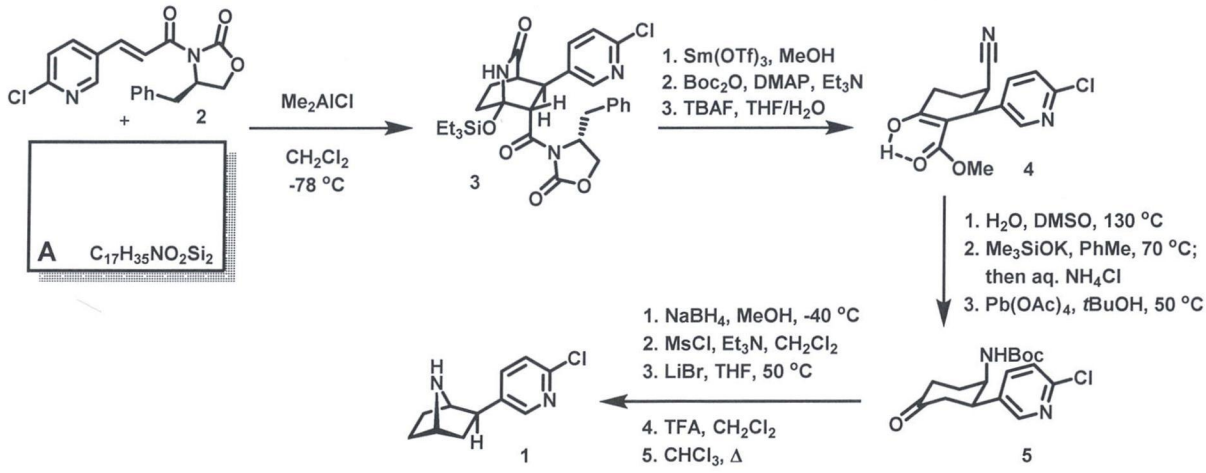
Assignment 2: Problem Session

1. Frog Poison!

(−)-Epibatidine (**1**) is a rare chlorinated alkaloid isolated from the phantasmal poison frog *Epipedobates tricolor*. It is a potent analgesic about 200 times more active than morphine. Although toxicity of the alkaloid itself prevents clinical application, many derivatives have been under investigation for pain treatment. The scheme below depicts an asymmetric total synthesis of (−)-epibatidine primarily based on undergraduate chemistry.



1a. Suggest a five-step synthesis of compound **2** starting from phenylalanine.

1b. Provide the structure of the missing reactant **A**.

1c. Provide a mechanism for the cycloaddition between **2** and **A** and comment on the regio- and stereoselectivity.

1d. Provide intermediates for each step in the conversion of **3** to **4** and provide a plausible mechanism for the last step. *Hint: the Boc group is not attached to the N atom!*

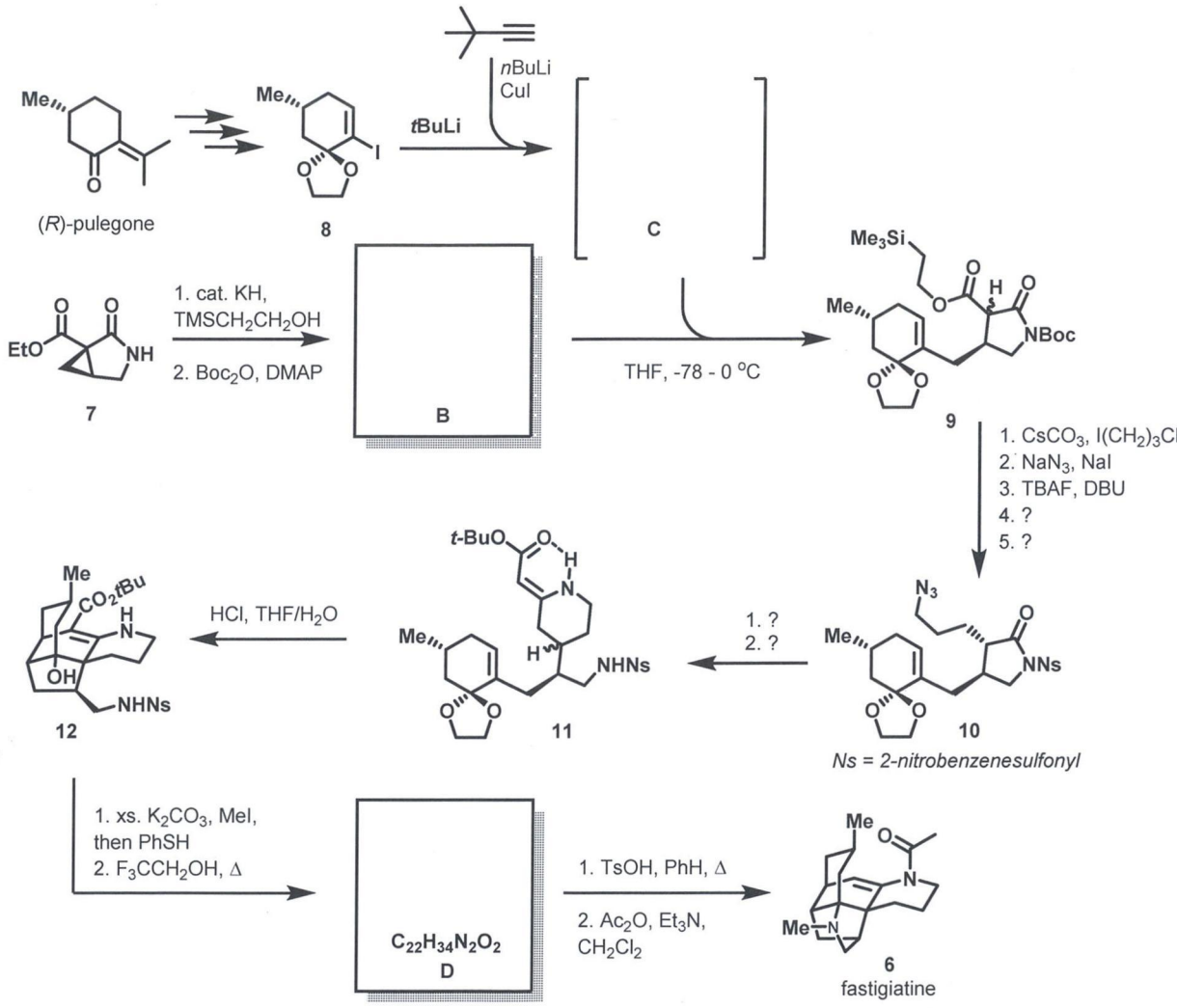
1e. Provide intermediates for each step in the conversion of **4** to **5**.

1f. Provide intermediates for each step in the conversion of **5** to **1**.

Hint:	Reactions or reagents associated to the following names are used in the synthesis: Arbuzov • Diels-Alder • Evans • Grob • Hoffmann • Horner-Wadsworth-Emmons • Krapcho

2. [3+3] equals 5 (rings).

The complex alkaloid fastigiatine is synthesized in a relatively short sequence by a biomimetic construction of the polycyclic ring system.



2a. Provide the structures of **B** and **C** and a plausible mechanism for their coupling to give **9**.

2b. Provide intermediates and missing reagents for each step in for the conversion of **9** to **10**.

2c. Provide the missing reagents for the conversion of **10** to **11**.

2d. Provide a plausible mechanism for the conversion of **11** to **12**.

2e. Provide the structure of **D** and a plausible mechanism for its formation (second step of **12** → **D**). Explain why this reaction does not proceed via an S_N1 or S_N2 mechanism.

Hint:	Reactions associated to the following names are used in the synthesis: Claisen • Finkelstein • Mannich • Staudinger