Problem 26: Chemical and Stereochemical Structure of Coniine

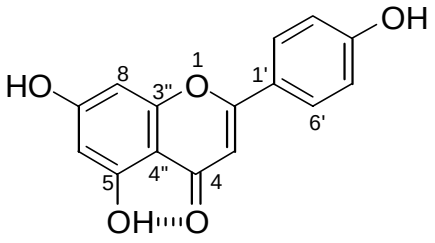
Coniine is a toxic compound found in the plant hemlock (conium maculatum), with which the ancient Greek philosopher Socrates was poisoned. Coniine is a nitrogenous compound belonging to the alkaloid family.
Find the chemical and stereochemical structure of coniine by completing the following series of reactions. Also, draw the structures of the intermediates A, B, C.

$$\text{Coniine} \xrightarrow[\text{2. } Ag_2O\text{ ,}H_2O\text{, Ä}]{\text{1. } CH_3J\text{ (Hofmann exhaustive methylation)}} \text{A } (C_{10}H_{21}N) \text{ optically active}$$

$$\text{A} \xrightarrow[\text{2. } Ag_2O\text{ ,}H_2O\text{, Ä}]{\text{1. } CH_3J\text{ (Hofmann exhaustive methylation)}} \text{1, 4 -octadiene + 1, 5-octadiene}$$

$$\text{Coniine} \xrightarrow[\text{NaOH, } 0^0\text{C}]{C_6H_5CH_2OCOCl} \text{B} \xrightarrow[\text{Ä}]{KMnO_4} \text{C} \xrightarrow{H_2\text{ /Pd/C}} \text{(S) -5-aminooctanoic acid}$$

Problem 27: The Chemistry and Identification of Flavonoids
Cistus L is an aromatic, erect branched shrub and is a significant element of Greek flora. It can be found in stony slopes and hills and it can also be found in pinewoods. In folk medicine the flower branches of Cistus monospeliensis have been used for asthma, while the leaves may replace tea. Flavonoids are widely distributed in plants as glycosides or as free aglycons. They are known to exhibit a broad spectrum of pharmacological properties including antimicrobial, antitumor, antiviral, enzymes inhibition and central vascular system activity.
Apigenin is a very widely distributed flavonoid. Its structure is shown below:



Apigenin

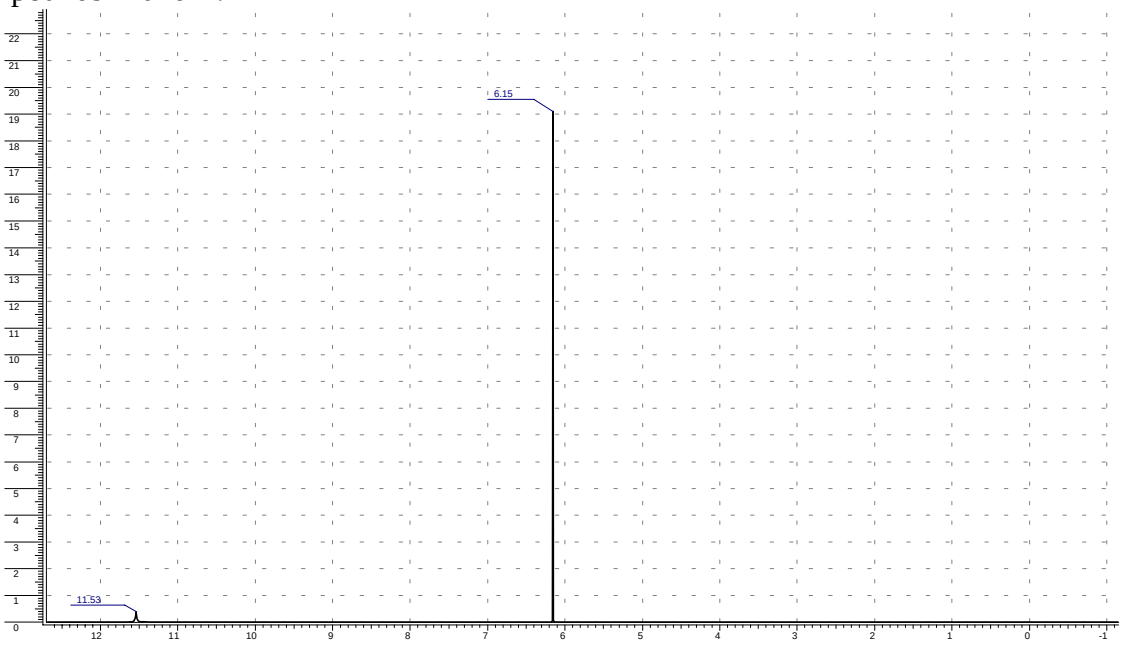
1 In the following reactions draw the structures of products B and C.

- $\text{Apigenin} \xrightarrow[\text{2. excess MeI}]{\text{1. NaH/DMF}} \text{B}$
- $\text{Apigenin} \xrightarrow[\text{pyridine}]{\text{acetic anhydride(excess)}} \text{C}$

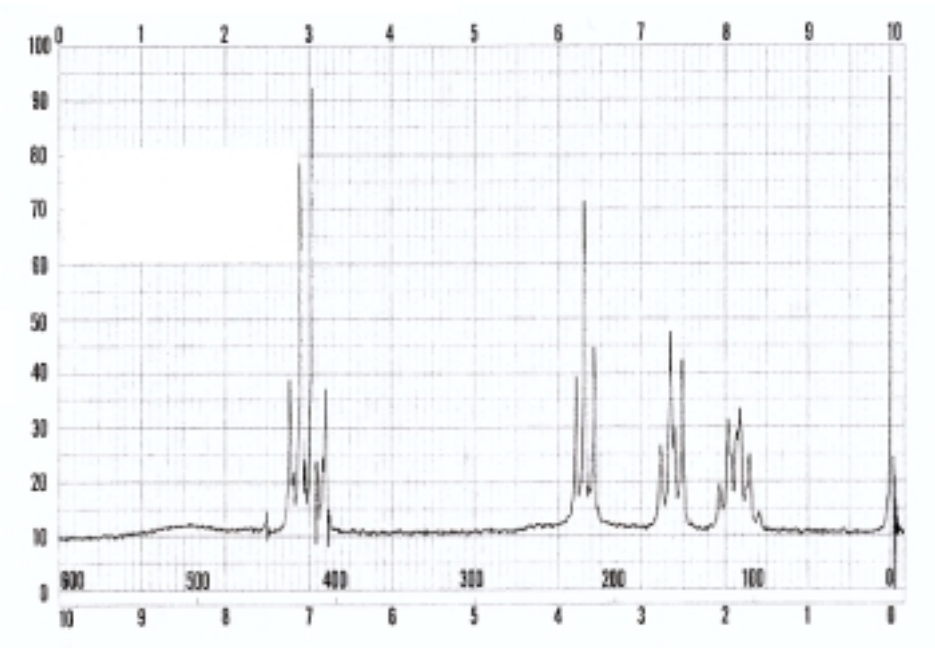
2 Apigenin can form a hydrogen bond between the phenolic hydroxyl group attached to C-5 and the carbonyl group at C-4.
The ^{1}H-NMR resonance of the phenolic proton at C-5 will be shifted due to hydrogen bond:
a) down field, b) up field, c) not shifted
3 When treated with 2M NaOH, **apigenin** gives among others products D and E

$$\text{Apigenin} \xrightarrow{\text{NaOH 2M}} \text{D+E}$$

Compound D ($C_6H_6O_3$) gives a positive test with $FeCl_3$ and its ^{1}H NMR spectrum consists of only one aromatic single peak (spectrum I). Compound E ($C_9H_{12}O_2$) also gives a positive test with $FeCl_3$. In the ^{1}H-NMR spectrum the aliphatic region shows two triplet and one multiplet peaks while the aromatic region consists of two doublets (spectrum II). Draw the structure of compounds D and E.



Spectrum I, Compound D ($C_6H_6O_3$)



Spectrum II, Compound E ($C_9H_{12}O_2$)

4 Indicate with arrows the three carbon atoms in structure C that will give rise to characteristic peaks in ^{13}C-NMR which distinguish structure C from B.

Problem 28: Synthesis of peptides

Peptides are linear polyamides formed by end to end linkage of a-aminoacids most frequently of the L- (or S) configuration.

1. Which dipeptides could result from condensing L- alanine and L-phenylalanine? Use stereo representations in your answer.

2. The stepwise elongation of the peptide chain almost invariably starts from the C terminal aminoacid (employed in the form of ester) to which each successive aminoacid unit (employed in the form of N- aminoacid derivative) is linked, followed by removal of the N substituent before the next unit is added. The substituent most often employed is an alkoxycarbonyl group ROCO- and the derivatives are then called carbamates.
Why does the presence of such a substituent (protecting group) on the amine nitrogen impede that amine from forming an amide linkage with a carboxyl group?

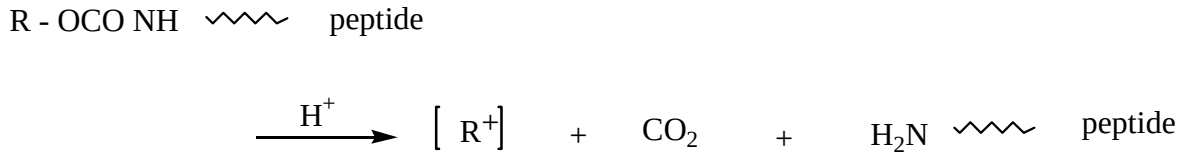
1- Because the nitrogen has only one H
2- Because the group lowers the electron density on nitrogen
3- Because the group hinders the approach of the carboxyl
4- Because of electrostatic repulsion
5- Because it is already an amide

3. Draw the resonance structures for an amide moiety. Use stereo representations and curved arrows to show the flow of electron density.

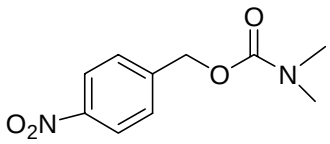
4. Which of the following reagents would you use to prepare the benzyl carbamate of an amine (Bergmann-Zervas protecting group)? Write the reaction

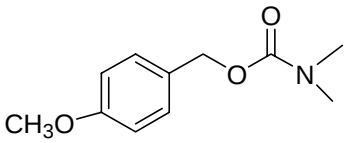
1. $C_6H_5CH_2OCOCNH_2$, 2. $C_6H_5CH_2OCO_2CH_3$, 3. $C_6H_5CH_2OCO_2C(CH_3)_3$,
4. $C_6H_5CH_2)C)Cl$, 5. C_6H_5OCOCl

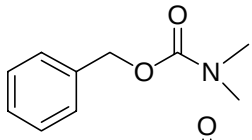
5. The removal of an alkoxycarbonyl protecting group is often accomplished by the action of acid that triggers a fragmentation represented schematically as follows:

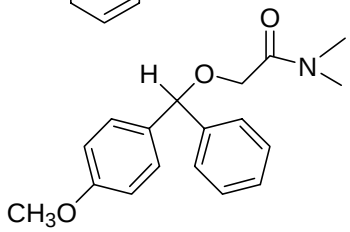


Rank the following carbamates according to increasing lability under acidic conditions:

A.


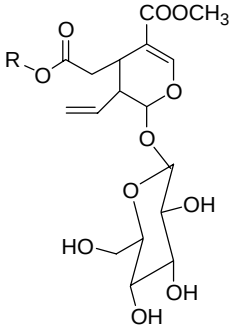
B.


C.


D.


Problem 29: Oleuropein hydrolysis

One of the geographical areas where nutritional habits have drawn attention as a prototype of nutrition is Crete. In a five country study, Cretan diet has been associated with low rates of coronary heart disease (CHD). The mortality rate from CHD was 7 in 10000 subjects, while it was 566, 424, 317 and 200 in Finland, USA, the Netherlands and Italy, respectively. This is mainly attributed to the high olive oil consumption, which is rich in oleuropein (**A**), a powerful antioxidant. (R represents an alkylpolyphenolic group)



A

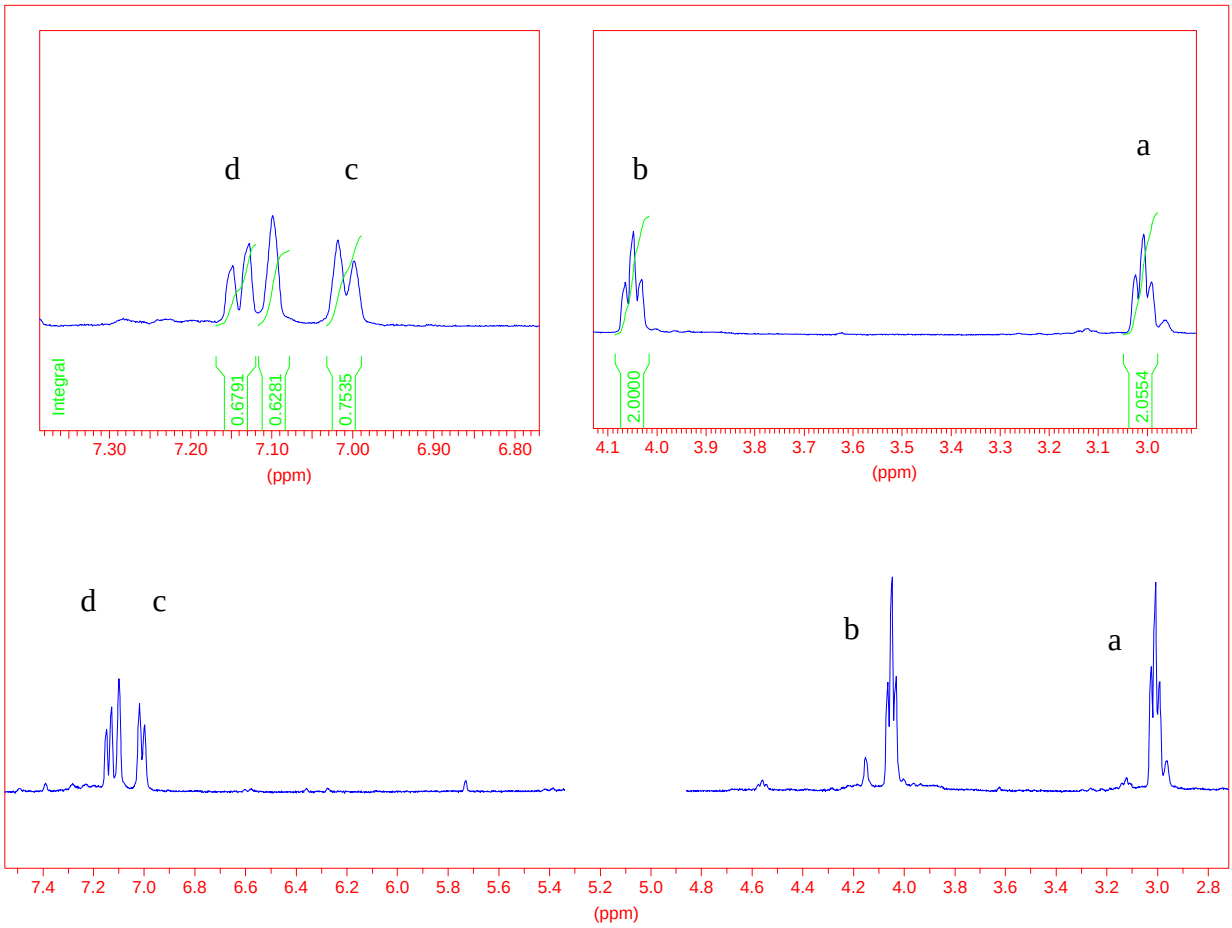
1. The acid-catalyzed hydrolysis of oleuropein gives apart from glucose, two other compounds, one polyphenolic (A1) and one monoterpenoid (A2).

Indicate with an arrow in the formula of oleuropein:

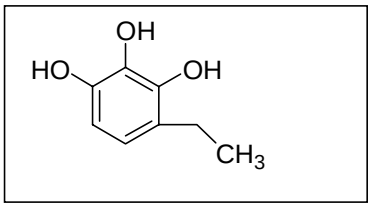
(a) The oxygen atom that will be protonated in the acid hydrolysis leading to polyphenolic compound A1.

(b) The carbon-oxygen bond that will be cleaved in order to form glucose.

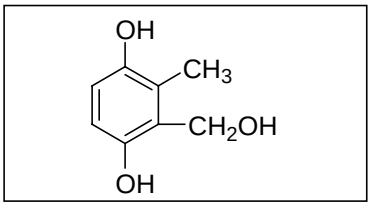
2. In the mass spectrum of A1, the peak corresponding to the molecular ion is situated at 154 mass units. The ^{1}H-NMR spectrum of A1 is shown below. The hydroxylic protons are exchangeable and therefore do not appear in the spectrum:



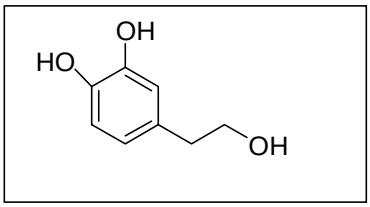
Choose the correct structure of A1 that can be deduced on the basis of ^{1}H-NMR and mass spectrum information given.



A



B

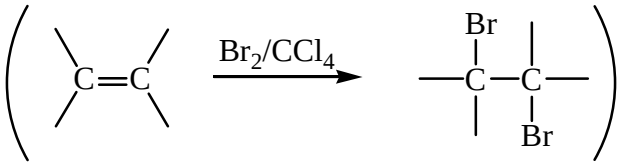


C

3 Draw the structure of A1 and use the letters a, b, c and d to designate the protons that correspond to the respective peaks in the ^{1}H-NMR spectrum.

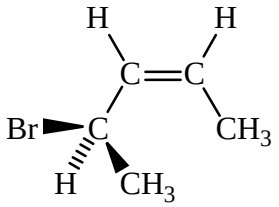
Problem 30: Fischer projections and optical activity

It is known that the addition of bromine to a double bond occurs with anti stereochemistry.

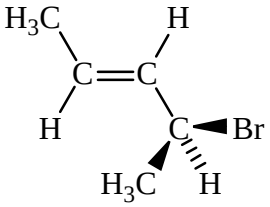


Write the products of bromination for the following alkenes, using Fischer projections. Indicate if the products are optically active.

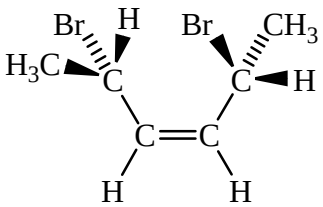
a)



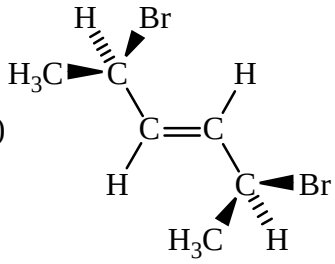
b)



c)



d)

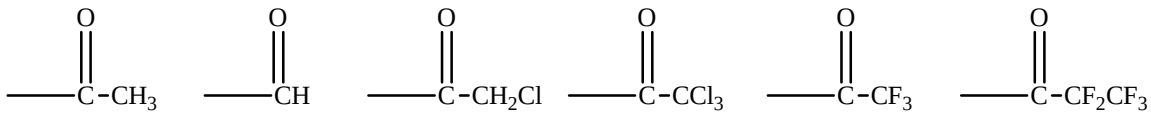


Problem 31: Alkyne identification

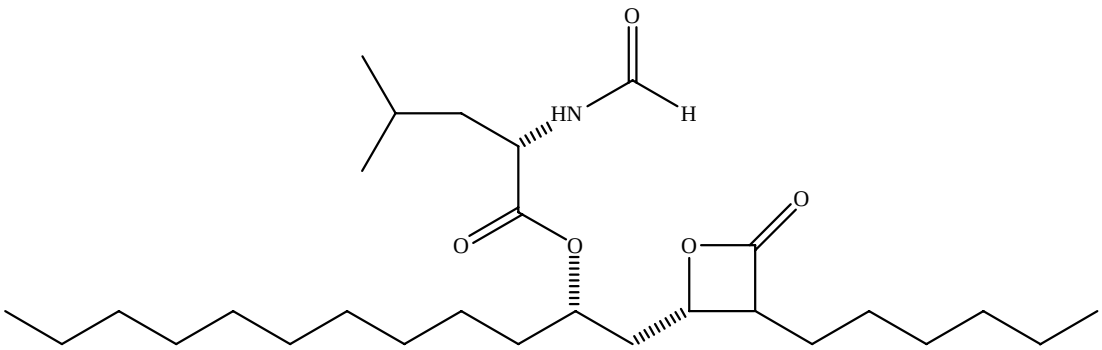
An optically active alkyne A contains 89,5% C and 10,4% H. After hydrogenation over Pd/C catalyst it is converted to 1-methyl-4-propyl cyclohexane. When compound A reacts with CH_3MgBr no gas is liberated. Hydrogenation of A over Lindlar catalyst, followed by ozonolysis and reaction with $KMnO_4$ gives product B whose ^{13}C NMR spectrum shows a peak at 207 ppm. Product B reacts with I_2/NaOH and gives a yellow precipitate, which is filtered. Acidification of the filtrate gives an optically active product C, whose ^{13}C NMR spectrum does not have any peak over 175 ppm.
Give the structures of A, B and C.

Problem 32: Lipases

Lipases are enzymes that hydrolyze the ester bonds of triacylglycerols, while proteases hydrolyze the amide bonds in proteins and peptides. Compounds that inhibit the hydrolysis of triacylglycerols and peptides may be useful for the treatment of various diseases.
The mechanism of action of the above enzymes starts with the attack of the hydroxyl group of serine to the ester or amide bond.
Our approach for the development of serine proteases inhibitors involves the replacement of the scissile amide bond by an activated carbonyl group. Thus, the hydroxyl of the active site serine reacts with the activated carbonyl forming a stable acyl enzyme adduct, which is not further hydrolyzed.
1. Rank the following carbonyl groups by decreasing reactivity against the hydroxyl group of serine:



2. Tetrahydrolipstatin is a potent inhibitor of digestive lipases (in clinical use for the treatment of obesity). Indicate with an arrow the carbonyl group of tetrahydrolipstatin that is attacked by the active site serine of lipases.



3. Esters and amides can be hydrolyzed under acid or basic conditions. Rank the compoundsby decreasing reactivity towards aqueous hydroxide ion.