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Graduate School
Health and Drug Sciences

M1 Development of Drug and Health Products

TU07 : The Medicinal Chemist's Toolbox

2nd Session 2021-2022

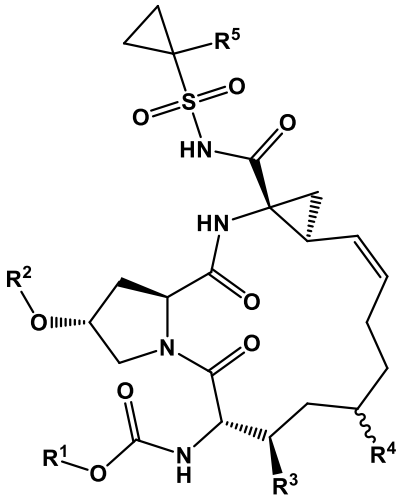
Main Strategies of Drug Discovery (around 30 minutes)

Question 1:

1. What are the main sources of natural products ? Provide an example of a drug from each source.
2. Could you provide some details on the efforts that led to solve the challenge of Trabectedine industrial production ?

Question 2:

The results of the **h**epatitis **C** **v**irus protease (HCV-NS3) domain inhibition and microsomal stability tests (**HLM**, **H**uman **L**iver **M**icrosomes assay), for macrolactams **1** to **7**, are collected in Table 1.



Macrolactams 1-7

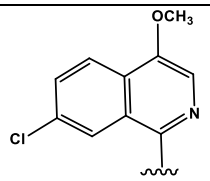
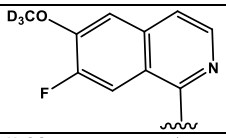
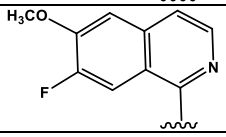
Lactame	R^1	R^2	R^3	R^4	R^5	[IC_{50}] HCV-NS3 GT-3a* (nM)	HLM** $t_{1/2}$ (min)
1	*t*Bu		CH_3	H	H	11	11,5
2	*t*Bu		H	H	H	51	6,4
3	*t*Bu		CH_3	(*R*)-CH_3	H	4,4	6,7
4	*t*Bu		CH_3	(*S*)-CH_3	H	50	ND
5	$CF_3(CH_3)_2C$		CH_3	H	H	12,8	20
6	$CF_3(CH_3)_2C$		C_2H_5	(*R*)-CH_3	CH_3	4,5	33
7	$CF_3(CH_3)_2C$		C_2H_5	(*R*)-CH_3	CH_3	6,3	28

Table 1.* HCV-NS3 genotype-3a producing a non-structural hepatitis C viral protein whose protease domain is a target for screening direct-acting antivirals. **Test HLM (Human Liver Microsomes). ND = not determined

1. Among these 7 macrolactams, find the one(s) which correspond(s) to the definition of a "**hit**" **molecule**? **Justify your answer**. *(2 pts)*

2. Interpret the effect of the addition of the **CH_3 group** in position R^4 on the activity of these molecules. *(3 pts)*

3. According to the results gathered in Table 1, propose the nature of the amino acids which are located opposite the R^4 group at the active site of the enzyme. Among the 20 natural amino acids, give the name of 2 amino acids likely to be located at this site in the enzyme. *(2 pts)*

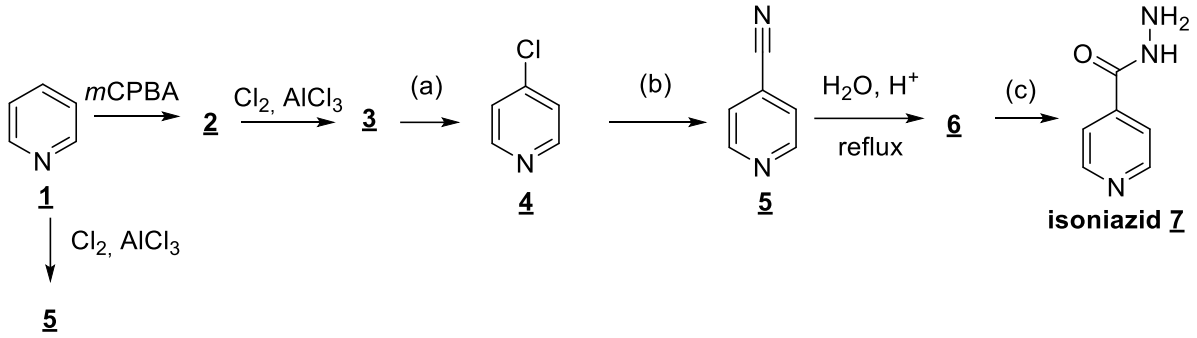
4. Interpret the influence of the substitution of the ter-butyl group (*t*Bu) by a trifluoro-tert-butyl ($CF_3(CH_3)_2C$-) on the inhibition of the HCV-NS3 genotype-3a protease and on the microsomal stability (HLM). *(1 pt)*

5. Which molecule would you select as the lead molecule for preclinical development? Justify your answer. *(2 pts)*

Approaches of the Synthesis of Natural and Synthetic Drugs (around 1h30)

<u>Exercise 1:</u> Synthesis of Isoniazid

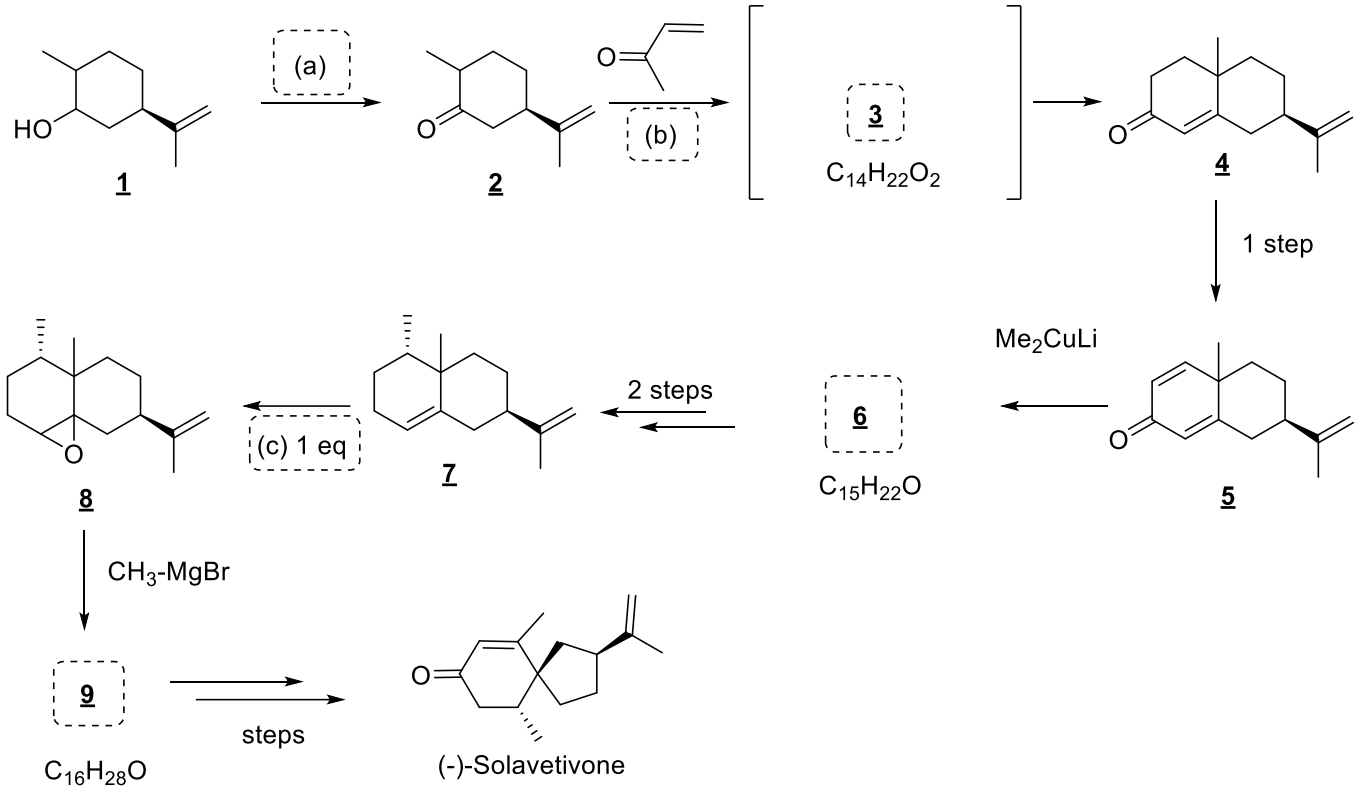
Isoniazid is an antibiotic used for the treatment of tuberculosis.



1. a. Give the structures of compounds **2** and **3**.
   b. Justify the regioselectivity observed in the transformation of compound **2** into product **3**.
2. Which reactant (a) can be used to transform compound **3** into 4-chloropyridine **4**?
3. Which compound(s) **5** will be obtained when using Cl_2, $AlCl_3$ directly with pyridine **1**?
4. a. Propose conditions (b) allowing transformation of intermediate **4** into product **5**.
   b. What type of reaction is it? Is this reaction easy or not on a pyridine ring?
5. Compound **5** is hydrolyzed by aqueous acidic conditions. What is the structure of product **6**?
6. Propose conditions (c) allowing transformation of intermediate **6** into **isoniazid 7**.

Exercise 2: Synthesis of (-)-Solavetivone

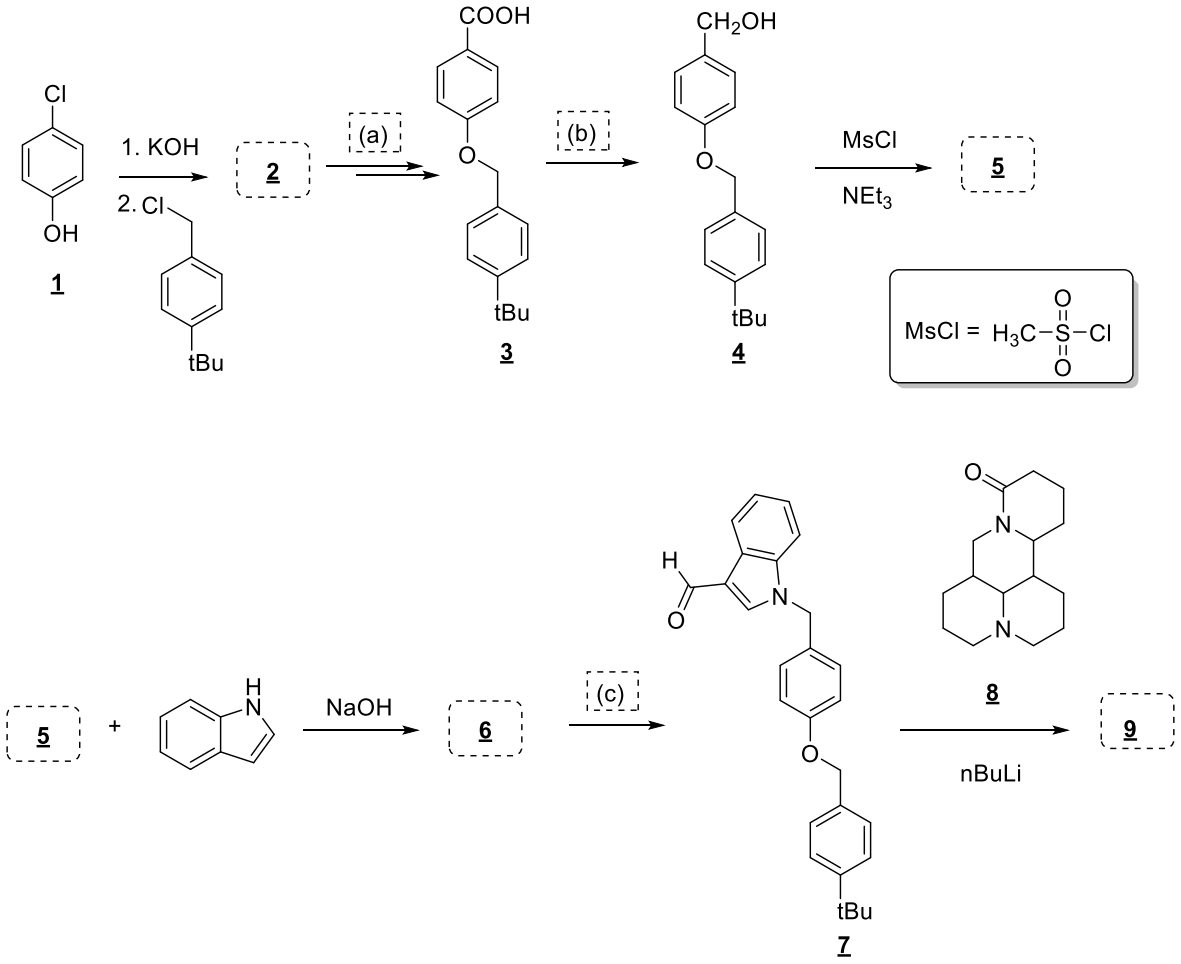
Solavetivone is a phytoalexin, a product produced by Solanaceae family (potatoes, tomatoes) in case of external stress, such as a fungus infestation, inhibiting growth of the plant.



1. a. Give a reagent (a) for the transformation of compound **1** into compound **2**.
   b. What is the name of this reaction?
2. Give the reaction conditions (b) in complement of methylvinylketone for the reaction leading to product **4** from **2**.
3. a. Give the structure of intermediate **3**.
   b. Give the mechanism for the step between intermediate **3** and **4**.
4. What is the name of the sequence from compound **2** to **4**?
5. a. Draw the structure of product **6**.
   b. If MeLi was used as the reagent in place of Me_2CuLi, which product would be obtained?
6. Give the reagent (c) for the reaction leading to **8** from compound **7**. Explain the regioselectivity observed.
7. If two equivalents of reagent (c) would be used, anticipate the structure of the obtained product.
8. a. Predict the structure of product **9** obtained from the addition of CH_3MgBr onto substrate **8**.
   b. What kind of precaution should be taken during the reaction implying a magnesium derivative and why?

Exercise 3: Synthesis of sophoridine derivatives

Here we present the synthesis of compound **9** a derivative of sophoridine **8**. Sophoridine is a molecule used in the Chinese pharmacopeia to treat cancer.



1. a. Give the structure of compound **2**.
   b. Explain each step to access to compound **2** from reagent **1** (type of reaction, role of the reagents used, intermediate formed).
2. Propose conditions (a) allowing access to compound **3** starting from derivative **2** (2 steps).
3. Propose reagent (b) allowing access to compound **4** starting from derivative **3**. What type of reaction is it?
4. Give the structure of compound **5**.
5. Give the structure of compound **6**. What type of reaction is it? What role plays NaOH in the reaction?
6. Propose conditions (c) allowing access to compound **7** starting from derivative **6**. What is the name of this reaction? Explain its regioselectivity.
7. An aldol reaction is performed with compound **7** and sophoridine **8**. Find the structure of the final product **9**. Give the mechanism of this step.