Problem 1 – CALC, EQUIL – Determination of protein content by the Kjeldahl method

The Kjeldahl method was developed in 1883 by the Danish chemist Johan Kjeldahl. It was designed to determine the nitrogen content in organic compounds. Although 140 years have passed, this method is still used to determine protein content in food. The method consists of three stages: digestion, distillation, titration, and calculations.

Part I. Digestion stage

At the digestion stage, nitrogen in a sample is converted into ammonium ions. Digestion is achieved by adding excess concentrated sulfuric acid to the sample and boiling the mixture for a few hours.

a) Write the equation for the reaction between heated conc. H_2SO_4 acid and **i)** C; **ii)** S.

b) Will boiling concentrated sulfuric acid convert nitrate ions into ammonium ions? Circle the correct answer: Yes / No.

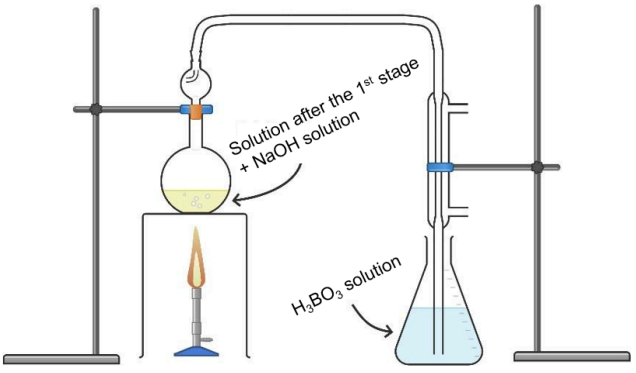
Concentrated sulfuric acid is a 98% H_2SO_4 solution. Interestingly, pure, anhydrous sulfuric acid contains not only H_2SO_4 molecules. As the equilibrium is reached, HSO_4^-, $HS_2O_7^-$, $H_2S_2O_7$, H_3O^+, and $H_3SO_4^+$ species are also found.

c) 1 kg of 98% H_2SO_4 solution contains 8.0 mmol of H_3O^+ ions and 4.4 mmol of $HS_2O_7^-$ ions. Determine which ions (HSO_4^-, $H_2S_2O_7$, $H_3SO_4^+$) concentration equals to 14.9, 11.3, and 3.6 mmol.

d) Choose the correct answer.

- ☐ The addition of NaCl and/or Na_2SO_4 will increase the boiling point of H_2SO_4. There is little to no difference if NaCl or Na_2SO_4 is used.
- ☐ The addition of NaCl will increase the boiling point of H_2SO_4. For faster digestion, it is significantly better to add NaCl than Na_2SO_4.
- ☐ The addition of Na_2SO_4 will increase the boiling point of H_2SO_4. For faster digestion, it is significantly better to add Na_2SO_4 than NaCl.
- ☐ The addition of NaCl and/or Na_2SO_4 will reduce the boiling point of H_2SO_4.
- ☐ The addition of NaCl and/or Na_2SO_4 will reduce the boiling point of H_2SO_4, however, salt will act as a catalyst.

Part II. Distillation stage



At the distillation stage, the solution from the digestion stage with formed $(NH_4)_2SO_4$ is exposed to an excess NaOH solution. Ammonium ions react with hydroxide ions:

$$NH_4^+ + OH^- \rightleftharpoons NH_3 + H_2O \ (\mathbf{1})$$

e) Is the solution with NaOH excess a buffer solution after the first stage? Circle the correct answer: Yes / No.

f) Calculate the equilibrium constant for **reaction 1**, knowing that the pH of the 0.50 M $(NH_4)_2SO_4$ solution is 4.63.

Generated ammonia reacts with the excess boric acid. Boric acid is very convenient to use since there is no need to know its exact concentration. After the reaction, the solution can be titrated with a strong acid. In solution, boric acid is ionized by water:

$$H_3BO_3 + H_2O \rightleftharpoons [H_2BO_3]^- + H_3O^+, \ pK_{a1} = 9.24 \ (pK_{a1} >> pK_{a2}; \ pK_{a3})$$

However, studies have shown that boric acid solution contains $[H_4BO_4]^-$ ions due to the reaction below:

$$H_3BO_3 + 2H_2O \rightleftharpoons [H_4BO_4]^- + H_3O^+, \text{ reaction } pK_a = 9.14.$$

g) Assume that both reactions occur in the boric acid solution. Calculate the pH of 0.10 M H_3BO_3 solution.

h) Draw H_3O^+, H_3BO_3, and $[H_4BO_4]^-$ Lewis structures, including formal charges. Determine central atom geometry (by VSEPR).

Part III. Titration and calculations stage

After titration, the amount of protein in the sample is calculated by multiplying the mass of nitrogen by a specific numeral factor which is 6.38, 5.95, and 6.25 for milk, rice, and meat, respectively.

i) After testing 10.0 g of rice, 19.50 cm^3 of the 1.00 M HCl solution was used to titrate the final solution. Calculate how many grams of protein are in the rice sample.

Knowing that the protein content is determined by the Kjeldahl method, the Chinese company "Sanlu Group" added melamine to their production for babies. The aim was to increase the amount of protein to be determined. This led to the deaths of 6 children. After investigation, imprisonments and death penalties were assigned to responsible people.

j) Assume that all nitrogen atoms in melamine are converted to ammonium ions. Calculate how many grams of protein 1.00 grams of melamine imitates in milk.

Problem 2 – APPLIED, ELECTRO, STRUCT – Applications of the 7th group elements

Part I. Manganese – coryphaeus among battery materials

Manganese is predominantly used in making alloys and batteries. Interestingly, manganese compounds were used in one of the first rechargeable batteries (Leclanché cell) and are still considered promising materials for future batteries.

Show that novel aqueous Mn-ion battery is comparable to metal-ion and lead-acid batteries from the following considerations. In the case of metal-ion batteries, neglect the electrolytes, respectively; in the case of Pb-acid, account for 35 wt% H_2SO_4 aqueous electrolyte.

The theoretical energy density of the Mg-ion battery is 134 Wh kg^{-1}; its pros and cons are X and Y (see below).

a) Calculate the theoretical energy densities of the batteries. Assign letters (A–F) denoting advantages and disadvantages (pros & cons) to the corresponding batteries.

A. Electrolyte instability and high cost, low abundance of elements used.

B. Good overall safety, low electrode and electrolyte cost, high abundance of elements used.

C. Robustness, low electrode and electrolyte cost, and wide temperature range.

D. High energy density and good overall performance.

E. Low energy density and environmental issues.

F. Low voltage and moderate energy density.

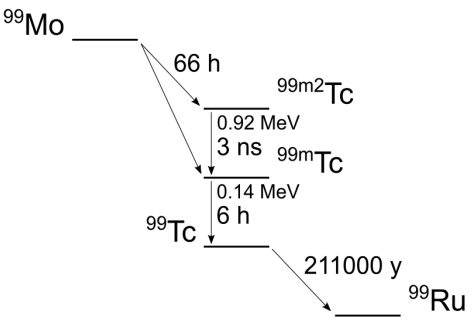
X. Good safety, high energy density, high abundance of Mg.

Y. Electrolyte instability and high cost, low energy density and voltage.

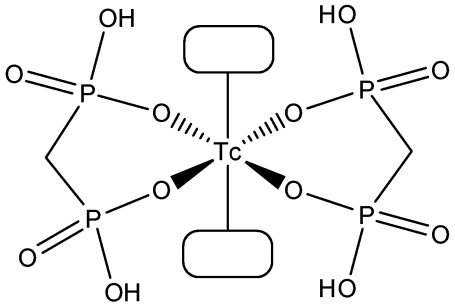
Battery	Li-ion	Pb-acid	Mn-ion	Mg-ion
Reaction	$LiC_6 + FePO_4 \rightleftharpoons LiFePO_4 + 6C$	$Pb + PbO_2 + 2H_2SO_4 \rightleftharpoons 2PbSO_4 + 2H_2O$	$Mn_{0.2}V_2O_5{\cdot}H_2O + 0.8Mn \rightleftharpoons MnV_2O_5{\cdot}H_2O$	$2Mg + Mo_6S_8 \rightleftharpoons Mg_2Mo_6S_8$
EMF [V]	3.3	2.1	1.3	1.1

Part II. Technetium – the lightest of unstable elements

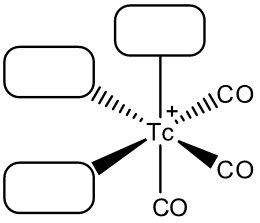
b) Fill in the blanks in the text and add missing groups (O, OH, H_2O) to the structures below.



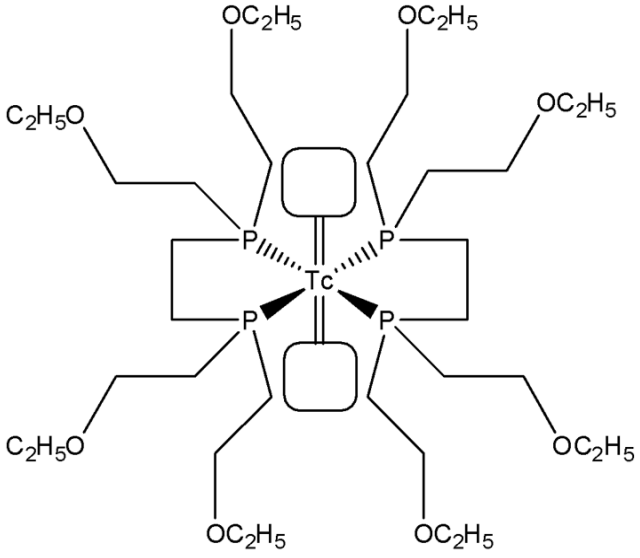
^{99m}Tc is one of the most frequently used isotopes in medicinal nuclear imaging. It is prepared in technetium-99m generators as a decay product of ^{99}Mo, obtained in a nuclear reactor in the fission of uranium-235: $^{235}U + {}^{1}n \rightarrow$ ____ + ^{99}Mo + 3 ^{1}n. Obtained ^{99}Mo undergoes ____ decay into meta-stable isomers ^{99m}Tc and ^{99m2}Tc according to the generic decay diagram (with half-lives and energy levels). ^{99m}Tc undergoes ____ decay of ____ keV comparable to the 20–150 keV X-ray range used in conventional radiography. Differently from the latter, detecting the ^{99m}Tc radiation from within the patient's body in a gamma camera gives ____-dimensional images of tissues and organs. The imaging is taken before half of ^{99m}Tc decays, i.e. within ____ hours after administrating the radiopharmaceutical. ^{99m}Tc radioactivity reduces to 1% of the initial activity in ____ hours. The radioactivity of ^{99}Tc is _____% of the initial activity of ^{99m}Tc. In most ^{99m}Tc radiopharmaceuticals, ^{99m}Tc (eluted from a technetium-99m generator) is turned into a coordination compound with specific biochemical properties: _____ attaches to hydroxyapatite and is used to scan bones, _____ penetrates lipid membranes and is used to scan the heart, _____ crosses the blood-brain barrier and is used to scan the brain.



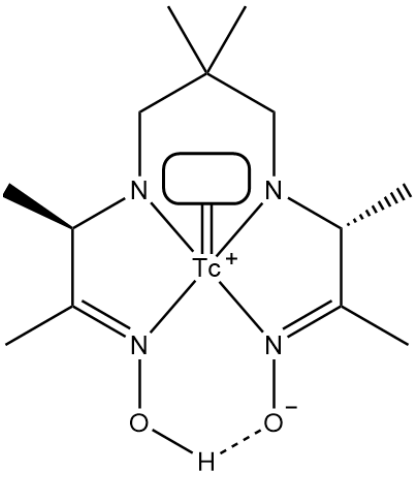
Diphosphonate



Carbonyl



Tetrofosmin

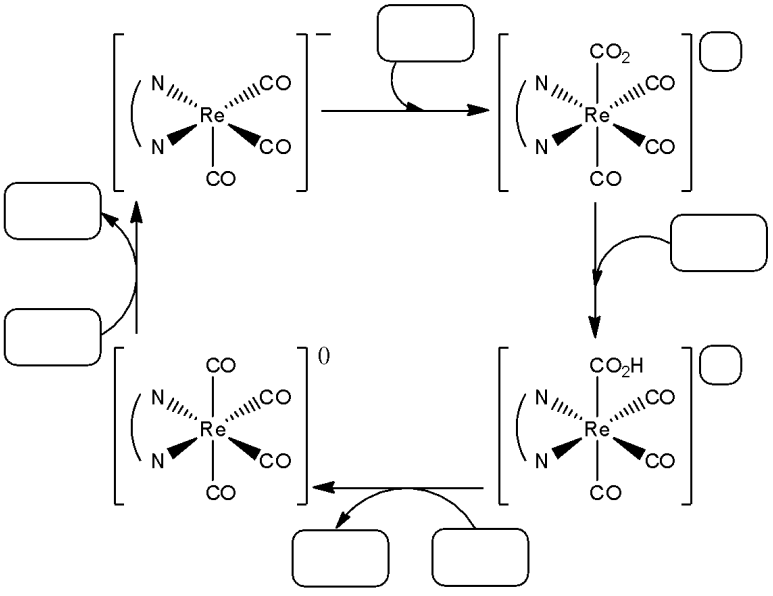


Exametazime

With more targeted imaging and therapy, the future applications of ^{99m}Tc for labeling biomolecules will likely be diverse and far-reaching. Technetium _____ is an essential precursor to specific coordination compounds: it contains two types of ligands – one is a good leaving group, and the other one is strongly bound to technetium.

Part III. Rhenium – an element of supermaterials

Rhenium is used in superalloys and catalysts. Rhenium chlorides are precursors for making catalytic coordination compounds. In reaction with chlorine, rhenium forms solid compound **A** (w_{Cl} = 48.77%), which thermally decomposes into molecular chloride **B** (w_{Cl} = 36.35%) and chlorine. Chloride **A** is also formed in the decomposition of molecular chloride **C**, which is unstable at room temperature. The coordination number of Re (including Re–Re bonds) is the same in molecules of **A** $[Cl_aRe(\mu\text{-}Cl)]_2$, **B** $[Cl_bRe(\mu\text{–}Cl)]_3$, and **C**, where μ denotes that chloride is bridging two rhenium atoms (Re–Cl–Re).



c) Draw the structural formulas of the molecules **A**–**C**.

Rhenium's possible applications in catalysis include the reduction of CO_2 to CO.

d) Fill in the blanks (charges, reagents, and products) in the catalytic cycle illustrating the electrochemical reduction mechanism (with H^+ and e^-).

Part IV. Bohrium – probably the most boring element in the Universe

Bohrium belongs to the family of superheavy elements, which could act as powerful nuclear fuel, for example, for future fission-propelled space missions. Isotopes with the "magic" number of protons (114) or neutrons (184) could theoretically have half-lives large enough to be used in nuclear reactors. The half-life of synthesized isotopes (2.9 s for ^{271}Bh, 8.8 s for ^{272}Bh, and 54 s for ^{274}Bh) shows a trend for stabilization ($\log T_{1/2} = aA^{1/6} + b$) towards the "island of stability" near the double-magic ^{298}Fl.

e) Estimate the half-life (in years) of the most stable isotope of Bh.

f) Predict whether bohrium would find any application in the future.

Problem 3 – KINETICS – Simple Surface Chemistry

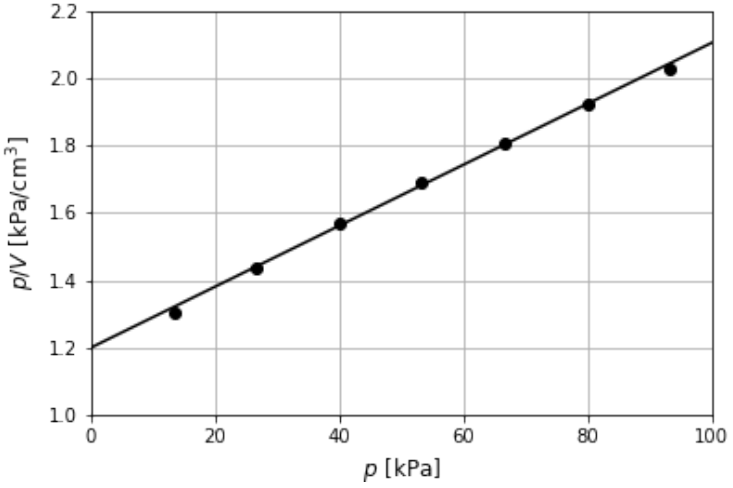
The surface coverage ($\theta = N_{occ}/N_{max}$, where N_{occ} is the number of occupied sites and N_{max} is the maximum number of adsorption sites) dependence on pressure is described by adsorption isotherms. The most used adsorption isotherm is the Langmuir adsorption isotherm. To derive the Langmuir isotherm, we consider the following rates for adsorption and desorption:

$$r_{ad} = k_{ad} p(1 - \theta)^n \text{ and } r_{des} = k_{des}\theta^n$$

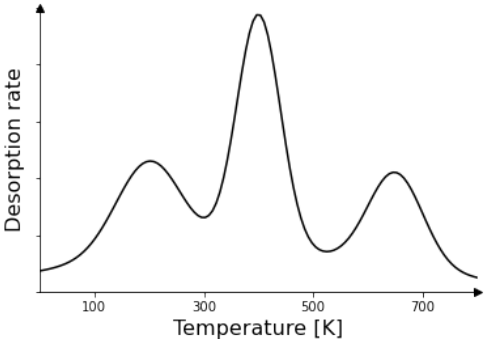
a) Assuming steady state, show that the surface coverage θ dependence on pressure p and adsorption/desorption rate constant ratio ($\alpha = k_{ad}/k_{des}$) takes the form $\theta = \frac{(\alpha p)^{1/n}}{1+(\alpha p)^{1/n}}$.

Further, we will consider a special case – non-dissociative adsorption – in which the first-order rate law is observed for adsorption and desorption ($n = 1$). In this case, the adsorption isotherm is $\theta = \frac{\alpha p}{1+\alpha p}$. However, in experiments, we cannot measure occupied sites directly. Instead, we consider the volume of gas adsorbed V versus the volume of gas adsorbed at full coverage $V_{max,}$ and therefore, the resulting isotherm in terms of volumes is $\theta = V/V_{max} = \frac{\alpha p}{1+\alpha p}$. With simple algebra, we can linearize the equation: $\frac{p}{V} = \frac{1}{\alpha V_{max}} + \frac{1}{V_{max}} p$.

The following plot was obtained in an experiment of CO adsorption on charcoal at 273 K. Solid dots show experimental data points, and the solid line shows the best-fit line.



b) Using the plot, determine α and V_{max}.

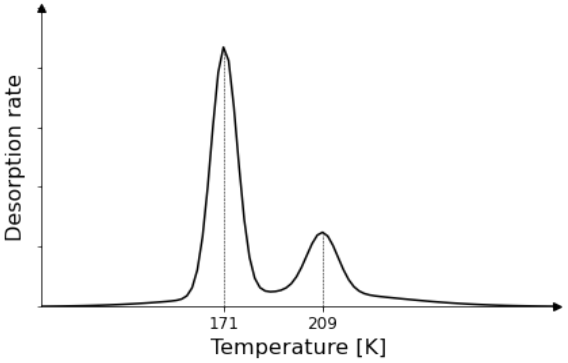


A useful method to study the kinetics of desorption and determine the desorption activation energy is thermal desorption spectroscopy (TDS). In this method, a sample is heated with a linear change in temperature, and the desorption rate is observed. At the temperature where rapid desorption starts, a peak in rate is observed, but after the sample is heated further, the rate decreases due to a lack of adsorbed species. Schematic representation of spectra observed in the studies is shown in the figure – multiple peaks represent multiple adsorption sites with their respective desorption activation energies.

To extract desorption activation energy E_d, we start from the desorption rate equation and consider that the desorption rate constant follows Arrhenius law, where ν is the pre-exponential factor: $-d\theta/dt = k_{des}\theta = \nu\theta\cdot\exp(-E_d/k_BT)$. Considering that the temperature change during the experiment is $T = T_0 + \beta t$, where β is the heating rate, and integrating the rate law, one obtains the relation, where T_{max} is the temperature at the top of the peak:

$$\frac{E_d}{k_B T_{max}^2} = \frac{\nu}{\beta}\exp\left(-\frac{E_d}{k_B T}\right).$$

c) Show that the expression can be rewritten as $E_d = k_B T_{max}(\ln(\nu T_{max}/\beta) - 3.64)$, where $\ln(E_d/k_B T_{max}) \approx 3.64$.

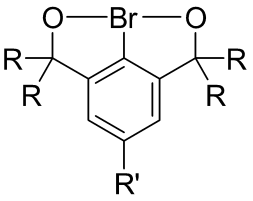


A TDS experiment was performed to investigate the desorption of ethylbenzene on pyrolytic graphite. Two peaks in the spectra were observed, one at 171 K and one at 209 K. The peak at 209 K corresponds to desorption from the adsorption layer directly on the surface, while the peak at 171 K corresponds to desorption from further layers.

d) Calculate the desorption activation energies (expressed in kJ mol^{-1}) for ethylbenzene desorption from pyrolytic graphite. Assume heating rate β = 1 K s^{-1}, pre-exponential factor $\nu = 10^{12}$ s^{-1}. *Hint: the formula from* ***c)*** *provided results for desorption activation energy per atom.*

One of the method's shortcomings is that it relies on a good guess of the pre-exponential factor.

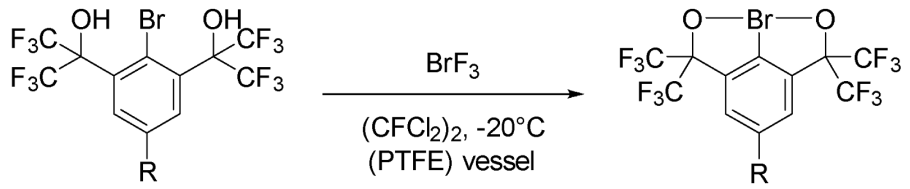
e) Calculate the error in the predicted desorption activation energy for desorption at 209 K if the actual pre-exponential factor is 1000 times larger.



Problem 4 – INORG, STRUCT – Bromine goes hyper mode

Bromine(III) reagents are fascinating compounds in the realm of organic chemistry due to their unique attributes. While their stability and high oxidizing power can make them difficult to handle, they have also served as tools for innovative synthetic conversions. In this problem, you will explore the synthesis of some hypervalent bromine(III) reagents (such as the one on the right), some of which have been investigated at the Latvian Institute of Organic Synthesis (LIOS).

Traditionally, compounds like **2** have been synthesized from BrF_3 and an aryl bromide **1** according to the following scheme:



1 **2**

Preparation of BrF_3 through a chemical process is difficult since it involves using two dangerous compounds, Br_2 and F_2, which require special safety measures. Additionally, the reaction produces two other substances that need to be separated using fractional distillation, which adds to the complexity of the process.

a) Write the formulas for the two side products.

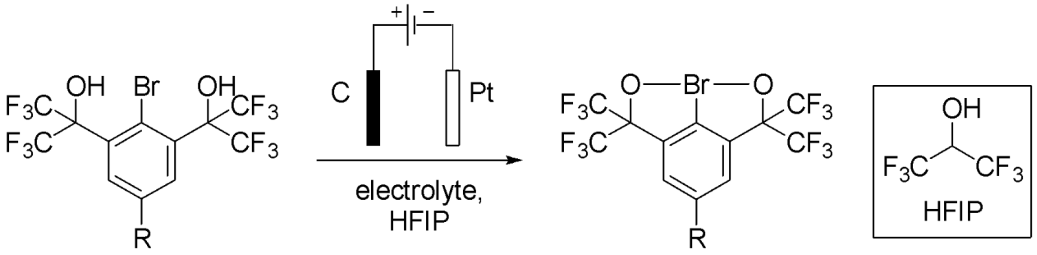
Another complication arises from the fact that BrF_3 is highly reactive and can react not only with water (forming two acids and oxygen) but also with other common solvents like acetonitrile CH_3CN (yielding a fluoroalkane and two elementary substances) and even glass (yielding two gases and a brown liquid) at room temperature.

b) Write equations of the reactions of BrF_3 with **i)** water; **ii)** acetonitrile; **iii)** silicon dioxide.

c) Another complication arises from the ability of BrF_3 to homolyse into radicals and promote unwanted side reactions. Provide a radical mechanism (should consist of three separate radical reactions) of potential fluorination of a generic alkane RCH_3. Note that any other trivalent bromine compounds are highly unlikely to form.

d) Provide two more side products that might form from different termination steps.

A novel method of synthesizing compound **2** has been developed at LIOS, which involves the oxidation of **1** in an undivided electrochemical cell:

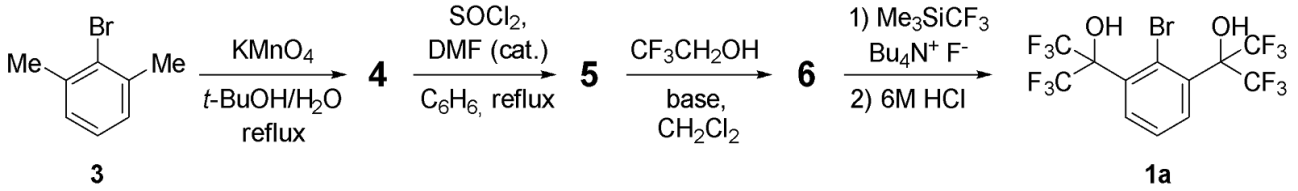


1 **2**

e) Write a half-reaction equation for the process ccurring on the opposite electrode. Circle the correct answers in the text.

The reaction occurs on the (carbon / platinum) electrode and it is the (anode / cathode). In reaction **1** → **2**, the bromine's hybridization changes from (*sp* / sp^2 / sp^3 / sp^3d / sp^3d^2 / sp^3d^3) to (*sp* / sp^2 / sp^3 / sp^3d / sp^3d^2 / sp^3d^3), while it's geometry (according to VSEPR) changes from (linear / bent / T-shaped / tetrahedral / octahedral / trigonal bipyramidal) to (linear / bent / T-shaped / tetrahedral / octahedral / trigonal bipyramidal) with the angle O–Br–C in compound **2** being close to (45° / 60° / 75° / 90° / 105° / 120°).

The synthesis of compound **1a** can be implemented starting from compound **3** according to the following scheme:



3 **1a**

f) Draw the structures of the intermediate compounds **4**–**6**. Note that the molecular formula of compound **6** is $C_{12}H_7BrF_6O_4$.

The electrochemical modification is also appealing due to its non-intrusive nature to monitor the reaction's progress without external interference. By interrupting the chemical reaction and conducting a cyclic voltammetry experiment, we can obtain a cyclic voltammogram that shows the relationship between current and the electric potential. Since the same redox event is being observed, the potential will be the same, enabling the comparison of the peak current i_p at various time points. The peak current i_p is proportional to the surface area A, and the potential sweep rate v. This relationship is represented by the Randles–Sevcik equation:

$$i_p = 2.69 \cdot 10^5 \cdot z^{\frac{3}{2}} \cdot A \cdot c \cdot D^{\frac{1}{2}} \cdot v^{\frac{1}{2}},$$

where z – number of electrons transferred; A – reactive surface area; c – concentration; D – diffusion coefficient; v – potential sweep rate.

g) Assume that you have acquired peak currents of the oxidation of **1** before starting the experiment ($i_{p,0}$) and at a certain time point t ($i_{p,t}$). Derive an equation for calculating the reaction yield at a time point t.

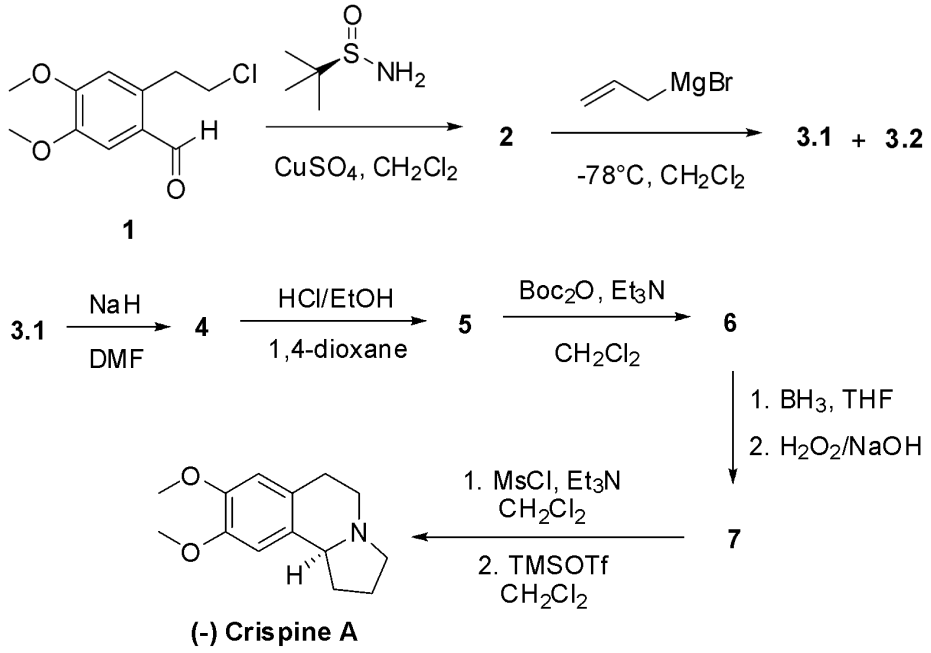
However, the Randles-Sevcik equation only applies to reversible systems. Experimental evidence suggests that the functional group R could alter whether a particular compound for this reaction will undergo reversible oxidation, therefore rendering this method unsuitable for monitoring reaction progress. An alternative technique involves utilizing quantitative IR spectroscopy to monitor the formation of the Br–O bond by measuring its absorption (at a constant λ) using the Beer–Lambert equation. However, there are a few issues: ambiguity regarding the molar extinction coefficient and path length; background absorption; a synthetic chemist's laziness in calculating intermediate values. These challenges may be overcome by: obtaining absorption values of the product at a known concentration; acquiring background absorption; deriving the equation for them.

h) Derive the equation for calculating the yield of the reaction **1** → **2** and calculate it for a reaction with a starting concentration of **1**, c_0 = 1 mM, where the measured absorption at a time point t is A_t = 0.986 AU, if the background absorption A_0 = 0.054 AU and the measured absorption of a 0.5 mM sample of **2** is A_x = 0.729 AU.

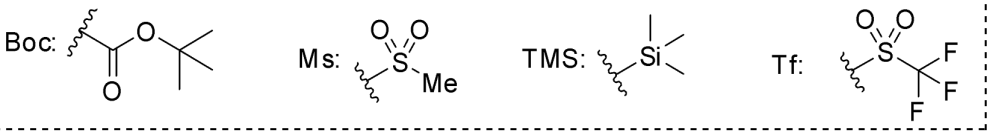
Problem 5 – SYNTH – Synthetic alkaloids

Alkaloids crispine A and crispine B have been isolated as bioactive constituents from the plant *Carduus crispus L.* which has been used for the treatment of cold, stomach ache, and rheumatism. Significant cytotoxic activities of these compounds on some human cancer cells have also been reported. Crispine A and crispine B both are very similar in structure, both belong to a family of pyrroloisoquinoline alkaloids.

Synthesis of enantiopure (−)-crispine A started from aldehyde **1**. Treatment of this aldehyde **1** with (*R*)-*tert*-butanesulfinamide in the presence of anhydrous $CuSO_4$ afforded compound **2**. Addition of allylmagnesium bromide to compound **2** at −78 °C in CH_2Cl_2 gave the mixture of two diastereomers, **3.1** (major) and **3.2** (minor). The diastereomeric mixture was easily separated by column chromatography, and only compound **3.1** was used in further synthesis steps. Over the next several steps, compound **3.1** was finally converted to (−)-crispine A, as shown below.



DMF – dimethylformamide; THF – tetrahydrofuran



a) Provide structures of compounds **2**, **3.1**, and **3.2** with stereochemistry.

b) Provide structures of compounds **4**, **5**, **6**, and **7** with stereochemistry.

c) Write the absolute configuration of (−)-crispine A stereocenter using *R*/*S* nomenclature.

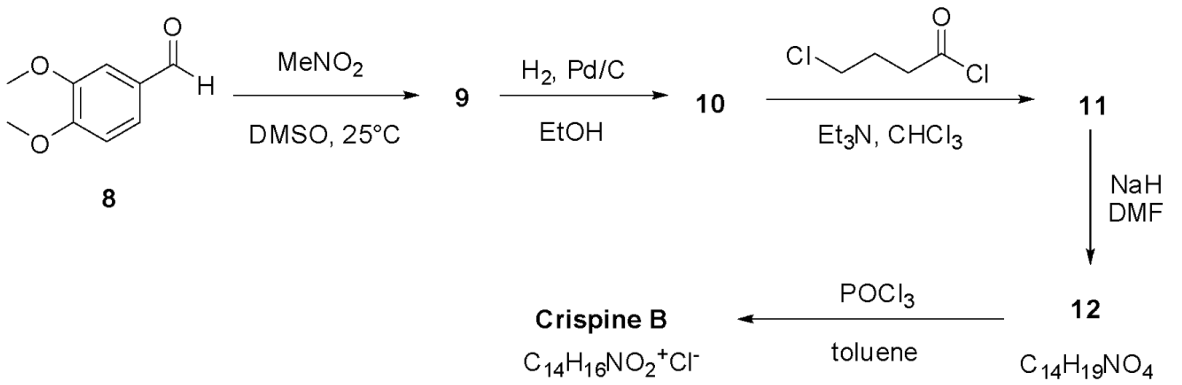
If the mixture of compounds **3.1** and **3.2** was used in the synthesis without separation, the liquid mixture of two enantiomers (−)-crispine A and (+)-crispine A would be finally obtained. This mixture has a specific rotation of −72.8°. Enantiopure (−)-crispine A has a specific rotation of −91.0°. The formula for enantiomeric excess calculation: ee = $(\omega_1 - \omega_2)/(\omega_1 + \omega_2)$, where ω_1 is a fraction of one enantiomer in the mixture, and ω_2 is a fraction of the other enantiomer in the mixture.

d) Calculate the enantiomeric excess of this mixture of (−)-crispine A and (+)-crispine A. Calculate the ratio of enantiomers in the mixture and clearly indicate which enantiomer is major and which is minor.

e) Choose the correct statement(s).

- ☐ (−)-enantiomer is always (*R*)-isomer.
- ☐ (−)-enantiomer is always (*S*)-isomer.
- ☐ (−)-enantiomer always has a positive specific rotation value.
- ☐ (−)-enantiomer always has a negative specific rotation value.
- ☐ There are no correct statements.

Synthesis of crispine B started from aldehyde **8**. After several chemical transformations, crispine B was obtained. It is known that crispine B is a salt whose cation has the molecular formula $C_{14}H_{16}NO_2^+$. DMSO – dimethyl sulfoxide.



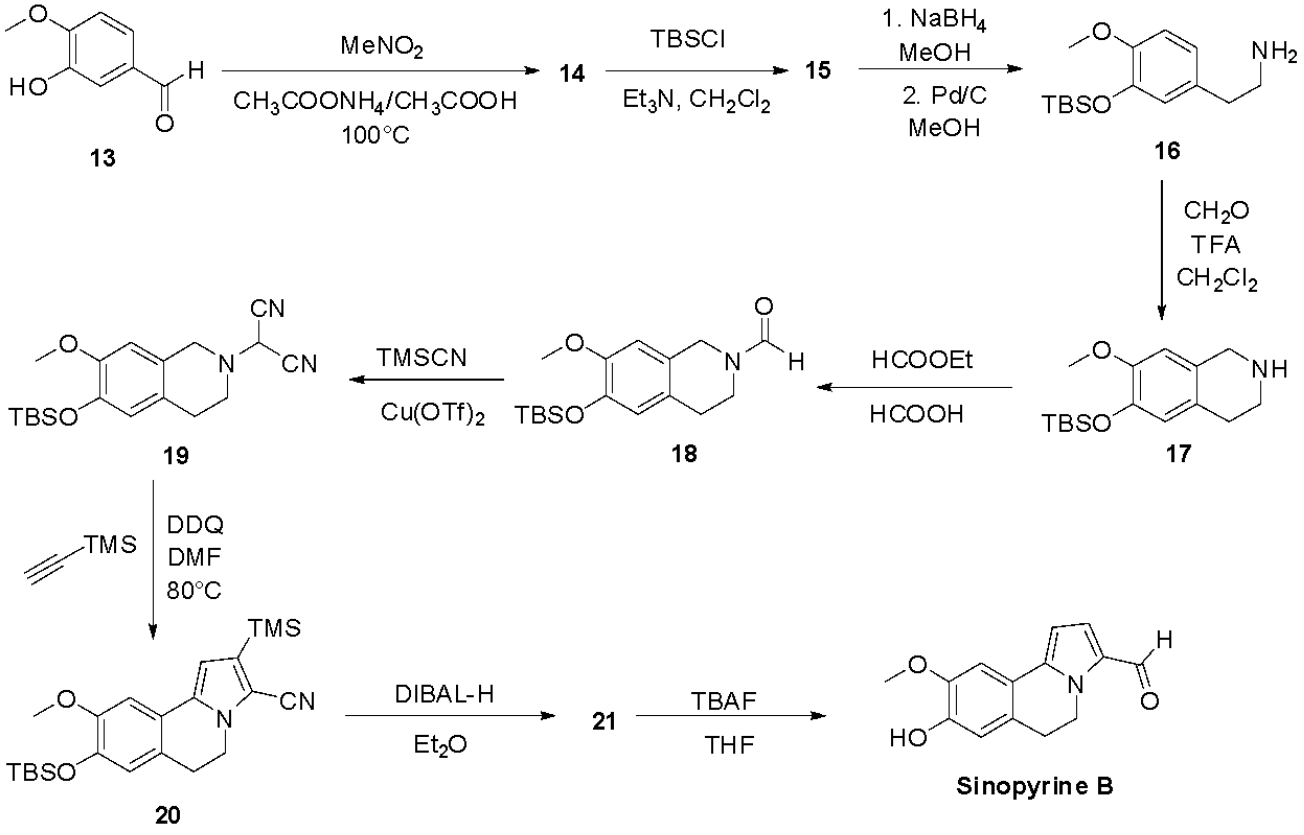
^{1}H NMR spectral data of compounds **9** and crispine B:

Compound **9** ^{1}H NMR ($CDCl_3$) δ: 2.74 (br. s., 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.50 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.62 (dd, *J* = 9.6, 13.2 Hz, 1H), 5.42 (dd, *J* = 3.2, 9.6 Hz, 1H), 6.86-6.94 (m, 3H).

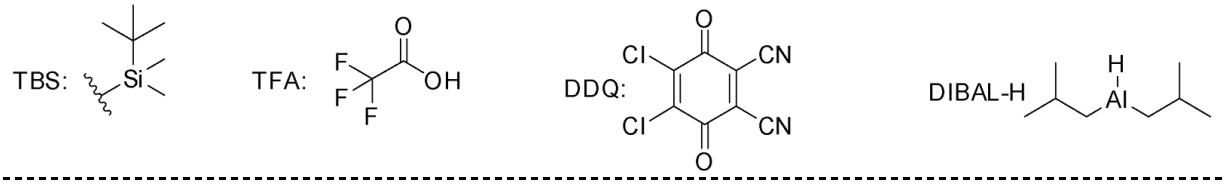
Crispine B ^{1}H NMR (deuterated MeOH) δ: 2.63 (q, 2H), 3.89 (t, 2H), 4.08 (s, 3H), 4.10 (s, 3H), 4.91 (t, 2H), 7.57 (s, 1H), 7.65 (s, 1H), 8.07 (d, *J* = 6.8 Hz, 1H), 8.36 (d, *J* = 6.8 Hz, 1H).

f) Provide structures of compounds **9**, **10**, **11**, **12**, and crispine B. Stereochemical information is not required.

Another alkaloid structurally very similar to crispine A and crispine B is sinopyrine B, which is found in the plant *Sinomenium acutum*. It can be synthesized from aldehyde **13**.



TBAF – tetrabutylammonium fluoride



Compound **14** ^{1}H NMR (deuterated DMSO) δ: 3.81 (s, 3H), 6.84 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.46 (s, 1H), 8.01 (d, *J* = 13.4 Hz, 1H), 8.13 (d, *J* = 13.4 Hz, 1H), 10.00 (br. s., 1H).

g) Draw structural formulas of compounds **14**, **15** and **21**.

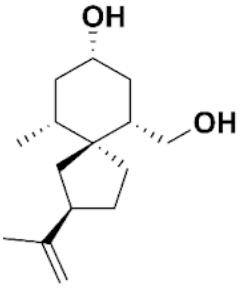
h) The reaction **16** → **17** is called Pictet-Spengler isoquinoline synthesis reaction. Draw the mechanism of **16** → **17**.

i) One of the key steps in this synthesis is a three-stage reaction **19** → **20** when a pyrrole ring is formed. Everything starts with a ylide formation after HCN removal. Then, a cycloaddition reaction occurs. And finally, the pyrrole ring is formed in the presence of DDQ. Draw the correct resonance structure of the most stable intermediate ylide which is formed after HCN removal and which actually participates in further reaction steps. Also, draw the structure of the compound which forms just after the cycloaddition reaction (before DDQ starts acting).

j) Write the name for the cycloaddition reaction using two different systems by writing appropriate numbers instead of letters α, β, γ and δ. When written in parentheses (...), numbers indicate the number of atoms in each reactant that participated in the cycloaddition reaction. When written in brackets [...], numbers indicate the number of electrons in each reactant that participated in the cycloaddition reaction.

k) What is the role of DDQ in this reaction: **i)** Oxidizing agent; **ii)** Reducing agent; **iii)** Catalyst; **iv)** Inhibitor?

Problem 6 – MECH, STEREO, SYNTH – Lubiminol

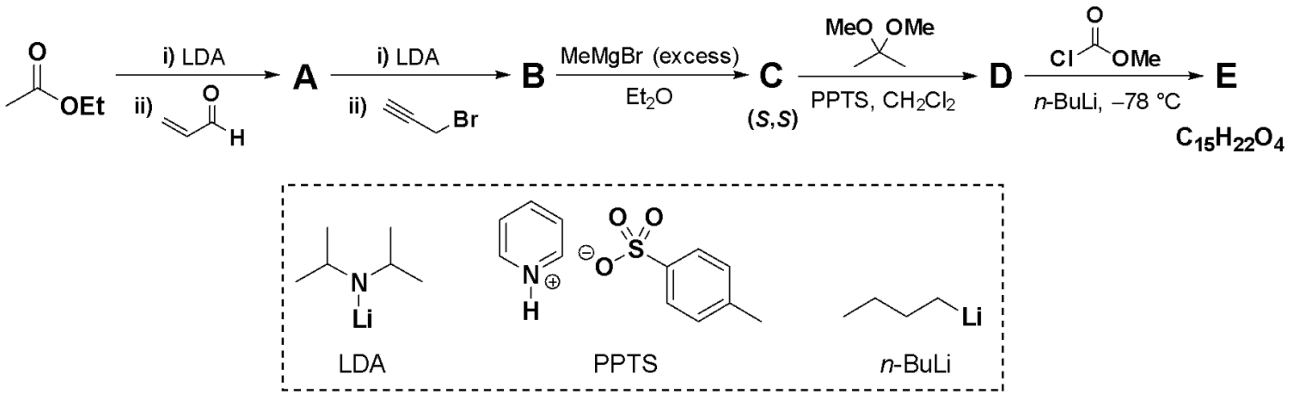


lubiminol

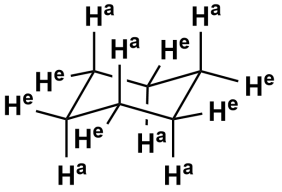
Phytoalexins are naturally occurring antimicrobial compounds produced by plants in response to pathogens at the site of infection. In this way, they serve an essential role in the general defense mechanism against plant diseases. Phytoalexins can counter the invading organism in various ways, including delaying the maturation, disrupting metabolism, breaking down cell walls, or inhibiting its reproduction.

Lubiminol is a spirocyclic phytoalexin first isolated from potato plants infected with a particular species of fungus (*Phytophthora infestans* or *Glomerella cingulata*). Although lubiminol has bioactive properties itself, it is an intermediate in the biosynthetic pathway of more substantial and potent antifungal agents.

In this task, you will look into the highly stereoselective total synthesis of lubiminol utilizing a radical cascade as the key step in constructing its spirocyclic core. The sequence began with a stereoselective aldol addition of ethyl acetate lithium enolate to acrolein, which gave the β-hydroxy ester **A** predominantly as its *R*-isomer. Propargylation with propargyl bromide in the presence of LDA then yielded **B**, which in turn was converted into **C** with an excess of methyl Grignard. Protection of **C** as an acetone acetal and subsequent treatment with methyl chloroformate gave compound **E**.



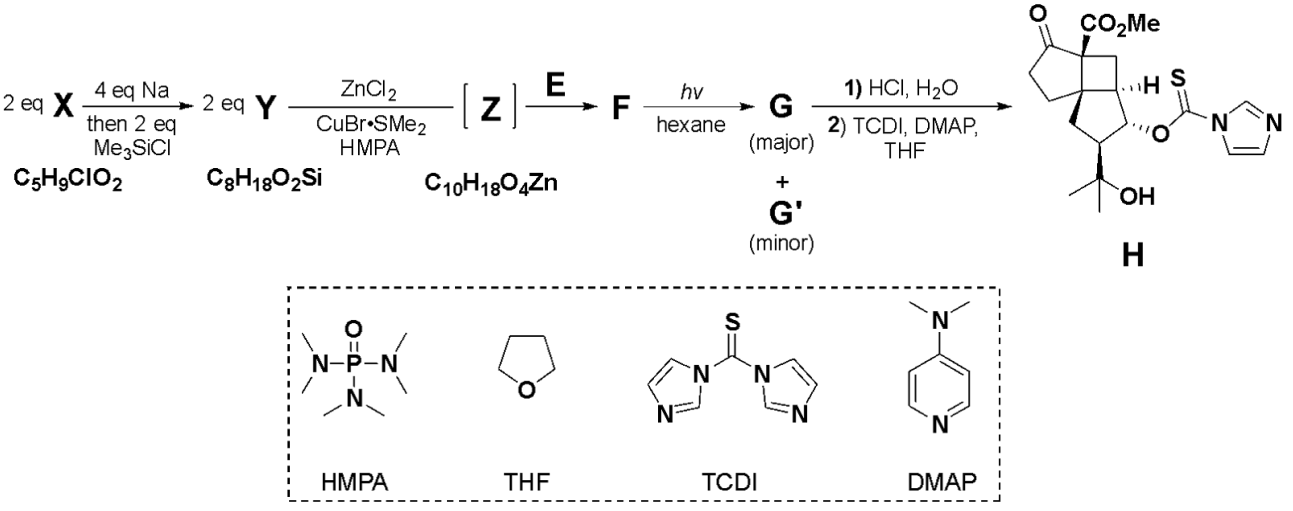
a) Draw the structural formulas of **A**–**E** with stereochemistry.



The stereoselectivity of the formation of **A** derives from the energetic differences in the two possible transition states and the outcome can be rationalized by the Zimmerman-Traxler model. By this rationale, the addition of the lithium enolate proceeds via a cyclic six-membered chair-like transition state, resemblant of the chair-conformation of cyclohexane (see the figure). The stereochemical outcome is ultimately determined by the spatial arrangement of the electrophile in the transition state. The lowest energy transition state is such where the electrophile's bulkiest substituent is positioned equatorially, and the smallest substituent is positioned axially. In the figure, axial protons of C_6H_{12} are denoted as H^a, and equatorial protons as H^e.

b) Account for the stereochemistry of **A** by applying the Zimmerman–Traxler model. Denote bonds which are being formed or broken with a dashed line (- - -).

Next, compound **E** was converted into enone **F** via a formal [3+2] cycloaddition. For this purpose, a zinc homoenolate **Z** was generated in situ from 2 equivalents of **Y** and 1 equivalent of $ZnCl_2$. Note that 1 equivalent of **Z** can react with up to 2 equivalents of **E**. Compound **Y** can be formed by treating **X** with sodium and trapping the resulting alkoxide with trimethylsilyl chloride. It is known that **Y** is cyclic, whereas **X** and **Z** are not. Irradiation of **F** with UV light yielded **G** and **G'** as the major and minor products, respectively. Upon deprotection and carbamothioate formation, compound H was obtained.



c) Draw the structures of **X**, **Y**, **Z**, **F**, **G** and **G'**, taking stereochemistry into account.

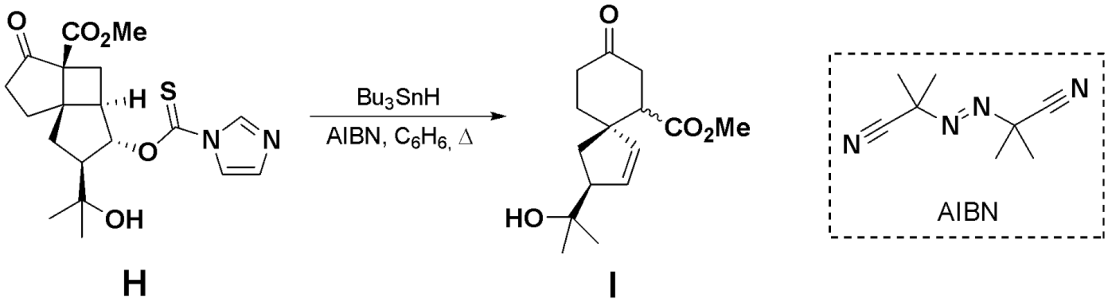
d) Circle the correct classification for the pericyclic reaction **F** → **G**:

electrocyclization / cycloaddition / sigmatropic rearrangement / cycloreversion / cheletropic reaction / ene reaction / the correct answer is not listed

e) Circle the correct answer. Based on Woodward-Hoffman rules, reaction **F** → **G** is:

conrotatory / disrotatory / neither conrotatory nor disrotatory

Compound **H** paved the way to the key step: a radical cascade that gave access to spirocycle **I**. The first step of the cascade is a well-known name reaction.

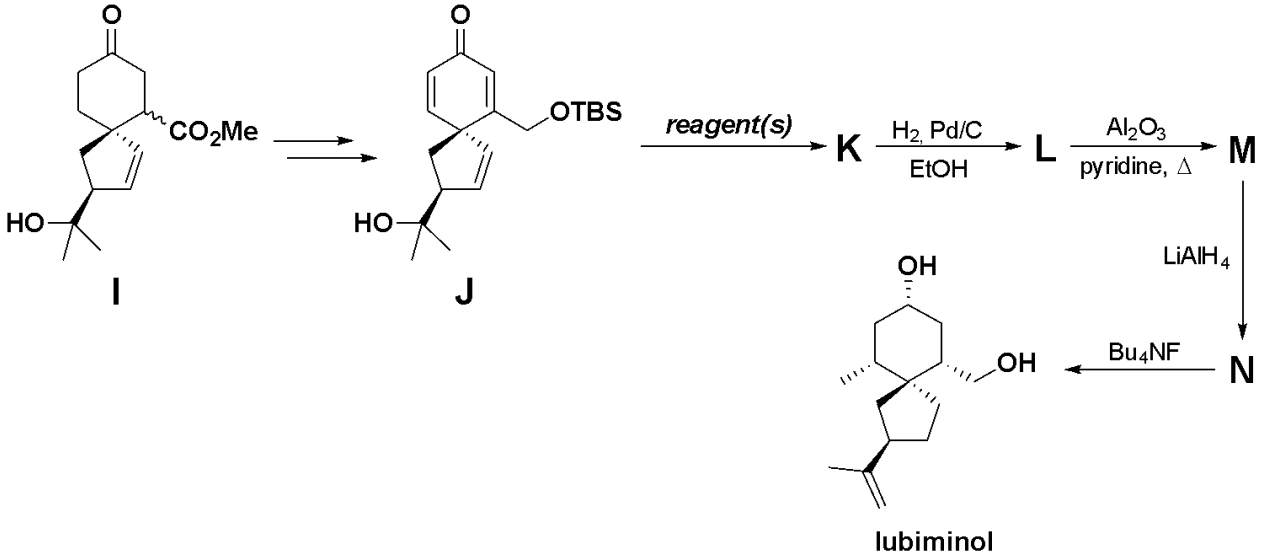


H **I**

f) The first step of the radical cascade is called a: **i)** Barton–McCombie reaction; **ii)** Mitsunobu reaction; **iii)** Wolff–Kishner reduction; **iv)** Corey–Fuchs reaction.

g) Sketch the mechanism of the reaction **H** → **I** using curly fish-hook arrows to indicate the flow of electrons. Clearly indicate any by-products that are formed in the process.

From compound **I**, precursor **J** was prepared over 7 steps. Subjecting **J** to *conditions* gave compound **K** stereoselectively. That was hydrogenated to give compound **L**, where all carbon-carbon bonds are saturated. From there, only two trivial steps remained to complete the synthesis.



I **J** lubiminol

h) Choose the appropriate reagent(s) for converting **J** into **K: i)** *i*-Pr_2NLi, MeI, **ii)** MeMgBr, **iii)** $(Me_3O)BF_4$, **iv)** Me_2CuLi, **v)** Me_3SI, NaH.

i) Draw the structural formulas of **K**–**N** with stereochemistry.