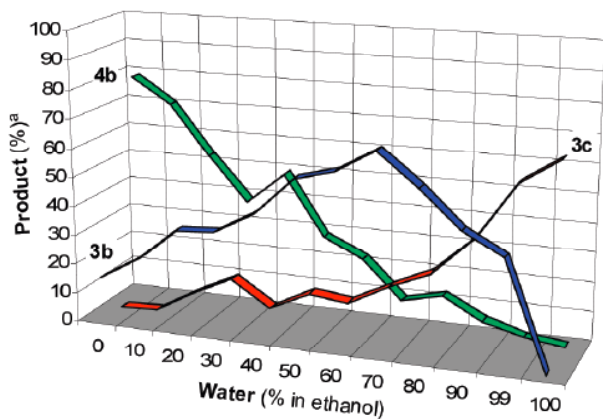
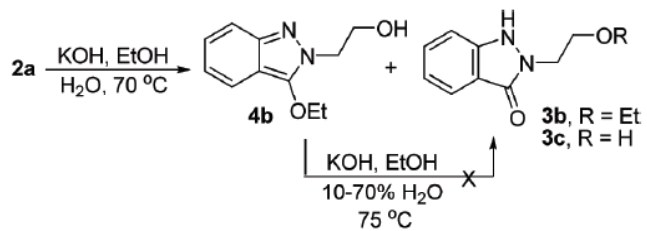
| entry | R <sup>1</sup> | R <sup>2</sup> | ROH/H <sub>2</sub> O (%) | time (h) | temp (°C) | reaction              | yield (%)       |
|-------|----------------|----------------|--------------------------|----------|-----------|-----------------------|-----------------|
| 1     | H              | H              | <i>i</i> -PrOH/10        | 4        | 60        | <b>2a</b> → <b>5a</b> | 24 <sup>b</sup> |
| 2     | H              | H              | <i>i</i> -PrOH/10        | 24       | 60        | <b>2a</b> → <b>5a</b> | 5 <sup>c</sup>  |
| 3     | H              | Me             | MeOH/70                  | 32       | 70        | <b>2b</b> → <b>5b</b> | 30 <sup>c</sup> |
| 4     | H              | Me             | EtOH/30                  | 12       | 70        | <b>2b</b> → <b>5b</b> | 65 <sup>c</sup> |
| 5     | H              | Me             | <i>i</i> -PrOH/10        | 32       | 70        | <b>2b</b> → <b>5b</b> | 67 <sup>c</sup> |
| 6     | Me             | H              | <i>i</i> -PrOH/10        | 18       | 60        | <b>2c</b> → <b>5c</b> | 84 <sup>c</sup> |
| 7     | Bn             | H              | <i>i</i> -PrOH/0         | 18       | 70        | <b>2d</b> → <b>5d</b> | 10 <sup>c</sup> |
| 8     | Bn             | H              | <i>i</i> -PrOH/10        | 18       | 60        | <b>2d</b> → <b>5d</b> | 88 <sup>c</sup> |
| 9     | <i>i</i> -Pr   | H              | <i>i</i> -PrOH/10        | 18       | 60        | <b>2e</b> → <b>5e</b> | 80 <sup>c</sup> |

<sup>a</sup> Isolated yield after silica gel chromatography. <sup>b</sup> Reaction was prematurely evaluated. Isolated yield after silica gel chromatography; starting material was recovered in 53% yield. <sup>c</sup> Yield as determined by crude LC/MS trace.

**Table 2.** Oxazoloindazoles React To Give Indazolones

| entry | R <sup>1</sup> | R <sup>2</sup> | time (h) | Reaction              | yield (%) <sup>a</sup> |
|-------|----------------|----------------|----------|-----------------------|------------------------|
| 1     | H              | H              | 8        | <b>5a</b> → <b>3d</b> | 97                     |
| 2     | H              | Me             | 144      | <b>5b</b> → <b>3e</b> | 40                     |
| 3     | Me             | H              | 14       | <b>5c</b> → <b>3f</b> | 92                     |
| 4     | Bn             | H              | 18       | <b>5d</b> → <b>3g</b> | 72                     |

<sup>a</sup> Isolated yield after silica gel chromatography.



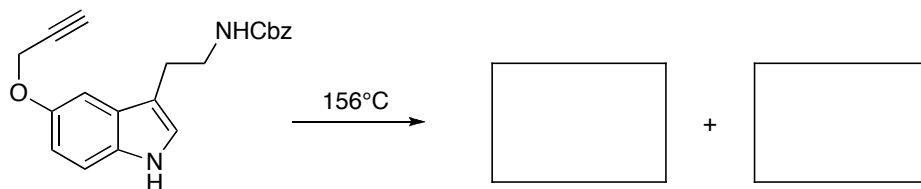
<sup>a</sup>As determined by crude LC/MS trace.

**Figure 2.** Effect of the concentration of water on 1*H*-indazolone formation.

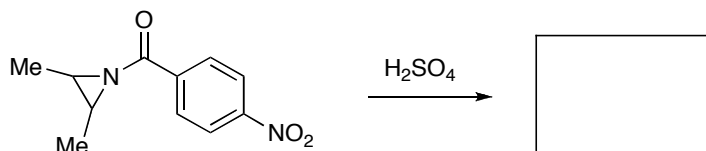


**Question # 5 (5 points each, 40 each):** Please provide the products for the following transformations.

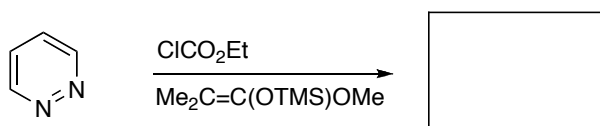
**A.**



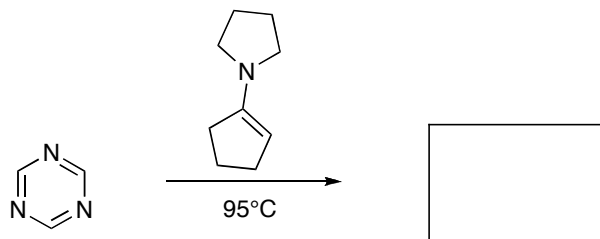
**B.**



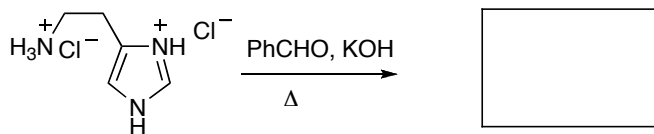
**C.**



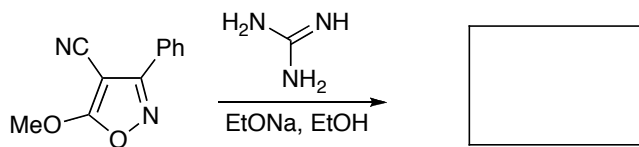
**D.**



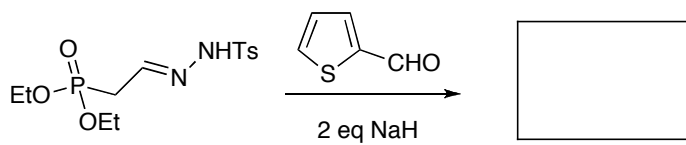
**E.**



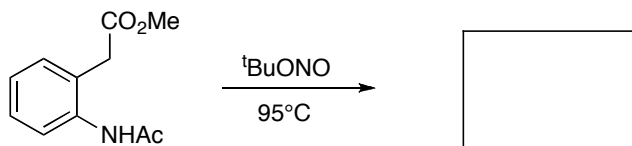
**F.**



**G.**

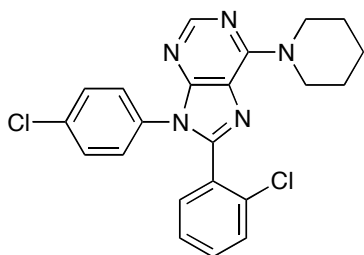


**H.**

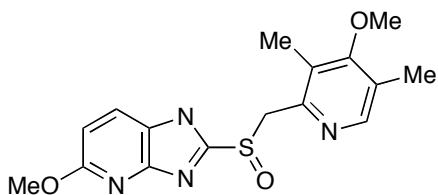


**Question # 6: (10 points each, 160 points)** This is the grand finale. Based on everything you have learned, each one of these should take 60 seconds to conceive and 4 minutes to execute on paper. Thus, please provide syntheses of the following heterocycles from simple starting materials:

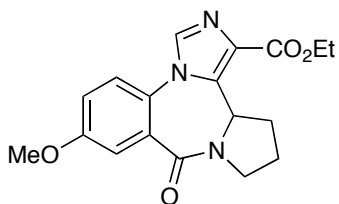
**A.**



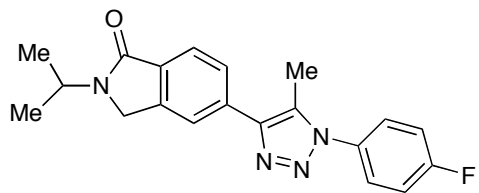
**B.**



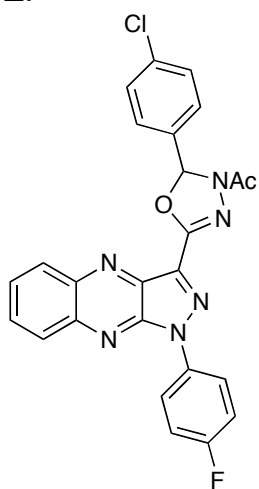
**C.**



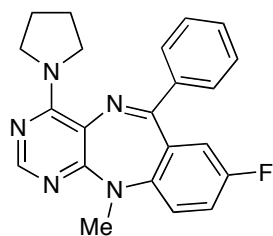
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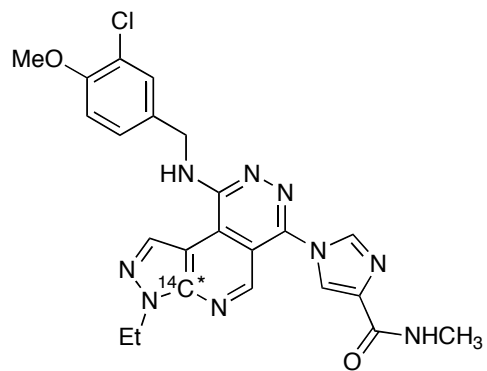
**E.**



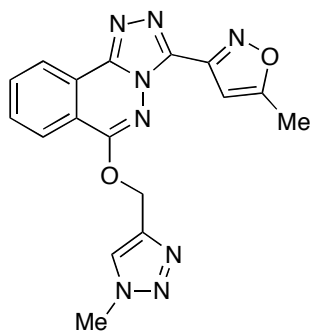
**F.**



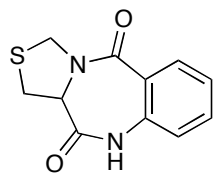
**G.**



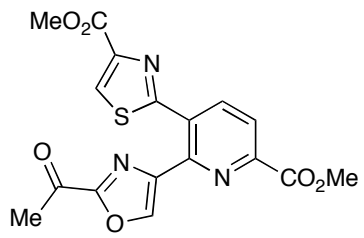
**H.**



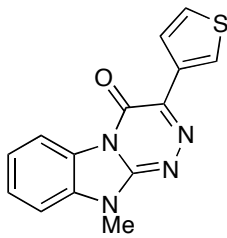
**I.**



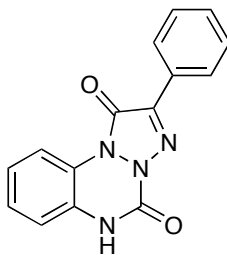
**J.**



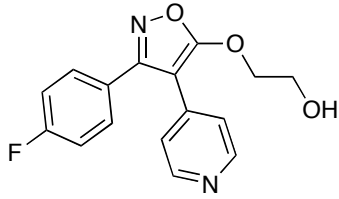
**K.**



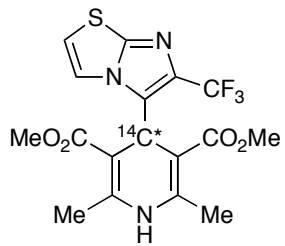
**L.**



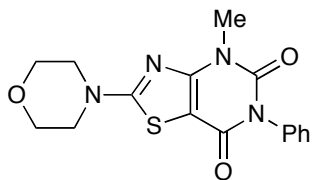
**M.**



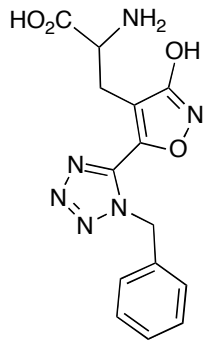
**N.**



**O.**

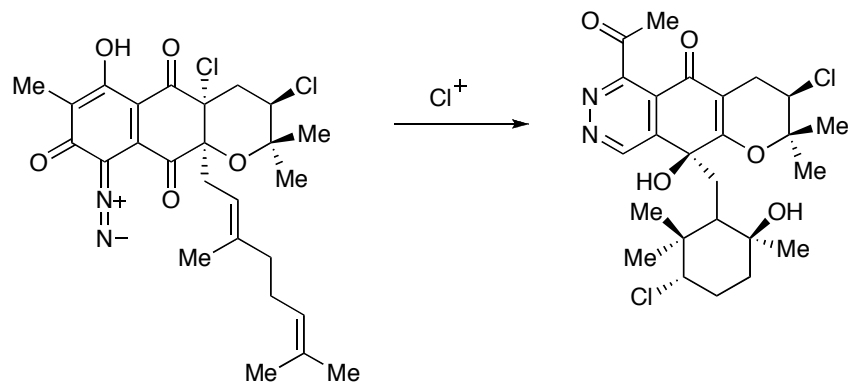


**P.**





**Bonus Question: (20 points)** The Moore group at Scripps Institute of Oceanography recently disclosed their effort at elucidating the mechanism of rearrangement of an aryl diazoketone to afford the pyridazine natural product azamerone. Please provide a pathway for this rearrangement.



It was a joy to have each one of you in class! Have a great summer!

