

**Title of the Course: Total Synthesis of Natural Products
(2021-2022 Fall Semester)**

**Total Time: 3h
Thursday 20-Jan-2022, 16:15–19:15, CE1103**

Please show your ID or Student Card

Materials allowed:

- **Writing materials (pen, pencil ...).**
- **Drink and food.**

Name:

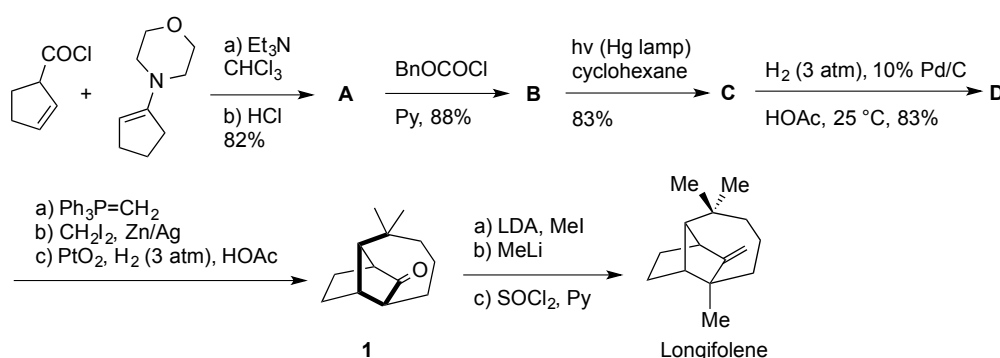
Signature:

Question 1 (20 points)

In Scheme 1 are summarized the key transformations of Oppolzer's total synthesis of longifolene.

a) Please propose the structures of the products **A**, **B**, **C** and **D**.

b) Compound **1** is converted to the natural product in three steps. Please draw a possible reaction pathway and the structures of the intermediates that account for the conversion of **1** to longifolene.

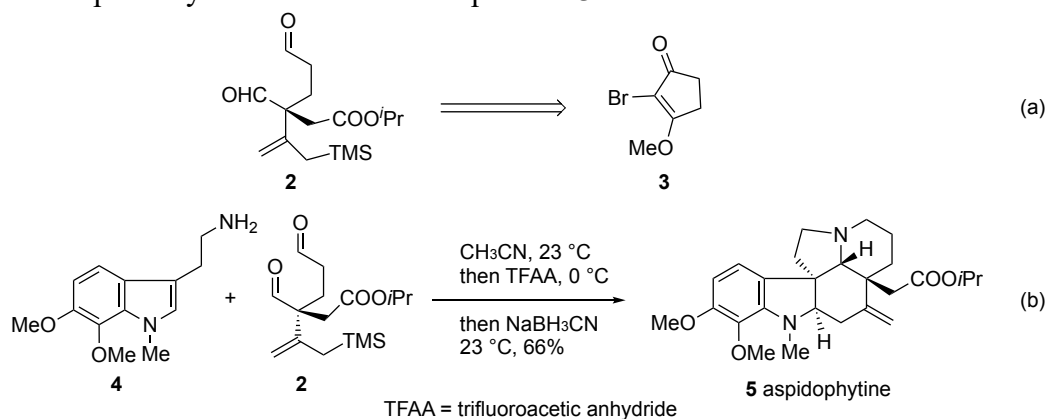


Scheme 1

Question 2 (20 points)

a) The enantioenriched dialdehyde **2**, a key intermediate in Corey's total synthesis of aspidophytine, is synthesized from 2-bromo-3-methoxycyclopent-2-en-1-one (**3**). Please propose a forward enantioselective synthesis of **2** from **3** (Scheme 2a).

b) Reaction of 6,7-dimethoxy-*N*-methyltryptamine (**4**) with dialdehyde **2** under conditions specified in Scheme 2b affords aspidophytine (**5**) in 66% yield. Please propose a possible reaction pathway for the formation of product **5** from **2** and **4**.

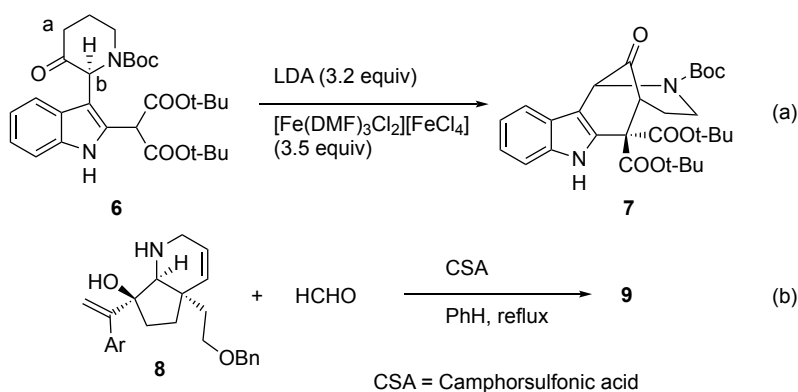


Scheme 2

Question 3 (15 points)

a) Two key steps in Overman's total synthesis of actinophyllic acid are intramolecular oxidative coupling of dienolate of **6** (Scheme 3a) and a domino aza-Cope/Mannich sequence. Please explain (using conformational analysis) why one of the C_α -protons is deprotonated selectively instead of C_β -H, hence the regioselective cyclization of **6** to **7**.

b) Provide the structure of **9** formed via an aza-Cope/Mannich reaction of **8** with formaldehyde (Scheme 3b).



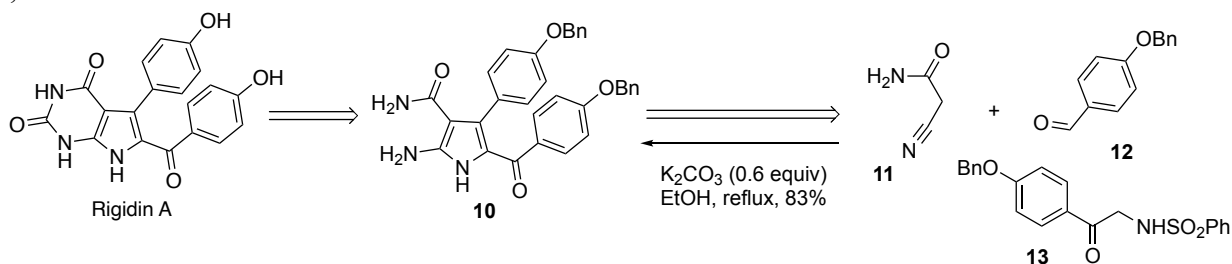
Scheme 3

Question 4 (15 points)

The tetrasubstituted pyrrole **10**, a key intermediate on the way to rigidin A, is synthesized by a three-component reaction of α -cyanoacetamide (**11**), aldehyde **12** and ketone **13** (Scheme 4).

a) Please provide a step-by-step disconnection of rigidin A (a retro-synthetic scheme) that eventually leads to the three building blocks **11**, **12** and **13**.

b) Please provide a possible reaction mechanism accounting for the formation of **10** from **11**, **12** and **13**.

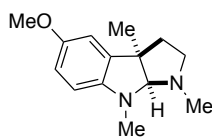


Scheme 4

Question 5 (10 bonus points)

a) Provide a reasonable retro-synthetic analysis of ($\pm$)-esermethole (Figure 1).

b) Propose possible conditions for the forward synthesis of racemic esermethole according to your synthetic plan.



($\pm$)-Esermethole

Figure 1