1. Recently, Boger published an elegant synthesis of spegazzinine (DOI: 10.1021/ol300599p). The synthesis is shown below.

(a) The synthesis begins with nitrobenzene 1, which is converted into indole 2 in one step. Show the mechanism for this transformation.

(b) Indole 2 is converted into tryptamine 3 in a series of standard transformations. Show how this classic transformation could be accomplished.

(c) Show intermediates A through D in the completion of the spegazzinine synthesis.

(d) Provide a mechanism for the conversion of 4 to A.
2. Isonitriles have a rich and complex chemistry that can be usefully exploited in synthesis. The following problems relate to this interesting functional group which may be activated by electrophilic attack to give nitrilium species.

\[
\text{R-} \text{NH}_2 + \text{aq. KOH} \rightarrow \text{R-N\equiv C} \quad \text{(isonitrile (isocyanide))} \quad \text{E}^+ \rightarrow \text{R-} \text{N\equiv C-E} \quad \text{nitrilium cation}
\]

(a) Volatile isonitriles have a powerful odor and this property formed the basis of a classical qualitative test for primary amines via their in situ conversion to RNC compounds using a combination of KOH in chloroform (as above). How does this isonitrile synthesis work? (6 points)

(b) Isonitriles are deployed in the Ugi four-component coupling reaction (e.g., as below). Formulate a mechanism for this multi-stage process and briefly comment on the value of such a transformation to the fields of medicinal chemistry and chemical biology. (10 points)

(c) Danishefsky and co-workers recently devised novel amide forming processes that rely on isonitriles as either coupling partners (type Ia reaction) or as coupling agents for the reaction of thioacids with amines (type IIb reaction). Provide mechanisms to account for the outcome of these reactions. (12 points)

(d) Treatment of azide A with PMe₃ gives a new compound with formula C₁₇H₂₂N₂O₃. What is its structure? (5 points)

A. As has been known for some time, the reactant is present as a mixture of regio- and stereoisomers:

Provide a mechanistic explanation for how this occurs.

B. Provide a detailed explanation for how you would identify and measure the ratio of isomers of this reactant.

C. The Schmidt reaction of the above compound (1.5 eq. SnCl₄, CH₂Cl₂, reflux) gave a 1.2:1 ratio of products, whereas Compound 11a (and its regio/stereoisomers) gave a 20:1 mixture of diastereomeric products.

Provide a mechanistic rationale for the selective formation of one diastereomer. Be sure to include an explanation for how the gem-dimethyl system enhances that selectivity.

D. This selective reaction was applied in a formal synthesis of the natural product pinnaic acid. Show the steps involved in making the Schmidt precursor, and predict the stereochemical outcome of the ring expansion.

Pinnaic Acid
4. Regan Thomson and co-workers recently published an elegant synthesis of allenes via a traceless Petasis reaction (*JACS* 2012, 134, 5782-5785). This reaction is based on the pioneering work by Nicos Petasis shown below (see *JACS* 1998, 120, 11798-1799).

**Petasis borono-Mannich reaction** (*Petasis and Zavialov JACS* 1998, 120, 11798-1799)

\[
\text{Ph} = \text{BF}_3 \quad \text{K} \\
\text{OH} \quad \text{OH} \quad \text{Ph} \\
+ \quad \text{BnNHMe} \\
\text{EtOH, H}_2\text{O} \\
\text{rt, 87\%} \\
\rightarrow \quad \text{Compound 3} \\
\text{C}_{19}\text{H}_{23}\text{NO}_2 
\]

**Allene Synthesis via Traceless Petasis reaction** (*Thomson and co-workers JACS* 2012, 134, 5782-5785)

\[
\text{Ph} = \text{BF}_3 \quad \text{K} \\
\text{OH} \quad \text{OH} \quad \text{Ph} \\
+ \quad \text{H}_2\text{N}-\text{NH} \\
\text{SO}_2 \quad \text{NO}_2 \\
\text{5} \\
\text{La(OTf)}_3 \\
(10 \text{ mol \%}) \\
\text{MeCN, 86\%} \\
\rightarrow \quad \text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{Ph} \\
\text{6} \\
\text{Ph} \\
\text{OH} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{Ph} \\
\text{H} \\
\text{9} \\
\text{8} \\
\text{steps} 
\]

(a) Please provide the structure, including stereochemistry, for compound 3.

(b) Please provide a complete mechanism for the conversion of 1 and 2 into 3. You must include electron flow/reaction arrows as well as formal charges to receive full credit.

(c) Based on your knowledge learned from the conversion of 1 and 2 into 3, please provide a complete mechanism to explain the conversion of 4 and 2 with 5 to form allene 6. You must include electron flow/reaction arrows as well as formal charges to receive full credit.

(d) In the same communication, Thomson and co-workers reported the conversion of 8 into 9. Please provide a reasonable synthetic sequence for the conversion of 8 into 9.
5. The following questions are based on a previously distributed article: Houk and coworkers, J. Am. Chem. Soc. 2007, 129, 5419-5429.

A. What is the absolute binding of biotin to avidin? Give some numbers for other binding constants to show how much stronger biotin-avidin binding is in comparison. [5 points]

B. Origins of binding:
   i) Prior to this work, what were the three hypotheses as to the origins of biotin-avidin binding? [8 points]
   ii) What is meant by “cooperative hydrogen bonding”? Use figures to illustrate this phenomenon in the biotin-avidin or biotin-streptavidin complex. [8 points]
   iii) Explain why the cooperative hydrogen bonding in biotin-avidin is weaker than in biotin-streptavidin, but avidin is a stronger binder to biotin than streptavidin. [12 points]

![Chemical reaction](image)

A. Phil Baran reported a remarkable ring contraction to form the key β-lactam moiety of Chartelline-C. There are no less than four possible ways for this rearrangement to happen. Please draw four possibilities. In order to receive full credit, please label each possibility and the related curved arrows clearly. [12 points]

B. Which do you think is the most likely mechanism? Explain [5 points]

C. Checking the hypotheses: No intermediates of this process has been reported or isolated.

i) How would you verify the correct mechanism experimentally? What do you propose to do exactly to distinguish between two of the mechanisms you have outlined in the first part of this question? Is it feasible? What are the potential problems with your proposal? [8 points]

ii) How would you verify the correct mechanism computationally? What do you propose to do exactly to distinguish between two of the mechanisms you have outlined in the first part of this question? Is it feasible? What are the potential problems with your proposal? [8 points]